Cholangiocarcinoma

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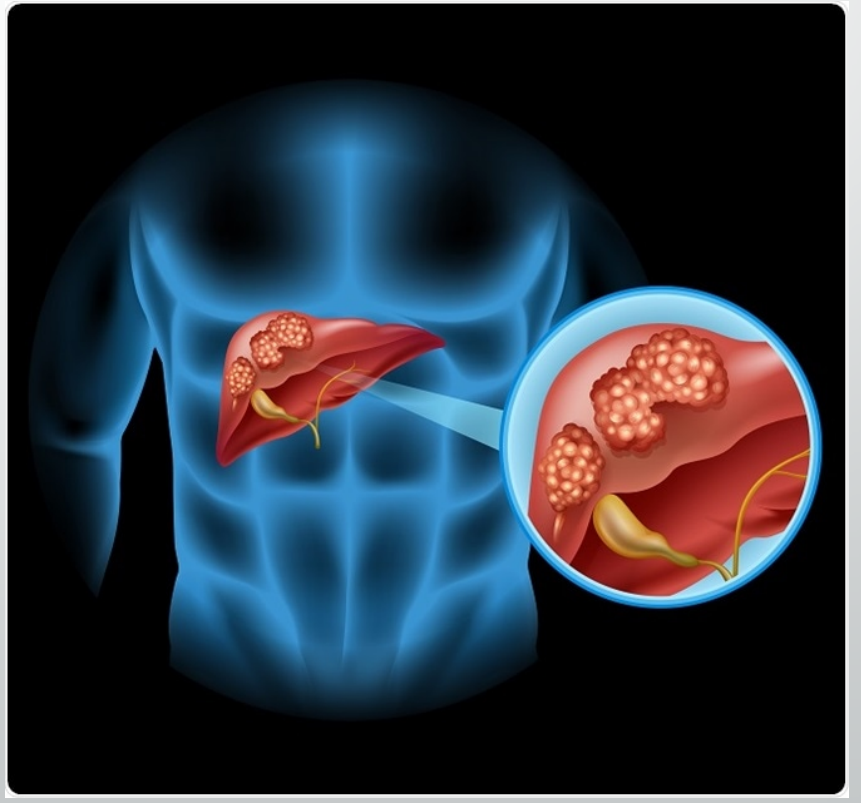
October 26th, 2024

Disclosures

- None

Cholangiocarcinoma

- Outline
  - Introduction
  - Resectable Disease
  - Metastatic Disease
  - Future Directions

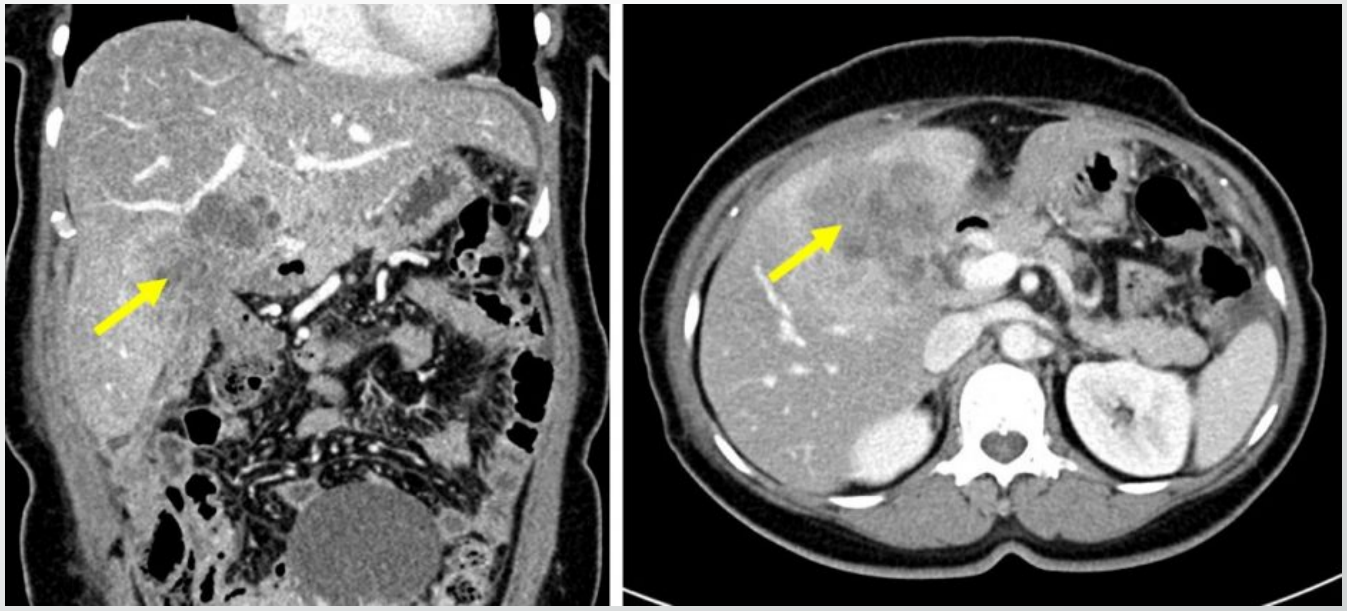


Cholangiocarcinoma: Risk Factors

- No predisposing factors are identified in most patients diagnosed with CCA, although there is evidence that particular risk factors may be associated with the disease in some patients. These risk factors, like those for gallbladder cancer, are associated with the presence of chronic inflammation. Primary sclerosing cholangitis, chronic calculi of the bile duct (hepatolithiasis), choledochal cysts, and liver fluke infections are well-established risk factors for CCA.

Cholangiocarcinoma: Signs and Symptoms

- jaundice
- dark urine
- clay colored stool
- pain in the abdomen
- fever
- itchy skin
- nausea and vomiting
- weight loss for an unknown reason



Molecular pathology

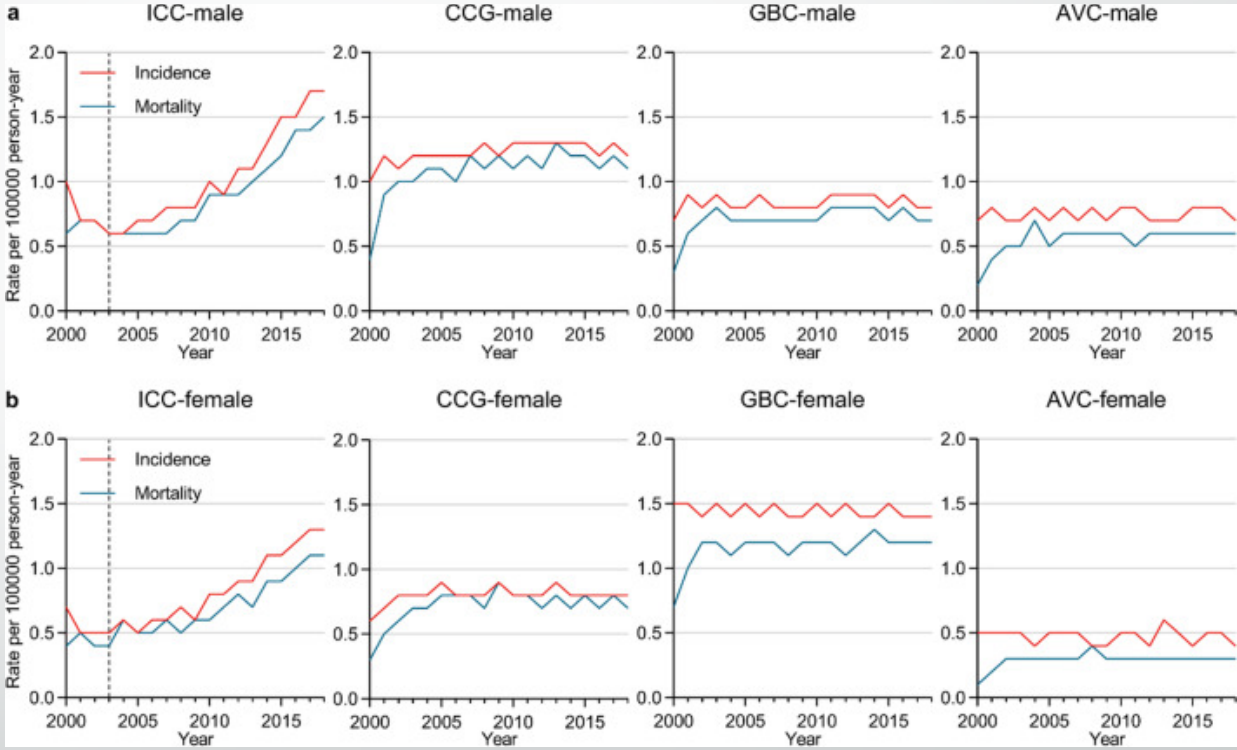
- Precursors to cholangiocarcinoma
  - Biliary intra-epithelial neoplasia (BilN) – more common
  - Intra-ductal papillary neoplasm (IPMN)

- Precursors harbor mutations in p53 & loss of SMAD4

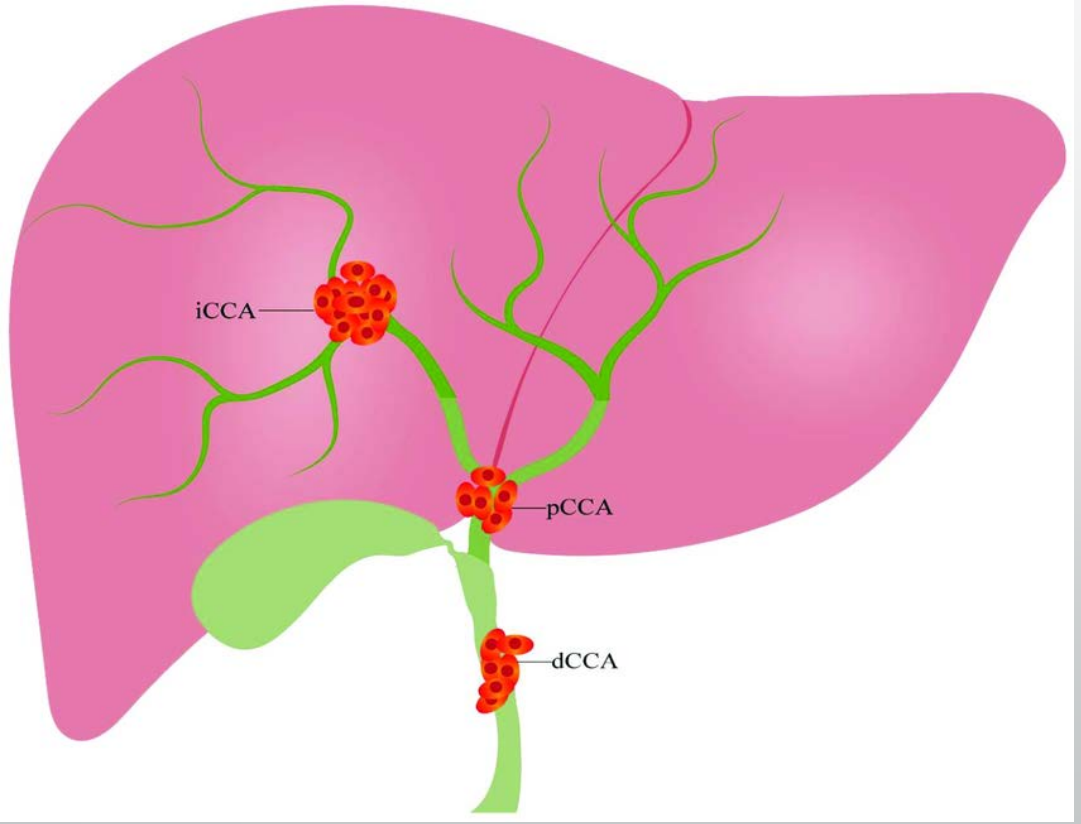
- Molecular defects involves oncogenes & tumor suppresor genes
  - Oncogenes
    - K-ras, c-erbB-2, BRAF, PIK3CA, CTNNB1, EGFR
  - Tumor suppressor genes
    - p53, SMAD4, CDKN2A

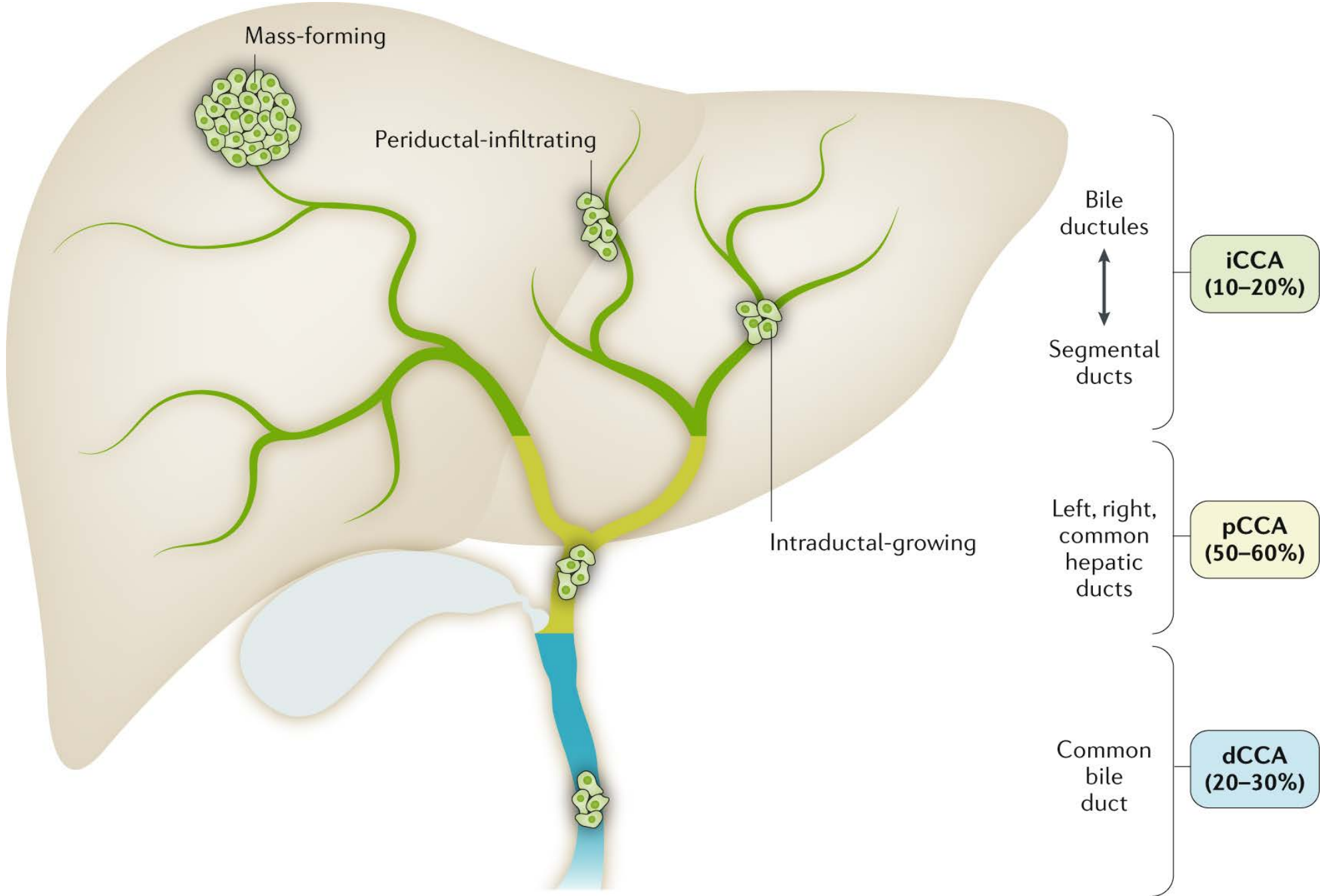
Biliary Tract Cancers

- Incidence:
  - ~2% of all cancer-related deaths worldwide yearly
  - 5 yr survival 7-20%

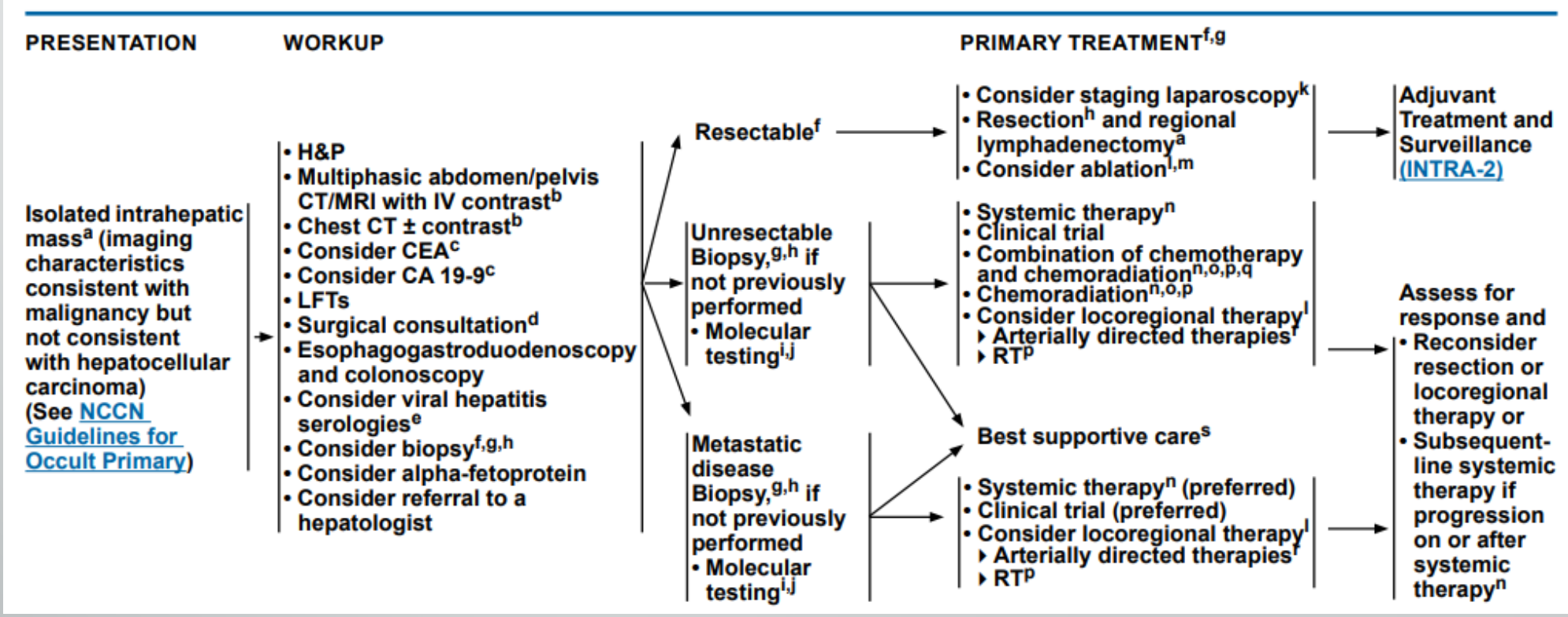


Cholangiocarcinoma: Location, location, location




Mass-forming
Periductal-infiltrating
Intraductal-growing
Bile ductules
Segmental ducts
iCCA (10–20%)
Left, right, common hepatic ducts
pCCA (50–60%)
Common bile duct
dCCA (20–30%)

Cholangiocarcinoma: workup



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*

American Joint Committee on Cancer (AJCC)
TNM Staging for Intrahepatic Bile Duct Tumors (8th ed., 2017)

***Table 5.* Definitions for T, N, M**

T		**Primary Tumor**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma *in situ* (intraductal tumor)
T1		Solitary tumor without vascular invasion, ≤5 cm or >5 cm
	T1a	Solitary tumor ≤5 cm without vascular invasion
	T1b	Solitary tumor >5 cm without vascular invasion
T2		Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3		Tumor perforating the visceral peritoneum
T4		Tumor involving local extrahepatic structures by direct invasion

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis present

***Table 6.* AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

NCCN Guidelines Version 4.2024
Biliary Tract Cancers

American Joint Committee on Cancer (AJCC)
TNM Staging for Perihilar Bile Duct Tumors (8th ed., 2017)

Table 7. **Definitions for T, N, M**

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals bilaterally with contralateral portal vein or hepatic artery involvement

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 8. **AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IVA	Any T	N2	M0
Stage IVB	Any T	Any N	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

American Joint Committee on Cancer (AJCC)
TNM Staging for Distal Bile Ducts Tumors (8th ed., 2017)

Table 9. **Definitions for T, N, M**

T	Primary Tumor
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor invades the bile duct wall with a depth less than 5 mm
T2	Tumor invades the bile duct wall with a depth of 5–12 mm
T3	Tumor invades the bile duct wall with a depth greater than 12 mm
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

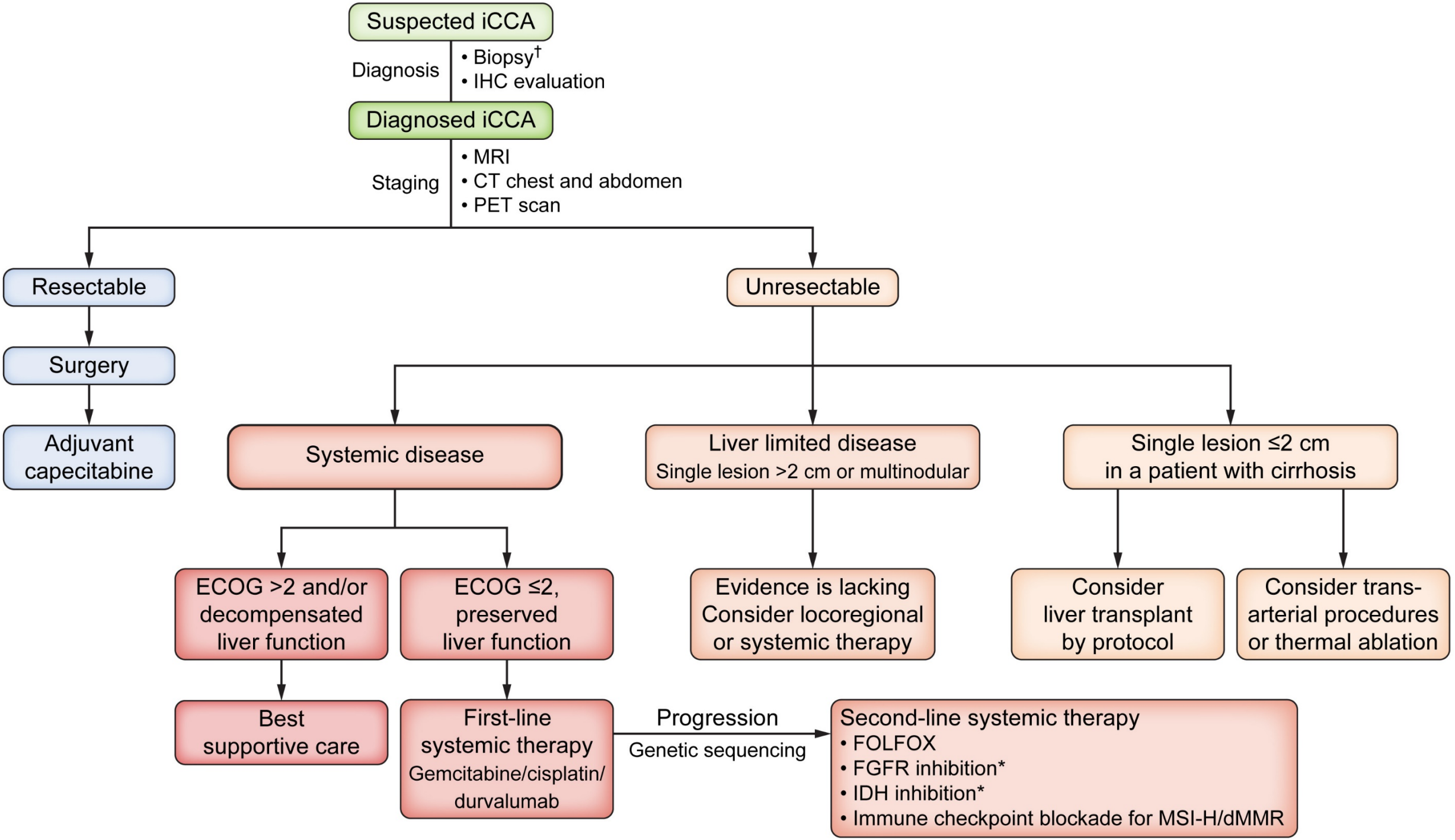
M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 10. **AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IV	Any T	Any N	M1

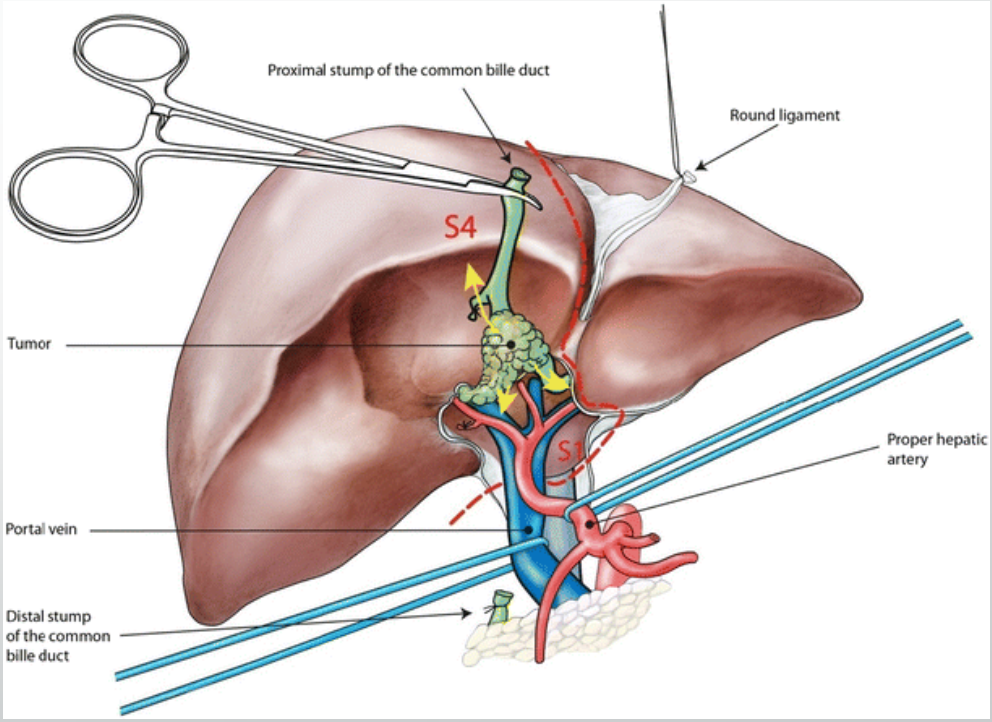
Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

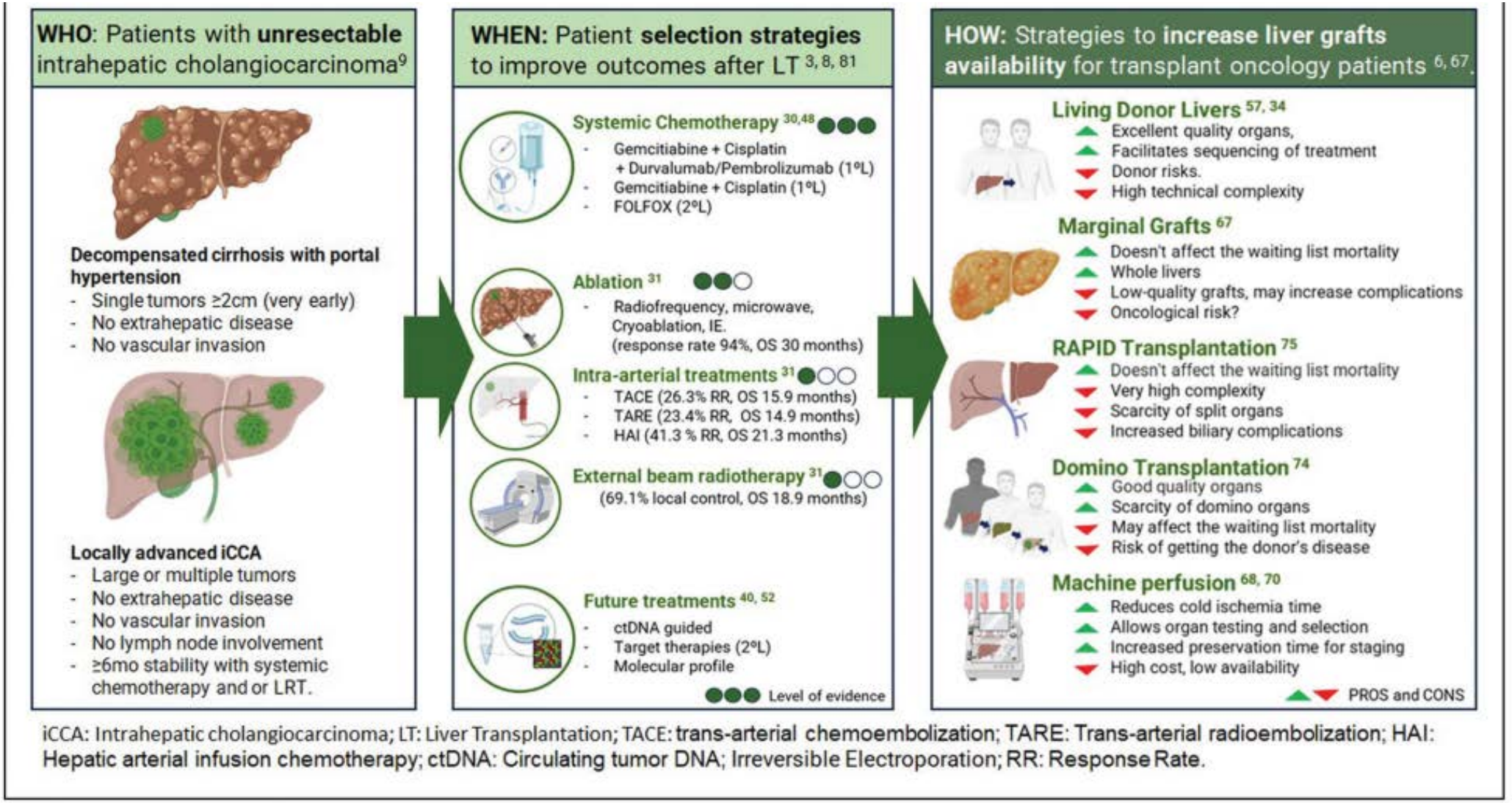

Suspected iCCA
Diagnosis
• Biopsy†
• IHC evaluation
Diagnosed iCCA
Staging
• MRI
• CT chest and abdomen
• PET scan
Resectable
Surgery
Adjuvant capecitabine
Unresectable
Systemic disease
Liver limited disease
Single lesion >2 cm or multinodular
Single lesion ≤2 cm
in a patient with cirrhosis
ECOG >2 and/or decompensated liver function
ECOG ≤2, preserved liver function
Evidence is lacking
Consider locoregional or systemic therapy
Consider liver transplant by protocol
Consider trans-arterial procedures or thermal ablation
Best supportive care
First-line systemic therapy
Gemcitabine/cisplatin/ durvalumab
Progression
Genetic sequencing
Second-line systemic therapy
• FOLFOX
• FGFR inhibition*
• IDH inhibition*
• Immune checkpoint blockade for MSI-H/dMMR

Cholangiocarcinoma: Resectability

Bilateral hepatic duct involvement up to secondary radicals.
Bilateral hepatic artery involvement.
Encasement of the portal vein proximal to its bifurcation.
Atrophy of one hepatic lobe with contralateral portal vein encasement.
Atrophy of one hepatic lobe with contralateral biliary radical involvement.
Distant metastasis.



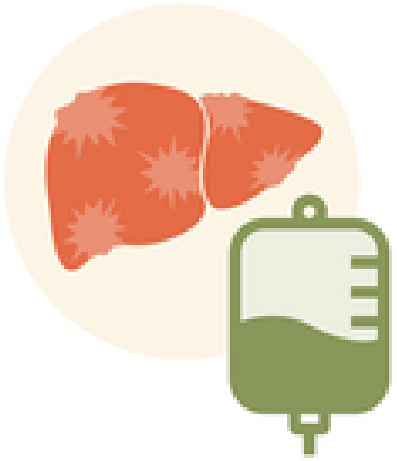
Cholangiocarcinoma:Transplantation



iCCA: Intrahepatic cholangiocarcinoma; LT: Liver Transplantation; TACE: trans-arterial chemoembolization; TARE: Trans-arterial radioembolization; HAI: Hepatic arterial infusion chemotherapy; ctDNA: Circulating tumor DNA; Irreversible Electroporation; RR: Response Rate.

Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma

What are the outcomes for liver Tx after neoadjuvant therapy in patients with intrahepatic cholangiocarcinoma (iCCA)?



Single-center study (2010-2021)

Criteria for liver Tx:

- Locally advanced, unresectable iCCA
- Demonstrate disease stability for 6 months on neoadjuvant therapy
- No extrahepatic disease

18 candidates underwent liver Tx

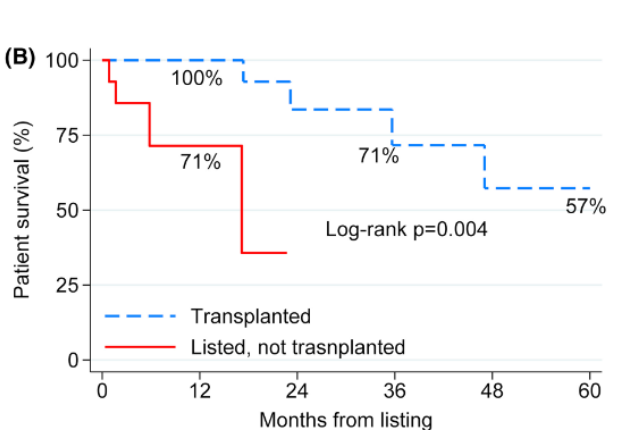
Liver Tx recipients overall survival:

1-year	100%
3-years	71%
5-years	57%

7 patients had recurrences and were treated with systemic therapy and resection

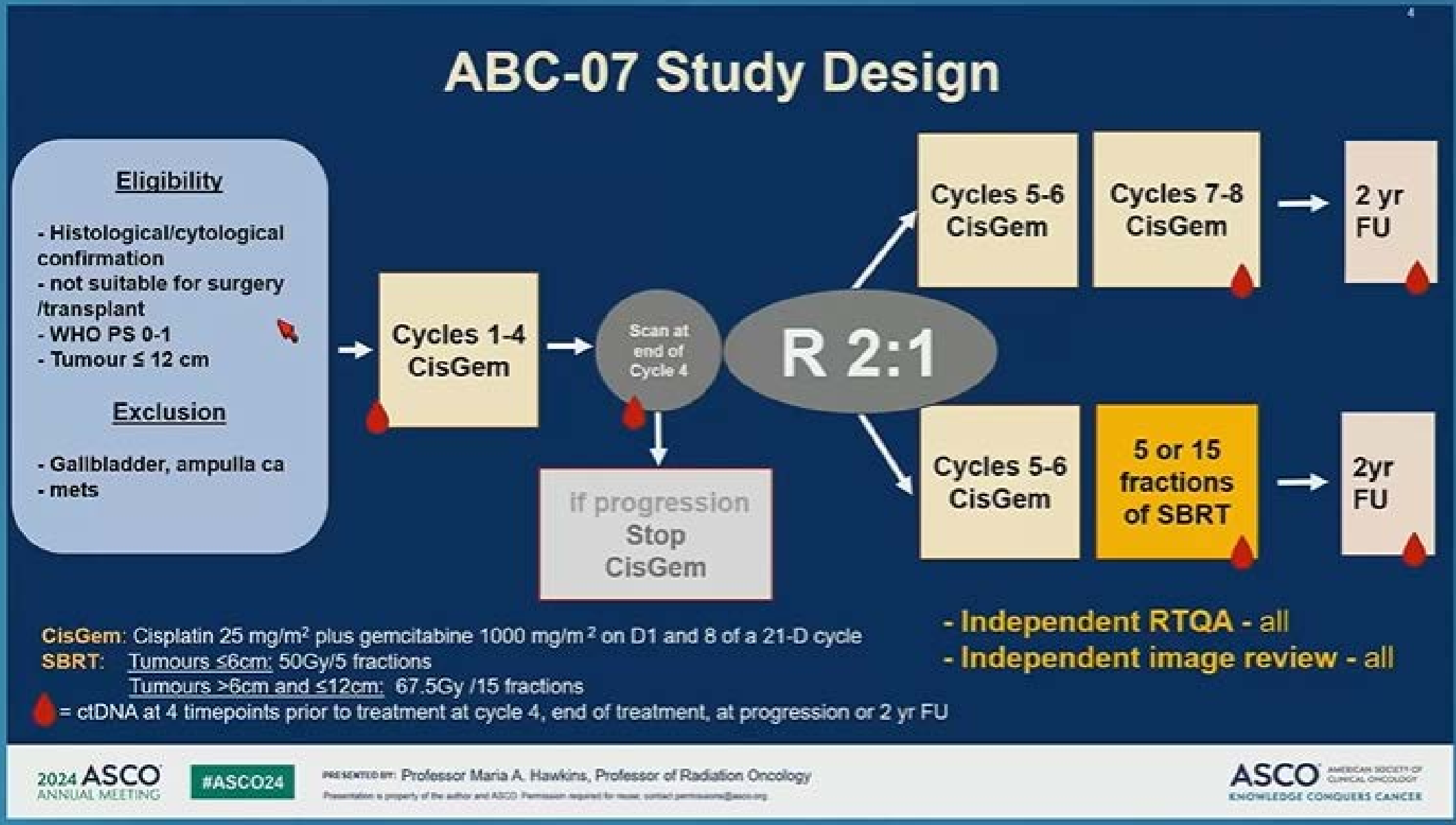
AJT

McMillan et al | *Created by the AJT Editorial Office* | 10.1111/ajt.16906



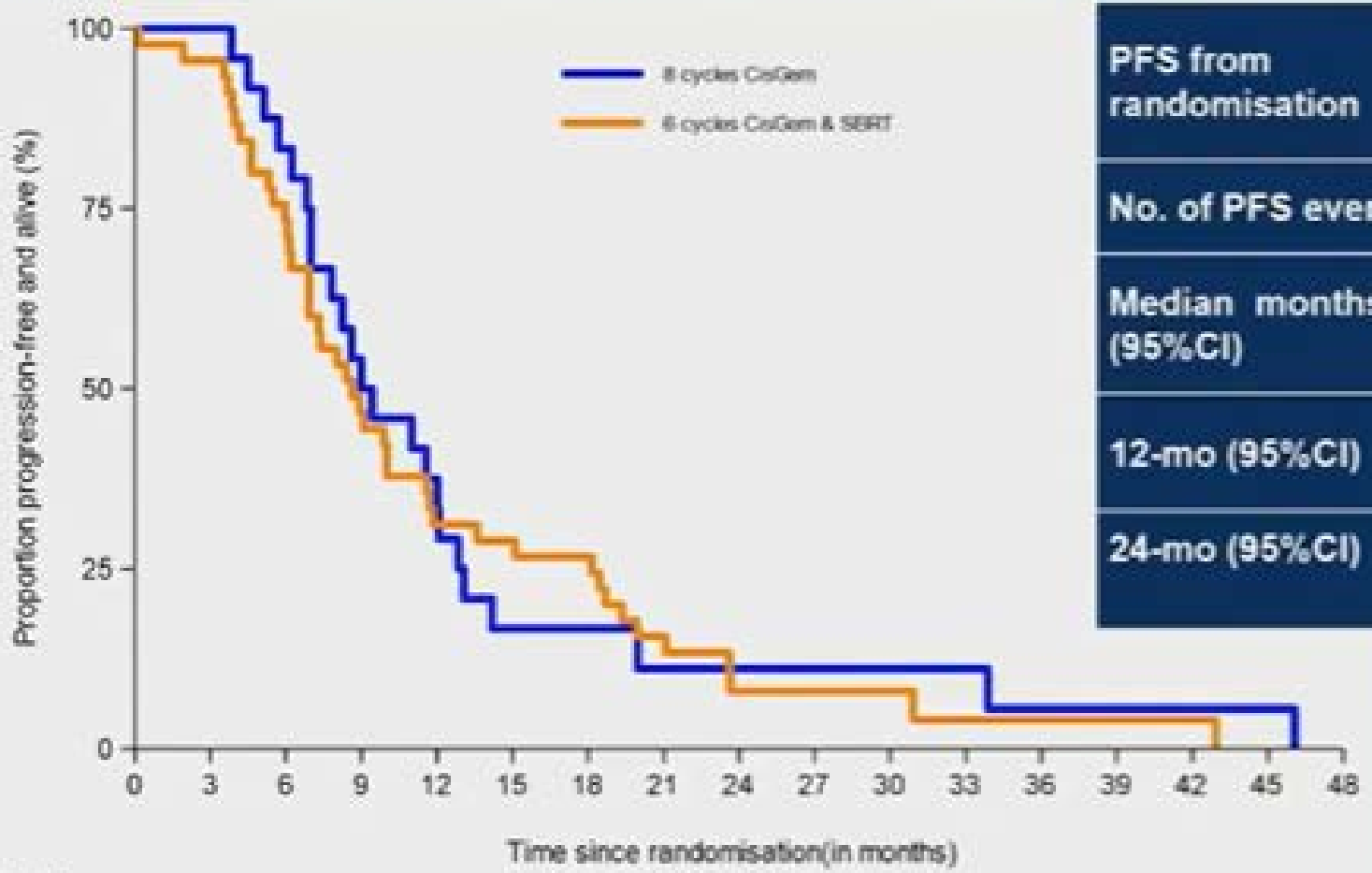
McMillan et al, Am J. Transplantation 2022: 22:823-832

ABC-07 Study Design



PRESENTED BY: Professor Maria A. Hawkins, Professor of Radiation Oncology

1º - Progression Free Survival (PFS) from randomisation



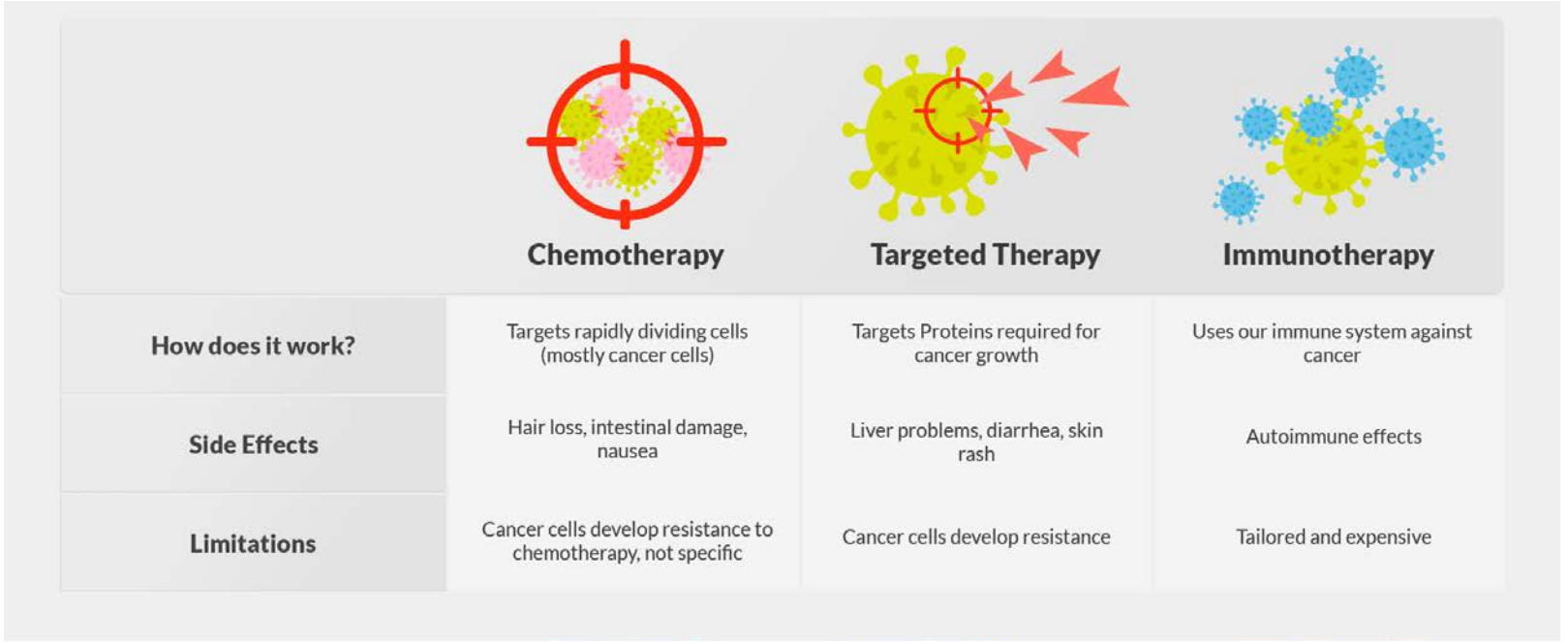
PFS from randomisation	6 CisGem + SBRT N=45	8 CisGem N=24
No. of PFS events	43 (96%)	23 (96%)
Median months (95%CI)	8.6 (6.9 to 11.6)	9.0 (7.0 to 12.1)
12-mo (95%CI)	31.1% (18.4% to 44.7%)	37.5% (19.0% to 56.0%)
24-mo (95%CI)	8% (2.2% to 18.7%)	11.1% (2.3% to 28.0%)

HR: 1.1 95% (CI 0.7 to 1.8)
p = 0.731

Histotripsy: Using ultrasound to treat liver tumors

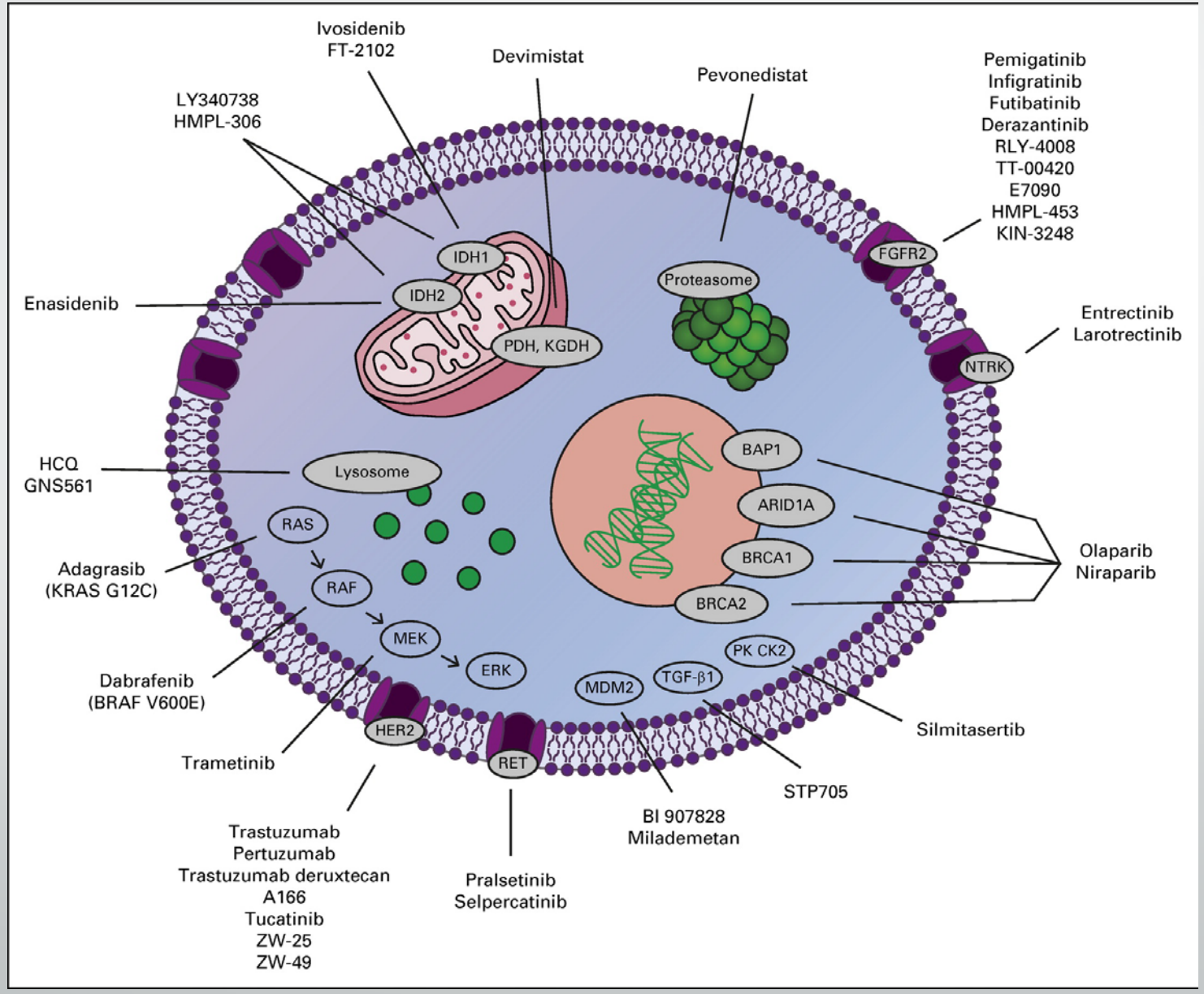

CANCER TREATMENT OPTIONS
HORMONE THERAPY
IMMUNOTHERAPY
SURGERY
RADIATION THERAPY
BONE MARROW TRANSPLANTATION
TARGETED THERAPY
CHEMOTHERAPY

Chemotherapy vs. Targeted Therapy vs Immunotherapy



	Chemotherapy	Targeted Therapy	Immunotherapy
How does it work?	Targets rapidly dividing cells (mostly cancer cells)	Targets Proteins required for cancer growth	Uses our immune system against cancer
Side Effects	Hair loss, intestinal damage, nausea	Liver problems, diarrhea, skin rash	Autoimmune effects
Limitations	Cancer cells develop resistance to chemotherapy, not specific	Cancer cells develop resistance	Tailored and expensive

Targeted Agents



National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Biliary Tract Cancers

PRINCIPLES OF MOLECULAR TESTING

Table 1: Recommendations for Molecular Testing in Unresectable or Metastatic Biliary Tract Cancers[a-d]

Recommended Molecular Testing	Anatomic Subsite		
	Gallbladder	Intrahepatic CCA	Extrahepatic CCA
NTRK gene fusion	X	X	X
MSI-H/dMMR	X	X	X
TMB-H	X	X	X
BRAF V600E mutation	X	X	X
FGFR2 fusion or rearrangement	–	X	X
IDH1 mutation	–	X	X
HER2 *(ERBB2)* overexpression and/or amplification	X	X	X
RET gene fusion	X	X	X
KRAS G12C mutation	X	X	X

MSI-H: microsatellite instability-high
dMMR: mismatch repair deficient
TMB-H: tumor mutational burden-high

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NCCN Guidelines Version 4.2024
Biliary Tract Cancers

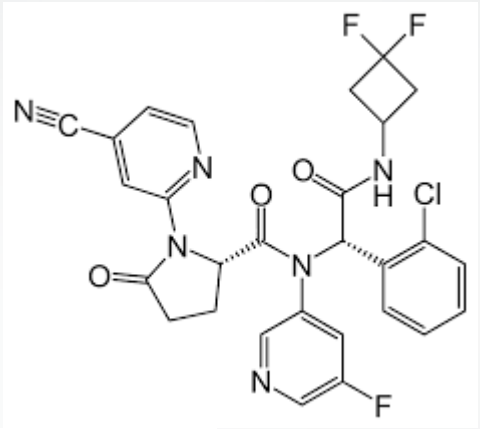
PRINCIPLES OF MOLECULAR TESTING

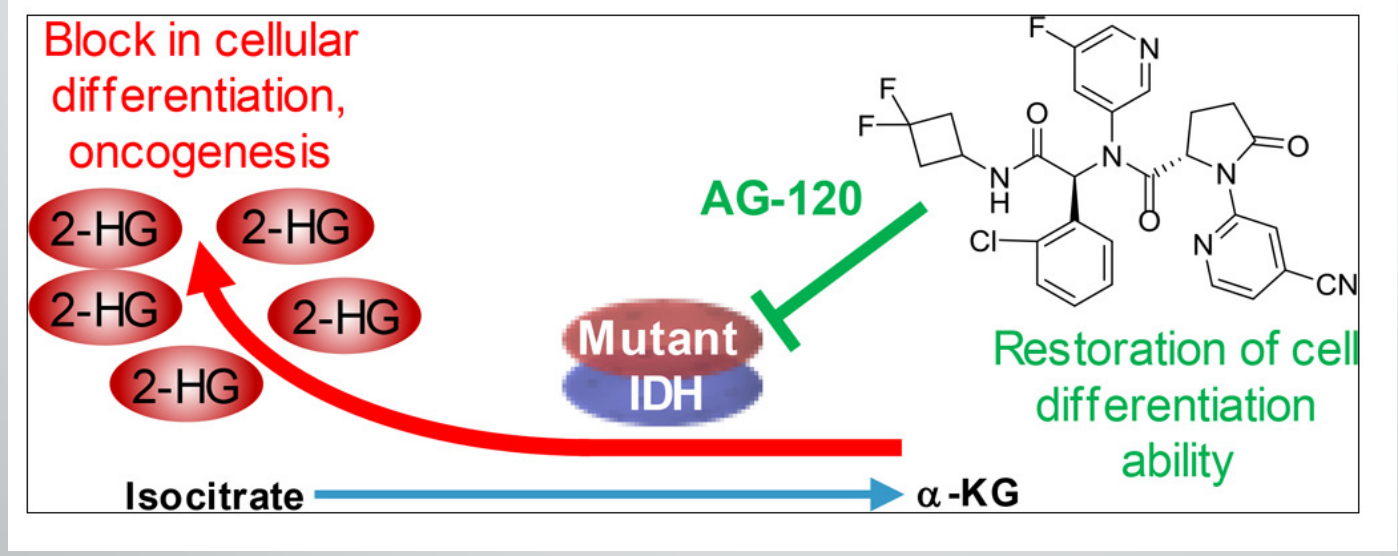
Table 2: Incidence of Therapeutic Targets in Advanced Biliary Tract Cancers

Aberration	Approximate Incidence[e]
NTRK fusion	<1%
MSI-H/dMMR	1%–3%
TMB-H	<5%
BRAF V600E mutation	1%–5%
FGFR2 fusion or rearrangement	9%–15% of intrahepatic CCAs and rare in other subsites
IDH1 mutation	10%–20% of intrahepatic CCAs and rare in other subsites
HER2 (*ERBB2*) overexpression and/or amplification	5%–20% of CCAs, 15%–30% of gallbladder cancer
RET fusion	<1%
KRAS G12C mutation	1%

Targeted Agents

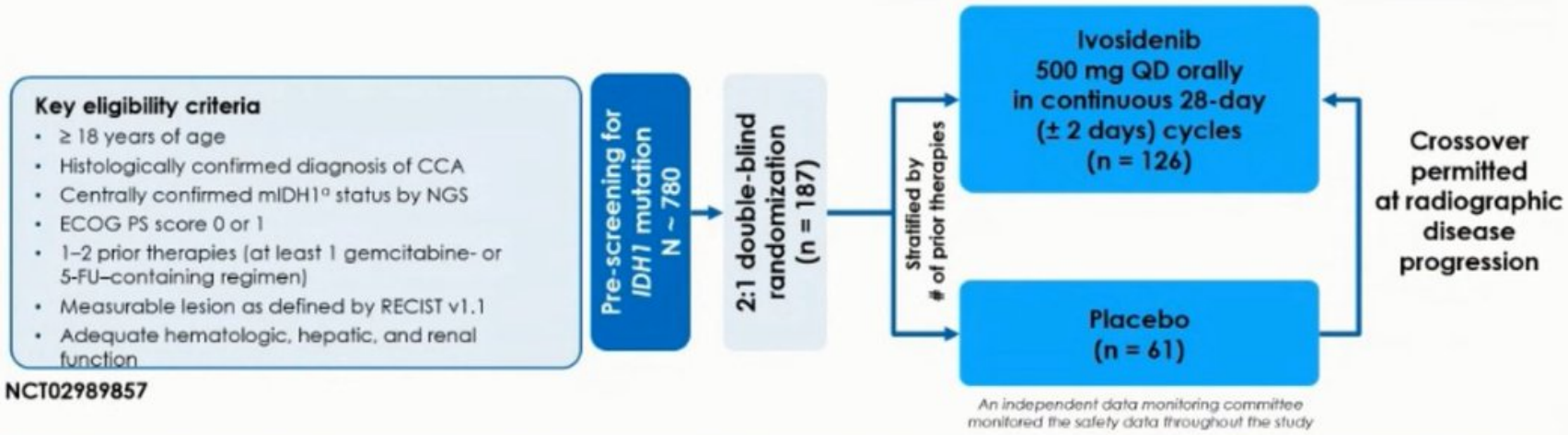
Gene alterations	ESCAT score	Available or potential targeted therapy[a]
IDH1 mutations	IA	Ivosidenib
FGFR2 fusions	IB	Infigratinib, pemigatinib, futibatinib, derazantinib, erdafitinib
dMMR/MSI	IC	Pembrolizumab, nivolumab
NTRK fusions	IC	Entrectinib, larotrectinib
$BRAF^{V600E}$ mutations	IIB	Encorafenib, dabrafenib, vemurafenib
ERBB2 (*HER2*) amplifications, mutations	IIIIA	Trastuzumab, pertuzumab, tucatinib, lapatinib, neratinib, trastuzumab deruxtecan, trastuzumab emtansine, afatinib, dacomitinib
PIK3CA hotspot mutations	IIIA	Alpelisib, copanlisib
BRCA 1/2 mutations	IIIA	Olaparib
MET amplification	IIIA	Crizotinib, capmatinib
KRAS G12C	–	Adagrasib
RET	–	Selpercatinib, pralsetinib




Block in cellular differentiation, oncogenesis
2-HG
2-HG
2-HG
2-HG
2-HG
AG-120
Mutant IDH
Restoration of cell differentiation ability
Isocitrate
α-KG


NDC 72694-617-60
TIBSOVO®
(ivosidenib tablets)
250 mg
Dispense the enclosed Medication Guide to each patient
Swallow tablets whole. Do not split, crush, or chew the tablet.
Rx only
60 Tablets
IVO
250

Phase 3 ClarIDHy study: Study design and endpoints

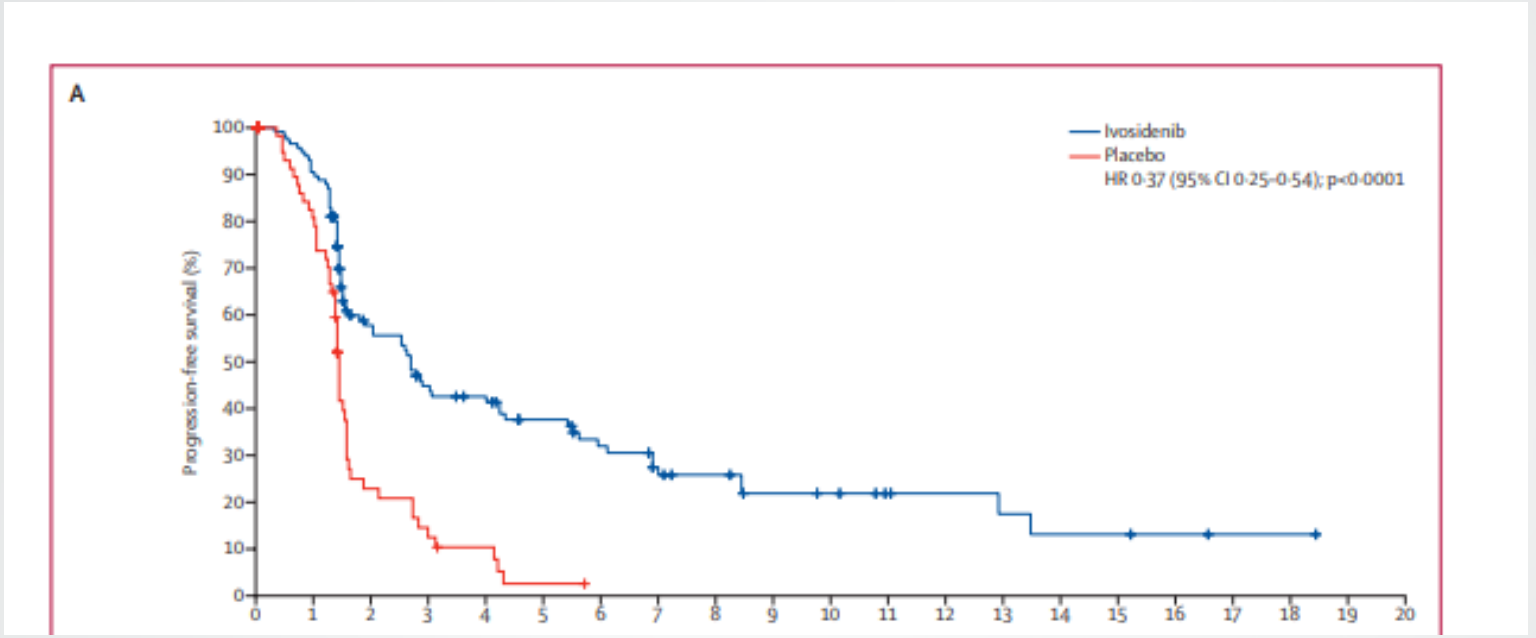


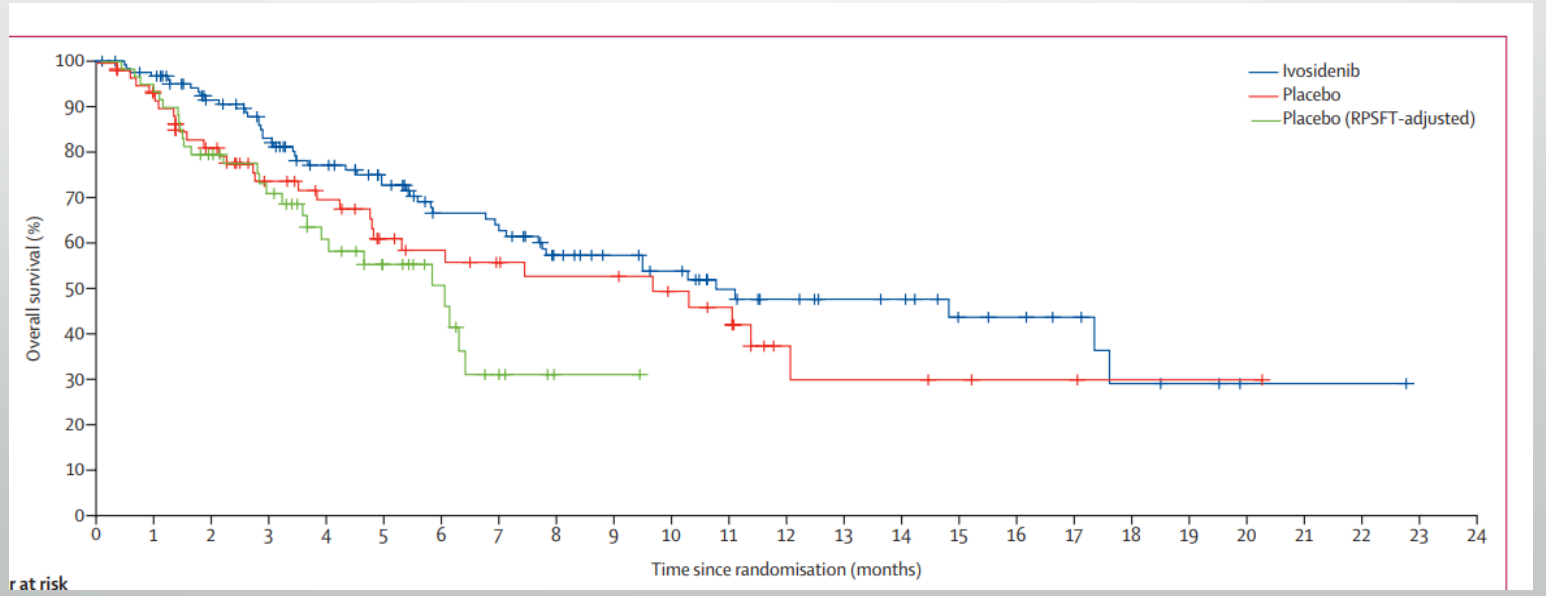
- **Primary endpoint:** PFS by blinded independent radiology center (IRC)
- **Key secondary endpoints:** OS; objective response rate; PFS by local review; pharmacokinetics/ pharmacodynamics; health-related quality of life (HRQOL);[b] safety and tolerability

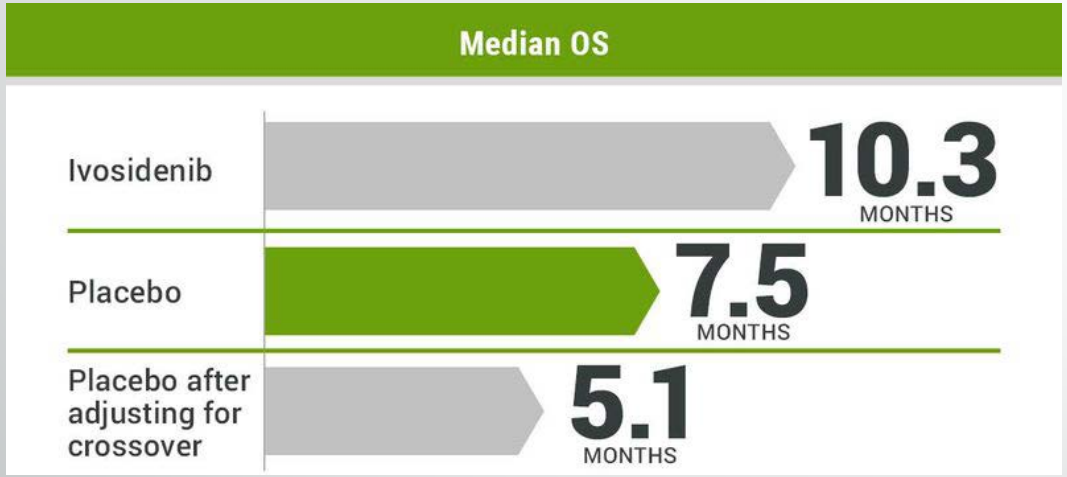
[a]IDH1 mutation status prospectively confirmed by NGS-based Oncomine™ Focus Assay on formalin-fixed, paraffin-embedded tumor tissue in a Clinical Laboratory Improvement Amendments–certified laboratory
[b]Assessed using EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BIL21, and PGI questions

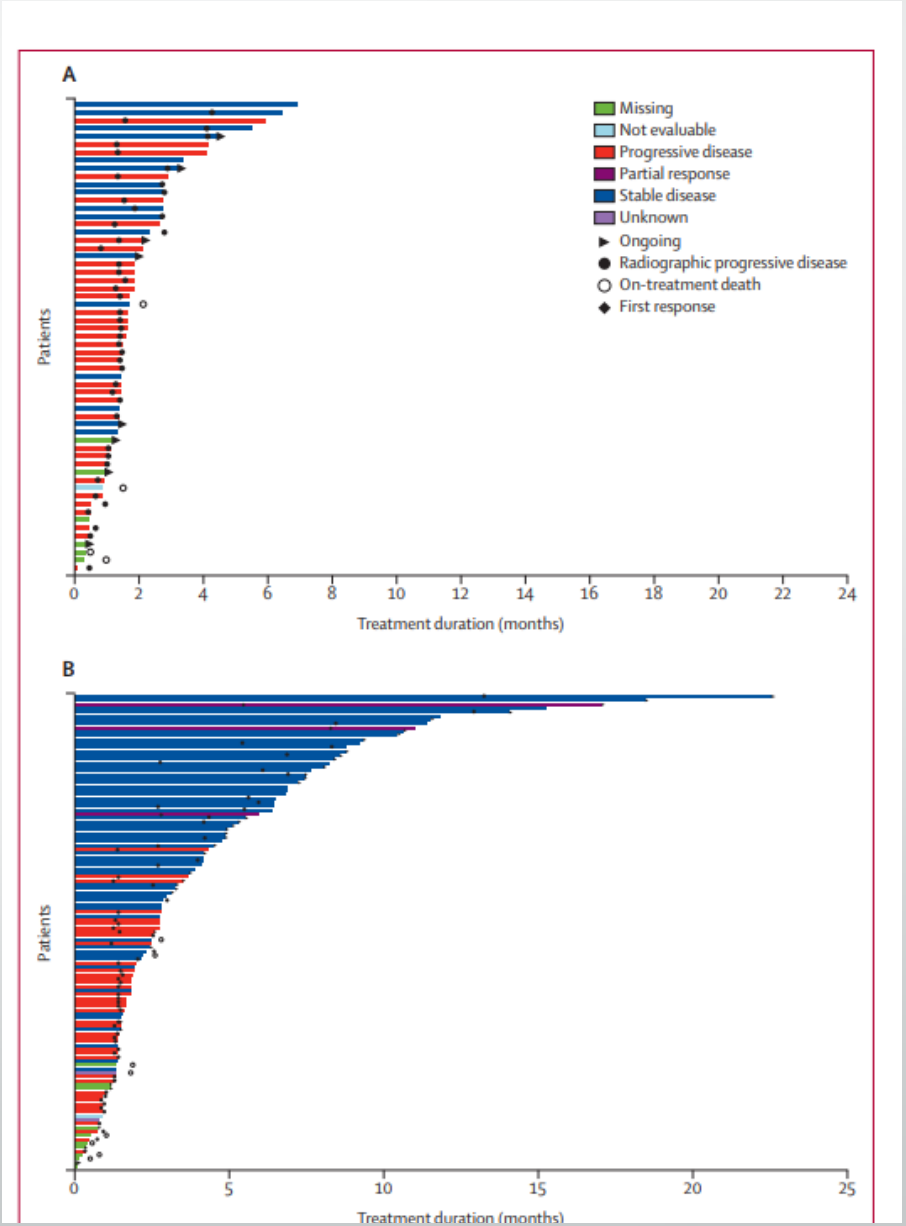
CCA = cholangiocarcinoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = 5-level EuroQoL-5 Dimension questionnaire; FU = fluorouracil; NGS = next-generation sequencing; PGI = Patient Global Impression; QD = once daily; QLQ-BIL21 = Cholangiocarcinoma and Gallbladder Cancer module; QLQ-C30 = Quality of Life Questionnaire Core 30; RECIST = Response Evaluation Criteria in Solid Tumors

Abou-Alfa GK et al. *Lancet Oncol* 2020;21:796–807.

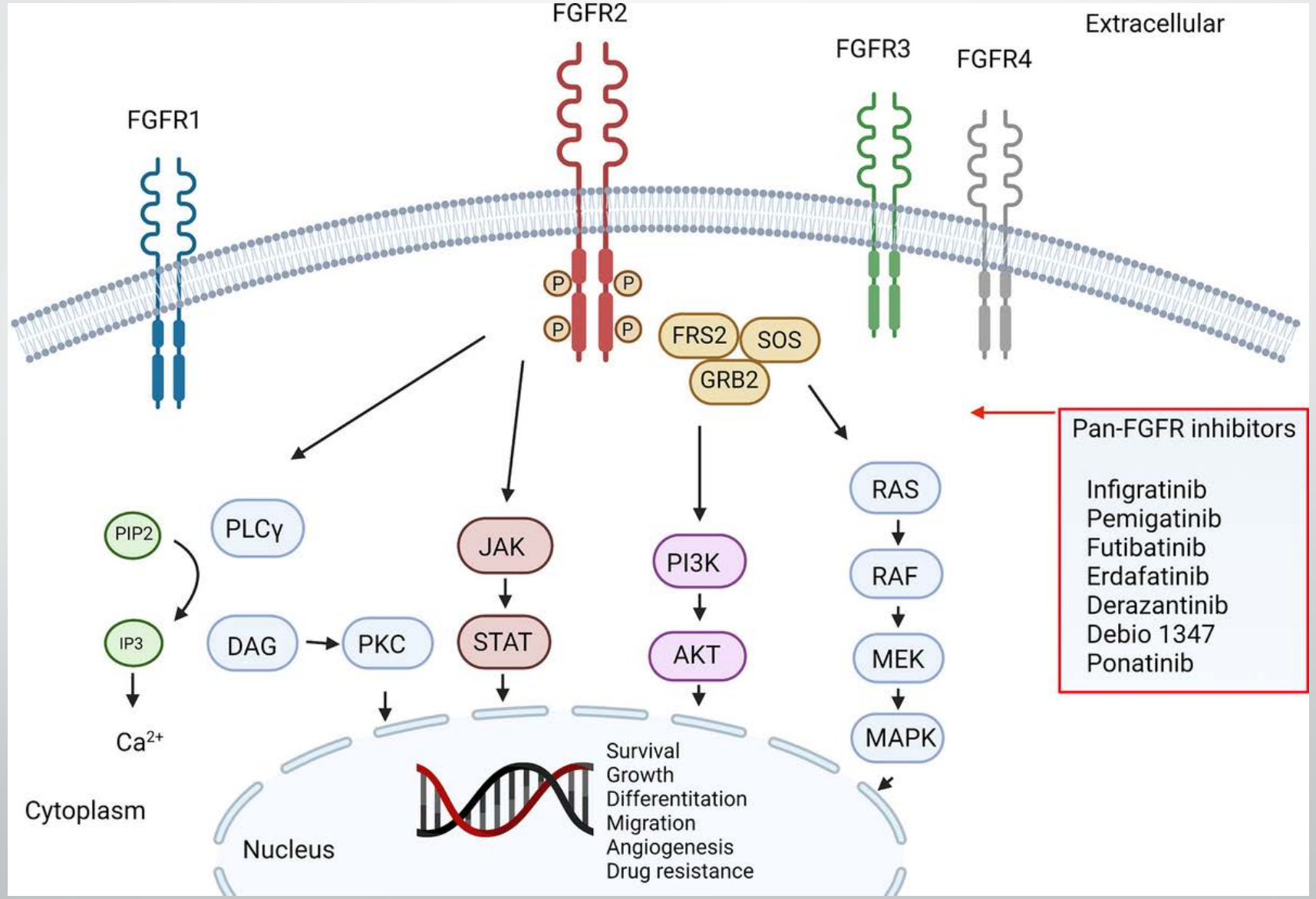

A
Ivosidenib
Placebo
HR 0·37 (95% CI 0·25–0·54); p<0·0001
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20


Ivosidenib
Placebo
Placebo (RPSFT-adjusted)
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Time since randomisation (months)
r at risk

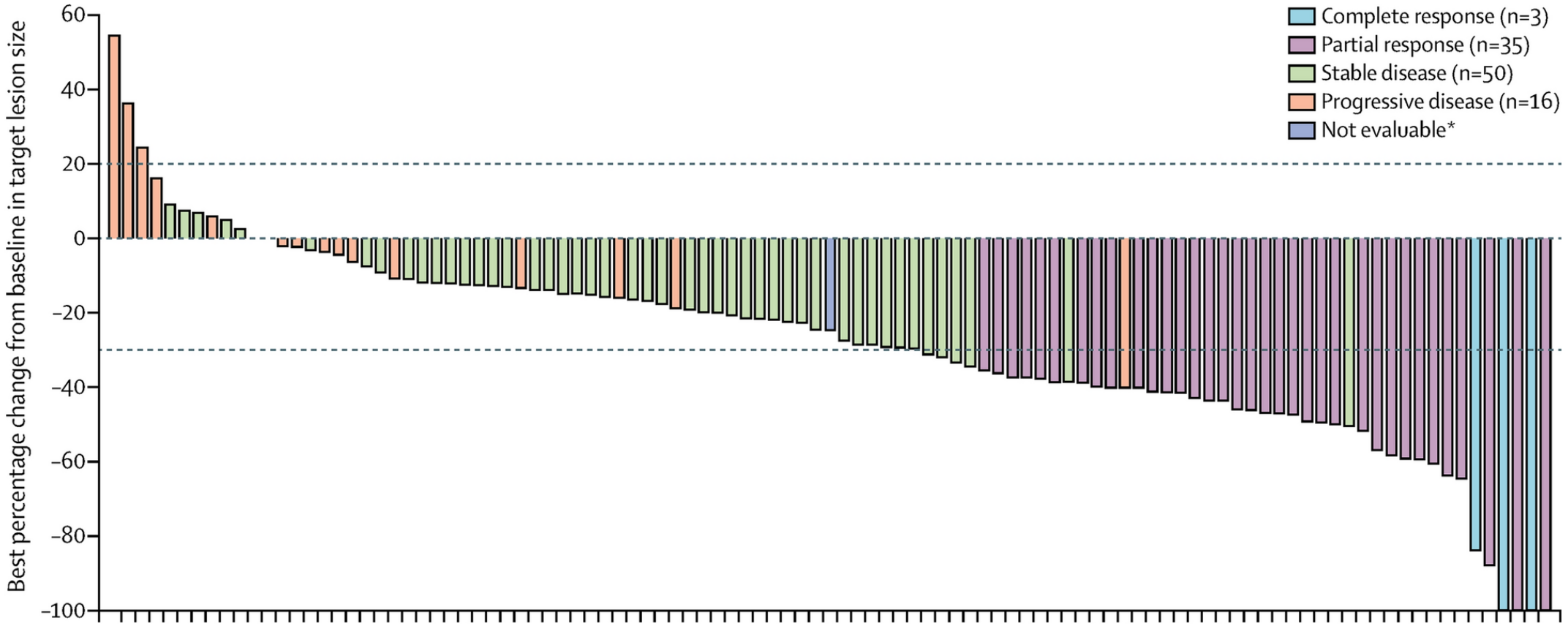

Median OS
Ivosidenib
10.3
MONTHS
Placebo
7.5
MONTHS
Placebo after adjusting for crossover
5.1
MONTHS


A
Missing
Not evaluable
Progressive disease
Partial response
Stable disease
Unknown
Ongoing
Radiographic progressive disease
On-treatment death
First response
Patients
0 2 4 6 8 10 12 14 16 18 20 22 24
Treatment duration (months)
B
Patients
0 5 10 15 20 25
Treatment duration (months)

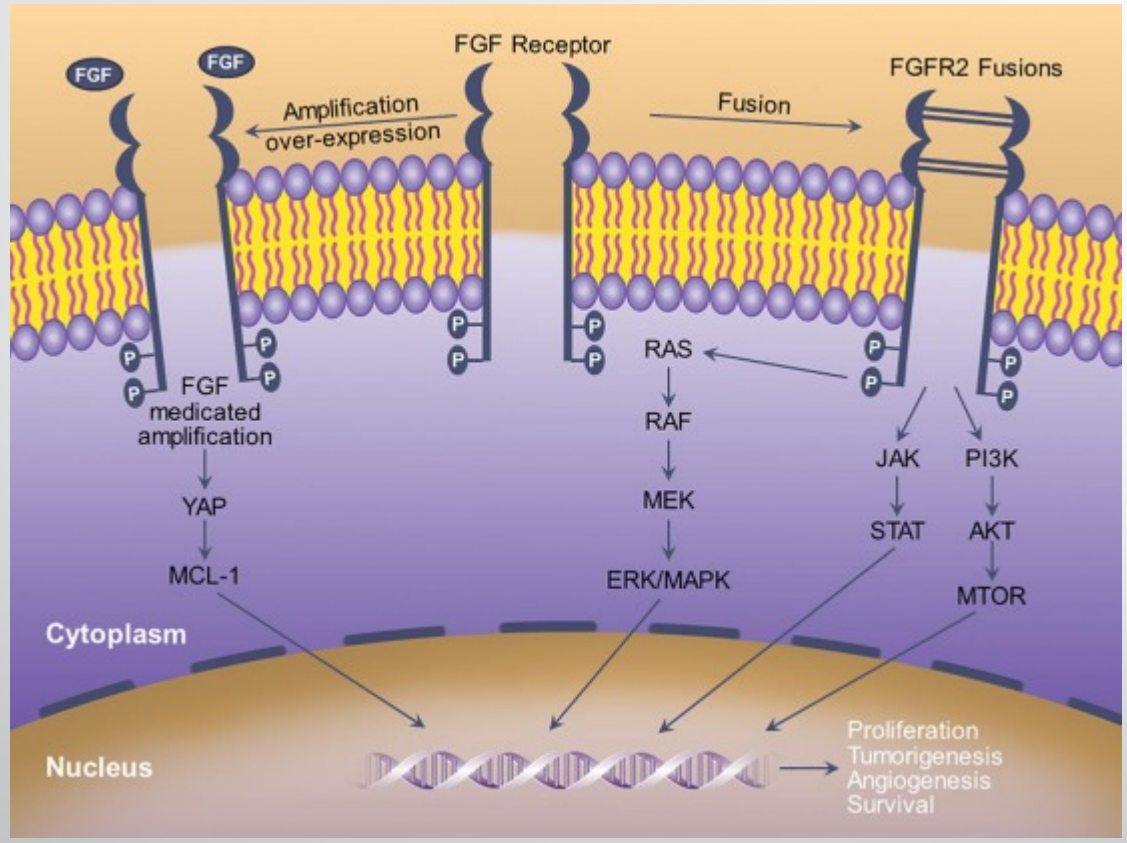
Cholangiocarcinoma: FGFR

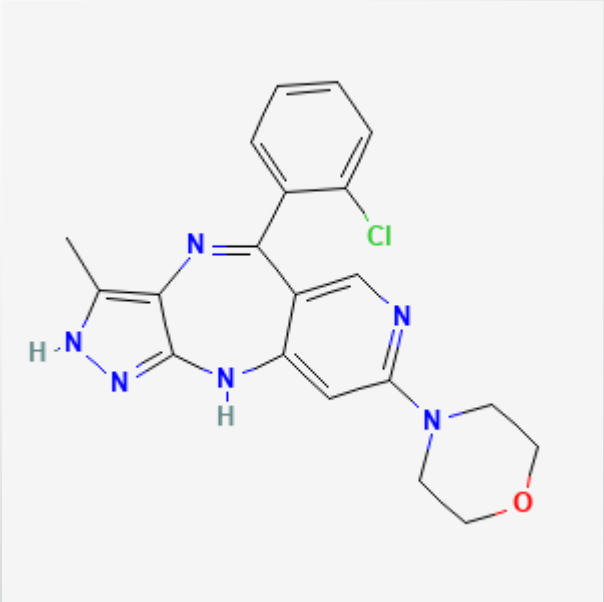


Pemigatinib



Tinengotinib: Second Generation FGFR

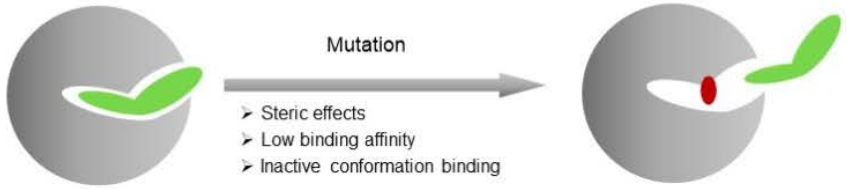




Tinengotinib: The Next Generation FGFR Inhibitor

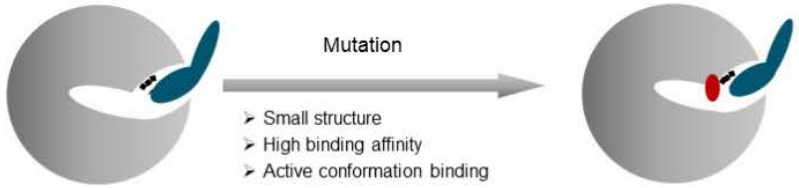
Tinengotinib Binds to FGFR2 in a Unique Mode

Pemigatinib (r), Infigratinib (r), Futibatinib (ir) approved for CCA patients with FGFR2 fusion/rearrangement



67% of FGFRi-treated iCCA patients developed FGFR2 KD mutations at progression#

Tinengotinib (r) has unique binding to FGFR2, overcoming acquired resistance mutations

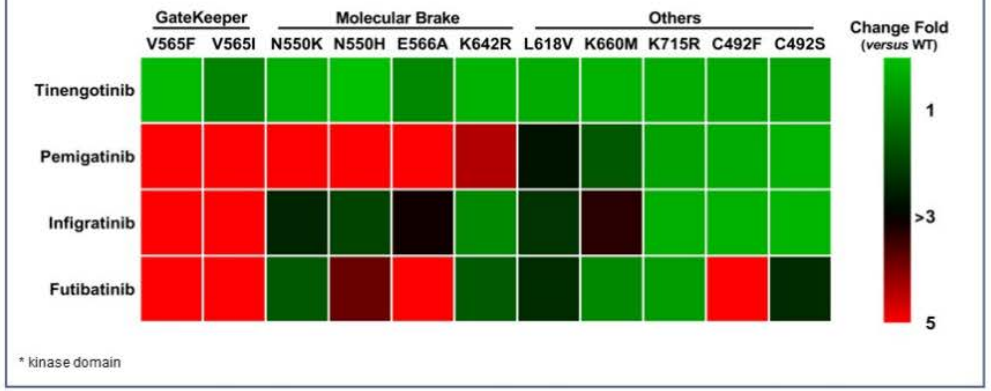


r: reversible, ir: irreversible

Characteristics of tinengotinib binding mode to FGFR2:

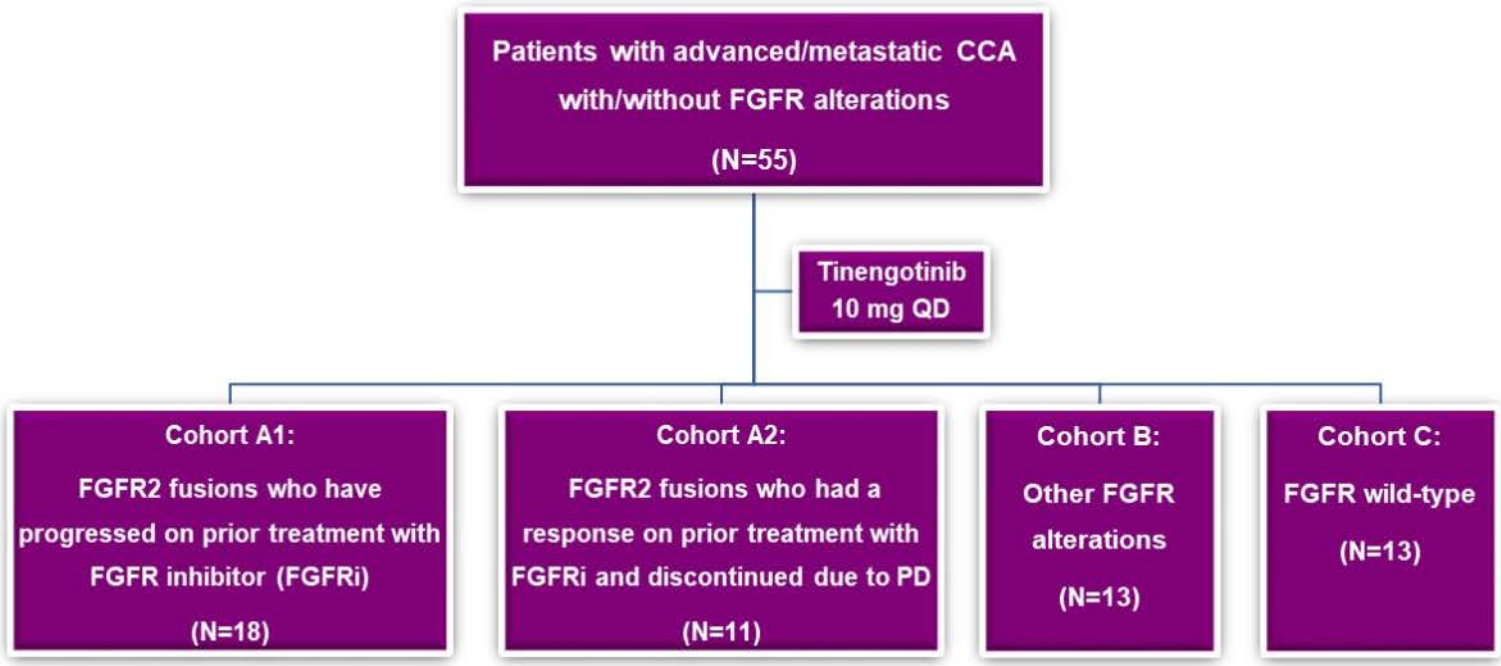
- Targets an FGFR2 binding site away from the inner pocket to avoid an impact by mutations.
- Binds distinctly to the active configuration of FGFR2 with high affinity by 3 H-bond.
- Overcomes resistance mutations acquired from treatment with 1st generation FGFR inhibitors.

Tinengotinib Shows Excellent Potency to FGFR2 KD* Mutations



* kinase domain

Study Design



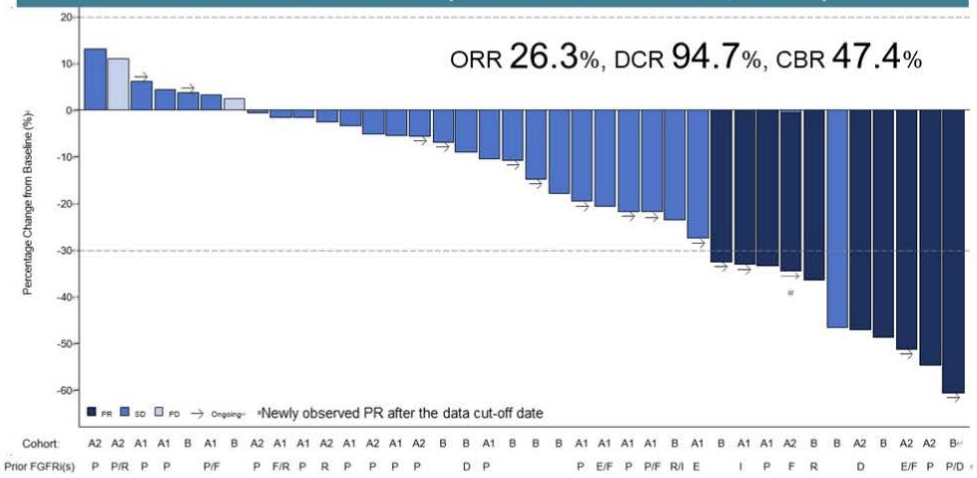
Treatment until disease progression, unacceptable toxicity, or other discontinuation criterion was met

Endpoints

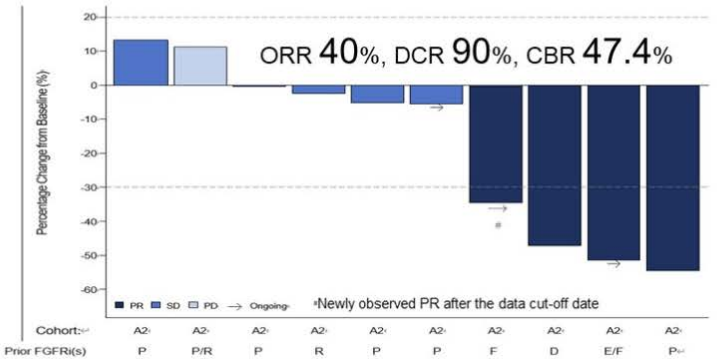
- **Primary :** ORR
- **Secondary:** Safety, DCR, PFS, OS

Tinengotinib- Best Overall Response
(CCA with FGFR alteration)

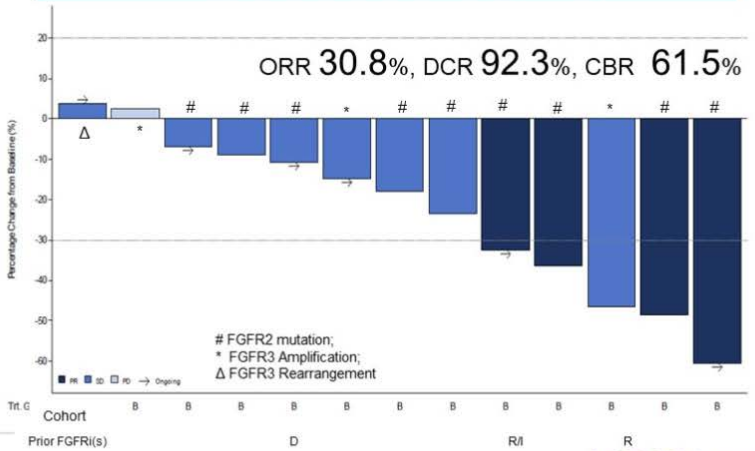
FGFR Altered CCA (Cohorts A1+A2+B, N=38)



Acquired Resistance to Prior-FGFRi in CCA (N=10)



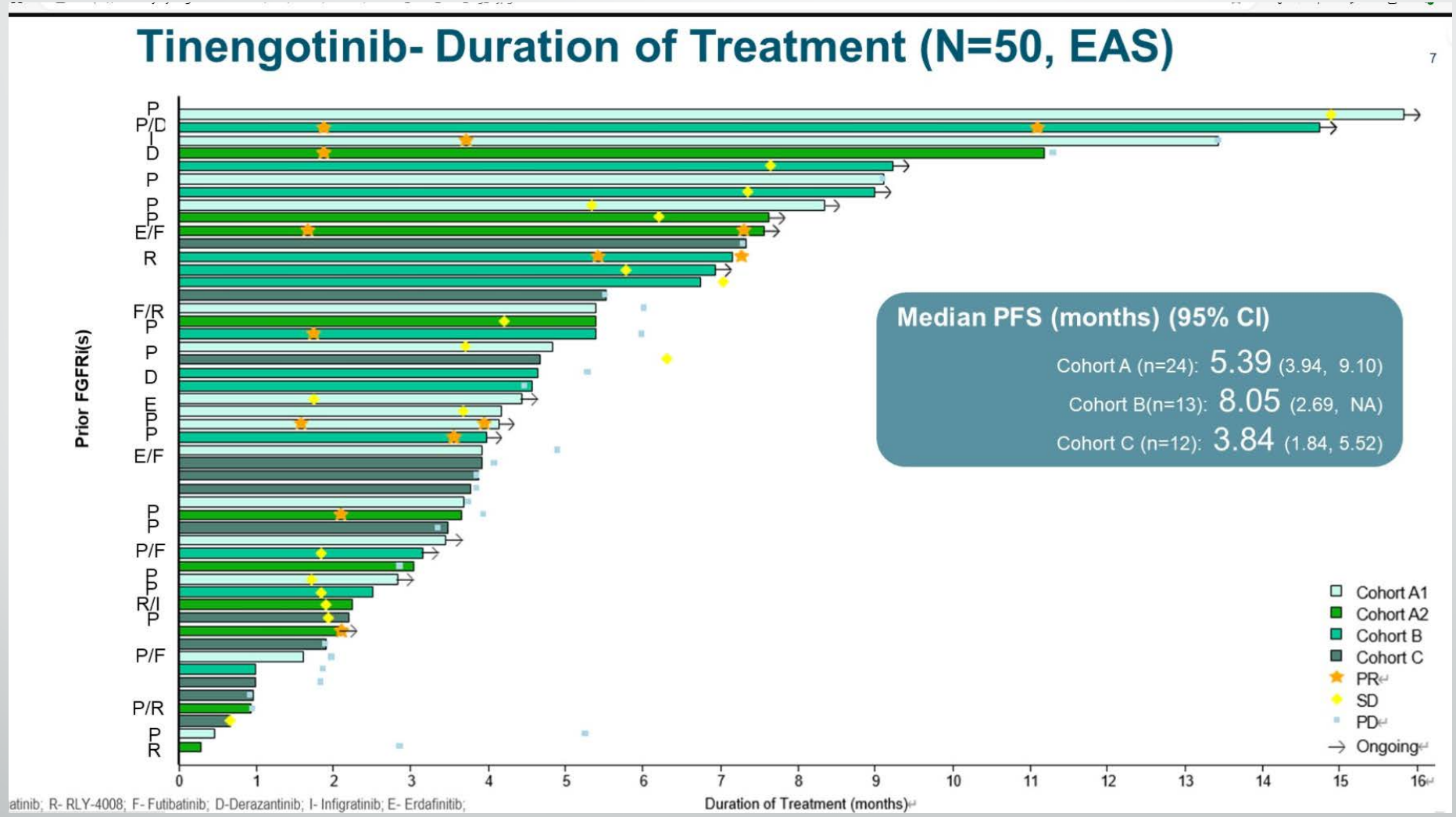
Other FGFR-Altered CCA (N=13)



ORR: overall response rate, DCR: disease control response, CBR: clinical benefit rate, CR + PR + **SD >= 24 weeks**.

P- Pemigatinib; R- RLY-4008; F- Futibatinib; D-Derazantinib; I- Infigratinib; E- Erdafinitib;

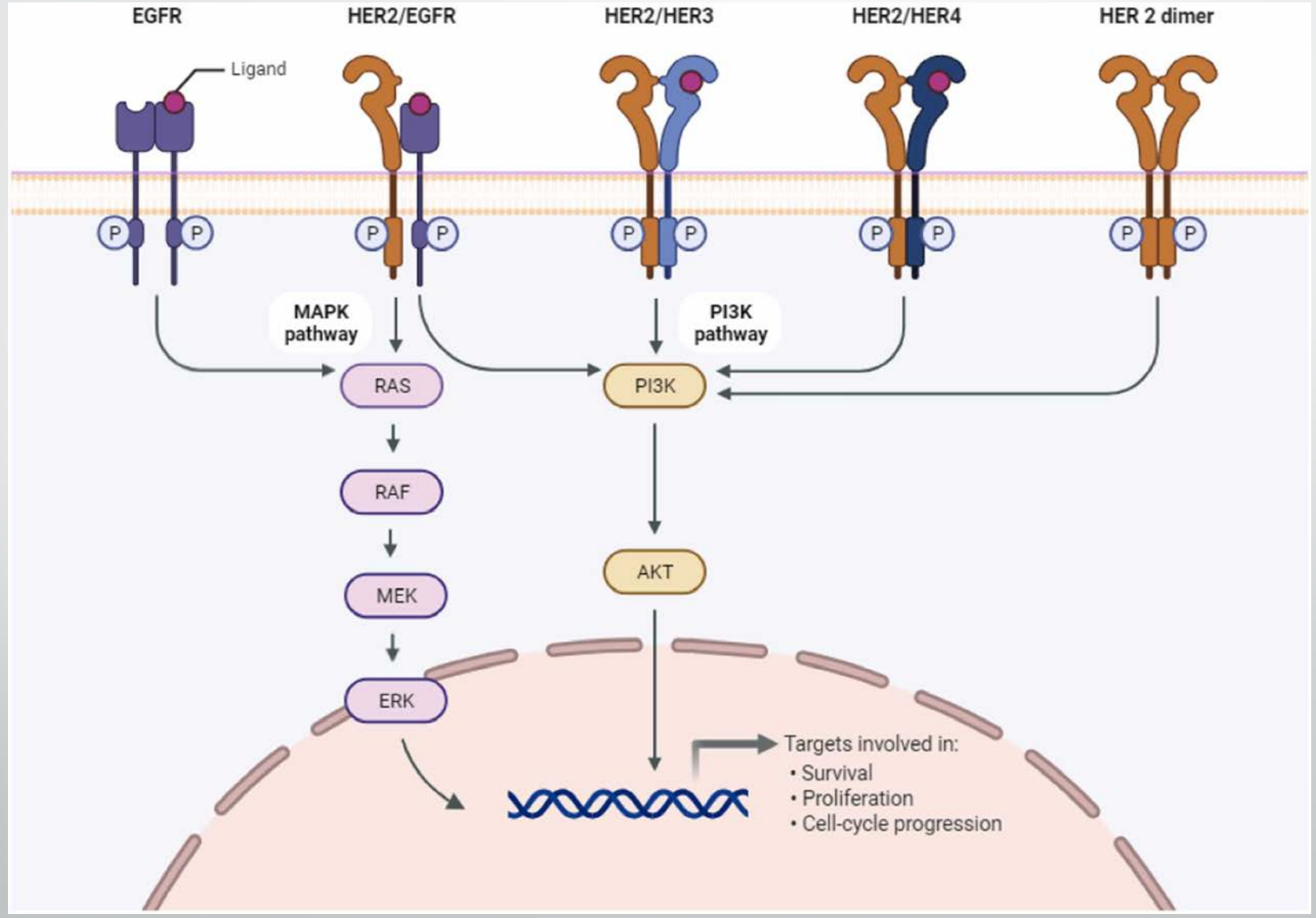
PRESENTED BY: Milind Javle, M.D.

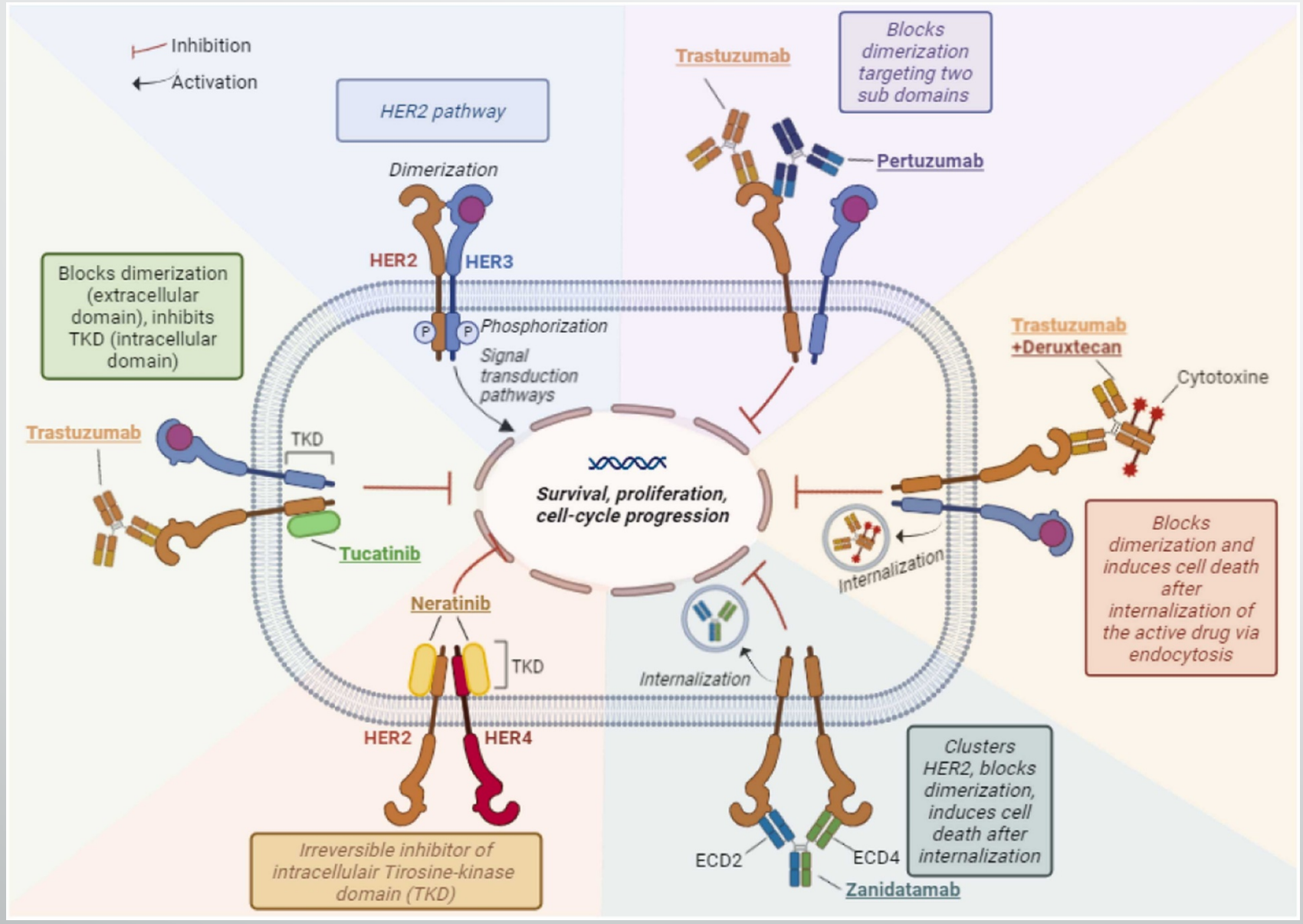

Tinengotinib- Duration of Treatment (N=50, EAS)
7
Prior FGFRi(s)
P
P/D
I
D
P
P
P
E/F
R
F/R
P
P
D
E
P
P
E/F
P
P
P/F
P
P
R/I
P
P/F
P/R
P
R
Median PFS (months) (95% CI)
Cohort A (n=24): 5.39 (3.94, 9.10)
Cohort B(n=13): 8.05 (2.69, NA)
Cohort C (n=12): 3.84 (1.84, 5.52)
Cohort A1
Cohort A2
Cohort B
Cohort C
PR
SD
PD
Ongoing
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Duration of Treatment (months)
atinib; R- RLY-4008; F- Futibatinib; D-Derazantinib; I- Infigratinib; E- Erdafinitib;

Conclusions

- **Tinengotinib is a next-generation FGFR inhibitor with promising efficacy in CCA with FGFR alterations that is refractory to current FGFR targeted therapy**
- **Promising efficacy was shown:**
  - 26.3% ORR, 94.7% DCR, 47.4% CBR in CCA patients harboring FGFR alterations (Cohort A1+A2+B).
  - 40% ORR, 90% DCR, 47.4% CBR in CCA patients with acquired resistance to prior-FGFRi (s) (Cohort A2).
  - 30.8% ORR, 92.3% DCR, 61.5% CBR, 8.05 months of mPFS in CCA patients with other FGFR-alteration (Cohort B).
  - 75% DCR, 8.3% CBR, 3.84 months of mPFS in CCA patients FGFR wide-type patients (Cohort C).
- Tinengotinib shows promising efficacy in CCA patients with other FGFR alterations (e.g. point mutations), who are not eligible for FGFR2 targeted therapies under approved indications.
- Tinengotinib was well-tolerated and side effects were manageable.
- **A phase III, randomized, controlled, global multicenter study is currently enrolling to further evaluate the efficacy and safety of tinengotinib versus physician's choice in patients with FGFR-altered, chemotherapy and FGFR-inhibitor refractory/relapsed cholangiocarcinoma (NCT05948475, ASCO GI 2024 Abstract #TPS575).**

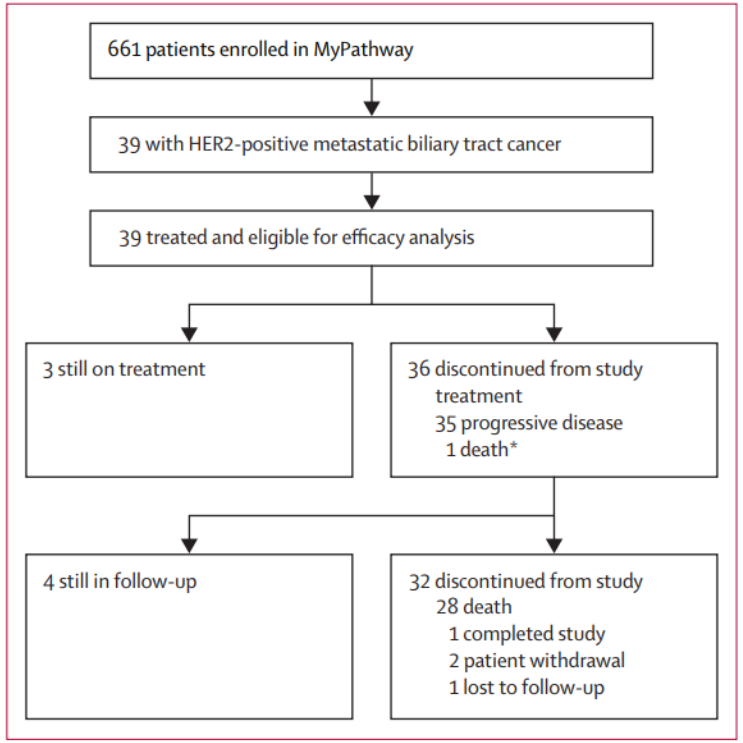
Cholangiocarcinoma: HER2

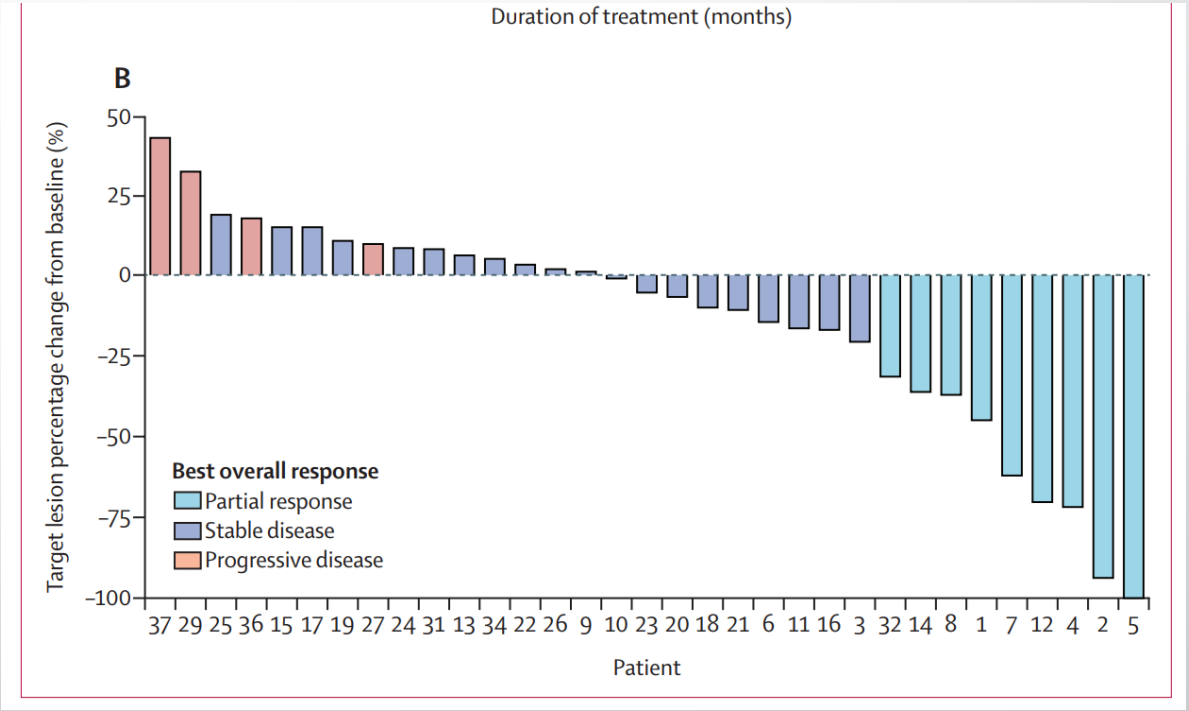



Inhibition
Activation
HER2 pathway
Dimerization
HER2
HER3
Phosphorization
Signal transduction pathways
Blocks dimerization (extracellular domain), inhibits TKD (intracellular domain)
Trastuzumab
TKD
Tucatinib
Survival, proliferation, cell-cycle progression
Neratinib
TKD
HER2
HER4
Irreversible inhibitor of intracellulair Tirosine-kinase domain (TKD)
Trastuzumab
Blocks dimerization targeting two sub domains
Pertuzumab
Trastuzumab +Deruxtecan
Cytotoxine
Internalization
Blocks dimerization and induces cell death after internalization of the active drug via endocytosis
Internalization
ECD2
ECD4
Zanidatamab
Clusters HER2, blocks dimerization, induces cell death after internalization

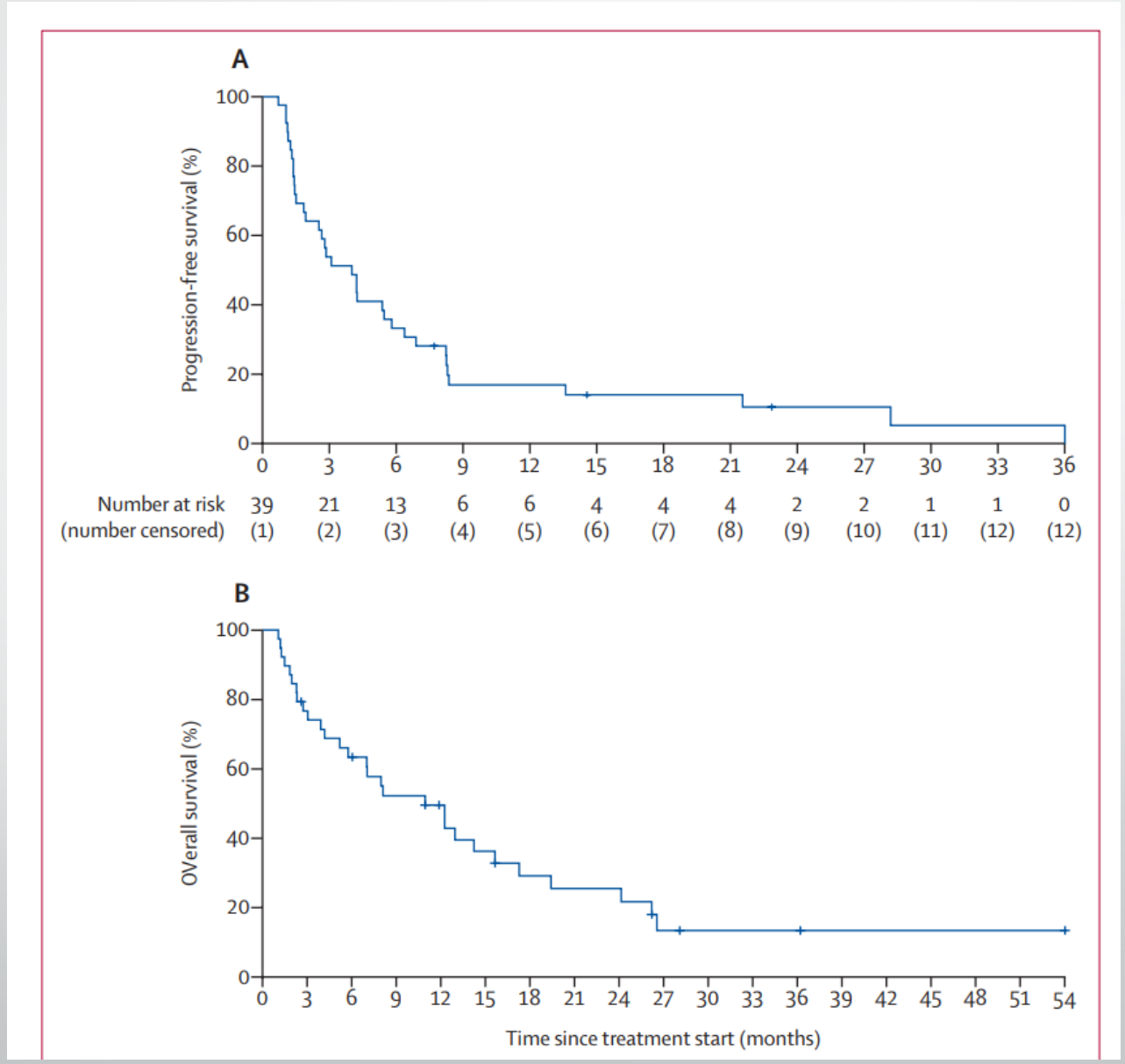
Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study

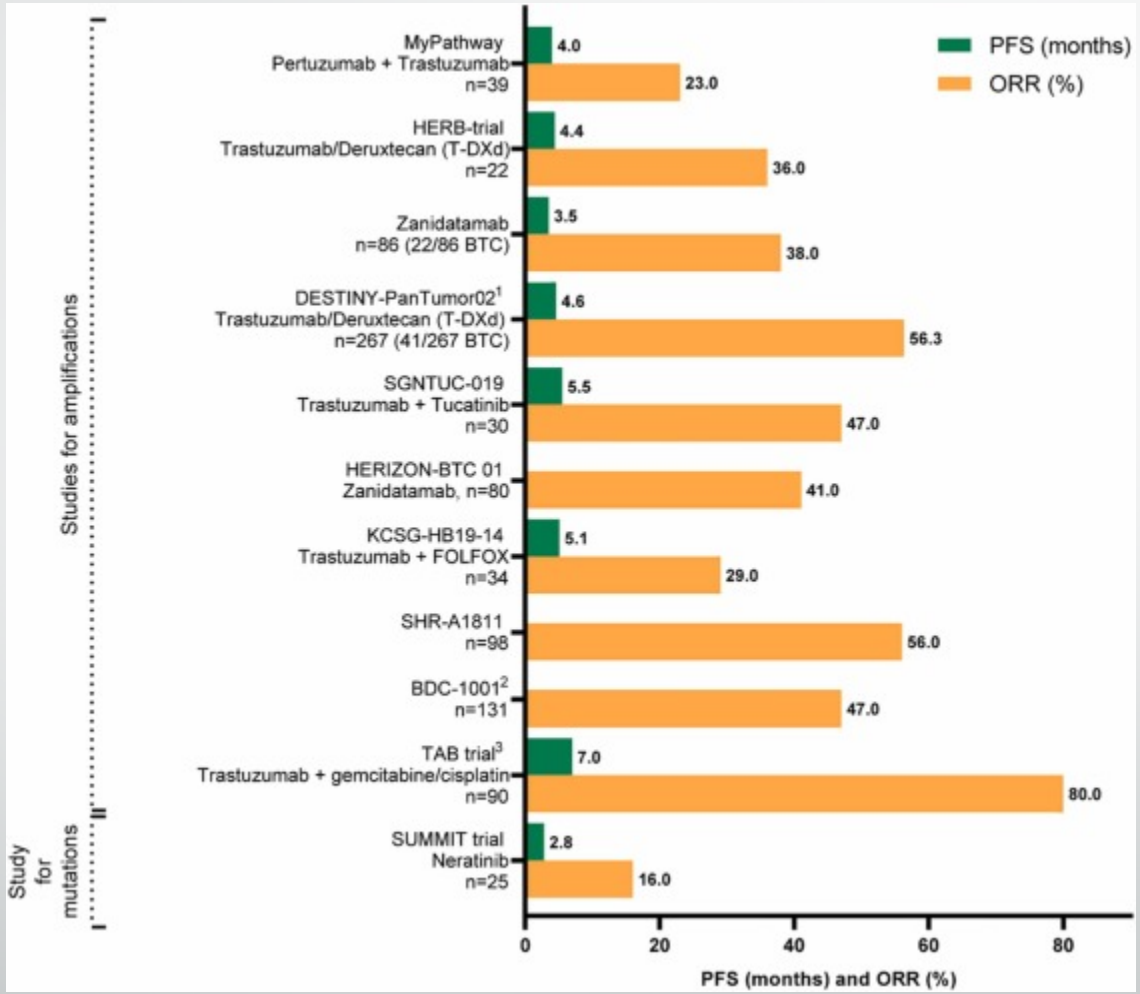
Milind Javle, Mitesh J Borad, Nilofer S Azad, Razelle Kurzrock, Ghassan K Abou-Alfa, Ben George, John Hainsworth, Funda Meric-Bernstam, Charles Swanton, Christopher J Sweeney, Claire F Friedman, Ron Bose, David R Spigel, Yong Wang, Jonathan Levy, Katja Schulze, Vaikunth Cuchelkar, Arisha Patel, Howard Burris





Cholangiocarcinoma:HER2




PFS (months)
ORR (%)
Studies for amplifications
Study for mutations
MyPathway
Pertuzumab + Trastuzumab
n=39
4.0
23.0
HERB-trial
Trastuzumab/Deruxtecan (T-DXd)
n=22
4.4
36.0
Zanidatamab
n=86 (22/86 BTC)
3.5
38.0
DESTINY-PanTumor02[1]
Trastuzumab/Deruxtecan (T-DXd)
n=267 (41/267 BTC)
4.6
56.3
SGNTUC-019
Trastuzumab + Tucatinib
n=30
5.5
47.0
HERIZON-BTC 01
Zanidatamab, n=80
41.0
KCSG-HB19-14
Trastuzumab + FOLFOX
n=34
5.1
29.0
SHR-A1811
n=98
56.0
BDC-1001[2]
n=131
47.0
TAB trial[3]
Trastuzumab + gemcitabine/cisplatin
n=90
7.0
80.0
SUMMIT trial
Neratinib
n=25
2.8
16.0
0
20
40
60
80
PFS (months) and ORR (%)

PRINCIPLES OF SYSTEMIC THERAPY[a]
TARGETED THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[12,13]
  - Larotrectinib[14]
  - Repotrectinib[15]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[f,i,16,17,18]
- For TMB-H tumors:
  - Nivolumab + ipilimumab (category 2B)[f,19]
- For *RET* gene fusion-positive tumors:
  - Pralsetinib (category 2B)[20]
  - Selpercatinib (category 2B)[21]

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

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[12,13]
  - Larotrectinib[14]
  - Repotrectinib[15]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[f,g,i,16,17,18]
  - Dostarlimab-gxly (category 2B)[f,g,j,22]
- For TMB-H tumors:
  - Nivolumab + ipilimumab[f,g,k,19]
  - Pembrolizumab[f,g,i,23]
- For *BRAF* V600E-mutated tumors
  - Dabrafenib + trametinib[24,25]
- For CCA with *FGFR2* fusions or rearrangements:
  - Futibatinib[26]
  - Pemigatinib[27]
- For CCA with *IDH1* mutations
  - Ivosidenib (category 1)[28,29]
- For HER2-positive tumors:
  - Fam-trastuzumab deruxtecan-nxki (IHC3+)[30]
  - Trastuzumab[l] + pertuzumab[31]
  - Tucatinib + trastuzumab[l,32]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib[21]
  - Pralsetinib (category 2B)[20]
- For *KRAS* G12C mutation-positive tumors:
  - Adagrasib[33]


CAUTION
HANDLE WITH CARE
CHEMOTHERAPY
DISPOSE OF PROPERLY

PRINCIPLES OF SYSTEMIC THERAPY[a]

Neoadjuvant Therapy[b] (for gallbladder cancer only)

Preferred Regimens
- None

Other Recommended Regimens
- See Principles of Systemic Therapy, Primary Treatment for Unresectable and Metastatic Disease (BIL-C 2 of 5)

Useful in Certain Circumstances
- None

Adjuvant Therapy[c,1]

Preferred Regimens
- Capecitabine (category 1)[d,2]

Other Recommended Regimens
- Gemcitabine + capecitabine[3]
- Gemcitabine + cisplatin
- Single agents:
  - 5-fluorouracil
  - Gemcitabine

Useful in Certain Circumstances
- None

Agents Used with Concurrent Radiation

- 5-fluorouracil
- Capecitabine

[a] Order does not indicate preference.
[b] The decision to use neoadjuvant therapy needs to be individualized and in close consultation with surgical oncologist and multidisciplinary team. A period of 2 to 6 months with reassessment every 2 to 3 months is reasonable. There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. The listed regimens are extrapolated from the metastatic setting.

[c] Adjuvant therapy up to 6 months. Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with BTC, especially in patients with lymph node-positive disease.
[d] The phase III BILCAP study shows improved overall survival for adjuvant capecitabine in the per-protocol analysis, and the overall survival did not reach statistical significance in the intent-to-treat analysis. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 2019;20:663-673.

References Continued

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Biliary Tract Cancers

NCCN Guidelines Index
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PRINCIPLES OF SYSTEMIC THERAPY[a]

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Durvalumab + gemcitabine + cisplatin (category 1)[e,f,g,4]
- Pembrolizumab + gemcitabine + cisplatin (category 1)[f,g,5]

Other Recommended Regimens

- Gemcitabine + cisplatin (category 1)[6]
- Capecitabine + oxaliplatin
- FOLFOX
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- Targeted therapy (BIL-C 3 of 5)

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

Preferred Regimens

- FOLFOX[7]

Other Recommended Regimens

- FOLFIRI[8]
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[9]
- Regorafenib (category 2B)[10]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

Useful in Certain Circumstances

- Targeted therapy (BIL-C 3 of 5)
- Nivolumab (category 2B)[f,g,11]

TOPAZ-1 study design

TOPAZ-1 is a double-blind, multicenter, global, Phase 3 study

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

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)

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**

Primary objective
- Overall survival

Secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

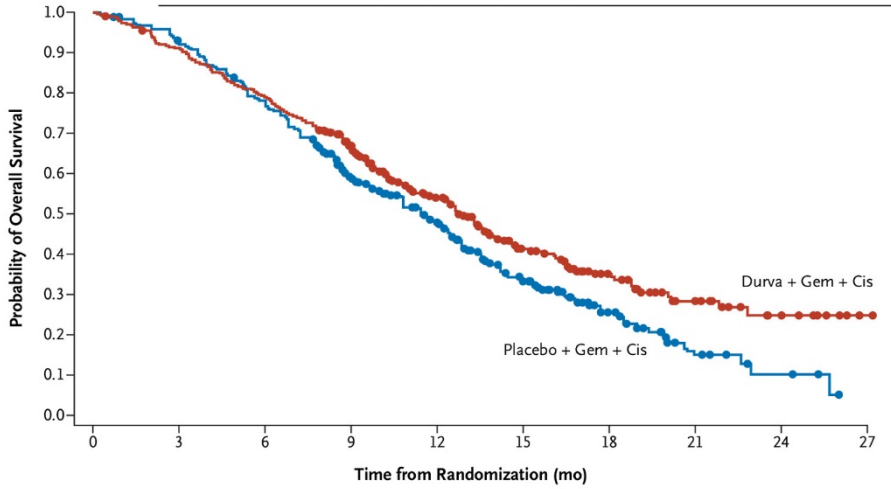
BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC; intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

PRESENTED BY: Do-Youn Oh, MD, PhD

Cholangiocarcinoma: TOPAZ-1 Trial

A

	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)		

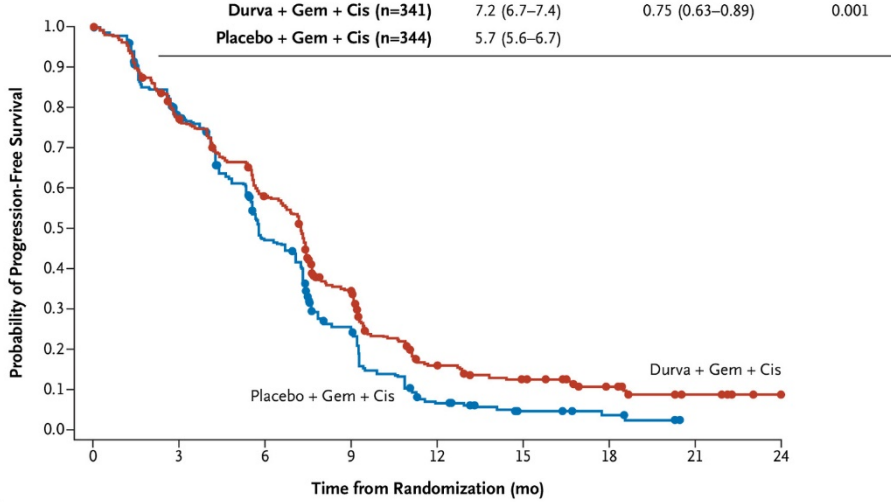


No. at Risk

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

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	149	137	80	71	39	31	17	14	11	7	7	5	4	2	2	0	0	0	0

Cholangiocarcinoma: TOPAZ-1 Trial

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=341)	Placebo plus Gemcitabine and Cisplatin (n=343)
Objective response rate — no. (%)†	91 (26.7)	64 (18.7)
Complete response	7 (2.1)	2 (0.6)
Partial response	84 (24.6)	62 (18.1)
Disease control rate — no. (%)‡	291 (85.3)	284 (82.6)
Median duration of response (IQR) — mo§	6.4 (4.6–17.2)	6.2 (3.8–9.0)
Patients with continued response — %		
≥3 mo	88.9	89.0
≥6 mo	59.3	54.2
≥9 mo	32.6	25.3
≥12 mo	26.1	15.0
Median time to response (IQR) — mo¶	1.6 (1.3–3.0)	2.7 (1.4–4.1)

Cholangiocarcinoma: TOPAZ-1 Trial

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=338)	Placebo plus Gemcitabine and Cisplatin (n=342)
Adverse events — no. (%)		
Any grade	336 (99.4)	338 (98.8)
Serious	160 (47.3)	149 (43.6)
Grade 3 or 4	256 (75.7)	266 (77.8)
Leading to discontinuation of any study treatment	44 (13.0)	52 (15.2)
Leading to death	12 (3.6)	14 (4.1)
Treatment-related adverse events — no. (%)		
Any grade	314 (92.9)	308 (90.1)
Serious	53 (15.7)	59 (17.3)
Grade 3 or 4	212 (62.7)	222 (64.9)
Leading to discontinuation of any study treatment	30 (8.9)	39 (11.4)
Leading to death*	2 (0.6)	1 (0.3)

* Treatment-related adverse events leading to death were ischemic stroke and hepatic failure in the durvalumab treatment group and polymyositis in the placebo treatment group.

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

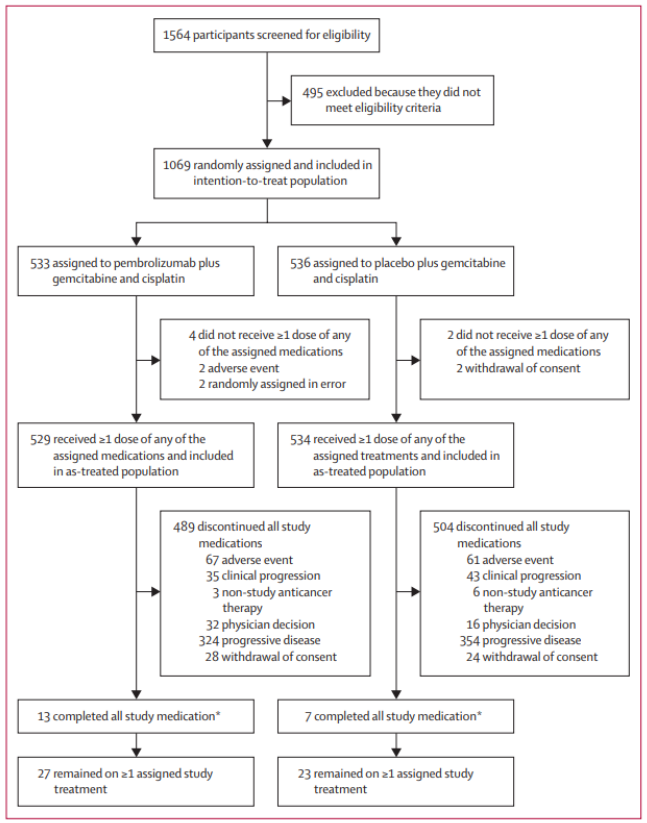
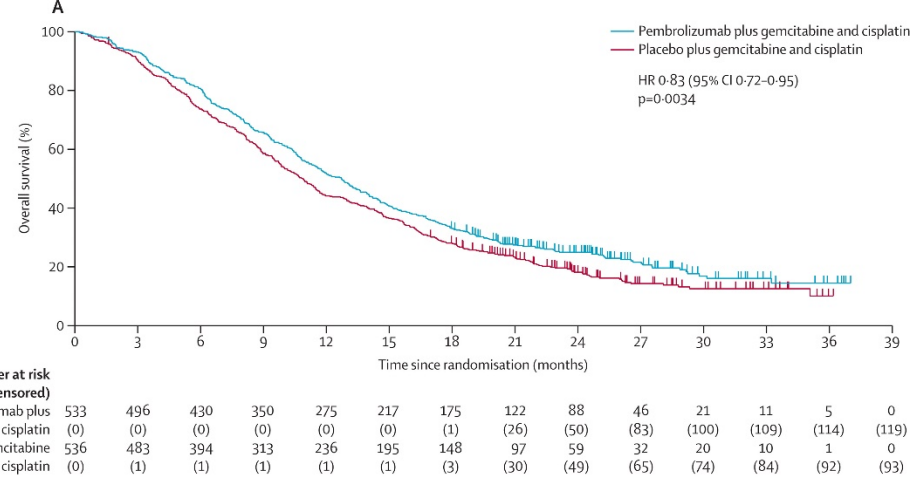


Figure 1: **Trial profile**

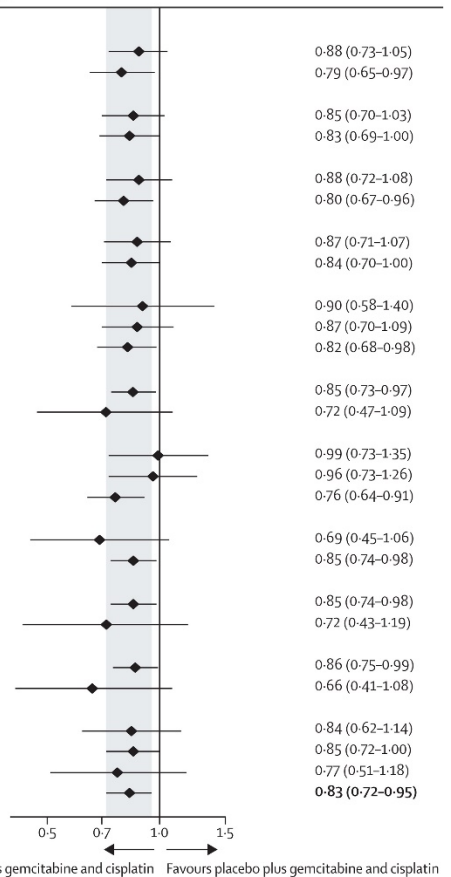
*Completed includes participants who received 35 cycles of pembrolizumab or placebo without alternative reason



Number at risk (number censored)														
Pembrolizumab plus gemcitabine and cisplatin	533 (0)	496 (0)	430 (0)	350 (0)	275 (0)	217 (0)	175 (1)	122 (26)	88 (50)	46 (83)	21 (100)	11 (109)	5 (114)	0 (119)
Placebo plus gemcitabine and cisplatin	536 (0)	483 (1)	394 (1)	313 (1)	236 (1)	195 (1)	148 (3)	97 (30)	59 (49)	32 (65)	20 (74)	10 (84)	1 (92)	0 (93)

B

	Events/participants		Hazard ratio (95% CI)
	Pembrolizumab plus gemcitabine and cisplatin	Placebo plus gemcitabine and cisplatin	
Age (years)			
<65	210/269	242/298	0·88 (0·73–1·05)
≥65	204/264	201/238	0·79 (0·65–0·97)
Sex			
Female	200/253	220/264	0·85 (0·70–1·03)
Male	214/280	223/272	0·83 (0·69–1·00)
Geographical region			
Asia	185/242	201/244	0·88 (0·72–1·08)
Not Asia	229/291	242/292	0·80 (0·67–0·96)
ECOG performance status			
0	186/258	177/228	0·87 (0·71–1·07)
1	227/274	266/308	0·84 (0·70–1·00)
Smoking status			
Current	42/56	38/49	0·90 (0·58–1·40)
Former	160/205	160/191	0·87 (0·70–1·09)
Never	212/272	244/295	0·82 (0·68–0·98)
Antibiotic use within 1 month of study start			
No	364/471	403/493	0·85 (0·73–0·97)
Yes	50/62	40/43	0·72 (0·47–1·09)
Site of origin			
Extrahepatic	78/98	83/105	0·99 (0·73–1·35)
Gallbladder	102/115	104/118	0·96 (0·73–1·26)
Intrahepatic	234/320	256/313	0·76 (0·64–0·91)
Disease status			
Locally advanced	37/60	52/66	0·69 (0·45–1·06)
Metastatic	377/473	391/470	0·85 (0·74–0·98)
Biliary stent or drain			
No	388/500	406/495	0·85 (0·74–0·98)
Yes	26/33	37/41	0·72 (0·43–1·19)
Previous chemotherapy			
No	382/483	408/488	0·86 (0·75–0·99)
Yes	32/50	35/48	0·66 (0·41–1·08)
PD-L1 combined positive score			
<1	86/113	87/110	0·84 (0·62–1·14)
≥1	287/363	309/365	0·85 (0·72–1·00)
Unknown	41/57	47/61	0·77 (0·51–1·18)
Overall	**414/533**	**443/536**	**0·83 (0·72–0·95)**



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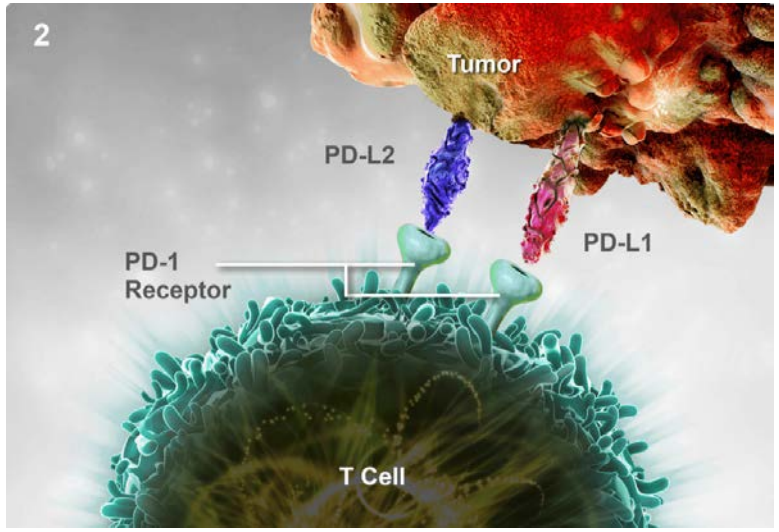
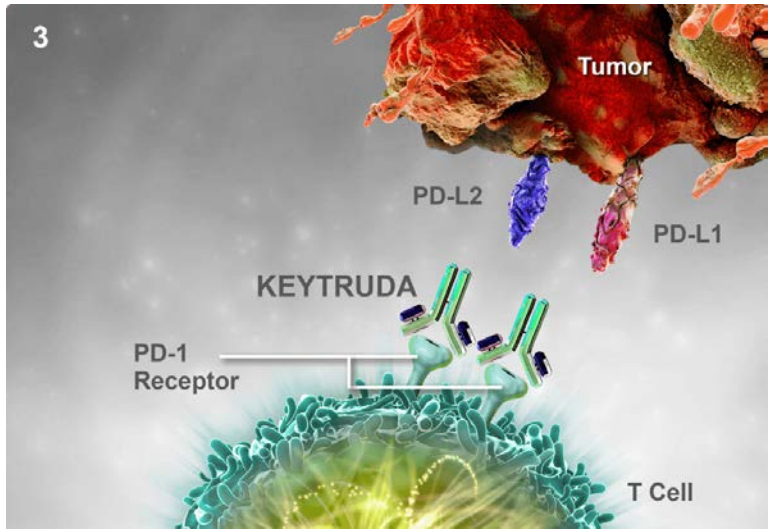


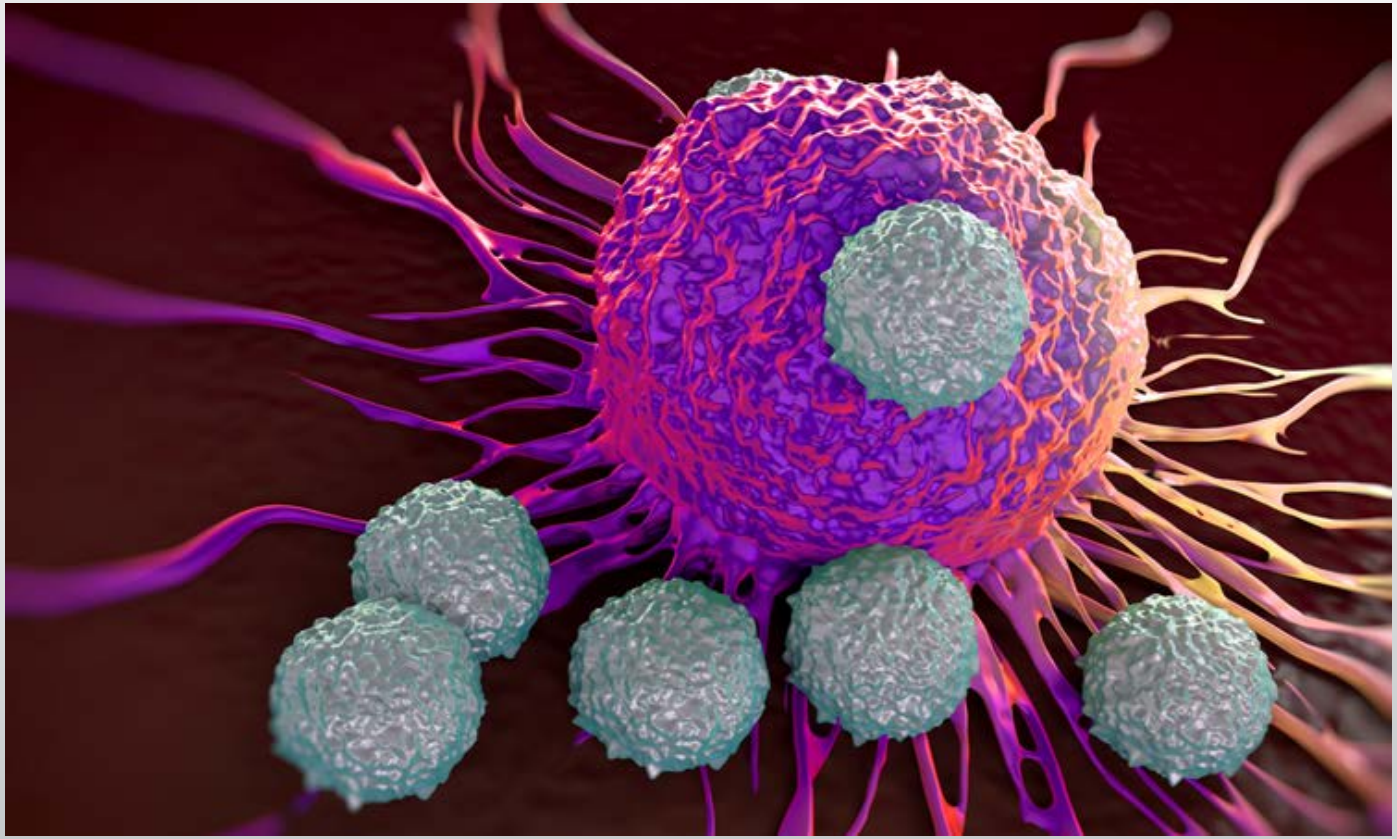


	Pembrolizumab plus gemcitabine and cisplatin group (n=533)	Placebo plus gemcitabine and cisplatin group (n=536)
Objective response rate	153 (29% [95% CI 25–33])	153 (29% [95% CI 25–33])
Disease control rate	399 (75% [95% CI 71–79])	407 (76% [95% CI 72–80])
Best overall response		
Complete response	11 (2%)	7 (1%)
Partial response	142 (27%)	146 (27%)
Stable disease*	246 (46%)	254 (47%)
Progressive disease	102 (19%)	96 (18%)
Not evaluable†	8 (2%)	9 (2%)
Not assessed‡	24 (5%)	24 (4%)
Time to response, months	2·8 (IQR 1·5–4·1)	2·8 (IQR 1·5–4·2)
Duration of response,§ months	9·7 (95% CI 6·9–12·2)	6·9 (95% CI 5·7–8·2)
Extended duration of response§		
≥3 months	93% (95% CI 88–96)	91% (95% CI 85–95)
≥6 months	67% (95% CI 57–74)	56% (95% CI 46–64)
≥9 months	51% (95% CI 41–60)	39% (95% CI 29–48)
≥12 months	41% (95% CI 30–51)	28% (95% CI 19–39)

Data are n (% [95% CI]), n (%), median (IQR) for time to response, median (95% CI) for duration of response, or % (95% CI) for extended duration of response. *Stable disease includes participants with stable disease, non-complete response or non-progressive disease, and no evidence of disease. †Not evaluable includes participants whose post-baseline imaging assessments were not evaluable for best overall response. ‡Not assessed includes participants for whom no post-baseline imaging assessments were available. §Estimated using the Kaplan-Meier method.

Table 2: **Summary of response in the intention-to-treat population at the first interim analysis**

Cholangiocarcinoma: Future Directions



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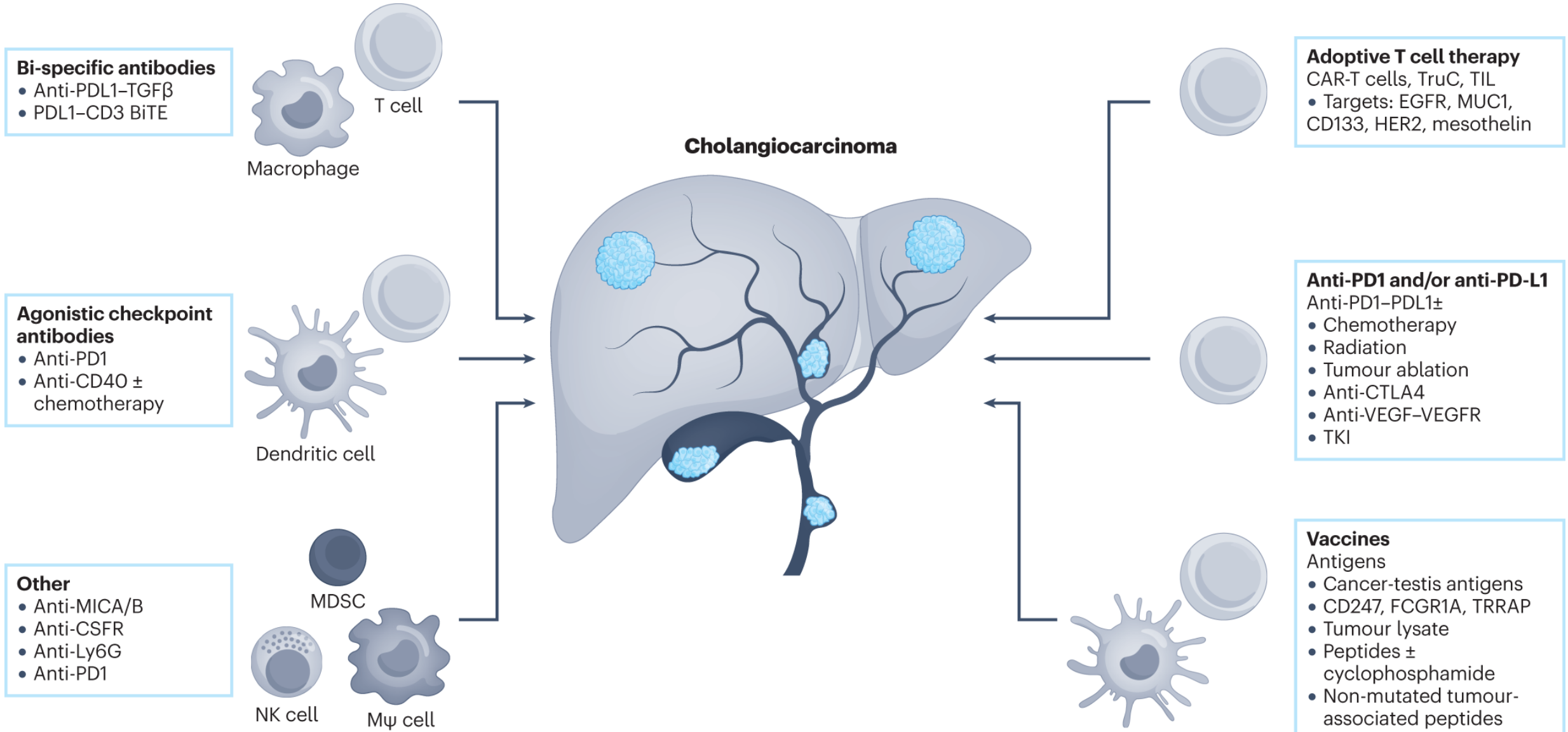
Cancer Immunotherapy in Cholangiocarcinoma

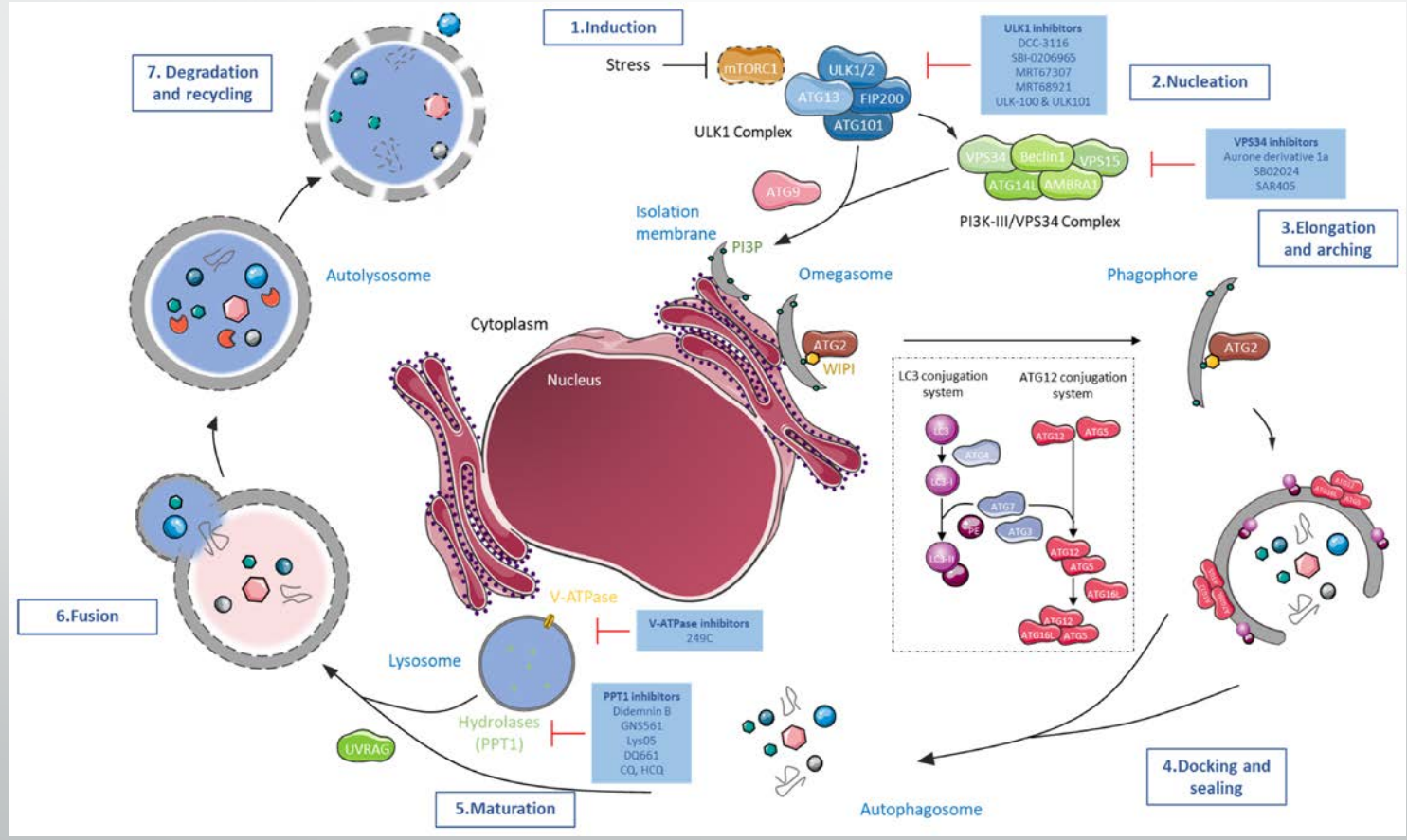


Cholangiocarcinoma: Combination Trials

Study details	Phase	N	Drug	Drug target	Patient population	NCT number
Yoo et al. 2020 [165]	2	159	Bintrafusp alpha (M7824)	PD-L1 + TGF-βR	BTC	NCT03833661
Baretti et al. 2018 [166]	2	44	Entinostat + nivolumab	PD-1 + HDAC1/3	CCA and pancreatic cancer	NCT03250273
LEAP-005 Lwin et al. 2020 [167]	2R	187	Pembrolizumab + lenvatinib vs. lenvatinib	PD-1 + multi-kinase	Various solid tumors including BTC	NCT03797326
NCT04550624	2	40	Pembrolizumab + lenvatinib	PD-1 + multi-kinase	CCA	NCT04550624
NCT04976634	2	400	Pembrolizumab + lenvatinib + belzutifan	PD-1 + multi-kinase + HIF-2α	Various solid tumors including BTC	NCT04976634
IMMUNO-BIL Boilève et al. 2021 [168]	2	106	Durvalumab + tremelimumab with or without paclitaxel	PD-L1 + CTLA-4	BTC	NCT03704480
NCT04720131	2	39	Camrelizumab + apatinib + capecitabine	PD-L1 + multi-kinase	BTC	NCT04720131
NCT03092895	2	152	SHR-1210 + apatinib vs. FOLFOX or GemOx	PD-L1 + multi-kinase	Primary liver cancer or BTC	NCT03092895

Cholangiocarcinoma: Clinical Trials

- A Phase 1b/2a Study of GNS561 in Combination with Trametinib in Advanced KRAS Mutated Cholangiocarcinoma



Cholangiocarcinoma: Conclusion

- Rapid Advances in both Targeted Therapies and Immunotherapy
- Combination Therapies being explored
- New Targets
- Immune Therapy: CAR-T, T-Cell engagers, bispecific antibodies, immune conjugates