Carcinoma de vías biliares: claves de las guías clínicas y su aplicación práctica

11st Dec 2025

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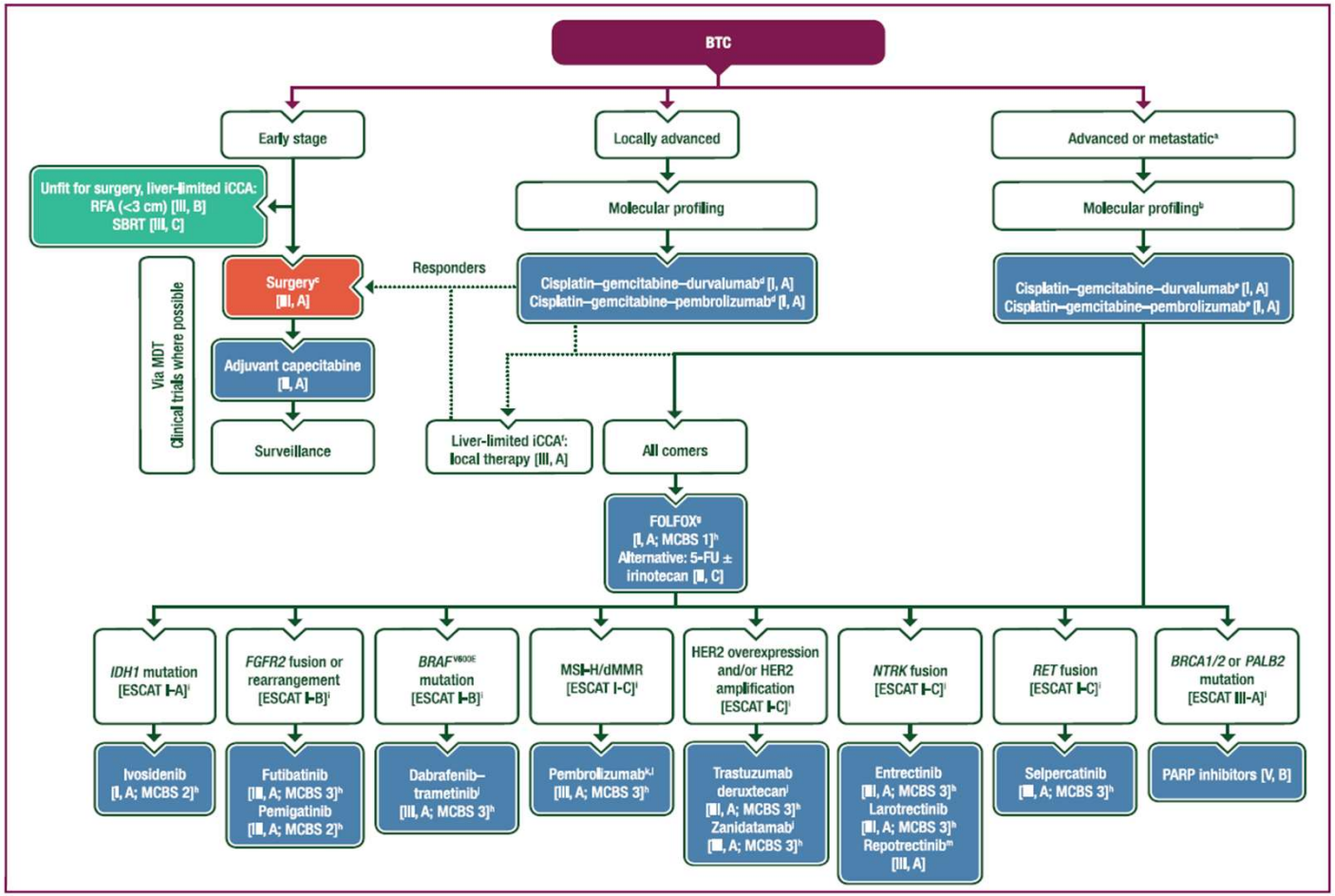
BTC –ESMO GUIDELINES eUpdate 2024



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EARLY DX

ADEQUATE NGS

CURRENT RESTRICTIONS

MOLECULAR PROFILING

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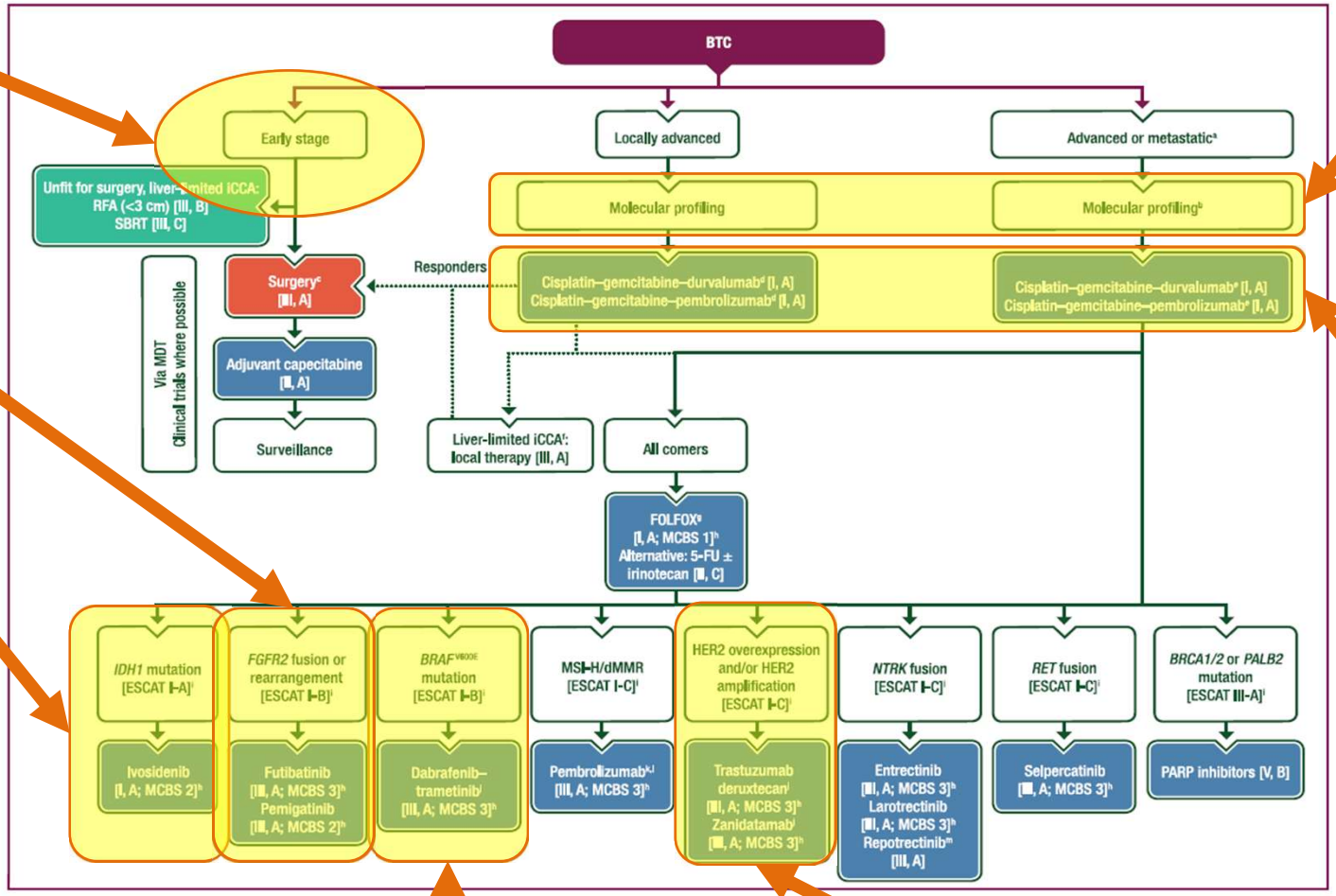

NO ACCESS

FUNDING AWAITED

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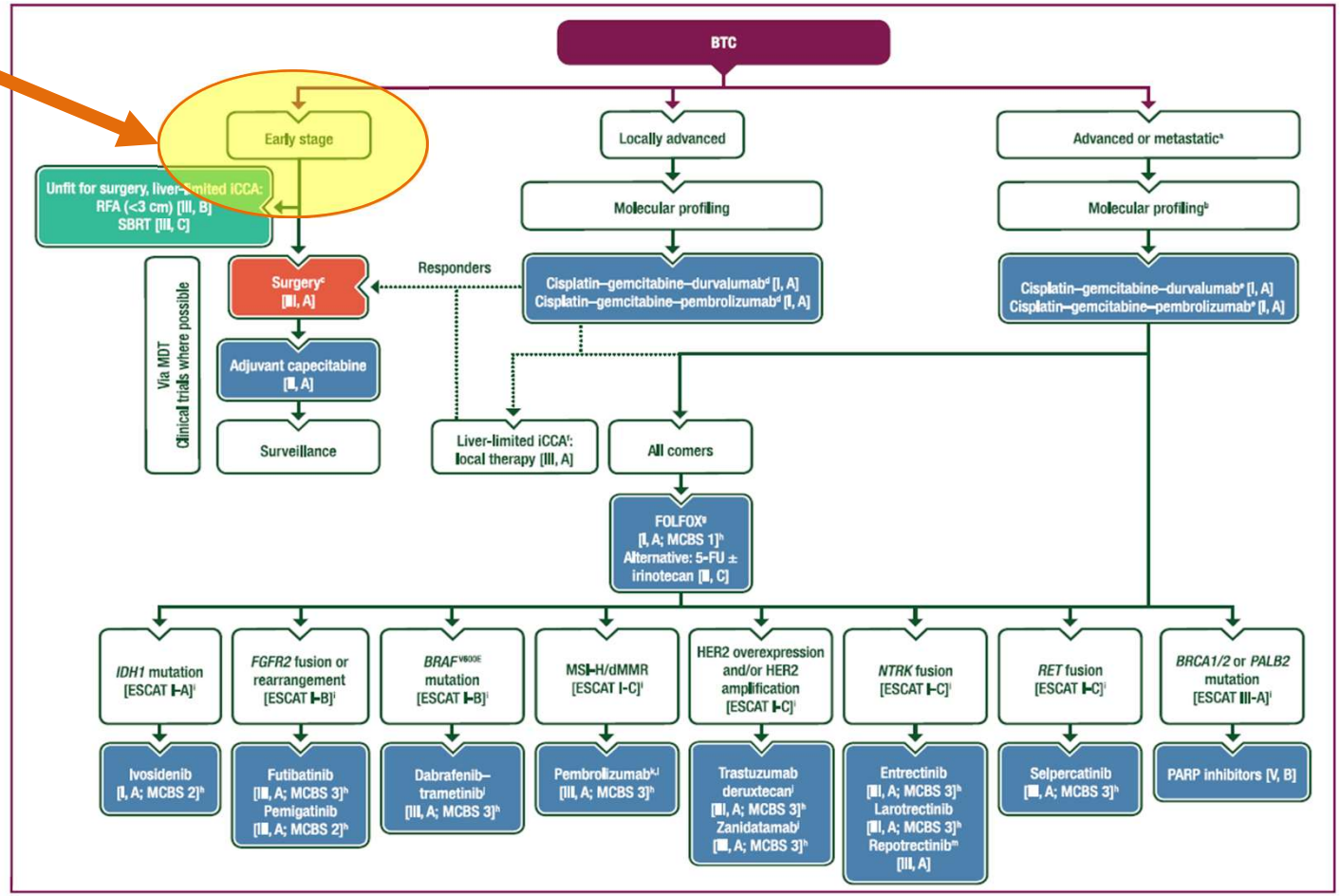
EARLY DX



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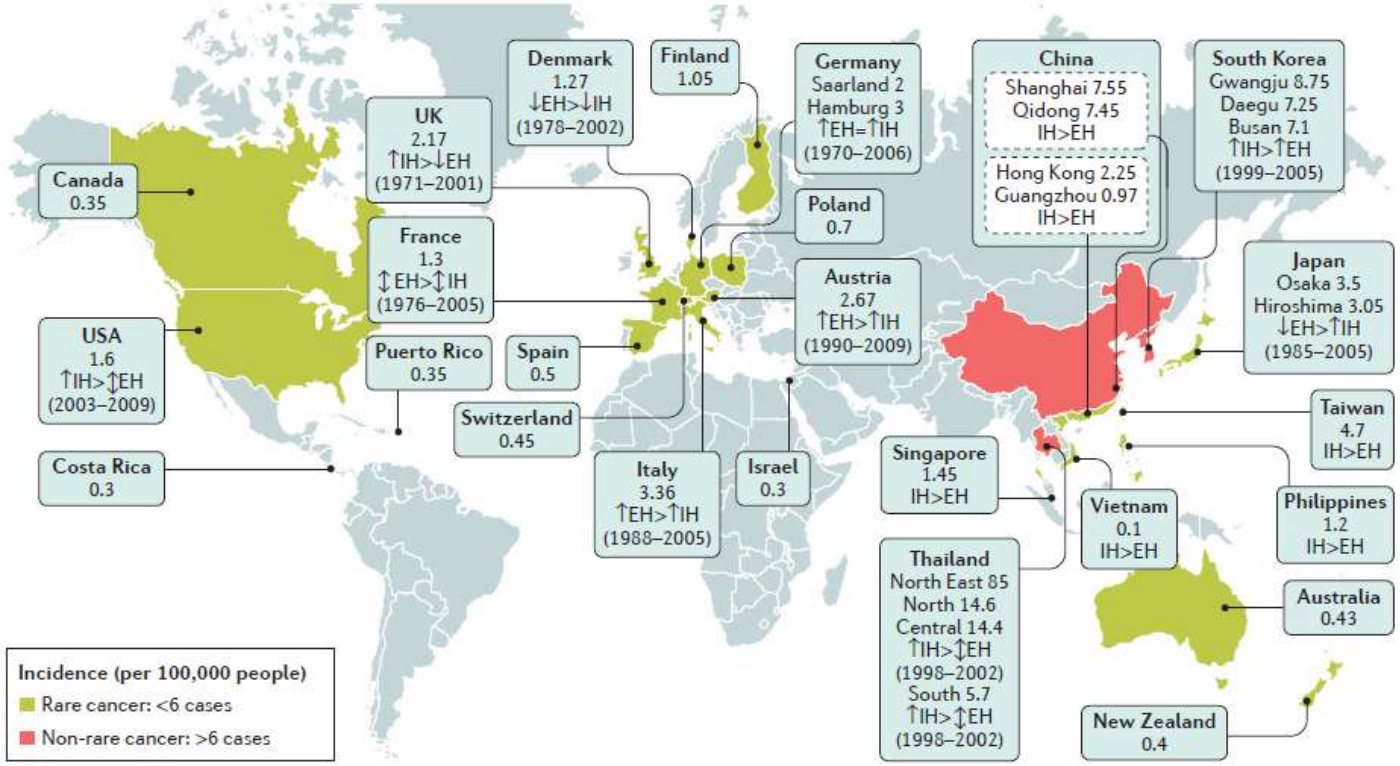
CCA: Epidemiology

- Rare cancers
  - Incidence: <6/100,000
- Incidence increasing
  - iCCA
- Poor prognosis
  - 5-year OS (<20%)
  - Late diagnosis
    - 70% advanced stages
  - High relapse rate

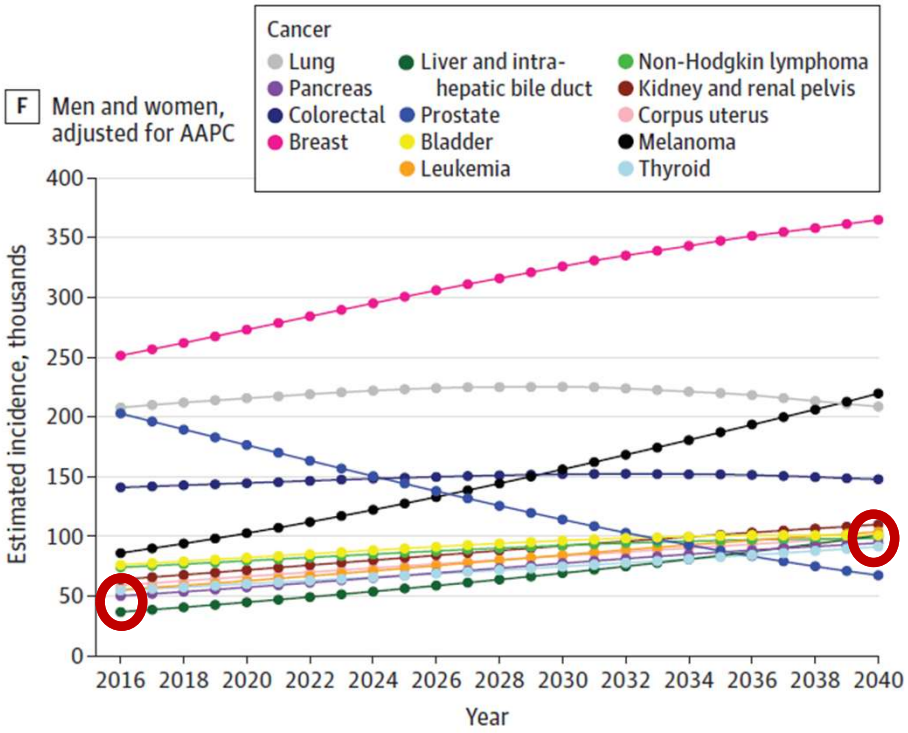


CCA, cholangiocarcinoma; EH, extrahepatic; iCCA, intrahepatic cholangiocarcinoma; IH, intrahepatic; OS, overall survival.

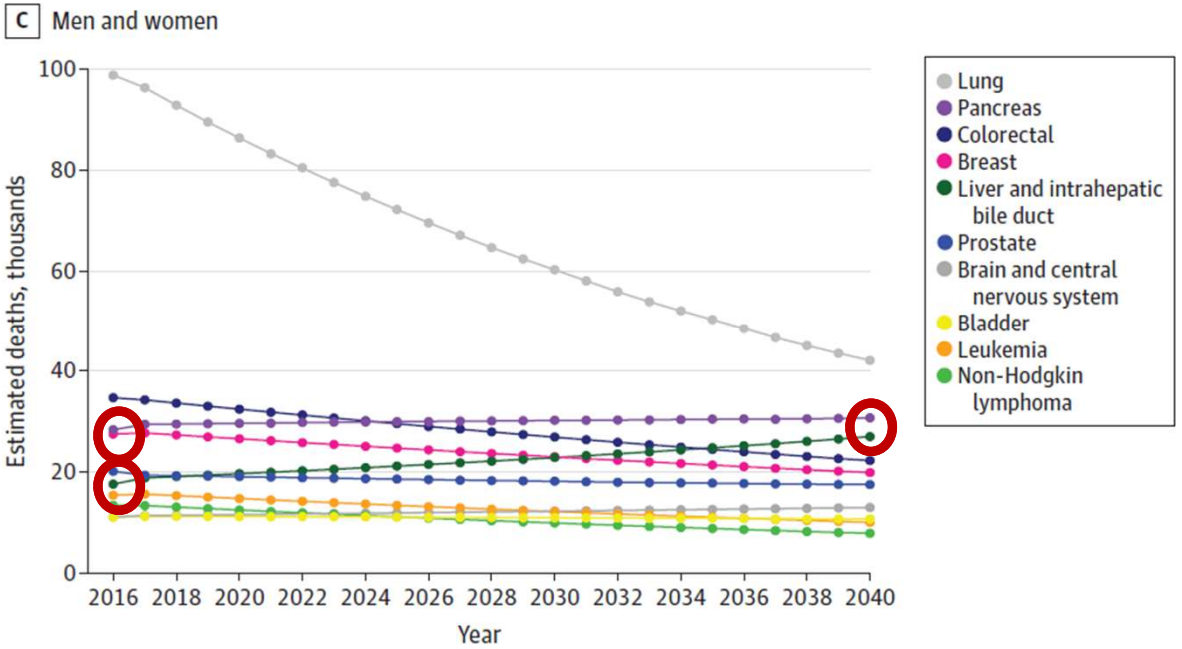
Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261–80; DeOliveira ML, et al. *Ann Surg*. 2007;245:755–62; Valle JW, et al. *Ann Oncol*. 2016;27(Suppl 5):v28–37.

CCA: Incidence/mortality increasing

Estimated **incidence** projections (2016 → 2040)



Estimated **cancer death** projections (2016 → 2040)

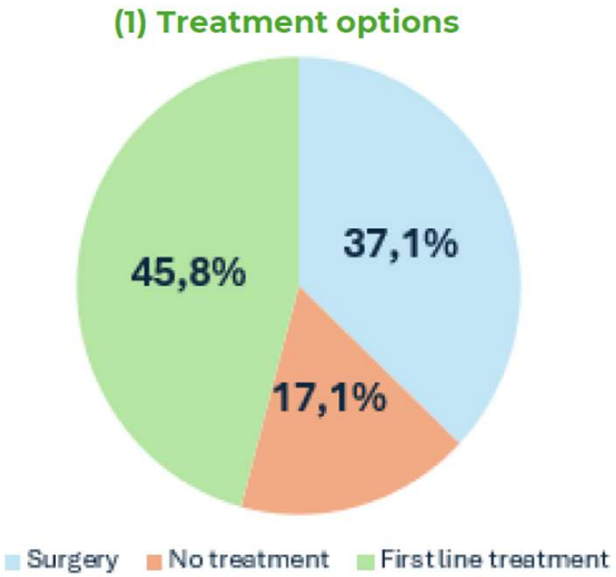


HPB cancers will be the second and third most common causes of cancer death by 2040

AAPC, average annual percent change; CCA, cholangiocarcinoma; HPB, hepato pancreatic biliary.
Rahib L, et al. *JAMA Netw Open*. 2021;4:e214708.

BTC - delayed diagnosis an ongoing issue

- 35 patients: iCCA (42.9%), dCCA (17.1%), gallbladder (14.3%), ampullary (14.3%) and pCCA (11.4%).
- Majority of patients (60%) had metastases at diagnosis. Only 37.1% had surgery and 17.1% did not receive any treatment.



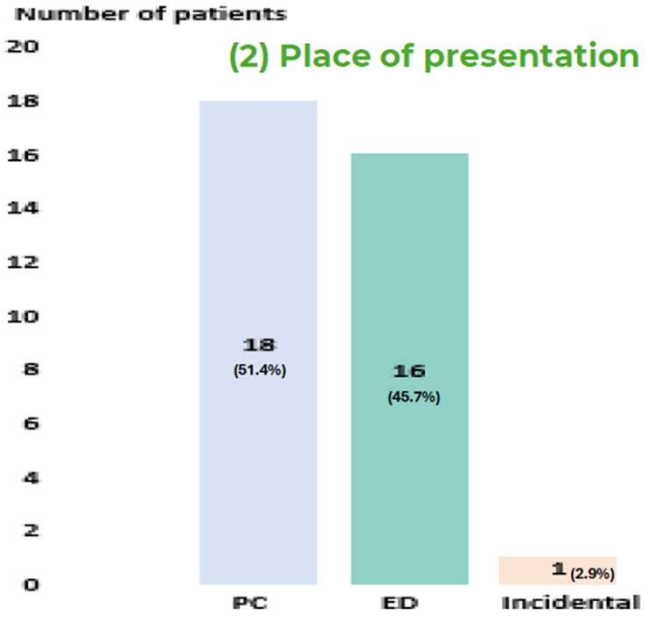
Conclusions:

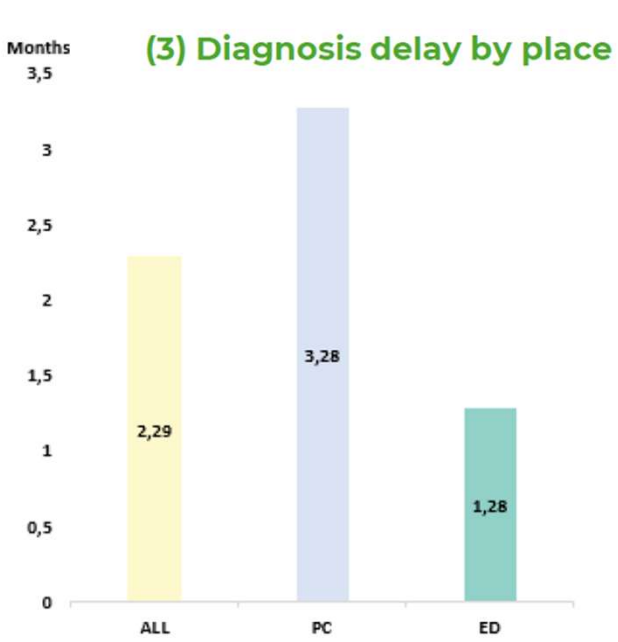
- Biliary tumours are often **diagnosed at advanced stages** due to significant **diagnostic delays** caused by **non-specific symptoms**.
- These delays **limit curative treatment options** and **worsen prognosis**.
- **Improved early detection strategies and awareness are crucial** to enhancing outcomes and survival rates.

Martirena el at, CCF 2025

BTC - delayed diagnosis an ongoing issue

- Majority 51.4% of patients were diagnosed through primary care (PC) and 45.7% in the emergency department (ED)
- Median time from symptom onset to diagnosis was 2.29 months (3.28mo for PC and 1,28mo for ED; p=0.39)





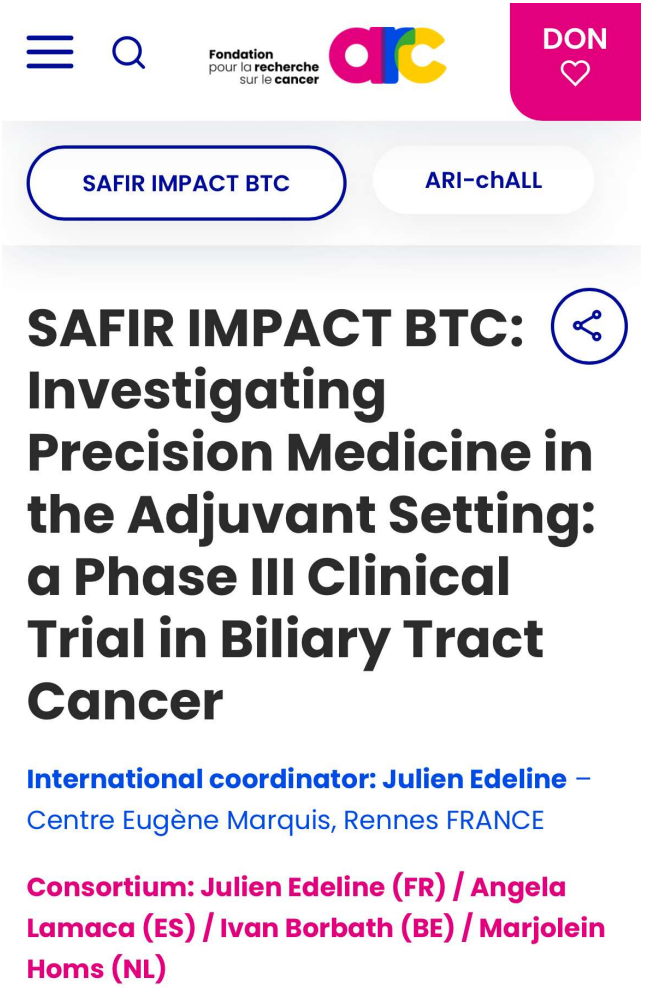
Conclusions:

- Biliary tumours are often **diagnosed at advanced stages** due to significant **diagnostic delays** caused by **non-specific symptoms**.
- These delays **limit curative treatment options** and **worsen prognosis**.
- **Improved early detection strategies and awareness are crucial** to enhancing outcomes and survival rates.

Martirena el at, CCF 2025

SAFIR IMPACT BTC

- Targeted therapies in the Adjuvant setting: phase III clinical trial
- Capecitabine vs Targeted therapies
- Funded secured (ATTRACT 2025) – Coordinator: Dr Edeline
  - Spain: Dr Lamarca- FJD + TTD



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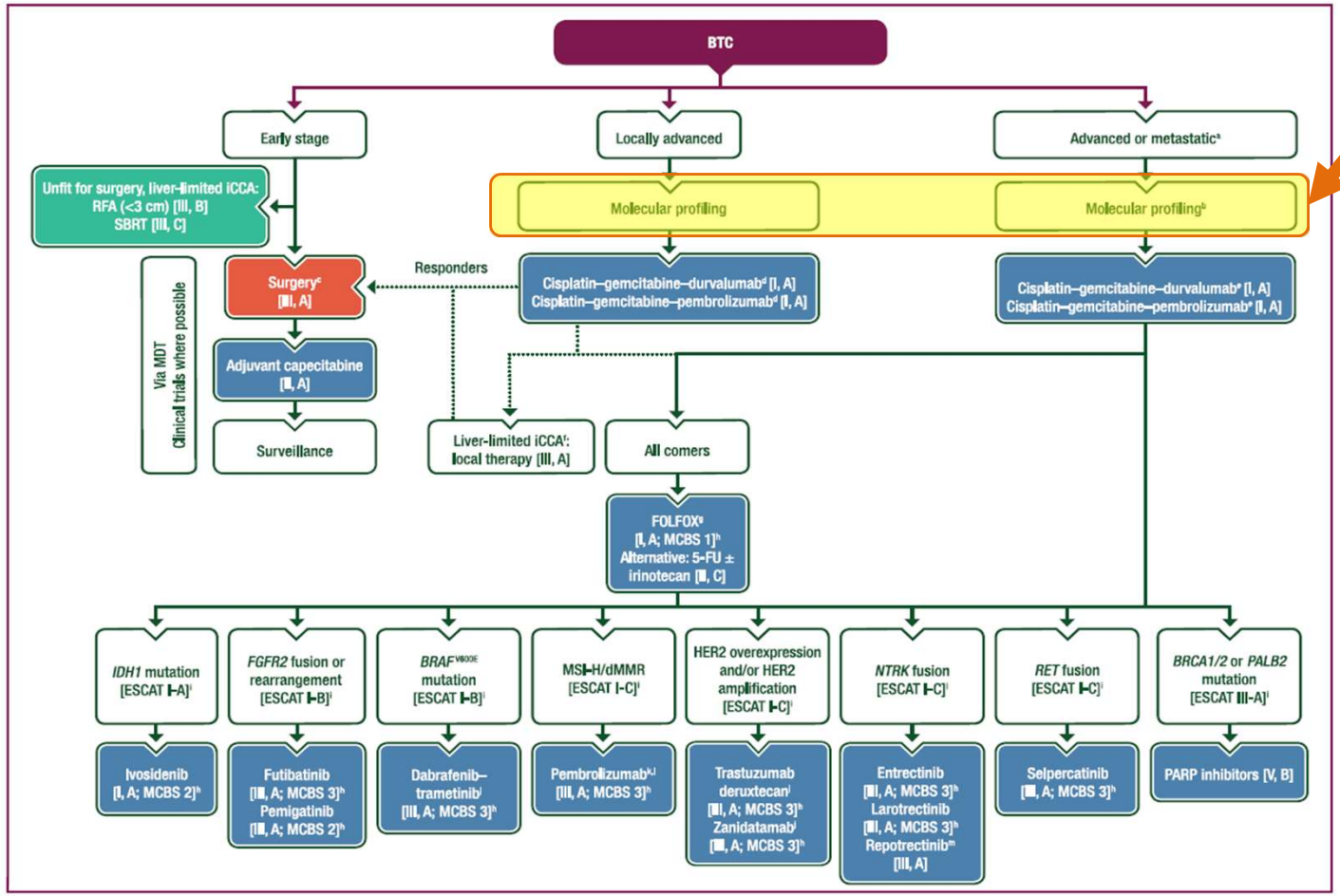
BTC – ESMO GUIDELINES eUpdate 2024 - SPANISH REALITY



MOLECULAR PROFILING

Vogel ESMO Open 2024

When and how to test patients

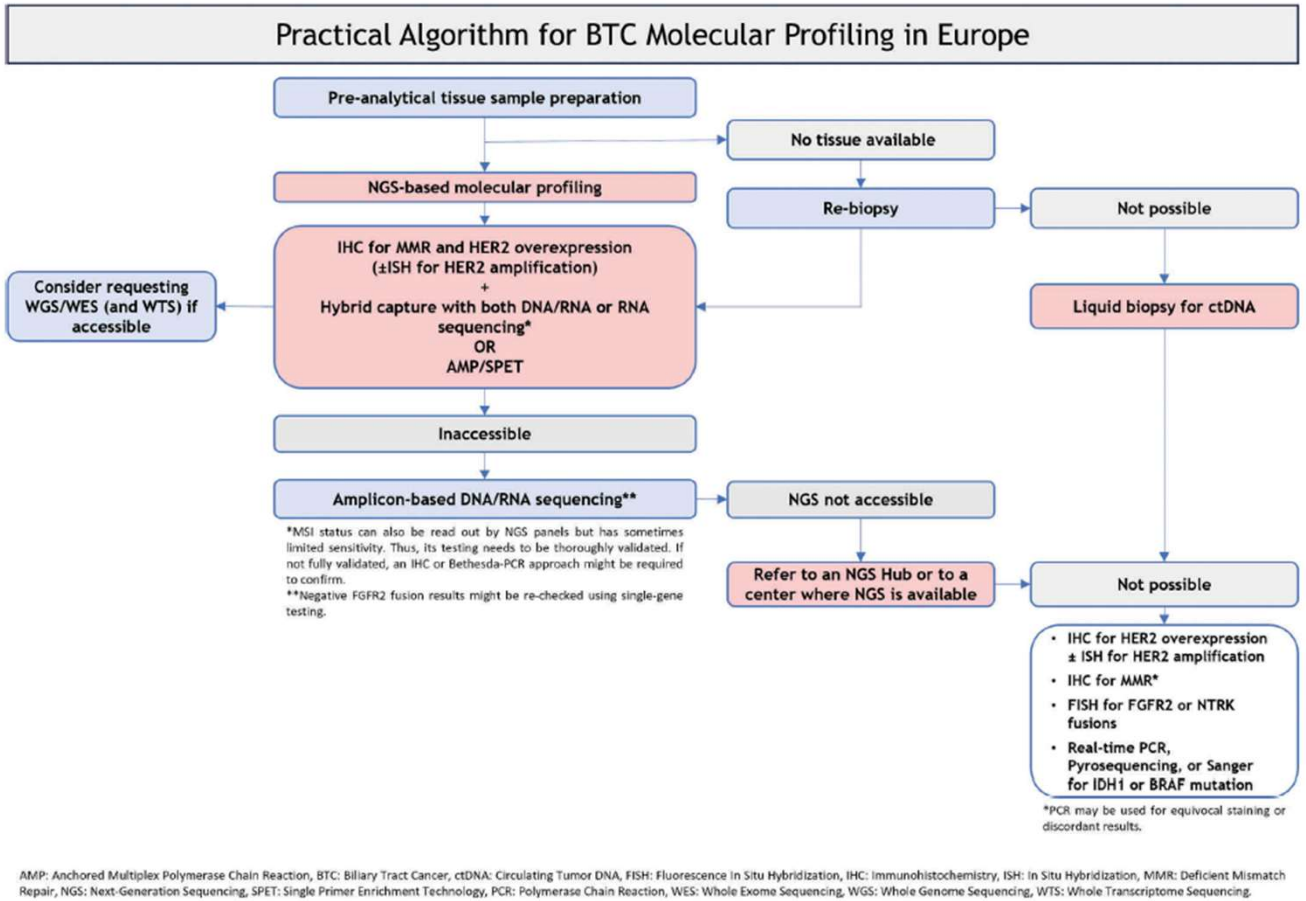
When and how to test patients

- As soon as possible following diagnosis (of advanced disease)
- Unless within a trial, not recommended to hold 1st-line therapy waiting for results

When and how to test patients

- Multigene tumour NGS testing – RNA-based may provide better sensitivity for fusions
- IHC for HER2 and MMR may be quicker and reliable
- ctDNA may be of use if tissue not available

MOLECULAR PROFILING IN BTC – ALGORITHM



AMP: Anchored Multiplex Polymerase Chain Reaction, BTC: Biliary Tract Cancer, ctDNA: Circulating Tumor DNA, FISH: Fluorescence In Situ Hybridization, IHC: Immunohistochemistry, ISH: In Situ Hybridization, MMR: Deficient Mismatch Repair, NGS: Next-Generation Sequencing, SPET: Single Primer Enrichment Technology, PCR: Polymerase Chain Reaction, WES: Whole Exome Sequencing, WGS: Whole Genome Sequencing, WTS: Whole Transcriptome Sequencing.

Figure 2. Practical algorithm for BTC molecular profiling in Europe. Approximate section requirements: NGS-based sequencing (10), MMR IHC (6), HER2 IHC (4), HER2 IHC ± FISH (≥3), MSI/MMR IHC ± PCR (≥5), FISH for FGFR2/NTRK (2), IDH1/BRAFV600E by PCR/Sanger (4–6). BTC: biliary tract cancer, ctDNA: circulating tumor DNA, dMMR: deficient mismatch repair, FISH: fluorescence in situ hybridization, IHC: immunohistochemistry, MMR: mismatch repair, MSI: microsatellite instability, NGS: next-generation sequencing, PCR: polymerase chain reaction, WES: whole exome sequencing, WGS: whole genome sequencing.

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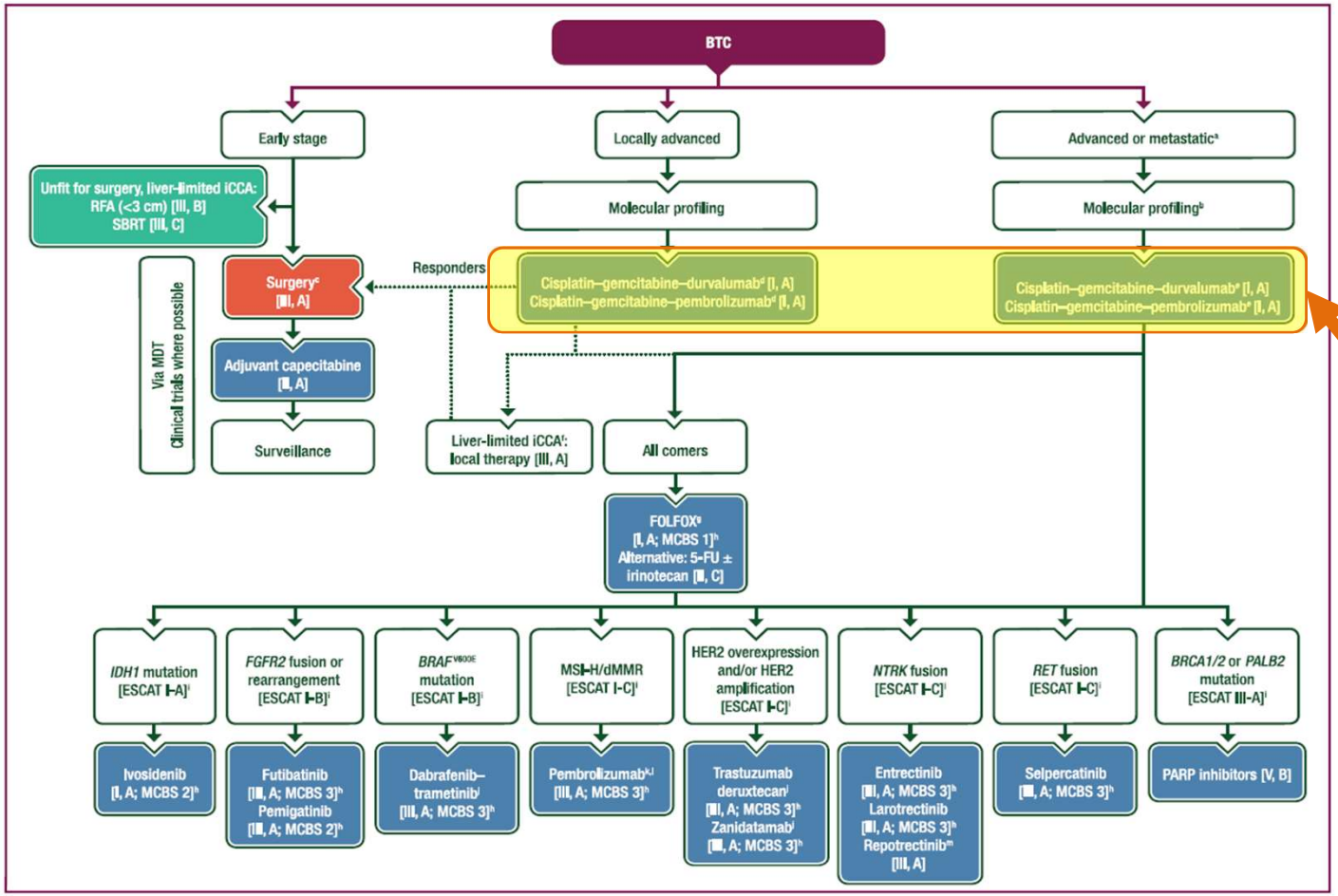

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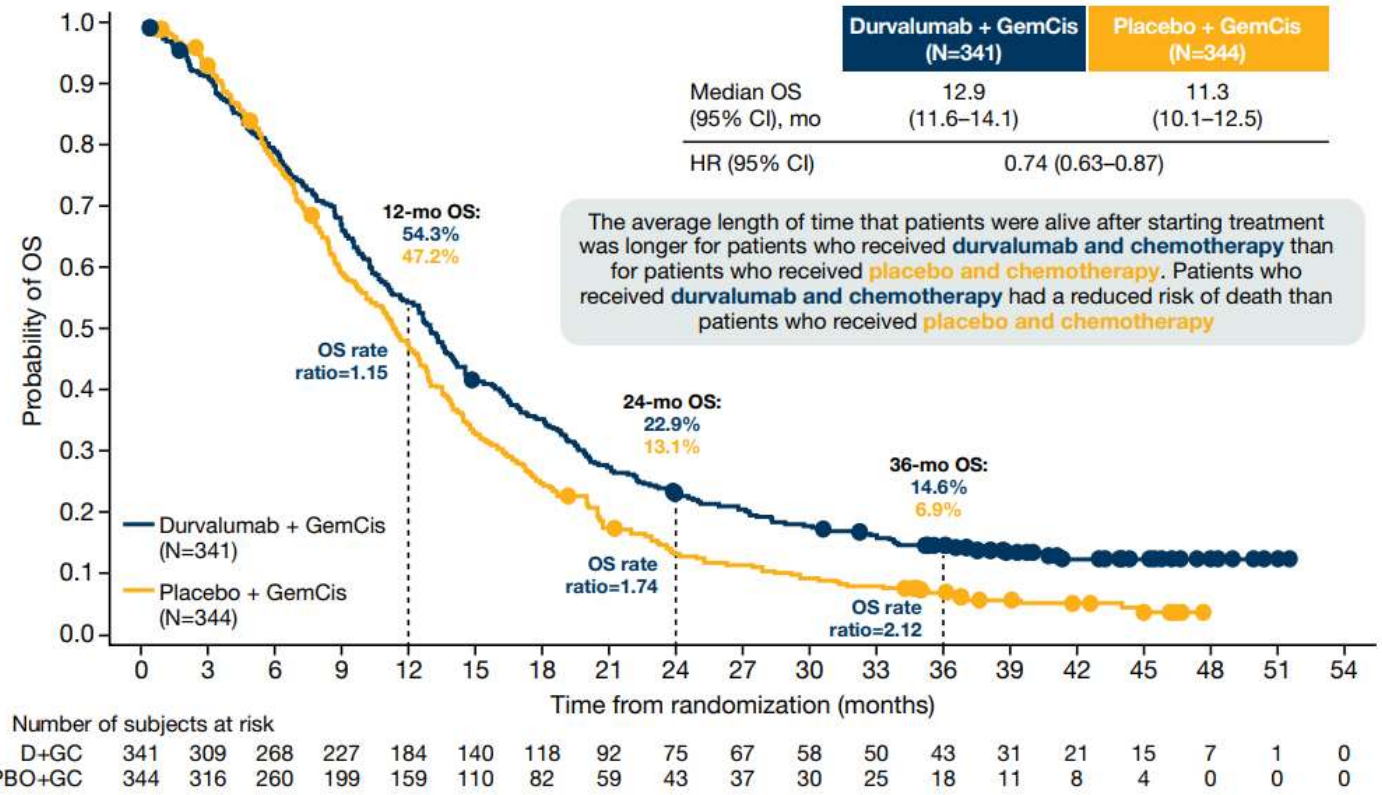
TOPAZ-1 LONG TERM BENEFIT CCF 2024



Activity data confirmed

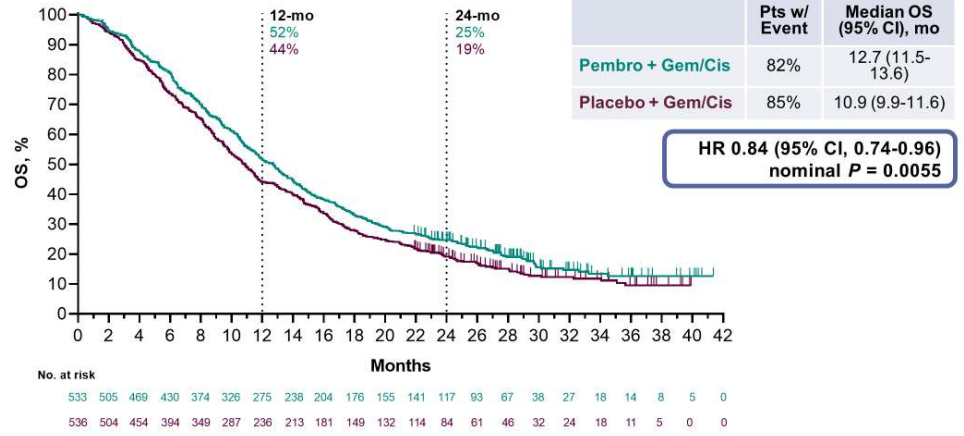
Oh et al, CCF 2024

First-line – Pembrolizumab + CisGem (KEYNOTE-966)

Updated data with longer follow-up: activity confirmed

- **Here, we present an updated efficacy and safety analysis with an additional 4 months of follow-up**
  - Median follow-up[2] = 29.5 months (39 additional OS events)
  - Median duration on treatment = 6.37 mo in pembrolizumab arm and 5.54 mo in placebo arm

Updated Overall Survival Kaplan-Meier Curve



	Pts w/ Event	Median OS (95% CI), mo
Pembro + Gem/Cis	82%	12.7 (11.5-13.6)
Placebo + Gem/Cis	85%	10.9 (9.9-11.6)

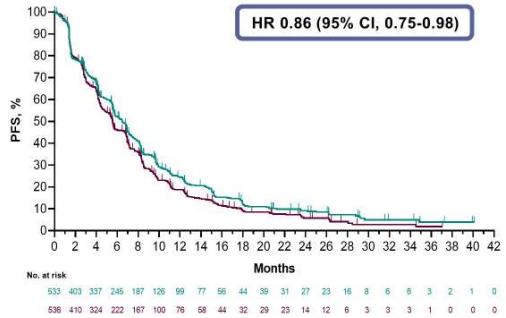
HR 0.84 (95% CI, 0.74-0.96)
nominal *P* = 0.0055

Data cutoff date: April 13, 2023.

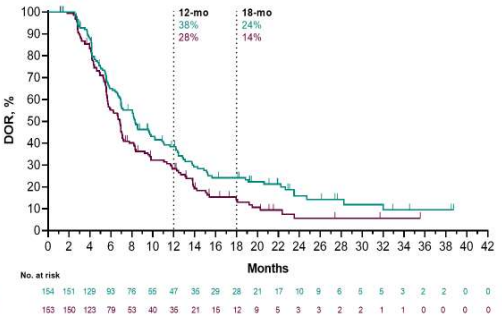
Updated Progression-Free Survival and Duration of Response Kaplan-Meier Curves

	Pts w/ Event	Median PFS (95% CI), mo
Pembro + Gem/Cis	81%	6.5 (5.7-6.9)
Placebo + Gem/Cis	85%	5.6 (4.9-6.5)

HR 0.86 (95% CI, 0.75-0.98)



	Pts w/ Event	Median DOR (range), mo	ORR (95% CI), %
Pembro + Gem/Cis	29%	8.3 (1.2+ to 38.7+)	28.9 (25.1-32.9)
Placebo + Gem/Cis	29%	6.9 (1.1+ to 35.5+)	28.5 (24.8-32.6)



Data cutoff date: April 13, 2023.

Finn et al, ESMO Asia 2023

TOURMALINE – IO + OTHER CHEMO BACKBONE

Enrollment start: August 2023 | Expected study end: March 2026

Study enrollment is ongoing; enrollment is intended at 43 sites across 8 countries

- Durvalumab + nonCisGem chemo
- CisGem PS2
- Ampullary tumours included

TOURMALINE study design: a Phase 3b, single-arm, multicenter, international study evaluating the safety and efficacy of durvalumab in combination with gemcitabine-based chemotherapy regimens in participants with aBTC

Screening (Day -28 to -1) (N≈210 screened)

Adults with histologically-confirmed locally advanced or metastatic BTC, including iCCA, eCCA, GBC, and AoV cancer; prior curative treatment is permitted with no minimum time to recurrence, including participants with residual disease

Treatment period of durvalumab plus gemcitabine-based chemotherapy for up to 8 cycles (N≈140)

Durvalumab (60-minute IV infusion in the first cycle [Day 1] and 30-minute IV infusion in the following cycles) + gemcitabine-based chemotherapy

Durvalumab 1500 mg Q3W plus
- Gemcitabine monotherapy Q3W
- GemCis (WHO/ECOG PS 2 only) Q3W
- Gemcitabine + oxaliplatin Q3W
- Gemcitabine + carboplatin Q3W
- Gemcitabine + S-1 Q3W
- GemCis + albumin-bound paclitaxel Q3W

or

Durvalumab 1500 mg Q4W plus GemCis + S-1 Q2W

Maintenance period of durvalumab every 4 weeks ± gemcitabine-based chemotherapy*

Durvalumab 1500 mg Q4W maintenance, at investigator's discretion or until disease progression or unacceptable toxicity

Gemcitabine-based chemotherapy maintenance, at investigator's discretion*

Safety and survival follow-up

Safety follow-up period will be for 90 days after the last dose of durvalumab

Survival follow-up will occur every 3 months

*With the exception of paclitaxel.

aBTC, advanced biliary tract cancer; AoV, ampulla of Vater; BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; iCCA, intrahepatic cholangiocarcinoma; IV, intravenous; PS, performance status; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; S-1, tegafur-gimeracil-oteracil; WHO, World Health Organization.

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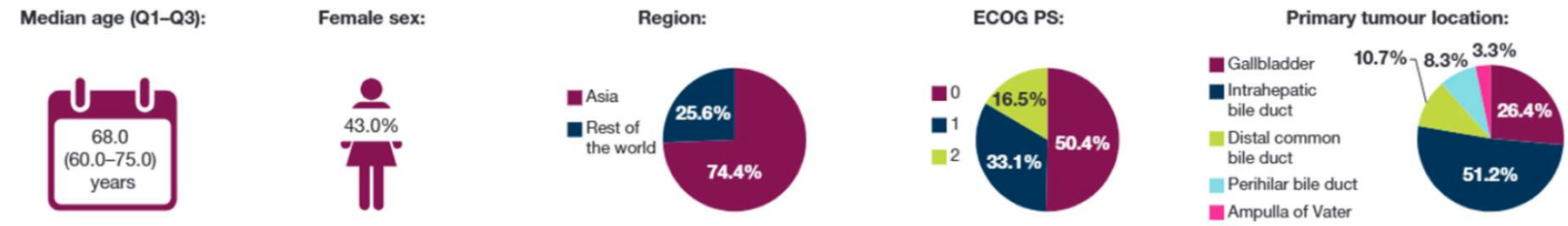
TOURMALINE – IO + OTHER CHEMO BACKBONE

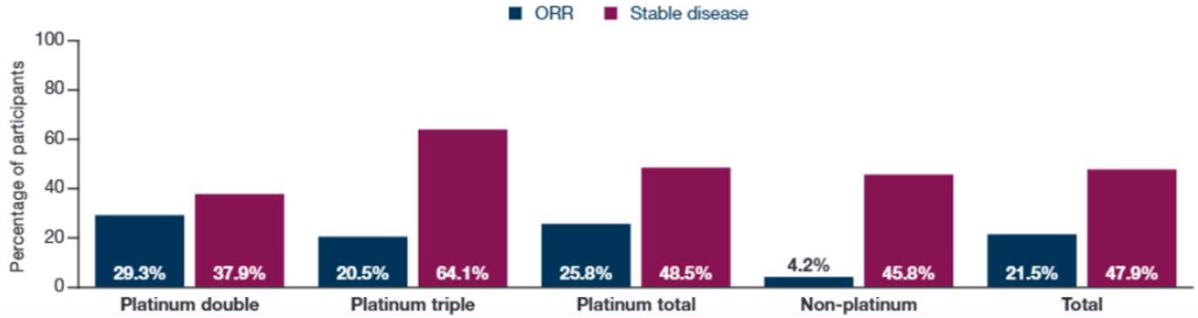
Figure 2. Overall participant demographics and clinical characteristics (N=121)



*Includes M1 subtypes.

ECOG PS, Eastern Cooperative Oncology Group performance status; M0, no distant metastasis; M1, metastatic; Mx, metastasis cannot be measured; Q, quartile; TNM, tumour / node / metastasis.

Figure 3. 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).

CI, confidence interval; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

Oh et al ESMO-GI 2025

TOURMALINE – IO + OTHER CHEMO BACKBONE

Table 2. 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.

AE, adverse event; PRAE, possibly related (to any study treatment) adverse event; PRSAE, possibly related (to any study treatment) serious adverse event; SAE, serious adverse event.

Safety (Table 2)

- 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

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TOURMALINE – Asian Population

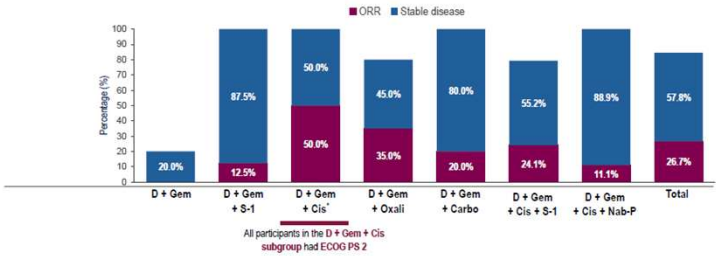
Baseline demographics and disease characteristics

	D + Gem	D + Gem + S-1	D + Gem + Cis	D + Gem + Oxali	D + Gem + Carbo	D + Gem + Cis + S-1	D + Gem + Cis + Nab-P	Total
N	5	8	14	20	5	29	9	90
Age, median (Q1–Q3), years	78.0 (76.0–80.0)	72.0 (52.5–73.5)	68.5 (65.0–75.0)	65.5 (58.0–69.0)	58.0 (50.0–67.0)	65.0 (54.0–74.0)	63.0 (49.0–71.0)	66.5 (56.0–74.0)
Female sex, n (%)	4 (80.0)	3 (37.5)	8 (57.1)	8 (40.0)	1 (20.0)	8 (27.6)	4 (44.4)	36 (40.0)
Primary tumour location, n (%)								
Gallbladder	3 (60.0)	2 (25.0)	5 (35.7)	8 (40.0)	1 (20.0)	7 (24.1)	1 (11.1)	27 (30.0)
Intrahepatic bile duct	1 (20.0)	4 (50.0)	5 (35.7)	10 (50.0)	3 (60.0)	17 (58.6)	6 (66.7)	46 (51.1)
Distal common bile duct	0	1 (12.5)	3 (21.4)	0	1 (20.0)	2 (6.9)	1 (11.1)	8 (8.9)
Perihilar bile duct	1(20.0)	1 (12.5)	0	1 (5.0)	0	3 (10.3)	1 (11.1)	7 (7.8)
Ampulla of Vater	0	0	1 (7.1)	1 (5.0)	0	0	0	2 (2.2)
ECOG PS, n (%)								
0	2 (40.0)	8 (100.0)	0	6 (30.0)	3 (60.0)	24 (82.8)	8 (88.9)	51 (56.7)
1	2 (40.0)	0	0	14 (70.0)	2 (40.0)	5 (17.2)	1 (11.1)	24 (26.7)
2	1 (20.0)	0	14 (100)	0	0	0	0	15 (16.7)
TNM classification, n (%)								
M0	3 (60.0)	2 (25.0)	3 (21.4)	1 (5.0)	1 (20.0)	9 (31.0)	3 (33.3)	22 (24.4)
M1	2 (40.0)	6 (75.0)	10 (71.4)	19 (95.0)	4 (80.0)	20 (69.0)	6 (66.7)	67 (74.4)
Mx	0	0	1 (7.1)	0	0	0	0	1 (1.1)

TOURMALINE First Subject In: 16 August 2023; Last Subject In: 07 March 2025; Last Study Subject Dosed: 17 March 2025; The final DCO is defined by the time of the OS Final Analysis, which will take place when there is 65% OS maturity or the last participant has had the opportunity to be followed up for a minimum of 12 months, whichever occurs first (expected March 2026). At data cut-off, 90 participants from Asia (Korea [n=49]; Japan [n=36]; Singapore [n=5]) had received treatment.
Carbo, carboplatin; Cis, cisplatin (NIMP); D, durvalumab (IMP); DCO, data cut-off; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem, gemcitabine (NIMP); IMP, Investigational medicinal product; M0, no distant metastasis; M1, metastatic; Mx, metastasis cannot be measured; Nab-P, albumin bound paclitaxel (NIMP); NIMP, Non-IMP; Oxali, oxaliplatin; OS, overall survival; Q1, lower quartile; Q3, upper quartile; S-1, tegafur-gimeracil-oteracil; TNM, tumour, nodes, metastasis.

Data cut-off: 7 Aug 2024

Objective response rate



All participants in the D + Gem + Cis subgroup had ECOG PS 2

N	5	8	14	20	5	29	9	90
ORR, % (95% CI)†	0 (0–52.18)	12.5 (0.32–52.65)	50.0 (23.04–76.96)	35.0 (15.39–59.22)	20.0 (0.51–71.64)	24.1 (10.30–43.54)	11.1 (0.28–48.25)	26.7 (17.89–37.03)
Complete	0	0	0	1 (5.0)	0	0	0	1 (1.1)
Partial	0	1 (12.5)	7 (50.0)	6 (30.0)	1 (20.0)	7 (24.1)	1 (11.1)	23 (25.6)
Stable disease, n (%)	1 (20.0)	7 (87.5)	7 (50.0)	9 (45.0)	4 (80.0)	16 (55.2)	8 (88.9)	52 (57.8)

*Responses exclude unconfirmed responses. †95% CI calculated using the binomial exact method (Clopper-Pearson).
Carbo, carboplatin; CI, confidence interval; Cis, cisplatin (NIMP); D, durvalumab (IMP); Gem, gemcitabine (NIMP); IMP, Investigational medicinal product; N, number of subjects per cell; Nab-paclitaxel, albumin bound paclitaxel (NIMP); NIMP, Non-IMP; Oxali, oxaliplatin; ORR, objective response rate; PS, performance status; S-1, tegafur / gimeracil / oteracil.
RECIST version 1.1 Response Evaluation Criteria in Solid Tumours version 1.1.

Data cut-off: 7 Aug 2024

Oh et al ESMO-Asia 2025

CisGemDurva; Ps2; GLOBAL POPULATION

TOURMALINE – Asian Population

Safety and ORR for the D + Gem + Cis subgroup (ECOG PS 2) in the global ITT population

	D + Gem + Cis (n=18)
Any Grade 3 / 4 PRAE within 6 months of treatment initiation, n (%)	9 (50.0)
Any AE, n (%)	17 (94.4)
Any AE possibly related to study treatment*	16 (88.9)
Any Grade 3 / 4 AE	13 (72.2)
Any AE with an outcome of death	1 (5.6)
Any AE leading to discontinuation of any treatment	2 (11.1)
Any SAE, n (%)	6 (33.3)
Any SAE possibly related to any study treatment*	0
Any Grade 3 / 4 SAE	3 (16.7)
SAE leading to discontinuation of any treatment	2 (11.1)
Any immune-mediated AE†, n (%)	4 (22.2)
Any infusion related AE, n (%)	1 (5.6)
Hypersensitivity / anaphylactic reactions AE, n (%)	0

	D + Gem + Cis (n=18)
ORR‡, % (95% CI)§	44.4 (21.53, 69.24)
Complete response	0
Partial response	8 (44.4)
Stable disease	8 (44.4)

*Investigator assessed. †Immune mediated AEs are identified from AEs of special interest and adverse events of possible interest using a programmatic approach. ‡Responses exclude unconfirmed responses. §95% CI calculated using the binomial exact method (Clopper-Pearson). RECIST version 1.1 Response Evaluation Criteria in Solid Tumours version 1.1. All other treatment groups had n=0 or n=2 (D + G) for ECOG PS 2 data.
AE, adverse event; Cis, cisplatin (NIMP); CI, confidence interval; D, durvalumab (IMP); ECOG, Eastern Cooperative Oncology Group; Gem, gemcitabine (NIMP); IMP, investigational medicinal product; ITT, intention to treat; NIMP, Non-IMP; ORR, objective response rate; PRAE, possibly related adverse event; PS, performance status;

Data cut-off: 7 Aug 2024

ESMO

Oh et al ESMO-Asia 2025

TOURMALINE – CisGemDurva PS2 efficacy and toxicity

Safety and ORR for the D + Gem + Cis subgroup (ECOG PS 2) in the global ITT population

	D + Gem + Cis (n=18)
Any Grade 3 / 4 PRAE within 6 months of treatment initiation, n (%)	9 (50.0)
Any AE, n (%)	17 (94.4)
Any AE possibly related to study treatment*	16 (88.9)
Any Grade 3 / 4 AE	13 (72.2)
Any AE with an outcome of death	1 (5.6)
Any AE leading to discontinuation of any treatment	2 (11.1)
Any SAE, n (%)	6 (33.3)
Any SAE possibly related to any study treatment*	0
Any Grade 3 / 4 SAE	3 (16.7)
SAE leading to discontinuation of any treatment	2 (11.1)
Any immune-mediated AE†, n (%)	4 (22.2)
Any infusion related AE, n (%)	1 (5.6)
Hypersensitivity / anaphylactic reactions AE, n (%)	0

	D + Gem + Cis (n=18)
ORR‡, % (95% CI)§	44.4 (21.53, 69.24)
Complete response	0
Partial response	8 (44.4)
Stable disease	8 (44.4)

*Investigator assessed. †Immune mediated AEs are identified from AEs of special interest and adverse events of possible interest using a programmatic approach. ‡Responses exclude unconfirmed responses. §95% CI calculated using the binomial exact method (Clopper-Pearson). RECIST version 1.1 Response Evaluation Criteria in Solid Tumours version 1.1. All other treatment groups had n=0 or n=2 (D + G) for ECOG PS 2 data.
AE, adverse event; Cis, cisplatin (NIMP); CI, confidence interval; D, durvalumab (IMP); ECOG, Eastern Cooperative Oncology Group; Gem, gemcitabine (NIMP); IMP, investigational medicinal product; ITT, intention to treat; NIMP, Non-IMP; ORR, objective response rate; PRAE, possibly related adverse event; PS, performance status;

Dr Do-Youn Oh

Data cut-off: 7 Aug 2024

ESMO

TOURMALINE GLOBAL POPULATION; **CisGemDurva PS2**
Oh et al ESMO-Asia 2025

Table 3. Summary of Safety Data in the Safety Analysis Set.

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.

Table 2. Tumor Response in the Full Analysis Set.*

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)

TOPAZ WHOLE POPULATION **CisGemDurva PS0-1**
Oh et al NEJM Evidence 2022

Hospital Universitario Fundación Jiménez Díaz
Grupo quirónsalud
Oncohealth Institute

Oh et al ESMO-Asia 2025; Oh et al NEJM Evidence 2022

IIS FJD Instituto de Investigación Sanitaria Fundación Jiménez Díaz
UAM Universidad Autónoma de Madrid

TOURMALINE – Asian Population

Conclusions

- In participants from Asia, the safety profiles of durvalumab in combination with seven different gemcitabine-based chemotherapy regimens were manageable
  - Safety results were comparable to those reported for the TOPAZ-1 study
- Interim ORR in the Asian subgroup is comparable with the ORR observed in the durvalumab plus gemcitabine and cisplatin arm in TOPAZ-1
- The overall survival analysis is pending and will be presented at a future congress

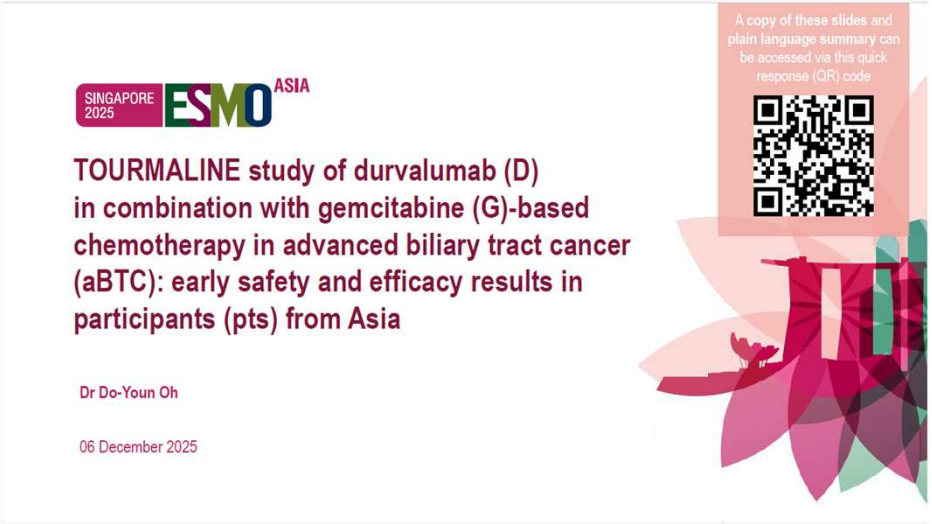
ORR, objective response rate.

A copy of these slides and plain language summary can be accessed via this quick response (QR) code

Dr Do-Youn Oh

TOURMALINE – Asian Population

- My take home message!

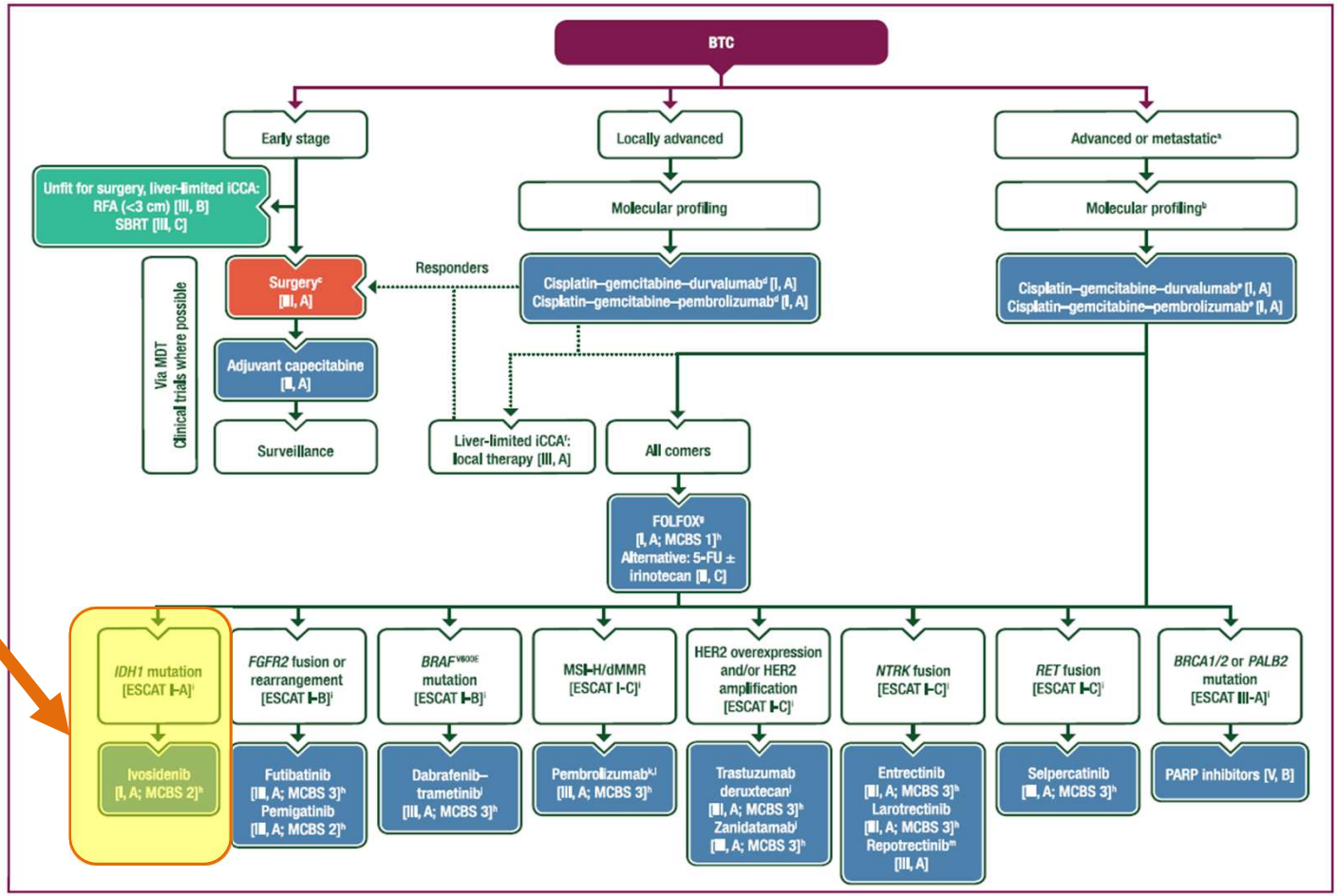


- Doublet better than monotherapy
- CisGemDruva is feasible in PS2!
- Important due to approval status of Durvalumab in many countries (limited to this chemo backbone)

Personal opinion- Dr Angela Lamarca; based on data from Oh et al ESMO-Asia 2025

BTC – ESMO GUIDELINES eUpdate 2024 - SPANISH REALITY

CURRENT RESTRICTIONS

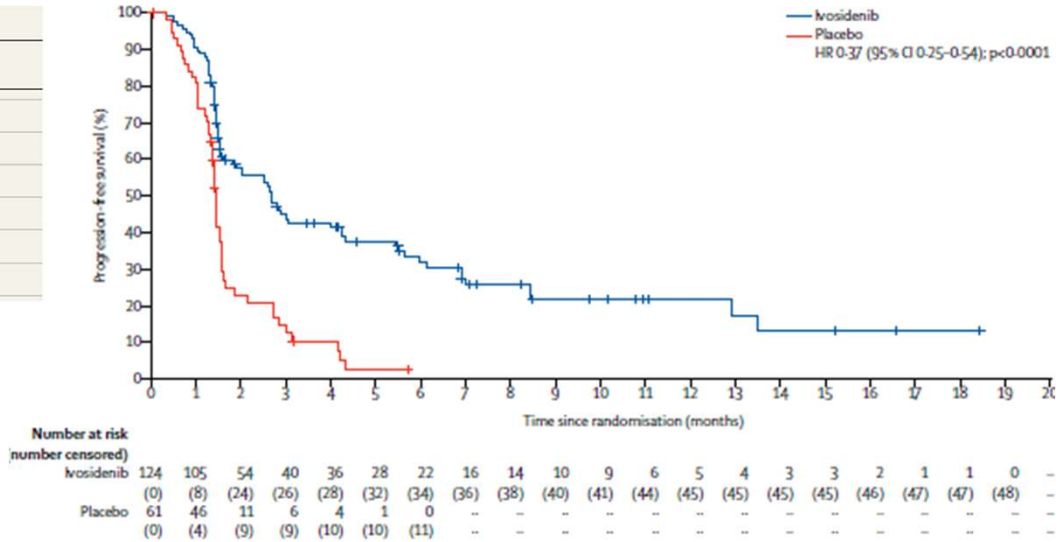


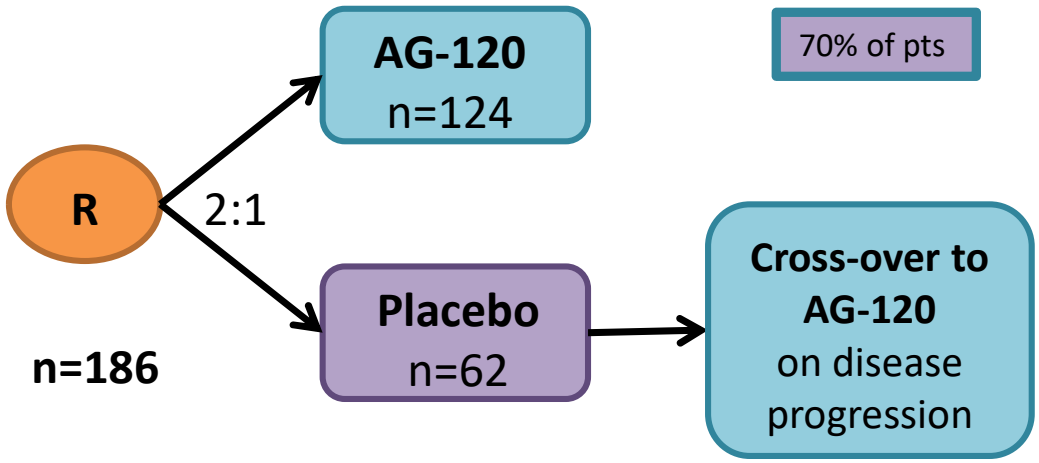
Vogel ESMO Open 2024

Targeting IDH-1 in CCA: ClarIDHy

Phase III study, second/third-line, placebo-controlled (ClarIDHy) [NCT02989857]

Characteristic	Patients, No. (%) Ivosidenib (n = 126)	Placebo (n = 61)
IDH1 mutation		
R132C	86 (68)	45 (74)
R132L	21 (17)	7 (11)
R132G	17 (13)	6 (10)
R132S	2 (2)	1 (2)
R132H	0	2 (3)





70% of pts

- mPFS (months): 2.7 (Ivosidenib) vs 1.4 (placebo); HR 0.37 (95% CI 0.25-0.54)
  - 6 months PFS rate: 32% vs 0%;
  - 12 months PFS rate: 22% vs 0%
- OS data update 2021:
  - mOS (months; adjusted for cross-over): 10.3 vs 5.1 months (HR = 0.49; 95% CI 0.34–0.70; p < 0.0001)
  - mOS (months; unadjusted for cross-over): 10.3 vs 7.5 months (HR = 0.79; 95% CI 0.56–1.12; one-sided p = 0.093)

AG-120 (Ivosidenib) is a first-in-class, potent, oral inhibitor of the mutant IDH1 enzyme

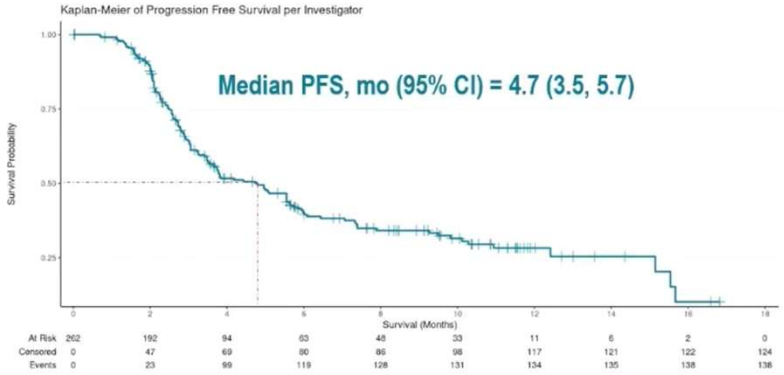
Abou-Alfa et al Lancet Oncol 2020; Zhu Jama Oncol 2021

ProvIDHe – Phase 3b - Ivosidenib for mIDH1-CCA

- Efficacy data – ESMO GI 2025

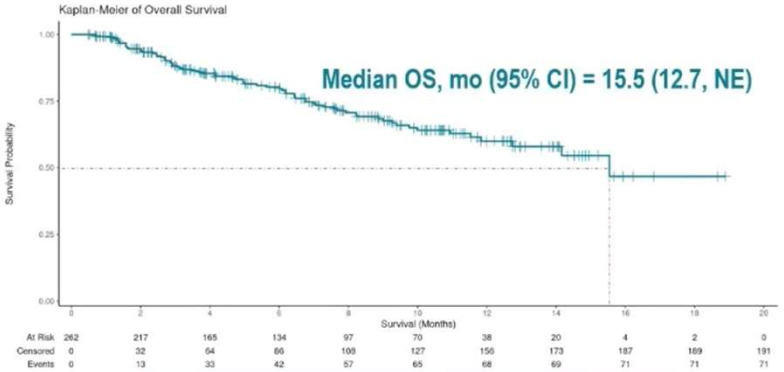
Efficacy results

in the Full Analysis Set (N = 262)



	N = 262
Progression-Free Survival (months) [1]	
Median (95% CI) *[2]*	4.7 (3.5, 5.7)
Kaplan-Meier PFS Rate (%) [3]	
3 months	64.2
6 months	40.1
12 months	28.2

Percentages are based on N.
[1] Progression free survival (PFS) = (Earliest Date of PD or Death – Enrollment Date + 1) / 30.4375.
[2] Median estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] Based on Survival Distribution Function estimates from product-limit method.



	N = 262
Overall Survival (months) [1]	
Median (95% CI) *[2]*	15.5 (12.7, NE)
Kaplan-Meier Survival Rate (%) [3]	
3 months	88.3
6 months	80.3
12 months	60.0

Percentages are based on N.
[1] Overall survival (OS) = (Death – Enrollment Date + 1) / 30.4375.
[2] Median estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] Based on Survival Distribution Function estimates from product-limit method.

John Bridgewater, MD, PhD

Bridgewater et al. ESMO GI 2025

ProvIDHe – Phase 3b - Ivosidenib for mIDH1-CCA

- Efficacy data – ESMO GI 2025

Best Overall Response per Investigator

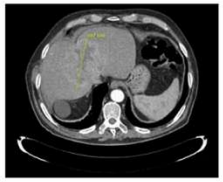
	N = 262
Best Overall Response, n (%)[1]	
Complete Response (CR)	0
Partial Response (PR)	15 (5.7)
Stable Disease (SD)	120 (45.8)
Progressive Disease (PD)	62 (23.7)
Objective Response Rate (CR or PR), n (%)	**15 (5.7)**
95% CI of Response Rate [2]	(3.2, 9.3)
Duration of Response (months) [3]	**N= 15**
Median (95% CI)	10.1 (3.0, NE)
Disease Control Rate (CR+PR+SD), n (%)	
	135 (51.5)

Percentages are based on N.
[1] Patients who did not achieve CR, PR, SD, PD are excluded from Best Overall Response summary as they are considered to not have achieved a best response.
[2] CI: confidence interval. CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method
[3] Duration of Response = (Earliest Date of PD or Death – Date of First CR or PR + 1) / 30.4375.

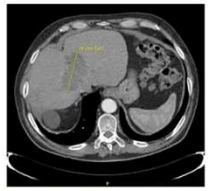
John Bridgewater, MD, PhD

PR per RECIST

(Decrease from 102 to 78 mm, CT scan showed a complete disappearance of the arterial phase wash-in, consistent with complete necrosis of the lesion)



October 2023



January 2024

Images courtesy of Dr Andrea Casadei-Gardini

Conclusion

- ✓ This interim analysis focused on **preliminary efficacy outcomes** of patients enrolled in the **ProvIDHe study** encompassing the largest cohort of patients with m*IDH1* CCA treated in a real-world setting.
- ✓ In total, **262 patients with m*IDH1* CCA** were included in the Full Analysis Set. The **median PFS** was **4.7 (3.5, 5.7) months** and the **median OS 15.5 (12.7, NE) months**.
- ✓ These findings **corroborate the efficacy observed in the ClarIDHy** trial, reinforcing the therapeutic potential of ivosidenib.
- ✓ The study is still ongoing, and future analyses will consolidate these results.

John Bridgewater, MD, PhD

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Bridgewater et al. ESMO GI 2025

Current Ivosidenib funding approval in Spain

MINISTERIO DE SANIDAD

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MIENTAS DE SIBILIDAD

Consumo de medicamentos

Información dirigida a la industria

Principio activo o asociación*	IVOSIDENIB

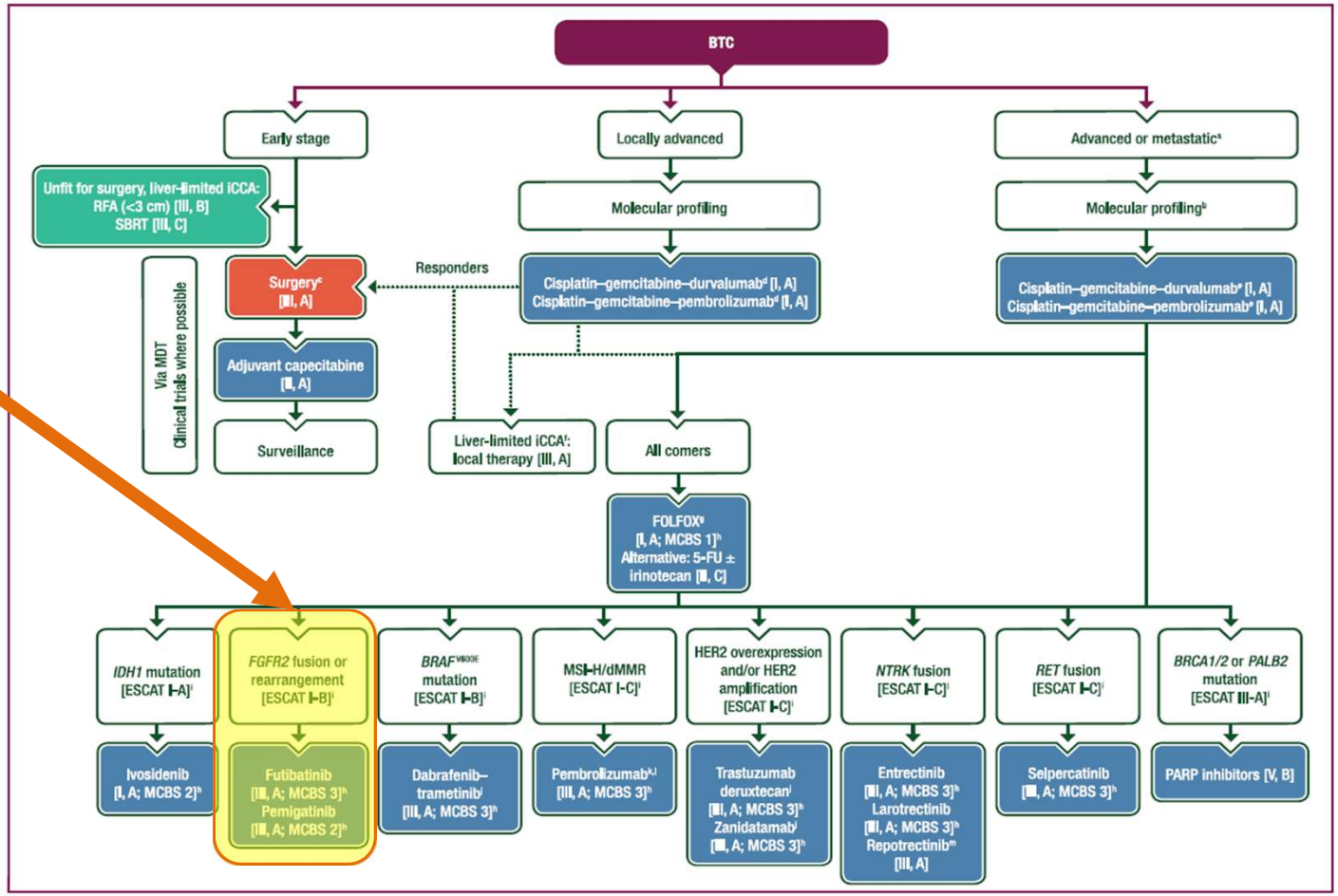
Indicación autorizada	Situación expediente indicación	Resolución expediente de financiación indicación
Tibsovo en monoterapia está indicado para el tratamiento de pacientes adultos con colangiocarcinoma localmente avanzado o metastásico con mutación IDH1 R132 que hayan recibido al menos una línea previa de tratamiento sistémico (ver sección 5.1).	Resuelto	Sí, con restricción a la indicación autorizada: Se financia en monoterapia para el tratamiento de pacientes adultos con colangiocarcinoma localmente avanzado o metastásico con mutación IDH1 R132 que hayan recibido al menos una línea previa de tratamiento sistémico y que no sean candidatos a FOLFOX.

- Residual neuropathy, prior myelosuppression…
- Not evidence based restriction

https://www.sanidad.gob.es/profesionales/medicamentos.do?metodo=verDetalle&cn=764181

BTC – ESMO GUIDELINES eUpdate 2024 - SPANISH REALITY

ADEQUATE NGS



Vogel ESMO Open 2024

MOLECULAR PROFILING IN BTC – FGFR2 fusions

WHY IS IT IMPORTANT NOT TO MISS FGFR2 FUSIONS IN CCA?

Pemigatinib : FIGHT-202 (phase II)

- Median follow-up: 42,9 months
- ORR 37%
- Median PFS 7 months
- Median OS 17.5 months

Futibatinib : FOENIX-CCA2 (phase II)

- Median follow-up 17.1 months
- ORR: 42%
- Median PFS 9.0 months
- Median OS 21.7 months

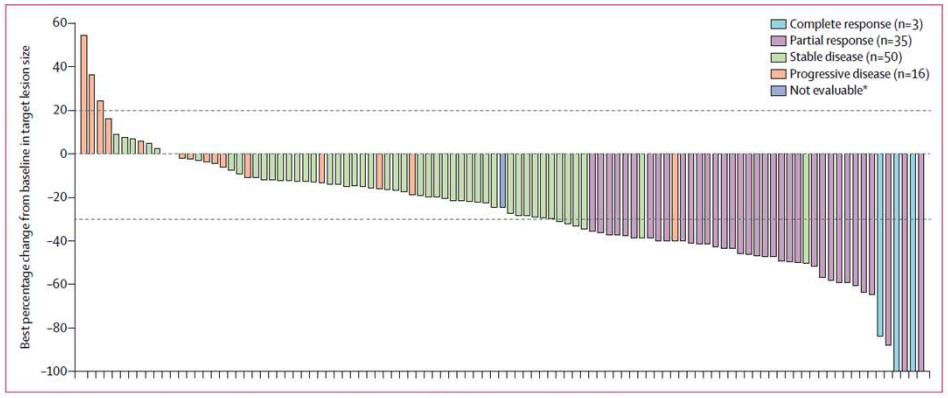
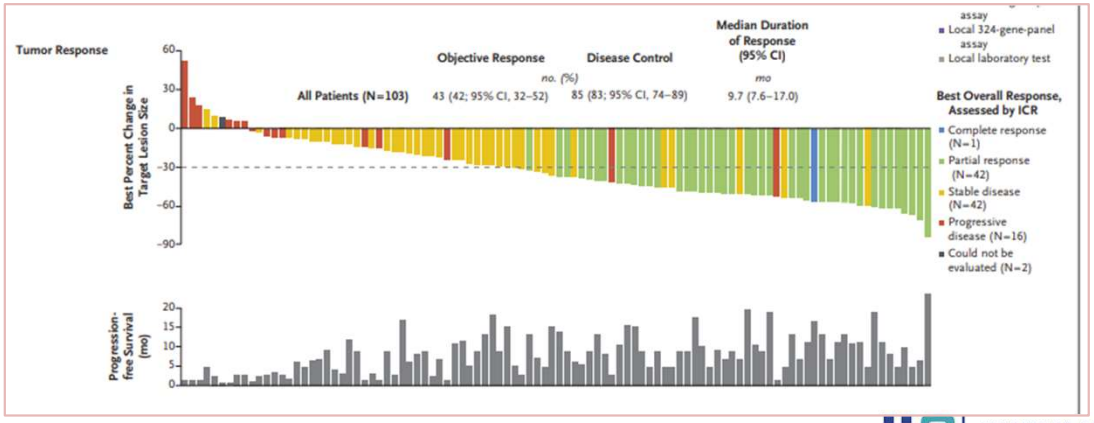


Figure 2: Best percentage change from baseline in target lesion size for individual patients with *FGFR2* fusions or rearrangements
Coloured bars indicate confirmed responses assessed by RECIST 1·1. FGFR=fibroblast growth factor receptor. RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1. *Patient had a decrease in target lesion size but was not evaluable for response using RECIST.



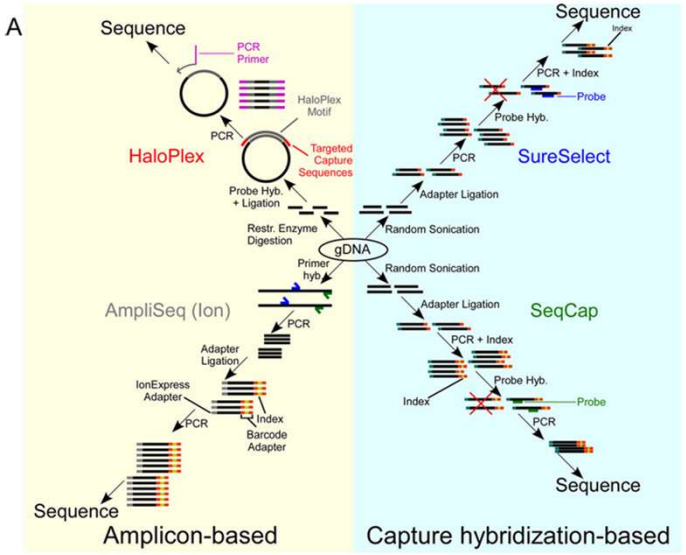
Abou-Alfa Lancet Oncol 202; Vogel ESMO-GI 2023; Goyal et al NEJM 2023

MOLECULAR PROFILING IN BTC – FGFR2 fusions

"For targeted NGS, two primary enrichment approaches, hybrid capture and amplicon-based approaches, are widely used."

"**Amplicon-based enrichment**

- Relies on multiplex PCR to amplify specific target regions using carefully designed primers.
- Is **faster, cost-effective**, and requires **minimal DNA or RNA input**, making it well-suited for targeted analyses
- Amplicon-based enrichment is advantageous for identifying known mutations
- However, amplicon-based enrichment has **notable limitations**. It depends on prior knowledge of the genetic alterations, which restricts its ability to detect unknown or novel variants, such as previously uncharacterized gene fusions. "



"**Hybrid capture method**

- Allows for the selective capture of both the target genes and their flanking sequences, enabling the detection of gene fusions in a partner-agnostic manner
- High sensitivity and specificity for variant detection, providing uniform coverage and the ability to screen for complex biomarkers such **as microsatellite instability (MSI) and tumor mutational burden (TMB)**
- Particularly suited for comprehensive genomic profiling in cancers like CCA, where structural variants such as FGFR2 fusions are clinically significant"

FGFR2 fusions, multiple partners, many unknown! Amplicon-based not fit for purpose in CCA….

Stenzinger Expert Revire of Molec Diag 2024; Samorodnitsky et al, Juman Mutation 2015

MOLECULAR PROFILING IN BTC – FGFR2 fusions

METHODS

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Evaluation of Hybridization Capture Versus Amplicon-Based Methods for Whole-Exome Sequencing

Eric Samorodnitsky,[1] Benjamin M. Jewell,[1] Raffi Hagopian,[1] Jharna Miya,[1] Michele R. Wing,[1] Ezra Lyon,[1] Senthilkumar Damodaran,[1,2] Darshna Bhatt,[1] Julie W. Reeser,[1] Jharna Datta,[1] and Sameek Roychowdhury[1,2,3]*

[1]*Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio 43210;* [2]*Division of Medical Oncology, Department of Internal Medicine, The Ohio State University, Columbus, Ohio 43210;* [3]*Department of Pharmacology, The Ohio State University, Columbus, Ohio 43210*

Communicated by Graham R. Taylor

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Published online 25 June 2015 in Wiley Online Library (www.wiley.com/humanmutation). DOI: 10.1002/humu.22825

ABSTRACT: Next-generation sequencing has aided characterization of genomic variation. While whole-genome sequencing may capture all possible mutations, whole-exome sequencing remains cost-effective and captures most phenotype-altering mutations. Initial strategies for exome enrichment utilized a hybridization-based capture approach. Recently, amplicon-based methods were designed to simplify preparation and utilize smaller DNA inputs. We evaluated two hybridization capture-based and two amplicon-based whole-exome sequencing approaches, utilizing both Illumina and Ion Torrent sequencers, comparing on-target alignment, uniformity, and variant calling. While the amplicon methods had higher on-target rates, the hybridization capture-based approaches demonstrated better uniformity. All methods identified many of the same single-nucleotide variants, but each amplicon-based method missed variants detected by the other three methods and reported additional variants discordant with all three other technologies. Many of these potential false positives or negatives appear to result from limited coverage, low variant frequency, vicinity to read starts/ends, or the need for platform-specific variant calling algorithms. All methods demonstrated effective copy-number variant calling when evaluated against a single-nucleotide polymorphism array. This study illustrates some differences between whole-exome sequencing approaches, highlights the need for selecting appropriate variant calling based on capture method, and will aid laboratories in selecting their preferred approach.

Hum Mutat 36:903–914, 2015. Published 2015 Wiley Periodicals, Inc.*

Study comparing hybrid capture with amplicon-based methods

- Hybrid capture was superior to amplicon-based enrichment regarding sequencing complexity, uniformity, and SNV and CNV detection accuracy
- Fewer false-positive and false-negative results with hybrid capture, further supporting its utility in high-quality genomic profiling
- However, hybrid capture requires larger DNA or RNA inputs and is more time-consuming and costly compared with other approaches

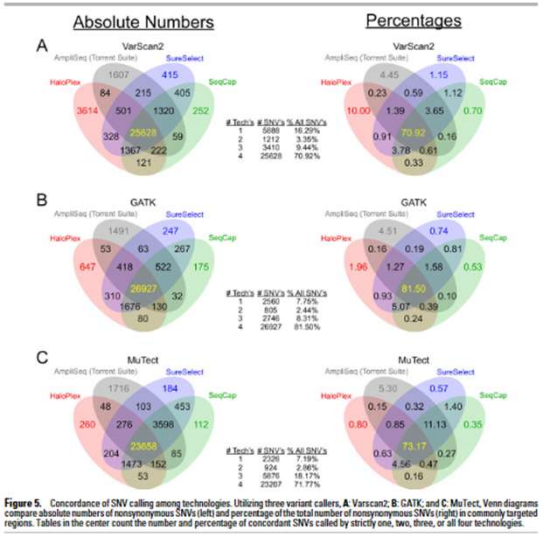


Figure 5. Concordance of SNV calling among technologies. Utilizing three variant callers, **A**: Varscan2; **B**: GATK; and **C**: MuTect, Venn diagrams compare absolute numbers of nonsynonymous SNVs (left) and percentage of the total number of nonsynonymous SNVs (right) in commonly targeted regions. Tables in the center count the number and percentage of concordant SNVs called by strictly one, two, three, or all four technologies.

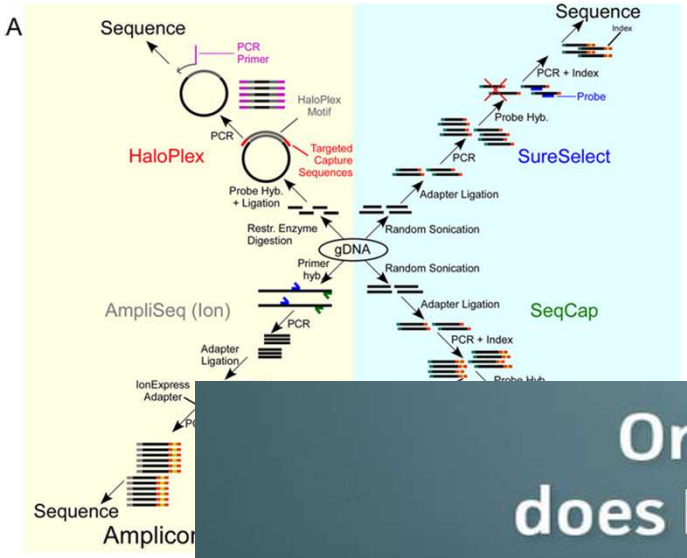
Samorodnitsky et al, Juman Mutation 2015

MOLECULAR PROFILING IN BTC – FGFR2 fusions

"For targeted NGS, two primary enrichment approaches, hybrid capture and amplicon-based approaches, are widely used."

ABSTRACT: Next-generation sequencing has aided characterization of genomic variation. While whole-genome sequencing may capture all possible mutations, whole-exome sequencing remains cost-effective and captures most phenotype-altering mutations. Initial strategies for exome enrichment utilized a hybridization-based capture approach. Recently, amplicon-based methods were designed to simplify preparation and utilize smaller DNA inputs. We evaluated two hybridization capture-based and two amplicon-based whole-exome sequencing approaches, utilizing both Illumina and Ion Torrent sequencers, comparing on-target alignment, uniformity, and variant calling. While the amplicon methods had higher on-target rates, the hybridization capture-based approaches demonstrated better uniformity. All methods identified many of the same single-nucleotide variants, but each amplicon-based method missed variants detected by the other three methods and reported additional variants discordant with all three other technologies. Many of these potential false positives or negatives appear to result from limited coverage, low variant frequency, vicinity to read starts/ends, or the need for platform-specific variant calling algorithms. All methods demonstrated effective copy-number variant calling when evaluated against a single-nucleotide polymorphism array. This study illustrates some differences between whole-exome sequencing approaches, highlights the need for selecting appropriate variant calling based on capture method, and will aid laboratories in selecting their preferred approach.

Hum Mutat 36:903–914, 2015. Published 2015 Wiley Periodicals, Inc.*



PDAC Ovarian Breast Bladder CRC CCA Lung Other BTC

Stenzinger Expert Revire of Molec Diag 2024; Samorodnitsky et al, Juman Mutation 2015

MOLECULAR PROFILING IN BTC – FGFR2 fusions

Amplicon-based enrichment

B24-17957

INFORME DE RESULTADOS DEL ESTUDIO DE SECUENCIACIÓN MASIVA OBTENIDOS CON PANEL Oncomine™ Precision Assay (ThermoFisher Scientific)

1. ¿Es la muestra adecuada para el estudio de secuenciación masiva?

Sí.

2. Variantes detectadas:

a. Alteraciones relevantes a nivel de ADN:

i. Mutaciones puntuales e inserciones/deleciones (indels):

Gen Relevante	*Transcrito de referencia*	Exón	*ADN*	*Proteína*	*Frecuencia alélica*

ii. Variación en el número de copias (CNVs):

Gen Relevante	*Transcrito de referencia*	*Nº Copias*	*Interpretación*

b. Alteraciones relevantes a nivel de ARN (Reordenamientos/fusiones):

Gen Relevante	*Transcrito de referencia*	*ID Fusión*	*Isoforma*	*Nº Lecturas*

c. Otras alteraciones a nivel de ADN:

i. Mutaciones puntuales e inserciones/deleciones (indels):

Gen	*Transcrito de rerencia*	*Exón*	*ADN*	*Proteína*	*Frecuencia alélica*

ii. Variación en el número de copias (CNVs):

Gen	*Transcrito Referencia*	*Nº Copias*	*Interpretación*
CDKN2A		0	Pérdida

d. Otras alteraciones a nivel de ARN (Reordenamientos/fusiones):

Gen	*Transcrito de referencia*	*ID Fusión*	*Isoforma*	*Nº Lecturas*

Observaciones:

Hybrid capture method

Identificación de la muestra: B24-017957 A1

Molecular

Interpretación de Resultados

Perfil mutacional obtenido:

Variantes patogénicas y probablemente patogénicas:
Fusión Génica: NM_022970.3 (FGFR2):e17::NM_001258298.2(KIAA1598):e.8 (FGFR2 TRASLOCADO)
Pérdida en homocigosis de MTAP
Pérdida en homocigosis de CDKN2A
Pérdida en heterocigosis de BAP1
BAP1 NM_004656.4 Exón c.588G>Ap.(W196*)(VAF:8,31%)

CORRECCIÓN A FECHA 12/11/2025

Error detectado tras consulta con Servicio de Soporte OncoDNA en relación al gen MTAP. Este gen MTAP presenta una copia génica en lugar de ninguna. Por tanto, se debe considerar que la pérdida de MTAP es en heterocigosis y no en homocigosis como se reportó inicialmente. El caso debe considerarse como MTAP perdido en HETEROCIGOSIS.

Carga mutacional (Tumor mutational burden, TMB):

Baja carga mutacional: 3.3 Mut/Mb (mutaciones/megabase menor a 10)

Inestabilidad de microsatélites:

No se detecta inestabilidad de microsatélites: 22.39% (inestabilidad de microsatélites en menos de un 40% de los marcadores analizados)

HRD:

GS (Genomic Scar): 40.6 (HRD POSITIVO) (Un valor mayor a 37 confiere un estado HRD positivo)

Hospital Universitario Fundación Jiménez Díaz
Grupo quirónsalud
Oncohealth Institute

IIS FJD Instituto de Investigación Sanitaria Fundación Jiménez Díaz
UAM Universidad Autónoma de Madrid

MOLECULAR PROFILING IN BTC – FGFR2 fusions

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Observaciones:

METODOLOGÍA Y ESPECIFICACIONES DEL PANEL

Caracterización molecular del tumor mediante estudio de secuenciación masiva con el panel Oncomine™ Precision Assay (ThermoFisher Scientific) utilizando el equipo Ion Torrent Genexus System. Los datos se analizan en el Torrent Suite mediante el programa Genexus Software v6.6.2.1.
LISTA DE GENES INCLUIDOS EN EL PANEL Oncomine™ Precision Assay:

- Mutaciones puntuales e inserciones/deleciones (INDELs) en 45 genes (ADN):
AKT1, AKT2, AKT3, ALK, AR, ARAF, BRAF, CDK4, CDKN2A, CHEK2, CTNNB1, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, NTRK1, NTRK2, NTRK3, PDGFRA, PIK3CA, PTEN, RAF1, RET, ROS1, SMO, TP53.

- Variaciones en el nº de copias (CNVs) en 14 genes (ADN):
ALK, AR, CD274, CDKN2A, EGFR, ERBB2, ERBB3, FGFR1, FGFR2, FGFR3, KRAS, MET, PIK3CA, PTEN.
El ensayo solo detecta pérdidas en los genes *PTEN* y *CDKN2A*; para el resto de genes se estudian amplificaciones focales.

- Reordenamientos /Fusiones intergénicas en 16 genes (ARN):
ALK, AR, BRAF, EGFR, ESR1, FGFR1, FGFR2, FGFR3, MET, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, RET, ROS1, RSPO2, RSPO3.

- Reordenamientos /Fusiones intragénicas en 3 genes:
AR, EGFR y *MET.*

Hospital Universitario Fundación Jiménez Díaz
Grupo quirónsalud
Oncohealth Institute

Hybrid capture method

Identificación de la muestra: B24-017957 A1

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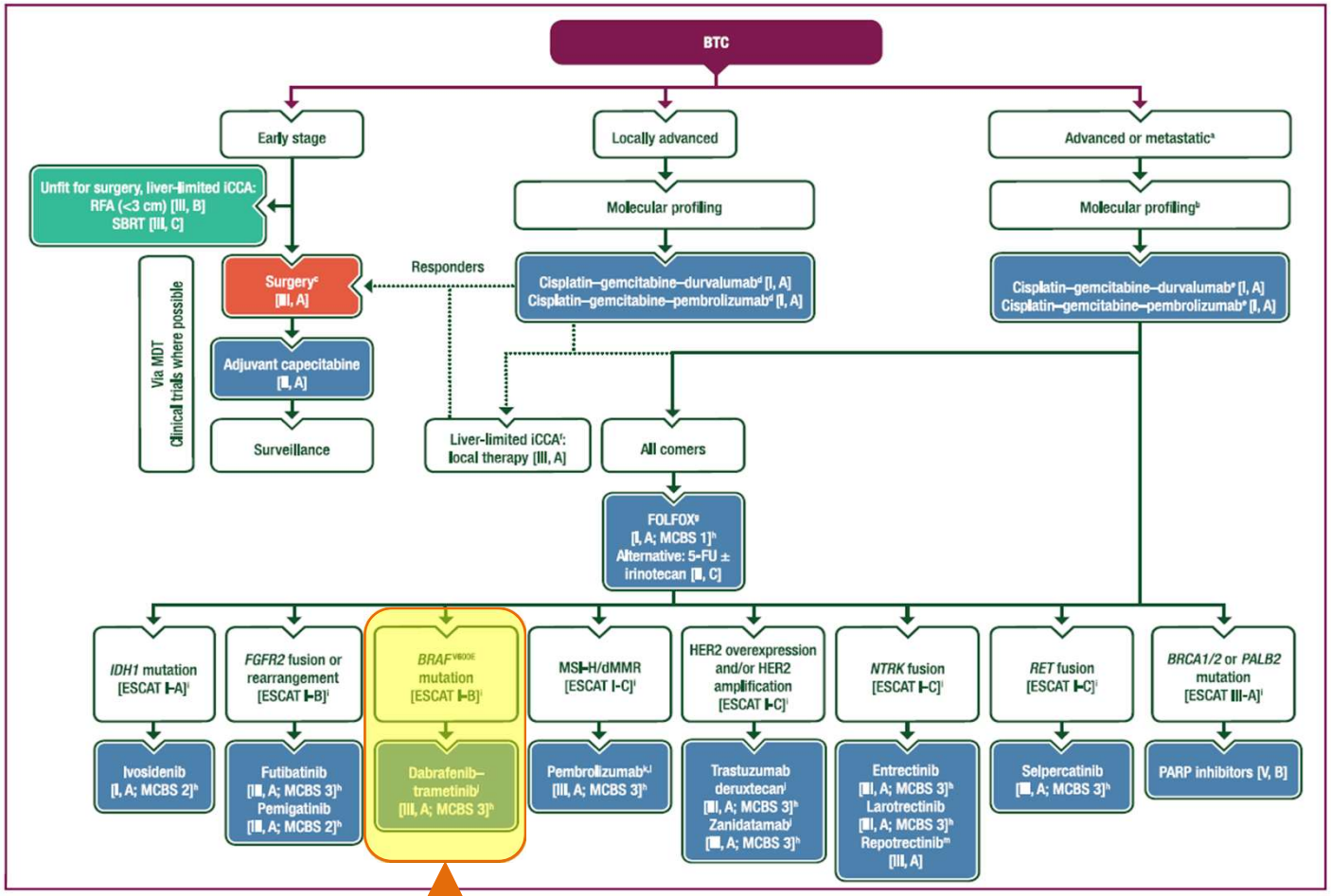
Molecular

Metodología

Determinación por secuenciación masiva dirigida estudios del estado mutacional de regiones específicas de 638 genes con OncoDEEP® Kit DNA & RNA (CE-IVD) (OncoDNA, Gosselies, Bélgica) mediante Illumina NextSeq 500 (Illumina, San Diego, CA) a partir de 30-50 ng de ADN y ARN tumoral obtenido de muestras de tejido tumoral fijado en formol y embebido en parafina. El panel cubre las regiones exónicas y regiones hotspot de 638 genes, con gran relevancia en tumores sólidos, permitiendo identificar mutaciones puntuales, inserciones, deleciones, alteración en el número de copias, pérdidas de heterocigosidad y traslocaciones génicas, además de inestabilidad de microsatélites, carga mutacional (TMB) y HRD.
El análisis e interpretación de los resultados se realiza mediante el Software OncoKDM™ y posterior validación de los datos conforme a los criterios establecidos, considerando una cobertura media de las regiones de al menos 350x y reportando variantes con un límite de detección del 5%* para alteraciones puntuales. La técnica empleada presenta limitaciones inherentes al propio ensayo, incluyendo, de manera ocasional, baja cobertura de algunas regiones estudiadas. La clasificación e informe de los resultados obtenidos están basados en las guías de estandarización de la Asociación de Patología Molecular y el Colegio Americano de Patólogos (AMP y CAP) (Jennings et al, 2017), y la guía de clasificación de accionabilidad clínica de variantes (ESCAT) de la Sociedad Europea de Oncología Médica (ESMO) (Mateo J, et al 2018).
**Sensibilidad y valor predictivo positivo superior al 99%. Estos límites de detección se establecen para muestras que presenten un valor de DV900 mayor a 49.5% y 30ng para DNA y DV200 mayor a 60% y 50ng para RNA con más de un 30% de porcentaje tumoral y como mínimo 20 millones de lecturas por muestra.*

IIS FJD INSTITUTO DE INVESTIGACIÓN SANITARIA FUNDACIÓN JIMÉNEZ DÍAZ
UAM Universidad Autónoma de Madrid

BTC – ESMO GUIDELINES eUpdate 2024 - SPANISH REALITY



NO ACCESS

Vogel ESMO Open 2024

Dabrafenib and trametinib: mBRAF ^{V600E} BTC

- **Phase II study; n=43**

- ORR 51% (95% CI 36-67) – investigator assessed
- **ORR 47% (95% CI 31-62)** – central review
- Duration of response: 9 months (95% CI 6-14)
- PFS: 9 months (95% CI 5-10)
- OS: 14 months (95% CI 10-33)

➢ **Promising activity and manageable safety profile.**

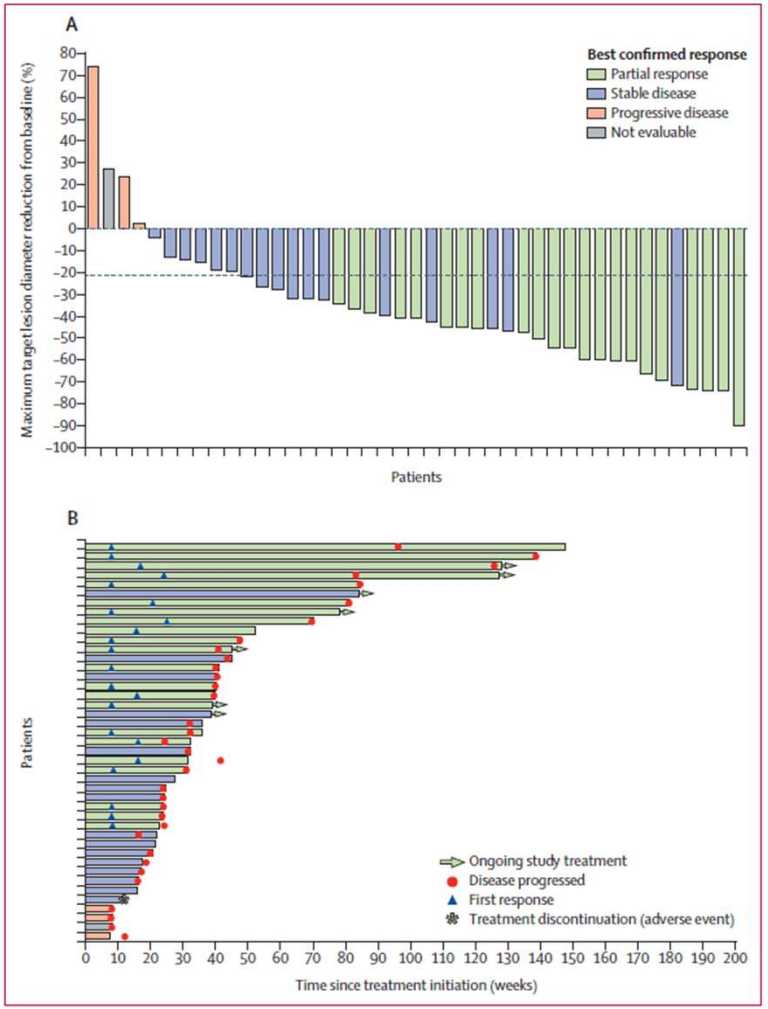


Figure 1: Change in target lesion diameters and treatment duration in the intention-to-treat evaluable population (n=43)

Subbiah et al, LancetOncol 2020

Dabrafenib and trametinib: mBRAF ^{V600E} BTC

FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation

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On June 22, 2022, the Food and Drug Administration granted accelerated approval to dabrafenib (Tafinlar, Novartis) in combination with trametinib (Mekinist, Novartis) for the treatment of adult and pediatric patients ≥ 6 years of age with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. Dabrafenib in combination with trametinib is not indicated for patients with colorectal cancer because of

Content current as of:
06/23/2022

Regulated Product(s)
Drugs

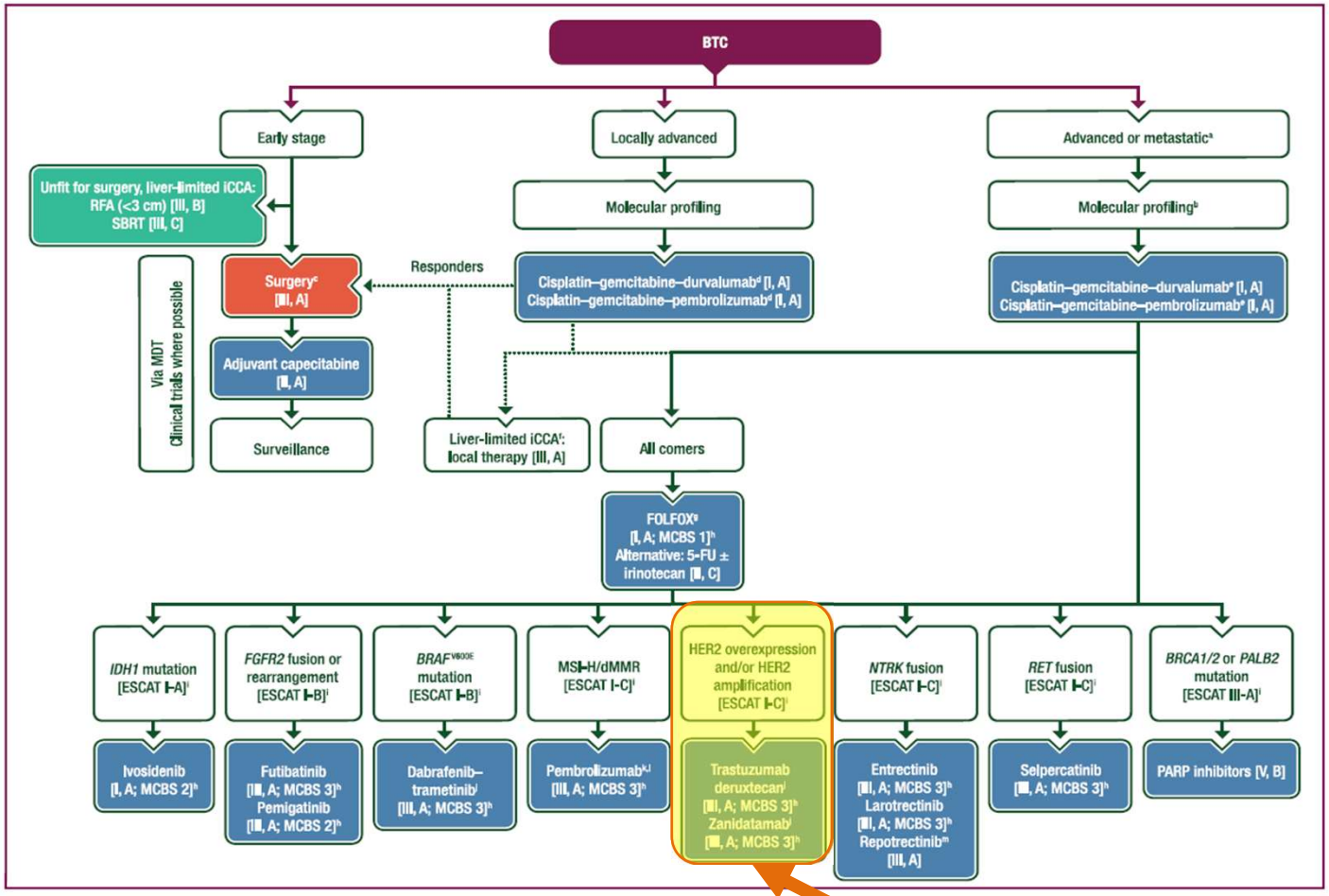
Tumour agnostic approval (FDA)….
BUT
NOT EMA approved…

Oncohealth Institute

IIS FJD Instituto de Investigación Sanitaria Fundación Jiménez Díaz

UAM Universidad Autónoma de Madrid

BTC – ESMO GUIDELINES eUpdate 2024 - SPANISH REALITY

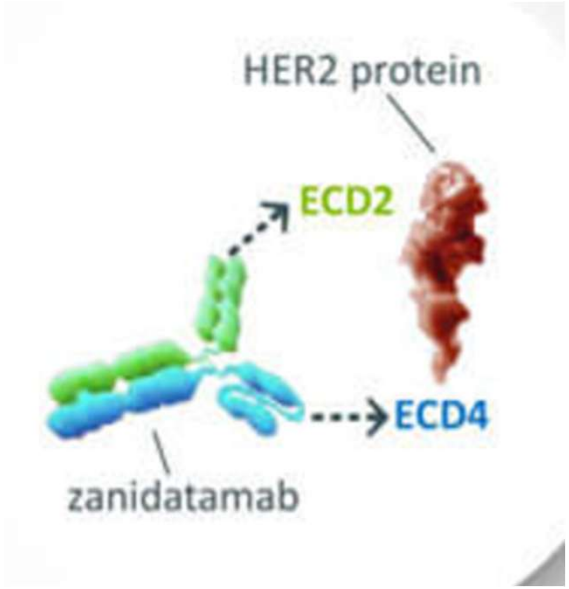


Vogel ESMO Open 2024

Targeting HER-2 – novel approaches

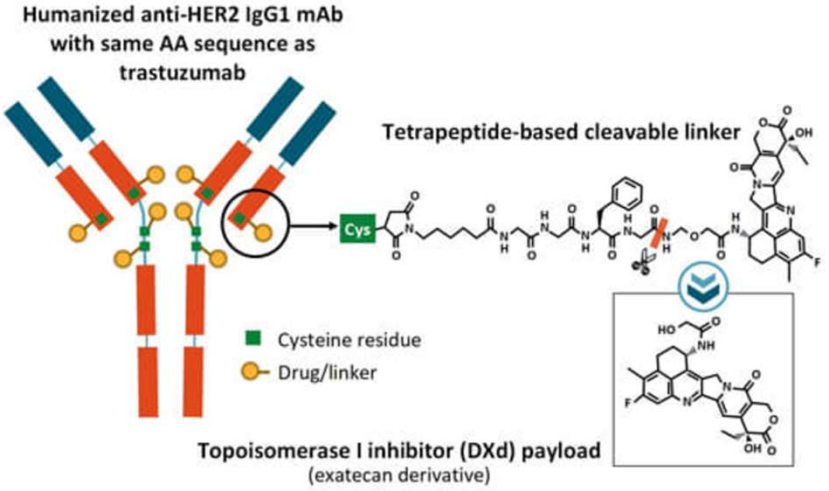
Zanidatamab

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



Trastuzumab deruxtecan (T-DXd; DS-8201)

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



Targeting HER-2 – novel approaches

Zanidatamab

FDA
EMA

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

Table 2. Disease Response in Patients With HER2-Positive BTC (Cohort 1)

Disease Response Endpoints[a]	n=80
cORR,[b] n (%) [95% CI]	33 (41.3) [30.4, 52.8]
Complete response, n (%)	2 (2.5)
Partial response, n (%)	31 (38.8)
Stable disease, n (%)	22 (27.5)
Progressive disease, n (%)	24 (30.0)
DCR,[c] n (%) [95% CI]	55 (68.8) [57.4, 78.7]
CBR,[d] n (%) [95% CI]	38 (47.5) [36.2, 59.0]

[a]Efficacy analysis (i.e., all patients in Cohort 1 who received any dose of zanidatamab) per ICR. [b]One patient was not evaluable. [c]Best overall response of stable disease or confirmed complete response or partial response. [d]Stable disease >=24 weeks or confirmed best overall response of complete response or partial response.

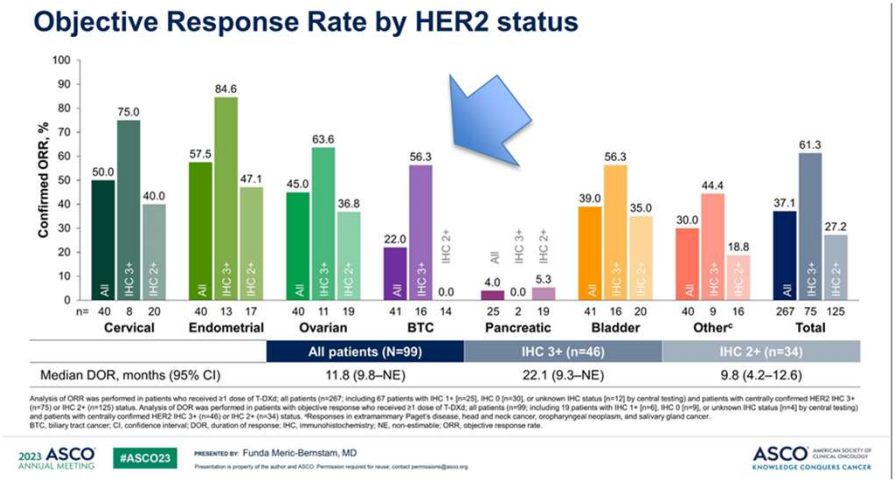
BTC, biliary tract cancer; CI, confidence interval; CBR, clinical benefit rate; cORR, confirmed objective response rate; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; ICR, independent central review.

- With additional follow-up, the cORR (41.3%) and the disease control rate (68.8%) were maintained
  - One additional patient achieved a complete response (n=2; 2.5%)
  - Although the trial was not designed to detect treatment effects by HER2 status, in a pre-planned subgroup analysis of cORR by HER2 expression, responses were observed in patients with IHC 3+ tumors (cORR: 51.6%) and IHC 2+ tumors (cORR: 5.6%)

Trastuzumab deruxtecan (T-DXd; DS-8201)

FDA
(Tumour Agnostic)

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



Pant ASCO 2024; Meric-Bernstam ASCO 2023

Targeting HER-2 – novel approaches

Zanidatamab

FDA
EMA

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FDA and EMA approved but funding decision pending in Spain

Early access programme available (hospital-funded)

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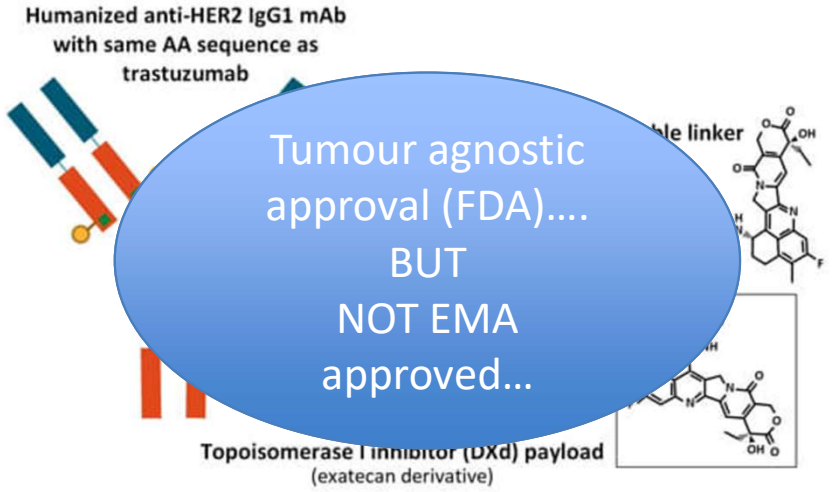

Tumour agnostic approval (FDA)….
BUT
NOT EMA approved…

Hospital Fundación Jiménez Díaz Grupo quirónsalud

Oncohealth Institute

IIS FJD Instituto de Investigación Sanitaria Fundación Jiménez Díaz

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TAKE HOME MESSAGES

- **Early stage**
  - Adjuvant treatment not the best
  - Patients are diagnosed late- research for early diagnosis is a MUST
- **Advanced disease – 1st line**
  - Molecular testing: IHC (HEr2), NGS (others) ASAP in advanced disease; good use of tissue
  - CisGem + durvalumab or pembrolizmunab is SOC – should be accessible to all
- **Advanced disease: subsequent lines**
  - Targeted preferable to chemotherapy if targetable alterations are identified
  - FOLFOX / Irinotecan-based modest activity
  - Access limited for some therapies
  - Adequate testing for specific targets – fFGFR2, MTAP?
  - Clinical trials can be as good as approved therapies

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Targeting HER-2 – novel approaches – ongoing trials

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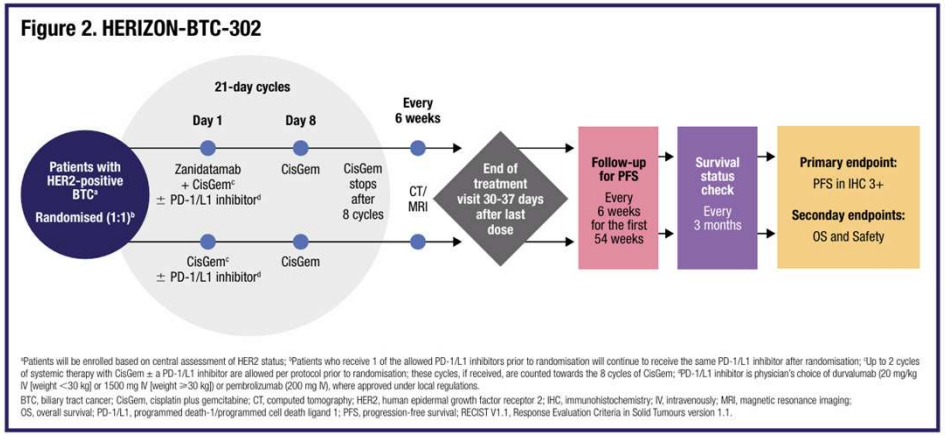

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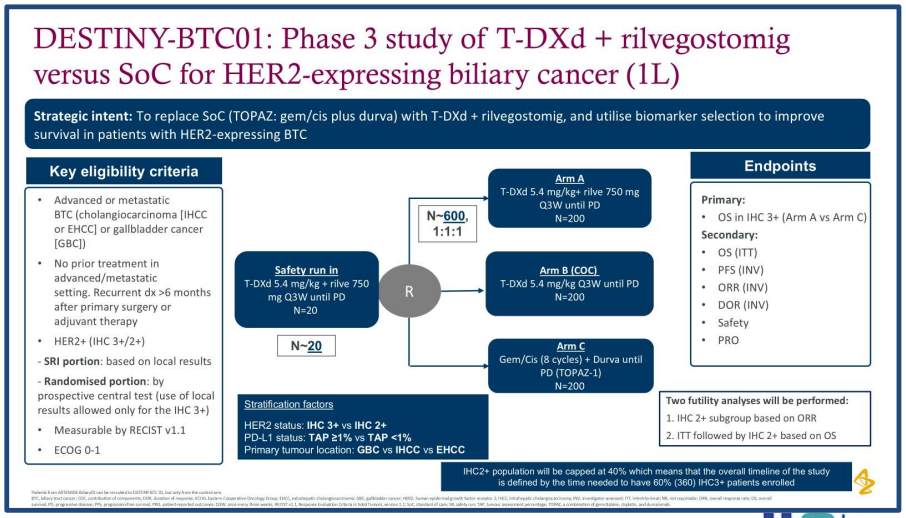


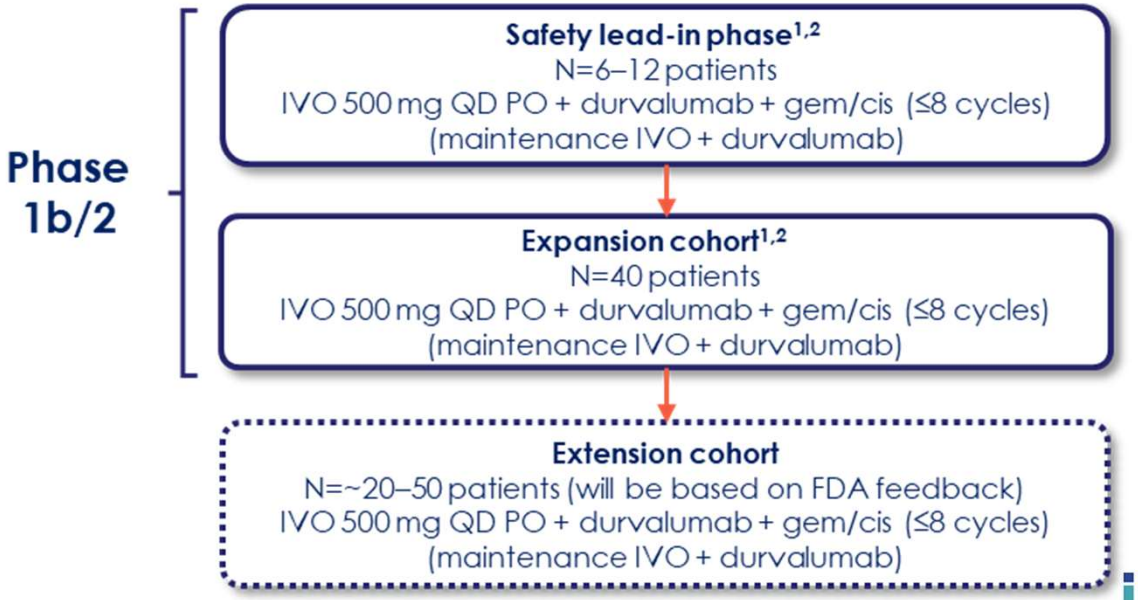
Macarulla et al, ESMO 2024;

Ivosidenib in the first-line setting – ongoing trial

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



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

FGFR inhibitors in CCA: Futibatinib - ongoing

Study of Futibatinib in Patients With Advanced Cholangiocarcinoma With FGFR2 Fusion or Rearrangement (FOENIX-CCA4)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT05727176

Recruitment Status : Recruiting
First Posted : February 14, 2023
Last Update Posted : June 15, 2023

See **Contacts and Locations**

Sponsor:
Taiho Oncology, Inc.

Information provided by (Responsible Party):
Taiho Oncology, Inc.

Study Description Go to

Brief Summary:
This is an open-label, multinational, randomized Phase 2 study confirming the clinical benefit of 20 mg futibatinib and evaluating the safety and efficacy of 16 mg futibatinib in previously treated CCA harboring FGFR2 gene fusions and other rearrangements.

Condition or disease	Intervention/treatment	Phase
Advanced Cholangiocarcinoma FGFR2 Fusions Gene Rearrangement	Drug: TAS-120	Phase 2

Expanded Access: An investigational treatment associated with this study has been approved for sale to the public. More info ...

Detailed Description:

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- Patients will receive futibatinib at an oral dose of 16 mg, administered daily (QD) on every day of a 21-day cycle.
- Patients will receive futibatinib at an oral dose of 20 mg, administered daily (QD) on every day of a 21-day cycle.

Patients may continue to receive continuous futibatinib until documentation of progressive disease (PD) per RECIST 1.1, or until other withdrawal criteria are met, whichever comes first.

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	120 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Phase 2 Study of **Futibatinib** 20 mg and 16 mg in Patients With Advanced Cholangiocarcinoma With FGFR2 Fusions or Rearrangements
Actual Study Start Date :	May 12, 2023
Estimated Primary Completion Date :	June 2025
Estimated Study Completion Date :	June 2026

Primary end-point: ORR

Hospital Universitario Fundación Jiménez Díaz Grupo quirónsalud

Oncohealth Institute

Clinicaltrials.gov

de Madrid

FGFR inhibitors in CCA: Tinengotinib - ongoing

- FIRST-308 (phase III)

Randomised phase III
TT420 vs physician choice after progression to prior iFGFR

Drug Candidate	Target/ Mechanism (MOA)	Indication	Mono/ Combo	Status	Commercial rights	Partner
		CCA[1] FGFR2 acquired resistance	Mono	US	Global	N/A
		CCA[1] FGFR2 primary resistanc	Mono	US		
		CCA[1] Non-FGFR	Mono	US		
TT-00420 ★	Unique MTK(FGFR mut ,Aurora A/B,VEGFRs,JAK 1/2,CSF1R)	TNBC[2]	Mono	US/China	Global	N/A
			Combo with Chemo	US/China		
		BTC	Combo with PD-L1	China	Global	Roche Collaboration
		Solid tumors[7]	Mono	US/China	Global	N/A

U.S. National Library of Medicine
ClinicalTrials.gov

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Home > Search Results > Study Record Detail

Save this study

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

of this study is the responsibility of the study sponsor and investigators. Listing a n evaluated by the U.S. Federal Government. Know the risks and potential alk to your health care provider before participating. Read our disclaimer for

ClinicalTrials.gov Identifier: NCT05948475

Recruitment Status : Not yet recruiting
First Posted : July 17, 2023
Last Update Posted : July 17, 2023
See Contacts and Locations

Study Description Go to

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

Condition or disease	Intervention/treatment	Phase
Cholangiocarcinoma	Drug: Tinengotinib 8 mg Drug: Tinengotinib 10 mg Drug: Physician's Choice	Phase 3

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.

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	200 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
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
Estimated Study Start Date :	September 2023
Estimated Primary Completion Date :	May 2026

Transthera website; Clinicaltrials.gov

BTC – ESMO GUIDELINES eUpdate 2024 - SPANISH REALITY

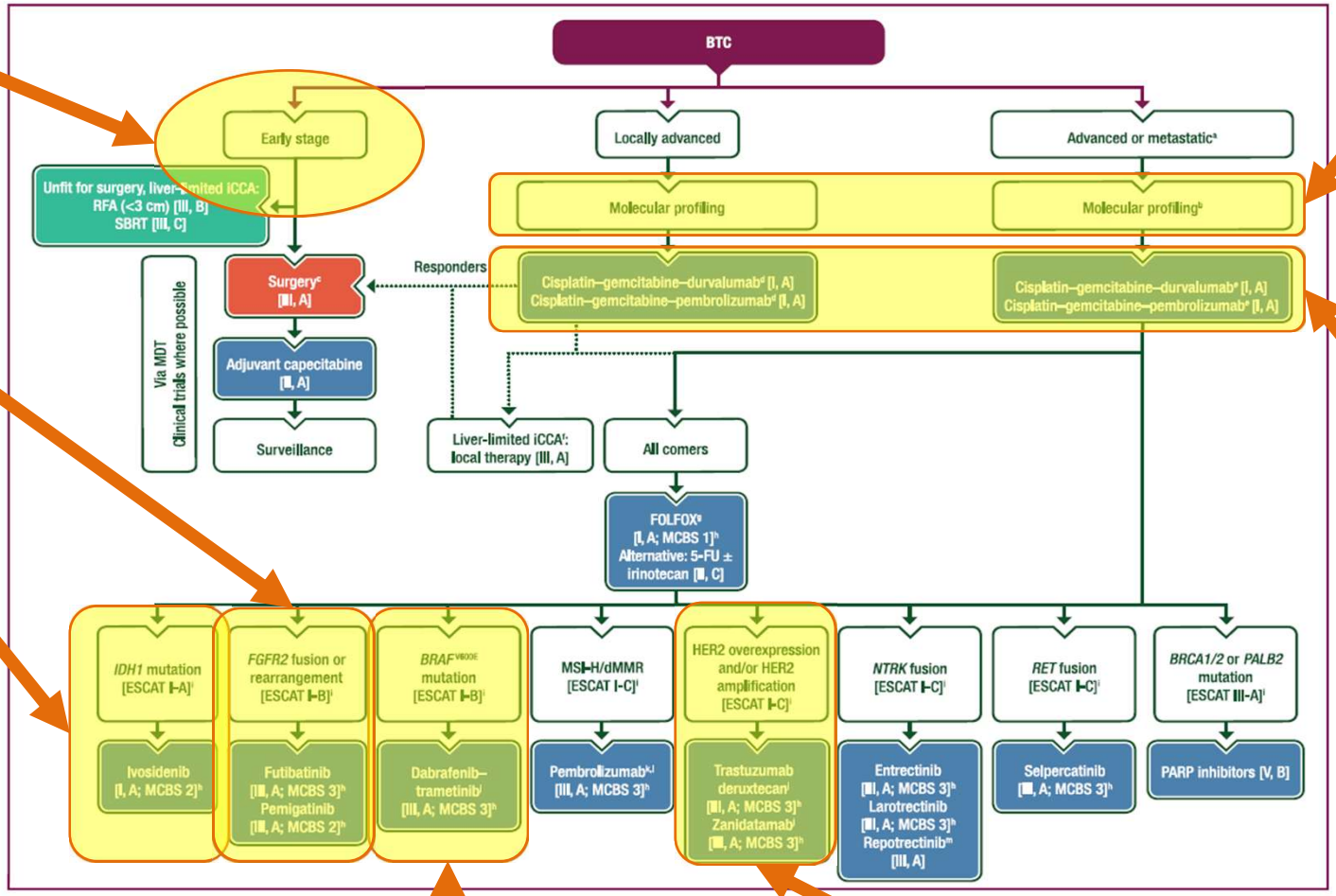
EARLY DX

ADEQUATE NGS

CURRENT RESTRICTIONS

MOLECULAR PROFILING

INEQUITY IN ACCESS

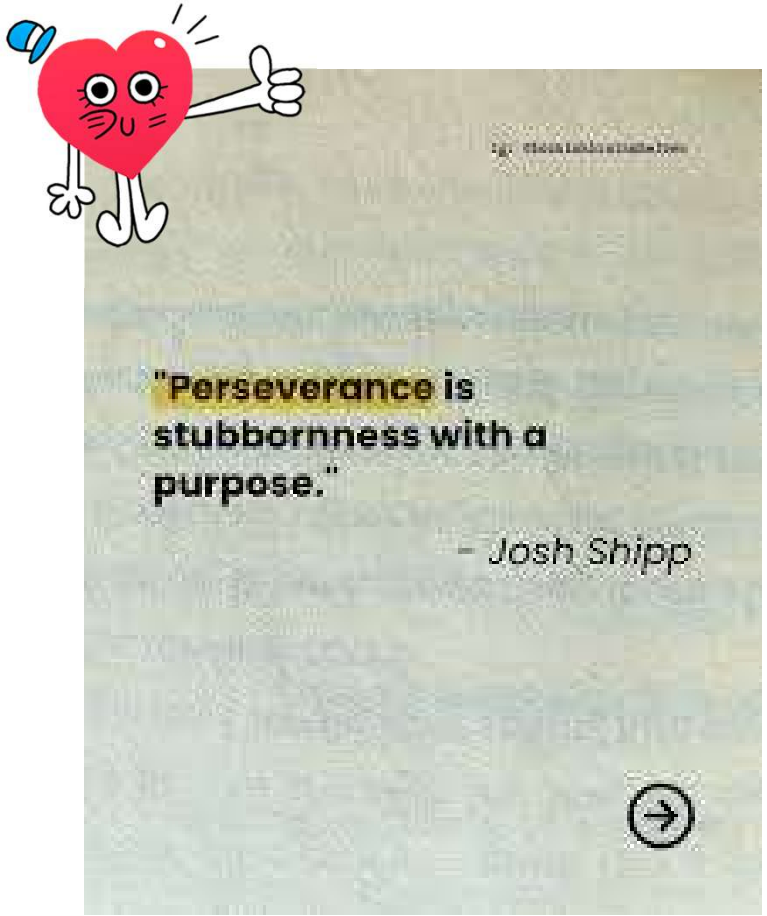


NO ACCESS

FUNDING AWAITED

Vogel ESMO Open 2024

We will make it work



"Our patients deserve better"

Dr John Bridgewater

¿Y yo, qué puedo hacer?

ATUVIBI

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Grupo quirónsalud
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European Network for the Study of Cholangiocarcinoma (ENS-CCA)

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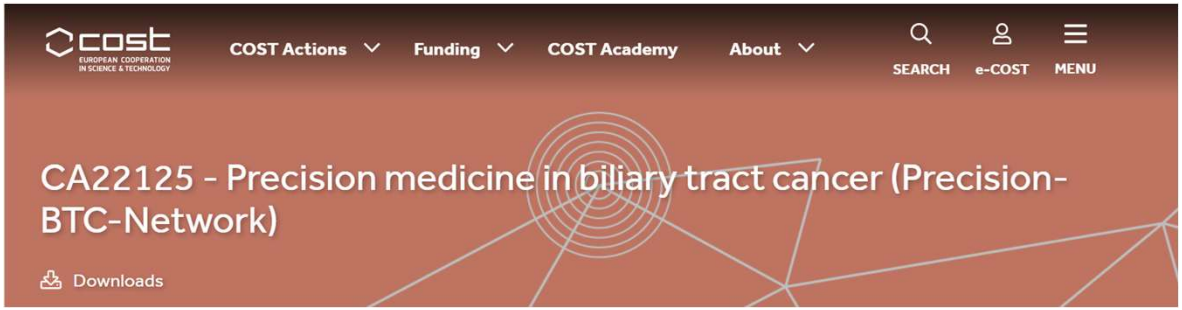
¿Y yo, qué puedo hacer?

Join our COST-Action: Precision BTC



Working Groups

Number	Title	Leader
1	Identification of epidemiological heterogeneity in Europe to apply precision prevention	Dr Vincenzo CARDINALE
2	Personalised early detection of BTC	Dr Pedro RODRIGUES
3	Personalisation of treatment for patients with BTC	Dr Anna SABOROWSKI
4	Patient-centric support management	Prof Ana LLEO
5	Artificial intelligence	Prof Jesper B ANDERSEN
6	Drug development using preclinical models	Dr Monique VERSTEGEN

WG	Year	Deliverables
WG1	Y1	✓ Establishing a pan-European registry for patients with all subtypes of BTC
	Y2-4	✓ Publications derived from data analyses from the pan-European registry database of BTC
	Y4	✓ Surveillance guidelines in patients at risk of developing BTC
WG2	Y1	✓ Guidelines on SOPs and DQM for collection and storage of BTC biological sample
	Y2-4	✓ Scientific publications on the diagnostic performance of different types of biomarkers in BTC
	Y4	✓ Scientific publication on the association of based-image biomarkers and histomorphology in biliary cancers
	Y4	✓ Publication of a Consensus on MRI in BTC
WG3	Y1	✓ Systematic review on the gaps of delivering precision oncology in biliary cancers
	Y2	✓ Publication of a retrospective analysis of the clinical outcome of biliary cancers, including GBC and AC
	Y3-4	✓ Publication of the optimization of biomarker development for patient stratification and development of novel strategies for personalised treatment in BTC
WG4	Y1-2	✓ Publication derived from surveys to stakeholders about specific needs in personalized management of patients with BTC
	Y1,3	✓ Patient education sheets and videos in different languages with useful information for patients/caregivers (disease, treatments and their potential adverse events, etc)
	Y4	✓ Publication of oncology nursing care in BTC patients
WG5	Y1-2	✓ Review on challenges of artificial intelligence to assess the reliability of models, provide clinical products and in holistic data integration
	Y3-4	✓ Scientific publication on the association of artificial intelligence based-image biomarkers, histomorphology and genomic data in BTC
WG6	Y1	✓ Review on challenges for the development of novel therapeutic strategies in BTC
	Y2-4	✓ Scientific publication on preclinical models developed for the application of drug discovery and drug validation and developing novel compounds to be taken into clinical experimentation
	Y3	✓ Proceedings from an academia-pharma interaction
All WGs	Y1-4	✓ Material and reports of training schools and bi-annual meeting
	Y2-4	✓ Publication of results of mentoring program and recordings of mentorship lectures available online

https://www.cost.eu/actions/CA22125/

Thank you for your attention

Angela.Lamarca@quironsalud.es

@DrAngelaLamarca

Thank you GI Oncology TEAM FJD

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Research Fellow: Dr Gonzalez

PhD Students: Dr Martirena, Dr Fernandez

Research Nurses and Technicians: Sergio Galan, Carmen Candau, David Alonso

Study Coordinators: Berta Lopez, David Garcia

Data Entry: Leticia Sanchez, Paola Krystel

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