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ADIS DRUG EVALUATION

Ceritinib: a Review in ALK-Positive Advanced NSCLC

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Abstract Ceritinib (Zykadia™) is an oral, selective inhibitor of the anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase which, after genetic rearrangement, acts as an oncogenic driver in a proportion of non-small cell lung cancers (NSCLCs). The drug is approved in several countries worldwide for the treatment of patients with ALK-positive, advanced NSCLC who have previously received the first-generation ALK inhibitor crizotinib (indication details may vary by country). Approval was based on its clinical benefit in this setting in the phase I and II trials known as ASCEND-1 and −2. Across these noncomparative studies, 36–56 % of patients achieved a response with ceritinib (at the recommended dosage of 750 mg once daily) and the responses were durable, lasting up to a median of 10 months. Patients survived free from progression for a median of up to 7 months and had a median overall survival of up to 17 months. Moreover, efficacy outcomes in patients with brain metastases were generally consistent with those of the overall study populations. Ceritinib has an acceptable tolerability profile, with gastrointestinal issues, fatigue and liver test abnormalities being the most common adverse reactions. Thus, ceritinib is a valuable treatment option for patients with ALK-positive advanced NSCLC who have already received crizotinib therapy.

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Ceritinib: clinical considerations
Potent oral inhibitor of ALK, a kinase that forms an 'oncogenic driver' in some patients with NSCLC
Active against certain ALK mutations that confer resistance to the first-generation ALK inhibitor crizotinib
Up to 56 % of patients with ALK-positive advanced NSCLC previously treated with crizotinib respond to ceritinib
Acceptable tolerability profile

1 Introduction

Lung cancer is the world's most common cancer [1], with the majority of cases (85–90 %) being non-small cell lung cancer (NSCLC) [2]. Symptoms of NSCLC do not usually present until the disease is advanced, by which time the patient's prognosis is generally poor (e.g. stage IIIA, IIIB and IV disease 5-year survival rates are ≈14, ≈5, and ≈1 %, respectively) [3].

Pharmacological treatment options for advanced NSCLC were once limited to platinum-based chemotherapy regimens, although have since been expanded with the introduction of various targeted therapies, made possible by the discovery that a considerable proportion of NSCLCs carry targetable 'oncogenic drivers' (i.e. gene alterations resulting in uncontrolled cell growth/proliferation) [4]. The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase which, after genetic rearrangement [usually involving a chromosomal fusion between *ALK* and the *echinoderm microtubule-associated protein-like 4* (*EML4*) gene], acts as an oncogenic driver in around 4–5 % of all NSCLCs [5]. Testing patients for ALK

rearrangements is now routine practice [2, 6], with those carrying such rearrangements (i.e. with ALK-positive disease) usually being younger, non-smokers, with NSCLC of the adenocarcinoma subtype [2, 4].

The first agent available for the treatment of advanced ALK-positive NSCLC was the multitargeted tyrosine kinase inhibitor crizotinib, which is now recommended as a first-line therapy in this setting in the USA [6] and EU [2]. However, as with other oncogenic driver-targeted therapies, the clinical benefit of the drug is often of limited duration due to the development of resistance, with progression usually occurring within 11 months of starting therapy [7]. This limitation, together with the fact that the brain is a common site of disease progression with crizotinib (due to the drug's poor blood–brain-barrier penetration), has prompted the development of various next-generation ALK inhibitors [4, 7], of which ceritinib (Zykadia™) is the first to be widely commercially available.

Ceritinib is approved in several countries, including the USA [8] and those of the EU [9], for the treatment of adults with ALK-positive, advanced [9] or metastatic [8] NSCLC who have previously received crizotinib [9] or have progressed on, or are intolerant to, crizotinib [8]. This article focuses on pharmacological, therapeutic efficacy and tolerability data relevant to the use of ceritinib in these indications.

2 Pharmacodynamic Properties of Ceritinib

Ceritinib is a potent inhibitor of ALK, with only 200 pmol/L of the drug being required to inhibit ALK by 50 % in vitro [10]. Ceritinib is highly selective for ALK in in vitro and cellular assays, although inhibition of some other targets (including IGF-1R, InsR, STK22D and ROS1) may also occur at clinically relevant concentrations of the drug [8, 10]. Ceritinib suppresses the phosphorylation of ALK, as well as that of various proteins (e.g. STAT3 [8], ERK, ribosomal S6, and AKT [11]) with roles in downstream signalling pathways involved in regulating cell proliferation (i.e. JAK-STAT3, MEK-ERK, mTOR and PI3K-AKT, respectively). The drug inhibits proliferation of ALK-positive cell lines that express EML4-ALK [8, 9, 11] or NPM-ALK [8] fusion proteins, but appears to have little effect on cancer cell lines driven by EGFR, HER2, KRAS, or PI3K [11]. Consistent with these findings, ceritinib displays antitumour activity in treatment-naïve mouse [11] and rat [10] xenograft models of EML4-ALK NSCLC, causing dose-dependent inhibition of tumour growth.

Compared with crizotinib, ceritinib was 20-fold more potent against ALK in an enzymatic assay, up to 39-fold more potent in inhibiting the growth of ALK-rearranged NSCLC cell lines, and provided more durable antitumour activity in EML4-ALK NSCLC mouse xenografts [11].

Moreover, ceritinib appears to overcome some of the resistance issues associated with crizotinib, supporting its use in NSCLC patients who have progressed on crizotinib (Sect. 4). In general, ceritinib was able to potently inhibit the growth of cell lines expressing ALK with mutations known to commonly confer resistance to crizotinib (e.g. I1171T, L1196M, S1206Y, G1269A), although displayed little, if any, benefit over crizotinib against cell lines with less common crizotinib resistance mutations (e.g. C1156Y, G1202R, 1151T-ins, L1152R, F1174C) [11, 12]. In support of these findings, ceritinib potently suppressed the growth of crizotinib-resistant NSCLC mouse xenografts with wild-type or I1171T or L1196M mutant EML4-ALK, but was less active or inactive against xenografts with other EML4-ALK mutations (namely C1156Y and G1202R) [11]. However, among ALK inhibitor (ALKi)-treated patients with ALK-positive NSCLC participating in a phase I study (ASCEND-1; Sect. 4), six of the seven evaluable patients with baseline ALK resistance mutations, including E1129V, L1196M, C1156Y and I1171T, F1174V, had partial responses with ceritinib [13].

Ceritinib has also demonstrated activity against cell lines that are resistant to the next-generation ALKi alectinib due to expression of ALK with I117IT or V1180L mutations (mutations which also confer resistance to crizotinib) [14]. However, as with other targeted therapies, tumours can develop resistance to ceritinib, with 5 of 11 cancer biopsies from ALK-positive NSCLC patients with acquired resistance to ceritinib having F1174 or G1202 ALK mutations [11].

QT interval prolongation can occur with ceritinib. Among 304 patients who received ceritinib 50–750 mg across the clinical development programme, the corrected QT (QTc) interval was >500 ms or was increased from baseline by >60 ms in <1 and 3 % of patients, respectively [8], with a pharmacokinetic analysis suggesting that QTc interval increases may be dependent on the ceritinib concentration [8, 9]. At average steady-state concentrations in patients with advanced ALK-positive cancer, ceritinib 750 mg (i.e. the recommended dose) was associated with an increase from baseline in QTc interval with a two-sided 90 % confidence interval upper limit of 16 ms, according to data from the ASCEND-1 trial [9] (Sect. 4).

3 Pharmacokinetic Properties of Ceritinib

Absorption of oral ceritinib is estimated to be ≥25 % [9]. Ceritinib reached peak plasma levels (C_{max}) ≈6 h after repeated oral administration of the recommended 750 mg dose in patients with various advanced cancers, including NSCLC; the C_{max} of the drug increased slightly more than proportional to dose across multiple doses of 50–750 mg [15]. Ceritinib achieves steady-state after ≈15 days of daily oral

administration [8, 9, 15] and the mean accumulation ratio after 3 weeks is 6.2 [8, 9]. The absolute bioavailability of oral ceritinib is not known [8, 9]. Ceritinib should be taken on an empty stomach (Sect. 6) [8, 9], as administering a single dose of ceritinib 500 or 750 mg with food versus in a fasted state increased exposure to the drug considerably (area under the concentration-time curve from time 0 to infinity was increased by 54–73 %) in two healthy volunteer studies [16].

In vitro, ceritinib is highly plasma protein bound (≈97 %), independent of concentration, and displays a blood-to-plasma ratio of 1.35, indicating slightly greater distribution to red blood cells than to plasma [8, 9]. A single 750 mg dose of the drug administered to patients has an apparent volume of distribution of 4230 L [8]. The blood-to-brain exposure ratio of ceritinib in humans is not currently known, although is ≈15 % in rats [9].

The main component circulating in plasma after a single oral dose of ceritinib 750 mg is unchanged parent drug (82 %) [8], although 11 metabolites can be found circulating at low levels (each accounting for ≤2.3 % of the dose) [9]. Biotransformation of ceritinib primarily involves mono-oxygenation, O-dealkylation and N-formylation, with glucuronidation and dehydrogenation being secondary pathways; O-dealkylated ceritinib also undergoes thiolation [9]. Metabolic clearance of ceritinib occurs predominantly via CYP3A, according to in vitro data [8, 9].

Ceritinib is excreted predominantly via the faeces (92.3 vs. 1.3 % via the urine) following a single oral dose of 750 mg [8], with 68 % of the dose being excreted in faeces unchanged [8, 9]. The drug has a mean apparent terminal half-life of 41 h and a mean apparent clearance (CL/F) of 88.5 L/h after a single 750 mg dose [8]; however, when this dose is administered daily, the steady-state CL/F of the drug is 2.6-fold lower (33.2 L/h), indicating nonlinear pharmacokinetics over time [8, 9].

3.1 Special Populations and Drug Interactions

Plasma concentrations of ceritinib may be increased by hepatic impairment [8, 9]. On the basis of population pharmacokinetic analysis data, no dosage adjustments are necessary for patients with mild hepatic impairment [8, 9]. However, as data for ceritinib in patients with moderate or severe hepatic impairment are currently lacking, US dosage recommendations have not been determined for these patients [8] and the drug is not recommended in these settings in the EU [9].

According to population pharmacokinetic analyses, ceritinib exposure is not impacted to any clinically relevant extent by age, gender or race [8, 9] or by bodyweight [8], and no adjustment of dosage is necessary in patients with mild or moderate renal impairment [creatinine clearance (CR_{CL}) of 60 to <90 and 30 to <60 mL/min, respectively]. However, there are no data for ceritinib in patients with severe renal impairment (CR_{CL} <30 mL/min) [8, 9], and as a result, the drug should be used with caution in these patients in the EU [9].

As ceritinib is a CYP3A substrate, agents that inhibit or induce CYP3A may increase or decrease ceritinib plasma concentrations. Consequently, strong inhibitors and inducers of CYP3A should be avoided, as should grapefruits and their juice (as these may also inhibit CYP3A) [8, 9]. However, if it is necessary to coadminister ceritinib with a strong CYP3A inhibitor, reduction of the ceritinib dosage is recommended [8, 9]. Ceritinib bioavailability may also be reduced if coadministered with gastric acid-reducing drugs, as the solubility of ceritinib lessens with increasing pH [8, 9]; however, proton pump inhibitors did not alter exposure to ceritinib to any clinically meaningful extent at steady state in a subgroup of patients with ALK-positive advanced NSCLC participating in the ASCEND-1 trial (Sect. 4) [8].

In vitro, ceritinib is not a substrate of transporter proteins such as BCRP, MRP2, OCT1, OAT2 or OATP1B1 [8], but is a substrate of p-gp [8, 9]. Consequently, concentrations of the drug may be increased if coadministered with medicinal products that inhibit p-gp [8, 9]; in the EU, such coadministration requires caution and monitoring for adverse reactions [9]. Recent preclinical data indicate that p-gp/ABCB1 and BCRP/ABCG2 transporters may restrict accumulation of ceritinib in the brain [17].

Clinically relevant concentrations of ceritinib do not inhibit MRP2, OCT1, or OCT2, renal OAT1 or OAT3, or hepatic OATP1B1 or OATP1B3 transporters in vitro [8, 9], although are predicted to inhibit BCRP and p-gp of the intestines [9]. If drugs transported by BCRP or p-gp are coadministered with ceritinib, their plasma concentrations may be increased; consequently, in the EU, such coadministration requires caution and adverse reaction monitoring [9].

Clinical concentrations of ceritinib also inhibit CYP3A [8, 9], CYP2C9 [8, 9] CYP2A6 [9] and CYP2E1 [9] in vitro [8, 9], and may therefore reduce the clearance of drugs that are substrates of these enzymes. If coadministered with ceritinib, drugs predominantly metabolized by CYP3A or CYP2C9 may require dosage reductions [9]; those with narrow therapeutic indices should be avoided [8, 9]. Caution and adverse reaction monitoring is advised in the EU if coadministering ceritinib with CYP2A6 or CYP2E1 substrates [9]. Moreover, plasma concentrations, and thus efficacy, of oral contraceptives may be reduced if coadministered with ceritinib [9].

4 Therapeutic Efficacy of Ceritinib

This section focuses on key efficacy data supporting the recommended use of oral ceritinib 750 mg once daily in patients with ALK-positive advanced NSCLC previously treated with crizotinib, available from two open-label, noncomparative,

multicentre, phase I or II trials: ASCEND-1 [15, 18, 19] and ASCEND-2 [20–22].

ASCEND-1 enrolled adults (aged ≥18 years) with locally advanced or metastatic ALK-positive cancer that had progressed despite standard treatment, who had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2 and adequate end-organ function; prior ALKi therapy was allowed [15, 18]. The trial had an initial dose-escalation phase (ceritinib 50–750 mg once daily; reviewed in detail previously [23]) conducted in 59 patients that determined the maximum tolerated ceritinib dosage to be 750 mg once daily (primary trial objective); this dosage was then further evaluated in an expansion phase [15]. Overall, the trial enrolled 304 patients with ALK-positive cancer, 290 of whom had NSCLC [24]; however, only data from the subset of 163 patients with NSCLC previously treated with ALKi therapy who received the approved ceritinib dosage (i.e. 750 mg once daily) are discussed here. Of these 163 patients, 56 % had received three or more prior therapies, all had previously received crizotinib and 91 % had experienced disease progression on, or within 2 weeks of completing, ALKi therapy (i.e. crizotinib, with or without subsequent alectinib) [18].

In ASCEND-2, eligible patients were adults (aged ≥18 years) with locally advanced or metastatic ALK-positive NSCLC that had progressed despite 1–3 lines of chemotherapy (one of which must have been platinum based) followed by crizotinib [20, 22] and had a WHO performance status of 0–2 [20]. Most patients (78 %) enrolled in the study had received either two or three prior chemotherapy/targeted therapies [20].

Both trials required patients to have measurable disease (at least one measurable lesion, where specified [18]) as per Response Evaluation Criteria In Solid Tumors [18, 20], and excluded patients with symptomatic metastases of the CNS that were neurologically unstable or managed with increasing doses of corticosteroid [19, 22]. Among the ALK-positive NSCLC patients previously treated with an ALKi included in ASCEND-1 [18] and −2 [20], the median patient age was 52 and 51 years and most were either Caucasian (66 and 60 %) or Asian (29 and 38 %), had NSCLC of adenocarcinoma histology/cytology (93 and 92 %) and had brain metastases (60 and 71 %). The median duration of follow-up was ≈11 months in each study [18, 20].

4.1 Clinical Outcomes

Across ASCEND-1 [18] and −2 [20], use of oral ceritinib 750 mg once daily in adults with advanced ALK-positive NSCLC, previously treated with crizotinib and other standard therapies, was associated with an overall response rate (ORR) of 36–56 %, as assessed by the investigators (primary outcome [20]) or blinded independent review committee (BIRC) (Table 1). Responses to ceritinib were durable (lasting a median of up to ≈10 months) and patients had a median progression-free survival (PFS) of up to ≈7 months and a median overall survival of up to ≈17 months (Table 1) [18, 20].

According to pre-planned [20] and retrospective [18] subgroup analyses of ASCEND-1 [18] and −2 [20], clinical benefit was also seen with ceritinib in patients who entered the trials with brain metastases, with efficacy outcomes generally being consistent with those observed in the overall study populations. In the 100 patients with brain metastases at the ASCEND-2 baseline (72 % of whom had already received brain radiation therapy), ceritinib was associated with an ORR and disease control rate (DCR) of 33 and 74 % and a median duration of response (DOR) and PFS of 9.2 and 5.4 months, according to investigator assessment [20]. Moreover, among the 20 patients whose brain metastases were selected as target lesions in this study, investigator review reported an intracranial ORR of 45 % and an intracranial DCR of 80 %. BIRC assessments were generally consistent with these findings [20]. Similarly, retrospective investigator assessment of the 98 patients who entered ASCEND-1 with brain metastases reported an ORR of 51 %, with both the median DOR and median PFS being 6.9 months [18].

In additional subgroup analyses of ASCEND-1, the ORR benefit of ceritinib was generally consistent regardless of patient/disease characteristics, such as age, gender, disease burden, and the number of metastatic sites or prior treatment regimens, although it was 1.8-fold higher (with non-overlapping 95 % CIs) in patients with an ECOG PS of 0 versus ≥1 ($n = 38$ and 125) and in Asian versus Caucasian patients ($n = 47$ and 108) [24]. However, the ORR difference between Asian and Caucasian patients ($n = 82$ and 156) in a similar analysis of ASCEND-1 that included patients with ALK-positive NSCLC, regardless of prior ALKi therapy, was not considered to be significant (68.3 vs. 53.8 %) [data from an abstract/poster] [25].

4.2 Patient-Reported Outcomes

Where reported (ASCEND-2), ceritinib recipients generally maintained overall health-related quality of life (HR-QOL) over the first 13 treatment cycles, as measured by the global quality of life score of the European Organization for Research and Treatment of Cancer quality of life questionnaire-C30 (QLQ-C30) [20]. Patients also experienced improvements in lung cancer symptoms (measured by Lung Cancer Symptom Scale scores) during this period, although only pain improved to a clinically meaningful extent (at cycle 7). By the end of treatment, deterioration of these measures had occurred, probably due to disease progression [20]. Of note, ceritinib was initially associated with clinically meaningful worsening of nausea/vomiting, diarrhoea and appetite loss (measured by QLQ-C30 symptom score); all but diarrhoea improved towards baseline over the 13 cycles, although all

Table 1 Efficacy of oral ceritinib 750 mg once daily in adults with ALK-positive advanced non-small cell lung cancer previously treated with crizotinib and other standard therapies. Results of phase I (ASCEND-1) or II (ASCEND-2) trials

Study	No. of FAS pts	Median duration of follow-up [months] (data cutoff)	ORR [CR; PR] (% of pts)		Median DOR (months)		Median PFS (months)		Median OS (months)
			INV	BIRC	INV	BIRC	INV	BIRC	
ASCEND-1 [18]	163	11.1 (14 Apr 2014)	56.4 (1.8; 54.6)[a]	46.0 (2; 44)	8.3	8.8	6.9	7.0	16.7
ASCEND-2 [20]	140	11.3 (13 Aug 2014)	38.6 (2.9; 35.7)	35.7 (0; 35.7)	9.7	9.7	5.7	7.2	14.9

Tumours were evaluated using RECIST v1.0 (ASCEND-1) or v1.1 (ASCEND-2)

BIRC blinded independent central review committee assessed, *CR* complete response, *DOR* duration of response, *FAS* full analysis set, *INV* investigator assessed, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *pts* patients

[a] Primary outcome

three symptoms had worsened to a clinically relevant extent at the end of treatment [20]. Findings for these measures over nine treatment cycles were broadly similar, regardless of whether patients did, or did not have, brain metastases, although clinically meaningful improvements in overall HR-QOL and lung cancer symptoms appeared to occur more often in those without brain metastases (data from an abstract) [21].

5 Tolerability of Ceritinib

This section focuses on data for oral ceritinib 750 mg once daily, mainly from a pooled analysis of four open-label, non-comparative trials in patients with ALK-positive cancers, mainly NSCLC (515 patients; 10 patients had other cancers) [9]. In this analysis, in which the median exposure to ceritinib was 33 weeks, the most common (>40 % incidence) adverse reactions were gastrointestinal (GI) issues (diarrhoea, nausea, vomiting, abdominal pain, decreased appetite), fatigue and liver test abnormalities (Fig. 1) [9]. The grade 3 or 4 adverse reactions that occurred most frequently (≥5 % incidence) were liver test abnormalities, fatigue, diarrhoea, nausea and hyperglycaemia (no quantitative data reported) [9]. Ceritinib demonstrated a similar tolerability profile, regardless of patient age (< or ≥65 years), although there are currently no data in patients aged >85 years [9].

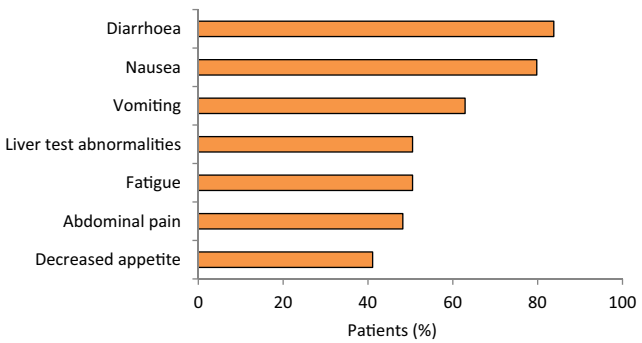

Fig. 1 Adverse reactions (any grade) that occurred in >40 % of patients with ALK-positive cancers, mainly NSCLC, who received ceritinib 750 mg once daily in four noncomparative trials (pooled analysis; see text for further details) [9]

Data for ceritinib 750 mg once daily in ALK-positive NSCLC patients from the individual ASCEND-1 [18] and ASCEND-2 [20] studies are generally consistent with these findings. For instance, the most common adverse events (AEs) in ASCEND-2 were nausea, diarrhoea and vomiting (63–81 % of patients); however, these were generally grade 1 or 2 in severity when considered related to ceritinib, were manageable by interrupting/reducing the dose of the drug, and rarely (2 %) caused treatment discontinuation [20]. Fewer than 12 % of patients discontinued ceritinib because of AEs in ASCEND-1 and −2 [18, 20], and of the patients who interrupted or reduced the dose of the drug (76 and 54 %), most did so because of AEs (86 and 84 %) [20].

Around half of the patients in ASCEND-1 and −2 had grade 3 or 4 AEs possibly related to ceritinib (46 [20] or 51 [18] %), with elevated ALT (16 %) and elevated γ-glutamyltransferase (9 %) being the most frequent where specified [20]. Serious AEs considered possibly related to ceritinib occurred in 12 and 17 % of patients in the respective trials [18, 20], with the most common being pneumonitis (3 % of patients), diarrhoea, nausea, increased ALT, hyperglycaemia and pericarditis (each 1 % of patients) where reported [18]. Adverse reactions (most commonly pneumonia; four patients) were fatal in 5 % of ceritinib recipients in ASCEND-1 [8].

5.1 Adverse Events of Special Interest

In the pooled analysis, the GI or hepatotoxicity events associated with ceritinib each resulted in dosage reductions/interruptions in around one-third of patients, and most patients (85 %) with GI events required use of agents such as anti-emetics/anti-diarrhoeals; however, <1 % of patients discontinued ceritinib for either GI or hepatotoxicity issues [9]. Patients should be monitored for GI toxicity and managed accordingly using standards of care (anti-emetics, anti-diarrheals, fluid replacement); regular monitoring of liver function parameters (e.g. ALT, AST and total bilirubin) is also recommended [8, 9].

QT interval prolongation can occur with ceritinib (Sect. 2), potentially increasing the likelihood of ventricular tachyarrhythmias and sudden death [9]. In the pooled analysis, QT interval prolongation was reported in 6.5 % of patients, although was rarely grade 3 or 4 in severity (0.8 % of patients) [9]. Ceritinib should be avoided in patients with congenital long QT syndrome and requires periodic electrocardiogram and electrolyte monitoring in at-risk patients (e.g. those with relevant cardiac disease, bradyarrhythmias, electrolyte abnormalities, or taking QT interval-prolonging drugs) [8, 9]. Few ceritinib recipients in the pooled analysis developed bradycardia and/or sinus bradycardia (1.9 %), and all cases were grade 1 in severity [9]. However, BP and heart rate should be monitored regularly and, where possible, concomitant use of other bradycardia-inducing drugs avoided [8, 9].

Interstitial lung disease (ILD)/pneumonitis was also uncommon with ceritinib in the pooled analysis (3.2 % of patients had any grade events; 1.9 % of patients had grade 3 or 4 events) [9]. Interrupting ceritinib generally improves/resolves the condition [9], although some cases have been severe, life-threatening, or fatal [8, 9]. Monitoring ceritinib recipients for pulmonary pneumonitis symptoms is recommended [8, 9].

Fewer than 10 % of ceritinib recipients in the pooled analysis experienced hyperglycaemia (7.8 % of patients had any grade events; 5 % of patients had grade 3 or 4 events), although those with diabetes and/or using concomitant corticosteroids had a greater risk [9]. Fasting serum glucose should be monitored before, and periodically during, ceritinib therapy and anti-hyperglycaemic agents used as necessary [8, 9]. Lipase and amylase levels should also be monitored before starting ceritinib therapy [8, 9]; increases in each of these enzymes occurred in 4.6 % of ceritinib recipients in the pooled analysis, although only 0.4 % of patients developed pancreatitis [9].

Of note, among the patients who experienced ILD/pneumonitis, QT interval prolongation, bradycardia or hyperglycaemia in this analysis, few (<2 %) required dosage reduction/interruption or discontinuation of ceritinib [9].

6 Dosage and Administration of Ceritinib

For the treatment of adults with ALK-positive, advanced [9] or metastatic [8] NSCLC who have previously received crizotinib [9] or have progressed on, or are intolerant to, crizotinib [8], the recommended ceritinib dosage is 750 mg taken orally once daily on an empty stomach (i.e. not within 2 h of eating) [8, 9]; the capsules should not be crushed or chewed [9]. Treatment should be continued for as long as clinical benefit is seen [9] or until disease progression or unacceptable toxicity [8]. Local prescribing information should be consulted for details regarding contraindications, warnings, precautions, management recommendations (including dosage reductions, interruptions, and discontinuations) for tolerability issues of particular interest (Sect. 5.1), and use in special patient populations.

7 Current Status of Ceritinib in ALK-Positive Advanced NSCLC

Oral ceritinib is indicated in the USA [8], the EU [9] and several other countries worldwide for the treatment of adults with ALK-positive, advanced [9] or metastatic [8] NSCLC who have previously received crizotinib [9] or have progressed on, or are intolerant to, crizotinib [8]. As such, ceritinib satisfies a previously unmet need, as historically, the only option available for such patients was standard cytotoxic chemotherapy that was poorly tolerated and only marginally effective [26]. The importance of these findings are evident in the most recent US and Canadian treatment guidelines for NSCLC, which recommend the use of ceritinib in this setting [6, 27].

Approval of ceritinib was based on the findings of the non-comparative phase I and II trials, known as ASCEND-1 and −2, in which the drug (at the recommended dosage of 750 mg once daily) displayed an acceptable tolerability profile and was associated with ORRs of 36–56 % in adults with advanced ALK-positive NSCLC, previously treated with crizotinib and other standard therapies (Sect. 4.1). Responses to ceritinib were durable, and patients survived free from progression for up to 7 months and had an overall survival of up to 17 months (median values; Sect. 4.1). However, why outcomes were generally of a lesser magnitude in ASCEND-2 than ASCEND-1 is not known and was to some extent unexpected [28]. Efficacy outcomes in patients with brain metastases in these trials were generally consistent with those observed in the overall study populations, although further data are necessary to confirm these findings. Indeed, one of the further trials underway in the ASCEND programme is the phase II ASCEND-7 trial, designed to assess the use of ceritinib specifically in patients with ALK-positive NSCLC metastatic to the brain and/or leptomeninges, including those who have been previously treated [29].

As with brain metastases, most other patient/disease characteristics appeared to have minimal impact on the ORR benefit of ceritinib, although whether Asian patients may benefit slightly more from the drug than Caucasian patients is not yet clear (Sect. 4.1). Further data for ceritinib in Asian patients with ALK-positive NSCLC are available from a small phase I trial in Japanese patients (19 with NSCLC and one with another cancer type), 80 % of whom had received prior ALKi therapy [30]. However, a larger phase I/II trial in Chinese patients with ALK-positive NSCLC previously treated with crizotinib is ongoing (NCT02040870).

At present, there are no data directly comparing ceritinib with other agents typically used in the treatment of advanced ALK-positive NSCLC. However, phase III trials are underway comparing ceritinib with standard chemotherapy

regimens in adults with ALK-positive NSCLC, including those who have previously received chemotherapy and crizotinib (ASCEND-5) [31]; data are awaited with interest. Further trials would also be beneficial to determine the optimal sequence of ALKi therapies; indeed, a phase II trial in patients with advanced ALK-positive NSCLC is currently assessing the use of ceritinib subsequent to treatment with alectinib, the only other commercially available next-generation ALKi (NCT02450903). Alectinib is approved in Japan for patients with advanced, unresectable ALK-positive NSCLC [32] and has recently been approved in the USA for ALK-positive NSCLC patients with intolerance to, or worsening of disease after, crizotinib therapy [33], thus further expanding ALKi options.

Although new anticancer therapies can be expensive, limited data (available from abstracts) suggest that ceritinib may be a cost-effective option for the treatment of ALK-positive NSCLC previously treated with crizotinib in Canada (from a healthcare perspective) [34] or previously treated with chemotherapy or an ALKi in the UK (from a National Health Service and Personal Social Service perspective) [35]. Moreover, according to one modelled estimation, the drug may also have economic benefits over chemotherapy in this setting due to being associated with greater work productivity in both patients and caregivers (abstract data [36]). Further robust pharmacoeconomic analyses would be beneficial.

In conclusion, ceritinib is a valuable treatment option for patients with ALK-positive advanced NSCLC who have already received crizotinib therapy.

Data selection sources: Relevant medical literature (including published and unpublished data) on ceritinib was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 16 September 2016], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Ceritinib, Zykadia, LDK-378, anaplastic lymphoma kinase, ALK, non-small cell.
Study selection: Studies in patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who received ceritinib. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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Compliance with Ethical Standards

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