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ASP8273 tolerability and antitumor activity in tyrosine kinase inhibitor-naïve Japanese patients with *EGFR* mutation-positive non-small-cell lung cancer

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Epidermal growth factor receptor (*EGFR*) activating mutations occur in approximately 50% of East Asian patients with non-small-cell lung cancer (NSCLC) and confer sensitivity to tyrosine kinase inhibitors (TKIs). ASP8273 is an irreversible EGFR-TKI, given orally, that inhibits *EGFR* activating mutations and has shown clinical activity in patients with *EGFR* mutation-positive NSCLC. Epidermal growth factor receptor-TKI-naïve Japanese adult patients (≥20 years) with NSCLC harboring *EGFR* mutations were enrolled in this open-label, single-arm, phase II study (ClinicalTrials.gov identifier NCT02500927). Patients received ASP8273 300 mg once daily until discontinuation criteria were met. The primary end-point was to determine the safety of ASP8273 300 mg; the secondary end-point was antitumor activity defined by RECIST version 1.1. Thirty-one patients (12 men and 19 women; median age, 64 years [range, 31-82 years]) with *EGFR* mutation-positive NSCLC were enrolled; as of 23 February 2016, 25 patients (81%) were still on study. Of the 31 patients, 27 (87%) had an exon 19 deletion (n = 13, 42%) or an L858R (n = 14, 45%) *EGFR* activating mutation, and two (7%) had an L861Q mutation. Five patients (16%) had other *EGFR* activating mutations, two had an activating mutation and the T790M resistance mutation. The most commonly reported treatment-emergent adverse event was diarrhea (n = 24, 77%). All patients had at least one post-baseline scan; one patient (3%) achieved a confirmed complete response, 13 (42%) had a confirmed partial response, and 15 (48%) had confirmed stable disease (disease control rate, 94% [n = 29/31]) per

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; CI, confidence interval; CR, complete response; DCR, disease control rate (patients with CR, PR, or SD per RECIST version 1.1); ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ex19del, deletion of exon 19; NCI, National Cancer Institute; NSCLC, non-small-cell lung carcinoma; ORR, overall response rate (patients with CR or PR per RECIST version 1.1); PFS, progression-free survival; PR, partial response; SD, stable disease; TEAE, treatment-emergent AE; TKI, tyrosine kinase inhibitor; ULN, upper limit of normal; WT, wild type.

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investigator assessment. Once-daily ASP8273 at 300 mg was generally well tolerated and showed antitumor activity in TKI-naïve Japanese patients with *EGFR* mutation-positive NSCLC.

KEYWORDS
clinical trial, epidermal growth factor receptor, non-small-cell carcinoma, signal transduction inhibitors/kinase inhibitor, tyrosine kinase inhibitor

1 | INTRODUCTION

Epidermal growth factor receptor mutations are estimated to be present in approximately 50% of NSCLC patients in East Asian countries.[1] The presence of *EGFR* activating mutations in NSCLC patients can result in increased malignant cell survival, proliferation, invasion, metastatic spread, and tumor angiogenesis.[2,3] The most common *EGFR* mutations are exon 19 deletions and exon 21 L858R substitutions.[2,4] These mutations confer sensitivity to TKIs and account for approximately 90% of *EGFR* mutations seen in patients with NSCLC.[5]

The presence of *EGFR* activating mutations in NSCLC patients is an important predictor of response and outcome to treatment with EGFR-TKIs and patients with these mutations have experienced antitumor activity and prolonged PFS following treatment with the reversible EGFR-TKIs gefitinib and erlotinib.[6,7] Clinical efficacy, however, is often limited by an acquired drug resistance, most commonly caused by a point mutation (T790M) in the gene encoding *EGFR*. Approximately 50%-60% of patients treated with TKIs develop T790M-mediated resistance, suggesting that, along with activating mutations, the T790M mutation is an important factor in determining the appropriate treatment strategy in these patients.[8,9]

ASP8273 is an oral irreversible EGFR-TKI that inhibits the kinase activity of EGFR containing the ex19del or L858R activating mutation and the T790M resistance mutation. In preclinical studies, ASP8273 inhibited the kinase activity of *EGFR*-containing activating mutations, ex19del, and exon 21 L858R. ASP8273 also inhibited the kinase activity of *EGFR* containing both an activating mutation and the T790M resistance mutation (ie ex19del/T790M and T790M/L858R). ASP8273 inhibited EGFR phosphorylation in NCI-H1975 cells and maintained inhibition for 24 hours after washout. ASP8273 is a third-generation EGFR-TKI that inhibits T790M mutant EGFR selectively with less activity against WT EGFR than second-generation EGFR-TKIs (gefitinib and erlotinib). In vitro biochemical enzymatic assays have shown that ASP8273 specifically inhibits EGFR ex19del, L858R, ex19del/T790M, and L858R/T790M with the IC_{50} values of 5.5, 4.6, 0.26, and 0.41 nmol/L, respectively; the IC_{50} value against WT EGFR was 13 nmol/L. In a phase I dose escalation/dose expansion study, ASP8273 showed clinical antitumor activity in patients with *EGFR*-mutant lung cancers and was generally well tolerated. The recommended phase II dose was established as 300 mg.

The primary objective of this phase II study was to determine the safety of 300 mg ASP8273 in EGFR-TKI-naïve adult patients with NSCLC harboring *EGFR* activating mutations. A key secondary objective was to determine the antitumor activity. Here we report the results from study initiation date, June 2015, until the February 2016 cut-off date.

2 | MATERIALS AND METHODS

2.1 | Study design and treatment

This open-label, single-arm, phase II study (NCT02500927) was undertaken at 11 medical centers in Japan. Eligible patients were aged ≥20 years, EGFR-TKI treatment-naïve with a histologically or cytologically confirmed diagnosis of stage IIIB/IV NSCLC, and a documented activating *EGFR* mutation (ex19del, L858R, G719X, or L861Q). Patients had an ECOG performance status of 0 or 1, and at least one measurable lesion based on RECIST version 1.1. Patients received 300 mg ASP8273 orally, given once daily during cycles lasting 21 days. ASP8273 was continued as long as patients received clinical benefit according to investigator assessment (eg absence of unacceptable toxicity or imaging-confirmed disease progression) or until patients withdrew consent.

The primary end-point was to determine the safety and tolerability of ASP8273 based on physical assessments, AEs, clinical laboratory tests, ophthalmologic examination, and ECOG performance status. Adverse events were graded with the NCI's Common Terminology Criteria for Adverse Events version 4.0. Laboratory safety assessments included monitoring hematology and blood chemistry.

The key secondary end-point was to determine the antitumor activity of ASP8273, based on investigator-assessed ORR and DCR according to RECIST version 1.1, and the investigator-assessed PFS.

The study was designed by the study sponsor in collaboration with the investigators, and was carried out in accordance with the protocol,

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles of the Declaration of Helsinki.

2.2 | Procedures

Target and non-target tumor lesions were assessed by the investigator using RECIST version 1.1. Tumor lesions were tested with an imaging technique such as radiography, computed tomography, or MRI at baseline, at the start of subsequent cycles (every 3 weeks), and at discontinuation. After cycle 3, tumors were assessed in odd numbered cycles. Additionally, *EGFR* mutations of histological samples were analyzed at a central *EGFR* gene testing laboratory using the therascreen EGFR RGQ PCR Kit (Qiagen) for patients who opted to do so. For this purpose, either tumor biopsy samples of the primary or metastatic lesions or an archived tumor tissue sample were used. Samples for *EGFR* activating mutations (ex19del, L858R, L861Q, S768I, G719A, G719S, G719C, and exon 20 insertion mutation) and for the *EGFR*-T790M mutation were also analyzed.

2.3 | Statistical analysis

All patients who received at least one dose of ASP8273, who had acceptable images for baseline tumor assessment, and who were evaluated for at least one efficacy end-point after start of treatment were included in the full analysis set. Patients who received at least one dose of ASP8273 were included in the safety analysis set.

The frequency and percentage of AEs by subcategories including relation to study drug, severity, and events leading to study drug interruption were summarized. Quantitative and qualitative laboratory values were summarized at each visit; laboratory results were classified as low, normal, or high and shifts from baseline were noted.

The antitumor effect of ASP8273 was assessed based on RECIST version 1.1. The ORR was defined as the proportion of patients whose best overall response over the entire exposure period was rated as CR or PR. The DCR, which was defined as the proportion of patients whose best overall response over the entire exposure period was rated as CR, PR, or SD, was calculated. The median follow-up time for PFS was estimated according to the Kaplan–Meier estimate of potential follow-up.

3 | RESULTS

3.1 | Disposition, demographics, and disease characteristics

Thirty-three patients provided informed consent and were screened for the study; two patients failed inclusion or exclusion criteria as described in the trial profile (Figure 1).

A total of 31 Japanese patients (12 men and 19 women; median age, 64 years [range, 31-82 years]) were enrolled from 11 centers in Japan (Table 1). Based on local testing, 27 patients had either an ex19del (n = 13, 42%) or an L858R (n = 14, 45%) *EGFR* activating mutation, two patients had L861Q mutation (7%) and five patients (16%) had other *EGFR* activating mutations. Some samples were

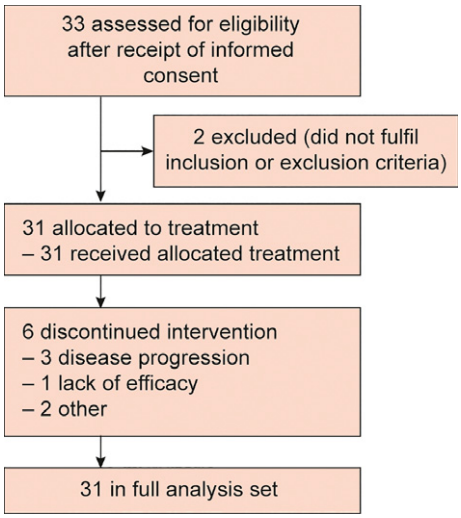

FIGURE 1 Profile of phase II trial of ASP8273 tolerability and antitumor activity in tyrosine kinase inhibitor-naïve Japanese patients with *EGFR* mutation-positive non-small-cell lung cancer

TABLE 1 Demographics and baseline disease characteristics in Japanese patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer treated with ASP8273 300 mg (n = 31)

Characteristic	
Age, years; median (min, max)	64 (31, 82)
Age group (y), n (%)	
<75	25 (81)
≥75	6 (19)
Sex, n (%)	
Male	12 (39)
Female	19 (61)
Cancer type, n (%)	
Adenocarcinoma	30 (97)
Squamous cell carcinoma	1 (3)
ECOG performance status, n (%)	
0	18 (58)
1	13 (42)
EGFR mutation status (local laboratory testing), n (%)	
Ex19del	13 (42)
L858R	14 (45)
L861Q	2 (7)
Other	5 (16)
History of tobacco use, n (%)	
Never	17 (55)
Current user	3 (10)
Former user	11 (36)

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; max, maximum; min, minimum.

tested centrally (for the patients who opted to have their tumor samples analyzed) and results were similar.

Overall, the majority of patients (77%, 24/31) were diagnosed with NSCLC based on histological diagnosis. A total of 97% (n = 30/31) of patients had a pathologic diagnosis of adenocarcinoma and one patient had a pathologic diagnosis of squamous cell carcinoma; all but one patient had stage IV NSCLC. As of February 23, 2016, 81% (n = 25/31) remained on treatment.

The median duration of exposure was 112 days for 300 mg and 139 days for all doses (including dose decreased to 200 or 100 mg). Dose reduction was experienced by 23% (n = 7/31) of patients and dose interruption by 55% (n = 17/31) of patients; all dose reductions were due to an AE. Dose interruption due to an AE was experienced by 42% (n = 13/31) of patients and dose interruption due to other reasons was experienced by 29% (n = 9/31) of patients. The median duration of interruption was 1 day (range, 0 to 42 days) for all dose levels.

3.2 | Safety

ASP8273 at 300 mg had a tolerable toxicity profile, with diarrhea and peripheral neuropathy being common TEAEs. All 31 (100%) patients reported ≥1 treatment-related AE during the study (Table 2), the most common of which were diarrhea (68%, n = 21), peripheral sensory neuropathy (39%, n = 12), alanine aminotransferase increased (36%, n = 11), and nausea. No deaths were reported during the study; serious TEAEs considered related to ASP8273 were reported in 10% (n = 3/31) of patients and included hepatotoxicity, increased ALT, increased AST, and dehydration. There were no TEAEs leading to permanent discontinuation of study drug. Treatment-related TEAEs leading to drug interruption, including anemia, sinus bradycardia, nausea, vomiting, fatigue, malaise, pyrexia, hepatotoxicity, increased ALT, increased AST, decreased neutrophils, decreased appetite, dehydration, hyponatremia, renal impairment, and epistaxis were reported in 36% (n = 11/31) of patients. Treatment-emergent AEs of special interest were hyperglycemia (n = 1, 3%), prolonged QT interval on electroencephalogram (n = 1, 3%), and interstitial lung disease-like events (n = 0).

Potentially clinically significant values in liver enzymes were reported, including increased alkaline phosphatase >1.5 × ULN (n = 7), increased ALT or AST >3 × ULN (n = 6), increased ALT >5 × ULN (n = 3) and increased AST >5 × ULN (n = 1), and increased ALT >10 × ULN (n = 1). There was no patient with ALT and/or AST >3 × ULN and total bilirubin >2 × ULN. Baseline ECOG performance status was grade 1 for 42% (n = 13/31) of patients. Three patients had a maximum post-baseline ECOG performance status of grade 2; however, no ECOG performance status score was grade ≥3 in severity.

3.3 | Antitumor activity

In total, 30 of the 31 patients had evaluable target lesion data. As detailed in Table 3 and Figure 2(A), one patient experienced a CR, 13 achieved PR, 15 achieved SD, and one had progressive disease. The ORR (defined as CR + PR) was 45% (n = 14/31; 95% CI, 27.3-64.0), and the DCR was 94% (n = 29/31; 95% CI, 78.6-99.2) for derived ASP8273 response assessments with confirmation. The PFS rate at 6 months was 86% (95% CI, 67-94). The median duration of PFS could not be estimated, as 81% (25/31) of patients were ongoing without death or progressive disease after more than 105 days, and had not received new anticancer therapy. Among patients with ex19del (n = 13), ASP8273 was associated with an ORR of 31% (95% CI, 9.1-61.4) and DCR of 85% (95% CI, 55-98). In patients with the L858R mutation (n = 14), ASP8273 300 mg was associated with an ORR of 57% (95% CI, 29-82) and DCR of 100% (95% CI,

TABLE 2 Treatment-related adverse events occurring in ≥5% of the total population Japanese patients with *EGFR* mutation-positive non-small-cell lung cancer, n (%)

	ASP8273 300 mg (n = 31)
Diarrhea	21 (68)
Peripheral sensory neuropathy	12 (39)
Alanine aminotransferase increased	11 (36)
Nausea	10 (32)
Hyponatremia	10 (32)
Dry mouth	8 (26)
Aspartate aminotransferase increased	8 (26)
Dry skin	7 (23)
Decreased appetite	7 (23)
Stomatitis	6 (19)
Vomiting	5 (16)
Rash	5 (16)
Dysgeusia	5 (16)
Malaise	5 (16)
Fatigue	4 (13)
Platelet count decreased	4 (13)
Pyrexia	3 (10)
Blood creatinine increased	3 (10)
Hypoalbuminemia	3 (10)
Muscle spasms	3 (10)
Epistaxis	3 (10)
Keratitis	2 (7)
Abdominal discomfort	2 (7)
Oral dysesthesia	2 (7)
Oral pain	2 (7)
Blood alkaline phosphatase increased	2 (7)
Protein total increased	2 (7)
Dysesthesia	2 (7)
Peripheral neuropathy	2 (7)
Paresthesia	2 (7)
Urinary retention	2 (7)
Dermatitis acneiform	2 (7)
Pruritis	2 (7)

TABLE 3 Tumor response in Japanese patients with *EGFR* mutation-positive non-small-cell lung cancer, overall and by *EGFR* mutation status, following treatment with ASP8273

	ASP8273 300 mg		
Response, n (%)	Overall, n = 31	Ex19del, n = 13	L858R, n = 14
CR	1 (3)	0 (0)	1 (7)
PR	13 (42)	4 (31)	7 (50)
SD	15 (48)	7 (54)	6 (43)
PD	1 (3)	1 (8)	0 (0)
NE	1 (3)	1 (8)	0 (0)
ORR (CR + PR)	14 (45)	4 (31)	8 (57)
DCR (CR + PR + SD)	29 (94)	11 (85)	14 (100)

CR, complete response; DCR, disease control rate; Ex19del, exon 19 deletion; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

77-100). Although PFS could not be estimated at the data cut-off of February 23, 2016, PFS was evaluable at a later data cut (November 12, 2016). Median PFS values for all patients, ex19del-positive patients, and patients with L858R mutation were 11.3 months (range, 0.7-15.5; Figure 2B), 8.3 months (range, 0.72-12.55; Figure 2C), and 15.5 months (range 1.38-15.51; Figure 2D), respectively.

4 | DISCUSSION

This phase II study suggests that ASP8273 is tolerable at a dosage of 300 mg and shows antitumor activity in EGFR-TKI-naïve patients with NSCLC harboring *EGFR* activating mutations. No deaths or TEAEs leading to permanent discontinuation were reported. A number of treatment-related toxicities seen with ASP8273 were similar to other drugs in its class (eg diarrhea, nausea, and fatigue), hyponatremia and paresthesia/neuropathy might occur more frequently with ASP8273. Although the exact etiology of peripheral sensory neuropathy is not known, certain confounding factors may include previous treatment with chemotherapy, concomitant medications, radiation therapy, advanced age, or hyponatremia. However, most patients in this study (n = 25/31, 81%) had not received other drug treatments for their underlying disease prior to treatment, and most had not undergone radiation therapy (n = 22/31, 71%). In a study

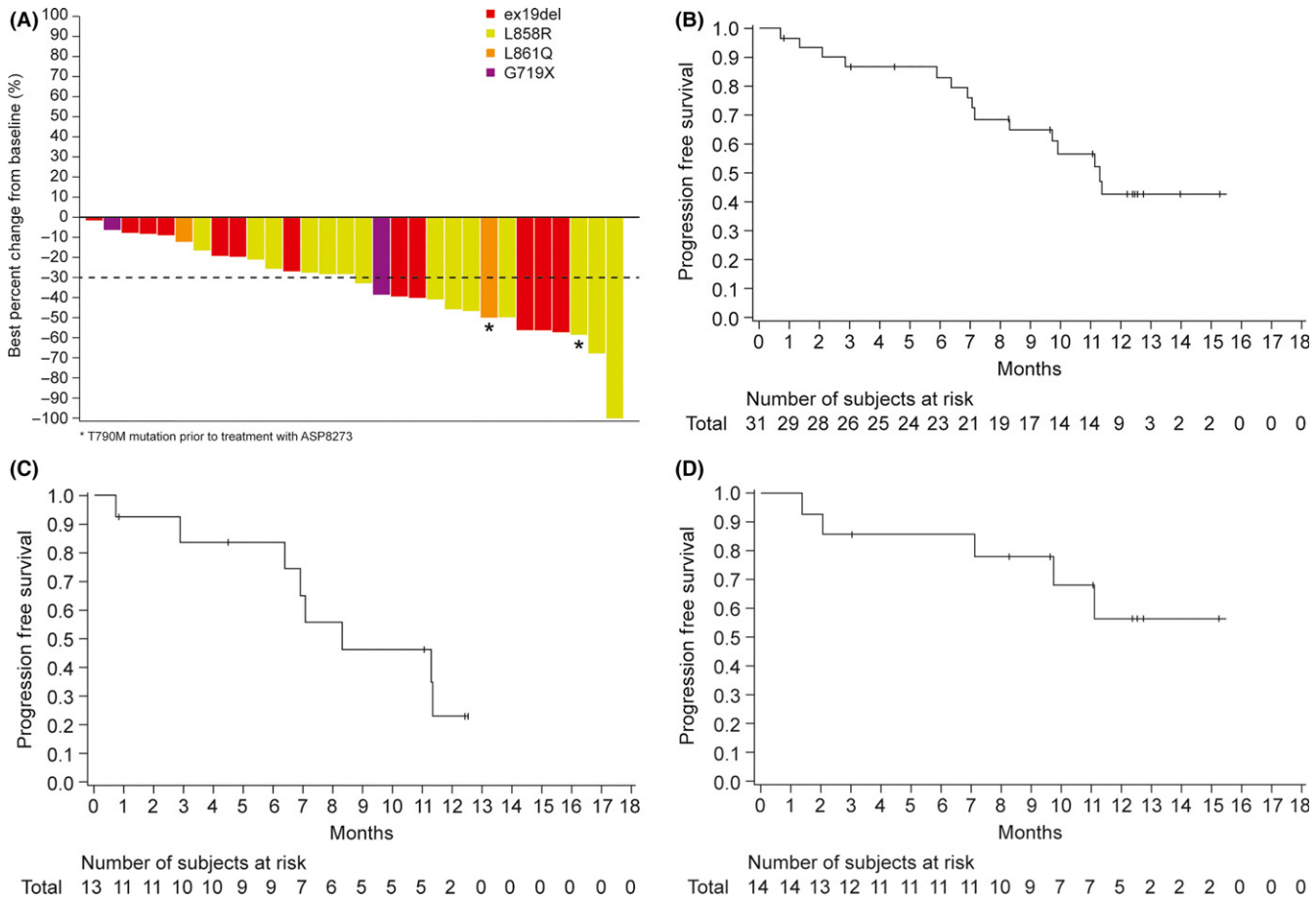

FIGURE 2 Antitumor activity in tyrosine kinase inhibitor-naïve Japanese patients with *EGFR* mutation-positive non-small-cell lung cancer treated with ASP8273. A, Best percent change from baseline in target-lesion size. B, Progression-free survival of all subjects receiving ASP8273. C, Progression-free survival of patients with exon 19 deletion (ex19del)-positive mutation. D, Progression-free survival of patients with L858R mutation

comparing gefitinib with chemotherapy for the treatment of NSCLC with mutated *EGFR*, one patient out of 114 who received gefitinib experienced sensory neuropathy, and 62 of 113 (55%) patients who received chemotherapy experienced sensory neuropathy.[10] Instances of peripheral sensory neuropathy were of low severity (grade ≤2, n = 12; grade ≥3, n = 0), and patients who experienced hyponatremia (grade ≤2, n = 3; grade ≥3, n = 7) were able to continue treatment with ASP8273 as the condition resolved. Across the study, no patient reported interstitial lung disease, a common occurrence among patients with NSCLC. Although potentially clinically significant values in liver enzymes and total bilirubin were noted, there was no patient with ALT and/or AST >3 × ULN and total bilirubin >2 × ULN. One patient in the study had an ALT value >10 × ULN. This safety/tolerability profile was similar to that observed with ASP8273 in the first-in-human study (NCT02192697), carried out in Asia, which enrolled patients who had progressed on a prior EGFR-TKI (phase I) and who were T790M-positive (phase II).

EGFR T790M-mediated resistance to EGFR-TKIs is a dominant resistance mechanism. In this study, subjects harboring the L858R activating mutation showed higher efficacy than those with ex19del, although the study cohort was very limited. Additionally, two of the 31 enrolled patients (6%) presented with T790M prior to treatment. The T790M mutation has been considered a rare phenomenon prior to exposure to EGFR-TKIs, however, in a meta-analysis that included seven studies and 281 patients with NSCLC, Ma et al[11] noted that 39% of patients were found to harbor the T790M mutation prior to treatment with TKIs. Although ASP8273 antitumor activity in EGFR-TKI-naïve patients with NSCLC harboring *EGFR* mutations was not as robust as seen with gefitinib or erlotinib in patients with activating mutations, ASP8273 has shown similar antitumor effects as osimertinib in a limited group of patients harboring the T790M mutation.[12]

Although these findings are based on a limited number of patients (n = 31), they reflect similar results found in the first-in-human study and a larger study undertaken at 10 sites in the USA. In the US-based, open-label phase I study (NCT02113813) of ASP8273 in 110 NSCLC patients with *EGFR* T790M who had progressed on a prior EGFR-TKI, clinical antitumor activity of ASP8273 was supported by decreased circulating *EGFR* T790M cell-free DNA to below the level of detection, confirming successful on-target inhibition.[13]

Together, these results reveal that ASP8273 has antitumor activity and was tolerated well by patients with advanced disease. Generally, these ASP8273 clinical data provide further insight into achieving the optimal antitumor effects of third-generation EGFR-TKIs when used as first-line treatment for patients with *EGFR* activating mutations L858R and ex19del.

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