ESMO IN FOCUS WEBINAR ASIA - GASTROINTESTINAL CANCERS

Raghav Sundar

Chair

Yale School of Medicine
New Haven, CT

ESMO WEBINAR SERIES

ESMO IN FOCUS

INTRODUCTION

Programme

26 October 2024

5 min	**Welcome & Introduction** Raghav Sundar
15 min	**Unmet needs in GI cancers: rare tumours and research in organ-preserving modalities** Raghav Sundar
15 min	**Integrating immunotherapy in the management of patients with advanced colorectal cancer** Thierry André
15 min	**Breakthroughs in HCC treatment** Angela Lamarca
15 min	**Emerging data on optimisation of combination regimens for patients with advanced HER2+ gastric cancer** Izuma Nakayama
20 min	**Questions & Answers** All faculty
5 min	**Concluding remarks** Angela Lamarca

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Angela Lamarca
Chair
Fundacion Jimenez Diaz
University Hospital, Madrid

Thierry André
Speaker
Sorbonne Université and
Saint Antoine Hospital,
Paris

Izuma Nakayama
Speaker
National Cancer Center
Hospital East, Kashiwa

INTRODUCTION

Learning objectives

- To update oncologists on state of the art management of patients with gastrointestinal cancers
- To provide expert insights on biology-informed implementation of precision oncology in gastrointestinal cancers
- To highlight ongoing clinical research in gastrointestinal cancers

Thank you!

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UNMET NEEDS IN GI CANCERS

Rare tumors and research in organ-preserving modalities

Raghav Sundar, MBBS PhD

Yale School of Medicine and Yale Cancer Center

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DISCLOSURES

Advisory board

Bristol Myers Squibb, Merck, Eisai, Bayer, Taiho, Novartis, MSD, GSK, DKSH, Astellas, Pierre-Fabre, Tavotek, Astra Zeneca, Sanofi, Daichii Sankyo, Beigene

Honoraria for talks

MSD, Eli Lilly, BMS, Roche, Taiho, Astra Zeneca, DKSH, Ipsen, Daiichi Sankyo, Beigene, Astellas

Travel

Roche, Astra Zeneca, Taiho, Eisai, DKSH, Ipsen, CytoMed, Paxman

Research funding

Paxman Coolers, MSD, Natera, CytoMed

Patents

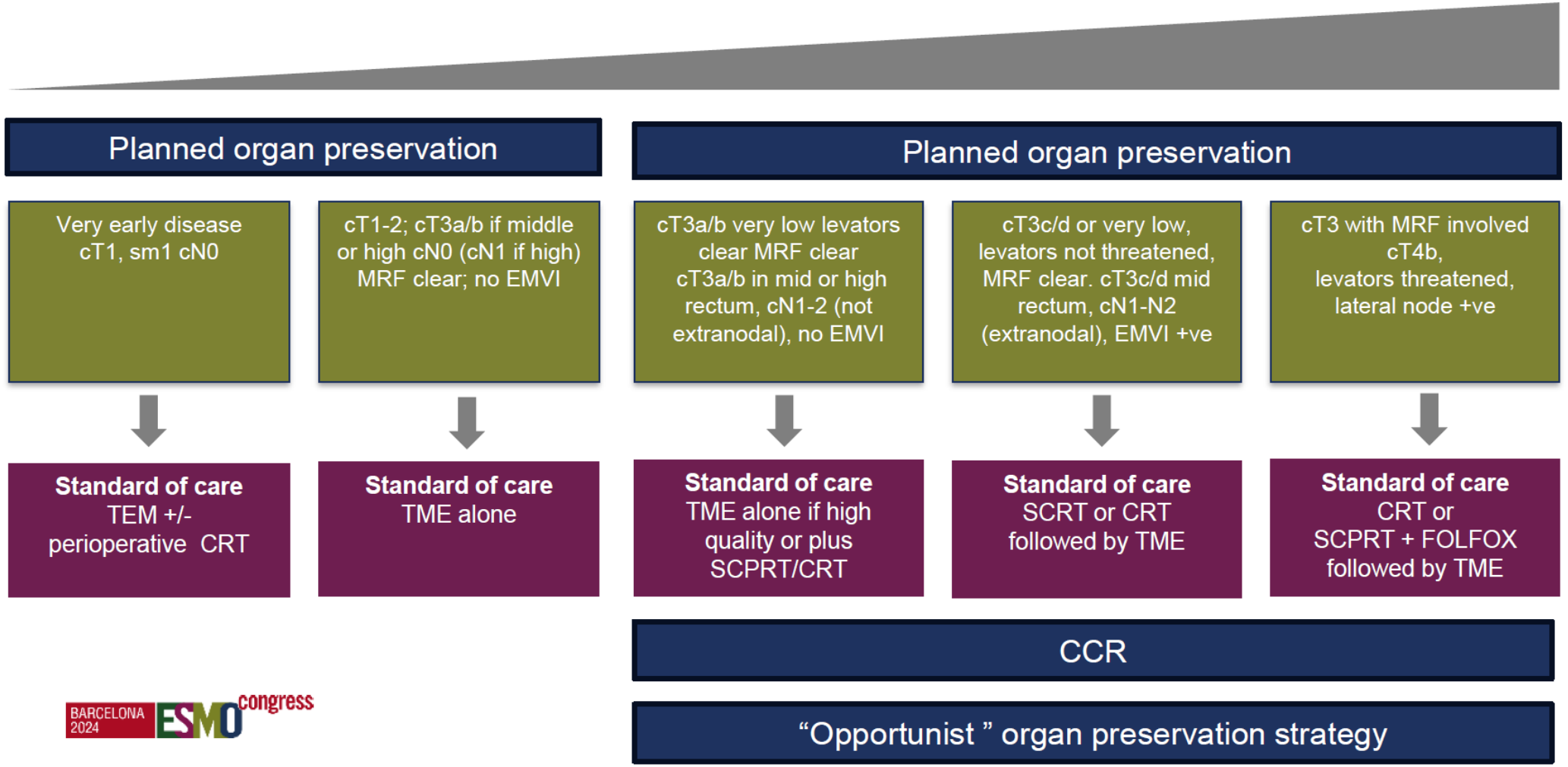
Paxman, Auristone

RATIONALE FOR ORGAN PRESERVATION IN RECTAL CANCER

- PATIENT PREFERENCE
- Surgical Risks
  - TME: overall morbidity (~30-40%), mortality (2-3%), urinary and sexual dysfunction
  - Permanent stoma for low tumors
- Frailty/Inability to undergo surgery
- Ageing population and increase in early-onset CRC
- Increase in response rates with better systemic therapy, TNT approach and biomarker selection (MSI-H/dMMR)
- TME surgery remains a standard of care management for non-metastatic rectal cancer

Hendren SK et al. Annals of surgery2005; 242(2): 212-23
Araujo RO et al. Supportive Care in Cancer. 2022 Aug;30(8):6557
Andres Cervantes, Mehdi Karoui, Dirk Arnold and Rachel Riechelmann ESMO Webinar 2023
Christos Karapetis, ESMO Asia 2022
David Sebag-Montefiore, ESMO 2024

ORGAN PRESERVATION IN RECTAL CANCER



BARCELONA 2024 ESMO congress

Slide courtesy David Sebag-Montefiore ESMO 2024

Total Neoadjuvant Treatment (TNT) including Non-Operative Management (NOM) for Proficient Mismatch Repair Locally Advanced Rectal Cancer (pMMR LARC): First Results of NO-CUT Trial

Amatu A.[1], Zampino M. G.[2], Bergamo F.[3], Mosconi S.[4], Sibio D.[1], Gerardi M. A.[2], Prete A. A.[3], Filippone F. R.[4], Ferrari G.[1], Borin S.[2], Galuppo S.[3], Mariano S.[1], Tosi F.[1], Bonazzina E.[1], Patelli G.[1,5,6], Ghezzi S.[1], Lazzari L.[6], Bencardino K.[1], Sartore-Bianchi A.[1,5], and Siena S.[1,5]
on behalf of the NO-CUT Trial Cooperative Group

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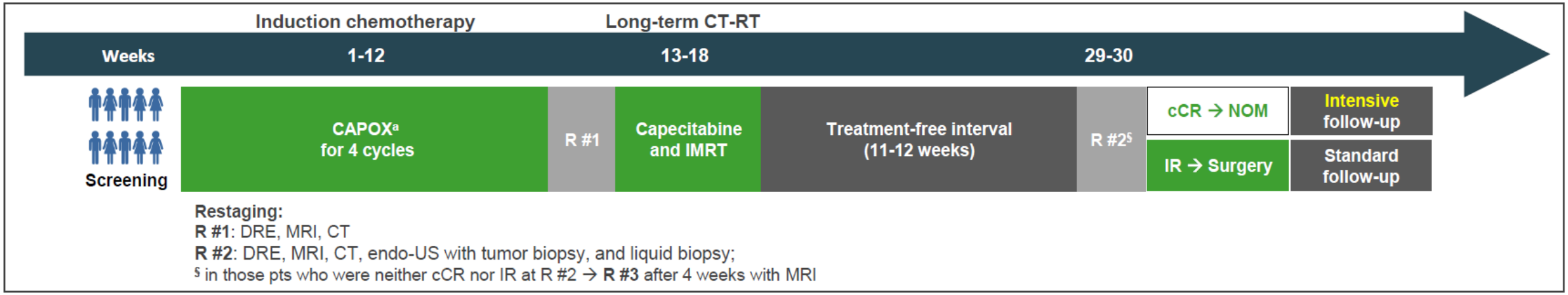
[5] Università degli Studi di Milano, Milan, Italy
[6] IFOM ETS The AIRC Institute of Molecular Oncology

NO-CUT TRIAL DESIGN

180 patients with mid/low cT3-4 and/or cN1-2, cM0, pMMR/MSS, rectal adenocarcinoma; ECOG PS 0-1, fit for surgery



- **Primary endpoint**: % of patients alive and distant relapse free at 30 months ($DRFS_{30}$, H_0: 75% and H_1: 82%); at least 44 NOM patients were needed, with an $\alpha = 10\%$ and $\beta = 20\%$ to reject H_0
- **Secondary endpoints**: cCR rate, organ preservation rate in NOM patients

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PATIENT CHARACTERISTICS

- Between June 2018 and August 2023, 180 patients were enrolled across 4 high-volume centers
- Median follow-up at time of analysis is 27 months (range 3-68)
- One death due to toxicity (0.5%), 9 (5%) to tumor progression, and 2 (1%) to other causes

Number of patients		180
Median age (range)		62 (31-83)
Sex (%)	Female	80 (44)
	Male	100 (56)
ECOG PS (%)	0	131 (73)
	1	47 (26)
	≥2	2 (1)
Tumor location (%)	Low	73 (41)
	Medium	107 (59)
Clinical T stage (%)	T1	2 (1)
	T2	13 (7)
	T3	133 (74)
	T4	32 (18)
Clinical TNM stage (%)	II	20 (11)
	III	160 (89)
Median CEA, ng/mL (range)		2.8 (0.2-183)

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RESPONSE RATES

- 26% patients achieved cCR and proceeded with NOM
- 90% patients who had IR underwent surgery
- T stage was confirmed as a clinical predictor of cCR
- Tumor location (low) was associated with response

		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)	

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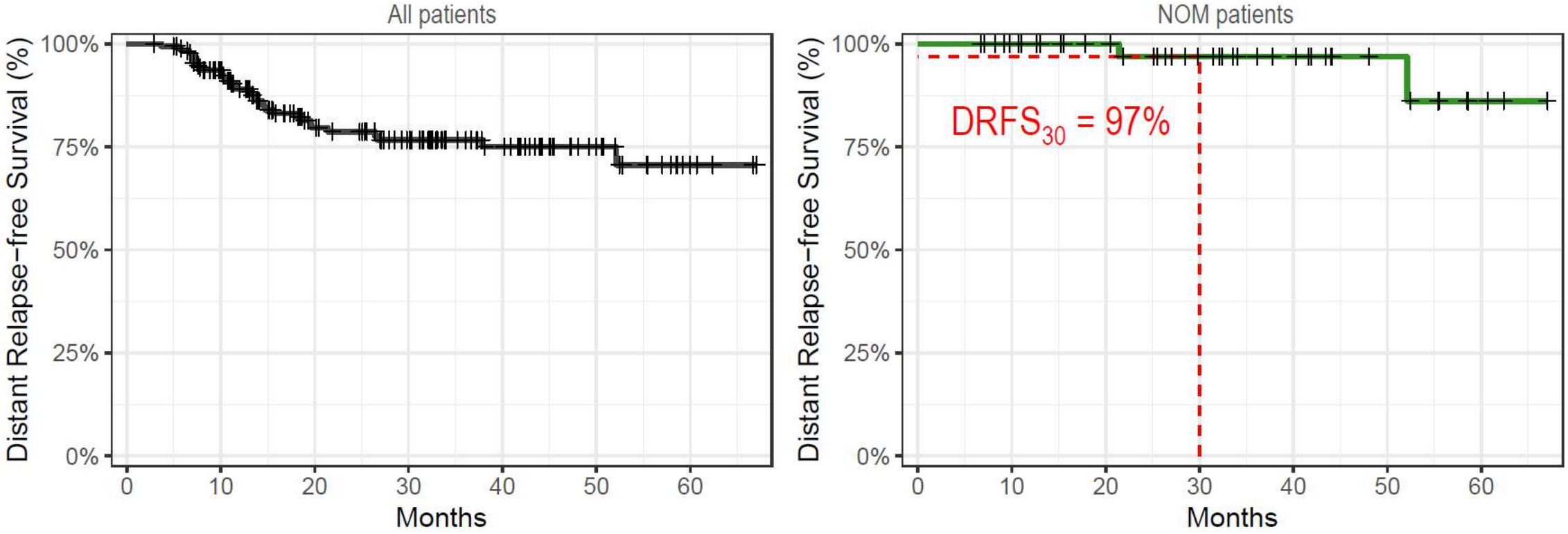
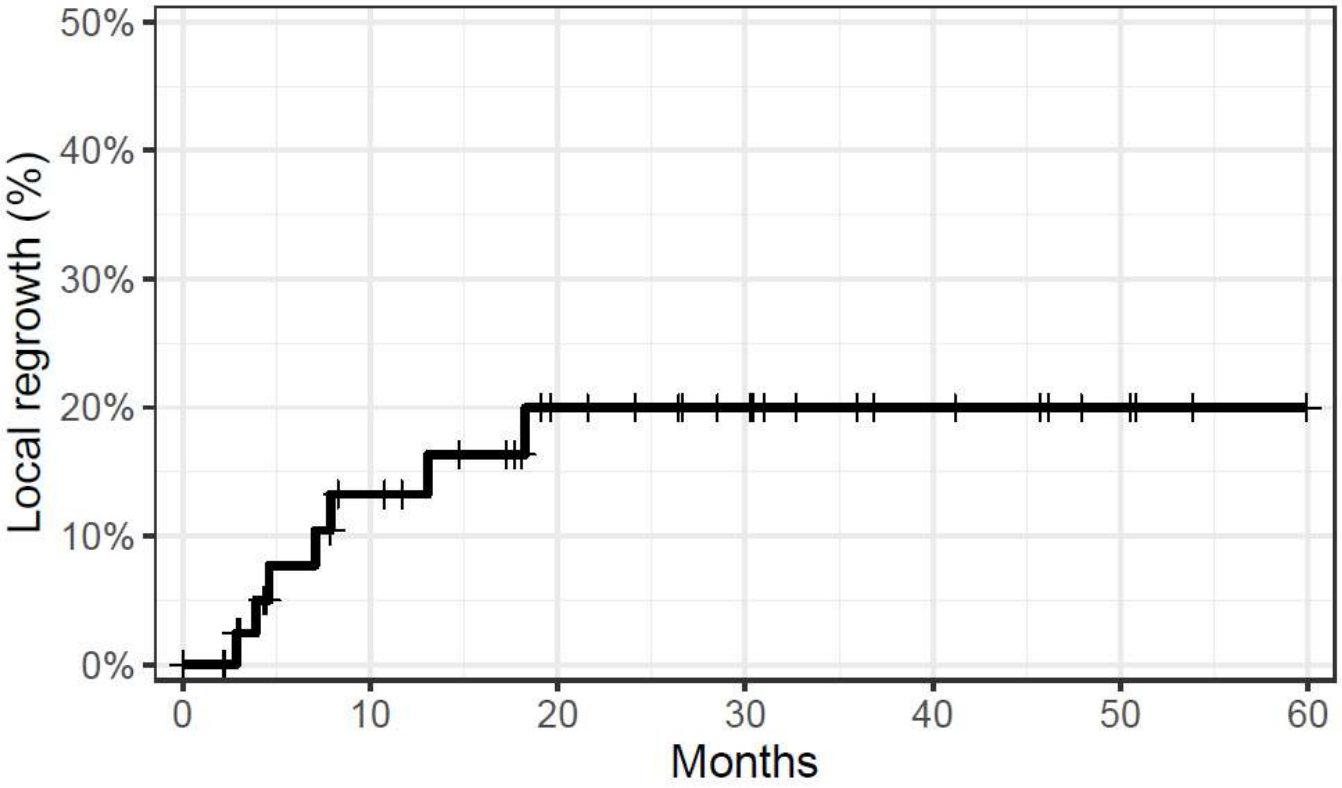
PRIMARY ENDPOINT: DISTANT RFS



Primary endpoint (Distant Relapse-Free Survival at 30 months, $DRFS_{30}$) was met:

- **In NOM pts (n = 46) $DRFS_{30}$ 96.9% (95%CI 91.0-100.0)**
- In **all pts** (n = 180) $DRFS_{30}$ 76.7% (95%CI 69.8-84.2)

ORGAN PRESERVATION RATE



- **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

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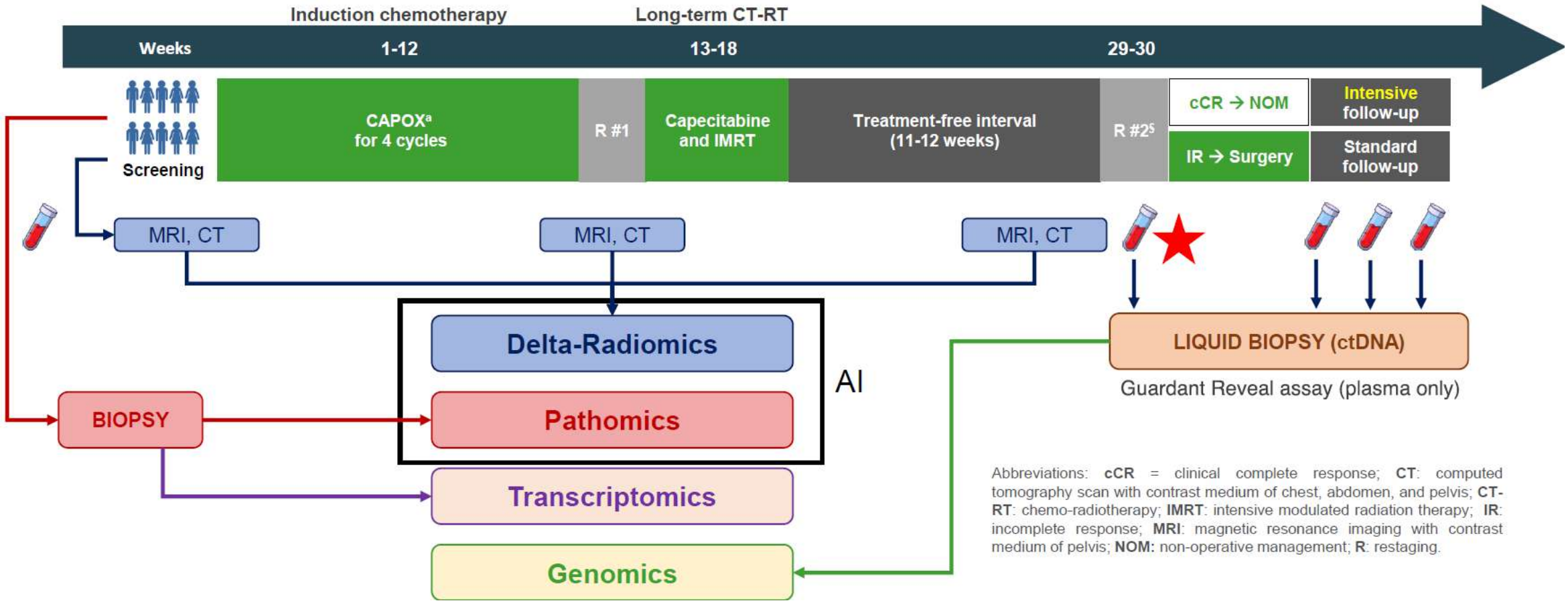
NO-CUT TRANSLATIONAL PROGRAM



Abbreviations: **cCR** = clinical complete response; **CT**: computed tomography scan with contrast medium of chest, abdomen, and pelvis; **CT-RT**: chemo-radiotherapy; **IMRT**: intensive modulated radiation therapy; **IR**: incomplete response; **MRI**: magnetic resonance imaging with contrast medium of pelvis; **NOM:** non-operative management; **R**: restaging.

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AUTHOR CONCLUSIONS

- In NO-CUT Trial, one out of 4 patients (26%) with locally advanced pMMR/MSS adenocarcinoma of low-mid rectum benefited from Total Neoadjuvant Therapy (TNT)
- Non-Operative Management:
  - did not jeopardize Distant Relapse-Free Survival ($DRFS_{30}$ 97%)
  - led to organ preservation in 85% (39/46)

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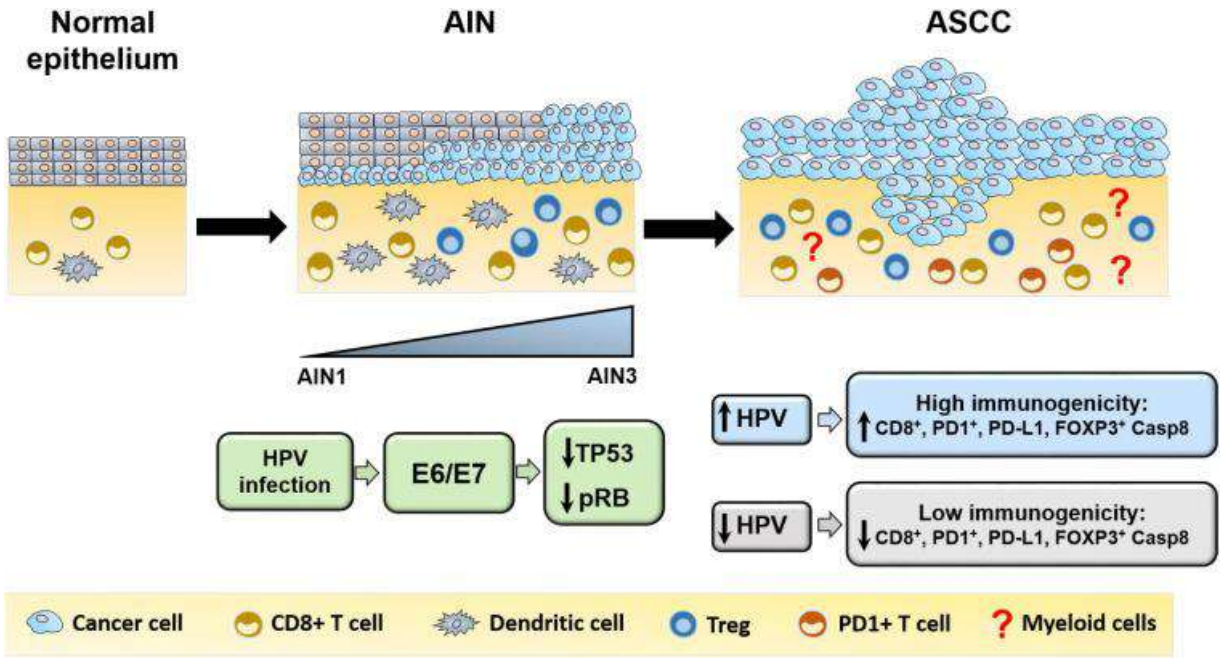
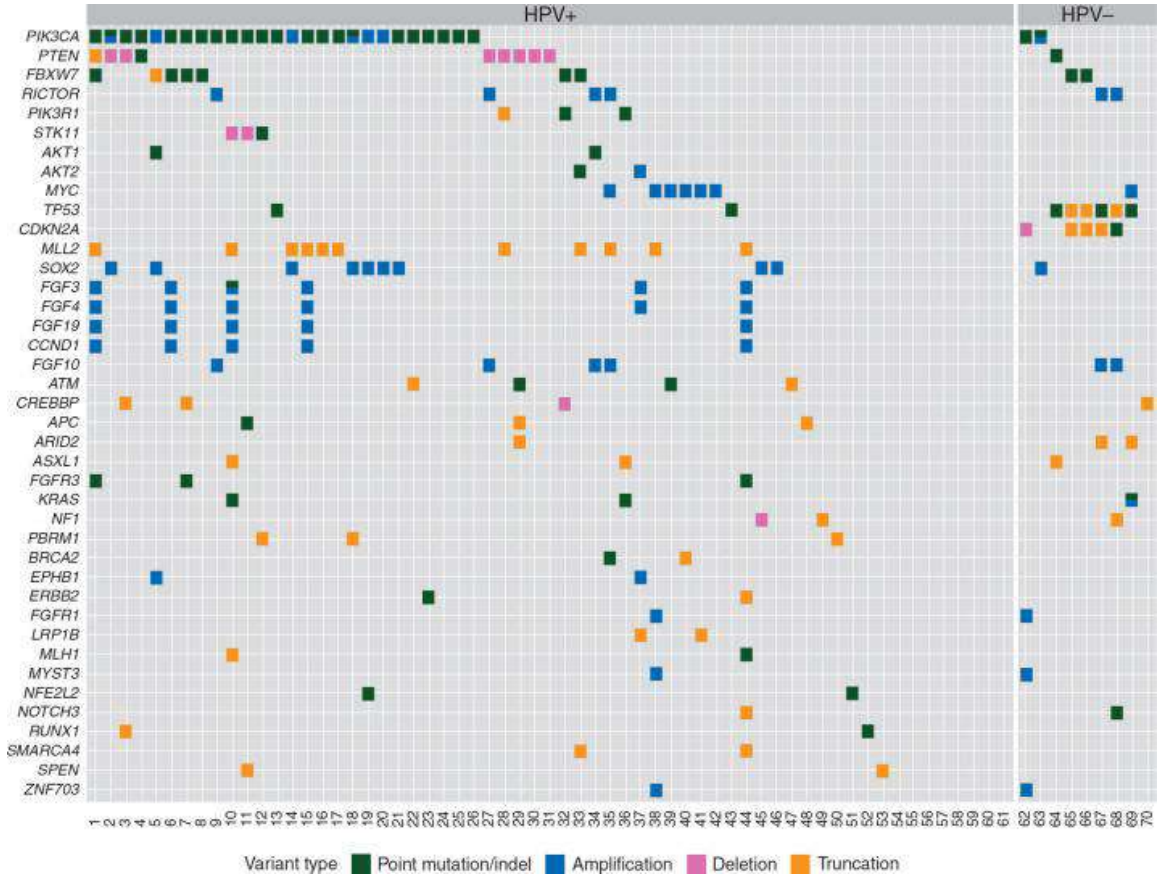
PUTTING NO-CUT INTO PERSPECTIVE

- cCR rates from NO-CUT are consistent with previous TNT trials (~15-50%)
- TNT -> cCR -> W&W is a reasonable approach that is emerging with supportive data from observational studies, prospective cohorts and clinical trials
- However, patient counselling on surgery remaining a standard of care, need for surgery for incomplete responses and salvage for local recurrence as well as stricter follow-up schedule for W&W must be carefully laid out
- Also important to consider if we have the resources for W&W (scan, endoscopy, specialist review)
- The need for TNT (especially in very early disease) and optimal TNT regimen is not addressed yet
- Personalized management is key

ANAL SQUAMOUS CELL CANCER



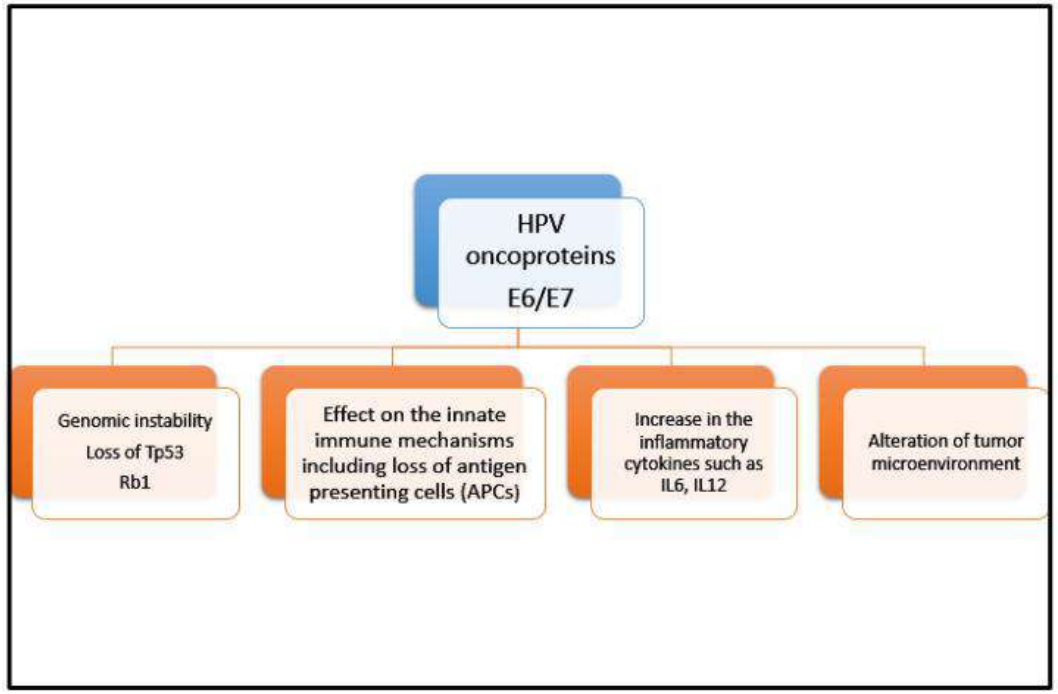
Martin et al, Bio Bio Act 2017



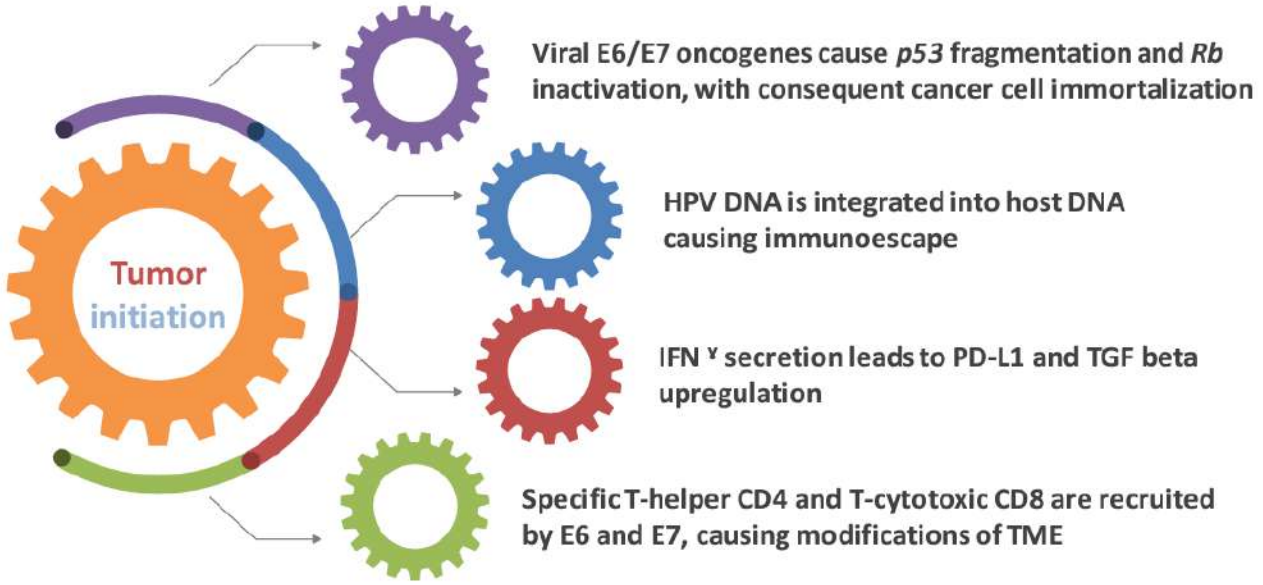
Chung et al, Ann Oncol 2016

Low incidence of MSI-H/dMMR

HPV MODULATED TME CHANGES AND IMMUNOGENICITY



Dhawan et al, Curr Oncol 2023



Lonardi, ESMO Webinar 2023

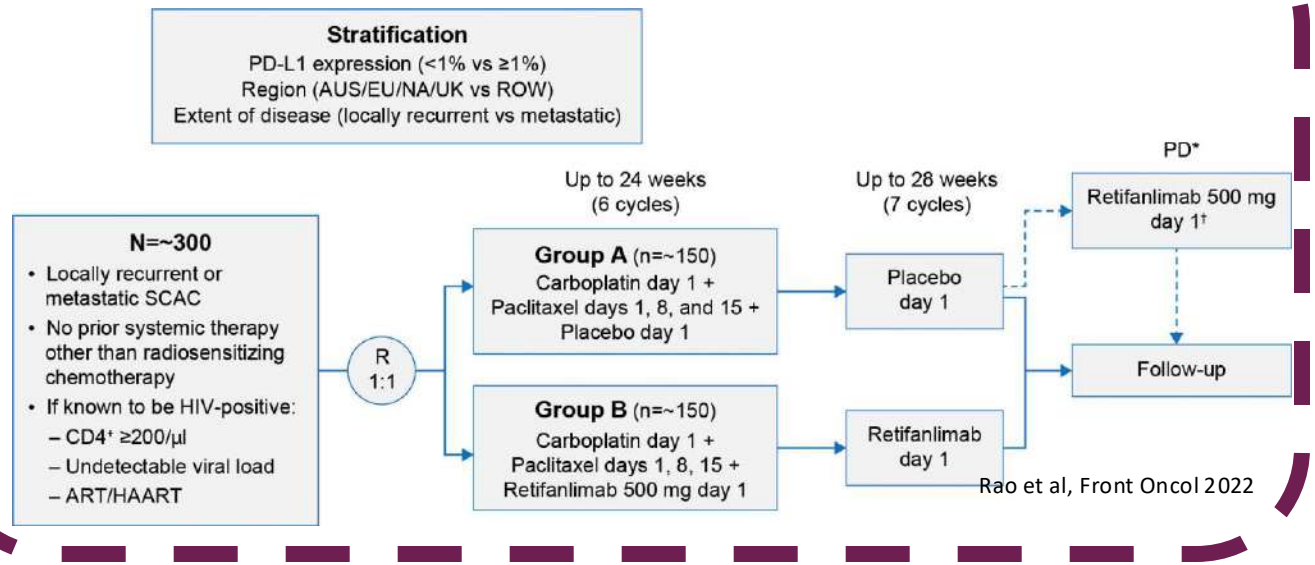
IMMUNE CHECKPOINT BLOCKADE IN ANAL CANCER

Second line and beyond studies

Trial	ICI	Single Agent/Combo	N	ORR	PFS	Ref
NCI9673	Nivolumab	Single	37	24%	4.1m	Morris et al, Lancet Oncol 2017
KEYNOTE 028	Pembrolizumab	Single	25	17%	3.0m	Ott et al, Ann Oncol 2017
KEYNOTE 158	Pembrolizumab	Single	112	11%	2.0m	Marabelle et al, Lancet Gas Hep 2022
CARACAS	Avelumab	Single	30	10%	2.0m	Lonardi et al, J Imm Can, 2021
		Cetuximab	30	17%	3.9m	
NCT03074513	Atezolizumab	Bevacizumab	20	11%	4.1m	Morris et al, ESMO 2022
POD1UM 202	Retifanlimab	Single	94	14%	2.3m	Rao et al, ESMO Open 2022

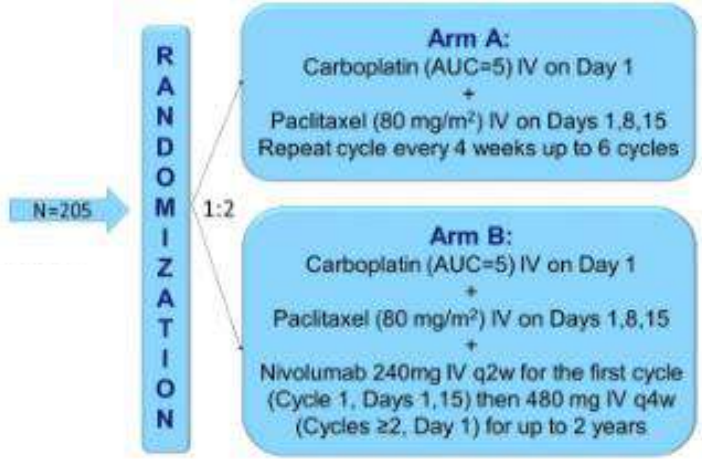
FIRST LINE TRIALS

POD1UM-303/InterAACT 2



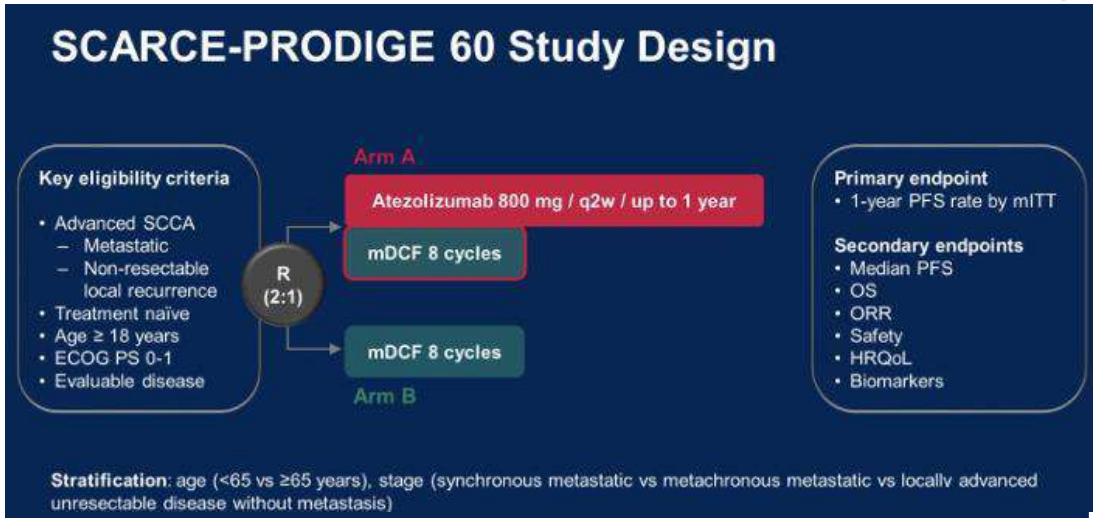
Rao et al, Front Oncol 2022

ECOG-ACRIN EA2176

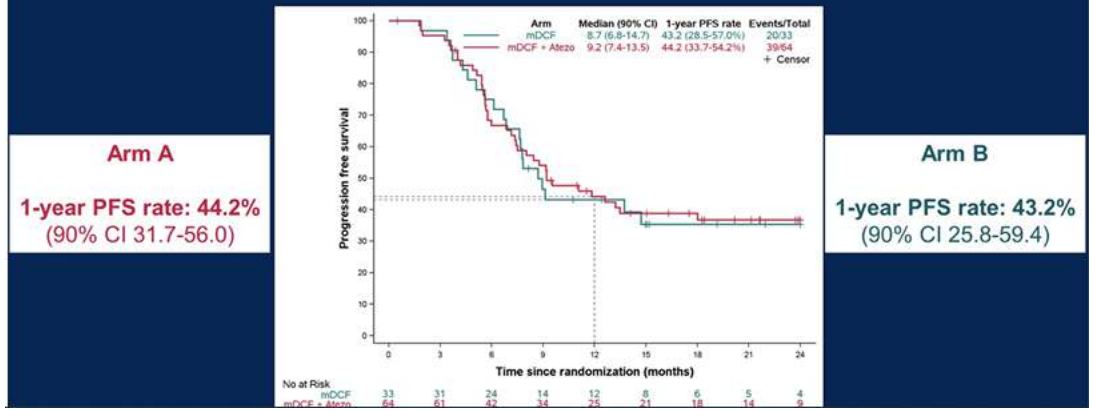


Roth et al, ASCO 2021

SCARCE-PRODIGE 60 Study Design

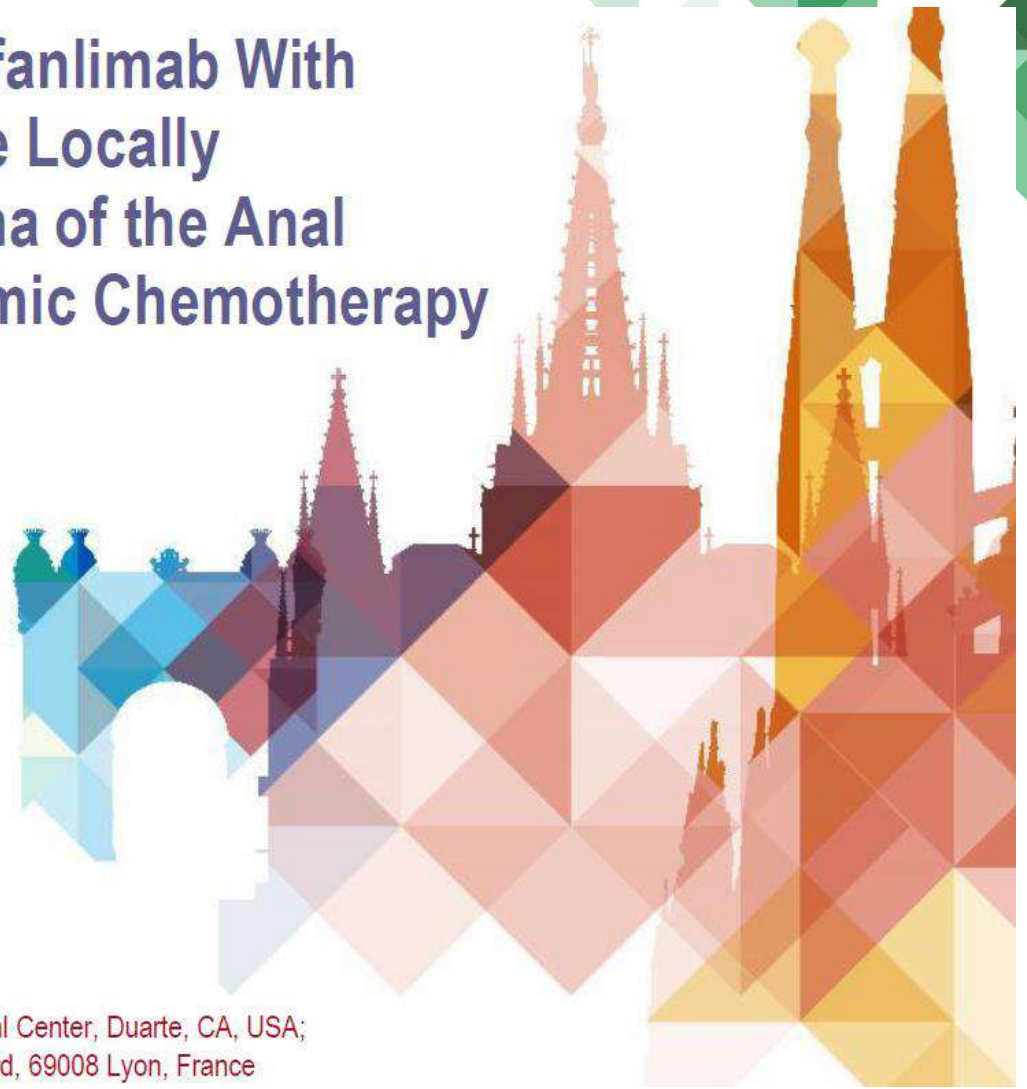


Primary endpoint – 1-year PFS rate



Kim et al ASCO 2022

POD1UM-303/InterAACT 2: Phase 3 Study of Retifanlimab With Carboplatin-Paclitaxel in Patients With Inoperable Locally Recurrent or Metastatic Squamous Cell Carcinoma of the Anal Canal (SCAC) Not Previously Treated With Systemic Chemotherapy



Sheela Rao,[1,*] Emmanuelle Samalin-Scalzi,[2] Ludovic Evesque,[3] Meher Ben Abdelghani,[4] Federica Morano,[5] Amitesh Roy,[6] Laetitia Dahan,[7] Stefano Tamberi,[8] Amandeep (Singh) Dhadda,[9] Mark Saunders,[10] Nathalie Casanova,[11] Rosine Guimbaud,[12] Astrid Lievre,[13] Joan Maurel,[14] Marwan Fakih,[15] Peixin Zhang,[16] Jill Harrison,[16] Mark Jones,[16] Jean-Philippe Spano,[17,†] Pauline Rochefort[18,†]

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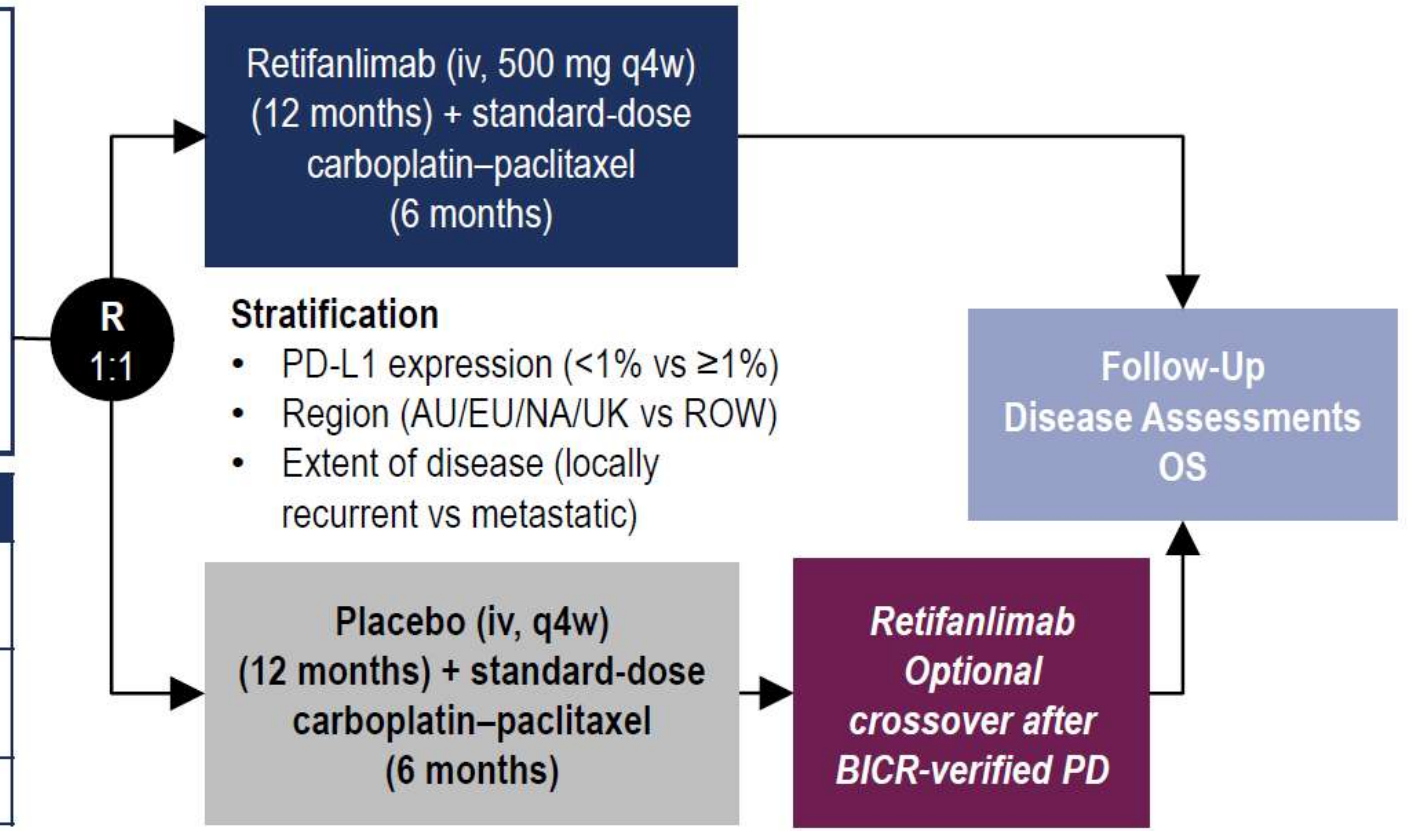
[1]Royal Marsden Hospital NHS Foundation Trust, Sutton, Surrey, UK; [2]Institut Régional du Cancer de Montpellier, 34090 Montpellier, France; [3]Centre Antoine Lacassagne, 06100 Nice, France; [4]Centre Paul Strauss, 67100 Strasbourg, France; [5]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [6]Flinders Medical Centre, Flinders University, Bedford Park, Adelaide, South Australia, Australia; [7]Hôpital de la Timone, Marseille, France; [8]Presidio Ospedaliero Ravenna–Ospedale Santa Maria delle Croci, Ravenna, Italy; [9]Castle Hill Hospital, Cottingham, UK; [10]The Christie Hospital, Manchester, UK; [11]Leeds Cancer Centre, Leeds, UK; [12]CHU de Toulouse, Toulouse, France; [13]CHU Rennes - Hopital Pontchaillou, 35000 Rennes, France; [14]Hospital Clinic de Barcelona, CIBEREHD, Barcelona, Spain; [15]City of Hope National Medical Center, Duarte, CA, USA; [16]Incyte Corporation, Wilmington, DE, USA; [17]Groupe Hospitalier Pitie-Salpetriere, Paris, France; [18]Centre Léon Bérard, 69008 Lyon, France

POD1UM-303/INTERAACT 2 STUDY DESIGN

Patients with locally recurrent or metastatic SCAC

- No prior chemotherapy except as radiosensitising treatment or (neo) adjuvant therapy ≥6 months prior to study entry
- Patients with HIV and well-controlled infection were eligible
- **Planned enrolment: N=300**

Study Endpoints	
Primary	PFS by BICR (HR=0.67 at >80% power, alpha=0.025 [1-sided])
Secondary	OS (key secondary, alpha=0.025 [1-sided] if PFS is statistically significant), ORR, DOR, safety, PK
Exploratory	PFS2, PROs, HIV control, immunogenicity



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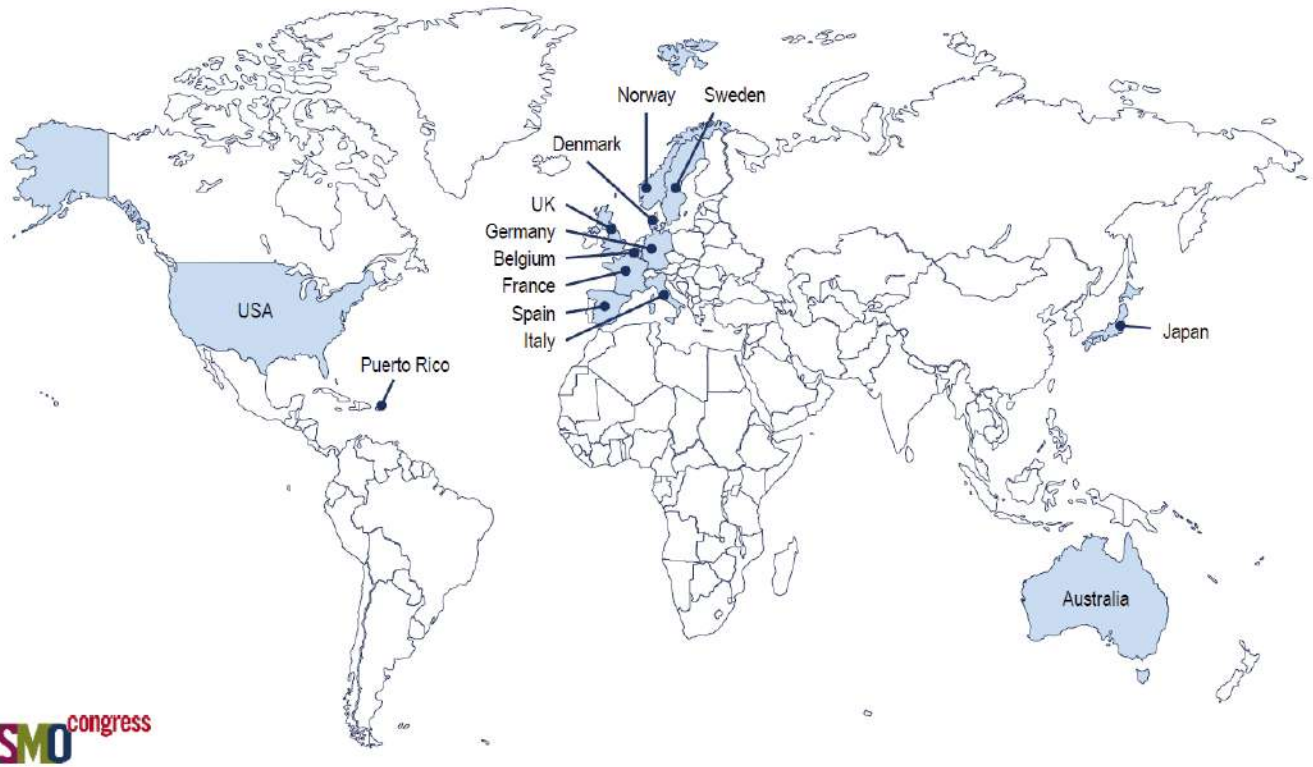
PARTICIPATING SITES



Australia: Roberts, Roy, Strickland

Belgium: Demols, Van Fraeyenhove

Denmark: Jensen, Serup-Hansen

France: Ben Abdelghani, Borg, Capitain, Dahan, Di Fiore, Ducreux, Evesque, Guimbaud, Lievre, Rochefort, Samalin-Scalzi, Smith, Spano, Tougeron

Germany: Arnold, Folprecht, Gonzalez-Carmona

Italy: Berardi, Ciardiello, Di Bartolomeo, Ghidini, Lonardi, Maiello, Masi, Scartozzi, Siena, Tamberi, Zampino

Japan: Baba, Hamaguchi, Kasahara, Kojima, Kudo, Masuishi, Takashima

Norway: Gronlie Guren, Loes

Spain: Castillon, Feliu Batlle, Ladron, Martinez, Morales, Polo Marques, Santasusana, Suarez

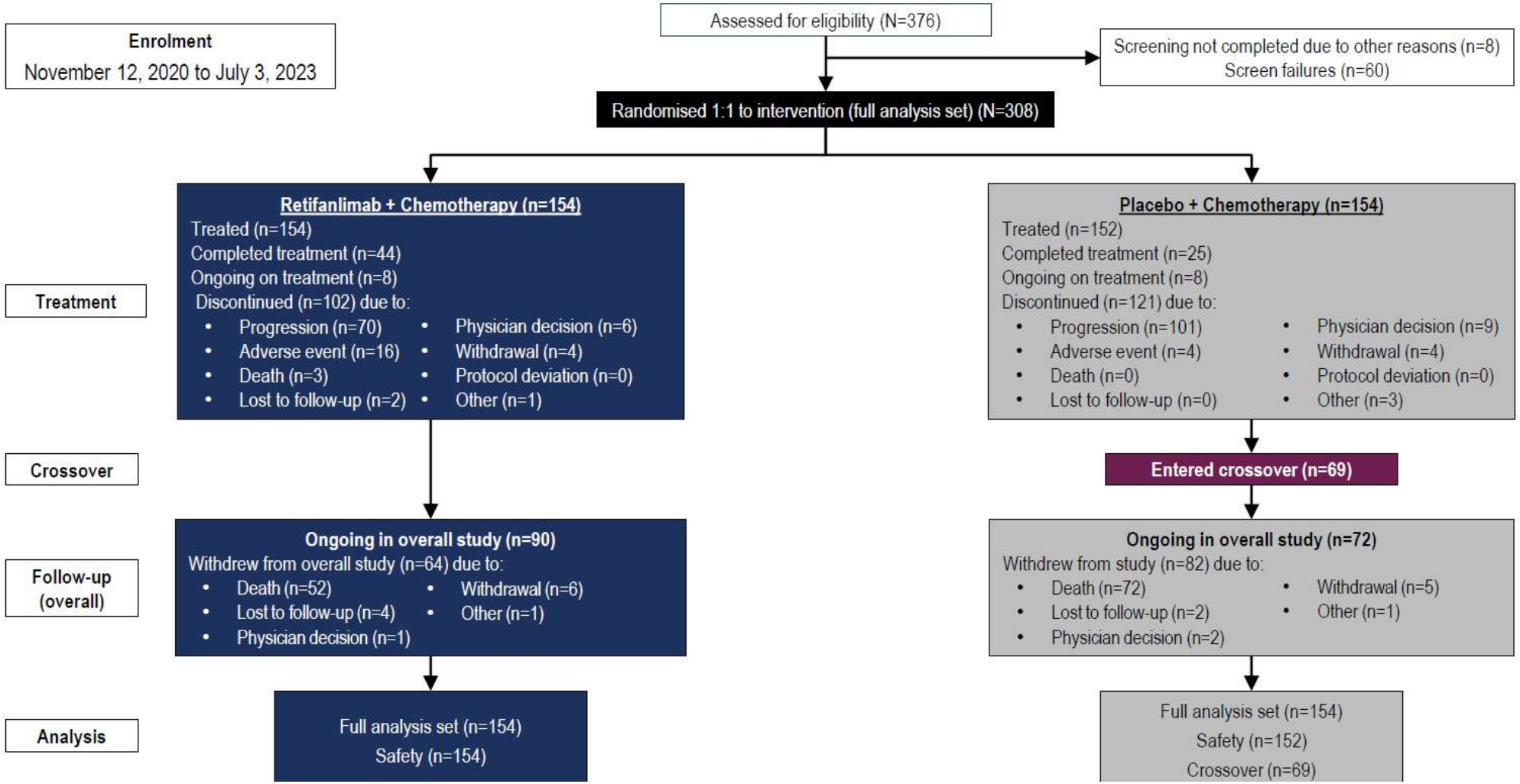
Sweden: Johansson, Lagerback, Leon

UK: Casanova, Dhadda, Essapen, Gilbert, Goldstein, Jadon, Minear, Muirhead, Rao, Saunders, Williamson

USA: Challagalla, Cho, Cohn, Cruz-Correa (Puerto Rico), Dar, Du, Fakih, Gaffar, Gupta, Hubbard, Kochenderfer, Lu, Paulson, Scott, Uyeki

ESMO congress

CONSORT



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PATIENT CHARACTERISTICS

Characteristic	Placebo + Carboplatin–Paclitaxel (n=154)	Retifanlimab + Carboplatin–Paclitaxel (n=154)
Median age, years	61	62
Female, %	77	68
White, %	89	86
Prior RT, %	73	68
Metastatic disease, %*	**83**	**82**
Liver, %	36	36
ECOG PS 0, %	56	53
HIV+, %	3	4
PD-L1 expression status ≥1, %*,†	**91**	**90**

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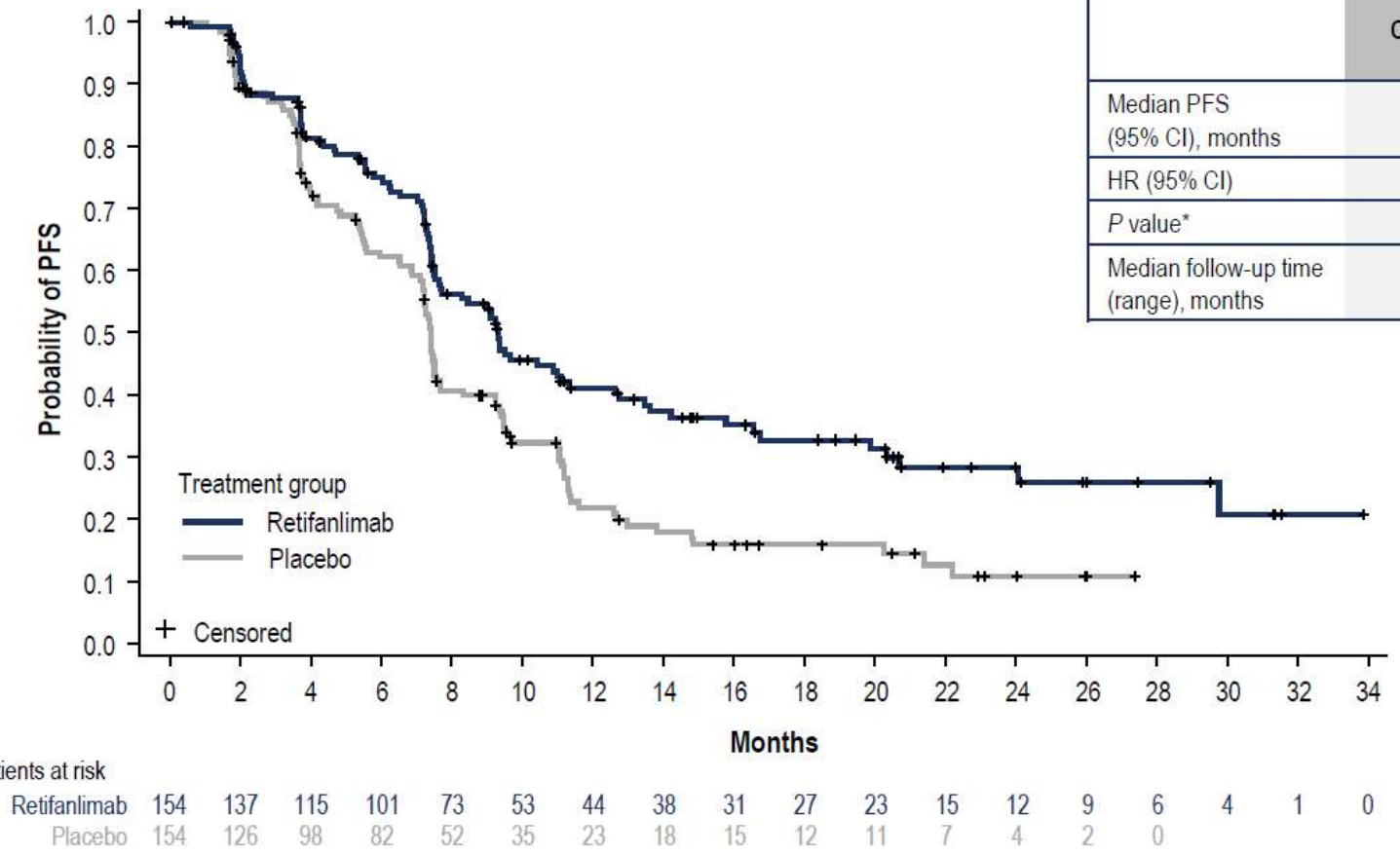
PRIMARY ENDPOINT: PFS



	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)

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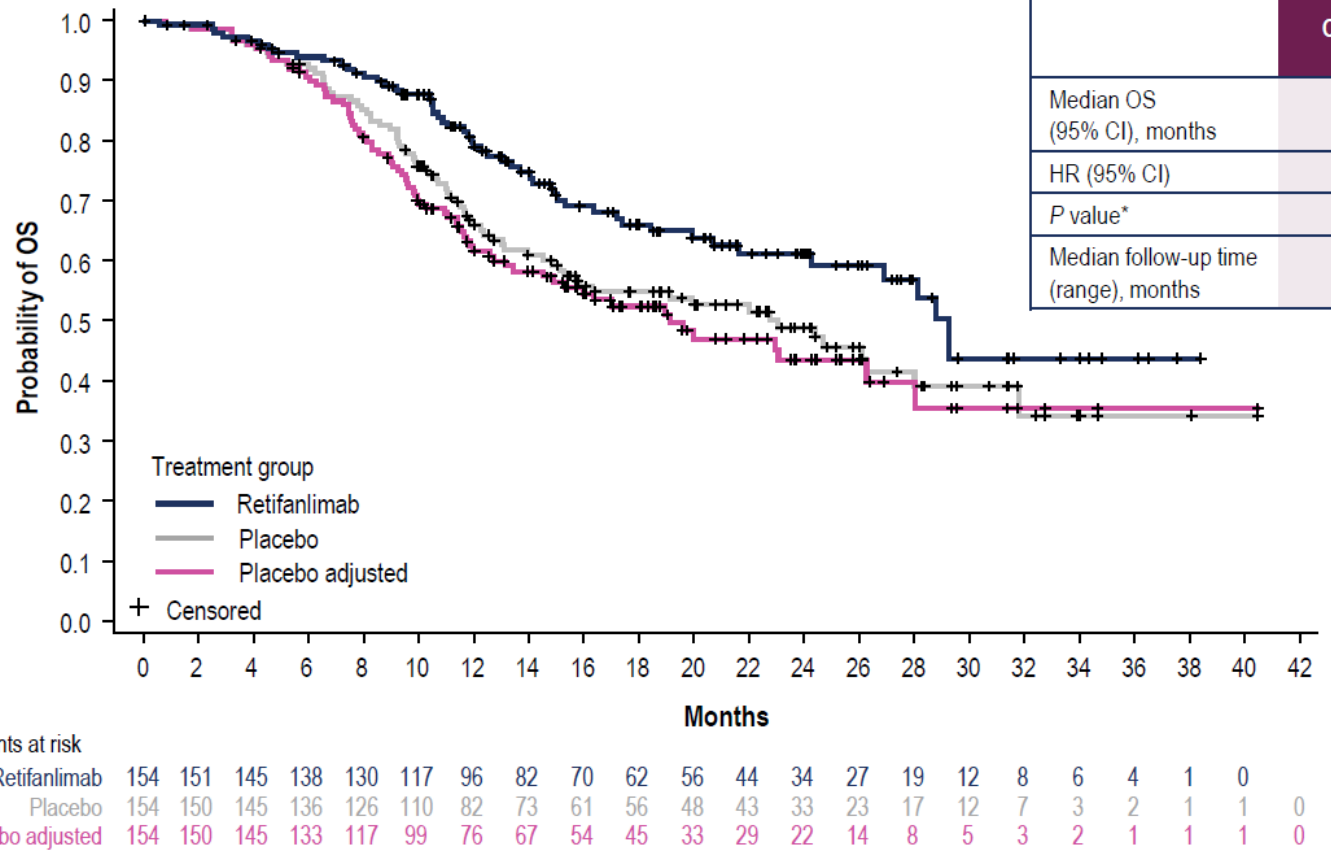
OVERALL SURVIVAL



	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)

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OBJECTIVE RESPONSE RATE

	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)

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ADVERSE EVENTS

Most Common (≥3%) Grade 3 or Higher TEAEs

MedRA Preferred Term	Placebo + Carboplatin–Paclitaxel (n=152)	Retifanlimab + Carboplatin–Paclitaxel (n=154)	Total (N=306)
Neutropenia	45 (29.6)	54 (35.1)	99 (32.4)
Anaemia	31 (20.4)	30 (19.5)	61 (19.9)
Neutrophil count decreased	13 (8.6)	26 (16.9)	39 (12.7)
White blood cell count decreased	13 (8.6)	14 (9.1)	27 (8.8)
Diarrhoea	9 (5.9)	8 (5.2)	17 (5.6)
Leukopenia	6 (3.9)	6 (3.9)	12 (3.9)
Asthenia	5 (3.3)	6 (3.9)	11 (3.6)
Sepsis	6 (3.9)	5 (3.2)	11 (3.6)
Pulmonary embolism	5 (3.3)	5 (3.2)	10 (3.3)
Vomiting	6 (3.9)	4 (2.6)	10 (3.3)

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)

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AUTHOR CONCLUSIONS

- This first and largest known phase 3 trial of a checkpoint inhibitor in SCAC, a disease with high unmet medical need, demonstrated benefit of addition of retifanlimab to standard of care chemotherapy
- The study met its PFS primary endpoint:
  - 9.3 months with retifanlimab vs 7.4 months with placebo (HR, 0.63 [95% CI, 0.47, 0.84]; *P*=0.0006)
- Retifanlimab improved OS vs placebo by 6 months, with a strong trend towards statistical significance at data cutoff (OS follow-up ongoing)
- ORR, DOR and DCR all showed improvement with retifanlimab vs placebo
- Treatment was generally well tolerated, and safety was consistent with other chemotherapy plus checkpoint inhibitor regimens
  - Delivery of chemotherapy was not compromised by retifanlimab administration
- Retifanlimab plus carboplatin–paclitaxel represents a potential new reference treatment and standard of care for patients with advanced SCAC

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PUTTING POD1UM-303 INTO PERSPECTIVE

Study	Study arms	Patients	ORR	PFS	OS
InterAAct	5FU/ Cisplatin	N=46	57%	5.7mo	12.3mo
	Carboplatin/ Paclitaxel	N=45	59%	8.1mo	20.0mo
SCARCE C17-02 Prodige 60	Docetaxel/Cisplatin/ 5-FU	N=33	78%	8.7mo	n.r.
	Docetaxel/Cisplatin/ 5-FU/Atezolizumab	N=64	75%	9.4mo	24.8mo
POD1UM-303	Carboplatin/ Paclitaxel	N=154	44.2%	7.4mo	23.0mo
	Carboplatin/Paclitaxel /Retifanlimab	N=154	55.8%	9.3mo	29.2mo

Kim S et al Lancet Oncol 2024, Rao S et al J Clin Oncol 2020 and Rao S et al ESMO 2024

Slide courtesy Dominik Modest, ESMO 2024

PUTTING POD1UM-303 INTO PERSPECTIVE

- POD1UM-303 is the first phase 3 RCT to demonstrate a survival benefit of the addition of anti-PD-1 immune checkpoint inhibition to chemotherapy in 1st line advanced/metastatic anal squamous cell carcinoma
  - Awaiting data from subgroups and biomarkers
- It should be considered a new SOC
- Regulatory approval and availability of retifanlimab is awaited
- Unclear if other checkpoint inhibitors have similar effect
  - SCARCE-PRODIGE 60 negative (DCF +/- Atezolizumab)
  - Awaiting data from EA2176 (Carboplatin/Paclitaxel +/- Nivolumab)
- Addition of immunotherapy to chemotherapy appears to be have a larger benefit as compared mono-immunotherapy (cross-over did not affect OS much)

Thank you

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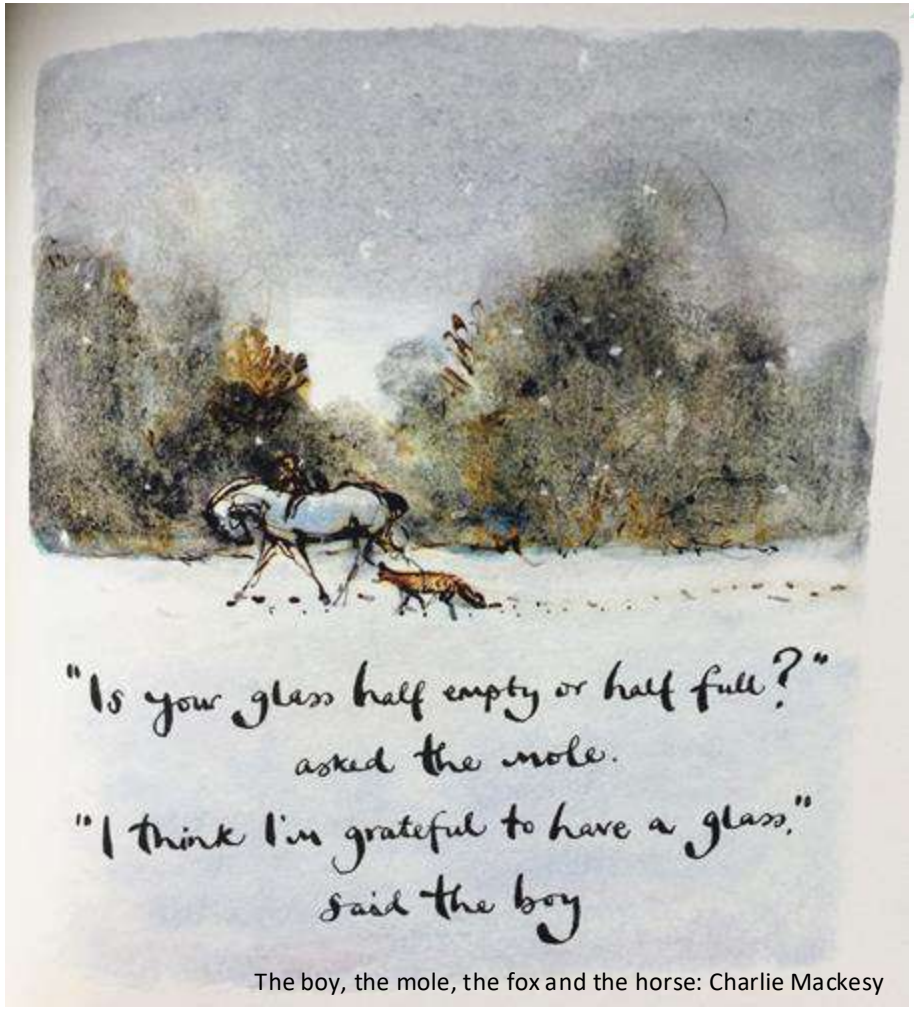


The boy, the mole, the fox and the horse: Charlie Mackesy

INTEGRATING IMMUNOTHERAPY IN THE MANAGEMENT OF PATIENTS WITH ADVANCED COLORECTAL CANCER

Thierry André

ESMO WEBINAR SERIES

ESMO IN FOCUS

Disclosures

Consulting or advisory role and/or honoraria:

Abbvie, Aptitude Health, Amgen, Astra-Zeneca, Astellas, Bristol-Myers Squibb, Gritstone Oncology, GlaxoSmithKline, Gilead, MSD Co., Inc, Nimbus, Roche/Ventana, Sanofi, Seagen, Servier, Takeda, and Pfizer.

DMC member role

Inspirna

Support for meetings

Bristol Myers Squibb , Merck & Co. Inc. and Takeda.

502O: Pembrolizumab in combination with CAPOX and bevacizumab in patients with microsatellite stable metastatic colorectal cancer and a high immune infiltrate: Preliminary results of FFCD 1703 POCHI trial

Pembrolizumab in combination with CAPOX and bevacizumab in patients with microsatellite stable (pMMR/MSS) metastatic colorectal cancer and a high immune infiltrate: a proof of concept study.

Preliminary results of FFCD 1703 POCHI trial

D. Tougeron, J.F. Emile, A. Bodere, E. Barbier, J. Bez, L.M. Dourthe, H. Perrier, S.Corbinais, V. Le Brun-Ly, K. Bideau, B. Chibaudel, F. Khemissa, J. Hartwig, M.Laly, A. Lievre, C. Toullec, M. Muller, P. Laurent-Puig, C. Lepage, J. Taieb.

Poitiers, Boulogne-Billancourt, Saint Malo, Dijon, Strasbourg, Marseille, Caen, Limoges, Quimper, Levallois-Perret, Perpignan, Caluire et Cuire, La Roche-sur-Yon, Rennes, Avignon, Nancy, Paris.

POCHI TRIAL: Immunoscore

- Immunoscore©: Standardized and validated digital pathology-based immune score, based on CD3+ and CD8+ TIL in the center and periphery of the tumour.

- TuLIS: Automated, validated and reproducible method for analysis of CD3+ TIL at invasion front.

- TuLIS is validated in PETACC8 trial
- No score is validated to determine efficacy of ICI

➔ **Use of the 2 tests to determine patient eligibility**

Tougeron D, Abstract 502O

Galon J et al., Science 2006;
Allard MA et al., Diagn Pathol 2012;
Emile JF et al., Eur J Cancer 2017

POCHI TRIAL

- **Single arm, open-label, multi-centre phase II study.**

- pMMR and MSS unresectable metastatic CRC
- available primary tumour containing tumour-free margin
- At least one positive test (immunoscore and/or TuLIS)
- No prior treatment for metastatic disease

→ Every 3 weeks:
CAPOX (standard)
+ bevacizumab 7.5mg/kg
+ pembrolizumab 200 mg

Primary objective: Number of patients alive and without progression at 10 months based on RECIST 1.1 criteria evaluated by the investigator (PFS at 10 months, H0:50% and H1:70%, alpha 5% and power 85%).

55 patients to be enrolled.

Between April 2021 and August 2024, 196 patients were screened in 41 active centers.

36 patients had at least one positive immune score (18%) but 30 analyzed (3 with non-inclusion criteria and 3 with no follow-up data)

28 TuLIS positive, 8 immunoscore© positive (6 positives with both scores).

	N=30 (%)
Median age	67 years
Men/Women	63%/37%
ECOG PS 0/1	87%/13%
Primary tumour site: right/left/rectum	**40%/50%/10%**
Metachronous/synchronous metastases	**53%/47%**
RAS/BRAF-mutated tumor	63%/10%
Liver metastases	**50%**
Lung metastases	**33%**

Tougeron D, Abstract 502O

POCHI TRIAL

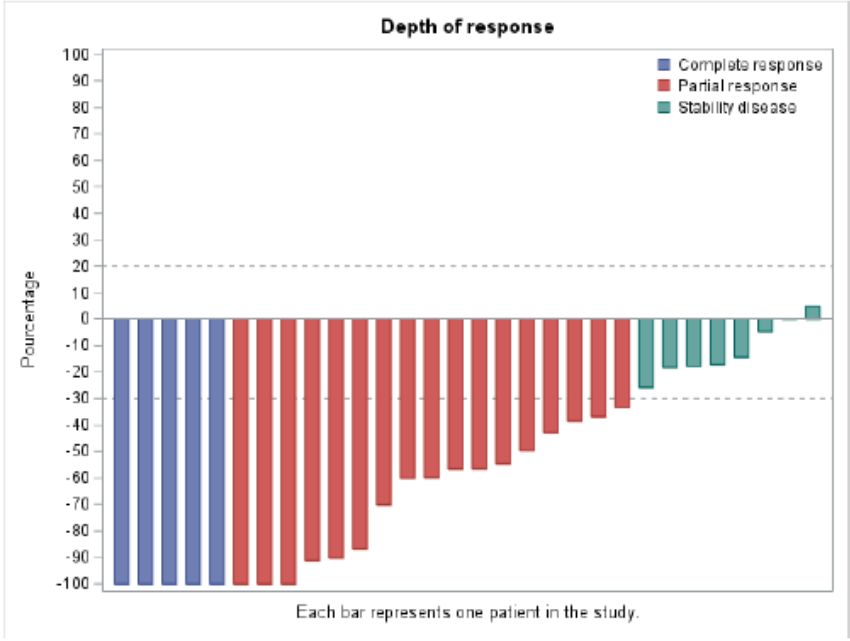
RESULTS 1

- **Median follow-up was 21 months (min 3.4 - max 33.9) (cut-off August 26, 2024).**
  - **ORR: 74%**
  - **DCR: 100%**

	N (%)
Complete response	**5 (17%)**
Partial response	**17 (57%)**
Stable disease	8 (27%)

- **Median DoR = 10 months**

Waterfall plot of treatment response

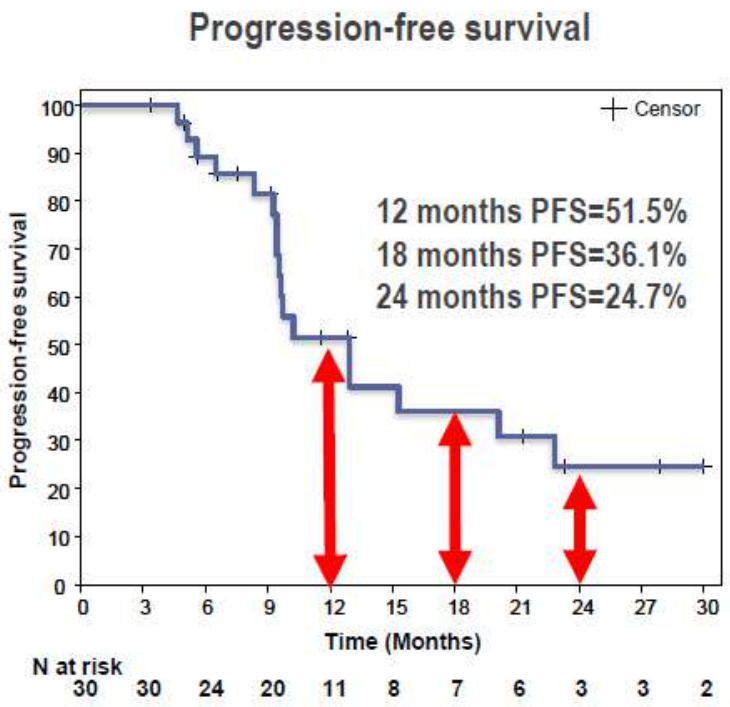


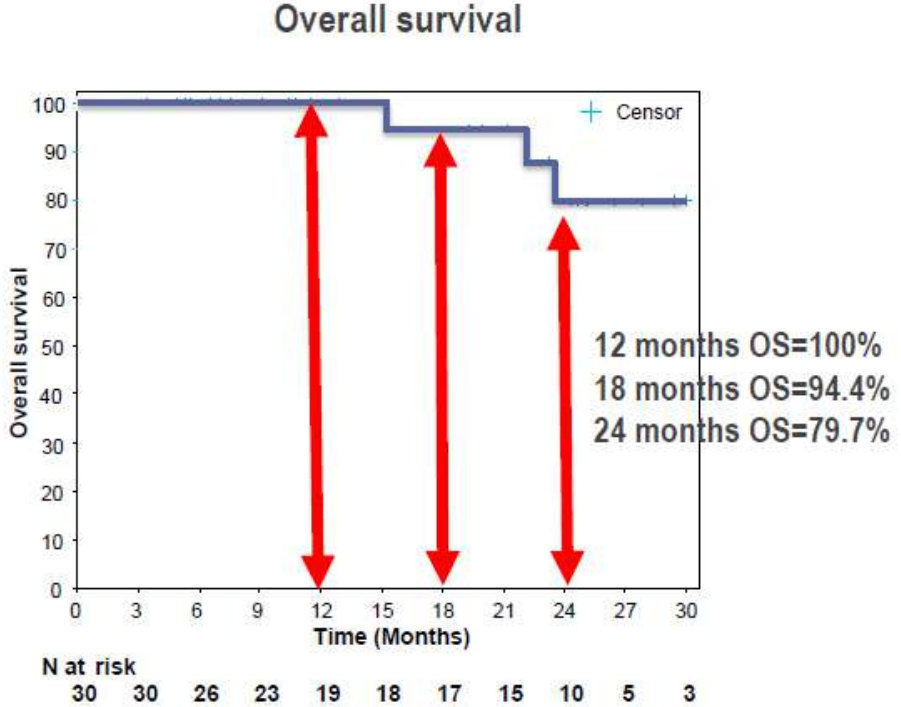
N(%)	Grade 3-4*
Patients with at least one grade 3-4 adverse event	**21 (70.0)**
Diarrhoea	6 (20.0)
Neutrophil count decrease	3 (10.0)
Fatigue	5 (16.7)
Adrenal Insuffiency	1 (3.3)
Hyperglycemia	1 (3.3)

Tougeron D, Abstract 502O

POCHI TRIAL

Result 2





All tumors were confirmed both pMMR and MSS (centralized).

No tumor has *POLE* mutation or high tumour mutation burden (TMB) (n=22).

No correlation was observed between TMB and response to treatment.

Tougeron D, Abstract 502O

POCHI: Authors Conclusions

- High efficacy in first line of pembrolizumab, combined with XELOX in pMMR mCRC **with high immune infiltrates** with **17% CR and 100 DCR**
- Expected safety profile
- **Study still enrolling**
- The impressive response rate **justify** evaluation of the combination of IO and chemotherapy in **a phase III tri**al dedicated to pMMR /MSS mCRC patients with a high immune-infiltrate

Tougeron D, Abstract 502O

POCHI Discussion

- Inclusion in POCHI possible only if resection of the primary because immuno-score used need invasive margine, and thus **access to the colon cancer resection specimen**

- It is a phase II with possible inclusion biais

- In the future for a phase III wich Immunoscore will you have to use
  - Tulis simple academic immunoscore
  - Devellopement of Immuno-score® by Veratis ?
  - **Immunoscore Immune Checkpoint (IC)** develloped by Veratis company (on biopsy)

André T

LBA24: neoadjuvant immunotherapy in locally advanced mmr-deficient (dMMRr) colon cancer: 3-year disease -free survival from the NICHE-2 study

Neoadjuvant immunotherapy in locally advanced MMR-deficient colon cancer

3-year disease-free survival from NICHE-2

M. Chalabi[1], L. van den Dungen, Y. Verschoor, S. Balduzzi, P. de Gooyer, N. Kok, E. Kerver, C. Grootscholten, E. Voest, J. Burger, E. Hendriks, T. de Wijkerslooth, A. Tin, T. Aukema, S. Oosterling, A. Aalbers, J. van den Berg, M. Van Leerdam, T. Schumacher, J. Haanen

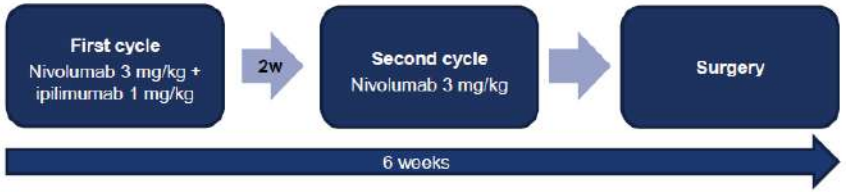
[1]Netherlands Cancer Institute, Amsterdam

NICHE-2 study design

Investigator-initiated, non-randomized multicenter study

Key eligibility criteria

- Non-melastatic dMMR colon cancer, previously untreated
- cT3 and/or N+ based on radiographic staging
- No clinical or radiologic signs of obstruction or perforation



Endpoints and statistical design

- Two primary endpoints
  - Safety
  - **3-year disease free survival (DFS)**
- Secondary endpoints
  - Pathologic response rate
  - Translational research
  - **Circulating tumor DNA dynamics**

A 3-year DFS of 93% would be deemed successful, at a power of 80% and a two-sided alpha of 0.025 using a one-sample log rank test assuming a historical 82% DFS[1]

M Chalabi, Abstract LBA24

[1]Historical 82% DFS was calculated with the assumption of 60% stage III and 40% stage II tumors. The historical 3-year DFS used for these calculations was 75% for stage III tumors and 90% for stage II disease.

NICHE 2

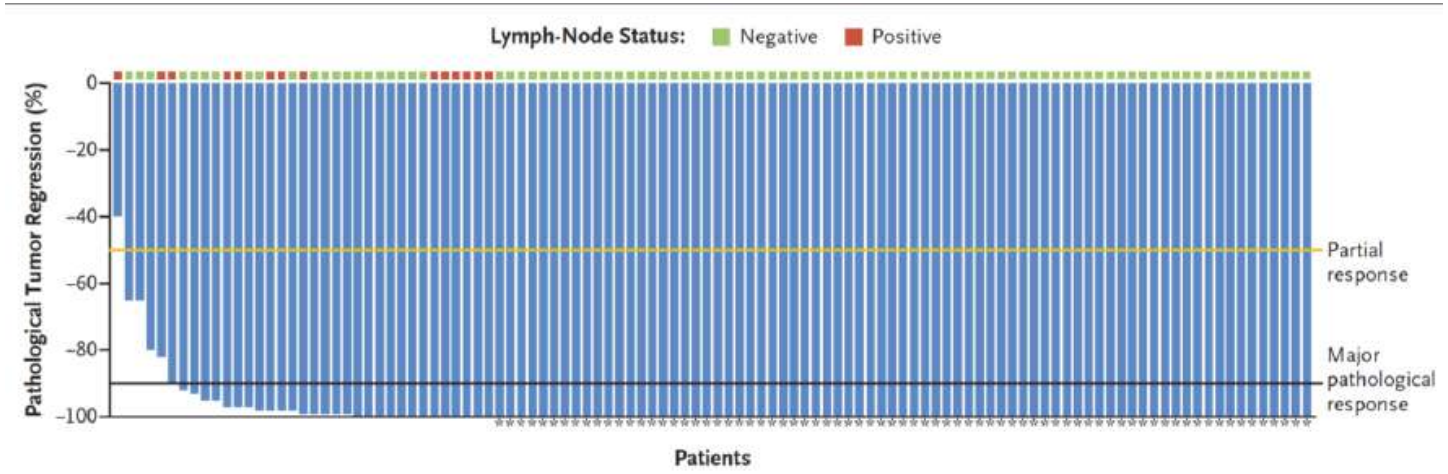
Characteristic	All patients, *n* = 115
Median age (range) – yr	60 (20-82)
Female sex – no. (%)	67 (58)
Tumor stage – no. (%)	
cT2	17 (15)
cT3 or cT3-4	24 (21)
cT4a	41 (36)
cT4b	33 (29)
Nodal status – no. (%)	
cN0	38 (33)
cN+	77 (67)
Lynch syndrome – no. (%)	37 (33)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 6, 2024 VOL. 390 NO. 21

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

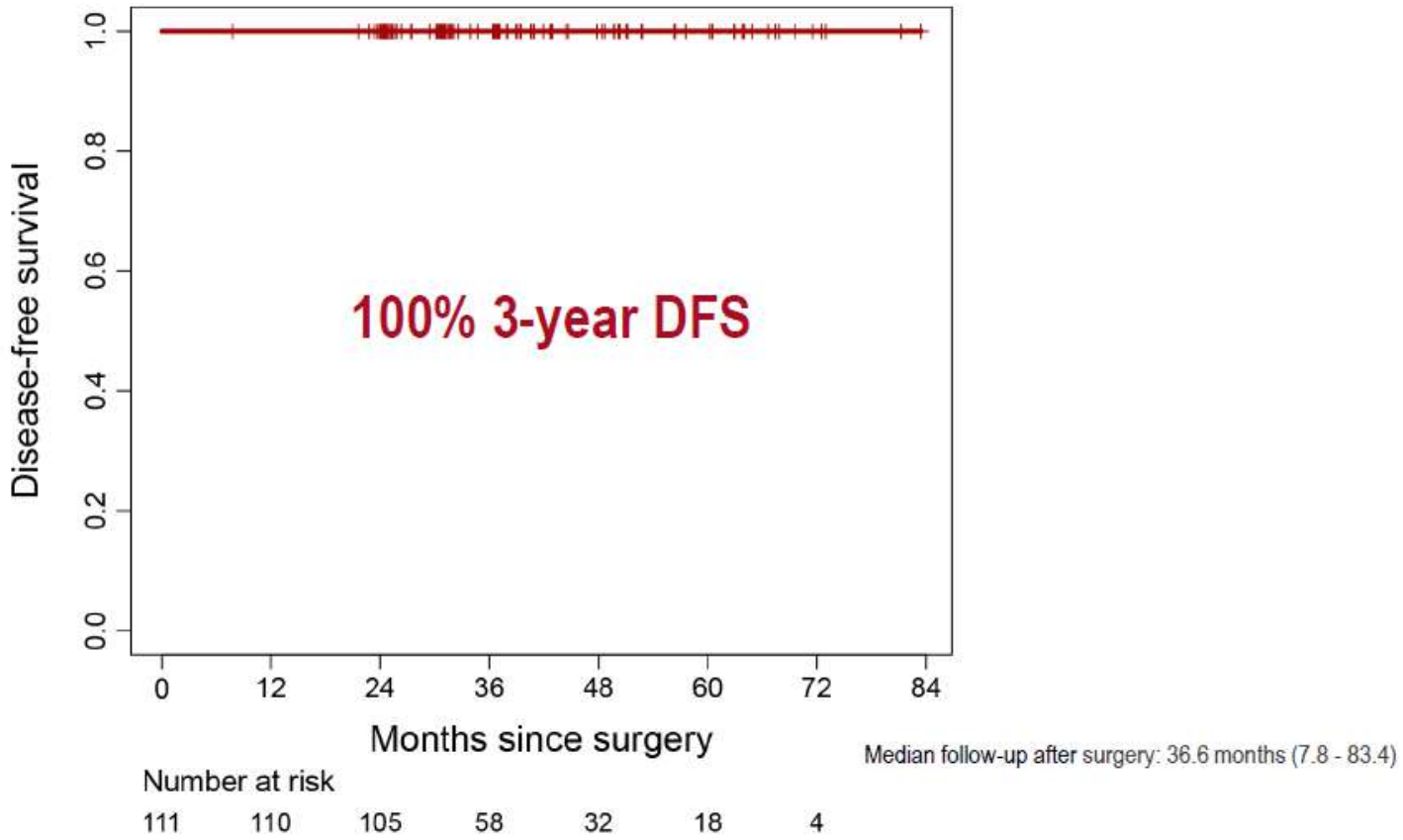
Pathologic response in **98%** of 111 patients in efficacy analysis

- Major pathologic response (≤10% residual viable tumor): **95%**
- Pathologic complete response: **68%**



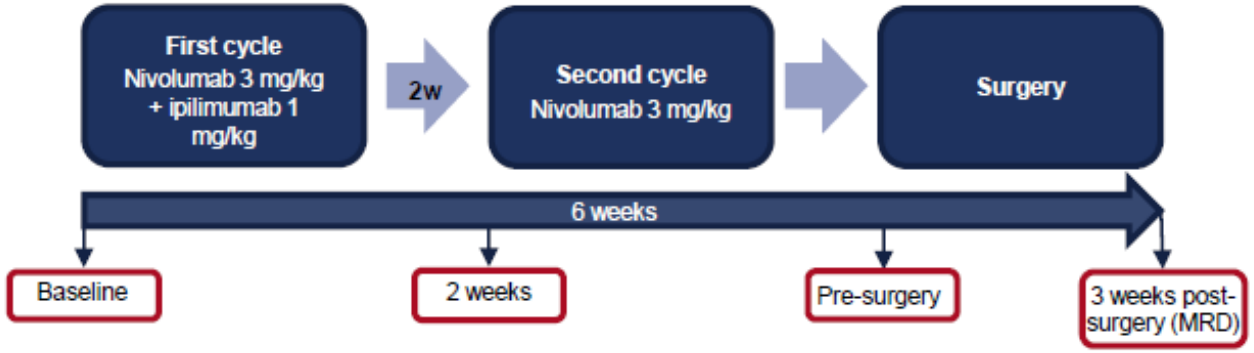
M Chalabi, Abstract LBA24

NICHE 2: 3-Year DFS 100%

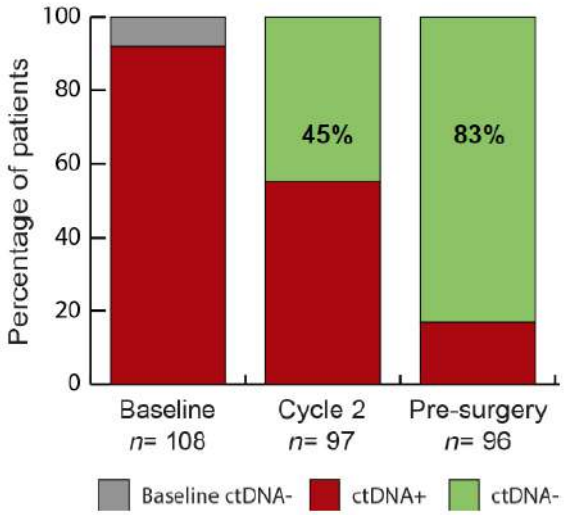


M Chalabi, Abstract LBA24

NICHE 2: Circulating ctDNA



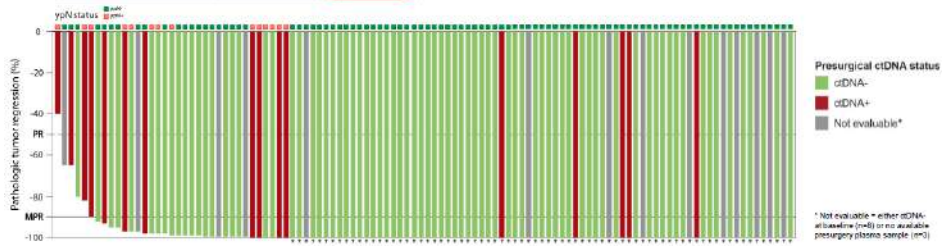
Tissue-informed Signatera ctDNA assay



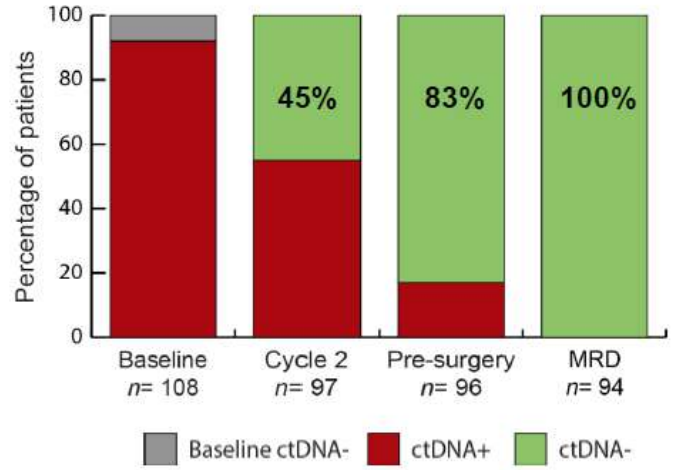
ctDNA pre-surgery		
Response group	ctDNA-	ctDNA+
pCR (*n* = 65)	60 (92%)	5 (8%)
MPR (*n* = 27)	19 (70%)	8 (30%)
PR (*n* = 3)	1 (33%)	2 (67%)
NR (*n* = 1)	0	1 (100%)

16 patients remained ctDNA positive pre-surgery

8/14 ypN+ patients



All patients were ctDNA negative at the MRD time point (3 weeks after surgery)



M Chalabi, Abstract LBA24

NICHE 2: Author Conclusion

- Unprecedented 3-year DFS of 100%in patients with high-risk, locally advanced dMMR colon cancer with only two cycles of neoadjuvant immune Check point ihnibitors

- Collaboration between regulatory authorities, pharmaceutical companies and academic researchers is essential to bring this highly effective treatment to patients

- All patients were ctDNA negative at MRD time point, in line with 0% recurrences

M Chalabi, Abstract LBA24

DISCUSSION

- Amazing results with **the dream to avoid adjuvant chemo and this dream is reality** for all patients in this study!

- Surgery alone is the standard of care for stage II MSI/SMMR with DFS at 90% in historical studies

- Not sure in NICHE it is a majority of High Risk stage 3 or High Risk stage 2
  - The ability of preoperative CT scan to predict pT and pN stages is limited for localized MSI/dMMR CC[1]
  - Over treatement of stage II cured by surgery

- Next step is organ preservation

- Can ctDNA help define in which patients organ preservation can be envisaged with the problem of colonoscopic monitoring?

1 Duval m et al; ESMO open 2024

Thank you for your attention

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ESMO WEBINAR SERIES

ESMO IN FOCUS

BREAKTHROUGHS IN HCC TREATMENT

Dr Angela Lamarca MD, PhD, MSc
Department of Medical Oncology, Oncohealth Institute
Health Research Institute IIS-FJD, UAM
Fundación Jimenez Diaz University Hospital
Madrid, Spain

ESMO WEBINAR SERIES

ESMO IN FOCUS

DECLARATION OF INTEREST

Travel and educational support from Ipsen, Pfizer, Bayer, AAA, SirtEx, Novartis, Mylan, Delcath Advanz Pharma and Roche. Speaker honoraria from Merck, Pfizer, Ipsen, Incyte, AAA/Novartis, QED, Servier, Astra Zeneca, EISAI, Roche, Advanz Pharma and MSD.

Advisory and consultancy honoraria from EISAI, Nutricia, Ipsen, QED, Roche, Servier, Boston Scientific, Albireo Pharma, AstraZeneca, Boehringer Ingelheim, GENFIT, TransThera Biosciences, Taiho and MSD.

Principal Investigator-associated Institutional Funding form QED, Merck, Boehringer Ingelheim, Servier, Astra Zeneca, GenFit, Panbela Therapeutics, Novocure GmbH, Camurus AB, Albireo Pharma, Taiho, TransThera, JazzTherapeutics and Roche.

Member of the Knowledge Network and NETConnect Initiatives funded by Ipsen.

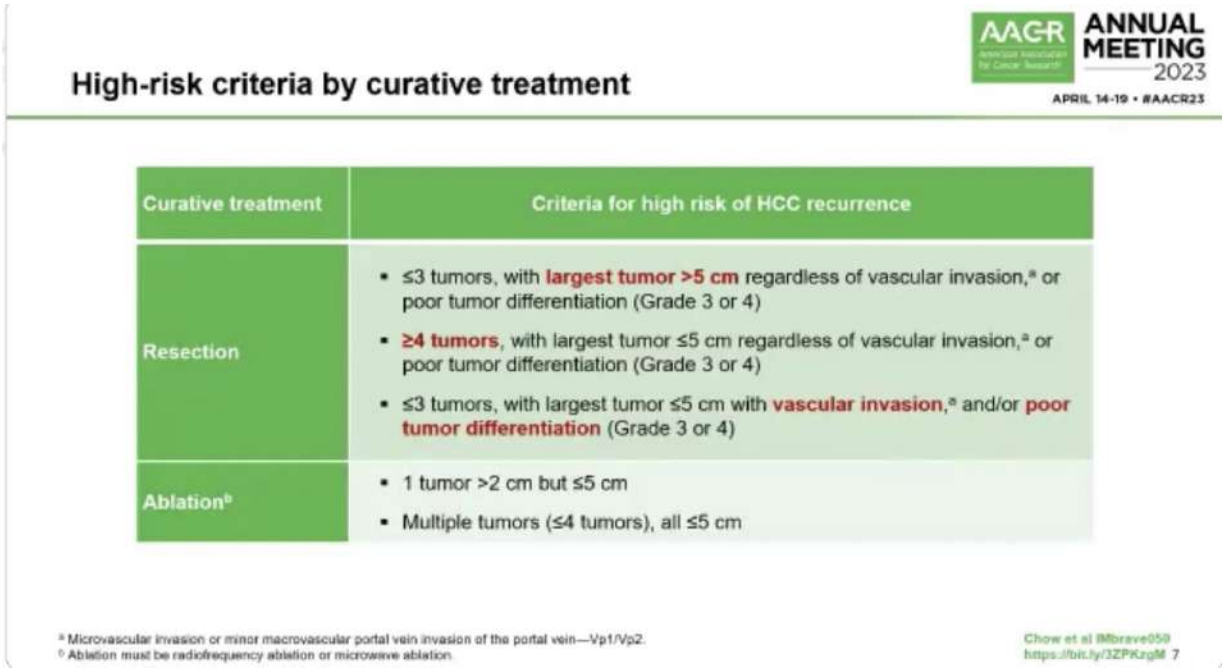
LBA3: Transarterial chemoembolization (TACE) with or without lenvatinib (len) plus pembrolizumab (pembro) for unresectable non-metastatic hepatocellular carcinoma (HCC): phase 3 LEAP-012 study

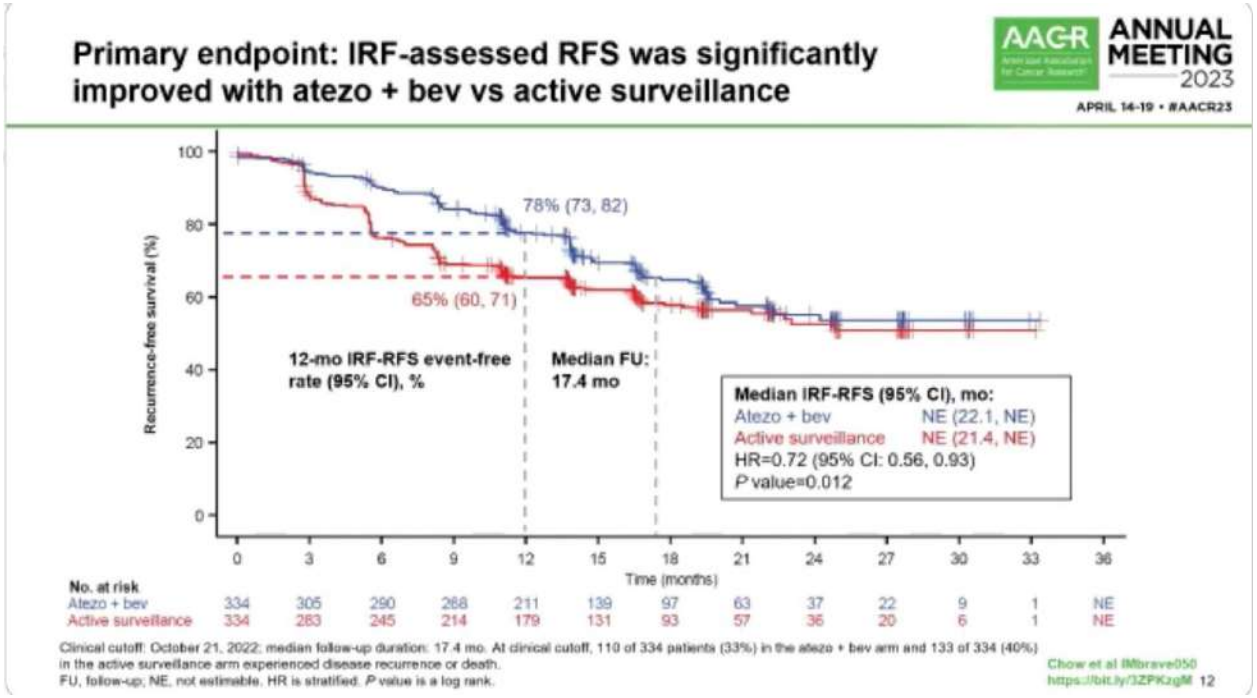
950P: EMERALD1

947MO: Five-year overall survival (OS) and OS by tumour response measures from the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma (uHCC)

IMBRAVE-050 (PRIOR DATA)

Adjuvant AtezoBev x12 months vs observation (n= 668)





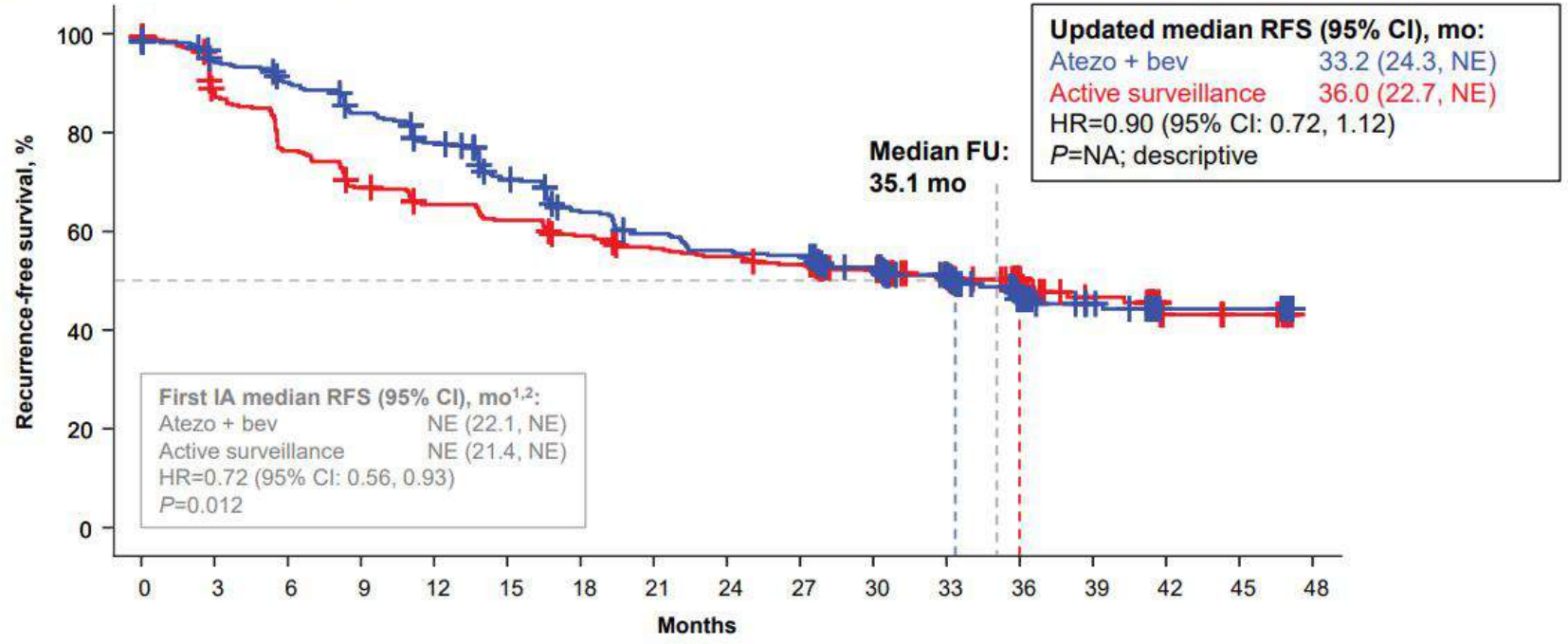
OS data immature

Grade 5 tox: 1.8%

Chow et al, AACR 2023; Qin Lancet 2023

IMBRAVE-050 (ESMO 2024 RESULTS UPDATED)

Early RFS benefit was not maintained with longer follow-up



No. at risk																	
Atezo + bev	334	305	290	268	245	216	191	177	167	164	147	123	62	45	18	18	NE
Active surveillance	334	285	247	221	207	197	185	175	170	164	145	124	63	42	16	14	NE

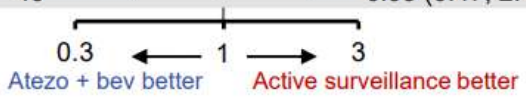
Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. At clinical cutoff, 162 of 334 patients (49%) in the atezo + bev arm and 164 of 334 (49%) in the active surveillance arm experienced disease recurrence or death. HRs are stratified. *P* values are log rank.
FU, follow-up; NA, not applicable; NE, not estimable. 1. Qin et al. Lancet 2023. 2. Chow et al. AACR 2023 [abstract CT003].

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1 6

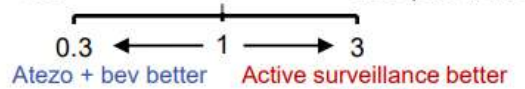
IMBRAVE-050 (ESMO 2024 RESULTS UPDATED)

RFS was consistent across clinically relevant subgroups

Baseline risk factors	No. of patients	Unstratified HR (95% CI)
All patients	668	0.91 (0.73, 1.13)
<65 years old	427	0.98 (0.75, 1.28)
≥65 years old	241	0.78 (0.54, 1.13)
Male	555	0.91 (0.72, 1.15)
Female	113	0.96 (0.53, 1.73)
Asian	545	0.90 (0.70, 1.15)
White	78	0.79 (0.42, 1.48)
Other race	45	1.32 (0.61, 2.86)
ECOG PS 0	527	0.84 (0.65, 1.07)
ECOG PS 1	141	1.19 (0.75, 1.88)
PD-L1 ≥1%	294	0.98 (0.70, 1.37)
PD-L1 <1%	269	0.73 (0.53, 1.02)
Unknown PD-L1	105	1.39 (0.78, 2.49)
1 high-risk feature[a]	312	0.85 (0.60, 1.22)
>1 high-risk features[a]	273	0.94 (0.69, 1.27)
BCLC 0/A	572	0.92 (0.73, 1.18)
BCLC B	56	0.78 (0.39, 1.56)
BCLC C	40	0.99 (0.47, 2.11)



Baseline risk factors	No. of patients	Unstratified HR (95% CI)
Hepatitis B etiology	418	0.96 (0.72, 1.27)
Hepatitis C etiology	72	1.04 (0.55, 1.99)
Non-viral etiology	86	0.91 (0.50, 1.64)
Unknown etiology	92	0.64 (0.36, 1.13)
Resection	585	0.89 (0.71, 1.12)
Ablation	83	1.04 (0.55, 1.97)
In patients who underwent resection:		
1 tumour	526	0.91 (0.71, 1.17)
>1 tumours	59	0.75 (0.39, 1.45)
Tumour size >5 cm	327	0.84 (0.64, 1.12)
Tumour size ≤5 cm	258	1.10 (0.73, 1.65)
mVI present	358	0.96 (0.72, 1.28)
mVI absent	227	0.78 (0.53, 1.15)
Poor tumour differentiation	244	0.83 (0.58, 1.17)
No poor tumour differentiation	341	0.94 (0.69, 1.28)
Received TACE	67	1.20 (0.62, 2.31)
Did not receive TACE	518	0.86 (0.67, 1.10)
Within up-to-7 criteria	302	1.01 (0.70, 1.46)
Outside up-to-7 criteria	283	0.84 (0.62, 1.13)

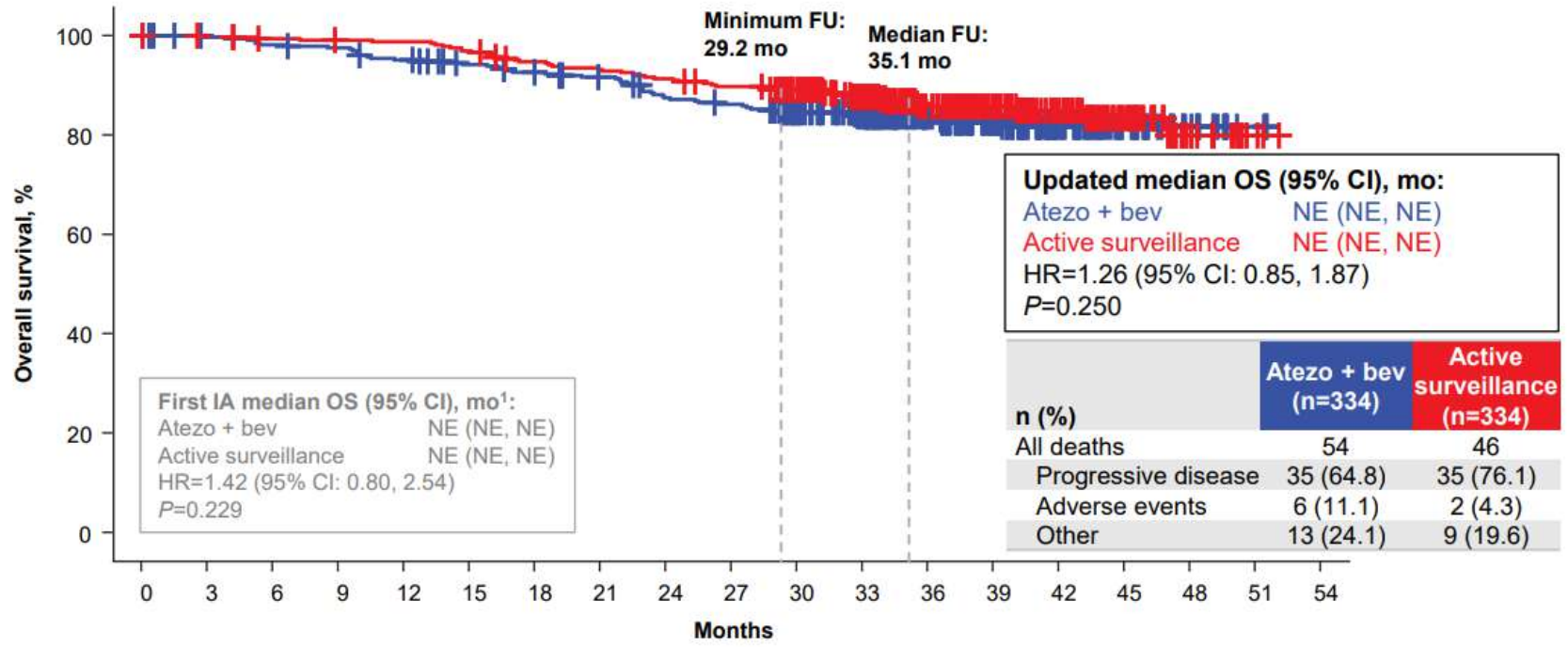


Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo.
[a] Patients who underwent ablation were categorized as NA.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

IMBRAVE-050 (ESMO 2024 RESULTS UPDATED)

Updated OS remained immature but showed numerical improvement from the first IA



n (%)	Atezo + bev (n=334)	Active surveillance (n=334)
All deaths	54	46
Progressive disease	35 (64.8)	35 (76.1)
Adverse events	6 (11.1)	2 (4.3)
Other	13 (24.1)	9 (19.6)

No. at risk

Atezo + bev	334	327	322	319	310	301	294	286	271	266	243	206	142	101	60	34	16	3	NE
Active surveillance	334	327	323	321	320	314	304	299	293	286	266	226	157	108	71	38	15	3	NE

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. HRs are stratified. *P* values are log rank.
1. Qin et al. Lancet 2023.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

IMBRAVE-050 (ESMO 2024 RESULTS UPDATED)

BARCELONA 2024 ESMO congress

Recurrence patterns

First post-baseline unequivocal recurrence

	Atezo + bev (n=334)	Active surveillance (n=334)
Patients with recurrence, n	141	160
Location of recurrence, n (%)		
Intrahepatic only	103 (73.0)	109 (68.1)
Extrahepatic only	35 (24.8)	44 (27.5)
Both intra- and extrahepatic	3 (2.1)	7 (4.4)
Outside Milan criteria, n (%)		
Yes	51 (36.2)	67 (41.9)
No	89 (63.1)	89 (55.6)
NA[a]	1 (0.7)	4 (2.5)
Outside up-to-7 criteria, n (%)		
Yes	51 (36.2)	67 (41.9)
No	89 (63.1)	89 (55.6)
NA[a]	1 (0.7)	4 (2.5)

Patients with intrahepatic recurrence
(regardless of extrahepatic recurrence)

	Atezo + bev (n=334)	Active surveillance (n=334)
Intrahepatic recurrence, n	106	116
Macrovascular invasion, n (%)		
Yes	14 (13.2)	15 (12.9)
No	92 (86.8)	100 (86.2)
Not evaluable	0	1 (0.9)
Tumour liver lobe invasion, n (%)		
Unilobar	99 (93.4)	110 (94.8)
Bilobar	7 (6.6)	6 (5.2)

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. [a] Patients were considered NA for Milan and up-to-7 criteria if they did not have extrahepatic spread or MVI and had ≥1 non-measurable lesion.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

IMBRAVE-050 (ESMO 2024 RESULTS UPDATED)

BARCELONA 2024 ESMO congress

First post-recurrence treatment

	Atezo + bev (n=147)	Active surveillance (n=156)
Curative intent, n (%)	49 (33.3)	59 (37.8)
Resection	28 (19.0)	28 (17.9)
Radiofrequency ablation	17 (11.6)	17 (10.9)
Microwave ablation	4 (2.7)	13 (8.3)
Other	0	1 (0.6)
Locoregional, n (%)	45 (30.6)	18 (11.5)
Embolisation	32 (21.8)	13 (8.3)
Radiation	13 (8.8)	5 (3.2)
Systemic therapy, n (%)	33 (22.4)	72 (46.2)
Atezolizumab + bevacizumab	3 (2.0)	61 (39.1)
Immunotherapy	2 (1.4)	2 (1.3)
Immunotherapy + TKI/immunotherapy + VEGF(R) mAb	11 (7.5)	2 (1.3)
Other	4 (2.7)	1 (0.6)
TKI	12 (8.2)	6 (3.8)
VEGF(R) mAb	1 (0.7)	0

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. Recurrence was assessed by the investigator. For the active surveillance arm, resection/radiofrequency ablation/microwave ablation received at crossover screening and crossover atezo + bev treatment, whichever was the first, was included. mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor).

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

11

IMBRAVE-050 (ESMO 2024 RESULTS UPDATED)

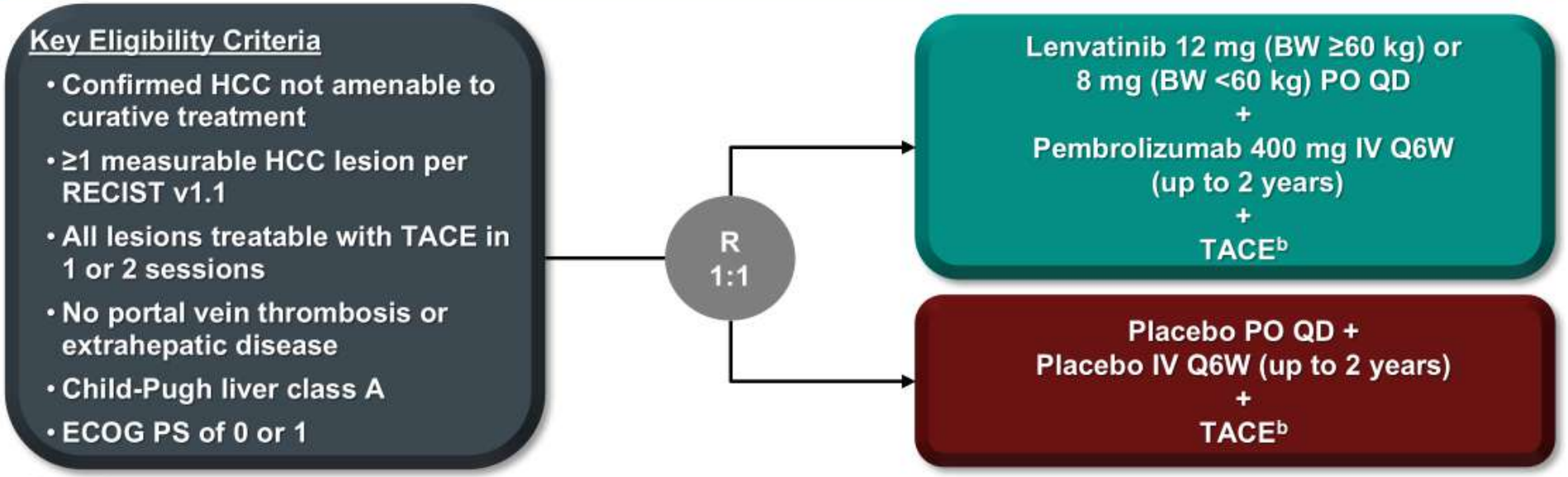
Conclusions

- IMbrave050 was the first Phase 3 study to demonstrate that an adjuvant immunotherapy-based regimen could delay recurrence following curative intent resection or ablation at the prespecified IA[1]
- In this updated analysis, initial RFS benefit with atezolizumab + bevacizumab vs active surveillance was not sustained over time (HR, 0.90; 95% CI: 0.72, 1.12)
  - Post hoc analyses showed a pronounced delaying of recurrence with atezolizumab plus bevacizumab within the first 12 months after resection with curative intent in some patients
- OS continued to be immature at the updated IA, with >80% of patients alive in both arms after 2 years
  - Updated OS HR was >1 (HR, 1.26; 95% CI: 0.85, 1.87), that showed numerical improvement with atezolizumab + bevacizumab vs active surveillance between the first and second IA[1]
- The safety profile of adjuvant atezolizumab + bevacizumab remained manageable and consistent with that of each agent and with the underlying HCC; no new safety concerns were observed
- The benefit-risk profile based on this updated analysis does not support atezolizumab + bevacizumab as an adjuvant therapy for all patients with high-risk HCC; efficacy follow-up for OS will continue
- These results will inform ongoing and future approaches to improve outcomes for patients with early HCC

1. Qin et al. Lancet 2023.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

LEAP-012 Study Design (NCT04246177)



Stratification Factors

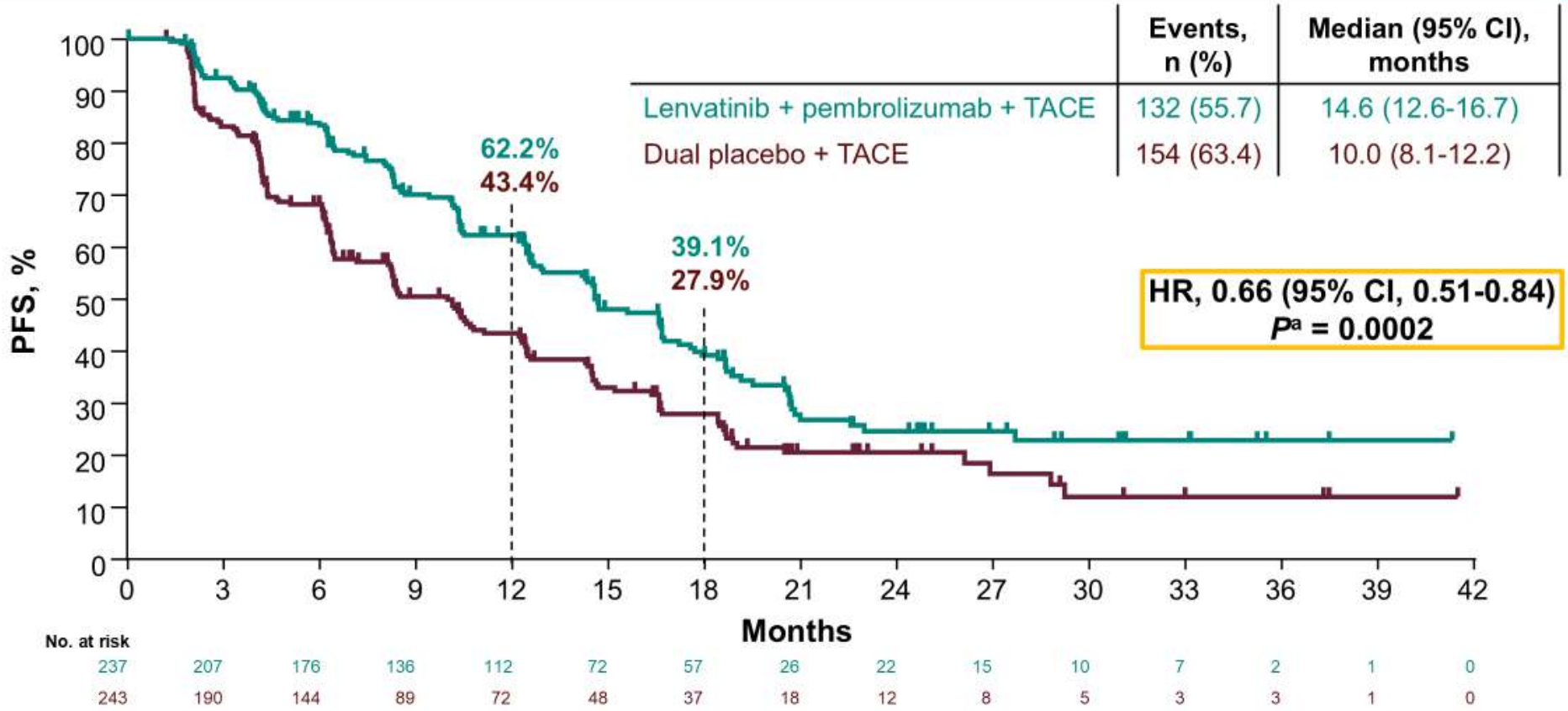
- Study site
- Alpha fetoprotein (≤400 ng/mL vs >400 ng/mL)
- ECOG PS (0 vs 1)
- ALBI grade (1 vs 2 or 3)
- Tumor burden score[1,a] (≤6 vs >6 but ≤12 vs >12)

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

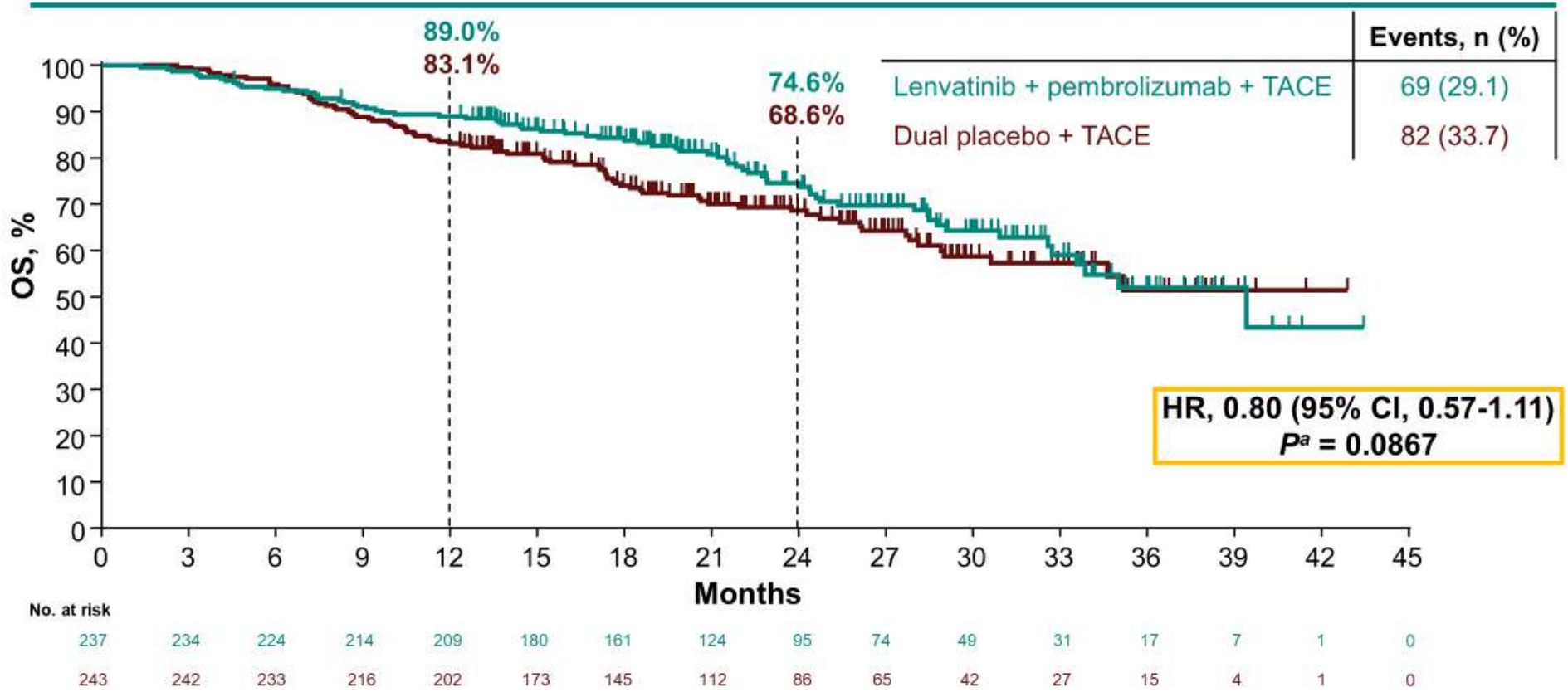
1. Wang Q et al. *J Hepatol.* 2019;70:893-903.
[a]Largest tumor in centimeters + number of tumors. [b]2-4 weeks after the start of systemic therapy with a maximum of 2 treatments per tumor (4 total) and no more than 1 treatment per month.
[c]Per RECIST v1.1 by BICR. [d]Per mRECIST by BICR.

Progression-Free Survival per RECIST v1.1 by BICR



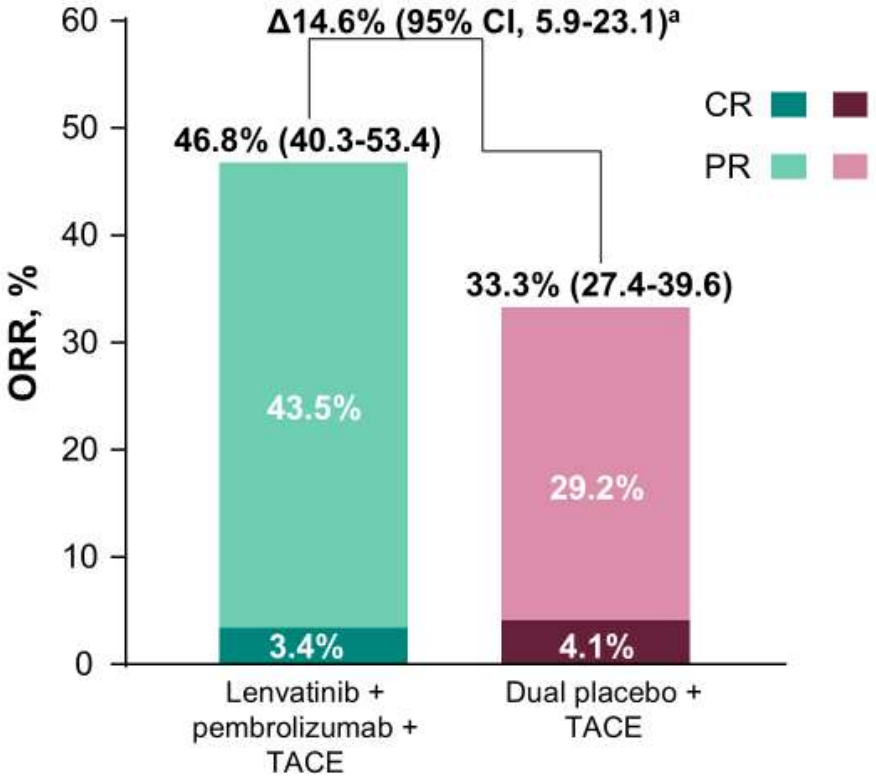
[a]One-sided *P* from re-randomization test; threshold *P* = 0.025. Data cutoff date for IA1: January 30, 2024.

Overall Survival



[a]One-sided *P* from re-randomization test; threshold *P* = 0.025. Data cutoff date for IA1: January 30, 2024.

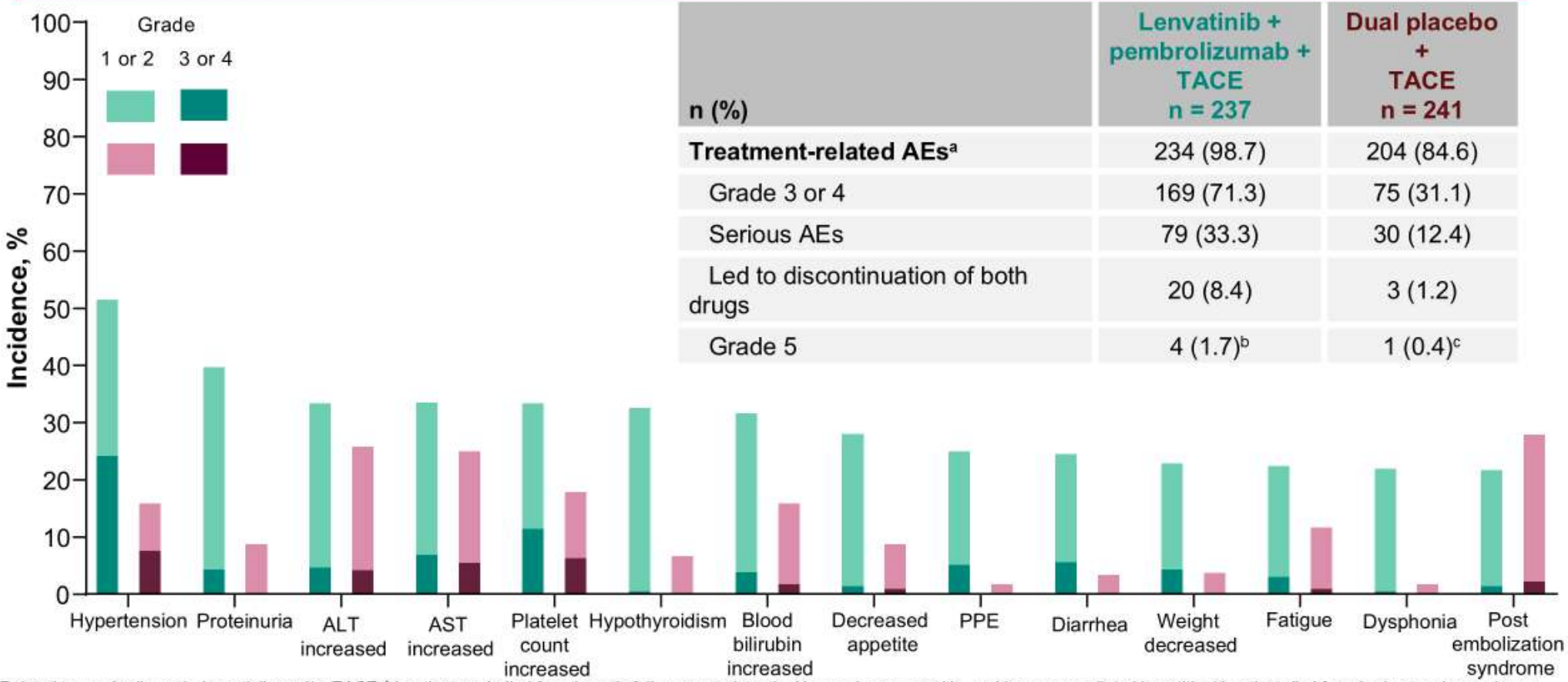
Objective Response Rate per RECIST v1.1 by BICR



	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 243
Best overall response, % (95% CI)[b,c]		
Complete response	3.4 (1.5-6.5)	4.1 (2.0-7.4)
Partial response	43.5 (37.1-50.0)	29.2 (23.6-35.4)
Stable disease	42.6 (36.2-49.2)	48.1 (41.7-54.6)
Progressive disease	6.8 (3.9-10.7)	14.8 (10.6-19.9)
Duration of response, median (range), months	12.6 (1.3+ to 39.1+)	10.7 (2.0+ to 39.5+)
Disease control rate	89.5 (84.8-93.1)	81.5 (76.0-86.2)

[a]Estimated from stratified analysis. [b]Patients with insufficient data for assessment of response: 2.1% in the lenvatinib + pembrolizumab + TACE group and 1.6% in the dual placebo + TACE group. [c]Patients without postbaseline assessments: 1.7% in the lenvatinib + pembrolizumab + TACE group and 2.1% in the dual placebo + TACE group. Data cutoff date for IA1: January 30, 2024.

Most Common Treatment-Related Adverse Events[a] (≥25%)



n (%)	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 241
Treatment-related AEs[a]	234 (98.7)	204 (84.6)
Grade 3 or 4	169 (71.3)	75 (31.1)
Serious AEs	79 (33.3)	30 (12.4)
Led to discontinuation of both drugs	20 (8.4)	3 (1.2)
Grade 5	4 (1.7)[b]	1 (0.4)[c]

[a]Related to pembrolizumab, lenvatinib, and/or TACE. [b]1 patient each died from hepatic failure, gastrointestinal hemorrhage, myositis, and immune-mediated hepatitis. [c]1 patient died from brain stem hemorrhage.
Data cutoff date for IA1: January 30, 2024.

Llovet et al, ESMO 2024

Conclusions

- The LEAP-012 study showed a clinically meaningful and statistically significant improvement in the primary end point of PFS for patients with intermediate-stage HCC who received lenvatinib + pembrolizumab + TACE vs dual placebo + TACE
  - HR, 0.66 (95% CI, 0.51-0.84); *P* = 0.0002
  - Early separation at the first 9-week scan was observed and continued beyond 24 months
- Although immature, a favorable OS trend was observed with lenvatinib + pembrolizumab + TACE and OS will be tested at future analyses in accordance with the statistical analysis plan
  - HR, 0.80 (95% CI, 0.57-1.11); *P* = 0.0867
- In combination with TACE, the safety profile of lenvatinib + pembrolizumab was manageable and consistent with known safety profiles of lenvatinib, pembrolizumab, and TACE
  - No new safety concerns were identified
- **Treatment with lenvatinib + pembrolizumab + TACE may be a new option for patients with intermediate-stage HCC**

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EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)

R 1:1:1 N=616

- **Arm A: Durvalumab‡** (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ placebo** for bevacizumab (Q3W)
- **Arm B: Durvalumab†** (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ bevacizumab** (15 mg/kg Q3W)
- **Arm C: Placebo** for durvalumab (Q4W) **+ TACE§** → **Placebo** for durvalumab (Q3W) **+ placebo** for bevacizumab (Q3W)

Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE 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. ‡Durvalumab / placebo started ≥7 days after TACE. §DEB-TACE or cTACE. Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure. ‖Only new lesions consistent with progression that were not eligible for TACE occurring prior to the first on study imaging at 12 weeks were considered progression events; standard mRECIST progression criteria were used after the 12-week imaging.

BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead-transarterial chemoembolization; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W / Q4W, every 3 / 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

ASCO Gastrointestinal Cancers Symposium #GI24

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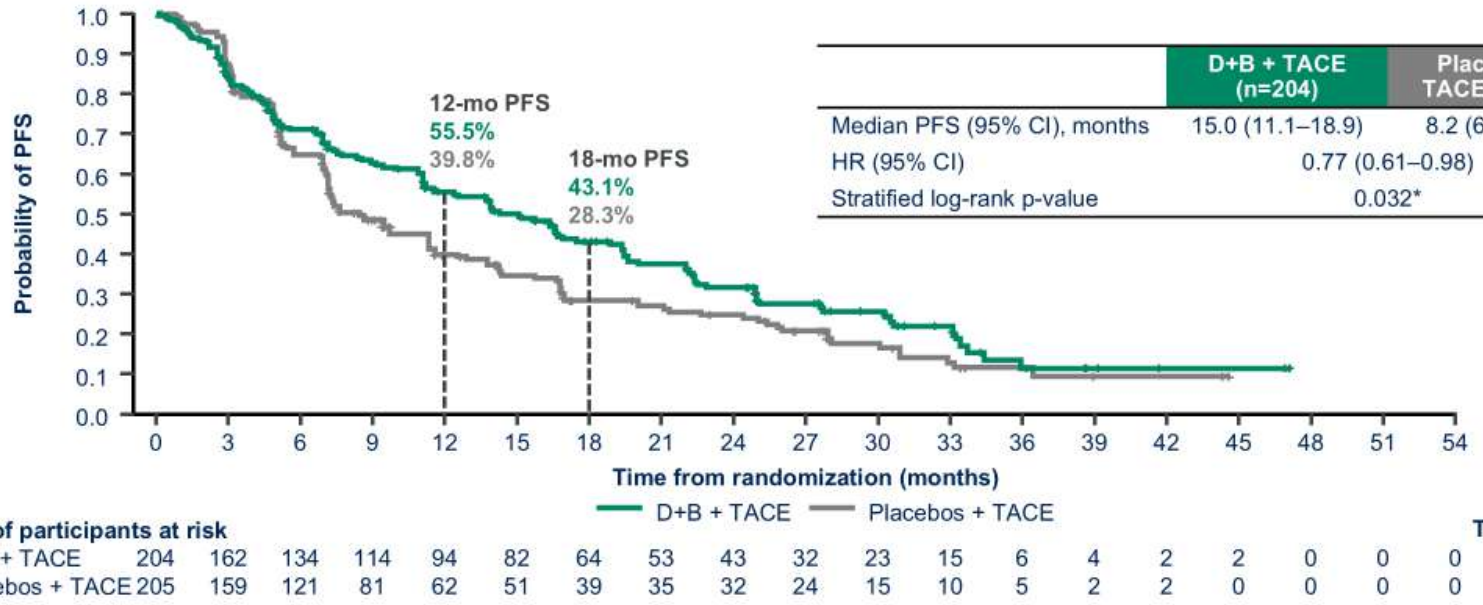
PFS with D+B + TACE versus placebos + TACE: primary endpoint

Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

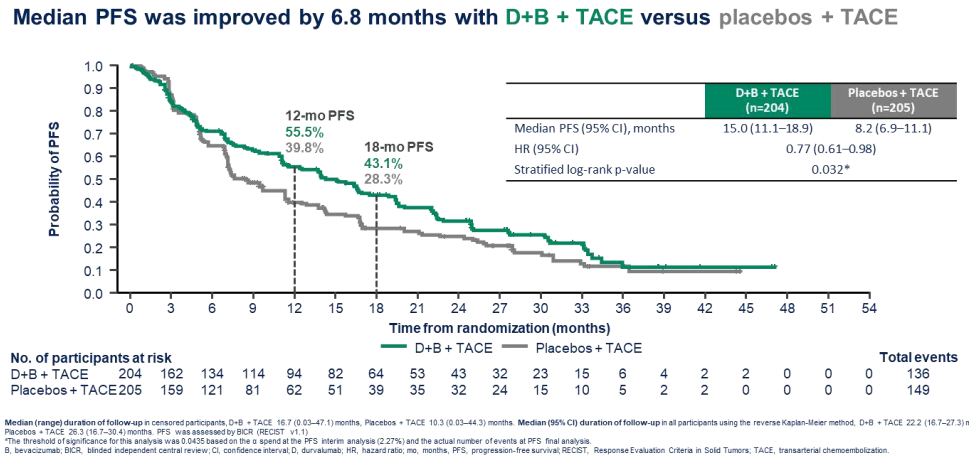
No. of participants at risk																				Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

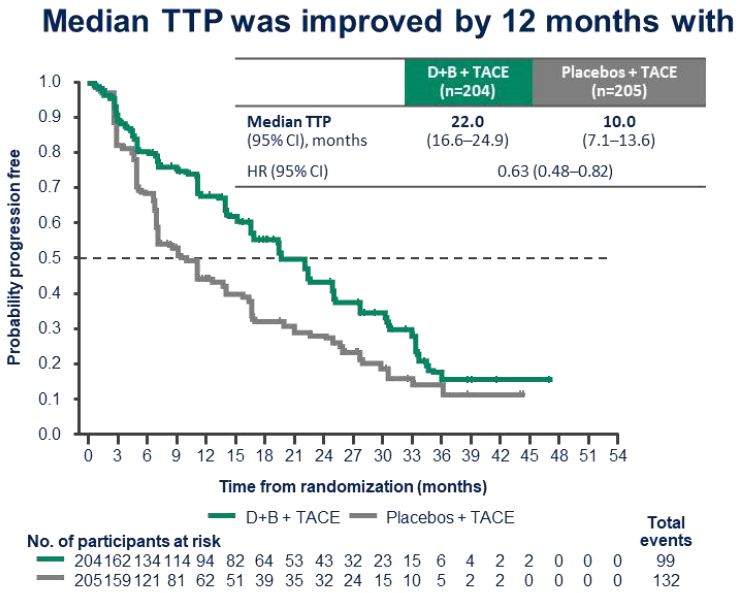
Median (range) duration of follow-up in censored participants, D+B + TACE 16.7 (0.03–47.1) months, Placebos + TACE 10.3 (0.03–44.3) months. **Median (95% CI) duration of follow-up** in all participants using the reverse Kaplan-Meier method, D+B + TACE 22.2 (16.7–27.3) months, Placebos + TACE 26.3 (16.7–30.4) months. PFS was assessed by BICR (RECIST v1.1)

*The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mo, months; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

THE PFS AND TTP DISCREPANCY IN EMERALD-1





PFS
Events: progression or death
In the exp arm = 136/204 events – 66.6%
In the control arm = 149/205 events – 72.7%

TTP
Events: progression (excludes deaths without progression)
In the exp arm = 99/204 events – 48.5%
In the control arm = 132/205 events – 64.4%

Then: Deaths without progression (difference in events):
In the exp arm = 37/204 events – 18.1%
In the control arm = 17/205 events – 8.3%

Lencioni et al, ASCO-GI 2024 – shown calculations by Dr Lamarca

IS THIS BECAUSE OF TOXICITY? NO

Poster 4122

Safety analysis by treatment periods from EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization with durvalumab with or without bevacizumab in participants with embolization-eligible unresectable hepatocellular carcinoma

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Objective

- To assess safety during the two treatment periods of the EMERALD-1 study, the durvalumab-transarterial chemoembolization (D-TACE) period and the durvalumab-bevacizumab (D-B) period

Conclusions

- Durvalumab (D) + bevacizumab (B) + transarterial chemoembolization (TACE) had a manageable safety profile across the D-TACE and D-B periods, consistent with the individual agents and underlying disease
- Safety was consistent across treatment arms during the D-TACE period, suggesting that D was well tolerated in combination with TACE
- In the D-B period, there were more Grade 3–4 adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation in the D + B + TACE arm versus the other arms; however, these differences are reduced when adjusting for exposure
- Although the sample size was small, concurrent administration of D, B, and TACE was well tolerated in participants who received additional TACE procedures following disease progression after initiation of combination therapy in the D-B period
- These data further support D + B + TACE as a new potential standard of care in embolization-eligible unresectable hepatocellular carcinoma (uHCC)

Plain language summary

Why did we perform this research?

- Transarterial chemoembolization (TACE) has been the standard treatment for people with unresectable hepatocellular carcinoma (HCC) eligible for TACE for >20 years
- TACE may prime tumors to be susceptible to two other types of anticancer therapy: immunotherapy, which attacks tumors using the immune system, and anti-vascular endothelial growth factor (VEGF) therapy, which inhibits VEGF – a protein that, when expressed in tumors, can promote blood flow to the tumor and have a modifying effect on immune function
- EMERALD-1 assessed an immunotherapy called durvalumab (D) and an anti-VEGF therapy called bevacizumab (B) in combination with TACE in participants with TACE-eligible HCC

How did we perform this research?

- People with HCC were treated with either (a) D + B + TACE; (b) D + TACE; or (c) TACE alone
- The EMERALD-1 regimen has two treatment phases: D was given in combination with TACE (D-TACE period) and in combination with B (D-B period)
- This analysis assessed safety during the study's two treatment phases, the D-TACE period and the D-B period

What were the findings of this research?

- During both treatment phases, side effects were manageable and consistent with those expected for the treatments and the disease

What are the implications of this research?

- Treatment with D + B + TACE could become a new standard treatment for people with unresectable HCC eligible for TACE

Where can I access more information?

Information about the medicines being used in this study and the people who could participate can be found here: https://clinicaltrials.gov/study/NCT03778957

This study was funded by AstraZeneca

Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2024 by Stephen L. Chan

Poster | Narrated poster video

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Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2024, Chicago, IL, USA, May 31–June 4

Corresponding author email address: stephen_stephen@cuhk.edu.hk

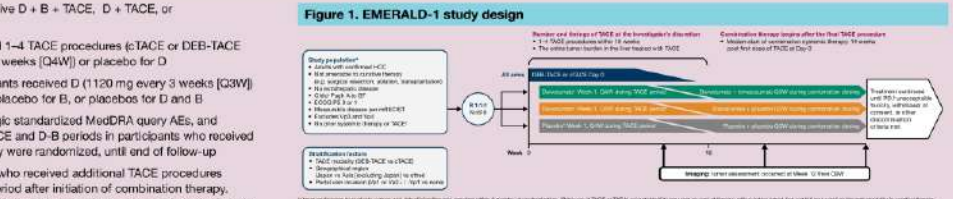
Introduction

- The global Phase 3 EMERALD-1 study demonstrated a statistically significant and clinically meaningful improvement in progression-free survival for D + B + TACE versus placebo + TACE in participants with embolization-eligible uHCC (**Figure 2**)[1]
- The EMERALD-1 regimen was administered in two phases: D was given in combination with TACE (D-TACE period) and in combination with B (D-B period). Therefore, it is important to understand and characterize the safety of D when given in combination with TACE and B
- This post hoc analysis assessed safety in the two individual treatment periods of the EMERALD-1 study

Methods

- Participants were randomized 1:1:1 to receive D + B + TACE, D + TACE, or placebo + TACE (**Figure 1**)
- In the D-TACE period, participants received 1–4 TACE procedures (cTACE or DEB-TACE [investigator choice]) + D (1500 mg every 4 weeks [Q4W]) or placebo for D
- In the D-B period, post-last TACE, participants received D (1120 mg every 3 weeks [Q3W]) + B (15 mg/kg Q3W), D (1120 mg Q3W) + placebo for B, or placebos for D and B
- Duration of exposure (DoE), AEs, hemorrhagic standardized MedDRA query AEs, and causality of AEs were assessed in the D-TACE and D-B periods in participants who received any study treatment in the arm to which they were randomized, until end of follow-up
- A separate analysis assessed participants who received additional TACE procedures following a progression event in the D-B period after initiation of combination therapy. This was performed in the safety analysis set (participants who received ≥1 dose of study treatment, by treatment received, regardless of randomization)

Figure 1. EMERALD-1 study design



Results and interpretation

Duration of exposure and safety summary:

- **D-TACE period:** DoE to D or placebo for D was similar across treatment arms
- **D-B period:** DoE to D or placebo for D, along with DoE to B or placebo for B, was longest in the D + B + TACE arm (**Table 1**)
- In both study periods, most AEs were non-serious and low-grade across treatment arms (**Table 1**)
- **D-B period:** higher rates of SAEs, maximum Grade 3–4 AEs, and AEs leading to discontinuation were observed in the D + B + TACE arm versus the other arms; however, differences in rates are reduced when adjusting for DoE (**Table 1**)
- **D-TACE period:** three fatal AEs were assessed by the investigator as possibly related to D or placebo for D, with two events (liver injury and multiple organ dysfunction syndrome) in the D + B + TACE arm and one event (dermatomyositis) in the placebos + TACE arm (**Table 1**)
- **D-B period:** three fatal AEs were assessed by the investigator as possibly related to B or placebo for B, with one event (arterial hemorrhage) in the D + TACE arm and two events (upper gastrointestinal hemorrhage and esophageal varices hemorrhage) in the placebos + TACE arm (**Table 1**)

Most common AEs:

- The most frequent AEs overall and across treatment periods are shown in **Figure 3**

Hemorrhagic AEs:

- **D-TACE period:** hemorrhagic AEs of any grade occurred in two (1.0%) participants in the D + B + TACE arm, 16 (8.3%) in the D + TACE arm, and 9 (4.5%) in the placebos + TACE arm
- **D-B period:** 42 (21.8%), 11 (5.7%), and 20 (10.0%) participants experienced hemorrhagic AEs of any grade in the D + B + TACE, D + TACE, and placebos + TACE arms, respectively. The higher frequency of hemorrhagic AEs with D + B + TACE was mostly driven by low-grade AEs
- Across the two treatment periods, no fatal hemorrhagic events occurred in participants who received B; fatal hemorrhagic AEs occurred in six (3.1%) and two (1.0%) participants in the D + TACE and placebos + TACE arms, respectively

Safety of concurrent TACE in the D-B period:

- Safety was well tolerated in participants who received additional TACE procedures after initiation of combination therapy following a progression event in the D-B period (**Table 2**)

Figure 2. PFS in EMERALD-1[1]

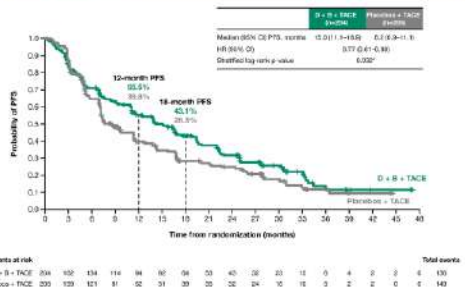


Figure 3. Most common AEs overall and in the D-TACE and D-B periods

Table 1. Duration of exposure and safety summary

	D-TACE Period			D-B Period			Overall		
	D + B + TACE (n=100)	D + TACE (n=100)	Placebos + TACE (n=100)	D + B + TACE (n=100)	D + TACE (n=100)	Placebos + TACE (n=100)	D + B + TACE (n=100)	D + TACE (n=100)	Placebos + TACE (n=100)
Median (range) DoE to D or placebo for D, months	2.8 (0.2–25.3)	2.8 (0.2–30.8)	2.8 (0.9–26.1)	10.5 (0.3–38.1)	6.9 (0.7–46.9)	8.3 (0.7–43.0)	9.5 (0.2–40.8)	8.5 (0.2–47.3)	8.7 (0.2–46.5)
Median (range) DoE to B or placebo for B, months	N/A	N/A	N/A	9.4 (0.3–38.5)	6.9 (0.7–45.5)	8.3 (0.7–43.0)	9.4 (0.3–38.5)	6.9 (0.7–45.5)	8.3 (0.7–43.0)
n (%) [event rate per 100 patient-years†]									
Any AE	139 (72.0) [59.6]	144 (74.0) [66.2]	148 (74.0) [65.1]	147 (76.2) [63.0]	133 (68.5) [61.2]	132 (66.0) [58.1]	185 (94.9) [78.4]	185 (94.9) [84.3]	180 (92.3) [81.5]
Possibly related to study treatment‡	56 (29.0) [24.0]	59 (30.8) [27.2]	41 (20.5) [18.0]	116 (59.1) [49.8]	76 (39.4) [35.0]	69 (34.5) [30.3]	139 (71.3) [59.2]	133 (63.4) [61.4]	90 (46.2) [39.6]
Provoked by TACE	99 (66.0) [58.6]	72 (37.3) [33.2]	65 (42.5) [37.4]	10 (5.3) [7.7]	10 (5.3) [7.4]	21 (10.5) [9.2]	97 (50.3) [41.3]	82 (42.5) [37.5]	65 (47.8) [41.3]
Serious AEs (including AEs with outcome of death)	31 (15.1) [13.3]	36 (15.7) [16.6]	30 (13.0) [13.2]	67 (34.7) [28.7]	41 (21.2) [18.9]	35 (17.5) [15.4]	89 (45.1) [38.3]	69 (35.6) [31.8]	62 (31.6) [27.3]
Possibly related to study treatment‡	6 (3.1) [2.6]	4 (2.1) [1.8]	5 (2.5) [2.2]	28 (14.5) [12.0]	6 (3.1) [2.8]	5 (2.5) [2.2]	33 (17.1) [14.2]	10 (5.2) [4.6]	10 (5.1) [4.4]
Provoked by TACE	14 (7.2) [5.8]	11 (5.7) [5.1]	10 (8.2) [7.0]	4 (2.1) [1.7]	6 (3.1) [2.8]	4 (2.0) [1.8]	15 (7.8) [7.7]	15 (7.8) [6.9]	10 (5.1) [4.4]
Any AE maximum Grade 3 or 4	29 (15.0) [12.4]	29 (15.0) [13.4]	26 (13.0) [11.4]	60 (31.1) [25.7]	36 (18.7) [16.6]	22 (11.0) [9.7]	89 (41.5) [34.3]	54 (28.0) [24.9]	46 (23.0) [20.2]
Possibly related to study treatment‡	9 (4.1) [3.8]	4 (2.1) [1.8]	4 (2.0) [1.8]	39 (19.7) [16.8]	10 (5.2) [4.6]	8 (4.0) [3.5]	43 (22.5) [18.4]	13 (6.7) [6.0]	12 (6.3) [5.3]
Provoked by TACE	17 (8.5) [7.3]	14 (7.3) [6.5]	14 (7.2) [6.2]	1 (0.5) [0.4]	2 (1.0) [0.9]	4 (2.0) [1.8]	18 (9.3) [7.7]	16 (8.3) [7.4]	17 (9.0) [7.5]
Any AE with outcome of death	6 (3.1) [2.6]	9 (4.7) [4.2]	5 (2.5) [2.2]	16 (8.3) [6.9]	6 (3.1) [2.8]	6 (3.0) [2.6]	22 (11.4) [9.4]	15 (7.8) [6.9]	11 (5.9) [4.8]
Possibly related to D or placebo for D	2 (1.0) [0.9]	0 N/A	1 (0.5) [0.4]	0 N/A	0 N/A	0 N/A	2 (1.0) [0.9]	0 N/A	1 (0.5) [0.4]
Possibly related to B or placebo for B	0 N/A	0 N/A	0 N/A	0 N/A	1 (0.5) [0.5]	2 (1.0) [0.9]	0 N/A	1 (0.5) [0.5]	2 (1.0) [0.9]
Provoked by TACE	0 N/A	0 N/A	1 (0.5) [0.4]	0 N/A	0 N/A	0 N/A	0 N/A	0 N/A	1 (0.5) [0.4]
Any AE leading to discontinuation of study treatment	7 (3.6) [3.0]	11 (5.7) [5.1]	5 (2.5) [2.2]	42 (21.8) [18.0]	12 (6.7) [5.6]	10 (5.0) [4.4]	49 (25.4) [21.0]	24 (12.4) [11.1]	15 (7.9) [6.6]
Possibly related to study treatment‡	3 (1.6) [1.3]	1 (0.5) [0.5]	2 (1.0) [0.9]	15 (8.3) [7.1]	5 (2.6) [2.3]	4 (2.0) [1.8]	21 (10.9) [9.0]	6 (3.1) [2.8]	6 (3.0) [2.6]
Provoked by TACE	1 (0.5) [0.4]	1 (0.5) [0.5]	2 (1.0) [0.9]	0 N/A	0 N/A	0 N/A	1 (0.5) [0.4]	1 (0.5) [0.5]	2 (1.0) [0.9]
Any immune-mediated AE§	23 (11.8) [9.9]	21 (10.9) [9.7]	10 (5.0) [4.4]	37 (19.2) [15.9]	25 (13.0) [11.6]	11 (5.5) [4.9]	56 (29.0) [24.2]	34 (17.8) [15.7]	20 (10.0) [8.8]

Includes participants who received any amount of study treatment in the arm to which they were randomized.
*Number of participants with AEs, divided by the total number of days at risk for all patients in given group, multiplied by 365.25, multiplied by 100. Assessed by the investigator as possibly related to D and/or that respective placebo.
§Adjudicated immune-mediated AEs.
AE, adverse event; B, bevacizumab; D, durvalumab; DoE, duration of exposure; N/A, not applicable; TACE, transarterial chemoembolization.

Table 2. Safety of concurrent TACE in the D-B period*

	D-B Period		
	D + B + TACE (n=32)	D + TACE (n=31)	Placebos + TACE (n=40)
Any AE, n (%)	17 (77.3)	21 (67.7)	31 (77.5)
Possibly related to study treatment†	7 (31.8)	9 (29.0)	8 (20.0)
Provoked by TACE	11 (50.0)	13 (41.9)	12 (30.0)
Serious AEs (including AEs with outcome of death), n (%)	6 (27.3)	8 (25.8)	9 (22.5)
Possibly related to study treatment†	2 (9.1)	1 (3.2)	0
Any AE maximum Grade 3 or 4, n (%)	7 (31.8)	6 (19.4)	6 (15.0)
Possibly related to study treatment†	3 (13.6)	1 (3.2)	0
Any AE with outcome of death,‡ n (%)	0	0	1 (2.5)
Any AE leading to discontinuation of study treatment, n (%)	2 (9.1)	1 (3.2)	0
Possibly related to study treatment†	1 (4.5)	1 (3.2)	0
Provoked by TACE	0	0	0
Any immune-mediated AE, n (%)	5 (22.7)	5 (16.1)	5 (12.5)
Any hemorrhagic AE, n (%)	3 (13.6)	1 (3.2)	5 (12.5)
Hemorrhagic AE of Grade 3 or 4, n (%)	1 (4.5)	0	0

Includes participants from the safety analysis set.
*Or placebo for B; was both for at least 14 days before and after a TACE procedure. †Assessed by the investigator as possibly related to D or B or their respective placebos. ‡No AEs with the outcome of death were possibly related to study treatment.
AE, adverse event; B, bevacizumab; D, durvalumab; TACE, transarterial chemoembolization.

Acknowledgments

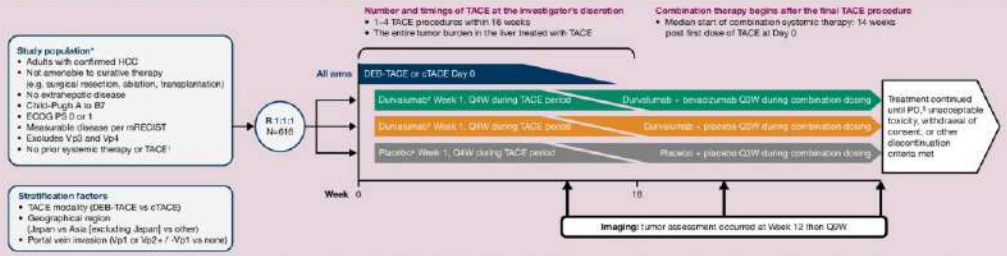
This study was sponsored by AstraZeneca. The authors would like to thank the participants, their families and caregivers, and all investigators involved in the study. Medical writing support, under the direction of the authors, was provided by Rachel Bland, PhD, CMC Connect, a division of HFW Health Medical Communications, funded by AstraZeneca, in accordance with Good Publication Practice (GPP 2022) guidelines.

Reference

1. Lencioni R, et al. J Clin Oncol 2024 [Epub] ahead of print.

IS THIS BECAUSE OF TOXICITY? NO

Figure 1. EMERALD-1 study design



*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE 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. ‡Diplacebo started >7 days after first TACE procedure; dosa mavsot to accommodate TACE if necessary. Diplacebo Q4W until >14 days after last TACE. §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.
cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; R, randomized; TACE, transarterial chemoembolization; Q3W / Q4W / Q6W, every 3 / 4 / 9 weeks.

Table 1. Duration of exposure and safety summary

	D-TACE Period			D-B Period			Overall		
	D + B + TACE (n=193)	D + TACE (n=193)	Placebos + TACE (n=200)	D + B + TACE (n=193)	D + TACE (n=193)	Placebos + TACE (n=200)	D + B + TACE (n=193)	D + TACE (n=193)	Placebos + TACE (n=200)
Median (range) DoE to D or placebo for D, months	2.8 (0.2–25.3)	2.8 (0.2–30.8)	2.8 (0.9–26.1)	10.5 (0.3–38.1)	6.9 (0.7–45.5)	8.3 (0.7–43.0)	9.3 (0.2–40.6)	8.5 (0.2–47.3)	8.7 (0.9–45.5)
Median (range) DoE to B or placebo for B, months	N/A	N/A	N/A	9.4 (0.3–36.5)	6.9 (0.7–45.5)	8.3 (0.7–43.0)	9.4 (0.3–36.5)	6.9 (0.7–45.5)	8.3 (0.7–43.0)
n (%) [event rate per 100 patient-years*]									
Any AE	139 (72.0) [59.6]	144 (74.6) [66.3]	148 (74.0) [65.1]	147 (76.2) [63.0]	133 (68.9) [61.3]	132 (66.0) [58.0]	183 (94.8) [78.4]	183 (94.8) [84.3]	186 (93.0) [81.8]
Possibly related to study treatment†	56 (29.0) [24.0]	59 (30.6) [27.2]	41 (20.5) [18.0]	114 (59.1) [48.9]	76 (39.4) [35.0]	69 (34.5) [30.3]	138 (71.5) [59.2]	103 (53.4) [47.4]	90 (45.0) [39.6]
Provoked by TACE	90 (46.6) [38.6]	72 (37.3) [33.2]	85 (42.5) [37.4]	18 (9.3) [7.7]	16 (8.3) [7.4]	21 (10.5) [9.2]	97 (50.3) [41.6]	82 (42.5) [37.8]	95 (47.5) [41.8]
Serious AEs (including AEs with outcome of death)	31 (16.1) [13.3]	36 (18.7) [16.6]	30 (15.0) [13.2]	67 (34.7) [28.7]	41 (21.2) [18.9]	35 (17.5) [15.4]	89 (46.1) [38.2]	69 (35.8) [31.8]	62 (31.0) [27.3]
Possibly related to study treatment†	6 (3.1) [2.6]	4 (2.1) [1.8]	5 (2.5) [2.2]	28 (14.5) [12.0]	6 (3.1) [2.8]	5 (2.5) [2.2]	33 (17.1) [14.2]	10 (5.2) [4.6]	10 (5.0) [4.4]
Provoked by TACE	14 (7.3) [6.0]	11 (5.7) [5.1]	16 (8.0) [7.0]	4 (2.1) [1.7]	6 (3.1) [2.8]	4 (2.0) [1.8]	18 (9.3) [7.7]	15 (7.8) [6.9]	19 (9.5) [8.4]
Any AE maximum Grade 3 or 4	29 (15.0) [12.4]	29 (15.0) [13.4]	26 (13.0) [11.4]	60 (31.1) [25.7]	36 (18.7) [16.6]	22 (11.0) [9.7]	80 (41.5) [34.3]	54 (28.0) [24.9]	46 (23.0) [20.2]
Possibly related to study treatment†	6 (3.1) [2.6]	4 (2.1) [1.8]	4 (2.0) [1.8]	38 (19.7) [16.3]	10 (5.2) [4.6]	8 (4.0) [3.5]	43 (22.3) [18.4]	13 (6.7) [6.0]	12 (6.0) [5.3]
Provoked by TACE	17 (8.8) [7.3]	14 (7.3) [6.5]	14 (7.0) [6.2]	1 (0.5) [0.4]	2 (1.0) [0.9]	4 (2.0) [1.8]	18 (9.3) [7.7]	16 (8.3) [7.4]	17 (18.5) [7.5]
Any AE with outcome of death	6 (3.1) [2.6]	9 (4.7) [4.2]	5 (2.5) [2.2]	16 (8.3) [6.9]	6 (3.1) [2.8]	6 (3.0) [2.6]	22 (11.4) [9.4]	15 (7.8) [6.9]	11 (5.5) [4.8]
Possibly related to D or placebo for D	2 (1.0) [0.9]	0 N/A	1 (0.5) [0.4]	0 N/A	0 N/A	0 N/A	2 (1.0) [0.9]	0 N/A	1 (0.5) [0.4]
Possibly related to B or placebo for B	0 N/A	0 N/A	0 N/A	0 N/A	1 (0.5) [0.5]	2 (1.0) [0.9]	0 N/A	1 (0.5) [0.5]	2 (1.0) [0.9]
Provoked by TACE	0 N/A	0 N/A	1 (0.5) [0.4]	0 N/A	0 N/A	0 N/A	0 N/A	0 N/A	1 (0.5) [0.4]
Any AE leading to discontinuation of study treatment	7 (3.6) [3.0]	11 (5.7) [5.1]	5 (2.5) [2.2]	42 (21.8) [18.0]	13 (6.7) [6.0]	10 (5.0) [4.4]	49 (25.4) [21.0]	24 (12.4) [11.1]	15 (7.5) [6.6]
Possibly related to study treatment†	3 (1.6) [1.3]	1 (0.5) [0.5]	2 (1.0) [0.9]	18 (9.3) [7.7]	5 (2.6) [2.3]	4 (2.0) [1.8]	21 (10.9) [9.0]	6 (3.1) [2.8]	6 (3.0) [2.6]
Provoked by TACE	1 (0.5) [0.4]	1 (0.5) [0.5]	2 (1.0) [0.9]	0 N/A	0 N/A	0 N/A	1 (0.5) [0.4]	1 (0.5) [0.5]	2 (1.0) [0.9]
Any immune-mediated AE‡	23 (11.9) [9.9]	21 (10.9) [9.7]	10 (5.0) [4.4]	37 (19.2) [15.9]	25 (13.0) [11.5]	11 (5.5) [4.8]	56 (29.0) [24.0]	45 (23.3) [20.7]	20 (10.0) [8.8]

Includes participants who received any amount of study treatment in the arm to which they were randomized.
*Number of participants with AEs, divided by the total number of days at risk for AEs across all participants in given group, multiplied by 365.25, multiplied by 100. †Assessed by the investigator as possibly related to D or B or their respective placebos.
‡Adjudicated immune-mediated AEs.
AE, adverse event; B, bevacizumab; D, durvalumab; DoE, duration of exposure; N/A, not applicable; TACE, transarterial chemoembolization.

Table 2. Safety of concurrent TACE in the D-B period*

	D-B Period		
	D + B + TACE (n=22)	D + TACE (n=31)	Placebos + TACE (n=40)
Any AE, n (%)	**17 (77.3)**	**21 (67.7)**	**31 (77.5)**
Possibly related to study treatment†	7 (31.8)	9 (29.0)	8 (20.0)
Provoked by TACE	11 (50.0)	13 (41.9)	12 (30.0)
Serious AEs (including AEs with outcome of death), n (%)	**6 (27.3)**	**8 (25.8)**	**9 (22.5)**
Possibly related to study treatment†	2 (9.1)	1 (3.2)	0
Any AE maximum Grade 3 or 4, n (%)	**7 (31.8)**	**6 (19.4)**	**6 (15.0)**
Possibly related to study treatment†	3 (13.6)	1 (3.2)	0
Any AE with outcome of death,‡ n (%)	**0**	**0**	**1 (2.5)**
Any AE leading to discontinuation of study treatment, n (%)	**2 (9.1)**	**1 (3.2)**	**0**
Possibly related to study treatment†	1 (4.5)	1 (3.2)	0
Provoked by TACE	0	0	0
Any immune-mediated AE, n (%)	**5 (22.7)**	**5 (16.1)**	**5 (12.5)**
Any hemorrhagic AE, n (%)	**3 (13.6)**	**1 (3.2)**	**5 (12.5)**
Hemorrhagic AE of Grade 3 or 4, n (%)	**1 (4.5)**	**0**	**0**

Includes participants from the safety analysis set.
*B (or placebo for B) was held for at least 14 days before and after a TACE procedure. †Assessed by the investigator as possibly related to D or B or their respective placebos. ‡No AEs with the outcome of death were possibly related to study treatment.
AE, adverse event; B, bevacizumab; D, durvalumab; TACE, transarterial chemoembolization.

Acknowledgments

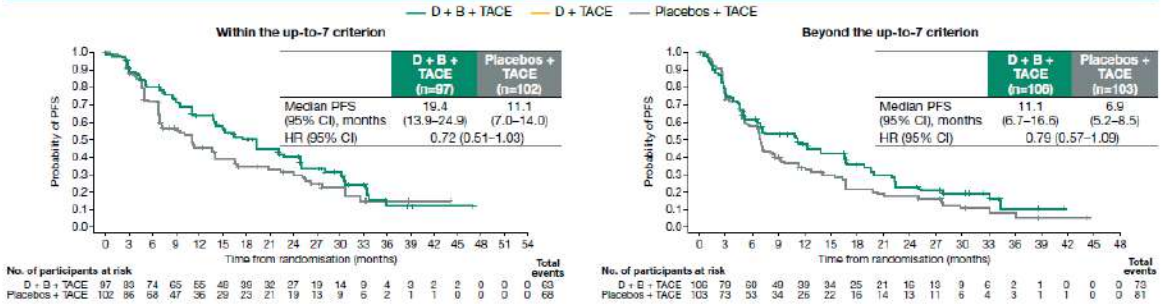
This study was sponsored by AstraZeneca. The authors would like to thank the participants, their families and caregivers, and all investigators involved in this study. Medical writing support, under the direction of the authors, was provided by Derrick Bond, PharmD, CMC Connect, a division of IPG Health Medical Communications, funded by AstraZeneca, in accordance with Good Publication Practice (GPP 2022) guidelines.

Reference

1. Lencioni R, et al. *J Clin Oncol* 2024;42(suppl 3). Abs LBA432.

EMERALD-1 (ESMO 2024 UPDATE)

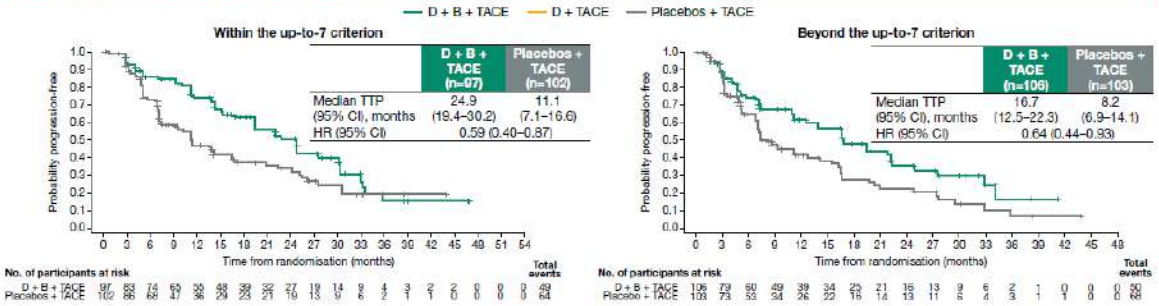
Figure 3. PFS by baseline tumour burden



Within the up-to-7 criterion	D + B + TACE (n=97)	Placebos + TACE (n=102)
Median PFS (95% CI), months	19.4 (13.9–24.9)	11.1 (7.0–14.0)
HR (95% CI)	0.72 (0.51–1.03)	

Beyond the up-to-7 criterion	D + B + TACE (n=106)	Placebos + TACE (n=103)
Median PFS (95% CI), months	11.1 (6.7–16.6)	6.9 (5.2–8.5)
HR (95% CI)	0.79 (0.57–1.09)	

Figure 4. TTP by baseline tumour burden



Within the up-to-7 criterion	D + B + TACE (n=97)	Placebos + TACE (n=102)
Median TTP (95% CI), months	24.9 (19.4–30.2)	11.1 (7.1–16.6)
HR (95% CI)	0.59 (0.40–0.87)	

Beyond the up-to-7 criterion	D + B + TACE (n=106)	Placebos + TACE (n=103)
Median TTP (95% CI), months	16.7 (12.5–22.3)	8.2 (6.9–14.1)
HR (95% CI)	0.64 (0.44–0.93)	

Plain language summary

Why did we perform this research?

- Transarterial chemoembolisation (TACE) has been the standard treatment for people with unresectable hepatocellular carcinoma (uHCC) eligible for TACE for >20 years
- TACE may prime tumours to be susceptible to two other types of anticancer therapy: immunotherapy, which attacks tumours using the immune system, and anti-vascular endothelial growth factor (VEGF) therapy, which inhibits VEGF – a protein that, when expressed in tumours, can promote blood flow to the tumour and have a modifying effect on immune function
- Recent findings from the EMERALD-1 study showed that participants with uHCC eligible for TACE who were treated with TACE in combination with durvalumab (an immunotherapy) and bevacizumab (an anti-VEGF therapy) had significantly reduced risk of disease progression (cancer spreading, growing or getting worse) or death compared with participants treated with TACE alone
- Tumour burden (the size and number of tumours that a person has) can impact how well treatment might work for a person with HCC, and the up-to-7 criterion measures tumour burden based on tumour number and diameter
- We performed this research to see how well durvalumab plus bevacizumab plus TACE, durvalumab plus TACE, and TACE alone worked, and assessed the safety of each treatment based on participants' tumour burden at the start of the EMERALD-1 study

How did we perform this research?

- Participants were split into two groups depending on their tumour burden at the start of the study
- We examined how long participants with uHCC lived without their cancer growing, spreading or getting worse after being treated with durvalumab plus bevacizumab plus TACE or TACE alone. The safety of treatment was also assessed

What were the findings of this research?

- Participants with uHCC who were treated with durvalumab plus bevacizumab plus TACE were more likely to live longer without their cancer growing, spreading or getting worse than those treated with TACE alone, regardless of their tumour burden at the start of the study
- Side effects were manageable and consistent with those expected for the treatments and the disease

What are the implications of this research?

- Treatment with durvalumab plus bevacizumab plus TACE could become a new standard treatment for people with uHCC eligible for TACE, regardless of tumour burden

Where can I access more information?

- Information about the medicines being used in this study and the people who could participate can be found here: https://clinicaltrials.gov/study/NCT03778957

This study was funded by AstraZeneca
Poster presented at ESMO Congress 2024 by Masatoshi Kudo

LEAP-012 vs EMERALD-1

Observations with CURRENT data

*BASELINE CHARACTERISTICS: more VHB, BCLC-A, ALBI1 in LEAP-012

	Lenvatinib + pembrolizumab + TACE n = 237		Lenvatinib + pembrolizumab + TACE n = 237
Age, median (range), yrs	65.0 (31-87)	Child-Pugh score A5	204 (86.1)
Age, ≥65 yrs	128 (54.0)	BCLC stage[d]	
Sex, male	192 (81.0)	A	80 (33.8)
Geographic region, Asia (without Japan)	135 (57.0)	B	135 (57.0)
ECOG PS 0	216 (91.1)	C	21 (8.9)
HBV status – positive[a]	153 (64.6)	ALBI grade 1[e]	171 (72.2)
HCV status – positive[b]	42 (17.7)	Tumor burden score[1,f]	
Viral etiology[c]	179 (75.5)	≤6	112 (47.3)
Alcohol etiology	107 (45.1)	>6 and ≤12	120 (50.6)
AFP ≤400 ng/mL	200 (84.4)	>12	5 (2.1)

		D+B + TACE (n=204)*
Age (years)	Median	64.5
Sex, n (%)	Male	162 (79.4)
Geographical region, n (%)	Japan	15 (7.4)
	Asia (non-Japan)	107 (52.4)
	Others	82 (40.1)
TACE modality, n (%)	DEB-TACE	84 (41.2)
	cTACE	119 (58.3)
Etiology of liver disease, n (%)	HBV	75 (36.8)
	HCV	42 (20.6)
	Non-viral	86 (42.2)
BCLC stage, n (%)	A	51 (25.0)
	B	117 (57.4)
	C	35 (17.2)
Portal vein invasion, n (%)	No	188 (92.2)
	Yes	16 (7.8)
Screening ECOG PS, n (%)	0	167 (81.9)
	1	37 (18.1)
Baseline PD-L1†, n (%)	High (≥1%)	61 (29.9)
	Low (<1%)	93 (45.6)
	Unknown	50 (24.5)
Child-Pugh score, n (%)	A	200 (98.0)
	B	4 (2.0)
ALBI at baseline, n (%)	Grade 1	117 (57.4)
	Grade ≥2	87 (42.6)
Tumor burden at baseline, n (%)	Within up-to 7 criteria (≤7)	97 (47.5)
	Beyond up-to-7 criteria (>7)	106 (52.0)
HAP score, n (%)	A	66 (32.4)
	B	74 (36.3)
	C	41 (20.1)
	D	20 (9.8)
	Missing	3 (1.5)

Lenvioni et al ASCO GI 2024; Llovet et al ESMO 2024

LEAP-012 vs EMERALD-1

Observations with CURRENT data

*Both have PFS benefit

- HR 0.66 (LEAP-012) vs 0.77 (EMERALD-1)
- ▲ Median PFS (months): 4.6 (LEAP-012) vs 6.8 (EMERALD-1)

*Curves separate earlier in LEAP-012

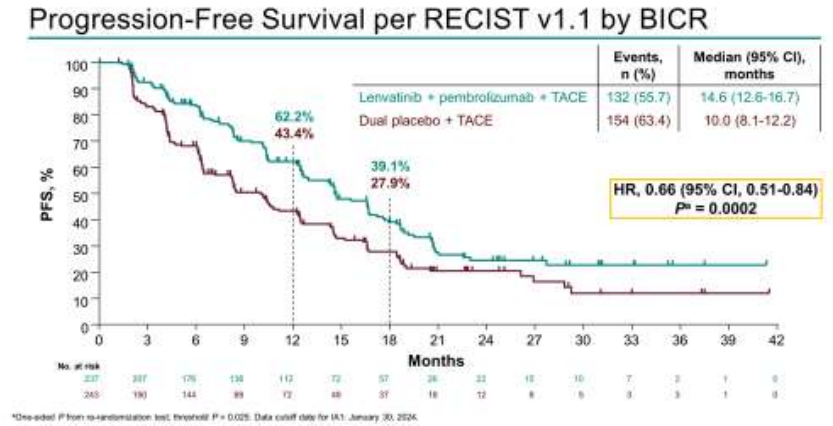
*ORR benefit in LEAP-012 and EMERALD-1

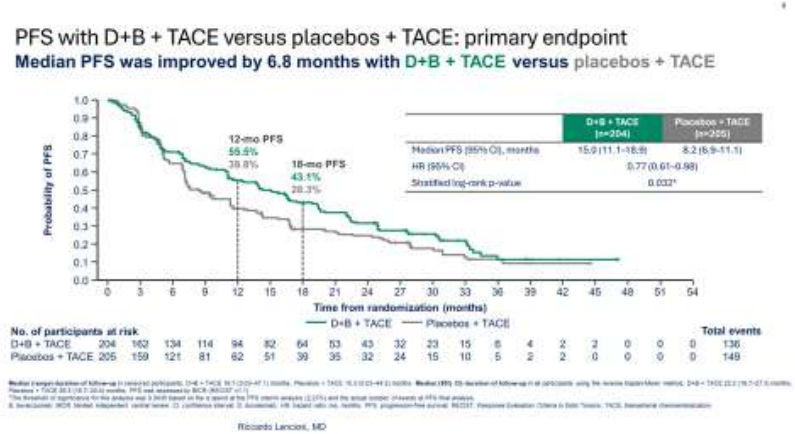
*EMERALD-1 showed discrepancies between PFS and TTP (no TTP data in LEAP-012)

*Toxicity does not seem to be an issue - higher rate of discontinuation due to AEs (both 8.4% (LEAP-012) vs any/both 24.7% (EMERALD-1))

*Impact on OS?

- Promising (LEAP-012) vs Not available yet (EMERALD-1)





Lenvioni et al ASCO GI 2024; Llovet et al ESMO 2024

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Dr Angela Lamarca (@DrAngelaLamarca)
Invited Discussant LBA3

TAKE HOME MESSAGES

TODAY	I agree "Treatment with lenvatinib + pembrolizumab + TACE may be a new option for patients with intermediate-stage HCC" - significant improvement in PFS (early separation of curves), promising OS, manageable toxicity
INTO CONTEXT	Second positive study in the field – confirms hypothesis Other options could include durvalumab and bevacizumab (EMERALD-1), even though data shown up to today may seem to be "more robust" for LEAP-012 (lenvatinib and pembrolizumab)
FUTURE	Other ongoing clinical trials are exploring other combinations – will have to wait other studies → We feel very close to systemic therapies moving earlier into patients pathway
CHALLENGES	Doors open to new problem: what to do at progression? We are still missing biomarkers!!! Surrogate end-points for OS (PFS robust enough?)

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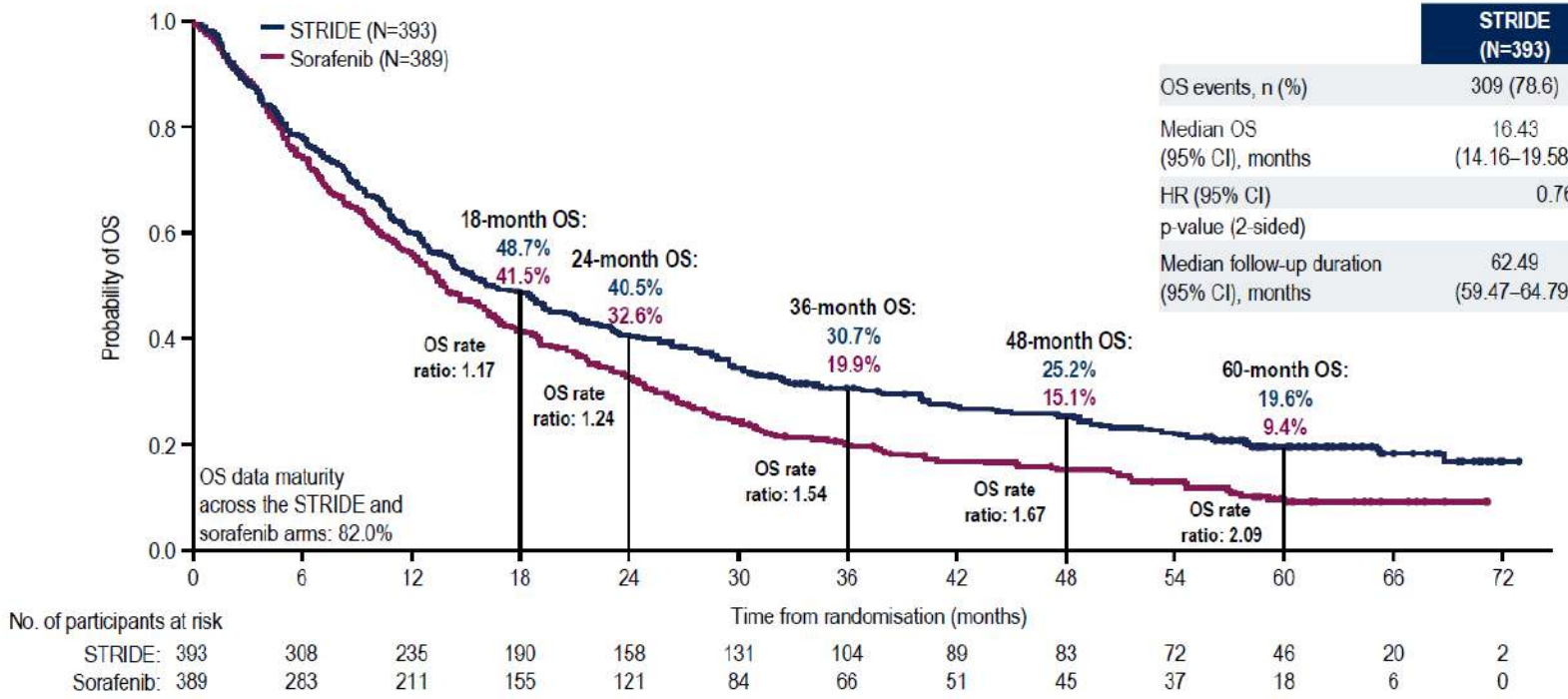
Dr Angela Lamarca (@DrAngelaLamarca)
Invited Discussant LBA3

HIMALAYA 2024 ESMO UPDATE (5-YEAR OS)

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)

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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.

HIMALAYA 2024 ESMO UPDATE (5-YEAR OS)

Five-year OS by disease control for STRIDE versus sorafenib

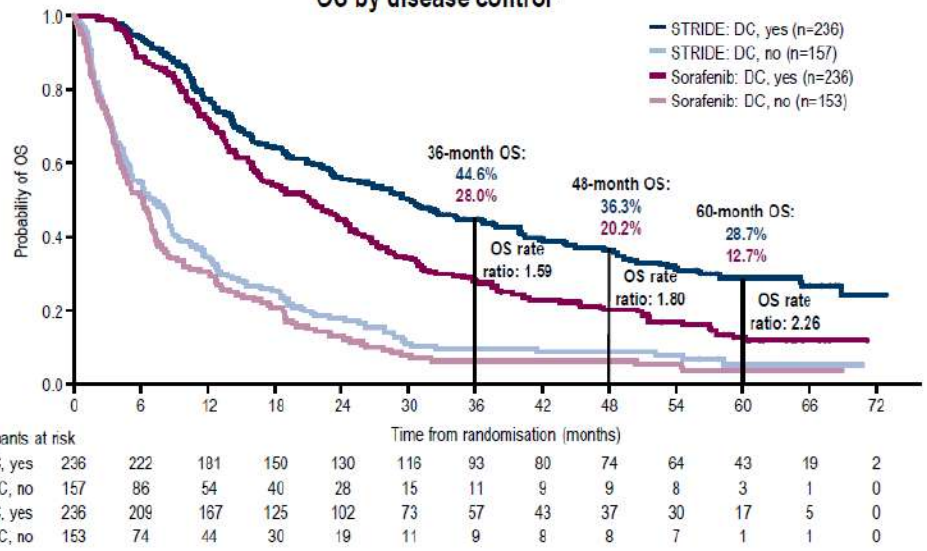
OS benefit with STRIDE was enhanced in participants experiencing disease control per RECIST v1.1, with OS rates of 28.7% for STRIDE and 12.7% for sorafenib at 5-years and the OS rate ratios for STRIDE versus sorafenib increasing over time

Best objective response (RECIST v1.1)

	Full analysis set[1]		eLTS† (≥48 months)	
	STRIDE (n=393)	Sorafenib (n=389)	STRIDE (n=83)	Sorafenib (n=45)
BOR, n (%)				
CR	12 (3.1)	0	10 (12.0)	0
PR	67 (17.0)	20 (5.1)	41 (49.4)	7 (15.6)
SD	157 (39.9)	216 (55.5)	23 (27.7)	30 (66.7)
PD	141 (35.9)	118 (30.3)	8 (9.6)	6 (13.3)
NE	16 (4.1)	35 (9.0)	1 (1.2)	2 (4.4)
Median TTR (IQR), months	2.17 (1.84–3.98)	3.78 (1.89–8.44)	2.10 (1.84–3.94)	5.49 (1.64–11.01)
Median DoR (IQR), months	22.34 (8.54–NR)	18.43 (6.51–25.99)	NR (20.50–NR)	NR (8.31–NR)
DCR*, n (%)	**236 (60.1)**	**236 (60.7)**	**74 (89.2)**	**37 (82.2)**

eLTS included participants regardless of response

OS by disease control*



No. of participants at risk

STRIDE: DC, yes	236	222	181	150	130	116	93	80	74	64	43	19	2
STRIDE: DC, no	157	86	54	40	28	15	11	9	9	8	3	1	0
Sorafenib: DC, yes	236	209	167	125	102	73	57	43	37	30	17	5	0
Sorafenib: DC, no	153	74	44	30	19	11	9	8	8	7	1	1	0

Responses were based on investigator assessment according to RECIST v1.1. Responses were confirmed. Response data for both the full analysis set and eLTS were from the primary analysis (data cut-off: 27 August 2021). Updated analysis data cut-off: 01 March 2024.
*Disease control was defined as CR, PR or SD. †eLTS were defined as participants surviving ≥48 months beyond randomisation.
BOR, best objective response; CR, complete response; DC, disease control; DCR, disease control rate; DoR, duration of response; eLTS, extended long-term survivors; IQR, interquartile range; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTR, time to response.
1. Abou-Alfa GK, et al. *NEJM Evid* 2022;1(8):EVIDoa2100070.

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HIMALAYA 2024 ESMO UPDATE (5-YEAR OS)

Conclusions

- This 5-year updated analysis of the HIMALAYA study presents the longest follow-up to date in Phase 3 studies in uHCC
- STRIDE sustained an OS benefit versus sorafenib and demonstrated unprecedented long-term survival benefit at 5-years, with a 5-year survival rate of 19.6% with STRIDE versus 9.4% with sorafenib
- OS benefit with STRIDE was improved in participants with disease control
    - Any degree of tumour shrinkage was associated with long-term survival, with participants experiencing deep responses benefitting most
- These findings indicate that conventional response measures may not fully capture the benefits of STRIDE
- The STRIDE regimen maintained a tolerable and differentiated safety profile from other current uHCC therapies[1–4]

These findings demonstrate that STRIDE continues to set new benchmarks in uHCC, with 1 in 5 patients alive at five years

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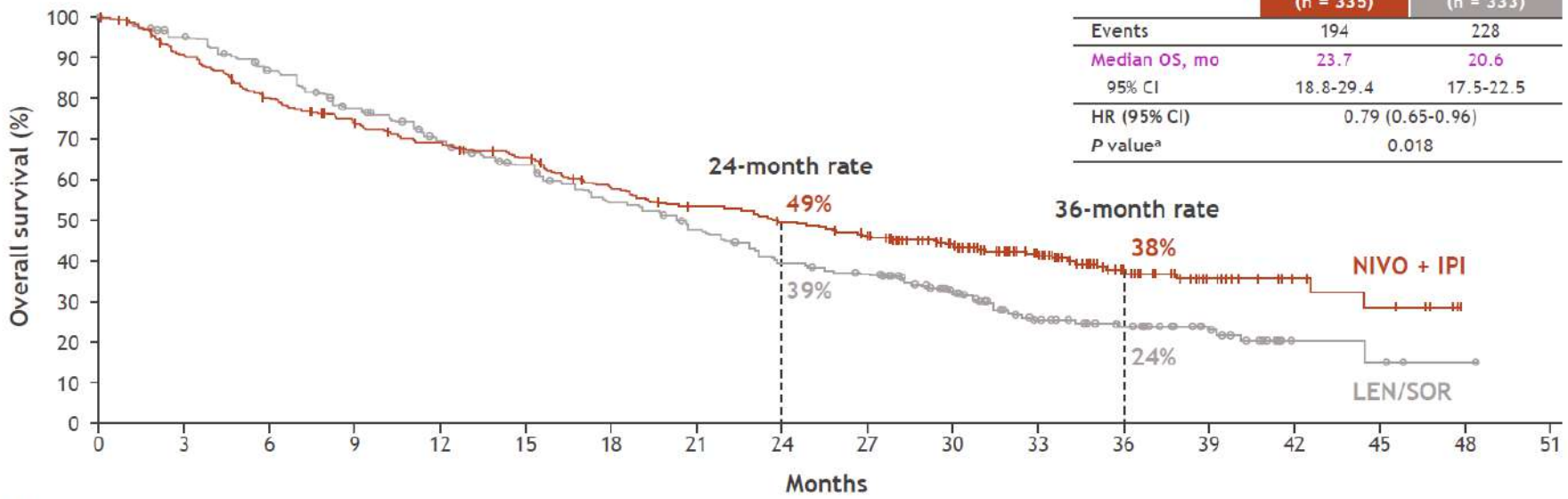
OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab; uHCC, unresectable hepatocellular carcinoma.

1. Abou-Alfa GK, et al. *NEJM Evid* 2022;1(8):EVIDoa2100070. 2. Llovet JM, et al. *N Engl J Med* 2008;359:378–390. 3. Finn RS, et al. *N Engl J Med* 2020;382:1894–1905. 4. Yau T, et al. *JAMA Oncol* 2022;6:e204564.

CHECKMATE 9DW 2024 ESMO UPDATE

CheckMate 9DW

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	

No. at risk

NIVO + IPI	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
LEN/SOR	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

- 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

Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257.

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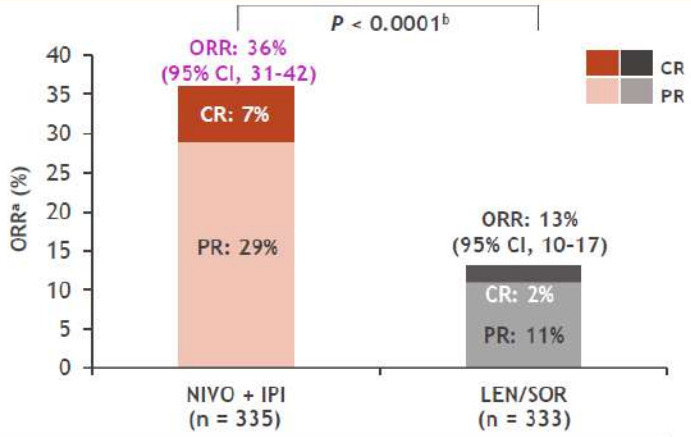
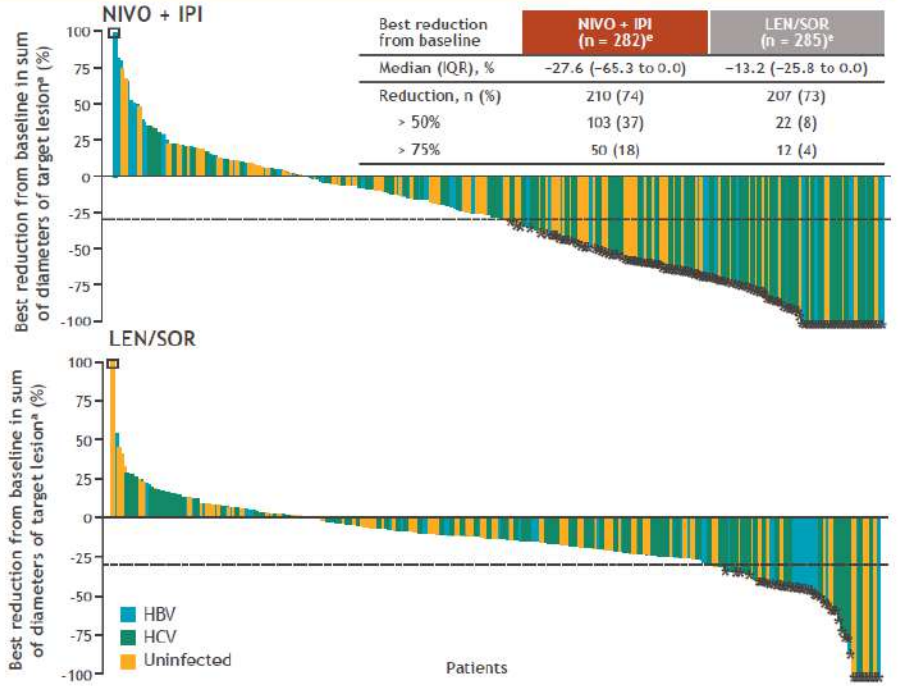
CHECKMATE 9DW 2024 ESMO UPDATE

CheckMate 9DW

Objective response



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)



Best reduction from baseline	NIVO + IPI (n = 282)[e]	LEN/SOR (n = 285)[e]
Median (IQR), %	−27.6 (−65.3 to 0.0)	−13.2 (−25.8 to 0.0)
Reduction, n (%)	210 (74)	207 (73)
> 50%	103 (37)	22 (8)
> 75%	50 (18)	12 (4)

- Statistically significant and clinically meaningful improvement in ORR with NIVO + IPI vs LEN/SOR, with a higher complete response rate (7% vs 2%, respectively) and durable responses
- Responses with NIVO + IPI were observed regardless of etiology

[a]Assessed by BICR based on RECIST v1.1. [b]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: *P* value ≤ 0.025. [c]Includes non-CR/non-PD: NIVO + IPI, n = 6 (2%); LEN/SOR, n = 7 (2%). Non-CR/non-PD refers to patients with persistence of 1 or more non-target lesion(s). [d]In confirmed responders (NIVO + IPI: n = 121; LEN/SOR: n = 44). [e]Response evaluable patients defined as those with a best overall response of CR, PR, SD, non-CR/non-PD, or PD; target lesion(s) assessed at baseline; and ≥ 1 on-study assessment of all baseline target lesion(s). Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1. Asterisk symbol, responders; square symbol, percent change truncated to 100%. Ten patients with HBV-HCV coinfections were categorized to HCV.

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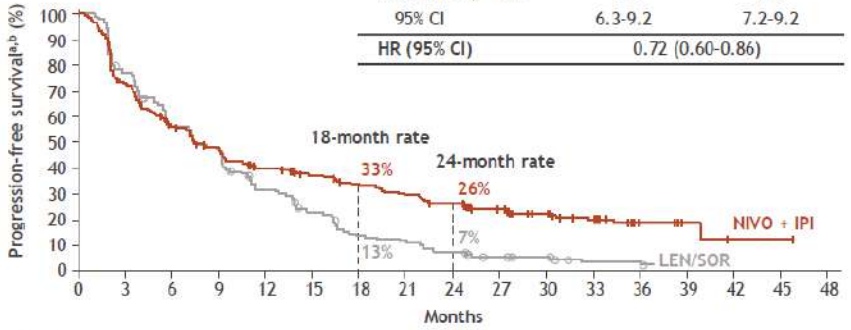
CHECKMATE 9DW 2024 ESMO UPDATE

CheckMate 9DW

PFS and PFS2 per investigator

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)	

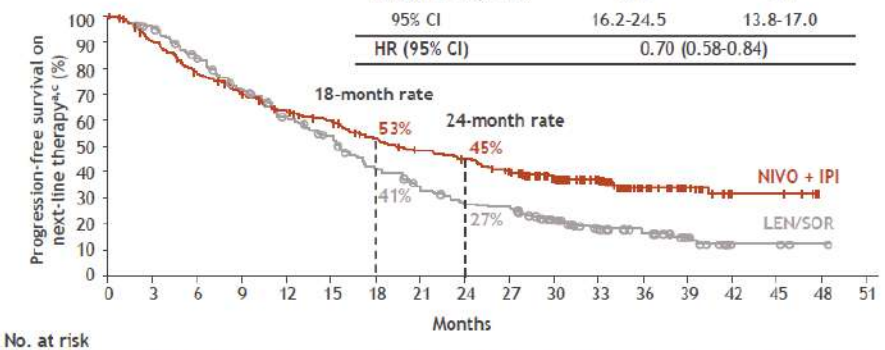


No. at risk

NIVO + IPI	335	236	173	143	114	101	89	78	69	53	35	23	9	3	1	1	0
LEN/SOR	333	243	170	140	88	62	34	28	18	11	8	3	2	0	0	0	0

Progression-free survival on next-line therapy (PFS2)

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	206	257
Median PFS2,[a,c] mo	19.3	15.4
95% CI	16.2-24.5	13.8-17.0
HR (95% CI)	0.70 (0.58-0.84)	



No. at risk

NIVO + IPI	335	298	256	228	205	189	163	148	136	120	90	61	33	18	6	6	0	0
LEN/SOR	333	310	269	229	190	162	124	101	80	76	50	32	25	13	3	3	1	0

- Numerically higher PFS[b] rates with NIVO + IPI vs LEN/SOR at 18 and 24 months
- PFS2[c] favored NIVO + IPI over LEN/SOR with a 30% reduction in the risk of death or disease progression on subsequent systemic therapy
- Subsequent systemic anticancer therapies were received by 38% vs 52% of patients in the NIVO + IPI vs LEN/SOR arm; subsequent immunotherapies were received by 13% vs 35% of patients, respectively

[a]Assessed by investigator based on RECIST v1.1. [b]Time from randomization to first documented radiological progression or death. [c]Time from randomization to documented progression (radiological or clinical) after next-line of therapy (i.e. subsequent systemic anticancer therapy) or death or to the start of second next-line systemic therapy.

CHECKMATE 9DW 2024 ESMO UPDATE

Conclusions

- NIVO + IPI demonstrated a statistically significant and clinically meaningful OS benefit vs LEN/SOR in patients with unresectable HCC naive to systemic therapy
  - Longer median OS and long-term survival benefit with higher 24- and 36-month OS rates
- NIVO + IPI demonstrated a statistically significant and clinically meaningful ORR benefit vs LEN/SOR with higher CR rate and durable responses
  - Responses with NIVO + IPI were observed regardless of etiology
- Efficacy of NIVO + IPI vs LEN/SOR was also supported by numerically higher PFS rates at 18 and 24 months
- Numerically longer median PFS2 was observed with NIVO + IPI vs LEN/SOR, supporting long-term benefit of NIVO + IPI
- The safety profile of NIVO + IPI was manageable and consistent with the established safety profile of the regimen
  - Most treatment-related hepatic events were grade 1/2 laboratory abnormalities, which generally resolved using established management algorithms
  - The majority of IMAEs were grade 1/2, were manageable, and did not result in treatment discontinuation
- **These results further support NIVO + IPI as a potential new 1L standard-of-care treatment for patients with unresectable HCC**

Decaens et al, ESMO 2024

TAKE HOME MESSAGES

Early Stage

NO ROLE of adjuvant Atezolizumab-Bevacizumab after ablation or curative resection (IMBRAVE-050)

Other trials awaited

Intermediate Stage

TACE can be improved:

Pembrolizumab-Lenvatinib + TACE improves outcomes (LEAP-012)

Another option on top of Durvalumaba-Bevacizumab + TACE (EMERALD-1)

Advanced Stage

Role of CTLA-4 consolidated:

HIMALAYA (5-year OS data)

CHECKMATE-9DW (deep responses)

Thank you for your attention

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EMERGING DATA ON OPTIMISATION OF COMBINATION REGIMENS FOR PATIENTS WITH ADVANCED HER2+ GASTRIC CANCER

Analyzing the Path Forward

Izuma Nakayama

Dept. of Gastrointestinal Oncology

National Cancer Center Hospital East

ESMO WEBINAR SERIES

ESMO IN FOCUS

DISCLOSURE

- Izuma Nakayama. reports receiving

- Honoraria from Bristol-Myers Squibb,, Ono Pharmaceutical, Daiichi Sankyo, Eli Lilly, and Astellas
- Research grant from Astellas Pharma
- Research funding (all to institution) from Merck Pharmaceutical, Daiichi Sankyo, Chugai Pharma, Ono Pharmaceutical, and Boehringer Ingelheim, outside the submitted work.

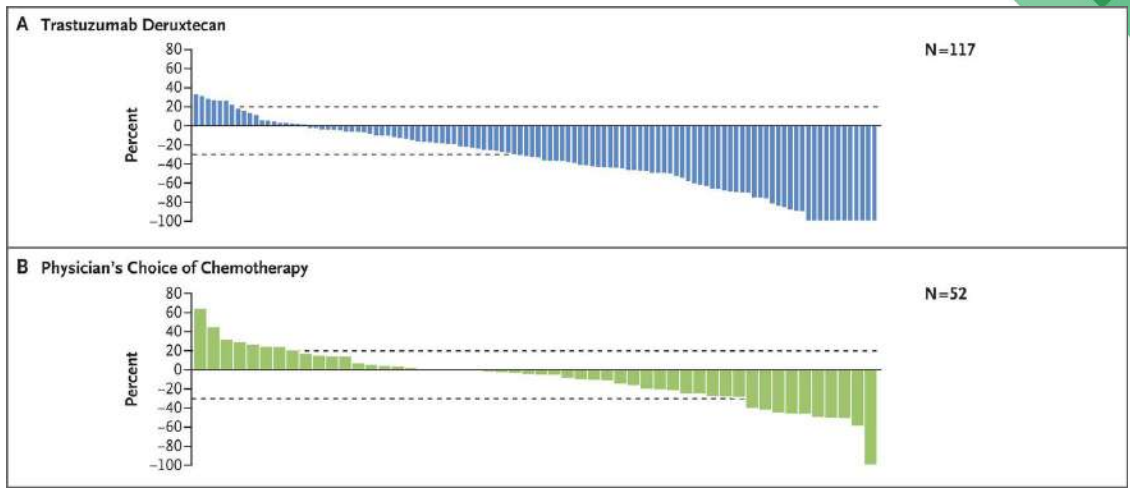
BACKGROUND : T-DXD FOR HER2 (+) GC/GEJC

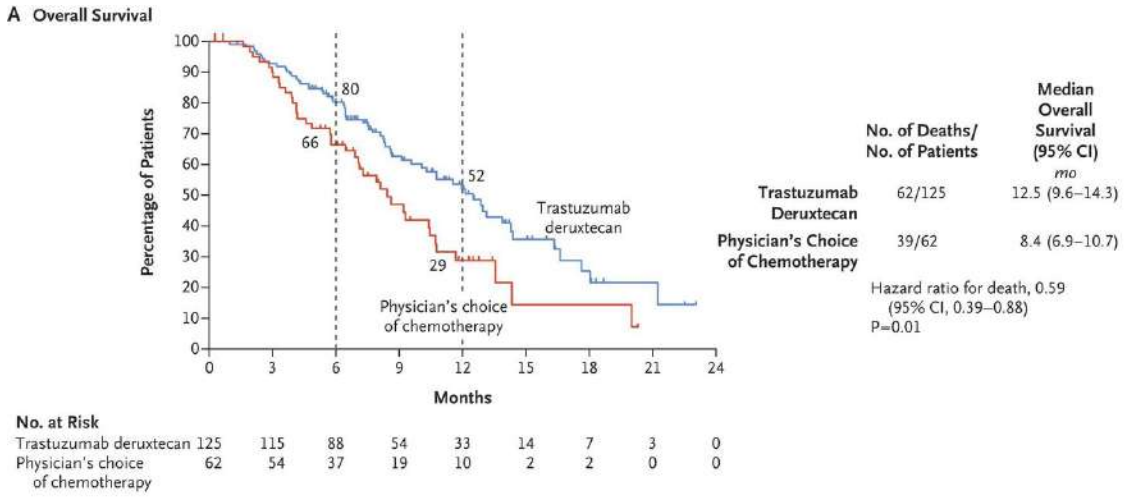
DESTINY-Gastric 01 (Open label, randomized Ph II)

✓ Met primary endpoint
(unconfirmed ORR : T-DXd 51% vs. 14%, P <0.001)

✓ Significantly improved OS
(median : T-DXd 12.5 ms vs. 8.4 ms,
HR 0.59 95% CI 0.39 – 0.88, P = 0.03)

➡ Standard of care for HER2(+) mGC/GEJC in ≥3L in Japan/South Korea





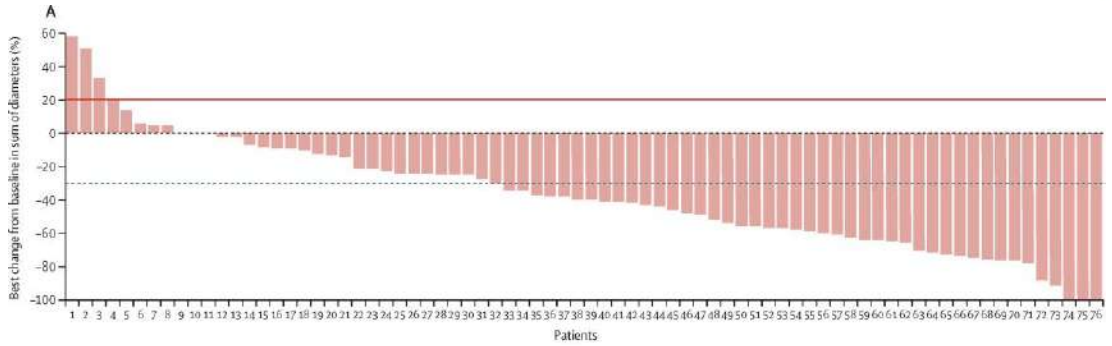
Shitara K, et al. NEJM 2020

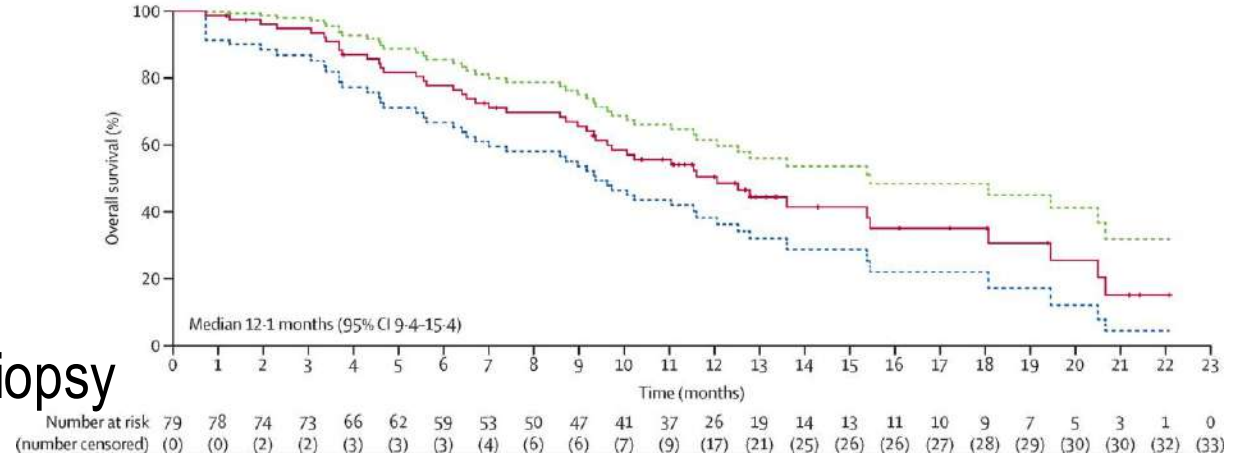
BACKGROUND : T-DXD FOR HER2 (+) GC/GEJC

DESTINY-Gastric 02 (Single-arm, Ph II)

- ✓ Met primary endpoint
  with ORR : 42% (95% CI 30.8 – 53.4)

- ✓ Showed promising efficacy
  median PFS : 5.6 months
  median OS : 12.1 months





➡Standard care as **2L** in EU and USA
for **confirmed HER2 (+)** on a post-progression biopsy

DESTINY-Gastric 04 : A randomized phase III of T-DXD vs. RAM and PTX is ongoing

Van Cutsem E, et al. Lancet Oncol 2023

BACKGROUND : 1L TREATMENT FOR HER2 (+) GC/GEJC

Final analysis of KEYNOTE-811 (Randomized Phase III)

Janjigian YY, et al. NEJM 2024

Key Eligibility Criteria
- Advanced, unresectable G/GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2+ by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

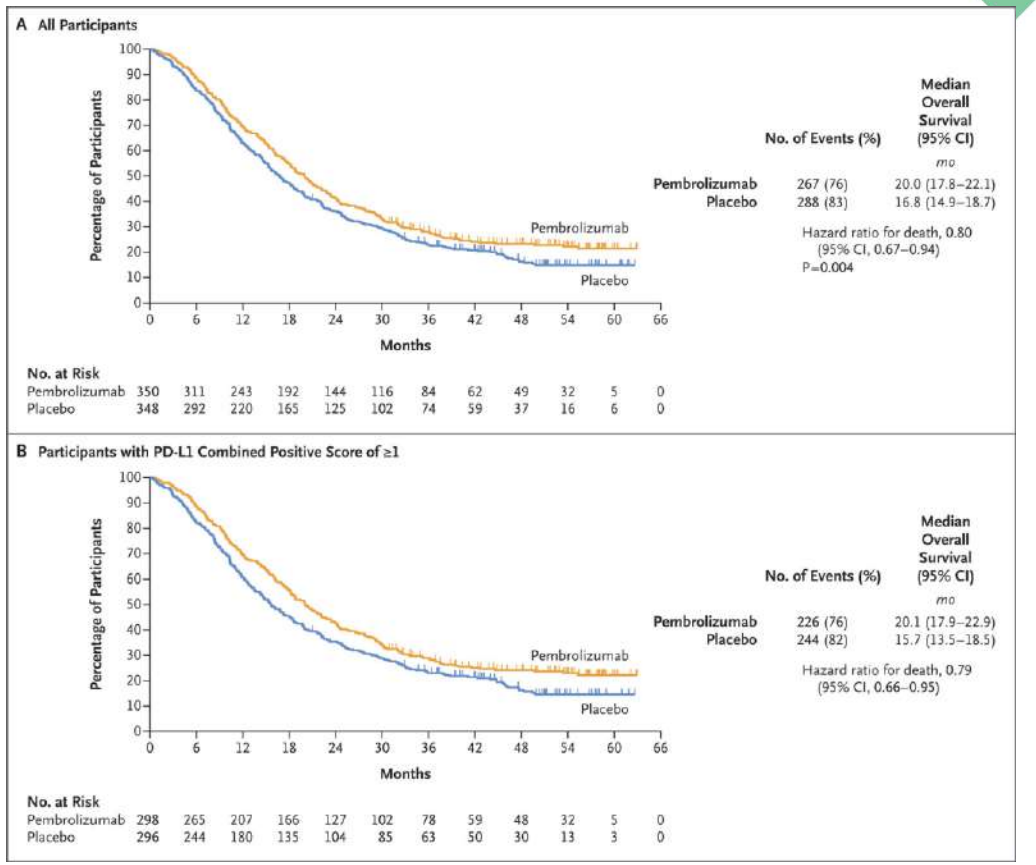
R 1:1
N=698

Pembrolizumab 200 mg IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Stratification Factors
- Geographic region
- PD-L1 CPS <1 vs CPS ≥1
- Chemotherapy choice

Endpoints
- Dual primary: OS, PFS
- Secondary: ORR, DOR , safety



✓ Met primary endpoint

OS HR 0.80 (0.67 – 0.94) [ITT]
HR 0.79 (0.66 – 0.95) [CPS ≥1]

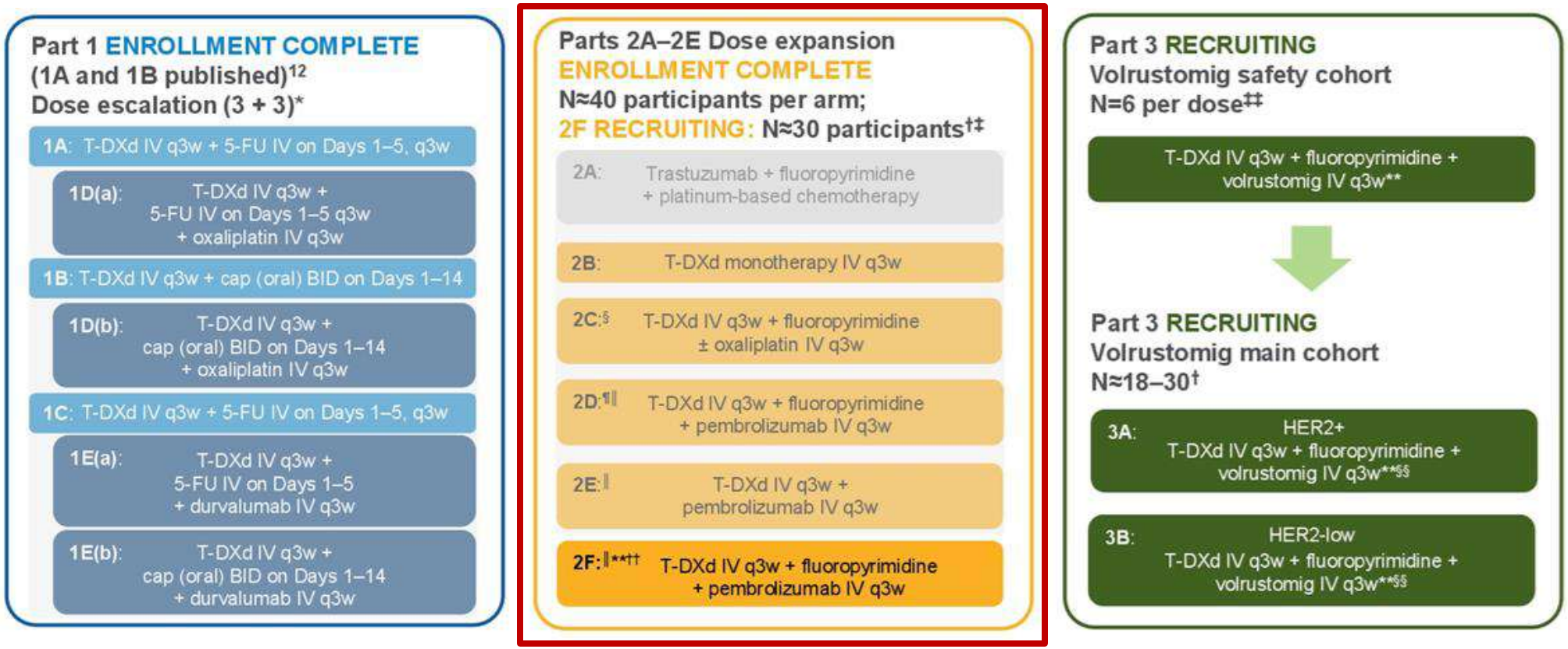
PFS HR 0.72 (0.60 – 0.87) [ITT]
HR 0.70 (0.58 – 0.85) [CPS ≥1]

Pembro+Tmab+CTx is novel standard for HER2 (+)/PD-L1 CPS ≥1 mGC/GEJC

DESTINY-GASTRIC 03

Janjigian YY, et al. ASCO 2022, ASCO GI 2024 TPS

1401O: Trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients (pts) with advanced/metastatic HER2-positive (HER2+) esophageal, gastric or gastroesophageal junction adenocarcinoma (GEJA)

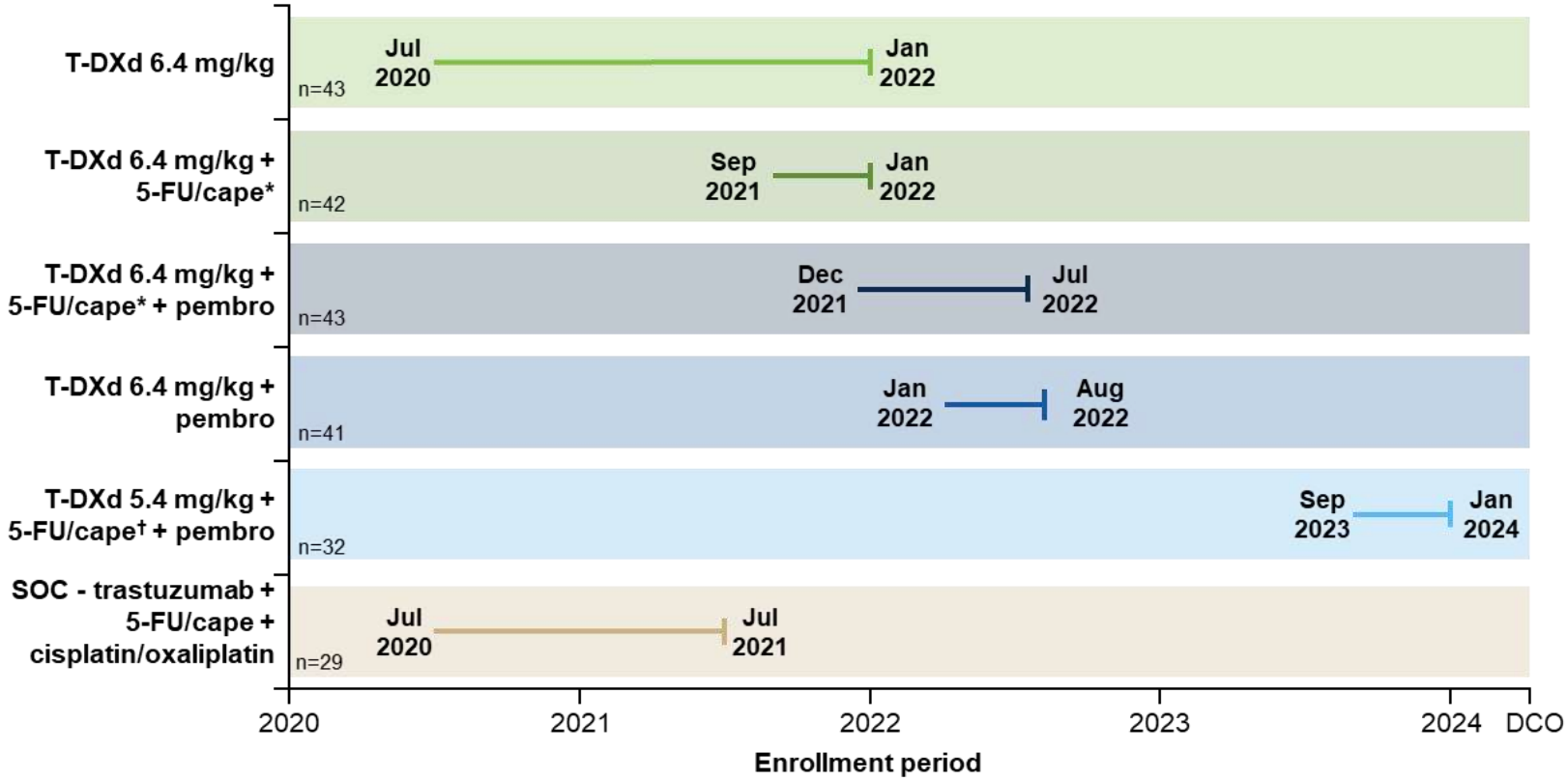


Part 1 showed the safety and preliminary efficacy of T-DXd + 5FU/Cape (ORR : 50%/43%) in ≥2L

DESTINY-GASTRIC 03 PART 2

Janjigian YY, et al. ESMO 2024

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	Secondary	Exploratory
Confirmed ORR by investigator assessment	• ORR, DOR, and PFS by investigator assessment, and OS • Safety and tolerability	Antitumor activity by PD-L1 status

T-DXd (6.4 or 5.4 mg/kg) ± 5-FU/Cape ± Pembrolizumab evaluated in multi-cohorts in 1L

DESTINY-GASTRIC 03 PART 2

Janjigian YY, et al. ESMO 2024

Baseline demographics and clinical characteristics by treatment arms

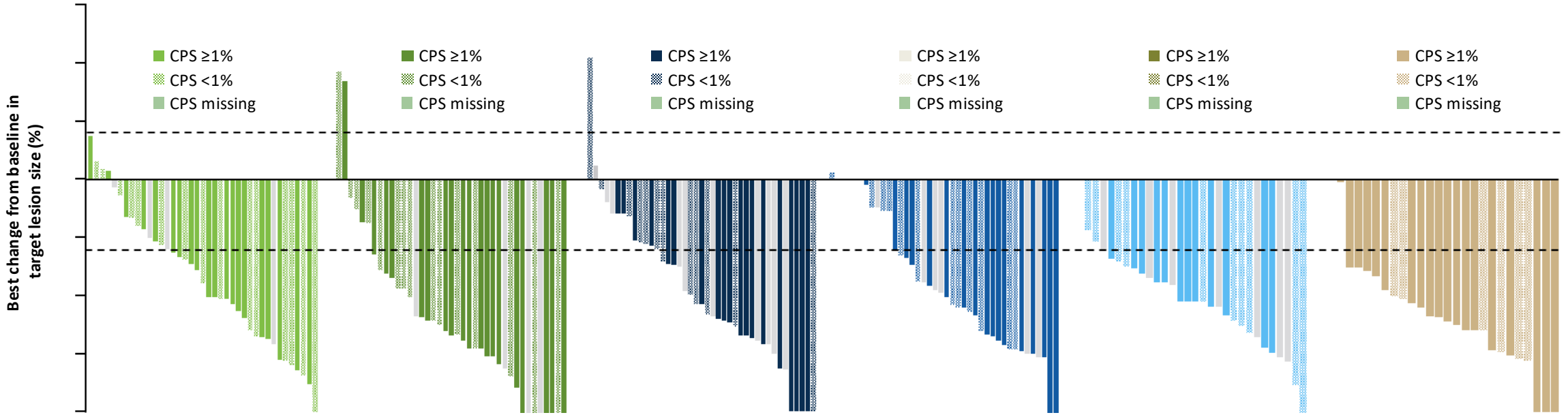
Overall N=229	T-DXd 6.4 mg/kg n=43	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m^2 n=41	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m^2 + pembro n=43	T-DXd 6.4 mg/kg + pembro n=41	T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m^2 + pembro n=32	SOC - trastuzumab + 5-FU/cape + cisplatin/oxaliplatin n=29
Median age, years (range)	61 (41–85)	60 (27–82)	65 (41–80)	66 (33–81)	61 (20–78)	64 (31–83)
Female, n (%)	13 (30)	10 (24)	10 (23)	8 (20)	3 (9)	10 (34)
Race, Asian, n (%)	12 (28)	14 (34)	19 (44)	16 (39)	15 (47)	14 (48)
Geographic region, n (%)						
Asia	12 (28)	13 (32)	19 (44)	16 (39)	15 (47)	14 (48)
Rest of the world	31 (72)	28 (68)	24 (56)	25 (61)	17 (53)	15 (52)
ECOG PS, n (%)						
0	21 (49)	19 (46)	23 (53)	23 (56)	17 (53)	13 (45)
1	22 (51)	22 (54)	20 (47)	18 (44)	15 (47)	16 (55)
Primary tumor site,* n (%)						
Esophageal	0	0	8 (19)	10 (24)	4 (13)	0
Gastric	29 (67)	22 (54)	27 (63)	25 (61)	20 (63)	22 (76)
GEJ	14 (33)	19 (46)	8 (19)	6 (15)	7 (22)	6 (21)
Local HER2 status,† n (%)						
IHC 3+ / IHC 2+/ISH+	37 (86) / 5 (12)	36 (88) / 5 (12)	35 (81) / 7 (16)	32 (78) / 9 (22)	26 (81) / 6 (19)	26 (90) / 3 (10)
Central HER2 status, n (%)						
IHC 3+ / IHC 2+/ISH+	30 (70) / 0	31 (76) / 1 (2)	30 (70) / 4 (9)	24 (59) / 2 (5)	16 (50) / 3 (9)	18 (62) / 1 (3)
Missing/Pending	5 (12)	3 (7)	4 (9)	2 (5)	6 (19)	5 (17)
Central PD-L1 status, n (%)						
CPS ≥1% / CPS <1%	21 (49) / 15 (35)	22 (54) / 15 (37)	20 (47) / 13 (30)	18 (44) / 16 (39)	13 (41) / 11 (34)	20 (69) / 7 (24)
Missing/Pending	7 (16)	4 (10)	10 (23)	7 (17)	8 (25)	2 (7)

DESTINY-GASTRIC 03 PART 2

Janjigian YY, et al. ESMO 2024

ORR 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

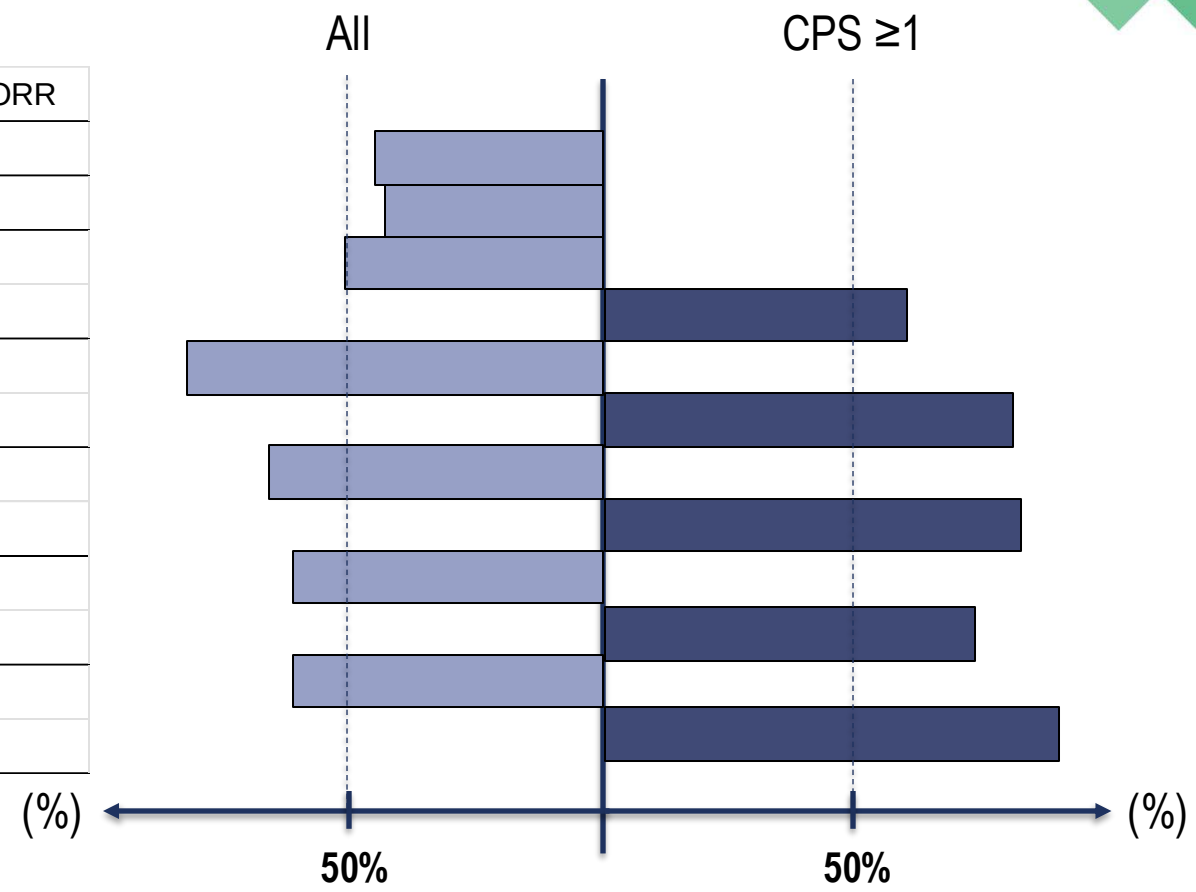


DESTINY-GASTRIC 03 PART 2

Janjigian YY, et al. ESMO 2024

		T-DXd	5FU/Cape	Pembrolizumab	confirmed ORR
DG-01		6.4mg/kg			43%*
DG-02		6.4mg/kg			42%*
DG-03	all	6.4mg/kg			49%
	CPS ≥1				57%
	all	6.4mg/kg	1,000mg/m2		78%
	CPS ≥1				77%
	all	6.4mg/kg		200mg	63%
	CPS ≥1	6.4mg/kg			78%
	all	6.4mg/kg	1,000mg/m2	200mg	58%
	CPS ≥1	6.4mg/kg			70%
	all	5.4mg/kg	750mg/m2	200mg	59%
	CPS ≥1	5.4mg/kg			85%

*according to independent review committee



Similar ORRs of T-DXd monotherapy (40 – 50%) were seen irrelevant to treatment line

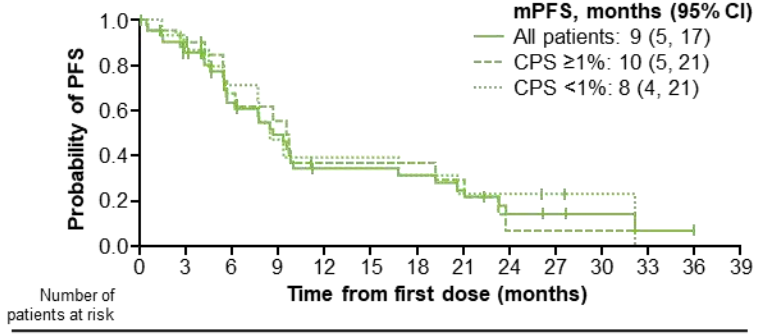
Addition of 5FU/cape and/or pembro to T-DXd showed 10 – 25% increase in ORR

DESTINY-GASTRIC 03 PART 2

Janjigian YY, et al. ESMO 2024

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

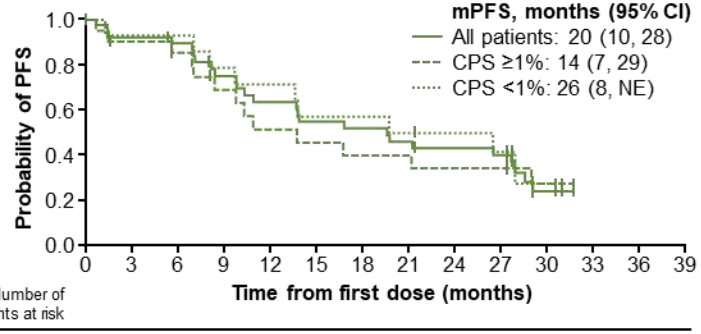
T-DXd 6.4 mg/kg n=43



Number of patients at risk

All patients	43	34	23	17	11	11	10	7	4	3	2	1	0	0
CPS ≥1%	21	18	12	9	5	5	5	3	1	1	1	1	0	0
CPS <1%	15	12	9	6	5	5	4	3	3	2	1	0	0	0

T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² n=41

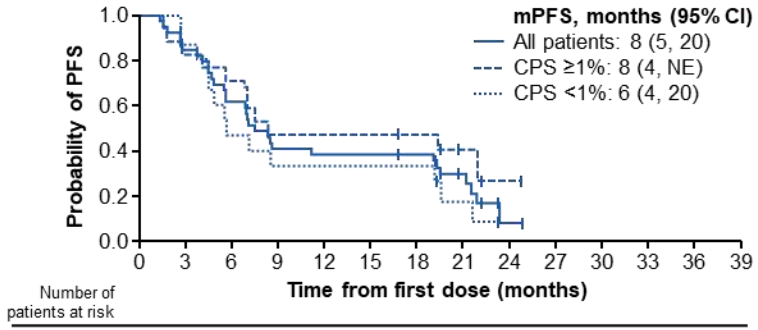


Number of patients at risk

All patients	41	35	32	26	22	19	18	16	14	13	4	0	0	0
CPS ≥1%	22	18	16	12	9	8	7	7	6	6	2	0	0	0
CPS <1%	15	13	13	11	10	8	8	7	6	5	2	0	0	0

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

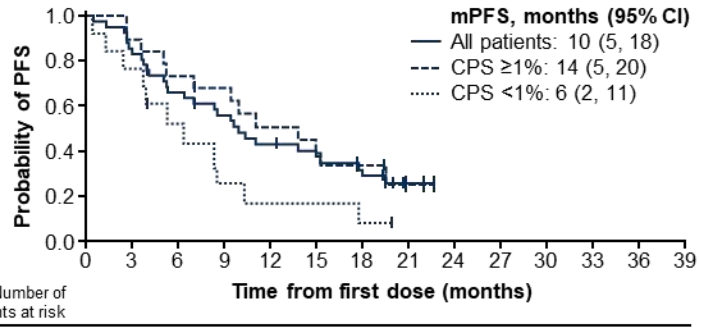
T-DXd 6.4 mg/kg + pembro n=41



Number of patients at risk

All patients	41	33	24	16	15	15	14	7	1	0	0	0	0	0
CPS ≥1%	18	14	12	8	8	8	7	3	1	0	0	0	0	0
CPS <1%	16	13	7	5	5	5	5	2	0	0	0	0	0	0

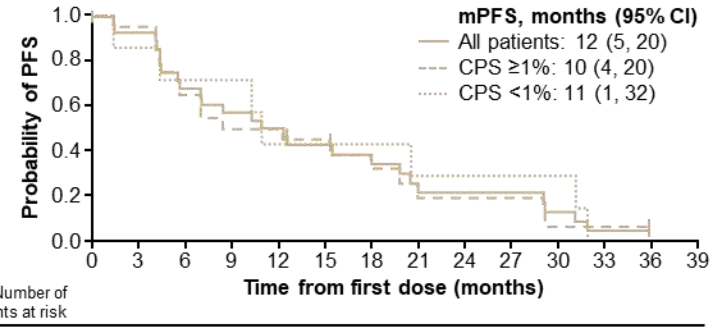
T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro n=43



Number of patients at risk

All patients	43	36	27	22	17	14	11	2	0	0	0	0	0	0
CPS ≥1%	20	17	14	12	9	7	5	2	0	0	0	0	0	0
CPS <1%	13	10	6	3	2	2	1	0	0	0	0	0	0	0

SOC - trastuzumab + 5-FU/cape + cisplatin/oxaliplatin n=29



Number of patients at risk

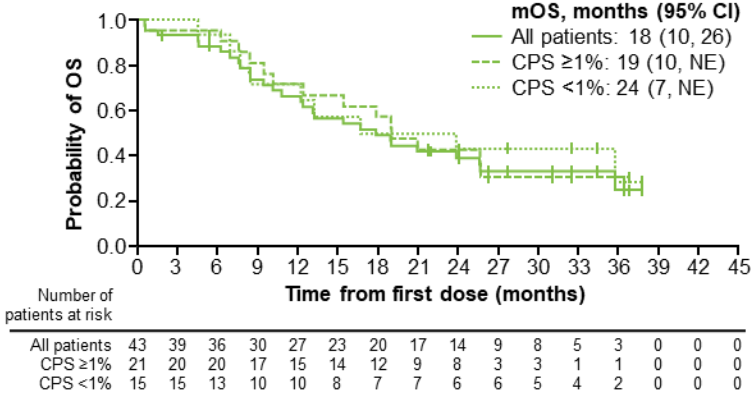
All patients	29	26	19	16	14	11	8	5	5	5	3	1	0	0
CPS ≥1%	20	19	13	10	10	8	5	3	3	3	1	1	0	0
CPS <1%	7	6	5	5	3	3	3	2	2	2	2	0	0	0

DESTINY-GASTRIC 03 PART 2

Janjigian YY, et al. ESMO 2024

Overall survival in all patients and by PD-L1 status

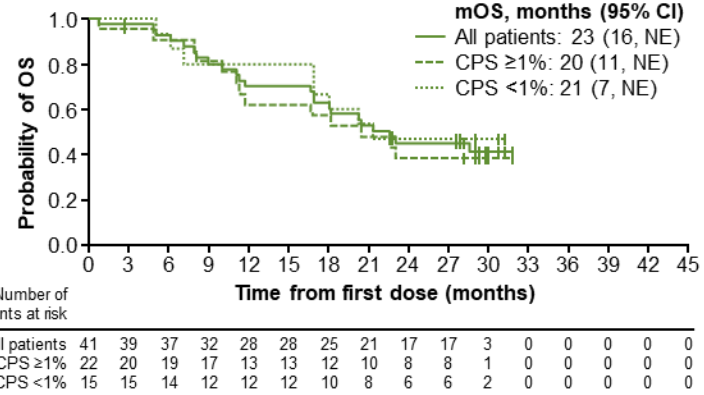
T-DXd 6.4 mg/kg
n=43



Number of patients at risk

All patients	43	39	36	30	27	23	20	17	14	9	8	5	3	0	0	0
CPS ≥1%	21	20	20	17	15	14	12	9	8	3	3	1	1	0	0	0
CPS <1%	15	15	13	10	10	8	7	7	6	6	5	4	2	0	0	0

T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m²
n=41

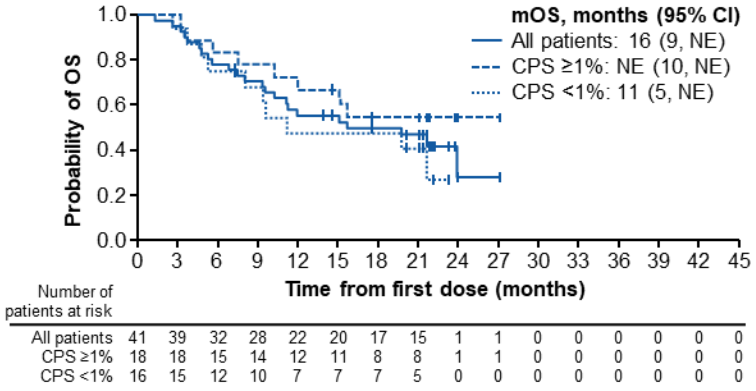


Number of patients at risk

All patients	41	39	37	32	28	28	25	21	17	17	3	0	0	0	0	0
CPS ≥1%	22	20	19	17	13	13	12	10	8	8	1	0	0	0	0	0
CPS <1%	15	15	14	12	12	12	10	8	6	6	2	0	0	0	0	0

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

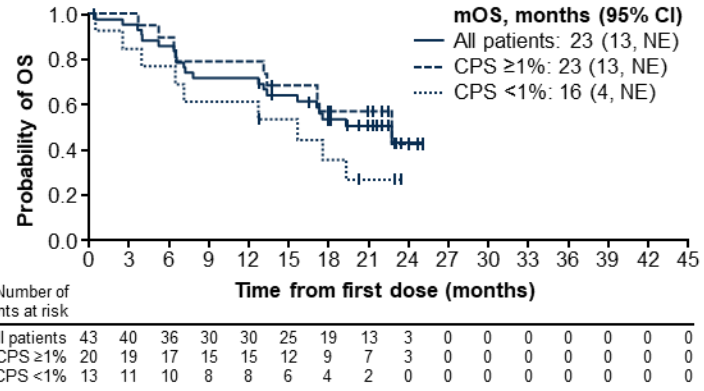
T-DXd 6.4 mg/kg + pembro
n=41



Number of patients at risk

All patients	41	39	32	28	22	20	17	15	1	1	0	0	0	0	0	0
CPS ≥1%	18	18	15	14	12	11	8	8	1	1	0	0	0	0	0	0
CPS <1%	16	15	12	10	7	7	7	5	0	0	0	0	0	0	0	0

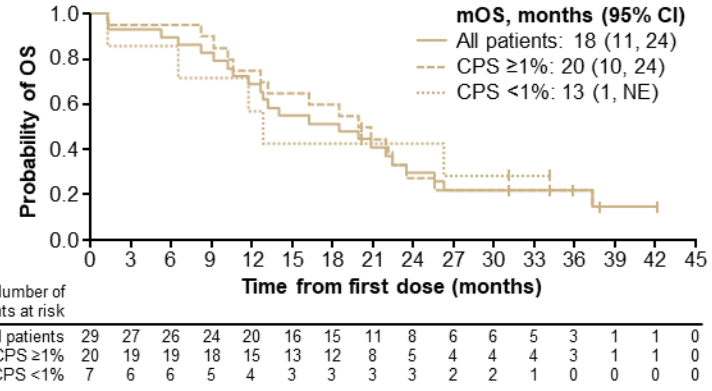
T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro
n=43



Number of patients at risk

All patients	43	40	36	30	30	25	19	13	3	0	0	0	0	0	0	0
CPS ≥1%	20	19	17	15	15	12	9	7	3	0	0	0	0	0	0	0
CPS <1%	13	11	10	8	8	6	4	2	0	0	0	0	0	0	0	0

SOC - trastuzumab + 5-FU/cape + cisplatin/oxaliplatin
n=29



Number of patients at risk

All patients	29	27	26	24	20	16	15	11	8	6	6	5	3	1	1	0
CPS ≥1%	20	19	19	18	15	13	12	8	5	4	4	4	3	1	1	0
CPS <1%	7	6	6	5	4	3	3	3	3	2	2	1	0	0	0	0

DESTINY-GASTRIC 03 PART 2

Adverse events summary

Janjigian YY, et al. ESMO 2024

	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro n=43	T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro n=32
Median follow up, months	17	5
All-causality AEs, n (%)	43 (100)	27 (84)
Grade ≥3 AEs	**39 (91)**	**11 (34)**
Most common all-causality Grade ≥3 AEs (≥10%		
Anemia	11 (26)	2 (6)
Diarrhea	7 (16)	0
Fatigue†	1 (2)	0
Febrile neutropenia	5 (12)	0
Hypokalemia	8 (19)	0
Leukopenia†	5 (12)	0
Lipase increased	2 (5)	0
Nausea	8 (19)	1 (3)
Neutropenia†‡	11 (26)	5 (16)
Thrombocytopenia†	5 (12)	1 (3)

	DCO: October 27, 2022 T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro n=43	DCO: May 6, 2024 T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro n=32
Median duration of follow up, months	4.1	4.6
Median T-DXd treatment duration, months	3.5	4.8
Median T-DXd treatment cycles, n	5.0	7.0
Median 5-FU / cape treatment cycles, n	5 / 4	8 / 6
Median pembro treatment cycles, n	5	7
All-causality AEs, n (%)	42 (98)	27 (84)
Grade ≥3 AEs	**31 (72)**	**11 (34)**
Treatment-related SAEs, n (%)	19 (44)	1 (3)
Any treatment-related AE leading to discontinuation, n (%)	10 (23)	5 (16)
Any AE leading to discontinuation of T-DXd	5 (12)	1 (3)
Any AE leading to discontinuation of 5-FU/cape	1 (2) / 8 (19)	1 (3) / 3 (9)
Any AE leading to discontinuation of pembro	5 (12)	1 (3)
Any treatment-related AE with outcome death, n (%)	2 (5)	0

T-DXd 6.4mg/kg in combination with full dose 5FU/cape and pembro not feasible

T-DXd 5.4mg/kg in combination with reduced dose 5FU/cape and pembro manageable

DESTINY-GASTRIC 03 PART 2

Janjigian YY, et al. ESMO 2024

Authors' conclusions

- T-DXd 6.4 mg/kg demonstrated antitumor activity as a first-line treatment for HER2+ GC/GEJA, with a confirmed ORR of 49%, a median PFS of 9 months, and a median OS of 18 months
- Combining T-DXd 6.4 mg/kg with fluoropyrimidine showed a confirmed ORR of 78%, a median PFS of 20 months, and a median OS of 23 months, with a manageable safety profile in HER2+ GC/GEJA, irrespective of PD-L1 status
- T-DXd 6.4 mg/kg with full-dose fluoropyrimidine and pembrolizumab demonstrated antitumor activity in HER2+ GC/GEJA, specifically in tumors with a PD-L1 CPS ≥1%; however, it was associated with a high level of toxicities, including ILD, leading to treatment discontinuations
- T-DXd 5.4 mg/kg and reduced-dose fluoropyrimidine with pembrolizumab has a manageable safety profile, with promising early antitumor activity in HER2+ GC/GEJA
- Studies evaluating the combination of T-DXd with fluoropyrimidine and immunotherapy are planned for patients with HER2+ CPS ≥1% GC/GEJA

A randomized phase III trial will start

DISCUSSION POINTS FOR FUTURE DEVELOPMENT

- Is combination with T-DXd, 5FU/cape and aPD-1 enough?
  Is addition of anti-CTLA-4 to triplet regimen required? Feasible?

- Is it possible for ADC to extend the boundary of anti-HER2 agent beyond conventional HER2-positive (IHC 3+ or 2+/FISH-positive)?
  Is HER2-low new horizon?

- Is T-DXd optimal ADC?

ADDING ANTI-CTLA-4

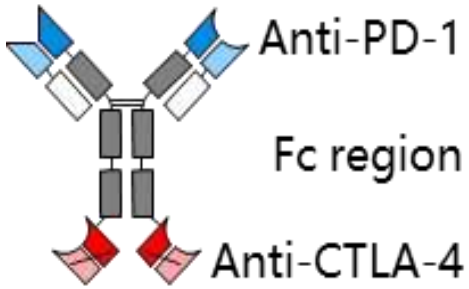
Stein A, et al. JAMA Oncology 2022
Jiafu Ji, et al. AACR 2024

- **AIO INTEGA (rPII) : Tras + Nivo + Ipi (3mg/kg) vs. Tras + Nivo + mFOLFOX6 for HER2 (+)**

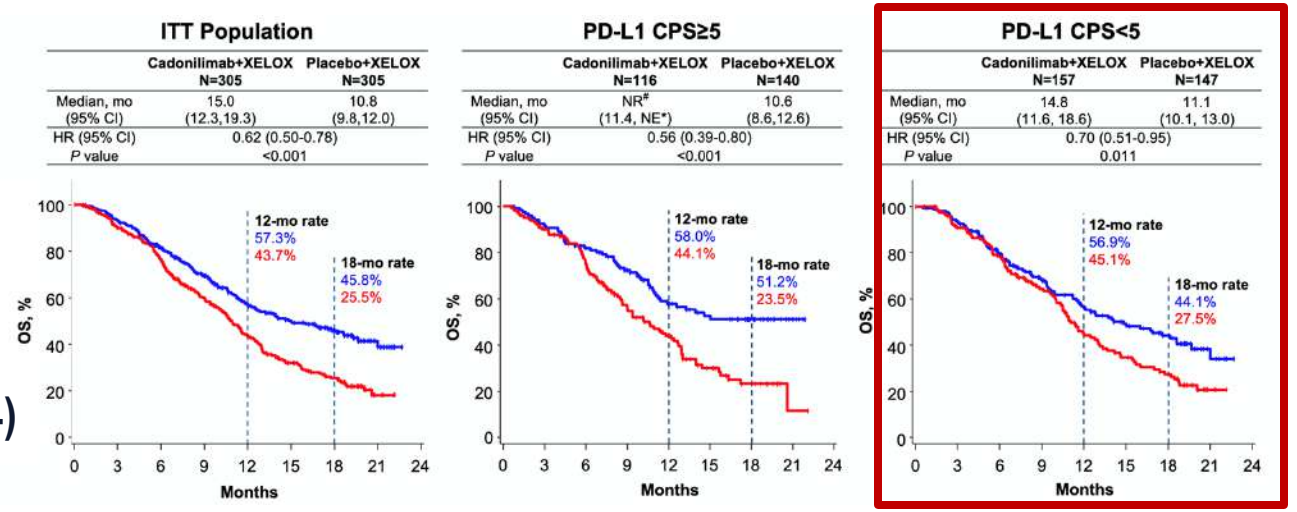
➡OS at 12ms (Primary) : 57% in ipi-arm vs. 70% in FOLFOX-arm
inferior median OS (16.4 vs. 21.8 ms) and PFS (3.2 vs. 10.7 ms) in ipi-arm

➡**Replacement** of chemo-backbone by ipilimumab was **negative**
Adding aCTLA-4 still **unknown**

- **COMPASSION15 (rPIII) : CAPOX with or without Cadonilimab (aPD-1/CTLA-4) for HER2 (-)**



Cadonilimab (aPD-1/CTLA-4)



Significant efficacy over **chemo alone**

Attractive for CPS low

Further study needed!

- **T-DXd + FP + volrustomig (bis Ab for PD1/CTLA-4) being under investigation in Part 3**

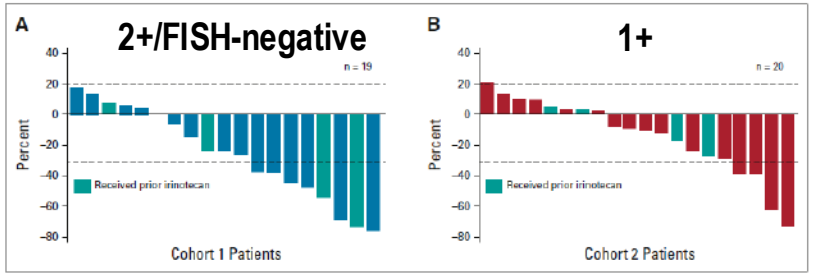
BEYOND THE BOUNDARY OF HER2-POSITIVE

original reports

Trastuzumab Deruxtecan in Anti–Human Epidermal Growth Factor Receptor 2 Treatment–Naive Patients With Human Epidermal Growth Factor Receptor 2–Low Gastric or Gastroesophageal Junction Adenocarcinoma: Exploratory Cohort Results in a Phase II Trial

Kensei Yamaguchi, MD[1]; Yung-Jue Bang, MD, PhD[2]; Satoru Iwasa, MD[3]; Naotoshi Sugimoto, MD[4]; Min-Hee Ryu, MD, PhD[5]; Daisuke Sakai, MD[6]; Hyun Cheol Chung, MD, PhD[7]; Hisato Kawakami, MD, PhD[8]; Hiroshi Yabusaki, MD[9]; Jeeyun Lee, MD[10];

Yamaguchi K and Shitara K et al. JCO 2022



Antitumor signal of T-DXd demonstrated in HER2-low AGC

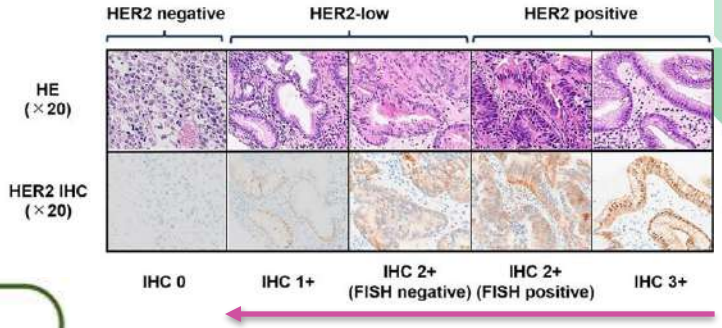
Part 3 RECRUITING
Volrustomig safety cohort
N=6 per dose‡‡

T-DXd IV q3w + fluoropyrimidine + volrustomig IV q3w**

Part 3 RECRUITING
Volrustomig main cohort
N≈18–30†

3A: HER2+
T-DXd IV q3w + fluoropyrimidine + volrustomig IV q3w**§§

3B: HER2-low
T-DXd IV q3w + fluoropyrimidine + volrustomig IV q3w**§§



EPOC 2203

NCC NATIONAL CANCER CENTER JAPAN
EPOC
Exploratory Oncology Research & Clinical Trial Center

Phase Ib part (N=3-6)

T-DXd (5.4mg/kg)+CAPOX+Nivo

T-DXd: 5.4 mg/kg, day1, intravenous q3w
Capecitabine: 750 mg/m² twice daily days 1-14
Oxaliplatin: 70 mg/m² day1
Nivolumab: 360 mg/body day1, q3w

If DLT in ≤ 1 patient → **Phase II part (N=25)**

If DLT in ≥2 patients → **T-DXd (4.4 mg/kg)+CAPOX+Nivo**

If DLT in ≤ 1 patient → **Phase II part (N=25)**

If DLT in ≥2 patients → Discontinued

Phase Ib part employs conventional 3+3 design

Primary endpoint
・Phase Ib DLT
・Phase II ORR (local assessment)
Secondary endpoints
PFS, OS, DOR, DCR, AEs

Abbreviations: CAPOX, capecitabine and oxaliplatin; Nivo, nivolumab; DLT, dose limiting toxicity; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; DOR, duration of response; DCR, disease control rate; AEs, adverse events

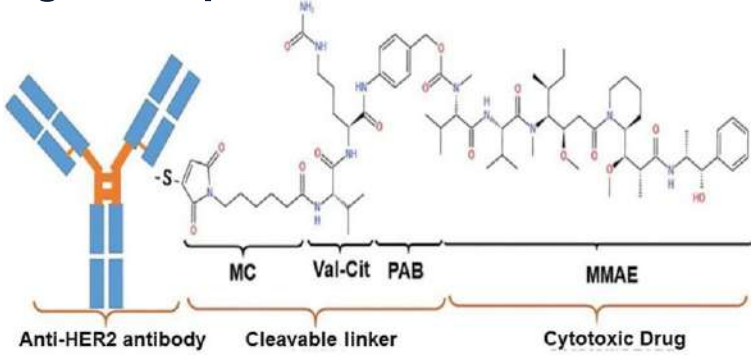
Aoki Y, Nakayama I and Shitara K, et al. ESMO GI 2024

- **Expansion of treatment target from HER2-positive to HER2-expressing AGC being investigated**

DISTAMAB VEDOTIN (RC48) : ADC FOR HER2 WITH MMAE

Single arm phase II RCTS trial for HER2 IHC 3+/2+

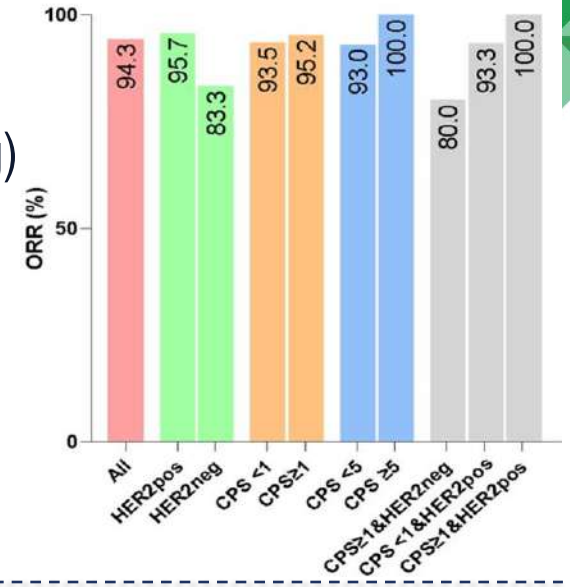
Song L, et al. ASOC 2024



RC48 (2.5mg/kg) + Tislelizumab + S1 (40 – 60mg)

- Remarkable response with **94.3%**
- Attractive for **CPS <1** and **HER2-low (2+/FISH -)**
- Manageable AE with starting full dose of S-1

Objective response rates

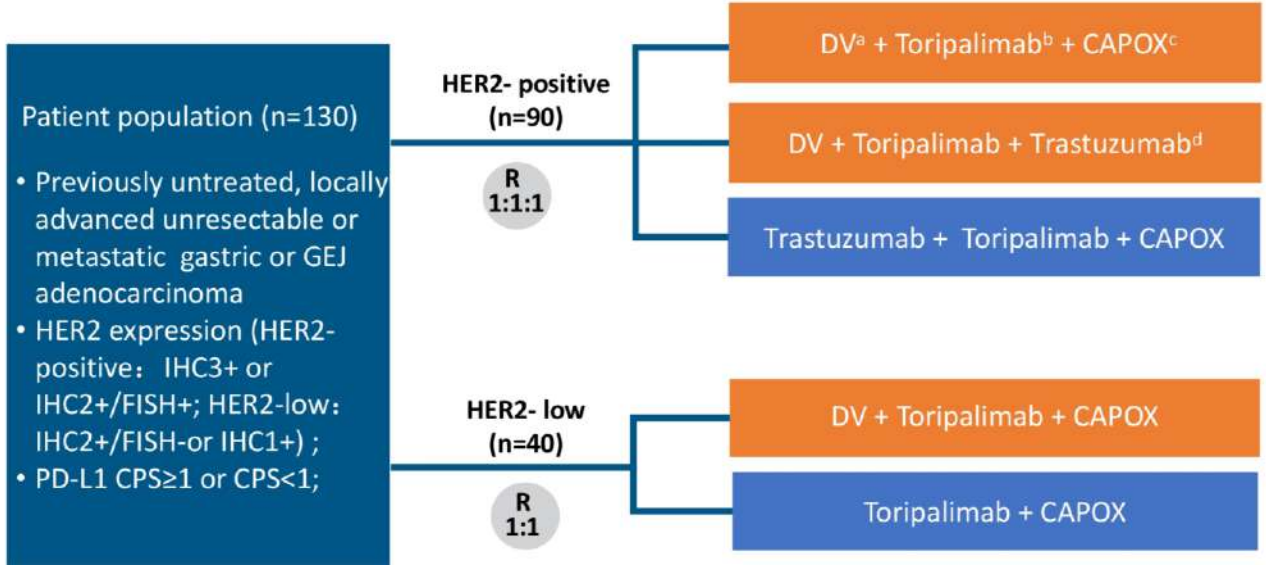


➡**A randomized phase III RCTS-2 being initiated**

Randomized phase II/III trial for HER2 expressing AGC (IHC 1+ /2+/3+)

Shen L, et al. ASCO GI TPS 2024

- **No dose reduction**
  RC48 2.5mg/kg
  Cape 1,000mg/m^2
  Ox 130mg/m^2



➡**Phase III**

MY TAKE-AWAY

- Adding I-O to trastuzumab with chemo is new standard for HER2-positive AGC in 1L
- Combination therapy with T-DXd is a promising targeted therapy
- Dose optimization is required in combination with T-DXd plus chemo to manage tox
- Treatment target of anti-HER2 will be expand to HER2-expressing AGC
- Combination with newer ADC and full dose of chemo is feasible with promising efficacy

Thank you for your kind attention

国立がん研究センター
東病院
National Cancer Center Hospital East

Acknowledgement for
patients and their families participating in clinical trials