Traitement systémique des cancers des voies biliaires

Jean-Frédéric Blanc

Oncologie Digestive

CHU Bordeaux

OBJECTIFS PEDAGOGIQUES

- Connaître l’épidémiologie et les facteurs de risque
- Connaître les modalités diagnostiques et les anomalies moléculaires influençant la prise en charge
- Connaître la prise en charge oncologique des formes résécables
- Connaître la prise en charge oncologique des formes avancées

CONFLITS D’INTERET

- ASTRA-ZENECA
- ROCHE
- MSD
- INCYTE
- SERVIER
- TAHIO ONCOLOGY

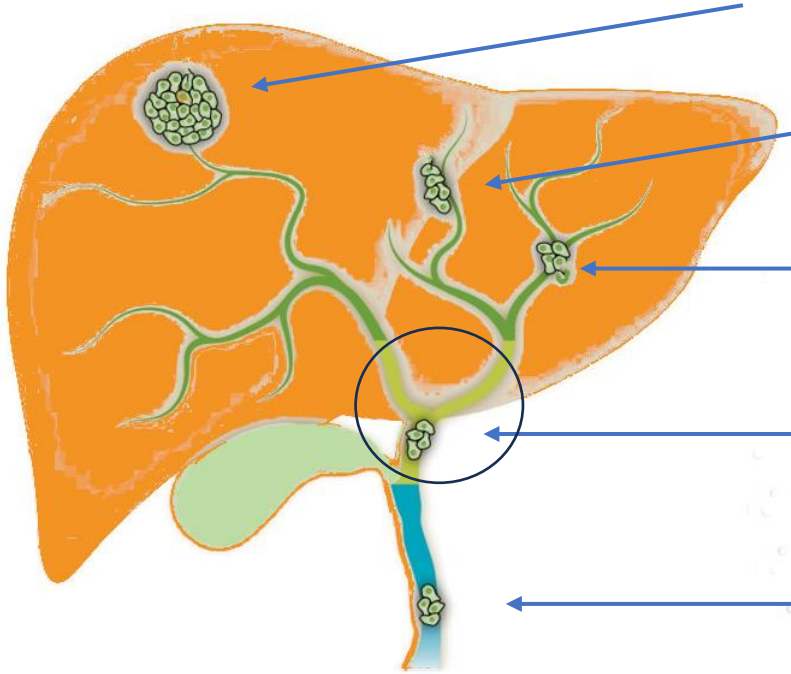
Maladie chronique du foie

Cirrhose
Hépatite
B, C
MAFLD

CSP
Maladie de
Caroli
Lithiases
Parasites
Kyste du
cholédoque

Alcool
Tabac
Diabète
Obésité

Maladie inflammatoire biliaire



CC à petits canaux « mass-forming »

CC à grands canaux péri-canalaire

CC à grands canaux intra-canalaire

CC péri-hilaire

CC extrahépatique

62%

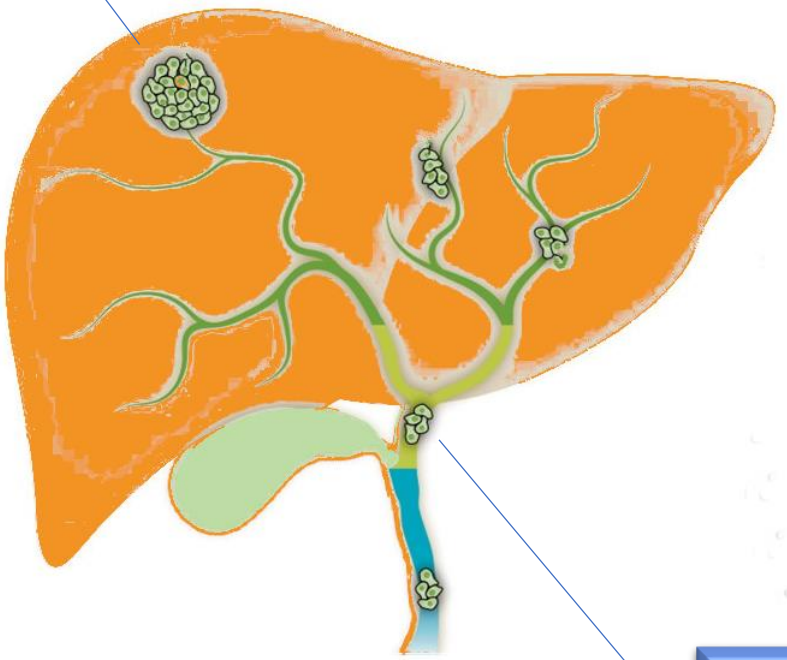
38 %

2000 cas / an

3000 cas / an (avec vésicule et ampoule)

Ghiringhelli F, et al. HPB (Oxford). 2023 Jun;25(6):693-703

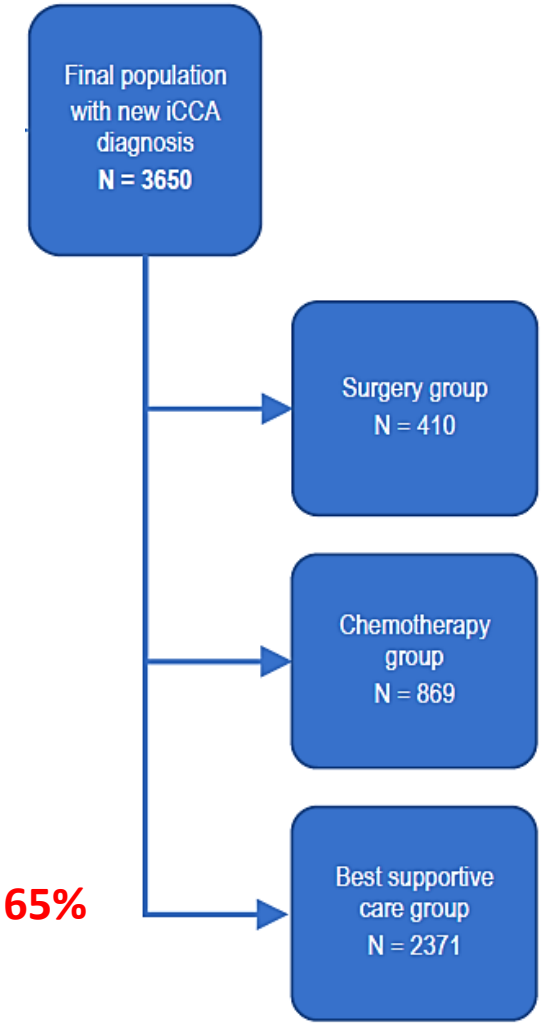
- Diagnostic tardif ou fortuit
- Errance diagnostique: Cholangiocarcinome Vs métastase, tumeurs bénignes
- Hépatopathie sous-jacente



- Ictère
- Sténose bénigne vs maligne
- Bilan de résécabilité

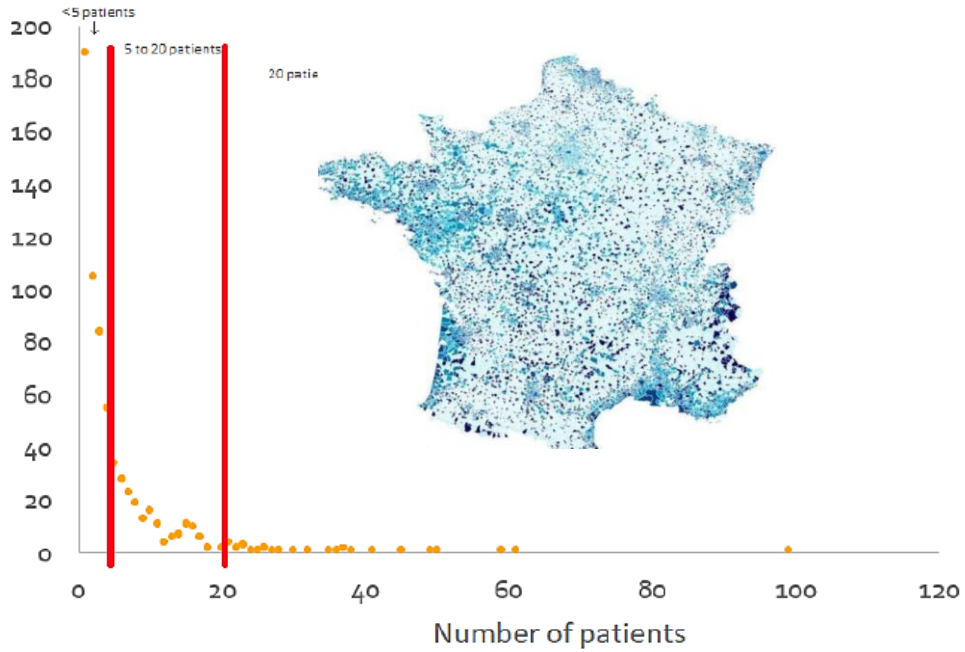
Patient healthcare trajectories of intrahepatic cholangiocarcinoma in France: A nationwide retrospective analysis

Cindy Neuzillet,[a] Corinne Emery,[b] Clément Teissier,[b] Stéphane Bouée,[c*] and Astrid Lièvre[d]



65%

1 patients sur 4 = décès au 1er séjour



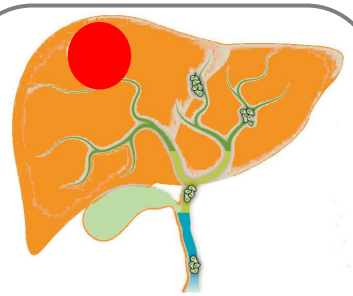
2014-2015

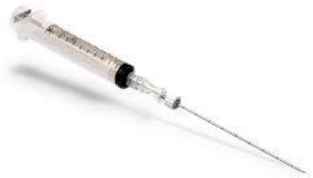
Accès précoce durvalumab (10/2022 - >)

> 380 centres

2022-24

Lancet Reg Health Eur 2022

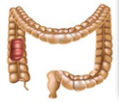




Adénocarcinome

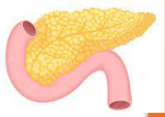
- Tubulaire, de type cholangiolaire
  - Mucus - CK7+ CK19+ CK20- TTF1-, GATA3- HepPar- (CRP +) (S100P-) (N-cadhérine+, NCAM+)
  - **CCi cholangiolo cellulaire**
- Glandulaire, Massif, Papillaire
  - Mucus(Bleu alcian) CK7 , CK20 GATA3 , TTF1
- Trabéculaire, Glandulaire, Massif
  - Mucus - Stroma fibreux - CK7- CK19- CK20- Hep Par 1 + et/ ou ARG1+ et /ou GLY-3 +
  - **CHC**

Métastases

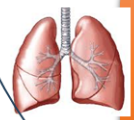


Mucus +/- CK7- / CK20+ SATB2+ CDX2+ TTF1- GATA3- CRP -

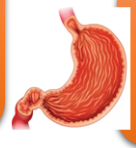
Mucus +/ - CK7+/ CK20- CRP- GATA3+, TTF1- GCDFP-15 +/-, RO+/-



Mucus + CK7+/CK20- CRP - , SATB2+/- (ANXA1+,ANXA10+) (CK17+), (SMAD4-) (S100P+)



CK7+/CK20- TTF1+ / GATA3 - TTF1- et NapsinA + CRP -



CK7+ / CK 20- Mucus +/- CRP-, TTF1 - CDX2-/+, SATB2-

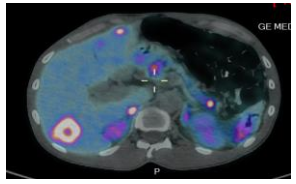
Cholangiocarcinome

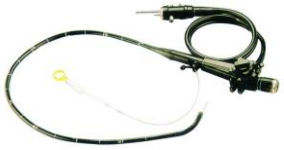
Grand canal

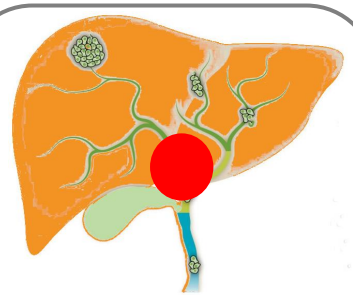
CK7+ / CK20- SATB2-, CDX2 +/ - TTF1 - , GATA3 - Grandes glandes Cellules cylindriques Bleu alcian ++ CRP - / + (S100P +) (N cadhérine - , NCAM-)

Petit canal

CK7+/ CK20- SATB2 - , CDX2 – TTF1 - , GATA3 - Petits tubes et cordons Cellules cubiques ou cylindriques basses Bleu alcian – CRP + (S100P -) (N cadhérine + , NCAM +)







RCP

Tumeur potentiellement résécable ou éligible à une greffe hépatique

Tumeur non résécable, ni éligible à la transplantation hépatique

Sans drainage biliaire pré-opératoire nécessaire

Indication de drainage

Sans drainage biliaire nécessaire

Echo-endoscopie +/-ponction adénopathies (G2+) si:
-doute diagnostique
-risque chirurgical élevé
-projet transplantation

CPRE
Brossage et Biopsies

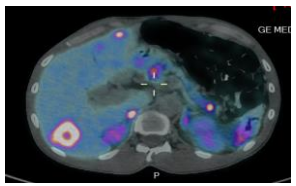
Echo-endoscopie + biopsie

Prélèvements négatifs malgré relecture anapath expert *

Nouvelle CPRE /cholangioscopie avec biopsies ciblées

*** Si suspicion diagnostique forte et tumeur résécable: ne pas retarder la prise en charge chirugicale**

CA 19-9
IgG4



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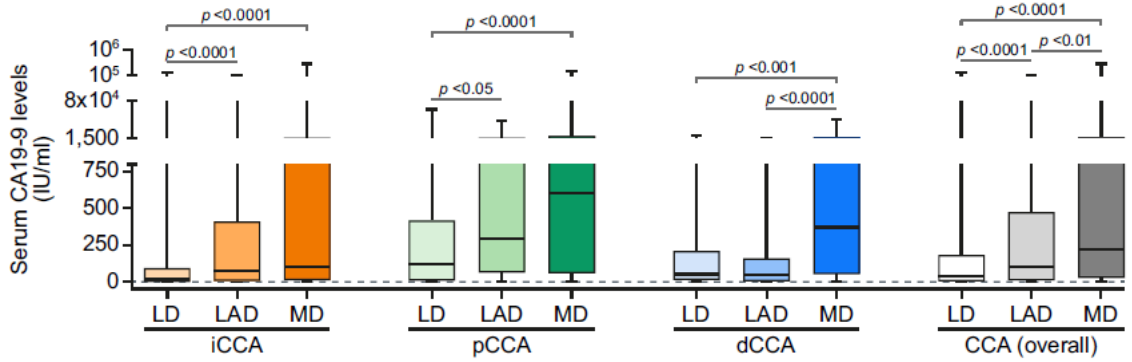
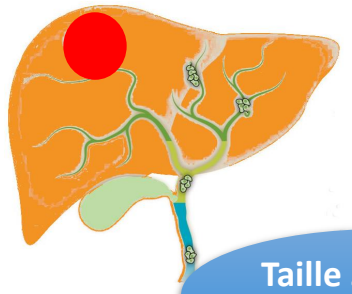
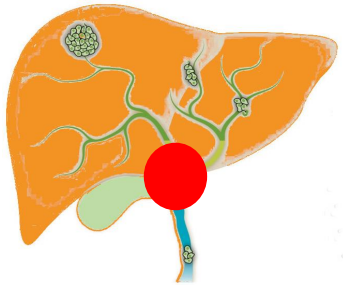
CA 19-9 > 37

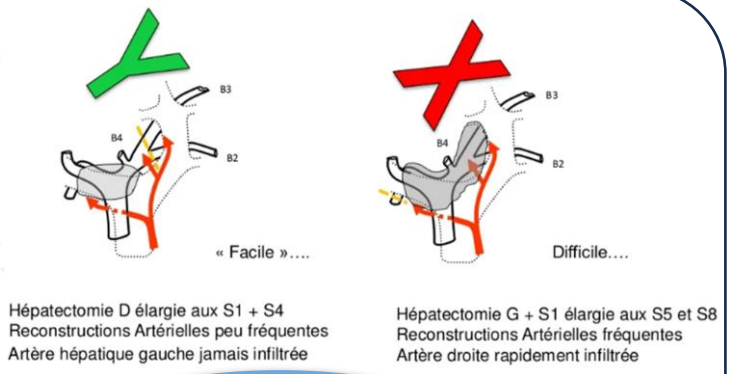


	R0		R1	
	N0	N+	N0	N+
mOS, months (95% CI)	52.2 (33.5–71.0)	23.3 (15.5–31.0)	29.3 (23.1–35.5)	21.8 (17.9–25.8)



Taille 50-75 mm
Nombre





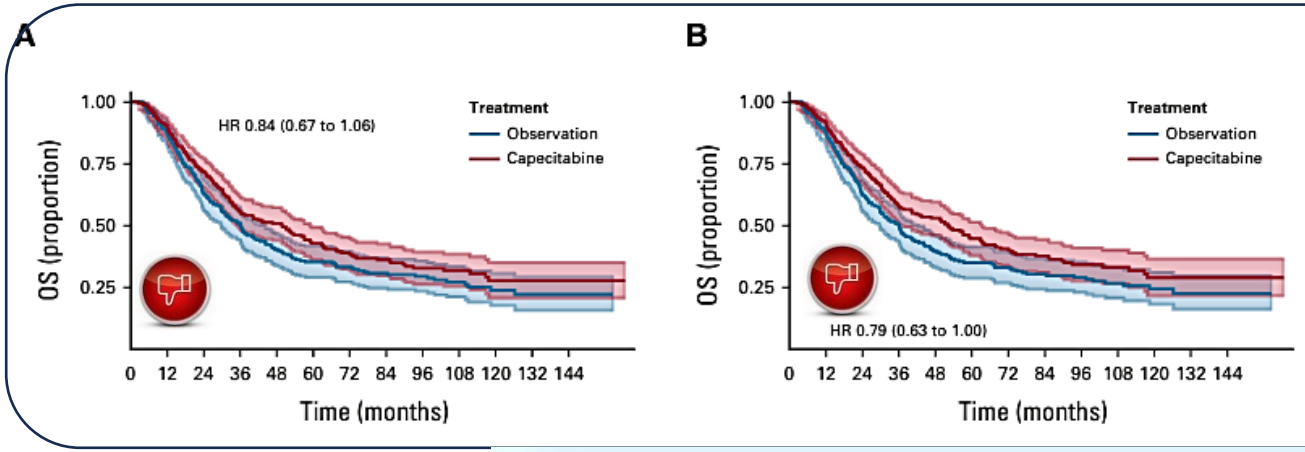
Bili > 50 µmol/l

Bilan Nutritionnel: cancer, ictère, sepsis…

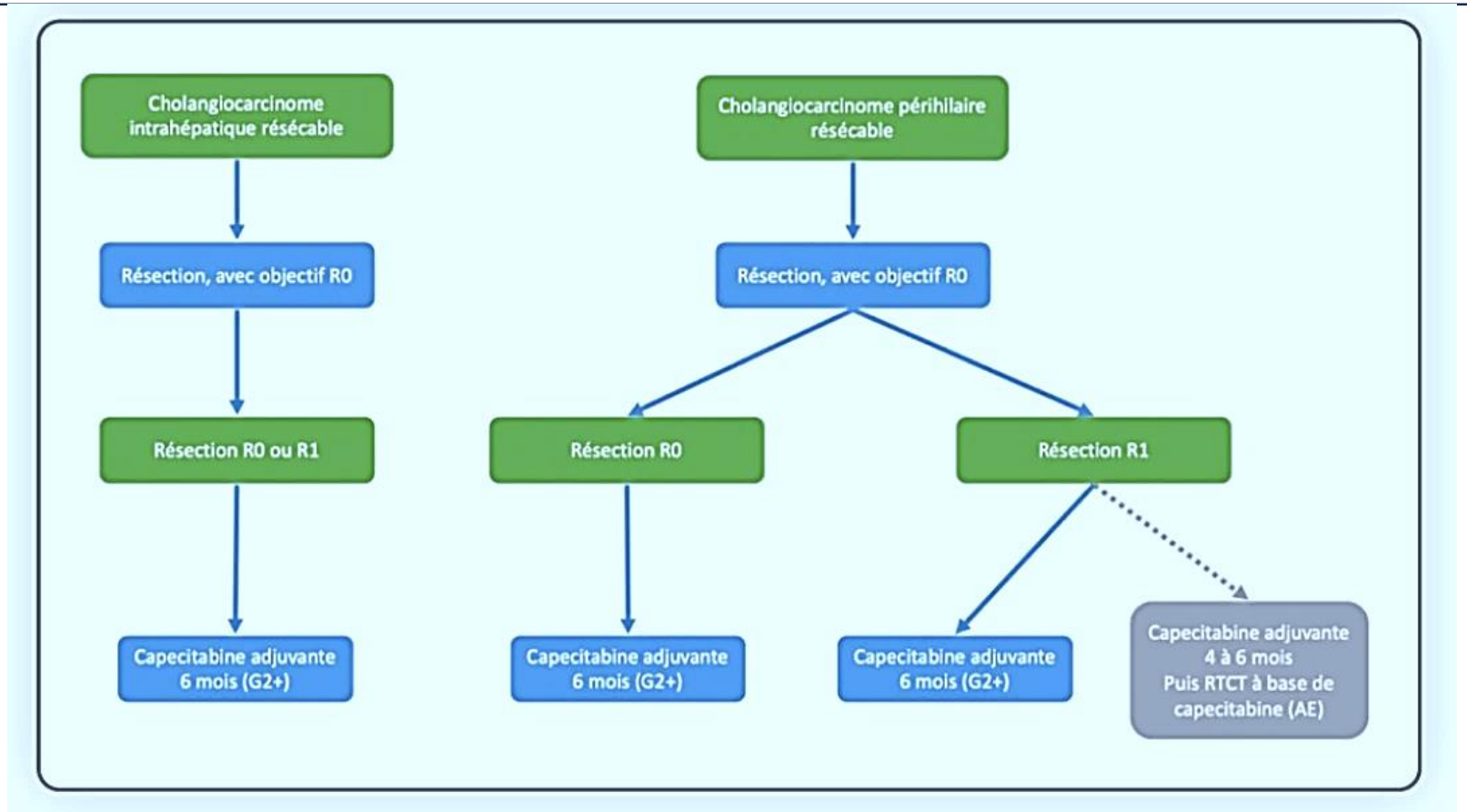
Bilan de l'hépatopathie / biliopathie sous-jacente

ECOG

Izquierdo-Sanchez L, et al. *J Hepatol*. 2022;76:1109–21.



Traitement Adjuvant



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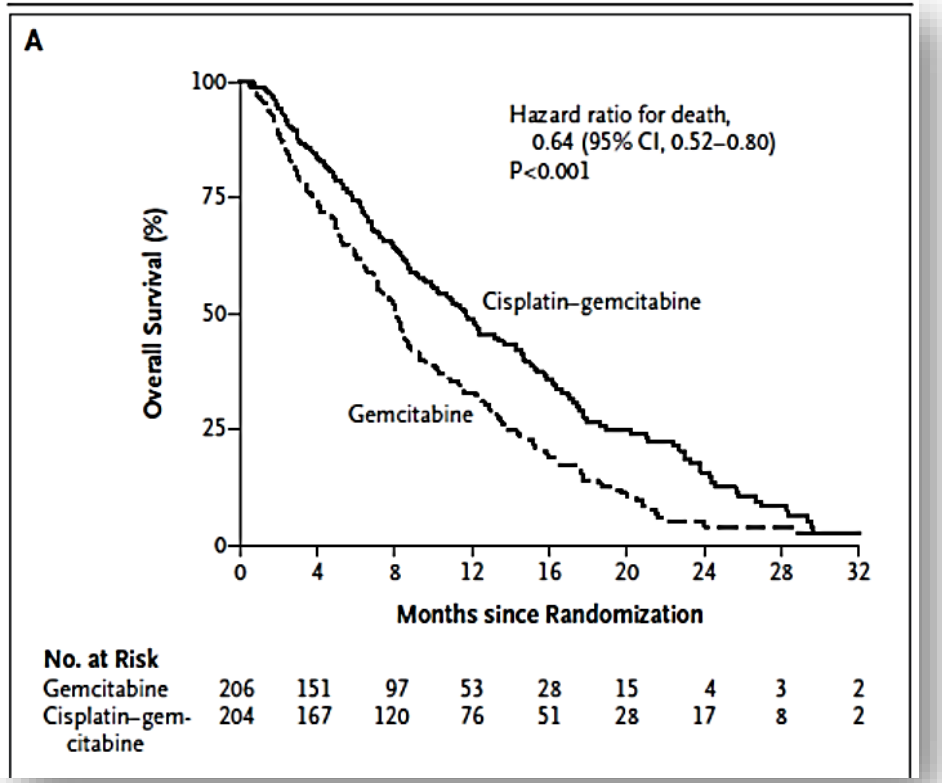
Bridgewater Jet al. Journal of Clinical Oncology 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

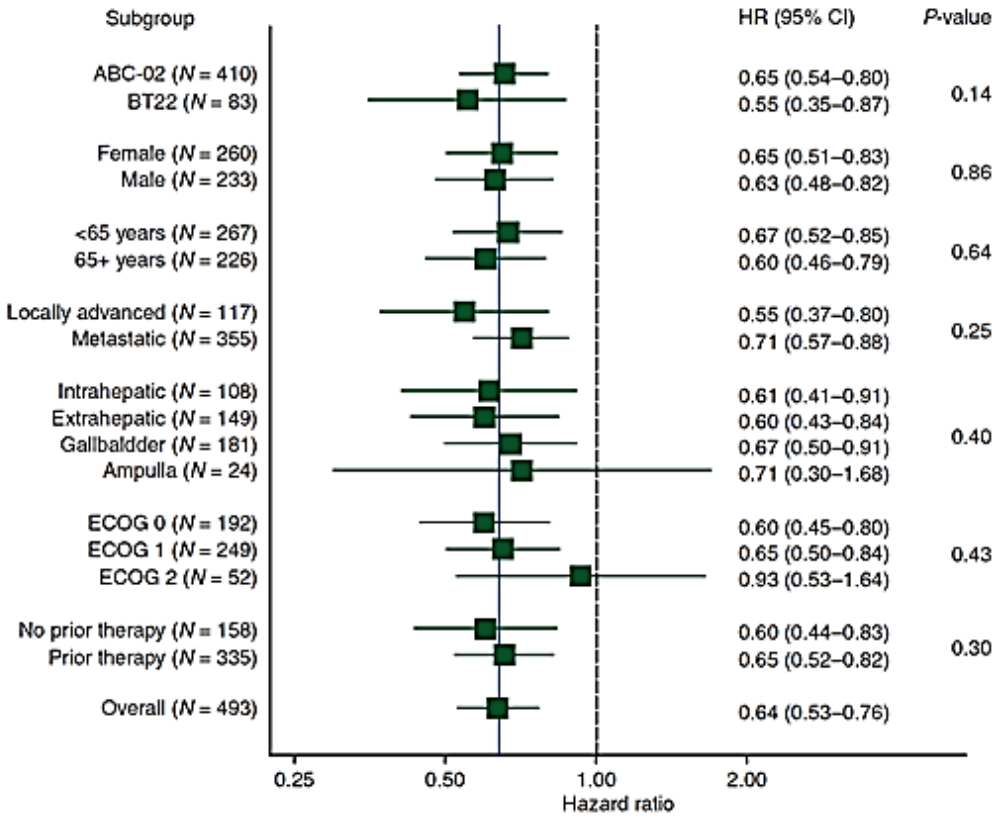
Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D.,



11,7 vs 8,1 mois

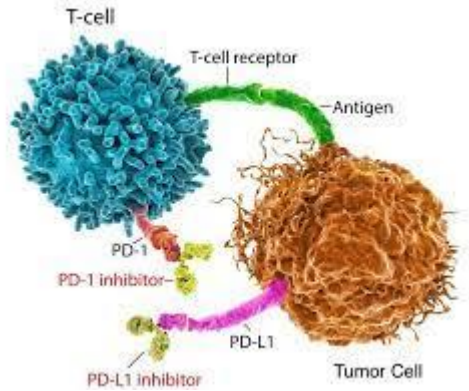
Première Ligne



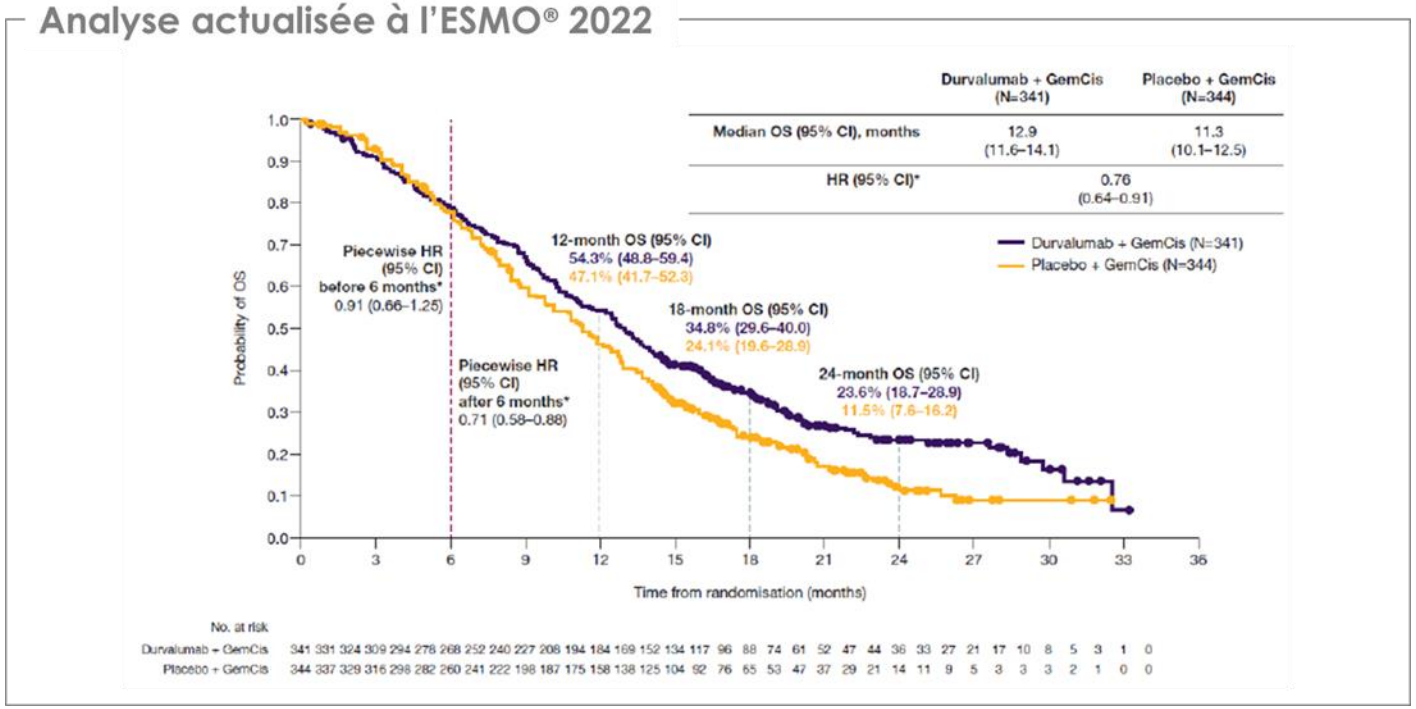
Valle et al., Ann Oncol 2014

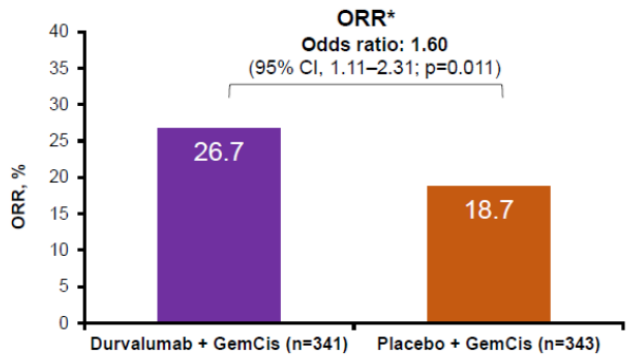
A Phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin in patients with advanced biliary tract cancer: TOPAZ-1

Do-Youn Oh,[1] Aiwu Ruth He,[2] Shukui Qin,[3] Li-Tzong Chen,[4] Takuji Okusaka,[5] Arndt Vogel,[6] Jin Won Kim,[7] Thatthan Suksomboon charoen,[8] Myung Ah Lee,[9] Masayuki Kitano,[10] Howard Burris,[11] Mohamed Bouattour,[12] Suebpong Tanasanvimon,[13] Renata Zaucha,[14] Antonio Avallone,[15] Juan Cundom,[16] Nana Rokutanda,[17] Julia Xiong,[17] Gordon Cohen,[17] Juan W. Valle[18]



Analyse actualisée à l'ESMO® 2022





	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=343)
ORR, n (%)	91 (26.7)	64 (18.7)
CR, n (%)	7 (2.1)	2 (0.6)
PR, n (%)	84 (24.6)	62 (18.1)
DCR, n (%)†	291 (85.3)	284 (82.6)

AAP

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

R (1:1) N=685

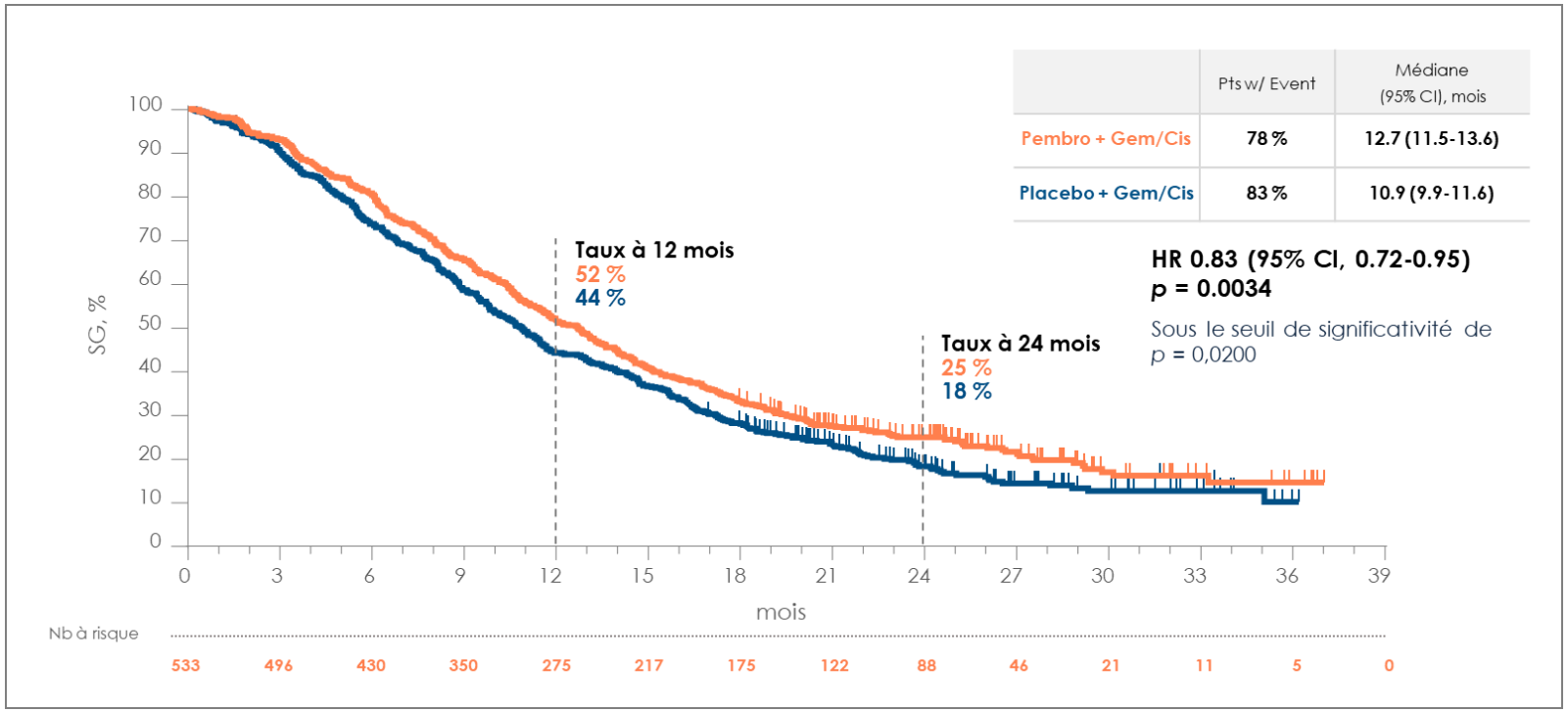
- **Durvalumab 1500 mg Q3W + GemCis (up to 8 cycles)** → **Durvalumab 1500 mg Q4W until PD**
- **Placebo Q3W + GemCis (up to 8 cycles)** → **Placebo Q4W until PD**

NEW STANDARD

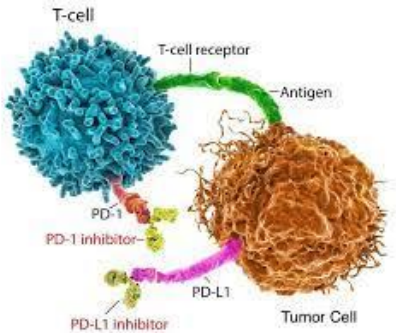
- Oh D-Y, et al. NEJM evidence 2022 Jun

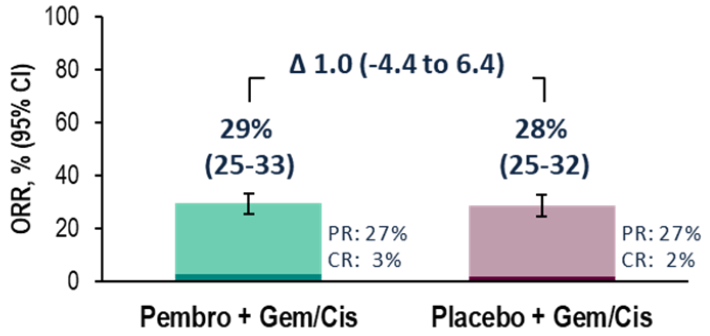
Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial

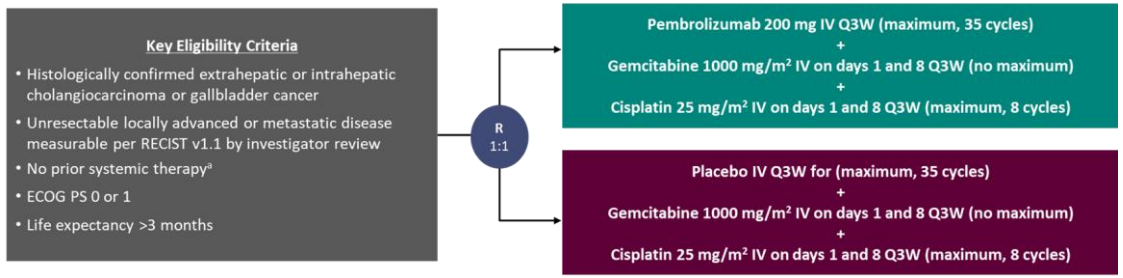
Robin Kate Kelley, Makoto Ueno*, Changhoon Yoo, Richard S Finn, Junji Furuse, Zhenggang Ren, Thomas Yau, Heinz-Josef Klümpen, Stephen L Chan, Masato Ozaka, Chris Verslype, Mohamed Bouattour, Joon Oh Park, Olga Barajas, Uwe Pelzer, Juan W Valle, Li Yu, Usha Malhotra, Abby B Siegel, Julien Edeline, Arndt Vogel*, on behalf of the KEYNOTE-966 Investigators†*



	Pts w/ Event	Médiane (95% CI), mois
Pembro + Gem/Cis	78 %	12.7 (11.5-13.6)
Placebo + Gem/Cis	83 %	10.9 (9.9-11.6)







Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial

Angela Lamarca, Daniel H Palmer, Harpreet Singh Wasan, Paul J Ross, Yuk Ting Ma, Arvind Arora, Stephen Falk, Roopinder Gillmore, Jonathan Wadsley, Kinnari Patel, Alan Anthoney, Anthony Maraveyas, Tim Iveson, Justin S Waters, Claire Hobbs, Safia Barber, W David Ryder, John Ramage, Linda M Davies, John A Bridgewater, Juan W Valle, on behalf of the Advanced Biliary Cancer Working Group

***Lancet Oncol* 2021; 22: 690–701**

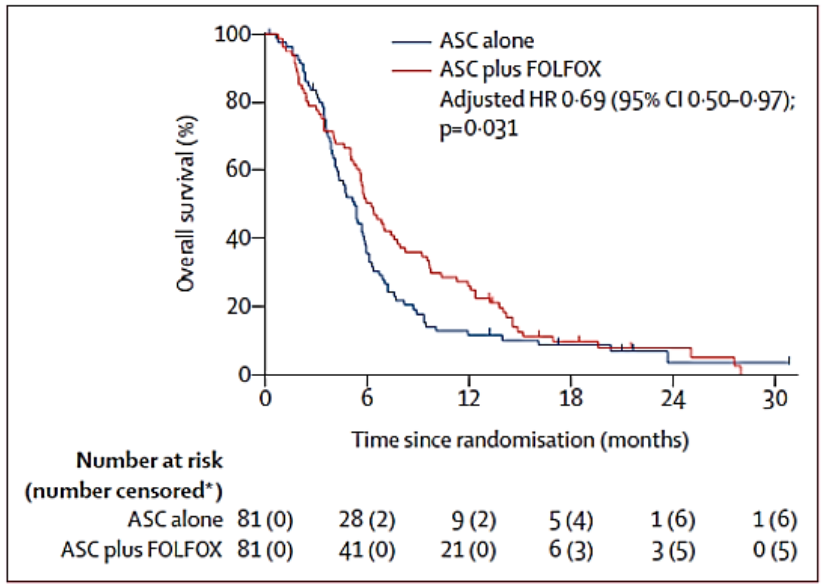


Figure 2: **Overall survival**
The HR is adjusted for the three stratification factors (platinum sensitivity, serum albumin concentration, and disease stage). ASC=active symptom control. FOLFOX=folinic acid, fluorouracil, and oxaliplatin. HR=hazard ratio. *Numbers are cumulative.

Seconde Ligne

7 mois

Second-Line Chemotherapy for Advanced Biliary Tract Cancer After Failure of the Gemcitabine-Platinum Combination: A Large Multicenter Study by the Association des Gastro-Entérologues Oncologues

Bertrand Brieau, MD[1]; Laetitia Dahan, MD, PhD[2,3]; Yann De Rycke, PhD[4]; Tarek Boussaha, MD[5]; Philippe Vasseur, MD[6,7]; David Tougeron, MD, PhD[6,7]; Thierry Lecomte, MD, PhD[8,9]; Romain Coriat, MD, PhD[1,10]; Jean-Baptiste Bachet, MD, PhD[11,12]; Pierre Claudez, MD[13]; Aziz Zaanan, MD[14,15]; Pauline Soibinet, MD[16]; Jérome Desrame, MD[17]; Anne Thirot-Bidault, MD[18]; Isabelle Trouilloud, MD[19]; Florence Mary, MD[20]; Lysiane Marthey, MD[21]; Julien Taieb, MD, PhD[14,15]; Wulfran Cacheux, MD, PhD[22]; and Astrid Lièvre, MD, PhD[23,24]

Cancer September 15, 2015

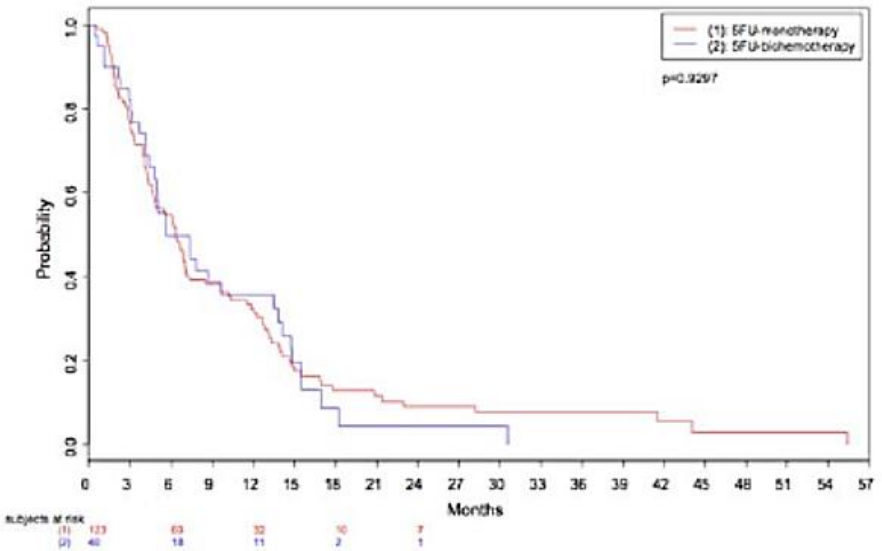


Figure 4. Overall survival with second-line chemotherapy: 5-FU monotherapy versus 5-FU–based bichemotherapy. 5-FU indicates 5-fluorouracil.

Second-line chemotherapy in advanced biliary cancer: a systematic review

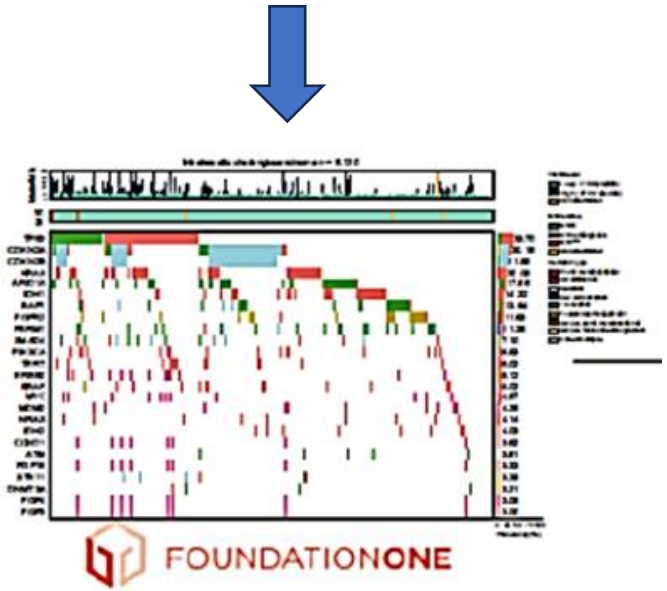
A. Lamarca[1], R. A. Hubner[1], W. David Ryder[2] & J. W. Valle[1]*

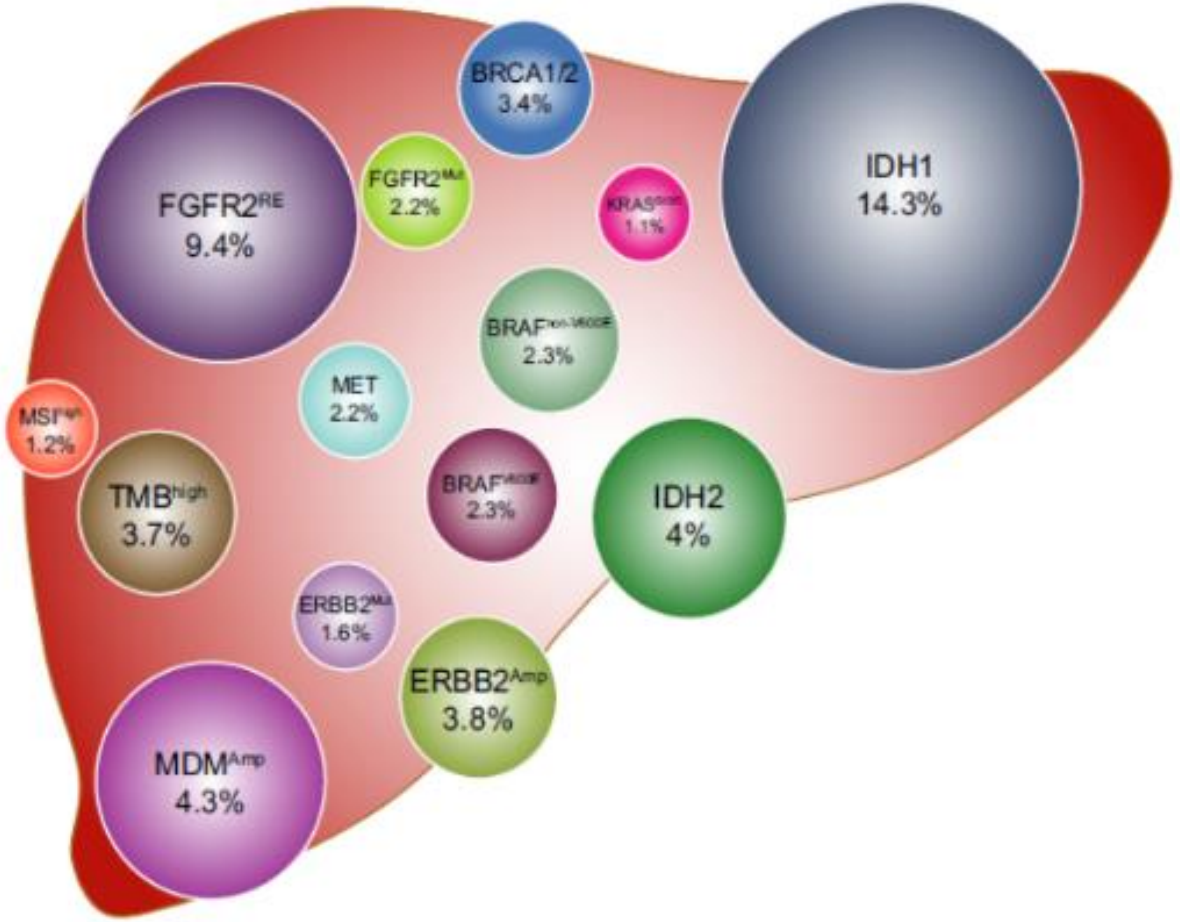
[1]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester; [2]MAHSC Clinical Trials Unit, The Christie NHS Foundation Trust, Manchester, UK

Table 3. Response and survival data in the 23 studies analysed

Variable	Subgroup	Studies with data available	Total studies	Weighted mean	95% CI
OS (months)	**Overall**	**20**	**23**	**7.2**	**6.2–8.2**
	Phase II	12	14	6.6	5.1–8.1
	Retrospective analysis	8	9	7.7	6.5–8.9

6,130 iCCA samples

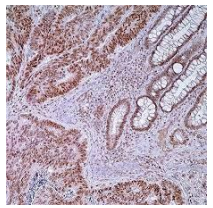


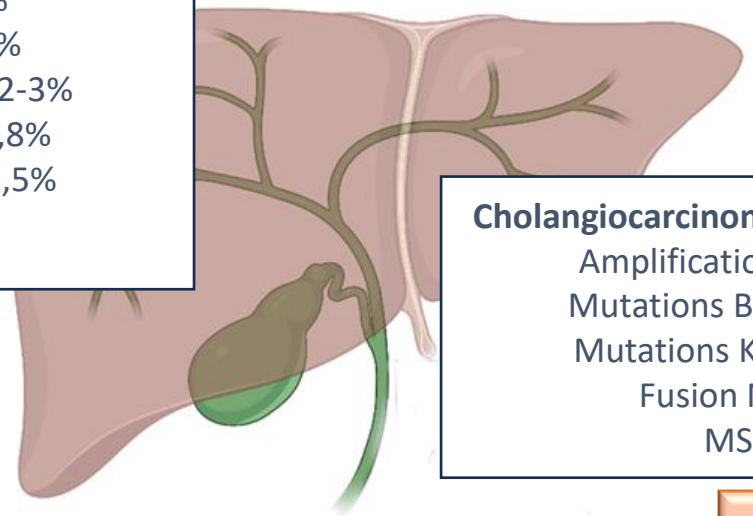


Kendre G et al. J Hepatol 2023 : 78(3):614-626

Cholangiocarcinomes intrahépatiques

Mutations IDH1 14%
Fusions FGFR2 9-15%
Mutations BRAF V600E 2-3%
Amplification ERBB2 3,8%
Mutations Kras G12C 1,5%
Fusion NTRK < 1%
MSI 1,2%





Cholangiocarcinomes extra-hépatiques

Amplification ERBB2 15%
Mutations BRAF V600E 3%
Mutations Kras G12C 1,5%
Fusion NTRK < 1%
MSI 1,2%

Expression HER2
Immunohistochimie + Confirmation par hybtidation in situ / recherche amplification si IHC 2+

Recherche de **mutations**
Séquençage ADN (NGS) ou ARN

IDH1, BRAF, K-Ras (G12C..)

Statut MMR/MSI
Immunohistochimie + Confirmation du Statut MSI-H si dMMR en immunohistochimie

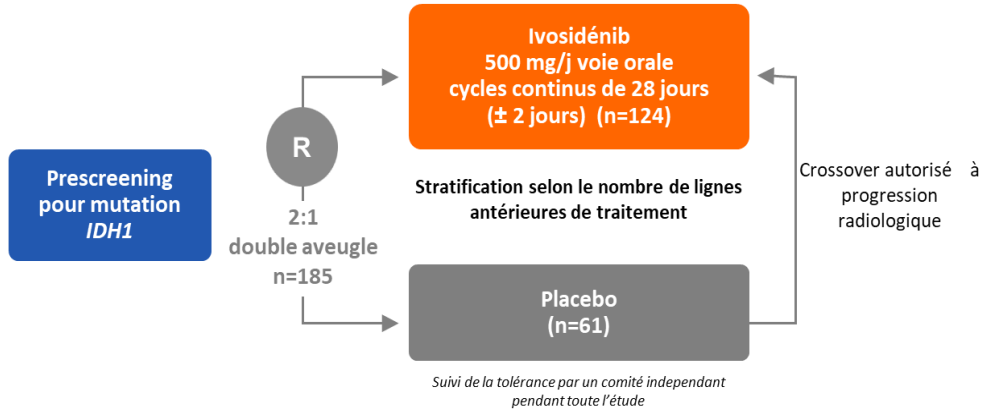
Recherche de **fusions** par
Séquençage ARN (NGS)

Fusion FGFR2, NTRK

Mutation IDH1

Principaux critères d'inclusion

- Age ≥ 18 ans
- **Diagnostic de cholangiocarcinome (CCA) confirmé histologiquement**
- **Confirmation centralisée du statut m/IDH1 en NGS**
- ECOG PS 0 ou 1
- 1-2 lignes antérieures de traitement (dont au moins une ligne avec gemcitabine ou 5-FU)
- Lésion mesurable selon RECIST v1.1
- Fonctions hématologique, hépatique et rénale adéquates
- QTcF < 450 ms



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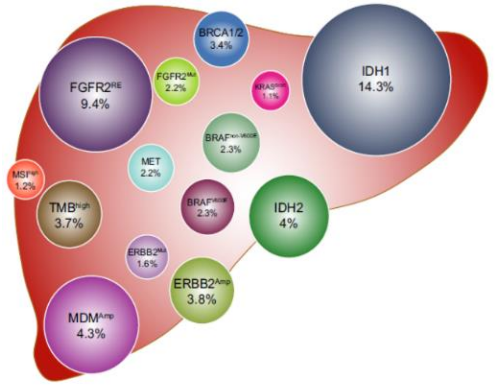
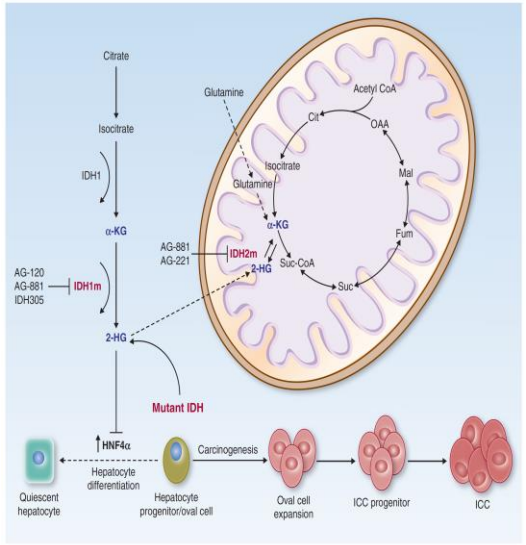
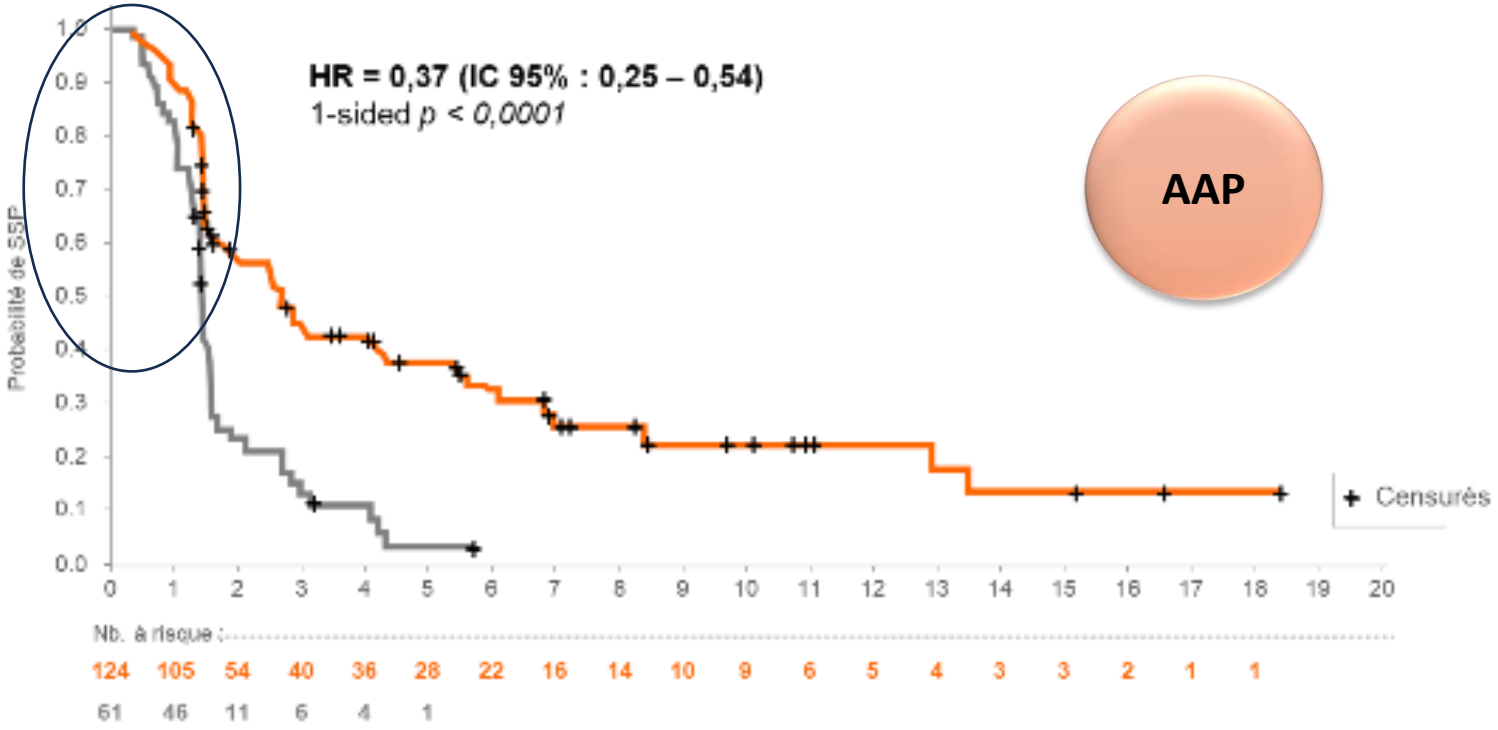






AAP

Valle JW et al., Cancer Discov 2017; 7(9):943-962
ZHU AX et al. JAMA Oncol 2021;7(11):1669-1677

Mécanismes d'activation de la voie FGFR2

Activating mutations	Chromosomal rearrangements	Gene amplification
Leading to constitutive activation of the kinase domain or ligand-independent receptor dimerisation	eg, Translocations resulting in gene fusions that allow ligand-independent receptor dimerisation	Inducing protein overexpression, receptor accumulation and activation of downstream signalling pathways

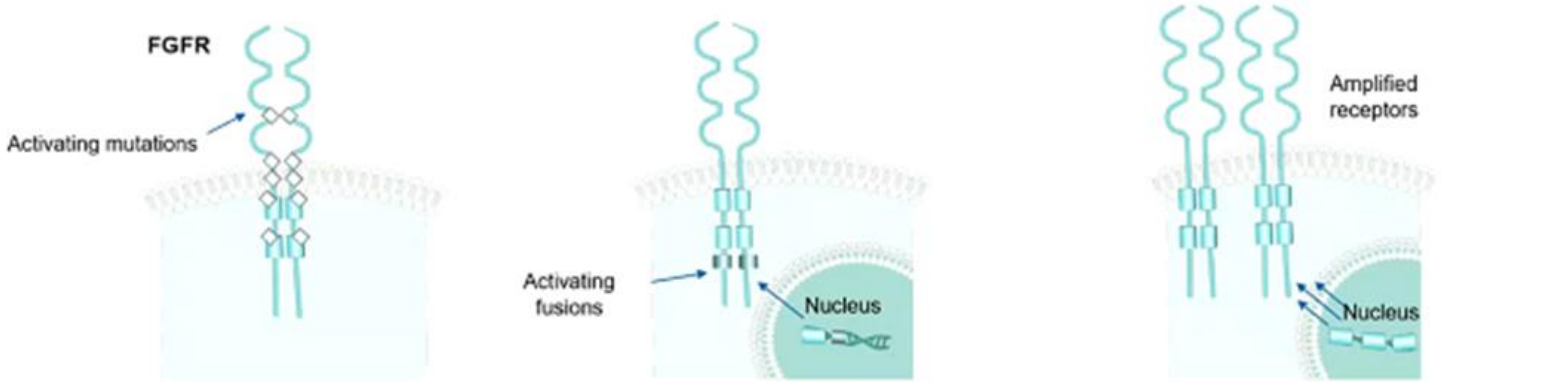
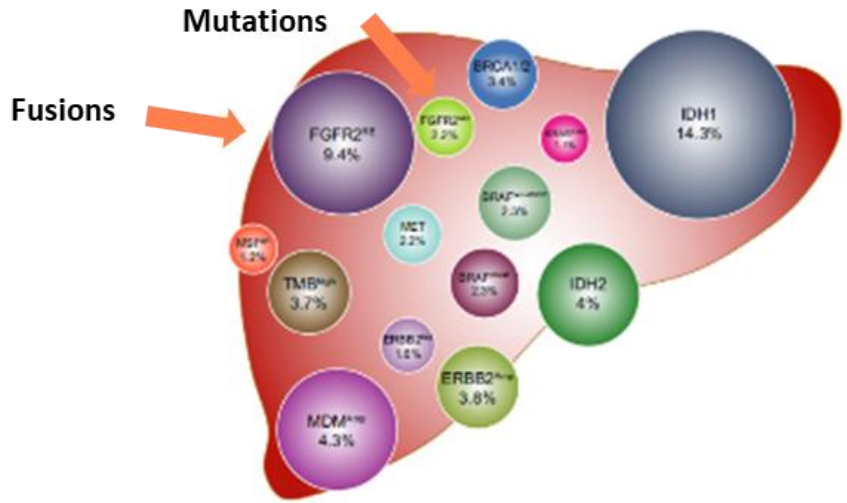
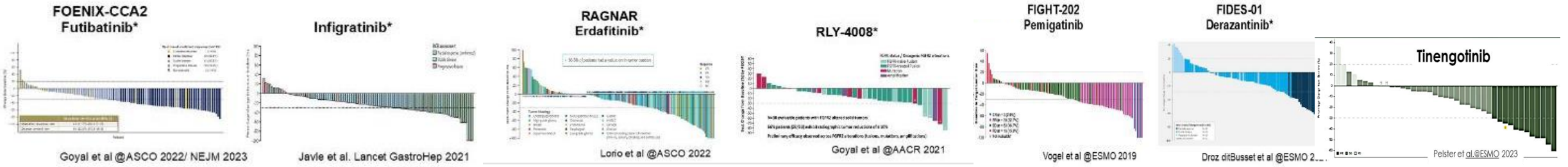
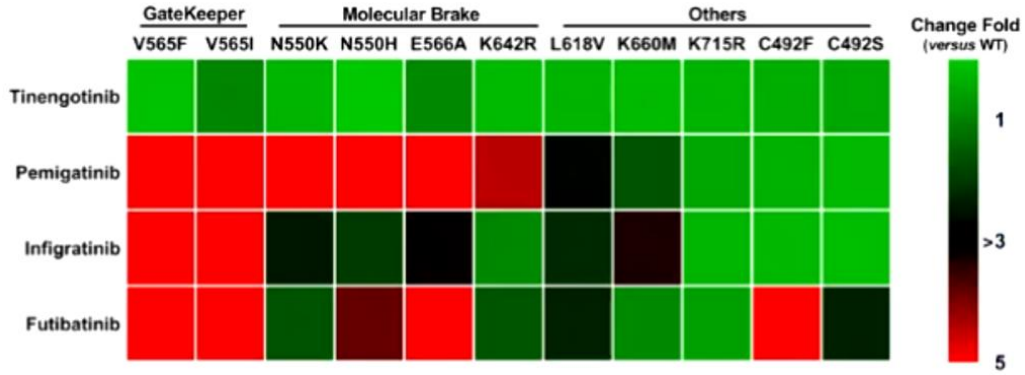


Figure adapted from Babina I, Turner N. 2017.[1]

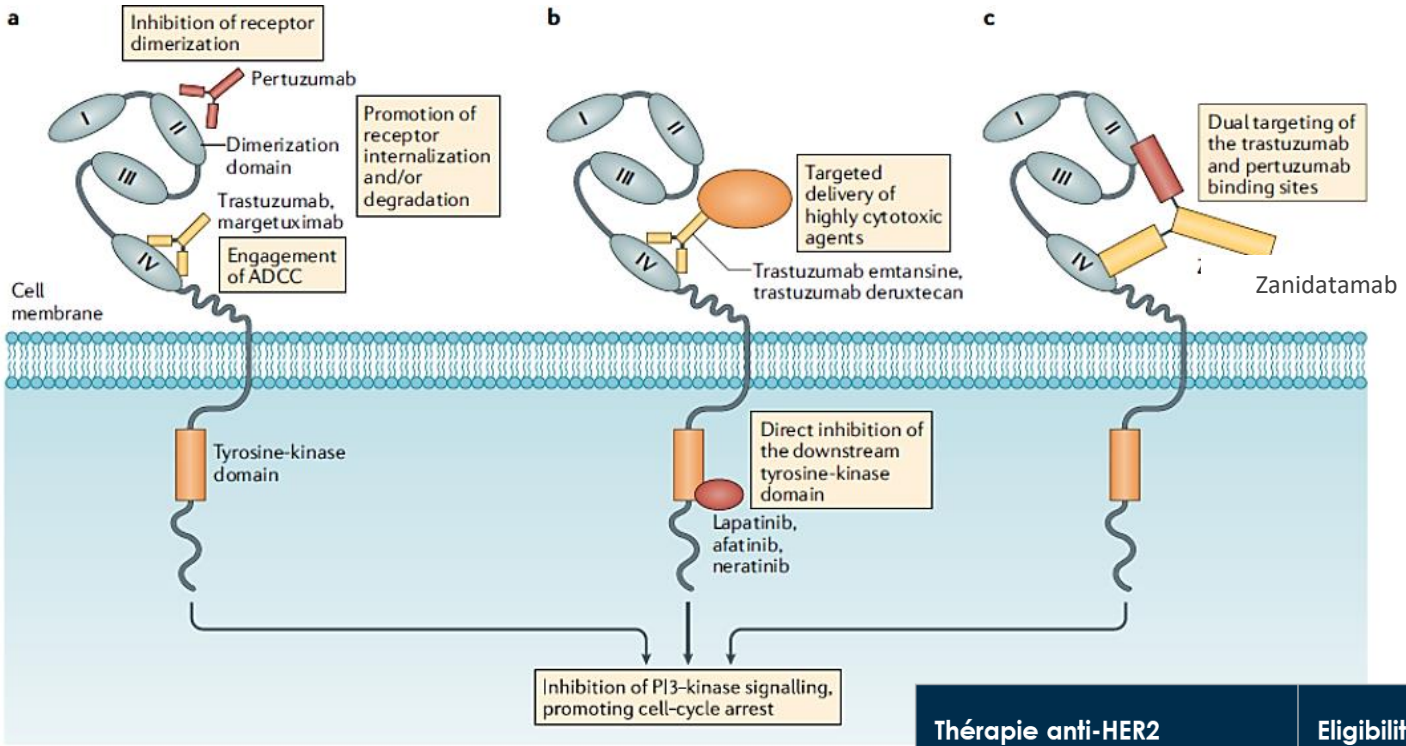


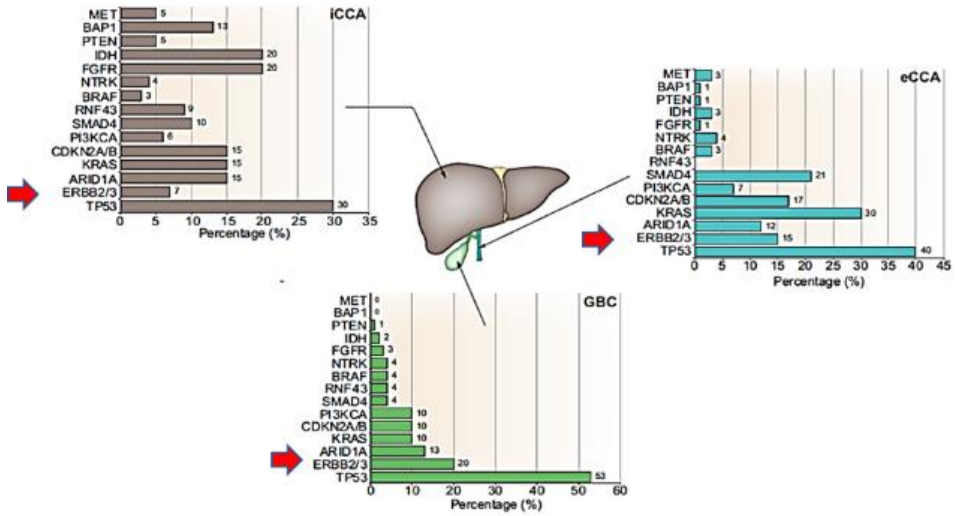
	AMM					
	Pemigantinib	**Futibatinib**	**Derazantinib**	**Infigratinib**	**RLY-4008**	**Tinengotinib**
Action	**Réversible**	**Irréversible**	**Irréversible**	**Réversible**	**Irréversible**	**Réversible**
Cible	**Pan FGFR**	**Pan FGFR**	**Pan FGFR**	**Pan FGFR**	**FGFR2**	**FGFR1-3 JAK, VEGFR**
Phase	**II**	**II**	**II**	**II**	**I**	**I**
Taux de réponse	**38,5%**	**41,7%**	**22%**	**23,1%**	**63-88%**	**29%-40% ***
SSP (mois)	**7**	**8,9**	**7,8**	**7,3**	**?**	**?**
Survie Globale(mois)	**17,5**	**21,7**	**17,2**	**12,2**	**?**	**?**





** Fusions et mutations*



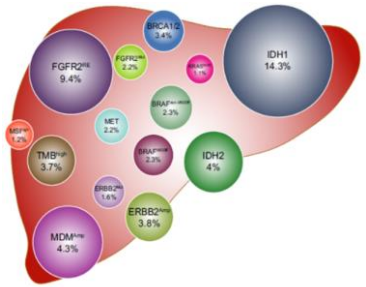


HER2

Thérapie anti-HER2	Eligibilité	Effectif	ORR	SSRm (mois)	SGm (mois)
Pertuzumab + tratuzumab[1]	HER2 surexpression (IHC 3+) ou amplification par FISH ou NGS	N=39	23%	4.0	10,9
Nératinib[2]	HER2 mutation	N = 25	16%	2.8	5,4
Trastuzumab déruxtécan[3]	HER2 IHC 3+ ou IHC 2+/amplification par FISH	N = 22	36.4%	5.1	7,1
	HER2 faible	N=8	12.5%	3.5	8,9
Tucatinib + trastuzumab [4]	HER2 surexpression (IHC3+) ou amplification par FISH ou NGS	N = 29	46.7%	5.5	15,5
Zanidatamab [5]	HER2 surexpression (IHC 2-3+) et amplification par FISH	N=80	41.3%	5.5	Non mature

AAC

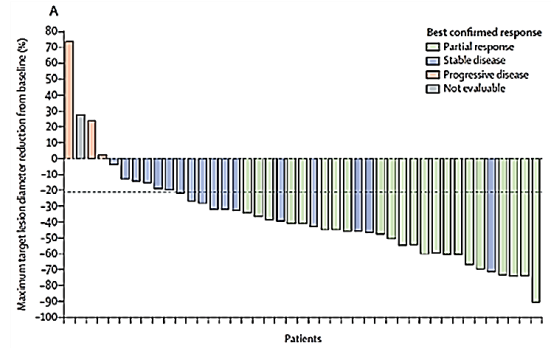
[1] Javle et al. Lancet Oncol 2021; [2] Harding et al. Nat Commun 2023; [3] Ohba et al. J Clin Oncol 2022 (abstract) 4 Nakamara Y ASCO 2023, 5 Harding Lancet Oncol 2023



BRAF V600E (2,5%)

Dabrafenib plus trametinib in patients with *BRAF^{V600E}*-*mutated* biliary tract cancer (ROAR)

Subbiah V et al. Nat Med 2023; 29(5):1103-1112.



- Survie globale médiane : 14 mois
- Survie sans progression médiane 9 mois

Kras G12C (1,1%)

Adagrasib in Advanced Solid Tumors Harboring a *KRAS^{G12C}* Mutation

Bekaii-Saab TS et al. J Clin Oncol. 2023 Apr 26

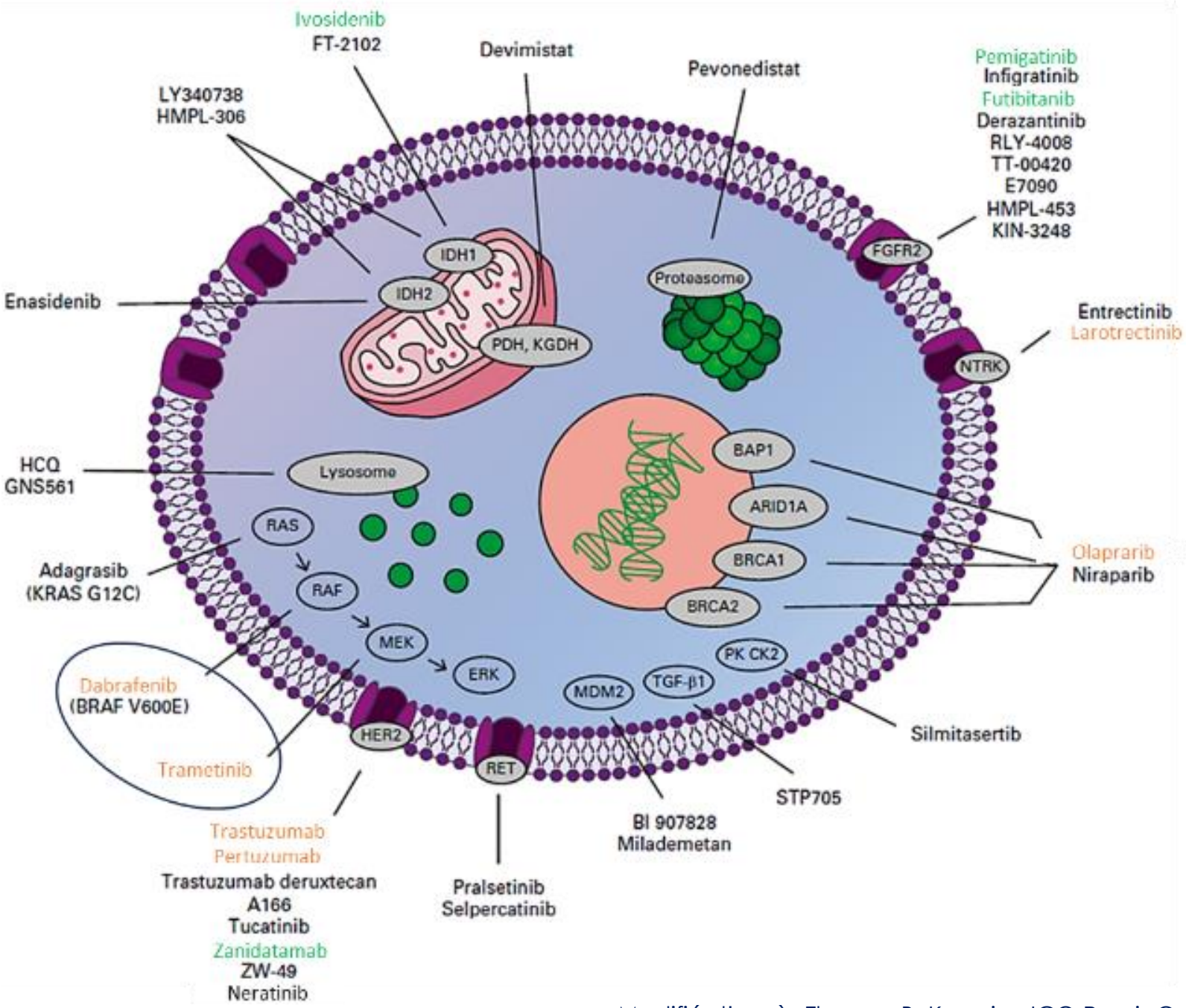
Tumor Type	ORR, % (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
Biliary tract cancer	n = 12 41.7 (15.2 to 72.3)	n = 12 8.6 (2.7 to 11.3)	n = 12 15.1 (8.6 to NE)

MSI high (1,2%)

Pembrolizumab in MSI high or dMMR cancers: updated analysis from the phase II KEYNOTE-158 study

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

	Cholangiocarcinoma/ biliary tract *n* = 22
ORR, % (95% CI)	40.9 (20.7-63.6)
Best objective response, *n* (%)	
CR	3 (13.6)
PR	6 (27.3)
SD	3 (13.6)
PD	8 (36.4)
Not evaluable	—
No assessment	2 (9.1)
DOR, median (range), months	30.6 (6.2 to 40.5+)
Median PFS, months (95% CI)	4.2 (2.1-24.9)
PFS rate ≥3 years[a], %	12.7
Median OS, months (95% CI)	19.4 (6.5-NR)
OS rate ≥3 years[a], %	30.3



Modifié d'après Thomas B. Karasic, JCO Precis Oncol 7:e2200573. © 2023

POINTS FORTS

- 1/ Les cholangiocarcinomes constituent un groupe hétérogène de tumeurs (intra-hépatiques, péri-hilaires et extra-hépatiques) aux profils cliniques, biologiques et évolutifs différents.
- 2/ L'inflammation chronique (cholangite sclérosante primitive, lithiases, parasites) est un facteur de risque du cholangiocarcinome. Les hépatopathies chroniques sont des facteurs de risque de cholangiocarcinome intra-hépatique .
- 3/ La capécitabine pendant 6 mois est le traitement adjuvant standard après résection R0 ou R1 d'un cholangiocarcinome.
- 4/ Le traitement standard de première ligne des cancers avancés est l'association gemcitabine, cisplatine et un anticorps anti PD 1 ou PDL1.
- 5/ En cas de maladie avancée, le profil moléculaire doit être réalisé à visée théranostique dès le début de la prise en charge thérapeutique .