MAYO CLINIC

Shifting Landscape in the treatment of Biliary Tract Cancers: The role of Immunotherapy and other Targeted therapies

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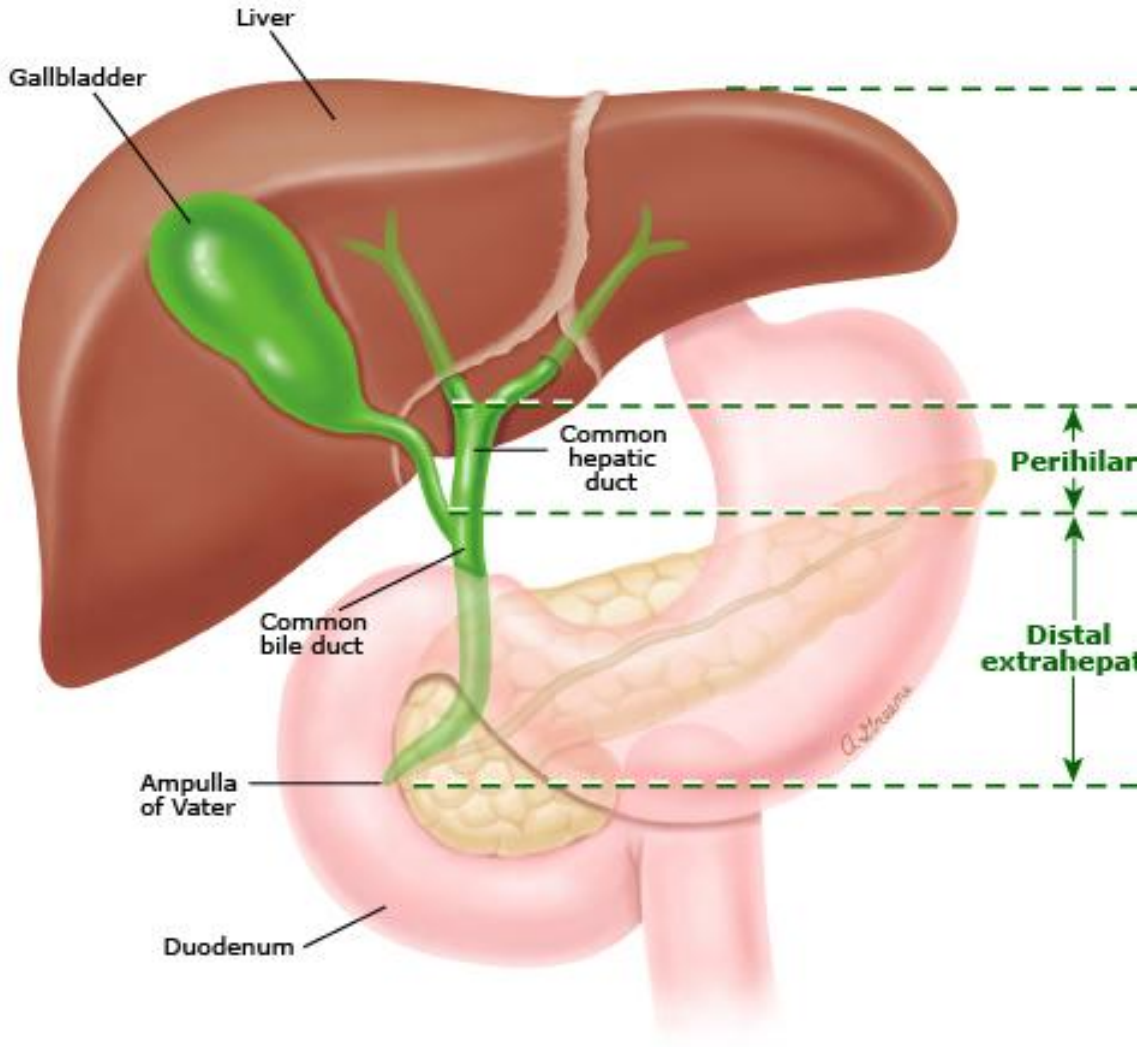
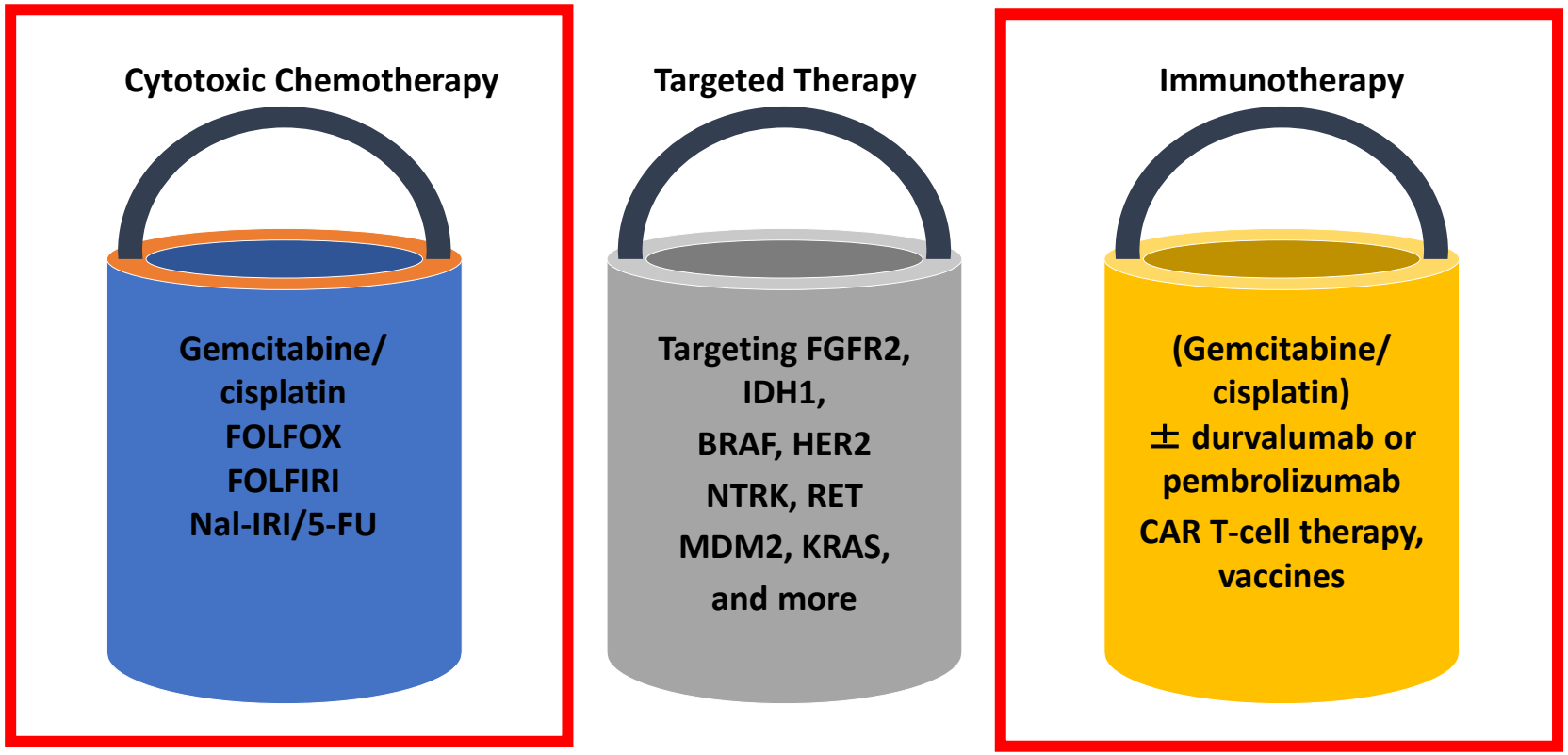
Anatomic Classification of Biliary Tract Cancers

- Based on AJCC 8th edition
- BTCs include
  - Intrahepatic cholangiocarcinoma (iCCA)
  - Extrahepatic cholangiocarcinoma (eCCA)
  - Gallbladder cancer



Classifications defined by: Amin MB et al. *CA Cancer J Clin*. 2017;67(2):93-99.

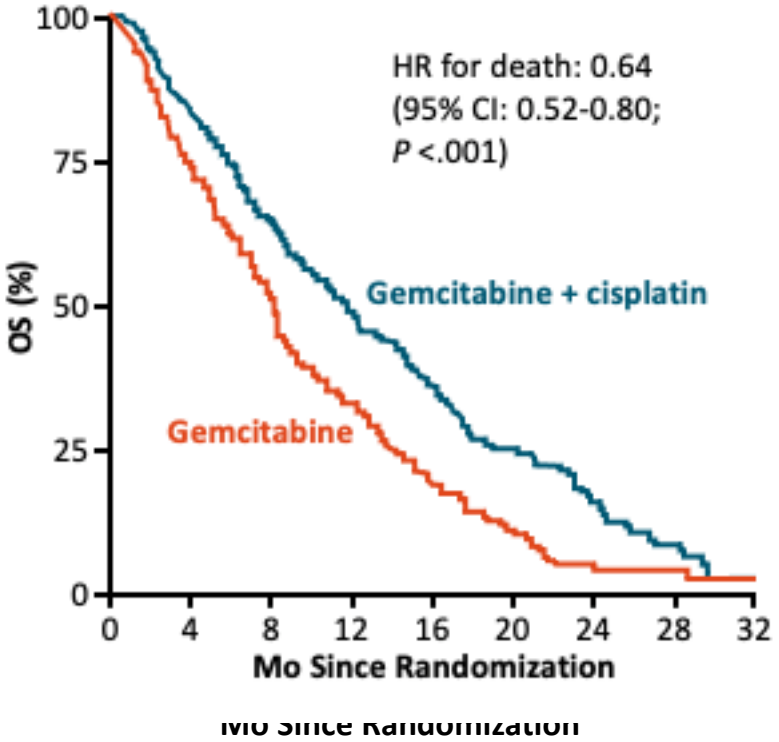
Systemic Therapy for Advanced BTC



Frontline Therapy for Advanced BTC

Historical Data for Frontline Treatment of Advanced BTC
ABC-02: Gemcitabine + Cisplatin vs Gemcitabine

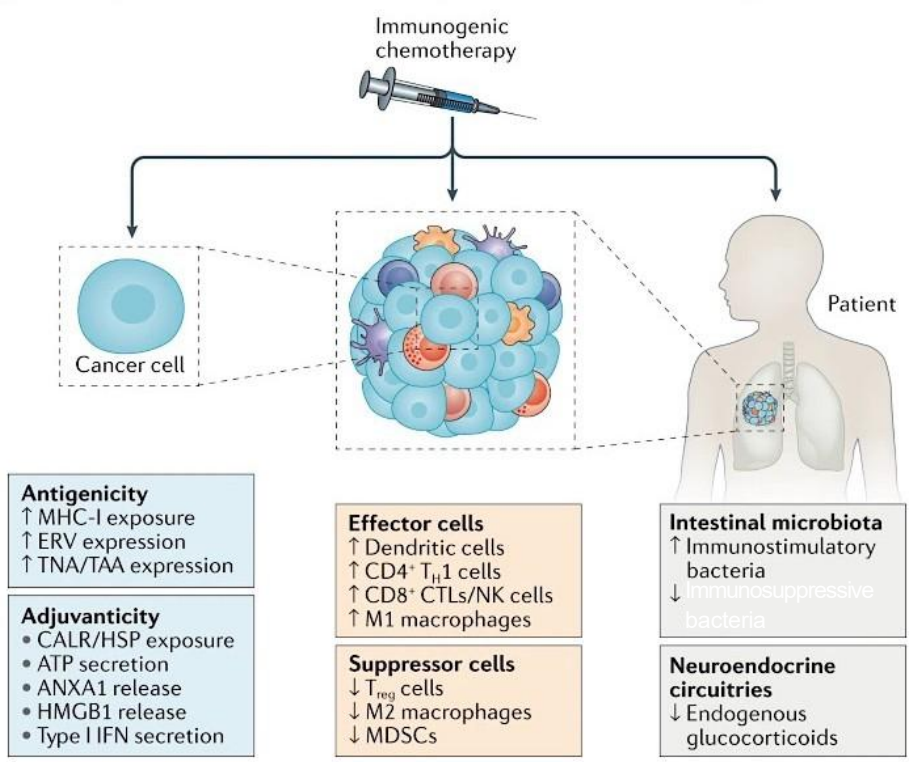
- Randomized phase III trial of gemcitabine + cisplatin vs gemcitabine for advanced cholangiocarcinoma, gallbladder, and ampullary cancer; no prior systemic chemotherapy for advanced disease (N = 410)
  - 37 centers in UK NCRN
- Results:
  - mOS: 11.7 vs 8.1 mo (HR: 0.64; *P* <.001)
  - mPFS: 8.0 vs 5.0 mo (HR: 0.63; *P* <.001)
  - ORR: 26.1% vs 15.5% (NR)



Valle. NEJM. 2010;362:1273.

Immune Checkpoint Inhibitor + Chemotherapy: Potential Mechanisms of Augmented Immune Response

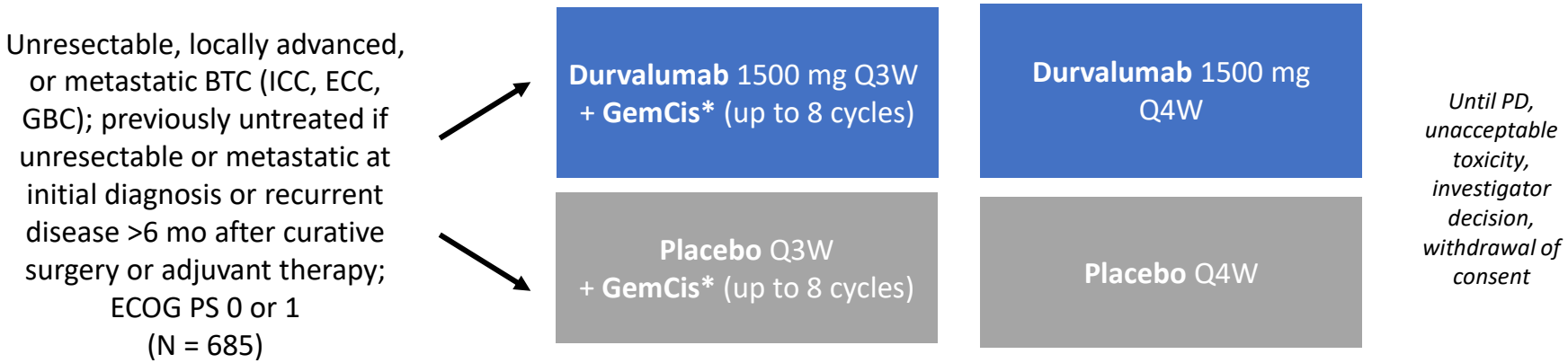
- Chemotherapy can promote immune responses in various ways[1]:
  - Cytotoxicity eliciting pro-inflammatory cytokines
  - Triggering immune cell infiltration
    - Cisplatin causes ferroptosis[2]
  - Inhibition of suppressive immune cells
  - Increased tumor immunogenicity
    - Gemcitabine can promote MHC1 expression and Ag presentation[3]



1. Galluzzi et al. *Nat Rev Clin Oncol.* 2020;17:725-41. 2. Zhou et al. *Front Pharmacol.* 2022;13. 3. Gravett et al. *Oncoimmunology* 2018;7.

TOPAZ-1: Durvalumab and Gemcitabine + Cisplatin in Patients With Advanced BTC

- Multicenter, randomized, double-blind phase III study



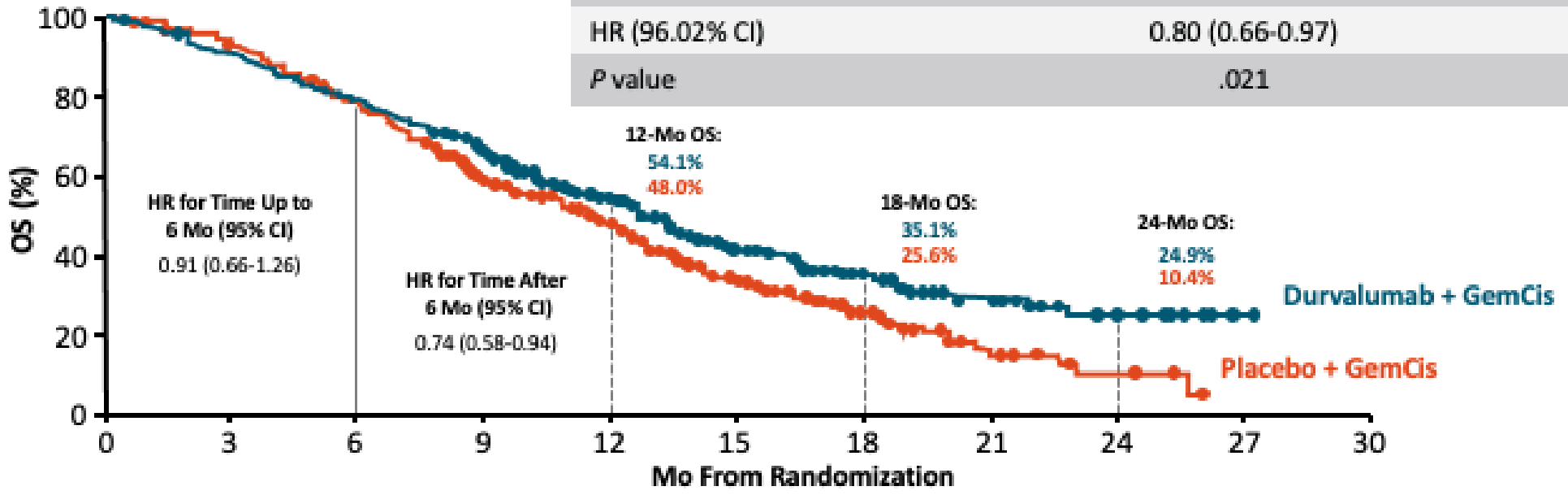
*GemCis treatment: gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Days 1 and 8 Q3W administered up to 8 cycles.

- Primary endpoint: OS
- Key secondary endpoints: PFS, ORR, DoR, efficacy by PD-L1 status, safety

Oh. NEJM Evid. 2022;1.

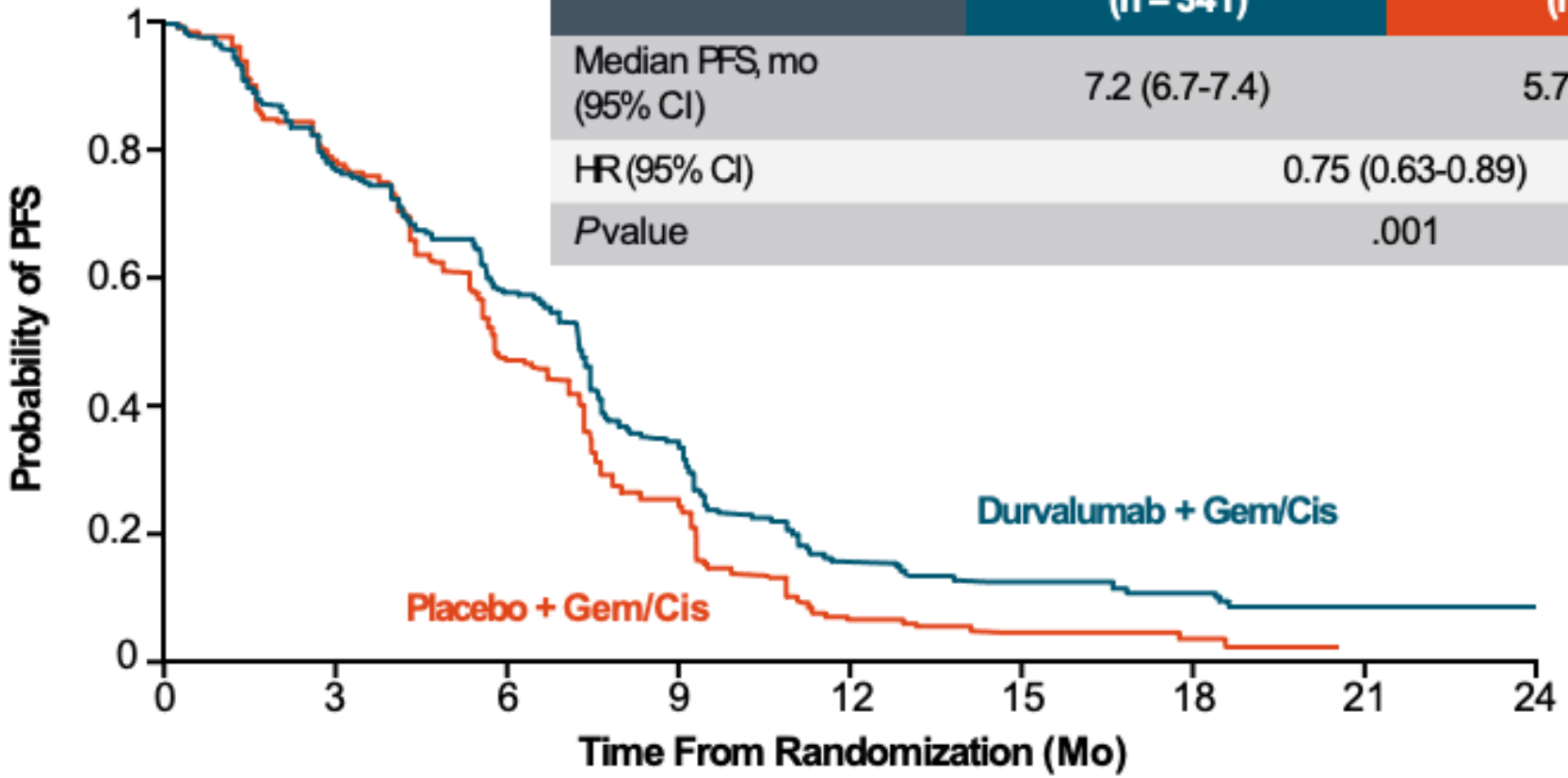
TOPAZ-1: mOS

Parameter	Durvalumab + GemCis (n = 341)	Placebo + GemCis (n = 344)
Median OS, mo (95% CI)	12.8 (11.1-14.0)	11.5 (10.1-12.5)
HR (96.02% CI)	0.80 (0.66-0.97)	
P value	.021	



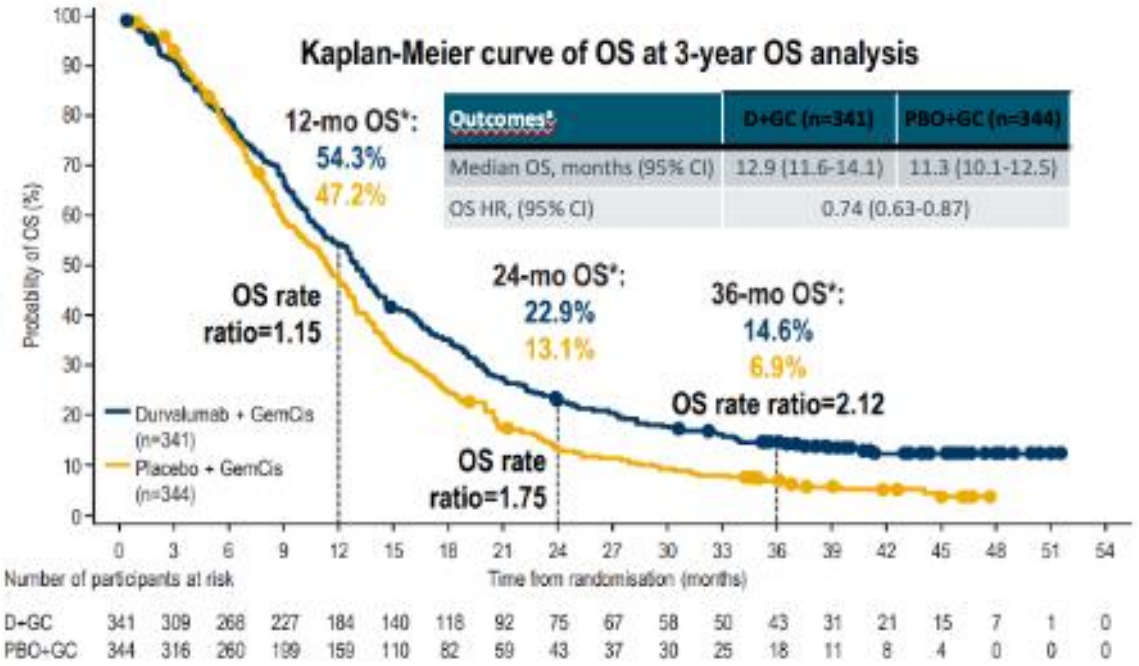
TOPAZ-1: PFS

Parameter	Durvalumab + Gem/Cis (n = 341)	Placebo + Gem/Cis (n = 344)
Median PFS, mo (95% CI)	7.2 (6.7-7.4)	5.7 (5.6-6.7)
HR (95% CI)	0.75 (0.63-0.89)	
P value	.001	



TOPAZ-1: 3 Yr OS Data

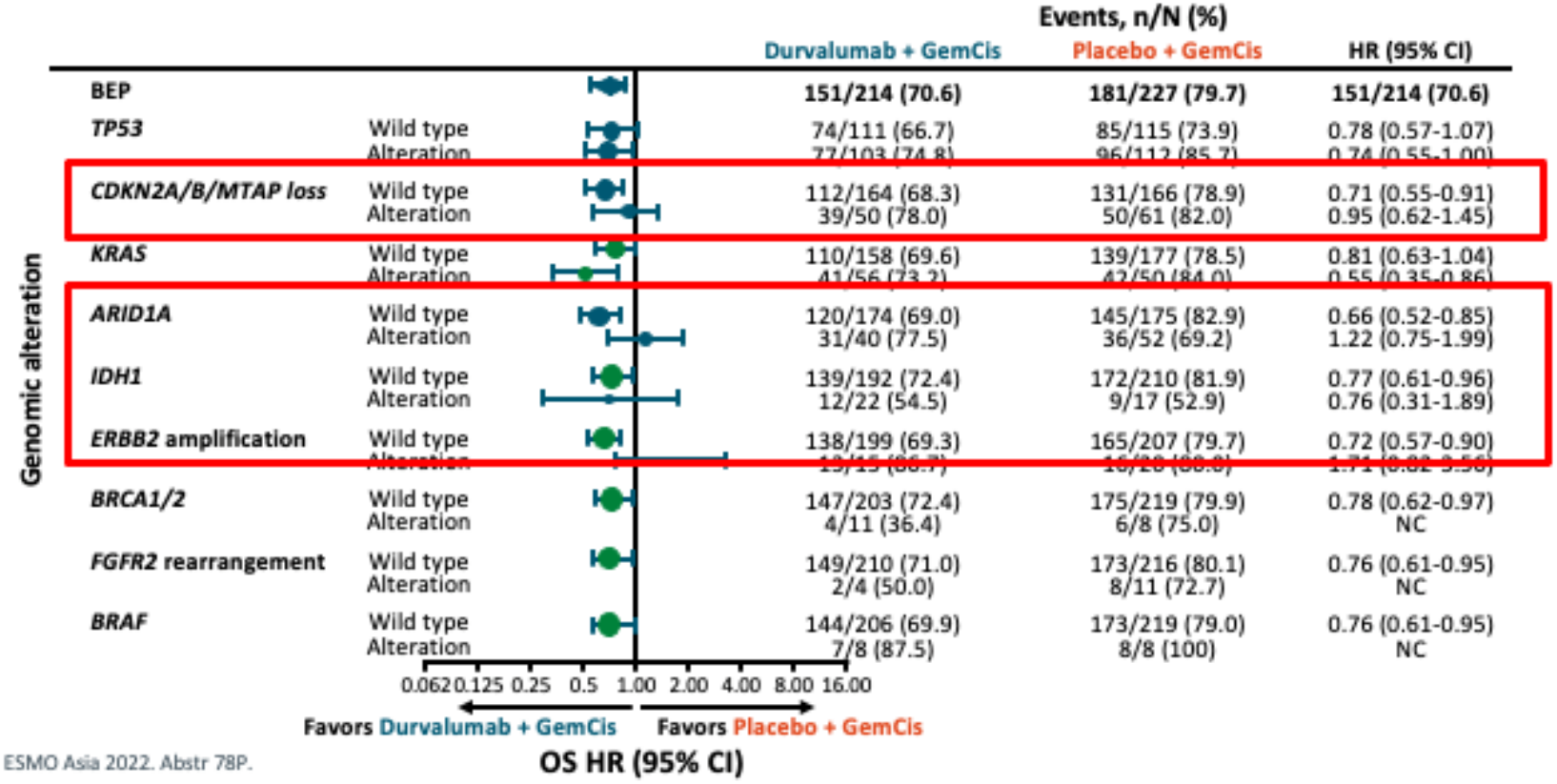
- Median follow-up: 41.3 months
- No meaningful changes in serious adverse events and treatment-related serious adverse events from previous analyses
- Greater proportion of DURVA+GC group alive ≥30 months after randomization
  - DURVA+GC: 58/341 (17.0%)
  - Placebo+GC: 30/543 (8.7%)



[a]DOC: 23 Oct 2023.

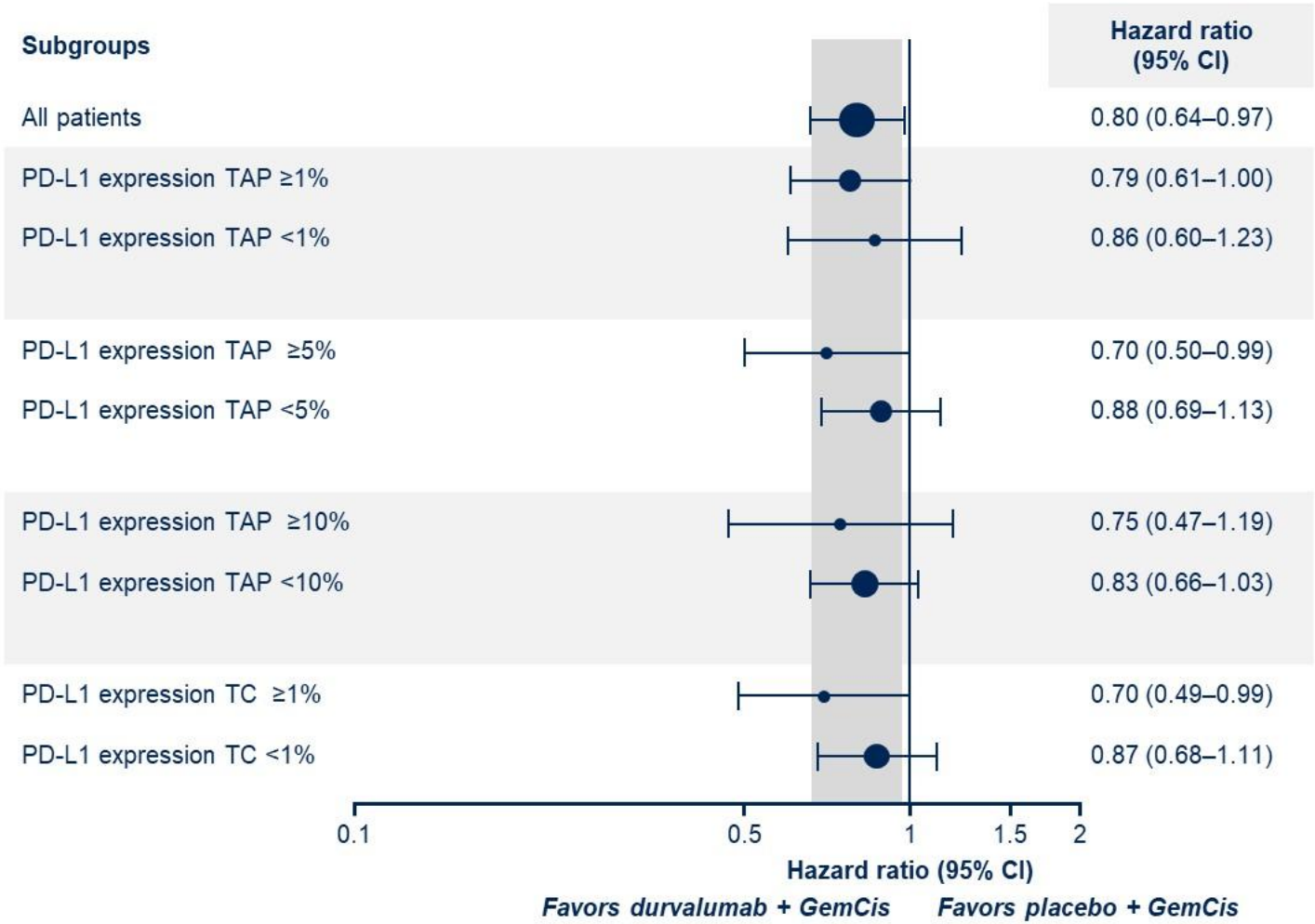
Oh D, et al. Presented at the 2024 ESMO Gastrointestinal Cancers Annual Congress. https://medicalinformation.astrazeneca-us.com/home/congress-pdf-viewer.html?pdfPath=https://d27mnwjqm5ztsa.cloudfront.net/4d4d150a-bf20-4c76-945a-ce2a670c3c99/8d4ef5d5-e1f1-4ce8-bace-24d20ef9b34e/8d4ef5d5-e1f1-4ce8-bace-24d20ef9b34e_source__v.pdf&pdfTitle=Three-year%20survival,%20safety%20and%20extended%20long-term%20survivor&documentNumber=303131.

TOPAZ-1: OS Subgroup Analysis, Mutation Status

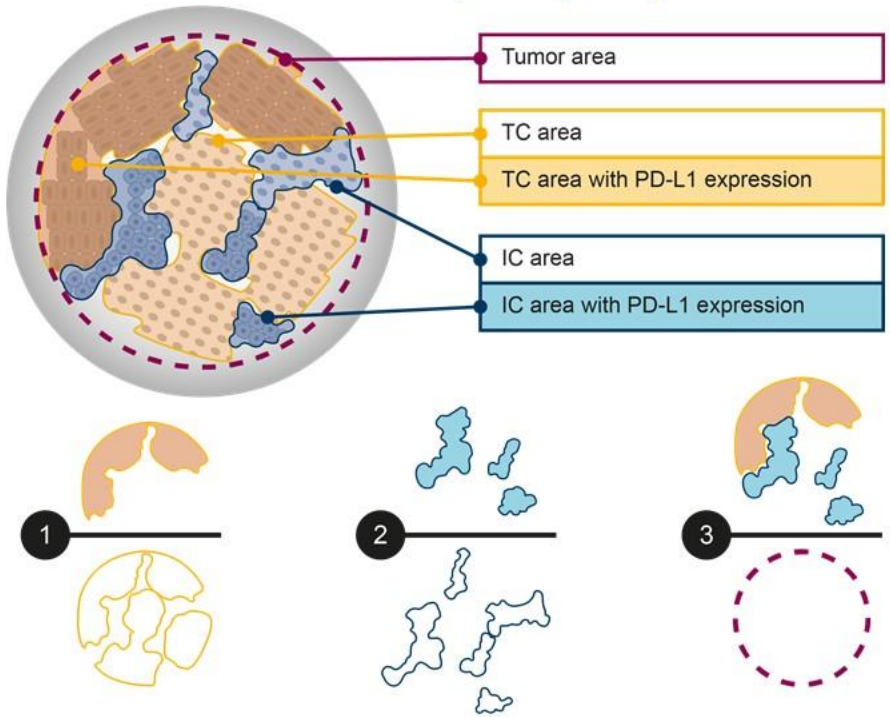


Oh. ESMO Asia 2022. Abstr 78P.

OS in subgroups by PD-L1 expression



Tumor Area Positivity (TAP) score using the Ventana PD-L1 (SP263) Assay



1. TC: proportion of TCs with PD-L1 membrane staining at any intensity
2. IC: proportion of tumor-associated ICs with PD-L1 cytoplasmic/membrane staining at any intensity
3. **Combined TCs and ICs:** Proportion of tumour area occupied by TCs with membrane and ICs with cytoplasmic/membrane PD-L1 staining at any intensity (TAP score)

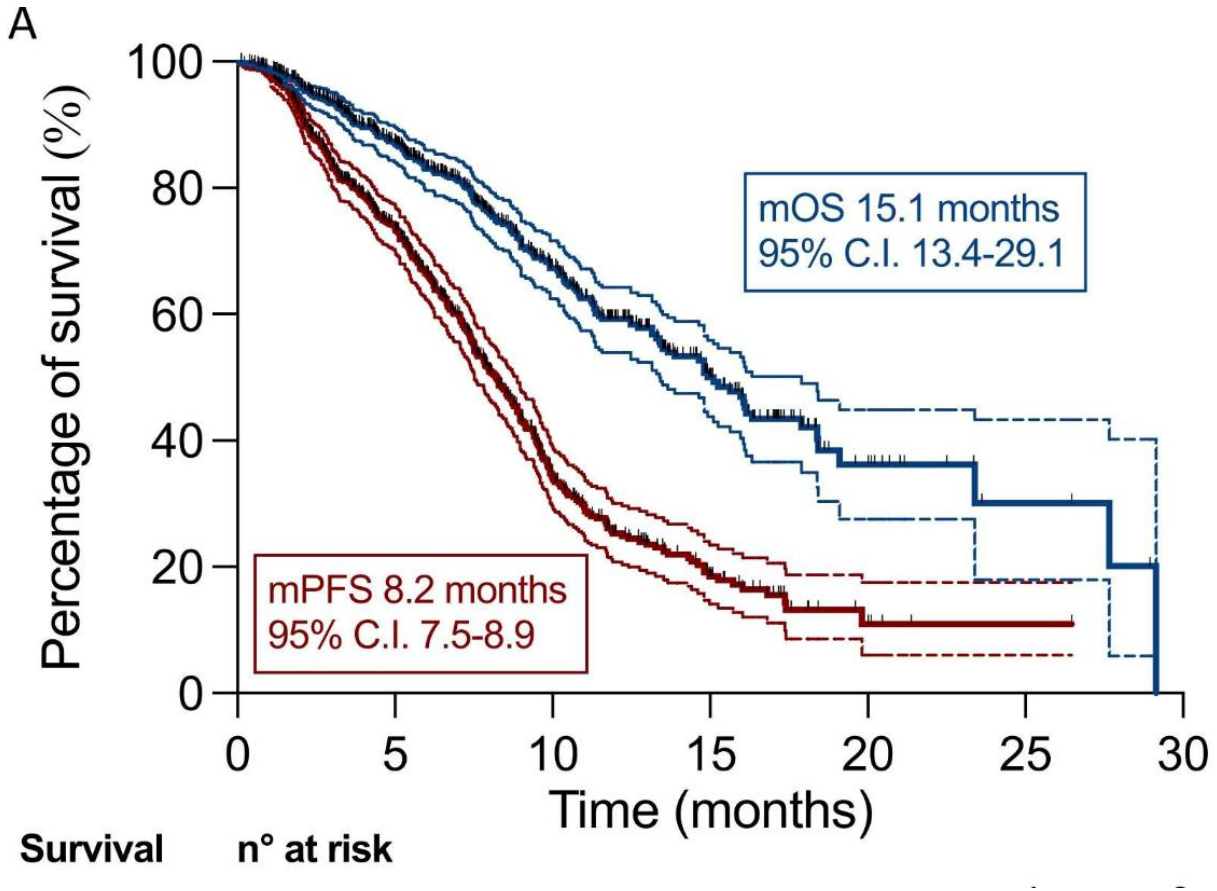
CI, confidence interval; IC, immune cell; OS, overall survival; PD-L1, programmed cell death ligand-1; TC, tumor cell; TAP, tumor area positivity

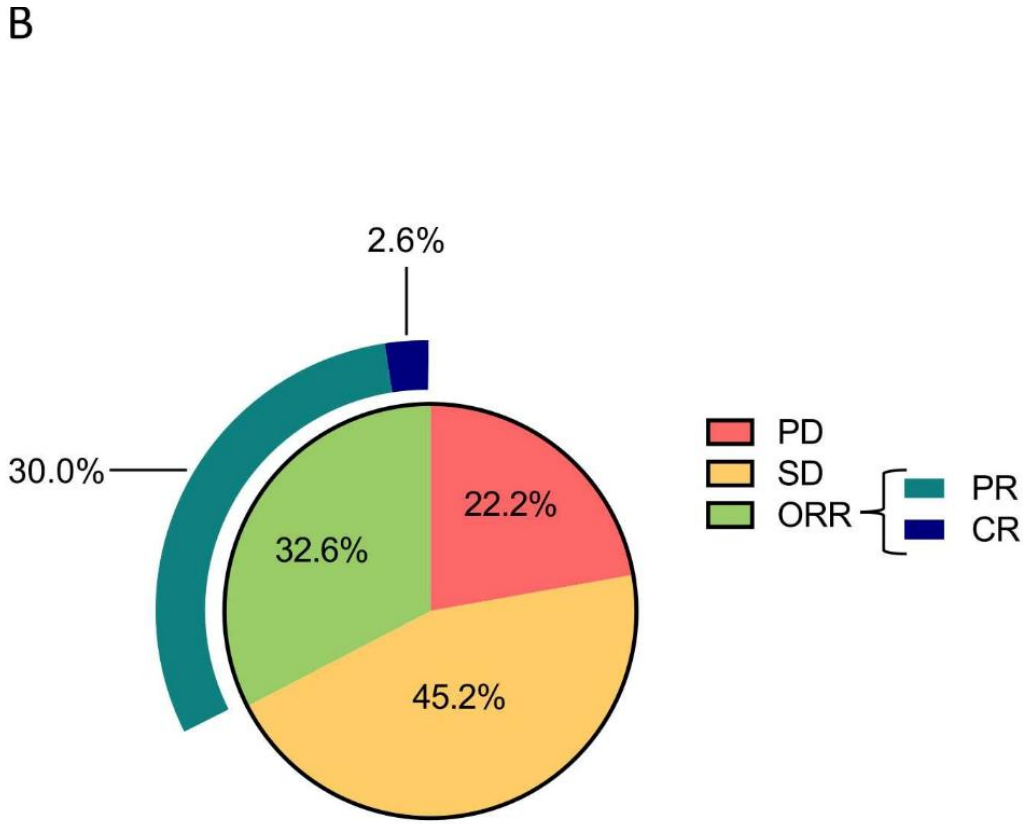
TOPAZ-1: Safety

AE	Durvalumab + GemCis (n = 338)	Placebo + GemCis (n = 342)
Median duration of exposure, mo (range)		
□ Durvalumab/placebo	7.3 (0.1-24.5)	5.8 (0.2-21.5)
□ Gemcitabine	5.2 (0.1-8.3)	5.0 (0.2-8.6)
□ Cisplatin	5.1 (0.1-8.3)	4.9 (0.2-8.5)
Any AE, n (%)	336 (99.4)	338 (98.8)
Any TRAE, n (%)	314 (92.9)	308 (90.1)
Any grade 3/4 AE, n (%)	256 (75.7)	266 (77.8)
Any grade 3/4 TRAE, n (%)	212 (62.7)	222 (64.9)
Any serious AE, n (%)	160 (47.3)	149 (43.6)
Any serious TRAE, n (%)	53 (15.7)	59 (17.3)
Any AE leading to discontinuation, n (%)	44 (13.0)	52 (15.2)
Any TRAE leading to discontinuation, n (%)	30 (8.9)	39 (11.4)
Any AE leading to death, n (%)	12 (3.6)	14 (4.1)
Any TRAE leading to death, n (%)	2 (0.6)	1 (0.3)
Any immune-mediated AE, n (%)	43 (12.7)	16 (4.7)

Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: A large real-life worldwide population (N=666) from 11 countries

Rimini M , …. Bekaii-Saab T … et al. EJC 2024





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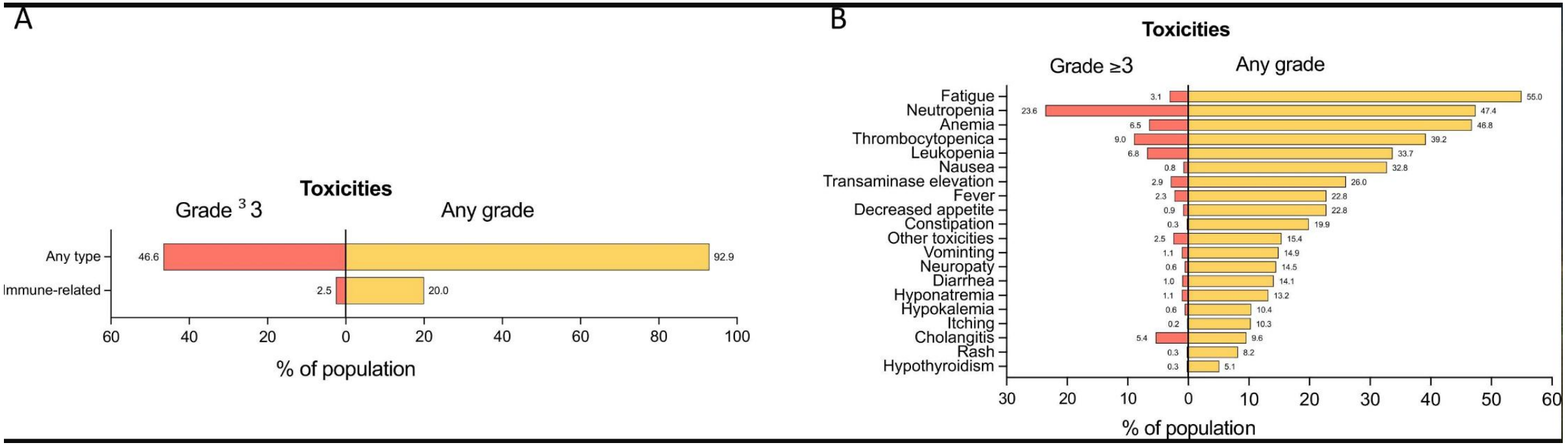
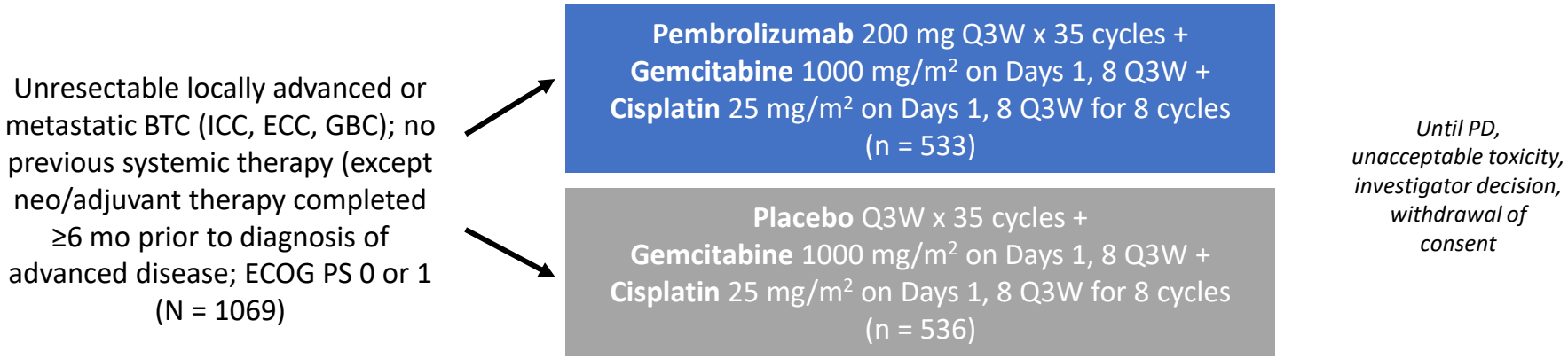


KEYNOTE-966: Pembrolizumab and Gemcitabine + Cisplatin in Patients With Advanced BTC

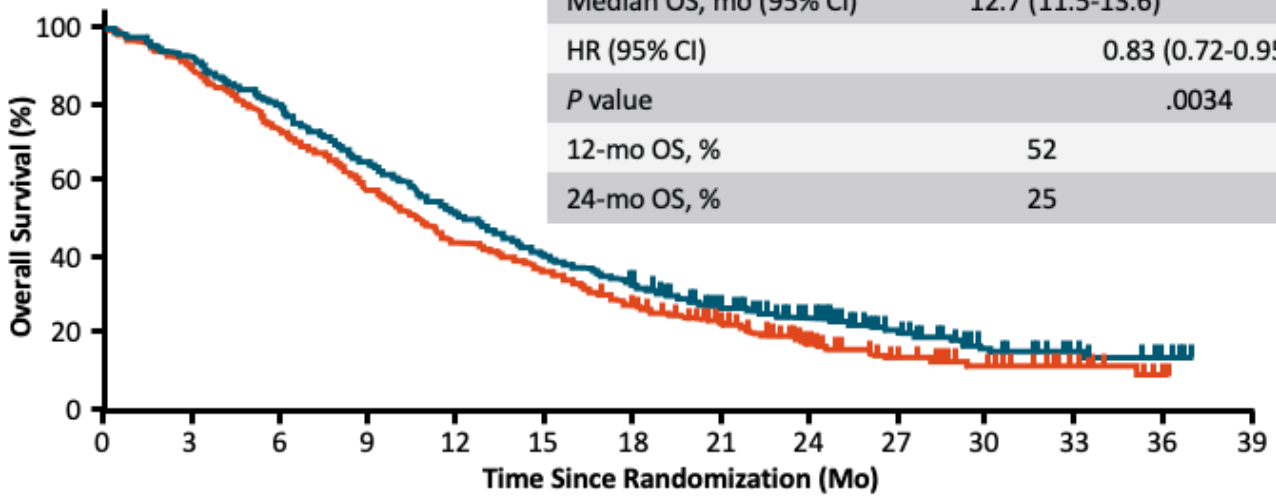
- Multicenter, randomized, double-blind phase III study



  - Primary endpoint: OS
  - Key secondary endpoints: PFS, ORR, DoR, safety

Kelley. Lancet. 2023:S0140-6736(23)00727-4.

KEYNOTE-966: OS



Parameter	Pembrolizumab + GemCis (n = 533)	Placebo + GemCis (n = 536)
Median OS, mo (95% CI)	12.7 (11.5-13.6)	10.9 (9.9-11.9)
HR (95% CI)	0.83 (0.72-0.95)	
P value	.0034	
12-mo OS, %	52	44
24-mo OS, %	25	18

- Pembrolizumab vs placebo: median PFS, 6.5 vs 5.6 mo (HR: 0.86; *P* = .023); ORR, 29% vs 29%
- Combination now FDA approved for patients with locally advanced unresectable or metastatic BTC

Kelley. Lancet. 2023:S0140-6736(23)00727-4. Pembrolizumab PI.

KEYNOTE-966: 3-Year OS

KEYNOTE-966: 3-Year Data

- Median follow-up: 36.6 months
- Comparable safety profiles for PEMBRO and placebo – no difference in grade 3-5 toxicity
- Median duration of response, months (range)
  - PEMBRO+GC: 8.3 (1.2+ to 44.3+)
  - Placebo+GC: 6.9 (1.1+ to 41.1+)

Overall Survival

Outcomes[a]	D+GC (n=341)	PBO+GC (n=344)
Median OS, months (95% CI)	12.7 (11.5-13.6)	10.9 (9.9-11.6)
OS HR, (95% CI)	0.86 (0.75-0.98), nominal *P* = .0099	

Finn RS, et al. Presented at the 2024 ASCO Annual Meeting. https://www.mrlcompendium.com/ASCO-MP_2024/index.html#accordion-hepatobiliary.

KEYNOTE-966: Safety

	Pembro + Gem/Cis (n = 529)	Placebo + Gem/Cis (n = 534)
Any	524 (99%)	532 (<100%)
Treatment-related	493 (93%)	500 (94%)
Grade 3-4 as maximum grade	420 (79%)	400 (75%)
Treatment-related	369 (70%)	367 (69%)
Led to death	31 (6%)	49 (9%)
Treatment-related	8 (2%)[a]	3 (1%)[b]
Led to discontinuation of ≥1 study medication	138 (26%)	122 (23%)
Treatment-related	102 (19%)	81 (15%)
Led to discontinuation of all study medication	35 (7%)	39 (7%)
Treatment-related	18 (3%)	14 (3%)

- Immune-related AE requiring systemic steroids: 9% vs. 5%

Impact of Hepatitis B infection on Efficacy and safety of Pembrolizumab plus GC in BTC

Figure 2. Kaplan-Meier curves of overall survival for patients with HBV infection status at baseline

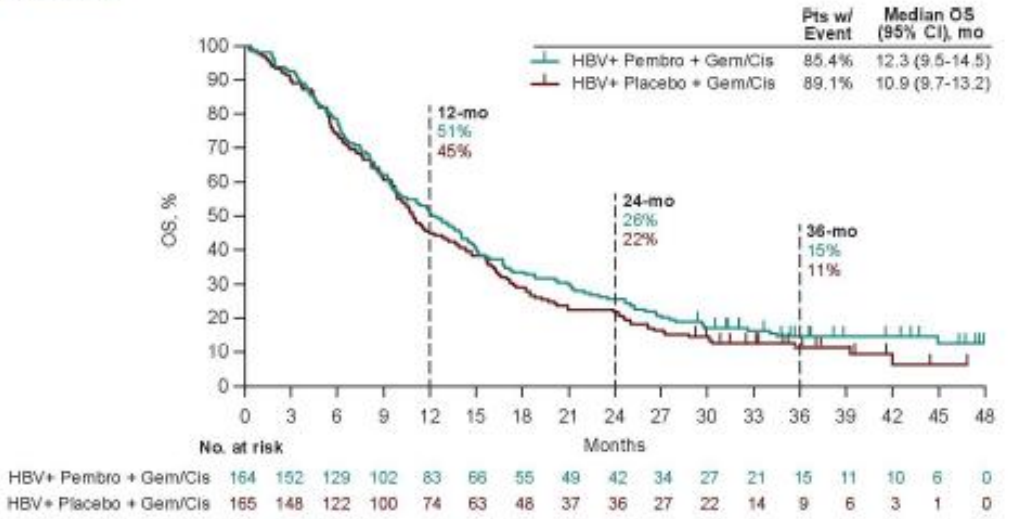
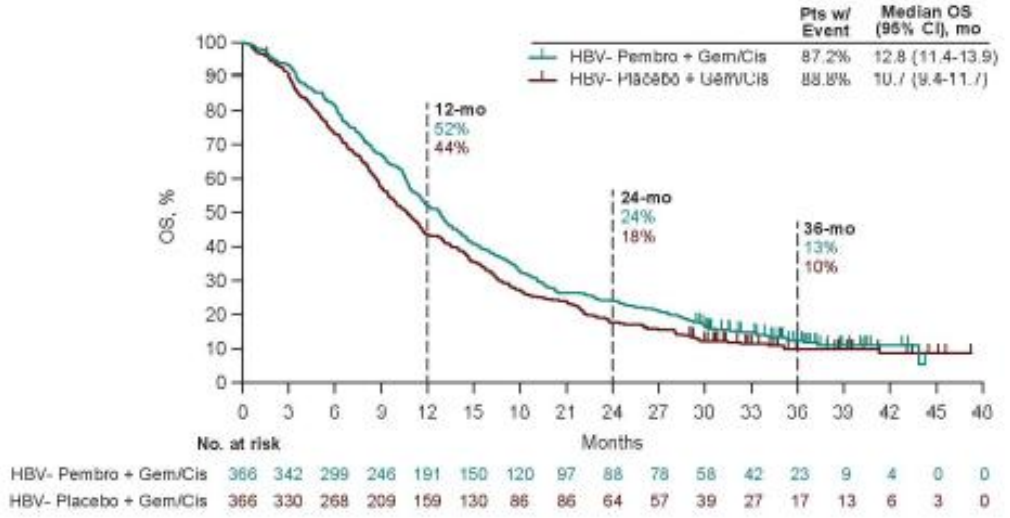


Figure 3. Kaplan-Meier curves of overall survival for patients without HBV infection status at baseline



Summary of Key Efficacy and Safety Outcomes From TOPAZ-1 and KEYNOTE-966

Outcome	TOPAZ-1[1] (Median follow-up: 15.9 months GEM-CIS, 16.8 months GEM-CIS+DURVA)		KEYNOTE-966[2] (Median follow-up: 25.6 months)	
	GEM-CIS	GEM-CIS+DURVA	GEM-CIS	GEM-CIS+PEMBRO
Median OS, months	11.5	12.8[a]	10.9	12.7[a]
ORR, %	19	27	29	29
Median PFS, months	5.7	7.2	5.6	6.5
TRAEs leading to discontinuation, %	11.4	8.9	15	19
TRAEs leading to death, %	0.3	0.6	1	2[b]
Immune-mediate AEs, %	4.7	12.7	13[c]	22[c]
Most common AEs	Anemia, nausea, decreased neutrophil count	Nausea, constipation, neutropenia	Decreased neutrophil count, anemia	Decreased neutrophil count, anemia

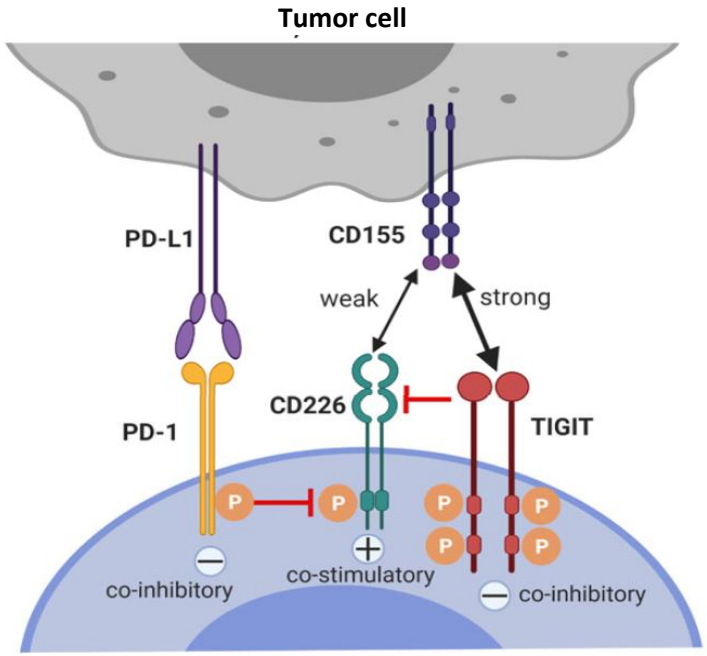
[a]Significantly longer than GEM-CIS alone; [b]Includes 1 potentially immune-mediated event (pneumonitis); [c]Includes infusion reactions.

1. Oh D, et al. *NEJM Evid*. 2022;1(8). doi:10.1056/EVIDoa2200015; 2. Kelley RK, et al. *Lancet*. 2023 Jun 3;401(10391):1853-1865.

Coordinated targeting of PD-1 and TIGIT with rilvegostomig

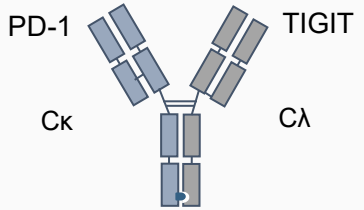
Co-operative inhibition of both targets may increase the effect of checkpoint blockade

PD-1 and TIGIT are mediating converging, inhibitory signals



Adapted from Ge et al., Frontiers in Immunology (2021)

Rilvegostomig (AZD2936) - Fc-silent, anti-PD-1/-TIGIT bi-specific

Category	AZD2936
Bispecific format **DuetMab**	
Fc isotype	Human IgG1-TM (***Fc-silent***)
PD-1 arm	LO115 V genes inserted on Kappa LC and Hole HC
TIGIT arm	COM902 (LO) V genes inserted as Lambda LC and Knob HC

Rilvegostomig is designed with a triple-mutant IgG1 backbone to avoid unselective removal of TIGIT expressing immune cells by Fc-mediated ADCC.

ADCC: antibody dependent cellular cytotoxicity, TIGIT: T cell immunoreceptor with Ig and ITIM domains

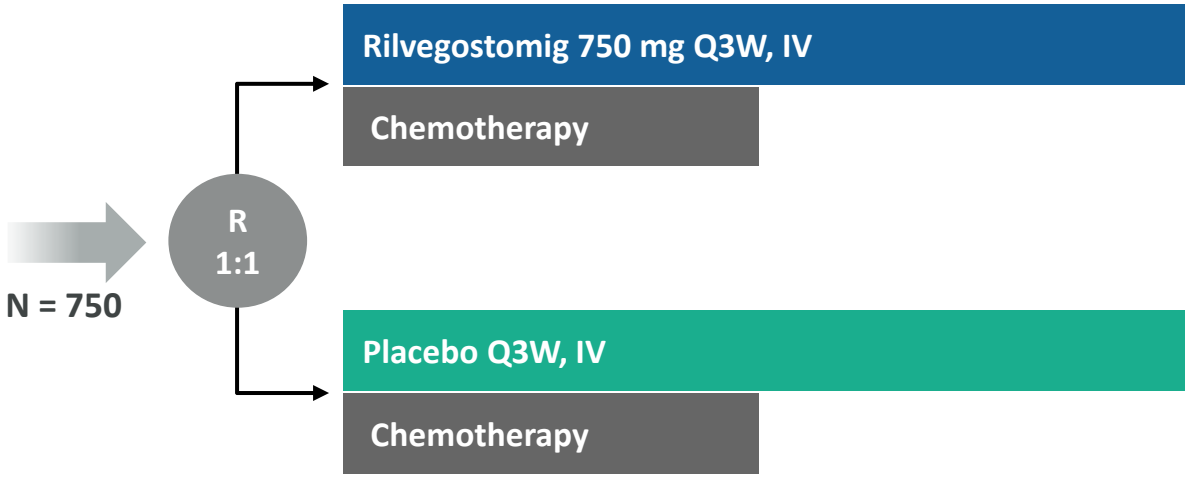
Study Design

Rilvegostomig plus investigator's choice of chemotherapy after resection of BTC

POPULATION

- Histologically confirmed BTC (ICCA, ECCA, or GBC)
- Macroscopically complete resection (R0/1)
- Randomized ≤ 12 weeks after resection
- Tumor sample available from resection
- Disease free by imaging prior to randomization
- No anti-cancer therapy for BTC prior to surgery
- ECOG 0-1

TREATMENT



ENDPOINTS

Primary:

RFS

Secondary:

OS

PFS

PRO

Chemotherapy (Investigator's Choice) :

- **Capecitabine:** 1250mg/m^2 BID for 2 weeks on, 1 week off for 8 cycles or per local practice, oral
- **S-1:** 40 – 60 mg BID (based on BSA) for 4 weeks on, 2 weeks off for 4 cycles, IV
- **Gem/Cis**: Gemcitabine 1000mg/m^2 + Cisplatin 25mg/m^2 Days 1& 8 Q3W for 8 cycles, oral

ARTEMIDE biliary01

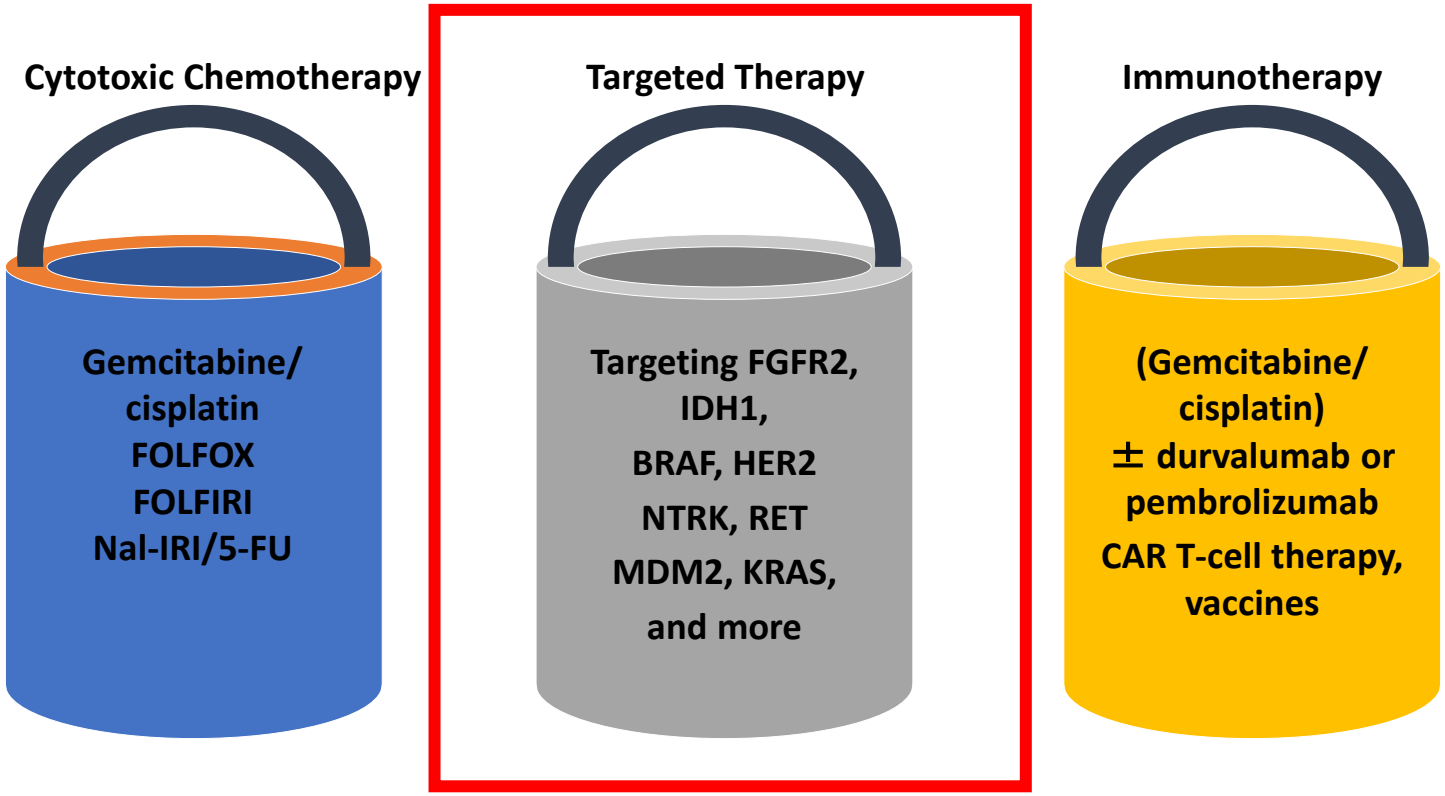
Source: www.clinicaltrials.gov

Bekaii-Saab T et al CCF 2024

Conclusions

- Gemcitabine + Cisplatin + Immune checkpoint inhibitor (**pembrolizumab or durvalumab)** is the current standard for 1st line therapy for advanced BTC as it improves median overall survival (OS) over GEM+CIS alone
  - OS improvements are modest but longer tail on the curve with adding ICI
- Acceptable safety with the addition of immunotherapy to GEM+CIS
- Ongoing studies underway to determine role of IO in combination with other chemotherapies

Systemic Therapy for Advanced BTC



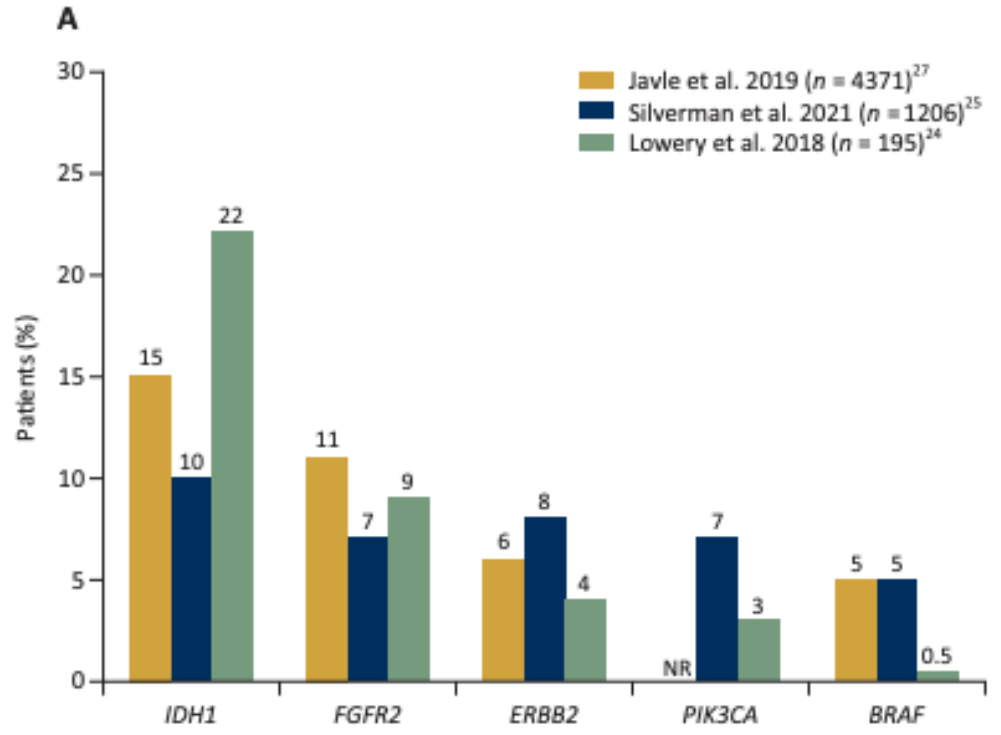
NCCN Guideline Recommendations for Molecular Testing in Advanced Biliary Tract Cancer

- Comprehensive molecular profiling recommended for patients with unresectable/metastatic BTC who are candidates for systemic therapy to detect potentially actionable molecular alterations

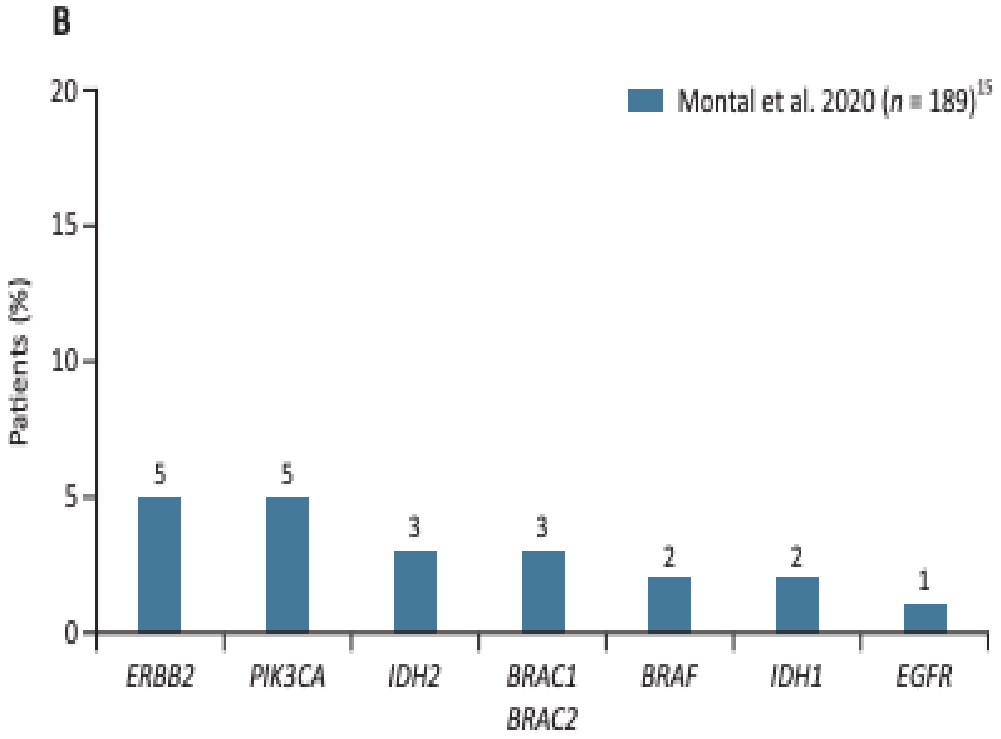
Alteration	Incidence, %	Recommended Subsite Testing			Methods
		GBC	ICC	ECC	
NTRK fusion	<1	X	X	X	NGS panel
MSI-H/dMMR	1-3	X	X	X	IHC, NGS, PCR
TMB-H	<5	X	X	X	NGS panel
BRAF V600E mut	1-5	X	X	X	NGS, PCR
RET fusion	<1	X	X	X	NGS panel
FGFR2 fusion/rearr	9-15 in ICC, rare in other	–	X	X	NGS, FISH
IDH1 mut	10-20 in ICC, rare in other	–	X	X	NGS panel/hotspot test
HER2 amp/overexp	5-20 CC, 15-30 GBC	X	X	X	IHC, FISH, NGS
KRAS G12C mut	1	X	X	X	NGS panel

- cfDNA assessment can be considered if initial biopsy yields insufficient tumor tissue

Commonly altered genes with actionable alterations in BTC



Intrahepatic CCA (iCCA)



Extrahepatic CCA (eCCA)

Bekaii-Saab T , et al. *Annals of Oncology* ; 2021

FGFR Inhibitor Efficacy in *FGFR2* Fusion BTC

	Pemigatinib (N=107)	**Infigratinib (N=108)**	**Futibatinib (N=103)**
ORR	36%	23% (1 prior Line of Rx 34%)	42%
DCR	82%	84%	83%
mPFS	6.9 mos	7.3 mos	9 mos
mDOR	7.5 mos	5 mos	9.7 mos
mOS	21.1 mos	12.2 mos	21.7 mos
Toxicities (G3/4)	64% Hyperphosphatemia, Alopecia, Diarrhea	64% Hyperphosphatemia, Stomatitis, Fatigue	57% Hyperphosphatemia, Diarrhea, Dry mouth

1. Abou-Alfa GK et al. *Lancet Oncol*. 2020;21(5):671-684; 2. Javle M, Bekaii-Saab T et al. Lancet GH, 20213. Goyal L et al. NEJM 2023;

HER2 Inhibitor Strategies in HER2+ BTC

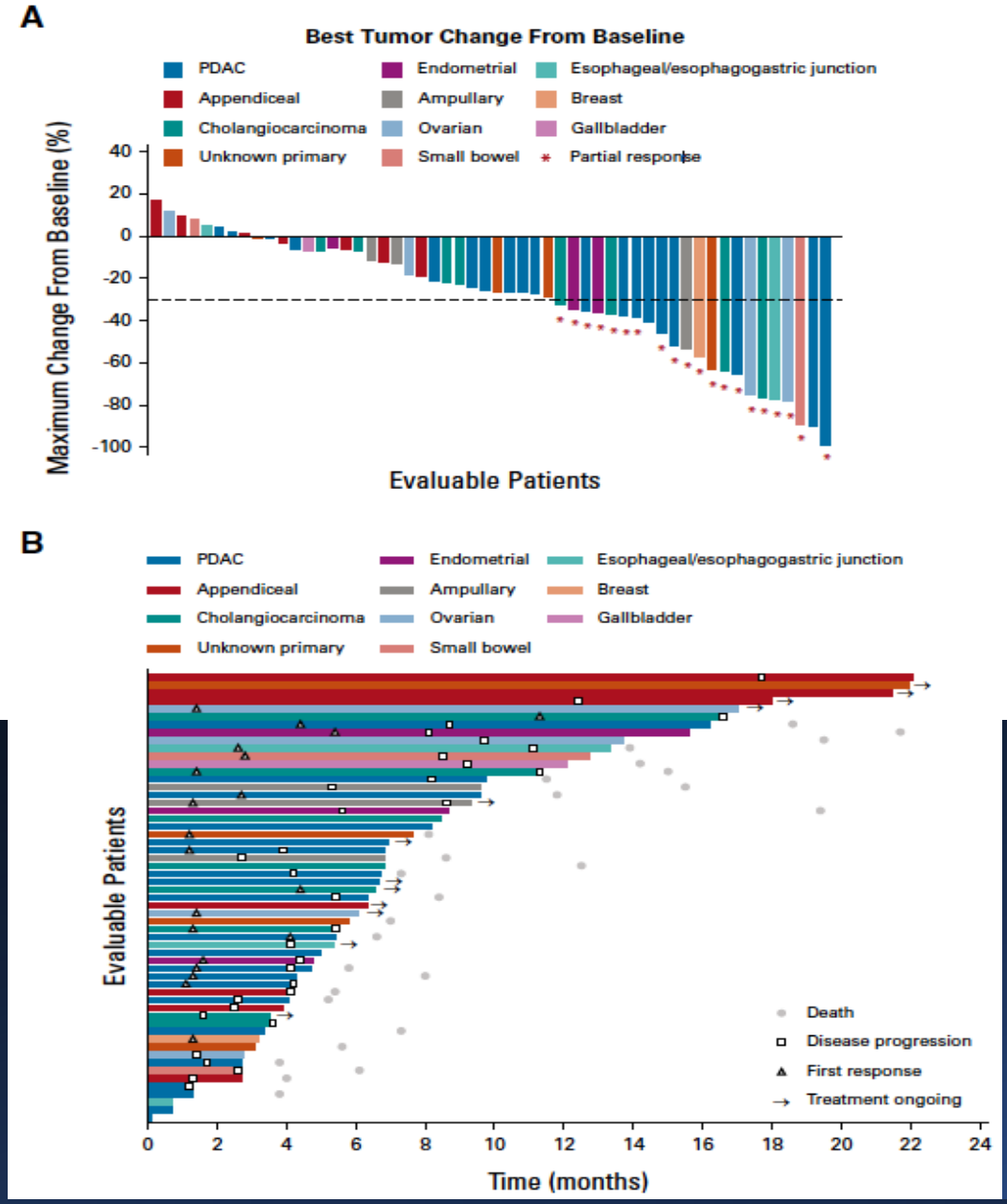
	Pertuzumab/Trastuzumab (MyPathway - N=39)[a]	Tucatanib/Trastuzumab (SGNTUC019 - N= 30)[a]	Trastuzumab Deruxtecan (HERB; NCCH1805 N=22)[b]	Trastuzumab Deruxtecan (DESTINY PanT02 N=16)[c]	Zanidatamab (HERIZON-BTC-01- N= 80)[d]
ORR	23%	46.6%	36.4%	56.3%	41.3%
DCR	74%	76.6%	86.5%	66% (@12wks)	68.8%
mPFS	4.0 mos	5.5 mos	5.1 mos	7.4 mos	5.5 mos
mOS	10.9 mos	15.5 mos	7.1 mos	12.4 mos	NR (70% @ 9 mos)
DOR	10.8 mos	6 mos	7.4 mos	NR separately	12.9 mos
Toxicities (G3/4)	46%	60%	81.3%	73.2%	57.5%

[a] IHC 3+ or FISHC/ISH+ or Ampl by NGS
[b] IHC 3+ or 2+/ISH+
[c] IHC 3+
[d] IHC 3+ or 2+ and ISH+

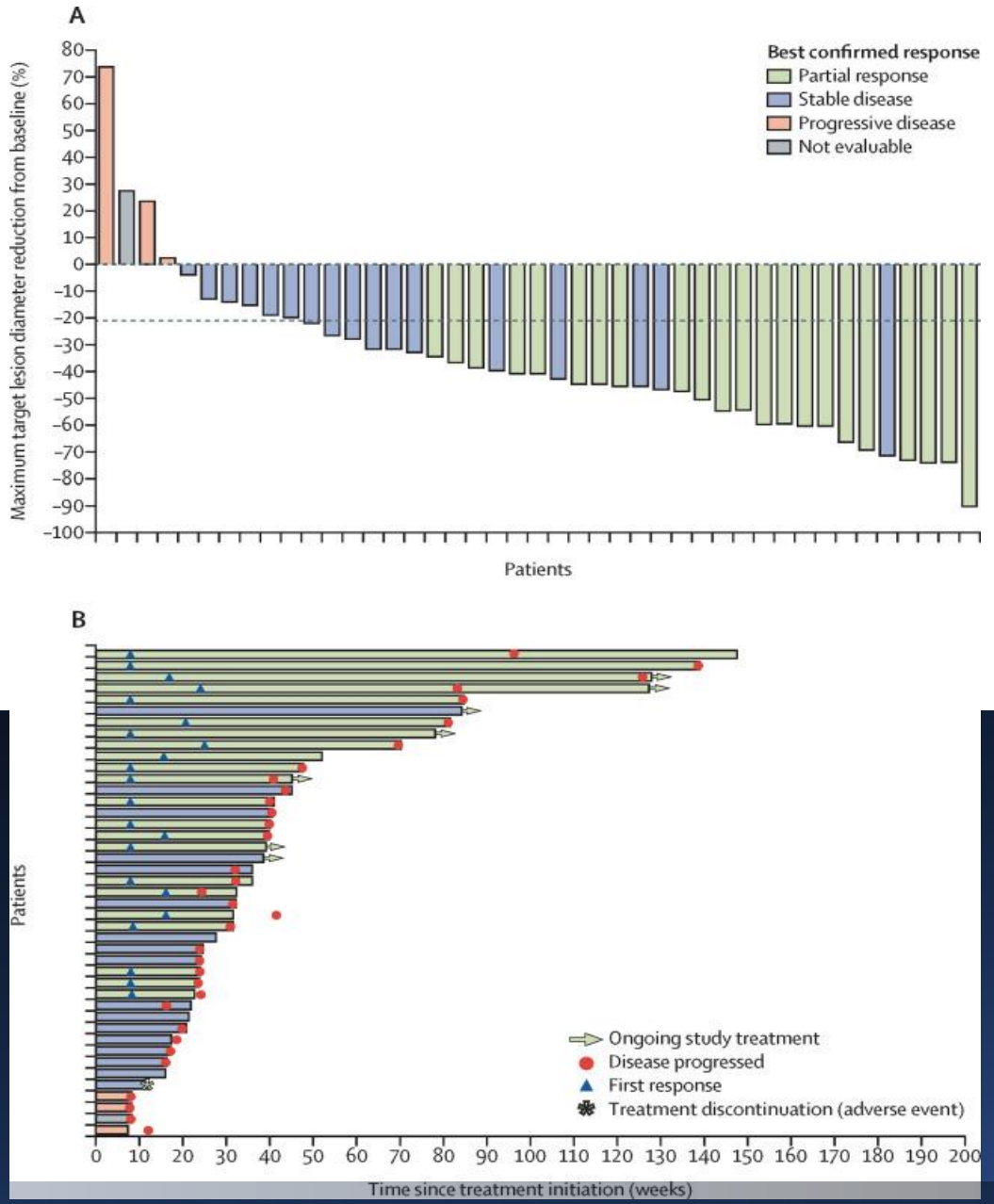
1. Javle, et al , Lancet Oncol, 2021 ; 2. Nakamura et al , J Clin Oncol , 2023; 3.Ohba et al . J Clin Oncol 2024; 4. Meric-Bernstram et al . J. Clin Oncol 2024; 5. Harding et al . Lancet Oncol- 2023

Targeting KRAS G12C mutations

Bekaii-Saab T et al. JCO 2023



BRAF-V600E mutated BTC : The ROAR Basket Trial with Dabrafenib + Trametinib



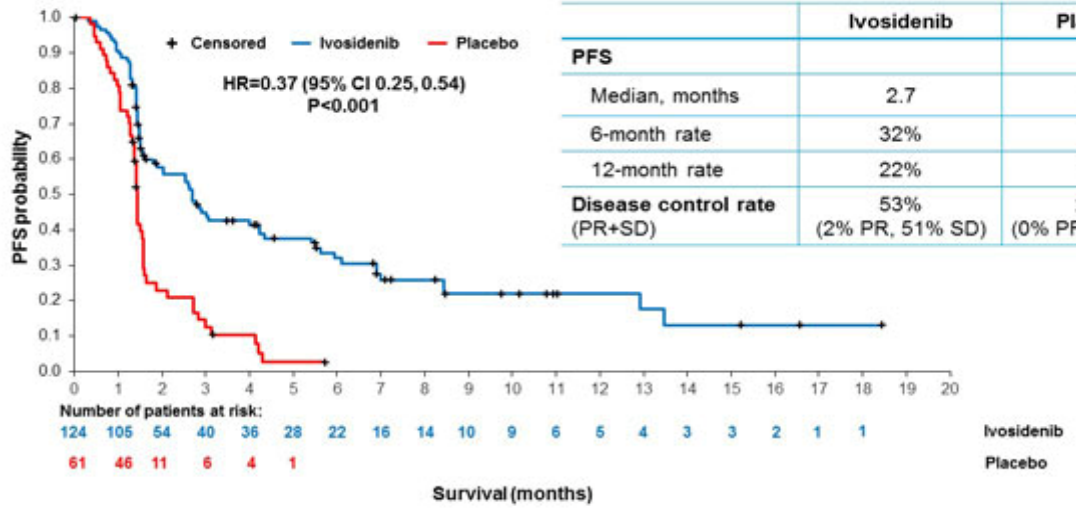
Subbiah V, et al. *Lancet Oncol* 2020;21:1234–1243

Abou-Alfa et al, Lancet Oncol 2020

Zhu et al JAMA Oncology 2021

Targeting IDH-1 in iCCA: Ivosidenib vs. Placebo

ClarIDHy: PFS by IRC

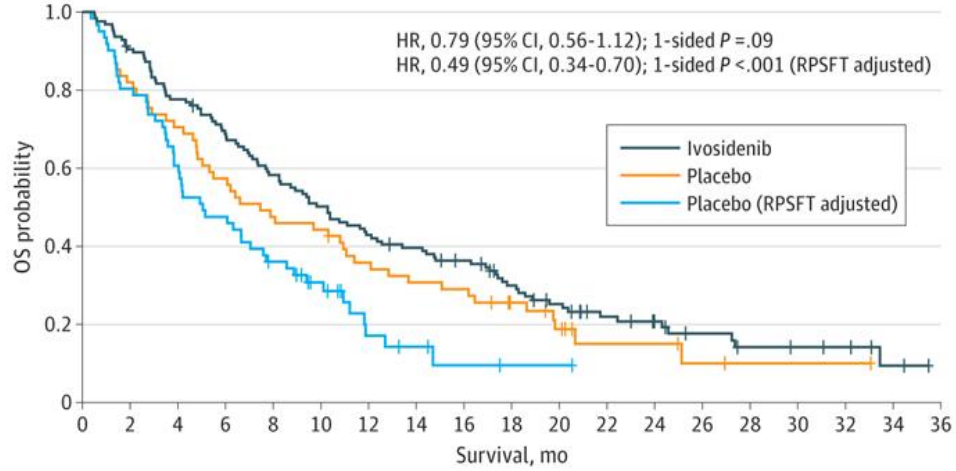


	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

NE=not estimable; PR=partial response; SD=stable disease.

Progression-free survival by Independent Review Committee.

A Overall survival



No. at risk

Ivosidenib	126	113	97	85	72	62	53	48	42	32	25	18	14	10	7	6	5	2
Placebo	61	50	43	35	29	27	21	18	17	12	8	4	4	2	1	1	1	
Placebo (RPSFT adjusted)	61	49	37	29	21	14	6	4	2	1	1							

Conclusions : 2L and Targeted Therapies

- NGS (+ emerging liquid platforms) testing is central to future applications of novel therapies in Biliary Cancer
  - Applying genomic technology and molecular classification critically and timely in cholangiocarcinoma is changing the therapeutic landscape.
- Molecularly targeted agents such as those targeting FGFR2, HER2 , KRAS G12C, BRAF-V600E , IDH1 and other rare targets (NTRK , ROS, MSI-H etc) are providing patients with advanced cholangiocarcinoma new treatment options
  - Ongoing efforts to expand the role of targeted therapies to others.
  - Drug resistance mechanisms and novel strategies to overcome drug resistance

QUESTIONS & ANSWERS

CASES

Case

67-year-old female with intrahepatic cholangiocarcinoma status post resection.

- Stage pT1aN0cM0
- adjuvant chemotherapy with capecitabine completed.
  - NGS: ARID1A, SMAD4, MSS, TMB= 0
- Biopsy proven recurrence within the liver 14 months post diagnosis
- After discussion with the hepatobiliary multiD team, Treatment with definitive SRS using cyberknife (rather than re-resection) consisting of 5000cGy in 5 fractions.

What is role for systemic therapy with “adjuvant” intent? PS= 1