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Multicenter phase I/II trial of gemcitabine, oxaliplatin and nab-paclitaxel as first-line treatment for patients with advanced biliary tract cancer

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A R T I C L E I N F O

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A B S T R A C T

Introduction: The prognosis of patients with advanced biliary tract cancer (BTC) is still poor, and new strategies improving patients' outcome are needed. In our trial we investigated safety and activity of nab-paclitaxel in combination with gemcitabine and oxaliplatin as first-line systemic treatment for patients with advanced BTC.
Methods: In this investigator-initiated, multicenter, dose-escalation, single-arm phase I/II trial, patients were accrued into cohorts of 3 patients and dose escalation was performed following the standard 3 + 3 rule. Primary endpoint was the proportion of patients free from progression at 6 months. Secondary endpoints included safety and tolerability of the combination; progression-free survival (PFS); overall survival (OS); objective response rate (ORR); duration of response.
Results: Between July 2017 and December 2020, 67 patients were treated. Among the 10 patients in the phase I, no dose-limiting toxicity was observed, and dose level 2 was defined as recommended phase II dose for the phase II part. At data cutoff, the 6-month PFS rate was 49.1 % (95 % CI 40.8–57.5 %) with 28 patients out of 57 free from progression or death at 6 months. Median PFS was 6.3 months (95 % CI 3.6–10.1) and median OS was 12.4 months (95 % CI 8–23). ORR was 20.89 %. Most common grade 3 and grade 1–2 drug-related adverse events were neutropenia and peripheral neuropathy, respectively.
Conclusion: Triple chemotherapy demonstrated a favorable safety profile. However, the study did not meet its primary endpoint. Future studies will clarify the benefit of chemotherapy combinations in different settings.
This trial is registered with ClinicalTrials.gov, NCT03943043.

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1. Introduction

Biliary tract cancer (BTC) refers to a heterogeneous group of tumors including intrahepatic (iCCA), extrahepatic (perihilar and distal) cholangiocarcinoma (eCCA), gallbladder cancer (GBC) and ampullary carcinoma [1].

Considered rare, the incidence rate is below 6/100,000 per year [2,3]. BTC is frequently diagnosed at advanced stage with a 5-year survival < 20 % [3,4].

Phase III ABC-02 trial established first-line standard of care for patients with advanced BTC, demonstrating superiority of cisplatin plus gemcitabine (CisGem) versus gemcitabine (Gem), with a median overall survival (mOS) of 11.7 versus 8.1 months [5]. First-line therapy has remained unchanged for a decade, with only two Japanese phase III trials evaluating S-1 versus CisGem [6], and in combination with CisGem [7] reporting positive results.

An alternative first-line regimen used in clinical practice is the combination of Gem and oxaliplatin (GEMOX) [8] sometimes preferred to the cisplatin-based regimen due to the different safety profile and the possibility of avoiding intravenous hyperhydration [9]. However no clinical trials directly compared GEMOX versus CisGem.

Recently, the combination of first-line chemotherapy and immunotherapy was proven superior to chemotherapy. The phase III TOPAZ-1 study demontrated an improved mOS with CisGem plus durvalumab versus CisGem (12.8 versus 11.5 months), with a good safety profile [10,11]. These findings have reshaped the therapeutic scenario establishing a new first-line standard of care [12]. Efficacy of immunotherapy has been further supported by the phase III KEYNOTE-966 trial, demontrating an improvement in mOS with CisGem plus pembrolizumab (12.7 months) versus placebo (10.9 months) [13].

The knowledge that approximately 40–45 % of subjects with iCCA have potentially actionable alterations in studies conducted in Western countries has paved the way for molecularly targeted agents for patients previously treated with chemotherapy [14,15]. Chemotherapy intensification is a potential strategy when different agents are combined in a synergistic way. Efficacy of first-line Gem plus nab-paclitaxel in metastatic pancreatic cancer is partly referred to nab-paclitaxel increasing intratumoral Gem levels [16]. BTC is also a stroma-rich tumor [17], suggesting that nab-paclitaxel could have a synergistic effect in combination with Gem also in this disease. A phase II study tested this regimen as first-line treatment for patients with advanced BTC and, although it did not meet its primary endpoint, showed an activity similar to CisGem with an acceptable safety profile [18].

A phase II study investigated the combination of CisGem and nab-paclitaxel showing promising progression-free survival (PFS) and OS, with a manageable safety profile [19]. However, the subsequent phase III SWOG 1815 trial did not meet its primary endpoint of improved OS versus CisGem [20].

We conducted an Italian multicenter, dose-escalation, single-arm phase I/II trial to investigate the safety and activity of nab-paclitaxel in combination with GEMOX as first-line treatment for patients with advanced BTC.

2. Methods

2.1. Patients

Eligible patients were 18 years or more; had histologically-confirmed unresectable or metastatic BTC; had not received prior chemotherapy (adjuvant therapy was permitted > 6 months before enrollment); had Eastern Cooperative Oncology Group (ECOG) performance status (PS) score 0–1; had measurable or evaluable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [21]. Main exclusion criteria included grade ≥ 2 peripheral neuropathy by Common Terminology Criteria for Adverse Events (CTCAE) 4.0 [22] and symptomatic brain metastases or carcinomatous meningitis. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study protocol was approved by institutional independent ethics committee at each participating center. All patients provided written informed consent prior to enrollment.

2.2. Trial Design

This is an investigator-initiated, multicenter, dose-escalation, single-arm phase I/II trial of nab-paclitaxel in combination with GEMOX involving patients with unresectable or metastatic BTC not previously treated with chemotherapy. The phase I part of the study was conducted at IRCCS Humanitas Research Hospital in Milan, Italy. The phase II part was conducted at 7 Italian sites.

In the phase II part of the study, nab-paclitaxel in combination with GEMOX was administered at the recommended phase II dose (RP2D), on days 1 and 14 every 28 days, until clinical or radiographic disease progression per RECIST v1.1 [19], unacceptable toxicity, or for a maximum of 24 weeks.

2.3. Endpoints and assessments

The primary objective of the phase I part of the study was to establish the maximum tolerated dose (MTD) and define RP2D. The primary objective of the phase II part of the study was to determine clinical activity of GEMOX and nab-paclitaxel assessed by the proportion of patients free from progression at 6 months (primary endpoint). Secondary endpoints for the whole study included safety and tolerability; PFS; OS; best objective response rate (ORR); duration of response. PFS was calculated from the date of first treatment cycle to the date of disease progression or death, whichever came first. OS was defined as the time between first treatment cycle and death from any cause. ORR was defined as the proportion of patients with partial response (PR) or complete response (CR) according to RECIST v1.1. Adverse Events (AEs) were graded according to CTCAE, version 4.03 and monitored until at least 30 days after the last dose of chemotherapy or until the last study visit. Physical examination, vital signs, ECOG PS score, hematology and biochemistry were assessed on day 1 of each cycle; CA 19–9 levels were measured every 8 weeks. Tumor imaging assessments were performed within 4 weeks prior to the first dose of chemotherapy, then every 8 weeks until disease progression. Patients were evaluated until disease progression, unacceptable toxicity, or consent withdrawal. After disease progression, patients were monitored for survival at 12-week intervals.

2.4. Statistical analysis

In the phase I part of the study, eligible patients were grouped into cohorts of 3 patients at each dose level and dose escalation was performed following the standard 3 + 3 rule. Starting from dose-level 0, 3 patients received intravenous Gem 1000 mg/m2, oxaliplatin 80 mg/m2, nab-paclitaxel 100 mg/m2 on days 1 and 14 of a 28-day cycle. If no DLTs were reported, treatment was continued with the same schedule on days 1 and 14 every 28 days and 3 new patients were treated with the next dose level (Table 1 and Figure 1).

If > 1 of 3 or 6 patients in any cohort developed DLTs, MTD was considered reached. DLT was defined as treatment-related toxicity

Table 1
Dose levels.

Dose Level	Gemcitabine (mq/m2)	Oxaliplatin (mg/m2)	nab-Paclitaxel (mq/m2)
-1	800	80	80
0	1000	80	100
+ 1	1000	80	125
+ 2	1000	80	150

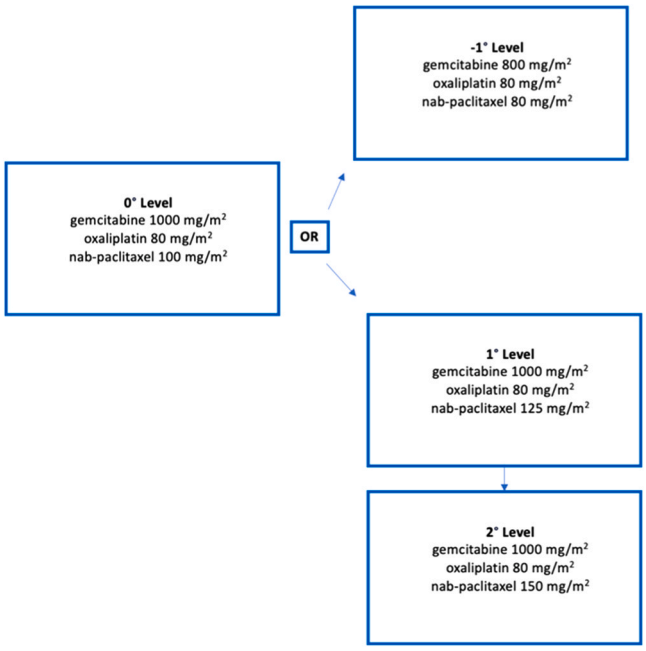

Fig. 1. Study design.

according to CTCAE v 4.03 occurred during cycle 1 (from day 1 to day 28) likely related to the study treatment and fulfilling any of these criteria: grade $\geq$ 3 anemia or leukopenia; grade 3 febrile neutropenia or grade 4 neutropenia; grade 3 thrombocytopenia with grade $\geq$ 2 bleeding or grade 4 thrombocytopenia with or without bleeding; grade $\geq$ 3 non-hematological toxicity (except alopecia and fatigue); other significant drug-related (DR) toxicity deemed to be dose limiting or that caused the patient to discontinue treatment; any toxicity considered to be a DLT had to be reported as a serious AE.

The phase II part of the study followed the Fleming-A′ Hern design. A 6-month PFS rate of 75 % was required for the treatment to be considered effective, whereas a 6-month PFS rate $\leq$ 60 % should be excluded. With an alpha error of 0.10 (one sided) and a power of 85 %, the calculated sample size was 56 patients. Thirty-nine of 56 patients without progressive disease or death at 6 months needed to be observed for the study treatment to be considered active. All patients who received at least one dose of treatment were considered in the intention-to-treat population analysis. Patient characteristics were summarized as median and range for continuous variables and as numbers and percentages for discrete variables. Dose modifications, interruptions and discontinuations were described. Safety was assessed through tolerability and AE recording. PFS and OS were described with the Kaplan Meier method. A p-value < 0.05 was considered statistically significant for all sub-estimates. All analyses were performed using SAS v. 9.4.

3. Results

3.1. Patient characteristics

Between July 2017 and December 2020, 78 patients signed the informed consent, 10 patients did not receive the study treatment due to liver function alteration, one patient had inadequate clinical conditions, and 67 received the study treatment. 10 patients were treated in the single-center phase I portion of the study and 57 patients in the multicenter phase II portion. Median age was 65 (range 39–77) years, most patients had iCCA (58.20 %), and most patients had metastatic disease (74.62 %). Patient characteristics are summarized in Table 2.

Table 2
Baseline patient characteristics.

Baseline Characteristics	Phase I n = 10 (%)	Phase II n = 57 (%)	Overall n = 67 (%)
Age (yrs), median (range)	61 (45-75)	66 (39-77)	65 (39-77)
Sex			
Male	8 (80)	36 (63.2)	44 (65.67)
Female	2 (20)	21 (36.8)	23 (34.32)
Baseline ECOG PS, n (%)[a]			
0	5 (50)	41 (71.92)	46 (68.65)
1	5 (50)	15 (26.31)	20 (29.85)
Primary Tumor site			
iCCA	6 (60)	33 (57.89)	39 (58.20)
eCCA	1 (10)	17 (29.82)	18 (26.86)
GBC	1 (10)	7 (12.28)	8 (11.94)
Ampullary	2 (20)	0	2 (2.98)
Disease stage			
Metastatic	7 (70)	43 (75.43)	50 (74.62)
Locally advanced	3 (30)	14 (24.56)	17 (25.37)
Prior Surgery			
Yes	1 (10)	12 (21.05)	13 (19.40)
No	9 (90)	45 (78.94)	54 (80.59)
Prior Adjuvant CT			
Yes	0	7 (12.28)	7 (10.44)
No	10 (100)	50 (87.71)	60 (89.55)
Baseline CA 19-9, IU/mL (range)[b]	205.1 (11.1-12736)	75.5 (2-20000)	84.5 (2-20000)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; CT, Chemotherapy; iCCA, intrahepatic cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder carcinoma.
[a] ECOG PS was missing in 1 patient
[b] Baseline CA 19–9 was missing in 7 patients.

3.2. Safety

Between July 2017 and December 2018, 10 patients were enrolled in the phase I portion of the study. The first cohort of 3 patients received GEMOX plus nab-paclitaxel at dose level 0 (Gem 1000 mg/m2 + oxaliplatin 80 mg/m2 + nab-paclitaxel 100 mg/m2) with no DLT. The following cohort of 3 patients received the combination treatment at dose level 1 (Gem 1000 mg/m2 + oxaliplatin 80 mg/m2 + nab-paclitaxel 125 mg/m2) with no DLT. We enrolled 3 patients at dose level 2 (Gem 1000 mg/m2 + oxaliplatin 80 mg/m2 + nab-paclitaxel 150 mg/m2), 1 patient discontinued due to non-DR cholangitis, and 1 more patient was enrolled (4 patients at level 2), with no DLT. Dose level 2 was determined to be the RP2D. Although no DLTs were observed among the 10 patients enrolled in phase I portion, dose reductions due to AEs occurring beyond the DLT period were needed.

In the phase I part of the study, oxaliplatin was reduced because of grade 2 peripheral neuropathy in 2 patients; oxaliplatin and nab-paclitaxel were reduced due to grade 3 peripheral neuropathy and grade 1 persistent peripheral neuropathy in 1 patient each; oxaliplatin, nab-paclitaxel and Gem were reduced due to grade 2 neutropenia in 2 patients. Treatment was delayed in 3 patients due to grade 3 neutropenia and grade 1 thrombocytopenia (n = 1), grade 2 neutropenia (n = 1), and grade 2 pain, fatigue, oral mucositis, and peripheral neuropathy (n = 1). Treatment with nab-paclitaxel was discontinued in 2 patients due to grade 2 peripheral neuropathy (n = 1) and grade 1 persistent peripheral neuropathy (n = 1).

Overall, we observed 339 AEs across 59 (88 %) patients. 203 AEs (59.88 %) were considered DR, 136 (40.11 %) non-DR; 11 AEs (3.24 %) were DR and serious, and 192 AEs (56.64 %) were DR and non-serious. 50 (74.6 %) patients had at least 1 DR AE and 47 (70.1 %) at least 1 non-DR AE. Out of a total of 67 patients, most common grade 3 DR AEs were neutropenia (10.4 %), peripheral neuropathy (7.5 %), fatigue (6 %), and anemia (3 %). Most common grade 4 DR AEs were neutropenia (3 %) and thrombocytopenia (3 %) (Table 3). Four patients experienced grade 5 AEs including DR sepsis, non-DR biliary tract infection, hepatic failure, hyponatremia (1 patient each). Second-line treatments were not

Table 3
Summary of drug-related adverse events in the phase I and II portion of the study.

AE	G1-2	G3	G4	G5
	n (%)	n (%)	n (%)	n (%)
Peripheral neuropathy	30 (44.7)	5 (7.5)	0	0
Fatigue	20 (29.8)	4 (6)	0	0
Nausea	11 (16.4)	1 (1.5)	0	0
Alopecia	8 (11.9)	2 (3)	0	0
Thrombocytopenia	8 (11.9)	1 (1.5)	2 (3)	0
Diarrhea	8 (11.9)	1 (1.5)	0	0
Fever	8 (11.9)	1 (1.5)	0	0
Mucositis	7 (10.4)	1 (1.5)	0	0
Arthralgia	7 (10.4)	0	0	0
Neutropenia	6 (8.9)	7 (10.4)	2 (3)	0
Vomiting	6 (8.9)	0	0	0
Anemia	6 (8.9)	2 (3)	0	0
Constipation	3 (4.4)	0	0	0
Pain	2 (3)	1 (1.5)	0	0
AST increased	2 (3)	0	0	0
Infusion related reaction	2 (3)	0	0	0
Localized edema	2 (3)	0	0	0
Myalgia	2 (3)	0	0	0
ALT increased	2 (3)	0	0	0
Blood bilirubin increased	1 (1.5)	0	0	0
Creatinine increased	1 (1.5)	0	0	0
Epistaxis	1 (1.5)	0	0	0
Gastritis	1 (1.5)	0	0	0
Hyperuricemia	1 (1.5)	0	0	0
Paronychia	1 (1.5)	0	0	0
Pruritus	1 (1.5)	0	0	0
Rash	1 (1.5)	0	0	0
Sinus tachycardia	1 (1.5)	0	0	0
ALP increased	1 (1.5)	0	0	0
Ascites	1 (1.5)	0	0	0
Febrile neutropenia	0	1 (1.5)	1 (1.5)	0
Gamma-GT increased	0	1 (1.5)	0	0
Gastric ulcer	0	1 (1.5)	0	0
Hypoalbuminemia	0	1 (1.5)	0	0
Hypokalemia	0	1 (1.5)	0	0
Toxic epidermal necrosis	0	0	1 (1.5)	0
Sepsis	0	0	0	1 (1.5)
Other	14 (20.8)	0	1 (1.5)	0

Abbreviations: AE, adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; n = number of patients with ≥ 1 event drug-related

mandatorily collected. Among 22 patients with available second-line therapy information, 17 patients received FOLFIRI, 2 patients CisGem, and 3 patients monotherapy (2 patients irinotecan, 1 patient 5-fluorouracil). No patients received oxaliplatin-based regimens, regardless of toxicity, since they received oxaliplatin in the study.

3.3. Efficacy

Median follow-up was 26 months (range 0.3–56). At the data cutoff date (March 1, 2022), 28 patients out of 57 were free from progression or death at 6 months (49.1 % [95 % CI 40.8–57.5 %]). The primary endpoint of the study was not met, requiring 39 out 56 patients free from progression or death at 6 months. Median PFS was 6.3 months (95 % CI 3.6–10.1) (Figure 2), and mOS 12.4 month (95 % CI 8–23) (Figure 3). Estimated PFS rates were 17.7 % at 12 months, and 6.3 % at 24 months. Estimated OS rates were 52 % at 12 months, and 25 % at 24 months. A post-hoc analysis according to primary tumor site showed PFS of 10 months and 5.3 months (p = 0.64) and OS of 20.6 months and 9.5 months (p = 0.18) for patients with eCCA and iCCA, respectively (Table S1).

In the phase I portion, 2 patients had PR (20 %), 6 had SD (60 %), and 2 PD (20 %) as best response. In the phase II portion, 49 out of 57 patients were evaluable for response. Among the 8 patients not

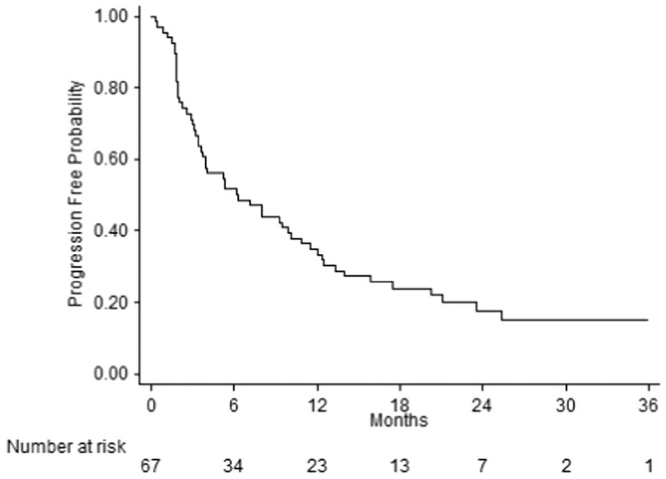

Fig. 2. Kaplan-Meier curve of progression-free survival in the whole study population.

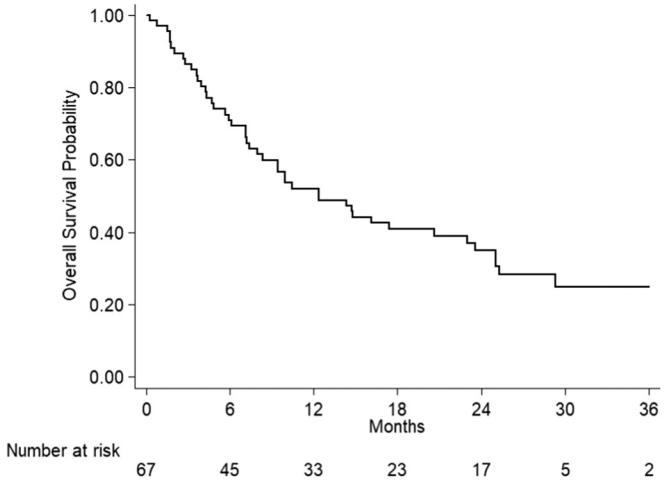

Fig. 3. Kaplan-Meier curve of overall survival in the whole study population.

evaluable for response, 2 died before the first tumor assessment, 2 had clinical disease progression, 2 were lost to follow-up, 1 withdrew the informed consent, and 1 was not evaluated due to investigator's decision. ORR was 20.89 % (14/67 patients), 2 patients achieved CR (2.98 %), 12 patients had PR (17.91 %), 31 patients had SD (46.26 %), and 14 patients had PD as best response (20.89 %) (Table 4). Median duration of response was 16.5 months (range 2.5-not estimable) with 4 patients with ongoing PR at the time of trial closure. A post-hoc analysis of PFS, OS, and ORR for the different phases of the study is reported in Table S2.

Table 4
Best treatment response.

	Phase I n = 10 (%)	Phase II n = 57 (%)	Overall n = 67 (%)
CR	0	2 (3.50)	2 (2.98)
PR	2 (20)	10 (17.54)	12 (17.91)
SD	6 (60)	25 (43.85)	31 (46.26)
PD	2 (20)	12 (21.05)	14 (20.89)
NE	0	8 (14.03)	8 (11.94)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

4. Discussion

Biliary tract cancer is a highly lethal malignancy with an urgent need for more effective treatments.

In molecularly unselected populations, recent studies explored triple chemotherapy regimens reporting mostly negative results, including the phase II-III PRODIGE 38 AMEBICA trial comparing 5-fluorouracil, oxaliplatin, and irinotecan versus CisGem, and the phase III SWOG 1815 trial comparing nab-paclitaxel plus CisGem versus CisGem [20,23].

In these trials CisGem was the standard comparator arm, while the activity of GEMOX had previously been shown in an international phase II study [8]. However, a systematic review of studies evaluating CisGem or GEMOX in advanced BTC showed a longer mOS for CisGem (11.7 vs 9.5 months) although GEMOX was slightly better tolerated and could represent an alternative to CisGem not requiring hyperhydration to prevent nephrotoxicity [9]. Given the absence of randomized trials, it is not conclusive to establish the superiority of either regimen.

With the hypothesis of a more favorable safety profile [8,9], we investigated the combination of GEMOX and nab-paclitaxel in chemotherapy-naïve patients with advanced BTC. The treatment was well-tolerated and we defined the RP2D as the maximum dose level. Among patients treated in the phase II part, AEs were those expected with the 3 drugs used in the combination therapy with no new safety signals. However, the primary endpoint was not met, in line with the negative findings of previously reported trials testing triple chemotherapy combinations in Western populations [20,23]. The only positive phase III trial testing a triple chemotherapy is the Japanese KHBO1401-MITSUBA trial comparing CisGem and S-1 versus CisGem and showing a survival benefit with the triple combination. However, the all Japanese population limits the generalizability of the results [6].

It is intriguing to hypothesize differential efficacy of triple chemotherapy in different patient subgroups. In the SWOG 1815 trial, an exploratory analysis demonstrated a survival benefit in patients with locally advanced disease and with GBC [20]. In the PRODIGE 38 AMEBICA trial, the combination of CisGem showed better outcomes in patients $\geq$ 65 years, male, and with iCCA [23]. Our study was not powered to detect a difference in subgroups of patients. However, a post-hoc analysis showed numerically longer PFS and OS in patients with eCCA compared to those with iCCA. These findings should be interpreted with caution since the difference was not statistically significant, patients with eCCA included in the trial were only 18 (26.89 %), and literature data showed better outcomes in patients with iCCA [24,25]. Regarding baseline characteristics, we observed a predominance of male patients (44 vs 23), which we cannot exclude being associated with a worse prognosis, although published data on response to treatment based on gender are not consistent [26].

The findings from all these studies suggest that a different approach based on the primary tumor site and the disease stage should be considered for future research.

Our study has several limitations as the small sample size, the lack of a control arm, the absence of a centralized imaging review which might have had an impact on the results as the primary endpoint of PFS, and the incomplete data about post-study treatments. Also representing a limitation is the lack of information about molecular profiling, not required in Italy at the time of the study. Therefore, we cannot assess any potential association between molecular alterations and treatment efficacy. The multicenter nature of the trial can be considered a strength given the broader baseline characteristics of the included patients, but also a limitation due to potential differences in local procedures at the participating centers.

5. Conclusion

Although the tested combination showed a good safety profile, our trial did not meet its primary endpoint. Based on available exploratory analyses [20], a triple chemotherapy combination could be considered in clinical trials in the neoadjuvant setting [27] or for locally advanced disease and according to primary tumor site.

Statement of ethics

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study protocol was approved by institutional independent ethics committee at each participating center. All patients provided written informed consent prior to enrollment. This study was reviewed and approved by the Independent Ethic Committee of IRCSS Humanitas Research Hospital, Via Manzoni, 56 Rozzano (Milan), Italy, approval number 106/17, 22nd May 2017.

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CRediT authorship contribution statement

Silvia Noventa: Writing – review & editing, Data curation. **Armando Santoro:** Writing – review & editing, Data curation, Conceptualization. **Silvia Bozzarelli:** Writing – review & editing, Data curation. **Lorenza Rimassa:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Francesca Bergamo:** Writing – review & editing, Data curation. **Mario Domenico Rizzato:** Writing – review & editing, Data curation. **Michele Milella:** Writing – review & editing, Data curation. **Camilla Zecchetto:** Writing – review & editing, Data curation. **Laura Giordano:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Alberto Zaniboni:** Writing – review & editing, Data curation. **Rita Balsano:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Caterina Soldà:** Writing – review & editing, Data curation. **Tiziana Pressiani:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Alessandra Auriemma:** Writing – review & editing, Data curation. **Hector Soto Parra:** Writing – review & editing, Data curation. **Mario Scartozzi:** Writing – review & editing, Data curation. **Daris Ferrari:** Writing – review & editing, Data curation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: TP reports consulting fees from Bayer, Ipsen and AstraZeneca; institutional research funding from Roche, Bayer, Astra Zeneca; travel expenses from Roche. RB reports lecture fees from AstraZeneca; travel expenses from Roche. MM reports Personal Honoraria from AstraZeneca, MSD Oncology, Ipsen, Hippocrates Research, Viatris, Servier; Consulting or Advisory role from AstraZeneca, MSD Oncology, Janssen Oncology; Steering Committee, Data Monitoring Committee from Novartis, OncoSil; Institutional Research Funding from Roche. FB received personal honoraria as invited speaker from Eli-Lilly, MSD, EISAI, Bristol Myers Squibb, AstraZeneca, Pierre Fabre; participation in advisory board for Servier, AAA Novartis. DF reports lecture fees from MSD. HSP reports Advisory board Merck Sharp & Dohme, Bristol Myer Squibb, Pfizer, Roche, Takeda, Astrazeneca, Eli-lilly, Sanofi. CS reports Consulting or advisory role for MSD, Eisai; Speakers' Bureau for Roche, MSD. AZ reports speaker bureau for Merck serono, Amgen, Servier, Sanofi, MSD. LR reports consulting fees from AbbVie, AstraZeneca,

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Data Availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114196.

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