The Implications of Recent Datasets for the Current and Future Management of Gastrointestinal Cancers — An ESMO Congress 2024 Review

A CME/MOC-Accredited Live Webinar

Tuesday, October 15, 2024
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD
Philip A Philip, MD, PhD, FRCP

Moderator

Neil Love, MD

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Faculty

Tanios Bekaii-Saab, MD
David F and Margaret T Grohne Professor of Novel Therapeutics for Cancer Research I
Chair and Consultant, Division of Hematology and Medical Oncology
Co-Leader, Advanced Clinical and Translational Science Program
Mayo Clinic Comprehensive Cancer Center (All Sites)
Professor, Mayo Clinic College of Medicine and Science
Mayo Clinic in Arizona
Phoenix, Arizona

Philip A Philip, MD, PhD, FRCP
Professor of Oncology and Pharmacology
Leader, GI and Neuroendocrine Oncology
Henry Ford Cancer Institute
Wayne State University
Detroit, Michigan

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Commercial Support

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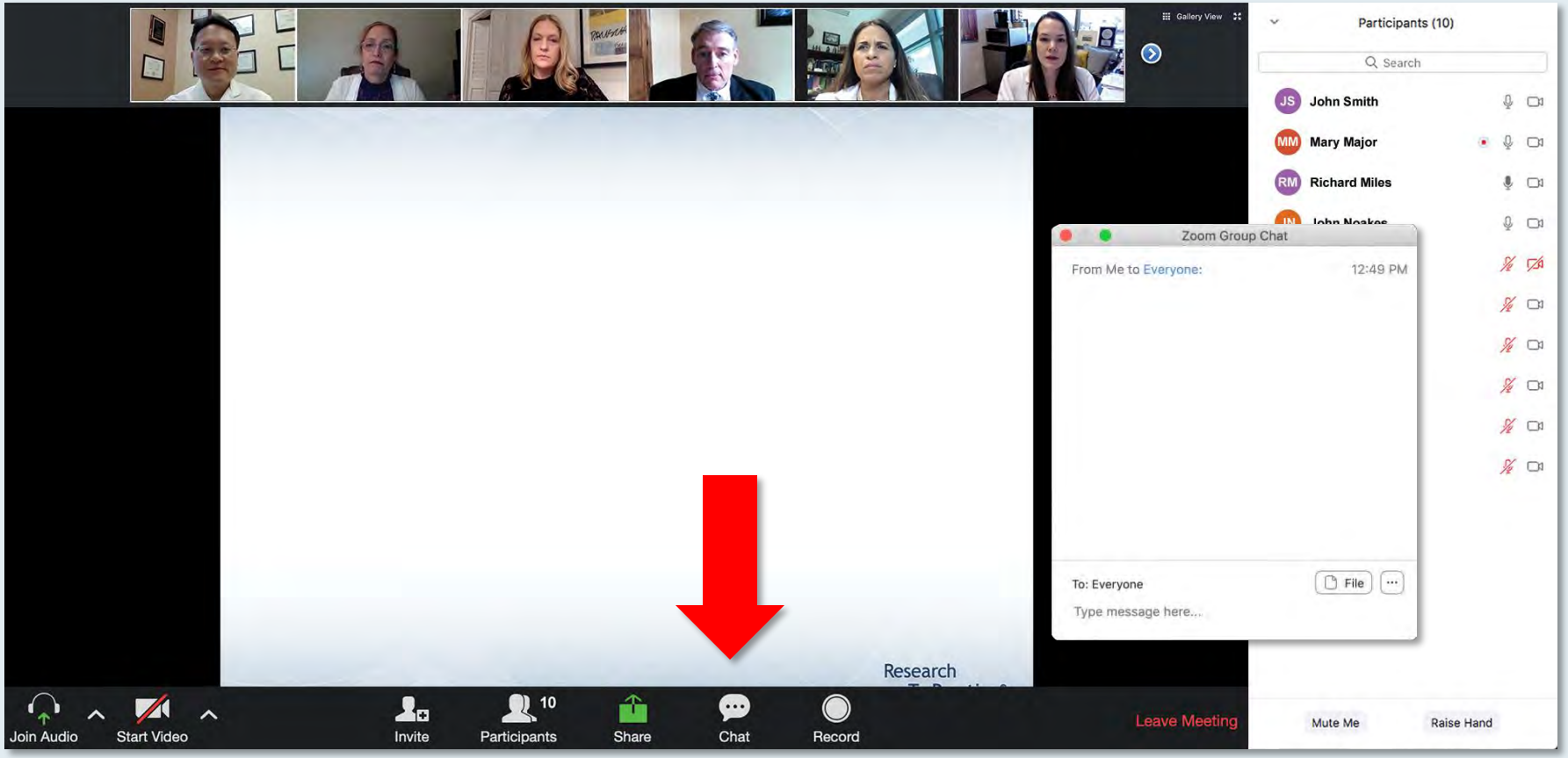

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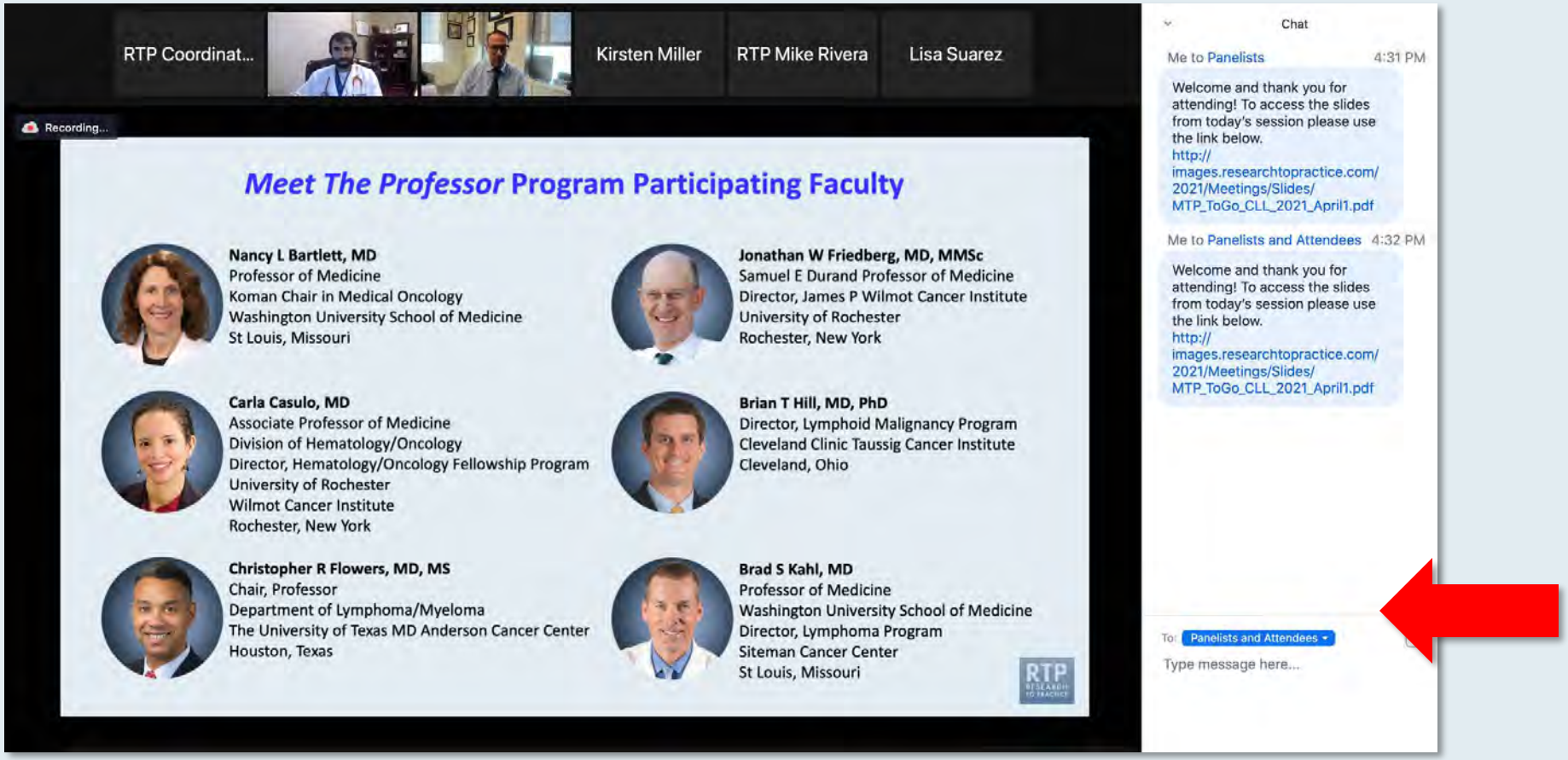

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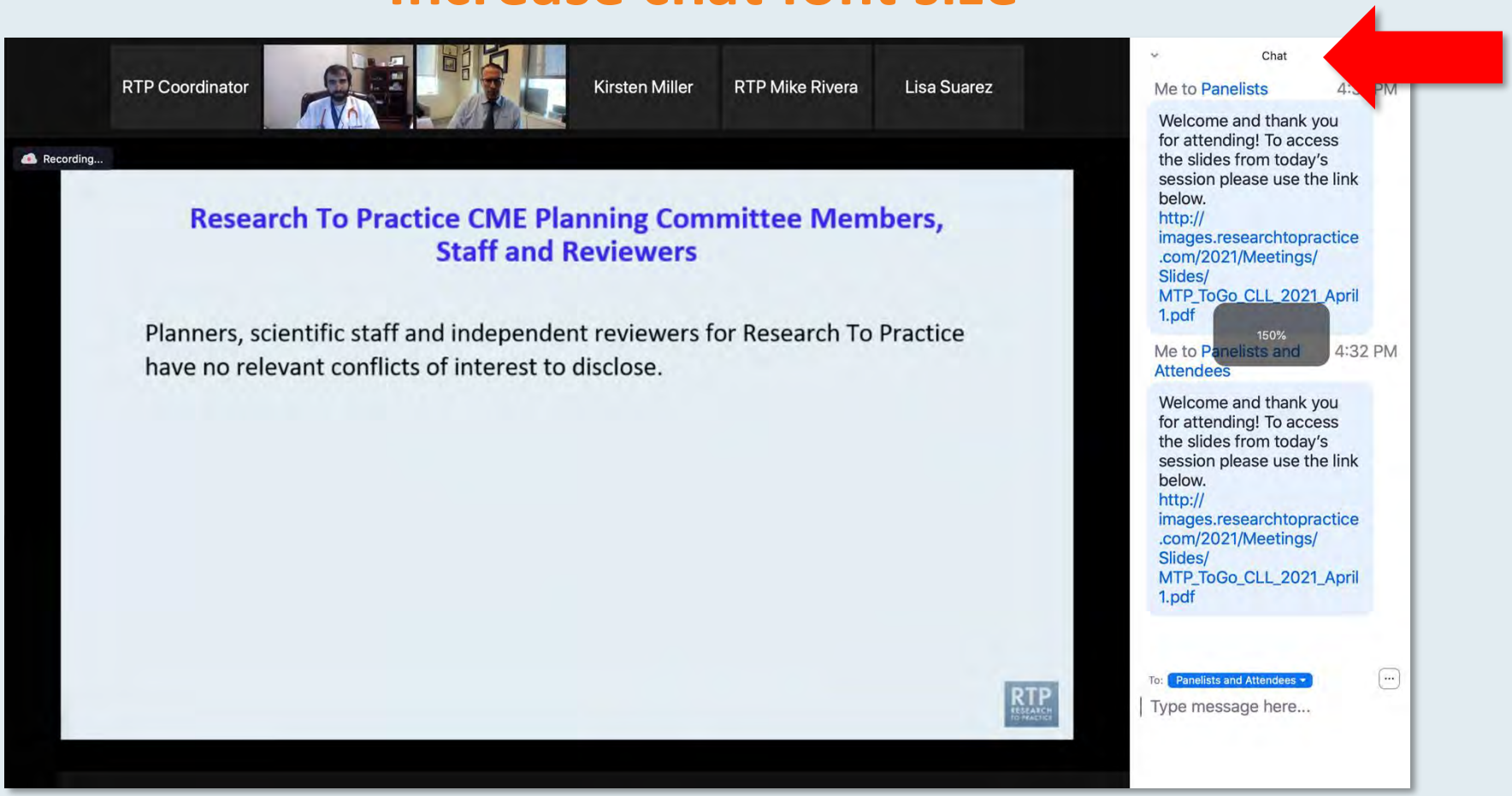

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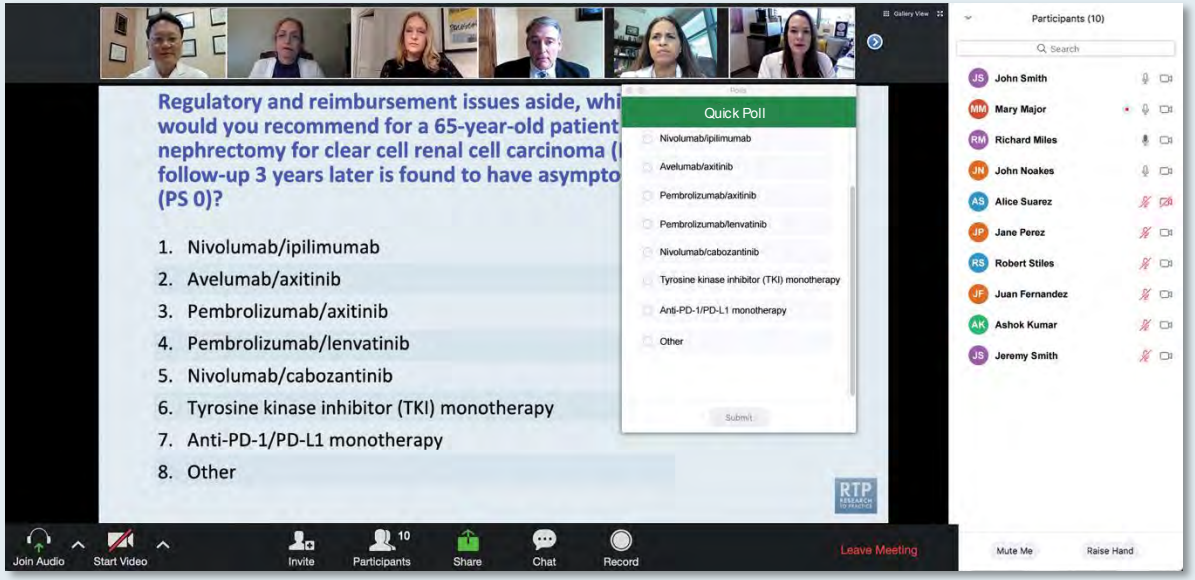

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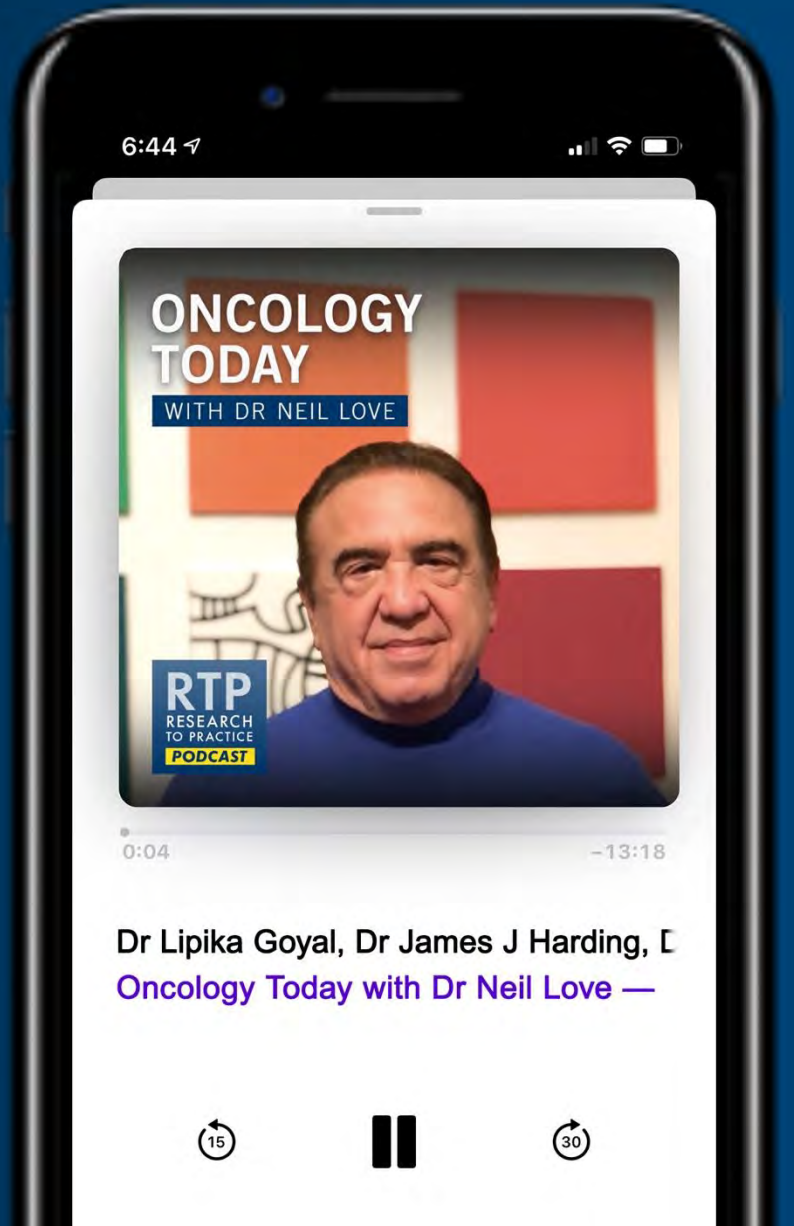

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Prostate Cancer

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Lung Cancer Update: Antibody-Drug Conjugates and New Approaches

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Gynecologic Cancers

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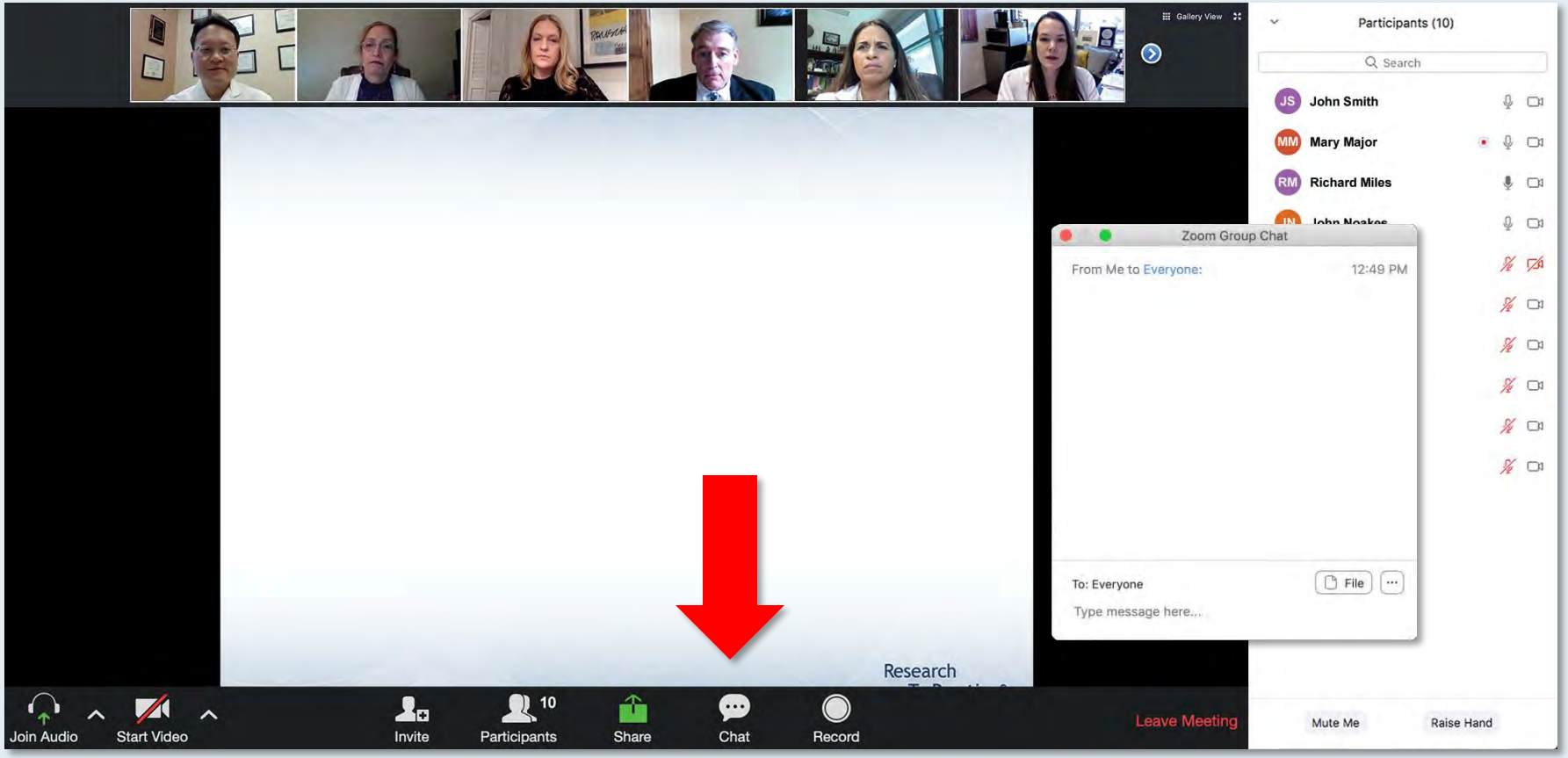

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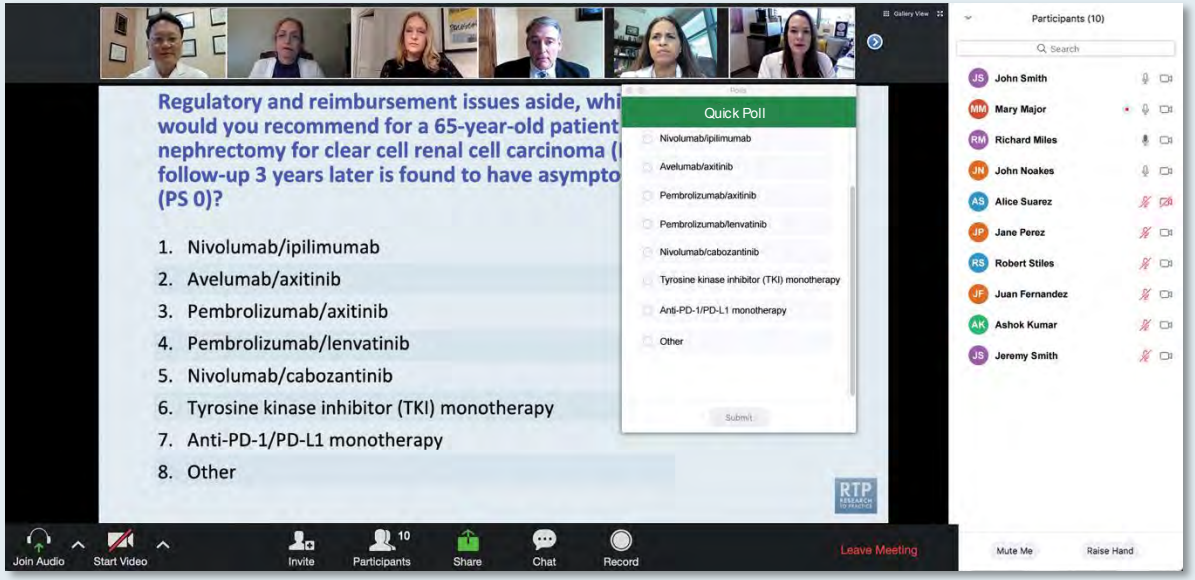

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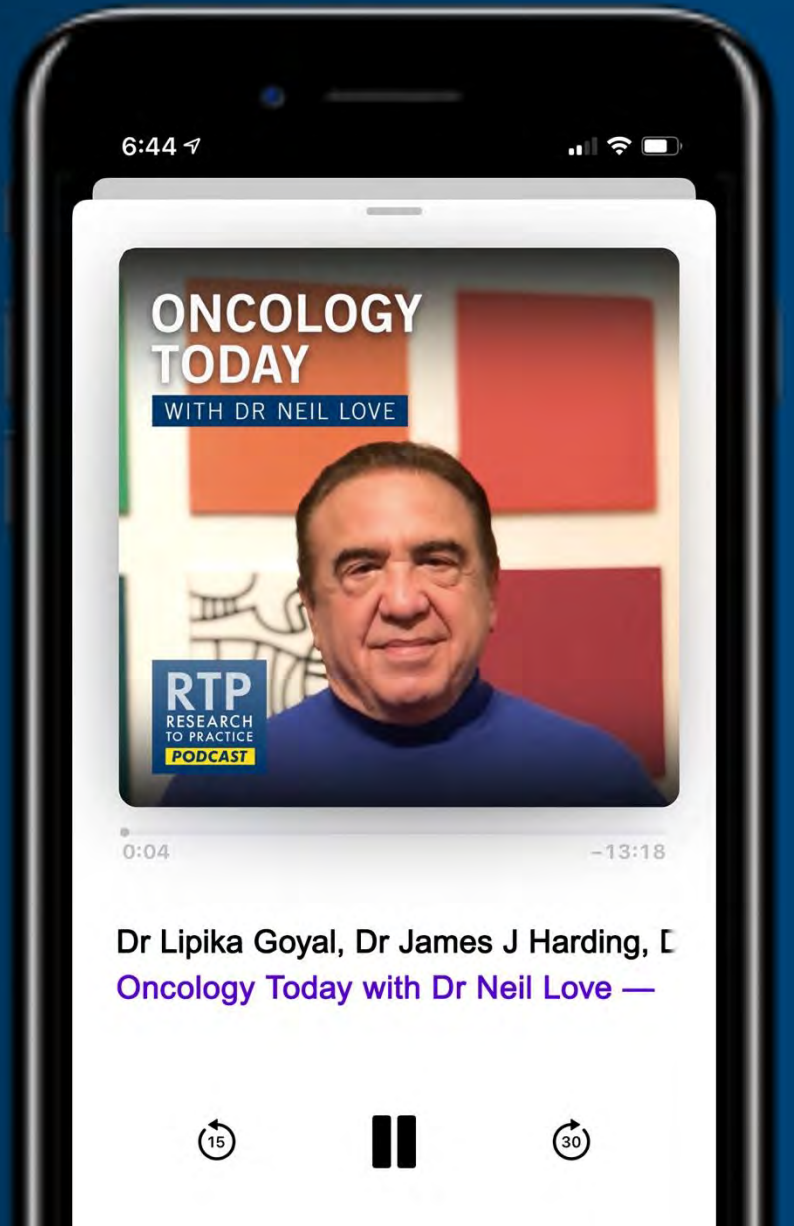

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Module 2: Gastroesophageal Cancers, Hepatocellular Cancer and Biliary Tract Cancers – Dr Bekaii-Saab

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Agenda

Module 1: Colorectal Cancer, Anal Cancer and Pancreatic Cancer – Dr Philip

Module 2: Gastroesophageal Cancers, Hepatocellular Cancer and Biliary Tract Cancers – Dr Bekaii-Saab

Post-ESMO 2024

Philip Agop Philip, MD, PhD, FRCP

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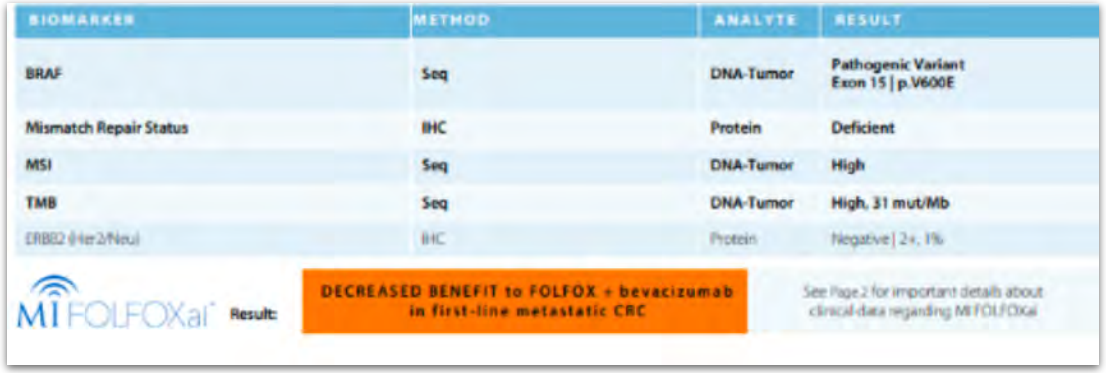
Detroit, Michigan
USA

Dr. Philip - Case #1: Colorectal Cancer

- 76-year-old male with good health
- Feb 2021 –
  - Left hemicolectomy for acute bowl obstruction
    - Mucinous adenocarcinoma
    - pT3pN1aM0 (1/15 LN)
    - MSI-high, TMB 31, *BRAF*^{V600E}, PD-L1 = 0
  - Post-op plasma ctDNA = 0
- April to July 2021–
  - Adjuvant CAPOX x 4 cycles



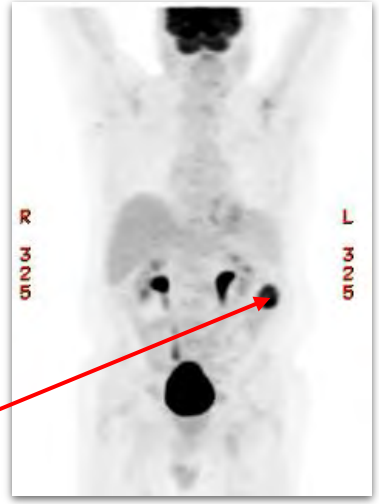
BIOMARKER	METHOD	ANALYTE	RESULT
BRAF	Seq	DNA-Tumor	Pathogenic Variant Exon 15 | p.V600E
Mismatch Repair Status	IHC	Protein	Deficient
MSI	Seq	DNA-Tumor	High
TMB	Seq	DNA-Tumor	High, 31 mut/Mb
ERBB2 (Her2/Neu)	IHC	Protein	Negative | 2+, 1%

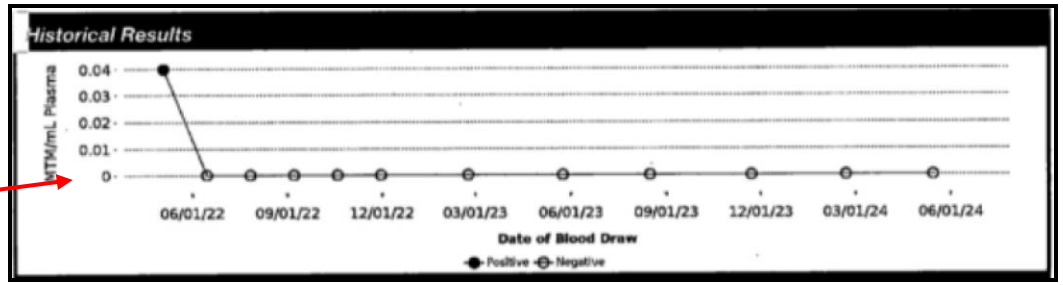
MI FOLFOXai® Result: DECREASED BENEFIT to FOLFOX + bevacizumab in first-line metastatic CRC

See Page 2 for important details about clinical data regarding MI FOLFOXai

Dr. Philip - Case #1 Colorectal Cancer

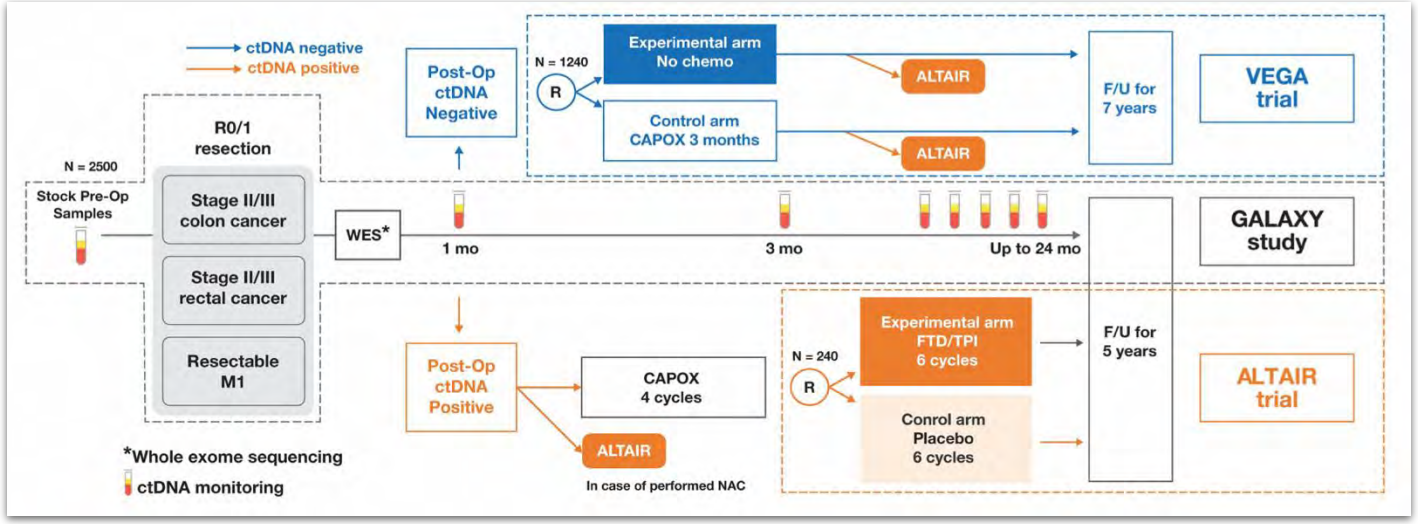
- Sept 2021 –
  - ctDNA positive
- Dec 2021 –
  - Left flank pain + rising CEA
  - Left flank mass biopsy = adenoc
  - MRI shows peritoneal carcinomatosis
  - Plasma ctDNA = positive
- Feb 2022 –
  - Ipilimumab and nivolumab
  - Quick normalization of the plasma ctDNA
- June 2022 –
  - Hand arthropathy grade 2
    - Maintained on pred 5 mg QD & hydroxychloroquine
- Feb 2024 –
  - Off any treatment
  - Radiographic and ctDNA complete response



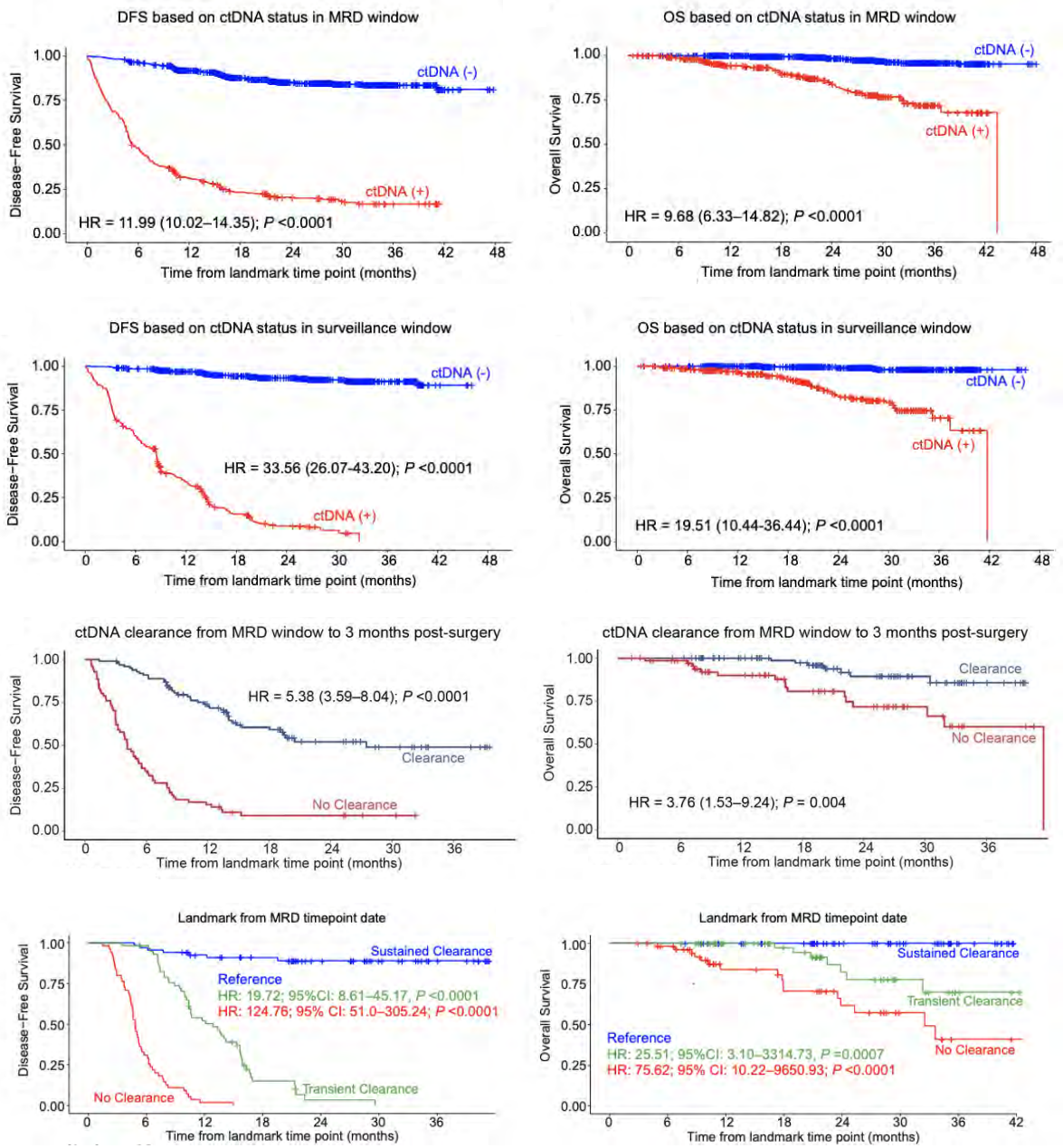


Association of ctDNA-based MRD detection and MRD clearance with short-term overall survival in patients with resectable colorectal cancer: Updated analysis of CIRCULATE-Japan GALAXY

- Prospective observational study
- Tumor informed MRD assay at 1, 3, 6, 9, 12, 18, & 24 months
- MRD window post surgery = 2-10 weeks
- Median follow up time = 23 months
- Stage I 10%, stage III/IV > 50%
  - T3-T4 73%
  - N1-N2 46%
- Adjuvant therapy received in 42%



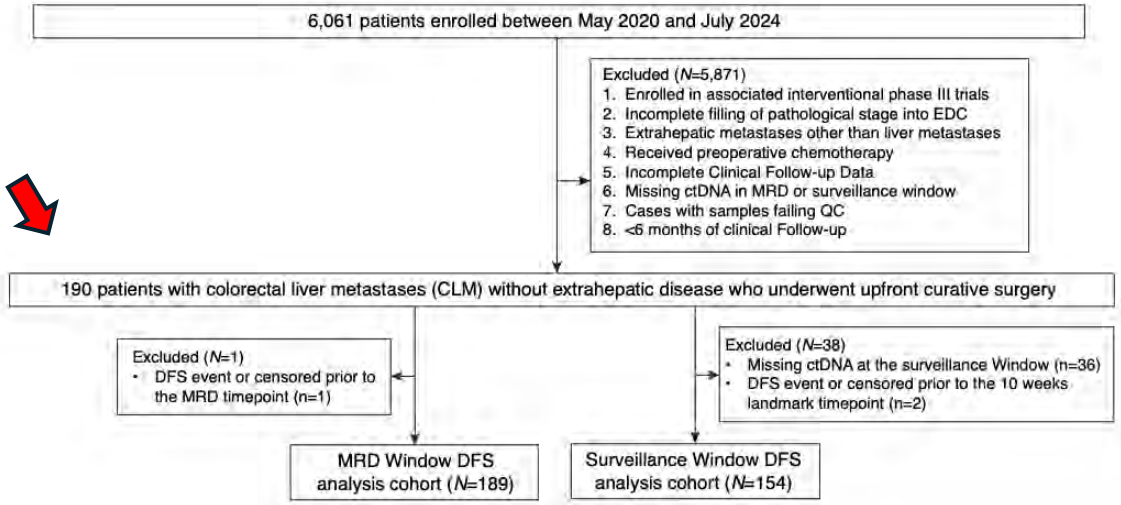
Nagata J et al. ESMO 2024;Abstract 553P



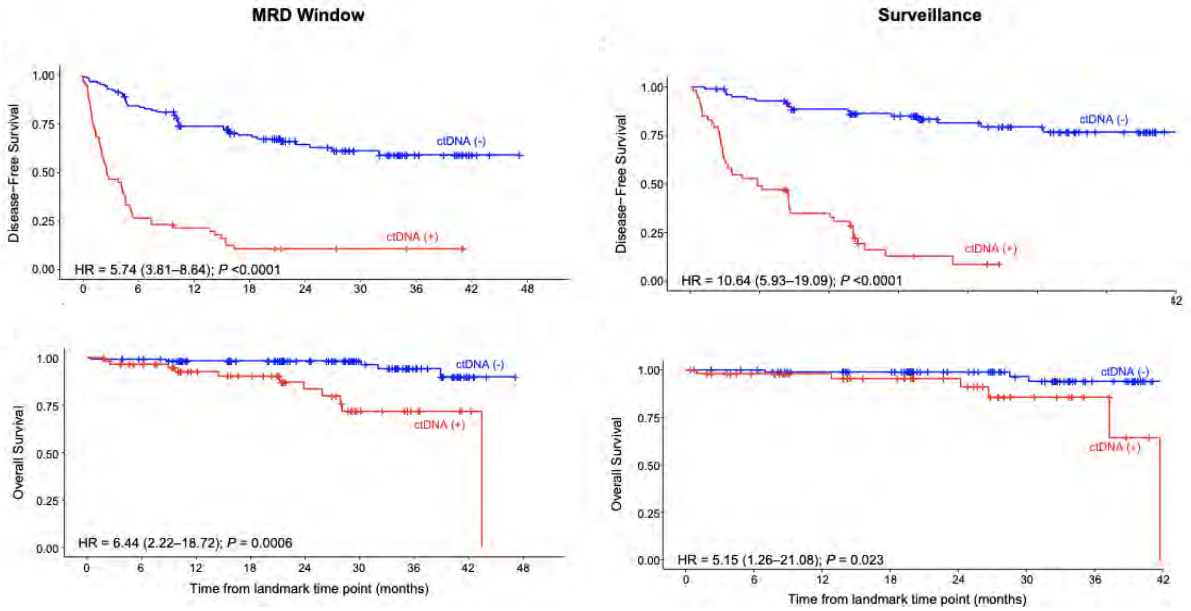
Results

- MRD positivity was significantly associated with poorer 24- and 36-month OS and DFS
- ctDNA clearance was significantly associated with superior DFS and OS
- 9.3% of MRD-negative patients developed molecular recurrence of whom > 80% recurred by 12 months and > 95% recurred by 18 months after surgery

Survival benefit of adjuvant chemotherapy based on molecular residual disease detection in resected colorectal liver metastases: Subgroup analysis from CIRCULATE-Japan GALAXY

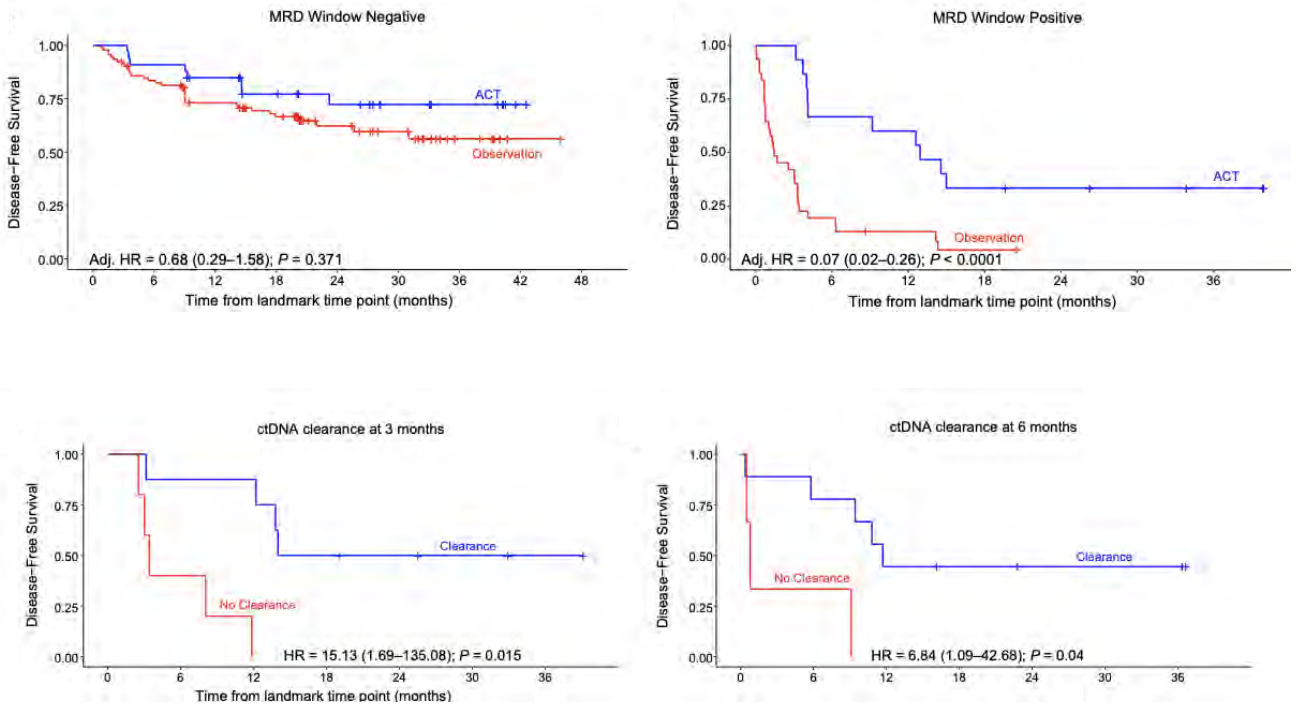


ctDNA positivity in the MRD window as well as during surveillance was associated with significantly inferior DFS/OS



Kataoka K et al. ESMO 2024;Abstract 558P

Survival benefit of adjuvant chemotherapy based on molecular residual disease detection in resected colorectal liver metastases: Subgroup analysis from CIRCULATE-Japan GALAXY (continued)



Potential benefit of adjuvant therapy in MRD positive subgroup but no statistical benefit in the MRD negative subgroup

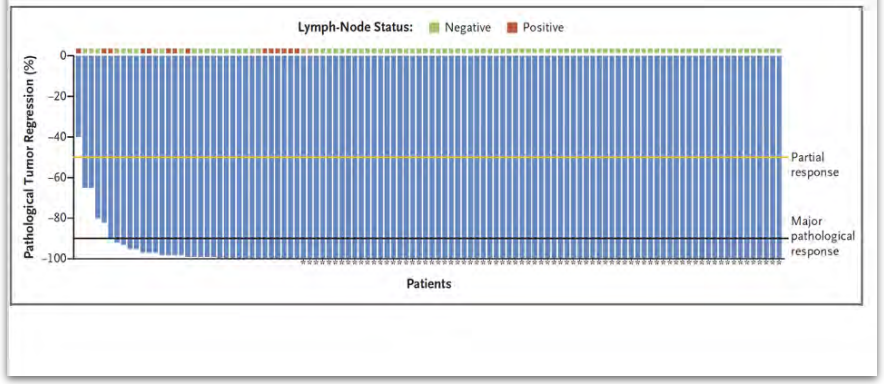
Kataoka K et al. ESMO 2024;Abstract 558P

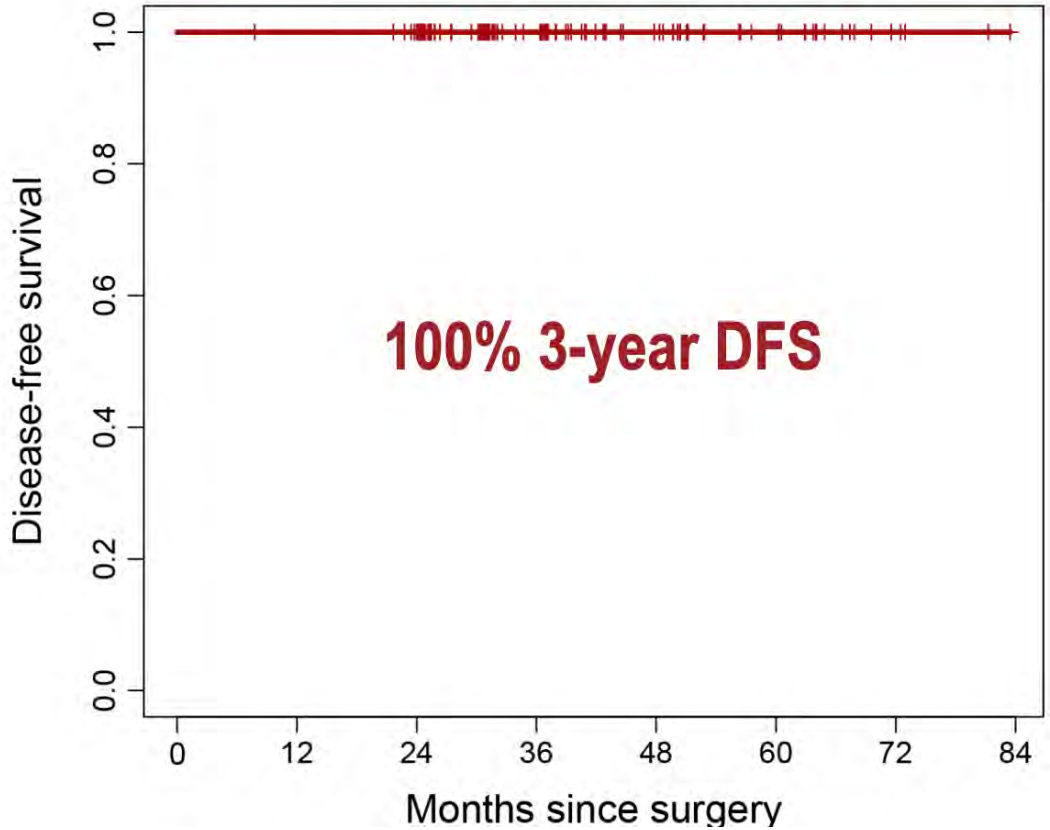
Neoadjuvant immunotherapy in locally advanced MMR-deficient colon cancer: 3-year disease-free survival from NICHE-2

98% pathologic response

95% Major pathologic response (<10% residual viable tumor)

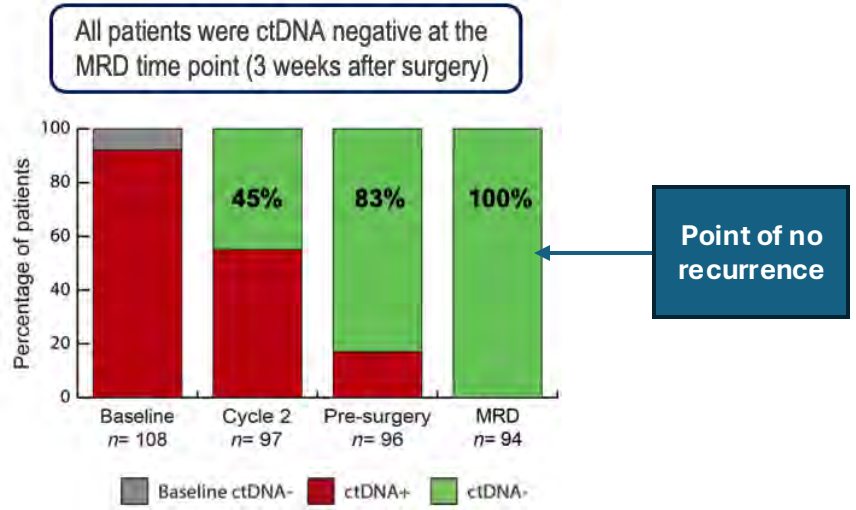
68% pathologic CR



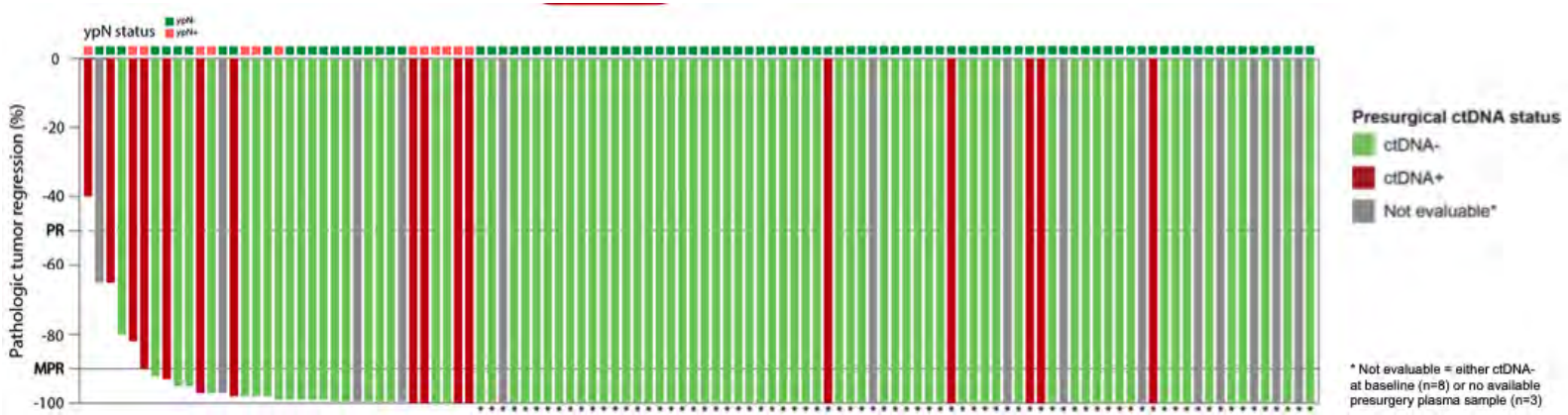


Chalabi M et al. ESMO 2024;Abstract LBA24

• NICHE-2: ctDNA kinetics and outcome

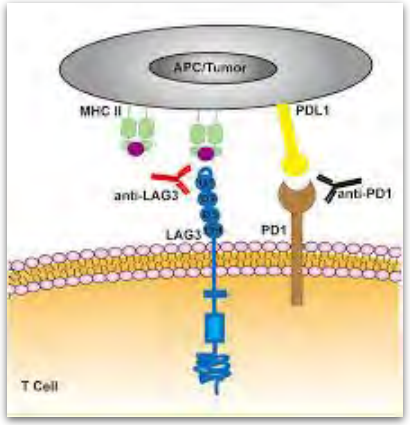


- Baseline detection in 92% of patients
- 45% of patients cleared ctDNA after ONLY one cycle
- Patients who clear ctDNA stay ctDNA negative

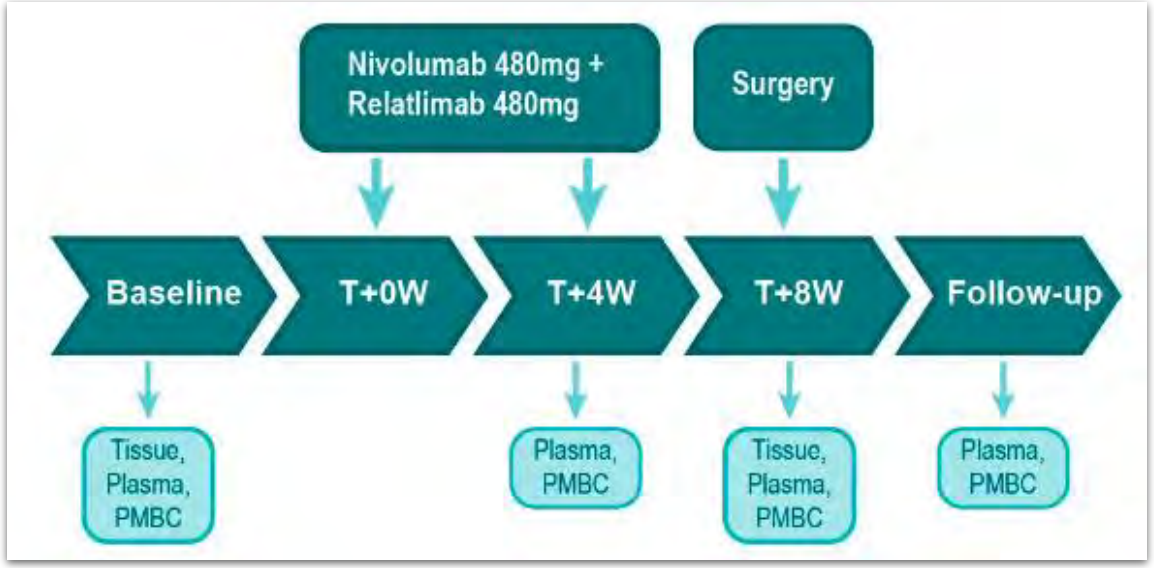


Chalabi M et al. ESMO 2024;Abstract LBA24

Neoadjuvant nivolumab (nivo) plus anti-LAG3 relatlimab (rela) in MMR-deficient colon cancer: Results of the NICHE-3 study



Age	65 (21-85)
Radiographic T2 T3/T3-4a T4a T4b	 2% 31% 44% 24%
Radiographic cN0 cN+	 37% 63%
Lynch	19%



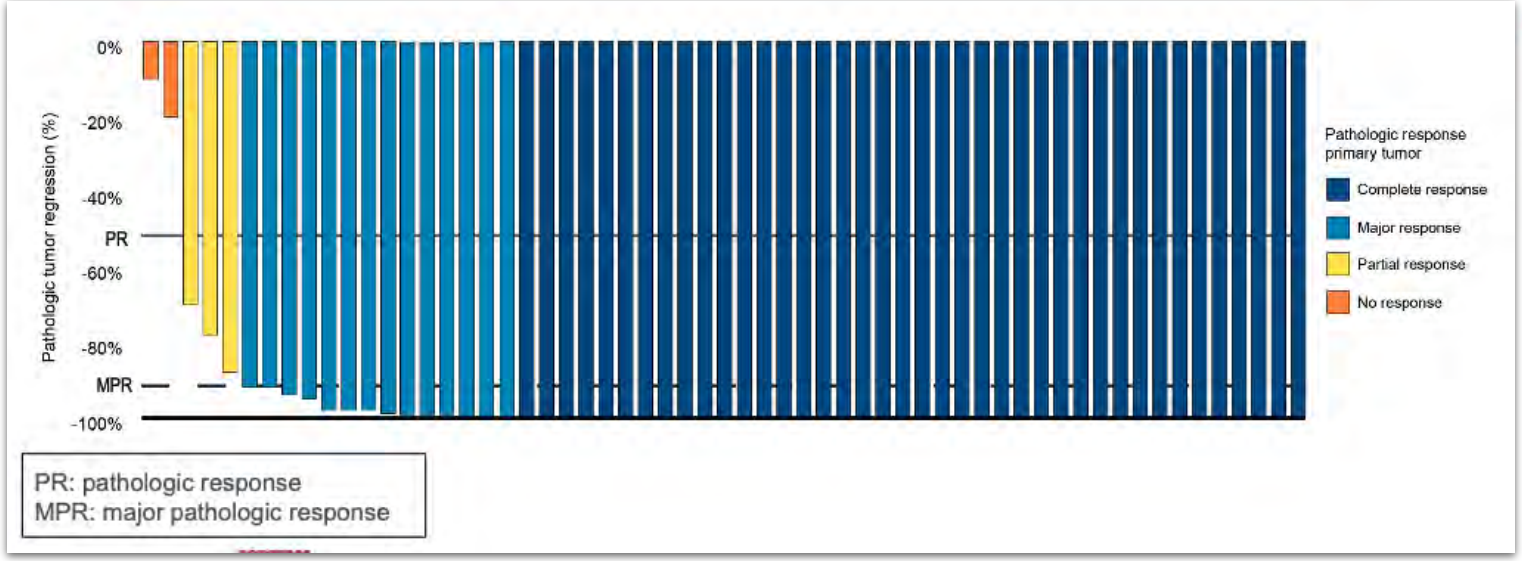
Primary Endpoint = path response rate (≤50% residual disease)

De Gooyer PG et al. ESMO 2024;Abstract 503O

NICHE-3 study results

Primary endpoint was met with a pathologic response observed in 57/59 (97%) patients

Of which **92% major** pathologic responses and **68% pathologic complete responses**



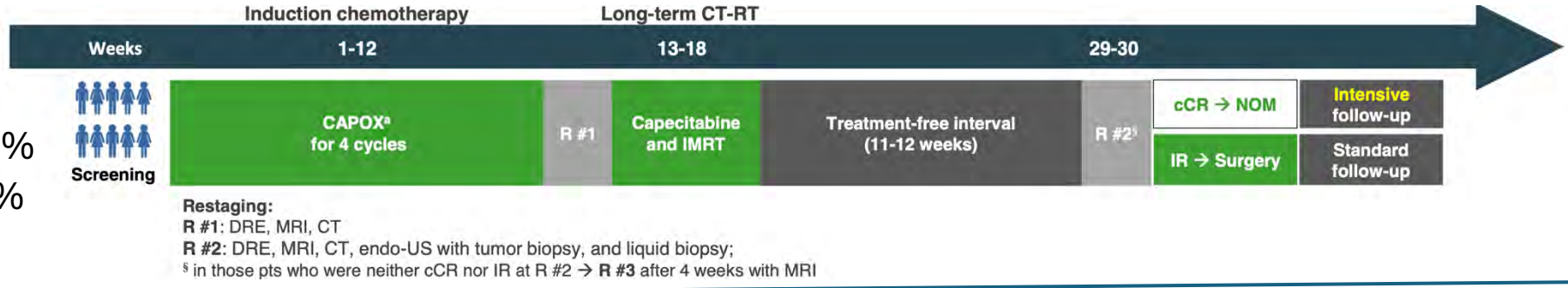
Immune-related adverse events (*n* = 59)	*n* (%)
Any grade irAE	47 (80%)
Grade 3-4	**6 (10%)**

Immune-related adverse events (*n* = 59)	Grade 3	Grade 4
Colitis	2 (3%)	
Hepatitis	2 (3%)	1 (2%)
Thyroid dysfunction	1 (2%)	

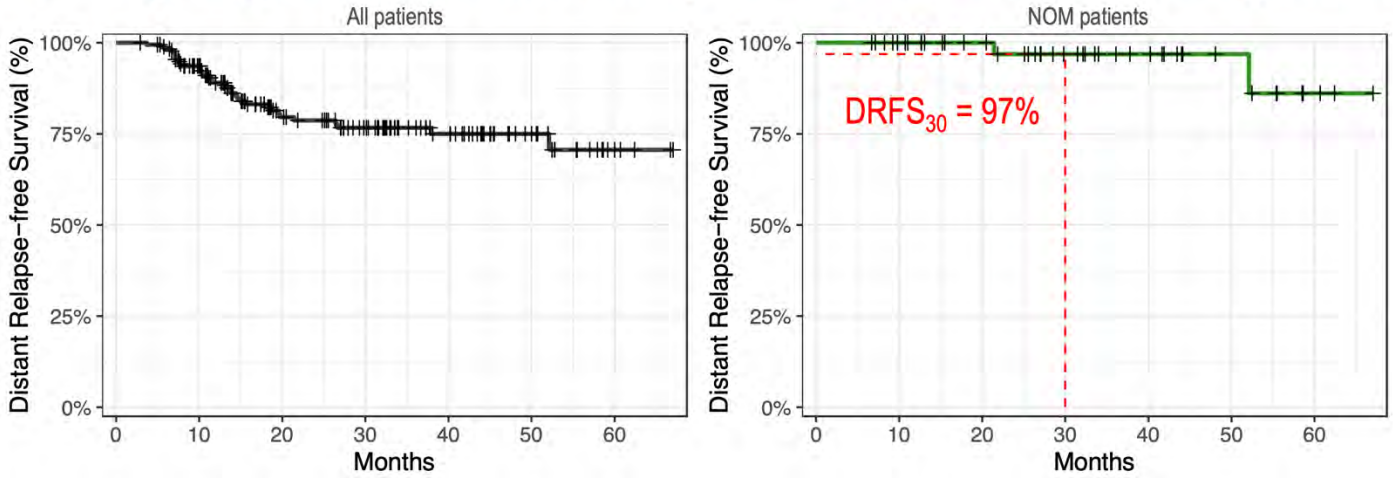
De Gooyer PG et al. ESMO 2024;Abstract 503O

Total neoadjuvant treatment (TNT) with non-operative management (NOM) for proficient mismatch repair locally advanced rectal cancer (pMMR LARC): First results of NO-CUT trial

N = 180
Mid 59%, Low 41%
cT3 74%, cT4 18%
sII 11%, sIII 89%



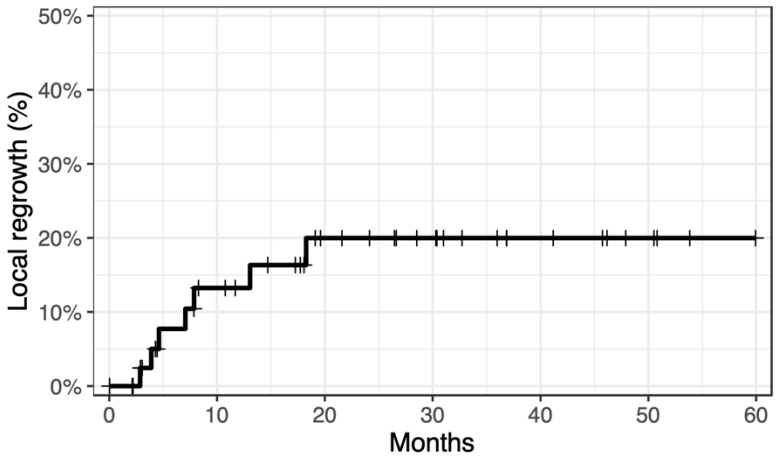
Primary Objective: Distant Relapse-Free Survival in NOM patients



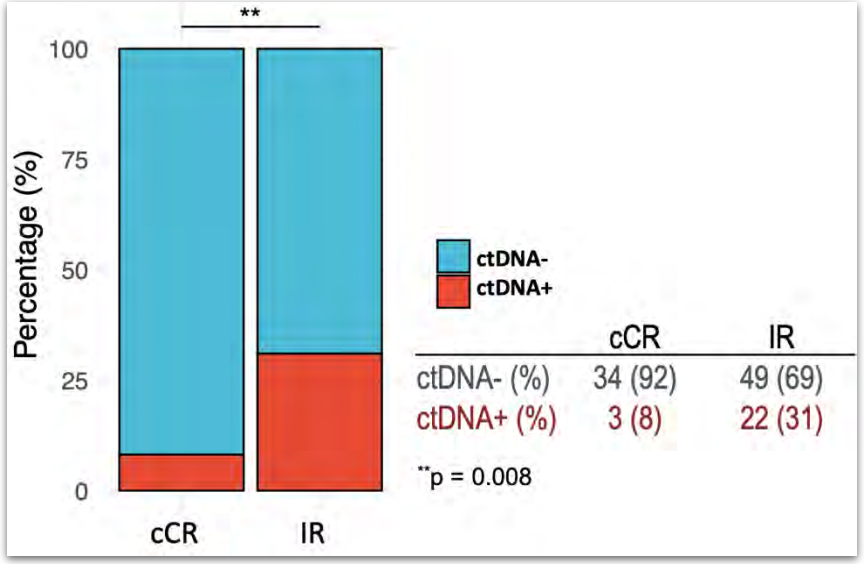
Amatu A et al. ESMO 2024;Abstract 509O

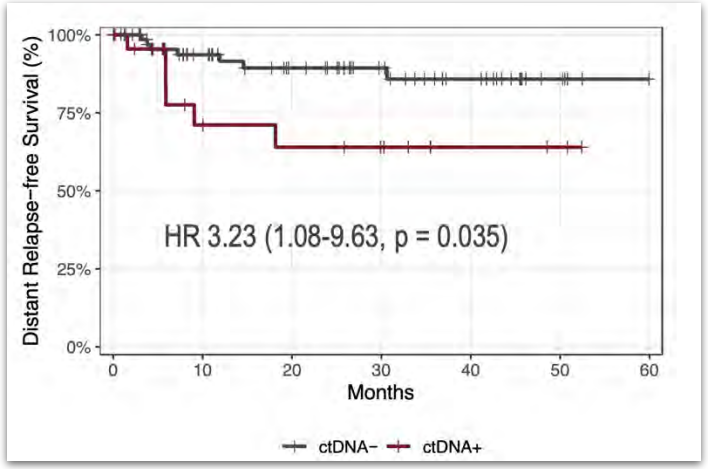
NO-CUT trial: secondary analyses

		cCR (%)	IR (%)	p-value
Number of patients		46 (26)	134 (74)	-
Tumor location	Low	26 (36)	47 (64)	0.017
	Medium	20 (19)	87 (81)	
Clinical T stage	T1	2 (100)	0 (0)	0.004
	T2	5 (39)	8 (61)	
	T3	37 (28)	96 (72)	
	T4	2 (6)	30 (94)	
Clinical TNM stage	II	9 (45)	11 (55)	0.065
	III	37 (23)	123 (77)	



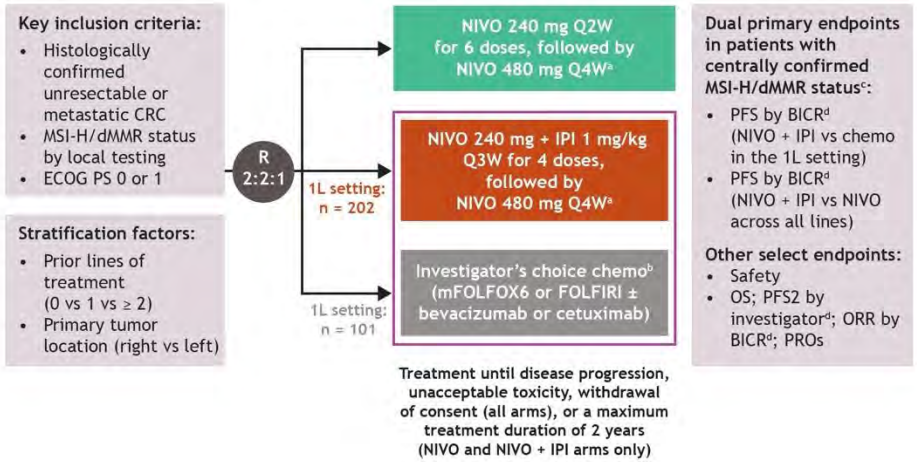
- **Organ preservation rate was 85% (39/46)**
- All patients with Local Regrowth (LR) underwent rescue surgery, 42% (3/7) sphincter sparing
- All LR occurred between 4 and 18 months

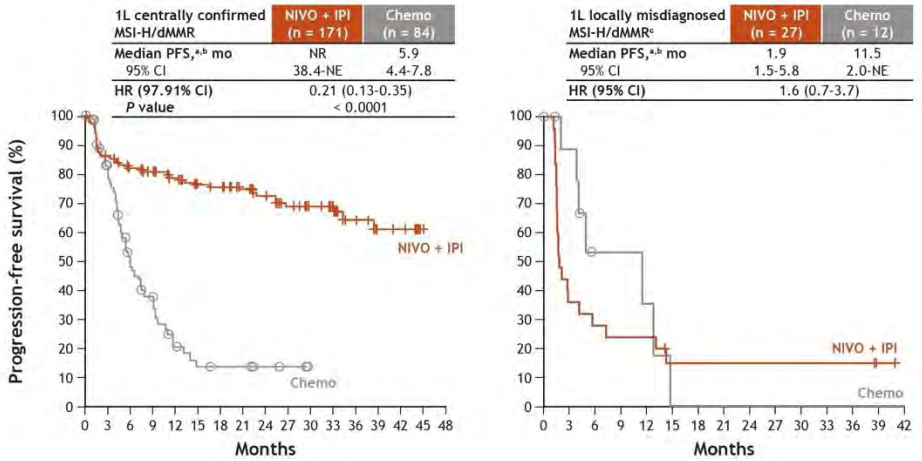




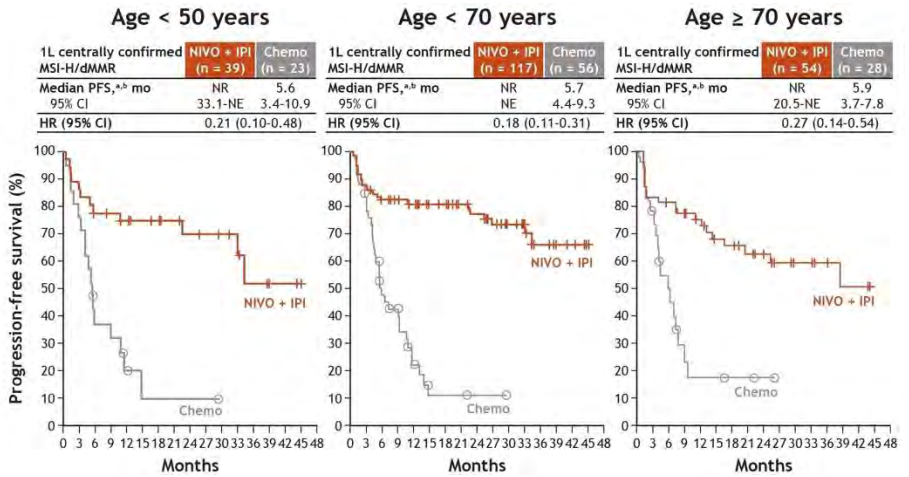
Amatu A et al. ESMO 2024;Abstract 509O

Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Subgroup efficacy and expanded safety analyses from CheckMate 8HW





1L all treated patients, n/N (%)	NIVO + IPI		Chemo	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Age				
< 70 years	112/140 (80)	32/140 (23)	55/58 (95)	27/58 (47)
≥ 70 years	48/60 (80)	14/60 (23)	28/30 (93)	15/30 (50)
Sex				
Male	74/94 (79)	21/94 (22)	42/43 (98)	19/43 (44)
Female	86/106 (81)	25/106 (24)	41/45 (91)	23/45 (51)

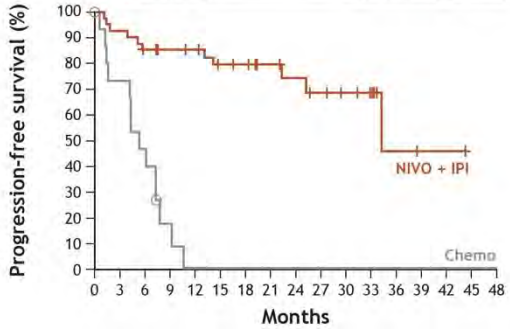


André T et al. ESMO 2024;Abstract 541P

CheckMate 8HW: Results in subgroups based on molecular markers and liver involvement

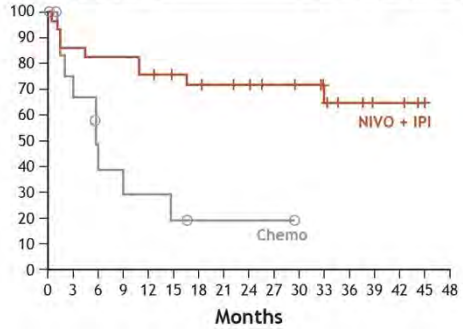
BRAF/KRAS/NRAS wild-type

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 41)	Chemo (n = 17)
Median PFS,[a,b] mo	34.3	5.4
95% CI	25.3-NE	1.5-7.4
HR (95% CI)	0.08 (0.03-0.23)	



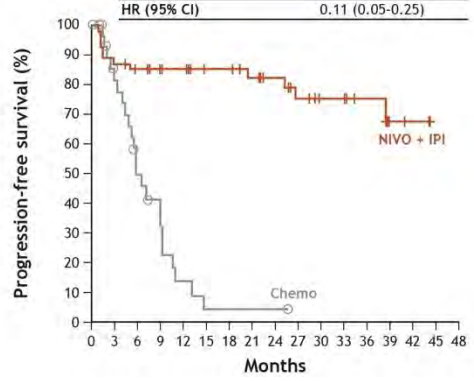
KRAS/NRAS mutant

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 30)	Chemo (n = 15)
Median PFS,[a,b] mo	NR	5.7
95% CI	33.1-NE	1.4-14.8
HR (95% CI)	0.24 (0.09-06.63)	



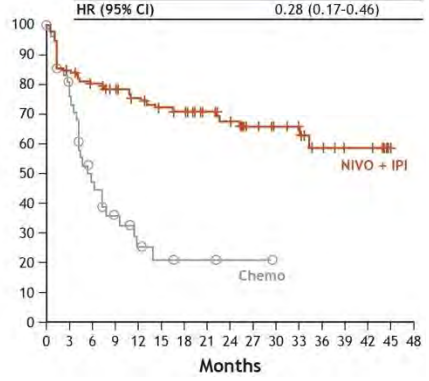
Liver metastases: Yes

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 55)	Chemo (n = 32)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.3-9.2
HR (95% CI)	0.11 (0.05-0.25)	



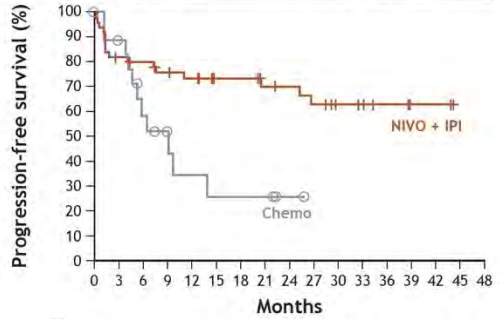
Liver metastases: No

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 114)	Chemo (n = 52)
Median PFS,[a,b] mo	NR	5.4
95% CI	34.3-NE	4.2-9.6
HR (95% CI)	0.28 (0.17-0.46)	



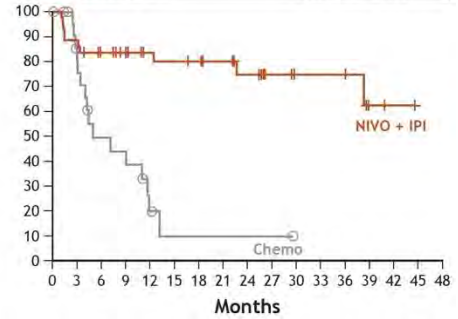
BRAF mutant

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 50)	Chemo (n = 22)
Median PFS,[a,b] mo	NR	9.2
95% CI	25.3-NE	4.2-NE
HR (95% CI)	0.37 (0.17-0.81)	



BRAF/KRAS/NRAS unknown

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 46)	Chemo (n = 28)
Median PFS,[a,b] mo	NR	4.9
95% CI	38.4-NE	3.4-11.6
HR (95% CI)	0.17 (0.07-0.41)	



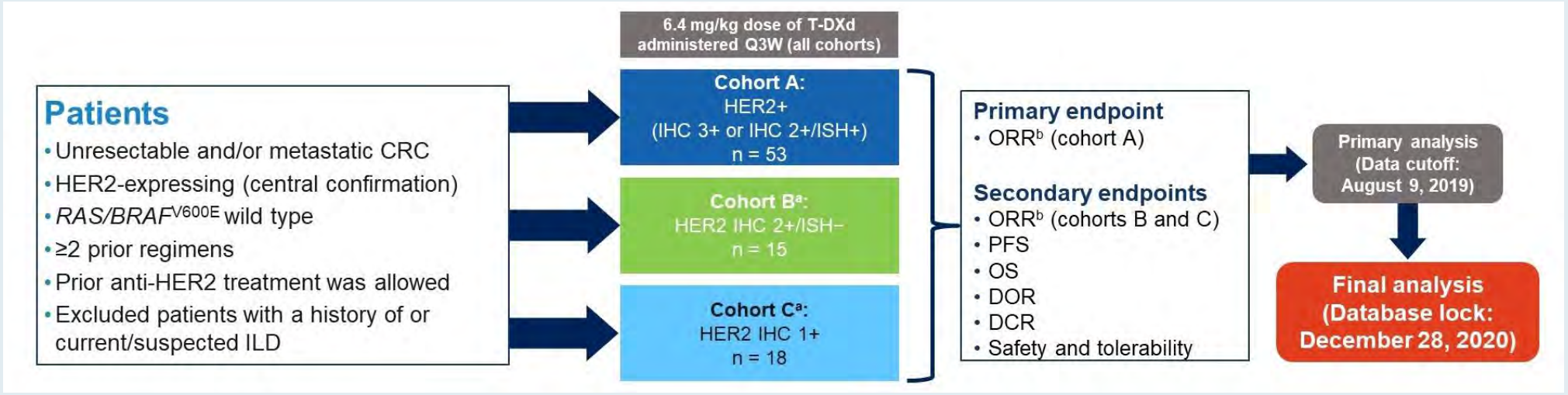
1L all treated patients, n (%)	NIVO + IPI (n = 200) Any grade	NIVO + IPI (n = 200) Grade 3/4	Chemo (n = 88) Any grade	Chemo (n = 88) Grade 3/4
TRAEs,[a]				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths	2 (1)[b]		0 (0)[c]	
TRAEs occurring in ≥ 10% of patients[a]				
Pruritus	45 (23)	0	4 (5)	0
Diarrhea	42 (21)	2 (1)	45 (51)	4 (5)
Hypothyroidism	32 (16)	2 (1)	0	0
Asthenia	28 (14)	2 (1)	31 (35)	5 (6)
Fatigue	26 (13)	1 (< 1)	12 (14)	0
Rash	21 (11)	2 (1)	7 (8)	1 (1)
ALT increased	20 (10)	3 (2)	3 (3)	0
Adrenal insufficiency	20 (10)	6 (3)	0	0
Nausea	10 (5)	0	41 (47)	2 (2)
Decreased appetite	10 (5)	1 (< 1)	20 (23)	1 (1)
Anemia	5 (3)	0	14 (16)	3 (3)
Vomiting	4 (2)	0	18 (20)	1 (1)
Neutropenia	3 (2)	0	19 (22)	9 (10)
Alopecia	3 (2)	0	10 (11)	0
Stomatitis	1 (< 1)	0	11 (13)	0
Neutrophil count decreased	1 (< 1)	1 (< 1)	14 (16)	6 (7)
Peripheral neuropathy	0	0	12 (14)	1 (1)

André T et al. ESMO 2024;Abstract 541P

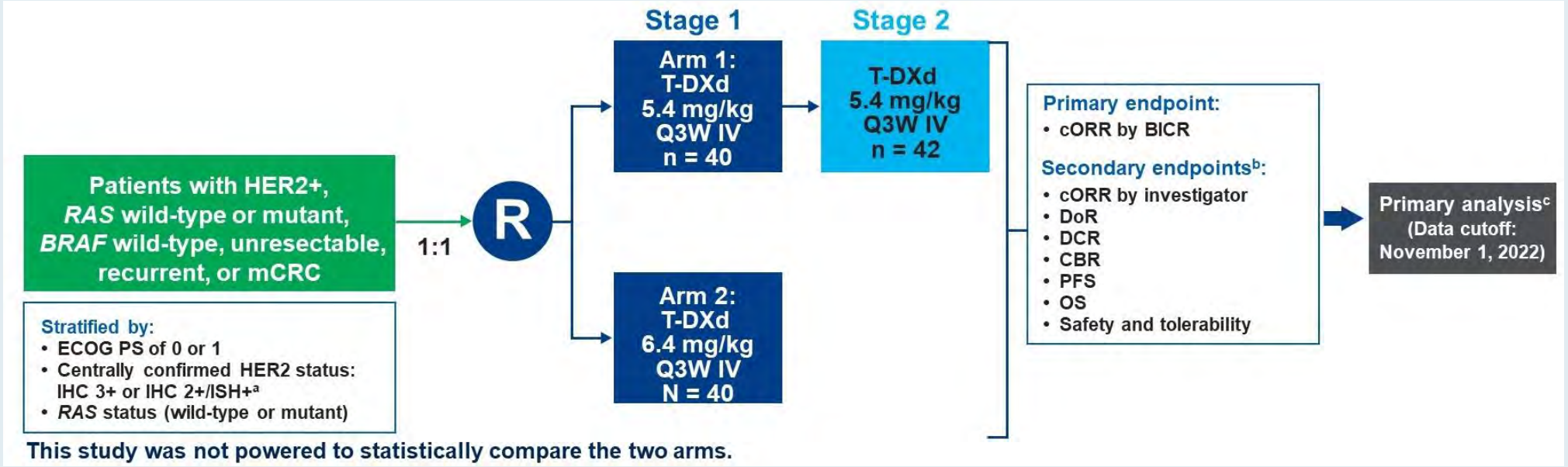
Questions?

Targeting HER2-Expressing mCRC Using T-DXd: DESTINY-CRC01 and DESTINY-CRC02 Phase II Studies

DESTINY-CRC01



DESTINY-CRC02



Raghav KPS et al. ASCO 2023;Abstract 3501.
Yoshino T et al. Gastrointestinal Cancers Symposium 2022;Abstract 119.

ORR = objective response rate; PFS = progression-free survival; OS = overall survival; DOR = duration of response; DCR = disease control rate; cORR = confirmed ORR; BICR = blinded independent central review; CBR = clinical benefit rate

Phase II DESTINY-CRC01 and DESTINY-CRC02 Trials: Efficacy

DESTINY-CRC01

	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A n = 53	HER2 IHC 2+/ISH– Cohort B n = 15	HER2 IHC 1+ Cohort C n = 18
Confirmed ORR by ICR, n (%)	24 (45.3) [95% CI, 31.6-59.6]	0 [95% CI, 0.0-21.8]	0 [95% CI, 0.0-18.5]
CR	0	0	0
PR	24 (45.3)	0	0
SD	20 (37.7)	9 (60.0)	4 (22.2)
PD	5 (9.4)	5 (33.3)	10 (55.6)
NE[a]	4 (7.5)	1 (6.7)	4 (22.2)
DCR, % (95% CI)	83.0 (70.2-91.9)	60.0 (32.3-83.7)	22.2 (6.4-47.6)
Median DOR (95% CI), months	7.0 (5.8-9.5)	NE (NE-NE)	NE (NE-NE)
Median treatment duration (95% CI), months	5.1 (3.9-7.6)	2.1 (1.4-2.6)	1.4 (1.3-1.5)
Median PFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)
Median OS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

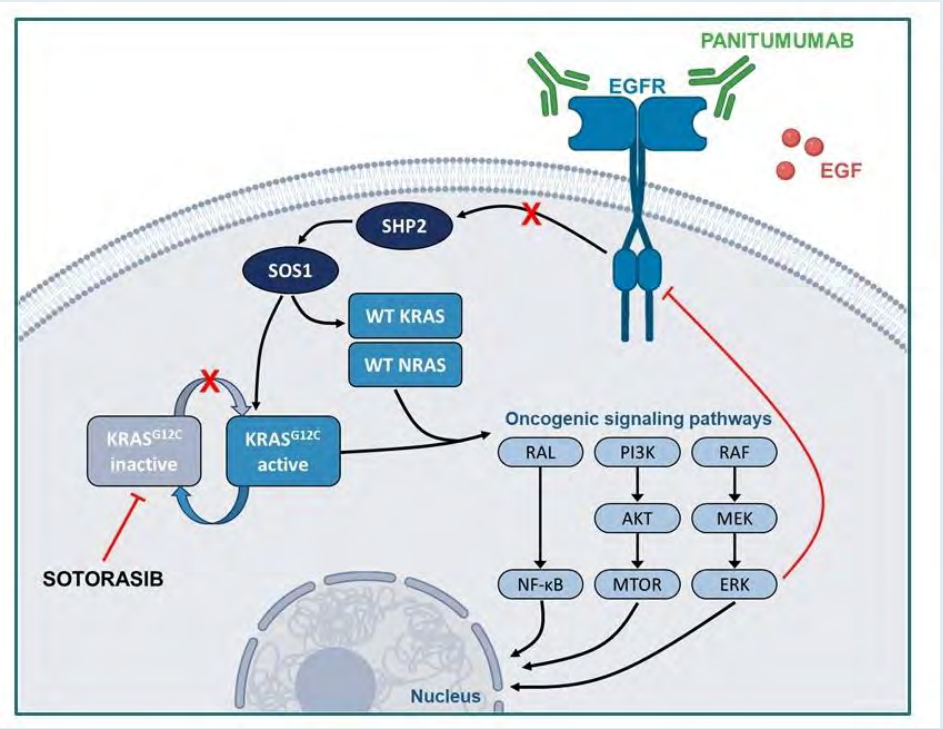
DESTINY-CRC02

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

Raghav KPS et al. ASCO 2023;Abstract 3501.
Yoshino T et al. Gastrointestinal Cancers Symposium 2022;Abstract 119.

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

Sotorasib with Panitumumab for mCRC with a KRAS G12C Mutation: Phase III CodeBreaK 300 Study



Key eligibility criteria

- ≥ 18 years of age
- *KRAS* G12C–mutated mCRC, identified through central molecular testing
- ≥ 1 prior line of therapy for mCRC; progressed on or after fluoropyrimidine, irinotecan, and oxaliplatin*
- ECOG ≤ 2
- Measurable disease per RECIST 1.1
- No prior $KRAS^{G12C}$ inhibitor†

Stratified by: prior anti-angiogenic therapy (yes / no), **time from diagnosis of mCRC** (≥ 18 mo / < 18 mo), **ECOG status** (0 or 1 / 2)

Randomization 1:1:1 (N = 160)

- Sotorasib 960 mg daily + panitumumab 6 mg/kg 2QW (n = 53)
- Sotorasib 240 mg daily + panitumumab 6 mg/kg 2QW (n = 53)
- Investigator's choice: Trifluridine/tipiracil or regorafenib (n = 54)

Primary endpoint: PFS by BICR (measured by CT / MRI and assessed by RECIST v1.1)

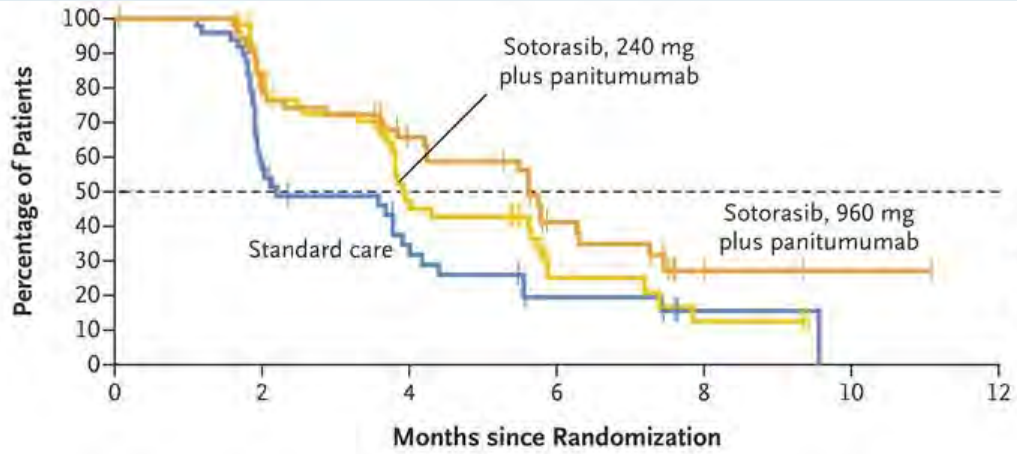
Key secondary endpoints: OS, ORR

OS analysis was performed at 50% maturity and was not powered for statistical significance

Fakih M et al. ASCO 2024;Abstract LBA3510.

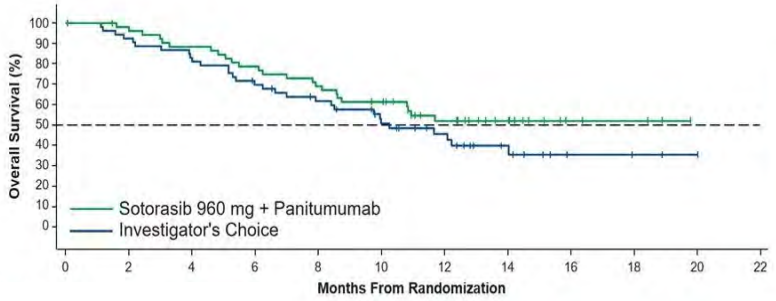
Phase III CodeBreaK 300 Study: Survival

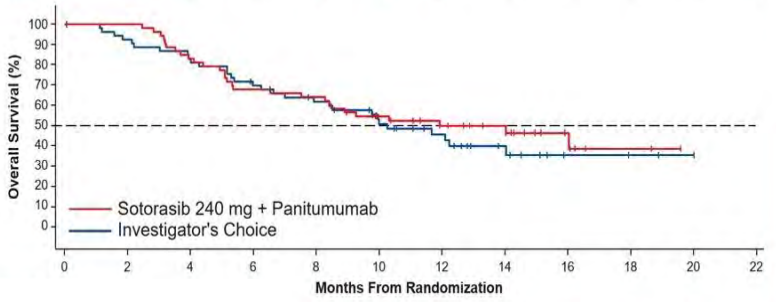
PFS
(Primary endpoint)



	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.49 (0.30–0.80)	0.006
Sotorasib, 240 mg plus Panitumumab	3.91	0.58 (0.36–0.93)	0.03
Standard Care	2.20		

Final OS analysis
(Secondary endpoint)



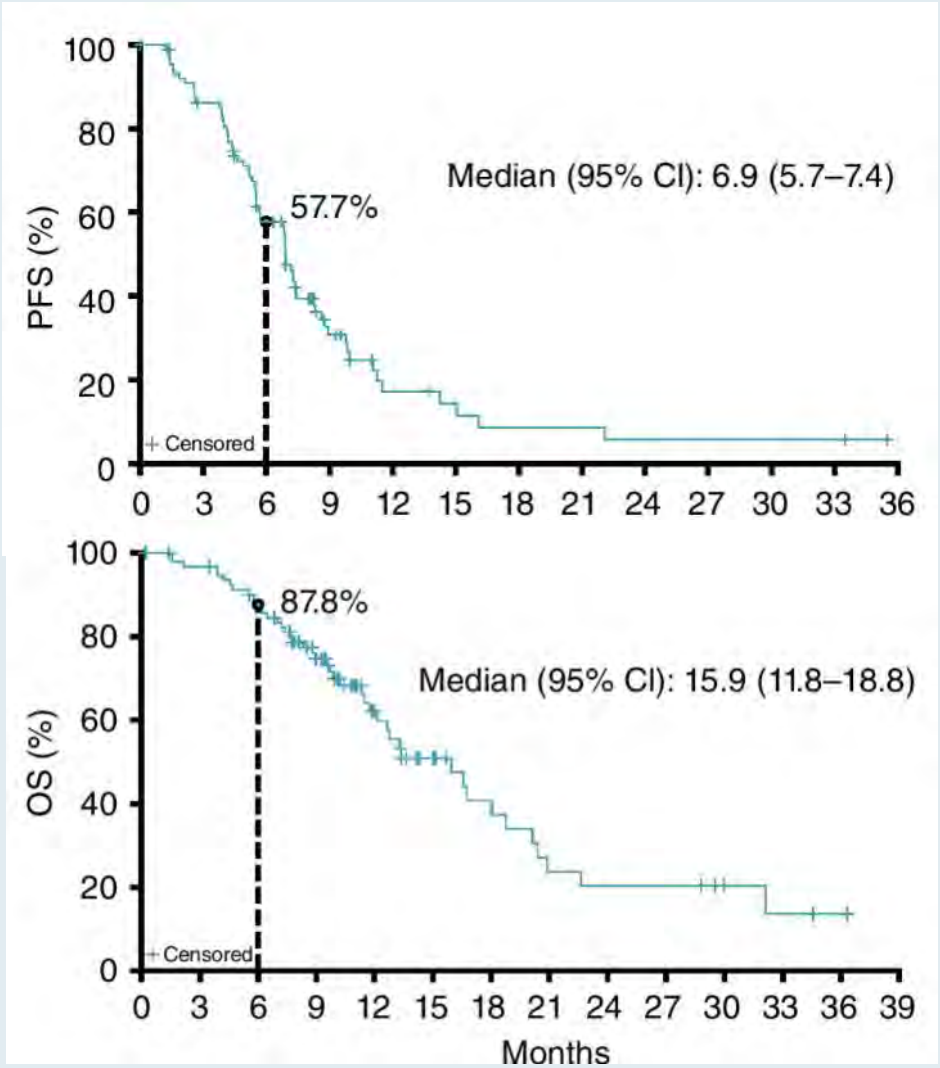


	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median (95% CI) OS, months*	NE (8.6–NE)	11.9 (7.5–NE)	10.3 (7.0–NE)
HR (95% CI)†	0.70 (0.41–1.18)	0.83 (0.49–1.39)	–
P-value (2-sided)‡	0.20	0.50	–
Number of deaths (%)	24 (45)	28 (53)	30 (56)

- After a median follow-up of 13.6 months, sotorasib (240 mg and 960 mg) + panitumumab showed a trend of improved OS versus investigator's choice, with 30% reduction in risk of death for sotorasib 960 mg + panitumumab

Fakih M et al. ASCO 2024;Abstract LBA3510.
Fakih MG et al. *N Engl J Med* 2023;389:2125-39.

Adagrasib and Cetuximab for mCRC with a KRAS G12C Mutation: The Phase I/II KRYSTAL-1 Trial



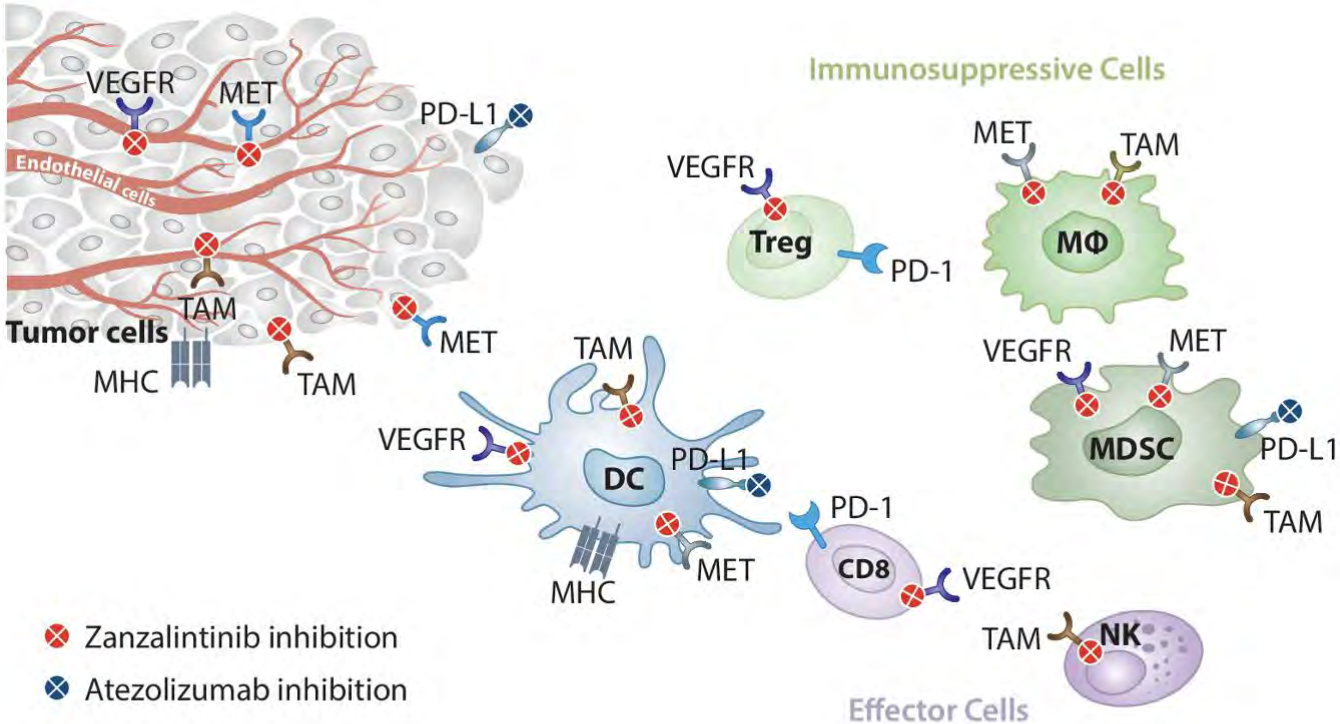
	Adagrasib + cetuximab CRC cohort ($N = 94$)	
	Per BICR	Per investigator
ORR, *n* (%)	32 (34.0)	40 (42.6)
95% CI	24.6-44.5	32.4-53.2
BOR, *n* (%)		
Complete response	0 (0.0)	0 (0.0)
Partial response	32 (34.0)	40 (42.6)
Stable disease	48 (51.1)	41 (43.6)
Progressive disease	6 (6.4)	5 (5.3)
Not evaluable	8 (8.5)	8 (8.5)
DCR, *n* (%)	80 (85.1)	81 (86.2)
95% CI	76.3-91.6	77.5-92.4
Median DOR, months	5.8	5.9
95% CI	4.2-7.6	5.5-7.6
Median PFS, months	6.9	6.9
95% CI	5.7-7.4	5.9-7.4
Median OS, months	15.9	
95% CI	11.8-18.8	

NOTE: Data as of June 30, 2023 (median follow-up: 11.9 months).

Yaeger R et al. *Cancer Discov* 2024;14(6):982-93.

Zanzalintinib (XL092) and Atezolizumab: Mechanism of Action

Zanzalintinib is a novel TKI targeting VEGFR, MET, and the TAM kinases (TYRO3, AXL, MER), which are involved in tumor angiogenesis, metastasis, and immunosuppression.



Zanzalintinib and atezolizumab combination

- Zanzalintinib inhibits VEGFR, MET, and TAM kinases and may enhance the activity of atezolizumab by promoting an immune-permissive tumor microenvironment
- Atezolizumab binds to PD-L1 to activate cytotoxic T-cell activity and promote T-cell proliferation

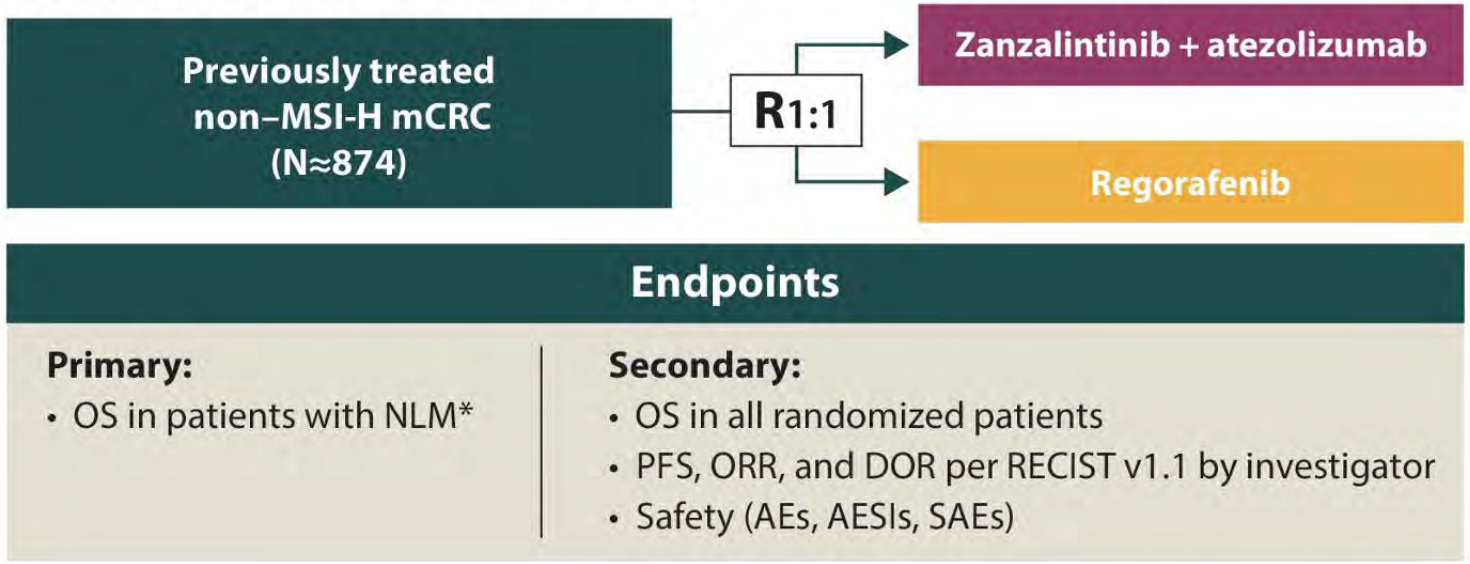
Saeed A et al. ASCO 2024;Abstract TPS3634.

STELLAR-303: A Phase III Study of Zanzalintinib/Atezolizumab versus Regorafenib for Previously Treated Metastatic CRC

Inclusion criteria

- Histologically/cytologically confirmed adenocarcinoma of the colon or rectum
- Documented *RAS* status (mutant or wild-type) by tissue-based analysis
- Documented to have non–MSI-H or non-dMMR mCRC by tissue-based analysis
- Measurable disease per RECIST v1.1 by investigator
- ECOG performance status 0 or 1
- Radiographically progressed on, refractory to, or intolerant to SOC therapy for mCRC
- Progressed during treatment with or within 4 months of most recent SOC therapy
- Archival or fresh tumor tissue
- Age ≥18 years
- Adequate organ and marrow function

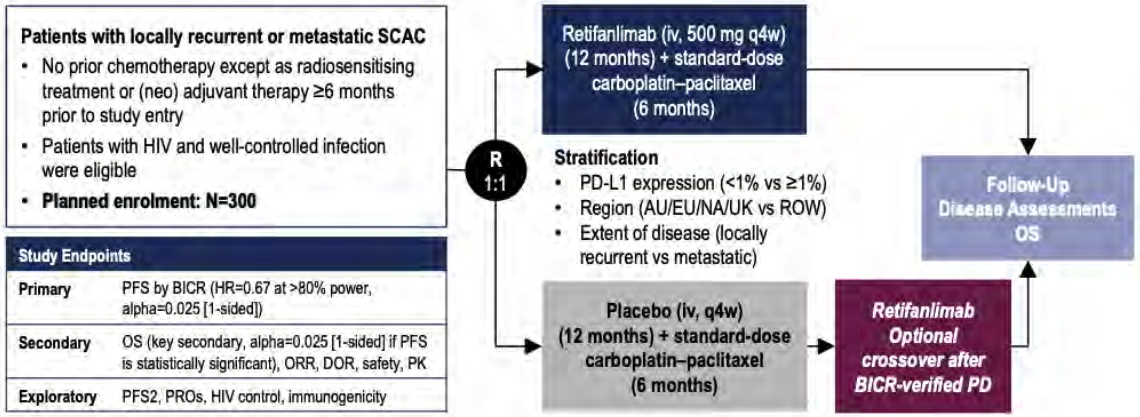
Figure 2. STELLAR-303 Study Design



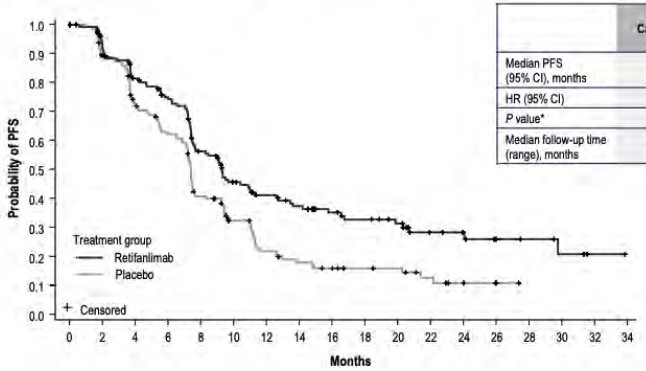
SOC = standard of care; NLM = no liver metastases

Saeed A et al. ASCO 2024;Abstract TPS3634.

POD1UM-303/InterAACT 2: Phase III study of retifanlimab with carboplatin-paclitaxel (c-p) in patients (Pts) with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal (SCAC) not previously treated with systemic chemotherapy (Chemo)

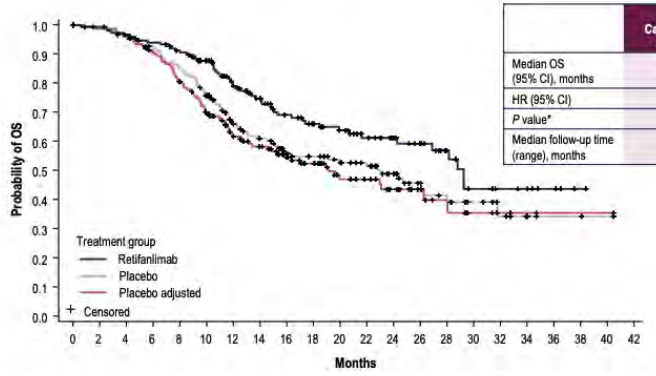


PFS by BICR (Primary Endpoint)



	Placebo + Carboplatin–Paclitaxel (n=154)	Retifanlimab + Carboplatin–Paclitaxel (n=154)
Median PFS (95% CI), months	7.4 (7.1, 7.7)	9.3 (7.5, 11.3)
HR (95% CI)		**0.63 (0.47, 0.84)**
P value*		**0.0006**
Median follow-up time (range), months	7.1 (0.0, 27.4)	7.6 (0.0, 33.9)

OS Adjusted for Crossover



	Placebo + Carboplatin–Paclitaxel (Adjusted; n=154)	Retifanlimab + Carboplatin–Paclitaxel (n=154)
Median OS (95% CI), months	19.1 (13.4, 27.9)	29.2 (24.2, NE)
HR (95% CI)		**0.63 (0.44, 0.90)**
P value*		**0.0055***
Median follow-up time (range), months	12.0 (0.0, 40.4)	14.8 (0.6, 38.3)

Rao S et al. ESMO 2024;Abstract LBA2

POD1UM-303/InterAACT 2: secondary analyses

	Placebo + Carboplatin–Paclitaxel (n=154)	Retifanlimab + Carboplatin–Paclitaxel (n=154)
ORR (95% CI), % CR, %	44 (36, 52) 14	56 (48, 64) 22 *P*=0.0129†
Median DOR (95% CI), months	7.2 (5.6, 9.3)	14.0 (8.6, 22.2)
DCR (95% CI), %	80 (73, 86)	87 (81, 92)

Most Common (≥2%) Immune-Related TEAEs

MedRA Preferred Term	Placebo + Carboplatin–Paclitaxel (n=152)	Retifanlimab + Carboplatin–Paclitaxel (n=154)	Total (N=306)
Peripheral sensory neuropathy	15 (9.9)	17 (11.0)	32 (10.5)
Hypothyroidism	5 (3.3)	22 (14.3)	27 (8.8)
Hyperthyroidism	1 (0.7)	13 (8.4)	14 (4.6)
Pruritus	3 (2.0)	11 (7.1)	14 (4.6)
Adrenal insufficiency	0	8 (5.2)	8 (2.6)
Rash maculo-papular	3 (2.0)	3 (1.9)	6 (2.0)

A potential new standard of care for advanced anal squamous cell cancer

Rao S et al. ESMO 2024;Abstract LBA2

Questions?

Dr. Philip - Case #2: Pancreatic Cancer

- 77-year-old male
- May 2021 –
  - Umbilical mass = adenocarcinoma, *KRAS*^{wt}
  - CT = multiple liver lesions, panc body mass, peritoneal nodules
- June 2021 –
  - Gemcitabine nab-paclitaxel – quickly changed to Q 2 weeks
  - Radiographic improvement with drop in CA199
  - Marked fluid retention
- June 2023 –
  - CT progression and rising CA199

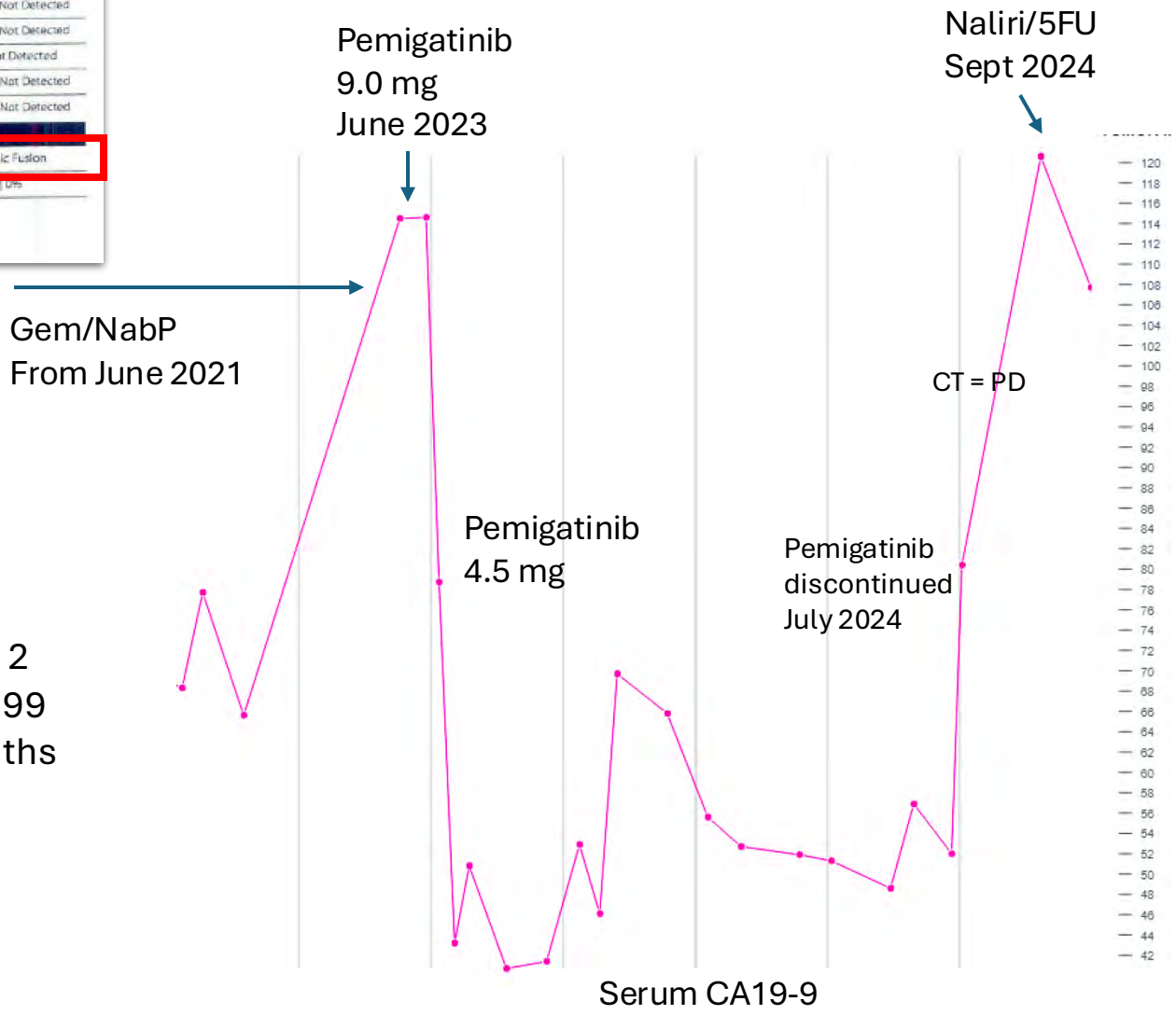
Dr. Philip - Case #2: Pancreatic Cancer

Biomarker	Method	Analyte	Result
KRAS	Seq	DNA-Tumor	Mutation Not Detected
MSI	Seq	DNA-Tumor	Stable
Mismatch Repair Status	IHC	Protein	Proficient
NTRK1/2/3	Seq	RNA-Tumor	Fusion Not Detected
Tumor Mutational Burden	Seq	DNA-Tumor	Low, 1 mut/Mb
ATM	Seq	DNA-Tumor	Mutation Not Detected
BRAF	Seq	RNA-Tumor	Fusion Not Detected
		DNA-Tumor	Mutation Not Detected

Biomarker	Method	Analyte	Result
BRCA1	Seq	DNA-Tumor	Mutation Not Detected
BRCA2	Seq	DNA-Tumor	Mutation Not Detected
NRG1	Seq	RNA-Tumor	Fusion Not Detected
PALB2	Seq	DNA-Tumor	Mutation Not Detected
SMAD4	Seq	DNA-Tumor	Mutation Not Detected
FGFR2 ✓	Seq	RNA-Tumor	Pathogenic Fusion
PD-L1 (SP142)	IHC	Protein	Negative | 0%

Pemigatinib x 12 months

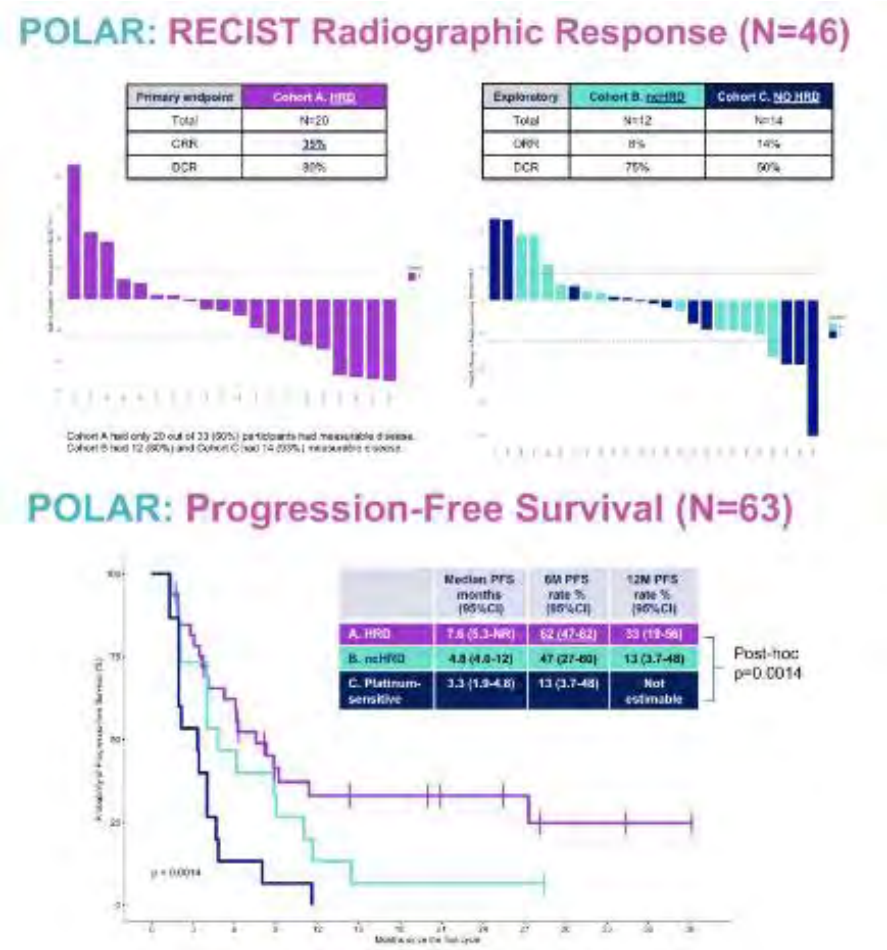
- 9 mg QD
  - → 4.5 mg QD
    - → 4.5 mg alternate days
- Hyponatremia Gr 3/ hyperphosphatemia Gr 2
- Radiographic improvement and drop in CA199
- Currently alive with disease 3 years + 3 months since initial presentation



Phase II trial of Pembrolizumab and OLApaRib (POLAR) maintenance for select patients (pts) with metastatic pancreatic cancer (mPC) with (A) homologous recombination deficiency (HRD), (B) non-core HRD (ncHRD) and (C) exceptional response to platinum

Park W et al. ESMO 2024;Abstract 1504MO

Phase II trial of Pembrolizumab and OLApaRib (POLAR) maintenance for select patients (pts) with metastatic pancreatic cancer (mPC) with (A) homologous recombination deficiency (HRD), (B) non-core HRD (ncHRD) and (C) exceptional response to platinum (continued)

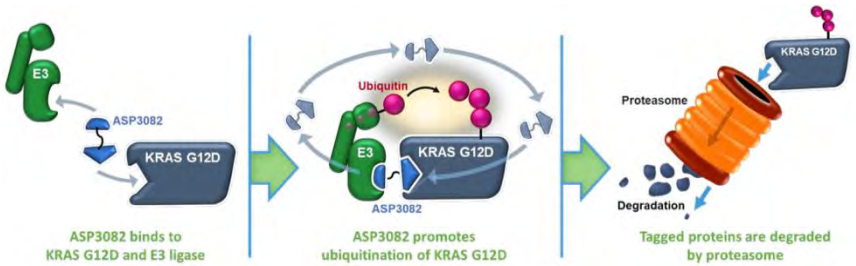


Need a randomized trial to determine the olaparib + IO efficacy (ongoing SWOG-S2100)

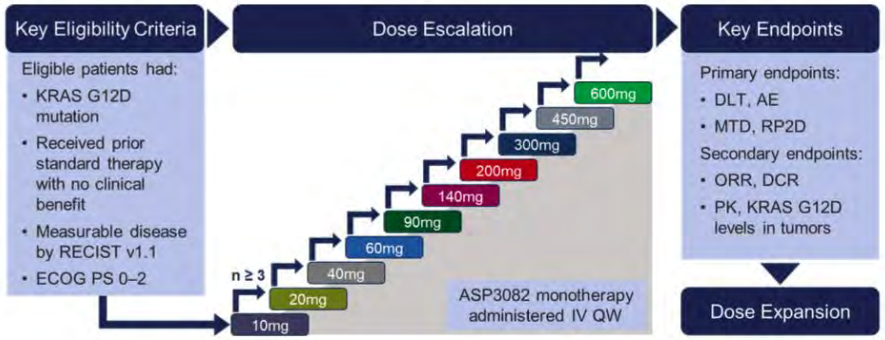
Not all HRD mutations respond the same to olaparib

Park W et al. ESMO 2024;Abstract 1504MO

Preliminary safety and clinical activity of ASP3082, a first-in-class, KRAS G12D selective protein degrader in adults with advanced pancreatic (PC), colorectal (CRC), and non-small cell lung cancer (NSCLC)



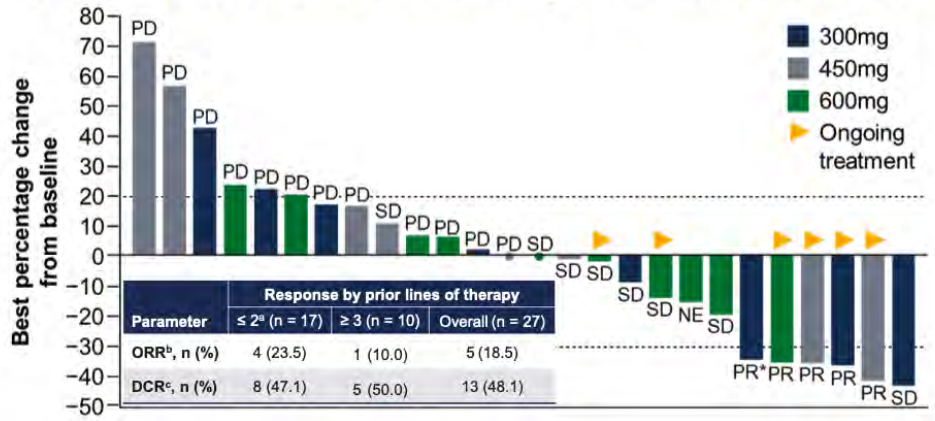
Tumor type, n (%)		
PDAC	31 (64.6)	74 (66.7)
NSCLC	15 (31.3)	19 (17.1)
CRC	1 (2.1)	16 (14.4)
Other[b]	1 (2.1)	2 (1.8)
Median number of prior lines of systemic anticancer therapy (range)	2 (1–5)	2 (1–7)



Park W et al. ESMO 2024;Abstract 608O

Preliminary safety and clinical activity of ASP3082, a first-in-class, KRAS G12D selective protein degrader in adults with advanced pancreatic (PC), colorectal (CRC), and non-small cell lung cancer (NSCLC) (continued)

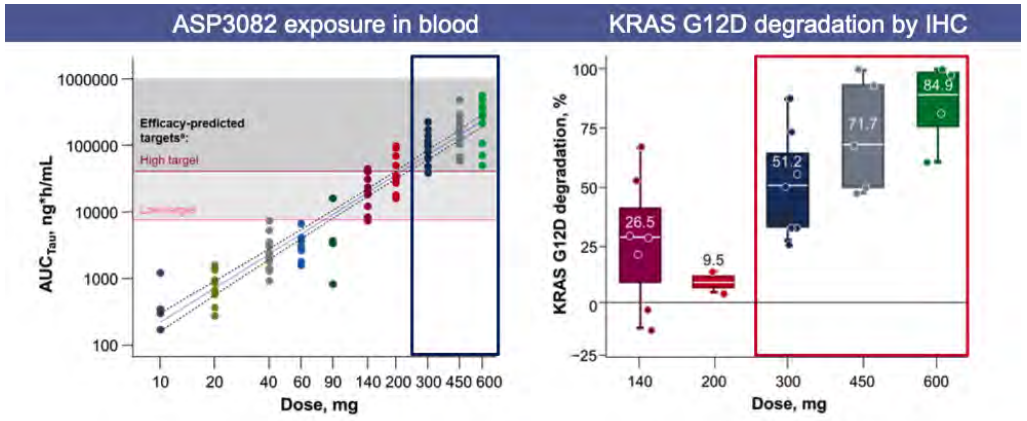
Responses to ASP3082 300–600mg in patients with PDAC



Parameter	Response by prior lines of therapy		
	≤ 2[a] (n = 17)	≥ 3 (n = 10)	Overall (n = 27)
ORR[b], n (%)	4 (23.5)	1 (10.0)	5 (18.5)
DCR[c], n (%)	8 (47.1)	5 (50.0)	13 (48.1)

Characteristic, n (%)	ASP3082 monotherapy QW			
	Any grade		Grade 3	
	300–600mg (n = 48)	Overall (N = 111)	300–600mg (n = 48)	Overall (N = 111)
TRAEs	43 (89.6)	83 (74.8)	5 (10.4)	7 (6.3)
TRAEs occurring in ≥ 5% of all patients				
Infusion-related reaction	17 (35.4)	21 (18.9)	0	0
Fatigue	6 (12.5)	20 (18.0)	1 (2.1)	1 (0.9)
Rash[a]	10 (20.8)	13 (11.7)	0	0
Urticaria	9 (18.8)	11 (9.9)	0	0
Nausea	5 (10.4)	10 (9.0)	0	0
Pruritus	6 (12.5)	9 (8.1)	0	0
AST increased	6 (12.5)	8 (7.2)	2 (4.2)	2 (1.8)
Vomiting	3 (6.3)	6 (5.4)	0	0

- No Gr4 or Gr5 TRAEs



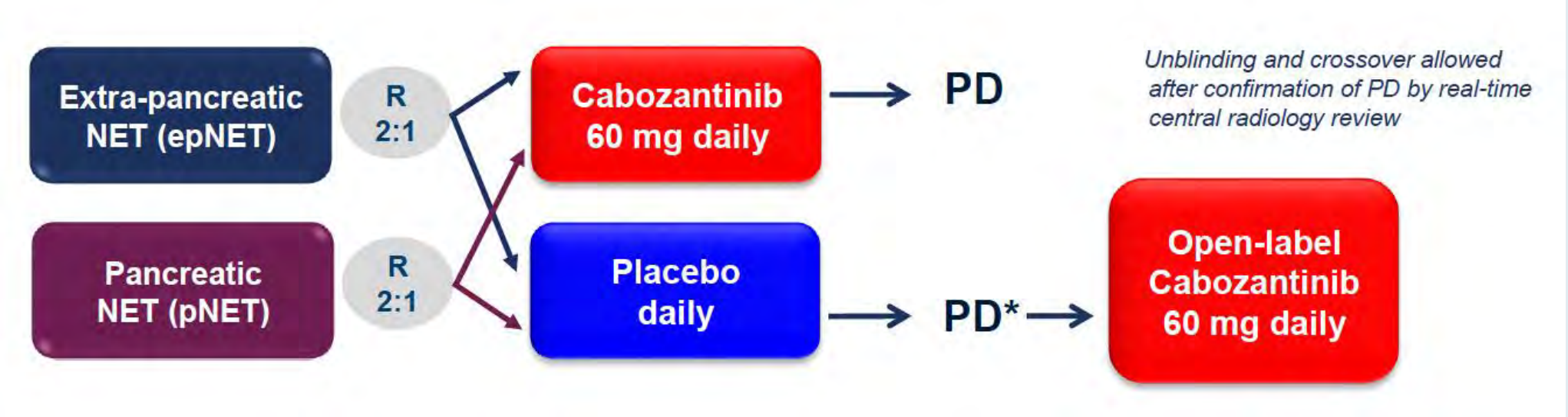
Encouraging single agent activity in pre-treated advanced pancreatic cancer

Well tolerated

Park W et al. ESMO 2024;Abstract 608O

Questions?

CABINET/Alliance A021602 Trial: Cabozantinib for Advanced Neuroendocrine Tumors After Disease Progression on Prior Therapy



Extra-pancreatic NET Cohort

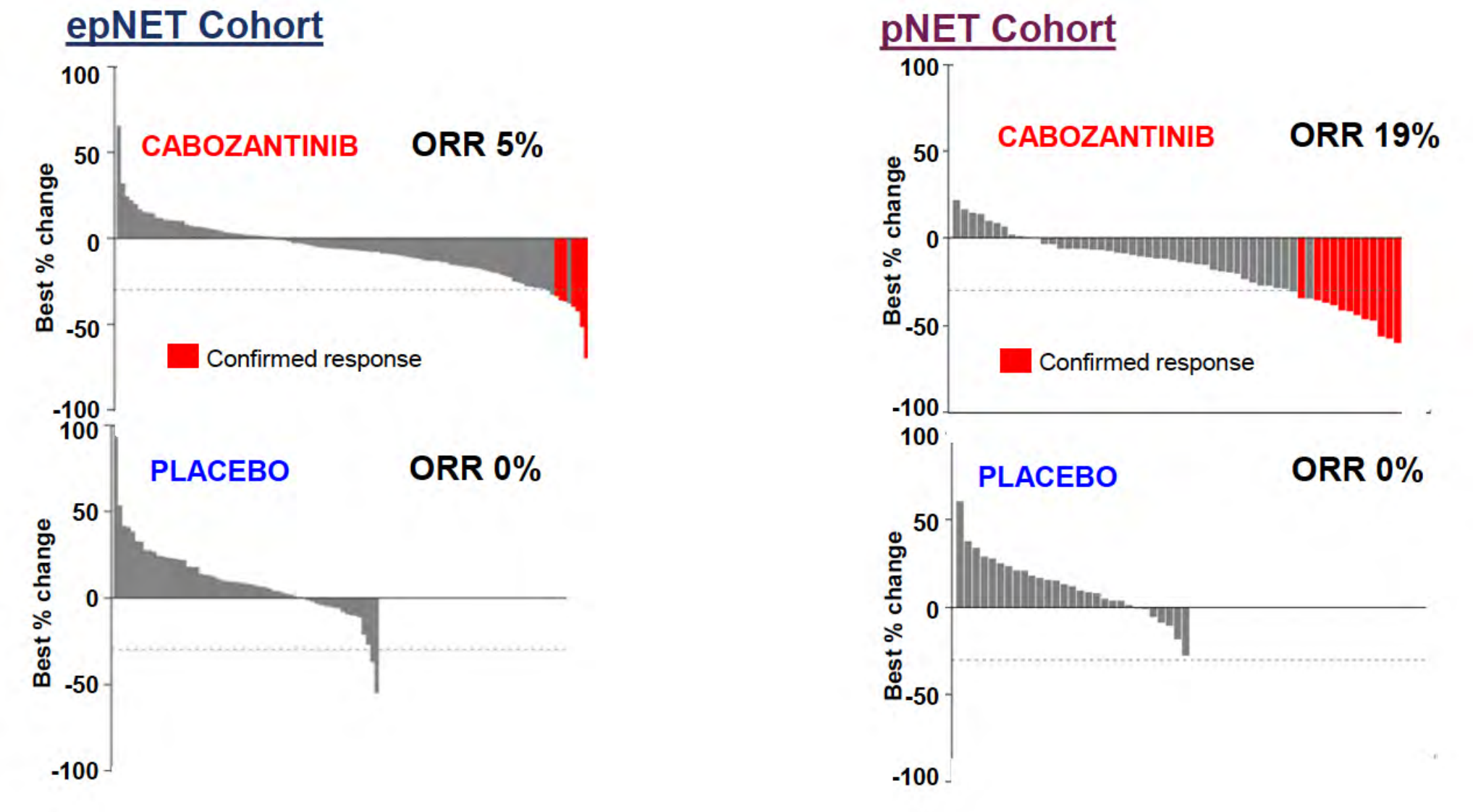
	CABOZANTINIB (N=134)	PLACEBO (N=69)
Primary tumor site, n (%)		
Gastrointestinal	70 (52)	46 (67)
Lung	27 (20)	12 (17)
Thymus	6 (5)	4 (6)
Unknown	22 (16)	2 (3)
Other	5 (4)	2 (3)
Pancreas*	4 (3)	3 (4)

Pancreatic NET Cohort

	CABOZANTINIB (N= 64)	PLACEBO (N=31)
Primary tumor site		
Pancreas	62 (97)	30 (97)
Ileum*	1 (2)	0
Cecum*	0	1 (3)
Stomach*	1 (2)	0

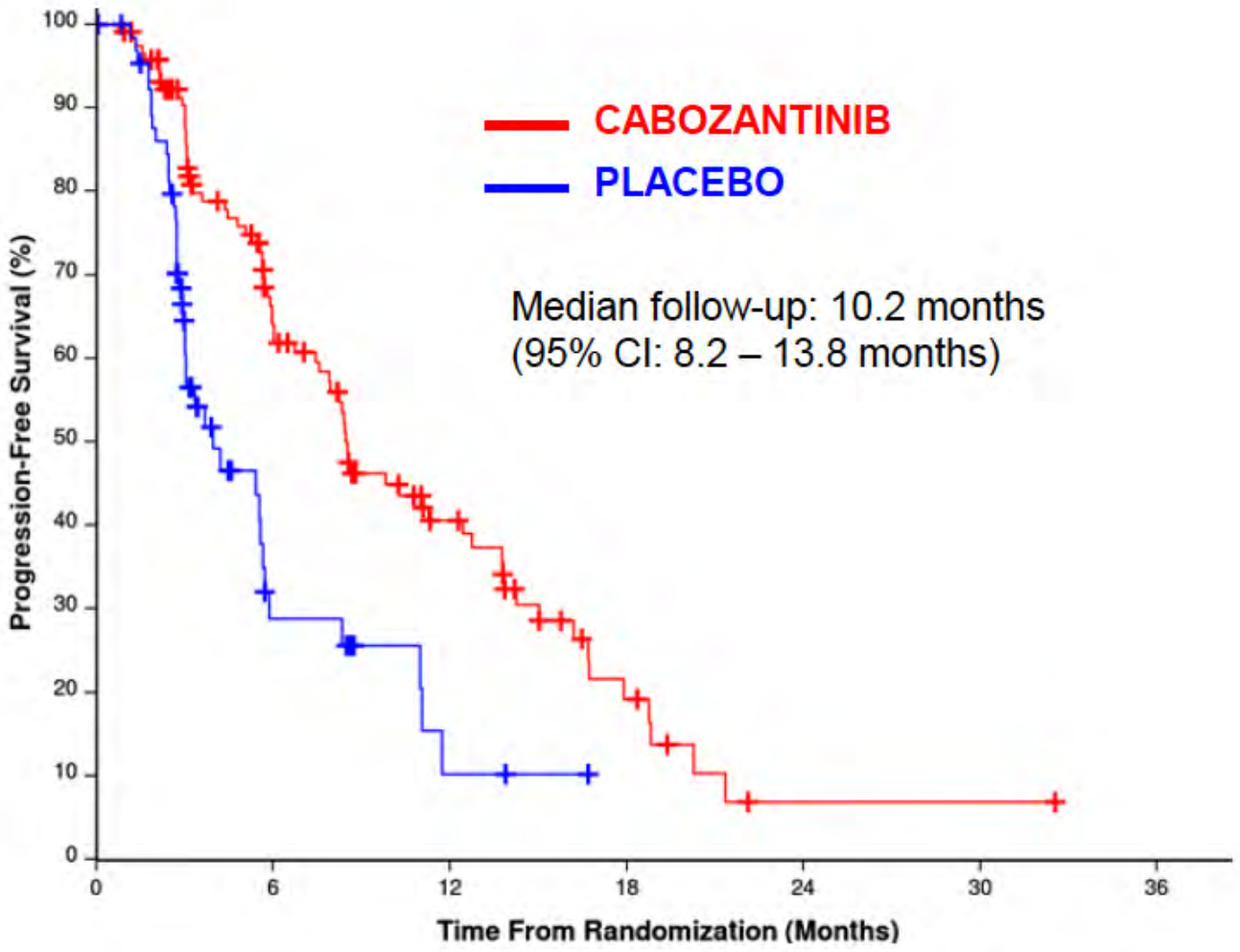
Chan JA et al. ESMO 2024;Abstract 1141O.

CABINET/Alliance A021602: Cabozantinib versus Placebo – Objective Response Rate (ORR)



Chan JA et al. ESMO 2024;Abstract 1141O.

CABINET/Alliance A021602: Extrapancreatic NET Cohort – PFS

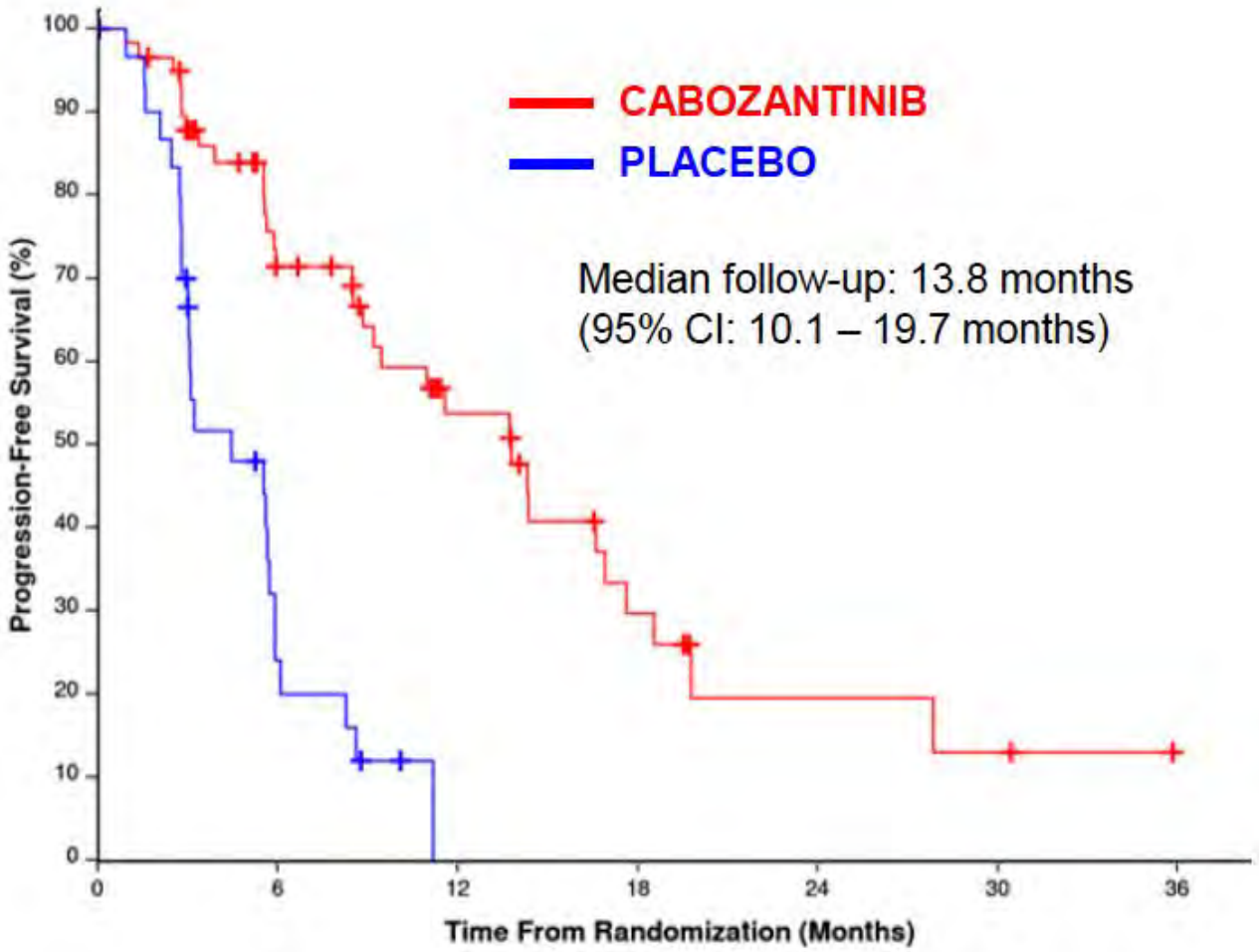


Stratified HR = 0.38
(95% CI: 0.25 – 0.59)
log-rank p<0.0001

Median PFS
Cabozantinib = 8.4 months
(95% CI: 7.6 – 12.7 months)
Placebo = 3.9 months
(95% CI: 3.0 – 5.7 months)

Chan JA et al. ESMO 2024;Abstract 1141O.

CABINET/Alliance A021602: Pancreatic NET Cohort – PFS



Stratified HR = 0.23
(95% CI: 0.12 – 0.42)
log-rank p<0.0001

Median PFS
Cabozantinib = 13.8 months
(95% CI: 9.2 – 18.5 months)
Placebo = 4.4 months
(95% CI: 3.0 – 5.9 months)

Chan JA et al. ESMO 2024;Abstract 1141O.

Questions?

Agenda

Module 1: Colorectal Cancer, Anal Cancer and Pancreatic Cancer – Dr Philip

Module 2: Gastroesophageal Cancers, Hepatocellular Cancer and Biliary Tract Cancers – Dr Bekaii-Saab

RTP RESEARCH TO PRACTICE

MAYO CLINIC

The Implications of Recent Datasets for the Current and Future Management of Gastrointestinal Cancers (GE and HB Cancers) An ESMO Congress 2024 Review

Tanios Bekaii-Saab, MD

David F. and Margaret T. Grohne Professor of Novel Therapeutics for Cancer Research I

Chair and Consultant, Division of Hematology and Medical Oncology

Professor, Mayo Clinic College of Medicine and Science

Mayo Clinic in Arizona

Gastro-Esophageal Cancers (GE)

Dr. Bekaii-Saab - GE Case

- 71 -year-old female long standing history of GERD presents with odynophagia, 20 lbs weight loss and poor appetite .
- EGD Fungating, partially obstructive GEJ mass extending to cardia with biopsy confirming poorly differentiated adenocarcinoma with pMMR , HER2 1+ and CPS >1.
- CT scans of chest abdomen and pelvis reveal multiple liver lesions consistent with metastatic disease. Biopsy of one of the lesions suggests confirming poorly differentiated adenocarcinoma c/w GE primary. Tissue was sent for NGS testing. TMB was low, CPS > 5 , HER2 non-amplified and RAS/RAF WT. The tumor sample was positive for CLDN 18.2 expression .
- The patient was started on FOLFOX - Nivolumab

Nivolumab adjuvant therapy for esophageal cancer: a review based on subgroup analysis of CheckMate 577 trial

Yan Lin[1], Huan-Wei Liang[2], Yang Liu[2] and Xin-Bin Pan[2*]

[1]Department of Gastroenterology, Jiangbin Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi, China, [2]Department of Radiation Oncology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, China

Front Immunol 2023;14:1264912.

Pathological complete response to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with or without durvalumab in resectable gastric and gastroesophageal junction cancer: subgroup analysis by region from the Phase 3, randomized, double-blind MATTERHORN study

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Methods

MATTERHORN is a global, Phase 3, randomized, double-blind, placebo-controlled study

Study population
- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N1-3 M0)
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America, and South America

Stratification factors
- Geographic region: Asia versus non-Asia
- Clinical lymph node status: positive versus negative
- PD-L1 status: TAP <1% versus TAP ≥1%*

Randomized (1:1) N=948

Pre-operative		Post-operative (1-year duration)	
2 doses of durvalumab or placebo 4 doses FLOT		2 doses of durvalumab or placebo 4 doses FLOT	10 doses of durvalumab or placebo
Durvalumab plus FLOT	SURGERY	Durvalumab† plus FLOT	Durvalumab
Placebo plus FLOT	SURGERY	Placebo† plus FLOT	Placebo

Primary objective:
- EFS

Key secondary objectives:
- Central review of pathological complete response by modified Ryan criteria
- OS

Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative), followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles

FLOT: 5-fluorouracil 2600 mg/m², oxaliplatin 85 mg/m², docetaxel 50 mg/m², leucovorin 200 mg/m² on Days 1 and 15 of a 4-week cycle for 2 cycles (4 doses) pre- and post-operative; durvalumab: 1500 mg on Day 1 of a 4-week cycle, 2 cycles (2 doses) of durvalumab or placebo pre- and post-operative, followed by 10 cycles (10 doses) of durvalumab or placebo on Day 1 of a 4-week cycle.
*Measured by VENTANA PD-L1 (SP263) assay. †Durvalumab or placebo monotherapy may be continued if post-operative FLOT is discontinued due to toxicity.
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GEJ, gastroesophageal junction; OS, overall survival; PD-L1, programmed cell death ligand-1; PS, performance status; Q2W, every 2 weeks; Q4W, every 4 weeks; TAP, tumor area positivity.

ASCO Gastrointestinal Cancers Symposium #GI24 PRESENTED BY: Yelena Y. Janjigian, MD

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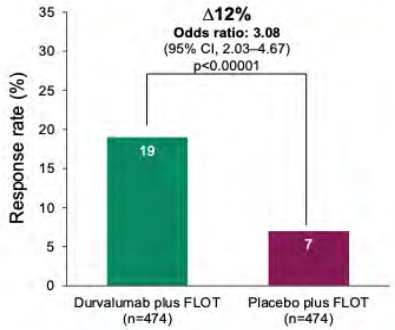
Pathological complete response

Durvalumab plus FLOT showed statistically significant improvement in pathological complete response



Participants achieve pathological complete response if there is no residual visible tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.
Janjigian YY, et al. *Annal Oncol* 2023;34:S1315-S1316.

ASCO Gastrointestinal Cancers Symposium #GI24 PRESENTED BY: Yelena Y. Janjigian, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Janjigian Y et al. Gastrointestinal Cancers Symposium2024;Abstract LBA246.

Questions?

First-line (1L) zolbetuximab + chemotherapy in patients (pts) with claudin 18.2 (CLDN18.2) +, HER2-, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: A pooled final analysis of SPOTLIGHT + GLOW

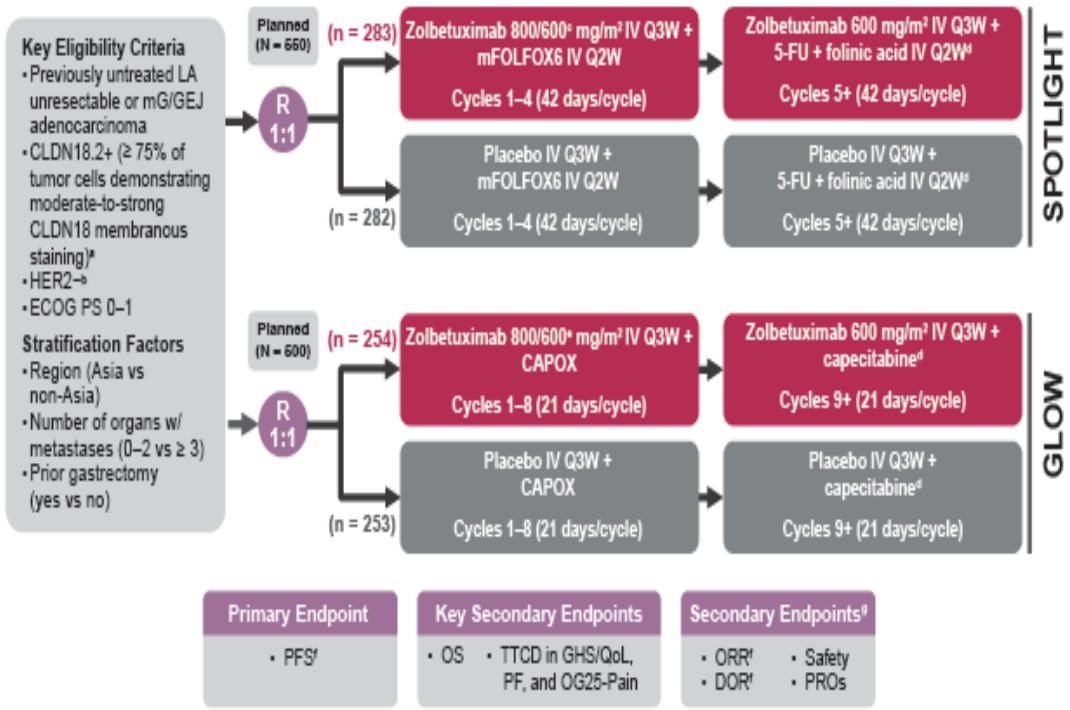


Figure 2. PFS[a,b] in the Combined Final Analysis[c]

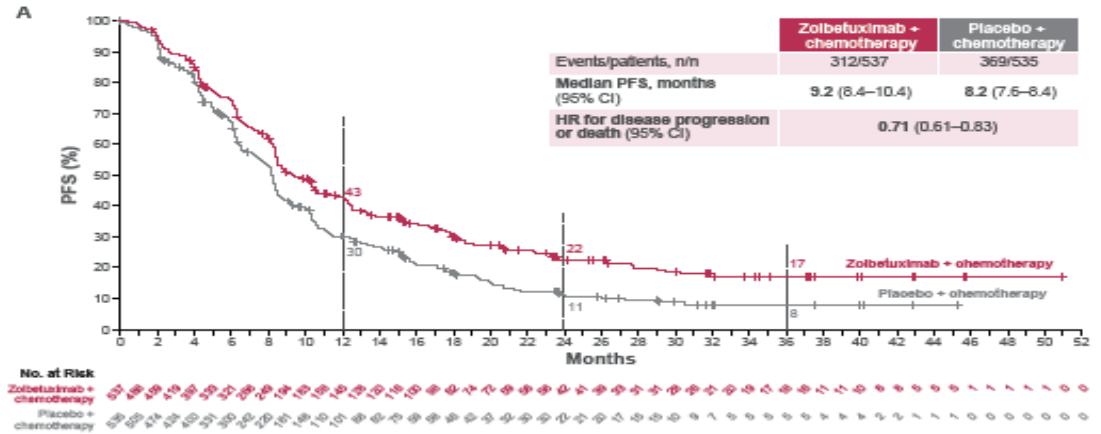
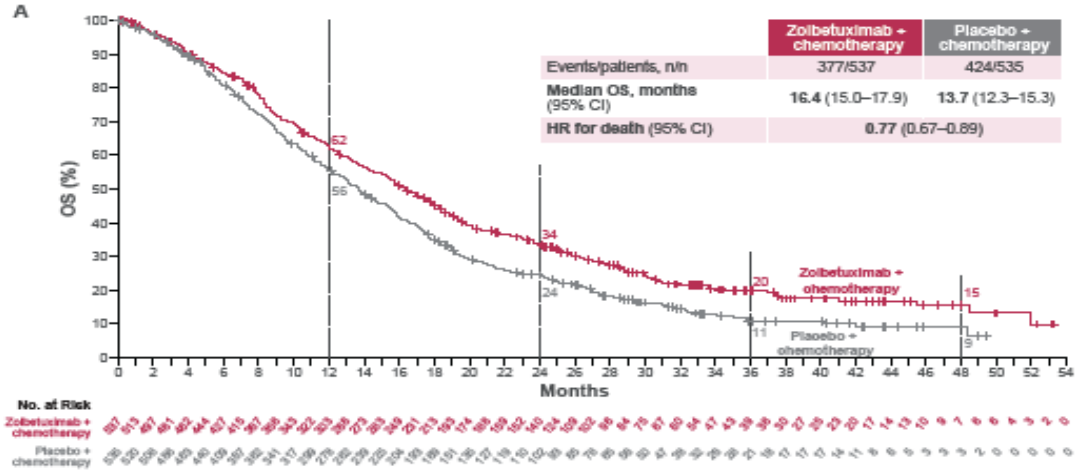


Figure 3. OS[a] in the Combined Final Analysis[b]



Kang Y-K et al. ESMO 2024;Abstract 1438P.

Consensus guidance for management of nausea/vomiting in patients treated with zolbetuximab + chemotherapy: A RAND/UCLA modified Delphi panel study

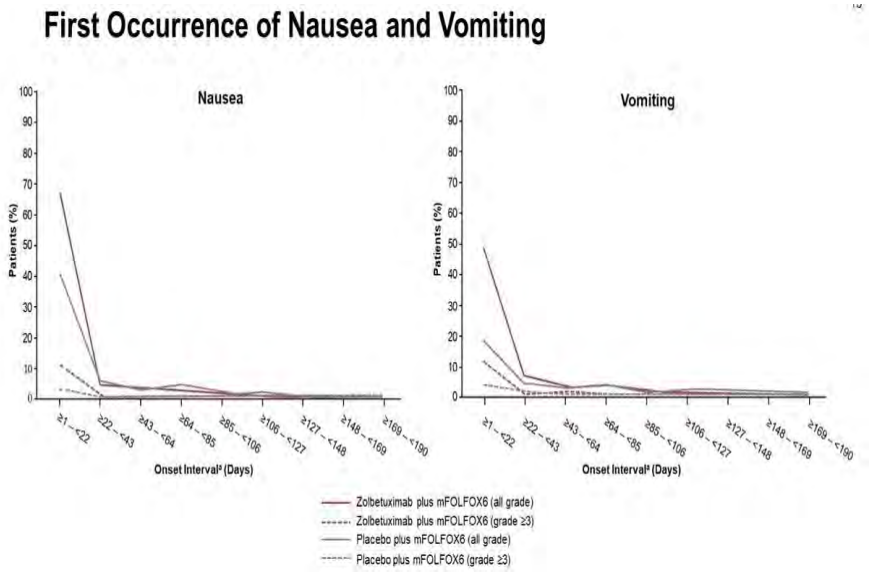
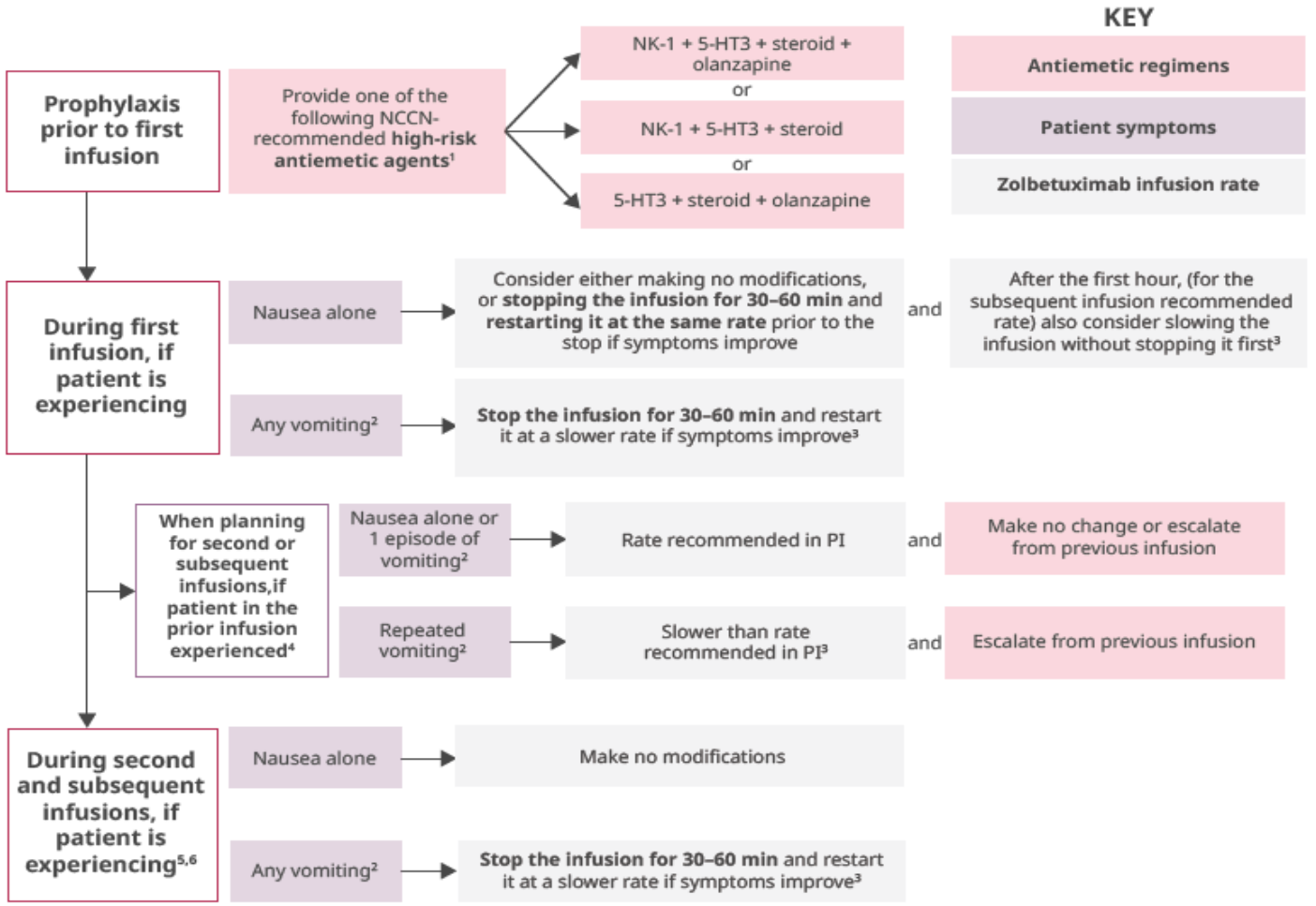


Figure 1. Consensus Guidance on the Prevention and Management of Nausea and Vomiting in Patients Treated With Zolbetuximab + Chemotherapy



Klempner S et al. ESMO GI 2024;Abstract 506P.

Questions?

Frontline Management in 2024 (Minus Claudin)

Biomarker	mPFS in ITT Experimental vs. Control	mOS in ITT Experimental vs. Control	Representative Trial
HER2	10.0m vs 8.1m (all pts) 9.5m vs 9.5m (PD-L1-)	20.0m vs 16.8m (all pts)* 18.2m vs 20.4m (PD-L1-)*	KEYNOTE-811
PD-L1	7.7m vs 6.0m (CPS ≥ 5) 7.7m vs 6.9m (all pts)	14.4m vs 11.1m (CPS ≥ 5) 13.8m vs 11.6m (all pts)	CheckMate 649
PD-L1	6.9m vs 5.6m (all pts) 6.9m vs 5.6m (CPS ≥ 1)	12.9m vs 11.5m (all pts) 13.0m vs 11.4m (CPS ≥ 1)	KEYNOTE-859
PD-L1	6.9m vs 6.2m (all pts) 7.2m vs 5.9m (PD-L1 ≥ 5)	15.0m vs 12.9m (all pts) 17.2m vs 12.6m (PD-L1 ≥ 5)	RATIONALE-305
dMMR* subgroup	11.2m (Pembro alone) NR (Pembro + chemo)	NR (~71% 2yr OS, Pembro) NR (~65% 2yr OS, P + CTX)	KEYNOTE-062
dMMR* subgroup	Not Reported	44.8m vs 8.8m (CPS ≥ 5) 38.7m vs 12.3m (all pts)	CheckMate 649

Janjigian YY et al. Lancet. 2023;402(10418):2197-2208. Janjigian YY et al. Lancet. 2021;398(10294):27-40. Rha SY et al. Lancet Oncol. 2023;24(11):1181-1195. Qiu MZ et al. BMJ. 2024;385:e078876. Shitara K et al. JAMA Oncol. 2020;6(10):1571-1580.

Oncologic Drugs Advisory Committee (ODAC) Meeting Regarding Class Evaluation of PD-L1 Expression Levels for Immune Checkpoint Inhibitors in Gastric and Esophageal Cancers

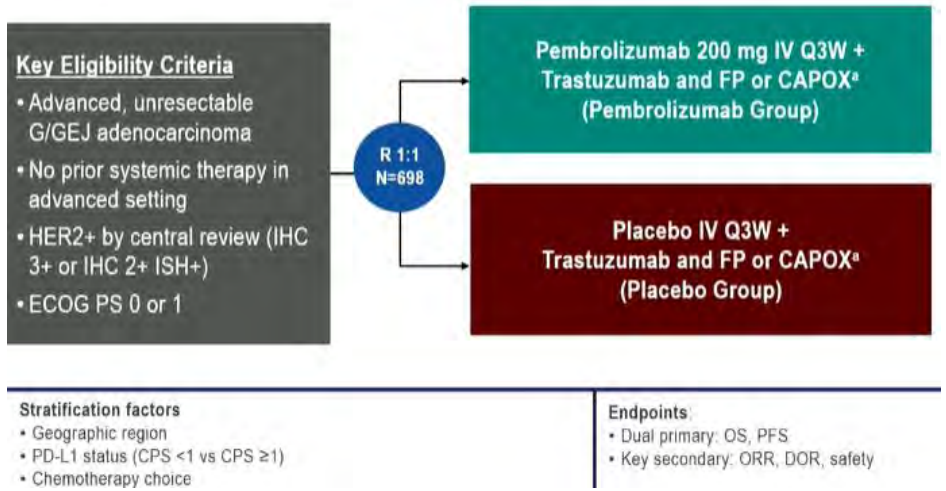
Press Release: September 26, 2024

"Today the U.S. Food and Drug Administration (FDA) held a public meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss the class-wide risk-benefit assessment of PD-L1 expression level cutoffs for immune checkpoint inhibitors in gastric and esophageal cancers. The Committee voted 10-2, with one advisor abstaining, that the risk-benefit is not favorable for the use of PD-1 inhibitors in first-line advanced HER2 negative microsatellite stable gastric and gastroesophageal junction (GEJ) adenocarcinoma in patients with PD-L1 expression <1 and 11-1, with one advisor abstaining, that the risk-benefit is not favorable for the use of anti-PD-1 antibodies in first-line unresectable or metastatic esophageal squamous cell carcinoma (ESCC) with PD-L1 expression <1.

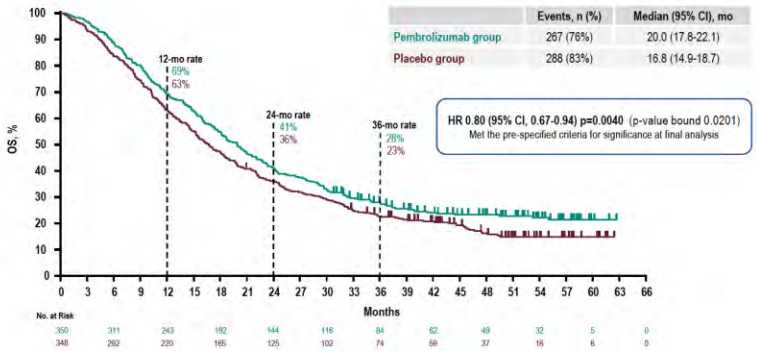
The ODAC is a source of independent, expert advice and recommendations on marketed and investigational medicines for use in the treatment of cancer. The Committee offers non-binding recommendations to the Agency, which will then render a decision and discuss outcomes with [manufacturers of checkpoint inhibitors]."

https://news.bms.com/news/details/2024/Bristol-Myers-Squibb-Statement-on-Oncologic-Drugs-Advisory-Committee-ODAC-Meeting-Regarding-Class-Evaluation-of-PD-L1-Expression-Levels-for-Immune-Checkpoint-Inhibitors-in-Gastric-and-Esophageal-Cancers-/default.aspx

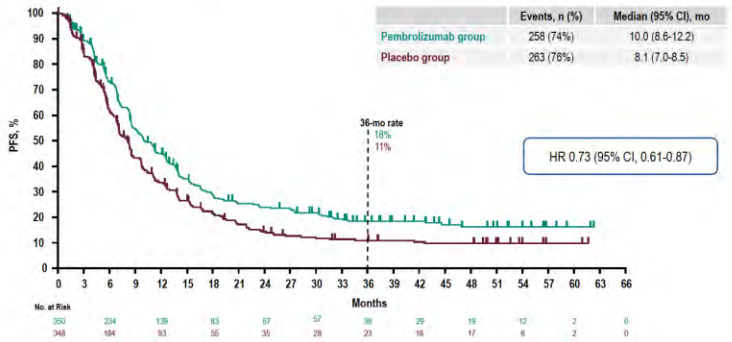
Final overall survival for the phase 3, KEYNOTE-811 study of pembrolizumab plus trastuzumab and chemotherapy for HER2+ advanced, unresectable or metastatic G/GEJ adenocarcinoma.



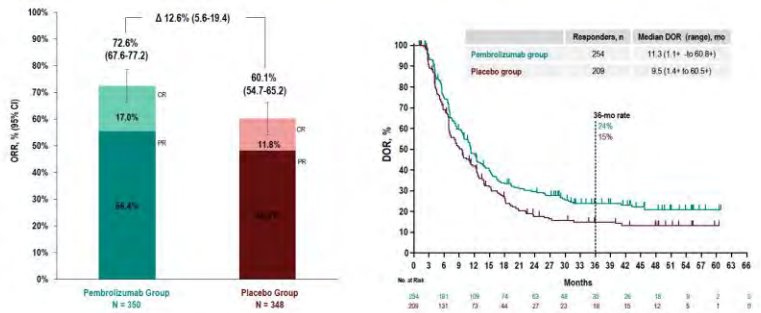
Overall Survival at Final Analysis (ITT)



Progression-free Survival at Final Analysis (ITT) (RECIST V1.1, BICR)



Summary of Antitumor Response at Final Analysis (ITT)



Janjigian YY et al. ESMO 2024;Abstract 1400O.

Final overall survival for the phase 3, KEYNOTE-811 study of pembrolizumab plus trastuzumab and chemotherapy for HER2+ advanced, unresectable or metastatic G/GEJ adenocarcinoma.

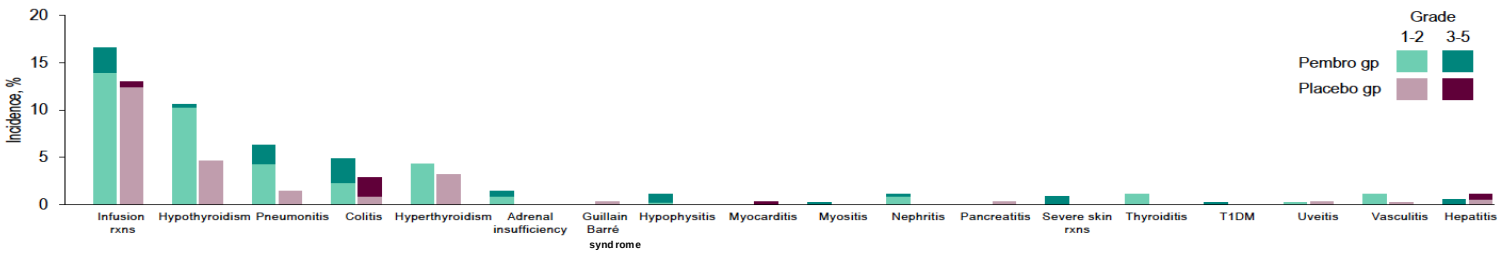
Survival Outcomes by Pre-specified Subgroup PD-L1 CPS 1 Status

	PD-L1 CPS ≥1		PD-L1 CPS <1	
	Pembrolizumab Group N = 298	Placebo Group N = 296	Pembrolizumab Group N = 52	Placebo Group N = 52
PFS, median (95% CI), mo	10.9 (8.5-12.5)	7.3 (6.8-8.4)	9.5 (8.3-12.6)	9.5 (7.9-13.0)
HR (95% CI)	0.72 (0.60-0.87)		0.99 (0.62-1.56)	
OS, median (95% CI), mo	20.1 (17.9-22.9)	15.7 (13.5-18.5)	18.2 (13.9-22.9)	20.4 (16.4-24.7)
HR (95% CI)	0.79 (0.66-0.95)		1.10 (0.72-1.68)	

Immune-Mediated Adverse Events and Infusion Reactions

Adverse Events of Interest in all Treated Patients

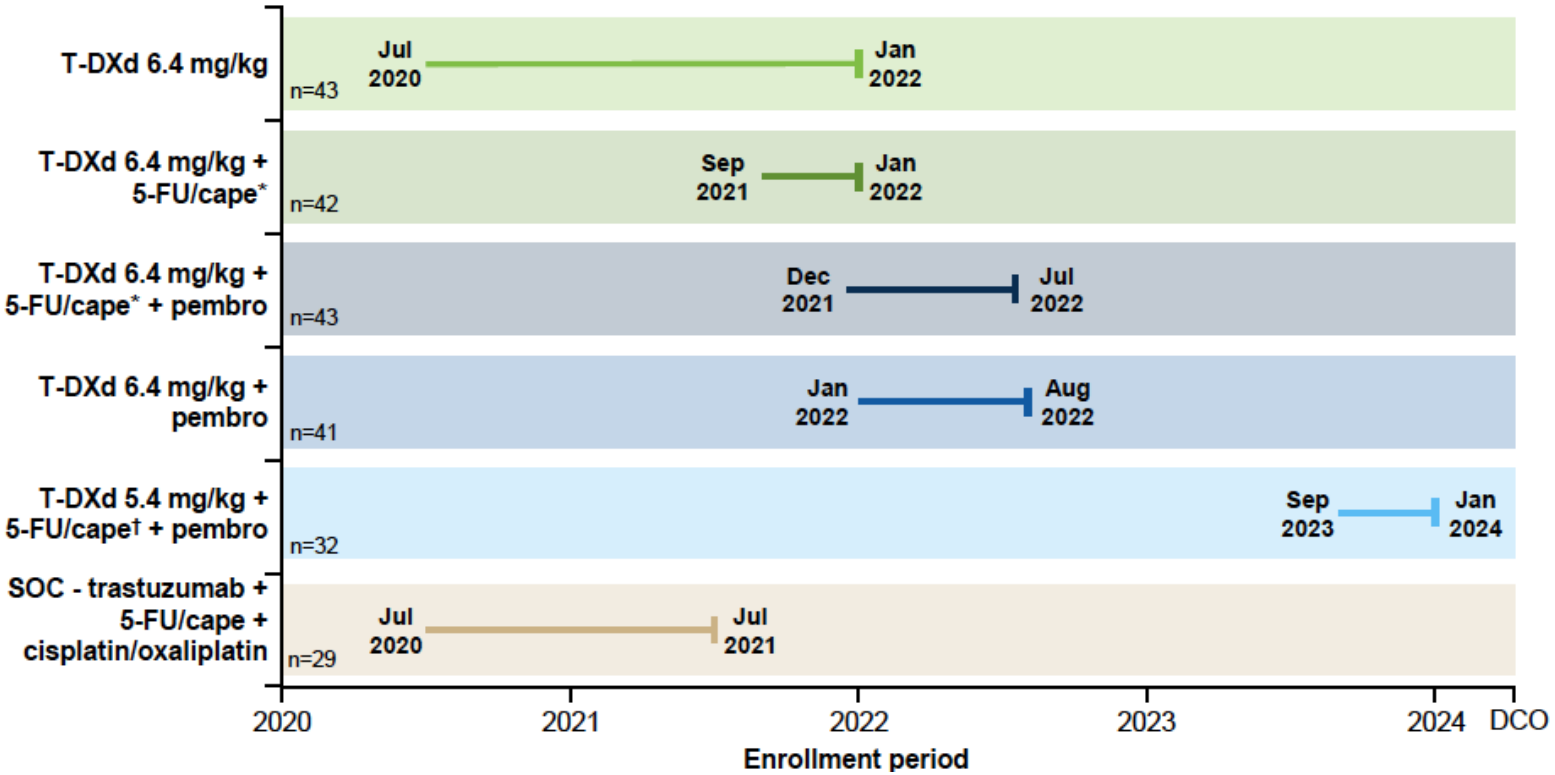
AEs, n (%)	Pembrolizumab Group N = 350	Placebo Group N = 346
Any	140 (40)	86 (25)
Serious	37 (11)	15 (4)
Grade 3-4	38 (11)	11 (3)
Grade 5	3 (1)	1 (<1)
Led to discontinuation of any drug	27 (8)	14 (4)



Janjigian YY et al. ESMO 2024;Abstract 1400O.

Trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients (pts) with advanced/metastatic HER2-positive (HER2+) esophageal, gastric or gastroesophageal junction adenocarcinoma (GEJA): DESTINY-Gastric03

Part 2 of DESTINY-Gastric03, a Phase 1b/2 trial (NCT04379596), with **non-contemporaneous and non-randomized arms**



Patient population

- Adults ≥18 years
- Unresectable, locally advanced or metastatic esophageal adenocarcinoma/GC/GEJA
- HER2+ (IHC 3+ or IHC 2+/ISH+ per local assessment)
- Treatment naïve for metastatic disease
- ECOG PS of 0 or 1

Part 2 endpoints

Primary

Confirmed ORR by investigator assessment

Secondary

- ORR, DOR, and PFS by investigator assessment, and OS
- Safety and tolerability

Exploratory

Antitumor activity by PD-L1 status

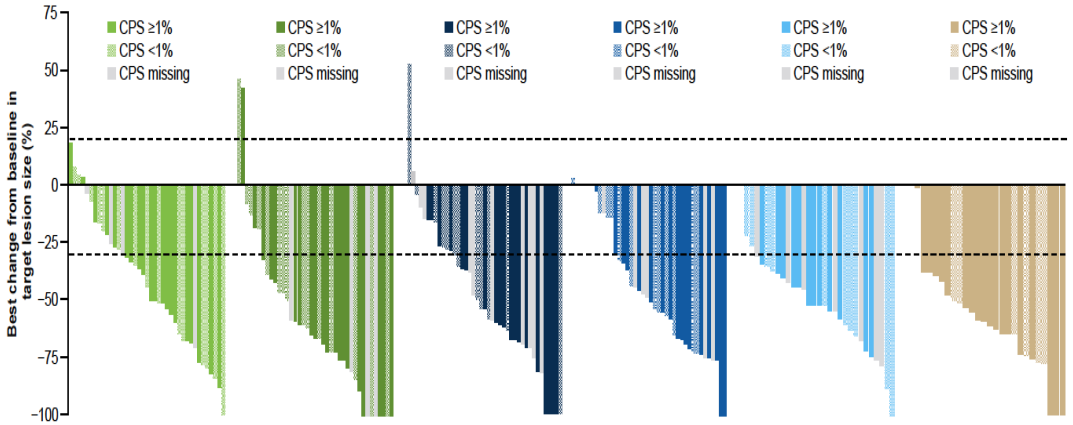
Janjigian YY et al. ESMO 2024;Abstract 1401O.

Trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients (pts) with advanced/metastatic HER2-positive (HER2+) esophageal, gastric or gastroesophageal junction adenocarcinoma (GEJA): DESTINY-Gastric03

Janjigian YY et al. ESMO 2024;Abstract 1401O.

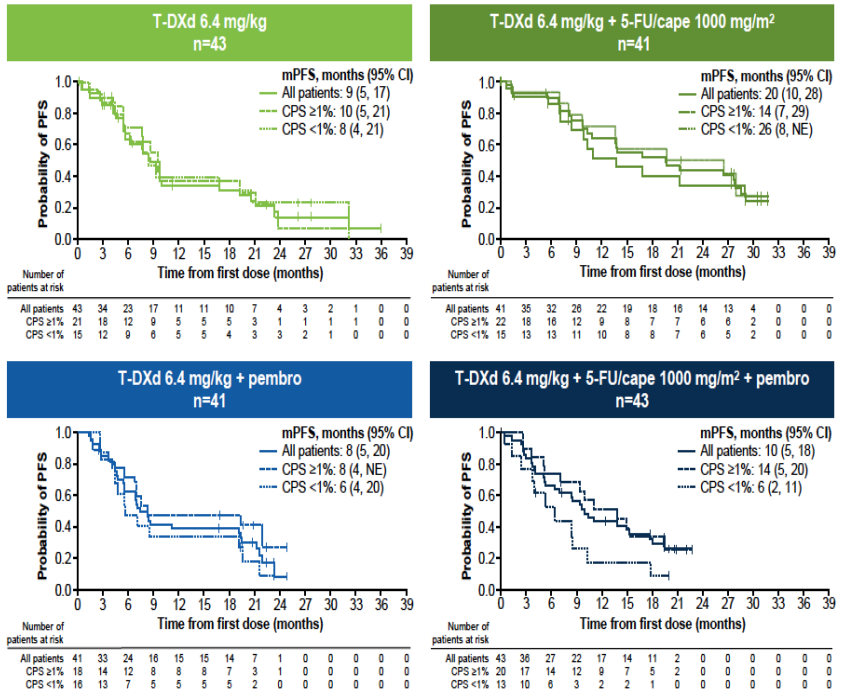
Objective response rate and best percentage change from baseline in target lesion size

	T-DXd 6.4 mg/kg n=43	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² n=41	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro n=43	T-DXd 6.4 mg/kg + pembro n=41	T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro n=32	SOC - trastuzumab + 5-FU/cape + cisplatin/oxaliplatin n=29
mFollow up, months	17	21	17	15	5	18
mDOR, months (95% CI)	18 (6, 30)	20 (12, 28)	17 (8, NE)	18 (5, 21)	NE (2, NE)	14 (5, 20)
Confirmed ORR, % (95% CI)	49 (33, 65)	78 (62, 90)	58 (42, 73)	63 (46, 78)	59 (40, 77)	76 (56, 90)
CPS ≥1%	57	77	70	78	62	85
CPS <1%	53	73	39	44	46	71



Assessments were by Investigator using RECIST 1.1. Best percentage change is the maximum reduction or minimum increase from baseline in the target lesion size; the dashed lines at −30% and 20% change in target lesion size indicate the thresholds for partial response and progressive disease, respectively.

Progression-free survival in all patients and by PD-L1 status



Data for arm T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro are immature

Treatment related SAE, n (%)	**8 (19)**	**7 (17)**	**22 (51)**	**14 (34)**	**1 (3)**
Treatment related deaths, n (%)	**0**	**1 (2)**	**4 (9)**	**4 (10)**	**0**
Grade ≥3 drug related ILD/Pneumonitis, n (%)	**0**	**0**	**3(7)**	**1(2)**	**0**

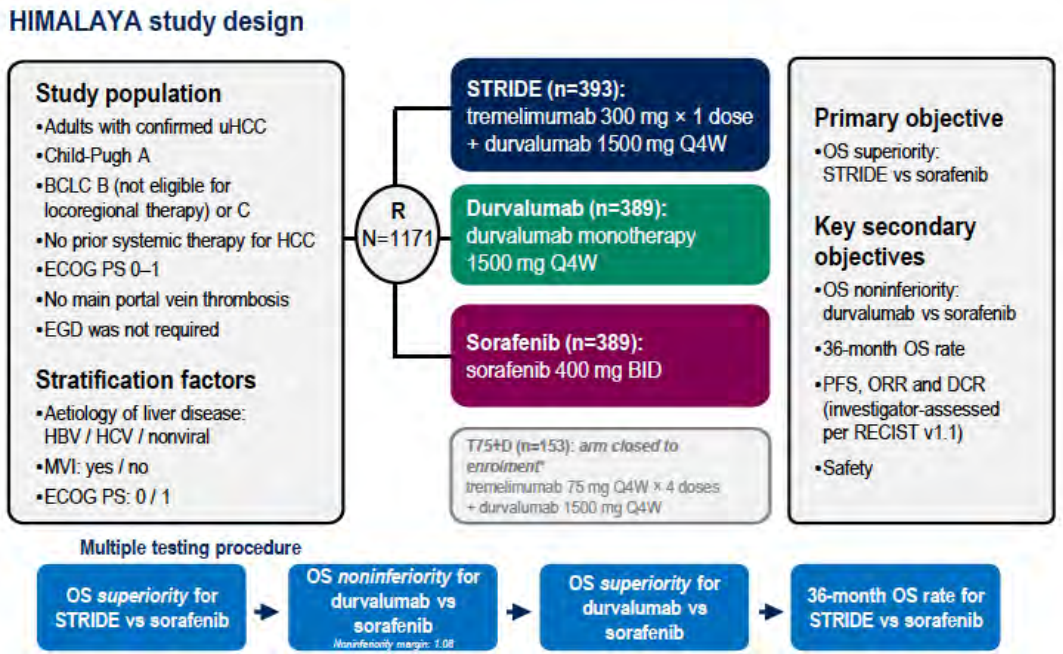
Questions?

Hepatocellular Cancer (HCC)

Dr. Bekaii-Saab - HCC Case

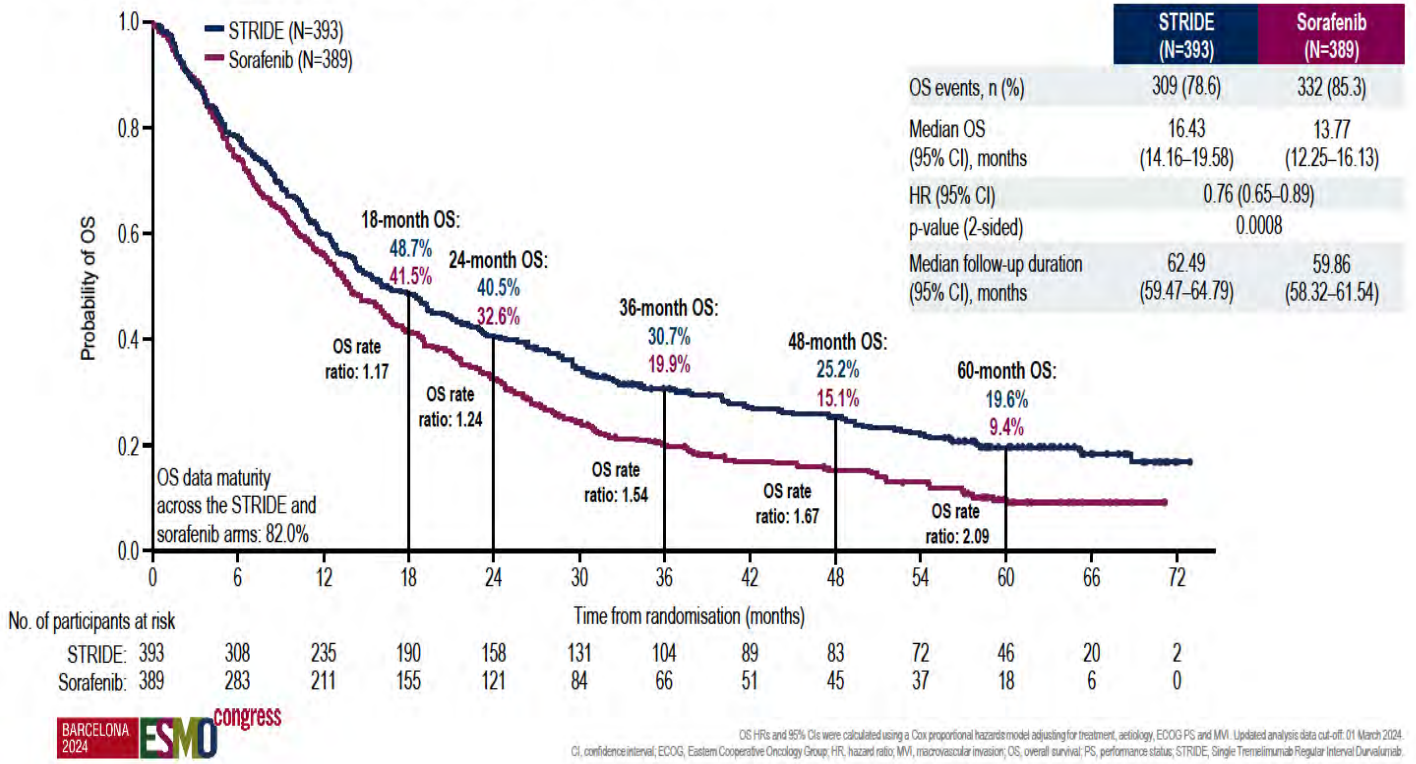
- 65 -year-old male presents with abdominal pain and weight loss in October 2022. Labs normal except for an elevated AST/ALT. CT abdomen/pelvis for abdominal pain showed 6.5 cm mass in the inferomedial margin of the liver.
- The patient undergoes surgical resection in December 2022 with clear margins and evidence of a moderately differentiated HCC
- AFP remains elevated at 65
- April 2023 a restaging CT of the chest, abdomen and pelvis shows numerous pulmonary nodules and a left liver mass consistent with HCC and large. AFP is now 1645
- May 2023, we initiated Durvalumab/Tremelimumab (STRIDE) with evidence of good tolerability except for mild diarrhea that was controllable. CT scans suggest a favorable response and in December 2023, repeat CTs chest show resolution of all pulmonary nodules with a significant decrease of the liver mass. His AFP is now WNL
- The patient remains on Durvalumab with good tolerability and a near CR

Five-year overall survival (OS) and OS by tumour response measures from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma (uHCC).



Five-year updated OS for STRIDE versus sorafenib

STRIDE demonstrated a sustained OS benefit versus sorafenib, with OS rates of 19.6% versus 9.4% at 5 years and the OS rate ratios for STRIDE versus sorafenib increasing over time



	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS (95% CI), months	16.43 (14.16–19.58)	13.77 (12.25–16.13)
HR (95% CI)	0.76 (0.65–0.89)	
p-value (2-sided)	0.0008	
Median follow-up duration (95% CI), months	62.49 (59.47–64.79)	59.86 (58.32–61.54)

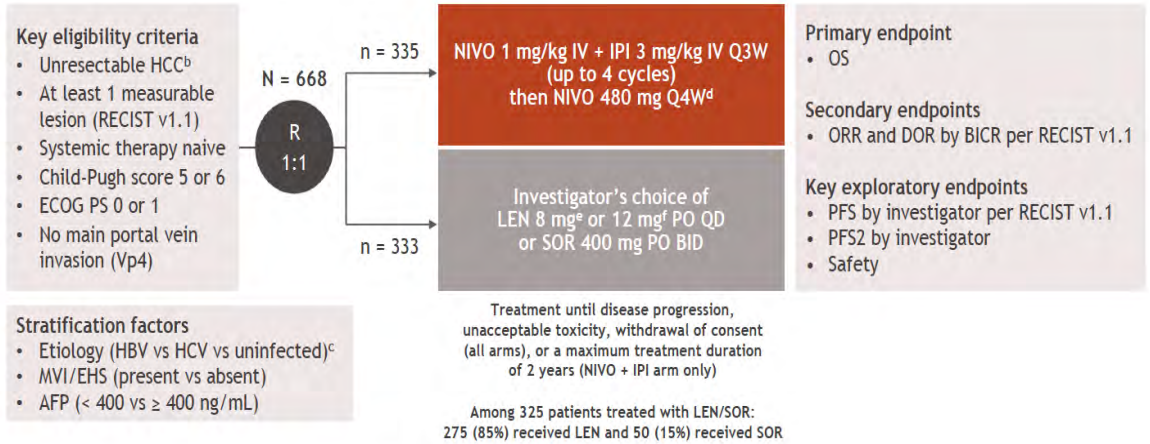
BARCELONA 2024 ESMO congress

OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. Updated analysis data cut-off: 01 March 2024.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MVI, macrovascular invasion; OS, overall survival; PS, performance status; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

Rimassa L et al. ESMO 2024;Abstract 947MO.

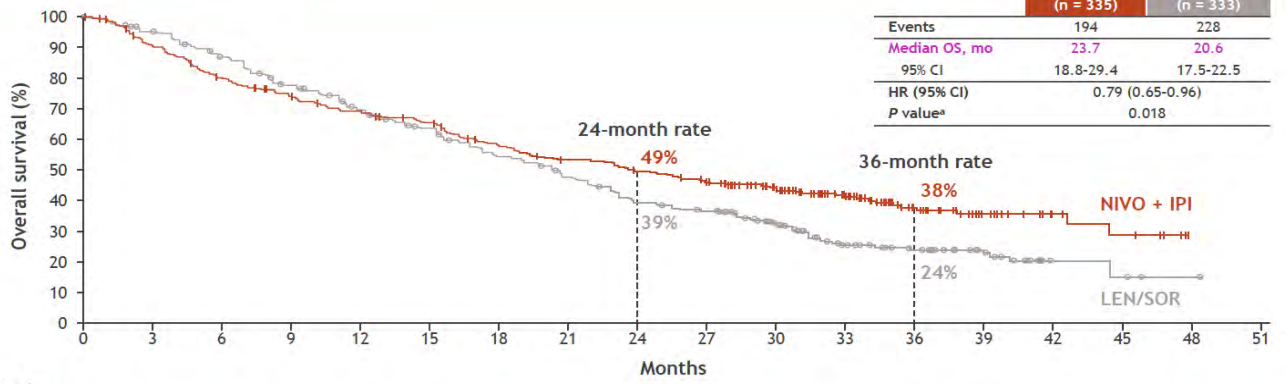
Nivolumab (NIVO) plus ipilimumab (IPI) vs lenvatinib (LEN) or sorafenib (SOR) as first-line (1L) treatment for unresectable hepatocellular carcinoma (uHCC): Expanded analyses from CheckMate 9DW.

- CheckMate 9DW is a global, phase 3, randomized, open-label study of NIVO in combination with IPI compared with LEN or SOR as 1L treatment in patients with unresectable HCC[a]



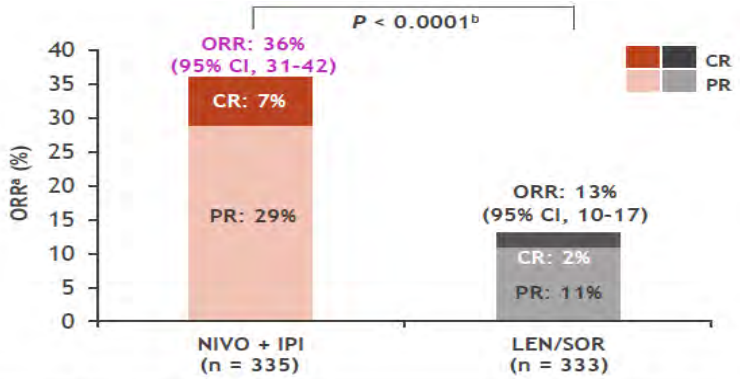
- At data cutoff (January 31, 2024), the median follow-up[g] was 35.2 months (range, 26.8-48.9)

Overall survival



	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	194	228
Median OS, mo	23.7	20.6
95% CI	18.8-29.4	17.5-22.5
HR (95% CI)	0.79 (0.65-0.96)	
P value[a]	0.018	

- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR
  - Longer median OS and long-term survival benefit with higher OS rates at 24 and 36 months



Best overall response,[a] %		
SD[c]	32	62
PD	20	14
Not evaluable	12	11
Median TTR (range),[a,d] mo	2.2 (1.1-11.6)	3.7 (0.6-11.2)
Median DOR (95% CI),[a,d] mo	30.4 (21.2-NE)	12.9 (10.2-31.2)

Progression-free survival

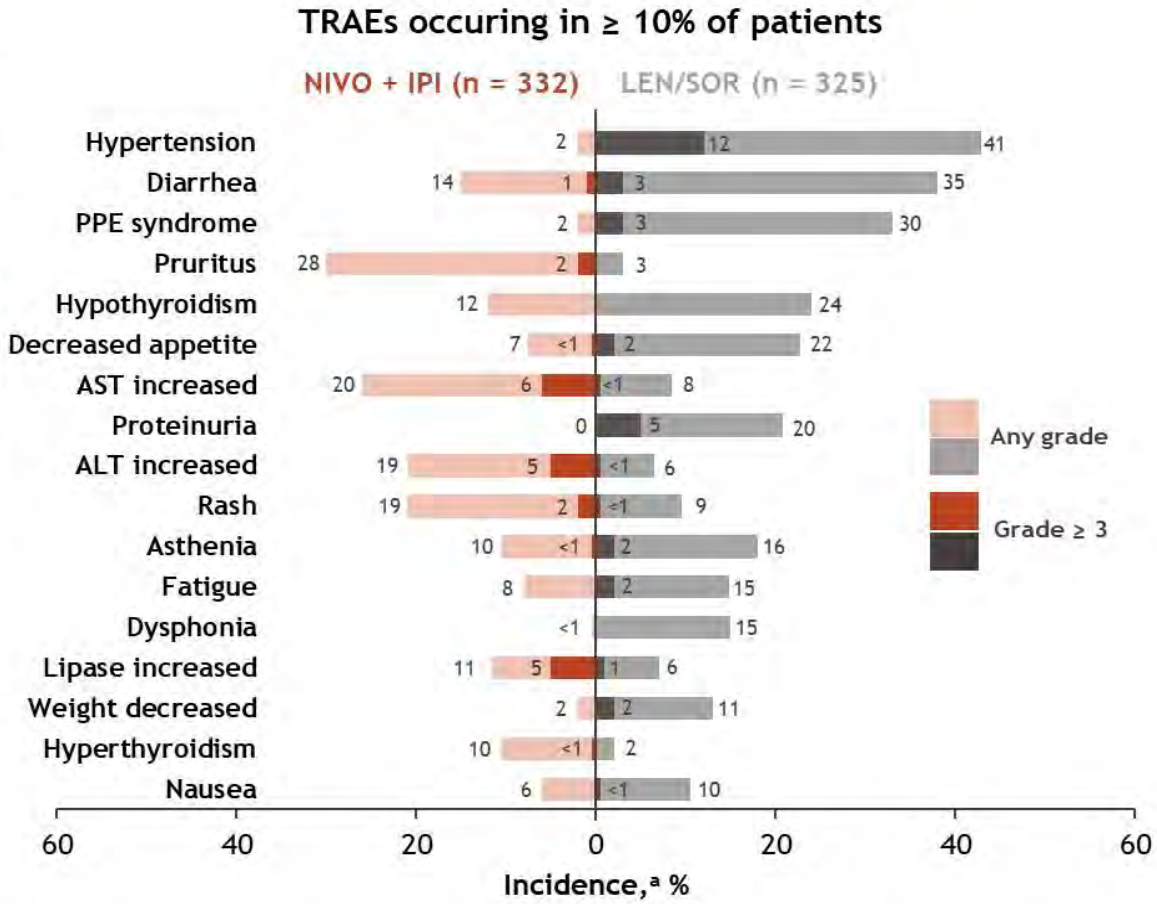
	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	242	281
Median PFS,[a,b] mo	7.5	7.5
95% CI	6.3-9.2	7.2-9.2
HR (95% CI)	0.72 (0.60-0.86)	

Decaens T et al. ESMO 2024;Abstract 965MO.

Treatment-related adverse events

All treated patients, n (%)	NIVO + IPI (n = 332)	LEN/SOR (n = 325)
Median (range) duration of treatment, mo	4.7 (< 1 to 24.4)	6.9 (< 1 to 45.8)

All treated patients, n (%)	NIVO + IPI (n = 332)		LEN/SOR (n = 325)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs[a]				
Any TRAEs	278 (84)	137 (41)	297 (91)	138 (42)
Serious TRAEs	94 (28)	83 (25)	47 (14)	42 (13)
TRAEs leading to discontinuation	59 (18)	44 (13)	34 (10)	21 (6)
Treatment-related deaths[b]	12 (4)[c]		3 (< 1)[d]	



[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Treatment-related deaths were reported regardless of time frame. [c]TRAEs leading to death in the NIVO + IPI arm included immune-mediated hepatitis (n = 4), hepatic failure (n = 3), hepatic insufficiency (n = 1), decompensated cirrhosis (n = 1), diarrhea-colitis (n = 1), autoimmune hemolytic anemia (n = 1), and dysautonomia (n = 1). [d]TRAEs leading to death in the LEN/SOR arm included hepatorenal syndrome (n = 1), ischemic stroke (n = 1), and acute kidney injury (n = 1).

Questions?

Transarterial chemoembolization (TACE) with or without lenvatinib (len) + pembrolizumab (pembro) for intermediate-stage hepatocellular carcinoma (HCC): Phase III LEAP-012 study

LEAP-012 Study Design (NCT04246177)

Key Eligibility Criteria

- Confirmed HCC not amenable to curative treatment
- ≥1 measurable HCC lesion per RECIST v1.1
- All lesions treatable with TACE in 1 or 2 sessions
- No portal vein thrombosis or extrahepatic disease
- Child-Pugh liver class A
- ECOG PS of 0 or 1

R 1:1

- Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) PO QD + Pembrolizumab 400 mg IV Q6W (up to 2 years) + TACE[b]
- Placebo PO QD + Placebo IV Q6W (up to 2 years) + TACE[b]

Stratification Factors

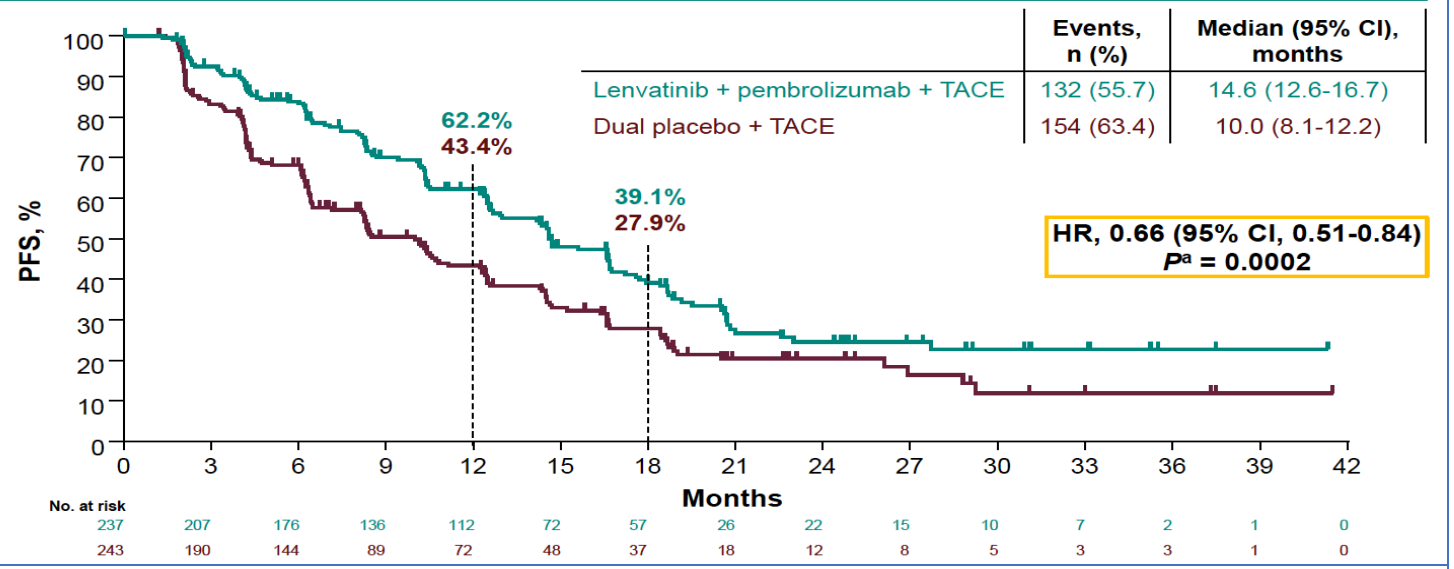
- Study site
- Alpha fetoprotein (≤400 ng/mL vs >400 ng/mL)
- ECOG PS (0 vs 1)
- ALBI grade (1 vs 2 or 3)
- Tumor burden score[1,a] (≤6 vs >6 but ≤12 vs >12)

End Points

- Primary: PFS[c] and OS
  - IA1 is the **final analysis** for PFS
  - Initial alpha of 0.025 (1-sided) allocated to PFS; passed to OS if PFS is statistically significant
- Secondary: ORR,[c,d] DOR,[c,d] DCR,[c,d] TTP,[c,d] PFS,[d] and safety

1. Wang Q et al. *J Hepatol*. 2019;70:893-903.
[a]Largest tumor in centimeters + number of tumors. [b]2-4 weeks after the start of systemic therapy with a maximum of 2 treatments per tumor (4 total) and no more than 1 treatment per month.
[c]Per RECIST v1.1 by BICR. [d]Per mRECIST by BICR.

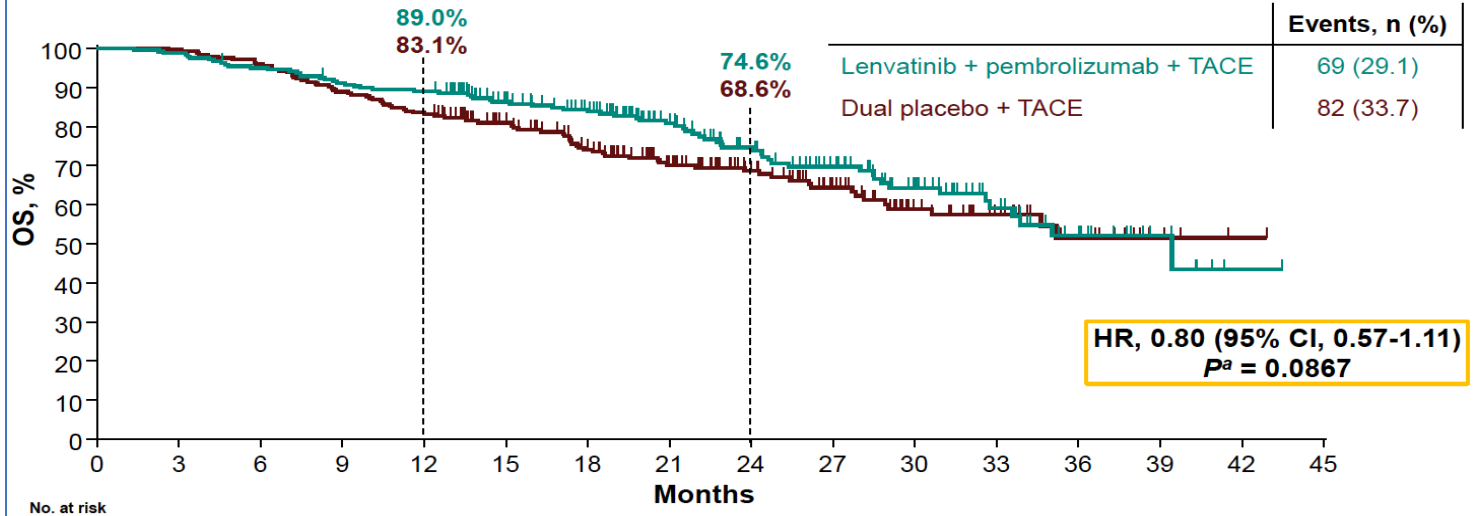
Progression-Free Survival per RECIST v1.1 by BICR



	Events, n (%)	Median (95% CI), months
Lenvatinib + pembrolizumab + TACE	132 (55.7)	14.6 (12.6-16.7)
Dual placebo + TACE	154 (63.4)	10.0 (8.1-12.2)

HR, 0.66 (95% CI, 0.51-0.84)
P^a = 0.0002

Overall Survival



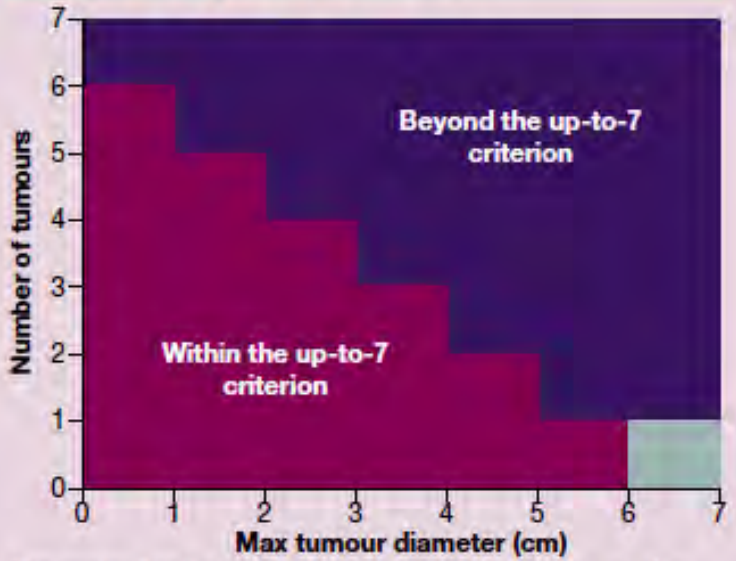
	Events, n (%)
Lenvatinib + pembrolizumab + TACE	69 (29.1)
Dual placebo + TACE	82 (33.7)

HR, 0.80 (95% CI, 0.57-1.11)
P^a = 0.0867

Llovet J et al. ESMO 2024;Abstract LBA3.

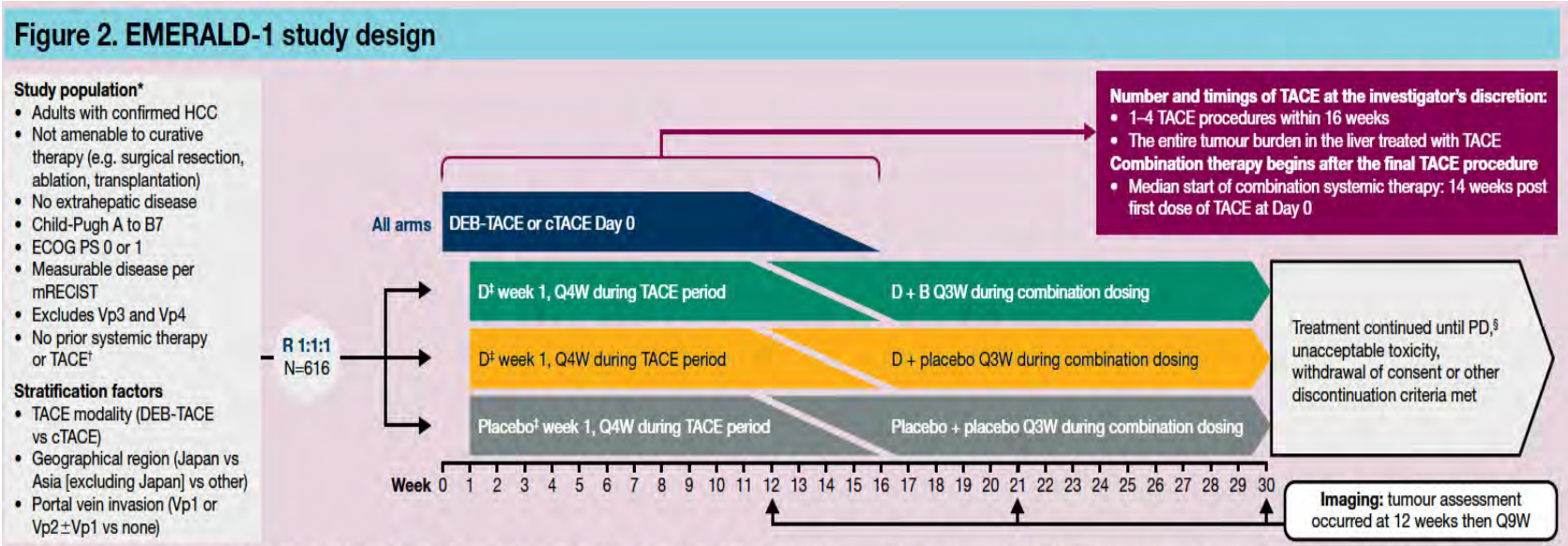
Outcomes by baseline tumour burden in EMERALD-1: A phase III, randomised, placebo (PBO)-controlled study of durvalumab (D) ± bevacizumab (B) with transarterial chemoembolisation (TACE) in participants (pts) with embolisation-eligible unresectable hepatocellular carcinoma (uHCC)

Figure 1. Up-to-7 criterion



The up-to-7 criterion is defined as HCC with seven as the sum of the number of tumours and size of tumour (cm). This includes all combinations of a given HCC from one nodule up to 6 cm in size (1+6=7) to many tumours fulfilling seven as tthe sum of the size plus number of tumours (i.e. two tumours up to 5 cm in size, three tumours up to 4 cm in size, four tumours up to 3 cm in size and five tumours up to 2 cm in size).[5]

Figure 2. EMERALD-1 study design



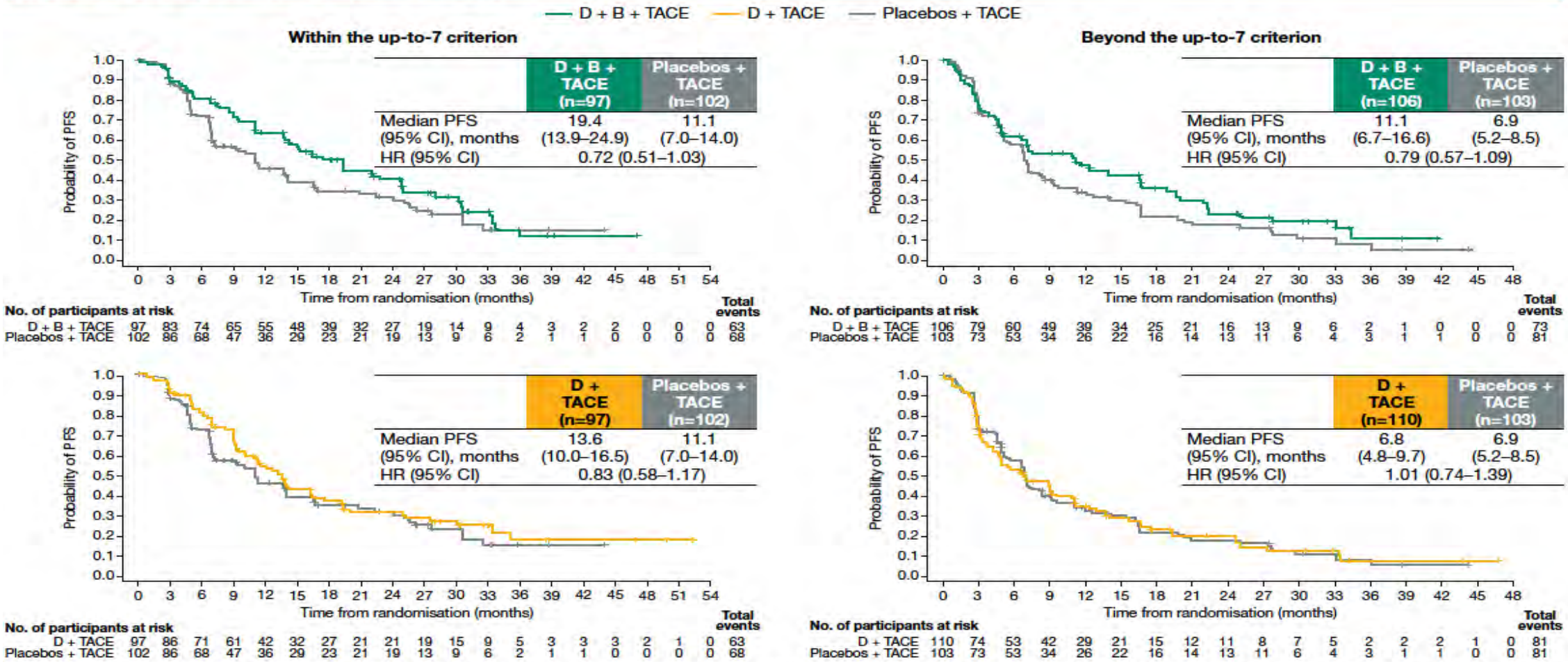
*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomisation. †Prior use of TACE or transarterial embolisation is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡D/placebo started ⩾7 days after first TACE procedure; doses moved to accommodate TACE if necessary. §Investigator-determined mRECIST-defined radiological disease progression; participants with mRECIST-defined progression may continue to receive study treatment, including additional TACE, at the discretion of the investigator and participant, and in consultation with the AstraZeneca study physician.

B, bevacizumab; cTACE, conventional transarterial chemoembolisation; D, durvalumab; DEB-TACE, drug-eluting bead transarterial chemoembolisation; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; R, randomised; TACE, transarterial chemoembolisation; Q3W/Q4W/Q9W, every 3/4/9 weeks.

Kudo M et al. ESMO 2024; Abstract 950P.

Outcomes by baseline tumour burden in EMERALD-1: A phase III, randomised, placebo (PBO)-controlled study of durvalumab (D) ± bevacizumab (B) with transarterial chemoembolisation (TACE) in participants (pts) with embolisation-eligible unresectable hepatocellular carcinoma (uHCC)

Figure 3. PFS by baseline tumour burden



PFS was assessed by BICR per RECIST v1.1. The HR and CIs were estimated using a stratified Cox proportional hazards model, with the CI being calculated using a profile likelihood approach. The model was adjusted for treatment and stratified by TACE modality (DEB-TACE vs cTACE), geographical region (Japan vs Asia [excluding Japan] vs other) and portal vein invasion (Vp1 or Vp2±Vp1 vs none). Median PFS was calculated using the Kaplan-Meier technique.

B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; cTACE, conventional transarterial chemoembolisation; D, durvalumab; DEB-TACE, drug-eluting bead transarterial chemoembolisation; HR, hazard ratio; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolisation.

Kudo M et al. ESMO 2024; Abstract 950P.

Questions?

Biliary Tract Cancer (BTC)

Durvalumab (TOPAZ1) or Pembrolizumab (K966) plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

Agent	Durvalumab		Pembrolizumab	
Trial	**TOPAZ1**		**K966**	
	Durvalumab (N=341)	Placebo (N=344)	Pembrolizumab (N=533)	Placebo (N=536)
ORR (%)	27%	19%	29%	29%
Median PFS, mos	7.2	5.7	6.5	5.6
	0.75 (95% CI, 0.63 to 0.89) P=0.001		HR 0.87 (95% CI, 0.76 to 0.99)	
Median OS, mos	12.8	11.5	12.7	10.9
	0.80 (95% CI, 0.66 to 0.97) P=0.021		HR 0.83 (95% CI 0.72 to 0.95) P=0.0034	
Adverse Events (G3/4/5)	63%	65%	70%	69%

Oh DY et al. *NEJM Evid* 2022;1(8):EVIDoa2200015. Kelley RK et al. *Lancet* 2023;401(10391):1853-1865.

FGFR Inhibitor Efficacy in *FGFR2* Fusion BTC

	Pemigatinib (N=107)	Infigratinib (N=108)	Futibatinib (N=103)
ORR	36%	23% (1 prior Line of Rx 34%)	42%
DCR	82%	84%	83%
mPFS	6.9 mos	7.3 mos	9 mos
mDOR	7.5 mos	5 mos	9.7 mos
mOS	21.1 mos	12.2 mos	21.7 mos
Toxicities (G3/4)	64% Hyperphosphatemia, Alopecia, Diarrhea	64% Hyperphosphatemia, Stomatitis, Fatigue	57% Hyperphosphatemia, Diarrhea, Dry mouth

1. Abou-Alfa GK et al. *Lancet Oncol.* 2020;21(5):671-684; 2. Javle M et al. Lancet GH, 20213. Goyal L et al. NEJM 2023.

HER2 Inhibitor Strategies in HER2+ BTC

	Pertuzumab/Trastuzumab (MyPathway - N=39)[a]	Tucatinib/Trastuzumab (SGNTUC-019 - N= 30)[a]	Trastuzumab Deruxtecan (HERB; NCCH1805 N=22)[b]	Trastuzumab Deruxtecan (DESTINY-PanT02 N=16)[c]	Zanidatamab (HERIZON-BTC-01- N= 80)[d]
ORR	23%	46.6%	36.4%	56.3%	41.3%
DCR	74%	76.6%	81.8%	66% (@12wks)	68.8%
mPFS	4.0 mos	5.5 mos	5.1 mos	7.4 mos	5.5 mos
mOS	10.9 mos	15.5 mos	7.1 mos	12.4 mos	NR (70% @ 9 mos)
DOR	10.8 mos	6 mos	7.4 mos	8.6 mos	12.9 mos
Toxicities (G3/4)	46%	60%	81.3%	73.2%	57.5%

[a] IHC 3+ or FISHC/ISH+ or Ampl by NGS
[b] IHC 3+ or 2+/ISH+
[c] IHC 3+
[d] IHC 3+ or 2+ and ISH+

1. Javle, et al Lancet Oncol, 2021; 2. Nakamura et al , J Clin Oncol 2023; 3.Ohba et al . J Clin Oncol 2024; 4. Meric-Bernstram et al J. Clin Oncol 2024; 5. Harding et al Lancet Oncol 2023

Questions?

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Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A Multitumor Hybrid Symposium in Partnership with Florida Cancer Specialists & Research Institute

Saturday, October 26, 2024

HR-Positive Breast Cancer

Faculty

Joyce O'Shaughnessy, MD

Seth Wander, MD, PhD

Prostate Cancer

Faculty

Matthew R Smith, MD, PhD

Sandy Srinivas, MD

Moderator

Neil Love, MD

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Lung Cancer

Faculty

Sarah B Goldberg, MD, MPH

Joshua K Sabari, MD

Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Faculty

Brad S Kahl, MD

Sonali M Smith, MD

Moderator

Neil Love, MD

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Saturday, October 26, 2024

Multiple Myeloma

Faculty

Shaji K Kumar, MD

Noopur Raje, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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