Accelerating Innovation in Biliary Tract Cancer

Restructuring Treatment Models With Immunotherapy & Targeted Platforms in Advanced Disease

PeerView Live

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Our Goals for Today

- **Summarize the importance** of biomarker testing, current safety/efficacy evidence on immunotherapies and targeted platforms, and updated guidelines in biliary tract cancer
- **Develop tailored treatment plans** with systemic treatment options in BTC that considers molecular findings, clinical trial evidence, and practice guidelines
- **Formulate team-based strategies** to address important considerations with treatment delivery in BTC, including patient education, shared decision-making, treatment-specific dosing/scheduling, and AE management

A Call To Reinforce New Evidence in BTC

Addressing Healthcare Gaps With Modern Strategies

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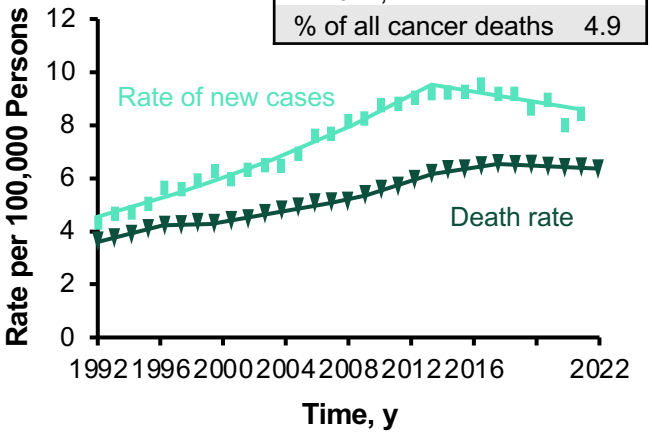
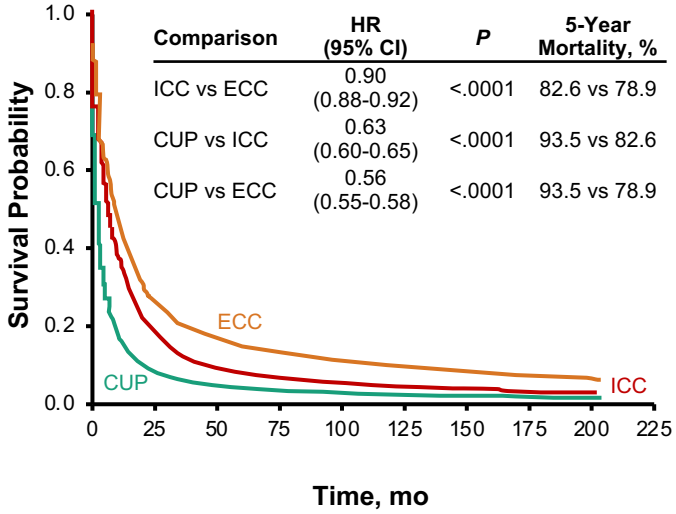
Rising Incidence of Cholangiocarcinoma[1,2]

Estimated new cases in 2024, n	41,630
% of all new cancer cases	2.1

Estimated deaths in 2024, n	29,840
% of all cancer deaths	4.9

5-Year Relative Survival, %
21.7
2014-2020





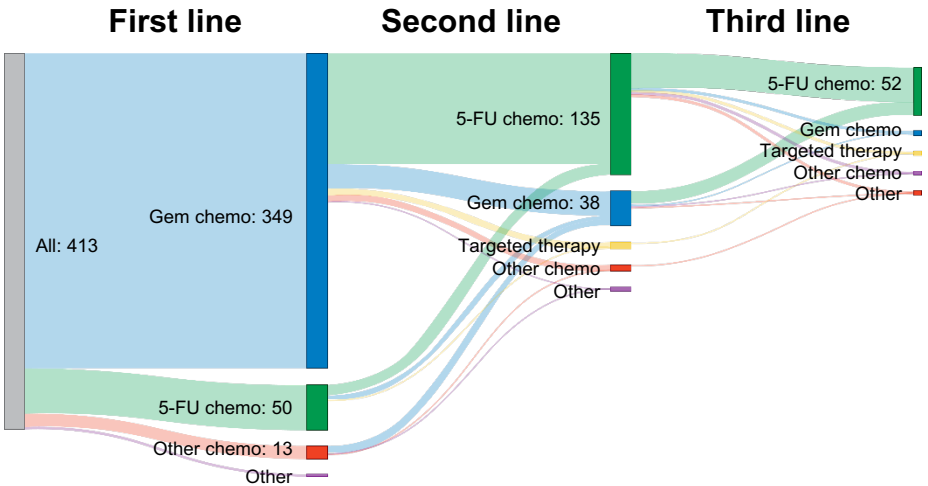
Comparison	HR (95% CI)	*P*	5-Year Mortality, %
ICC vs ECC	0.90 (0.88-0.92)	<.0001	82.6 vs 78.9
CUP vs ICC	0.63 (0.60-0.65)	<.0001	93.5 vs 82.6
CUP vs ECC	0.56 (0.55-0.58)	<.0001	93.5 vs 78.9

1. Javle M et al. *Oncologist*. 2022;27:874-883. 2. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. SEER 2024.

Current Shortcomings in the Management of Advanced Biliary Tract Cancers[1,2]

A recent assessment of 1,009 oncology providers treating patients with advanced CCA found that 81% were not confident in their ability to use targeted therapies in patients with advanced CCA

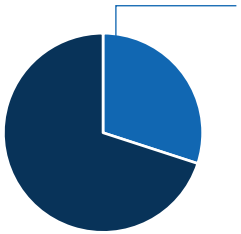
Moreover…



- ~85% of patients were initiated on gemcitabine-based chemotherapy as their first-line treatment
- Less than half (46%) of patients initiated second-line treatments
- Few patients (~17%) moved to third line of treatment
- All-cause mortality was 53% and nearly 70% of patients required at least one hospital stay

1. Parikh K et al. ASCO GI 2021. Abstract 347. 2. Wang L et al. *Future Oncol*. 2024;20(34):2625-2636.

Current Shortcomings in the Management of Advanced Biliary Tract Cancers[1-3]

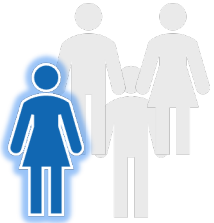


<30% of adult patients with CCA are offered treatment via a clinical trial

Clinical trial enrollment is challenged by molecular heterogeneity of the tumor, insufficient tissue biopsy, and relative rarity of CCA

- Leads to disparate outcomes; impact on prognosis not yet understood

Only ~50% - 64% of CCA patients undergo molecular testing, which impacts their eligibility to receive personalized interventions



Gaps in precision-guided care include insufficient tumor biopsy for testing, lack of timely reporting of results, and limited patient and clinician awareness of genomic alterations and its impact in CCA

1. Pear S et al. ASCO GI 2022. Abstract 407. 2. Spencer K et al. *JNCI.* 2023;870-880. 3. Snow S et al. *Curr Oncol.* 2024;31(3):1359-1375.

Patient Education & Shared Decision-Making Is Key To Improved Treatment Outcomes

- Facilitates informed treatment selection
- Improved symptom management:
  Patients learn how to recognize, report, and manage adverse events with modern treatment approaches
- Tools available to assist with patient/care partner understanding on major clinical trial data (eg, plain language summaries) to make informed therapeutic decisions and promote patient engagement
- Collectively, enhancing treatment experience is key to maintaining patient adherence and commitment to managing their disease

The Cholangiocarcinoma Foundation Is an Excellent Resource for Professionals, Patients, and Caregivers[a]

The Cholangiocarcinoma Foundation's (advocacy@cholangiocarcinoma.org) mission is to find a cure and improve the quality of life for those affected by cholangiocarcinoma (bile duct cancer)

Visit https://cholangiocarcinoma.org/ for multiple resources that patients can use to

- Get the latest information about their disease
- Connect with other patients
- Participate in clinical trials

And much more!

Selected resources include

International Cholangiocarcinoma Patient Registry (ICPR)
https://cholangiocarcinoma.org/international-cholangiocarcinoma-patient-registry-icpr

Find a Specialist
https://cholangiocarcinoma.org/specialist-map

Find and Learn About Clinical Trials
https://cholangiocarcinoma.org/professionals/research/clinical-trials

Download our practice aid to share information about the Cholangiocarcinoma Foundation with your patients

[a] In support of improving patient care, this activity has been planned and implemented by PVI, PeerView Institute for Medical Education, and the Cholangiocarcinoma Foundation.

PeerView

Embracing Breakthroughs in BTC

Collaborative Discussions on Effectively Integrating Immunotherapy Platforms in Advanced Disease

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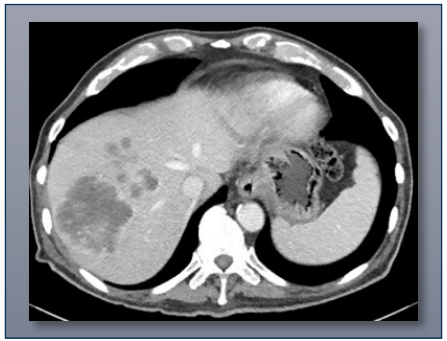
Introduction to Brian, a 60-Year-Old Male Patient With Newly Diagnosed Disease

Brian, aged 60 years, presents with a history of abdominal pain and unintentional weight loss

- Imaging reveals metastatic intrahepatic cholangiocarcinoma
- ECOG PS 1; no relevant biomarkers detected

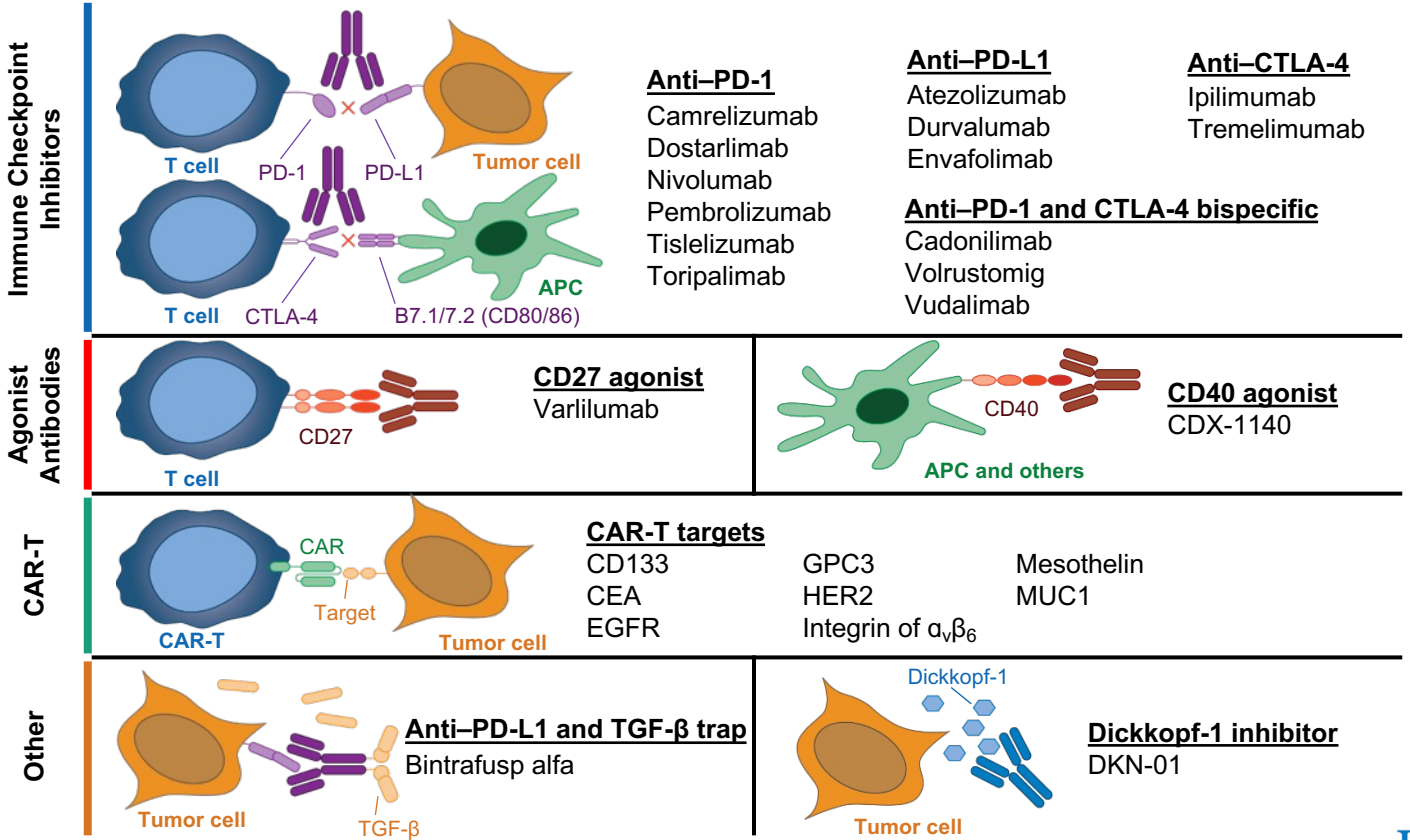


Discussion

What treatment options would you consider for this patient?

Let's review the evidence…

Review of Immunotherapy Targets and Options[1]



1. Lo JH et al. *Cancers.* 2023;15:3312.

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NCCN Practice Guidelines: First-Line Treatment Options for Unresectable and Metastatic BTC[1]

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances: Targeted Therapy[a]
• **Durvalumab** + gemcitabine + cisplatin (category 1) • **Pembrolizumab** + gemcitabine + cisplatin (category 1)	• Gemcitabine + cisplatin (category 1) • Capecitabine + oxaliplatin • FOLFOX • Gemcitabine + albumin-bound paclitaxel • Gemcitabine + capecitabine • Gemcitabine + oxaliplatin • Single agents – 5-fluorouracil – Capecitabine – Gemcitabine	• For MSI-H/dMMR tumors – **Pembrolizumab** • For TMB-H tumors – **Nivolumab + ipilimumab** (category 2B) • For *NTRK* gene fusion–positive tumors – Entrectinib; larotrectinib; repotrectinib • For *RET* gene fusion–positive tumors – Pralsetinib; selpercatinib (category 2B)

[a] Based on the evidence, durvalumab or pembrolizumab + gemcitabine/cisplatin are preferred regimens for all patients with advanced BTC, including those with MSI-H/dMMR status

1. NCCN Clinical Practice Guidelines in Oncology. Biliary Tract Cancers. Version 6.2024. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf.

NCCN Practice Guidelines: Subsequent-Line Treatment Options for Unresectable and Metastatic CCA[1]

Subsequent-Line Therapy for Biliary Tract Cancers If Disease Progression		
Preferred Regimens	**Other Recommended Regimens***	**Useful in Certain Circumstances: Targeted Immunotherapy[a]**
• FOLFOX	• FOLFIRI • Liposomal irinotecan + fluorouracil + leucovorin (category 2B) • Regorafenib (category 2B) • **Durvalumab** + gemcitabine + cisplatin (category 1) • **Pembrolizumab** + gemcitabine + cisplatin (category 1)	• For MSI-H/dMMR tumors – **Pembrolizumab** – **Dostarlimab** (category 2B) • For TMB-H tumors – **Nivolumab + ipilimumab** – **Pembrolizumab** • Nivolumab (category 2B)

[a] For patients who have not been previously treated with a checkpoint inhibitor when used as subsequent-line therapy

1. NCCN Clinical Practice Guidelines in Oncology. Biliary Tract Cancers. Version 6.2024. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf.

Phase 3 TOPAZ-1 Trial: First-Line Immunotherapy + Chemotherapy in Patients With Advanced Biliary Cancers[1]

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

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, or GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - Initially unresectable vs recurrent
- Primary tumor location
  - ICC vs ECC vs GBC

R 1:1

N = 685

Durvalumab 1,500 mg Q3W **+ gemcitabine/cisplatin** (up to 8 cycles) → **Durvalumab** 1,500 mg Q4W until PD

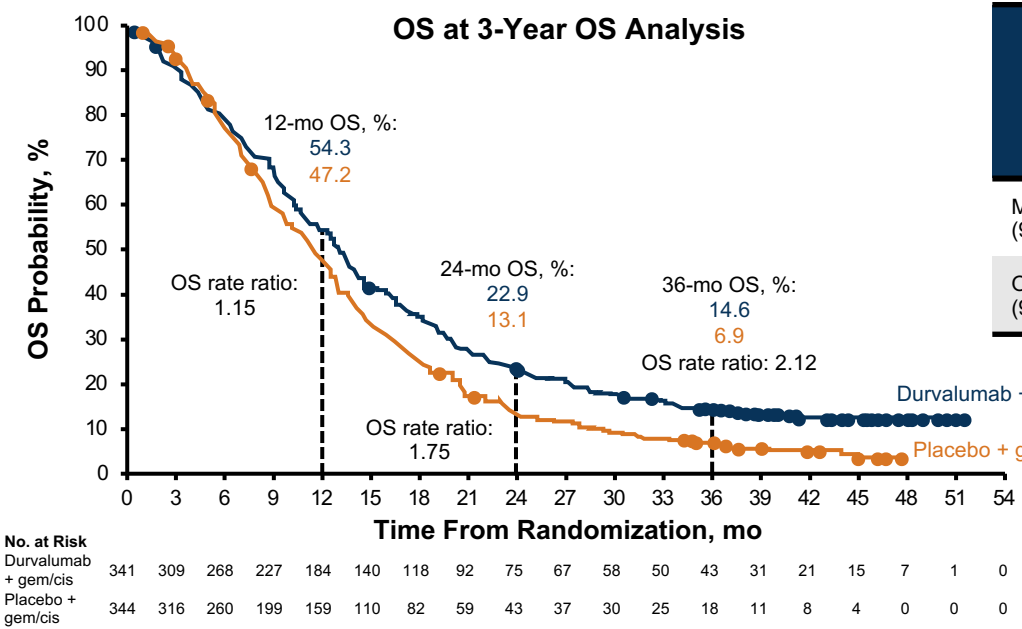
Placebo Q3W **+ gemcitabine/cisplatin** (up to 8 cycles) → **Placebo** Q4W until PD

- **Primary endpoint:** OS
- **Key secondary endpoints:** PFS, ORR, DOR, and safety
- **Exploratory endpoints:** efficacy and safety by primary tumor location (ICC vs ECC vs GBC)

1. https://clinicaltrials.gov/ct2/show/NCT03875235.

Phase 3 TOPAZ-1 Trial: 3-Year OS Update of Durvalumab + Gem/Cis vs Placebo + Gem/Cis[1]

- OS benefit with durvalumab + gem/cis continued at the updated DCO

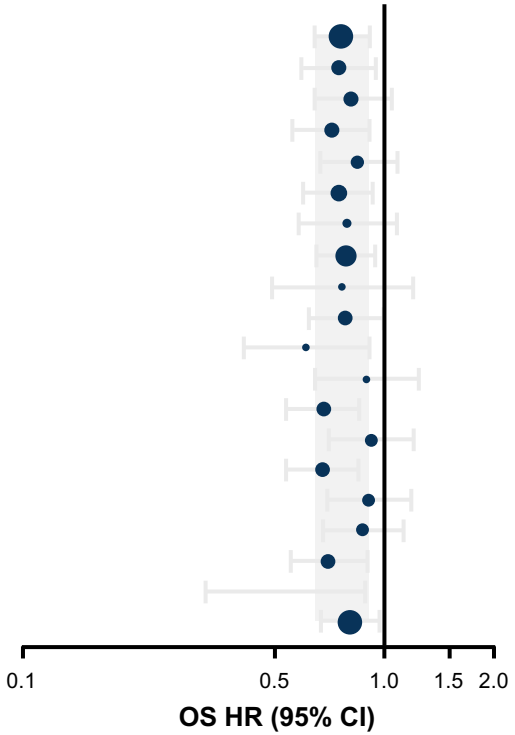


	Primary Analysis DCO: Aug 11, 2021		3-Year OS Analysis DCO: Oct 23, 2023	
	Durva + Gem/Cis (n = 341)	Placebo + Gem/Cis (n = 344)	Durva + Gem/Cis (n = 341)	Placebo + Gem/Cis (n = 344)
Median OS (95% CI), mo	12.8 (11.1-14.0)	11.5 (10.1-12.5)	12.9 (11.6-14.1)	11.3 (10.1-12.5)
OS HR (95% CI)	0.80 (0.66-0.97)		0.74 (0.63-0.87)	

At 36 months, the survival rate in the durvalumab + gem/cis arm was more than double the survival rate in the placebo + gem/cis arm

1. Oh D-Y et al. *Lancet.* 2024;9:694-704.

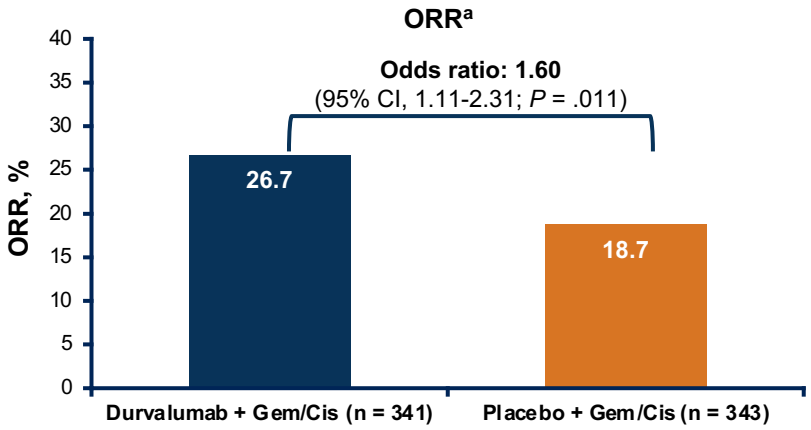
TOPAZ-1: Subgroup Analysis of OS[1]

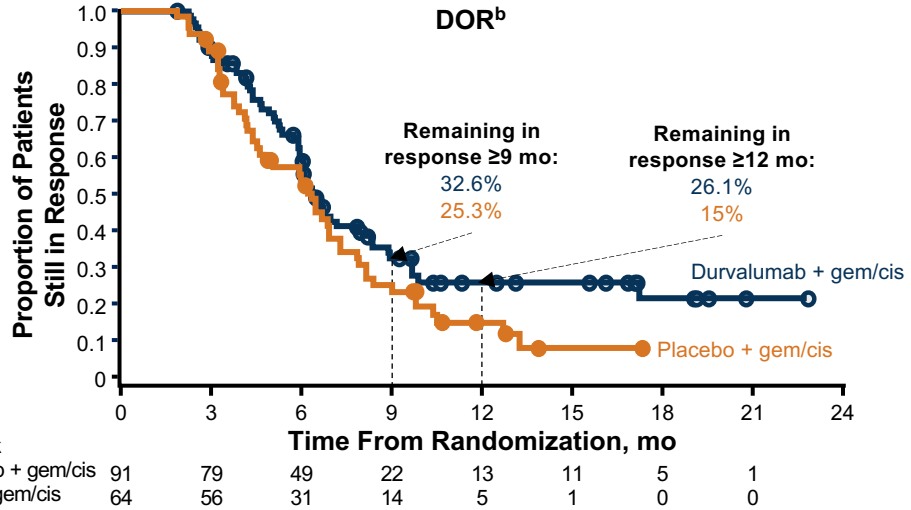


	Durvalumab + Gem/Cis, n/N (%)	Placebo + Gem/Cis, n/N (%)	OS HR (95% CI)
All participants	248/341 (72.7)	279/334 (81.1)	0.76 (0.64-0.91)
Sex: men	126/169 (74.6)	148/176 (84.1)	0.75 (0.59-0.95)
Sex: women	122/172 (70.9)	131/168 (78)	0.81-0.64-1.04)
Age at randomization: <65 years of age	123/181 (68)	150/184 (81.5)	0.72 (0.56-0.91)
Age at randomization: ≥65 years of age	125/160 (78.1)	129/160 (80.6)	0.84 (0.66-1.08)
PD-L1 expression: high (TAP ≥1%)	149/199 (74.9)	172/207 (83.1)	0.75 (0.60-0.93)
PD-L1 expression: low/negative (TAP <1%)	71/103 (68.9)	81/103 (78.6)	0.79 (0.58-1.09)
Disease status at randomization: initially unresectable	209/274 (76.3)	240/279 (86)	0.79 (0.65-0.95)
Disease status at randomization: recurrent	39/67 (58.2)	39/64 (60.9)	0.76 (0.49-1.20)
Primary tumor location: intrahepatic cholangiocarcinoma	136/190 (71.6)	153/193 (79.3)	0.78 (0.62-0.99)
Primary tumor location: extrahepatic cholangiocarcinoma	45/66 (68.2)	55/65 (84.6)	0.61 (0.41-0.91)
Primary tumor location: gallbladder cancer	67/85 (78.8)	71/86 (82.6)	0.90 (0.64-1.25)
Race: Asian	134/185 (72.4)	174/201 (86.6)	0.68 (0.54-0.85)
Race: non-Asian	114/156 (73.1)	105/143 (73.4)	0.92 (0.70-1.20)
Region: Asia	130/178 (73)	170/196 (86.7)	0.68 (0.54-0.85)
Region: rest of the world	118/163 (72.4)	109/148 (73.6)	0.91 (0.70-1.18)
WHO/ECOG PS: (0) normal activity	126/173 (72.8)	125/163 (76.7)	0.87 (0.68-1.12)
WHO/ECOG PS: (1) restricted activity	122/168 (72.6)	154/181 (85.1)	0.70 (0.55-0.89)
Diagnostic stage: locally advanced	22/38 (57.9)	45/57 (78.9)	0.54 (0.32-0.88)
Diagnostic stage: metastatic	226/303 (74.6)	234/286 (81.8)	0.80 (0.67-0.97)

1. Oh D-Y et al. ESMO 2022. Abstract 56P.

TOPAZ-1: Durvalumab + Gem/Cis Demonstrated a Higher ORR and More Rapid Tumor Responses[1]





	Durvalumab + Gem/Cis (n = 341), n (%)	Placebo + Gem/Cis (n = 343), n (%)
ORR	91 (26.7)	64 (18.7)
CR	7 (2.1)	2 (0.6)
PR	84 (24.6)	62 (18.1)
DCR[c]	291 (85.3)	284 (82.6)

	Durvalumab + Gem/Cis (n = 91)	Placebo + Gem/Cis (n = 64)
Median DOR, mo (quartile 1-3)	6.4 (4.6-17.2)	6.2 (3.8-9)
Median time to response, mo (quartile 1-3)	1.6 (1.3-3)	2.7 (1.4-4.1)

[a] By investigator assessments using RECIST v1.1 based on patients in the final analysis set who had measurable disease at baseline. [b] Analysis of DOR was based on patients in the full analysis set who had an objective response and measurable disease at baseline. [c] Analysis of DCR was based on all patients in the full analysis set.

1. Oh D-Y et al. ASCO GI 2022. Abstract 378.

TOPAZ-1: Summary of AEs and Treatment Exposure[1,a]

	Durvalumab + Gem/Cis (n = 338)	Placebo + Gem/Cis (n = 342)
Median duration of exposure, mo (range)		
Durvalumab/placebo	7.33 (0.1-24.5)	5.77 (0.2-21.5)
Gemcitabine	5.19 (0.1-8.3)	5.03 (0.2-8.6)
Cisplatin	5.13 (0.1-8.3)	4.88 (0.2-8.5)
Event, n (%)		
Any AE	336 (99.4)	338 (98.8)
Any TRAE	314 (92.9)	308 (90.1)
Any grade 3/4 AE	256 (75.7)	266 (77.8)
Any grade 3/4 TRAE	212 (62.7)	222 (64.9)
Any serious AE	160 (47.3)	149 (43.6)
Any serious TRAE	53 (15.7)	59 (17.3)
Any AE leading to discontinuation	44 (13)	52 (15.2)
Any TRAE leading to discontinuation	30 (8.9)	39 (11.4)
Any AE leading to death	12 (3.6)	14 (4.1)
Any TRAE leading to death	2 (0.6)	1 (0.3)
Any immune-mediated AE	43 (12.7)	16 (4.7)

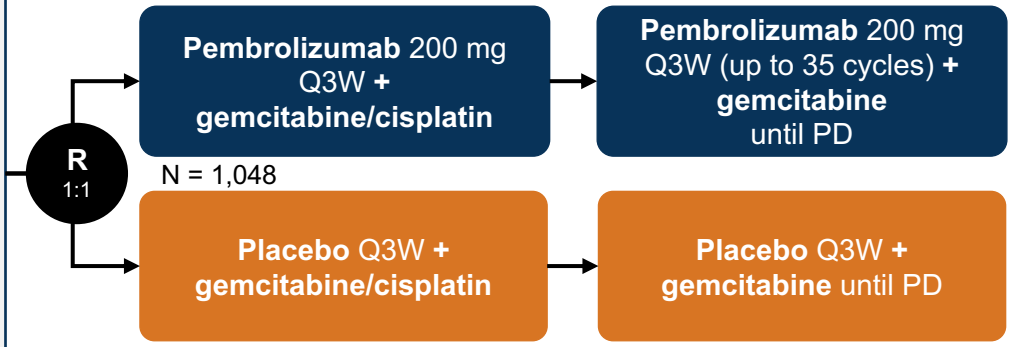
[a] Includes AEs with onset date on or after the date of the first dose or AEs that worsened after the first dose. Includes AEs occurring up to 90 days following the date of the last dose or up to the first subsequent therapy.

1. Oh D-Y et al. ASCO GI 2022. Abstract 378.

KEYNOTE-966: Pembrolizumab + Gem/Cis vs Gem/Cis Alone in First-Line Advanced and/or Unresectable BTC[1]

Screening/baseline

- Histologically confirmed diagnosis of advanced (metastatic) and/or unresectable (locally advanced) BTC (ampullary cancer excluded)
- Measurable disease based on RECIST v1.1, as determined by the site investigator
- No prior systemic therapies
- No CNS metastases and/or carcinomatous meningitis
- Participants with a history of hepatitis B/C can be enrolled if they meet study criteria
- Availability of archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion
- Life expectancy >3 months
- Adequate organ function



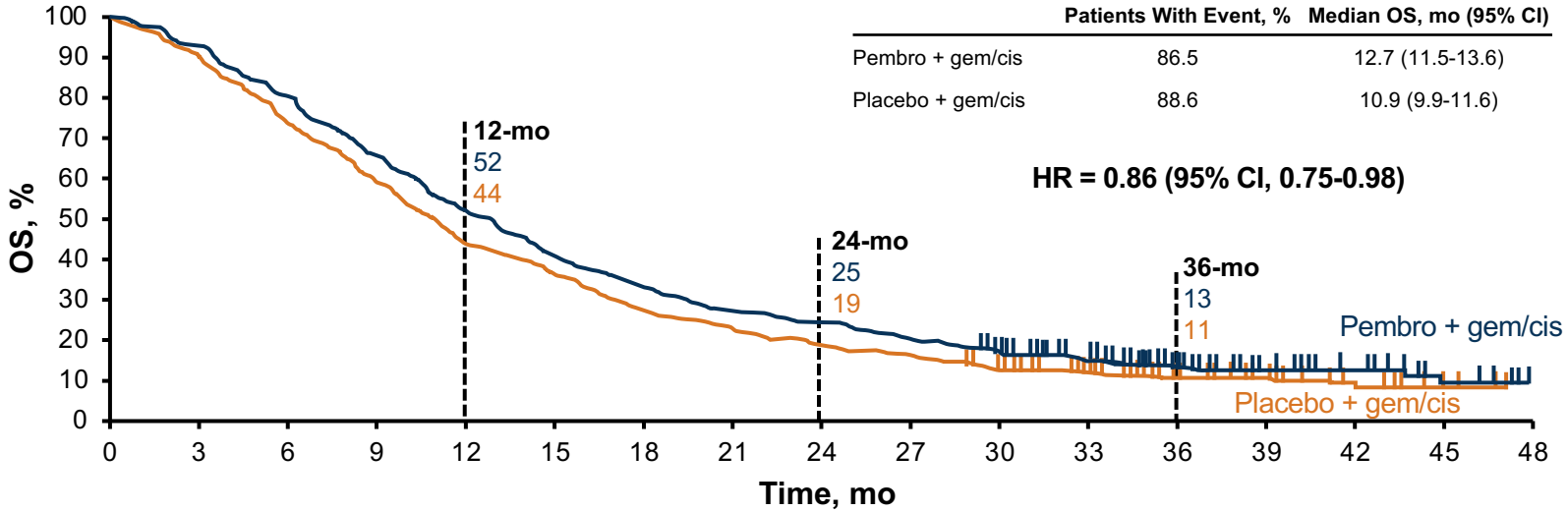
Maintenance therapy

- For pembrolizumab, treatment continued for a maximum of 35 cycles, or approximately 24 months
- For gemcitabine, treatment could be continued beyond 8 cycles; for cisplatin, treatment could be administered for a maximum of 8 cycles

- **Primary objective:** OS
- **Secondary objectives:** ORR (RECIST v1.1; BICR), DOR (RECIST v1.1; BICR), and PFS (RECIST v1.1; BICR)
- **Safety outcomes:** number of patients experiencing >1 AE and discontinuations due to AEs

1. Kelley RK et al. *Lancet*. 2023;401:1853-1865.

KEYNOTE-966: Pembrolizumab + Gem/Cis Demonstrated Significant Overall Survival Improvement



	Patients With Event, %	Median OS, mo (95% CI)
Pembro + gem/cis	86.5	12.7 (11.5-13.6)
Placebo + gem/cis	88.6	10.9 (9.9-11.6)

HR = 0.86 (95% CI, 0.75-0.98)

No. at Risk

Pembro + gem/cis	533	496	430	350	275	217	176	147	131	113	86	64	39	21	15	6	0
Placebo + gem/cis	536	483	394	313	236	195	149	125	102	86	63	43	27	20	10	4	0

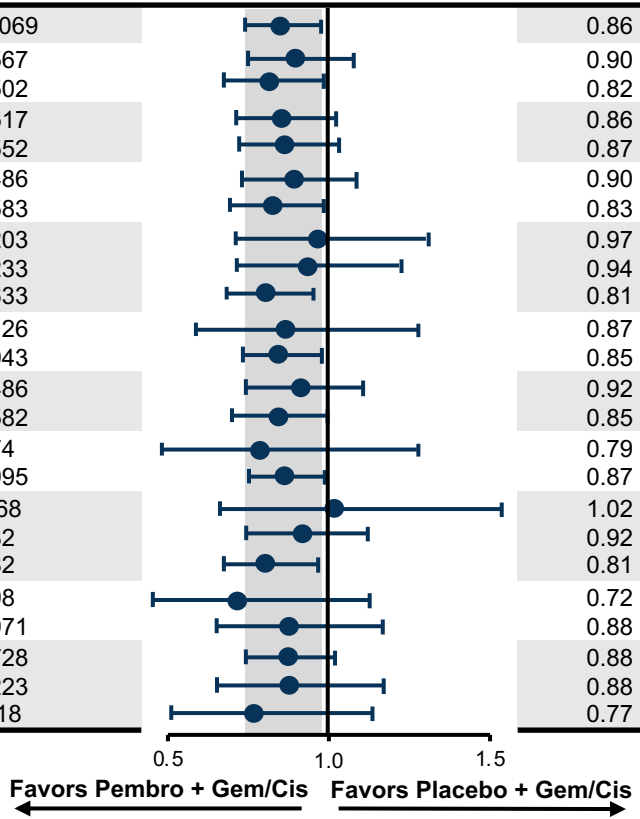
After an additional 11 months of follow-up from final analysis, improvement of OS was maintained, and DOR remained longer in the pembrolizumab arm (8.3 vs 6.9 mo)[1]

In October 2023, the FDA approved the combination for locally advanced unresectable or metastatic BTC[2]

1. Finn R et al. ASCO 2024. Abstract 4093. 2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-chemotherapy-biliary-tract-cancer.

KEYNOTE-966: Overall Survival Subgroup Analysis[1]

Subgroups		Patients With Event	HR (95% CI)
All patients		936/1,069	0.86 (0.75-0.98)
Age, y	≥65	497/567	0.90 (0.76-1.08)
	<65	439/502	0.82 (0.68-0.99)
Sex	Women	460/517	0.86 (0.72-1.03)
	Men	476/552	0.87 (0.73-1.04)
Geographic region	Asia	422/486	0.90 (0.74-1.09)
	Non-Asia	514/583	0.83 (0.70-0.99)
Site of origin	Extrahepatic	175/203	0.97 (0.72-1.31)
	Gallbladder	219/233	0.94 (0.72-1.23)
	Intrahepatic	542/633	0.81 (0.69-0.96)
Disease presentation	Locally advanced	105/126	0.87 (0.59-1.28)
	Metastatic	831/943	0.85 (0.74-0.98)
ECOG PS	0	406/486	0.92 (0.75-1.11)
	1	529/582	0.85 (0.71-1.00)
Biliary stent/drain	Yes	68/74	0.79 (0.49-1.28)
	No	868/995	0.87 (0.76-0.99)
Smoking status	Never	92/268	1.02 (0.67-1.54)
	Former	33/82	0.92 (0.75-1.13)
	Current	33/82	0.81 (0.68-0.97)
Prior chemotherapy	Yes	77/98	0.72 (0.46-1.13)
	No	859/971	0.88 (0.77-1.01)
PD-L1 status	CPS ≥1	646/728	0.88 (0.75-1.02)
	CPS <1	191/223	0.88 (0.66-1.17)
	Indeterminate	99/118	0.77 (0.52-1.14)



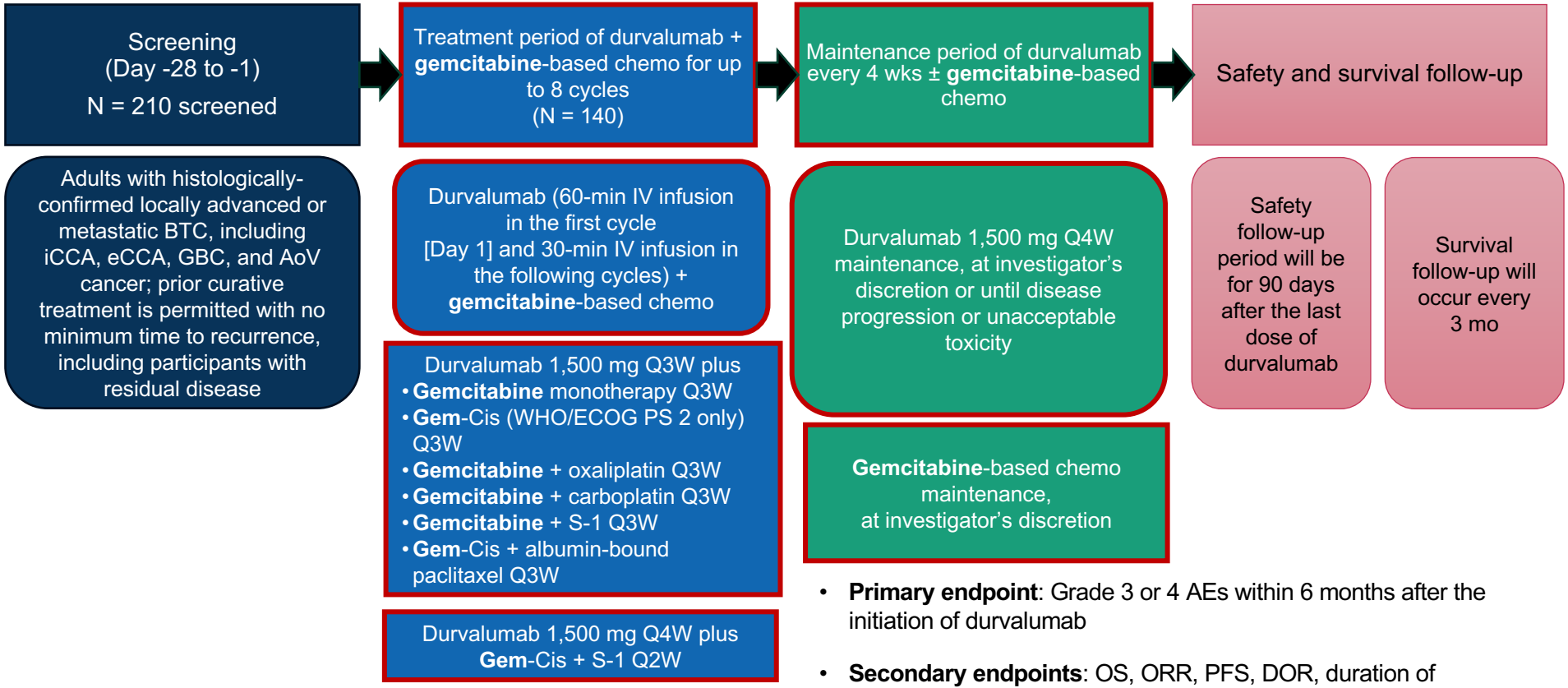
1. Finn R et al. ASCO 2024. Abstract 4093.

KEYNOTE-966: Safety Profiles Remain Consistent and Comparable Between Treatment Arms[1]

Subgroup, n (%)	Pembro + Gem/Cis (n = 529)	Placebo + Gem/Cis (n = 534)
Any	524 (99.9)	532 (99.6)
Treatment related	493 (93.2)	500 (93.6)
Grade 3-4 as maximum grade	420 (79.4)	399 (74.7)
Treatment related	370 (69.9)	367 (68.7)
Led to death	31 (5.9)	50 (9.4)
Treatment related	8 (1.5)	3 (0.6)
Led to discontinuation of ≥1 study medication	140 (26.5)	124 (23.2)
Treatment related	103 (19.5)	82 (15.4)
Led to discontinuation of all study medication	35 (6.6)	39 (7.3)
Treatment related	18 (3.4)	14 (2.6)

1. Finn R et al. ASCO 2024. Abstract 4093.

Phase 3b TOURMALINE: Safety/Efficacy of Durvalumab + Gemcitabine-Based Chemotherapy in Advanced BTC



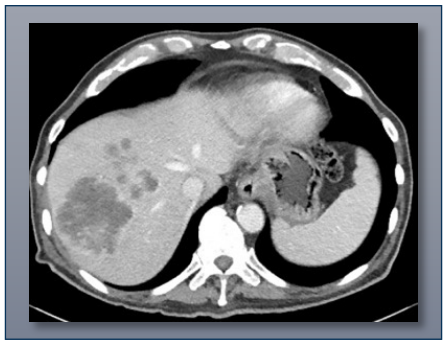
- **Primary endpoint**: Grade 3 or 4 AEs within 6 months after the initiation of durvalumab
- **Secondary endpoints**: OS, ORR, PFS, DOR, duration of treatment, HRQOL, safety and tolerability

1. Vogel A et al. ASCO 2024. Abstract TPS4188.

Back to Brian's Case: Frontline Treatment Selection For Advanced BTC

Brian, aged 60 years, presents with a history of abdominal pain and unintentional weight loss

- Imaging reveals metastatic intrahepatic cholangiocarcinoma
- ECOG PS 1; no relevant biomarkers detected



Discussion

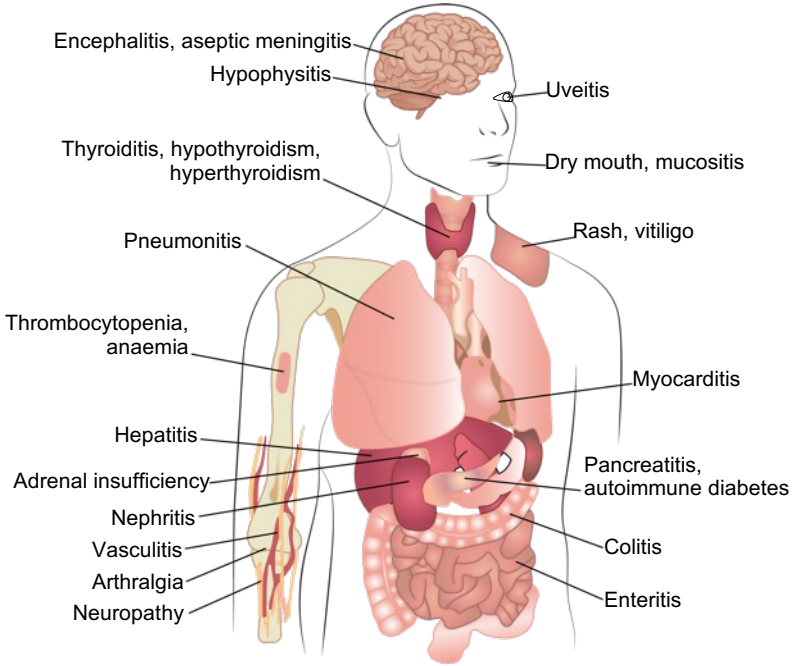
In the patient above, what 1L treatment regimen would you recommend? Immunotherapy + chemotherapy? Chemotherapy alone?

Other Trials With Immunotherapy[1]

Drug	Phase	NCT
Adjuvant rilvegostomig + chemotherapy	3	NCT06109779
Neoadjuvant durvalumab + tremelimumab + gem-cis	2	NCT06017297
Durvalumab + gemcitabine/cisplatin/nab-paclitaxel in the resectable setting	2	NCT05640791
Durvalumab + SNDX-6532	2	NCT04301778
Durvalumab + tremelimumab + RT in the second-line setting	2	NCT03482102
Durvalumab + tremelimumab + paclitaxel (IMMUNO-BIL)	2	NCT03704480
Bispecific antibodies ± standard agents	2	NCT05775159
Nivolumab monotherapy in the second-line setting	2	NCT02829918
Nivolumab + rucaparib in the second-line setting	2	NCT03639935
Atezolizumab + gem-cis +/- bevacizumab	2	NCT04677504
Nal-irinotecan + nivolumab in the second-line setting	1/2	NCT03785873

1. https://clinicaltrials.gov.

What Are the Most Common AEs of PD-1/PD-L1 Therapy?[1]

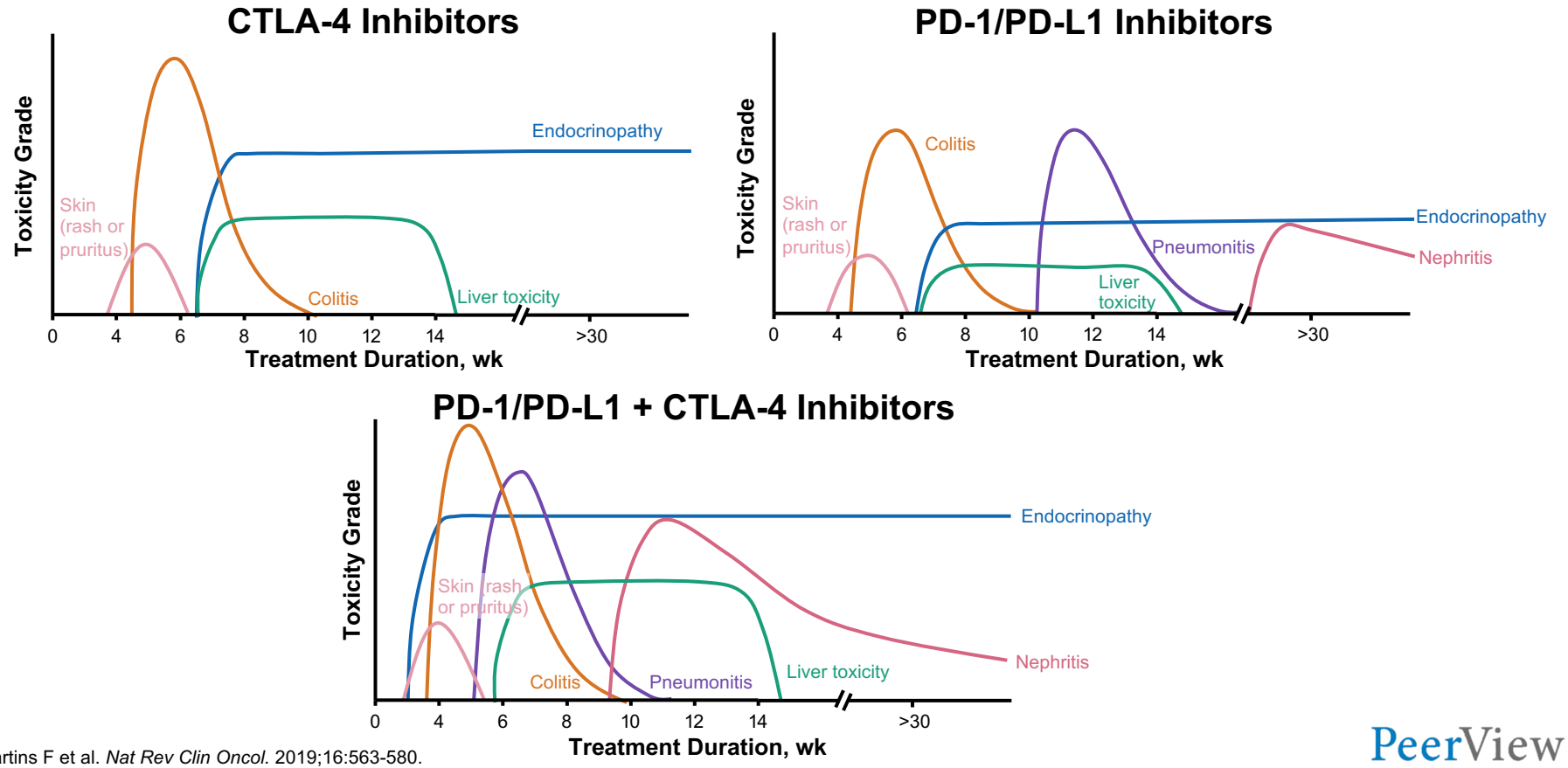


- Any organ can be affected
- New symptoms are usually related to the therapy
- AEs can occur throughout the course of therapy
- Combination IO can increase the risk for AEs

Adverse Event	Estimated Frequency, %
Skin changes (eg, redness, itching)	40-50
Hypothyroidism	20-30
Hyperthyroidism	5-10
Colitis	10-30
Hepatitis	5-10
Nephritis	5-10
Pneumonitis	5-10
Hypophysitis	1-3
Type 1 diabetes mellitus	1-3
Pancreatitis	1-3
Myositis	1-3
Myocarditis	1-3
Encephalitis	1-2

1. Postow MA et al. *N Engl J Med*. 2018;378:158-168.

Patterns and Duration of Common Immune-Related AEs[1]



1. Martins F et al. *Nat Rev Clin Oncol.* 2019;16:563-580.

irAE Grading and Management[1]

Grade 1: minimal or no symptoms; diagnostic changes only

- In general, checkpoint inhibitor therapy should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities

Grade 2: mild to moderate symptoms

- Hold checkpoint inhibitor therapy for most grade 2 toxicities
- Consider resuming immunotherapy when symptoms and/or laboratory values revert to grade 1 or lower
- Corticosteroids (initial dose of 0.5-1 mg/kg/d of prednisone or equivalent) may be administered; 1-2 mg/kg/d of prednisone is recommended for diarrhea/colitis

Grades 3/4: severe or life-threatening symptoms

- **Grade 3 toxicities**
  - Hold checkpoint inhibitor therapy
  - Initiate high-dose corticosteroids (prednisone 1-2 mg/kg/d or methylprednisolone IV 1-2 mg/kg/d)
  - If symptoms do not improve with 48-72 hours of high-dose corticosteroids, infliximab may be offered for some toxicities
  - Taper corticosteroids over the course of at least 4-6 weeks
  - When symptoms and/or laboratory values revert to grade 1 or lower, rechallenging with immunotherapy may be offered; however, caution is advised, especially in those patients with early-onset irAEs; dose adjustments are not recommended
- **Grade 4 toxicities**
  - In general, permanent discontinuation of checkpoint inhibitor therapy is warranted, with the exception of endocrinopathies that have been controlled by hormone replacement

1. NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

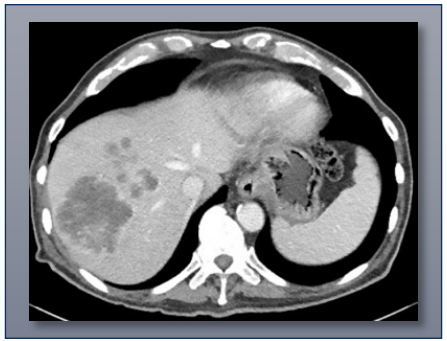
Case Continued: Toxicity Management Considerations For Immunotherapy Regimens

Brian, aged 60 years, presents with a history of abdominal pain and unintentional weight loss

- Imaging reveals metastatic intrahepatic cholangiocarcinoma
- ECOG PS 1; no relevant biomarkers detected

The patient is started on a durvalumab + gemcitabine/cisplatin regimen

- **Upon follow up, the patient presents with a grade 2 colitis**



Discussion

How do you manage this irAE?
What other potential toxicities should the care team be prepared to monitor/manage when integrating immunotherapy regimens?

Fortifying Precision Tactics in BTC

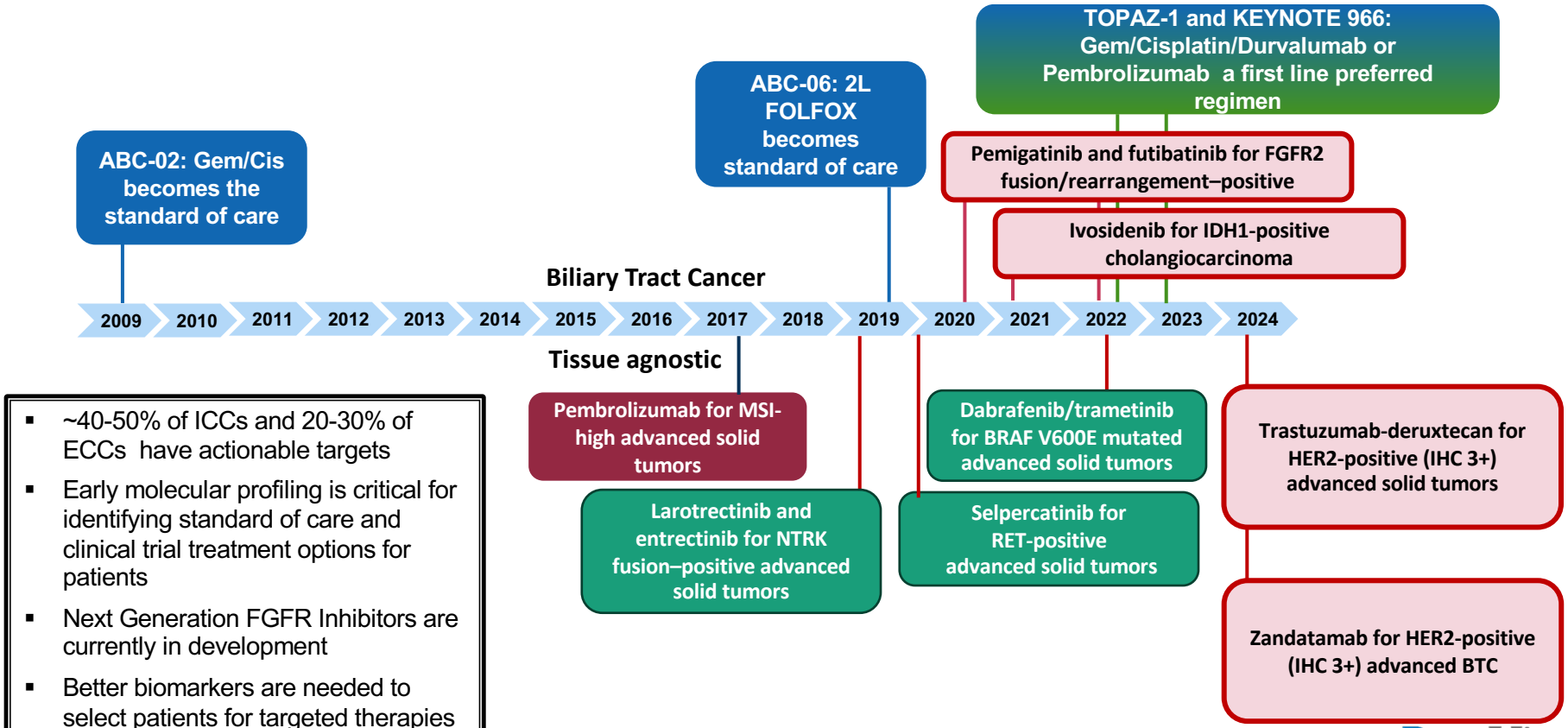
The Evolving Use of Targeted Therapy in Biliary Tract Cancer

Lipika Goyal, MD, Mphil
Director of Gastrointestinal Oncology
Associate Professor of Medicine
Division of Oncology
Stanford School of Medicine
Palo Alto, California

Targeted Therapy and *FGFR* inhibitors on CCA

1. Molecular profiling and FDA approved targeted therapies
2. FDA approved FGFR inhibitors
3. Mechanisms of Resistance to FGFR inhibitors
4. Next Generation FGFR inhibitors

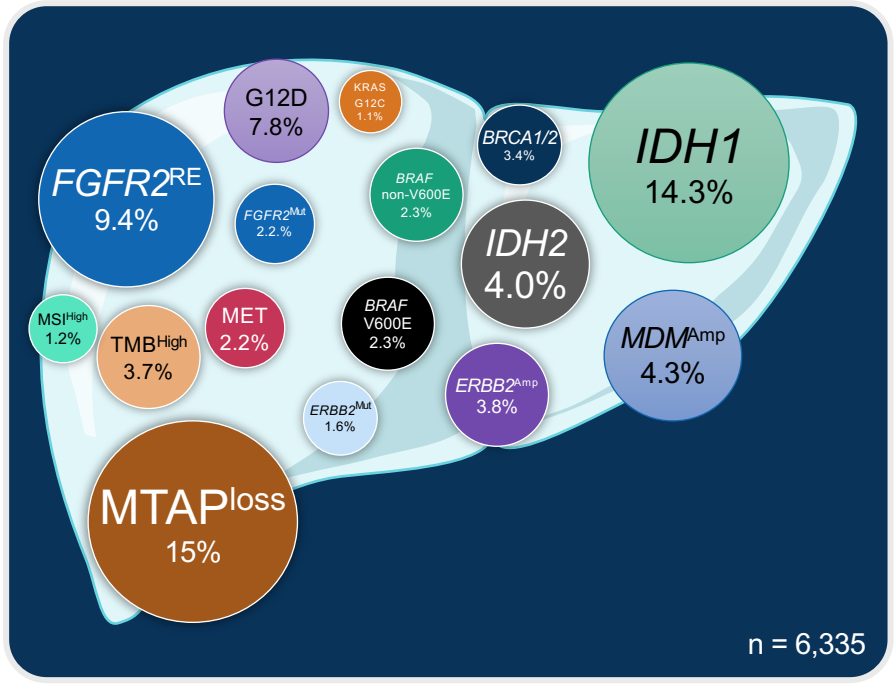
Precision Oncology is Key for Management of Cholangiocarcinoma



- ~40-50% of ICCs and 20-30% of ECCs have actionable targets
- Early molecular profiling is critical for identifying standard of care and clinical trial treatment options for patients
- Next Generation FGFR Inhibitors are currently in development
- Better biomarkers are needed to select patients for targeted therapies in CCA

Many Targeted Therapies Are Already Available Today, With Others In Ongoing Trials[1]

Intrahepatic Cholangiocarcinoma



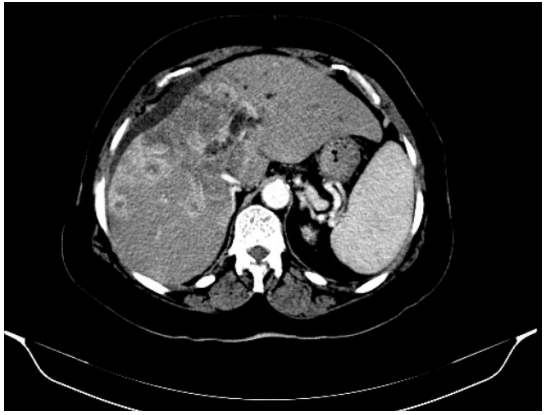
NCCN Guideline-Recommended Targeted Agents

FGFR^{RE} 9.4%	Pemigatinib, futibatinib
IDH1 14.3%	Ivosidenib
ERB2^{AMP} 3.8%	T-DXd, pertuzumab/trastuzumab, tucatinib/trastuzumab, zanidatamab
BRAF V600E 2.3%	Dabrafenib/trametinib
NTRK	Entrectinib, Larotrectinib, repotrectinib
RET	Pralsetinib, selpercatinib
MSI-H/ dMMR	Pembrolizumab. dostarlimab
TMB^{high} 3.7%	Nivolumab/ipilimumab, pembrolizumab

1. Kendre G et al. *J Hepatol.* 2023;78:614-626.

Introduction to Sherry, a 65-Year-Old Female Patient Progressing On Upfront Therapy

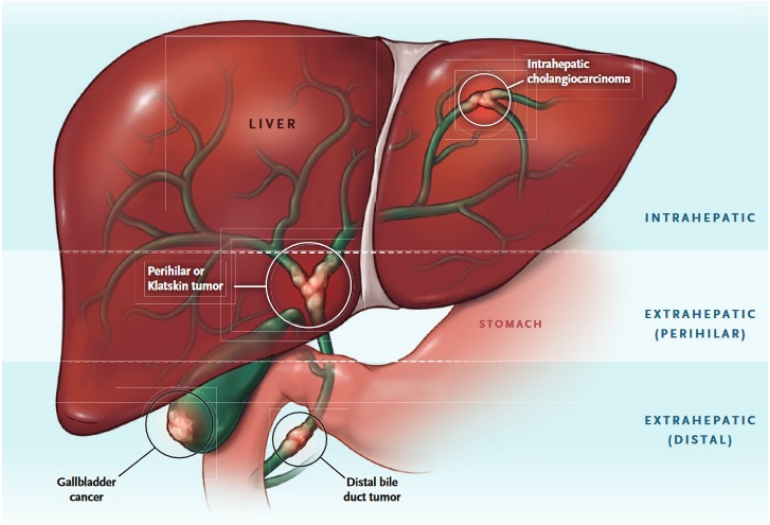
Sherry, A 65-year-old female patient with unresectable CCA was treated with upfront durvalumab + gemcitabine/cisplatin, however, she progressed 4 months later. The patient would like to discuss the next steps to manage their advanced disease.



Discussion

You are exploring options for 2L targeted treatment– what additional testing would you order?

NCCN Guidelines: Molecular Profiling is Recommend in BTC[1]



Biliary Tract Cancer

- Gallbladder Cancer
- Intrahepatic Cholangiocarcinoma
- Extrahepatic Cholangiocarcinoma

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

[a]For MSI, there are three possible methods for testing: IHC, NGS, PCR
[b]TMB can be tested with NGS panel but has inherent platform variation

1. NCCN Clinical Practice Guidelines. Biliary Tract Cancers. Version 6.2024. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf.

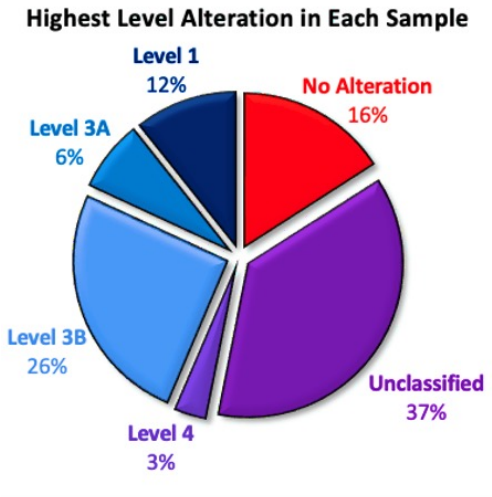
Diagnostic Approaches for *FGFR* Fusions[1]

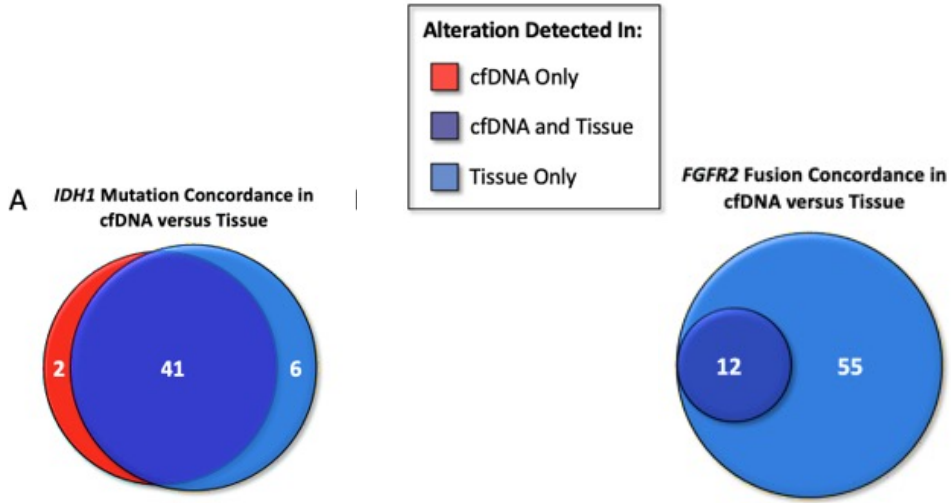
Different *FGFR* fusion detection methods each have different strengths and limitations

Approach	Description	Advantage	Limitation
NGS	• Includes WGS, WES, whole transcriptome sequencing and targeted sequencing of subsets of genes or regions using commercially available IVD panels	• Does not require extensive validation • Focused approach with higher sensitivity; can analyze DNA and/or RNA	• Technically demanding • DNA more stable than RNA, but the detection of novel fusions is limited • RNA-based methods can distinguish in-frame, transcribed gene fusions but sensitivity depends on fusion expression level
Amplicon-based approach	• Uses specific primers to amplify known fusion partners from RNA or DNA samples • Designed to detect gene fusions starting from a small amount of input material	• Suitable for low input samples and degraded RNA; simplified workflow and fast execution	• Limited in detecting novel fusions; requires prior knowledge of fusion partners.
Anchored multiplex PCR	• Uses gene-specific primers anchored to exon-intron boundaries and universal reverse primers to amplify known and unknown genomic regions	• Detects known/unknown fusions • Enriches target regions with knowledge of only one end	• Requires specific primer design • Potential complexity in data interpretation
FISH	• Fluorescently-labelled DNA probes that bind to specific target sequences • Detected by fluorescence microscopy • WT signal pattern shows two pairs of close/fused signals, and colors split apart with translocations	• Detects specific gene translocations and amplifications • Can be performed on FFPE samples (live cells not required) • Relatively fast turnaround time	• Low resolution • Restricted to DNA detection • Cannot detect complex rearrangements, eg intrachromosomal rearrangements (~50% of *FGFR*2 fusions in iCCA) can lead to false positives
IHC	• Provides information on protein localization	• Inexpensive and simple • Useful for detecting overexpression	• Low sensitivity for rare fusions • No proven method for detecting FGFR fusions reliably • Limited to protein detection

1. De Luca A et al. *Int J Mol Sci.* 2020;21(18):6856.

Liquid Biopsy for Detection of *FGFR2* Fusions?





44% of patients with actionable alteration[1]

87% detection for *IDH1* mutations[1]

18% detection for *FGFR2* fusions[1]

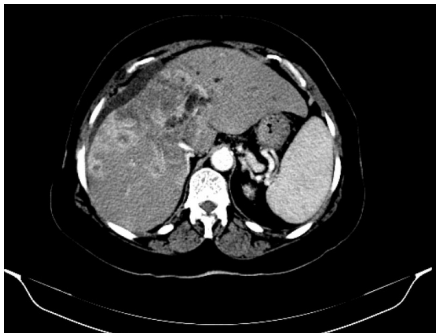
Concordance 87% for *FGFR2* fusions/rearrangements in FOENIX CCA2[2]

1. Berchuck et al. *Ann Oncol*. 2022; 33:1269-1283. 2. Goyal et al. *N Engl J Med*. 2023;388:228-239.

Case Continued: Sherry, a 65-Year-Old Female Patient Progressing On Upfront Therapy

Sherry, A 65-year-old female patient with unresectable CCA was treated with upfront durvalumab + gemcitabine/cisplatin, however, she progressed 4 months later. The patient would like to discuss the next steps to manage their advanced disease.

The patient above undergoes NGS testing, and an *FGFR2-BICC1* fusion is captured.



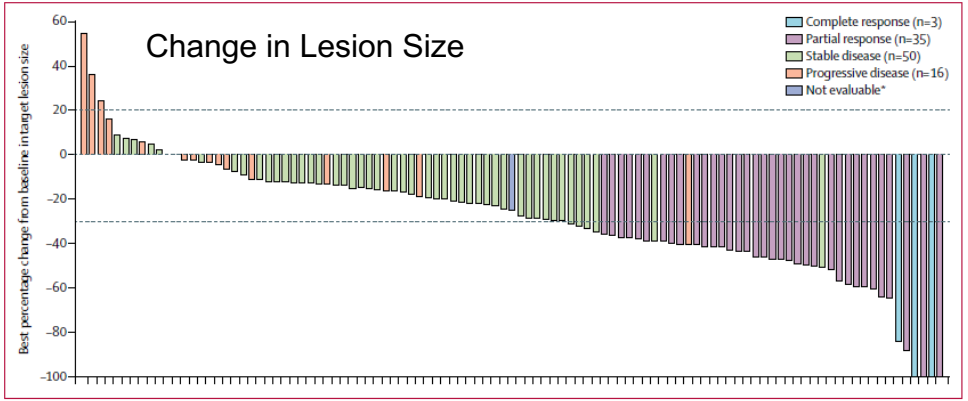
Discussion

How would you proceed?
What considerations inform your choice of approved therapies?
Let's review the evidence…

Evidence Supporting Two Approved FGFR Inhibitors for *FGFR2* Fusion/Rearrangement + Cholangiocarcinoma

Pemigatinib[1]
Reversible FGFR1–3 inhibitor

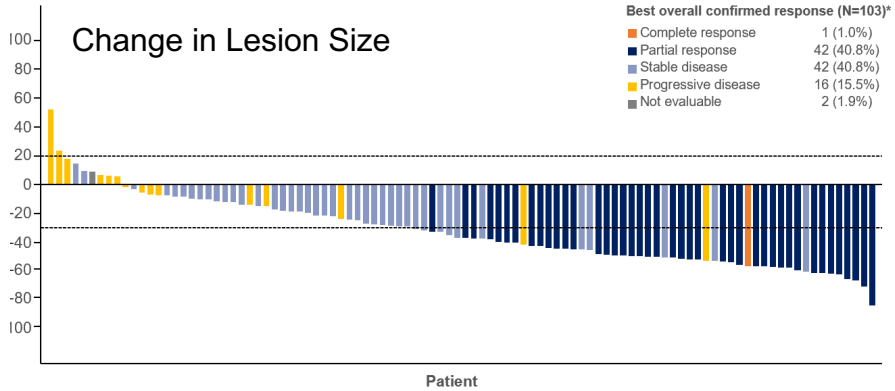
ORR: 35.5%
DCR: 82.2%
PFS: 6.9 months
DOR: 9.1 months



FDA approved 2020, EMA approved 2021

Futibatinib[2]
Irreversible FGFR1–4 inhibitor

ORR: 41.7%
DCR: 82.5%
PFS: 9.0 months
DOR: 9.7 months

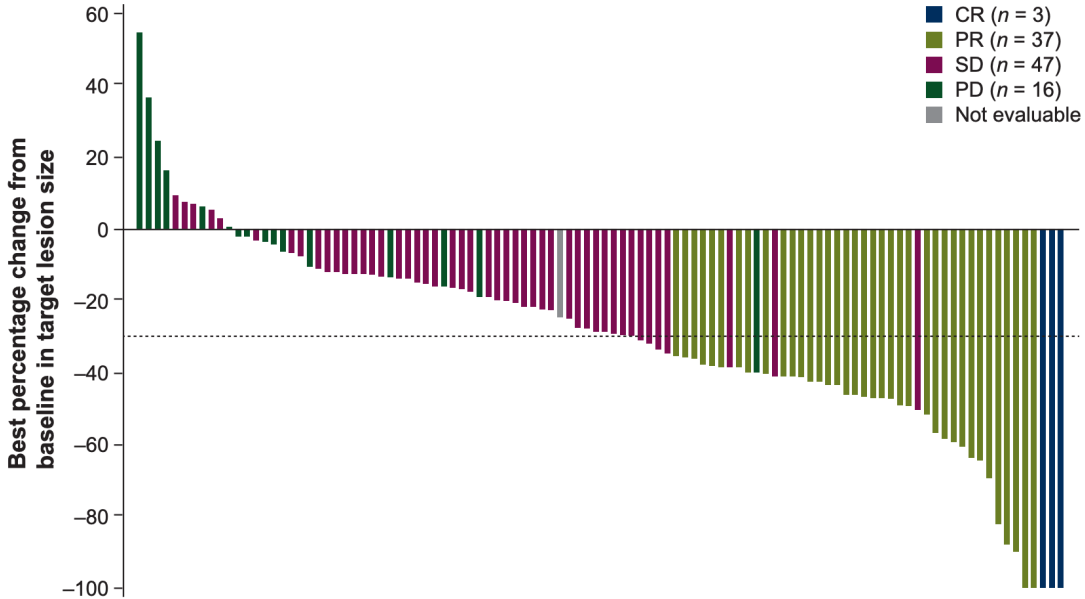


FDA and PMDA approved 2022
EMA approved 2023

1. Abou-Alfa G, et al. *Lancet Oncol*. 2020;21(5):671-684. 2. Goyal et al. *N Engl J Med*. 2023;388:228-239.

Final Results From FIGHT-202 Consistent With Prior Efficacy Evidence With Pemigatinib in BTC

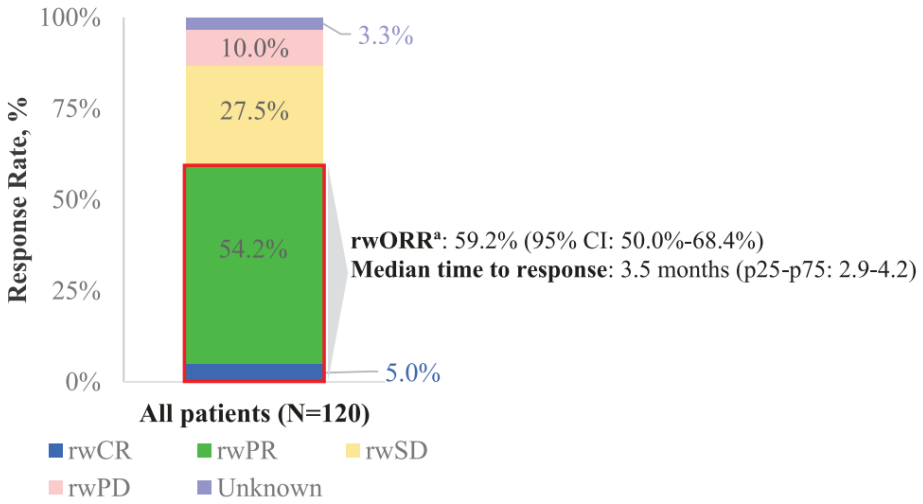
- Median follow-up was 45.4 months.
- ORR in cohort A was 37.0%
- Complete and partial responses were observed in 3 and 37 patients, respectively
- Median DOR was 9.1 (6.0-14.5) months

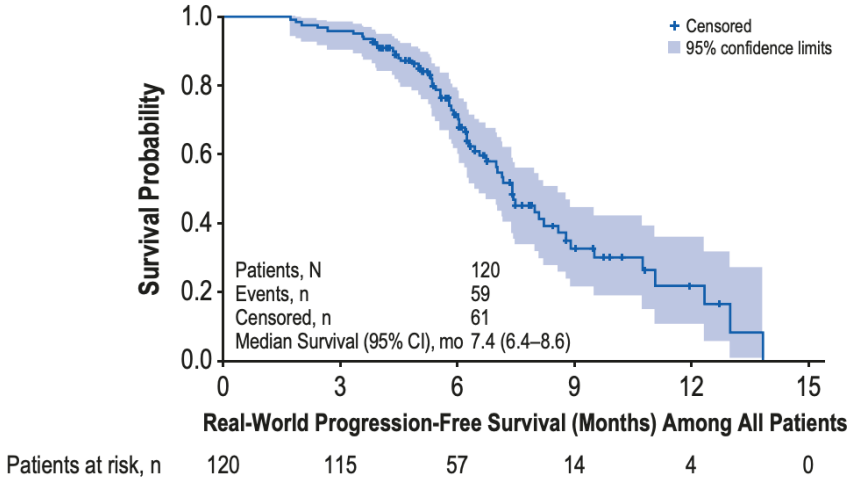


1. Vogel A, et al. ESMO Open. 2024 Jun;9(6):103488.

What Do Real-World Findings Reveal About the Efficacy of FGFR Inhibitors?

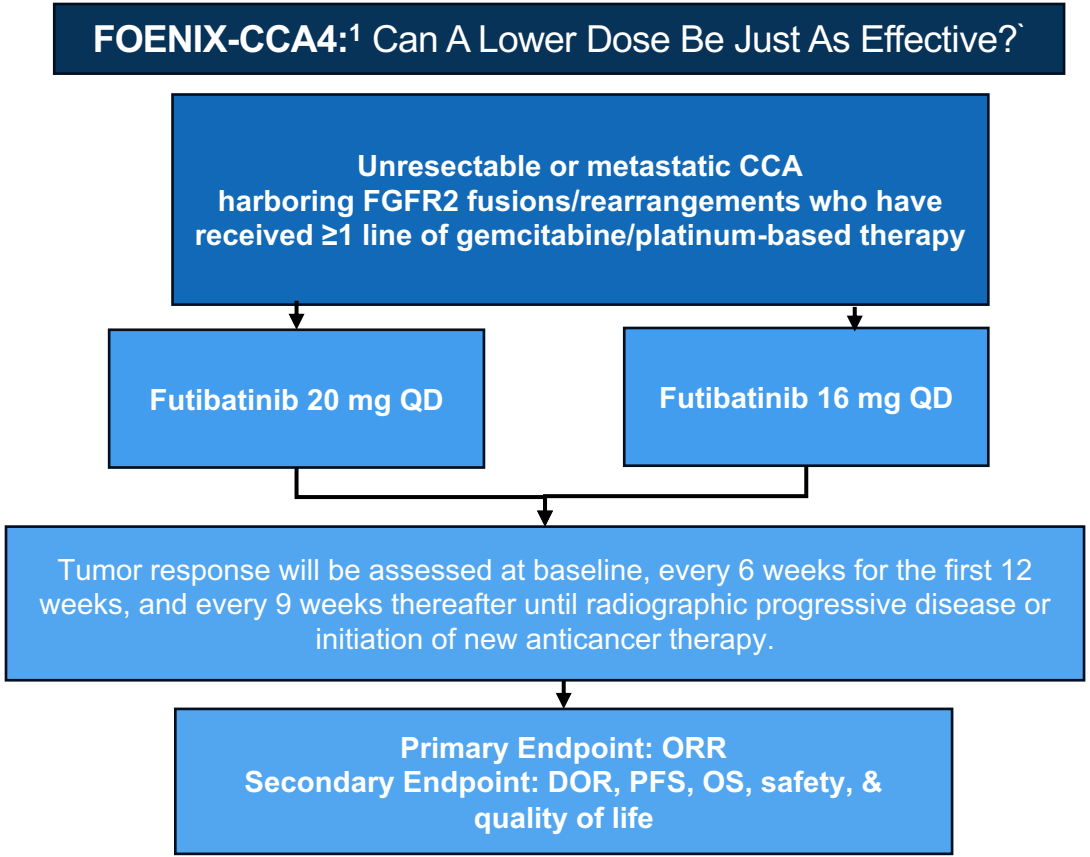
- Real-world study assessing the use of pemigatinib among a diverse population of patients with CCA (N = 120)
- Real-world findings support the clinical benefits demonstrated in FIGHT-202.





1. Saverno K, et al. Oncologist. 2024 Aug 21:Online ahead of print.

Future Considerations With Futibatinib

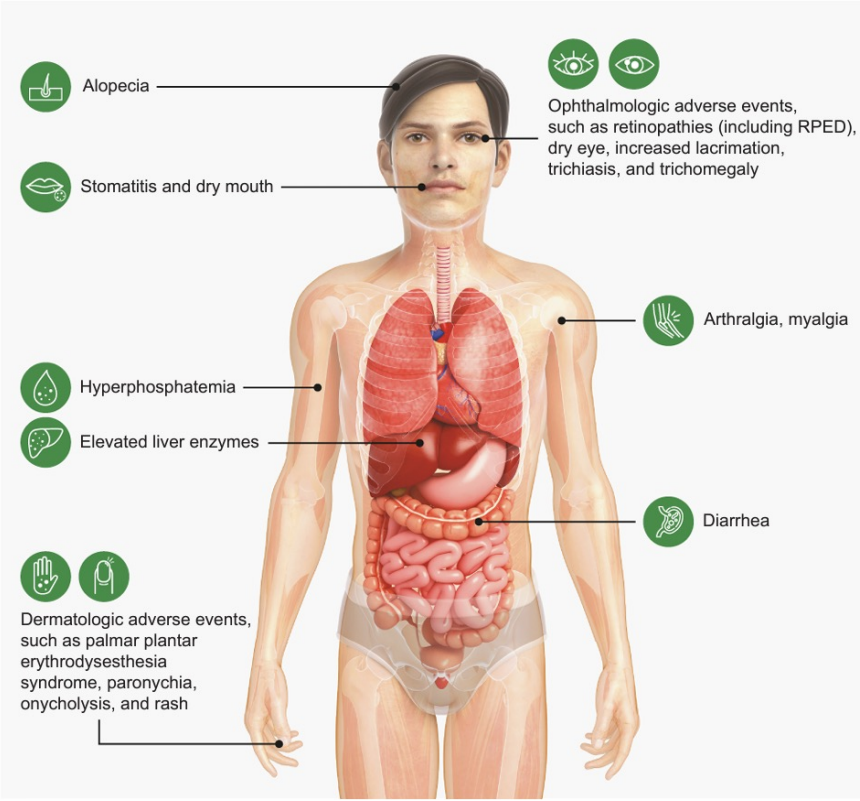


FOENIX-CCA3

Phase 3 study evaluating futibatinib vs. gem-cis chemotherapy as a first-line treatment option in BTC

1. Macarulla T et al. *JCO.2024.42.3_suppl.TPS572*

Key Toxicities of FGFR Inhibitors



- Hyperphosphatemia is the most common side effect of FGFR inhibitors
- Baseline eye exam prior to starting FGFR inhibitors is recommended

1. Meric-Bernstam et al. *Clin Cancer Res.* 2024;30:1466-77.

Management of FGFR Inhibitor–Associated Hyperphosphatemia[1]

- Educate patients on dietary modification to reduce risk of hyperphosphatemia
- Consult a nutrition professional (eg, registered dietitian, nutritionist) for individualized dietary planning
- Phosphate-lowering agents should be considered in patients with elevated phosphorous levels (≥7 mg/dL)

Phosphorous Levels	Grade	Intervention[a]
Sharp rise (25%) in phosphorous levels at the first check; 3.5-5.5 mg/dL	1	• Reinforce on low-phosphate diet
5.5-6.9 mg/dL	2	• Start phosphate binder at lowest possible dose; recheck phosphorous levels in 1 wk • Dose escalation of phosphate binder or addition of phosphaturic agent; consider acetazolamide if phosphorous levels remain elevated after 7 d of initial intervention
7-9.9 mg/dL	3	• Maximum recommended dose of phosphate binder in combination with phosphaturic agent, acetazolamide 250 mg 2 or 3 x/d • Recheck levels in 2 wk; if still ≥7 mg/dL, consider dose interruption for 2 wk • Restart FGFR inhibitor at usual dose; if phosphorous levels recurs at ≥7 mg/dL, consider first- or second-dose reduction when phosphorous levels reach <7 mg/dL
≥10 mg/dL	4	• Hold FGFR inhibitor • Maximum recommended dose of phosphate binder in combination with phosphaturic agent, acetazolamide 250 mg 2 or 3 x/d; reassess phosphorous levels every 2 wk • First- or second-dose reduction when phosphorous levels reach <7 mg/dL • Permanent discontinuation if phosphorus level >10 mg/dL after two dose reductions

[a] Phosphorous levels should be checked on day 4 and day 21 of each cycle (for a 4-week cycle); day 4 and day 14 of each cycle (for a 3-week cycle).

1. Kommalapati A et al. *Cancers*. 2021;13:2968.

Case Continued: Sherry, a 35-Year-Old Female Patient Progressing On Upfront Therapy

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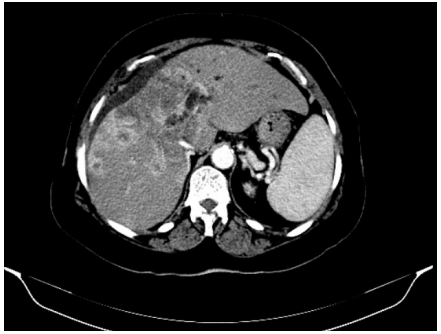
The patient above undergoes NGS testing, and an *FGFR2-BICC1* fusion is captured.

The patient is initiated with futibatinib, and routine monitoring reveals a phosphorus level of 6.5 mg/dL.

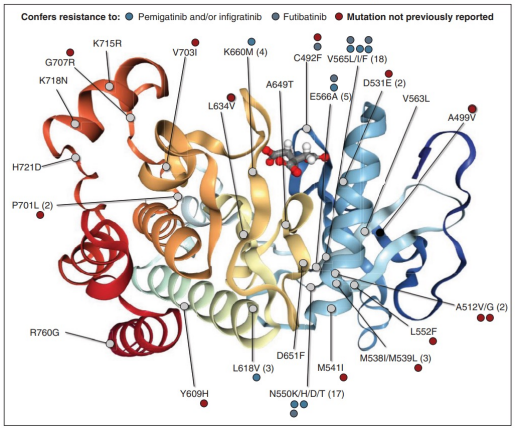


Discussion

How would you manage this AE?

What systemic therapy would you offer next if post-progression ctDNA analysis showed an FGFR2 V565I mutation?

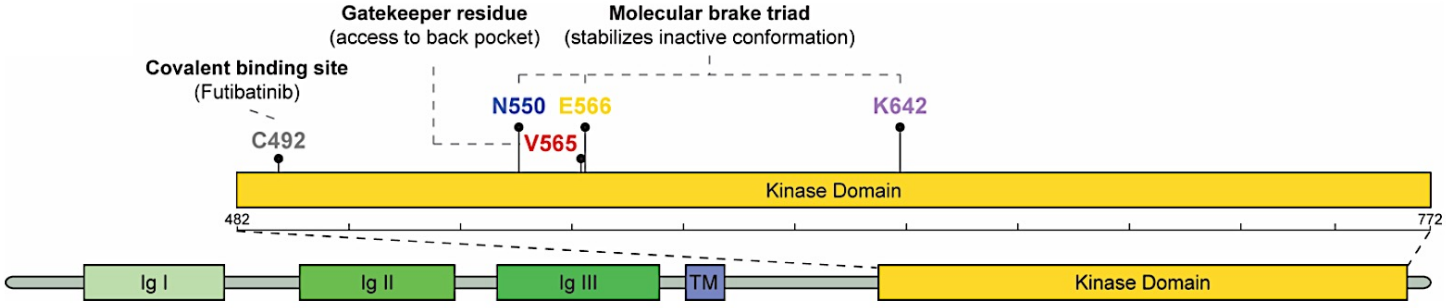
Challenge: Cancer Acquires Resistance to Drugs[1-2]

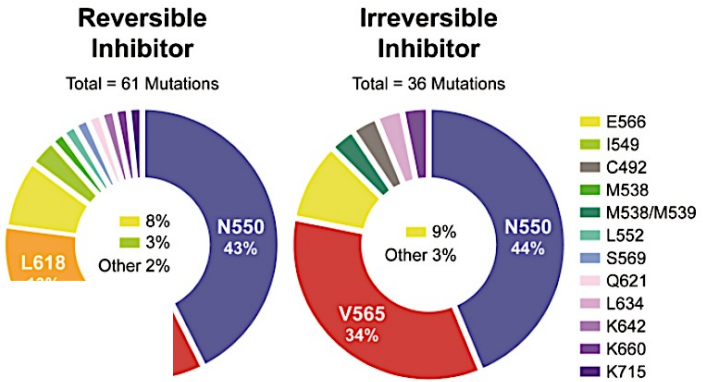


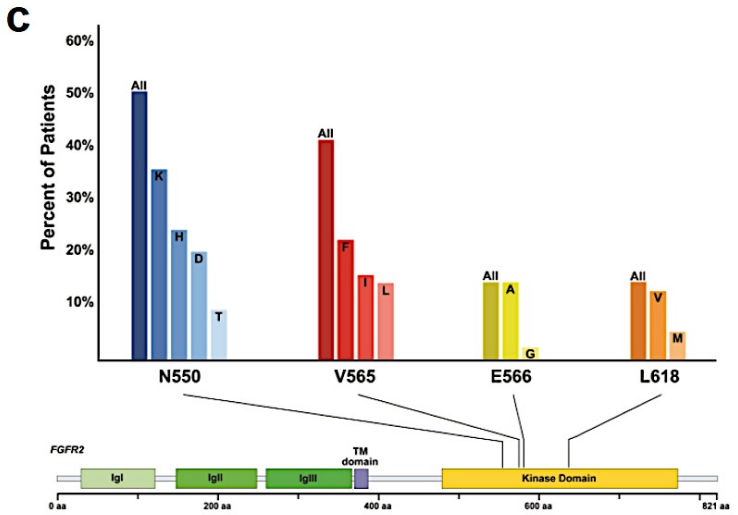
- Serial biopsies show that *FGFR2* mutations emerge at cancer progression
- These clones lead to drug failure and shortened benefit from FGFR inhibitors

1. Ofuji, K. et al. *Int J Oncol.* 2015; 46: 497-504. 2. Berchuck et al. *Ann Oncol*. 2022; 33:1269-1283.

FGFR Resistance Mediated Via Mutations in the FGFR2 Kinase Domain in Cholangiocarcinoma[1-3]







1. Goyal et al. *Annals of Onc.* 2024. 2. Varghese et al. *JCO Precis Oncol.* 2021; 5:PO.20.00178. 3. Wu et al. *Clin Cancer Res*. 2024;30(1):198-208.

Next-Generation FGFR Inhibitors

Lirafugratinib (RLY-4008)
- Highly selective irreversible FGFR2 inhibitor
- Early signals of activity in patients with prior FGFR inhibitors
- Early signals of activity in patients with *FGFR2* mutations and amplifications
- Fewer on target AEs such as hypophosphatemia and diarrhea

Tinengotinib (TT-00420)
- FGFR, VEGFR, CSF1R pathways
- Targets acquired mutations after treatment with FGFR inhibitors

CGT4859
- A potent, selective, reversible FGFR2 inhibitor with best-in-class potential
- Trial assessing efficacy are ongoing

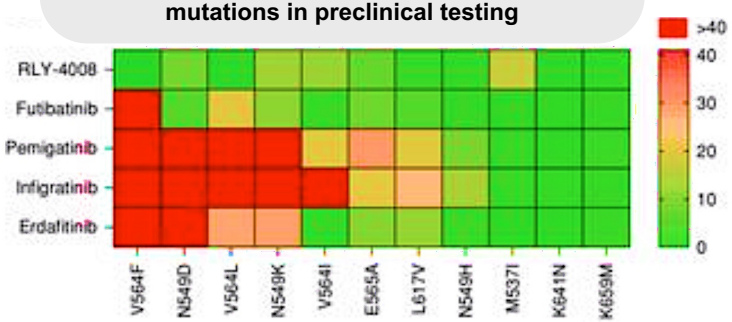
TYRA-200
- FGFR1/2/3 inhibitor with potency against activating FGFR2 gene alterations
- Study evaluating the safety, tolerability, PK, and preliminary antitumor activity

Lirafugratinib (RLY-4008) : The First Highly Selective *FGFR2* Inhibitor[1-5]

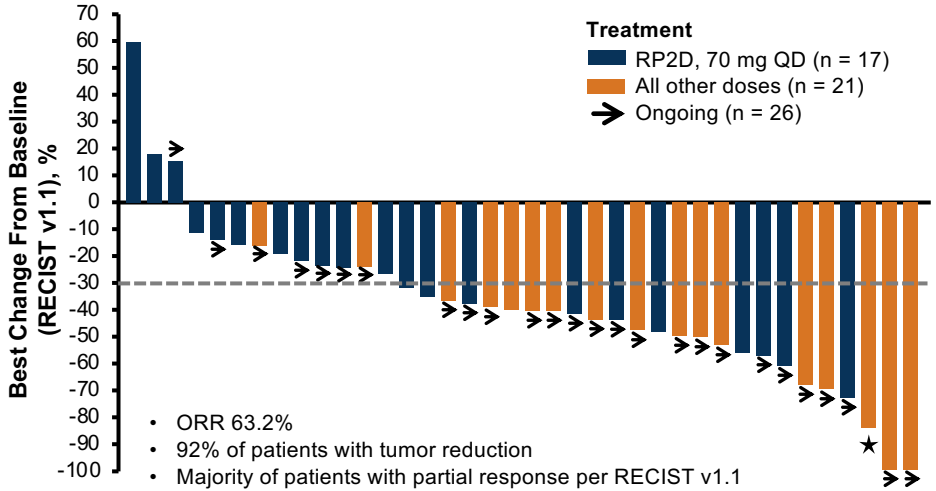
In contrast to pan-FGFRi, RLY-4008 is a potent and selective FGFR2 inhibitor

Inhibitor	Mechanism of Action	Biochemical IC50 (nM)[2-5]			
		FGFR1	*FGFR2*	*FGFR3*	*FGFR4*
RLY-4008	Irreversible FGFR2 selective	864.3	3.1	274.1	17,633
Infigratinib	Reversible Pan-FGFRi	1.1	1	2	61
Pemigatinib	Reversible Pan-FGFRi	0.39	0.46	1.2	30
Futibatinib	Irreversible Pan-FGFRi	1.8	1.4	1.6	3.7

RLY-4008 overcomes multiple FGFR2 resistance mutations in preclinical testing



Patients With *FGFR2* Fusions or Rearrangements, FGFRi-Naïve (N = 38)

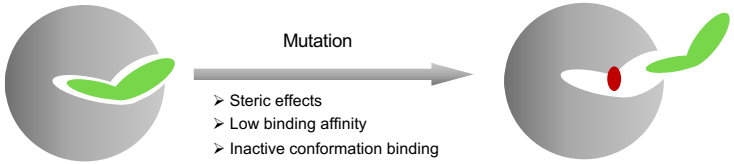


1. Schönherr H. et al. Presented at MedChem GRC meeting; August 7-12, 2022. 2. Goyal L. et al. Presented at AACR Annual Meeting; April-9-14;2021. 3. Sootome H. et al. *Cancer Res.* 2020;80(22):4986-4997. 4. Subbiah,etal, *Cancer Discov*, 2023. 5. Hollebecque et al. *Annals of Oncology*. 2022;33(suppl 7):S808-S869.

Tinengotinib (TT-00420): The Next Generation *FGFR* Inhibitor[1]

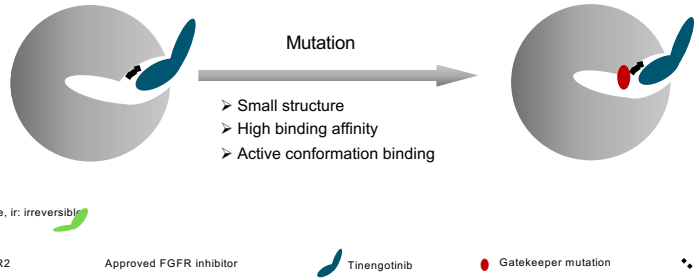
Tinengotinib Binds to FGFR2 in a Unique Mode

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#

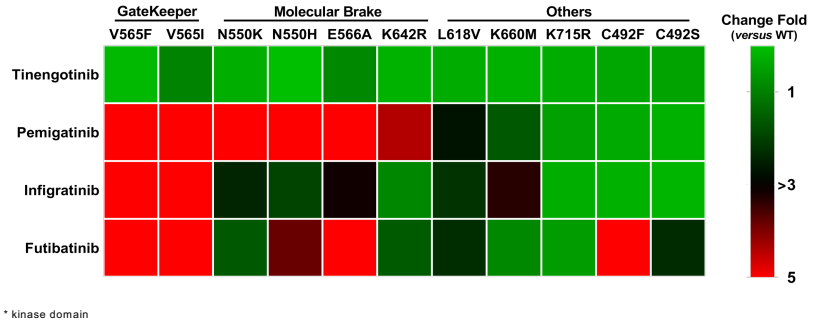
Tinengotinib (r) has unique binding to FGFR2, overcoming acquired resistance mutations



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 confirmation of FGFR2 with high affinity by 3 H-bond.
- Overcomes resistance mutations acquired from treatment with 1st generation FGFR inhibitors.

Tinengotinib Shows Excellent Potency to FGFR2 KD* Mutations

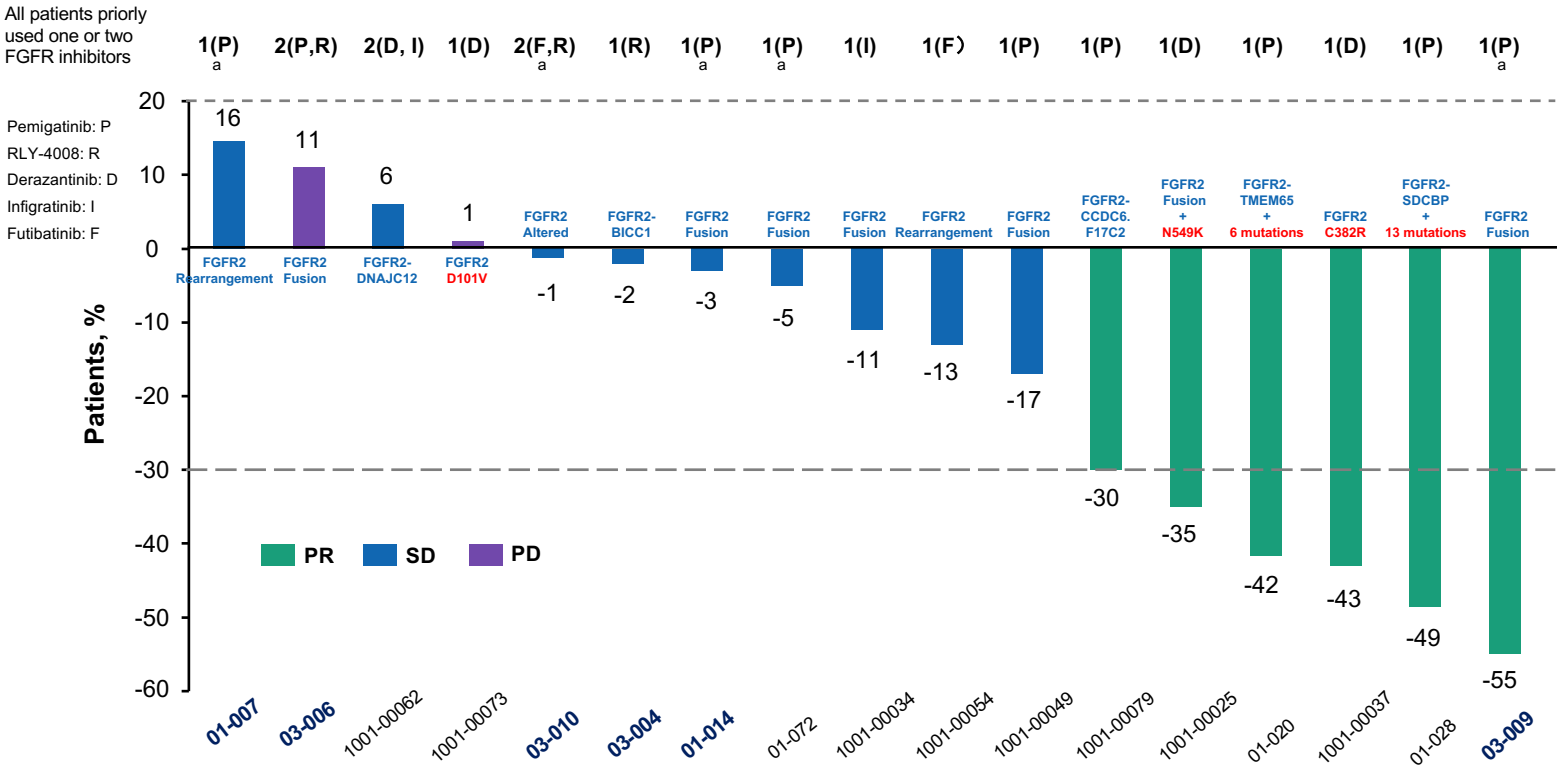


* kinase domain

1. Javle et al. ASCO GI 2024. Abstract TPS575.

PeerView

Tinengotinib (TT-00420): Evaluable CCA Patients With *FGFR2* Alterations, Pretreated by FGFRi (N = 17)[1]

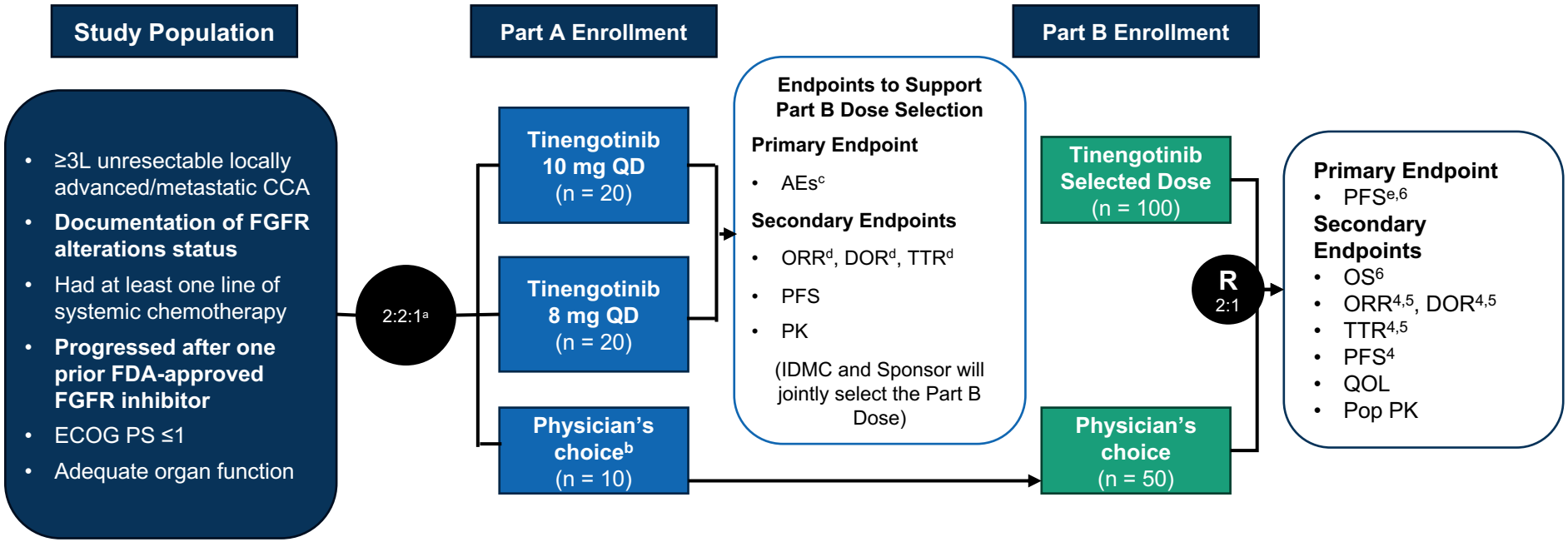


In 2021, TT-00420 received a fast-track designation for the treatment of patients with CCA who have no available standard treatment options

[a] Still on treatment of TT-00420 on or before May 30, 2022.

1. Piha-Paul SAA et al. *J Clin Oncol*. 2021;39(suppl 15):3090. 2. Javle et al. ASCO GI 2024. Abstract 434.

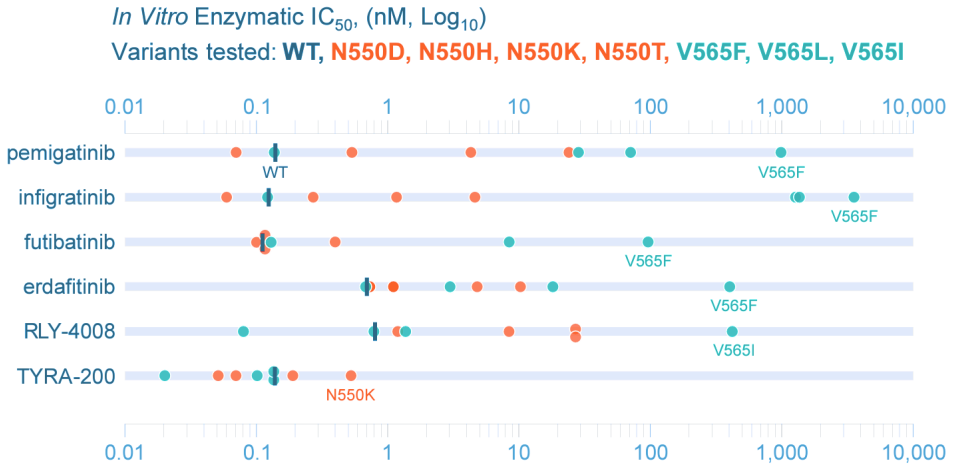
FIRST-308: Phase III Trial of Tinengotinib in *FGFR*-Altered Cholangiocarcinoma After Prior FGFR Inhibitor

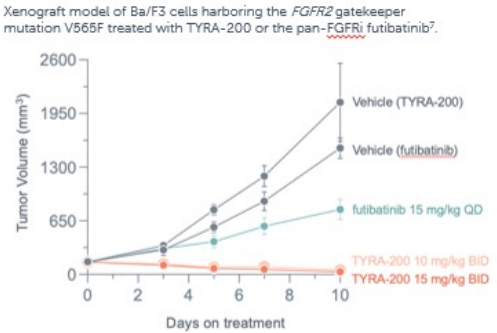


[a] Subjects will be stratified by region (North America, Europe, and Asia) and number of prior chemotherapies (1 vs ≥ 2), and investigator's choice of chemotherapy for patients on the Physician's Choice arm. [b] Physician's Choice will be limited to 5-fluorouracil, folinic acid or leucovorin plus oxaliplatin (FOLFOX), fluorouracil, leucovorin plus irinotecan (FOLFIRI). Note: 5-FU single agent or 5-FU plus leucovorin are not allowed. [c] Incidence, Duration, and Severity of AEs. Subjects treated at the same dose of tinengotinib from other oncology trials will be included in the analysis for dose selection.[d] Assessed by Investigators [e] Assessed by blinded independent central review (BICR). [f] Time to response (TTR).

1. Javle et al. ASCO GI 2024. Abstract TPS575.

TYRA-200 is a reversible FGFR1-3 inhibitor in Clinical Development





TYRA-200 Development is Focusing on FGFR Inhibitor-Resistant Tumors

- MTD
  - Part A: FGF/FGFR+ all comers
- R2PD
  - Part B: FGFR2+ ICC, prior FGFRi

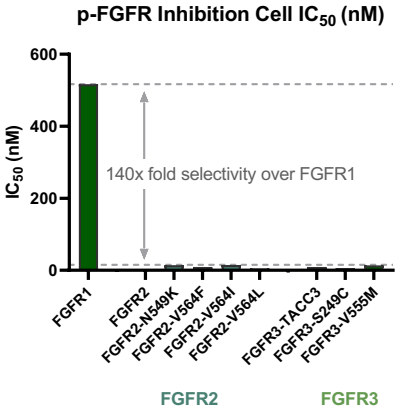
1. Allen E et al. *European Journal of Cancer*. 2022;174:S16.

CGT4859 is Designed to Fulfill Unmet Need in FGFR Inhibitor Class[1]

Target Product Profile

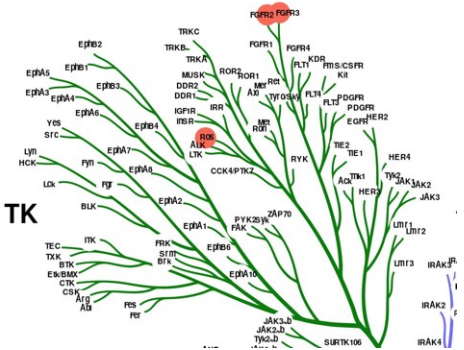
FGFR1 Sparing	Improved target engagement over time by avoiding hyperphosphatemia
Potent on Mutations	Retains high potency against prevalent gatekeeper and molecular brake mutations
Reversible Inhibition	Possibility for improved tolerability Active against potential C491S mutation
Safety	Highly selective for FGFR across the kinome
Low DDI Potential	Low potential for CYP-mediated DDI based on in vitro data, BCS Class 1 or 2

CGT4859



CGT4859 exhibits140x selectivity over FGFR1, low nM potency on FGFR2 WT and retains activity across FGFR2 mutations

In a panel of 371 kinases, only FGFR2, FGFR3, and ROS showed ≥ 50%inhibition



1. https://clinicaltrials.gov/study/NCT06777316

PeerView

Phase 3 PROOF 301 Trial: Lessons From Infigratinib

Enrollment

Patients aged ≥18 years with unresectable locally advanced or metastatic CCA:

- *FGFR*2 fusion or rearrangement
- ECOG PS 0-1
- No systemic therapy for unresectable locally advanced or metastatic disease
  - 1 prior cycle of gemcitabine-based chemotherapy for locally advanced/metastatic CCA is allowed.

Stratified by:

- Disease state (locally advanced vs metastatic disease)
- Geographic region (North America, Western Europe, Asia Pacific, RoW)
- Prior neoadjuvant/adjuvant treatment (yes/no)
- Received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced/metastatic CCA (yes/no)

R
2:1

Treatment

Infigratinib monotherapy
125 mg qd x 21 days Q28 days

Treatment given until radiographic PD by BICR or unacceptable toxicity

Gemcitabine + cisplatin
1000 mg/m² and 25 mg/m², respectively, d1 & 8 Q21 days

Patients may be eligible to cross over to infigratinib after PD confirmed by BICR

Infigratinib showed promising efficacy in treating FGFR-rearranged CCA. A follow-up Phase 3 **study ended early**, making it **difficult to draw definitive conclusions** about its efficacy compared to gemcitabine plus cisplatin. Studying rare tumor subgroups identified by biomarkers in rare malignancies is challenging. It highlights the **need to explore alternative approaches** to acquire data for meeting regulatory requirements.

Lessons and Take-Homes From PROOF-301

- Efficacy of infigratinib as a first-line treatment for FGFR2-fusion positive cholangiocarcinoma
- Importance of accurate FGFR2 biomarker testing
- Potential for resistance development
- Need for further research on combination therapies to overcome resistance mechanisms

1. Abou-Alfa et al. ASCO GI 2024. Abstract 516.

Leveraging The Evidence Against *IDH* mutations In Biliary Tract Cancer

Ghassan Abou-Alfa, MD, JD, MBA
New York, New York
Professor
Memorial Sloan Kettering Cancer Center
Weill Cornell College at Cornell University
Trinity College Dublin

Current NCCN Guidelines On Subsequent-Line Targeted Options

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[1]

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors
  - Entrectinib
  - Larotrectinib
  - Repotrectinib
- For MSI-H/dMMR tumors
  - Pembrolizumab
  - Dostarlimab (category 2B)
- For TMB-H tumors
  - Nivolumab + ipilimumab
  - Pembrolizumab
- For *BRAF* V600E–mutated tumors
  - Dabrafenib + trametinib

- For CCA with *FGFR2* fusions or rearrangements
  - Futibatinib
  - Pemigatinib
- For CCA with *IDH1* mutations
  - **Ivosidenib** (category 1)
- For HER2-positive tumors
  - Zanidatamab (IHC 3+)
  - Trastuzumab + pertuzumab
  - Fam-trastuzumab deruxtecan (IHC 3+)
  - Tucatinib + trastuzumab
- For *RET* gene fusion-positive tumors
  - Selpercatinib for CCA
  - Pralsetinib (category 2B)
- For *KRAS* G12C mutation-positive tumors
  - Adagrasib

1. NCCN Clinical Practice Guidelines in Oncology. Biliary Tract Cancers. Version 6.2024. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf.

Phase 3 ClarIDHy Trial: IDH1 Inhibitor Ivosidenib Versus Placebo in Second-Line Setting[1-6]

Key Eligibility Criteria
- Aged ≥18 years
- Histologically confirmed CCA
- Centrally confirmed m*IDH1* status
- ECOG PS 0 or 1
- 1-2 prior therapies (≥1 regimen containing gemcitabine or 5-FU)
- Measurable lesion, as defined by RECIST v1.1
- Adequate hematologic, hepatic, and renal function
- N = 185

R 2:1

- Ivosidenib 500 mg once daily orally continuous 28-day (±2 d) cycles (n = 124)
- Placebo (n = 61) → Crossover to ivosidenib at disease progression

- **Stratification:** number of prior therapies
- **Primary endpoint:** PFS by blinded independent radiology center

Led to FDA approval (August 2021) and NCCN guideline recommendation for patients with *IDH1*-mutant advanced CCA

	Ivosidenib (n = 126)	Placebo (n = 61)
Median OS, mo	10.3	7.5
6-month OS rate, %	69	57
12-month OS rate, %	43	36

	Ivosidenib (n = 126)	Placebo (n = 61)
Median PFS, mo	2.7	1.4
6-month PFS rate, %	32	NE
12-month PFS rate, %	22	NE
Disease control rate, % (PR + SD)	53 (2% PR, 51% SD)	28 (0% PR, 28% SD)

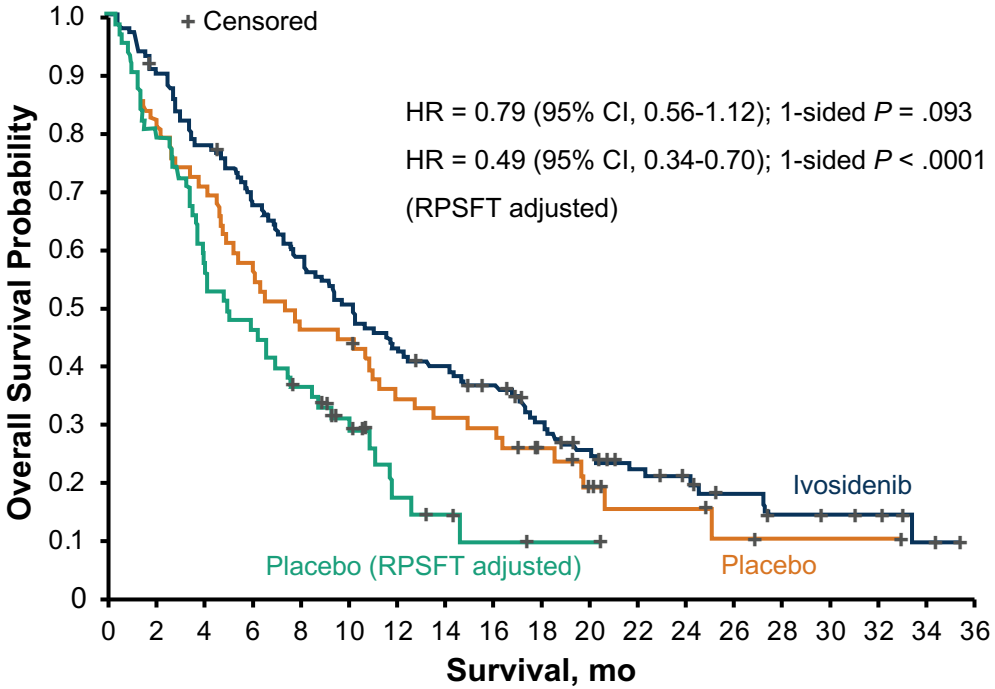
1. https://clinicaltrials.gov/ct2/show/NCT02989857. 2. Abou-Alfa GK et al. *Lancet Oncol.* 2020;21:796-807. 3. NCCN Clinical Practice Guidelines in Oncology. Biliary Tract Cancers. Version 6.2024. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. 4. Zhu A et al. ASCO GI 2021. Abstract 268.
5. Abou-Alfa GK et al. ASCO 2021. Abstract 4069. 6. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-advanced-or-metastatic-cholangiocarcinoma.

Phase 3 ClarIDHy Trial: IDH1 Inhibitor Ivosidenib Versus Placebo in Second-Line Setting[1-2]

Outcome	Ivosidenib (n = 126)	Placebo (n = 61)
OS		
Median, mo	10.3	7.5
6-mo rate, %	69	57
12-mo rate, %	43	36
PFS		
Median, mo	2.7	1.4
6-mo rate, %	32	NE
12-mo rate, %	22	NE
DCR, % (PR + SD)	53 (2% PR, 51% SD)	28 (0% PR, 28% SD)

1. Abou-Alfa GK et al. *Lancet Oncol*. 2020;21:796-807. 2. Zhu A et al. *JAMA Oncol*. 2021;7:1669-1677.

ClarIDHy: Final Analysis of OS[1]

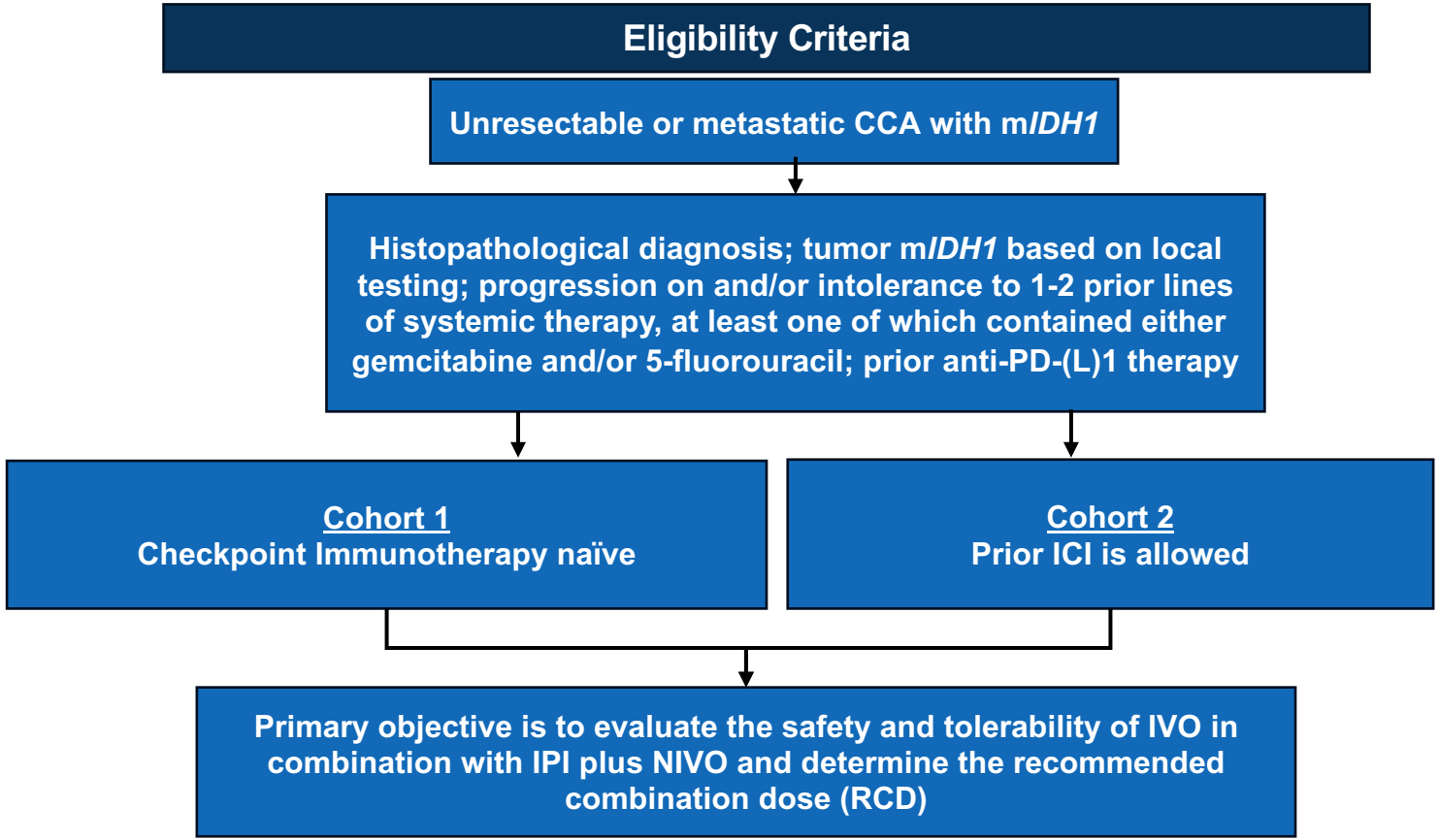


	Ivosidenib (n = 126)	Placebo (n = 61)
Median OS, mo	10.3	7.5
6-month OS rate, %	69	57
12-month OS rate, %	43	36

Rank-preserving structural failure time method was used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib; with this method, the median OS with placebo adjusts to 5.1 months

1. Zhu A et al. *JAMA Oncol*. 2021;7:1669-1677.

Safety Lead-In & Dose Expansion Study on Ivosidenib[1]



1. Kelley K et al. *JCO*.2024.42.16_suppl.TPS4197.

ClarIDHy: Summary of Treatment Emergent Adverse Events[1]

TEAE, n (%)	Placebo (n = 59)	Ivosidenib (n = 123)	Total Ivosidenib (n = 166)[a]
Nausea	17 (29)	51 (41)	63 (38)
Diarrhea	10 (17)	43 (35)	55 (33)
Fatigue	10 (17)	38 (31)	48 (29)
Cough	5 (8)	31 (25)	36 (22)
Abdominal pain	9 (15)	30 (24)	37 (22)
Ascites	9 (15)	28 (23)	33 (20)
Decreased appetite	11 (19)	30 (24)	36 (22)
Anemia	3 (5)	22 (18)	30 (18)
Vomiting	11 (19)	28 (23)	33 (20)

- The most common grade 3 or higher TEAE reported in both treatment groups was ascites (11 patients [9%] who received ivosidenib and 4 patients [7%] who received placebo)
- TEAEs leading to dose reductions and interruptions were uncommon with 5 patients (4%) in the ivosidenib group requiring a dose reduction vs none in the placebo group
- TEAEs leading to study drug discontinuation occurred for 9 patients (7%) in the ivosidenib group vs 5 patients (8%) in the placebo group

[a] Total ivosidenib includes 43 patients initially assigned to placebo who had crossed over to ivosidenib upon radiographic disease progression and unblinding.

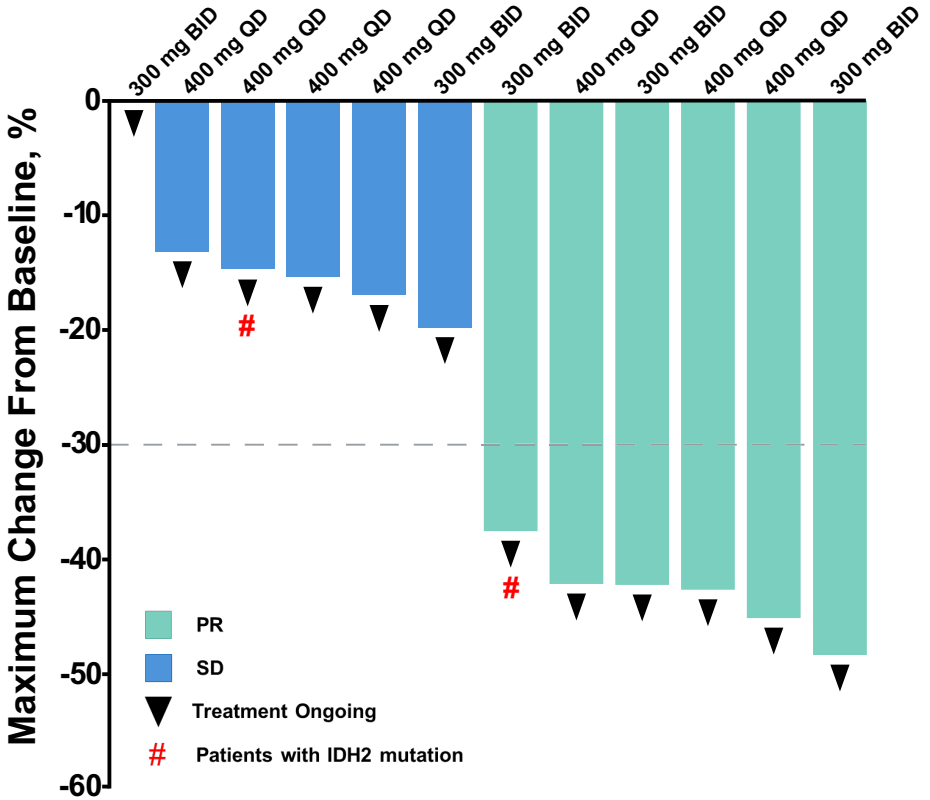
1. Zhu A et al. *JAMA Oncol*. 2021;7:1669-1677.

Emerging IDH-Targeted Agents and Strategies[1]

Drug	Phase	NCT
Olaparib and durvalumab	2	NCT03991832
Olaparib and ceralasertib	2	NCT03878095
LY3410738	2	NCT04521686
HMPL-306	1	NCT04762602

1. https://clinicaltrials.gov.

Antitumor Activity of LY3410738 and Cis-Gem in Treatment Naïve iCCA



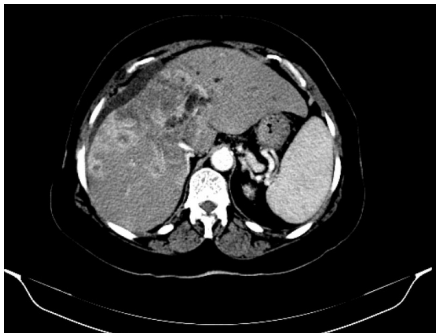
Best Overall Response[a]	LY3410738 + CISGEM (N = 13)[c]
ORR[b], %	46%
PR, n (%)	6 (46%)[d]
SD, n (%)	6 (46%)
mPFS, months (95% CI)	NE (5.9, NE)
Median follow-up months (95% CI)	4.1 (1.9, 7.8)

1. Harding et al. *Annals of Oncology*. 2023;34:S161.

Case Variation: Sherry, a 65-Year-Old Female Patient Progressing On Upfront Therapy

Sherry, A 65-year-old female patient with unresectable CCA was treated with upfront durvalumab + gemcitabine/cisplatin, however, she progressed 4 months later. The patient would like to discuss the next steps to manage their advanced disease.

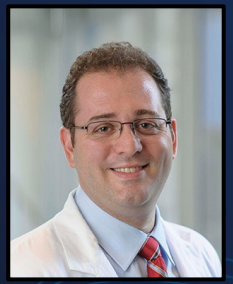
The patient above undergoes NGS testing, and an *IDH1* mutation is captured.



Discussion

Would your treatment decision change? What regimen would you select? Are there any emerging combination strategies you might consider via a clinical trial (eg, targeted + immunotherapy)?

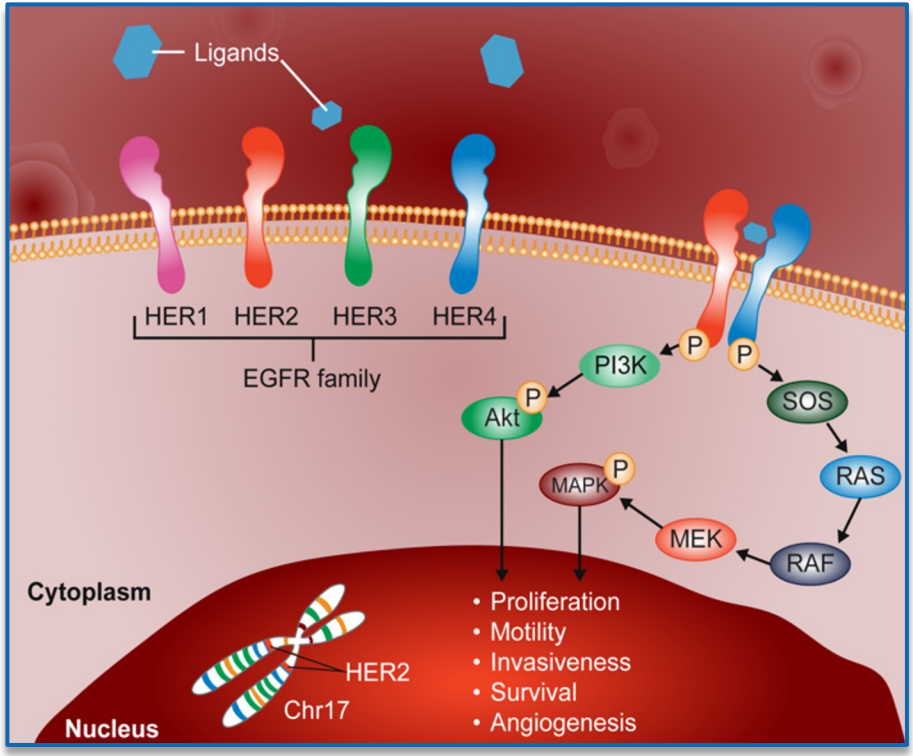
Establishing New Treatment Standards For HER2-Positive BTC



James J. Harding, MD
Gastrointestinal Medical Oncologist
Early Drug Development Specialist
Memorial Sloan Kettering Cancer Center
New York, New York

ERBB Family: Targeting HER2 and HER3[1,2]

- Human epidermal growth factor receptor (HER) family includes
  - Epidermal growth factor receptor (EGFR)
  - HER2 (ERBB2)
  - HER3 (ERBB3)
  - HER4 (ERBB4)
- Share common structural features
- Aberrantly activated in multiple cancers
- Serves as drug targets and biomarkers for precision oncology



1. Adapted from Ross JS. *Drug News Perspect*. 2009;22:93-106. 2. Adapted from Reinholz MM et al. *Lancet Oncol*. 2009;10:267-277.

How Do We Select Among Available Treatment Options For HER2+ BTC?

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[1]

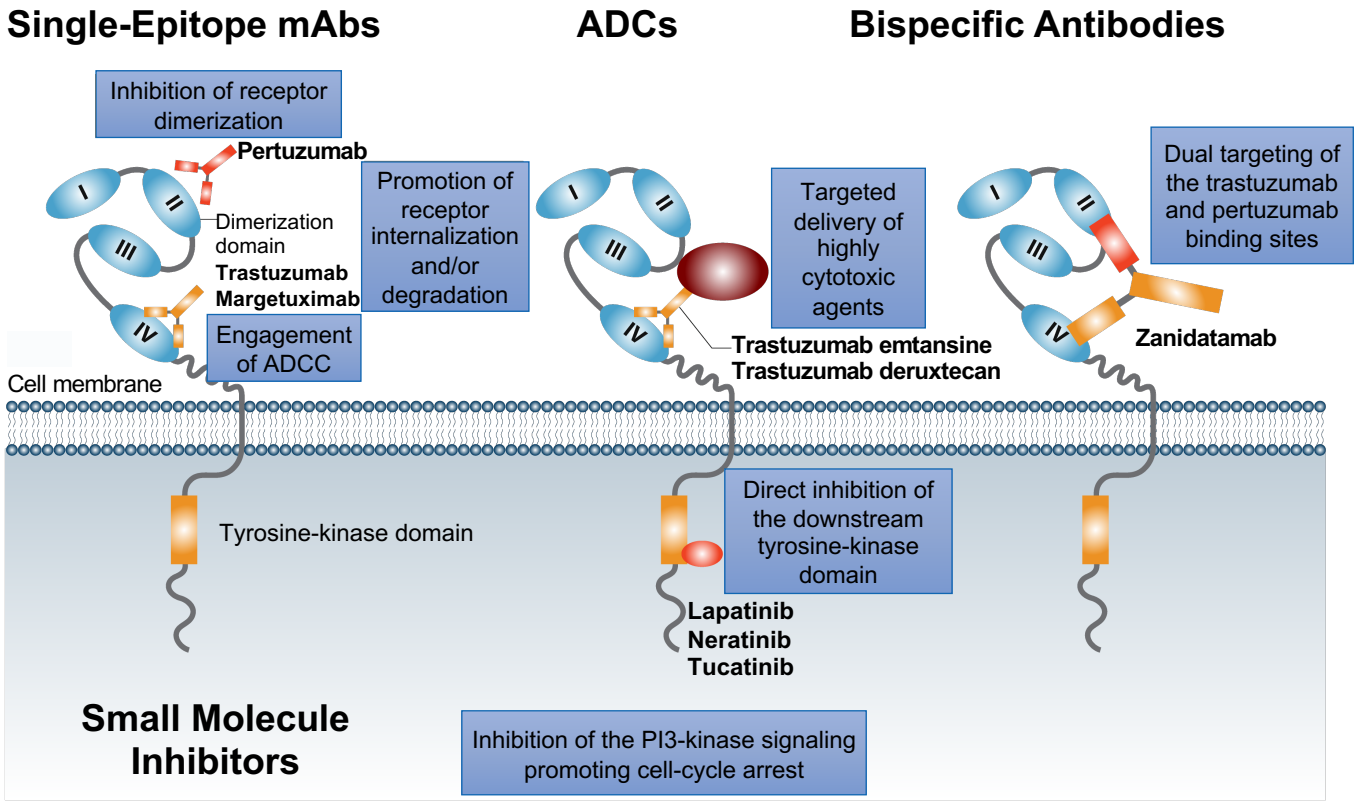
Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors
  - Entrectinib
  - Larotrectinib
  - Repotrectinib
- For MSI-H/dMMR tumors
  - Pembrolizumab
  - Dostarlimab (category 2B)
- For TMB-H tumors
  - Nivolumab + ipilimumab
  - Pembrolizumab
- For *BRAF* V600E–mutated tumors
  - Dabrafenib + trametinib

- For CCA with *FGFR2* fusions or rearrangements
  - Futibatinib
  - Pemigatinib
- For CCA with *IDH1* mutations
  - Ivosidenib (category 1)
- For HER2-positive tumors
  - **Zanidatamab** (IHC 3+)
  - **Trastuzumab + pertuzumab**
  - **Trastuzumab deruxtecan** (IHC 3+)
  - **Tucatinib + trastuzumab**
- For *RET* gene fusion-positive tumors
  - Selpercatinib for CCA
  - Pralsetinib (category 2B)
- For *KRAS* G12C mutation-positive tumors
  - Adagrasib

1. NCCN Clinical Practice Guidelines in Oncology. Biliary Tract Cancers. Version 6.2024. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf.

Mechanisms of Action of Agents Targeting HER2[1]



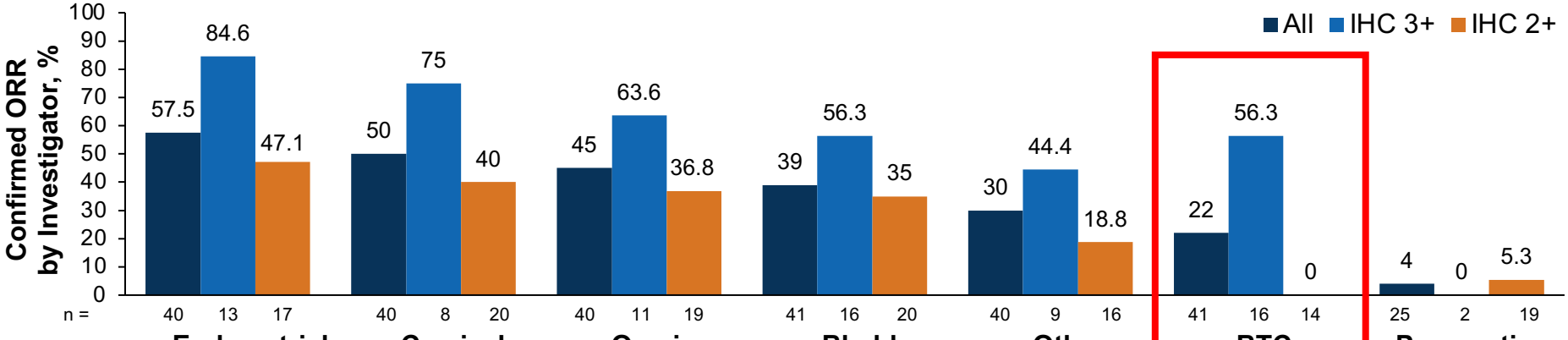
1. Oh DY, Bang YJ. *Nat Rev Clin Oncol*. 2020;17:33-48.

Overview of Clinically Available HER2 Targeted Therapy

Criteria	Agent	Mechanism	Design	N	ORR
SNV	Neratinib	TKI	Basket	25	16%
SNV	Trastuzumab Deruxtecan	ADC	Basket	19	10.5%
AMP OR IHC2/3+ OR Both	Trastuzumab + Pertuzumab	MoA	Basket	39	25%
IHC 2/3+	Trastuzumab Deruxtecan	ADC	Phase 2	35	36.5%
			Basket	41	25% IHC 3+ 56.7%
AMP and IHC 2/3+	Zanidatamab	Bispecific	Phase 2	80	41.1% IHC 3+ 51.6%
AMP or IHC 2/3+	Trastuzumab + Tucatinib	TKI + MoA	Basket	30	46.7%

DESTINY-PanTumor02: Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors (NCT04482309)[1]

Objective Response and Duration of Response



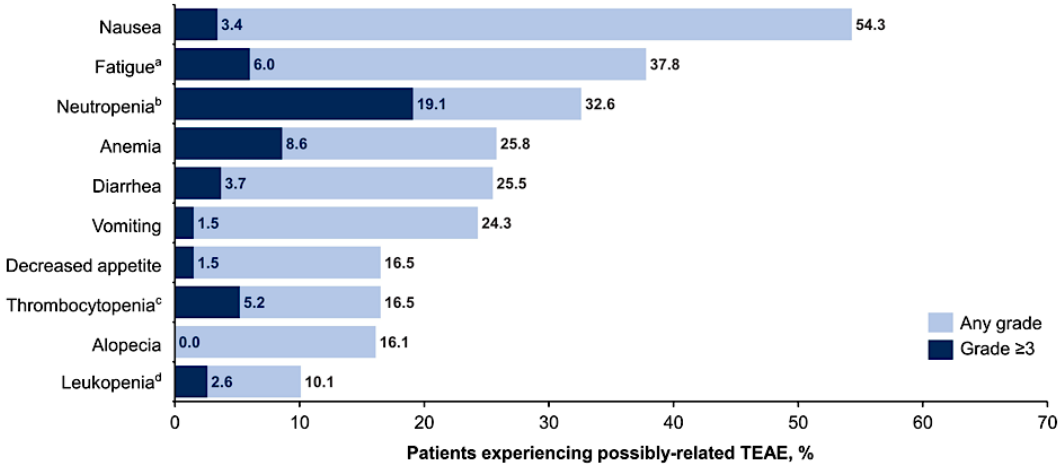
	Endometrial	Cervical	Ovarian	Bladder	Other	BTC	Pancreatic
Median DOR, mo (95% CI)	NR (9.9-NR)	14.2 (4.1-NR)	11.3 (4.1-22.1)	8.7 (4.3-11.8)	22.1 (4.1-NR)	8.6 (2.1-NR)	5.7 (NR-NR)

	All Patients (N = 267)	IHC 3+ (n = 75)	IHC 2+ (n = 125)
ORR, % (95% CI)	37.1 (31.3-43.2)	61.3 (49.4-72.4)	27.2 (19.6-35.9)
Median DOR, mo (95% CI)	11.3 (9.6-17.8)	22.1 (9.6-NR)	9.8 (4.3-12.6)

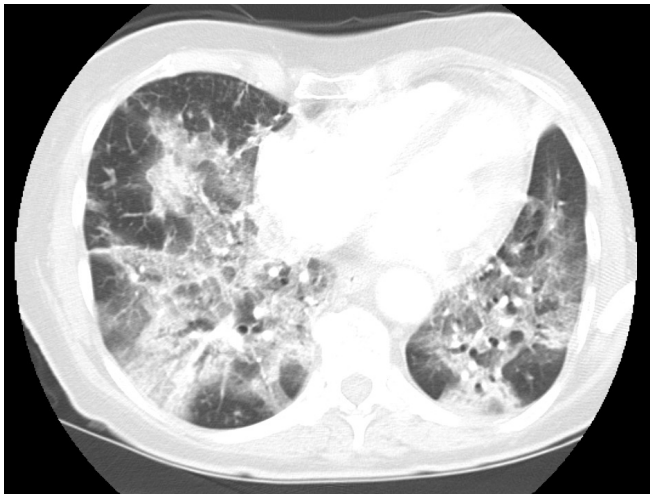
1. Meric-Bernstam F et al. ESMO 2023. Abstract LBA34.

Trastuzumab Deruxtecan: Notable AEs

- Drug-Related TEAEs in ≥ 10% patients



ILD/Pneumonitis



1. Meric-Bernstam F et al. ESMO 2023. Abstract LBA34.

Detecting and Managing T-DXd–Related ILD: The Five "S" Rules[1]

1 Screen

- Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on baseline risk
- Screening continues during treatment, with regular clinical assessments to exclude signs/ symptoms of ILD

2 Scan

- The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest
- A baseline scan is recommended, with repeat scans to be performed every 6-12 weeks

3 Synergy

- Minimizing the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected

4 Suspend Treatment

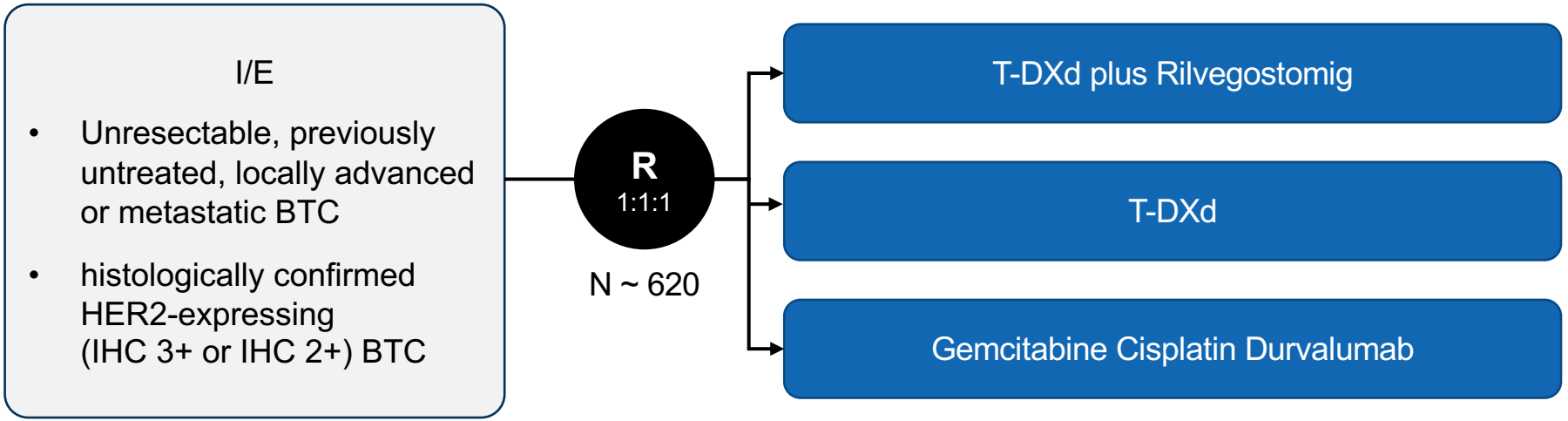
- T-DXd should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves

5 Steroids

- The mainstay for treating T-DXd–induced ILD remains corticosteroids, with the dose adapted to the toxicity grade

1. Tarantino P, Tolaney SM. *JCO Oncol Pract*. 2023;19:526-527.

DESTINY-BTC-01: Phase 3 Study of T-DXd and Rilvegostomig Vs SOC in Advanced HER2-Expressing Biliary Tract Cancer[1]



Primary objective:

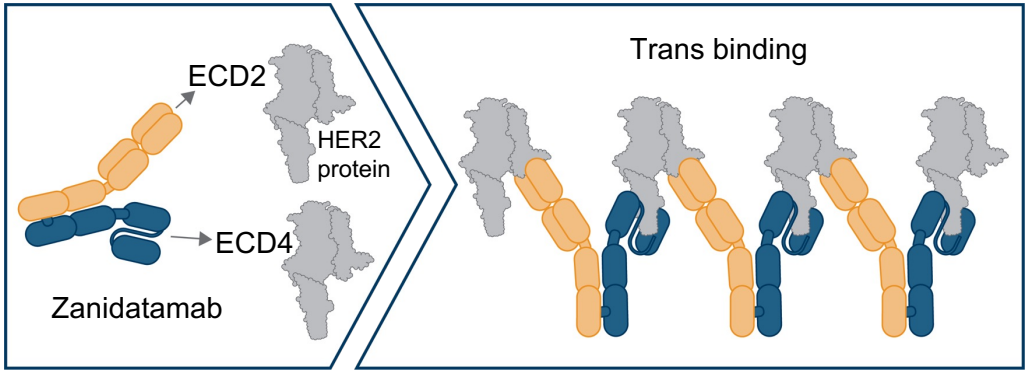
- Overall Survival HER2 3+
- Safety Run

1. https://clinicaltrials.gov/study/NCT06467357.

Zanidatamab (ZW25), A Bispecific Antibody for HER2-Expressing Cancers[1]

Zanidatamab's unique binding geometry

- Biparatopic binding targets two distinct HER2 epitopes and results in HER2 binding across a range of expression levels (low to high)
  - The geometry of zanidatamab prevents it from binding to the same HER2 molecule
  - Binding occurs on 2 separate HER2 molecules in *trans*

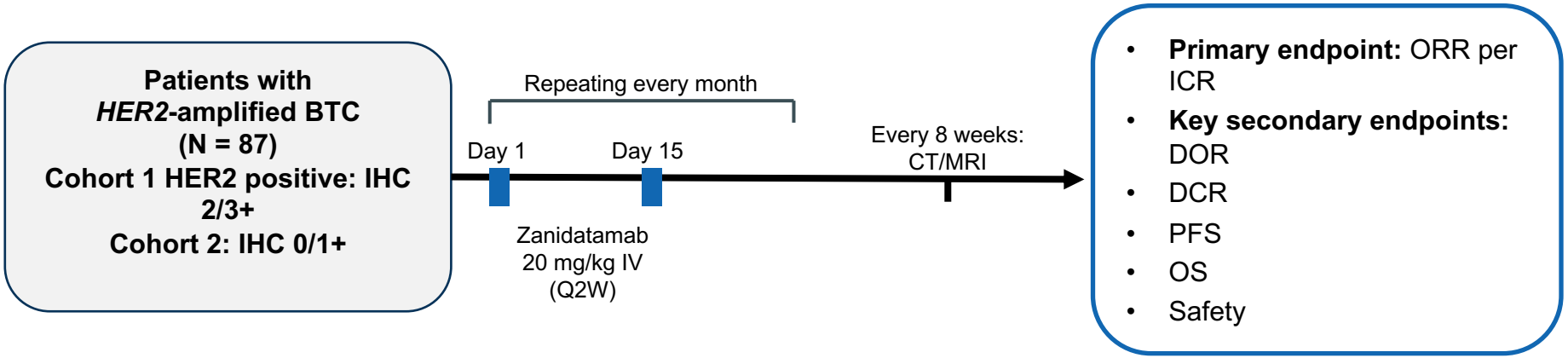


Dual HER2-binding of zanidatamab drives unique MOA

- HER2-receptor cross-linking, clustering, internalization, and downregulation
  - Enhanced receptor clustering on cell surface (cluster internalization, receptor downregulation) compared to trastuzumab ± pertuzumab
  - Inhibition of cellular proliferation
- Fc-mediated cytotoxicity: ADCC, ADCP, CDC

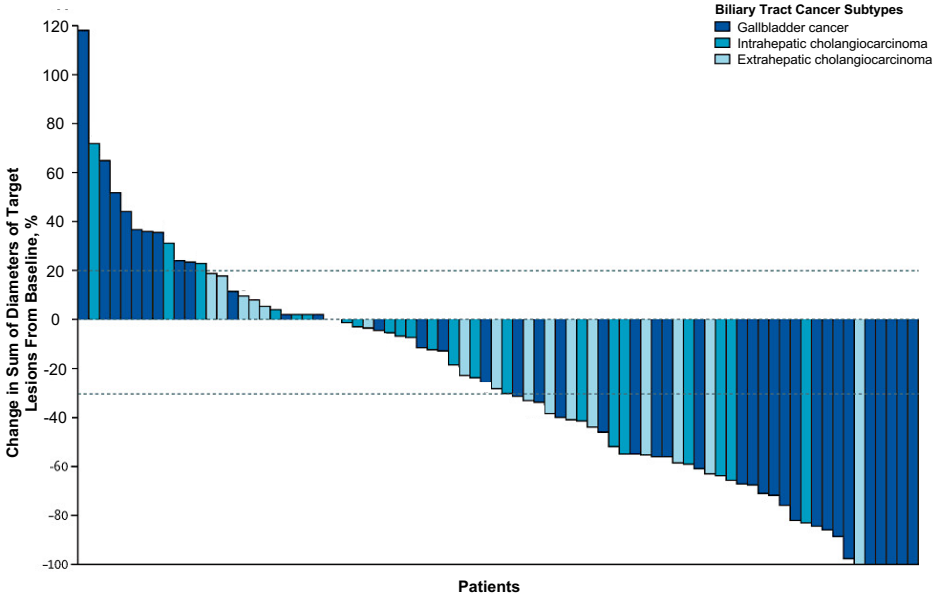
1. Weisser NE et al. *Nature Commun*. 2023;14:1394.

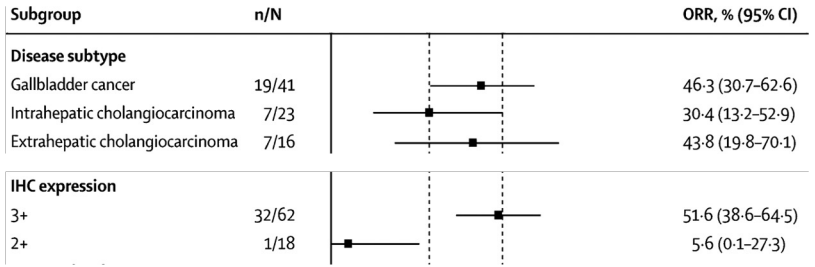
HERIZON-BTC-01 Trial: A Global Phase 2b Study of Zanidatamab Monotherapy in HER2-Amplified BTC[1,a]



1. Pant S et al. ASCO 2024. Abstract 4091.

HERIZON-BTC-01: Antitumor Activity of Zanidatamab in HER2-Amplified BTC



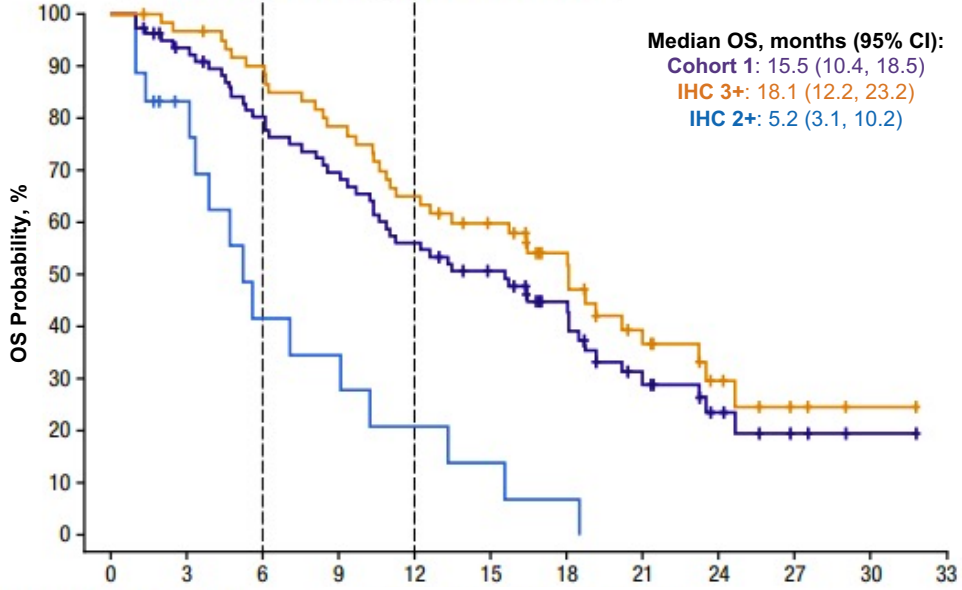


	By ICR Assessment (n = 80)	By Investigator Assessment (n = 80)
Confirmed ORR, % (95% CI)	41.3 (30.4-52.8)	41.3 (30.4-52.8)
Confirmed BOR, n (%)		
CR	1 (1.3)	4 (5)
PR	32 (40)	29 (36.3)
SD	22 (27.5)	21 (26.3)
PD	24 (30)	25 (31.3)
NE	1 (1.3)	1 (1.3)
DCR (CR + PR + SD), % (95% CI)	68.8 (57.4-78.7)	67.5 (56.1-77.6)
CBR (CR + PR + [SD ≥6 mo]), % (95% CI)	47.5 (36.2-59.0)	47.5 (36.2-59.0)

1. Pant S et al. ASCO 2024. Abstract 4091.

HERIZON-BTC-01: Zanidatamab Demonstrates Improved Overall Survival for HER2-Amplified BTC[1]

Survival probability, % (95% CI)	6-month OS	12-month OS
	Cohort 1: 80.3 (69.4, 87.6)	Cohort 1: 56.2 (44.3, 66.5)
	IHC 3+: 90.1 (79.2, 95.4)	IHC 3+: 65.0 (51.6, 75.6)
	IHC 2+: 41.7 (17.5, 64.4)	IHC 2+: 20.8 (5.1, 43.7)



1. Pant S et al. ASCO 2024. Abstract 4091.

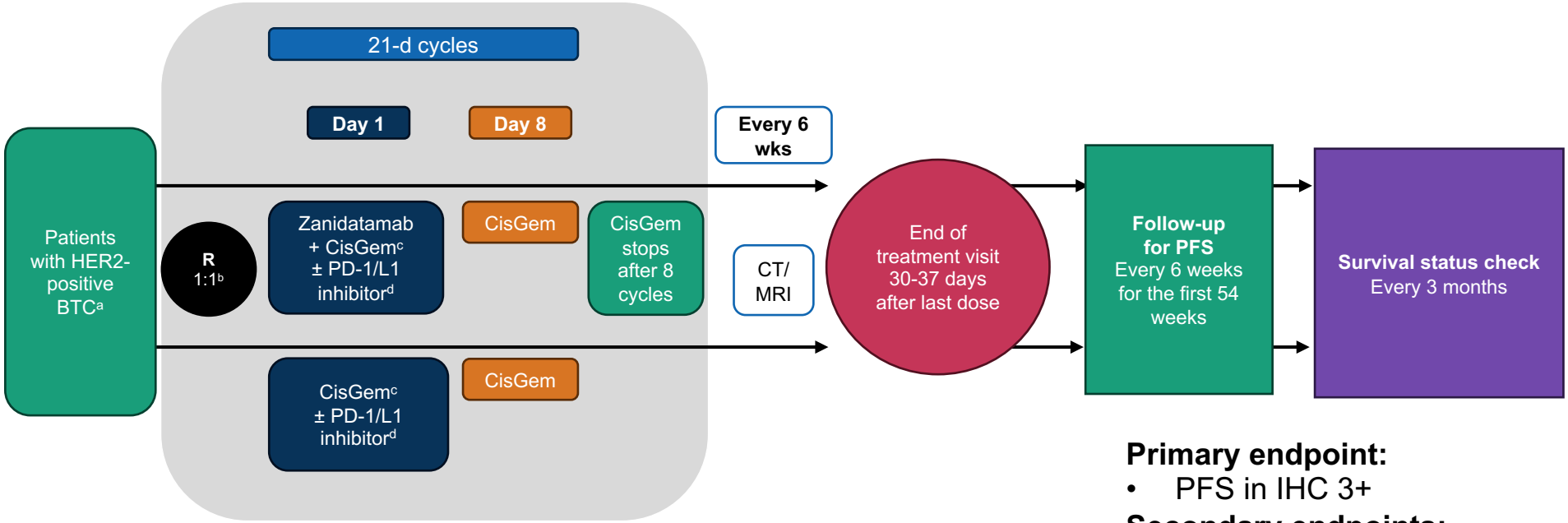
Zanidatamab: Long-Term Safety Profile[1]

- **The safety profile of zanidatamab was largely unchanged with additional follow-up**
- **There were no deaths related to zanidatamab treatment**
- **TRAEs leading to dose reductions remained infrequent**
  - Grade 3 diarrhea (n=1), grade 1 diarrhea and grade 1 nausea (n=1), and grade 2 weight decreased (n=1)
- **One patient experienced serious TRAEs since the prior analysis** (alanine aminotransferase increased and aspartate aminotransferase increased)
- **No patients discontinued treatment due to TRAEs since the prior analysis**

All Patients (Cohort 1 and Cohort 2)	N=87	
Any TEAE, n (%)	84 (96.6)	
Any TRAE, n (%)	63 (72.4)	
Grade 1-2	45 (51.7)	
Grade 3-4[a]	18 (20.7)	
Grade 5	0 (0)	
Serious TRAEs[b]	8 (9.2)	
TRAEs leading to treatment discontinuation, n (%)	2 (2.3)[c]	
Most common TRAEs,[d] n (%)	**All grades**	**Grades 3-4**
Diarrhea	32 (36.8)	4 (4.6)
Infusion-related reaction	29 (33.3)	1 (1.1)
Ejection fraction decreased	9 (10.3)	3 (3.4)
Nausea	8 (9.2)	1 (1.1)
Alanine aminotransferase increased	6 (6.9)	1 (1.1)
Aspartate aminotransferase increased	6 (6.9)	2 (2.3)
Vomiting	6 (6.9)	0 (0)
Fatigue	5 (5.7)	0 (0)
Anemia	4 (4.6)	3 (3.4)
AESI, n (%)		
Infusion-related reaction	29 (33.3)	1 (1.1)
Confirmed cardiac events	5 (5.7)	3 (3.4)
Non-infectious pulmonary toxicities	1 (1.1)	1 (1.1)

1. Pant S et al. ASCO 2024. Abstract 4091.

HERIZON-BTC-302: Assessment of Zanidatamab in the First-Line Setting[1]



Primary endpoint:

- PFS in IHC 3+

Secondary endpoints:

- OS and Safety

[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.

1. Harding et al. ASCO 2025. Abstract TPS648.

Quality of Life Outcomes With Zanidatamab[1]

EQ-5D-5L QOL Outcomes in Patients With HER2+ BTC by Tumor Response

	Best Confirmed Overall Tumor Response							
	CR		PR		SD		PD	
	BL (n = 1)	BONT (n = 1)	BL (n = 31)	BONT (n = 32)	BL (n = 21)	BONT (n = 22)	BL (n = 24)	BONT (n = 19)
Median VAS score	40	80	80	95	80	88	80	70
Median VAS change from baseline[a]	–	40	–	10	–	5	–	-10
Least severe response level (no problem), n (%)								
Mobility	0	0	23 (74)	30 (94)	16 (76)	19 (86)	15 (63)	12 (63)
Self-care	0	0	28 (90)	31 (97)	18 (86)	19 (86)	23 (96)	16 (84)
Usual activities	0	0	23 (74)	29 (91)	11 (52)	15 (68)	16 (67)	10 (53)
Pain/discomfort	0	1 (100)	15 (48)	28 (88)	10 (48)	13 (59)	10 (42)	7 (37)
Anxiety/depression	0	0	18 (58)	28 (88)	12 (57)	14 (64)	13 (54)	14 (74)

[a] Out of patients with a baseline and ≥1 postbaseline score.

1. Wasan HS et al. ESMO 2023. Abstract 101P.

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Abbreviations

1L: first line
2L: second line
5-FU: 5-fluorouracil
AACR: American Association for Cancer Research
ADC: antibody–drug conjugate
ADCC: antibody-dependent cellular cytotoxicity
ADCP: antibody-dependent cellular phagocytosis
AESI: adverse events of special interest
APC: antigen-presenting cell
ASCO GI: American Society of Clinical Oncology Gastrointestinal
ASCO: American Society of Clinical Oncology
BC: breast cancer
BICR: blinded independent central review
BL: baseline
BONT: best on-treatment score
BTC: biliary tract cancer
CAR-T: chimeric antigen receptor T cell
CAR: chimeric antigen receptor
CBR: confirmed best overall response
CCA: cholangiocarcinoma
CD: cluster of differentiation
CDC (Fc-mediated):
cORR: confirmed overall response rate
COVID-19: coronavirus disease 2019
CPS: combined positive score
CR: complete response
CRC: colorectal cancer
ctDNA: circulating tumor DNA
CTLA-4: cytotoxic T-lymphocyte–associated protein 4
CUP: carcinoma of unknown head/neck primary
DCO: data cutoff
DCR: disease control rate
dMMR: deficient mismatch repair
DOR: duration of response
Durva: durvalumab
ECC: extrahepatic cholangiocarcinoma
ECD2: extracellular domain 2
ECD4: extracellular domain 4
ECOG PS: Eastern Cooperative Oncology Group performance status
EORTC: European Organization for Research and Treatment of Cancer
EQ-5D-5L: EuroQol 5 Domains Health-Related Quality of Life Questionnaire
ESMO: European Society for Medical Oncology
FGFR: fibroblast growth factor receptor
FGFR2: fibroblast growth factor receptor 2
FGFRi: fibroblast growth factor receptor inhibitor
FISH: fluorescence in situ hybridization
FOLFIRI: leucovorin + fluorouracil + irinotecan
FOLFOX: folinic acid, fluorouracil, and oxaliplatin
GBC: gallbladder cancer
GEA: gastroesophageal adenocarcinoma
GEJ: gastroesophageal junction
Gem/cis: gemcitabine and cisplatin
HER3: human epidermal growth factor 3
HER4: human epidermal growth factor 4
ICC: intrahepatic cholangiocarcinoma

Abbreviations

ICI: immune checkpoint inhibitor
ICPR: in-hospital cardiopulmonary resuscitation
ICR: independent central review
IDH1: isocitrate dehydrogenase 1
IHC: immunohistochemistry
ILD: interstitial lung disease
IO: immunotherapy
IPI: ipilimumab
irAE: immune-related adverse event
IRR: incidence rate ratio
ISH: in situ hybridization
IVO: ibrutinib, venetoclax, and obinutuzumab
LVEF: left ventricular ejection fraction
mAb: monoclonal antibody
MAPK: mitogen-activated protein kinase
mDOR: median duration of response
MEK: mitogen-activated protein kinase
MET: mesenchymal epithelial transition
mPFS: median progression-free survival
MSI-H: microsatellite instability high
MSI: microsatellite instability
NCCN: National Comprehensive Cancer Network
NCI: National Cancer Institute
NE: not evaluable
NGS: next-generation sequencing
NIVO: nivolumab
NR: not reached
ORR: overall response rate
PD-1: programmed cell death protein 1
PD-L1: programmed death-ligand 1
PD: progressive disease
PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase
PPES: palmar-plantar erythrodysesthesia syndrome
PR: partial response
Q2W: every 2 weeks
Q3W: every 3 weeks
Q4W: every 4 weeks
QD: once daily
QW: every week
RAS: renin-angiotensin system
RCD: regulated cell death
RECIST: Response Evaluation Criteria in Solid Tumors
RP2D: recommended phase 2 dose
RPSFT: rank preserving structural failure time
RT: radiation therapy
RW: real world
SAE: severe/serious adverse event
SD: stable disease
SDM: shared decision-making in medicine
SEER: Surveillance, Epidemiology, and End Results Program
SOS: son of sevenless homolog
T-DXd: trastuzumab deruxtecan
TAP: tumor area positivity
TEAE: treatment-emergent adverse event
TGF-β: transforming growth factor-beta
TMB-H: tumor mutational burden high
TMB: tumor mutational burden
TRAE: treatment-related adverse event
VAS: visual analog scale
VEGFR: vascular endothelial growth factor receptor
WCGI: World Congress on Gastrointestinal Cancer