Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice

Therapeutic strategies in molecular subtypes of biliary tract cancers and HCC

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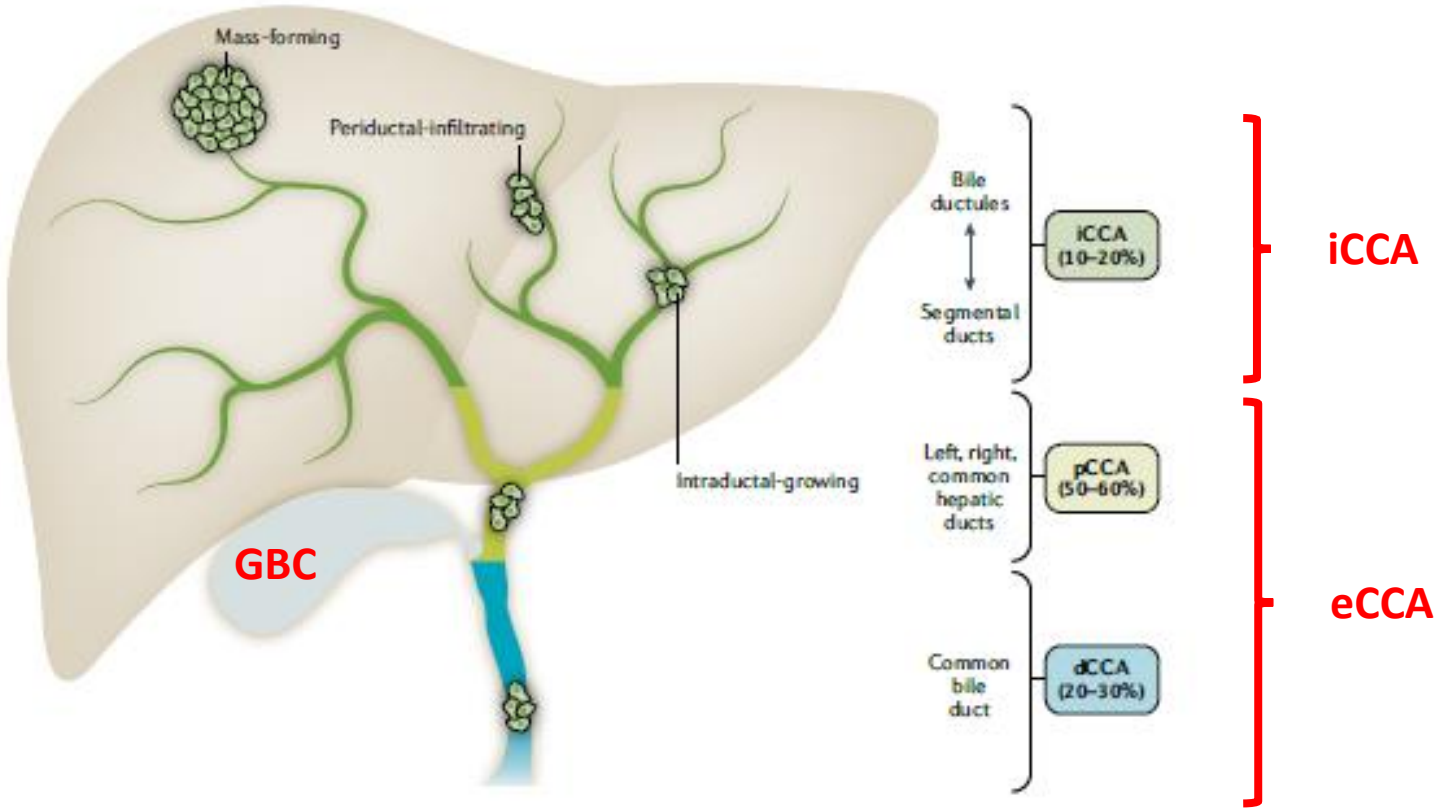
Disclosures C. Verslype

Consultancy and research grants:
Bayer, Ipsen, Roche

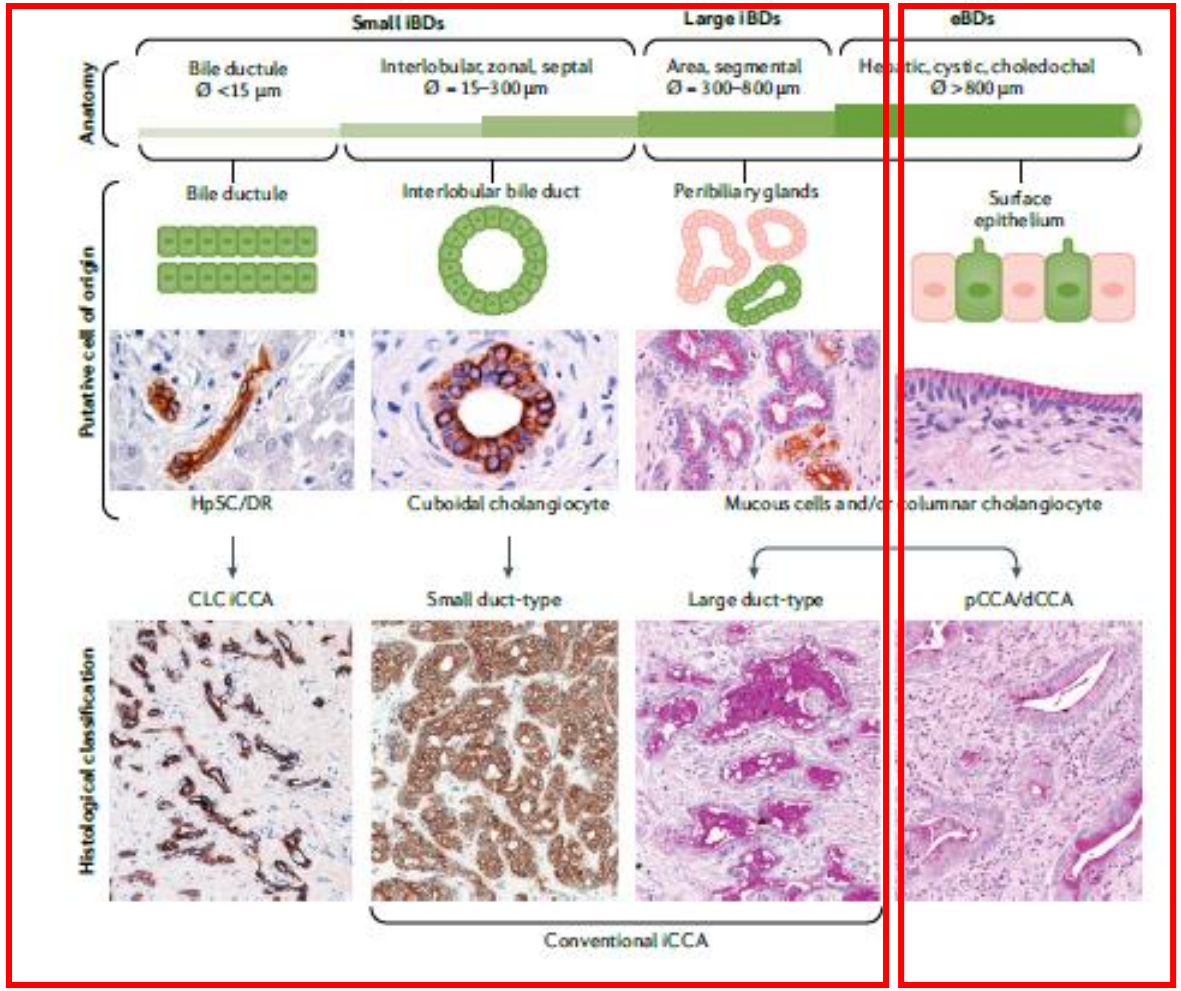
CCA: location



Banales et al. 2020, adapted

Viral, cirrhosis

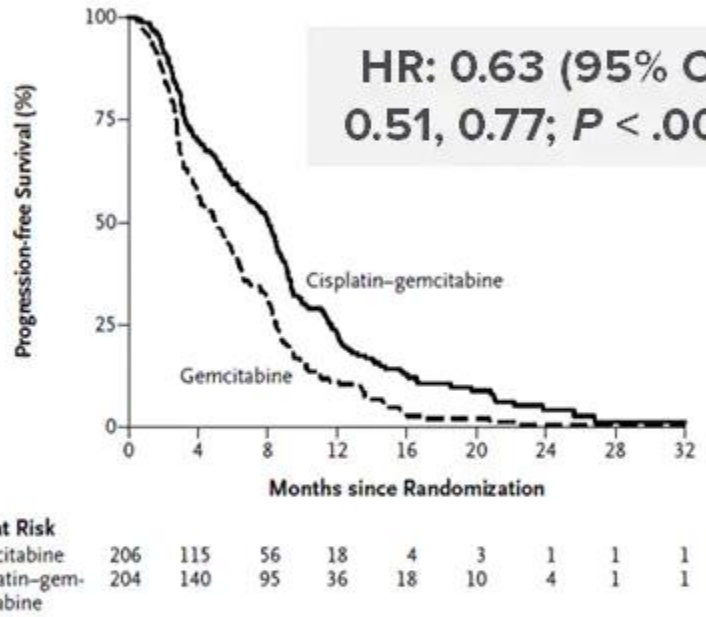
PSC, liver flukes



Banales et al. 2020, adapted

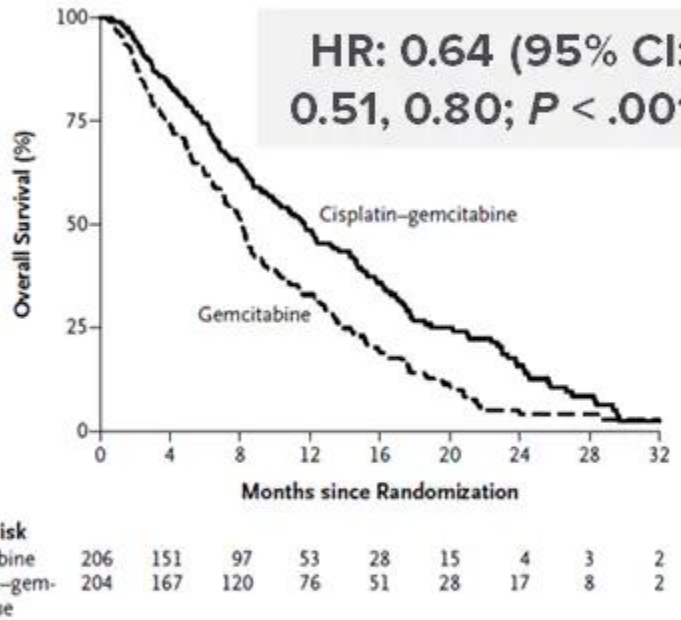
Standard First-Line Treatment for Biliary Tract Cancer
Gemcitabine +/- Cisplatin

ABC-02: PFS[a]



No. at Risk									
Gemcitabine	206	115	56	18	4	3	1	1	1
Cisplatin–gemcitabine	204	140	95	36	18	10	4	1	1

ABC-02: OS[a]



No. at Risk									
Gemcitabine	206	151	97	53	28	15	4	3	2
Cisplatin–gemcitabine	204	167	120	76	51	28	17	8	2

	PFS (months)		OS (months)	
Study	Gemcitabine	Cisplatin Gemcitabine	Gemcitabine	Cisplatin Gemcitabine
ABC-02[a]	5.0	8.0	8.1	11.7
BT-22[b]	3.7	5.8	7.7	11.2

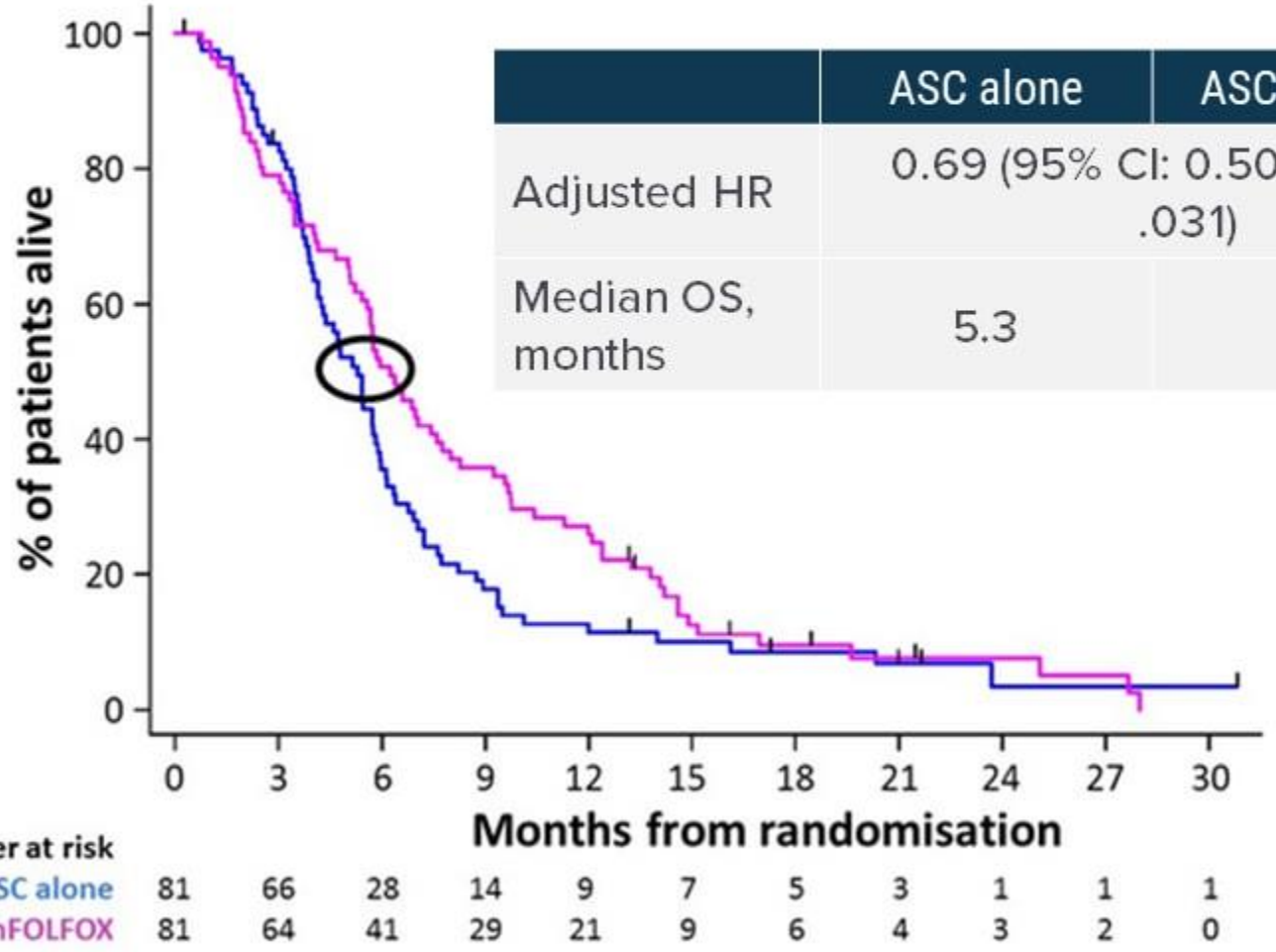
Patient selection criteria:[a,b]

- Good ECOG PS
- Good liver function
- Clinical trial availability (preferable option)

a. Valle J, et al. N Engl J Med. 2010;362:1273-1281; b. Okusaka T, et al. Br J Cancer. 2010;103:469-474.

Second-Line Treatment Option in CCA
FOLFOX

ABC-06: OS (ITT population)



	ASC alone	ASC + mFOLFOX
Adjusted HR	0.69 (95% CI: 0.50, 0.97; *P* = .031)	
Median OS, months	5.3	6.2

ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ITT, intent-to-treat.
Larmaca A, et al. ASCO 2019. Presentation 4003.

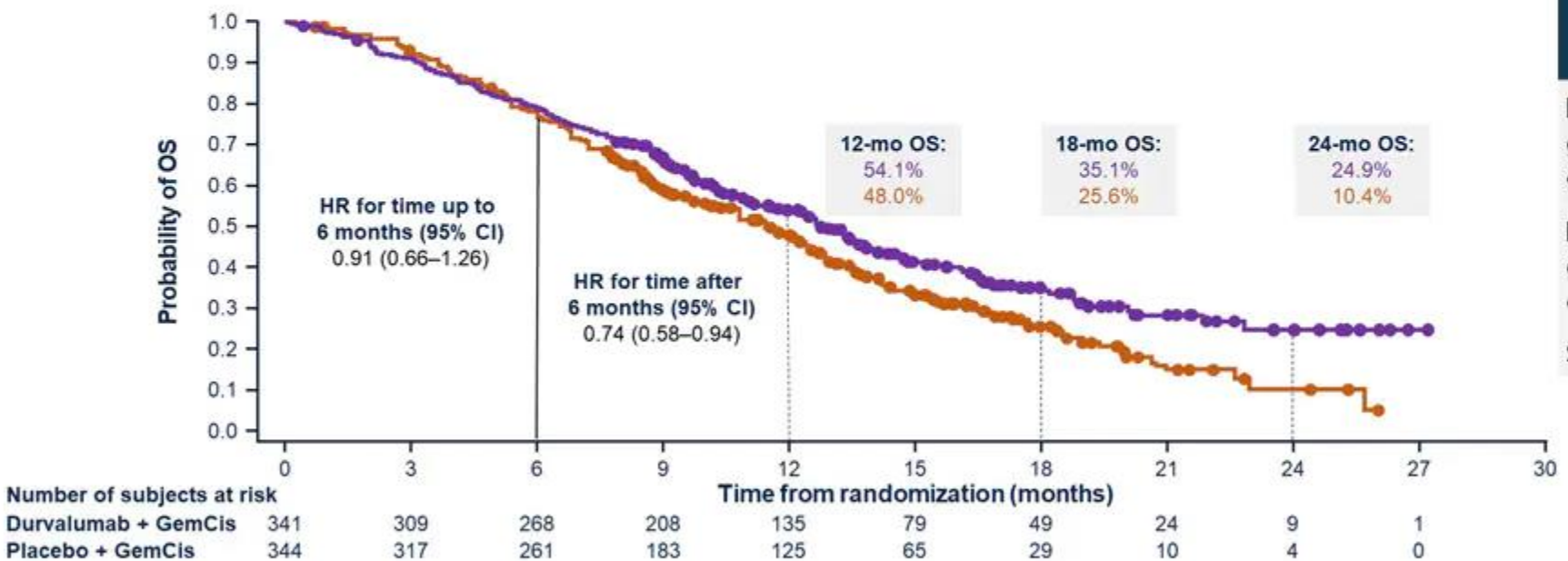
Patient selection criteria:

- Good ECOG PS
- Good liver/renal function
- No targetable alterations
- No clinical trial availability

Durvalumab in Untreated Advanced Biliary Tract Cancer
Topaz-1 Trial

Randomized, double-blind, placebo-controlled phase 3 study of first-line durvalumab vs SOC

OS



	Median OS, Months (95% CI)	Hazard Ratio (95% CI)	*P* Value
Durvalumab + gemcitabine cisplatin (n = 341)	12.8 (11.1 to 14.0)	0.80 (0.66 to 0.97)	.021
Placebo + gemcitabine cisplatin (n = 344)	11.5 (10.1 to 12.5)		

Statistical significance cut-offs for OS: *P* = .03

Gemcis: max 8 cycles!

- Grade 3/4 TRAEs: 62.7% (n = 212/338) in durvalumab + SOC and 64.9% (n = 222/342) in SOC
- Most common 3/4 TRAEs: anemia (23.7% (n = 80/338) durvalumab + SOC vs 22.5% (n = 77/342 SOC) and decreased neutrophils (21.0% (n = 71/338) vs 25.7% (n = 88/342)

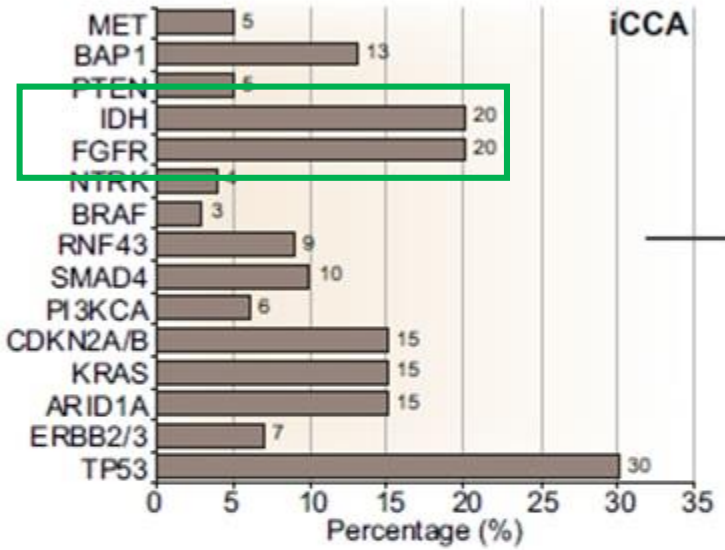
Oh DY, et al. Presented at: ASCO GI 2022; January 20-22, 2022. Presentation 378.

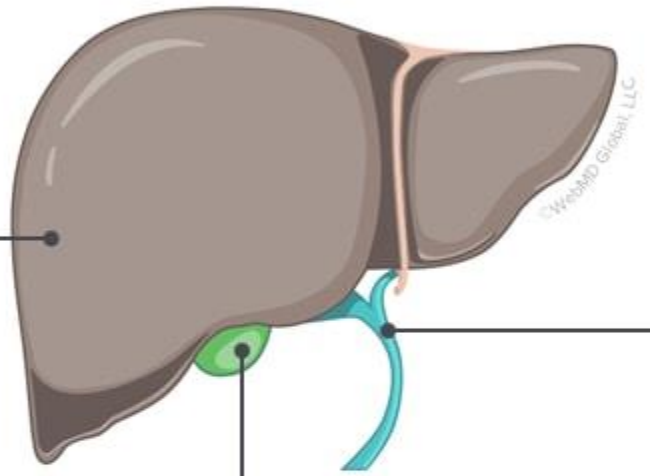
Molecular profiling

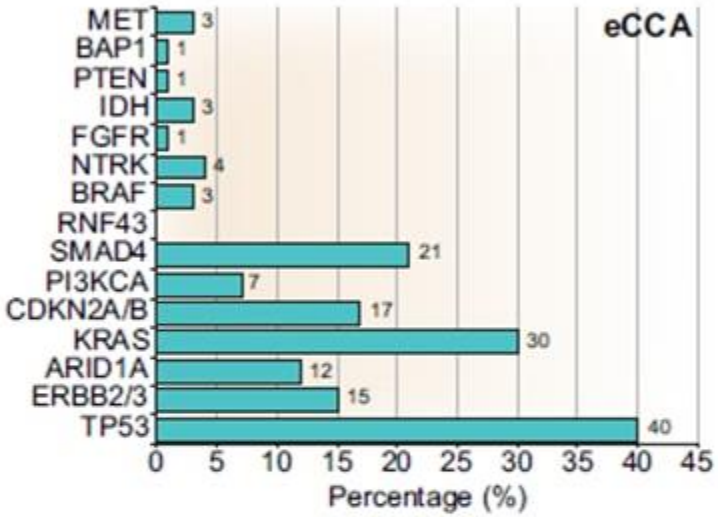
- Methodology:
  - Targeted DNA sequencing: quest for actionable mutations
  - Whole-genome expression: transcriptome based classification (mostly done on resection specimens)

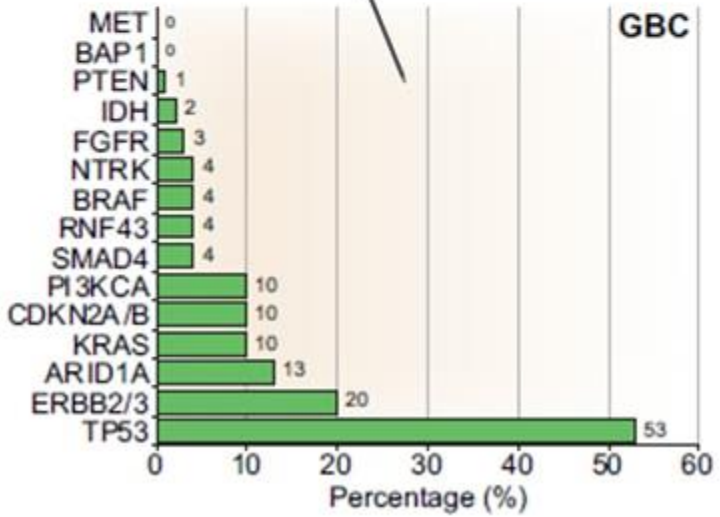
- Aim: to guide systemic treatments (for advanced disease)

Molecular Profiling of Biliary Tract Cancers







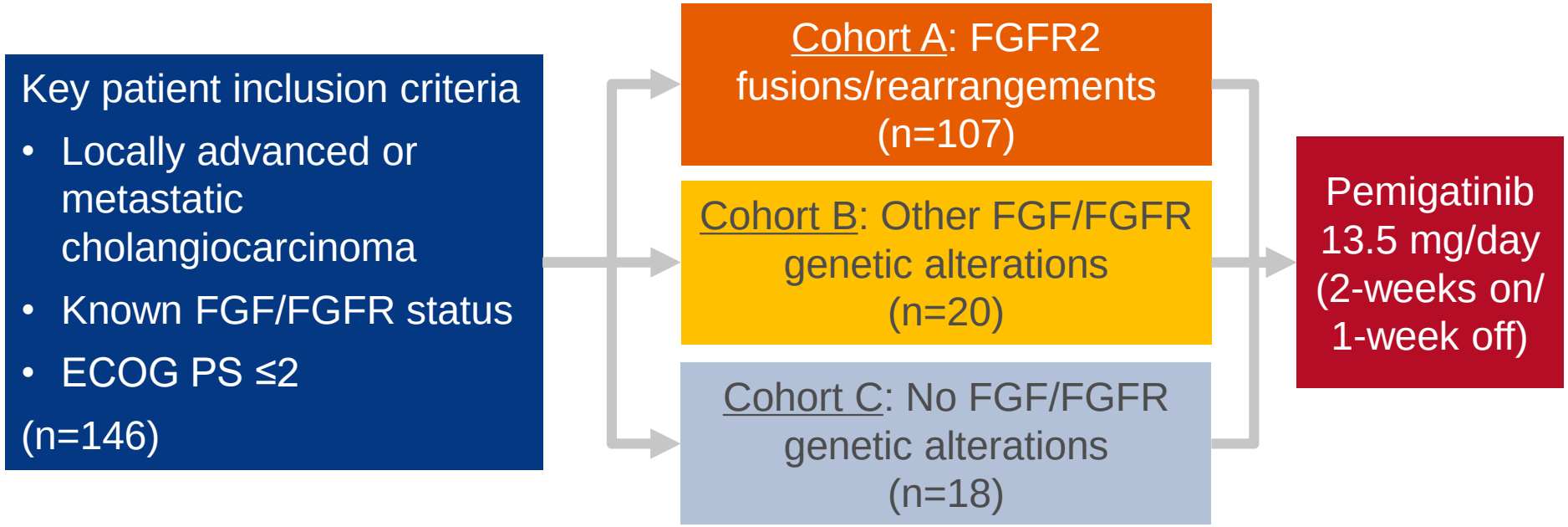


Lamarca A, et al. J Hepatol. 2020;73:170-185.

FIGHT-202: A phase II study of pemigatinib in patients (pts) with previously treated locally advanced or metastatic cholangiocarcinoma (CCA)

Study objective

- To investigate the efficacy and safety of pemigatinib in patients with locally advanced or metastatic cholangiocarcinoma



PRIMARY ENDPOINT

- ORR

SECONDARY ENDPOINTS

- DoR, DCR, PFS, OS, safety

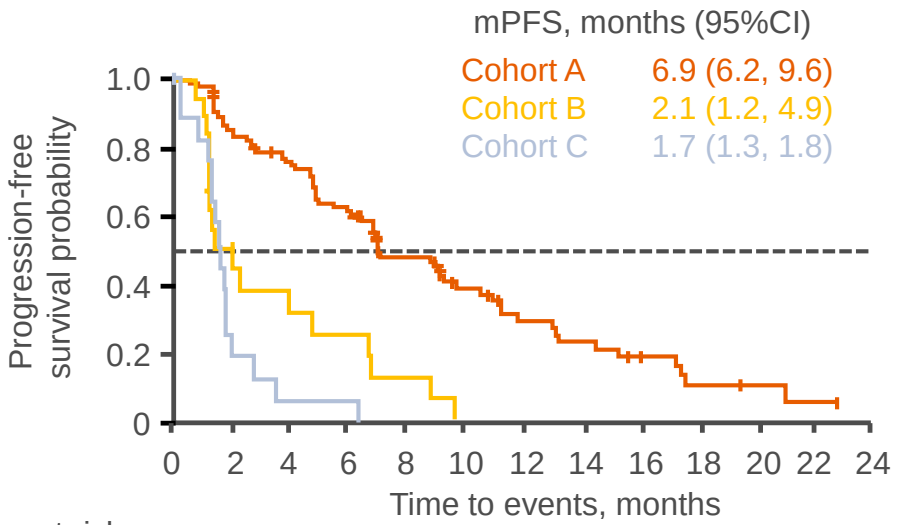
Vogel A, et al. Ann Oncol 2019;30(suppl):abstr LBA40

Abou-Alfa et al. Lancet Oncol 2020

FIGHT-202: A phase II study of pemigatinib in patients (pts) with previously treated locally advanced or metastatic cholangiocarcinoma (CCA)

Key results (cont.)

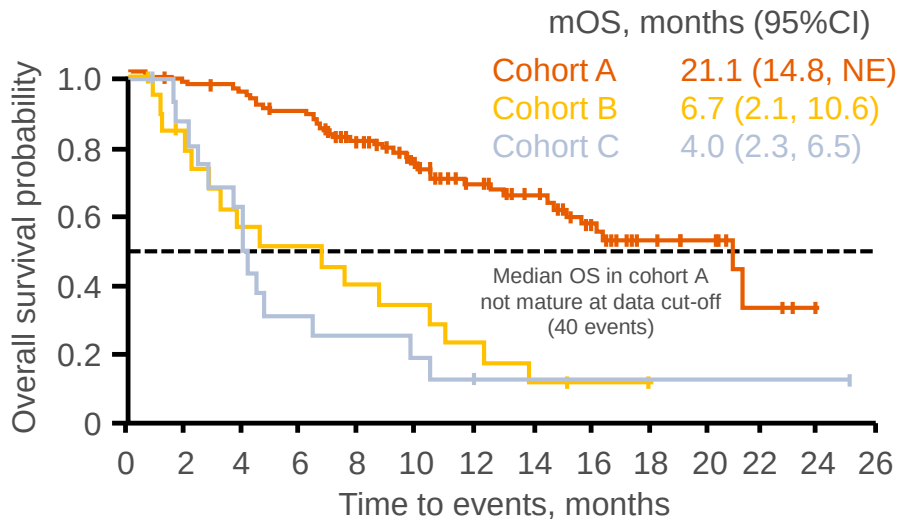
PFS



No. at risk

A	107	88	76	61	37	22	14	11	7	4	2	1	0
B	20	9	6	4	2	0	0	0	0	0	0	0	0
C	18	3	1	1	0	0	0	0	0	0	0	0	0

OS



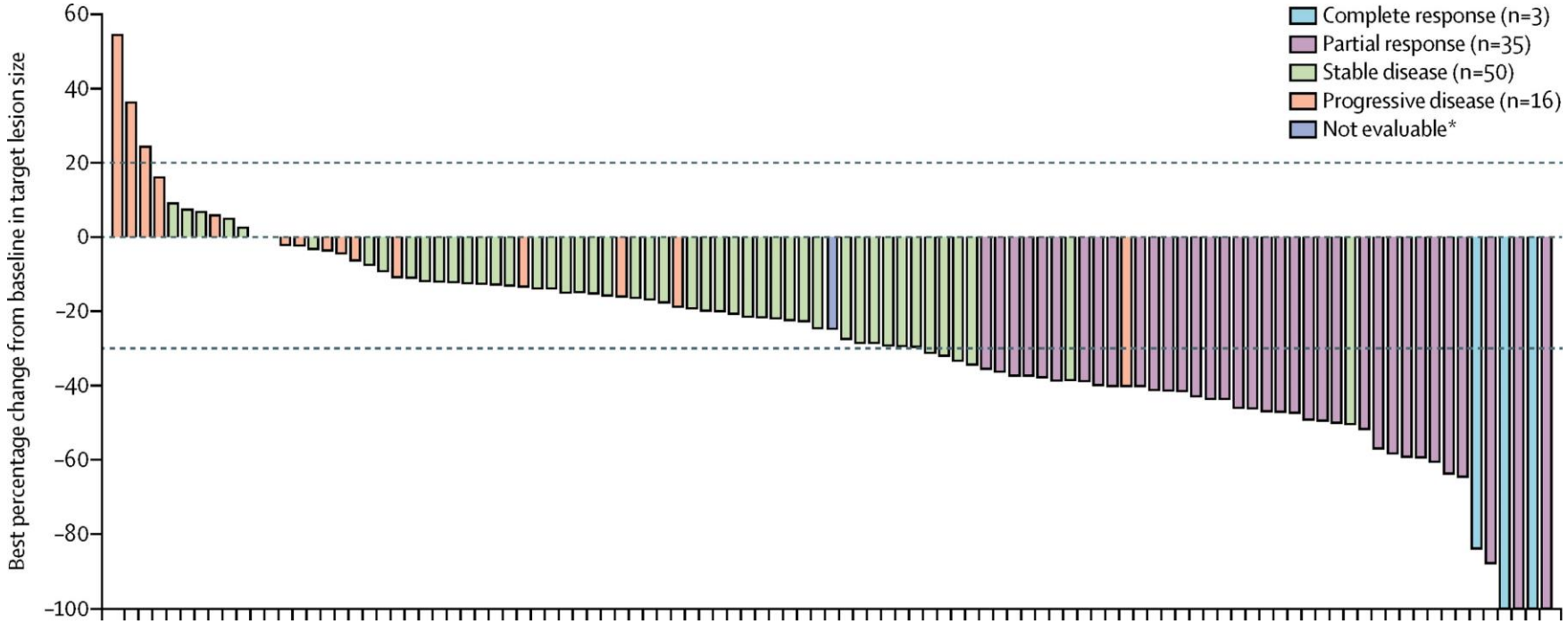
A	107	102	99	92	73	52	41	34	24	12	9	3	0	0
B	20	14	10	9	7	6	4	2	1	1	0	0	0	0
C	18	13	8	5	4	3	1	1	1	1	1	1	1	0

	Cohort A	Cohort B	Cohort C
Median duration of follow-up, months (range)	15.4 (7.0–24.7)	19.9 (16.2–23.5)	24.2 (22.0–26.1)
Median duration of treatment, months (range)	7.2 (0.2–24.0)	1.4 (0.2–12.9)	1.3 (0.2–4.7)

Vogel A, et al. Ann Oncol 2019;30(suppl):abstr LBA40

Abou-Alfa et al. Lancet Oncol 2020

FIGHT-202: A phase II study of pemigatinib in patients (pts) with previously treated locally advanced or metastatic cholangiocarcinoma (CCA)



Abou-Alfa et al. Lancet Oncol 2020

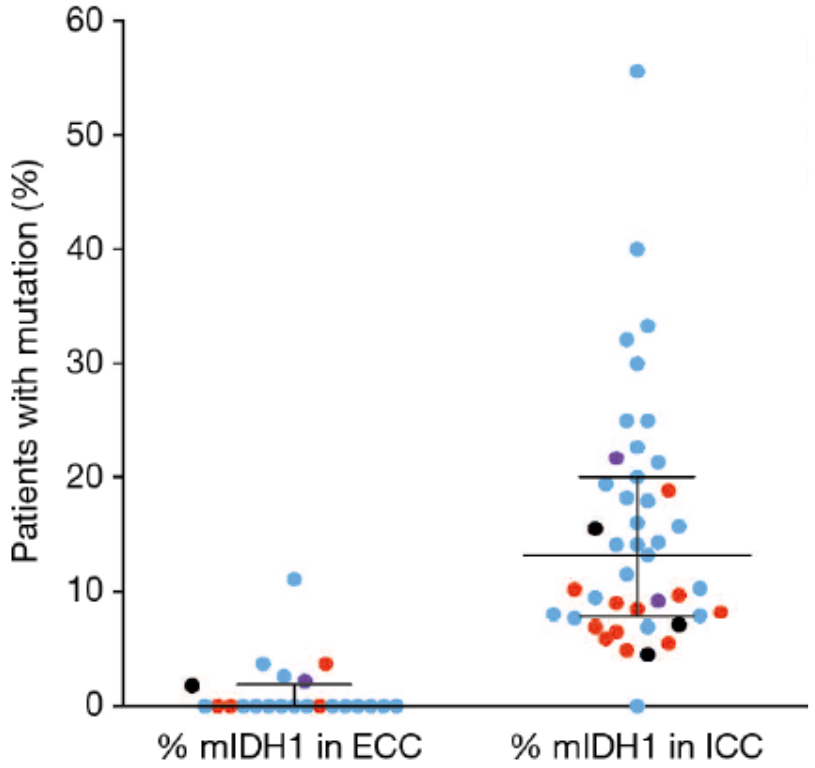
FGFR2 Targeted Agents in Locally Advanced or Metastatic CCA *Phase 2 Clinical Trials*

Study	Drug	Key Inclusion Criteria	N	ORR	Median PFS	TRAEs	Most Frequent TRAEs
FIGHT-202 Abou-Alfa, ASCO® 2021[a]	**Pemigatinib** (Selective FGFR1–3, reversible	Cohort 1: *FGFR* fus/rea	108	37.0%	7.0	Grade 3 to 4: 64%[b]	Hyperphosphatemia (59%)
Javle, Lancet Gastro Hepatol 2021[c]	**Infigratinib** Selective FGFR1–3, reversible)	*FGFR* fus/rea	108	23.1%	7.3	Grade 3 to 4: 64%	Hyperphosphatemia (77%)
FOENIX-CCA2 Goyal, ASCO® 2020[d]	**Futibatinib** (Selective FGFR1-4, irreversible)	*FGFR* fus/rea	103	41.7%	9	Grade ≥ 3: 57%	Hyperphosphatemia (85%)
FIDES-01 Droz Dit Busset, ESMO 2021[e]	**Derazantinib** (TKI, reversible)	*FGFR* fus/rea	103	21.4%	8.0	Grade 3: 35%	Hyperphosphatemia (76%)

TRAE, treatment-related adverse event.

a. Abou-Alfa GK, et al. Presented at: ASCO® 2021; June 4-8, 2021. Presentation 4086; b. Abou-Alfa GK, et al. Lancet Oncol. 2020;21:671-684; c. Javle M, et al. Lancet Gastroenterol Hepatol. 2021;6:803-815; d. Goyal L, et al. Presented at: AACR 2021; April 9-14, 2021. Abstract CT010; e. Droz Dit Busset M, et al. ESMO 2021; September 16-21, 2021. Poster 47P.

IDH1 mutations in cholangiocarcinoma: systematic review



Isocitrate Dehydrogenase-1 (IDH1) mutations:

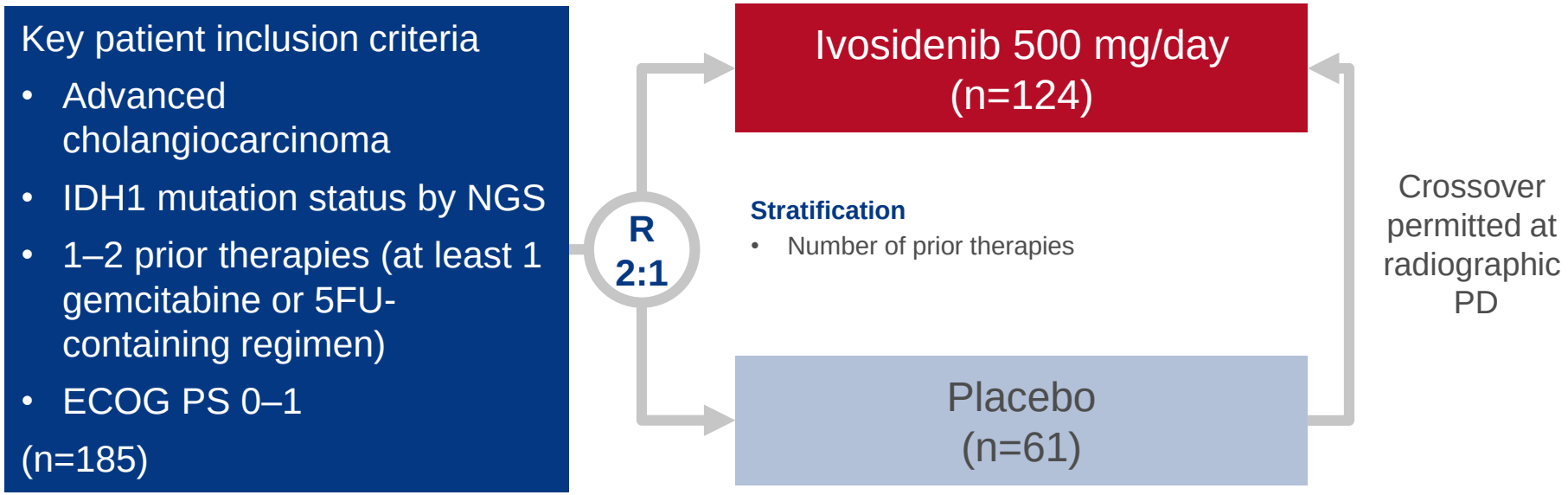
- 45 publications, n pts=5,393
- IDH1 mutation found in iCCA 13.1%; eHCC 0.8%
- Higher in non-Asian centres compared to Asian centres (16.5% vs. 8.8%; OR= 2.06)
- mIDH1 was not a prognostic factor (OS, PFS or TTP)

Boscoeet al J Gastrointest. Oncol 2019

ClarIDHy: A global, phase III, randomized, double-blind study of ivosidenib (IVO) vs placebo in patients with advanced cholangiocarcinoma (CC) with an isocitrate dehydrogenase 1 (IDH1) mutation

Study objective

- To investigate the efficacy and safety of ivosidenib in patients with advanced cholangiocarcinoma and IDH1 mutation



PRIMARY ENDPOINT

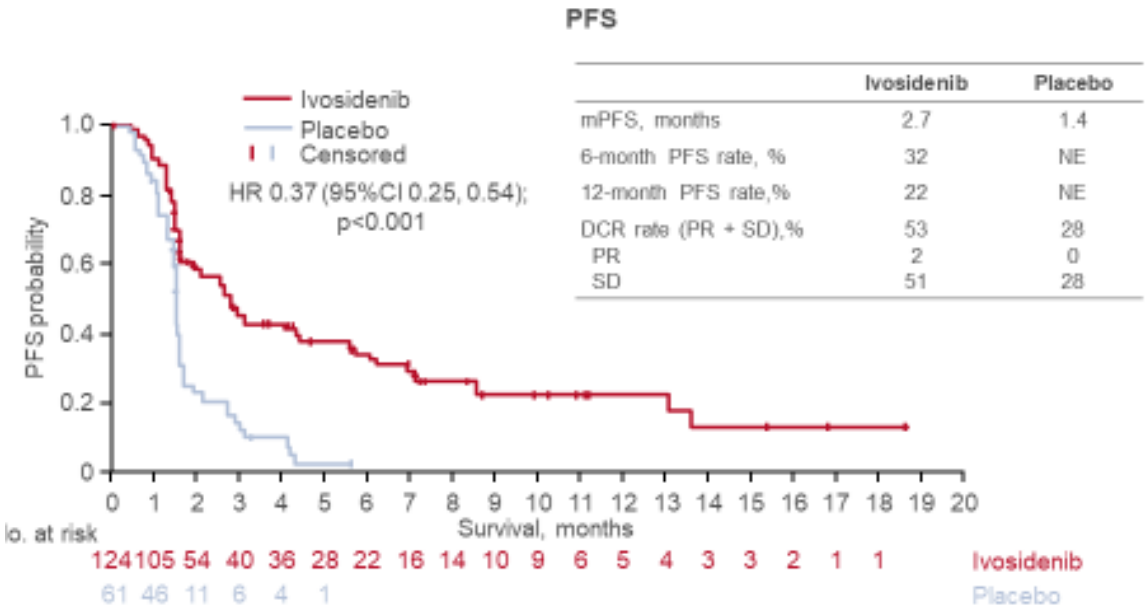
- PFS

SECONDARY ENDPOINTS

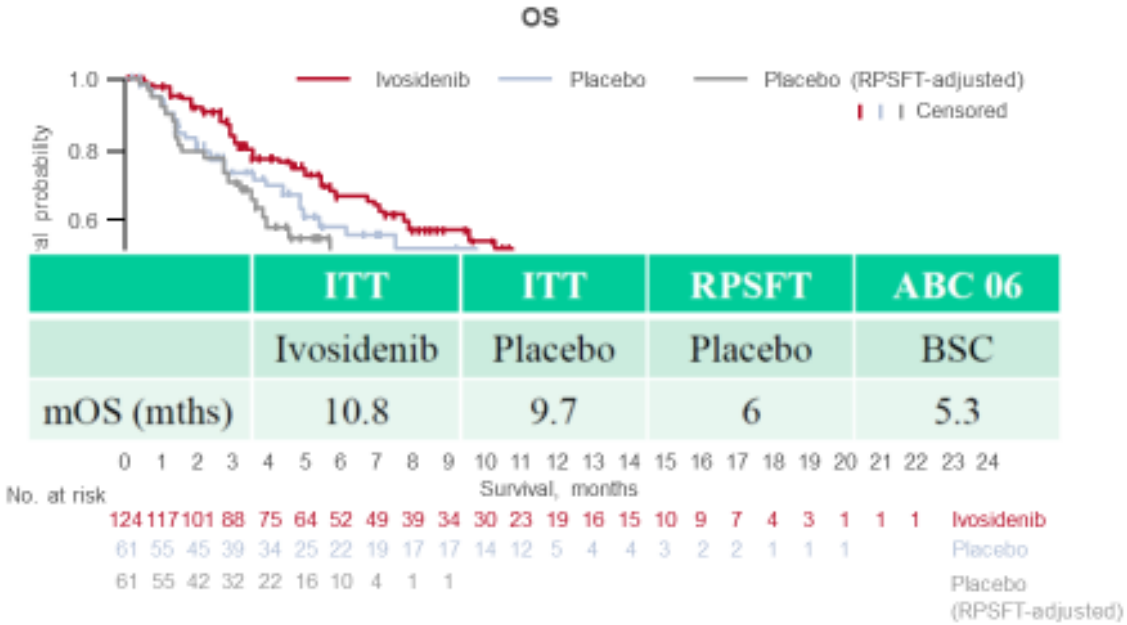
- OS, ORR, QoL, safety

Abou-Alfa GK, et al. Lancet Oncol 2020

ClarIDHy: A global, phase III, randomized, double-blind study of ivosidenib (IVO) vs placebo in patients with advanced cholangiocarcinoma (CC) with an isocitrate dehydrogenase 1 (IDH1) mutation



	Ivosidenib	Placebo
mPFS, months	2.7	1.4
6-month PFS rate, %	32	NE
12-month PFS rate,%	22	NE
DCR rate (PR + SD),%	53	28
PR	2	0
SD	51	28



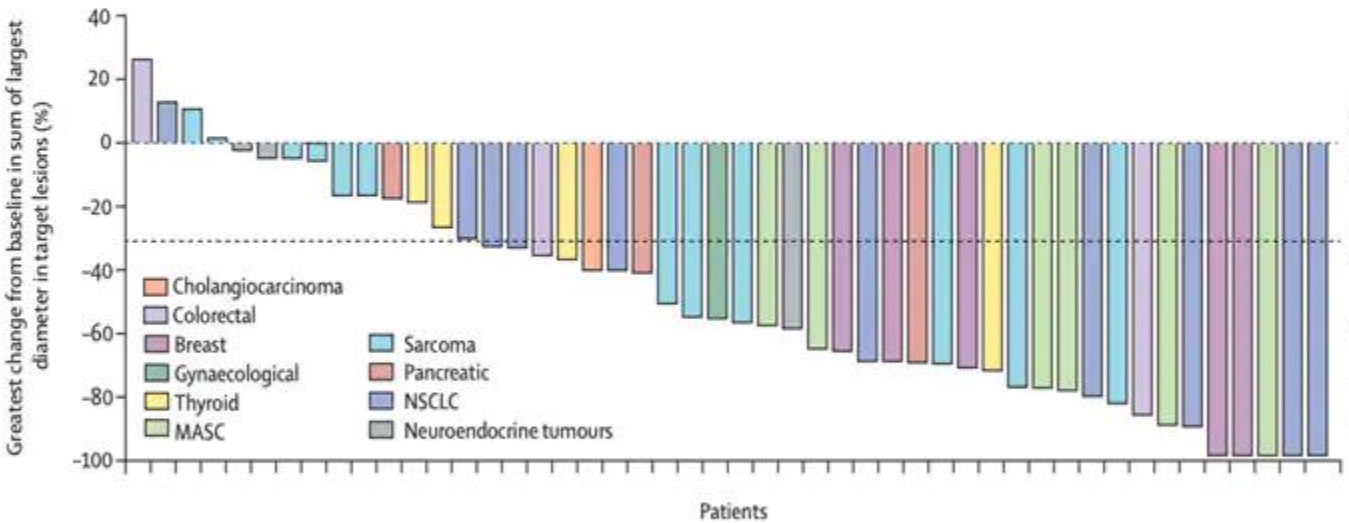
	ITT	ITT	RPSFT	ABC 06
	Ivosidenib	Placebo	Placebo	BSC
mOS (mths)	10.8	9.7	6	5.3

Abou-Alfa GK, et al. Lancet Oncol 2020

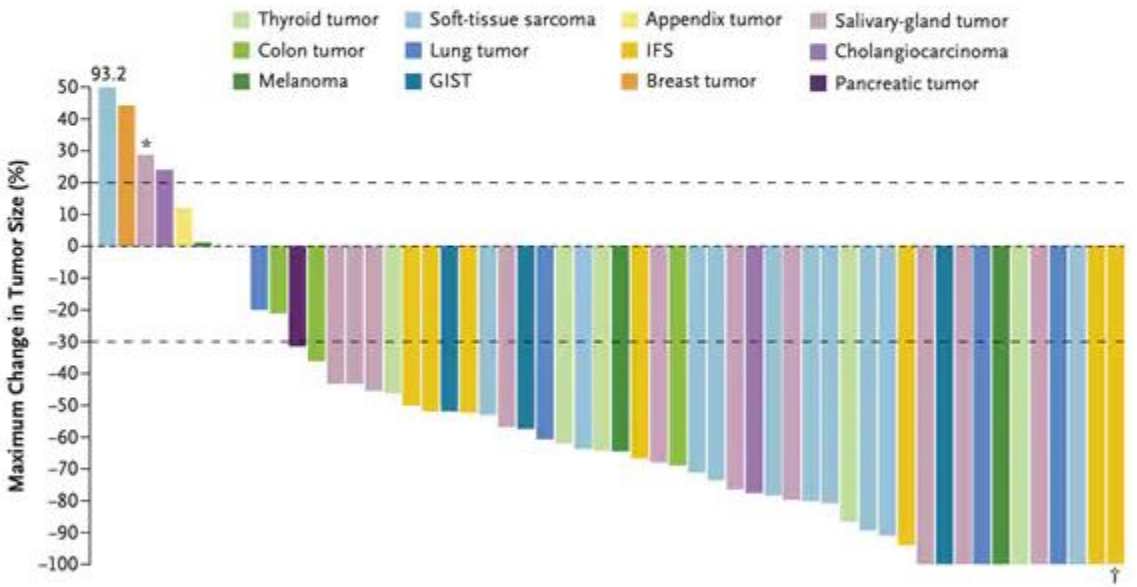
NTRK Inhibitors in *TRK* Fusion Positive Solid Tumors
Phase 1/2 Trials

NTRK fusions have been detected in ~ 3.5% of CCAs[a]

Maximum change in tumor size according to type with entrectinib[b]



Maximum change in tumor size according to type with larotrectinib[c]



Adverse events:[b]

- Most common grade ≥ 3 AEs in the NTRK fusion-positive safety population: increased weight (10%; n = 7/68) and anemia (12%; n = 8/68)
- Most common serious TRAEs in the NTRK fusion-positive safety population: nervous system disorders (4%; n = 3/68)

Adverse events:[c]

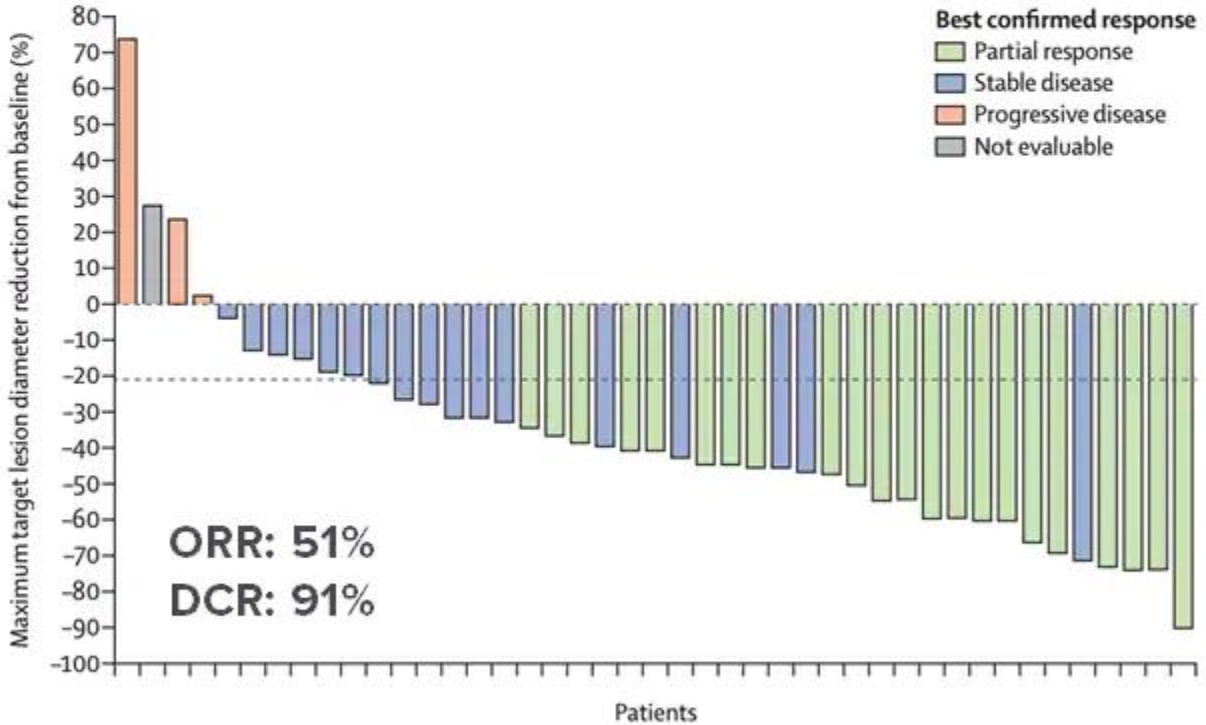
- Most common AEs: anemia (11%), increase in alanine amino-transferase or aspartate aminotransferase level (7%), weight increase (7%), and decrease in neutrophil count (7%)
- No grade 4 or 5 events were considered by the investigators to be related to treatment

a. Marin JJG, et al. Cancers (Basel). 2021;13:2358; b. Doebele RC, et al. Lancet Oncol. 2020;21:271-282; c. Drilon A, et al. N Engl J Med. 2018;378:731-739.

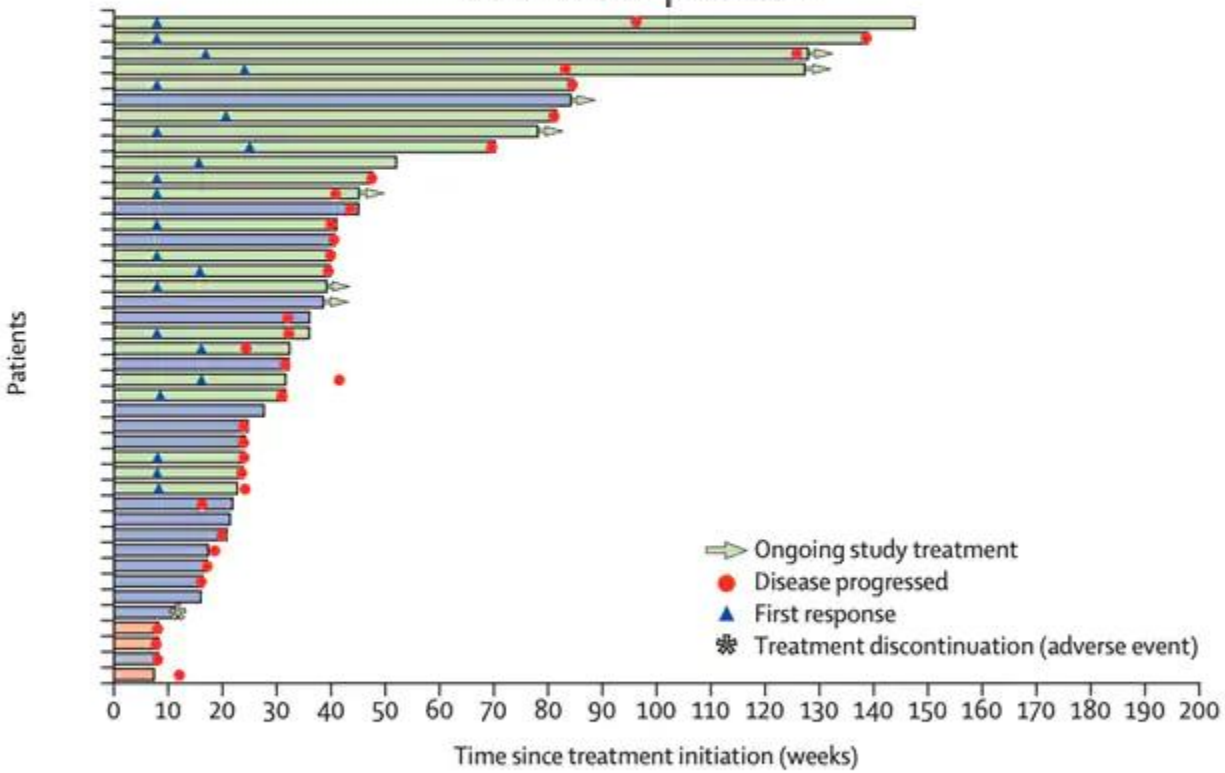
Dabrafenib + Trametinib in *BRAF* V600E+ Biliary Tract Cancer
ROAR Trial

Open-label, single-arm, multicenter phase 2 trial

Investigator-assessed maximum percent change from baseline in sum of the longest diameters of target lesion



Treatment duration and time to event for individual patients



- Median PFS: 9 months (95% CI: 5, 10)
- Median OS: 14 months (95% CI: 10, 33)

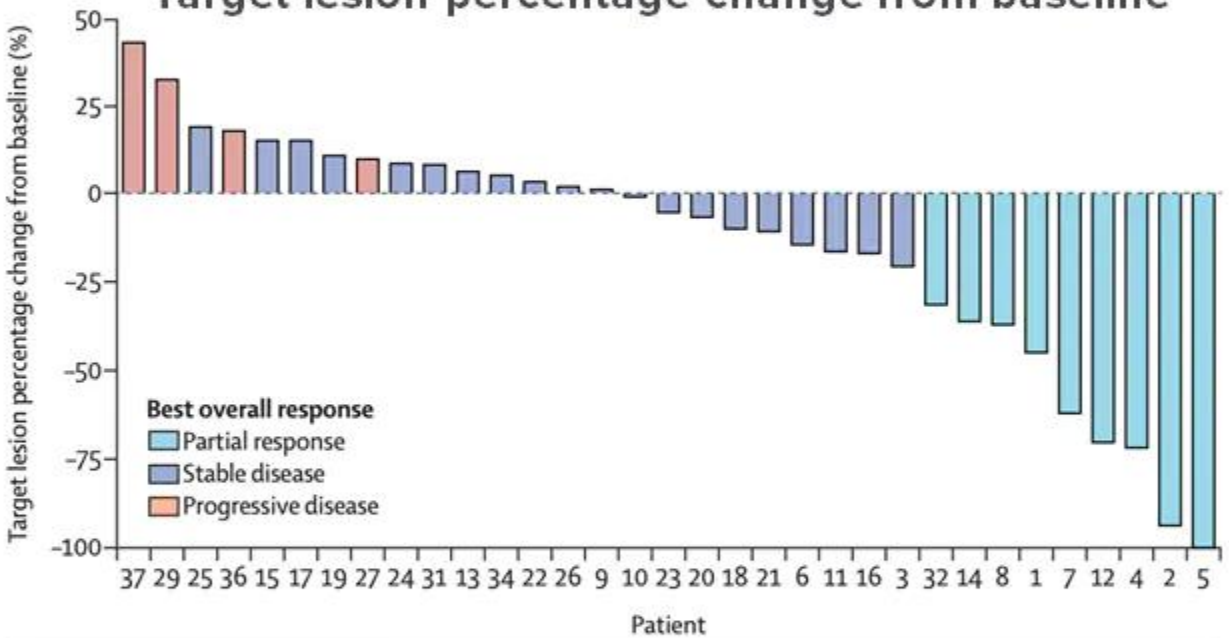
- Most common any grade AE: pyrexia 67% (n = 29/43)
- Serious TRAEs: 19% (n = 8/43), the most frequent was pyrexia

Subbiah V, et al. Lancet Oncol. 2020;21:1234-1243.

Trastuzumab + Pertuzumab in *HER2* Overexpressing Metastatic Biliary Tract Cancer: *MyPathway Trial*

Nonrandomized phase 2a multiple basket trial

Target lesion percentage change from baseline



Clinical outcome summary

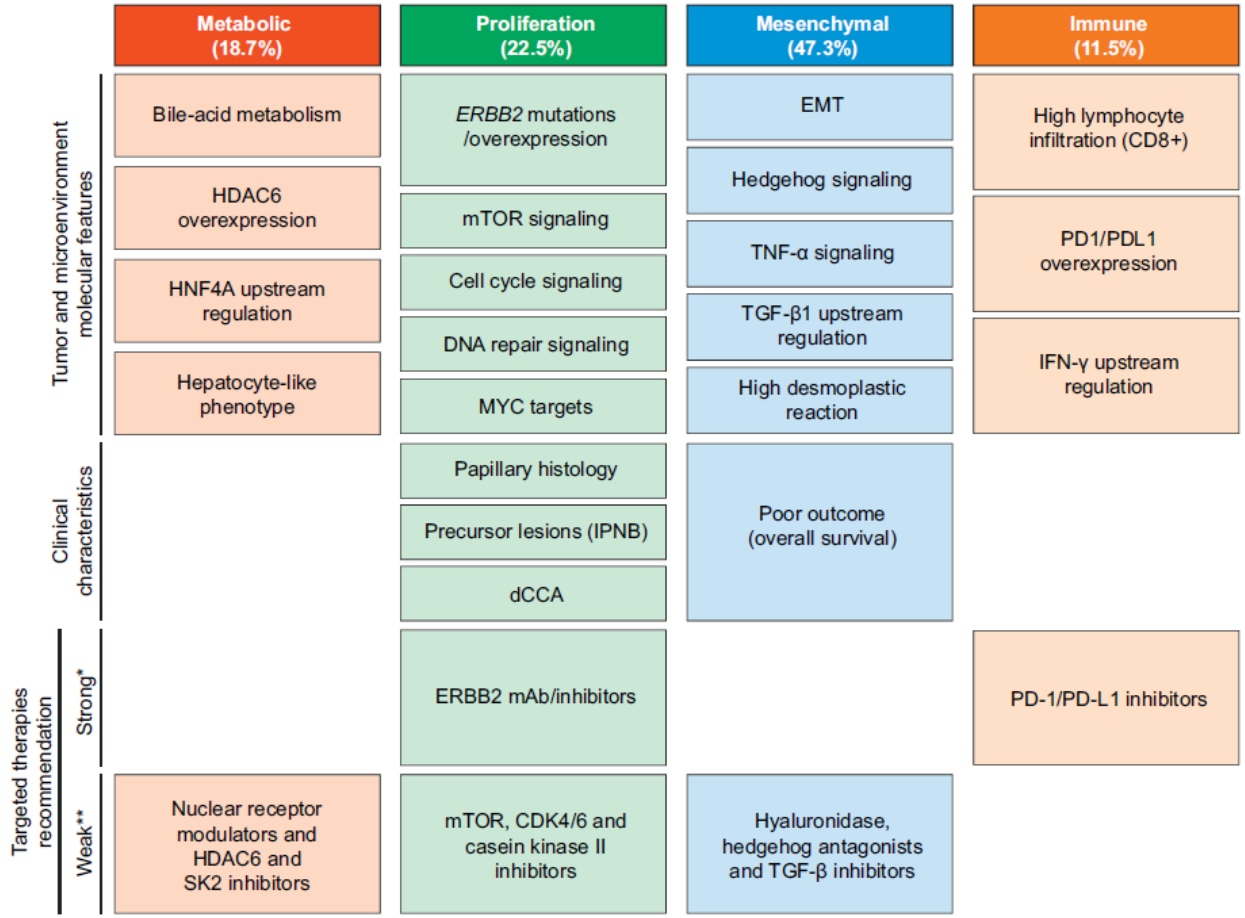
	Total (n = 39)
Best response	
Partial response	9 (23%)
Stable disease > 4 months	11 (28%)
Stable disease ≤ 4 months	9 (23%)
Progressive disease	10 (26%)
Objective response rate	9 (23%; 11 to 39)
Disease control rate	20 (51%; 35 to 68)
Duration of response, month	10.8 (0.7 to 25.4)
PFS, months	4 (1.8 to 5.7)
OS, months	10.9 (5.2 to 15.6)

Adverse events:

- Grade 3 TRAEs: 8% (n = 3/39) including increased alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, and blood bilirubin
- Serious AEs: 26% (n = 10/39)

Javle M et al. Lancet Oncol. 2021;22:1290-1300.

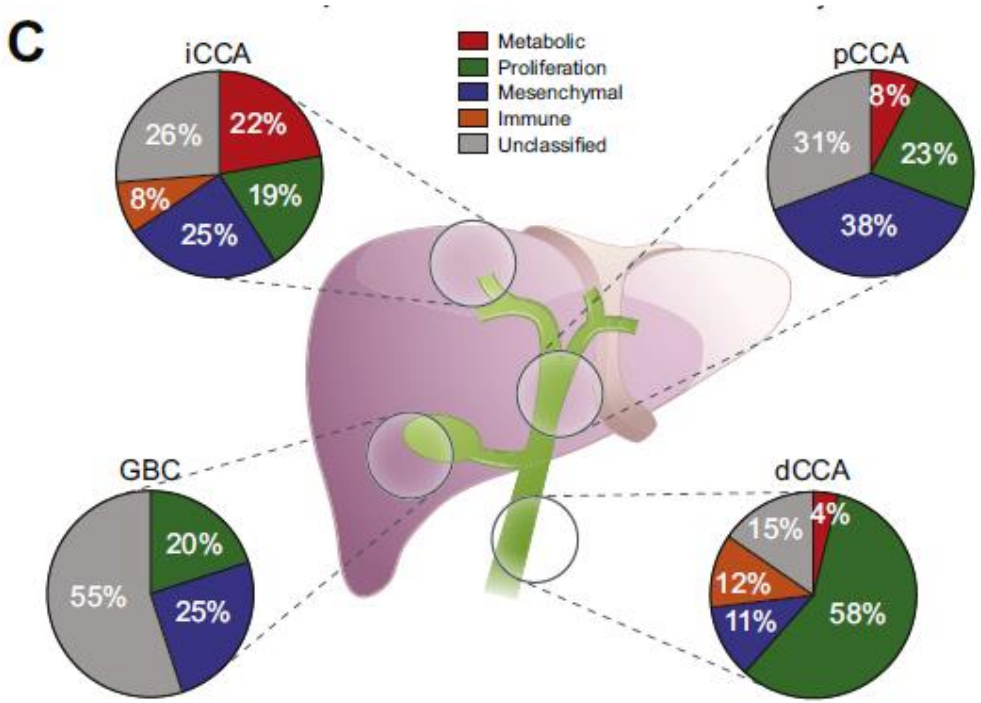
eCCA: transcriptome based classification



Montal et al. 2020, J Hepatol

eCCA molecular classifier

	Metabolic (18.7%)	Proliferation (22.5%)	Mesenchymal (47.3%)	Immune (11.5%)
Tumor and microenvironment molecular features	Bile-acid metabolism	*ERBB2* mutations /overexpression	EMT	High lymphocyte infiltration (CD8+)
	HDAC6 overexpression	mTOR signaling	Hedgehog signaling	PD1/PDL1 overexpression
	HNF4A upstream regulation	Cell cycle signaling	TNF-α signaling	
	Hepatocyte-like phenotype	DNA repair signaling	TGF-β1 upstream regulation	IFN-γ upstream regulation
		MYC targets	High desmoplastic reaction	
Clinical characteristics		Papillary histology	Poor outcome (overall survival)	
		Precursor lesions (IPNB)		
		dCCA		
Targeted therapies recommendation Strong*		ERBB2 mAb/inhibitors		PD-1/PD-L1 inhibitors
Targeted therapies recommendation Weak**	Nuclear receptor modulators and HDAC6 and SK2 inhibitors	mTOR, CDK4/6 and casein kinase II inhibitors	Hyaluronidase, hedgehog antagonists and TGF-β inhibitors	

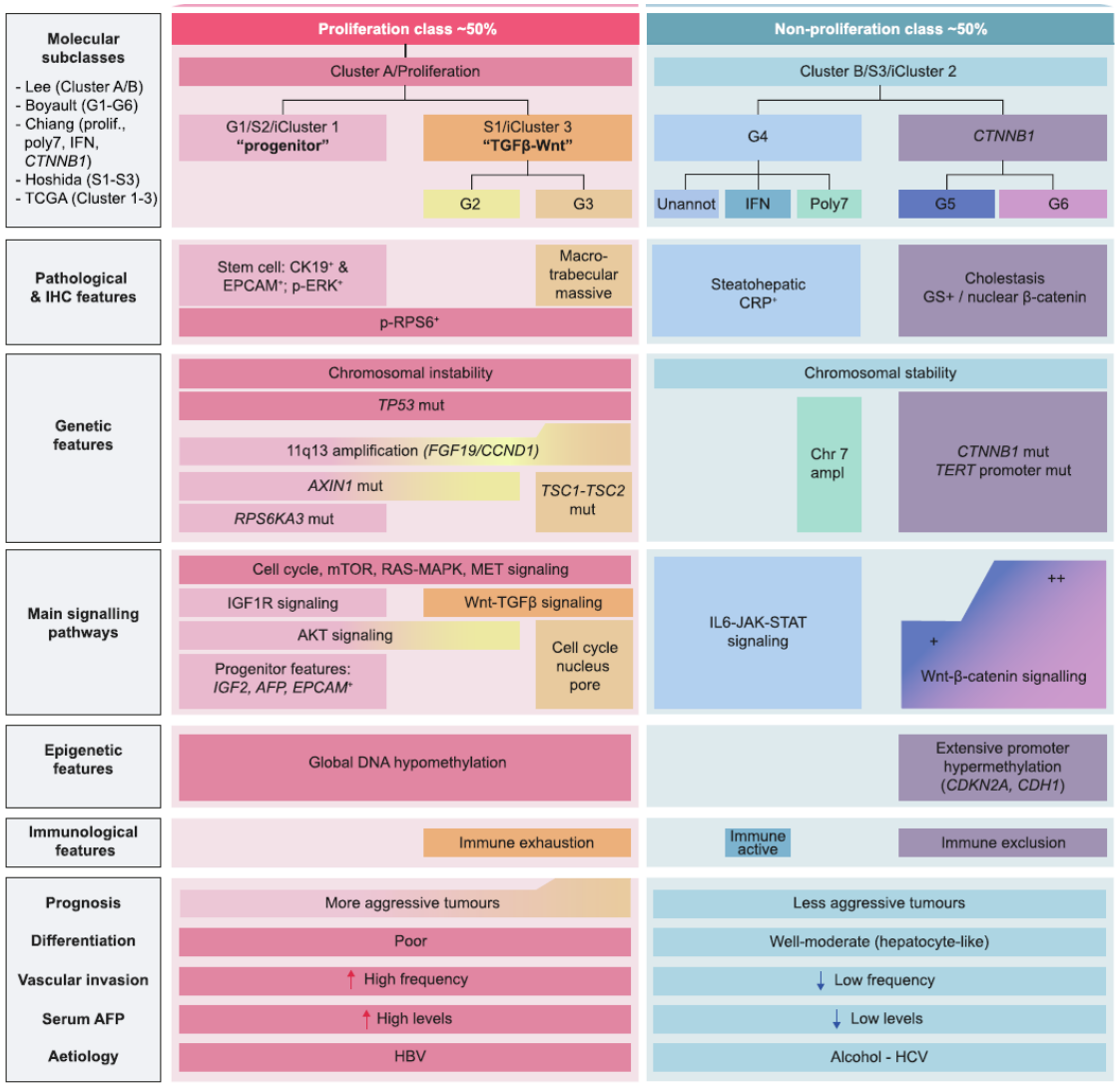


Montal et al. 2020, J Hepatol

Cholangiocarcinoma: conclusions

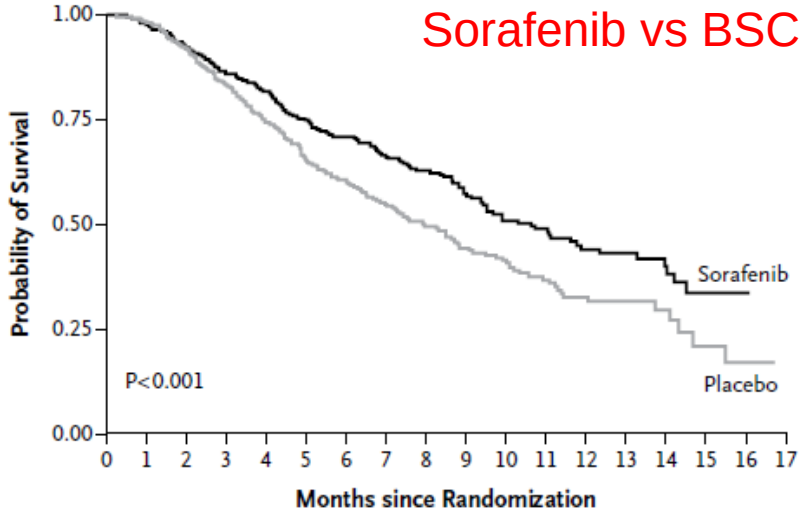
- CCA is heterogeneous according to location, histology, putative cell of origin and risk factors
- iCCA and eCCA are distinct molecular entities
- iCCA: molecular profiling may reveil actionable mutations in > 50% of patients, less in eCCA (FGFR2, IDH1/2, MMR, NTRK, BRAF, HER2)

HCC

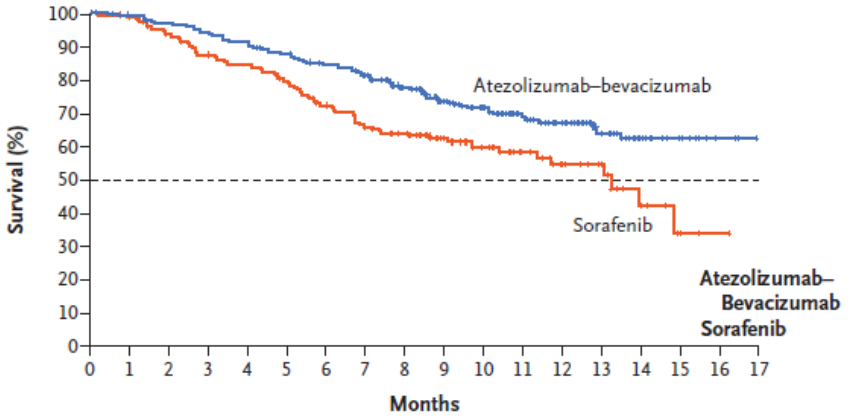


Reboisseau and Nault, J Hepatol 2020

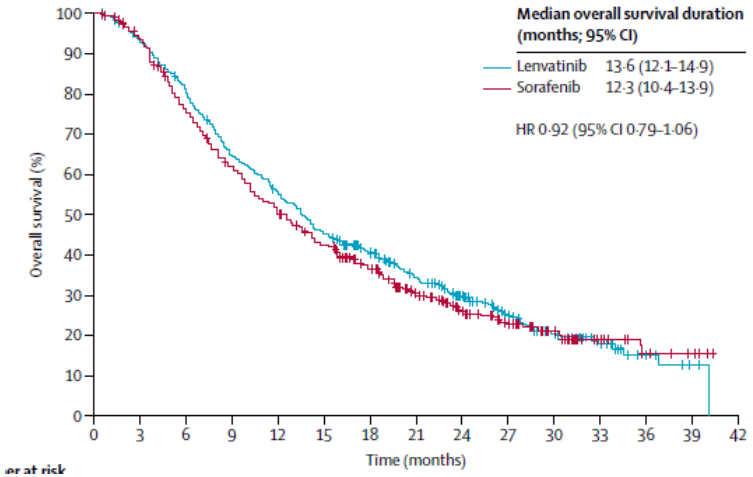
Sorafenib vs BSC



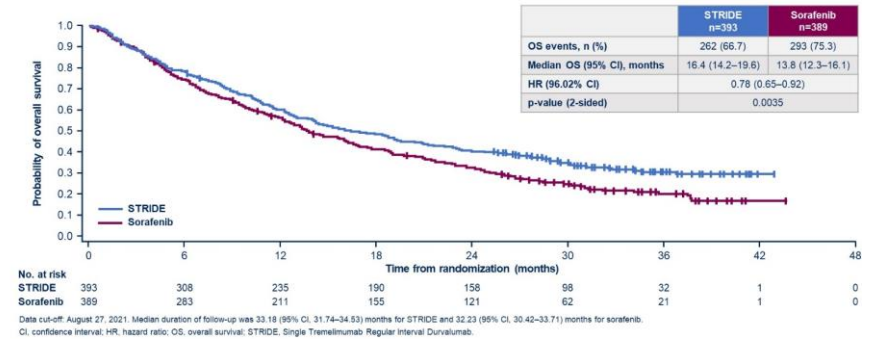
Atezo-Beva vs Sorafenib



Lenvatinib vs Sorafenib

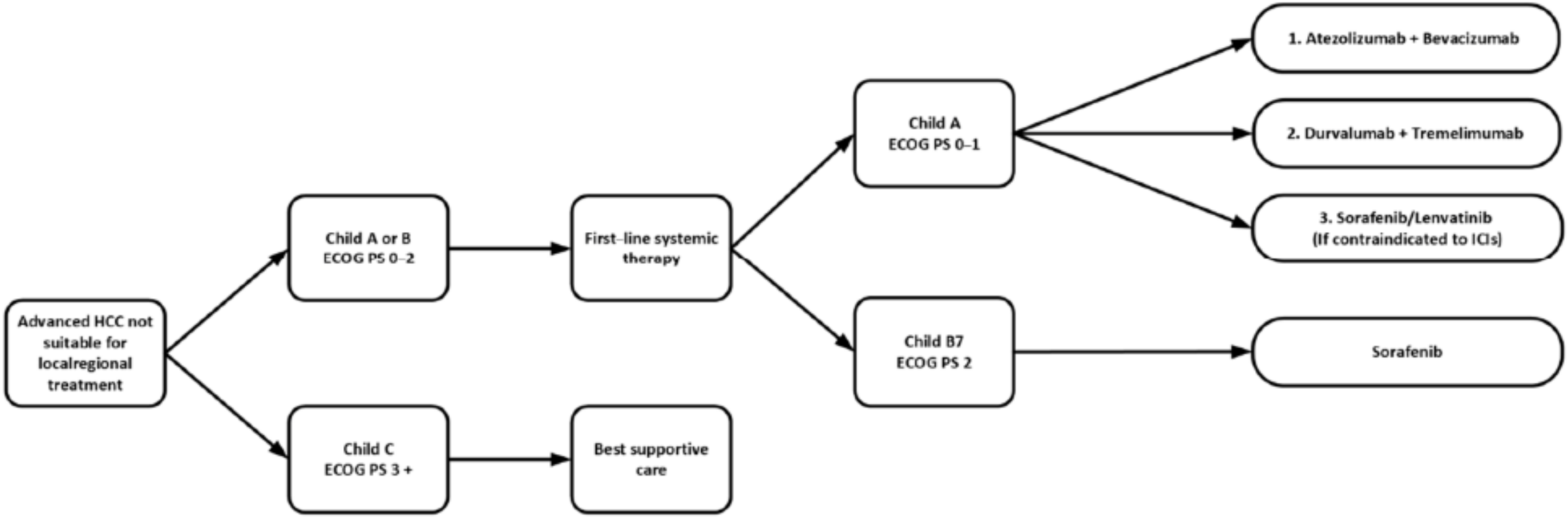


STRIDE vs Sorafenib



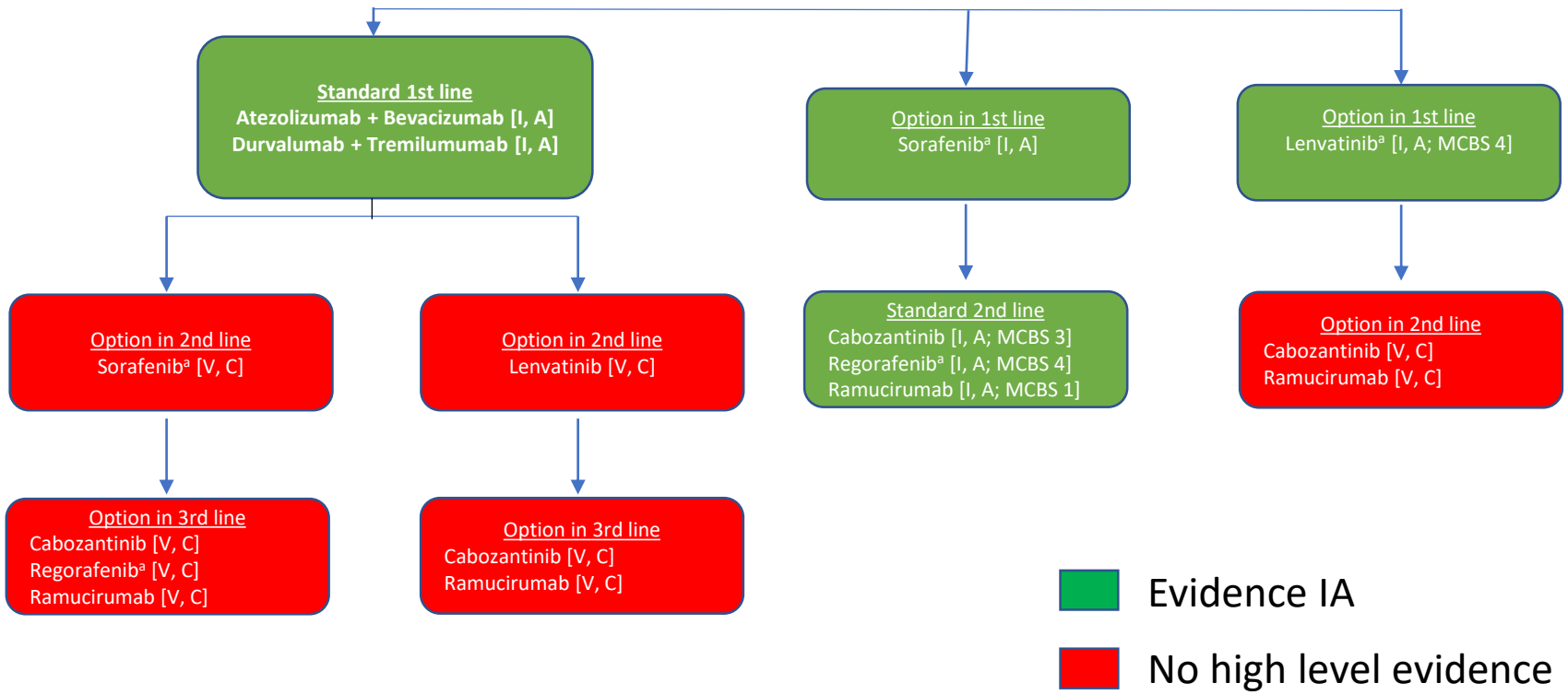
Llovet et al, NEJM, 2008; Kudo et al, Lancet Oncol, 2018; Fin et al, NEJM, 2020; Abou-Alfa et al. NEJM 2022

HCC: therapeutic algorithm



Feng MY et al. *Curr Oncol*. 2022;29:5489-5507. doi:10.3390/curroncol29080434

HCC: therapeutic algorithm

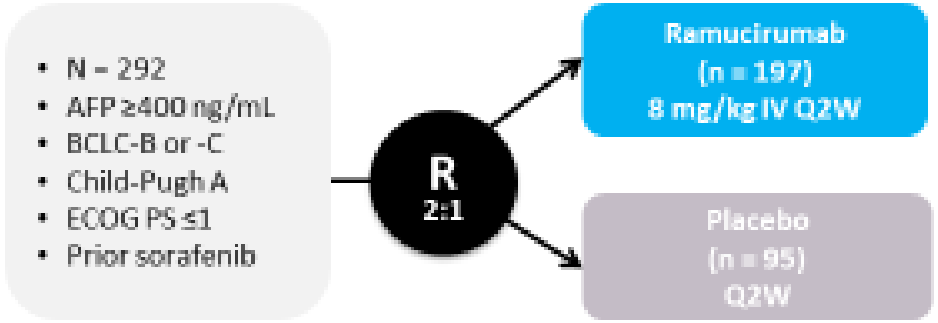


Biomarkers for patient selection in HCC

- Immunostaining (PD1, PDL1, CD3, CD8): inconsistent results
- Genomic biomarker, TMB: more data needed
- *CTNNB1* mutations: associated with immune-excluded phenotype, but a subtype (enriched in CD8+ T cell and immune activation signatures) may respond to immune checkpoint blockade

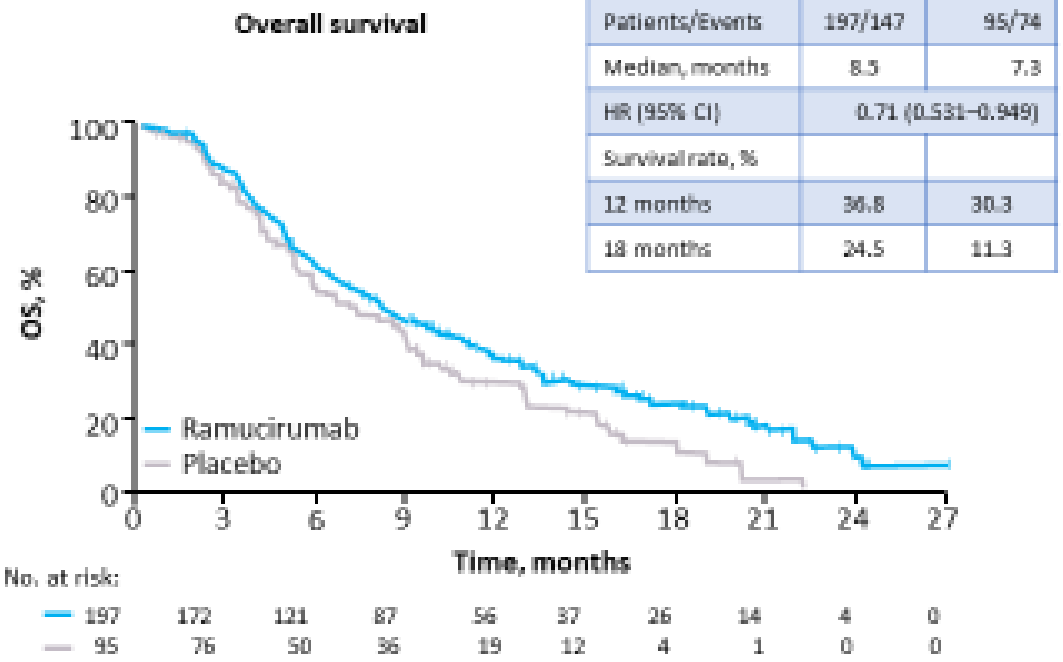
Review: Yang et al. Nature Reviews gastroenterol hepatol 2022

AFP as predictive biomarker for ramucirumab



- *Included patients with progression or intolerance to sorafenib*
- *Primary endpoint: OS*
- *Secondary endpoints: PFS, TTP, ORR*

	RAM	PBO
Patients/Events	197/147	95/74
Median, months	8.5	7.3
HR (95% CI)	0.71 (0.531–0.949)	
Survival rate, %		
12 months	36.8	30.3
18 months	24.5	11.3

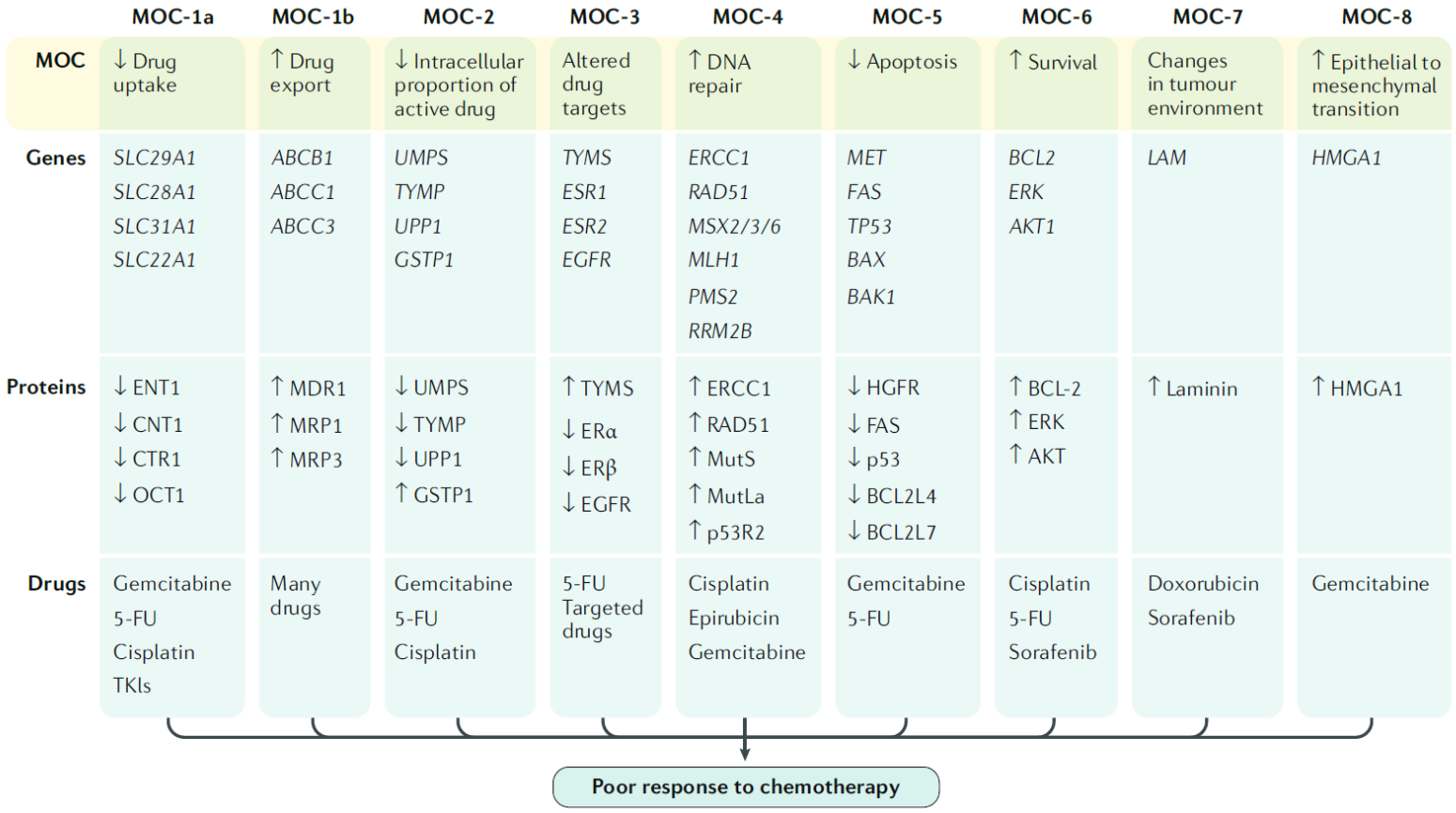


Zhu et al. Lancet Oncol 2019

HCC: conclusions

- Several subclasses of HCC have been identified based on genetic alterations and transcriptomic dysregulation, that are closely related to risk factors, histology and prognosis
- No robust predictive biomarkers of response to targeted therapy and immunotherapy exist, except for AFP > 400 ng/ml for ramucirumab
- Active field of research

Resistome



Banales et al. Nature Reviews in Gastroenterology & Hepatology 2020