Targeted therapy in Bile duct cancers

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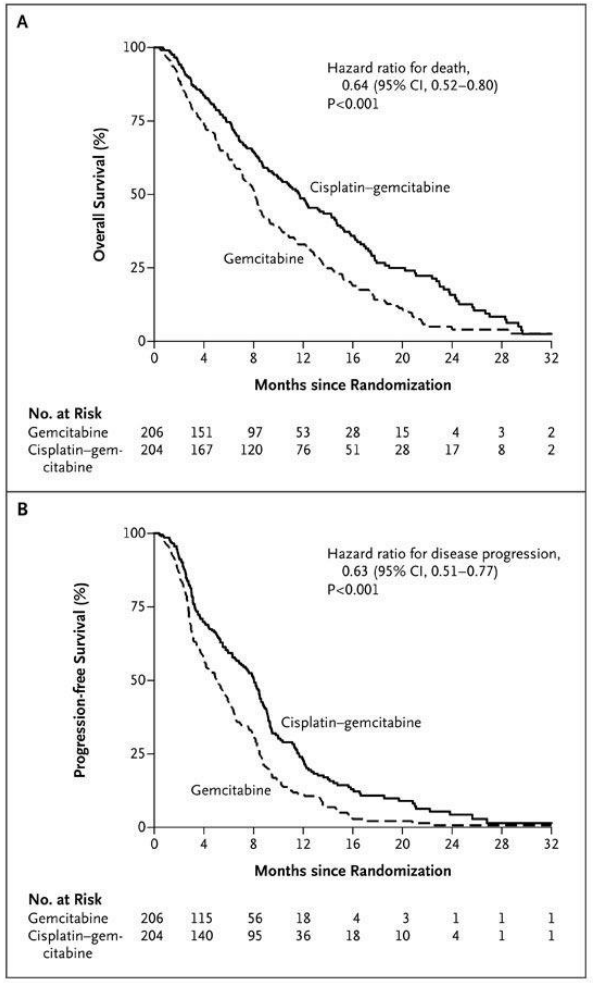
"Bummer of a birthmark, Hal."

Outcomes in Patients with Biliary Tract Cancer Who Received Gemcitabine Alone versus Cisplatin plus Gemcitabine.



OS :

- 11.7 months cisplatin–gemcitabine
- 8.1 months gemcitabine group

(hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; P<0.001)

Valle J et al. N Engl J Med 2010;362:1273-1281.

The NEW ENGLAND JOURNAL of MEDICINE

Target therapies

Infectious disease

1800

- Mercury
- Arsenic

1950

Beta-Lactamase

Protease inh

Oncology

2000

- Platinum
- Arsenic
- Etc

2020

Proteosome inh

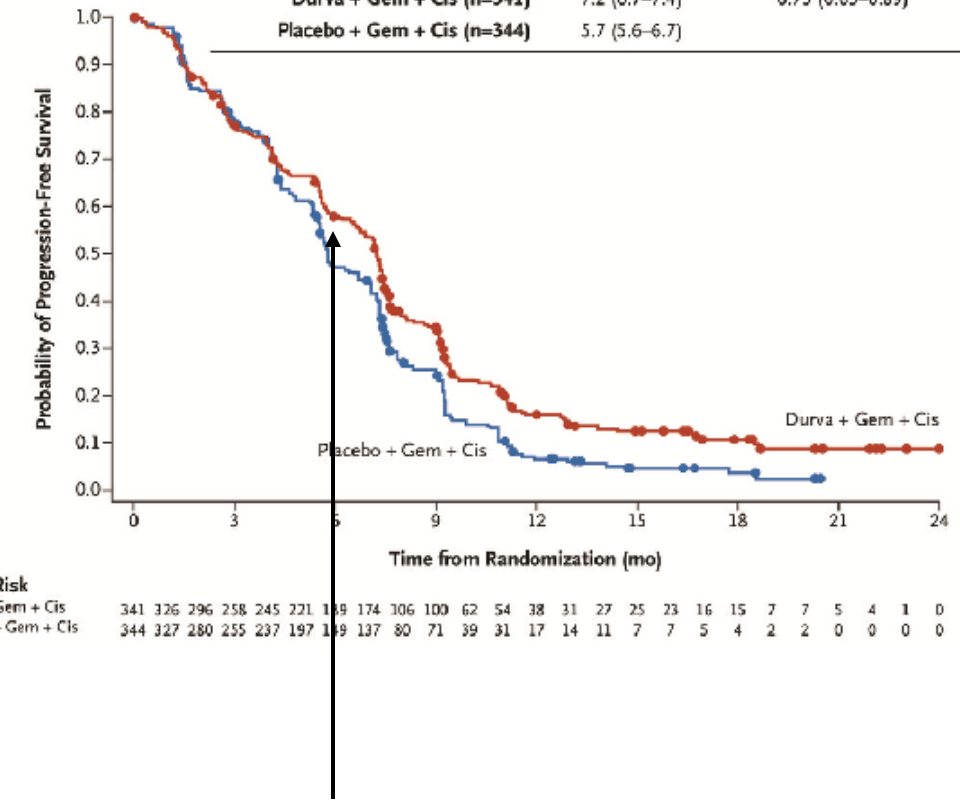
Immunotherapy

Target du jour

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

B

	Median Progression-free Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	7.2 (6.7–7.4)	0.75 (0.63–0.89)	0.001
Placebo + Gem + Cis (n=344)	5.7 (5.6–6.7)		

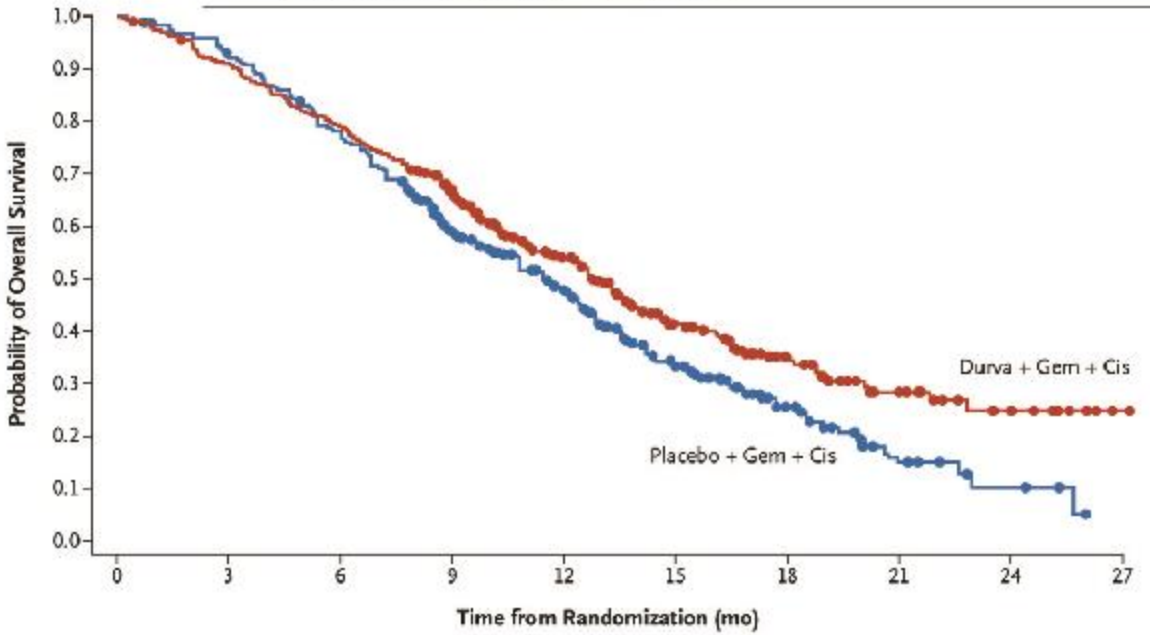


No. at Risk

Durva + Gem + Cis	341	326	296	258	245	221	189	174	106	100	62	54	38	31	27	25	23	16	15	7	7	5	4	1	0
Placebo + Gem + Cis	344	327	280	255	237	197	159	137	80	71	39	31	17	14	11	7	7	5	4	2	2	0	0	0	0

END of Chemotherapy

	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		

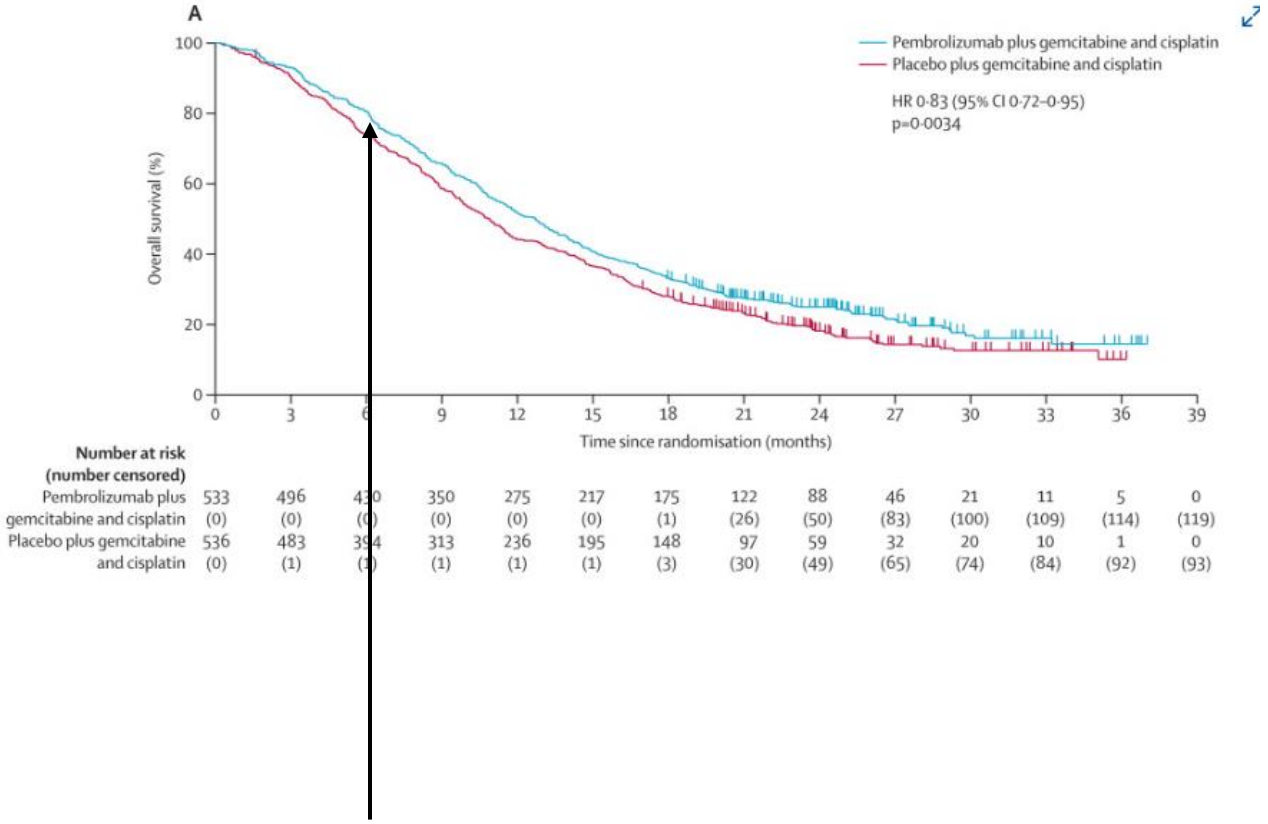


No. at Risk

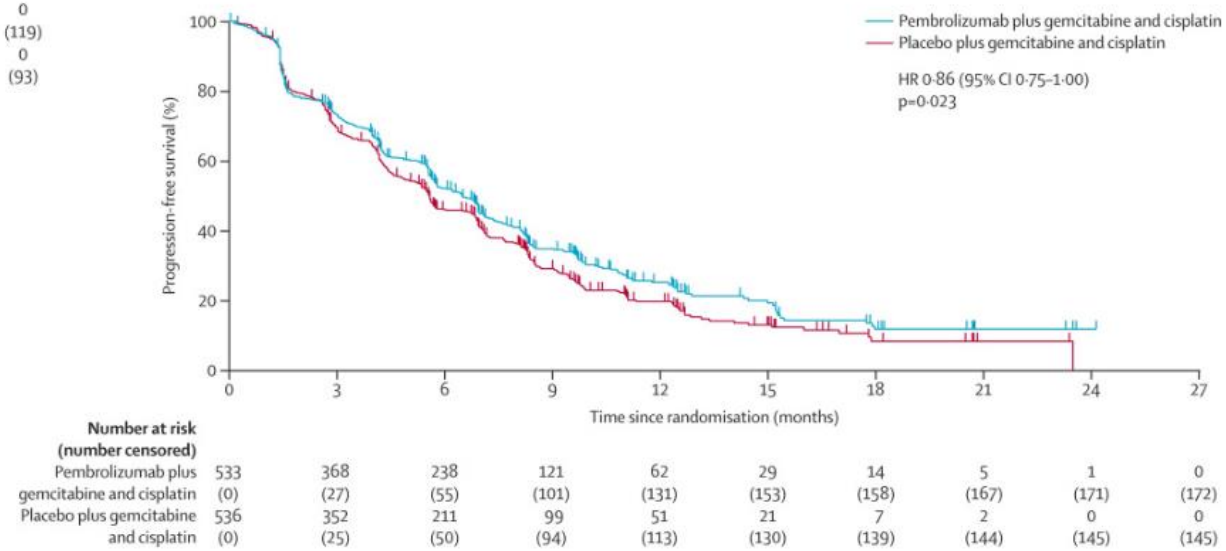
Durva + Gem + Cis	341	331	324	309	294	278	268	252	238	208	174	151	135	118	93	79	74	57	49	39	29	24	15	12	9	8	4	1
Placebo + Gem + Cis	344	337	329	317	299	283	261	242	220	183	159	143	125	97	78	65	52	40	29	21	15	10	8	4	4	3	0	0

Oh D-Y et al. NEJM Evid2022;1:EVIDoa2200015

Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966)

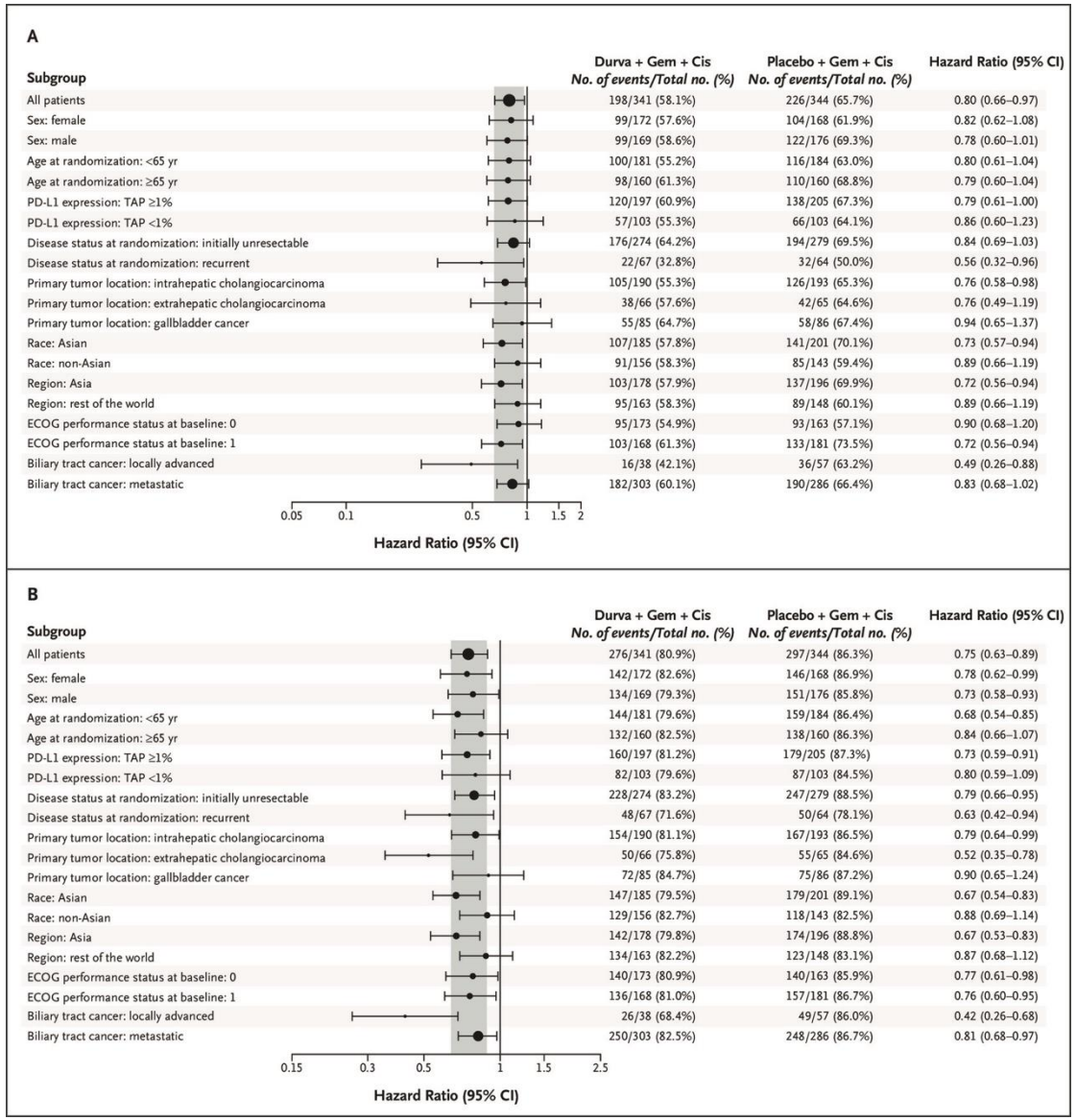


END of Cisplatin

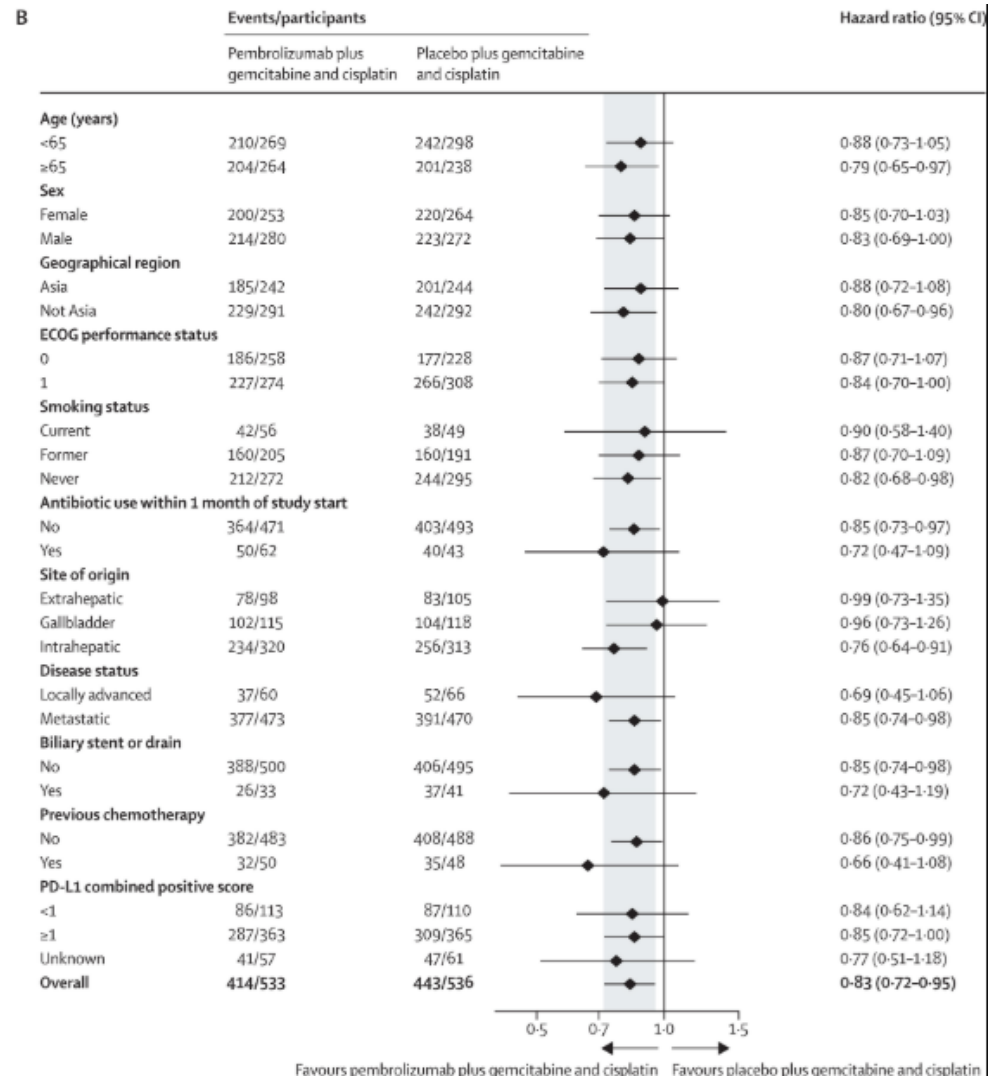


Kelley, Robin KateAkce, Mehmet et al.The Lancet, Volume 401, Issue 10391, 1853 - 1865

TOPAZ-1



KEYNOTE 966



Standard of Care in Advanced BTCs

GemCis (GC), gemcitabine/cisplatin; 1L, first-line; 2L, second-line; FOLFOX, fuluorouracil/leucovorin/oxaliplatin; nal-IRI, liposomal irinotecan; FF, leucovorin/fuluorouracil; BSC, best supportive care; CAP, capecitabine; S-1, tegafur/gimeracil/oteracil; ORR, objective response rate; D, durvalumab.

- GemCis has been the standard 1L chemotherapy since the results of the ABC-02 trial were reported.[1] Recently, the survival benefit of additional durvalumab was demonstrated in TOPAZ-1 trial.[2]
- Concerning 2L chemotherapy, FOLFOX[3] and nal-IRI + FF[4] have demonstrated superiority over BSC or FF, and fluoropyrimidine monotherapy (e.g., CAP, S-1[5]) is a treatment option.
- These cytotoxic regimens and agents for BTCs in the 2L setting have modest activity with an ORR of 5–15%.

	1L setting		2L setting		
	GC	**GC + D**	**FOLFOX**	**nal-IRI + FF**	**S-1**
ORR (%)	18.7	26.7	5.0	14.8	7.5
mPFS (mo)	5.7	7.2	4.0	7.1	2.5
mOS (mo)	11.5	12.8	6.2	8.6	6.8

1. NEJM 2010;362:1273. 2. JCO 2022;40(suppl):378. 3. Lancet Oncol 2021;22:690. 4. Lancet Oncol 2021;22:1560. 5. Cancer Chemother Pharmacol 2013;71:1141.

PRINCIPLES OF SYSTEMIC THERAPY[a,k]
TARGETED THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[13,14]
  - Larotrectinib[15]
  - Repotrectinib[16]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[g,l,17-20]
- For TMB-H tumors:
  - Nivolumab + ipilimumab (category 2B)[g,21]
- For *RET* gene fusion-positive tumors:
  - Pralsetinib (category 2B)[22]
  - Selpercatinib (category 2B)[23]

Next Slide
2/2

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[i]

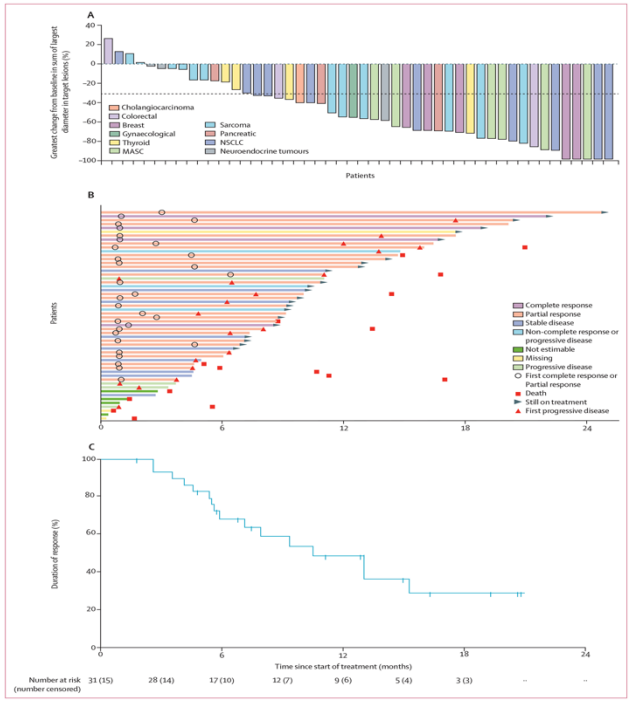
Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors[m]:
  - Entrectinib[13,14]
  - Larotrectinib[15]
  - Repotrectinib[16]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[g,h,l,17-20]
  - Dostarlimab-gxly (category 2B)[g,h,n,24]
- For TMB-H tumors:
  - Nivolumab + ipilimumab[g,h,o,21]
  - Pembrolizumab[g,h,l,17,25]
- For *BRAF* V600E-mutated tumors
  - Dabrafenib + trametinib[26,27]
- For CCA with *FGFR2* fusions or rearrangements[p]:
  - Futibatinib[28]
  - Pemigatinib[29]
  - Erdafitinib[q,30]
- For CCA with *IDH1* mutations
  - Ivosidenib (category 1)[31,32]
- For HER2-positive tumors:
  - Fam-trastuzumab deruxtecan-nxki (IHC3+)[33]
  - Trastuzumab + pertuzumab (IHC3+/ISH+/NGS amplification)[34]
  - Tucatinib + trastuzumab (IHC3+/ISH+/NGS amplification)[35]
  - Zanidatamab-hrii (IHC3+)[36]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib[23]
  - Pralsetinib (category 2B)[22]
- For *KRAS* G12C mutation-positive tumors:
  - Adagrasib[37]

[a] Order does not indicate preference.
[g] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[h] For patients who have not been previously treated with a checkpoint inhibitor when used as subsequent-line therapy because there is a lack of data for use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[i] Treatment selection depends on clinical factors including previous treatment regimen/agent, somatic molecular testing results, and extent of liver dysfunction.
[k] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[l] There are limited clinical trial data to support pembrolizumab in this setting.
[m] Repotrectinib is an option if there was progression on a prior therapy, which may include prior NTRK inhibitors. Entrectinib and larotrectinib should not be used if there was progression on prior NTRK inhibitors.
[n] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
[o] For patients with disease refractory to standard therapies or who have no standard treatment options available.
[p] Futibatinib and pemigatinib are preferred over erdafitinib.
[q] The data available for this agent are from a smaller trial.

References on BIL-C 4 of 5

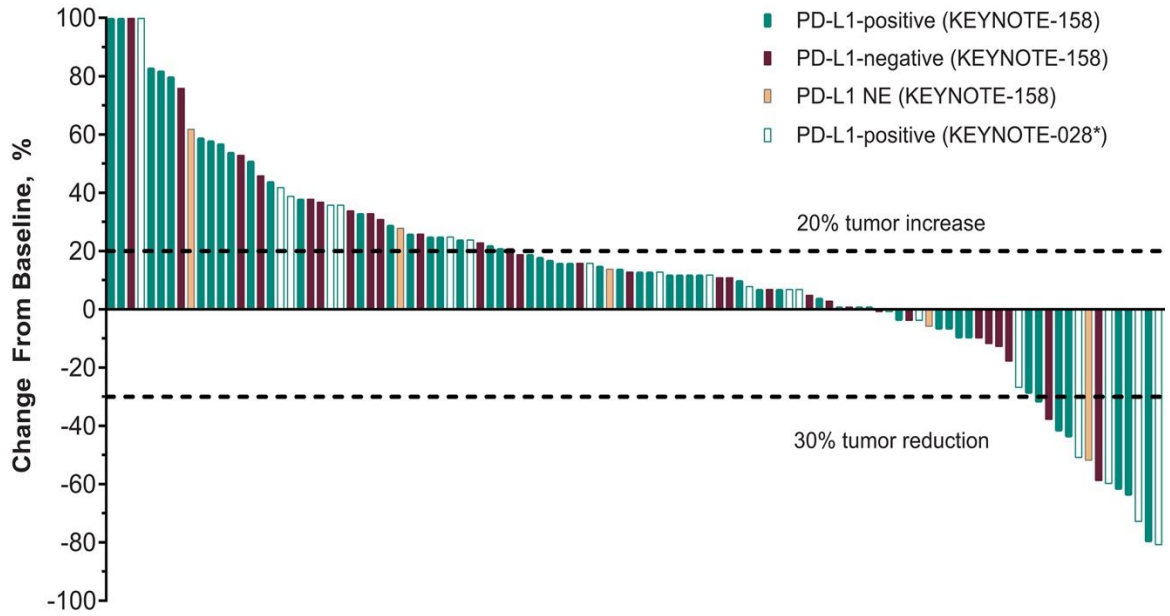
Note: All recommendations are category 2A unless otherwise indicated.

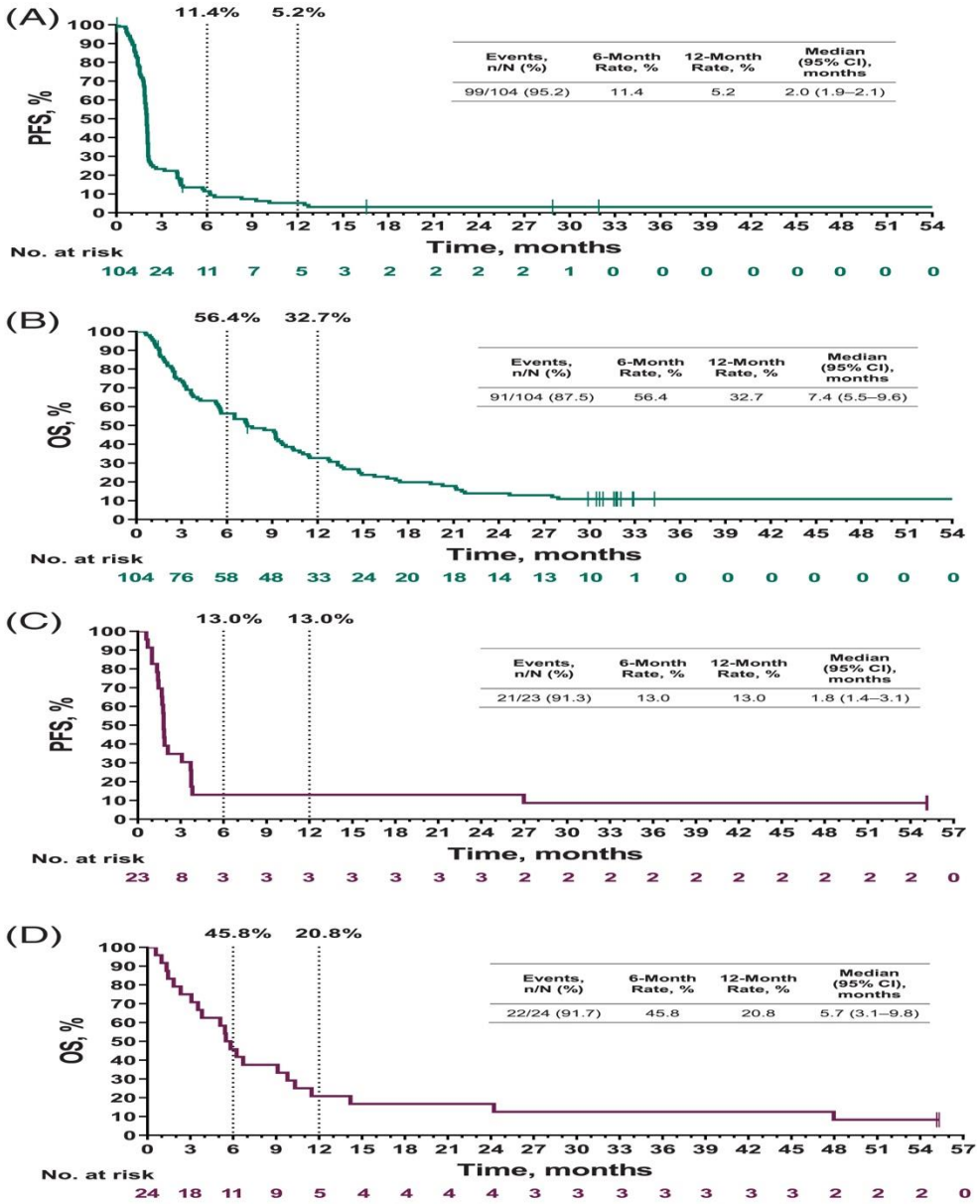


MSI-H Cholangiocarcinoma

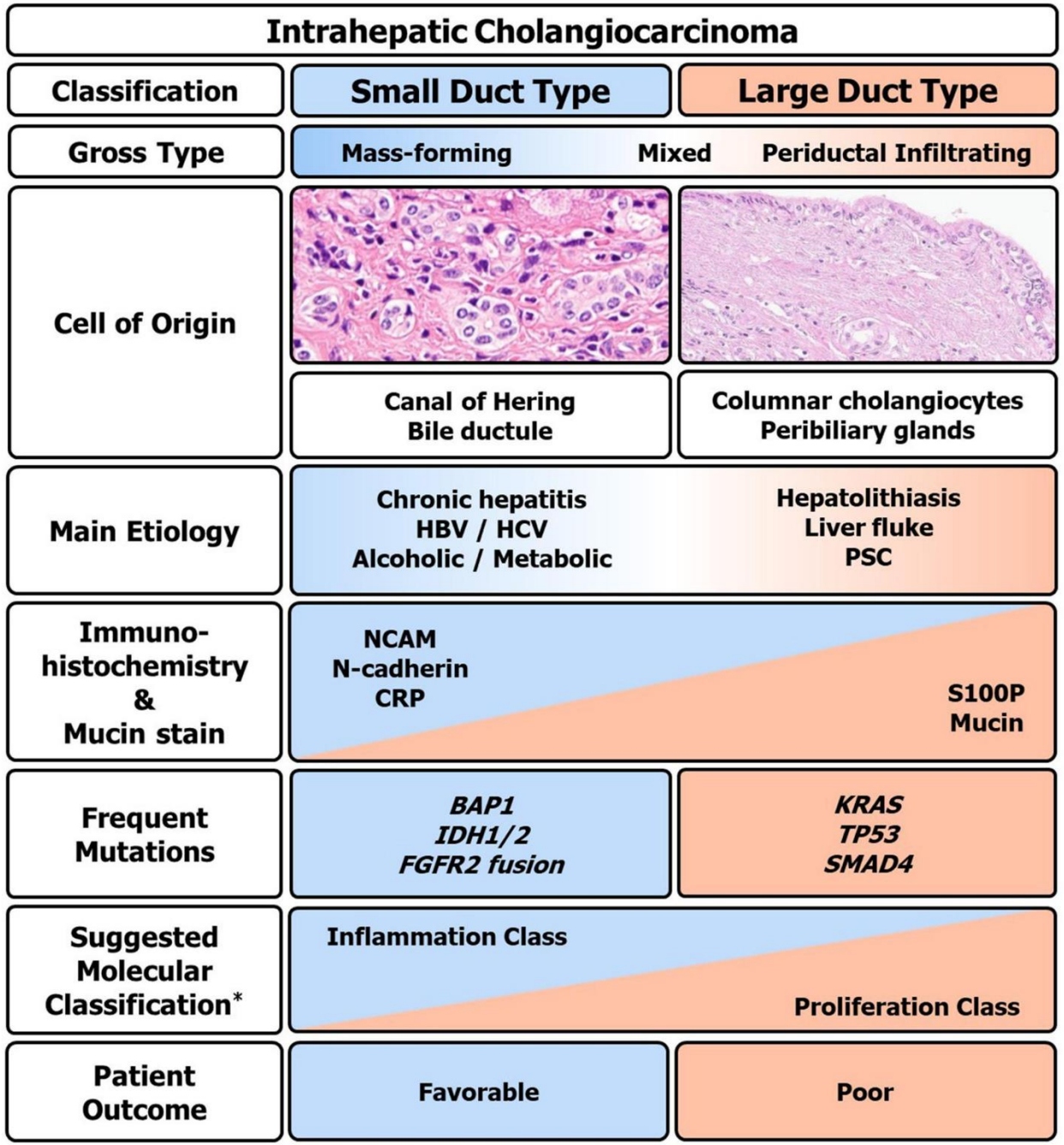
Type of BTC	Frequency, % (n)	Study	Year of report
Intrahepatic cholangiocarcinoma	18.2% (4/22)	(6)	2001
Intrahepatic cholangiocarcinoma	4.7% (1/23)	(7)	2002
Ampullary carcinoma	5.6% (3/54)	(8)	2010
Gallbladder carcinoma	7.8% (6/77)	(9)	2015
Cholangiocarcinoma	1.4% (1/74)	(10)	2017
Biliary tract cancer	2.1% (8/375)	(11)	2018
Biliary tract cancer	0% (0/99)	(12)	2018

Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies

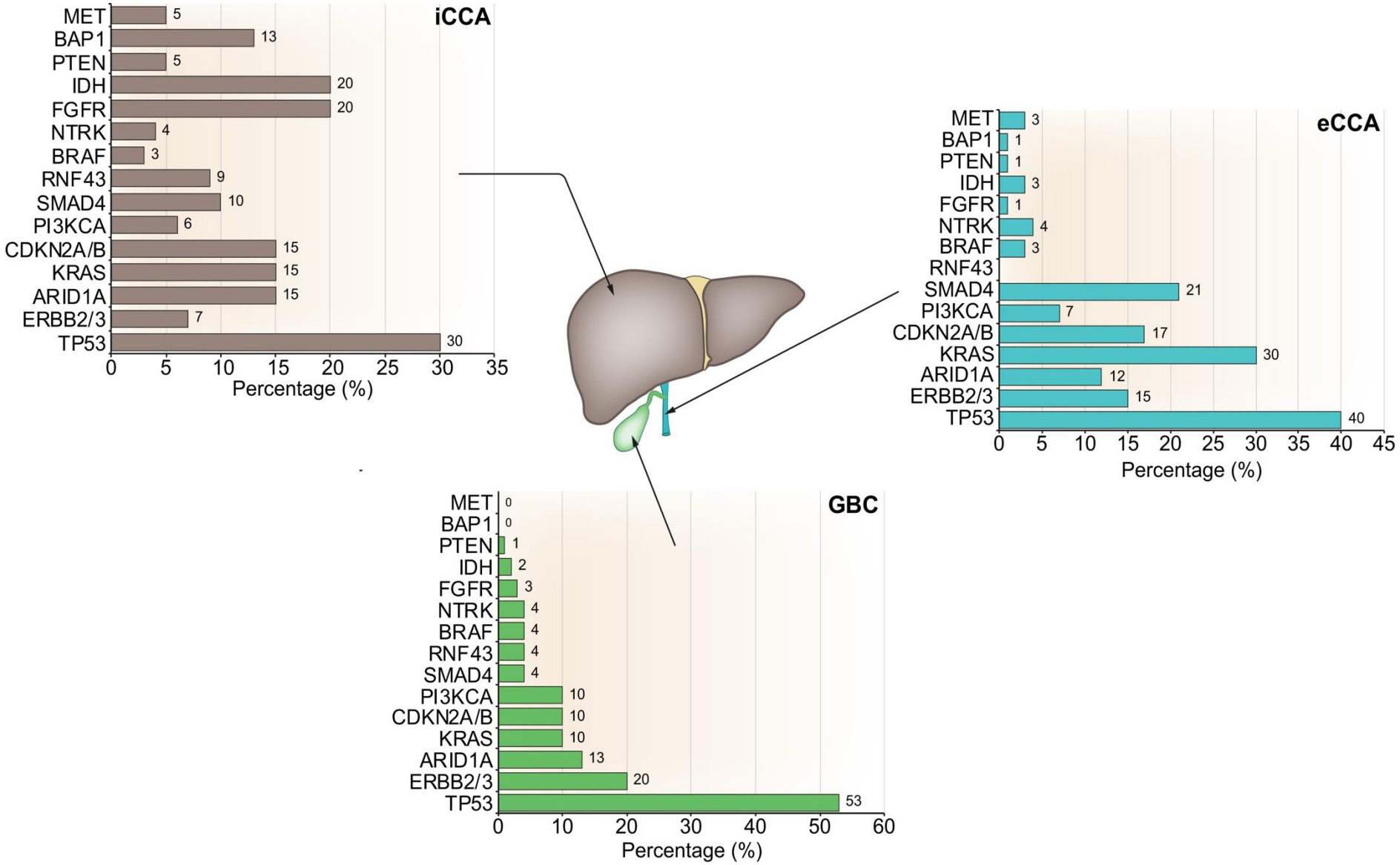




Intl Journal of Cancer, Volume: 147, Issue: 8, Pages: 2190-2198, First published: 02 May 2020, DOI: (10.1002/ijc.33013)



Front. Med., 31 March 2022



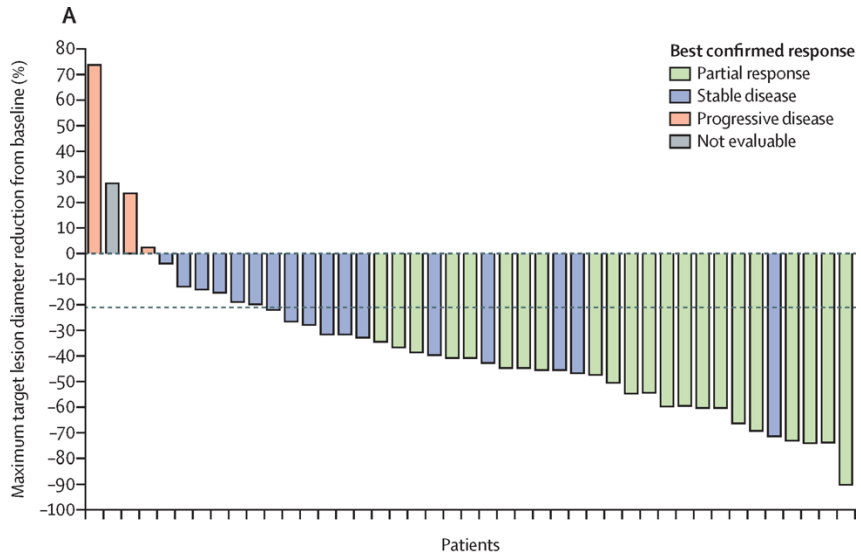
Journal of Hepatology 2020 73170-185DOI: (10.1016/j.jhep.2020.03.007)

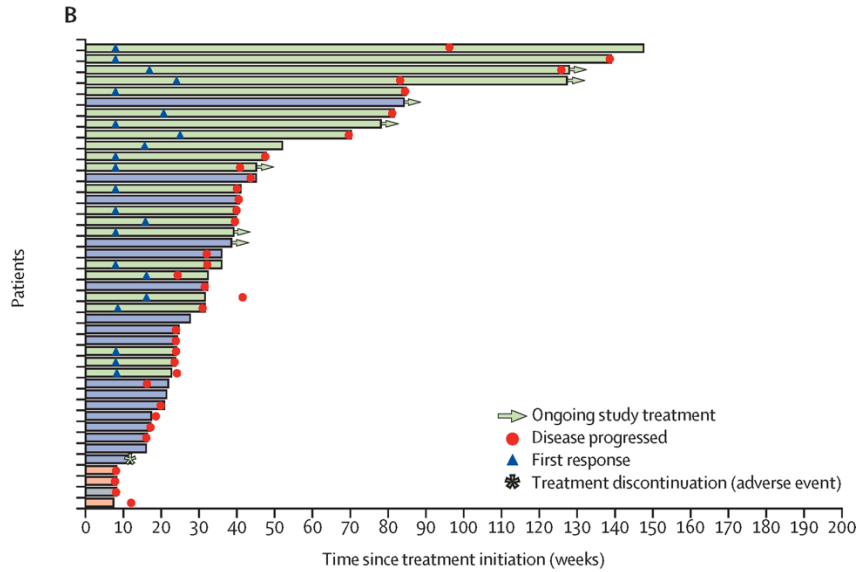
CCA type	Gross pattern	Precancerous lesion	Underlying disease	Tissue markers[a]	Frequent mutations
iCCA — CLC	Mass-forming	None	Viral, cirrhosis	NCAM	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4* Increased *IDH1* and *TP53*
iCCA — small duct type	Mass-forming	None	Viral, cirrhosis	NCAM, N-cadherin, SMAD4, BAP1^{loss}	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4* Increased *IDH1/2*, *FGFR2* fusion
iCCA — large duct type	Periductal infiltrating (±mass-forming) or intraductal growing	Biliary epithelial neoplasia, IPNB, ITPN, mucinous cystic neoplasm	Primary sclerosing cholangitis, liver flukes	Mucin[b], MUC5AC, MUC6, S100P, SMAD4^{loss}, BAP1	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4* Increased *KRAS* and *TP53*
pCCA–dCCA	Periductal infiltrating or intraductal growing	Biliary epithelial neoplasia, IPNB, ITPN, mucinous cystic neoplasm	Primary sclerosing cholangitis, liver flukes	Mucin[b], MUC5AC, MUC6, S100P, SMAD4^{loss}, BAP1	*KRAS*, *TP53*, *SMAD4*, *ERBB3*, *PRKACA–PRKACB* fusions, *ELF3*

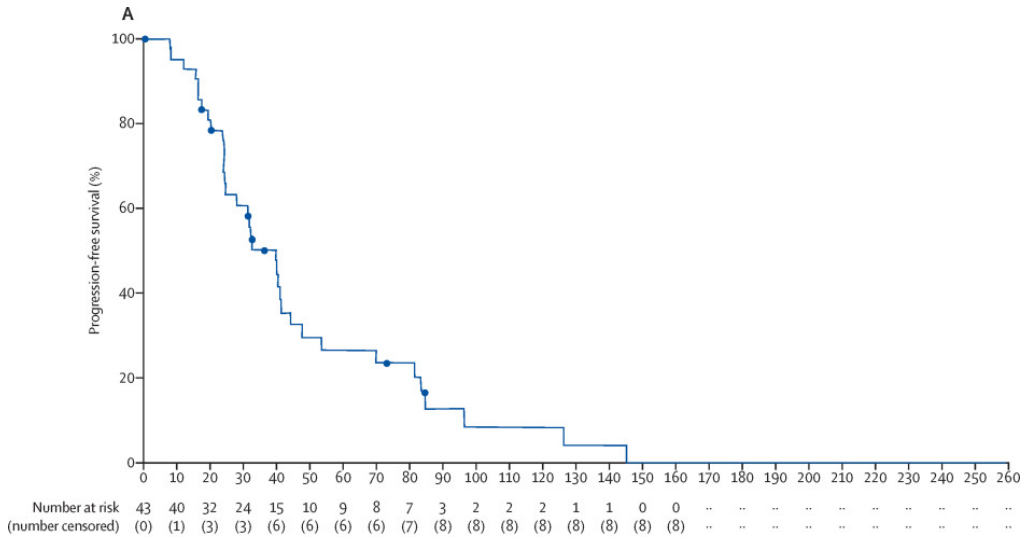
CCA, cholangiocarcinoma; CLC, cholangiolocarcinoma; dCCA, distal cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; IPNB, intraductal papillary neoplasm of the bile duct; ITPN, intraductal tubulopapillary neoplasm; pCCA, perihilar cholangiocarcinoma. [a]Markers from single-centre experience; international criteria and consensus on a definite panel of markers are still needed. [b]Mucin refers to histomorphological stains periodic acid–Schiff (PAS) or Alcian PAS.

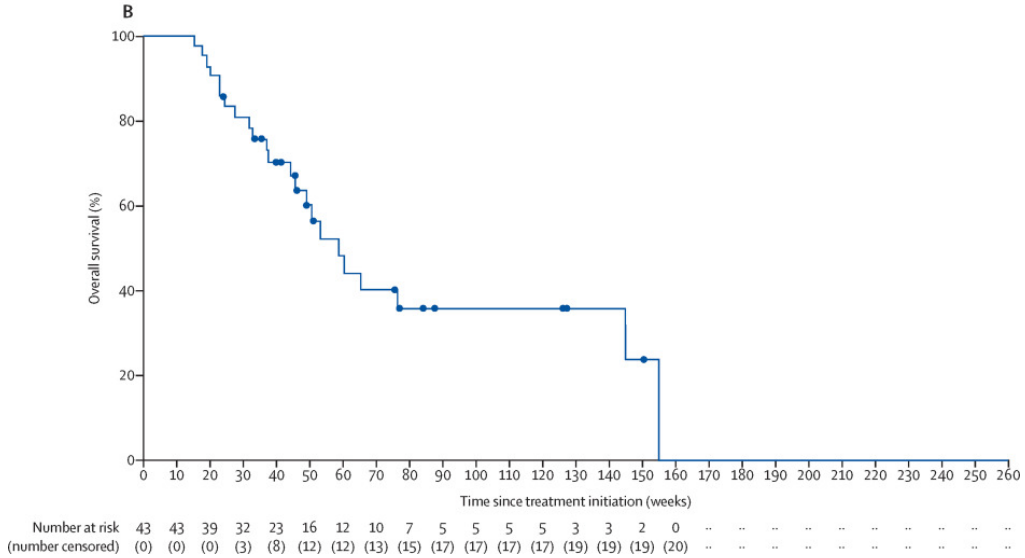
Nature Reviews Gastroenterology & Hepatology **volume 17**, pages557–588 (2020)

Dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial

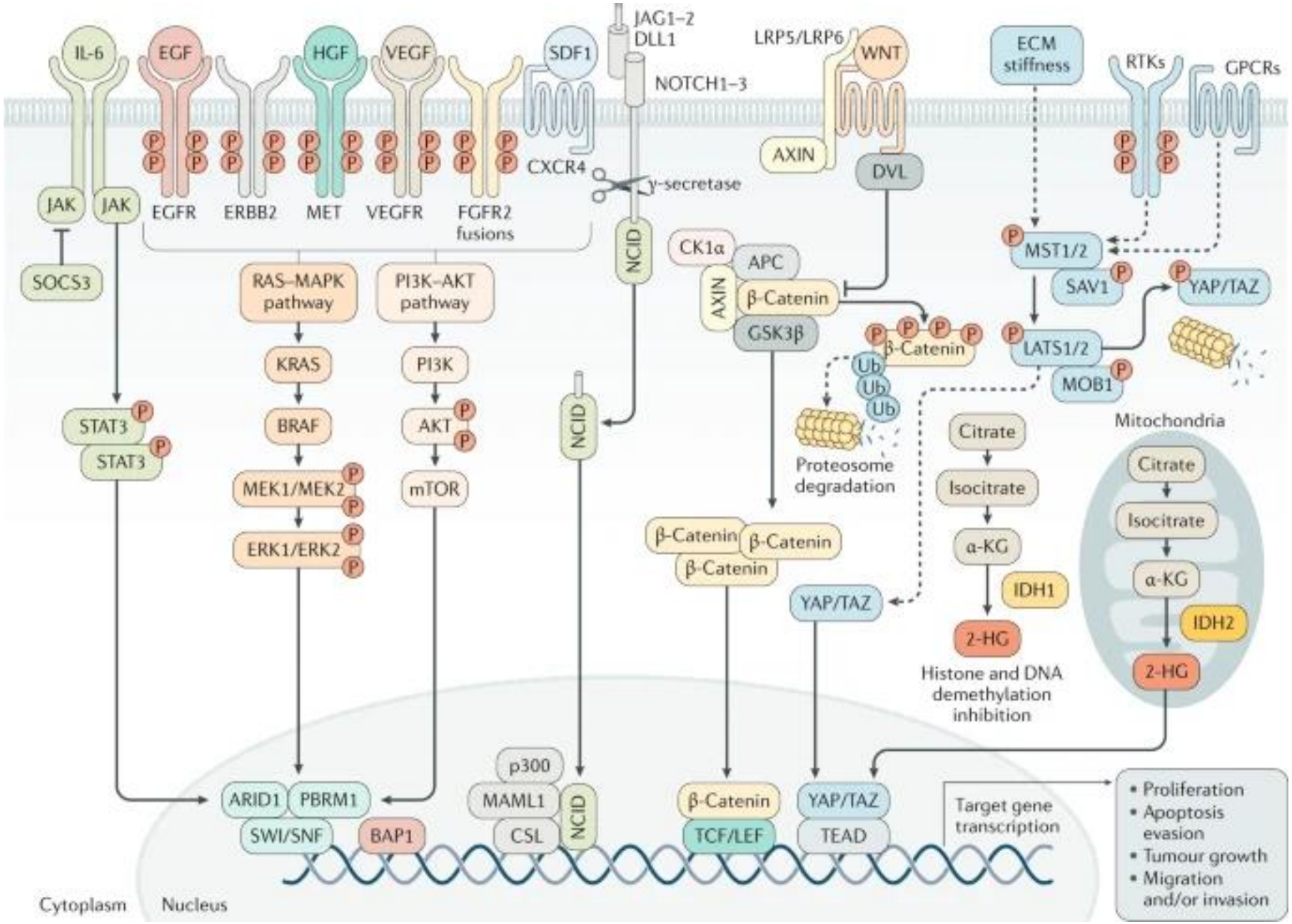




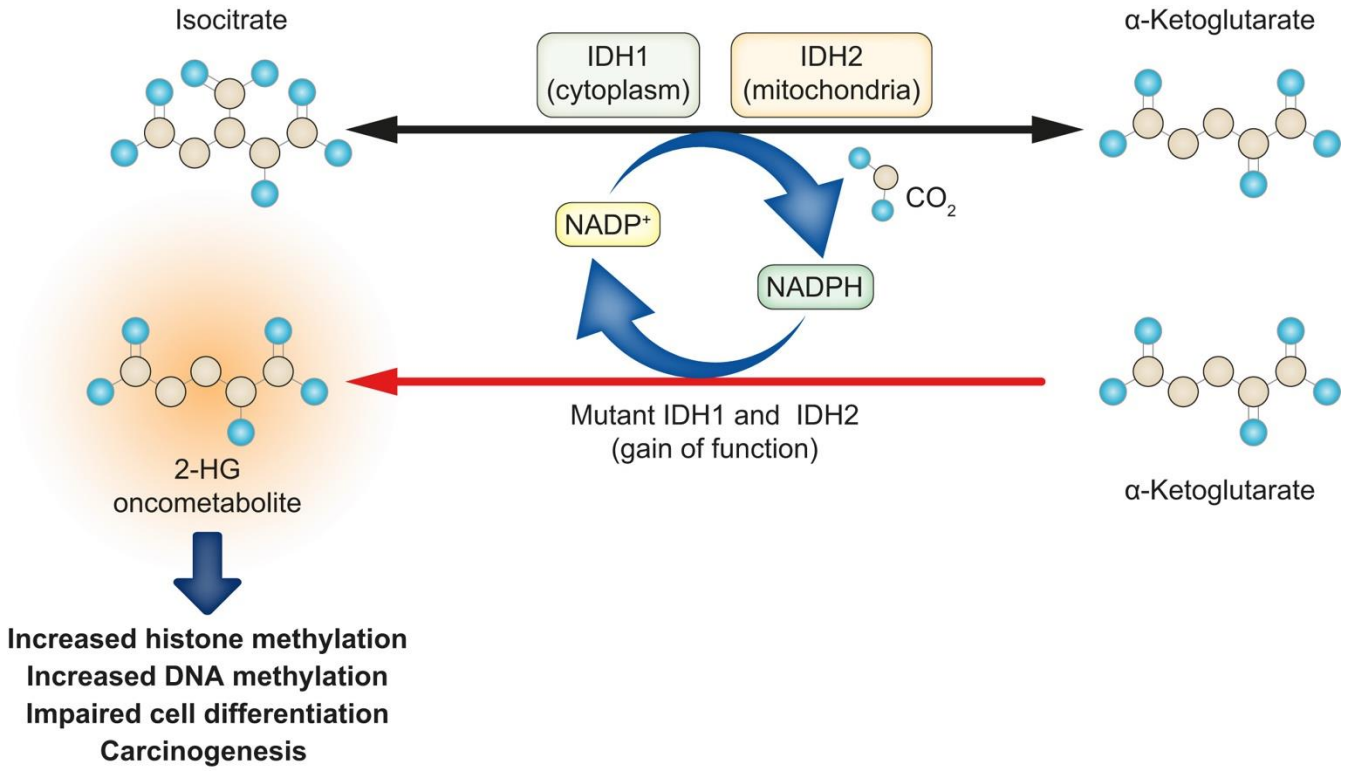




The Lancet VOLUME 21, ISSUE 9, P1234-1243, SEPTEMBER 01, 2020



Nature Reviews Gastroenterology & Hepatology **volume 17**, pages557–588 (2020)



Journal of Hepatology 2020 73170-185DOI: (10.1016/j.jhep.2020.03.007)

Changes in genetic expression

From: **Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial**

JAMA Oncol. Published online September 23, 2021. doi:10.1001/jamaoncol.2021.3836

JAMA Oncology

RCT: Efficacy of Ivosidenib for Patients With Advanced Cholangiocarcinoma With *IDH1* Mutation

POPULATION

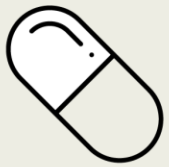
68 Men, 119 Women

Adults with cholangiocarcinoma with *IDH1* mutation and disease progression after 1 or 2 prior treatment regimens

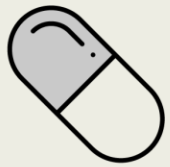
Median age (range), 62 y (33-83 y)

INTERVENTION

187 Patients randomized



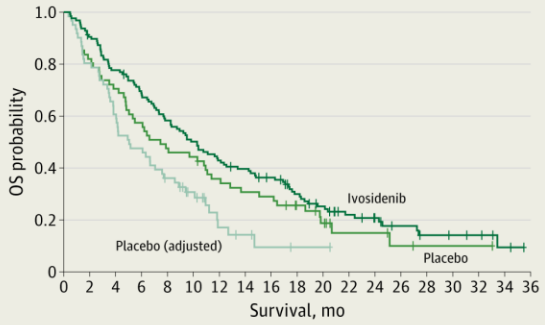
126 Ivosidenib
Ivosidenib, 500 mg once daily



61 Placebo
Placebo medication once daily (43 crossed over from placebo to ivosidenib at time of final analysis)

FINDINGS

Ivosidenib resulted in a favorable overall survival benefit vs placebo



Median overall survival:
Ivosidenib, 10.3 mo (95% CI, 7.8-12.4)
Placebo, 7.5 mo (95% CI, 4.8-11.1)
HR, 0.79 (95% CI, 0.56-1.12); 1-sided *P* =.09;
after adjustment for crossover from placebo to ivosidenib:
HR, 0.49 (95% CI, 0.34-0.70); 1-sided *P* <.001

SETTINGS / LOCATIONS

49 Hospitals in France, Italy, South Korea, Spain, UK, and US

PRIMARY OUTCOME

The primary outcome previously reported was progression-free survival by blinded independent radiology center. The key secondary outcome reported here was overall survival

Zhu AX, Macarulla T, Javle MM, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with *IDH1* mutation: the phase 3 randomized clinical ClarIDHy trial. *JAMA Oncol*. Published online September 23, 2021. doi:10.1001/jamaoncol.2021.3836

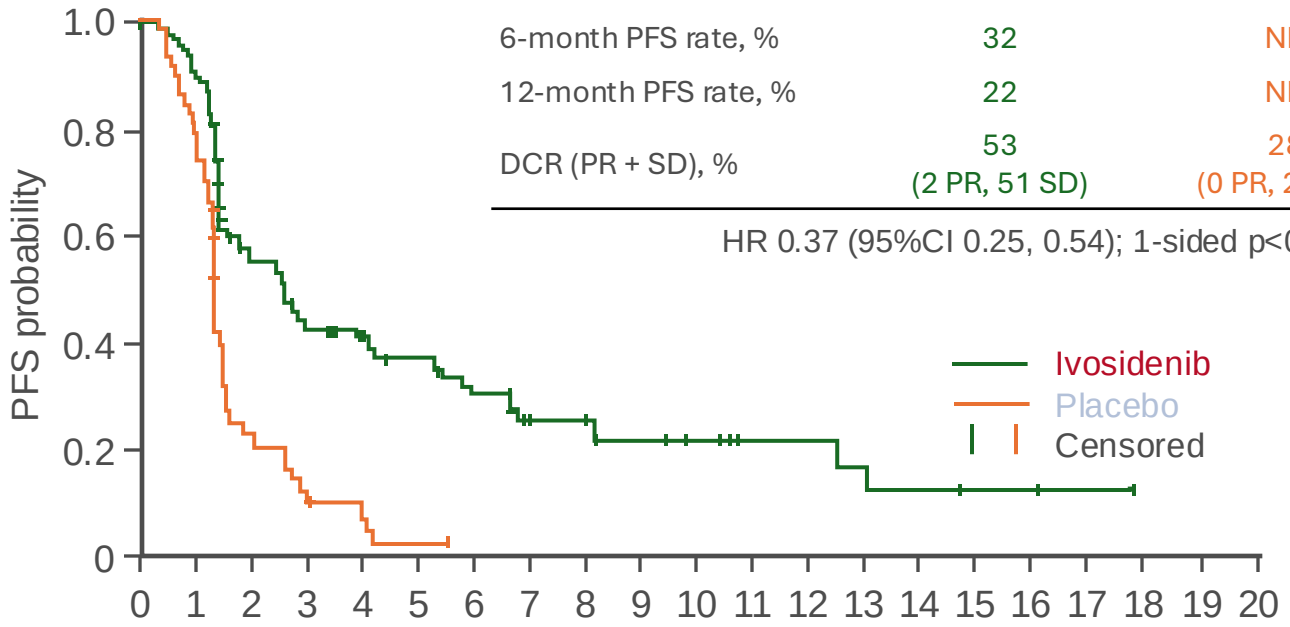
Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (IDH1) mutation

Key results

Progression-free survival

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

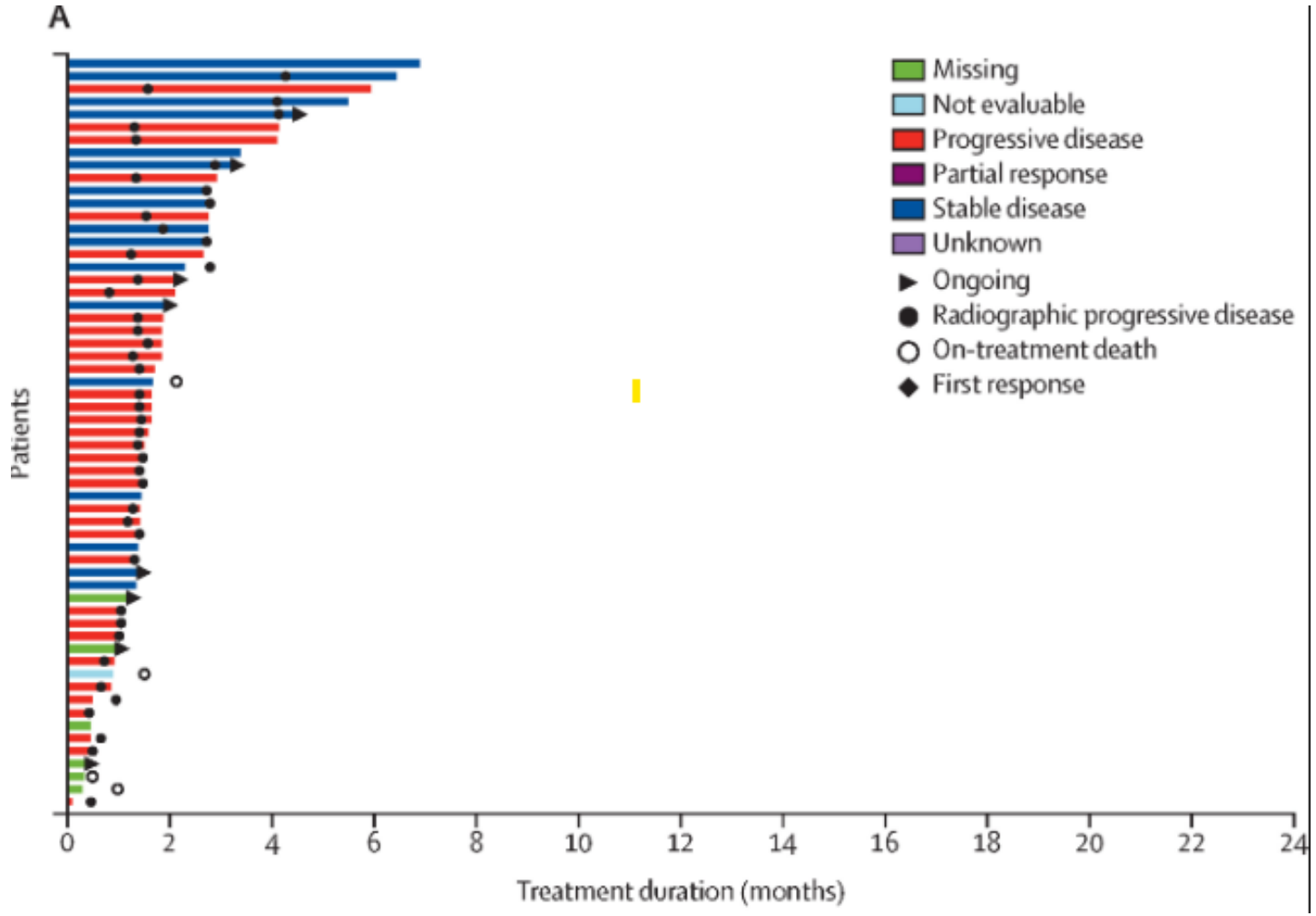
HR 0.37 (95%CI 0.25, 0.54); 1-sided p<0.0001



No. at risk

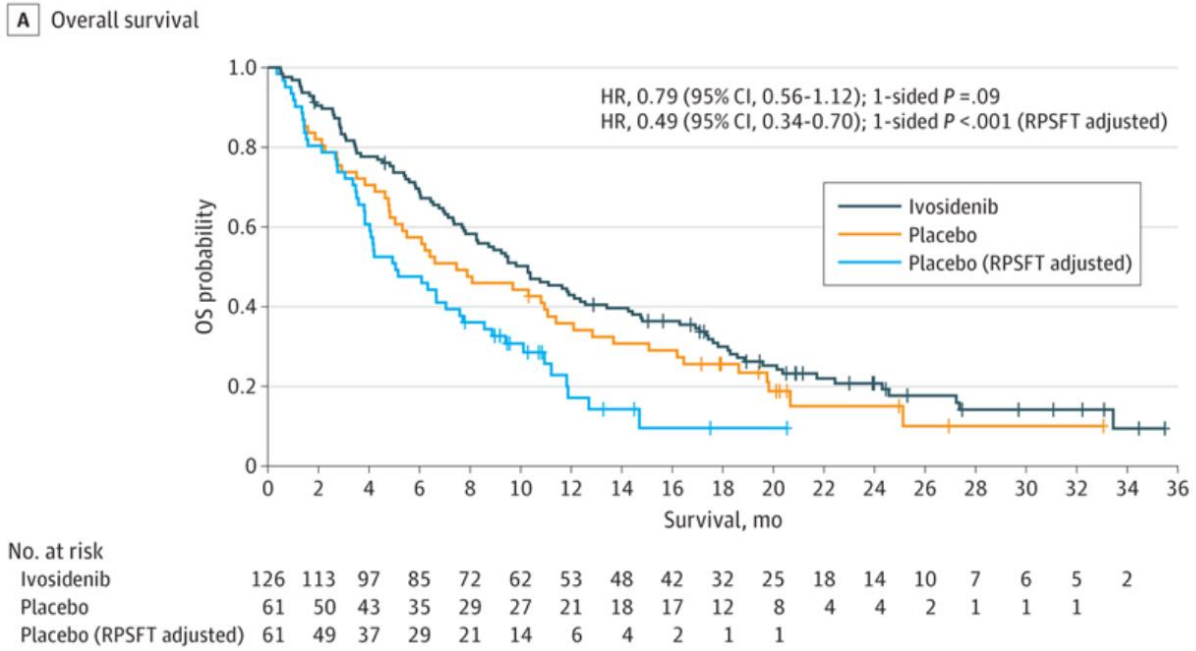
Ivosidenib	124	105	54	40	36	28	22	16	14	10	9	6	5	4	3	3	2	1	1
Placebo	61	46	11	6	4	1													

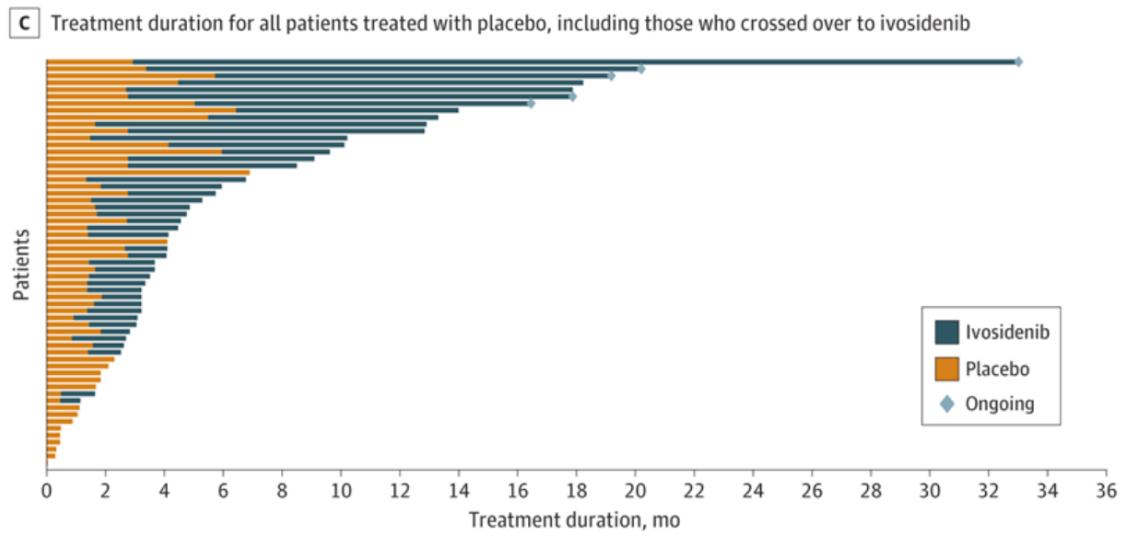
Zhu AX, et al. J Clin Oncol 2021;39(suppl):abstr 266



Abou-Alfa, Ghassan K et al.The Lancet Oncology, Volume 21, Issue 6, 796 - 807

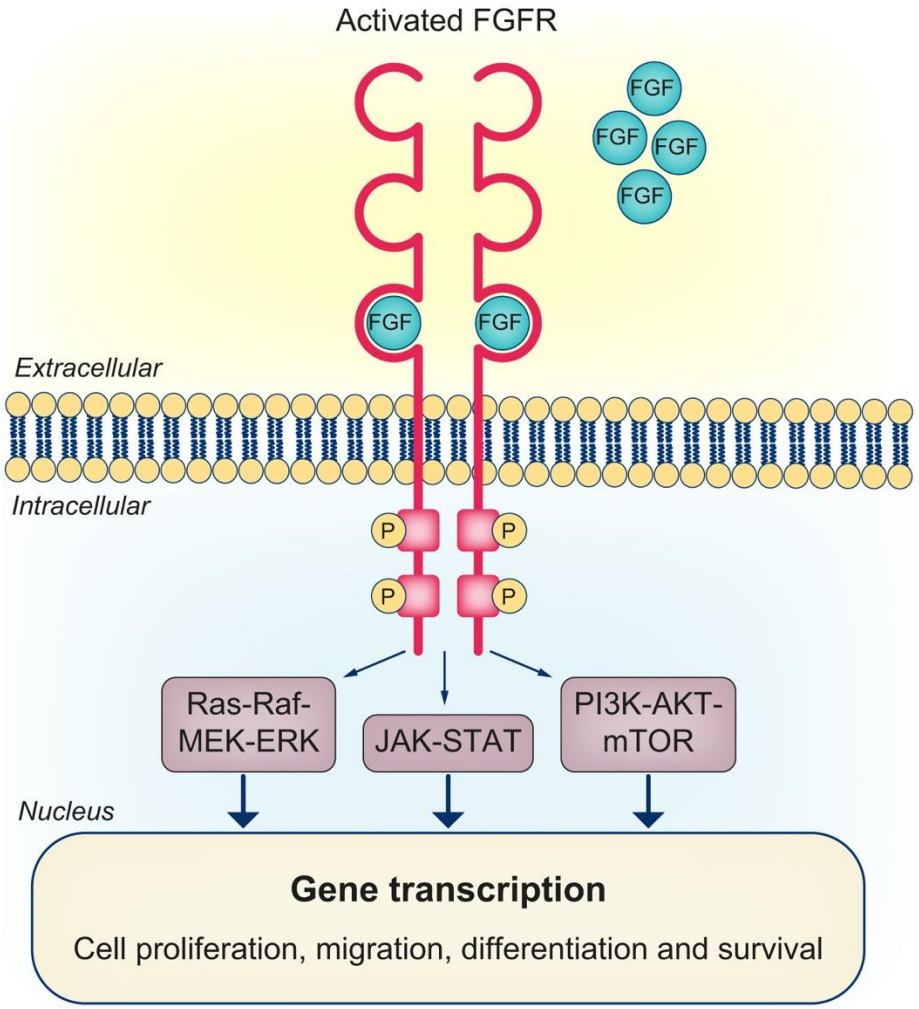
Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomize





Treatment group	Events/patients, No.	OS, median (95% CI), mo
Ivosidenib	100/126	10.3 (7.8-12.4)
Placebo	50/61	7.5 (4.8-11.1)
Placebo adjusted by RPSFT	49/61	5.1 (3.8-7.6)

JAMA Oncol. Published online September 23, 2021. doi:10.1001/jamaoncol.2021.3836



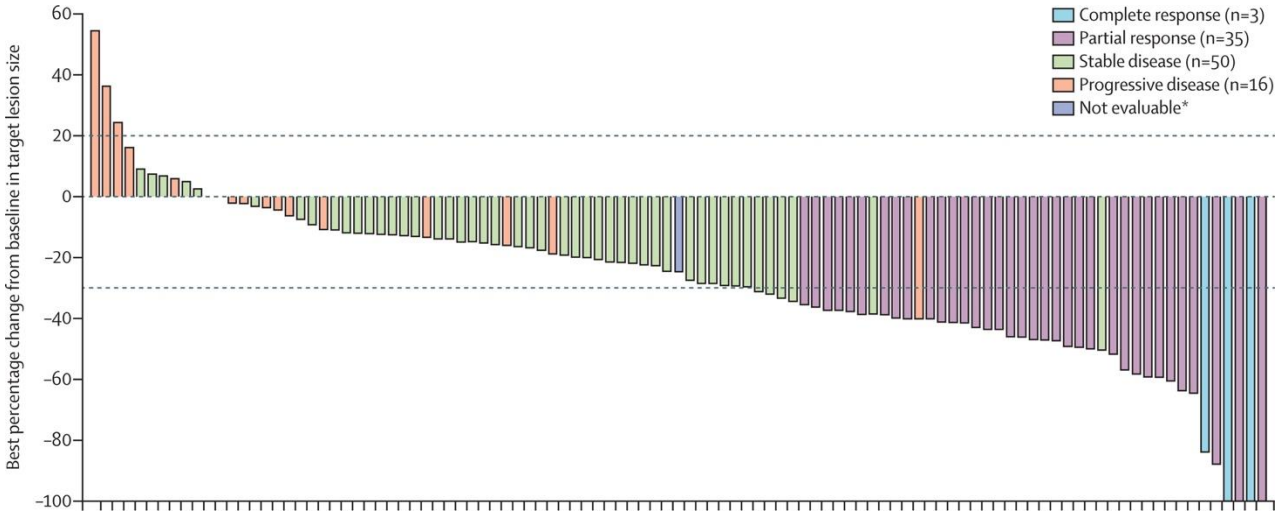
Journal of Hepatology 2020 73170-185DOI: (10.1016/j.jhep.2020.03.007)

Table 1. Current status of development of FGFR2 inhibitors in iCCA.

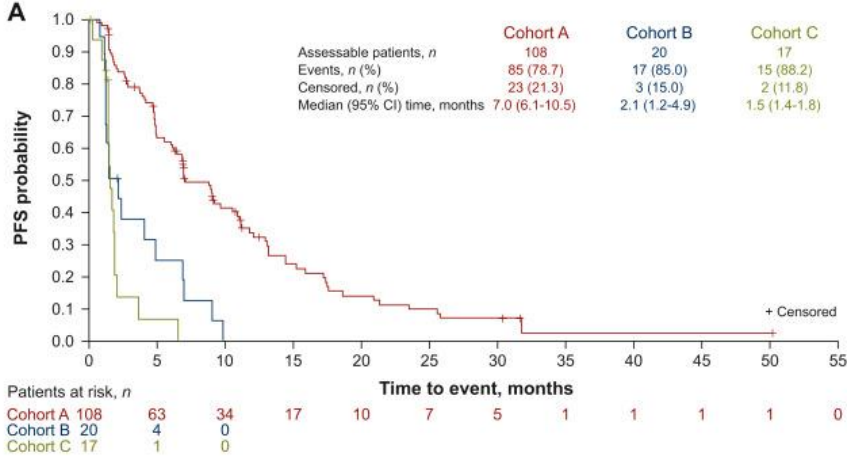
Drug; Author, reference	Type of molecule	Current status of drug development	CCA population tested	Treatment administered	Response rate achieved	Treatment-related toxicity
Pemigatinib-INCB054828 (Incyte®)[145,146]	Selective oral TKI Target: FGFR 1-3 and VEGFR2.	Phase II study (FIGHT-202; NCT02924376) presented ESMO[145] 2018 with updated data ESMO 2019.[146] Ongoing Phase III trial in the first-line setting (FIGHT-302; NCT03656536).	Previously treated CCA (146 patients). • Cohort A (*FGFR2* fusions): 107 patients (98% iCCA; 93% ≥2 prior therapies) • Cohort B (other FGF/FGFR alterations): 20 patients (65% iCCA). • Cohort C (no FGF/FGFR alterations): 18 patients (61% iCCA)	INCB054828 13.5 mg once daily on a 21-day cycle (2 weeks on, 1 week off) until disease progression or unacceptable toxicity.	• Cohort A (FGFR2 translocations): ORR: 35.5% (3 CR), mDOR: 7.5 months, DCR: 82% mPFS 6.9 months (95% CI 6.2–9.6) • Cohort B (other FGF/FGFR alterations): 0% PR; mPFS 1.4 months* • Cohort C (no FGF/FGFR alterations): 0% PR; mPFS 1.5 months*	Any grade: hyperphosphatemia (60%), alopecia (49%), diarrhoea (47%), fatigue (43%), nail toxicities (42%), and dysgeusia (40%). Grade 3/4 toxicities: hyponatremia (8%) and hypophosphatemia (7%)*. Discontinuation (9%), dose reduction (14%) and interruption (42%) due to AEs.
Infigratinib-BGJ398 (QED®/ Novartis®)[139,147]	Selective oral TKI Target: FGFR 1-3 (IC50 0.9, 1.4 and 1 nM, respectively)/ FGFR4 (IC50 60 nM).	Phase II study (NCT02150967) published in 2018[139] with updated data (+28 patients with FGFR2 fusion) presented ESMO 2018.[147] Ongoing Phase III trial in the first-line setting (PROOF; NCT03773302).	Previously treated CCA (61 patients → 84[$]) *FGFR2* fusions: 48 patients → expanded up to 71 patients[147$] • *FGFR2* mutation: 8 patients • *FGFR2* amplification: 3 patients	BGJ398 125 mg once daily for 21 days, then 7 days off (28-day cycles).	• PR: 14.8%; DCR: 75.4% • *FGFR2* fusions: 18.8% PR; DCR 83.3%; mPFS 5.8 months (9% CI 4.3–7.6) → expanded cohort[$]: 31.0% PR; DCR 83.6%, mPFS 6.8 months (95% CI 5.3–7.6) • *FGFR2* mutation: 0% PR • *FGFR2* amplification: 0% PR	Any grade: hyperphosphatemia (72.1%), fatigue (36.1%), stomatitis (29.5%), and alopecia (26.2%). Grade 3/4 (41%/66.2%[$]): hyperphosphatemia (16.4%/ 12.7%[$]), hypophosphatemia (14.1%[$]), mucositis (6.6%), and palmar-plantar erythrodysaesthesia (4.9%). Most common any grade TEAEs: hyperphosphatemia (73.2%), fatigue (49.3%), stomatitis (45.1%), alopecia (38.0%), and constipation
TAS-120 (futibatinib) (Taiho®)[148,149]	Highly selective (irreversible) oral TKI Target: FGFR 1-4 (inhibits all 4 subtypes of FGFR with enzyme IC50 values of 3.9 nM, 1.3 nM, 1.6 nM and 8.3 nM for FGFR1, FGFR2, FGFR3 and FGFR4, respectively) Inhibits mutant and wild-type FGFR2 with similar IC50 (wild-type FGFR2, 0.9 nM; V565I, 1–3 nM; N550H, 3.6 nM; E566G, 2.4 nM).	Safety and preliminary efficacy data available from phase I/II trial (presented ESMO Asia and ESMO GI 2018) (NCT02052778); phase II part currently recruiting.	Cohort of pretreated CCA (45 patients) harbouring FGF/FGFR aberrations. • *FGFR2* gene fusions: 28 patients (62%) • Other FGF/FGFR aberrations: 17 (38%) 13 patients received ≥1 prior reversible FGFRi.	TAS-120 (maximum tolerated dose defined as 20 mg once a day) until disease progression or unacceptable toxicity. CCA pts were enrolled at 16 mg (24 patients), 20 mg (14 patients), and 24 mg (7 patients) dosing levels.	• *FGFR2* fusions: 25% PR; SD 54%; DCR: 79% • Other FGF/FGFR aberrations: 3/17 (17.6%) PR (all had FGFR2 rearrangements; 1 also had *FGFR2* amplification) • Prior FGFRi: 4/13 (30.8%) P (3 with *FGFR2* gene fusions 1 with *FGFR2* amplification	
ARQ087-Derazantinib (Basilea/ ArQule®)[140,150]	Non-selective oral multi-TKI with potent pan-FGFR activity. Targets: RET, PDGFR, KIT, SRC, and FGFR1-3 (IC50 1.8 for FGFR2 IC50 4.5 for FGFR1 and FGFR3). IC50 for FGFR4 34 nM.	Preliminary data from the phase I/II basket trial indicated activity in FGFR2 fusion-positive iCCA (3/12 (25%) PR) (NCT01752920).[140] Data for iCCA with FGFR2 fusion were separately reported.[150] Currently being evaluated in a phase II trial in iCCA (FIDES-01 trial; NCT03230318).	Pretreated iCCA patients (35 patients) with *FGFR2* genetic aberrations. 29/35 patients had *FGFR2* fusion-positive tumours.	ARQ087 300 (33 patients) or 400 mg (2 patients) daily until disease progression or unacceptable toxicity. Recommended phase II dose: 300 mg QD.[163]	• 30 patients evaluable for response: 20% PR (all *FGFR2* fusion-positive) • *FGFR2* fusion-positive patients[£]: 20.7% PR; 82.8% DCR, mPFS 5.7 months.	Any grade (89%): nausea (37%), dry mouth (29%), asthenia (26%), fatigue (23%), vomiting (23%), abnormal LFTs (20%), dysgeusia (20%), alopecia (14%), diarrhoea (14%), vision blurred (14%), and conjunctivitis (11%). Grade 3/4: asthenia (6%), and abnormal LFTs (6%).
Debio1347 (Debiopharm Group ®)[151,152]	Selective oral TKI Target: FGFR 1-3 (IC50 of 9.3 nM, 7.6 nM, 22 nM, and 290 nM for FGFR1, FGFR2, FGFR3, and FGFR4, respectively).	Safety shown in phase I trial (NCT1948297). CCA data reported by Cleary *et al.*[151] and Ng 2019.[152] Currently phase II basket trial ongoing recruiting patients with *FGFR1-3* fusions (tumour-agnostic) (FUZE trial; NCT03834220).	Patients with pretreated biliary tract (iCCA (6 patients; 3 *FGFR2* fusion) and GBC (2 patients; none with *FGFR2* fusions) with alterations of FGFR 1, 2, or 3. Separately, data on 9 CCA[152] (all iCCA; 5 *FGFR2* fusion) were reported[&].	Debio 1347 at doses between 60 and 150 mg orally daily in 28-day cycles until disease progression or unacceptable toxicity.	• 1/8 PR (*FGFR2* deletion); DCR 62.5%. • For the iCCA updated cohort[&]: 2/9 (22%) PR (1 in a patient with *FGFR2* translocation).	Any grade: hyperphosphatemia (8/8), nail changes (5/8), nausea (5/8), dry mouth (4/8) and stomatitis (3/8). Grade ≥3: hyperphosphatemia (4/8); (33%[&]).
JNJ-42756493-Erdafitinib (Janssen®)[153,154]	Selective oral TKI Target: FGFR 1–4 (IC50 <1 nM).	Phase I trial data available (NCT01703481); new trial ongoing and recruiting cohort of cholangiocarcinoma (NCT02699606).	Patients with re-treated solid tumours harbouring activating *FGFR* genomic alterations (187 patients; 11 CCA).	JNJ-42756493-dose escalation: 9 mg once daily and 10 mg intermittently (7 days on/7 days off), as previously published.[187]	• CCA cohort in response evaluable patients with *FGFR* mutation/fusion: 27.3% (3/11) PR (all at 10 mg dose). • Updated data[@]: mDOR 12.9 months; DCR: 55%; mPFS: 5.1 months (1.6–16.4).	Any grade[@]: stomatitis (82%), hyperphosphatemia (64%), dry mouth (55%), dysgeusia (45%), dry skin (45%), and asthenia (45%) Grade ≥3[@]: stomatitis (18%).

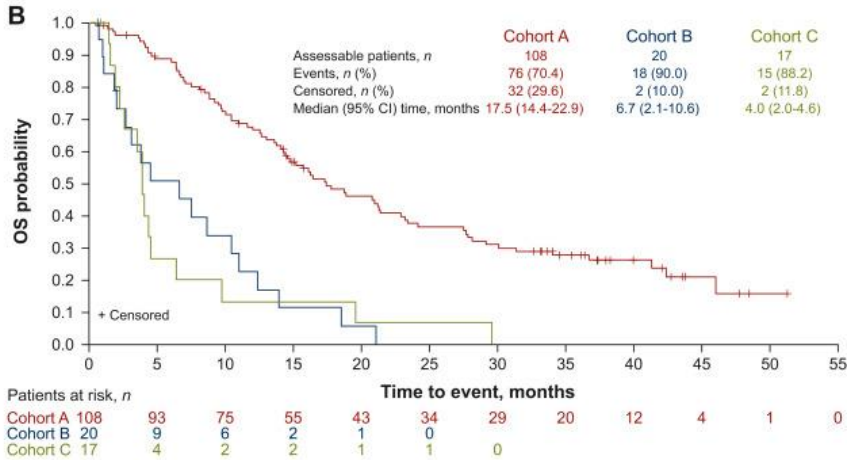
Data extracted from.[139,140,145–154] IC50 data also extracted from.[162]
AEs, adverse events; CCA, cholangiocarcinoma; CR, complete response; DCR, disease control rate; FGFR, fibroblast growth factor receptor; GBC, gallbladder cancer; IC50, half maximal inhibitory concentration; iCCA, intrahepatic cholangiocarcinoma; LFTs, liver function tests; mDOR, median duration of response; mPFS, median progression-free survival; PDGFR, platelet-derived growth factor receptor; PR, partial response; ORR, objective response rate; TEAEs, treatment-emergent adverse events; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
*Data from.[145]
[$]Data from expanded *FGFR2* fusion cohort patients.[147]
[£]Data for patients with *FGFR2* fusion only.[150]
[&]Cohort of 9 patients with CCA.[152]
[@]Updated data CCA cohort.[154]

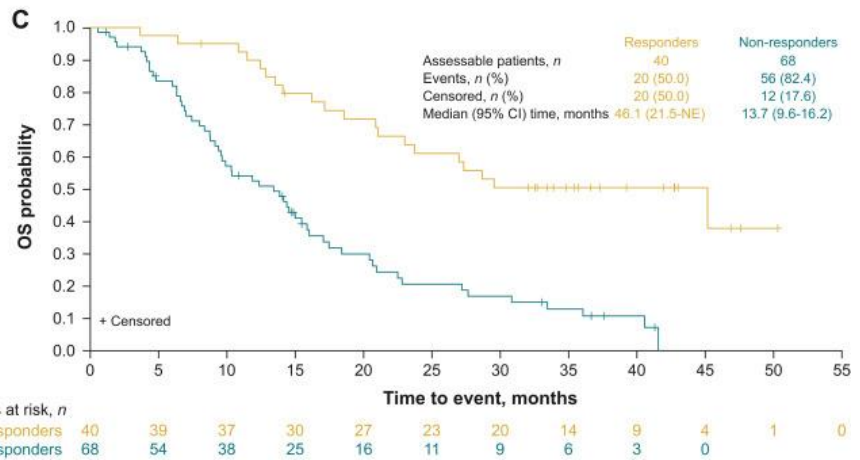
An open-label study of pemigatinib in cholangiocarcinoma: final results from FIGHT-202



(A) FGFR2 rearrangements or fusions
(B) other *FGF*/*FGFR* alterations
(C) no *FGF*/*FGFR* alterations







ESMO Open Volume 9, Issue 6, June 2024, 103488

Table 3. Treatment-related treatment-emergent adverse events (safety-assessable population)

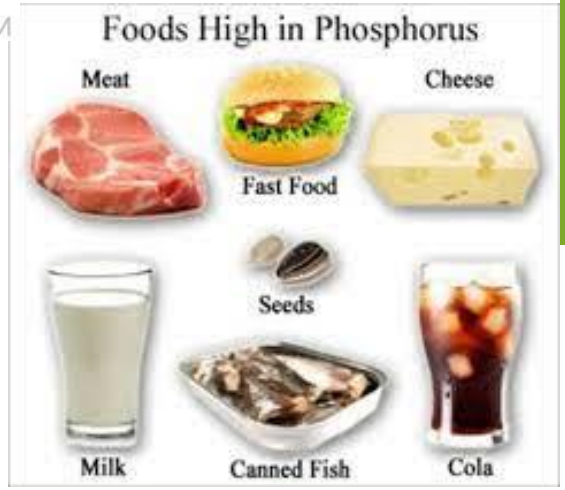
Events	*FGFR2* fusions or rearrangements ($n = 108$)		Other *FGF/FGFR* alterations ($n = 20$)		No *FGF/FGFR* alterations ($n = 17$)		Total ($N = 147$)[a]	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any treatment-related TEAE, *n* (%)[b]	102 (94.4)	40 (37.0)	17 (85.0)	6 (30.0)	14 (82.4)	1 (5.9)	135 (91.8)	48 (32.7)
Hyperphosphatemia	55 (50.9)	0	11 (55.0)	0	12 (70.6)	0	79 (53.7)	0
Alopecia	61 (56.5)	0	3 (15.0)	0	2 (11.8)	0	68 (46.3)	0
Diarrhea	44 (40.7)	4 (3.7)	5 (25.0)	0	4 (23.5)	1 (5.9)	53 (36.1)	5 (3.4)
Stomatitis	43 (39.8)	9 (8.3)	4 (20.0)	0	3 (17.6)	0	51 (34.7)	9 (6.1)
Dysgeusia	42 (38.9)	0	3 (15.0)	0	3 (17.6)	0	50 (34.0)	0
Fatigue	38 (35.2)	2 (1.9)	4 (20.0)	0	6 (35.3)	0	48 (32.7)	2 (1.4)
Dry mouth	38 (35.2)	0	2 (10.0)	0	1 (5.9)	0	43 (29.3)	0
Nausea	32 (29.6)	2 (1.9)	2 (10.0)	0	3 (17.6)	0	38 (25.9)	2 (1.4)
Decreased appetite	25 (23.1)	0	5 (25.0)	1 (5.0)	4 (23.5)	0	35 (23.8)	1 (0.7)
Dry eye	33 (30.6)	0	0	0	0	0	34 (23.1)	1 (0.7)
Dry skin	24 (22.2)	1 (0.9)	0	0	0	0	26 (17.7)	1 (0.7)
Arthralgia	21 (19.4)	5 (4.6)	2 (10.0)	1 (5.0)	0	0	23 (15.6)	6 (4.1)
Palmar–plantar erythrodysesthesia syndrome	22 (20.4)	6 (5.6)	1 (5.0)	0	0	0	23 (15.6)	6 (4.1)
Constipation	21 (19.4)	0	1 (5.0)	0	0	0	22 (15.0)	0
Hypophosphatemia	17 (15.7)	11 (10.2)	2 (10.0)	2 (10.0)	0	0	19 (12.9)	13 (8.8)
Vomiting	15 (13.9)	1 (0.9)	1 (5.0)	0	1 (5.9)	0	17 (11.6)	1 (0.7)
Pain in extremity	15 (13.9)	0	0	0	0	0	15 (10.2)	0
Weight decreased	11 (10.2)	1 (0.9)	3 (15.0)	0	0	0	14 (9.5)	1 (0.7)
Hyponatremia	3 (2.8)	1 (0.9)	3 (15.0)	3 (15.0)	2 (11.8)	0	8 (5.4)	4 (2.7)

FGF, fibroblast growth factor; FGFR, FGF receptor; TEAE, treatment-emergent adverse event.

[a]Total number includes two patients who did not have confirmed *FGF/FGFR* status by central laboratory testing and were not assigned to any cohort.

[b]All any-grade TEAEs occurring in ≥10% and grade ≥3 TEAEs occurring in ≥2% of the total population are shown.

"That's pork—the meat of the pig. It makes an excellent substitute for tofu."

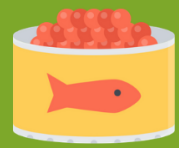


27 High Phosphorus Foods

Beverages
beer/ale
chocolate drinks
cocoa
dark colas
drinks made with milk
canned iced teas
beverages w. phosphate

Dairy Products
cheese
liquid nondairy creamer
custard
ice cream
milk
pudding
cream soups
most yogurt

Protein
oysters
sardines
beef liver
chicken liver
fish roe
organ meats

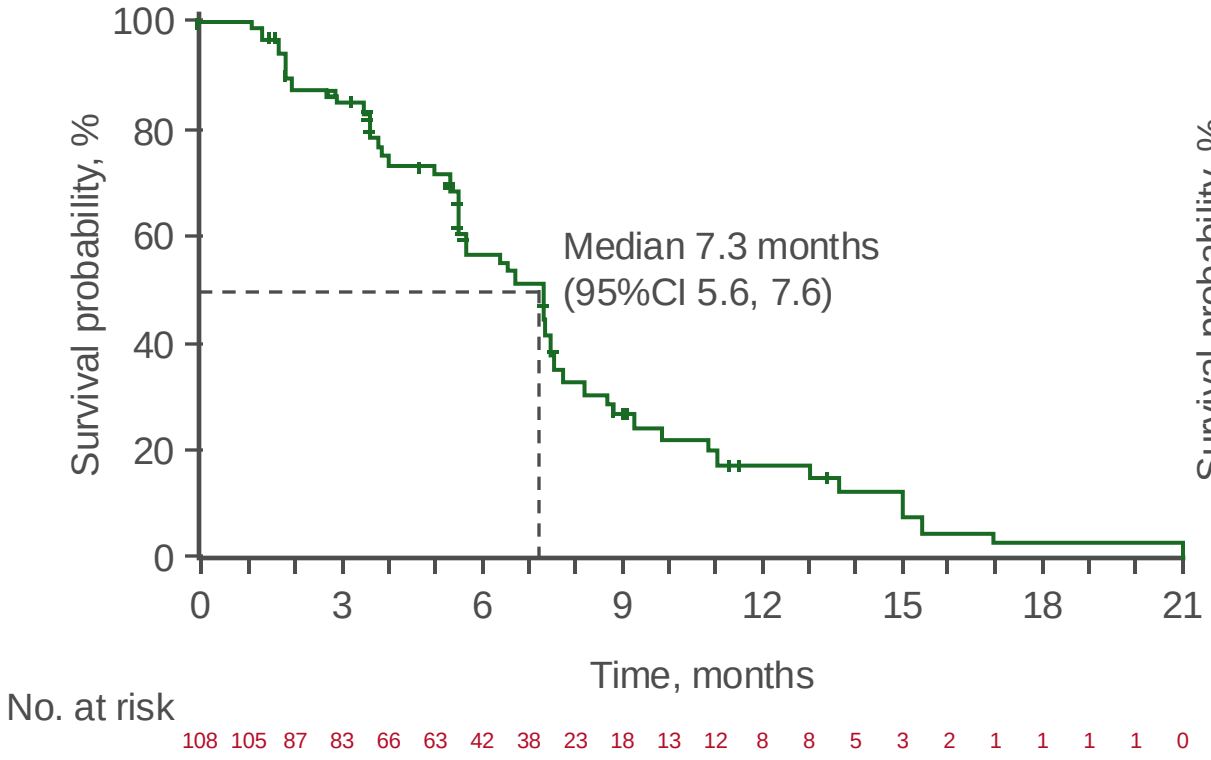


Other
chocolate candy
caramels
oat bran muffin
processed foods
pizza
brewer's yeast

Final results from a phase II study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously treated advanced cholangiocarcinoma harboring an FGFR2 gene fusion or rearrangement

Key results

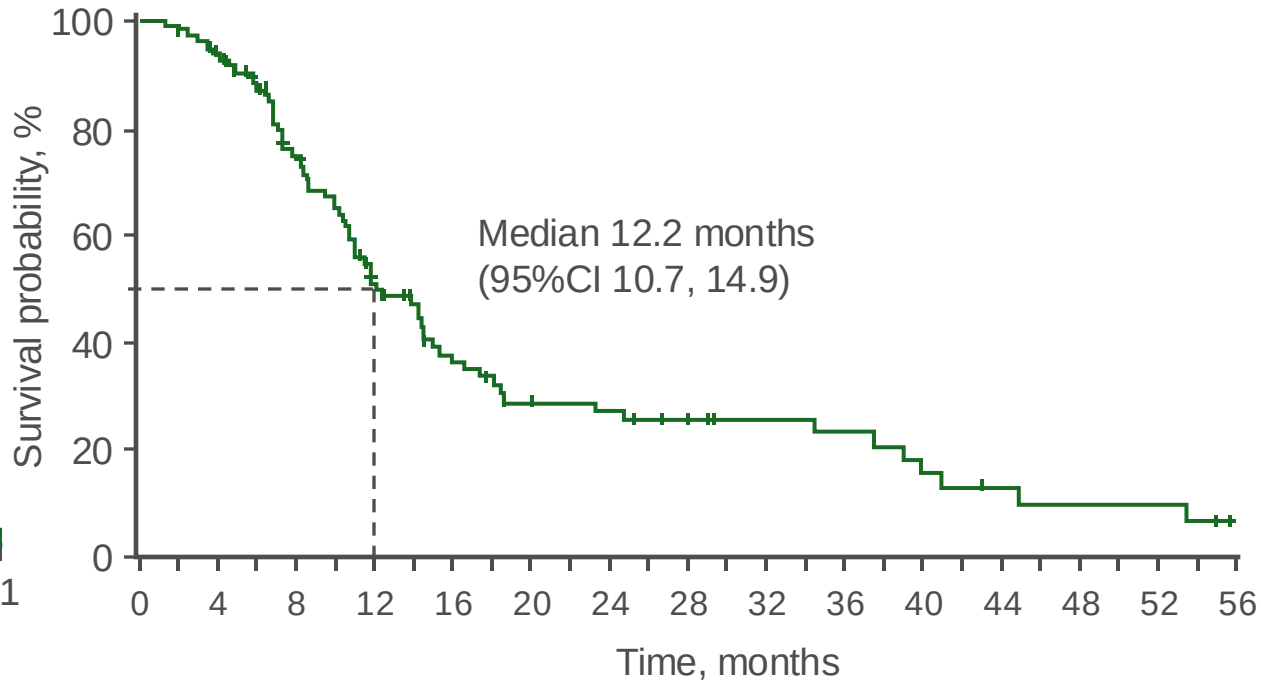
Progression-free survival



No. at risk

108	105	87	83	66	63	42	38	23	18	13	12	8	8	5	3	2	1	1	1	0

Overall survival



108	105	96	83	66	58	41	35	26	22	18	17	16	14	13	10	10	10	9	8	7	5	4	3	3	3	3	2	0

Javle MM, et al. J Clin Oncol 2021;39(suppl):abstr 265

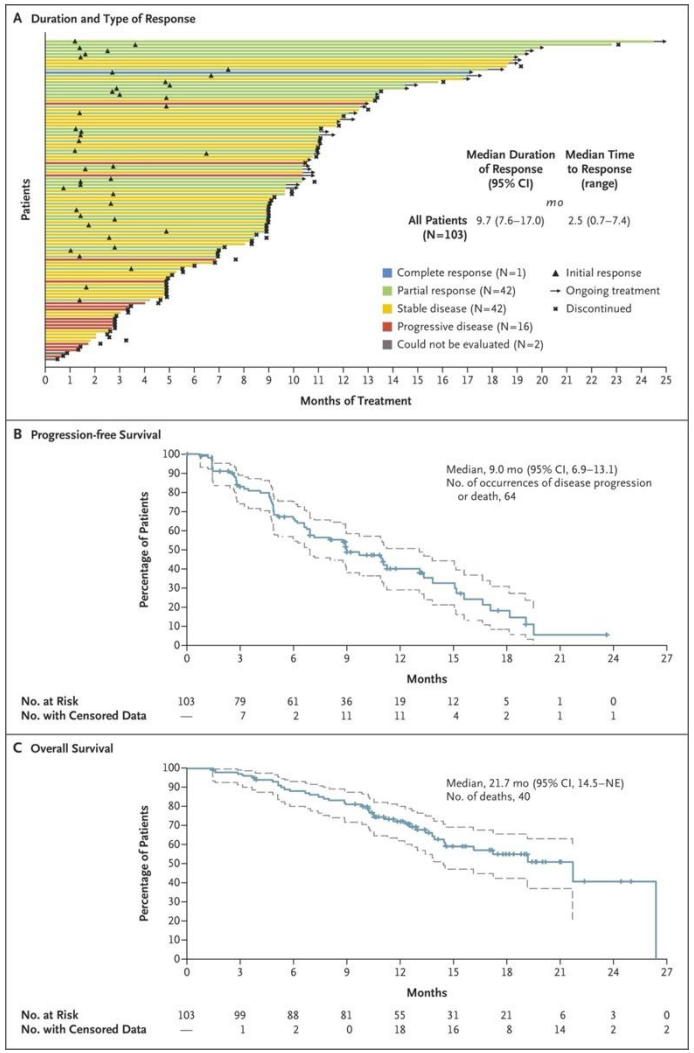
Inhibitory Activity of Futibatinib, Pemigatinib, Infigratinib, and Erdafitinib against Acquired Resistance Mutations in the FGFR2 Kinase Domain.

FGFR2 Mutation	Kinase Domain Region	Factor Change in IC_{50} vs. Wild-Type *FGFR2*			
		Futibatinib	Pemigatinib	Infigratinib	Erdafitinib
Wild-type	—	1	1	1	1
N550D	Regulatory triad	2	102	81	10
N550K	Regulatory triad	8	164	68	13
V563L	—	3	5	14	1
V565I	Gatekeeper	4	42	>236	1
V565L	Gatekeeper	44	335	>236	23
E566A	Regulatory triad	3	8	12	1
E566G	Regulatory triad	2	6	10	1
K642I	Regulatory triad	2	20	15	22
K642R	Regulatory triad	2	7	16	1
K660M	Activation loop	5	23	63	19

Goyal L et al. N Engl J Med2023;388:228-239

The NEW ENGLAND JOURNAL of MEDICINE

Duration and Type of Response, Progression-free Survival, and Overall Survival among Patients Who Received Futibatinib.



Goyal L et al. N Engl J Med2023;388:228-239

The NEW ENGLAND JOURNAL of MEDICINE

HER2 Expression in BTCs

ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; Bp, perihilar; Bd, distal; GBC, gallbladder cancer; AVC, Ampulla of Vater cancer.

- In BTCs, HER2 overexpression, gene amplification, or both have been reported in several studies, and HER2-positive rates in GBC, ECC, and ICC are estimated to be 30%, 10–20%, and 5%, respectively.[1]
- Through our preliminary study, we confirmed that the HER2 expression patterns in BTCs are more similar to those of gastric cancer than breast cancer, including heterogeneity.
- We also recently reported on the HER2 expression status according to the guidelines for HER2 testing in gastroesophageal adenocarcinoma in 454 cases (Table).[2]

	ICC	ECC-Bp	ECC-Bd	GBC	AVC
HER2-positive rate (%)	3.7	3.0	18.5	31.3	16.4

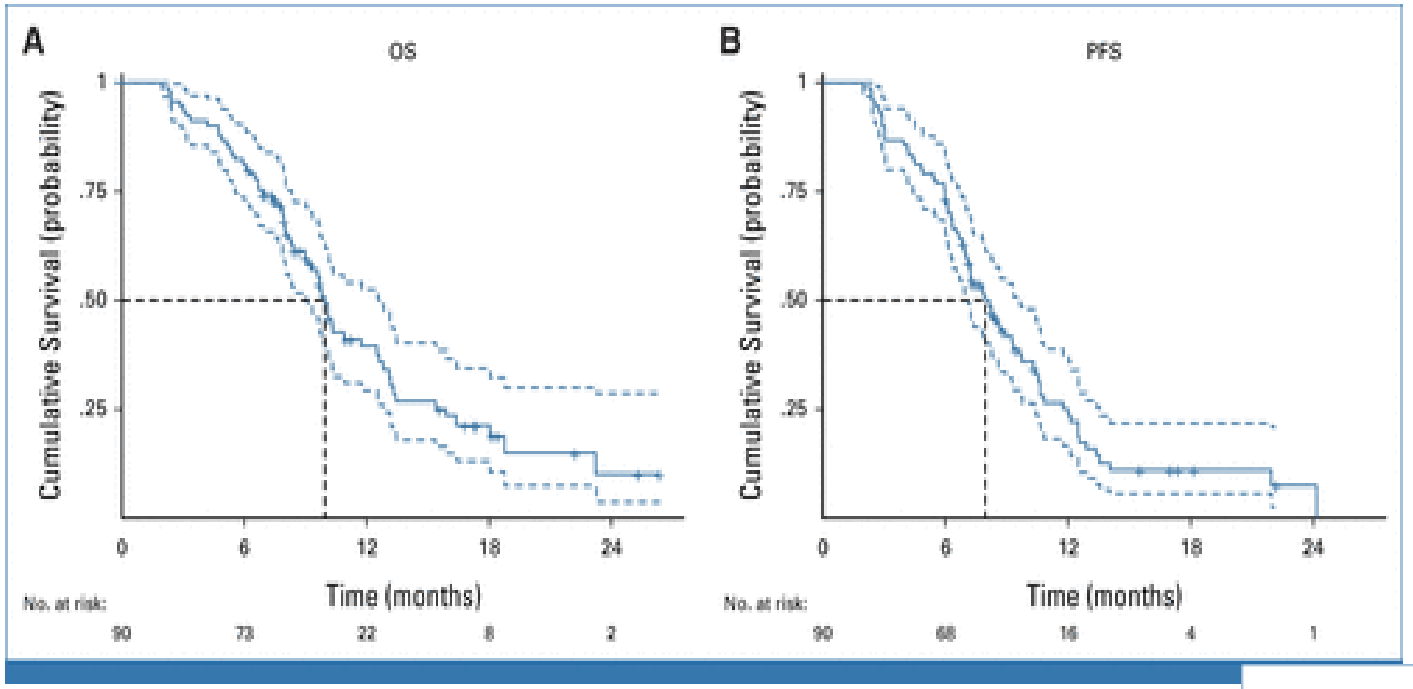
1. Cancer Discov 2017;7:943–62. 2. Hum Pathol 2020;105:9.

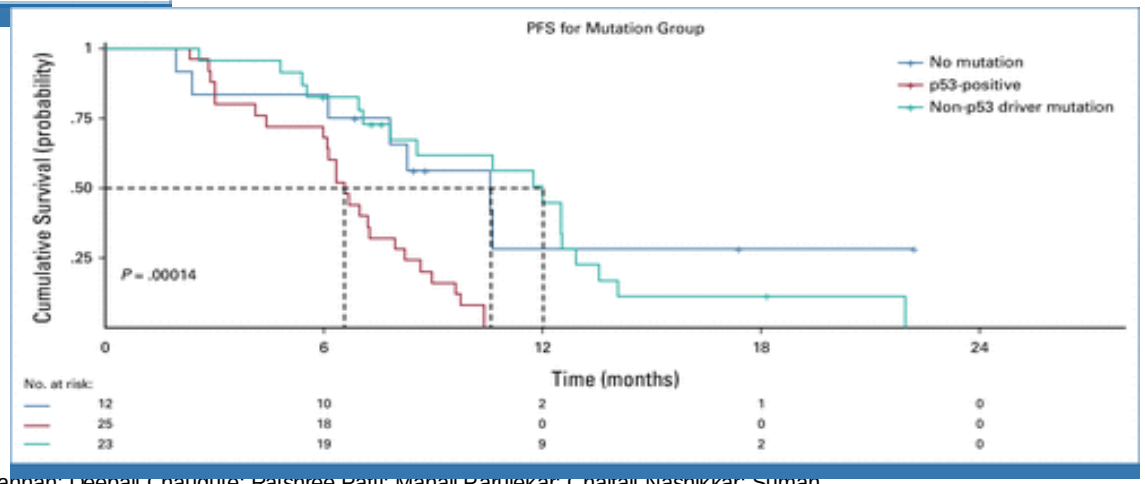
Screening Study (HERB preSCR)

- BTC pts were screened by central pathological examination using IHC and ISH in archival tissue at the SCRUM-Japan 30 sites into HER2-positive (defined as IHC 3+ or IHC 2+/ISH +), HER2-low-expressing (defined as IHC/ISH status of 0/+, 1+/-, 1+/+, or 2+/-), or HER2-negative (defined as IHC/ISH status of 0/-) pts.
- Between Mar 2019 and Mar 2020, 300 BTC pts were screened. Of the 296 pts with IHC and ISH results, 61 pts had HER2-positive, and 120 pts had HER2-low-expressing tumors.

n=296	**Positive (n=61, 20.6%)**		**Low-expressing (n=120, 40.5%)**				**Neg. (38.9%)**	
IHC	3+		2+		1+		0	
ISH	+	-	+	-	+	-	+	-
n	17	0	44	53	8	49	10	115

Trastuzumab Plus Gemcitabine-Cisplatin for Treatment-Naïve Human Epidermal Growth Factor Receptor 2-Positive Biliary Tract Adenocarcinoma





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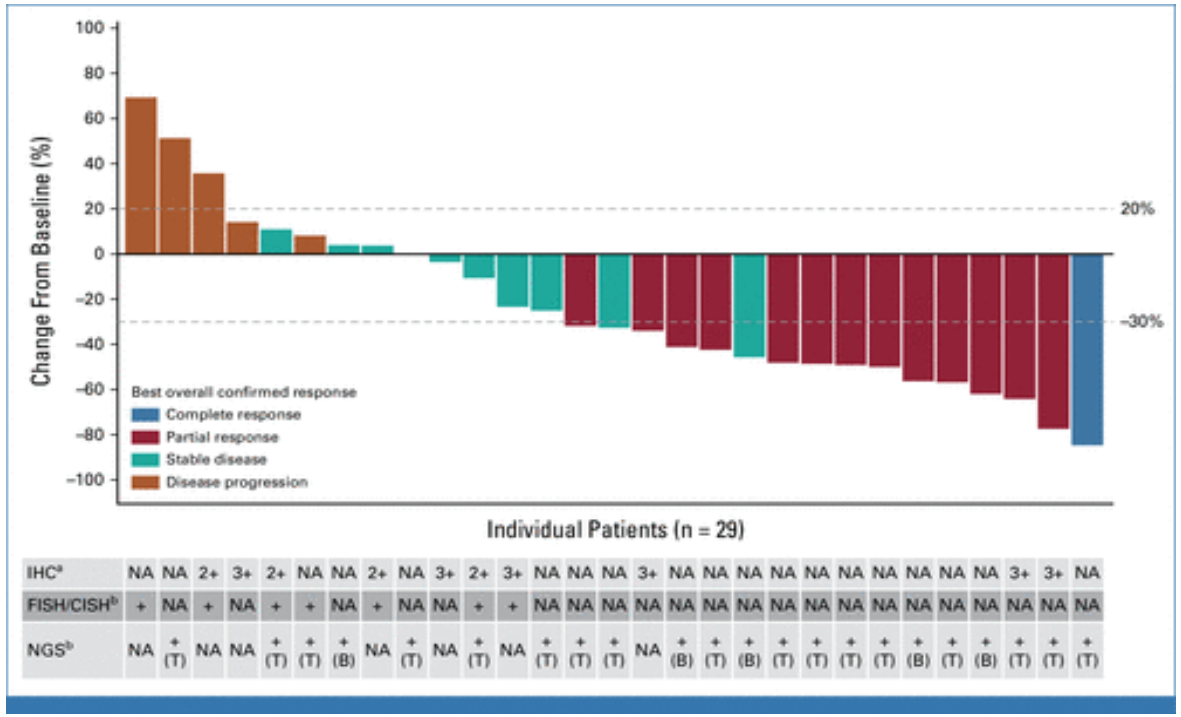
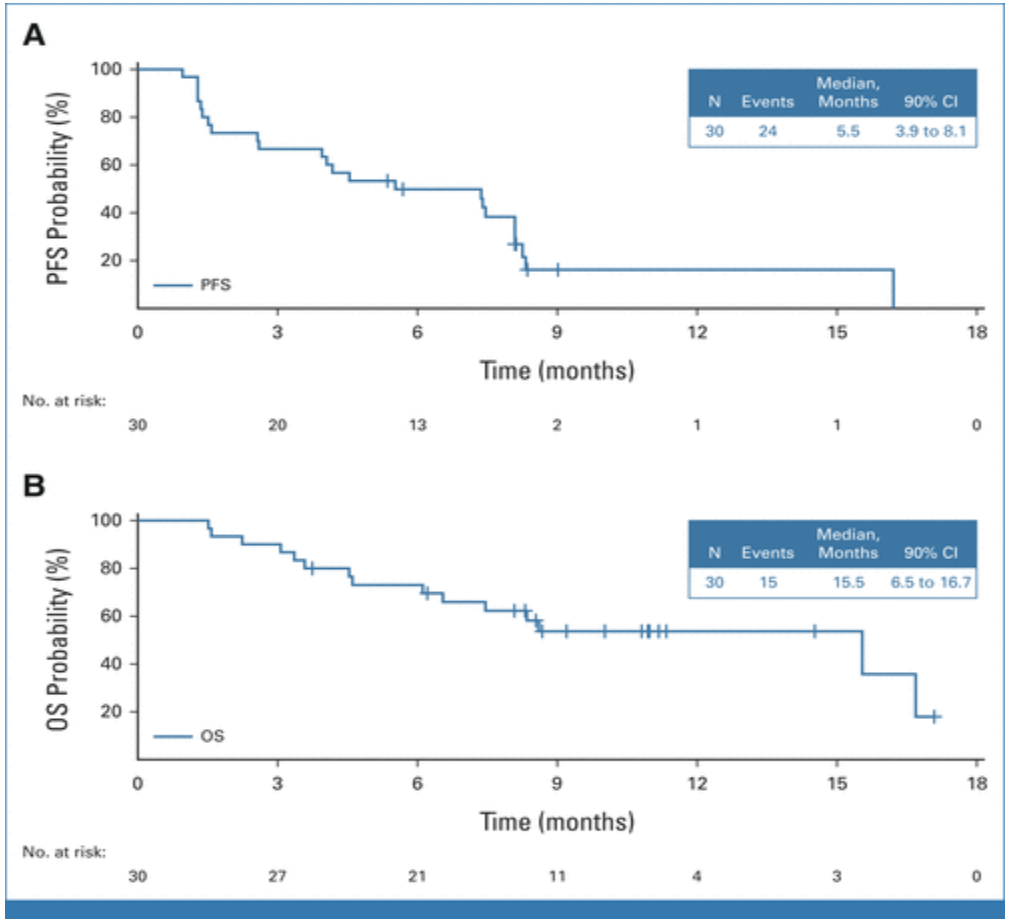
DOI: 10.1200/JCO.23.01193

Tucatinib and Trastuzumab for Previously Treated Human Epidermal Growth Factor Receptor 2–Positive Metastatic Biliary Tract Cancer (SGNTUC-019): A Phase II Basket Study





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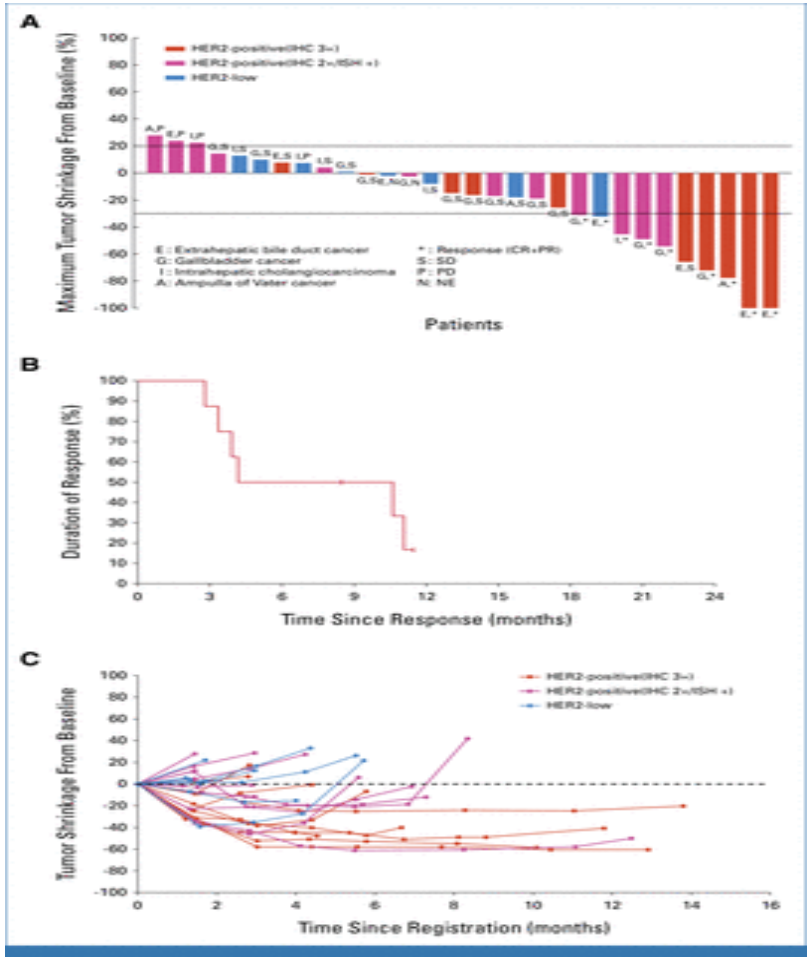
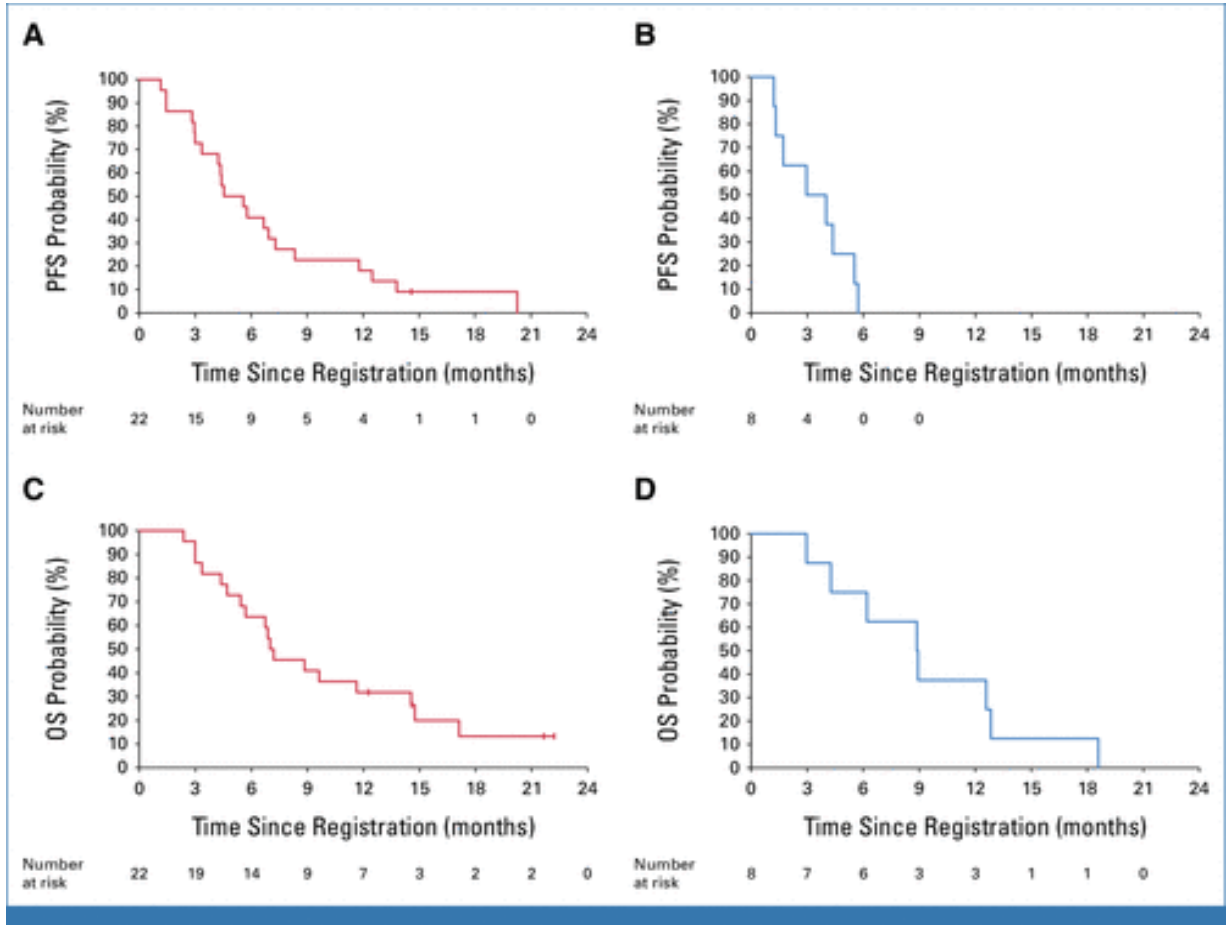
DOI: 10.1200/JCO.23.00606

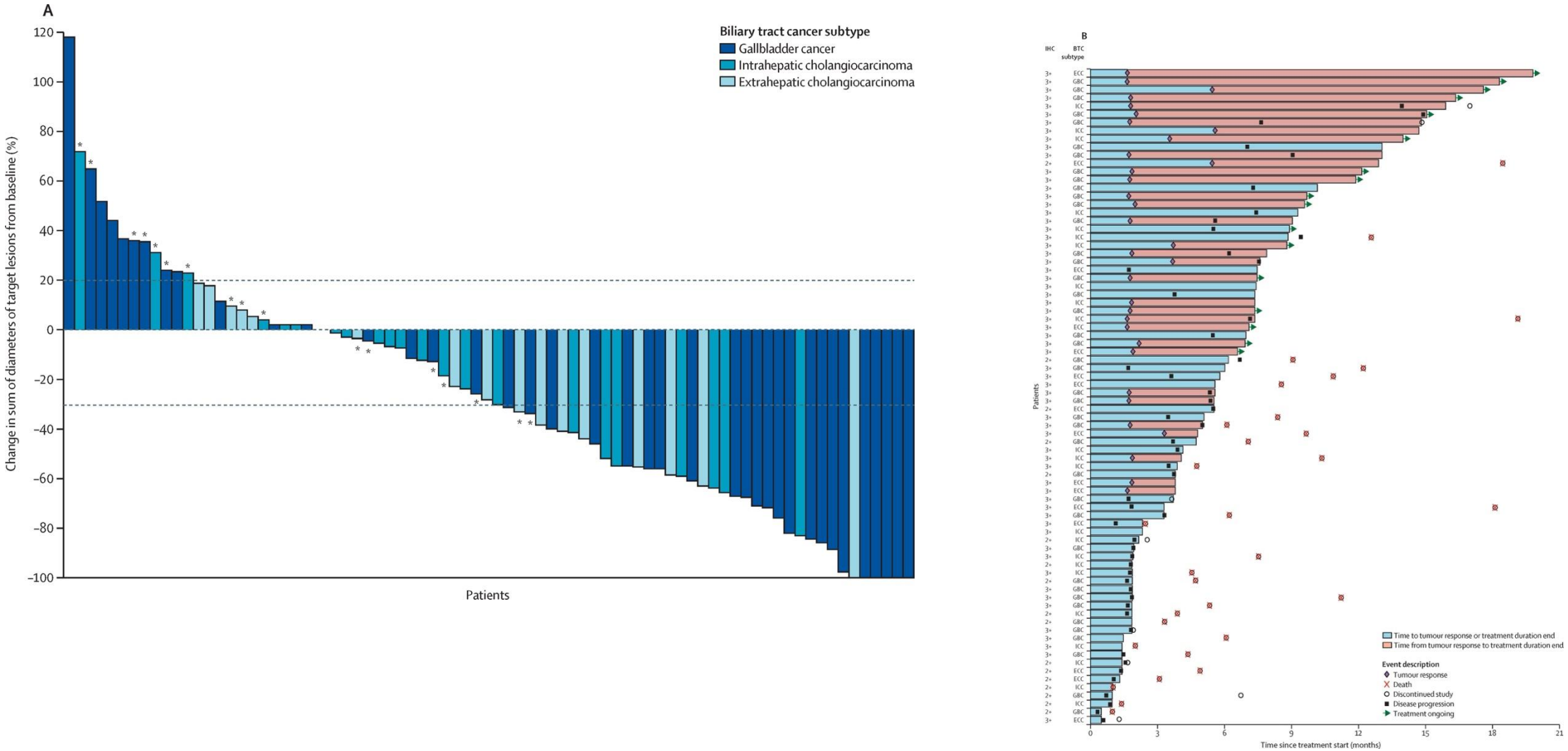
Trastuzumab Deruxtecan in Human Epidermal Growth Factor Receptor 2–Expressing Biliary Tract Cancer (HERB; NCCH1805): A Multicenter, Single-Arm, Phase II Trial



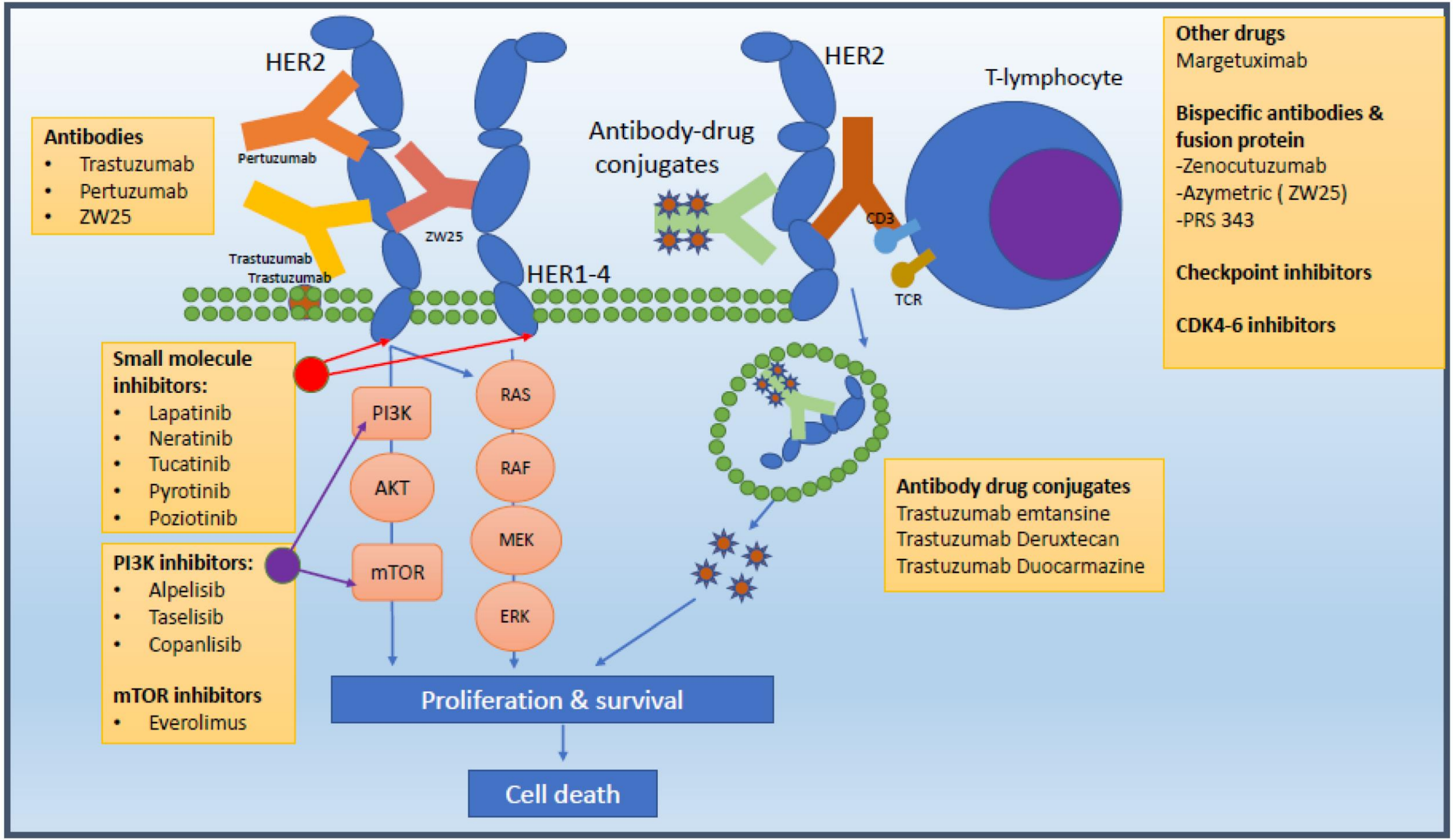


Published in: Akihiro Ohba; Chigusa Morizane; Yasuyuki Kawamoto; Yoshito Komatsu; Makoto Ueno; Satoshi Kobayashi; Masafumi Ikeda; Mitsuhito Sasaki; Junji Furuse; Naohiro Okano; Nobuyoshi Hiraoka; Hiroshi Yoshida; Aya Kuchiba; Ryo Sadachi; Kenichi Nakamura; Naoko Matsui; Yoshiaki Nakamura; Wataru Okamoto; Takayuki Yoshino; Takuji Okusaka JCO 2024 08-5
DOI: 10.1200/JCO.23.02010

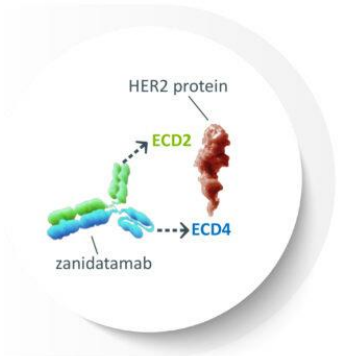
Zanidatamab for *HER2*-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study



Harding, James JAbou-Alfa, Ghassan et al.The Lancet Oncology, Volume 24, Issue 7, 772 - 782


HER2
Pertuzumab
ZW25
Trastuzumab
Trastuzumab
HER1-4
Antibody-drug conjugates
HER2
T-lymphocyte
CD3
TCR
Antibodies
• Trastuzumab
• Pertuzumab
• ZW25
Other drugs
Margetuximab
Bispecific antibodies & fusion protein
-Zenocutuzumab
-Azymetric (ZW25)
-PRS 343
Checkpoint inhibitors
CDK4-6 inhibitors
Small molecule inhibitors:
• Lapatinib
• Neratinib
• Tucatinib
• Pyrotinib
• Poziotinib
PI3K
AKT
mTOR
RAS
RAF
MEK
ERK
PI3K inhibitors:
• Alpelisib
• Taselisib
• Copanlisib
mTOR inhibitors
• Everolimus
Antibody drug conjugates
Trastuzumab emtansine
Trastuzumab Deruxtecan
Trastuzumab Duocarmazine
Proliferation & survival
Cell death

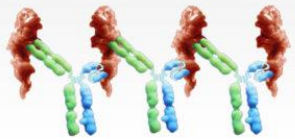
Zanidatamab: A Biparatopic Bispecific Antibody for HER2-Expressing Cancers



Zanidatamab's Unique Binding Geometry Promotes:

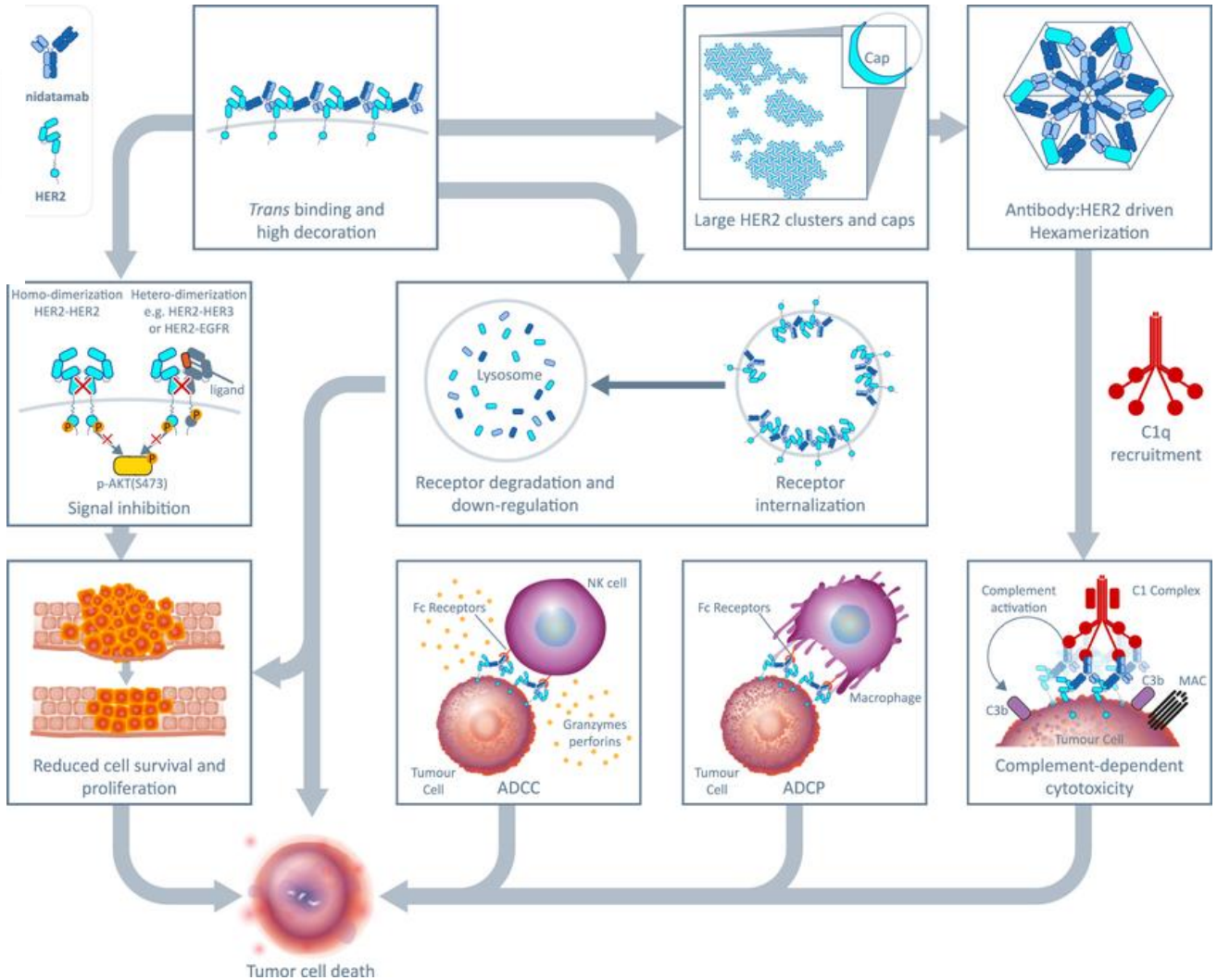
- Biparatopic – targets two distinct HER2 epitopes and results in HER2 binding across a range of expression levels (low to high)
- HER2-receptor cross-linking, clustering, internalization, and downregulation
  - Enhanced receptor clustering on cell surface (cluster internalization, receptor downregulation)
  - Inhibition of cellular proliferation
- Fc-mediated cytotoxicity: ADCC, ADCP, CDC

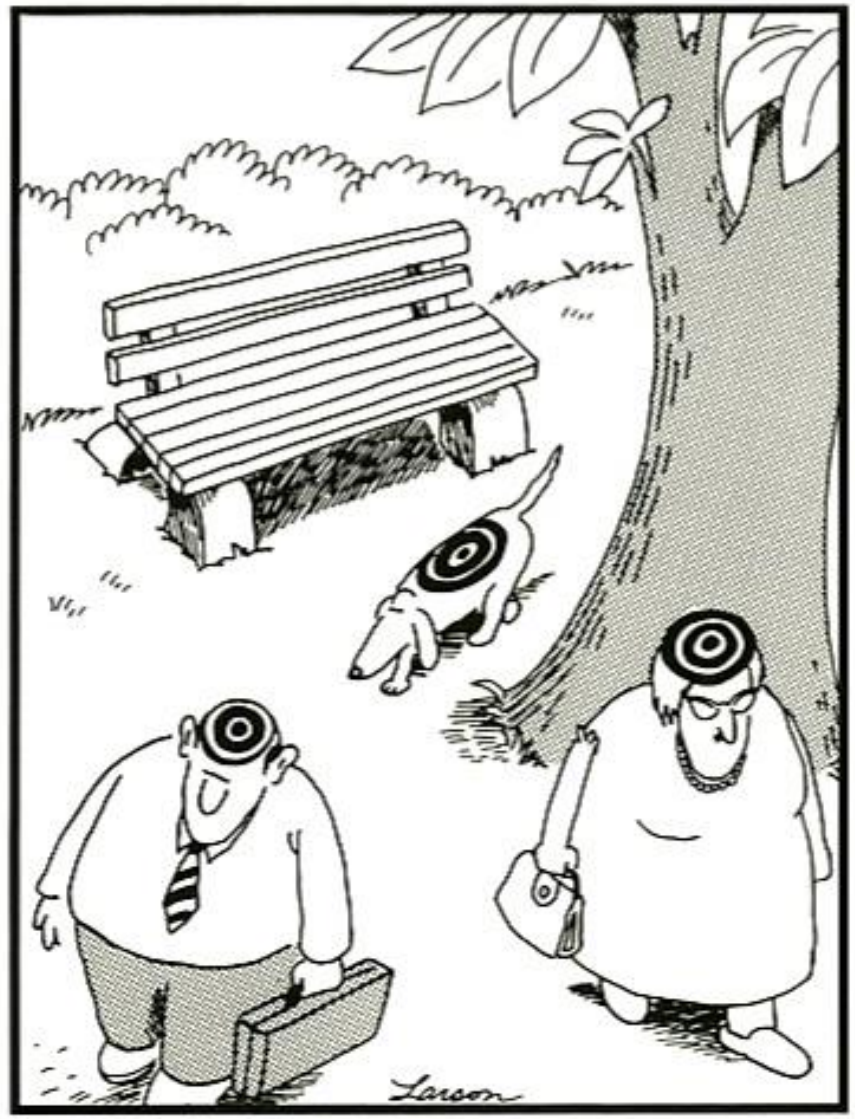
Dual HER2-Binding of Zanidatamab Drives Unique MOA



The geometry of zanidatamab prevents it from binding to the same HER2 molecule

Note: Zanidatamab has been granted Breakthrough Therapy designation by the FDA for patients with previously-treated HER2 gene-amplified BTC as well as two Fast Track designations, one for previously treated or recurrent HER2-positive BTC and another for first-line GEA in combination with standard of care chemotherapy. Zanidatamab also received Orphan Drug designation for the treatment of BTC and GEA in the United States and for gastric cancer and BTC in the European Union.
ADCC: antibody-dependent cellular cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; CDC: complement-dependent cytotoxicity; ECD: extracellular domain; Fc: fragment crystallizable region of antibody; HER2: human epidermal growth factor receptor 2





How birds see the world.