PRACTICAL INSIGHTS FOR EARLY DIAGNOSIS AND MANAGEMENT OF BILIARY TRACT CANCERS

Future Approaches in BTC: Unmet Needs, Emerging Therapies, and Areas for Improvement

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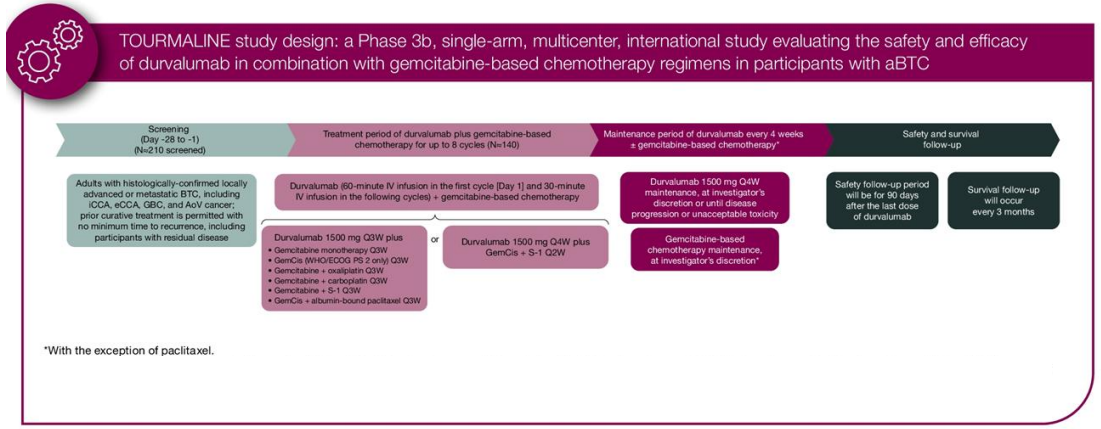
The content of this presentation was independently developed by the author.

Tourmaline - IO + Chemo (non CISGEM)

- Durvalumab + nonCisGem chemo
- Ampullary tumours included

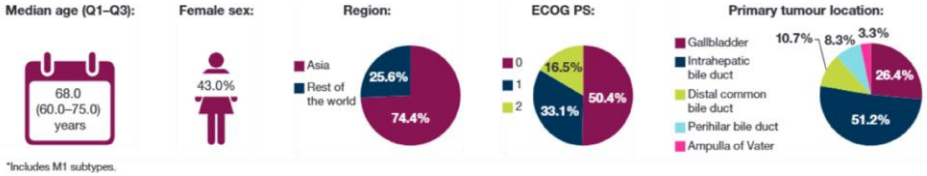


IO: InmunoOncology; **Chemo**: Chemotherapy; **CISGEM**: Cisplatin plus Gemcitabine; **aBTC**: advanced Biliary Tract Cancer; **AoV**: Ampulla of Water; **BTC**: Biliary Tract Cancer; **eCCA**:extrahepatic Cholangiocarcinoma; **ECOG**: Eastern Cooperative Oncology Group; **GBC**: Gallbladder Cancer; **GemCis**: Gencitabine and Cisplatin; **iCCA:** intrahepatic Cholangiocarcinoma; **IV**: Intravenous; **PS**: Performance Status; **Q2W:** Every 2 weeks; **Q3W**: Every 3 Weeks; **Q4W**: Every 4 weeks; **S-1**: tegatur-gimeracil-oteracil; **WHO**: World Health Organization

Ikeda M, Oh D-Y, He AR, Macarulla Mercade T, Dane A, Park JO, et al. Safety of 30 min infusion of durvalumab... TOURMALINE early results [Abstract]. En: ESMO Asia Congress 2024; 2024 Dic 6-8; Singapur. Abstract 133O.

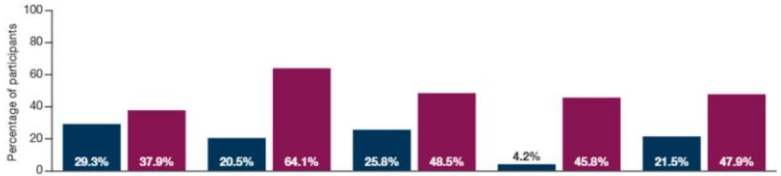
Tourmaline - IO + Chemo (non CISGEM)

- **Overall participant demographics and clinical characteristics (N = 121)**



*Includes M1 subtypes.

- **Objective response rate in the safety analysis set**



	Platinum double	Platinum triple	Platinum total	Non-platinum	Total
N	58	39	97	24	121
ORR,* % (95% CI)	**29.3 (18.1–42.7)**	**20.5 (9.3–36.5)**	**25.8 (17.4–35.7)**	**4.2 (0.1–21.1)**	**21.5 (14.5–29.9)**
Complete, n (%)	1 (1.7)	0	1 (1.0)	0	1 (0.8)
Partial, n (%)	16 (27.6)	8 (20.5)	24 (24.7)	1 (4.2)	25 (20.7)
Stable disease, n (%)	**22 (37.9)**	**25 (64.1)**	**47 (48.5)**	**11 (45.8)**	**58 (47.9)**
Not evaluable, n (%)	**11 (19.0)**	**4 (10.3)**	**15 (15.5)**	**8 (33.3)**	**23 (19.0)**

The safety analysis set consisted of all participants who received at least one dose of study treatment. *Based on investigator assessments according to RECIST v1.1. 95% CI calculated using the binomial exact method (Clopper-Pearson).

IO: InmunoOncology; **Chemo**: Chemotherapy; **CISGEM**: Cisplatin plus Gemcitabine; **ECOG PS**: Eastern Cooperative Oncology Group Performance Status; **M0**: No distant Metastasis; **M1**: Metastatic; **Mx**: Metastasis cannot be measured; **Q**: Quartile; **TNM**: Tumour Mode Metastasis; **CI**: Confidence Interval; **ORR**: Objective Response Rate; **RECIST 1.1**: Response Evaluation Criteria in Solid Tumours, version 1.1

Oh D-Y, Ikeda M, He AR, Macarulla Mercade T, Dane A, Park JO, et al. Early safety and efficacy from the phase IIIb TOURMALINE study of durvalumab (D) in combination with gemcitabine (G)-based chemotherapy in advanced biliary tract cancer (aBTC) [Poster]. En: ESMO Gastrointestinal Cancers Congress 2025; 2025 Jul 2-5; Barcelona, España. Abstract 323P.

Tourmaline - IO + Chemo (non CISGEM)

- **Adverse events in the safety analysis set**

	Platinum double	Platinum triple	Platinum total	Non-platinum	Total*
N	58	39	97	24	121
Any Grade 3 / 4 PRAE within 6 months of treatment initiation,†‡ n (%)	**29 (50.0)**	**16 (41.0)**	**45 (46.4)**	**10 (41.7)**	**55 (45.5)**
Any AE, n (%)	**52 (89.7)**	**38 (97.4)**	**90 (92.8)**	**22 (91.7)**	**112 (92.6)**
Any PRAE†	47 (81.0)	38 (97.4)	85 (87.6)	21 (87.5)	106 (87.6)
Any AE leading to discontinuation of any study treatment	8 (13.8)	5 (12.8)	13 (13.4)	2 (8.3)	15 (12.4)
Any AE leading to discontinuation of durvalumab	4 (6.9)	1 (2.6)	5 (5.2)	1 (4.2)	6 (5.0)
Any AE with an outcome of death§	3 (5.2)	0	3 (3.1)	0	3 (2.5)
Any SAE, n (%)	**18 (31.0)**	**12 (30.8)**	**30 (30.9)**	**10 (41.7)**	**40 (33.1)**
Any PRSAE†	4 (6.9)	3 (7.7)	7 (7.2)	5 (20.8)	12 (9.9)
Any infusion-related AE,‖ n (%)	**2 (3.4)**	**5 (12.8)**	**7 (7.2)**	**0**	**7 (5.8)**
Any infusion-related AE possibly related to durvalumab	1 (1.7)	4 (10.3)	5 (5.2)	0	5 (4.1)
Any immune-mediated AEs,¶ n (%)	**7 (12.1)**	**4 (10.3)**	**11 (11.3)**	**2 (8.3)**	**13 (10.7)**
Requiring systemic corticosteroids	6 (10.3)	2 (5.1)	8 (8.2)	2 (8.3)	10 (8.3)
Requiring ≥40 mg prednisone equivalent steroids	2 (3.4)	0	2 (2.1)	2 (8.3)	4 (3.3)

The safety analysis set consisted of all participants who received at least one dose of study treatment. *Platinum total plus non-platinum. †As assessed by the investigator. Missing responses are counted as related. ‡Grade 3: severe; Grade 4: life-threatening. §Not related to any study treatment. ‖Derived from preferred term. ¶Identified from AEs of special interest and AEs of possible interest using a programmatic approach.

Safety

- Grade 3/4 PRAEs within 6 months of initiation of any study treatment by DCO occurred in 45.5% (n=55) of participants overall.
- Safety was generally comparable between non-platinum versus platinum and platinum double versus triple groups.
  - ✓ Rates of serious adverse events (SAEs) and possibly related SAEs were higher in the non-platinum versus platinum groups.
- Three (2.5%) participants had adverse events (AEs) with an outcome of death, all not related to any study treatment and within the platinum group.
- Seven (5.8%) participants had an infusion-related AE, all within the platinum group.
- 13 (10.7%) participants had at least one immune-mediated AE.

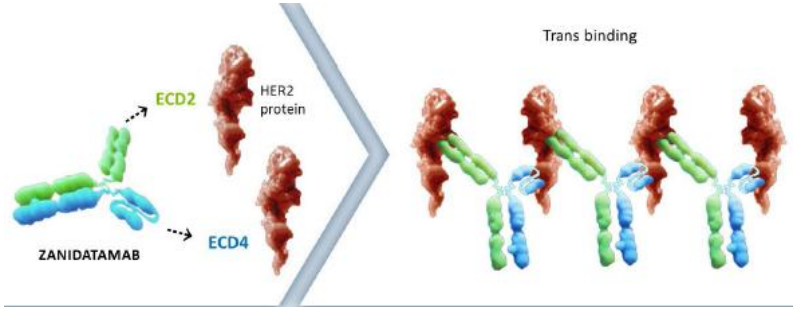
IO: InmunoOncology; **Chemo**: Chemotherapy; **CISGEM**: Cisplatin plus Gemcitabine; **AE**: Adverse Event; **PRAE**: Possible related (to any study treatment) Adverse Event; **PRSAE**: Possible related (to any study treatment) Serious Adverse Event; **SAE**: Serious Adverse Event

Oh D-Y, Ikeda M, He AR, Macarulla Mercade T, Dane A, Park JO, et al. Early safety and efficacy from the phase IIIb TOURMALINE study of durvalumab (D) in combination with gemcitabine (G)-based chemotherapy in advanced biliary tract cancer (aBTC) [Poster]. En: ESMO Gastrointestinal Cancers Congress 2025; 2025 Jul 2-5; Barcelona, España. Abstract 323P.

Targeting HER-2 Novel approaches/ongoing trials

Zanidatamab: antibody directed against two non-overlapping domains of HER2.

Zanidatamab (FDA/EMA) [1]

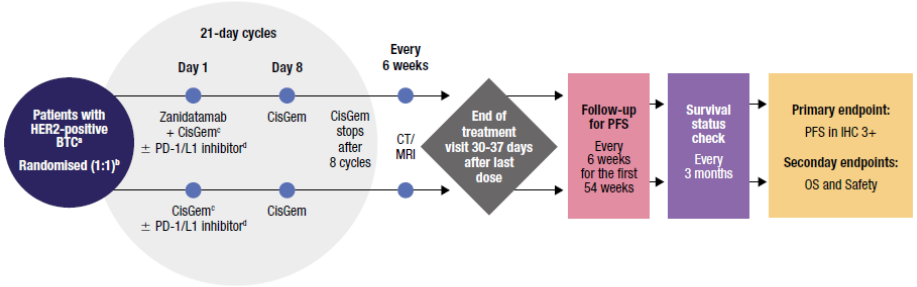


Previously-treated advanced BTC; monotherapy

Zanidatamab

HERIZON-BTC-02: Phase 3 study of Zanidatamab + Soc versus SoC for Advanced HER2-Positive Biliary Tract Cancer (1L) [2]

Figure 2. HERIZON-BTC-302



[a]Patients will be enrolled based on central assessment of HER2 status; [b]Patients who receive 1 of the allowed PD-1/L1 inhibitors prior to randomisation will continue to receive the same PD-1/L1 inhibitor after randomisation; [c]Up to 2 cycles of systemic therapy with CisGem ± a PD-1/L1 inhibitor are allowed per protocol prior to randomisation; these cycles, if received, are counted towards the 8 cycles of CisGem; [d]PD-1/L1 inhibitor is physician's choice of durvalumab (20 mg/kg IV [weight <30 kg] or 1500 mg IV [weight ≥30 kg]) or pembrolizumab (200 mg IV), where approved under local regulations.

HER-2: Human Epidermal Growth Factor Receptor 2**; ECD:** ExtraCellular Domain**; FDA:** Food and Drug Administration; **EMA**: European Medicines Agency; **BTC**: Biliary Tract Cancer; **SoC**: Standard of care; **CisGem**: Cisplatin plus Gemcitabine; **CT**: Computed Tomography; **IHC**: Immunohistochemistry; **IV:** Intravenous; **MRI:** Magnetic Resonance Imaging; **OS**: Overal Survival; **PD-1/L1**:Programmed Death-1/Programmed cell death Ligand 1; **PFS**: Progression –Free Survival; **RECIST V1.1**: Response Evaluation Criteria in Solid Tumours version 1.1

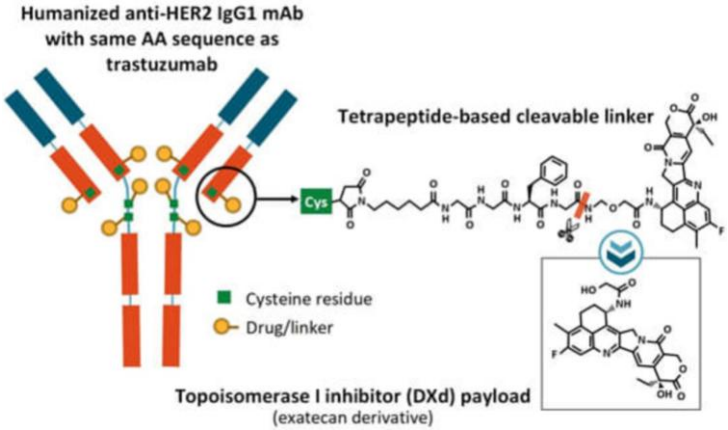
1. Pant S, Fan J, Oh DY, Choi HJ, Kim JW, Chang HM, et al. Results from the Pivotal Phase 2b HERIZON-BTC-01 Study: Zanidatamab in Previously-treated HER2-amplified Biliary Tract Cancer (BTC). En: American Society of Clinical Oncology Annual Meeting; 2023 Jun 2-6; Chicago, IL. Alexandria (VA): ASCO; 2023. Abstract 4014; 2. Macarulla T, Harding JJ, Pant S, Mei C, Garfin P, Okusaka T, et al. HERIZON-BTC-302: A phase III study of zanidatamab with standard-of-care (SOC) therapy vs SOC alone for first-line (1L) treatment of human epidermal growth factor receptor 2 (HER2)-positive advanced/metastatic biliary tract cancer (BTC) [Abstract]. En: ESMO Congress 2024; 2024 Sep 13-17; Barcelona, España. Abstract 62TiP.

Targeting HER-2 Novel approaches/ongoing trials

T-DXd: antibody-drug conjugate → humanized monoclonal anti-HER2 antibody + topoisomerase I inhibitor

Trastuzumab deruxtecan (T-DXd; DS-8201)

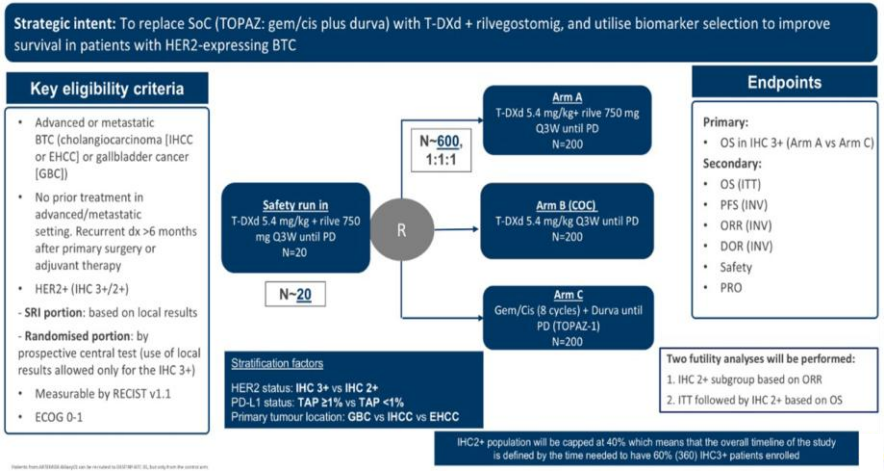
FDA (Tumour Agnostic)[1]



Previously-treated advanced BTC; monotherapy

Trastuzumab deruxtecan (T-DXd; DS-8201)[1]

DESTINY-BTC01: Phase 3 study of T-DXd + rilvegostomig versus SoC for HER2-expressing biliary cancer (1L)



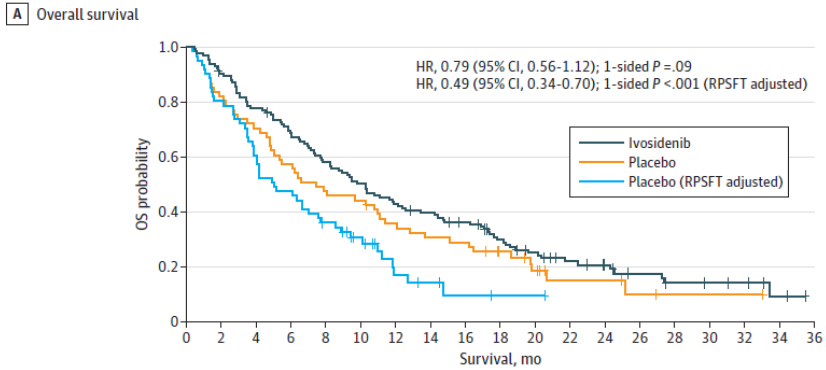
FDA: Food and Drug Administration; **HER2**: Human Epidermal growth factor Receptor 2; **IgG1 mAb**: Immunoglobulin G subclass 1 monoclonal Antibody; **BTC**: Biliary Tract Cancer; **IHCC:** Intrahepatic Cholangiocarcinoma; **EHCC**: Extrahepatic Cholangiocarcinoma; **IHC**: Immunohistochemistry; **SRI:** Soluble Resistance-related Calcium-binding Interactor; **RECIST**: Response Evaluation Criteria in Solid Tumours; **ECOG 0-1**: Eastern Cooperative Oncology Group 0-1; **Q3W:** every3 Weeks; **PD:** Progressive Disease; **PD-L1**: Programmed Death-Ligand 1; **TAP:** Tumour Assortment Percentage; **TOPAZ**: Combination of gemcitabine, cisplatin and durvalumab; **COC:** Continuation of Care; **OS (ITT):** Overall Survival (Intent-To-Treat); **PFS (INV)**: Progression-Free Survival (INVestigator); **ORR**: Objective Response Rate; **DOR**: Duration of Response; **PRO**: Patient Reported Outcome

1. Macarulla. Educational Session at ESMO 2024

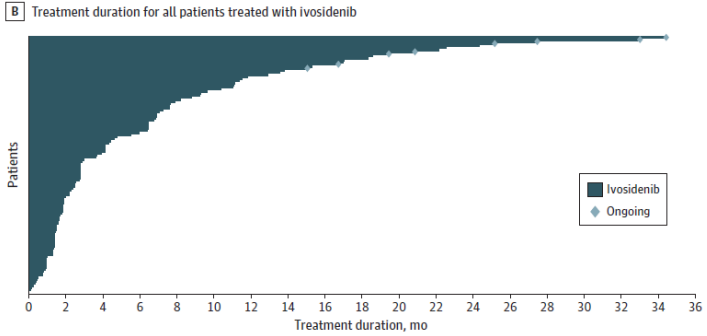
Targeting IDH-1 in CCA: Ivosidenib (ClarIDHy Trial)

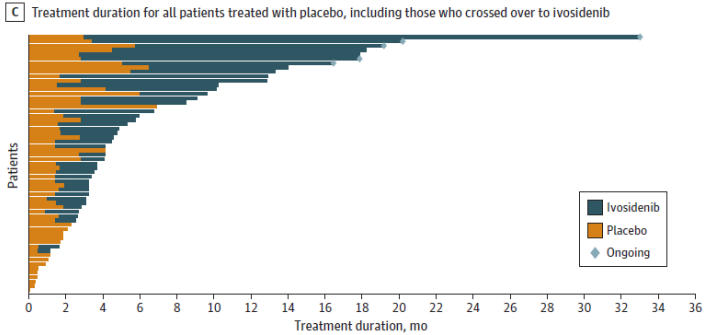
FDA/EMA

Updated Outcome data 2021. Overall Survival and Treatment Duration in the Intent-to-Treat Population



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





Previously-treated advanced BTC (Biliary Tract Cancer); monotherapy

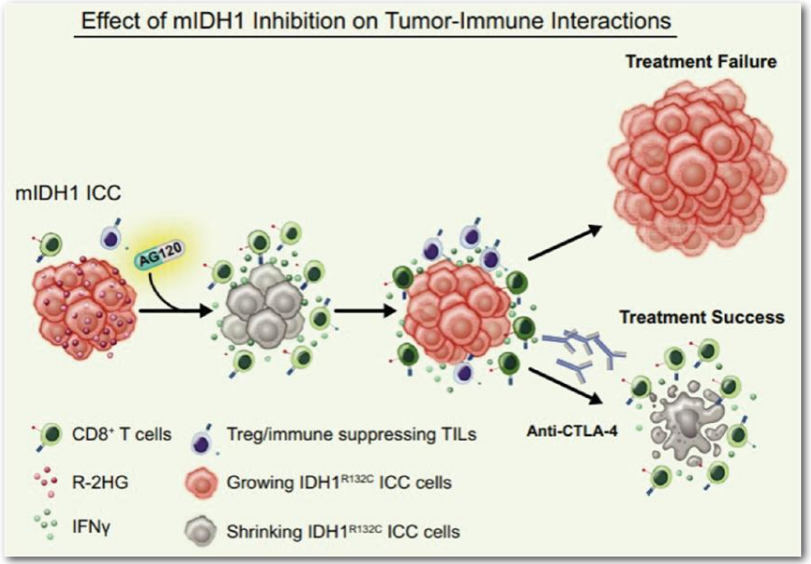
IDH-1: Isocitrate Dehydrogenase 1; **CCA:** Cholangiocarcinoma; **OS:** overall survival; **m0**: No distant Metastasis; **RPSFT:** Rank-Preserving Structural Failure Time

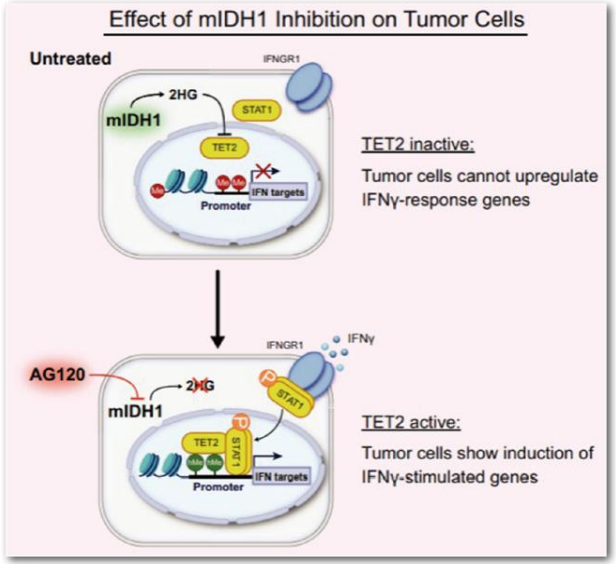
Andrew X. Zhu, MD, PhD; Teresa Macarulla, MD; Milind M. Javle, MD; R. Kate Kelley, MD; Sam J. Lubner, MD, et al. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation The Phase 3 Randomized Clinical ClarIDHy Trial. JAMA Oncology 2021 Volume 7, Number 11. 1669-1677

Immunophenotype of IDHm CCA

Mutant IDH Inhibits IFNγ-TET2 Signaling to Promote Immunoevasion and Tumor Maintenance in Cholangiocarcinoma[1] → IDHm-CCA are "cold tumours"

- mIDH1 inhibition restores antitumor immunity → conversion into "hot tumours".
- Immune suppression via TET2 inactivation is the primary mean by which mIDH1 maintains cholangiocarcinoma survival.
- **New combination of mIDH1 inhibitors and immune checkpoint blockade** targeting regulatory T cells. (Figure)[2]





IDH-1: Isocitrate Dehydrogenase 1; **CCA:** Cholangiocarcinoma; **IDHm**: Isocitrate Dehydrogenase mutated; **mIDH1**: mutant Isocitrate Dehydrogenase 1; **IFNγ-TET2**: Interferon-gamma signaling pathway involving TET2; **TET2:** Ten-Eleven Translocation 2; **ICC:** Intrahepatic Cholangiocarcinoma; **AG120**: Ivosidenib; **CD8⁺T cells**: Cytotoxic T Lymphocytes; **TILs:** Tumour-Infiltrating Lymphocytes; **Anti-CTLA-4:** Anti-Cytotoxic T-Lymphocyte-Associated Protein 4; **IFNGR1:** Interferon Gamma Receptor 1; **STAT 1:** Signal Transducer and Activator of Transcription 1

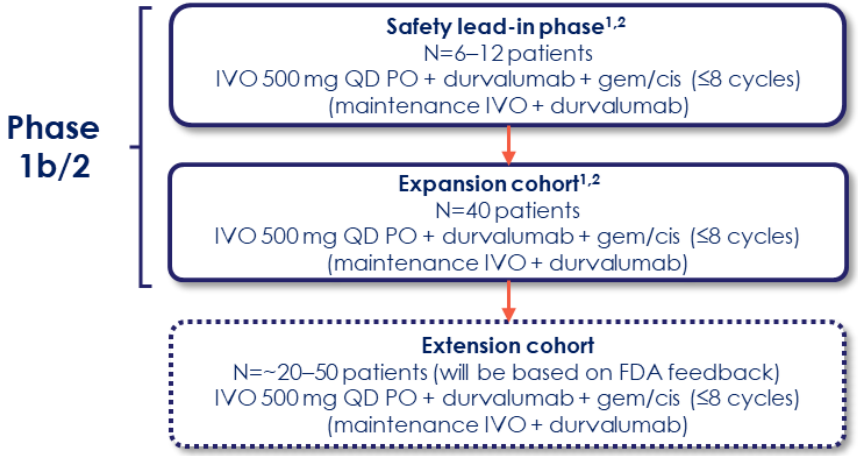
1. Wu M-J, Shi L, Dubrot J, Merritt j, Vijay V, Wei T-Y,et al. Mutant-IDH inhibits Interferon-TET2 signaling to promote immunoevasion and tumor maintenance in cholangiocarcinoma. Cancer Discov. 2022 March 01; 12(3): 812–835. doi:10.1158/2159-8290.CD-21-1077;
2. Wu M-J, Shi L, Merritt J, Zhu AX, Bardeesy N. Biology of IDH mutant cholangiocarcinoma. Hepatology [Internet]. 2022;75(5):1322–37. Available from: http://dx.doi.org/10.1002/hep.32424.

Immunophenotype of IDHm CCA

A Phase 1b/2, safety lead-in and dose expansion, open-label, multicentre trial investigating the safety, tolerability, and preliminary activity of **IVO in combination with durvalumab and gemcitabine/cisplatin** as 1L therapy in participants with locally advanced, unresectable or metastatic CCA with an *IDH1* mutation

Ongoing clinical trial

Safety (n = 6) completed



IDHm: Isocitrate Dehydrogenase mutated; **CCA:** Cholangiocarcinoma; **IVO:** Ivosidenib; **QD PO:** every day Orally; **FDA:** Food and Drug Administration

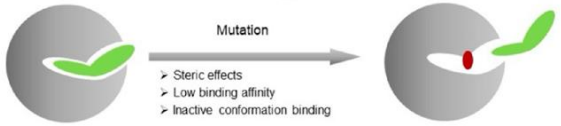
Adapted from: ClinicalTrials.gov. NCT06501625. Available at: https://clinicaltrials.gov/study/NCT06501625.

FGFR inhibitors in CCA: Tinengotinib

Tinengotinib: The Next Generation FGFR Inhibitor

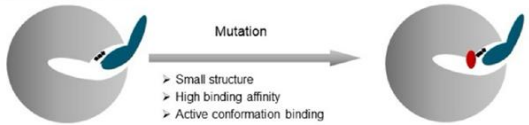
Tinengotinib Binds to FGFR2 in a Unique Mode

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

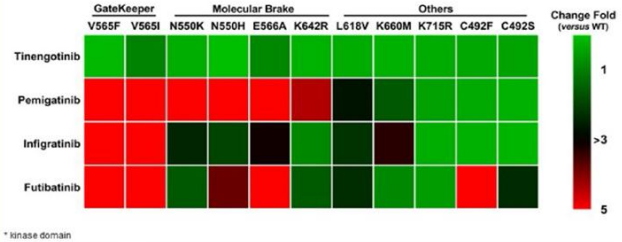


r: reversible, ir: irreversible

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

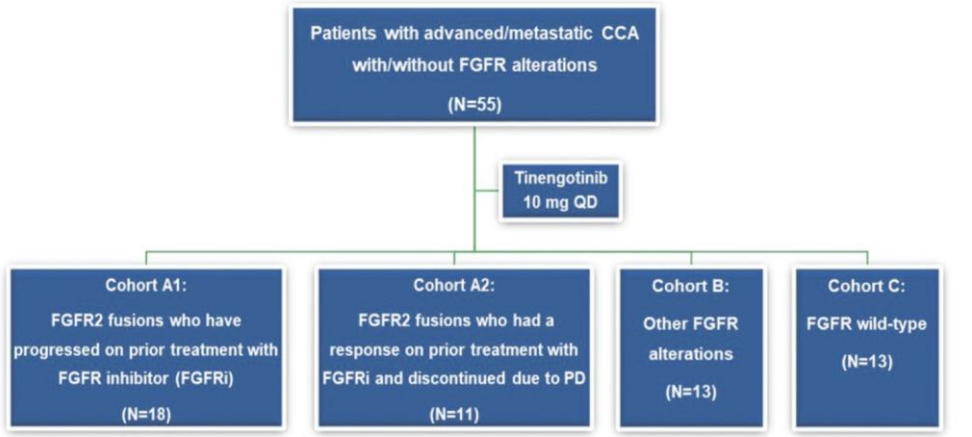


IDHm: Isocitrate Dehydrogenase mutated; **CCA:** Cholangiocarcinoma; **IVO:** Ivosidenib; **QD PO:** every day Orally; **FDA:** Food and Drug Administration

Javle MM, Mahipal A, Fonkoua LAK, Fountzilas C, Li D, Pelster M, et al. Efficacy and safety results of FGFR1-3 inhibitor, tinengotinib, as monotherapy in patients with advanced, metastatic cholangiocarcinoma: Results from phase II clinical trial. In: ASCO Gastrointestinal Cancer Symposium (ASCO-GI) 2024; 2024 Jan 18-20; San Francisco, CA. Alexandria (VA): American Society of Clinical Oncology (ASCO). Abstract 434.

FGFR inhibitors in CCA: Tinengotinib

Tinengotinib, an FGFR1-3 inhibitor, as monotherapy in patients with advanced, metastatic cholangiocarcinoma: Study Design of a phase II clinical trial



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

Endpoints

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

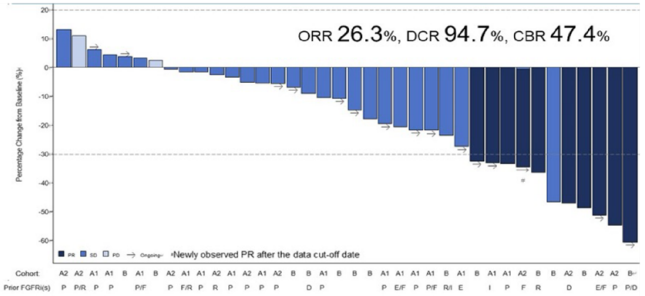
FGFR: Fibroblast Growth Factor Receptor; **CCA:** Cholangiocarcinoma; **QD:** every day; **PD:** Progressive Disease; **ORR**: Objective Response Rate; **DCR**: Disease Control Rate; **PFS:** Progression-Free Survival; **DOR**: Duration of Response; **OS**: Overall Survival

Javle MM, Mahipal A, Fonkoua LAK, Fountzilas C, Li D, Pelster M, et al. Efficacy and safety results of FGFR1-3 inhibitor, tinengotinib, as monotherapy in patients with advanced, metastatic cholangiocarcinoma: Results from phase II clinical trial. In: ASCO Gastrointestinal Cancer Symposium (ASCO-GI) 2024; 2024 Jan 18-20; San Francisco, CA. Alexandria (VA): American Society of Clinical Oncology (ASCO). Abstract 434.

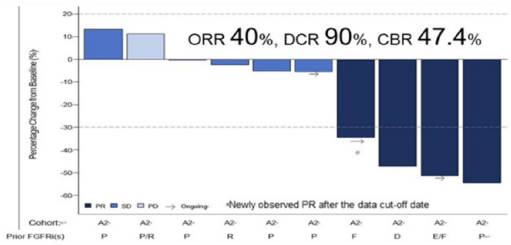
FGFR inhibitors in CCA: Tinengotinib

Tinengotinib - Best Overall Response (CCA with FGFR alteration)

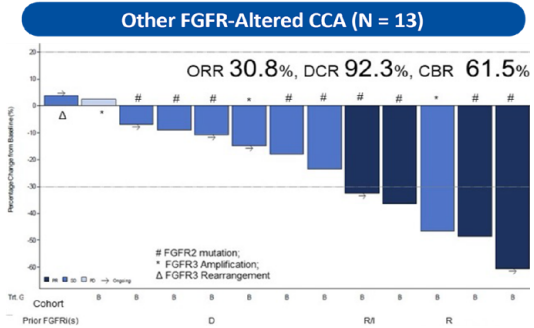
FGFR Altered CCA (Cohorts A1+A2+B, N = 38)



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;

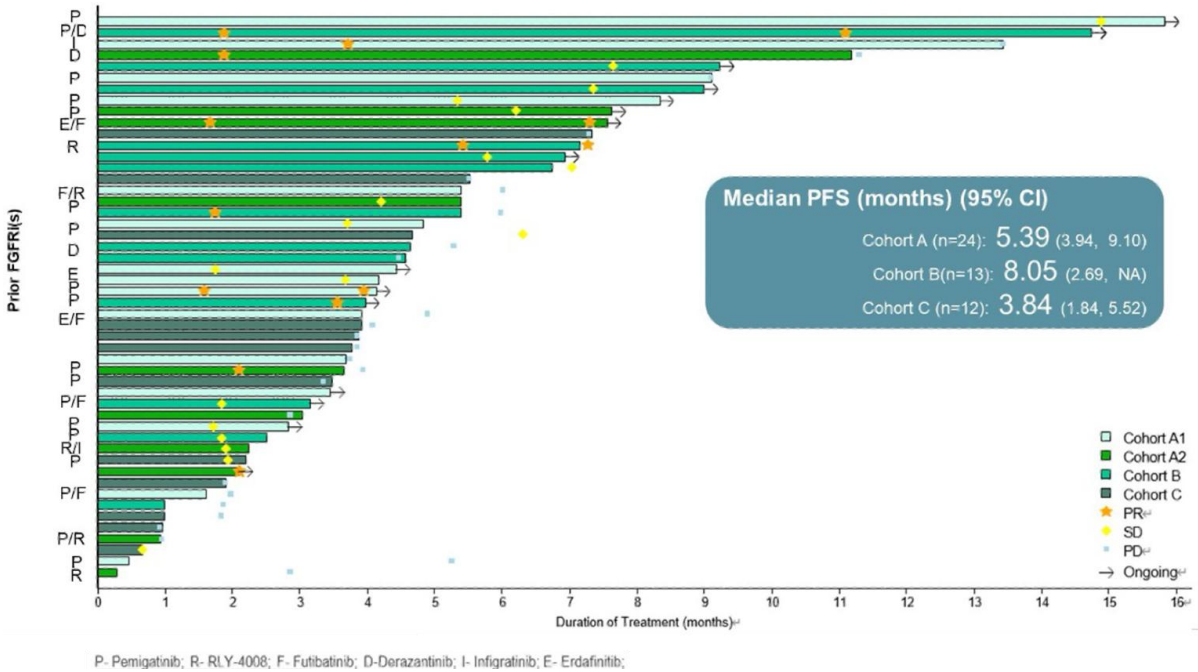
FGFR: Fibroblast Growth Factor Receptor; **CCA:** Cholangiocarcinoma

Javle MM, Mahipal A, Fonkoua LAK, Fountzilas C, Li D, Pelster M, et al. Efficacy and safety results of FGFR1-3 inhibitor, tinengotinib, as monotherapy in patients with advanced, metastatic cholangiocarcinoma: Results from phase II clinical trial. In: ASCO Gastrointestinal Cancer Symposium (ASCO-GI) 2024; 2024 Jan 18-20; San Francisco, CA. Alexandria (VA): American Society of Clinical Oncology (ASCO). Abstract 434.

FGFR inhibitors in CCA: Tinengotinib

Efficacy and safety results of FGFR1-3 inhibitor, tinengotinib, as monotherapy in patients with advanced, metastatic cholangiocarcinoma: Results from phase II clinical trial

Tinengotinib - Duration of Treatment (N = 50, EAS)

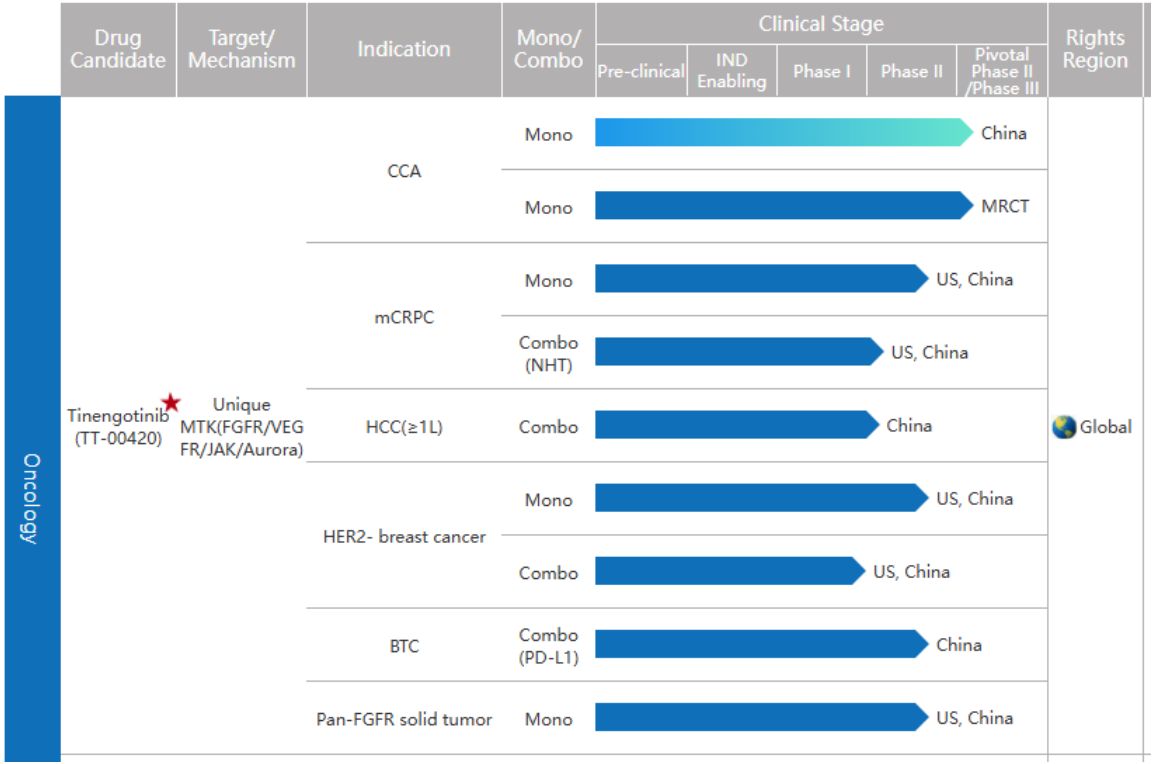


P- Pemigatinib; R- RLY-4008; F- Futibatinib; D-Derazantinib; I- Infigratinib; E- Erdafinitib;

FGFR: Fibroblast Growth Factor Receptor; **CCA:** Cholangiocarcinoma

Javle MM, Mahipal A, Fonkoua LAK, Fountzilas C, Li D, Pelster M, et al. Efficacy and safety results of FGFR1-3 inhibitor, tinengotinib, as monotherapy in patients with advanced, metastatic cholangiocarcinoma: Results from phase II clinical trial. In: ASCO Gastrointestinal Cancer Symposium (ASCO-GI) 2024; 2024 Jan 18-20; San Francisco, CA. Alexandria (VA): American Society of Clinical Oncology (ASCO). Abstract 434.

FGFR inhibitors in CCA: Tinengotinib



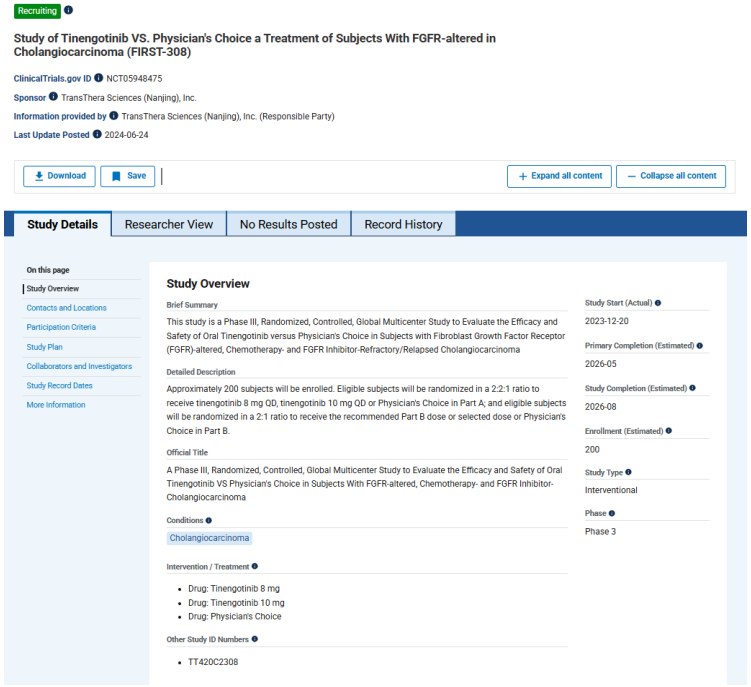
FGFR: Fibroblast Growth Factor Receptor; **CCA:** Cholangiocarcinoma; **MTK:** Multi-Targeted Kinase; **VEG:** Vascular Endothelial Growth factor; **JAK**: Janus Kinase; **mCRPC:** Metastatic Castrate-Resistant Prostate Cancer; **HCC:** Hepatocellular Carcinoma; **HER2**: Human Epidermal growth factor Receptor 2

TransThera Sciences (Nanjing), Inc. Interim Results Announcement for the Six Months Ended 30 June 2025. Hong Kong: TransThera Sciences (Nanjing), Inc. (via HKEXnews); 2025 Aug 25 [citado 2025 Nov 3]. Disponible en: https://www1.hkexnews.hk/listedco/listconews/sehk/2025/0825/2025082501394.pdf

FGFR inhibitors in CCA: Tinengotinib

Randomised phase III

TT420 vs physician choice after progression to prior iFGFR



Recruiting

Study of Tinengotinib VS. Physician's Choice a Treatment of Subjects With FGFR-altered in Cholangiocarcinoma (FIRST-308)

ClinicalTrials.gov ID NCT05948475

Sponsor TransThera Sciences (Nanjing), Inc.

Information provided by TransThera Sciences (Nanjing), Inc. (Responsible Party)

Last Update Posted 2024-06-24

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Study Details | Researcher View | No Results Posted | Record History

On this page
- Study Overview
- Contacts and Locations
- Participation Criteria
- Study Plan
- Collaborators and Investigators
- Study Record Dates
- More Information

Study Overview

Brief Summary

This study is a Phase III, Randomized, Controlled, Global Multicenter Study to Evaluate the Efficacy and Safety of Oral Tinengotinib versus Physician's Choice in Subjects with Fibroblast Growth Factor Receptor (FGFR)-altered, Chemotherapy- and FGFR Inhibitor-Refractory/Relapsed Cholangiocarcinoma

Detailed Description

Approximately 200 subjects will be enrolled. Eligible subjects will be randomized in a 2:2:1 ratio to receive tinengotinib 8 mg QD, tinengotinib 10 mg QD or Physician's Choice in Part A; and eligible subjects will be randomized in a 2:1 ratio to receive the recommended Part B dose or selected dose or Physician's Choice in Part B.

Official Title

A Phase III, Randomized, Controlled, Global Multicenter Study to Evaluate the Efficacy and Safety of Oral Tinengotinib VS Physician's Choice in Subjects With FGFR-altered, Chemotherapy- and FGFR Inhibitor-Cholangiocarcinoma

Conditions

Cholangiocarcinoma

Intervention / Treatment

- Drug: Tinengotinib 8 mg
- Drug: Tinengotinib 10 mg
- Drug: Physician's Choice

Other Study ID Numbers

- TT420C2308

Study Start (Actual) 2023-12-20

Primary Completion (Estimated) 2026-05

Study Completion (Estimated) 2026-08

Enrollment (Estimated) 200

Study Type Interventional

Phase Phase 3

FGFR: Fibroblast Growth Factor Receptor; **CCA:** Cholangiocarcinoma

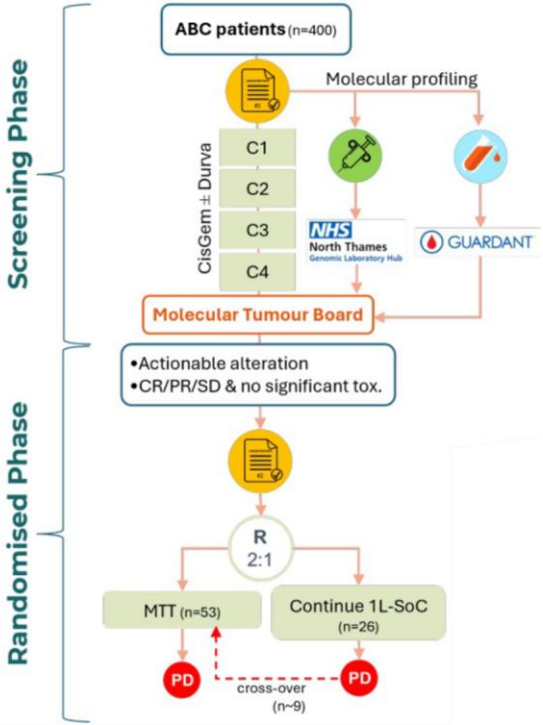
Clinicaltrials.gov [Internet]. Clinicaltrials.gov. [cited 2025 Oct 28]. Available from: https://www.clinicaltrials.gov/study/NCT05948475

SAFIR/ABC-10 – Maintenance targeted therapies

Participating countries:	UK, France, Belgium
No. of sites in UK:	15
First site open in any country:	UCLH opened 29/05/2024
No. of patients in UK:	Screening phase: 400; Randomised phase: 78

Targeted Therapies

- **Futibatinib** / FGFR2 fusion/rearrangement and FGFR2 mutation
- **Ivosidenib** / IDH1 mutation
- **Zanidatamab** / HER2 amplification
- **Neratinib + Trastuzumab** / HER2 mutation
- **Encorafenib + Binimetinib** / BRAFV600E mutation



UCLH: University College London Hospital; **FGFR:** Fibroblast Growth Factor Receptor 2; **IDH-1:** Isocitrate Dehydrogenase 1; **HER-2:** Human Epidermal Growth Factor Receptor 2; **BRAFV600E:** BRAF gene mutation V600E; **CR:** Complete Response; **PR:** Partial Response; **SD:** Stable Disease; **MTT:** Molecular Targeted Therapy; 1L **SoC**: First Line Standard of care; **PD**: Progressive Disease

Courtesy of Prof J Bridgewater.

SAFIR/ABC-10 – Maintenance targeted therapies

Molecular alteration		Test	Incidence	Agent	ESCAT	Pharma
'Established' targets and drug	**FGFR2 fusion**	RNA-seq	10%	Futibatinib	II-B	Taiho
	FGFR2 mutation	NGS	2%	Futibatinib	II-B	Taiho
	FGFR2 EID	NGS	1%	Futibatinib	III-A	Taiho
	IDH1 mutation	NGS	10%	Ivosidenib	II-B	Servier
	HER2 amp	NGS (+/-IHC/FISH)	10%	Zanidatamab	III-A	Zymeworks
	HER2 mut	NGS	5%	Neratinib + Trastuzumab	III-A	PFO / Accord Healthcare
	BRAFV600E/K/D/R mut	NGS	3%	Encorafenib-Binimetinib	III-A	Pierre-Fabre
	NTRK fusion	RNA-seq	0,5%	NTRK inhibitors (marketed)	II-B	SoC
	MSI	NGS (+/- IHC)	3%	Encorafenib-Binimetinib	II-B	SoC

FGFR2: Fibroblast Growth Factor Receptor 2;**EID:** Extracellular Domain In-frame Deletion; **IDH1:** Isocitrate Dehygrogenase 1; **HER2:** Human Epidermal Growth Factor Receptor 2; **BRAFV600E:** BRAF gene mutation V600E; **NTRK:** Neurotrophic Tyrosine Receptor Kinas; ; **MSI:** Microsatellite Instability; ; **NGS:** Next Generation Sequencing; **RNA-seq:** Ribonucleic Acid sequencing; **IHC:** Inmunohistochemistry; **FISH:** Fluorescent In Situ Hybridization

Courtesy of Prof J Bridgewater.

Targetable KRAS mutations in BTC

- Beyond G12C…. → G12D → Pan KRAS

CANCER DISCOVERY

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Volume 13, Issue 2
1 February 2023

RESEARCH BRIEFS | FEBRUARY 06 2023

Efficacy of a Small-Molecule Inhibitor of Kras^{G12D} in Immunocompetent Models of Pancreatic Cancer

Samantha B. Kemp; Noah Cheng; Nune Markosyan; Rina Sor; Il-Kyu Kim; Jill Hallin; Jason Shoush; Liz Quinones; Natalie V. Brown; Jared B. Bassett; Nikhil Joshi; Salina Yuan; Molly Smith; William P. Vozniak; Kia Z. Perez-Vale; Benjamin Kahn; Feiyan Mo; Timothy R. Donahue; Caius G. Radu; Cynthia Clendenin; James G. Christensen; Robert H. Vonderheide; Ben Z. Stanger

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Author & Article Information

Cancer Discov (2023) 13 (2): 298–311.

https://doi.org/10.1158/2159-8290.CD-22-1066 Article history

Related Content

A commentary has been published: A Splendid New Beginning at the End of a 40-Year Quest: The First KRAS^{G12D} Inhibitor in Pancreatic Cancer

A related article has been published: In This Issue

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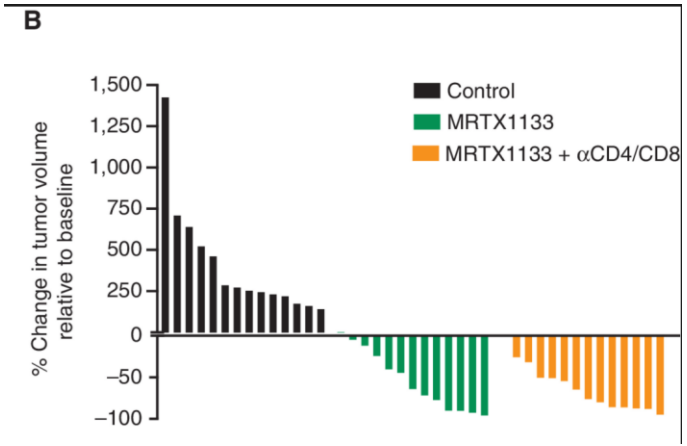
Article Contents

Abstract
INTRODUCTION
RESULTS
DISCUSSION
METHODS
Authors' Disclosures
Authors' Contributions
Acknowledgments
References
Supplementary data

Abstract

Mutations in the *KRAS* oncogene are found in more than 90% of patients with pancreatic ductal adenocarcinoma (PDAC), with Gly-to-Asp mutations (*KRAS*^{G12D}) being the most common. Here, we tested the efficacy of a small-molecule KRAS^{G12D} inhibitor, MRTX1133, in implantable and autochthonous PDAC models with an intact immune system. *In vitro* studies validated the specificity and potency of MRTX1133. *In vivo*, MRTX1133 prompted deep tumor regressions in all models tested, including complete or near-complete remissions after 14 days. Concomitant with tumor cell apoptosis and proliferative arrest, drug treatment led to marked shifts in the tumor microenvironment (TME), including changes in fibroblasts, matrix, and macrophages. T cells were necessary for MRTX1133's full antitumor effect, and T-cell depletion accelerated tumor regrowth after therapy. These results validate the specificity, potency, and efficacy of MRTX1133 in immunocompetent *KRAS*^{G12D}-mutant PDAC models, providing a rationale for clinical testing and a platform for further investigation of combination therapies.



KRAS: Kirsten Rat Sarcoma virus; **BTC:** Biliary Tract Cancer

Kemp SB, Cheng N, Markosyan N, Sor R, Kim I-K, Hallin J, et al. Efficacy of a small-molecule inhibitor of KrasG12D in immunocompetent models of pancreatic cancer. Cancer Discov [Internet]. 2023;13(2):298–311. Available from: http://dx.doi.org/10.1158/2159-8290.CD-22-1066

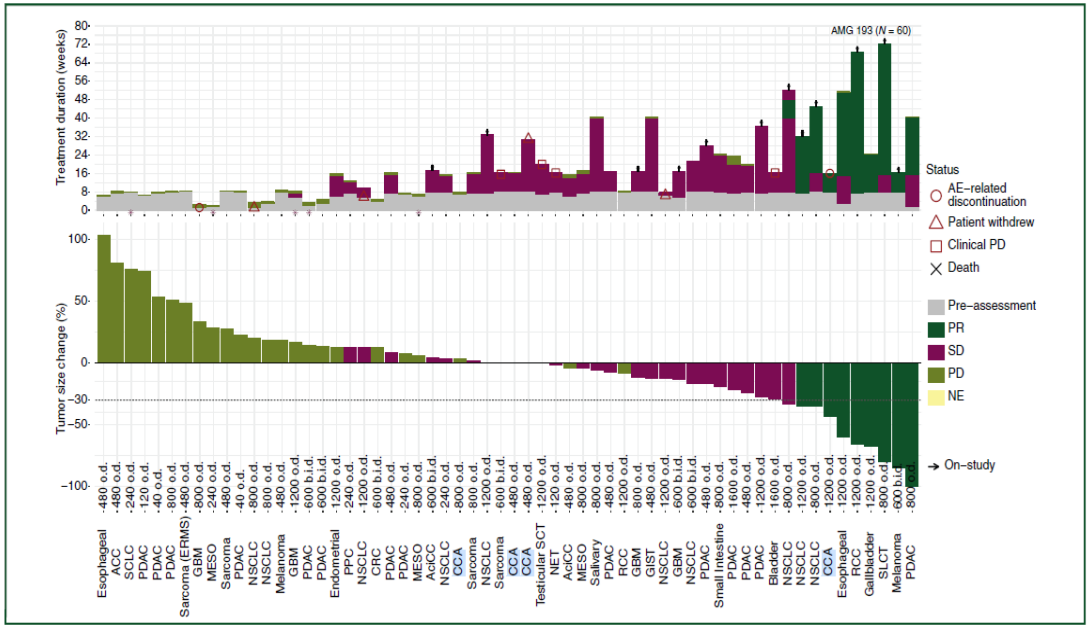
AMG 193, an iPRMT5 for MTAP loss

- MTA-cooperative PRMT5 inhibitor in patients with MTAP-deleted tumours.
- MTAP homozygously deleted in approximately 15% of all human cancers

Table 1. Baseline demographics and disease characteristics

	Dose-exploration (*N* = 80)
Tumor type, *n* (%)[a]	
PDAC	19 (23.8)
NSCLC	14 (17.6)
BTC	7 (8.8)
GBM	5 (6.3)
Gastric/esophageal	2 (2.5)
Others[b]	33 (41.3)

a PDAC includes adenocarcinoma pancreas, pancreatic carcinoma metastatic, and pancreatic carcinoma; NSCLC includes non-small cell lung cancer, squamous cell carcinoma of lung and lung neoplasm malignant; BTC includes gallbladder, cholangiocarcinoma, bile duct/biliary tract, ampulla of Vater and duodenal papillary carcinoma; GBM includes glioblastoma and glioblastoma multiforme; esophageal/gastric includes esophageal adenocarcinoma, esophageal carcinoma, and esophageal squamous cell carcinoma.

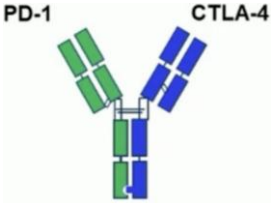


CCA: Cholangiocarcinoma; **CRC:** Carcinosarcoma; AciCC: Acidophil Cell Carcinoma; **PDAC:** adenocarcinoma pancreas, pancreatic carcinoma metastatic, and pancreatic carcinoma; **NSCLC:** non-small cell lung cancer, **BTC:** gallbladder, cholangiocarcinoma, bile duct/biliary tract, ampulla of Vater and duodenal papillary carcinoma; **GBM**; glioblastoma and glioblastoma multiforme: **SCLC:** small cell lung cancer; **MESO:** Mesonephric Carcinoma; **PPC:** Positive Peritoneal Cytology;

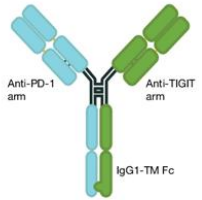
Adapted from: Rodon J, Prenen H, Sacher A, Villalona-Calero M, Penel N, El Helali A, et al. First-in-human study of AMG 193, an MTA-cooperative PRMT5 inhibitor, in patients with MTAP-deleted solid tumors: results from phase I dose exploration. Ann Oncol [Internet]. 2024;35(12):1138–47. Available from: http://dx.doi.org/10.1016/j.annonc.2024.08.2339

GEMINI - Bispecific Antibodies

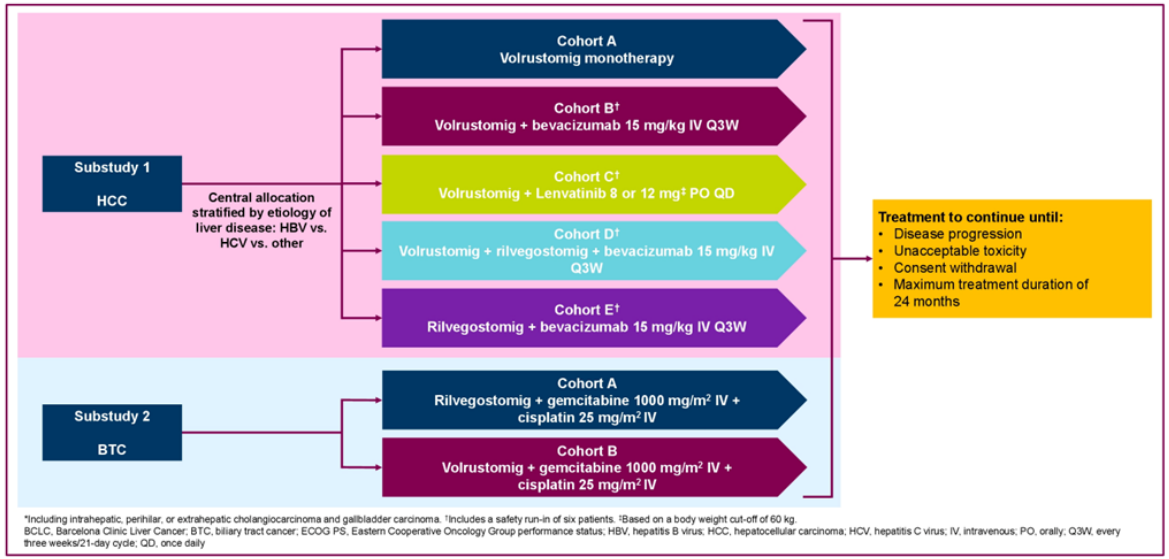
Volrustomig
MEDI5752



Rilvegostomig
AZD2936



GEMINI-Hepatobiliary study design



CCA: Cholangiocarcinoma; **PDAC:** adenocarcinoma pancreas, pancreatic carcinoma metastatic, and pancreatic carcinoma; **NSCLC:** non-small cell lung cancer, **BTC:** gallbladder, cholangiocarcinoma, bile duct/biliary tract, ampulla of Vater and duodenal papillary carcinoma; **GBM**; glioblastoma and glioblastoma multiforme: **SCLC:** small cell lung cancer.

Zhou J, Wang B, Zhang Z, Zhu J, Xu J, Sun Y, et al. A phase 2 study of novel first-line immuno-oncology-based treatments in patients with advanced hepatobiliary cancers. In: ASCO Annual Meeting 2024; 2024 May 31-Jun 4; Chicago, IL. Alexandria (VA): American Society of Clinical Oncology (ASCO). Abstract TPS4187.

Coming trials – ARTEMIDE

A Phase 3, randomized study of adjuvant rilvegostomig plus chemotherapy in resected biliary tract cancer: ARTEMIDE-Biliary01

Jia Fan,[1] Tanios S. Bekaii-Saab,[2] Luca Aldrighetti,[3] John Bridgewater,[4] Cristina R. Ferrone,[5] James J. Harding,[6] Masafumi Ikeda,[7] Jennifer J. Knox,[8] Julie Wang,[9] Hamzeh Kayhanian,[10] Xin Chen,[11] Sally Yan Bai,[10] Moritz Drachsler,[10] Do-Youn Oh[12]

[1]Department of Liver Surgery & Transplantation Center, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Mayo Clinic Comprehensive Cancer Center, Phoenix, AZ, USA; [3]Hepatobiliary Surgery, IRCCS San Raffaele Hospital, Milan, Italy; [4]UCL Cancer Institute, University College London, London, UK; [5]Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [8]Department of Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada; [9]AstraZeneca, New York, NY, USA; [10]AstraZeneca, Cambridge, UK; [11]AstraZeneca, Gaithersburg, MD, USA; [12]Division of Medical Oncology, Department of Internal Medicine, Seoul National University Hospital; Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

ARTEMIDE biliary01

TPS4199

Plain language summary

Why are we performing this research?

- Some people with biliary tract cancer (BTC) that is diagnosed in the early stages of the disease undergo surgery to remove the tumor, followed by treatment with chemotherapy. However, the cancer often comes back and new treatment options are needed
- ARTEMIDE-Biliary01 is a study that is aiming to find out if a new treatment called rilvegostomig can stop cancer from coming back in patients with early stage BTC when given with chemotherapy after surgery

How are we performing this research?

- Patients who have previously undergone surgery to remove their tumor will be randomly allocated to one of two treatment groups: rilvegostomig plus chemotherapy or placebo (an inactive substance) plus chemotherapy
- The study will measure the length of time after being randomly allocated to treatment that patients are alive without their cancer coming back, comparing patients in the group treated with rilvegostomig with the group not treated with rilvegostomig

Who will participate in this study?

- Approximately 750 people with early stage BTC will be enrolled from 21 countries across the globe

Where can I access more information?

- This study is ongoing and no results are available yet; expected completion is September 2030
- More information about this study can be found here: https://classic.clinicaltrials.gov/ct2/show/NCT06109779. You may also speak to your doctor about clinical studies

This study is funded by AstraZeneca
Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2024 by Jia Fan

Background

- BTC is a rare but aggressive heterogenous group of gastrointestinal cancers that arise from the intrahepatic or extrahepatic bile ducts (cholangiocarcinoma) or the gallbladder[1,2]
- While resection is a potentially curative treatment option for BTC, less than 35% of patients are diagnosed in the early stages of disease and are eligible for curative therapy[3,4]
- Adjuvant treatments have been used in patients with early stage BTC but, until recently, data were limited to non-randomized, non-controlled retrospective studies[3]
- Capecitabine and tegafur/uteracil/gimeracil (S-1) are commonly used for the adjuvant treatment of BTC, based on the BILCAP and ASCOT studies.[5,6] Gemcitabine plus cisplatin is the preferred chemotherapy in advanced BTC and may also be used in the adjuvant setting[7]
- Recurrence rates remain high with current adjuvant treatments in early stage BTC.[5,6] New adjuvant treatments are needed to reduce disease recurrence and improve outcomes in patients with BTC

Rationale

- Immunotherapy is efficacious as adjuvant therapy in other cancer types[8]
- Results from the TOPAZ-1 and KEYNOTE-966 studies support combining immunotherapy and chemotherapy in advanced BTC, including in locally advanced non-metastatic disease[9-13]
- Dual inhibition of programmed cell death-1 (PD-1) or programmed cell death ligand-1 (PD-L1) and the novel immune checkpoint, T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), has shown promising results across multiple tumor types, including BTC, with an acceptable tolerability profile, either in single-arm studies or compared with PD-1 or PD-L1 inhibition alone[11-14]
- Rilvegostomig is an anti-PD-1/anti-TIGIT bi-specific monoclonal antibody that appears active and well tolerated in non-small-cell lung cancer[15]
- Combining rilvegostomig with standard of care adjuvant chemotherapy may improve outcomes in patients with early stage BTC after curative intent resection when compared with adjuvant chemotherapy alone

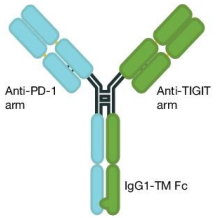
BTC: Biliary Tract Cancers; **PD-1:** Programmed cell-death-1; **PD-L1:** Programmed Death-Ligand 1; **TIGIT**: T cell immunoglobulin and immunoreceptor tyrosine-based inhibitor motf domain.

Fan J, Bekaii-Saab TS, Aldrighetti LA, Bridgewater JA, Ferrone CR, Harding JJ, et al. A phase 3, randomized study of adjuvant rilvegostomig plus chemotherapy in resected biliary tract cancer: ARTEMIDE-Biliary01. In: ASCO Annual Meeting 2024; 2024 May 31-Jun 4; Chicago, IL. Alexandria (VA): American Society of Clinical Oncology (ASCO). Abstract TPS4199.

Coming trials – ARTEMIDE

Rilvegostomig is a monovalent, bi-specific, humanized IgG1 antibody targeting PD-1 and TIGIT[15]

Rilvegostomig structure



Rilvegostomig enhances CD8 T cell-mediated killing*,†

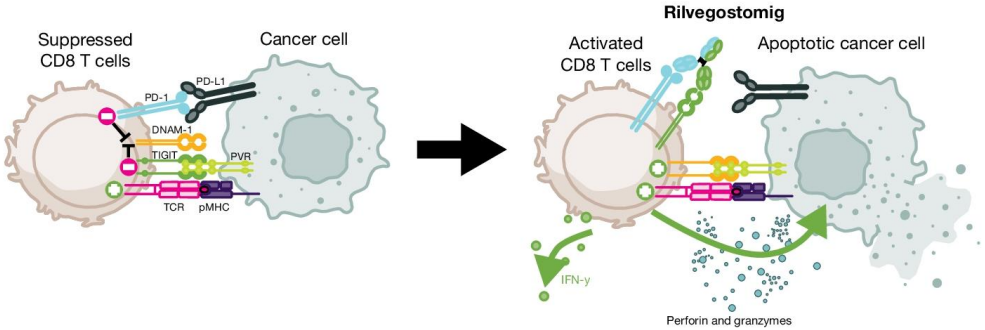


*Figure created with BioRender.com. †Reprinted with permission from Rohrberg K, et al. *J Clin Oncol* 2023;41(suppl 16):9050 (presented at the American Society of Clinical Oncology Annual Meeting 2023).
CD8, cluster of differentiation 8; DNAM-1, deoxyribonucleic acid polymerase III subunit tau (DNAX) accessory molecule-1; IFN-γ, interferon-gamma; IgG1, immunoglobulin gamma 1; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; pMHC, peptide major histocompatibility complex; PVR, poliovirus receptor; TCR, T-cell receptor; TIGIT, T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitor motif domain.

CD8, cluster of differentiation 8; **DNAM-1,** deoxyribonucleic acid polymerase III subunit tau (DNAX) accessory molecule-1; **IFN-γ,** interferon-gamma; **IgG1,** immunoglobulin gamma 1; **PD-1,** programmed cell death-1; **PD-L1,** programmed cell death ligand-1; **pMHC,** peptide major histocompatibility complex; **PVR,** poliovirus receptor; TCR, T-cell receptor; **TIGIT,** T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitor motif domain

Fan J, Bekaii-Saab TS, Aldrighetti LA, Bridgewater JA, Ferrone CR, Harding JJ, et al. A phase 3, randomized study of adjuvant rilvegostomig plus chemotherapy in resected biliary tract cancer: ARTEMIDE-Biliary01. In: ASCO Annual Meeting 2024; 2024 May 31-Jun 4; Chicago, IL. Alexandria (VA): American Society of Clinical Oncology (ASCO). Abstract TPS4199.

Coming trials – ARTEMIDE

ARTEMIDE-Biliary01 (NCT06109779) study design

A Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study to assess the efficacy and tolerability of rilvegostomig plus adjuvant chemotherapy versus placebo plus adjuvant chemotherapy in patients with BTC at risk of recurrence after resection with curative intent

Patients with BTC at risk of recurrence after resection with curative intent

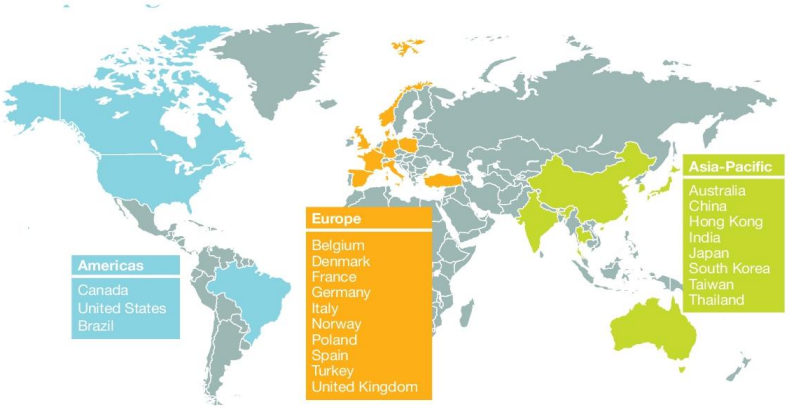
Approximately 750 patients randomized 1:1

Arm A:	Arm B:
Rilvegostomig IV Q3W plus investigator's choice of chemotherapy	Placebo IV Q3W plus investigator's choice of chemotherapy

Investigator's choice of chemotherapy:

- Capecitabine 1250 mg/mg² PO BID, 2 weeks on/1 week off, 21-day cycles or per local practice
- S-1 40–60 mg PO BID (based on body surface area), 4 weeks on/2 weeks off, 42-day cycles
- Gemcitabine 1000 mg/m² IV plus cisplatin 25 mg/m² IV, Days 1 and 8 of each 21-day cycle

Enrollment start: December 2023 | Expected study end: September 2030

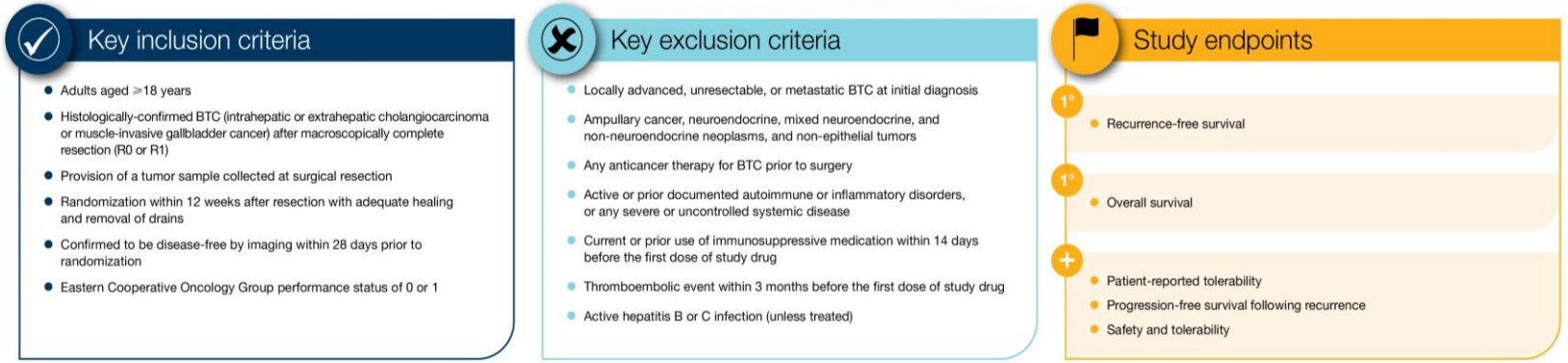


Study enrollment is ongoing; enrollment is intended at approximately 200 sites across 21 countries

BID: twice daily; **BTC:** Biliary Tract Cancer; **IV:** intravenous; **PO:** oral; **Q3W:** every three weeks; **S-1:** tegafur/oteracil/gimeracil

Fan J, Bekaii-Saab TS, Aldrighetti LA, Bridgewater JA, Ferrone CR, Harding JJ, et al. A phase 3, randomized study of adjuvant rilvegostomig plus chemotherapy in resected biliary tract cancer: ARTEMIDE-Biliary01. In: ASCO Annual Meeting 2024; 2024 May 31-Jun 4; Chicago, IL. Alexandria (VA): American Society of Clinical Oncology (ASCO). Abstract TPS4199.

Coming trials – ARTEMIDE



BTC: Biliary Tract Cancer.

Fan J, Bekaii-Saab TS, Aldrighetti LA, Bridgewater JA, Ferrone CR, Harding JJ, et al. A phase 3, randomized study of adjuvant rilvegostomig plus chemotherapy in resected biliary tract cancer: ARTEMIDE-Biliary01. In: ASCO Annual Meeting 2024; 2024 May 31-Jun 4; Chicago, IL. Alexandria (VA): American Society of Clinical Oncology (ASCO). Abstract TPS4199.

New Drugs – ADCs

CANCER RESEARCH

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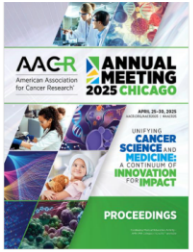
Volume 85, Issue 8_Supplement_1
15 April 2025



POSTER PRESENTATIONS - PROFFERED ABSTRACTS | APRIL 21 2025

Abstract 724: Target identification for antibody-drug-conjugate (ADC) therapy in biliary tract cancers (BTC) FREE

Aruj Dhyani; Zeynep Tarcan; Joanne Chou; Rohit Thummalapalli; Walid Chatila; Sharanya Nag; Ezra Rosen; Sydney Bowker; Wungki Park; Elisa De Stanchina; Sarat Chandarlapaty; David Solit; William Jarnagin; Marinela Capanu; Eileen M O'Reilly; Ghassan K Abou-Alfa; Olca Basturk; James Harding

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+ Author & Article Information

Cancer Res (2025) 85 (8_Supplement_1): 724.

https://doi.org/10.1158/1538-7445.AM2025-724

Split-Screen Views Share Tools Versions

Background:

BTCs are an uncommon malignancy with poor prognosis. ADCs have efficacy in several solid tumors with antigen surface expression serving as a potential biomarker in some instances. Herein, we evaluate the protein expression and heterogeneity of ADC target antigens and their prognostic implications in BTC.

Methods:

Utilizing an IRB-approved, retrospective biospecimen protocol, we constructed tissue microarrays (TMA) from resected, early staged intrahepatic cholangiocarcinoma (IHC), extrahepatic cholangiocarcinoma (EHC) and gallbladder cancer (GB). IHC for Nectin-4, TROP2, c-MET, CLDN18.2 was assessed. Positivity defined as ≥10% weakly stained tumor cells and quantified by H-score (intensity × percentage). HER2 IHC scored per standard colon criteria. Clinicopathological factors and outcomes were associated with ADC target expression.

ADC: antibody-drug-conjugate; **BTC:** Biliary Tract Cancer; TMA: tssue microarrays; **IHC:** Intrahepatic cholangiocarcinoma; **EHC:** extrahepatic cholangiocarcinoma; **GB:** gallbladder cancer

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New Drugs – ADCs

Modest to high expression of Nectin-4, TROP2, c-MET and CLDN18.2 was identified across BTC anatomic subtypes, suggesting a potential role for ADCs to these antigens in patients with BTC.

Differential Expression of ADC targets in BTC across anatomic subsite

	cMET			TROP2			CLDN 18.2			Nectin 4			Her2	
	Positive N (%)	H-Score, median (IQR)	H Score >200	Positive N (%)	H-Score, median (IQR)	H Score >200	Positive N (%)	H-Score, median (IQR)	H Score >200	Positive N (%)	H-Score, median (IQR)	H Score >200	Equivocal N (%)	Positive N (%)
Total	49 (75%)	100 (20,200)	3 (4.6%)	54 (83%)	100 (100,200)	8 (12%)	30 (46%)	0 (0,100)	2 (3.1%)	43 (66%)	100 (0,200)	1 (1.5%)	1 (1.5%)	5 (7.7%)
ICC	16 (62%)	65 (0,100)	0 (0%)	17 (65%)	100 (0,150)	3 (12%)	10 (38%)	0 (0,100)	0 (0%)	17 (65%)	100 (0,200)	0 (0%)	1 (3.8%)	2 (7.7%)
ECC	25 (89%)	100 (100,200)	3 (11%)	26 (93%)	100 (100,190)	3 (11%)	16 (57%)	55 (0,100)	2 (7.1%)	20 (71%)	100 (0,200)	1 (3.6%)	0 (0%)	2 (7.1%)
GB	8 (73%)	25 (5,100)	0 (0%)	11 (100%)	170 (140,200)	2 (18%)	4 (36%)	0 (0,30)	0 (0%)	20 (71%)	100 (0,200)	0 (0%)	0 (0%)	1 (9.1%)

ADC: antibody-drug-conjugate; **BTC:** Biliary Tract Cancer;

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