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Original Research

A phase II, randomised study of mFOLFOX6 with or without the Akt inhibitor ipatasertib in patients with locally advanced or metastatic gastric or gastroesophageal junction cancer

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KEYWORDS
Ipatasertib;
Gastric cancer;
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mFOLFOX6;

Abstract ***Background:*** Akt activation is common in gastric/gastroesophageal junction cancer (GC/GEJC) and is associated with chemotherapy resistance. Treatment with ipatasertib, a pan-Akt inhibitor, may potentiate the efficacy of chemotherapy in GC/GEJC.
Patients and methods: In this randomised, double-blind, placebo-controlled, multicentre, phase II trial, patients with locally advanced or metastatic GC/GEJC not amenable to curative therapy were randomised 1:1 to receive ipatasertib or placebo, plus mFOLFOX6 (modified

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Akt inhibitor

regimen of leucovorin, bolus and infusional 5-fluorouracil [5-FU], and oxaliplatin). The co-primary end-point was progression-free survival (PFS) in the intent-to-treat (ITT) population and in phosphatase and tensin homolog (PTEN)–low patients. Secondary end-points included PFS in patients with PI3K/Akt pathway–activated tumours; overall survival, investigator-assessed objective response rate and duration of response in the ITT population; and safety assessments.

Results: In 153 enrolled patients, the median PFS (ITT) was 6.6 months (90% confidence interval [CI], 5.7–7.5) with ipatasertib/mFOLFOX6 versus 7.5 months (90% CI, 6.2–8.1) with placebo/mFOLFOX6 (hazard ratio, 1.12; 90% CI, 0.81–1.55; $P = 0.56$). No statistically significant PFS benefit was observed in biomarker-selected patient subgroups (PTEN-low and PI3K/Akt pathway–activated tumours) with ipatasertib/mFOLFOX6 versus placebo/mFOLFOX6. Other secondary end-points did not favour the ipatasertib/mFOLFOX6 treatment arm. The percentages of patients with ≥1 adverse event (AE, 100% versus 98%) and grade ≥3 AEs (79% versus 74%) were similar between arms. Higher rates of AEs leading to treatment withdrawal (16% versus 6%) and serious AEs were reported in the ipatasertib arm (54% versus 43%). Thirty-nine and 29 deaths occurred in the ipatasertib and placebo arms, respectively.

Conclusions: Ipatasertib/mFOLFOX6 compared with placebo/mFOLFOX6 did not improve PFS in unselected or biomarker-selected patients. No unexpected safety concerns were observed.

Trial registration: ClinicalTrials.gov (NCT01896531).

1. Introduction

Activating alterations in the phosphoinositide 3-kinase (PI3K)/Akt pathway are common in human cancers, including gastric/gastroesophageal junction cancer (GC/GEJC) [1] and can lead to chemoresistance [2]. Aberrant PI3K/Akt pathway activation can occur through multiple mechanisms and is associated with poor prognosis [3]. Up to 36% of GC/GEJC tumours have loss of phosphatase and tensin homolog (PTEN), a negative regulator of PI3K/Akt signalling [3]. *PIK3CA* mutations are commonly found in GC/GEJC [4]. Increased PI3K protein expression was observed in 62.9% of patients with GC in a Korean retrospective study and significantly correlated with tumour invasiveness, phenotype and poor survival [5]. Clinical trials have demonstrated the clinical activity of Akt inhibitors in multiple tumour types, either as monotherapy or in combination with other agents [1,6].

Ipatasertib (GDC-0068) is a potent, novel, selective, adenosine triphosphate-competitive, small-molecule inhibitor of all three Akt isoforms. In preclinical cancer xenograft models, ipatasertib demonstrated anti-tumour activity in tumours with high levels of phosphorylated Akt, PTEN loss and *PIK3CA* mutations [6–10]. Ipatasertib inhibits PI3K/Akt signalling at clinically achievable doses [8]. In a phase I study in patients with diverse solid tumours, ipatasertib was well tolerated, and 34% of patients experienced stable disease [10]. Many of these patients had PI3K/Akt pathway–activated tumours, providing the rationale for further clinical studies of ipatasertib in tumours known to harbour activating alterations in this pathway, including GC/GEJC.

Akt inhibitors enhance the anti-tumour activity of chemotherapy in GC models [11]. Given that Akt activation is common in GC/GEJC tumours and associated with chemotherapy resistance, treatment with ipatasertib may potentiate the efficacy of chemotherapy in GC/GEJC. Fluoropyrimidine-based regimens are effective as first-line therapy for advanced GC/GEJC [12]. A randomised, double-blind, placebo-controlled, multicentre, phase II trial (NCT01896531) compared the efficacy and safety of ipatasertib plus mFOLFOX6 (modified regimen of leucovorin, bolus and infusional 5-fluorouracil [5-FU] and oxaliplatin) versus placebo plus mFOLFOX6 in patients with locally advanced or metastatic GC/GEJC not amenable to curative therapy.

2. Methods

The study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from patients before enrolment, in agreement with approved protocols from ethics committees at each site.

2.1. Patients

Eligible patients had histologically confirmed, inoperable, locally advanced; metastatic; or recurrent GC/GEJC not amenable to curative therapy. Other eligibility criteria included measurable disease per Response

Evaluation Criteria in Solid Tumors (RECIST) v1.1, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, life expectancy ≥12 weeks, and adequate haematologic and organ function. Key exclusion criteria included prior chemotherapy for inoperable locally advanced, metastatic or, recurrent GC/GEJC (neoadjuvant or adjuvant chemotherapy and/or radiation therapy was allowed if completed ≥6 months before randomisation); known human epidermal growth factor receptor 2 (HER2)–positive disease; radiation treatment within 28 days of randomisation (palliative radiation treatment to peripheral sites such as bone metastases was permitted if the patient had recovered from all acute, reversible effects and the medical monitor was notified); and previous therapy for GC/GEJC with an Akt, PI3K and/or a mammalian target of rapamycin (mTOR) kinase inhibitor.

2.2. Study design and procedures

Patients were randomised 1:1 to receive ipatasertib or placebo, plus mFOLFOX6 (S1) and stratified by adjuvant treatment, including chemotherapy with radiation (yes versus no), geographic location (Asia versus United States versus European Union) and tumour PTEN status (H score 0 to 100 versus 101 to 200 versus >200). H score was defined based on cytosolic PTEN staining [13]. Baseline tumour tissues were analysed for presence and type of *PIK3CA* or *AKT* mutations and *PIK3CA* amplification (see Supplementary Material). Crossover from placebo to ipatasertib was not permitted.

Ipatasertib (600 mg) or placebo was administered orally once daily (QD) on day 1 of cycle 1 through day 7 of each 14-day cycle until disease progression (per investigator assessment) or intolerable toxicity. If intolerable toxicity attributed to ipatasertib 600 mg occurred, the dose could be split to 300 mg twice daily or reduced to 400 mg QD or 200 mg QD. Following day 1 administration of ipatasertib or placebo, all patients initiated mFOLFOX6:oxaliplatin (85-mg/m^2 intravenous [IV] infusion over 2 h on day 1 every 14 days) coadministered with leucovorin 400 mg/m^2, then 5-FU 400 mg/m^2 administered as bolus IV infusion, followed by 5-FU 2400-mg/m^2 IV continuous infusion over 46–48 h (or 5-FU 1200-mg/m^2/d continuous IV infusion over 2 days). After cycle 8, oxaliplatin was discontinued and patients received ipatasertib/placebo followed by chemotherapy with bolus 5-FU, leucovorin, and IV 5-FU, as described previously.

2.3. Assessments

The primary end-point was progression-free survival (PFS), defined as time from randomisation to first occurrence of disease progression per investigator-assessed RECIST v1.1, or death on study ≤30 days after the last dose of study treatment from any cause in the intent-to-treat (ITT) population and in patients with PTEN-low tumours. Secondary end-points were overall survival (OS), investigator-assessed objective response rate (ORR) per RECIST v1.1, duration of response (DOR) and time to disease progression in the ITT population and PFS in the patient subgroup with PI3K/Akt–activated tumours.

Safety assessments included adverse event (AE) incidence, description and severity graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 and Medical Dictionary for Regulatory Activities (MedRA) version 18.1 terminology for AEs. All AEs and serious AEs (SAEs) collected until 30 days after the last dose of study treatment or initiation of another therapy were analysed.

2.4. Statistical analysis

This trial was hypothesis generating and was not powered to detect statistically significant differences in PFS across arms. The sample size was determined such that the upper bound of the two-sided 90% CI for a target clinically meaningful hazard ratio (HR) of 0.6 in patients with PTEN-low tumours would be close to 1, which required 48 PFS events. Assuming an estimated 60% of patients had PTEN-low tumours, the target enrolment of 150 patients (75 patients randomised to each arm) included ≈90 patients with PTEN-low tumours. The final PFS analysis was planned when 48 or 80 PFS events had occurred in patients with PTEN-low tumours or in all enrolled patients, respectively.

PFS and OS were evaluated by survival analysis. Primary and secondary efficacy analyses were conducted in all randomised patients and in predefined biomarker subgroups: PTEN-low (tumour samples that were PTEN immunohistochemistry [IHC] in 0 <10% of the tumour cells; see Supplementary Material) and PI3K/Akt–activated (tumour samples that were PTEN IHC in 0 ≥90% of the tumour cells, samples with *PIK3CA* mutations or *PIK3CA* amplification [ratio ≥1.5]; see Supplementary Material). Patients without post-baseline tumour assessments were considered non-responders. DOR was assessed in all patients with an objective tumour response. Safety analyses were conducted in all patients who received any dose of the study treatment.

3. Results

3.1. Patient characteristics

Between 14th August 2013 and 19th December 2014, 153 patients were enrolled and randomised (S2). Patient characteristics were generally similar between treatment arms (Table 1). The proportion of patients with ECOG PS 1 was slightly higher in the placebo versus ipatasertib

Table 1
Patient baseline demographics and clinical characteristics.

Characteristic	Ipatasertib + mFOLFOX6 (n = 71)	Placebo + mFOLFOX6 (n = 82)
Age, median (range), y	58.0 (26–74)	63.0 (27–87)
Male, n (%)	52 (73.2)	60 (73.2)
Baseline weight, mean (SD), kg[a]	64.92 (16.11)	67.12 (18.86)
ECOG PS at enrolment, n (%)[b]		
0	25 (35.2)	22 (26.8)
1	46 (64.8)	59 (72.0)
Geographic region, n (%)		
Europe	16 (22.5)	20 (24.4)
United States	13 (18.3)	18 (22.0)
Asia	42 (59.2)	44 (53.7)
Primary tumour site, n (%)		
Stomach	49 (69.0)	54 (65.9)
GEJ	22 (31.0)	28 (34.1)
Lauren histological type, n (%)[c]		
Diffuse	21 (29.6)	10 (12.3)
Intestinal	10 (14.1)	21 (25.9)
Mixed	5 (7.0)	4 (4.9)
Unknown	35 (49.3)	46 (56.8)
Prior gastrectomy, n (%)	19 (26.8)	25 (30.5)
Adjuvant chemotherapy ± radiation therapy, n (%)	9 (12.7)	10 (12.2)
Prior systemic therapy, n (%)	3 (4)	11 (29)
Neoadjuvant	2 (2.8)	8 (9.8)
Adjuvant	3 (4.2)	4 (4.9)
Prior radiotherapy, n (%)	3 (4.2)	11 (13.4)
AJCC stage, n (%)[c]		
IA	1 (1.4)	1 (1.2)
IB	1 (1.4)	4 (4.9)
IIA	2 (2.9)	4 (4.9)
IIB	1 (1.4)	4 (4.9)
IIIA	4 (5.7)	2 (2.4)
IIIB	4 (5.7)	7 (8.5)
IIIC	3 (4.3)	2 (2.4)
IV	54 (77.1)	58 (70.7)
Sites of metastasis, n (%)		
Liver	28 (39.4)	32 (39.0)
Lung	12 (16.9)	12 (14.6)
Bone	7 (9.9)	6 (7.3)
Lymph node	48 (67.6)	56 (68.3)
Peritoneal	30 (42.3)	25 (30.5)
No. of metastatic sites, n (%)		
1	26 (36.6)	33 (40.2)
2	20 (28.2)	24 (29.3)
3	15 (21.1)	17 (20.7)
≥4	10 (14.1)	8 (9.8)
PTEN H score, n (%)[d]		
0–100	37 (51.4)	45 (54.2)
101–200	25 (35.2)	31 (37.8)
>200	6 (8.3)	6 (7.3)

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; mFOLFOX6, modified regimen of leucovorin, 5-fluorouracil and oxaliplatin; PTEN, phosphatase and tensin homolog; SD, standard deviation.

[a] ECOG PS data missing for 1 patient in placebo/mFOLFOX6 arm.
[b] n = 81 for ipatasertib/mFOLFOX6.
[c] n = 70 for placebo/mFOLFOX6.
[d] n = 68 for ipatasertib/mFOLFOX6.

arm (72.0% versus 64.8%). The ipatasertib arm had more patients with a diffuse type of GC (29.6% versus 12.3%), while the placebo arm had more patients with intestinal-type disease (25.9% versus 14.1%). A greater proportion of patients treated with ipatasertib/mFOLFOX6 than with placebo/mFOLFOX6 had peritoneal metastases (42.3% versus 30.5%).

As of the primary data cut-off (3rd June 2015), 64 patients (91.4%) had discontinued ipatasertib, and 73 patients (89%) had discontinued placebo; disease progression was the most common reason (S2). The same proportion of patients in each group discontinued 5-FU (bolus and IV; S2). Four patients with response to study treatment discontinued early and subsequently underwent surgery with curative intent (1 in ipatasertib arm and 3 in placebo arm). Forty-seven patients (66.2%) in the ipatasertib arm and 34 (41.5%) in the placebo arm discontinued from the study survival follow-up, most commonly due to death. Mean treatment duration, dose intensity and dose modifications of all study drugs are reported in S3.

Of patients with tumours evaluable for PTEN expression (N = 150), 15 of 71 (21.1%) and 21 of 82 (25.6%) in the ipatasertib and placebo arms, respectively, had PTEN-low tumours (S4A). Forty-six patients (23 in each arm) were included in the PI3K/Akt pathway–activated subgroup (tumours with PTEN IHC 0 in ≥90% of the tumour cells [n = 11; S4A]) + tumours with *PIK3CA* mutations [n = 10; S4A, S4B] or *PIK3CA* amplification using ratio ≥1.5 [n = 31; S4A, S4C] + PTEN IHC 0 ≥90% [n = 11]).

3.2. Efficacy

Forty-eight (67.6%) and 57 (69.5%) patients in the ipatasertib/mFOLFOX6 and placebo/mFOLFOX6 arms, respectively, had PFS events. Median PFS was 6.6 months (90% CI, 5.7–7.5) with ipatasertib/mFOLFOX6 versus 7.5 months (90% CI, 6.2–8.1) with placebo/mFOLFOX6 in the ITT population (HR, 1.12; 90% CI, 0.81–1.55; P = 0.56) (Table 2; Fig. 1). In the PTEN-low subgroup, median PFS was 7.1 months (90% CI, 5.4–9.9) with ipatasertib/mFOLFOX6 and 7.4 months (90% CI, 6.5–14.7) with placebo/mFOLFOX6 (HR, 1.07; 90% CI, 0.54–2.11; P = 0.86) (Table 2; Fig. 1). No statistically significant PFS benefit was observed with ipatasertib/mFOLFOX6 versus placebo/mFOLFOX6 in any clinical subgroup (S5). Additionally, patients in the PI3K/Akt pathway–activated subgroup demonstrated no benefit with the combination study treatment (Fig. 1).

In the ITT population, median OS was longer in the placebo arm (15.7 months; 90% CI, 13.5–19.8; event

Table 2
Efficacy summary.

	Ipatasertib + mFOLFOX6 (n = 71)		Placebo + mFOLFOX6 (n = 82)
PFS in all randomised patients			
Patients with event, n (%)	48 (67.6)		57 (69.5)
Median time to event (90% CI), months	6.57 (5.72–7.52)		7.52 (6.24–8.11)
HR (90% CI)[a]		1.12 (0.81–1.55)	
PFS in patients with PTEN-low tumours[b]			
Patients with event, n (%)	11 (73.3)		13 (61.9)
Median time to event (90% CI), months	7.10 (5.39–9.92)		7.39 (6.51–14.69)
HR (90% CI)[a]		1.07 (0.54–2.11)	
OS in all randomised patients			
Patients with event, n (%)	39 (54.9)		29 (35.4)
Median time to event (90% CI), months	12.12 (10.28–14.55)		15.67 (13.54–19.81)
HR (90% CI)[a]		1.85 (1.23–2.79)	
OS in patients with PTEN-low tumours[b]			
Patients with event, n (%)	8 (53.3)		5 (23.8)
Median time to event (90% CI), months	14.82 (11.99–16.26)		NE
HR (90% CI)[a]		1.65 (0.64–4.28)	
ORR			
ORR, n (%) [90% CI]	37 (52) [42–62]		46 (56) [47–65]
CR, n (%)	2 (3)		5 (6)
PR, n (%)	35 (49)		41 (50)
SD, n (%)	20 (28)		25 (30)
Unevaluable	6 (8.5)		2 (2.4)
Difference in ORR (90% CI), %[a]		−4.0 (−17.3 to −9.3)	
P value[c]		0.62	

CI, confidence interval; CR, complete response; HR, hazard ratio; mFOLFOX6, modified regimen of leucovorin, 5-fluorouracil and oxaliplatin; NE, not evaluated; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PTEN, phosphatase and tensin homolog; SD, stable disease.

[a] Unstratified analysis; HR of ipatasertib/mFOLFOX6 versus placebo/mFOLFOX6.

[b] PTEN-low defined as no cytoplasmic PTEN expression (IHC = 0) in ≥10% of tumour cells; n = 15 for ipatasertib/mFOLFOX6 and n = 21 for placebo/mFOLFOX6.

[c] By log-rank test.

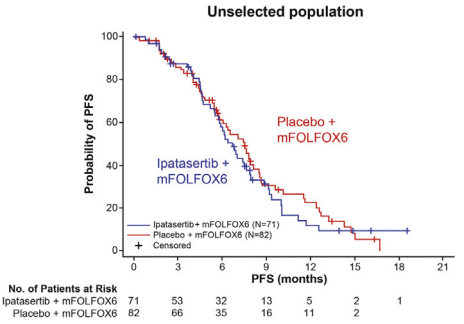
rate, 35.4%) versus the ipatasertib arm (12.1 months; 90% CI, 10.3–14.6; event rate, 54.9%; HR, 1.85; 90% CI, 1.23–2.79) (Table 2). A similar OS trend was observed in the PTEN-low subgroup though based on fewer events (Table 2). More patients in the placebo versus ipatasertib arm received post-progression therapies (64.6% versus 49.3%; S6). Objective responses (mostly partial responses) were observed in over half of the patients in both arms (Table 2). An additional 28–30% of patients in both arms had stable disease as the best response. No further analyses of tumour response in patients with PI3K/Akt pathway–activated tumours were performed. Maximum changes in tumour size from baseline are shown in S7. One patient who had a complete response had an activating mutation in *AKT1* (E17K mutation) in a tumour biopsy sample in her gastric cancer performed locally by the investigator. This patient was a 73-year-old women with stage IV gastric cancer of the intestinal type, with metastases to the peritoneum; she continued single-agent ipatasertib for 36 months and remained progression free during this time.

3.3. Safety

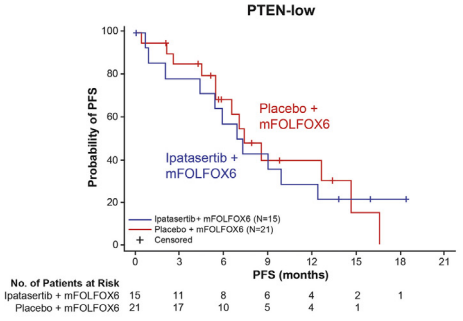
The percentages of patients with ≥1 AE (all grade), grade ≥3 AEs and AEs leading to interruption of ipatasertib/placebo were similar between arms (Table 3). Patients receiving ipatasertib had a greater number of AEs leading to treatment withdrawal and dose reduction (Table 3).

The most common AEs were nausea, diarrhoea and decreased appetite (S8). AEs ≥10% higher with ipatasertib versus placebo included diarrhoea, vomiting, rash, fatigue, stomatitis, nausea and decreased appetite. Neutropenia was ≥10% greater in the placebo versus ipatasertib arm. Of note, more patients in the ipatasertib arm compared with the placebo arm had a decrease in body weight from baseline (23% versus 12%).

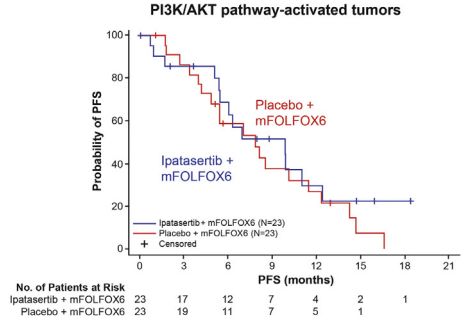
Higher rates of SAEs were reported in the ipatasertib arm (Table 3). The most common SAEs (≥5% of patients in any arm) were diarrhoea, vomiting and nausea. Five patients in the ipatasertib arm (7.1%) and 2 in the placebo arm (2.4%) had AEs within 30 days of last study treatment resulting in death. Only one AE resulting in death—a 58-year-old female patient who developed cardiac arrest during the ninth cycle of 5-FU infusion (infusion day 2, ipatasertib day 2 of cycle 9, following 8 previous cycles of mFOLFOX6)—was considered related to ipatasertib and infusional 5-FU treatment. Including all deaths that occurred during treatment and post-treatment follow-up, 39 and 29 deaths occurred in the ipatasertib and placebo arms, respectively (Table 3).



ITT population	Ipatasertib 600mg + mFOLFOX6 (n=71)	Placebo + mFOLFOX6 (n=82)
Subjects with event, n (%)	48 (68)	57 (70)
Median, months (90% CI)	6.6 (5.7, 7.5)	7.5 (6.2, 8.1)
Unstratified HR (90% CI) p-value (log-rank)	1.12 (0.81, 1.55) 0.56	



PTEN-low tumors	Ipatasertib 600mg + mFOLFOX6 (n=15)	Placebo + mFOLFOX6 (n=21)
Subjects with event, n (%)	11 (73)	13 (62)
Median, months (90% CI)	7.1 (5.4, 9.9)	7.4 (6.5, 14.7)
Unstratified HR (90% CI) p-value (log-rank)	1.07 (0.54, 2.11) 0.86	



PI3K/AKT pathway-activated tumors	Ipat 600mg + mFOLFOX6 (n=23)	Placebo + mFOLFOX6 (n=23)
Subjects with event, n (%)	13 (57)	13 (62)
Median, months (90% CI)	9.9 (6, 11)	7.8 (5.4, 10.1)
Unstratified HR (90% CI) p-value (log-rank)	0.75 (0.41, 1.35) 0.41	

Fig. 1. Progression-free survival (PFS) in the ITT, PTEN-low and PI3K/Akt pathway–activated tumour populations. HR, hazard ratio; ITT, intent-to-treat; mFOLFOX6, modified regimen of leucovorin, 5-fluorouracil and oxaliplatin; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog.

Table 3
Safety summary.

AE, n (%)	Ipatasertib + mFOLFOX6 (n = 70)	Placebo + mFOLFOX6 (n = 82)
Patients with ≥1 AE		
AE	70 (100)	80 (98)
Serious AE	38 (54)	35 (43)
Grade ≥3 AE	55 (79)	61 (74)
AE related to any study drug	68 (97)	79 (96)
Grade ≥3 AE related to any study drug	47 (67)	50 (61)
AEs leading to interruption of ipatasertib/placebo	42 (60)	52 (63)
AEs leading to withdrawal due to any component of mFOLFOX6 regimen	19 (27)	13 (16)
≥1 AE that led to dose reduction of study drug	32 (46)	12 (15)
Deaths, n (%)	39 (56)	29 (35)
PD causing death	32 (46)	26 (32)
AE resulting in death	5 (7)[a]	2 (2)[b]
Cause of death unknown	2 (3)	0

AE, adverse event; mFOLFOX6, modified regimen of leucovorin, 5-fluorouracil and oxaliplatin; PD, progressive disease.

[a] AEs resulting in deaths in ipatasertib arm: gastric perforation at stent site, respiratory failure from pneumonia, gastrointestinal bleed from PD, sudden death from cardiac arrest, out-of-hospital cardiac arrest.

[b] AEs resulting in deaths in placebo arm: cerebral gas embolism, aspiration pneumonia from PD in lungs.

4. Discussion

This trial of ipatasertib as first-line therapy in metastatic GC/GEJC did not meet its study end-point for PFS in the ITT or biomarker-defined patient subgroups. No significant differences were observed in the secondary end-points, including OS, ORR and DOR. This is consistent with previous studies evaluating therapies targeting the PI3K/Akt pathway in GC that have also failed to show improved efficacy [14].

PFS in the placebo arm was consistent with previous studies of first-line regimens of chemotherapy combined with targeted agents for GC [15–18]. Median OS in the placebo arm of this study, however, was remarkably higher than in previous studies. Possible factors include differences in baseline patient characteristics, post-progression therapies and other prognostic factors (e.g. sites of metastasis). Additionally, this study was conducted mostly at academic medical centres.

Biomarker analyses did not identify any subgroups associated with improved PFS in the ipatasertib-treated arm, including the predefined subgroups of patients with PTEN-low and PI3K/Akt pathway–activated tumours. However, these subgroup analyses were significantly underpowered, and further studies are needed to identify predictive biomarkers. Other studies have reported

comparable frequencies of *PIK3CA* gene mutations in GC to those observed here; they reported that neither *PIK3CA* mutation status nor *PIK3CA* gene amplification were prognostic of survival, [19,20] and *PIK3CA* 'hotspot' mutations were not associated with PI3K pathway protein levels or activation [19].

Although ipatasertib did not improve PFS in this trial, it has demonstrated efficacy in other advanced malignancies. In the phase II LOTUS trial in metastatic triple-negative breast cancer, first-line treatment with ipatasertib combined with paclitaxel yielded modest improvement in PFS in the ITT population, with greater improvement observed in patients with *PIK3CA*/*Akt1*/PTEN pathway–activated tumours [6]. A phase Ib/II study in metastatic castration-resistant prostate cancer previously treated with docetaxel demonstrated improved PFS with ipatasertib plus the anti-androgen abiraterone versus placebo plus abiraterone, particularly in patients with PTEN-loss tumours [21].

Safety results were generally consistent with known safety profiles of PI3K/Akt pathway inhibitors [1] and results reported in previous ipatasertib studies (mostly gastrointestinal-related AEs and grade 1–2 severity), with no new or unexpected safety concerns [6,10]. More AEs leading to dose withdrawal and/or reduction and more deaths occurred with ipatasertib/mFOLFOX6 versus placebo/mFOLFOX6. AEs leading to withdrawal due to any component of the mFOLFOX6 regimen were more common in patients in the ipatasertib versus placebo arms. The dose intensity of mFOLFOX6 did not appear to be affected by ipatasertib. However, the lower dose intensity of ipatasertib/placebo and/or higher rate of withdrawals in the ipatasertib arm due to toxicity may have contributed to lower-than-expected efficacy. In regard to the patient who died from cardiac arrest, no clinically significant cardiovascular safety signals were identified from the ipatasertib non-clinical studies. Furthermore, cardiac toxicity has not been reported as an identified or potential risk with ipatasertib administration in other clinical studies in patients with metastatic triple-negative breast cancer or metastatic prostate cancer. It is noted that this patient discussed in the study did develop severe chest pain during the infusion of fluorouracil.

5. Conclusions

In conclusion, although this study did not meet its primary end-point of improved PFS in patients with GC/GEJC treated with ipatasertib/mFOLFOX6 compared with placebo/mFOLFOX6, ipatasertib is being explored in other studies at lower doses to improve tolerability [6].

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Data sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Author contributions

JA provided study concepts and study design; HCC, MN, YKK, YB, JA and IC helped in data acquisition; HCC assisted in quality control of data and algorithms; HCC, MN, NX, YKK, YB, WC, JA and IC contributed toward data analysis and interpretation; NX helped in statistical analysis; and all the authors took part in manuscript preparation, editing and review.

Conflict of interest

YJB has been a consultant/advisor for ADC Therapeutics, AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly, FivePrime, Genentech/Roche, Green Cross, Merck Serono, Merck Sharp & Dohme, Novartis, Ono, Pfizer, Samyang Biopharm, Taiho and Takeda and has received research grants from Astellas, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Boston Biomedical, Bristol-Meyers Squibb, CKD Pharma, Curis, Daiichi Sankyo, Eli Lilly, FivePrime, Genentech/Roche, GlaxoSmithKline, Green Cross, Hanmi, MacroGenics, Merck Serono, Merck Sharp & Dohme, Novartis, Ono, Otsuka, Pfizer, Taiho and Takeda.

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HCC has received research grants from Eli Lilly, GlaxoSmithKline, Merck Serono, Merck Sharp & Dohme, Ono and Taiho, served on speakers bureaus for Eli Lilly, Foundation Medicine and Merck Serono and has been a consultant for Bristol-Meyers Squibb, Celltrion, Eli Lilly, Merck Serono, Merck Sharp & Dohme, Quintiles and Taiho.

ZAW has been a consultant for Array, FivePrime, Genentech, Merck Serono, Merck Sharp & Dohme and Novartis.

WC has nothing to disclose but was a stockholder and employee of Genentech/Roche.

SG, NX, DM and RM are employees of Genentech, Inc.

IC has served as an advisor for AstraZeneca, Bayer, Bristol-Meyers Squibb, Eli Lilly, FivePrime, Merck Serono, Merck Sharp & Dohme and Roche, received research funding from Eli Lilly, Janssen-Cilag, Merck Serono and Sanofi Oncology and honoraria from Eli Lilly.

MN and JAA have nothing to disclose.

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Appendix A. Supplementary data

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