# Cholangiocarcinoma
## comprehensive care
## Oncologist perspective

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April 28th, 2021

SRINAGARIND
Center of Excellence

# Disclosure

## Invited speaker

- AstraZeneca, Baxter, BMS, Eisei, MSD, Novartis, Takeda

## Clinical trials

- AstraZeneca, Roche

# OUTLINES

## Introduction

- Epidemiology
- Update in diagnosis and classification

## Systemic therapy in CCA

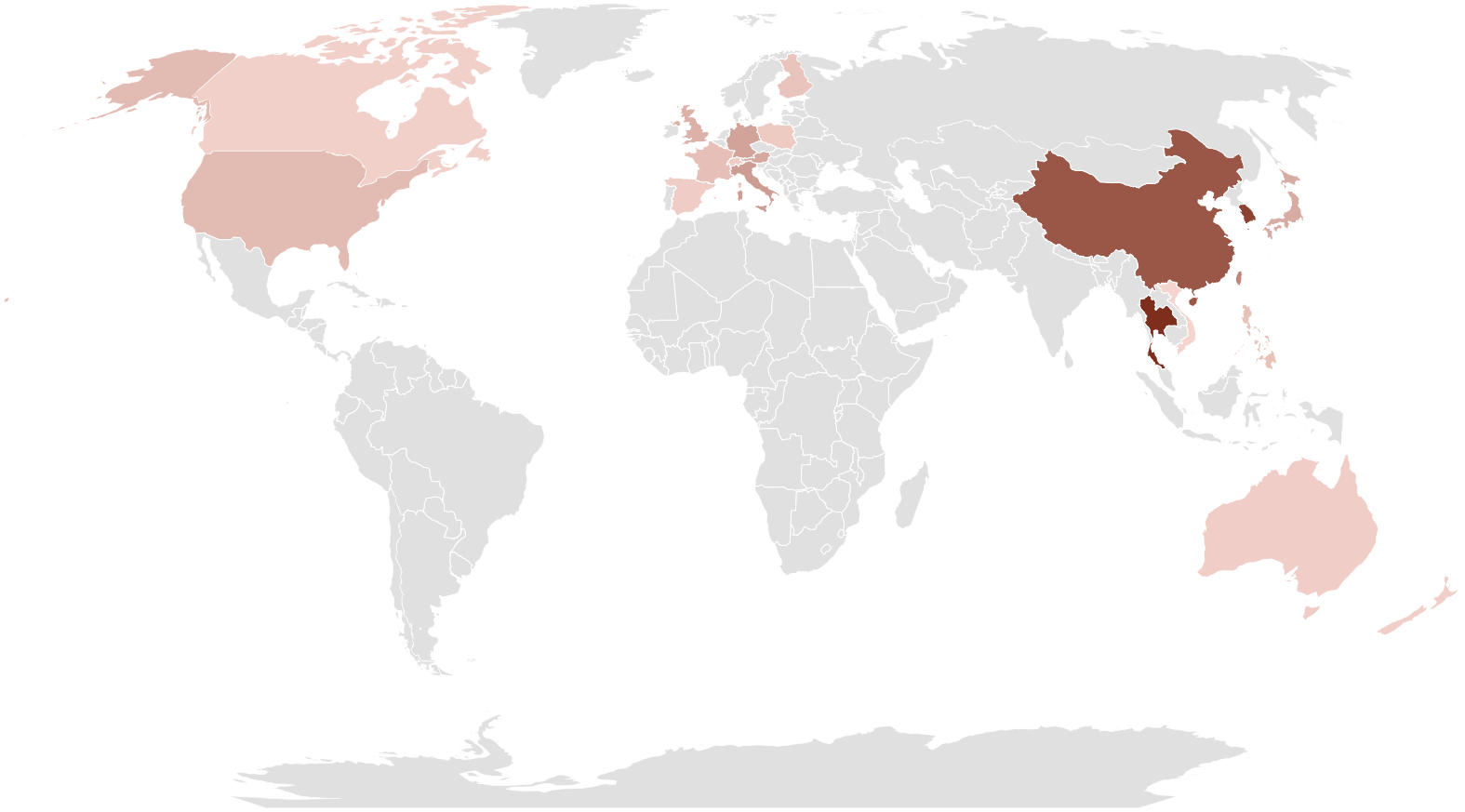
- Update in systemic therapy
- Real-world data
- Ongoing clinical trials

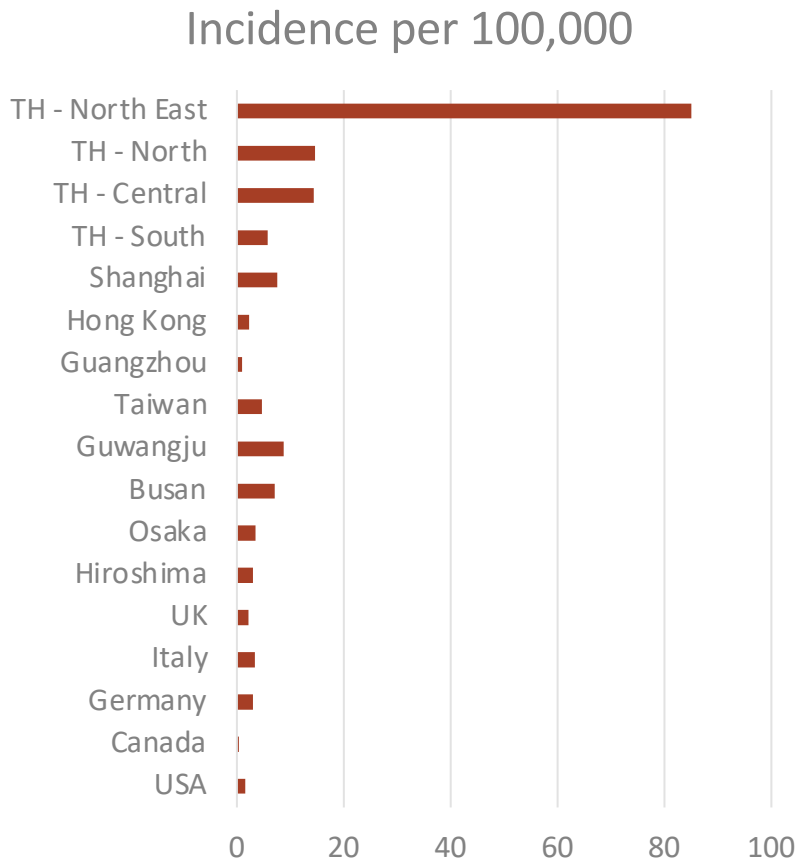
## Comprehensive care in CCA

- MDT

# Introduction

# Cholangiocarcinoma in Thailand

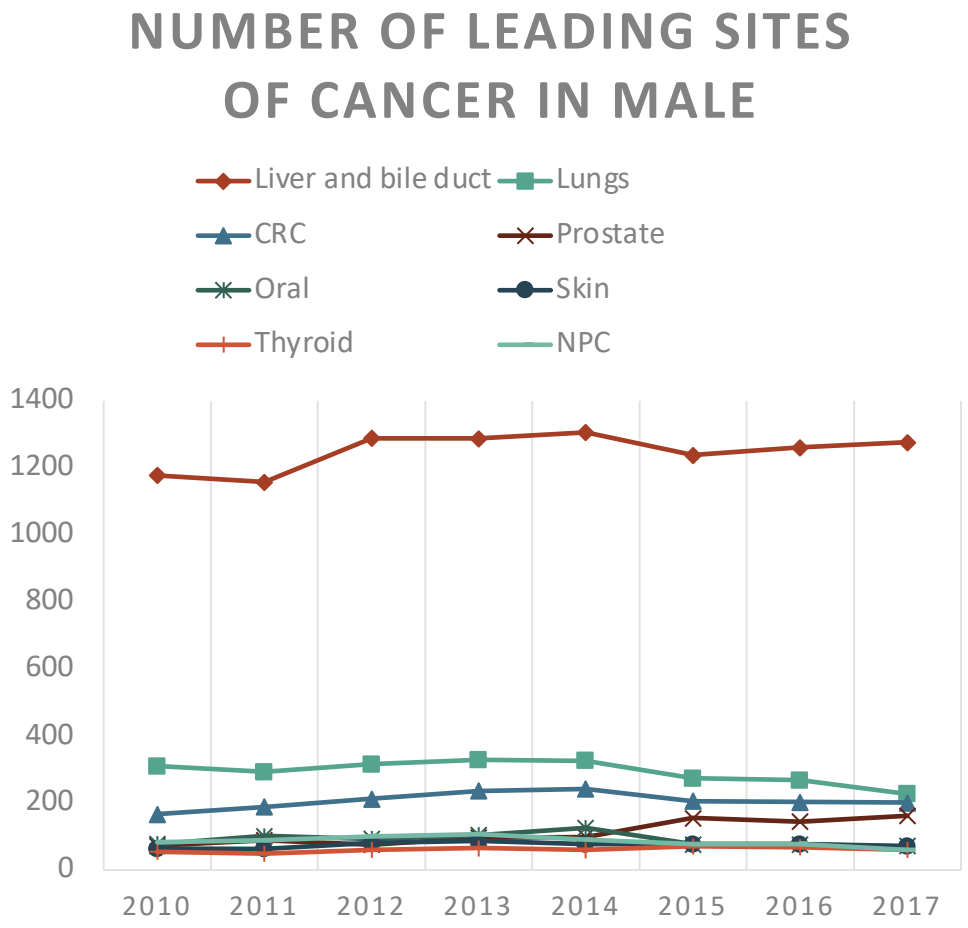


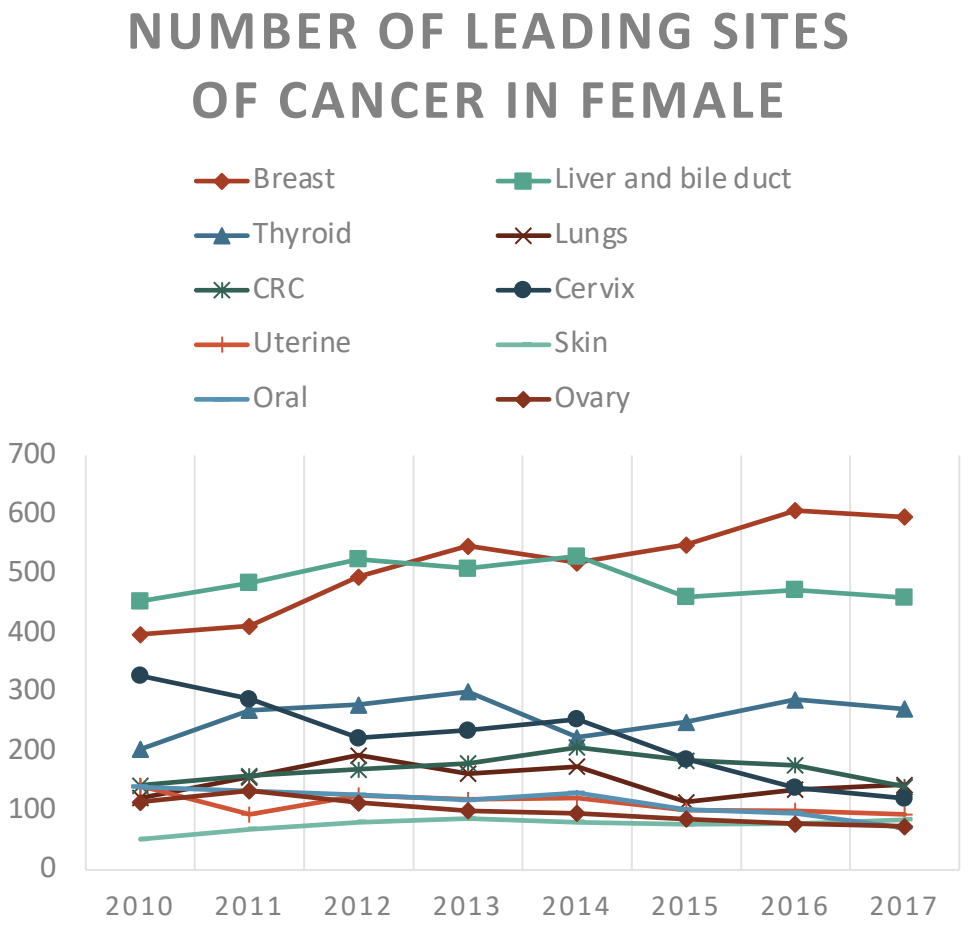





1. Adapted from Jesus M. Banales, Nature Reviews Gastroenterology & Hepatology volume 13, pages261–280(2016). doi:10.1038/nrgastro.2016.51

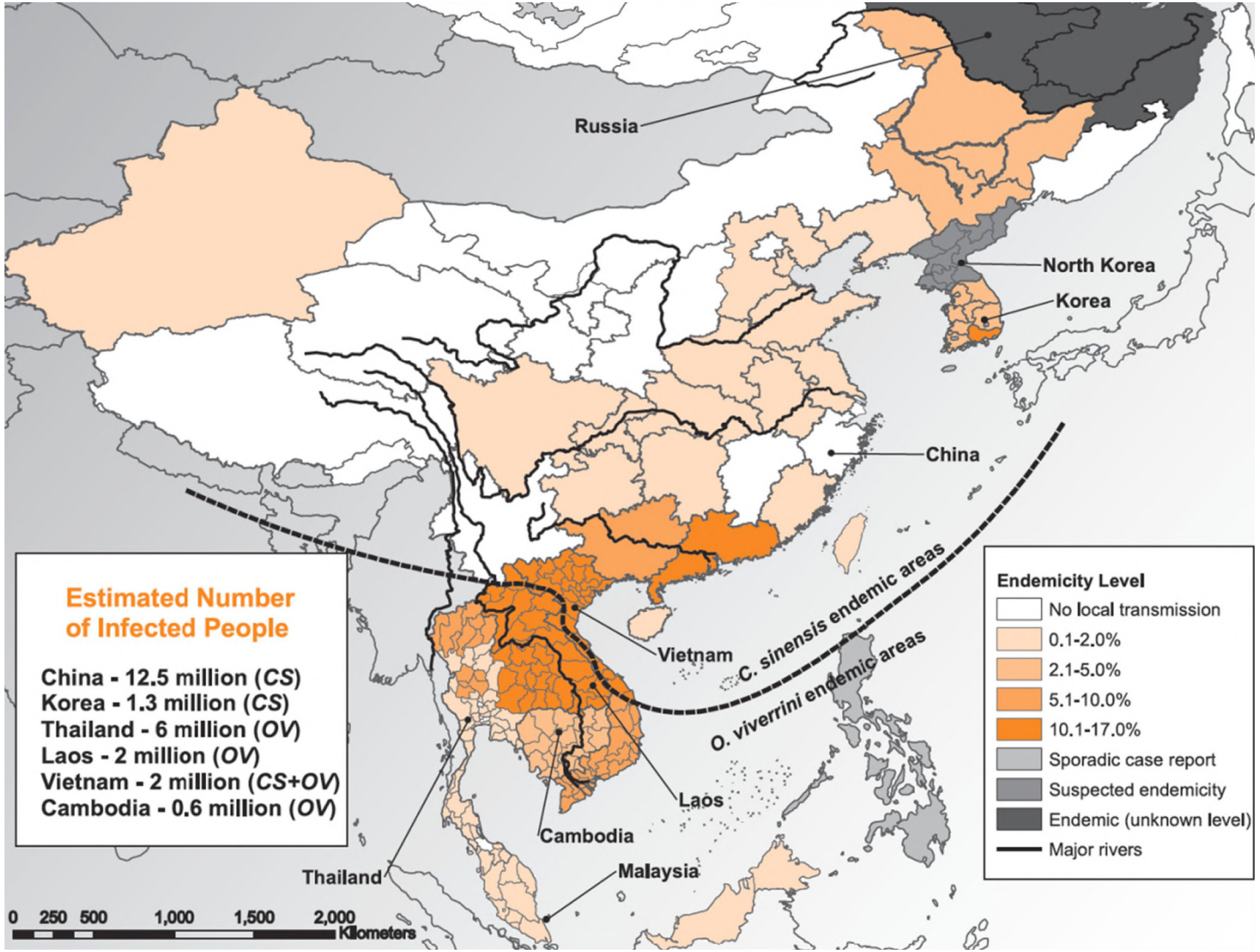
# Srinagarind hospital cancer registry



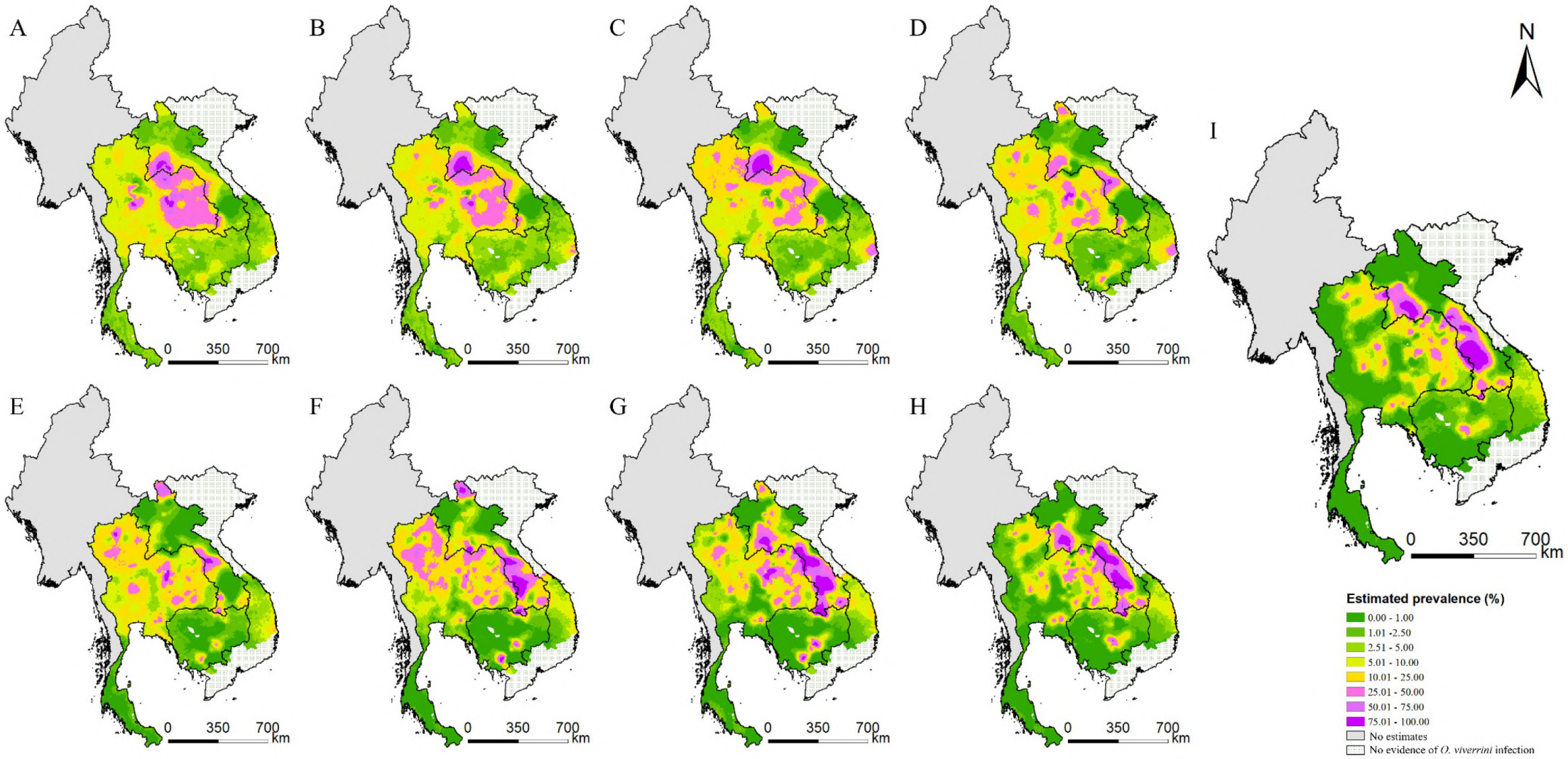
# Risk factor


**Figure 3. Hematoxylin and eosin stained adult worms of the most important liver flukes. A, *Opishorchis felineus*, scale bar 2 mm; B, *Opithorchis vivverini*, scale bar 1 mm; and C, *Clonorchis sinensis* scale bar 2 mm. There is no proportion between worm size.** (permission obtained from Dr. Edoardo Pozio, Istituto Superiore Di Sanita', Department of Infectious, Parasitic and Immune-Mediated Diseases)



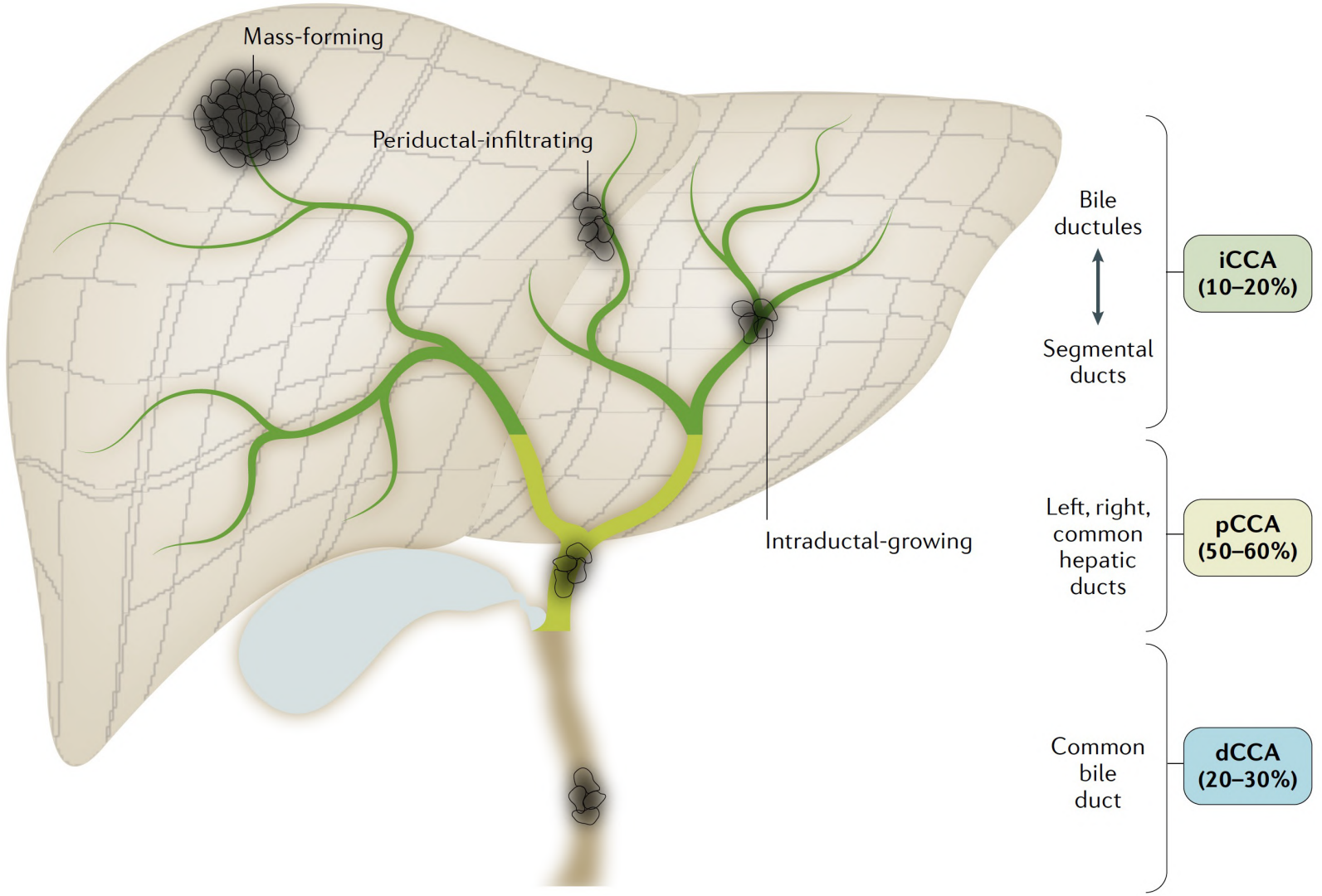

1. Murell, K.D., Pozio, E. 2017. https://doi.org/10.14321/waterpathogens.
2. José M. Correiada Costa, Banchob Sripa, Frontiers in Genetics 5(e1961):444 DOI: 10.3389/fgene.2014.00444

# Prevalence of liver fluke infestation




1. Ting-Ting Zhao, Elife. 2021 Jan 12;10:e59755. doi: 10.7554/eLife.59755.

# Classification



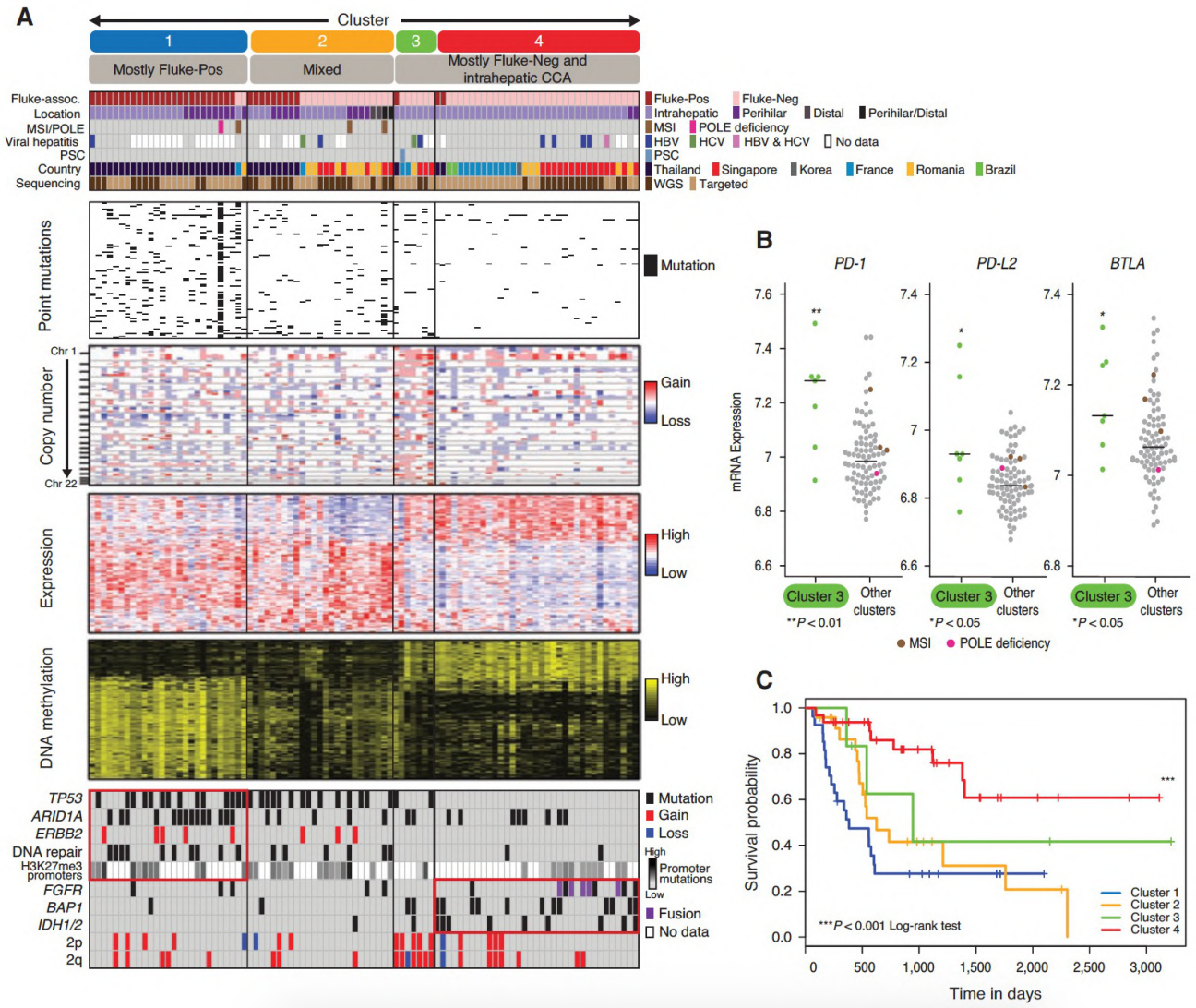

1. Jesus M. Banales, Nat Rev Gastroenterol Hepatol. 2020 Sep;17(9):557-588. doi: 10.1038/s41575-020-0310-z.

# Molecular subtype of CCA

analyzed 489 CCAs from 10 countries, combining

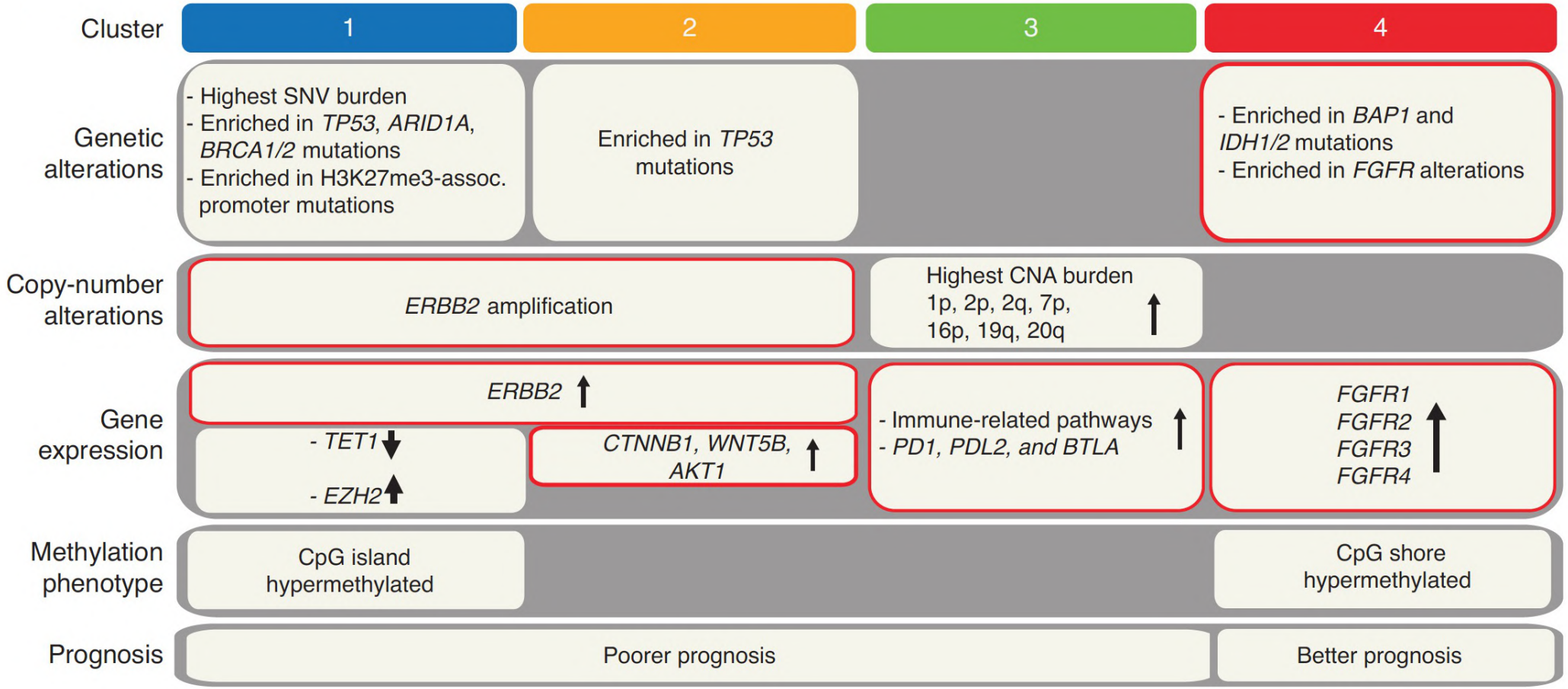
- whole-genome (71 cases)
- targeted/exome
- copy-number
- gene expression
- DNA methylation information

Integrative clustering defined 4 CCA clusters




1. Apinya Jusakul, Cancer Discov; 7(10); 1116–35. DOI: 10.1158/2159-8290.CD-17-0368

# Molecular subtype of CCA




ERBB2 amplifications were more frequent in Fluke-Pos cases

**10.4%** in Fluke-Pos vs. 2.7% in Fluke-Neg CCA, $P < 0.01$

1. Apinya Jusakul, Cancer Discov; 7(10); 1116–35. DOI: 10.1158/2159-8290.CD-17-0368

RESEARCH ARTICLE

# Whole-Genome and Epigenomic Landscapes of Etiologically Distinct Subtypes of Cholangiocarcinoma

Apinya Jusakul[1,2,3], Ioana Cutcutache[4], Chern Han Yong[1,4], Jing Quan Lim[2,5], Mi Ni Huang[4], Nisha Padmanabhan[1], Vishwa Nellore[6], Sarinya Kongpetch[2,7,8], Alvin Wei Tian Ng[9], Ley Moy Ng[10], Su Pin Choo[11], Swe Swe Myint[2], Raynoo Thanan[12], Sanjanaa Nagarajan[2], Weng Khong Lim[1,2], Cedric Chuan Young Ng[2], Arnoud Boot[1,4], Mo Liu[1,4], Choon Kiat Ong[5], Vikneswari Rajasegaran[2], Stefanus Lie[2,13], Alvin Soon Tiong Lim[14], Tse Hui Lim[14], Jing Tan[2], Jia Liang Loh[2], John R. McPherson[4], Narong Khuntikeo[7,15], Vajaraphongsa Bhudhisawasdi[15], Puangrat Yongvanit[7], Sopit Wongkham[12], Yasushi Totoki[16], Hiromi Nakamura[16], Yasuhito Arai[16], Alexander Yaw Fui Chung[19], London Lucien Peng Jin[19], Irinel Popescu[21], Philippe Broet[23], Sen-Yung Hsieh[24], Di-Xian Luo[28], André Lopes Carvalho[29], André Luiz [30], Ludmil B. Alexandrov[32], Raluca Gordân[6,33], Steven G[35], Bin Tean Teh[1,2,10,34,36], and Patrick Tan[1,10,34,37]

**Fluke-positive CCAs (clusters 1/2)**
are enriched in *ERBB2* amplifications and *TP53* mutations

**Fluke-negative CCAs (clusters 3/4)**
exhibit high copy-number alterations and *PD-1 / PD-L2* expression, or epigenetic mutations ( *IDH1/2, BAP1* ) and *FGFR / PRKA* -related gene rearrangements.

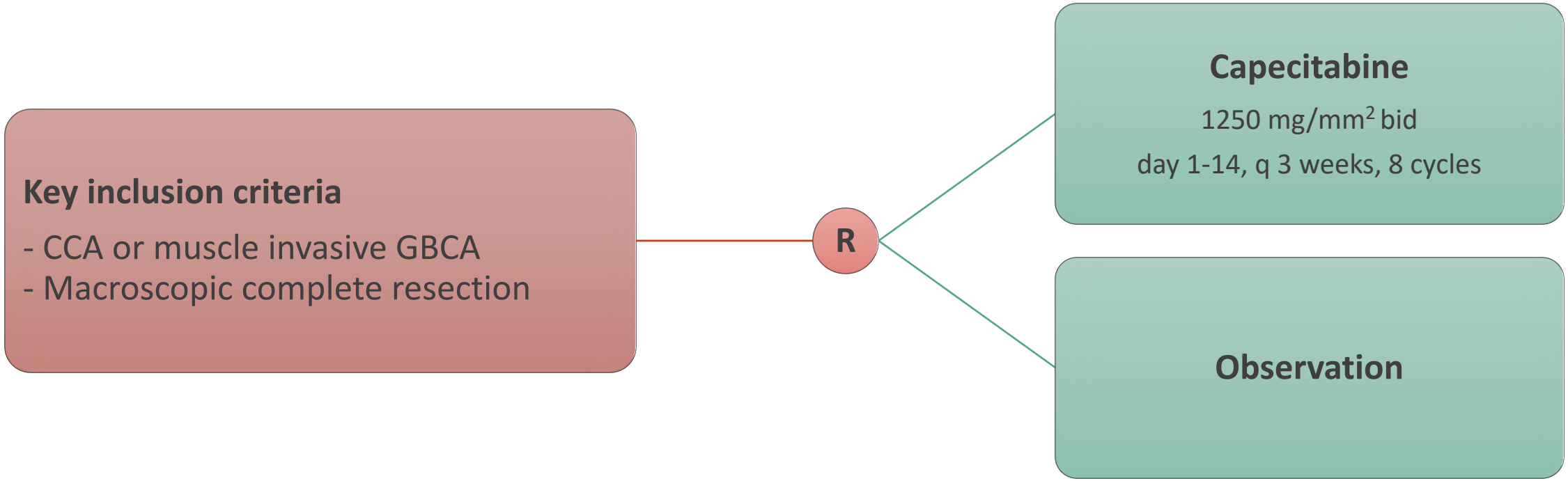
1. Apinya Jusakul, Cancer Discov; 7(10); 1116–35. DOI: 10.1158/2159-8290.CD-17-0368

# Systemic therapy

# Early stage

# BILCAP study

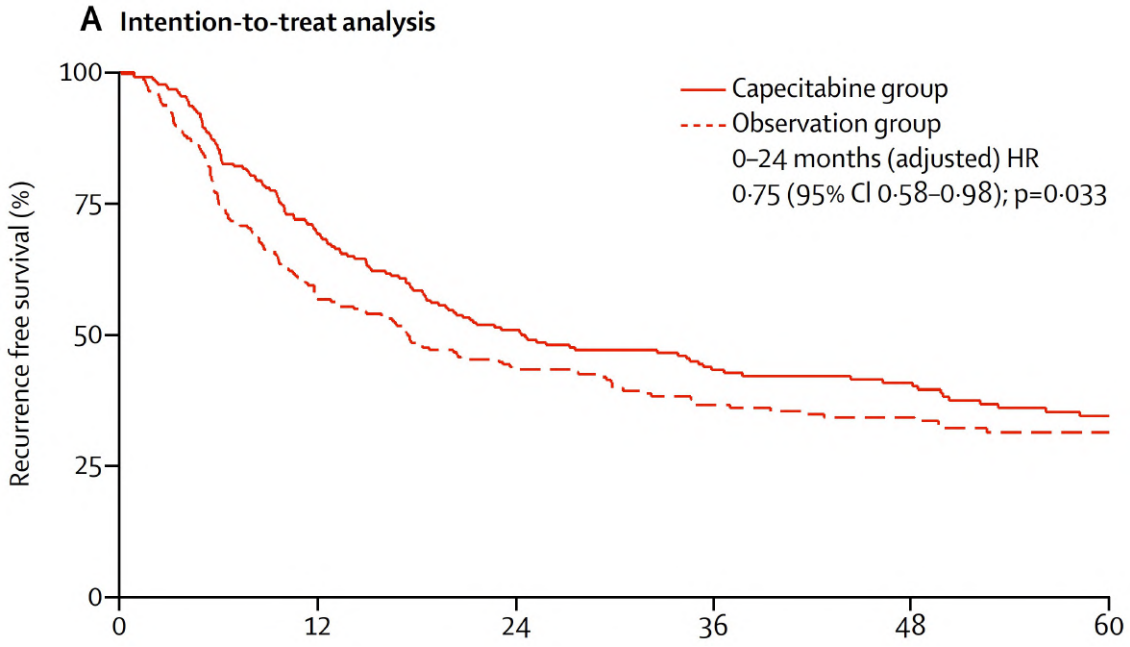
Randomized, controlled, phase 3, 44 centers in the United Kingdom

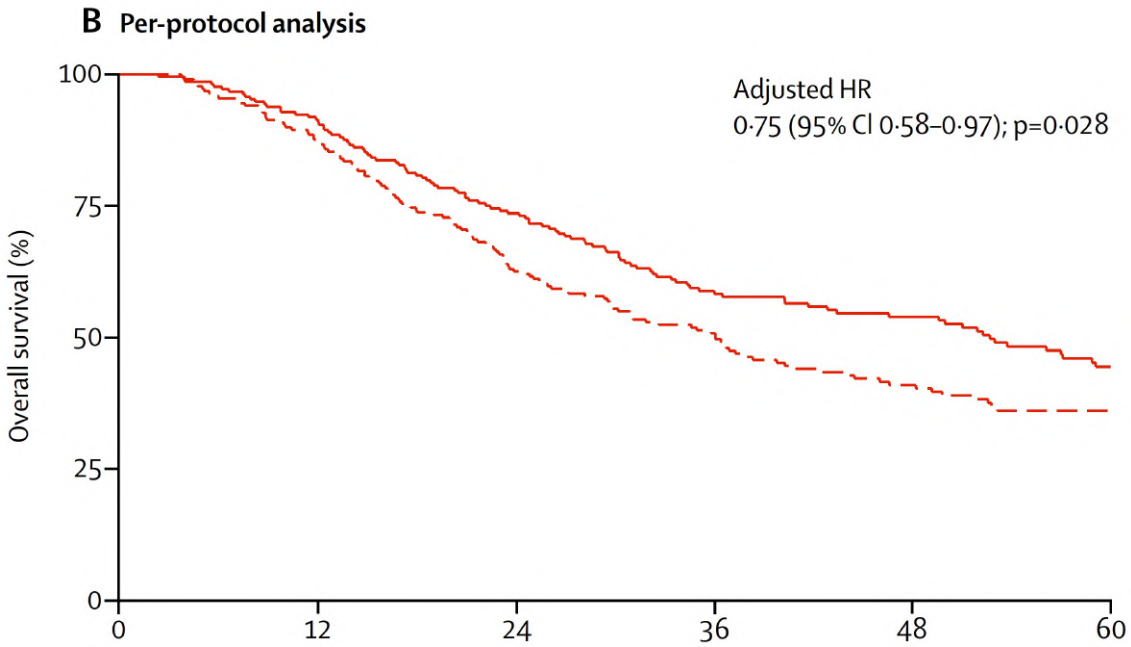



**Primary end-point: Overall survival (ITT)**
**Secondary end-point: Overall survival (per protocol)**

1. John N Primrose, Lancet Oncol. 2019 May;20(5):663-673. doi: 10.1016/S1470-2045(18)30915-X.

# BILCAP study



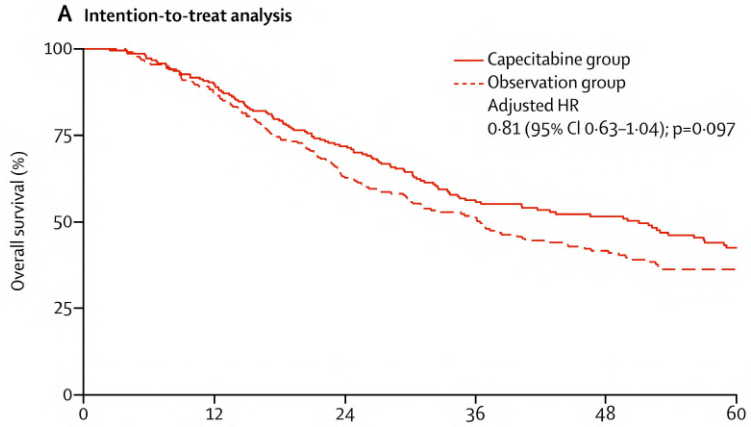




**↑mRFS 17.5 > 24.4 months**

**↑mOS 36 > 53 months**

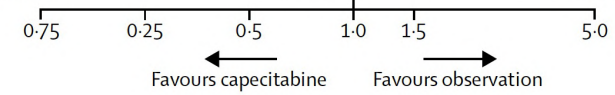
1. John N Primrose, Lancet Oncol. 2019 May;20(5):663-673. doi: 10.1016/S1470-2045(18)30915-X.

# BILCAP study




**Not met primary end-point**

| | Observation group (events/patients) | Capecitabine group (events/patients) | HR (95% CI) | $p_{heterogeneity}$ |
|---|---|---|---|---|
| Age, years | | | | |
| >60 | 82/145 | 76/145 | 0·87 (0·63–1·19) | 0·45 |
| ≤60 | 49/79 | 38/78 | 0·71 (0·46–1·08) | |
| Sex | | | | |
| Female | 58/111 | 54/112 | 0·93 (0·64–1·35) | 0·27 |
| Male | 73/113 | 60/111 | 0·70 (0·50–0·99) | |
| Maximum tumour size, mm | | | | |
| >50 | 22/34 | 15/35 | 0·65 (0·33–1·26) | 0·46 |
| ≤50 | 82/145 | 73/142 | 0·86 (0·62–1·18) | |
| Lymph node status | | | | |
| Positive | 76/102 | 70/108 | 0·74 (0·53–1·03) | 0·73 |
| Negative | 55/122 | 44/115 | 0·81 (0·54–1·20) | |
| Tumour stage | | | | |
| I | 22/61 | 19/57 | 0·87 (0·47–1·60) | 0·68 |
| II | 97/144 | 77/137 | 0·74 (0·55–1·00) | |
| III | 12/18 | 17/28 | 1·04 (0·49–2·20) | |
| Grade | | | | |
| Not known | 7/12 | 6/15 | 0·62 (0·21–1·84) | 0·50 |
| Poorly differentiated | 45/56 | 40/64 | 0·60 (0·39–0·93) | |
| Moderately differentiated | 65/120 | 55/110 | 0·90 (0·63–1·29) | |
| Well differentiated | 14/36 | 13/34 | 0·93 (0·43–1·98) | |
| ECOG performance status | | | | |
| 0 | 55/101 | 44/100 | 0·71 (0·48–1·06) | 0·70 |
| 1 | 72/116 | 37/116 | 0·89 (0·64–1·24) | |
| 2 | 4/7 | 3/7 | 0·71 (0·16–3·20) | |
| Resection status | | | | |
| R1 | 61/84 | 58/84 | 0·90 (0·63–1·29) | 0·42 |
| R0 | 70/140 | 56/139 | 0·73 (0·51–1·04) | |
| Primary tumour site | | | | |
| Intrahepatic cholangiocarcinoma | 24/41 | 19/43 | 0·65 (0·35–1·18) | 0·47 |
| Hilar cholangiocarcinoma | 37/63 | 37/65 | 1·08 (0·68–1·71) | |
| Muscle-invasive gallbladder carcinoma | 19/40 | 19/39 | 0·84 (0·43–1·63) | |
| Lower common bile duct cholangiocarcinoma | 51/80 | 42/76 | 0·70 (0·47–1·06) | |
| **Overall** | **131/224** | **114/223** | **0·81 (0·63–1·04)** | |




1. John N Primrose, Lancet Oncol. 2019 May;20(5):663-673. doi: 10.1016/S1470-2045(18)30915-X.

# GeCiCCA study - ongoing

Randomized, controlled, phase 3, multicenter centers in Thailand

CHOLANGIOCARCINOMA SCREENING AND CARE PROGRAM

**Key inclusion criteria**

- CCA
- R0/R1 resection

R

**Cisplatin** 25 mg/mm2

**Gemcitabine** 1000 mg/mm2

day 1, 8, q 3 weeks, 8 cycles

**Gemcitabine** 1000 mg/mm2

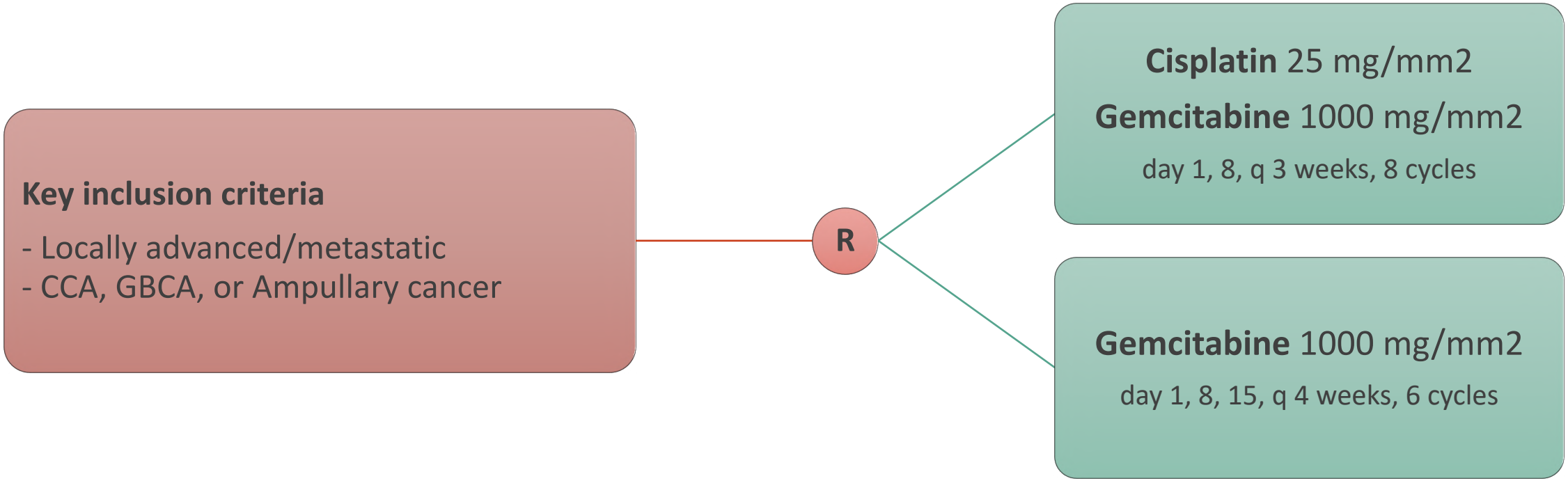
day 1, 8, 15, q 4 weeks, 6 cycles

**Primary end-point: Overall survival (ITT)**

# Advanced stage

# ABC-02 study

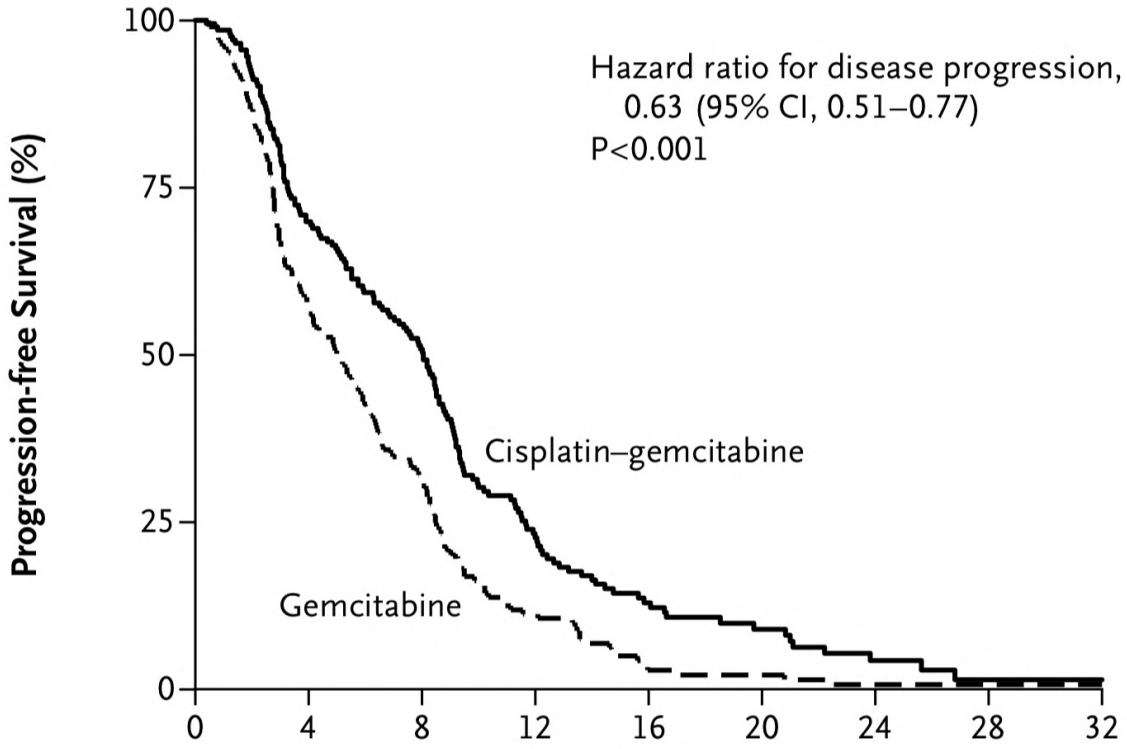
Randomized, controlled, phase 3, 37 centers in the United Kingdom



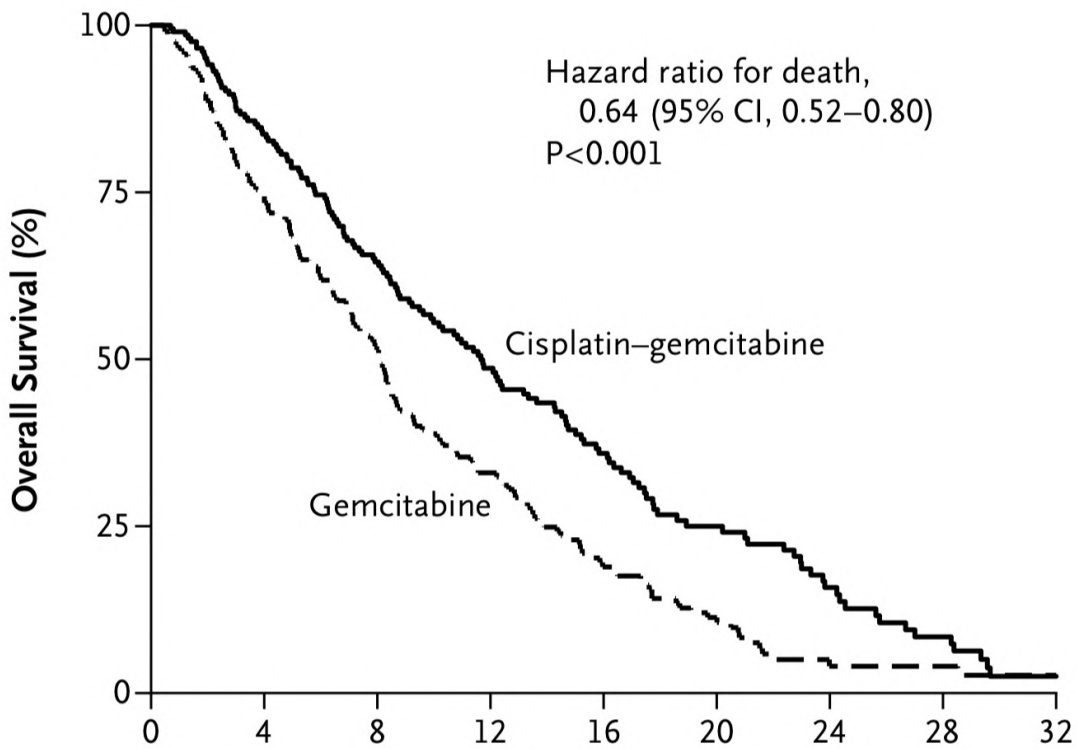

**Primary end point: Overall survival**

1. Juan Valle, N Engl J Med 2010; 362:1273-1281DOI: 10.1056/NEJMoa0908721

# ABC-02 study




↑mPFS 5 > 8 months

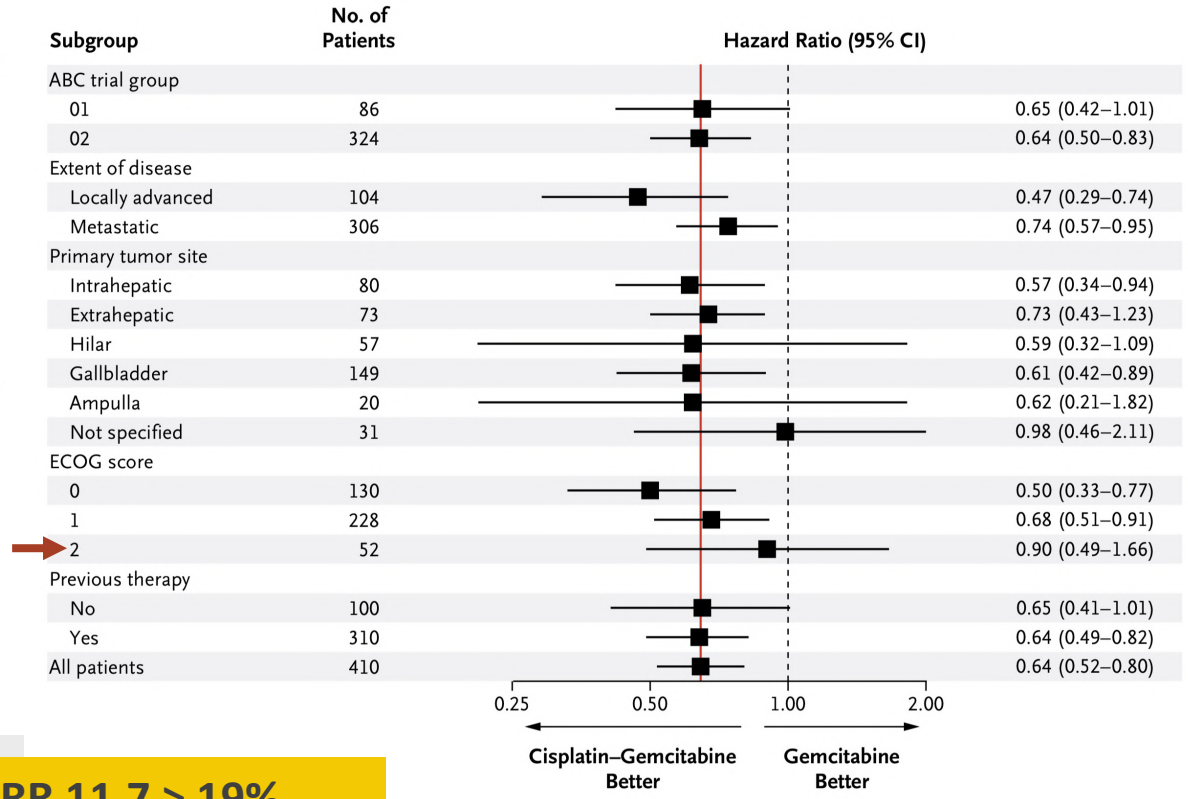



↑mOS 8.1 > 11.7 months

1. Juan Valle, N Engl J Med 2010; 362:1273-1281DOI: 10.1056/NEJMoa0908721

# ABC-02 study

| | Treatment arm | | p value |
|---|---|---|---|
| | Gem | CisGem | |
| **All evaluable patients** | **N=142** | **N=161** | |
| Complete response | 1 (0.7) | 1 (0.6) | |
| Partial response | 21 (14.8) | 41 (25.5) | |
| Stable disease | 80 (56.3) | 89 (55.3) | |
| Progresive disease | 40 (28.2) | 30 (18.6) | |
| Tumour control (CR+PR+SD) | 102 (71.8) | 131 (81.4) | 0.049 |
| Difference (95% CI) | 9.5% (0.1, 19.0) | | |
| **Gallbladder tumours** | **N=56** | **N=61** | |
| Complete response | 0 (0) | 0 (0) | |
| Partial response | 12 (21.4) | 23 (37.7) | |
| Stable disease | 31 (55.4) | 29 (47.5) | |
| Progresive disease | 13 (23.2) | 9 (14.8) | |
| Tumour control (CR+PR+SD) | 43 (76.8) | 52 (85.2) | 0.242 |
| Difference (95% CI) | 8.5% (-5.7, 22.7) | | |
| **Bile duct and ampullary tumours** | **N=86** | **N=100** | |
| Complete response | 1 (1.2) | 1 (1.0) | |
| Partial response | 9 (10.5) | 18 (18.0) | |
| Stable disease | 49 (57.0) | 60 (60.0) | |
| Progresive disease | 27 (31.4) | 21 (21.0) | |
| Tumour control (CR+PR+SD) | 59 (68.6) | 79 (79.0) | 0.106 |
| Difference (95% CI) | 10.4% (-2.2, 23.0) | | |




↑ORR 11.7 > 19%

1. Juan Valle, N Engl J Med 2010; 362:1273-1281DOI: 10.1056/NEJMoa0908721

# Gemcitabine-based combination CMT

| CMT | Study | Design | n | Population %CCA/GBC | ORR | PFS mo | OS mo |
|---|---|---|---|---|---|---|---|
| **Gemcitabine + Cisplatin** | ABC-02[1] | Phase III | 410 | 59/36 | 26.1%* | 8 | 11.7 |
| | Japanese[2] | Phase III | 83 | 57/39 | 19.5% | 5.8 | 11.2 |
| **Gemcitabine + S1** | JCOG 0805[3] | Phase II | 101 | 56.8/37.3 | 36.4% vs 17.4% | 7.1 vs 4.2 | 12.5 vs 9.0 |
| **Gemcitabine + S1** | FUGA-BT[4] | Phase III non-inferiority | 354 | 57/39 | 29.8% vs 32.4% | 6.8 vs 5.8 | 15.1 vs 13.4 |
| **Gemcitabine + Capecitabine** | Canadian[5] | Phase II | 45 | 53/47 | 31% | 7 | 14 |
| | Korean[6] | Phase II | 44 | 68/16 | 32% | 6 | 14 |
| | Swiss[7] | Phase II | 44 | 80/18 | 25% | 7.2 | 13.2 |
| **Gemcitabine + nabPaclitaxel** | PrECOG[8] | Phase II | 74 | 100/0 | 25% | 7.7 | 12.4 |

***Subgroup CCA**
- ORR 19%
- DCR 79%

vs S-1

vs Gem/Cis

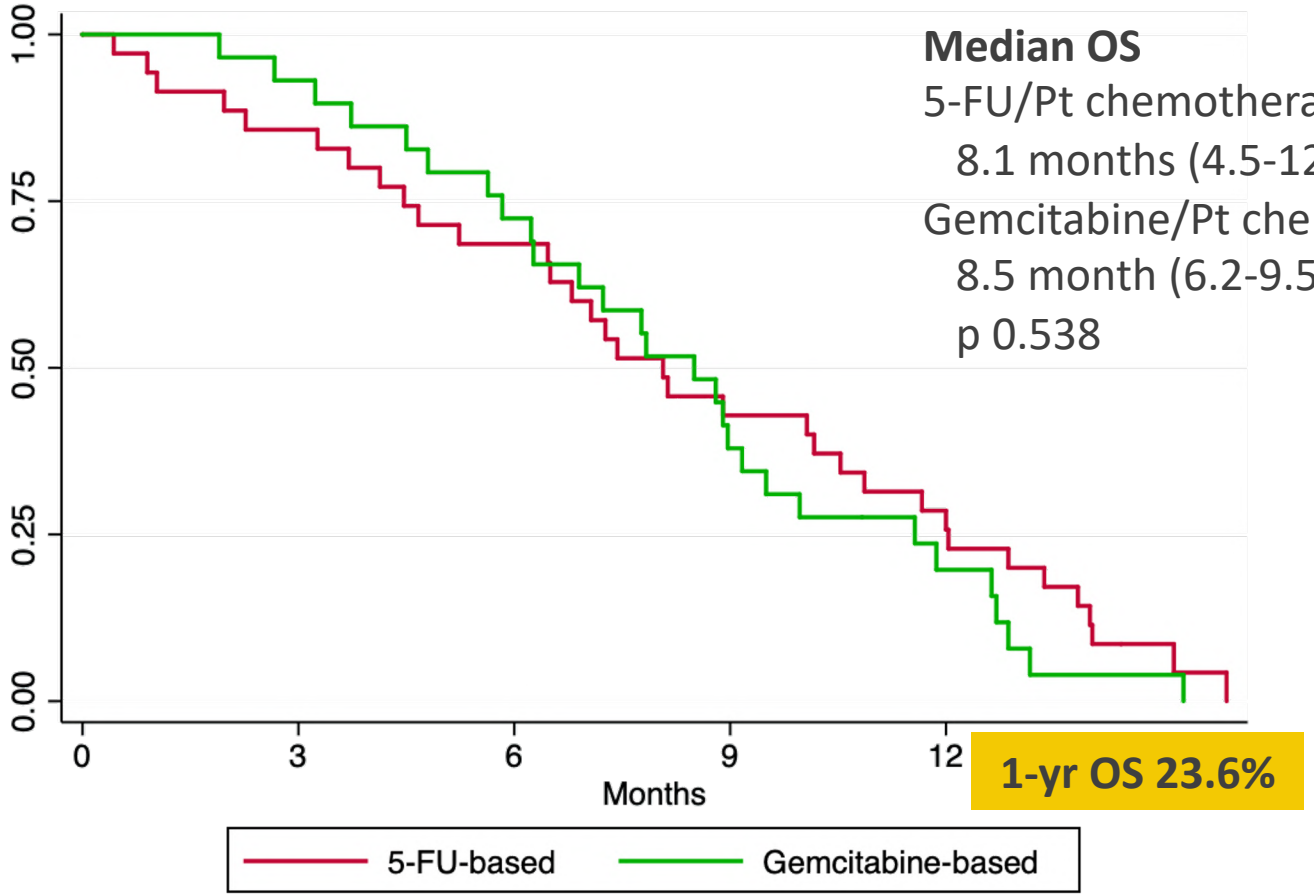

1. Juan Valle, N Engl J Med 2010; 362:1273-1281DOI: 10.1056/NEJMoa0908721
2. Okusaka T., Br J Cancer. 2010 Aug 10;103(4):469-74. doi: 10.1038/sj.bjc.6605779. Epub 2010 Jul 13.
3. Chigusa Morizane, Cancer Sci. 2013 Sep;104(9):1211-6. doi: 10.1111/cas.12218.
4. Mizusawa J., Jpn J Clin Oncol. 2016 Apr;46(4):385-8. doi: 10.1093/jjco/hyv213. Epub 2016 Feb 18. Chigusa Morizane, Abstract DOI: 10.1200/JCO.2018.36.4_suppl.205 Journal of Clinical Oncology 36, no. 4_suppl (February 1 2018) 205-205.
5. Jennifer J. Knox, DOI: 10.1200/JCO.2005.51.008 Journal of Clinical Oncology 23, no. 10 (April 1 2005) 2332-2338.
6. Cho JY., Cancer. 2005 Dec 15;104(12):2753-8. DOI: 10.1002/cncr.21591
7. Koeberle D., J Clin Oncol. 2008 Aug 1;26(22):3702-8. doi: 10.1200/JCO.2008.16.5704.
8. Vaibhav Sahai, JAMA Oncol. 2018;4(12):1707-1712. doi:10.1001/jamaoncol.2018.3277

# Outcome of first-line chemotherapy in Thailand

| Study | Population | Treatment | n | ORR* | DCR | mPFS | mOS |
|---|---|---|---|---|---|---|---|
| Thanasombunsukh, 2015 Retrospective | Thai, Chiang Mai Radiographic-diagnosed CCA | Gemcitabine/ Cisplatin | 223 | **20.6%** | 61.9 | **5.4 mo** | **9.7 mo** |
| Sanlung, 2018 Retrospective | Thai, Khon Kaen Histology-proven CCA | Gem/Pt chemo | 29 | 9.5% | 42.9% | - | 8.5 mo (6.2-9.5) |
| | | 5-FU/Pt chemo | 25 | 8.3% | 41.7% | - | 8.1 mo (4.5-12) |
| Mungwattana, 2015 Retrospective | Thai, Khon Kaen Histology-proven CCA | Gem-based chemo | 81 | 4.8% | 31.0% | - | 7.4 mo (6.3-8.4) |
| | | 5-FU-based chemo | 143 | 0% | 24.4% | - | 7.4 mo (6.7-8.6) |

*Evaluable lesion

# First-line Chemotherapy in CCA Srinagarind hospital Retrospective data




**Median OS**

5-FU/Pt chemotherapy

8.1 months (4.5-12)

Gemcitabine/Pt chemotherapy

8.5 month (6.2-9.5)

p 0.538

**1-yr OS 23.6%**

1. Thanachai Sanlung 2018, unpublished data

# ABC-06 study design

Phase III, randomised, open-label

## Inclusion criteria

- Histo/cytologically verified **advanced BTC**
- **ECOG performance score 0-1**
- **Progression after 1st-line CisGem**
- Max **6 weeks progression to randomisation**
- Adequate haematological, renal & hepatic function

R

1:1

### Arm A

**Active Symptom Control (ASC)**

- May include: biliary drainage, antibiotics, analgesia, steroids, anti-emetics etc
- 4-weekly clinical review

### Arm B

**Active Symptom Control + mFOLFOX**

- Chemotherapy every 14 days for up to 12 cycles
- Day 1: Oxaliplatin 85mg/m$^2$, L-folinic acid 175 mg (or folinic acid 350 mg), 5 FU 400 mg/m$^2$ (bolus), 5 FU 2400 mg/m$^2$ 46 hours continuous infusion
- 4-weekly clinical review after chemotherapy
- 3-monthly radiological assessment

## Follow up

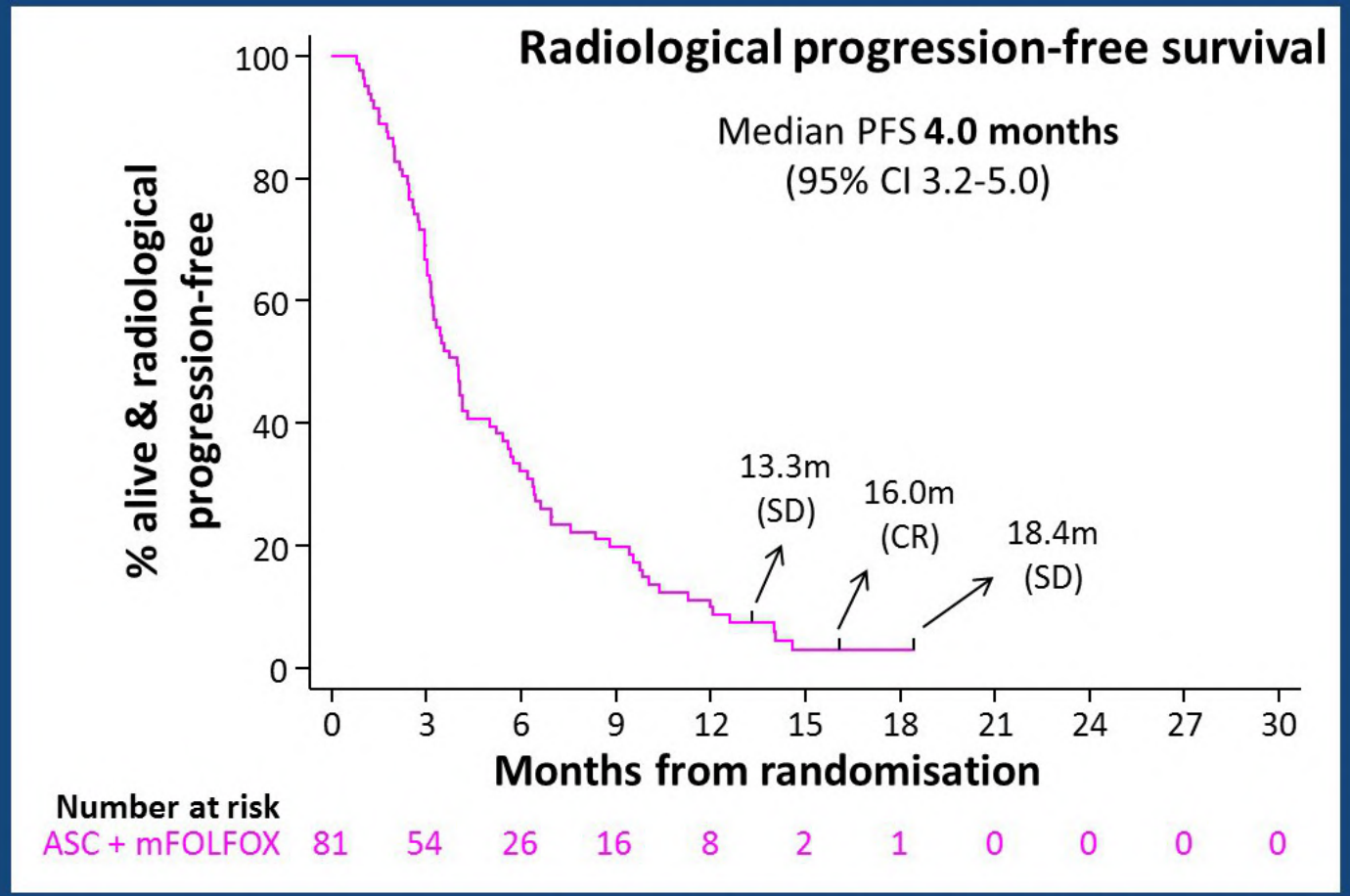
- **Overall survival** = primary end-point
- Until death or until completion of 12 months after enrolment of the final patient (whichever happened first)

**Stratification factors**

- **Platinum sensitivity** (yes vs. no; determined from first-line CisGem*)
- **Serum albumin** (<35 vs. ≥35 g/L)
- **Stage** (locally advanced vs. metastatic disease)

*determined from first-line CisGem: sensitive (progression after three months (90 days) of day 1 of the last cycle of 1st-line CisGem), refractory (progression during 1st line CisGem), resistant (progression within the first three months (90 days) after completion of day 1 of the last cycle of 1st line CisGem). CisGem: cisplatin and gemcitabine; BTC: biliary tract cancer; ECOG: Eastern Cooperative Oncology Group

# Secondary end-points: radiological PFS and best Response Rate (Arm B; ITT)




| Best response rate (RECIST v.1.1) | Arm B (ASC + mFOLFOX) n=81 pts | |
|---|---|---|
| | n | % |
| **Complete response** (CR) | 1 | 1 |
| **Partial response** (PR) | 3 | 4 |
| **Stable disease** (SD) | 23 | 28 |
| **Response rate** (CR + PR) | **4** | **5** |
| **Disease-control rate** (CR+ PR + SD) | **27** | **33** |
| **Progressive disease** | 30 | 37 |
| **Death** | 23 | 28 |
| **Not evaluable** (non measurable disease) | 1 | 1 |

PFS: progression-free survival; m: months; RECIST: Response Evaluation Criteria in Solid Tumors; pts: patients; RR: response rate; DCR: disease control rate; ITT: intention-to-treat

# Primary end-point: Overall Survival (ITT)

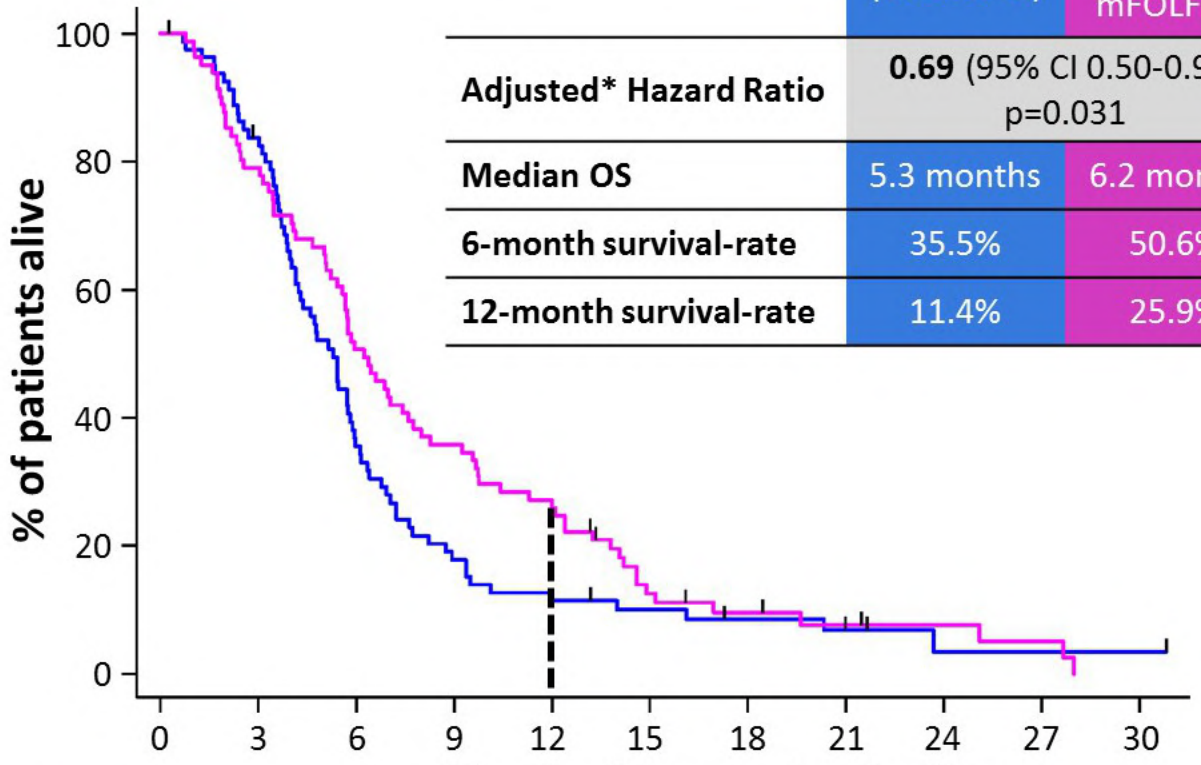
- The **primary end-point was met**: adjusted* HR was 0.69 (95% CI 0.50-0.97; p=0.031) for OS in favour of ASC + mFOLFOX arm (vs ASC)

- 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

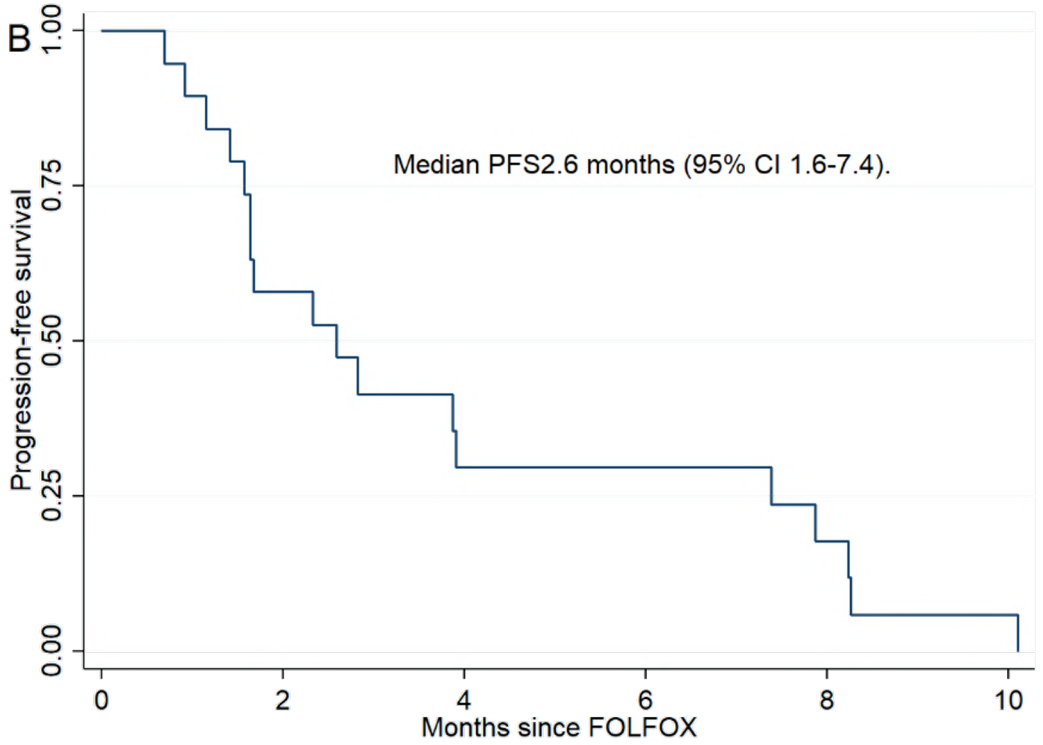
## Overall survival by trial arm

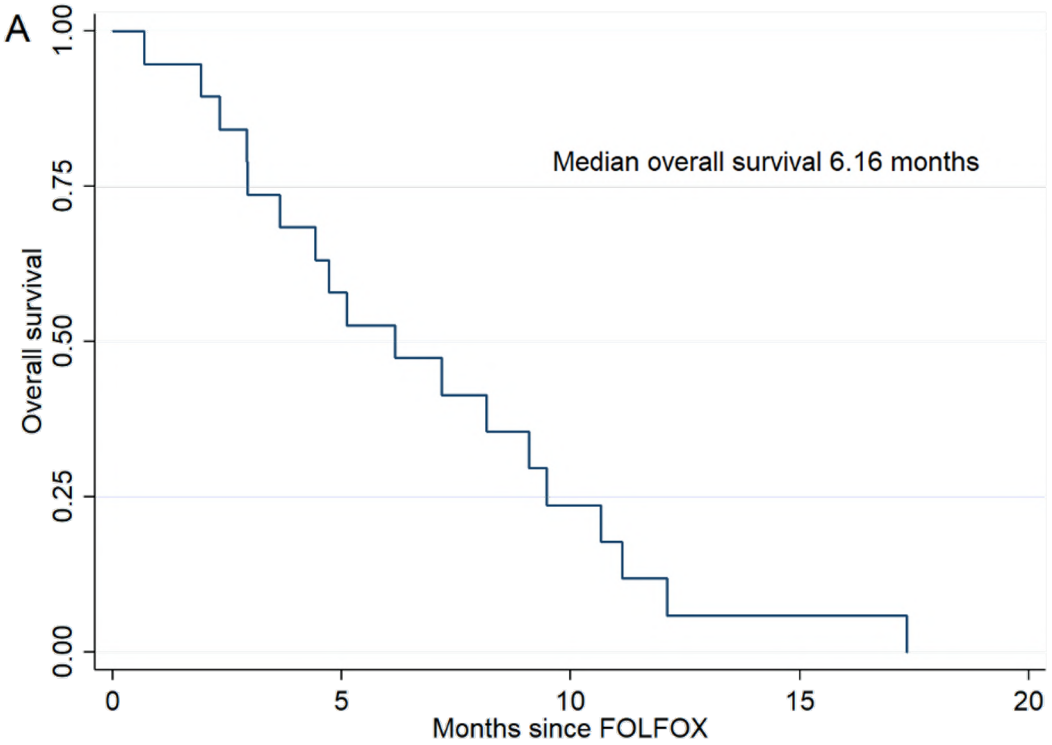
| | Arm A (ASC alone) | Arm B (ASC + mFOLFOX) |
|---|---|---|
| Adjusted* Hazard Ratio | **0.69** (95% CI 0.50-0.97) p=0.031 | |
| Median OS | 5.3 months | 6.2 months |
| 6-month survival-rate | 35.5% | 50.6% |
| 12-month survival-rate | 11.4% | 25.9% |




| Number at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ASC alone | 81 | 66 | 28 | 14 | 9 | 7 | 5 | 3 | 1 | 1 | 1 |
| ASC + mFOLFOX | 81 | 64 | 41 | 29 | 21 | 9 | 6 | 4 | 3 | 2 | 0 |

# Second-line FOLFOX in CCA Srinagarind hospital Retrospective data




**mPFS 2.6 months**

**mOS 6.16 months**

**DCR 77% (15% PR & 62% SD)**

1. Punyaporn Cheewasathianchai, Outcomes of FOLFOX4 chemotherapy as a second-line treatment for advanced biliary tract cancer .

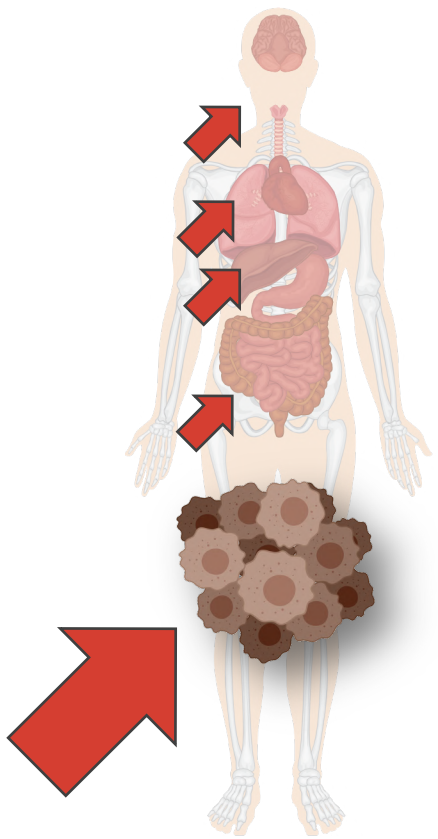
# Subsequent systemic anti-cancer therapies

| Subsequent line of systemic anti-cancer therapy | Total n=162 | | Arm A (ASC alone) n=81 pts | | Arm B (ASC + mFOLFOX) n=81 pts | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Yes** | 22 | 14 | 12 | 15 | 10 | 12 |
| **Phase I** | 5 | 3 | 3 | 4 | 2 | 2 |
| **Chemotherapy** | 17 | 10 | 9 | 11 | 8 | 10 |
| FOLFOX/CAPOX | 7 | 4 | 5* | 6 | 2 | 2 |
| CisGem | 4 | 2 | 3 | 4 | 1 | 1 |
| FOLFIRI | 1 | 1 | 0 | 0 | 1** | 1 |
| Gemcitabine + Carboplatin | 1 | 1 | 0 | 0 | 1 | 1 |
| Gemcitabine | 1 | 1 | 0 | 0 | 1 | 1 |
| 5-Fluorouracil | 1 | 1 | 0 | 0 | 1 | 1 |
| Irinotecan | 1 | 1 | 0 | 0 | 1 | 1 |
| Dendritic cell vaccine therapy | 1 | 1 | 1 | 1 | 0 | 0 |

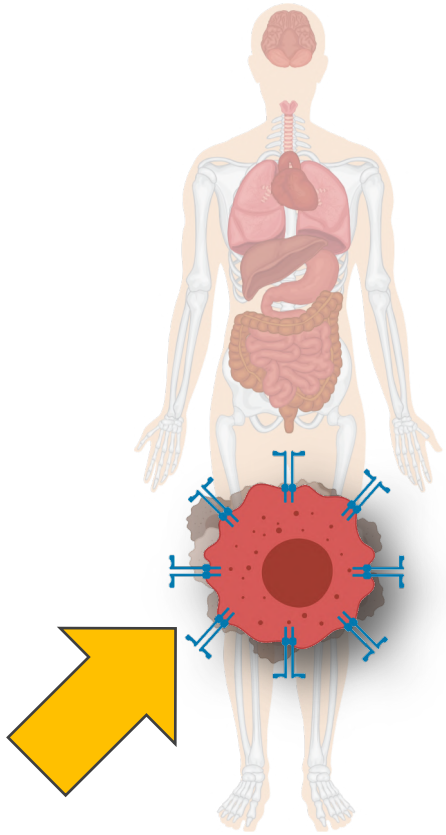
*1 patient was treated with: 2nd and 3rd liner FOLFOX + 4th line capecitabine
**1 patient received CisGem (4th line)

FOLFOX: 5-FU+oxaliplatin; CAPOX: capecitabine + oxaliplatin;
CisGem: cisplatin +gemcitabine; FOLFIRI: 5-fluorouracil + irinotecan

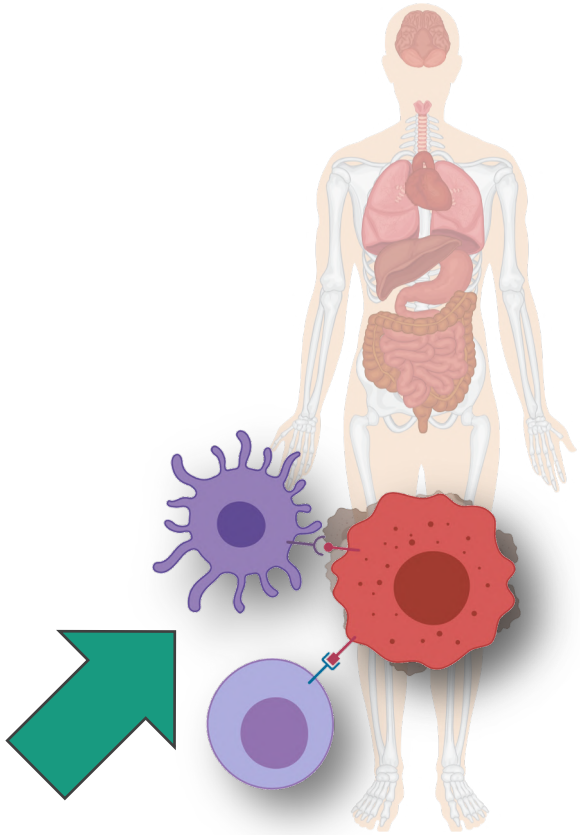
# Current Cancer Systemic Therapy



Chemotherapy

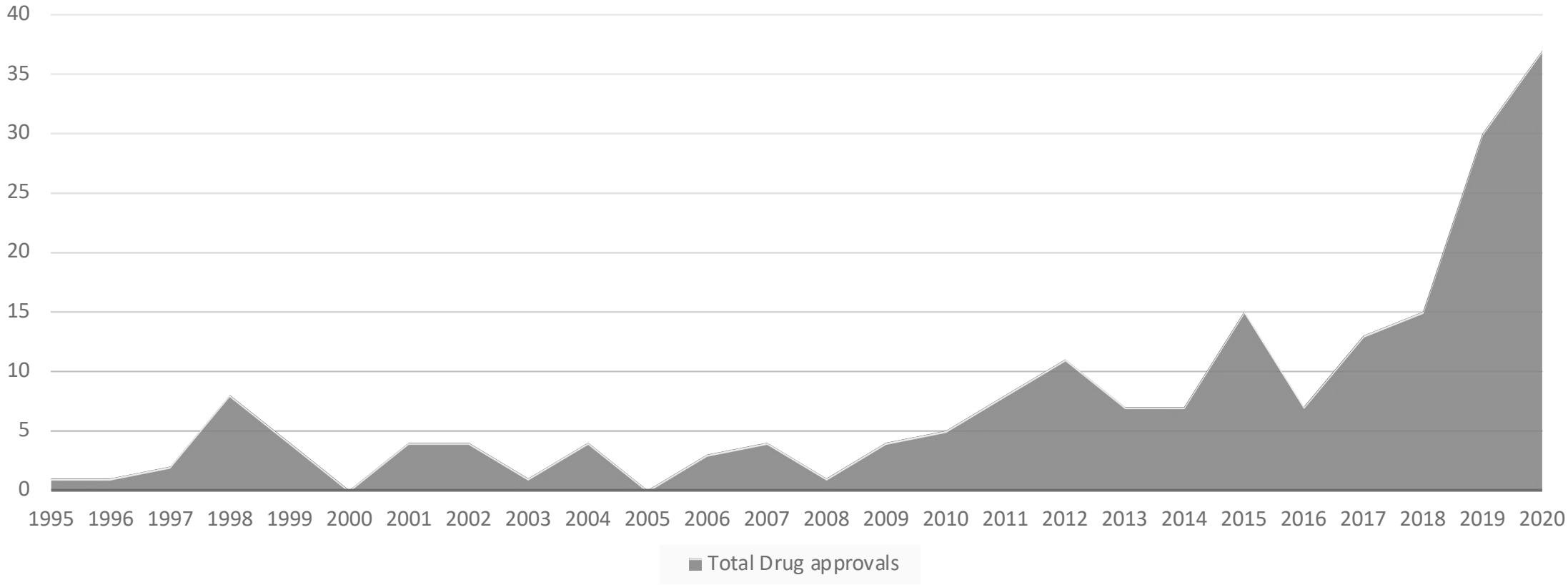


Targeted therapy



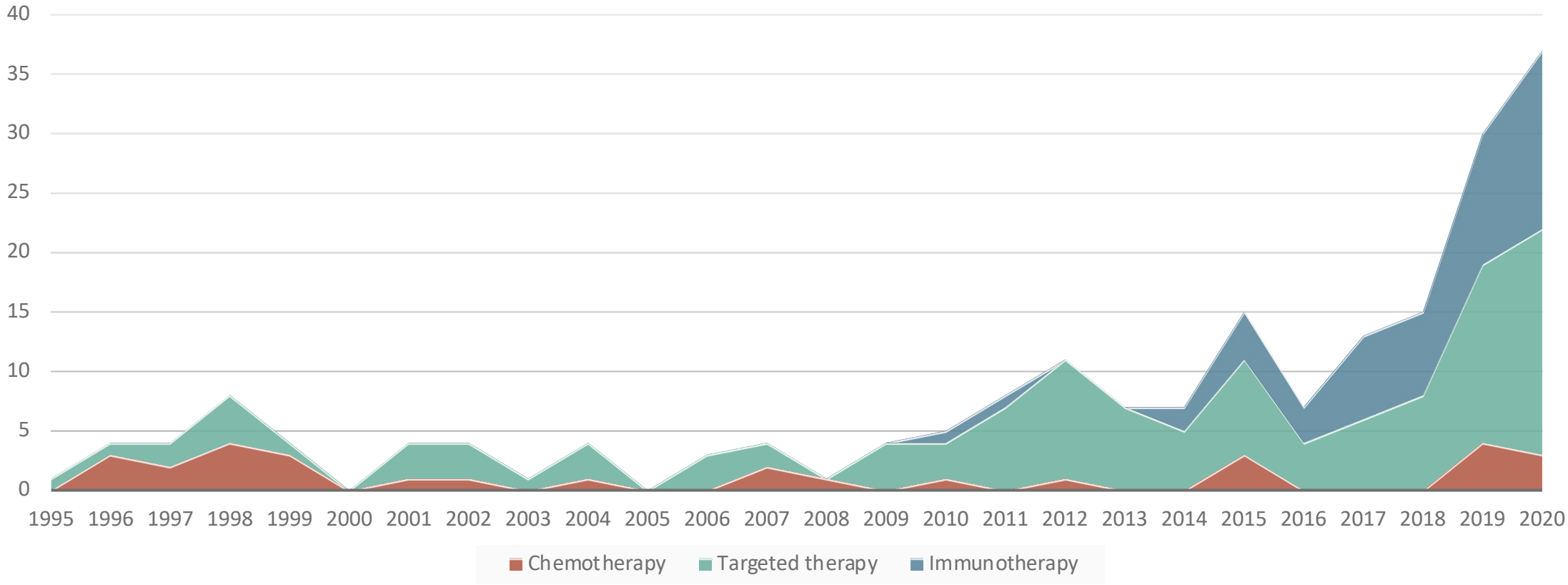
Immunotherapy

# US-FDA approved indication for solid cancer treatment



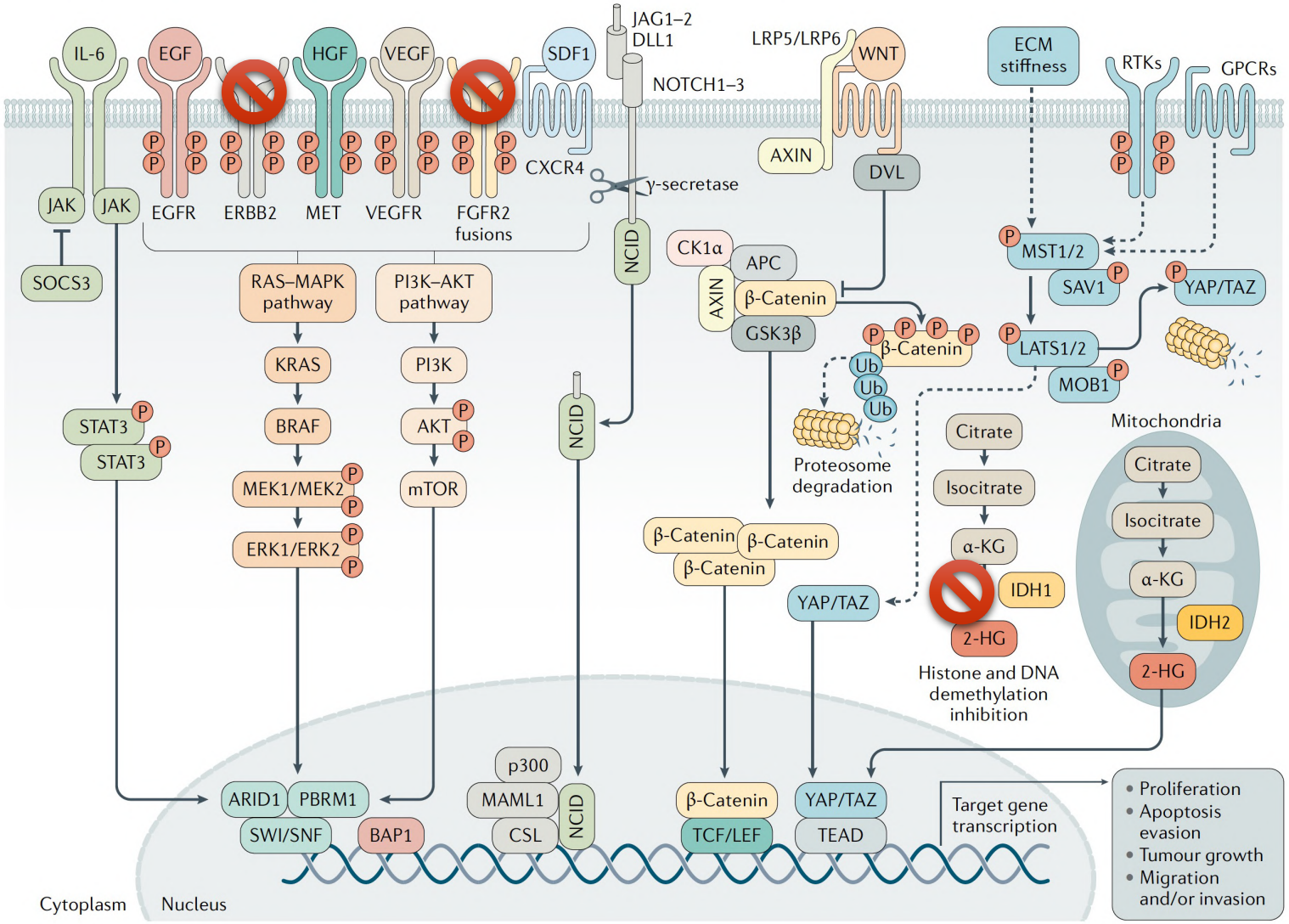

1. Adapted from https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology
2. https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications ; Online accessed Nov 20th , 2020

# US-FDA approved indication for solid cancer treatment




1. Adapted from https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology
2. https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications ; Online accessed Nov 20th , 2020

# Targeted therapy




1. Jesus M. Banales, Nat Rev Gastroenterol Hepatol. 2020 Sep;17(9):557-588. doi: 10.1038/s41575-020-0310-z.

# Trastuzumab combination with first-line chemotherapy in the advanced CCA

Phase II single-arm Simon's minimax two-stage designs
n = 27 were planned

CHOLANGIOCARCINOMA SCREENING AND CARE PROGRAM

## Key inclusion criteria

- Locally advanced or metastatic CCA
- Positive HER-2 amplification or mutation by IHC, FISH or NGS
- Chemotherapy and Trastuzumab naïve or end of adjuvant therapy > 12 months
- Age 18-80 years, ECOG 0-1
- Measurable lesion, adequate organ function

**Trastuzumab +**

**Cisplatin + Gemcitabine [1,2]**

[1]Trastuzumab 6(8) mg/kg IV q 3 weeks
Cisplatin 25 mg/mm$^2$ and
Gemcitabine 1000 mg/mm3 day 1, 8 q 3 weeks
Up to 8 cycles
[2]Evaluation CT scan every 12 weeks

**Primary end-point:** ORR by RECIST 1.1
**Secondary end-point:** PFS, OS, DCR, QOL, AEs

# Immunotherapy therapy

- **MSI-H tumor**
  - Pembrolizumab
- **KEYNOTE-966 - ongoing**
  - Pembrolizumab + Gemcitabine/Cisplatin
- **TOPAZ-1 - ongoing**
  - Durvalumab + Gemcitabine/Cisplatin

1. Jesus M. Banales, Nat Rev Gastroenterol Hepatol. 2020 Sep;17(9):557-588. doi: 10.1038/s41575-020-0310-z.

# NCCN guidelines 5.2020

## Primary Treatment for Unresectable and Metastatic Disease

**Preferred Regimens**

- Gemcitabine + cisplatin[4] (category 1)

**Other Recommended Regimens**

- 5-fluorouracil + oxaliplatin
- 5-fluorouracil + cisplatin
- Capecitabine + cisplatin
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel (cholangiocarcinoma only)
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B)
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

**Useful in Certain Circumstances**

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[5–7]
  - Larotrectinib[8]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[d,e,9]

## Subsequent-line Therapy for Biliary Tract Cancers if Disease Progression

**Preferred Regimens**

- FOLFOX[10]

**Other Recommended Regimens**

- FOLFIRI[11] (category 2B)
- Regorafenib[12] (category 2B)
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above[f]

**Useful in Certain Circumstances[f]**

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[5–7]
  - Larotrectinib[8]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[d,e,9]
- For cholangiocarcinoma with *FGFR2* fusions or rearrangements:
  - Pemigatinib[13]
- For cholangiocarcinoma with *IDH1* mutations
  - Ivosidenib[14]

# Comprehensive care in CCA

# Comprehensive care in CCA

## Disease factors

- Diagnosis
- Staging
  - Early stage
    - Survival 3-5 yr
  - Advanced stage
    - Survival <1 yr

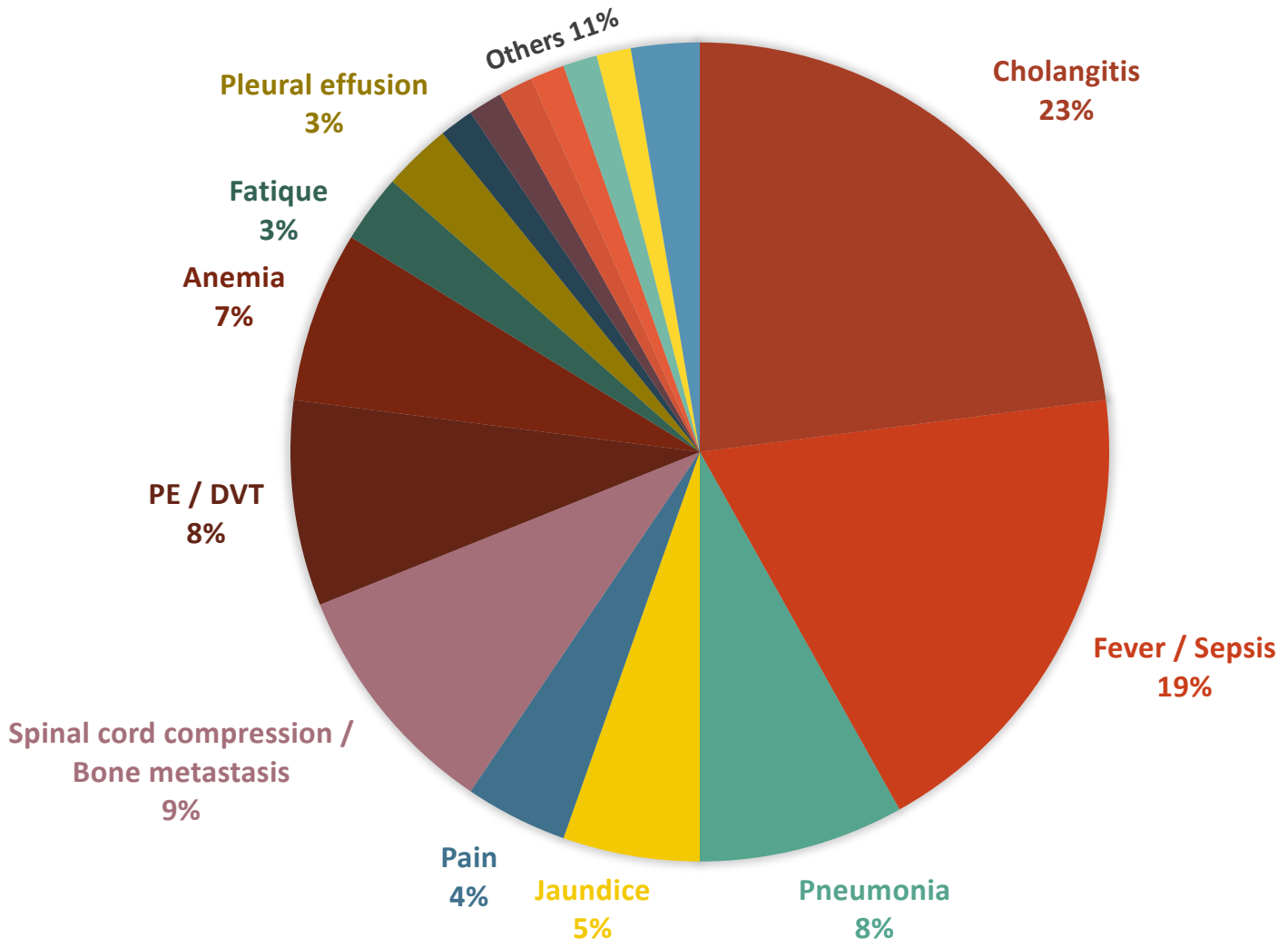
## Treatment factors

- Goal
- Option > Chemotherapy

## Patient factors

- Performance status

# IPD Complication of CCA patients




**Others 11%**

- Ascites
- Stroke
- GI bleeding
- Liver abscess
- Brain metastasis
- AKI
- Electrolyte imbalance

# Comprehensive care in CCA

## Disease factors

- Diagnosis
- Staging
  - Early stage
    - Survival 3-5 yr
  - Advanced stage
    - Survival <1 yr

## Treatment factors

- Goal
- Option > Chemotherapy

## Patient factors

- Performance status
  - ECOG 0-1 (2?)
- Complication
  - TB <3 (5?)
  - ALT AST <100 (150-200?)
- Underlying disease
- Reimbursement / Socioeconomic status
- Patient (and relative) preference

# One-slide CHOLANGIOCARCINOMA advice

## Early stage

- Resection alone : relapse-free 1½ years, OS 3 years
- Adjuvant Capecitabine : relapse-free +½ year, OS + 1½ years

## Advanced stage


**Response 2/10**
**Progression-free 8 months (5 mo?)**

**Overall survival 11 months (8 mo?)**

**~5-FU/Pt (UC)**

**Response 1/10**
**Progression-free 4 months**

**Overall survival 6 months**

**FOLFIRI?**

# Take home messages

- CCA is a major problem in Thailand, especially in the northeast.
- 1-2 lines of chemotherapy are approved in advanced CCA with an expected survival of almost 1 year.
- Careful patient selection and comprehensive multidisciplinary care are important.


Q&A