Adjuvant Therapy Biliary Cancer Yes!!!!

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Adjuvant Treatment in Biliary Tract Cancer

Background

- 11,420 new cases of Biliary Cancer diagnosed
- 3,710 deaths from these cancers occurred
- Only 1 in 5 diagnosed with resectable disease

Adjuvant Treatment in Biliary Tract Cancer

Rational

- High risk of relapse following surgery for localized Biliary Tract Cancer
- 5-yr OS=31% in resected intrahepatic cholangiocarcinoma; Median survival =27 months[1]
- No proven (neo)-adjuvant treatment exists
- In the palliative setting:

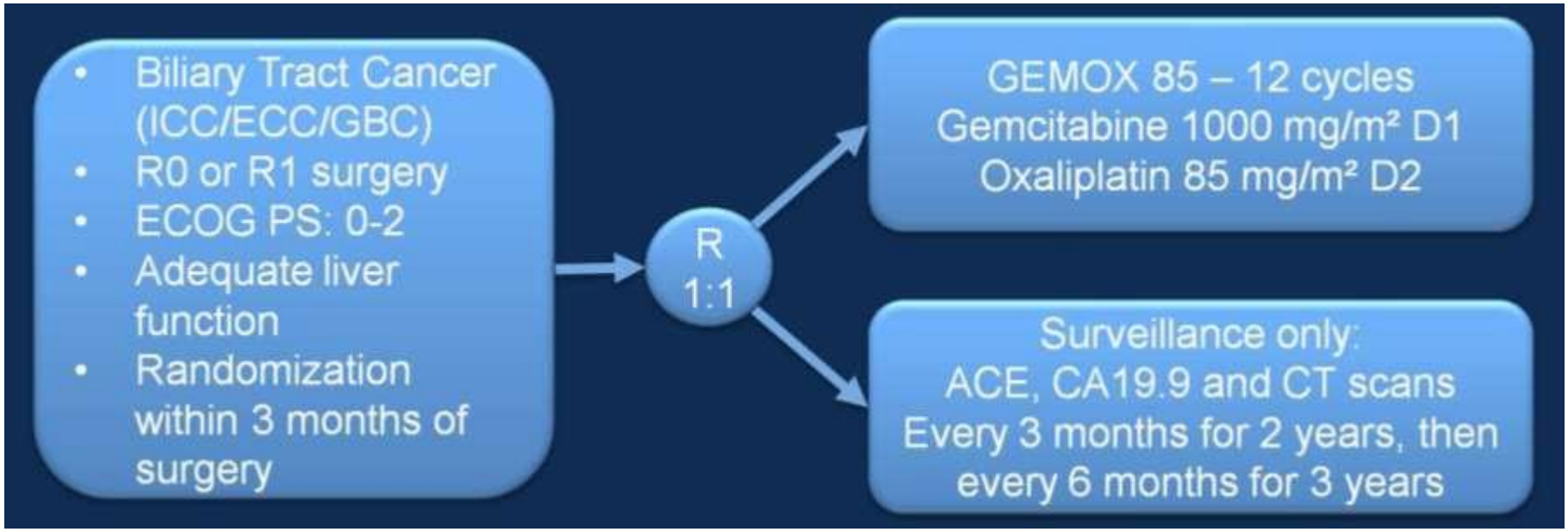
-Combination of gemcitabine-cisplatin improves Overall Survival (ABC-02[2] and BT22[3])

-GEMOX is considered an active regimen based on data from phase II trials[4]

[1]De Jong et al .J Clin Oncol 2011; [2]Valle NEJM 2010; [3]Okusaka Brit J Cancer 2010; [4] Andre Brit J Cancer 2008

GEMOX vs surveillance following surgery of localized biliary tract cancer: results of the PRODIGE 12 - ACCORD 18 (UNICANCER GI) phase III trial

DESIGN



Stratification factors: tumor site(ICC vs ECC/Hilar vs GBC); R0 vs R1; N0 vs N+ vs NX; center.

Endpoints

- 2 Co-primary endpoints
  - Relapse-free survival (RFS)
  - Quality of life
- Hypothesis: Increase median RFS from 18 to 30 mos (HR=0.60)
- Secondary endpoints: OS, DFS, Tolerability/Toxicity, Translational research

Patients and tumors

- 196 patients included, 2 withdrew consent (GEMOX arm)

	GEMOX (N=95)	Surveillance (N=99)
Gender: M:F	57 (60%) : 38 (40%)	50 (50%) : 49 (50%)
Age (years): median [min-max]	63.0 [33.0-83.0]	63.0 [40.0-80.0]
ECOG PS		
0	51 (54%)	63 (64%)
1	37 (39%)	31 (31%)
2	5 (5%)	2 (2%)
unknown	2 (2%)	3 (3%)

	GEMOX (N=95)	Surveillance (N=99)
Primary tumor		
Intrahepatic Cholangiocarcinoma	41 (43%)	45 (46%)
Perihilar Cholangiocarcinoma	10 (11%)	5 (5%)
Distal Cholangiocarcinoma	27 (28%)	28 (28%)
Gallbladder Adenocarcinoma	17 (18%)	21 (21%)
N+	35 (37%)	36 (36%)
Nx	11 (12%)	15 (15%)
R1	13 (14%)	12 (12%)

Treatment

GEMOX Arm:

- Median of 12 cycles

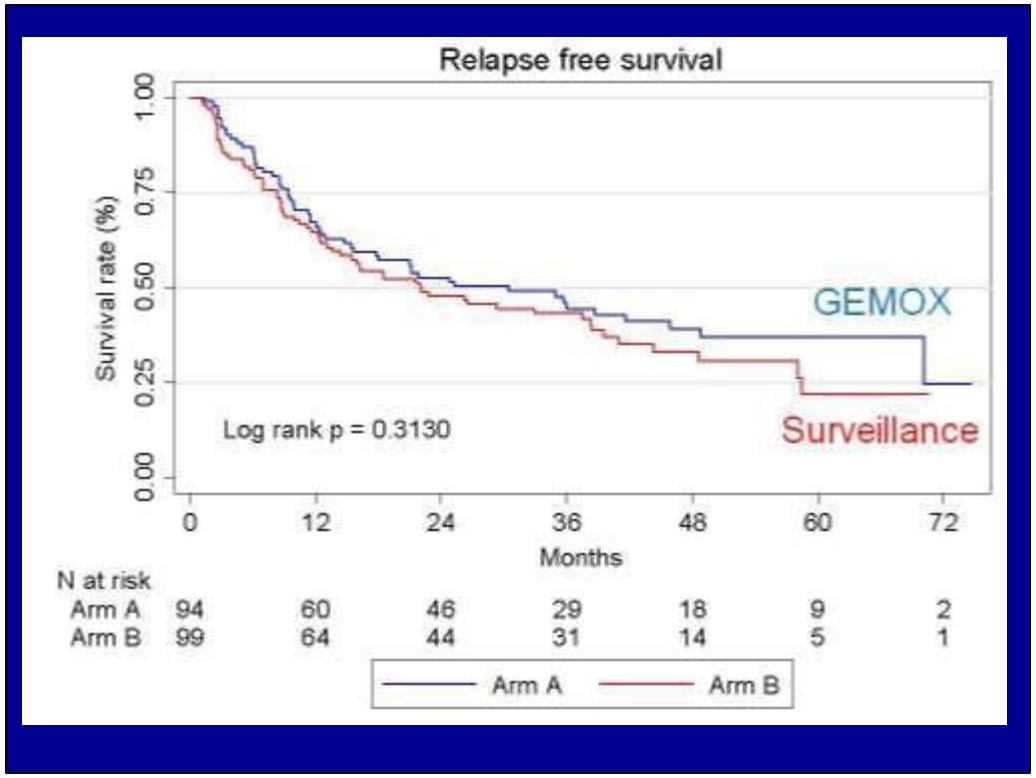
- Mean of 9.3 cycles

-Median of 10 cycles with oxaliplatin

-Mean of 8.5 cycles with oxaliplatin

-31/94 patients (33.0%) had 12 cycles with GEMOX

Relapse-Free Survival

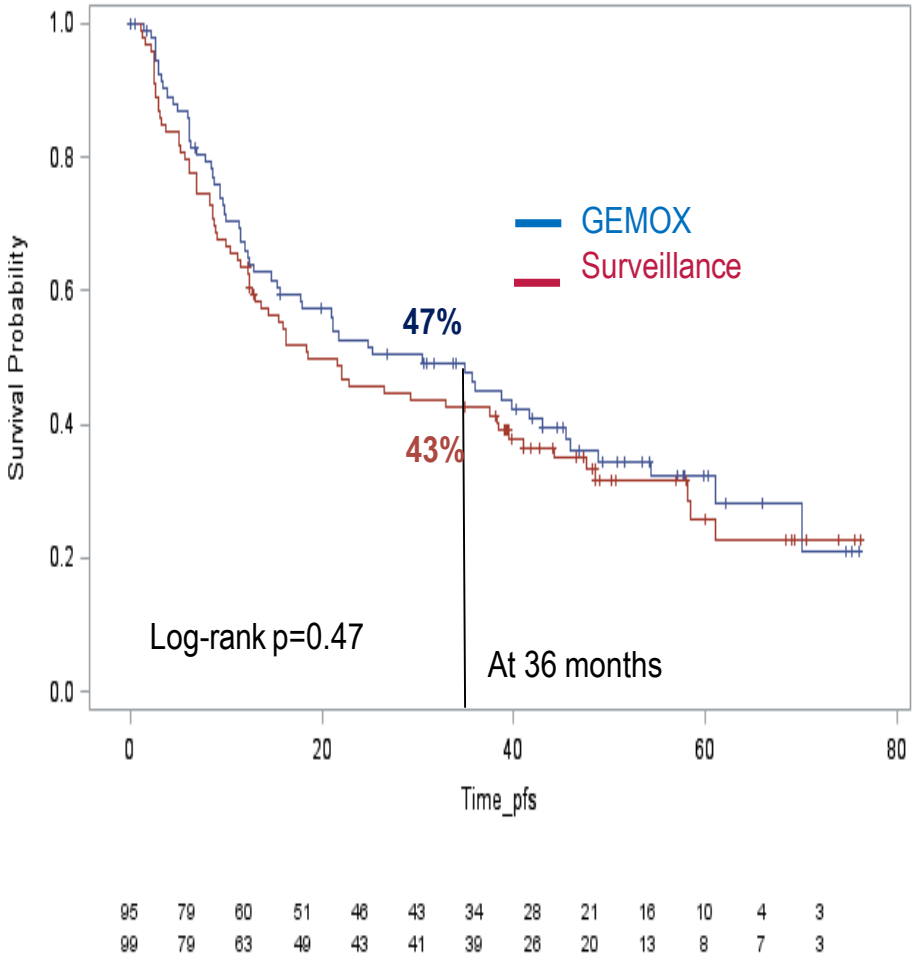


	GEMOX	Surveillance
Median RFS	30.4 months [95% CI: 15.4-45.8]	22.0 months [95%CI: 13.6-38.3]
4-year RFS	39.3% [95%CI: 28.4-50.0]	33.2% [95%CI: 23.1-43.7]

Median FU: 44.3 months

HR= 0.83 (95% CI:0,58-1.19), p=0.31

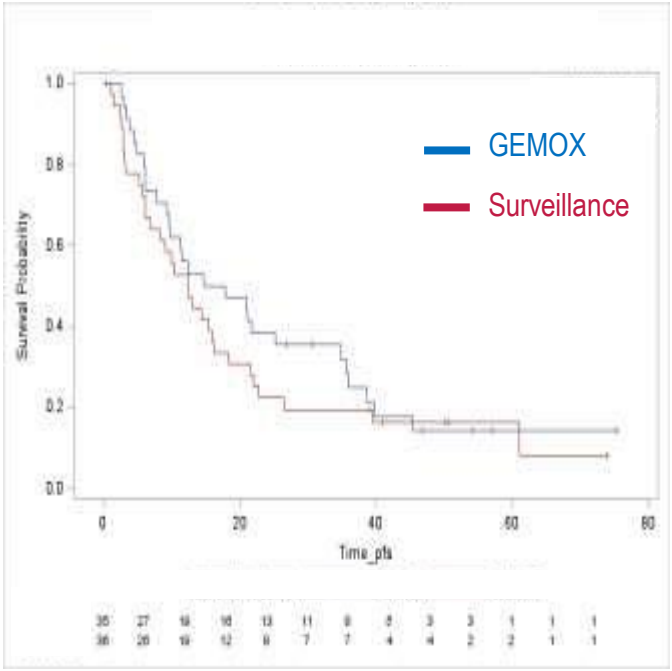
Relapse-Free Survival



- Median follow-up of 46.5 months
- 126 events reached:
  - GEMOX: 55 progressions and 4 deaths
  - Surveillance: 61 progressions and 6 deaths
- Median RFS:
  - GEMOX: 30.4 months [15.4-43.0]
  - Surveillance: 18.5 months [12.6-38.2]
- HR=0.88 [0.62-1.25], p=0.47

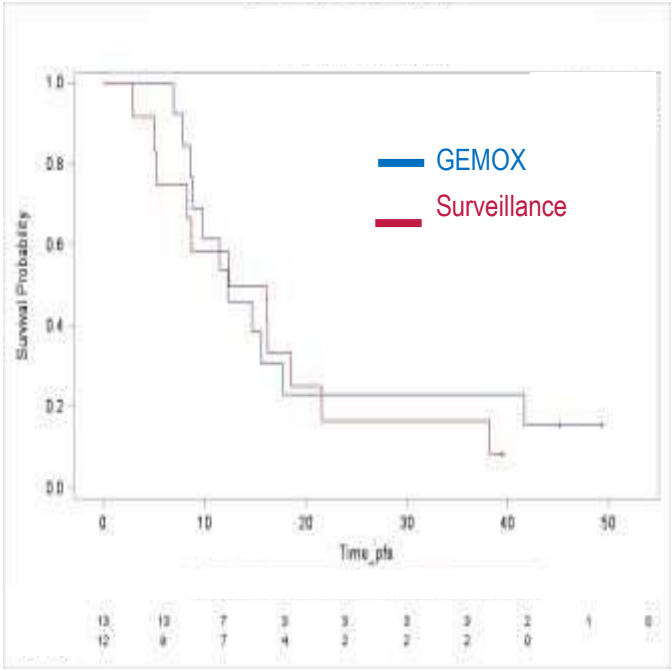
RFS in subgroups

N+



HR=0.81, p=0.41

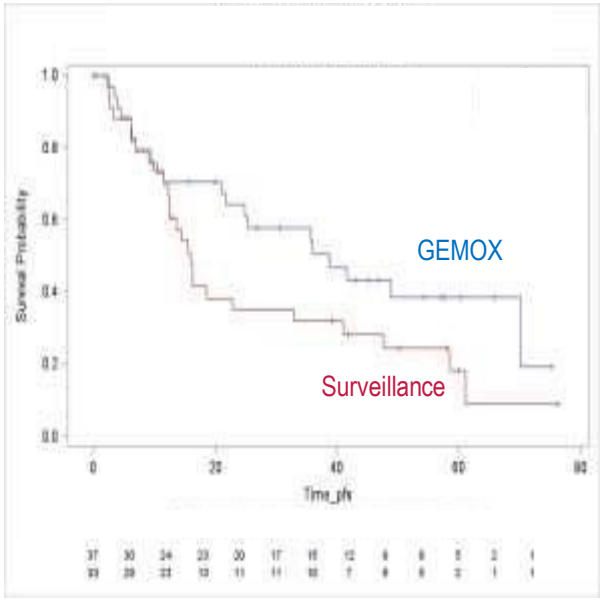
R1



HR=0.83, p=0.68

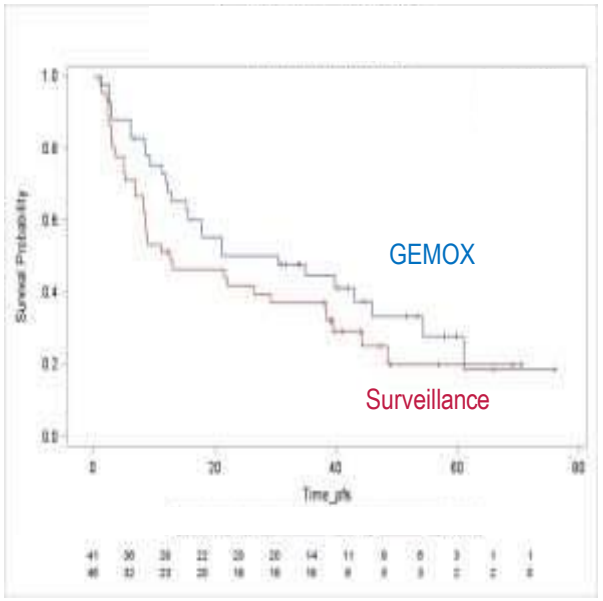
RFS in subgroups

Extrahepatic Cholangiocarcinoma



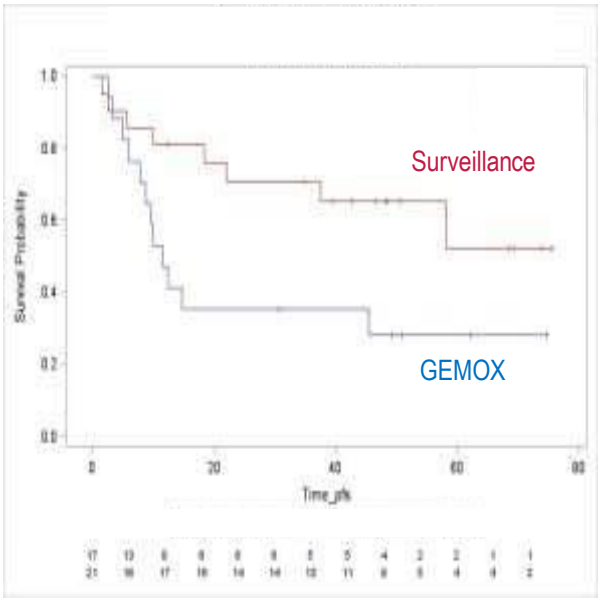
HR=0.60, p=0.09

Intrahepatic Cholangiocarcinoma



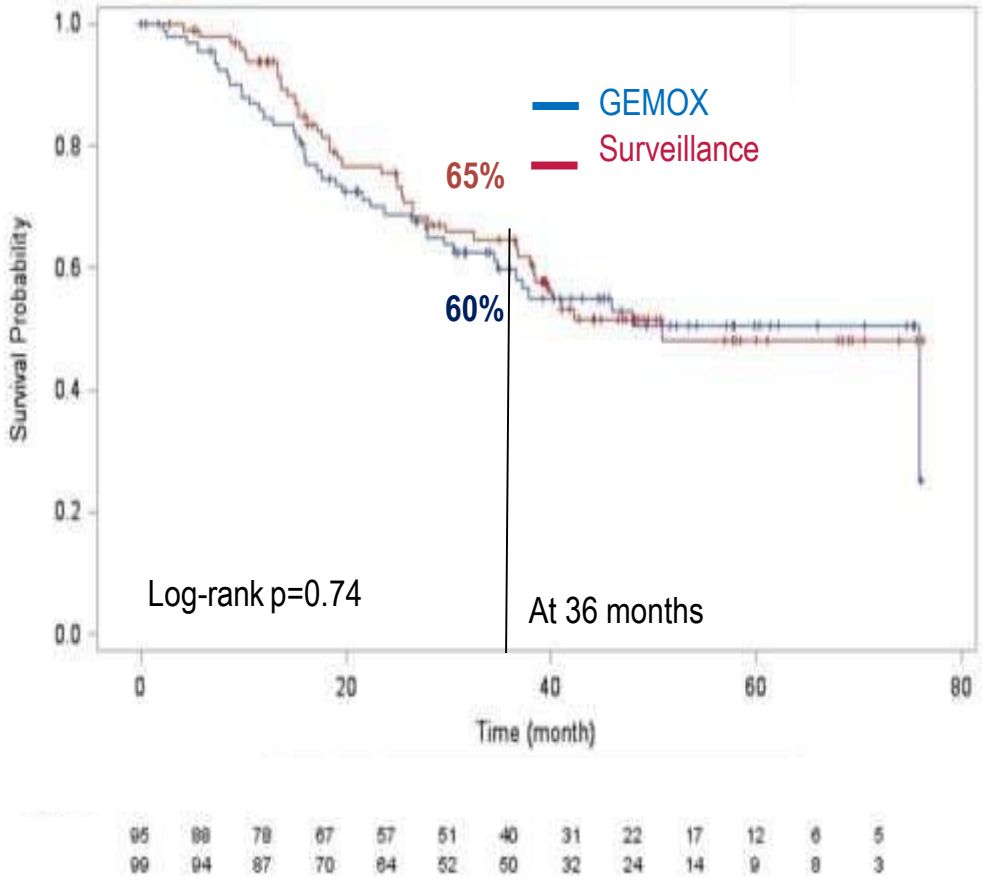
HR=0.71, p=0.20

Gallbladder Cancer



HR=2.56, p=0.042

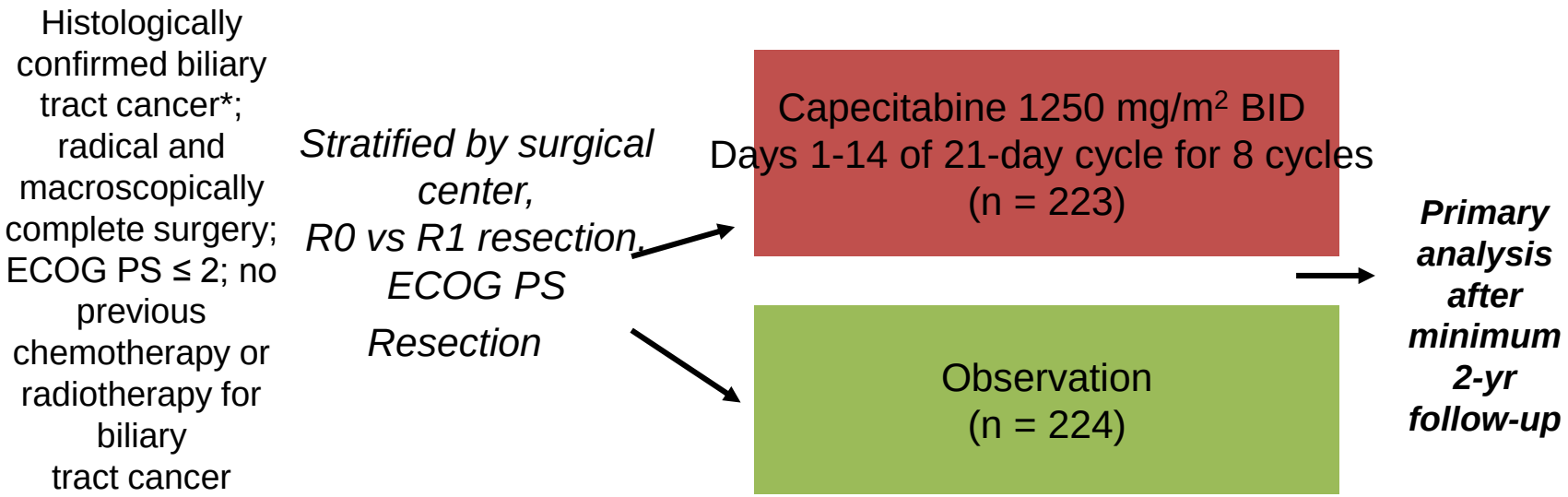
Overall Survival



- 41 deaths in each arm
  - 42% of patients died
- Median OS:
  - GEMOX: 75.8 months [34.4-NR]
  - Surveillance: 50.8 months [38.0-NR]
- HR= 1.08 [0.70-1.66], p=0.74
- No trend toward benefit in any subgroup
  - Significantly worse survival in GBC, HR=3.39, p=0.025

BILCAP: Study Design

Open-label, randomized, controlled phase III trial



*Included: intrahepatic CC, hilar CC, muscle-invasive gallbladder cancer, and lower common bile duct CC
Excluded: pancreatic, ampullary, mucosal (T1a) gallbladder cancers; incomplete recovery from prior surgery

- Primary endpoint: OS
- Secondary endpoints: RFS, toxicity, QoL, health economics

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BILCAP: Baseline Characteristics

Characteristic, %	Capecitabine Arm (n = 223)	Observation Arm (n = 224)
Male	50	50
Median age, yrs (IQR)	62 (55-68)	64 (55-69)
Tumor site ▪ Intrahepatic CC ▪ Hilar CC ▪ Muscle-invasive gall bladder carcinoma ▪ Lower common bile duct CC	 19 29 17 34	 18 28 18 36
Resection status, R0/R1	62/38	63/38
ECOG PS, 0/1/2	5/52/3	45/52/3
Tumor size, mm (IQR)	25 (19-45)	25 (20-44)
Lymph node status, N0/N1/not evaluable	45/48/7	48/46/6

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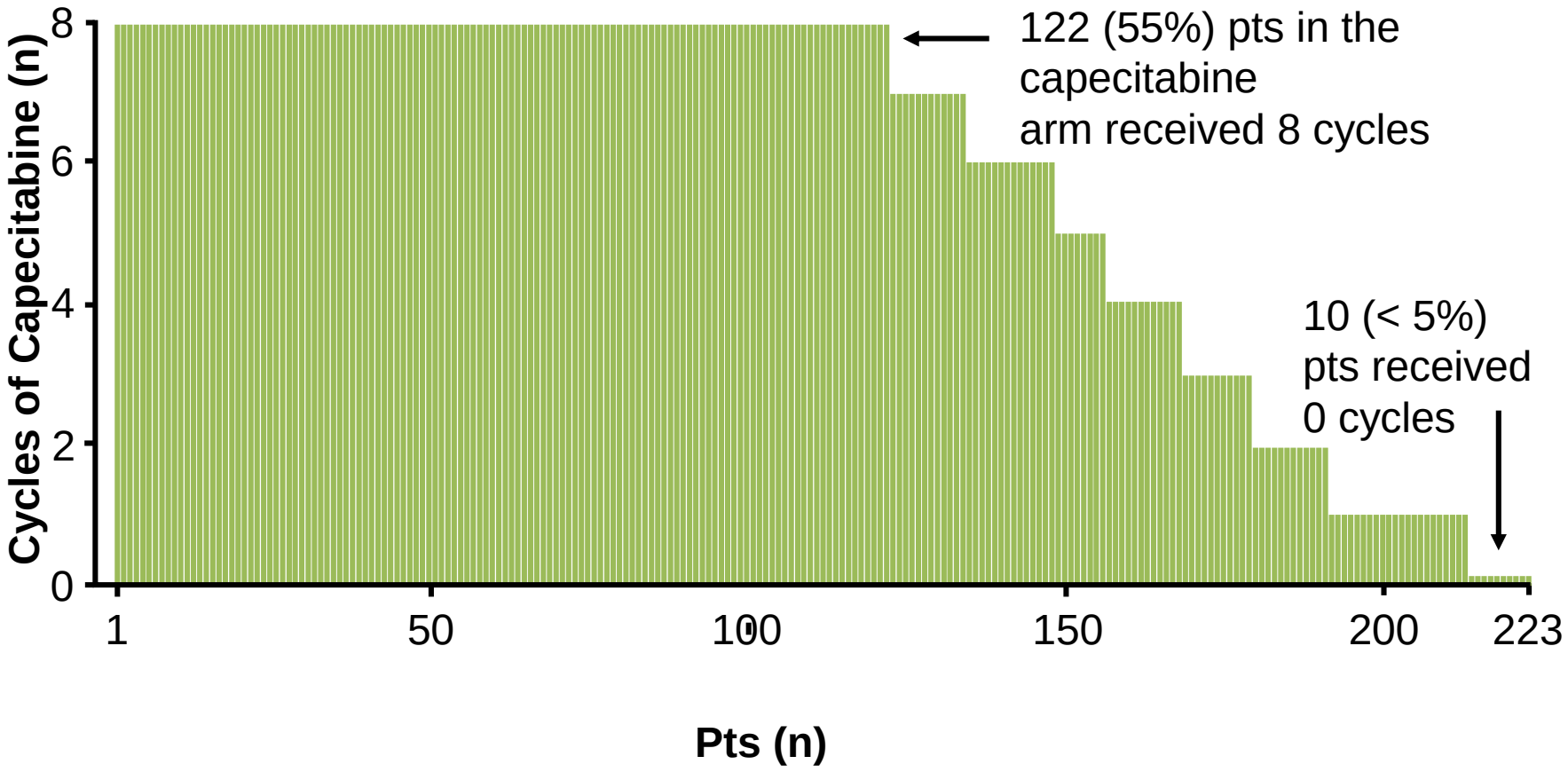
BILCAP: Treatment Compliance

Median capecitabine dose: 1250 mg/m^2 BID (IQR: 1061-1250 mg/m^2)



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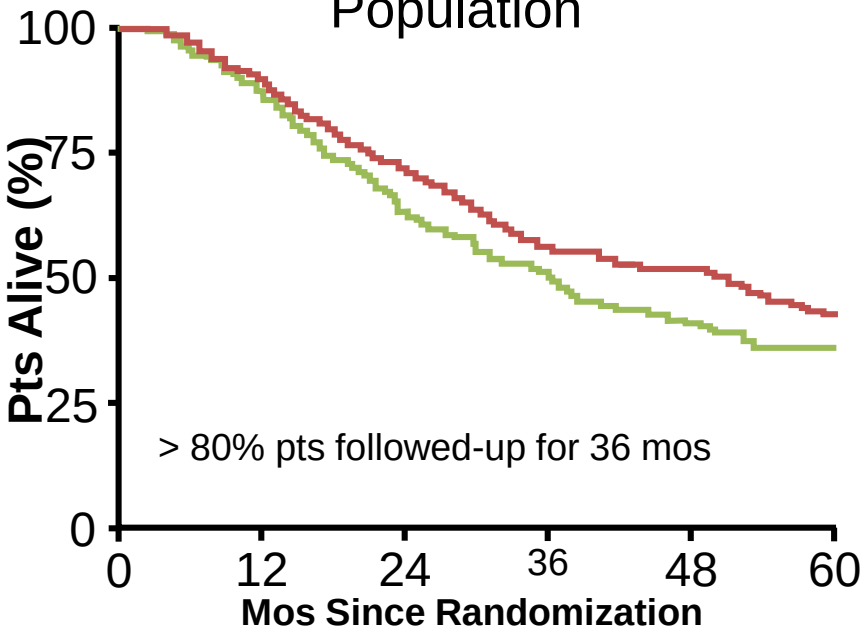
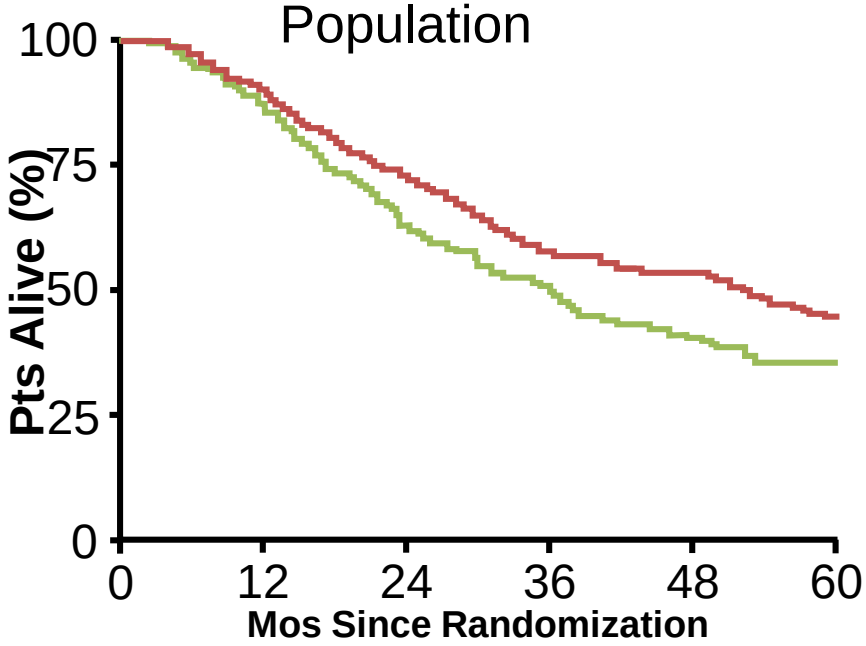
BILCAP: OS

Sensitivity analyses adjusting for further prognostic factors (gender, nodal status, disease grade) HR 0.70 (95% CI: 0.55-0.91; *P* = .007)

ITT Population



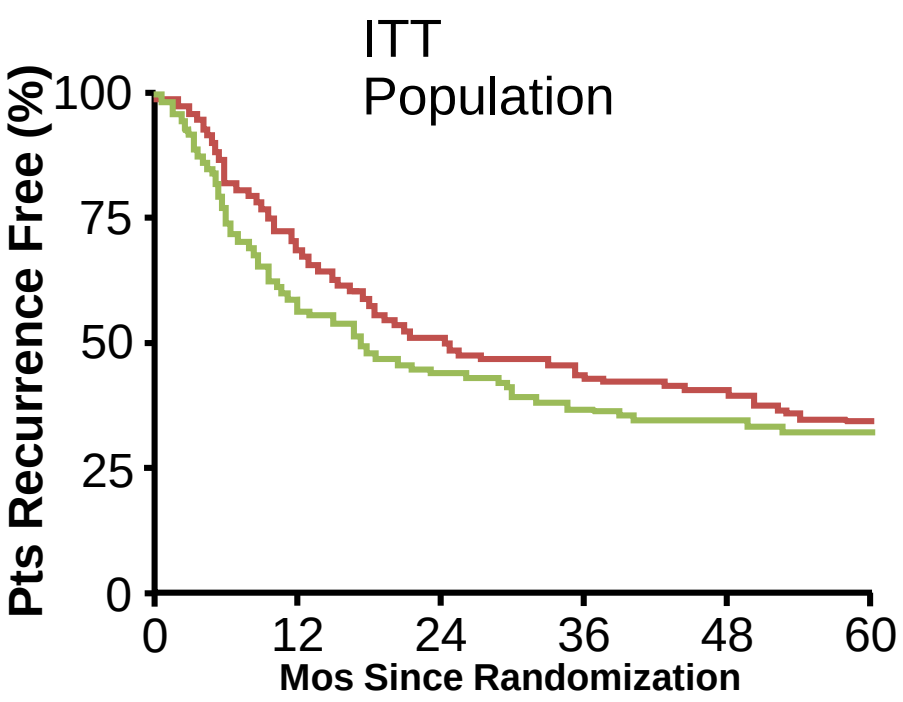
Per Protocol Population

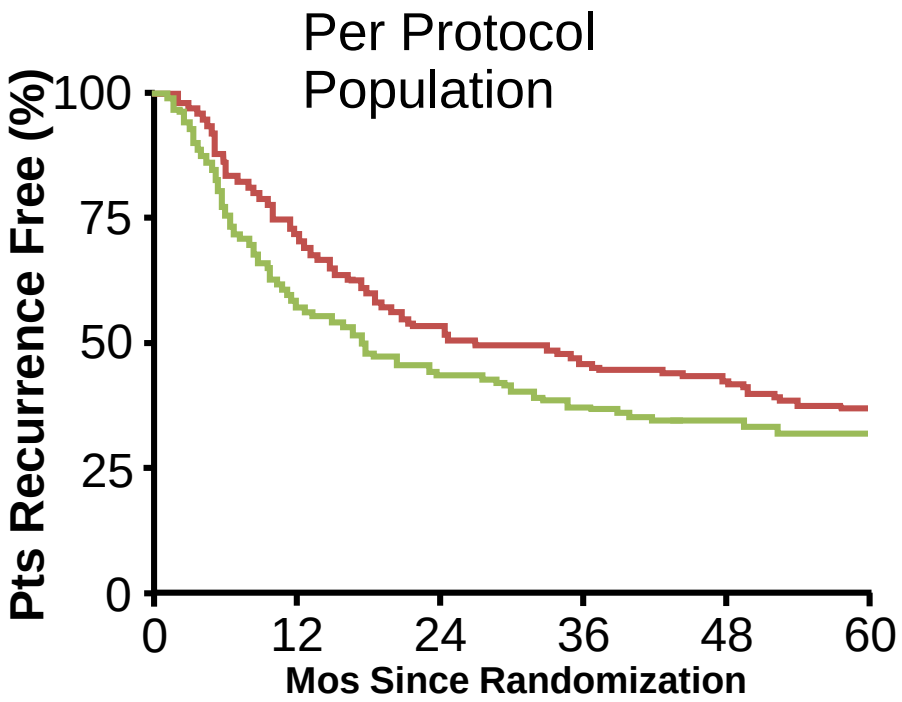


Treatment	Median OS, Mos (95% CI)	HR (95% CI)
Capecitabine	51.1 (34.6-59.1)	0.81 (0.63-1.04) P = .097
Observation	36.4 (29.7-44.5)	

Treatment	Median OS, Mos (95% CI)	HR (95% CI)
Capecitabine	52.7 (40.3-NR)	0.75 (0.58-0.97) P = .028
Observation	36.1 (29.6-44.2)	

BILCAP: Relapse-Free Survival





Treatment	Median RFS, Mos (95% CI)	HR (95% CI)
Capecitabine	24.6 (18.9-36.7)	0.76 (0.58-0.99) P = .039
Observation	17.6 (12.8-27.6)	

Treatment	Median RFS, Mos (95% CI)	HR (95% CI)
Capecitabine	25.9 (19.8-46.3)	0.71 (0.54-0.92) P = .011
Observation	17.6 (12.0-23.8)	

BILCAP: Safety and QoL

Safety population included 213 patients who received capecitabine

Adverse Event, n (%)	All Grades	Grades 1/2	Grades 3/4
Fatigue	175 (82)	159 (75)	16 (8)
Plantar-palmar erythema	174 (82)	130 (61)	44 (21)
Diarrhea	137 (64)	121 (57)	16 (8)
Nausea	108 (51)	106 (50)	2 (1)
Mucositis/stomatitis	96 (45)	94 (44)	2 (1)
Vomiting	50 (24)	49 (23)	1 (0.5)
Neutropenia	49 (23)	45 (21)	4 (2)
Hyperbilirubinemia	45 (21)	42 (20)	3 (1)
Thrombocytopenia	26 (12)	25 (12)	1 (0.5)
Alopecia	20 (9)	20 (9)	0 (0)

SAE	n (%)
All	93 (44)
Pts with ≥ 1 SAE	69 (32)
SAEs by treatment arm	**n**
Capecitabine arm ▪SAE	47 (64 events) 30 (33 events)
Observation arm ▪SAE resulting in death	22 (29 events) 3

QoL was not reduced in capecitabine arm compared with placebo

Conclusions

- YES to Adjuvant Chemotherapy in Biliary Cancers
- Adjuvant GEMOX in the ACCORD trial was underpowered.
- Adjuvant capecitabine associated with improved OS in pts with resected biliary tract cancer in the BILCAP trial
  - The authors suggested that capecitabine should become standard of care in this setting
- Capecitabine treatment produced modest toxicity
- QoL in capecitabine arm comparable to observation arm

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Obrigado!!