Single-Agent Versus Combination Chemotherapy in Patients with Advanced Non-small Cell Lung Cancer and a Performance Status of 2

Prognostic Factors and Treatment Selection Based on Two Large Randomized Clinical Trials

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Purpose: Data from two randomized phase III trials were analyzed to evaluate prognostic factors and treatment selection in the first-line management of advanced non-small cell lung cancer patients with performance status (PS) 2.

Patients and Methods: Patients randomized to combination chemotherapy (carboplatin and paclitaxel) in one trial and single-agent therapy (gemcitabine or vinorelbine) in the second were included in these analyses. Both studies had identical eligibility criteria and were conducted simultaneously. Comparison of efficacy and safety was performed between the two cohorts. A regression analysis identified prognostic factors and subgroups of patients that may benefit from combination or single-agent therapy.

Results: Two hundred one patients were treated with combination and 190 with single-agent therapy. Objective responses were 37 and 15%, respectively. Median time to progression was 4.6 months in the combination arm and 3.5 months in the single-agent arm ($p < 0.001$). Median survival times were 8.0 and 6.6 months, and 1-year survival rates were 31 and 26%, respectively. Albumin <3.5 g, extrathoracic metastases, lactate dehydrogenase ≥ 200 IU, and 2 comorbid conditions predicted outcome. Patients with 0–2 risk factors had similar outcomes independent of treatment, whereas patients with 3–4 factors had a nonsignificant improvement in median survival with combination chemotherapy.

Conclusion: Our results show that PS2 non-small cell lung cancer patients are a heterogeneous group who have significantly different outcomes. Patients treated with first-line combination chemotherapy had a higher response and longer time to progression, whereas overall survival did not appear significantly different. A prognostic model may be helpful in selecting PS 2 patients for either treatment strategy.

Key Words: NSCLC, Performance status 2, Paclitaxel poliglumex, Gemcitabine, Vinorelbine, STELLAR, Prognostic model, Combination chemotherapy, Single-agent chemotherapy.

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Impaired performance status (PS) in non-small cell lung cancer (NSCLC) is associated with a poor prognosis and reduced tolerance to treatment. Although current guidelines support the use of systemic chemotherapy in patients with advanced NSCLC and PS 2, there is no consensus on specific treatment recommendations, particularly with respect to single-agent versus combination chemotherapy.[1,2]

Two large phase III randomized trials in advanced NSCLC patients with PS 2 compared paclitaxel poliglumex (PGT)/carboplatin to paclitaxel/carboplatin in one study (STELLAR 3), and single-agent PGT to either vinorelbine or gemcitabine in the second (STELLAR 4). These studies, whose results have been published elsewhere,[3,4] had identical eligibility criteria, were conducted simultaneously, and together represent the largest PS 2 patient population enrolled in randomized trials to date.

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We conducted a retrospective analysis of these data to evaluate the efficacy and safety of the two treatment strategies in the first-line management of advanced NSCLC patients with PS 2. A regression analysis was conducted to determine prognostic factors and identify patient subsets that might benefit from single-agent or combination chemotherapy.

PATIENTS AND METHODS

Eligibility Criteria and Treatment Plan

The study designs for STELLAR 3 and STELLAR 4 and the patient cohorts analyzed in this report are summarized in Figure 1. Briefly, STELLAR 3 was a phase III study comparing paclitaxel 225 mg/m^2 with PGT 210 mg/m^2, each in combination with carboplatin (area under the curve = 6), given every 3 weeks for up to 6 cycles. STELLAR 4 was a phase III comparison of single-agent PGT versus investigator's choice of gemcitabine or vinorelbine. At study initiation, the dose of PGT was 235 mg/m^2. As a result of toxicity in the first 96 patients, the dose of PGT was reduced to 175 mg/m^2 in all subsequent patients. PGT was administered on day 1 of each 21-day cycle for up to 6 cycles. Gemcitabine (1000 mg/m^2) was administered on days 1, 8, and 15 of each 28-day cycle, and vinorelbine (30 mg/m^2) was administered on days 1, 8, and 15 of each 21-day cycle. Both studies were conducted in North America, Western, and Eastern Europe between December 2002 and December 2003 (STELLAR 3), and December 2002 and June 2004 (STELLAR 4). There was no duplication of institutions. Both studies were approved by the institutional review boards and all patients provided written informed consent.

Eligible patients in both studies had confirmed NSCLC, an ECOG PS of 2, stage IV or stage IIIB disease not amenable to combined modality therapy, or recurrent disease previously treated with radiation and/or surgery. Prior systemic chemotherapy was not permitted. Patients with stable, treated brain metastases were eligible. Additional eligibility criteria included a baseline absolute neutrophil count ≥1500/μl; platelet count ≥100,000/μl; creatinine ≤1.5 times the upper limit of normal (ULN); bilirubin ≤ULN; transaminases ≤2.5 times ULN (≤5 times ULN in patients with hepatic metastases); and alkaline phosphatase ≤2.5 times ULN unless bone metastases were present.

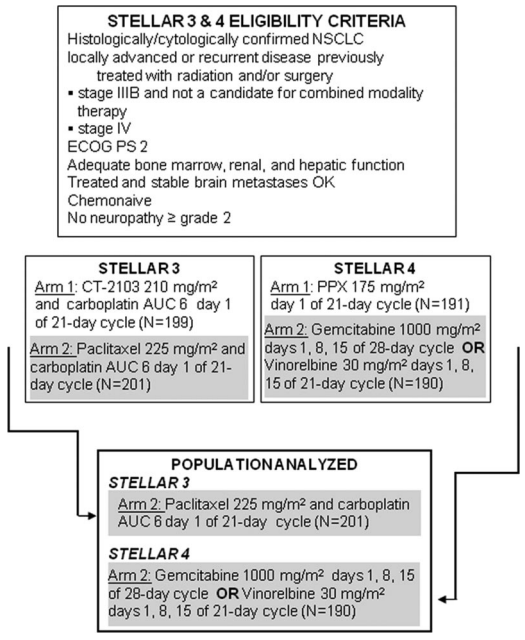


FIGURE 1. STELLAR 3 and 4 STUDY diagrams.

Statistical Considerations

The primary study end point in both STELLAR 3 and 4 was overall survival. Secondary objectives included response rate, assessed by response evaluation criteria in solid tumors (RECIST[5]), time to progression (TTP), disease control, safety, and quality of life. STELLAR 3 targeted accrual of 370 evaluable patients with 80% power and 0.05 type I error to show a 1.5-month improvement in median survival from a projected baseline of 4 to 5.5 months. In STELLAR 4, the original sample size was 370 patients. After the dose of PGT was reduced, the randomization ratio was adjusted to 2:1 and an additional 279 patients (185 randomized to PGT and 94 randomized to the comparator) were accrued, resulting in 80% power and 0.05 type I error to detect a 1.5-month median survival difference between the 2 treatment arms. The unstratified logrank test was used for the primary comparison of survival, which included all randomized patients. Toxicities were evaluated in all patients who received any amount of study drug using the National Cancer Institute Common Toxicity Criteria, version 2, and were compared using the Fisher's exact test. In both studies, disease-related symptoms were measured by the Functional Assessment of Cancer Therapy-Lung Cancer Scale.

This analysis compares efficacy and safety outcomes for patients treated in the control arms of both studies ("combination chemotherapy": carboplatin/paclitaxel and "single-agent therapy": gemcitabine or vinorelbine). Comparison of response and toxicity rates between patients treated with combination chemotherapy versus single agent therapy was made using the Fisher's exact test. Based on the fact that no statistically significant difference in outcomes was observed between the control and the experimental arms in both trials, the regression analysis was performed in the entire population of STELLAR 3 and 4 to increase the power. The Cox proportional hazards model was used for identification of prognostic factors associated with survival and Kaplan-Meier estimates were used to assess medians and percentiles.

RESULTS

Baseline Characteristics

There were 201 patients in the combination cohort and 190 patients in the single-agent cohort. In the latter, 32 patients received vinorelbine and 155 received gemcitabine. Patient demographics are shown in Table 1. The majority of patients were accrued from Eastern European sites. Median age was 63 and 64, respectively, with approximately 23% of patients aged 70 or older in both groups. Approxi-

TABLE 1. Baseline Characteristics by Chemotherapy Regimen

	Combination (n = 201)	Single-Agent (n = 190)
Gender		
Male	156 (78%)	134 (70%)
Female	45 (22%)	56 (30%)
Age (years)		
Median	63	64
Range	36–89	30–90
Geographic location		
United States	45 (22%)	24 (12.6%)
Western Europe and Canada	27 (13%)	25 (13.2%)
Rest of world	129 (64%)	141 (74.2%)
Disease stage at randomization		
IIIA	0	2 (1%)
IIIB	55 (27%)	59 (31%)
IV	146 (73%)	129 (68%)
Extrathoracic disease		
Yes	108 (56%)[a]	84 (44%)
No	84 (44%)	104 (55%)
Unknown	0	2 (1%)
History of brain metastases		
Yes	15 (7%)	6 (3%)
No	186 (93%)	184 (97%)
Smoking history		
Yes	171 (85%)	156 (82%)
No	30 (15%)	34 (18%)

Combination therapy: STELLAR 3, Single-agent therapy: STELLAR 4.
[a] Extrathoracic disease assessed in 192 patients with measurable disease.

mately 27% of the combination cohort and 31% of the single-agent cohort had stage IIIB disease. Nearly 50% of patients presented with extrathoracic disease, including 7 and 3%, respectively, with brain metastases. The percentage of never-smokers ranged from 15 to 18%. For both cohorts, 73 and 80% of the patients had more than 2 comorbid conditions, and 40 and 35%, respectively, had >5% weight loss.

Patient Disposition and Drug Exposure

Patients treated with combination chemotherapy received a median of 4 cycles of protocol therapy, with 41% of patients completing the 6 prescribed cycles. Patients treated with single-agent therapy received a median of 4 cycles, with 23% of patients completing all 6 cycles. Principal reasons for discontinuation of protocol therapy were, in the combination and single-agent groups, respectively, disease progression (34 and 59%) and adverse events (20 and 17%). Dose reductions were required in 17% of patients in the combination cohort and 13% of patients receiving single-agent therapy. Hematologic adverse events accounted for the majority of dose reductions in both the combination cohort and the single-agent cohort (50 and 68%, respectively).

Toxicity

Overall, grade 3–4 events were recorded in 40% of patients treated with combination chemotherapy and 22% of patients treated with single-agent therapy (Table 2). Grade 5 events were noted only in the combination cohort (2%). Grade 3–4 neutropenia (16%) and thrombocytopenia (7%) were more frequent in the combination cohort compared with the single-agent cohort (7% and <1%), while grade 3–4 anemia occurred in about 5% of patients in both groups. Febrile neutropenia occurred in 2 and <1% of patients, respectively. Other notable grade 3–4 nonhematological toxicities in the combination versus single-agent cohorts included nausea (5% versus 1%), diarrhea (4% versus 0%), and peripheral neuropathy (11% versus 0%). Median FACT-LCS scores at baseline were 17.0 in both treatment cohorts; by the end-of-treatment assessment, the median score had increased to 18.0 in the combination therapy group but had decreased to 16.5 in the single-agent treatment group.

Efficacy

Objective partial responses were observed in 38% of patients with measurable disease treated with combination chemotherapy, whereas 16% of patients treated with single-agent therapy experienced an objective response (Table 3).

TABLE 2. Number (%) Selected Treatment-Related Adverse Events by Chemotherapy Regimen (Safety Population)

	Combination n = 198			Single-Agent n = 187		
	Grade 3/4	Grade 5	Total	Grade 3/4	Grade 5	Total
Any AE	79 (39.9%)	3 (2%)	176 (89%)	42 (22.5%)	0	126 (67%)
Neutropenia	31 (15.6%)	0	53 (27%)	13 (7%)	0	25 (13%)
Anemia NOS	9 (4.5%)	0	37 (19%)	10 (5%)	0	46 (25%)
Febrile neutropenia	4 (2%)	1 (<1%)	5 (3%)	1 (<1%)	0	1 (<1%)
Thrombocytopenia	14 (7%)	0	25 (13%)	1 (<1%)	0	17 (9%)
Peripheral sensory neuropathy	11 (6%)	0	68 (34%)	0	0	2 (1%)
Fatigue	5 (3%)	0	16 (8%)	5 (3%)	0	22 (12%)
Nausea	10 (5%)	0	70 (35%)	2 (1%)	0	42 (22%)
Diarrhea	7 (4%)	0	25 (13%)	0	0	7 (4%)

Combination therapy: STELLAR 3, Single-agent therapy: STELLAR 4; AE, adverse event.

TABLE 3. Efficacy Parameters by Chemotherapy Regimen

	Combination	Single-Agent
Tumor response (patients with baseline measurable disease)	$n = 192$	$n = 179$
RECIST criteria–(number/%) with confirmed and unconfirmed CR/PR	73 (38%)	29 (16%)
Other efficacy parameters	$n = 201$	$n = 190$
Disease control (number/%)	138 (69%)	113 (59%)
Median time to progression in months	4.6	3.6
Median overall survival in months (95% confidence interval)	8.0 (6.9–9.6)	6.6 (5.8–7.3)
12-mo overall survival (Kaplan-Meier estimation)	31%	26%
24-mo overall survival (Kaplan-Meier estimation)	11%	10%

Combination therapy: STELLAR 3, Single-agent therapy: STELLAR 4.
CR, complete response; PR, partial response.

Median time to progression was 4.6 months in the combination cohort and 3.5 months in the single-agent cohort ($p < 0.001$). Because of the administration schedule, assessment times for gemcitabine, the treatment most frequently used in the single-agent cohort, were 2 weeks longer than for vinorelbine or combination chemotherapy, which makes an exact comparison problematic. Median survival times were 8.0 months and 6.6 months, for the combination and the single-agent cohorts, respectively (Figure 2). One-year survival rates were 31 and 26% (Table 3). These differences were not statistically significant.

Median survival on the experimental arm (CT-2103/carboplatin) of Stellar 3 was 7.8 months, and the 1-year survival rate was 31%. In Stellar 4, median survival on the experimental arm (CT-2103) was 7.2 months and the 1-year survival rate was 26%.

Exploratory Analyses

A regression analysis was performed to identify patient subsets that may benefit from either combination or single-agent chemotherapy. A Cox multivariate model using stepwise selection was then performed, and 4 of the factors remained significant: albumin <3.5 g (hazard ratio [HR] 1.8; $p < 0.0001$); extrathoracic metastases (HR 1.5; $p < 0.0001$); LDH ≥200 IU (HR 1.4; $p = 0.0006$); and 2 or more comorbid conditions (HR 1.4; $p = 0.0014$).

Of the 781 evaluable patients enrolled in the 2 trials, 52 (6.7%) had no risk factors; 207 patients (26.7%) had 1; 243 (31.4%) had 2; 143 (18.5%) had 3; and 41 (5.3%) had all 4 risk factors. The median survival times for these 5 subgroups are shown in Figure 3. Patients were subsequently grouped into a low-risk (0–2 factors) versus a high-risk subset (3–4 factors). The median survival for the 502 low-risk patients was 8.8 months compared with 4.8 months for the 184 high-risk patients, with 1-year survival rates of 35 and 15%, respectively ($p < 0.001$).

When comparing outcome by treatment received, median survival was identical at 8.8 months in the low-risk

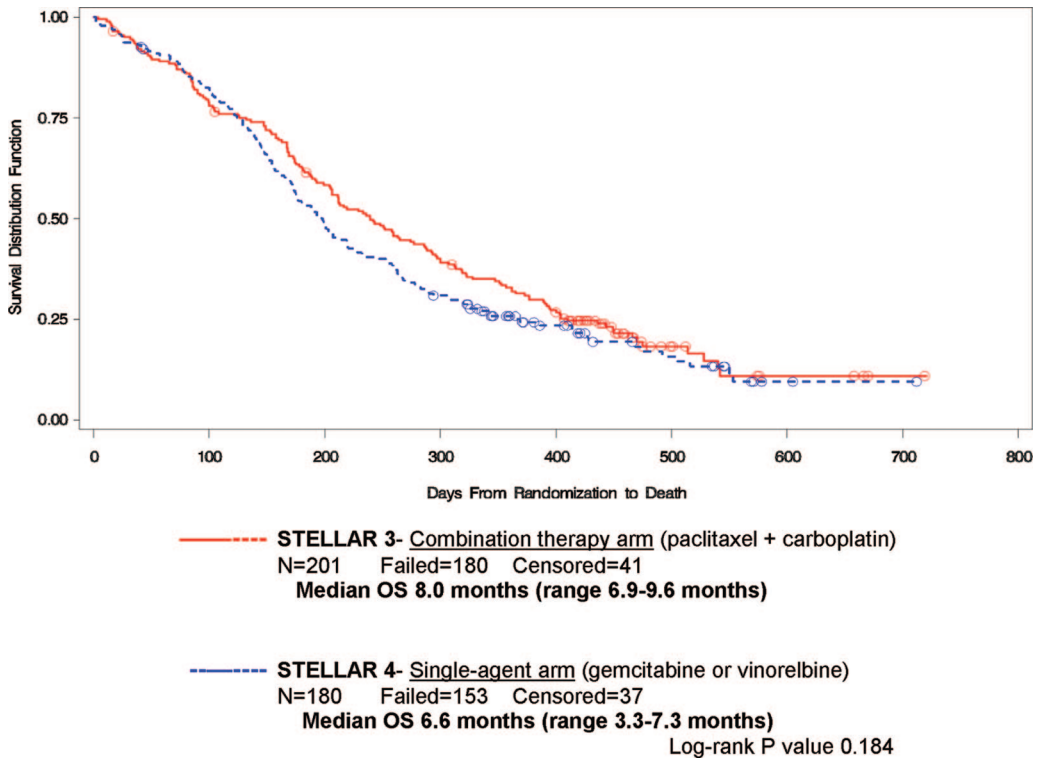
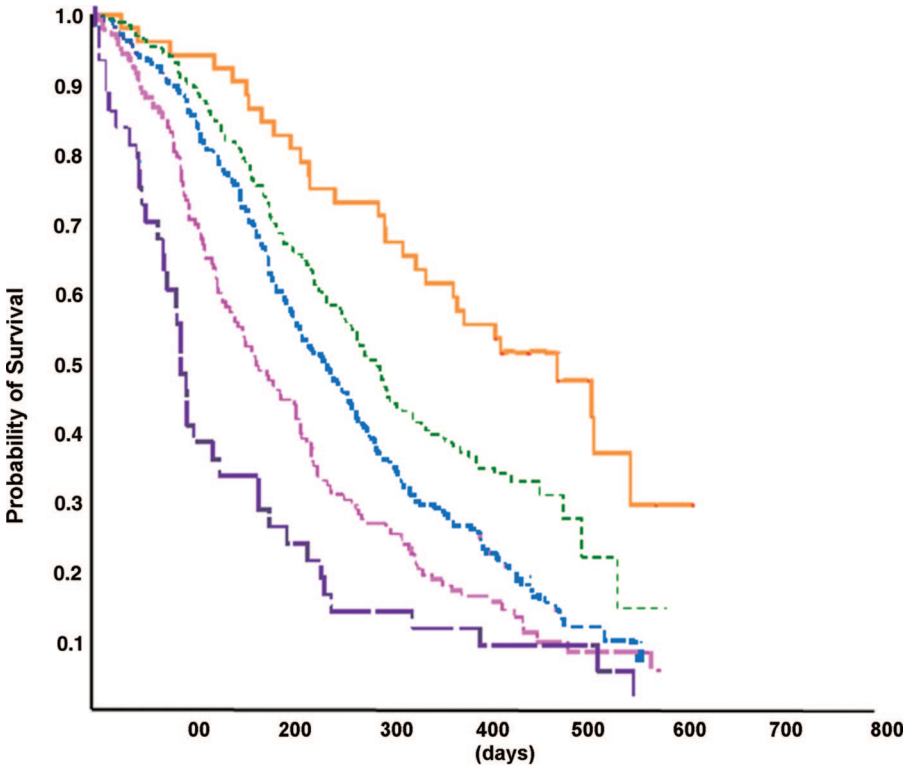


FIGURE 2. Overall survival in days using Kaplan-Meier estimation (combination versus single-agent therapy).



Estimated Survival by Risk Factors			
# of risk factors	N	# of events	Median Time (days/months)
0	52	29	468/15.6
1	207	135	284/9.5
2	243	197	233/7.8
3	143	128	161/5.4
4	41	40	90/3.0

FIGURE 3. Overall survival (in days) by risk. Factors using Kaplan-Meier estimation (All STELLAR 3 and 4 patients).

subset treated with combination chemotherapy or single-agent therapy, with 1-year survival rates of 37 and 33%, respectively. In the high-risk subset, median survival was 5.8 months, and 1-year survival was 18% for patients treated with combination compared with 4.3 months and 13% for patients treated with single-agent therapy ($p = 0.2$).

Analysis of adverse events in the low-risk versus high-risk groups showed similar toxicity profiles, with the exception of more adverse events because of progressive disease in high-risk patients (53% versus 40%). The rates of grade 3–4 neutropenia (12.2% and 11.5%) and neuropathy (14.8% and 13.7%) ≥grade 2 were similar in the low-risk compared with the high-risk groups. Tolerability was acceptable overall, and further subset analysis was not performed on these groups.

DISCUSSION

Patients with a poor PS constitute approximately 30 to 40% of advanced NSCLC patients seen in clinical practice.[6] Early data showed that these patients did not seem to benefit from treatment and experienced a high rate of fatal toxicities from chemotherapy.[7] This resulted in the exclusion of PS 2 patients from cooperative group clinical trials for over a decade and led to an absence of randomized data or guidelines for this subset of patients.

The STELLAR 3 and 4 trials are the largest trials ever conducted in PS 2 patients with advanced NSCLC. These trials had identical eligibility criteria and were conducted simultaneously in similar geographic regions. The patients enrolled in the control arms of each of the 2 trials were treated with combination chemotherapy and single-agent therapy, respectively, and therefore provide a unique opportunity to assess, within a uniform population, the efficacy and safety of each approach in the first-line management of PS 2 patients.

Patients treated with combination chemotherapy had a significantly better response rate and longer time to progression compared with those treated with single-agent therapy. Median survival trended in favor of patients treated with combination chemotherapy but did not reach statistical significance. The 1-year survival rates were similar between the two cohorts. Toxicity, particularly neutropenia and peripheral neuropathy, was more prevalent in patients treated with combination chemotherapy. However, the rate of fatal toxic-

ities and quality of life parameters were similar in the two cohorts.

The regression analysis further defined the value of combination versus single-agent therapy in this subset of patients. The four risk factors identified in our model, some of which have also been shown to be of prognostic importance in patients with PS 0–1,[8] were strong predictors of survival in the PS 2 population analyzed. Further, grouping of patients based on the number of risk factors showed that in the low-risk group, combination chemotherapy and single-agent therapy yielded comparable survival, whereas in the high-risk group, a trend toward better median survival, represented by a 1.5-month absolute improvement, was noted in patients treated with combination chemotherapy. Although the number of patients in the low-risk subset was sufficiently robust, the number of patients in the high-risk category was small and a significant difference cannot be excluded.

Although these data are derived from a retrospective analysis and therefore should be interpreted with some caution, they seem to be in agreement with recent clinical trials. A randomized trial of carboplatin and gemcitabine versus gemcitabine alone has so far been the only such trial dedicated to PS 2 patients.[9] However, it was stopped before reaching its accrual goal, resulting in loss in statistical power. In the 170 randomized patients, objective responses were significantly higher in the combination arm (36.4% versus 11.5%). Progression-free survival was 4.01 versus 2.79 months ($p = 0.324$) and median survival time was 6.9 versus 5.2 months respectively (0.383). Toxicity was worse with the combination regimen but quality of life scores trended worse with the single-agent arm. Of interest, baseline LDH level was also a significant predictor of outcome. A previous Cancer and Leukemia Group B trial comparing carboplatin-paclitaxel with single-agent paclitaxel included 99 eligible PS 2 patients and showed a significantly superior response rate, time to progression, and overall survival for patients treated with combination chemotherapy.[10] Overall, these results are strikingly similar to our current analysis and lend credence to the overall conclusions.

Our results show that PS2 NSCLC patients are a heterogeneous group who have significantly different outcomes. Patients treated with first-line combination chemotherapy had a higher response and longer TTP, whereas overall survival did not seem significantly different. A prognostic model may be helpful in selecting PS 2 patients for either treatment strategy. However, the controversy around the optimal treatment for PS 2 patients with advanced NSCLC remains unresolved and can only be addressed by prospective randomized clinical trials.

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