Update on Management of Advanced Biliary Tract Cancer

Jagdeep Singh,
D.M. (Medical Oncology-Haematology),
DMC-AOI, Ludhaian.

Biliary Tract Cancer

- Biliary tract cancer (BTC) or cholangiocarcinoma, arises from the biliary epithelium:
  - Of small ducts in the periphery of the liver (intrahepatic)
  - Main ducts of the hilum (extrahepatic), extending into the gallbladder
- Incidence and epidemiology of biliary tract cancer are fluid and complex.

Epidemiology Of Biliary Tract Cancer

- 3% of GI malignancy
- Incidence:
  - Intra-hepatic cholangiocarcinoma is increasing
  - Extra-hepatic cholangiocarcinoma is decreasing internationally

Etiology

- Risk Factors
  - Primary sclerosing cholangitis
  - Parasites: Clonorchis infection
  - Lynch syndrome: biliary papillomatosis
  - Cholelithiasis
  - HCV infection
  - Metabolic: DM, obesity

Treatment Approach :

- Standard
  - Operable candidate: surgery → adjuvant therapy
  - Inoperable candidate: systemic therapy
- Variable approach in different centers
  - Locoregional therapy for IHC
  - Role of radiotherapy in adjuvant setting
  - Photodynamic therapy in EHC

First Line Therapy

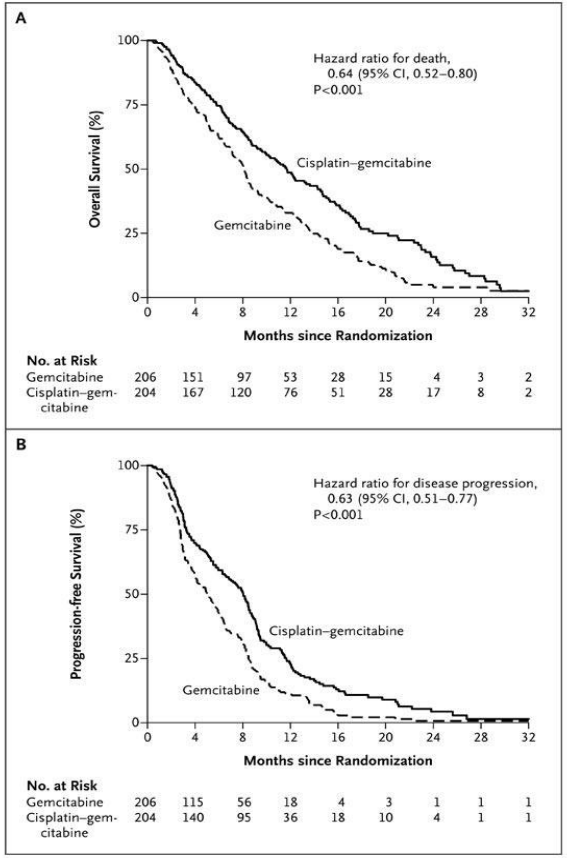
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthoney, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators*

	Treatment arm		p value
	Gem	CisGem	
All evaluable patients	**N=142**	**N=161**	
Complete response	1 (0.7)	1 (0.6)	
Partial response	21 (14.8)	41 (25.5)	
Stable disease	80 (56.3)	89 (55.3)	
Progresive disease	40 (28.2)	30 (18.6)	
Tumour control (CR+PR+SD)	102 (71.8)	131 (81.4)	0.049
Difference (95% CI)	9.5% (0.1, 19.0)		

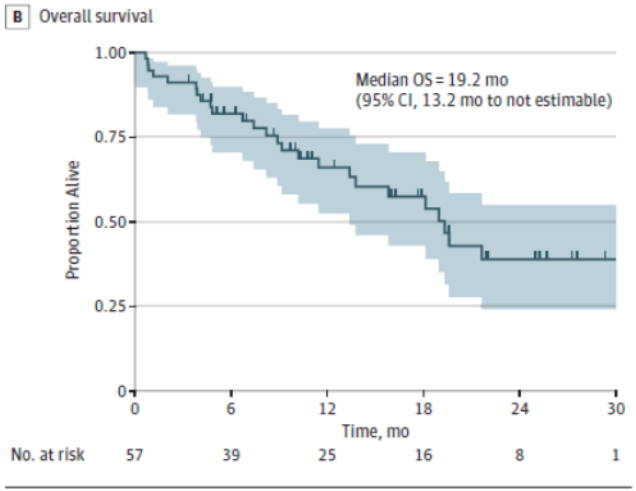


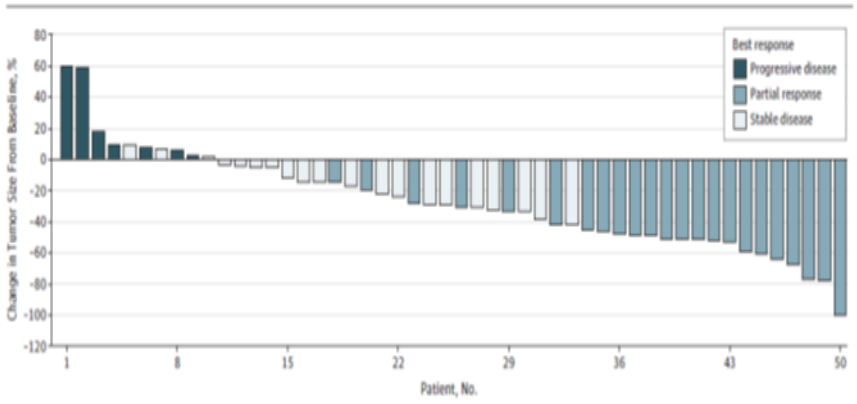
- OS: 11.7 vs. 8.1 months
- HR=0.64

JAMA Oncology | Original Investigation

Gemcitabine, Cisplatin, and nab-Paclitaxel for the Treatment of Advanced Biliary Tract Cancers
A Phase 2 Clinical Trial

Rachna T. Shroff, MS, MD; Milind M. Javle, MD; Lianchun Xiao, MS; Ahmed O. Kaseb, MD; Gauri R. Varadhachary, MD; Robert A. Wolff, MD; Kanwal P. S. Raghav, MD; Michiko Iwasaki, RN; Peter Masci, CCRC; Ramesh K. Ramanathan, MD; Daniel H. Ahn, MD; Tanios S. Bekaii-Saab, MD; Mitesh J. Borad, MD

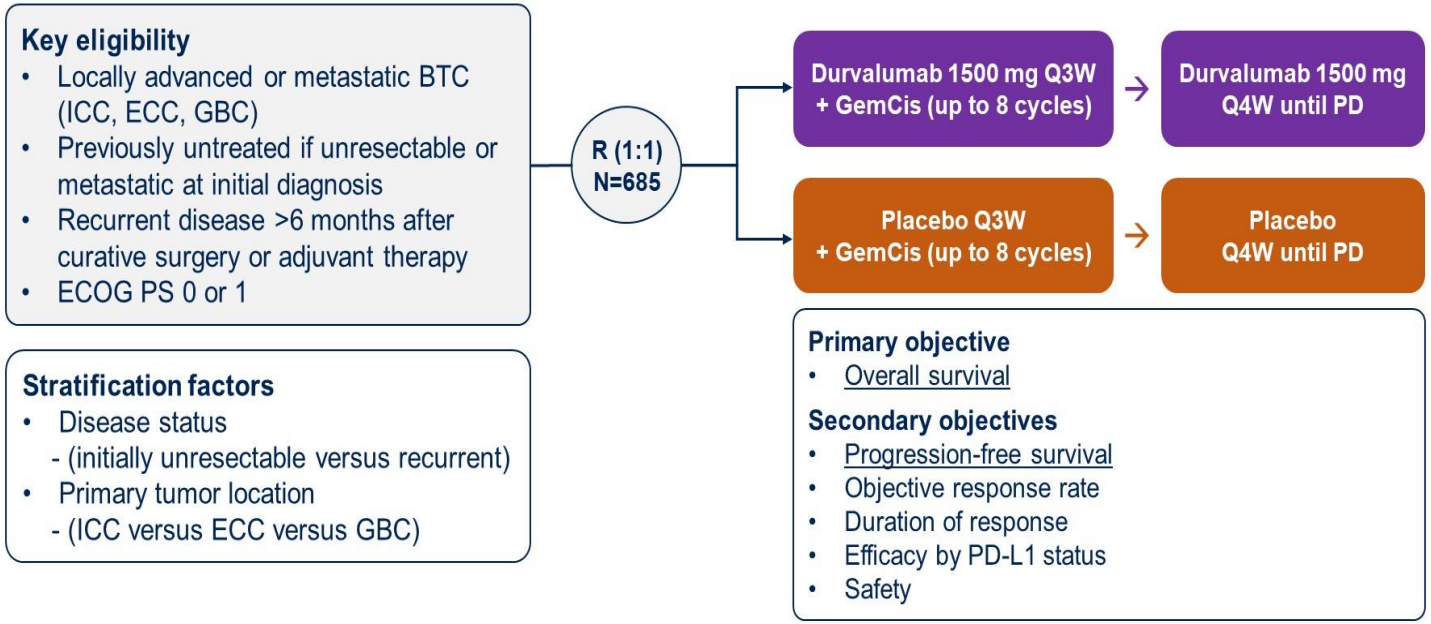




- RR=45%
- G3-4 AE=58% (33% G3-4 neutropenia)

TOPAZ-1 study design

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



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.

Patient demographics and baseline characteristics

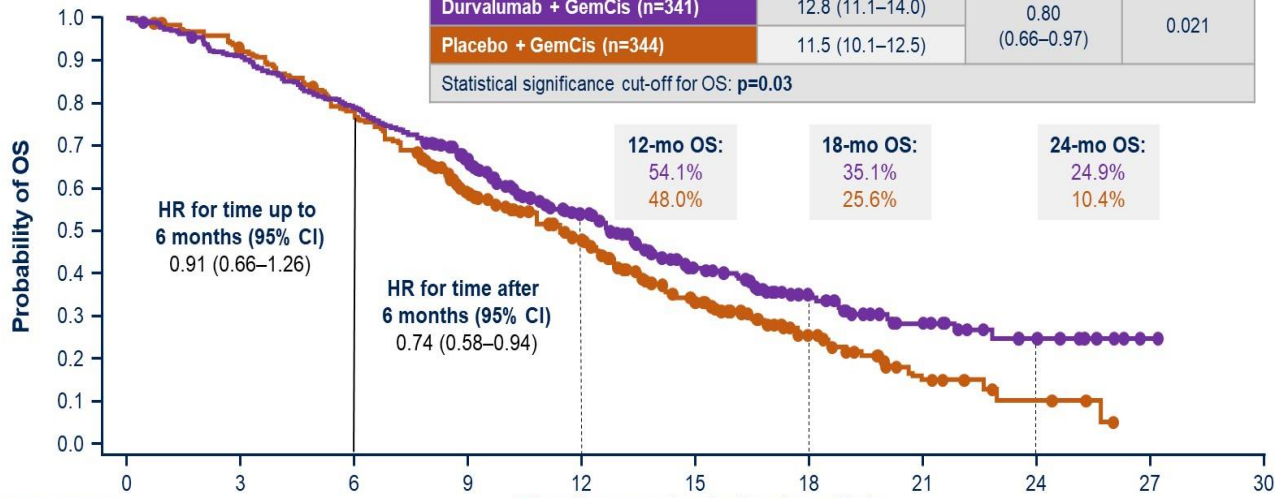
	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Median age (range), years	64 (20–84)	64 (31–85)
Sex, female, n (%)	172 (50.4)	168 (48.8)
Race, n (%)		
Asian	185 (54.3)	201 (58.4)
White	131 (38.4)	124 (36.0)
Black or African American	8 (2.3)	6 (1.7)
American Indian or Alaska Native	0	1 (0.3)
Other	17 (5.0)	12 (3.5)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of the world	163 (47.8)	148 (43.0)
ECOG PS 0 at screening, n (%)	173 (50.7)	163 (47.4)
Primary tumor location at diagnosis, n (%)		
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)
Disease status at randomization, n (%)		
Initially unresectable	274 (80.4)	279 (81.1)
Recurrent	67 (19.6)	64 (18.6)
Disease classification at diagnosis,* n (%)		
Metastatic	303 (88.9)	286 (83.1)
Locally advanced	38 (11.1)	57 (16.6)
PD-L1 expression,* n (%)		
TAP ≥1%	197 (57.8)	205 (59.6)
TAP <1%	103 (30.2)	103 (29.9)

*Data missing for remaining patients. Unless otherwise indicated, measurements were taken at baseline.

ECOG, Eastern Cooperative Oncology Group; GemCis, gemcitabine and cisplatin; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

Primary endpoint: OS

	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			

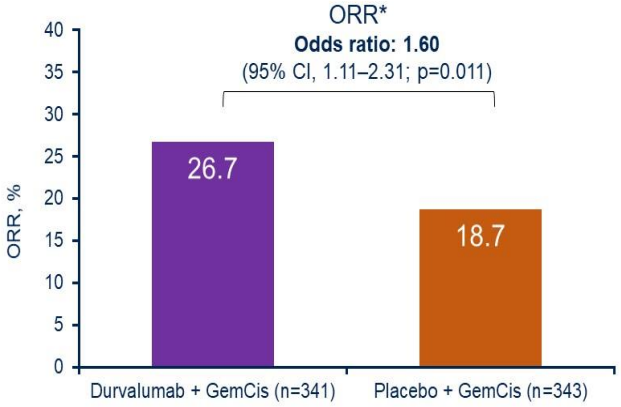


Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

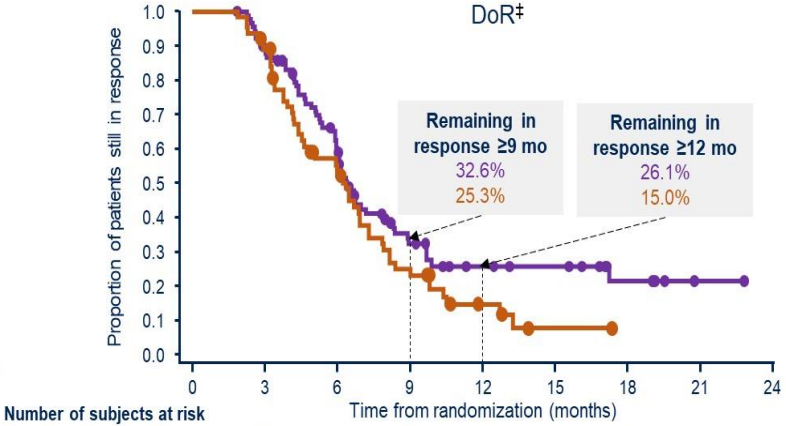
Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.

CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, month; OS, overall survival.

Secondary endpoint: Tumor response



	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=343)
ORR, n (%)	91 (26.7)	64 (18.7)
CR, n (%)	7 (2.1)	2 (0.6)
PR, n (%)	84 (24.6)	62 (18.1)
DCR, n (%)†	291 (85.3)	284 (82.6)



Number of subjects at risk

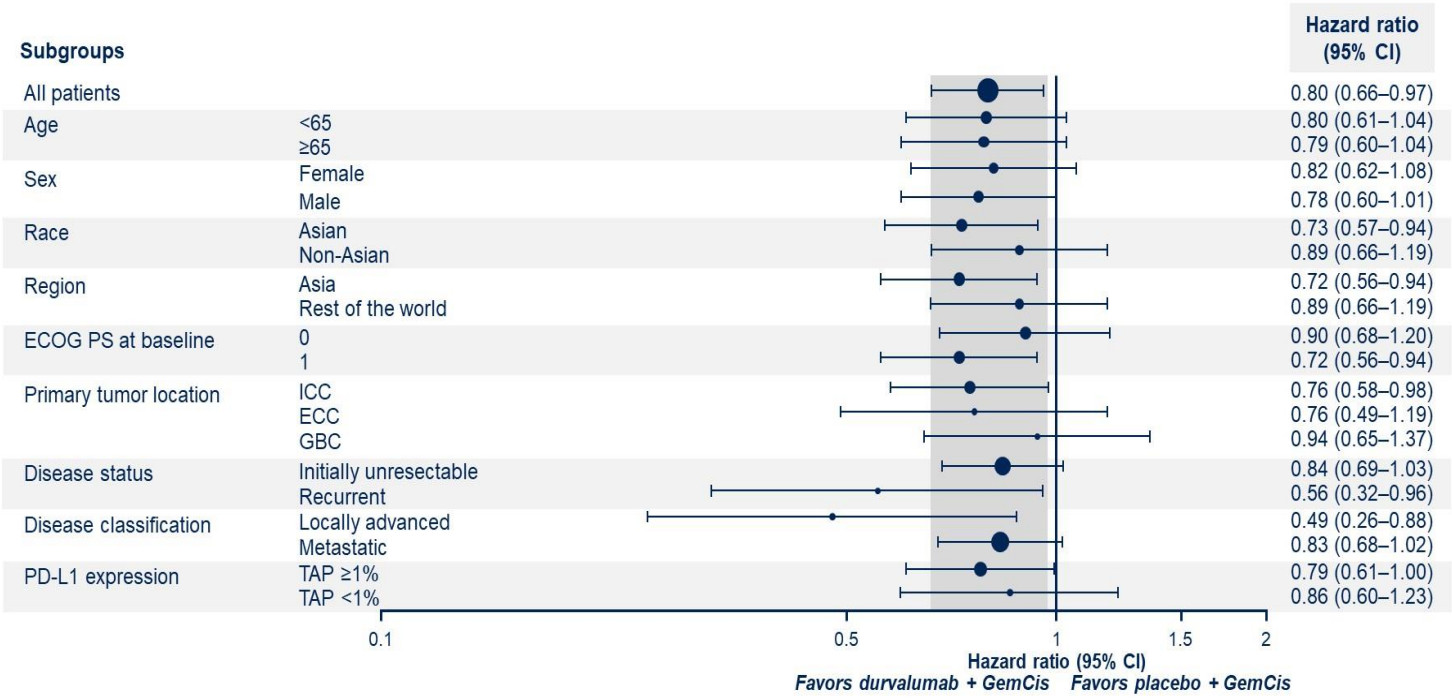
Durvalumab + GemCis	91	79	49	22	13	11	5	1
Placebo + GemCis	64	56	31	14	5	1	0	0

	Durvalumab + GemCis (n=91)	Placebo + GemCis (n=64)
Median DoR (quartile 1–3), months	6.4 (4.6–17.2)	6.2 (3.8–9.0)
Median time to response (quartile 1–3), months	1.6 (1.3–3.0)	2.7 (1.4–4.1)

*By investigator assessments using RECIST v1.1 based on patients in the final analysis set who had measurable disease at baseline. †Analysis of DCR was based on all patients in the full analysis set. ‡Analysis of DoR was based on patients in the full analysis set who had an objective response and measurable disease at baseline.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; GemCis, gemcitabine and cisplatin; mo, month; ORR, objective response rate; PR, partial response.

Subgroup analysis of OS



CI, confidence interval; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC, intrahepatic cholangiocarcinoma; OS, overall survival; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

Second-line therapy & beyond

Molecular Drivers in BTC

- BTC- all share genomic aberrations in cell cycle regulators (specifically CDKN2B) and chromatin remodeling (ARID1A)
- IHCC feature FGFR fusions, IDH1/2 substitutions, BRAF substitutions, and MET amplifications with a low KRAS mutational frequency
- ERBB2 amplification and PIK3CA/mTOR pathway aberrations were more common in EHCC and gallbladder tumors.

American Society of Clinical Oncology Educational Book 36 (May 19, 2016) e194-e203.

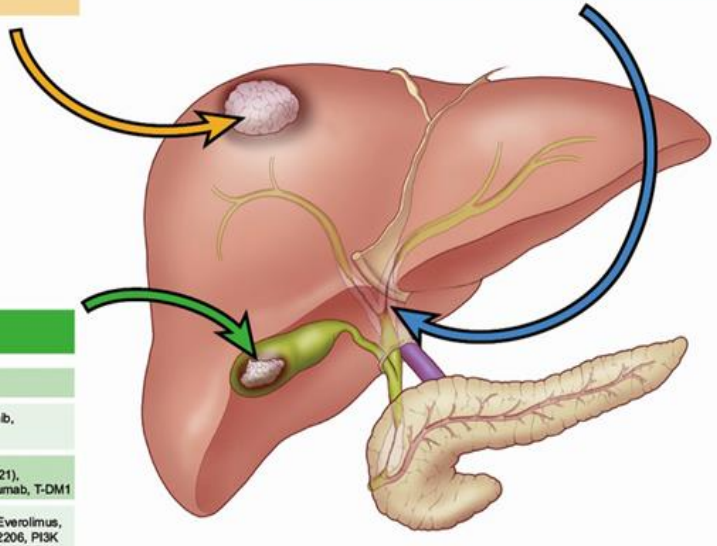
Oncogenic drivers in different subtype

IHCCA

Specific Targetable GAs	Prevalence	Targeted Therapies
FGFR2 Fusions	10% to 20%	BGJ398, Ponatinib, JNJ425756493, PRN1371, TAS-120, FGFR antibodies and FGFR trap molecules
IDH1/2	22% to 28%	AG-120, AG-881
BAP1	15% to 25%	Histone Deacetylase (HDAC) inhibitors like vorinostat and panobinostat

EHCCA

Specific Targetable GAs	Prevalence	Targeted Therapies
HER2/neu (mutation)	11% to 20%	Tyrosine Kinase Inhibitors like afatinib, neratinib, and dacomitinib
PRKACA and *PRKACB*	9%	Protein Kinase A inhibitors under development
ARID1A	5% to 12%	Histone Deacetylase (HDAC) inhibitors like vorinostat and panobinostat



GBC

Specific Targetable GAs	Prevalence	Targeted Therapies
EGFR	4% to 13%	Erlotinib, Cetuximab
HER2/neu (amplification)	10% to 15%	Trastuzumab, Lapatinib, Pertuzumab, T-DMI
ERBB3	0% to 12%	Seribantumab (MM-121), Pertuzumab, Trastuzumab, T-DM1
PTEN	0% to 4%	mTOR inhibitors like Everolimus, AKT inhibitor like MK2206, PI3K inhibitors like BKM120, BYL719 and SF1126
PIK3CA	6% to 13%	mTOR inhibitors like Everolimus, AKT inhibitor like MK2206, PI3K inhibitors like BKM120, BYL719 and SF1126

Jain A et al. JGO 2016; 7: 797-803
Valle J et al. Lancet 2021; 397: 428-44

JAMA Oncology | Original Investigation

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

Andrew X. Zhu, MD, PhD; Teresa Macarulla, MD; Milind M. Javle, MD; R. Kate Kelley, MD; Sam J. Lubner, MD; Jorge Adeva, MD; James M. Cleary, MD; Daniel V. T. Catenacci, MD; Mitesh J. Borad, MD; John A. Bridgewater, PhD; William P. Harris, MD; Adrian G. Murphy, MD; Do-Youn Oh, MD; Jonathan R. Whisenant, MD; Maeve A. Lowery, MD; Lipika Goyal, MD; Rachna T. Shroff, MD; Anthony B. El-Khoueiry, MD; Christina X. Chamberlain, PhD; Elia Aguado-Fraile, PhD; Sung Choe, PhD; Bin Wu, PhD; Hua Liu, PhD; Camelia Gliser, BS; Shuchi S. Pandya, MD; Juan W. Valle, MD; Ghassan K. Abou-Alfa, MD

Isocitrate dehydrogenase 1 (IDH1) variations occur in up to approximately 20% of patients with intrahepatic cholangiocarcinoma

Median OS was 10.3 with Ivosidenib vs 7.5 months with placebo (HR, 0.79)

THE LANCET
Oncology

ARTICLES | VOLUME 21, ISSUE 5, P671-684, MAY 01, 2020

Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study

Prof Ghassan K Abou-Alfa, MD • Vaibhav Sahai, MBBS • Antoine Hollebecque, MD • Gina Vaccaro, MD
Davide Melisi, MD • Raed Al-Rajabi, MD • et al. Show all authors

Published: March 20, 2020 • DOI: https://doi.org/10.1016/S1470-2045(20)30109-1 • Check for updates

FGFR2 fusions or rearrangements

ORR was 36%, including 3 complete responses

The median DOR was 9.1 months with responses lasting ≥ 6 months in 63% responding patients and ≥ 12 months in 18% patients

THE LANCET
Oncology

Sub

ARTICLES | VOLUME 21, ISSUE 9, P1234-1243, SEPTEMBER 01, 2020

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

Vivek Subbiah, MD • Prof Ulrik Lassen, MD • Elena Élez, MD • Prof Antoine Italiano, MD • Prof Giuseppe Curigliano, MD • Prof Milind Javle, MD • et al. Show all authors

Published: August 17, 2020 • DOI: https://doi.org/10.1016/S1470-2045(20)30321-1 • Check for updates

BRAF gene have been found in 5% of biliary tract tumours

BRAF inhibitor, and trametinib, a MEK inhibitor, achieved a 51% overall response rate in patients with BRAF V600E–mutated cholangiocarcinoma

2nd line Biomarker-driven trial

	Biomarker-driven						All comers
Targets	mIHD1[1]	FGFR2		HER2			Chemotherapy
Regimen	Ivosidenib vs. placebo	Pemigatinib[2]	Infigratinib[3]	Pertuzumab + Trastuzumab[4]	Zanidatamab HER2 +ve [5]	Trastuzumab deruxtecan HER2 +ve [6]	mFOLFOX vs. ASC[7]
N	124 vs. 61	107	108	39	21	22	81 vs. 81
ORR	2.4%	36%	23.1%	23%	40%	30%	5.0%
DCR	53%	82%	84.3%	51%	65%	80%	33%
mPFS	2.7 vs. 1.4m (HR=0.37)	6.9m	7.3m	4.0m	NR	3.5m	4m
mOS	10 vs. 7.5m (HR=0.79)	21.1m	12.2m	10.9m	NR	7.1m	6.2 vs. 5.3m (HR=0.69)

[1] Zhu AX et al. JAMA Oncol 2021; [2] Abou-alfa G Lancet Oncol 2020; [3] Javel et al. Lancet Gastro & Hepatol 2021; [4] Javel et al. Lancet Oncol 2021; [5] Meric-Bermstam ASCO 2021; [6] Ohba et a. ASCO 2022; [7] Lamarca et al Lancet Oncol 2021

	Frequency*	Targeted agents	Molecular test
IDH1	13% of intrahepatic cholangiocarcinoma cases[100,117]	Ivosidenib	Tumour next-generation DNA sequencing or targeted sequencing for hotspot mutations in coding region of IDH1
FGFR pathway	20% of intrahepatic cholangiocarcinoma cases[121]	Erdafitinib;[122] futibatinib;[121] infigratinib;[123] pemigatinib[101]	Tumour next-generation DNA sequencing including FGFR2 intronic region, targeted RNAseq, or FISH testing for FGFR2 translocation
BRAF	5% of intrahepatic cholangiocarcinoma cases[114,116]	Dabrafenib plus trametinib;[124] vemurafenib[125]	Tumour next-generation DNA sequencing or targeted sequencing for hotspot mutations in coding region of BRAF
MSI-high or MMR deficiency	2% of biliary tract cancer cases[126]	Pembrolizumab[126]	Multiple testing modalities available: PCR, immunohistochemistry, or tumour next-generation DNA sequencing
ERBB2 (HER2)	15–20% gallbladder cancer and extrahepatic cholangiocarcinoma cases[114,116]	..	Multiple testing modalities available including immunohistochemistry and FISH for expression and amplification, tumour next-generation DNA sequencing for mutations
NTRK	Rare	Entrectinib;[127] larotrectenib[128]	Tumour next-generation DNA sequencing including NTRK intronic region or targeted RNAseq, or FISH testing for NTRK translocation

IDH1=isocitrate dehydrogenase-1. FGFR=fibroblast growth factor receptor-2. FISH=fluorescent in-situ hybridisation. BRAF=activating serine threonine-protein kinase B-raf kinase. MSI=microsatellite instability. MMR=mismatch repair. ERBB2=receptor tyrosine-protein kinase erbB-2. NTRK=neurotrophic receptor tyrosine kinase. *All percentages are approximations.

Table 1: **Therapeutic targets and approach to molecular profiling in biliary tract cancers**

Jain A et al. JGO 2016; 7: 797-803
Valle J et al. Lancet 2021; 397: 428-44

How about immunotherapy?

INTERNATIONAL JOURNAL of CANCER

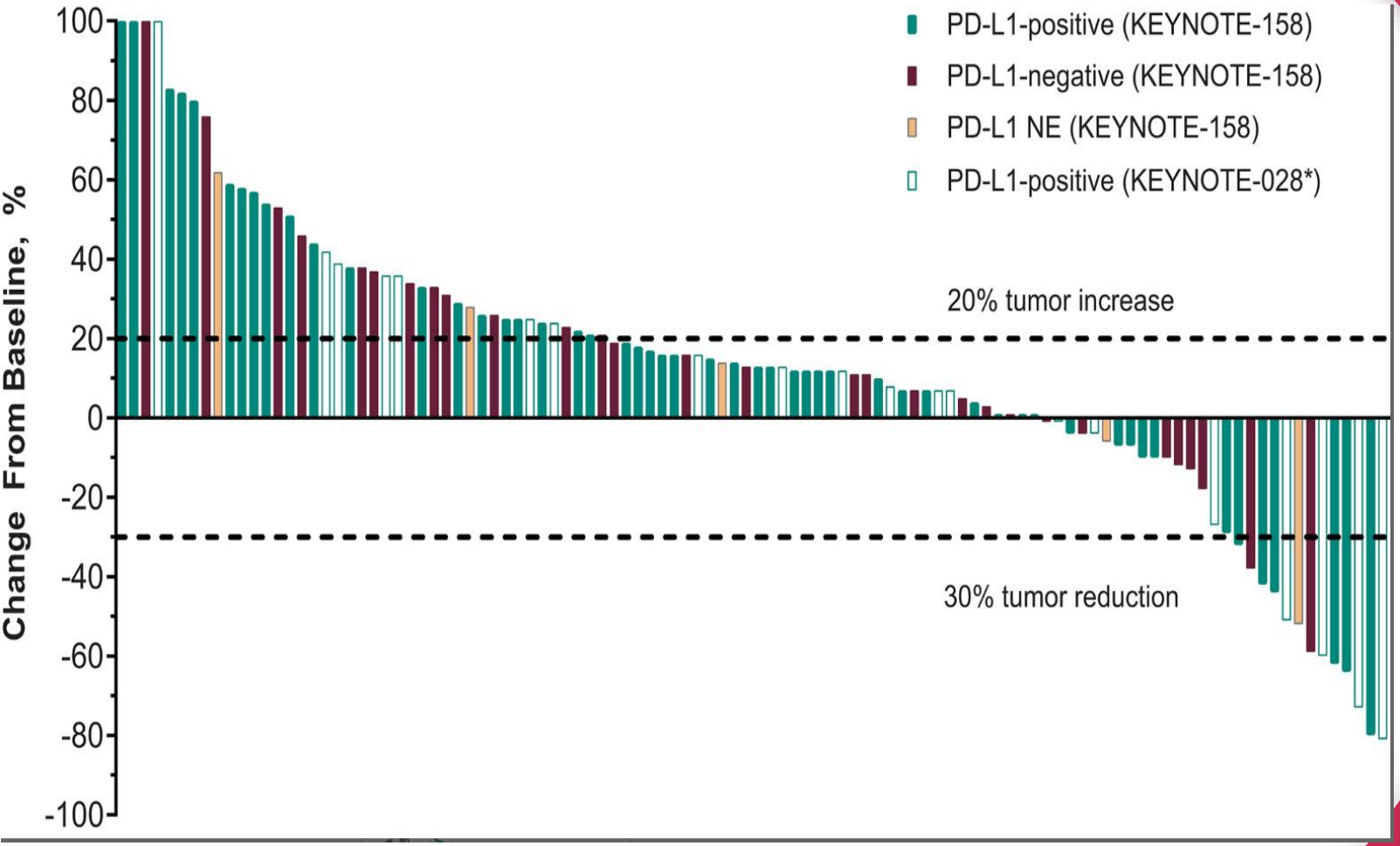
Cancer Therapy and Prevention | Free Access

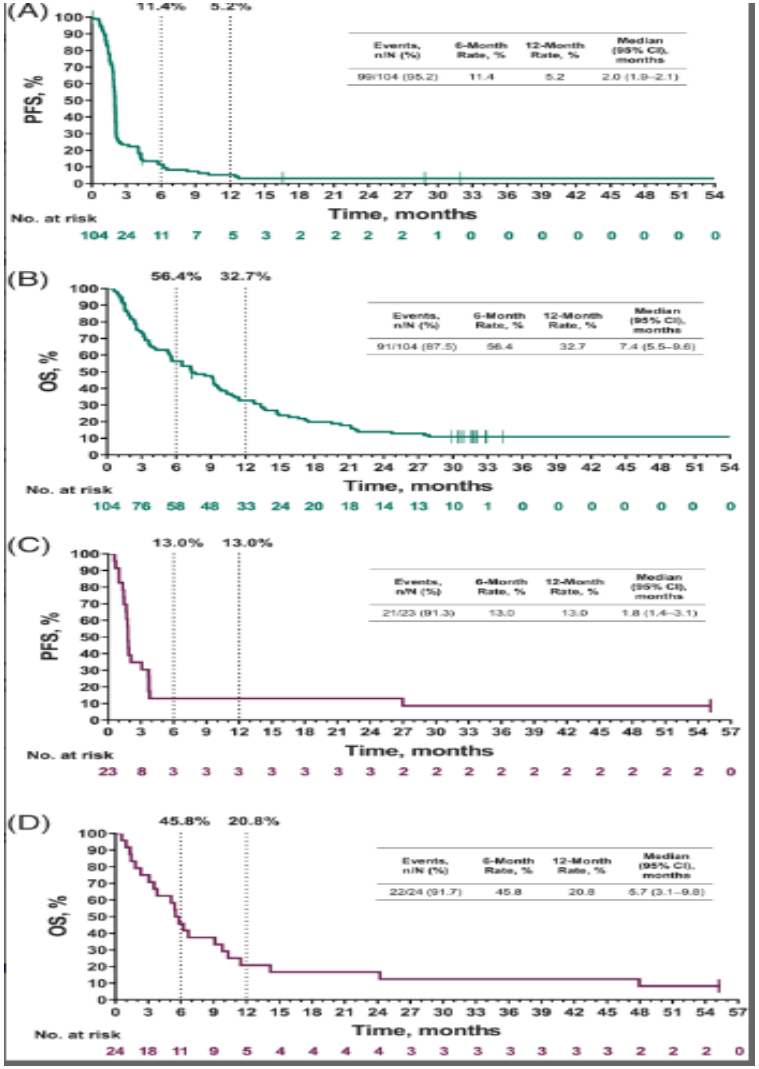
Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies

Sarina A. Piha-Paul, Do-Youn Oh, Makoto Ueno, David Malka, Hyun Cheol Chung, Adnan Nagrial, Robin K. Kelley, Willeke Ros, Antoine Italiano, Kazuhiko Nakagawa, Hope S. Rugo ... See all authors

First published: 02 May 2020 | https://doi.org/10.1002/ijc.33013 | Citations: 161

Piha-Paul SA et al. Int J Cancer. 2020; 147: 2190


PD-L1-positive (KEYNOTE-158)
PD-L1-negative (KEYNOTE-158)
PD-L1 NE (KEYNOTE-158)
PD-L1-positive (KEYNOTE-028*)
20% tumor increase
30% tumor reduction
Change From Baseline, %
100
80
60
40
20
0
-20
-40
-60
-80
-100



Early Phase studies

Lack comparative arm

Exact tumour location was not available for some patients

KEYNOTE-158, the ORR was 5.8%. PFS & OS were 11.4% & 56.4% at 6 months and 5.2% & 32.7 at 12 months

KEYNOTE-028, the ORR was 13.0%. PFS & OS was 13.0% & 45.8% at 6 and 13% & 20.8% at 12 months

JAMA Oncology | Original Investigation

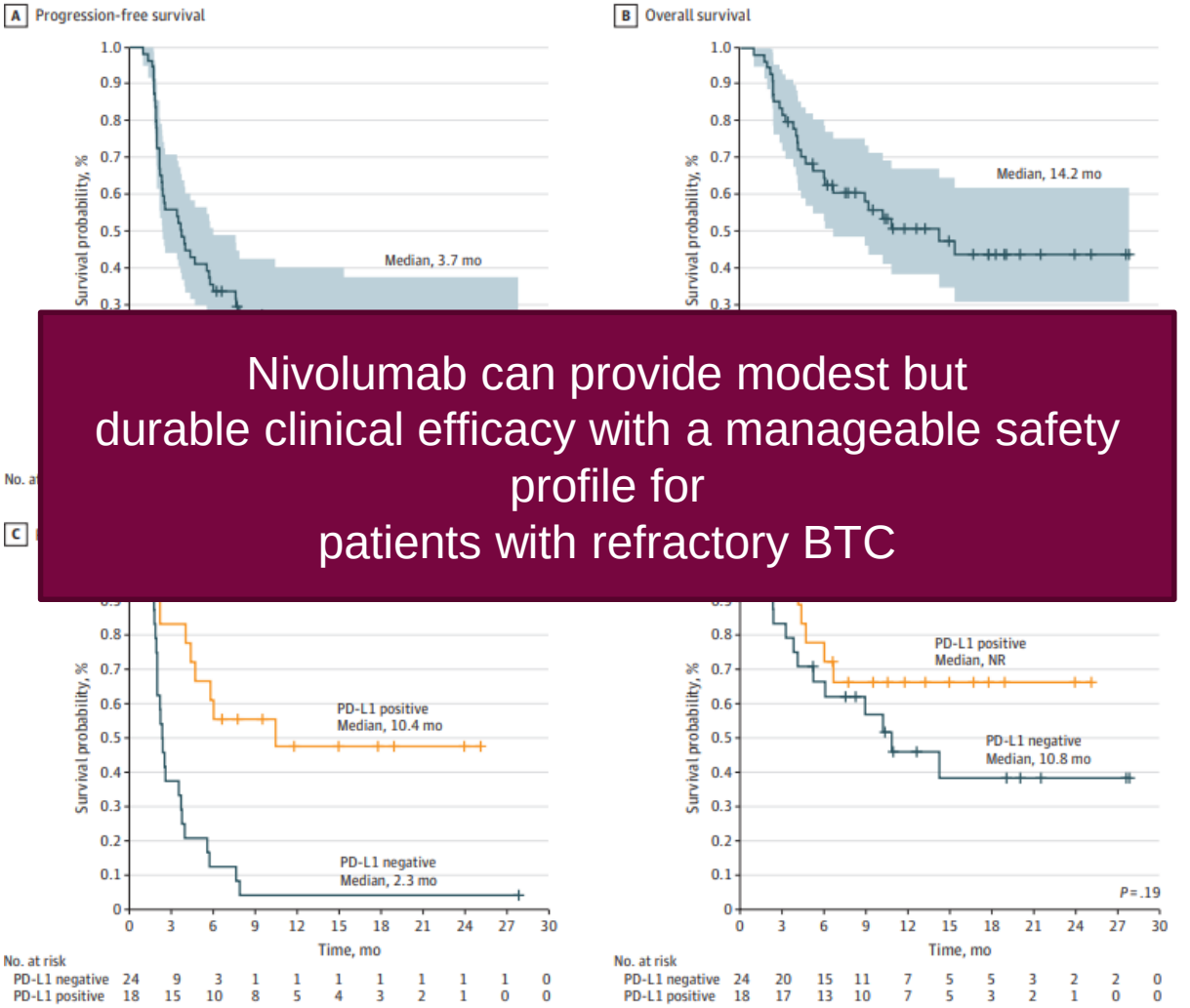
A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer

Richard D. Kim, MD; Vincent Chung, MD; Olatunji B. Alese, MD; Bassell F. El-Rayes, MD; Daneng Li, MD; Taymeyah E. Al-Toubah, BS; Michael J. Schell, PhD; Jun-Min Zhou, BS; Amit Mahipal, MD; Baek Hui Kim, MD; Dae Won Kim, MD

Table 1. Best Overall Response and Disease Control Rate

	No. (%) (n = 46)			
	RECIST, version 1.1		iRECIST	
Best overall response	Investigator review	Central review	Investigator review	Central review
CR (iCR)	0	0	0	0
PR (iPR)	10 (22)	5 (11)	10 (22)	6 (13)
	1 Unconfirmed	1 Unconfirmed	1 Unconfirmed	1 Unconfirmed
SD (iSD)	17 (37)	18 (39)	18 (39)	22 (48)
PD (iUPD + iCPD)	19 (41)	23 (50)	18 (39)	18 (39)
Disease control rate	27 (59)	23 (50)	28 (61)	28 (61)

Kim RD et al. JAMA Oncol. 2020; 6: 888



Nivolumab can provide modest but durable clinical efficacy with a manageable safety profile for patients with refractory BTC

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Gemcitabine + cisplatin[4] (category 1)
- Durvalumab + gemcitabine + cisplatin (category 1)[d,5]

Other Recommended Regimens

- 5-fluorouracil + oxaliplatin
- 5-fluorouracil + cisplatin (category 2B)
- Capecitabine + cisplatin (category 2B)
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B)
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,10,11]
- For *RET* gene fusion-positive tumors:
  - Pralsetinib (category 2B)[12]
  - Selpercatinib for CCA (category 2B)[13]

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

Preferred Regimens

- FOLFOX[14]

Other Recommended Regimens

- FOLFIRI[15] (category 2B)
- Regorafenib[16] (category 2B)
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[17]
- Durvalumab + gemcitabine + cisplatin (category 2B)[h,5]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,h,10,11]
  - Dostarlimab-gxly[f,h,i,18,19] (category 2B)
- For TMB-H tumors:
  - Pembrolizumab[e,f,h,20]
- For *BRAF*-V600E mutated tumors
  - Dabrafenib + trametinib[21,22]
- For CCA with *FGFR2* fusions or rearrangements:
  - Pemigatinib[23]
  - Infigratinib[24]
  - Futibatinib[25]
- For CCA with *IDH1* mutations
  - Ivosidenib[26,27]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib for CCA[13]
  - Pralsetinib (category 2B)[12]
- For HER2-positive tumors:
  - Trastuzumab[j] + pertuzumab[28]
- Nivolumab[f,h,29] (category 2B)
- Lenvatinib + pembrolizumab[f,h,30] (category 2B)

[d] Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy.
[e] There are limited clinical trial data to support pembrolizumab in this setting. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 2019;25:744-750.
[f] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] Treatment selection depends on clinical factors including previous treatment regimen/agent and extent of liver dysfunction.
[h] For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[i] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

Take Home Message

- Despite the advances in CCA management made in the last decade, the prognosis has remained poor for locally advanced and metastatic diseases
- Discovery of targetable mutations in IDH1, FGFR2, HER2, BRAF, and NTRK, as well as subgroups with PD-L1 expression and/or MSI-high/TMB-high has revolutionized the field
- 2nd line and beyond treatment options may give some responses in patients with targetable mutations

THANK YOU