

## Phase II study of gemcitabine plus oxaliplatin as first-line chemotherapy for advanced non-small-cell lung cancer

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This phase II study evaluated the response rate and tolerability of gemcitabine–oxaliplatin chemotherapy in non-small-cell lung cancer (NSCLC) patients. Chemonaive patients with stage IIIB or IV NSCLC received gemcitabine 1000 mg m<sup>-2</sup> on days 1 and 8, followed by oxaliplatin 130 mg m<sup>-2</sup> on day 1. Cycles were repeated every 21 days for up to six cycles. From February 2002 to May 2004, 60 patients were enrolled into the study in seven Italian institutions. We observed one complete response (1.7%) and 14 partial responses (23.3%), for an overall response rate of 25.0% (95% confidence interval, 14.7–37.9%). The median duration of response was 5.9 months (range 1.5–17.1 months). With a median follow-up of 6.7 months, median time to progressive disease and overall survival were 2.7 (range 1.9–3.4 months) and 7.3 months (range 7.2–8.6 months), respectively. The main grade 3–4 haematological toxicities were transient neutropenia in 11.7% and thrombocytopenia in 8.3% of the patients. Nausea/vomiting was the main grade 3–4 nonhaematological toxicity, occurring in 10.0% of the patients. Two (3.3%) patients developed grade 3 neurotoxicity. Our results show that gemcitabine–oxaliplatin chemotherapy is active and well tolerated in patients with advanced NSCLC, deserving further study, especially for patients not eligible to receive cisplatin.

British Journal of Cancer (2005) 93, 29–34. doi:10.1038/sj.bjc.6602667 www.bjancer.com

Published online 14 June 2005

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**Keywords:** oxaliplatin; gemcitabine; chemotherapy; non-small-cell lung cancer

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death in the world (Greenlee *et al*, 2001). Platinum-based chemotherapy is considered the standard treatment for advanced disease, with cisplatin considered the most effective for NSCLC (Non-Small Cell Lung Cancer Collaborative Group, 1995). New agents, such as taxanes and vinorelbine, administered with a platinum derivative, have resulted in improved median and 1-year survival times when compared with either cisplatin alone or older platinum-based combinations in randomised trials (Le Chevalier *et al*, 1994; Wozniak *et al*, 1998; Bonomi *et al*, 2000; Sandler *et al*, 2000).

Gemcitabine's mild toxicity profile, both in terms of haematological toxicity and visceral side effects, and novel mechanism of action have encouraged its use in combination with traditional agents, such as cisplatin. Gemcitabine–cisplatin chemotherapy is considered one of the most active regimens for advanced NSCLC, with an overall response rate (ORR) of 22–38% and median survival of 8.1–9.8 months in phase III trials (Crinò *et al*, 1999; Scagliotti *et al*, 2002; Schiller *et al*, 2002). Although several phase

III trials of new platinum-based doublets (Kelly *et al*, 2001; Schiller *et al*, 2002; Smit *et al*, 2003) have produced similar results, a recent meta-analysis showed an absolute 1-year survival benefit of 3.9% for gemcitabine–cisplatin chemotherapy when compared to other platinum-containing regimens (Le Chevalier *et al*, 2005).

Cisplatin has been the most widely used platinum derivative, but it is known to yield significant toxicities, including severe nausea and vomiting, and renal toxicity, requiring adequate hydration, ototoxicity and neuropathy. Oxaliplatin is a diamincyclohexane platinum compound, with a mechanism of action similar to that of cisplatin (Woynarowski *et al*, 2000), that has shown activity against a variety of cancer types, including colon (de Gramont *et al*, 1997) and NSCLC (Monnet *et al*, 1998). Oxaliplatin has a more manageable toxicity profile than cisplatin, with no renal toxicity and a lower incidence of haematological and gastrointestinal toxicities. It lacks the nephrotoxicity of cisplatin and causes less myelotoxicity than carboplatin, the leading cisplatin analog, and it may be active in cisplatin- and carboplatin-resistant tumours (Chollet *et al*, 1996; Raymond *et al*, 1998b). The main toxicity associated with oxaliplatin is a generally reversible peripheral neuropathy (Raymond *et al*, 1998a).

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Received 8 April 2005; revised 16 May 2005; accepted 16 May 2005;  
published online 14 June 2005

Oxaliplatin has demonstrated synergy with gemcitabine, with a sequence dependency that favours the administration of gemcitabine, followed by oxaliplatin (Faivre *et al*, 1999). A phase I trial, conducted by Shibata *et al* (2001), investigated the maximum tolerated dose of gemcitabine-oxaliplatin in patients with solid tumours. This study showed that oxaliplatin 130 mg m<sup>-2</sup> on day 1 could be safely administered with gemcitabine 1000 mg m<sup>-2</sup> on days 1 and 8 every 21 days. Using different schedules, other investigators (Faivre *et al*, 2002; Mavroudis *et al*, 2003) confirmed that gemcitabine-oxaliplatin is feasible, with no dose-limiting toxicities, easy to administer on an outpatient basis, and shows promising activity in patients with NSCLC and ovarian cancer.

On the basis of these data, we designed a phase II, multicentre trial to evaluate the response rate and tolerability of gemcitabine-oxaliplatin in untreated patients with stage IIIB or IV NSCLC, applying the same 3-week dosing schedule as per Shibata *et al*. Secondary end points were time to progressive disease (TTPD) and overall survival (OS).

## PATIENTS AND METHODS

### Patient selection

Chemonaive patients with histologically or cytologically confirmed locally advanced or metastatic stage IIIB or IV NSCLC not amenable to surgery or radiotherapy with curative intent were eligible for this study. Other eligibility criteria included the presence of at least one measurable lesion; age  $\geq 18$  to  $\leq 75$  years; Karnofsky performance status (KPS)  $\geq 70$ , life expectancy  $\geq 12$  weeks; adequate bone marrow reserve (absolute neutrophil count  $\geq 2.0 \times 10^9 l^{-1}$ , platelet count  $\geq 100 \times 10^9 l^{-1}$ ). Patients with asymptomatic brain metastases were eligible. No prior chemotherapy or immunotherapy or concomitant radiotherapy was allowed. Prior radiotherapy was acceptable if completed 4 weeks before study entry.

Exclusion criteria included inadequate liver function (bilirubin  $> 1.5$  times above normal range, aspartate transaminase (AST) and alanine transaminase (ALT)  $> 3$  times the normal range, or five times greater than the normal range in the presence of liver metastases); severe alteration of renal functionality (serum creatinine  $> 2 \times$  the upper limit of normal (ULN)); no second malignancies (except for carcinoma of the cervix uteri *in situ* and squamous cell carcinoma of the skin); peripheral neuropathy; untreated superior vena cava syndrome; hypercalcaemia requiring intravenous (i.v.) treatment; the presence of uncontrolled cardiac disease, uncontrolled diabetes mellitus, infections or other medical conditions that could have interfered with the trial.

Written informed consent was obtained from each patient before entering the study. The study was approved by the local Ethics Committee and was conducted in accordance with ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represented the greater protection of the individual.

### Treatment plan and dose adjustments

Gemcitabine (Gemzar<sup>®</sup>, Eli Lilly and Company, Indianapolis, IN, USA) 1000 mg m<sup>-2</sup> was administered as a 30-min i.v. infusion on days 1 and 8 of a 21-day cycle. Oxaliplatin (Eloxatin<sup>®</sup>, Sanofi-Synthelabo, Paris, France) 130 mg m<sup>-2</sup> was administered as a 2-h i.v. infusion on day 1, following gemcitabine. All patients were scheduled to receive at least two cycles of therapy, and up to six cycles if there was no evidence of disease progression. Treatment was stopped early in cases of patient refusal, severe toxicity, documented progressive disease (PD) or pregnancy. Patients with PD after two or four cycles or with stable disease after four cycles of chemotherapy were withdrawn from the study. Full supportive

therapy, corticosteroids, anticonvulsants and antibiotics were given as needed. Antiemetic premedication included 5-HT<sub>3</sub> antagonists. No routine use of haematopoietic growth factors was planned. No prophylactic antibiotics were used. All patients were treated on an outpatient basis.

Dose adjustments during treatment were based on haematological and nonhaematological toxicities. On day 1, if neutrophil count was  $< 1.5 \times 10^9 l^{-1}$  and/or platelet count was  $< 100 \times 10^9 l^{-1}$ , chemotherapy doses were delayed (for up to 2 weeks) and doses were reduced by 25% to allow recovery from haematological toxicity. On day 8, for a neutrophil count  $< 1.0$  and/or platelets  $< 75$ , the gemcitabine dose was omitted, and the cycle continued with one gemcitabine dose not given. Patients not recovering from haematological toxicity (neutrophil count  $> 1.0$  and platelets  $> 75$ ) within 2 weeks were withdrawn from the trial. Doses were reduced by 25% for any grade 3 nonhaematological toxicity (excluding nausea, vomiting and alopecia). Treatment was discontinued in the event of grade 4 or frequent grade 3 nonhaematological toxicity. For grade 2–4 neurological toxicity, oxaliplatin treatment was delayed until the patient recovered to grade 1, then the dose was reduced by 25%. If no recovery to grade 1 was achieved in 3 weeks, the patient was discontinued from the trial.

For hepatic toxicity, the day-1 gemcitabine dose was reduced by 25% for AST/ALT 1.6 to  $5.0 \times$  ULN, alkaline phosphatase  $\leq 5.0 \times$  ULN and bilirubin  $< ULN$ . Treatment was delayed for up to 2 weeks for AST/ALT  $> 5 \times$  ULN or alkaline phosphatase  $> 5 \times$  ULN or bilirubin  $> ULN$ . The day-1 gemcitabine dose was omitted for a total bilirubin  $> 1.5$  ULN. For nephrotoxicity, gemcitabine doses were reduced by 25% for serum creatinine  $> 1.5$ – $2.0$  ULN and creatinine clearance  $\geq 50$  ml min<sup>-1</sup>. Treatment was delayed for serum creatinine  $> 1.5$  UNL and creatinine clearance  $< 50$  ml min<sup>-1</sup> or serum creatinine greater than  $> 2.0$  UNL with any creatinine clearance value.

### Baseline and treatment assessments

Pretreatment evaluation included physical examination; KPS; chest X-ray; brain, thoracic and abdominal computer tomography scan (CT scan); bronchoscopy (if not performed at the time of diagnosis); bone scan; electrocardiogram; complete blood count and blood chemistry with liver function tests and creatinine clearance. On days 1 and 8, a physical exam (including weight) was performed, and KPS and blood count were assessed. All measurable and evaluable lesions were assessed by the same method used at baseline. Response to therapy was assessed every two cycles with clinical and/or radiological tumour assessment.

In responding patients, a confirmatory assessment was repeated after at least 4 weeks, according to the RECIST criteria (Therasse *et al*, 2000). Assessment of TTPD was determined by measuring the time interval from the beginning of treatment until the first documentation of progression or death due to any cause. Survival (OS) was determined by measuring the time interval from the beginning of the treatment to the date of death or last contact. Toxicity was evaluated according to NCI criteria (Common Toxicity Criteria, 1993). No quality of life questionnaire was used in the present study.

### Statistical plan

A two-stage design was used for the study. Using the Simon (1989) hypothesis, assuming a response rate of 40%, a probability of error of 5% and a power of 90%, a total of 54 patients were to be enrolled, with at least five responses to be noted in the first 19 patients. Treatment was considered effective if at least 16 objective responses were observed. Every patient included in the study was considered evaluable (intent-to-treat analysis). Response rates, including 95% confidence intervals (CIs), were calculated on an intent-to-treat basis. Time-to-event end points were calculated

using the Kaplan–Meier method, with the appropriate censoring (Kaplan and Meier, 1958).

## RESULTS

### Patient characteristics

From February 2002 to May 2004, a total of 60 patients were enrolled in this trial in seven Italian centres. Patients' characteristics at baseline are listed in Table 1. The majority of patients were male (71.7%), with a median age of 61 years (range 36–74). Performance status was 100 in 46.7% of patients; 51 (85.0%) patients had stage IV and nine (15.0%) had stage IIIB disease. Histology was predominantly adenocarcinoma (55.9% of the patients).

### Efficacy

As per the ITT analysis, the ORR was 25.0% (95% CI, 14.7–37.9%), including one complete response (CR: 1.7%) and 14 partial responses (PRs: 23.3%, Table 2). Two patients were not assessable

**Table 1** Baseline patient characteristics (N = 60)

Characteristics	No. of patients
Median age (range), years	61 (36–74)
Male/female (%)	43 (71.7)/17 (28.3)
KPS (%)	
100	28 (46.7)
90–80	31 (51.7)
70	1 (1.7)
Stage IIIB/IV (%)	9 (15.0)/51 (85.0)
Sites of metastasis	
Liver	6
Brain	4
Bone	4
Nodes	22
Others	17
No. of metastatic sites	
1	31
≥2	20
Histology (%)	
Adenocarcinoma	33 (55.0)
Squamous	17 (28.3)
Bronchioloalveolar	1 (1.7)
Undifferentiated	5 (8.3)
Other NSCLC	3 (5.0)
Unknown	1 (1.7)

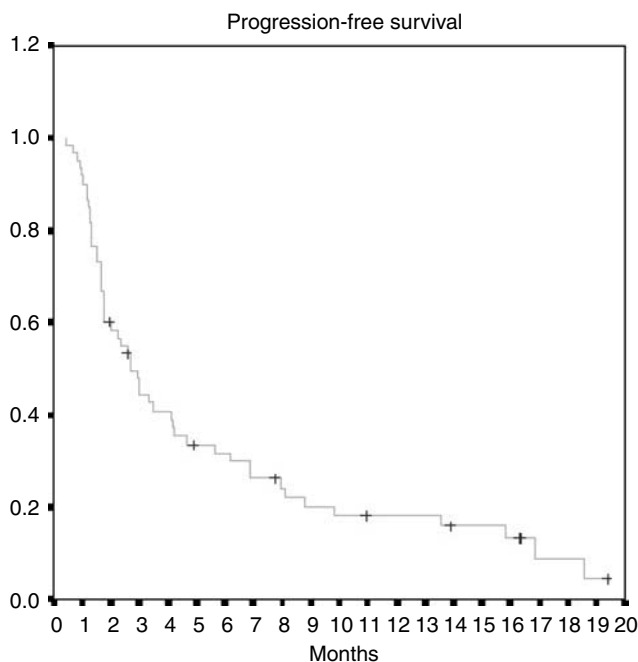
KPS = Karnofsky performance status; NSCLC = non-small-cell lung cancer.

**Table 2** Best overall response (N = 60)

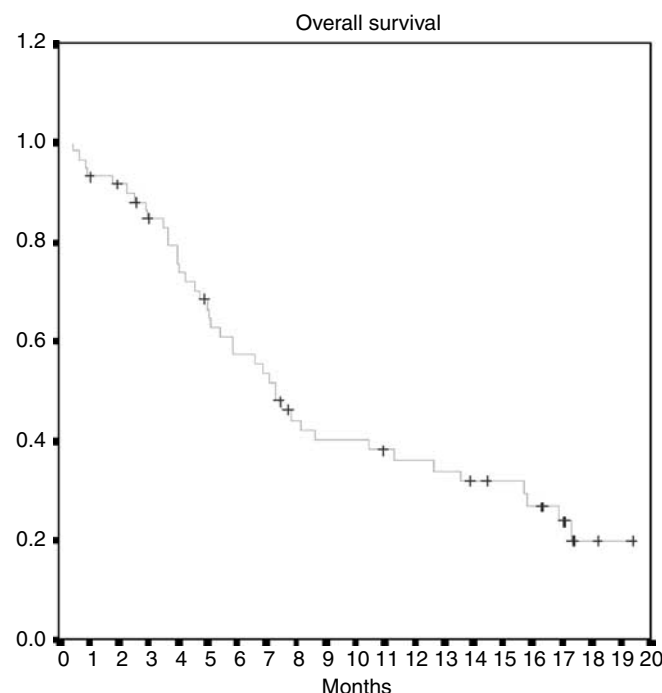
Response	n (%)
ORR	15 (25.0)
CR	1 (1.7)
PR	14 (23.3)
SD	18 (30.0)
PD	25 (41.7)
Not assessable	2 (3.3)

ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

for response because they discontinued the trial after the first cycle, one for heart attack and the other for cardiac failure; neither event was related to the study drugs. The median duration of response was 5.9 months (range 1.5–17.1 months). With a median follow-up time of 6.7 months, the median TtPD was 2.7 (range 1.9–3.4 months), median OS time was 7.3 months (range 7.2–8.6 months) and 1-year survival was 36% (Figures 1, 2).



**Figure 1** Kaplan–Meier curve for progression-free survival.



**Figure 2** Kaplan–Meier curve for OS.

**Table 3** Worst grade 3–4 NCI haematological toxicity

Toxicity	By patient (N = 60)		By cycle (N = 209)	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Neutropenia	6 (10.0)	1 (1.7)	16 (7.7)	1 (0.5)
Thrombocytopenia	4 (6.7)	1 (1.7)	10 (4.8)	1 (0.5)
Anaemia	1 (1.7)	0	1 (0.5)	0
Leukopenia	1 (1.7)	0	1 (0.5)	0

**Table 4** Worst grade 3–4 NCI nonhaematological toxicity

Toxicity	By patient (N = 60)		By cycle (N = 209)	
	Grade 1–2 n (%)	Grade 3–4 n (%)	Grade 1–2 n (%)	Grade 3–4 n (%)
Gastrointestinal	37 (61.7)	6 (10.0)	126 (60.3)	9 (4.3)
Neurological	27 (45.0)	2 (3.3)	52 (24.9)	2 (1.0)
Hepatic	17 (28.3)	2 (3.3)	73 (34.9)	2 (1.0)
Dermatological	11 (18.3)	1 (1.7)	12 (5.7)	1 (0.5)
Cardiovascular	7 (11.7)	2 (3.3)	7 (3.3)	2 (1.0)
Pulmonary	15 (25.0)	1 (1.7)	31 (14.8)	1 (0.5)

### Treatment administration

A total of 209 chemotherapy courses were administered, with a median of 3.9 cycles per patient (range 1–6), and 16 (26.7%) patients received all six cycles. The planned dose intensity was  $666.6 \text{ mg m}^{-2} \text{ week}^{-1}$  for gemcitabine and  $43.3 \text{ mg m}^{-2} \text{ week}^{-1}$  for oxaliplatin. Dose intensity for all 60 patients was  $615 \text{ mg m}^{-2} \text{ week}^{-1}$  for gemcitabine and  $42.4 \text{ mg m}^{-2} \text{ week}^{-1}$  for oxaliplatin, with 92.3% of the planned gemcitabine dose and 97.9% of the planned oxaliplatin dose delivered.

### Toxicity

The main haematological toxicities (Table 3) were transient grade 3–4 neutropenia observed in seven (11.7%) patients, grade 3–4 thrombocytopenia not requiring platelet transfusion in five (8.3%) patients and grade 3 anaemia in one (1.7%) patient. No neutropenic fever or bleeding episodes were recorded. Nonhaematological toxicity was generally manageable (Table 4). Grade 3 nausea/vomiting occurred in five (8.3%) and grade 4 occurred in one (1.7%) patients. Two (3.3%) patients developed grade 3 neurotoxicity requiring oxaliplatin dose reduction. Two (3.3%) patients had grade 4 cardiovascular toxicity consisting of extrasystoles and atrial flutter. A total of 25.0% of the patients displayed grade 1–2 pulmonary symptoms, such as dyspnea, but this was due to disease progression. Grade 1 nephrotoxicity occurred in one (1.7%) patient. Two serious adverse events were reported during the study. One patient died after the first course due to heart attack and the other patient died due to cardiac failure. Neither of these deaths was considered treatment-related.

### DISCUSSION

Our study confirmed the promising activity and favourable toxicity profile of gemcitabine–oxaliplatin in patients with stage IIIB/IV NSCLC. We observed an ORR of 25.0%, with one CR and

14 PRs. The median duration of response was 5.9 months (range 1.5–17.1 months). Median TtPD was 2.7 months (range 1.9–3.4 months) and median OS was 7.3 months (range 7.2–8.6 months).

The 25% ORR observed in the present study seems to be not different from the 20–22% response rate obtained with gemcitabine when used as single agent (Abratt *et al*, 1994; Gatzemeier *et al*, 1996). However, although our study population was relatively young and with good performance status, a large percentage of stage IV patients was enrolled, including individuals with unfavourable prognostic factors, such as brain metastases.

Two trials have evaluated the activity and toxicity of gemcitabine–oxaliplatin in NSCLC patients (Faivre *et al*, 2002; Franciosi *et al*, 2003). Both trials included pretreated patients, and response rates ranged from 16 to 34%. The 16% response rate reported in the Franciosi trial was lower than that reported in our study (25.0%), probably because our study was conducted only in chemo-naïve patients. In the study conducted by Faivre *et al*, 12 of the 35 patients (34.2%) enrolled in the trial responded to the therapy, including two platinum-resistant patients. These results are better than those observed in our trial, probably because of the different characteristics of our cohort, which included a larger percentage of stage IV disease (85% in our study vs 71%), and a lower percentage of patients with a performance status of 100 (46.7% in our study vs 85.7%).

The response rate observed with gemcitabine–oxaliplatin in the present trial was also comparable to the activity of oxaliplatin-based combinations observed in other phase II studies. Oxaliplatin has been evaluated in combination with vinorelbine (Monnet *et al*, 2001) and in combination with taxanes (Winegarden *et al*, 2004), producing response rates of 19 and 37%, respectively.

One of the most important findings of our trial is the low toxicity profile demonstrated by gemcitabine–oxaliplatin. In phase II trials, single-agent gemcitabine was administered at the dose of  $1000\text{--}1250 \text{ mg m}^{-2}$  on days 1, 8 and 15 (Anderson *et al*, 1994; Gatzemeier *et al*, 1996; Le Chevalier *et al*, 1997), or at the dose of  $1250 \text{ mg m}^{-2}$  on days 1 and 8 when used in combination with cisplatin (Castellano *et al*, 1998). Planned dose intensity of gemcitabine in our study was lower than those reported by others (Anderson *et al*, 1994; Gatzemeier *et al*, 1996; Le Chevalier *et al*, 1997; Castellano *et al*, 1998), providing an additional explication for the excellent toxicity profile demonstrated by this regimen. We used the  $130 \text{ mg m}^{-2}$  dose per cycle for oxaliplatin and  $2000 \text{ mg m}^{-2}$  dose per cycle for gemcitabine evaluated in other reports (Franciosi *et al*, 2003; Mavroudis *et al*, 2003), and further demonstrated that the haematological and nonhaematological toxicities with this regimen are generally mild or moderate. The tolerability of the regimen is underscored by the fact that we were able to deliver full doses of the planned therapy to the majority of patients. The main grade 3–4 haematological toxicities were transient neutropenia and thrombocytopenia (11.7 and 8.3% of patients, respectively). Nausea/vomiting was the main grade 3–4 nonhaematological toxicity, occurring in six (10.0%) patients. Only two (3.3%) patients developed significant (grade 3) neurotoxicity.

The low incidence of side effects in our trial is of particular relevance to clinical practice because it suggests that gemcitabine–oxaliplatin could be used in patients ineligible for standard platinum-based therapy, such as the elderly or unfit. At the present time, single-agent therapy is the standard treatment for elderly or unfit patients (Gridelli *et al*, 2003), but there is clear evidence that two-drug combinations are better than single-agent therapy (Sederholm, 2002; Lilienbaum *et al*, 2005), and platinum-based chemotherapy should be considered for selected elderly patients (Bunn and Lilienbaum, 2003).

In conclusion, our findings further demonstrate that gemcitabine–oxaliplatin is active and well tolerated in patients with advanced NSCLC. The favourable toxicity profile of this regimen also justifies its use in patients in whom cisplatin may not be feasible, such as the elderly or unfit. Oxaliplatin hopefully will

become an alternative to cisplatin whose toxicity profile is not acceptable for many patients with NSCLC. In the era of targeted therapies, this combination deserves to be studied further in

association with new agents, such as the antivasular endothelial growth factor bevacizumab, or the monoclonal antibody anti-epidermal growth factor receptor cetuximab.

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