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CANCER THERAPY AND PREVENTION

Fluropyrimidine single agent or doublet chemotherapy as second line treatment in advanced biliary tract cancer

Cindy Neuzillet[1] | Andrea Casadei-Gardini[2] | Bertrand Brieau[3,4] | Caterina Vivaldi[5] | Giovanni Brandi[6] | David Tougeron[7] | Roberto Filippi[8,9] | Angélique Vienot[10] | Nicola Silvestris[11,12] | Anne-Laure Pointet[13] | Sara Lonardi[14] | Benoît Rousseau[15] | Mario Scartozzi[16] | Laetitia Dahan[17] | Giuseppe Aprile[18,19] | Samuel Le Sourd[20] | Ludovic Evesque[21] | Aurélia Meurisse[22,23] | Astrid Lièvre[24]† | Dewi Vernerey[22,23]† | the AGEO (Association des Gastro-Entérologues Oncologues) Investigators | GICO (Italian Group of Cholangiocarcinoma) Investigators

[1]Medical Oncology Department, Curie Institute, and Versailles Saint-Quentin University, Saint-Cloud, France

[2]Department of Oncology and Hematology, Division of Oncology, University of Modena and Reggio Emilia, Modena, Italy

[3]Gastroenterology, Cochin University Hospital, Paris, France

[4]Gastroenterology Unit, Clinique Jules Verne, Nantes, France

[5]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

[6]Oncology, Policlinico S. Orsola-Malpighi, Bologna, Italy

[7]Hepato-Gastroenterology, Poitiers University Hospital, Jean Bernard Hôpital, Poitiers, France

[8]Department of Oncology, University of Turin, Torino, Italy

[9]Centro Oncologico Ematologico Subalpino, Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

[10]Oncology, Besançon University Hospital, Besançon, France

[11]Department of Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy

Abbreviations: 5FU, 5-fluorouracil; 95%CI, 95% confidence interval; aBTC, advanced biliary tract cancer; BTC, biliary tract cancer; CA19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group; FOLFOX, 5FU, folinic acid, and oxaliplatin; GEMCIS, gemcitabine plus cisplatin; GEMOX, gemcitabine plus oxaliplatin; HR, hazard ratio; L1, first-line (treatment); L2, second-line (treatment); OS, overall survival; PFS, progression-free survival; PS, performance status; XELIRI, capecitabine plus irinotecan.

†Co-last authors

AGEO Investigators: Tarek Boussaha, Oncology, Centre Multidisciplinaire d'Oncologie-CePo, Lausanne, Switzerland; Alexandra Heurgué, Hepatology and Digestive Oncology, Reims University Hospital, Reims, France; Jérôme Desramé, Gastroenterology and Hepatology, Jean Mermoz Private Hospital, Lyon, France; Thierry Lecomte, Hepato-Gastroenterology and GI Oncology, Tours University Hospital, Tours, France; Wulfran Cacheux, Medical Oncology, Curie Institute, Saint-Cloud, France; Jean-Baptiste Bachet, Hepato-Gastroenterology and GI Oncology, AP-HP, Pitié-Salpétrière University Hospital, Paris, France; Jean-Marc Phelip, Hepato-Gastroenterology and GI Oncology, Saint Etienne University Hospital, Saint Etienne, France; Vincent Hautefeuille, Hepato-Gastroenterology and GI Oncology, Amiens Picardie University Hospital, Amiens, France; Nassim Hammoudi, Saint Louis University Hospital, AP-HP, Paris, France; Florence Mary, Gastroenterology, Avicenne University Hospital, AP-HP, Bobigny, France; Christophe Locher, Hepato-Gastroenterology, Meaux Hospital, Meaux, France; Anne Bidault-Thirot, Anthony Private Hospital, Anthony, France; Lysiane Marthey, Béclère University Hospital, AP-HP, Clamart, France; Yann Touchefeu, Hepato-Gastroenterology and GI Oncology, Nantes University Hospital, Nantes, France; Valérie Moulin, Hepato-Gastroenterology, La Rochelle Hospital, La Rochelle, France; Aziz Zaanan, Gastroenterology and GI Oncology, George Pompidou European University Hospital, AP-HP, Paris, France; Julien Taïeb, Gastroenterology and GI Oncology, George Pompidou European University Hospital, AP-HP, Paris, France.*GICO Investigators*:Mariaelena Casagrande, Department of Oncology, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy; Sabina Murgioni, Medical Oncology 1 Unit, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padua, Italy; Daniele Santini, Department of Medical Oncology, Università "Campus Bio-Medico di Roma", Rome, Italy; Lorenzo Fornaro, Unit of Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Francesco Montagnani, Department of Oncology, Azienda Sanitaria locale di Biella, Ponderano, Italy; Francesco Leone: Department of Oncology, Azienda Sanitaria Locale di Biella, Ponderano, Italy; Luca Faloppi, Oncology, University Hospital and University of Cagliari, Cagliari, Italy; Elisa Giommoni, Azienda ospedaliero-Universitaria Careggi, Florence, Italy; Stefania Eufemia Lutrino, Department of Medical Oncology, Antonio Perrino Hospital, Brindisi, Italy; Andrea Palloni, Oncology, Policlinico S. Orsola-Malpighi, Bologna, Italy; Oronzo Brunetti, Medical Oncology Unit - IRCCS Istituto Tumori "Giovanni Paolo II" - Bari; Antonella Argentiero, Medical Oncology Unit - IRCCS Istituto Tumori "Giovanni Paolo II" - Bari; Francesca Bergamo, Unit of Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Enrico Vasile, Unit of Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Eleonora Lai, Medical Oncology Unit, University of Cagliari, Cagliari, Italy; Marco Puzzoni, Medical Oncology Unit, University of Cagliari, Cagliari, Italy; Pina Ziranu, Medical Oncology Unit, University of Cagliari, Cagliari, Italy; Vincenzo Dadduzio, Medical Oncology 1 Unit, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padua, Italy; Mario Rizzato, Medical Oncology 1 Unit, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padua, Italy; Antonio Pellino, Medical Oncology 1 Unit, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padua, Italy; Massimo Aglietta, Division of Medical Oncology, Candiolo Cancer Institute, FPO-IRCCS, Candiolo (TO), Italy; Alessandro Cappetta, Department of Oncology, Ospedale San Bortolo, Azienda ULSS8 Berica - Distretto Est, Vicenza, Italy; Silvio Ken Garattini, Department of Medicine (DAME), University of Udine, 33 100 Udine (UD), Italy; Debora Basile, Department of Medicine (DAME), University of Udine, 33 100 Udine (UD), Italy.

[12]Medical Oncology Unit - IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy

[13]Gastroenterology and GI Oncology, George Pompidou European University Hospital, AP-HP, Paris, France

[14]Medical Oncology 1 Unit, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padua, Italy

[15]Medical Oncology, Henri Mondor University Hospital, Créteil, France

[16]Medical Oncology Unit, University of Cagliari, Cagliari, Italy

[17]Pôle "DACCORD" (Digestif, Anatomie pathologique, Chirurgie, CISIH, Oncologie, Radiothérapie, Dermatologie), Service d'Oncologie Digestive, CHU Timone, Marseille, France

[18]Department of Oncology, Ospedale San Bortolo, Azienda ULSS8 Berica - Distretto Est, Vicenza, Italy

[19]Department of Oncology, University Hospital of Udine, Udine, Italy

[20]Gastroenterology and Hepatology, Centre Eugène Marquis, Rennes, France

[21]Medical Oncology, Centre Antoine Lacassagne, Nice, France

[22]Methodology and Quality of Life in Oncology Unit, Besançon University Hospital, Besançon, France

[23]Univ. Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, Interactions Hôte-Greffon-Tumeur/Ingénierie Cellulaire et Génique, Besançon, France

[24]Gastroenterology, Pontchaillou University Hospital, Rennes University, Inserm U1242, Rennes, France

Correspondence
Cindy Neuzillet, Department of Medical Oncology, Curie Institute, Versailles Saint-Quentin University (UVSQ), 35 rue Dailly, 92210 Saint-Cloud, France.
Email: cindy.neuzillet@gmail.com
Dewi Vernerey, Methodology and Quality of Life in Oncology Unit (INSERM UMR1098), Besançon University Hospital, 3 Boulevard Fleming, 25000 Besançon, France.
Email: dvernerey@chu-besancon.fr

Abstract

Fluoropyrimidine (FP) plus platinum chemotherapy has been recently established as a second-line (L2) preferred option in advanced biliary tract cancer (aBTC) (ABC-06 phase III trial). However, the overall survival (OS) benefit was limited and comparison with FP monotherapy was not available. Our aim was to assess the OS of patients treated with a FP monotherapy compared to a doublet with irinotecan or platinum in L2. We performed a retrospective analysis of two large multicenter prospective cohorts: a French cohort (28 centers) and an Italian cohort (9 centers). All consecutive patients with aBTC receiving FP-based L2 after gemcitabine plus cisplatin/gemcitabine plus oxaliplatin L1 between 2003 and 2016 were included. A subgroup analysis according to performance status (PS) and an exploratory analysis according to platinum sensitivity in L1 were planned. In the French cohort (n = 351), no significant OS difference was observed between the FP monotherapy and doublet groups (median OS: 5.6 vs 6.8 months, $P = .65$). Stratification on Eastern Cooperative Oncology Group (ECOG) PS showed similar results in PS 0-1 and 2. Median OS was not different between FP monotherapy, platinum- and irinotecan-based doublets (5.6 vs 7.1 vs 6.7 months, $P = .68$). Similar findings were observed in the Italian cohort (n = 174) and in the sensitivity analysis in pooled cohorts (n = 525). No L2 regimen seemed superior over others in the platinum resistant/refractory or sensitive subgroups. Our results suggest that FP monotherapy is as active as FP doublets in aBTC in L2, regardless of the patient PS and country, and could be a therapeutic option in this setting.

KEYWORDS
cholangiocarcinoma, combination chemotherapy, monotherapy, overall survival, palliative chemotherapy

1 | INTRODUCTION

Biliary tract cancer (BTC) is a rare disease (<6/100 000 cases per year) yet the second leading cause of primary liver cancer after hepatocellular carcinoma.[1] Most patients are diagnosed at an advanced stage (70%), not amenable to curative surgery.[1] Chemotherapy with gemcitabine plus cisplatin (GEMCIS) is the reference first-line therapy (L1) in advanced biliary tract cancer (aBTC), based on the results of the ABC-02 phase III trial.[2]

After failure (progression or toxicity) of L1, about one third of patients are eligible for a second line (L2) chemotherapy.[3] Patients with aBTC in the L2 setting display prognostic heterogeneity.[3-6] In a previous

work including nearly 800 patients from four independent cohorts, we showed that not all patients seemed to benefit from L2 chemotherapy, and that altered Eastern Cooperative Oncology Group (ECOG) performance status (PS) is the strongest risk factor associated with shorter overall survival (OS) in L2.[7] We also identified absence of primary tumor resection, L1 discontinuation for progression, presence of peritoneal carcinomatosis, and high carbohydrate antigen 19-9 (CA19-9) serum level as other independent prognostic biomarkers for OS in this setting.[7]

Second-line therapies for aBTC are as well heterogeneous, with no high-level prospective evidence available until recently.[8,9] In routine clinical practice, most patients receive fluoropyrimidine (FP, ie, intravenous 5-fluorouracil [5FU] or oral capecitabine) in monotherapy or combined with platinum or irinotecan, based on retrospective cohorts or small single-arm phase II studies.[3,5-9] Recently, a randomized phase II study reported improved progression-free survival (PFS) using capecitabine plus irinotecan (XELIRI regimen) L2 over single agent irinotecan (median PFS: 3.7 vs 2.4 months, $P = .036$), with an acceptable safety profile.[10] Moreover, the ABC-06 phase III study, presented at ASCO 2019, showed the superiority of 5FU, folinic acid and oxaliplatin (FOLFOX regimen) over best supportive care in patients with aBTC previously treated with GEMCIS and ECOG PS 0-1 (median OS: 6.2 vs 5.3 months, hazard ratio [HR]: 0.69, $P = .031$), with preliminary results suggesting a more pronounced benefit in platinum-resistant (defined by progression within the first 3 months after the last cycle of GEMCIS L1) or refractory (progression during GEMCIS L1) patients.[11] Based on these results, the National Comprehensive Cancer Network (NCCN) selected FOLFOX as preferred regimen in L2 in aBTC. However, the survival benefit was limited (<1 month) and no prospective data with FP single-agent are available for comparison. Monotherapy may be noninferior to combination chemotherapy in this setting.[12]

In our study, we aimed to assess the OS according to chemotherapy regimen and ECOG PS (strongest prognostic factor in L2) in patients treated with (a) FP monotherapy vs combination, and (b) irinotecan-based vs platinum-based doublets, in two large independent cohorts.

What's new?

Advanced biliary tract carcinoma is usually diagnosed at an advanced stage, and requires first-line chemotherapy. For those patients who go on to second-line chemotherapy, most receive fluoropyrimidine (FP) alone or in combination. Here, the authors compared overall survival between patients given a second-line treatment of FP monotherapy versus those given FP plus either irinotecan or platinum. They stratified patients by therapy regimen and by ECOG performance status, which is considered the best prognostic factor for second-line treatment. They found that overall survival was comparable, whether patients received FP alone or in combination, even after controlling for performance status.

2 | MATERIAL AND METHODS

2.1 | Patients

All consecutive patients with histologically proven aBTC who were treated between January 2003 and January 2016 in 28 centers were included in the French (AGEO CT2BIL) cohort and their data were retrospectively collected. Patients were considered eligible if they (a) were ≥18 years old, (b) had aBTC (metastatic, locally advanced or recurrent after surgery) not amenable to curative treatment, (c) had progressed or were intolerant to L1 with gemcitabine plus platinum (GEMCIS or gemcitabine plus oxaliplatin [GEMOX]) and (d) received a FP-based L2 (single agent or combination with irinotecan or platinum). Patients were excluded if they (a) had been treated with gemcitabine plus platinum doublet in the adjuvant setting, (b) received L1 gemcitabine single-agent or (c) had an ampullary carcinoma.

The Italian (GICO) cohort included consecutive patients with aBTC who received L2 between January 2003 and January 2016 with the same inclusion criteria in nine centers.

The database was registered and declared to the National French Commission for bioinformatics data and patient liberty (CNIL) and approved by the Advisory Committee on Information Processing in the field of health research (CCTIRS) (Declaration number: 14-115). An institutional informed nonopposition form was signed by all patients with cancer at the time of the first visit in the Departments of Medical Oncology. This form allows use their clinical and biological data for the study. No additional specific consent was necessary for our study according to French regulatory procedures.

For the Italian cohort, the study was reviewed and approved by the Area Vasta Emilia Nord Ethics committee for all participating Italian centers (Protocol number 183/2019).

Demographics, cancer history and treatment, pathological, clinical, biological and radiological (tumor response according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 criteria) data were retrospectively collected from medical records. Description of the L2 chemotherapy regimens is provided in Supporting Information Methods. Dose adjustments due to toxicities and patient PS were carried out according to the investigator's choice.

2.2 | Statistical analysis

Median value (interquartile range) and frequency (percentage) were provided for the description of continuous and categorical variables, respectively. Medians and proportions were compared using Student's *t* test and chi-square test (or Fisher's exact test, if appropriate), respectively.

The main aim was to assess the OS according to chemotherapy regimen in patients treated with (a) FP monotherapy vs combination, and (b) irinotecan-based vs platinum-based doublets, in two large independent cohorts, with a French (AGEO CT2BIL) and an Italian (GICO)

TABLE 1 Patient characteristics in the two cohorts

	France (AGEO CT2BIL) (n = 351)	Italy (GICO) (n = 174)	*P* value
Sex[a]			
Male	193 (55.0%)	87 (50.0%)	.28
Age (y), median (IQR)	65.4 (58.2-71.5)	65.5 (57.3-70.4)	.34
Missing	0	1	
Primary tumor site			
Intrahepatic	180 (51.4%)	103 (59.2%)	.12
Extrahepatic/hilar	101 (28.9%)	36 (20.7%)	
Gallbladder	69 (19.7%)	35 (20.1%)	
Missing	1	0	
Prior resection of primary tumor[a,b]			
Yes	90 (25.6%)	51 (29.3%)	.37
Radiotherapy			
Yes	24 (6.9%)	12 (6.9%)	1.00
Missing	3	0	
Biliary drainage			
Yes	119 (34.5%)	42 (24.3%)	**.018**
Missing	6	1	
Type of L1 regimen[a]			
Gemcitabine + oxaliplatin	322 (91.7%)	93 (53.5%)	**<.0001**
Gemcitabine + cisplatin	29 (8.3%)	81 (46.6%)	
Best response to L1			
CR	14 (4.0%)	1 (0.6%)	.055
PR/SD	208 (59.8%)	99 (57.5%)	
PD	126 (36.2%)	72 (41.9%)	
Missing	3	2	
Duration of L1 (mo.), median (IQR)[c]	5.9 (3.2-10.9)	5.9 (3.5-8.8)	.80
Missing	0	2	
Reason for L1 discontinuation			
Toxicity	32 (9.1%)	11 (6.4%)	**.013**
Other	39 (11.1%)	35 (20.5%)	
PD	280 (79.8%)	125 (73.1%)	
Missing	0	3	
PS at the beginning of L2			
0	54 (16.1%)	52 (30.2%)	**.0003**
1	176 (52.4%)	85 (49.4%)	
2	106 (31.5%)	35 (20.4%)	
Missing	15	2	
Disease stage at the beginning of L2			
Metastatic	333 (94.9%)	167 (96.5%)	.39
Locally advanced	18 (5.1%)	6 (3.5%)	
Missing	0	1	
Metastatic sites			
Liver[a]—yes	216 (61.5%)	113 (64.9%)	.48
Lung—yes	102 (29.1%)	52 (30.1%)	.81
Missing	0	1	
Bone—yes	34 (9.7%)	18 (10.5%)	.78
Missing	0	2	
Lymph node—yes	130 (37.0%)	95 (54.9%)	**.0001**
Missing	0	1	
Peritoneum—yes	133 (37.9%)	49 (28.3%)	**.031**
Missing	0	1	
Total bilirubin (μmol/L), median (IQR)	12.0 (7.0-17.0)	10.3 (7.5-16.6)	.73
Missing	91	34	
Albumin (g/L), median (IQR)	34.1 (30.0-38.0)	35.0 (29.0-39.0)	.44
Missing	208	73	
Serum CA19-9 (UI/mL), median (IQR)	169.0 (44.5-1291.0)	150.0 (38.8-973.2)	.74
Missing	135	31	
Type of L2 regimen[a]			
Fluoropyrimidine monotherapy	63 (17.9%)	98 (56.3%)	**<.0001**
Fluoropyrimidine + irinotecan	194 (55.3%)	60 (34.5%)	
Fluoropyrimidine + platinum	94 (26.8%)	16 (9.2%)	
L3 chemotherapy			
Yes	150 (43.5%)	46 (26.4%)	**.0002**
Missing	6	0	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CR, complete response; IQR, interquartile range; L1, first-line treatment; L2, second-line treatment; L3, third-line treatment; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease.

Note: *P* < .05 are in bold.

[a]No missing data.

[b]Prior resection of the primary tumor was defined as surgery with R0/R1 resection and no evidence of disease within 1 month postsurgery.

[c]Duration of L1 was calculated from the date of first administration of L1 to the date of first administration of L2.

cohorts from two different countries, with different patient populations and clinical practices, to validate the external reproducibility of the results. A sensitivity analysis on the overall population combining the two cohorts was also performed to increase the sample size and assess the robustness of the results obtained from each cohort.

OS with L2 was calculated from the date of first administration of L2 to the date of death from any cause. Survival data were censored at the last follow-up. OS with L2 was estimated using the Kaplan-Meier method and described using median or rate at specific time points with 95% confidence intervals (95% CIs). Follow-up duration was calculated using a reverse Kaplan-Meier estimation.[13]

TABLE 2 Patient characteristics in the French (AGEO CT2BIL) cohort according to monotherapy, irinotecan-based or platinum-based combination regimen in second line

	Fluoropyrimidine monotherapy (n = 63)	Fluoropyrimidine + irinotecan (n = 194) or Fluoropyrimidine + platinum (n = 94) (n = 288)	*P* value	Fluoropyrimidine + irinotecan (n = 194)	Fluoropyrimidine + platinum (n = 94)	*P* value
Sex[a]						
Male	36 (57.1%)	157 (54.5%)	.70	101 (52.1%)	56 (59.6%)	.23
Age[a] *(y)*, median (IQR)	66.9 (60.6-71.7)	65.0 (57.9-71.4)	.24	64.7 (58.2-70.4)	66.1 (56.8-72.7)	.69
Primary tumor site						
Intrahepatic	40 (63.5%)	140 (48.8%)	.10	95 (49.0%)	45 (48.4%)	.31
Extrahepatic/ hilar	13 (20.6%)	88 (30.7%)		55 (28.4%)	33 (35.5%)	
Gallbladder	10 (15.9%)	59 (20.6%)		44 (22.7%)	15 (16.1%)	
Missing	0	1		0	1	
Prior resection of primary tumor[a,b]						
Yes	12 (19.1%)	78 (27.1%)	.19	46 (23.7%)	32 (34.0%)	.064
Radiotherapy						
Yes	7 (11.1%)	17 (6.0%)	.17	8 (4.2%)	9 (9.6%)	.071
Missing	0	3		3	0	
Biliary drainage						
Yes	18 (29.0%)	101 (35.7%)	.32	65 (34.4%)	36 (38.3%)	.52
Missing	1	5		5	0	
Type of L1 regimen[a]						
Gemcitabine + oxaliplatin	61 (96.8%)	261 (90.6%)	.11	174 (89.7%)	87 (92.5%)	.43
Gemcitabine + cisplatin	2 (3.2%)	27 (9.4%)		20 (10.3%)	7 (7.5%)	
Best response to L1						
CR	2 (3.2%)	12 (4.2%)	.63	8 (4.1%)	4 (4.3%)	.051
PR/SD	41 (65.1%)	167 (58.6%)		104 (53.9%)	63 (68.5%)	
PD	20 (31.7%)	106 (37.2%)		81 (42.0%)	25 (27.2%)	
Missing	0	3		1	2	
Duration of L1 (mo.)[a,c]	6.9 (3.5-11.5)	5.5 (3.2-10.7)	.34	5.3 (3.2-10.8)	6.5 (3.2-10.0)	.58
Reason for L1 discontinuation[a]						
Toxicity	7 (11.1%)	25 (8.7%)	.73	11 (5.7%)	14 (14.9%)	**.0009**
Other	8 (12.7%)	31 (10.8%)		15 (7.7%)	16 (17.0%)	
PD	48 (76.2%)	232 (80.6%)		168 (86.6%)	64 (68.1%)	
PS at the beginning of L2						
0	9 (14.8%)	45 (16.4%)	**.010**	25 (13.1%)	20 (23.8%)	.077
1	23 (37.7%)	153(55.6%)		112 (58.6%)	41 (48.8%)	
2	29 (47.5%)	77 (28.0%)		54 (28.3%)	23 (27.4%)	
Missing	2	13		3	10	
Disease stage at the beginning of L2[a]						
Metastatic	60 (95.2%)	273 (94.8%)	1.00	188 (96.9%)	85 (90.4%)	**.043**
Locally advanced	3 (4.8%)	15 (5.2%)		6 (3.1%)	9 (9.6%)	
Metastatic sites						
Liver[a]—yes	44 (69.8%)	172 (59.7%)	.13	116 (59.8%)	56 (59.6%)	1.00
Lung[a]—yes	22 (34.9%)	80 (27.8%)	.26	54 (27.8%)	26 (27.7%)	.98
Bone[a]—yes	8 (12.7%)	26 (9.0%)	.37	23 (11.9%)	3 (3.2%)	**.016**

(Continues)

TABLE 2 (Continued)

	Fluoropyrimidine monotherapy (n = 63)	Fluoropyrimidine + irinotecan (n = 194) or Fluoropyrimidine + platinum (n = 94) (n = 288)	*P* value	Fluoropyrimidine + irinotecan (n = 194)	Fluoropyrimidine + platinum (n = 94)	*P* value
Lymph node[a]—yes	20 (31.7%)	110 (38.2%)	.34	84 (43.3%)	26 (27.7%)	**.010**
Peritoneum[a]—yes	24 (38.1%)	109 (37.8%)	.97	76 (39.2%)	33 (35.1%)	.50
Total bilirubin (μmol/L), median (IQR)	15.0 (9.5-17.0)	11.0 (6.0-17.0)	**.028**	11.0 (6.0-17.0)	12.0 (6.9-17.0)	.20
Missing	19	72		50	22	
Albumin (g/L), median (IQR)	34.2 (30.2-37.0)	34.1 (30.0-38.4)	.53	34.9 (30.0-38.0)	32.6 (29.7-39.5)	.99
Missing	37	171		115	56	
Serum CA19-9 (UI/mL), median (IQR)	319.5 (52.9-5580)	141.5 (38.0-987.5)	**.035**	141.5 (36.0-963.0)	135.3 (51.0-1406.0)	.48
Missing	27	108		72	36	
L3 chemotherapy						
Yes	20 (32.8%)	130 (45.8%)	.063	81 (42.2%)	49 (53.3%)	.098
Missing	2	4		2	2	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CR, complete response; IQR, interquartile range; L1, first-line treatment; L2, second-line treatment; L3, third-line treatment; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease.
Note: $P < .05$ are in bold.
[a]No missing data.
[b]Prior resection of the primary tumor was defined as surgery with R0/R1 resection and no evidence of disease within 1 month postsurgery.
[c]Duration of L1 was calculated from the date of first administration of L1 to the date of first administration of L2.

Due to the high prognostic weight of ECOG PS, we preplanned to perform subgroup analyses according to ECOG PS (0-1 vs 2).[7]

Following the results of the ABC-06 trial, we also considered an exploratory analysis according to platinum sensitivity.[11] Platinum status was determined from L1 GEMCIS/GEMOX, according to the definition used in the ABC-06 trial[11]: sensitive (progression after 3 months of the last administration of platinum), refractory (progression under platinum chemotherapy) and resistant (progression within the first 3 months after completion the last administration of platinum).

Finally, post hoc power calculations to detect a minimal clinically meaningful difference in OS with doublet vs monotherapy, defined as HR ≤ 0.70 (grade 2) or HR ≤ 0.65 (grade 3) based on ESMO magnitude of benefit scale v1.1,[14] were performed in each cohort.

All analyses were performed using SAS version 9.4 and R software version 2.15.2. *P* values of less than .05 were considered statistically significant, and all tests were two-sided.

3 | RESULTS

3.1 | Population-based prospective cohorts

The French (AGEO CT2BIL) cohort included 351 patients treated in L1 with GEMOX (92%) or GEMCIS (8%) and in L2 with a FP alone or combined with platinum or irinotecan in 28 centers (Table 1). With a median follow-up since the beginning of L2 chemotherapy of 34.0 months (95% CI = 28.9-51.4), 299 (85.2%) patients had died.

The Italian (GICO) cohort included 174 patients with the same inclusion criteria treated in nine centers. The two cohorts displayed statistically significant differences in terms of (a) biliary drainage, (b) type of L1 regimen, (c) reason for L1 discontinuation, (d) ECOG PS at the beginning of L2, (e) lymph node and (f) peritoneal metastases, (g) type of L2 regimen and (h) third-line (L3) administration (Table 1).

3.2 | Fluoropyrimidine monotherapy vs doublet in the French (AGEO CT2BIL) cohort

In the French cohort, patients receiving L2 with FP monotherapy had more often ECOG PS 2 compared to patients receiving a doublet chemotherapy (47.5% vs 28.0%, $P = .010$) and displayed higher bilirubin and CA19-9 levels (albeit with a high rate of missing data for these two biological variables) ($P = .028$ and $P = .035$, respectively) (Table 2). Patient characteristics in the two groups were otherwise similar (Table 2).

No significant OS difference was observed between the two groups (doublet vs monotherapy) in the overall cohort (median OS: 6.8 vs 5.6 months, HR: 0.936, 95% CI: 0.701-1.250, $P = .65$) (Figure 1A). Subgroup analyses according to ECOG PS showed similar results in patients with ECOG PS 0-1 (median OS: 7.8 vs 8.4 months, HR: 1.127, 95% CI: 0.750-1.694, $P = .57$) (Figure 1B) and ECOG PS 2

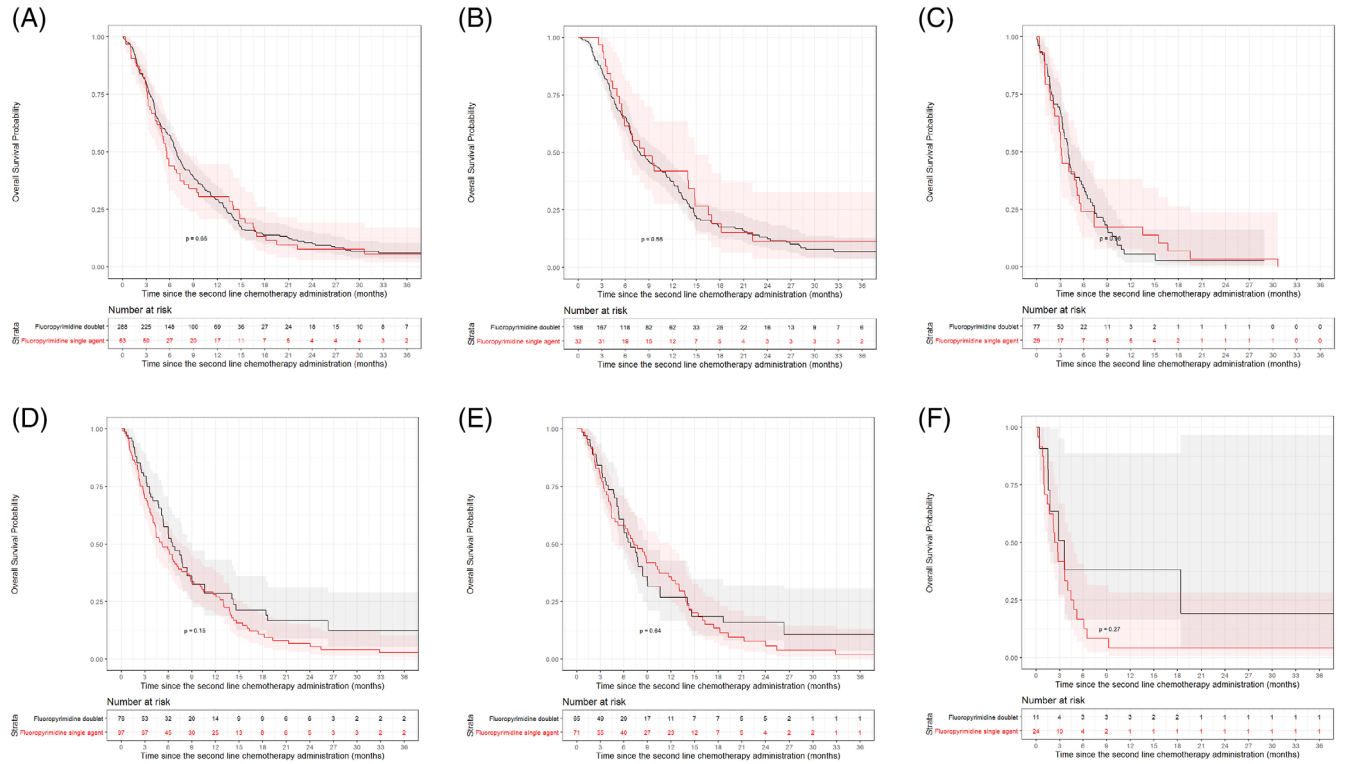

FIGURE 1 Kaplan-Meier curves of the overall survival estimation for patients treated with a combination or a monotherapy as second line treatment. *French (AGEO CT2BIL) cohort*: overall population (hazard ratio [HR]: 0.936, 95% CI: 0.701-1.250, *P* = .6532) (A), subgroup of patients with ECOG PS 0-1 (HR: 1.127, 95% CI: 0.750-1.694, *P* = .5654) (B) and 2 (HR: 1.005, 95% CI: 0.637-1.586, *P* = .9816) (C). *Italian (GICO) cohort*: overall population (HR: 0.782, 95% CI: 0.556-1.100, *P* = .1572) (D), subgroup of patients with ECOG PS 0-1 (HR: 0.915, 95% CI: 0.623-1.344, *P* = .6521) (E) and 2 (HR: 0.631, 95% CI: 0.278-1.435, *P* = .2723) (F) [Color figure can be viewed at wileyonlinelibrary.com]

(median OS: 4.0 vs 3.2 months, HR: 1.005, 95% CI: 0.637-1.586, *P* = .98) (Figure 1C). There was no difference according to the localization of the primary tumor between FP monotherapy or doublet, in intrahepatic cholangiocarcinoma (*P* = .49), in extrahepatic cholangiocarcinoma (*P* = .94) and in gallbladder cancer (*P* = .82).

3.3 | Fluoropyrimidine monotherapy vs doublet in the Italian (GICO) cohort

Similar results were obtained in the Italian cohort: no significant OS difference between FP doublet vs monotherapy (HR: 0.782, 95% CI: 0.556-1.10, *P* = .16) (Table 3 and Figure 1D). No benefit of doublet chemotherapy vs monotherapy was observed across the ECOG PS subgroups (Figure 1E,F).

3.4 | Monotherapy vs platinum-based vs irinotecan-based doublet in the French (AGEO CT2BIL) cohort

Patients receiving platinum-based chemotherapy (n = 94, 26.8%; which consisted in a platinum switch in most patients: oxaliplatin to cisplatin/carboplatin or cisplatin to oxaliplatin) were less likely to have stopped L1 for disease progression than those receiving irinotecan-based chemotherapy (68.1% vs 86.6%, *P* = .0009) (Table 2). In addition, patients in the FP plus platinum doublet group had more often locally advanced tumors (9.6% vs 3.1%, *P* = .043), and less frequent lymph node and bone metastases (*P* = .010 and *P* = .016, respectively) (Table 2). ECOG PS distribution was not different between these two groups (*P* = .077).

No significant OS difference was observed between the three groups (median OS: 5.6 vs 7.1 vs 6.7 months in FP monotherapy, vs FP plus platinum vs FP plus irinotecan doublet, respectively, HR: 0.879, 95% CI: 0.629-1.227 for platinum doublet vs monotherapy and HR: 0.972, 95% CI: 0.717-1.319 for irinotecan doublet vs monotherapy, *P* = .68) (Figure 2A). Stratification on ECOG PS showed similar results in PS 0-1 (median OS: 8.4 vs 11.1 vs 7.5 months, HR: 1.007, 95% CI: 0.636-1.595 for platinum doublet vs monotherapy vs and HR: 1.202, 95% CI: 0.788-1.835 for irinotecan doublet vs monotherapy, *P* = .47) (Figure 2B) and 2 (median OS: 3.2 vs 4.1 vs 4.0 months, HR: 1.089, 95% CI: 0.615-1.928 for platinum doublet vs monotherapy and HR: 0.969, 95% CI: 0.596-1.576 for irinotecan doublet vs monotherapy, *P* = .90) subgroups (Figure 2C).

3.5 | Platinum-based and irinotecan-based doublet in the Italian (GICO) cohort

Similar results were obtained in the Italian cohort: no significant OS difference between FP monotherapy vs FP plus platinum vs FP plus irinotecan

TABLE 3 Patient characteristics in the Italian (GICO) cohort according to monotherapy, irinotecan-based or platinum-based combination regimen in second line

	Fluoropyrimidine monotherapy (n = 98)	Fluoropyrimidine + irinotecan (n = 60) or Fluoropyrimidine + platinum (n = 16) (n = 76)	*P* value	Fluoropyrimidine + irinotecan (n = 60)	Fluoropyrimidine + platinum (n = 16)	*P* value
Sex[a]						
Male	41 (41.8%)	46 (60.5%)	**.015**	35 (58.3%)	11 (68.8%)	.45
Age (y), median (IQR)	66.2 (59.5-71.8)	63.3 (55.3-69.2)	**.029**	62.5 (54.9-69.4)	63.6 (58.3-68.8)	.82
Missing	1	0		0	0	
Primary tumor site[a]						
Intrahepatic	62 (63.3%)	41 (54.0%)	.43	35 (58.3%)	6 (37.5%)	.27
Extrahepatic/ hilar	19 (19.4%)	17 (22.3%)		13 (21.7%)	4 (25.0%)	
Gallbladder	17 (17.4%)	18 (23.7%)		12 (20.0%)	6 (37.5%)	
Prior resection of primary tumor[a,b]						
Yes	32 (32.7%)	19 (25.0%)	.27	14 (23.3%)	5 (31.3%)	.53
Radiotherapy[a]						
Yes	7 (7.1%)	5 (6.6%)	.88	4 (6.7%)	1 (6.3%)	1.00
Biliary drainage						
Yes	23 (23.7%)	19 (25.0%)	.84	14 (23.3%)	5 (31.3%)	.53
Missing	1	0		0	0	
Type of L1 regimen[a]						
Gemcitabine + oxaliplatin	63 (64.3%)	30 (39.5%)	**.0011**	26 (43.3%)	4 (25.0%)	.25
Gemcitabine + cisplatin	35 (35.7%)	46 (60.5%)		34 (56.7%)	12 (75.0%)	
Best response to L1						
CR	0 (0%)	1 (1.3%)	.69	1 (1.7%)	0 (0%)	1.00
PR/SD	56 (58.3%)	43 (56.6%)		34 (56.7%)	9 (56.3%)	
PD	40 (41.7%)	32 (42.1%)		25 (41.7%)	7 (43.8%)	
Missing	2	0		0	0	
Duration of L1 (mo.)[c]	5.7 (3.5-8.7)	5.9 (3.4-8.8)	.92	5.9 (3.6-9.4)	6.3 (3.3-8.6)	.69
Missing	1	1		1	0	
Reason for L1 discontinuation						
Toxicity	4 (4.2%)	7 (9.3%)	.13	4 (6.8%)	3 (18.8%)	**.019**
Other	24 (25%)	11 (14.7%)		6 (10.2%)	5 (31.2%)	
PD	68 (70.8%)	57(76.0%)		49 (83.1%)	8 (50.0%)	
Missing	2	1		1	0	
PS at the beginning of L2						
0	28 (29.2%)	24 (31.6%)	.23	18 (30.0%)	6 (37.5%)	.63
1	44 (45.8%)	41 (53.9%)		32 (53.3%)	9 (56.3%)	
2	24 (25.0%)	11 (14.4%)		10 (16.7%)	1 (6.3%)	
Missing	2	0		0	0	
Disease stage at the beginning of L2						
Metastatic	92 (94.9%)	75 (98.7%)	.23	60 (100%)	15 (93.8%)	.21
Locally advanced	5 (5.1%) 1	1 (1.3%) 0		0 (0%) 0	1 (6.2%) 0	

TABLE 3 (Continued)

	Fluoropyrimidine monotherapy (n = 98)	Fluoropyrimidine + irinotecan (n = 60) or Fluoropyrimidine + platinum (n = 16) (n = 76)	*P* value	Fluoropyrimidine + irinotecan (n = 60)	Fluoropyrimidine + platinum (n = 16)	*P* value
Metastatic sites						
Liver[a]—yes	62 (63.3%)	51 (67.1%)	.60	41 (68.3%)	10 (62.5%)	.77
Lung—yes	29 (29.9%)	23 (30.3%)	.96	19 (31.7%)	4 (25.0%)	.76
Missing	1	0		0	0	
Bone—yes	11 (11.3%)	7 (9.3%)	.67	5 (8.3%)	2 (13.3%)	.62
Missing	1	1		0	1	
Lymph node—yes	52 (53.6%)	43 (56.6%)	.70	33 (55.0%)	10 (62.5%)	.78
Missing	1	0		0	0	
Peritoneum—yes	25 (25.8%)	24 (31.6%)	.40	18 (30.0%)	6 (37.5%)	.57
Missing	1	0		0	0	
Total bilirubin (μmol/L), median (IQR)	10.3 (7.4-15.9)	10.3 (7.5-17.2)	.87	9.8 (7.2-17.1)	11.1 (8.4-19.3)	.50
Missing	22	12		10	2	
Albumin (g/L), median (IQR)	35.0 (29.0-38.0)	35.5 (29.0-40.0)	.70	35.5 (26.0-39.5)	35.0 (32.0-43.0)	.40
Missing	39	34		28	6	
Serum CA19-9 (UI/mL), median (IQR)	95.5 (30.1-614.0)	292 (64.45-1624.5)	**.028**	156.2 (48.7-1272.0)	848.0 (133.7-2430)	.11
Missing	23	8		6	2	
L3 chemotherapy						
Yes	28 (28.6%)	18 (23.7%)	.47	14 (30.4%)	4 (25.0%)	1.00
Missing	0	0		0	2	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CR, complete response; IQR, interquartile range; L1, first-line treatment; L2, second-line treatment; L3, third-line treatment; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease.
Note: $P < .05$ are in bold.
[a]No missing data.
[b]Prior resection of the primary tumor was defined as surgery with R0/R1 resection and no evidence of disease within 1 month postsurgery.
[c]Duration of L1 was calculated from the date of first administration of L1 to the date of first administration of L2.

doublets (median OS: 5.2 vs 6.0 vs 7.5 months in FP monotherapy, vs FP plus platinum vs FP plus irinotecan doublet, HR: 1.140, 95% CI: 0.634-2.053 for platinum doublet vs monotherapy and HR: 0.709, 95% CI: 0.487-1.031 for irinotecan doublet vs monotherapy, $P = .14$) (Table 3 and Figure 2D). As reported in the French cohort, patients receiving platinum-based doublet (n = 16, 9.2%) were more likely to have stopped L1 owing to toxicity or other reason rather than disease progression ($P = .019$). In contrast, there was no significant imbalance in ECOG PS distribution between monotherapy and doublet regimens in the Italian cohort ($P = .23$). No OS difference was observed across the ECOG PS subgroups (Figure 2E,F).

3.6 | Sensitivity analysis in the pooled cohorts

In order to increase the sample size and study power, we performed a sensitivity analysis on the overall population combining the two cohorts (n = 524 patients evaluable for OS). Our results were validated in this pooled cohort, with no significant OS difference between FP doublet chemotherapy vs monotherapy (median OS: 6.8 vs 5.6 months, HR: 0.879, 95% CI: 0.721-1.072, $P = .20$ in the overall population and median OS: 7.5 vs 7.8 months, HR: 0.950, 95% CI: 0.742-1.215, $P = .68$ in the ECOG PS 0-1 subgroup, respectively), and between monotherapy vs FP plus platinum vs FP plus irinotecan doublets (median OS: 5.6 vs 6.8 vs 6.7 months, HR: 0.875, 95% CI: 0.679-1.128 for platinum doublet vs monotherapy vs and HR: 0.881, 95% CI: 0.710-1.092 for irinotecan doublet vs monotherapy, $P = .44$ in the overall population and median OS: 7.8 vs 8.4 vs 7.5 months, HR: 0.909, 95% CI: 0.664-1.245 for platinum doublet vs monotherapy vs and HR: 0.971, 95% CI: 0.746-1.264 for monotherapy vs irinotecan doublet, $P = .83$ in the ECOG PS 0-1 subgroup) (Table S1 and Figure S1).

3.7 | Exploratory analysis according to platinum sensitivity

We further analyzed patient OS with FP monotherapy, platinum or irinotecan doublet L2 based on their platinum sensitivity (sensitive vs

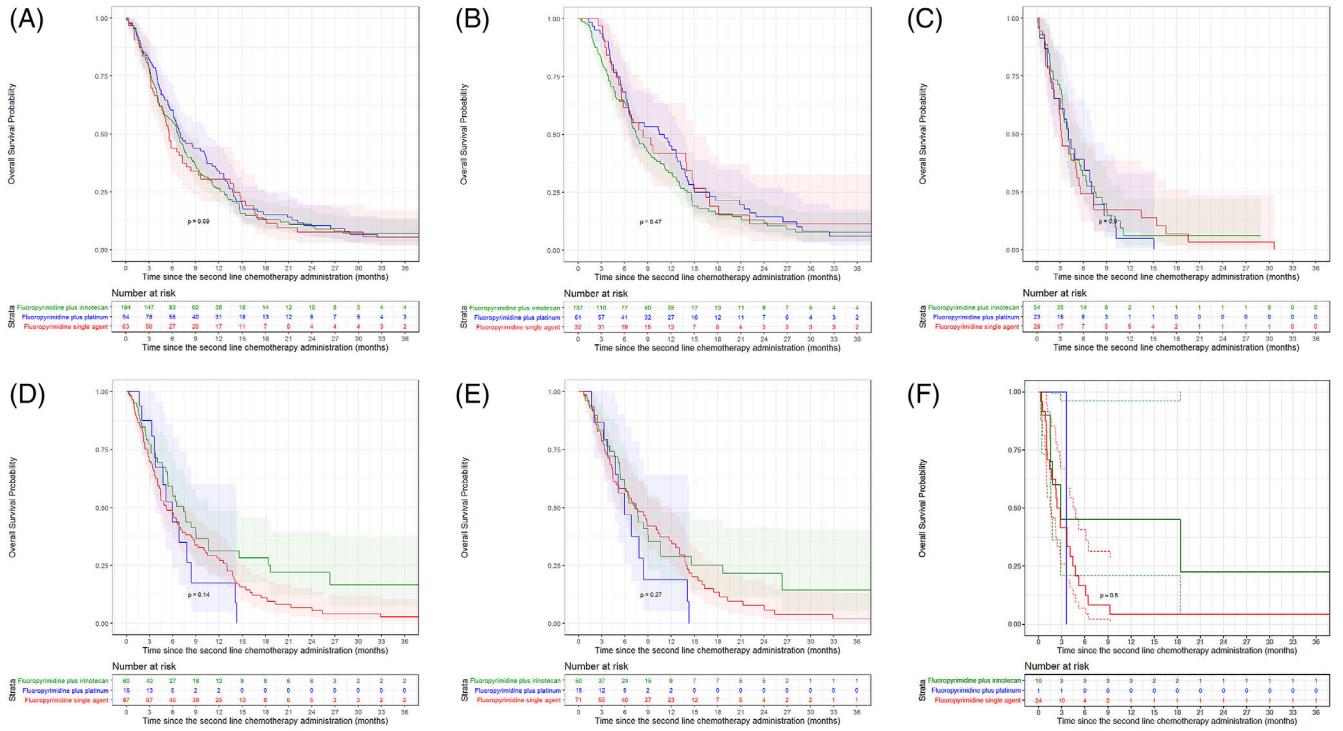

FIGURE 2 Kaplan-Meier curves of the overall survival estimation for patients treated with a monotherapy or a combination with irinotecan or platinum second-line treatment. *French (AGEO CT2BIL) cohort*: overall population (hazard ratio [HR]: 0.879, 95% CI: 0.629-1.227 for platinum doublet vs monotherapy and HR: 0.972, 95% CI: 0.717-1.319 for irinotecan doublet vs monotherapy, *P* = .6846) (A), subgroup of patients with PS 0-1 (HR: 1.007, 95% CI: 0.636-1.595 for platinum doublet vs monotherapy and HR: 1.202, 95% CI: 0.788-1.835 for irinotecan doublet vs monotherapy, *P* = .4730) (B) and 2 (HR: 1.089, 95% CI: 0.615-1.928 for platinum doublet vs monotherapy and HR: 0.969, 95% CI: 0.596-1.576 for irinotecan doublet vs monotherapy, *P* = .9048) (C). *Italian (GICO) cohort*: overall population (HR: 1.140, 95% CI: 0.634-2.053 for platinum doublet vs monotherapy and HR: 0.709, 95% CI: 0.487-1.031 for irinotecan doublet vs monotherapy, *P* = .1439) (D), subgroup of patients with ECOG PS 0-1 (HR: 1.396, 95% CI: 0.747-2.610 for platinum doublet vs monotherapy and HR: 0.814, 95% CI: 0.533-1.242 for irinotecan doublet vs monotherapy, *P* = .2737) (E) and 2 (HR: 1.021, 95% CI: 0.135-7.711 for platinum doublet vs monotherapy and HR: 0.596, 95% CI: 0.250-1.418 for irinotecan doublet vs monotherapy, *P* = .5005) (F) [Color figure can be viewed at wileyonlinelibrary.com]

resistant/refractory) in L1 (Tables S2A and S2B).[11] In the French cohort, no significant OS difference was found between the different L2 regimens in the platinum resistant/refractory subgroup (median OS: 5.3, 6.5 and 6.1 months, with FP monotherapy, FP plus platinum and FP plus irinotecan, respectively, *P* = .63) (Figure S2A) and a non-significant OS trend in favor of FP plus irinotecan was observed in the platinum sensitive subgroup (median OS: 5.6, 5.4 and 9.9 months, *P* = .16; FP plus irinotecan vs FP plus platinum: HR: 0.602, 95% CI: 0.356-1.017, *P* = .058) (Figure S2B). Of note, patients who received FP plus irinotecan doublet in this subgroup had more often ECOG PS 0-1 (82.9% vs 53.9% in the FP plus platinum doublet, *P* = .031), and the OS trend in favor of FP plus irinotecan disappeared when we considered only patients with PS 0-1 (HR: 0.924, 95% CI: 0.465-1.834, *P* = .82), showing that it was driven by the imbalance in ECOG PS distribution. This favorable survival trend with irinotecan-based doublet was not observed in the Italian cohort, where there was no OS difference between the regimens according to platinum sensitivity (Tables S3A and S3B and Figure S2C,D). Similar results were obtained in the sensitivity analysis on pooled cohorts (FP plus irinotecan vs FP plus platinum: in platinum sensitive patients, HR: 0.589, 95% CI: 0.365-0.951, *P* = .031 and HR: 0.866, 95% CI: 0.475-1.579, *P* = .64 in overall population and ECOG PS 0-1, respectively; in platinum resistant patients, HR: 0.993, 95% CI: 0.721-1.367, *P* = .96 and HR: 0.839, 95% CI: 0.574-1.227, *P* = .37 in overall population and ECOG PS 0-1, respectively).

3.8 | Post hoc power calculations

Post hoc power calculations to detect a significant association between treatment (doublet vs monotherapy) and OS based on ESMO magnitude of benefit scale v1.1[14] were provided in Table S4.

4 | DISCUSSION

Beyond failure of L1, up to 30% to 40% of aBTC patients remain in a good clinical condition and are able to receive subsequent line(s) of therapy.[10] Until 2019, there was no recommended regimen in this setting and the type of chemotherapy regimen varied according to the center/national clinical practices.[2,3] Following the presentation of the results of the ABC-06 phase III trial, FOLFOX chemotherapy has

become the preferred option in patients previously treated with GEMCIS, albeit with a modest OS benefit.[11] These results are not applicable to patients treated with GEMOX in L1 and FOLFOX has not been compared to any other chemotherapy regimen in L2. Overall, there is insufficient evidence to recommend specific regimens for L2 in aBTC patients, and prospective randomized trials are needed.

In our study, we demonstrated, using two large independent cohorts gathering a total of 525 patients, that there was no OS difference between FP monotherapy and doublets, even after stratification on patient ECOG PS, which is a major prognostic indicator.[7] We analyzed first each cohort (France and Italy) separately to validate the external reproducibility of our results. Even though the data were retrospectively collected, our study population is well annotated, with a low rate of missing data, and the results were reproduced in both cohorts despite differences in several factors including type of L1 regimen, reason for L1 discontinuation, ECOG PS at the beginning of L2, type of L2 regimen and L3 administration, thereby highlighting their robustness. Moreover, the overall population (pooled cohorts) is the largest cohort available in aBTC in the L2 setting. The power to detect a HR ≤ 0.70 in each cohort separately was limited but the complementary analysis on the overall population (n = 524 patients evaluable for OS) allowed us to rule out a clinically meaningful difference in OS between FP monotherapy or doublets with a high statistical power of 93%, and had a sufficient power (≥80%) to detect a difference of 1.9 months in median OS.

Although evidence of activity of capecitabine is available in BTC in the adjuvant setting (BILCAP phase III study[15]), data regarding FP monotherapy in aBTC, and particularly in L2, are limited. Only one small randomized phase II trial evaluated capecitabine alone or combined with mitomycine C in 57 patients with aBTC: the results were disappointing with a 6-month PFS rate of 8% with capecitabine and 10% with capecitabine plus mitomycine C.[16] In Asian countries, three single-arm phase II trials with S-1 monotherapy after progression on L1 chemotherapy suggested that this compound was safe and moderately efficacious in L2.[17-19] Retrospective cohorts and meta-analyses reported conflicting results about the efficacy of FP doublets vs monotherapy.[3,5-9,12] Single-agent FP are expected to be less toxic and our results suggest that they may be as effective as doublets in L2, thereby representing a potentially interesting option in this setting where health related quality of life is a central issue. In particular, in the subset of patients with ECOG PS 0-1, median OS with FP monotherapy reached 8.4 and 7.3 months in the French and Italian cohorts, respectively, which compared favorably with the OS of patients treated with FOLFOX in the ABC-06 study. This trial lacked a FP monotherapy arm for proper comparison. The ongoing NALIRICC randomized Phase II trial (NCT03043547) is evaluating 5FU plus NalIRI combination vs 5FU in patients with aBTC in L2, and will provide prospective data to answer to this question.

In addition, the question of the best chemotherapy regimen in L2 according to response to L1 remains unanswered and has been recently put under the spotlight following preliminary subgroup analyses from the ABC-06 trial, which showed that patients with platinum resistant/refractory disease (62.3%) seemed to benefit the most from FOLFOX L2 (HR [95% CI]: 0.63 [0.41-0.96] vs 0.81 [0.47-1.4] in the platinum sensitive group).[11] In our study, no association was observed between platinum sensitivity and OS with the different regimens (FP monotherapy, FP plus platinum doublet or FP plus irinotecan doublet), and the nonsignificant trend in favor of irinotecan in platinum sensitive patients was explained by an imbalance in patient ECOG PS. However, patients receiving platinum-based chemotherapy represented a small subgroup of patients (26.8% in the French cohort and 9.2% in the Italian cohort), were more likely to have stopped L1 for reasons other than disease progression and had more often altered ECOG PS in the French cohort. Therefore, our results are limited by small sample size and potential confounding bias, and additional prospective studies are warranted to draw definitive conclusions.

In summary, we previously showed that all patients with aBTC do not benefit from L2 administration and that the CT2BIL score (mainly driven by ECOG PS) may be useful in this setting.[7] In this article, our results suggest that FP monotherapy is as active as FP doublets in aBTC in L2, regardless of the patient PS and platinum sensitivity status, and could be a therapeutic option in this setting. This would warrant further prospective evaluation in randomized controlled trials.

In the next future, the management of patients with aBTC may change with the advent of active targeted therapies in specific molecular subsets (fibroblast growth factor receptor 2 [*FGFR2*], isocitrate dehydrogenase 1 [*IDH1*], and neurotrophic tyrosine receptor kinase [*NTRK*] gene alterations and microsatellite instability [MSI]); positive results from Phase II and III trials have been recently presented, which were not available at the time our study was performed.[20-24] Therefore, in patients with aBTC who are fit for L2 (CT2BIL score/ECOG PS) after progression under gemcitabine/platinum L1, performing a molecular profiling of the tumor may allow patient access to personalized targeted therapy beside classical chemotherapy, opening new therapeutic opportunities to improve patient's survival and quality of life.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Design of the work: Cindy Neuzillet, Astrid Lièvre, Dewi Vernerey; *Acquisition of data*: Cindy Neuzillet, Andrea Casadei-Gardini, Bertrand Brieau, Caterina Vivaldi, Giovanni Brandi, David Tougeron, Roberto Filippi, Angélique Vienot, Nicola Silvestris, Anne-Laure Pointet, Sara Lonardi, Benoît Rousseau, Mario Scartozzi, Laetitia Dahan, Giuseppe Aprile, Samuel Le Sourd, Ludovic Evesque, Astrid Lièvre; *Data management*: Cindy Neuzillet, Aurélia Meurisse; *Analysis/interpretation of data*: Cindy Neuzillet, Astrid Lièvre, Dewi Vernerey; *Manuscript writing*: Cindy Neuzillet, Astrid Lièvre, Dewi Vernerey; *Manuscript revision and approval*: all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The database was registered and declared to the National French Commission for bioinformatics data and patient liberty (CNIL) and approved by the Advisory Committee on Information Processing in the field of health research (CCTIRS) (Declaration number: 14-115). An institutional informed nonopposition form was signed by all patients with cancer at the time of the first visit in the Departments of Medical Oncology. This form allows use their clinical and biological data for the study. No additional specific consent was necessary for this study according to French regulatory procedures. For the Italian cohort, the study was reviewed and approved by the Area Vasta Emilia Nord Ethics committee for all participating Italian centers (Protocol number 183/2019).

ORCID

Cindy Neuzillet https://orcid.org/0000-0001-7037-7477
Caterina Vivaldi https://orcid.org/0000-0001-9307-2326
David Tougeron https://orcid.org/0000-0002-8065-9635
Benoît Rousseau https://orcid.org/0000-0003-3556-5178
Astrid Lièvre https://orcid.org/0000-0003-2118-717X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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