ORIGINAL ARTICLE

Multicenter, Retrospective Study to Evaluate Necitumumab Plus Cisplatin and Gemcitabine After Immune Checkpoint Inhibitors in Advanced Squamous Cell Lung Cancer in Japan: The NINJA Study

*Corresponding author.

Drs. Murata and Tanzawa contributed equally to this work.

Disclosure: Dr. Tanzawa reports receiving research grants from AstraZeneca and Nippon Kayaku; and honoraria from AstraZeneca and Chugai Pharmaceutical. Dr. Misumi reports receiving honoraria from Chugai Pharmaceutical and AstraZeneca. Dr. Yoshioka reports receiving research grants from Daiichi Sankyo, AstraZeneca, Janssen Pharmaceutical, Merck Sharp & Dohme, Novartis, Delta Fly Pharma, and Boehringer Ingelheim; receives consulting fees from Delta Fly Pharma; and receives honoraria from Eli Lilly, Chugai Pharmaceutical, Merck Sharp & Dohme, AstraZeneca, Boehringer Ingelheim, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol Myers Squibb, Novartis, Kyowa Kirin, Nippon Kayaku, Otsuka Pharmaceutical, Amgen, Pfizer, NIPRO Pharma, and Daiichi Sankyo. Dr. Miyauchi reports receiving research grants from Chugai Pharmaceutical, Eli Lilly; receives honoraria from Taiho Pharmaceutical, Daiichi Sankyo, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Merck Sharp & Dohme, Kyowa Kirin, Merck, Pfizer, Ono Pharmaceutical, Eisai, Otsuka Pharmaceutical, Chugai Pharmaceutical, Amgen, ThermoFisher Scientific, Nippon Kayaku, Takeda Pharmaceutical, Eli Lilly, and Sysmex; and reports participation on the Advisory Board of Chugai Pharmaceutical, Boehringer Ingelheim, Eli Lilly, Merck, Daiichi Sankyo, and Ono Pharmaceutical. Dr. Ninomiya reports receiving honoraria from AstraZeneca, Boehringer Ingelheim, Kyowa Kirin, Eli Lilly, Chugai Pharmaceutical, Nippon Kayaku, Taiho Pharmaceutical, Merck Sharp & Dohme, Ono Pharmaceutical, Novartis, Takeda Pharmaceutical, Pfizer, Bristol Myers Squibb, and Elekta. Dr. Takeshita reports receiving honoraria from Taiho Pharmaceutical, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Merck Sharp & Dohme, Kyowa Kirin, Ono Pharmaceutical, Chugai Pharmaceutical, Nippon Kayaku, Takeda Pharmaceutical, and Eli Lilly. Dr. Okamoto reports receiving research grants from AnHeart Therapeutics, AstraZeneca, Bristol Myers Squibb, Chugai Pharmaceutical, Covidien, Daiichi Sankyo, KM Biologics, Merck, Merck Sharp & Dohme, Boehringer Ingelheim, Nippon Kayaku, Ono Pharmaceutical, Pfizer, and Taiho Pharmaceutical; and receives honoraria from Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly, Johnson & Johnson, Merck Sharp & Dohme, Boehringer Ingelheim, Nippon Kayaku, Novartis, Ono Pharmaceutical, Pfizer, Shionogi, Taiho Pharmaceutical, Takeda Pharmaceutical, and Towa Pharmaceutical. Dr. Sugawara reports receiving research grants from AnHeart Therapeutics, AstraZeneca, Chugai Pharmaceutical, Merck Sharp & Dohme, Daiichi Sankyo, Bristol Myers Squibb, Boehringer Ingelheim, Ono Pharmaceutical, AbbVie, Amgen, Taiho Pharmaceutical, Takeda Pharmaceutical, and Clinipace; and receives honoraria from AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol Myers Squibb, Merck Sharp & Dohme, Boehringer Ingelheim, Pfizer, Taiho Pharmaceutical, Eli Lilly, Novartis, Kyowa Kirin, Takeda Pharmaceutical, Nippon Kayaku, Merck, Amgen, AbbVie, Otsuka Pharmaceutical, Thermo Fisher Scientific, and Towa Pharmaceutical. Dr. Kawashima reports receiving honoraria from AstraZeneca, Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, Kyowa Kirin, and Life Technologies Japan. Dr. Hashimoto reports receiving honoraria from AstraZeneca, Nippon Kayaku, and Boehringer Ingelheim. Dr. Mori reports receiving honoraria from AstraZeneca, Chugai Pharmaceutical, Eli Lilly, Merck Sharp & Dohme, Novartis, Otsuka Pharmaceutical, Taiho Pharmaceutical, Shionogi, Boehringer Ingelheim, Daiichi Sankyo, Kyowa Kirin, Nippon Kayaku, Ono Pharmaceutical, Pfizer, and Takeda Pharmaceutical. Dr. Miyanaga reports receiving honoraria from AstraZeneca, Nippon Kayaku, Merck, Kyowa Kirin, and Pfizer. Dr. Hisashi Tanaka reports receiving honoraria from Ono Pharmaceutical, Bristol Myers Squibb, AstraZeneca, Chugai Pharmaceutical, Boehringer Ingelheim, Pfizer, and Eli Lilly. Dr. Sato reports receiving honoraria from AstraZeneca, Merck Sharp & Dohme, Novartis, Chugai Pharmaceutical, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical, Nippon Kayaku, Bristol Myers Squibb, Eli Lilly, Takeda Pharmaceutical, and Kyowa Kirin. Dr. Hata reports receiving research grants from Merck Sharp & Dohme, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Taiho Pharmaceutical, and Chugai Pharmaceutical; and receives honoraria from Eli Lilly, Chugai Pharmaceutical, Pfizer, AstraZeneca, Boehringer Ingelheim, Taiho Pharmaceutical, and Merck Sharp & Dohme. Dr. Kozuki reports receiving research grants from Chugai Pharmaceutical, AstraZeneca, Eli Lilly, Taiho Pharmaceutical, Bristol Myers Squibb, Ono Pharmaceutical, Merck Sharp & Dohme, Kyowa Kirin, Merck, Daiichi Sankyo, Amgen, AbbVie, Sanofi, Eisai, Labcorp Development, IQVIA, Gilead Sciences, Pfizer, and Bayer; receives consulting fees from Chugai Pharmaceutical, AstraZeneca, Ono Pharmaceutical, Pfizer, Daiichi Sankyo, Bayer, and AbbVie; and receiving honoraria from Chugai Pharmaceutical, AstraZeneca, Eli Lilly, Taiho Pharmaceutical, Bristol Myers Squibb, Ono Pharmaceutical, Merck Sharp & Dohme, Pfizer, Kyowa Kirin, Boehringer Ingelheim, Merck, Nippon Kayaku, Novartis, Daiichi Sankyo, Takeda Pharmaceutical, Bayer, Sawai, and Amgen. Dr. Kawamura reports receiving honoraria from AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol Myers Squibb, and Nippon Kayaku. Dr. Suzuki reports receiving honoraria from Boehringer Ingelheim and AstraZeneca. Dr. T. Yamaguchi reports receiving honoraria from Ono Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, Merck Sharp & Dohme, Bristol Meyers Squibb, and Nippon Kayaku. Dr. Hiroshi Tanaka reports receiving research grants from AstraZeneca, Chugai Pharmaceutical, Merck Sharp & Dohme, Ono Pharmaceutical, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Takeda Pharmaceutical, Taiho Pharmaceutical, Merk, Boehringer Ingelheim, Amgen, and AbbVie; and received honoraria from AstraZeneca, Chugai Pharmaceutical, Merck Sharp & Dohme, Ono Pharmaceutical, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Takeda Pharmaceutical, Taiho Pharmaceutical, Merk, Boehringer Ingelheim, Sun Pharmaceutical, Eisai, and Novartis. Dr. S. Watanabe reports receiving research grants from Boehringer Ingelheim and Nippon Kayaku; and received honoraria from Eli Lilly, Chugai Pharmaceutical, Ono Pharmaceutical, Taiho Pharmaceutical, Kyowa Kirin, Takeda Pharmaceutical, Novartis, Bristol Myers Squibb, Daiichi Sankyo, Nippon Kayaku, Merk, and Celltrion. Dr. Kuyama reports receiving honoraria from Daiichi Sankyo, Chugai Pharmaceutical, Bristol Myers Squibb, Eli Lilly, Hisamitsu, Boehringer Ingelheim, AstraZeneca, Pfizer, and Taiho Pharmaceutical. Dr. Y. Misumi reports receiving research grants from BeiGene, Eli Lilly, AstraZeneca, AbbVie, Ono Pharmaceutical, Taiho Pharmaceutical, Nippon Kayakui, Novartis, Boehringer Ingelheim, Nobel Pharma, and Bristol Myers Squibb; and received honoraria from AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, Taiho Pharmaceutical, and Nippon Kayaku. Dr. K. Watanabe reports receiving a research grant from Merck Sharp & Dohme. Dr. Seki reports receiving research grants from Eli Lilly, Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer, Ono Pharmaceutical, Nippon Kayaku, Takeda Pharmaceutical, and Boehringer Ingelheim; and received honoraria from Eli Lilly, AstraZeneca, Merck Sharp & Dohme, Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer, Ono Pharmaceutical, Nippon Kayaku, Takeda Pharmaceutical, Daiichi Sankyo, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, and Merck. The remaining authors declare no conflict of interest.

Address for correspondence: Nobuhiko Seki, MD, PhD, Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8606, Japan. E-mail: nseki@med.teikyo-u.ac.jp

Cite this article as: Murata Y, Tanzawa S, Misumi T, et al. Multicenter, retrospective study to evaluate necitumumab plus cisplatin and gemcitabine after immune checkpoint inhibitors in advanced squamous cell lung cancer in Japan: The NINJA study. *JTO Clin Res Rep*. 2023;4:100593.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2023.100593

Yasunori Murata, MD, PhD,[a] Shigeru Tanzawa, MD, PhD,[b] Toshihiro Misumi, PhD,[c] Hiroshige Yoshioka, MD, PhD,[d] Eisaku Miyauchi, MD, PhD,[e] Kiichiro Ninomiya, MD, PhD,[f] Masafumi Takeshita, MD, PhD,[a] Kensaku Ito, MD, PhD,[g] Tatsuro Okamoto, MD, PhD,[g] Shunichi Sugawara, MD, PhD,[h] Yosuke Kawashima, MD,[h] Kazuki Hashimoto, MD,[i] Masahide Mori, MD, PhD,[i] Akihiko Miyanaga, MD, PhD,[j] Anna Hayashi, MD,[j] Hisashi Tanaka, MD, PhD,[k] Ryoichi Honda, MD, PhD,[l] Masafumi Nojiri, MD, PhD,[m] Yuki Sato, MD,[n] Akito Hata, MD,[o] Ken Masuda, MD, PhD,[p] Toshiyuki Kozuki, MD, PhD,[q] Takahisa Kawamura, MD, PhD,[r] Takuji Suzuki, MD, PhD,[s] Teppei Yamaguchi, MD, PhD,[t] Kazuhiro Asada, MD, PhD,[u] Satoshi Tetsumoto, MD, PhD,[v] Hiroshi Tanaka, MD, PhD,[w] Satoshi Watanabe, MD, PhD,[x] Yukihiro Umeda, MD, PhD,[y] Kakuhiro Yamaguchi, MD, PhD,[z] Shoichi Kuyama, MD, PhD,[aa] Kosuke Tsuruno, MD, PhD,[bb] Yuki Misumi, MD, PhD,[cc] Hiroshi Kuraishi, MD, PhD,[dd] Ken Yoshihara, MD, PhD,[ee] Akira Nakao, MD, PhD,[ff] Akihito Kubo, MD, PhD,[gg] Toshihiko Yokoyama, MD, PhD,[hh] Kana Watanabe, MD, PhD,[ii] Nobuhiko Seki, MD, PhD[b,*]

[a]*Department of Respiratory Medicine, Ichinomiya Nishi Hospital, Aichi, Japan*
[b]*Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan*
[c]*Department of Data Science, National Cancer Center Hospital East, Chiba, Japan*
[d]*Department of Thoracic Oncology, Kansai Medical University Hospital, Osaka, Japan*
[e]*Department of Respiratory Medicine, Tohoku University Hospital, Miyagi, Japan*
[f]*Center for Comprehensive Genomic Medicine, Okayama University Hospital, Okayama, Japan*
[g]*Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan*
[h]*Department of Pulmonary Medicine, Sendai Kousei Hospital, Miyagi, Japan*
[i]*Department of Thoracic Oncology, National Hospital Organization Osaka Toneyama Medical Center, Osaka, Japan*
[j]*Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan*
[k]*Department of Respiratory Medicine, Hirosaki University Graduate School of Medicine, Aomori, Japan*
[l]*Department of Respiratory Medicine, Asahi General Hospital, Chiba, Japan*
[m]*Department of Respiratory Medicine, Kanazawa Medical University, Ishikawa, Japan*
[n]*Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Hyogo, Japan*
[o]*Division of Thoracic Oncology, Kobe Minimally Invasive Cancer Center, Hyogo, Japan*
[p]*Department of Respiratory Medicine, Hiroshima Prefectural Hospital, Hiroshima, Japan*
[q]*Department of Thoracic Oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Ehime, Japan*
[r]*Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan*
[s]*Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan*
[t]*Department of Thoracic Oncology, Aichi Cancer Center Hospital, Aichi, Japan*
[u]*Department of Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan*
[v]*Department of Respiratory Medicine and Clinical Immunology, Suita Municipal Hospital, Osaka, Japan*
[w]*Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan*
[x]*Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*
[y]*Third Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui, Fukui, Japan*
[z]*Department of Respiratory Medicine, Hiroshima University Hospital, Hiroshima, Japan*
[aa]*Department of Respiratory Medicine, National Hospital Organization Iwakuni Clinical Center, Yamaguchi, Japan*
[bb]*Department of Respiratory Medicine, Iizuka Hospital, Fukuoka, Japan*
[cc]*Department of Respiratory Medicine, Yokohama Municipal Citizen's Hospital, Kanagawa, Japan*
[dd]*Department of Pulmonary Medicine, Nagano Red Cross Hospital, Nagano, Japan*
[ee]*Department of Internal Medicine, Division of Medical Oncology and Respiratory Medicine, Shimane University Faculty of Medicine, Shimane, Japan*
[ff]*Department of Respiratory Medicine, Fukuoka University Hospital, Fukuoka, Japan*
[gg]*Department of Respiratory Medicine and Allergology, Aichi Medical University, Aichi, Japan*
[hh]*Department of Respiratory Medicine, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Aichi, Japan*
[ii]*Department of Respiratory Medicine, Miyagi Cancer Center, Miyagi, Japan*

Received 28 June 2023; revised 5 October 2023; accepted 14 October 2023
Available online - 20 October 2023

ABSTRACT

Introduction: Necitumumab plus gemcitabine and cisplatin (GCN) is a standard therapy for patients with advanced lung squamous cell carcinoma (LSqCC). However, the efficacy and tolerability of GCN in second-line or later treatment for patients previously treated with immune checkpoint inhibitors (ICIs) remain unknown.

Methods: This multicenter, retrospective, cohort study assessed the efficacy and tolerability of GCN initiated between November 1, 2019 and March 31, 2022 as second-line to fourth-line treatment in patients with advanced LSqCC who had been pretreated with ICIs. The primary end point was progression-free survival (PFS).

Results: A total of 93 patients from 35 institutions in Japan were enrolled. The median PFS, median overall survival (OS), and objective response rate were 4.4 months (95% confidence interval [CI]: 3.8–5.3), 13.3 months (95% CI: 9.6–16.5), and 27.3% (95% CI: 18.3–37.8), respectively. The median PFS, median OS, and objective response rate for second-line, third-line, and fourth-line treatment groups were 4.8 months, 3.8 months, and 4.3 months ($p = 0.24$); 15.7 months, 11.6 months, and 10.1 months ($p = 0.06$); and 31.0%, 13.6%, and 37.5% ($p = 0.22$), respectively. The severity of GCN-related skin disorders was associated with longer PFS ($p < 0.05$) and OS ($p < 0.05$). The frequencies of grade $\geq$3 skin disorders, hypomagnesemia, pneumonitis, and febrile neutropenia were 16.1%, 7.5%, 1.1%, and 4.3%, respectively. There were no treatment-related deaths.

Conclusions: GCN for ICI-pretreated patients with LSqCC seems tolerable and offers promising efficacy regardless of treatment line, and ICI pretreatment might enhance GCN efficacy.

Keywords: Necitumumab; Immune checkpoint inhibitor; Platinum rechallenge; Skin disorder; Lung squamous cell carcinoma

Introduction

Necitumumab is an anti–immunoglobulin G1 monoclonal antibody against EGFR that is approved in the United States and Japan for the treatment of patients with advanced lung squamous cell carcinoma (LSqCC) as the first anti-EGFR antibody drug in the field of lung cancer. Necitumumab inhibits the growth of tumors by binding to EGFR with high affinity and blocking signal transmission by means of EGFR.[1]

The international phase 3 SQUIRE study was conducted to exhibit the superiority, in terms of overall survival (OS), of the gemcitabine and cisplatin (GC) plus necitumumab (GCN) group compared with the GC group of patients with untreated advanced LSqCC, for whom GC had been considered standard therapy. The results revealed that the primary end point of OS was significantly longer in the GCN group than in the GC group (11.5 versus 9.9 mo; hazard ratio [HR] = 0.84, 95% confidence interval [CI]: 0.74–0.96], $p = 0.01$).[2] In Japan, the phase 1b/2 JFCM study also investigated the efficacy and safety of GCN for patients with untreated advanced LSqCC. As in the SQUIRE study, the primary end point of OS was significantly longer in the GCN group than in the GC group (14.9 versus 10.8 mo; HR = 0.66, 95% CI: 0.47–0.93, $p = 0.02$).[3] On the basis of these results, GCN has become one of the standard regimens for patients with advanced LSqCC.

However, the efficacy and tolerability of GCN have not been exhibited in patients previously treated with immune checkpoint inhibitors (ICIs). Moreover, the efficacy and tolerability of GCN in patients previously treated with platinum-based chemotherapy are also unclear.

Therefore, a multicenter, retrospective, cohort study was conducted using real-world data in Japan to assess the efficacy and tolerability of GCN as second-line or later treatment for patients with LSqCC previously treated with ICIs.

This study is abbreviated the NINJA study (Multicenter Retrospective Study to Evaluate Necitumumab plus cisplatin and gemcitabine after immune checkpoint inhibitors in advanced squamous cell lung cancer in Japan).

Materials and Methods

Study Design

The NINJA study was designed as a multicenter, noninterventional, retrospective, cohort study. The purpose of this study was to evaluate the efficacy and tolerability of GCN in second-line or later treatment for patients with LSqCC previously treated with ICIs.

Patient Eligibility

The eligibility criteria were as follows: (1) pathologic diagnosis of squamous cell lung cancer; (2) patient aged 20 years or older at the initiation of GCN; (3) postoperative recurrence (regardless of the time to recurrence), recurrence after radical therapy for locally advanced cancer (regardless of the time to recurrence), or advanced stage cancer; (4) GCN was initiated between November 1, 2019 and March 31, 2022; (5) previous ICI treatment (ICI monotherapy, combination therapy with

different ICIs, or platinum-doublet chemotherapy plus ICIs); and (6) GCN was initiated in second to fourth-line treatment.

In the postoperative recurrent population, the initial treatment after confirmation of recurrence was defined as the first-line treatment regardless of the presence of perioperative chemotherapy, in which ICI treatment had not been approved in Japan. In the stage III population, the initial treatment after confirmation of recurrence from radical treatment including ICI was defined as second-line treatment.

Treatment Delivery

Chemotherapy comprised a maximum of four 3-week cycles of gemcitabine 1250 mg/m^2 administered intravenously on days 1 and 8, and cisplatin 75 mg/m^2 administered on day 1. Necitumumab at an absolute dose of 800 mg was given intravenously on days 1 and 8 before gemcitabine was administered. After the end of chemotherapy, patients who were free of disease progression continued to receive single-agent necitumumab on the same treatment schedule until radiographic documentation of disease progression, the occurrence of toxic effects necessitating cessation. Dose modifications of chemotherapy and necitumumab were in line with the SQUIRE study, as follows: (1) the first dose reduction to gemcitabine at 950 mg/m^2, cisplatin at 56 mg/m^2, necitumumab at 600 mg; and (2) the second dose reduction to gemcitabine at 625 mg/m^2, cisplatin at 38 mg/m^2, and necitumumab at 400 mg. These dosages and schedules were modified at the discretion of the physician.

End points and Assessments

The primary end point was progression-free survival (PFS). The secondary end points were OS, time to treatment failure (TTF), objective response rate (ORR), disease control rate (DCR), maximum shrinkage of the target lesion, tolerability, and associations between the efficacy of GCN and various factors, including the severity of skin disorders because of GCN (acneiform rash, dry skin, paronychia, and other skin disorders), GCN treatment line, disease stage, programmed death-ligand 1 (PD-L1) expression. Furthermore, associations between the efficacy of GCN and platinum-free interval (PFI) and the best response of anticancer therapies administered immediately before GCN were analyzed as exploratory analysis.

PFS was defined as the time from the first dose of GCN to the first radiographic documentation of objective progression or death from any cause. OS was defined as the time from the first dose of GCN to death from any cause. TTF was defined as the time from the first dose of GCN to the date of the first radiographic documentation of progressive disease (PD), death by any cause, discontinuation of treatment for any reasons, or initiation of new anticancer therapy. ORR was defined as the proportion of patients with a best response of complete response (CR) or partial response (PR). DCR was defined as the proportion of patients with a best response of CR, PR, or stable disease. PFI was defined as the time from the last dose of platinum chemotherapy to the initiation of GCN.

Antitumor efficacy including ORR, DCR, and tumor shrinkage were determined by the investigators at each institution with reference to the Response Evaluation Criteria in Solid Tumors version 1.1 As a retrospective study, the timing of end point evaluation was not specified in the protocol and was determined by the physician.

The clinical data extracted according to the protocol were all obtained from the medical records of each institution by the prespecified case report form. Necitumumab-related adverse events specified in advance were venous thromboembolism, arterial thromboembolism, infusion-related reaction, hypomagnesemia, pneumonitis (interstitial lung disease), skin disorders, and bleeding. Tolerability was assessed by clinical and laboratory events in accordance with Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

The intention-to-treat (ITT) population was defined as the patients who received one or more of three drugs in the first cycle of GCN. The efficacy analysis was performed in the patients who received all three drugs on day 1 in the first cycle of GCN. The safety analysis was performed in the ITT population.

For the ORR and DCR, point estimates were calculated, and exact 95% CIs were calculated on the basis of a binomial distribution. Fisher's exact test was used to compare groups.

PFS, OS, and TTF were estimated using Kaplan-Meier methods to obtain median survival time. The 95% CIs were calculated using the Brookmeyer-Crowley method. Log-rank testing was used to compare groups.

The two-tailed significance level was 5%. The analysis was carried out using Statistical Analysis System version 9.4 (SAS Institute Inc., Cary, NC).

Ethics

This study was approved by the Teikyo University ethics review board (approval no. 22-002; UMIN000048656). The study was conducted in accordance with ethical principles on the basis of the

Table 1. Patient Characteristics

Characteristic	N = 93
Age, y, *n* (%)	
Median (range)	68 (36-78)
<75	85 (91.4)
≥75	8 (8.6)
Sex, *n* (%)	
Male	78 (83.9)
Female	15 (16.1)
ECOG performance status, *n* (%)	
0	27 (29.0)
1	64 (68.8)
2	2 (2.2)
3/4	0 (0)
Smoking history, *n* (%)	
Ever-smoker	89 (95.7)
Never smoker	4 (4.3)
History of thrombosis, *n* (%)	
Yes	5 (5.4)
No	88 (94.6)
History of pneumonitis (interstitial lung disease), *n* (%)	
Yes	13 (14.0)
No	80 (86.0)
Tumor histologic type, *n* (%)	
Squamous cell carcinoma	93 (100.0)
Disease stage, *n* (%)	
Postoperative recurrence	5 (5.4)
III	48 (51.6)
IV	40 (43.0)
PD-L1 status, *n* (%)	
≥50%	22 (23.6)
1%-49 %	37 (39.8)
<1%	21 (22.6)
Unknown	13 (14.0)
Treatment line of GCN therapy, *n* (%)	
Second-line	62 (66.7)
Third-line	23 (24.7)
Fourth-line	8 (8.6)

Strategies using frontline immunotherapy		Interval between the last dose of ICIs to the first dose of GCN (days)	
		(median)	(range)
Postoperative recurrence	5 (5.4)	55	(22-134)
Chemoradiotherapy followed by ICI	1 (1.1)	22	(22)
Chemotherapy + ICI	2 (2.1)	104	(74-134)
ICI + ICI	1 (1.1)	35	(35)
ICI monotherapy	1 (1.1)	55	(55)
Stage III	48 (51.6)	57	(19-478)
Chemoradiotherapy followed by ICI	35 (37.6)	74	(19-478)
Chemoradiotherapy with concurrent ICI	3 (3.2)	51	(30-100)
Radiotherapy with concurrent ICI	1 (1.1)	295	(295)
Chemotherapy + ICI	5 (5.4)	38	(19-75)
ICI + ICI	1 (1.1)	40	(40)
ICI monotherapy	3 (3.2)	36	(34-42)
Stage IV	40 (43.0)	46	(14-877)
Chemotherapy + ICI	26 (28.0)	57	(14-877)
ICI + ICI	3 (3.2)	28	(28-143)
ICI monotherapy	11 (11.8)	29	(19-99)

ECOG, Eastern Cooperative Oncology Group; GCN, gemcitabine + cisplatin + necitumumab; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1.

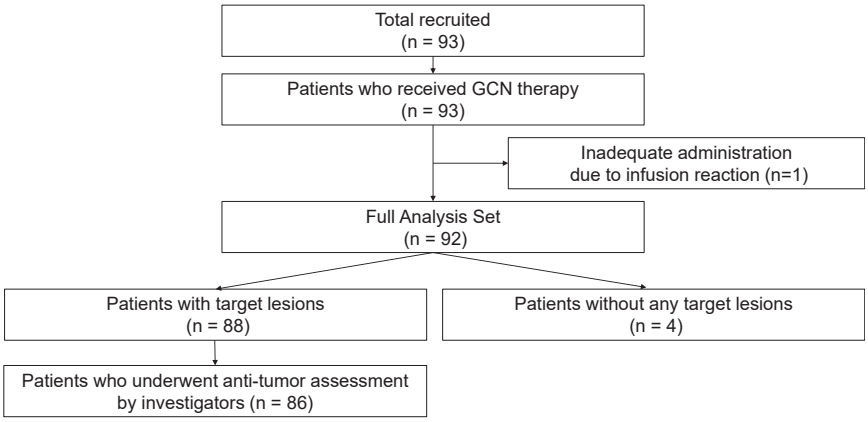

Figure 1. Patient recruitment and follow-up flow diagram. GCN, gemcitabine and cisplatin plus necitumumab.

Declaration of Helsinki and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects, and in compliance with the study protocol. An opt-out method was used to provide explanations to the patients and obtain consent, in which the study content was disclosed by a method prescribed by each participating institution.

Results

Patient Characteristics

A total of 93 patients from 35 institutions in Japan were enrolled, whose characteristics are presented in Table 1. The median age was 68 years, with most patients younger than 75 years old (91.4%). Almost all patients (97.8%) had performance status 0 or 1. Five patients had a history of thromboembolism, and 13 patients had a history of pneumonitis (11 patients with radiation pneumonitis after chemoradiotherapy and two patients with idiopathic pulmonary fibrosis). All patients in stage III received radical radiotherapy. GCN was initiated as second-line, third-line, or fourth-line treatment in 66.7%, 24.7%, and 8.6% of patients, respectively.

The flow diagram for patient recruitment and follow-up is illustrated in Figure 1. All patients received one or more cycles of GCN. One patient discontinued GCN because of grade 4 infusion-related reactions that occurred immediately after the initiation of necitumumab followed by the scheduled administration of cisplatin and gemcitabine in the first cycle on day 1. This patient, therefore, was included only in the safety analysis, not in the full analysis set. PFS, OS, and TTF were, thus, investigated in 92 patients. Antitumor efficacy was analyzed in 88 patients with target lesions. A waterfall plot including 86 patients in whom antitumor efficacy had been assessed on radiographic imaging was analyzed. Safety analysis was conducted for all 93 patients.

Treatment regimens administered immediately before initiating GCN are illustrated in Supplementary Table 1. ICIs and platinum-based chemotherapies were used immediately before GCN in 77 patients (82.8%) and in 62 patients (66.7%), respectively.

Treatment Delivery

In the first cycle of GCN, the median doses of cisplatin, gemcitabine, and necitumumab were 75 mg/m^2 (range: 0–80 mg/m^2), 1250 mg/m^2 (range: 0–1250 mg/m^2), and 800 mg/body (range: 800–800 mg/body), respectively. Reduced doses of cisplatin and gemcitabine were administered at the initiation of the first cycle in 12.9% (12/93) and 36.6% (34/93) of patients, respectively. Four cycles of GCN as induction therapy were completed in 59.1% (55/93), whereas necitumumab maintenance therapy was initiated in 48.4% (45/93). The median number of cycles administered as maintenance therapy was 3 (range: 1–10).

Efficacy

As of the data cutoff for this analysis (June 30, 2022), 87.0% (80 of 92) of patients who received GCN had disease progression, and 53.3% (49 of 92) of patients died. The median duration of follow-up was 8.8 months (range: 1.3–27.6). The median PFS was 4.4 months (95% CI: 3.8–5.3) (Fig. 2*A*). The median OS was 13.3 months (95% CI: 9.6–16.5), and the median TTF was 4.0 months (95% CI: 2.8–4.6) (Fig. 2*B* and Supplementary Fig. 1).

The results of efficacy analyses for each GCN treatment line are illustrated in Supplementary Figure 2. The median PFS in the second-line, third-line, and fourth-line treatment groups were 4.8, 3.8, and 4.3 months, respectively ($p = 0.24$). Similarly, the median OS in the three groups were 15.7, 11.6, and 10.1 months, respectively ($p = 0.06$).

Antitumor efficacy is presented in Table 2. The ORR was 27.3% (95% CI: 18.3–37.8), and the DCR was 88.6%

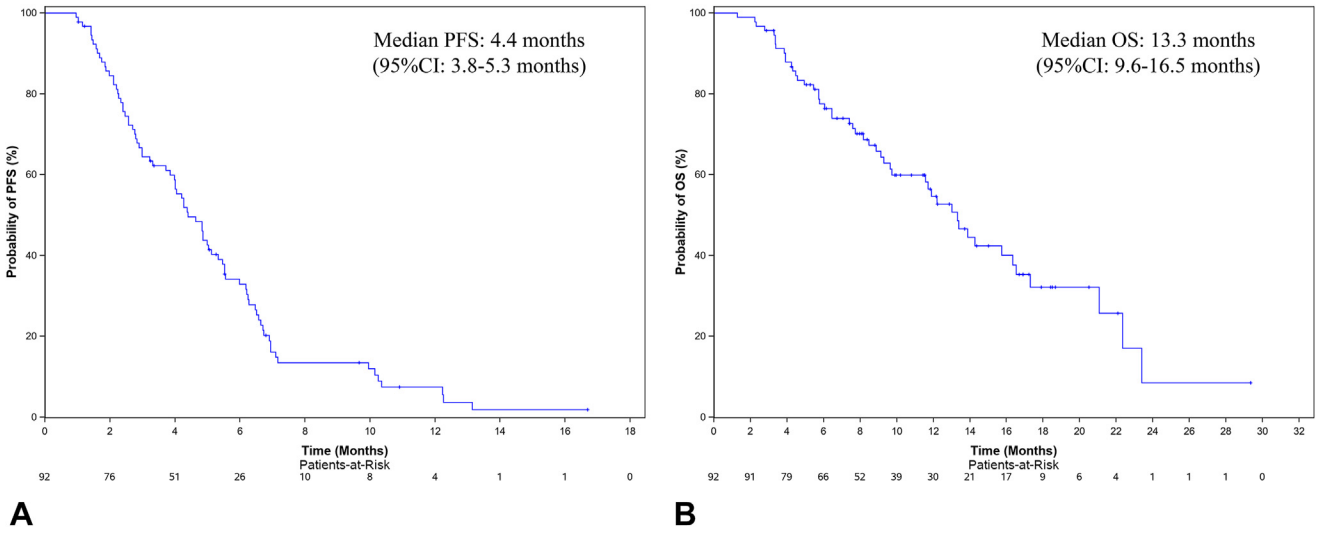

Figure 2. The Kaplan-Meier curves of PFS (*A*) and OS (*B*) in the full analysis set. PFS, progression-free survival; OS, overall survival; CI, confidence interval.

(95% CI: 80.1–94.4). Furthermore, the ORR in the three groups were 31.0% (95% CI: 19.5–44.5), 13.6% (95% CI: 2.9–34.9), and 37.5% (95% CI: 8.5–75.5), respectively ($p = 0.22$). The waterfall plot is illustrated in Supplementary Figure 3. The median best shrinkage rate was −13.0% (range: −88.3 to 193.3).

Results of the relationship between the severity of GCN-related skin disorders and efficacy are illustrated in Figure 3. The median PFS in grade 0, 1, 2, and 3 skin disorder subgroups were 2.3, 4.0, 5.0, and 5.5 months, respectively, indicating that the severity of GCN-related skin disorders associated with prolonged PFS (grade 0 subgroup versus grade 3 subgroup, $p < 0.05$) (Fig. 3*A*). Similarly, the median OS were 4.6, 12.2, 13.9, and 22.3 months, respectively, indicating the same tendency, as in Figure 3*A* (grade 0 subgroup versus grade 3 subgroup, $p < 0.05$) (Fig. 3*B*).

The results of GCN efficacy in each stage are illustrated in Supplementary Figure 4. The median PFS in the postoperative recurrence, stage III, and stage IV subgroups were 6.2, 4.6, and 4.2 months, respectively ($p = 0.51$). The median OS was not evaluable in the postoperative recurrence group (which have no events), 13.3 months in the stage III group, and 11.9 months in the stage IV group ($p = 0.31$).

Table 2. Antitumor Efficacy

	N = 88[a]							
Variables	All N = 88		Second line n = 58		Third line n = 22		Fourth line n = 8	
Objective response rate								
No. of patients with response	24		18		3		3	
% of patients (95% CI)	27.3	(18.3-37.8)	31.0	(19.5-44.5)	13.6	(2.9-34.9)	37.5	(8.5-75.5)
Disease control rate								
No. of patients with response	78		52		18		8	
% of patients (95% CI)	88.6	(80.1-94.4)	89.7	(78.8-96.1)	81.8	(59.7-94.8)	100.0	(63.1-100.0)
Best overall response, *n* (%)								
Complete response	0		0		0		0	
Partial response	24	(27.3)	18	(31.0)	3	(13.6)	3	(37.5)
Stable disease	54	(61.4)	34	(58.7)	15	(68.2)	5	(62.5)
Progressive disease	8	(9.1)	4	(6.9)	4	(18.2)	0	
Not evaluable	2	(2.3)	2	(3.4)	0		0	

Note: Tumor response assessed by clinical investigators.
[a]Excluding four patients who did not have any target lesions.
CI, confidence interval.

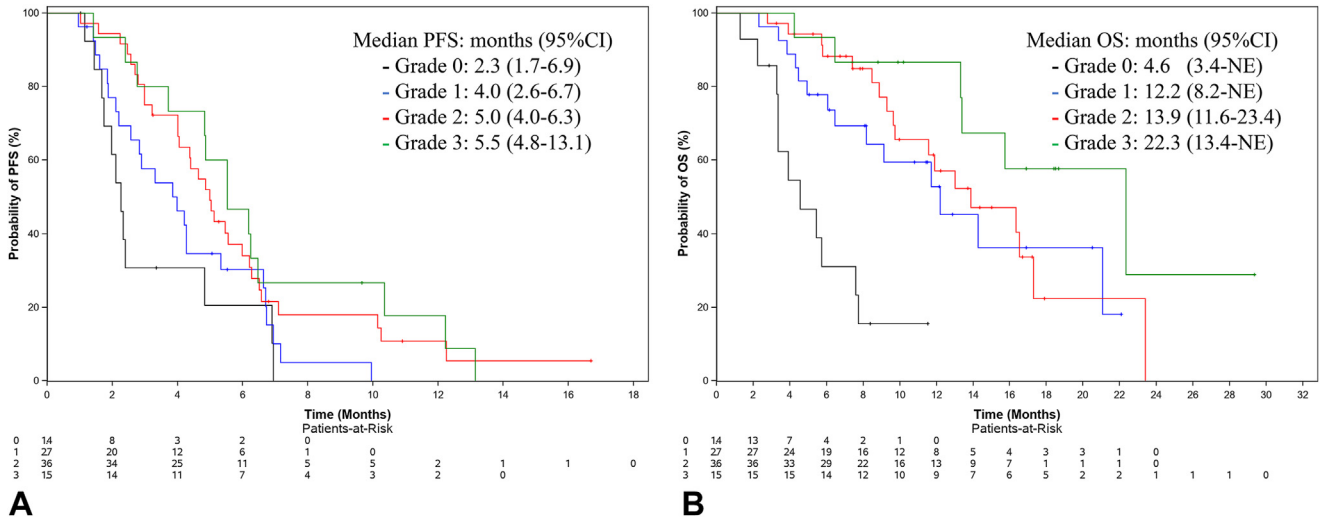

Figure 3. The Kaplan-Meier curves of PFS (*A*) and OS (*B*) by grade of skin disorders. PFS, progression-free survival; OS, overall survival; CI, confidence interval; NE, not evaluated.

The results of GCN efficacy by PD-L1 expression are illustrated in Supplementary Figure 5. The median PFS in the less than 1%, 1% to 49%, and greater-than-or-equal-to 50% subgroups were 4.6, 4.9, and 4.5 months, respectively ($p = 0.47$). Similarly, the median OS in these three subgroups were 11.6, 12.2, and 16.3 months, respectively ($p = 0.27$).

The results of GCN efficacy by PFI greater than180 or less than or equal to 180 days are detailed in Supplementary Figure 6. The median PFS in the greater than180 or less than or equal to 180 days subgroups were 5.3 and 3.3 months, respectively, indicating that PFI greater than 180 days was associated with prolonged PFS ($p < 0.05$). The median OS in these two subgroups were 13.4 and 9.1 months, respectively, suggesting a similar but statistically nonsignificant tendency ($p = 0.15$).

The results of GCN efficacy according to the best response of anticancer therapies administered immediately before GCN are detailed in Supplementary

Table 3. Summary of Treatment-Related Adverse Events

Event	Any Grade	
	Number of Patients With Event (%)	Grade ≥3
Treatment-related adverse events of special interest		
Skin and subcutaneous tissue disorders	78 (83.9)	15 (16.1)
Acneiform rash	70 (75.3)	14 (15.1)
Dry skin	37 (39.8)	3 (3.2)
Paronychia	21 (22.6)	3 (3.2)
Nail discoloration	1 (1.1)	0
Hypomagnesemia	55 (59.1)	7 (7.5)
Arterial thromboembolism	5 (5.4)	2 (2.2)
Thromboembolic event (venous thromboembolism)	3 (3.2)	1 (1.1)
Infusion-related reaction	3 (3.2)	2 (2.2)
Pneumonitis (interstitial lung disease)	3 (3.2)	1 (1.1)
Upper gastrointestinal hemorrhage	2 (2.2)	2 (2.2)
Hematuria	1 (1.1)	3 (1.1)
Other treatment-related adverse events[a]		
Decreased neutrophil count	Null	26 (28.0)
Decreased platelet count	Null	22 (23.7)
Decreased white blood cells	Null	9 (9.7)
Febrile neutropenia	Null	4 (4.3)
Anemia	Null	3 (3.2)
Pneumonia	Null	3 (3.2)

[a]Included are grade 3 or worse events that were reported in at least 3% of patients.

Figures 7 and 8. The median PFS in the CR plus PR plus stable disease and in the PD subgroups were 4.8 and 4.3 months, respectively ($p = 0.19$). The median OS in these two subgroups were 15.7 and 11.7 months, respectively ($p < 0.05$). Similarly, the median PFS in the CR plus PR and stable disease plus PD subgroups were 5.5 and 4.0 months, respectively ($p < 0.05$). The median OS in these two subgroups were 16.5 and 11.6 months, respectively ($p < 0.05$).

Tolerability

Treatment-related adverse events are summarized in Table 3. In the ITT population, the median time from the last dose of ICI to the initiation of GCN was 50 days (range: 14–877 days). Platinum-based chemotherapy was administered before GCN in 81 patients (87.1%). In these 81 patients, the median time from the last dose of platinum chemotherapy to the initiation of GCN was 250 days (range: 15–973 d).

Skin disorders, particularly acneiform rash with an incidence of 75.3% for all grades and 15.1% for grade 3 or higher were the most common adverse events, followed by hypomagnesemia, with an incidence of 59.1% for all grades and 7.5% for grade 3 or higher. The incidences of grade 3 or higher arterial thromboembolism and venous thromboembolism were 2.2% and 1.1%, respectively. In patients with a history of thrombosis before initiating GCN, no adverse events of worsening thrombosis were observed. The incidence of pneumonitis was 3.2% for all grades and 1.1% for grade 3 or higher. Among patients with a history of pneumonitis, worsening pneumonitis was not seen in any patients. Of the hematotoxicities, grade 3 or higher neutropenia and thrombocytopenia were seen in 28.0% and 23.7%, respectively. No new safety signals were observed. Furthermore, no grade 5 adverse events were observed during the study period.

Post-GCN Therapy

At the time of analysis, GCN had been discontinued in 93.5% (87 of 93) of patients. Reasons for GCN discontinuation were disease progression in 73.6% (64 of 87), adverse events in 23.0% (20 of 87), and patient request in 3.4% (3 of 87).

Post-GCN anticancer therapies are presented in Supplementary Table 2.

In the ITT population, 69.9% (65 of 93) of patients received anticancer therapy after GCN. The transition rates to post-GCN anticancer therapy were 71.0% (44 of 62), 65.2% (15 of 23), and 75.0% (6 of 8), in the second-line, third-line, and fourth-line treatment groups, respectively.

S-1 (21.5%; 14 of 65), docetaxel (20.0%; 13 of 65), ICI rechallenge (16.9%; 11 of 65), and ramucirumab plus docetaxel (RD) (15.4%; 10 of 65) were the most typically used regimens in post-GCN therapies.

Discussion

In this NINJA study, the efficacy and tolerability of GCN in second-line or later treatment for patients with ICI-pretreated LSqCC were investigated. Furthermore, the relationship between the severity of necitumumab-related skin disorders and the efficacy of GCN was also evaluated. To the best of our knowledge, these results represent the first real-world data providing meaningful information in current clinical settings.

In the NINJA study, the median PFS, median OS, and ORR were 4.4 months, 13.3 months, and 27.3% (24/88), respectively, and these efficacies were observed regardless of treatment line. Considering that the median PFS, median OS, and ORR in the SQUIRE and JFCM studies were 5.7 months, 11.5 months, and 31.2% (170 of 545), and 4.2 months, 14.9 months, and 51.1% (46 of 90), respectively, the high efficacy of GCN in the NINJA study was maintained, although most patients (87.1%) were treated with platinum rechallenge therapy in second-line or later treatment. In fact, in a meta-analysis investigating the efficacy of platinum rechallenge in second-line treatment for NSCLC, median PFS, median OS, and ORR were reported to be 3.9 months, 8.7 months, and 27.5%, respectively, and it was concluded that platinum rechallenge is a valid option for second-line treatment.[4] Furthermore, the results of the exploratory analysis in the NINJA study suggested that both PFI greater than 180 days and antitumor responses of the therapies administered immediately before GCN were associated with longer survival benefit.

Currently, RD is recommended as a second-line treatment for patients with advanced LSqCC that has progressed after platinum-doublet chemotherapy.[5,6] This recommendation is based on the REVEL study, in which the median PFS, median OS, and ORR in the RD-treated group of LSqCC were 4.2 months, 9.5 months, and 26.8% (42 of 157), respectively.[7] Recently, a retrospective, observational study has been conducted in Japan to evaluate the efficacy and tolerability of RD as second-line treatment for patients with NSCLC after platinum-doublet chemotherapy plus ICIs (REACTIVE study). In this study, the median PFS, median OS, and ORR of patients with nonadenocarcinoma were 3.0 months, 8.9 months, and 22.5% (20 of 89), respectively.[8] Therefore, from the results of the NINJA and REACTIVE studies, GCN seems to offer treatment efficacy comparable to that of RD as second-line treatment for patients previously treated with ICIs. Moreover, in patients with

LSqCC, tumor localization tends to be on the hilar side, resulting in a possible mass effect, including displacement or invasion of the trachea, main bronchi, and major blood vessels.[9] Therefore, some patients with LSqCC are presumed to be ineligible for ramucirumab. Thus, GCN may offer a promising treatment option, especially for such patients.

Furthermore, in the current study, concerns about toxicities (including hematotoxicity), skin disorders, and pneumonitis need to be discussed because of the study background that GCN was administered after platinum-based chemotherapy or ICIs.

Regarding hematotoxicity, in the NINJA, SQUIRE, and JFCM studies, the incidences of grade 3 or higher neutropenia were 28.0%, 24.3%, and 42.2%; those for grade 3 or higher thrombocytopenia were 23.7%, 10.2%, 20.0%; and those for grade 3 or higher febrile neutropenia were 4.3%, less than 1%, and 12.2%,[2,3] respectively, suggesting the tolerability of GCN in second-line or later treatment. However, the doses of cisplatin and gemcitabine in the NINJA study had been reduced from the first cycle in 12.9% (12 of 93) and 36.6% (34 of 93) of patients, respectively, indicating the possibility that this dose reduction contributed to less hematotoxicity. Currently, the phase 2 NESSIE study (jRCTs051200138) to evaluate the efficacy and safety of GCN as second-line treatment after platinum-doublet chemotherapy plus ICIs is ongoing.[10] In this prospective study, the same dose of GCN as in first-line treatment is being given to confirm the tolerability of second-line GCN.

Regarding skin disorders, in the NINJA study, the incidence of grade 3 or higher skin disorders, including acneiform rash, was 16.1% (15 of 93), which seems higher than those of 8.2% (44 of 538) and 10.0% (9/90) in the SQUIRE and JFCM studies, respectively. One possible explanation for this phenomenon in the NINJA study may be the involvement of ICI pretreatment. The biological half-lives of the ICIs used in the NINJA study are reportedly 15 to 27 days.[11–16] Moreover, the binding of nivolumab, as one of the ICIs, to programmed cell death protein 1 molecules expressed in T cells is reported to be maintained for more than 20 weeks after its last administration.[17] In the NINJA study, the median time from the last dose of ICI to the initiation of GCN was 50 days, and GCN may, therefore, have been initiated in many patients with its activity preserved. In fact, in a phase 1 trial of combination therapy with necitumumab 800 mg on day 1 and day 8 every 3 weeks and pembrolizumab 200 mg on day 1 every 3 weeks, grade 3 or higher skin disorders were reported in as many as 13% of patients. The use of necitumumab together with ICIs may have increased the incidence of grade 3 or higher skin disorders. However, dose-limiting toxicities were not reached. Furthermore, the discontinuation rate of study treatment because of adverse events was reported to be as low as 9% (6/64).[18] From this perspective, the potential increase in grade 3 or higher skin disorders with GCN in patients previously treated with ICIs seems tolerable. Likewise, regarding the efficacy of GCN, it is assumed that ICI pretreatment might enhance the GCN efficacy on the basis of the same mechanism as described above.

Regarding pneumonitis because of GCN, the incidences of grade 3 or higher pneumonitis in the NINJA study and the above-mentioned phase 1 study were 1.1% (1 of 93) and 1.6% (1 of 64), respectively. Meanwhile, the incidences in the SQUIRE and JFCM studies were less than 1% (1 of 538) and 1.1% (1 of 90), respectively, suggesting that GCN is unlikely to be associated with a higher incidence of pneumonitis even among patients previously treated with ICIs. On the other hand, in the phase 2 JVCG study of RD as the standard second-line therapy, grade 3 and higher pneumonitis was reported in 2.6% (2 of 76) of Japanese patients who had not received ICI treatment,[19] whereas in the REACTIVE study, the incidence of grade 3 or higher pneumonitis was 4.9% (14 of 288) in Japanese patients who had received ICI treatment before RD. Recently, the phase 2 SCORPION study, which prospectively evaluated the efficacy and safety of RD after ICI treatment reported the incidence of grade 3 or higher pneumonitis as 9.1% (3 of 33) in Japanese patients.[20] Therefore, unlike GCN, RD may exhibit some synergistic effects with ICI pretreatment in Japanese patients regarding pneumonitis, although necitumumab also needs further validation through the NESSIE study. Therefore, the treatment strategy of second-line GCN followed by third-line RD seems promising to achieve long-term OS in patients with good PS, which would also be supported by the high transition rate to post-GCN treatment of approximately 70% after GCN in the NINJA study.

Finally, the NINJA study suggested that increasing severity of skin disorders (including acneiform rash) caused by GCN might be related to longer PFS and OS. The relationship between skin disorders from anti-EGFR antibodies and their clinical efficacies has already been reported for cetuximab and panitumumab in colon cancer and for cetuximab in head and neck cancer.[21–25] Moreover, even in the phase 3 FLEX study combining cetuximab with cisplatin plus vinorelbine in untreated patients with advanced NSCLC, the patient group in which acneiform rash seemed in the first cycle exhibited significantly longer PFS and OS than the patient group in which no acneiform rash seemed (median PFS: 5.4 versus 4.3 mo, HR = 0.631, $p < 0.01$; median OS: 15.0 versus 8.8 months, HR = 0.741, $p < 0.01$).[26] Similarly,

for necitumumab, the patient group in which acneiform rash seemed by the second cycle exhibited longer OS than the patient group in which no acneiform rash seemed in the SQUIRE study (median OS: 13.6 versus 10.2 mo, HR = 0.656, $p = 0.0001$).[27] However, all these reports did not evaluate the relationship between the severity of skin disorders and treatment efficacy. Therefore, the current NINJA study would be significant because the results suggested that, even when the patients suffer from severe skin disorders caused by GCN, GCN treatment would be worth continuing with active skin management in terms of treatment efficacy.

The limitation of the present study is summarized by the fact that it was a retrospective study with various patient and treatment backgrounds and less strict end point evaluation. In this study, more than half of the patients were stage III, the GCN treatment line varied widely, and various methods of ICI administration had been used in previous treatment, including ICI monotherapy, combination therapy with different ICIs, platinum-doublet chemotherapy plus ICIs, and maintenance ICI monotherapy after radiation. Therefore, strict conclusions could not be drawn on the relationship between the pretreatment ICI and the efficacy or tolerability of GCN. However, the NESSIE study is currently ongoing, and the results could elucidate some of these issues in the future.

In conclusion, as the largest retrospective study in Japan, the results of the current NINJA study suggest that GCN for ICI-pretreated patients might be well tolerated and offer promising efficacy regardless of the treatment line, and ICI pretreatment might enhance the GCN efficacy.

CRediT Authorship Contribution Statement

Yasunori Murata: Resources, Validation, Writing-original draft, Writing-review and editing, Final manuscript approval.

Shigeru Tanzawa: Conceptualization, Methodology, Resources, Data analysis, Project administration, Validation, Visualization, Writing-original draft, Writing-review and editing, Final manuscript approval.

Toshihiro Misumi: Conceptualization, Methodology, Data analysis, Project administration, Validation, Visualization, Writing-original draft, Writing-review and editing, Final manuscript approval.

Hiroshige Yoshioka: Conceptualization, Methodology, Project administration, Resources, Validation, Writing-review and editing, Final manuscript approval.

Eisaku Miyauchi: Conceptualization, Methodology, Project administration, Resources, Validation, Writing-review and editing, Final manuscript approval.

Kiichiro Ninomiya: Conceptualization, Methodology, Project administration, Resources, Validation, Writing-review and editing, Final manuscript approval.

Masafumi Takeshita: Resources, Validation, Writing-review and editing, Final manuscript approval.

Kensaku Ito: Resources, Writing-review and editing, Final manuscript approval.

Tatsuro Okamoto: Resources, Writing-review and editing, Final manuscript approval.

Shunichi Sugawara: Resources, Writing-review and editing, Final manuscript approval.

Yosuke Kawashima: Resources, Writing-review and editing, Final manuscript approval.

Kazuki Hashimoto: Resources, Writing-review and editing, Final manuscript approval.

Masahide Mori: Resources, Writing-review and editing, Final manuscript approval.

Akihiko Miyanaga: Resources, Writing-review and editing, Final manuscript approval.

Anna Hayashi: Resources, Writing-review and editing, Final manuscript approval.

Hisashi Tanaka: Resources, Writing-review and editing, Final manuscript approval.

Ryoichi Honda: Resources, Writing-review and editing, Final manuscript approval.

Masafumi Nojiri: Resources, Writing-review and editing, Final manuscript approval.

Yuki Sato: Resources, Writing-review and editing, Final manuscript approval.

Akito Hata: Resources, Writing-review and editing, Final manuscript approval.

Ken Masuda: Resources, Writing-review and editing, Final manuscript approval.

Toshiyuki Kozuki: Resources, Writing-review and editing, Final manuscript approval.

Takahisa Kawamura: Resources, Writing-review and editing, Final manuscript approval.

Takuji Suzuki: Resources, Writing-review and editing, Final manuscript approval.

Teppei Yamaguchi: Resources, Writing-review and editing, Final manuscript approval.

Kazuhiro Asada: Resources, Writing-review and editing, Final manuscript approval.

Satoshi Tetsumoto: Resources, Writing-review and editing, Final manuscript approval.

Hiroshi Tanaka: Resources, Writing-review and editing, Final manuscript approval.

Satoshi Watanabe: Resources, Writing-review and editing, Final manuscript approval.

Yukihiro Umeda: Resources, Writing-review and editing, Final manuscript approval.

Kakuhiro Yamaguchi: Resources, Writing-review and editing, Final manuscript approval.

Shoichi Kuyama: Resources, Writing-review and editing, Final manuscript approval.

Kosuke Tsuruno: Resources, Writing-review and editing, Final manuscript approval.

Yuki Misumi: Resources, Writing-review and editing, Final manuscript approval.

Hiroshi Kuraishi: Resources, Writing-review and editing, Final manuscript approval.

Ken Yoshihara: Resources, Writing-review and editing, Final manuscript approval.

Akira Nakao: Resources, Writing-review and editing, Final manuscript approval.

Akihito Kubo: Resources, Writing-review and editing, Final manuscript approval.

Toshihiko Yokoyama: Resources, Writing-review and editing, Final manuscript approval.

Kana Watanabe: Resources, Writing-review and editing, Final manuscript approval.

Nobuhiko Seki: Conceptualization, Methodology, Supervision, Funding acquisition, Project administration, Validation, Writing-original draft, Writing-review and editing, Final manuscript approval.

Acknowledgments

This study was conducted by the NINJA study group under a funding contract with Nippon Kayaku Co., Ltd., Japan. The sponsor did not have any role in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; and in the decision to submit the article for publication. The authors thank the patients, their families, and all the investigators who participated in this study.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100593.

References

1. Kuenen B, Witteveen PO, Ruijter R, et al. A phase I pharmacologic study of necitumumab (IMC 11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies. *Clin Cancer Res*. 2010;16:1915–1923.
2. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first line therapy in patients with stage IV squamous non-small cell lung cancer (SQUIRE): an open label, randomized, controlled phase 3 trial. *Lancet Oncol*. 2015;16:763–774.
3. Watanabe S, Yoshioka H, Sakai H, et al. 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. *Lung Cancer*. 2019;129:55–62.
4. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Ardine M, Barni S. Platinum rechallenge in patients with advanced NSCLC: a pooled analysis. *Lung Cancer*. 2013;81:337–342.
5. Singh N, Temin S, Baker S Jr, et al. Therapy for stage IV non-small-cell lung cancer without driver alterations: ASCO living guideline. *J Clin Oncol*. 2022;40:3323–3343.
6. Hendriks LE, Kerr K, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:358–376.
7. Paz-Ares LG, Pérol M, Ciuleanu TE, et al. Treatment outcomes by histology in REVEL: a randomized phase III trial of ramucirumab plus docetaxel for advanced non-small cell lung cancer. *Lung Cancer*. 2017;112:126–133.
8. Nakamura A, Yamaguchi O, Mori K, et al. Multicentre real-world data of ramucirumab plus docetaxel after combined platinum-based chemotherapy with programmed death-1 blockade in advanced non-small cell lung cancer: NEJ051 (REACTIVE study). *Eur J Cancer*. 2023;11:62–72.
9. Theros EG. Varying manifestations of peripheral pulmonary neoplasms: a radiologic-pathologic correlative study. *Am J Roentgenol*. 1977;128:893–914.
10. Yoshioka H. Multicenter phase II study of cisplatin, gemcitabine, and necitumumab in patients with unresectable, advanced or recurrent squamous cell carcinoma of the lung who have failed on or relapsed after initial treatment with a combination of immune checkpoint inhibitors and platinum-based chemotherapy: NESSIE study (NESSIE study (WJOG14120L)): jRCTs051200138. Japan Registry of Clinical Trials. https://jrct.niph.go.jp/en-latest-detail/jRCTs051200138. Accessed June 28, 2023.
11. Sheng J, Srivastava S, Sanghavi K, et al. Clinical pharmacology considerations for the development of immune checkpoint inhibitors. *J Clin Pharmacol*. 2017;57(suppl 10):S26–S42.
12. Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. *Clin Cancer Res*. 2015;21:4286–4293.
13. Stroh M, Winter H, Marchand M, et al. Clinical pharmacokinetics and pharmacodynamics of atezolizumab in metastatic urothelial carcinoma. *Clin Pharmacol Ther*. 2017;102:305–312.
14. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol*. 2010;28:3167–3175.
15. Weber JS, O'Day S, Urba W, et al. Phase I/II study of ipilimumab for patients with metastatic melanoma. *J Clin Oncol*. 2008;26:5950–5956.
16. Baverel PG, Dubois VFS, Jin CY, et al. Population pharmacokinetics of durvalumab in cancer patients and association with longitudinal biomarkers of disease status. *Clin Pharmacol Ther*. 2018;103:631–642.

17. Osa A, Uenami T, Koyama S, et al. Clinical implications of monitoring nivolumab immunokinetics in non-small cell lung cancer patients. *JCI Insight*. 2018;3:e59125.
18. Besse B, Garrido P, Cortot AB, et al. Efficacy and safety of necitumumab and pembrolizumab combination therapy in patients with Stage IV non-small cell lung cancer. *Lung Cancer*. 2020;142:63–69.
19. Yoh K, Hosomi Y, Kasahara K, et al. A randomized, double-blind, phase II study of ramucirumab plus docetaxel versus placebo plus docetaxel in Japanese patients with stage IV non-small cell lung cancer after disease progression on platinum-based therapy. *Lung Cancer*. 2016;99:186–193.
20. Matsuzawa R, Morise M, Ito K, et al. Multi-center, phase II study of docetaxel (DTX) plus ramucirumab (RAM) following platinum-based chemotherapy plus ICIs in patients with NSCLC: SCORPION study. *J Thorac Oncol*. 2021;16(suppl):S1102–S1103.
21. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351:337–345.
22. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. 2007;357:2040–2048.
23. Peeters M, Siena S, Van Cutsem E, et al. Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy. *Cancer*. 2009;115:1544–1554.
24. Racca P, Fanchini L, Caliendo V, et al. Efficacy and skin toxicity management with cetuximab in metastatic colorectal cancer: outcomes from an oncologic/dermatologic cooperation. *Clin Colorectal Cancer*. 2008;7:48–54.
25. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol*. 2010;11:21–28.
26. Gatzemeier U, von Pawel J, Vynnychenko I, et al. First-cycle rash and survival in patients with advanced non-small-cell lung cancer receiving cetuximab in combination with first-line chemotherapy: a subgroup analysis of data from the FLEX phase 3 study. *Lancet Oncol*. 2011;12:30–37.
27. Bonomi P, Peterson P, Socinski M, et al. Rash as a marker for the efficacy of necitumumab in the SQUIRE study. *J Thorac Oncol*. 2015;10(suppl):1–62.