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Real-life experience of ceritinib in crizotinib-pretreated *ALK*$^+$ advanced non-small cell lung cancer patients

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ABSTRACT Here we report our experience of ceritinib in crizotinib-pretreated patients with anaplastic lymphoma kinase (*ALK*) positive (*ALK*$^+$) non-small cell lung cancer (NSCLC) in a French temporary authorisation for use (TAU) study.

The French TAU study included crizotinib-pretreated patients with advanced *ALK*$^+$ or ROS proto-oncogene 1 positive (*ROS1*$^+$) tumours. Patients received oral ceritinib (750 mg·day^{-1} as a starting dose) and best tumour response (as evaluated by the investigator) and safety were reported every 3 months.

A total of 242 TAUs were granted from March 12, 2013 to August 05, 2015. Of the 242 patients, 228 had *ALK*$^+$ NSCLC and 13 had *ROS1*$^+$ NSCLC. The median age of *ALK*$^+$ patients (n=214) was 58.5 years, 51.9% were female, 70.8% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 and 50.0% had brain metastases. Of the 149 efficacy evaluable *ALK*$^+$ NSCLC patients, 5.4% had a complete response (CR), 47.0% had a partial response (PR) and 22.8% had stable disease (SD). At September 05, 2015, the median duration of ceritinib treatment (n=182) was 3.9 months but 5.5 months for patients (n=71) with a follow-up of ⩾12 months. Higher objective response rate (ORR) was observed for patients with ECOG PS 0 to 1 (55.0% *versus* 42.4%) and those receiving prior crizotinib for >5 months (51.6% *versus* 36.1%). Treatment-related adverse events (AEs) were reported in 118 of 208 patients (56.7%), the most common being diarrhoea (22.1%) and hepatic toxicity (19.7%).

Ceritinib (750 mg·day^{-1}) demonstrated efficacy similar efficacy to ASCEND-1, ASCEND-2 and phase 3 ASCEND-5 trials with manageable safety in crizotinib-pretreated patients with *ALK*$^+$ NSCLC.

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Ceritinib (750 mg per day) showed similar efficacy as in clinical trials in crizotinib-pretreated *ALK*$^+$ NSCLC patients http://ow.ly/8oXe30h27D0

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Introduction

Anaplastic lymphoma kinase (*ALK*) rearrangements occur in approximately 5% of patients with non-small cell lung cancer (NSCLC) [1]. Crizotinib is the first *ALK*-targeted approved agent and targets *cMET*, *ALK* and *ROS1* [2, 3]. Results from phase 3 trials have demonstrated the superiority of crizotinib over chemotherapy in patients with *ALK*-rearranged (*ALK*$^+$) NSCLC in both second-line and first-line settings [4, 5]. However, most patients responding on crizotinib acquire resistance within 1 year, with recurrence most commonly occurring in the brain or liver [6–8]. Ceritinib (LDK378) is a selective oral *ALK*-inhibitor with a potency 20-times greater than crizotinib in enzymatic assays and a nanomolar potency against patient-derived crizotinib-resistant tumour cell lines [9].

Ceritinib is approved for the treatment of patients with *ALK*$^+$ metastatic or advanced NSCLC previously treated with crizotinib by several health authorities, including the United States Food & Drug Administration (FDA) and the European Medicines Agency (EMA) [10, 11].

In the phase 1 ASCEND-1 study, ceritinib (750 mg·day^{-1}) demonstrated robust anti-tumour activity (both intracranial and extracranial) in heavily pretreated patients with *ALK*$^+$ NSCLC, for both *ALK*-inhibitor naïve and *ALK*-inhibitor pretreated patients [12, 13]. Also, in two phase 2 studies, ceritinib (750 mg·day^{-1}) demonstrated a high objective response rate (ORR) as well as intracranial responses with promising progression-free survival (PFS) in patients with *ALK*$^+$ NSCLC, for both *ALK*-inhibitor naïve (ASCEND-3) and crizotinib-pretreated patients (ASCEND-2) [14, 15]. More recently, two phase 3 trials have confirmed that ceritinib was more effective than chemotherapy in first-line (ASCEND-4) [16] and second-line (ASCEND-5) [17] settings.

Regulatory processes and local reimbursement can delay the availability to patients of new and promising drugs. The French compassionate-use program, the Temporary Authorisation for Use or TAU program, helps to provide early access of new and promising drugs. It is also a unique opportunity to gain insight into the safety and effectiveness of innovative drugs in a real-life situation. Therefore, we report the efficacy and safety data of ceritinib (at 750 mg·day^{-1}) in *ALK*$^+$ NSCLC patients from the TAU program.

Patients and methods

TAU program design and treatment

A TAU is granted on the basis of a positive benefit–risk ratio assessment by the French National Agency for Medicines and Health Products Safety (the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)). There are two types of TAU: 1. a nominative TAU available on a named-patient basis under the responsibility of the prescribing physician; and 2. a cohort TAU intended to apply to a group of patients and established at the request of a pharmaceutical company for specific indications [18, 19].

The first nominative TAU for ceritinib was granted on March 12, 2013. On January 24, 2014, the ANSM, in agreement with Novartis, established a Protocol for Therapeutic Use and Information Collection (PUT) concerning this nominative TAU and, on September 12, 2014, granted a cohort TAU for ceritinib and validated the PUT for it. The first patient was enrolled in the cohort TAU on October 07, 2014 and it ended on August 05, 2015, the date on which commercial batches of Zykadia (ceritinib) were made available to hospital pharmacies.

The TAU program was conducted at centres across France. All patients received from their physicians both verbal information and a patient's information leaflet on the TAU program (explaining the drug and its known adverse effects (AEs)) before enrolment, as specified by the PUT.

Patients received oral ceritinib (750 mg·day^{-1}) until disease progression, unacceptable toxicity, or a patient's or physician's decision led to treatment being stopped. Treatment beyond progression was allowed, at the physician's discretion, for patients still deriving clinical benefit from it.

Patients included in the TAU

The TAU program included patients with advanced *ALK*$^+$ NSCLC, *ROS1*$^+$ NSCLC, or other *ALK*$^+$ tumours. *ALK* and *ROS1* testing were performed by the French National Cancer Institute certified genetics centres [1]. Patients with *ALK*$^+$ NSCLC were eligible if they had advanced NSCLC with *ALK*-rearrangement, as demonstrated by fluorescent in situ hybridisation (FISH) and/or immunohistochemistry (IHC), and were considered ineligible for or unable to enrol in ongoing clinical trials of ceritinib in France at that time (ASCEND-4 (NCT01828099) and ASCEND-5 (NCT01828112), see https://clinicaltrials.gov). All patients were pretreated with crizotinib.

Data collection and assessment

The patients enrolled on the TAU program were required to have a mandatory follow-up, as specified by the PUT, with prospective data collection (forms completed by the physician). Patient demographics and baseline clinical characteristics were recorded at the first visit, although smoking habit was not registered. Data were collected every 3 months for the following outcomes: ORR (proportion of patients with complete response (CR) or partial response (PR), as assessed by the investigator), stable disease (SD), progressive disease (PD), and safety.

Best tumour response was evaluated radiologically by the investigator (Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was preferred). Confirmation of response was not required. Efficacy data were provided for all evaluable patients with *ALK*$^+$ NSCLC. Safety assessments included monitoring of AEs, laboratory abnormalities and vital signs. All AEs were defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0). Patients were monitored until at least 28 days after the last dose of the study drug. The end date of treatment was considered as the date of the last dose in case of permanent discontinuation or the last assessment date (last date recorded within the PUT or the cut-off date). Patients were not followed up after completing treatment with ceritinib.

Safety analyses were reported for all patients with NSCLC (*ALK*$^+$/*ROS1*$^+$) who received ⩾1 dose of ceritinib and safety data were collected from January 24, 2014 (date of named patient PUT implementation) until October 07, 2015. In accordance with the rules for reporting AEs within the scope of a TAU program, in most cases the prescriber reported events for which a causal relationship with ceritinib was suspected. AEs for which the prescriber did not consider a causal relationship were defined by default as "suspected" if the assessment was missing for serious AEs and as "unassessable" if the assessment was missing for nonserious AEs.

Statistical analysis

Descriptive statistics was used for analyses of patient and disease characteristics. The Kaplan–Meier method was used for estimating overall treatment duration and subgroup analyses. SAS version 9.3 (SAS, Cary, NC, USA) was used to perform all statistical calculations. Statistical analyses were performed by Novartis Pharma SAS, France.

Results

Patients' disposition in the TAU

A total of 242 TAUs were granted from March 12, 2013 to August 05, 2015 (118 nominative TAUs and 124 cohort TAUs). Of the 242 patients included in the TAU program, 228 had *ALK*$^+$ NSCLC, 13 had *ROS1*$^+$ NSCLC and the remaining patient had an *ALK*+ inflammatory fibroblastic tumour (IMT) (figure 1). *ROS1*$^+$ data are not communicated here. As of September 05, 2015, 214 patients with *ALK*$^+$ NSCLC were followed up within the scope of the PUT (the remaining 14 patients included before PUT implementation were not analysed, in the context of French clinical research rules). Some 167 physicians across 106 hospitals enrolled ⩾1 patient.

Of the 214 patients with *ALK*$^+$ NSCLC, an initial form, a follow-up form, or a treatment discontinuation form were available for 193 of those treated with ceritinib (750 mg·day^{-1}). Of these 193 patients, 117 (60.6%) discontinued the treatment. Reasons for discontinuation of treatment were disease progression (n=68), AEs (n=10), patient's request (n=7), death (n=19), and unknown reasons (n=13).

Baseline characteristics of ALK$^+$ NSCLC patients (n=214)

Baseline characteristics of patients with *ALK*$^+$ NSCLC at ceritinib introduction are shown in table 1. The median time between diagnosis and the start of treatment with ceritinib among the evaluable patients

(n=206, 96.3%) was 23.2 months (range 1.7–192.8). The median age was 58.5 years (range 19.0–89.9) and 51.9% of patients were female. The majority of patients (70.8%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1. Histological type was available for 207 patients (96.7%) and 199 patients (96.1%) had adenocarcinoma. In total, 50.0% patients (105 out of 210) had brain metastases. All 213 patients for whom previous treatment data were available had received crizotinib in different lines of therapy. 15 patients (7.0%) received only one line of therapy (crizotinib) before ceritinib. A total of 97 patients (45.5%) received ceritinib as a third-line therapy after previously receiving chemotherapy and crizotinib, while 101 patients (47.4%) received ceritinib as a fourth-line therapy or further. Altogether, 73% of patients received ceritinib immediately after crizotinib. Furthermore, crizotinib was stopped due to AEs in 16 patients.

Efficacy for ALK$^+$ NSCLC patients (n=193)

Of the 193 patients with *ALK*$^+$ NSCLC who started ceritinib (90.2%), a documented radiological and/or clinical efficacy data assessment was available for 149 patients (77.2%). Of these, 8 patients (5.4%) had a CR, 70 (47.0%) had a PR and 34 (22.8%) had SD (table 2). On September 05, 2015 the median duration of ceritinib treatment (n=182) was 3.9 months (range 0.4–23.0; immature data, as only 123 patients were documented as permanent discontinuation). In the 71 patients followed up for ⩾12 months, the median duration of ceritinib treatment was 5.5 months (range 0.4–23.0). A total of 16 patients (22.5%) were still receiving ceritinib or were censored at the cut-off date of September 05, 2015 (77.5% maturity) (table 3).

Table 4 shows efficacy data for patients according to ECOG PS and the presence or absence of brain metastases. Patients with ECOG PS 0–1 had a numerically higher ORR (55.0% *versus* 42.4%) and a longer duration of treatment (median duration 4.6 months *versus* 2.3 months) compared to those with ECOG PS ⩾2. The ORR in patients with brain metastases was 48.6% while in patients with 1–3 metastatic localisations (n=138) and >3 localisations (n=12) it was 52.9% and 66.7%, respectively.

Although ORR and treatment duration were similar in patients who received ⩽2 previous and >2 previous lines of treatment, ORR was lower in patients who received prior crizotinib treatment for ⩽5 months (36.1%) compared to those receiving >5 months of crizotinib treatment (>51.6%) (table 5). However,

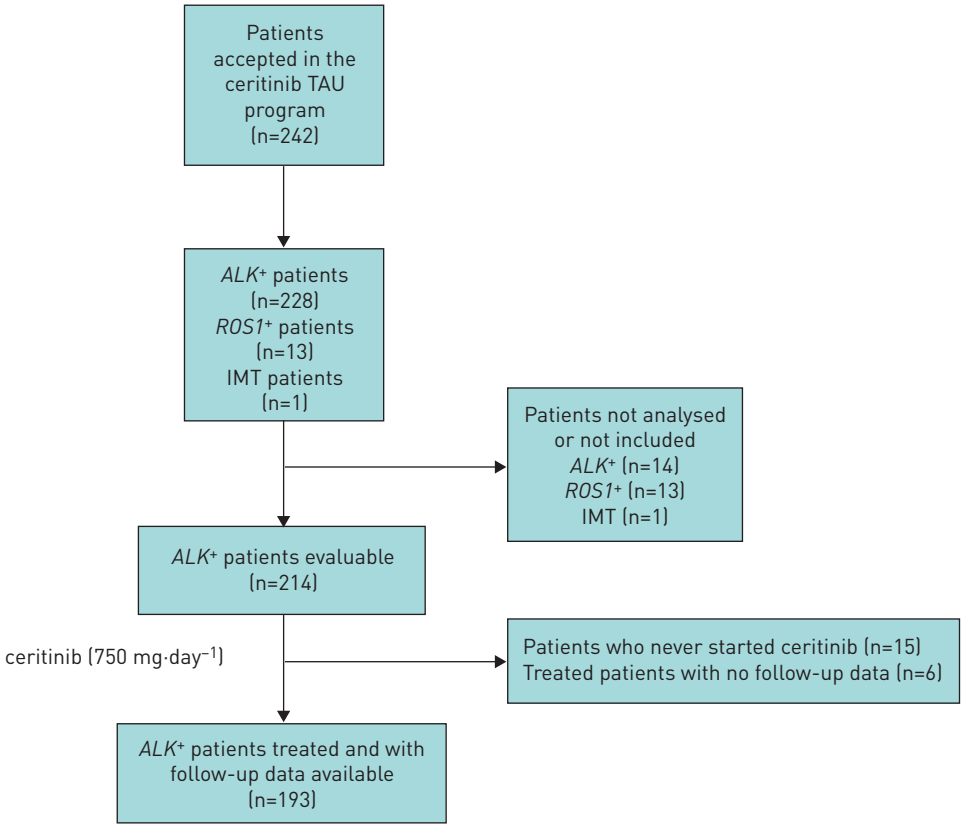

FIGURE 1 Patient disposition in the temporary authorisation for use (TAU) programme. *ALK*$^+$: anaplastic lymphoma kinase positive; *ROS1*$^+$: ROS proto-oncogene 1 positive; IMT: inflammatory fibroblastic tumour

efficacy did not differ between patients treated immediately after receiving crizotinib (ORR 53.2%) compared to those who received crizotinib followed by chemotherapy (ORR 51.3%). Finally, among the 15 patients who received only one prior line of treatment (crizotinib only), ten patients were evaluable for efficacy and the ORR was 75.0%.

The ORR was similar in patients with and without dose reduction for treatment-related AEs (55.4% and 49.3%, respectively). Furthermore, the median duration of treatment was not shorter in patients with dose reductions (4.9 months *versus* 2.7 months).

Safety of patients receiving ceritinib during the TAU program (n=225)

A total of 208 out of 225 patients with NSCLC (93.7%) were assessable for toxicity. Treatment-related AEs were reported in 56.7% of patients and the severity of AEs was assessed by physicians as severe in 35.6% of patients. The most common AEs suspected to be related to the study drug were diarrhoea (22.1%), hepatic toxicity (19.7%), nausea (16.8%) and vomiting (16.3%) (table 6).

TABLE 1 Baseline characteristics of patients with anaplastic lymphoma kinase positive (*ALK*$^+$) non-small cell lung cancer (NSCLC)

Characteristic	Patients (n=214)
Age years (n=211)	58 (19–90)
Sex (n=214)	
Female	111 (51.9)
ECOG performance status (n=205)	
0–1	145 (70.7)
⩾2	60 (28.9)
Histology (n=207)	
Adenocarcinoma	199 (96.1)
Undifferentiated carcinoma	2 (1.0)
Other	6 (2.9)
Number of metastatic sites (n=177)	
0–2	117 (66.1)
⩾3	60 (33.9)
Metastatic localizations (n=210)	
Brain	105 (50.0)
***ALK* test method (n=203)**	
FISH only	107 (52.7)
IHC only	19 (9.4)
FISH and IHC	74 (36.5)
Other	3 (1.5)
Time from initial diagnosis to inclusion in TAU months (n=206)	23.2 (1.7–192.8)
Prior medication regimens (including crizotinib) (n=213)	
1 (crizotinib only)	15 (7.0)
2	97 (45.5)
>2	101 (47.4)
Median	2
Treatment line for crizotinib administration[#] (n=213)	
1	27 (12.7)
2	130 (61.0)
3	35 (16.4)
⩾4	37 (17.4)
Crizotinib as last prior regimen[#] (n=213)	
Yes	156 (73.2)
Duration of crizotinib treatment months (n=208)	9.1 (0.1–52.0)
25%–75%	5.0–15.0
Reason to stop crizotinib[#] (n=222)	
Disease progression	203 (91.4)
Toxicity	16 (7.2)
Other	3 (1.4)

Data are presented as n (%) or median (range) unless otherwise stated. ECOG: Eastern Cooperative Oncology Group; FISH: fluorescent *in situ* hybridisation; IHC: immunohistochemistry; TAU: temporary authorisation for use. [#]: crizotinib could be administered as more than one line/regimen for the same patient.

Ceritinib was permanently discontinued in 13 patients (6.3%) due to the following: liver toxicity with fatal outcome and suspected interaction between ceritinib and levetiracetam (n=1), severe dehydration leading to kidney failure then acute respiratory failure after volume overload (n=1), acute respiratory failure (n=1), digestive disorders (n=8), hepatic cytolysis associated with digestive disorders (n=1) and thrombocytopenia (n=1). A total of 67 patients (32.2%) had dose reductions and/or dose interruptions due to AEs.

Overall, eight drug-related deaths were reported (four from the 13 patients who permanently discontinued ceritinib). These deaths were attributed as follows: hepatic failure (n=1), severe dehydration with renal and respiratory failure (n=1), acute respiratory distress (n=1), metastatic haemorrhage (n=1) and deaths of unknown reason (n=4).

Discussion

The TAU program for ceritinib is the largest real-life cohort for ceritinib use in crizotinib-pretreated *ALK*$^+$ NSCLC patients outside of clinical trials [20, 21]. The diagnosis of *ALK*-rearrangement was robust and was performed in >90% of cases using the FISH break-apart method, which has been validated by a nationwide quality assurance program [22]. Only 9.4% of *ALK*$^+$ disease was diagnosed only by IHC testing and, more recently, the use of IHC for first screening and then FISH for confirmation of positive *ALK*-cases has become a widely used algorithm in routine practice in France [23].

ALK$^+$ NSCLC patients included in the TAU program had a poor prognosis profile and were heavily pretreated at the time of ceritinib introduction: 29.3% had PS ⩾2 (including 22.4% PS 2, 4.9% PS 3 and 2% PS 4), 33.9% had ⩾3 metastatic localisations, 51.2% had brain metastases and 47.4% received >2 prior treatment regimens (including crizotinib). Furthermore, 15 out of 214 patients with *ALK*$^+$ NSCLC (7%) could not initiate ceritinib treatment due to death or rapid deterioration. These findings were very similar to those of crizotinib-pretreated *ALK*$^+$ patients in the ceritinib registration trials (ASCEND-1 and ASCEND-2) and the phase 3 ASCEND-5 trial (table 7).

The prior treatments were in line with the European Society for Medical Oncology (ESMO) recommendations for care in advanced NSCLC [24]; however, at that time, crizotinib was not authorised for use in first-line treatment in France. First-line treatment included platinum-based combination in 85.0% of cases with pemetrexed in 61.5% of patients and addition of bevacizumab in 18% of patients. A total of 10.6% of patients received platinum-based combination as a second-line treatment, although monochemotherapy was most commonly used (21.7%), with pemetrexed being administered in 9.6% of patients.

Patients in the TAU program were able to receive crizotinib for a median duration of 9.1 months (12.7% received crizotinib in first-line treatment, 61.0% in second-line treatment and 33.8% in ⩾4 treatment lines). Duration of crizotinib exposure was longer than the 7.7 months PFS observed in the PROFILE 1007 trial [4], probably reflecting the wide use of crizotinib beyond progression in real-life settings and before access to ceritinib in the market. The majority of the TAU patients (73.2%) received crizotinib as the last regimen before ceritinib and very few of them received another *ALK*-targeted therapy (such as alectinib (n=10) or crizotinib plus HSP90 inhibitor (n=11)).

In the TAU program, ORR was reported in 52.4% of patients which is comparable to the ORR reported in the ASCEND-1 trial in *ALK*-inhibitor pretreated patients (56%) [12] and greater than the ORR in the ASCEND-2 and ASCEND-5 trials (38.6% and 39.1%, respectively) (table 7) [15, 17]. Although response

TABLE 2 Physician-assessed response and treatment duration in patients with anaplastic lymphoma kinase positive (*ALK*$^+$) non-small cell lung cancer (NSCLC)

Radiological tumour evaluation	*ALK*$^+$ NSCLC patients (n=149)
CR	8 (5.4)
PR	70 (47.0)
SD	34 (22.8)
PD	19 (12.8)
Not realised	18 (12.1)
ORR	78 (52.3)
DCR	112 (75.2)
Duration months (n=182)	3.9 (0.4–23.0)

Data is presented as n (%) or median (range). CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate; DCR: disease control rate.

TABLE 3 Duration of ceritinib treatment according to duration of follow-up in patients with anaplastic lymphoma kinase positive (*ALK*$^+$) non-small cell lung cancer (NSCLC)

	All evaluable *ALK*$^+$ patients[#]	Patients with follow-up ⩾6 months	Patients with follow-up ⩾12 months[¶]
Subjects n	182	136	71
Duration	5.8	6.8	8.1
months	3.9 (0.4–23.0)	5.5 (0.4–23.0)	5.5 (0.4–23.0)

Data are presented as mean or median (range) unless otherwise stated. [#]: discontinuation of ceritinib was documented for 117 out of 182 patients (64.2%) at the cut-off (64.3% maturity); [¶]: 16 out of 71 patients (22.5%) were still receiving ceritinib or were censored at cut-off (77.5% maturity).

was not reviewed centrally, investigators had to report tumour evaluation centrally every 3 months. Finally, although investigators usually overestimate the ORR compared to centralised review [25], the disease control rate (DCR) observed was very similar in both the TAU cohort and the ASCEND trials (table 7), confirming the similar efficacy of ceritinib both in real-life and in clinical trials.

As the TAU program involved collection of data but no monitoring of data after discontinuation of treatment it is difficult to calculate/estimate the survival outcomes (PFS and overall survival (OS)). As such, exposure duration is an acceptable estimate to compare with the PFS data in clinical trials. The median duration of ceritinib exposure for all evaluable patients in the TAU program was 3.9 months (range 0.4–23.0). Exposure duration was also calculated for patients who were followed up for ⩾6 months and ⩾12 months (which is similar to the follow-up for ASCEND-1) (table 7). With 74.7% and 39% of patients with ⩾6 months and ⩾12 months follow-up, respectively, the median ceritinib exposure in the TAU program was 5.5 months in both cohorts (similar to the PFS observed in the ASCEND trials) (table 7). Moreover, 22% of patients were still on ceritinib with a follow-up of more than 12 months.

Efficacy data were not reported for about 20% of the patients in the TAU program. It has to be noted that, being a compassionate use program, TAU methodology is different from clinical trial methodology (including the capacity to collect and/or clean follow-up data) and less robust. There is no monitoring and data are retrospectively collected from the TAU program charts. Furthermore, a significant proportion of patients were enrolled in the TAU program in the last weeks before closure, and, as such, follow-up and efficacy data were not available for all patients at the time of analysis.

Efficacy was observed in all patient subgroups in the TAU program. No major differences in ORR or the median duration of response of ceritinib were observed in relation to the presence or absence of brain

TABLE 4 Physician-assessed response and treatment duration in patients with anaplastic lymphoma kinase positive (*ALK*$^+$) non-small cell lung cancer (NSCLC) according to subgroups based on Eastern Cooperative Oncology Group (ECOG) performance status and presence of brain metastases

Radiological tumour evaluation	ECOG performance status		Brain metastases	
	0–1 (n=134)	2–4 (n=51)	Present (n=97)	Absent (n=64)
Assessed response				
Evaluable subjects	109	33	72	50
CR	8 (7.3)	0 (0.0)	2 (2.8)	4 (8.0)
PR	52 (47.7)	14 (42.4)	33 (45.8)	26 (52.0)
SD	28 (25.7)	4 (12.1)	18 (25.0)	6 (12.0)
PD	11 (10.1)	8 (24.2)	8 (11.1)	8 (16.0)
Not realised	9 (8.3)	6 (18.2)	10 (13.9)	5 (10.0)
Not evaluable	1 (0.9)	1 (3.0)	1 (1.4)	1 (2.0)
ORR	60 (55.0)	14 (42.4)	35 (48.6)	30 (60.0)
Treatment duration				
Subjects	131	43	92	60
Duration months	4.6 (0.4–22.4)	2.3 (0.4–19.9)	3.3 (0.4–23.0)	4.5 (0.4–22.2)

Data are presented as n, n (%) or median (range) unless otherwise stated. CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate.

TABLE 5 Physician-assessed response in patients with anaplastic lymphoma kinase positive (*ALK*$^+$) non-small cell lung cancer (NSCLC) according to subgroups based on the number of previous lines of treatment, the duration of previous treatment with crizotinib and dose reduction

Radiological tumour evaluation	Previous lines of treatment		Duration of previous crizotinib treatment[#]				Dose reduction[¶]	
	⩽2 lines (n=98)	>2 lines (n=94)	<Q1 (n=47)	Q1–Q2 (n=47)	Q2–Q3 (n=46)	⩾Q3 (n=49)	With dose reduction (n=84)	Without dose reduction (n=109)
Assessed response								
Evaluable subjects	72	76	36	31	35	43	74	75
CR	5 (6.9)	3 (3.9)	0 (0.0)	4 (12.9)	2 (5.7)	2 (4.7)	5 (6.8)	3 (4.0)
PR	35 (48.6)	35 (46.1)	13 (36.1)	12 (38.7)	20 (57.1)	23 (53.5)	36 (48.6)	34 (45.3)
SD	18 (25.0)	15 (19.7)	10 (27.8)	5 (16.1)	7 (20.0)	10 (23.3)	17 (23.0)	17 (22.7)
PD	10 (13.9)	9 (11.8)	10 (27.8)	3 (9.7)	3 (8.6)	3 (7.0)	8 (10.8)	11 (14.7)
Not realised	3 (4.2)	13 (17.1)	3 (8.3)	5 (16.1)	3 (8.6)	5 (11.6)	6 (8.1)	10 (13.3)
Not evaluable	1 (1.4)	1 (1.3)	0 (0.0)	2 (6.5)	0 (0.0)	0 (0.0)	2 (2.7)	0 (0.0)
ORR	40 (55.5)	38 (50.0)	13 (36.1)	16 (51.6)	22 (62.8)	25 (58.2)	41 (55.4)	37 (49.3)
Treatment duration								
Subjects	91	90	43	45	43	47	83	99
Duration months	3.8 (0.4–23.0)	3.7 (0.4–22.4)	2.3 (0.4–15.9)	3.0 (0.4–23.0)	5.1 (0.4–19.9)	7.6 (0.9–22.2)	4.9 (0.4–22.2)	2.7 (0.4–23.0)

Data are presented as n, n (%) or median (range). CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate. [#]: <Q1 means <5 months of crizotinib, Q1–Q2 means 5 to <9.2 months of crizotinib, Q2–Q3 means 9.2 to <16 months of crizotinib >Q3 means >16 months of crizotinib. [¶]: dose reduction is <750 mg·day^{-1} of ceritinib or a temporary discontinuation in the first 6 months of treatment.

metastases at inclusion and ⩽2 or >2 previous lines of treatment. Patients with ECOG PS ⩾2 had a lower ORR; however, comparison to other data is limited for these patients since they are rarely included in clinical studies.

Efficacy was similar (ORR 53% *versus* 51%) regardless of whether ceritinib was administered immediately after crizotinib or not but there was a possible trend for a longer treatment duration in the case of ceritinib

TABLE 6 Summary of adverse events (AEs) suspected of being related to the study drug

Event	Any grade (n=208)	Severe (n=208)
Any AE	138 (66.3)	105 (50.3)
Any AE considered to be drug related	118 (56.7)	74 (35.6)
Drug reduction and/or interruption	67 (32.2)	
Drug discontinuation	13 (6.3)	
Most common AEs		
Diarrhoea	46 (22.1)	12 (5.8)
Nausea	35 (16.8)	11 (5.3)
Vomiting	34 (16.3)	11 (5.3)
Hepatic toxicity (ALT/AST-increased or other)	41 (19.7)	26 (12.5)
Abdominal pain	12 (5.8)	1 (0.5)
Weight decrease	12 (5.8)	5 (2.4)
Asthenia	10 (4.8)	7 (3.4)
Decreased appetite	9 (4.3)	5 (2.4)
Creatinine increase/renal insufficiency	14 (6.7)	8 (3.8)
Fatigue	6 (2.9)	2 (1.0)
Pericardial tamponade/effusion	5 (2.4)	3 (1.4)
Hyperglycaemia	3 (1.4)	2 (1.0)
Dyspnoea	3 (1.4)	3 (1.4)
Thrombocytopenia	4 (1.9)	3 (1.4)
Skin disorders	2 (1.0)	0 (0.0)
Dehydration	2 (1.0)	2 (1.0)

Data are presented as n (%). ALT: alanine aminotransferase; AST: aspartate aminotransferase.

being administered immediately (4.2 months *versus* 3.3 months, respectively). As suggested by the PROFILE 1007 and PROFILE 1014 trials for crizotinib [4, 5], delaying *ALK*-inhibitor exposure may decrease its efficacy (table 3). Finally, patients with longer response to crizotinib (>16 months) benefited longer from ceritinib in the TAU program (median duration of exposure: 7.6 months (range 0.9–22.2)). These results seem to confirm observations in clinical practice and are probably explained by the characteristics and aggressiveness of the tumours associated with maintained good/long response through each of the successive lines of *ALK*-inhibitors. Interestingly, it has also been reported that the efficacy of *ALK*-inhibitors (especially crizotinib) might be related to the type of *ALK*-rearrangement [26]. Comparative molecular analysis of patients with appropriate clinical profiles would be of interest at diagnosis and at disease progression.

The safety profile for ceritinib in the TAU program was similar to that reported in clinical trials of ceritinib. The most common AEs suspected to be related to the study drug were diarrhoea (22.1%), hepatic toxicity (19.7%), nausea (16.8%) and vomiting (16.3%) (table 6). Although, the TAU program was not able to properly capture the full spectrum of side-effects compared to a prospective clinical trial, it was interesting to note that 32.2% of patients had dose reductions and/or interruptions due to AEs compared to 62%, 54.3% and 73.0% in the ASCEND-1, ASCEND-2 and ASCEND-5 trials, respectively [12, 15, 17]. The lower percentage of dose reductions in the TAU program may be attributed to a better understanding by the physicians of the management of gastro-intestinal (GI) events, thereby preventing the need to reduce doses, and the sharing of best practice and emerging data on better management of GI issues. Only 13 patients (6.3%) permanently discontinued ceritinib in the TAU program. Of note, patients who had dose reductions did not experience a shorter duration of treatment than patients who did not (4.9 months *versus* 2.7 months in patients with no dose reduction), which reflects the usefulness of reducing dosage to maintain treatment in the case of unacceptable AEs (*e.g.* GI AEs and hepatitis). This finding also suggests

TABLE 7 Characteristics and outcomes of patients from the French temporary authorisation for use (TAU) ceritinib study with other ceritinib data in crizotinib-pretreated patients with anaplastic lymphoma kinase positive (*ALK*$^+$) non-small cell lung cancer (NSCLC)

	French TAU ceritinib study	ASCEND-1 (phase 1)	Gainor cohort	ASCEND-2 (phase 2)	ASCEND-5 (phase 3)
Subjects n	214	163	73[#]	140	115
ECOG %					
PS 0–1	70.8	87.1	NA	85.7	92.2
PS 2–4	29.3	12.9	NA	14.3[¶]	7.8[¶]
Prior lines %					
1	7	16	NA	0	0
2	45.5	27.6	NA	43.6	87.8
>2	47.4	56.0	NA	56.4	11.3[+]
Brain metastases %	51	61	NA	71	56.5
ORR %	52.4	56.4	NA	38.6	39.1
DCR %	75.2	74.2	NA	77.1	76.5
Median ceritinib duration/exposure months	3.9 (all patients) 5.5 (>12 months follow-up, 78% maturity)				
Median PFS months	NA	6.9	7.8	5.7	5.4
Median OS months	Not evaluable or not mature	16.7	49.4 (from diagnosis) 30.3 (from crizotinib start)	14.9 (42% maturity)	18.1 (~50% maturity)
Dose reduction/ interruption %	32.2	62 (reduction) 74 (interruption)	NA	54.3	80.0
Discontinuation due to AEs %	6.3	11	NA	7.9	5.2

ECOG: Eastern Cooperative Oncology Group; PS: performance status; NA: not available; ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; OS: overall survival; AE: adverse event. [#]: 71 subjects from ASCEND-1; [¶]: PS 2; [+]: three prior lines of therapy.

that patients and physicians have together learned to better manage side-effects in the real-life use of ceritinib during the TAU program. It is to be hoped that progress will come from pharmacology data obtained from the ASCEND trials and better knowledge of the pharmacokinetics of ceritinib with food intake, as recently illustrated in the ASCEND-8 preliminary data (presented at the World Conference on Lung Cancer (WCLC) 2016), which suggests that taking ceritinib (450 mg·day^{-1}) with food has similar exposure and significantly reduces GI toxicity [27].

Although the TAU program is different from the clinical trial setting where patients are followed even after treatment discontinuation, the patients included in the TAU program were of high unmet need and warranted early access to ceritinib treatment. In conclusion, ceritinib (750 mg·day^{-1}) demonstrated similar efficacy for crizotinib-pretreated patients with *ALK*$^{+}$ NSCLC in the TAU program as is seen in clinical trials and with a manageable safety profile.

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