Fourth Annual
National General Medical Oncology Summit

Saturday, March 1, 2025

Moderator

Neil Love, MD

Faculty

Rahul Aggarwal, MD
Aditya Bardia, MD, MPH
Mitesh J Borad, MD
Virginia F Borges, MD, MMSc
Harold J Burstein, MD, PhD
Rashmi Chugh, MD
Christopher Flowers, MD, MS
Jonathan Goldman, MD
Nicole Lamanna, MD
Natasha B Leighl, MD, MMSc
Amit Mahipal, MD, MPH
William K Oh, MD
David M O'Malley, MD
Joyce O'Shaughnessy, MD
Krish Patel, MD
Richard F Riedel, MD
Kerry A Rogers, MD
Simron Singh, MD, MPH
Brian M Slomovitz, MD
Jonathan Strosberg, MD

Module 8: Biliary Tract Cancers

Targeted Therapeutic Approaches for Patients with BTCs — Dr Mahipal

Integration of Immune Checkpoint Inhibitors into Current Biliary Tract Cancer (BTC) Management — Dr Borad

Module 8: Biliary Tract Cancers

Targeted Therapeutic Approaches for Patients with BTCs — Dr Mahipal

Integration of Immune Checkpoint Inhibitors into Current Biliary Tract Cancer (BTC) Management — Dr Borad

Targeted Therapeutic Approaches for Patients with BTCs

Amit Mahipal, MBBS, MPH

Professor

Director GI Oncology

UH Seidman Cancer Center

Case Western Reserve University

March 1, 2025

University Hospitals
Seidman Cancer Center
Cleveland | Ohio

Case Western Reserve University
CASE COMPREHENSIVE CANCER CENTER

Part of a NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

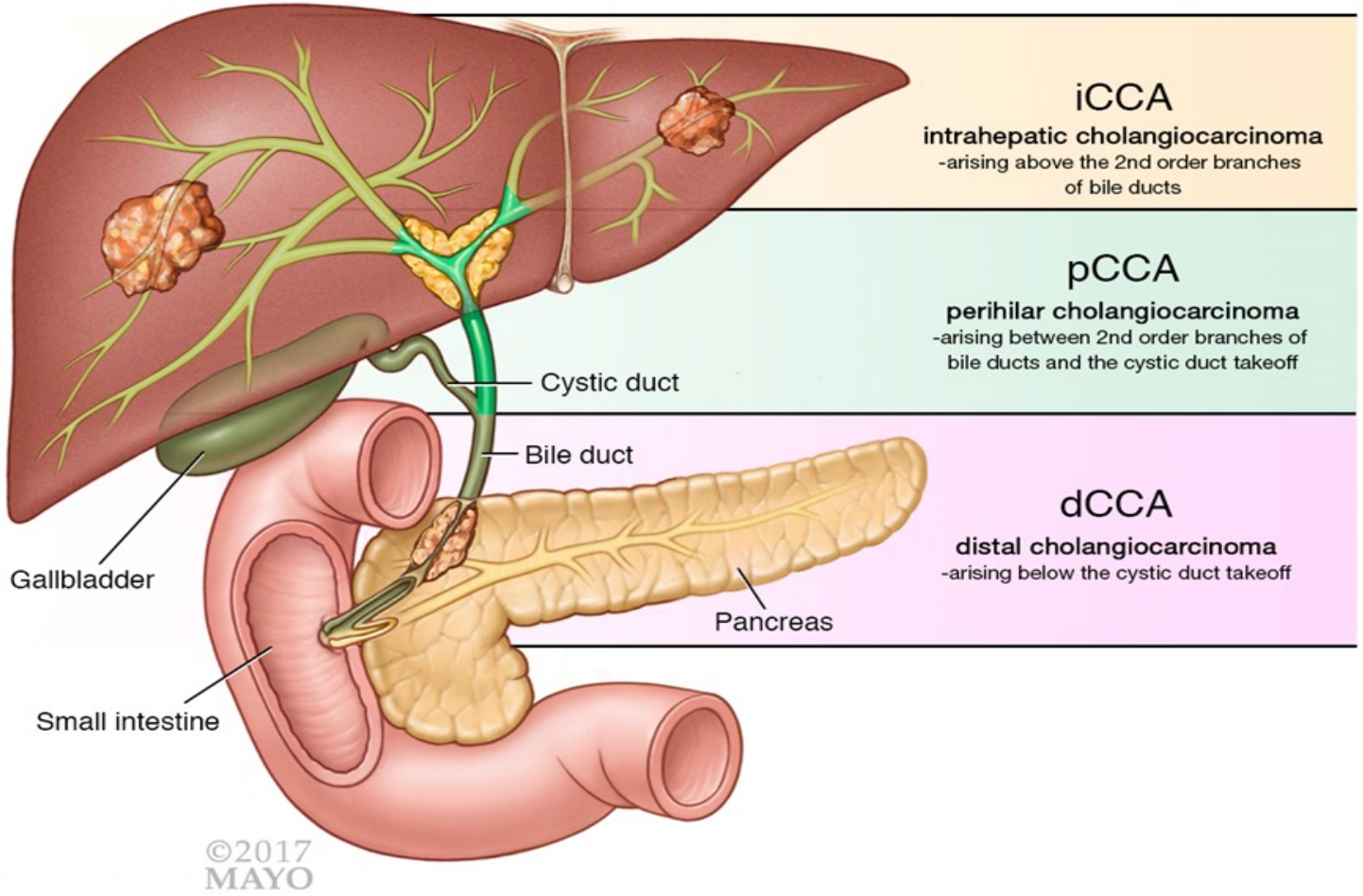
Disclosures

No relevant conflicts of interest to disclose

Background

- Annual incidence in US: 12,190
- Overall incidence has increased progressively worldwide over the past four decades.
- Aggressive disease with five-year overall survival rates for advanced stage disease <2%.
- Only 15-20% of the patients are candidates for surgical resection.

Anatomical Classification



Mutation Profile

Intrahepatic	Prevalence
FGFR1-3 fusions, amplifications, and mutations	11-45%
IDH1 or *IDH2* mutation	23-28%
TP53 mutation	2.5-44%
ARID1A mutation	15-36%
MCL-1 mutation	16-21%
EGFR expression	11-27%
CDKN2A or CDNK2B loss	6-30%
KRAS mutation	11-25%
MCL1 amplification	21%
SMAD4 mutation	4-17%
MLL3 mutation	15%
BAP1 mutation	13%
HER3 amplification	7%
CDK6 mutation	6%

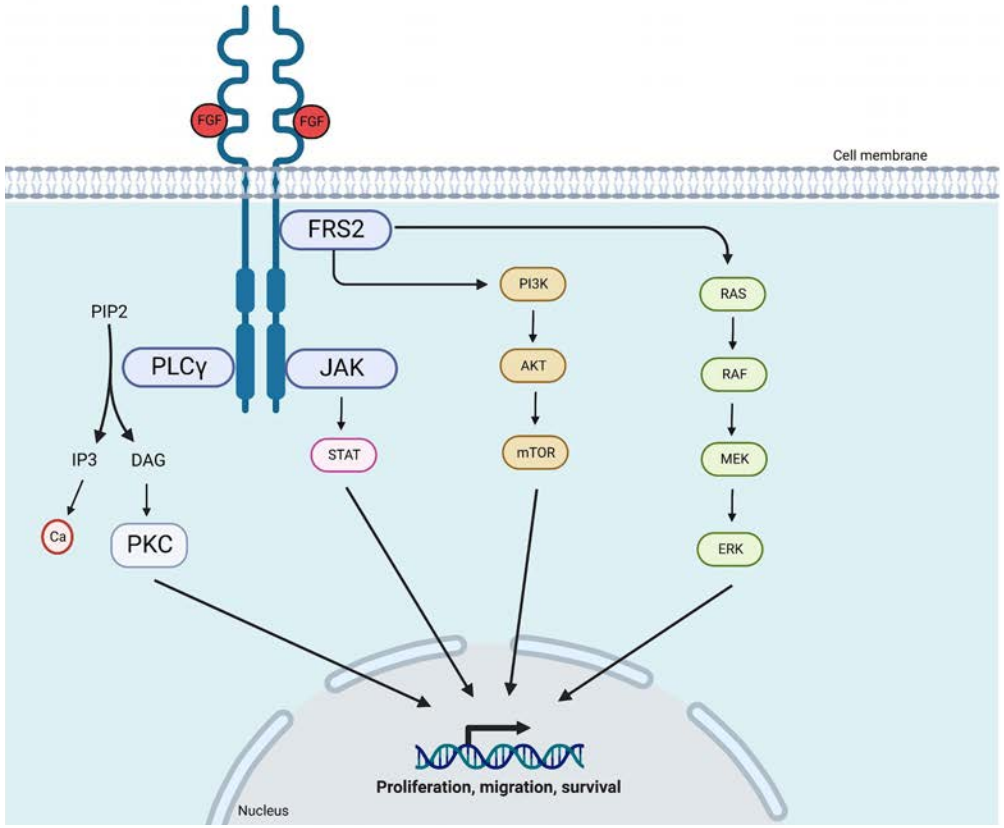
Gallbladder cancer	Prevalence
TP53 mutation	47-59%
HER2 amplification	10-19%
CDKN2A or CDKN2B loss	6-19%
ARID1A mutation	13%
PIK3CA mutation	6-12.5%
NRAS mutation	6%
BRAF mutation	6%
GNAS mutation	6%

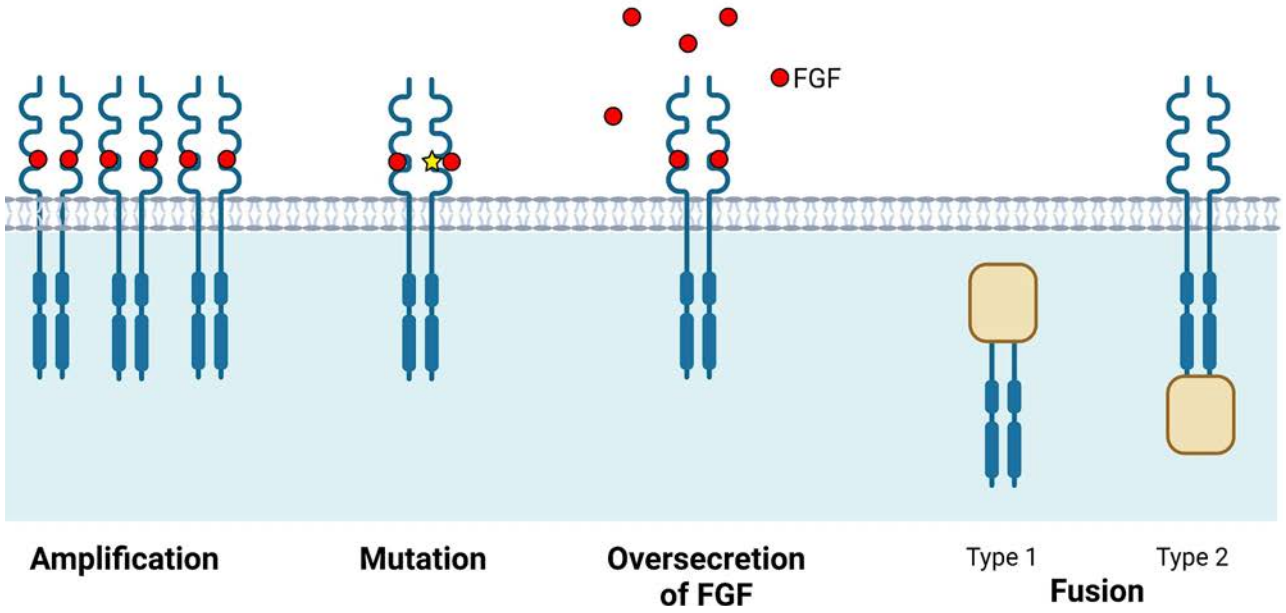
Extrahepatic	Prevalence
TP53 mutation	40%
KRAS mutation	8-42%
SMAD4 mutation	21%
CDKN2A or CDKN2B loss	17%
HER2 amplification	11-17%
ARID1A mutation	12%
EGFR expression	5-9%
PIK3CA mutation	7%

FGFR fusion partner	Frequency
FGFR2-AHCYL	7/102 (7%)
FGFR2-BICC1	2/102 (2%)
	41/107 (38%)
	1/28 (4%)
FGFR2-PPHLN1	17/107 (16%)
FGFR2-MGEA5	1/6 (17%)
FGFR2-TACC3	1/6 (17%)
	1/28 (4%)
FGFR-KIAA1598	1/28 (4%)

Tella et al Lancet Oncology 2020; Kayhaniyan et al. WJGO 2017

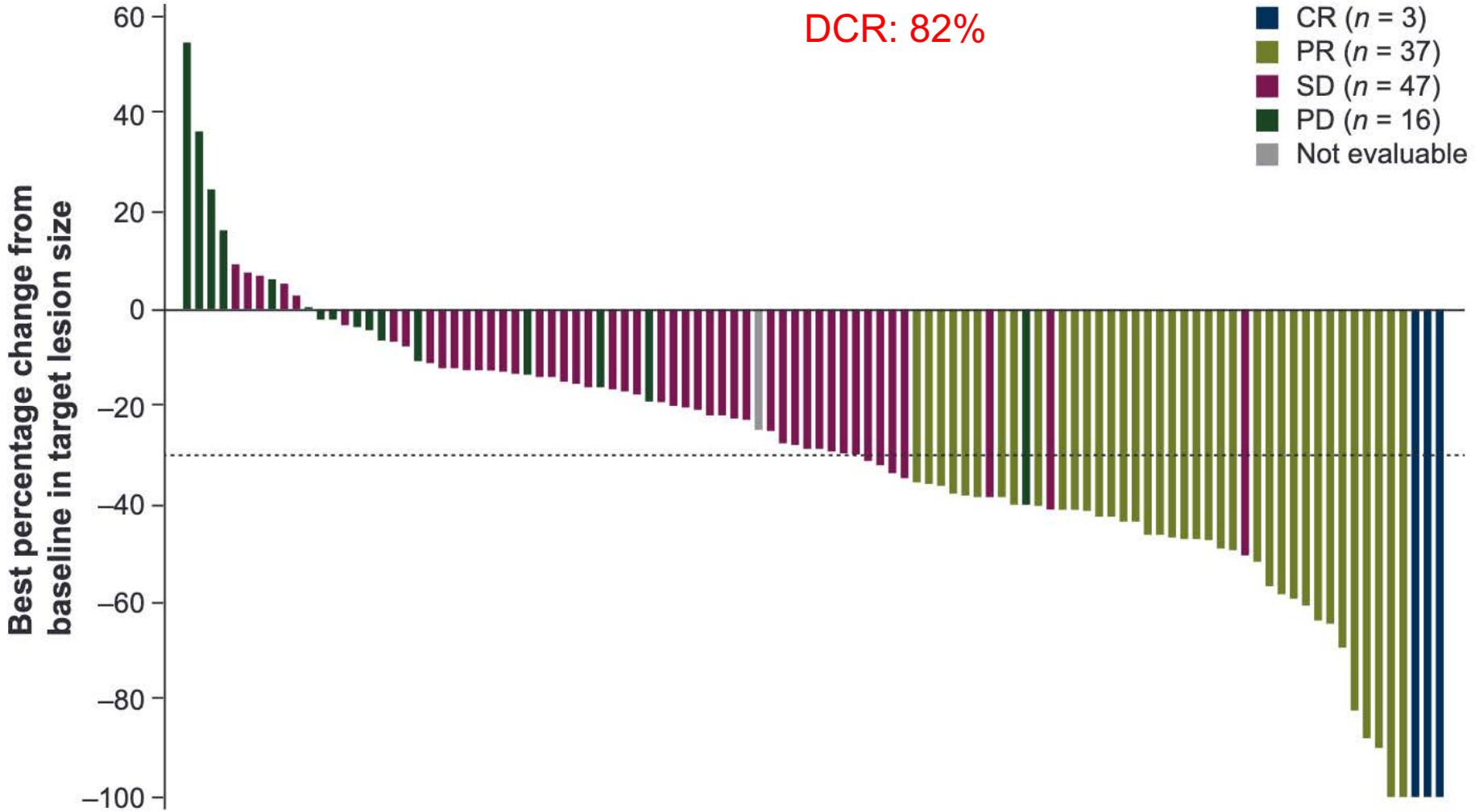
Fibroblast Growth Factor Receptor-2 (FGFR2) as an Oncogenic Pathway





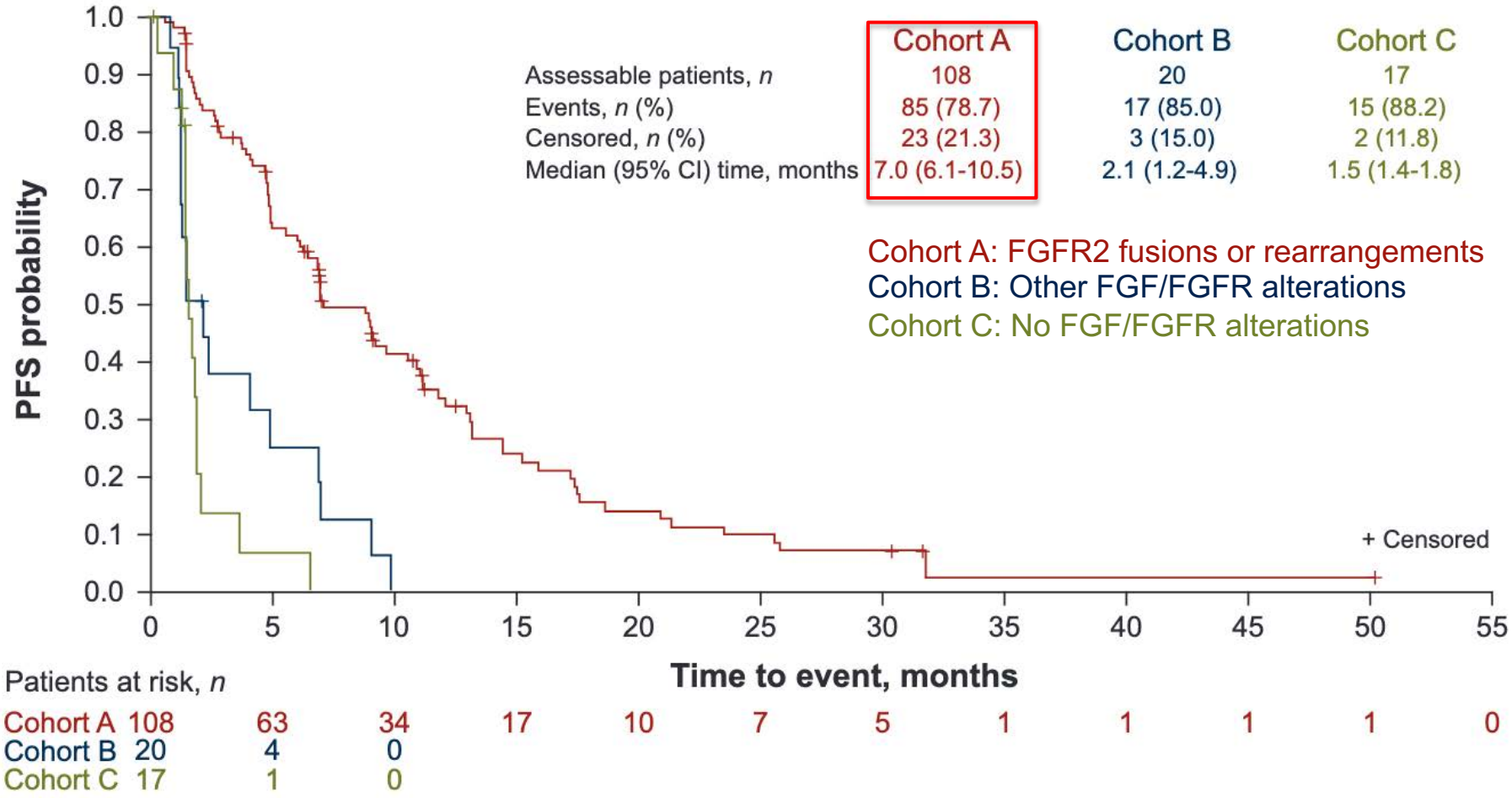
FIGHT-202: Pemigatinib

ORR: 37%
DCR: 82%



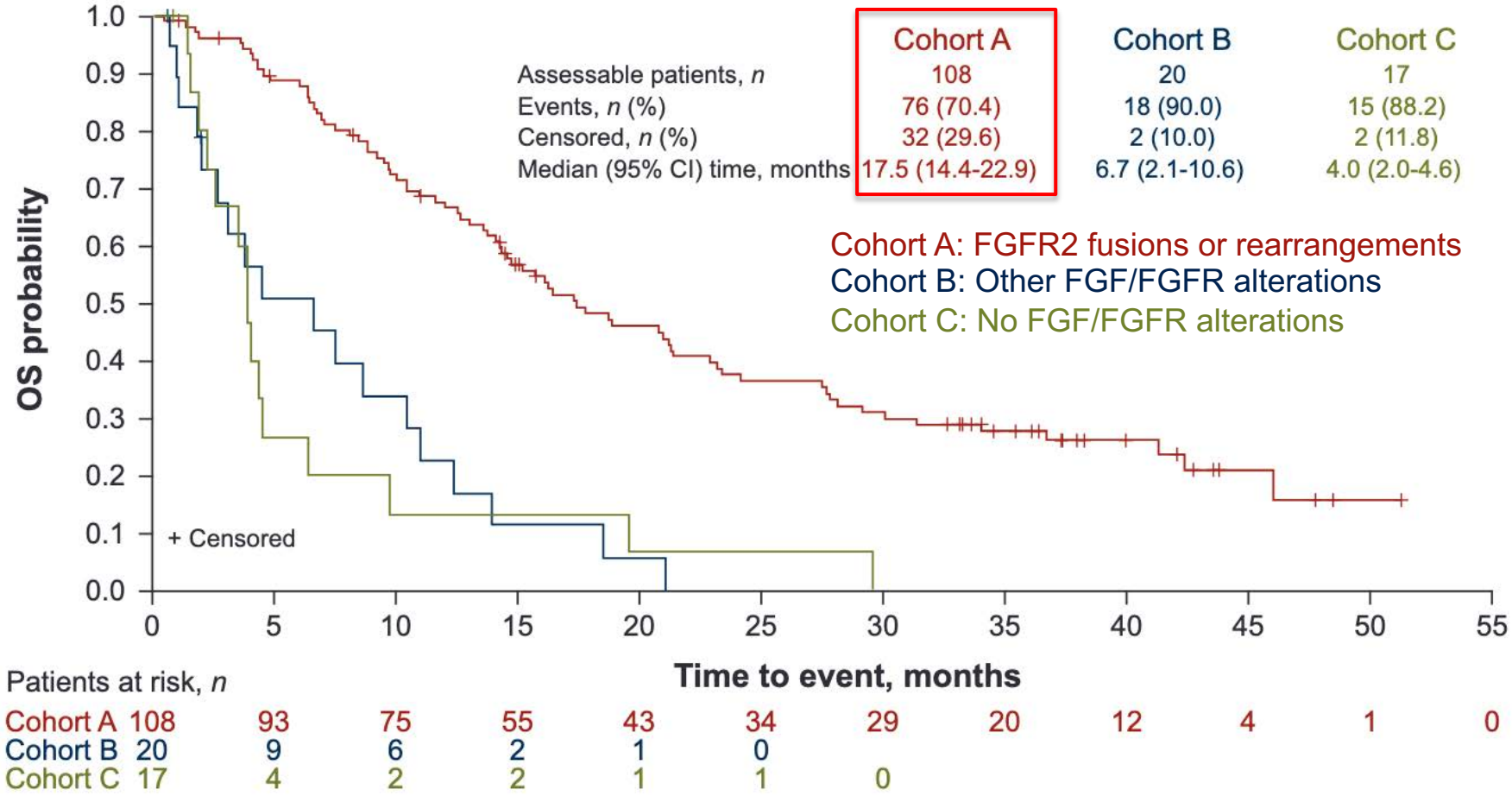
Vogel A, Sahai V, Hollebecque A et al. *ESMO Open* 2024;9(6):103488.

FIGHT-202: Pemigatinib



Vogel A, Sahai V, Hollebecque A et al. *ESMO Open* 2024;9(6):103488.

FIGHT-202: Pemigatinib



Vogel A, Sahai V, Hollebecque A et al. *ESMO Open* 2024;9(6):103488.

Futibatinib in Cholangiocarcinoma

The NEW ENGLAND JOURNAL of MEDICINE

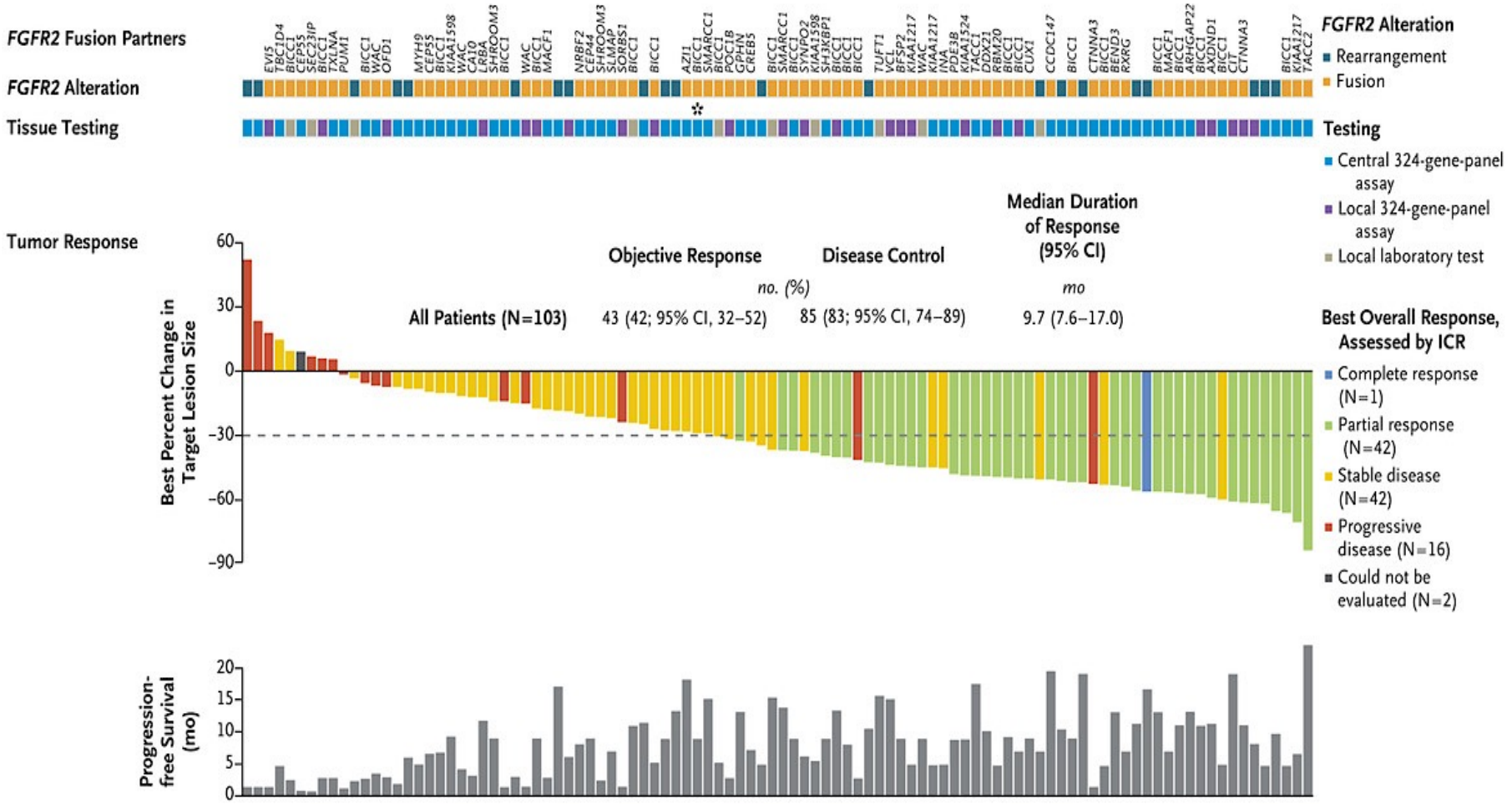
ORIGINAL ARTICLE

Futibatinib for *FGFR2*-Rearranged Intrahepatic Cholangiocarcinoma

L. Goyal, F. Meric-Bernstam, A. Hollebecque, J.W. Valle, C. Morizane, T.B. Karasic, T.A. Abrams, J. Furuse, R.K. Kelley, P.A. Cassier, H.-J. Klümpen, H.-M. Chang, L.-T. Chen, J. Tabernero, D.-Y. Oh, A. Mahipal, M. Moehler, E.P. Mitchell, Y. Komatsu, K. Masuda, D. Ahn, R.S. Epstein, A.-B. Halim, Y. Fu, T. Salimi, V. Wacheck, Y. He, M. Liu, K.A. Benhadji, and J.A. Bridgewater, for the FOENIX-CCA2 Study Investigators*

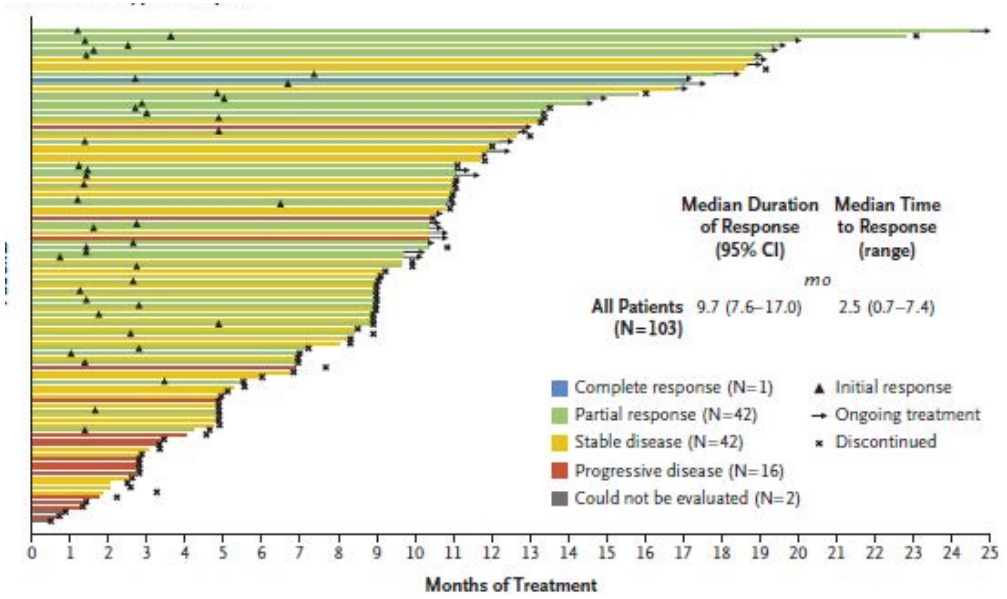
FOENIX-CCA2: Futibatinib

ORR: 43%
DCR: 85%

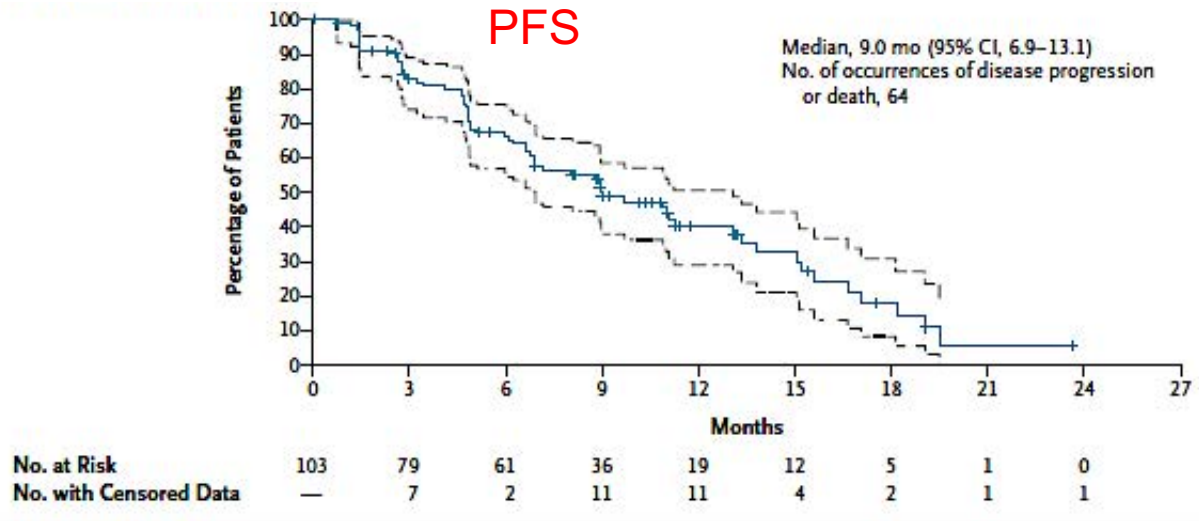


FOENIX-CCA2: Futibatinib

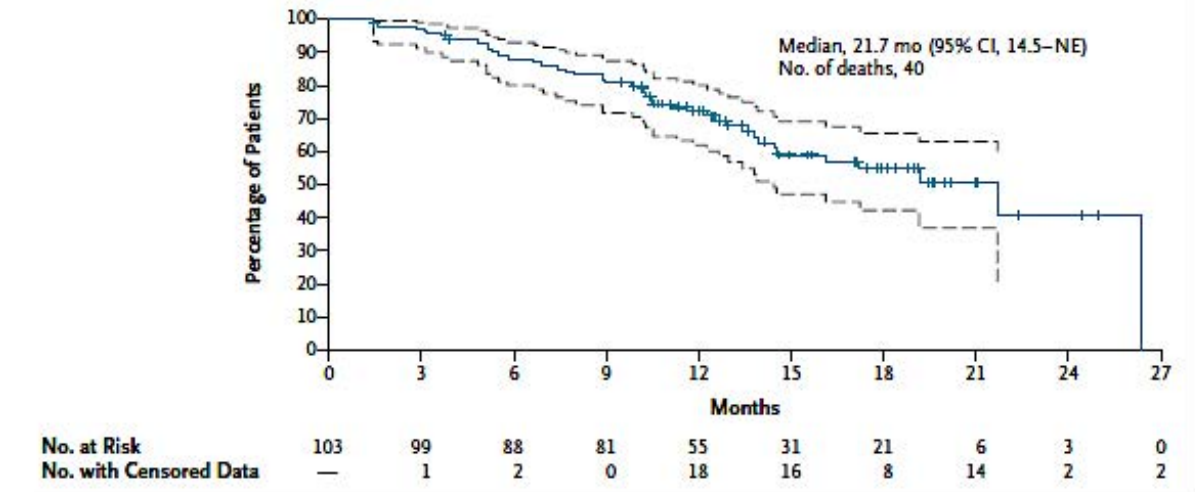
DOR



PFS



OS



FGFR inhibitors related toxicities

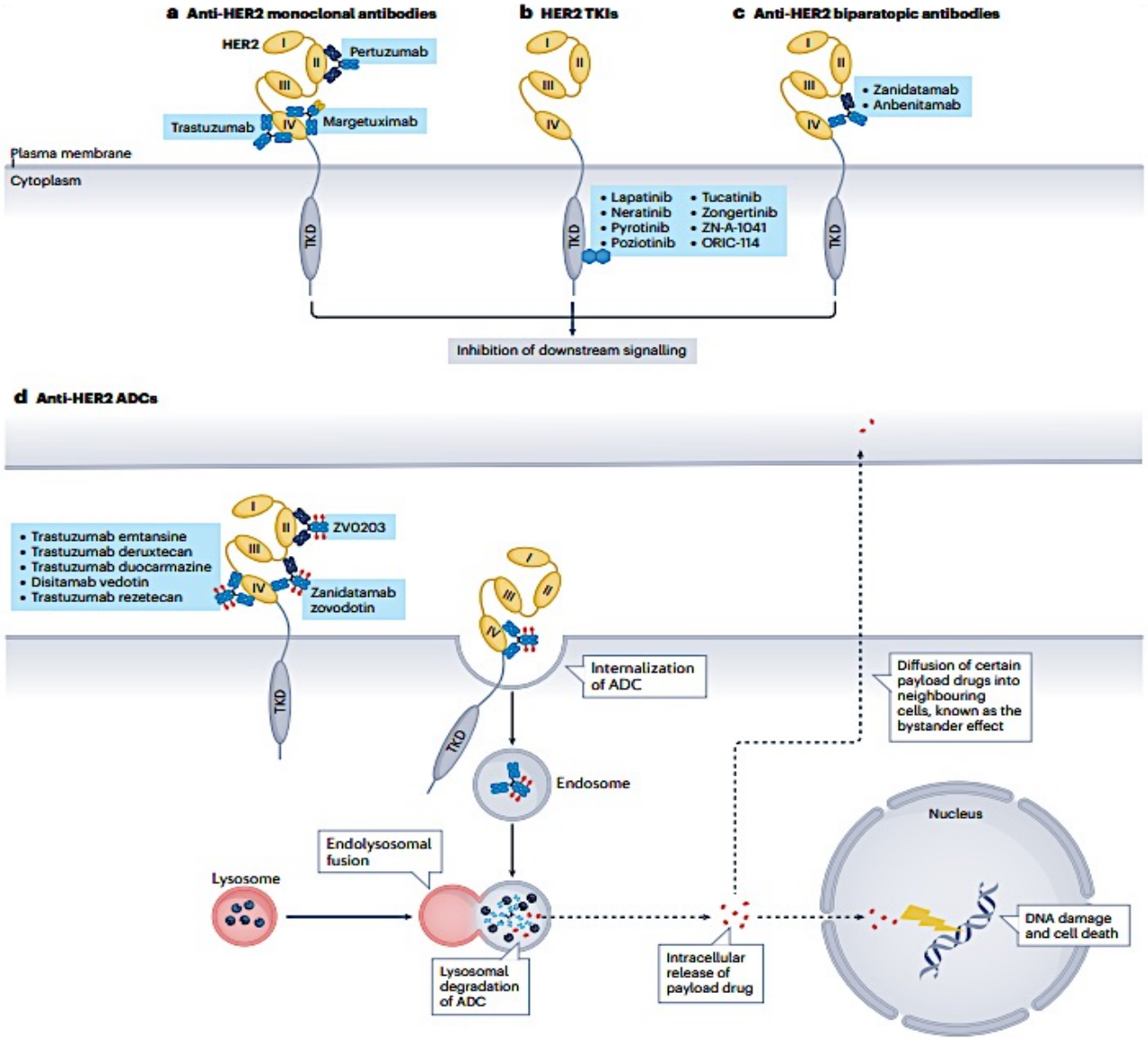
Drug	Hyperphosphatemia		Hypophosphatemia		Diarrhea		Dry eye		Stomatitis		Fatigue		Abnormal AST		HFS	
	Grade (%)															
	All	3-4	All	3-4	All	3-4	All	3-4	All	3-4	All	3-4	All	3-4	All	3-4
Pemigatinib	55	0	12	7	37	3	22	1	32	5	32	1	2	1	15	4
Infigratinib	77	10	22	13	24	3	34	1	55	15	40	4	21	2	33	6
Zoligratinib	80	70	-	-	27	0	10	0	30	7	30	0	13	3	20	-
Erdafitinib	71	5	-	-	59	4	22	0	56	12	29	3	26	2	34	6
Futibatinib	85	30	-	-	28	0	17	1	20	6	25	6	18	7	21	5

Goyal et al. NEJM 2023

FGFR2 Inhibitors

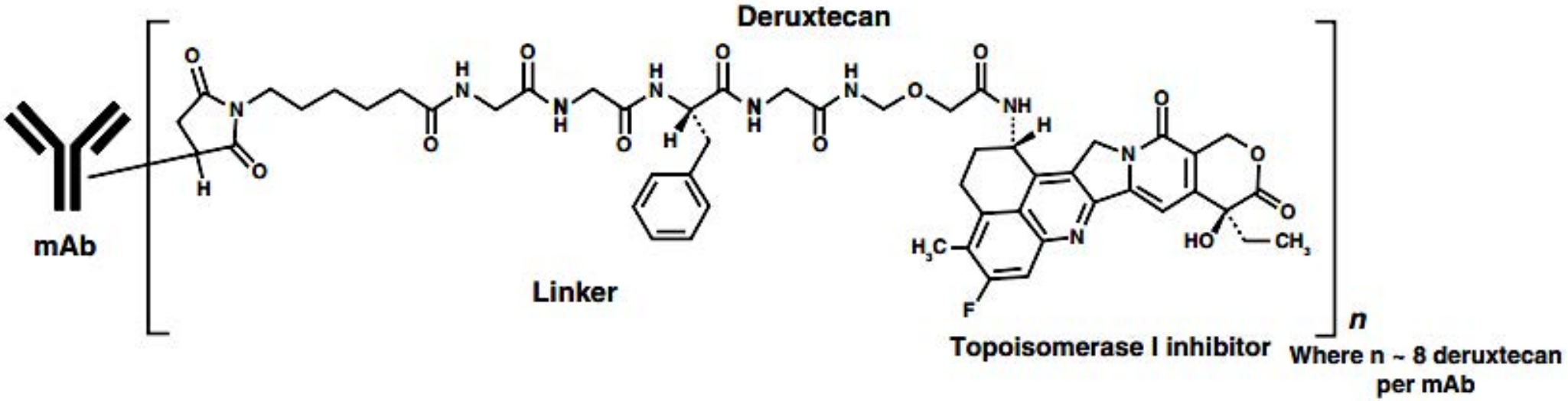
- FGFR inhibitors have shown great activity in 2nd line or later with ORR 35-41% and DCR of 80%-85%
- First line trials comparing to chemotherapy aborted due to slow accrual
- Unfortunately, resistance develops with primary mechanisms being FGFR mutations at binding sites
- Currently 2 FDA approved drugs
  - Pemigatinib
  - Futibatinib
- Novel agents being developed
  - RLY-4008
  - Tinengotinib

HER2 targeted agents

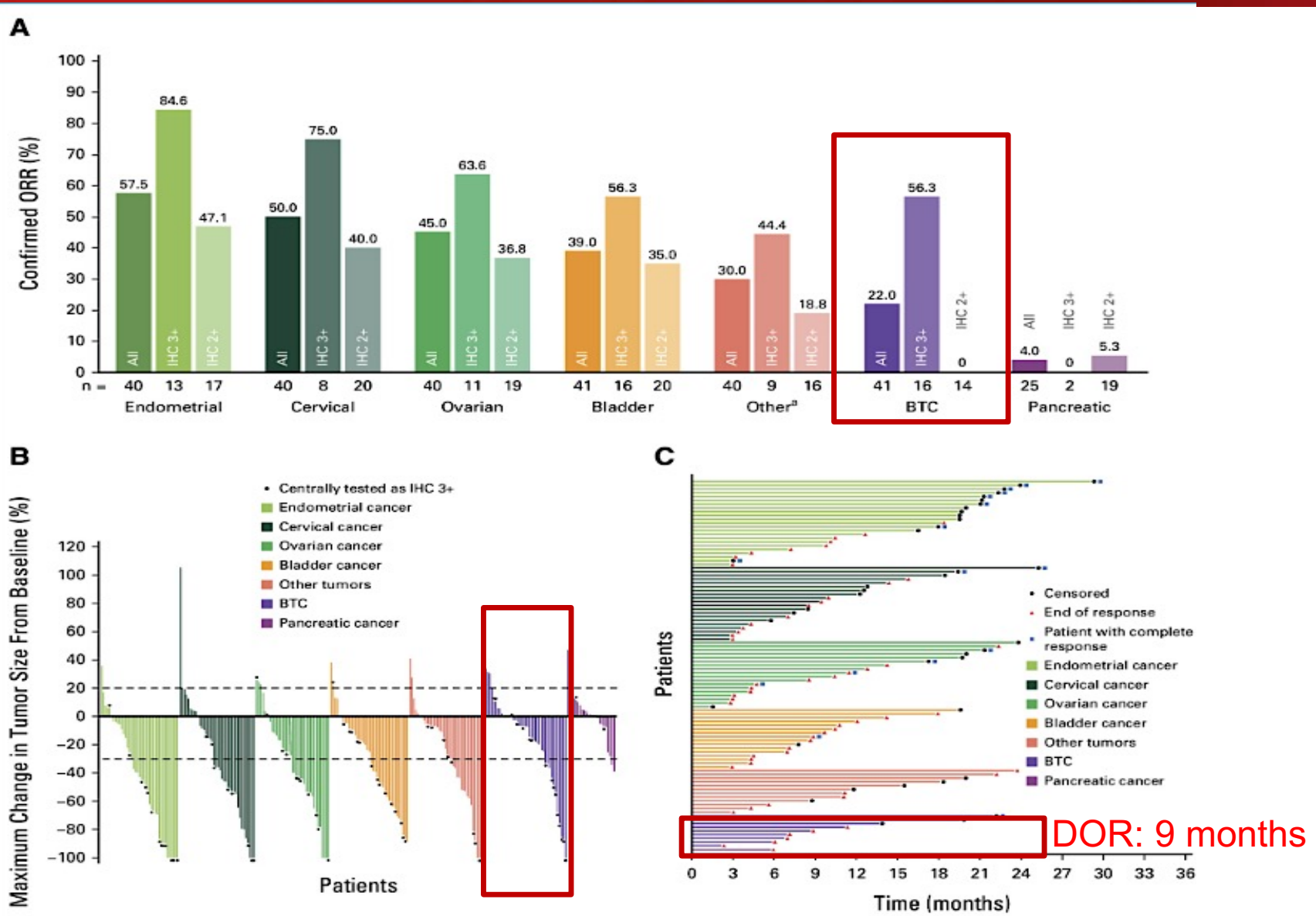


Yoon et al. Nature Reviews Clinical Oncology 2024

Trastuzumab Deruxtecan: ADC



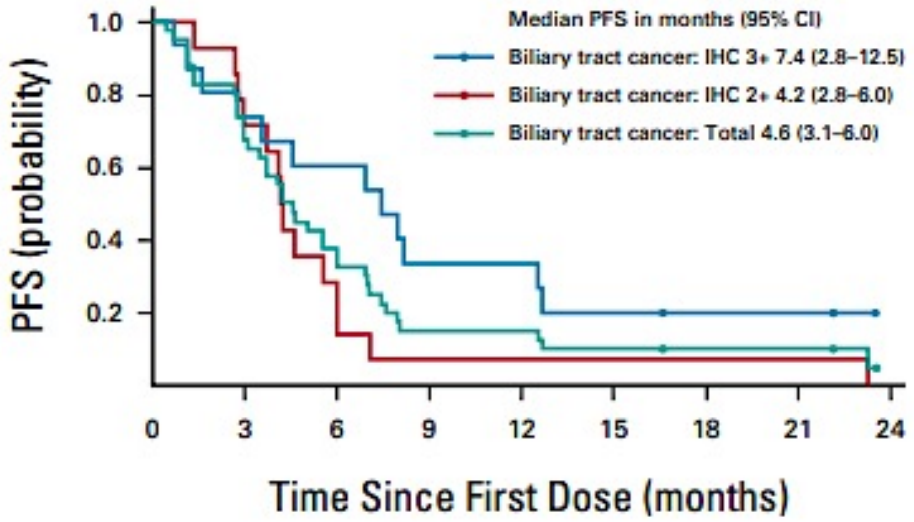
DESTINY-PanTumor02: Trastuzumab Deruxtecan



DESTINY-PanTumor02: Trastuzumab Deruxtecan

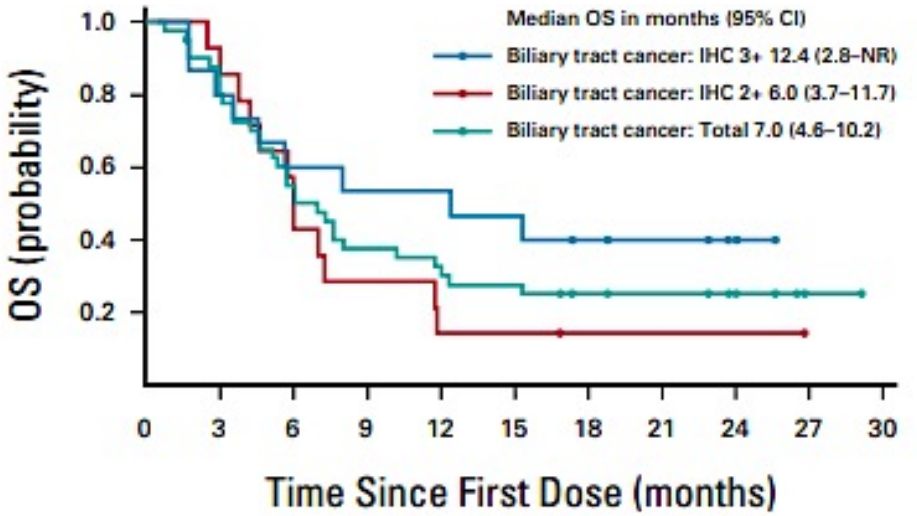
Adverse Event	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)	Bladder Cancer (n = 41)	Other Tumors (n = 40)	Biliary Tract Cancer (n = 41)	Pancreatic Canc (n = 25)
Drug-related adverse events, No. (%)	36 (90.0)	36 (90.0)	34 (85.0)	38 (92.7)	34 (85.0)	33 (80.5)	15 (60.0)
Grade ≥3	14 (35.0)	19 (47.5)	21 (52.5)	17 (41.5)	15 (37.5)	16 (39.0)	7 (28.0)
Serious adverse events	4 (10.0)	3 (7.5)	11 (27.5)	4 (9.8)	6 (15.0)	5 (12.2)	3 (12.0)
Leading to discontinuation	3 (7.5)	3 (7.5)	1 (2.5)	4 (9.8)	6 (15.0)	5 (12.2)	1 (4.0)
Leading to dose modification[a]	13 (32.5)	13 (32.5)	18 (45.0)	15 (36.6)	13 (32.5)	13 (31.7)	0
Associated with death	2 (5.0)	0	0	1 (2.4)	1 (2.5)	0	0
Most common drug-related adverse events (>10% of total patients), No. (%)							
Nausea	29 (72.5)	26 (65.0)	22 (55.0)	21 (51.2)	23 (57.5)	19 (46.3)	7 (28.0)
Anemia	7 (17.5)	15 (37.5)	15 (37.5)	12 (29.3)	11 (27.5)	10 (24.4)	4 (16.0)
Diarrhea	16 (40.0)	15 (37.5)	8 (20.0)	13 (31.7)	6 (15.0)	8 (19.5)	3 (12.0)
Fatigue	10 (25.0)	9 (22.5)	11 (27.5)	11 (26.8)	12 (30.0)	9 (22.0)	4 (16.0)
Vomiting	16 (40.0)	10 (25.0)	7 (17.5)	6 (14.6)	15 (37.5)	9 (22.0)	3 (12.0)
Neutropenia	4 (10.0)	8 (20.0)	5 (12.5)	11 (26.8)	9 (22.5)	9 (22.0)	4 (16.0)
Decreased appetite	8 (20.0)	7 (17.5)	8 (20.0)	8 (19.5)	7 (17.5)	7 (17.1)	2 (8.0)
Asthenia	11 (27.5)	9 (22.5)	6 (15.0)	3 (7.3)	8 (20.0)	6 (14.6)	3 (12.0)
Alopecia	9 (22.5)	8 (20.0)	5 (12.5)	5 (12.2)	7 (17.5)	9 (22.0)	2 (8.0)
Thrombocytopenia	2 (5.0)	2 (5.0)	5 (12.5)	6 (14.6)	7 (17.5)	5 (12.2)	3 (12.0)

DESTINY-PanTumor02: : Trastuzumab Deruxtecan



No. at risk:

Biliary tract cancer: IHC 3+	16	11	9	5	5	3	2	2	0
Biliary tract cancer: IHC 2+	14	10	3	1	1	1	1	1	0
Biliary tract cancer: Total	41	27	14	6	6	4	3	3	0



No. at risk:

Biliary tract cancer: IHC 3+	16	12	9	8	8	7	5	4	1	0
Biliary tract cancer: IHC 2+	14	12	7	4	2	2	1	1	1	0
Biliary tract cancer: Total	41	32	21	15	12	11	8	7	4	1	0

Meric-Bernstam et al JCO 2024

DESTINY-BTC01

- DESTINY-BTC01 is an open-label, multicenter, randomized, Phase 3 study of first-line T-DXd with rilvegostomig or T-DXd monotherapy vs SOC in patients with HER2-expressing, unresectable, locally advanced, or metastatic BTC
- An initial safety run-in will enroll approximately 20 patients to evaluate the safety and tolerability of T-DXd in combination with rilvegostomig
  - In the absence of pre-determined safety signals and per independent data monitoring committee review, patients will be randomized 1:1:1 to three treatment arms (A, B, and C)

Patient population (N≈620)

- Unresectable, locally advanced, or metastatic BTC
- Histologically confirmed HER2 IHC 3+/2+ tumors (proportion of patients enrolled with IHC 2+ tumors will be capped at 40% of the total randomized population)
- No prior treatment in the advanced/metastatic disease setting
- WHO/ECOG performance status of 0 or 1
- Measurable disease per RECIST 1.1*

Stratification factors

- HER2 expression status: IHC 3+ vs IHC 2+
- PD-L1 status: tumor area positivity ≥1% vs <1%
- Primary tumor location: gallbladder cancer vs intrahepatic cholangiocarcinoma vs extrahepatic cholangiocarcinoma

Safety run-in (n≈20)
T-DXd 5.4 mg/kg† + rilvegostomig

Safety review of treatment combination

1:1:1 randomization

Arm A (n≈200)
T-DXd 5.4 mg/kg Q3W‡ + rilvegostomig

Arm B (n≈200)
T-DXd 5.4 mg/kg Q3W‡

Arm C (n≈200)
Gemcitabine 1000 mg/m^2 + cisplatin 25 mg/m^2 + durvalumab 1500 mg (SOC)§

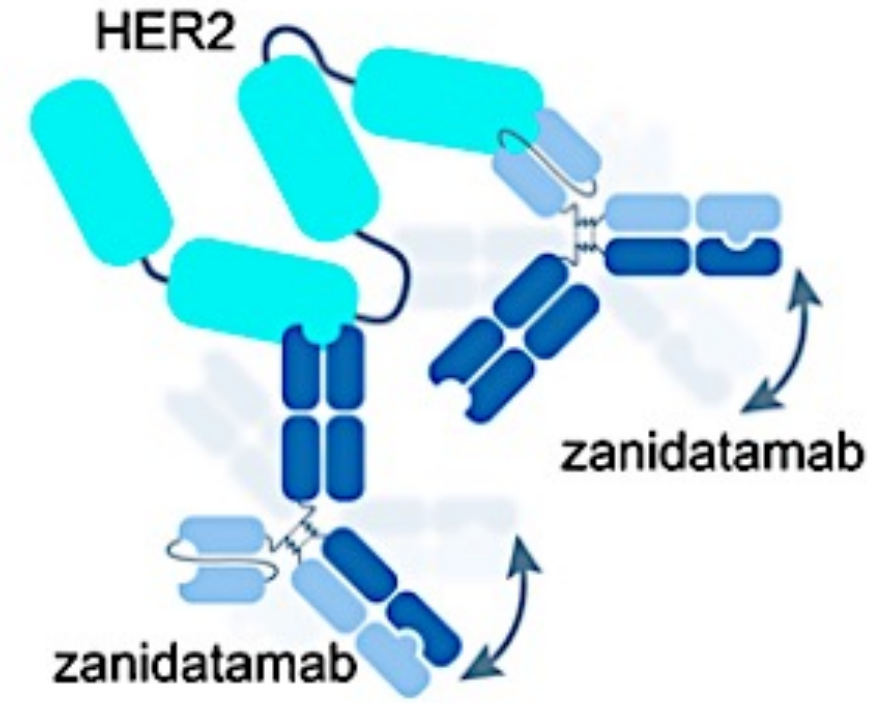
For more information about DESTINY-BTC01, please visit https://clinicaltrials.gov/study/NCT06467357

Ikeda M et al. ESMO Asia 2024; Abstract 261TiP.

Zanidatamab: biparatopic antibody

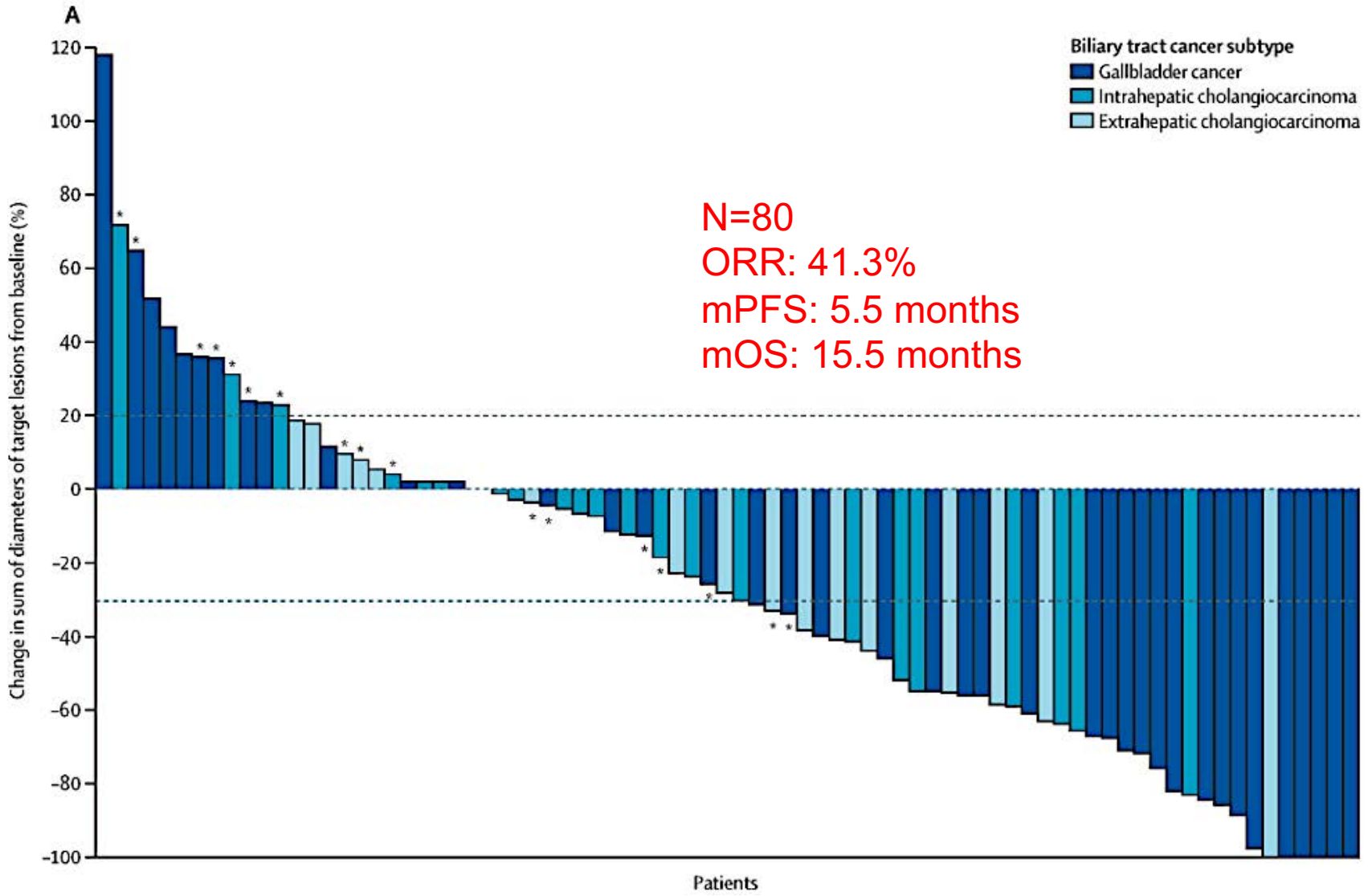
Binds to epitope II and IV of HER2

- Enhance HER2 Signal Blockade
- Immune mediated cytotoxicity
- HER2 Internalization



Wichman et al. Nature Communications 2023

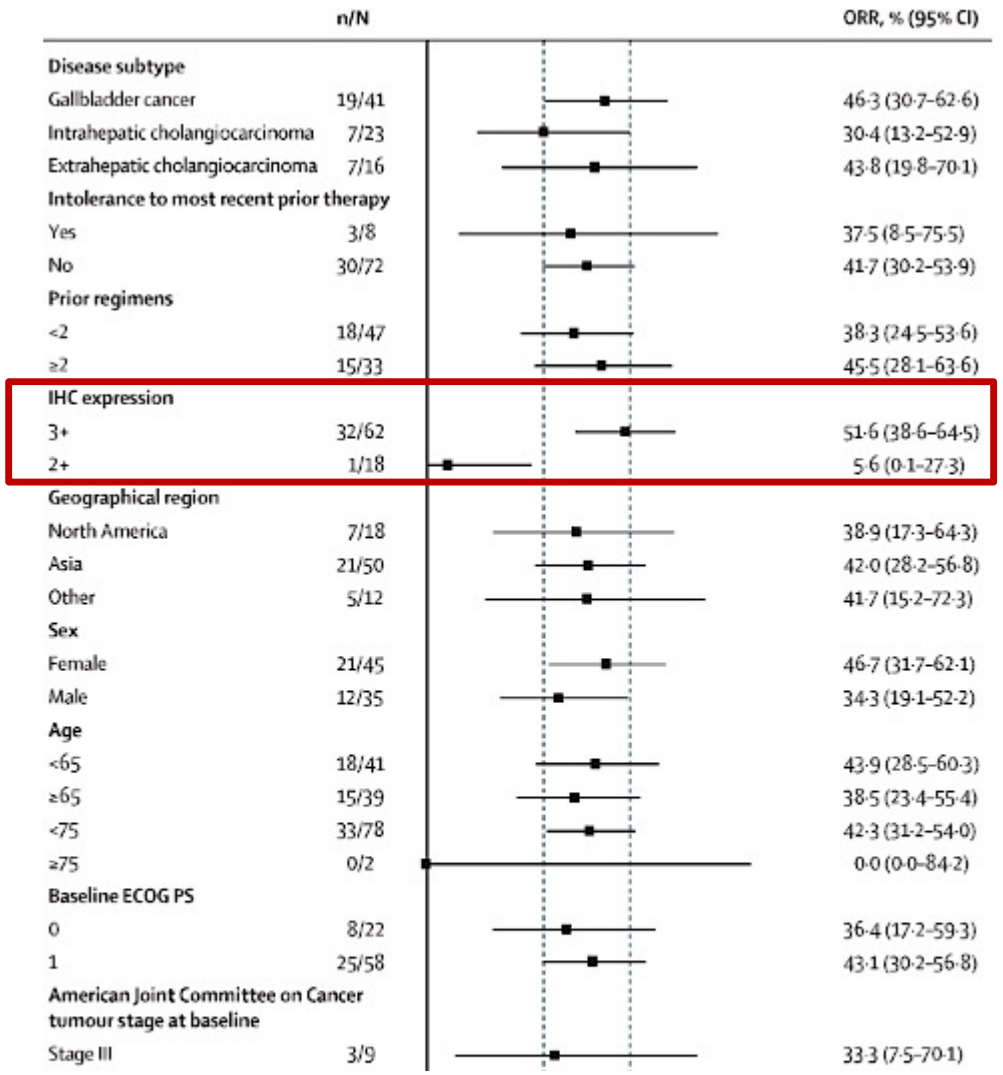
HERIZON-BTC-01: Zanidatamab



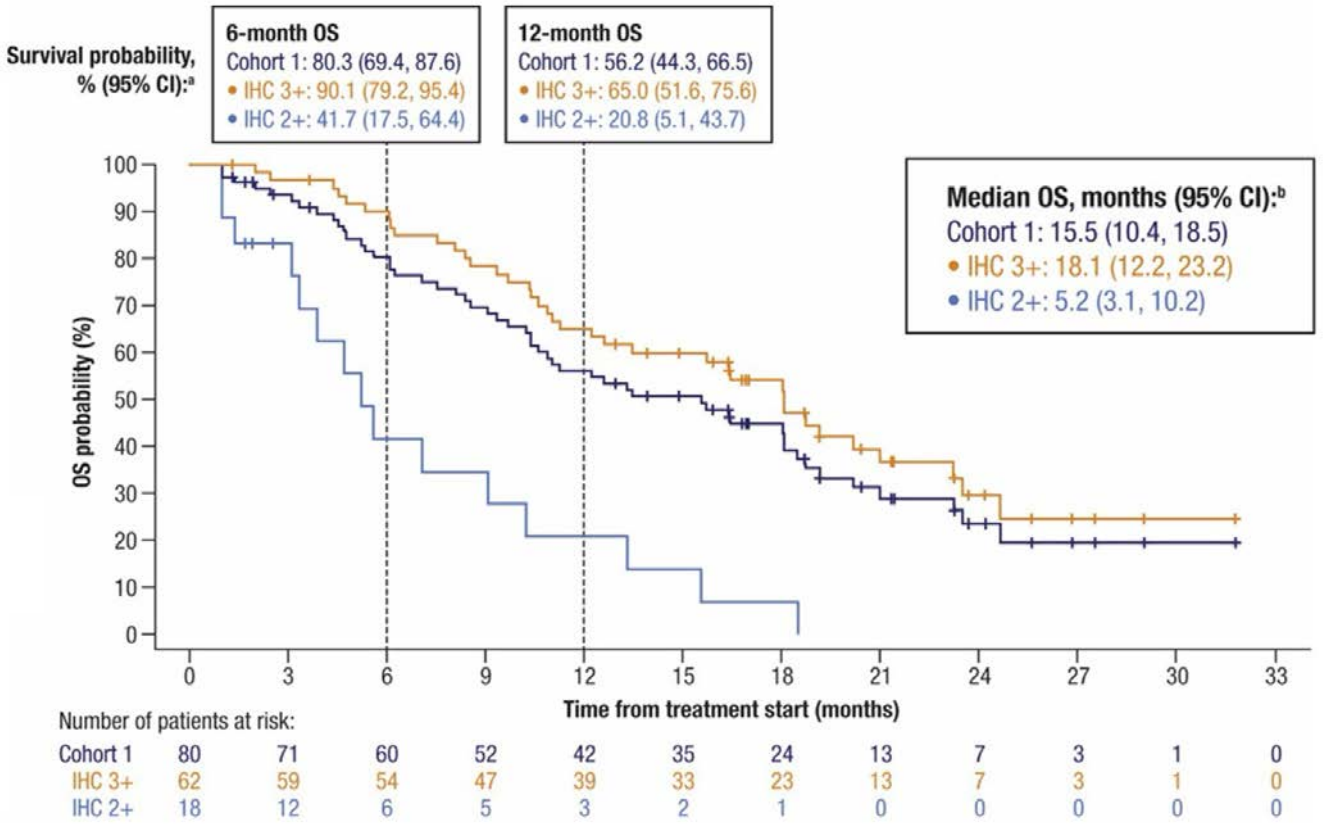
N=80
ORR: 41.3%
mPFS: 5.5 months
mOS: 15.5 months

Harding et al. Lancet Oncol 2023; Pant S et al. ASCO 2024; Abstract 4091.

HERIZON-BTC-01: Zanidatamab



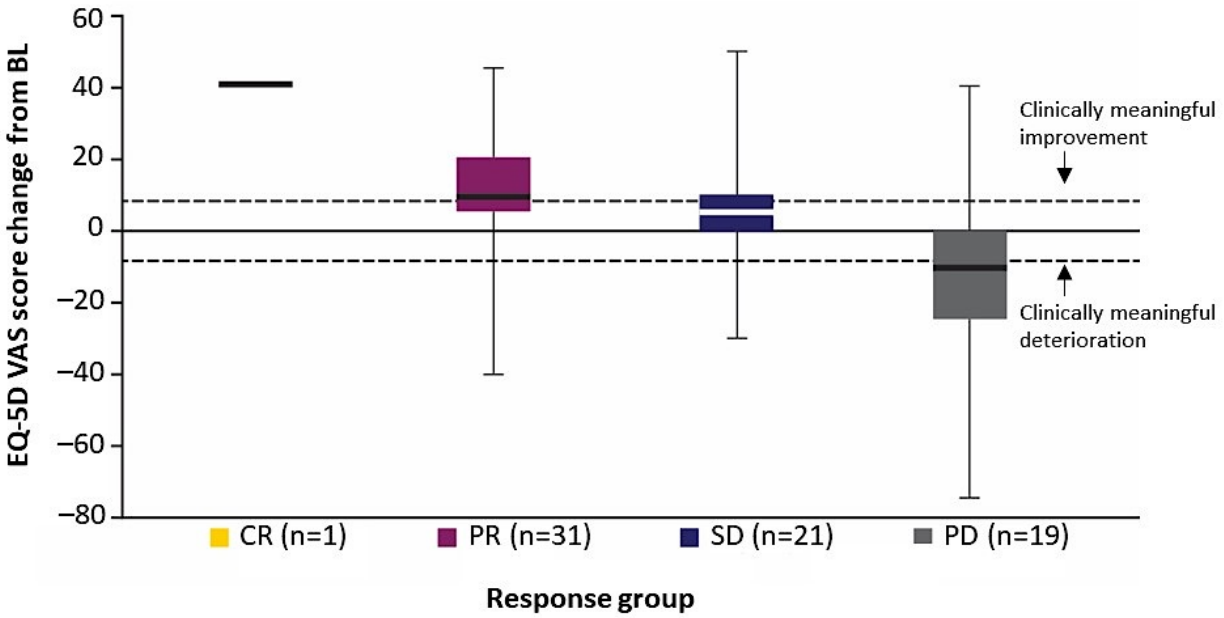
Primary benefit is in HER2 3+



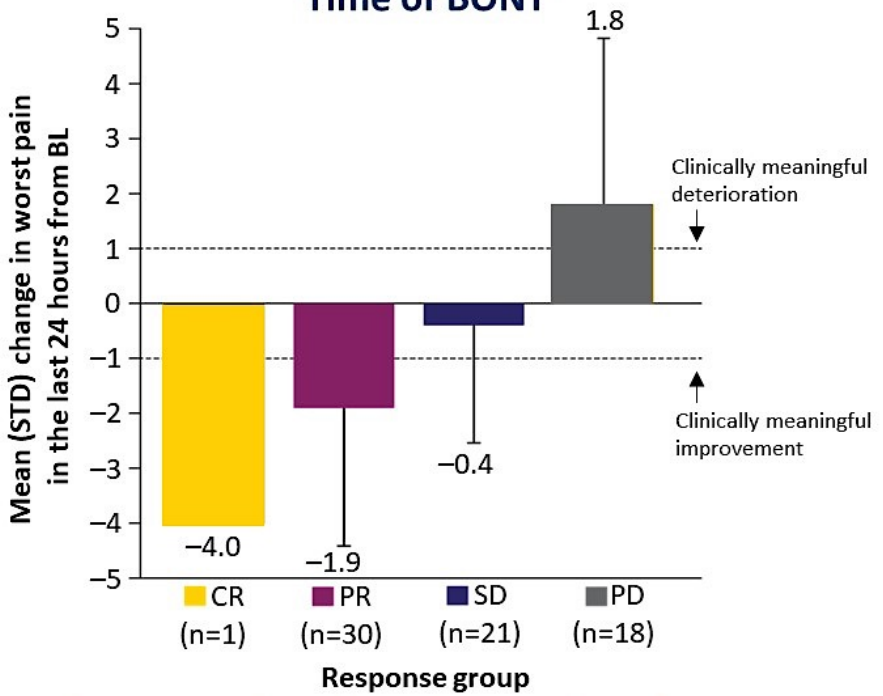
Results support recent FDA approval for previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer.

HERIZON-BTC-01: Improved HRQoL and Pain With Response to Treatment

Change in EQ-5D VAS Scores from BL at Time of BONT by Tumor Response[1]



Change from BL in Worst Pain in the Last 24 Hours at Time of BONT



- In cohort 1, cORR was 41% (33 patients); 1% CR (n=1), 40% PR (n=32), 28% SD (n=22), 30% PD (n=24), and 1% NE (n=1)[2,a]
- Clinically meaningful improvements in EQ-5D VAS scores from BL (≥7 points)[3] were reported by patients who responded to zanidatamab (CR and PR) at the time of BONT[1]
- Patients with CR and PR reported clinically meaningful improvements in worst pain in the last 24 hours (≥1 point decrease),[4] while patients with PD reported clinically meaningful deterioration in worst pain from BL to BONT

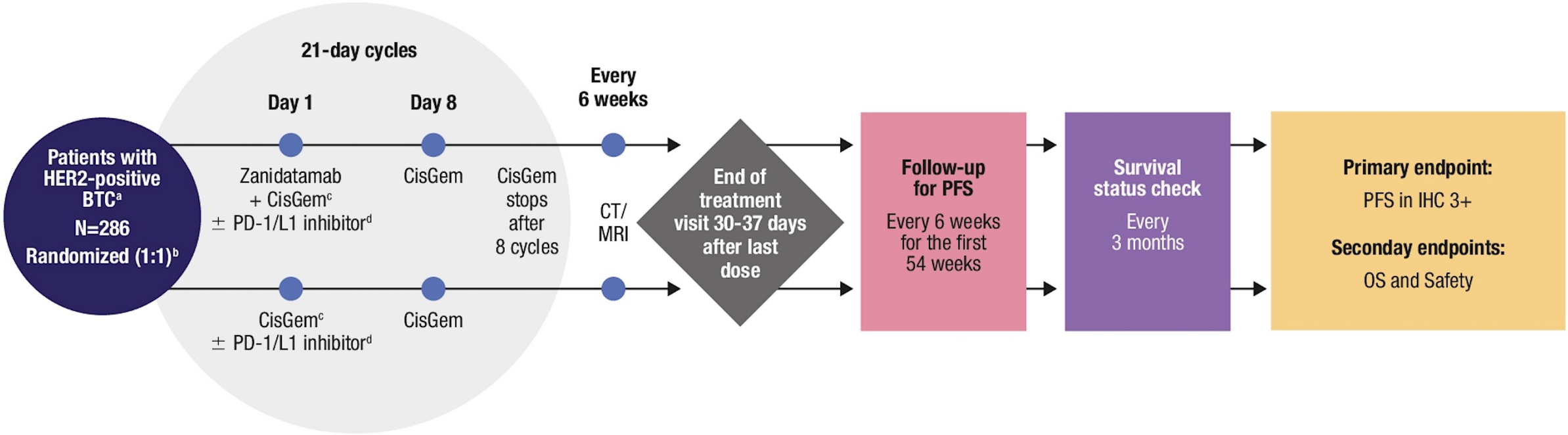
HERIZON-BTC-01: Zanidatamab

	Grade 1–2	Grade 3
Any adverse event	47 (54%)	16 (18%)
Diarrhoea	28 (32%)	4 (5%)
Infusion-related reaction	28 (32%)	1 (1%)
Ejection fraction decreased	5 (6%)	3 (3%)
Nausea	7 (8%)	1 (1%)
Alanine aminotransferase increased	6 (7%)	0
Aspartate aminotransferase increased	5 (6%)	1 (1%)
Vomiting	6 (7%)	0
Fatigue	5 (6%)	0
Anaemia	2 (2%)	2 (2%)
Hypokalaemia	1 (1%)	1 (1%)
Platelet count decreased	1 (1%)	1 (1%)
Blood bilirubin increased	0	1 (1%)
Enteritis	0	1 (1%)
Lipase increased	0	1 (1%)
Oral candidiasis	0	1 (1%)
Pneumonitis	0	1 (1%)
Stomatitis	0	1 (1%)

Harding et al. Lancet Oncol 2023

HERIZON-BTC-302

HERIZON-BTC-302 is an ongoing, global, phase 3, randomized, open-label trial (NCT06282575) investigating the efficacy and safety of zanidatamab with CisGem +/- a PD-1/L1 inhibitor vs CisGem alone +/- a PD-1/L1 inhibitor (physician's choice of pembrolizumab or durvalumab if locally approved) as first-line treatment for patients with advanced HER2-positive BTC

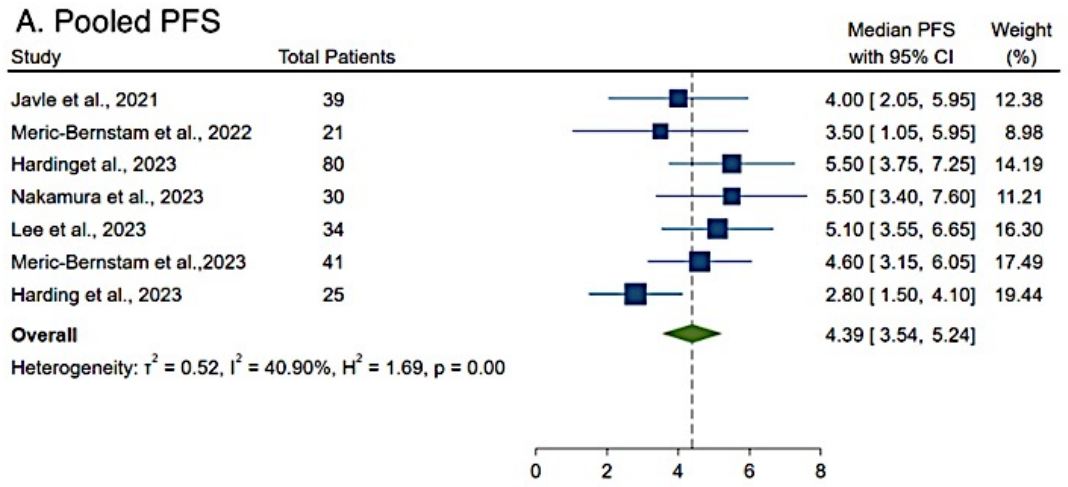


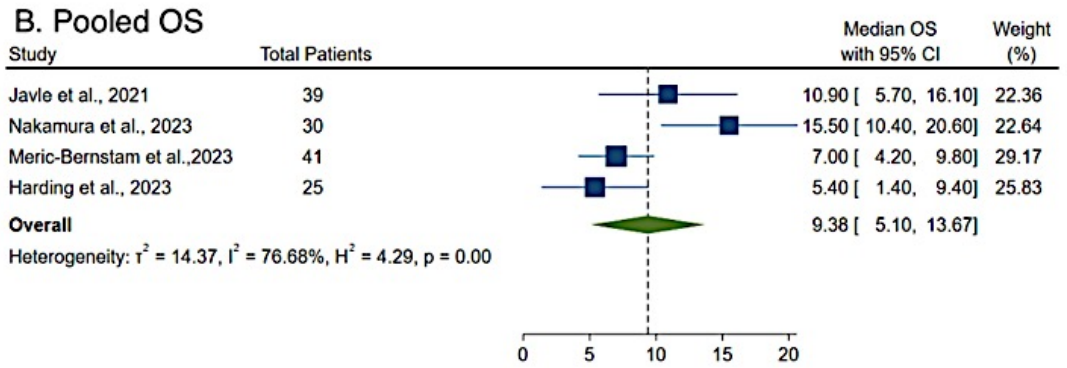
[a]Patients will be enrolled based on central assessment of HER2 status; [b]Patients who receive 1 of the allowed PD-1/L1 inhibitors prior to randomization will continue to receive the same PD-1/L1 inhibitor after randomization; [c]Up to 2 cycles of systemic therapy with CisGem ± a PD-1/L1 inhibitor are allowed per protocol prior to randomization; 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.

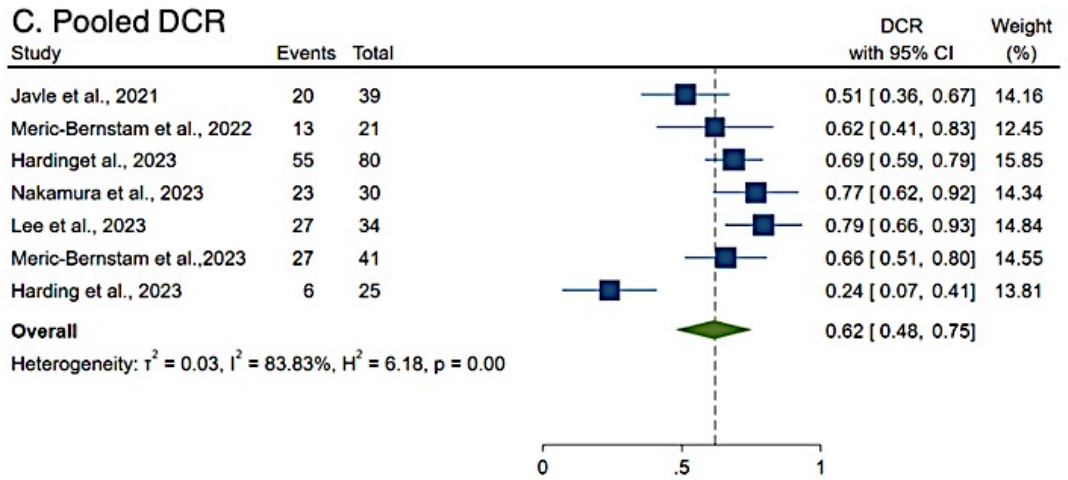
BTC, biliary tract cancer; CisGem, cisplatin plus gemcitabine; CT, computed tomography; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenously; MRI, magnetic resonance imaging; OS, overall survival; PD-1/L1, programmed death-1/programmed cell death ligand 1; PFS, progression-free survival; RECIST V1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

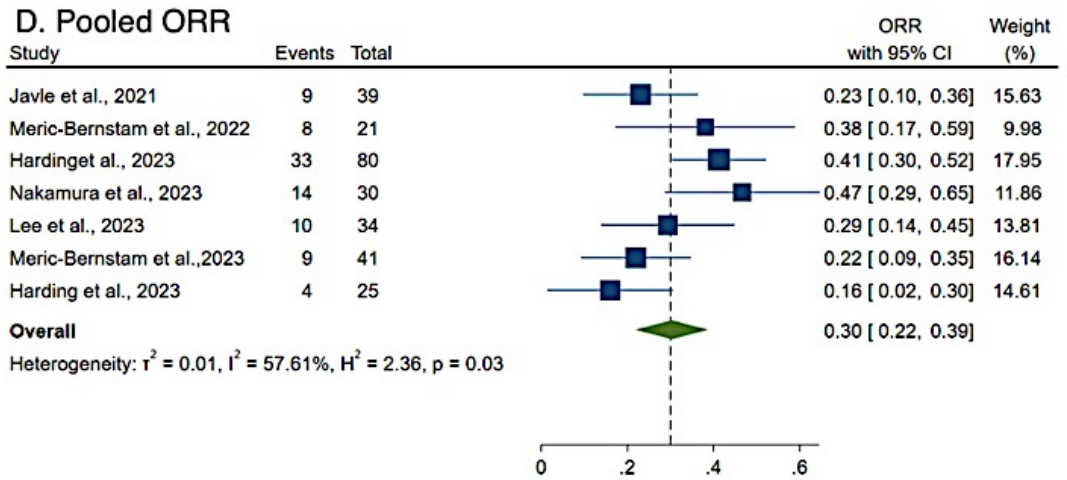
Harding J et al. ASCO GI 2025; Abstract TPS648.

HER2 therapies in BTC: Pooled Analysis





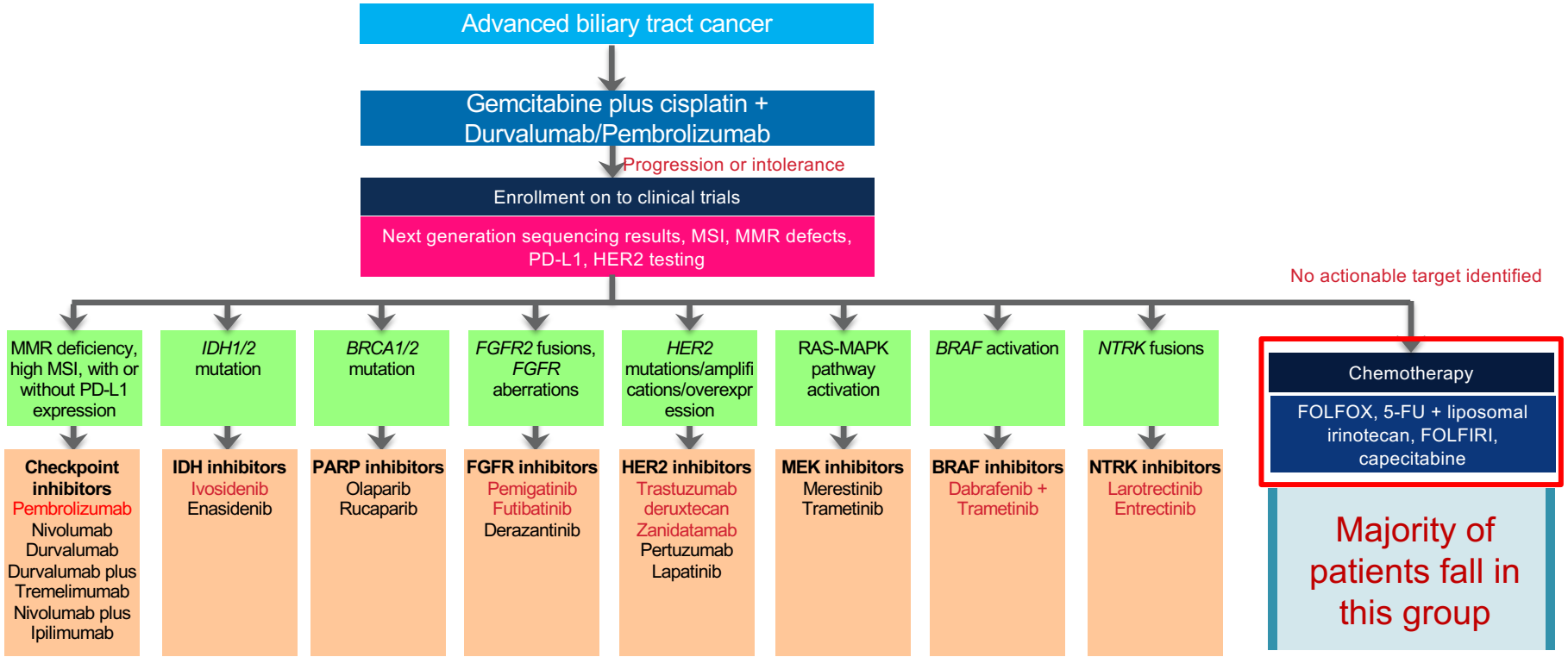




Future for HER2+ BTC

- Moving HER2 directed therapies in first line setting
- DESTINY-BTC01
  - Trastuzumab deruxtecan + rilvegostomig vs SOC
  - Primary Endpoint: OS in HER2 3+ by IHC
- HERIZON-BTC-302
  - Zanidatamab + gemcitabine + cisplatin +/- PD1 inhibitor vs SOC
  - Primary Endpoint: PFS in HER2 3+ by IHC
- Will require results of biomarker testing prior to starting first line treatment

Treatment Algorithm



Discussion Questions

- Regulatory and reimbursement issues aside, what regimen would you generally recommend as the next line of therapy for a patient with asymptomatic, low-volume HER2-positive BTC who experienced disease progression on chemotherapy in combination with immunotherapy? What about for a patient with symptomatic, higher-volume disease?

- Regulatory and reimbursement issues aside, what would be your preferred first-line systemic treatment for an older, frail patient with advanced HER2-positive BTC? Would you consider HER2-targeted therapy?

Discussion Questions

- In which clinical settings, if any, would you like to be able to administer HER2-targeted therapy to a patient with HER2-low (IHC 1+ or 2+) BTC?
- How should acute GI toxicity be managed in a patient with metastatic HER2-positive BTC who is receiving trastuzumab deruxtecan? What screening procedures should be followed to monitor for ILD in these patients?
- What adverse events have been associated with the bispecific antibody zanidatamab?

Module 8: Biliary Tract Cancers

Targeted Therapeutic Approaches for Patients with BTCs — Dr Mahipal

Integration of Immune Checkpoint Inhibitors into Current Biliary Tract Cancer (BTC) Management — Dr Borad

INTEGRATION OF IMMUNE CHECKPOINT INHIBITORS INTO CURRENT BILIARY TRACT CANCER (BTC) MANAGEMENT

MITESH J. BORAD, M.D.

Getz Family Research Professor at Mayo Clinic Arizona
Professor of Medicine, Mayo Clinic College of Medicine and Science

Co-Leader, Novel Therapeutics and Therapeutic Modalities Program
Mayo Clinic Comprehensive Cancer Center

Director, Precision Cancer Therapeutics Lab

MAYO CLINIC

Fourth Annual National GMO Summit
Miami Beach, FL
February 28-March 2, 2025

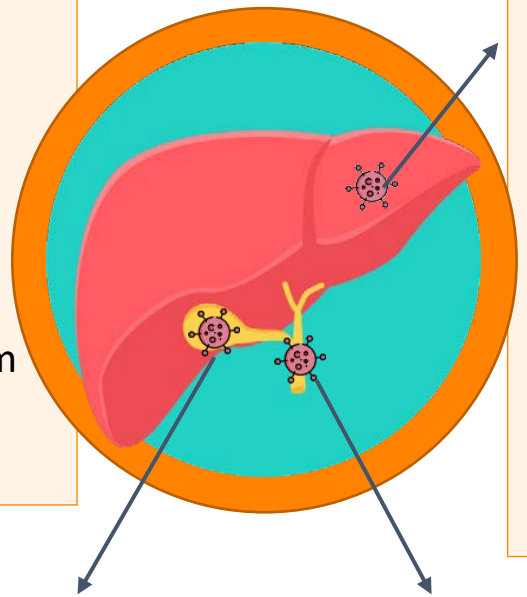
Disclosures

Advisory Committees	Elevar Therapeutics
Consulting Agreements	Guardant Health, Jazz Pharmaceuticals Inc
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Biond Biologics, Dragonfly Therapeutics, Eisai Inc, Elevation Oncology, Incyte Corporation, Kinnate Biopharma, Nuvectis Pharma Inc, Pfizer Inc, Relay Therapeutics, Revolution Medicines, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC
Data and Safety Monitoring Boards/Committees	Accession Therapeutics

Biliary Cancers[1]

Biliary cancers

- >90% of cases are adenocarcinoma
- Level 1 evidence for adjuvant chemotherapy: capecitabine
- Palliative first-line chemotherapy: cisplatin/gemcitabine
- No second-line palliative chemotherapy with a demonstrated survival benefit over active symptom control
- Median overall survival: ~12 months



Intrahepatic cholangiocarcinoma

- Risk factors: primary sclerosing cholangitis, cirrhosis, *Opisthorchis viverrini* or *Clonorchis sinensis*, obesity, diabetes, chronic hepatitis B and C, hepatolithiasis, Lynch syndrome, biliary papillomatosis, biliary duct morphologic anomalies
- Typically presents as incidental hepatic lesion(s)
- Radioembolization or radiation can be considered for liver-predominant disease

Gallbladder cancer

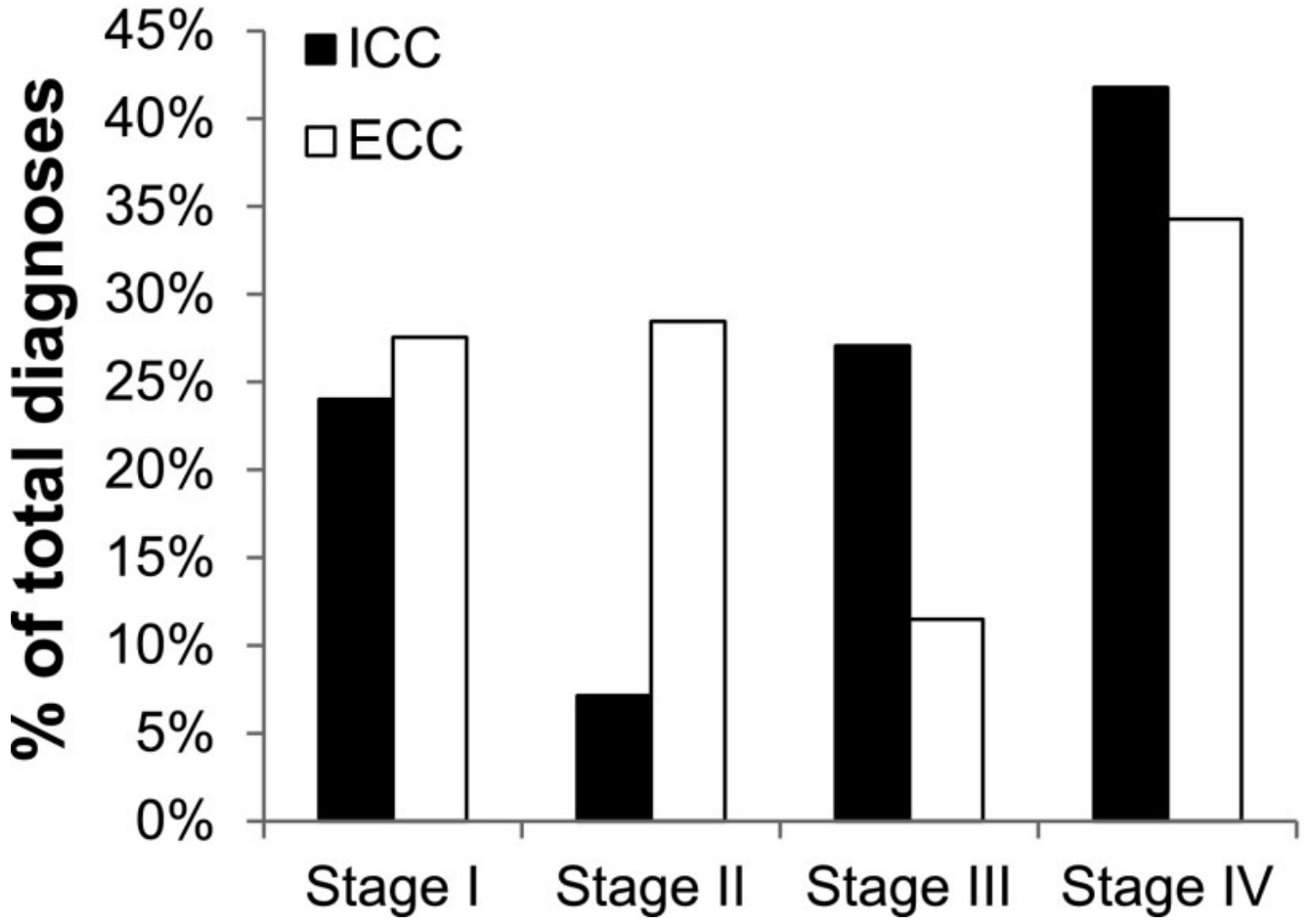
- Females > males
- Risk factors: gallstones, gallbladder polyps, chronic cholecystitis, *Salmonella typhi*, obesity, diabetes
- Typically presents as an incidental finding following cholecystectomy (localized stage) or with the abdominal pain (advanced stage)

Extrahepatic cholangiocarcinoma

- Males > females
- Risk factors: primary sclerosing cholangitis, gallstones, Lynch syndrome, *Opisthorchis viverrini* or *Clonorchis sinensis*, bile duct morphologic anomalies
- Typically presents with obstructive jaundice

1. Valle JW et al. *Cancer Discov*. 2017;7:943-962.

STAGE DISTRIBUTION OF BTCs



SAHA ET AL, ONCOLOGIST 2016

Case Vignette

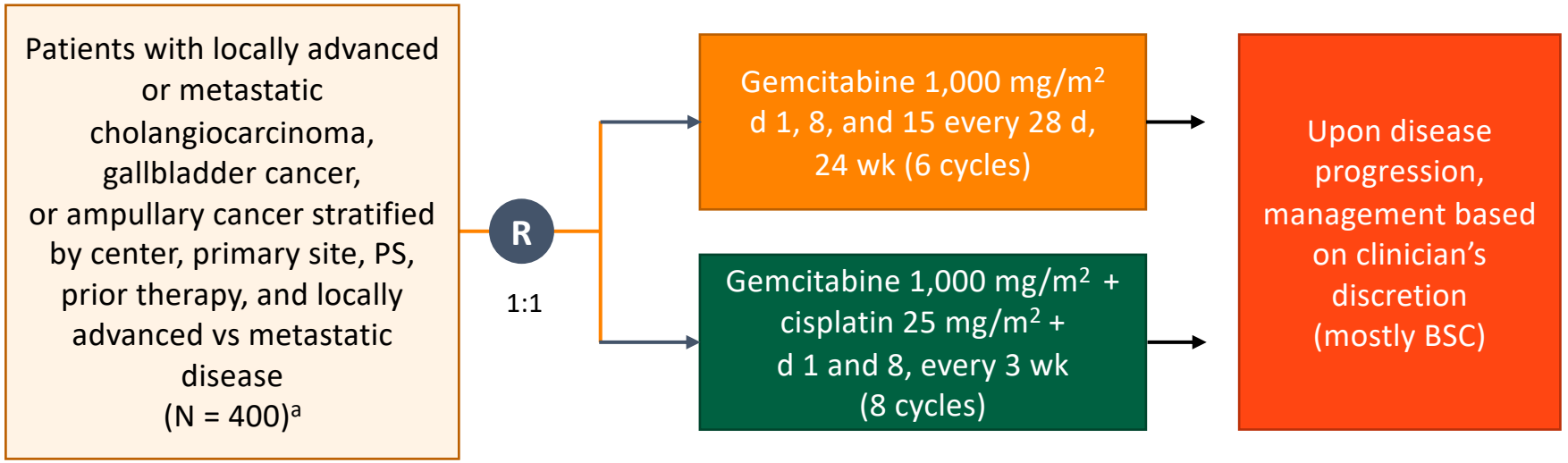
40 year old female with history of metastatic intrahepatic cholangiocarcinoma

- ECOG PS = 1
- Lesions in liver, lungs and bones
- TMB = 2 mutations/Megabase, PD-L1 < 1%
- SMAD4 mutation, TP53 mutation (tissue)
- Serum creatinine = 1.1 mg/dl, AST/ALT < 3 x ULN, bilirubin WNL
- No ongoing myelosuppression

Case Vignette

- *What regimen would you consider for systemic therapy ?*
  1. *FOLFOX*
  2. *FOLFOX + bevacizumab*
  3. *Gemcitabine/cisplatin/durvalumab*
  4. *Gemcitabine/cisplatin/pembrolizumab*
  5. *Either 3 or 4*

Phase 3 ABC-02 Trial: Gemcitabine vs Cisplatin/ Gemcitabine in Advanced Biliary Cancers[1]



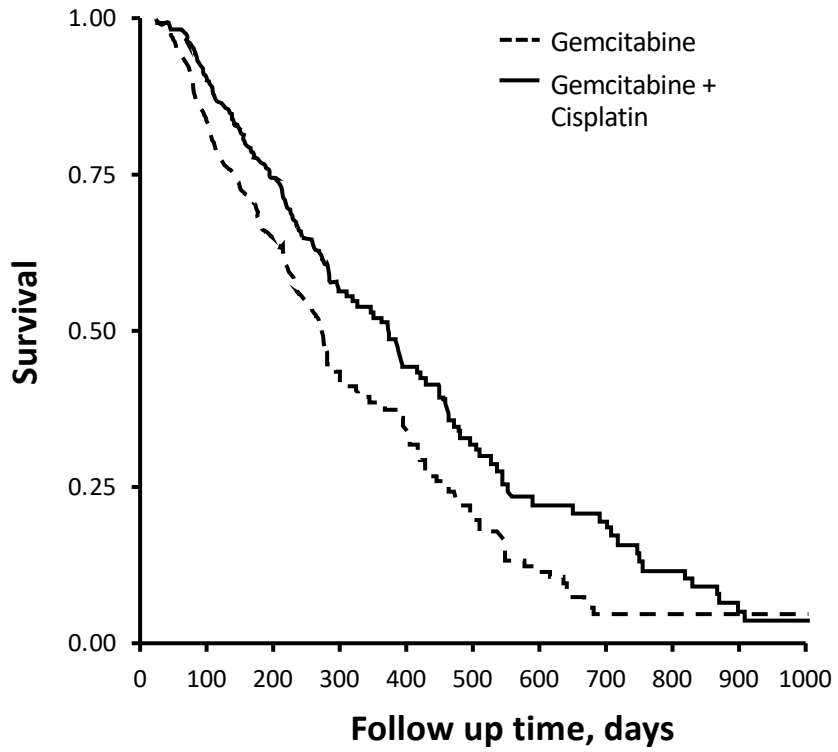
- **Primary endpoint:** OS
- **Secondary endpoints:** PFS, tumor response, AEs

+ QOL

[a] Includes 86 patients from ABC-01

1. Valle J et al. *N Engl J Med*. 2010;362:1273-1281

ABC-02: Survival Data (ITT)[1]

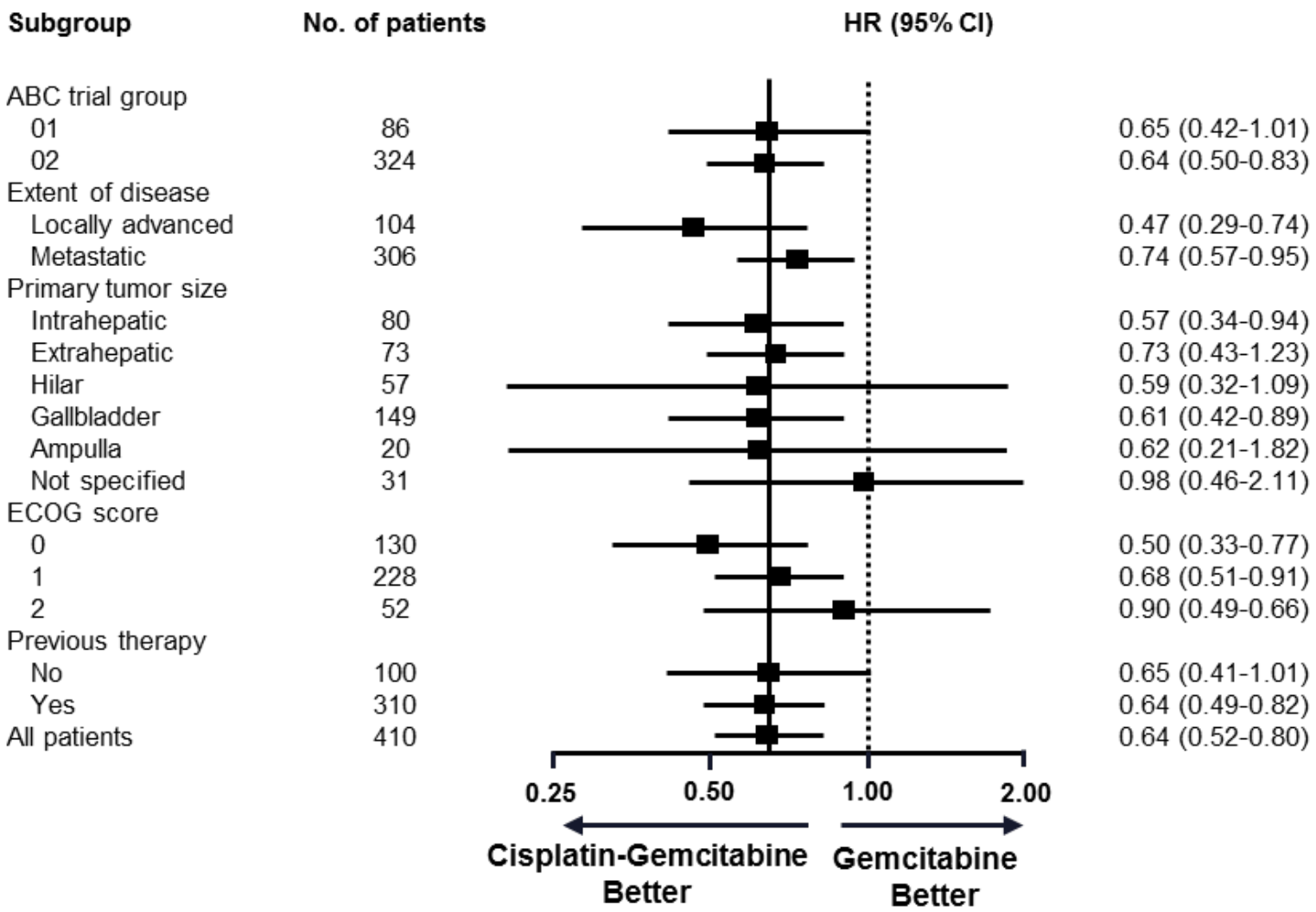


Treatment Arm	Gem	Gem + Cis
No. of patients	n = 206	n = 204
Deaths, n (%)	141 (68.5)	122 (59.8)
Median survival, mo	8.3	11.7
Log rank *P*	.002	
HR (95% CI)	0.70 (0.54, 0.89)	

Number at Risk											
Gem	206	137	87	50	34	18	9	2	2	1	1
Gem + Cis	204	156	99	64	45	27	16	12	7	2	1

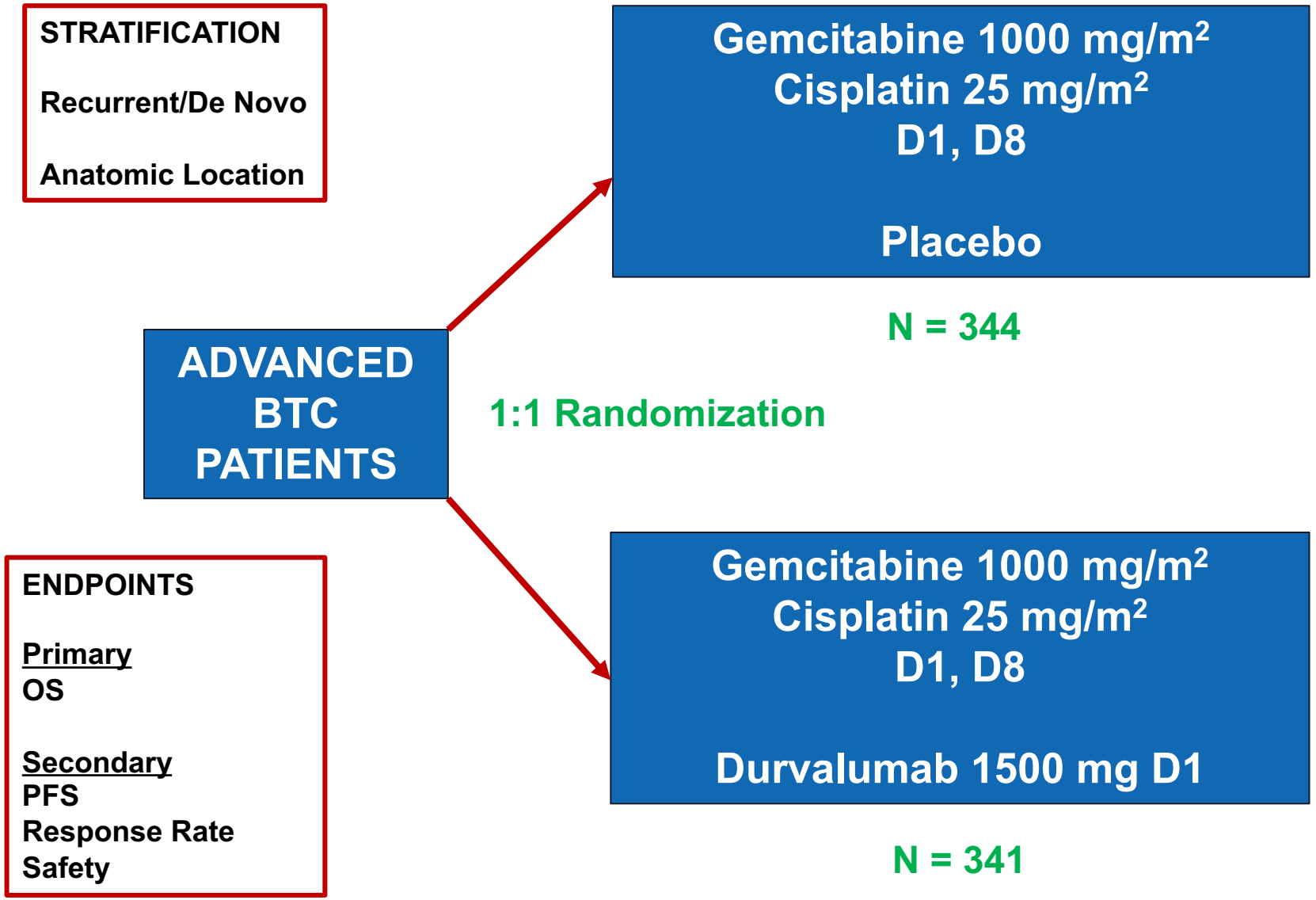
1. Valle J et al. *N Engl J Med*. 2010;362:1273-1281

ABC-02: Prespecified Factors[1]



1. Valle J et al. *N Engl J Med*. 2010;362:1273-1281

TOPAZ-1 STUDY



Gemcitabine/Cisplatin +/- Durvalumab : TOPAZ-1 STUDY

OVERALL SURVIVAL = 12.8 vs. 11.5 mth

PFS = 7.2 vs. 5.7 mth

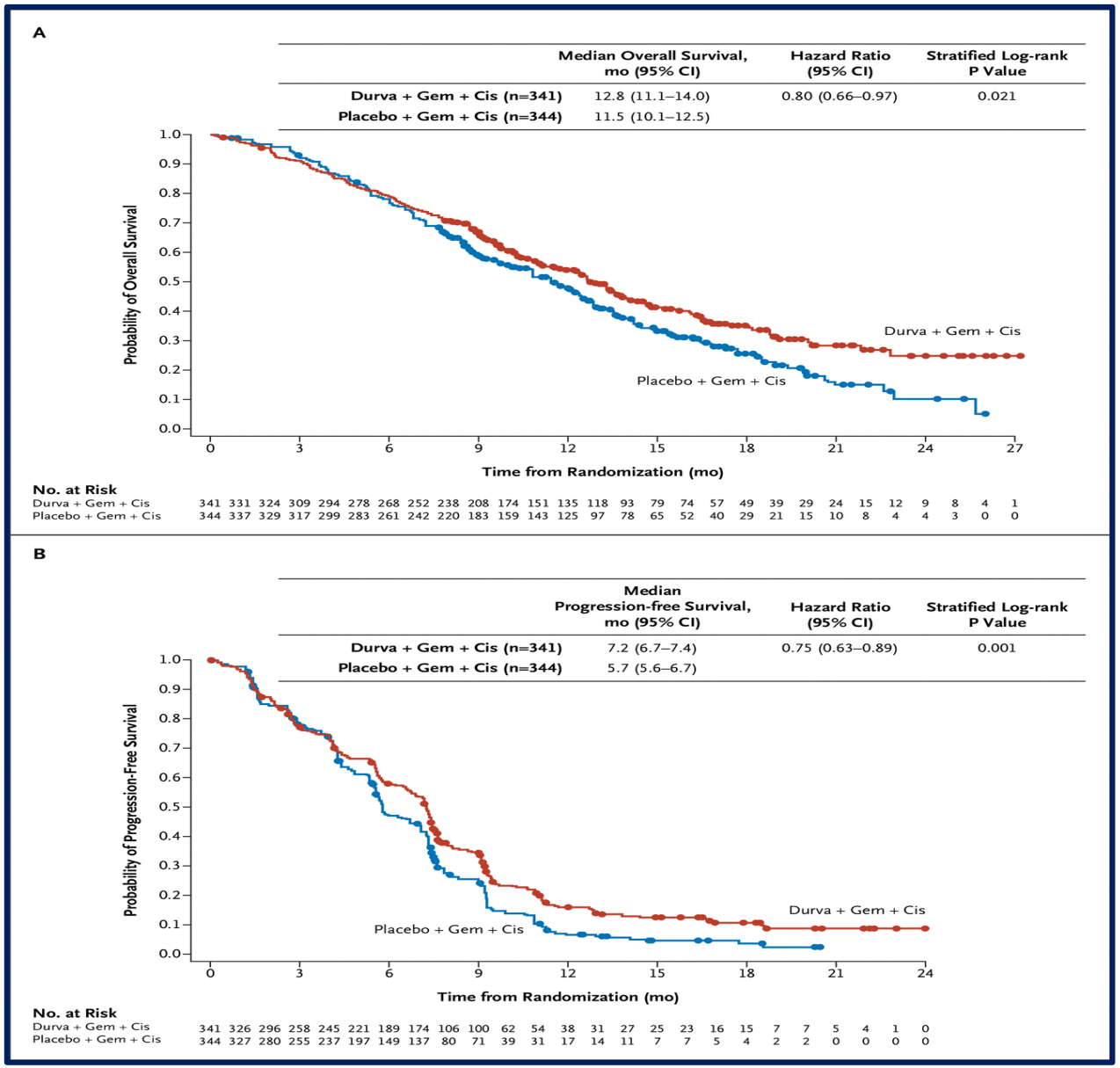
RESPONSE RATE = 26.7% vs. 18.7%

ADVERSE EVENT RATE NOT INCREASED

TIME TO RESPONSE = 1.6 vs. 2.7 mth

DURATION OF RESPONSE = 6.4 vs. 6.2 mth

RESPONSE AT 12 MTH = 26.1% vs. 15%

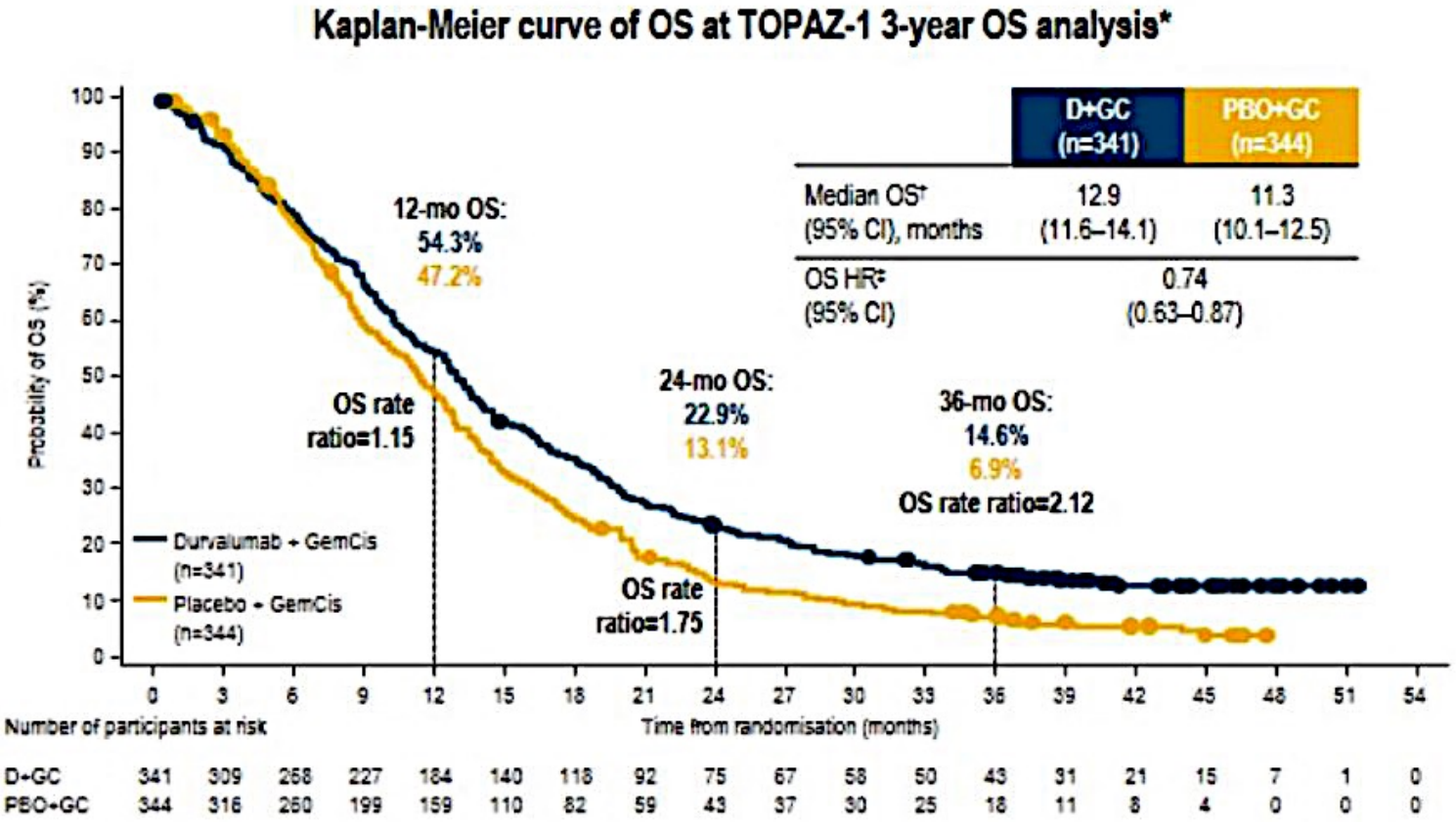


OH ET AL, NEJM EVID 2022

Gemcitabine/Cisplatin +/- Durvalumab : TOPAZ-1 STUDY

- The Phase 3 TOPAZ-1 (NCT03875235) study demonstrated that durvalumab + GemCis significantly improved overall survival versus placebo + GemCis in participants with advanced BTC[1]

- At 36-months, the survival rate in the durvalumab + GemCis arm was more than double the survival rate in the placebo + GemCis arm, with a manageable safety profile[2]



OH ET AL, CCF ANNUAL MEETING 2024

KEYNOTE-966 Study Design
Randomized, Double-Blind, Phase 3 Trial

Key Eligibility Criteria

- Histologically confirmed extrahepatic or intrahepatic cholangiocarcinoma or gallbladder cancer
- Unresectable locally advanced or metastatic disease measurable per RECIST v1.1 by investigator review
- No prior systemic therapy[a]
- ECOG PS 0 or 1
- Life expectancy >3 months

R
1:1

Pembrolizumab 200 mg IV Q3W (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W (maximum, 8 cycles)

Placebo IV Q3W for (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W (maximum, 8 cycles)

Stratification Factors

- Geographic region (Asia vs not Asia)
- Disease stage (locally advanced vs metastatic)
- Site of origin (extrahepatic vs gallbladder vs intrahepatic)

- **Primary End Point:** OS
- **Secondary End Points:** PFS, ORR, and DOR assessed per RECIST v1.1 by blinded, independent central review (BICR) and safety

Treatment was continued until disease progression, unacceptable toxicity, investigator decision, or, for pembrolizumab and cisplatin, the maximum number of cycles was reached.
[a]Neoadjuvant or adjuvant chemotherapy was permitted if it was completed ≥6 months before the diagnosis of unresectable or metastatic disease.
ClinicalTrials.gov identifier: NCT04003636.

Gemcitabine/Cisplatin +/- Pembrolizumab : KEYNOTE-966

Kelley KEYNOTE-966 AACR 2023

OVERALL SURVIVAL = 12.7 vs. 10.9 mth

PFS = 6.5 vs. 5.6 mth

RESPONSE RATE = 29% vs. 29%

ADVERSE EVENT RATE NOT INCREASED

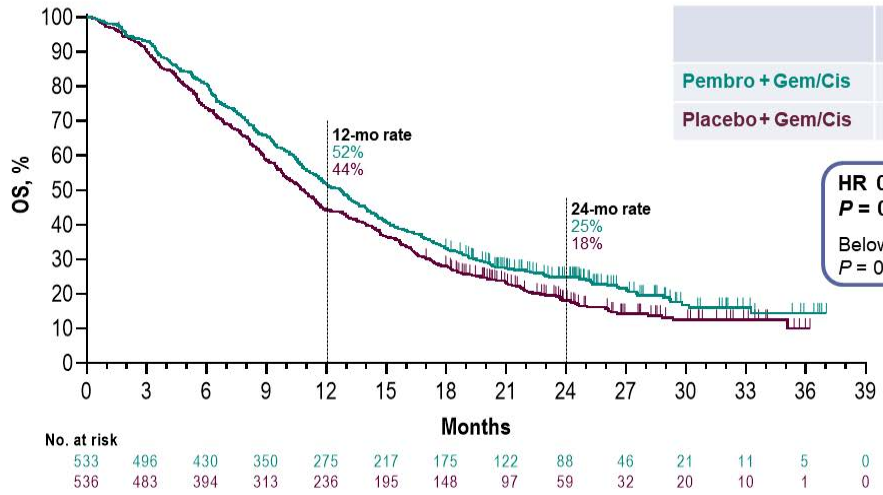
DURATION OF RESPONSE = 8.3 vs. 6.9 mth

RESPONSE AT 12 MTH = 38% vs. 27%

N = 1069 PATIENTS

KELLEY ET AL, LANCET 2023
FINN ET AL, ASCO 2024

Overall Survival at Final Analysis



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	78%	12.7 (11.5-13.6)
Placebo + Gem/Cis	83%	10.9 (9.9-11.6)

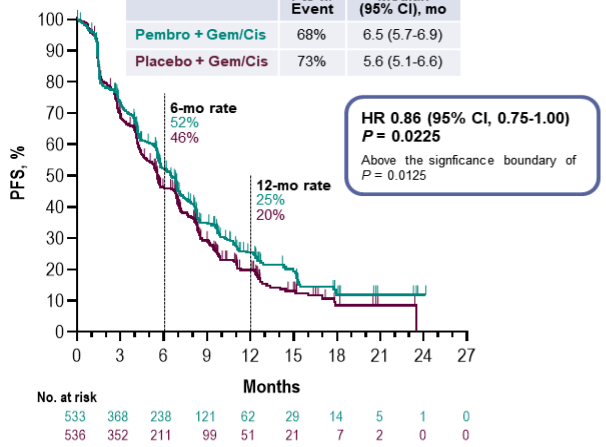
HR 0.83 (95% CI, 0.72-0.95)
P = 0.0034
Below the signficance boundary of *P* = 0.0200

Kelley KEYNOTE-966 AACR 2023

Progression-Free Survival

Interim Analysis 1

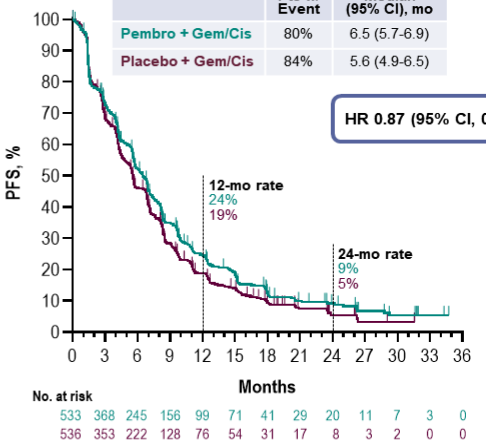
	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	68%	6.5 (5.7-6.9)
Placebo + Gem/Cis	73%	5.6 (5.1-6.6)



HR 0.86 (95% CI, 0.75-1.00)
P = 0.0225
Above the signficance boundary of *P* = 0.0125

Final Analysis

	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	80%	6.5 (5.7-6.9)
Placebo + Gem/Cis	84%	5.6 (4.9-6.5)



HR 0.87 (95% CI, 0.76-0.99)

PFS was assessed per RECIST v1.1 by BICR.
Data cutoff date: December 15, 2021 (IA1) and December 15, 2022 (FA). IA1 was the prespecified final analysis of PFS. PFS analysis at FA was exploratory.

TOURMALINE study design

Participant population
- ≥18 years
- Histologically confirmed locally advanced or metastatic BTC including iCCA, eCCA, GBC and AoV
- WHO / ECOG PS 0–2*
- Prior curative treatment permitted, with no minimum time to recurrence, including patients with residual disease

Screening: Day -28 to -1

N=140

Durvalumab + investigator's choice of gemcitabine-based chemotherapy†

Durvalumab 1500 mg, Q3W + gemcitabine-based chemotherapy† Q3W (up to 8 cycles), including:
- Gemcitabine monotherapy
- Gemcitabine + cisplatin (WHO / ECOG PS 2 only)
- Gemcitabine + oxaliplatin
- Gemcitabine + carboplatin
- Gemcitabine + S-1
- Gemcitabine + cisplatin + albumin-bound paclitaxel

OR

Durvalumab 1500 mg Q4W (up to 4 cycles) + gemcitabine + cisplatin + S-1† Q2W

Durvalumab 1500 mg Q4W until disease progression‡ or unacceptable toxicity
+
Gemcitabine-based chemotherapy§ maintenance, at investigator's discretion

Primary endpoint:
- Incidence of Grade 3 or 4 PRAEs within 6 months

Secondary endpoints:
- Safety and tolerability
- Median OS
- OS at 12, 18 and 24 months
- ORR per RECIST 1.1
- Median PFS per RECIST 1.1
- PFS at 12 and 18 months
- DCR at 24 and 32 weeks per RECIST 1.1
- DoR per RECIST 1.1
- Duration of treatment
- EORTC QLQ-C30
- EORTC QLQ-BIL21

*A cap of 20% was applied to participants with a WHO / ECOG PS of 2.

†Participant caps may be applied to gemcitabine-based chemotherapy groups, to achieve a sufficient number of participants in each of these groups. ‡Treatment through progression is permitted after careful assessment of derived clinical benefit and risk of the treatment, followed by discussion and agreement between the investigators and the participant. §After 8 cycles of chemotherapy are complete, gemcitabine-based chemotherapy may be continued in combination with durvalumab in the maintenance phase at investigator's discretion (with the exception of paclitaxel).
AoV, ampulla of Vater; BTC, biliary tract cancer; DCR, disease control rate; DoR, duration of response; eCCA, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRAE, possibly related adverse event; PS, performance status; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; QLQ-BILI21, 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Module; QLQ-C30, 30-Item Quality of Life Questionnaire; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; S-1, tegafur / gimeracil / oteracil; WHO, World Health Organization.

Participant demographics and clinical characteristics

At data cut-off (27 March 2024), 62 participants had the opportunity to complete at least two cycles of durvalumab and were included in the early safety data review

	D + G + Oxali	D + G + Cis	D + G + Cis + S-1	D + G + Cis + Pac	D + G + S-1	D + G + Carbo	D + G	Total
	N=21	N=14	N=8	N=6	N=5	N=4	N=4	N=62
Age, median, years (Q1–Q3)	66.0 (58.0–70.0)	67.0 (62.0–75.0)	62.0 (45.5–67.0)	58.5 (44.0–71.0)	72.0 (50.0–72.0)	66.5 (50.0–77.5)	79.0 (77.0–81.0)	66.0 (58.0–73.0)
Geographical location, n (%)								
Japan	0	0	8 (100)	0	5 (100)	0	3 (75.0)	16 (25.8)
Korea	20 (95.2)	12 (85.7)	0	6 (100)	0	3 (75.0)	1 (25.0)	42 (67.7)
United States	1 (4.8)	2 (14.3)	0	0	0	1 (25.0)	0	4 (6.5)
Metastatic / locally advanced disease, n (%)								
Locally advanced	2 (9.5)	1 (7.1)	4 (50.0)	3 (50.0)	1 (20.0)	1 (25.0)	2 (50.0)	14 (22.6)
Metastatic (or both)	19 (90.5)	13 (92.9)	4 (50.0)	3 (50.0)	4 (80.0)	3 (75.0)	2 (50.0)	48 (77.4)
WHO/ECOG PS, n (%)								
0	7 (33.3)	0	6 (75.0)	5 (83.3)	5 (100)	2 (50.0)	1 (25.0)	26 (41.9)
1	14 (66.7)	0	2 (25.0)	1 (16.7)	0	2 (50.0)	2 (50.0)	21 (33.9)
2	0	14 (100)	0	0	0	0	1 (25.0)	15 (24.2)
Primary tumour location, n (%)								
Gallbladder	8 (38.1)	5 (35.7)	3 (37.5)	0	2 (40.0)	1 (25.0)	2 (50.0)	21 (33.9)
Intrahepatic bile duct	11 (52.4)	6 (42.9)	5 (62.5)	4 (66.7)	2 (40.0)	1 (25.0)	1 (25.5)	30 (48.4)
Distal common bile duct	0	2 (14.3)	0	1 (16.7)	0	1 (25.0)	0	4 (6.5)
Perihilar bile duct	1 (4.8)	0	0	1 (16.7)	1 (20.0)	1 (25.0)	1 (25.0)	5 (8.1)
Ampulla of Vater	1 (4.8)	1 (7.1)	0	0	0	0	0	2 (3.2)

Carbo, carboplatin; Cis, cisplatin; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; G, gemcitabine; Oxali, oxaliplatin; Pac, albumin-bound paclitaxel; PS, performance status; Q, quartile; S-1, tegafur / gimeracil / oteracil; WHO, World Health Organization.

Adverse events in the safety analysis set

There were no new safety signals with the addition of durvalumab to various gemcitabine-based chemotherapy regimens

	D + G + Oxali	D + G + Cis	D + G + Cis + S-1	D + G + Cis + Pac	D + G + S-1	D + G + Carbo	D + G	Total
	N=21	N=14	N=8	N=6	N=5	N=4	N=4	N=62
Any AEs, n (%)	21 (100)	14 (100)	7 (87.5)	6 (100)	5 (100)	4 (100)	4 (100)	61 (98.4)
Possibly related to any study treatment*	17 (81.0)	12 (85.7)	7 (87.5)	6 (100)	5 (100)	3 (75.0)	4 (100)	54 (87.1)
CTCAE Grade 3 or 4†	15 (71.4)	8 (57.1)	2 (25.0)	4 (66.7)	5 (100)	4 (100)	4 (100)	42 (67.7)
CTCAE Grade 3 or 4, possibly related to any study treatment*,†	11 (52.4)	7 (50.0)	1 (12.5)	2 (33.3)	5 (100)	3 (75.0)	2 (50.0)	31 (50.0)
Outcome of death	0	0	0	0	0	0	0	0
Leading to discontinuation of any study treatment	1 (4.8)	1 (7.1)	0	1 (16.7)	0	0	0	3 (4.8)
Any SAEs, n (%)	3 (14.3)	4 (28.6)	1 (12.5)	3 (50.0)	1 (20.0)	3 (75.0)	3 (75.0)	18 (29.0)
Possibly related to any study treatment*	1 (4.8)	0	0	0	1 (20.0)	1 (25.0)	1 (25.0)	4 (6.5)
CTCAE Grade 3 or 4†	3 (14.3)	1 (7.1)	1 (12.5)	3 (50.0)	1 (20.0)	3 (75.0)	3 (75.0)	15 (24.2)
CTCAE Grade 3 or 4, possibly related to any study treatment*,†	1 (4.8)	0	0	0	1 (20.0)	1 (25.0)	1 (25.0)	4 (6.5)
Leading to discontinuation of any study treatment	0	1 (7.1)	0	0	0	0	0	1 (1.6)
Any immune-mediated AEs, n (%)‡	8 (38.1)	4 (28.6)	1 (12.5)	2 (33.3)	1 (20.0)	1 (25.0)	1 (25.0)	18 (29.0)

*As assessed by the investigator. Missing responses are counted as related. †Grade 3: severe, Grade 4: life-threatening. ‡Immune-mediated AEs are identified from AEs of special interest and AEs of possible interest and are assessed by the investigator.
AE, adverse event; Carbo, carboplatin; Cis, cisplatin; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab; G, gemcitabine; Oxali, oxaliplatin; Pac, albumin-bound paclitaxel; Q, quartile; S-1, tegafur / gimeracil / oteracil; SAE, serious adverse event.

Most common adverse events of any grade by preferred term (Part 1)

	D + G + Oxali	D + G + Cis	D + G + Cis + S-1	D + G + Cis + Pac	D + G + S-1	D + G + Carbo	D + G	Total
	N=21	N=14	N=8	N=6	N=5	N=4	N=4	N=62
Subjects with any AE, n (%)*	21 (100)	13 (92.9)	7 (87.5)	6 (100)	5 (100)	3 (75.0)	4 (100)	59 (95.2)
Haematologic AEs								
Neutrophil count decreased	9 (42.9)	5 (35.7)	0	3 (50.0)	3 (60.0)	2 (50.0)	0	22 (35.5)
Platelet count decreased	7 (33.3)	4 (28.6)	1 (12.5)	2 (33.3)	1 (20.0)	3 (75.0)	0	18 (29.0)
Anaemia	2 (9.5)	4 (28.6)	2 (25.0)	0	2 (40.0)	2 (50.0)	3 (75.0)	15 (24.2)
White blood cell count decreased	0	2 (14.3)	1 (12.5)	0	1 (20.0)	1 (25.0)	0	5 (8.1)
Non-haematologic AEs								
Nausea	9 (42.9)	4 (28.6)	4 (50.0)	3 (50.0)	0	2 (50.0)	0	22 (35.5)
Fatigue	9 (42.9)	2 (14.3)	1 (12.5)	5 (83.3)	0	0	0	17 (27.4)
Constipation	2 (9.5)	5 (35.7)	4 (50.0)	0	1 (20.0)	2 (50.0)	2 (50.0)	16 (25.8)
Rash	4 (19.0)	6 (42.9)	0	2 (33.3)	1 (20.0)	2 (50.0)	1 (25.0)	16 (25.8)
Pyrexia	4 (19.0)	4 (28.6)	3 (37.5)	0	0	1 (25.0)	1 (25.0)	13 (21.0)
Dyspepsia	6 (28.6)	2 (14.3)	0	1 (16.7)	0	0	0	9 (14.5)
Insomnia	3 (14.3)	3 (21.4)	0	1 (16.7)	1 (20.0)	1 (25.0)	0	9 (14.5)

*Only AEs with a frequency of ≥5% are reported, if a subject experienced more than one AE, the subject will be counted once for each preferred term.
AE, adverse event; Carbo, carboplatin; Cis, cisplatin; D, durvalumab; G, gemcitabine; Oxali, oxaliplatin; Pac, albumin-bound paclitaxel; S-1, tegafur / gimeracil / oteracil.

Conclusions

- The ongoing Phase 3b TOURMALINE study is assessing the safety and efficacy of durvalumab in combination with gemcitabine-based chemotherapy as a first-line treatment for participants with advanced BTC
- In this early safety review of 62 participants who had the opportunity to complete at least two cycles of durvalumab, out of approximately 140 participants enrolled in the TOURMALINE study, the population included participants who would have been excluded from the TOPAZ-1 study such as those with WHO / ECOG PS of 2 and those with ampulla of Vater cancer. Key findings included:

Safety was manageable with no new safety signals observed with the addition of durvalumab to various gemcitabine-based chemotherapy regimens

Reducing the infusion duration of durvalumab from 60 minutes to 30 minutes did not increase the number of infusion-related reactions in this safety analysis

BTC, biliary tract cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; WHO, World Health Organization.

Case Vignette

40 year old female with history of metastatic intrahepatic cholangiocarcinoma

- ECOG PS = 1
- Lesions in liver, lungs and bones
- TMB = 2 mutations/Megabase, PD-L1 < 1%
- SMAD4 mutation, TP53 mutation (tissue)
- Received gemcitabine/cisplatin/durvalumab
- Now progressing by imaging
- Serum creatinine = 1.0 mg/dl, AST/ALT < 3 x ULN, bilirubin WNL
- No ongoing myelosuppression

Case Vignette

- *What regimen would you consider for systemic therapy ?*
  1. *FOLFOX*
  2. *5-FU/nanoliposomal irinotecan*
  3. *Tremelimumab*
  4. *Either 1 or 2*

Phase 3 ABC-06 Trial: mFOLFOX vs Active Symptom Control in Advanced Biliary Cancers[1]

Key Inclusion Criteria

- Histo/cytologically verified advanced biliary cancer
- ECOG PS 0-1
- Progression after first-line cisplatin/gemcitabine
- ≤6 wk progression to randomization
- Adequate hematologic, renal, and hepatic function

R

1:1

Active Symptom Control (ASC)

- May include: biliary drainage, antibiotics, analgesia, steroids, anti-emetics, etc.
- 4-weekly clinical review

ASC + mFOLFOX

- Chemotherapy every 14 days for up to 12 cycles
- Day 1: Oxaliplatin 85 mg/m^2, L-folinic acid 175 mg (or folinic acid 350 mg), 5-FU 400 mg/m^2 (bolus), 5-FU 2,400 mg/m^2 46 hours continuous infusion
- 4-weekly clinical review after chemotherapy
- 3-monthly radiological assessment

Follow-up until death or completion of 12 mo after enrollment of the final patient (whichever happened first)

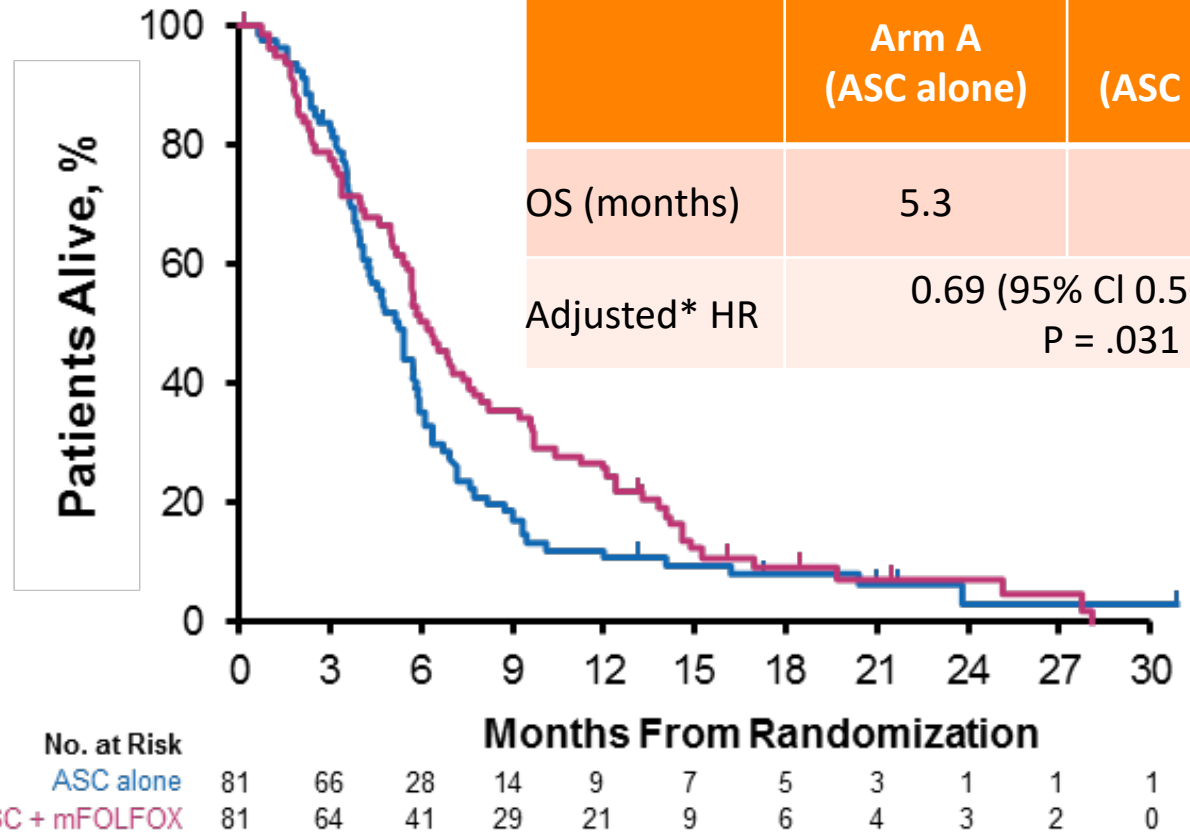
- Stratification: platinum sensitivity, serum albumin, stage
- **Primary endpoint**: OS

1. Lamarca A et al. ASCO 2019. Abstract 4003

ABC-06: Overall Survival (ITT)[1]

- The primary endpoint was met: adjusted[a] HR was 0.69 (95% CI: 0.50-0.97; *P* = .031) for OS in favor of ASC + mFOLFOX arm (6.2 months) vs ASC alone (5.3 months)
- No marked evidence was identified against the key proportional hazards assumption[b]; confirming the validity of using the Cox Regression analysis

Overall Survival by Trial Arm



	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
OS (months)	5.3	6.2
Adjusted* HR	0.69 (95% CI 0.50-0.97) P = .031	

[a] Adjusted for platinum sensitivity, albumin, and stage. [b] Proportional hazards assumption test *P* = .6521.

1. Lamarca A et al. ASCO 2019. Abstract 4003.

NIFTY: Multicenter, Open-label, Randomized Phase 2B Study

Patients with metastatic BTC
- Histologically or cytologically confirmed BTC
- At least one measurable lesion per RECIST v1.1
- Radiological progression on prior 1st-line GemCis
- No prior 2nd-line chemotherapy
- ECOG PS 0-1
- Adequate organ function

Stratification
- Tumor site (intrahepatic vs extrahepatic/ gallbladder)
- Prior curative-intent surgery
- Participating center

N=174

R (1:1)

Nal-IRI plus 5-FU/LV
Nal-IRI 70 mg/m^2 (D1), 5-FU 2400 mg/m^2 (D1-2), LV 400 mg/m^2 (D1)

5-FU/LV
5-FU 2400 mg/m^2 (D1-2), LV 400 mg/m^2 (D1)

Until progression or intolerable toxicity

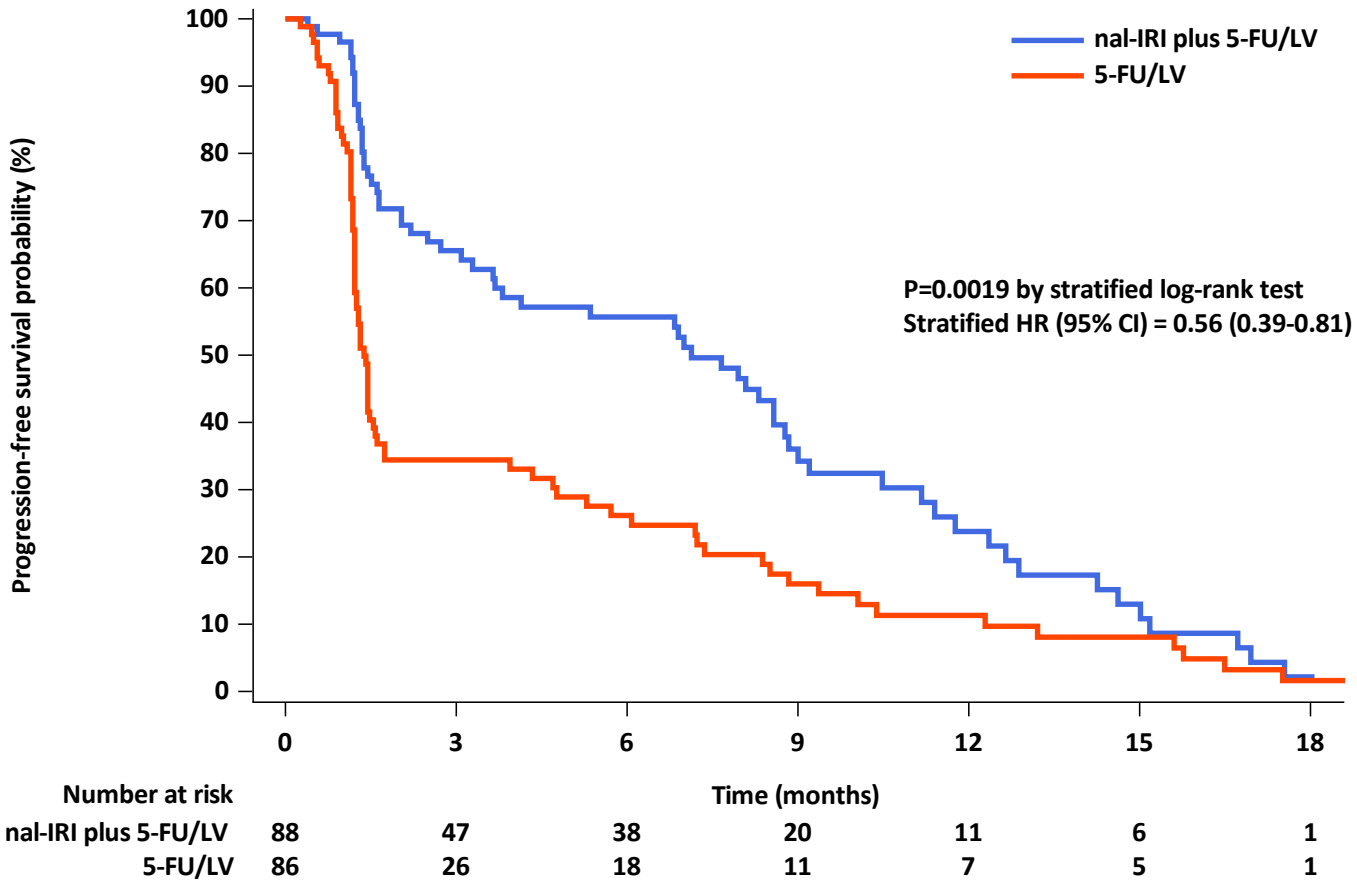
Primary endpoint
- BICR*-assessed PFS (RECIST v1.1)

Secondary endpoints
- Investigator-assessed PFS
- OS
- ORR (RECIST v1.1)
- Safety profile (CTCAE v4.03)
- QoL (EORTC-QLQ-C30)

*BICR=blinded independent central review

ClinicalTrials.gov identifier: NCT03524508

Primary Endpoint: BICR-Assessed PFS

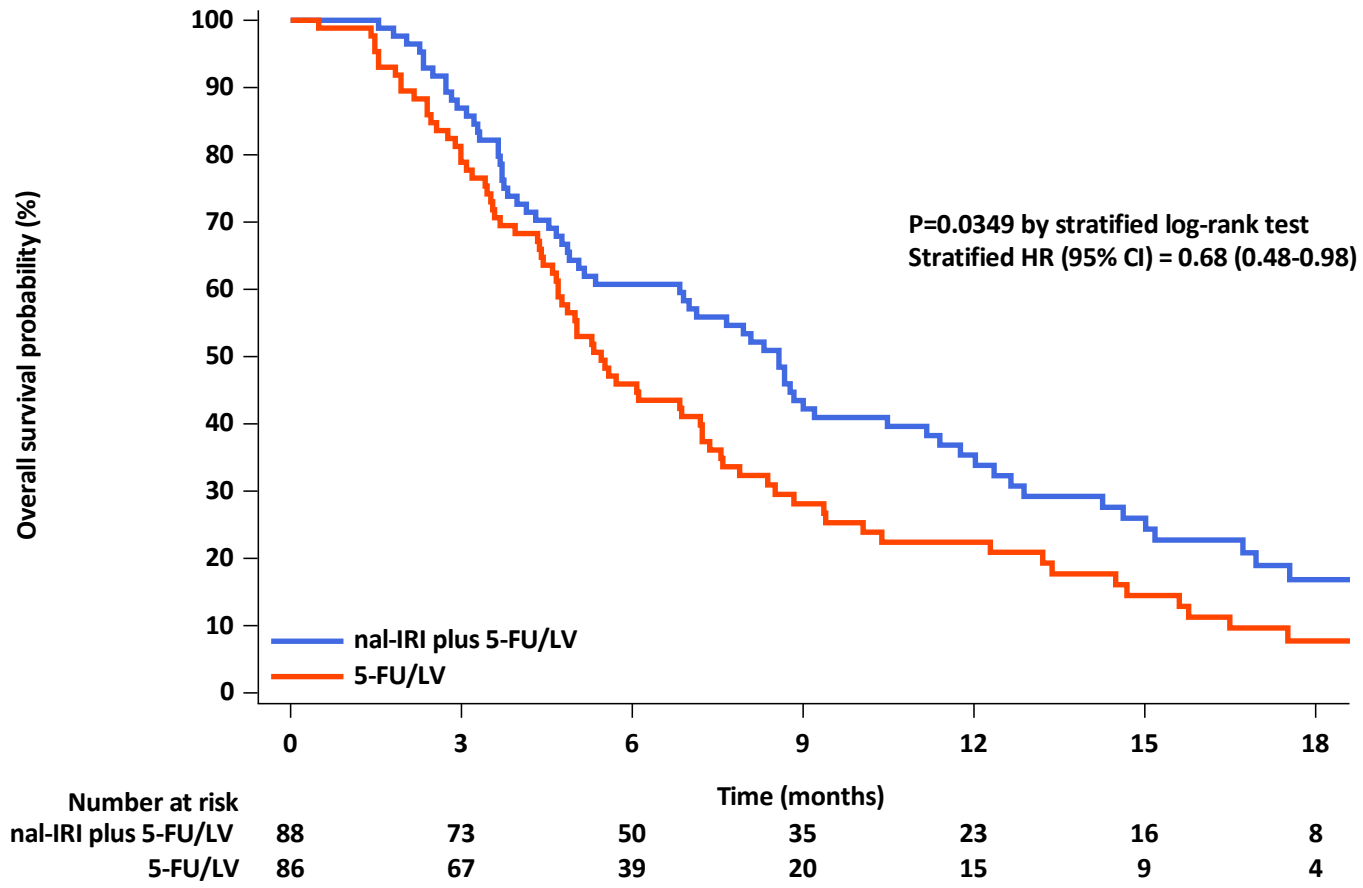


Median follow-up period: 11.8 months (IQR 7.7-18.7)

	Nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	64 (72.7%)	79 (91.9%)
mPFS, months (95% CI)	7.1 (3.6-8.8)	1.4 (1.2-1.5)
	HR, 0.56 95% CI, 0.39-0.81 *P*=0.0019	
6-month PFS rate, % (95% CI)	55.7% (44.7-66.6)	26.2% (16.6-35.8)

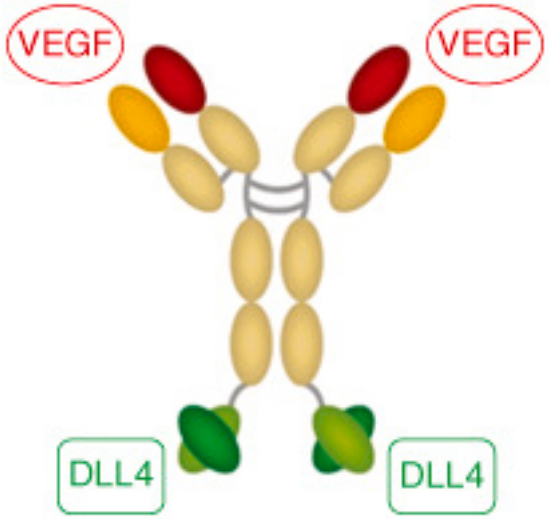
RESPONSE RATE: 14.8% vs 5.8%, p = 0.0684

Secondary Endpoint: Overall Survival

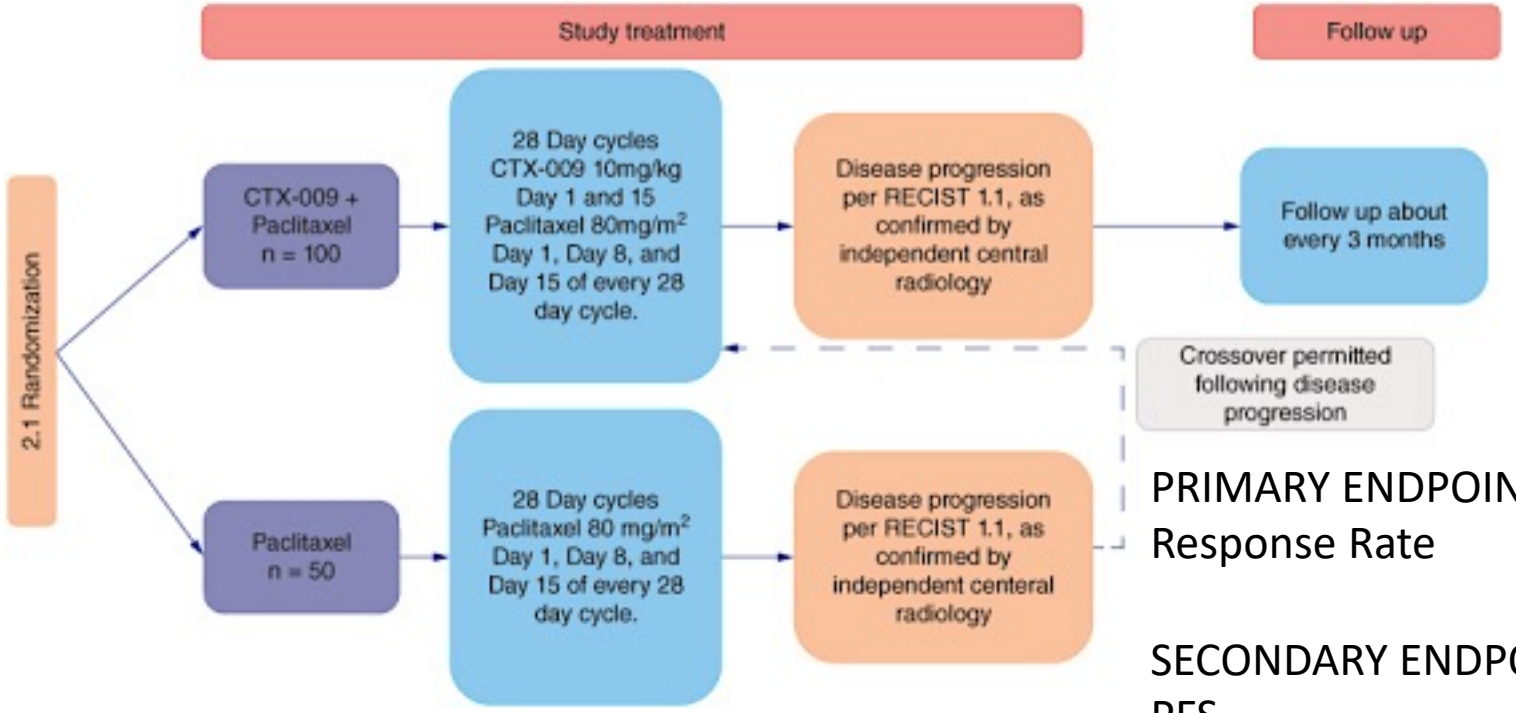


	Nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	64 (72.7%)	74 (86.0%)
mOS, months (95% CI)	8.6 (5.4-10.5)	5.5 (4.7-7.2)
	HR, 0.68 95% CI, 0.48-0.98 *P*=0.0349	
6-month OS rate, % (95% CI)	60.7% (50.3-71.2)	45.9% (35.3-56.5)
1-year OS rate, % (95% CI)	35.4% (24.9-45.9)	22.4% (13.1-31.7)

COMPANION-002 : Paclitaxel +/- CTX-009 in 2nd Line BTC



CTX-009



PRIMARY ENDPOINT
Response Rate

SECONDARY ENDPOINTS
PFS
DOR
DCR
QoL

PRELIMINARY DATA FROM SINGLE ARM PHASE IB/II STUDY (OH ET AL, ASCO 2023)

PACLITAXEL + CTX-009 RESPONSE RATE 37.5% (9 OF 24)

DURATION OF RESPONSE = 6.9 MTH, PFS = 9.4 MTH

AZAD ET AL, FUTURE ONC 2024

Discussion Question

- What do you usually recommend as second-line therapy for a patient with intrahepatic cholangiocarcinoma who has experienced disease progression on gemcitabine/cisplatin/durvalumab and has no targetable mutations?

Module 9: Non-Hodgkin Lymphoma

Role of Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies for Non-Hodgkin Lymphoma (NHL)
— Dr Patel

Other Available and Emerging Novel Therapies for NHL
— Dr Flowers

Module 9: Non-Hodgkin Lymphoma

Role of Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies for Non-Hodgkin Lymphoma (NHL)
— Dr Patel

Other Available and Emerging Novel Therapies for NHL
— Dr Flowers

CAR T Cells and Bispecific Antibodies in NHL

Krish Patel, MD

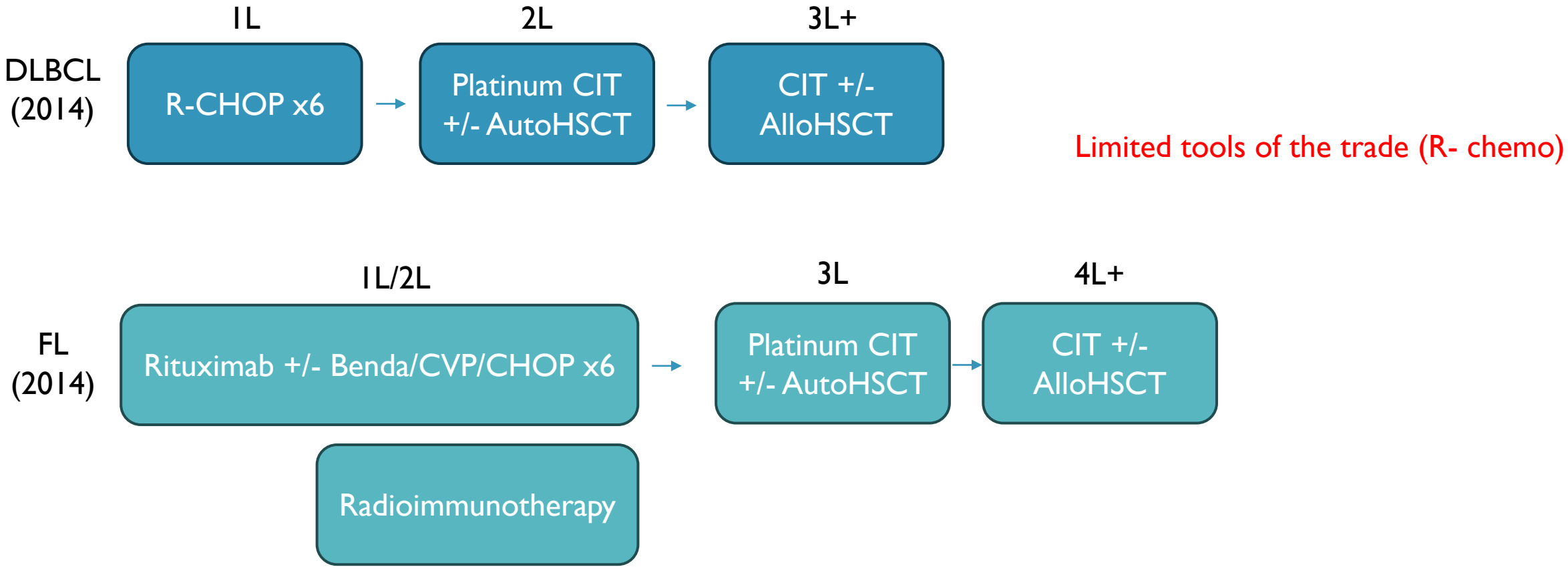
Director of Lymphoma Research

SCRI Sarah Cannon Research Institute

Disclosures

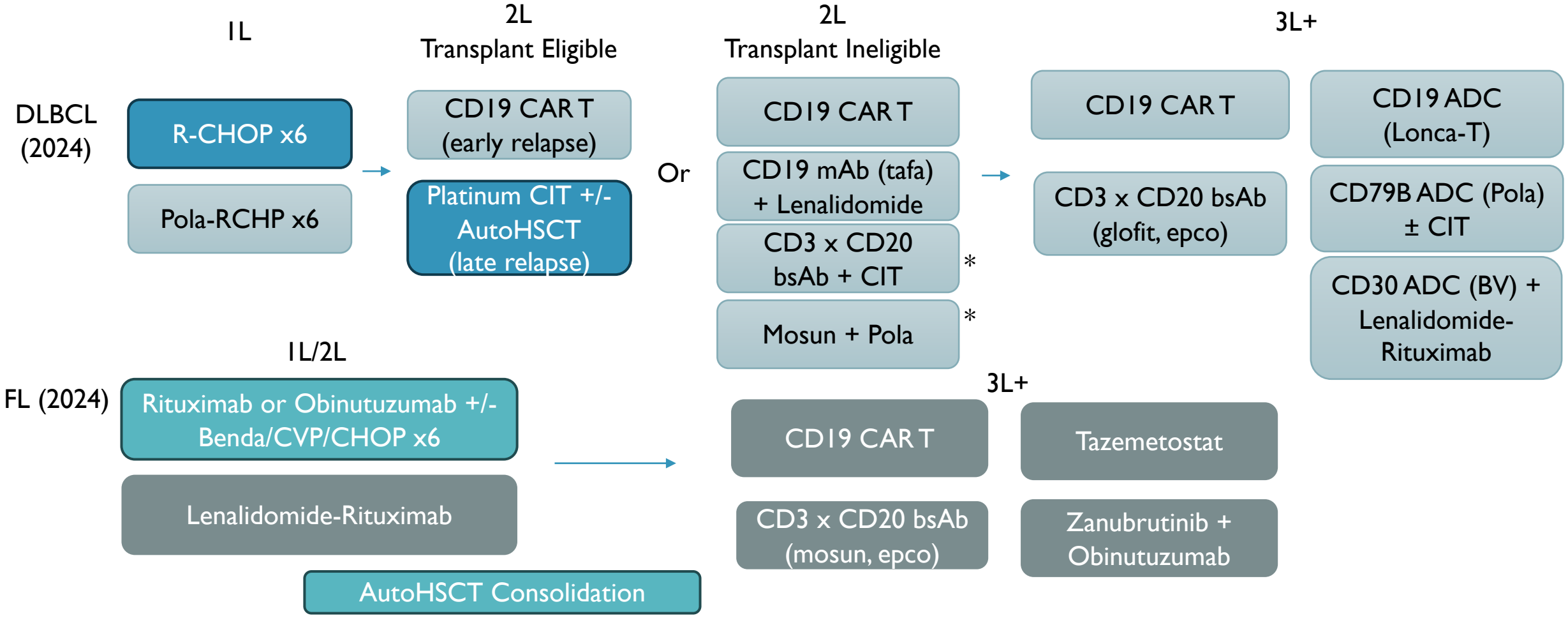
Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Caribou Biosciences Inc, Fate Therapeutics, Genentech, a member of the Roche Group, Johnson & Johnson Pharmaceuticals, Kite, A Gilead Company, Lilly, Merck, Nurix Therapeutics Inc, Pfizer Inc
Contracted Research (Funding to Institution)	AbbVie Inc, Adaptive Biotechnologies Corporation, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Caribou Biosciences Inc, Century Therapeutics, CRISPR Therapeutics, Fate Therapeutics, Genentech, a member of the Roche Group, Johnson & Johnson Pharmaceuticals, Kite, A Gilead Company, Lilly, Merck, Nurix Therapeutics Inc, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Sana, Xencor

A decade of change: Lymphoma circa 2014



Adapted from NCCN Guidelines V3.2014

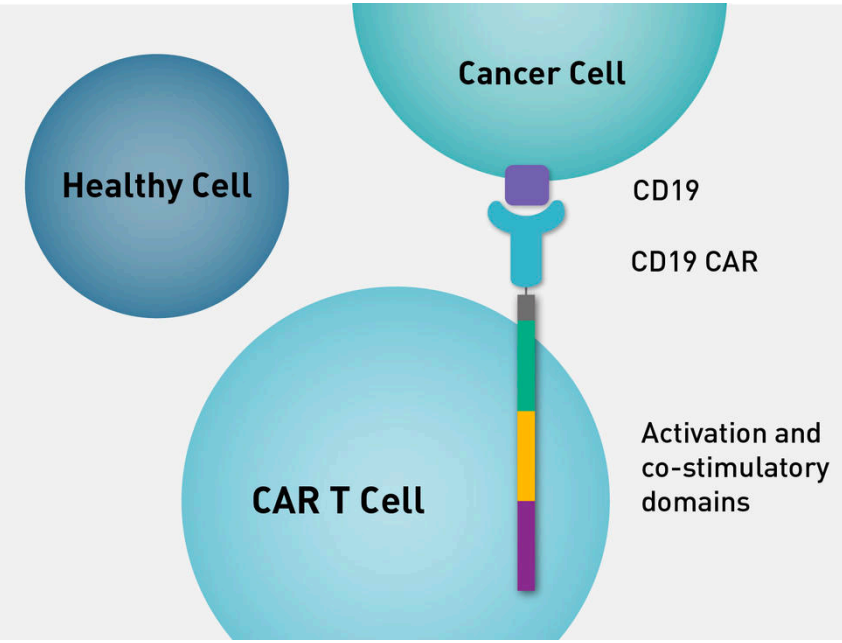
Lymphoma Circa 2025



Adapted from NCCN Guidelines v 2.2025. *Not FDA approved

Immunotherapy in Lymphoma

CAR T



Deep & potentially durable responses

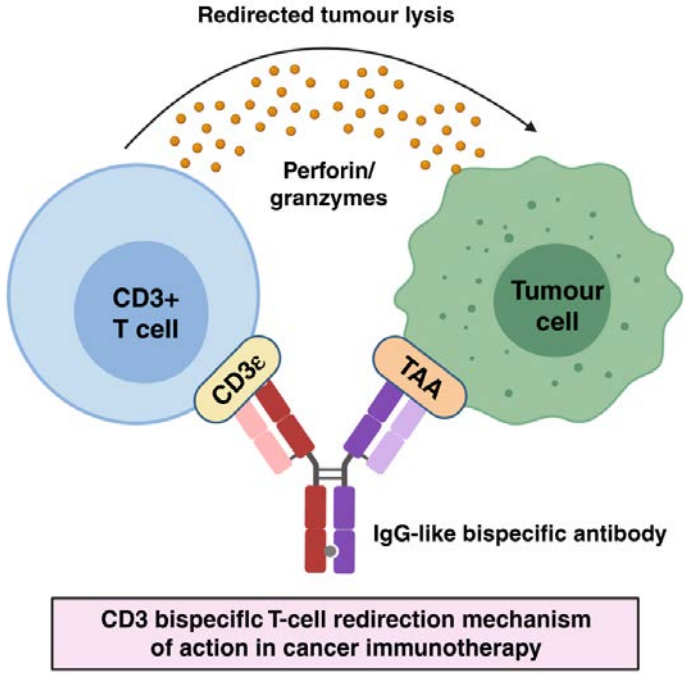
Risk of CRS, neurotoxicity, immune suppression

Targets

Approved: CD19 (2L+)

Investigational: CD20, CD22, CD30, CD79b, ROR1

Bispecific Antibodies

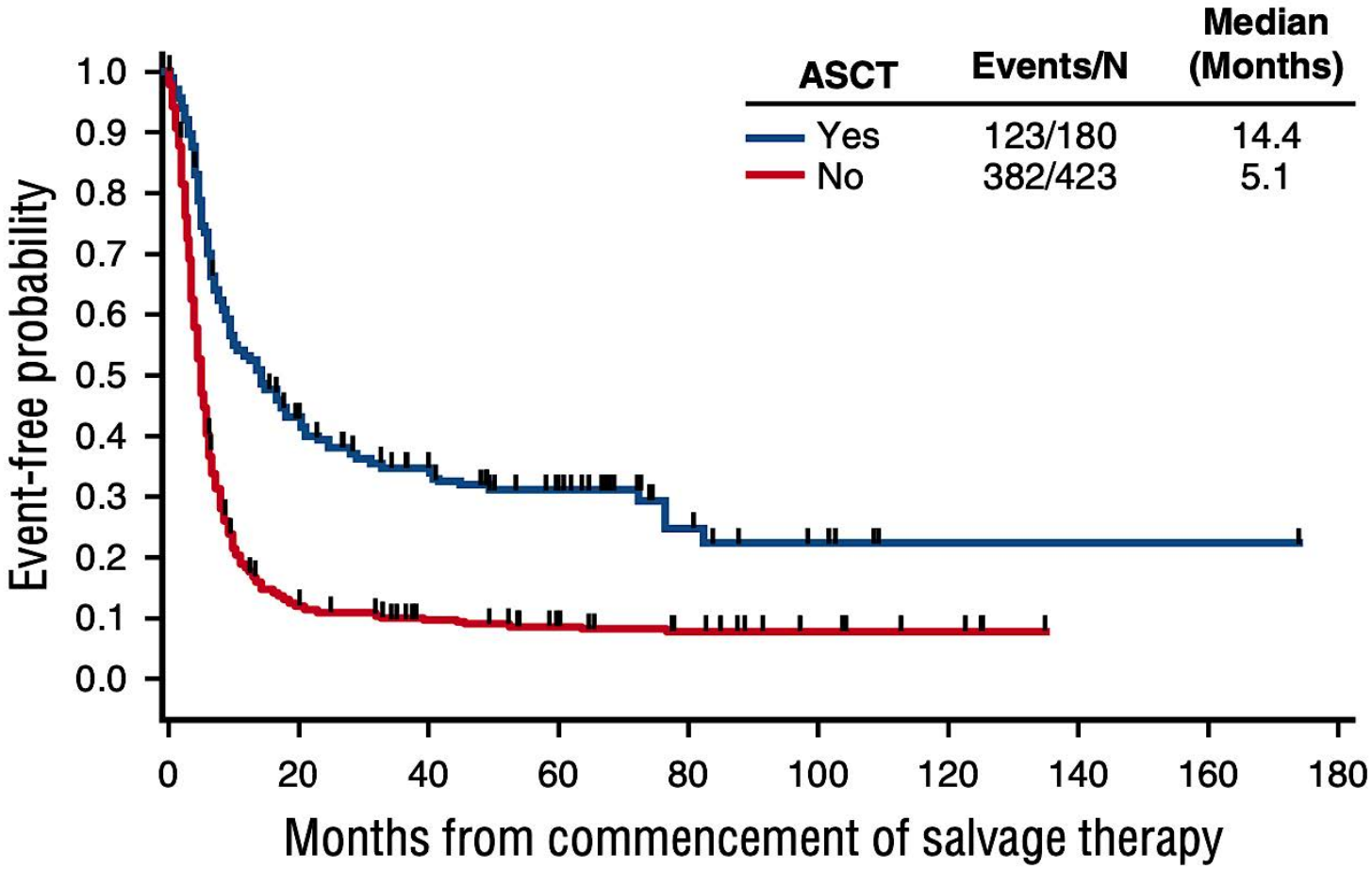


Targets

Approved: CD20 (3L)+

Investigational: CD19, CD22, CD30, CD79b, ROR1

R/R DLBCL: Outcomes in 2L+ historically poor

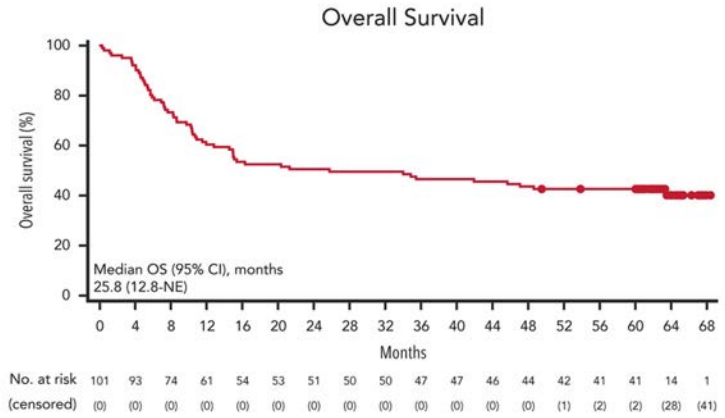


Long term outcomes are poor in patients w/ R/R DLBCL

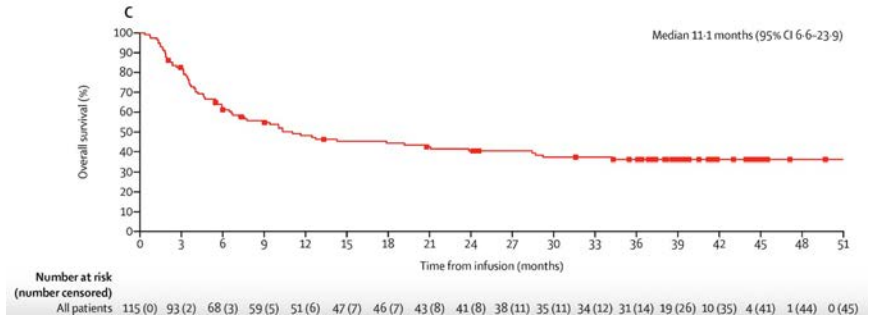
Worse in those who were not historically transplant candidates

Crump M et al Blood 2017

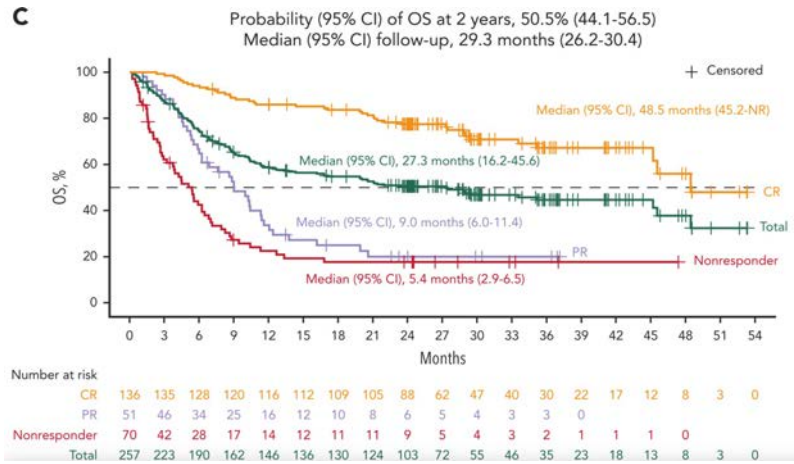
3L DLBCL: CAR T-Cell Outcomes



ZUMA1 (axi-cel)
5 yr OS 42.6%



JULIET (tis-cel)
3 yr OS 36%

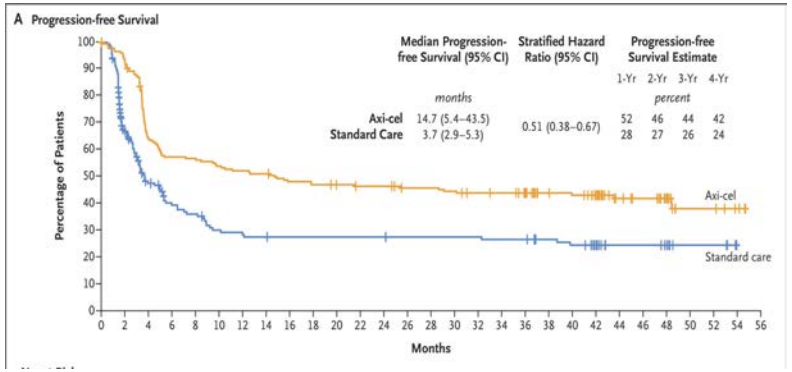


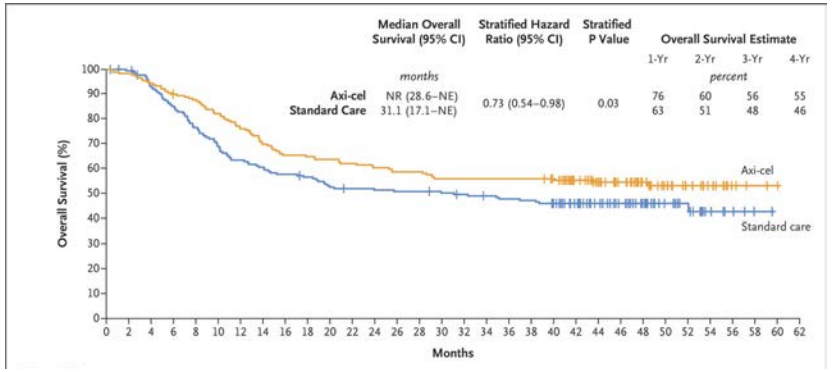
TRANSCEND 001 (liso-cel)
2 yr OS 50.5%

Patients achieving CR can achieve curative outcome

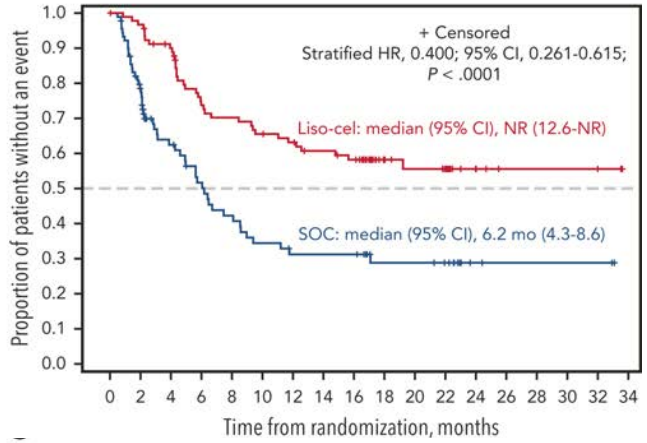
Neelapu S et al Blood 2023. Schuster S et al Lancet Onc 2021, Abramson J et al. Blood 2024.

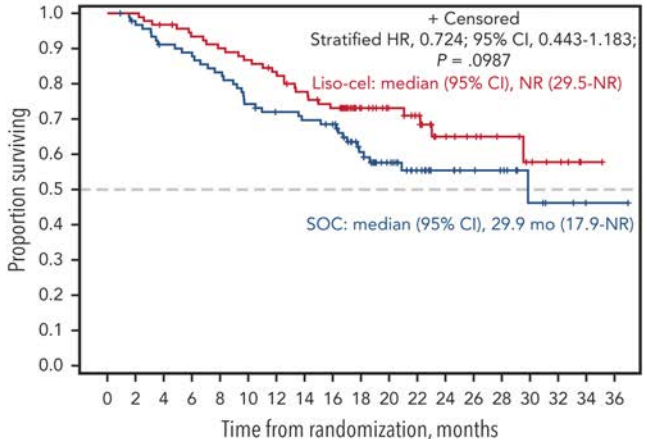
2L DLBCL: CAR T cell for all?



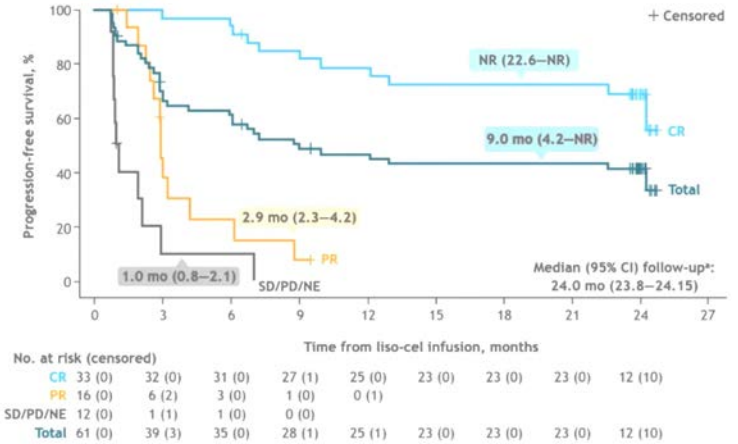


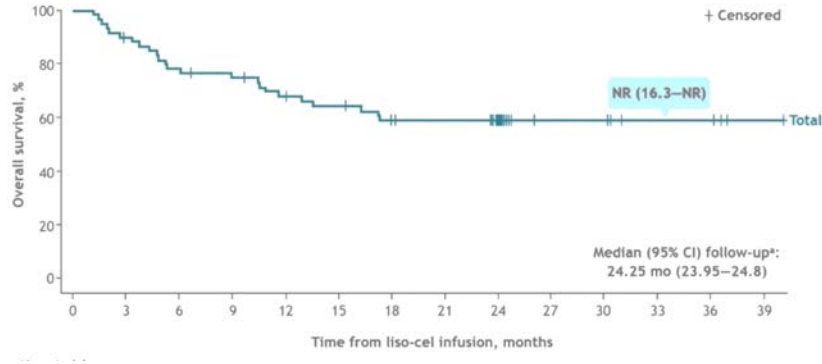
ZUMA-7
(2L Early Relapse; Axi-cel vs SOC)
CR 65% vs 32%
4yr PFS 42% vs 24%
4y OS 55% vs 46%





TRANSFORM
(2L Early Relapse; Liso-cel vs SOC)
CR 74% vs 43%
18 month PFS 58% vs 29%
18 month OS 73% vs 61%





PILOT
(2L transplant ineligible, Liso-cel)
CR 54%
18 month PFS 43%
18 month OS 59%

Westin J et al NEJM 2023; Abramson J et al Blood 2023; Sehgal A et al ASH 2023

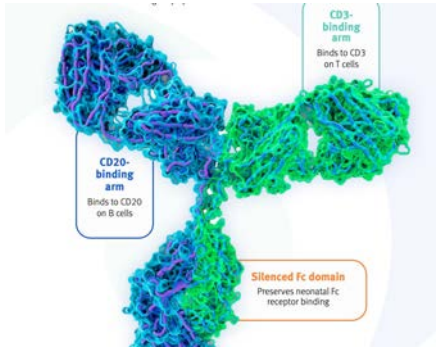
CD19 CAR T Toxicity in 2L Trials

	ZUMA-7 (Axi-cel)	TRANSFORM (Liso-cel)
All Grade CRS	92%	48%
Grade 3/4 CRS	6%	1%
All Grade Neurotoxicity	60%	11%
Grade 3/4 Neurotoxicity	20%	4%
Hypogammaglobulinemia	11%	11%
Grade 3/4 Infections	16.5%	15%
Grade 3/4 Thrombocytopenia	15%	50%

Westin J et al NEJM 2023; Abramson J et al Blood 2023

Epcoritamab & Glofitamab in 3L+ R/R LBCL

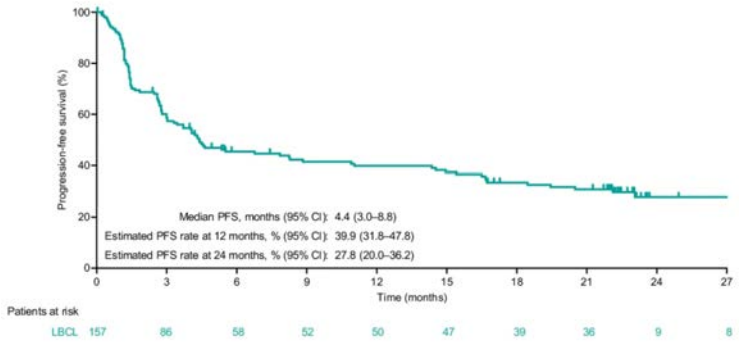
Epcoritamab



C1D1, D8 0.16mg/0.8mg SC step up
C1D15 to C3 48mg weekly SC
C4-9 48mg SC q2w
C10+ 48mg SC q4w

ORR 63%, CR 40%

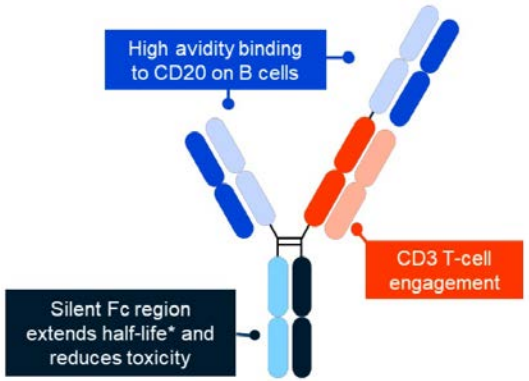
PFS



Median PFS 4.4 mths
6 month PFS 44% (95% CI, 36 to 52)

Landmark PFS (C3 CR)
36 mth 52% PFS

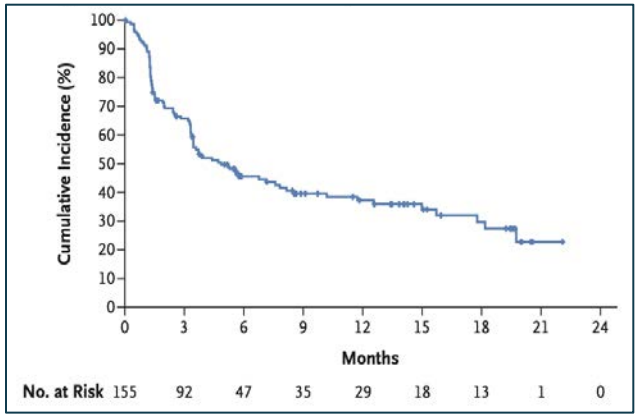
Glofitamab



C1D1 Obinutuzumab
C1D8, D15 2.5mg/10mg IV Step up
C2-12 30mg IV once every 21 days

ORR 62%, CR 40%

PFS



Median PFS 4.9 mths
12 month PFS 37% (95% CI, 28 to 46)

Landmark PFS (C3 CR)
36 mth 52% PFS

Karimi Y et al ASCO 2024; Thieblemont C et al JCO 2022; Dickinson M et al NEJM 2022; Hutchings M et al ASH 2023

Epcoritamab & Glofitamab in 3L+ R/R LBCL

EPCORE NHL-1 LBCL

Demographics	LBCL, N=157
Median age (range), y	64 (20–83)
≥75 y, n (%)	29 (18)
ECOG PS, n (%)	
0	74 (47)
1	78 (50)
2	5 (3)
Disease Type, n (%)	**LBCL, N=157**
DLBCL[a]	139 (89)
De novo	97/139 (70)
Transformed	40/139 (29)
DLBCL with DH/TH rearrangements by central FISH[b]	12/88 (14)
HGBCL	9 (6)
PMBCL	4 (3)
FL G3B	5 (3)
Prior Treatments	**LBCL, N=157**
Median time from initial diagnosis to first dose, y	1.6
Median time from end of last therapy to first dose, mo	2.4
Median prior lines of therapy (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (71)
Primary refractory[c] disease, n (%)	96 (61)
Refractory[c] to last systemic therapy, n (%)	130 (83)
Refractory[c] to ≥2 consecutive lines of therapy, n (%)	119 (76)
Prior ASCT, n (%)	31 (20)
Prior CAR T therapy, n (%)	61 (39)
Refractory[c] to CAR T therapy	46/61 (75)

NP30179 LBCL

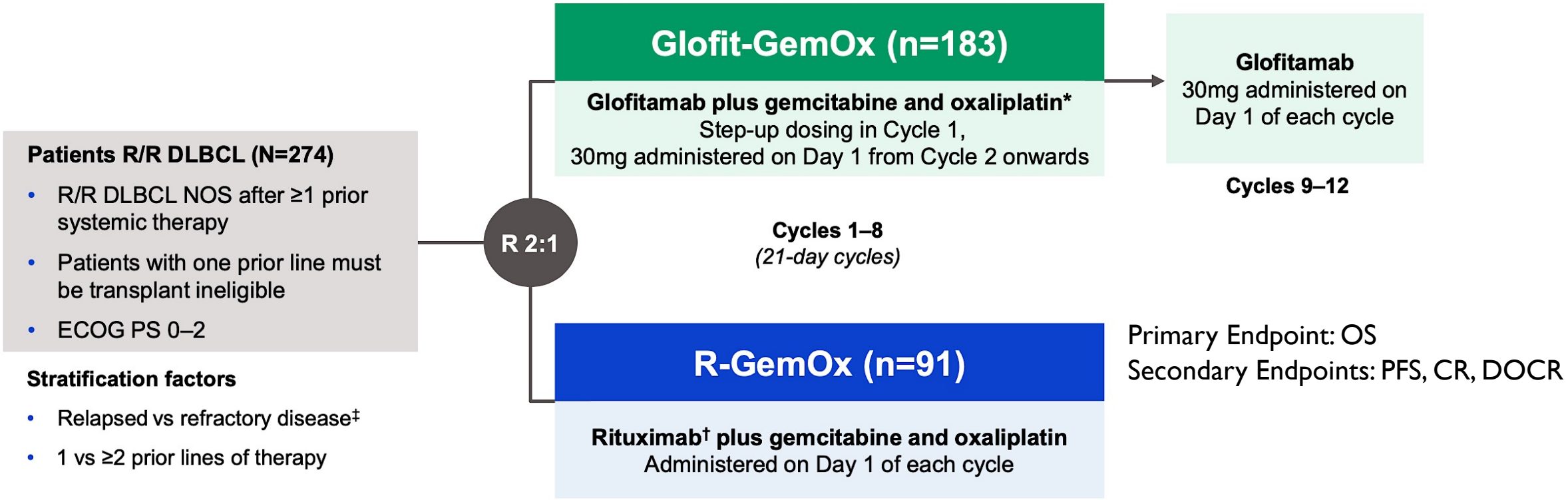
n (%)*		N=154†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I	10 (6.5)
	II	25 (16.2)
	III	31 (20.1)
	IV	85 (55.2)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	18 (11.7)

n (%)*	N=154
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior anti-CD20 Ab	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR-T	46 (29.9)
Refractory to any prior anti-CD20	128 (83.1)

Majority (60-70%) of patients receiving 4L Bsab
~1/3 prior CAR T-cell therapy
CR rate comparable in post CAR T (~35-40%)

Thieblemont C et al JCO 2022, Hutchings M et al ASH 2023

STARGLO: Transplant ineligible R/R DLBCL



Abramson J et al. EHA 2024

STARGLO: Baseline Characteristics

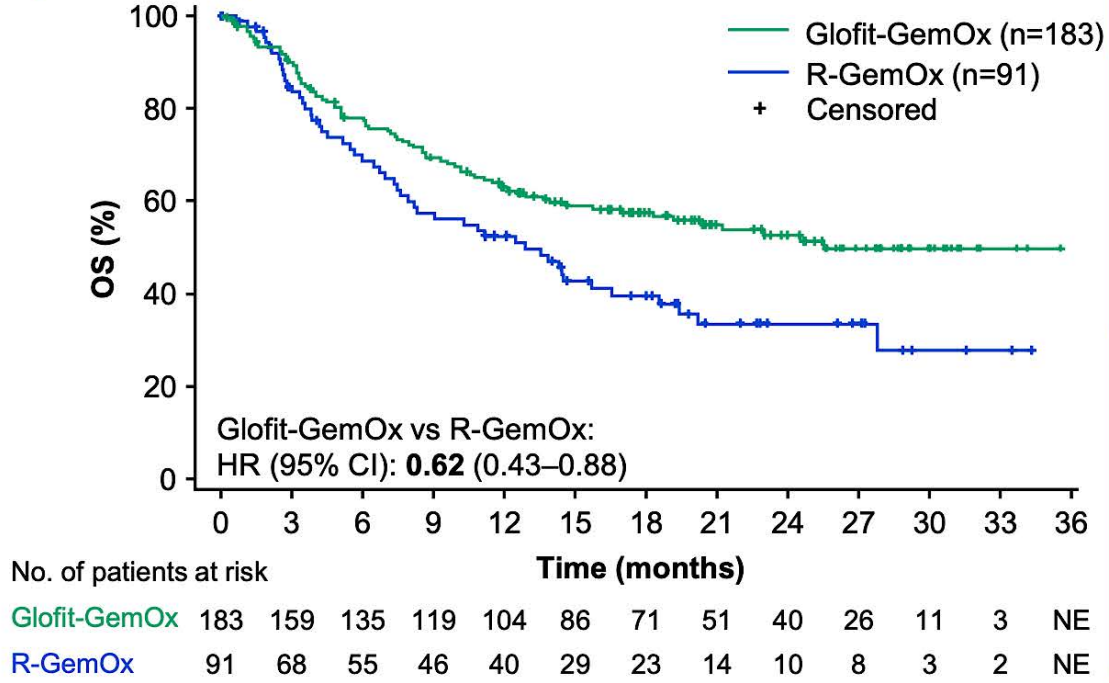
n (%), unless otherwise stated		R-GemOx (n=91)	Glofit-GemOx (n=183)
Age, years	Median (range) ≥65 years	68.0 (20–84) 56 (61.5)	68.0 (22–88) 116 (63.4)
Sex	Male	53 (58.2)	105 (57.4)
Race	Asian Black or African American White Unknown	51 (56.0) 1 (1.1) 33 (36.3) 6 (6.6)	86 (47.0) 2 (1.1) 82 (44.8) 13 (7.1)
ECOG PS	0 1 2	44 (50.0) 36 (40.9) 8 (9.1)	72 (40.0) 89 (49.4) 19 (10.6)
Ann Arbor stage	I–II III–IV	20 (22.0) 70 (76.9)	60 (32.8) 123 (67.2)
Number of prior lines of therapy	1	57 (62.6)	115 (62.8)
	≥2	34 (37.4)	68 (37.2)
Primary refractory	Yes	47 (51.6)	106 (57.9)
R/R to last prior therapy	Relapsed / refractory	37 (40.7) / 54 (59.3)	71 (38.8) / 112 (61.2)
Bulky disease (≥10cm)	Present	14 (15.4)	23 (12.6)
Cell of origin at initial diagnosis	GCB Non-GCB (including ABC) Unknown	29 (31.9) 50 (54.9) 12 (13.2)	60 (32.8) 103 (56.3) 20 (10.9)
Prior CAR T-cell therapy	Received	8 (8.8)	13 (7.1)

ABC, activated B-cell-like; CAR, chimeric antigen receptor; GCB, germinal center B-cell-like.

Abramson J et al. EHA 2024

STARGLO: Overall Survival

Updated analysis

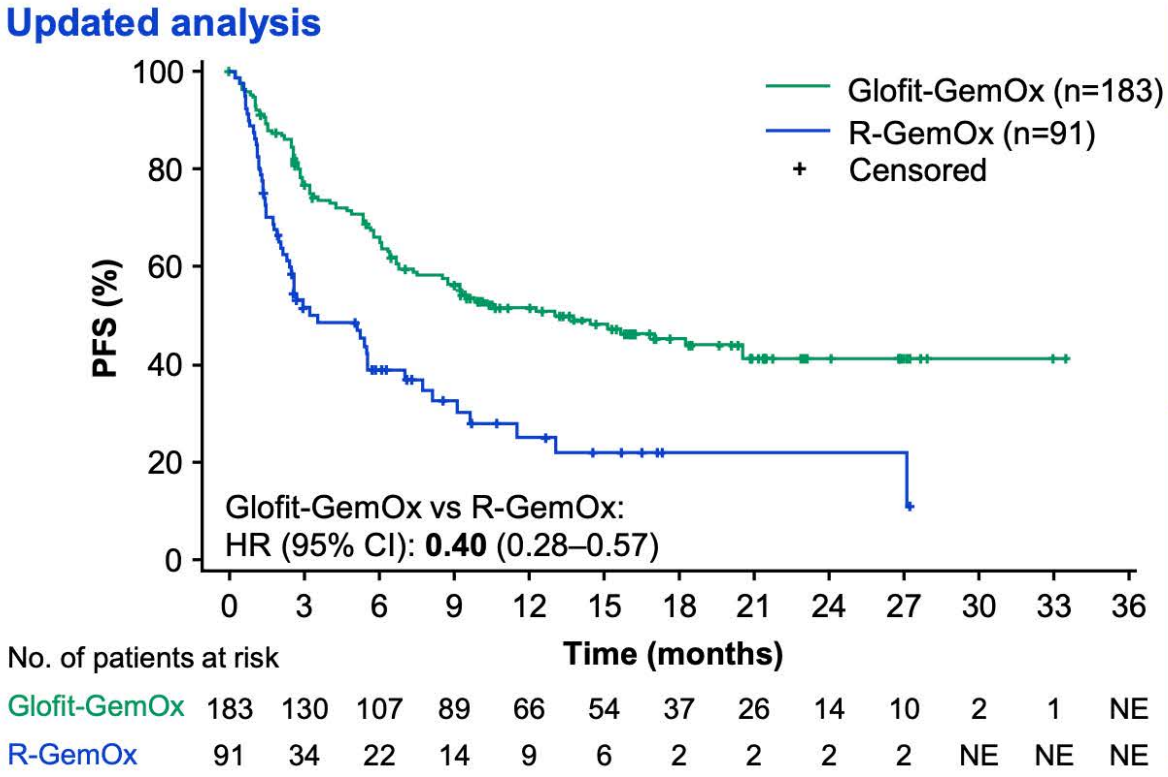


	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)
HR (95% CI)	**0.62** (0.43–0.88)	
p-value*	0.006	
24-month OS (95% CI)	33.5% (22.2–44.9)	52.8% (44.8–60.7)

Median OS 25.5 mths Glofit-GemOx vs 12.9 mths R-GemOX
2 yr OS 53% vs 34%

Abramson J et al. EHA 2024

STARGLO: PFS



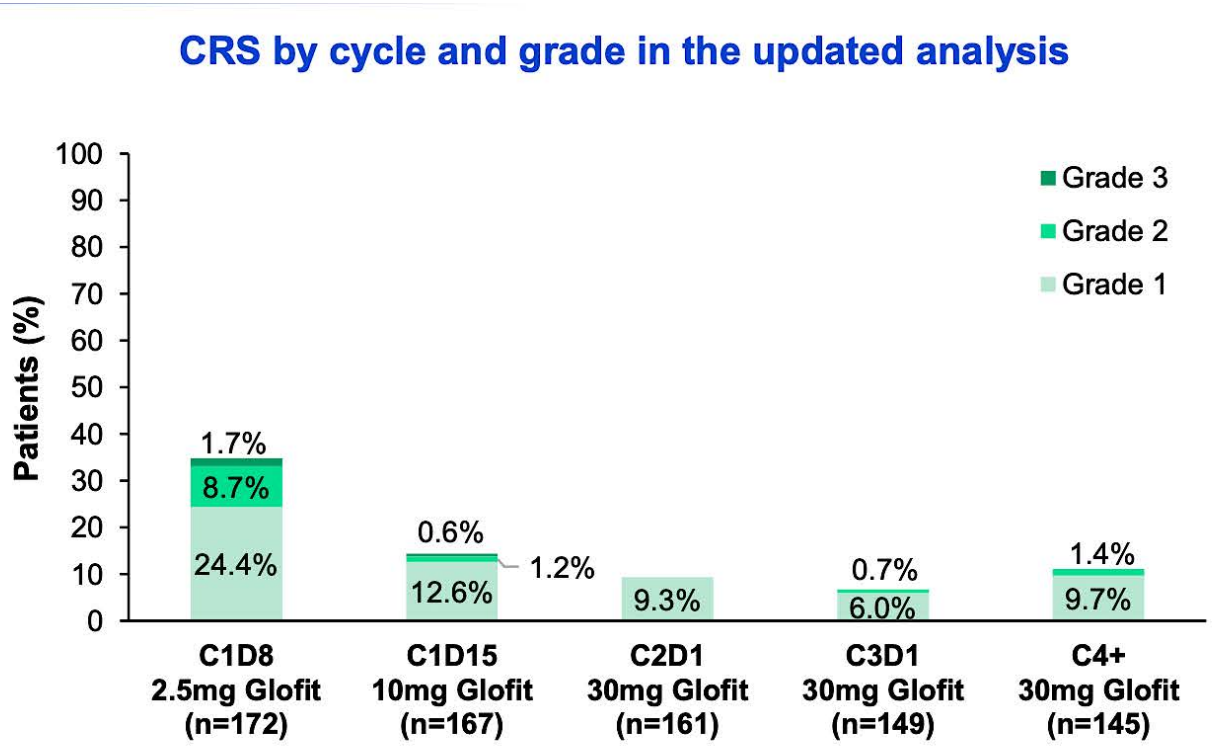
	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 9.6 months)		
PFS, median (95% CI); months	3.3 (2.5–5.6)	12.1 (6.8–18.3)
HR (95% CI)	**0.37** (0.25–0.55)	
p-value*	<0.000001	
Updated analysis (median follow-up: 16.1 months)		
PFS, median (95% CI); months	3.6 (2.5–7.1)	13.8 (8.7–20.5)
HR (95% CI)	**0.40** (0.28–0.57)	
p-value*	<0.000001*	
12-month PFS (95% CI)	25.2% (13.6–36.9)	51.7% (44.0–59.4)

Median PFS 13.8 mths Glofit-GemOx vs 3.6 mths R-GemOX
12 mth PFS 52% vs 25%
CR 58.5% vs 25.3%

Abramson J et al. EHA 2024

STARGLO: CRS

n (%) of patients with ≥1 CRS AE*	Glofit-GemOx (Glofit exposed) n=172
Any grade†	76 (44.2)
Grade 1	54 (31.4)
Grade 2	18 (10.5)
Grade 3	4 (2.3)‡
Median time to CRS onset, hours (range)	
2.5mg glofitamab (C1D8)	13.5 (4.4–134.9)
10mg glofitamab (C1D15)	32.4 (7.4–564.3)
Median CRS duration, hours (range)	
2.5mg glofitamab (C1D8)	22.7 (0.0–168.0)
10mg glofitamab (C1D15)	24.0 (0.0–248.5)
Tocilizumab for CRS management, n / n (%)	28 / 76 (36.8)
Corticosteroids for CRS management, n / n (%)	39 / 76 (51.3)



Abramson J et al. EHA 2024

MCL: outcomes post cBTKi are poor

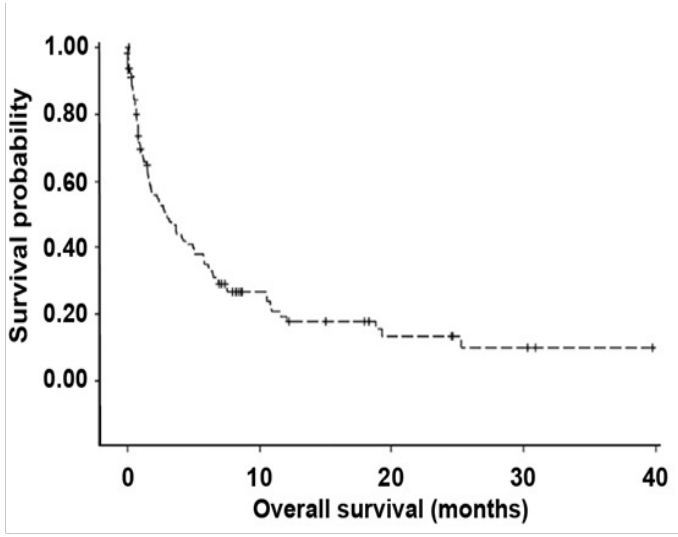


Fig 1

Analysis of n = 114 global patients
Median OS = 2.9 months

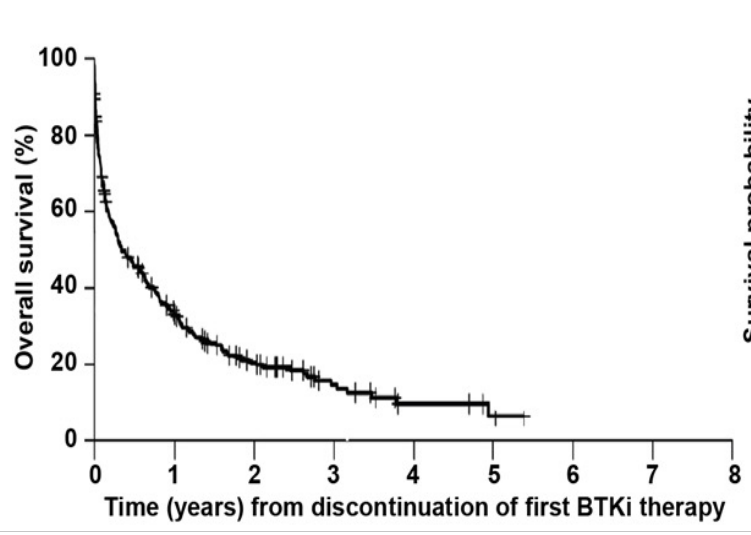


Fig 2

Analysis of n = 238 European patients
Median OS = 4 months

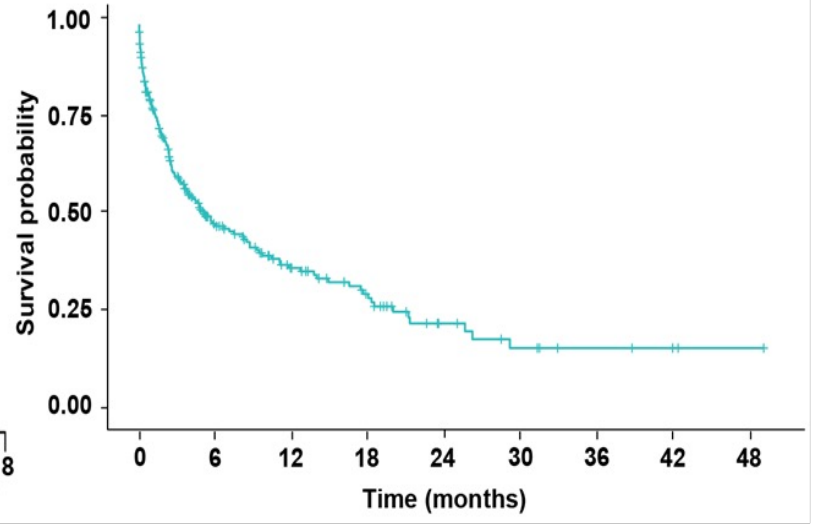


Fig 3

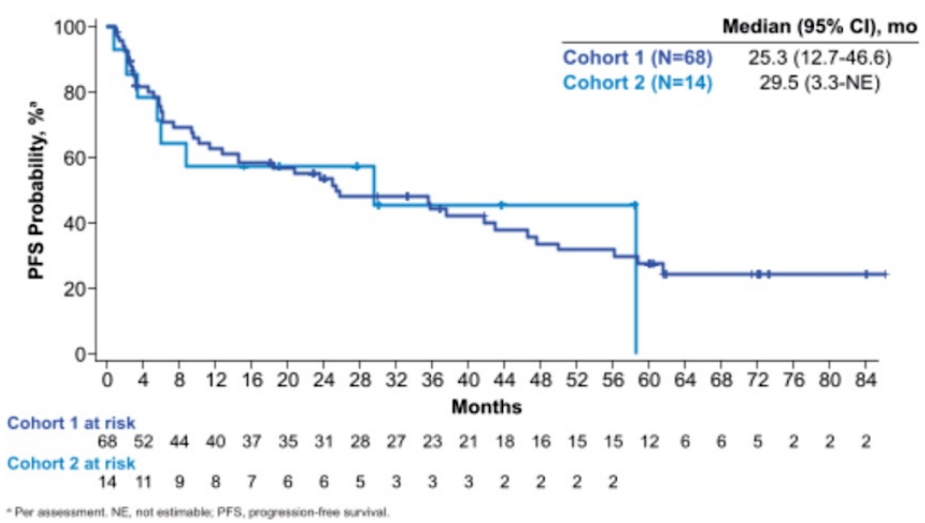
Analysis of n = 247 Japanese patients
Median OS = 5.6 months

Overall survival in patients with MCL progressing on cBTKi are very poor

Martin P et al. Blood 2016; Hess G et al. Br J Haematol 2022; Rai S et al. Adv Ther 2022.

CAR T-cell Therapy in R/R MCL

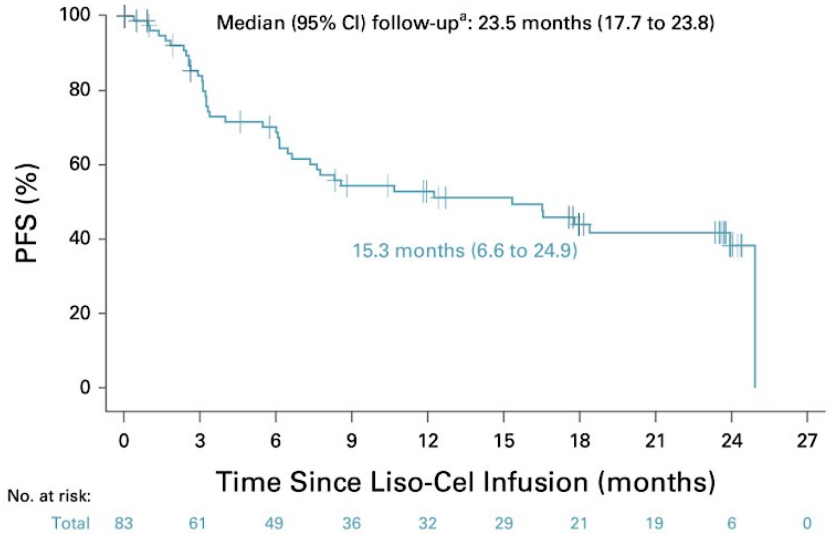
ZUMA-2: Brexu-cel
5 yr PFS: MCL 3L+



BTKi resistant
ORR 93%, CR 67% (best response)
~32% 4.5 yr PFS

CRS 91% (Gr3+ 15%)
Neurotox 63% (Gr3+ 31%)

TRANSCEND NHL 001: Liso-cel
2 yr PFS: MCL 3L+

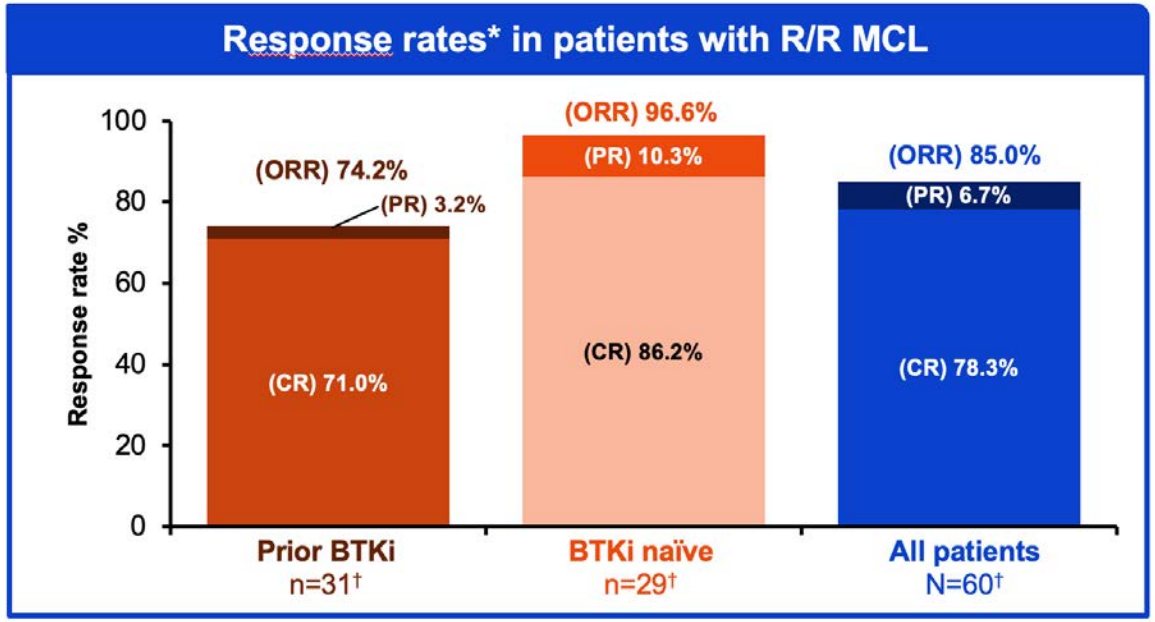


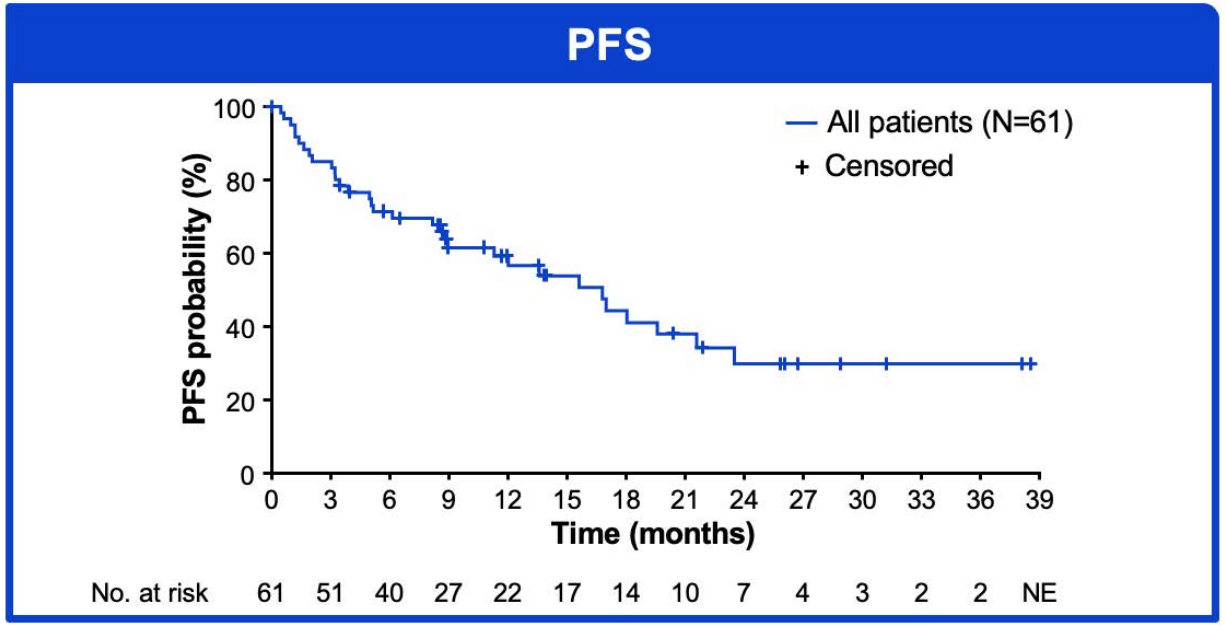
BTKi resistant
ORR 83%, CR 72% (best response)
43.9% 1.5 yr PFS

CRS 61% (Gr3+ 1%)
Neurotox 31% (Gr3+ 9%)

Wang M et al JCO 2022; Wang M et al JCO 2023

Glofitamab in R/R MCL: Efficacy





All: ORR ~85%, CR 78%

cBTKi exposed: ORR ~74%, CR 71%

Median f/u 19.6 mths, median PFS 16.8 mths (8.6 mths BTK exposed)

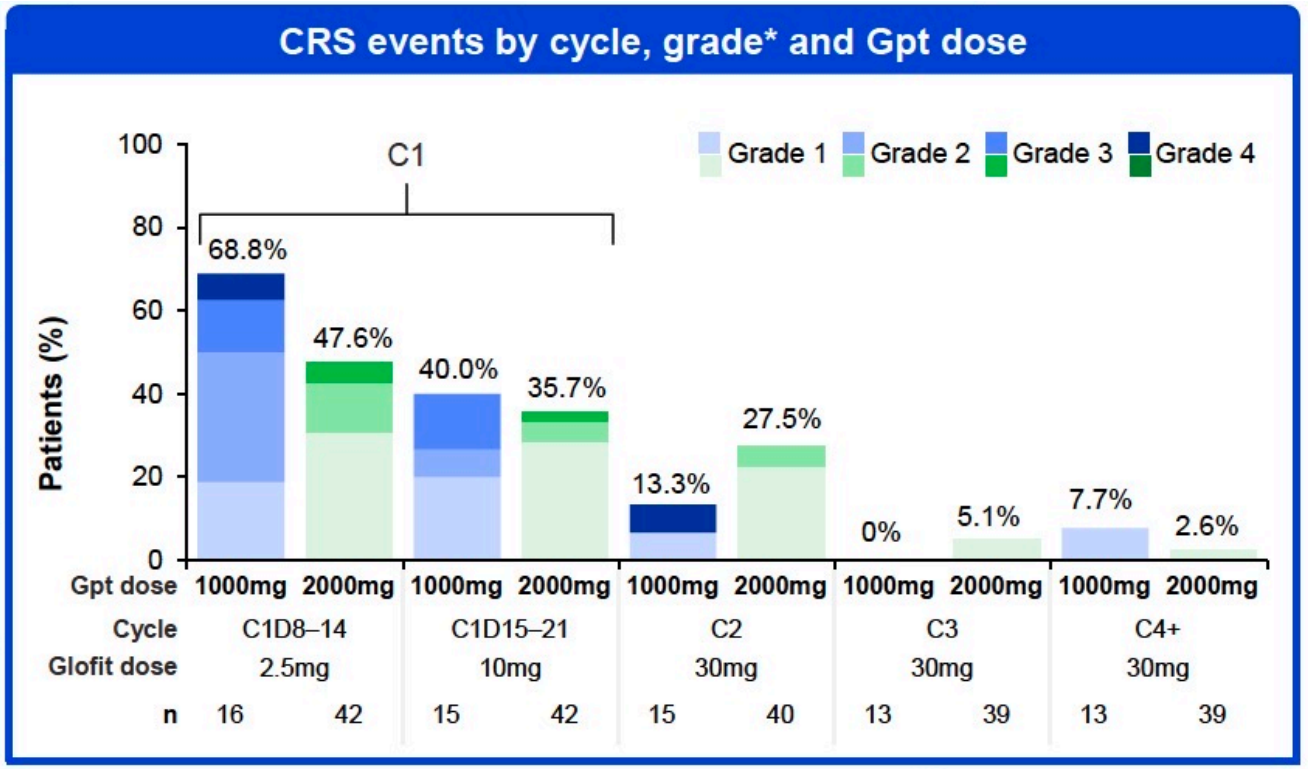
54% PFS at 15 mths (33% BTK exposed)

Sept 4, 2023 data cutoff; Glofitimab is not FDA approved for R/R MCL

Phillips T et al EHA 2024

Glofitamab in R/R MCL: Safety

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
Any grade CRS*	14 (87.5)	28 (63.6)	42 (70.0)
Grade 1	4 (25.0)	18 (40.9)	22 (36.7)
Grade 2	6 (37.5)	7 (15.9)	13 (21.7)
Grade 3	2 (12.5)	3 (6.8)	5 (8.3)
Grade 4	2 (12.5)	0	2 (3.3)
Serious AE of CRS†	11 (68.8)	12 (27.3)	23 (38.3)



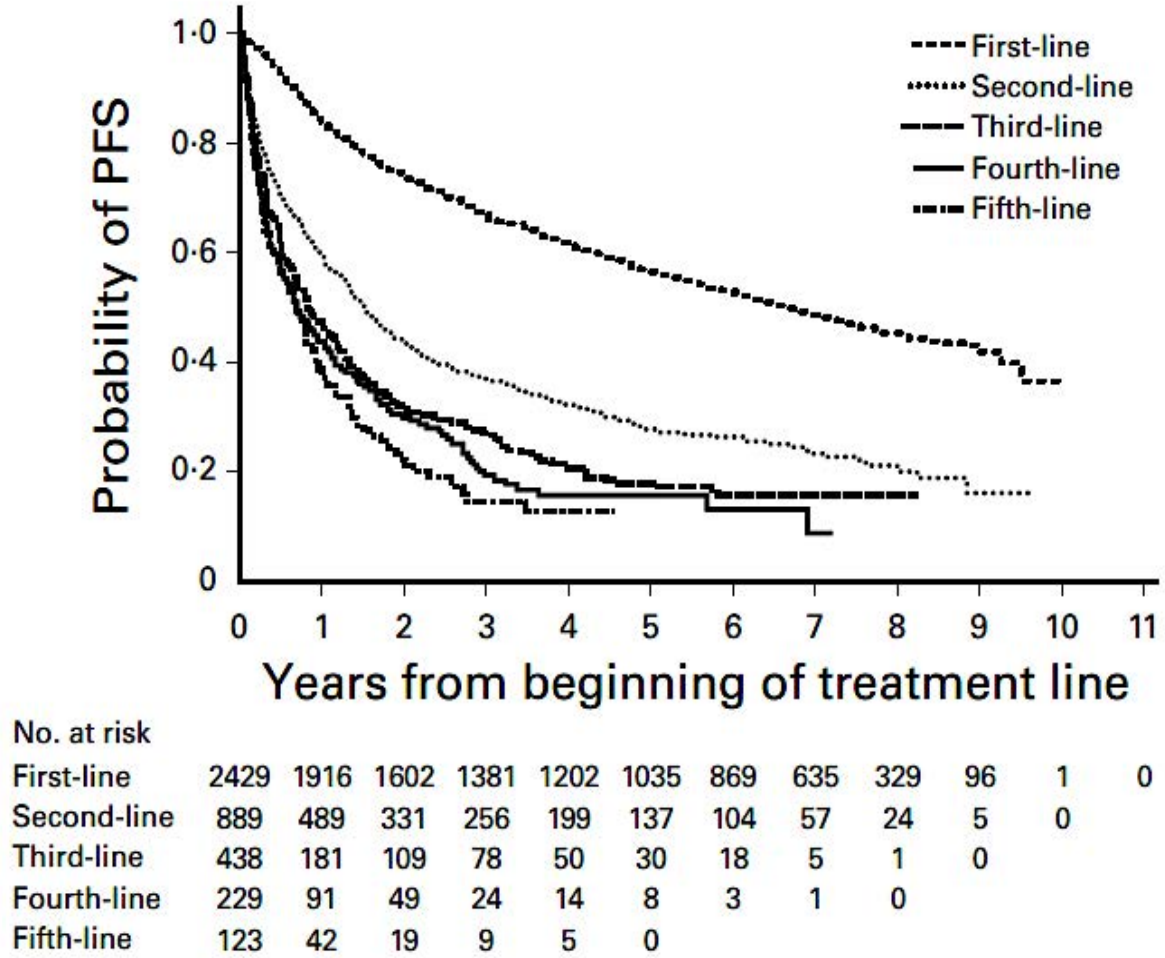
CRS common, ↓ w/ 2000mg Obinutuzumab pre dose
Higher grade CRS still an issue (~15% ICU admissions)…

Phillips T et al EHA 2024

Sept 4, 2023 data cutoff

R/R FL: PFS with CIT diminishes by LOT

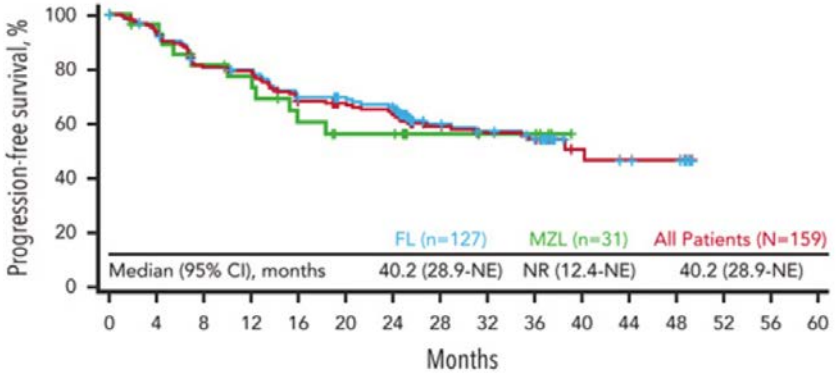
Treatment Line	Median PFS, Years (95% CI)
First	6.62 (6.10-7.20)
Second	1.50 (1.35-1.70)
Third	0.83 (0.68-1.09)
Fourth	0.69 (0.50-0.97)
Fifth	0.68 (0.43-0.88)



Link BK, et al. Br J Haematol. 2019.

CAR-T Cell Therapy in R/R FL

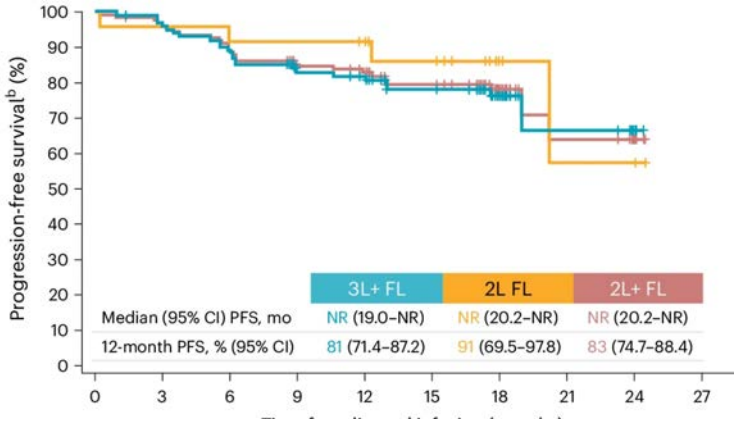
ZUMA-5 PFS



3L+ Axi-cel (n=127 FL)
ORR 94% CR 79%
5 yr PFS 49.8%
5 yr OS 69%

CRS 84% (Gr 3+ 8%)
Neurotox 77% (Gr 3+ 21%)

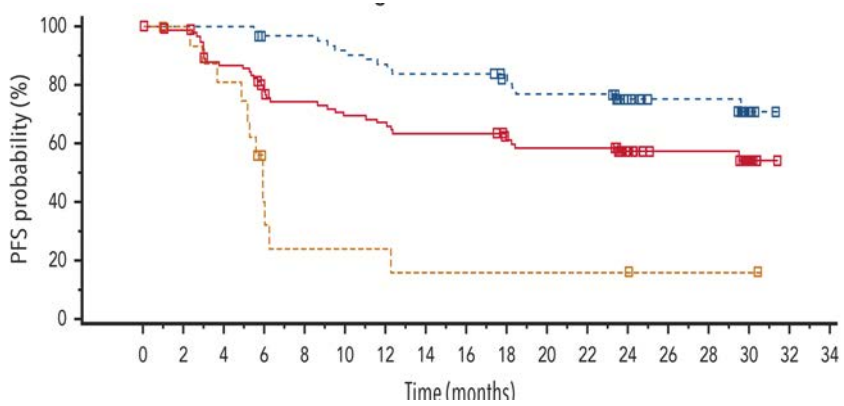
TRANSCEND FL PFS



2L+ Liso-cel (n=124)
ORR 97% CR 94%
1 yr PFS 81%
1 yr OS 91%

CRS 59% (Gr 3+ 1%)
Neurotox 15% (Gr 3+ 2%)

ELARA PFS



3L+, Tis-cel (n=91)
ORR 86% CR 69%
2 yr PFS 57.4%
2 yr OS 87.7%

CRS 48.5% (Gr 3+ 0%)
Neurotox 4.1% (Gr 3+ 1%)

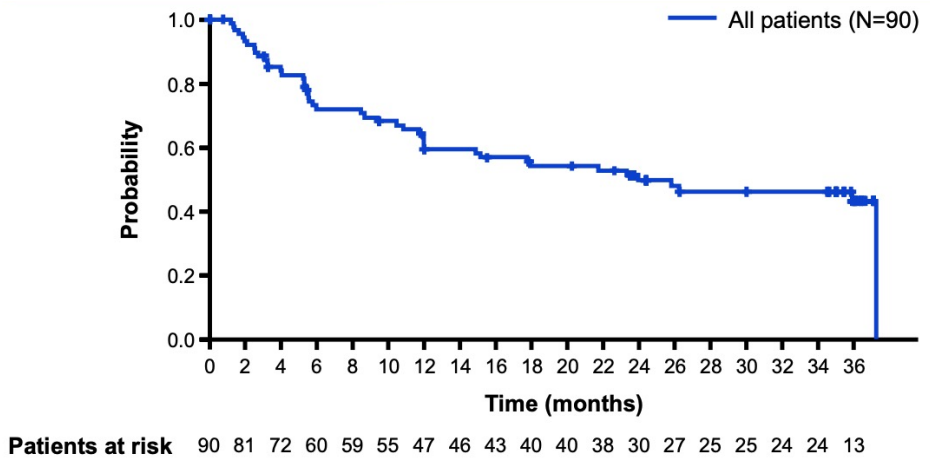
Neelapu et al Blood 2024; Morschhauser F et al Nat Med 2024; Dreyling et al Blood 2024

Bispecific antibodies in R/R FL

Mosunetuzumab (3L+, n=90)

C1D1: 1mg
C1D8: 2mg
C1D15 60mg
C2D1: 60mg;
C3, day 1 and onward: 30mg
Total 8-17 cycles

ORR 78%, CR 60%



3 yr PFS 43.2%
3 yr OS 82%

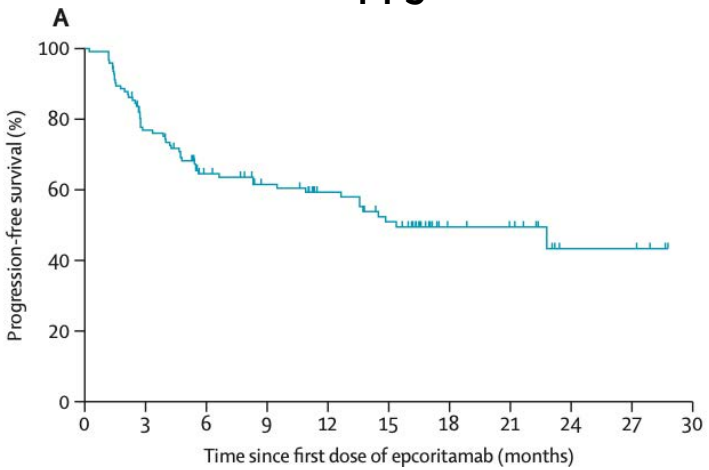
CRS 29% (Gr3+ 2%)

Epcoritamab (3L+ FL, n=128)

C1D1 0.16mg
C1D8 0.8mg SC
C1D15* to C3 48mg weekly SC
C4-9 48mg SC q2w
C10+ 48mg SC q4w

ORR 82%, CR 63%

PFS

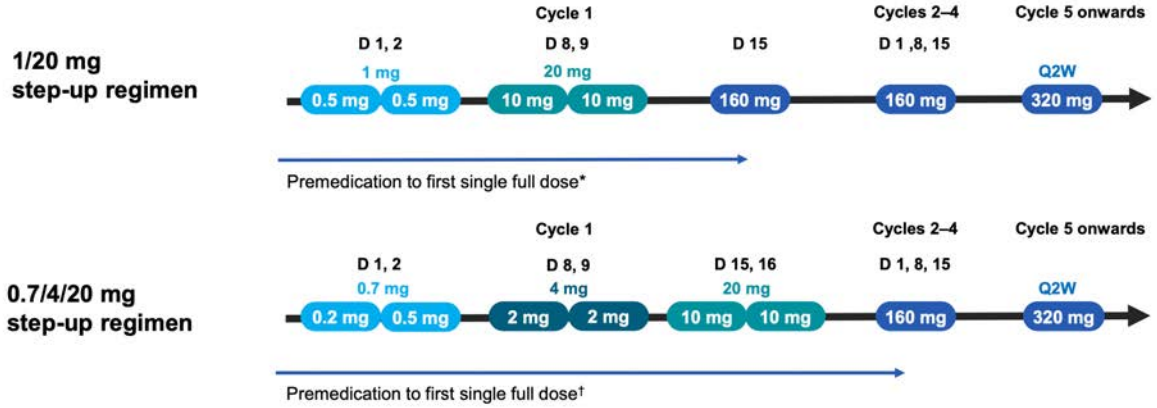


18 month PFS 49.4%
18 month OS 70.2%

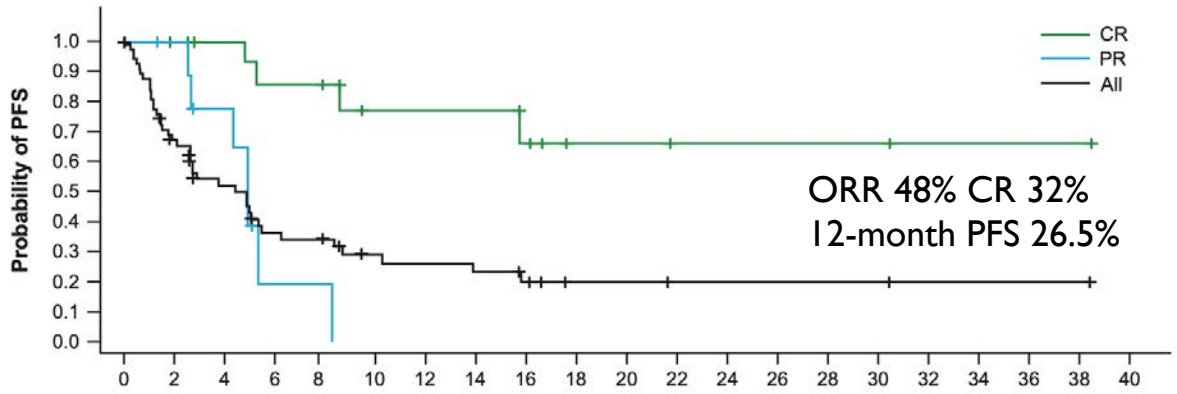
CRS 65% (Gr3+ 2%)
CRS optimization cohort 49%, (Gr3+ 0%)

Sehn L et al Blood 2025; Linton KM et al Lancet Haem 2024

Odronextamab* in DLBCL and FL



3L+ DLBCL post CAR T: PFS

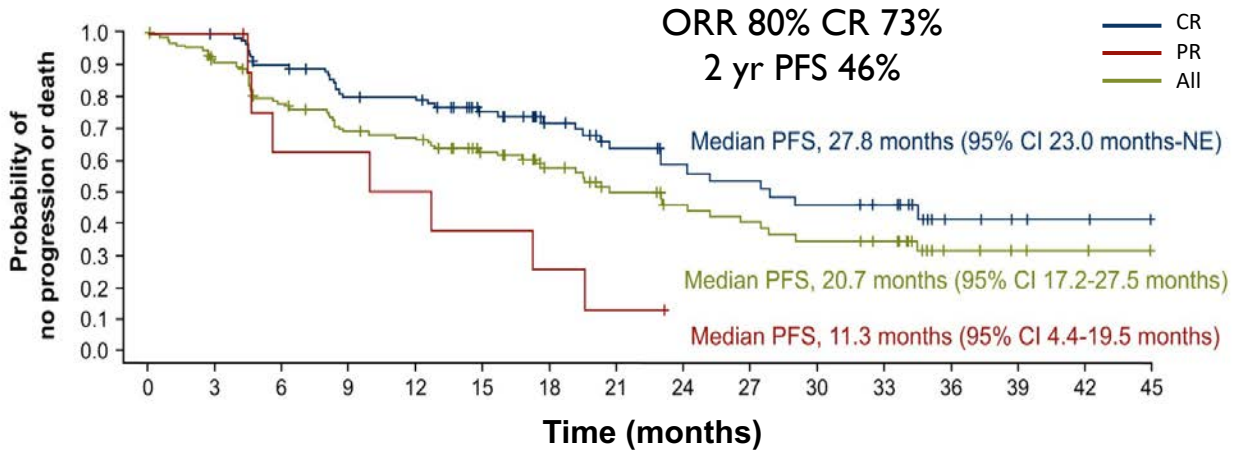


3L+ FL: PFS

Safety

DLBCL: CRS 55% (Gr3+ 4%)

FL: CRS 56% (Gr3+ 2%)



Matasar M et al. ASH 2024;Abstract 866; Kim TM et al. Ann Onc 2024; * Odronextamab is not FDA approved for any indication and is considered an investigational agent

Conclusions

- DLBCL
  - CAR T cells are a curative therapy option in 2L+ settings
  - Bispecific antibodies can result in prolonged CRs (?curative)
- MCL
  - CAR T-cell therapy can result in prolonged CR post cBTKi progression, but carries significant toxicity risk
  - Bispecific antibodies appear to be active in R/R MCL, but not yet approved
- FL
  - CAR T cells can result in prolonged CR (?curative)
  - Bispecific antibodies can result in prolonged CR

Discussion Question

- Regulatory and reimbursement issues aside, which third-line treatment would you most likely recommend for a 60-year-old patient with follicular lymphoma (FL) (EZH2 wild type) who developed disease progression 18 months after starting first-line bendamustine/rituximab (BR) and 6 months after starting second-line lenalidomide/rituximab (R^2)?

- Regulatory and reimbursement issues aside, how would you generally sequence CAR T-cell therapy and bispecific antibodies for patients with R/R FL?

Discussion Question

- Regulatory and reimbursement issues aside, which third-line therapy would you most likely recommend for a 70-year-old patient with Stage IV DLBCL and no significant comorbidities who received first-line R-CHOP and subsequently experienced disease progression on second-line R-DHAP followed by transplant?

- Based on your knowledge of available data, for older (eg, 70-year-old) patients, which CAR T-cell therapy do you view most favorably for DLBCL when globally considering both efficacy and tolerability?

Discussion Question

- Regulatory and reimbursement issues aside, which third-line therapy would you most likely recommend for an 87-year-old patient with Stage IV DLBCL and a history of congestive heart failure, diabetes mellitus and coronary artery disease who received first-line polatuzumab vedotin/R-CHP and subsequently experienced disease progression on second-line tafasitamab/lenalidomide?

Module 9: Non-Hodgkin Lymphoma

Role of Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies for Non-Hodgkin Lymphoma (NHL)
— Dr Patel

Other Available and Emerging Novel Therapies for NHL
— Dr Flowers

Other Available and Emerging Novel Therapies for NHL

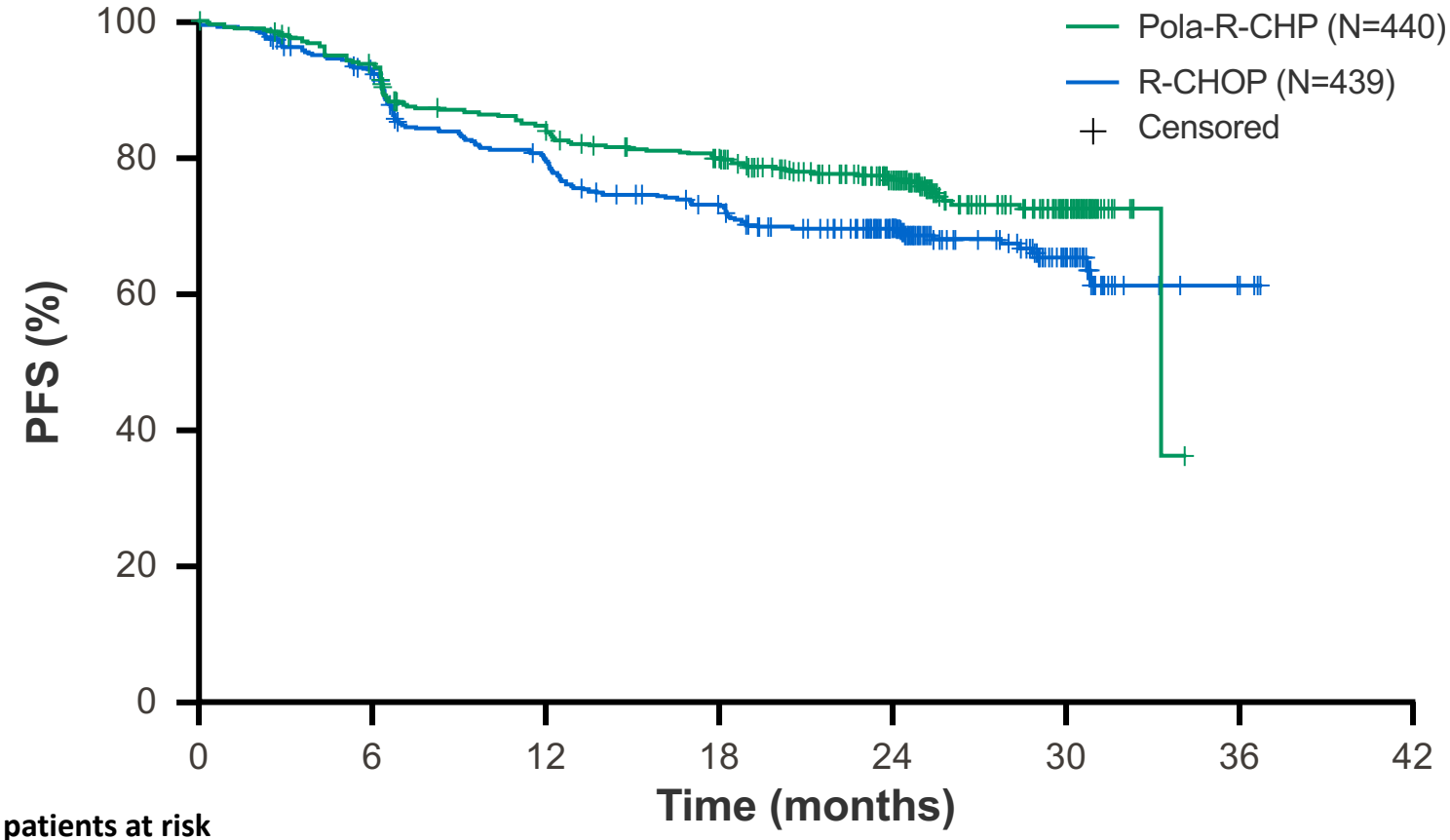
Christopher Flowers, MD, MS
Division Head, Division of Cancer Medicine
Chair, Professor, Department of Lymphoma/Myeloma
John Brooks Williams and Elizabeth Williams
Distinguished University Chair in Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Disclosures

Consulting Agreements	AbbVie Inc, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Celgene Corporation, Denovo Biopharma, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Karyopharm Therapeutics
Contracted Research	4D Pharma PLC, AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Alaunos Therapeutics, Allogene Therapeutics, Amgen Inc, Bayer HealthCare Pharmaceuticals, Celgene Corporation, Cellectis, EMD Serono Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Guardant Health, Iovance Biotherapeutics, Janssen Biotech Inc, Kite, A Gilead Company, MorphoSys, Nektar Therapeutics, Novartis, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Sanofi, Takeda Pharmaceuticals USA Inc, TG Therapeutics Inc, Xencor
Nonrelevant Financial Relationships	Burroughs Wellcome Fund, Cancer Prevention and Research Institute of Texas (CPRIT Scholar in Cancer Research), Eastern Cooperative Oncology Group, Foresight Diagnostics, National Cancer Institute, N-Power Medicine Inc, V Foundation

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS vs R-CHOP



No. of patients at risk

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

HR 0.73 **(P=0.02)**

95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** vs R-CHOP
- **24-month PFS:** 76.7% with Pola-R-CHP vs 70.2% with R-CHOP (Δ**=6.5%**)

Tilly et al. *NEJM* 2021

Five-year analysis of the POLARIX study: Prolonged follow-up confirms positive impact of polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) on outcomes

Gilles Salles[1], Franck Morschhauser[2], Laurie H. Sehn[3], Alex F. Herrera[4], Jonathan W. Friedberg[5], Marek Trněný[6], Georg Lenz[7], Jeff P. Sharman[8], Charles Herbaux[9], John M. Burke[10], Matthew Matasar[11], Graham P. Collins[12], Yuqin Song[13], Antonio Pinto[14], Shinya Rai[15], Koji Izutsu[16], Calvin Lee[17]*, Saibah Chohan[18], Matthew Sugidono[17], Yanwen Jiang[17], Connie Lee Batlevi[17], Mark Yan[18], Jamie Hirata[17]*, Hervé Tilly[19], Christopher R. Flowers[20]

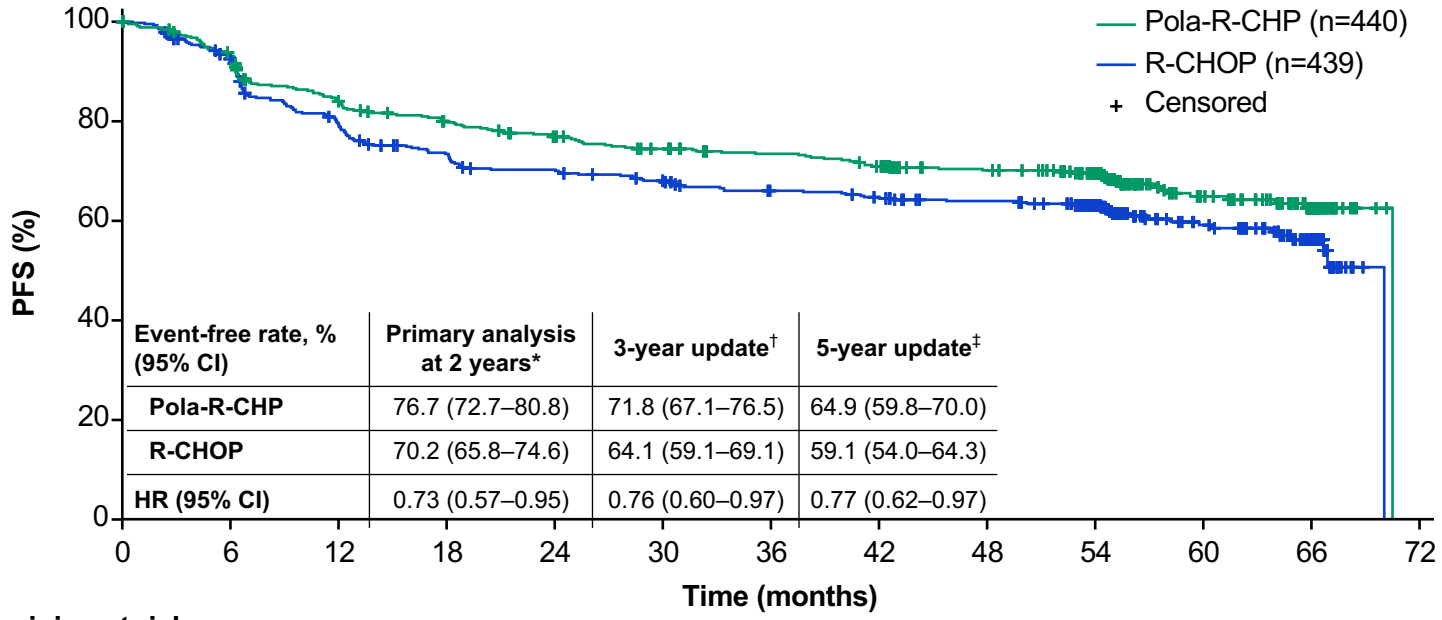
[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]University of Lille, Lille, France; [3]BC Cancer Centre for Lymphoid Cancer and the University of British Columbia, Vancouver, BC, Canada; [4]City of Hope, Duarte, CA, USA; [5]Wilmot Cancer Institute, University of Rochester, Rochester, NY, USA; [6]Charles University, Prague, Czech Republic; [7]University Hospital Münster, Münster, Germany; [8]Willamette Valley Cancer Institute and Research Center, Florence, OR, USA; [9]University of Montpellier, Montpellier, France; [10]Rocky Mountain Cancer Centers/US Oncology, Aurora, CO, USA; [11]Rutgers Cancer Institute, New Brunswick, NJ, USA; [12]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [13]Peking University Cancer Hospital, Beijing, China; [14]National Cancer Institute, Fondazione G. Pascale, IRCCS, Naples, Italy; [15]Department of Hematology and Rheumatology, Kindai University, Faculty of Medicine, Osaka-Sayama City, Japan; [16]National Cancer Center Hospital, Tokyo, Japan; [17]Genentech, Inc., South San Francisco, CA, USA; [18]Hoffmann-La Roche Ltd, Mississauga, Canada; [19]Centre Henri-Becquerel and University of Rouen, Rouen, France; [20]M.D. Anderson Cancer Center, Houston, TX, USA

**This affiliation was active at the time of the analysis*

Presented at the 66th ASH Annual Meeting | December 7–10, 2024

Initial PFS benefit of Pola-R-CHP over R-CHOP is maintained at 5 years

PFS in the global ITT population



Event-free rate, % (95% CI)	Primary analysis at 2 years*	3-year update†	5-year update‡
Pola-R-CHP	76.7 (72.7–80.8)	71.8 (67.1–76.5)	64.9 (59.8–70.0)
R-CHOP	70.2 (65.8–74.6)	64.1 (59.1–69.1)	59.1 (54.0–64.3)
HR (95% CI)	0.73 (0.57–0.95)	0.76 (0.60–0.97)	0.77 (0.62–0.97)

Patients remaining at risk

Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE

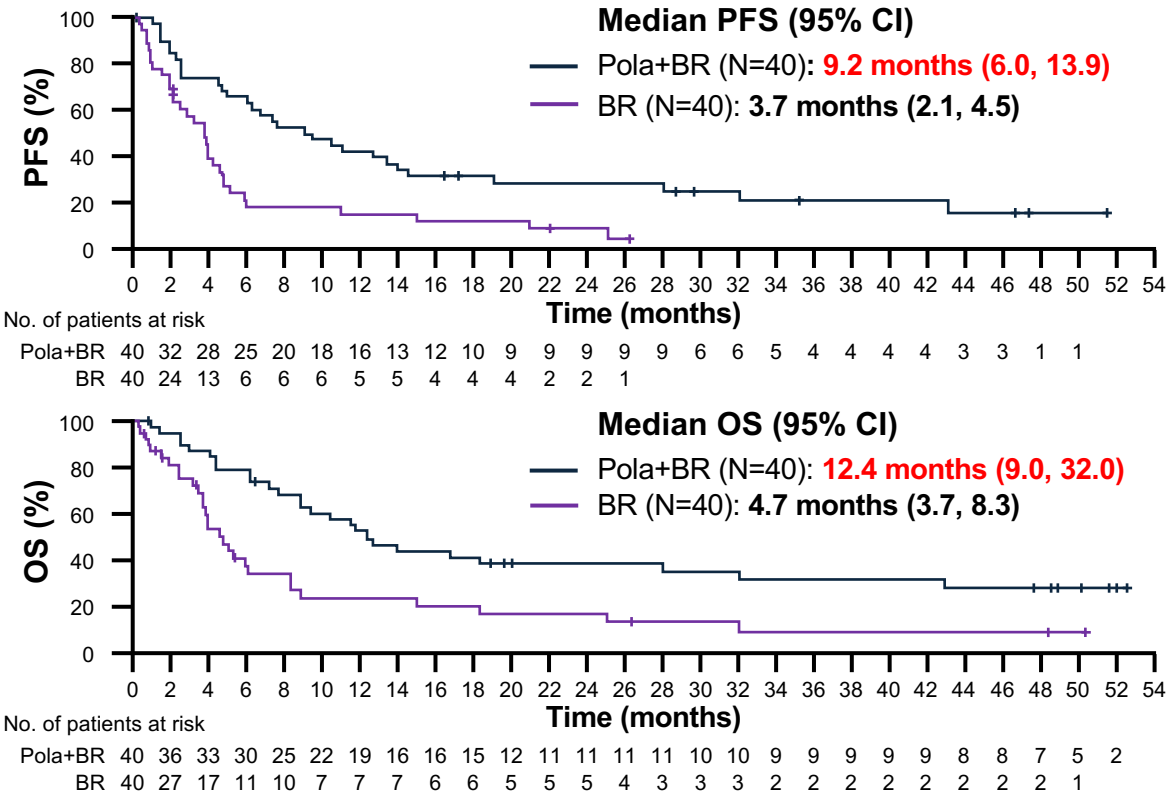
At the 5-year follow up, Pola-R-CHP had a **sustained and significant PFS benefit**, confirming results from the primary analysis of PFS at 2 years of follow up (HR 0.73).[1]

*Data cut-off: June 28, 2021; †Data cut-off: June 15, 2022; ‡Data cut-off: July 5, 2024.
CI, confidence interval; HR, hazard ratio; NE, not evaluable.

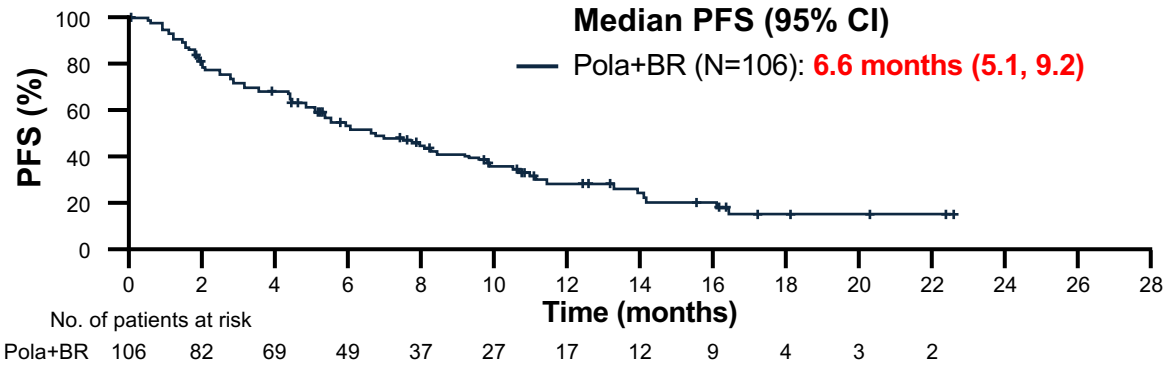
1. Tilly H, *et al. N Eng J Med* 2022;386:351–63.

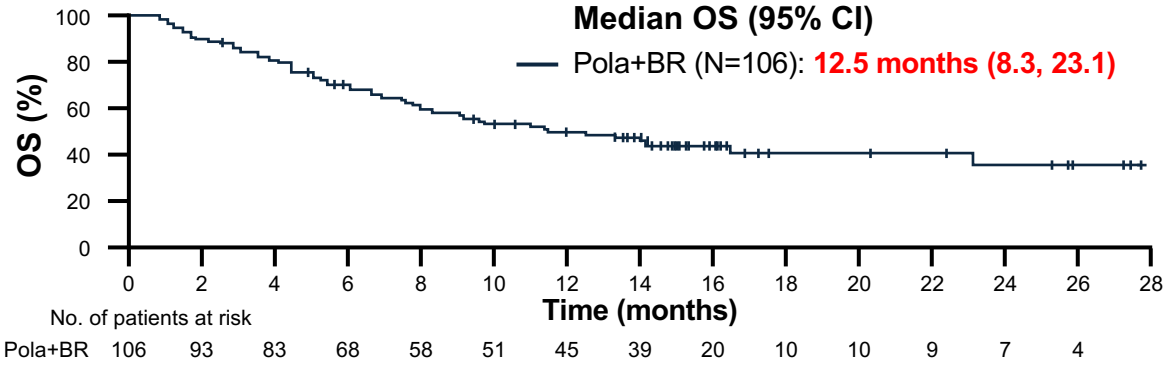
Pola-BR PFS and OS

Randomized



Extension cohort



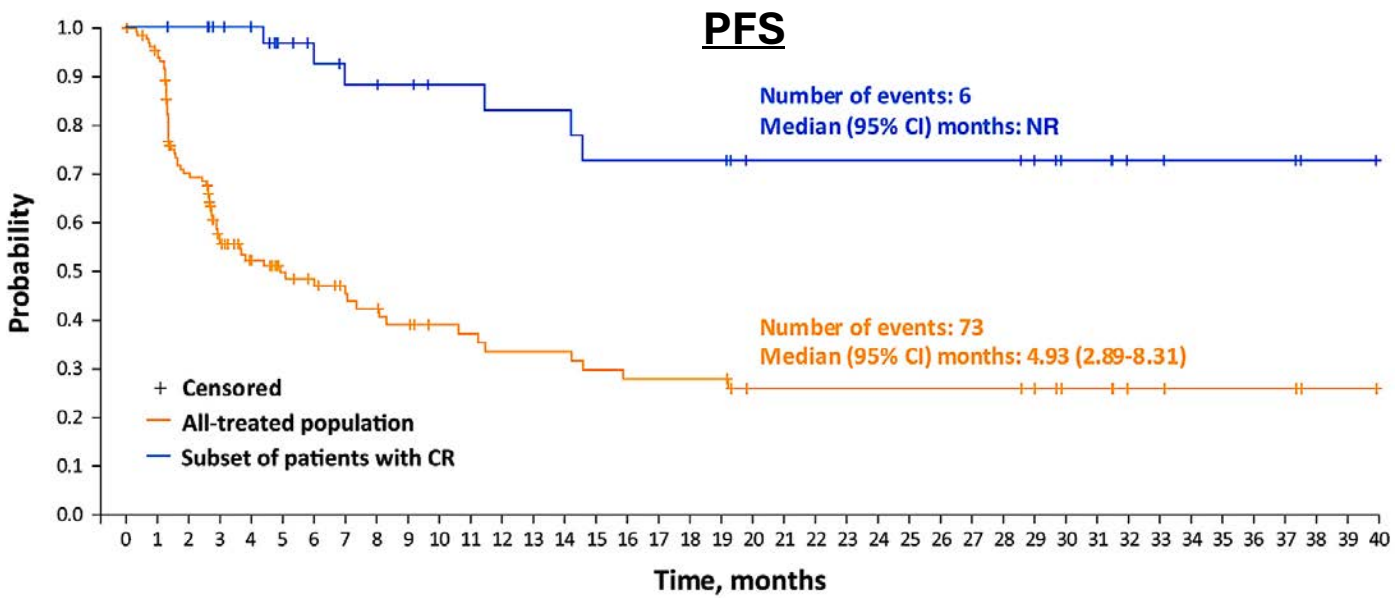


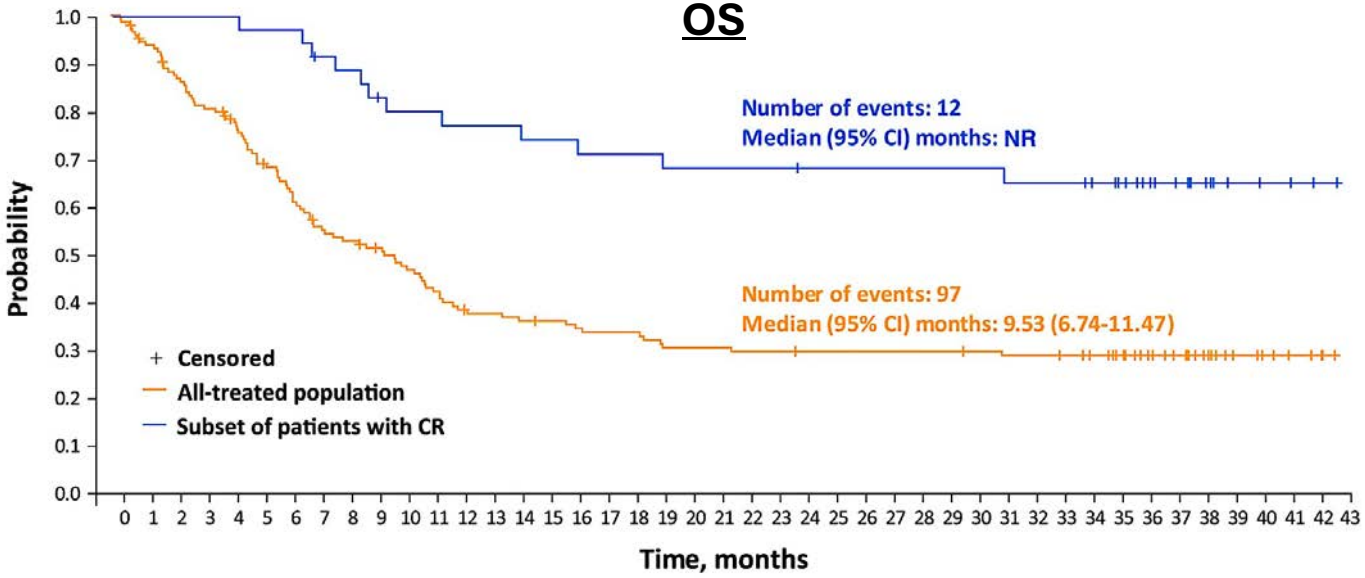
Sehn LH et al. ASH 2020. Abstract 3020.

- The significant survival benefit with Pola+BR persists with longer follow-up
- Response rates in the extension cohort consistent with the randomized Pola+BR arm
- The 2-year PFS 28.4% and the 2-year OS 38.2% for patients in the randomized Pola+BR cohort

BR, bendamustine plus rituximab; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; pola, polatuzumab.

Loncastuximab Tesirine: Survival

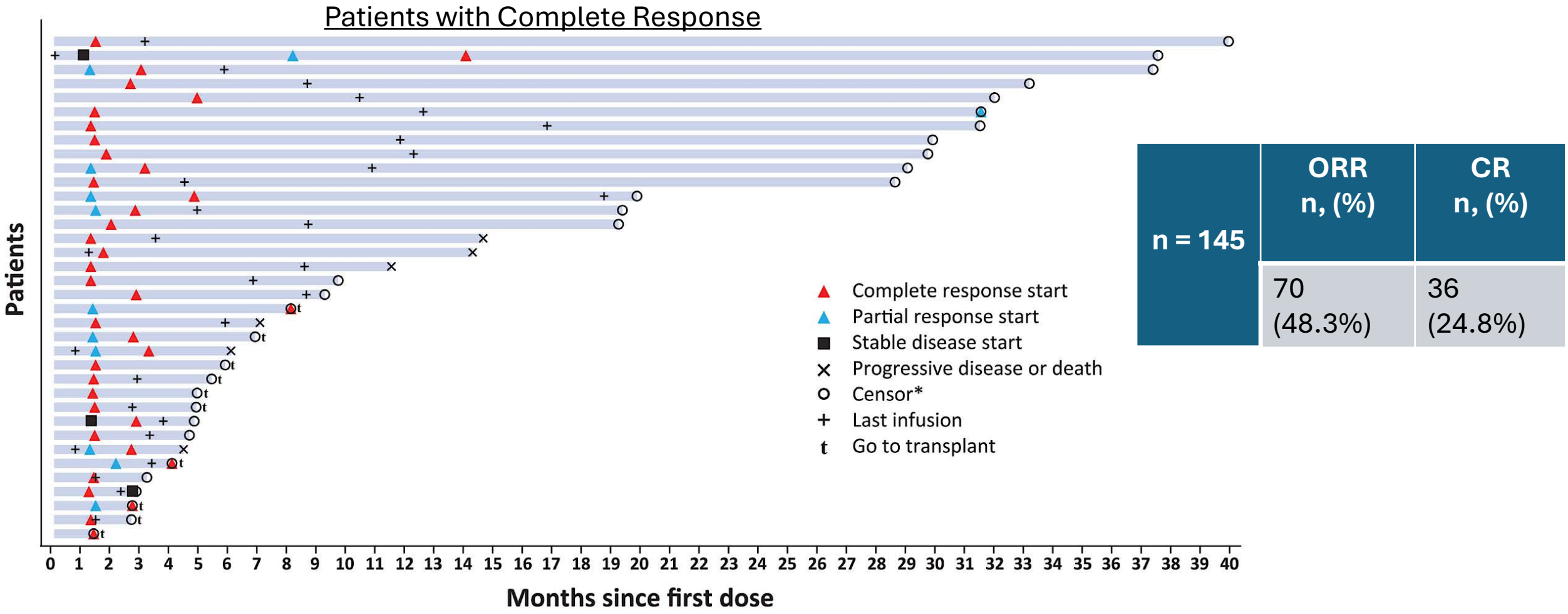




	All-Treated Population	Patients with CR
Median PFS	4.9 months (95% CI: 2.9-8.3)	Not reached
Median OS	9.5 months (95% CI: 6.7-11.5)	Not reached

Caimi PF, Ai WZ, Alderuccio JP, et al. *Haematologica*. 2024;109(4):1184-1193. Published 2024 Apr 1.

Loncastuximab Tesirine: Responses



n = 145	ORR n, (%)	CR n, (%)
	70 (48.3%)	36 (24.8%)

Loncastuximab Tesirine: Safety

	All-treated N=145		Best response of CR N=36	
	All grades N (%)	Grade ≥3 N (%)	All grades N (%)	Grade ≥3 N (%)
Any TEAE	143 (98.6)	107 (73.8)	36 (100)	27 (75.0)
Increased GGT	61 (42.1)	25 (17.2)	18 (50.0)	7 (19.4)
Neutropenia	58 (40.0)	38 (26.2)	15 (41.7)	10 (27.8)
Thrombocytopenia	48 (33.1)	26 (17.9)	13 (36.1)	7 (19.4)
Fatigue	40 (27.6)	2 (1.4)	8 (22.2)	-
Anemia	38 (26.2)	15 (10.3)	13 (36.1)	3 (8.3)
Nausea	34 (23.4)	-	11 (30.6)	-
Cough	33 (22.8)	1 (0.7)	8 (22.2)	-
Increased blood ALP	29 (20.0)	1 (0.7)	10 (27.8)	-
Peripheral edema	29 (20.0)	2 (1.4)	12 (33.3)	1 (2.8)
Pyrexia	28 (19.3)	2 (1.4)	6 (16.7)	-
Diarrhea	25 (17.2)	3 (2.1)	10 (27.8)	2 (5.6)
Increased AST	23 (15.9)	1 (0.7)	7 (19.4)	-
Hypokalemia	23 (15.9)	6 (4.1)	7 (19.4)	2 (5.6)
Hypophosphatemia	23 (15.9)	8 (5.5)	8 (22.2)	4 (11.1)
Increased ALT	22 (15.2)	4 (2.8)	5 (13.9)	1 (2.8)
Decreased appetite	22 (15.2)	-	6 (16.7)	-
Leukopenia	21 (14.5)	13 (9.0)	7 (19.4)	5 (13.9)
Hypomagnesemia	20 (13.8)	1 (0.7)	6 (16.7)	1 (2.8)
Pruritus	19 (13.1)	-	8 (22.2)	-
Rash	19 (13.1)	1 (0.7)	8 (22.2)	-
Vomiting	19 (13.1)	-	7 (19.4)	-
Abdominal pain	17 (11.7)	4 (2.8)	4 (11.1)	-
Constipation	17 (11.7)	-	6 (16.7)	-
Dyspnea	17 (11.7)	2 (1.4)	5 (13.9)	-
Insomnia	16 (11.0)	-	2 (5.6)	-
Pleural effusion	16 (11.0)	3 (2.1)	6 (16.7)	1 (2.8)
Erythema	15 (10.3)	1 (0.7)	7 (19.4)	1 (2.8)
Headache	15 (10.3)	1 (0.7)	3 (8.3)	-
Photosensitivity reaction	15 (10.3)	3 (2.1)	2 (5.6)	1 (2.8)

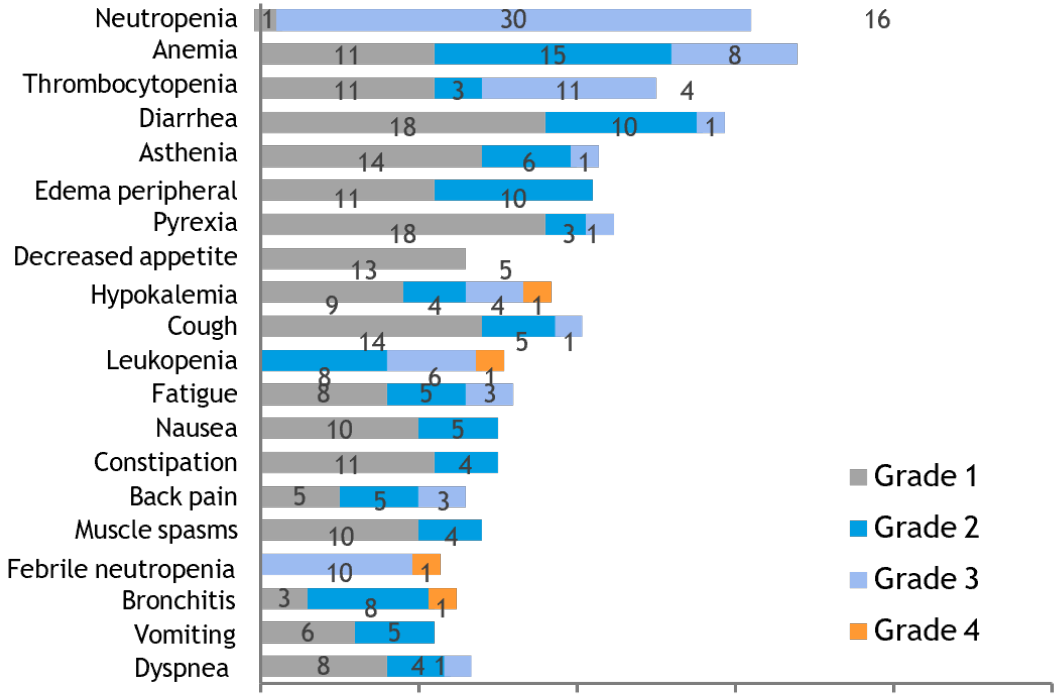
Tafasitamab + Lenalidomide: Outcomes

Characteristics	Primary analysis	3-year follow-up	Final 5-year data	5-year data for patients with 1 prior line of therapy, N=40	5-year data for patients with ≥2 prior lines of therapy, N=40
Data cut-off date	Nov 30, 2018	Oct 30, 2020	Nov 14, 2022	Nov 14, 2022	Nov 14, 2022
Best ORR, N (%) [95% CI]	48 (60.0) [48.4-70.9]	46 (57.5) [45.9-68.5]	46 (57.5) [45.9-68.5]	27 (67.5) [50.9-81.4]	19 (47.5) [31.5-63.9]
CR rate, N (%) [95% CI]	34 (42.5) [32.0-54.0]	32 (40.0) [29.2-51.6]	33 (41.3) [30.4-52.8]	21 (52.5) [36.1-68.5]	12 (30.0) [16.6-46.5]
PR rate, N (%) [95% CI]	14 (17.5) [10.0-28.0]	14 (17.5) [9.9-27.6]	13 (16.3) [8.9-26.2]	6 (15.0) [5.7-29.8]	7 (17.5) [7.3-32.8]
Median DoR in months [95% CI]	21.7 [21.7-NR]	43.9 [26.1-NR]	NR [33.8-NR]	NR [9.1-NR]	NR [26.1-NR]
Median PFS in months [95% CI]	12.1 [5.7-NR]	11.6 [6.3-45.7]	11.6 [5.7-45.7]	23.5 [7.4-NR]	7.6 [2.7-45.5]
Median OS in months [95% CI]	NR [18.3-NR]	33.5 [18.3-NR]	33.5 [18.3-NR]	NR [24.6-NR]	15.5 [8.6-45.5]

Duell J, Abrisqueta P, Andre M, et al. *Haematologica*. 2024;109(2):553-566. Published 2024 Feb 1.

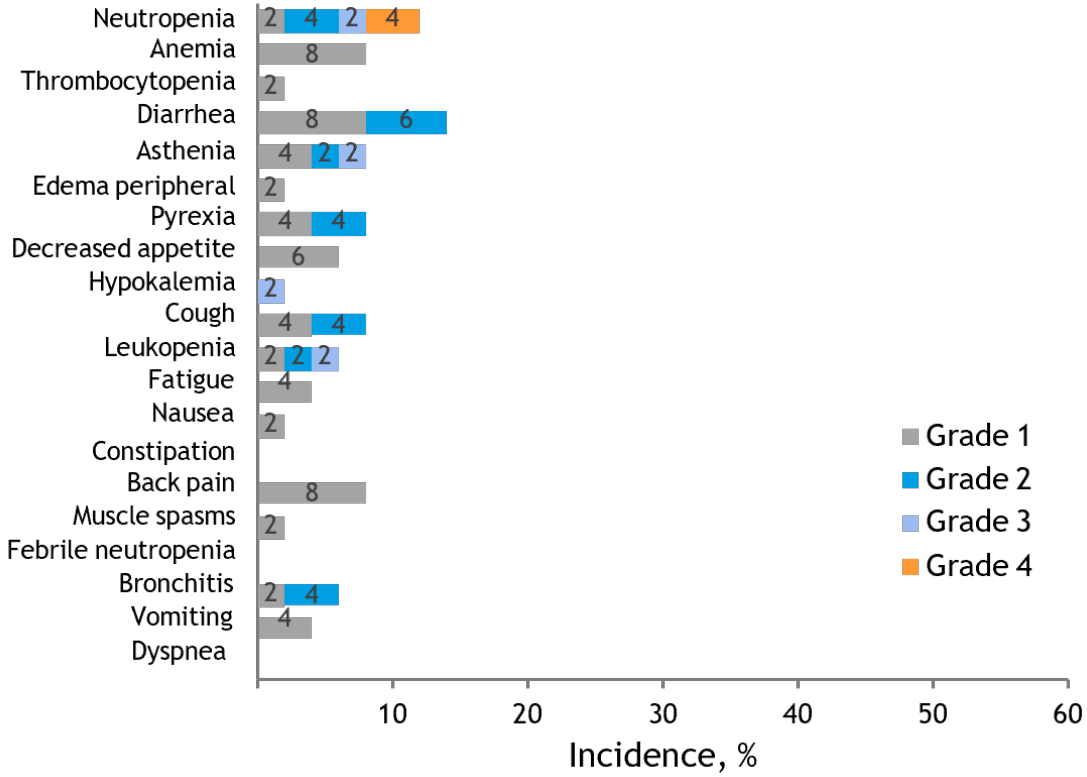
Tafasitamab + Lenalidomide: Safety

Tafasitamab + LEN Combination (Up to 12 Cycles) N=80, Median Exposure 6.2 Months[a]



- 37 patients (43%) required lenalidomide dose reduction
- 62/80 patients (78%) were able to stay at dose ≥ 20mg/d

Tafasitamab Monotherapy (Cycle 13 Onward or After LEN Discontinuation) N=51, Median Exposure 4.1 Months[a]



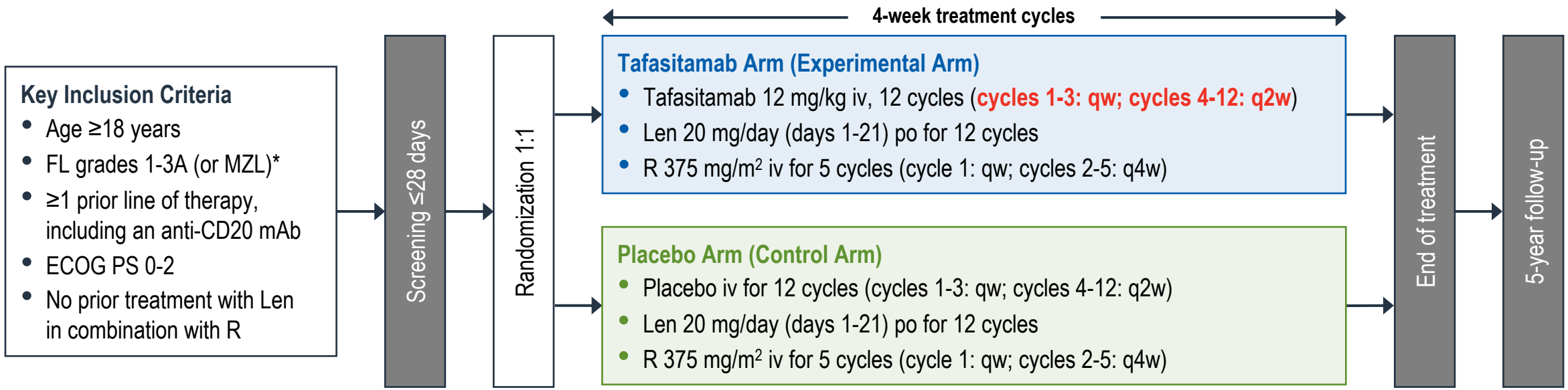
- Incidence and severity of TEAEs are lower during the tafasitamab monotherapy phase
- Ten patients (12%) discontinued tafasitamab + LEN because of AEs

[a]AE collection period included 30 days after end of treatment

AEs, adverse events; LEN, lenalidomide; TEAEs, treatment-emergent AEs .

Salles G et al. *Lancet Oncol.* 2020;21(7):978-988.

inMIND study: phase 3, tafa-R2 vs R2



Stratification Factors (Patients With FL)

- POD24
- **Refractoriness to prior anti-CD20 mAb therapy**
- Number of prior lines of therapy (1 or ≥2)

Study Endpoints in FL Population (Investigator Assessed Unless Specified)

- **Primary study endpoint:** **PFS**
- **Key secondary:** PET-CR rate in the FDG-avid population, OS
- **Select other secondary:** PFS by IRC, ORR, DOR, safety, QoL, MRD
- **Exploratory:** TTNT, B-cell recovery, Ig levels, CD19 expression

inMIND study: phase 3, tafa-R2 vs R2

PET-CR (FDG-Avid Population)	Tafasitamab + Len + R	Placebo + Len + R
Patients with FDG-avid disease at baseline	251	254
Patients with postbaseline PET assessments, n (%)*	201/251 (80.1)	205/254 (80.7)
Best metabolic response based on PET, n (%)†		
CMR	124 (49.4)	101 (39.8)
PMR	37 (14.7)	39 (15.4)
NMR/SD	19 (7.6)	12 (4.7)
PMD	19 (7.6)	51 (20.1)
Not done	50 (19.9)	46 (19.3)
PET-CR rate, % (95% CI)	**49.4** (43.1, 55.8)	**39.8** (33.7, 46.1)
Odds ratio (95% CI)	**1.5 (1.04, 2.13)**	
Nominal *P* value	**0.0286**	

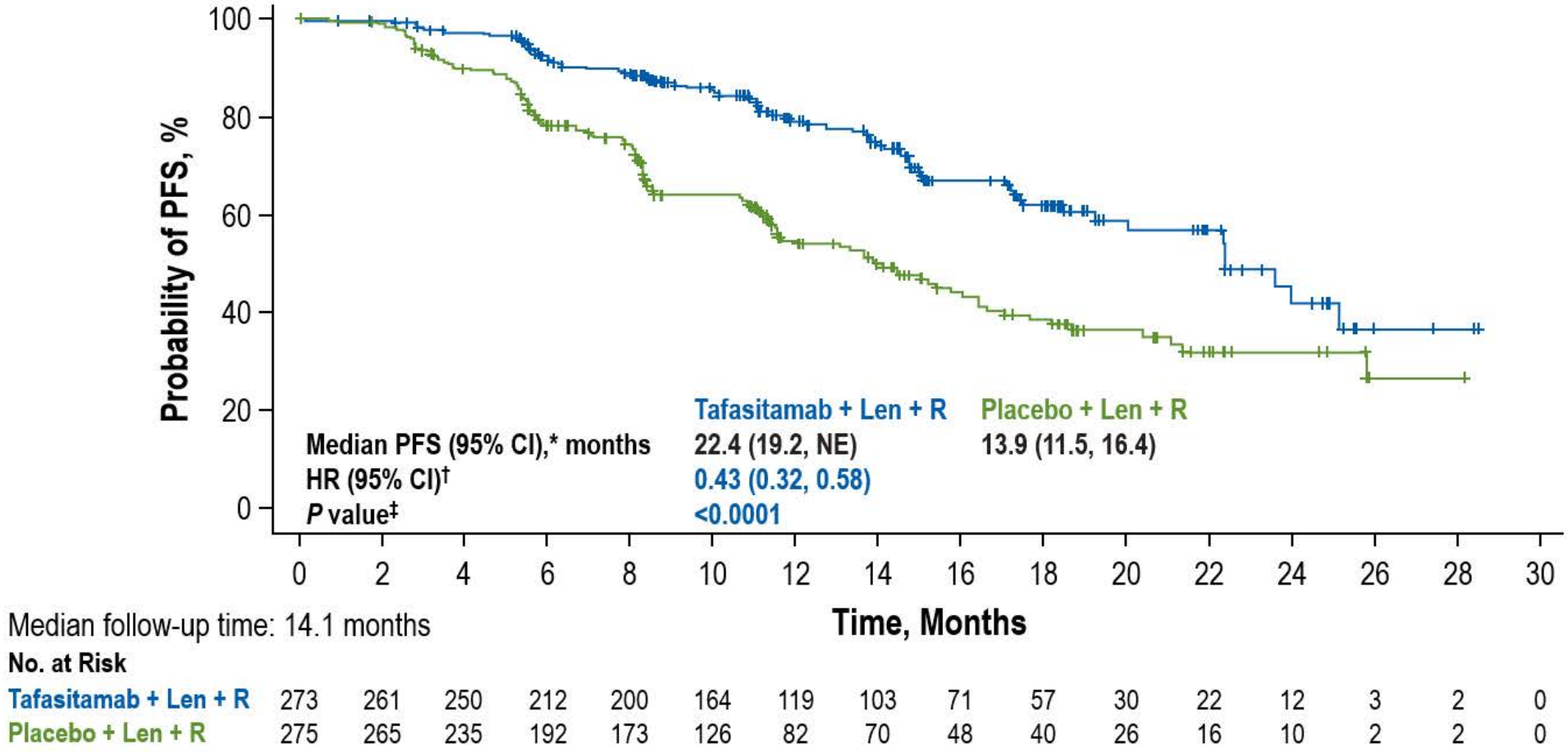
ORR (ITT Population)	Tafasitamab + Len + R	Placebo + Len + R
Patients, n	273	275
Best overall response, n (%)‡		
CR	142 (52.0)	112 (40.7)
PR	86 (31.5)	87 (31.6)
SD	28 (10.3)	46 (16.7)
PD	7 (2.6)	20 (7.3)
NE	2 (0.7)	0
Not done	8 (2.9)	10 (3.6)
ORR, % (95% CI)	**83.5** (78.6, 87.7)	**72.4** (66.7, 77.6)
Odds ratio (95% CI)	**2.0 (1.30, 3.02)**	
Nominal *P* value	**0.0014**	

Significant improvement in PET-CR rate and ORR was observed with tafasitamab

Sehn et al. ASH 2024

inMIND study: phase 3, tafa-R2 vs R2

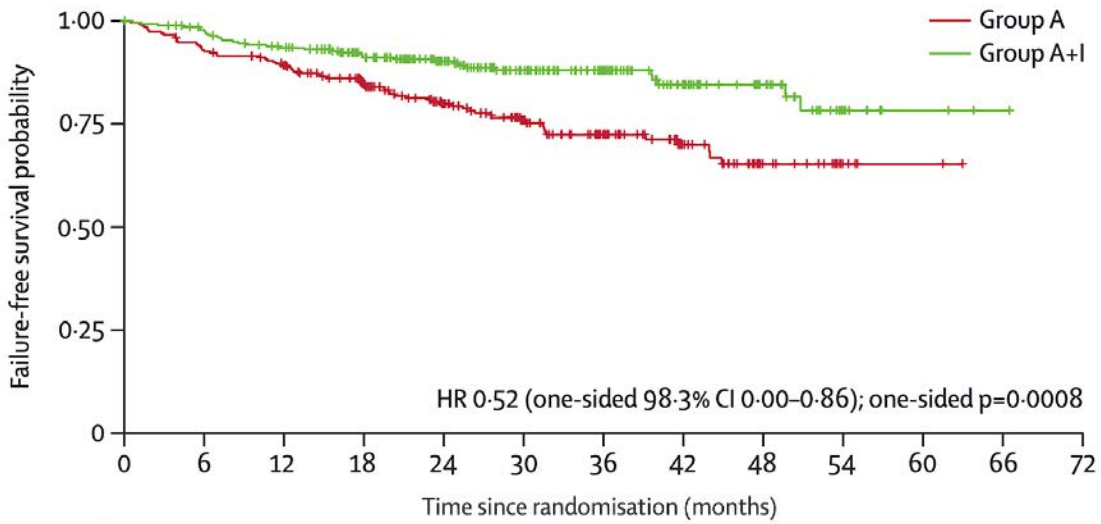
Primary endpoint: PFS

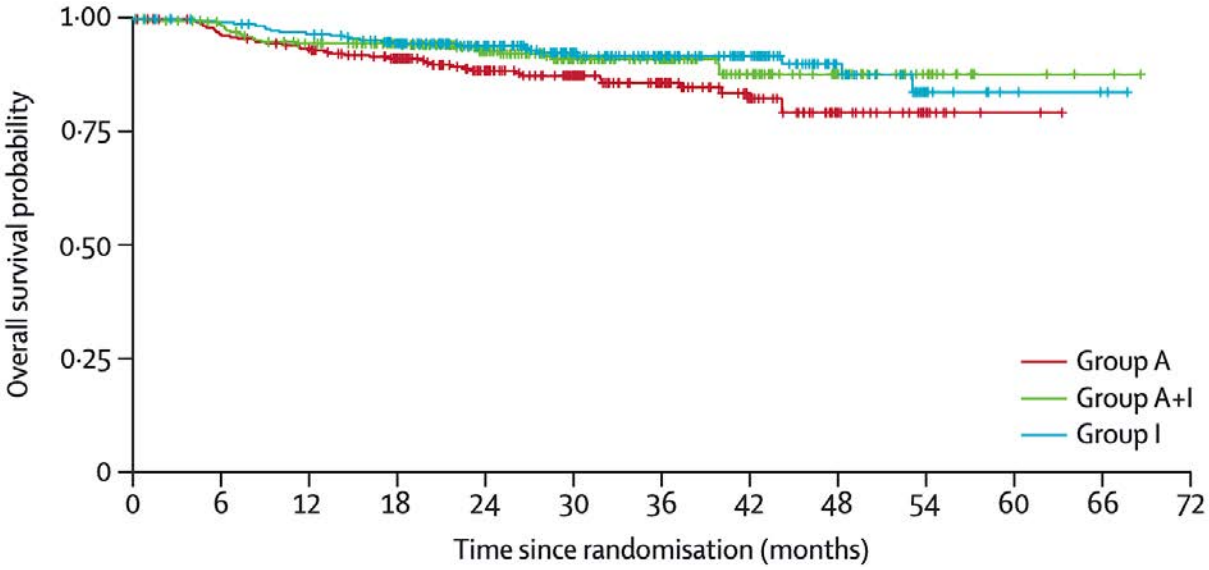


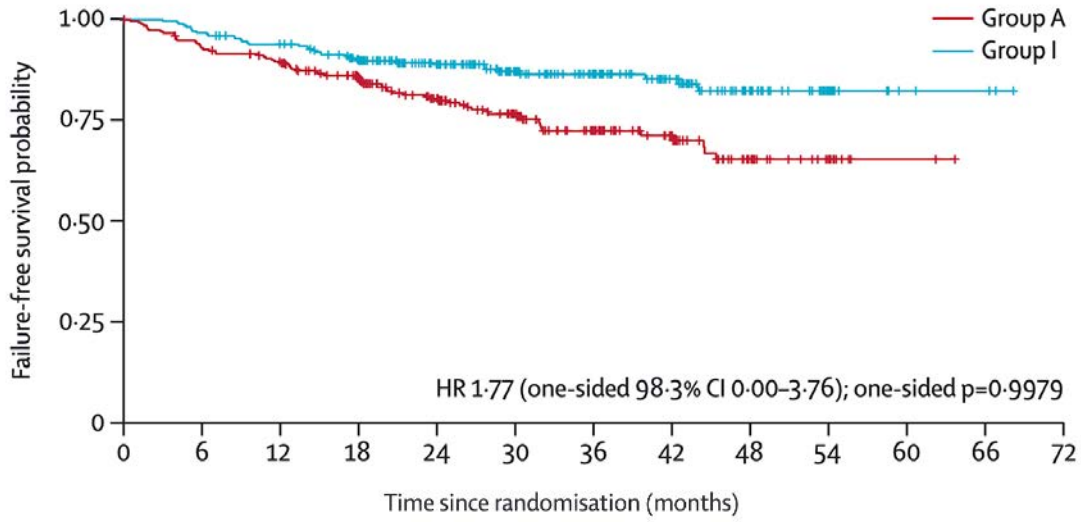
Significant improvement in PFS was observed with tafasitamab

Sehn et al. ASH 2024

Ibrutinib combined with immunochemotherapy +/- ASCT vs immunochemotherapy and ASCT in previously untreated patients with MCL



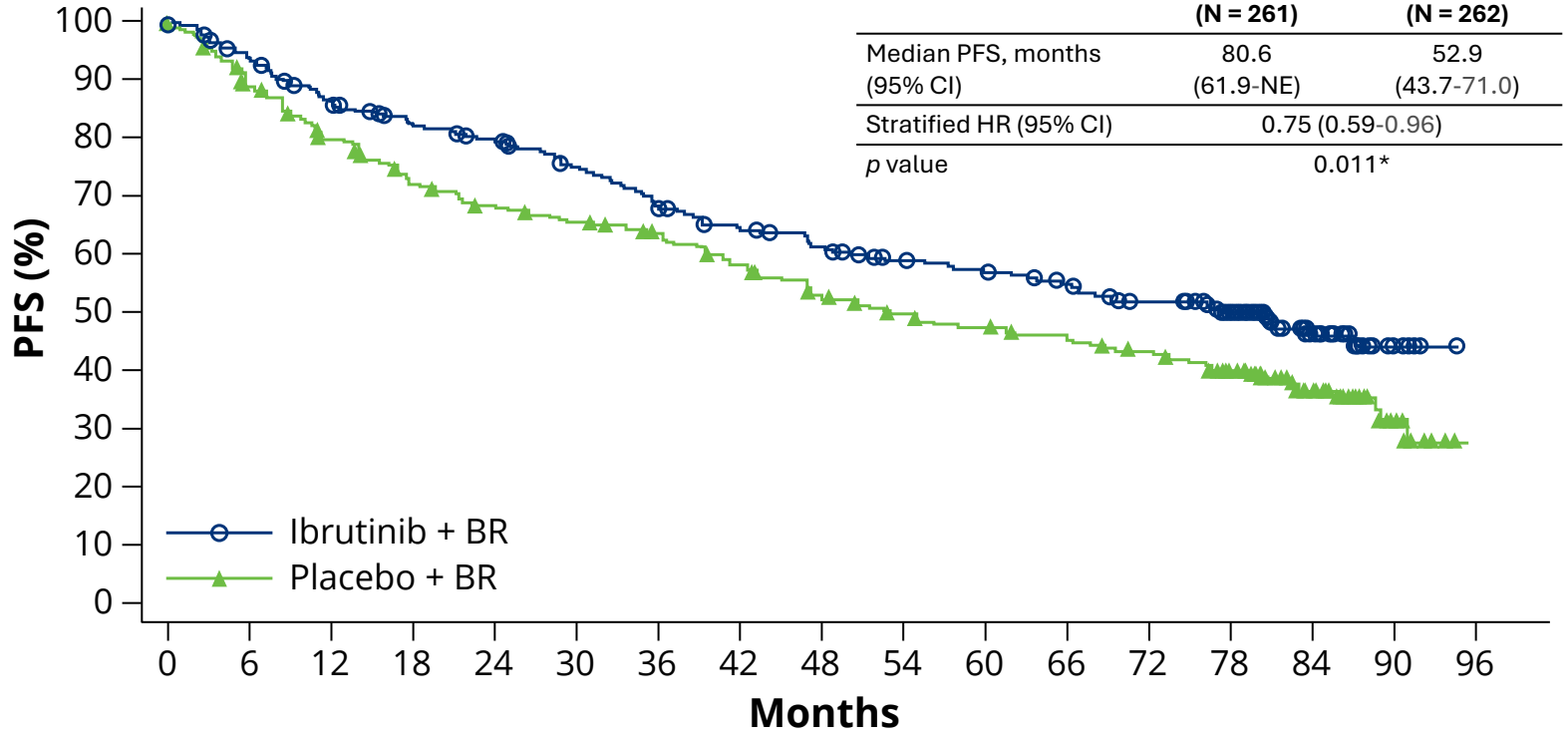




Adding ibrutinib to first-line treatment resulted in superior efficacy in younger mantle cell lymphoma patients with increased toxicity when given after ASCT. Whether ASCT adds to an ibrutinib-containing regimen is not yet determined.

Dreyling M, Doorduijn J, Giné E, et al. *Lancet*. 2024;403(10441):2293-2306.

Primary End Point of Improved PFS Was Met



	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median PFS, months (95% CI)	80.6 (61.9-NE)	52.9 (43.7-71.0)
Stratified HR (95% CI)	0.75 (0.59-0.96)	
p value	0.011*	

Patients at Risk

Ibrutinib + BR	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
Placebo + BR	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0

- Ibrutinib + BR and R maintenance showed:
- **25% reduction** in risk of PD or death
- **Significant improvement in median PFS by 2.3 years** (6.7 vs 4.4 years)

LB3439

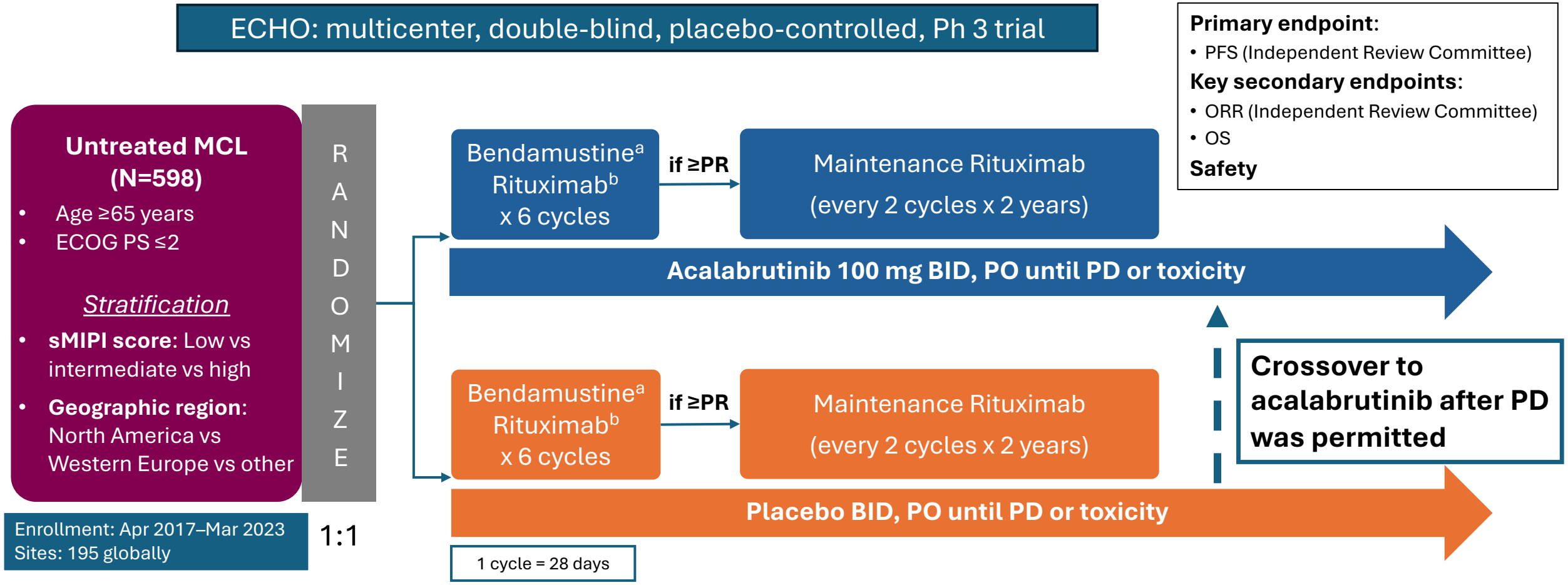
Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma (MCL): Results from the phase 3, double-blind, placebo-controlled ECHO trial

Michael Wang[1], Jiri Mayer[2], David Belada[3], Yuqin Song[4], Wojciech Jurczak[5], Jonas Paludo[6], Michael P. Chu[7], Iryna Kryachok[8], Laura Fogliatto[9], Chan Cheah[10], Marta Morawska[11,12], Juan-Manuel Sancho[13], Yufu Li[14], Caterina Patti[15], Cecily Forsyth[16], Jingyang Zhang[17], Robin Lesley[17], Safaa Ramadan[18], Simon Rule[18], Martin Dreyling[19]

[1]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [2]University Hospital Brno, Brno, Czech Republic;
[3]4th Department of Internal Medicine – Haematology, Charles University, Hospital and Faculty of Medicine, Hradec Králové, Czech Republic;
[4]Peking University Cancer Hospital & Institute, Beijing, China; [5]Malopolskie Centrum Medyczne S.C, Krakow, Poland;
[6]Mayo Clinic, Rochester, MN, USA; [7]Cross Cancer Institute, University of Alberta, Edmonton, Canada; [8]National Cancer Institute, Kyiv, Ukraine;
[9]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [10]Sir Charles Gairdner Hospital, Nedlands, Australia; [11]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; [12]Hematology Department, St. John's Cancer Center, Lublin, Poland;
[13]ICO-IJC-Hospital Germans Trias i Pujol, Badalona, Spain; [14]Henan Cancer Hospital, Zheng Zhou, China;
[15]A.O.O.R. Villa Sofia Cervello, Palermo, Italy; [16]Central Coast Haematology, North Gosford, Australia;
[17]AstraZeneca, South San Francisco, CA, USA; [18]AstraZeneca, Cambridge, UK; [19]Klinikum der Universitaet Munchen, Muenchen, Germany

Presented at the European Hematology Association (EHA) Annual Meeting; June 13–16, 2024; Madrid, Spain

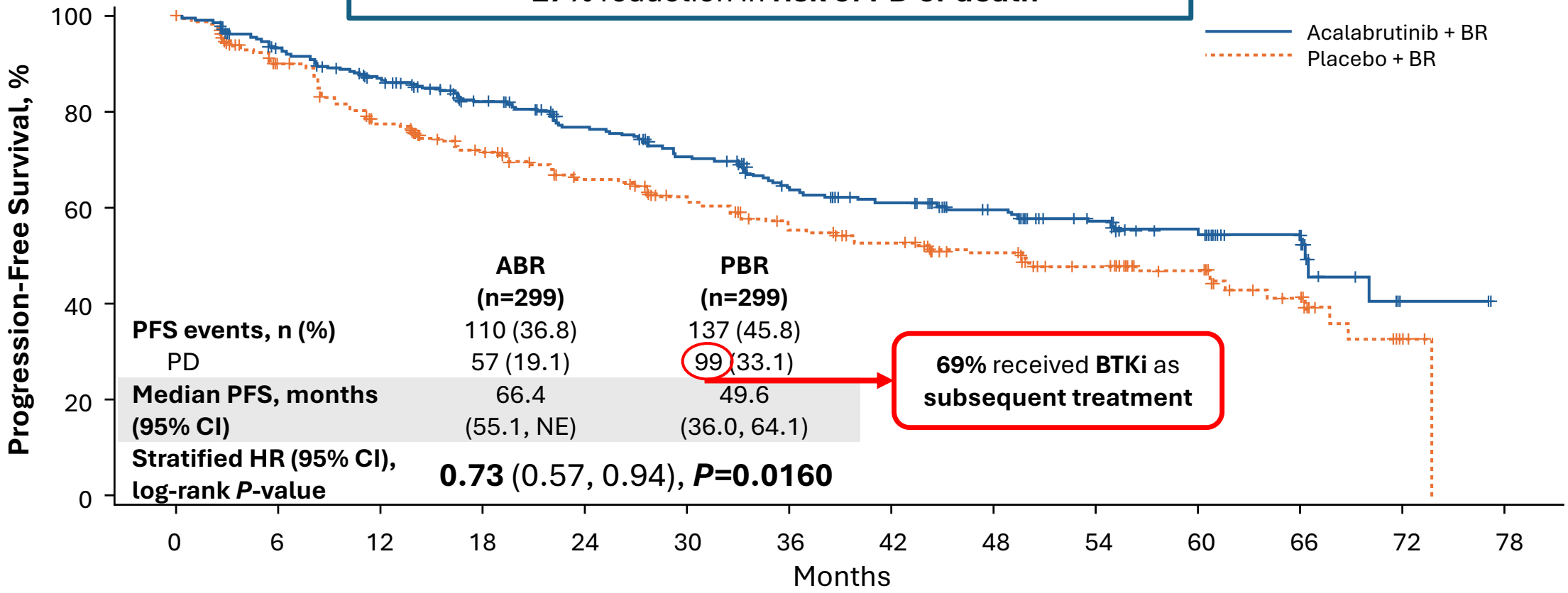
Study Design



[a]Bendamustine 90 mg/m^2 on days 1 and 2. [b]Rituximab 375 mg/m^2 on day 1.
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, orally; PR, partial response.

PFS (primary endpoint) Was Significantly Improved With Acalabrutinib + BR

- **Significant improvement in median PFS by ~17 mo**
  - **27%** reduction in **risk of PD or death**[a]



	ABR (n=299)	PBR (n=299)
PFS events, n (%)	110 (36.8)	137 (45.8)
PD	57 (19.1)	99 (33.1)
Median PFS, months (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
Stratified HR (95% CI), log-rank *P*-value	**0.73** (0.57, 0.94), ***P*=0.0160**	

69% received **BTKi** as **subsequent treatment**

Number at risk

Acala + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

[a]At a median follow-up of 45 months.

ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; NE, not estimable; PBR, placebo + bendamustine + rituximab; PD, progressive disease; PFS, progression-free survival.

Adverse Events of Interest

	Acalabrutinib + BR (n=297)		Placebo + BR (n=297)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Event, n (%)				
Atrial fibrillation	18 (6.1)	11 (3.7)	13 (4.4)	5 (1.7)
Hypertension	36 (12.1)	16 (5.4)	47 (15.8)	25 (8.4)
Major bleeding[a]	7 (2.4)	6 (2.0)	16 (5.4)	10 (3.4)
Infections[b]	232 (78.1)	122 (41.1)	211 (71.0)	101 (34.0)
Second primary malignancies (excluding non-melanoma skin)[b]	29 (9.8)	16 (5.4)	32 (10.8)	20 (6.7)
Median treatment exposure (range), months	29 (0.1, 80.1)		25 (0.03, 76.4)	

[a]Grouping of preferred terms; defined as a hemorrhagic event that is serious, or grade ≥3 in severity, or that is a CNS hemorrhage (any severity grade). [b]Grouping of preferred terms.
BR, bendamustine + rituximab; CNS, central nervous system.

Impact of COVID-19

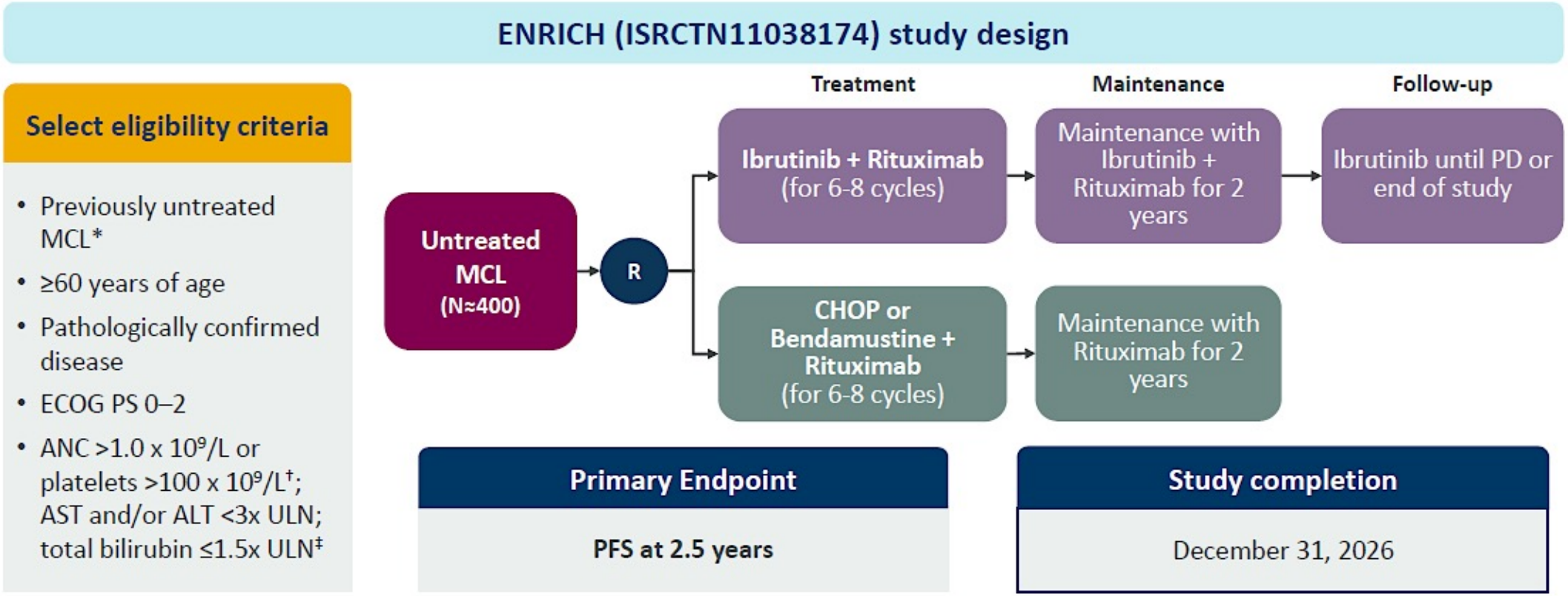
n (%)	COVID-19–related AEs	
	Acalabrutinib + BR (n=297)	Placebo + BR (n=297)
Any AE	121 (40.7)	88 (29.6)
Grade ≥3	60 (20.2)	50 (16.8)
Grade 5	28 (9.4)	20 (6.7)
SAEs	60 (20.2)	52 (17.5)
Grade ≥3	58 (19.5)	48 (16.2)
AE leading to acalabrutinib/ placebo discontinuation	31 (10.4)	19 (6.4)

Data from safety analysis set – main study period.
AE, adverse event; BR, bendamustine + rituximab; COVID-19, coronavirus disease 2019; SAE, serious adverse event.

I-R vs CIT in untreated MCL – ENRICH study

Elderly/Frail Patients

ENRICH: Ibrutinib plus anti-CD20 monoclonal antibody ± venetoclax in older patients with untreated MCL



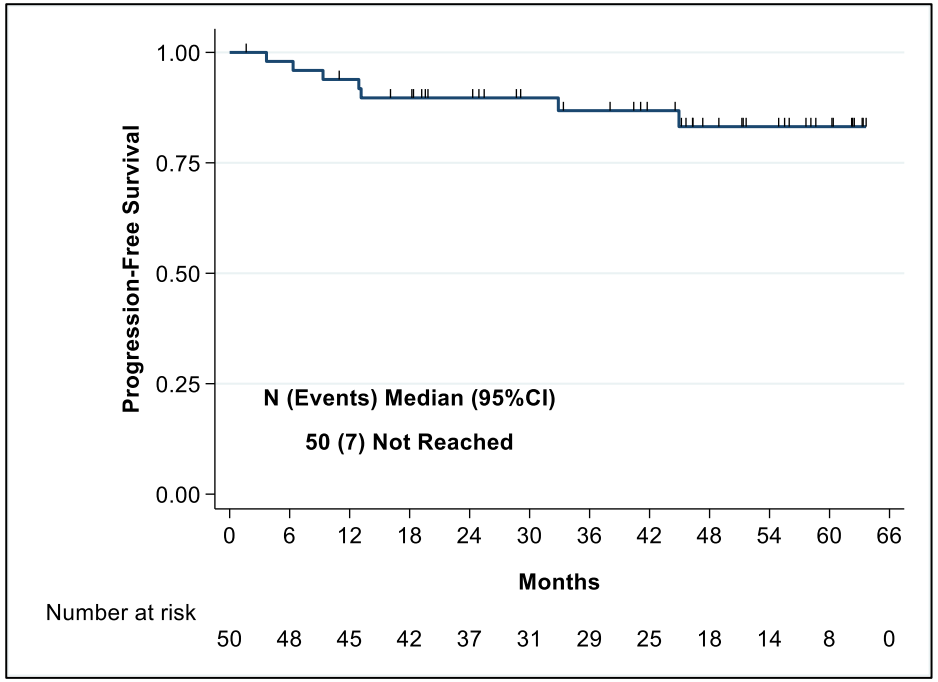
Lewis DJ et al. ASH 2024

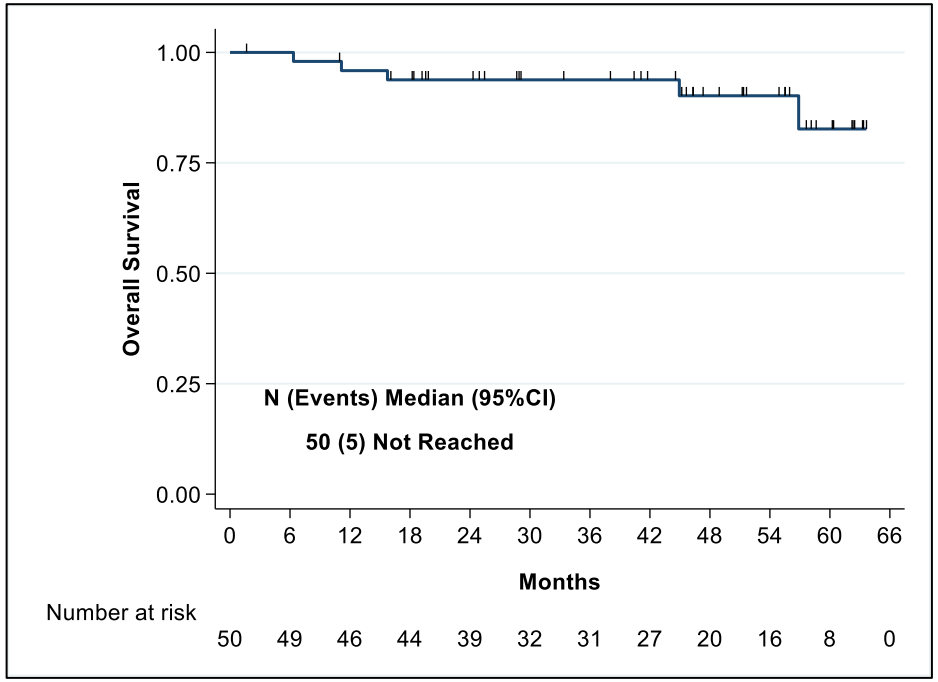
I-R vs CIT in untreated MCL – ENRICH study

- N=397 patients - IR (n=199) and R-chemo (n=198; R-CHOP n=53, BR n=145).
- MFU 47.9 months.
- The PFS with IR was superior to R-chemo, with a hazard ratio (HR) of 0.69, (95% CI 0.52-0.90, p=0.003).
- The 5 y OS for IR is 57.7% compared to 54.5% for R-Chemo, HR = 0.87 (95% CI 0.64-1.18).
- Grade 3 or higher atrial fibrillation was reported in 6.6% of IR and 0.5% of R-chemo participants.
- Quality of life (EORTC QLQ-C30) at mid-treatment was higher for the IR arm compared to R-chemotherapy.

Lewis DJ et al. ASH 2024

Frontline IR in elderly MCL
Time to event outcomes – MFU 45 months





- ORR 96%, CR 71%
- **28/50 patients came off study for various reasons [4 progression, 21 toxicities (10 grade 3 atrial fibrillation) and 3 miscellaneous reasons]**

- **Overall, 17 of 50 (34%) patients developed atrial fibrillation.**
- **Of these 17 patients, nine patients (53%) were without a history of atrial fibrillation**
- **11 (22%) patients had grade 3 atrial fibrillation**

Jain P et al JCO 2022

Frontline AR in elderly MCL-Responses

Response (ITT)	All patients
Week 12 Best response#	N (%)
Evaluable patients*	49
ORR	46/50 (92)
CR	37/50 (74)
PR	9/50 (18)
Best response$	
Evaluable patients	49
ORR	46/50 (92)
CR	46/50 (92)
MRD at LFU (n=32)##	19/32 (60%) MRD negative
Median number of AR cycles to reach CR (range)	3(2-7)

*# Without ITT- ORR/CR was 94%/76% while ORR/CR with PET-CT scan alone was 93%/78% at 12 weeks;*49 evaluable (1 patient discontinued treatment within first 3 cycles for grade 3 adverse events) and 3 were non-responders; $ Best response without ITT – ORR/CR was 94% each;## 13/32 were MRD negative (all CMR)*

Jain P et al. ASH 2024.

First line - ZVO combination in *TP53* mutated MCL

- **Z+V+O - obinu (up to 8 cycles), Ven start at C3**
- **N=25, untreated TP53 mutated MCL**
- **ORR 76% and CR 68% at C3 and best ORR 96% (CR 88%)**
- **MFU – 28 months, 5 PD, 4 deaths (responders)**
- **11 pts completed 24 cycles, 80% uMRD Dced Rx**
- **2 year PFS 72%, 2 year OS 76%**
- **MC AE were diarrhea, COVID, neutropenia (16% gr 3), infusion reaction**

Kumar A et al Blood 2024

Discussion Questions

- Regulatory and reimbursement issues aside, which first-line therapy would you generally recommend for an otherwise healthy 65-year-old patient with Stage IV DLBCL? How does molecular subtype affect your decision-making?

- For which patients with DLBCL do you use loncastuximab tesirine? What have you observed in terms of efficacy and tolerability with this agent?

Discussion Questions

- In general, what is your usual first-line therapy for older and younger patients with MCL? How, if at all, does your approach differ based on patient comorbidities and PS?

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey you will shortly receive by email.

To Claim CME, NCPD or ACPE Credit
In-person attendees: Please refer to the program syllabus for the CME credit link or QR code.
Online/Zoom attendees: The CME credit link is posted in the chat room.