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A Phase II Study of Ibrutinib in Advanced Neuroendocrine Neoplasms

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Keywords
Ibrutinib · Carcinoid tumor · Pancreatic neuroendocrine tumor · Neuroendocrine neoplasm

Abstract
Background: Ibrutinib is an orally administered inhibitor of Bruton's tyrosine kinase (Btk). Preclinical data suggest that mast cells are recruited within neuroendocrine neoplasms (NENs) where they stimulate angiogenesis and tumor growth. Ibrutinib inhibits mast cell degranulation and has been associated with regression of tumors in a mouse insulinoma model. ***Methods:*** A prospective, phase II trial evaluated patients with advanced gastrointestinal (GI)/lung NENs and pancreatic NENs (pNENs) who had evidence of progression within 12 months of study entry on at least one prior therapy. Patients received ibrutinib 560 mg daily until unacceptable toxicity, progression of disease, or withdrawal of consent. The primary endpoint was objective response rate. ***Results:*** Twenty patients were enrolled on protocol from November 2015 to December 2017 (15 advanced GI/lung NENs and 5 pNENs). No patient reached an objective response. Median PFS was 3.0 months. A total of 44 drug-related adverse events (AEs) were captured as probably or definitely associated with ibrutinib. Five patients experienced probably or definitely related grade 3 AEs, and 1 patient experienced a probably related grade 4 AE. Five patients discontinued treatment prior to radiographic assessment. ***Conclusions:*** Ibrutinib does not show significant evidence of activity in well-differentiated gastroenteropancreatic and lung NENs.

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of malignancies characterized by a relatively indolent rate of growth and a propensity to produce and secrete a variety of hormones and vasoactive peptides. Although they may arise in many organs, NENs often originate in the gastrointestinal (GI) tract and lungs (in which case they are often called "carcinoid tumors") and in the pancreas [1]. The incidence of NENs has been steadily increasing in the last 40 years, and increased survival durations have been reported over time [2].

The therapeutic landscape of NENs has considerably widened in recent years [1]. Beyond somatostatin

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analogs, treatment options have expanded, with approvals by the Food and Drug Administration (FDA) of everolimus for treatment of progressive nonfunctioning GI and lung NENs, and of ^{177}Lu-dotatate for gastroenteropancreatic (GEP) NENs. Approved treatment options for progressive pancreatic NENs (pNENs) also include the tyrosine kinase inhibitor (TKI) sunitinib, in addition to everolimus and ^{177}Lu-dotatate. Cytotoxic therapies, such as capecitabine and temozolomide, have shown substantial activity in pNENs, as shown in both retrospective and prospective trials [1–4]. Despite such progress, the long-term outcomes of patients with advanced NENs still remain poor, and new, effective therapies are needed.

Mast cell activation is a novel potential target for NEN therapy. Evidence from a mouse model of pancreatic β-cell tumorigenesis suggests that chronic activation of the transcription factor Myc is sufficient to initiate and orchestrate a complex inflammatory and angiogenic response, characterized by a rapid influx of mast cells into the tumor and its adjacent mesenchyma [5]. Recruitment of mast cells within the microenvironment of insulinomas has been also shown to regulate neoangiogenesis and tumor macroscopic expansion, and inflammation has been therefore proposed as an "oncogene's weapon" playing a key role in the development of these neoplasms [5].

Ibrutinib is an orally administered covalent inhibitor of Bruton's tyrosine kinase (Btk), and is currently approved for the treatment of hematological malignancies including chronic lymphocytic leukemia, Waldenström's macroglobulinemia, and specific lymphoma subtypes [6]. It is administered at a 560-mg daily dose when used as a monotherapy, and at a 420-mg daily dose in combination with rituximab. Btk is critically involved in the signaling evoked by the activation of the B-cell receptor in lymphocytes, but it also plays a role in modulating mast cell degranulation, acting downstream of the high-affinity IgE receptor FcεRI [7]. In mice harboring Myc-driven insulinomas, systemic treatment with ibrutinib has been shown to induce collapse of tumor vasculature and dramatic tumor regression through the inhibition of mast cell degranulation. Moreover, the drug was found to inhibit directly the proliferation of NEN cells, although the mechanisms underlying this effect remain unclear [8].

Based on this preclinical evidence of activity in NENs, a phase II study was launched to investigate ibrutinib in patients with GEP and lung NENs, with the objective response rate (ORR) as the primary endpoint.

Patients and Methods

Patient Selection

This study was an open-label, single-arm phase II study consisting of 2 cohorts: GI/lung NENs (carcinoid tumors) and pNENs.

Subjects were adults (age ≥18 years) with locally advanced or metastatic well-differentiated (low or intermediate grade according to the WHO 2010 classification) GI/lung or pNENs, with evidence of progressive disease within 12 months of study entry. Any number of prior treatments was allowed, and concurrent therapy with somatostatin analogs was permitted in patients with secretory tumors. Other key eligibility criteria were measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, absolute neutrophil count ≥1,000 cells/μL, platelets ≥100,000 cells/μL, hemoglobin >10 g/dL, total bilirubin ≤1.5 × upper limits of normal (ULN), AST and ALT ≤2.5 × ULN, and creatinine ≤2.0 mg/dL. Key exclusion criteria included poorly differentiated histology and active cardiovascular disease.

Treatment and Evaluation

Ibrutinib was orally administered at a dose of 560 mg once daily and each cycle was defined as 4 weeks duration. Dose reduction by 140 mg per day was permitted for patients with persistent grade 2 toxicity impacting quality of life. The dose was held for any grade 3 or higher nonhematological toxicity, grade 3 or higher neutropenia with infection or fever, or grade 4 hematological events that were considered drug-related, and resumed once toxicity resolved to ≤grade 1. If the toxicity recurred, the dose was required to be reduced by one capsule (140 mg per day). A second dose reduction by 140 mg per day was allowed as needed for subsequent occurrences of toxicity. Permanent discontinuation was required for reoccurrence of severe toxicity following 2 dose reductions. If patients continued to experience the same drug-related toxicities that prompted dose reduction, despite 2 dose reductions, ibrutinib was required to be permanently discontinued and the patient taken off study. Patients were removed from the study if they required a dose hold for >3 weeks. Table 1 describes the dose modification and reduction guidelines that were followed in the protocol.

Evaluation visits were scheduled every 4 weeks along with standard blood tests (complete blood count, comprehensive metabolic panel). Chromogranin A (CgA) was monitored every 12 weeks and other secretory proteins or amines (e.g., 5-hydroxyindoleacetic acid) were monitored every 12 weeks, if patients presented with hormonally active tumors. Biochemical response was defined as ≥50% reduction in tumor marker from baseline. Baseline radiologic assessments of tumor burden (multiphasic CT or MRI scans) were completed within 28 days prior to initiation of study treatment and repeated every 12 weeks from start of treatment. RECIST version 1.1 was used for evaluation of the primary endpoint.

Sample Size Calculation

The primary endpoint was the ORR rate. Secondary endpoints included progression-free survival (PFS) at 1 year, overall survival (OS) at 1 year, duration of response, changes in tumor markers, and toxicity, measured according to version 4.03 of the NCI Common Terminology Criteria for Adverse Events (CTCAE).

The sample size calculation was based on the assumption that a true response rate of >18% (comparable to that seen with agents such as sunitinib in pNENs [9] or bevacizumab in GI/lung NENs

Table 1. Dose modification and reduction guidelines for drug-related toxicity

Toxicity	Dose modification	Dose reduction
Grade 1 or 2	Continue at current dose level with no modification	For any grade toxicity: First occurrence: restart treatment at 560 mg daily once recovered to ≤grade 1 Second occurrence: restart treatment at 420 mg daily once recovered to ≤grade 1 Third occurrence: restart treatment at 420 mg daily once recovered to ≤grade 1 Fourth occurrence: discontinue ibrutinib
Grade 2 (persistent) Grade ≥3 nonhematological toxicity Grade ≥3 neutropenia with infection or fever Grade 4 hematological toxicity	Dose reduced by one dose level Hold ibrutinib until resolution to ≤grade 1; Resume at original dose level and follow dose reduction guidelines	
Any grade toxicity requiring >3 weeks of dose hold	Permanently discontinue ibrutinib	

[10]) would generate interest in a larger randomized study, whereas a true response rate of >5% would not yield further interest in this agent. Based on a 2-cohort design (GI/lung NENs and pNENs), 30 patients in the GI/lung NEN cohort would test the hypothesis that the true response issue is 18 versus 5% with a power of 80% and a type 1 error of 6%, while 21 patients in the pNEN cohort were sufficient to test that hypothesis that the true response rate is 20 versus 5%, with a type 1 error of 8% and a power of 80%. Patients were enrolled in a Simon's 2-stage minimax design. In the GI/lung NEN cohort, 15 subjects would be enrolled into stage 1 and if 1 or more responses were observed, another 15 patients would be enrolled into stage 2. In the pNEN cohort, 12 patients would be enrolled into stage 1 and if 1 or more responses were observed, 9 more patients would be enrolled into stage 2. At the completion of both cohorts, 4 responses in the GI/lung NEN cohort and 3 in the pNEN cohort would indicate a significance of 6 and 8%, respectively.

Statistical Analysis

The Kaplan-Meier method was used to estimate all time-to-event functions. PFS was defined as time from start of treatment until disease progression or death as a result of any cause. OS was defined as time from start of treatment until death as a result of any cause, with patients censored at the date of last follow-up if still alive. Exact 95% CIs were calculated for each proportion of interest. Statistical analysis was performed using SAS® 9.4.

Results

Patient Population

A total of 20 patients were enrolled in 2 cohorts; 15 had advanced GI/lung NENs and 5 had pNENs. The median age of the patient population was 67 years; 11 males and 9 females. All patients had a performance status of 0 or 1, and more than half [11] received concurrent somatostatin analog. Table 2 summarizes the clinicopathological characteristics of the study population. Prior therapies are depicted in Figure 1.

Table 2. Patient demographics and tumor characteristics

	Patients, *n* (%)
Gender	
Female	9 (45)
Male	11 (55)
Age group	
<65 years	9 (45)
>65 years	11 (55)
Race	
White	19 (95)
Black	1 (5)
Ethnicity	
Hispanic	2 (10)
White	18 (90)
Primary site	
Small bowel	12 (60)
Pancreas	5 (25)
Lung	2 (10)
Thymus	1 (5)
Sites of metastases	
Liver	19 (95)
Numerous liver metastases	14 (70)
Oligometastases	5 (25)
Lymph nodes	13 (65)
Bone	8 (40)
Abdomen	5 (25)
Pancreatic/peripancreatic	5 (25)
Lung	3 (15)
Other (adnexa, pelvis, kidney)	3 (15)
Grade	
Grade 1	5 (25)
Grade 2	13 (65)
Unknown	2 (10)
On concurrent somatostatin analog	
Yes	12 (60)
No	8 (40)
Years since diagnosis	
1–3	9 (45)
4–9	7 (35)
10+	4 (20)

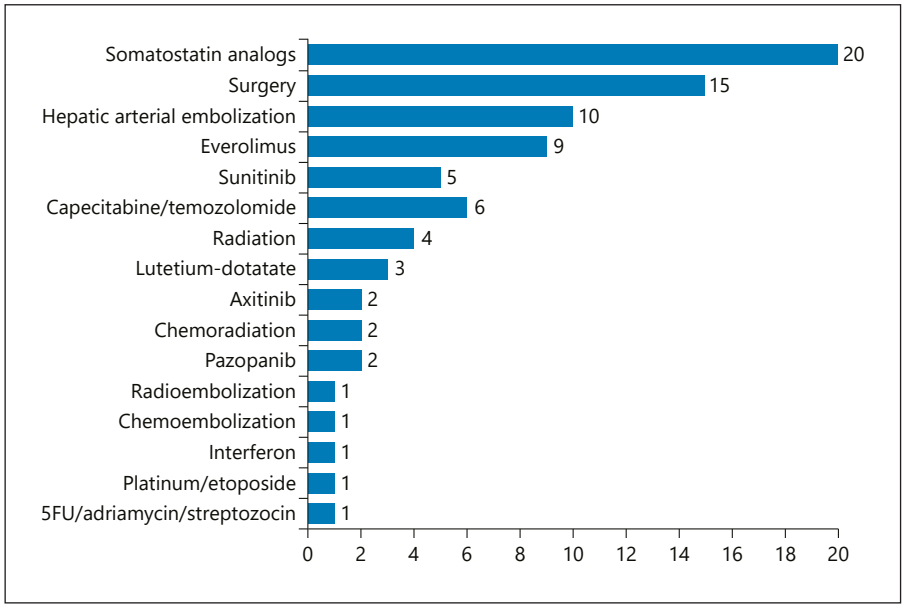

Fig. 1. Summary of prior therapies.

Duration of Therapy

Patients received a median of 3 treatment cycles. Reasons for discontinuation included radiographic tumor progression (14 patients), withdrawal of consent (1 patient), and toxicity (5 patients). Toxicities leading to treatment discontinuation included grade 2 fatigue and diarrhea, grade 3 abdominal pain (2 patients: GI/lung NEN), grade 3 arthralgias (2 patients: GI/lung NEN), and grade 4 hypoglycemia (1 patient: pNEN).

Radiologic and Biochemical Response

Sixteen patients were evaluable for radiographic response. Seven patients underwent MRI scans (5 due to better visualization of their liver disease and 2 due to iodine allergies), while the remainder underwent multiphasic CT scans. Four patients discontinued the study after 1 cycle due to treatment-related adverse events (AEs). There were no objective radiologic responders by RECIST. When best response to therapy was evaluated, 6 of 12 (50%) evaluable GI/lung NEN patients and 2 of 4 (50%) evaluable pNEN patients had stable disease lasting until at least the initial follow-up imaging study, while the other 50% of patients experienced continued tumor growth. Figure 2 demonstrates the best responses. The 4 patients who discontinued the study after 1 cycle were assigned a "progression date" of 84 days, when the first assessment is typically done.

All 20 patients had baseline chromogranin A, and 14 patients were evaluable for biochemical response. Eleven patients had baseline 24-h urine 5HIAA levels and 6 were evaluable for biochemical response. One patient exhibited an initial response with a 68.7% reduction in the CgA level; however, the value increased at the subsequent evaluation. No patients exhibited response in 5HIAA levels.

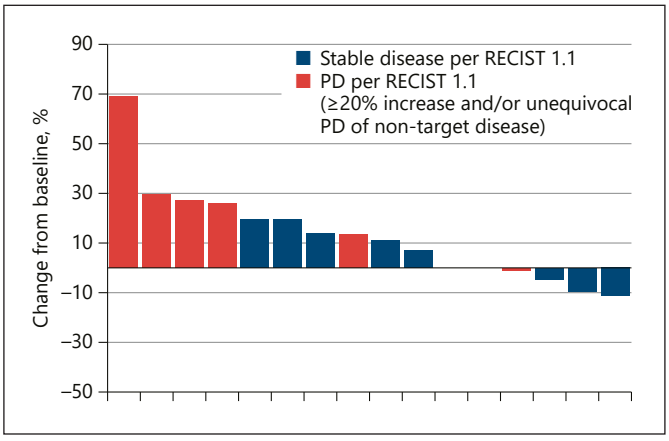

Fig. 2. Best responses according to RECIST 1.1. PD, progressive disease.

Because there were no objective responses among 15 GI/lung NEN patients, that study cohort ended after stage 1. For the pNEN patient cohort, we elected to stop the study after 5 non-responses rather than completing a stage 1 cohort of 12 patients.

Progression-Free and Overall Survival

All patients were evaluable for survival analysis. At the time of data cutoff on March 26, 2019, 9 patients had died

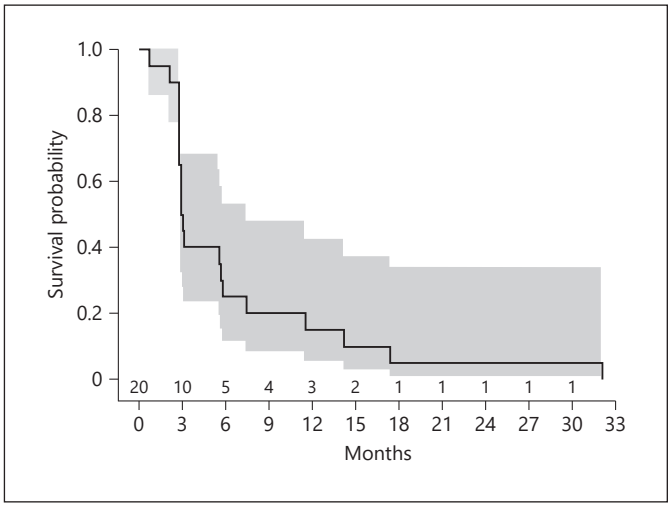

Fig. 3. Kaplan-Meier estimates of PFS. PFS, progression-free survival.

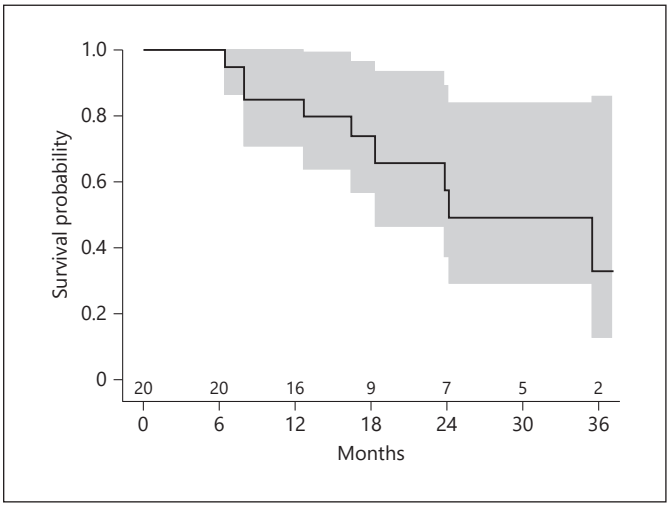

Fig. 4. Kaplan-Meier estimates of OS. OS, overall survival.

and 11 were alive, with follow-up duration for the surviving patients ranging from 8 to 37 months. As depicted in Figure 3, the median PFS was 3.0 months (95% CI 2.8–5.8). The 1-year PFS rate was 20.0% (95% CI 6.2–39.3) and the 2-year PFS rate was 10.0% (95% CI 1.7–27.2). The median OS was 24.1 months (95% CI 16.5–∞ months). The 1-year OS rate was 85.0% (95% CI 60.4–94.9), and the 2-year OS rate was 57.6% (95% CI 29.4–77.9; Fig. 4).

Safety

Overall, ibrutinib was well tolerated with only 28 moderate (grade 2), 15 severe (grade 3), and 1 life-threatening (grade 4) AEs that were considered at least possibly related to treatment (Table 3). Among these, 15 grade 3 and 1 grade 4 (hypoglycemia) toxicities were considered likely related to treatment including fatigue (19%), arthritis/arthralgia (19%), back pain (13%), musculoskeletal disorders (13%), hypoglycemia, neck pain, abdominal pain, rash, syncope, and weight loss (6%, each). The most common AEs overall were fatigue (6 patients), nausea (4 patients), abdominal pain (3 patients), and diarrhea (3 patients).

Discussion/Conclusion

To our knowledge, this is the first study of a Btk inhibitor in patients with advanced NENs. Preclinical data suggested that mast cells have a prominent role in NEN progression, and that inhibition of mast cell degranulation by ibrutinib may alter the natural history of disease [5, 8]. However, our study failed to demonstrate significant clinical activity associated with the Btk inhibitor in patients with GEP and lung NENs.

None of the 20 patients enrolled in this trial experienced an objective radiographic response, and patient accrual was therefore halted at interim analysis (stage 1) in the GI/lung NEN cohort. Accrual to the pNEN cohort was halted earlier than specified in the protocol due to lack of evidence of activity in the 5 patients enrolled as well as lack of activity in the GI/lung cohort. The median PFS duration of 3 months recorded in this study appears short for a population of patients with metastatic progressive NENs (with individual PFS times of 3, 3, 3, 6, and 17 months). By comparison, other oral targeted agents such as sunitinib [9] and everolimus [11, 12] were associated with median PFS durations exceeding 10 months in clinical trials enrolling similar patient populations.

Several reasons might explain the lack of anti-tumor activity observed in this trial for ibrutinib. First, animal models do not entirely recapitulate the biologic complexity of human NENs, and it is therefore possible that intratumor activation of mast cells does not have a critical role in the progression of human NENs. In this context, it should be noted that preclinical testing of ibrutinib was carried out in a mouse model (Ins-MycER^{TAM}; RIP7-Bcl-x_L) mimicking local, and not metastatic, disease [8]. Further preclinical studies using different small intestinal, lung, or pNEN cell lines might have been more predictive of clinical drug activity. Second, it is impossible to exclude

Table 3. Treatment-related toxicities (≥ grade 2 per CTCAE v4.03)

	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Gastrointestinal disorders			
Nausea	4 (14)	0	0
Vomiting	1 (3.5)	0	0
Diarrhea	4 (14)	0	0
Abdominal pain	3 (11)	1 (6)	0
General disorders and administration site conditions			
Fatigue	7 (25)	3 (20)	0
Infections and infestations			
Upper respiratory infection	1 (3.5)	0	0
Pneumonia	2 (7)	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia/arthritis	2 (7)	3 (20)	0
Back pain	1 (3.5)	2 (13)	0
Generalized muscle weakness	4 (14)	0	0
Neck pain	0	1 (6)	0
Skin and subcutaneous tissue disorders			
Rash maculo-papular	1 (3.5)	1 (6)	0
Other			
Weight loss	0	1 (6)	0
Hypoglycemia	0	0	1 (100)
Syncope	0	1 (6)	0

that human NEN cells might exploit alternate molecular mechanisms to sustain tumor neoangiogenesis when mast cells are inhibited in their degranulation potential by ibrutinib monotherapy. Third, although the dosage of ibrutinib used in this study mirrors the dosage commonly employed in hematological malignancies, one may wonder whether the drug reaches pharmacodynamically active concentrations within the microenvironment of a solid tumor.

In this study, treatment with ibrutinib was associated with significant but manageable toxicity. We recorded 16 grade 3 and 4 AEs including primarily fatigue, arthritis/arthralgia, back pain, and musculoskeletal disorders. In addition, 6 patients experienced probably or definitely related grade 3/4 AEs, with treatment-related toxicities leading to drug discontinuation in 4 of the 20 patients enrolled in our trial. Patient refusal to continue on study treatment prompted discontinuation in 2 of the 4 discontinuations. This toxicity profile is consistent with the known safety profile in earlier studies of the drug in patients with hematological malignancies [6].

The main limitation of this trial was its small sample size, particularly in the pNEN cohort which did not meet its target accrual. Given the overall lack of evidence of benefit seen in the first 20 patients enrolled in the trial, and the increase in number of approved and guidelines-recommended therapies for pNEN, a decision was made to stop accrual to the study.

In conclusion, our study failed to demonstrate significant antitumor activity associated with ibrutinib monotherapy in patients with advanced progressive NENs. Further research is needed to elucidate the molecular underpinnings driving the cross-talk between tumor cells and their microenvironment in order to discover new potential therapeutic targets in NENs.

Statement of Ethics

The protocol (ClinicalTrials.gov Identifier: NCT02575300) was approved by the Institutional Review Board and the study was conducted in accordance with Good Clinical Practice principles. Written informed consent was obtained from all participants.

Disclosure Statement

Dr. Jonathan R. Strosberg has consulted for Novartis and has received honoraria from Ipsen and Lexicon. Dr. Heloisa P. Soares has received honoraria from Novartis, Ipsen, and Lexicon. None of the other authors declares a personal or financial conflict of interest which could affect the outcome of this study.

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Author Contributions

T.A.-T. contributed to study management, analysis of data, and manuscript writing. M.J.S. contributed to design of the protocol, study enrollment, analysis of the data, and manuscript writing. H.P.S. enrolled patients on the study and contributed to analysis of the data. M.C. contributed to design of the protocol, analysis of the data, and manuscript writing. M.J.S. and J.-M.Z. contributed to data analysis. J.R.S contributed to design of the protocol, study enrollment, analysis of the data, and manuscript writing.

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