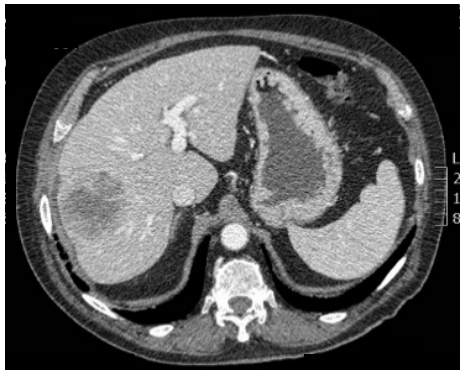
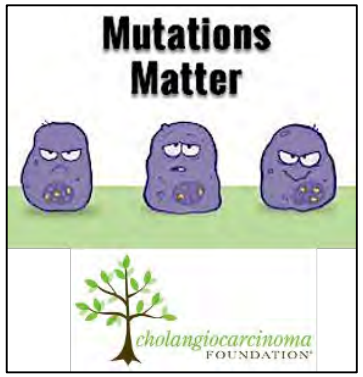




Cholangiocarcinoma

From Epidemiology to Therapy Through Its Biology

Professor Jesús Bañales, PhD

Biogipuzkoa Institute,
Donostia-San Sebastián, Spain

Conflict of interests

Relationship	Company/organisation
Consulting/advisory role	Albireo Pharma, CIMABay, Ikan Biotech, OWL-Rubió Metabolomics, Jazz, Astra Zeneca, Servier
Honoraria/lectures	Incyte, Intercept, Astra Zeneca
Research funding	Albireo, Incyte, Roche

CHOLANGIOCARCINOMA (CCA)

1. Epidemiology and general features
2. Natural course
3. Novel therapeutic strategies

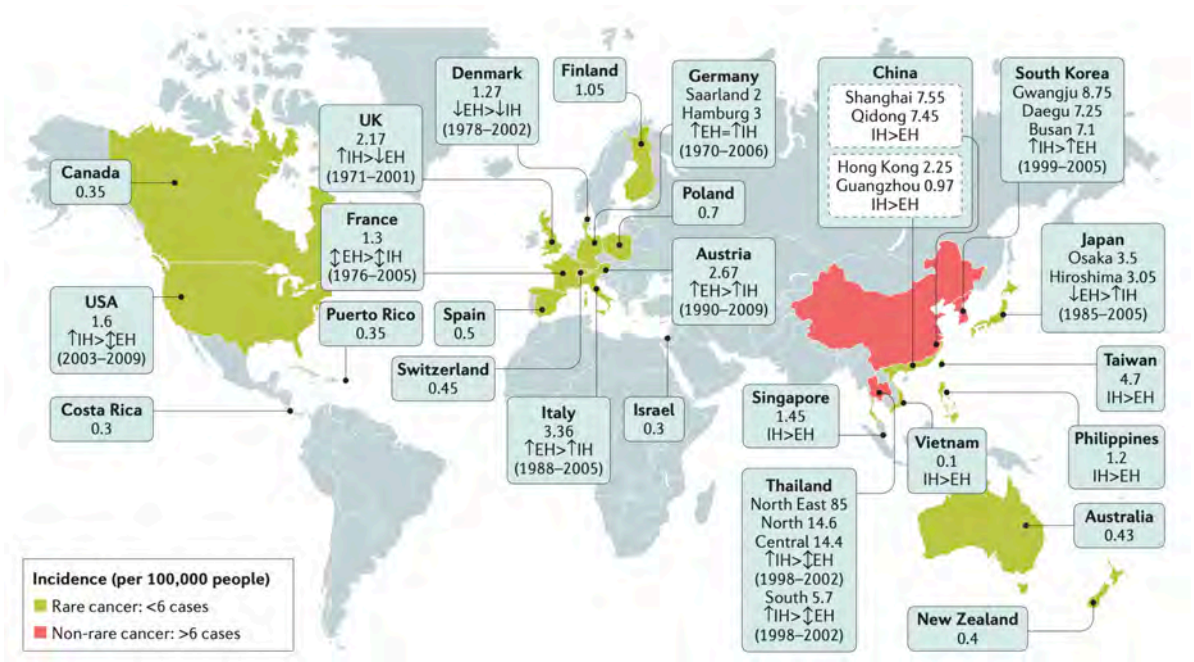
CHOLANGIOCARCINOMA (CCA)

1. Epidemiology and general features
2. Natural course
3. Novel therapeutic strategies

Cholangiocarcinoma (CCA)

- **Heterogeneous** group of malignancies with features of biliary tract differentiation
- **Second** most common primary liver cancer; CCA incidence is increasing worldwide

Worldwide CCA incidence rates



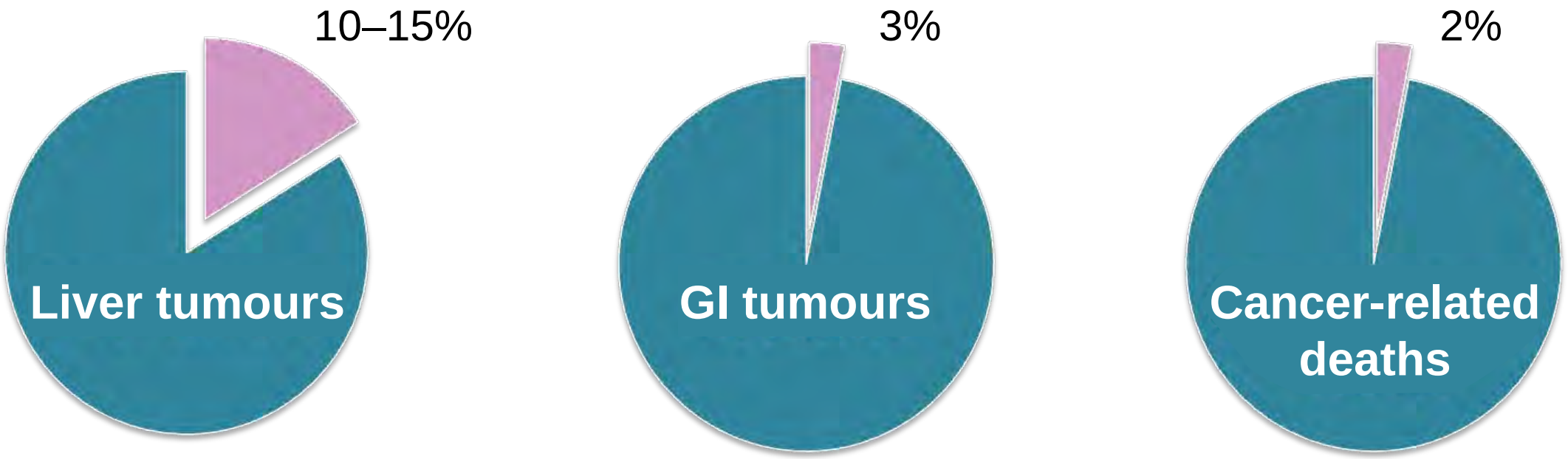
Eastern countries (Thailand, China and S Korea: >6/100,000)

Western countries (<4/100,000)

CCA, cholangiocarcinoma; EH, extrahepatic; IH, intrahepatic; S, South.

Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016

CCA



Underestimated: errors in diagnosis, coding and data retrieval

GI, gastrointestinal

Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020

Annual mortality

PERIOD

2000–2004 (**2002**)
2005–2009 (**2007**)
2010–2014 (**2012**)

- **<2** deaths
- **2–4** deaths
- **>4** deaths

(per 100,000 inhabitants)

- Not applicable

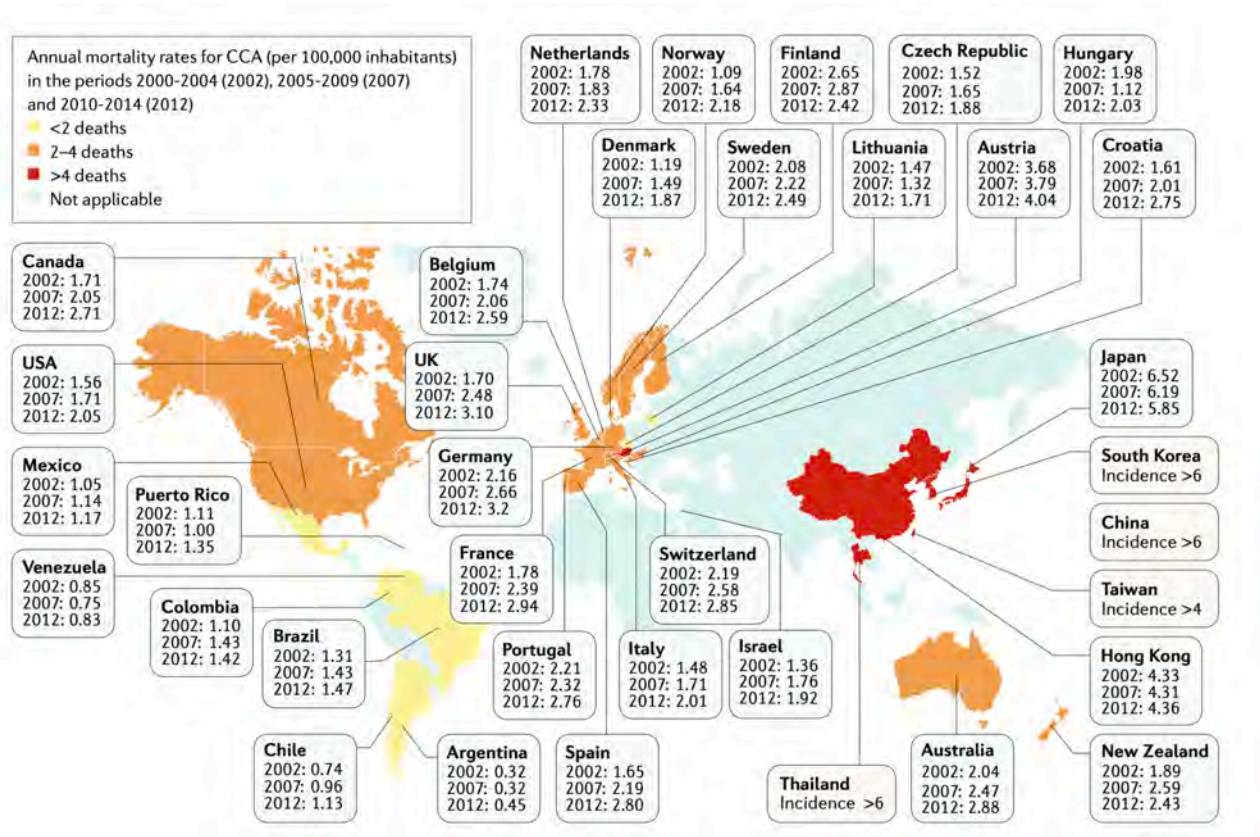
DATABASES

World Health Organization (WHO)
Pan-American Health Organization

32 COUNTRIES[2]

(Europe, Americas, Asia and Oceania)

Worldwide CCA mortality rates



POTENTIAL CAUSES: increased knowledge/awareness, better diagnosis and increasing incidence

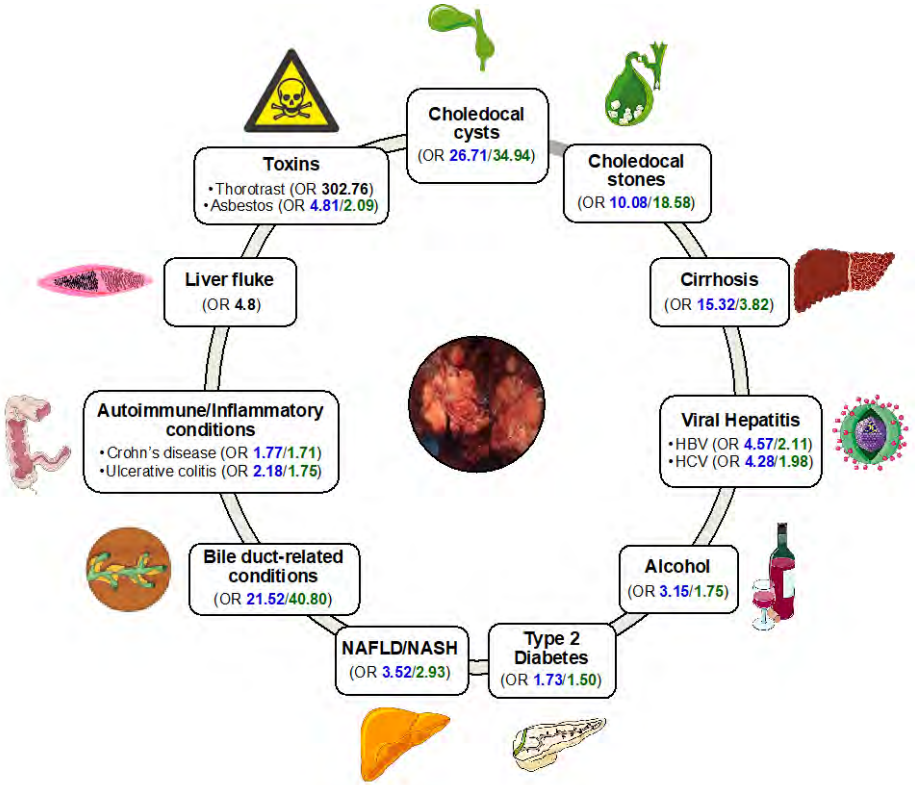
Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020

Risk factors

HIGH RISK[1]

- **Choledochal cysts**
- **Gallstones**
- **Cirrhosis**
- **Biliary diseases** (Caroli, **PSC**)
- **Virus** (HBV, HCV)
- **Liver flukes** (*O. viverrini* and *C. sinensis* in Asia)

Unclear aetiology (>50%)



MODERATE RISK but HIGHLY PREVALENT[1]

- Alcoholic liver disease
- Type II diabetes
- Tobacco use
- MASLD/MASH

AGE[2]**: median age = 66 years (75% >58 years)**

GERMLINE MUTATIONS[3,4]**: *BRCA1/2, ATM, BAP1*** ⇨ ↑ **CCA risk** (5% of cases)

1. Rodrigues PM,…,Banales JM. *Annu Rev Pathol*. 2021; 2. Izquierdo-Sanchez L,…,Banales JM. *J Hepatol*. 2022; 3. Lin J, et al. *Clin Cancer Res*. 2019; 4. Maynard H, et al. *Cancer* 2020

GWAS in CCA

Coordinator: **Dr. Lewis Roberts (Mayo Clinic, Rochester, USA)**

- >3000 CCA
- >1000 GBC

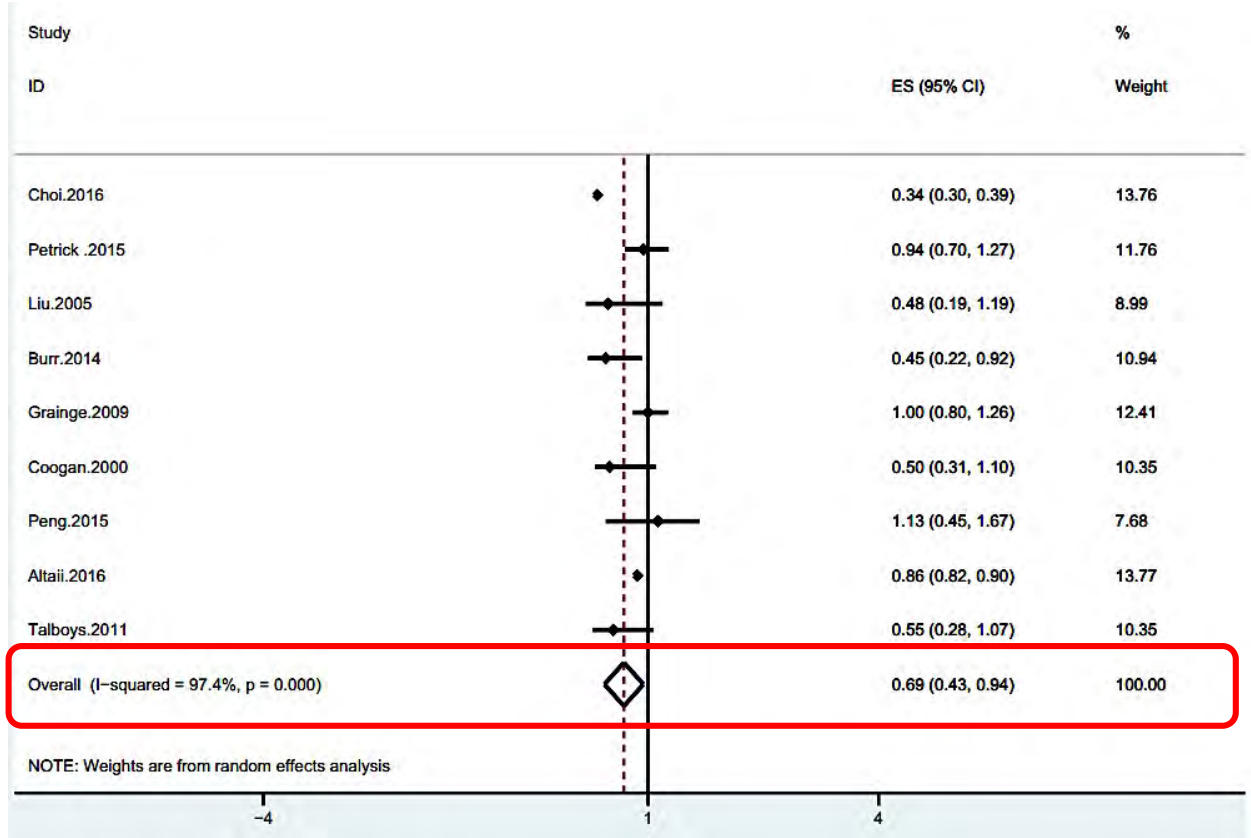
SNPs (genotyping)
National Cancer Institute (NCI, USA)

Next: **Validation Phase** (on going)


RISK

Aspirin: preventive?

Systematic review and meta-analysis (9 studies)
12,535 CCAs
92,970,450 Controls



Aspirin:

iCCA (OR=0.33)

eCCA (OR=0.56)

Xiong J, *et al*. *Cancer Manag Res* 2018

Aspirin: preventive?

The Asp-PSC trial

Asp-PSC: effect of aspirin on reducing cancer & improving outcomes in primary sclerosing cholangitis

Submission date
19/09/2023

Recruitment status
Not yet recruiting

Registration date
14/11/2023

Overall study status
Ongoing

Last Edited
01/12/2023

Condition category
Digestive System

- ✓ Prospectively registered
- ? Protocol not yet added
- ? SAP not yet added
- – Results not yet expected
- – Raw data not yet expected
- ✓ Record updated in last year

Prof. Shahid Khan

Prof. Simon Rushbrook

AMMF
THE CHOLANGIOCARCINOMA CHARITY

PSC Support

"ISRCTN12358813; https://doi.org/10.1186/ISRCTN12358813"

Statins & CCA

Taiwan[1]
Case-control study (2002-2011)
3,174 CCAs and 3,174 Controls

Variable	Cases/Controls 3174/3174	OR	(95% CI)
Medications	*n1/n2*		
All statins	720/840	0.80	(0.71, 0.90)***
Individual statin			
Simvastatin	262/368	0.68	(0.57, 0.80)***
Lovastatin	244/337	0.69	(0.58, 0.83)***
Pravastatin	131/197	0.65	(0.52, 0.82)***
Fluvastatin	143/183	0.77	(0.61, 0.96)*
Atorvastatin	357/489	0.69	(0.60, 0.80)***
Rosuvastatin	141/210	0.65	(0.52, 0.82)***

n, number of persons on the medicine. $^{**}P < 0.01$, $^{***}P < 0.001$

UK[2]
Case-control study (1990-2017)
3,118 CCAs and 15,519 Controls

Table 2 Association between statin use and biliary tract cancers, CPRD

Characteristic	Case (n=3118)	Control (n=15519)	Adjusted OR (95% CI)*
Any statin use			
Non-users	2159 (69.2)	10934 (70.5)	Ref
Ever	959 (30.8)	4585 (29.5)	0.92 (0.83 to 1.02)
Former†	199 (6.4)	831 (5.4)	1.10 (0.92 to 1.31)
Current	760 (24.4)	3754 (24.2)	0.88 (0.79 to 0.98)

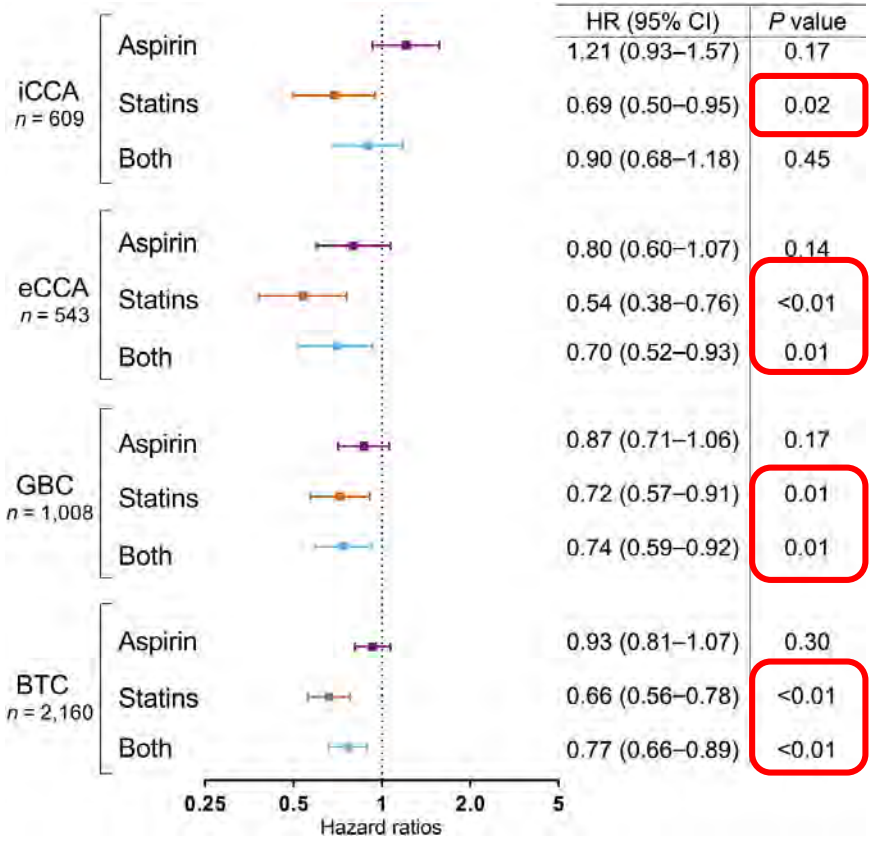
Statins
↓ CCA risk (12-20%)
More pronounced among long-term users

1. Peng YC, *et al. Br J Clin Pharmacol*. 2015; 2. Liu Z, *et al. Gut*. 2019

Aspirin and/or Statins: preventive?

Swedish population-based cohort

5.7 M people (without personal history of cancer)



2,160 individuals developed BTC

Low-dose aspirin → NOT associated with CCA risk

Statins +/- **low-dose aspirin** → ↓ risk iCCA & eCCA

Marcano-Bonilla L, *et al*. *Cancer Epidemiol Biomarkers Prev.* 2022

CHOLANGIOCARCINOMA (CCA)

1. Epidemiology and general features

2. **Natural course**

3. Novel therapeutic strategies

Diagnosis

- **Incidental finding** (~25% of cases)
- **Unspecific symptoms**

Jaundice

Fever

Weight loss

Fatigue

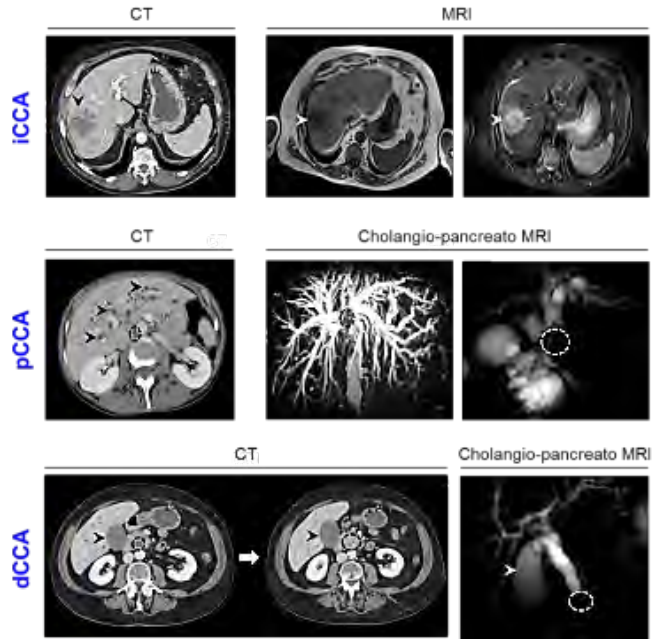
Abdominal pain

Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020

Diagnosis

IMAGING[1,2]

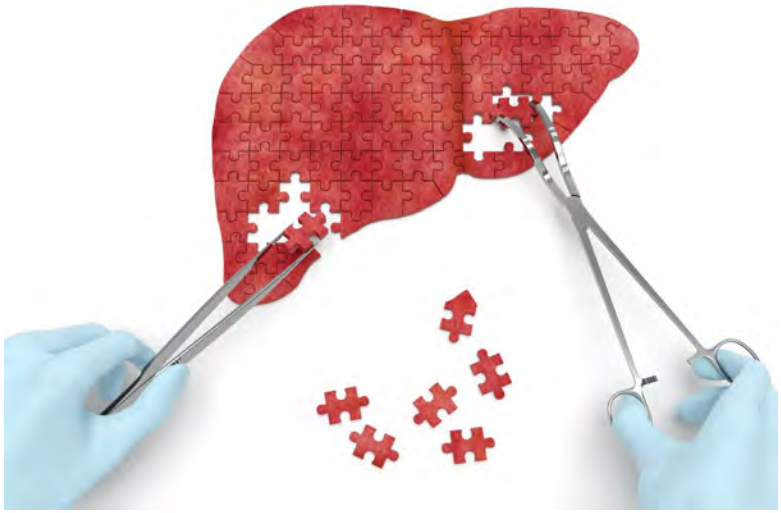
(CT, MRI, MRCP, PET)



NON-SPECIFIC TUMOUR MARKERS[1]

(CA19-9, CEA)

BIOPSY/CYTOLOGY[3]



CA, carbohydrate antigen; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; CT, computed tomography; dCCA, distal CCA; iCCA, intrahepatic CCA; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PET, positron-emission tomography.

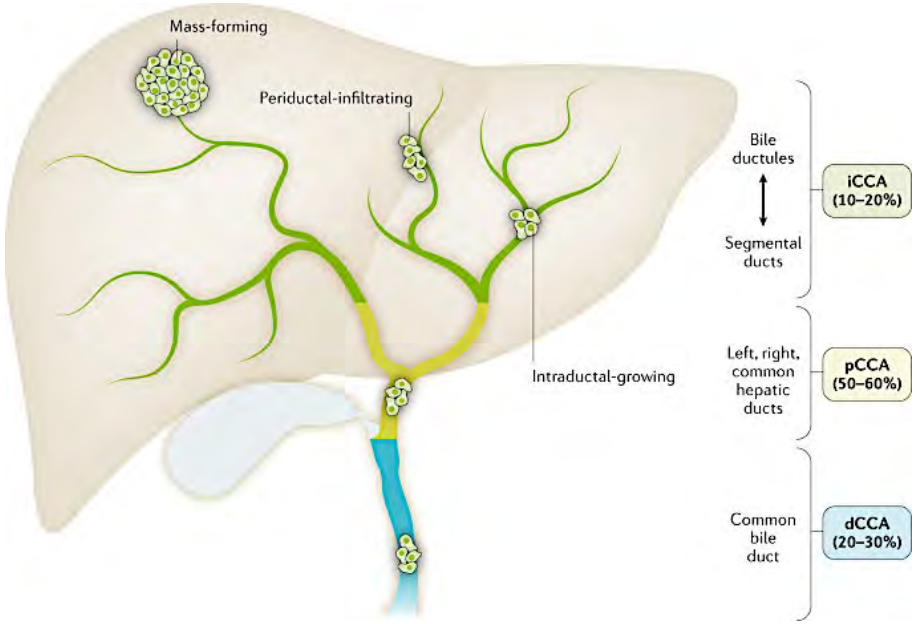
1. Van Beers BE. *HPB (Oxford).* 2008; 2. Oihane E,..., Banales JM. *Curr Drug Targets*. 2017; 3. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020

Classification

International Classification of Diseases, 11th Edition (ICD-11, 2019)[1]

Effective: January 2022

ANATOMICAL ORIGIN[2]



Potential differences[2]

Etiopathogenesis

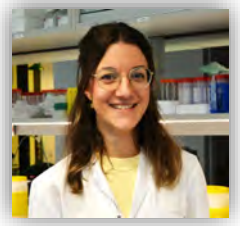
Risk factors

Incidence

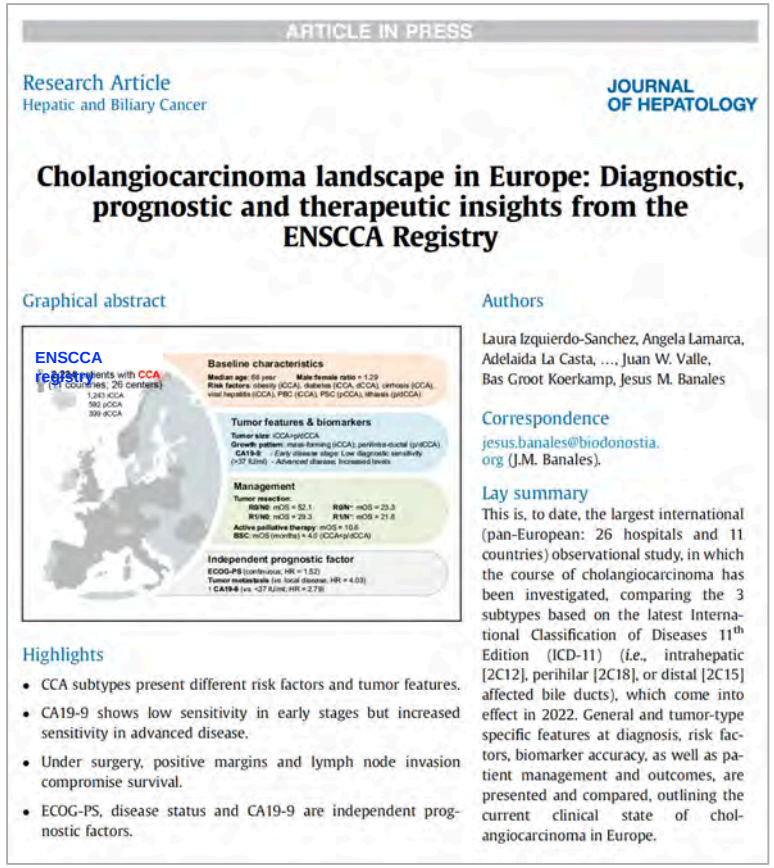
Prognosis

CCA, cholangiocarcinoma; dCCA, distal CCA; iCCA, intrahepatic CCA; pCCA, perihilar CCA.

1. World Health Organization. International Classification of Diseases 11th Revision. Version 02/2022. https://icd.who.int/browse11/l-m/en (accessed July 2022); 2. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020



Dr. Laura Izquierdo



ARTICLE IN PRESS

Research Article
Hepatic and Biliary Cancer

JOURNAL OF HEPATOLOGY

Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry

Graphical abstract

Highlights

- CCA subtypes present different risk factors and tumor features.
- CA19-9 shows low sensitivity in early stages but increased sensitivity in advanced disease.
- Under surgery, positive margins and lymph node invasion compromise survival.
- ECOG-PS, disease status and CA19-9 are independent prognostic factors.

Authors

Laura Izquierdo-Sanchez, Angela Lamarca, Adelaida La Casta, …, Juan W. Valle, Bas Groot Koerkamp, Jesus M. Banales

Correspondence

jesus.banales@biodonostia.org (J.M. Banales).

Lay summary

This is, to date, the largest international (pan-European: 26 hospitals and 11 countries) observational study, in which the course of cholangiocarcinoma has been investigated, comparing the 3 subtypes based on the latest International Classification of Diseases 11th Edition (ICD-11) (*i.e.*, intrahepatic [2C12], perihilar [2C18], or distal [2C15] affected bile ducts), which come into effect in 2022. General and tumor-type specific features at diagnosis, risk factors, biomarker accuracy, as well as patient management and outcomes, are presented and compared, outlining the current clinical state of cholangiocarcinoma in Europe.

European Network for the Study of Cholangiocarcinoma Database

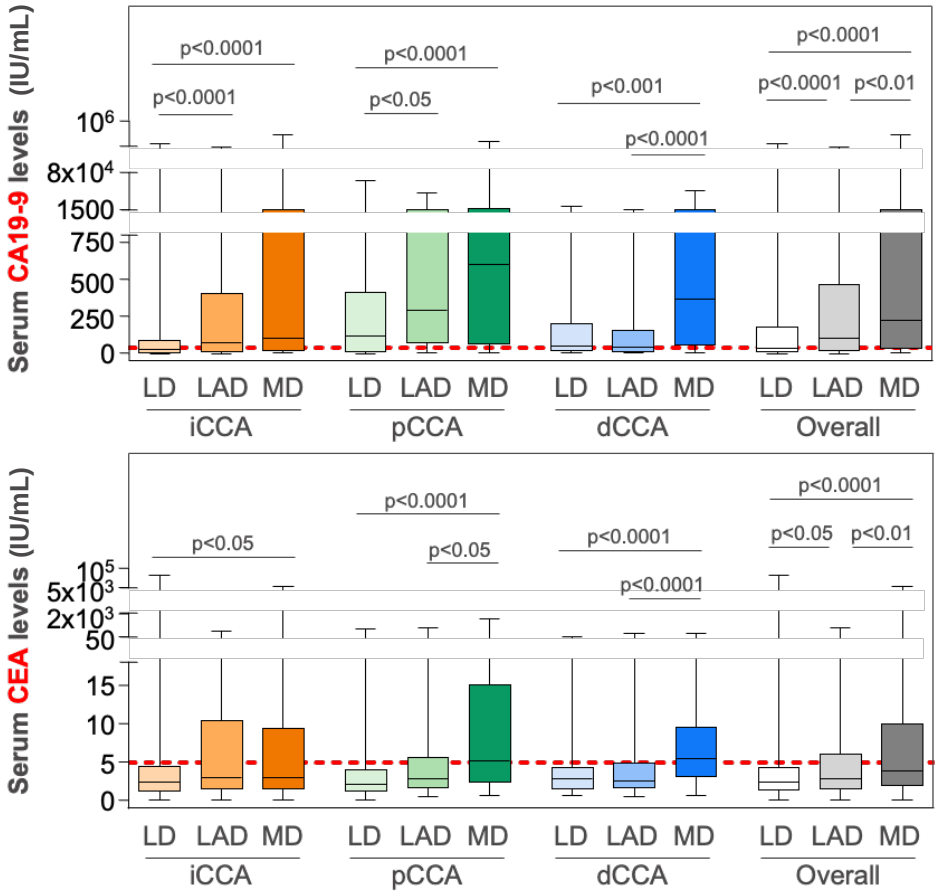
AIM

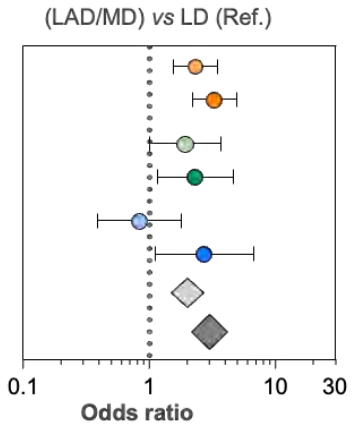
Investigate the **natural course** of CCA and its **subtypes** in hospitals from the ENSCCA

CA, carbohydrate antigen; CCA, cholangiocarcinoma; ECOG-PS, Eastern Cooperative Oncology Group performance status; ENSCCA, European Network for the Study of CCA.

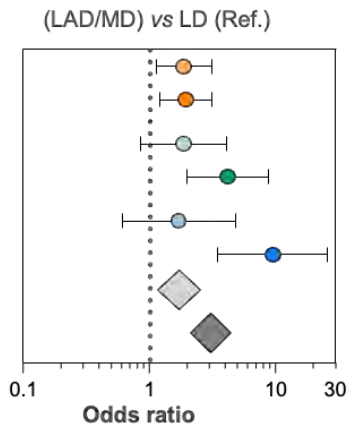
Izquierdo-Sanchez L,…,Banales JM. *J Hepatol*. 2022

Serum tumour biomarkers – *CA19.9 and CEA*





	LAD	MD
iCCA	**2.33** (1.56–3.48)	**3.30** (2.20–4.95)
pCCA	**1.93** (1.00–3.70)	**2.31** (1.16–4.61)
dCCA	**0.84** (0.39–1.81)	**2.73** (1.11–6.76)
CCA (overall)	**1.99** (1.47–2.70)	**3.04** (2.21–4.17)

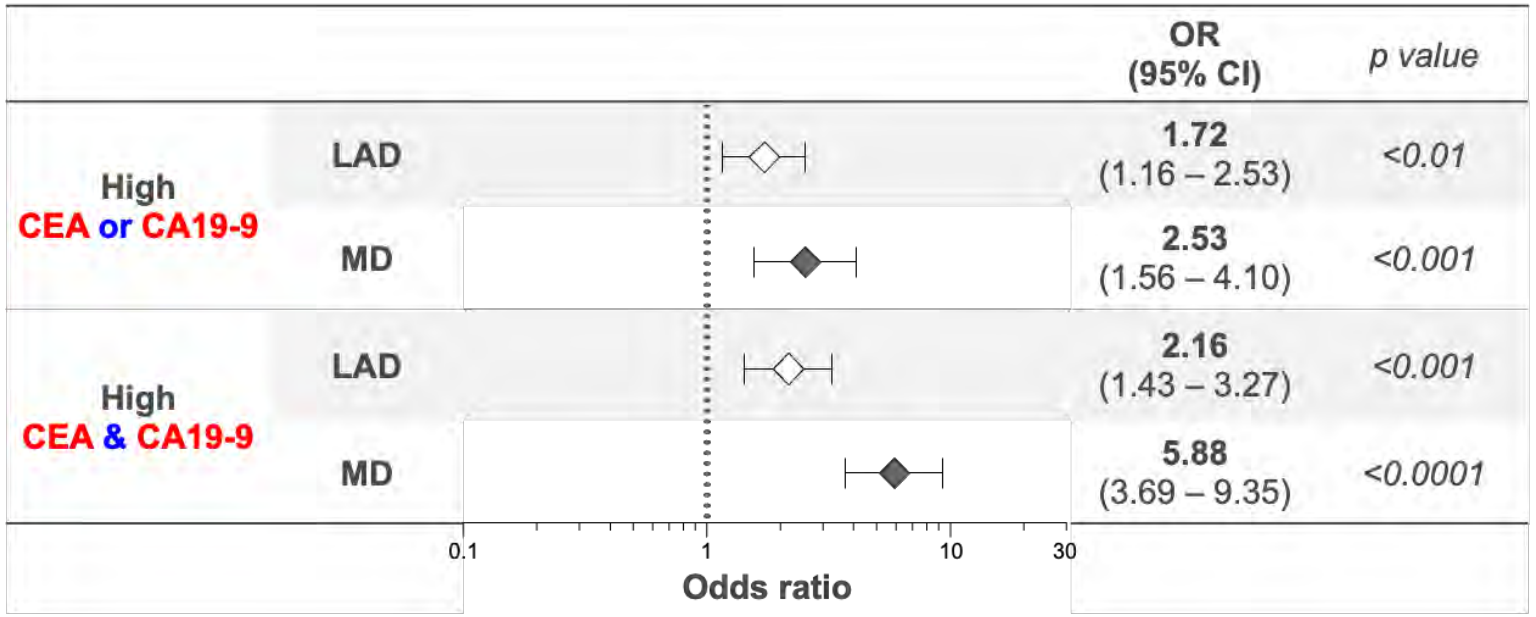


	LAD	MD
iCCA	**1.86** (1.13–3.07)	**1.92** (1.19–3.09)
pCCA	**1.85** (0.84–4.03)	**4.12** (1.96–8.68)
dCCA	**1.69** (0.60–4.78)	**9.40** (3.44–25.64)
CCA (overall)	**1.71** (1.16–2.51)	3.03 (2.11–4.35)

CA, carbohydrate antigen; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; dCCA, distal CCA; iCCA, intrahepatic CCA; LAD, locally advanced disease; LD, local disease; MD, metastatic disease; pCCA, perihilar CCA.

Izquierdo-Sanchez L,…,Banales JM. *J Hepatol*. 2022

Serum tumour biomarkers – *CA19.9 and CEA*



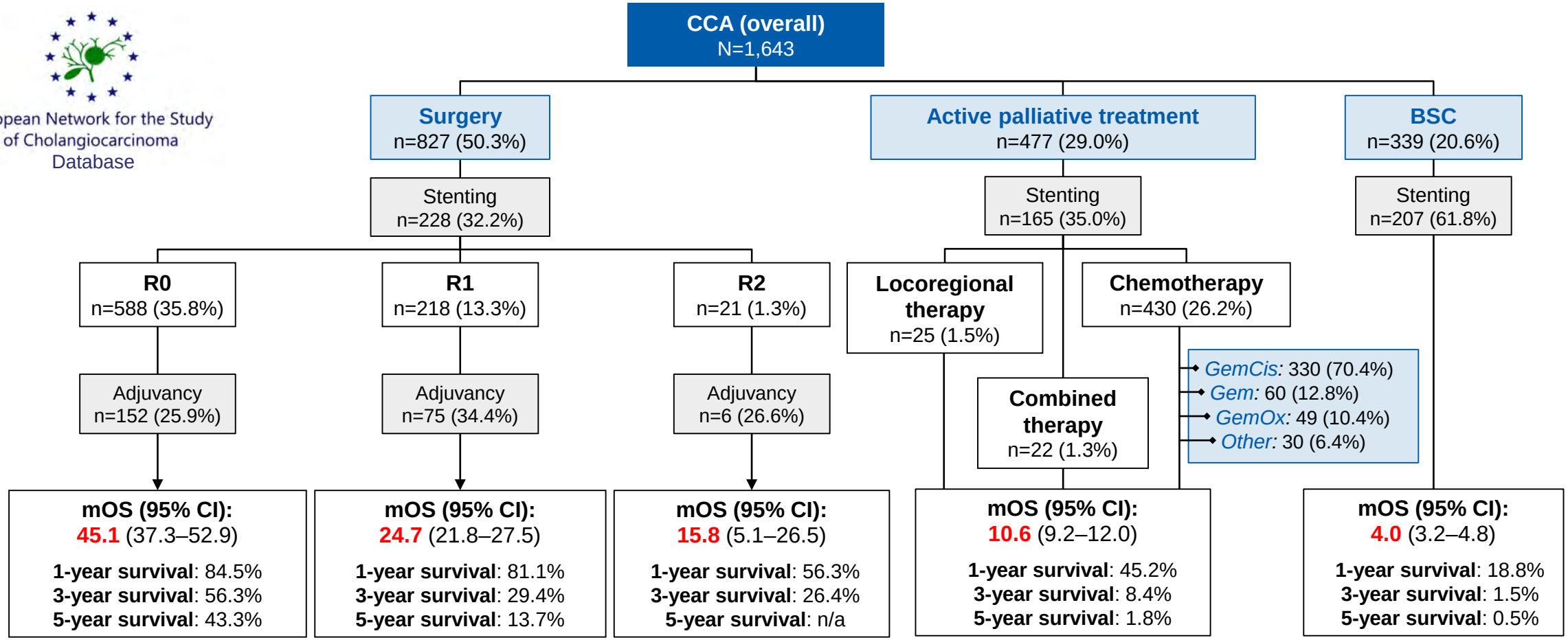
Note: CA19.9 (Lewis Ag A) is not expressed in 10% population (*FUT3* fucosyltransferase deficiency)

CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CI, confidence interval; LAD, locally advanced disease; MD, metastatic disease; OR, odds ratio.

Izquierdo-Sanchez L,…,Banales JM. *J Hepatol*. 2022

Clinical management and survival

European Network for the Study of Cholangiocarcinoma Database



Izquierdo-Sanchez L,…,Banales JM. *J Hepatol*. 2022

Prognosis

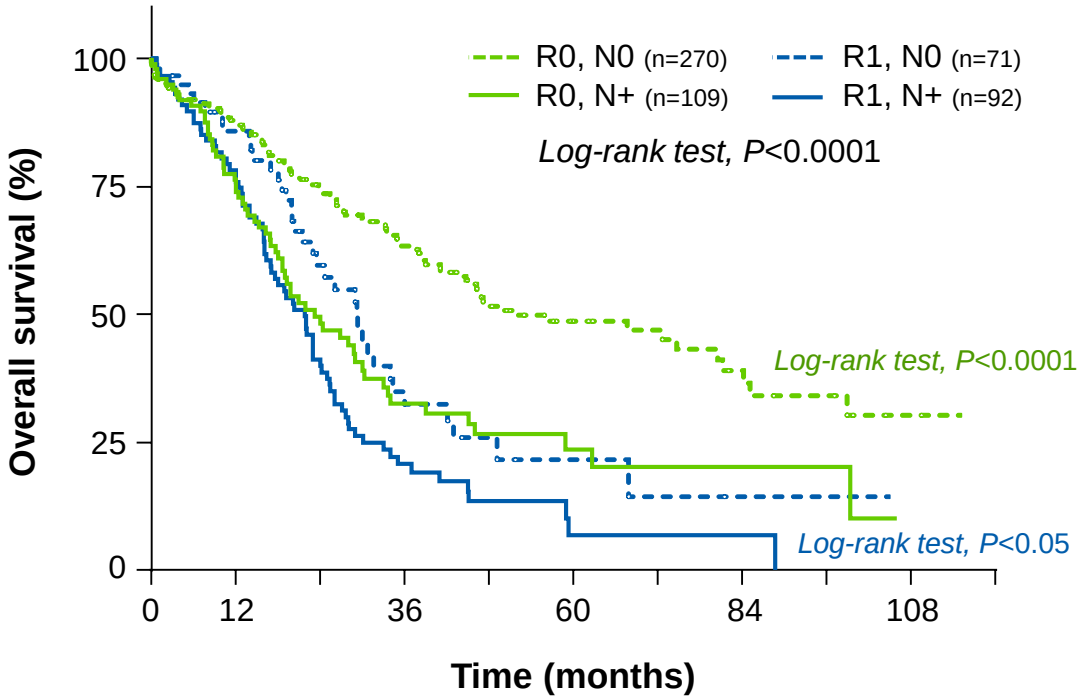
		UNIVARIATE			MULTIVARIATE		
COVARIABLES	**Deaths**, n(%)	**HR**	**95% CI**	*p value*	**HR**	**95% CI**	*p value*
Subtype of CCA, *(vs pCCA)*							
iCCA	1,348 (68.7)	**0.74**	0.65 – 0.84	*<0.0001*	**1.48**	0.74 – 2.97	*ns*
dCCA		**0.67**	0.57 – 0.78	*<0.0001*	**1.31**	0.50 – 3.44	*ns*
Age, *≥65 (vs <65)*	1,348 (68.7)	**1.28**	1.15 – 1.42	*<0.0001*	**1.24**	0.70 – 2.22	*ns*
Sex, *male (vs female)*	1,348 (68.7)	**1.12**	1.00 – 1.24	*<0.05*	**0.99**	0.58 – 1.70	*ns*
ECOG-PS, *(continuous)*	1,247 (72.2)	**1.66**	1.56 – 1.78	*<0.0001*	**1.52**	1.01 – 2.31	***<0.05***
Disease status, *(vs local disease)*							
locally advanced disease	1,098 (72.9)	**1.91**	1.65 – 2.22	*<0.0001*	**1.68**	0.87 – 3.25	*ns*
metastatic disease		**3.46**	2.98 – 4.02	*<0.0001*	**4.03**	1.82 – 8.92	***<0.01***
CEA, *≥5 (vs <5)*	487 (62.0)	**2.02**	1.67 – 2.43	*<0.0001*	**1.19**	0.65 – 2.19	*ns*
CA19-9, *≥37 (vs <37)*	660 (61.1)	**2.02**	1.70 – 2.37	*<0.0001*	**2.79**	1.46 – 5.33	***<0.01***
ALT, *≥45 (vs <45)*	853 (63.5)	**1.15**	1.00 – 1.31	*<0.05*	**1.26**	0.62 – 2.59	*ns*
AST, *≥40 (vs <40)*	1,180 (69.8)	**1.43**	1.27 – 1.61	*<0.0001*	**0.48**	0.21 – 1.09	*ns*
GGT, *≥71 (vs <71)*	1,189 (70.1)	**1.96**	1.68 – 2.28	*<0.0001*	**1.51**	0.69 – 3.31	*ns*
ALP, *≥129 (vs <129)*	1,014 (70.2)	**1.80**	1.57 – 2.06	*<0.0001*	**1.24**	0.57 – 2.71	*ns*
Albumin, *<5.2 (vs ≥5.2)*	556 (71.5)	**0.26**	0.08 – 0.82	*<0.05*	**0.28**	0.03 – 2.64	*ns*
Bilirubin, *≥1.3 (vs <1.3)*	1,209 (70.0)	**1.41**	1.26 – 1.58	*<0.0001*	**0.98**	0.49 – 1.95	*ns*

Note: **bold and red** text signifies data of interest.

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CA, carbohydrate antigen; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; CI, confidence interval; dCCA, distal CCA; ECOG-PS, Eastern Cooperative Oncology Group performance status; GGT, gamma glutamyltransferase; HR, hazard ratio; iCCA, intrahepatic CCA; ns, not significant; pCCA, perihilar CCA.

Izquierdo-Sanchez L,…,Banales JM. *J Hepatol*. 2022

Post-surgical evaluation: Lymph node invasion



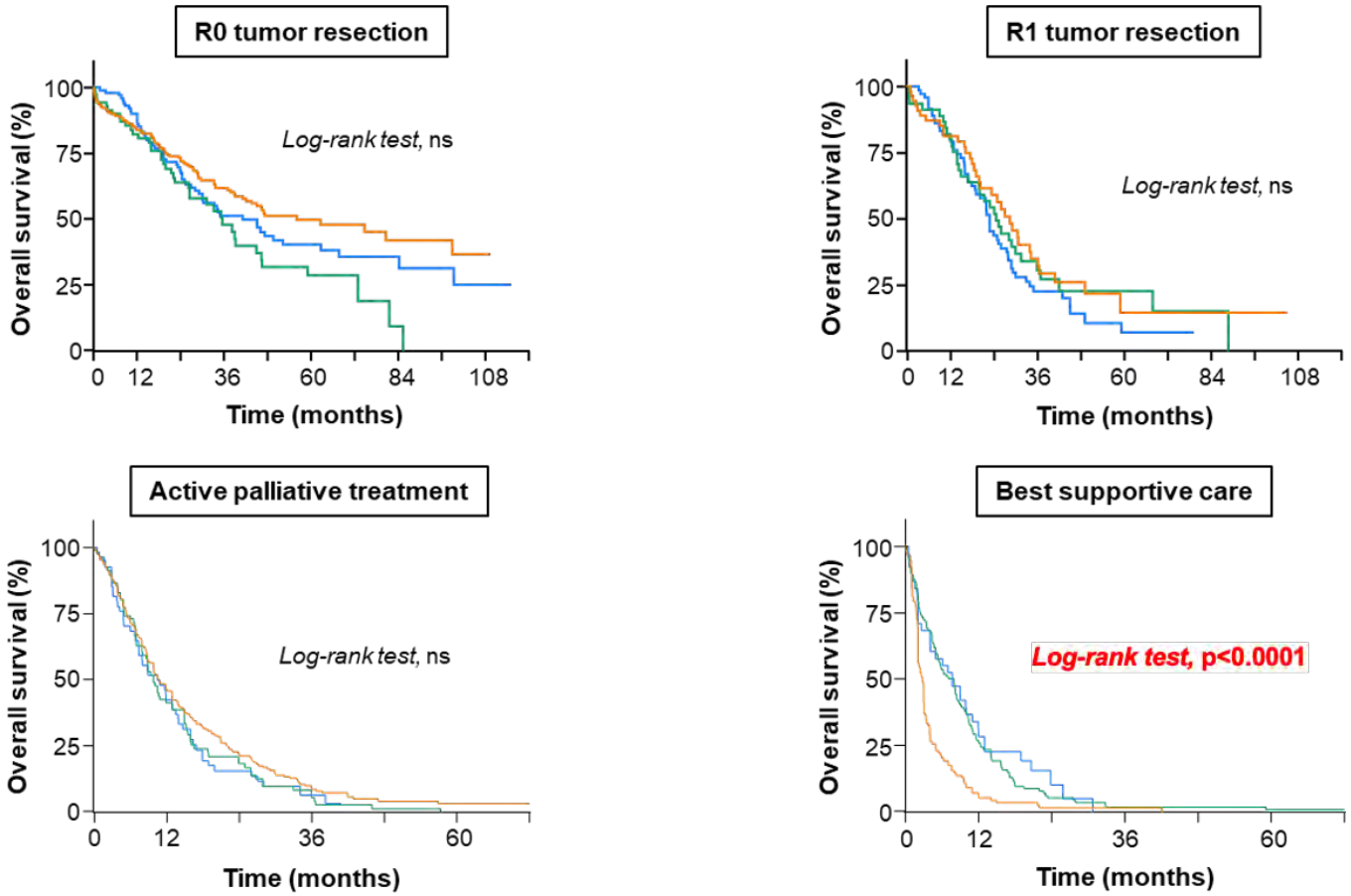
	R0		R1	
	N0	N+	N0	N+
mOS, months (95% CI)	**52.2** (33.5–71.0)	**23.3** (15.5–31.0)	**29.3** (23.1–35.5)	**21.8** (17.9–25.8)
HR (95% CI)	**1** (Ref)	**2.13** (1.55–2.94)	**1.88** (1.28–2.76)	**3.02** (2.22–4.11)
	0.33 (0.24–0.45)	**0.71** (0.50–0.99)	**0.62** (0.42–0.93)	**1** (Ref)

CI, confidence interval; ENSCCA, European Network for the Study of CCA; HR, hazard ratio; mOS, median overall survival; N+, evidence of node invasion; N0, no evidence of node invasion; R0, null margin tumour resection; R1, microscopic residual disease tumour resection; ref, reference datapoint.

Izquierdo-Sanchez L,…,Banales JM. *J Hepatol*. 2022

Clinical management and survival – *CCA subtypes*

iCCA
pCCA
dCCA

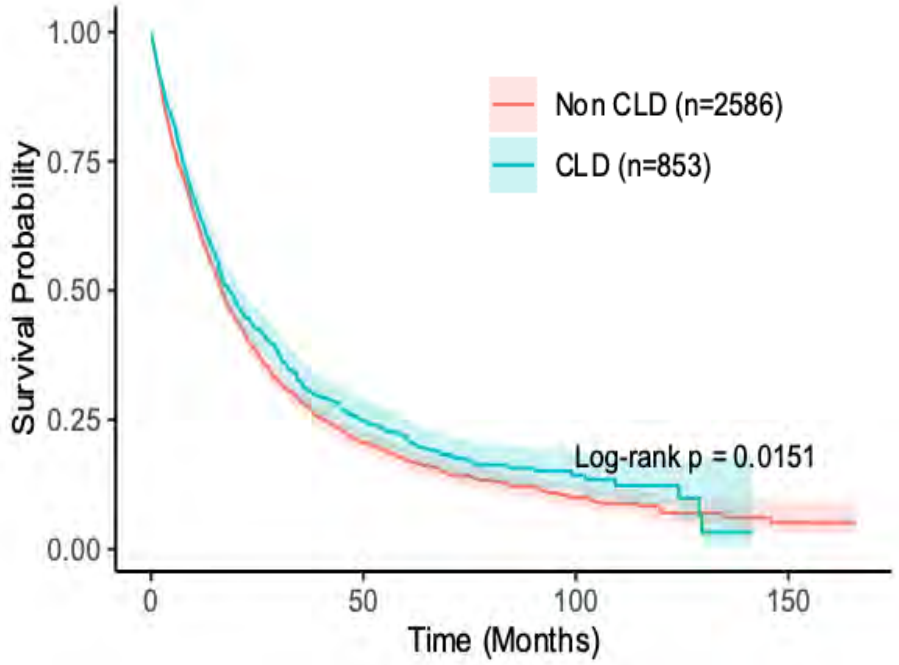


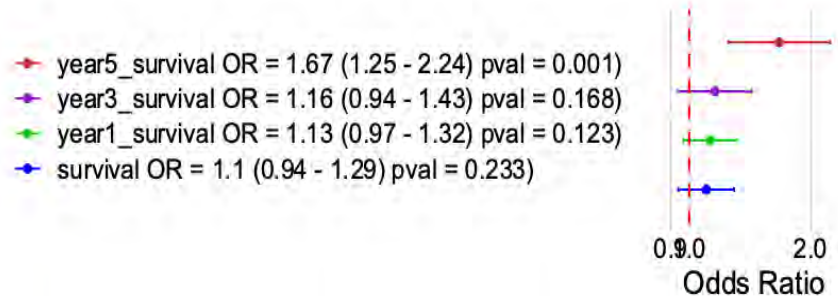
CCA, cholangiocarcinoma; dCCA, distal CCA; iCCA, intrahepatic CCA; ns, not significant; pCCA, perihilar CCA; R0, null margin tumour resection; R1, microscopic residual disease tumour resection.

Izquierdo-Sanchez L,…,Banales JM. *J Hepatol*. 2022

Cholangiocarcinoma in individuals with chronic liver disease is diagnosed earlier, leading to better prognosis

Laura Izquierdo-Sanchez[1,2], Julen Matin-Robles[1], Angela Lamarca[3], Adelaida La Casta[1], Heinz-Josef Klümpen[4], Arun Valsan[5], Stephanie Rössler[6,7], Chiara Braconi[8,9], Leonardo G. da Fonseca[10,11], Cristina Dopazo[12,13], Trine Folseraas[14,15,16,17], Bas Groot Koerkamp[18], Domingo Balderramo[19], Mariano Ponz-Sarvise[20], Javier Díaz Ferrer[21], Krzysztof Zieniewicz[22], Zeno Sparchez[23], Kirsten Utpatel[24], Markus Peck-Radosavljevic[25], Alejandro Forner[2,26], Ylenia Pérez Castaño[1], Luis Bujanda[1,2], Jesus M. Banales[1,2,27,28]; *on behalf of the International Cholangiocarcinoma Registry.*





Manuscript under preparation

THE LANCET Regional Health Americas

Cholangiocarcinoma in Latin America: a multicentre observational study alerts on ethnic disparities in tumour presentation and outcomes

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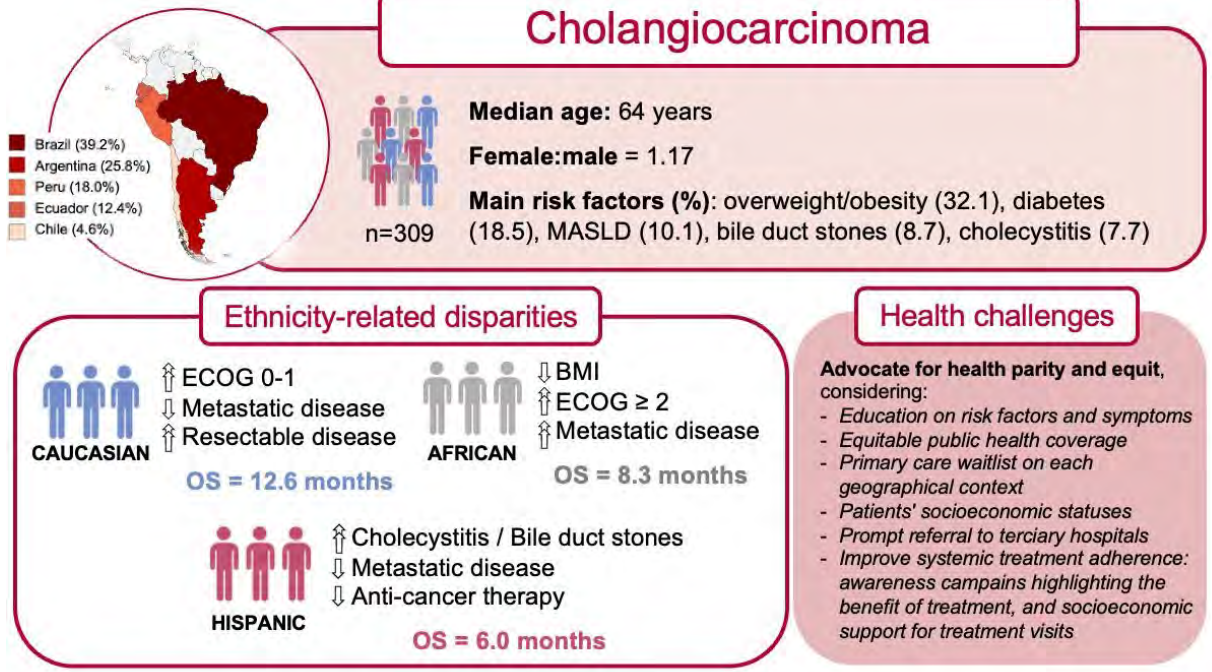
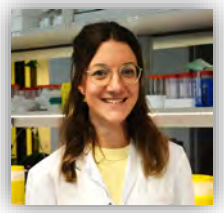


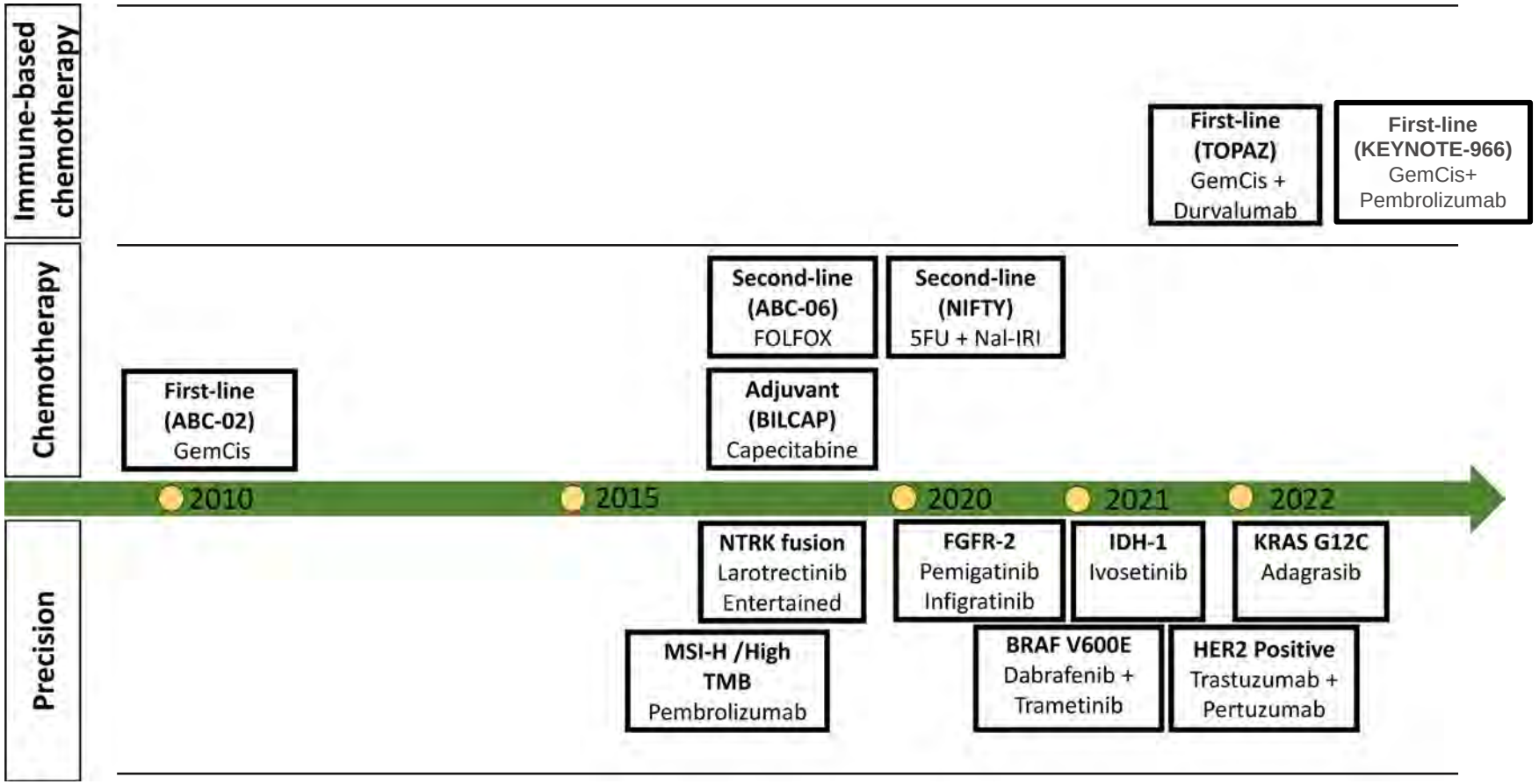
Dr. Leo Da Fonseca



Dr. Laura Izquierdo

Fonseca L,…,Banales JM. *Lancet Reg Health Am.* 2024

Systemic therapies



Harding JJ *et al*. *J Hepatol.* 2022

Immunotherapy – *Monotherapy*

- Low efficacy in BTC (CCA)

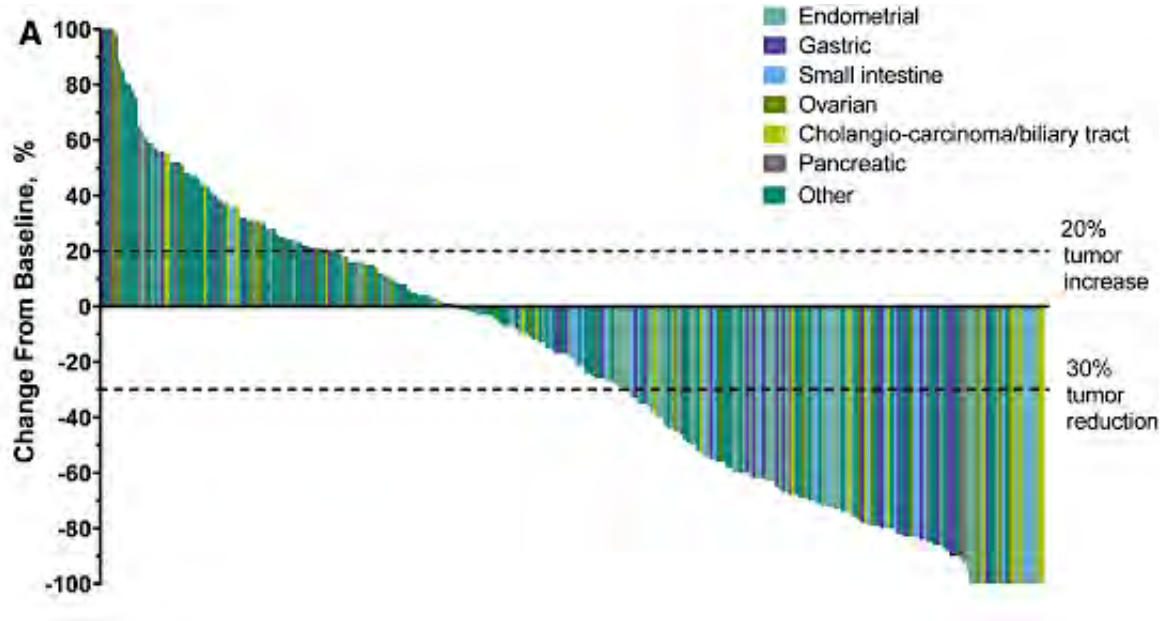
***Immune Check-point Inhibitors* (ICI)**
(PD-1, PD-L1, CTLA-4)

TREATMENT	POPULATION OF STUDY	ORR	REFERENCES
Durvalumab *(Anti-PD-L1)*	Unselected BTC *Asia*	4.8% (2/42)	Ioka et al. 2019 (NCT01938612)
Durvalumab + tremelimumab *(Anti-PD-L1 + anti-CTLA4)*	Unselected BTC *Asia*	10.8% (7/65)	Ioka et al. 2019 (NCT01938612)
Atezolizumab *(Anti-PD-L1)*	Unselected BTC *North America*	2.9% (1/34)	CTEP10139 (NCT03201458)
Nivolumab *(Anti-PD1)*	Unselected BTC *China*	20.0% (6/30)	Gou et al. 2019
Nivolumab *(Anti-PD1)*	Unselected BTC *USA*	22% (10/45)	Kim et al. 2019 (NCT02829918)
Nivolumab *(Anti-PD1)*	Unselected BTC *Japan*	3.3% (1/30)	Ueno et al. 2019 (JapicCTI-153098)
Pembrolizumab *(Anti-PD1)*	Unselected BTC *International*	5.8% (6/104)	Ueno et al. 2018 (KEYNOTE-158/NCT02628067)
Pembrolizumab *(Anti-PD1)*	PD-L1* BTC *Korea*	11.1% (4/36)	Kang et al. 2019 (NCT03201458)

Modified from Shroff R, CCF 2022

Immunotherapy – *Monotherapy in patients with **MSI-H/dMMR***

Pembrolizumab (anti-PD1)



Keynote-158 study

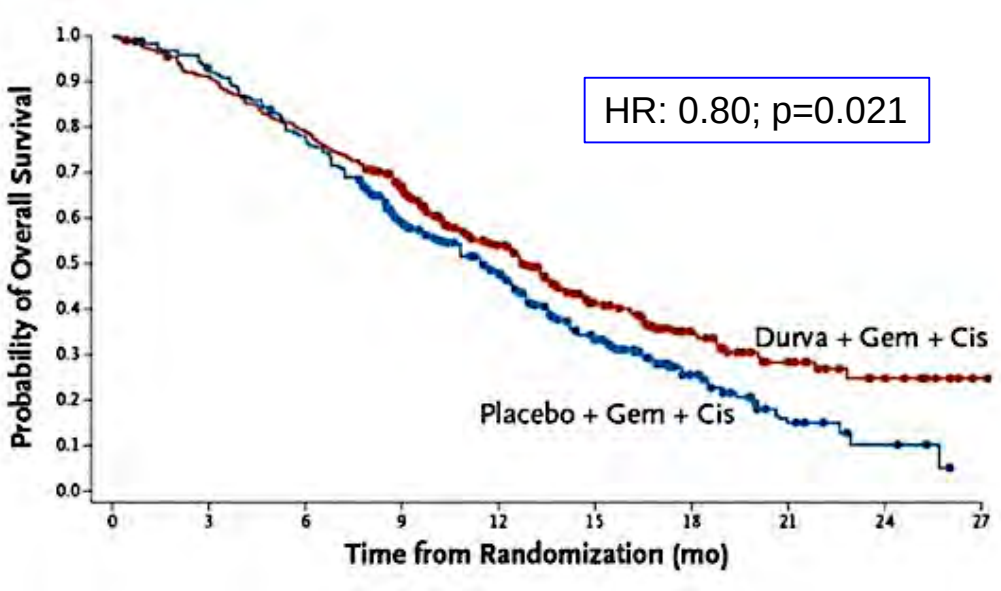
22/351 patients with CCA

- **Response rate: 40.9%**
- **Duration of response: 30.6 mo**
- **mPFS: 3.5 mo**
- **mOS: 19.4 mo**

Maio M, et al. *Ann Oncol*. 2022;33(9):929-938

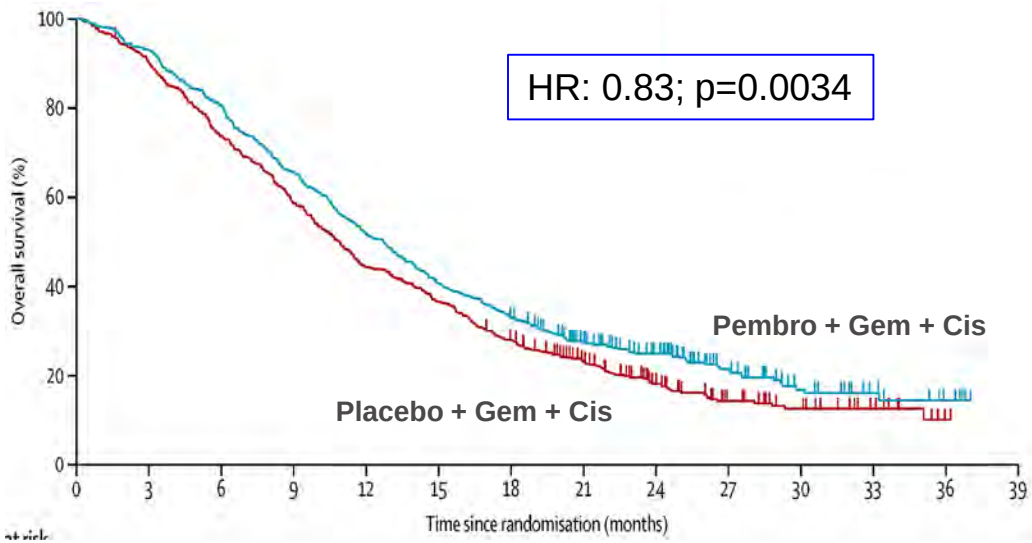
Immunotherapy – *combination therapies (**1st line**)*

TOPAZ-1[1]
Durvalumab (Anti-PD-L1) + GemCis
vs Placebo + GemCis



HR: 0.80; p=0.021

KEYNOTE-966[2]
Pembrolizumab (Anti-PD-1) + GemCis
vs Placebo + GemCis

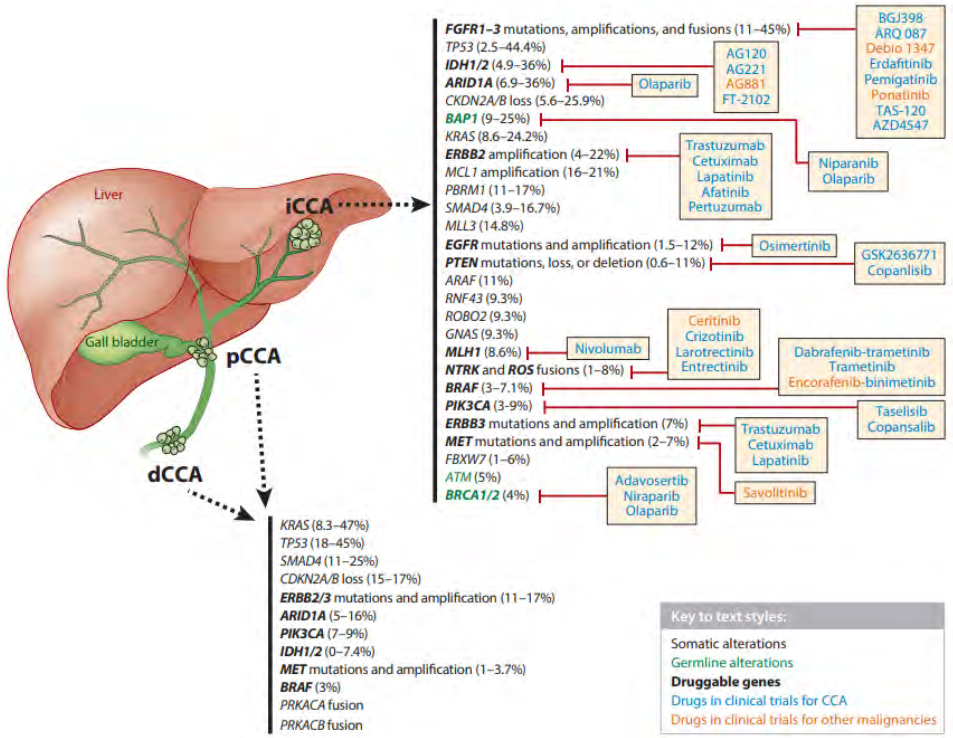


HR: 0.83; p=0.0034

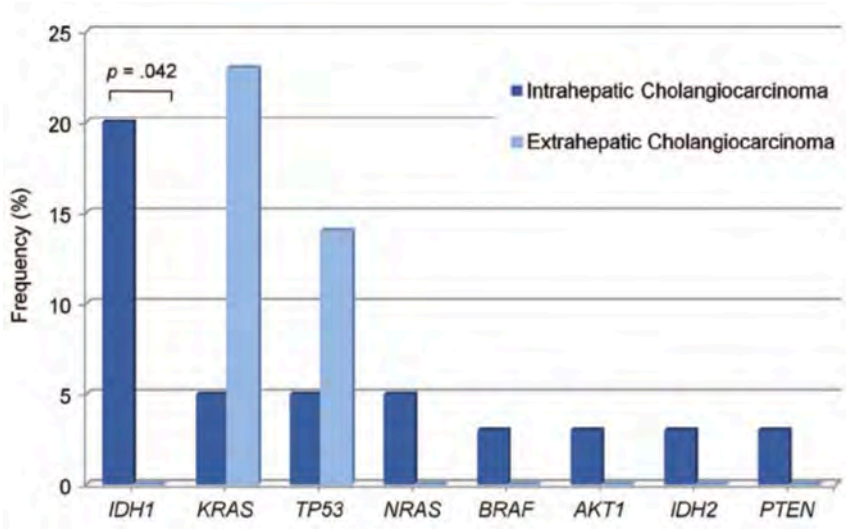
1. Do-Youn Oh, *et al. N Engl J Med-Evidence* 2022; 2. Kelly RK, *et al. Lancet* 2023

CCA tumors – *highly heterogeneous* (mut level)

Frequencies of most common genomic alterations in CCA and potential targeted therapies[1]



Frequency across CCA subtypes: iCCA vs eCCA (p/dCCA)[2]

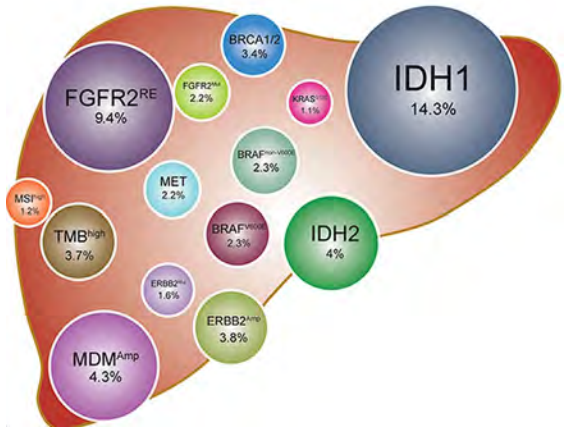


+FGFR2 fusions (10-15%) in iCCAs

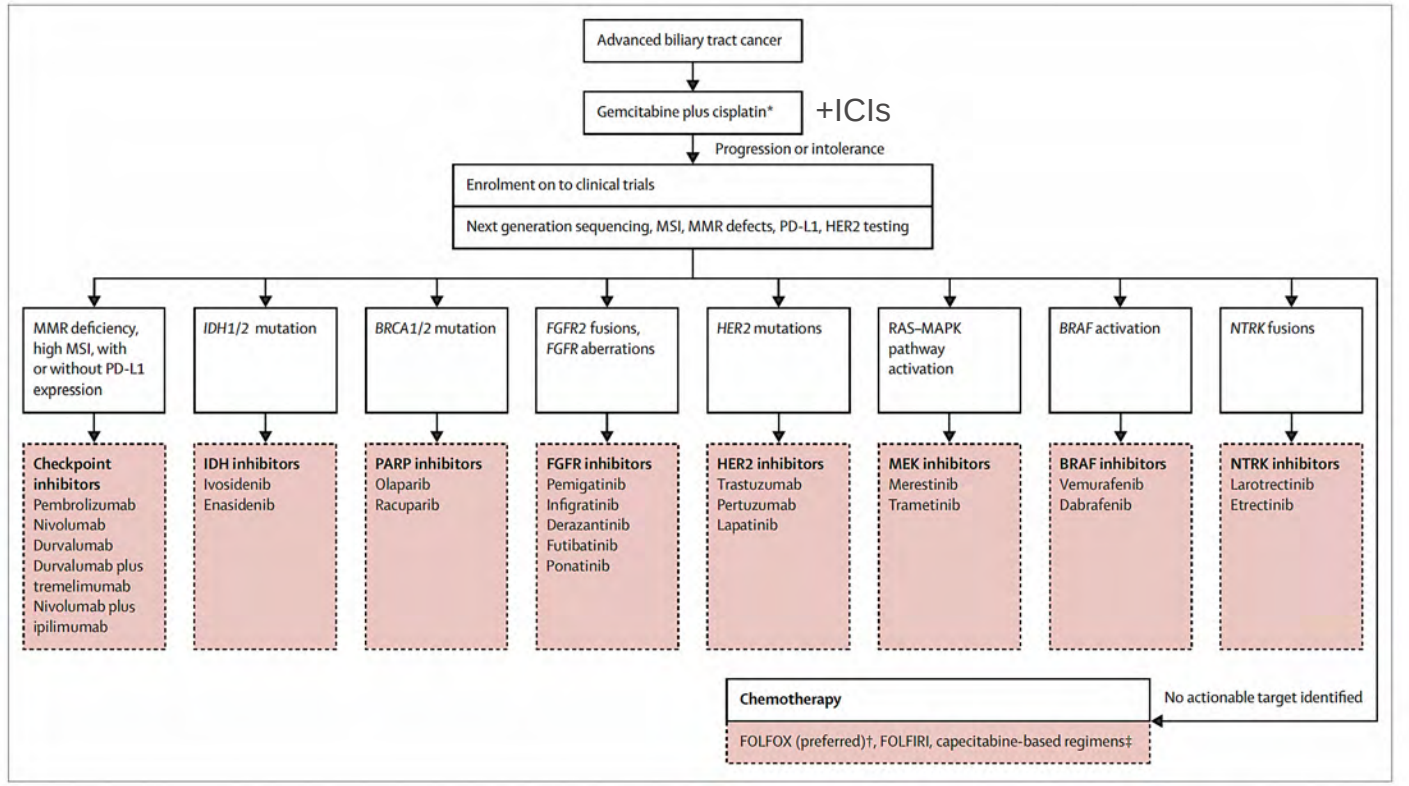
1. Rodrigues PM,…,Banales JM. *Annu Rev Pathol.* 2021; 2. Borger DR, *et al. The Oncologist* 2012

CCA tumors – *actionable alterations*

Precision medicine
(40% mutated genes are actionable)[1]



2nd line drugs for advanced BTC[2]



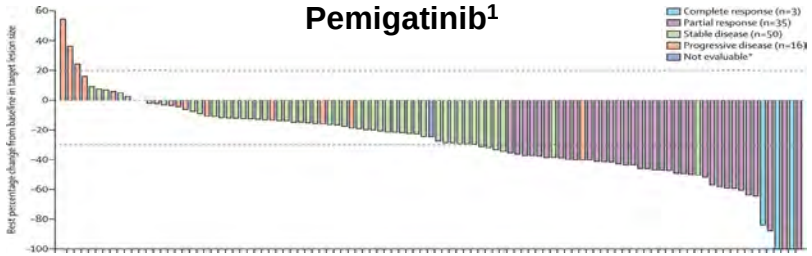
BTC, biliary tract cancer

1. Kendre G, et al. *J Hepatol.* 2023; 2. Modified from Tella SH, et al. *Lancet Oncol.* 2020

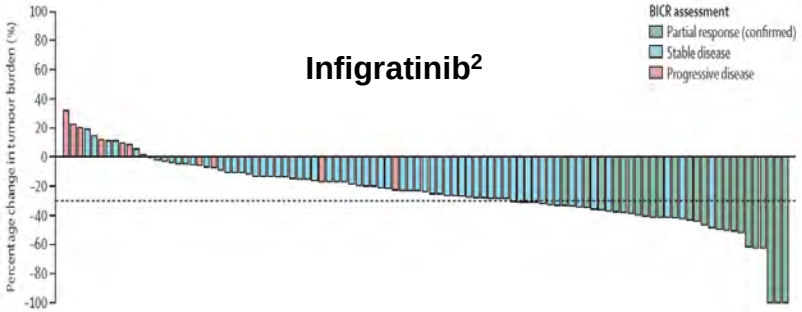
Targeted therapies – *2nd line*

FGFR2-fusions

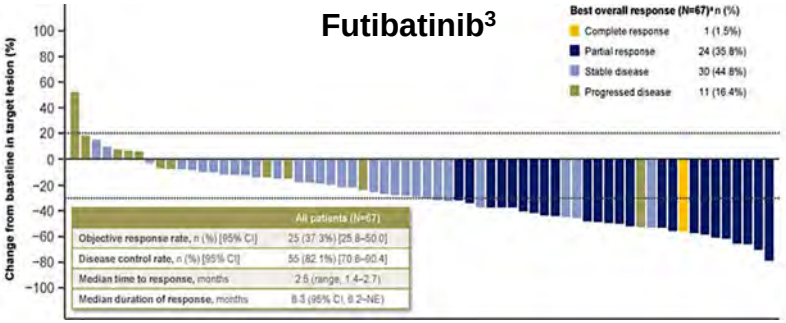
Pemigatinib[1]



Infigratinib[2]

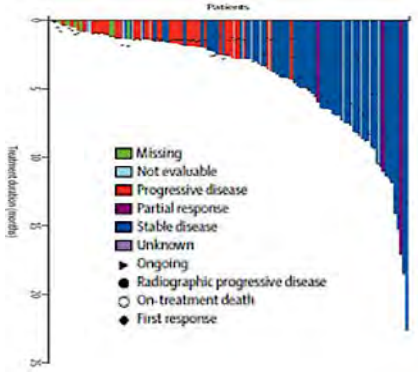


Futibatinib[3]



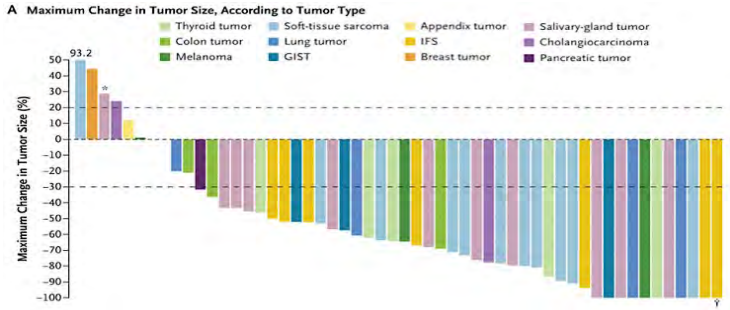
IDH1-mut

Ivosidenib[4]



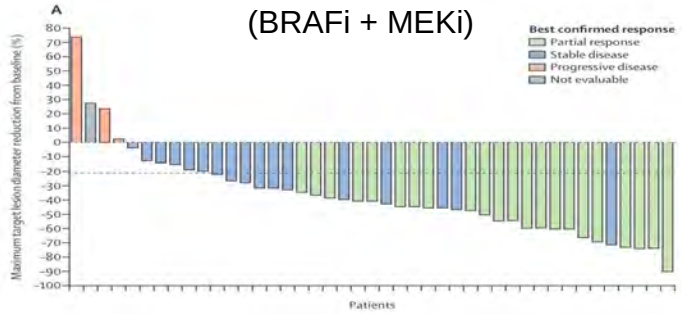
NTRK-fusions

Larotrectenib[5]



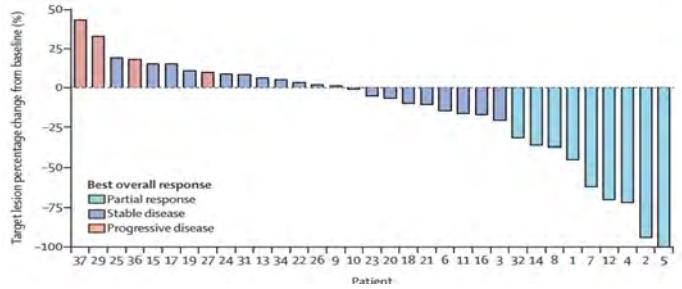
BRAF^{V600E} -mut

Dabrafenib + trametinib[6]
(BRAFi + MEKi)



ERBB2 mut/amplify

Pertuzumab + trastuzumab[7]
(Anti-HER2 Abs)



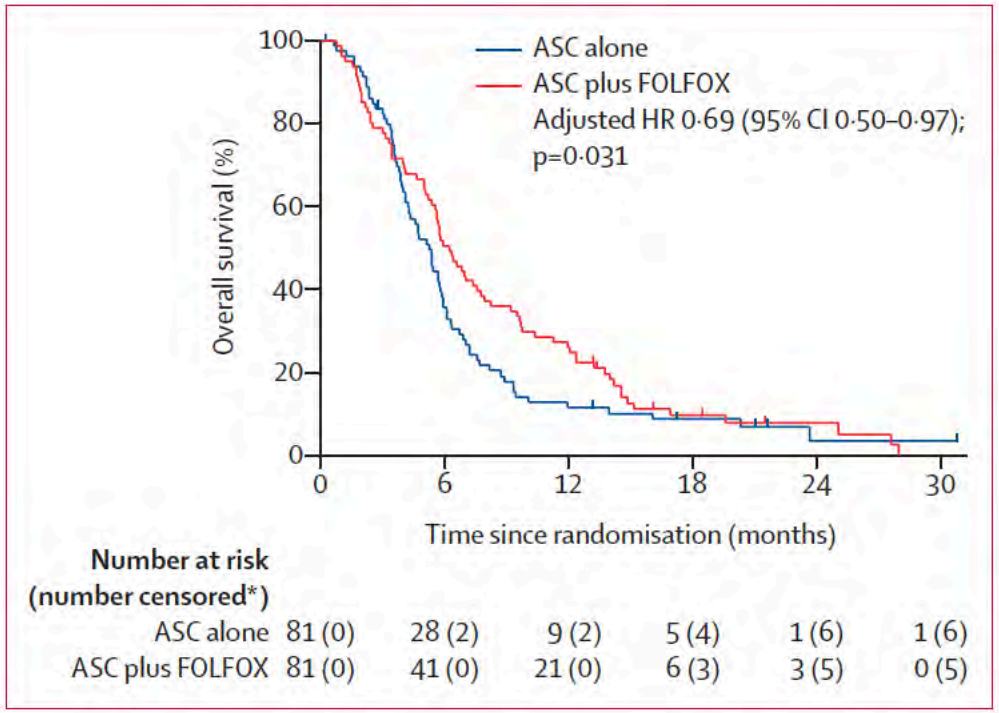
1. Abou-Alfa GK, et al. *Lancet Oncol*. 2020; 2. Javle M, et al. *Lancet Gastroenterol Hepatol*. 2021; 3. Meric-Bernstam F, et al. *Cancer Discov*. 2022; 4. Abou-Alfa GK, et al. *Lancet Oncol*. 2020; 5. Drilon A, et al. *N Engl J Med.* 2018; 6. Subbiah V, et al. *Lancet Oncol.* 2020; 7. Javle M. *Lancet Oncol* 2021

Systemic therapies – *2nd line*

ABC-06 (UK): Phase III

CCA & GBC (n=162)

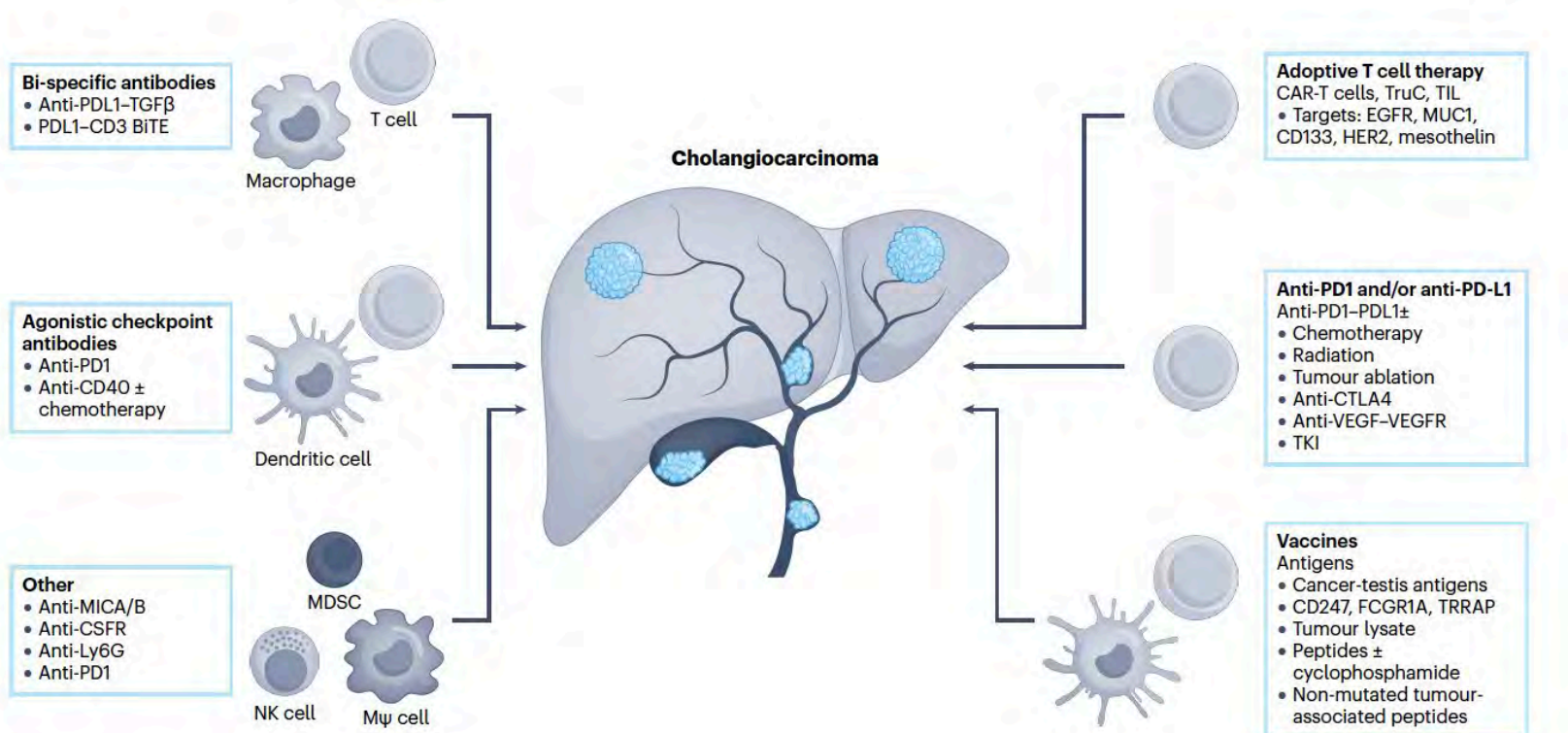
Fluorouracile + Oxaliplatine (FOLFOX) vs Observational



Group	mOS
FOLFOX	6.2
Observational	5.3

Lamarca A *et al. Lancet Oncol.* 2021

Immunotherapy – *next directions*



Tim F. Greten, *et al*. *Nat Rev Hepatol Gastroenterol*. 2023

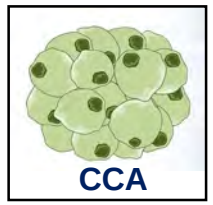
CHOLANGIOCARCINOMA (CCA)

1. Epidemiology and general features

2. Natural course

3. **Novel therapeutic strategies**

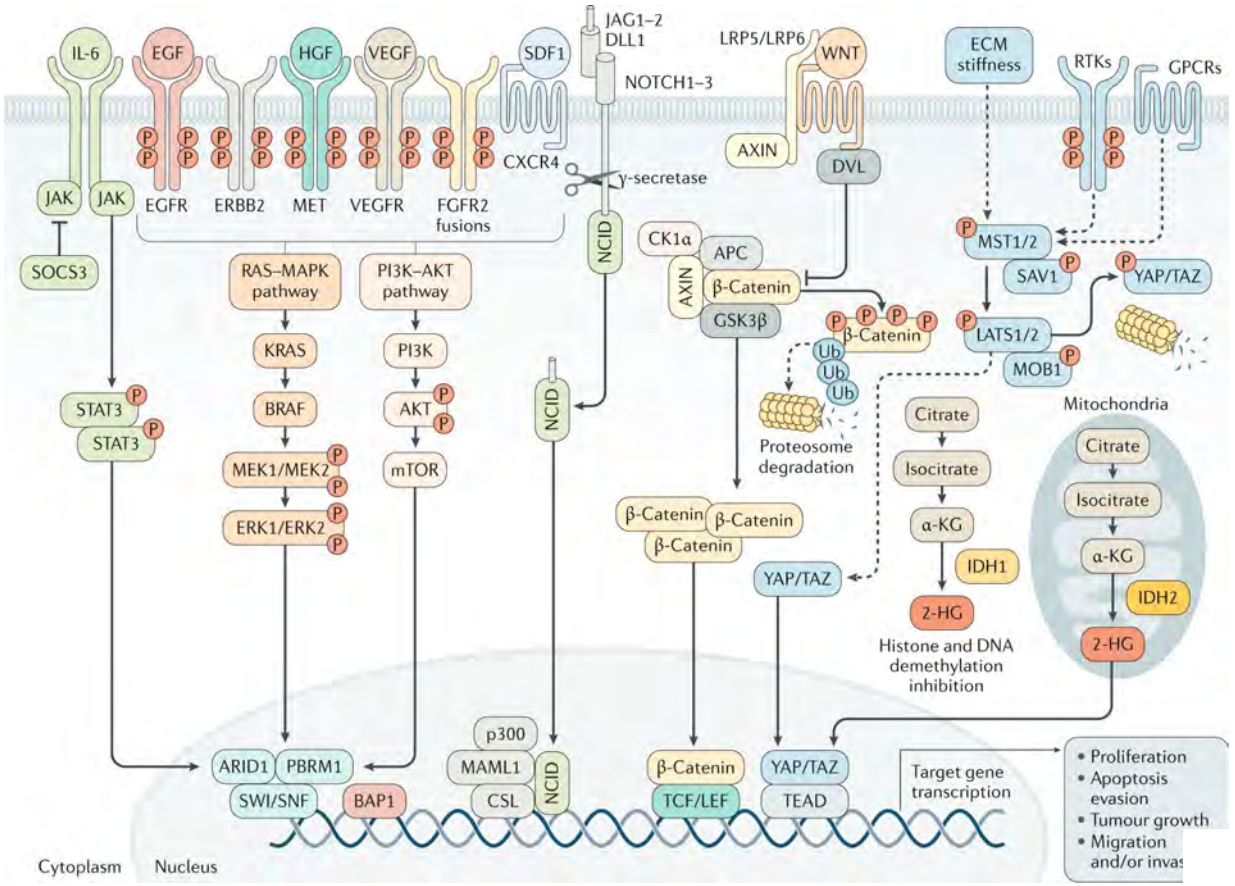
Signaling pathways and molecular networks



KEY SIGNALING PATHWAYS

- Inflammatory cytokines
- Growth factors
- NOTCH
- WNT/β-catenin
- HIPPO (YAP/TAZ)
- Bile acids

CCA develpment, evolution and progression



Banales JM, *et al*. *Nat Rev Gastroenterol Hepatol*. 2020

CCA – *metabolic reprogramming*

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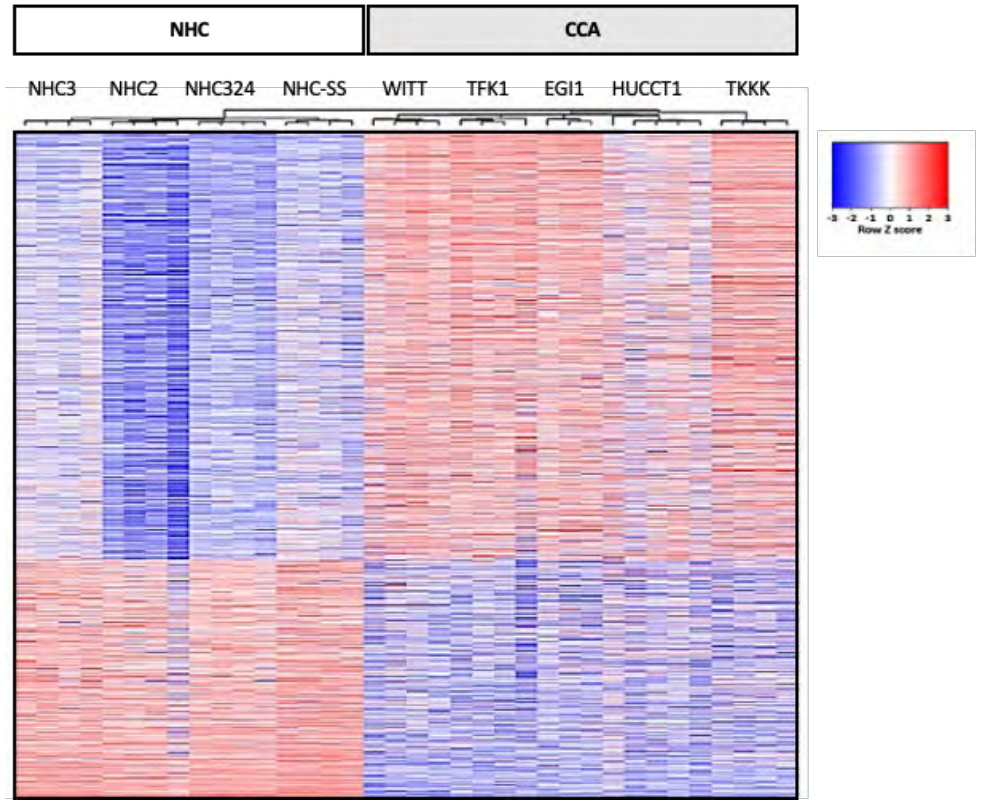
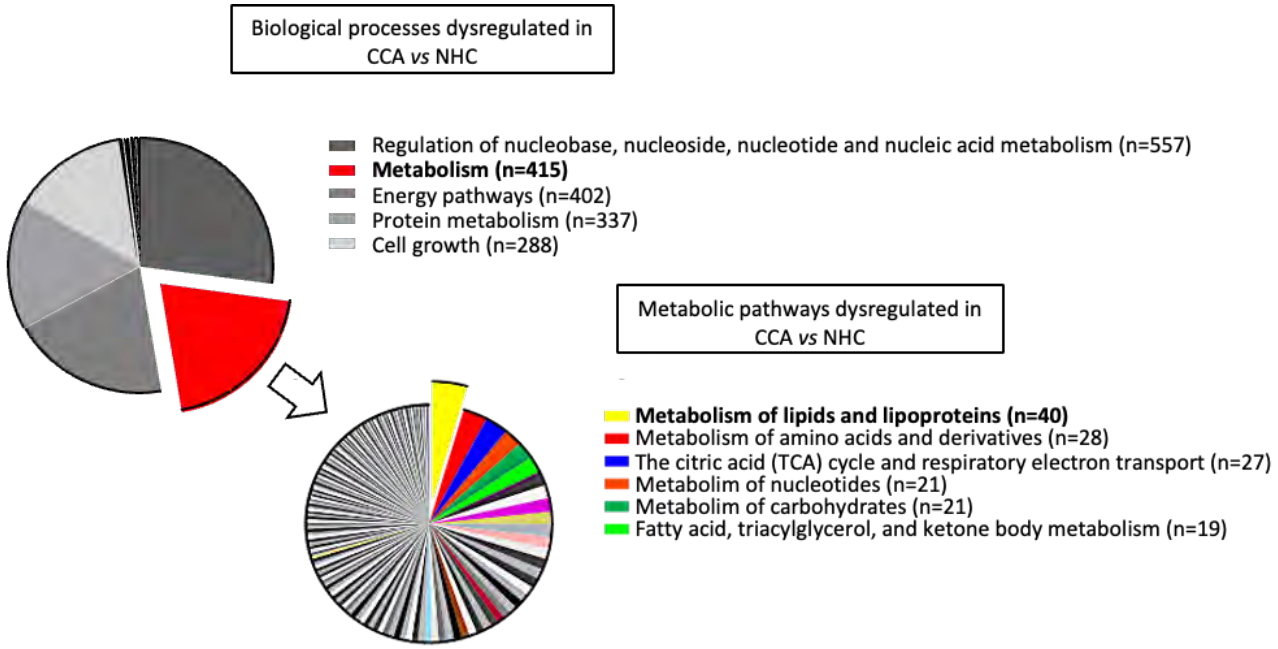
Prof. P. Aspichueta
(IIS Biobizkaia)

PROTEOME



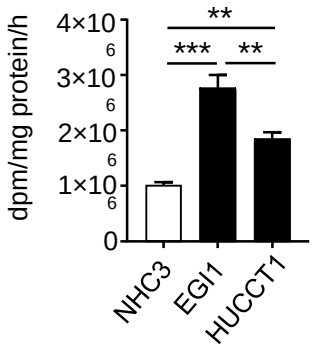


Ruiz de Gauna M,…,Banales/Aspichueta. *Hepatology* 2022

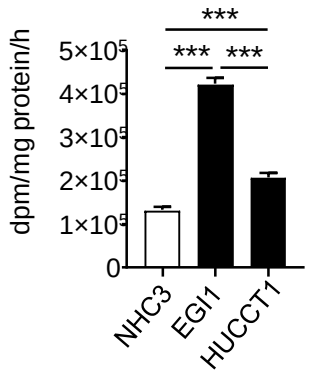
CCA – *increased lipid uptake*

Free fatty acids uptake of

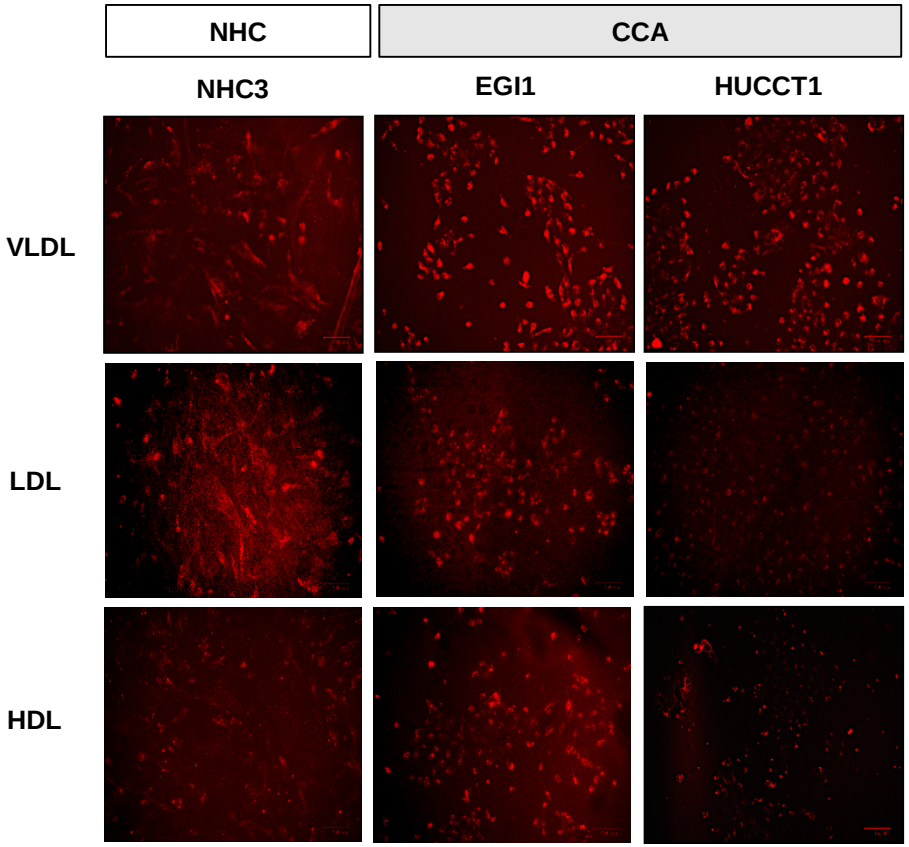
[^{3}H]-OLEATE UPTAKE

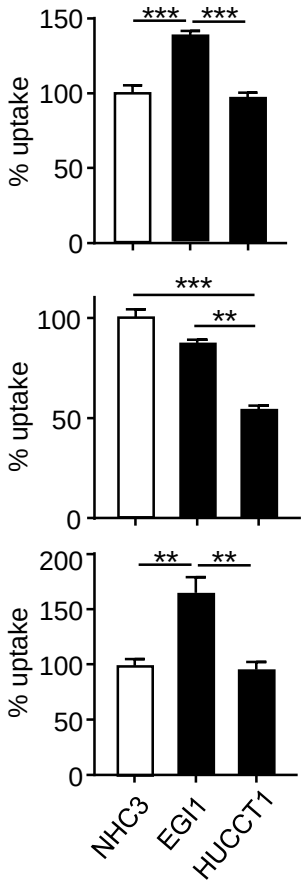


[^{14}C]-PALMITATE UPTAKE



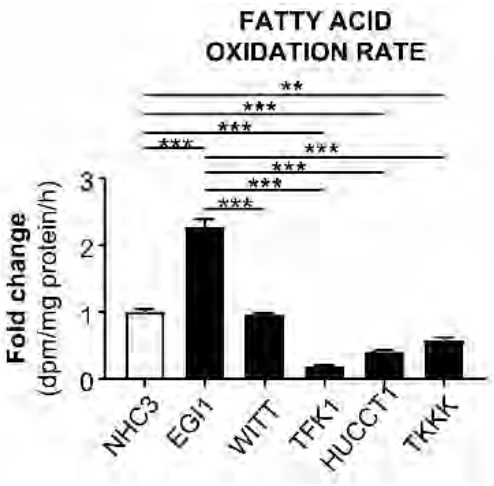
Lipoprotein uptake

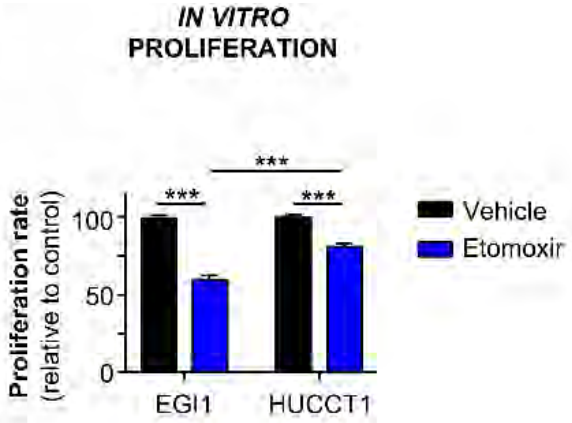


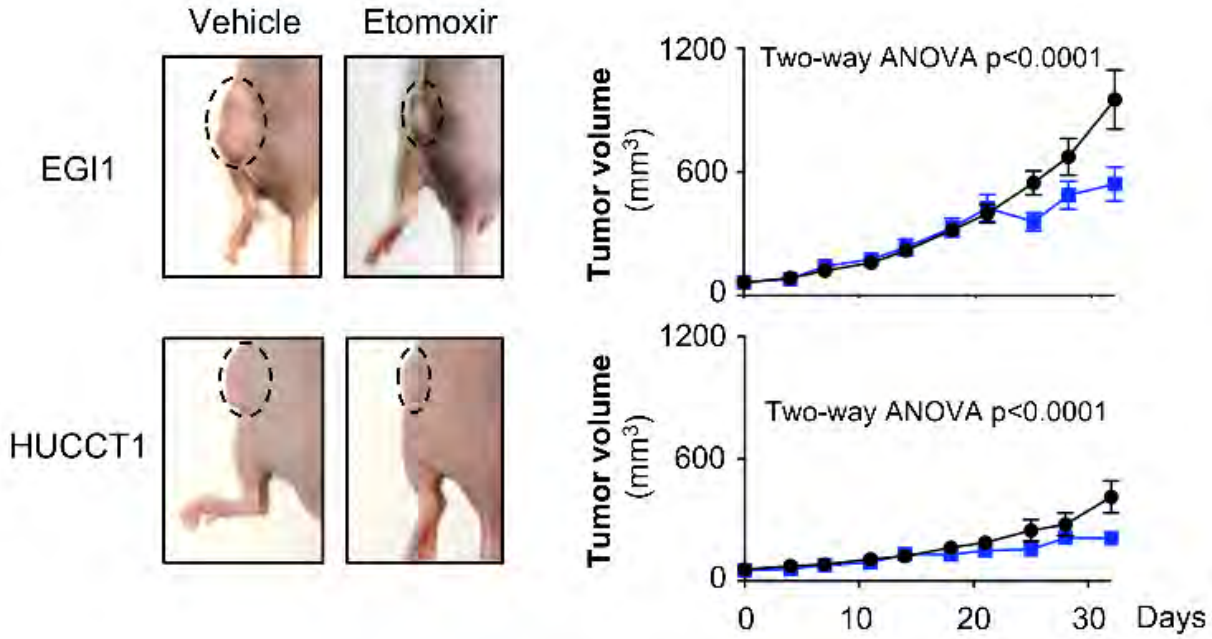


Ruiz de Gauna M,…,Banales/Aspichueta. *Hepatology* 2022

CCA – *energy source*

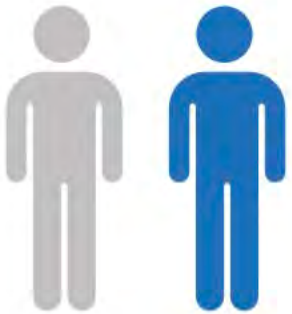




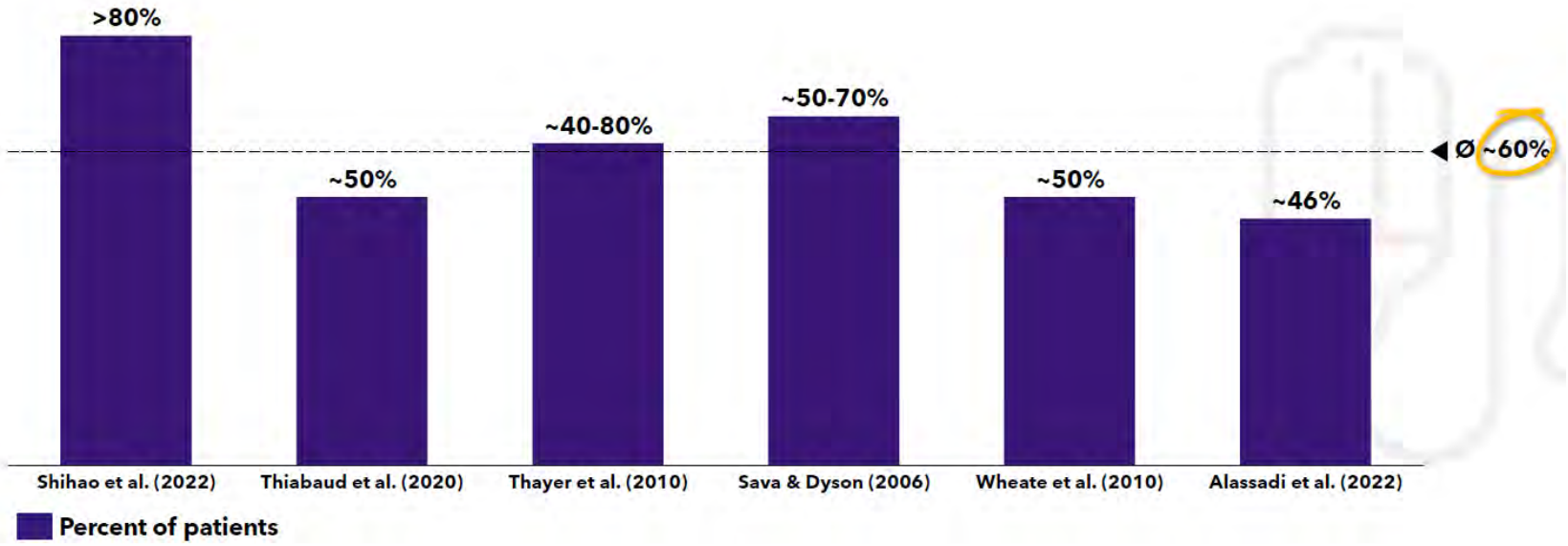


Ruiz de Gauna M,…,Banales/Aspichueta. *Hepatology* 2022

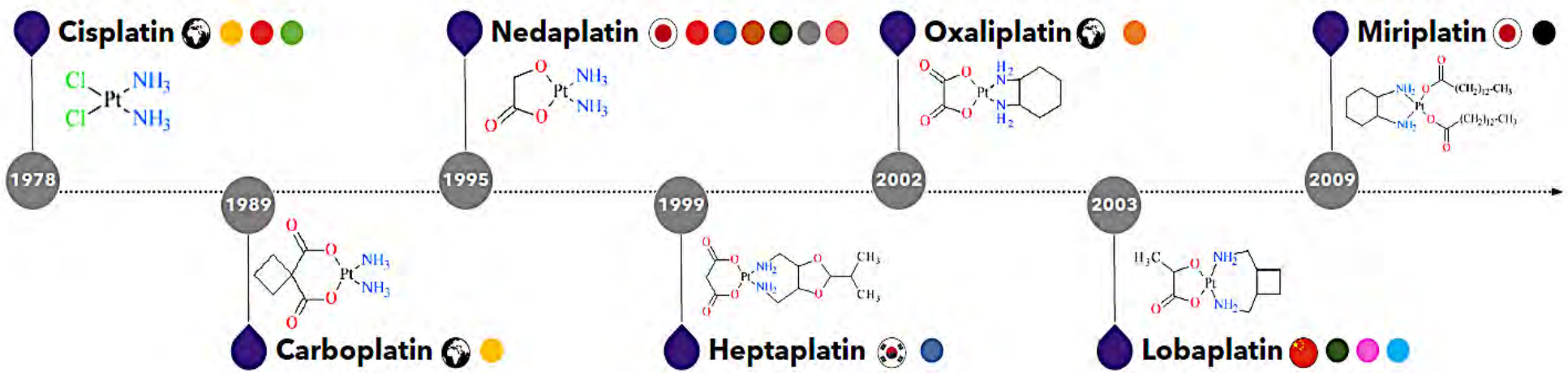
Use of platinum-based drugs in cancer treatment



1 in every 2 patients with **cancer** is currently being treated with platinum derivatives



Evolution of approved platinum-based drugs over time



Approved indications (no off-label included)

- Ovarian cancer
- Testicular cancer
- Bladder cancer
- Head & Neck cancer
- Oesophagus cancer
- Lung cancer
- Cervical cancer
- Prostate cancer
- Gastric cancer
- Colorectal cancer
- Breast cancer
- Leukaemia
- Liver cancer

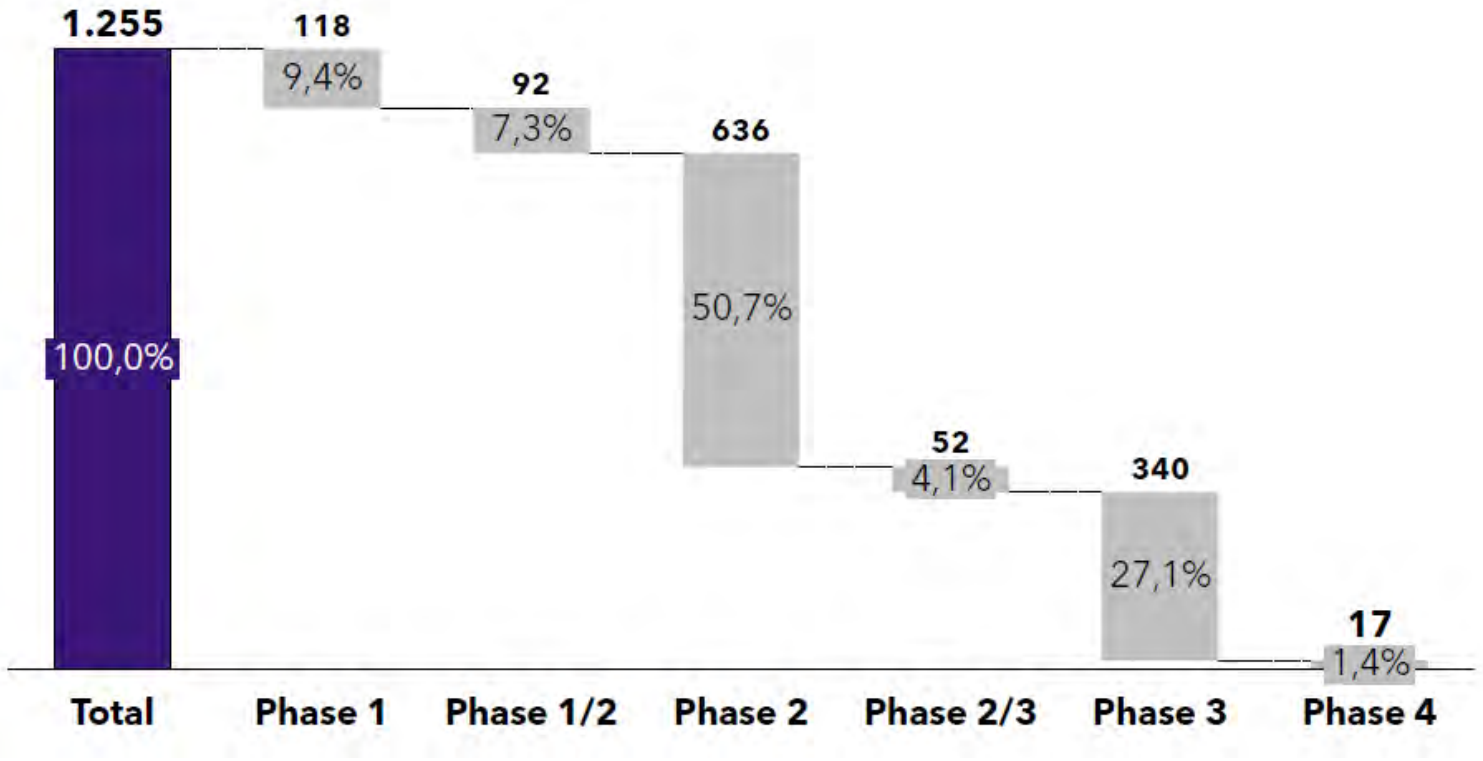
Cisplatin, Carboplatin & Oxaliplatin (worldwide approval)

Nedaplatin (Japan), Lobaplatin (China), Heptaplatin (Korea, iriplatin (Japan)

Kopacz-Bednarska A, Król T. *J Oncol.* 2022; 72: 96–105

Cisplatin – *clinical trials (in 2024)*

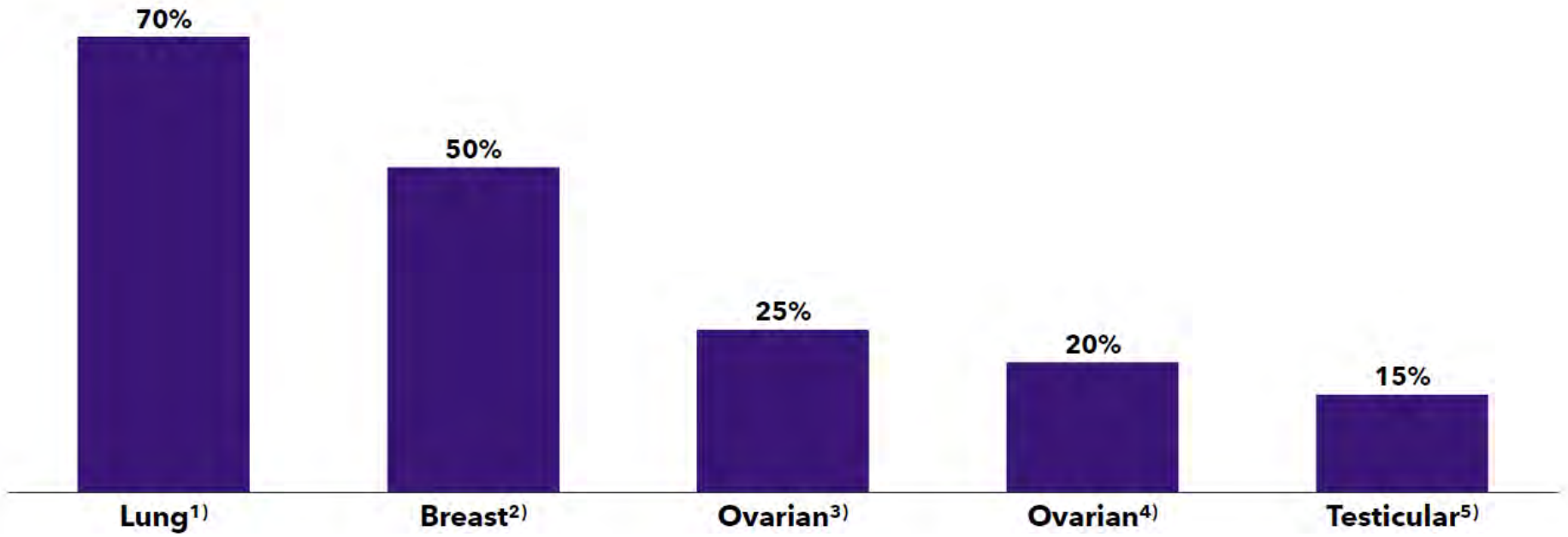
- Cisplatin is still under investigation in multiple clinical trials: **1.255** (mostly Phase 2)



Clinicaltrials.gov

Cisplatin – *resistance*

Major limitation in cancer treatment

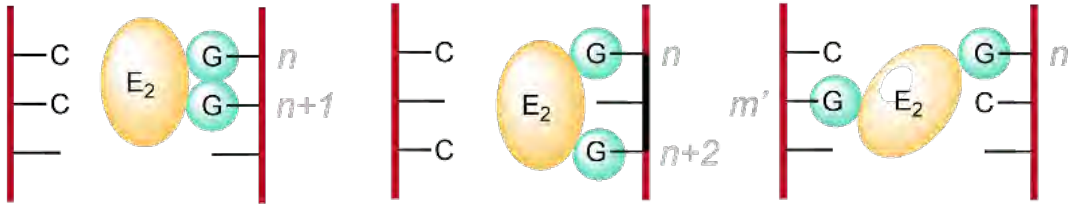


1. Gonzalez Rajal A, et al. *Elife.* 2021; 2.Pogribny PI, et al. Cancer Cell Biology. 2010; 3. Atallah GA, et al. *Int. J. Mol. Sci.* 2023; 4. Pothuri B. *Clin. Adv. Hematol. Oncol.* 2023;
5. González-Barrios R, et al. *Cancers.* 2022.

New chemotherapeutic agents – ***Aurkine*** (Basque: to find/against to)

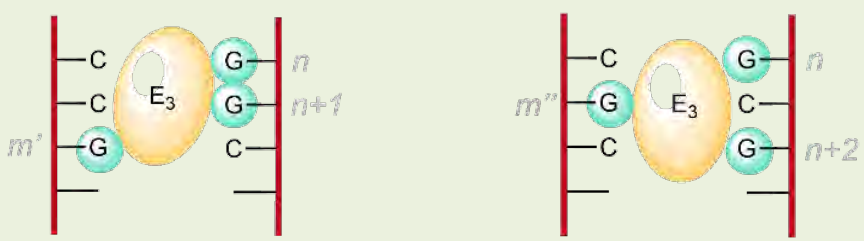
95% **5%**

Cisplatin **Cisplatin** **Cisplatin**

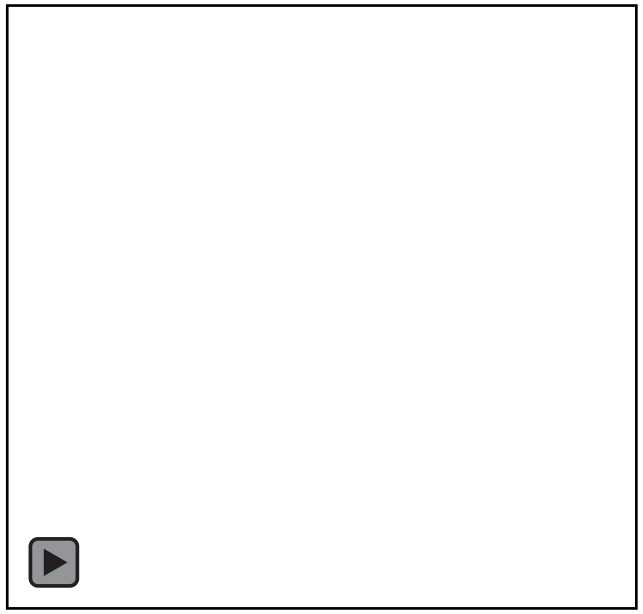


1,2-intrastrand *1,3-intrastrand* *1,2'-interstrand*

Aurkine **Aurkine**



3'-inter+1,2-intrastrand *2'-inter+1,3-intrastrand*



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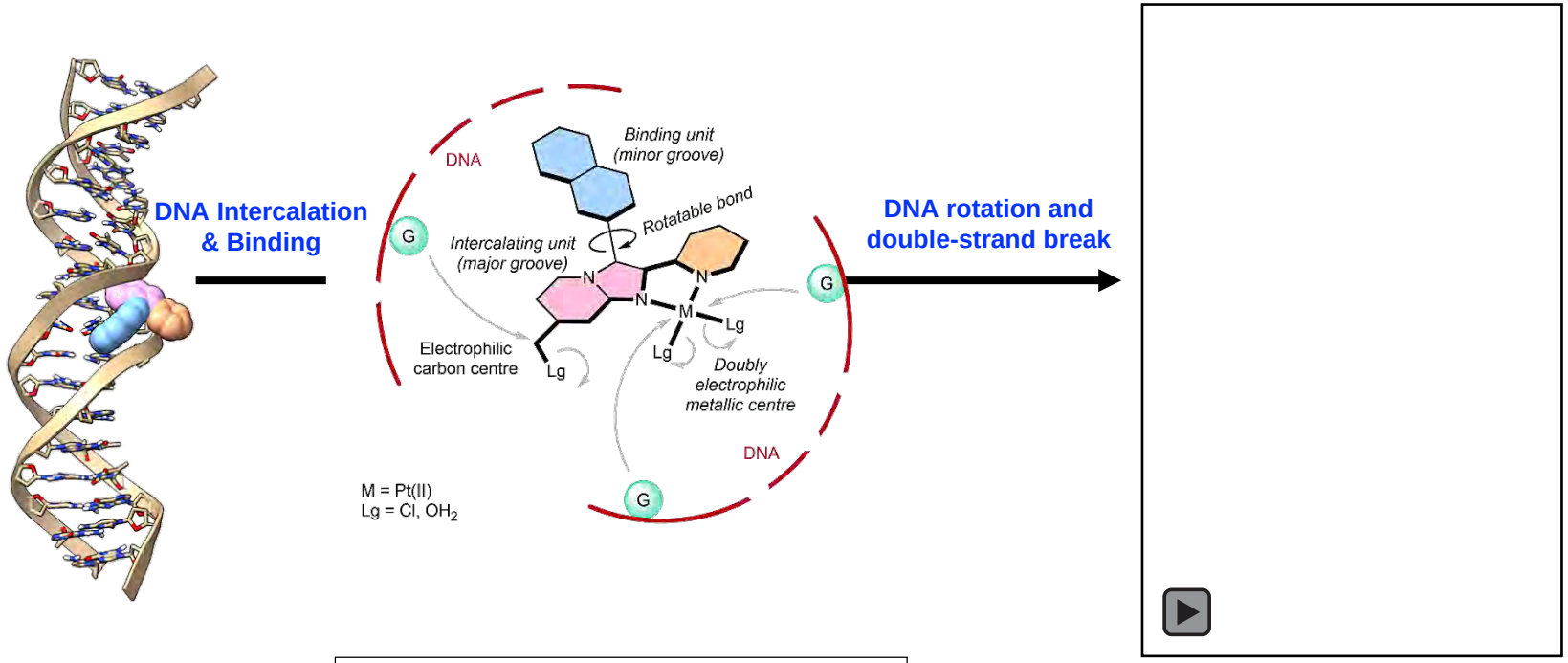
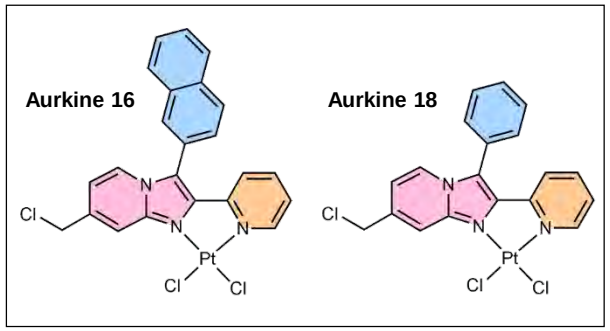
Dr. Ivan Rivilla (DIPC)

Dr. Irene Olaizola (IIS Biogipuzkoa)

New chemotherapeutic agents – *Aurkine*

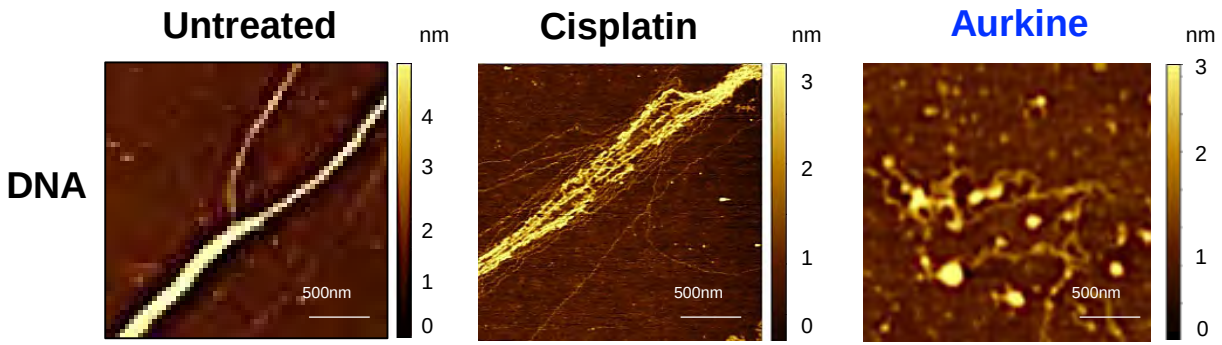




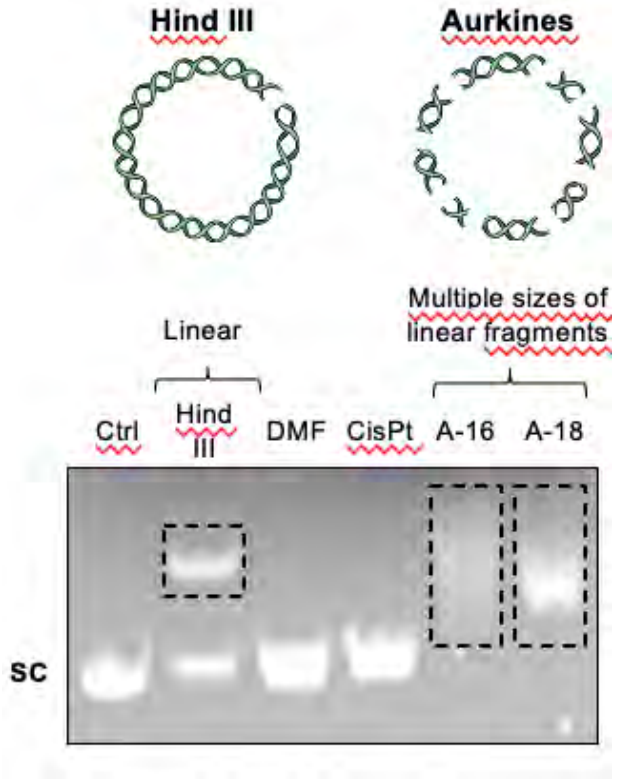
Aurkines completely disrupt the DNA structure

- Isolated DNA from *Escherichia Coli*

AFM studies
(**A**tomic **F**orce **M**icroscopy)

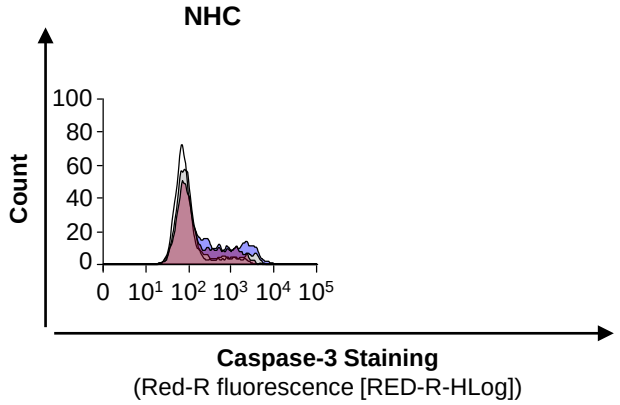


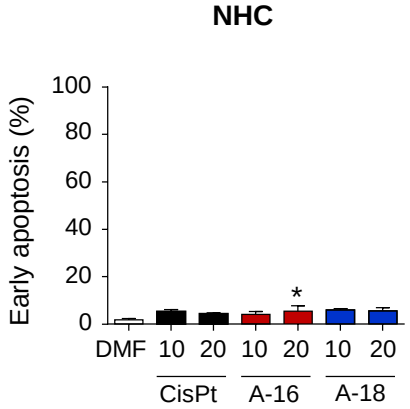
DNA bending ↑↑ DNA destruction



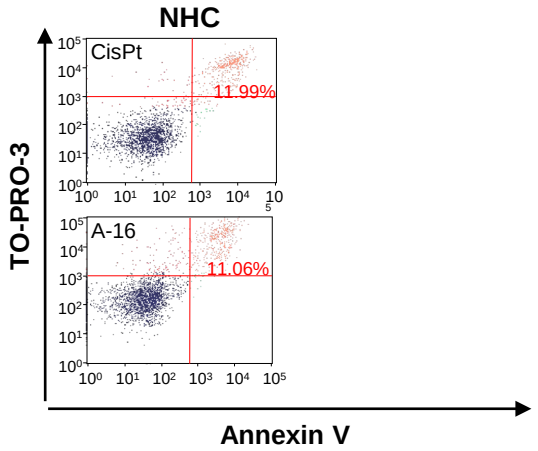
Aurkines promote apoptosis specifically in CCA cells

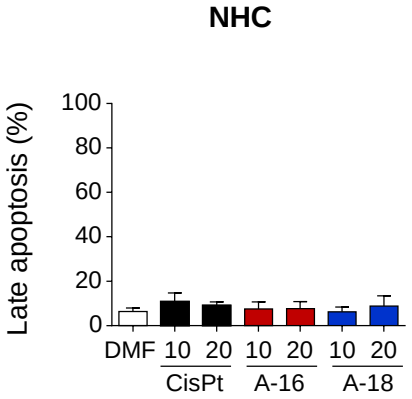
Early cell death (caspase-3)





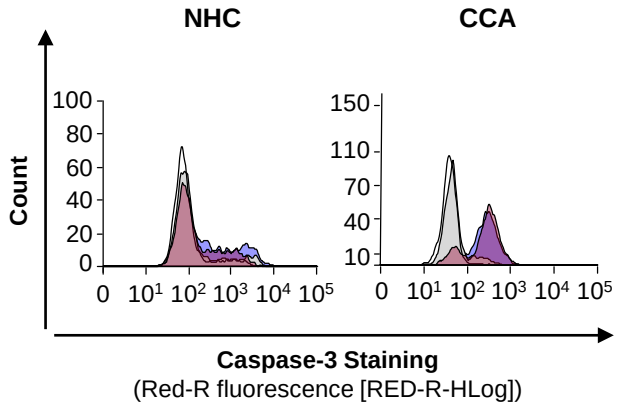
Late cell death (annexin-V – TO-PRO-3)

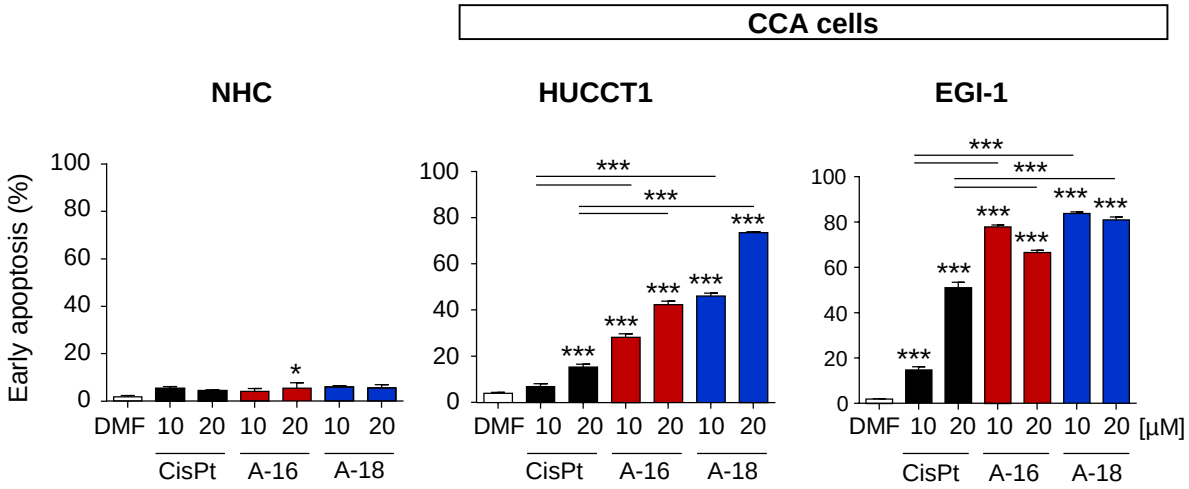




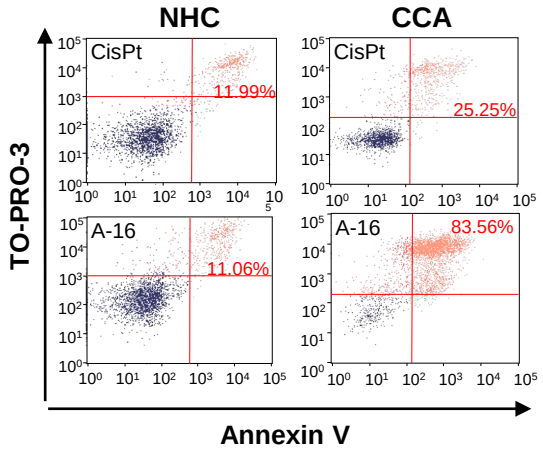
Aurkines promote apoptosis specifically in CCA cells

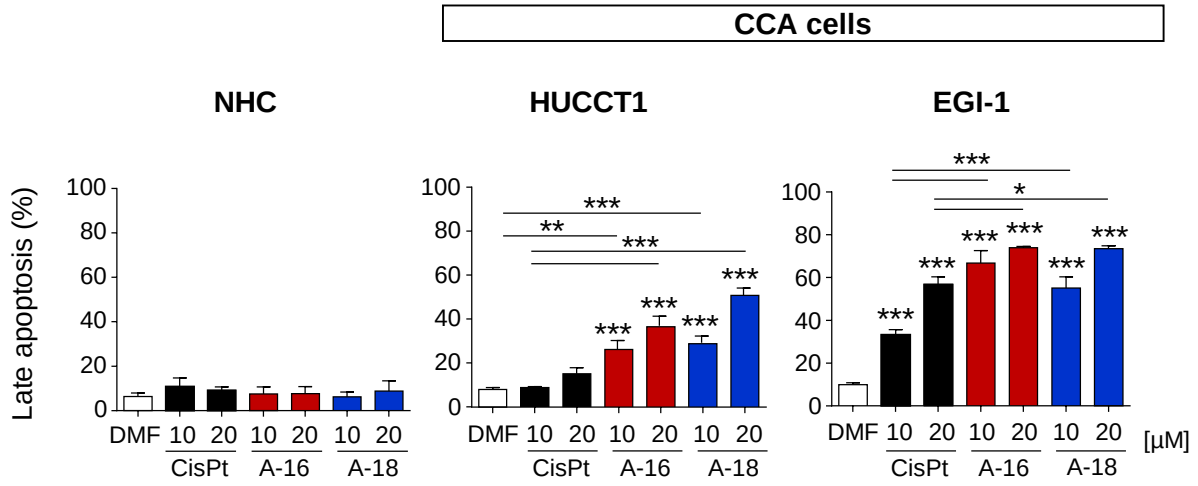
Early cell death (caspase-3)



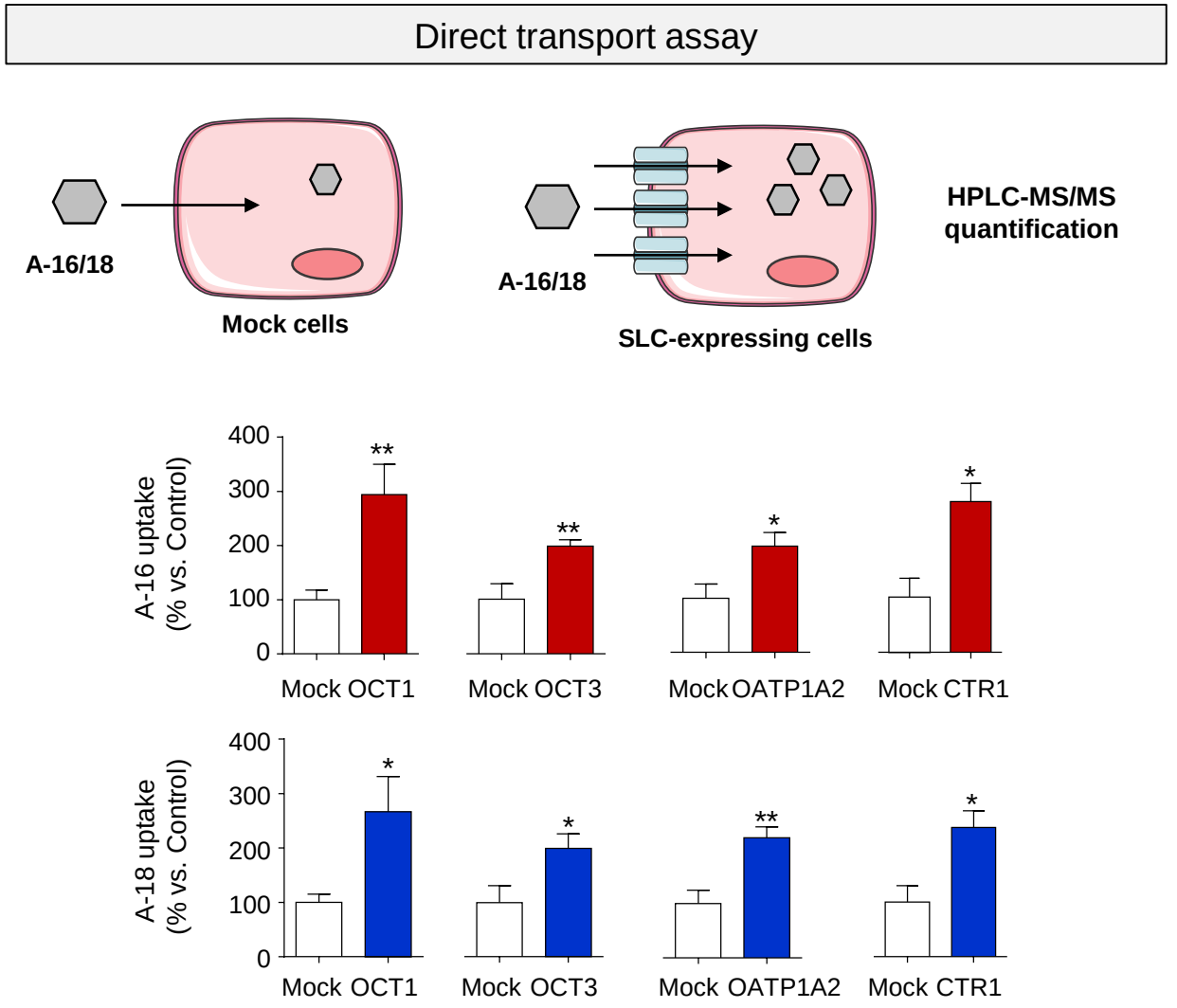


Late cell death (annexin-V – TO-PRO-3)

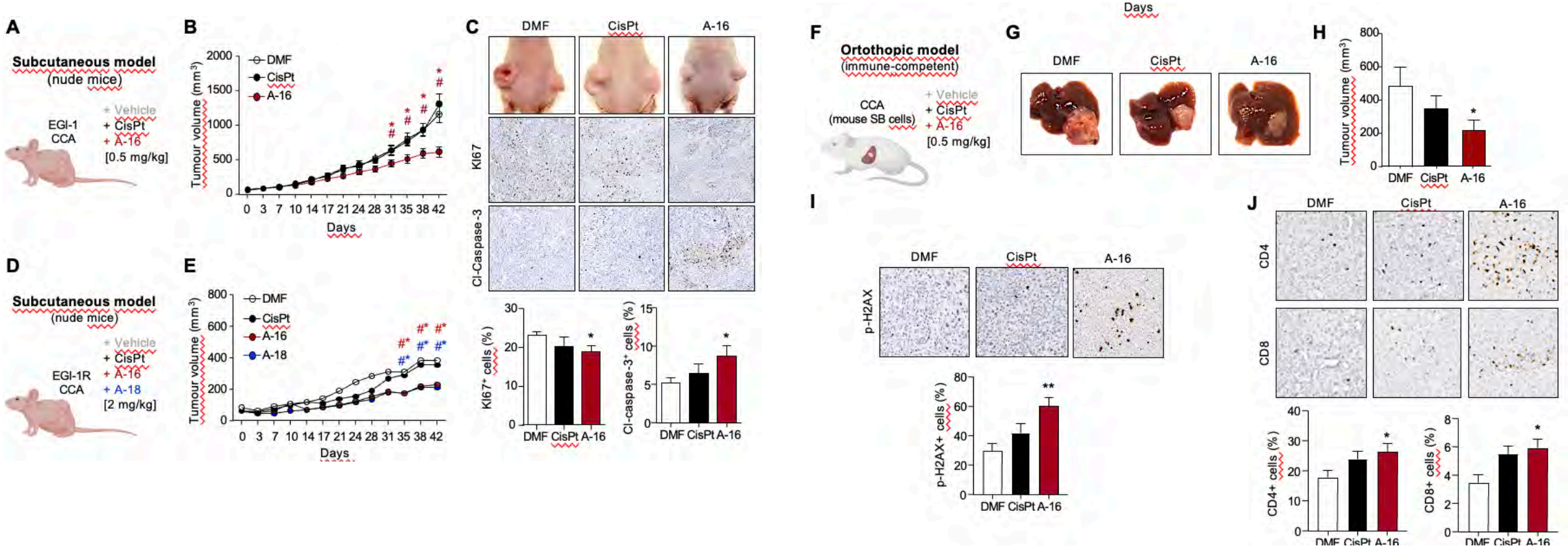




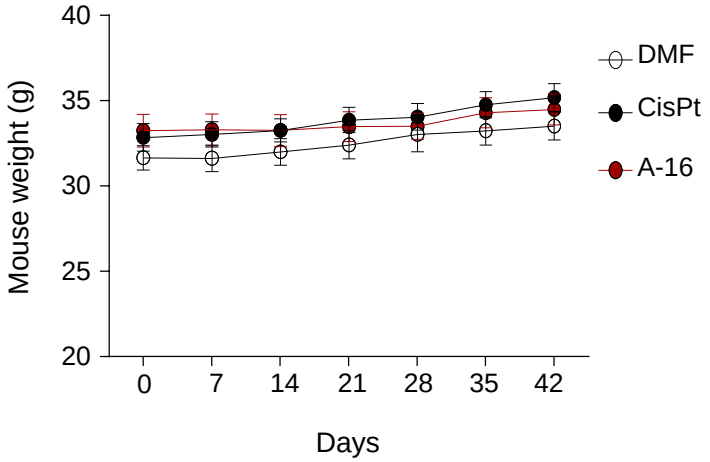
Aurkines uptake by cancer cells

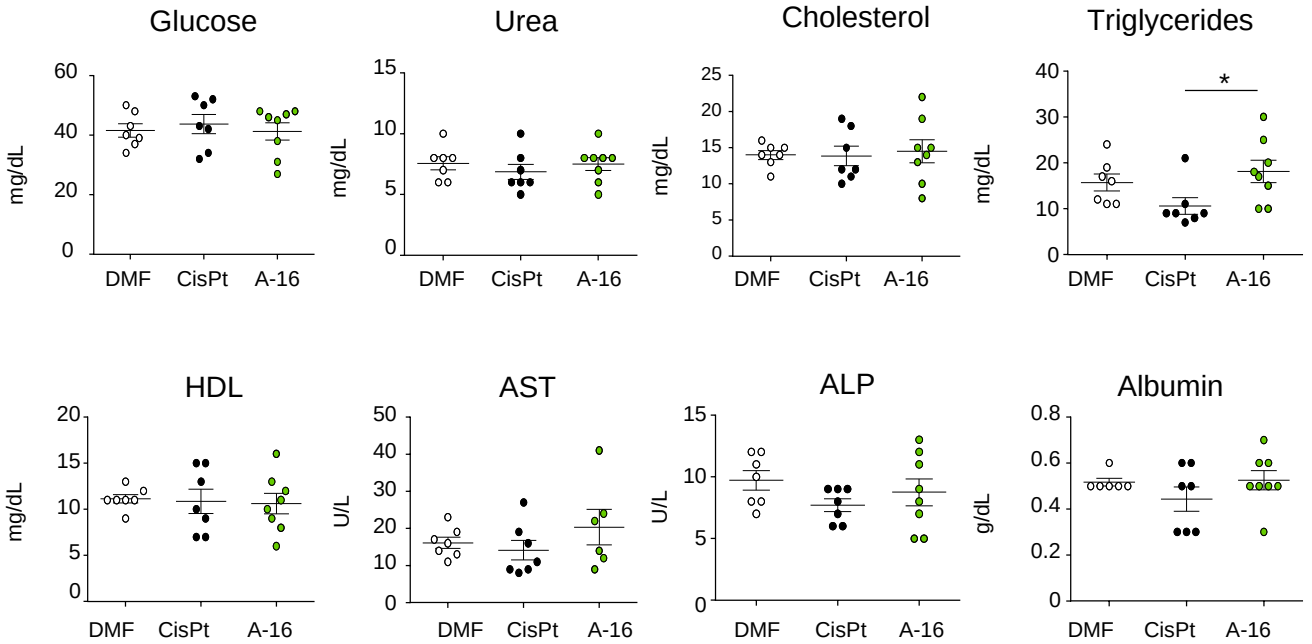


Aurkines inhibit CCA growth *in vivo*



No evidence of toxicity





New platinum derivatives selectively cause double-strand DNA breaks and death in naïve and cisplatin-resistant cholangiocarcinomas.

Olaizola I, Odriozola-Gimeno M, Olaizola P, Caballero-Camino FJ, Pastor-Toyos N, Tena-Garitaonandia M, Lapitz A, Val B, Guimaraes AR, Asensio M, Huici-Izagirre M, Rae C, de Sancho D, Lopez X, Rodrigues PM, Herraez E, Briz O, Izquierdo-Sanchez L, Eleta-Lopez A, Bittner AM, Martinez-Amesti A, Miranda T, Ilyas SI, Braconi C, Perugorria MJ, Bujanda L, Rivilla I, Marin JJG, Cossio FP, **Banales JM.**

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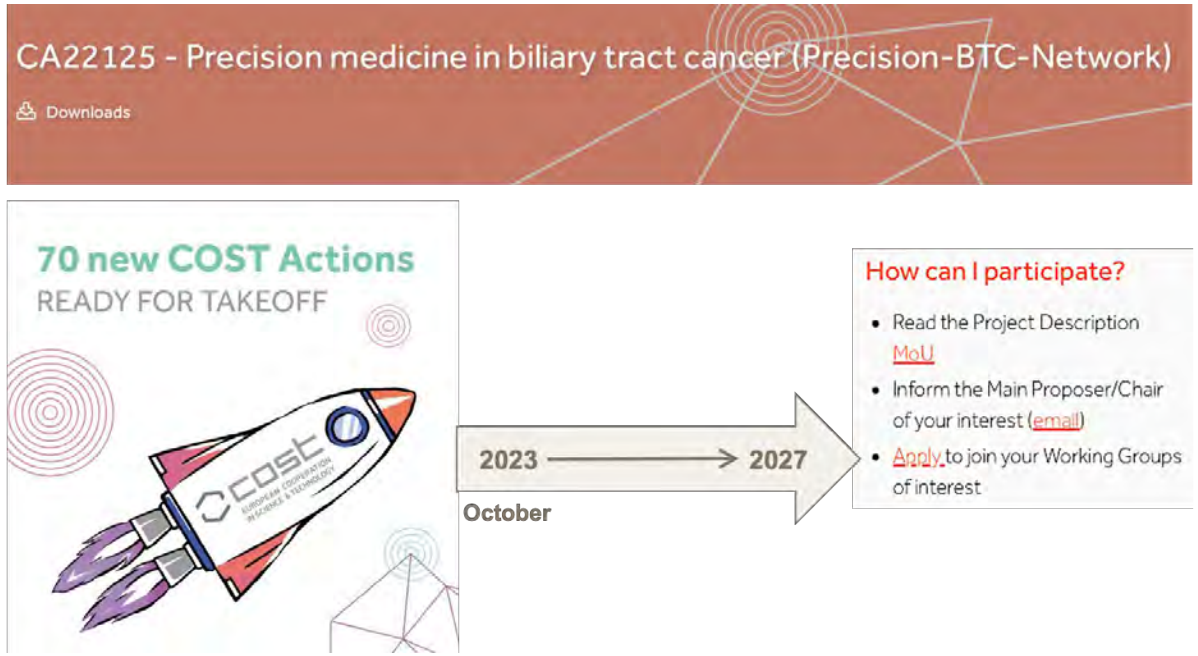
Conclusions

- The **incidence** of CCA is increasing globally
- **Highly heterogenous** (intra- & inter-tumor)
- **Imaging** methods (CT/MRI) may suggest the diagnosis but are not conclusive (biopsy needed)
- **Surgery with curative intent**, including **liver transplantation** in selective cases, is still the only potential **curative** options (but only ~30% candidates and high recurrence)
- ↑**CA19.9:** Disease stage (disseminated), Prognosis, Surrogate marker (treatment)
- **Adjuvant chemotherapy:** Capecitabine (6 months)
- **Chemotherapy** (Unresectable Tumors):
  - **1st line**
    - Immunotherapy + GemCis
    - Immunotherapy (**MSI**)
    - GemCis
  - **2nd line**
    - FOLFOX
    - FGFR2 inh; IDH1 inh
    - others: BRAF mut; HER2 mut/amp: NTRK fus
- **RECOMENDATION: tumor mutational profile** (tissue/serum) at diagnosis!!



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