Nuove prospettive nella terapia del colangiocarcinoma

Congresso Trisocietario
AIGO, SIED, SIGE,
Firenze, December 16, 2023

D. ALVARO, La Sapienza, Roma

Facoltà di Medicina
e Odontoiatria

Sapienza
Università di Roma

Conflict of Interest

Domenico Alvaro, Univ. La Sapienza di Roma

Disclosures:

A: VESTA, USA: Biliary Stem cells, Research Grants

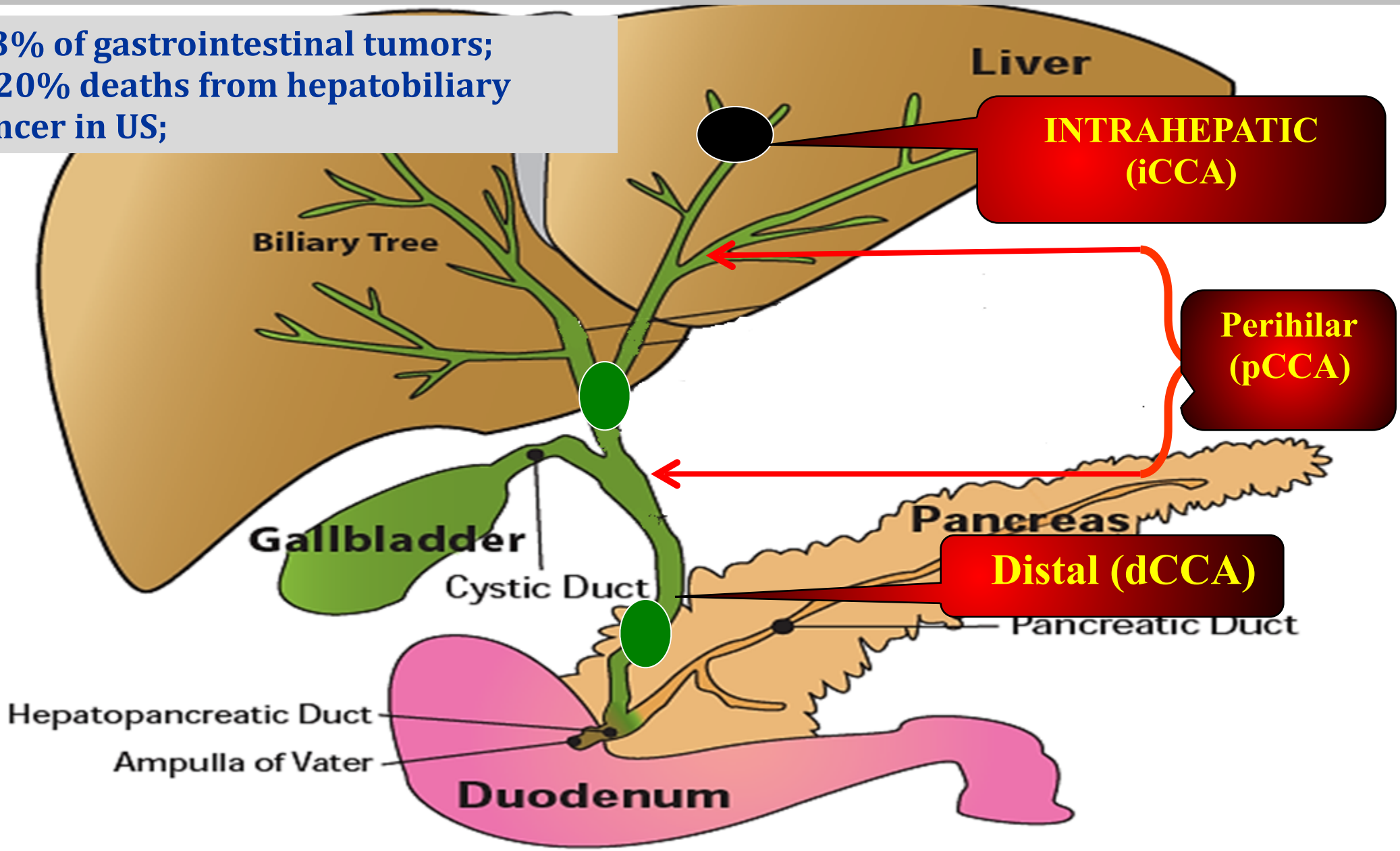
B: InterceptPharma/Advanz/Pharma : -Research Grants
-Consultant

C: Shionogi: Invited lectures

D: Aboca: -consultant
-Invited lectures

CCA: a heteroneneous family of cancer !

*..3% of gastrointestinal tumors;
*~20% deaths from hepatobiliary cancer in US;

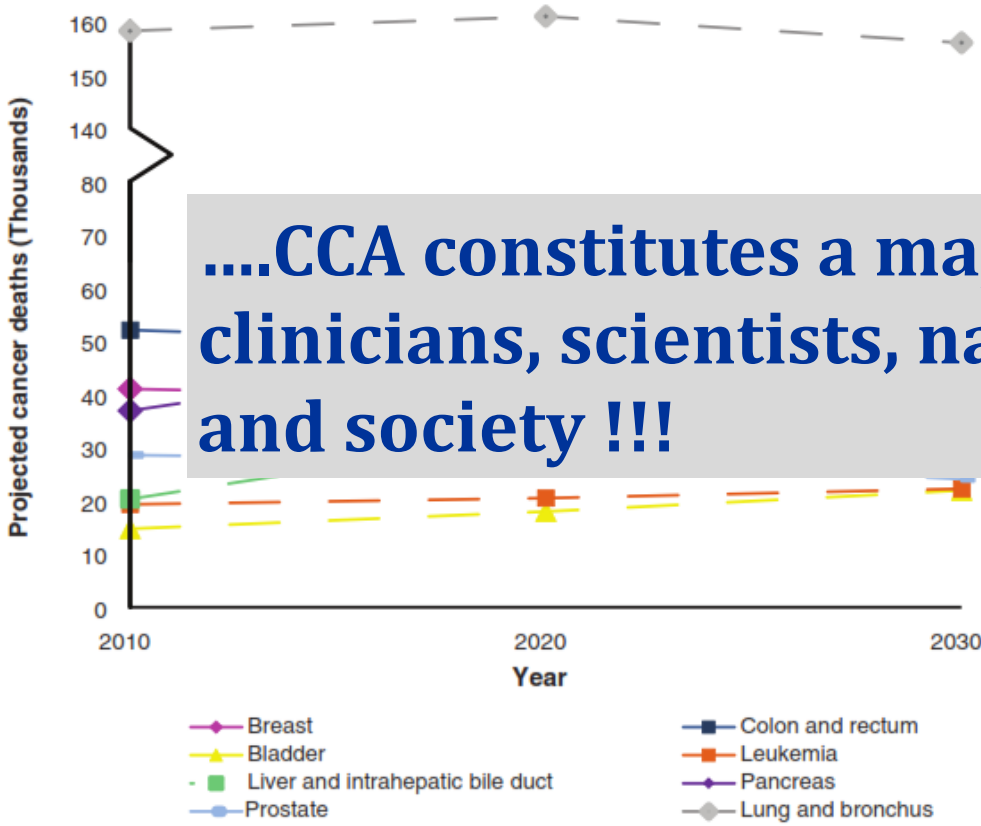


Perspective

Cancer Res; 74(11) June 1, 2014

Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

Lola Rahib[1], Benjamin D. Smith[2], Rhonda Aizenberg[1], Allison B. Rosenzweig[1], Julie M. Fleshman[1], and Lynn M. Matrisian[1]

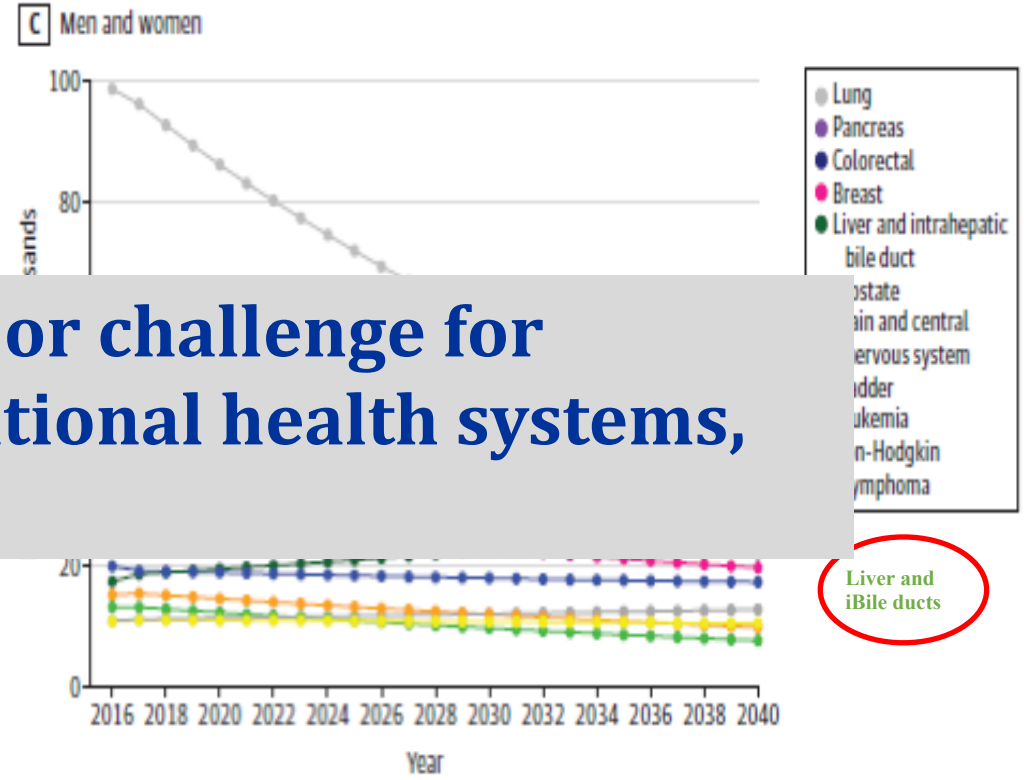


JAMA Network Open

Original Investigation | Oncology

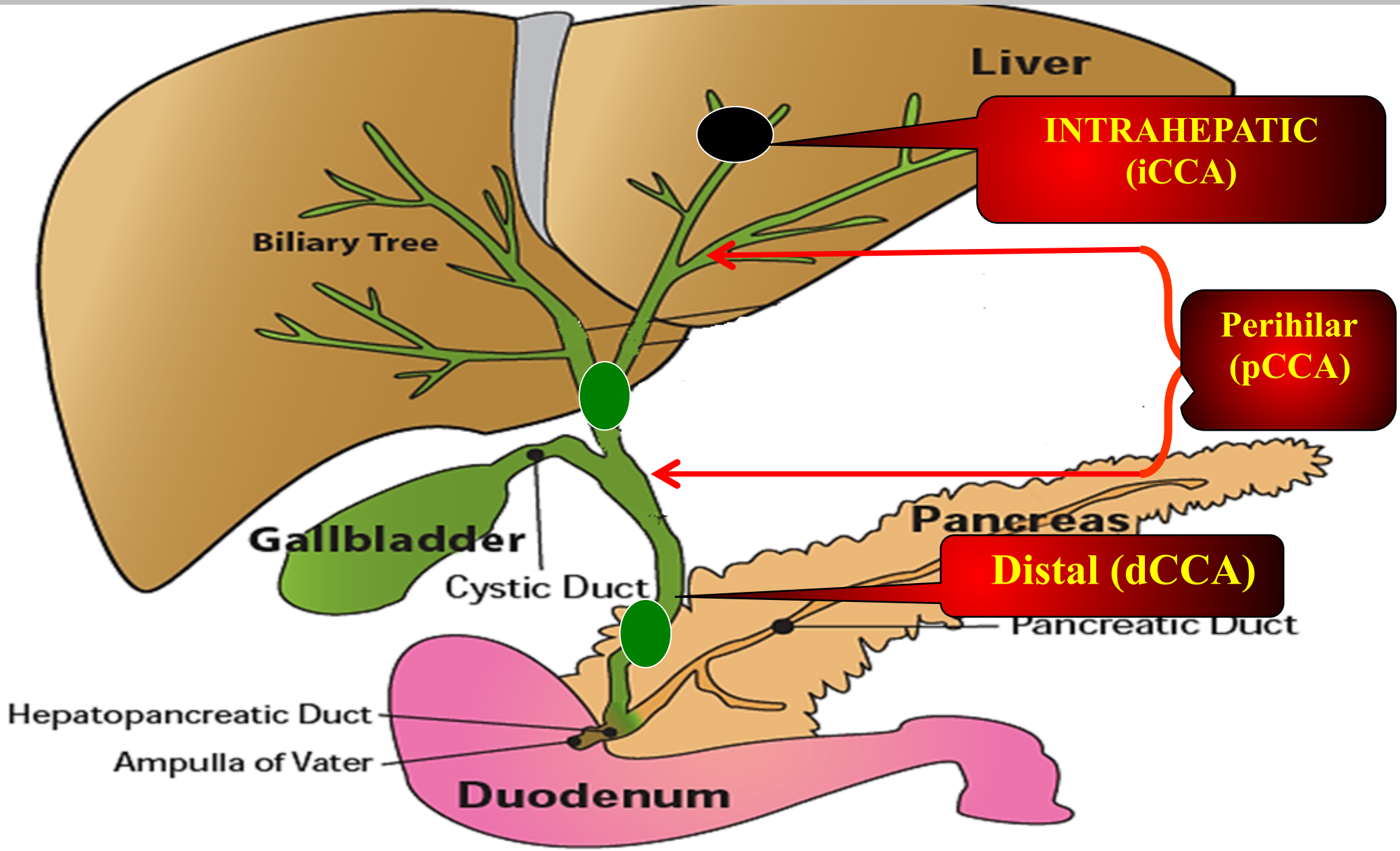
Estimated Projection of US Cancer Incidence and Death to 2040

Lola Rahib, PhD; Mackenzie R. Wehner, MD, MPhil; Lynn M. Matrisian, PhD, MBA; Kevin T. Nead, MD, MPhil



....CCA constitutes a major challenge for clinicians, scientists, national health systems, and society !!!

CCA: classification



SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ

Linea guida pubblicata nel Sistema Nazionale Linee Guida

Roma, 22 febbraio 2022

Associazione Italiana per lo Studio del Fegato (AISF)
International Hepato-Pancreato Biliary Association (IT-IHPBA)
Associazione Italiana di Oncologia Medica (AIOM)

European Network for the Study the CCA

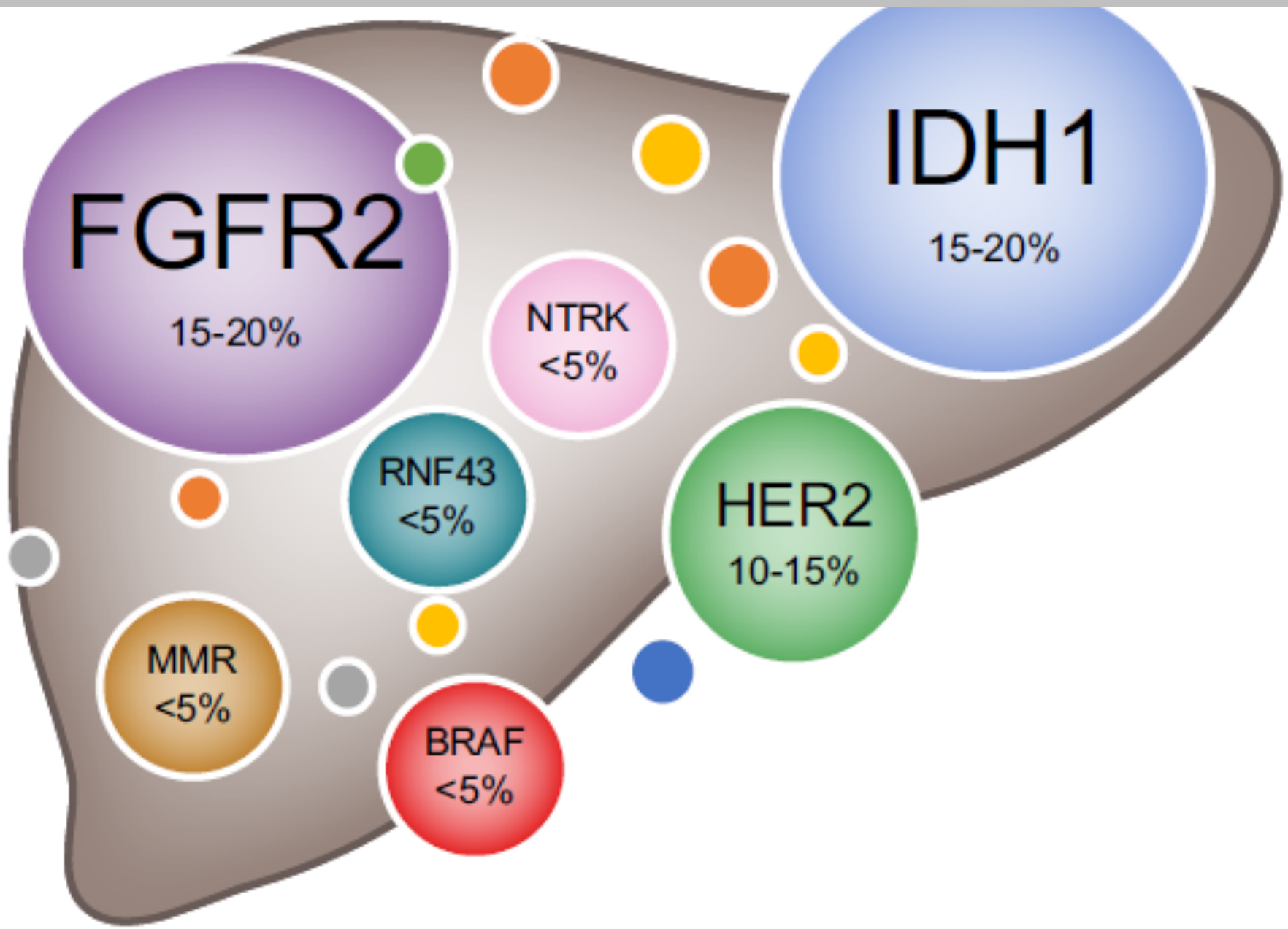
- Creation: May 2015 (Vienna, Austria). 50th EASL Congress

Members

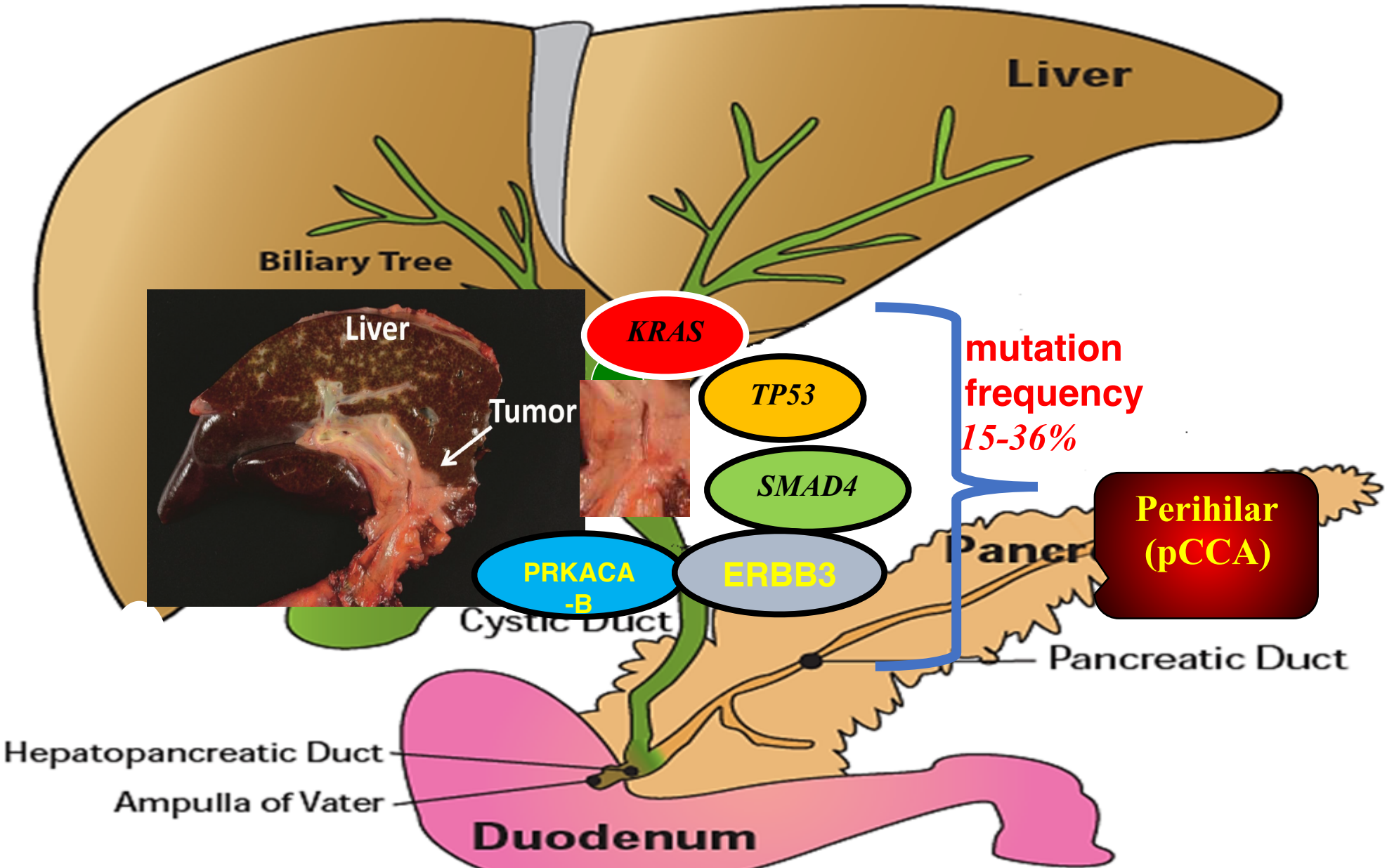
- **70 Research goups**
  (60 European; 8 USA)

- **26 European countries**
  (Austria, Belgium, Bosnia and Herzegovina, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands,, Norway, Poland, Portugal, Romania, Serbia, Slovenia, Spain, Sweden, Switzerland, Turkey and UK)

iCCA: Molecular Landscape



pCCA: Molecular Landscape



CCA: clinical features

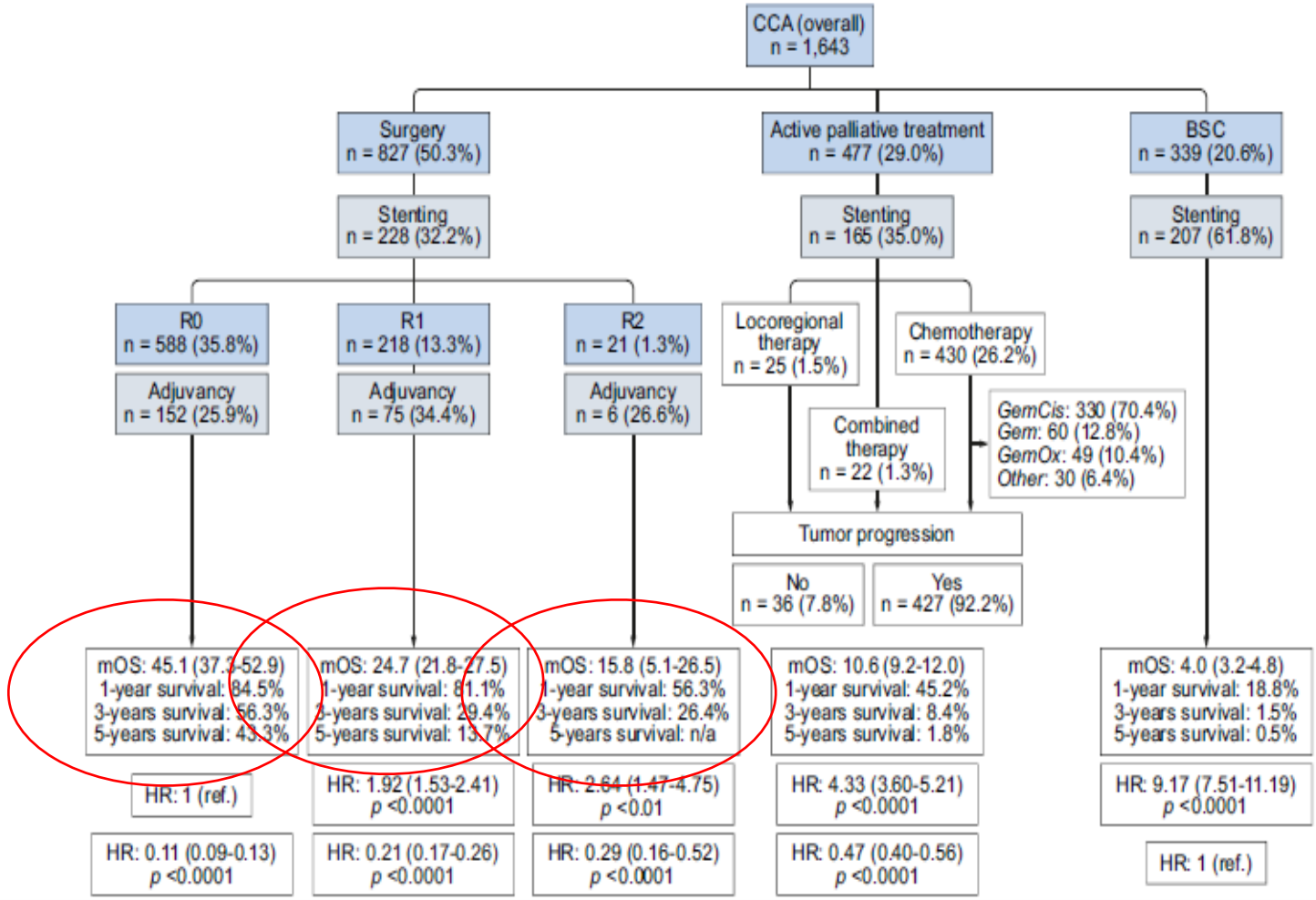
Research Article
Hepatic and Biliary Cancer

JOURNAL OF HEPATOLOGY
2021

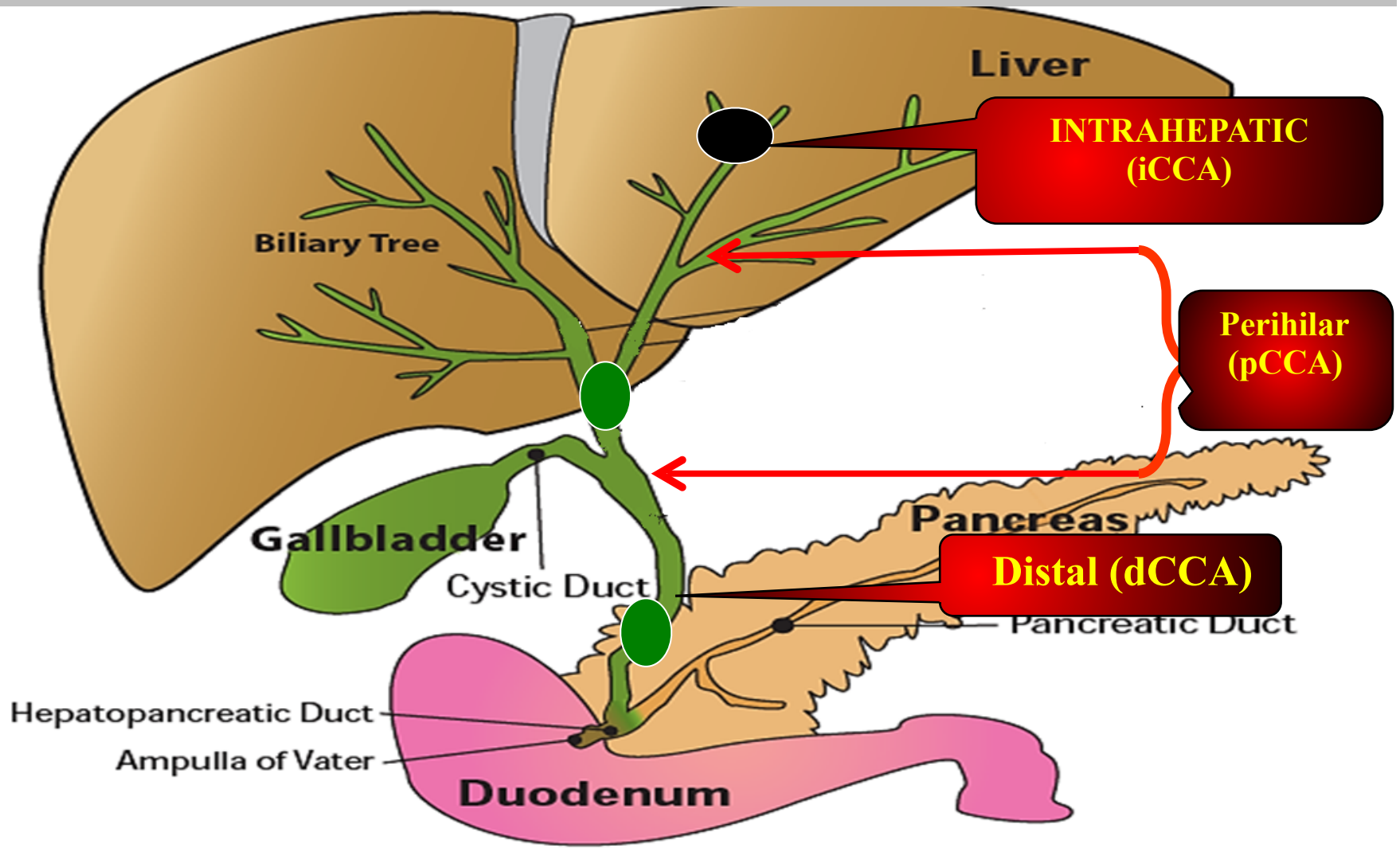
Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry

Laura Izquierdo-Sanchez[1,2], Angela Lamarca[3], Adelaida La Casta[1], Stefan Buettner[4], Kirsten Utpatel[5], Heinz-Josef Klümpen[6], Jorge Adeva[7], Arndt Vogel[8], Ana Lleo[9], Luca Fabris[10,11], Mariano Ponz-Sarvise[12], Raffaele Brustia[13], Vincenzo Cardinale[14], Chiara Braconi[15,16], Gianpaolo Vidili[17], Nigel B. Jamieson[15,18], Rocio IR. Macias[2,19], Jan Philipp Jonas[20,21], Marco Marzioni[22], Wacław Hołówko[23], Trine Folseraas[24,25,26,27], Juozas Kupčinskas[28], Zeno Sparchez[29], Marcin Krawczyk[30,31], Łukasz Krupa[32,33], Viorel Scripcariu[34], Gian Luca Grazi[35], Ana Landa-Magdalena[1], Jan NM. Ijzermans[4], Katja Evert[5], Joris I. Erdmann[36], Flora López-López[7], Anna Saborowski[8], Alexander Scheiter[5], Alvaro Santos-Laso[1], Guido Carpino[37], Jesper B. Andersen[38], Jose JG. Marin[2,19], Domenico Alvaro[39], Luis Bujanda[1,2], Alejandro Forner[2,40], Juan W. Valle[3], Bas Groot Koerkamp[4], Jesus M. Banales[1,2,41,42,*]

Clinical Management and Outcomes



CCA Treatment: SURGERY !!!!!!!



CCA Treatment: SURGERY !!!!!!!

Raccomandazione N.23: Si suggerisce ciclo dichemioterapia adiuvante di sei mesi con capecitabina nei pazienti con CCA sottoposti a resezione chirurgica con intento curativo (R0, R1) (forza della raccomandazione: DEBOLE a favore; qualità delle evidenze: ALTA).

….a 6-month course of oral fluoropyrimidine (capecitabine or S-1) should be considered following potentially curative resection of iCCA. (LoE 2, strong recommendation, strong consensus)

Raccomandazione N.24: Si suggerisce di considerare la radioterapia adiuvante nei pazienti con pCCA con resezione microscopicamente positiva dei margini chirurgici (R1) (forza della raccomandazione: DEBOLE a favore; qualità delle evidenze: MODERATA).

CCA: Treatment of unresectable disease, LOCOREGIONAL THERAPIES THERAPIES

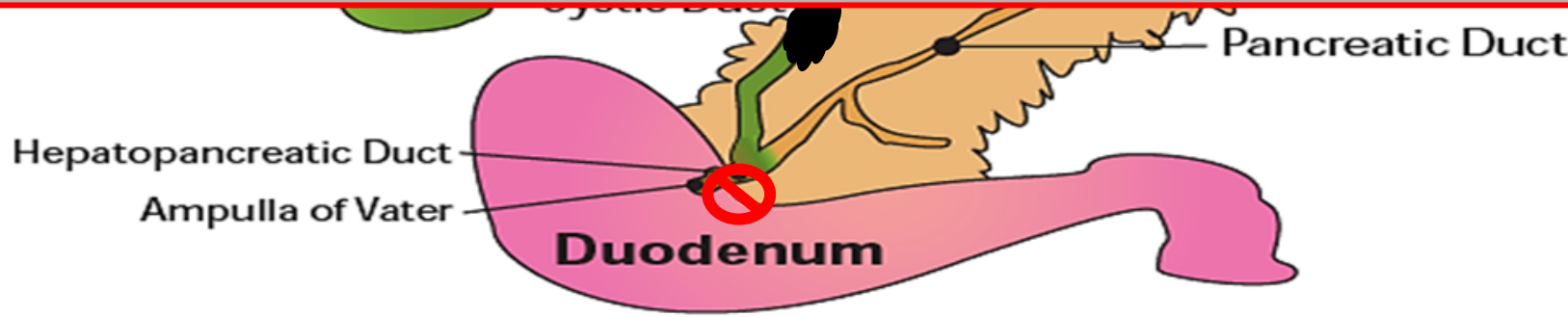
Raccomandazione N. 26:

La raccomandazione al ricorso a RFA o TARE o TACE o DEB-TACE o MWA o elettroporazione reversibile per i pazienti affetti da iCCA avanzato ma, principalmente localizzato nel fegato, è MOLTO DEBOLE a favore e, il ricorso ad una di queste procedure od a diverse procedure in sequenza, potrà essere considerata solamente in casi selezionati, in centri di riferimento e dopo attenta valutazione multidisciplinare e del rapporto rischio-beneficio per il paziente (qualità delle

Unresectable disease; First-line Systemic Therapies

Raccomandazione N. 27: Nei pazienti con CCA avanzato non resecabile e buon performance status (PS ECOG di 0-1), si raccomanda la combinazione di cisplatino e gemcitabina come chemioterapia di prima linea (forza della raccomandazione: FORTE a favore; qualità delle evidenze: ALTA).

…patients with unresectable iCCA and good performance status should be treated (first-line chemotherapy) with GemCis with the addition of durvalumab where available.
(LoE 1, strong recommendation, strong consensus)



A

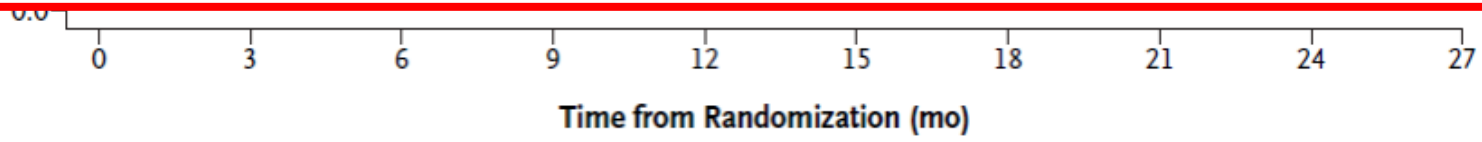
	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value

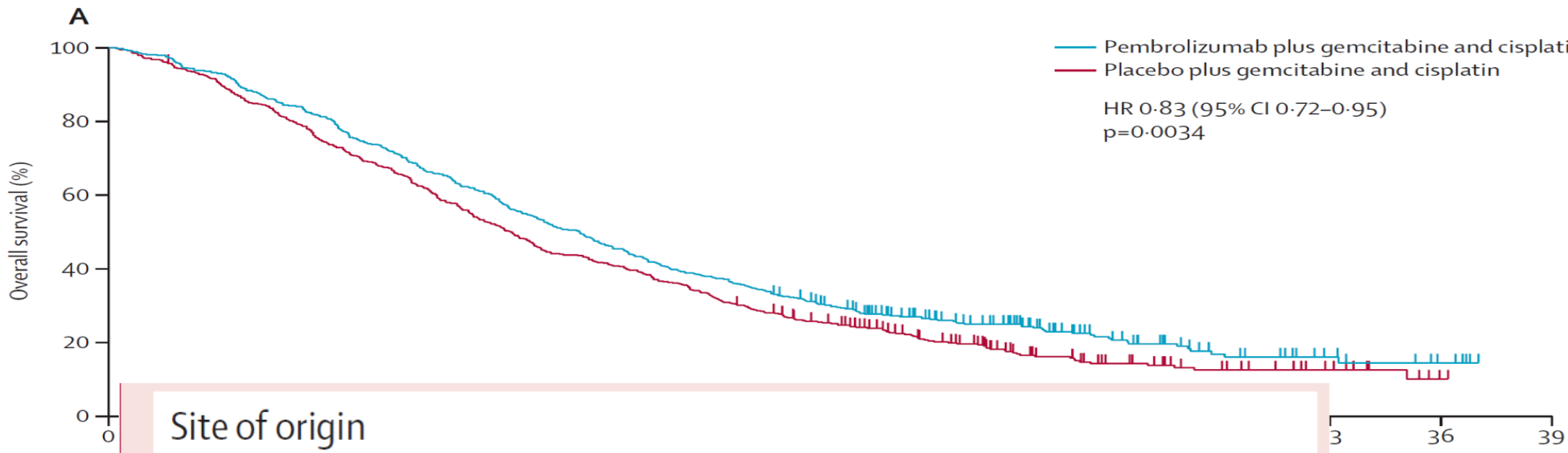
21 December 2022

Durvalumab (PD-L1inhibitor) ***plus chemotherapy approved in the EU as first immunotherapy regimen for patients with advanced biliary tract***

EASL-ILCA 2023 guidelines: Recommendation

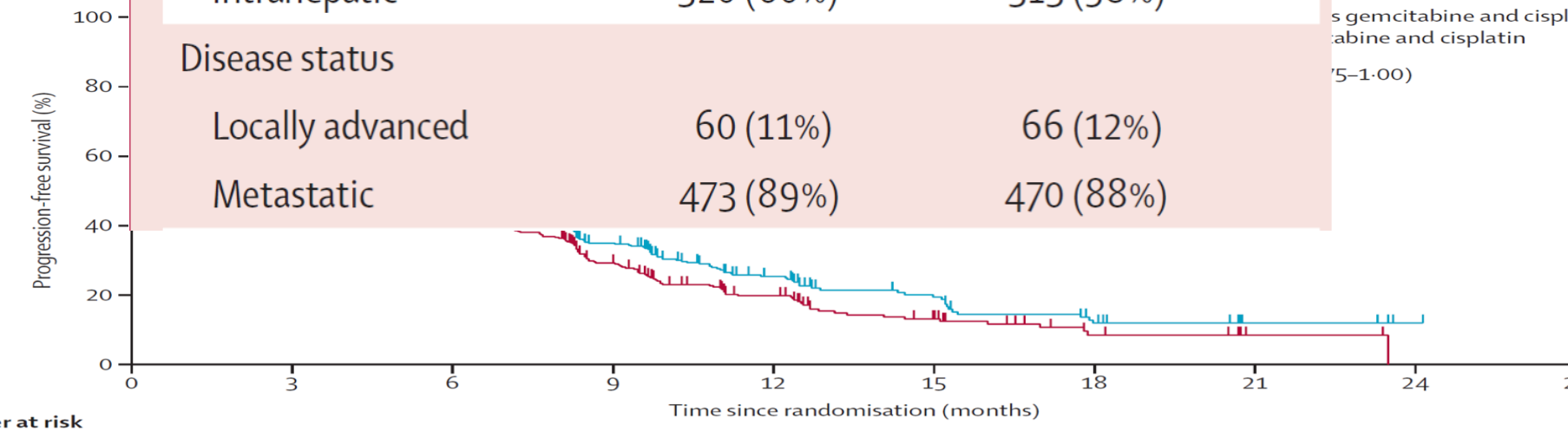
Patients with unresectable iCCA and good performance status should be treated with GemCis (as first-line chemotherapy), with the **addition of durvalumab** where available **(LoE 1, strong recommendation, strong consensus).**





Number at risk (number censored)										
Pembrolizumab plus gemcitabine and cisplatin	53						1	5	0
	(0						09)	(114)	(119)
Placebo plus gemcitabine and cisplatin	53						0	1	0
	(0						4)	(92)	(93)

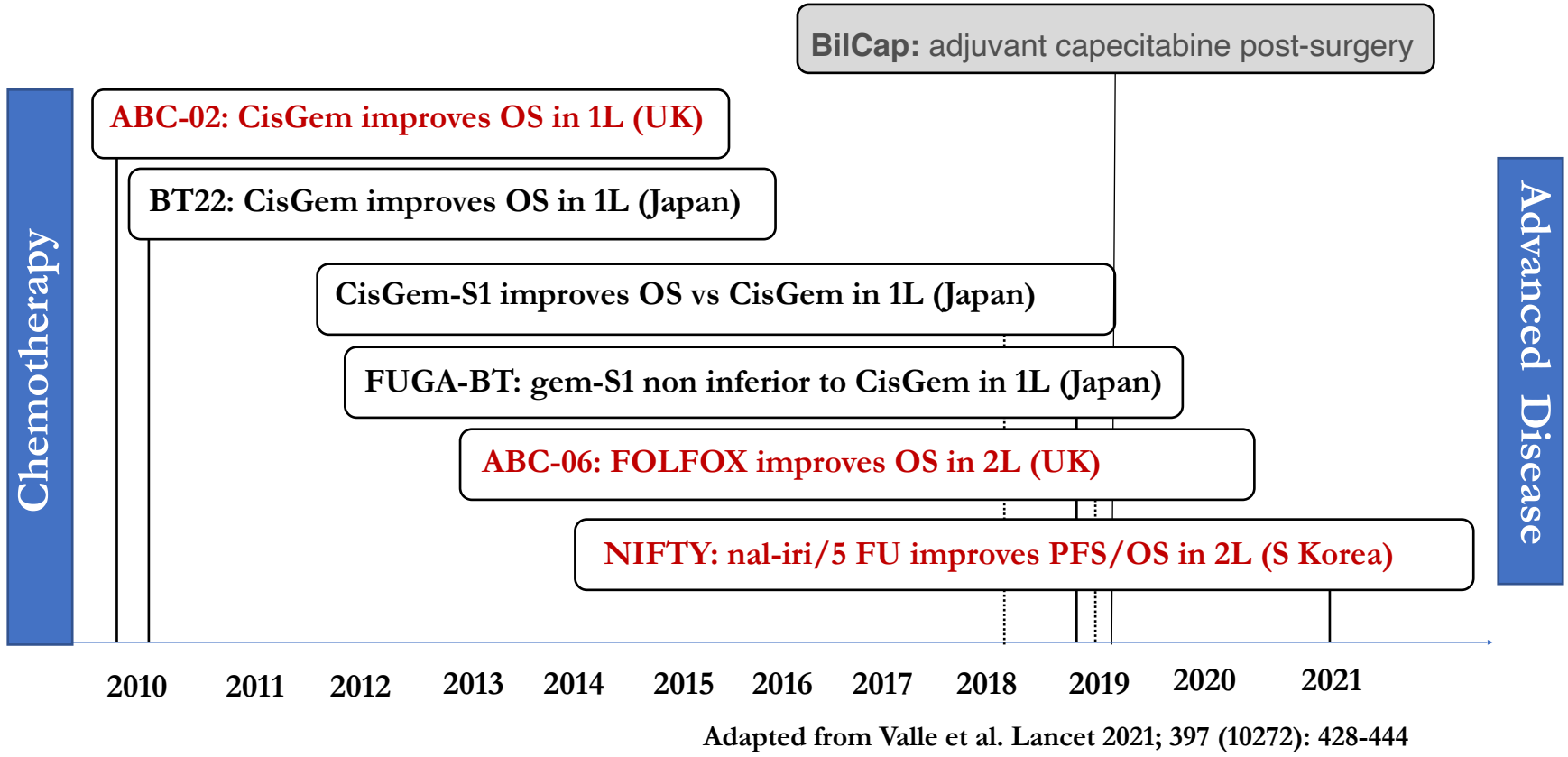
Site of origin		
Extrahepatic	98 (18%)	105 (20%)
Gallbladder	115 (22%)	118 (22%)
Intrahepatic	320 (60%)	313 (58%)
Disease status		
Locally advanced	60 (11%)	66 (12%)
Metastatic	473 (89%)	470 (88%)



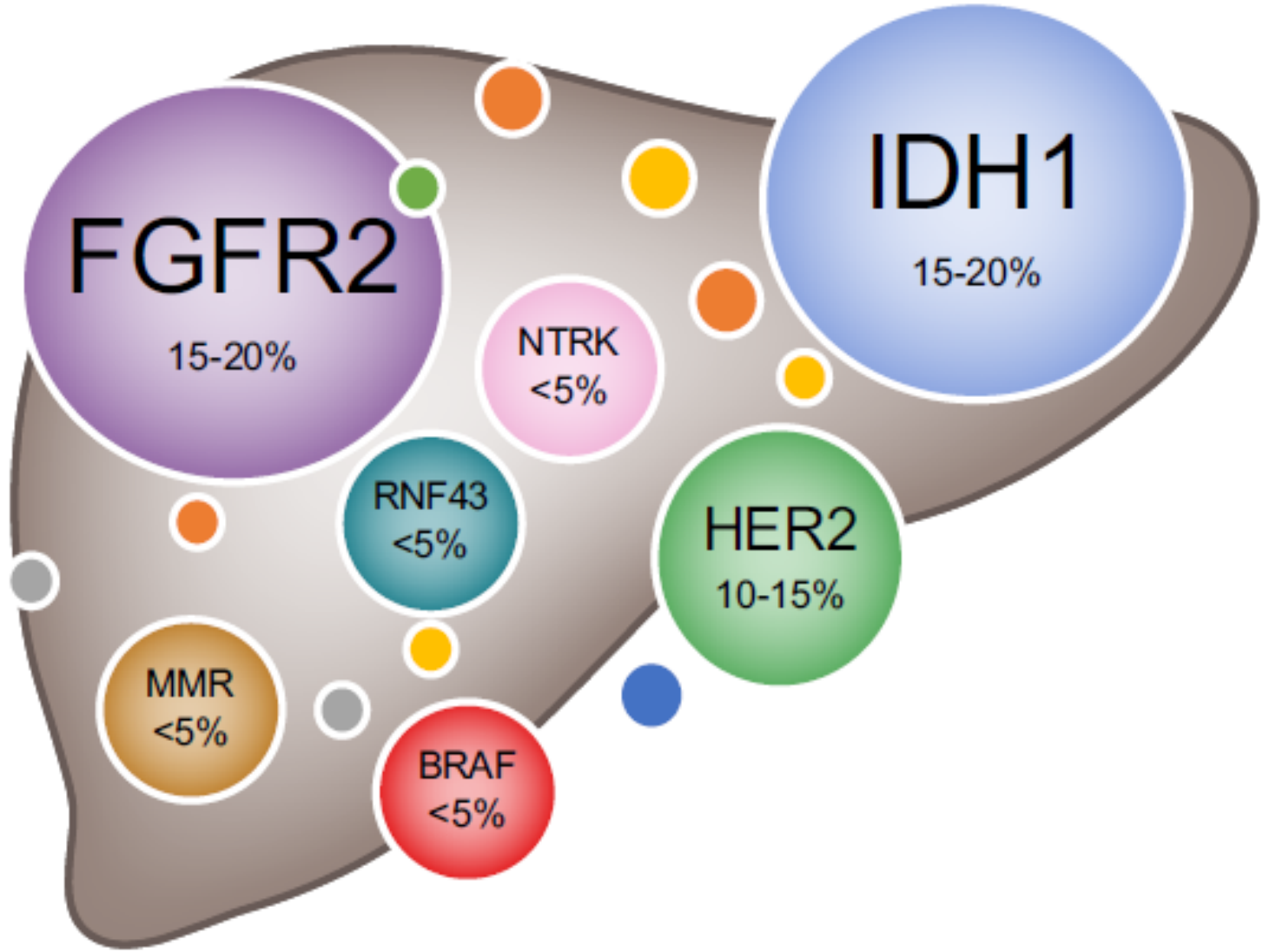
Number at risk (number censored)										
Pembrolizumab plus gemcitabine and cisplatin	533 (0)	368 (27)	238 (55)	121 (101)	62 (131)	29 (153)	14 (158)	5 (167)	1 (171)	0 (172)
Placebo plus gemcitabine and cisplatin	536 (0)	352 (25)	211 (50)	99 (94)	51 (113)	21 (130)	7 (139)	2 (144)	0 (145)	0 (145)

Systemic chemotherapy for CCA: the history

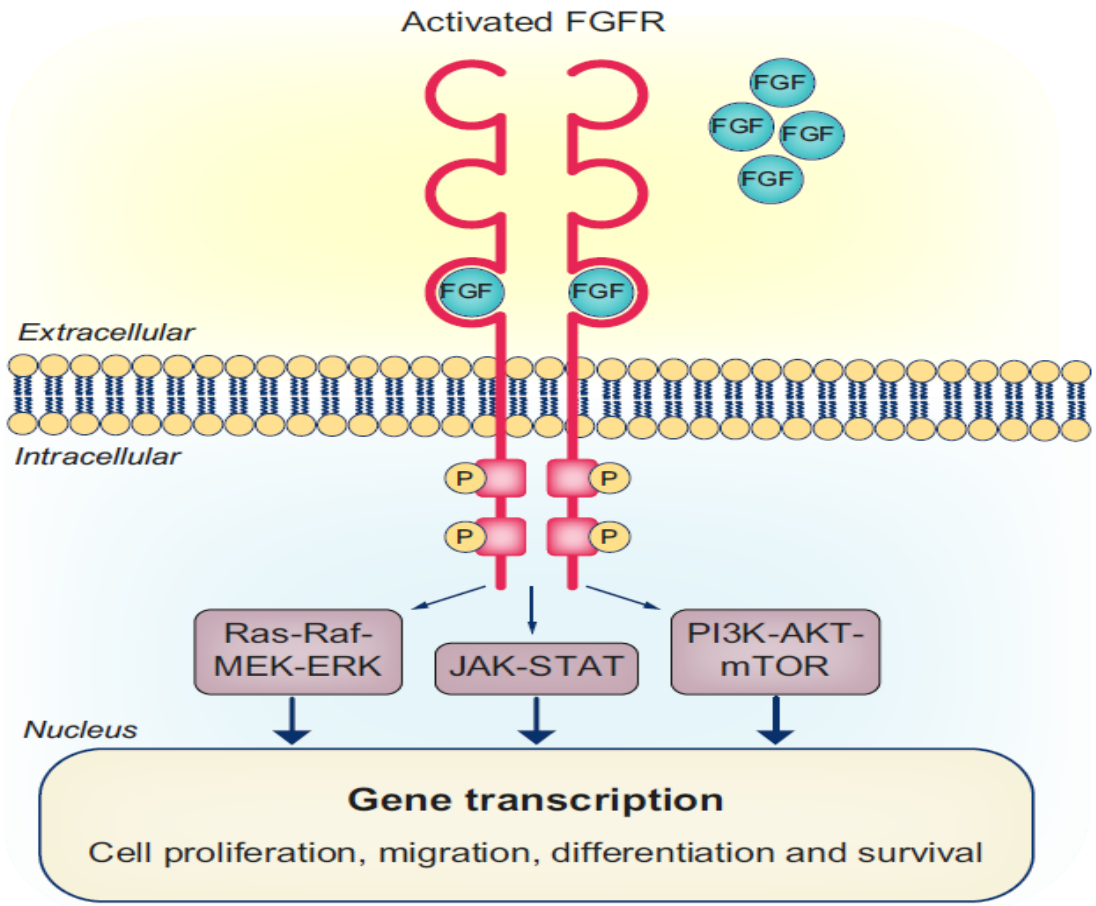
Chemotherapy for advanced disease: very slow progress



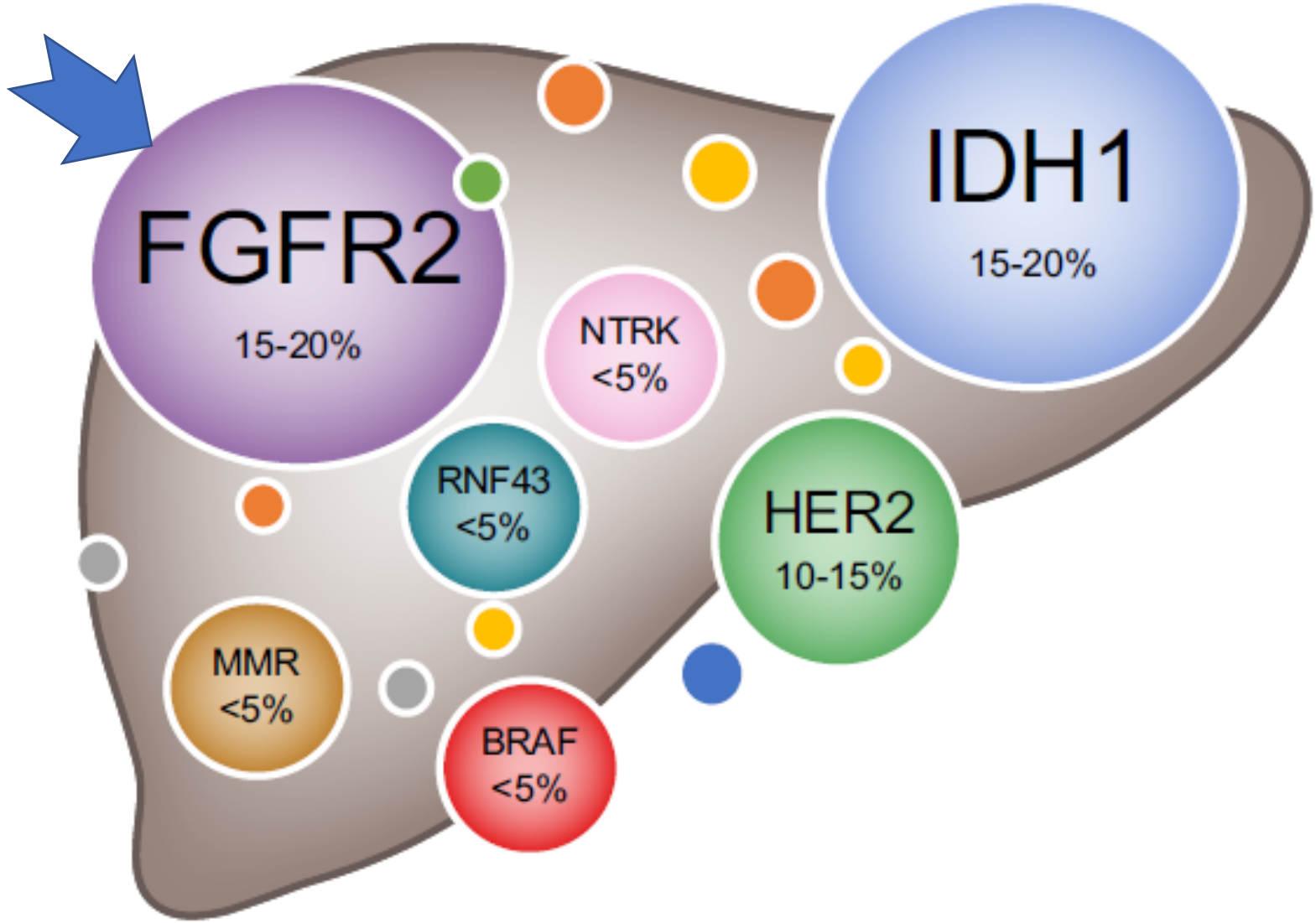
Adapted from Valle et al. Lancet 2021; 397 (10272): 428-444


FGFR2
15-20%
IDH1
15-20%
NTRK
<5%
RNF43
<5%
HER2
10-15%
MMR
<5%
BRAF
<5%

FGFR PATHWAY



differentiation and survival. A constitutively activated FGFR may therefore produce pathological


FGFR2
15-20%
IDH1
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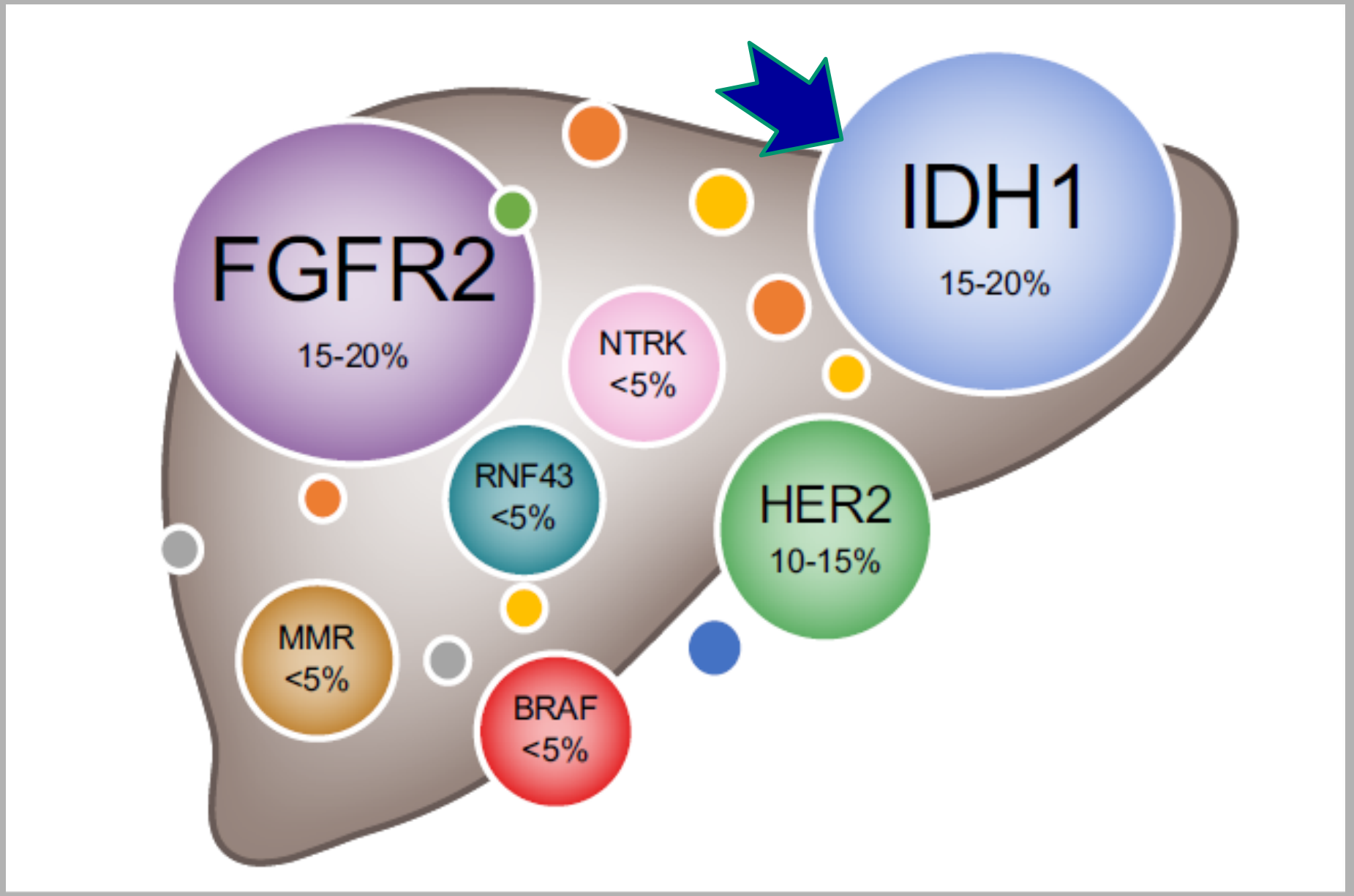
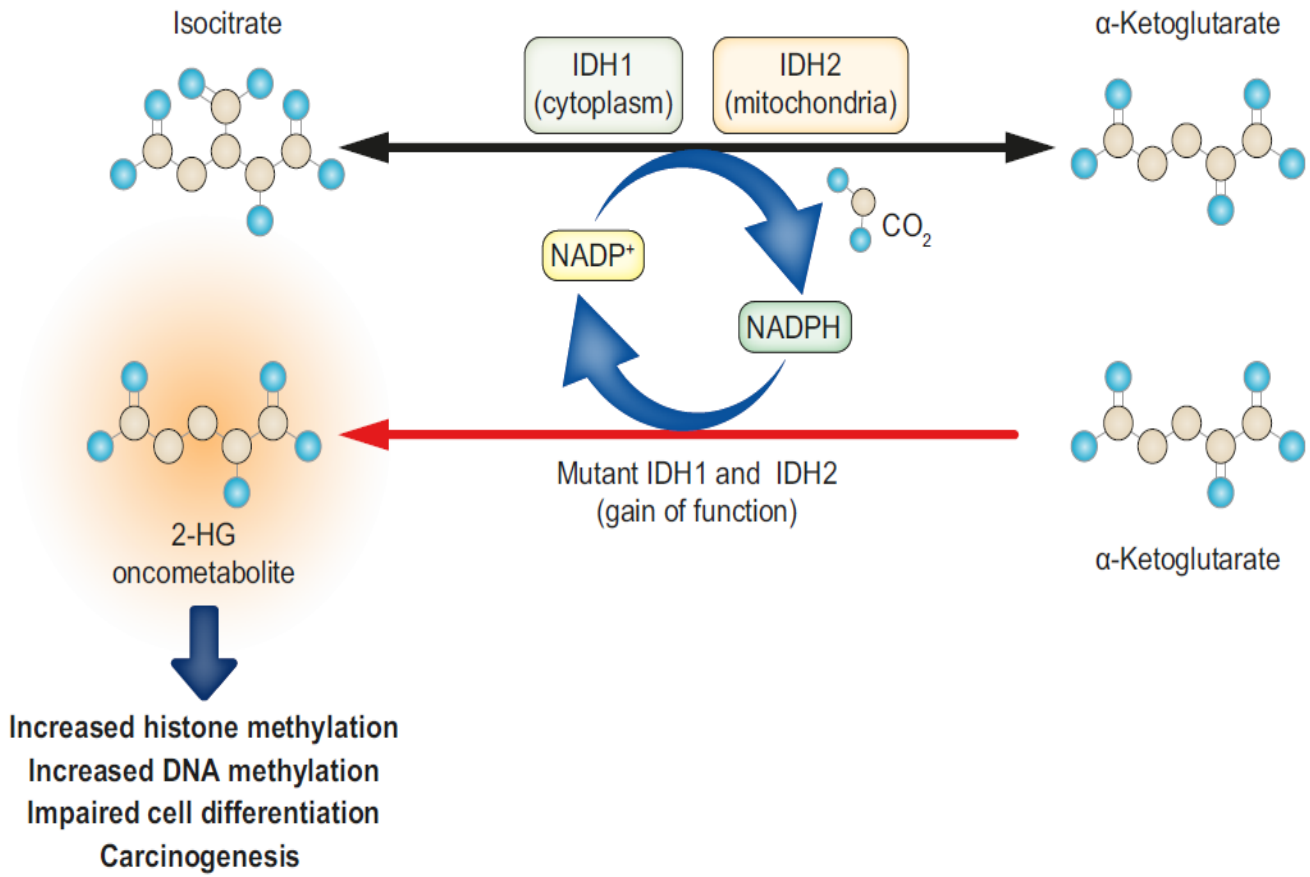
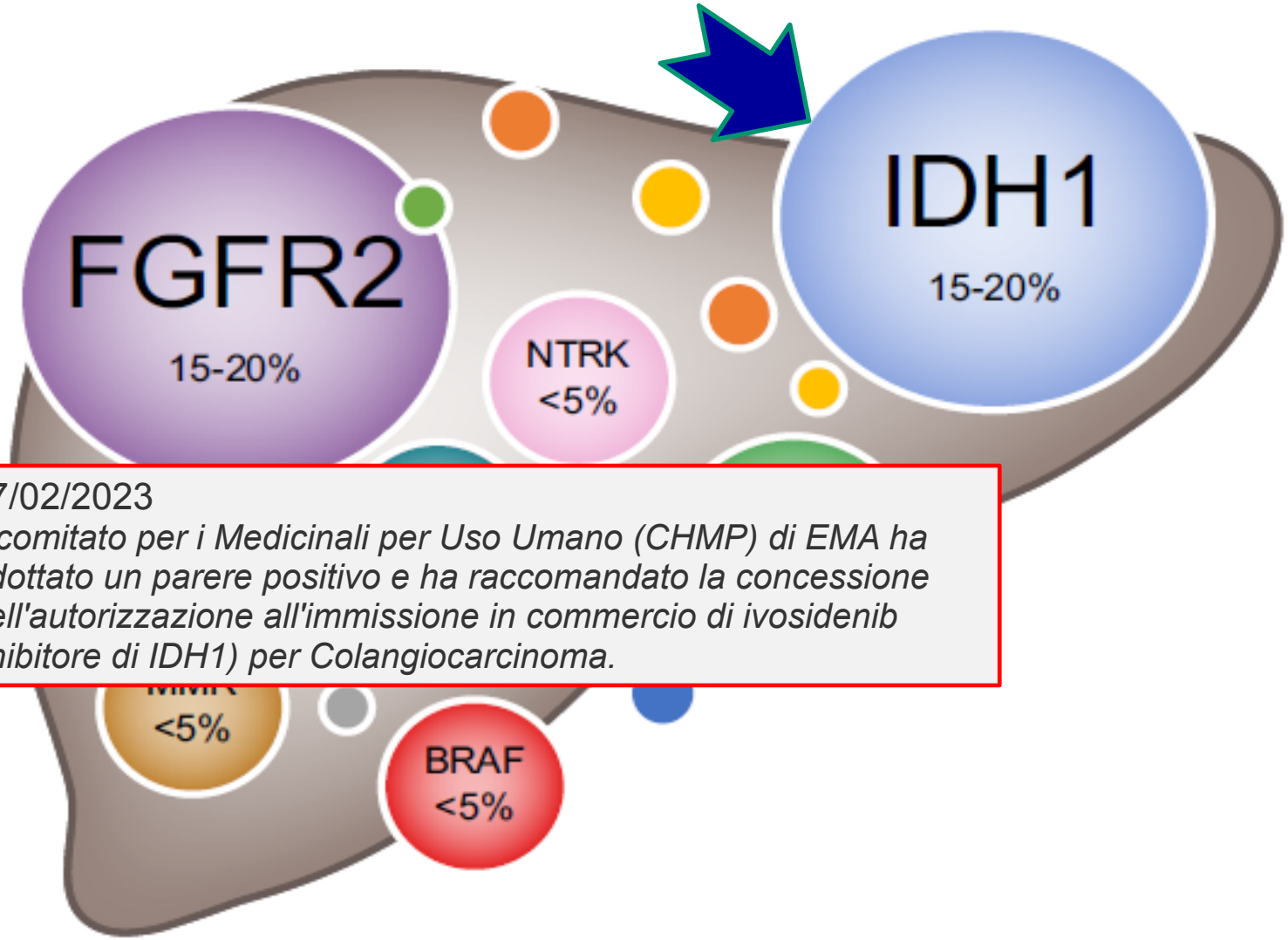
BRAF
<5%


FGFR2
15-20%
IDH1
15-20%
NTRK
<5%
RNF43
<5%
HER2
10-15%
MMR
<5%
BRAF
<5%

IDH INVOLVEMENT IN CELL METABOLISM



IDH, isocitrate dehydrogenase.



27/02/2023

Il comitato per i Medicinali per Uso Umano (CHMP) di EMA ha adottato un parere positivo e ha raccomandato la concessione dell'autorizzazione all'immissione in commercio di ivosidenib (inibitore di IDH1) per Colangiocarcinoma.

B

	Number of events/ number of patients		HR (95% CI)
	Ivosidenib	Placebo	
Previous lines of therapy			

EASL-ILCA clinical practice guidelines on the management of intrahepatic cholangiocarcinoma

MOLECULAR PROFILING

KQ: For patients with iCCA, does molecular profiling at time of diagnosis improve the proportion who receive a targeted therapy based upon tumour biomarker results at any time point in disease course?

Recommendation:

- **In pts …at high risk for recurrence (e.g. node or margin positive, vascular inva-sion, or multifocal intrahepatic disease), molecular profiling with a comprehensive panel is suggested at the time of diagnosis (LoE 5; weak recommendation, consensus).**

Ref: 1. Clinical Cancer Research 2018;24:4154–61. 2. Nat Genet 2015;47:1003–10. Hum Pathol 2012;43:1552–8. 3. Oncologist 2012;17:72–9. 4. Therap Adv Gastroenterol 2017;10:507–20.5. Hepatology 2020;72:1253–66. 6. Hum Pathol 2014;45:1630–8. 7. Gastroenterology 2013;144:829–40. 8. Cancer and Metastasis Reviews 2015;34:157–64. 9. Annals of Oncology 2021;32:1111–26. 10. Clinical Cancer Research 2022;28:1662–71.

Art. 96-*bis*.

(Incremento del Fondo per i* test Next-Generation Sequencing *per il colangiocarcinoma)

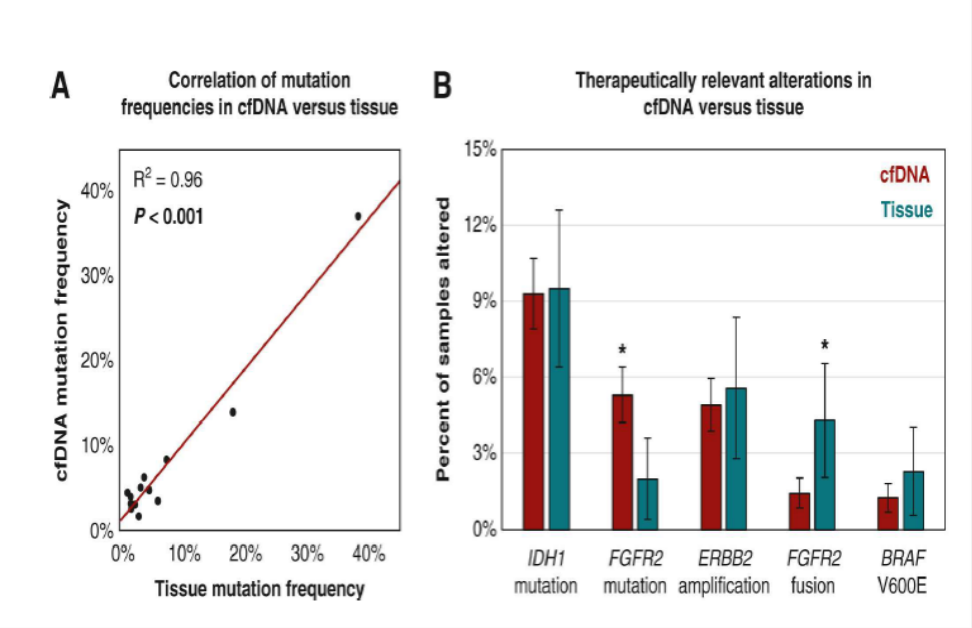
1. Lo stanziamento del Fondo per i *test Next-Generation Sequencing*, di cui al comma 684 dell'articolo 1 della legge 30 dicembre 2021, n. 234, è incrementato di 160 mila euro per l'anno 2023.

2. L'incremento del Fondo di cui al comma 1 è finalizzato al potenziamento dei *test* di *Next-Generation Sequencing* di profilazione genomica del colangiocarcinoma.

Results:

--Genetic alterations detected in cfDNA in 84% of patients, with targetable alterations detected in 44% of patients;

--Concordance between cfDNA and tissue for mutation detection was high for IDH1 mutations (87%) and BRAF V600E (100%), and low for FGFR2 fusions (18%).



Cancers **2022**, *14*, 4281. https://doi.org/10.3390/cancers14174281

Article

Prevalence of *ARID1A* Mutations in Cell-Free Circulating

Tissue vs. cfDNA:cholangiocarcinoma (N = 1537)

Cholangiocarcinoma ~14% vs. 10.9%
Hepatocellular carcinoma, ~ 12% vs. 10.6%;
Carcinoma of unknown primary, ~15% vs. 8.5%;

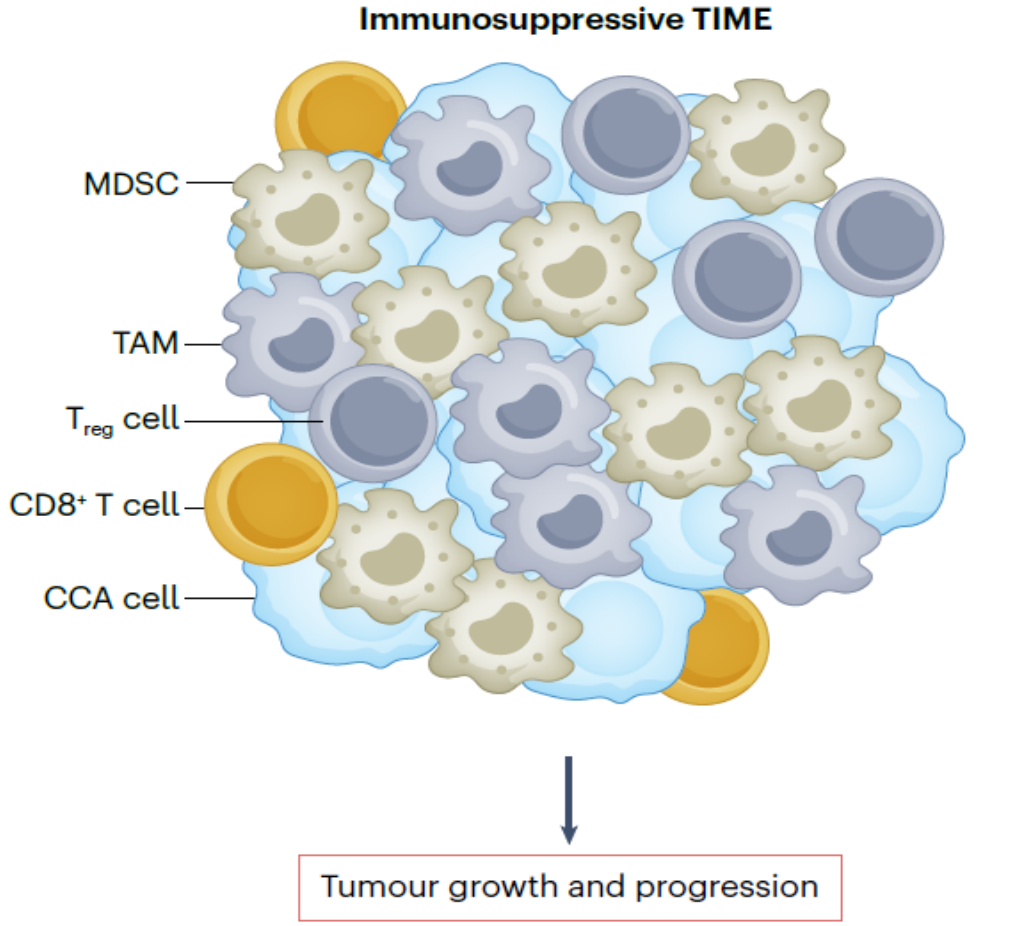
Cell Cycle	*CCNE1, CDH1, CDK1, CDK6, CDKN2A, FBXW7,* and *RB1*
DNA Damage	*ATM, BRCA1, BRCA2, CCND1,* and *MLH1*
PI3K/AKT/mTOR	*AKT1, MTOR, PIK3CA, PTEN, STK11,* and *TSC1*
RAS/RAF/MAPK	*ARAF, BRAF, ERBB2, GNA11, HRAS, KRAS, MAP2K1, MAP2K2, MAPK1, MAPK3, NF1, NRAS, RAF1,* and *RIT1*
Signal Transduction	*ALK, AR, DDR, ESR1, GATA3, GNAS, GNAQ, MYC, NOTCH1, NTRK1, NTRK3, PTPN11, RET, RHOA, ROS1,* and *SMAD4*
WNT/β-Catenin	*APC* and *CTNNB1*

CCA: Treatment of unresectable disease

TARGET THERAPIES

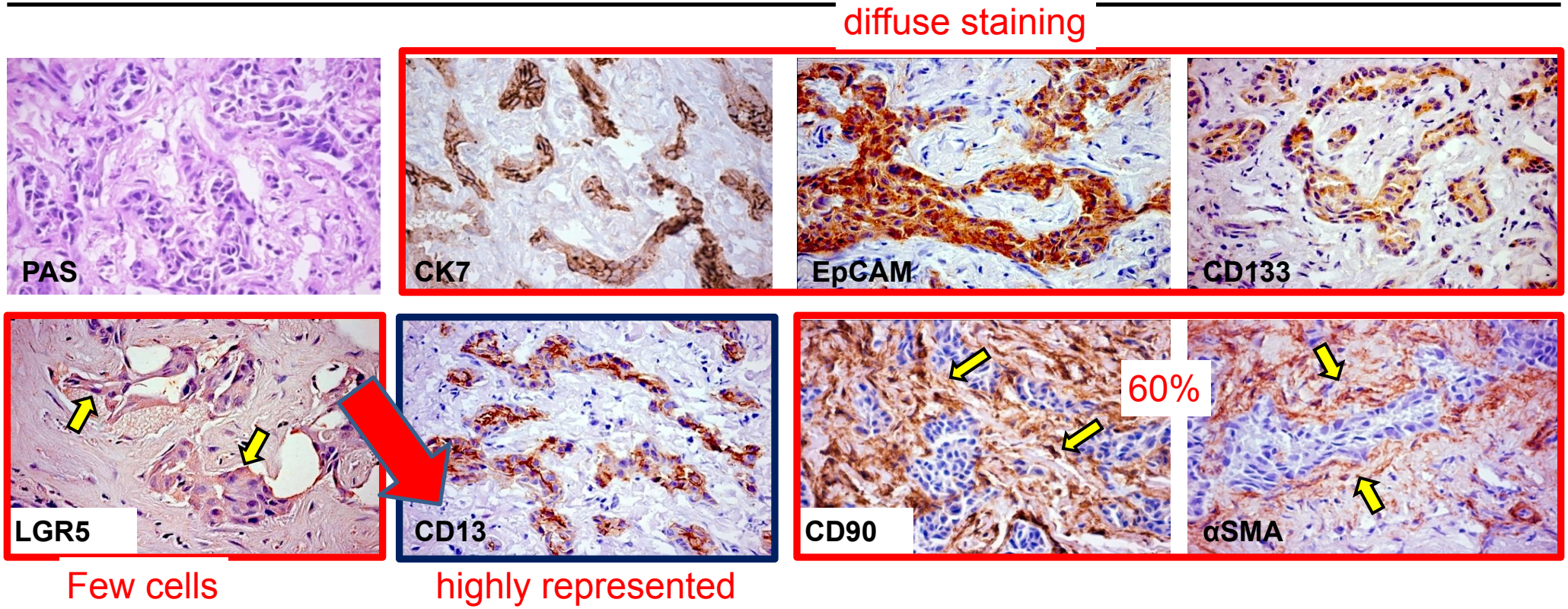
Molecular Target	Compound	Recommendations from NCCN Guidelines for Hepatology Cancers	FDA Status	EMA Status
BRAF V600E mutations	Dabrafenib + Trametinib	BRAF V600E mutated tumor	Accelerated approval for *BRAF* V600E mutaded tumors	Authorized for *BRAF* V60E mutaded NSCLC and melanoma; not approved for use across all solid
FGFR2 fusions or rearrangements	Infigratinib	CCA with *FGFR2* fusions or rearrangements	Accelerated approval for CCA with *FGFR2* fusions or rearrangements	Received orphan designation for use in BTC; not authorized for use
FGFR2 fusions or rearrangements	Pemigatinib	CCA with *FGFR2* fusions or rearrangements	Accelerated approval for CCA with *FGFR2* fusions or rearrangements	Authorized for CCA with *FGFR2* fusions or rearrangements
HER2 positive	Trastuzumab + Pertuzumab	HER2 positive tumors	Approved for HER2-positive breast cancer; not approved for use across all solid tumors for CCA	Authorized for HER2-positive breast ccancer; not approved for use across all solid tumors or CCA
IDH1 mutations	Invosidenib	CCA with *IDH1* mutations	Approved for CCA with *IDH1* mutations	Received orphan designaion for use in BTC; not authorized for use
MSI-H/dMMR	Dostarlimab-gxly	MSI-H/dMMR tumors	Accelerated approval for dMMR tumors	Authorized for MSI-H/dMMR endometrial ccancer; not approved for use across all solid tumors orCCA
MSIH/dMMR/ TMB-H	Pembrolizumab	MSI-H/dMMR/TMB-H tumors	Approved for MSI-H/dMMR/TMB-H tumors	Authorized for severalMSI-H/dMMR/TMB-H Tumors, including BTC; not authorized for TMB-H
NTRK fusions	Entrectinib	NTRK gene fusions-positive tumors	Accelerated approval for *NTRK* gene fusion-positive tumors	Authorized for *NTRK* gene fusion-positive tumors
NTRK fusions	Larotrectinib	NTRK gene fusions-positive tumors	Accelerated approval for *NTRK* gene fusion-positive tumors	Authorized for *NTRK* gene fusion-positive tumors
RET fusions	Pralsetinib	*RET* fusions-positive tumors	Accelerated approval for *RET* fusion-positive NSCLC; not spptoved for use across all solid tumors orCCA	Authorized for *RET* fusion-positive NSCLC; not approved for use across all solid tumors or CCA

CCAs are highly desmoplastic cancers characterized by:
-tumour immune-microenvironment (TiME).. poorly immunogenic;
-abundance of immunosuppressive cell types (myeloid-derived suppressor cells, tumour-associated macrophages (TAMs)
-abundance of heterogeneous cancer-associated fibroblasts (CAFs).



Sumera I. Ilyas et al.
Nature Clin. Oncology 2023

Immunophenotype of small-duct iCCA
Profile of Cancer Stem Cells



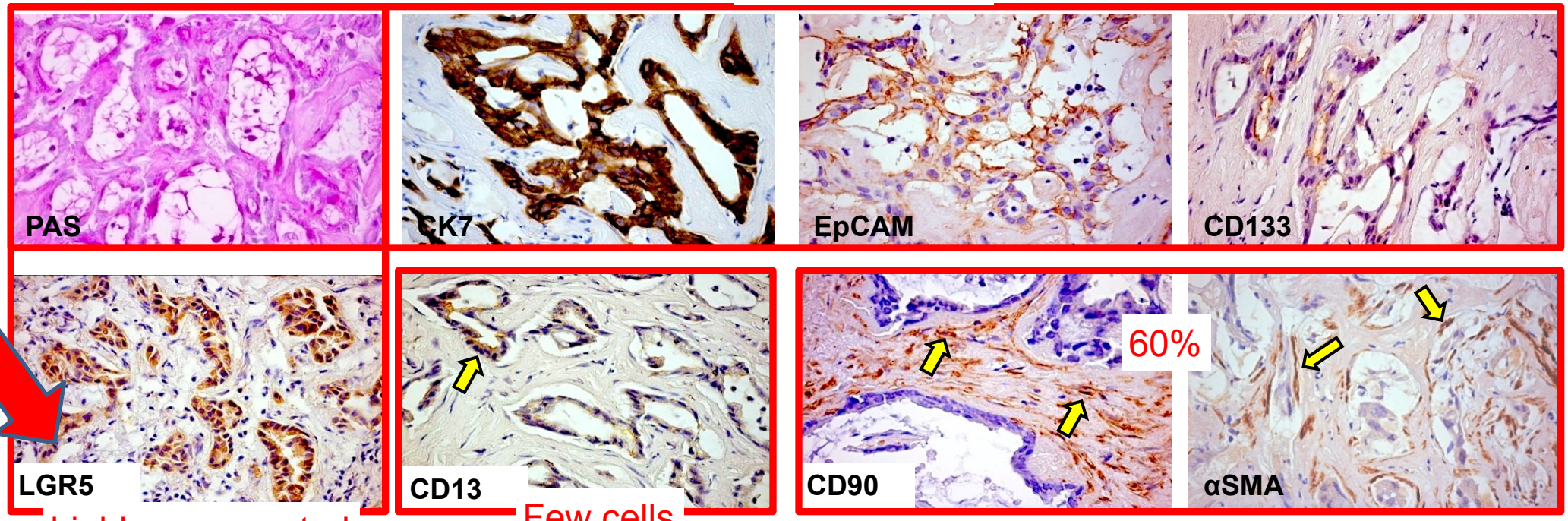
*Small-duct iCCA diffusely positive for K7, EpCAM, CD13 and CD133.

*LGR5 restricted to few tumor epithelial cells (arrows).

* CD90 and αSMA mostly expressed by tumor stromal cells (arrows).

Cardinale V. et al. AJP 2015

Immunophenotype of large-duct iCCA: profile of Cancer Stem Cells



*Large-duct iCCA diffusely pos. for K7, EpCAM, LGR5, CD133;

*CD13 restricted to few tumor epithelial cells (arrow);

*CD90 and αSMA mostly expressed by tumor stromal cells(arrows)

No difference between iCCA and pCCA.

LGR5 = large duct > small duct iCCA($p<0.05$)

CD13 = small duct > large duct iCCA ($p< 0.05$)

Cardinale V. et al. AJP 2015

Published in final edited form as:
J Hepatol. 2017 January ; 66(1): 102–115. doi:10.1016/j.jhep.2016.08.012.

Cholangiocarcinoma stem-like subset shapes tumor-initiating niche by educating associated macrophages

Chiara Raggi[1,†,*], **Margherita Correnti**[1,†], **Antonio Sica**[3,4], **Jesper B. Andersen**[5], **Vincenzo**

<u>…..cancer stem cells are able to manipulate stromal cells to their needs !</u>

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY, VOL. 72, NO. 3, 2020

Identification of Four Immune Subtypes Characterized by Distinct Composition and Functions of Tumor Microenvironment in Intrahepatic Cho

Sylvie Job,[1*] D… Gérard Pascal,[2,3]

The inflamed subtype (11%) presented a massive T lymphocyte infiltration, an activation of inflammatory and immune checkpoint pathways, and was associated with the longest patient survival. Potentially treatable with checkpoint blockade immunotherapy

Table 1 | Immune classifications of iCCA based on RNA-sequencing data

Subclass	Proportion of iCCAs (%)	Key features	Prognostic association (median OS, months)
Classification based on immune gene expression signatures[79]			
Immune-desert	46–48	TME signatures with weak expression of immune and myofibroblast signatures	42
Immunogenomic	9–13	Signatures of recruited innate immune cells, adaptive immune cells and activated fibroblasts Activation of inflammatory pathways	73
Myeloid	13–19	Strong expression of monocyte-derived and/or other myeloid signatures Low expression of lymphoid signatures	25
Mesenchymal	22–28	Strong expression of fibroblast signatures	19

Original research

Martin-Serrano MA, *et al*. *Gut* 2023;**72**:736–748. doi:10.1136/gutjnl-2021-326514

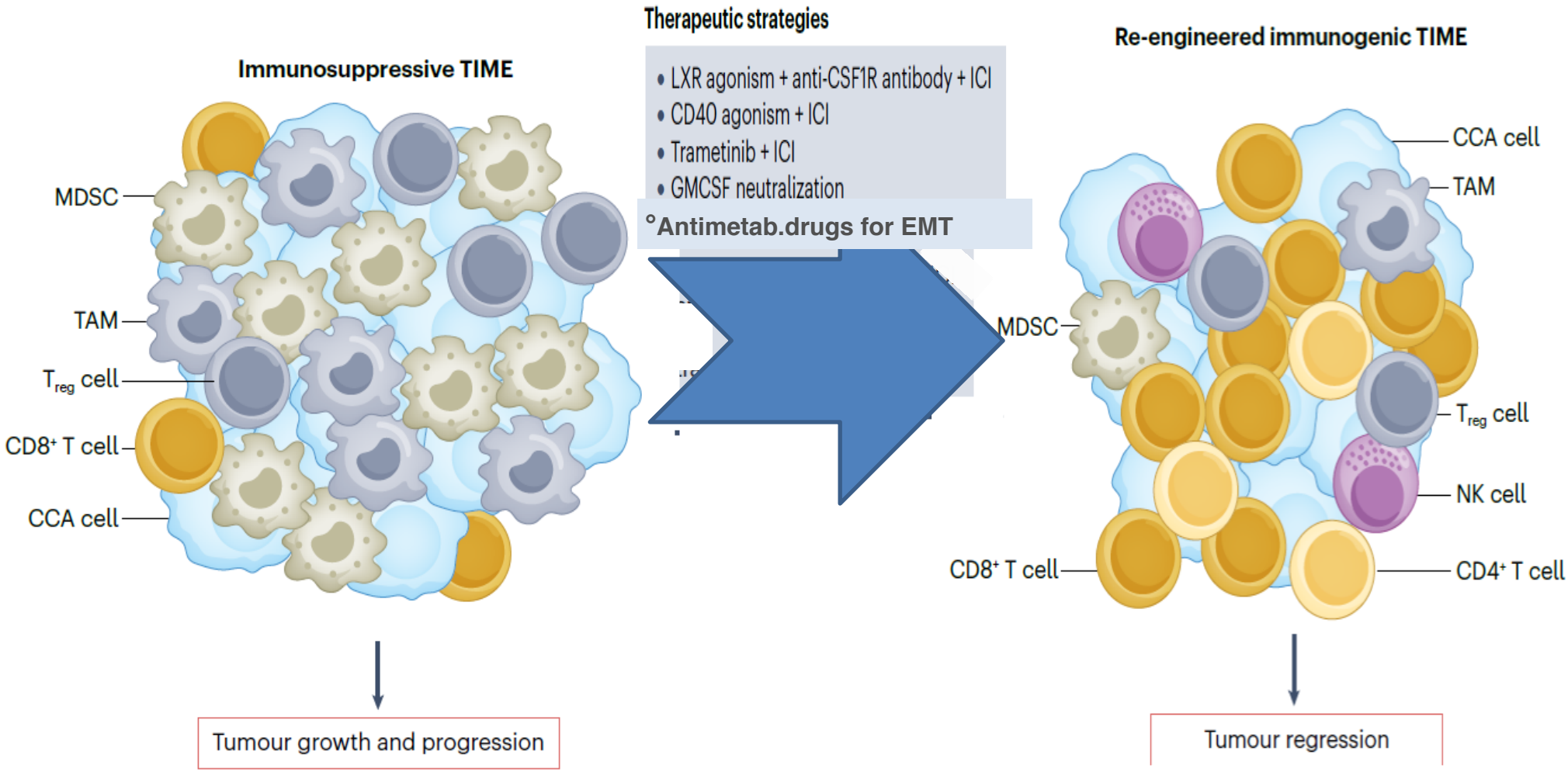
Novel microenvironment-based classification of intrahepatic cholangiocarcinoma with therapeutic implications

Miguel A Martin-Serrano,[1] Benjamin Kepecs,[2] Miguel Torres-Martin,[3] Emily R Bramel,[1,4]

Subclass	Proportion of iCCAs (%)	Key features	
Stroma, Tumour and Immune Microenvironment (STIM) classification[57]			
Immune classical	~10	High immune infiltration (63%) Moderate stromal infiltration (27%)	–[a]
Inflammatory stroma	~25	Moderate immune infiltration (43%) High stromal infiltration (50%) Abundant desmoplastic reaction and ECM deposition High stiffness Activated inflammatory stroma T cell exhaustion	–
Hepatic stem-like	~35	Low immune infiltration (28%) Low stromal infiltration (17%) Abundant tumour-promoting macrophages	–
Tumour classical	~10	Low immune infiltration (22%) Low stromal infiltration (12%) Activation of cell cycle pathways	–
Desert-like	~20	Low immune infiltration (22%) Low stromal infiltration (11%) Regulatory T cell enrichment	–

ECM, extracellular matrix; iCCA, intrahepatic cholangiocarcinoma; OS, overall survival; TME, tumour microenvironment. [a]In a multivariate analysis, the STIM classes were not independent predictors of outcome.

TARGETING THE TIME ! (Re-Engineering Immunogenic Time!



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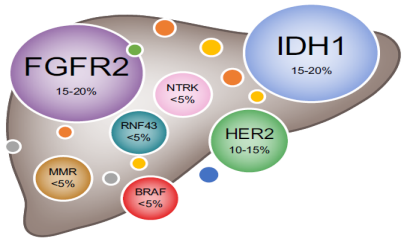
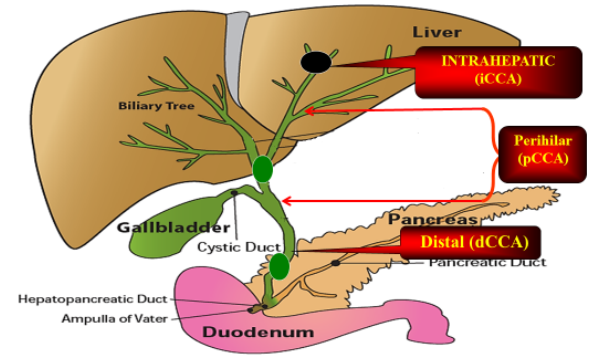


Take-home messages



- **Sub-classification of CCA (anatomical, radiologic, molecular) is a MUST !**
- The identification of **molecular soubgroups** is expanding treatment options in selected sub-populations
    - FGFR2, IDH1, HER2, $BRAF^{V600E}$, MSI-high, NTRK, etc.
- **Liquid-biopsy is promising ……in CCA !**
- **Co-mutational spectrum may act as a critical modifier of drug response.**
- **Re-Engineering Immunogenic tumor-microenvironment ..the next future ?!**
    - **Future efforts** are needed to explore:
        - Prognostic significance of molecular abnormalites
        - Impact of prior or post-study therapy
        - Primary and secondary resistance to target therapies
        - Rational therapeutic combinations