膽管癌治療進展及
標靶FGFR TKI副作用預防及處置

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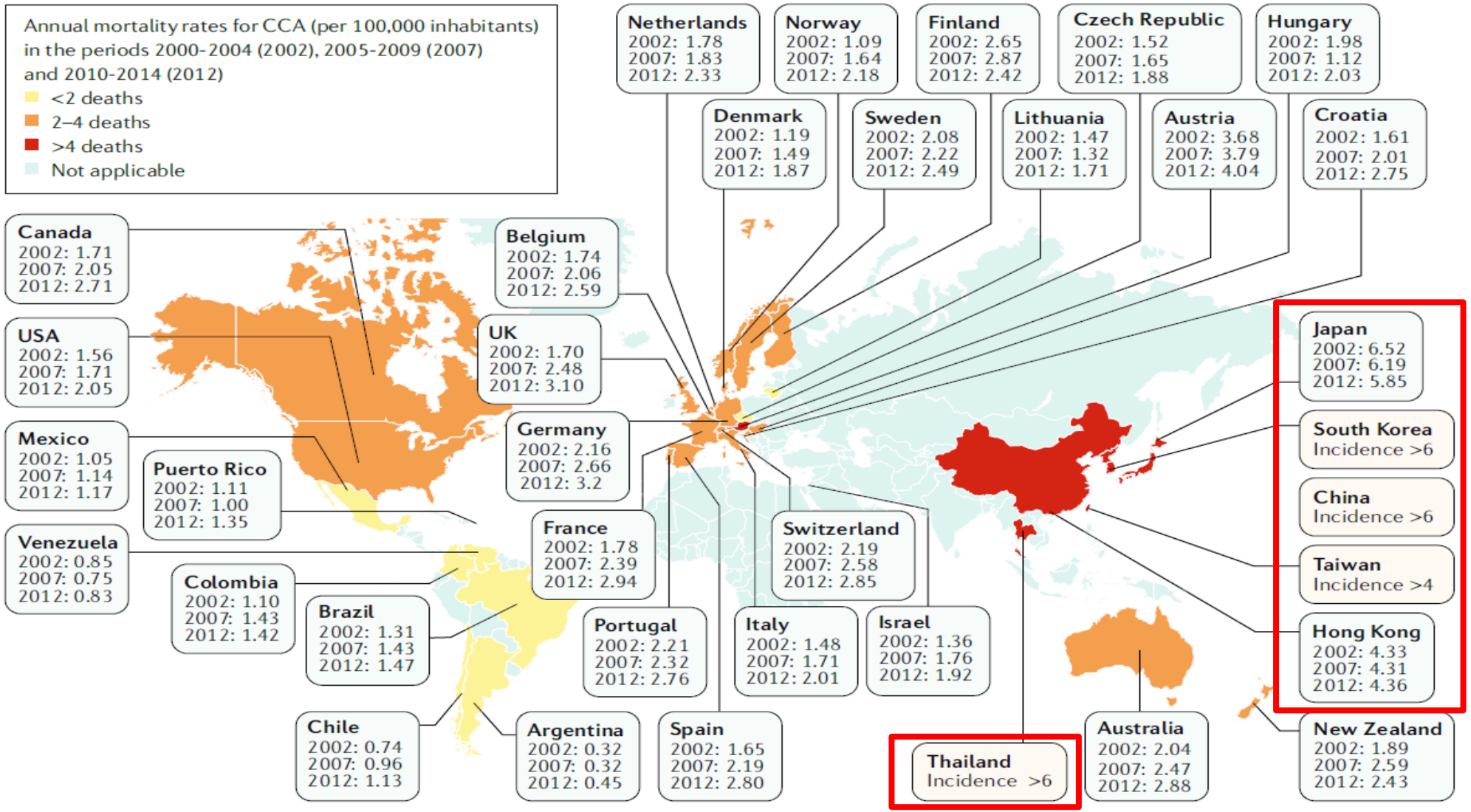
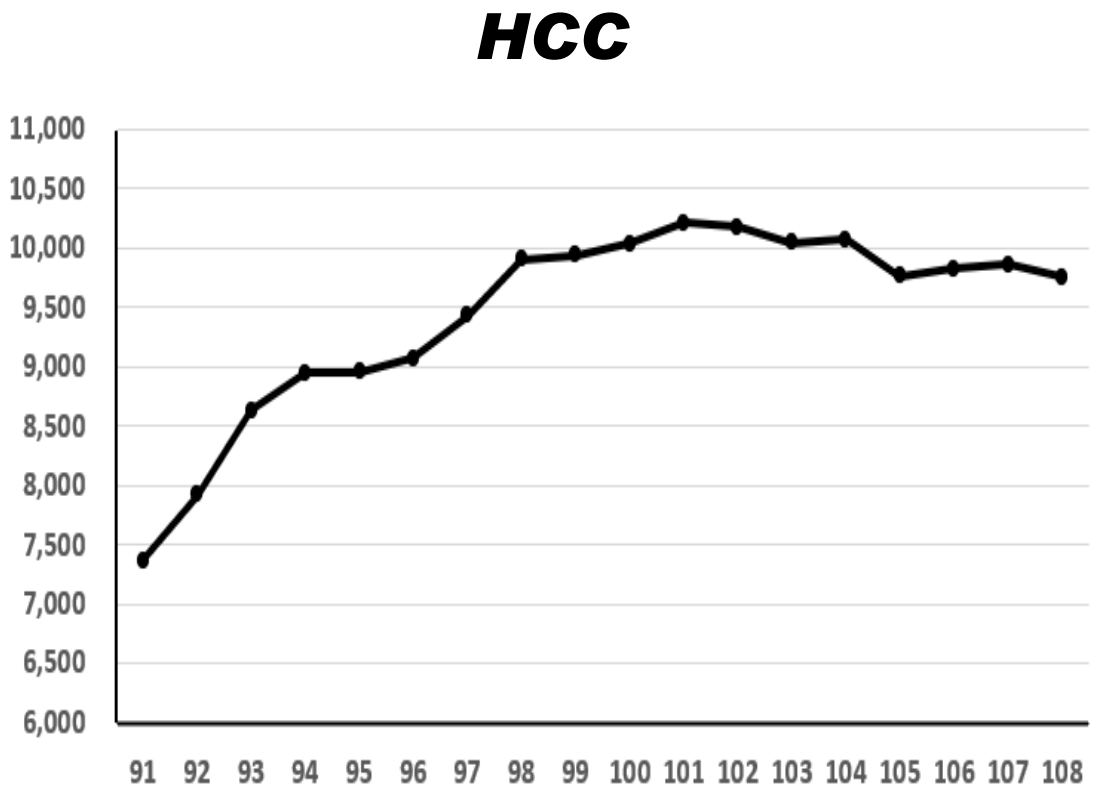
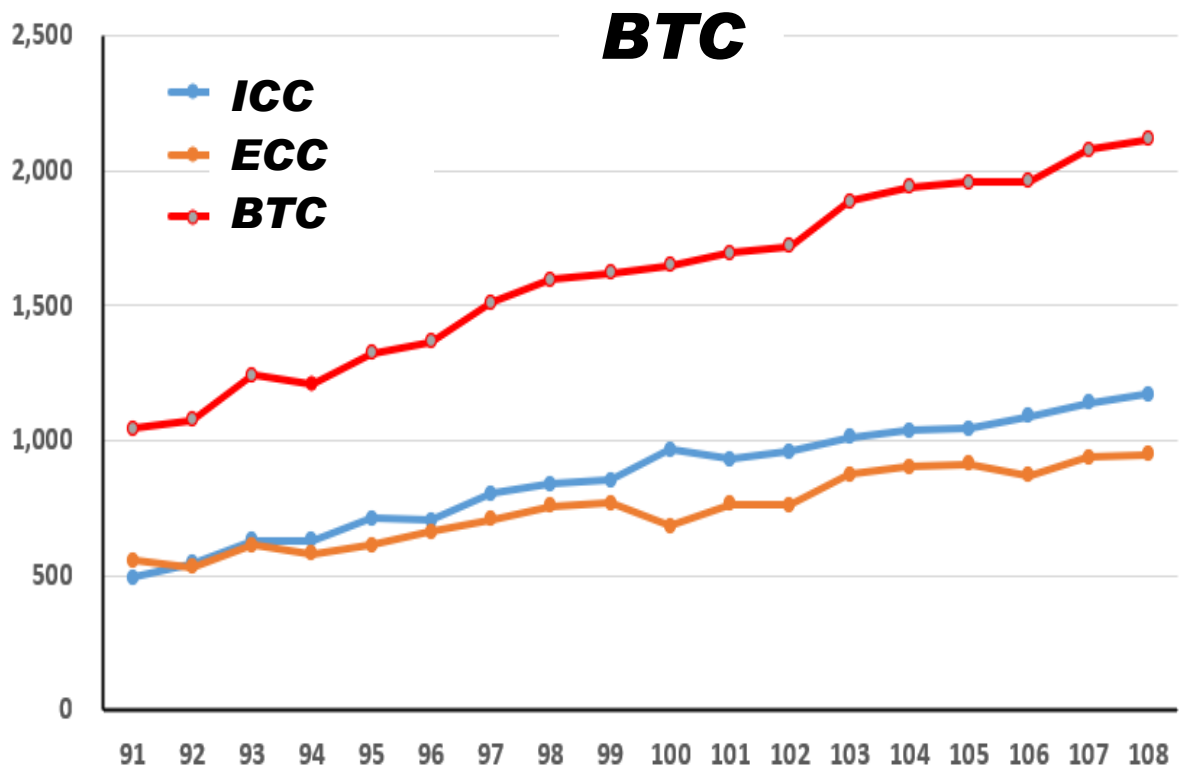
Mortality of Cholangiocarcinoma Worldwide



Banales JM, et al. Nat Rev Gastroenterol Hepatol. 2020;17:557-88.

Annual New Cases of Liver Cancers in Taiwan

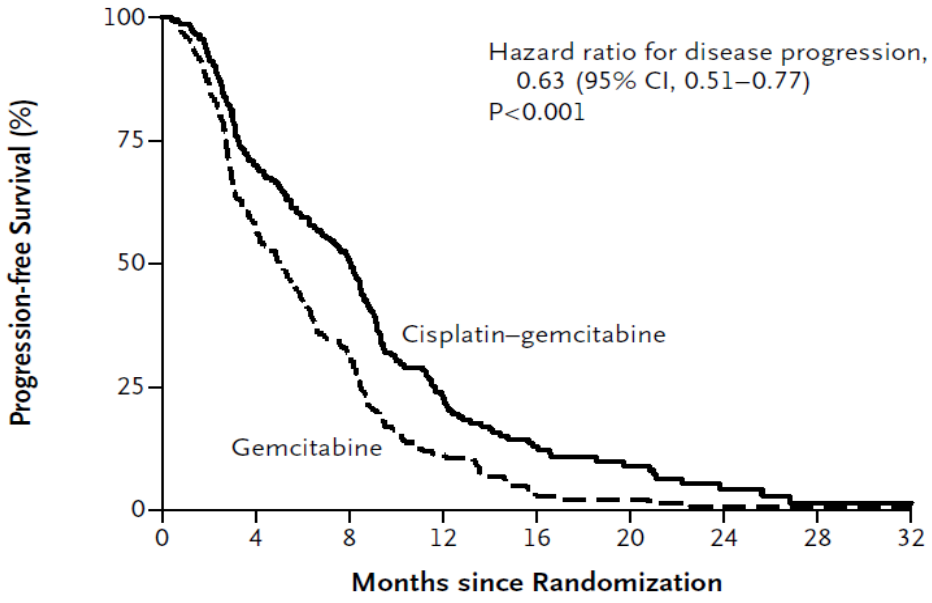




中華民國癌症登記報告.
https://www.hpa.gov.tw/Pages/List.aspx?nodeid=119

Unsatisfactory chemotherapeutic efficacy for biliary tract cancer

First-line: GemCis (ABC-02)

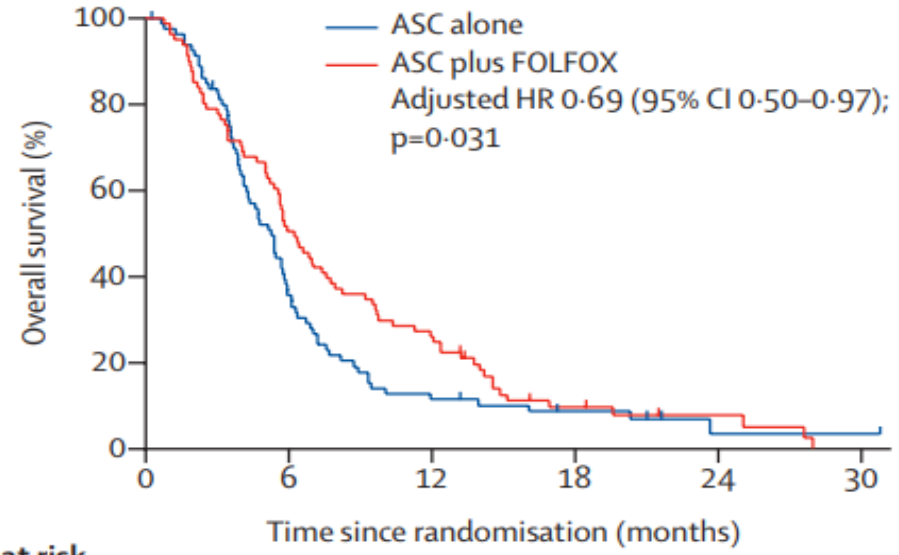


No. at Risk									
Gemcitabine	206	115	56	18	4	3	1	1	1
Cisplatin–gemcitabine	204	140	95	36	18	10	4	1	1

RR: 26.1% vs 15.5%
Median PFS: 8.0 vs 5.0 Months

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

Second-line: FOLFOX (ABC-06)



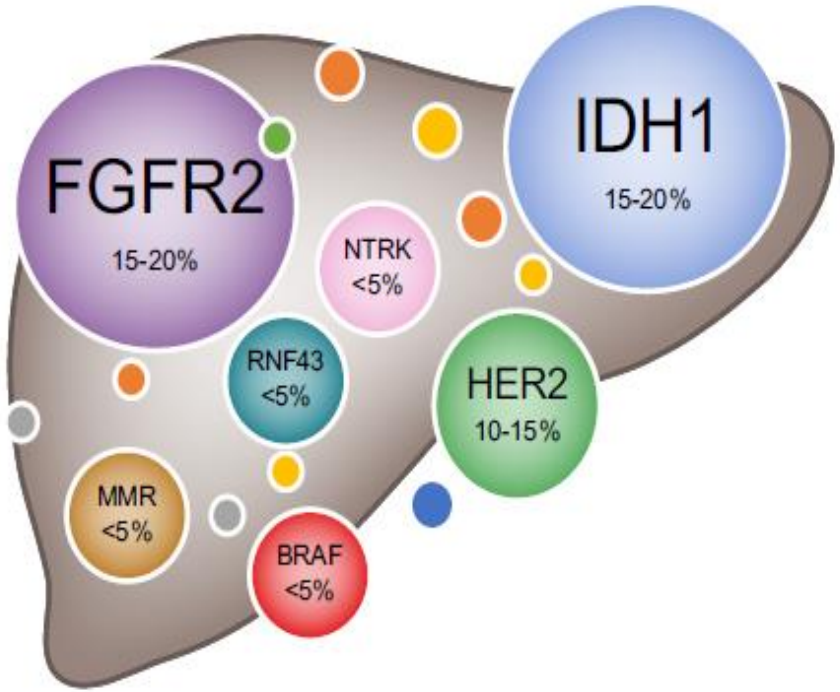
Number at risk (number censored*)						
ASC alone	81 (0)	28 (2)	9 (2)	5 (4)	1 (6)	1 (6)
ASC plus FOLFOX	81 (0)	41 (0)	21 (0)	6 (3)	3 (5)	0 (5)

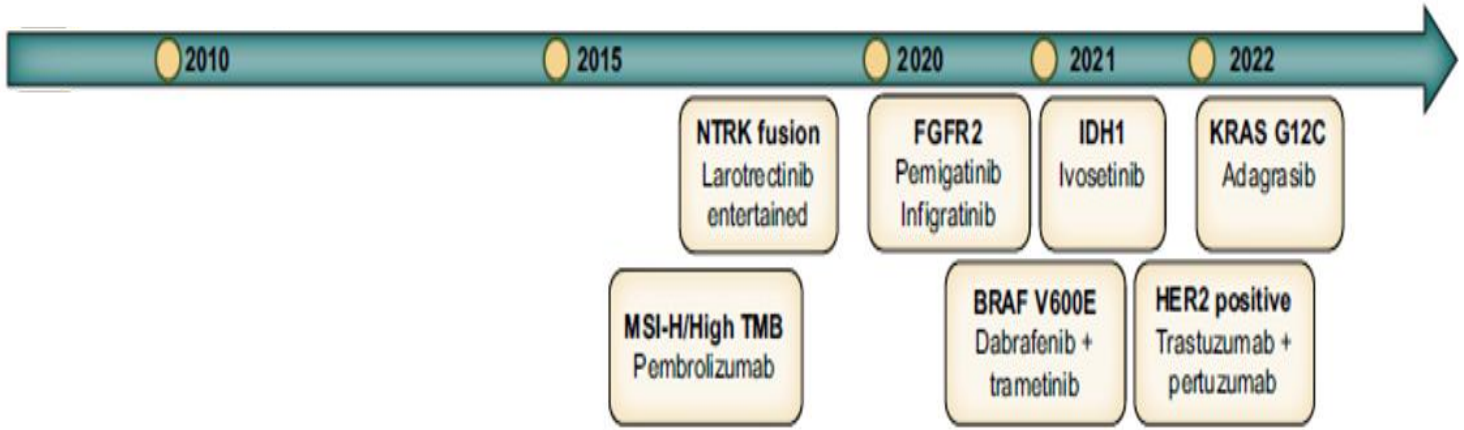
RR: 5% vs 0%
Median OS: 6.2 vs 5.3 Months

Lamarca A, et al. Lancet Oncol. 2021;22:690.

Diverse landscape of oncogenic drivers in CCA

ICC is a molecular target-rich disease.
***IDH1* and *FGFR* are the best understood targets to date.**

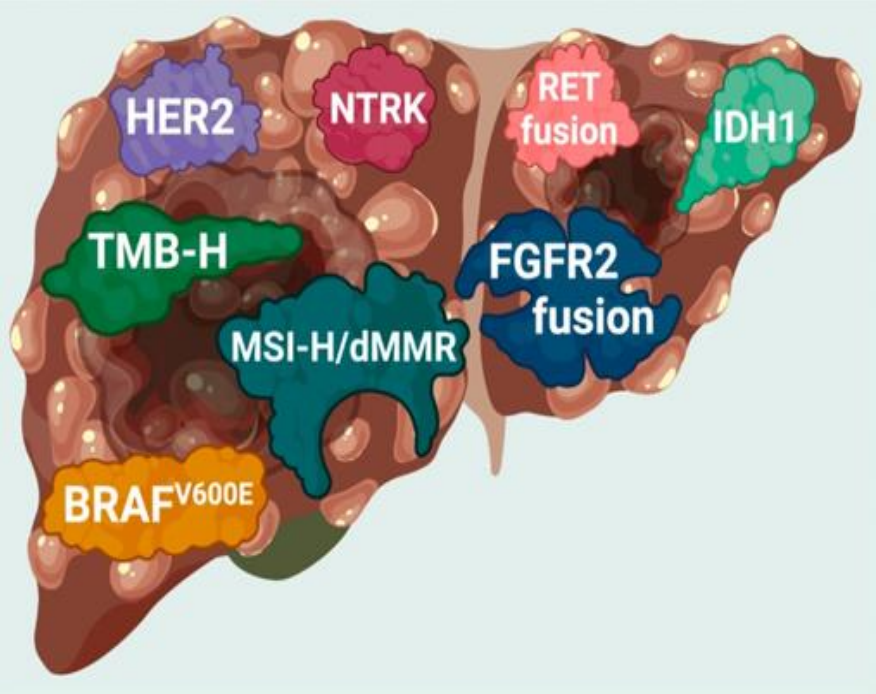




Lamarca A, et al. J Hepatol. 2020;73:170-85.
Harding JJ, et al. J Hepatol 2023;78:217.

ESMO RECOMMENDS ROUTINE USE OF NGS IN ADVANCED NSCLC, CHOLANGIOCARCINOMA, PROSTATE AND OVARIAN CANCERS

ICC is a molecular target-rich disease.



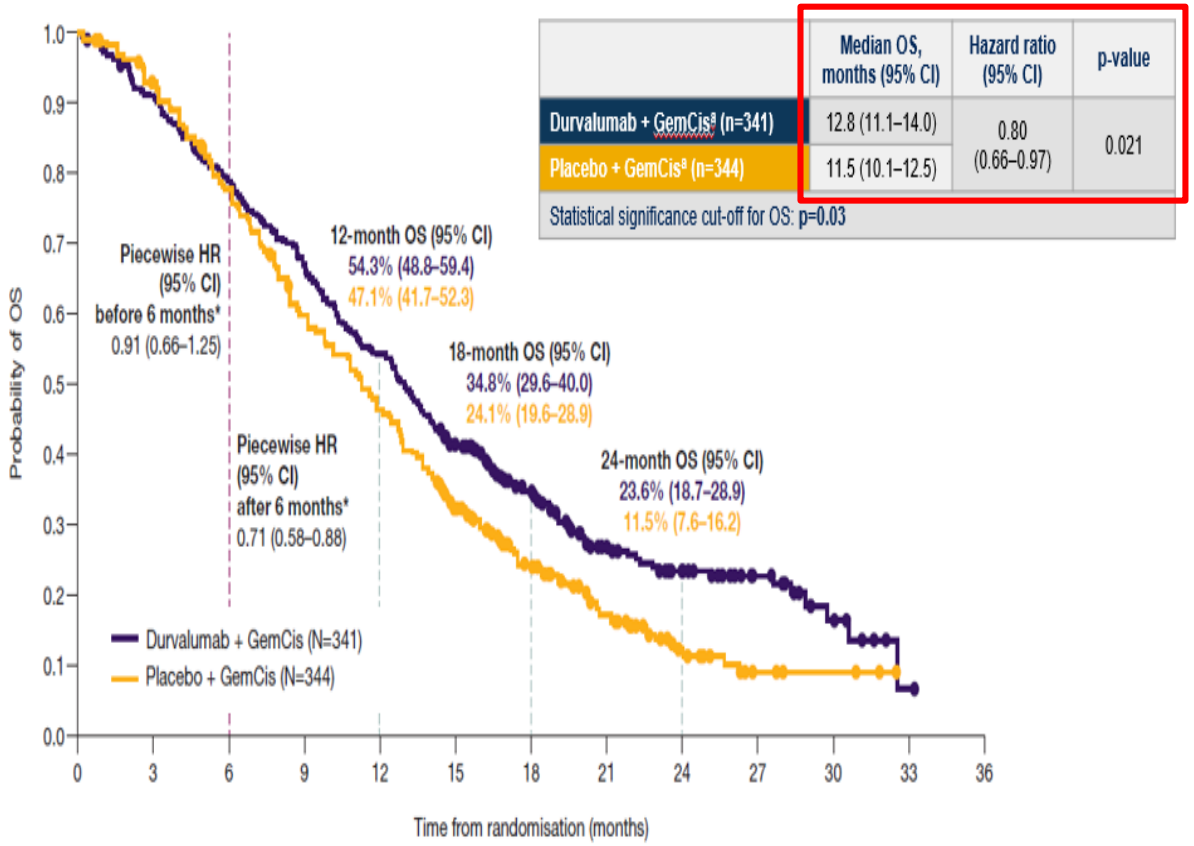
ESMO Precision Medicine Working Group (2020)

Gene	Alteration	Prevalence	ESCAT	References
IDH1	Mutations	20%	IA	Abou-Alfa G. K, et al. *Ann Oncol.* 2019[129]
FGFR2	Fusions	15%	IB	Vogel A, et al. *Ann Oncol.* 2019[130]
	MSI-H	2%	IC	Marabelle A, et al. *J Clin Oncol.* 2020[131]
NTRK	Fusions	2%	IC	Doebele RC, et al. *Lancet Oncol.* 2020[50]
BRAF^{V600E}	Mutations	5%	IIB	Wainberg Z, et al. *J Clin Oncol.* 2019[132]
ERBB2	Amplifications Mutations	10% 2%	IIIA	Javle MM, et al. *J Clin Oncol.* 2017[133]
PIK3CA	Hotspot mutations	7%	IIIA	André F, et al. *N Engl J Med.* 2019[72]
BRCA 1/2	Mutations	3%	IIIA	De Bono J, et al. *N Engl J Med.* 2020[93]
MET	Amplifications	2%	IIIA	Camidge D, et al. *J Clin Oncol.* 2018[52]

Mosele F, et al. Ann Oncol. 2020;31:1491-505.

Immune checkpoint inhibitors in advanced CCA

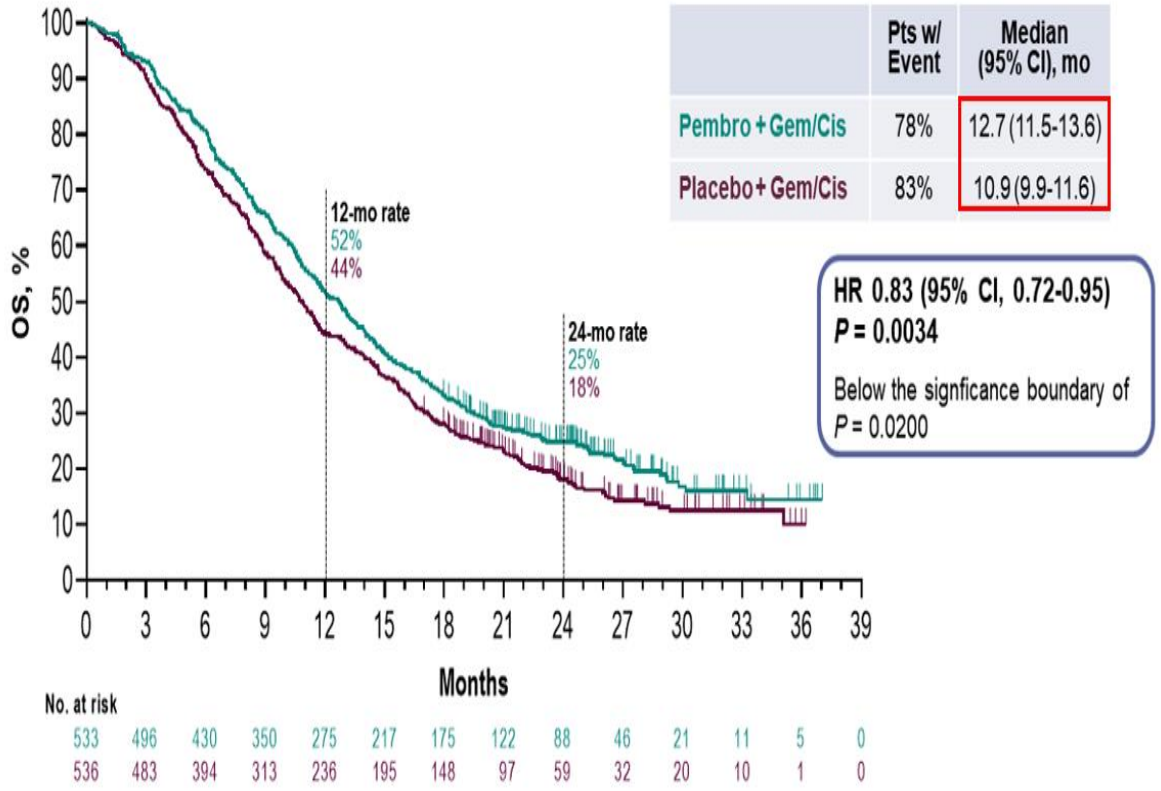
TOPAZ-1



	Median OS, months (95% CI)	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis[a] (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis[a] (n=344)	11.5 (10.1–12.5)		

Statistical significance cut-off for OS: p=0.03

KEYNOTE-966



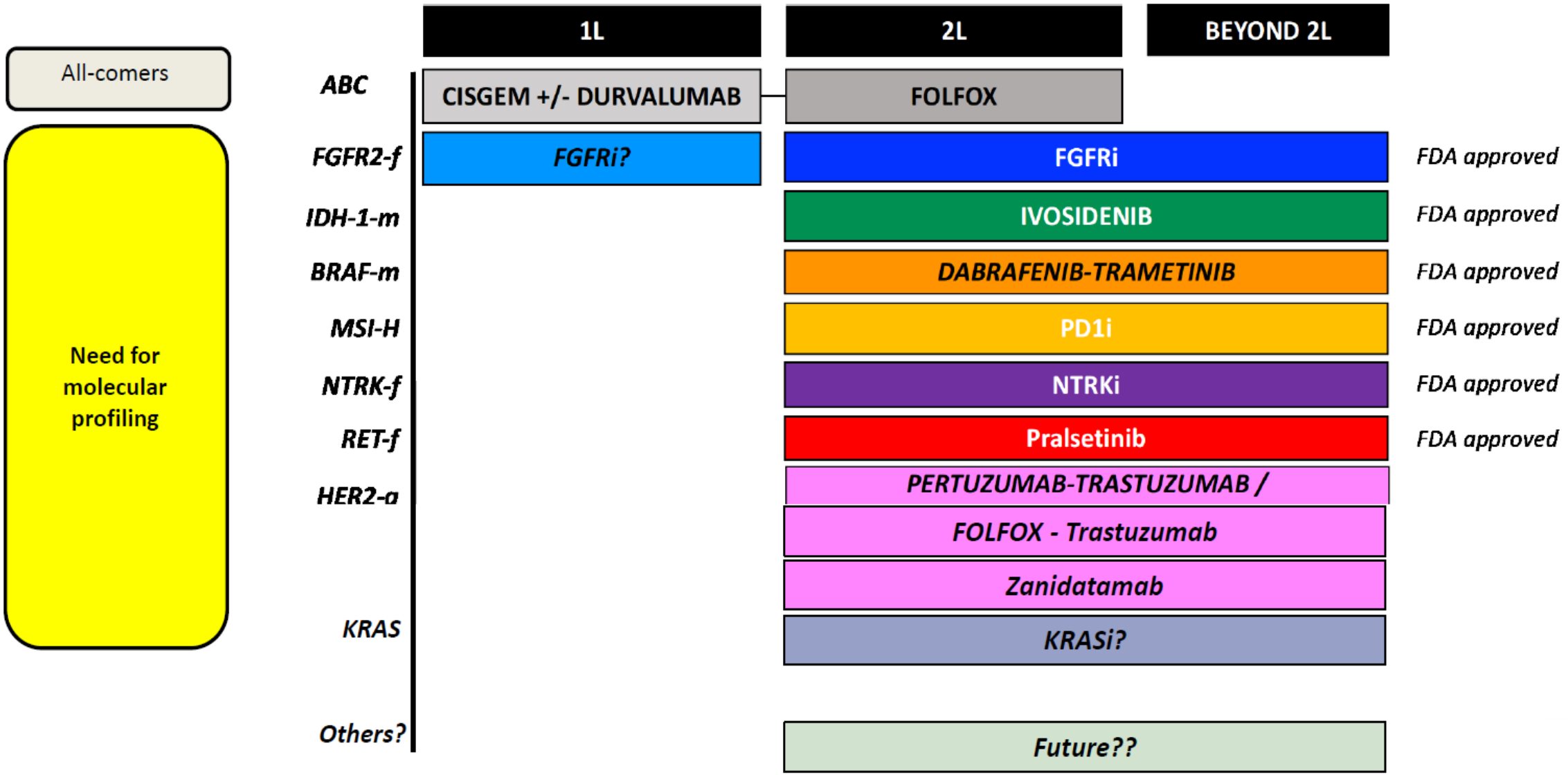
	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	78%	12.7 (11.5-13.6)
Placebo + Gem/Cis	83%	10.9 (9.9-11.6)

HR 0.83 (95% CI, 0.72-0.95)
P = 0.0034

Below the signficance boundary of *P* = 0.0200

Oh DY, et al. NEJM Evid. 2022;1:EVIDoa2200015.
Kelley RK, et al. Lancet. 2023;401:1853-65.

Molecular subtype-based treatments in advanced CCA

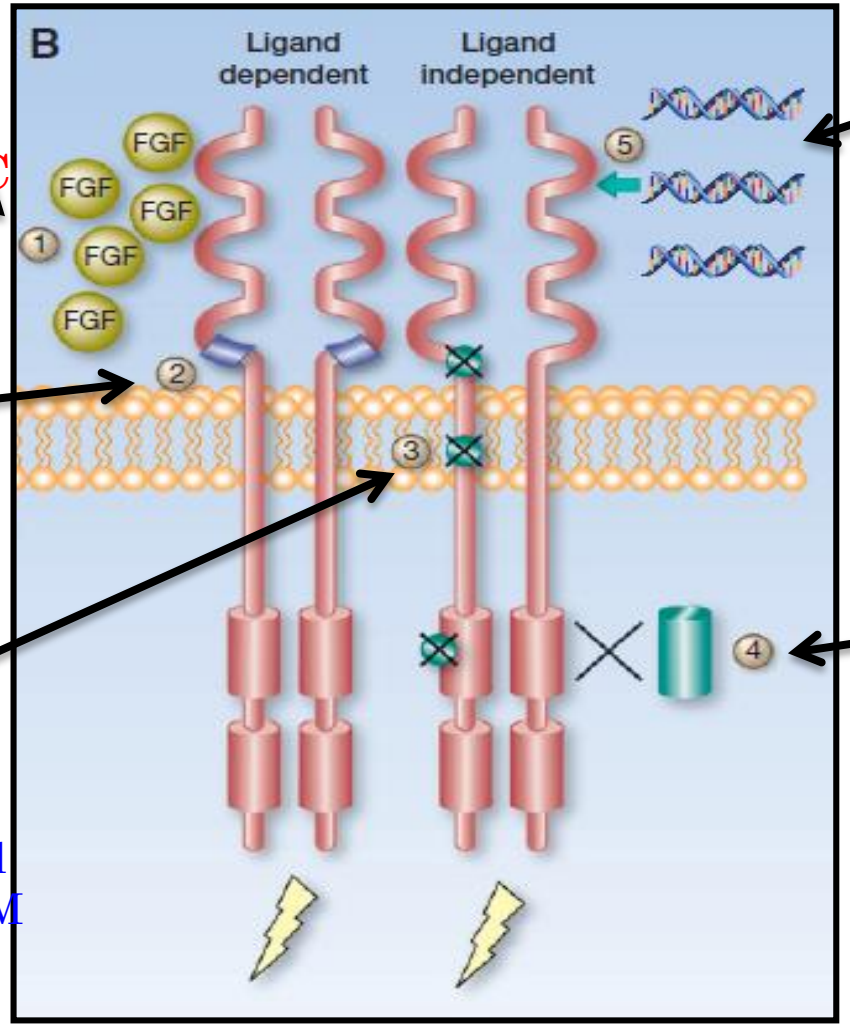


FGF/FGFR-related alterations and carcinogenesis

Autocrine
Paracrine
*FGF19/FGFR4: HCC
*FGF2: lung

Splice-variants
*FGFR2: bladder, prostate

Activating mutation
*FGFR2: endometrial
*FGFR3: bladder, MM
*FGFR4: RMS



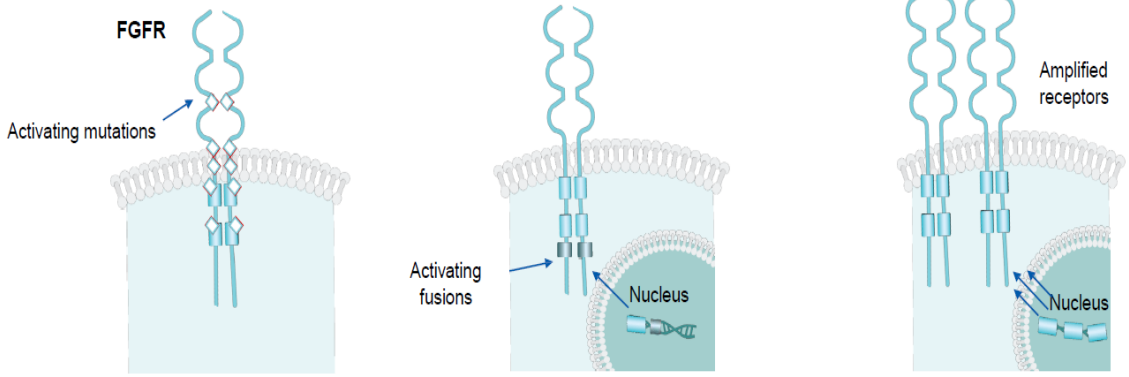
FGFR gene amplification
*FGFR1: breast (10%), NSCLC-SCC (22%)
*FGFR2: gastric

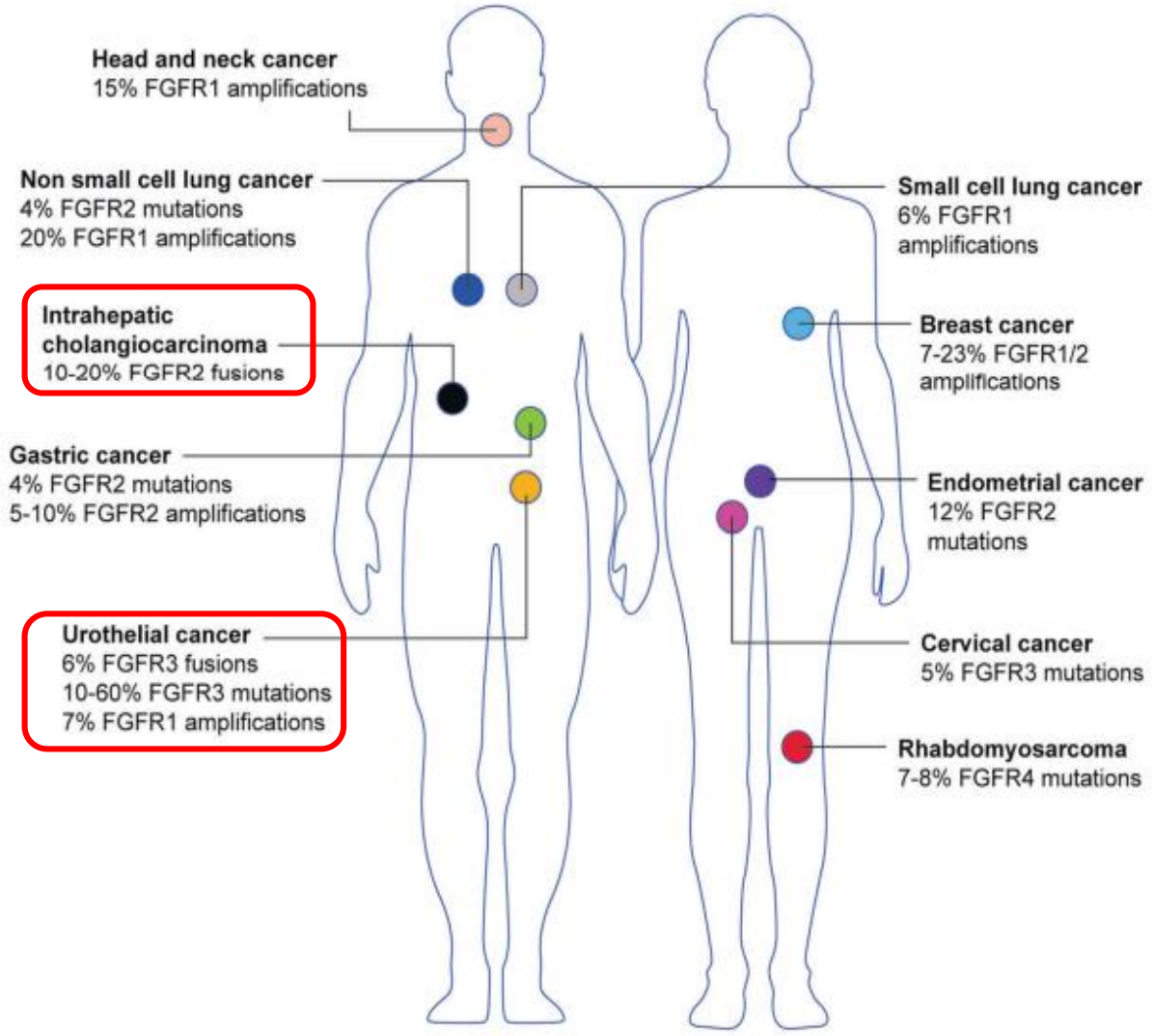
Chromosomal translocation
*FGFR2: cholangiocarcinoma
*FGFR3: bladder

Brooks AN, et al. Clin Cancer Res. 2012;18:1855-62.

FGFR Alterations in Tumors

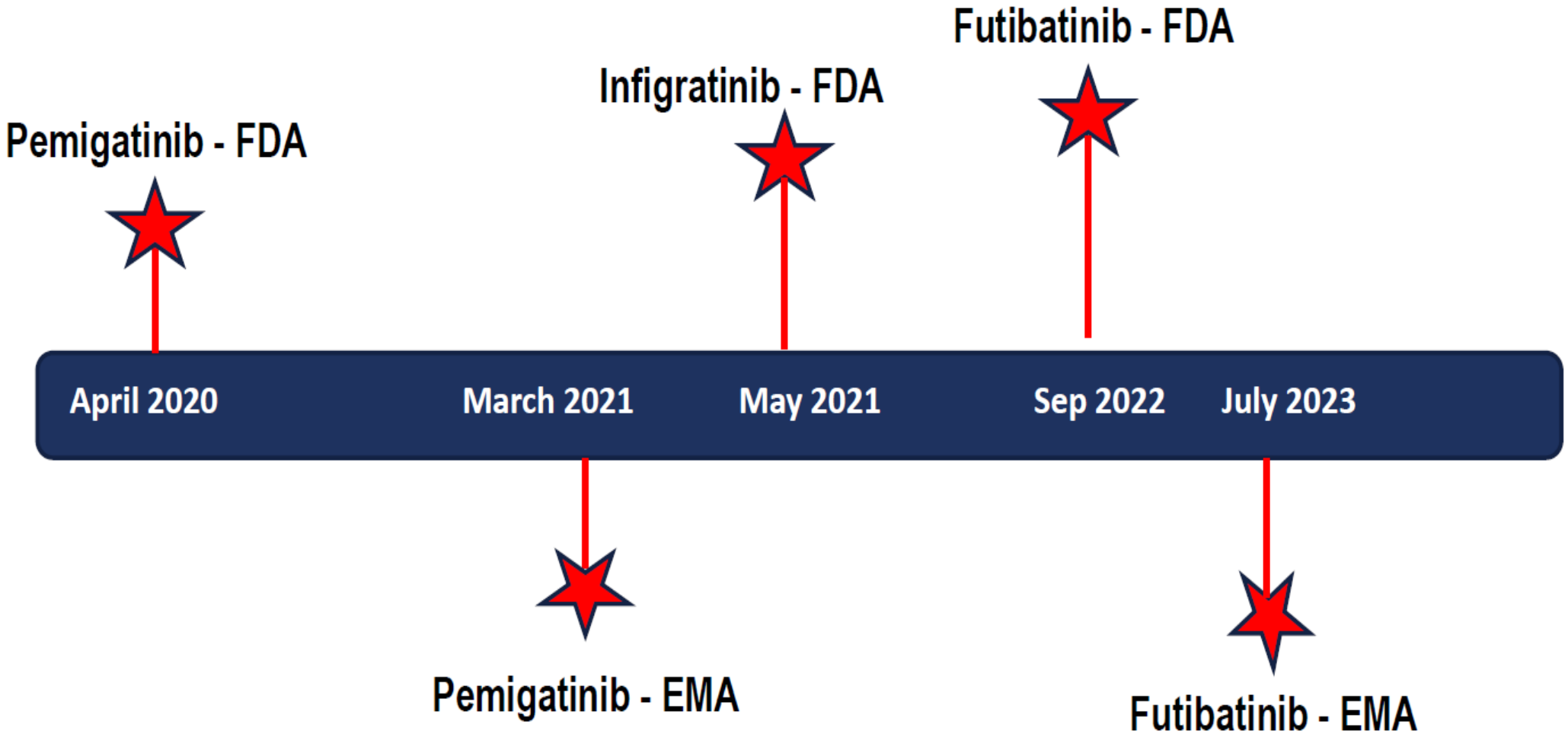
Activating mutations	Chromosomal rearrangements	Gene amplification
Leading to constitutive activation of the kinase domain or ligand-independent receptor dimerisation	eg, Translocations resulting in gene fusions that allow ligand-independent receptor dimerisation	Inducing protein overexpression, receptor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





Krook MA, et al. Br J Cancer. 2021;124:880-92.
Babina I, et al. Nat Rev Cancer. 2017;17:318-32.

Approval of FGFR inhibitors for CCA



Pemigatinib is a Selective and Potent Inhibitor of FGFR1, 2, and 3

***In Vitro* Inhibitory Activity**

	Pemigatinib[1] Incyte	Derazantinib[2] ArQule	Erdafitinib[3] Janssen	Futibatinib[4] Taiho	Infigratinib[5] QED Therapeutics	Rogaratinib[6] Bayer
FGFR1 IC_{50} (nM)	0.4	4.5	1.2	3.9	0.9	15
FGFR2 IC_{50} (nM)	0.5	1.8	2.5	1.3	1.4	<1
FGFR3 IC_{50} (nM)	1	4.5	3	1.6	1.0	19
FGFR4 IC_{50} (nM)	30	34	5.7	8.3	60	33
VEGFR2 IC_{50} (nM)	71	21	36.8	NR	180	120

- In the FIGHT-101 clinical study, pemigatinib exhibited low oral clearance and dose-dependent pharmacokinetics (PK); the terminal half-life was approximately 15 hours[7]

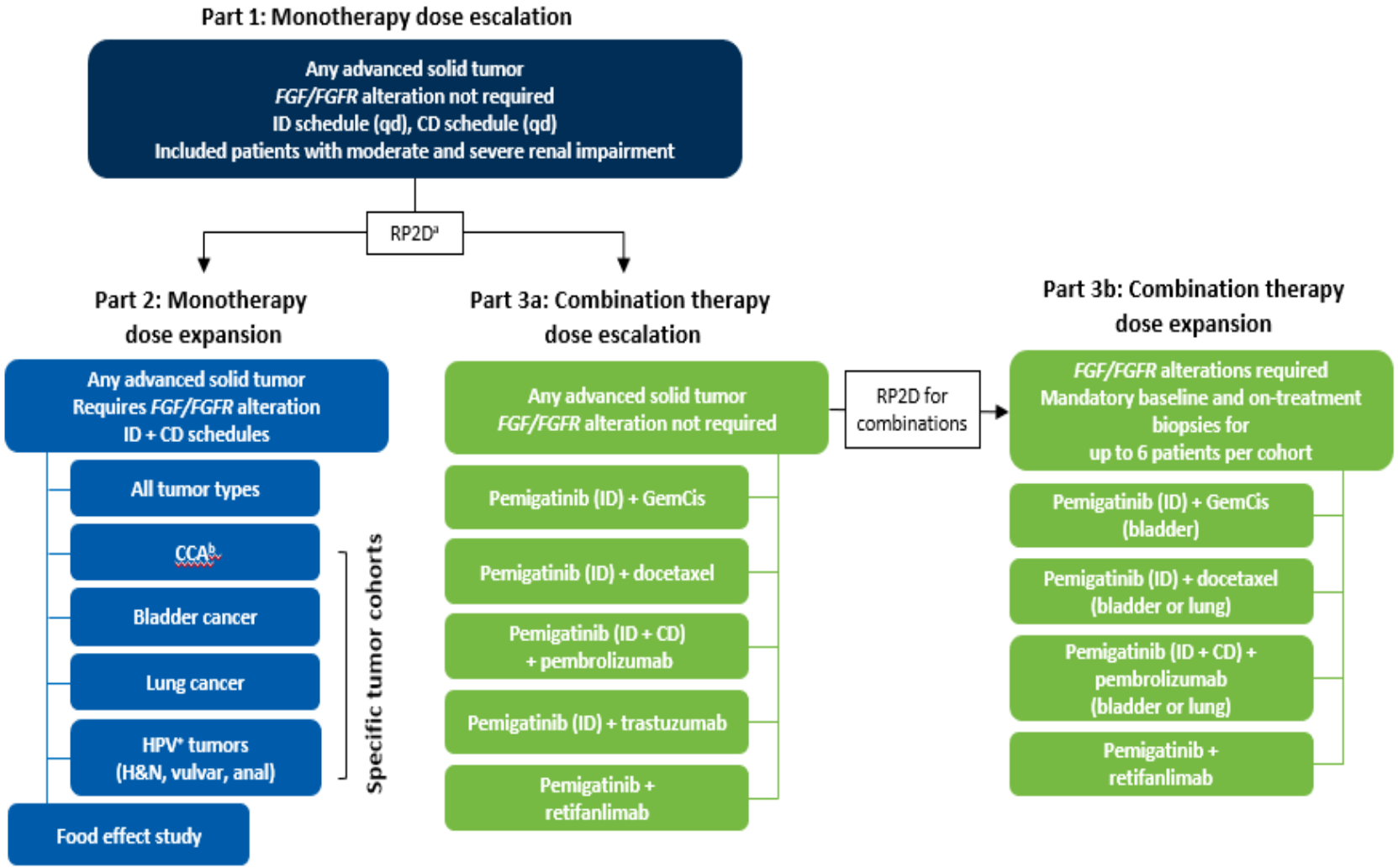
- **Pemigatinib, futibatinib, and infigratinib** have been approved by the FDA for adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusions or other rearrangements.

1. Liu PCC, et al. *PLoS One*. 2020;15:e0231877. 2. Hall T, et al. *PLoS ONE*. 2016;11:e0162594. 3. Perera TPS, et al. *Mol Cancer Ther*. 2017;16:1010-1020. 4. Kalyukina M, et al. *ChemMedChem*. 2019;14:494-500. 5. Guagnano V, et al. *J Med Chem*. 2011;54:7066-7083. 6. Collin MP, et al. *ChemMedChem*. 2018;13:437-445. 7. Saleh M, et al. AACR 2017. Poster CT111.

Phase 1/2, First-in Human, Open-Label Study of Pemigatinib in Patients With Refractory Advanced Malignancies[1,2]

fight-101

- Patients received oral pemigatinib:[1-4]
  - 1-20 mg qd on an ID schedule as monotherapy
  - 9 mg, 13.5 mg, or 20 mg qd on a CD schedule as monotherapy
  - 9 mg or 13.5 mg qd on an ID schedule in combination regimens
  - 13.5 mg qd or 20 mg qd on a CD schedule in combination regimens
  - 7.5 mg bid and 10 mg bid on a CD schedule as monotherapy



Subbiah V, et al. AACR-NCI-EORTC 2019. Poster A078.
Subbiah V, et al. *Ann Oncol.* 2022;33:522-533.

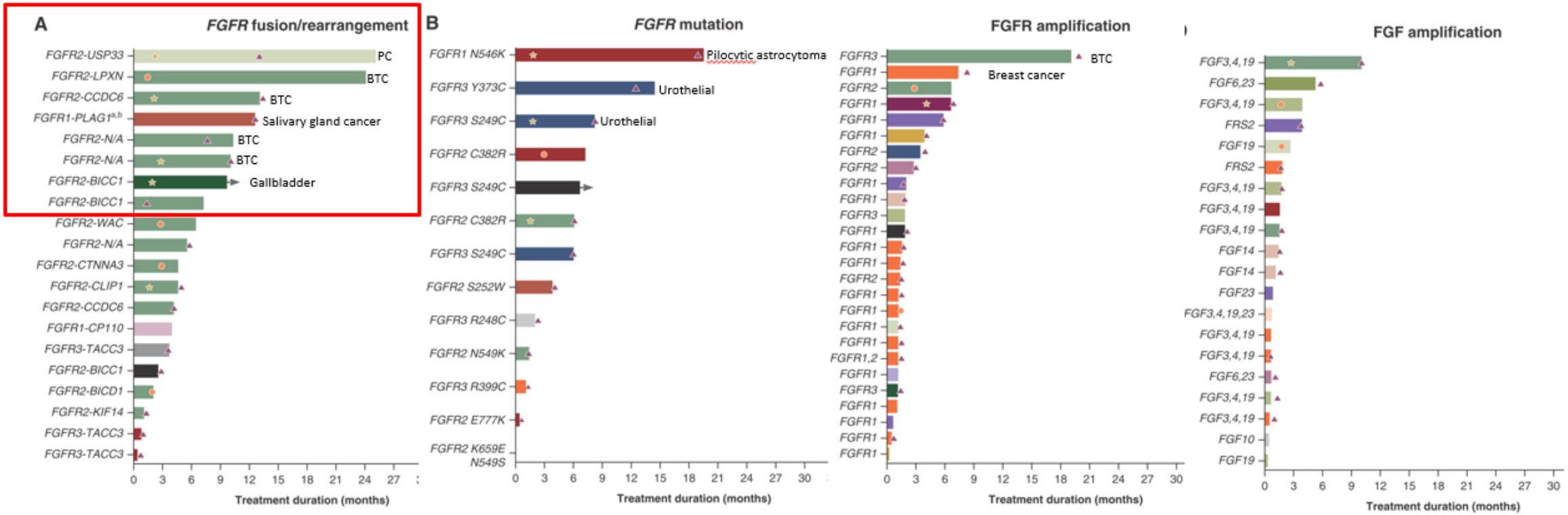
Table 2. Most common TEAEs and clinically notable TEAEs

Grade	ID								CD						All treated patients ($N = 128$)	
	1, 2, 4, or 6 mg ($n = 7$)		9 or 13.5 mg ($n = 57$)		20 mg ($n = 6$)		All ID ($n = 70$)		9 or 13.5 mg ($n = 43$)		20 mg ($n = 15$)		All CD ($n = 58$)			
	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3
TEAEs (preferred term) in ≥15% of all patients,[a] *n* (%)																
Hyperphosphatemia	1 (14.3)	0	43 (75.4)	1 (1.8)	4 (66.7)	0	48 (68.6)	1 (1.4)	35 (81.4)	2 (4.7)	13 (86.7)	0	48 (82.8)	2 (3.4)	96 (75.0)	3 (2.3)
Fatigue	2 (28.6)	0	23 (40.4)	3 (5.3)	2 (33.3)	1 (16.7)	27 (38.6)	4 (5.7)	18 (41.9)	6 (14.0)	5 (33.3)	3 (20.0)	23 (39.7)	9 (15.5)	50 (39.1)	13 (10.2)
Dry mouth	1 (14.3)	0	20 (35.1)	0	2 (33.3)	0	23 (32.9)	0	18 (41.9)	0	8 (53.3)	0	26 (44.8)	0	49 (38.3)	0
Stomatitis	0	0	13 (22.8)	1 (1.8)	3 (50.0)	0	16 (22.9)	1 (1.4)	21 (48.8)	8 (18.6)	7 (46.7)	2 (13.3)	28 (48.3)	10 (17.2)	44 (34.4)	11 (8.6)
Diarrhea	1 (14.3)	0	13 (22.8)	0	2 (33.3)	0	16 (22.9)	0	16 (37.2)	0	9 (60.0)	2 (13.3)	25 (43.1)	2 (3.4)	41 (32.0)	2 (1.6)
Alopecia	0	0	18 (31.6)	0	1 (16.7)	0	19 (27.1)	0	16 (37.2)	0	5 (33.3)	0	21 (36.2)	0	40 (31.3)	0
Constipation	0	0	16 (28.1)	1 (1.8)	2 (33.3)	0	18 (25.7)	1 (1.4)	15 (34.9)	0	4 (26.7)	1 (6.7)	19 (32.8)	1 (1.7)	37 (28.9)	2 (1.6)
Nausea	2 (28.6)	0	9 (15.8)	0	2 (33.3)	0	13 (18.6)	0	19 (44.2)	0	5 (33.3)	1 (6.7)	24 (41.4)	1 (1.7)	37 (28.9)	1 (0.8)
Dysgeusia	1 (14.3)	0	10 (17.5)	0	2 (33.3)	0	13 (18.6)	0	15 (34.9)	0	6 (40.0)	0	21 (36.2)	0	34 (26.6)	0
Decreased appetite	2 (28.6)	0	13 (22.8)	0	1 (16.7)	0	16 (22.9)	0	11 (25.6)	0	5 (33.3)	1 (6.7)	16 (27.6)	1 (1.7)	32 (25.0)	1 (0.8)
Anemia	1 (14.3)	0	12 (21.1)	2 (3.5)	2 (33.3)	0	15 (21.4)	2 (2.9)	10 (23.3)	3 (7.0)	5 (33.3)	4 (26.7)	15 (25.9)	7 (12.1)	30 (23.4)	9 (7.0)
Vomiting	1 (14.3)	0	9 (15.8)	1 (1.8)	1 (16.7)	0	11 (15.7)	1 (1.4)	12 (27.9)	0	4 (26.7)	1 (6.7)	16 (27.6)	1 (1.7)	27 (21.1)	2 (1.6)
Dry eye	0	0	8 (14.0)	0	1 (16.7)	0	9 (12.9)	0	13 (30.2)	1 (2.3)	4 (26.7)	0	17 (29.3)	1 (1.7)	26 (20.3)	1 (0.8)
Abdominal pain	0	0	12 (21.1)	2 (3.5)	1 (16.7)	0	13 (18.6)	2 (2.9)	8 (18.6)	1 (2.3)	3 (20.0)	1 (6.7)	11 (19.0)	2 (3.4)	24 (18.8)	4 (3.1)
AST increased	1 (14.3)	1 (14.3)	8 (14.0)	1 (1.8)	0	0	9 (12.9)	2 (2.9)	11 (25.6)	3 (7.0)	3 (20.0)	0	14 (24.1)	3 (5.2)	23 (18.0)	5 (3.9)
Hypercalcemia	1 (14.3)	1 (14.3)	6 (10.5)	0	0	0	7 (10.0)	1 (1.4)	10 (23.3)	0	4 (26.7)	1 (6.7)	14 (24.1)	1 (1.7)	21 (16.4)	2 (1.6)
ALT increased	1 (14.3)	1 (14.3)	5 (8.8)	0	0	0	6 (8.6)	1 (1.4)	12 (27.9)	3 (7.0)	2 (13.3)	0	14 (24.1)	3 (5.2)	20 (15.6)	4 (3.1)
Dehydration	2 (28.6)	0	7 (12.3)	0	1 (16.7)	0	10 (14.3)	0	6 (14.0)	1 (2.3)	4 (26.7)	0	10 (17.2)	1 (1.7)	20 (15.6)	1 (0.8)
Hypophosphatemia	0	0	12 (21.1)	4 (7.0)	1 (16.7)	0	13 (18.6)	4 (5.7)	5 (11.6)	1 (2.3)	2 (13.3)	2 (13.3)	7 (12.1)	3 (5.2)	20 (15.6)	7 (5.5)
Pain in extremity	1 (14.3)	0	5 (8.8)	0	1 (16.7)	0	7 (10.0)	0	10 (23.3)	2 (4.7)	3 (20.0)	0	13 (22.4)	2 (3.4)	20 (15.6)	2 (1.6)
Clinically notable TEAEs (category),[b] *n* (%)																
Hyperphosphatemia	1 (14.3)	0	43 (75.4)	1 (1.8)	4 (66.7)	0	48 (68.6)	1 (1.4)	35 (81.4)	2 (4.7)	13 (86.7)	0	48 (82.8)	2 (3.4)	96 (75.0)	3 (2.3)
Nail toxicity	0	0	12 (21.1)	1 (1.8)	3 (50.0)	0	15 (21.4)	1 (1.4)	20 (46.5)	2 (4.7)	6 (40.0)	1 (6.7)	26 (44.8)	3 (5.2)	41 (32.0)	4 (3.1)
Dry eye	0	0	9 (15.8)	0	2 (33.3)	0	11 (15.7)	0	15 (34.9)	1 (2.3)	4 (26.7)	0	19 (32.8)	1 (1.7)	30 (23.4)	1 (0.8)
Vision blurred	2 (28.6)	0	7 (12.3)	0	3 (50.0)	0	12 (17.1)	0	6 (14.0)	1 (2.3)	3 (20.0)	1 (6.7)	9 (15.5)	2 (3.4)	21 (16.4)	2 (1.6)
Hypophosphatemia	0	0	12 (21.1)	4 (7.0)	1 (16.7)	0	13 (18.6)	4 (5.7)	5 (11.6)	1 (2.3)	2 (13.3)	2 (13.3)	7 (12.1)	3 (5.2)	20 (15.6)	7 (5.5)
Eyelash changes	0	0	7 (12.3)	0	0	0	7 (10.0)	0	8 (18.6)	1 (2.3)	2 (13.3)	0	10 (17.2)	1 (1.7)	17 (13.3)	1 (0.8)
Vitreous detachment	0	0	0	0	0	0	0	0	2 (4.7)	0	0	0	2 (3.4)	0	2 (1.6)	0
Serous retinal detachment	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pemazyre Showed Promising Effect in CCA Patients Harboring *FGFR2* Fusion and Rearrangement

fight-101

Five of the 12 responders had cholangiocarcinoma



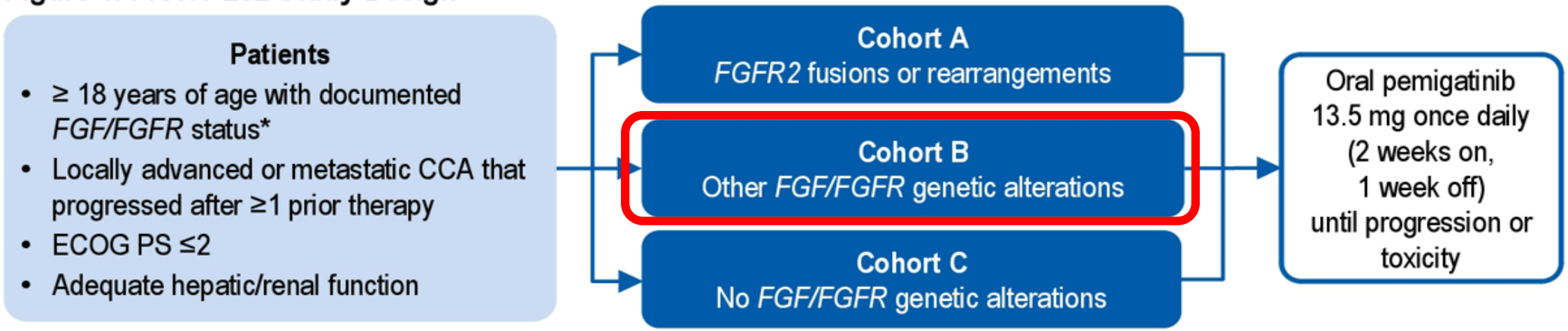
Subbiah V, et al. AACR-NCI-EORTC 2019. Poster A078.
Subbiah V, et al. *Ann Oncol.* 2022;33:522-533.

FIGHT-202 Study Design: Pemigatinib (FGFR 1-3 inhibitor)

(USFDA approved on Apr 2020, TFDA approved on Apr 2021)

- FIGHT-202 is an ongoing phase 2 single-arm, open-label, multicenter study investigating the efficacy and safety of pemigatinib in patients with locally advanced or metastatic CCA (NCT02924376; **Figure 1**)

Figure 1. FIGHT-202 Study Design



Primary endpoint:	Confirmed objective response rate (ORR) in cohort A by independent central review
Secondary endpoints:	ORR in cohorts B, A + B, and C; duration of response, disease control rate (DCR), progression free survival (PFS), overall survival (OS), and safety in all cohorts

Vogel A, et al. ESMO-WCGC 2022. Oral presentation 575.

fight-202

Demographics and baseline clinical characteristics

Characteristic	Cohort A (n=108)	Cohort B (n=20)	Cohort C (n=17)	Total (N=147)*
Median age, y (range)	55.5 (26–77)	63.0 (45–78)	65.0 (49–78)	59.0 (26–78)
Women, %	61	55	41	58
White, %	73	45	82	71
Median time since initial diagnosis, y (range)	1.3 (0.2–11.1)	0.7 (0.2–2.5)	1.0 (0.3–4.3)	1.1 (0.2–11.1)
ECOG PS, %				
0	43	35	35	41
1	53	50	47	52
2	5	15	18	7
Intrahepatic CCA, %	99	65	59	90
Metastatic disease, %	82	100	94	86
≥2 prior systemic therapies, %	40	40	35	39

Vogel A, et al. ESMO-WCGC 2022. Oral presentation 575.

fight-202

Response to pemigatinib

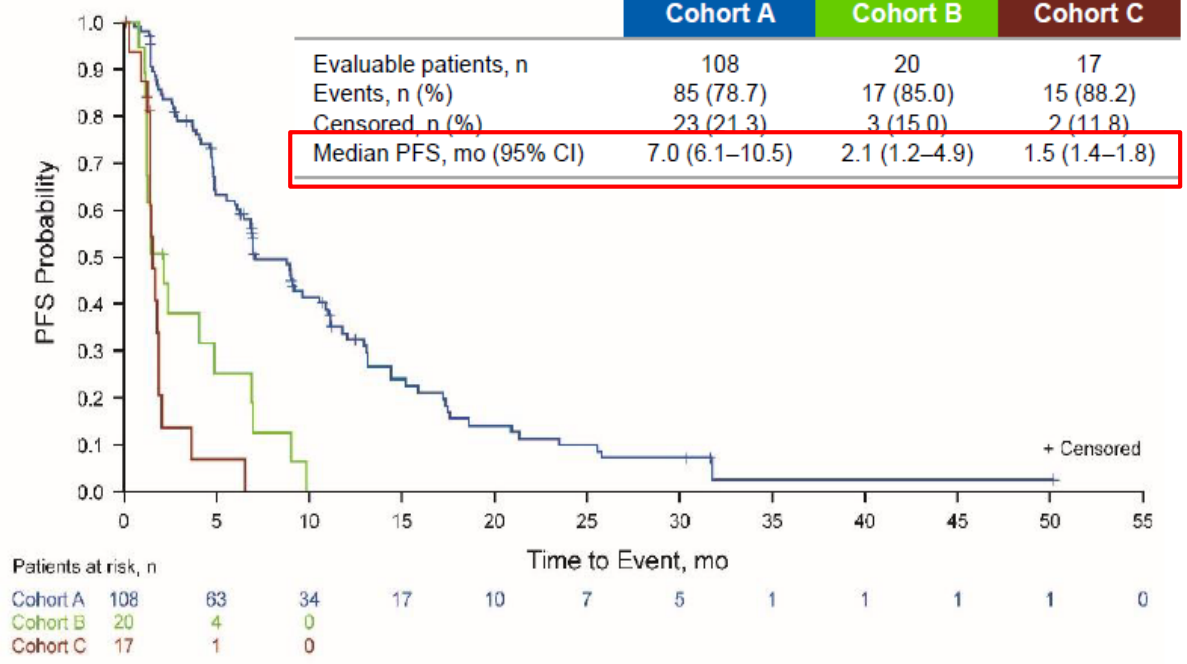
Parameter	Cohort A (n=108)	Cohort B (n=20)	Cohort C (n=17)
Duration of follow-up, median (range), mo	42.9 (19.9–52.2)	47.5 (43.7–51.1)	51.9 (49.5–53.7)
ORR,* % (95% CI)	37 (28–47)	0 (0–17)	0 (0–20)
DCR,† % (95% CI)	82 (74–89)	40 (19–64)	18 (4–43)
Best overall response, %			
Complete response	3	0	0
Partial response	34	0	0
Stable disease	45	40	18
Progressive disease	15	35	65
Not evaluable	3	25	18
DOR, median, mo (95% CI)	9.1 (6.0–14.5)	—	—

Vogel A, et al. ESMO-WCGC 2022. Oral presentation 575.

Progression-free and overall survival

Progression-free survival

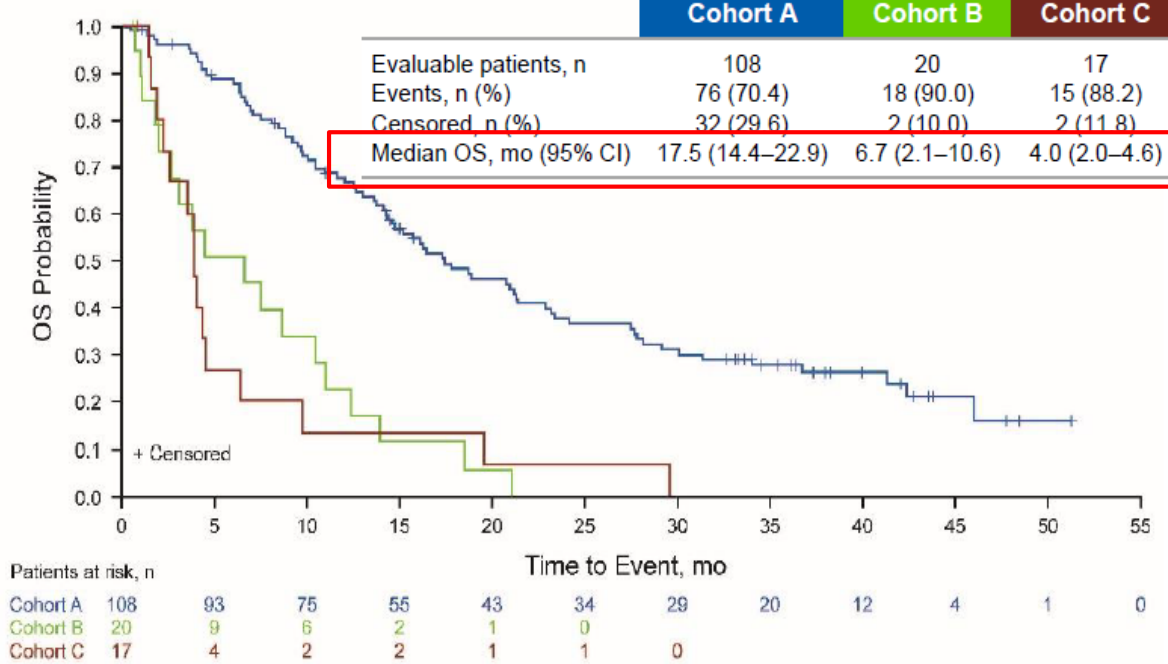
	Cohort A	Cohort B	Cohort C
Evaluable patients, n	108	20	17
Events, n (%)	85 (78.7)	17 (85.0)	15 (88.2)
Censored, n (%)	23 (21.3)	3 (15.0)	2 (11.8)
Median PFS, mo (95% CI)	7.0 (6.1–10.5)	2.1 (1.2–4.9)	1.5 (1.4–1.8)



Median PFS in cohort A was 7.0 mo
(95% CI: 6.1–10.5)

Overall survival

	Cohort A	Cohort B	Cohort C
Evaluable patients, n	108	20	17
Events, n (%)	76 (70.4)	18 (90.0)	15 (88.2)
Censored, n (%)	32 (29.6)	2 (10.0)	2 (11.8)
Median OS, mo (95% CI)	17.5 (14.4–22.9)	6.7 (2.1–10.6)	4.0 (2.0–4.6)



Reprinted from Vogel A, et al. with permission from the author.

Median OS in cohort A was 17.5 mo
(95% CI: 14.4–22.9)

Vogel A, et al. ESMO-WCGC 2022. Oral presentation 575.

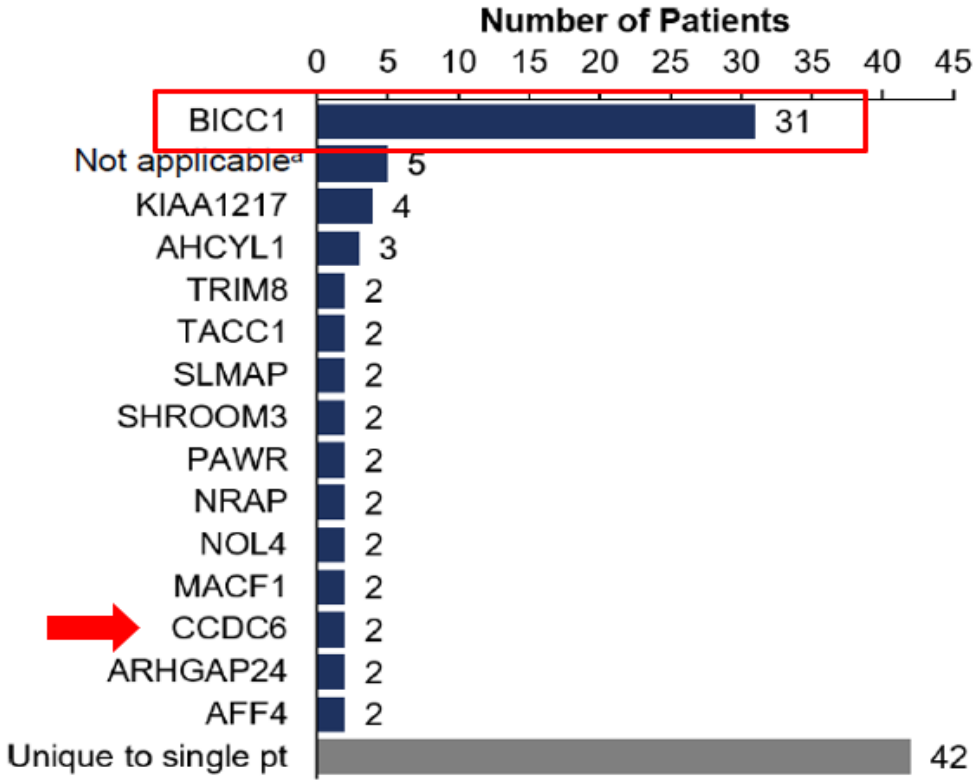
fight-202

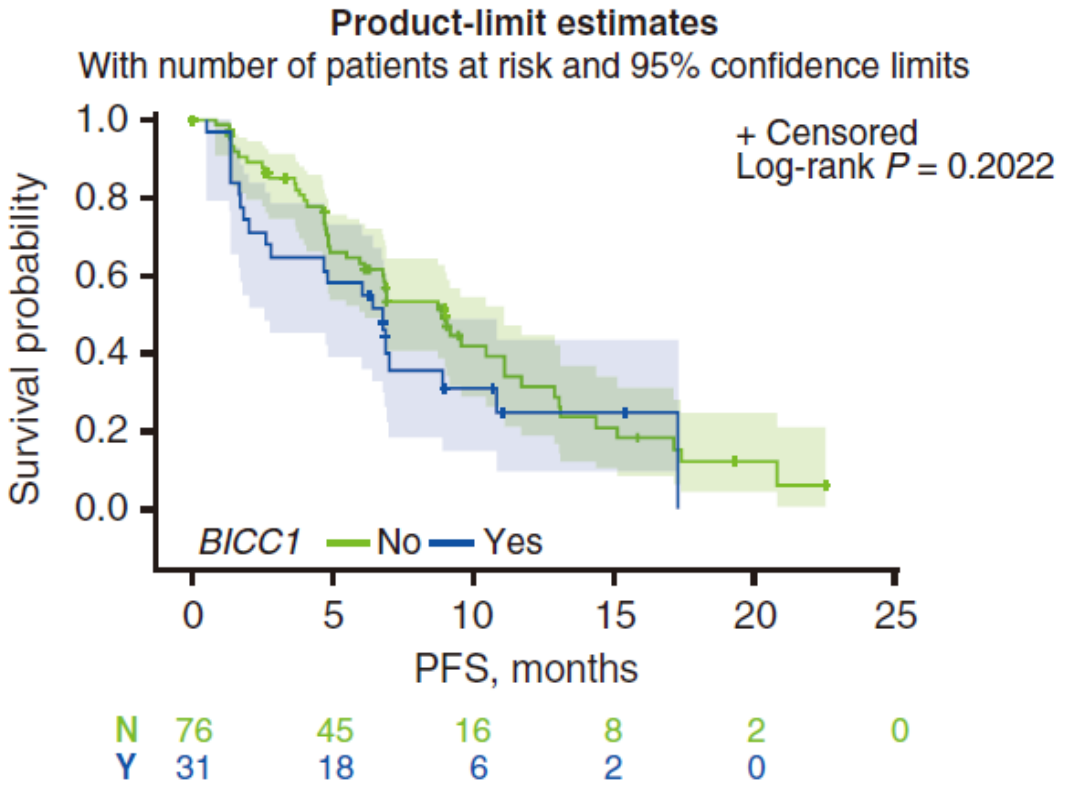
TEAEs occurring in ≥25% of patients overall

Event	Cohort A (n=108)		Cohort B (n=20)		Cohort C (n=17)		Total (N=147)*	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any TEAE, %	100	67	100	75	100	76	100	69
Hyperphosphatemia	56	0	65	0	71	0	59	0
Alopecia	59	0	20	0	18	0	50	0
Diarrhoea	54	4	25	0	35	6	48	3
Fatigue	46	5	25	0	53	18	44	5
Nausea	43	3	35	0	41	0	41	2
Stomatitis	43	9	30	0	18	0	38	7
Constipation	43	1	25	0	12	0	37	1
Dysgeusia	42	0	15	0	18	0	36	0
Decreased appetite	31	1	40	5	41	6	34	2
Dry mouth	39	0	25	0	6	0	34	0
Arthralgia	34	6	25	10	12	0	30	6
Vomiting	33	2	15	0	24	0	29	1
Dry eye	35	0	5	0	6	0	28	1

Abou-Alfa GK, et al. Lancet Oncol. 2020;21:671-684.
Vogel A, et al. ESMO-WCGC 2022. Oral presentation 575.

Rearrangement and fusion partner vs efficacy in FIGHT-202

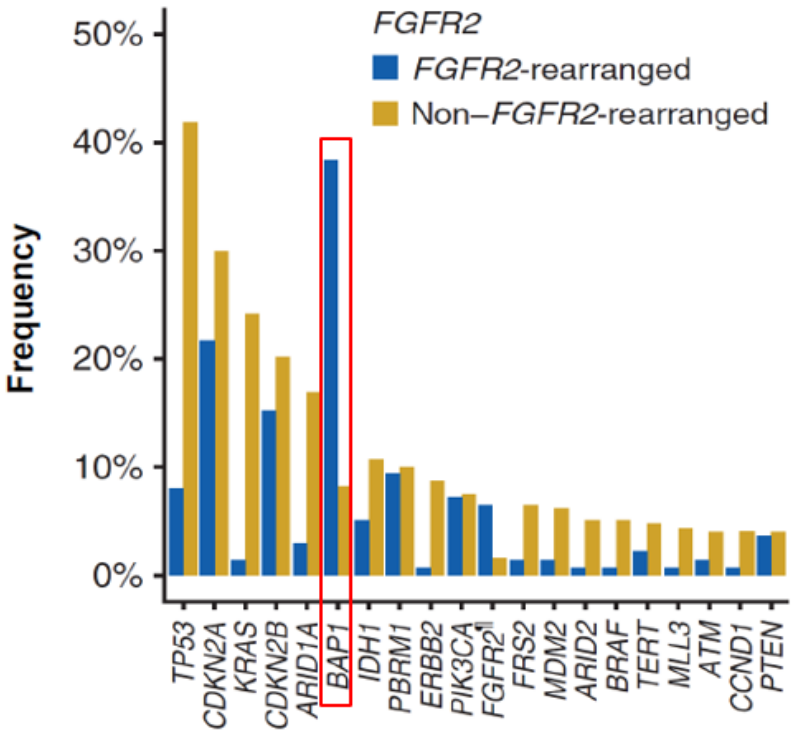




- No significant difference between fusion or rearrangement: ORR (40.0% vs. 34.8%, P = 0.70) and PFS(6.9 months vs. 7.0 months, P = 0.79)
- No significant difference between BICC1 fusion or non-BICC1 fusion: ORR (32.3% vs. 36.8%, P = 0.65) and PFS (6.8 months vs. 9.0 months, P = 0.20)

Abou-Alfa GK, et al. Lancet Oncol. 2020;21:671-84.
Silverman IM, et al. Cancer Discov. 2021;11:326-39.

Genomic co-alterations vs efficacy in FIGHT-202



Co-alteration rate:
FGFR2-rearranged: 63%
Non-FGFR2-rearranged: 75%

Group (*n*)		ORR (%)	OR (95% CI), *P* value	Median PFS (95% CI), months	PFS *P* value
FGFR2+ population (107)		35.5	—	6.9 (6.2-9.6)	—
Tumor suppressor	Unaltered (43)	37.2	0.88 (0.4-2.0), 0.76	**11.7 (9.1-17.4)**	**0.0003**
	Altered (64)	34.4		**6.8 (4.9-6.9)**	
BAP1	Unaltered (68)	30.9	1.7 (0.8-3.9), 0.19	9.1 (6.2-11.7)	0.06
	Altered (39)	43.6		6.9 (4.7-8.9)	
CDKN2A/B	Unaltered (86)	38.4	0.50 (0.2-1.5), 0.22	**9.0 (6.4-11.1)**	**0.03**
	Altered (21)	23.8		**6.4 (1.7-6.9)**	
PBRM1	Unaltered (97)	36.1	0.76 (0.2-3.1), 0.70	**7.0 (6.8-10.5)**	**0.05**
	Altered (10)	30.0		**4.7 (1.4-10.8)**	
TP53	Unaltered (98)	38.8	—[a]	**9.0 (6.8-11.1)**	**0.0003**
	Altered (9)	0		**2.8 (1.4-6.8)**	
PIK3CA	Unaltered (98)	35.7	0.90 (0.2-3.8), 0.89	8.8 (6.4-10.5)	0.10
	Altered (9)	33.3		5.2 (1.5-11.1)	
IDH1	Unaltered (102)	36.3	0.44 (0.05-4.1), 0.47	6.9 (6.1-9.6)	0.28
	Altered (5)	20.0		NE (1.4-NE)	

Tumor suppressors:
BAP1, CDKN2A/B, TP53, PBRM1, ARID1A, PTEN

Silverman IM, et al. Cancer Discov. 2021;11:326-39.

FGFR Inhibitor Landscape: Efficacy

	Pemazyre® (pemigatinb)	TRUSELTIQ™ (infigratinib)	Lytgobi® (futibatinib)
Pivotal study	FIGHT 202[1] (n=108)	Javle[2] (n=108)	FOENIX-CCA2[3] (n=103)
ORR (%)	37	23	42
CR (%)	3	1	1
PR (%)	34	22	41
SD (%)	45	66	42
DCR (%)	82 (73.9-89.1)	84.3 (76.0-90.6)	82.5 (73.8-89.3)
DOR (m)	9.1 (6.0-14.5)	5.0 (0.9-19.1)	9.5 (7.6-10.4)
PFS (m)	7.0 (6.1-10.5)	7.3 (5.6-7.6)	8.9 (6.7-11.0)
OS (m)	17.5 (14.4-22.9)	12.2 (10.7-14.9)	20 (16.4-24.6)
Responder	30.1 (21.5-NE)		
Non-responder	13.7 (9.6-16.1)		

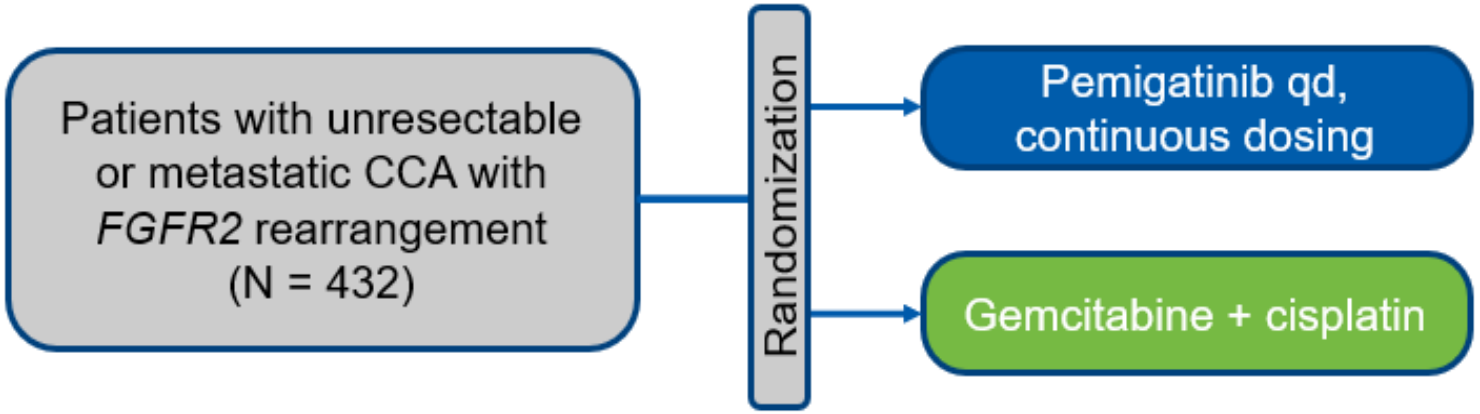
1. Vogel A, et al. ESMO-WCGC 2022. Oral presentation 575. Results of final analysis (January 17, 2017-July 8, 2021); 2. Javle M et al, ASCO GI 2021 Presentation 265. Final Analysis; 3. Goyal L. et al, ASCO 2022 Presentation 4006. Updated Analysis

FGFR Inhibitor Landscape: Safety

	Pemazyre® (pemigatinib)	TRUSELTIQ™ (infigratinib)	Lytgobi® (futibatinib)
FGFR inhibitor	Reversible 1-3 inhibitor	Reversible 1-3	Irreversible 1-4
Pivotal study	FIGHT 202[1] (n=146)	Javle[2] (n=108)	FOENIX-CCA2[3] (n=103)
Retinopathies*	6% / 0.6% (n=466, cross trials)	11% (n=351, cross trials) 17% (n=108)	9% (n=318, cross trial)
Hyperphosphatemia	60%	78% / 11%	91%
Alopecia	49%	38%	34%
Nail changes	43% / 2.1%	57% / 2%	52% / 1.9%
Stomatitis	35% / 5%	56% / 15%	30% / 6%

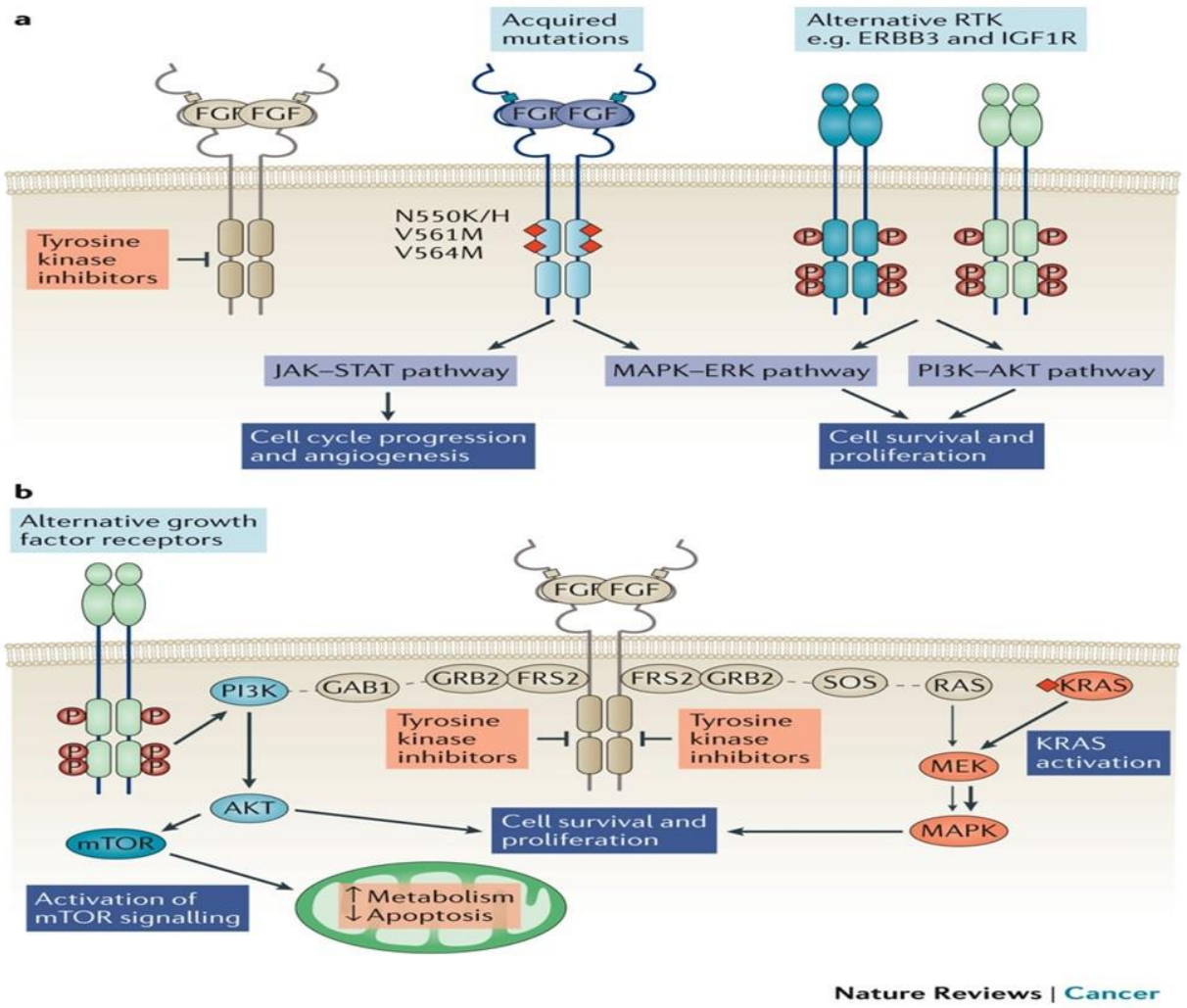
FIGHT-302
Phase 3 Study of Pemigatinib in First-Line Treatment of CCA

- An open-label, randomized, active-controlled study to evaluate the efficacy and safety of pemigatinib vs gemcitabine plus cisplatin chemotherapy in first-line treatment of unresectable or metastatic CCA with *FGFR2* rearrangement (NCT03656536)



- Primary outcome measure: PFS
- Secondary outcome measures: ORR, OS, DOR, DCR, number of treatment-emergent AEs, and QoL
- Sites: 213 centers in US, Austria, Belgium, Canada, China, Denmark, Finland, France, Ireland, Israel, Italy, Japan, Netherlands, Norway, Spain, Sweden, Switzerland, UK,

Acquired Resistance to FGFR Inhibitors

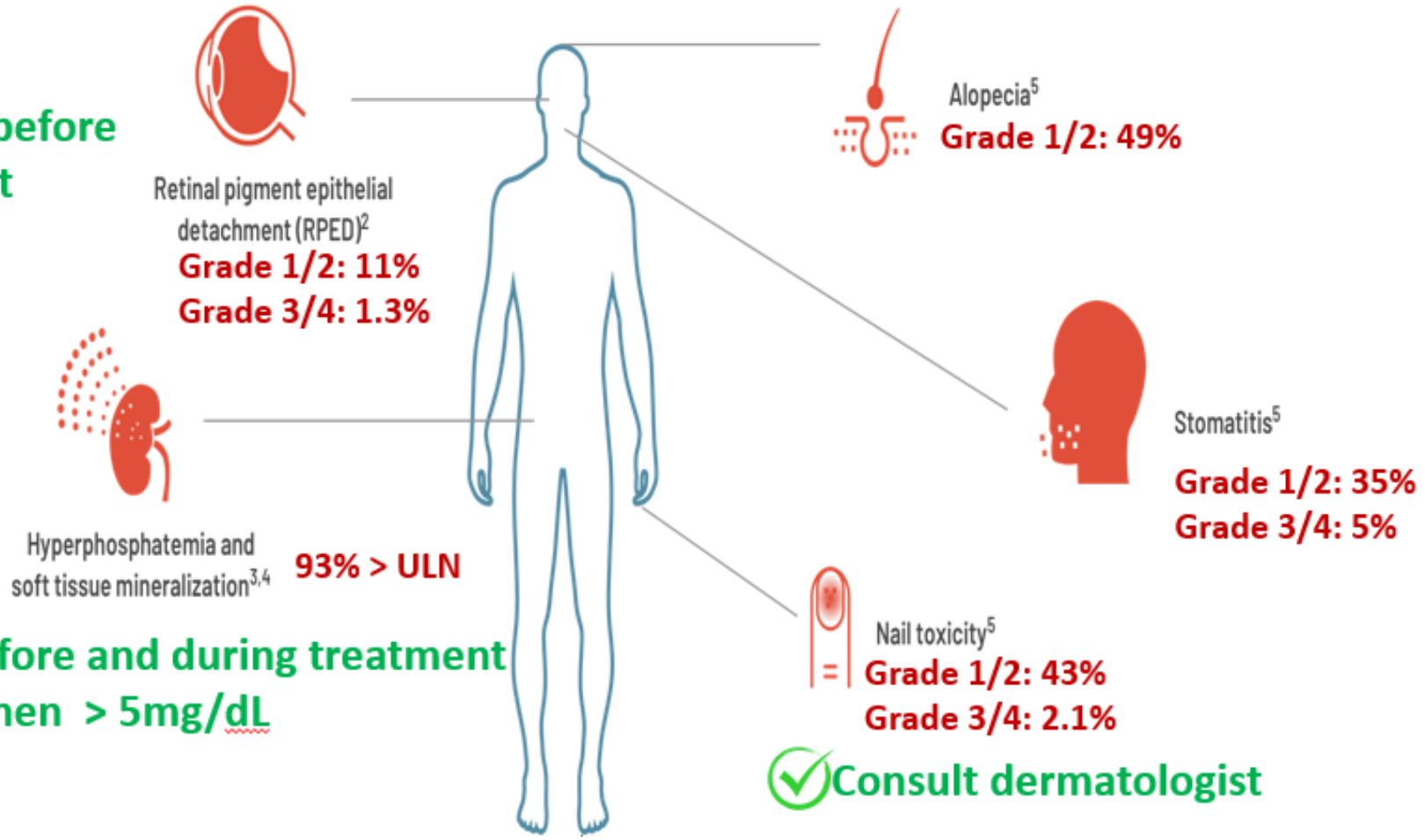


Babina, Nat Reviews 2017;17(5):318-332

Most common AEs of FGFR TKIs: hyperphosphatemia
Common AEs: fatigue, stomatitis, alopecia and nail toxicity
Watchful AEs: RPED

Among 635 patients who received a starting dose of Pemazyre 13.5 mg across clinical trials

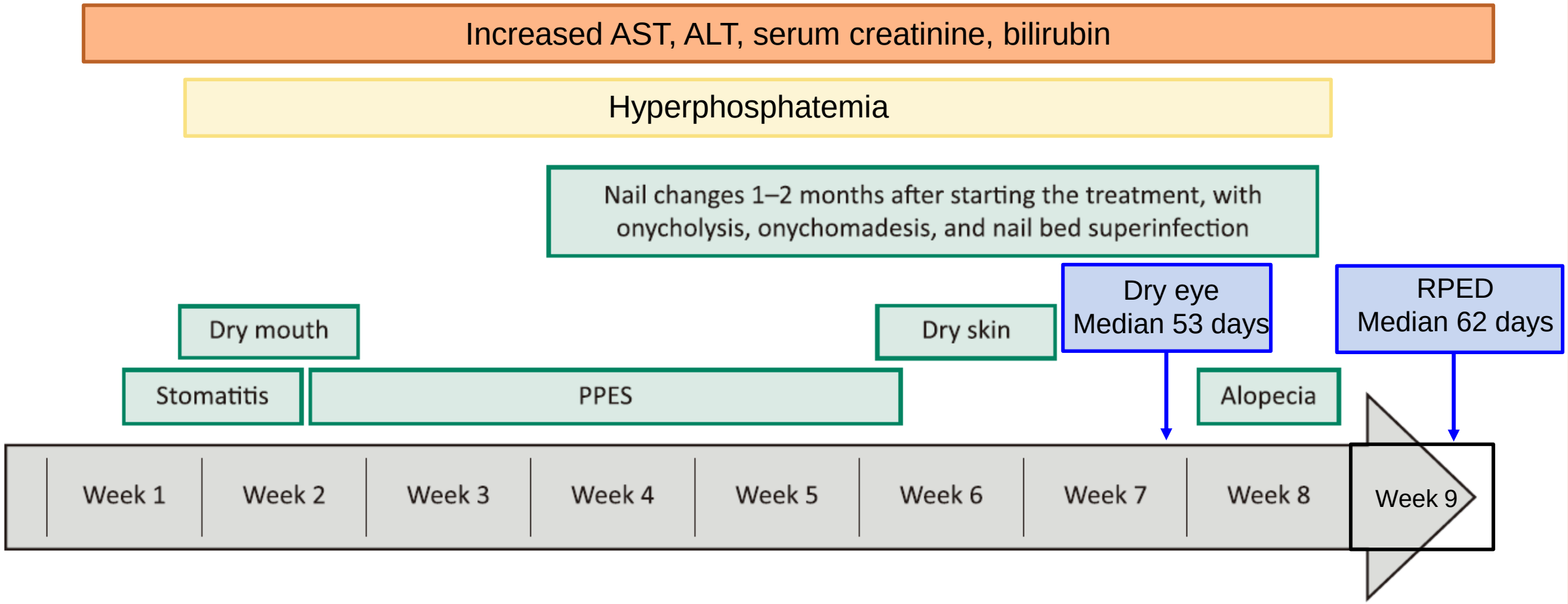
- Complete eye exam before and during treatment
- Check for retina abnormality



- Monitor phosphorus before and during treatment
- Low phosphorus diet when > 5mg/dL
- Consult dermatologist

https://hcp.pemazyre.com/adverse-reactions

Onset of FGFR inhibitor-related adverse events

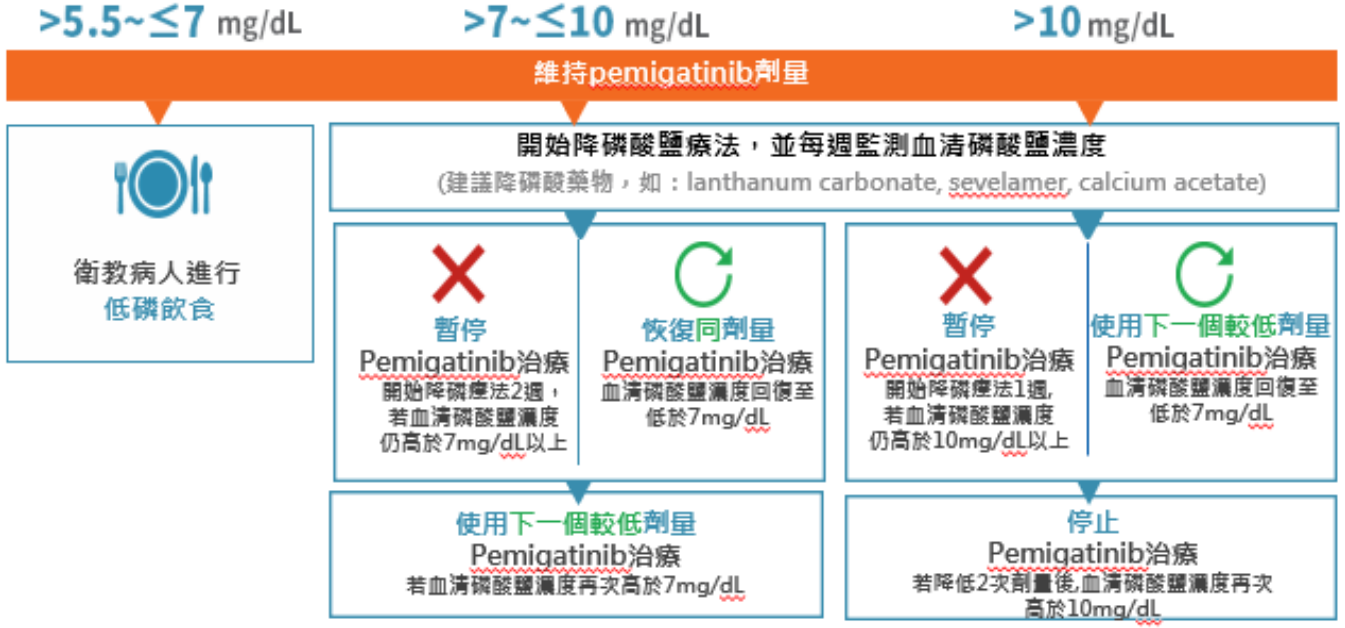


PPES: palmar-plantar erothrodysesthesia
RPED: retinal pigment epithelial detachment

Lacouture ME, et al. Oncologist. 2021;*26:*e316–e326.

PEMAZYRE (pemigatinib) AE and Dose Modification

高磷酸血症 ■ 建議療程開始前及治療期檢測



眼睛毒性 ■ 建議進行完整眼科檢查 ■ 如出現視覺症狀請照會眼科評估

指甲毒性 ■ 如發生症狀請照會皮膚科

Recommended Dose Reductions for Adverse Reactions

Start Initial Dose 起始劑量

13.5mg once daily for 14 days, followed by 7 days off, in 21-day cycles

First Dose Reduction 第一次調降 (9 mg)

Second Dose Reduction 第二次調 (4.5mg)

Discontinue Treatment 終止治療

Permanently discontinue if unable to tolerate pemigatinib 4.5 mg once daily

Pemazyre® Dosing Modification - Hyperphosphatemia

PEMAZYRE Recommended Dosage Modification: Hyperphosphatemia[1]

Serum phosphate **> 5.5 mg/dL**	Serum phosphate **> 7 to ≤10 mg/dL**	Serum phosphate **> 10 mg/dL**
(1) **Initiate a low-phosphate diet**	(2) **Initiate phosphate lowering therapy** Monitor serum phosphate weekly	(2) **Initiate phosphate lowering therapy** Monitor serum phosphate weekly
	(3) **Withhold PEMAZYRE** if levels are not <7 mg/dL within 2 weeks of starting phosphate-lowering therapy	(3) **Withhold PEMAZYRE** if levels are not ≤10 mg/dL within 1 week after starting phosphate-lowering therapy
	Resume PEMAZYRE at the same dose when phosphate levels are <7 mg/dL for first occurrence	**Resume PEMAZYRE at the next lower dose** level when phosphate levels are <7 mg/dL
	(4) **For subsequent recurrences, resume at a lower dose**	(4) If there is recurrence of serum phosphate >10 mg/dL following 2 dose reductions, **Permanently discontinue PEMAZYRE**

- 認識含磷高的食物：
- 含酵母的食物：如養樂多、優酪乳、優格、乳酪、健素糖、酵母粉。
- 乾豆類：綠豆、紅豆、黑豆。
- 全穀類：糙米、薏仁、乾蓮子、全麥製品、小麥胚芽。
- 內臟類：豬心、豬肝、雞胗...。
- 核果類：花生、瓜子、核桃、腰果、栗子、開心果、杏仁果。

PEMIGATINIB DOSING MODIFICATION – OPHTHALMOLOGICAL AEs

When to perform an ophthalmological examination[1]:

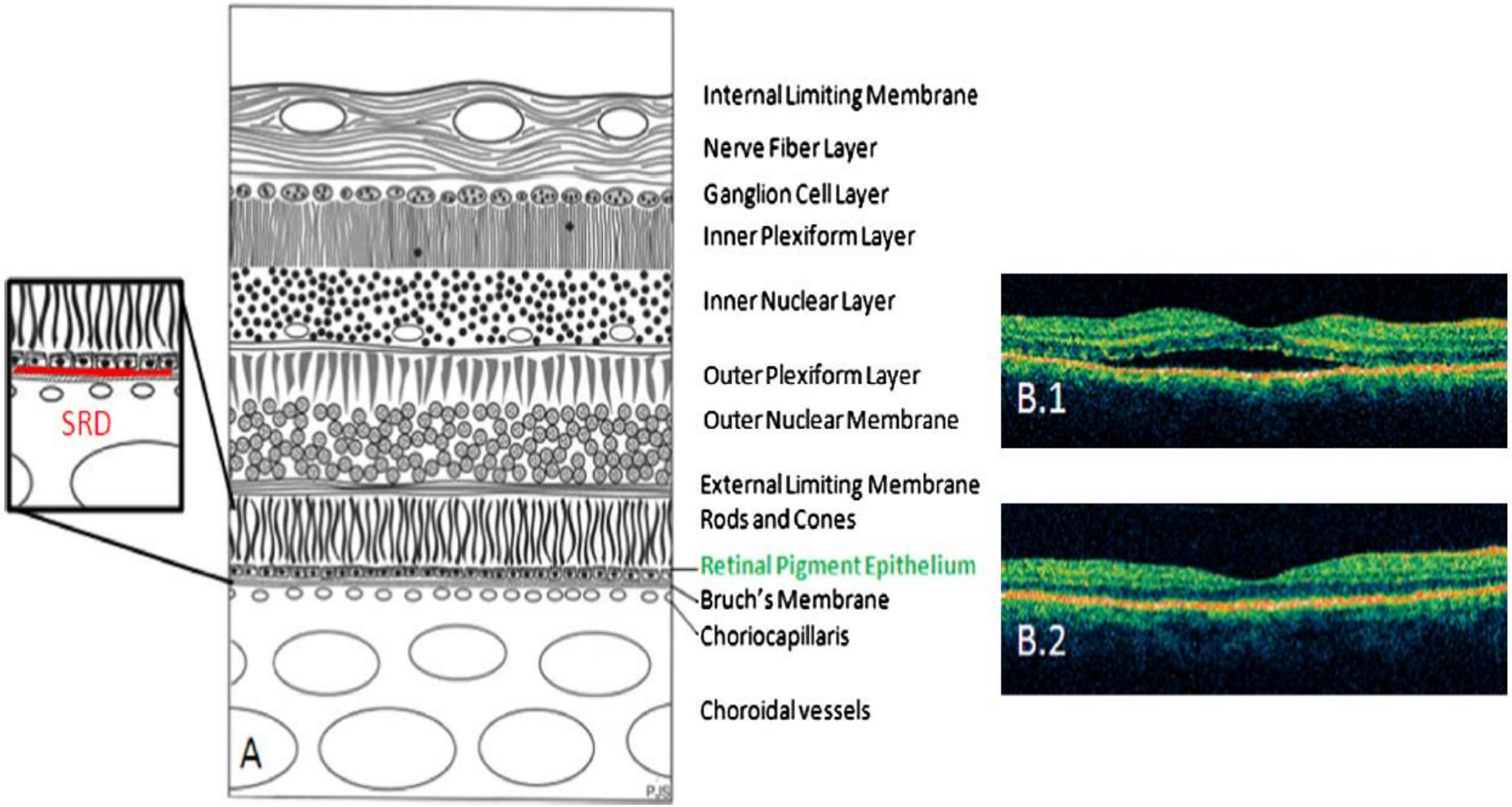
Prior to initiation of therapy → then → **Every 2 months** for the first 6 months of treatment → then → **Every 3 months** afterwards

▸ **and** Urgently at any time for visual symptoms

Management of Serous Retinal Detachment[1]

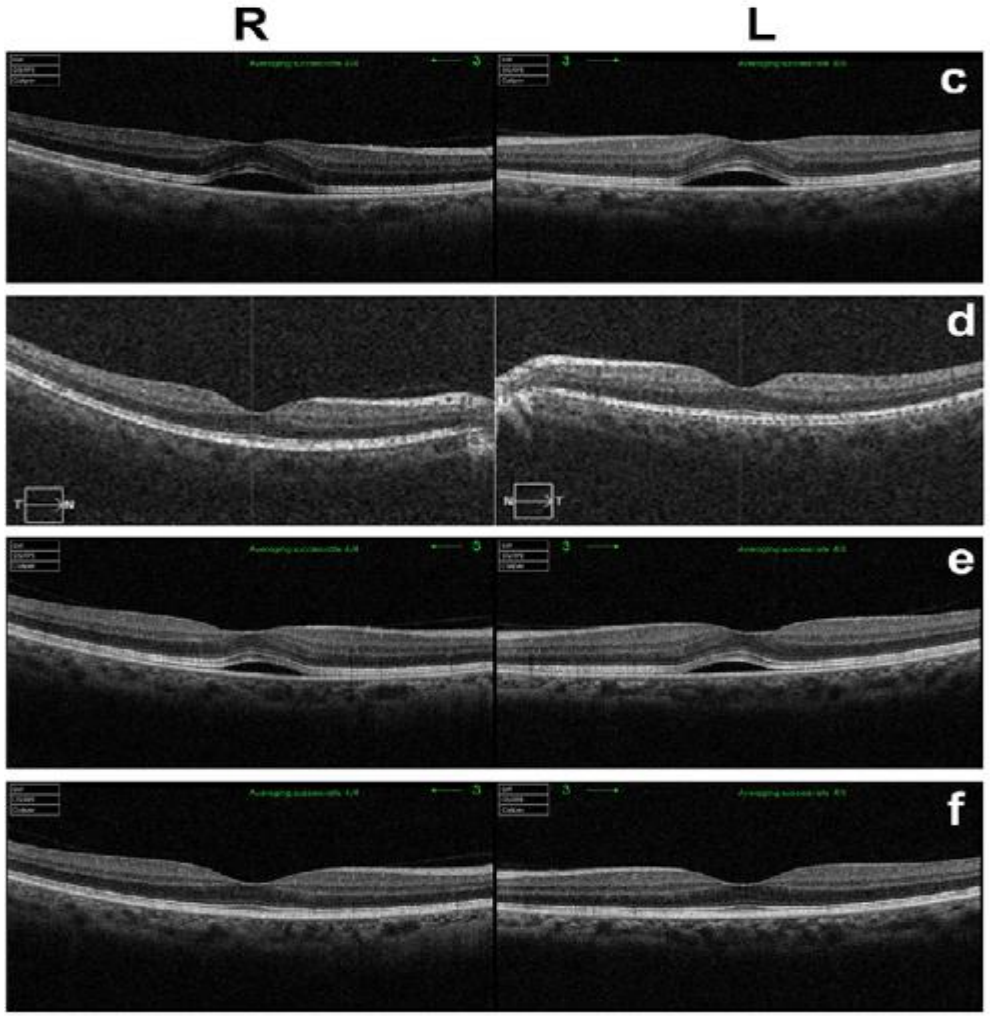
Gr.1	**Asymptomatic**	Continue PEMAZYRE at current dose. Monitor as described in Warnings and Precautions
Gr.2	**Moderate decrease in visual acuity** (best corrected visual acuity 20/40 or better or ≤3 lines of decreased vision from baseline); limiting instrumental activities of daily living.	Withhold until resolution. If resolves within 3 weeks, resume at the next lower dose level
Gr.3	**Marked decrease in visual acuity** (best corrected visual acuity worse than 20/40 or >3 lines of decreased vision from baseline up to 20/200); limiting activities of daily living.	Withhold until resolution. If resolves within 3 weeks, may resume at 2 dose levels lower. If recurs, consider permanent discontinuation
Gr.4	**Visual acuity worse than 20/200 in affected eye; limiting activities of daily living**	Permanently discontinue

Organization of the retina (vertical section)



Van der Noll R, et al. Cancer Treat Rev. 2013;39:664-72.

A 54 year-old Japanese woman with ICC (FGFR2-BICC1 fusion)
1st-line gemcitabine-S1; 2nd-line pemigatinib (partial response)



Optical coherence tomography (OCT)

After 7 days of 13.5 mg pemigatinib (cycle 1)
Grade 2 serous retinal detachment (SRD)

SRD recovered after interruption of pemigatinib for 8 days

SRD recurred after 13 days of 9 mg pemigatinib re-treatment

SRD recovered after interruption of pemigatinib for 9 days

Yukutake M, et al. Int Med. 2023;62:1151-5.


Thanks for your attention