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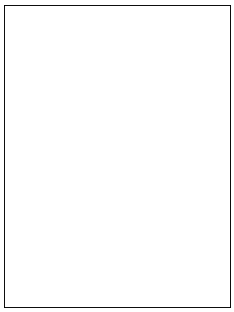

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Pooled Systemic Efficacy and Safety Data from the Pivotal Phase II Studies (NP28673 and NP28761) of Alectinib in *ALK*-positive Non-Small-Cell Lung Cancer

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Conflicts of Interest

Yang, received advisory board fees from Boehringer Ingelheim, Bayer, Astrazeneca, Roche/Genentech, Chugai, Clovis Oncology, Eli Lilly, MSD, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals and Daiichi Sankyo. Ou received personal fees for Pfizer, AstraZeneca, ARIAD and Roche outside the submitted work. De Petris received personal fees from Roche, AstraZeneca, Bristol-Meyer Squibb. Gadgeel received consultancy fees from Boehringer Ingleheim, ARIAD, Novartis and Genentech. Gandhi received consultancy fees from Genentech/Roche, Pfizer, Merck, Abbvie, AstraZeneca and personal fees from Merck and BMS IION foundation. Kim received personal fees from Roche. Barlesi received consulting fees from Roche. Govindan received travel accommodation fees and consulting fees from Merck, Boehringer Ingelheim, Celgene, Roche, Stemcentrix, Abbe Vie Inc and consultancy fees from GlaxoSmith Kline, Clovis, Helsinn healthcare. Dingemans received consultancy fees from Eli Lilly, AstraZeneca, Clovis, Boehringer Ingleheim, MSD. Crino declared no conflict of interest. Lena reports advisory board membership for Roche, MSD, Bristol-Meyer Squibb, Novartis, Pfizer, Astra Zeneca and meeting expenses for Roche, MSD, Bristol-Meyer Squibb, Lilly, Amgen. Popat received personal fees from Roche, Pfizer, Novartis outside the submitted work. Ahn declared no conflict of interest. Dansin received personal fees from BMS, AstraZeneca and Roche. Golding, Bordogna, Balas, Morcos and Zeaiter are employees and have stock ownership at Roche. Shaw received consulting fees from Ignyta, Taiho and ad board fees from Pfizer, Novartis, Genentech/Roche, Ariad, Daiichi-Sankyo, Blueprint Medicines, Loxo, EMD Serono and Foundation Medicine.

ABSTRACT

Introduction: Alectinib demonstrated clinical efficacy and an acceptable safety profile in two phase II studies (NP28761 and NP28673). Here we report pooled efficacy and safety data after 15 and 18 months' longer follow-up than the respective primary analyses.

Materials and methods: Enrolled patients had *ALK*-positive NSCLC and had progressed on, or were intolerant to, crizotinib. Patients received oral alectinib 600 mg twice daily. The primary endpoint in both studies was objective response rate (ORR) assessed by an independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Secondary endpoints included disease control rate (DCR); duration of response (DOR); progression-free survival (PFS); overall survival (OS); and safety.

Results: The pooled dataset included 225 patients (n=138 NP28673; n=87 NP28761). The response-evaluable (RE) population included 189 patients (84%; n=122 NP28673; n=67 NP28761). In the RE population, ORR by IRC was 51.3% (95% confidence interval [CI], 44.0–58.6; all partial responses), DCR was 78.8% (95% CI, 72.3–84.4), and median DOR was 14.9 months (95% CI, 11.1–20.4) after 58% of events. Median PFS by IRC was 8.3 months (95% CI, 7.0–11.3) and median OS was 26.0 months (95% CI, 21.4–not estimable). Grade ≥3 adverse events (AEs) occurred in 40% of patients, 6% withdrew treatment due to AEs and 33% had AEs leading to dose interruptions/modification.

Conclusion: This pooled data analysis confirmed the robust systemic efficacy of alectinib in *ALK*-positive NSCLC with a durable response rate. Alectinib also had an acceptable safety profile with a longer duration of follow-up.

Key Words: Alectinib; Non-Small-Cell Lung Cancer; NP28673; NP28761; Pooled Analysis.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) harboring a chromosomal rearrangement of the anaplastic lymphoma kinase (*ALK*) gene (*ALK*-positive NSCLC), represents a distinct molecular subset of the disease, which affects approximately 5% of patients.[1] Crizotinib is the current standard of care for *ALK*-positive NSCLC and has extended progression-free survival (PFS) compared with cytotoxic chemotherapy (10.9 months versus 7.7 months, respectively) in the first- and second-line treatment setting.[2,3] Unfortunately, almost half of crizotinib-treated patients relapse within the first year. This is usually as a result of poor control of disease within the central nervous system (CNS), which is the most common site of disease progression (PD),[4,5] or due to secondary *ALK* resistance mutations.[6,7,8]

Second-generation ALK inhibitors have been developed with the aim of improving efficacy in patients with *ALK*-positive NSCLC, including those with CNS metastases. The ALK inhibitor ceritinib was granted accelerated approval by the US Food and Drug Administration (FDA) in 2014 for use in patients with *ALK*-positive, metastatic NSCLC who had progressed on, or were intolerant to, crizotinib.[9] The European Medicines Agency (EMA) subsequently approved ceritinib in 2015 for use in the same indication.[10] The approvals were based on a phase I and phase II study of ceritinib in patients with *ALK*-positive NSCLC, which demonstrated median PFS of 5.7–6.9 months and objective response rates (ORRs) of 39–56%.[11,12] Recently, the FDA approval was extended to treatment-naïve patients with metastatic *ALK*-positive NSCLC.[13] The extended approval was based on results from the ASCEND-4 trial, which demonstrated superior PFS with ceritinib versus platinum-pemetrexed doublet chemotherapy in patients with treatment-naïve, *ALK*-positive NSCLC (median 16.6 vs 8.1 months; hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.42–0.73; p<0.0001);[14] a similar trend was observed in patients with CNS metastases at baseline, but this was not significant. ORRs were improved with ceritinib versus chemotherapy, respectively, in the overall study population (73% vs 27%) and in those with measurable CNS disease at baseline (46% vs 21%).[14]

Alectinib is a potent and highly selective ALK inhibitor that has demonstrated both systemic and CNS efficacy in *ALK*-positive NSCLC in a number of studies.[15–18] Alectinib was approved in Japan in 2014, for the treatment of ALK inhibitor-naïve patients with *ALK*-positive NSCLC, following results of a phase I/II study (AF001-JP). This study reported a high ORR of 93.5% (95% CI 82–99); follow-up for this study is still ongoing with a 3-year PFS rate of 62% (95% CI 45–75).[19] Similarly, significant clinical activity was reported with alectinib in two pivotal phase II studies, one global (NP28673; NCT01801111) and one North American (NP28761; NCT01871805), in patients with *ALK*-positive NSCLC who had received prior crizotinib. ORRs of 50.8% (95% CI 41.6–60.0) and 52.2% (95% CI 39.7–64.6) were observed in NP28673 and NP28761, respectively (data cut-off 27 April 2015), with median durations of response (DOR) of 14.1 months (95% CI 10.9–not estimable [NE]; 44% of events) and 13.5 months (95% CI 6.7–NE; 40% of events), respectively. Alectinib was well tolerated in the global and North American studies, as reflected by the rates of dose interruptions (23% and 36%, respectively), dose reductions (10% and 16%) and withdrawals due to adverse events (AEs) (9% and 2%, respectively) reported (27 April 2015 data cut-off).[17,18] Data from these two phase II studies led to the accelerated approval of alectinib in 2015 by the FDA for the treatment of patients with *ALK*-positive NSCLC who have progressed on, or are intolerant to, crizotinib.[20] Alectinib has also received conditional approval for the same patient population from the EMA. Data from the first-line, phase III, global ALEX study demonstrated that patients treated with alectinib had a longer PFS than patients treated with crizotinib.[21]

Here, we present pooled efficacy and safety analyses from these phase II studies with 15 and 18 months' longer follow-up than the respective primary analyses for NP28761 (data cut-off of 22 January 2016 versus 24 October 2014) and NP28673 (data cut-off of 1 February 2016 versus18 August 2014).

METHODS

Study Design

NP28673 and NP28761 were phase II, single-arm, open-label, multicenter studies. NP28673 was conducted across 16 countries at 56 sites and patients were enrolled between 20 June 2013 and 23 April 2014. NP28761 was undertaken in 27 centers across the USA and Canada, with patients enrolled between 3 May 2012 and 4 August 2014; this timeframe also included a phase I dose-finding step, hence, the phase II portion of the study commenced on 4 September 2013. Both studies were undertaken in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines, and written informed consent was obtained from all patients. Full methodology for each study has been published previously.[17,18]

Eligibility Criteria

Both studies enrolled patients who were aged ≥18 years, with locally advanced or metastatic *ALK*-positive NSCLC as assessed by an FDA-approved fluorescence *in situ* hybridization test. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2, and had progressed on crizotinib. Patients with asymptomatic baseline CNS metastases (treated or untreated with radiation) and those who had received prior chemotherapy were permitted to enroll into both studies. Patients were excluded if they had received prior ALK inhibitor treatment other than crizotinib.

Study Treatment

All patients received 600 mg oral alectinib twice daily with a meal, until PD, unacceptable toxicity, withdrawal or death. In both studies there was a minimum washout period of 7 days between the last dose of crizotinib and the first dose of alectinib.

Study Endpoints

The primary endpoint of the pooled analysis was ORR assessed by an Independent Review Committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST)

v1.1. The secondary endpoints for both studies included disease control rate (DCR), DOR, PFS, overall survival (OS), and safety. CNS secondary endpoints were also evaluated including CNS ORR and CNS DOR, and will be reported in a separate analysis.

Statistical Analysis

Response endpoints were assessed in the response-evaluable (RE) population, which comprised patients with measurable disease at baseline who received at least one dose of alectinib. The safety population comprised all patients who received at least one dose of alectinib. ORR was defined as the proportion of patients achieving a best overall response of confirmed complete response (CR) or partial response (PR) in the RE population. PFS and OS were assessed in the safety population. PFS was calculated from the date of first dose of alectinib until PD or death. OS was calculated from the date of first dose of alectinib until death. Time-to-event data (PFS, OS and DOR) were estimated using Kaplan-Meier analyses.

RESULTS

Patients

The pooled dataset comprised 225 patients (138 patients from study NP28673 and 87 patients from study NP28761) (Supplementary Fig. 1). The RE population according to IRC included 189 patients (84%), comprising 122 patients from study NP28673 and 67 patients from study NP28761. Baseline characteristics were similar across both studies (Table 1). Briefly, median patient age was 53 years (range, 22–79); 67% of patients had an ECOG PS of 1/2 and the majority of patients were White (74%). Overall, 136 (60%) patients had baseline CNS metastases and 174 (77%) had received prior chemotherapy (Table 1).

Efficacy

At the data cut-off (NP28673:1 February 2016 and NP28761: 22 January 2016), median follow-up for the pooled dataset was 18.8 months (range 0.6–29.7). In the RE

population, the ORR by IRC was 51.3% (95% CI 44.0–58.6), with 97/189 patients achieving a PR and there were no CRs. Stable disease (SD) was reported in 52/189 patients (28%) giving a DCR of 78.8% (95% CI 72.3–84.4). Median DOR was 14.9 months (95% CI 11.1–20.4) after 58% of events.

Of the patients who had received prior chemotherapy in the RE population (n=148), 73 (49%) achieved a PR; there were no CRs, giving an IRC-assessed ORR of 49.3% (95% CI 41.0–57.7). In total, 44/148 patients had SD (30%), resulting in a DCR of 79.1% (95% CI 71.6–85.3). The median DOR in this subgroup was also 14.9 months (95% CI 11.0–21.9) based on 59% of events.

Overall, 24/41 (59%) chemotherapy-naïve patients in the RE population achieved a PR; there were no CRs, giving an IRC-assessed ORR of 58.5% (95% CI 42.1–73.7). SD was reported in 8/41 patients (20%) giving a DCR in this population of 78.0% (95% CI 62.4–89.4). The median DOR was 11.2 months (95% CI 8.0–NE) after 54% of events.

A subgroup analysis of IRC-assessed ORR was performed to evaluate different prognostic factors, including gender, race, ECOG PS, CNS metastases at baseline, smoking status and prior chemotherapy. Objective response rates were generally consistent across most subgroups. Patients with an ECOG PS 0 had a numerically higher response rate compared with patients with ECOG PS 1 or 2 (65.6% [95% CI 52.3–77.3] versus 45.0% [95% CI 35.6–54.8] or 41.2% [95% CI 18.4–67.1], respectively). The analysis also showed a higher response rate in patients who were never-smokers at baseline compared with those who were past smokers (55.9% [95% CI 46.8–64.7] versus 39.0% [95% CI 26.5–52.6], respectively) (Table 2). However, it should be noted that the subgroups were relatively small and confidence intervals were overlapping.

In the pooled population, 156/225 patients (69%) had a PFS event according to the IRC at

the data cut-off. The median PFS was 8.3 months (95% CI 7.0–11.3) (Fig. 1) and the 6 month event-free rate was 59.9% (95% CI 53.5–66.4). For patients who had only received crizotinib treatment prior to receiving alectinib (51/225; 23%), the median PFS was 8.4 months (95% 5.6–16.6). With regards to OS, 96/225 patients (43%) had an OS event at the data cut-off. The median OS was 26.0 months (95% CI 21.4–NE) and the 6 month event-free rate was 85.3% (95% CI 80.6–89.9) (Fig. 2).

Safety

Safety was evaluated in the pooled safety population of 225 patients (138 patients from study NP28673 and 87 patients from study NP28761). The mean dose intensity of alectinib was 94.1%.

AEs occurring at a frequency of >20% (any grade) were constipation (38%), fatigue (34%), peripheral edema (28%), myalgia (25%), nausea (23%), cough (21%) and headache (21%). A summary of AEs occurring at a frequency of >10% are shown in Table 3. Grade 3–5 AEs occurred in 40% of patients and the most common were dyspnea (4%), elevated levels of blood creatine phosphokinase (4%), alanine aminotransferase (3%) and aspartate aminotransferase (3%). Seven patients (3%) died during the study, including two cases of hemorrhage and one case each of dyspnea, endocarditis, intestinal perforation, pulmonary embolism, and unspecified death. Only two deaths (1%) were considered by the investigator to be treatment-related (hemorrhage and intestinal perforation).

AEs leading to dose modification or interruptions occurred in 33% of patients (n=75), while AEs leading to treatment withdrawal were reported in 6% of patients (n=14) (Table 4).

DISCUSSION

Alectinib has demonstrated clinical systemic and CNS efficacy in two pivotal phase II trials, achieving high response rates and durable responses.[17,18] In the present analysis,

efficacy and safety data were pooled from these phase II trials, with 15 and 18 months' longer follow-up for NP28761 and NP28673, respectively. These data confirmed the clinical activity and acceptable safety profile of alectinib in patients with *ALK*-positive NSCLC, following treatment with crizotinib.

Despite the differences in standard-of-care for *ALK*-positive NSCLC between the USA and the rest of the world, the patient populations in NP28761 and NP28673 were very similar, with 80% and 74% of patients progressing on prior chemotherapy and crizotinib, respectively. Other baseline characteristics were also very similar across the two studies including patient age (median 54 versus 52 years); proportion of male patients (45 versus 44%); patients with an ECOG PS of 0/1 (90 versus 91%) and patients with baseline CNS disease (60 versus 61%) in the North American and global studies respectively, supporting the rationale for combining these datasets.

The ORR of 51.3% that we observed in the present analysis is consistent with the ORRs reported in the individual primary and updated analyses of NP28673 (49.2% and 50.8%, respectively) and NP28761 (47.8% and 52.2%, respectively).[17,18] In this pooled analysis, alectinib demonstrated efficacy regardless of prior treatment with chemotherapy, with an ORR of 49.3% for patients who received prior chemotherapy compared with 58.5% in patients who were chemotherapy-naïve.

Overall, the safety profile of alectinib in this pooled analysis was consistent with data reported in the primary publications.[17,18] Alectinib was well tolerated and the majority of AEs were grade 1/2 in severity, with only 1% of deaths reported as being treatment related. During the pooling of these study data, exposure-response analysis was also performed. Multivariate logistic regression and Cox proportional hazards analyses of the efficacy data demonstrated no statistically significant relationship between alectinib exposure and best overall response or PFS across the two studies, and logistic regression analysis

demonstrated no statistically significant relationship between alectinib exposure and safety endpoints.[22] These exploratory analyses confirm that the alectinib dosing regimen of 600 mg twice daily provides exposures within the expected plateau range of response, supporting its selection as the global dosing regimen.

Crizotinib was the first ALK inhibitor to be approved for the treatment of *ALK*-positive NSCLC and is the current standard of care. Crizotinib prolongs PFS, increases ORR and shows a greater improvement in global quality of life compared to chemotherapy in both previously-treated and treatment-naïve, *ALK*-positive NSCLC.[2,3] Ceritinib was also approved for the treatment of crizotinib-pretreated patients with *ALK*-positive NSCLC, after achieving ORR rates of 39–56% and a median PFS of 5.7–6.9 months in phase I and II studies.[11,12] Recently, ceritinib was also approved in the first-line setting for patients with *ALK*-positive NSCLC, based on superior PFS and ORRs versus chemotherapy reported in the ASCEND-4 trial.[14] The ORR and PFS for ceritinib are comparable with those of alectinib in this pooled analysis, but in the ASCEND-2 trial,[12] ceritinib was associated with high rates of dose interruptions (76%), modifications or discontinuations (54%). In contrast, alectinib demonstrated an acceptable safety profile and good tolerability in this pooled analysis, as reflected by the rates of dose interruptions and modifications (33%) and low withdrawal rates (6%). A recent study of the ALK inhibitor brigatinib, in the same setting as the two alectinib studies presented here, showed ORR of 45–54% and median PFS of 9.2–12.9 months with doses of 90 mg once daily (q.d) or 90 mg q.d for 7 days followed by 180 mg q.d, respectively. Compared with alectinib, brigatinib showed comparable rates of dose reductions (7%) and dose interruptions (18%) due to AEs at the lower dose, however, at the higher dose, brigatinib showed greater rates of dose reductions (20%), dose interruptions (36%) and discontinuations (8%).[23]

Here we report the systemic efficacy and safety of the pooled population, while an analysis of the activity of alectinib on CNS metastases in this pooled dataset has recently been

published.[24] Alectinib achieved a CNS ORR of 64.0% (95% CI 49.2–77.1) with a CNS DCR of 90.0% (95% CI 78.2–96.7) and CNS DOR of 10.8 months (95% CI 78.2–90.8), showing good CNS efficacy.

Two ongoing phase III studies are directly comparing the efficacy of alectinib with crizotinib in patients with ALK inhibitor-naïve *ALK*-positive NSCLC (ALEX, NCT02075840; J-ALEX, JapicCTI-132316). Following an interim analysis, results from the J-ALEX study were released early, as the primary endpoint of PFS demonstrated superiority compared with crizotinib treatment (HR 0.34 [99.6826% CI 0.17–0.70, stratified log-rank p<0.0001]; median PFS not reached [95% CI 20.3–NE] versus 10.2 months [95% CI 8.2–12.0], for alectinib versus crizotinib).[25, 24] Grade 3/4 AEs were observed at a greater frequency in the crizotinib arm (52%) compared with the alectinib arm (27%) and rates of drug interruptions were lower with alectinib than with crizotinib (29% versus 74%, respectively). Primary data from the global ALEX study also showed that alectinib had a superior PFS compared with crizotinib (12-month event-free survival rate, 68.4% [95% CI, 61.0–75.9] with alectinib versus 48.7% [95% CI, 40.4–56.9] with crizotinib.[21].

In conclusion, results from this pooled analysis showed that alectinib 600 mg twice daily demonstrated clinical activity and was well tolerated in patients with *ALK*-positive NSCLC who had progressed on crizotinib. Efficacy was shown in patients who had received prior chemotherapy as well as in those who were chemotherapy-naïve.

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418 **TABLE 1.** Demographic and Baseline Characteristics of the Pooled Population (ITT

419 Population)

	NP28761 (n=87)	NP28673 (n=138)	Difference Between Cohorts, %	Pooled Population (N=225)
Median age, years (range)	54 (29–79)	52 (22–79)	2 years	53 (22–79)
Sex, n (%)				
Male	39 (45)	61 (44)	1	100 (44)
Female	48 (55)	77 (56)	1	125 (56)
ECOG PS, n (%)				
0	30 (34)	44 (32)	2	74 (33)
1	48 (55)	81 (59)	4	129 (57)
2	9 (10)	13 (9)	1	22 (10)
Race, n (%)				
White	73 (84)	93 (67)	17	166 (74)
Asian	7 (8)	36 (26)	18	43 (19)
Other	3 (3)	4 (3)	0	7 (3)
Black/African American	3 (3)	1 (0.7)	2.3	4 (2)
Multiple	1 (1)	0 (0)	1	7 (3)
Unknown	0	3 (2)	2	1 (0.4)
American Indian/Alaska Native	0	1 (0.7)	0.7	1 (0.4)

CNS metastases, n (%)				
Yes	52 (60)	84 (61)	1	136 (60)
No	35 (40)	54 (39)	1	89 (40)
Histology, n (%)				
Adenocarcinoma	82 (94)	133 (96)	2	215 (96)
Other	5 (6)	5 (4)	2	10 (4)
Prior chemotherapy, n (%)				
Yes	64 (74)	110 (80)	6	174 (77)
No	23 (26)	28 (20)	6	51 (23)
Crizotinib + prior therapies				
Crizotinib only	23 (26)	28 (20)	6	51 (23)
+1 therapy	0	52 (38)	38	52 (23)
+2 therapies	19 (22)	16 (12)	10	35 (16)
+3 therapies	18 (21)	17 (12)	9	35 (16)
+4 therapies	14 (16)	16 (12)	4	30 (13)
+5 therapies	8 (9)	4 (3)	6	12 (5)
≥6 therapies	5 (6)	5 (4)	2	10 (4)
Smoking status				
Active smoker	0	3 (2)	2	3 (1)
Past smoker	33 (38)	39 (28)	10	72 (32)
Never-smoker	54 (62)	96 (70)	8	150 (67)

420 CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PS,
421 performance status.

422 **TABLE 2.** Subgroup Analyses of IRC Objective Response Rate in the Pooled Population

423 (IRC RE Population)

	Patients Per Subgroup (n=189)	Responders Per Subgroup	
		n (%)	95% CI
Sex			
Male	88	46 (52.3)	41.4–63.0
Female	101	51 (50.5)	40.4–60.6
Race			
White	137	70 (51.1)	42.4–59.7
Asian	38	23 (60.5)	43.4–76.0
Other	14	4 (28.6)	8.4–58.1
ECOG PS at baseline			
0	61	40 (65.6)	52.3–77.3
1	111	50 (45.0)	35.6–54.8
2	17	7 (41.2)	18.4–67.1
CNS metastases at baseline			
Yes	113	55 (48.7)	39.2–58.3
No	76	42 (55.3)	43.4–66.7
Prior chemotherapy			
Yes	148	73 (49.3)	41.0–57.7
No	41	24 (58.5)	42.1–73.7
Number of prior regimens			
1–2	89	48 (53.9)	43.0–64.6
3–9	100	49 (49.0)	38.9–59.2
Smoking status at screening			

Active smoker	3	3 (100.0)	29.2–100.0
Past smoker	59	23 (39.0)	26.5–52.6
Never-smoker	127	71 (55.9)	46.8–64.7
Time on prior crizotinib			
≤ median	105	48 (45.7)	36.0–55.7
≥ median	84	49 (58.3)	47.1–69.0
Best response on crizotinib			
Complete response	1	1 (100)	2.5–100.0
Partial response	84	50 (59.5)	48.3–70.1
Stable disease	43	19 (44.2)	29.1–60.1
Progressive disease	47	21 (44.7)	30.2–59.9
Unknown/N/A/NE	14	6 (42.9)	17.7–71.1

CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NE, not evaluable; N/A, not applicable; PS, performance status; RE, response evaluable.

Table 3. Adverse Events with an Incidence Rate of >10% in the Pooled Studies (ITT Population)

Adverse Event, n (%)	NP28761 (n=87)	NP28673 (n=138)	Difference Between Cohorts, %	Pooled Population (N=225)
Patients with ≥1 adverse event	84 (97)	135 (98)	1	219 (97)
Constipation	32 (37)	53 (38)	1	85 (38)
Fatigue	33 (38)	43 (31)	7	76 (34)
Peripheral edema	22 (25)	41 (30)	5	63 (28)
Myalgia	22 (25)	35 (25)	0	57 (25)
Nausea	21 (24)	30 (22)	2	51 (23)
Cough	18 (21)	30 (22)	1	48 (21)
Headache	21 (24)	26 (19)	5	47 (21)
Diarrhea	20 (23)	22 (16)	7	42 (19)
Dyspnea	17 (20)	23 (17)	3	40 (18)
Increased aspartate aminotransferase	18 (21)	18 (13)	8	36 (16)
Anemia	17 (20)	16 (12)	8	33 (15)
Weight increased	16 (18)	17 (12)	6	33 (15)
Asthenia	2 (2)	30 (22)	20	32 (14)
Upper respiratory tract infection	13 (15)	19 (14)	1	32 (14)
Vomiting	11 (13)	21 (15)	2	32 (14)
Increased alanine aminotransferase	16 (18)	15 (11)	7	31 (14)
Rash	8 (9)	22 (16)	7	30 (13)

Back pain	10 (11)	18 (13)	2	28 (12)
Increased blood bilirubin	9 (10)	18 (13)	3	27 (12)
Increased blood creatinine phosphokinase	20 (23)	6 (4)	19	26 (12)
Dizziness	11 (13)	15 (11)	2	26 (12)
Photosensitivity reaction	10 (11)	16 (12)	1	26 (12)
Arthralgia	10 (11)	15 (11)	0	25 (11)
Insomnia	11 (13)	12 (9)	4	23 (10)
Decreased appetite	5 (6)	17 (12)	6	22 (10)
Upper abdominal pain	4 (5)	17 (12)	7	21 (9)
Nasopharyngitis	3 (3)	16 (12)	9	19 (8)
Increased blood alkaline phosphatase	12 (14)	5 (4)	10	17 (8)
Hypokalemia	9 (10)	7 (5)	5	16 (7)
Oropharyngeal pain	2 (2)	14 (10)	8	16 (7)
Hypertriglyceridemia	11 (13)	0	13	11 (5)

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Table 4. Adverse Events Leading to Dose Modification, Interruption or Withdrawal in the Pooled Studies (ITT Population).

Outcome, n (%)	NP28761 (n=87)	NP28673 (n=138)	Pooled Population (N=225)
AE leading to withdrawal from study	2 (2)	12 (9)	14 (6)
AE leading to withdrawal from treatment	2 (2)	12 (9)	14 (6)
AE leading to dose modification or interruption	37 (43)	38 (28)	75 (33)
Serious AE leading to withdrawal from treatment	1 (1)	8 (6)	9 (4)
Serious AE leading to dose modification or interruption	9 (10)	13 (9)	22 (10)
Related AE leading to withdrawal from treatment	2 (2)	8 (6)	10 (4)
Related AE leading to dose modification or interruption	24 (28)	23 (17)	47 (21)

AE, adverse event

FIGURE LEGENDS

FIGURE 1. IRC Progression-free survival of the pooled population (ITT Population, N=225).

FIGURE 2. Overall survival of the pooled population (ITT Population, N=225).

SUPPLEMENTARY FIGURE 1. CONSORT diagram

*IRC RE population defined as patients with measurable disease at baseline according to the IRC.

(Not possible to include information regarding the reason for treatment discontinuations in either study, as these data are not availble).