2020 Comprehensive Oncology Review
Biliary Tract Cancers

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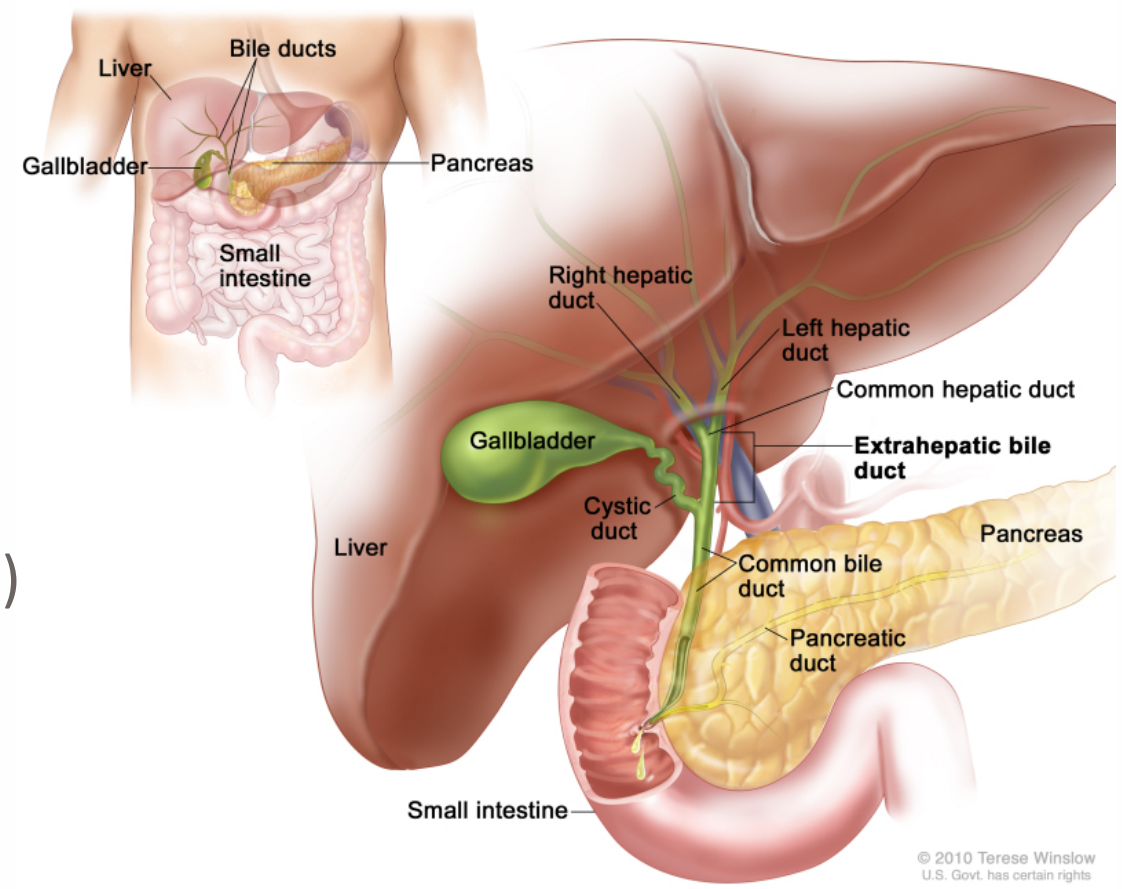
Biliary Tract Cancer: Classification

- **Cholangiocarcinoma**
  - Intrahepatic
  - Extrahepatic
    - Perihilar (Klatskin Tumor)
    - Distal
    - (Some include ampullary cancers)
- **Gallbladder cancer**



Biliary Tract Cancer: Statistics

- Relatively rare in United States (1-2 cases/100,000 population)
- Precise incidence/prevalence confounded by varying classifications in databases
- ~10,000-12,000 incident cases/year
  - ~9,000 extrahepatic/gallbladder
  - ~3,000 intrahepatic cholangiocarcinoma
- Changing Incidence Trends:
  - **Increase** of intrahepatic cholangiocarcinoma
  - **Decrease** of incidence of extrahepatic/gallbladder cancer
- Incidence increases with age (average 50-70 years)

Siegel RL, et al. *CA Cancer J Clin*. 2020.
Jepsen P, et al. *J Natl Cancer Inst*. 2007.
West J, et al. *Br J Cancer*. 2006.
Welzel TM, et al. *J Natl Cancer Inst*. 2006.
Shaib YH, *et al. Hepatol*. 2004.

Biliary Tract Cancer: Risk Factors

Frequently Sporadic; Often no identifiable strong risk factor

Intrahepatic	Extrahepatic	Gallbladder
Male > Female	Male > Female	Female > Male
Cirrhosis	Primary Sclerosing Cholangitis (10-15% lifetime risk)	Gallstones
Hepatitis B	Choledochal cyst (10-15% lifetime risk)	Obesity
Hepatitis C	Liver fluke infection	Hispanic/ Native American
Diabetes Mellitus	Diabetes Mellitus	Diabetes Mellitus
Obesity	Thorotrast exposure	
Alcohol Use		

Biliary Tract Cancers: Clinical Presentation

- **Intrahepatic Cholangiocarcinoma**
  - Often incidentally found on imaging
  - RUQ pain
  - Anorexia
  - Weight loss

- **Extrahepatic/Perihilar/Gallbladder**
  - Biliary obstruction/Cholangitis
  - Abdominal pain
  - Weight loss
  - **1-2% rate incidental gallbladder adenocarcinoma at time of cholecystectomy**

Biliary Tract Cancer: Diagnosis

- **Often misdiagnosed as cancer of unknown primary**
- **Biliary tract cancer is a CLINICAL diagnosis in setting of following:**
  - Dominant liver mass(es) (i.e. intrahepatic) or
  - Perihepatic/peripancreatic/gallbladder mass (i.e. extrahepatic) or
  - CBD biliary obstruction with suspicious/confirmed ERCP brushings (e.g. hilar/Klatzkin's tumor)

    +
  - Pathology suggesting upper GI or pancreaticobiliary primary source

    +
  - Ruled out for other primary GI cancer (i.e. rule out gastroesophageal mass or pancreatic mass)
- **Correct diagnosis is critical to guide treatment options, including new approved targeted agents and eligibility for clinical trials**

Biliary Tract Cancer: Staging

- Different staging systems for intrahepatic vs perihilar vs distal vs gallbladder

- TNM Staging (AJCC 8th edition, 2017)
  - Size and # tumors important for intrahepatic
  - Depth of invasion (in mm) important for extrahepatic
  - # lymph nodes important for all EXCEPT for intrahepatic

Biliary Tract Cancer: Staging Summary (AJCC 8th Ed)

	Intrahepatic	Perihilar	Extrahepatic	Gallbladder
T1	1 tumor w/o vascular invasion and is T1a = ≤5 cm T1b = ≥5 cm	Confined to bile duct	Bile duct wall invasion <5 mm	T1a: Invade lamina propia T1b: Invade muscle layer
T2	One tumor w/ vascular invasion OR Multiple tumors +/- vascular invasion	T2a/b: Invades adipose or liver tissue	Bile duct wall invasion 5-12 mm	T2a/b: Invades perimuscular connective tissue
T3	Any tumor perforating visceral peritoneum	Invades unilateral branches portal v or hepatic aa	Bile duct wall invasion >12 mm	Involvement of serosa or invasion of liver or adjacent organs
T4	Any tumor with direct invasion of local extrahepatic structures	Invades main PV or bilateral branches or CHA	Involves celiac axis, SMA, and/or CHA	Invades portal v, hepatic aa, or two or more extrahepatic organs
N1	Any + regional nodes	1-3	1-3	1-3
N2	N/A	≥4	≥4	≥4

Biliary Tract Cancers: Goals of Therapy

- Curative intent for resectable tumors
- Palliative for unresectable/metastatic disease
- General criteria for unresectable tumors
  - Distant metastatic disease
  - Nodal involvement beyond porta-hepatis
  - Extrahepatic adjacent organ invasion
  - Invasion of main portal vein and main hepatic artery

Surgical Management of Resectable Biliary Tract Cancer

Surgical Management

- Intrahepatic: Hepatic resection +/- portal LN dissection
- Perihilar/Distal: Bile duct resection + cholecystectomy + Whipple
- Gallbladder: Cholecystectomy + hepatic segmental resection (IVB/V), lymphadenectomy, possible bile duct excision

Resectable Perihilar Cholangiocarcinoma: Specific Points

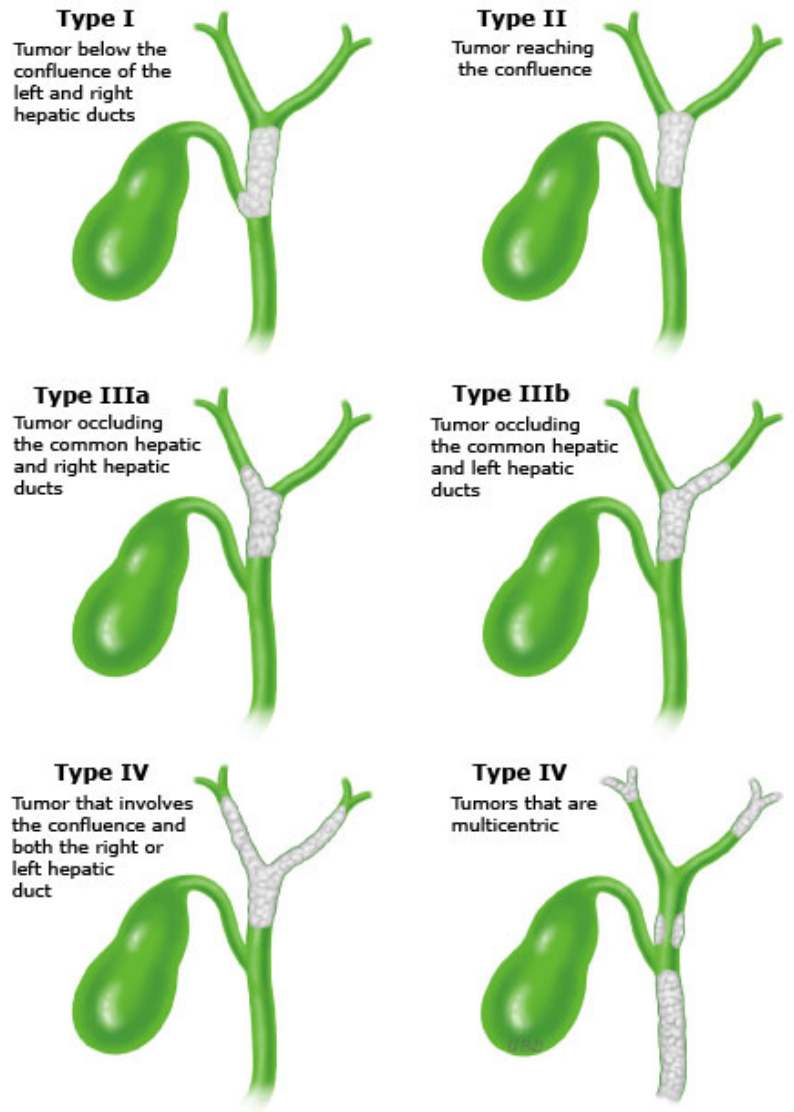
- High recurrence rates due to early involvement of confluence of hepatic ducts

- Neoadjuvant chemoradiation + liver transplantation for select patients:
  - Primary sclerosing cholangitis
  - Solitary tumor with radial diameter < 3 cm
  - No evidence of non-regional/distant disease

- Referral to specialized center/multidisciplinary evaluation important

- AVOID percutaneous biopsy in localized, perihilar disease given risk of seeding

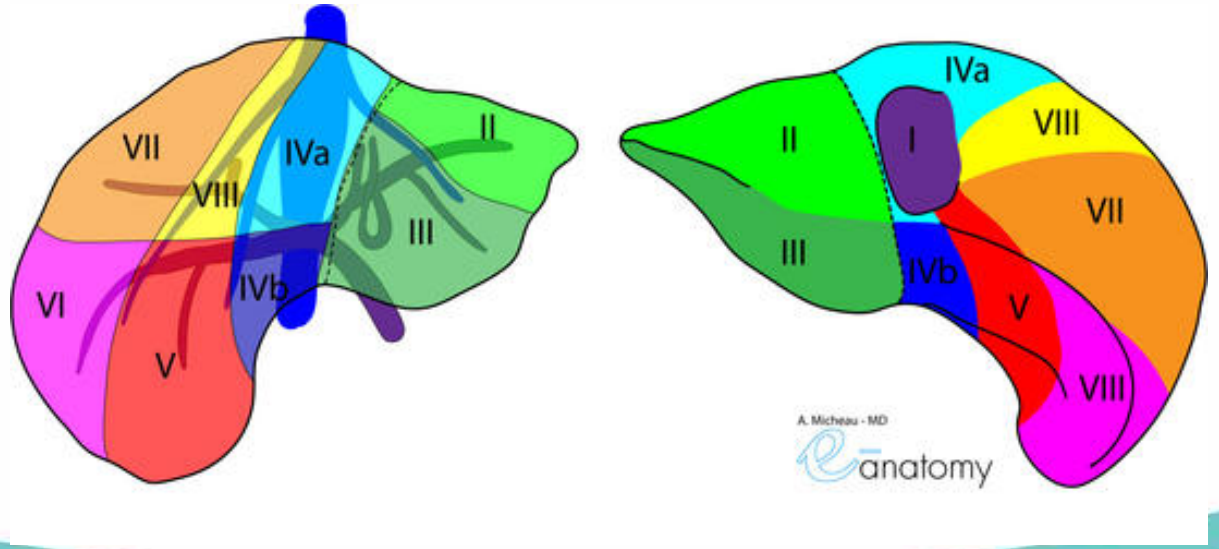
Bismuth-Corlette Classification



UpToDate, 2020

Resectable Gallbladder Cancer: Specific Points

- **Know ≥T1b = muscle invasive disease**
- **Simple cholecystectomy is sufficient for T1a disease** (75-100% long term survival)
- **For ≥T1b, extended resection is needed** (Cholecystectomy + hepatic segmental resection (segments IVB/V), lymphadenectomy, possible bile duct excision (7%-60% long term survival)



Adjuvant Therapy for Biliary Tract Cancer

Outcomes for Resectable Disease: Retrospective Series

Study	n	Tumor location	5-year survival
Nakeeb et al. *Ann Surg*. 1996	294	Intrahepatic, Hilar, and Distal	44% intrahepatic 11% hilar 28% distal
Jang et al. *Ann Surg*. 2005	151	Extrahepatic/Distal	32.5%
Fong et al. *Br J Surg*. 1996	104	Distal	54%
Choi et al. *Ann Surg Onc*. 2009	64	Intrahepatic	39.5%
DeOliveira et al. *Ann Surg*. 2007	564	Intrahepatic, Hilar, and Distal	63% intrahepatic 30% hilar 27% distal
Paik et al. *J Gastroenterol Hepatol*. 2008	97	Intrahepatic	31.1%
Lang et al. *J Am Coll Surg*. 2009	83	Intrahepatic	30% (if R0 resection)
Kosuge et al. *Ann Surg*. 1999	65	Hilar	51.6% (if R0 resection)
Tsao et al. *Ann Surg*. 2000	255 (US and Japan)	Hilar	43% (US) and 25% (Japan)

Adjuvant Therapy: Current NCCN Guidelines

	Gallbladder	Intrahepatic	Perihilar Extrahepatic
R0 N-	- Observe - Chemo (5FU or Gem) - CRT	- Observe - Chemo	- Observe - Chemo - CRT
R1/R2 N+	- CRT - Chemo - CRT/Chemo	- Chemo/CRT - CRT	- Chemo - CRT - CRT/Chemo

Important Points:

- **Adjuvant capecitabine is standard of care per BILCAP study** (Primrose JN et al, Lancet Oncol, 2019)
- **The role of radiation is still unclear**
- **Some small retrospective series suggest survival benefit with chemoradiation, typically in extrahepatic, margin+, or nodal+ disease**

Adjuvant Therapy: Historical Data

Large SEER analysis suggests benefit of adjuvant chemoradiation vs. chemotherapy alone for resected gallbladder cancer

- Recommend incorporating adjuvant chemoradiation in patients with at least T2 or N1 disease.

Meta-analysis conclusions-- based upon limited retrospective data from ~20 trials of biliary tract cancers:

- In patients with + nodes, suggestion of benefit from adjuvant therapy

  Chemotherapy OR chemoradiation: OR .49, p=.004

- In patients with + margins, suggestion of benefit from adjuvant therapy

  Mostly radiation or chemoradiation: OR 0.36, p=.002

- Unclear role of adjuvant radiation alone in node +, margin – patients

Wang SJ et al. JCO 29(35) Dec 2011
Horgan et al. JCO 30(16) April 2012

SWOG S0809: Adjuvant Chemotherapy + Chemoradiation in Extrahepatic Biliary Tract Cancer

- **Phase II trial, single arm trial attempted to establish a standard practice for adjuvant therapy of extrahepatic Cholangiocarcinoma/Gallbladder**
  - 79 evaluable patients
  - **pT2-4 AND either N+ or R1 resection**
  - 4 cycles Gemcitabine/Capecitabine → capecitabine-based chemoradiation 54-59 Gy

	All pts (%, 95% CI)	Extrahepatic	Gallbladder
2-yr OS	65 (53-74)	**68 (54-79)**	**56 (35-73)**
2-yr DFS	54 (40-66)	**54 (39-66)**	**48 (28-66)**
2-yr LR	11 (4-18)	13 (4-22)	8 (0-19)

*Differences in extrahepatic and gallbladder were not statically significant

- **Key results**:
  - Treatment well tolerated
  - 86% completed planned therapy
  - Promising median OS 34 months
  - Applicability of results limited by a Phase II, single arm study and to extrahepatic disease only

Ben-Josef E et al. J Clin Oncol, 2014;33:261-2622

BILCAP STUDY: ADJUVANT CAPECITABINE

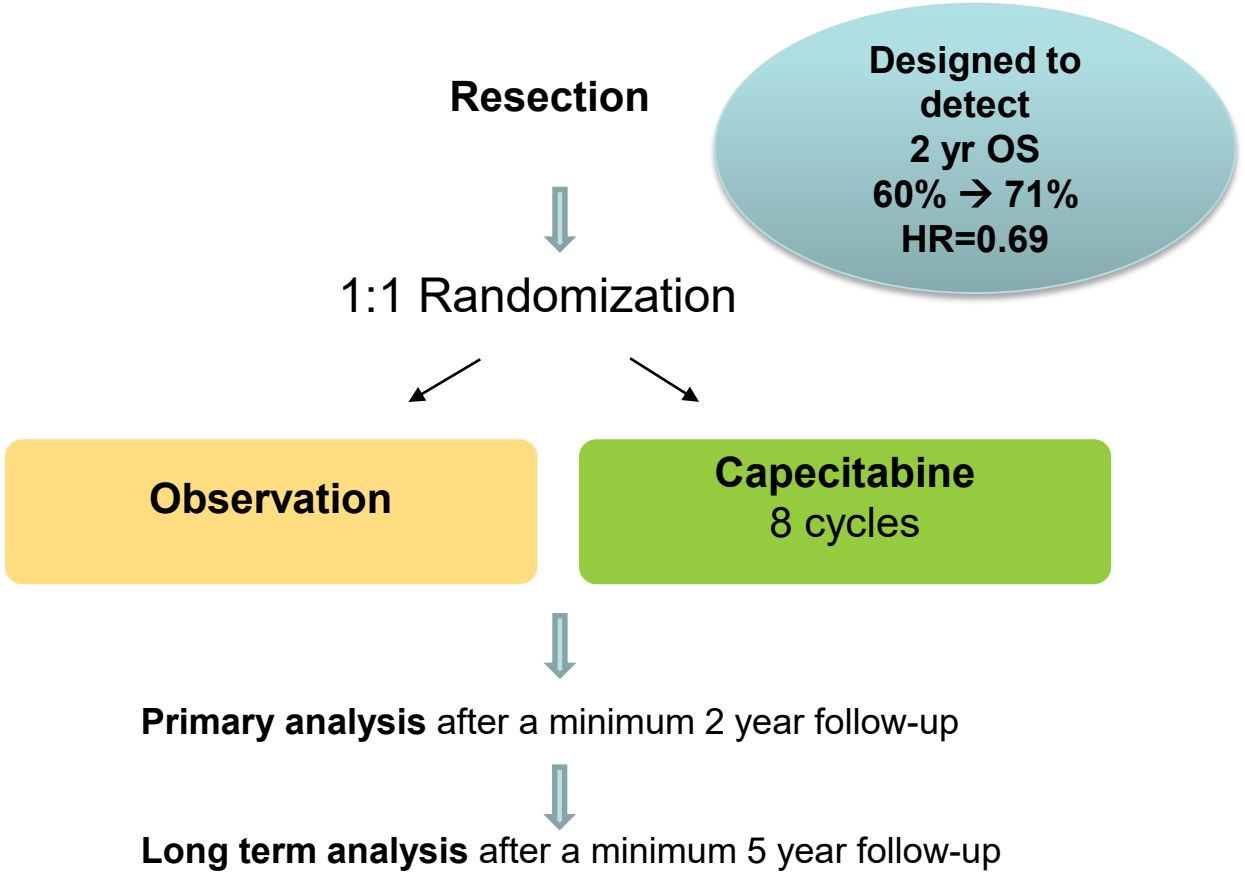
- Phase III randomized, open-label study

Interventions

- Observation vs
- Capecitabine (1250mg/m^2) twice a day on day 1 to 14 of a 3 weekly cycle for 24 weeks (8 cycles)
- Treatment initiated within 16 wks of surgery

Outcome measures

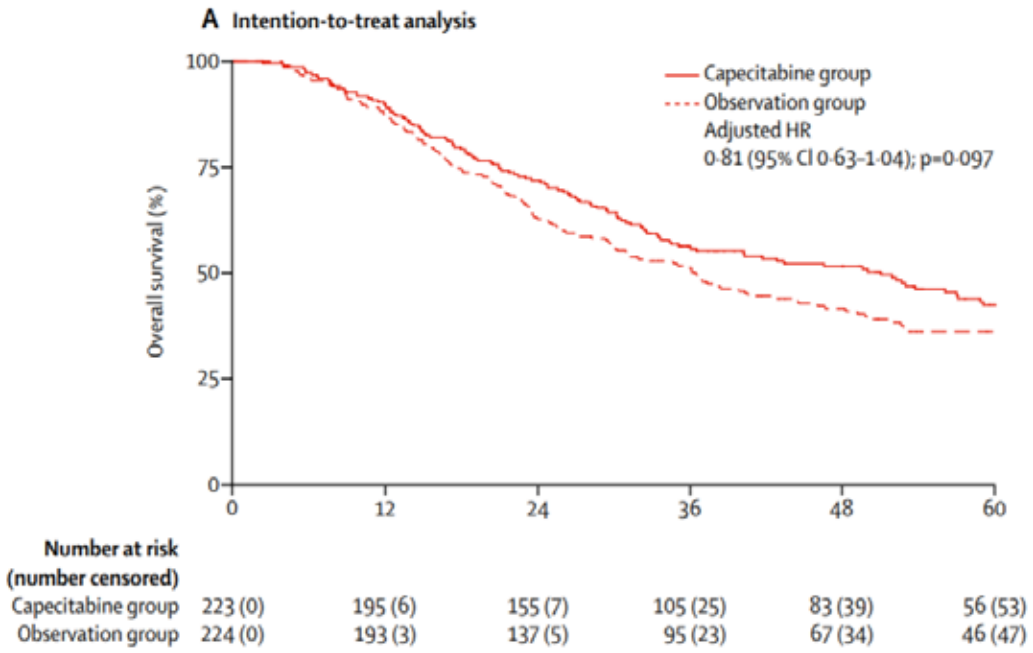
- Primary: Overall survival (OS) by intention-to-treat
- Secondary:
  - Outcome by per-protocol analysis
  - Relapse free survival (RFS)
  - Toxicity, Quality of life, Health economics



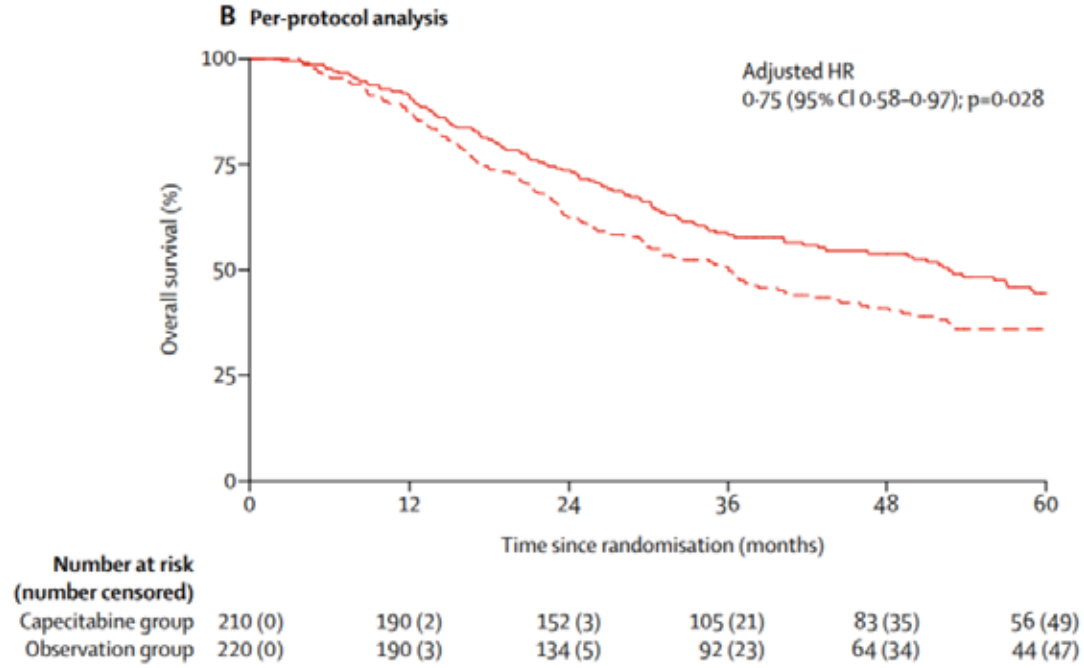
Primrose JN et al. Lancet Oncol 2019; 20: 663-73

BILCAP: Main Results

Intention-to-treat analysis



Per-protocol analysis

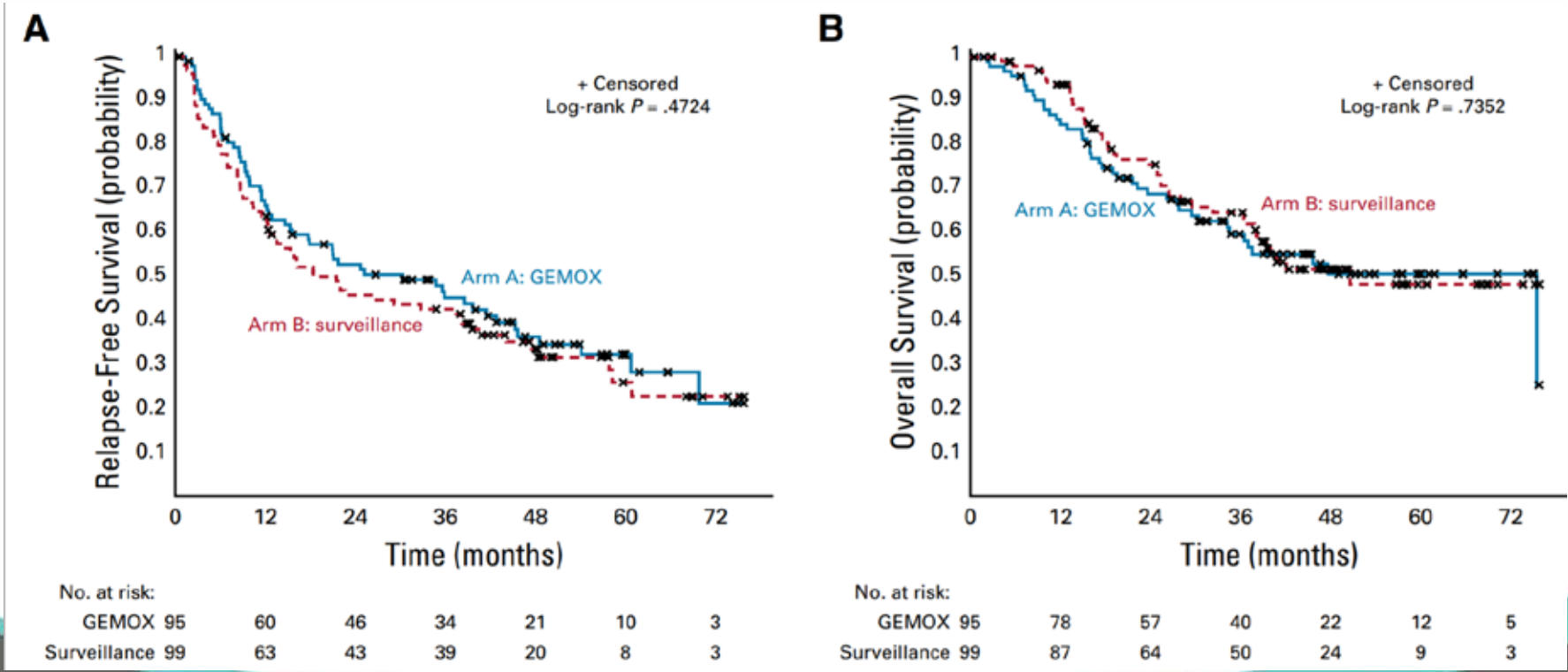


- No OS benefit in ITT analysis, but **OS benefit seen in Per-protocol Analysis**
- Difference of 17 patients ineligible/withdrawal of consent prior to starting treatment
- **Median OS: 53 mo vs 36 months**
- **Median RFS: 25.9 mo vs 17.5 mo (similar for both ITT and per-protocol analysis)**
- **Main Point: Adjuvant capecitabine is standard of care**

Primrose JN et al. Lancet Oncol 2019; 20: 663-73

? Benefit of Combination Adjuvant Chemo w/ GEMOX: Prodige 12/Accord 18/Unicancer GI STUDY

- Ph3 Adjuvant GEMOX x 6 mo vs surveillance
- Primary Endpoint: RFS / Secondary Endpoint: OS
- **Conclusion: No benefit of adjuvant GEMOX**



Edeline J et al. J Clin Oncol 2019; 37: 658-667.

BILCAP vs PRODIGE 12

	BILCAP (ITT Analysis)				PRODIGE 12			
	Cape N=223	Obs N=224	HR (95% CI)	p	GEMOX N=95	Obs N=99	HR (95% CI)	p
Median RFS	24.4 mo	17.5 mo	0.75 (0.58 – 0.98)	0.033	30.4 mo	18.5 mo	0.88 (0.62-1.25)	0.48
Median OS	51.1 mo	36.4 mo	0.81 (0.63-1.04)	0.097	75.8 mo	50.8 mo	1.08 (0.70-1.66)	0.74

- Possible reasons for conflicting outcomes
  - Different primary endpoint (OS in BILCAP vs RFS in PRODIGE 12)
  - Greater statistical power in BILCAP vs PRODIGE
  - Effects on OS benefit with therapy received at time of recurrence
- ACTICCCA-1 Trial Ongoing: Adjuvant Gemcitabine/Cisplatin vs Capecitabine

Primrose JN et al. Lancet Oncol 2019; 20: 663-73.
Edeline J et al. J Clin Oncol 2019; 37: 658-667.

Adjuvant Therapy Conclusions

- Adjuvant capecitabine prolongs survival in all grossly resected biliary tract cancers and is standard of care

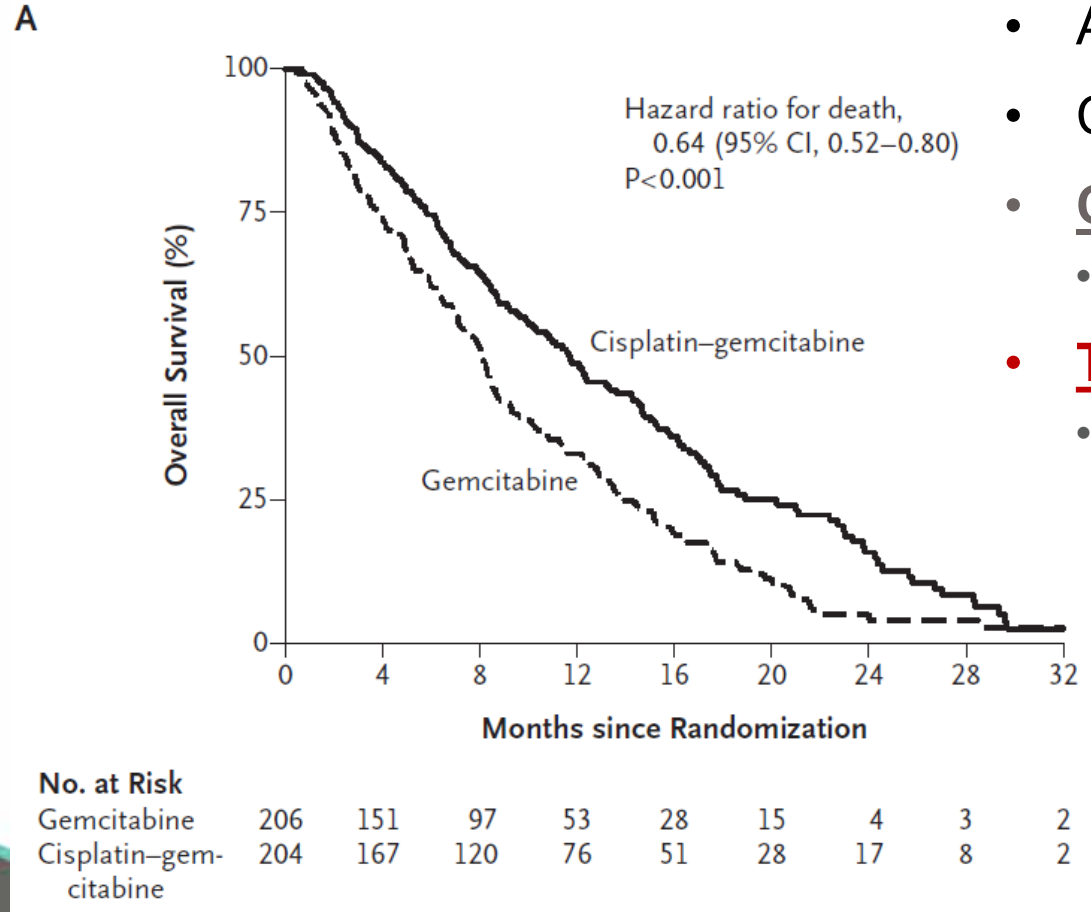
- Role of radiation for node/margin+ disease remains unclear although retrospective data supports its use
  - T2 or greater, M0 gallbladder
  - Extrahepatic disease (especially node+ or margin + based on SWOG S0809)

- Role of adjuvant combo chemo remains unclear (await ACTICCA-1 results)

2019 ASCO Practice Guideline for Resectable Biliary Tract Cancers:
Schroff RT et al. J Clin Oncol 2019; 37 (12): 1015-1027

Advanced/Metastatic Disease

Advanced/Metastatic Disease:
Gemcitabine/Cisplatin is Standard of Care in 1L



- ABC-02 Trial: Randomized, phase III study
- Conducted at 37 centers in UK
- **Control arm:**
  - Gemcitabine 1000 mg/m2 Days 1, 8, 15 q28 days
- **Treatment arm:**
  - Gemcitabine 1000 mg/m2 + Cisplatin 25mg/m2 Days 1,8 q21 days

- Improved DCR: 81.4% vs. 71.8% (p=0.049)
- **Median survival 11.7 vs. 8.1 months** (p<0.001)
- Treatment compliance better in the Gem + Cis arm

Valle J. et al. N Engl J Med 2010;362:1273-81.

ABC-06: FOLFOX is Standard 2L for Metastatic Disease

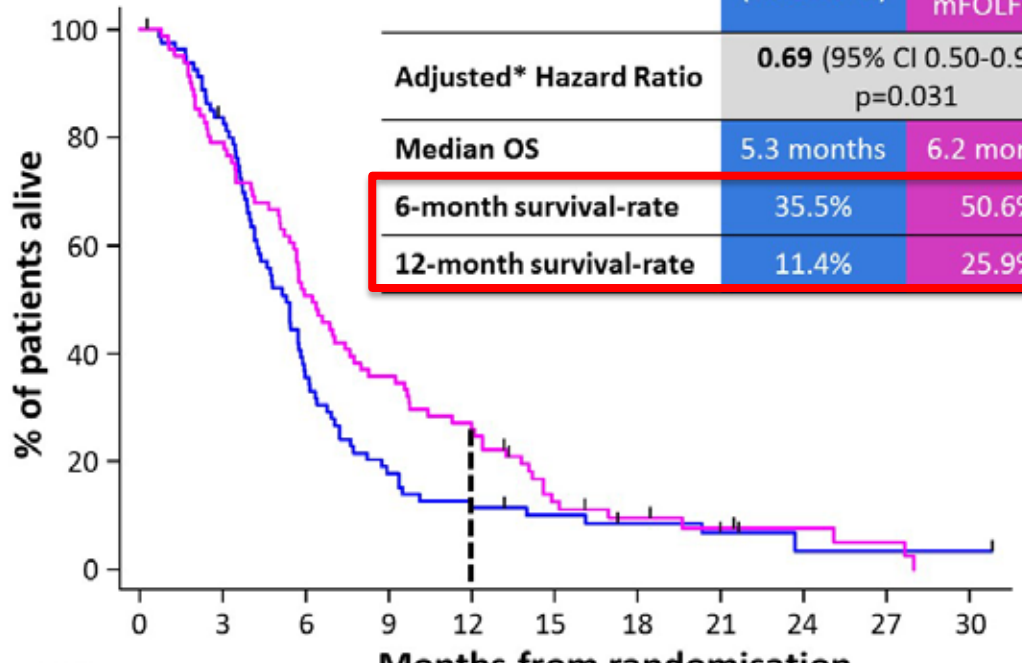
Primary end-point: Overall Survival (ITT)

- The **primary end-point was met**: adjusted* HR was 0.69 (95% CI 0.50-0.97; p=0.031) for OS in favour of ASC + mFOLFOX arm (vs ASC)

- No marked evidence was identified against the key proportional hazards assumption**; which confirmed the validity of using the Cox Regression analysis

*adjusted for platinum sensitivity, albumin and stage
**proportional hazards assumption test p-value 0.6521
ITT: intention-to-treat analysis; ASC: active symptom control

Overall survival by trial arm



	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
Adjusted* Hazard Ratio	**0.69** (95% CI 0.50-0.97) p=0.031	
Median OS	5.3 months	6.2 months
6-month survival-rate	35.5%	50.6%
12-month survival-rate	11.4%	25.9%

Lamarca A, et al. Abstract 4003. 2019 ASCO Annual Meeting

Targeted Therapy for Biliary Tract Cancers

	Intrahepatic	Extrahepatic	Gallbladder	Comments
% *FGFR2* fusions/ *FGFR1-3* alterations	**10-15**	0	3	• **Pemigatinib FDA Approved Apr 2020**[1] • ORR 35.5%; DCR ~80%
% *IDH 1/2* substitution	**15-20**	0	0	• In NCCN Guidelines; pending FDA Approval • ORR 2%, DCR 53%[2]
% MSI-H/dMMR	**1-3**	**1-3**	**1-3**	• In NCCN Guidelines • PD1 inhibitors: ORR 30-50%[3]
% *NTRK* fusions	**1-2**	**1-2**	**1-2**	• In NCCN Guidelines • Larotrectinib/Entrectinib: ORR ~40-70%[4-5]
% *BRAF V600E*	**5**	3	1	• ORR 36%, DCR 75% with BRAK/MEK inhibition[6]
% *ERBB2* (Her-2) amplification	3-4	**11**	**16**	• ORR ~40% with trastuzumab/pertuzumab[7] • Multiple ongoing basket trials with novel agents
% *ARIDA1A* Alterations	18	12	13	• Rationale for checkpoint inhibition and BET, EZH2, PARP inhibitors

KEY POINT:
Perform broad molecular profiling early in treatment course for advanced biliary tract cancer

*Table modified from 2019 ASCO Discussion by Dr. William P. Harris and data derived from Javle MM et al, Cancer 2016; 122(24) 3828-3847.

[1] Abou-Alfa GK et al. Lancet Oncol 2020; 21(5):671-684. [2]Abou-Alf GK et al. Lancet Oncol 2020; 21(6):796-807. [3]Le DT et al. N Engl J Med 2015. [4]Drilon A et al. N Engl J Med 2018;378:731-9. [5]Doebele RC et al. Lancet Oncol 2020; 21: 271–82. [6]Wainberg Z et al. ASCO GI 2019. Abstract 187. [7]Javle MM et al. ASCO GI 2017. Abstract 402.

FIGHT-202 Study: Pemigatinib in ≥2L for *FGFR* Altered Metastatic Biliary Tract Cancer

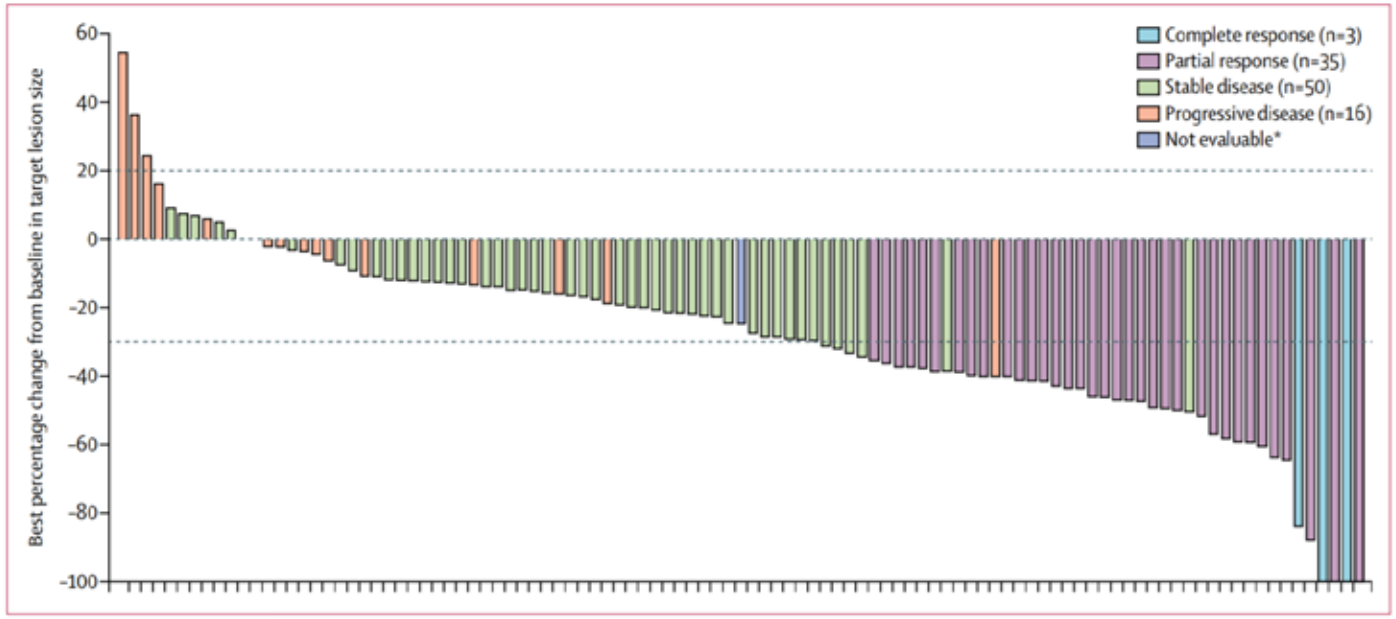
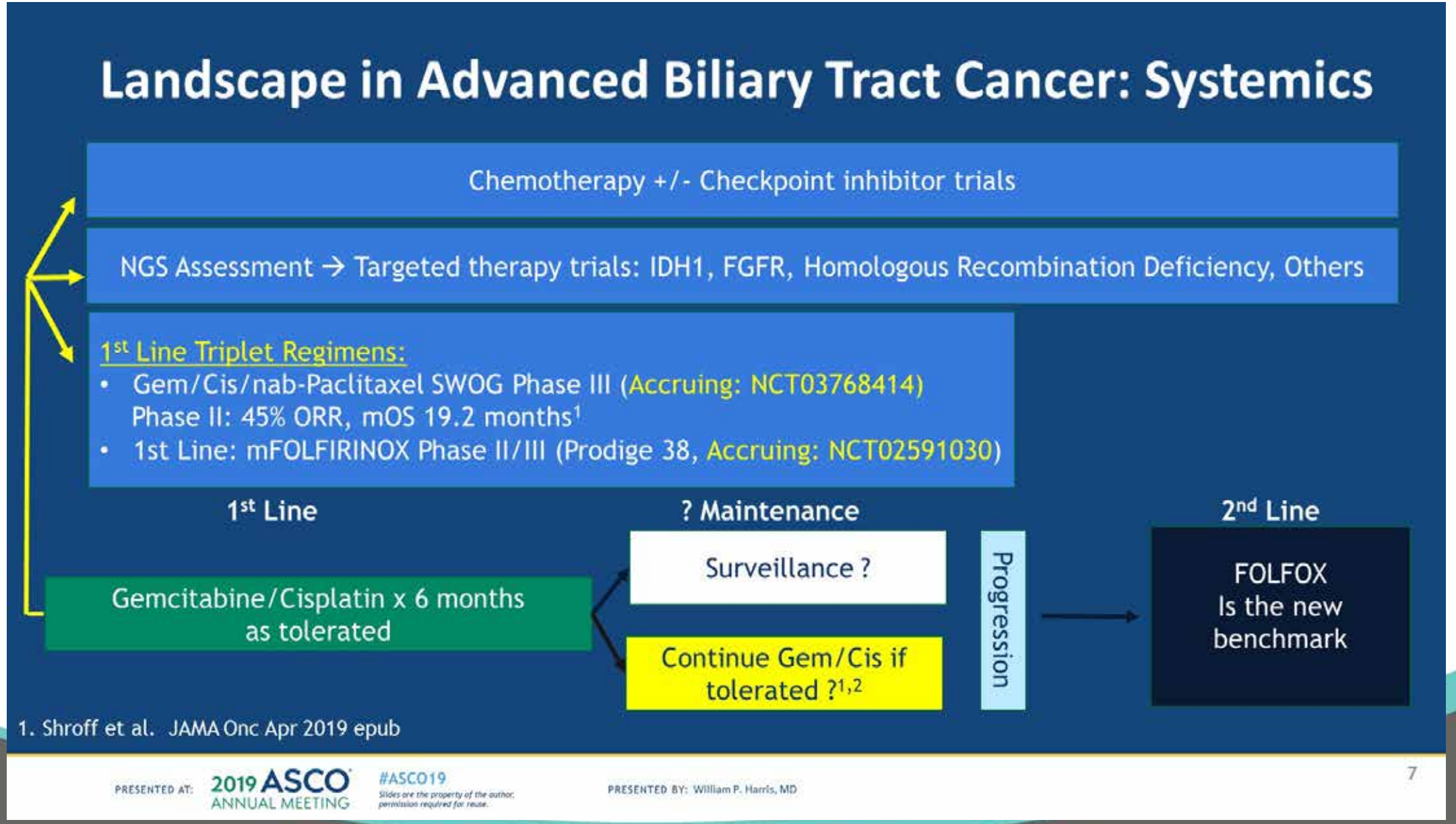


Figure 2: **Best percentage change from baseline in target lesion size for individual patients with *FGFR2* fusions or rearrangements**
Coloured bars indicate confirmed responses assessed by RECIST 1·1. FGFR=fibroblast growth factor receptor. RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1. *Patient had a decrease in target lesion size but was not evaluable for response using RECIST.

Abou-Alfa GK et al. Lancet Oncol 2020; 21(5):671-684.

- Phase 2, single arm global study
- Pts progressed 1 prior line tx, ECOG 0-2
- 3 cohorts: 1) *FGFR2* fusion/rearrangements 2) Other *FGF/FGFR* alterations 3) No *FGF/FGFR* alterations
- Tx: Pemigatinib (oral *FGFR1-3* inhibitor) 13.5 mg po daily D1-14 q21 days
- Primary endpoint: ORR
- Activity seen in *FGFR2* fusion pts w/ ORR 35.5%, DCR 82.2%
- Median PFS 6.9 mo, OS 21.1 mo
- Conclusion: Pemigatinib should be a standard of care option for advanced biliary cancers with *FGFR2* fusions

Evolving Landscape of Biliary Tract Cancer



Presented By William Harris at 2019 ASCO Annual Meeting

Conclusions for Biliary Tract Cancer

- Biliary tract cancer should be diagnosed in the correct clinical context
- Adjuvant capecitabine x 6 months prolongs survival for resected biliary tract cancer
- Possible benefit of adjuvant chemoradiation in retrospective series
  - Extrahepatic cholangiocarcinoma (especially node+ or margin +)
  - T2 or greater, M0 gallbladder
- ≥T1b (muscle invasive) gallbladder ca require extended hepatectomy + LN staging
- Gemcitabine + Cisplatin is the standard of care 1L treatment for advanced disease
- FOLFOX is now the established 2nd line treatment for advanced/metastatic disease
- Molecular profiling should be performed → High frequency of actionable mutations
- Pemigatinib is FDA approved for advanced biliary tract cancers with *FGFR2* fusions
- Consider clinical trial enrollment when available