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Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line treatment for stage IV squamous non-small cell lung cancer: A phase 1b and randomized, open-label, multicenter, phase 2 trial in Japan

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ABSTRACT

Objectives: This open-label, multicenter, phase 1b/2 study assessed necitumumab plus gemcitabine and cisplatin (GC + N) in patients with previously untreated squamous non-small cell lung cancer in Japan.
Materials and methods: The phase 1b part determined the gemcitabine dose for the phase 2 part, in which patients were randomized 1:1 to GC + N or gemcitabine and cisplatin (GC) (gemcitabine 1250 mg/m^2 on days 1 and 8; cisplatin 75 mg/m^2 on day 1 of maximum four 3-week cycles; nectimumab 800 mg on days 1 and 8 of a 3-

Abbreviations: ASBI, Average Symptom Burden Index; CI, confidence intervals; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; GC, gemcitabine and cisplatin; GC+N, necitumumab plus gemcitabine and cisplatin; HR, hazard ratio; IV, intravenously; IWRS, interactive web-response system; LCSS, Lung Cancer Symptom Scale; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QOL, quality-of-life; RECIST, Response Evaluation Criteria In Solid Tumors; TEAE, treatment-emergent adverse event; TTF, time-to-treatment failure

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week cycle continued until progressive disease or unacceptable toxicity). The primary endpoint of the phase 2 part was overall survival.

Results: In the phase 2 part, 181 patients received GC + N (N = 90) or GC (N = 91). Overall survival was significantly improved with GC + N versus GC (median, 14.9 months vs 10.8 months; hazard ratio [HR] = 0.66, 95% CI: 0.47 – 0.93, p = 0.0161). Improvements were also observed in progression-free survival (median, 4.2 months vs 4.0 months; HR = 0.56; p = 0.0004) and objective response rate (51% vs 21%; p < 0.0001). Survival was also significantly prolonged with GC + N versus GC for patients with epidermal growth factor receptor-positive tumors. Grade ≥3 treatment-emergent adverse events at ≥5% higher incidence with GC + N than GC were neutrophil count decreased (42% vs 35%), febrile neutropenia (12% vs 3%), decreased appetite (11% vs 4%), and dermatitis acneiform (6% vs 0%).

Conclusion: GC + N is well tolerated and has significant and clinically meaningful treatment benefit in the first-line treatment of patients with squamous non-small cell lung cancer in Japan. Clinicaltrials.gov identifier: NCT01763788.

1. Introduction

The epidermal growth factor receptor (EGFR) is expressed by most non-small cell lung cancer (NSCLC) tumors, in particular squamous NSCLC, and may play a role in tumorigenesis [1,2]. Necitumumab is a recombinant human immunoglobulin G1 monoclonal antibody that binds to EGFR with high affinity and prevents receptor activation by other ligands [3]. This results in inhibition of downstream signaling, which disrupts cell cycle progression and mitosis, blocks inhibition of apoptosis, and decreases angiogenesis through effects on angiogenic factor production [3].

The phase 3 SQUIRE study showed that necitumumab plus gemcitabine and cisplatin (GC + N) improved overall survival (OS) versus gemcitabine and cisplatin (GC) in the first-line treatment of patients with advanced squamous NSCLC (median, 11.5 months vs 9.9 months; stratified hazard ratio [HR] = 0.84; p = 0.01]) [4]. Progression-free survival (PFS) was also improved for GC + N versus GC (median, 5.7 months vs 5.5 months; stratified HR = 0.85; p = 0.02) [4]. The objective response rate (ORR) was 31% versus 29% [4], and time to deterioration for the six major symptoms associated with lung cancer, as measured on the Lung Cancer Symptom Scale (LCSS), was generally similar between GC + N and GC [4]. Subgroup analyses demonstrated that GC + N significantly prolonged OS in patients with EGFR-expressing tumors, but not in patients with non–EGFR-expressing tumors [5]. Higher incidences of at least one grade 3 or worse treatment-emergent adverse event (TEAE) and serious adverse events occurred with GC + N versus GC (72% vs 62% and 48% vs 38%, respectively) [4].

Japanese patients were not included in the phase 3 SQUIRE study. The objective of this open-label, multicenter phase 1b/2 study was to evaluate GC + N as first-line treatment of patients with stage IV squamous NSCLC in Japan and to assess the consistency of the results with those of the overall population in the SQUIRE study [4].

2. Material and methods

2.1. Eligibility

For both the phase 1b and 2 parts of this study, Japanese patients aged 20 years or older with stage IV squamous NSCLC, no prior anticancer therapy, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 were enrolled. Exclusion criteria included major cardiovascular disease within 6 months prior to enrollment and a history of interstitial pneumonia.

2.2. Study design and treatment

The phase 1b part was a single-arm, dose-escalation study to determine the recommended gemcitabine dose, based on a conventional 3 + 3 cohort design, for the phase 2 part. Gemcitabine 1000 mg/m^2 (the approved dose in Japan) was administered before the administration of gemcitabine 1250 mg/m^2 (the dose in the SQUIRE study). All patients received necitumumab, administered intravenously (IV) at an absolute dose of 800 mg on days 1 and 8; gemcitabine, administered IV at a dose of 1000 or 1250 mg/m^2 for a maximum of four 3-week cycles on days 1 and 8; and cisplatin, administered IV at a dose of 75 mg/m^2 for a maximum of four 3-week cycles on day 1. Patients with at least stable disease continued to receive necitumumab until disease progression, the development of unacceptable toxicity, or withdrawal by the patient or sponsor.

The phase 2 part was a randomized study to evaluate the efficacy and safety of GC + N versus GC. All patients were randomized using an interactive web-response system (IWRS) to receive GC + N or GC using the phase 1b recommended dose of gemcitabine 1250 mg/m^2. The IWRS assigned each patient a unique study identification number and randomized each patient to one of the two treatment arms on a 1:1 basis. The primary endpoint of the phase 2 part was OS. Secondary endpoints included PFS; ORR; time-to-treatment failure (TTF); health outcomes; the association of EGFR protein expression and OS, PFS, and ORR; and safety.

This study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, the International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and with the approval by each institution's ethical review board. Patients provided written informed consent. Clinicaltrials.gov identifier: NCT01763788.

2.3. Assessments

In the phase 2 part, OS was defined as the time from the date of randomization to the date of death from any cause and PFS was defined as the time from randomization until the first radiographic documentation of objective progression or death from any cause. Tumor responses were assessed using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 at baseline (within 21 days prior to randomization) and then every 6 weeks until radiographically documented progressive disease.

Disease-related symptoms and quality-of-life (QOL) were assessed with the self-administered LCSS. The LCSS includes six symptom and three global items measured on a 0–100-mm scale; higher scores represent greater symptom burden. The Average Symptom Burden Index (ASBI) was defined as the mean of six symptom-specific lung cancer questions and the total score was defined as the mean of all nine questions. For ASBI and LCSS total scores, worsening was defined as a 15-mm increase from the corresponding baseline scores.

EGFR protein expression was assessed by immunohistochemical assay in archived tumor tissue using the Dako EGFR pharmDx kit (K1494, Dako, Carpinteria, CA). EGFR staining on the cellular membrane was assessed as follows: positive staining was defined as immunoreactivity of tumor cell membranes at any intensity in > 1% of cells, whether it was complete or incomplete circumferential staining;

negative staining was defined as immunoreactivity of tumor cell membranes at any intensity in ≤1% of cells.

2.4. Statistical analyses

The phase 2 planned sample size was 180 patients (137 events), which had 68% power for a log-rank test at a 0.2 one-sided alpha. It was assumed that the expected median OS of GC + N and GC were 13.75 and 11 months (HR = 0.8), respectively. For the primary analyses, OS was estimated using the Kaplan-Meier method. The HR of GC + N to GC and confidence intervals (CI) were estimated using a Cox regression model stratified by the variables used for randomization (ECOG PS and sex), and treatment arms were compared using a stratified log-rank test. Only the analysis by EGFR protein expression status was defined at a significance level of 0.05, but there were no adjustments for multiplicity. The safety analyses were conducted on all patients who were treated with any study drugs in phase 1b or 2. The efficacy analyses in the phase 2 part were conducted on all patients who were randomized and received at least one dose of study treatment. The analysis by EGFR protein expression status in the phase 2 part was conducted on all patients who had a valid immunohistochemistry assay result.

3. Results

3.1. Patients

This study was conducted at 39 investigative sites in Japan. Patients were enrolled from 07 May 2013 and the study data cut-off date was 28 June 2017. Nine patients were enrolled and treated in the phase 1b part, and 183 patients were randomized (91 to GC + N; 92 to GC) in the phase 2 part, 181 of whom received at least one dose of study treatment (90 received GC + N; 91 received GC). One patient in the GC + N group did not receive treatment due to an adverse event and one patient in the GC group did not receive treatment due to subject withdrawal. Baseline characteristics were generally well balanced between treatment groups for the phase 2 part (Table 1).

In the phase 2 part, the median number of cycles was 4 (range: 1–4) for gemcitabine and cisplatin in both treatment groups. The median relative dose intensity was 81% and 81% for gemcitabine and 94% and 93% for cisplatin, for GC + N and GC, respectively. For necitumumab, the median number of cycles was 6 (range: 1–30) and the median relative dose intensity was 91%.

3.2. Survival and response

There were 137 OS events (deaths) at the time of data cut-off: 63 deaths (70%) with GC + N and 74 deaths (81%) with GC (Table 2). OS was improved with GC + N compared with GC (median, 14.9 months vs 10.8 months; stratified HR = 0.66 [95% CI: 0.47 – 0.93]; p = 0.0161) (Fig. 1A).

The OS improvement in favor of GC + N was consistent across prespecified subgroups based on age (< 70 years: HR = 0.68 [95% CI: 0.45–1.01]; ≥70 years: HR = 0.48 [95% CI: 0.25 – 0.92]) and ECOG PS (ECOG PS 0: HR = 0.46 [95% CI: 0.24 – 0.87]; ECOG PS 1: HR = 0.74 [95% CI: 0.49–1.10) (Fig. 1B).

Improvements in PFS (median, 4.2 months vs 4.0 months, stratified HR = 0.56 [95% CI: 0.41 – 0.78]; p = 0.0004) were also observed with GC + N compared with GC (Fig. 1C and Table 2). These improvements were also observed across prespecified subgroups (Supplementary Fig. 1). In addition, improvements were observed in TTF and ORR (Table 2). The waterfall plots for best percent change in tumor size are shown in Fig. 2.

Analysis of the HRs for time to worsening for ASBI and LCSS total score showed a treatment effect in favor of GC + N (HR = 0.47 [95% CI: 0.25 – 0.91] and HR = 0.27 [95% CI: 0.14 – 0.52] for ASBI and LCSS total score, respectively). The Kaplan-Meier analyses of time to worsening for the ASBI and LCSS total score are shown in Figs. 3A and B, respectively.

Archived tumor tissue was available for 180 of 181 (99%) patients. A total of 175 patients had a valid EGFR immunohistochemistry assay result available, comprising 87 patients receiving GC + N (69 EGFR-positive and 18 EGFR-negative) and 88 patients receiving GC (77 EGFR-positive and 11 EGFR-negative). For the subgroup of patients whose tumors were EGFR-positive, patients receiving GC + N had prolonged OS (median, 14.8 months vs 9.4 months; HR = 0.62 [95% CI: 0.43 – 0.90]; p = 0.011) and PFS (median, 4.2 months vs 3.9 months; HR = 0.54 [95% CI: 0.38 – 0.76]; p < 0.001) compared with those receiving GC (Table 2). For the subgroup of patients whose tumors were EGFR-negative, there was not a significant benefit for GC + N compared with GC for OS or PFS.

In the EGFR-positive subgroup, the ORR was higher with GC + N (54%) than with GC (18%) (p < 0.001) (Table 2). In the EGFR-negative subpopulation, ORR was not statistically significantly different between GC + N (39%) and GC (45%) (p = 0.728). The interaction p-value for treatment effect by EGFR status was 0.028 for ORR, which was statistically significant. However, the small sample size of the EGFR-negative population should also be taken into account when considering the ORR data and the HRs of OS and PFS for this population (Table 2).

Eighty-eight percent of patients treated with GC + N and 78% of patients treated with GC received post-discontinuation systemic anticancer therapy overall and for the first subsequent line (Supplementary Table 1). Within the first subsequent line, 44% of patients with GC + N and 30% of patients with GC received docetaxel, 16% with GC + N and 15% with GC received nivolumab, and 7% with GC + N and 11% with GC received carboplatin.

3.3. Safety

In the phase 1b part, there were no dose-limiting toxicities. Gemcitabine 1250 mg/m^2 was administered in the phase 2 part. The most commonly reported TEAEs (overall) in the phase 2 part, occurring

Table 1
Baseline demographic and clinical characteristics.

	GC + N N = 90	GC N = 91	Total N = 181
Sex, n (%)			
Female	11 (12)	10 (11)	21 (12)
Male	79 (88)	81 (89)	160 (88)
Age, years			
Median (range)	67 (35-78)	65 (31-77)	66 (31-78)
Age category, n (%)			
< 65 years	36 (40)	36 (40)	72 (40)
≥65 years	54 (60)	55 (60)	109 (60)
< 70 years	60 (67)	67 (74)	127 (70)
≥70 years	30 (33)	24 (26)	54 (30)
Race, n (%)			
Asian	90 (100)	89 (98)	179 (99)
White	0	1 (1)	1 (1)
Multiple	0	1 (1)	1 (1)
Histologic subtype, n (%)			
Squamous cell	90 (100)	91 (100)	181 (100)
Disease stage at initial diagnosis, n (%)			
Stage IV	90 (100)	91 (100)	181 (100)
ECOG PS, n (%)			
0	27 (30)	30 (33)	57 (31)
1	63 (70)	61 (67)	124 (69)
Smoking status, n (%)			
Light ex-smoker	1 (1)	5 (5)	6 (3)
Nonsmoker	4 (4)	4 (4)	8 (4)
Smoker	85 (94)	82 (90)	167 (92)

ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gemcitabine and cisplatin; GC + N, gemcitabine and cisplatin plus necitumumab.

Table 2
Summary of endpoints.

	GC + N N = 90	GC N = 91
Overall survival		
Deaths, n (%)	63 (70)	74 (81)
Stratified log-rank p-value (two-sided)[a]	0.0161	
Stratified hazard ratio (95% CI)[a,b]	0.66 (0.47 – 0.93)	
Median overall survival, months (95% CI)	14.9 (13.4 – 18.2)	10.8 (8.9 – 14.4)
3-month overall survival, % (95% CI)	98.9 (92.4 – 99.8)	95.6 (88.7 – 98.3)
6-month overall survival, % (95% CI)	90.0 (81.7 – 94.7)	75.8 (65.6 – 83.4)
Progression-free survival		
Deaths or disease progressions, n (%)	84 (93)	81 (89)
Stratified log-rank p-value (two-sided)[a]	0.0004	
Stratified hazard ratio (95% CI)[a,b]	0.56 (0.41 – 0.78)	
Median progression-free survival, months (95% CI)	4.2 (4.1 – 4.3)	4.0 (3.5 – 4.2)
3-month progression-free survival, % (95% CI)	83.7 (74.1 – 90.0)	64.8 (53.6 – 74.0)
6-month progression-free survival, % (95% CI)	23.3 (15.0 – 32.6)	6.4 (2.4 – 13.3)
Response		
Best overall response,[c] n (%)		
Complete response	0	0
Partial response	46 (51)	19 (21)
Stable disease	38 (42)	54 (59)
Progressive disease	3 (3)	16 (18)
Objective response rate,[d] % (95% CI)[e]	51.1 (40.8 – 61.4)	20.9 (12.5 – 29.2)
Unstratified odds ratio (95% CI)	4.1 (2.1 – 7.8)	
p-value[f]	< 0.0001	
Disease control rate,[g] % (95% CI)[e]	93.3 (88.2 – 98.5)	80.2 (72.0 – 88.4)
Unstratified odds ratio (95% CI)	4.1 (1.5 – 11.7)	
p-value[f]	0.0064	
Time-to-treatment failure[h]		
Events, n (%)	89 (99)	91 (100)
Median time, months (95% CI)	4.2 (4.0 – 4.2)	3.8 (2.9 – 4.0)
Stratified log-rank p-value (2-sided)[a]	0.0006	
Stratified hazard ratio (95% CI)[a,b]	0.59 (0.43 – 0.80)	

	EGFR positive		EGFR negative	
	GC + N N = 69	GC N = 77	GC + N N = 18	GC N = 11
Overall survival				
p-value[i]	0.011		0.554	
Hazard ratio (95% CI)[j]	0.62 (0.43 – 0.90)		0.76 (0.31 – 1.87)	
Median, months	14.8	9.4	19.6	19.1
Interaction p-value[i]	0.677			
Progression-free survival				
p-value[i]	< 0.001		0.953	
Hazard ratio (95% CI)[k]	0.54 (0.38 – 0.76)		0.97 (0.42 – 2.28)	
Median, months	4.2	3.9	4.2	4.2
Interaction p-value[i]	0.191			
Objective response rate, n (%)	37 (53.6)	14 (18.2)	7 (38.9)	5 (45.5)
Odds ratio (95% CI)	5.2 (2.5 – 11.0)		0.8 (0.2 – 3.5)	
p-value[i]	< 0.001		0.728	

Median overall survival and survival rates were estimated using the Kaplan-Meier method. The hazard ratio was estimated using the unstratified Cox regression model and an unstratified log-rank test. p-values were stratified by Eastern Cooperative Oncology Group performance status at baseline (0 vs 1) and sex (females vs males) from the case report form. For the subgroup analysis by EGFR status, the p-value was determined using the likelihood ratio chi-square test of significance. CI, confidence intervals; EGFR, epidermal growth factor receptor; GC, gemcitabine and cisplatin; GC + N, gemcitabine and cisplatin plus necitumumab.

[a] Stratified by Eastern Cooperative Oncology Group performance status at baseline (0 vs 1) and sex (females vs males) from the case report form.

[b] Hazard ratio is expressed as GC + N/GC and estimated from the Cox model.

[c] Response criteria used was RECIST 1.1.

[d] Objective response rate was defined as the proportion of treated patients achieving a best response of partial response or complete response.

[e] Confidence intervals were based on the normal approximation.

[f] P-value was calculated by Fisher's exact test.

[g] Disease control rate was defined as the proportion of treated patients achieving a partial response, complete response, or stable disease.

[h] Time-to-treatment failure was defined as the time from the date of randomization until the date of the first observation of radiographically documented progressive disease, death due to any cause, discontinuation of treatment for any reason, or initiation of new anticancer therapy.

[i] P-value obtained from likelihood ratio chi-squared test of significance.

[j] Hazard ratio for death from any cause comparing GC + N to GC within protein expression subgroup. A hazard ratio greater than 1 indicates increasing hazards with GC + N compared to GC within EGFR status subgroup.

[k] Hazard ratio for death from any cause or progressive disease comparing GC + N to GC within protein expression subgroup. A hazard ratio greater than 1 indicates increasing hazards with GC + N compared to GC within EGFR status subgroup.

with at least 10% (any grade) higher incidence for GC + N versus GC, were dermatitis acneiform (80% vs 7%), decreased appetite (70% vs 53%), white blood cell count decreased (54% vs 43%), dry skin (53% vs 9%), paronychia (49% vs 0%), stomatitis (41% vs 12%), hypomagnesemia (39% vs 9%), dysgeusia (21% vs 10%), and epistaxis (13% vs 2%) (Supplementary Table 2).

Grade ≥3 TEAEs were reported at similar rates with GC + N and GC (74 [82%] vs 74 [81%]) (Supplementary Table 2). The incidence of grade 3 TEAEs was lower with GC + N compared with GC (53% vs 66%, respectively) whereas the incidence of grade 4 TEAEs was higher with GC + N compared with GC (29% vs 15%). There were no grade 5 TEAEs. The most commonly reported grade ≥3 TEAEs (overall), with a difference of ≥5% between GC + N and GC, were: neutrophil count decreased (42% vs 35%), febrile neutropenia (12% vs 3%), decreased appetite (11% vs 4%), and dermatitis acneiform (6% vs 0%).

Treatment-emergent adverse events of special interest (AESIs), defined on the basis of the known safety profiles of other EGFR antibodies and previous clinical experience with necitumumab, gemcitabine, and cisplatin, are shown in Table 3. Any-grade skin reactions (98% overall vs 43%), hypomagnesemia (39% overall vs 9%), conjunctivitis (10% overall vs 2%), arterial thromboembolic events (7% overall vs 2%), and venous thromboembolic events (6% overall vs 2%) were the most common AESIs observed more often in patients with GC + N than with GC.

No patients died in the phase 1b part; in the phase 2 part, no patients died while on treatment or within 30 days of treatment discontinuation due to an adverse event. The incidence of discontinuation due to TEAEs (any grade) was 12% with GC + N and 7% with GC. TEAEs that occurred in ≥2% of patients that led to study treatment discontinuation included interstitial lung disease, which led to necitumumab discontinuation with GC + N (2%, one case each of grade 1 and grade 3), and anemia, which led to gemcitabine discontinuation with GC (2%, one case each of grade 2 and grade 3).

4. Discussion

Addition of necitumumab to gemcitabine and cisplatin resulted in a clinically meaningful improvement in OS in the first-line treatment of stage IV squamous NSCLC patients in Japan. The treatment effect with the addition of necitumumab was supported by the improvement in PFS. The ORR and TTF were also improved. While each of these outcomes numerically exceeded those of the phase 3 SQUIRE study, the findings are consistent between the two studies [4].

The LCSS results showed that necitumumab plus gemcitabine and cisplatin lengthened the time to worsening of symptoms and QOL. The early divergence of the Kaplan-Meier plots at around 1 month for the LCSS total score supports the benefit of necitumumab in first-line treatment.

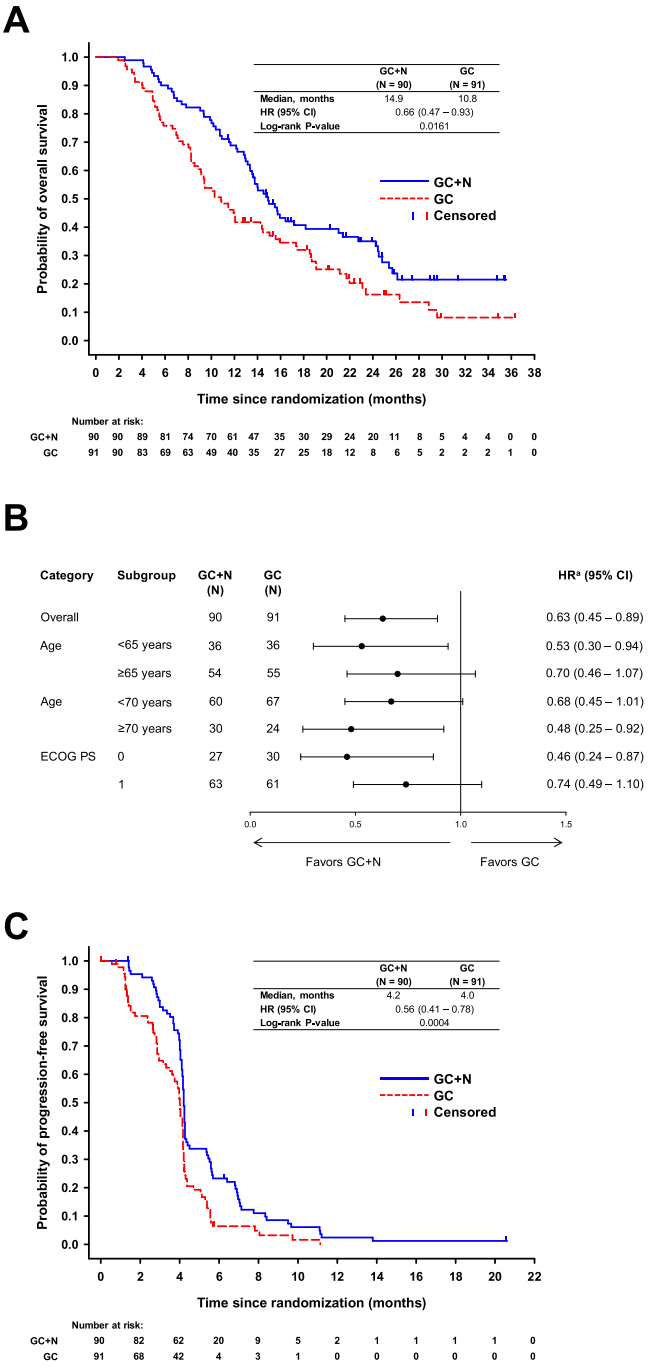

Fig. 1. Kaplan-Meier estimate of overall survival (A), forest plot of hazard ratio for overall survival subgroup analysis (B), and Kaplan-Meier estimate of progression-free survival (C). [a]Unstratified hazard ratio. CI, confidence intervals; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gemcitabine and cisplatin; GC + N, gemcitabine and cisplatin plus necitumumab; HR, hazard ratio.

The benefits for patients were achieved with an acceptable safety profile in Japan. The safety profile was consistent with that expected from the SQUIRE study [4], with skin reactions, hypomagnesemia, conjunctivitis, arterial thromboembolic events, and venous thromboembolic events being the most commonly reported TEAEs of special interest occurring at higher rates with GC + N. The incidence of febrile neutropenia was higher with GC + N compared with GC; however, there were no major differences between GC + N and GC in the incidence of serious infections (data not shown). Hypomagnesemia occurred at a higher incidence with GC + N compared with GC; however there were no clinically significant electrocardiogram findings in the phase 2 (data not shown).

The limitations of the study include the phase 1b/2 design and its limited sample size, which precluded confirmation of any potential benefits of the addition of necitumumab to gemcitabine and cisplatin. Some baseline characteristics in this study were different than those reported in the phase 3 SQUIRE study [4]; in particular, this study did not include patients with ECOG PS 2. Nonetheless, as the results of this study are similar to those of the phase 3 SQUIRE study, it is likely that the addition of necitumumab to gemcitabine and cisplatin may provide clinical benefit in Japanese patients with squamous NSCLC.

5. Conclusions

In conclusion, this study demonstrates a significant and clinically meaningful treatment benefit for necitumumab plus gemcitabine and cisplatin in the first-line treatment of patients with stage IV squamous NSCLC in Japan. This benefit was also observed in all predefined subgroups. Necitumumab plus gemcitabine and cisplatin is well tolerated. These data demonstrate a favorable benefit-risk profile for this combination treatment.

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Conflict of interest statement

Satoshi Watanabe reports non-financial support from Eli Lilly and Company during the conduct of the study, and personal fees from AstraZeneca, personal fees from Chugai Pharma, personal fees from Bristol-Myers Squibb, personal fees from Boehringer Ingelheim, personal fees from Ono Pharmaceutical, and personal fees from Taiho Pharmaceutical outside the submitted work; Hiroshige Yoshioka reports non-financial support from Eli Lilly and Company during the conduct of the study, and personal fees from Eli Lilly and Company, personal fees from Chugai Pharma, personal fees from Bristol-Myers Squibb, personal fees from Boehringer Ingelheim, personal fees from Ono Pharmaceutical, personal fees from Taiho Pharmaceutical, personal fees from Pfizer, personal fees from AstraZeneca, personal fees from Takeda, and personal fees from Merck Sharp & Dohme outside the submitted work; Hiroshi Sakai reports non-financial support from Eli Lilly and Company during the conduct of the study, and personal fees from Chugai Pharma, personal fees from Bristol-Myers Squibb, personal fees from Boehringer Ingelheim, personal fees from Ono Pharmaceutical, personal fees from Taiho Pharmaceutical, personal fees from Merck Sharp & Dohme, personal fees from AstraZeneca, and personal fees from Merck KGaA outside the submitted work; Katsuyuki Hotta reports non-financial support from Eli Lilly and Company during the conduct of the study, and personal fees from Chugai Pharma, personal fees from Bristol-Myers Squibb, personal fees from Boehringer Ingelheim, personal fees from Ono Pharmaceutical, personal fees from Taiho Pharmaceutical, personal fees from Merck Sharp & Dohme, personal fees from AstraZeneca, personal fees from Nippon Kayaku, personal fees from Novartis, personal fees from Eli Lilly and Company, and personal fees from Astellas Pharma outside the submitted work; Mitsuhiro Takenoyama reports non-financial support from Eli Lilly and Company during the conduct of the study, and personal fees from Chugai Pharma,

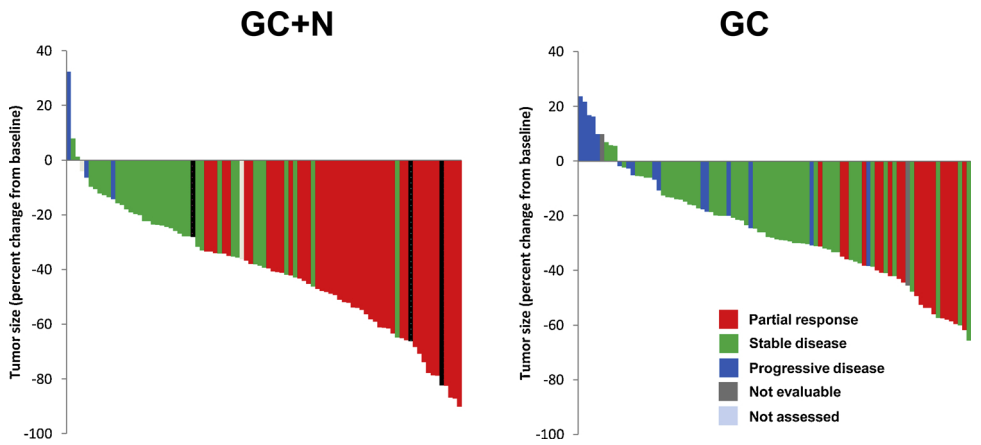

Fig. 2. Best percent change in tumor size. GC, gemcitabine and cisplatin; GC + N, gemcitabine and cisplatin plus necitumumab.

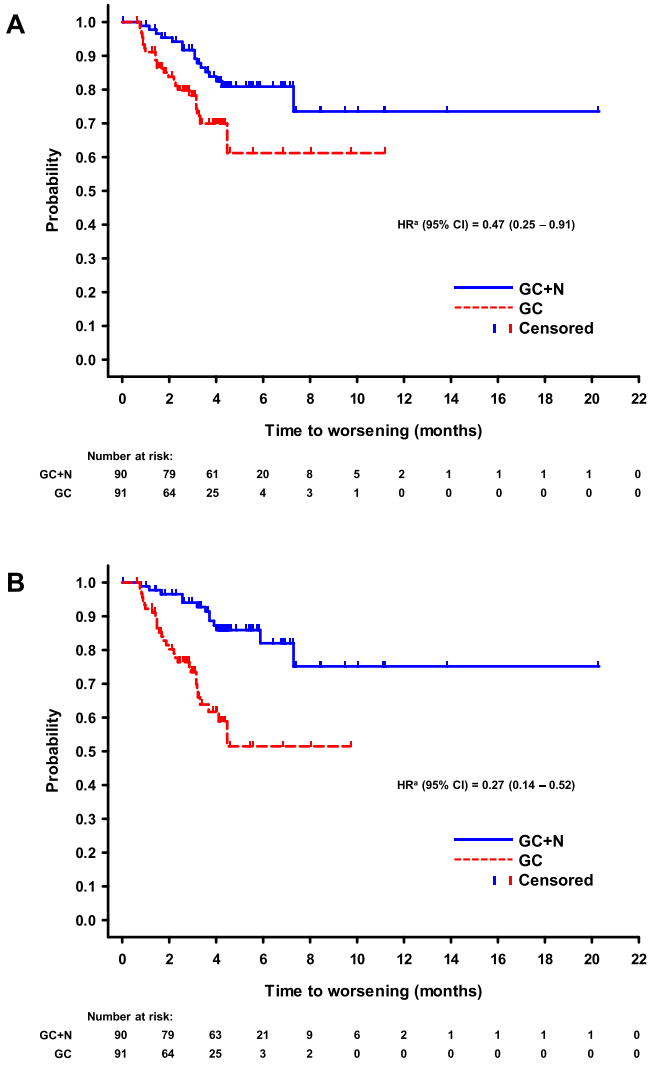

Fig. 3. Kaplan-Meier estimates of time to worsening based on (A) Average Symptom Burden Index and (B) Lung Cancer Symptom Scale total score. [a]Unstratified hazard ratio. CI, confidence intervals; GC, gemcitabine and cisplatin; GC + N, gemcitabine and cisplatin plus necitumumab; HR, hazard ratio.

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Table 3
Treatment-emergent adverse events of special interest and hematologic treatment-emergent adverse events.

	GC + N N = 90				GC N = 91	
	Overall		Chemotherapy phase		Overall	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
AESI, n (%)						
MedDRA preferred term						
Skin reactions	88 (98)	9 (10)	87 (97)	7 (8)	39 (43)	2 (2)
Dermatitis acneiform	72 (80)	5 (6)	72 (80)	5 (6)	6 (7)	0
Dry skin	48 (53)	0	47 (52)	0	8 (9)	0
Paronychia	44 (49)	4 (4)	36 (40)	2 (2)	0	0
Rash	10 (11)	0	7 (8)	0	7 (8)	0
Pruritus	8 (9)	0	7 (8)	0	3 (3)	0
PPES	6 (7)	0	6 (7)	0	0	0
Rash maculopapular	6 (7)	1 (1)	5 (6)	1 (1)	11 (12)	0
Skin fissures	5 (6)	0	4 (4)	0	0	0
Urticaria	4 (4)	0	3 (3)	0	6 (7)	1 (1)
Acne	3 (3)	0	2 (2)	0	0	0
Folliculitis	2 (2)	0	2 (2)	0	0	0
Rash pustular	2 (2)	0	1 (1)	0	0	0
Skin infection	2 (2)	0	1 (1)	0	4 (4)	0
Erythema	0	0	0	0	4 (4)	0
Hypomagnesemia	35 (39)	4 (4)	33 (37)	2 (2)	8 (9)	0
Hypomagnesemia	35 (39)	4 (4)	33 (37)	2 (2)	8 (9)	0
Conjunctivitis	9 (10)	0	8 (9)	0	2 (2)	0
Conjunctivitis	7 (8)	0	5 (6)	0	1 (1)	0
Arterial thromboembolic events	6 (7)	1 (1)	6 (7)	1 (1)	2 (2)	0
Embolism	4 (4)	1 (1)	4 (4)	1 (1)	1 (1)	0
Venous thromboembolic events	5 (6)	2 (2)	5 (6)	2 (2)	2 (2)	1 (1)
Deep vein thrombosis	2 (2)	0	2 (2)	0	1 (1)	0
Hypersensitivity/IRR	4 (4)	1 (1)	4 (4)	1 (1)	4 (4)	0
IRR	3 (3)	1 (1)	3 (3)	1 (1)	3 (3)	0
Interstitial lung disease	3 (3)	1 (1)	0	0	0	0
Interstitial lung disease	2 (2)	1 (1)	0	0	0	0
Hematologic TEAEs, n (%)						
MedDRA preferred term						
Neutropenia	13 (14)	7 (8)	10 (11)	3 (3)	13 (14)	8 (9)
Neutrophil count decreased	53 (59)	38 (42)	49 (54)	32 (36)	45 (49)	32 (35)
Thrombocytopenia	3 (3)	2 (2)	3 (3)	2 (2)	7 (8)	2 (2)
Platelet count decreased	49 (54)	18 (20)	48 (53)	18 (20)	46 (51)	21 (23)
Anemia	43 (48)	17 (19)	42 (47)	14 (16)	53 (58)	20 (22)

AESIs of any grade in at least two patients in the overall phase are presented in order of any grade incidence in the GC + N group. There were no grade 5 adverse events in either treatment group. Adverse events were graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0. The chemotherapy phase was defined as the period of time during which patients received chemotherapy in the GC + N group. AESI, adverse event of special interest; GC, gemcitabine and cisplatin; GC + N, gemcitabine and cisplatin plus necitumumab; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; PPES, palmar-plantar erythrodysesthesia syndrome; TEAEs, treatment-emergent adverse events.

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Appendix A. Supplementary data

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