The Oncologist®

Randomized Phase II Study of First-Line Biweekly Gemcitabine and Carboplatin Versus Biweekly Gemcitabine and Carboplatin plus Maintenance Gemcitabine in Elderly Patients with Untreated Non-Small Cell Lung Cancer: LOGIK0801

Koichi Takayama,[a,b] Masafumi Takeshita,[c] Koji Inoue,[c] Masao Ichiki,[d] Masaki Fujita,[e] Taishi Harada,[f] Yoshimasa Shiraishi,[b] Hiroshi Wataya,[g] Shoji Tokunaga,[h] Tadaaki Yamada,[a] Junji Uchino,[a] Kenji Sugio[i]

[a]Department of Pulmonary Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan; [b]Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [c]Department of Respiratory Medicine, Kitakyushu Municipal Medical Center, Kitakyushu, Japan; [d]Department of Respirology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan; [e]Department of Respiratory Medicine, Fukuoka University Hospital, Fukuoka, Japan; [f]Department of Respiratory Medicine, Japan Community Healthcare Organization Kyushu Hospital, Kitakyushu, Japan; [g]Division of Internal Medicine, Saiseikai Fukuoka General Hospital, Fukuoka, Japan; [h]Medical Information Center, Kyushu University Hospital, Fukuoka, Japan; [i]Department of Thoracic and Breast Surgery, Oita University, Faculty of Medicine, Oita, Japan

TRIAL INFORMATION

- **UMIN Clinical Trials Registry:** UMIN000039230
- **Sponsor:** Clinical Research Support Center Kyushu
- **Principal Investigator:** Koichi Takayama
- **IRB Approved:** Yes

LESSONS LEARNED

- The usefulness of maintenance gemcitabine (GEM) after biweekly carboplatin + GEM in elderly patients with non-small cell lung cancer could not be proved.
- Superior overall survival was obtained in the group that did not receive maintenance therapy.

ABSTRACT

Background. The primary objective of this randomized phase II study was to assess progression-free survival (PFS) in elderly patients with advanced non-small cell lung cancer (NSCLC) treated with gemcitabine (GEM) maintenance therapy versus best supportive care following first-line GEM plus carboplatin (CBDCA).

Methods. Elderly chemotherapy-naive patients with stage IIIB or IV NSCLC were randomly assigned 1:1 to the control arm or the study arm. All patients received biweekly combination therapy with GEM and CBDCA (1,000 mg/m^2 GEM and CBDCA at an area under the curve [AUC] of 3 on days 1 and 15, every 4 weeks). In the study arm, patients with objective response or stable disease follow-ing three or four cycles of initial chemotherapy received maintenance GEM.

Results. Eighty-four patients were enrolled. The objective response rates (ORRs) were 17.5% in the control arm and 14.0% in the study arm. The most common toxicity was neutropenia (control arm: 47.5% and study arm: 69.8%). The median progression-free survivals were 4.99 months (control arm) and 4.44 months (study arm), and the median overall survivals (OSs) were 21.7 months (control arm) and 8.2 months (study arm).

Conclusion. Our data do not support maintenance GEM after biweekly CBDCA+GEM in elderly patients with NSCLC. *The Oncologist* 2020;25:e1146–e1157
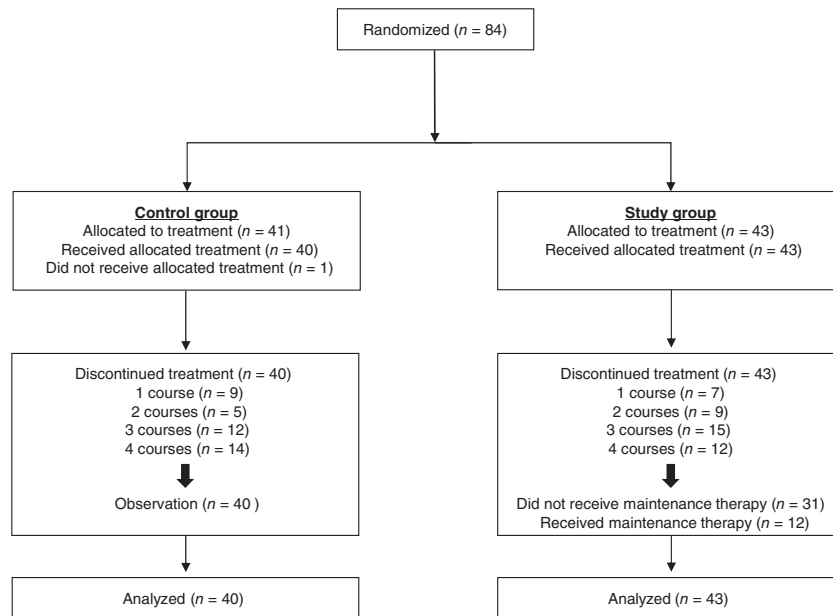
Figure 1. Trial schema.

DISCUSSION

Platinum-doublet chemotherapies have exhibited a similar efficacy and tolerability in young and elderly patients as single-agent chemotherapy [1–6]. GEM/CBDCA has an especially good effect, with an ORR of 20.3%, a median survival time of 14.2 months, and a 2-year survival rate of 38.3% in the phase II randomized WJTOG-0104 trial in Japan [7]. However, a high incidence (81.3%) of thrombocytopenia was observed, and therefore, the optimal dosage and administration schedules must still be defined. Our group previously conducted a clinical trial of biweekly GEM/CBDCA to establish a highly acceptable and useful treatment for elderly patients with NSCLC and reduce toxicity without lowering efficacy compared with the standard 3-week regimen. The ORR was 29.2% (3-week regimen in the WJTOG-0104 trial: 21.0%), the median PFS was 178 days (95% confidence interval [CI]: 122–198), and the median OS was 398 days (95% CI: 248–704; 3-week regimen in the WJTOG-0104 trial: 14.2 months) [8]. The toxicity profile was generally mild and tolerable. Therefore, the biweekly GEM/CBDCA regimen could be considered an alternative to the 3-week regimen.

The phase III PARAMOUNT trial of pemetrexed (PEM) maintenance after combination therapy with cisplatin (CDDP) plus PEM demonstrated a significant prolongation of PFS (4.1 months vs. 2.8 months, hazard ratio [HR] 0.62, 95% CI: 0.50–0.73, $p < .0001$) and OS (13.9 months vs. 11.0 months, HR 0.78, 95% CI: 0.64–0.96, $p = .0195$) [9]. No decrease in quality of life was observed, and although

toxicity was higher in the study group, it was within the permissible range. The phase III AVAPERL trial comparing bevacizumab versus PEM plus bevacizumab followed by CDDP plus PEM plus bevacizumab showed a significant PFS prolongation (7.4 months vs. 3.7 months, HR 0.48, 95% CI: 0.44–0.75, $p < .0001$) but no significant OS prolongation [10]. After four cycles of CDDP plus PEM, the continuation of PEM in patients without disease progression and with tolerable toxicities has been accepted as standard of care. Based on this result, the usefulness of maintenance GEM after biweekly administration of CBDCA+GEM was examined in this study. Eighty-four patients were enrolled from 12 institutions (Fig. 1). One patient did not undergo any treatment because of active infection and anemia. Therefore, efficacy and safety analyses were performed for the remaining 83 patients. The median follow-up period was 9.6 months. The PFS was slightly longer in the control group than in the study group (4.99 months vs. 4.44 months, $p = .47$), but it was not significant. However, the median OS was significantly longer in the standard therapy group than in the maintenance group (21.7 months vs. 8.2 months, $p = .045$). Rates of second-line therapy (55% vs. 44%) and, among them, epidermal growth factor receptor tyrosine kinase inhibitor administration (30% vs. 21%) were higher in the control group than in the study group. We believe that this contributed to the difference in OS. Our data do not support maintenance GEM after biweekly administration of CBDCA+GEM in elderly patients with NSCLC.

TRIAL INFORMATION

Disease	Advanced cancer
Disease	Lung cancer − NSCLC
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study	Phase II, randomized
PFS	p: .47, HR: 0.83
Primary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival

Additional Details of Endpoints or Study Design

In our previous research, we conducted a biweekly trial of gemcitabine plus carboplatin in elderly patients with non-small cell lung cancer and found a median progression-free survival of approximately 6 months. Therefore, the median progression-free survival in the standard group was expected to be 6 months. We assumed a clinically meaningful progression-free survival extension with a median progression-free survival in the study group of 9 months (hazard ratio 0.667). Assuming a one-sided log-rank test with an enrollment time of 2 years and an observational time of 1 year, = 0.2 and = 0.2, the numbers needed to enroll were both according to Schoenfeld & Richter methods. The combined groups were estimated to be 81 subjects, with the expectation of approximately 5% ineligible patients; the target sample size was 44 patients in each group, totaling 88 patients.

Investigator's Analysis	Inactive because results did not meet primary endpoint

DRUG INFORMATION: CONTROL ARM

Drug 1

Generic/Working Name	Carboplatin
Drug Class	Platinum compound
Dose	AUC 3 mg/mL × minute mg per
Route	IV
Schedule of Administration	Carboplatin AUC of 3 mg/mL × minute biweekly, on days 1 and 15 of each 28-day cycle

Drug 2

Generic/Working Name	Gemcitabine
Dose	1,000 mg/m^2
Route	IV
Schedule of Administration	Gemcitabine 1,000 mg/m^2 biweekly, on days 1 and 15 of each 28-day cycle

DRUG INFORMATION: STUDY ARM

Drug 1

Generic/Working Name	Carboplatin
Drug Class	Platinum compound
Dose	AUC 3 mg/mL × minute mg per
Route	IV
Schedule of Administration	Carboplatin AUC of 3 mg/mL × minute biweekly, on days 1 and 15 of each 28-day cycle

Drug 2

Generic/Working Name	Gemcitabine
Dose	1,000 mg/m^2
Route	IV

Schedule of Administration

Gemcitabine 1,000 mg/m^2 biweekly, on days 1 and 15 of each 28-day cycle. Patients with objective response or stable disease following three or four cycles of initial chemotherapy received maintenance gemcitabine 1,000 mg/m^2 biweekly.

The Oncologist®

PATIENT CHARACTERISTICS: CONTROL ARM	
Number of Patients, Male	29
Number of Patients, Female	11
Stage	IIIB: 10 IV: 28
Age	Median (range): 76
Performance Status: ECOG	0 — 19 1 — 21 2 — 0 3 — 0 Unknown —
Cancer Types or Histologic Subtypes	Adenocarcinoma, 25; SCC, 11; NOS, 4

PATIENT CHARACTERISTICS: STUDY ARM	
Number of Patients, Male	34
Number of Patients, Female	9
Stage	IIIB: 8 IV: 31
Age	Median (range): 77
Performance Status: ECOG	0 — 18 1 — 25 2 — 3 — Unknown —
Cancer Types or Histologic Subtypes	Adenocarcinoma, 21; SCC, 15; Large cell carcinoma, 1; NOS, 6

PRIMARY ASSESSMENT METHOD: CONTROL ARM	
Title	PFS
Number of Patients Enrolled	40
Number of Patients Evaluable for Toxicity	40
Number of Patients Evaluated for Efficacy	40
Evaluation Method	RECIST 1.0
Response Assessment CR	n = 1 (2.5%)
Response Assessment PR	n = 6 (15%)
Response Assessment SD	n = 21 (52.5%)
Response Assessment PD	n = 6 (15%)
Response Assessment OTHER	n = 6 (15%)
(Median) Duration Assessments PFS	4.99 months, CI: 3.29–6.28

KAPLAN-MEIER TIME UNITS, MONTHS					
Time of scheduled assessment and/or time of event	**No. progressed (or deaths)**	**No. censored**	**Percent at start of evaluation period**	**Kaplan-Meier %**	**No. at next evaluation/ No. at risk**
0.66	1	0	100.00	97.50	39
0.69	1	0	97.50	95.00	38
0.82	1	1	95.00	92.43	36
0.89	1	0	92.43	89.86	35

1.02	1	0	89.86	87.30	34
1.08	0	1	87.30	87.30	33
1.28	1	0	87.30	84.65	32
1.38	0	1	84.65	84.65	31
1.84	0	1	84.65	84.65	30
2.07	1	0	84.65	81.83	29
2.33	1	0	81.83	79.01	28
2.50	1	0	79.01	76.19	27
2.89	0	1	76.19	76.19	26
2.96	1	0	76.19	73.26	25
3.19	1	0	73.26	70.33	24
3.29	1	0	70.33	67.40	23
3.55	1	0	67.40	64.47	22
3.91	1	0	64.47	61.54	21
3.98	0	1	61.54	61.54	20
4.21	1	0	61.54	58.46	19
4.24	0	1	58.46	58.46	18
4.53	1	0	58.46	55.21	17
4.57	0	1	55.21	55.21	16
4.67	1	0	55.21	51.76	15
4.99	1	0	51.76	48.31	14
5.45	1	1	48.31	44.59	12
5.82	1	0	44.59	40.88	11
6.21	2	0	40.88	33.45	9
6.28	1	0	33.45	29.73	8
7.23	0	1	29.73	29.73	7
7.62	1	0	29.73	25.48	6
7.79	1	0	25.48	21.23	5
8.25	1	0	21.23	16.99	4
11.33	1	0	16.99	12.74	3
12.65	0	1	12.74	12.74	2
17.61	0	1	12.74	12.74	1
29.27	0	1	12.74	0.00	0
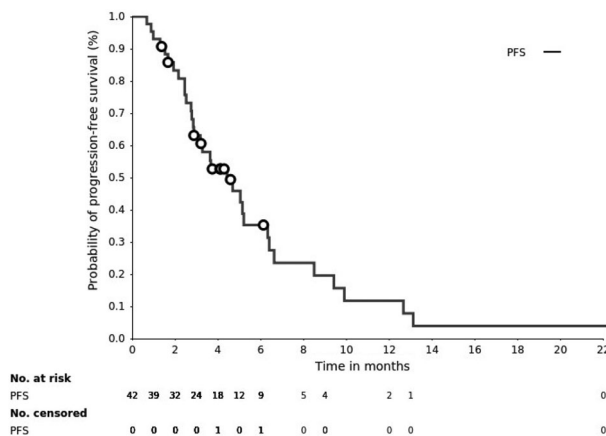
No. at risk										
PFS	42	39	32	24	18	12	9	5	4	2	1	0

No. censored										
PFS	0	0	0	0	1	0	1	0	0	0	0	0

Kaplan-Meier plot legend

Progression-free survival (PFS) curve by the Kaplan-Meier method. The median PFS in the control was 4.99 months (95% confidence interval [CI]: 3.29–6.28 months) and 4.44 months (95% CI: 2.86–6.34 months), respectively. No significant differences were noted in either arm ($p = .47$, log-rank test).

The Oncologist®

SECONDARY ASSESSMENT METHOD: CONTROL ARM

Title	OS
Number of Patients Enrolled	40
Number of Patients Evaluable for Toxicity	40
Number of Patients Evaluated for Efficacy	40
Evaluation Method	RECIST 1.0
(Median) Duration Assessments OS	21.7 months, CI: 9.7–24.6

KAPLAN-MEIER TIME UNITS, MONTHS

Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/No. at risk
2.20	1	0	100.00	97.50	39
2.53	0	1	97.50	97.50	38
3.98	1	0	97.50	94.93	37
4.44	1	0	94.93	92.37	36
4.86	1	0	92.37	89.80	35
4.93	1	0	89.80	87.24	34
5.06	0	1	87.24	87.24	33
6.18	1	0	87.24	84.59	32
6.28	1	0	84.59	81.95	31
7.13	1	0	81.95	79.31	30
7.16	1	0	79.31	76.66	29
8.31	0	1	76.66	76.66	28
8.94	1	0	76.66	73.92	27
9.66	1	0	73.92	71.19	26
9.89	1	0	71.19	68.45	25
10.61	0	1	68.45	68.45	24
11.04	0	1	68.45	68.45	23
12.94	0	1	68.45	68.45	22
13.57	0	1	68.45	68.45	21
14.69	1	0	68.45	65.19	20
16.43	0	1	65.19	65.19	19
16.82	0	1	65.19	65.19	18
18.14	0	1	65.19	65.19	17
18.43	0	1	65.19	65.19	16
21.75	1	0	65.19	61.12	15
21.78	1	0	61.12	57.04	14
22.54	1	0	57.04	52.97	13
23.29	1	0	52.97	48.89	12
23.75	1	0	48.89	44.82	11
23.95	0	1	44.82	44.82	10
24.57	1	0	44.82	40.34	9
27.04	1	0	40.34	35.85	8
27.07	1	1	35.85	30.73	6
28.71	0	1	30.73	30.73	5
28.98	1	0	30.73	24.59	4
31.54	1	0	24.59	18.44	3
38.64	1	0	18.44	12.29	2

| 52.04 | 0 | 1 | 12.29 | 12.29 | 1 |
| 52.53 | 0 | 1 | 12.29 | 0.00 | 0 |

No. at risk
OS   39 37 36 33 32 30 28 26 24 23 22 21 20   19 17   15 13 12 9   8 5   3   2   1

No. censored
OS   0 0 0 1 0 0 1 0 1 0 1 1 1 1 0   1 1   0 0 0 0   0 1 0   0   1

Kaplan-Meier plot legend

Overall survival (OS) curve by the Kaplan-Meier method. The median OS in the control was 21.7 months (95% confidence interval [CI]: 9.7–24.6 months) and 8.2 months (95% CI: 5.9–16.5 months), respectively. No significant differences were noted in either arm (p = .14, log-rank test).

PRIMARY ASSESSMENT METHOD: STUDY ARM	
Title	PFS
Number of Patients Enrolled	43
Number of Patients Evaluable for Toxicity	43
Number of Patients Evaluated for Efficacy	43
Evaluation Method	RECIST 1.0
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 6$ (14%)
Response Assessment SD	$n = 26$ (60.5%)
Response Assessment PD	$n = 9$ (20.9%)
Response Assessment OTHER	$n = 2$ (4.7%)
(Median) Duration Assessments PFS	4.44 months, CI: 2.86–6.34

KAPLAN-MEIER TIME UNITS, MONTHS					
Time of scheduled assessment and/or time of event	**No. progressed (or deaths)**	**No. censored**	**Percent at start of evaluation period**	**Kaplan-Meier %**	**No. at next evaluation/No. at risk**
0.69	1	0	100.00	97.67	42
0.89	1	0	97.67	95.35	41
0.99	1	0	95.35	93.02	40
1.31	1	0	93.02	90.70	39
1.38	0	1	90.70	90.70	38
1.54	1	0	90.70	88.31	37
1.68	1	2	88.31	85.79	34
1.94	1	0	85.79	83.26	33
2.17	1	0	83.26	80.74	32
2.46	2	0	80.74	75.70	30

Oncologist®

2.53	1	0	75.70	73.17	29
2.76	1	0	73.17	70.65	28
2.79	1	0	70.65	68.13	27
2.86	1	0	68.13	65.60	26
2.89	1	0	65.60	63.08	25
3.19	1	0	63.08	60.56	24
3.22	0	1	60.56	60.56	23
3.29	1	0	60.56	57.92	22
3.65	1	0	57.92	55.29	21
3.68	1	0	55.29	52.66	20
3.75	0	1	52.66	52.66	19
4.11	0	1	52.66	52.66	18
4.14	0	1	52.66	52.66	17
4.30	0	1	52.66	52.66	16
4.44	1	0	52.66	49.37	15
4.60	0	1	49.37	49.37	14
4.70	1	0	49.37	45.84	13
5.06	1	0	45.84	42.31	12
5.16	1	0	42.31	38.79	11
05.22	1	0	38.79	35.26	10
6.14	0	1	35.26	35.26	9
6.34	1	0	35.26	31.34	8
6.41	1	0	31.34	27.43	7
6.64	1	0	27.43	23.51	6
8.51	1	0	23.51	19.59	5
9.43	1	0	19.59	15.67	4
9.92	1	0	15.67	11.75	3
12.68	1	0	11.75	7.84	2
13.14	1	0	7.84	3.92	1
22.28	1	0	3.92	0.00	0
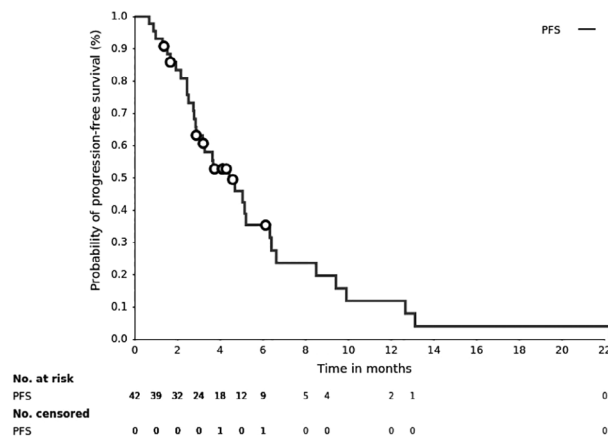
Kaplan-Meier plot legend

Progression-free survival (PFS) curve by the Kaplan-Meier method. Solid and dotted lines indicate the control and study arms, respectively. The median PFS in the control and study arms was 4.99 months (95% confidence interval [CI]: 3.29–6.28 months) and 4.44 months (95% CI: 2.86–6.34 months), respectively. No significant differences were noted in either arm (*p* = .47, log-rank test).
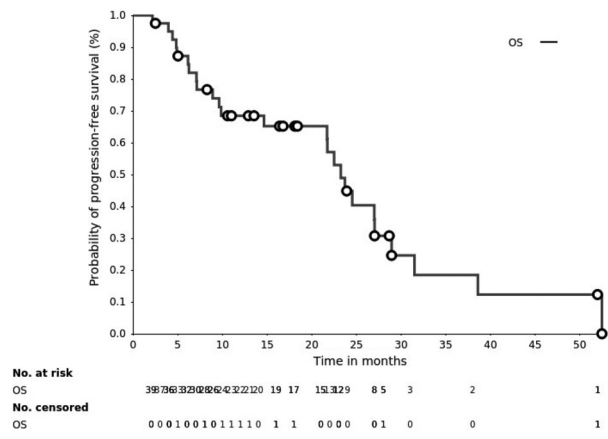
SECONDARY ASSESSMENT METHOD: STUDY ARM

Title	OS
Number of Patients Enrolled	43
Number of Patients Evaluable for Toxicity	43
Number of Patients Evaluated for Efficacy	43
Evaluation Method	RECIST 1.0
(Median) Duration Assessments OS	8.2 months, CI: 5.9–16.5

KAPLAN-MEIER TIME UNITS, MONTHS

Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/No. at risk
2.79	1	0	100.00	97.67	42
3.02	1	0	97.67	95.35	41
3.22	1	0	95.35	93.02	40
3.29	1	0	93.02	90.70	39
3.65	1	0	90.70	88.37	38
3.71	0	1	88.37	88.37	37
4.76	2	0	88.37	83.60	35
4.80	1	0	83.60	81.21	34
5.06	1	0	81.21	78.82	33
5.45	1	0	78.82	76.43	32
5.49	1	0	76.43	74.04	31
5.52	1	0	74.04	71.65	30
5.62	1	0	71.65	69.26	29
5.85	1	0	69.26	66.88	28
5.91	2	0	66.88	62.10	26
6.14	1	0	62.10	59.71	25
6.70	0	1	59.71	59.71	24
7.00	1	0	59.71	57.22	23
7.03	1	0	57.22	54.73	22
7.20	1	0	54.73	52.25	21
7.92	0	1	52.25	52.25	20
8.25	1	0	52.25	49.63	19
8.74	1	0	49.63	47.02	18
10.87	1	0	47.02	44.41	17
11.04	1	0	44.41	41.80	16
13.96	0	1	41.80	41.80	15
14.03	1	0	41.80	39.01	14
15.08	1	0	39.01	36.22	13
16.53	1	0	36.22	33.44	12
17.54	1	0	33.44	30.65	11
20.01	0	1	30.65	30.65	10
20.04	1	0	30.65	27.59	9
20.96	0	1	27.59	27.59	8
25.79	1	0	27.59	24.14	7
27.01	1	0	24.14	20.69	6
27.89	1	0	20.69	17.24	5
33.28	1	0	17.24	13.79	4
36.63	1	0	13.79	10.34	3
38.83	1	0	10.34	6.90	2

The Oncologist®

| 59.40 | 0 | 1 | 6.90 | 6.90 | 1 |
| 62.29 | 1 | 0 | 6.90 | 0.00 | 0 |

Kaplan-Meier plot legend

Overall survival (OS) curve by the Kaplan-Meier method. The median OS in the control was 21.7 months (95% confidence interval [CI]: 9.7–24.6 months) and 8.2 months (95% CI: 5.9–16.5 months), respectively. No significant differences were noted in either arm (p = .14, log-rank test).

ADVERSE EVENTS							
All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
White blood cell decreased	9%	15%	38%	35%	3%	0%	91%
Neutrophil count decreased	17%	15%	20%	30%	18%	0%	83%
Anemia	−1%	33%	38%	30%	0%	0%	101%
Platelet count decreased	27%	45%	20%	8%	0%	0%	73%
Aspartate aminotransferase increased	59%	38%	0%	3%	0%	0%	41%
Alanine aminotransferase increased	47%	45%	8%	0%	0%	0%	53%
Alkaline phosphatase increased	82%	15%	0%	3%	0%	0%	18%
Creatinine increased	70%	30%	0%	0%	0%	0%	30%
Blood bilirubin increased	92%	3%	5%	0%	0%	0%	8%
Hyponatremia	30%	60%	0%	10%	0%	0%	70%
Hyperkalemia	59%	30%	8%	3%	0%	0%	41%
Hypokalemia	82%	18%	0%	0%	0%	0%	18%
Hypocalcemia	57%	40%	3%	0%	0%	0%	43%
Nausea	47%	35%	10%	8%	0%	0%	53%
Vomiting	95%	0%	5%	0%	0%	0%	5%
Fatigue	57%	28%	10%	5%	0%	0%	43%
Diarrhea	92%	8%	0%	0%	0%	0%	8%
Constipation	54%	35%	8%	3%	0%	0%	46%
Febrile neutropenia	95%	0%	0%	5%	0%	0%	5%
Dyspepsia	87%	13%	0%	0%	0%	0%	13%
Alopecia	97%	3%	0%	0%	0%	0%	3%

Adverse Events Legend

Abbreviation: NC/NA, no change from baseline/no adverse event.

Hematologic and gastrointestinal toxicities were the most common adverse events, and no serious adverse events occurred.

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion	Study completed
Investigator's Assessment	Inactive because results did not meet primary endpoint

Lung cancer is mainly a disease of the elderly. Additionally, it is often detected at advanced stages, and patients are in poor general condition and often have many complications. Single-agent treatment with new anticancer drugs has been established as the standard treatment for this patient cohort. However, some argue that treatment should not be chosen solely on the basis of age, and studies of combination therapy in the elderly have also been conducted. Two phase III trials comparing a third-generation cytotoxic chemotherapy alone with platinum-based combination chemotherapy in elderly patients with non-small cell lung cancer (NSCLC) have been reported, with the majority of patients enrolled in both trials being older than 75 years. In Japan, the JCOG0803/WJOG4307L trial was conducted to compare weekly cisplatin (CDDP)+docetaxel (DTX) with DTX alone. This trial was discontinued as a result of an interim analysis showing that combination therapy was not superior to monotherapy (overall survival [OS] 13.3 months vs. 14.8 months, hazard ratio [HR] 1.18, 95% confidence interval [CI]: 0.83–1.69) [4]. The French IFCT0501 trial compared carboplatin (CBDCA) + weekly paclitaxel (PTX) with gemcitabine (GEM) or vinorelbine (VNR) and showed a significant prolongation of progression-free survival (PFS; 6.0 months vs. 2.8 months, HR 0.51, 95% CI: 0.42–0.62, $p < .0001$) and OS (10.3 months vs. 6.2 months, HR 0.64, 95% CI: 0.52–0.78, $p < .0001$) with CBDCA + weekly PTX therapy [5]. The combination of GEM and CBDCA is already widely administered as standard therapy for NSCLC in Europe and the U.S., and its effectiveness in elderly patients has also been reported [6]. In Japan, a randomized phase II study (WJTOG-0104) of GEM+CBDCA (every 3 weeks) versus GEM+VNR was conducted for patients with progressive NSCLC younger than 75 years, and GEM+CBDCA showed high efficacy for progressive NSCLC, with a median survival time of 14.2 months (GEM+VNR group: 12.6 months) and a 2-year overall survival rate of 38.3% (GEM+VNR group: 22.4%) [7]. However, a high incidence of thrombocytopenia was observed in the GEM+CBDCA group. Therefore, determining the optimal dose and administration schedules in Japanese patients is needed.

GEM is a nucleoside derivative, an antimetabolite that is internalized and then metabolized to triphosphates to inhibit DNA synthesis [11]. Myelosuppression is the main toxicity, and cumulative toxicity as seen with taxanes has not been reported [11]. As a single agent, GEM has yielded response rates of 14%–33% in patients receiving first-line treatment and 0%–25% in previously treated patients [12]. An international phase III comparative trial was performed to compare maintenance therapy with GEM alone and nontreatment after CDDP+GEM therapy, which is one of the standard regimens for advanced NSCLC [13]. They found that the maintenance treatment group had significantly longer time to progression than the nontreatment group among patients with good general condition. Additionally, the maintenance group had increased overall survival. However, this study enrolled younger patients, and the median age was 57 years; therefore, the tolerability and efficacy of this regimen in elderly patients are unclear. We investigated the efficacy and safety of maintenance GEM after biweekly CBDCA plus GEM in elderly patients in this study, but the primary endpoint of PFS was not met. One possible reason for the failure of maintenance therapy to prolong PFS is the low rate of transition to maintenance. The disease control rate in the study group was relatively good (81%), but the rate of patients who shifted to maintenance treatment was low (28%), which may have been because patients deviated from the specified date of administration (13.9%), were unable to continue treatment owing to adverse events (9.3%), and discontinued treatment for reasons other than disease progression. PFS (7.6 months, 95% CI: 4.4–12.7) and OS (16.5 months, 95% CI: 8.7–70.3) were favorable for the 13 patients who could be transited to maintenance treatment, but the usefulness of the maintenance treatment group was difficult to assess in this study because of the intention-to-treat analysis. Given the reasons for failure to transition to the maintenance treatment described above, it was considered that study arm regimen was not feasible in this study population. In the study by Brodowicz et al., the efficacy of maintenance treatment was confirmed only in patients with good Karnofsky Performance Status, suggesting that it is difficult for elderly patients to shift to maintenance treatment, even if their Performance Status is good [13].

REFERENCES

1. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 1999;91:66–72.

2. Gridelli C, Perrone F, Gallo C et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003;95:362–372.

3. Kudoh S, Takeda K, Nakagawa K et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non–small-cell lung cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006;24:3657–3663.

4. Abe T, Takeda K, Ohe Y et al. Randomized phase III trial comparing weekly docetaxel plus cisplatin versus docetaxel monotherapy every 3 weeks in elderly patients with advanced non-small-cell lung cancer: The intergroup trial JCOG0803/WJOG4307L. J Clin Oncol 2015;33:575–581.

5. Quoix E, Zalcman G, Oster JP et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:1079–1088.

6. Maestu I, Gómez-Aldaraví L, Torregrosa MD et al. Gemcitabine and low dose carboplatin in

the treatment of elderly patients with advanced non-small cell lung cancer. Lung Cancer 2003;42: 345–354.

7. Yamamoto N, Nakagawa K, Uejima H et al. Randomized phase II study of carboplatin/gemcitabine versus vinorelbine/gemcitabine in patients with advanced nonsmall cell lung cancer. Cancer 2006; 107:599–605.

8. Takayama K, Ichiki M, Matsumoto T et al. Phase II study on biweekly combination therapy of gemcitabine plus carboplatin for the treatment of elderly patients with advanced non-small cell lung cancer. *The Oncologist* 2019 [Epub ahead of print].

9. Paz-Ares LG, de Marinis F, Dediu M et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:2895–2902.

10. Barlesi F, Scherpereel A, Gorbunova V et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: Updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. Ann Oncol 2014;25:1044–1052.

11. Abe T, Takeda K, Ohe Y et al. Randomized phase III trial comparing weekly docetaxel plus cisplatin versus docetaxel monotherapy every 3 weeks in elderly patients with advanced non-small-cell lung cancer: The intergroup trial JCOG0803/WJOG4307L. J Clin Oncol 2015;33:575–581.

12. Kelly K. The role of single-agent gemcitabine in the treatment of non-small cell lung cancer. Ann Oncol 1999;10(suppl 5):S53–S56.

13. Brodowicz T, Krzakowski M, Zwitter M et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: A phase III trial. Lung Cancer 2006;52:155–163.

Click here to access other published clinical trials.