



October 28, 2023 - MULTIDISCIPLINARY APPROACHES TO CANCER SYMPOSIUM

Systemic Therapy Updates in Biliary Tract Cancers

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Financial Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- Discuss commonalities and differences among different racial/ethnic populations.
- Explore factors that determine the type of level of care between different patient populations.

Outline

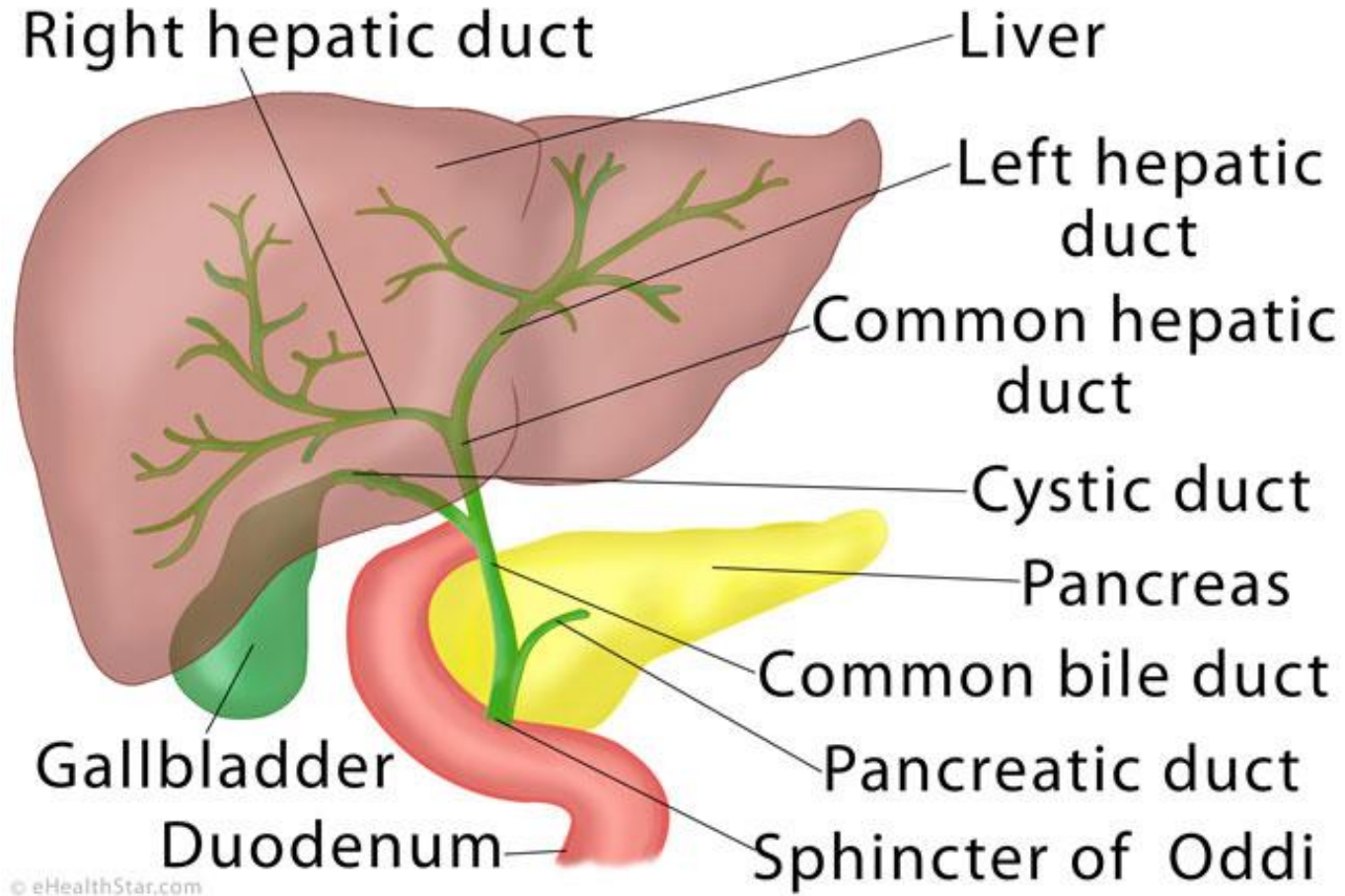
- Background Biliary Tract Cancer (BTC)
- Operable BTC => Adjuvant Therapy
- Borderline Operable or Non-Operable BTC
- Advanced/Metastatic BTC

Biliary Tract Cancers in the U.S.

- Total ~20,000 cases/year BTC
- Gallbladder ~12,000/year (GB)
- Extrahepatic Cholangiocarcinoma
 - Perihilar Cholangiocarcinoma (pCCA) ~4,000/year
 - Distal cholangiocarcinoma (dCCA) ~3,000/year
- Intrahepatic cholangiocarcinoma (iCCA) ~1000/year
- Over >5,000 deaths per year

Anatomy

Biliary Tree



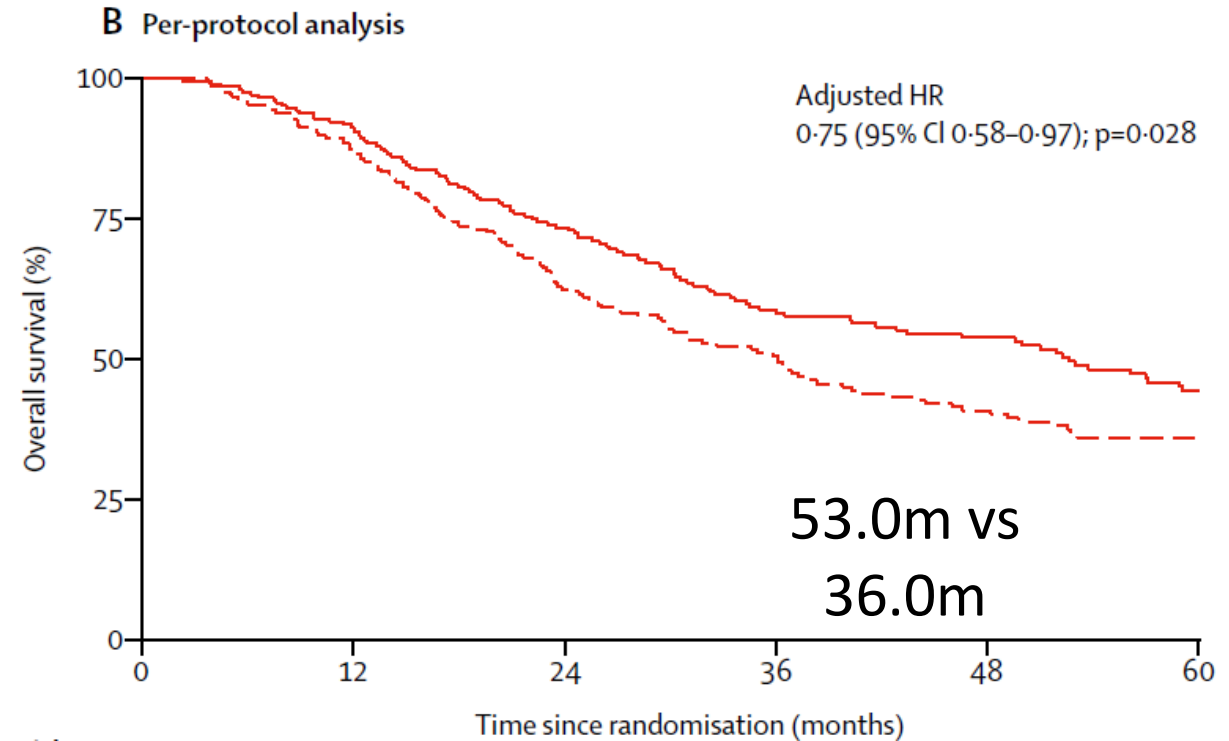
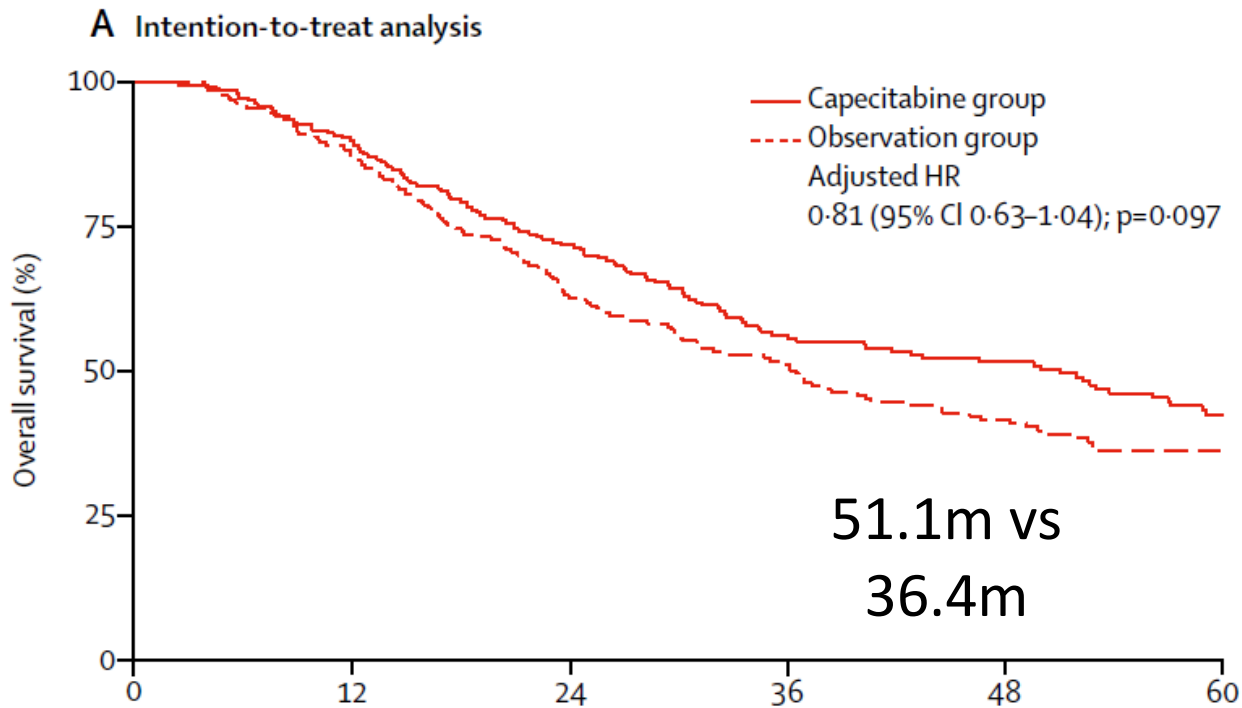
Biliary Tract Cancers

- Incidence has risen significantly for intrahepatic cholangiocarcinoma
- Associated with:
 - Autoimmune diseases – Primary sclerosing cholangitis, primary biliary cirrhosis
 - Infection – Clonorchis sinensis and Opisthorchis viverrini
 - Lynch syndrome
 - Gallstones
 - Gallbladder polyps
 - Biliary papillomatosis
 - HBV & HCV
 - Obesity
 - Diabetes

BILCAP Study

- Completely-resected cholangiocarcinoma (CCA) or gallbladder cancer (including liver and pancreatic resection, as appropriate),
- Randomized 1:1 to Cape (1250 mg/m² D1-14 every 21 days, for 8 cycles) or Obs.
- 447 participants were randomized to Cape (n = 223) or Obs (n = 224)
 - Median age was 63y
 - 19% intrahepatic, 28% hilar, 35% extrahepatic CCA, 18% muscle-invasive gallbladder cancers.
 - Resection margins: R0 in 279 (62%) and R1 in 168 (38%)
 - 207 (46%) were node-negative.

BILCAP Study – Overall Survival



BTC Adjuvant Therapy – SWOG S0809

- 79 patients with T2-4, LN+, or margin positive GB or EHCC
- Gemcitabine + Capecitabine -> Cap-RT
 - Gemcitabine at 1000mg/m² D1 & D8, q3wk
 - Capecitabine at 750mg/m² bid D1-15, q3wk
 - Capecitabine-RT at 665mg/m² days of XRT
 - RT 54-59.4 Gy and 45 Gy to regional lymphatics

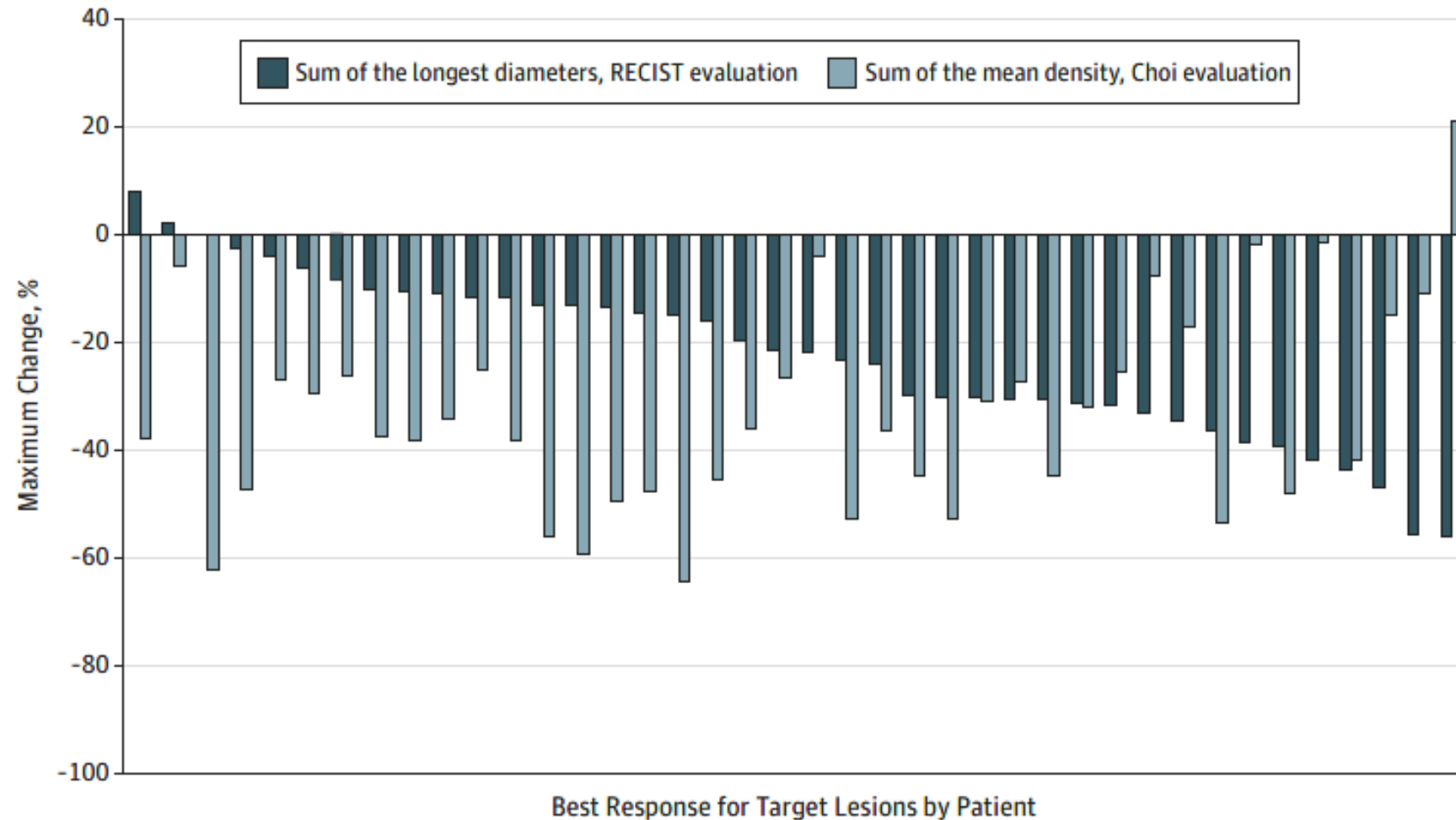
Borderline Operable or Non-Operable BTC

- Adjacent to critical structures (porta hepatis)
- Possible LN involvement
- Co-morbidities prohibit surgery

Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma

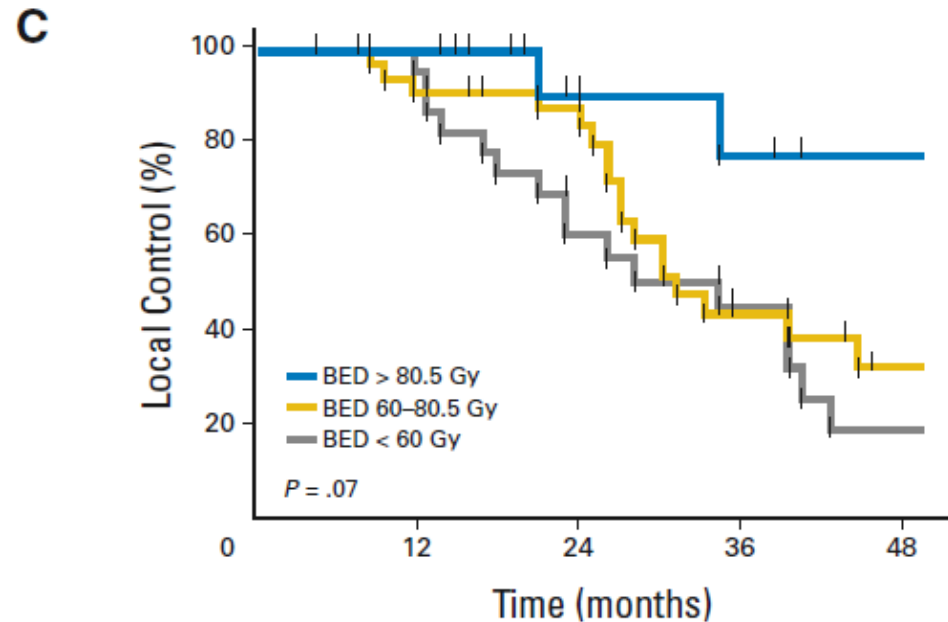
A Phase 2 Clinical Trial

Figure 2. Best Response for Target Lesions by Patient by Central Review

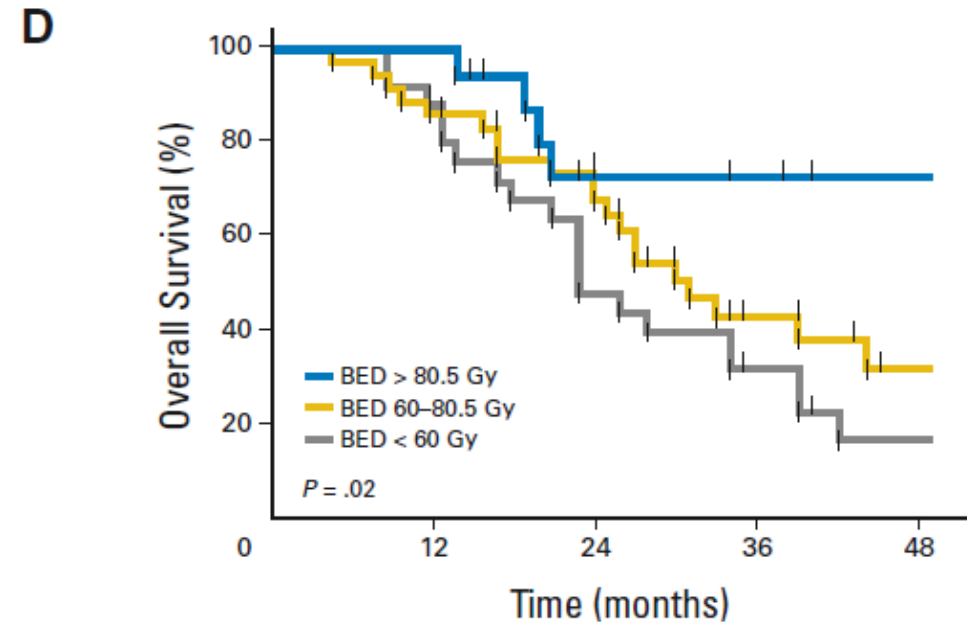


Locoregional Therapies

- Ablation & Radiotherapy
 - Reasonable to consider for non-surgical candidates with limited disease and normal liver function

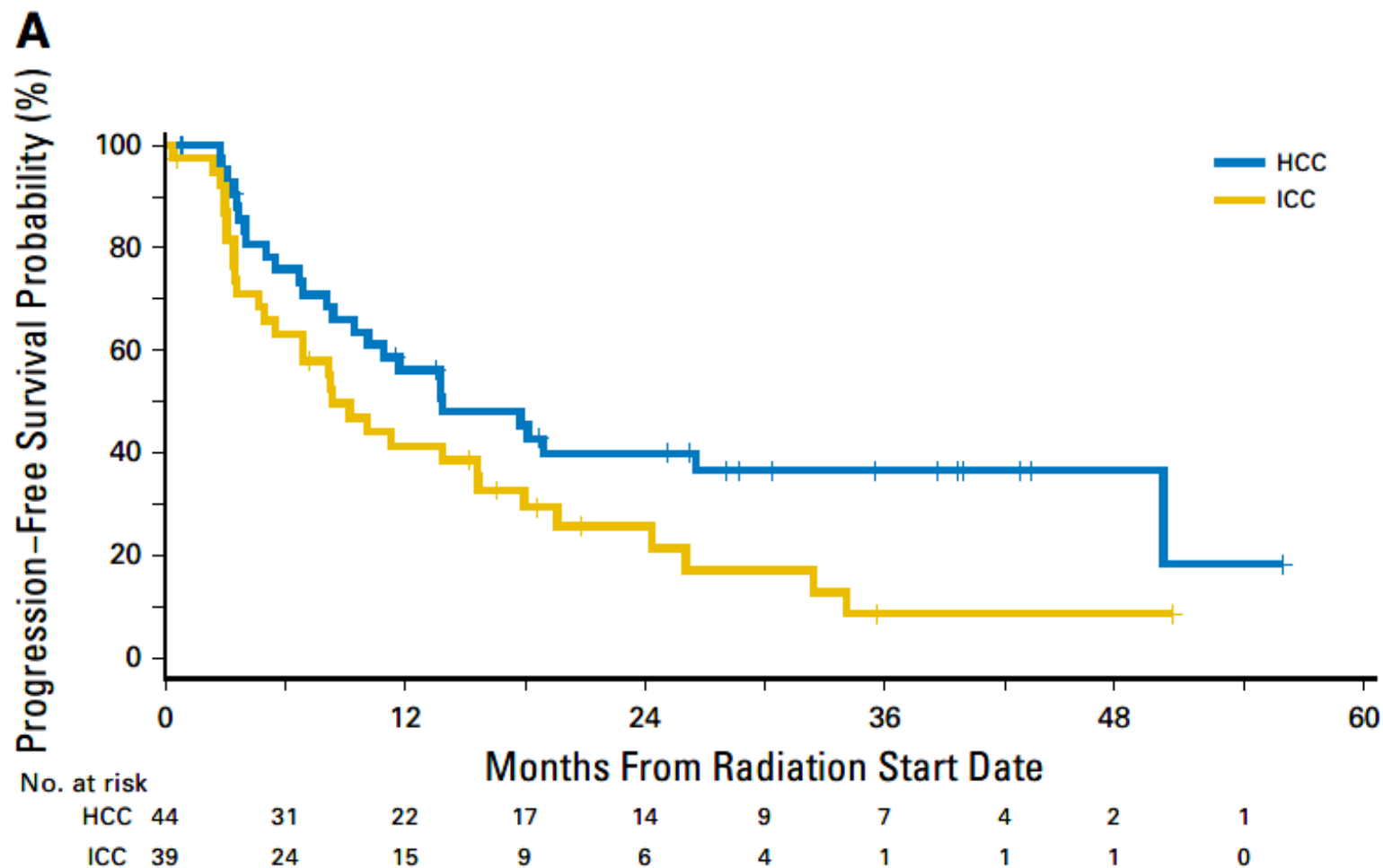


No. at risk	0	12	24	36	48
BED > 80.5 Gy	19	19	10	7	4
BED 60–80.5 Gy	35	30	21	10	4
BED < 60 Gy	25	22	16	8	3



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BED < 60 Gy	25	22	16	8	3

Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma



Systemic Therapies for Advanced BTC

1st Line

- Gemcitabine & Cisplatin + Durvalumab/Pembrolizumab
- Gemcitabine + Cisplatin
- Gemcitabine
- Capecitabine
- Targeted therapy (NTRK, RET, MSI-H)

2nd Line

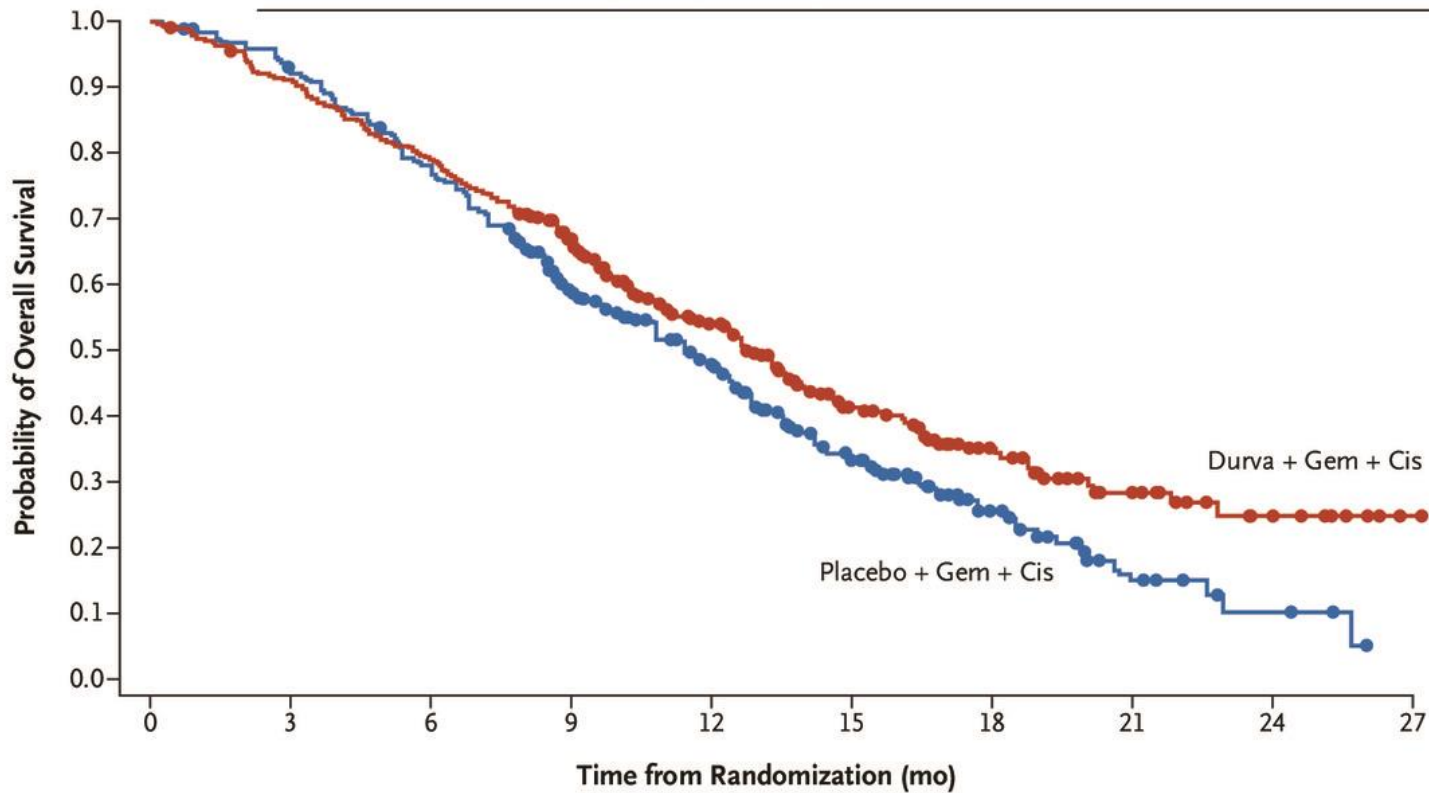
- FOLFOX/CAPOX
- FOLFIRI (5FU + nal-Iri)
- GEMOX
- Targeted therapy (FGFR2, IDH1, HER2, BRAF)
- Clinical Trials

Gem,

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

A

	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		

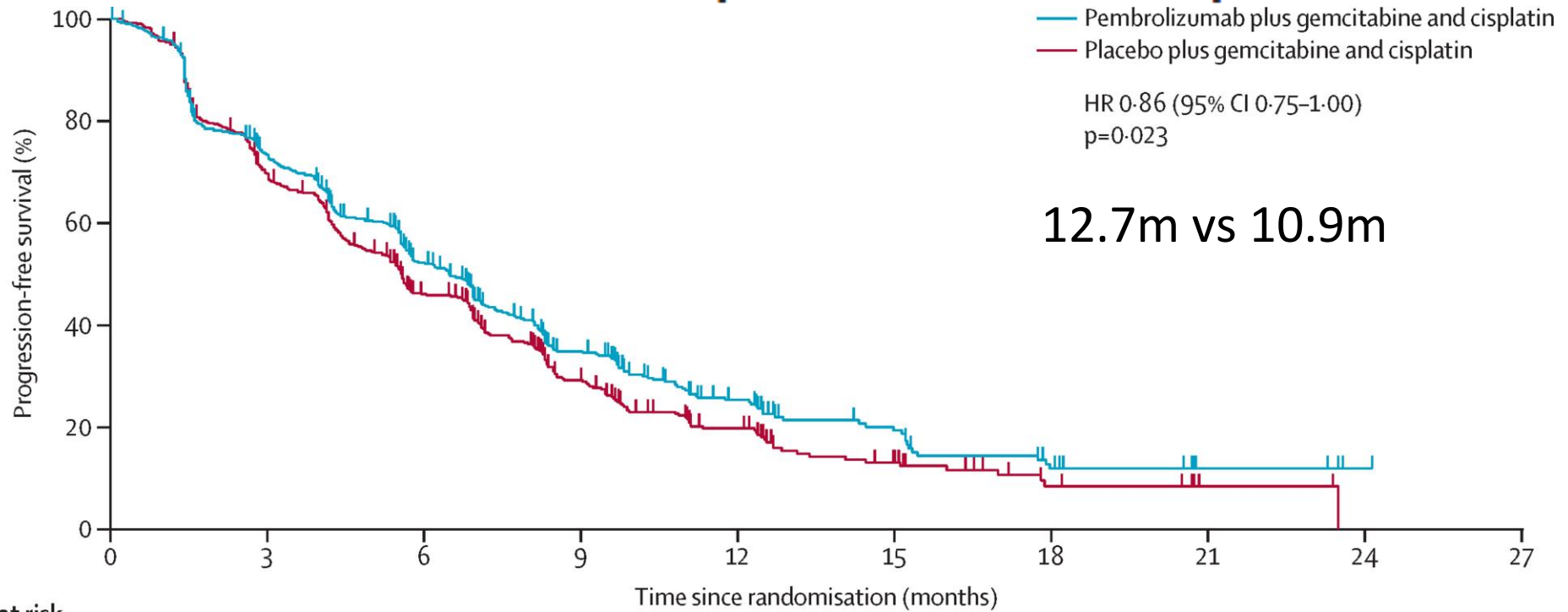


No. at Risk

Durva + Gem + Cis	341	331	324	309	294	278	268	252	238	208	174	151	135	118	93	79	74	57	49	39	29	24	15	12	9	8	4	1
Placebo + Gem + Cis	344	337	329	317	299	283	261	242	220	183	159	143	125	97	78	65	52	40	29	21	15	10	8	4	4	3	0	0

Gem/Cis+Pe

Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial



	0	3	6	9	12	15	18	21	24	27
Number at risk	533	368	238	121	62	29	14	5	1	0
(number censored)	(0)	(27)	(55)	(101)	(131)	(153)	(158)	(167)	(171)	(172)
Pembrolizumab plus gemcitabine and cisplatin	536	352	211	99	51	21	7	2	0	0
Placebo plus gemcitabine and cisplatin	(0)	(25)	(50)	(94)	(113)	(130)	(139)	(144)	(145)	(145)

BTC Genetics

	IHCCA	EHCCA	GBCA
TP53	21	35	55
KRAS	20	43	6
CDKN2A	---	16	26
ARID1A	14	12	10
IDH1	14	---	---
SMAD4	---	15	8
ERBB2	---	7	12
FGFR	6	---	---
BAP1	12	---	1
PIK3CA	6	7	9
BRAF	2	---	---

Target Therapies for Advanced BTC

Frontline

- NTRK
 - Larotrectinib & Entrectinib
- RET fusion
 - Selpercatinib & Pralsetinib
- MSI-H
 - Pembrolizumab or Nivolumab+Ipilimumab

Second Line

- FGFR2 fusion
 - Pemigatinib, Futibatinib, Infigratinib
- IDH1
 - Ivosidenib
- BRAF V600E
 - Dabrafenib+Trametinib
- HER2
 - Trastuzumab +/- pertuzumab

Pemigatinib (Fight-202) Phase II

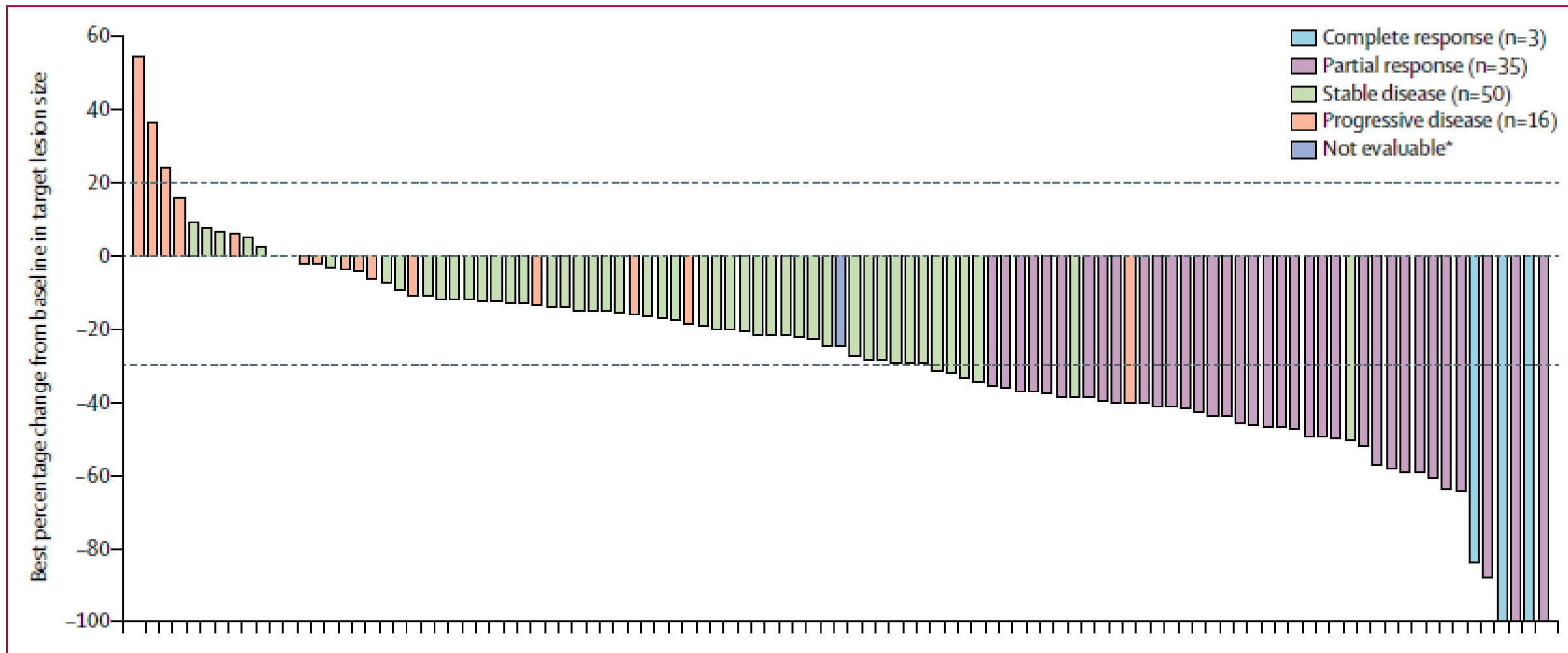
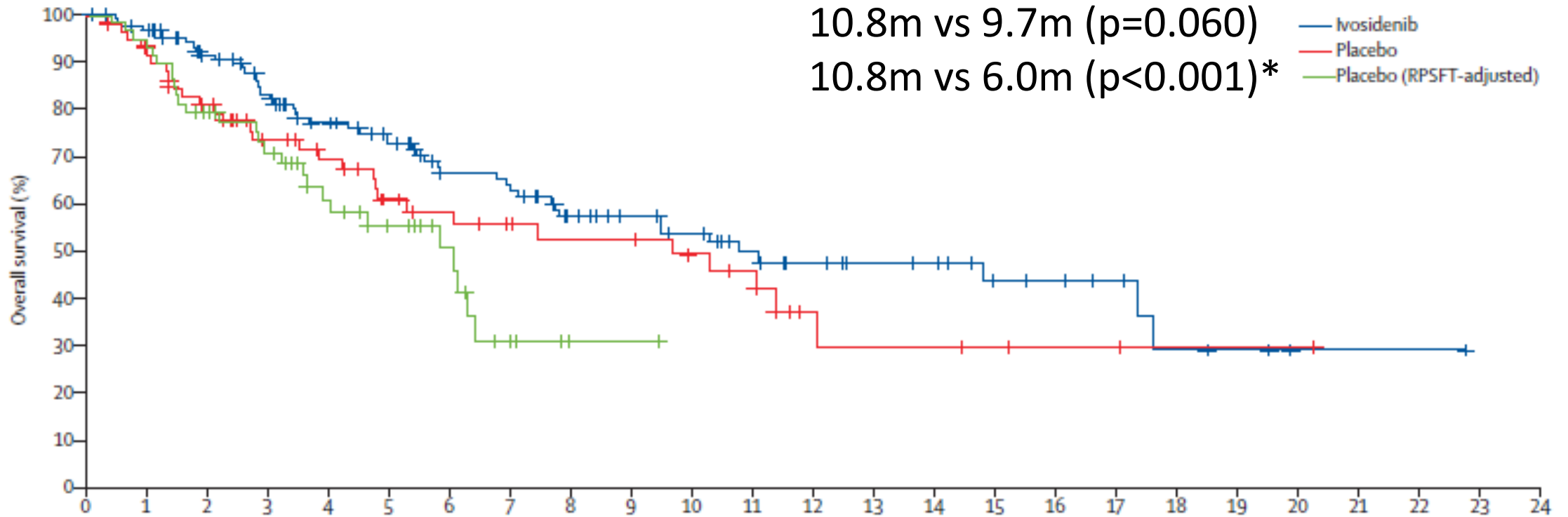


Figure 2: Best percentage change from baseline in target lesion size for individual patients with FGFR2 fusions or rearrangements

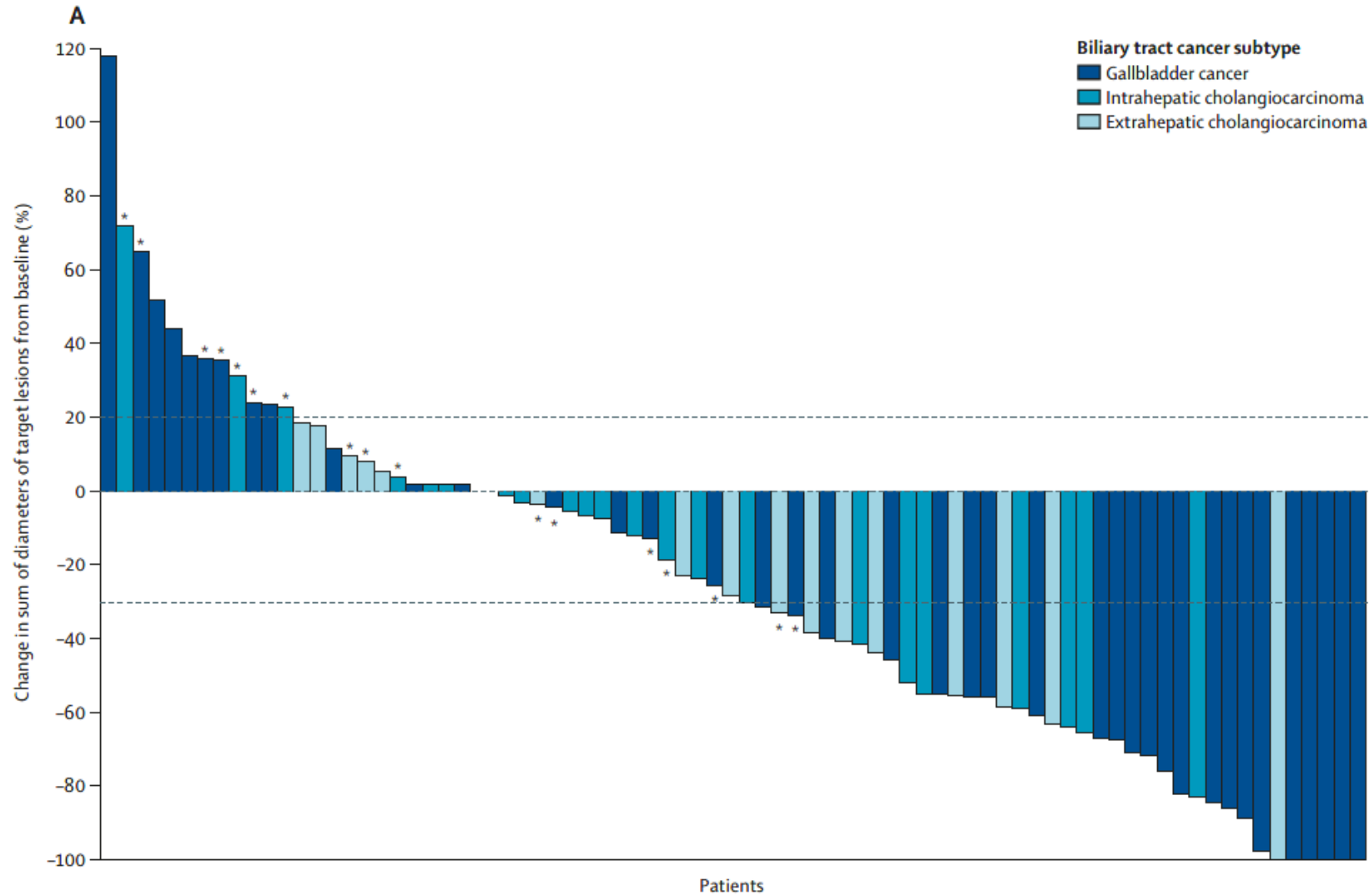
Ivosidenib in *IDH1*-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study



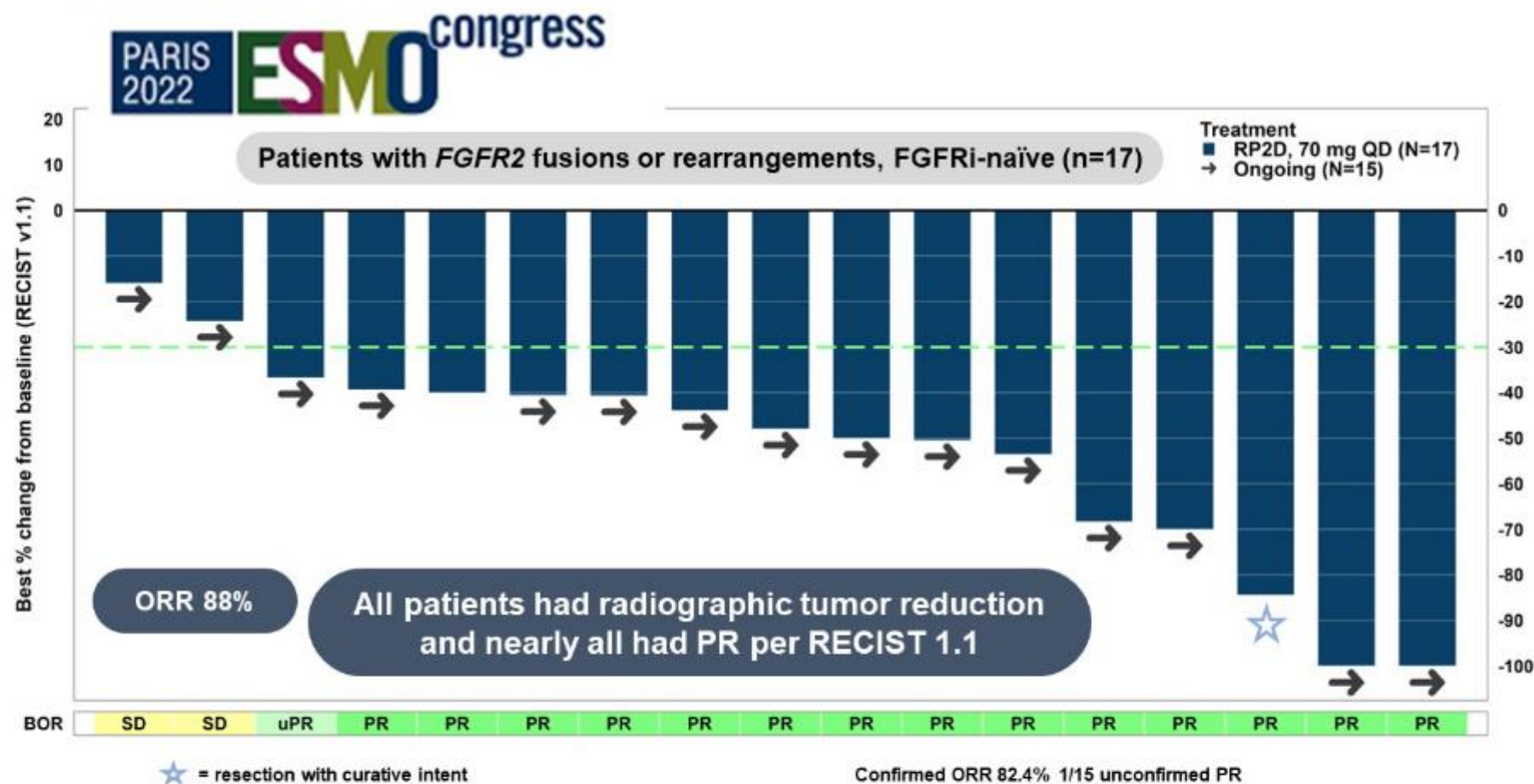
Emerging Therapies

- Zanidatamab, bispecific antibody for HER2-amplified BTC
 - HERIZON-BTC-01, Phase 2b with ORR of 41%
- RLY-4008, highly specific FGFR2 for BTC with FGFR2 alterations
 - ReFocus trial, Phase 1/2 with ORR of 73% in FGFR inhibitor–naïve patients with FGFR2 fusion–positive BTC

Zanidatamab for *HER2*-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study



ReFocus Next Steps: Phase 2 Pivotal Cholangiocarcinoma Ongoing



Pivotal enrollment anticipated completion: 2H 2023

Hollebecq et al. Efficacy of RLY-4008, a highly selective *FGFR2* inhibitor in patients (pts) with a *FGFR2*-fusion or rearrangement (*t/r*), *FGFR* inhibitor (*FGFRi*)-naïve cholangiocarcinoma (CCA): ReFocus trial. Oral Presentation, European Society for Molecular Oncology 2022, Paris, 9-13 October 2022. Data cut-off for ESMO 2022 as of 08/01/2022. ORR, Overall Response Rate, QD, once daily, PR, partial response, uPR: unconfirmed partial response, SD: Stable Disease

Bilirubin Management

- Consider MRCP
- Internal stent
 - Plastic requires replacing every 2-3 months
 - Metal are more permanent
- External Drain
- Consider urosidiol 300mg qd or bid

Summary

- Operable BTC => capecitabine x 6 months
- Borderline operable or non-operable BTC
 - Chemotherapy +/- Y90, HAI, SBRT, RFA
- Advanced/metastatic BTC
 - Frontline: Gemcitabine/Cisplatin + Durvalumab or Pembrolizumab
 - Second line: FOLFOX, FOLFIRI, clinical trial
- NGS is critical for targeted therapies
 - Frontline: NTRK, RET, MSI-H
 - Second line: FGFR2, IDH1, HER2, BRAF V600E

Thank You

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