Ceritinib for the Treatment of Late-Stage (Metastatic) Non–Small Cell Lung Cancer

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Disclosure of Potential Conflicts of Interest

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Abstract

Over the last decade the non-small cell lung cancer therapeutics landscape has been dominated by the increasing focus on identification and validation of molecular targets as well as identification of the best candidate agents to address these targets. Among the notable successes has been the approval of erlotinib, gefitinib and afatinib for the EGF receptor (EGFR) mutation and more recently crizotinib for anaplastic lymphoma kinase (ALK) gene rearrangement. Despite the excellent efficacy of crizotinib several mechanisms of resistance including secondary mutation in the ALK gene eventually result in disease progression and several second-generation ALK inhibitors, notably ceritinib has demonstrated evidence of clinical activity in this setting. This review discusses the data associated with the recent accelerated approval of ceritinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic lung adenocarcinoma with disease progression on or who are intolerant to crizotinib.
Introduction

Since the original report by Soda et al. that the anaplastic lymphoma kinase (ALK) gene fuses with the echinoderm microtubule-associated protein like 4 (EML4), resulting in potent transforming activity in non-small cell lung cancer (NSCLC) limited to the adenocarcinoma histologic subtype, it is well recognized that between 3 and 7% of NSCLC is molecularly defined by the presence of an inversion or translocation of chromosome 2p involving the ALK gene, resulting in a transforming fusion gene and represents a distinct molecular subset of disease (1, 2). Generally, all so far identified ALK gene rearrangements are constituted by two portions. The first is the highly conserved break point within ALK, located in the intron immediately upstream of the exons encoding the kinase domain; the second is the 5'-end partners containing a coiled-coil or leucine zipper domain responsible for oligomerization of fusion protein and ligand-independent activation of the ALK TK activity. Constitutive activation of downstream signaling pathways, such as the Ras/MAPK, PI3K/AKT, and JAK/STAT, results in uncontrolled cancer cell proliferation and survival. Thirteen variants of the EML4-ALK fusion have been described, according to the break point on EML4 (from exon 2 to exon 20(3)). Furthermore, in addition to EML4, the TRK-fused gene (TFG (4-6)) and the kinesin family member 5B (KIF5B (4-6)) have been described to be fused to ALK in rare cases (Table 1).

Mice transduced with NIH3T3 cells forced to express EML4-ALK fusion gene can be successfully treated with ALK inhibitors (ALKi). Apart from the EML4-ALK fusion gene, 11 other variants have been identified but it is still unclear whether these result in differential susceptibility to ALKi (3). In addition, chromosomal rearrangements involving
the gene encoding ROS1 proto-oncogene receptor tyrosine kinase (ROS1) define a distinct molecular subgroup of non-small-cell lung cancers that have shown sensitivity to ALKi in particular crizotinib (7) (Table 1).

The ALK tyrosine kinase inhibitor (ALK-TKI) crizotinib, which is a small molecule potent inhibitor targeting cMET, ALK and ROS1 tyrosine kinases, was the first in class shown to be effective for ALK-positive patients (ALK+) with advanced NSCLC demonstrating response rates of about 60% in a single-arm study which was grounds for accelerated FDA approval granted in October 2011(8-10). This study was followed by a randomized trial in which crizotinib demonstrated superiority over standard chemotherapy in patients previously treated with platinum-based chemotherapy. ALK inhibitors can inhibit ROS1 kinase activity in cell lines and crizotinib is also associated with clinically significant antitumor activity in patients with ROS1 NSCLC. A study investigating the use of crizotinib in ROS1 rearranged cancer demonstrated an overall response rate (ORR) of 72% (95% CI 58 to 84), with 33 partial responses (PR) and 3 complete responses (CR). Median duration of response was 17.6 months (95%CI, 14.4 to not reached), with 25 patients (50%) still in follow-up for progression at time of report. The pharmacokinetics, antitumor activity and safety profile of crizotinib in this group of patients were similar to those observed in patients with ALK-positive NSCLC (7).

Despite dramatic initial activity of crizotinib in ALK+ NSCLC, invariably crizotinib resistance develops typically within 1-2 years from beginning of treatment. The central nervous system (CNS) is a particularly common site of progressive disease in crizotinib-treated patients, suggesting the need for ALKi that not only can overcome acquired crizotinib resistance but also penetrate the blood–brain barrier (11, 12). This review
focuses on the use of ceritinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic lung adenocarcinoma.

**Ceritinib**

Among the several highly potent next-generation ALK-TKIs currently under investigation, LDK378 (ceritinib) has demonstrated promising anti-tumor activity and was granted FDA approval in April 2014.

Ceritinib contains modifications in the chemical structure that promote a more favorable interaction with the mutant lipophilic residues at the gatekeeper position of the kinase domain with a 20-fold higher *in vitro* potency against ALK than crizotinib. Ceritinib led to suppression of ALK phosphorylation as well as the downstream PI3K–AKT, MEK–ERK, and mTOR signaling pathways at lower doses than crizotinib. Whereas ceritinib was potent against the two lung cancer cell lines with ALK rearrangements, it was not potent against NSCLC or breast cancer cell lines driven by KRAS, EGFR, PI3K, or HER2 (13). In addition, in treatment-naïve H228 xenograft models, ceritinib demonstrated more durable antitumor activity than crizotinib (13). The kinase selectivity has been tested in a cellular proliferation assay against 16 different kinases, and aside from ALK, no inhibition below 100 nmol/L was observed (14). Unlike crizotinib, ceritinib does not inhibit the activity of MET, a tyrosine kinase that can be overexpressed, amplified, or mutated in NSCLC, leading to cell progression and survival. However, ceritinib does inhibit insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1 (15). The chemical architecture of ceritinib, including the chlorine in the 5-position of the pyrimidine may interact more favorably with a methionine gatekeeper in crizotinib-resistant ALK and could explain the activity of this
drug against several ALK resistance mutations such as L1196M, G1269A, I1171T and S1206Y. However, it doesn't overcome the ALK resistance mutations G1202R and F1174C.

ASCEND-1, the first phase I in human, single-arm study of ceritinib at 750 mg daily, included 255 patients, 246 ALK+ NSCLC, 67% of whom with at least two prior regimens and 66% of whom with prior ALKi (16). After a median 7 months follow-up, patients treated with ceritinib achieved an overall response rate (ORR) of 58.5% (95% confidence interval [CI] = 52.1%–64.8%) and a median progression-free survival (PFS) of 8.2 months (95% CI = 6.7–10.1). The median duration of response (DOR) was 9.7 months (95% CI = 7.0–11.4), with a median time to first response of 6 weeks.

Among 163 previously crizotinib-treated patients receiving 750 mg of ceritinib daily, ORR was 54.6% (95% CI = 46.6%–62.4%) and PFS was 6.9 months (95% CI = 5.4–8.4). In 83 patients without prior ALKi, ORR was 66.3% (95% CI = 55.1%–76.3%). At the time of data cutoff, the majority of these patients were still receiving ceritinib and median PFS had not been reached.

In the 124 patients who started the study with brain metastases, ceritinib achieved an ORR of 54.0% (95% CI = 44.9%–63.0%) and a median PFS of 6.9 months (95% CI = 5.4–8.4). Tumor shrinkage was seen in patients with brain metastases with (50%; 95% CI = 39.7%–60.3%) and without (69.2%; 95% CI = 48.2%–85.7%) prior ALK-TKI. Discontinuation of treatment due to adverse events occurred in 10% of patients, and 59% of patients required at least one dose reduction. The most common adverse events, occurring in more than half of patients, were diarrhea, nausea, vomiting, abdominal pain, and fatigue (15, 16).
The subgroup analysis between Asian and Caucasian patients showed that baseline demographics were similar but ALKi pretreatment had been received by 47 (29%) and 108 (66%) pts, respectively(17). Of 173 patients analyzed for efficacy the ORR was 69% (95% CI: 55.2, 80.9) in Asian patients (38/55) and 57% (95% CI: 47.3, 65.9) in Caucasian patients (67/118). The median duration of response (DOR) among responders was 10.1 months (95% CI: 7.3, not reached) and 6.9 months (95% CI: 4.5, 11.4) in the Asian and Caucasian patients, respectively. The observed differences between Asians and Caucasians for ORR and DOR were not explained by differences in ALKi pretreatment (17).

Two Phase III, ongoing, randomized trials are currently investigating the role of ceritinib both in chemotherapy and crizotinib previously treated (NCT01828112) ALK+ NSCLC versus single agent chemotherapy (pemetrexed or docetaxel), and in previously untreated (NCT01828099) ALK+ NSCLC versus platinum doublet chemotherapy (platinum/pemetrexed).

**Ceritinib Toxicity Profile**

Adverse reaction data are based on 255 patients treated with ceritinib 750 mg daily for ALK+ malignancies (n =246 NSCLC; n = 9 other ALK+ diseases) (16, 18). Serious adverse events (AE) were rare (≤2%), and included interstitial lung disease (ILD)/pneumonitis, convulsion, pneumonia, dyspnea, dehydration, hyperglycemia and nausea (18). The most common AE (≥1%) that resulted in discontinuation of therapy included ILD/pneumonitis, pneumonia and anorexia. Fatal AE were also rare (5% of patients) resulting from pneumonia (n = 4), respiratory failure (n = 1), ILD/pneumonitis (n = 1), pneumothorax (n = 1), gastric hemorrhage (n =1), general physical health
deterioration (n = 1), pulmonary tuberculosis (n = 1), cardiac tamponade (n = 1), and sepsis (n = 1). Neuropathies, including peripheral sensory or motor neuropathy, gait disturbance, paresthesia, hyposthesia, dysesthesia, neuralgia, hypotonia, or polynuropathy, occurred in 17% of patients. Vision abnormalities (9%) occurred infrequently but were clinically relevant. ILD/pneumonitis resulted in 1 death (0.4%).

Concentration-dependent QTc prolongation has also occurred (18).

**Mechanisms of Resistance to ALK Inhibitors**

Mechanisms of acquired resistance are heterogeneous and may evolve dynamically in response to different ALK-TKIs and may be divided into 2 groups: ALK-dominant or ALK-nondominant (Table 1). ALK-dominant mechanisms include second mutations and C1156Y, within the kinase domain of the EML4-ALK fusion gene in the same patient who acquired resistance to crizotinib (19). L1196M is a gatekeeper mutation that interferes with the binding of crizotinib. Other resistance mutations in the ALK gene have been discovered in the clinical setting or in mutagenesis screening, including L1152R, 1151Tins, G1202R, S1206Y, F1174C, D1203N, G1269A, and L1196M. ALK+ with NSCLC with acquired resistance to crizotinib were reported to exhibit new-onset ALK copy number gain, which may occur in combination with resistance mutations.

The known ALK-nondominant mechanisms leading to crizotinib resistance are mutations of other oncogenes such as the EGFR and KRAS genes (19), amplification of the KIT gene (20), increased autophosphorylation of EGFR (20), and transformation to sarcomatoid carcinoma (21) (Table 1). Recently several studies have suggested that ALK rearrangements co-occur with mutations in EGFR or KRAS at clinically relevant
frequencies. Gainor J. et al reported the genotyping data from 1683 patients with NSCLC finding 4 out of 75 ALK+ patients with KRAS mutations (22). Won JK et al. has profiled 1458 cases of lung cancer and found that 4 out of 91 cases had concomitant EGFR and ALK alterations. The possibility of coexistence of either EGFR or KRAS mutations has profound effect on therapeutic choices and highlights the need to extend the ALK testing to EGFR and KRAS-mutation positive cases. MET receptor expression but not MET gene amplification is significantly increased in ALK-positive NSCLC compared to ALK-negative counterpart (23). Because crizotinib is a dual inhibitor of MET and ALK, it is possible that the status of MET expression may impact the efficacy of crizotinib in ALK+ NSCLC under therapy. However, second generation ALKi have selective activity against ALK-TK and do not demonstrate activity against MET-TK.

Second-generation ALKi, such as alectinib (24, 25) and ceritinib (14), have been shown to be effective not only in crizotinib-naive patients but also in those resistant to crizotinib.

Unfortunately ceritinib resistance has already been reported in 11 ALK+ NSCLC by fluorescent in situ hybridization (FISH) showing mutations in 2 residues G1202R and F1174C respectively in 3 out of 11 and 2 out of 11 post-ceritinib biopsies (13). In vitro resistance to both crizotinib and ceritinib was reported in less common ALK-resistance mutations such as C1156Y, 1151T-ins and L1152P (13).

A novel ALK V1180L gatekeeper mutation from a cell line model and a second novel I1171T mutation from a patient who developed resistance to alectinib were recently reported (26). Both mutations demonstrated structural alterations with subsequent decrease binding affinity with alectinib and crizotinib. However, both
mutations were sensitive to ceritinib and other next-generation ALK-TKIs and treatment of the patient with ceritinib led to a marked response.

After the acquisition of resistance to ALKi, regardless of the use of crizotinib or second-generation ALKi, specific treatment strategies should be considered directed to inhibition of the specific resistance mechanisms. The association of an ALKi beyond the state of PD and an inhibitor of the specific resistance pathways (i.e. EGFR-TKI or KIT-TKI) would be appropriate. Also chemotherapy with pemetrexed should be considered for ALK+ patients with any possible mechanism of resistance to crizotinib.

**Other Second-Generation ALK Inhibitors**

Among the other second-generation ALKi alectinib and AP26133 are in more advanced development.

Alectinib is a potent, selective and orally available ALK-TKI with 10-fold greater potency than crizotinib with activity against other kinases, including MET, insulin-like growth factor 1 receptor (IGF1R) and ALK with or without the gatekeeper mutation (L1196M) (14). A single-arm, open-label, phase I/II trial was conducted in ALK+ NSCLC in Japan and demonstrated the excellent efficacy of alectinib (24). In contrast to the trials of crizotinib, positive results based on both FISH and IHC or reverse transcription polymerase chain reaction (RT-PCR) analysis were required for enrollment in that study. In the phase I portion, including 24 patients, a dose of 300 mg twice daily was chosen as the recommended dose in the phase II trial, which included 46 patients.

In the ongoing phase 2 portion of the study, 43/46 patients achieved an OR (93.5%, 95% CI 82.1-98.6) including 2 complete responses (CR) (4.3%, 0.5-14.8) and 41 partial responses (PR) (89.1%, 76.4-96.4). Grade 3 treatment-related AE were
recorded in 12/46 (26%) patients, including 2 patients with decreased neutrophil count and increased blood creatine phosphokinase. Serious AE occurred in 5 patients (11%) without reported grade 4 AE or deaths (24).

Intriguingly, no progression of CNS lesions was observed in 15 patients proved to harbor brain metastases by the time of data cutoff. The PFS at 1 year was 83% (95% CI, 68-92), although the median PFS was not reached.

Results from 47 patients enrolled in another phase I/II study, showed alectinib to be well tolerated, with the most common AE being fatigue (30%), myalgia (17%), and peripheral edema (17%). Dose-limiting toxic effects were recorded in 2 patients in the cohort receiving alectinib 900 mg twice a day. At data cut-off (median follow-up 126 days), investigator-assessed OR were noted in 24/44 (55%) patients, with a confirmed CR in 1 (2%), a confirmed PR in 14 (32%), and an unconfirmed PR in 9 (20%). 16 (36%) patients had stable disease (SD); the remaining 4 (9%) had progressive disease (PD). Of 21 patients with CNS metastases at baseline, 11 (52%) OR, 6 (29%) CR (3 unconfirmed), 5 (24%) PR (1 unconfirmed), 8 (38%) SD and the remaining 2 (10%) PD were reported. Alectinib 600 mg twice a day was chosen as the recommended dose for phase 2 (27).

AP26113 is a novel TKI that potently inhibits mutant activated forms of the ALK and EGFR genes as well as TKI-resistant forms, including L1196M of the ALK gene and T790M of the EGFR gene (28). Preliminary data for an ongoing dose-finding phase I/II study of AP26113 for advanced malignancy refractory to standard treatment showed the efficacy and safety of the compound in patients with NSCLC previously treated with ALK inhibitors or EGFR-TKIs. Among 57 evaluable ALK+ NSCLC patients, 41 (72%) responded.
Among 51 evaluable ALK+ NSCLC with prior crizotinib exposure, 35 (69%) responded. Duration of response was 1.6 to 14.7 months ongoing at the time of data cut-off. Among 49 patients with follow-up scans, median PFS was 10.9 months. Nine out of 13 ALK+ with untreated progressing CNS lesions at baseline and with follow-up scans had evidence of radiographic improvement in CNS, including one patient with improvement in leptomeningeal disease (29). The antitumor activity of at least 2 other second-generation ALKi, ASP3026 and X-396, has been shown in vitro studies, and these are currently under clinical investigation (NCT01401504 and NCT01625234). Table 2 summarize the trials with novel second generation ALK-inhibitors in clinical development.

**ALK-Fusion Detection Methods**

*ALK* gene fusion can be detected by several methods, including RT-PCR, the first published method used (2); FISH, the currently accepted method approved by the FDA; and IHC.

FISH is a relatively expensive assay that is able to detect all types of ALK rearrangements known to date, however its interpretation could be challenging even in the hands of experienced specialists. IHC is relatively inexpensive, fast, and familiar to most pathologists, can also be used universally, similar to FISH, as it can potentially detect overexpressed ALK chimeric protein produced by any rearrangement type. However, the variability of chimeric proteins with different levels of expression raises questions regarding the correct choice of antibody and signal enhancement system to avoid false-negative results. Artifacts that may lead to false-positive results are also relatively frequent and cannot be underestimated. RT-PCR is a highly sensitive and specific technique that allows the detection of even a few molecules of chimeric ALK
transcripts. However, the use of RT-PCR as a screening method for detecting ALK rearrangements may not be completely reliable for several reasons: poor quality of RNA obtained from formalin-fixed, paraffin-embedded tissues, which are mostly available in the clinical setting, and the necessity of PCR multiplexing because of the wide variation in fusion types.

It is clear that there are advantages and pitfalls of each method and an agreement regarding the optimal protocol for ALK testing has not yet been reached. IHC, FISH and multiplex RT-PCR methodologies showed good sensitivity, specificity, and concordance, when artifacts were characterized and excluded in a study that prospectively tested 36 NSCLC patients who had adenocarcinoma and 10 ALK+ samples. However, all ambiguous cases had to be confirmed as ALK rearranged by at least 2 of the 3 methods. Blackhall et al. have recently reported a prevalence of 6.2% of IHC positivity with a 2.2% of FISH-positivity in 1281 European NSCLC patients, showing that a screening strategy based on IHC or H-score might be feasible (30).

The concept of co-approval of therapeutic product and companion diagnostics has been encouraged as part of the strategy to promote personalized medicine (31). However molecular diagnostic testing is complex and several assays with different merits may be suitable in that regard especially when testing molecularly heterogeneous tumors such as NSCLC.

**When to Use Ceritinib in ALK-Positive NSCLC**

The optimal choice for first line therapy for ALK+ as well as the optimal sequence for therapies after progression to front-line therapy aiming at maximizing survival benefit and strategies to prevent or delay resistance remains to be determined. Although it is
not clear at present whether crizotinib or second-generation ALKi will be the superior treatment for ALK+ patients, a head to-head study comparing crizotinib with the second-generation ALKi would clarify this point. In fact, a randomized phase III trial comparing alectinib with crizotinib is currently being performed to address this issue (NCT02075840). The activity demonstrated by ceritinib and alectinib in patients with CNS disease involvement, suggests use of these agents preferentially in this clinical scenario.

Based on already described mechanisms of resistance to first and second-generation ALKi specific treatment strategies with combination therapy with EGFR-TKI, KIT-TKI, MET-TKI or pemetrexed-based therapy could be explored.

Conclusions and Challenges

The challenge of future studies is in the identification of the mechanisms underlying acquired resistance to ceritinib and new ALKi. In addition, combination between ALKi and other therapeutic strategies, such as inhibition of escape survival pathways and immunotherapy agents are potential alternatives to increase survival in ALK+ NSCLC patients.

References


(ALK+) NSCLC: subgroup analysis of the ASCEND-1 trial. J Clin Oncol 32:5s, 2014 (suppl; abstr 8078A).


Table 1. Sensitizing and resistance mechanisms to ALKi

<table>
<thead>
<tr>
<th>Sensitizing mechanisms</th>
<th>Resistance mechanisms</th>
</tr>
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<tbody>
<tr>
<td><strong>ALK-fusions</strong></td>
<td><strong>ALK dominant</strong></td>
</tr>
<tr>
<td>ALK-TRK</td>
<td>ALK copy number gain</td>
</tr>
<tr>
<td>ALK-KIF5B</td>
<td>CNS resistance</td>
</tr>
<tr>
<td><strong>ROS1-fusions</strong></td>
<td><strong>ALK nondominant</strong></td>
</tr>
<tr>
<td><strong>Partially ALK dependent</strong></td>
<td>Increased autophosphorylation of EGFR</td>
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<tr>
<td></td>
<td>Kit amplification</td>
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<td></td>
<td>Transformation to sarcomatoid carcinoma</td>
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<tr>
<td></td>
<td>MET amplification</td>
</tr>
<tr>
<td><strong>ALK independent</strong></td>
<td><strong>ALK independent</strong></td>
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<tr>
<td>KRAS mutations</td>
<td>EGFR mutations</td>
</tr>
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</table>
Table 2. Trials with novel second generation ALK-inhibitors in clinical development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cmax (ng/ml)</th>
<th>T₁/₂ (hours)</th>
<th>Authors/trial NCT number</th>
<th>Phase</th>
<th>Prior ALK-TKI</th>
<th>Pts N.</th>
<th>ORR</th>
<th>PFS</th>
<th>ORR in Pts with CNS disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceritinib</td>
<td>800±205</td>
<td>41</td>
<td>ASCEND-1(16)</td>
<td>I</td>
<td>Yes for 163</td>
<td>246</td>
<td>58%</td>
<td>Median PFS=8.2 months</td>
<td>ORR= 54%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NCT 01828112</td>
<td>III</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>Alectinib</td>
<td>676±186</td>
<td>20</td>
<td>Seto et al. (24)</td>
<td>I/II</td>
<td>No</td>
<td>Phase I=24, Phase II=46</td>
<td>93%</td>
<td>1yr PFS 83%; median PFS not</td>
<td>NA</td>
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<td></td>
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<td>Ongoing</td>
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<tr>
<td>Drug</td>
<td>Dose/MTD</td>
<td>Patients Evaluated</td>
<td>Response Rate</td>
<td>PFS M (Range)</td>
<td>CNS Disease Improvement</td>
<td></td>
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<tr>
<td>AP26113</td>
<td>402</td>
<td>29</td>
<td>57% evaluable</td>
<td>72%</td>
<td>9 out of 13 (69%)</td>
<td></td>
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</tr>
<tr>
<td>ASP3026</td>
<td>3150 (at MTD 525 mg dose)</td>
<td>21.8 to 84.6</td>
<td>57% evaluable</td>
<td>72%</td>
<td>Median PFS = 10.9 months</td>
<td></td>
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<td></td>
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<tr>
<td>X-396</td>
<td>NA</td>
<td>23 (at 200 mg dose)</td>
<td>57% evaluable</td>
<td>72%</td>
<td>CNS disease improved</td>
<td></td>
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**Notes:**
- Pts=patients; ORR=overall response rate; PFS=progression free survival; CNS=central nervous system; yr=year; NA=not available.
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