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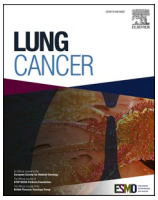

Research Paper

ENDOLUNG trial, part II. A phase II study of the Akt/mTOR inhibitor and autophagy inducer ibrilatazar (ABTL0812) in combination with paclitaxel/carboplatin in patients with squamous non-small cell lung cancer

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ABSTRACT

Background: Advanced squamous non-small cell lung cancer (sq-NSCLC) has long relied on chemotherapy and, more recently, on its combination with PD-1 immunotherapy. Ibrilatazar (ABTL0812) is an innovative oral agent that induces cytotoxic autophagy selectively in cancer cells. In the ENDOLUNG trial we have evaluated the efficacy and safety of ibrilatazar combined with chemotherapy in sq-NSCLC patients.
Methods: Patients with stage III/IV sq-NSCLC received ibrilatazar (1300 mg tid) alongside paclitaxel (175 mg/m2) and carboplatin (AUC 5) every 3 weeks for up to 8 cycles, followed by ibrilatazar maintenance until progression or toxicity. Primary endpoint was overall response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety.
Results: 40 patients were enrolled constituting the intention-to-treat (ITT) population (90 % male, median age 66, ECOG 0–1). The efficacy analysis (FA) subset included 25 patients, excluding 15 patients without a measurement

Abbreviations: AE, Adverse event; AKT, Protein kinase B; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; AUC, Area Under the Curve; cDNA, complementary DNA; CDR, Control disease rate; CP, Carboplatin plus paclitaxel; CR, Complete response; DDIT3, DNA damage inducible transcript 3; DLT, Dose limiting toxicities; DOR, Duration of response; ECOG, Eastern Cooperative Oncology Group; EDTA, Ethylenediaminetetraacetic acid; EGFR, Epithelial growth factor receptor; ER, Endoplasmic reticulum; FA, Full analysis population; FiH, First-in-human; GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; ITT, Intention to treat population; MAP1LC3B, Microtubule Associated Protein 1 Light Chain 3 Beta; MTD, Maximum tolerated dose; MTORC1, Mammalian target of rapamycin complex 1; ORR, Overall Response Rate; OS, Overall survival; PhD, Pharmacodynamic; PD, Progression diseases; PD1, Programmed cell death receptor 1; PFS, Progression-free survival; PI3K, Phosphoinositide 3-kinases; PK, Pharmacokinetics; PPAR, Peroxisome proliferator-activated receptor gamma; PR, Partial response; PTEN, Phosphatase and tensin homolog; RECIST, Response Evaluation Criteria in Solid Tumors; RPD2, Recommended phase 2 dose; SD, SBu disease; sq-NSCLC, Squamous non-small cell lung cancer; tid, Three times per day; TRIB3, Tribbles Pseudokinase 3; ULN, Upper limit of normal; UPR, Unfolded Protein Response.

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of the primary variable. For ITT and FA populations, the ORR was 32.5 % (95 % Confidence Interval (CI) 21.3–50.1) vs 52.0 % (95 % CI 34.2–65.9), the disease control rate (DCR) was 52.5 % (95 % CI: 36.1–68.5) vs 84.0 % (95 % CI: 63.9–95.5), the PFS was identical (6.2 months; 95 % CI: 4.4–8.8) and the OS was 18.4 months (95 % CI: 9.5-NC) and 22.5 months (95 % CI: 10.4-NC), respectively. Most common adverse events included asthenia (62.5 %), diarrhea (45.0 %), nausea (37.5 %), anemia (32.5 %) and neutropenia (27.5 %). Pharmacokinetic and pharmacodynamic data confirmed ibrilatazar activity.
Conclusions: Ibrilatazar combined with paclitaxel and carboplatin shows promising efficacy and safety in sq-NSCLC, warranting further clinical development.

1. Background

Advance squamous non-small cell lung cancer (sq-NSCLC) represents approximately 20–30 % of all identified cases of lung cancer. It is characterized by a bleak prognosis and shorter survival compared to non-squamous NSCLC[1]. Historically, the absence of specific abnormalities to target has led to the use of cytotoxic chemotherapy as the primary treatment approach for these tumors [13,14]. Recent advancements have introduced new therapeutic strategies, such as combining necitumumab with an epidermal growth factor receptor inhibitor alongside gemcitabine and cisplatin, which have demonstrated a modest clinical benefit and extended overall survival when compared to chemotherapy alone [13,14,16]. Additionally, immunotherapy approaches targeting the programmed cell death receptor-1 (PD-1) immune checkpoint in combination with carboplatin plus paclitaxel or nab-paclitaxel, have exhibited enhanced overall survival in metastatic sq-NSCLC during the phase 3 KEYNOTE-407 clinical trial[10]. Nevertheless, despite these significant efforts, the average overall survival rate remains unsatisfactory, and many patients do not respond or develop resistance to the treatments. Therefore, there is a clinical urgency to find new therapeutic strategies for these patients. Among the main mechanisms of the primary and acquired resistances to different therapies, including immunotherapies, the loss of PTEN and genetic alterations in the PIK3CA/AKT/MTORC1 axis are the most important. Indeed, these alterations could lead to Akt overactivation thus promoting cell proliferation and tumor growth[2,5,9,11,12,15].

Ibrilatazar (ABTL0812) is a first-in-class agent administered orally that effectively eliminates cancer cells by inducing cytotoxic autophagy through a dual mechanism of action[3,8]. Firstly, it inhibits the Akt/mTORC1 axis by overexpressing TRIB3, which is a result of PPARα/γ activation[3]. Secondly, it induces endoplasmic reticular (ER) stress and subsequently triggers the Unfolded Protein Response (UPR)[8]. These two actions synergistically induce a strong and sustained autophagy process, leading to selective cell death in cancer cells. Previous studies have demonstrated the efficacy of ibrilatazar and its mechanism of action, both as a standalone treatment and in combination with chemotherapy, in preclinical models of NSCLC[7,8]. Ibrilatazar specifically upregulates TRIB3 expression, leading to the inhibition of the PI3K/AKT/mTOR pathway and the induction of autophagy-induced cell death in NSCLC cells while sparing healthy cells. Furthermore, ibrilatazar has shown promising results in inhibiting tumor growth in xenografts of A549, H157 and H1975 cells lines. Interestingly, ibrilatazar enhances the effectiveness of chemotherapy (paclitaxel plus carboplatin) in these animal models without increasing treatment-related toxicity[7].

The primary aim of the ENDOLUNG phase I/IIa clinical trial was to investigate the combined effects of ibrilatazar with carboplatin and paclitaxel (CP) in individuals diagnosed with metastatic/recurrent endometrial cancer (EC) and advanced sq-NSCLC. During the phase I segment of the trial, the recommended ibrilatazar Phase 2 dose (RP2D) was established within a patient group encompassing both tumors. Subsequently, in the phase II segment, safety, effectiveness, pharmacokinetics, and pharmacodynamic biomarkers were assessed in each indication separately. This paper includes the details of the phase II segment, in participants with sq-NSCLC.

2. Methods

2.1. Study design and conduct

ENDOLUNG was an open-label phase I/IIa study of the combination of ibrilatazar plus CP in advanced or recurrent EC patients and sq-NSCLC. In summary, the phase I segment of the study used a 3 + 3 de-escalation design to test the combination of ibrilatazar with intravenous carboplatin and paclitaxel[6]. The trial was registered on September 19, 2016 with ClinicalTrials.gov registration NCT03366480 and with EudraCT number 2016–001352-21.

The starting dose level of ibrilatazar was 1300 mg three times per day (tid) based on PK/PhD modeling from a previous single-agent study. Ibrilatazar was administered daily along the study. De-escalation dose levels for ibrilatazar were 1000, 650, and 500 mg tid, and intrapatient de-escalation was not allowed. In addition to ibrilatazar, intravenous carboplatin area under the curve (AUC) 5 and paclitaxel 175 mg/m^2 were given every 21 days for up to 8 cycles. Ibrilatazar was given until disease progression, unacceptable toxicity, withdrawal of consent, or investigator's decision. Dose Limiting Toxicities (DLTs), if present, were the criteria for dose de-escalation. DLTs included specific adverse events (AEs) occurring during the first cycle of chemotherapy, such as severe neutropenia, thrombocytopenia, nausea and vomiting, liver enzyme elevations, and other significant non-hematological toxicities. An Escalation Committee, consisting of oncologists and company representatives, monitored AEs and determined if DLTs were attributed to the study drug. In the phase II part, a Simon's two-stage design was used, and ibrilatazar was administered at the recommended phase 2 dose (RPD2) determined in the phase I segment, in combination with carboplatin and paclitaxel at the same doses used in the phase I part.

2.2. Patient eligibility criteria

In the lung cohort, patients should have a histological diagnosis of squamous non-small cell lung cancer (sq-NSCLC). Patients with sq-NSCLC stage III who were not candidates to radical radiotherapy or stage IV were included. Other lung cancer subtypes such as mixed tumors, neuroendocrine or adenocarcinoma tumors were excluded.

Patients needed to meet specific criteria for measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigatoŕs review, requiring having at least one target lesion that would be used to evaluate the treatment response. Lesions showing progression within a previously treated radiation area were considered non-target lesions, except when clear progression was documented. Patients' Eastern Cooperative Oncology Group (ECOG) Performance Status should have been either 0 or 1.

The criteria for bone marrow function were defined as follows: an absolute neutrophil count of $\geq$ 1.5x10^9/L, a platelet count of $\geq$ 100x10^9/L, and a hemoglobin level of $\geq$ 10.0 g/dL. Additionally, certain limits were set for other blood parameters: total bilirubin should have been $\leq$ 1.5 times the upper limit of normal (ULN), AST (aspartate aminotransferase) should have been $\leq$ 2.5 times the ULN (or $\leq$ 5 times the ULN for patients with liver metastases), alkaline phosphatase (ALP) should have been $\leq$ 2.5 times the ULN (or $\leq$ 5 times the ULN for patients with liver metastases), and serum creatinine should have been $\leq$ 1.5

times the ULN.

Patients were not eligible if they had received prior treatment with an inhibitor of the PI3K/Akt/mTOR pathway, if they had received adjuvant chemotherapy or radiotherapy within the 6 months prior to inclusion, if they had symptomatic brain metastases, or if they had significant gastrointestinal issues that prevented them from taking oral medications or had malabsorption syndromes. The use of granulocyte colony-stimulating factors was permitted.

2.3. Endpoints and Assessments

In the ENDOLUNG phase II, the primary focus was the Objective Response Rate (ORR) by investigatoŕs analysis. Secondary endpoints included the assessment of progression-free survival (PFS) in terms of median duration and the percentage of patients without progression at the 6-month mark, along with the evaluation of duration of response (DOR) and overall survival (OS). PFS was defined as the duration between the initial administration of the dose and either the reappearance of the condition or mortality, whichever came first. DOR, on the other hand, was established as the shorter of the time from the time of initial response to tumor progression or death. Additionally, OS was defined as the period from the initial dose administration to death from any cause, with long-term monitoring being limited to a two-year timeframe.

To gauge the response for the efficacy analysis, the evaluation was rooted in the investigator's analysis of the tumor using CT-scans conducted at the baseline and subsequently every 8 weeks. The criteria for determining the size of measurable and non-measurable lesions, along with the guidelines for assessing tumors, adhered to RECIST v1.1 (Eisenhauer et al., 2009).

Additional secondary objectives in the phase II portion of the study included the assessment of the pharmacokinetics (PK) of ibrilatazar in plasma, coupled with the identification of pharmacodynamic (PhD) biomarkers indicative of the drug's activity.

2.4. Study of pharmacokinetic and pharmacodynamic biomarkers

Blood samples were collected for pharmacokinetic analysis at two distinct time points: the initial day of the run-in phase and the first day of the second chemotherapy cycle, separated by a 28-day interval. Subsequently, serial samples were promptly centrifuged to separate the plasma, which was then frozen and stored at −80 °C. The bioanalysis of ibrilatazar enantiomers was carried out using an established method accredited by Echevarne's Laboratory. The Faculty of Pharmacy at the University of Barcelona, Spain, conducted the assessment of plasma concentrations of ibrilatazar enantiomers for pharmacokinetic evaluation. The non-compartmental model, analyzed by Phoenix-WinNonlin ver.8.6.4 from Certara (Princeton, NJ, USA), was utilized to compute the pharmacokinetic metrics.

For the assessment of PD biomarkers such as *TRIB3*, *DDIT3*, and *MAP1LC3B*, whole blood samples were obtained, on the first day of the run-in period (Day 1) prior to drug administration and 8 h post-administration. Further samples were collected on the first day of the first chemotherapy cycle (Day 7) and on the first day of the second cycle (Day 28), also before drug administration. The process included isolating total RNA from the whole blood samples, converting it into cDNA, and subsequently quantifying gene expression via quantitative PCR (qPCR). The 2-ΔΔCt method was employed to calculate relative mRNA expression levels, which were then presented as ratios to the *GAPDH* housekeeping gene. The values in the graph reflect the mean of 2-ΔΔCt values accompanied by their respective SEMs. Statistical analysis was conducted based on ΔΔCt values, utilizing the *t*-test with ΔΔCt values. The TaqMan probes used for qPCR were as follows: *GAPDH* Hs99999905_m1; *TRIB3* Hs01082394_m1, *DDIT3* Hs99999172_m1, and *MAP1LC3B* Hs00917682_m1.

2.5. Sample size determination

The determination of the sample size was based on a two-stage optimal Simon's design that incorporated a futility boundary during the interim analysis. This Simon's design was meticulously crafted to achieve an 80 % statistical power at a nominal alpha level of 5 % for a one-sided test. The hypothesis was centered around the concept that by disregarding an ORR of $\leq$ 52 % in the FA population and directing the efforts toward enhancing the ORR to $\geq$ 72 %, we could effectively optimize the trial's assessment strategy.

In the initial stage, a minimum of 13 evaluable patients were planned to be included. Should this cohort yield fewer than 8 responders among the 13 patients, there was a provision for the potential discontinuation of the study. However, if 8 or more responders were observed, additional 30 patients would be enrolled (totaling 43 patients). Ultimately, the decision to cease accrual was made after reaching a total of 38 evaluable patients due to the gradual pace of recruitment. To note that patients who had taken part in the phase I were also encompassed in the evaluation of efficacy and safety in the phase II.

2.6. Ethical regulations

The research received approval from the relevant national authorities in Spain and France, as well as from the local Ethics Committees. Prior to enrollment, all patients signed their informed consent.

3. Results

3.1. Phase II patient demography and treatment

A total of forty patients were included between February 14, 2017, and February 12, 2020, with a median age of 66 years. From those, 90.0 % were men and 10.0 % women. ECOG was 1 in 100 % of patients. Additionally, 30 % were current smokers, 67.5 % former smokers and 37.5 % had received prior chemotherapy > 12 months before the

Table 1
Patients demography.

		Phase II
Variable		**Sq-NSCLC**
	N	40
Age, years	Median	66
	(range)	(49–76)
Weight, kg	Median	74.1
	(range)	(45.7–115.0)
Height, cm	Median	170
	(range)	(142–188)
Gender	M/F	36/4
ECOG	0/1	13/27
Race	Caucasian	40
Ethnicity	Hispanic or Latino	2
	Not Hispanic or Latino	35
	Not reported	3
Country	Spain	36
	France	4
Smoking status	Never/Smoker/Ex	1/12/27
Stage	Ia	1 (2.5 %)*
	IIIa	0
	IIIb	4 (10.0 %)
	IIIc	3 (7.5 %)
	IVa	12 (30.0 %)
	IVb	20 (50.0 %)
	Chemo	15 (37.5 %)
Prior anticancer therapy	Radiation	15 (37.5 %)
	Surgery	3 (7.5 %)

*The patient, initially diagnosed with stage Ia, relapsed over six months after prior treatment.
Despite presenting stage IV characteristics at study entry, their initial tumor stage remained categorized as stage Ia.

inclusion (Table 1).

The study aimed to assess the safety of ibrilatazar at different doses and determine the RP2D. In summary, ibrilatazar demonstrated a positive safety profile even at high doses, with no DTLs observed at the RP2D of 1300 mg administered three times a day.

3.2. Efficacy analysis

The analysis of efficacy was based on the efficacy analysis (FA) population, which included all patients with at least one measurement of the primary variable. Out of the total of 40 patients included in the ITT population, 15 individuals were excluded from the FA population. The reasons for premature withdrawal of these 15 patients were as follows: 8 withdrew consent (with at least 4 citing organoleptic discomfort), 4 experienced progressive disease, and 3 encountered side effects. Consequently, the FA population included 25 patients.

In the FA population, the responses were PR in 13 patients (52.0 %), SD in 8 patients (32.0 %), and PD in 4 patients (16.0 %). The cumulative ORR, including CR and PR, was 52.0 % (95 % CI: 34.2–65.9 %), and the disease control rate (DCR), including CR, PR, and SD was 84.0 % (95 % CI: 63.9–95.5 %) (Fig. 1, Table 2).

In the ITT population, the number of patients with PR and SD were the same as in the FA population with only change in the frequencies: 32.5 % and 20.0 % respectively. The number of PD were 8 patients (20.0 %). Consequently, the cumulative ORR was 32.5 % (95 % CI: 21.3–50.1 %) and the DCR 52.5 % (95 % CI: 36.1–68.5 %).

Both populations (ITT and FA) showed identical median PFS of 6.2 months (95 % CI: 4.4–8.8) and median DOR of 5.1 months (95 % CI: 3.9–7.4), as illustrated in Fig. 2A (Supp. Fig. 1A for ITT population) and Table 2 respectively. Additionally, the median OS was 22.5 months (95 % CI: 10.4-NC) in the FA population (Fig. 2B) and 18.4 months (95 % CI: 9.5-NC) in the ITT population (Supp. Fig. 1B). Median treatment line duration was 6.2 months in the FA population (Supp. Fig. 2A) and 3.9 months in the ITT population (Supp. Fig. 2B).

Table 2
Response rate summary.

Response Parameter	Intention to treat population n = 40	Efficacy analysis population n = 25
Complete Response, n (%)	0 (0.0%)	0 (0.0%)
Partial Response, n (%)	13 (32.5%)	13 (52.0%)
Stable Disease, n (%)	8 (20.0%)	8 (32.0%)
Progressive Disease, n (%)	8 (20.0%)	4 (16.0%)
Non-evaluable, n (%)	11 (27.5%)	0 (0.0%)
Overall Response Rate, n (%) 95% CI	13 (32.5%) 21.3–50.1	13 (52.0%) 34.2–65.9
Disease Control Rate, n (%) 95% CI	21 (52.5%) 36.1–68.5	21 (84.0%) 63.9–95.5
Duration of Response, median 95% CI	5.1 months 3.9–8.5 months	5.1 months 3.9–8.5 months
Progression-free survival, median 95% CI	6.2 months 4.4–8.8 months	6.2 months 4.4–8.8 months
Overall survival, median 95% CI	18.4 months 9.5-NC months	22.5 months 9.5-NC months

CI: Confidence interval.

3.3. Safety analysis

Regarding safety, in 39 out 40 patients (97.5 %) adverse effects (AEs) were observed, and 55 % patients had AEs grade 3 or higher. Ten patients (25 %) discontinued treatment due to AEs. AEs led to death in 4 patients (10.0 %). All grade 5 AEs presented the same frequency, general physical health deterioration (2.5 %), pulmonary embolism (2.5 %), septic shock (2.5 %) and sudden death (2.5 %) and were not associated with ibrilatazar, but rather represent complications commonly observed in this patient population. Regarding clinically significant hematological toxicities, anemia exhibited the highest frequency as an adverse event (32.5 %), with 5 % classified as grade 3 or higher. Neutropenia was observed in 27.5 % of patients, of which 25 % were grade 3 or higher. Thrombocytopenia was observed in 17.5 %, with 2.5 % falling into grade 3 or higher. Lastly, febrile neutropenia was identified in 7.5 %, all with a grade 3 or higher intensity. The most frequent non-hematological toxicities included asthenia (62.5 %), diarrhea (42.5 %), and nausea (37.5 %), with grade 3 or higher incidences at 2.5 %, 0 %, and 5.0 %, respectively. Other prevailing non-hematological AEs comprised alopecia (30.0 %), neurotoxicity (27.5 %), cough (25.0 %), dysgeusia (25.0 %), decreased appetite (25.0 %), and vomiting (25.0 %), with grade 3 or higher effects noted in 0 %, 2.5 %, 0 %, 0 %, 0 %, and 5.0 % of the patients, respectively (see Table 3, 4).

3.4. Pharmacokinetic of ibrilatazar enantiomers and biomarkers

To elucidate the pharmacokinetic profiles of both ibrilatazar and its corresponding enantiomer, an analysis was conducted wherein concentrations of the active compound were quantified in blood samples obtained from patients after 28 days of drug administration. Noteworthy, the determined levels of ibrilatazar, represented by its maximum observed concentration (C_{max}), minimum concentration (C_{min}), and the area under the concentration–time curve (AUC), were quantified in micromolar units. Importantly, no significant differences

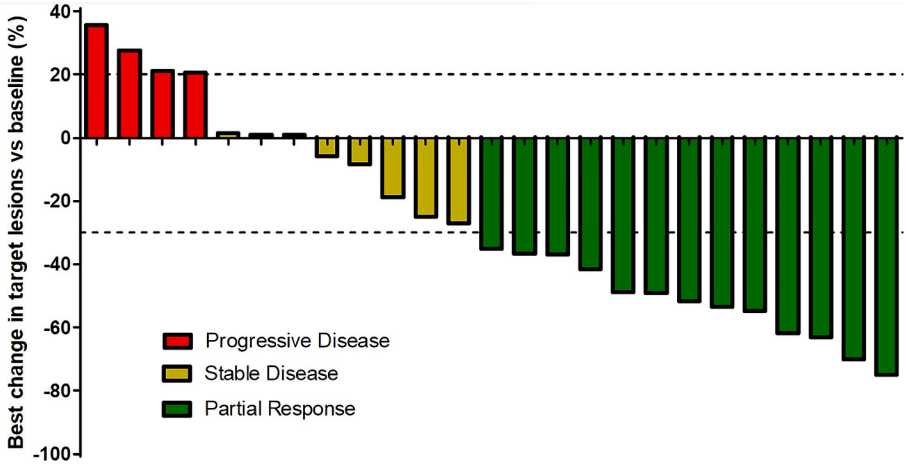
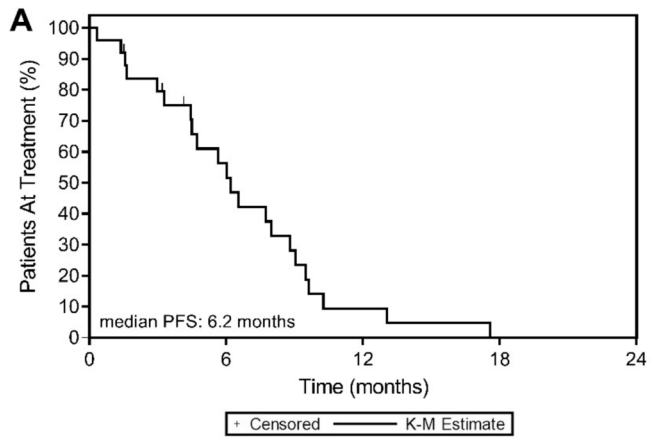
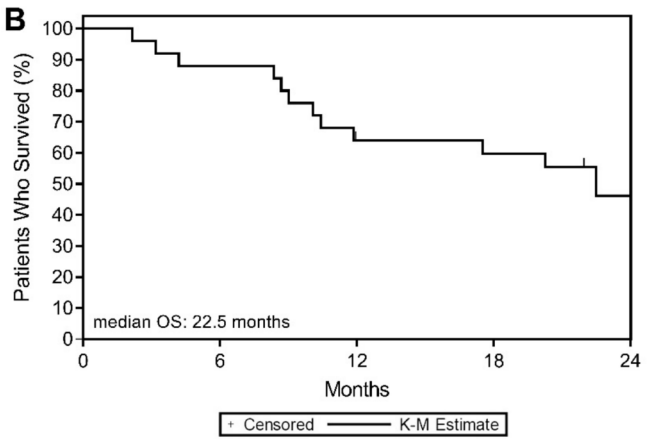


Fig. 1. Waterfall representation of best change from baseline of target lesions in sq-NSCLC patients.



Parameter	PFS
PFS, median, 95% CI	6.2 (4.4-8.8)
6-month event free rate, %, 95% CI	56.3 (33.8-73.8)
12-month event free rate, % 95% CI	9.4 (1.6-25.8)



Parameter	OS
OS, median, 95% CI	22.5 (10.4-ND)
6-month event free rate, %, 95% CI	88.0 (67.3-96.0)
12-month event free rate, % 95% CI	64.0 (42.2-79.4)

Fig. 2. Kaplan-Meier curve for Progression Free Survival (A) and Overall Survival (B) in sq-NSCLC Patients cohort.

were detected in pharmacokinetic parameters both after a single dose or during chronic administration, further suggesting no drug accumulation (Fig. 3, Table 5).

Finally, given the reported mechanism of action of ibrilatazar, an exploratory analysis was initiated to elucidate potential PhD biomarkers in blood samples. Consistently, *TRIB3* and *DDIT3* (alternatively termed *CHOP*), both previously described in preclinical assays, and *MAP1LC3B,* a critical gene controlling autophagy and potential biomarker, were analyzed in RNA from whole blood samples. Significantly, there was an increased expression of all three genes upon ibrilatazar treatment after 8 h, such induction lasted for 7 days. Moreover, this phenomenon persisted even after 28 days when ibrilatazar was combined with chemotherapy, thereby providing additional indications of a sustained synergistic effect between chemotherapy and ibrilatazar-mediated actions. Altogether, these findings further suggest the pharmacological efficacy of ibrilatazar through its capacity to induce autophagy, concurrently identifying *TRIB3*, *DDIT3*, and *MAP1LC3B* as noteworthy PhD biomarkers (Fig. 4).

Table 3
Summary of adverse events

	Patients (n=40)
Patients with SAEs	13 (32.5%)
Patients with AEs	39 (97.5%)
Patients with CTCAE grade:	
1 or 2 AEs	35 (87.5%)
3 AEs	14 (35.0%)
4 AEs	8 (20.0%)
5 AEs	4 (10.0%)
Patients with AEs:	
related to study treatment	31 (77.5%)
not related to study treatment	35 (87.5%)
Patients with AEs leading to drug discontinuation	10 (25.0%)

4. Discussion

In this study, the safety and effectiveness of ibrilatazar, a compound that stimulates autophagy, was assessed in combination with CP in patients with sq-NSCLC. The therapeutic potential of ibrilatazar in treating sq-NSCLC cancer is particularly promising due to the frequent genetic anomalies in the PI3K/AKT pathway observed in this cancer type[11]. The presence of specific mutations in the PI3K/AKT pathway holds profound implications for cancer progression in sq-NSCLC. Notably, mutations in the PIK3CA gene, encoding the catalytic subunit of PI3K, play a pivotal role[4]. Gain-of-function mutations in PIK3CA lead to constitutive activation of the PI3K pathway, driving uncontrolled cell proliferation and survival[11]. Moreover, alterations in PTEN, a negative regulator of the pathway, frequently seen in sq-NSCLC, result in diminished pathway inhibition, amplifying its oncogenic potential[15]. These mutations disrupt the intricate balance between growth-promoting and growth-inhibiting signals, fostering aggressive tumor behavior, resistance to apoptosis, and enhanced metastatic capabilities [11]. Therefore, exploring a maintenance approach targeting the MAPK pathway with ibrilatazar is of interest.

CP forms a fundamental chemotherapy treatment approach for patients with sq-NSCLC [13,14]. Remarkably, in diverse preclinical sq-NSCLC cancer models, ibrilatazar demonstrated an additive or synergistic effect when combined with CP, with no notable exacerbation of adverse effects observed during *in vivo* experiments [7,8]. Given these considerations, combining ibrilatazar and CP in treating NSCLC appeared rational. To ensure patient safety, a de-escalation phase I design was chosen instead of conventional escalation. This decision was based on the favorable safety profile established at higher doses and data from the single-agent phase I trial (FiH), which determined the RPD2 of ibrilatazar as 1300 mg tid[6]. At this dosage, no DLTs were recorded. All other treatment-related effects were graded as 1 or 2. Employing the de-escalation approach helped mitigate potential confounding effects of CP in determining the maximum tolerated dose (MTD) of ibrilatazar, thus averting the risk of underestimating the appropriate recommended phase 2 dose.

These study's findings are particularly noteworthy when compared to similar clinical trials, which examined the efficacy and safety of CP with placebo versus CP with other agents in newly diagnosed stage IV tumors. As an example, the KEYNOTE-407 study, which enrolled 100 % newly diagnosed stage IV tumors[10] in two arms, one treated with CP plus placebo and another with CP plus pembrolizumab, while our study included 80.0 % of such cases. In comparing efficacy results between the placebo arm of KEYNOTE-407 with our study, the ORR of the ENDO-LUNG were 52.0 % and 32.5 % in the FA and the ITT populations

Table 4
List of adverse events by grade that appeared in > 10 % of the patients or lead to a Grade 5 adverse event. Data indicate number and percentage of patients who experienced any type of adverse event.

	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any adverse event	39 (97.5 %)	3 (7.5 %)	14 (35.0 %)	10 (25.0 %)	8 (20.0 %)	4 (10.0 %)
Hematological						
Anemia	13 (32.5 %)	9 (22.5 %)	2 (5.0 %)	2 (5.0 %)	0 (0.0 %)	0 (0.0 %)
Neutropenia	11 (27.5 %)	0 (0.0 %)	1 (2.5 %)	4 (10.0 %)	6 (15.0 %)	0 (0.0 %)
Thrombocytopenia	7 (17.5 %)	3 (7.5 %)	3 (7.5 %)	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)
Febrile neutropenia	3 (7.5 %)	0 (0.0 %)	0 (0.0 %)	2 (5.0 %)	1 (2.5 %)	0 (0.0 %)
Non-hematological						
Asthenia	25 (62.5 %)	12 (30.0 %)	12 (30.0 %)	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)
Diarrhea	17 (42.5 %)	12 (30.0 %)	5 (12.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Nausea	15 (37.5 %)	10 (25.0 %)	3 (7.5 %)	1 (2.5 %)	1 (2.5 %)	0 (0.0 %)
Alopecia	12 (30.0 %)	8 (20.0 %)	4 (10.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Neurotoxicity	11 (27.5 %)	9 (22.5 %)	1 (2.5 %)	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)
Cough	10 (25.0 %)	8 (20.0 %)	2 (5.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Dysgeusia	10 (25.0 %)	8 (20.0 %)	2 (5.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Decreased appetite	10 (25.0 %)	7 (17.5 %)	3 (7.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Vomiting	10 (25.0 %)	7 (17.5 %)	1 (2.5 %)	1 (2.5 %)	1 (2.5 %)	0 (0.0 %)
Dyspnea	6 (15.0 %)	5 (12.5 %)	0 (0.0 %)	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)
Musculoskeletal pain	6 (15.0 %)	4 (10.0 %)	2 (5.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Pyrexia	5 (12.5 %)	5 (12.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Pain in extremity	5 (12.5 %)	4 (10.0 %)	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Neuropathy peripheral	5 (12.5 %)	4 (10.0 %)	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Stomatitis	5 (12.5 %)	2 (5.0 %)	3 (7.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Constipation	4 (10.0 %)	4 (10.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Abdominal pain upper	4 (10.0 %)	3 (7.5 %)	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Respiratory tract infection	4 (10.0 %)	0 (0.0 %)	3 (7.5 %)	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)
Pulmonary embolism	2 (5.0 %)	0 (0.0 %)	0 (0.0 %)	1 (2.5 %)	0 (0.0 %)	1 (2.5 %)
General physical health deterioration	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (2.5 %)
Sudden death	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (2.5 %)
Septic shock	1 (2.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (2.5 %)

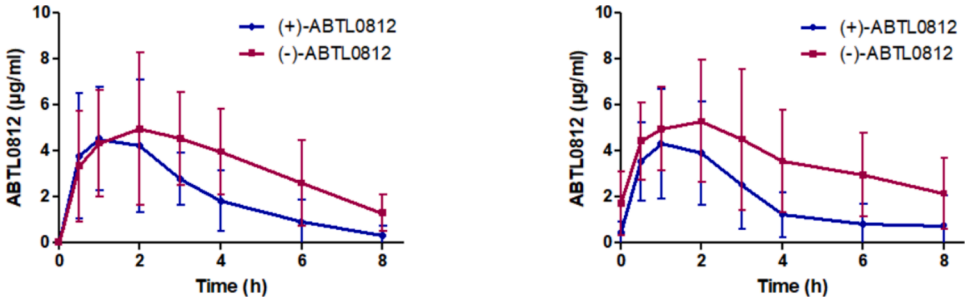


Fig. 3. Ibrilatazar (ABTL0812) plasma levels of its (+) and (−)-enantiomers after single administration (left panel) and 28-day administration 1300 mg tid.

Table 5
Pharmacokinetic parameters of ibrilatazar (ABTL0812) enantiomers after single and chronic administration.

	Single Dose		Chronic administration	
Parameter	**(−)-ABTL0812**	**(+)-ABTL0812**	**(−)-ABTL0812**	**(+)-ABTL0812**
AUC (µg·h/ml)	30.4 ± 11.1	17.0 ± 6.6	39.0 ± 12.3	17.1 ± 6.3
C_{max} (µg/ml)	6.5 ± 2.0	5.8 ± 2.9	6.4 ± 2.6	5.1 ± 2.2
C_{min} (µg/ml)	1.2 ± 0.8	0.3 ± 0.4	2.2 ± 1.5	0.8 ± 1.3
$T_{1/2}$ (h)	2.3 ± 1.2	1.3 ± 0.5	3.3 ± 1.6	1.7 ± 0.7
T_{max} (h)	2.5 ± 1.6	2.0 ± 1.4	2.2 ± 1.5	2.1 ± 1.9

respectively, with 31.7 % ORR reported for the placebo arm of KEYNOTE-407.

Regarding DCR, the FA population was of 84.0 % and 52.5 % in the ITT population of the ENDOLUNG study compared to 75.8 % in the KEYNOTE-407 study. In the ENDOLUNG study, the median PFS was 6.2 months, and DOR was 5.1 months for both the ITT and FA populations. In comparison, the placebo arm in KEYNOTE-407 study reported a median PFS of to 4.2 months PFS and a DOR of 4.8 months.

In terms of OS, the ENDOLUNG study showed a median OS of 22.5 months in the FA population and 18.4 months in the ITT population, compared to 11.3 months reported for the KEYNOTE-407. These results suggest that ibrilatazar combined with CP has the potential to serve as an efficacious treatment choice for patients with sq-NSCLC. The favorable outcomes observed with ibrilatazar highlight its potential as a valuable treatment option in sq-NSCLC and warrant further exploration in future studies, especially considering the evolving landscape of cancer therapies.

Of note, when the ENDOLUNG study was designed and executed, chemo-immunotherapy was not available for first line treatment of sq-NSCLC. Currently, chemo-immunotherapy has become the standard of

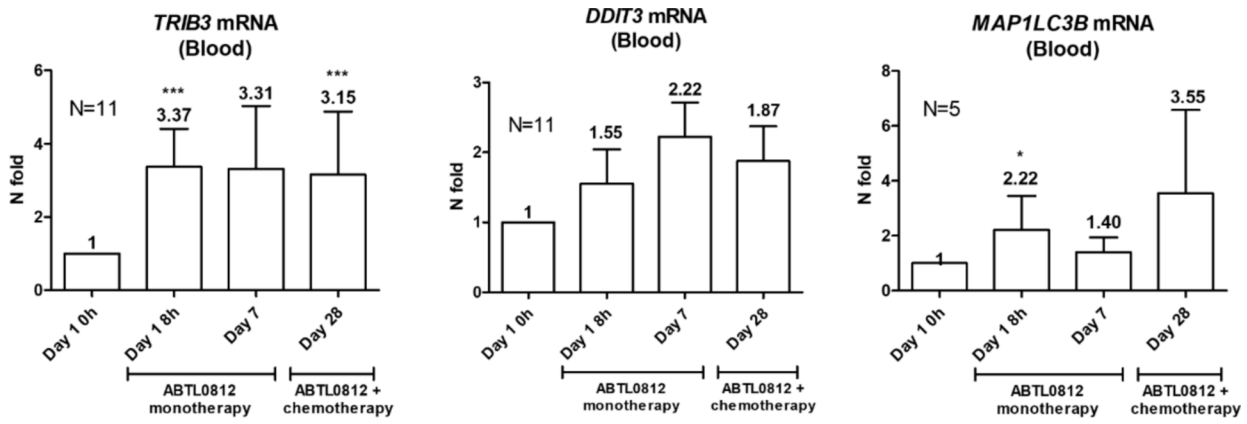


Fig. 4. Ibrilatazar (ABTL0812) pharmacodynamic biomarkers analyzed in blood samples from sq-NSCLC cancer patients. *TRIB3*, *DDIT3* and *MAP1LC3B* mRNA expression levels were evaluated by quantitative PCR in mRNA from whole blood samples. Values represented in the graph correspond to the mean of $2^{-\Delta\Delta Ct}$ values and its associated SEMs. Statistical analysis was performed using ΔΔCt values. * $p \leq 0,05$; ** $p \leq 0,01$; *** $p \leq 0,001$ vs. baseline levels (Day 1 0 h) by *t*-test.

care in the front-line for most advanced sq-NSCLC with PD-L1 < 50 % or not determined. Despite this, there are still patients that can present major contraindications for immunotherapy treatment, and therefore, other strategies that can increase activity of CP doublet chemotherapy should be explored for this poor prognosis disease. Also, the manageable safety profile observed in the ENDOLUNG trial and the multiple mechanisms of action of ibrilatazar, makes of interest the exploration of the quadruplet of CP chemo-immune treatment in addition to ibrilatazar in future preclinical and clinical studies.

In terms of safety, it should be noted that ibrilatazar has shown manageable toxicity's profile after the induction phase with chemotherapy alone, supporting the safety of the compound. Moreover, ibrilatazar has shown a safety profile compared to the placebo arm from KEYNOTE-407 study[10]. Notably, thirty-nine out of forty patients in the study encountered at least one adverse event (AE), with 87.5 % experiencing AEs of grade 1–2 and 55.0 % experiencing AEs of grade 3 or higher. While our study's safety profile appears to show an improvement compared to the KEYNOTE-407, where 68.2 % of patients experienced grade 3 or higher adverse events, it is important to consider the small sample size of our study, which limits direct comparisons. Additionally, it should be noted that the incidence of grade 5 adverse events was slightly higher in our study (10 %) compared to the 6.4 % reported in the KEYNOTE-407 study, although the small sample size of our study makes direct comparisons challenging. Among the hematological AEs, the results from this study show a safe profile when compared with this historical control, being anemia (32.5 % in this study vs 51.8 % in KEYNOTE-407), neutropenia (27.5 % vs 24.6 %) and thrombocytopenia (17.5 % vs 23.2 %) the most prevalent in both studies. By contrast, the number of gastrointestinal AEs was higher in this study, being asthenia (62.5 % in this study vs 21.1 % in KEYNOTE-407), diarrhea (42.5 % vs 23.2 %) and nausea (37.5 % vs 32.1 %) the most prevalent. In summary, this analysis suggests that the combination of ibrilatazar with CP did not lead to an increased occurrence of hematological AEs, although a tendency toward a higher frequency of gastrointestinal AEs was observed. The occurrence of this phenomenon could potentially be attributed to the administration of ibrilatazar in a liquid solution. In this context, a novel capsule-based formulation is undergoing evaluation within the framework of a phase 2 clinical trial (PanC-ASAP, NCT04431258) among patients diagnosed with pancreatic cancer.

The pharmacokinetic of ibrilatazar observed in this trial are in line with those from the FiH trial, where ibrilatazar was given as a single agent in patients with advanced solid tumors. These results indicate that there is no apparent interaction between ibrilatazar and chemotherapy, aligning with its demonstrated effectiveness against sq-NSCLC cells in preclinical models[7,8]. Importantly, biomarkers of activity exhibit rapid activation, with significant increases in TRIB3 and CHOP observed as early as 8 h after the first administration. These changes are sustained for at least 28 days following treatment initiation, even after two chemotherapy cycles. Collectively, the pharmacokinetic and pharmacodynamic analyses suggest that the administered doses are conducive to achieving therapeutic efficacy.

5. Conclusion

In summary, the phase I/IIa study of ibrilatazar in patients with advanced or sq-NSCLC cancer suggests that the addition of ibrilatazar to CP chemotherapy does not induce significant additional toxicities. Furthermore, preliminary efficacy data indicate promising activity for this combination in treating sq-NSCLC. Consequently, the improved benefit-to-safety ratio observed with ibrilatazar and CP, supports the need for further clinical exploration of this combination.

CRediT authorship contribution statement

Joaquim Bosch-Barrera: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Purificación Estévez-García:** Writing – review & editing, Investigation, Data curation. **Paloma Martín-Martorell:** Writing – review & editing, Investigation, Data curation. **Renaud Sabatier:** Writing – review & editing, Investigation, Data curation. **Ernest Nadal:** Writing – review & editing, Investigation, Data curation. **Elia Sais:** Writing – review & editing, Investigation, Data curation. **Pere Gascón:** Writing – review & editing, Conceptualization. **Ana Oaknin:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Jordi Rodon:** Writing – review & editing, Conceptualization. **Jose M. Lizcano:** Writing – review & editing, Investigation, Data curation. **Pau Muñoz-Guardiola:** Writing – review & editing, Data curation. **Gemma Fierro-Durán:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Oriol Pedrós-Gámez:** Writing – review & editing, Funding acquisition, Conceptualization. **Héctor Pérez-Montoyo:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Marc Yeste-Velasco:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Marc Cortal:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Antonio Pérez-Campos:** Writing – review & editing, Conceptualization. **José Alfón:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Carles Domènech:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Conceptualization. **Teresa Morán:** Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

The study was approved by the The Spanish Agency for Medicine and Health Products (AEMPS) and The Agence nationale de sécurité du médicament et des produits de santé (ANSM). The study was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and local laws. All patients provided written informed consent. The trial is registered with the USA Registry of Clinical Trials (ClinicalTrials.gov) with the trial ID number NCT03366480.

Authors' contributions

J.B.B. contributed to study design, data acquisition, data analysis and interpretation, and manuscript preparation and review. T.M., P.E.G, P. M.M, R.S., E.S. contributed to data acquisition and manuscript review. E. N., P.G., A.O., J.R. contributed to study design and manuscript review. J. M.L contributed to study design, statistical analysis, and manuscript review. J.M.L., P.M.G., O.P.G., contributed with quality control of data and algorithms, and manuscript review. C.D., J.A., H.P.M., M.Y.V., M.C., A.P.C. and G.F.D. contributed to study concept and design, and manuscript editing and review. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Appendix A. Supplementary material

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