ROLE OF CHEMOTHERAPY IN BILIARY CANCER

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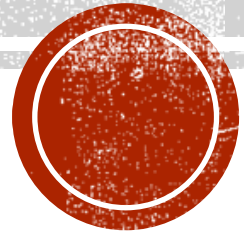
10 of Feb 2023



DISCLOSURES

- AstraZeneca
- Merk
- Jassen
- Amgen
- Serivo
- IPSEN
- MSD
- Lilly
- Bayer
- NewBridege

OBJECTIVES

- First line therapy for biliary cancer:
  - ABC-02 **(update)** / Japanese BT22 study Trial
  - TOPAZ-01 Trial
  - KEYNOTE 966 Trial
  - Pemigatinib vs. GemCis (FIGHT-302)
  - Infigratinib vs. GemCis (PROOF 301 trial)
  - Futibatinib vs. GemCis (FOENIX-CCA3)
  - GemCis + nab-paclitaxel vs. GemCis (SWOG/S1815)
  - FBI Trial
- Second line therapy biliary cancer:
  - ABC-06 Trial
  - NIFTY Trial √ but NALIRICC-AIO X
  - FIGHT-202 Trial
  - STARTRK-1 and STARTRK-2
  - KEYNOTE-028 , KEYNOTE-158
  - Surufatinib vs. Cape
  - TQB2450 + Anlotinib vs. Cape + Oxaliplatin or Cape + GEM
- Approach for biliary cancer management

FIRST LINE THERAPY(ABC-02);

- This randomized, controlled, phase III trial at 37 centers in UK.
-
- Recruit recurrent, or metastatic biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma)
- 410 patients randomized with (1:1) to :

  Cisplatin + Gemcitabine

  Gemcitabine alone for up to 24 weeks
- Primary outcome: OS

Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81. doi: 10.1056/NEJMoa0908721. PMID: 20375404.

FIRST LINE THERAPY(ABC-02);

Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.*

Variable	Gemcitabine (N = 206)	Cisplatin plus Gemcitabine (N = 204)	P Value
Age — yr			
Median	63.2	63.9	0.88
Range	23.4–84.8	32.8–81.9	
Sex — no. (%)			
Female	108 (52.4)	108 (52.9)	0.92
Male	98 (47.6)	96 (47.1)	
Extent of disease — no. (%)			
Locally advanced	49 (23.8)	55 (27.0)	0.46
Metastatic	157 (76.2)	149 (73.0)	
Primary tumor site — no. (%)			
Gallbladder	76 (36.9)	73 (35.8)	0.87
Bile duct	119 (57.8)	122 (59.8)	
Ampulla	11 (5.3)	9 (4.4)	
Type of tumor — no. (%)			
Adenocarcinoma	191 (92.7)	186 (91.2)	0.27
Carcinoma, type not specified	12 (5.8)	17 (8.3)	
Adenosquamous carcinoma	2 (1.0)	0	
Squamous-cell carcinoma	1 (0.5)	0	
Carcinosarcoma	0	1 (0.5)	
ECOG performance-status score — no. (%)			
0	64 (31.1)	66 (32.4)	0.72
1	117 (56.8)	111 (54.4)	
2	24 (11.7)	27 (13.2)	
Unknown	1 (0.5)	0	
Previous therapy — no. (%)			
No	50 (24.3)	50 (24.5)	0.96
Yes	156 (75.7)	154 (75.5)	
Type of previous therapy — no. (%)			
Curative surgery	48 (23.3)	37 (18.1)	0.20
Palliative surgery	40 (19.4)	37 (18.1)	0.74
Laparotomy	49 (23.8)	48 (23.5)	0.95
Biliary stenting	92 (44.7)	93 (45.6)	0.85
Radiotherapy	5 (2.4)	3 (1.5)	0.48
Adjuvant chemotherapy	5 (2.4)	3 (1.5)	0.74
Photodynamic therapy	1 (0.5)	1 (0.5)	1.00
Other therapy	81 (39.3)	76 (37.3)	0.14

Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81. doi: 10.1056/NEJMoa0908721. PMID: 20375404.

FIRST LINE THERAPY(ABC-02);

Subgroup	No. of Patients	Hazard Ratio (95% CI)
ABC trial group		
01	86	0.65 (0.42–1.01)
02	324	0.64 (0.50–0.83)
Extent of disease		
Locally advanced	104	0.47 (0.29–0.74)
Metastatic	306	0.74 (0.57–0.95)
Primary tumor site		
Intrahepatic	80	0.57 (0.34–0.94)
Extrahepatic	73	0.73 (0.43–1.23)
Hilar	57	0.59 (0.32–1.09)
Gallbladder	149	0.61 (0.42–0.89)
Ampulla	20	0.62 (0.21–1.82)
Not specified	31	0.98 (0.46–2.11)
ECOG score		
0	130	0.50 (0.33–0.77)
1	228	0.68 (0.51–0.91)
2	52	0.90 (0.49–1.66)
Previous therapy		
No	100	0.65 (0.41–1.01)
Yes	310	0.64 (0.49–0.82)
All patients	410	0.64 (0.52–0.80)

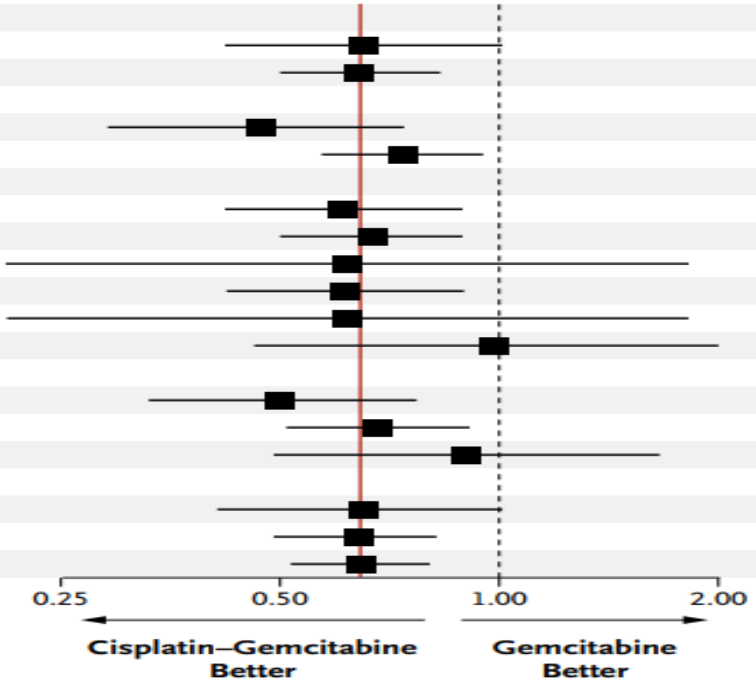


Figure 3. Hazard Ratio, According to Trial and Prespecified Baseline Factors.
ABC denotes Advanced Biliary Cancer, and ECOG Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning. The red line indicates the hazard ratio for death (0.64) in the intention-to-treat population.

Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81. doi: 10.1056/NEJMoa0908721. PMID: 20375404.

FIRST LINE THERAPY(ABC-02);

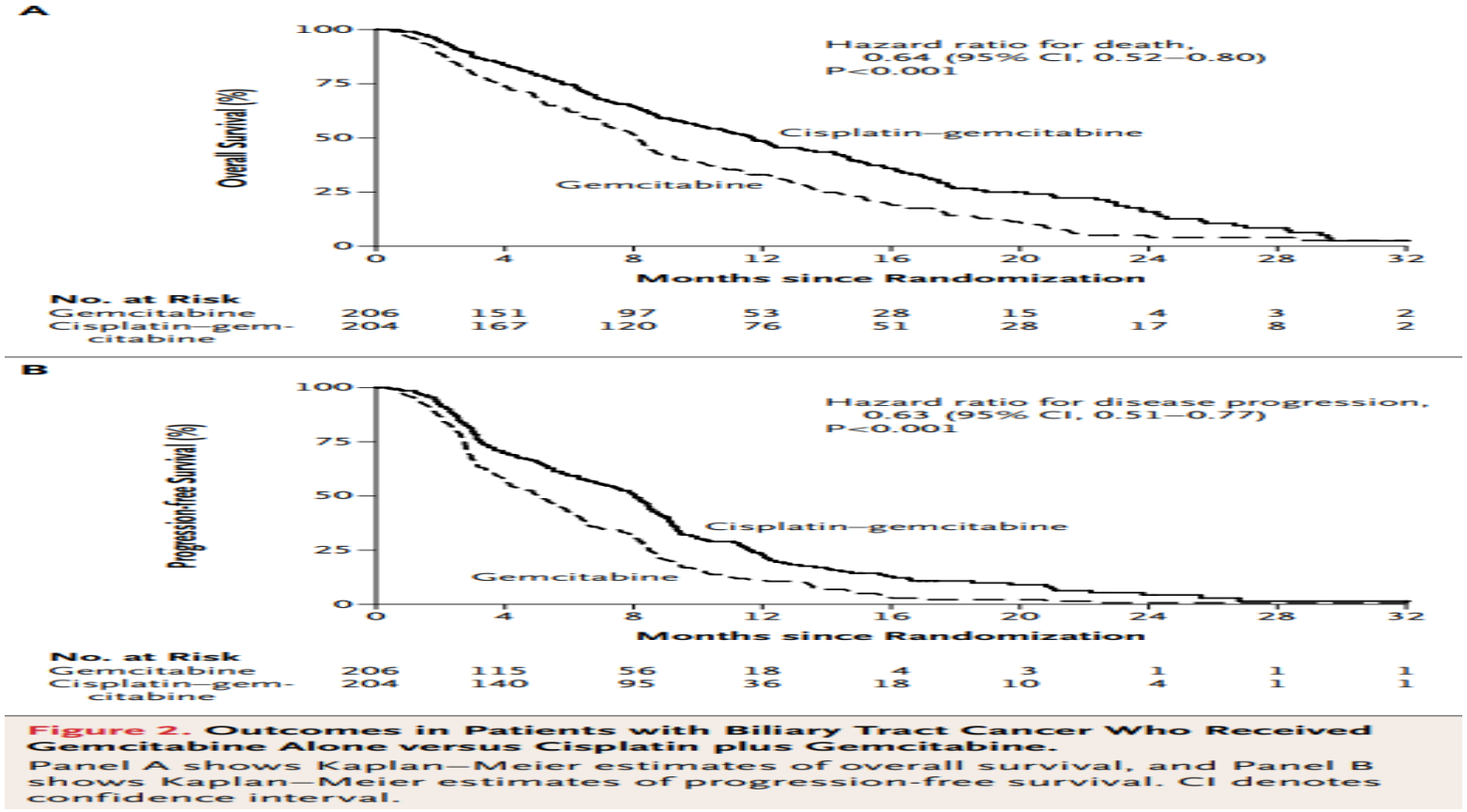


Figure 2. Outcomes in Patients with Biliary Tract Cancer Who Received Gemcitabine Alone versus Cisplatin plus Gemcitabine.
Panel A shows Kaplan–Meier estimates of overall survival, and Panel B shows Kaplan–Meier estimates of progression-free survival. CI denotes confidence interval.

Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81. doi: 10.1056/NEJMoa0908721. PMID: 20375404.

FIRST LINE THERAPY(ABC-02);

Table 2. Grade 3 or 4 Toxic Effects during Treatment, According to Treatment Group.

Variable	Gemcitabine (N = 199)	Cisplatin plus Gemcitabine (N = 198)	P Value
	number (percent)		
Hematologic toxic effects			
Decreased white-cell count	19 (9.5)	31 (15.7)	0.07
Decreased platelet count	13 (6.5)	17 (8.6)	0.44
Decreased hemoglobin level	6 (3.0)	15 (7.6)	0.04
Decreased neutrophil count	33 (16.6)	50 (25.3)	0.03
Any hematologic toxic effect	47 (23.6)	64 (32.3)	0.05
Liver function			
Increased alanine aminotransferase level	34 (17.1)	19 (9.6)	0.03
Other abnormal liver function	39 (19.6)	26 (13.1)	0.08
Any abnormal liver function	54 (27.1)	33 (16.7)	0.01
Nonhematologic toxic effects			
Alopecia	0	2 (1.0)	0.16
Anorexia	5 (2.5)	6 (3.0)	0.75
Fatigue	33 (16.6)	37 (18.7)	0.58
Nausea	7 (3.5)	8 (4.0)	0.78
Vomiting	11 (5.5)	10 (5.1)	0.65
Impaired renal function	2 (1.0)	3 (1.5)	0.83
Infection			
Without neutropenia	23 (11.6)	12 (6.1)	0.05
With neutropenia	14 (7.0)	20 (10.1)	0.28
Biliary sepsis	8 (4.0)	8 (4.0)	0.99
Any type	38 (19.1)	36 (18.2)	0.82
Deep-vein thrombosis	1 (0.5)	4 (2.0)	0.18
Thromboembolic event	3 (1.5)	7 (3.5)	0.20
Other	62 (31.2)	66 (33.3)	0.64
Any	100 (50.3)	108 (54.5)	0.39
Any grade 3 or 4 toxic effect	137 (68.8)	140 (70.7)	0.69

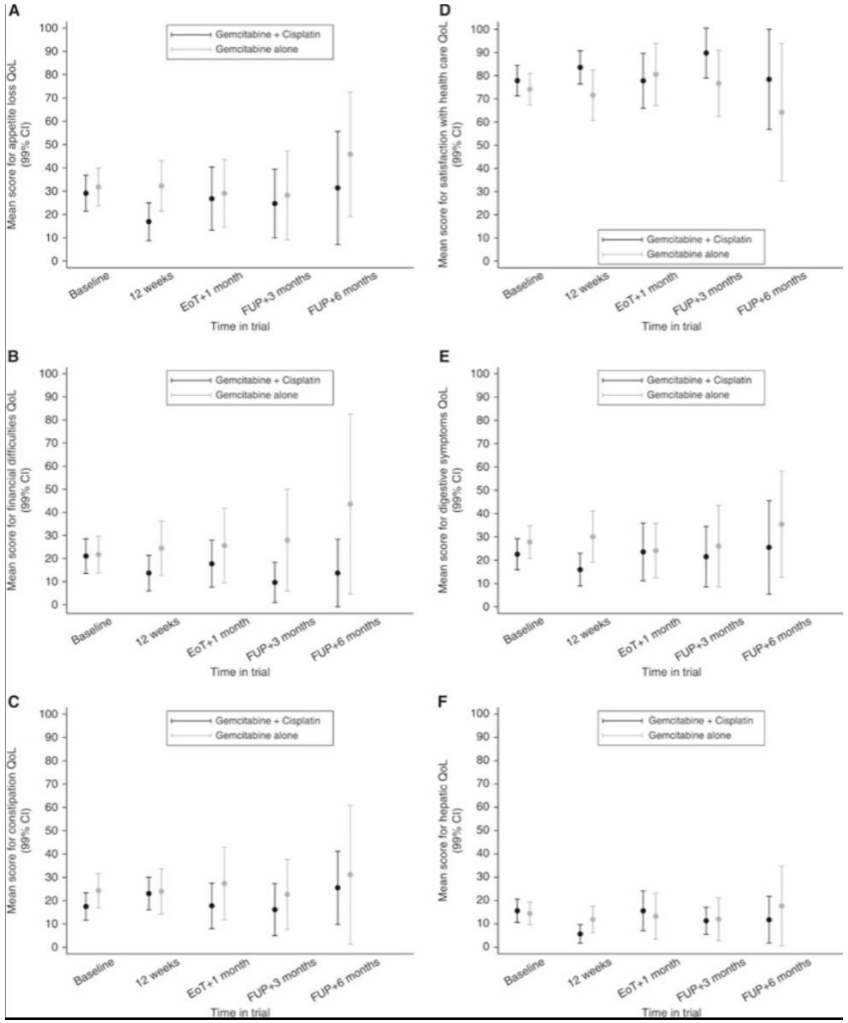
Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81. doi: 10.1056/NEJMoa0908721. PMID: 20375404.

FIRST LINE THERAPY(ABC-02 UPDATE);

- Most QoL scales showed a trend favoring the combined CisGem arm, including functional and symptomatic scales, although the differences were not statistically significant.

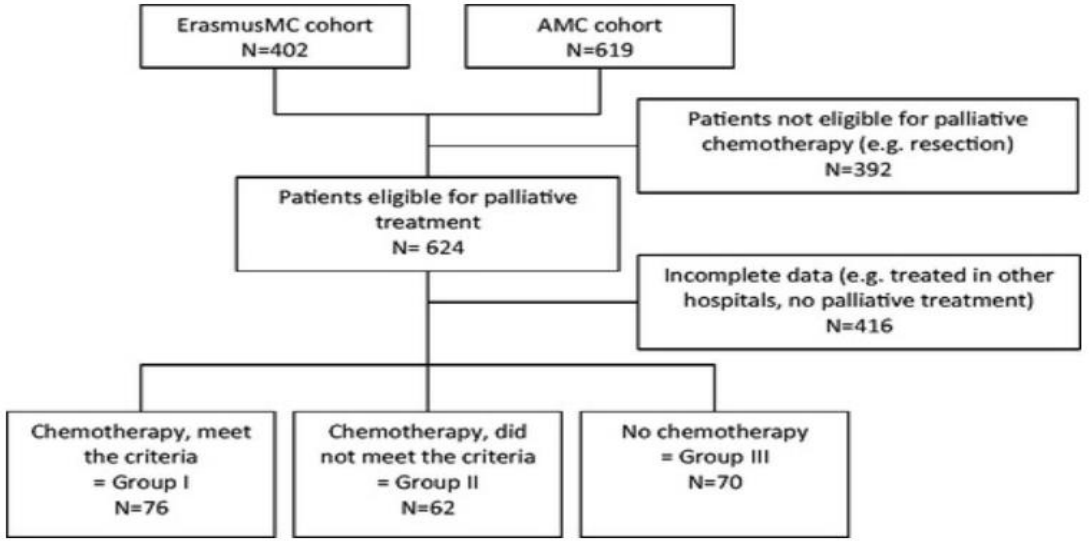
- Forty-five (11%)) patients survived at least 2 years (34 received CisGem and 11 Gem) and 21 (5%) 3 years or more (14 received CisGem and 7 Gem).

- After a median follow-up of 9.2 months and 398 deaths, the median OS was 11.7 months for CisGem and 8.1 months for Gem (HR)=0.65, 95% CI: 0.53-0.79, P<0.001).



Bridgewater J, Lopes A, Palmer D, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Valle J, Wasan H. Quality of life, long-term survivors and long-term outcome from the ABC-02 study. Br J Cancer. 2016 Apr 26;114(9):965-71. doi: 10.1038/bjc.2016.64. PMID: 27115567; PMCID: PMC4984909.

FIRST LINE THERAPY(ABC-02 DAILY PRACTICE);



Variable	Group II (*N*= 64)
Age >18 years *n* (%)	0 (0.0)
Histological or cytologic diagnosis *n* (%)	5 (7.8)
ECOG PS *n* (%)	1 (1.5)
Serum bilirubin level >1.5 times ULN *n* (%)	15 (23.4)
Serum liver-enzyme levels >5 times ULN *n* (%)	55 (85.9)
Serum ureum and creatinine level >1.5 times ULN *n* (%)	2 (3.1)
eGFR <45ml/min *n* (%)	2 (3.1)

J. Dierks, M. P. Gaspersz, A. Belkouz, J. L. A. van Vugt, R. J. S. Coelen, J. W. B. de Groot, A. J. ten Tije, W. G. Meijer, J. F. M. Pruijt, T. van Voorthuizen, D. J. van Spronsen, M. Rentinck, D. ten Oever, J. M. Smit, H. M. Otten, T. M. van Gulik, J. W. Wilmink, B. Groot Koerkamp & H. Klümpen (2018) Translating the ABC-02 trial into daily practice: outcome of palliative treatment in patients with unresectable biliary tract cancer treated with gemcitabine and cisplatin, Acta Oncologica, 57:6, 807-812, DOI: 10.1080/0284186X.2017.1418532

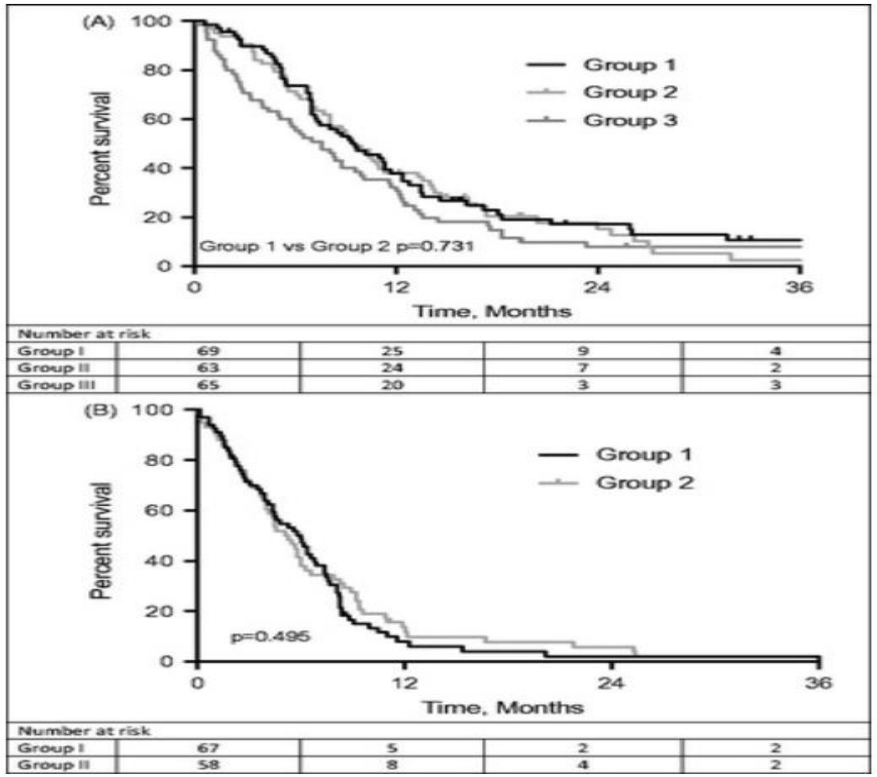
FIRST LINE THERAPY(ABC-02 DAILY PRACTICE);

- Retrospective analysis for 138 patients received first line chemotherapy with gemcitabine and cisplatin.
- Median OS of 69 patients in group I, 63 patients in group II was 9.6 months (95%CI = 6.7–12.5), 9.5 months (95%CI = 7.7–11.3)
- Median PFS was 6.0 months (95%CI = 4.4–7.6) in group I and 5.1 months (95%CI = 3.7–6.5) in group II.
- Toxicity and number of dose reductions (p = .974) were comparable between the two chemotherapy groups.

J. Dierks, M. P. Gaspersz, A. Belkouz, J. L. A. van Vugt, R. J. S. Coelen, J. W. B. de Groot, A. J. ten Tije, W. G. Meijer, J. F. M. Pruijt, T. van Voorthuizen, D. J. van Spronsen, M. Rentinck, D. ten Oever, J. M. Smit, H. M. Otten, T. M. van Gulik, J. W. Wilmink, B. Groot Koerkamp & H. Klümpen (2018) Translating the ABC-02 trial into daily practice: outcome of palliative treatment in patients with unresectable biliary tract cancer treated with gemcitabine and cisplatin, Acta Oncologica, 57:6, 807-812, DOI: 10.1080/0284186X.2017.1418532

FIRST LINE THERAPY(ABC-02 DAILY PRACTICE);

Figure 2. Survival rates: (A) overall survival, (B) progression-free survival.



J. Dierks, M. P. Gaspersz, A. Belkouz, J. L. A. van Vugt, R. J. S. Coelen, J. W. B. de Groot, A. J. ten Tije, W. G. Meijer, J. F. M. Pruijt, T. van Voorthuizen, D. J. van Spronsen, M. Rentinck, D. ten Oever, J. M. Smit, H. M. Otten, T. M. van Gulik, J. W. Wilmink, B. Groot Koerkamp & H. Klümpen (2018) Translating the ABC-02 trial into daily practice: outcome of palliative treatment in patients with unresectable biliary tract cancer treated with gemcitabine and cisplatin, Acta Oncologica, 57:6, 807-812, DOI: 10.1080/0284186X.2017.1418532

FIRST LINE THERAPY (TOPAZ-01);

- Double-blind, placebo-controlled, phase III study
- In 685 patients with untreated unresectable or metastatic biliary tract cancer or with recurrent disease
- Randomized with 1:1 to:
  - Durvalumab + Gemcitabine + Cisplatin * 8 Cycles then Durvalumab maintained

    Or
  - Placebo + Gemcitabine + Cisplatin
- Primary objective endpoint was OS.
- Secondary end points included PFS , ORR , and safety

June 1, 2022 DOI: 10.1056/EVIDoa2200015 NEJM Evid 2022; 1 (8)

FIRST LINE THERAPY (TOPAZ-01);

Table 1. Patient Demographics and Baseline Characteristics in the Full Analysis Set.*

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=341)	Placebo plus Gemcitabine and Cisplatin (n=344)	Total (N=685)
Median age (range) — yr	64 (20–84)	64 (31–85)	64 (20–85)
Female sex — no. (%)	172 (50.4)	168 (48.8)	340 (49.6)
Race — no. (%)			
Asian	185 (54.3)	201 (58.4)	386 (56.4)
Region — no. (%)			
Asia	178 (52.2)	196 (57.0)	374 (54.6)
Rest of the world	163 (47.8)	148 (43.0)	311 (45.4)
ECOG performance status of 0 — no. (%)	173 (50.7)	163 (47.4)	336 (49.1)
Primary tumor type — no. (%)			
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)	383 (55.9)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)	131 (19.1)
Gallbladder	85 (24.9)	86 (25.0)	171 (25.0)
Disease status — no. (%)			
Initially unresectable	274 (80.4)	279 (81.1)	553 (80.7)
Recurrent	67 (19.6)	64 (18.6)	131 (19.1)
Disease classification — no. (%)			
Locally advanced†	38 (11.1)	57 (16.6)	95 (13.9)
Metastatic	303 (88.9)	286 (83.1)	589 (86.0)
MSI status — no. (%)			
High	3 (0.9)	2 (0.6)	5 (0.7)
Stable	160 (46.9)	168 (48.8)	328 (47.9)
Missing‡	178 (52.2)	174 (50.6)	352 (51.4)
Virology status — no. (%)			
No viral hepatitis	187 (54.8)	174 (50.6)	361 (52.7)
Any viral hepatitis B	69 (20.2)	81 (23.5)	150 (21.9)
Active viral hepatitis B	8 (2.3)	14 (4.1)	22 (3.2)
Prior hepatitis C	8 (2.3)	10 (2.9)	18 (2.6)
Missing	82 (24.0)	83 (24.1)	165 (24.1)
PD-L1 expression — no. (%)			
TAP ≥1%	197 (57.8)	205 (59.6)	402 (58.7)
TAP <1%	103 (30.2)	103 (29.9)	206 (30.1)
Missing	41 (12.0)	36 (10.5)	77 (11.2)

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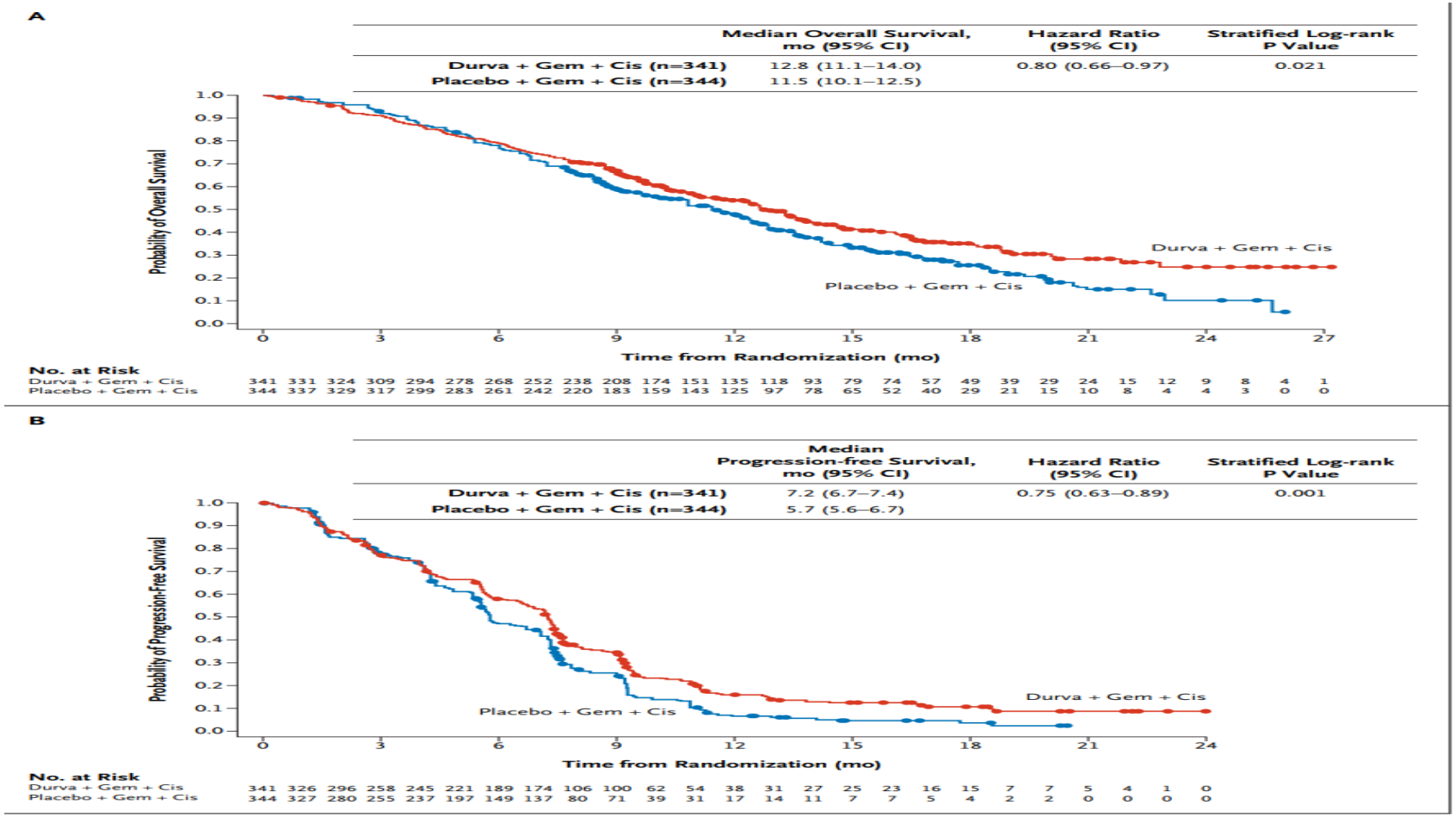
FIRST LINE THERAPY (TOPAZ-01);



igure 1. Kaplan–Meier Curves of Overall and Progression-Free Survival in the Full Analysis Set.
Meier curves are presented for overall survival (Panel A) and progression-free survival (Panel B). CI denotes confidence int

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FIRST LINE THERAPY (TOPAZ-01);

Table 2. Tumor Response in the Full Analysis Set.*

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=341)	Placebo plus Gemcitabine and Cisplatin (n=343)
Objective response rate — no. (%)†	91 (26.7)	64 (18.7)
Complete response	7 (2.1)	2 (0.6)
Partial response	84 (24.6)	62 (18.1)
Disease control rate — no. (%)‡	291 (85.3)	284 (82.6)
Median duration of response (IQR) — mo§	6.4 (4.6–17.2)	6.2 (3.8–9.0)
Patients with continued response — %		
≥3 mo	88.9	89.0
≥6 mo	59.3	54.2
≥9 mo	32.6	25.3
≥12 mo	26.1	15.0
Median time to response (IQR) — mo¶	1.6 (1.3–3.0)	2.7 (1.4–4.1)

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FIRST LINE THERAPY (TOPAZ-01);

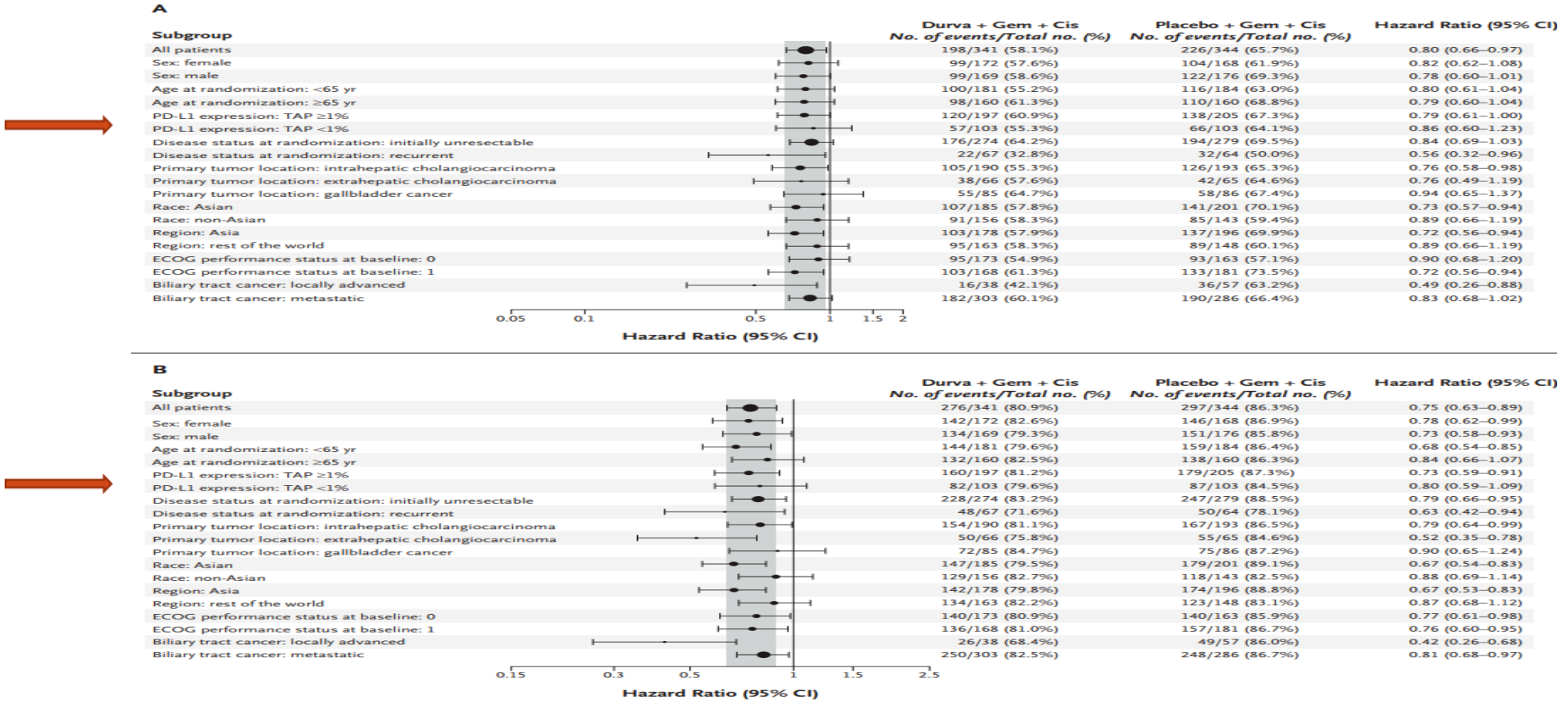

Figure 2. Forest Plots of Overall and Progression-Free Survival by Subgroup for Durvalumab versus Placebo in the Full Analysis Set.

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FIRST LINE THERAPY (TOPAZ-01);

Table 3. Summary of Safety Data in the Safety Analysis Set.

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=338)	Placebo plus Gemcitabine and Cisplatin (n=342)
Adverse events — no. (%)		
Any grade	336 (99.4)	338 (98.8)
Serious	160 (47.3)	149 (43.6)
Grade 3 or 4	256 (75.7)	266 (77.8)
Leading to discontinuation of any study treatment	44 (13.0)	52 (15.2)
Leading to death	12 (3.6)	14 (4.1)
Treatment-related adverse events — no. (%)		
Any grade	314 (92.9)	308 (90.1)
Serious	53 (15.7)	59 (17.3)
Grade 3 or 4	212 (62.7)	222 (64.9)
Leading to discontinuation of any study treatment	30 (8.9)	39 (11.4)
Leading to death*	2 (0.6)	1 (0.3)

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FIRST LINE THERAPY (KEYNOTE-966);

KEYNOTE-966:A randomized, double-blind, placebo-controlled, phIII study of pembrolizumab in combination with gemcitabine and cisplatin for the treatment of advanced BTC

Patients (N= 1069)

- Histologically confirmed advanced (metastatic) and/or unresectable (locally advanced) biliary tract cancer
- Measurable disease per RECIST v1.1
- History of hepatitis B or hepatitis C can be enrolled if study criteria are met
- Provide archival tumor tissue sample or newly obtained core or excisional biopsy of tumor lesion

Stratification: Region (Asia, non-Asia), stage (locally advanced, metastatic), and site of origin (gallbladder, intrahepatic CCA, or extrahepatic CCA)

R 1:1

Pembrolizumab 200 mg IV Q3W + Gemcitabine 1000 mg/m^2 Q3W/Cisplatin 25 mg/m^2 Q3W

Placebo 200 mg IV Q3W + Gemcitabine 1000 mg/m^2 Q3W/Cisplatin 25 mg/m^2 Q3W

Continue until:

- Disease progression
- Unacceptable toxicity
- Pembro/placebo up to 35 cycles. Additional 2nd course of

17 cycles allowed

- Cisplatin up to 8 cycles
- Gemcitabine will be continued until PD, unacceptable toxicity, or withdrawal from the study

End Points

Primary: OS

Secondary: PFS, ORR, DOR per RECIST 1.1 as assessed by BICR, safety and tolerability

LPI for global study reached June 8th 2021, N=1069
LPI for China Extension Sep 14th 2021, N= 46 (Total 158 ,~15%)

FIRST LINE THERAPY (KEYNOTE-966);

- Improvement in overall survival compared with Gemcitabine and Cisplatin alone

- The safety profile of pembrolizumab was similar to that reported in prior trials

FIRST LINE IMMUNOTHERAPY;

Trial	TOPAZ-01	KEYNOTE 966
Trial	III	III
Duration of IO therapy	Till PD/ sever irAE	2 years
Duration of Chemo.	Up to 8 cycles	Gemcitabine till PD or sever irAE
OS	HR 0.76	?
PFS	HR 0.75	?
FDA	Sep. 2022	?
irAE	known	?
QoL	?	?
Price	$$	$$

SECOND LINE THERAPY (ABC-06):

- Phase III, open-label, randomized trial done in 20 sites at UK.

- 162 patients with progression to first-line cisplatin and gemcitabine chemotherapy randomly (1:1) to :

➢ Active symptom control (ASC) + FOLFOX

or

➢ ASC alone

➢ Primary outcome was OS

Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore R, Wadsley J, Patel K, Anthoney A, Maraveyas A, Iveson T, Waters JS, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021 May;22(5):690-701. doi: 10.1016/S1470-2045(21)00027-9. Epub 2021 Mar 30. PMID: 33798493; PMCID: PMC8082275.

SECOND LINE THERAPY (ABC-06):

	ASC alone group (n=81)	ASC plus FOLFOX group (n=81)
Sex		
Female	44 (54%)	38 (47%)
Male	37 (46%)	43 (53%)
Age, years		
Median	65 (59–72)	65 (59–72)
Range	26–81	26–84
Platinum sensitivity*		
Resistant or refractory†	47 (58%)	54 (67%)
Sensitive	34 (42%)	27 (33%)
Albumin*		
<35 g/L	21 (26%)	19 (23%)
≥35 g/L	60 (74%)	62 (77%)
Disease stage*		
Locally advanced	15 (19%)	14 (17%)
Metastatic	66 (81%)	67 (83%)
Tumour site		
Intrahepatic	38 (47%)	34 (42%)
Extrahepatic	19 (23%)	26 (32%)
Gallbladder	17 (21%)	17 (21%)
Ampulla	7 (9%)	4 (5%)
Histology		
Adenocarcinoma	74 (91%)	73 (90%)
Other‡	7 (9%)	8 (10%)
Grade of differentiation		
Well	5 (6%)	9 (11%)
Moderately	41 (51%)	37 (46%)
Poorly	11 (14%)	9 (11%)
Not specified	23 (28%)	26 (32%)
Missing	1 (1%)	0
ECOG performance status		
0	28 (35%)	25 (31%)
1	52 (64%)	55 (68%)
Missing	1 (1%)	1 (1%)
Had previous surgery	38 (47%)	34 (42%)
Previous cisplatin and gemcitabine		
Duration, months	4·8 (2·9–5·3)	4·9 (2·8–5·5)
≥6 months	6 (7%)	13 (16%)§
Baseline CA19.9 (U/mL)¶	443 (46–5714)	162 (25–1903)
Baseline carcinoembryonic antigen (U/mL)¶	6 (3–16)	6 (3–24)
Baseline CA125 (U/mL)¶	42 (20–168)	52 (21–159)

Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore R, Wadsley J, Patel K, Anthoney A, Maraveyas A, Iveson T, Waters JS, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021 May;22(5):690-701. doi: 10.1016/S1470-2045(21)00027-9. Epub 2021 Mar 30. PMID: 33798493; PMCID: PMC8082275.

SECOND LINE THERAPY (ABC-06):

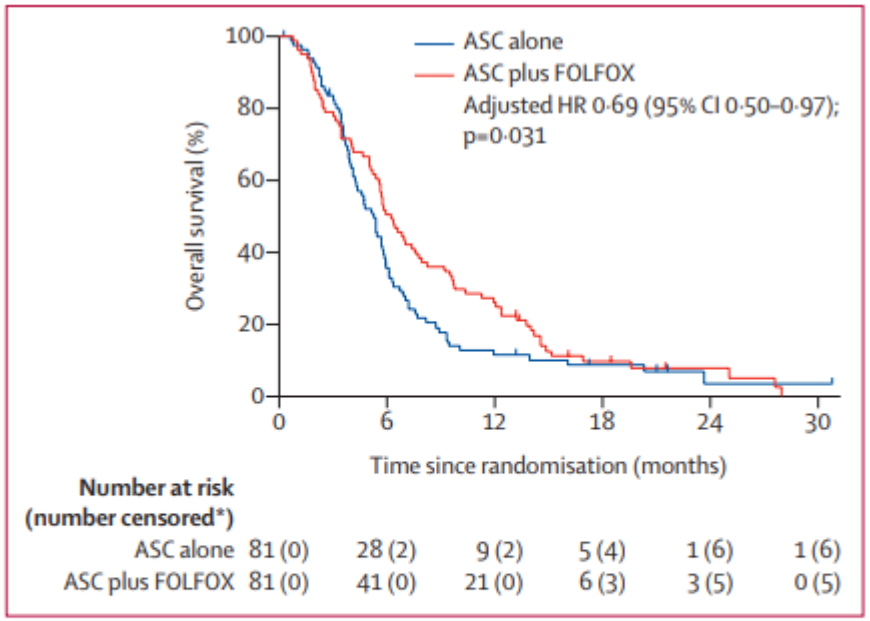


***Figure 2*: Overall survival**

The HR is adjusted for the three stratification factors (platinum sensitivity, serum albumin concentration, and disease stage). ASC=active symptom control. FOLFOX=folinic acid, fluorouracil, and oxaliplatin. HR=hazard ratio. *Numbers are cumulative.

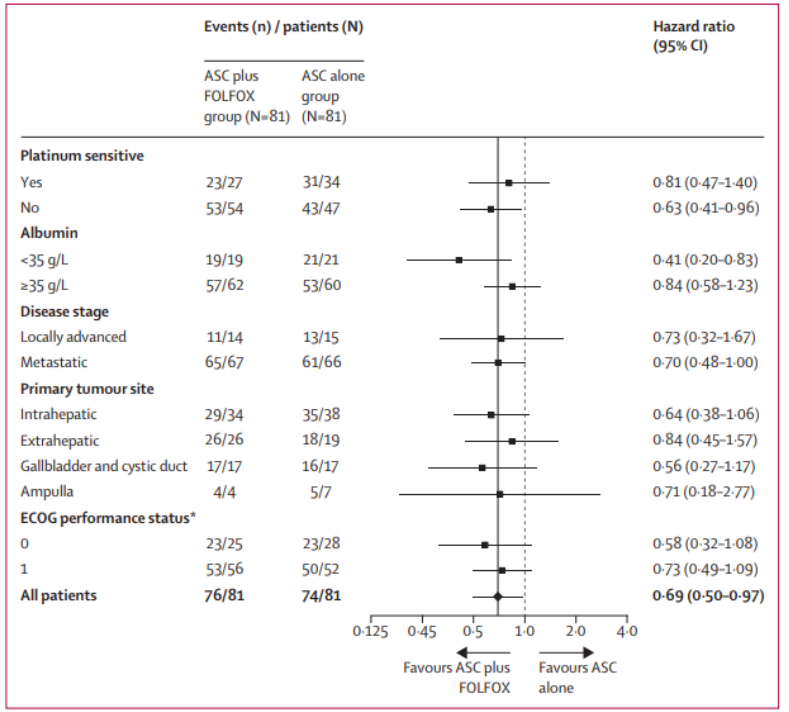


***Figure 3*: Subgroup analyses of overall survival**

Hazard ratios were adjusted by the three stratification factors (platinum sensitivity, serum albumin concentration, and disease stage), or the remaining two stratification factors where the factor of interest was itself a stratification factor. ASC=active symptom control. ECOG=Eastern Cooperative Oncology Group. FOLFOX=folinic acid, fluorouracil, and oxaliplatin. *ECOG performance status information was missing for one participant (death) in the ASC alone group.

Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore R, Wadsley J, Patel K, Anthoney A, Maraveyas A, Iveson T, Waters JS, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021 May;22(5):690-701. doi: 10.1016/S1470-2045(21)00027-9. Epub 2021 Mar 30. PMID: 33798493; PMCID: PMC8082275.

SECOND LINE THERAPY (ABC-06):

	Grade 1–2			Grade 3			Grade 4			Grade 5		
	All events (regardless of causality)		Chemotherapy-related events (ASC plus FOLFOX; n=81)	All events (regardless of causality)		Chemotherapy-related events (ASC plus FOLFOX; n=81)	All events (regardless of causality)		Chemotherapy-related events (ASC plus FOLFOX; n=81)	All events (regardless of causality)		Chemotherapy-related events (ASC plus FOLFOX; n=81)
	ASC alone (n=81)	ASC plus FOLFOX (n=81)		ASC alone (n=81)	ASC plus FOLFOX (n=81)		ASC alone (n=81)	ASC plus FOLFOX (n=81)		ASC alone (n=81)	ASC plus FOLFOX (n=81)	
Any*	35 (43%)	24 (30%)	37 (46%)	35 (43%)	39 (48%)	23 (28%)	3 (4%)	10 (12%)	5 (6%)	4 (5%)	7 (9%)	3 (4%)
Neuropathy	8 (10%)	55 (68%)	52 (64%)	0	1 (1%)	1 (1%)	0	0	0	0	0	0
Fatigue or lethargy	47 (58%)	58 (72%)	47 (58%)	6 (7%)	15 (19%)	9 (11%)	0	0	0	0	0	0
Nausea	32 (40%)	40 (49%)	30 (37%)	1 (1%)	1 (1%)	1 (1%)	0	0	0	0	0	0
Oral mucositis	4 (5%)	29 (36%)	28 (35%)	0	1 (1%)	1 (1%)	0	0	0	0	0	0
Anorexia	31 (38%)	47 (58%)	25 (31%)	6 (7%)	1 (1%)	1 (1%)	0	0	0	0	0	0
Diarrhoea	12 (15%)	27 (33%)	22 (27%)	2 (2%)	2 (2%)	2 (2%)	0	0	0	0	0	0
Thrombocytopenia	1 (1%)	18 (22%)	18 (22%)	0	0	0	0	0	0	0	0	0
Dysgeusia	11 (14%)	23 (28%)	16 (20%)	1 (1%)	0	0	0	0	0	0	0	0
Vomiting	16 (20%)	20 (25%)	14 (17%)	4 (5%)	3 (4%)	2 (2%)	0	0	0	0	0	0
Constipation	28 (35%)	35 (43%)	13 (16%)	1 (1%)	2 (2%)	0	0	0	0	0	0	0
Neutropenia	0	13 (16%)	12 (15%)	1 (1%)	8 (10%)	8 (10%)	0	2 (2%)	2 (2%)	0	0	0
Infection†	17 (21%)	19 (23%)	10 (12%)	3 (4%)	12 (15%)	6 (7%)	0	2 (2%)	1 (1%)	2 (2%)	1 (1%)	1 (1%)
Anaemia	5 (6%)	10 (12%)	9 (11%)	1 (1%)	2 (2%)	2 (2%)	0	0	0	0	0	0
Dry mouth	11 (14%)	20 (25%)	9 (11%)	0	1 (1%)	0	0	0	0	0	0	0
Pain	50 (62%)	42 (52%)	6 (7%)	5 (6%)	8 (10%)	0	1 (1%)	0	0	0	0	0
Tinnitus	2 (2%)	8 (10%)	5 (6%)	0	0	0	0	0	0	0	0	0
Myalgia	5 (6%)	10 (12%)	4 (5%)	1 (1%)	0	0	0	0	0	0	0	0
Oedema	9 (11%)	17 (21%)	4 (5%)	1 (1%)	0	0	0	1 (1%)	0	0	0	0
Dyspnoea	6 (7%)	13 (16%)	3 (4%)	1 (1%)	1 (1%)	0	0	0	0	0	0	0
Muscle weakness	9 (11%)	6 (7%)	3 (4%)	0	0	0	0	0	0	0	0	0
Thromboembolic event	2 (2%)	3 (4%)	3 (4%)	4 (5%)	0	0	0	0	0	0	0	0
Cough	4 (5%)	11 (14%)	2 (2%)	0	0	0	0	0	0	0	0	0
Dyspepsia	10 (12%)	8 (10%)	2 (2%)	0	0	0	0	0	0	0	0	0
Weight loss	9 (11%)	8 (10%)	2 (2%)	0	0	0	0	0	0	0	0	0
Abdominal distension	7 (9%)	3 (4%)	1 (1%)	0	2 (2%)	0	0	0	0	0	0	0
Biliary event‡	2 (2%)	2 (2%)	1 (1%)	13 (16%)	13 (16%)	2 (2%)	2 (2%)	2 (2%)	0	2 (2%)	1 (1%)	0
Catheter-related infection	0	2 (2%)	1 (1%)	0	2 (2%)	0	0	0	0	0	0	0
Erythema	1 (1%)	2 (2%)	1 (1%)	1 (1%)	0	0	0	0	0	0	0	0
Hypertension	4 (5%)	10 (12%)	1 (1%)	1 (1%)	4 (5%)	2 (2%)	0	0	0	0	0	0
Hypophosphatemia	0	2 (2%)	1 (1%)	1 (1%)	0	0	0	1 (1%)	0	0	0	0
Hypotension	1 (1%)	1 (1%)	1 (1%)	0	1 (1%)	0	0	0	0	0	0	0
Acute kidney injury	2 (2%)	0	0	0	1 (1%)	1 (1%)	0	0	0	0	2 (2%)	1 (1%)
Allergic reaction	0	0	0	0	1 (1%)	1 (1%)	0	0	0	0	0	0
Ascites	2 (2%)	10 (12%)	0	2 (2%)	2 (2%)	0	0	0	0	0	0	0
Cerebrovascular ischaemia	0	0	0	0	0	0	0	1 (1%)	0	0	0	0
Dehydration	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Diabetic ketoacidosis	0	0	0	0	0	0	0	0	0	0	1 (1%)	0
Fall	0	0	0	0	1 (1%)	0	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	0	1 (1%)	1 (1%)	0	1 (1%)	1 (1%)
Fracture (non-pathological)	0	0	0	0	1 (1%)	0	0	0	0	0	0	0

(Table 2 continues on next page)

Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore R, Wadsley J, Patel K, Anthoney A, Maraveyas A, Iveson T, Waters JS, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021 May;22(5):690-701. doi: 10.1016/S1470-2045(21)00027-9. Epub 2021 Mar 30. PMID: 33798493; PMCID: PMC8082275.

SECOND LINE THERAPY (ABC-06):

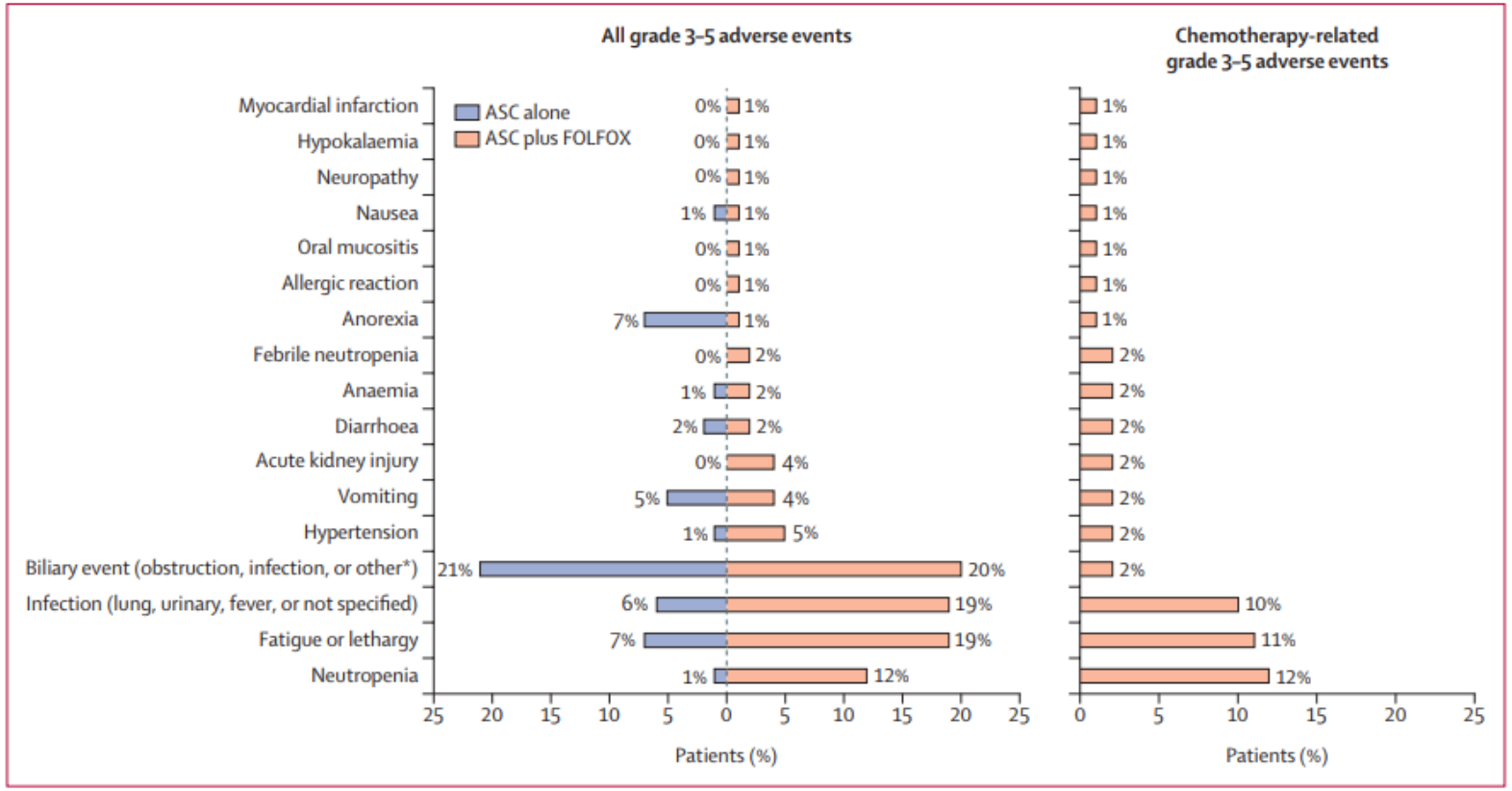


Figure 4: **Grade 3–5 adverse events and chemotherapy-related toxicity**
Grade 3–5 adverse events reported at least in 1% of patients in the ASC plus FOLFOX group that were considered to be chemotherapy related are summarised, alongside the incidence in each study group regardless of causality. Percentages are calculated in the intention-to-treat population. ASC=active symptom control. FOLFOX=folinic acid, fluorouracil, and oxaliplatin. *Includes liver infection, increased bilirubin or alkaline phosphatase, and hepatitis.

Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore R, Wadsley J, Patel K, Anthoney A, Maraveyas A, Iveson T, Waters JS, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021 May;22(5):690-701. doi: 10.1016/S1470-2045(21)00027-9. Epub 2021 Mar 30. PMID: 33798493; PMCID: PMC8082275.

SECOND LINE THERAPY (ABC-06 UPDATE):

- Quality of life & values of health.

- EQ-5D utility value , QlQ-30 summary score, QLQ-30 Physical health scale ,QLQ -30 social function scale QLQ-30 for pain, fatigue , nausea.

- QoL favor chemotherapy over ASC.

ESMO-abstract 2022

SECOND LINE THERAPY (NIFTY);

- Open-label, randomized, phase IIb at five academic institutions in South Korea.

- For 174 patients progressed on first-line Gemcitabine plus Cisplatin.

- Randomly assigned (1:1) to:

➢ Liposomal Irinotecan (70 mg/m^2) + Leucovorin (400 mg/m^2) and IV Fluorouracil (2400 mg/m^2 f) every 2 weeks

or

➢ leucovorin and fluorouracil only every 2 weeks

Yoo C, Kim KP, Jeong JH, Kim I, Kang MJ, Cheon J, Kang BW, Ryu H, Lee JS, Kim KW, Abou-Alfa GK, Ryoo BY. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol. 2021 Nov;22(11):1560-1572. doi: 10.1016/S1470-2045(21)00486-1. Epub 2021 Oct 14. PMID: 34656226.

SECOND LINE THERAPY (NIFTY);

- At a median follow-up of 11·8 months (IQR 7·7–18·7), the median PFS was significantly longer in the liposomal irinotecan plus fluorouracil and leucovorin group (7·1 months, 95% CI 3·6–8·8) than in the fluorouracil and leucovorin group (1·4 months, 1·2–1·5; HR 0·56, 95% CI 0·39–0·81; p=0·0019).

- Median OS was 8.6 months (5.4-10.5) and 5.5 months (4.7-7.2), respectively (HR=0.68 [0.48-0.98], p=0.0349).

- ORR was 14.8% and 5.8%, respectively (p=0.0684).

Yoo C, Kim KP, Jeong JH, Kim I, Kang MJ, Cheon J, Kang BW, Ryu H, Lee JS, Kim KW, Abou-Alfa GK, Ryoo BY. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol. 2021 Nov;22(11):1560-1572. doi: 10.1016/S1470-2045(21)00486-1. Epub 2021 Oct 14. PMID: 34656226.

SECOND LINE THERAPY (NIFTY);

- The most common grade 3–4 adverse events were neutropenia (21 [24%] of 88 in the liposomal irinotecan plus fluorouracil and leucovorin group *vs* one [1%] of 86 in the fluorouracil and leucovorin group) and fatigue or asthenia (11 [13%] *vs* 3 [3%]).

- Serious adverse events occurred in 37 (42%) patients receiving liposomal irinotecan plus fluorouracil and leucovorin and 21 (24%) patients receiving fluorouracil and leucovorin.

Yoo C, Kim KP, Jeong JH, Kim I, Kang MJ, Cheon J, Kang BW, Ryu H, Lee JS, Kim KW, Abou-Alfa GK, Ryoo BY. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol. 2021 Nov;22(11):1560-1572. doi: 10.1016/S1470-2045(21)00486-1. Epub 2021 Oct 14. PMID: 34656226.

SECOND LINE THERAPY (NALIRICC-AIO);

- Phase II randomized patients who progressed on Gemcitabine & Cisplatin
- In 100 Patients to nal-IRI/5FU or 5FU/LV

Table: 53MO NALIRICC-Trial results, median follow-up of 5,9 months

Treament arm	ORR [%]	mOS [months]	mPFS [months]	AEs ≥ 3 in % of pts
Arm A, Nal-IRI and 5-FU/LV, n=49	14.3	6.9	2.76	70.8
Arm B, 5-FU/LV, n=51	3.9	8.21	2.3	50

Conclusions: The NALIRICC-trial did not meet its primary EP. The addition of nal-IRI to 5-FU/LV did not improve PFS or OS compared to 5-FU/LV alone and was associated with higher toxicity. 5FU/LV may be considered as a reasonable alternative in 2nd line advanced BTC.

APPROACH FOR BILIARY CANCER

- 1st line for BTC is Cisplatin + Gemcitabine + Durvalumab

  Or ? Cisplatin + Gemcitabine +Pembrolizumab (HR 0.??)

- 1st line for BTC is Cisplatin + Gemcitabine

- Oxaliplatin may be substituted for Cisplatin when there is concern about renal function (1)

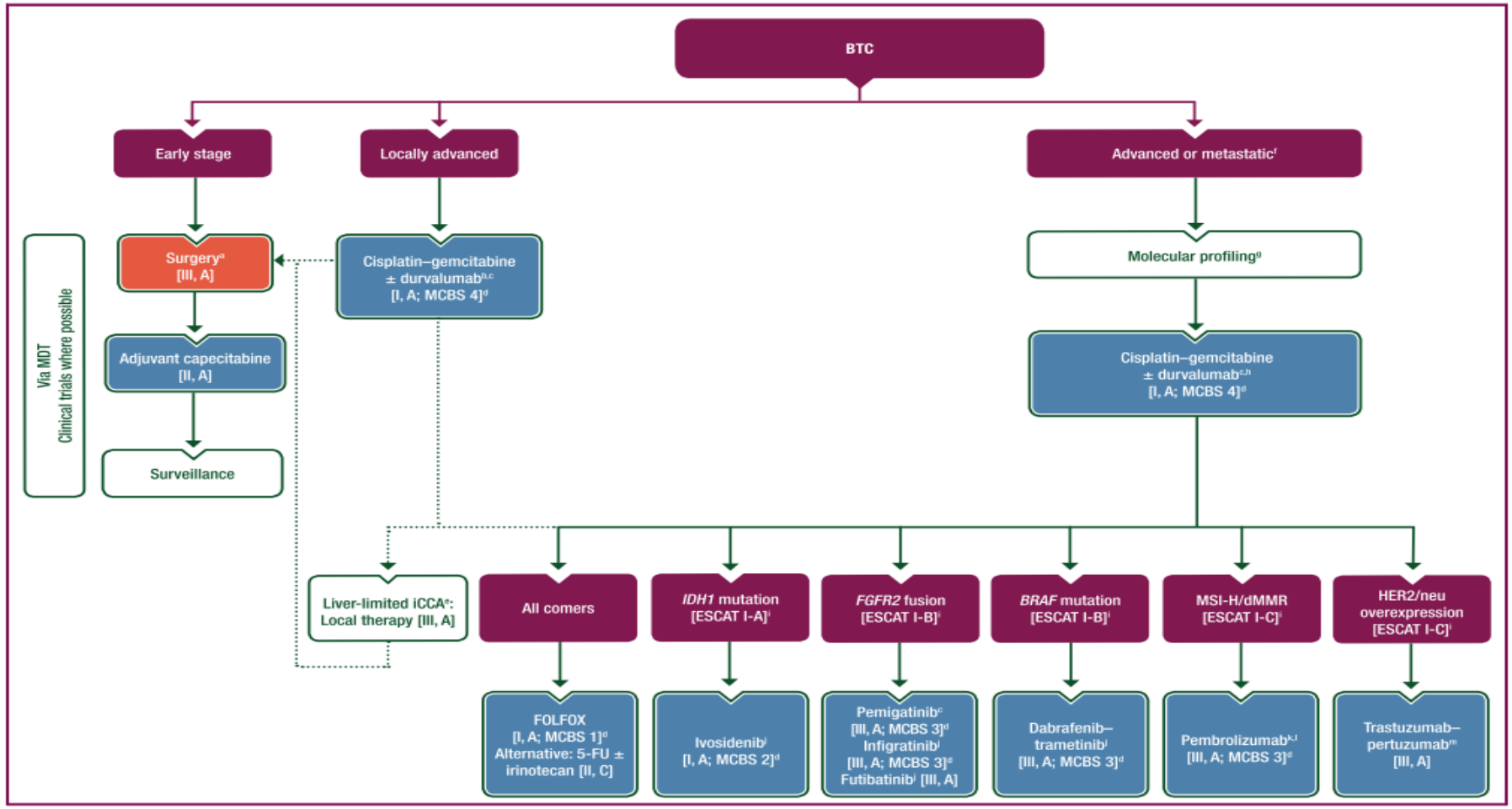
- Gemcitabine monotherapy may be preferred in patients with a PS of 2

- In patients with a PS of 1 Cisplatin + Gemcitabine may be considered in patients with moderately elevated bilirubin levels due to endoluminal disease despite optimal stenting (2)

1- Sharma A, Kalyan Mohanti B, Pal Chaudhary S, et al. Modified gemcitabine and oxaliplatin or gemcitabine þ cisplatin in unresectable gallbladder cancer: results of a phase III randomised controlled trial. Eur J Cancer. 2019;123:162-170.

2-Lamarca A, Benafif S, Ross P, Bridgewater J, Valle JW. Cisplatin and gemcitabine in patients with advanced biliary tract cancer (ABC) and persistent jaundice despite optimal stenting: Effective intervention in patients with luminal disease. Eur J Cancer. 2015 Sep;51(13):1694-703. doi: 10.1016/j.ejca.2015.05.018. Epub 2015 Jun 8. PMID: 26066735.

ESMO RECOMMENDATION NOV. 2022



TAKE HOME MASSAGES

- Chemotherapy with IO is the current standard of care for first line

- FOLFOX is the standard 2nd line unless patient have.....

- Molecular profiling is must for all advance BTC (40% will +Ve):

  (IDH = 10-20%, FGFR= 10-16% , HER-2=10-20%, BRAF=5%)

Thank you

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