Module 3: Ovarian Cancer

PARP Inhibitors and Strategies Targeting Folate Receptor Alpha (FRα) in Advanced OC — Dr Armstrong

Other Novel Agents and Strategies for the Treatment of Advanced OC — Dr O'Malley

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QUESTIONS?

Module 3: Ovarian Cancer

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

PARP Inhibitors and Strategies Targeting Folate Receptor Alpha (FRα) in Advanced OC

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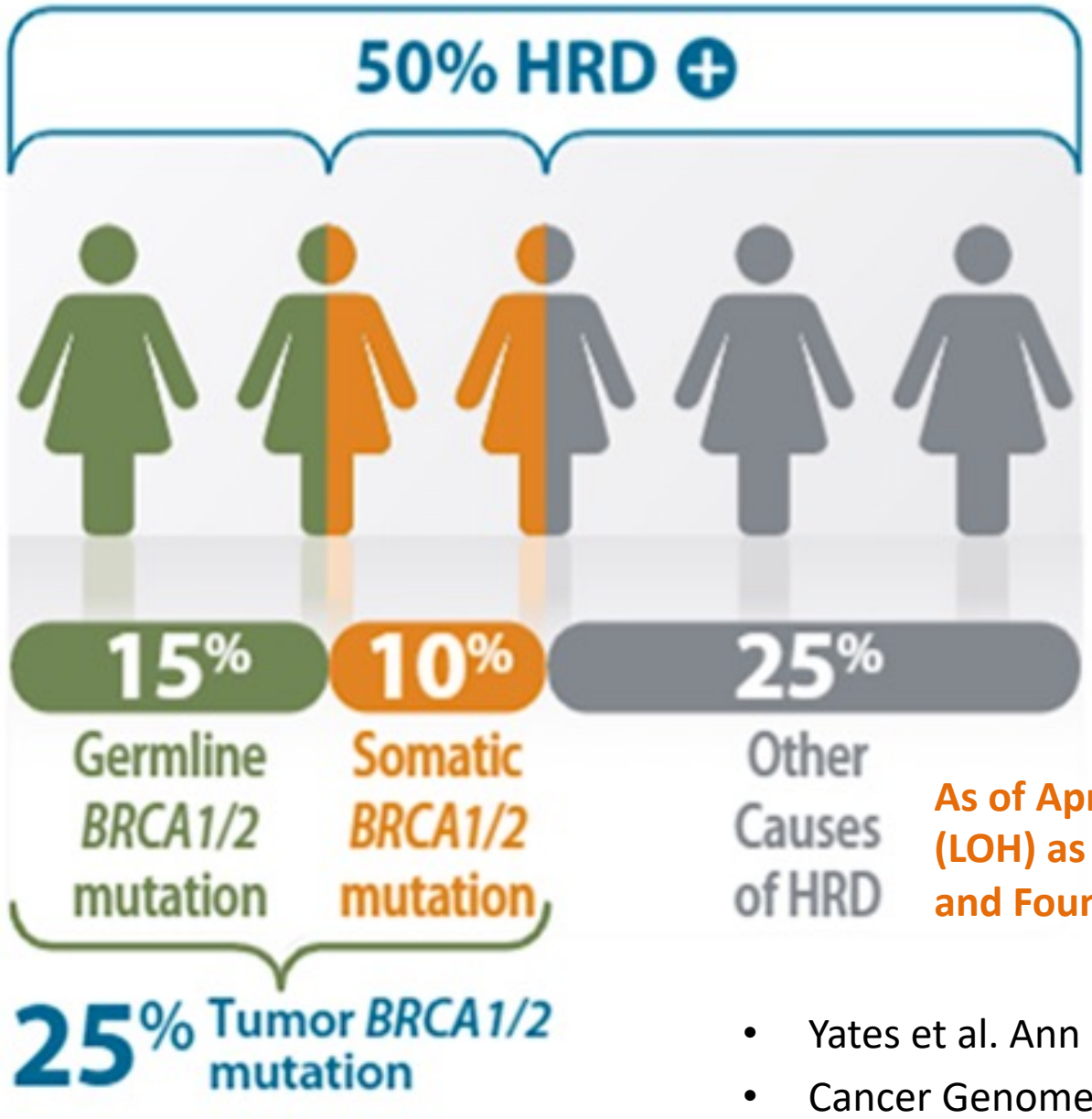
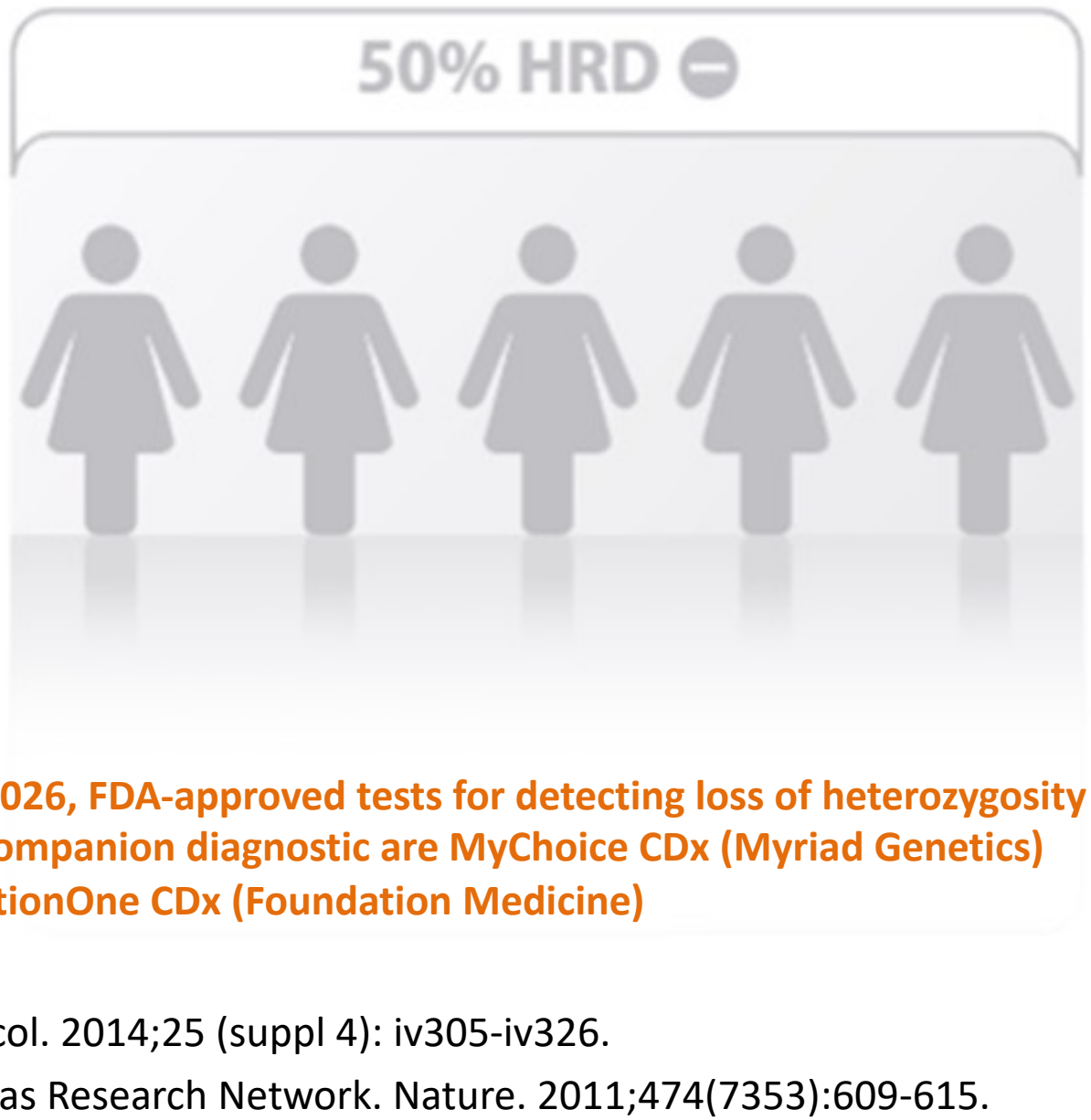
Disclosures

Contracted Research (Clinical Trial Support)	AstraZeneca Pharmaceuticals LP
Data and Safety Monitoring Boards/Committees	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genmab US Inc



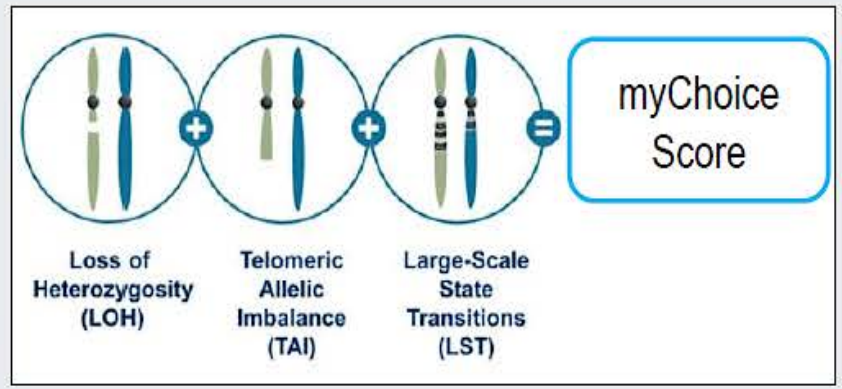


As of April 2026, FDA-approved tests for detecting loss of heterozygosity (LOH) as a companion diagnostic are MyChoice CDx (Myriad Genetics) and FoundationOne CDx (Foundation Medicine)

- Yates et al. Ann Oncol. 2014;25 (suppl 4): iv305-iv326.
- Cancer Genome Atlas Research Network. Nature. 2011;474(7353):609-615.

Testing for Homologous Recombination Deficiency (HRd) and Proficiency (HRp)

- Next generation sequencing of DNA from tumor tissue (Myriad Genetics myChoice® Test)
  - Provides a score based on algorithmic measurement of 3 tumor factors:
    - Loss of heterozygosity (LOH)
    - Telomeric allelic imbalance (TAI)
    - Large-scale state transitions (LST)



- Homologous recombination status is determined by the following:
  - HR-deficient tumors: Tissue test score ≥42 **OR** a *BRCA* mutation
  - HR-proficient tumors: Tissue test score <42
  - HR-not-determined

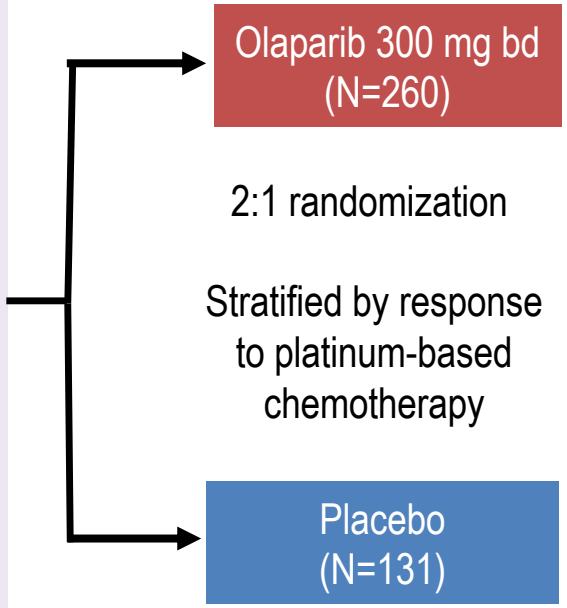
Foundation Medicine LOH

Genomic Instability Score (GIS), as determined by Foundation Medicine tumor analysis; must have genome-wide LOH ≥14%, a somatic *BRCA1* and/or *BRCA2* mutation, or a mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D* or *RAD54L* to be considered positive.

Swisher *et al. Lancet Oncol* 2017;18:75–87

Study design SOLO-1

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy



- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

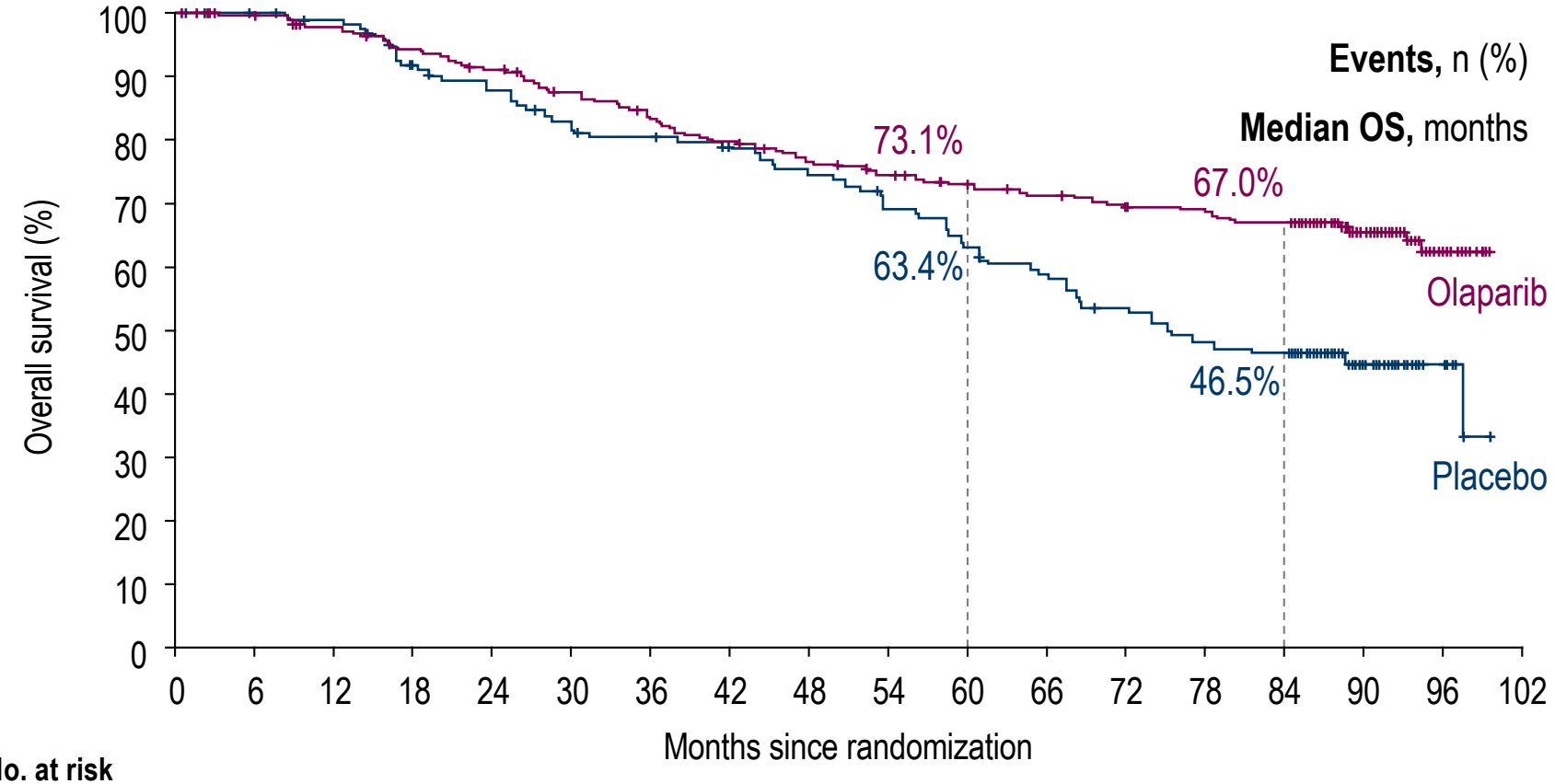
- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, response evaluation criteria in solid tumours; TOI, Trial Outcome Index

Moore K, et al. N Engl J Med 2018;379:2495-2505.

2022 SOLO1 7-year Survival Analysis (BRCA mutation carriers only)

(ESMO 2022, JCO 9/2022)



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**
HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*		

No. at risk

Olaparib	260	252	246	236	227	214	203	194	185	177	170	165	159	157	153	79	21	0
Placebo	131	128	125	114	108	100	97	92	87	80	73	67	60	54	52	21	6	0

44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

*P<0.0001 required to declare statistical significance

SOLO1 7-year OS: DiSilvestro P. et al. J Clin Oncol. 2022 Sep 9;JCO2201549. Online ahead of print. PMID: 36082969

PRIMA: STUDY DESIGN

- Newly diagnosed, FIGO stage III-IV high-grade serous or endometrioid*
- **Stage III with visible residual disease post-surgery**
- **Inoperable stage III disease**
- Any stage IV disease
- Had received NACT
- CR or PR after platinum-based chemotherapy

HRD testing prior to randomization

Randomize 2:1
N=733

Stratification:
- NACT
- CR/PR
- HRD-positive or HRD-negative/unknown

Maintenance therapy

Niraparib
200/300 mg PO QD†

Placebo

Primary endpoint

- PFS (BICR) in **HRD population** and step down to all-comers (RECIST 1.1)

Secondary endpoints

- OS
- PFS2
- TFST
- Safety
- PRO/HRQoL

- Patients with stage III disease with no visible residual disease (ie, complete cytoreduction) post-surgery were excluded
- In clinical practice, some physicians would treat PRIMA candidates with chemotherapy + bevacizumab as standard of care

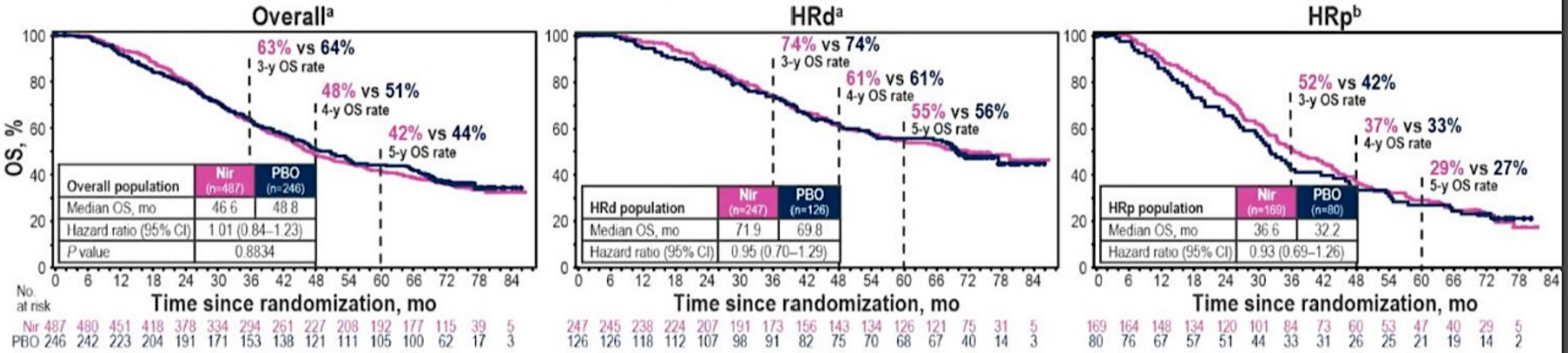
Niraparib is not approved for use outside the platinum-sensitive relapsed ovarian cancer setting.
*Includes patients with primary peritoneal and/or fallopian tube cancer. †Modified starting dose permitted to mitigate for hematological toxicity following protocol amendment.
BICR = blinded independent central review; CA-125 = cancer antigen-125; CR = complete response; FIGO = International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; HRQoL= health-related quality of life; NACT = neoadjuvant chemotherapy; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression; PR = partial response; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumours; TFST = time to first subsequent therapy.

1. Gonzalez-Martin A, et al. N Engl J Med. 2019;381(25):2391-2402; 2. Gonzalez-Martin A, et al. Presented at: ESMO; 27 September–1 October 2019; Barcelona, Spain. Abstract LBA1.

Courtesy of Robert L Coleman, MD

Final OS (62.5% maturity in overall population)

No difference in OS between niraparib and placebo arms in the overall, HRd, and HRp populations



- OS results for all prespecified biomarker-defined subgroups consistent with overall population[c]
- Assessment of long-term efficacy outcomes in high-risk aOC may be complicated by multiple factors[1]
  - Patient population[2–4]
  - Extended postprogression survival[1,5]
  - Subsequent therapy[1,5]

3-fold higher subsequent PARP inhibitor use in placebo than niraparib arms

[a]Hazard ratios and 95% CIs for overall and HRd populations calculated using stratified Cox proportional hazards model with randomization stratification factors. [b]Hazard ratio and 95% CI for HRp population calculated using unstratified Cox proportional hazards model. [c]OS results for the HRnd population (unstratified): hazard ratio (95% CI), 1.39 (0.88–2.19). aOC, advanced ovarian cancer; HRd, homologous recombination deficient; HRnd, homologous recombination status not determined; HRp, homologous recombination proficient; OS, overall survival; Nir, niraparib; PBO, placebo. 1. Matulonis UA, et al. *Cancer*. 2015;121(11):1737–1746. 2. Siegel RL, et al. *CA Cancer J Clin*. 2024;74(1):12–49. 3. Elattar A, et al. *Cochrane Database Syst Rev*. 2011;201(8):CD007565. 4. Sun C, et al. *PLoS One*. 2014;9(5):e95285. 5. Delgado A, et al. *Am J Cancer Res*. 2021;11(4):1121–1131.

Monk BJ et al. *Ann Oncol* 2024;35(11):981-92.

Study design PAOLA-1

Newly diagnosed FIGO stage III–IV high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer*

FIRST LINE

- **Surgery (upfront or interval)**
- **Platinum–taxane based chemotherapy**
- **≥3 cycles of bevacizumab†**

NED/CR/PR

N=806

Randomization

2:1

Maintenance therapy

Olaparib (300 mg BID) x2 years
+ bevacizumab†

Placebo x2 years
+ bevacizumab†

Stratification

- Tumour *BRCA*m status‡
- First-line treatment outcome¶

Primary endpoint
Investigator-assessed PFS (RECIST v1.1)

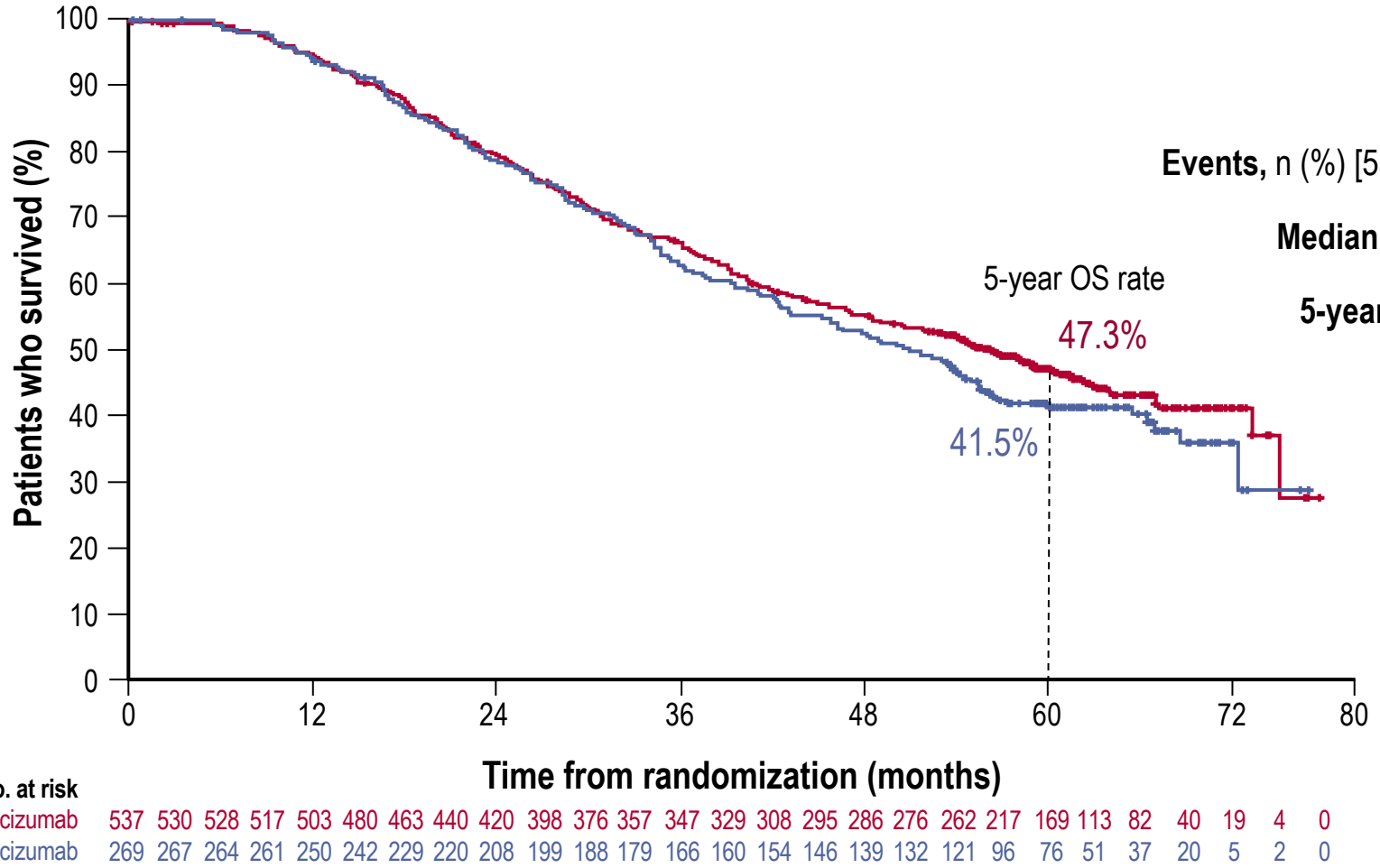
Sensitivity analysis
PFS by BICR

Secondary endpoints
TFST
PFS2, TSST
OS
HRQoL
Safety and tolerability

*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation
†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; ‡By central labs; ¶According to timing of surgery and NED/CR/PR
BICR, blinded independent central review; HRQoL, health-related quality of life; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

Ray-Coquard I, et al. N Engl J Med 2019;381:2416-2428.
Ray-Coquard IL, et al. Annals of Oncology 2019;30:v894-v895.

2022 PAOLA OS analysis: ITT population



	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [55% maturity]	288 (53.6)	158 (58.7)
Median OS, months	**56.5**	**51.6**
5-year OS rate, %	**47.3**	**41.5**
	HR 0.92 (95% CI 0.76–1.12); ***P*=0.4118**	

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **19.6%** (105/537)
Placebo + bevacizumab: **45.7%** (123/269)

No. at risk																											
Olaparib + bevacizumab	537	530	528	517	503	480	463	440	420	398	376	357	347	329	308	295	286	276	262	217	169	113	82	40	19	4	0
Placebo + bevacizumab	269	267	264	261	250	242	229	220	208	199	188	179	166	160	154	146	139	132	121	96	76	51	37	20	5	2	0

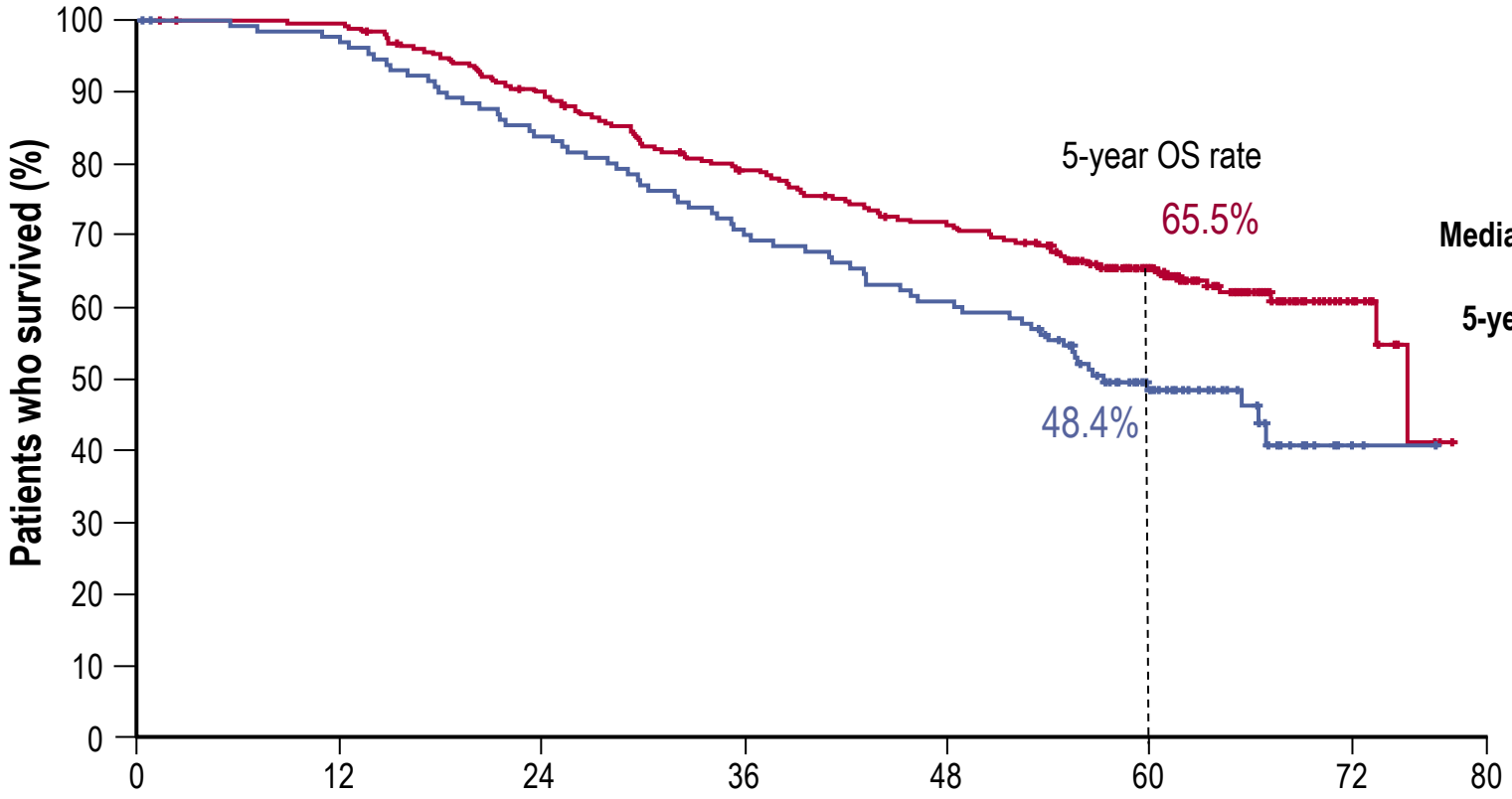
Median time from first cycle of chemotherapy to randomization = 6 months

PARP, poly(ADP-ribose) polymerase.

Ray-Coquard I et al. *Ann Oncol* 2023;34(8):681-92.

2022 PAOLA: OS prolonged in the HRD+ subgroup

HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**
HR 0.62 (95% CI 0.45–0.85)		

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

No. at risk																										
Olaparib + bevacizumab	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Placebo + bevacizumab	132	130	129	128	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	9	2	1	0

*Median unstable; <50% data maturity.

HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.

Ray-Coquard I et al. *Ann Oncol* 2023;34(8):681-92.

ATHENA–MONO Study Schema

Athena
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF NIVOLUMAB AND RUCAPARIB

Key Patient Eligibility

- Newly diagnosed, stage III–IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR
  - Received cytoreductive surgery (primary or interval; R0/complete resection permitted)
- ECOG PS 0 or 1
- No prior treatment for ovarian cancer, including any maintenance treatment, other than frontline platinum regimen

Randomization 4:4:1:1

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab 480 mg IV

Arm D (n≈100)
placebo PO + placebo IV

Treatment for 24 months*, or until radiographic progression, unacceptable toxicity, or other reason for discontinuation

Randomization Stratification Factors

- Tumor HRD test status†
- Disease status post-chemotherapy
- Timing of surgery

Study Analyses

ATHENA–MONO

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm D (n≈100)
placebo PO + placebo IV

ATHENA–COMBO

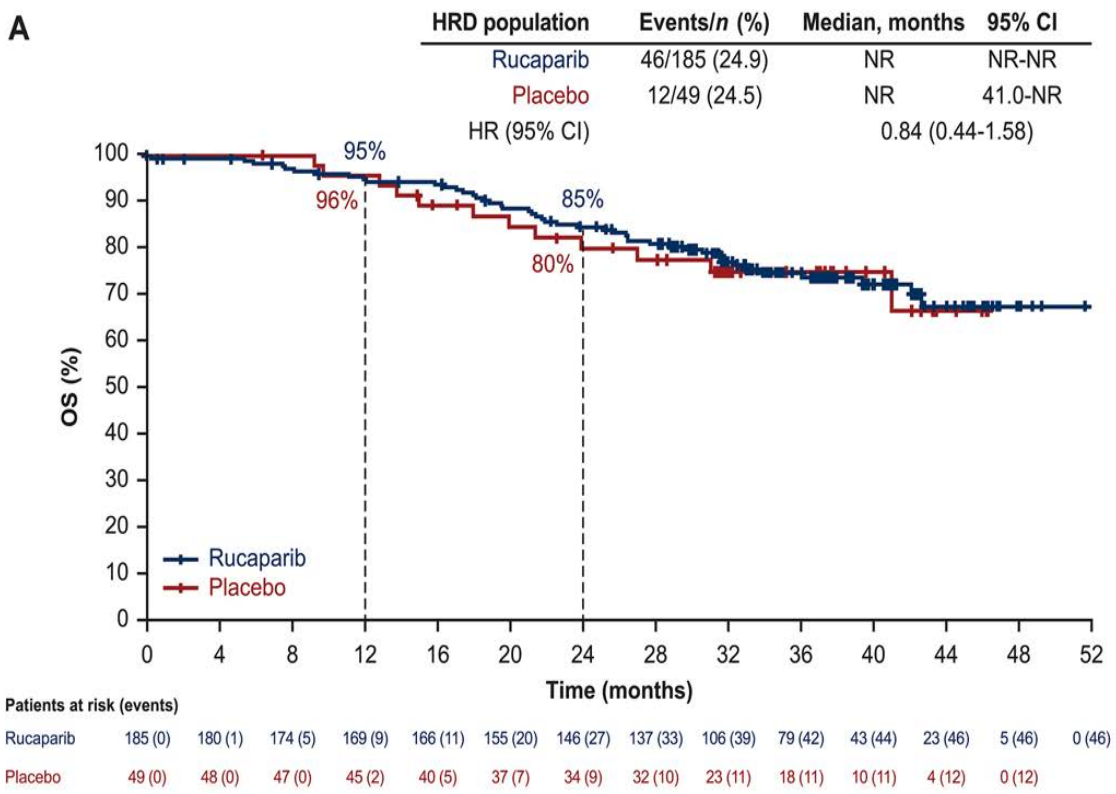
Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

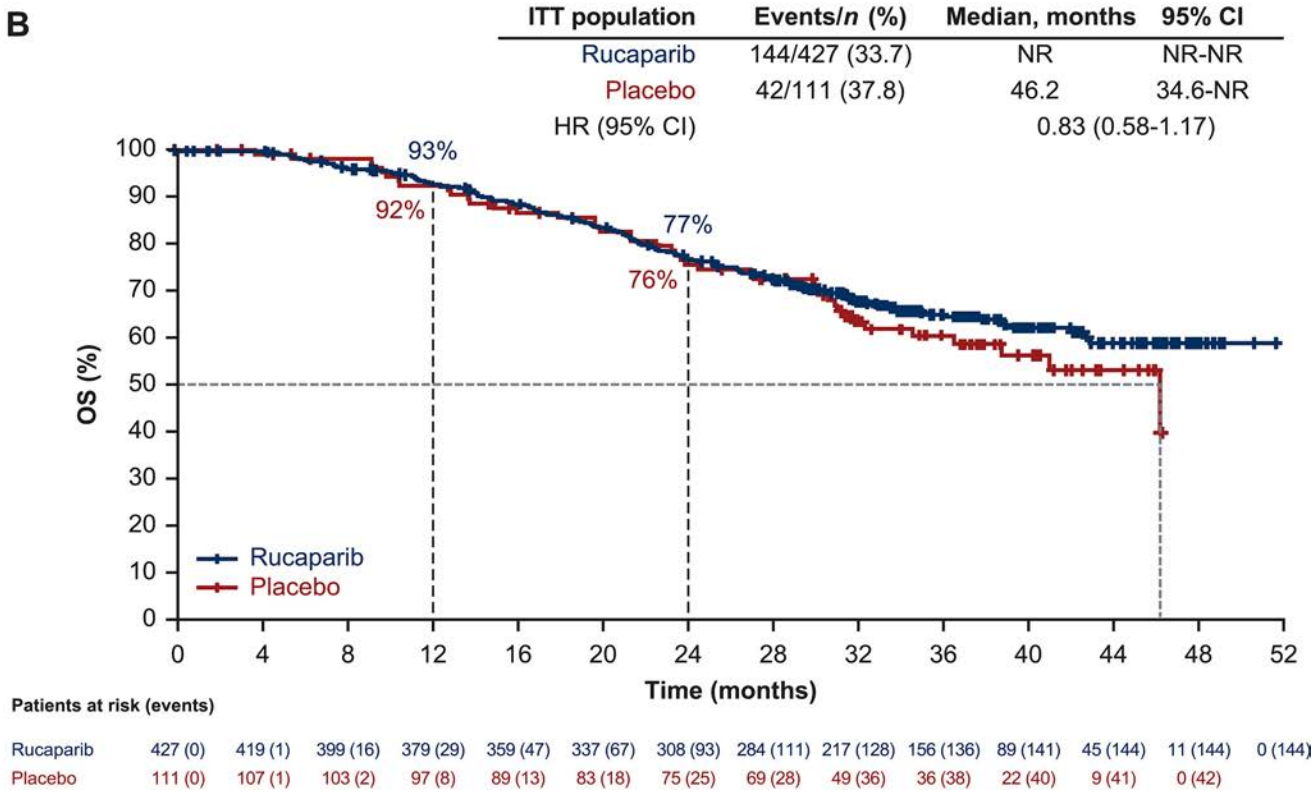
Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

After initiation of oral/IV combination study treatment (IV drug was initiated cycle 2 day 1; 28-day cycles). †Centrally assessed, determined by FoundationOne CDx ($BRCA^{mut}$, $BRCA^{wt}/LOH^{high}$ [LOH ≥16%], $BRCA^{wt}/LOH^{low}$ [LOH <16%], $BRCA^{wt}/LOH^{indeterminate}$). BID, twice daily; BRCA, *BRCA1* or *BRCA2*; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; IV, intravenous; LOH, loss of heterozygosity; mut, mutant; PO, by mouth; PR, partial response; wt, wild type.

Rucaparib maintenance for newly diagnosed advanced ovarian cancer: 5 years follow-up from ATHENA-MONO/GOG-3020/ENGOT-ov45 study

R.S. Kristeleit, et. al. *Annals of Oncology* Feb 2026





PARP inhibitor maintenance after initial therapy of ovarian cancer

	SOLO-1[1,6] (N=391)	PRIMA[2,8] (N=733)	PAOLA-1[3,7] (N=806)	VELIA[4] (N=1140)	ATHENA-MONO[5,9,10] (N=538)
PARP inhibitor	Olaparib	Niraparib	Olaparib	Veliparib	Rucaparib
Arms	1. Placebo 2. Olaparib	1. Placebo 2. Niraparib	1. Bev/placebo 2. Bev/olaparib	1. Chemo/placebo⇨placebo 2. Chemo/veliparib⇨placebo 3. Chemo/veliparib⇨veliparib	1. Placebo 2. Rucaparib
Population	HGS/endometrioid and BRCAmt	HGS/endometrioid	HGS/endometrioid or BRCAmt	HGS	HG Ovarian
Primary endpoint	**PFS** (investigator)	**PFS** (BICR) Hierarchical: HRD⇨ITT	**PFS** (investigator) Predefined subgroups: tBRCA status and HRD	**PFS** (investigator) Hierarchical: BRCAmt⇨HRD⇨ITT	**PFS** (investigator) Predefined subgroups: ITT, HRD positive
PFS Outcome	**HR 0.30** (13.8mos vs NR)	**HR 0.62** (8.2 vs 13.8 mos)	**HR 0.59** (16.6 vs 22.1 mos)	**HR 0.68** (Arm 1 vs 3) (17.3 vs 23.5 mos)	**HR 0.66** (8.2 vs 13.8 mos)
OS Outcome	**HR 0.55**[6] (NS) (75.2mos vs NR) p=0.0004	**HR 1.01**[8] (NS) (46.6m vs 48.8m)	**HR 0.92**[7] (NS) (51.6 vs 56.5mos)		**HR 0.83**[10] (NS) (46.2 mos vs NR)

[1]Moore NEJM 2018, [2]Gonzalez-Martin NEJM 2019, ESMO 2022, [3]Ray-Coquard NEJM 2019, [4]Coleman NEJM 2019. [5]Monk J Clin Oncol 2022, [6]DiSIlvestro JCO 2022, [7]Ray-Coquard ESMO 2022, [8]Monk Ann Oncol 2024, [9]Monk Ann Oncol 2024 [10]Kristeleit Ann Oncol 2026

NCCN Guidelines: First line Maintenance for CR/PR

- Germline or somatic BRCA mutation or HR deficient
  - If bevacizumab not used during primary chemotherapy
    - Olaparib, Niraparib or Rucaparib
  - If bevacizumab used during primary chemotherapy
    - Olaparib and bevacizumab
      - Niraparib and bevacizumab if olaparib intolerant
    - Olaparib, Niraparib or Rucaparib without bevacizumab
- HR Proficient
  - If bevacizumab used during primary chemotherapy
    - Bevacizumab
  - If bevacizumab not used during primary chemotherapy
    - Observe

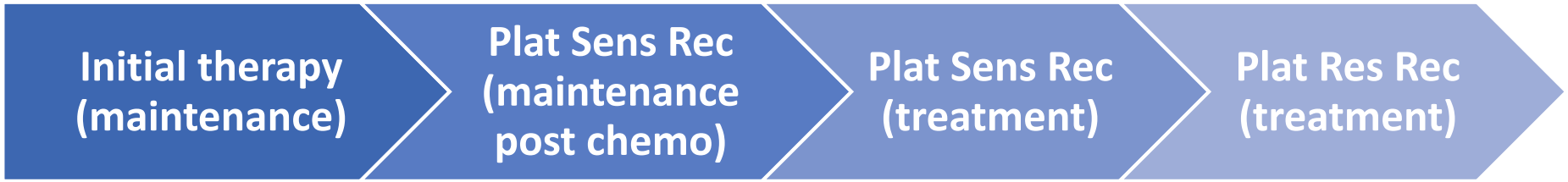
Courtesy of Deborah K Armstrong, MD

Courtesy of Deborah K Armstrong, MD

PARP Inhibitors in Ovarian Cancer

FDA Approval

Ovarian Cancer Clinical Setting



	Phase	Initial therapy (maintenance)	Plat Sens Rec (maintenance post chemo)	Plat Sens Rec (treatment)	Plat Res Rec (treatment)
BRCA mutated (*BRCAm or HRD)	III	SOLO-1 (olaparib)	SOLO-2 (olaparib)	ARIEL4 (rucaparib v chemo) SOLO-3 (olaparib vs chemo)	
	II			Study 42 (olaparib¥) XXX ARIEL2 (rucaparib#) XXX QUADRA (niraparib*¤) XXX	~~QUADRA (niraparib*)~~
All Comers	III	PAOLA-1 (olaparib/bev*) VELIA (veliparib) PRIMA (niraparib) + + + ATHENA-MONO (rucaparib)	Study 19 (olaparib) # # # NOVA (niraparib@) ≠ ≠ ≠ ARIEL3 (rucaparib) Δ Δ Δ	AVANOVA2 (niraparib+/-bev) GY-004 (olaparib +/- cedirinib)	
	II	OVARIO (niraparib/bev)	MEDIOLA (olaparib/durva or olaparib/durva/bev)	LIGHT study (olaparib) ARIEL2/Study 10 (rucaparib) CLIO (olaparib vs. chemo)	

XXX Withdrawal of FDA approval:
#Inferior OS in ARIEL4, rucaparib withdrawal by company (6/10/22)
¥SOLO-3 Inferior OS, olaparib withdrawal by company (8/26/22)
-Company requiring reconsent for SOLO-3, Study 42 and LIGHT
¤QUADRA single arm w/o comparator, niraparib withdrawal by company: (9/6/22)
XXX NCCN Change from Category 2A to Category 3
8/25/2022 ASCO Guidelines Update: PARPi monoRx should not be offered

@Notice of Inferior OS from NOVA trial (5/2022)
Δ Δ Δ 11/2022 rucaparib FDA approval restricted to BRCAmut (g/s) patients only
≠ ≠ ≠ 12/2022 niraparib FDA approval restricted to gBRCAmut patients only
+ + + 6/2025 niraparib FDA approval restricted to HRD or BRCAmut patients only
# # # 9/12/2023 olaparib FDA approval restricted to BRCAmut (g/s) patients only

MDS/AML in Ovarian Cancer PARP Inhibitor Maintenance Trials

JOHNS HOPKINS MEDICINE

Trial	Setting	Agent	PARPi Duration	MDS/AML Events by arm PARPi, n (%)	Comparator, n (%)
SOLO1[4]	1L maint	Olaparib	2 years	4/260 (1.5)	1/130 (0.8)
PRIMA[6] (2019)	1L maint	Niraparib	3 years	1/484 (0.2)	0/244
PRIMA[11] (2024)				11/484 (2.3%)	4/244 (1.6%)
*BRCA*m				6/142 (4%)	1/71 (1.4%)
PAOLA1[5]	1L maint	Olaparib	2 years	6/535 (1)	1/267 (0.4)
ATHENA MONO[9]	1L maint	Rucaparib	2 years	2/425 (0.5)	0/110
Study19[8]	PS maint	Olaparib	UDP, 18% >3yrs	2/136 (1.5)	1/129 (<1)
SOLO2[2]	PS maint	Olaparib	UDP, mean 29.1 mos	16/195 (8)	4/99 (4)
NOVA[3]	PS maint	Niraparib	UDP	13/367 (3.5)	3/179 (1.7)
g*BRCA*m				9/136 (6.6)	2/65 (3.1)
non-g*BRCA*m				4/231 (1.7)	1/114 (0.9)
ARIEL3[7]	PS maint	Rucaparib	UDP, median 8.3 mos	14/372 (3.8)	6/189 (3.2)
PARPi ≥24m[10]				9/79 (11.4)	
non-*BRCA*m				5/245 (2.0)	1/123 (0.8)
*BRCA*m				9/130 (6.9)	3/63 (4.8)
PARPi ≥24 mos				7/46 (15.2)	

[2]Poveda A, et al. Lancet Oncol 2021, [3]Matulonis U. et al. SGO 2021, [4]DiSilvestro P, et al. J Clin Oncol 2022, [5]Ray-Coquard I et al. NEJM Dec 2019, [6]Gonzalez-Martin A et al. NEJM 2019, [7]Coleman RL et al. IGCS 2022, [8]Lederman J et al. Lancet 2016 17: 1579-89, [9]Monk B et al. J Clin Oncol 2022, [10]O'Malley et al. Gyn Onc 10/2022, [11]Monk BJ et al. Ann Oncol Nov 2024

Rationale for FRα Targeting in Ovarian Cancer

JOHNS HOPKINS MEDICINE

- Limited normal tissue distribution: choroid plexus, proximal renal tubules, placenta, endometrium
- High level FRα expression in ovarian cancer
  - Increased in more advanced stages
  - Expression correlates with more malignant phenotype
  - Expression maintained on metastatic foci
- Alternate cellular folate uptake by reduced folate carrier (RFC) circumvents folate deficiency

Courtesy of Deborah K Armstrong, MD

FRα targeting agents

- Anti-FRα antibodies
  - Farletuzumab
- Antibody drug conjugates
  - Vintafolide (EC145)
  - STRO-02/Luveltamab tazevibulin
  - MORAB-002/Farletuzumab ecteribulin
  - Mirvetuximab soravtansine (MIRV)
  - Rinatabart sesutecan (Rina-S, exatecan payload)
  - Torvutatug samrotecan (exatecan payload)

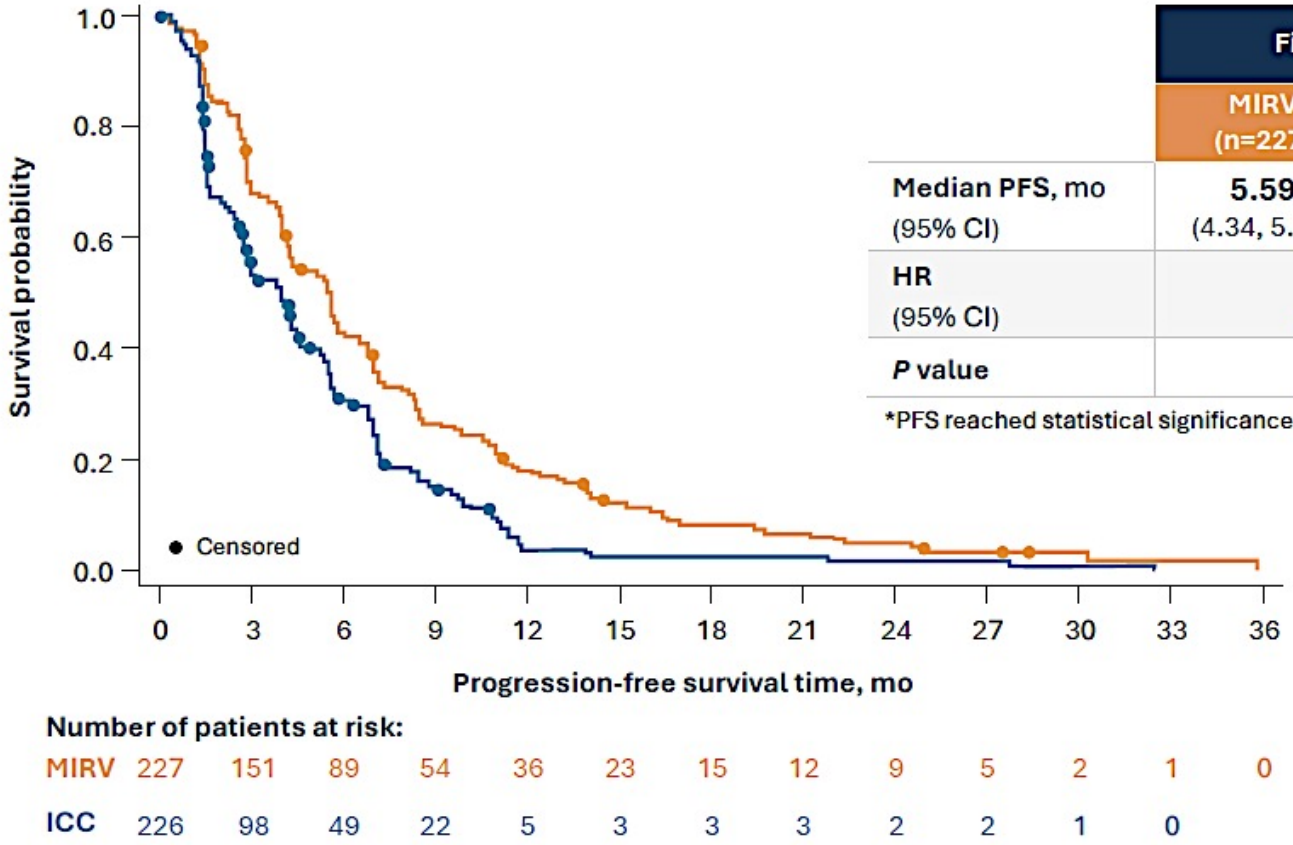
- Immune FRα approaches
  - Vaccines targeting FRα
  - Chimeric antigen receptor (CAR) T cells
- In contrast, anti-folate drugs such as pemetrexed and MTX enter via the reduced folate carrier

Courtesy of Deborah K Armstrong, MD

Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer

Van Gorp T et al. SGO 2025

Final Progression-Free Survival by Investigator



	Final analysis[a]		Primary analysis[b]	
	MIRV (n=227)	ICC (n=226)	MIRV (n=227)	ICC (n=226)
Median PFS, mo (95% CI)	**5.59** (4.34, 5.88)	**3.98** (2.86, 4.47)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
HR (95% CI)	**0.63** (0.51, 0.79)		0.65 (0.52, 0.81)	
***P* value**	<0.0001*		<0.0001	

*PFS reached statistical significance in primary analysis. The *P* value at the final analysis is descriptive.

At the final analysis, the HR for PFS (0.63) **continued to favor MIRV** over ICC, with patients treated with MIRV exhibiting a **37% reduction in risk of progression**

HR, hazard ratio; ICC, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine-gynx; PFS, progression-free survival.

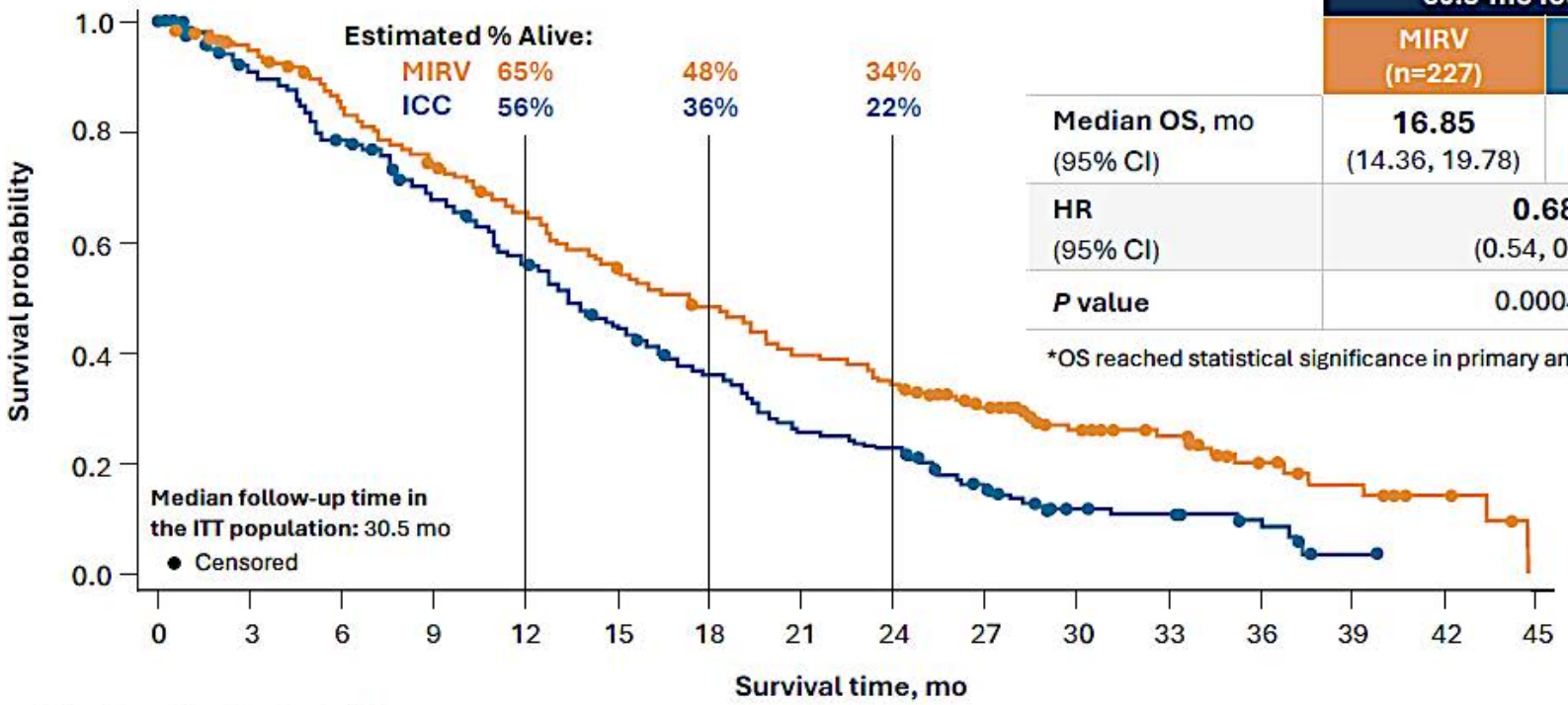
[a]Data cutoff: September 26, 2024. [b]Data cutoff: March 6, 2023.

Moore KN, et al. *N Engl J Med*. 2023;389(23):2162-2174.

Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer

Van Gorp T et al. SGO 2025

Final Overall Survival



Number of patients at risk:

MIRV	227	204	178	156	135	114	98	80	70	50	33	25	12	8	4	0
ICC	226	186	159	134	110	85	67	48	42	25	13	11	7	1	0	

	Final analysis[a] 30.5-mo follow-up		Primary analysis[b] 13.1-mo follow-up	
	MIRV (n=227)	ICC (n=226)	MIRV (n=227)	ICC (n=226)
Median OS, mo (95% CI)	**16.85** (14.36, 19.78)	**13.34** (11.37, 15.15)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
HR (95% CI)	**0.68** (0.54, 0.84)		0.67 (0.50, 0.89)	
P value	0.0004*		0.0046	

*OS reached statistical significance in primary analysis. The *P* value at the final analysis is descriptive.

At the final analysis, the HR for OS (0.68) **continued to favor MIRV** over ICC, with patients treated with MIRV exhibiting a **32% reduction in risk of death**

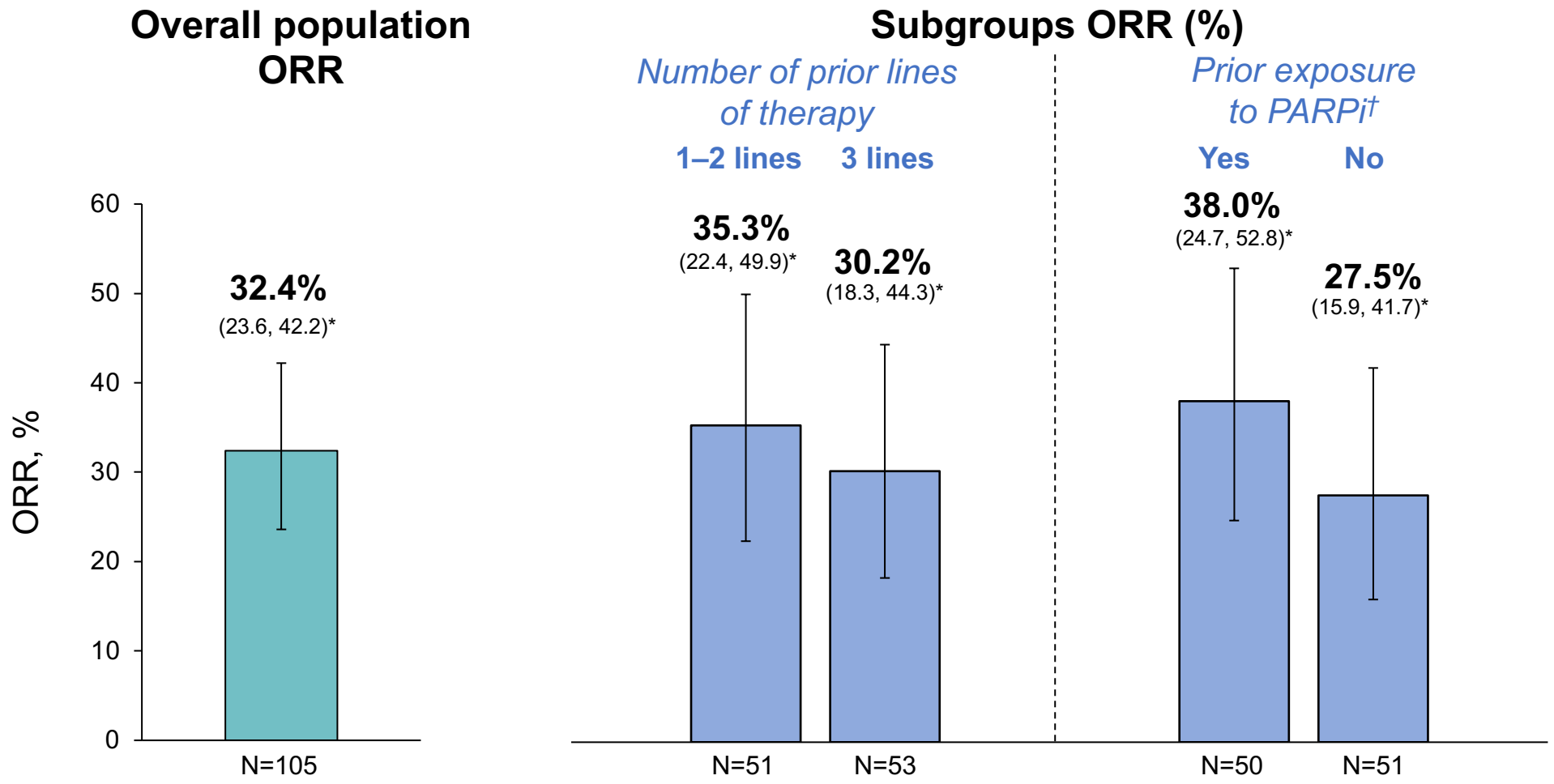
HR, hazard ratio; ICC, investigator's choice chemotherapy; ITT, intent-to-treat; MIRV, mirvetuximab soravtansine-gynx; OS, overall survival; PFS, progression-free survival.

[a]Data cutoff: September 26, 2024. [b]Data cutoff: March 6, 2023.

Moore KN, et al. *N Engl J Med*. 2023;389(23):2162-2174.

Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer

Matulonis U et al. SGO 2022



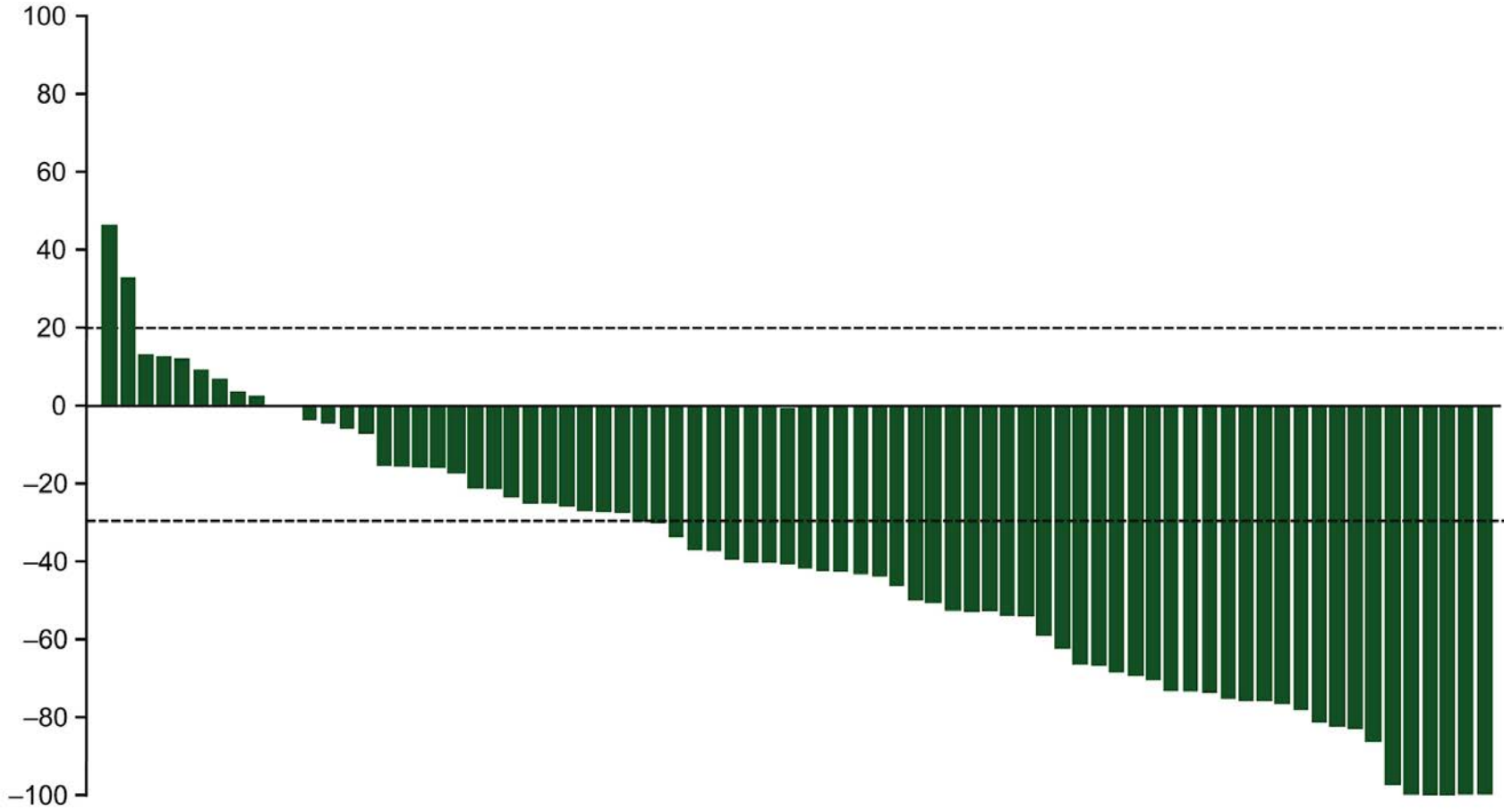
The denominator for the percentage is the number of patients in the investigator-assessed population in each analysis. Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable.

*95% exact CI is estimated by Clopper-Pearson method (Clopper-Pearson exact CI). †Prior PARPi exposure was uncertain for 4 patients in the investigator-assessed population.

CI, confidence interval; ORR, objective response rate; PARPi, poly ADP-ribose polymerase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.

Mirvetuximab in PSOC, FRA ≥75%. PICCOLO Trial

Alvarez Secord A. et al. Ann Oncol 2025



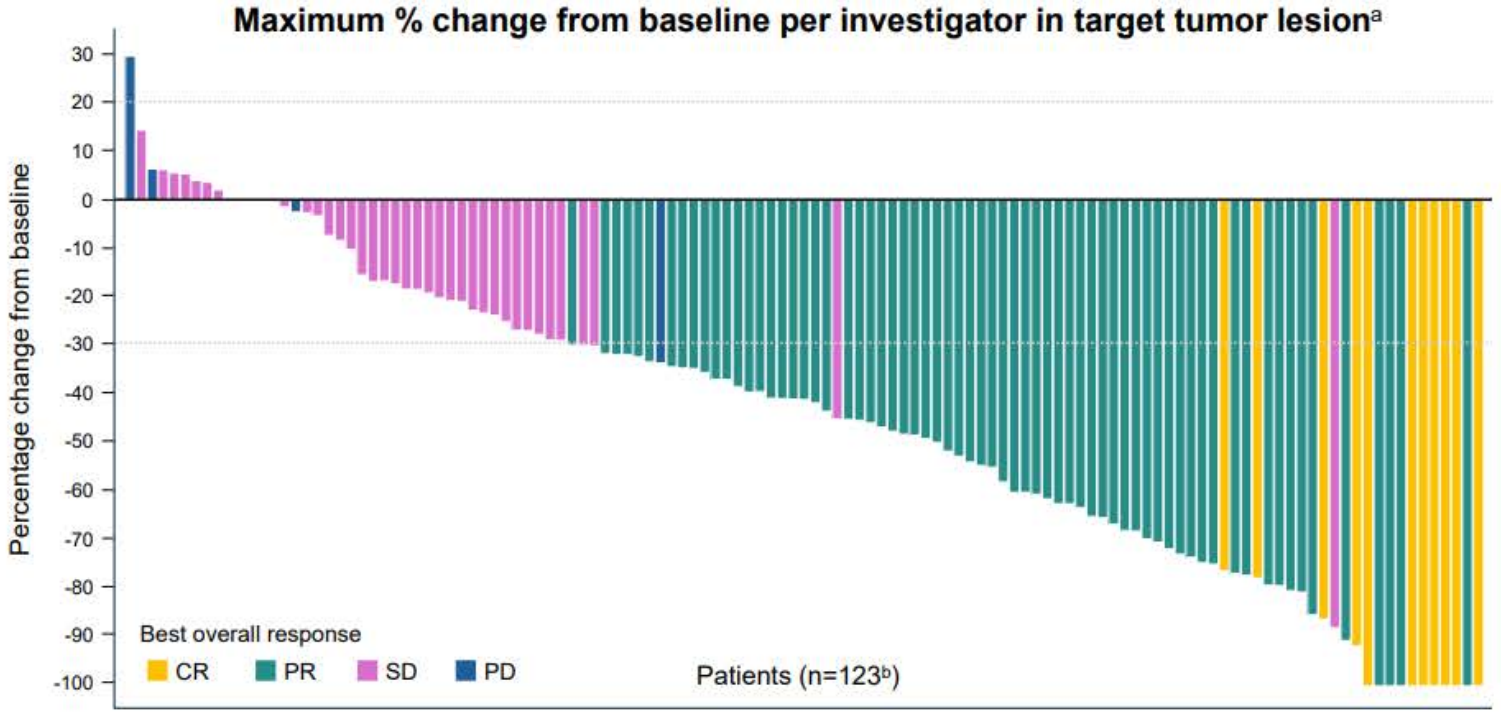
ORR 52%

Subgroup	ORR
1-2 prior lines of therapy	55%
3 prior lines of therapy	50%
≥4 prior lines of therapy	33%
Prior Bev	49%
No prior Bev	57%
PFI ≤12 months	42%
PFI >12 months	65%

Mirvetuximab Soravtansine Plus Carboplatin in Folate Receptor Alpha-Expressing Recurrent Platinum-Sensitive Ovarian Cancer
Konecny, GE et al. SGO 2026

Efficacy: Tumor Reduction in the Overall Population (≥25% FRα) in the Combination Phase

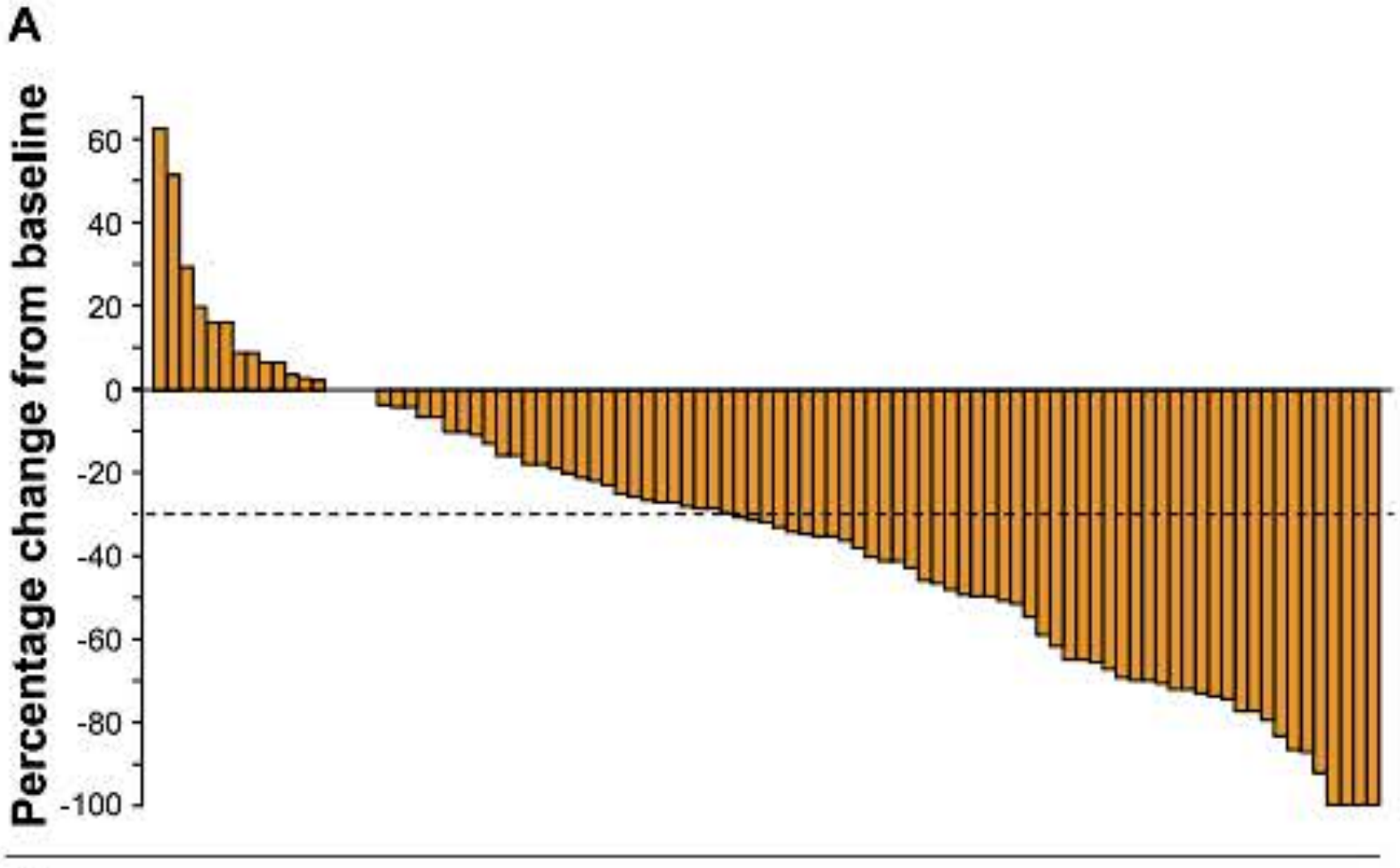
SGO ANNUAL MEETING ON WOMEN'S CANCER
SAN JUAN, PR
APRIL 10-13, 2026



FRα ≥25% n=125	
FRα ≥50% n=102	
ORR FRα ≥25%	62.4%
ORR FRα ≥50%	62.7%
mPFS FRα ≥25%	11.0 mos
mPFS FRα ≥50%	11.0 mos

- **91%** of patients (112/123) experienced a **reduction** in **target lesion size** after receiving combination MIRV + carboplatin
- **81%** of patients (101/125) had **no PD** after combination and continued to single-agent MIRV with sustained or deepened responses

Mirvetuximab and Bevacizumab in PROC
Gilbert L. et al. Gyn Onc 2023



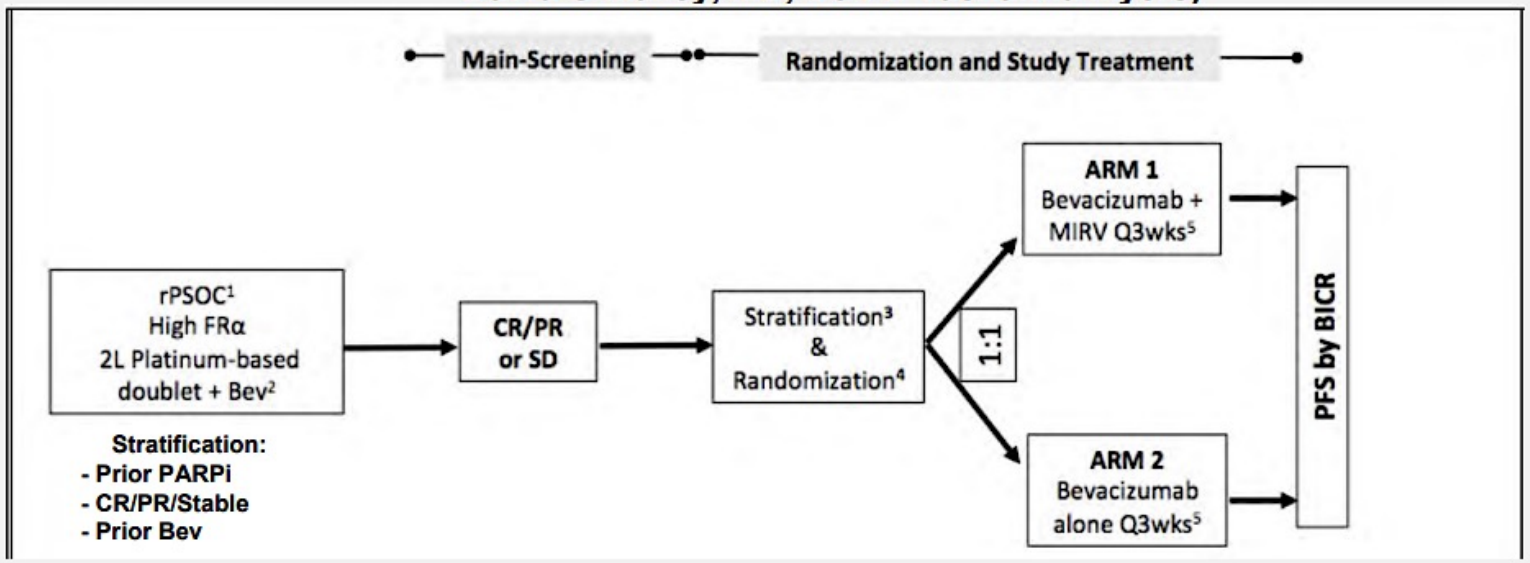
Subgroup	ORR
FRα ≥ 75% (n = 44)	48%
FRα 50–74% (n = 39)	41%
FRα 25–49% (n = 11)	36%
BEV-naïve (n = 39)	56%
BEV-pretreated (n = 55)	35%

NCCN listed for FRA ≥25%

Courtesy of Deborah K Armstrong, MD

GOG-3078 (GLORIOSA)

Randomized multicenter, open-label, phase 3 study of bevacizumab with or without mirvetuximab soravtansine for patients with FRα–positive recurrent platinum-sensitive epithelial ovarian cancer, fallopian tube, or primary peritoneal cancers who have not progressed after second line platinum-based chemotherapy plus bevacizumab (PI: David O'Malley, MD, Co-PI: Tashanna Myers)



- High grade epithelial ovarian, tubal or primary peritoneal cancer
- Platinum + chemo + Bevacizumab for planned 6 cycles (min of 4 and max of 8) including at least 3 of cycles of Bev
- Need to have a CR, PR, or stable disease after platinum regimen
- Treatment until progressive disease, unacceptable toxicity, withdrawal or death
- Maintenance tx must begin within 12 weeks of completing platinum doublet

QUESTIONS?

Module 3: Ovarian Cancer

PARP Inhibitors and Strategies Targeting Folate Receptor Alpha (FRα) in Advanced OC — Dr Armstrong

Other Novel Agents and Strategies for the Treatment of Advanced OC — Dr O'Malley

Other Novel Agents and Strategies for Advanced OC Treatment

David O'Malley, MD
Director & Professor,
Division of Gyn Oncology in OB/Gyn
John G. Boutselis Chair in Gynecologic Oncology
Co-Director, Gyn Oncology Phase I Program

Ovarian Cancer Portfolio Lead, GOG-P
BOD, GOG Foundation

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Creating a cancer-free world. One person, one discovery at a time.




Disclosures

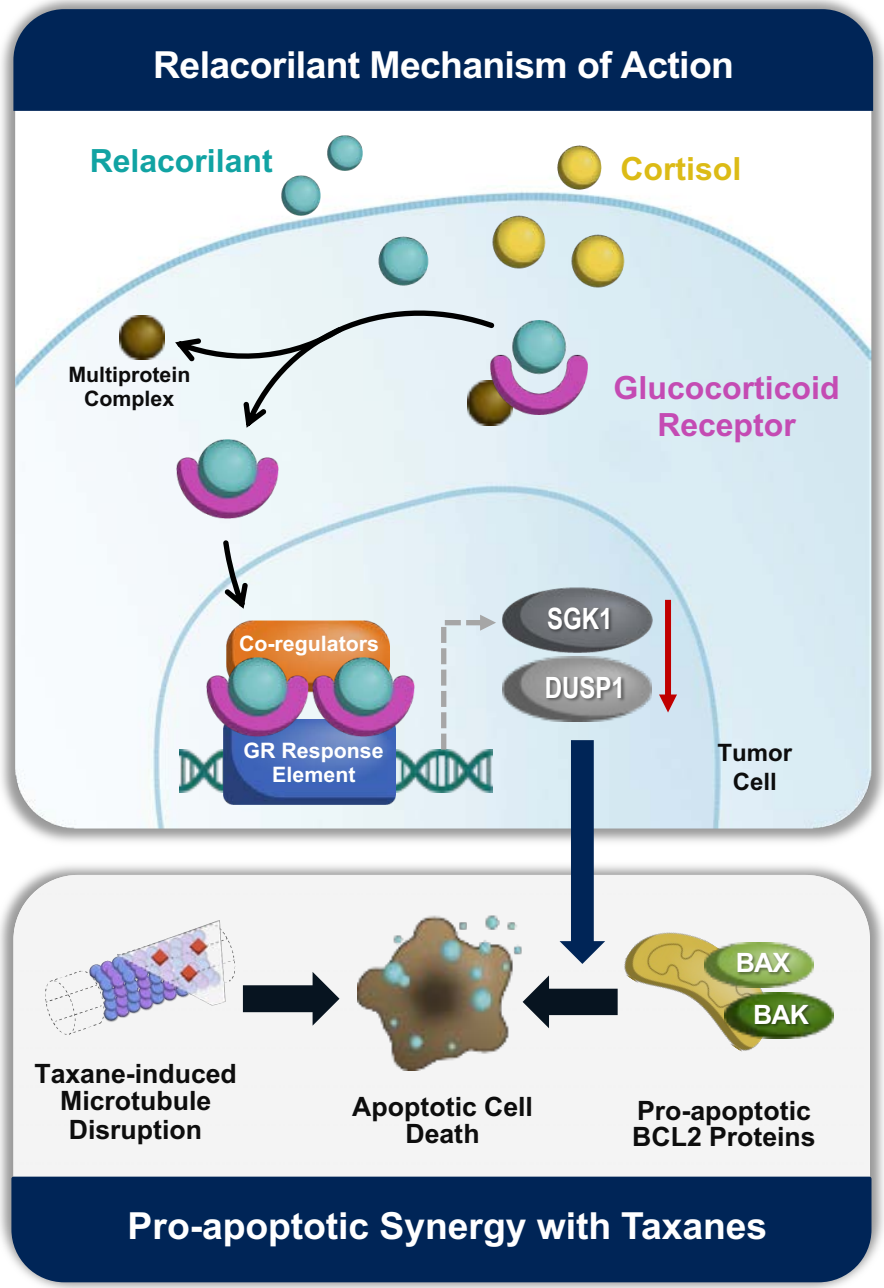
Consulting Agreements — Personal Fees (Consult and/or Advisory Boards)	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeOne, Corcept Therapeutics Inc, Daiichi Sankyo Inc, Duality Biologics, Genmab US Inc, GSK, Lilly, Merck, MSD, Novocure Inc, Pfizer Inc, Regeneron Pharmaceuticals Inc, Verastem Inc, Zentalis Pharmaceuticals
Contracted Research (Institution Received Funds for Research)	AbbVie Inc, Advaxis Inc, Agenus Inc, Alkermes, Aravive Inc, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, BeOne, Bristol Myers Squibb, Deciphera Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Exelixis Inc, F Hoffmann-La Roche Ltd, Genentech, a member of the Roche Group, Genmab US Inc, GSK, ImmunoGen Inc, Incyte Corporation, Iovance Biotherapeutics, Karyopharm Therapeutics, Leap Therapeutics Inc, Merck, Mersana Therapeutics Inc, MSD, Novartis, Novocure Inc, OncoC4, OncoQuest Inc, Pfizer Inc, pharmaand GmbH, Predictive Oncology Inc, Prelude Therapeutics, Regeneron Pharmaceuticals Inc, Seagen Inc, Sumitomo Pharma America, Sutro Biopharma, Tesaro, A GSK Company, Verastem Inc
Data and Safety Monitoring Boards/Committees	Frantz Viral Therapeutics

Strategies for Advanced OC Treatment

- ROSELLA (nab-paclitaxel +/- relacorilant)
- KEYNOTE-B96 (paclitaxel +/- Bev +/- pembro)
- DESTINY-PanTumor02 (T-DXd)
- Raludotatug Deruxtecan (R-DXd)
- Other promising novel agents

Background

- Patients with platinum-resistant ovarian cancer have an overall survival of ~1 year and need new treatments[1]
- Ovarian cancers express the glucocorticoid receptor (GR), a marker of poor prognosis[2]
- GR signaling reduces sensitivity to chemotherapy[3,4]
- Relacorilant is a novel, selective GR antagonist (SGRA) that restores the sensitivity of cancers to cytotoxic chemotherapy[3,5,6]



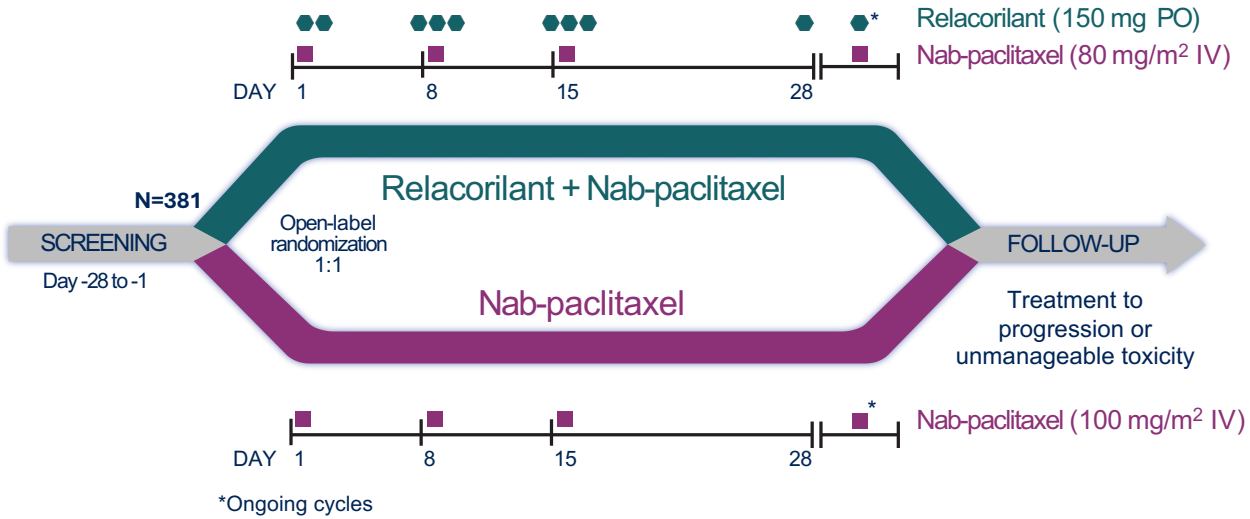
1. Martorana, et al. *Int J Gynecol Cancer*. 2025;35(1):100009. 2. Veneris, et al. *Gynecol Oncol*. 2017;146(1):153-60.
3. Greenstein, et al. *Oncotarget*. 2021;12(13):1243-55. 4. Melhelm, et al. *Clin Cancer Res*. 2009;15(9):3196-3204.
5. Stringer-Reasor, et al. *Gynecol Oncol*. 2015;138(3):656-62. 6. Munster, et al. *Clin Cancer Res*. 2022;28(15):3214-24.

ROSELLA | Study Schema

Population

- Epithelial ovarian, primary peritoneal, or fallopian tube cancer
- ECOG performance status 0 or 1
- Progression <6 months after the last dose of platinum therapy (excluding no response to, or progression in <1 month of primary platinum)
- 1–3 prior lines of therapy
- Prior bevacizumab required

NCT05257408



Stratification Factors

- Prior lines of therapy (1 vs >1)
- Region (North America vs Europe vs Korea, Australia, & Latin America)

Dual Primary Endpoints

- Progression-free survival (PFS) by RECIST v1.1 per blinded independent central review
- Overall survival (OS)

Secondary Endpoints

- PFS by RECIST v1.1 per Investigator
- ORR, DoR, CBR (RECIST v1.1)
- Response by CA-125 GCIG criteria
- Combined response (RECIST v1.1 and CA-125 GCIG criteria)
- Safety

First patient enrolled: Jan 5, 2023
Last patient enrolled: Apr 8, 2024
Primary results data cutoff: Feb 24, 2025
Final OS data cutoff: Jan 8, 2026
Conducted at 117 sites in 14 countries.

CA, cancer antigen; CBR, clinical benefit rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; GCIG, Gynecologic Cancer Intergroup; IV, intravenous; ORR, objective response rate; PO, by mouth; RECIST, Response Evaluation Criteria in Solid Tumors.

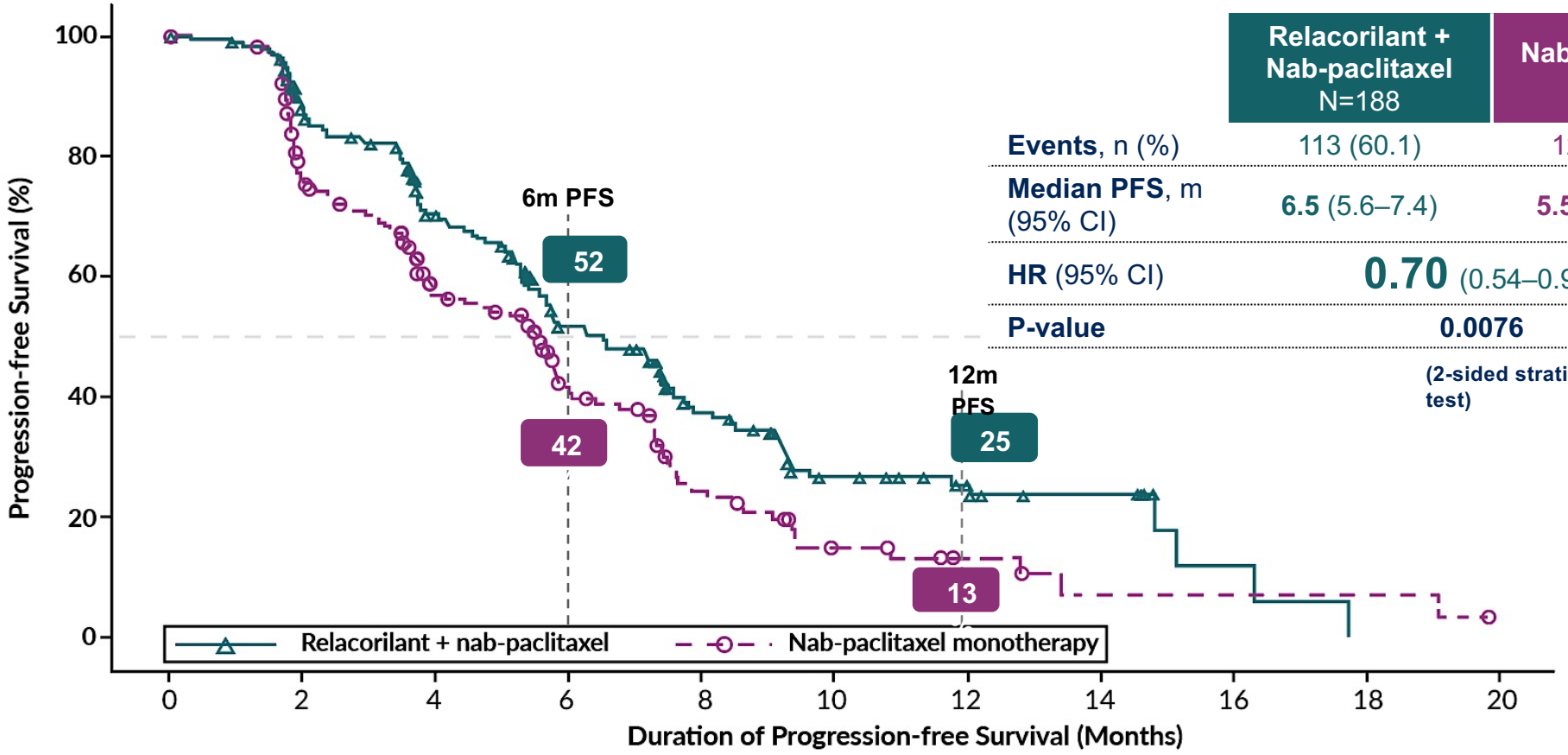
ROSELLA - Demographics

		Relacorilant + Nab-paclitaxel (N=188)	Nab-paclitaxel (N=193)
Age, median (range), years		**61** (26–85)	**62** (33–86)
Race, n (%)	White Black or African-American Asian (92% Korean) Other / Not Reported	136 **(72.3)** 3 **(1.6)** 22 **(11.7)** 27 **(14.4)**	135 **(69.9)** 2 **(1.0)** 26 **(13.5)** 30 **(15.5)**
Ethnicity, n (%)	Hispanic	16 **(8.5)**	17 **(8.8)**
Region	North America Europe Korea, Australia, and Latin America	45 **(23.9)** 107 **(56.9)** 36 **(19.1)**	45 **(23.3)** 109 **(56.5)** 39 **(20.2)**
ECOG Performance Status, n (%)*	1 or 2	53 **(28.2)**	63 **(32.6)**
BRCA1/2 Mutation, n (%)	Yes	23 **(12.2)**	24 **(12.4)**
Prior Lines of Therapy, n (%)	1 2 3	15 **(8.0)** 92 **(48.9)** 81 **(43.1)**	18 **(9.3)** 89 **(46.1)** 86 **(44.6)**
Primary Platinum Refractory, n (%)†	Yes	13 **(6.9)**	13 **(6.7)**
Prior Lines of Therapy in the Platinum-resistant Setting, n (%)	≥1	67 **(35.6)**	82 **(42.5)**
Prior Taxane in the Platinum-resistant Setting, n (%)	Yes	8 **(4.3)**	7 **(3.6)**
Prior Therapies, n (%)	Bevacizumab Taxanes Pegylated Liposomal Doxorubicin PARP Inhibitor	188 **(100)** 187 **(99.5)** 121 **(64.4)** 114 **(60.6)**	193 **(100)** 192 **(99.5)** 125 **(64.8)** 120 **(62.2)**

*In the nab-paclitaxel monotherapy arm, 1 patient had an ECOG performance status of 2. †Progressed within 3 months of the last dose of platinum from their first line platinum regimen. 97% of patients had high-grade serous carcinoma; 8 patients had high-grade endometrioid carcinoma and 2 patients had carcinosarcoma. BRCA, Breast Cancer Gene; ECOG, Eastern Cooperative Oncology Group; PARP, poly(ADP-ribose) polymerase.

Data cutoff: Feb 24, 2025

ROSELLA | Progression-Free Survival – BICR (Primary Analysis)



	Relacorilant + Nab-paclitaxel N=188	Nab-paclitaxel N=193
Events, n (%)	113 (60.1)	121 (62.7)
Median PFS, m (95% CI)	**6.5** (5.6–7.4)	**5.5** (3.9–5.9)
HR (95% CI)	**0.70** (0.54–0.91)	
P-value	**0.0076**	

(2-sided stratified log-rank test)

No. at risk (events/cumulative events)

Relacorilant + nab-paclitaxel	188 (0/0)	151 (22/22)	109 (29/51)	70 (27/78)	43 (18/96)	24 (11/107)	16 (1/108)	11 (1/109)	2 (2/111)	0 (2/113)	
Nab-paclitaxel monotherapy	193 (0/0)	129 (42/42)	85 (31/73)	47 (20/93)	21 (17/110)	9 (7/117)	5 (1/118)	2 (2/120)	2 (0/120)	2 (0/120)	0 (1/121)

Median follow-up time: 9.0 months; statistical significance threshold: P≤0.04. The Kaplan–Meier method was used to estimate the curves, median estimates and the 95% CIs for progression-free survival in each treatment arm. The HR and the associated 95% CI were estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates.
CI, confidence interval; HR, hazard ratio; m, months; PFS, progression-free survival.

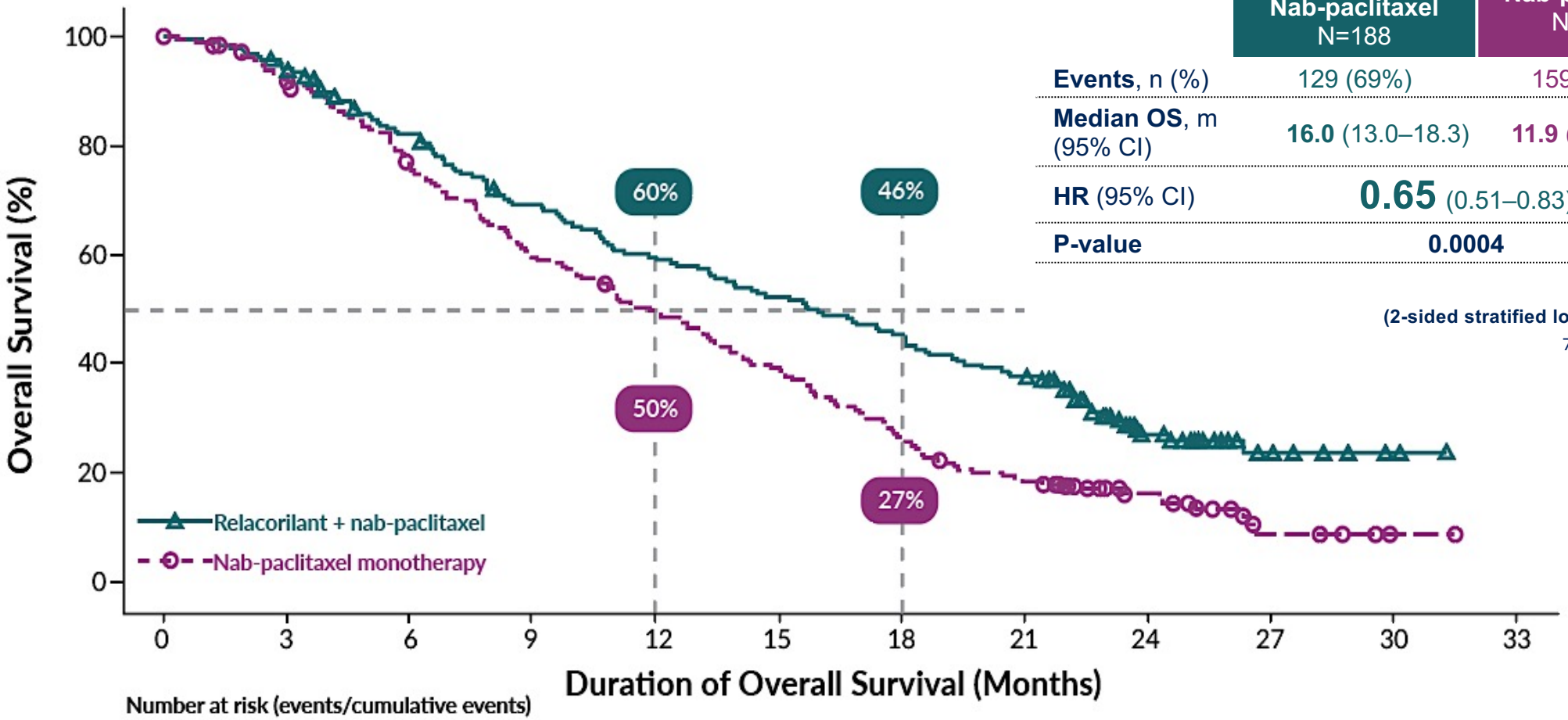
Data cutoff: Feb 24, 2025

ROSELLA | Overall Survival - Final Analysis

	Relacorilant + Nab-paclitaxel N=188	Nab-paclitaxel N=193
Events, n (%)	129 (69%)	159 (82%)
Median OS, m (95% CI)	**16.0** (13.0–18.3)	**11.9** (10.0–13.8)
HR (95% CI)	**0.65** (0.51–0.83)	
P-value	**0.0004**	

(2-sided stratified log-rank test)

76% maturity



Number at risk (events/cumulative events)

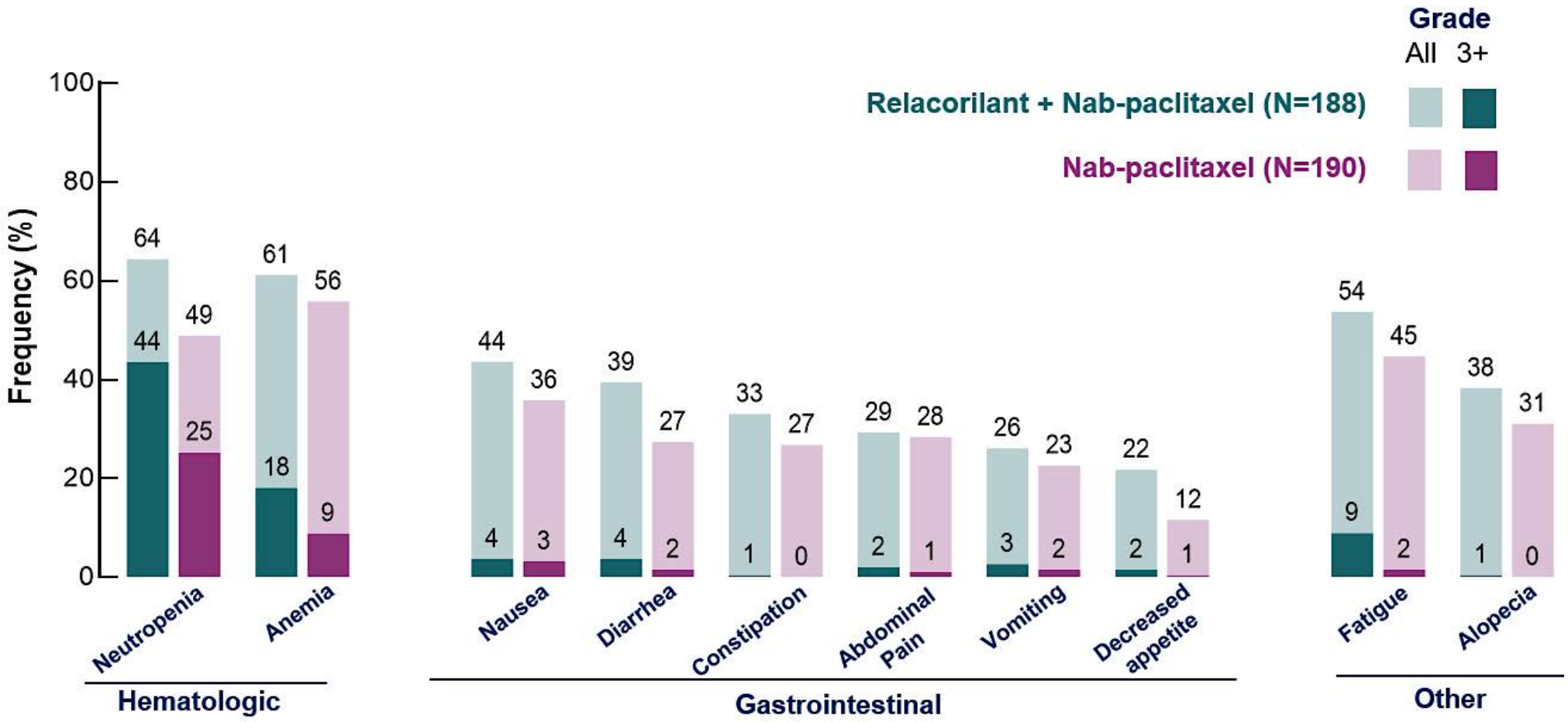
Relacorilant + nab-paclitaxel	188 (0/0)	176 (11/11)	148 (22/33)	123 (23/56)	106 (17/73)	93 (13/86)	81 (12/98)	67 (14/112)	28 (15/127)	10 (2/129)	3 (0/129)	0 (0/129)
Nab-paclitaxel monotherapy	193 (0/0)	173 (15/15)	142 (28/43)	110 (32/75)	91 (18/93)	72 (19/112)	49 (23/135)	33 (15/150)	18 (3/153)	5 (6/159)	1 (0/159)	0 (0/159)

Median follow-up time: 24.8 months; statistical significance threshold at the final analysis: P≤0.0499. The Kaplan–Meier method was used to estimate the curves, median estimates and the 95% CIs for OS in each treatment arm. The HR and the associated 95% CI were estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates.
CI, confidence interval; HR, hazard ratio; m, months; OS, overall survival.

Data cutoff: Jan 8, 2026

Presented By: Alexander B. Olawaiye, MD, SGO 2026

ROSELLA | Common (>20%) Adverse Events



When adjusted for duration of exposure, the incidence rates of neutropenia and anemia were similar between study arms.
Peripheral neuropathy occurred with similar frequency in both arms (19.1% and 17.4%).
5 SAEs of febrile neutropenia: 4 (2.1%) vs 1 (0.5%).* 5 SAEs of sepsis: 3 (1.6%) vs 2 (1.1%).*

Treatment-emergent adverse events that occurred in >20% of patients. Assessed in the safety population of patients who received at least one dose of study drug, N=378. Combined terms are presented for neutropenia (neutropenia, reduced neutrophil count, and febrile neutropenia), anemia (anemia, reduced hemoglobin, and reduced red blood cell count) and fatigue (fatigue and asthenia). SAEs, serious adverse events. *Comparing the relacorilant combination arm to the nab-paclitaxel monotherapy arm, respectively.

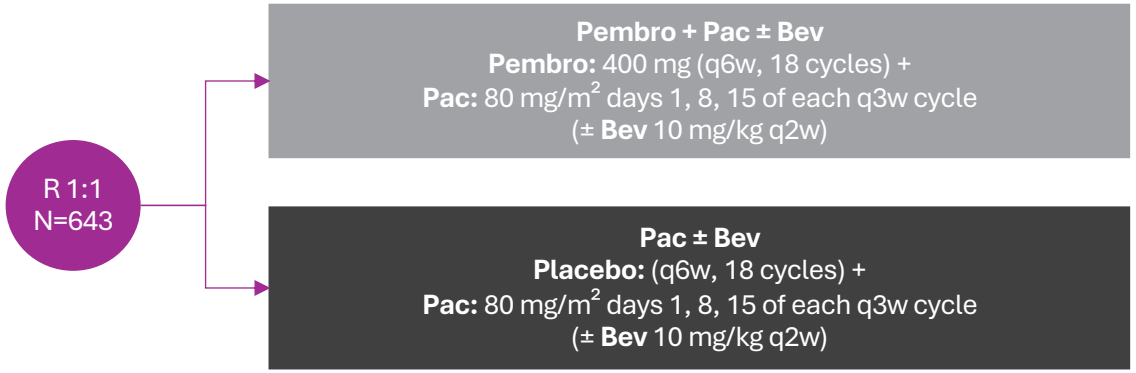
Data cutoff: Jan 8, 2026

KEYNOTE-B96: Phase 3 Trial of Pembro in PROC

Study Design and Patient Characteristics

Key Eligibility Criteria

- Histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
- 1 or 2 prior lines of therapy; at least 1 platinum-based Chemo
- Prior anti–PD-1 or anti–PD-L1, PARPi and Bev permitted
- Radiographic progression within 6 months after the last dose of platinum-based Chemo
- ECOG PS 0 or 1



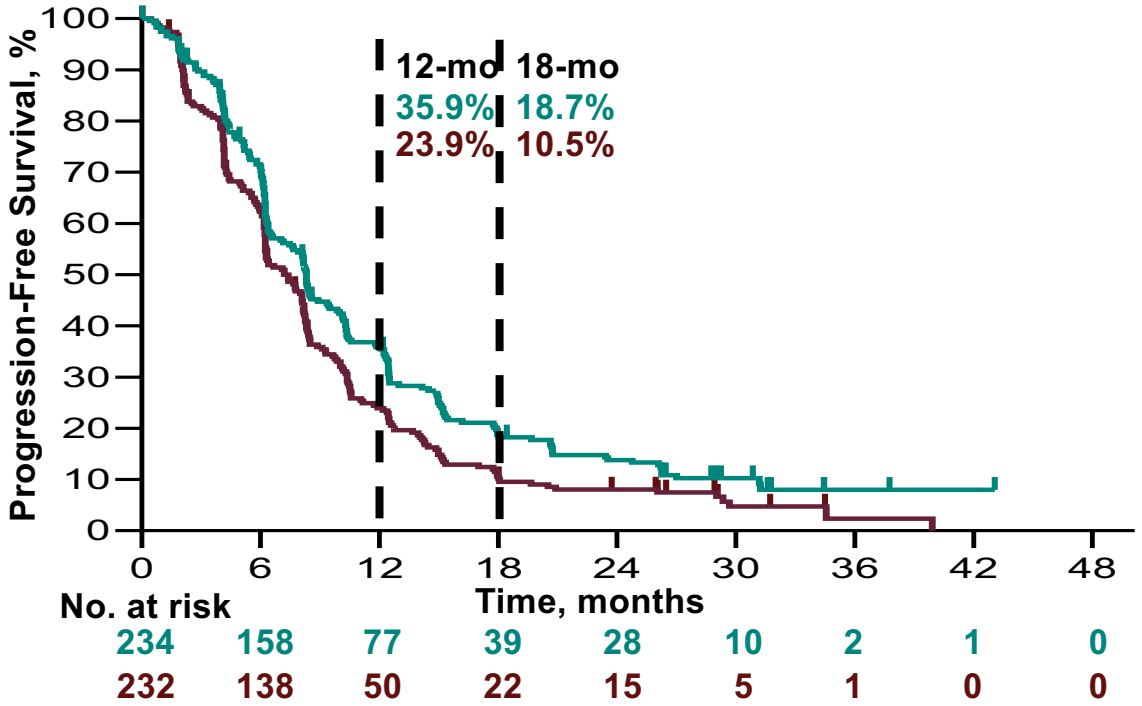
Primary endpoint: PFS per RECIST v1.1 by INV
Secondary endpoint: OS

Patient Characteristics	Pembro + Pac ± Bev (n=322)	Pac ± Bev (n=321)
Median age (range), years	62 (37-85)	61 (37-82)
Prior LOT, n (%)		
1	121 (38)	113 (35)
2	200 (62)	207 (65)
PD-L1 CPS, n (%)		
<1	88 (27)	89 (28)
1 to <10	133 (41)	132 (41)
≥10	101 (31)	100 (31)
Bev use, n (%)	235 (73)	236 (74)
Prior anticancer therapy, n (%)		
Anti–PD-1 or PD-L1	7 (2)	7 (2)
Bev	149 (46)	146 (46)
PARPi	112 (35)	123 (38)
ECOG PS 1, n (%)	142 (44)	144 (45)
Platinum-free interval, n (%)		
<3 months	137 (43)	162 (51)
≥3 to ≤6 months	183 (57)	154 (48)
>6 months	2 (1)	4 (1)

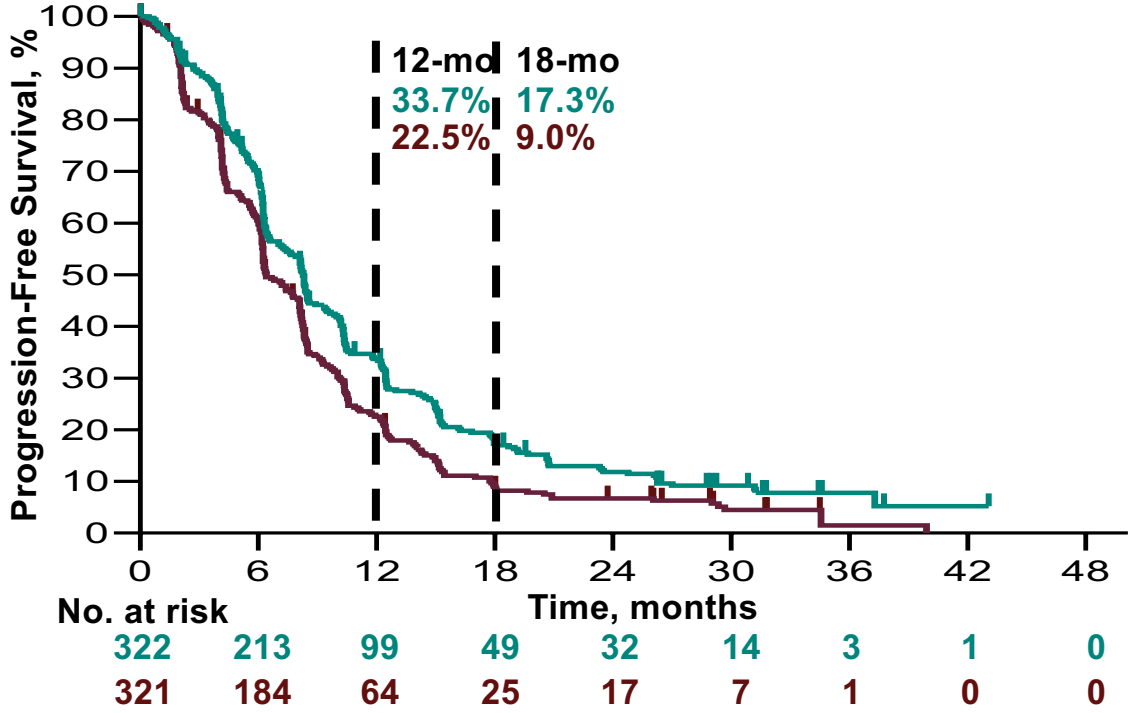
Colombo N, et al. ESMO 2025. Abstract LBA3; Monk B, et al. SGO 2026

PFS in CPS ≥1 and ITT Populations at Final Analysis

CPS ≥1 Population	Events	Median, mo (95% CI)	HR[a] (95% CI)
Pembro Arm	84.6%	8.3 (7.0–9.5)	0.76 (0.62–0.93)
Placebo Arm	88.8%	7.2 (6.2–8.1)	



ITT Population	Events	Median, mo (95% CI)	HR[a] (95% CI)
Pembro Arm	85.7%	8.3 (7.2–8.6)	0.73 (0.62–0.87)
Placebo Arm	89.1%	6.4 (6.2–8.1)	

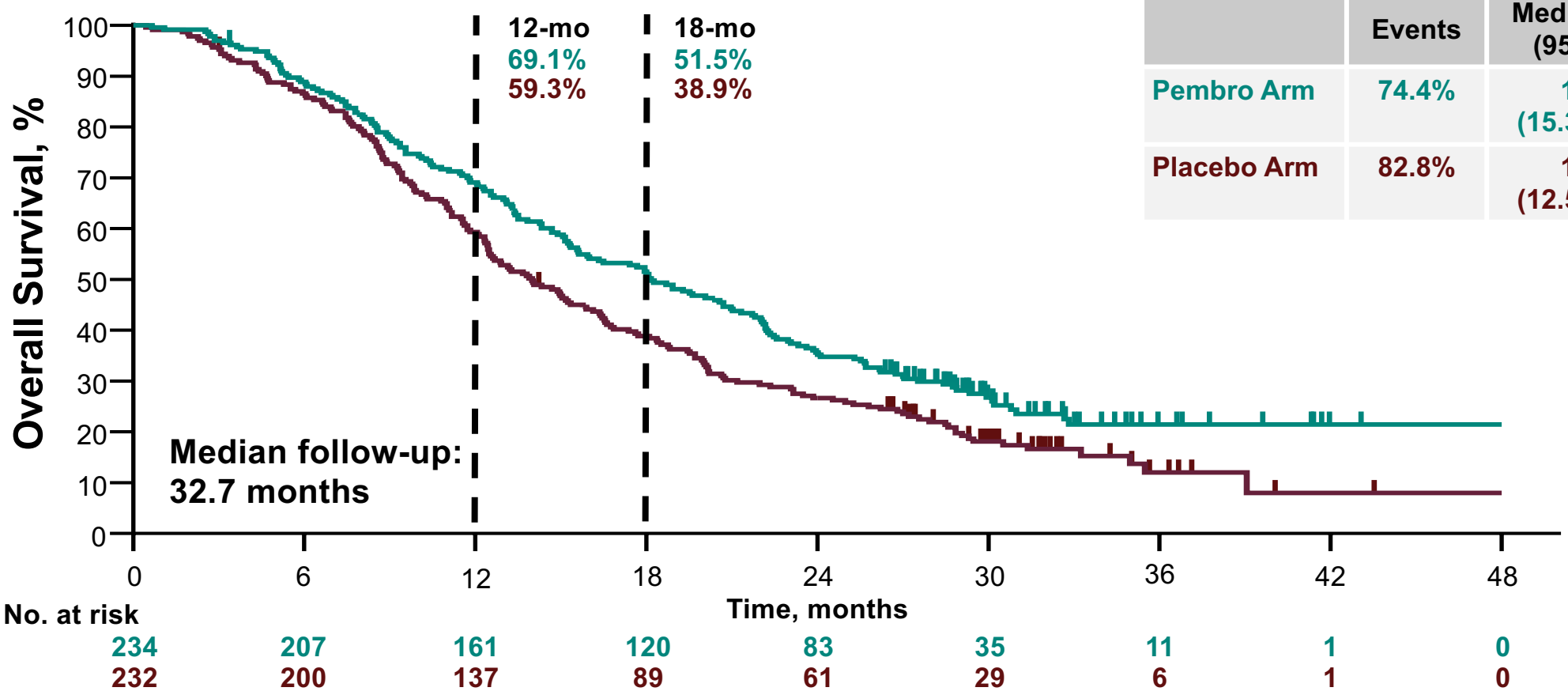


Median follow-up: 32.7 months

Monk SGO 2026

Response assessed per RECIST v1.1 by investigator review. [a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors.
Data cutoff date: September 5, 2025.

OS in CPS ≥1 Population at Final Analysis

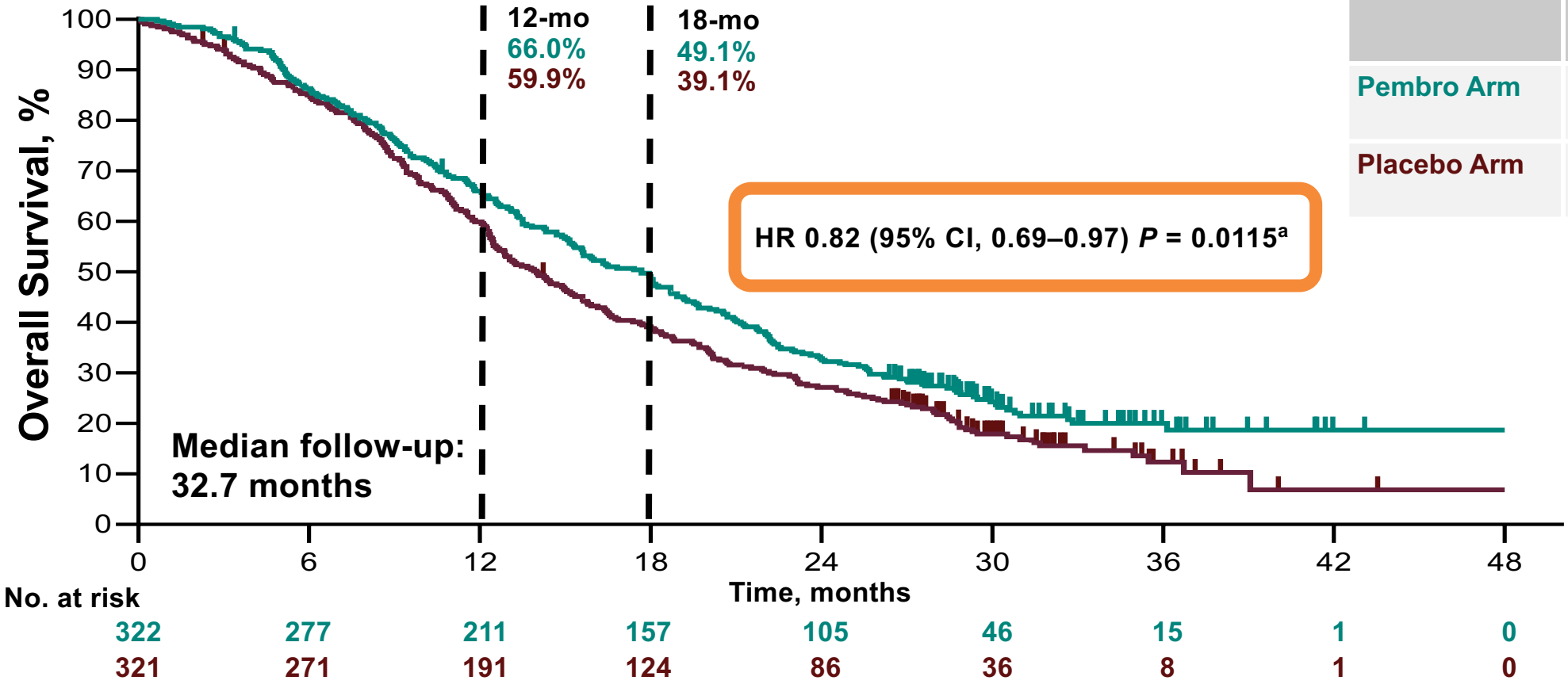


	Events	Median, mo (95% CI)	HR (95% CI)
Pembro Arm	74.4%	18.2 (15.3–21.3)	0.76 (0.62–0.93)
Placebo Arm	82.8%	14.0 (12.5–16.1)	

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: September 5, 2025.

Monk SGO 2026

OS in ITT Population at Final Analysis

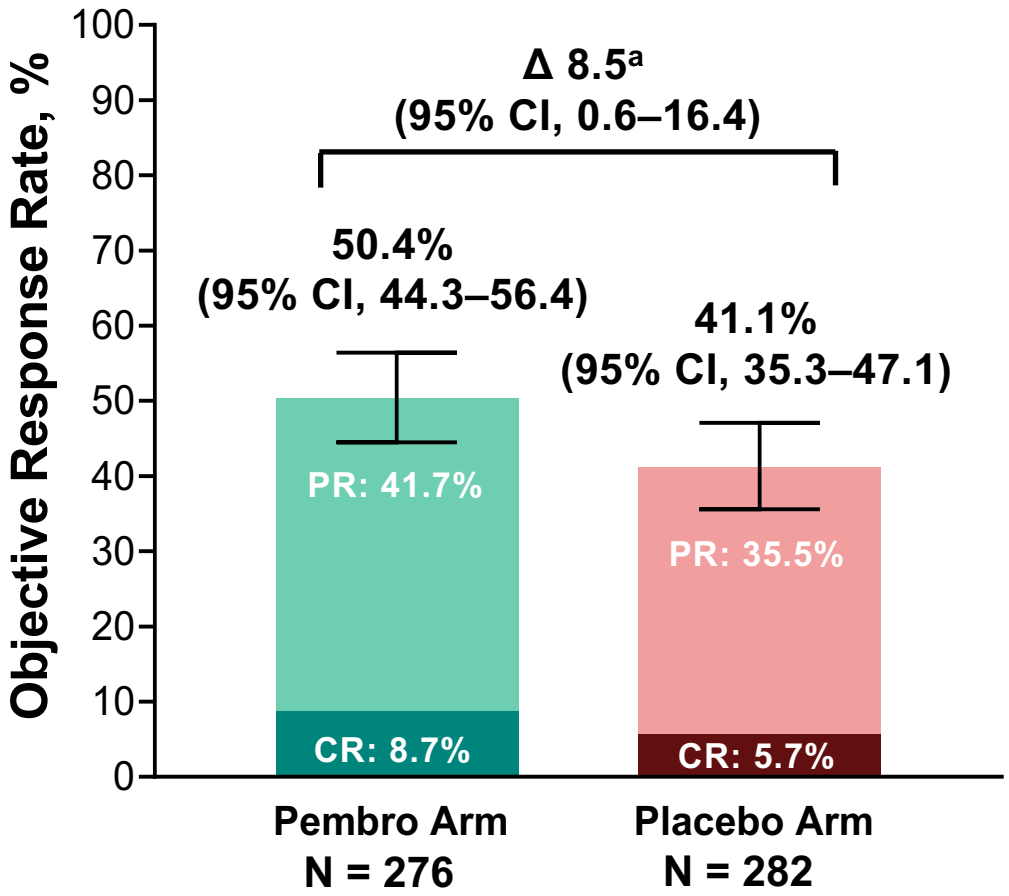


	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	76.7%	17.7 (15.2–19.2)
Placebo Arm	82.9%	14.0 (12.5–15.6)

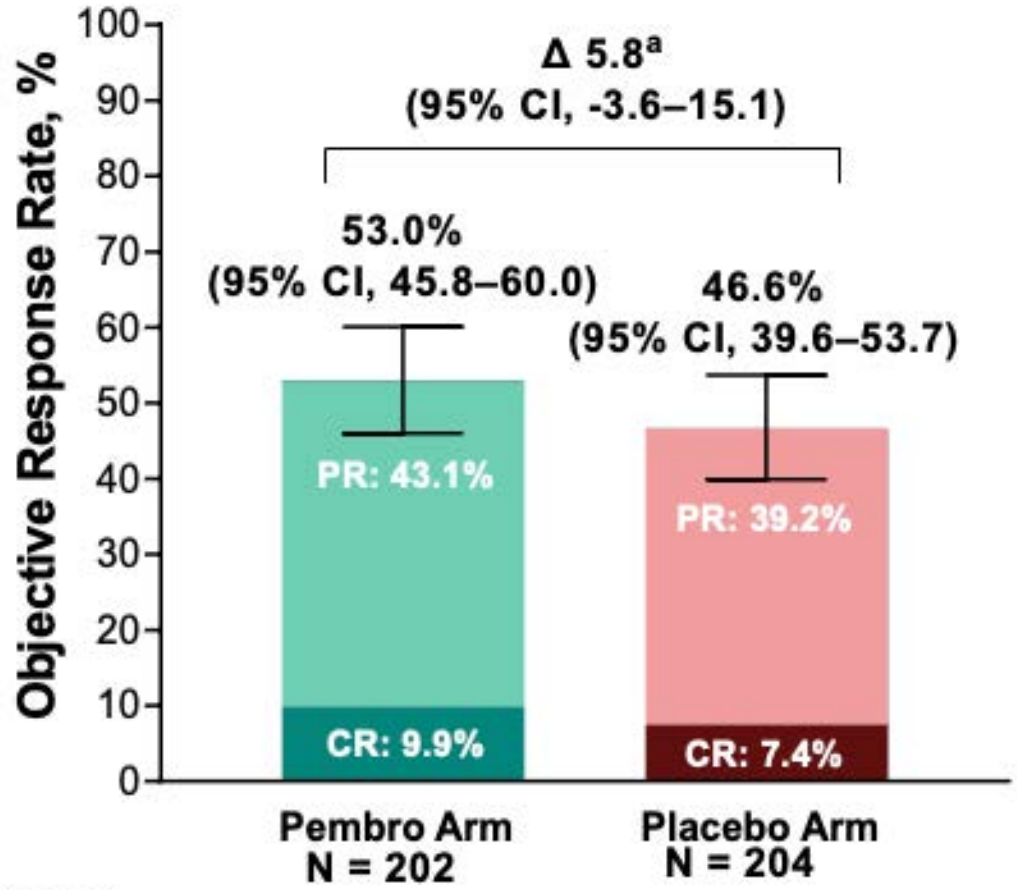
[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. The observed p-value crossed the prespecified nominal boundary of 0.0242 at this planned final analysis. Data cutoff date: September 5, 2025.

Monk SGO 2026

FINAL ANALYSIS
ORR ITT Population



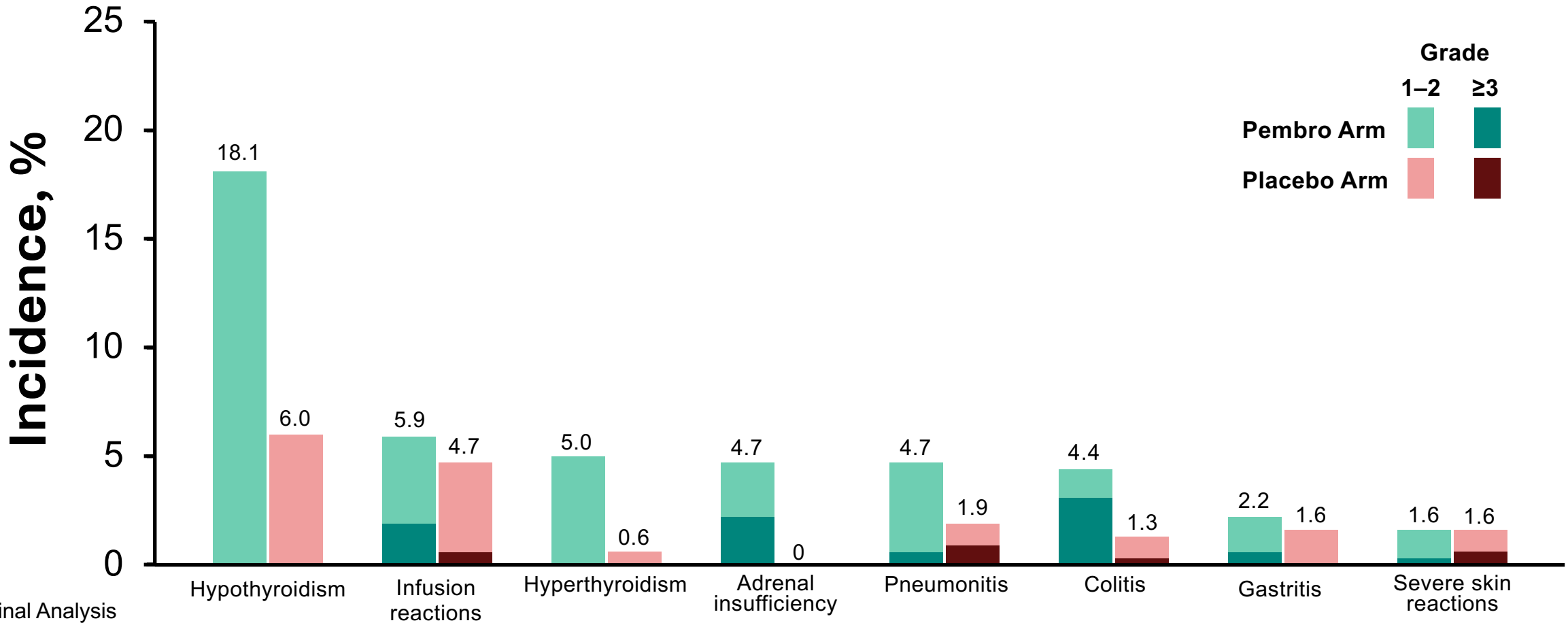
ORR CPS ≥1



- Final Analysis
- Monk SGO 2026

Response assessed per RECIST v1.1 by investigator review. [a]Delta estimated using Miettinen & Nurminen method stratified by the randomization stratification factors. Data cutoff date: September 5, 2025.

Immune-Mediated AEs and Infusion Reactions, Incidence ≥5 Participants in Either Arm*



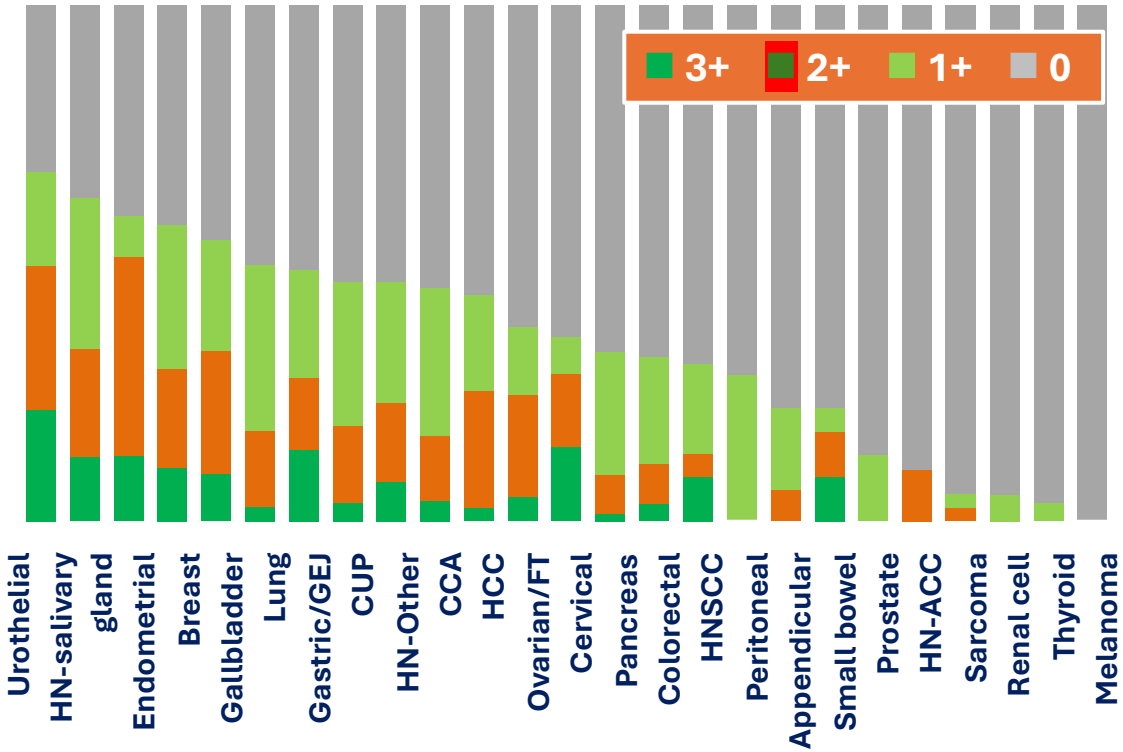
- Final Analysis
- Monk SGO 2026

Events were based on a list of preferred terms intended to capture the known risks of pembrolizumab and considered regardless of attribution to treatment by the investigator.
Data cutoff date: September 5, 2025.

ADCs

What Is the Incidence of HER2 Expression Across Solid Tumors?

Distribution of HER2 IHC expression levels across cancers



HER2 expression across solid tumors

Cancer types		Distribution of HER2 IHC scores across cancers				
		HER2 IHC expression levels, %				
		0	1+	2+	3+	Total, n
Breast		43	28	19	10	2611
Gastric/GEJ		51	21	14	14	208
Biliary tract	CCA	55	29	12	4	122
	Gallbladder	46	21	24	9	33
	Ampullary	50	33	17	0	6
GI—lower	Colorectal	68	21	8	3	577
	Appendiceal	78	16	6	0	50
	Small bowel	78	4	9	9	23
	Anal	100	0	0	0	5
GI—other	Pancreas	67	24	8	2	67
	HCC	56	19	25	0	32
	Mixed CCA and HCC	67	33	0	0	6
Gynecological	Endometrial	41	8	39	13	127
	Ovarian/FT	62	13	20	5	85
	Peritoneal	71	29	0	0	14
	Cervical	64	7	14	14	14
	Vaginal	100	0	0	0	2
	Vulvar	29	14	43	14	7
Head and neck	HN-ACC	90	0	10	0	10
	HN-Other	54	23	15	8	13
	HN-salivary gland	38	30	21	13	48
	HNSCC	70	17	4	9	23
Genitourinary	Urothelial	32	18	28	21	176
	Prostate	87	13	0	0	31
	Renal cell	95	5	0	0	19
	Germ cell/testicular	100	0	0	0	3
	Penile	100	0	0	0	1
Thoracic	Lung	50	32	15	3	211
	Thymic	100	0	0	0	4
Skin	Melanoma	100	0	0	0	14
	Non-melanoma skin	71	14	14	0	7
Other	Adrenal	67	0	33	0	3
	CUP	54	28	15	4	54
	CNS	50	50	0	0	2
	Sarcoma	95	3	3	0	37
	Thyroid	96	4	0	0	56
Total						

CCA = cholangiocarcinoma; CNS, central nervous system; CUP = cancer of unknown primary; FT = fallopian tube cancer; GEJ = gastroesophageal; GI = gastrointestinal; HCC = hepatocellular carcinoma; HER2 = human epidermal growth factor receptor 2; HN = head and neck; HN-ACC = head and neck-adenoid cystic carcinoma; HNSCC = head and neck squamous cell carcinoma; IHC = immunohistochemistry. *Row percentages were used in the construction of this table.

Uzunparmak, B. et al. *Ann Oncol*, 2023;34:1035-1046.

Prevalence of HER2 expression in Ovarian Cancer

- Largest study GINECO study of 320 patients (Tuefferd M, et al. PLoS One 2007)
  - Evaluated with IHC and FISH, using breast criteria (complete membrane staining)
  - HER2 2+ or 3+ was 13%
  - Potentially under-representation given breast criteria used

- Additional studies estimate up to ~20% prevalence of HER2 2+/3+
  - Chao WR, et al. Virchows Arch 2022 – HER2 in mucinous ovarian carcinoma
    - HER2 positive 18.2% by gastric criteria, 14.2% by breast criteria
  - Ersoy E, et al. Int J Gynecol Pathol 2022 – 100 cases high-grade serous carcinoma
    - 81 cases HER2 0/1+ and 18 were 2+ and 1 was 3+
  - Bookman MA, et al. J Clin Oncol 2003 – phase II GOG study of trastuzumab
    - Utilized complete membrane staining criteria
    - 11.4% were HER2 2+/3+ and 19% were HER2 1+

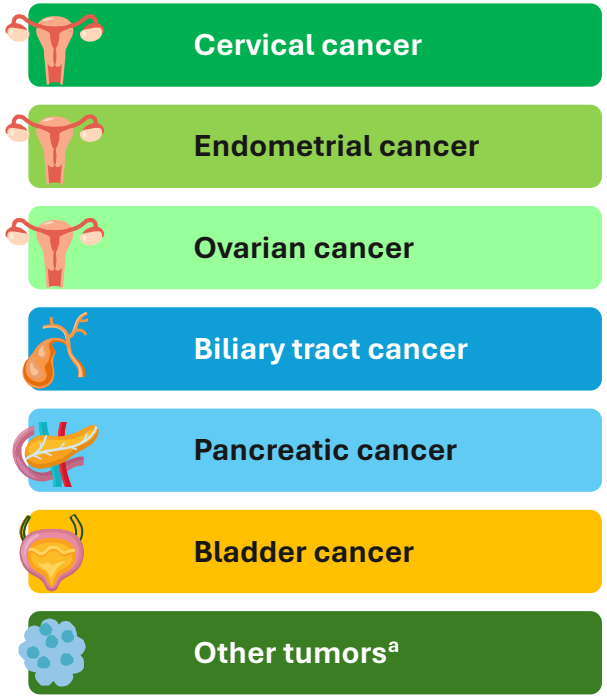
Phase 2 DESTINY-PanTumor02 Study of T-DXd for HER2-Expressing Solid Tumors

Tumor types were selected based on epidemiological frequency, prevalence of HER2 expression, and unmet medical need

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Hercep Test if local test not feasible (ASCO/CAP gastric cancer guidelines)
- Prior HER2-targeting therapy
- ECOG/WHO PS 0–1 restricted in strenuous activity

T-DXd
5.4 mg/kg
Q3W

n = 40 per cohort planned
(cohorts with no objective responses in the first 15 patients were to be closed)



Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR
- DCR
- PFS
- OS
- Safety

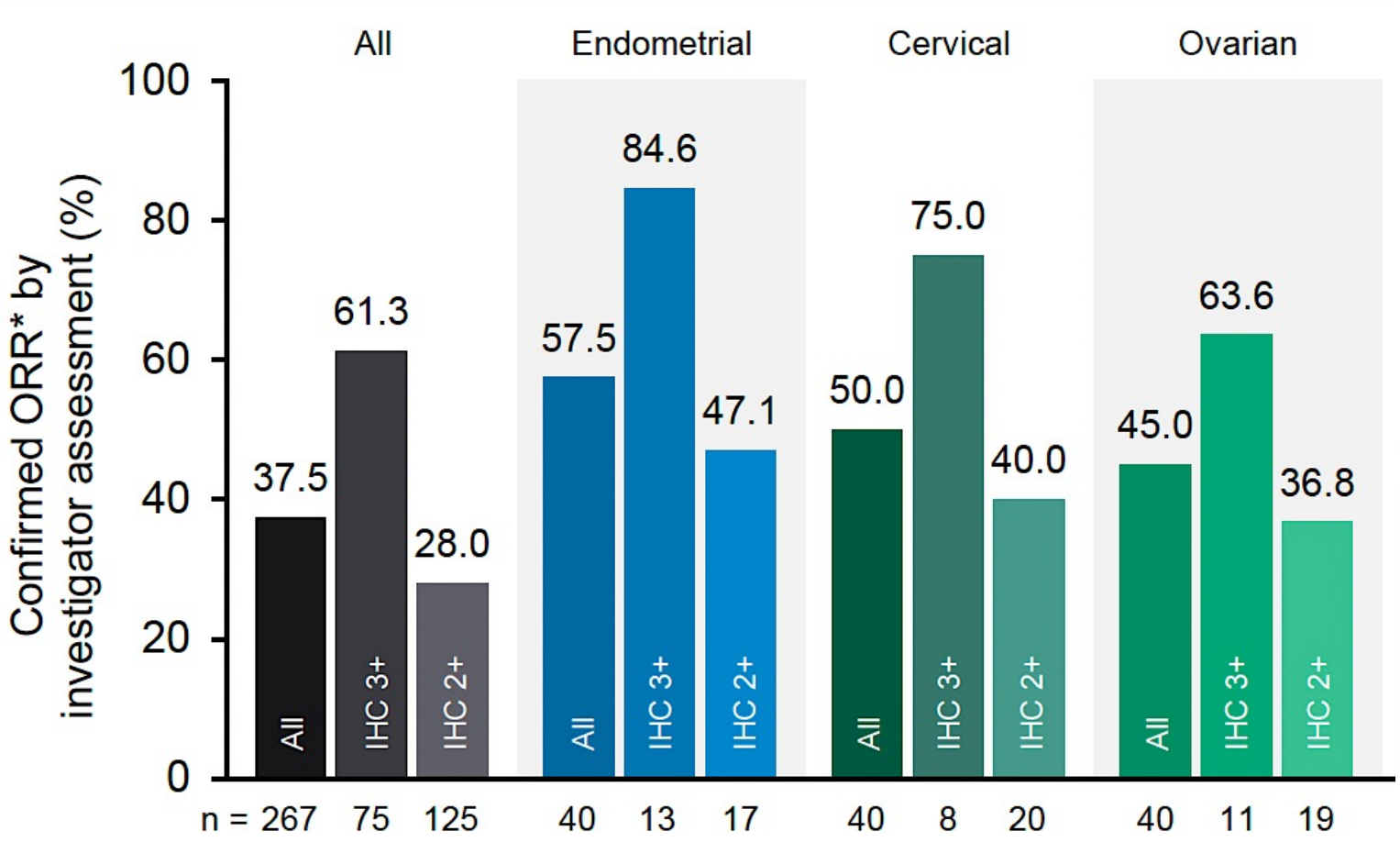
[a]Other tumors cohort: Salivary gland cancer (n = 19), malignant neoplasm of unknown primary site (n = 5), extramammary Paget disease (n = 3), cutaneous melanoma (n = 2), oropharyngeal neoplasm (n = 2), adenoid cystic carcinoma, head and neck cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, intestinal adenocarcinoma, appendiceal adenocarcinoma, esophageal squamous cell carcinoma, testicular cancer, and vulvar carcinoma (all n = 1).

2L+ = second-line or beyond; ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan; WHO = World Health Organization.

Makker, ESMO 2025; Makker SGO 2026

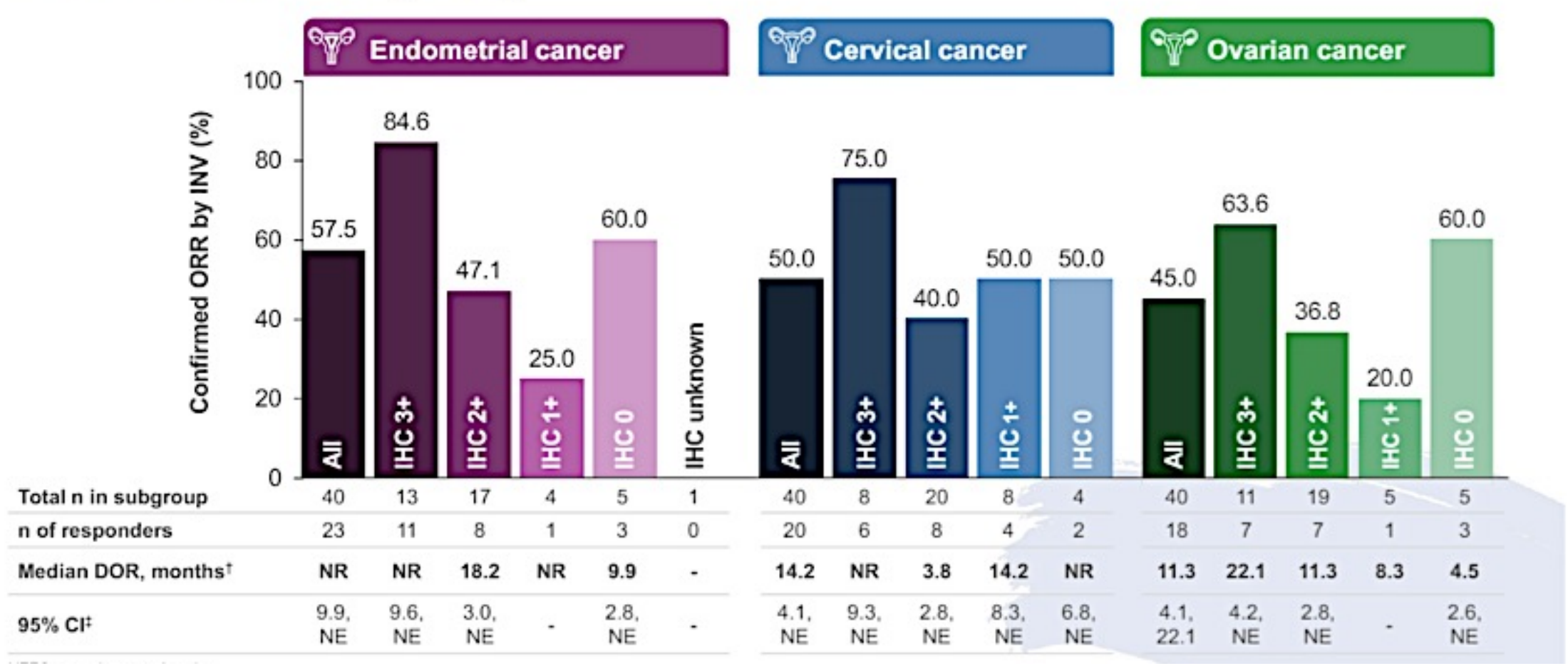
DESTINY-PanTumor02: Trastuzumab Deruxtecan for HER2+ Tumors

ORR by Central HER2 IHC Status



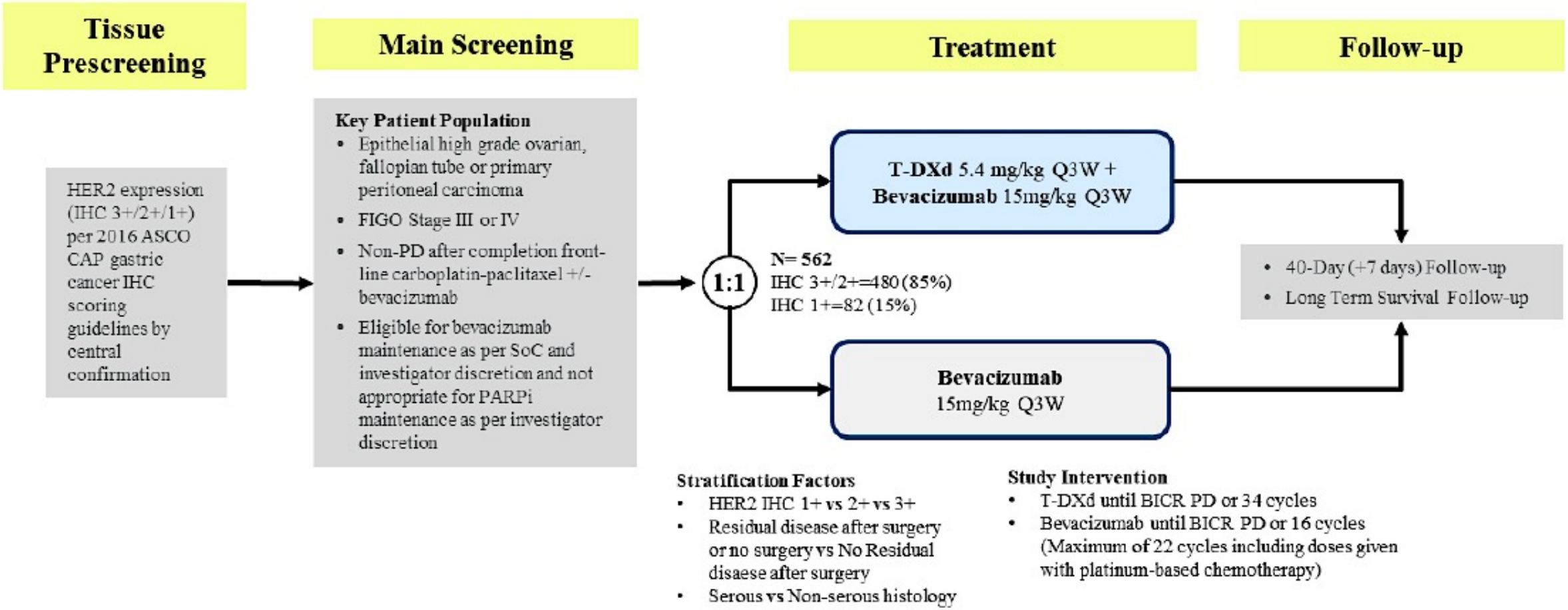
Makker, ESMO 2025; Makker SGO 2026

DESTINY-PanTumor02 - Response by HER2 Expression Level (Central) Gyn Cohorts



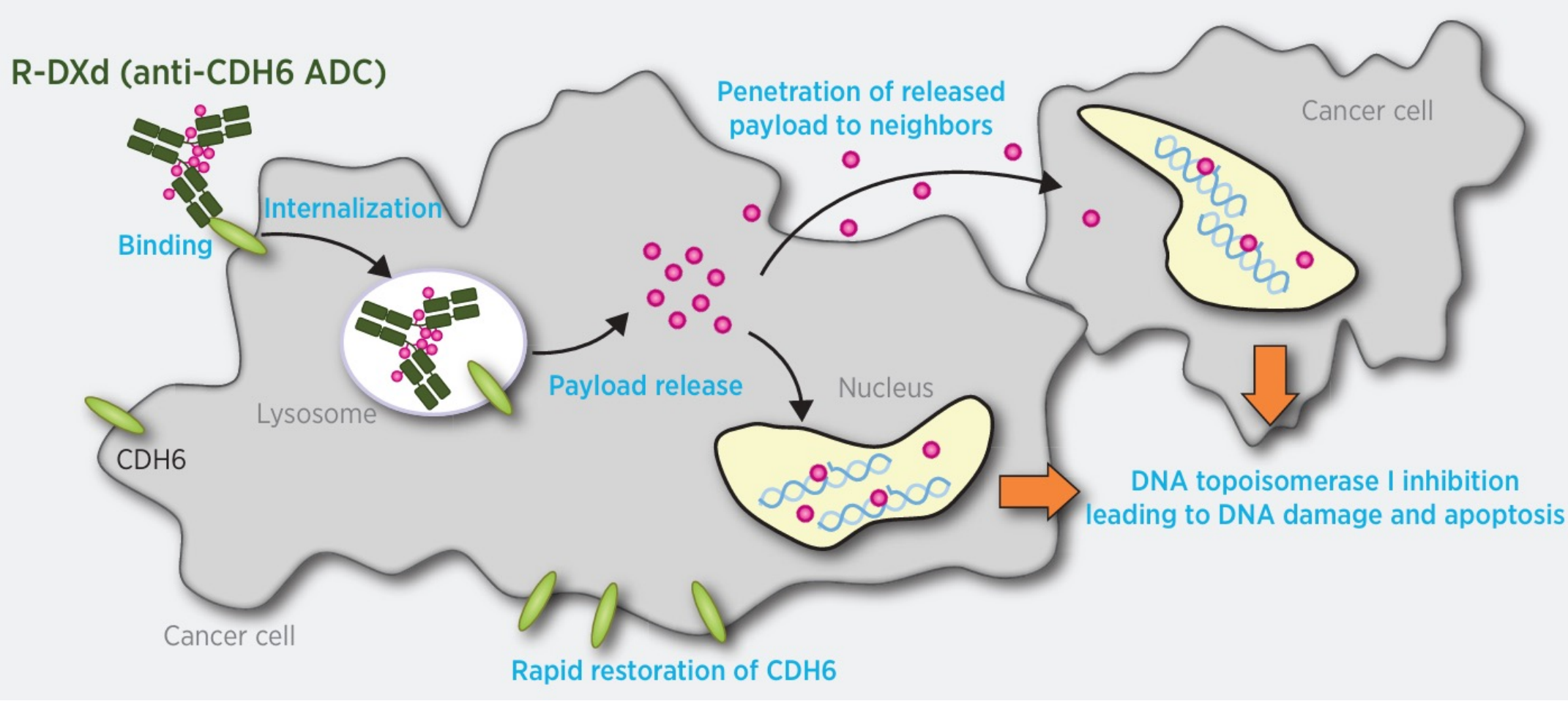
Lee JY, et al. International Gynecological Cancer Society 2023; November 5-7, 2023; Seoul, Korea.

GOG 3112/ENGOT-ov89
Phase 3 DESTINY-Ovarian01: T-DXd + Bevacizumab as 1L Maintenance Therapy in HER2-Expressing Ovarian Cancer



NCT06819007

R-DXd: Mechanistic Effects and Biologic Rationale



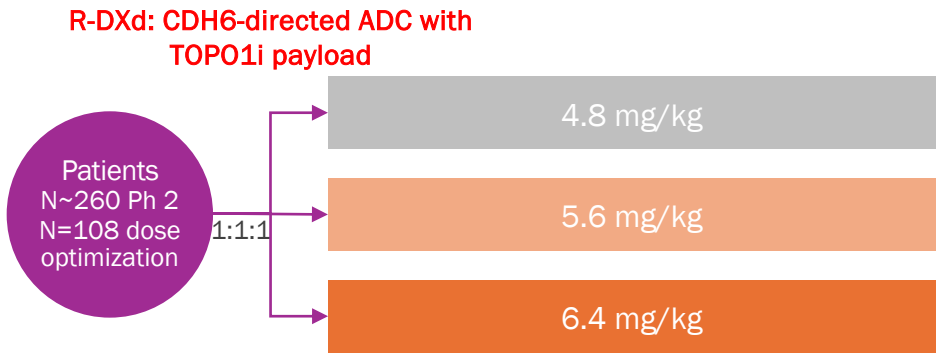
Suzuki H et al. Mol Cancer Ther. 2024;23(3):257-271

REJOICE-Ovarian-01: Phase 2 Dose-Optimization of Cadherin 6-Targeting R-DXd in PROC

Study Design and Patients

Key Eligibility Criteria

- High-grade serous/endometrioid OC, primary peritoneal, or fallopian tube cancer
- Platinum-resistant disease with 1-3 prior LOTs, including Bev and Mirv
- ECOG PS 0-1
- No prior CDH6-targeting agents or ADCs with a linked DXd and no selection by tumor CDH6 expression



Primary endpoint: ORR per BICR
Key secondary endpoints: ORR per INV, DOR per BICR and INV

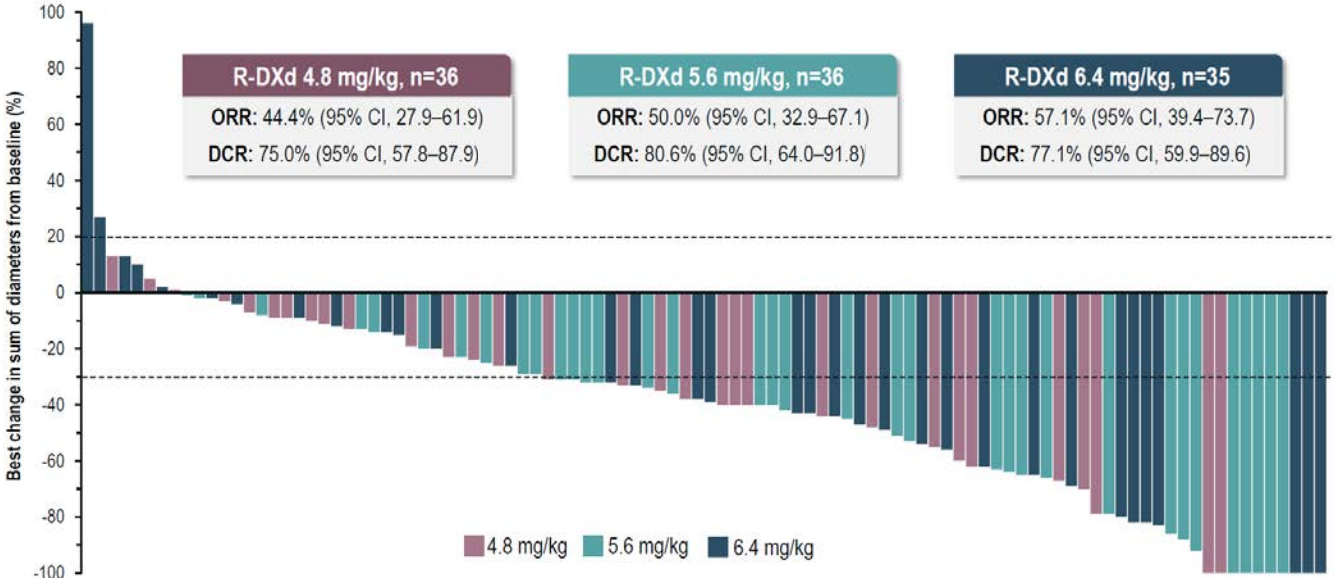
Patient Characteristics	R-DXd 4.8-6.4 mg/kg[a] (N=107)
Median age (range), years	60 (34-81)
pLOT, n (%)	
Bev	89 (83.2)
PARPi	75 (70.1)
Mirv	3 (2.8)
Last platinum-free interval, n (%)	
<3 months	47 (43.9)
3-6 months	60 (56.1)
Tumor CDH6 membrane positivity, n (%)	
Any positivity	95 (94.1)
<75% positivity	41 (40.6)
≥75% positivity	60 (59.4)
ECOG PS, n (%)	
0	61 (57.0)
1	46 (43.0)

Ray-Coquard IL, et al. ESMO 2025. Abstract LBA42.

REJOICE-Ovarian-01: Phase 2 Dose-Optimization of Cadherin 6-Targeting R-DXd in PROC

Key Efficacy and Safety

Antitumor response assessed by BICR per RECIST 1.1



Key Efficacy	R-DXd 4.8 mg/kg (n=36)	R-DXd 5.6 mg/kg (n=36)	R-DXd 6.4 mg/kg (n=35)	R-DXd 4.8-6.4 mg/kg (N=107)
Median follow-up (95% CI), months	5.6 (4.7-6.3)	5.6 (4.6-5.8)	5.2 (4.9-5.8)	N/A
ORR, % (95% CI)	**44.4 (27.9-61.9)**	**50.0 (32.9-67.1)**	**57.1 (39.4-73.7)**	**50.5 (40.6-60.3)**
DCR, % (95% CI)	**75.0 (57.8-87.9)**	**80.6 (64.0-91.8)**	**77.1 (59.9-89.6)**	**77.6 (68.5-85.1)**

Safety	R-DXd 4.8 mg/kg (n=36)	R-DXd 5.6 mg/kg (n=36)	R-DXd 6.4 mg/kg (n=35)	R-DXd 4.8-6.4 mg/kg (N=107)
TEAEs				
Any grade, %	35 (97.2)	36 (100)	35 (100)	106 (99.1)
Grade ≥3,%	16 (44.4)	20 (55.6)	20 (57.1)	56 (52.3)
TEAEs leading to				
Discontinuation, %	3 (8.3)	0	3 (8.6)	6 (5.6)
Dose reduction, n (%)	5 (13.9)	4 (11.1)	11 (31.4)	20 (18.7)
Dose delay, n (%)	8 (22.2)	7 (19.4)	10 (28.6)	25 (23.4)
Gr ≥3 ILD/pneumonitis, n (%)	1 (2.8)	0	0	1 (0.9)

Ray-Coquard IL, et al. ESMO 2025. Abstract LBA42.

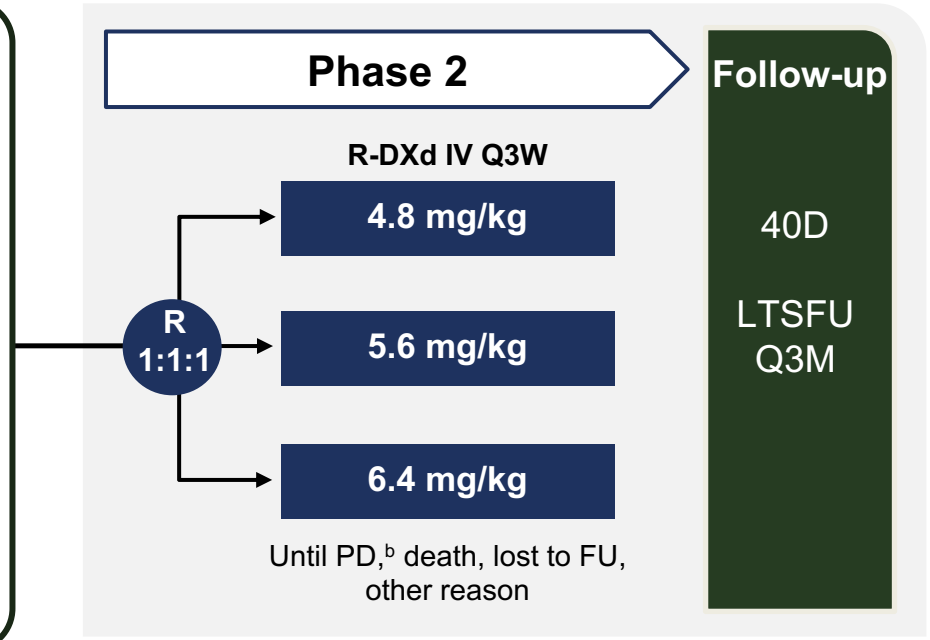
REJOICE-Ovarian01/GOG-3096: Phase 2/3 Randomized Study of R-DXd in Platinum-Resistant EOC

Key eligibility criteria:

- High-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer
- 1−3 prior LOT (inc. bevacizumab)
- Platinum-resistant disease
- Prior MIRV if high FRα[a]
- ECOG PS 0−1
- No prior CDH6-targeting agents or ADCs with linked TOPO I inhibitor
- Patients with primary platinum-refractory disease are not eligible

Stratification:

- Number of prior LOT (1 vs 2/3)
- CDH6 expression (high vs low)
- TPC (paclitaxel vs others; *Ph 3 only*)

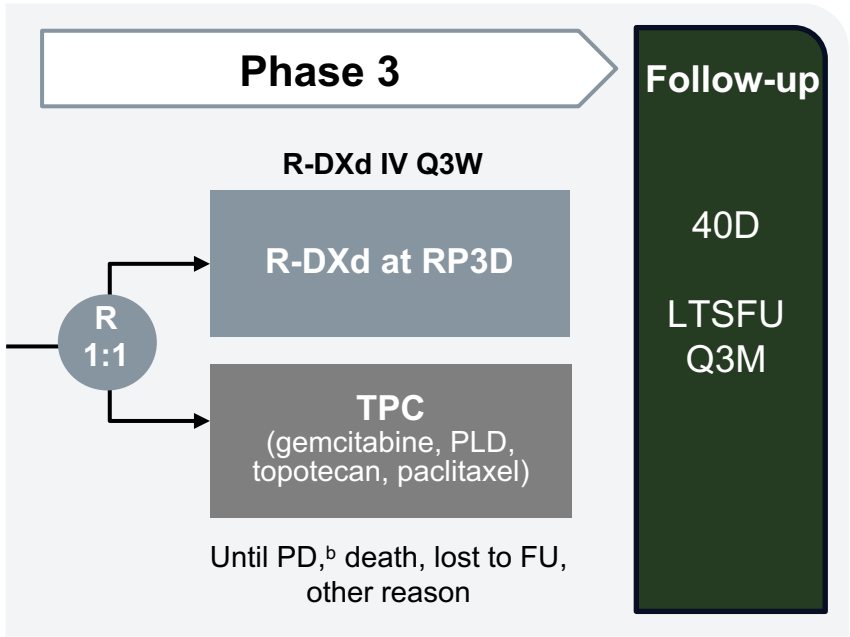


Primary endpoint:

- ORR per BICR[b]

Key secondary endpoints:

- ORR per inv[b]
- DOR



Primary endpoints:

- ORR per BICR[b]
- PFS per BICR[b]

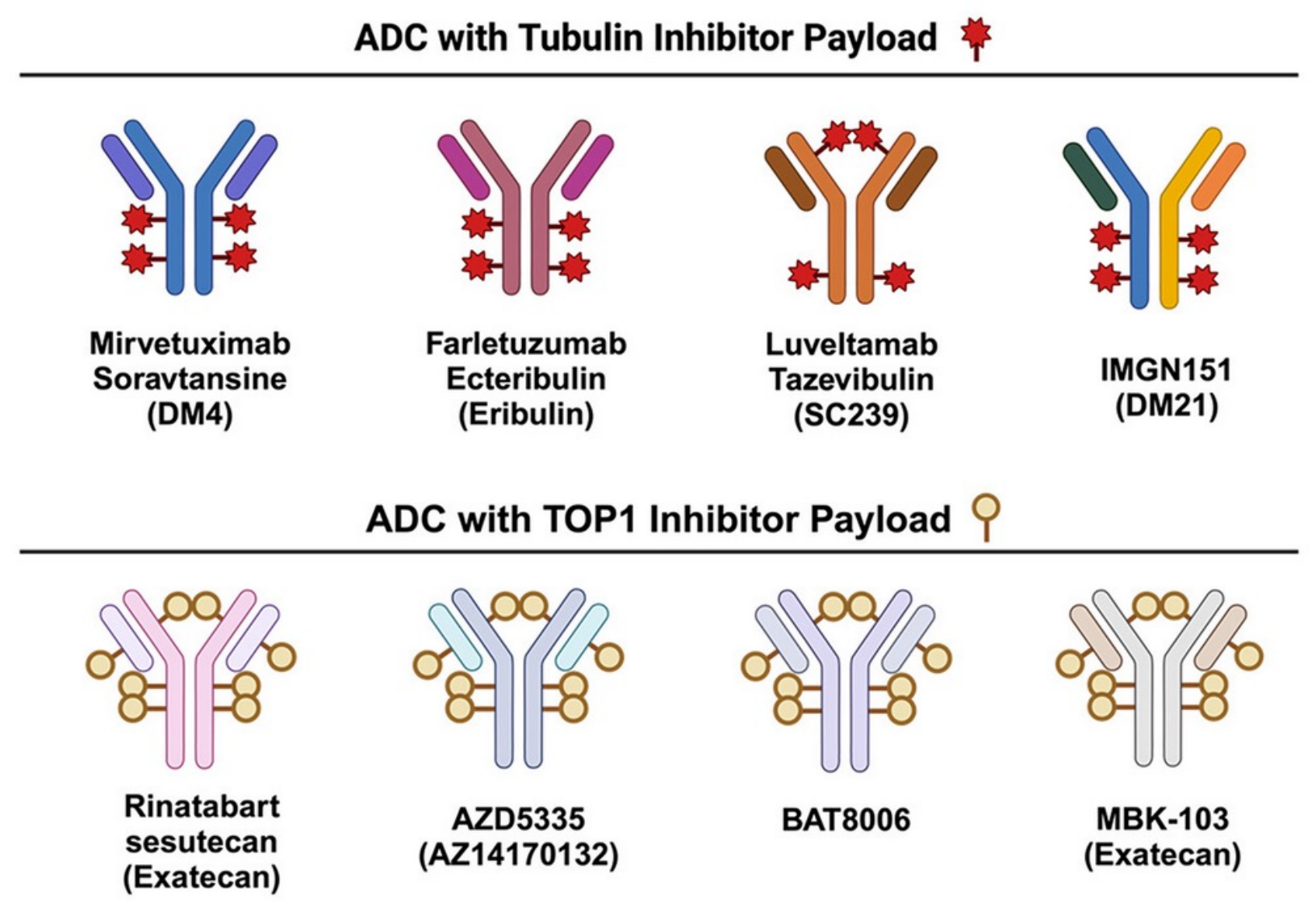
Key secondary endpoints:

- OS
- QOL

NCT06161025

NCT06161025. Accessed from: https://clinicaltrials.gov/study/NCT06161025?term=NCT06161025&rank=1; Ray-Coquard IL, et al. ESMO 2025. Abstract LBA42.

Schematic Diagrams of Approved and Investigational FRα-Directed Antibody-Drug Conjugates



Liu Y et al. *mAbs*, *17*(1). https://doi.org/10.1080/19420862.2025.2470309.

RTP RESEARCH TO PRACTICE

Recent Ovarian Cancer ADC Trials

Drug Name	Target	Payload	Preliminary Efficacy (ORR)*	Presented At
Torvutatug Samrotecan (AZD5335)	FRalpha	TOPO1 inhibitor	53.6% (ITT)	ESMO
Sofetabart Mipitecan (LY4170156)	FRalpha	TOPO1 inhibitor	33 – 61%	ESMO
Raludotatug deruxtecan (R-Dxd)	CDH6	TOPO1 inhibitor	50.5%	ESMO
TUB-040	NaPi2b	TOPO1 inhibitor	50%	ESMO
DS-3939a	TA-MUC1	TOPO1 inhibitor	1 confirmed CR (N=8)	ESMO
Mo-Rez (GSK5733584)	B7-H4	TOPO1 inhibitor	31-62%	SGO
JSKN003	HER2	TOPO1 inhibitor	64.4%	ASCO
Disitamab vedotin + anlotinib	HER2	Multi-target TKI + MMAE ADC	29.4%	ESMO

***Data are NOT intended for cross-trial comparison**

Phase 3 ADC Ovarian Cancer Clinical Trials

Clinical Situation	Drug Name	Trial ID	NCT
First-line (maintenance)	Trastuzumab Deruxtecan	GOG-3112 (DESTINYOvarian-01)	NCT06819007
First-line (maintenance)	Sacituzumab Tirumotecan (Sac-TMT)	GOG-3102/ENGOT-ov85 (TroFuse-021)	NCT07318558
Platinum sensitive (maintenance)	Sofetabart Mipitecan	GOG-3133 (FRAmework-01)	NCT07213804
Platinum sensitive (treatment)	Sofetabart Mipitecan	GOG-3133 (FRAmework-01)	NCT07213804
Platinum sensitive (maintenance)	Sacituzumab Tirumotecan (Sac-TMT)	GOG-3103/ENGOT-ov84 (TroFuse-022)	NCT06824467
Platinum sensitive (maintenance)	Rinatabart Sesutecan (Rina-S)	GOG-3134 (RAINFOL-04)	NCT07225270

Phase 3 ADC Ovarian Cancer Clinical Trials

Clinical Situation	Drug Name	Trial ID	NCT
Platinum resistant	Rinatabart Sesutecan (Rina-S)	GOG-3107 (RAINFOL-O2)	NCT06619236
Platinum resistant	Raludotatug Deruxtecan (R-Dxd)	GOG-3096 (REJOICE-Ovarian-01)	NCT06161025
Platinum resistant	**Torvu**tatug **Sam**rotecan (AZD5335)	GOG-3127 (TREVI-OC-01)	NCT07218809
Platinum resistant	**Sofet**abart **M**ipitecan (LY4170156)	GOG-3133 (FRAmework-01)	NCT07213804
Platinum resistant	**Mo**certatug **Rez**etecan (GSK5733584)	GOG-GOG-3132 (BEHOLD-Ovarian01)	NCT07286266

Evolving Landscape: Non-ADC Options in the PROC space

	GOG-3129/MAESTRA 1 (NCT07023672)[1]	GOG-3066/DENALI[2] (NCT05128825)	GOG-3076/OnPrime[3] (NCT05281471)	GOG-3121/ULTIMUS-1 (NCT07109414)
MOA	CDK2 inhibitor	Wee-1 inhibitor	Oncolytic vaccinia virus-based immunotherapy	Fascin inhibitor
Prior lines	2-4 prior lines of treatment	Up to 3 prior lines (4 prior lines permitted, if prior mirvetuximab)	Unlimited prior lines	Not reported
Biomarker	Cyclin E1 overexpression	Cyclin E1 + overexpression	All comers	All comers

	PYNNACLE (NCT04585750)[4]	MUC16xCD3 Bispecific (NCT06787612)
MOA	P53 reactivator	MUC16xCD3 Bispecific
Prior lines	Unlimited prior lines	Not Reported
Biomarker	TP53 Y220C mutation	Elevated CA125

1. Thaker PH, et al. Annals of Oncology. 2025 Sep 1;36:S790; 2. Leary A, et al. Molecular Cancer Therapeutics. 2025 Oct 22;24(10_Supplement):B013; 3. Holloway RW, et al. International Journal of Gynecological Cancer. 2023 Sep 1;33(9):1458-63; 4. Alison M. Schram et al. J Clin Oncol 2025, 43, TPS11581-TPS11581.

QUESTIONS?

Module 4: Relapsed/Refractory (R/R) Multiple Myeloma (MM)

Integrating CAR T-Cell Therapy and Bispecific Antibodies into the Management of R/R MM — Dr Raje

Antibody-Drug Conjugates and Other Emerging Therapies for R/R MM — Dr Lee

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Module 4: Relapsed/Refractory (R/R) Multiple Myeloma (MM)

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Module 4: Relapsed/Refractory (R/R) Multiple Myeloma (MM)

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

Integrating Chimeric Antigen Receptor (CAR) T-Cell Therapy and Bispecific Antibodies into the Management of Relapsed/Refractory (R/R) Multiple Myeloma (MM)

Noopur Raje, MD

Director, Center for Multiple Myeloma

Mass General Brigham Cancer Institute

Professor of Medicine

Harvard Medical School

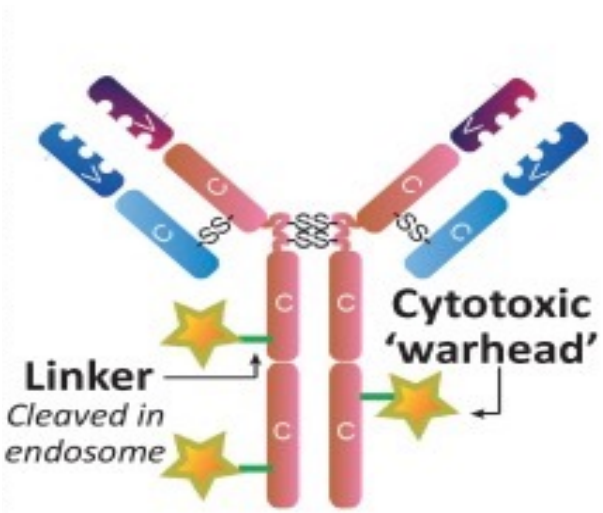
MASSACHUSETTS GENERAL HOSPITAL

Mass General Brigham
Cancer Institute

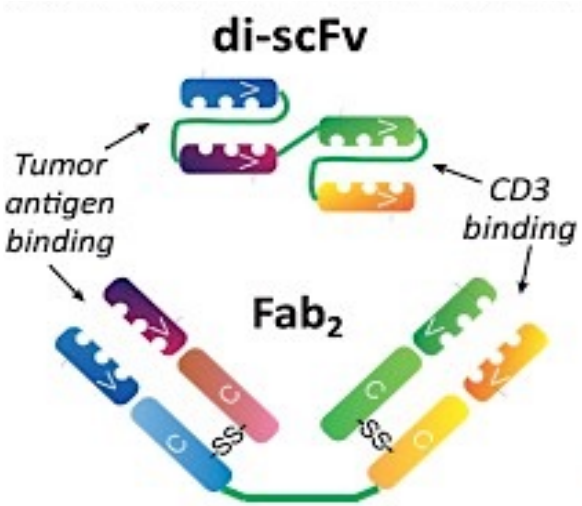
Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, GSK, Johnson & Johnson, Pfizer Inc, Sanofi

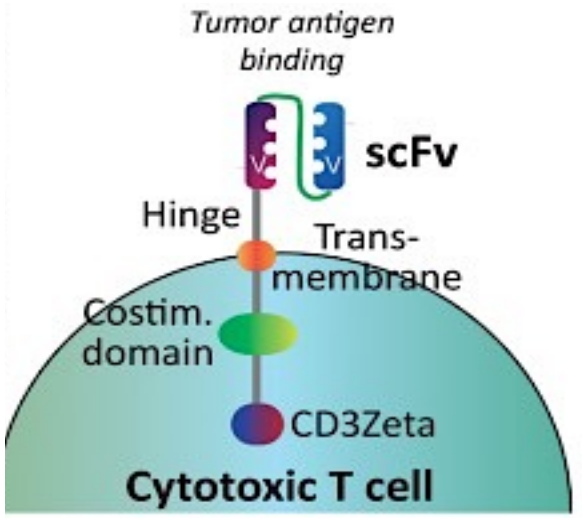
Immunotherapeutic approaches



Antibody–drug conjugate (ADC)



Bispecific T cell engaging antibodies



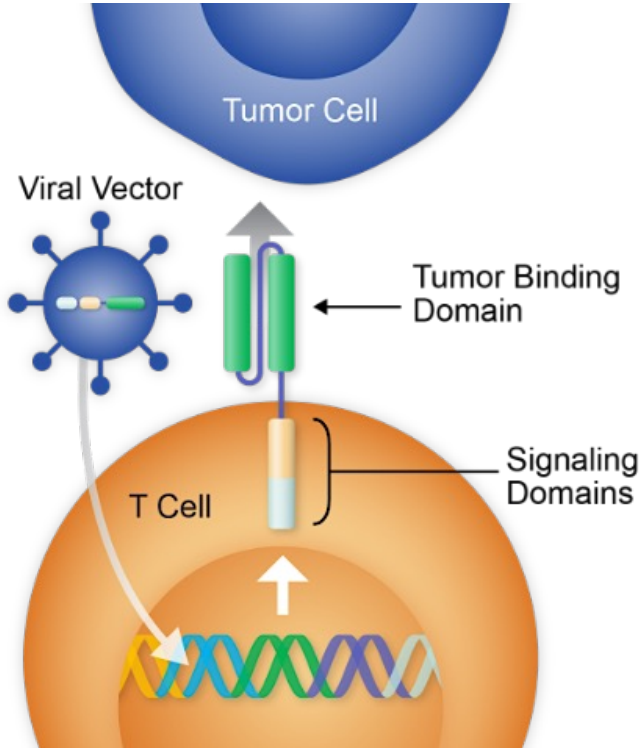
Chimeric antigen receptor (CAR) T cells

T cell redirecting therapies

Choudhry et al. Trends in Cancer 2018;4:567

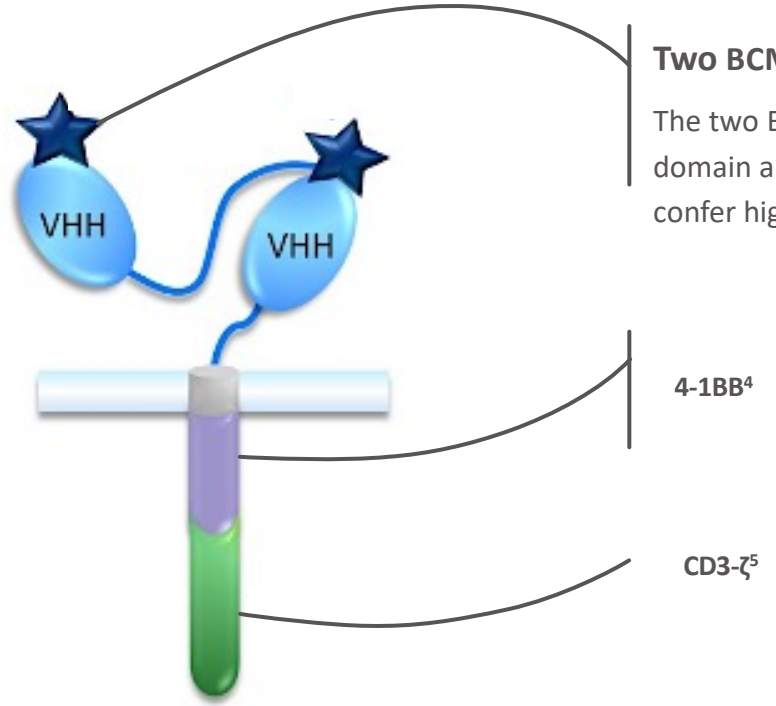
Ide-cel and Cilta-cel Constructs

Idecabtagene Vicleucel (ide-cel) CAR T



Second-generation CAR construct[1]

Ciltacabtagene Autoleucel (cilta-cel) CAR T



Dual epitope-binding CAR construct[1,2]

- BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; ide-cel, idecabtagene vicleucel; MM, multiple myeloma; MND, murine leukemia-derived promoter; scFv, single-chain variable fragment.
- 1. Raje N et al. *N Engl J Med*. 2019;380(18):1726-1737. 2. Friedman KM et al. *Hum Gene Ther*. 2018;29(5):585-601. 3. Song DG et al. *Cancer Res*. 2011;71(13):4617-4627. 4. Zhao WH et al. *J Hematol Oncol*. 2018;11(1):141. 5. Berdeja JG et al. ASCO 2020. Abstract 8505.

FDA-Approved Autologous CAR T Therapy for R/R MM

Initial approvals: patients with **R/R MM after ≥4 prior LOT, including an IMiD, PI, and an anti-CD38 mAb.**

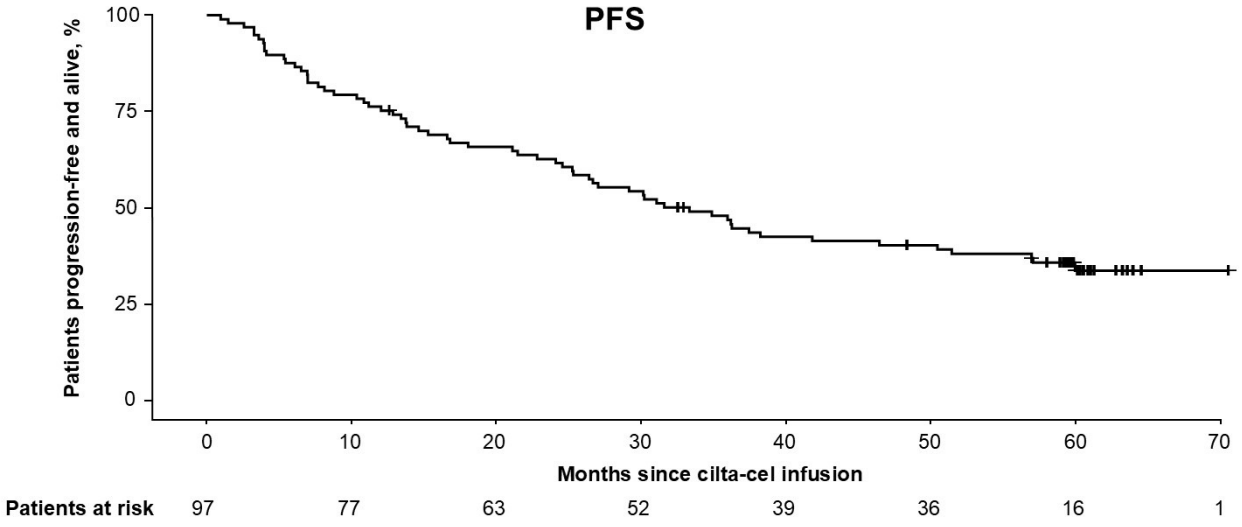
Expanded indications granted (April 2024):

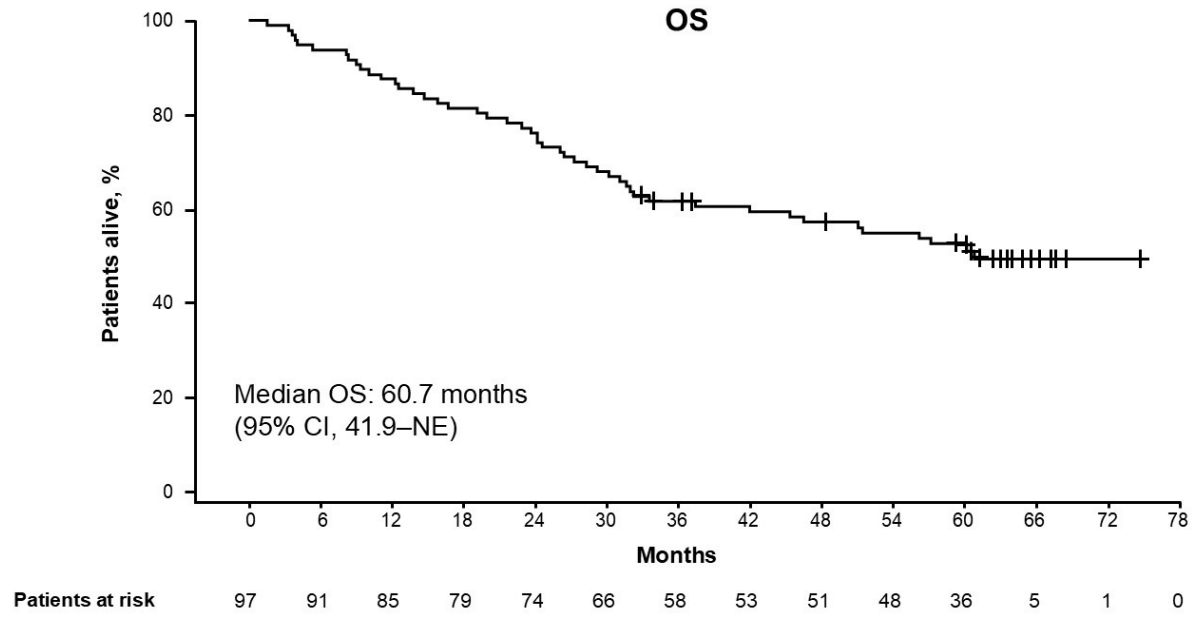
ide-cel after ≥2 prior LOT including an IMiD, PI, and an anti-CD38 mAb (KarMMa-3) and **cilta-cel after ≥1 prior LOT** including a PI and an IMiD and refractory to len (CARTITUDE-4).

Berdeja. Lancet. 2021;398:314. Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Image created from BioRender.com

CARTITUDE-1: Updated PFS and OS at ASCO 2025

Median follow-up: 61.3 mo





- 33% of patients were progression- and treatment-free at follow-up

Voorhees. ASCO 2025. Abstr 7507.

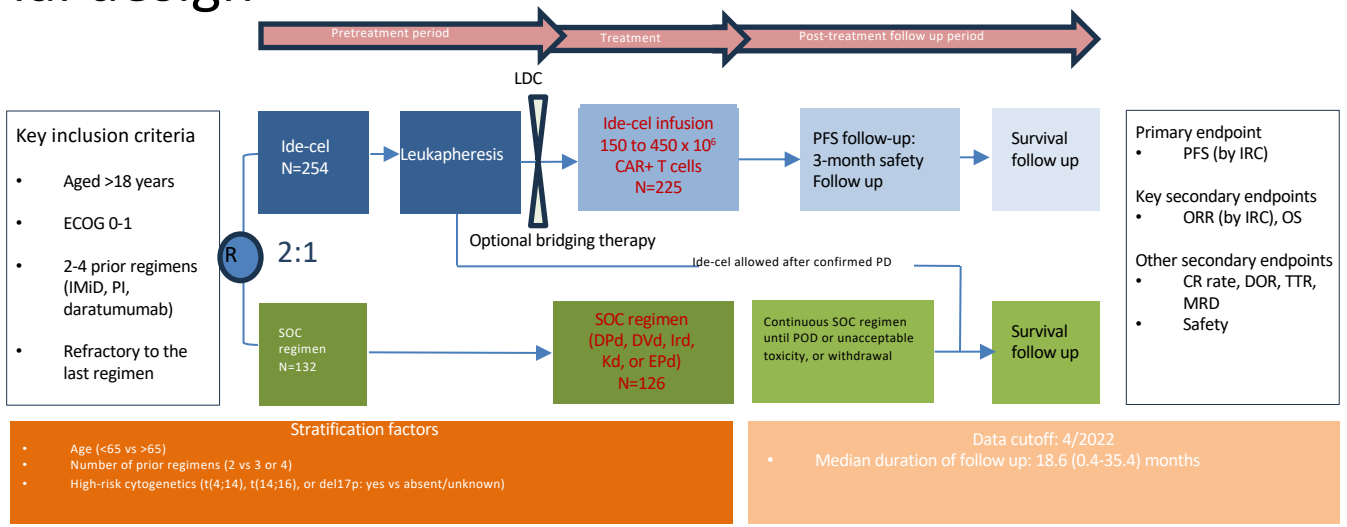
CARTITUDE-1: Long-term Safety and Future Directions

- Safety profile consistent for patients in long-term remission (no progression ≥5 yrs + ~28 mo follow-up)
  - No new cases of CNP or parkinsonism
  - 2 new cases of secondary primary malignancies – solid tumors
  - Some new cases of neurological events and grade 3 infections not related to cilta-cel
- Phase III studies for <u>newly diagnosed MM</u>
  - CARTITUDE-5: VRd + Cilta-cel vs VRd + Rd maintenance (NCT04923893)
  - CARTITUDE-6: DVrd + Cilta-cel vs DVRd + ASCT + DVRd (NCT05257083)

Voorhees. ASCO 2025. Abstr 7507.

KarMMa-3: Ide-cel vs SOC After 2-4 Lines

Trial design



Baseline characteristics

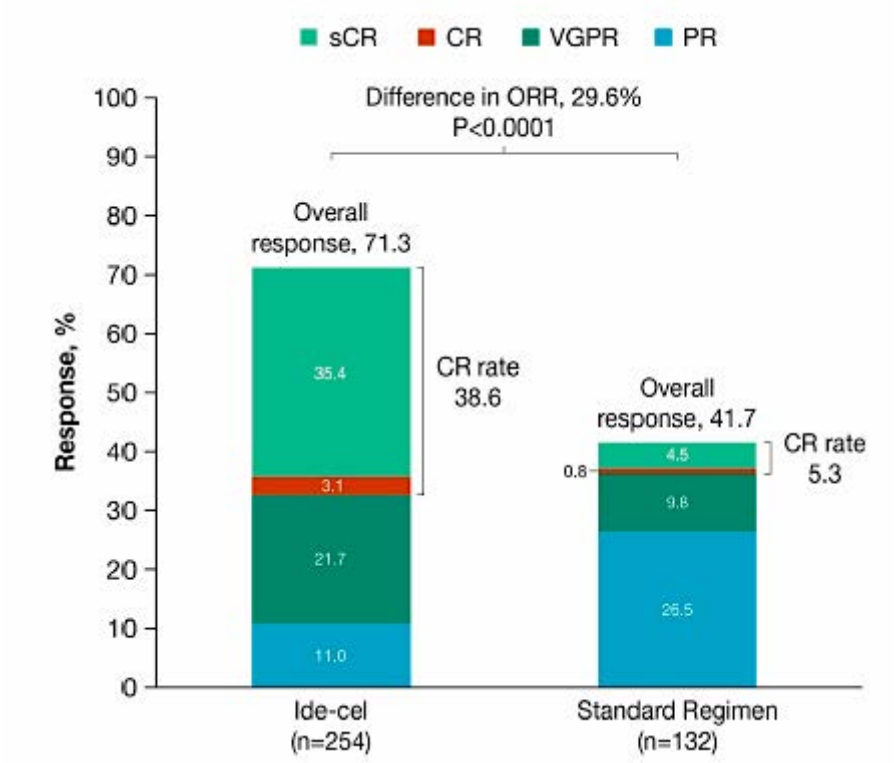
Median age	63 yrs
Median time since diagnosis	4.1 yrs
Median prior therapies	N=3
Triple-class refractoriness	66%
Daratumumab refractoriness	95%
High-risk cytogenetics	44%

Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

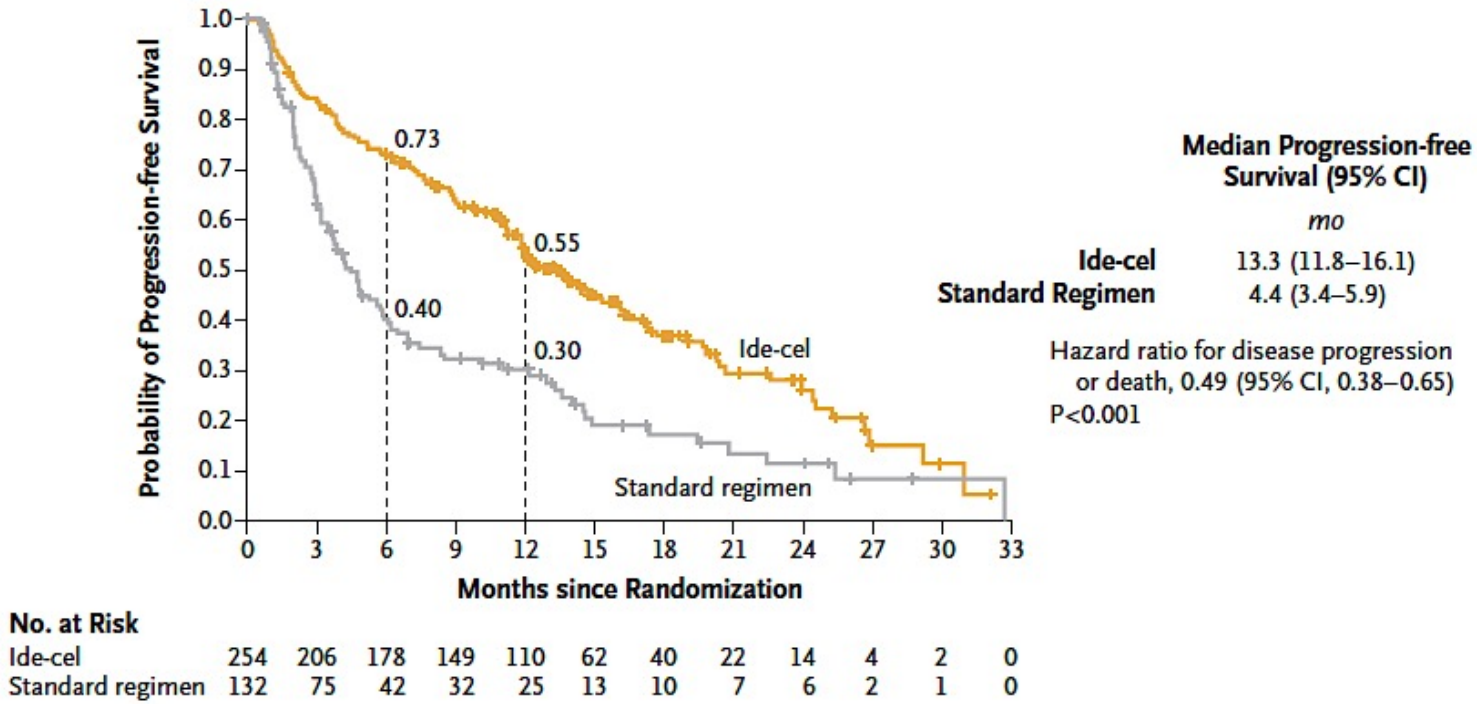
Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014

KarMMa-3: Response and PFS

Response



PFS



	Median Progression-free Survival (95% CI) *mo*
Ide-cel	13.3 (11.8–16.1)
Standard Regimen	4.4 (3.4–5.9)

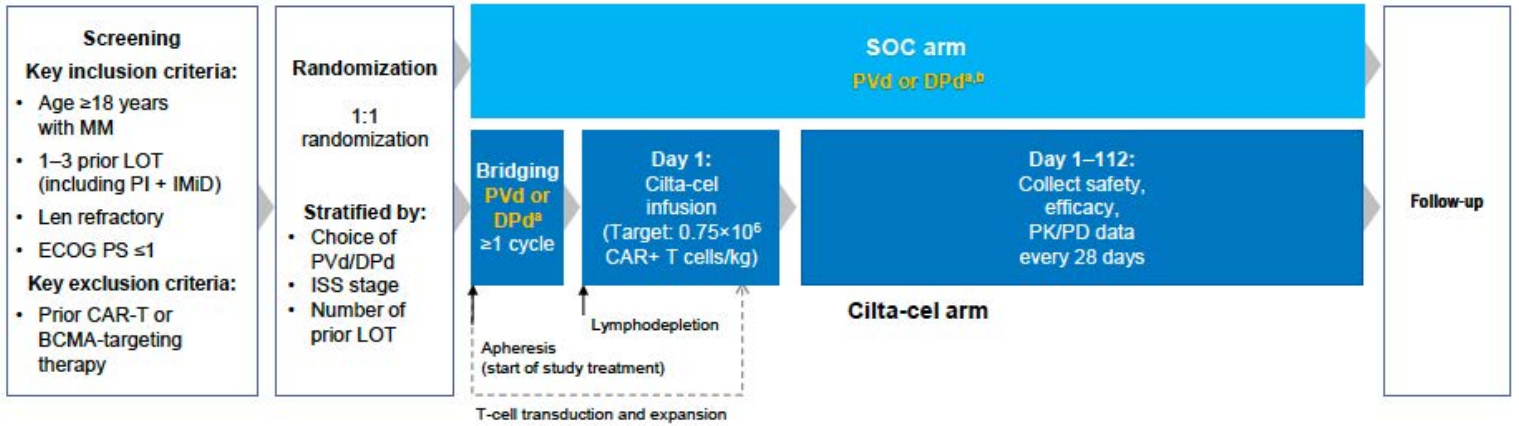
Hazard ratio for disease progression or death, 0.49 (95% CI, 0.38–0.65)
P<0.001

Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014

CARTITUDE-4: Cilta-cel vs DPd/PVd After 1-3 Lines

Trial design



Baseline characteristics

Median age	61.5 yrs
Median time since diagnosis	3 yrs
Median prior therapies	N=2
Triple-class refractoriness	14.4%
Daratumumab refractoriness	23.1%
High-risk cytogenetics	59.4%

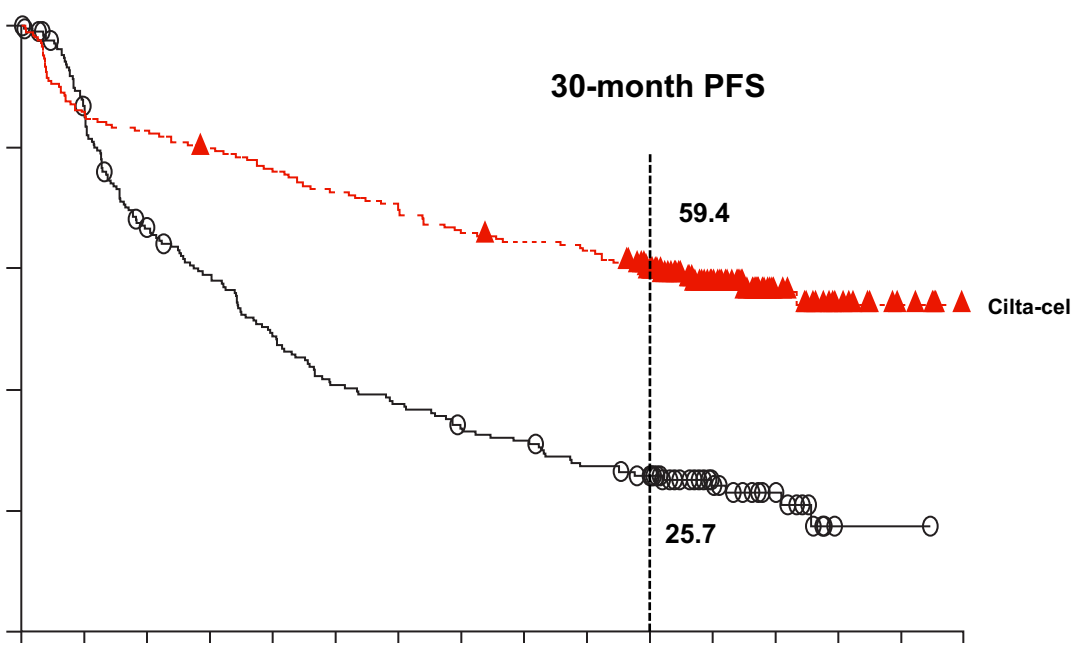
Phase 3 CARTITUDE-4 compared cilta-cel vs SOC in R/R patients MM after 1-3 prior lines

Jesús San-Miguel et al. N Engl J Med 2023; 389:335-347

CARTITUDE-4:PFS

- There is an increasing recognition of MRD as a primary clinical endpoint in MM as it is linked to improved PFS and OS[1-5]
- In CARTITUDE-4, patients who were randomized to cilta-cel had[6,a]
  - Significantly improved PFS vs SOC **(HR [95% CI], 0.29 [0.22–0.39]; *P*<0.0001[b])**
  - Median PFS was not reached with cilta-cel

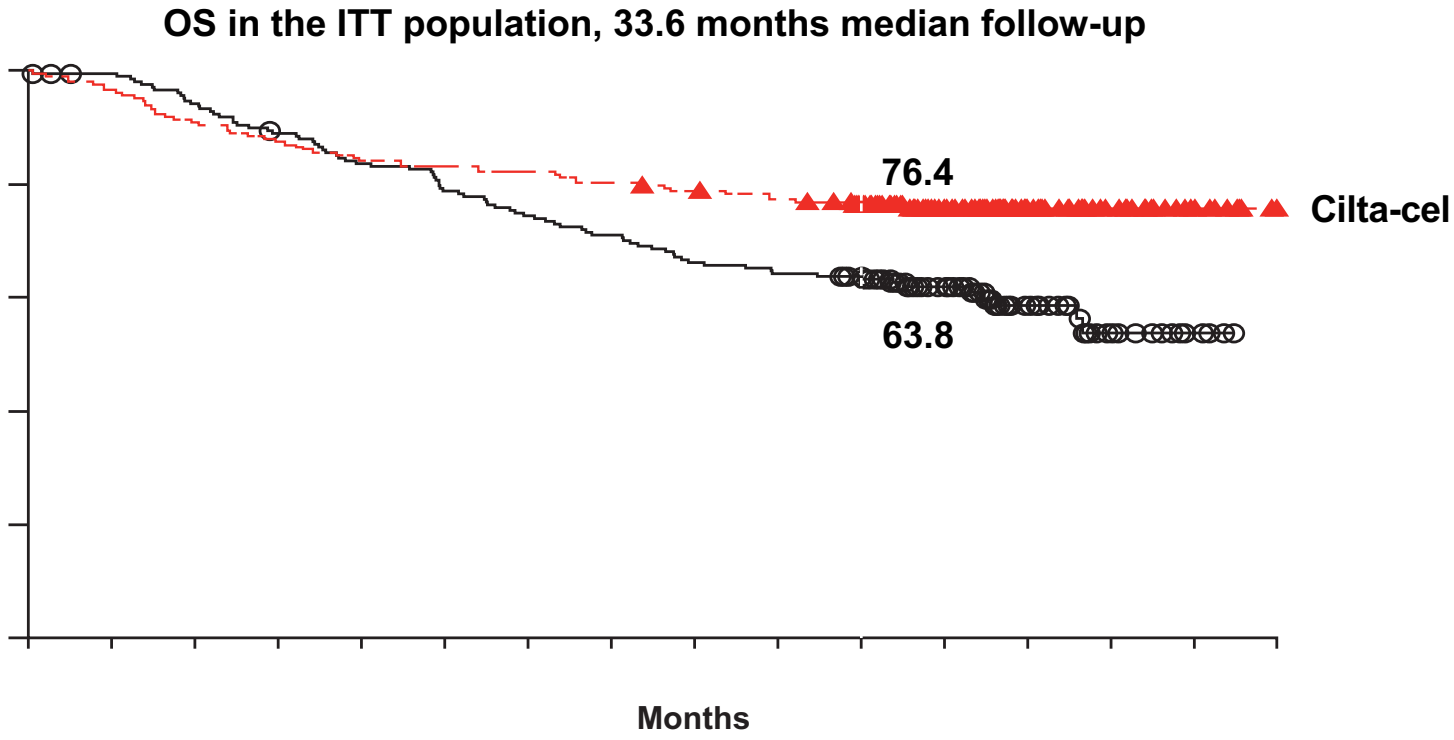
PFS in the ITT population, 33.6 months median follow-up



[a]Data cut-off date: May 1, 2024. [b]Nominal *P* value.
cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; ITT, intent-to-treat; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; SOC, standard of care.
1. US Food and Drug Administration. https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024#event-materials. Accessed November 30, 2024. 2. Avet-Loiseau H, et al. *Clin Lymphoma Myeloma Leuk* 2020;20:e30-e37. 3. Munshi NC, et al. *Blood Adv* 2020;4:5988-99. 4. Cavo M, et al. *Blood* 2022;139:835-44. 5. Landgren O, et al. *Blood* 2024;144:359-67. 6. Mateos MV, et al. Presented at IMS; September 25–28, 2024; Rio de Janeiro, Brazil. Oral #1437.

CARTITUDE-4: OS

- Cilta-cel also showed an OS benefit over SOC, with **HR, 0.55 (95% CI, 0.39–0.79; *P*=0.0009)**[1,a]
  - Median OS was not reached
- Overall MRD negativity, a secondary endpoint, was also higher in patients randomized to cilta-cel vs SOC (62.0% vs 18.5%)



[a]Data cut-off date: May 1, 2024. [b]Log-rank test. *P* value, 0.0009, crossed the prespecified boundary of 0.0108 as implemented by the Kim-DeMets spending function with parameter=2. [c]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

cilta-cel, ciltacabtagene autoleucel; CR, complete response; HR, hazard ratio; ITT, intent-to-treat; MRD, minimal residual disease; OS, overall survival; SOC, standard of care.

1. Mateos MV, et al. Presented at IMS; September 25–28, 2024; Rio de Janeiro, Brazil. Oral #1437.

State of Myeloma CAR-T in 2026

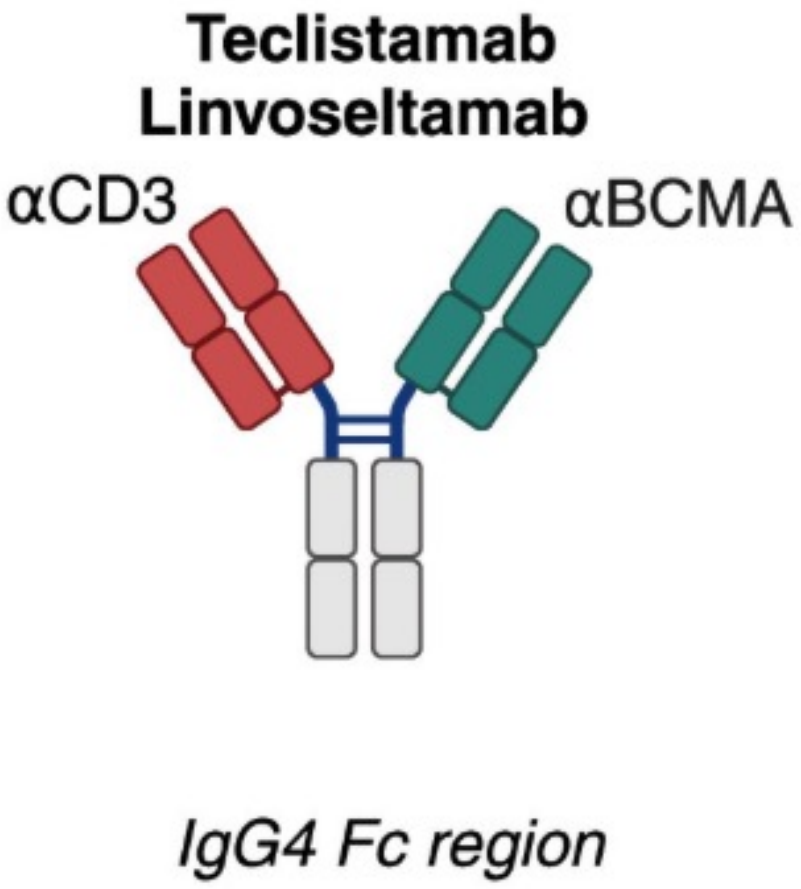
Barriers remain…

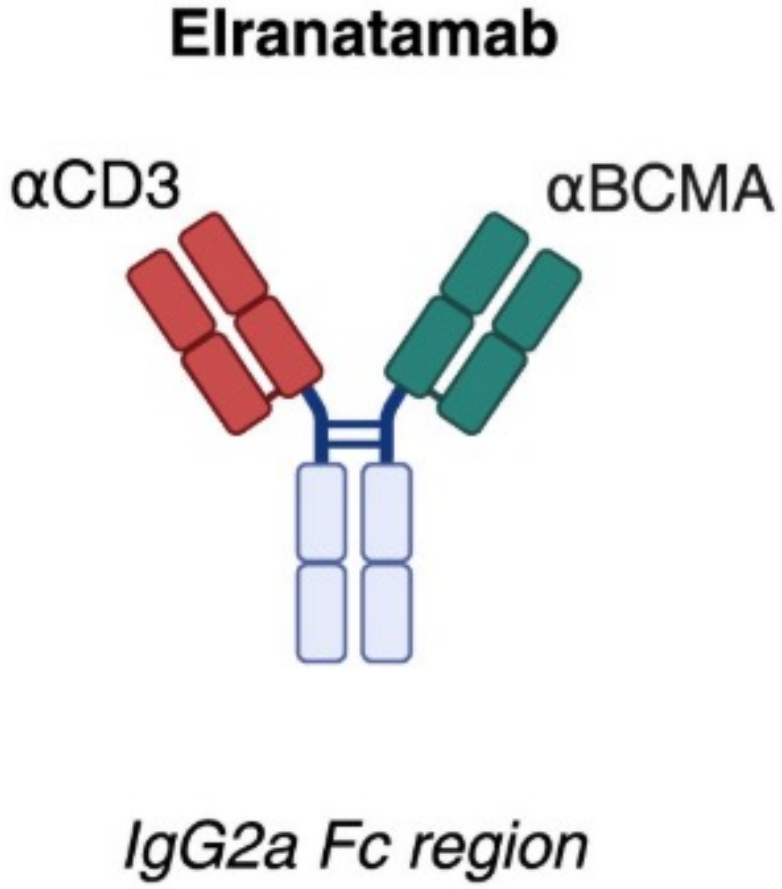
- Logistically challenging
- Autologous products
- Require apheresis and waiting period for cell infusion
- Need 3 days of lymphodepletion

Bispecifics

Why drive a CAR-T when you can take a ***bi***ke ride?

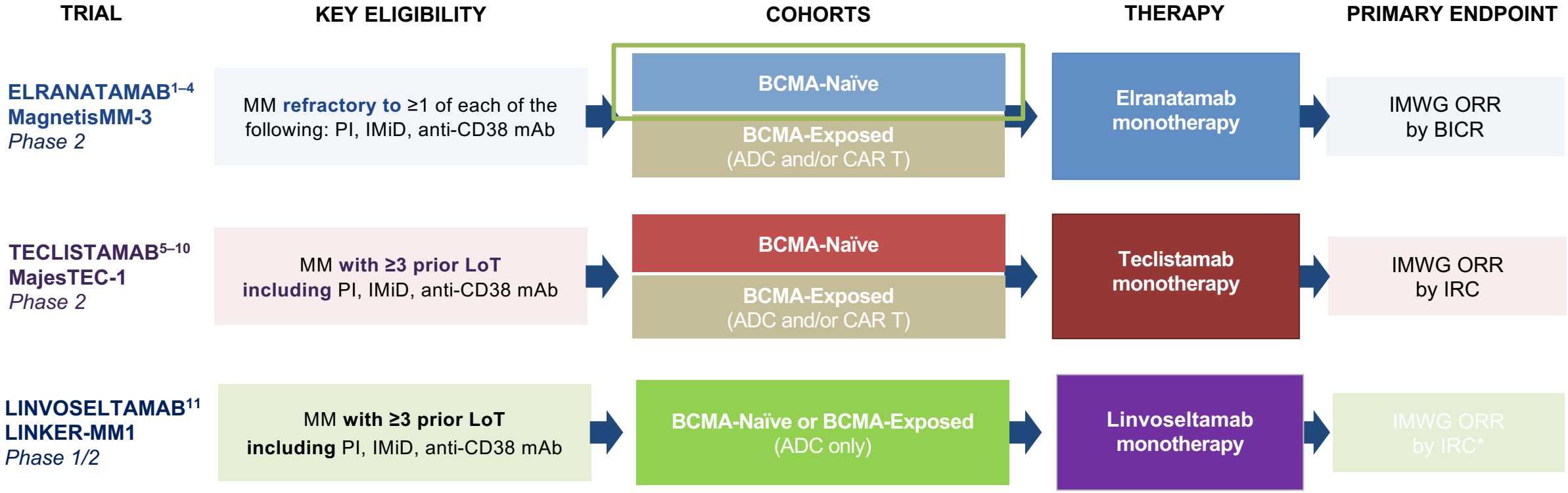
BCMA Bispecific T-Cell Antibodies





Waldschmidt et al. Clin Lymphoma Myeloma Leuk 2025

BCMA-directed BsAbs for RRMM: Registrational trials



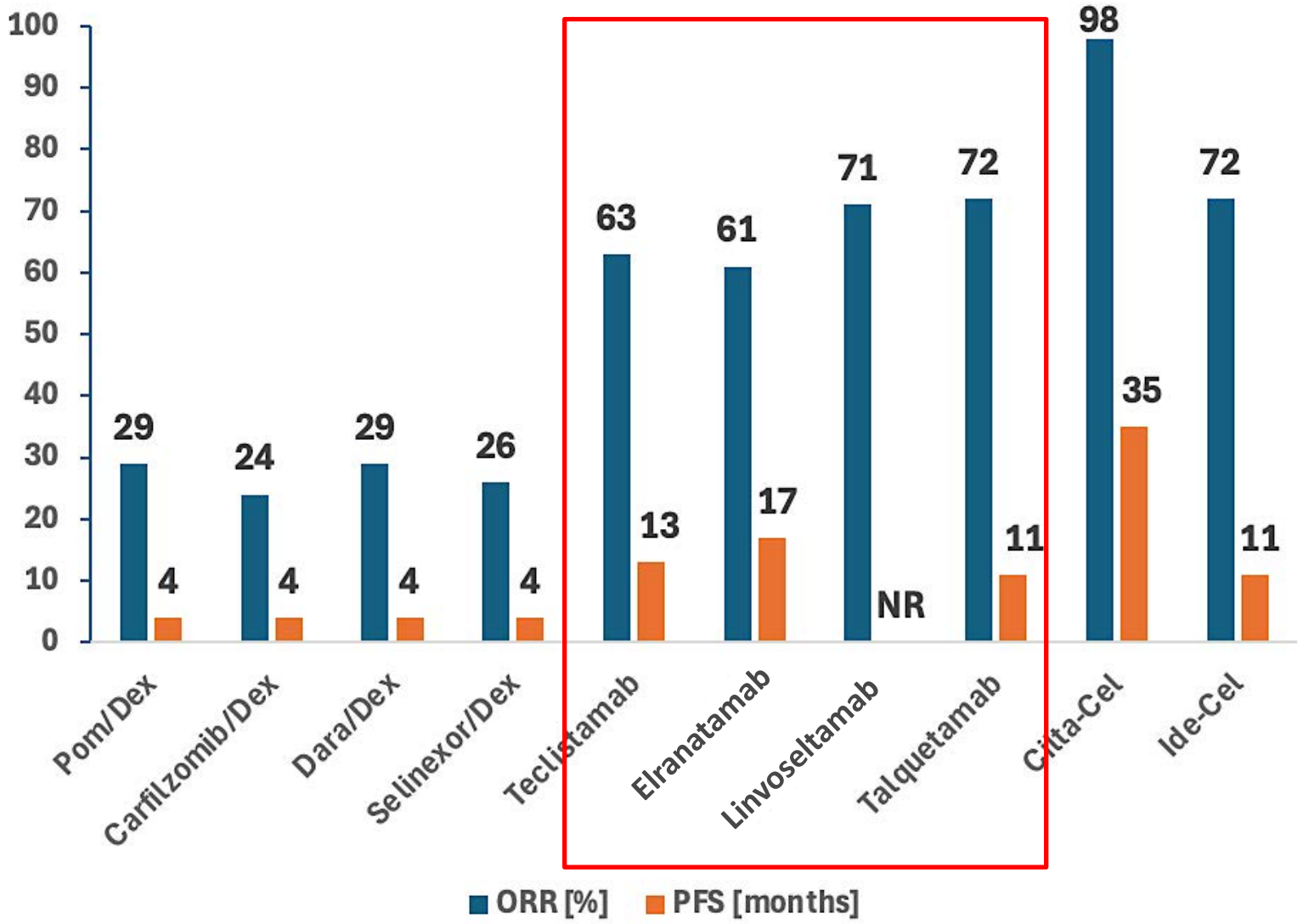
Linvoseltamab is not approved by the EMA

*Primary endpoint for Phase 2 of trial.

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BICR, blinded independent committee review; BsAb, bispecific antibody; CAR T, chimeric antigen receptor T-cell; CD, cluster of differentiation; EMA, European Medicines Agency; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IRC, independent review committee; LoT, lines of therapy; mAb, monoclonal antibody; MM, multiple myeloma; ORR, overall response rate; PI, proteasome inhibitor.

1. Clinicaltrials.gov. https://clinicaltrials.gov/study/NCT04649359. Accessed 21 August 2024. 2. ELREXFIO™ (elranatamab-bcmm) [prescribing information]. New York, NY. Pfizer Inc; August 2023. 3. ELREXFIO® (elranatamab) Summary of Product Characteristics. Bruxelles Belgium: Pfizer Europe; 2024. 4. ELREXFIO® (elranatamab). Sao Paulo, Brazil: Pfizer Brazil; 2024. 5. Clinicaltrials.gov. https://clinicaltrials.gov/study/NCT04557098. Accessed 21 August 2024. 6. Moreau P et al. *N Engl J Med*. 2022;387:495–505. 7. TECVAYLI® (teclistamab-cqyv) [prescribing information]. Horsham, PA. Janssen Biotech, Inc; February 2024. 8. TECVAYLI® (teclistamab) Summary of Product Characteristics. Beerse Belgium: Janssen-Cilag International; 2024. 9. TECVAYLI™ (teclistamab) Sao Paulo, Brazil: Janssen-Cilag Farmacêutica Ltda; 2024. 10. Touzeau C et al. ASCO 2022. Abstract 8013 (poster presentation). 11. Bumma N et al. *J Clin Oncol*. 2024;42:2702–2712.

PFS and ORR of Recently Approved Myeloma Drugs in RRMM



San Miguel et al, 2013, *Lancet Oncology*; Siegel et al, *Blood*, 2012; Lonial et al, *Lancet,* 2016; Chari et al, *NEJM* 2019; Moreau et al, *NEJM*, 2022; Lesokhin et al, *Nature Medicine*, 2023; Bumma et al, *JCO,* 2024; Chari et al, *NEJM*, 2022; Berdeja et al, Lancet, 2021; Munshi et al, NEJM, 2021

BCMA Bispecific T-Cell Antibodies Clinical Data

Drug	N	Route/Schedule	ORR at RP2D or higher doses tested to-date	CRS	Comments
Teclistamab **FDA-Approved, October 2022**	165	SC q week, then q2 weeks if ≥ CR for 6 months	63%, 59% ≥ VGPR, N=165	All grade (72%), grade 2 21%, Grade 3/4 (1%)	Median PFS 11.4 months Median DOR 24 months
Elranatamab **FDA-Approved, August 2023**	123	SC q week, then q2 weeks after 6 cycles with ≥ PR for ≥ 2 months, then q4 weeks starting week 49	61%, 56% ≥ VGPR (76 mg SC, N=123)	All grade (56%), grade 2 (14%); grade 3/4 (0%)	Median PFS: 17.2 months 18- month DOR: 68.8%
Linvoseltamab **FDA-Approved, July 2025**	117	IV q week, then q2 weeks starting week 16, then q4 weeks starting week 24 if ≥ VGPR	71%, 63% ≥ VGPR (200 mg cohort, N=117)	All grade (46%), grade 2 (10%), grade 3 (1%), (200 mg cohort)	Median DOR: 29.4 months 12-month median PFS: 70%

Garfall et al ASCO, 2024; Bumma et al, JCO 2024; Lesokhin et al, *Nature Medicine* 2023, Tomasson et al, *ASH* 2023; Lee HC et al. Clin Lymphoma Myeloma Leuk 2026

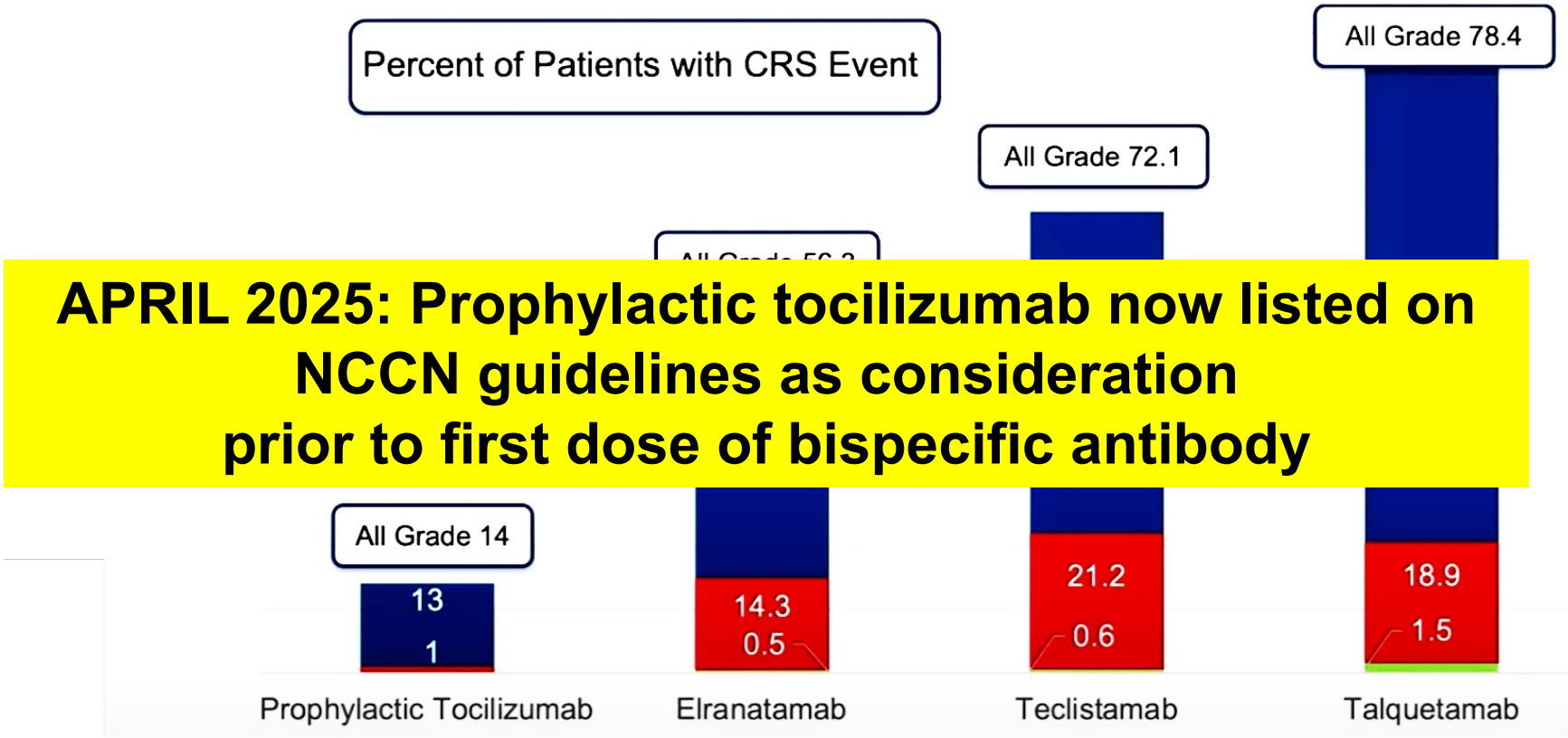
BCMA Bispecific Step-up Dosing Comparison

	Teclistamab	Elranatamab	Linvoseltamab
Step-up dosing (SUD) schedule	Day 1: 0.06 mg/kg Day 4: 0.3 mg/kg Day 7: 1.5 mg/kg	Day 1: 12 mg Day 4: 32 mg Day 8: 76 mg	Day 1: 5 mg Day 8: 25 mg Day 15: 200 mg
Recommended Hospitalization	48-hours after each SUD1, SUD2, SUD3	48 hours after SUD1 24 hours after SUD2	24 hours after SUD1 and SUD2
Subsequent dosing	1.5 mg/kg one week after first treatment dose and weekly thereafter	76 mg one week after first treatment dose and weekly through week 24; week 25 and every 2 weeks through week 48, week 49 and every 4 weeks thereafter	200 mg one week after day 15 and once weekly from week 4 to 13 for 10 doses

Hospitalization requirements can limit access to bispecifics!

teclistamab US PI; elranatamab US PI; linvoseltamab US PI

Tocilizumab Prophylaxis with Bispecific Step-up Dosing



APRIL 2025: Prophylactic tocilizumab now listed on NCCN guidelines as consideration prior to first dose of bispecific antibody

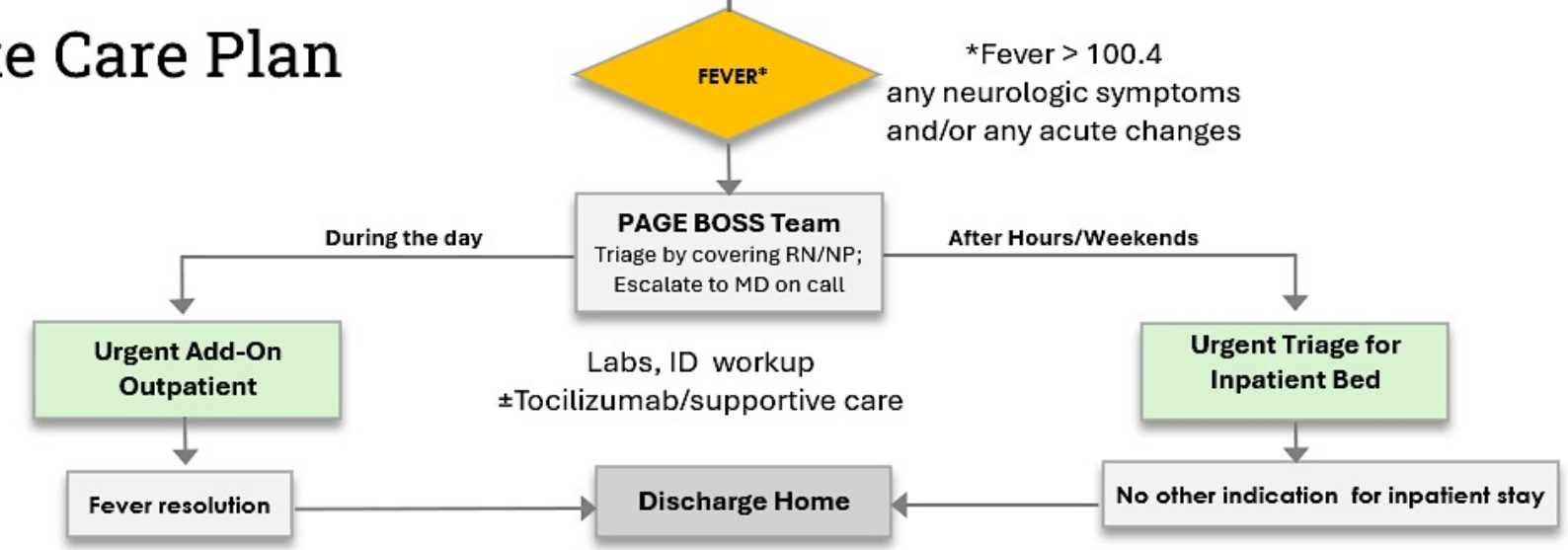
Prophylactic tocilizumab significantly reduces rates of CRS

Kowalski A. et al., *ASH 2024*, Abstract 932; Kowalski A et al, *Blood Advances*, 2025

BISPECIFIC OUTPATIENT STEP-UP DOSING WITH PROPHYLACTIC DEXAMETHASONE: THE BOSS PROGRAM EXPERIENCE at MGH

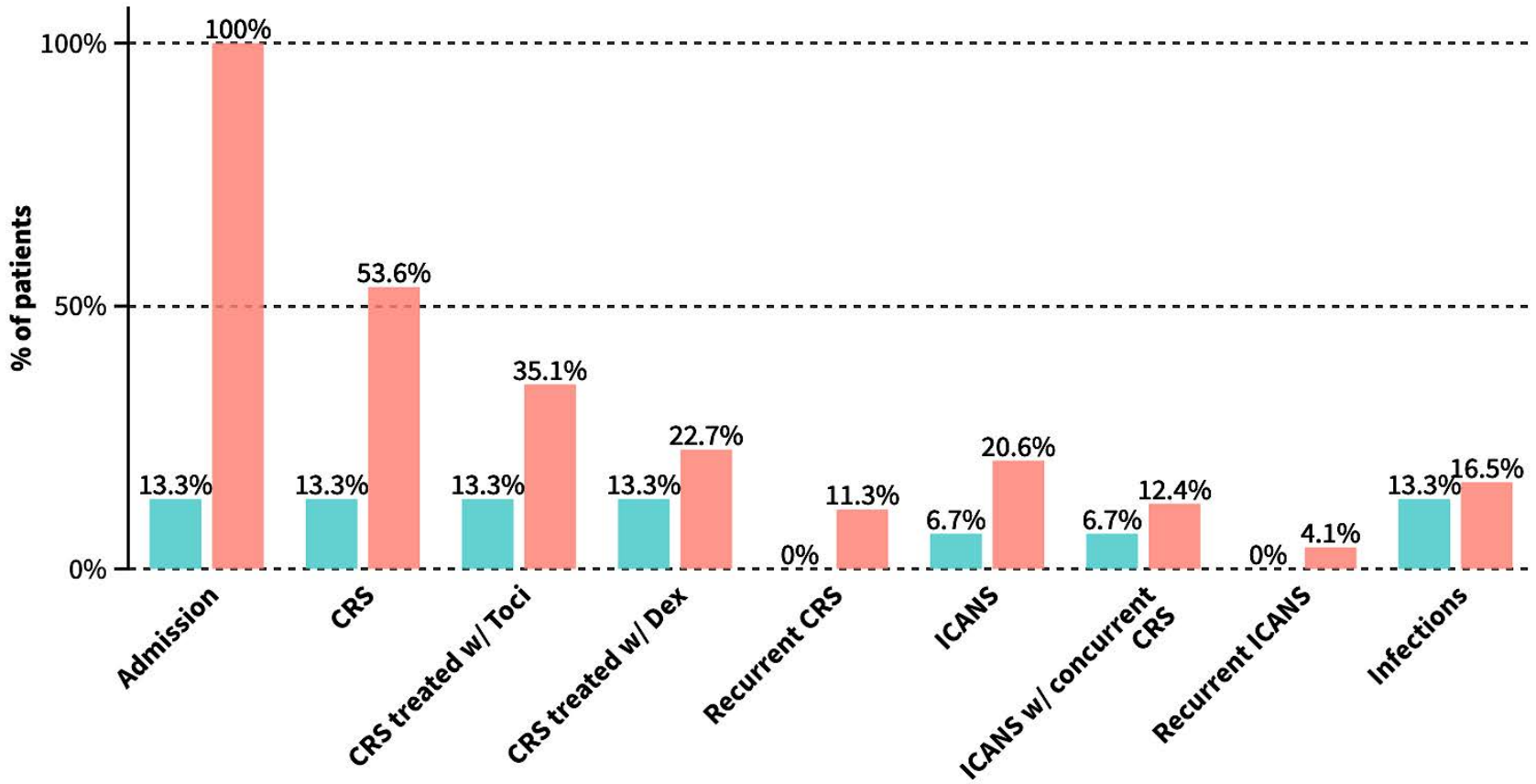
1 Treatment

2 Acute Care Plan



Cirstea et al IMS 2025

Toxicities and Management Among BOSS and iSUD Cohorts



Abbreviations: BOSS, bispecific outpatient safe step-up; iSUD, inpatient step-up dosing; CRS, cytokine release syndrome; ICANS, Immune effector cell-associated neurotoxicity syndrome; Toci, tocilizumab; Dex, dexamethasone

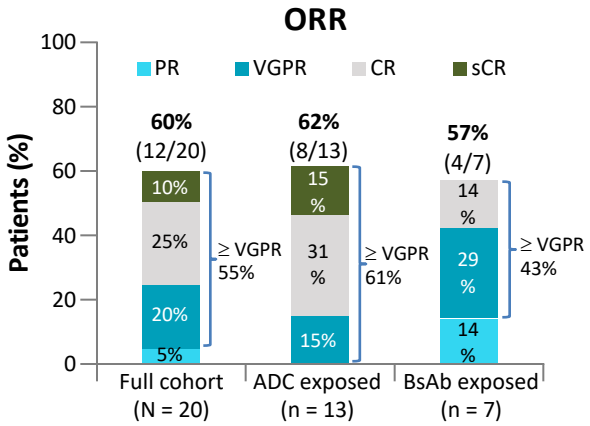
Figure 1: Grouped column chart illustrating percentage of patients experiencing CRS, ICANS, recurrent events, requiring admission or treatment with tocilizumab or dexamethasone across BOSS (n=15) and iSUD (n=97) cohorts

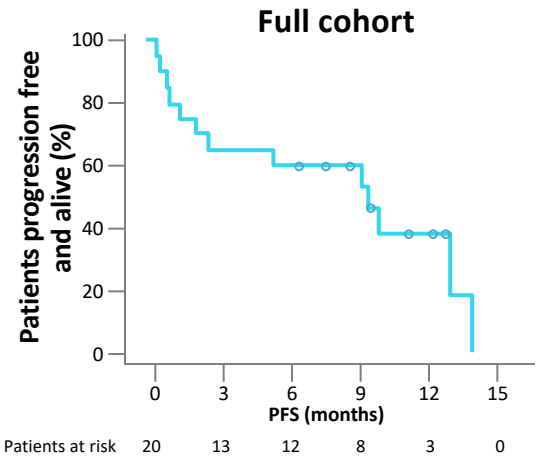
Comparing BCMA directed therapies

	Antibody Drug Conjugates	CAR T-Cell Therapy	Bispecific antibodies
Pros	• *Off the shelf* • *Encouraging response rates* • *1 hr infusion q3w* • *No CRS* • *Available in the community settings*	• Unprecedented ORR including MRD^- in heavily pre-treated pts • One time intervention; long chemotherapy holiday resulting in median PFS ~1 year	• Off the shelf • Deep responses • Limited severe CRS - ? Safety in frail elderly • Can be given in community settings after 1st cycle
Cons	• *Ocular toxicity – requires close collaboration with ophthalmology; potential impact on pt quality of life* • *Thrombocytopenia* • *Continuous treatment until progression* • *Modest ORR and PFS in triple class/penta refractory*	• Manufacturing time • Requires complex infrastructure • CRS ? role in frail elderly • Impact of bridging chemo on remission duration • long-term cytopenias • Cost given relapses (even in MRD-) • Management challenging • ACCESS: Traditional issues with BMT → Potential similar concerns with CAR-T. Traditionally underserved populations	• ? need for admissions with initial doses until CRS risk low • Dosing/schedule to be determined • Need for continuous treatment until progression • Toxicities require further study – infections, neurotoxicity

Sequencing: CAR-T Cell Therapy After BCMA-Targeted Therapy

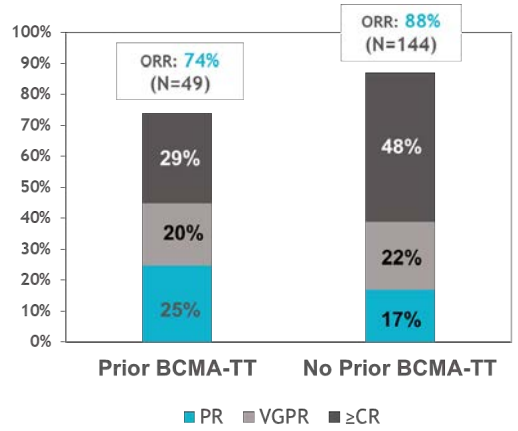
CARTITUDE-2, Cohort C: Cilta-cel
Patients with RRMM with previous exposure to PI, IMiD agent, anti-CD38 mAb, and a non-cellular BCMA-targeting therapy[1]

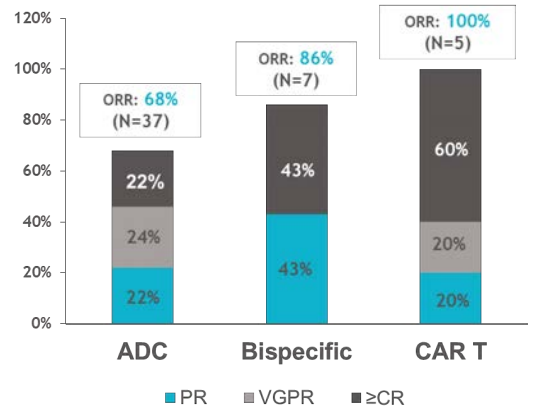


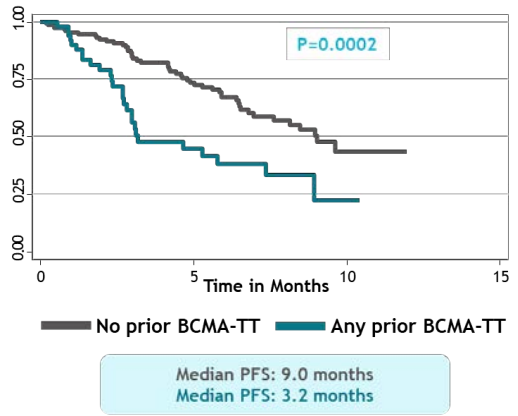


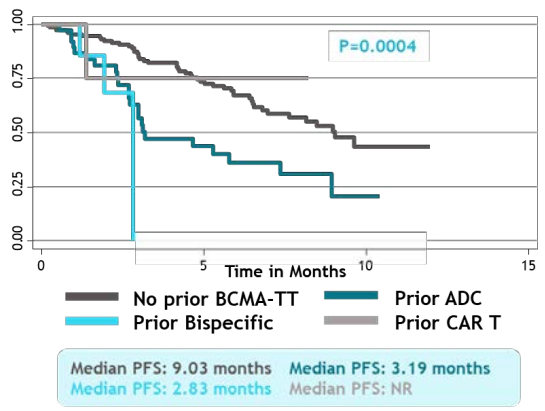
Median PFS			
	Full cohort (N = 20)	ADC exposed (n = 13)	BsAb exposed (n = 7)
PFS, mo (95% CI)	9.1 (1.5-13.2)	9.5 (1.0-15.2)	5.3 (0.6-NE)

Real-world experience of patients with multiple myeloma receiving ide-cel after a prior BCMA-targeted therapy[2]





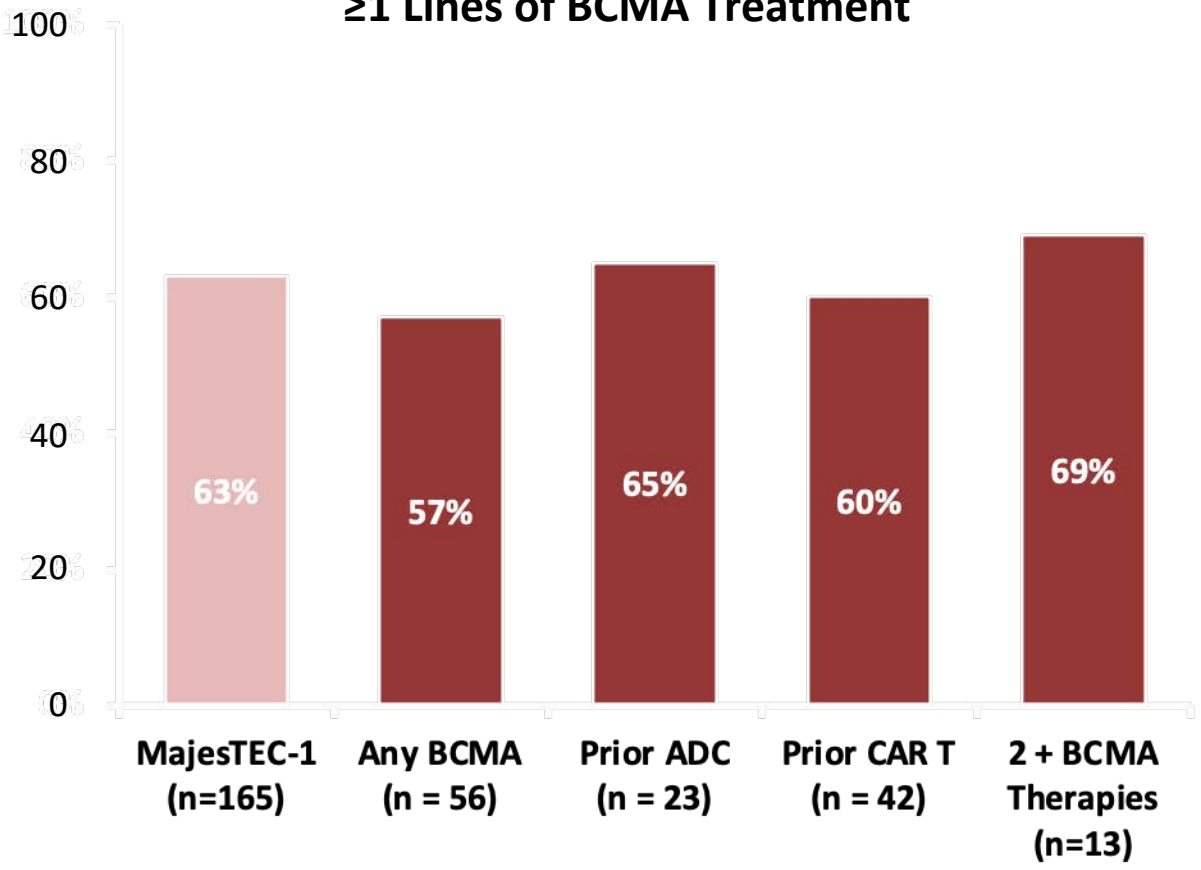




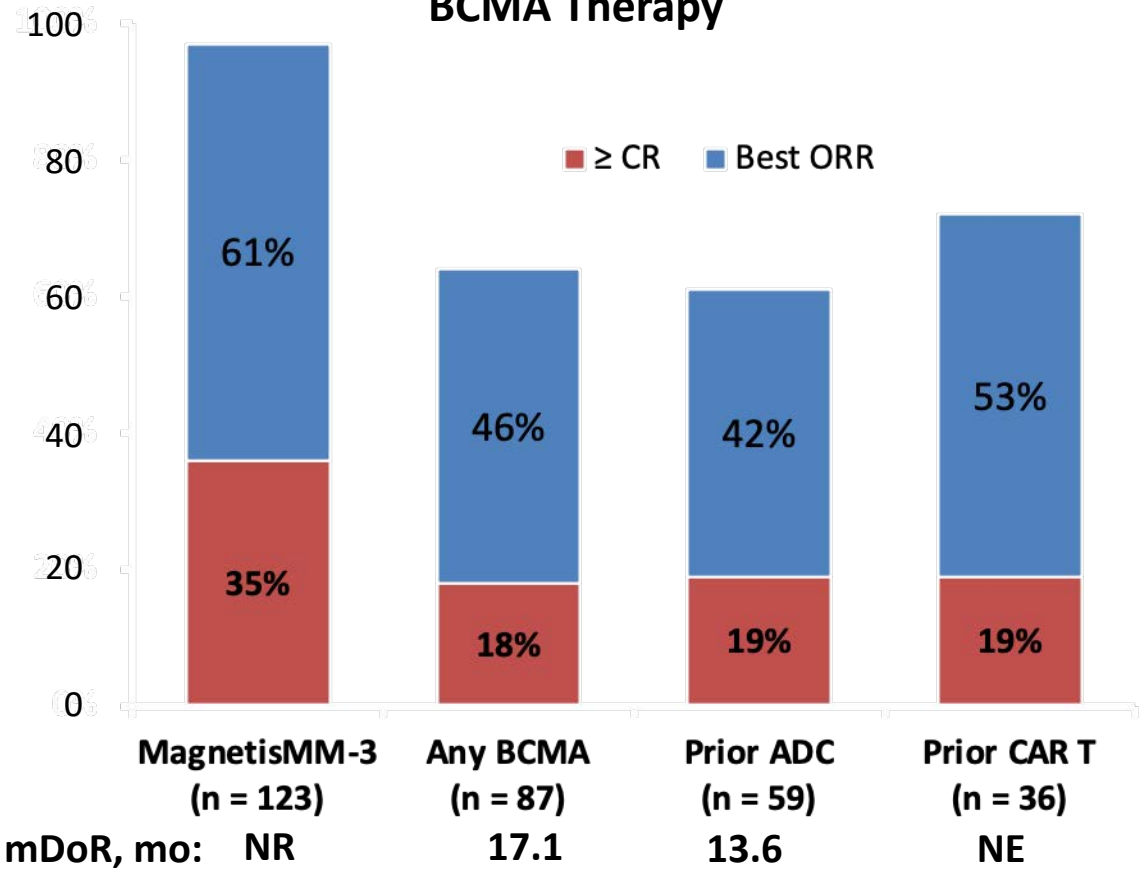
1. Cohen et al. *Blood*. 2023;141(3):219-230. 2. Ferreri CJ et al. *Blood Cancer J*. 2023;13:117; abstract 766.

Outcomes With Bispecific Antibodies After Prior BCMA-Directed Therapy

Teclistamab Best ORR With and Without Exposure to ≥1 Lines of BCMA Treatment



Pooled Analysis of Elranatamab Efficacy After Prior BCMA Therapy



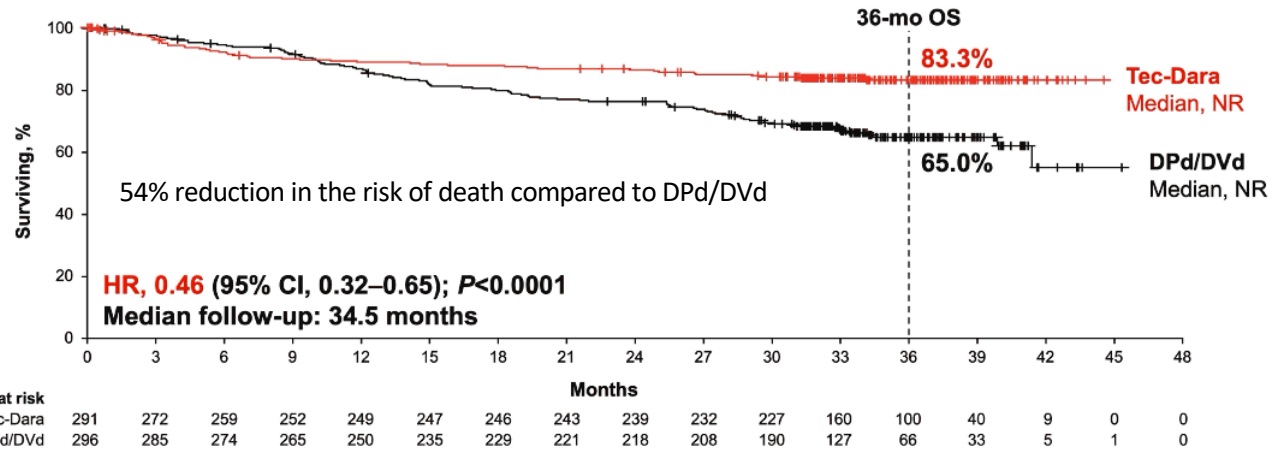
mDoR, mo: NR | 17.1 | 13.6 | NE

Moreau. NEJM. 2022;387:495. Dima. ASH 2023. Abstr 91.
Lesokhin. Nat Med. 2023;29;2259-2267. Nooka. ASCO 2023. Abstr 8008

Tec-Dara *vs* CART (Cilta-cel) in early relapse (1-3L)

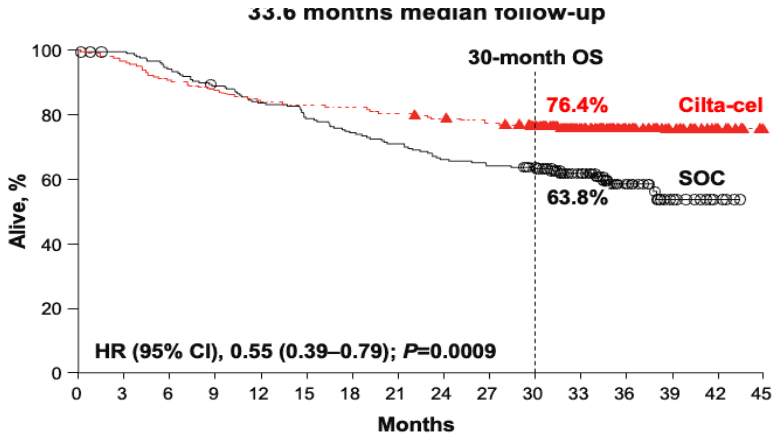
Tec-Dara not only delivered impressive depth of response and PFS — it also improved overall survival...

MajesTEC-3: OS



VS

CARTITUDE-4: PFS



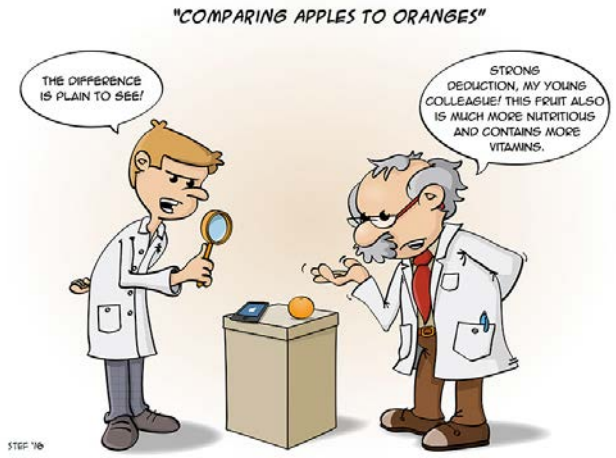
This brings up an important real-world question — if we can achieve durable control with off-the-shelf bispecifics like Tec-Dara, how does that stack up to CAR-T?

ASH 2025: Tec-Dara[1]

MajesTEC-3
ORR ~89%
≥CR ~82%
MRD-neg ~58%
Continuous therapy

Strength: immediate availability

Limitation: chronic infection risk



Standard of care: CAR-T (cilta-cel)[2]

CARTITUDE-4
ORR ~85%
≥CR ~70–75%
MRD-neg ~60%
Fixed, one-time therapy

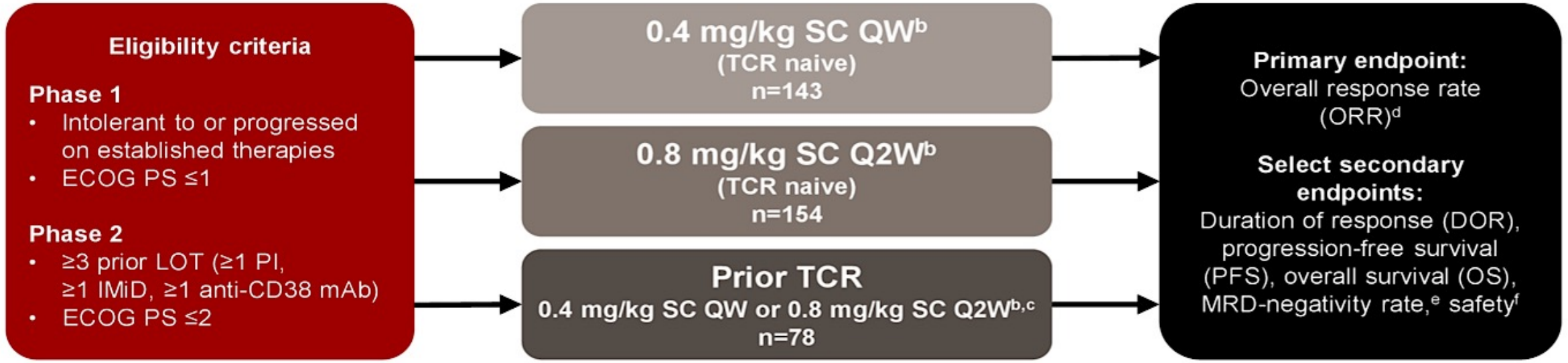
Strength: one-and-done

Limitation: manufacturing delay, acute toxicity

1. MV Mateos et al. MajesTEC-3. ASH 2025 LBA-6
2. S. Jagannah et al. JCO 2025

And should our first immunotherapy move be a bispecific?

Phase I/II MonumenTAL-1 Study: Design

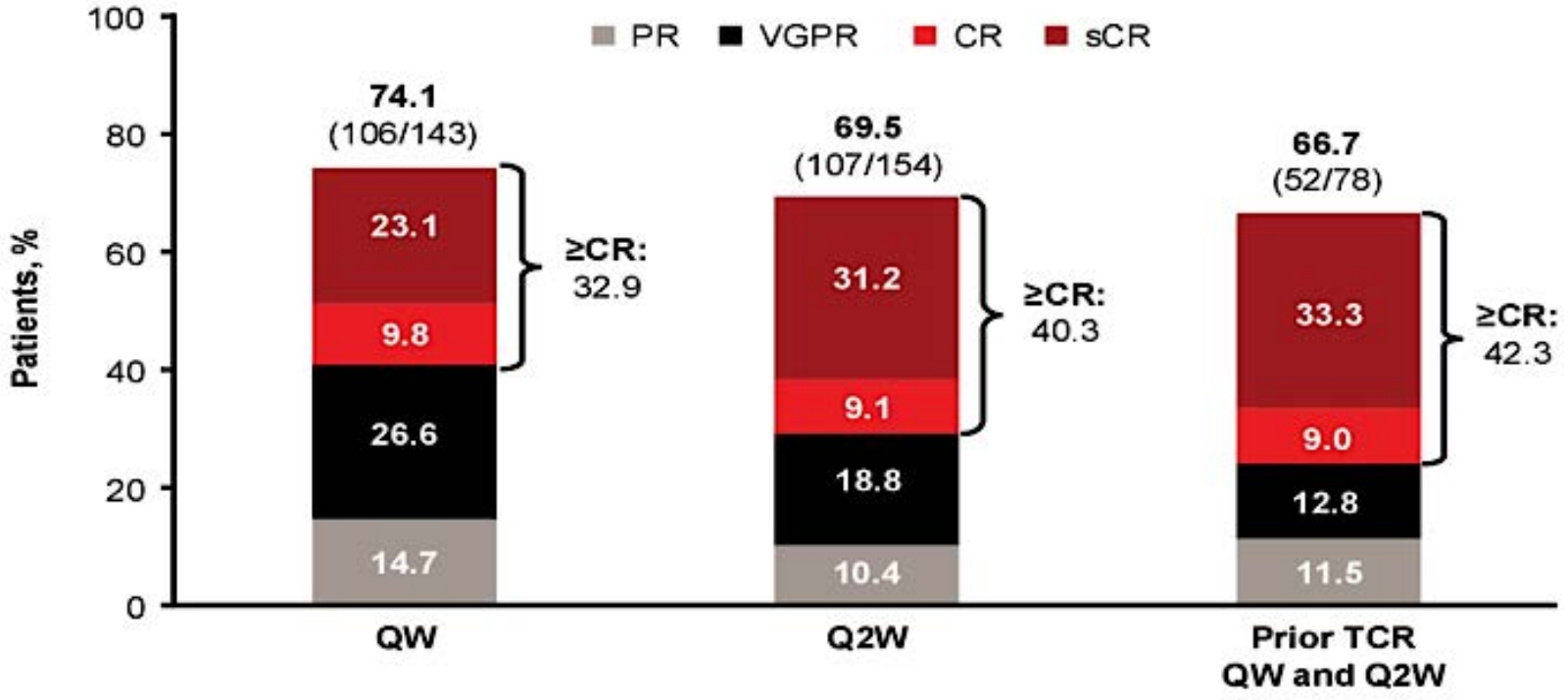


As of Sept 2024, 17, 27, and 18 patients remained on talquetamab in the QW, Q2W, and prior TCR QW and Q2W cohorts, respectively. All were responders (≥VGPR, most ≥CR), and 2 subsequently progressed during this time

Rasche L et al. ASCO 2025

Phase I/II MonumenTAL-1 Study: ORR

Figure 1. ORR[a] remained high, consistent with previous results[4]



[a]Due to rounding, individual response rates may not sum to the ORR. Since previous disclosure, 1 patient in the prior TCR QW and Q2W cohort deepened in response (CR to sCR). PR, partial response; sCR, stringent complete response.

Rasche L et al. ASCO 2025

Phase I/II MonumenTAL-1 Study: Additional Efficacy Outcomes*

Outcome	QW (n=100)	Q2W (n=90)	Prior TCR QW and Q2W[a] (n=58)
ORR, %	73.0	71.1	72.4
≥CR	35.0	43.3	50.0
VGPR	22.0	17.8	8.6
PR	16.0	10.0	13.8
Median time to best response of ≥CR,[b] mo (range)	2.27 (1.1–12.7)	6.24 (1.2–16.8)	2.66 (1.2–17.5)
Median time to best response of VGPR,[c] mo (range)	1.97 (1.1–6.2)	3.06 (0.3–18.9)	2.04 (1.2–2.1)
Median time to best response of PR,[d] mo (range)	1.28 (1.1–2.9)	2.07 (1.2–2.8)	1.13 (1.1–3.0)
Median DOR, mo (95% CI)[e]	10.2 (6.6–15.7)	17.9 (12.5–26.0)	19.2 (6.7–NE)
≥CR[b]	28.8 (18.9–NE)	26.1 (18.0–NE)	24.7 (19.2–NE)
VGPR[c]	6.4 (4.4–9.5)	9.3 (7.4–15.2)	4.8 (2.1–NE)
PR[d]	3.0 (1.9–5.6)	5.5 (0.9–6.5)	2.4 (1.9–4.6)
Median PFS (95% CI), mo	6.8 (5.5–10.4)	12.4 (9.6–18.2)	11.3 (4.8–21.4)
36-mo PFS, %	17.6 (10.7–26.0)	NE (NE–NE)	28.2 (16.0–41.7)
Median OS (95% CI), mo	NR (21.7–NE)	NR (33.2–NE)	30.6 (20.2–NE)
36-mo OS, %	50.5 (40.0–60.0)	NE (NE–NE)	46.4 (29.2–61.9)

Data reported from phase 2 only*
Rasche L et al. ASCO 2025

Phase I/II MonumenTAL-1 Study: AEs

AE (≥30% in any cohort), n (%)	QW (n=143)		Q2W (n=154)		Prior TCR QW and Q2W (n=78)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic AE						
Anemia	65 (45.5)	46 (32.2)	67 (43.5)	39 (25.3)	38 (48.7)	22 (28.2)
Neutropenia	50 (35.0)	44 (30.8)	44 (28.6)	33 (21.4)	40 (51.3)	37 (47.4)
Thrombocytopenia	39 (27.3)	29 (20.3)	46 (29.9)	28 (18.2)	30 (38.5)	22 (28.2)
Nonhematologic AE						
CRS	113 (79.0)	3 (2.1)	116 (75.3)	1 (0.6)	57 (73.1)	1 (1.3)
Dysgeusia[a]	103 (72.0)	NA	111 (72.1)	NA	59 (75.6)	NA
Infections[b]	87 (60.8)	33 (23.1)	109 (70.8)	33 (21.4)	61 (78.2)	20 (25.6)
Skin related[c]	85 (59.4)	0	113 (73.4)	1 (0.6)	53 (67.9)	0
Nail related[d]	80 (55.9)	0	84 (54.5)	0	47 (60.3)	0
Weight decreased	59 (41.3)	3 (2.1)	64 (41.6)	9 (5.8)	29 (37.2)	1 (1.3)
Rash related[e]	57 (39.9)	2 (1.4)	48 (31.2)	8 (5.2)	25 (32.1)	2 (2.6)
Pyrexia	57 (39.9)	4 (2.8)	44 (28.6)	2 (1.3)	27 (34.6)	0
Dry mouth	38 (26.6)	0	60 (39.0)	0	34 (43.6)	0
Fatigue	36 (25.2)	5 (3.5)	44 (28.6)	1 (0.6)	25 (32.1)	1 (1.3)

Rasche L et al. ASCO 2025

Challenges

- Moving therapies early can impact later therapies
- Sequencing and maintenance?
- With early—no more one and done?
- Combinations: ELISA; MAGENTA

Future for MM

- Use of fixed duration therapies using **MRD**
- Combine immunotherapies : **TOTAL IMMUNOTHERAPY**
- Transform chronicity into **CURE**

QUESTIONS?

Module 4: Relapsed/Refractory (R/R) Multiple Myeloma (MM)

Integrating CAR T-Cell Therapy and Bispecific Antibodies into the Management of R/R MM — Dr Raje

Antibody-Drug Conjugates and Other Emerging Therapies for R/R MM — Dr Lee

Antibody-Drug Conjugates (ADCs) and Other Emerging Novel Therapies for Relapsed/Refractory Multiple Myeloma

Fifth Annual National General Medical Oncology (GMO) Summit

April 25, 2026

Hans Lee, MD
Director, Multiple Myeloma Research
Sarah Cannon Research Institute

Disclosures

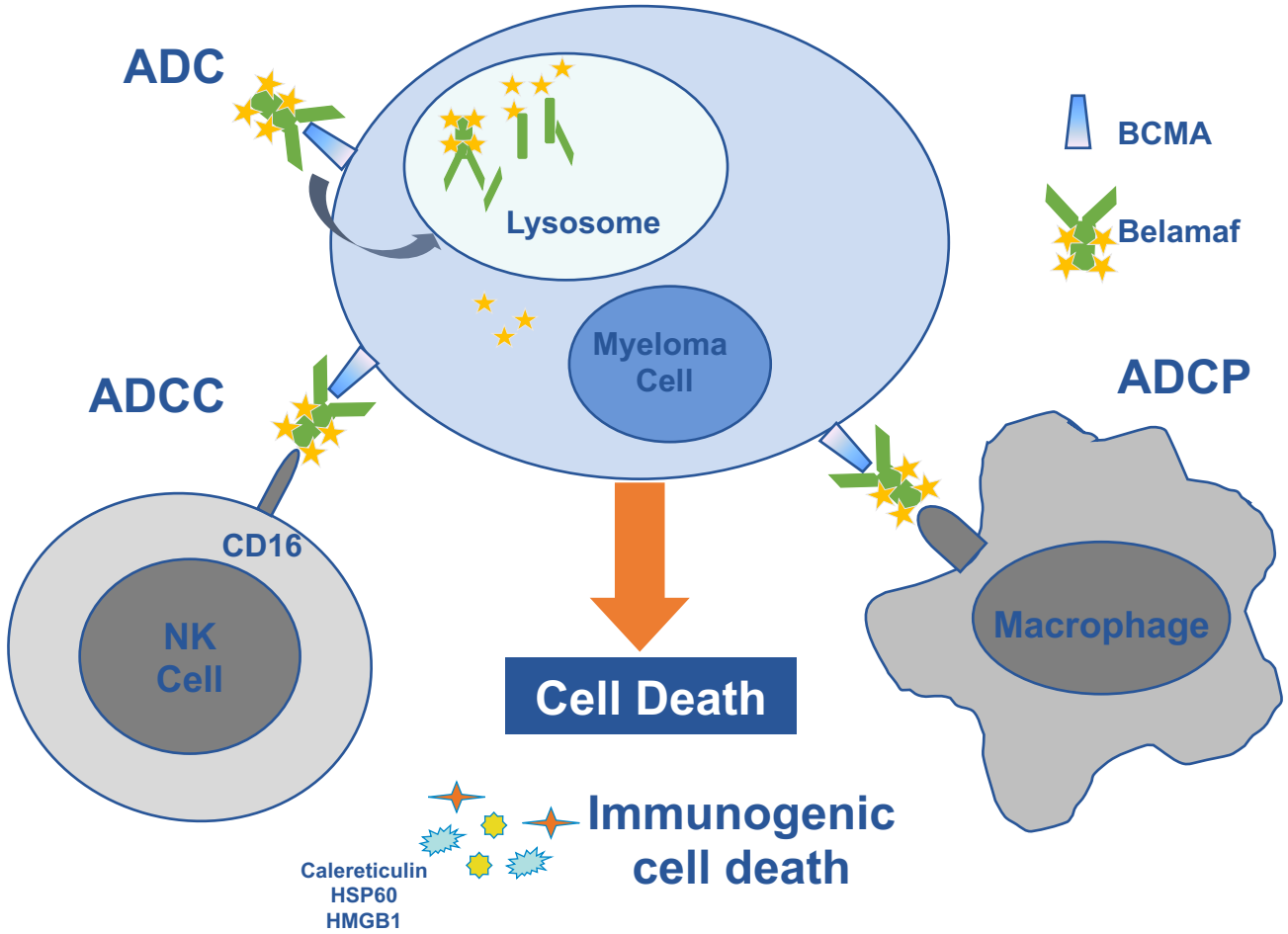
Consulting Agreements (Paid to Institution)	AbbVie Inc, Alexion Pharmaceuticals, Allogene Therapeutics, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, GSK, Janssen Biotech Inc, Legend Biotech, Medline, Pfizer Inc, Predicta Biosciences, Regeneron Pharmaceuticals Inc, Sanofi, Takeda Pharmaceuticals USA Inc
Consulting Agreements (Paid to Self)	Alexion Pharmaceuticals, Allogene Therapeutics, Bristol Myers Squibb, GSK, Janssen Biotech Inc, Menarini Group, Pfizer Inc, Regeneron Pharmaceuticals Inc, Sanofi, Takeda Pharmaceuticals USA Inc
Contracted Research	AbbVie Inc, Alexion Pharmaceuticals, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, GSK, Janssen Biotech Inc, Menarini Group, Moderna, Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc
Data and Safety Monitoring Boards/Committees	Allogene Therapeutics, Takeda Pharmaceuticals USA Inc

Agenda

- Belantamab mafodotin
  - Current application in relapsed/refractory myeloma
  - Management of ocular adverse events
  - Emerging data in newly diagnosed myeloma and ongoing studies

- CELMoDs
  - Iberdomide
  - Mezigdomide

Belantamab Mafodotin (Belamaf)



- **Antibody:** BCMA afucosylated monoclonal IgG1
- **Conjugate:** monomethyl auristatin F (anti-microtubulin drug)
- **Noncleavable** linker

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Tai YT et al *Blood,* 2014; de Oca RM et al, *Mol Cancer Ther, 2021*

DREAMM-7: BelaVd vs. DVd

RRMM, ≥1 line of therapy; with PD on/after most recent therapy; (N = 494)

Stratified by prior lines of tx (1 vs 2-3 vs ≥4), prior bortezomib (yes vs no), R-ISS (I vs II/III)

Belantamab Mafodotin + Bortezomib + Dexamethasone 21-day cycles (n = 243)	**Belantamab Mafodotin** 2.5 mg/kg IV Q3W
Daratumumab + Bortezomib + Dexamethasone 21-day cycles (n = 251)	**Daratumumab** 16 mg/kg IV Q4W

Tx continued until PD, unacceptable toxicity, end of study, or consent withdrawal

Belantamab mafodotin: 2.5 mg/kg IV Q3W cycle 1-8.
Bortezomib: 1.3 mg/m^2 SC Days 1, 4, 8, 11 cycles 1-8 (21-day cycle).
Daratumumab: 16 mg/kg IV cycle 1-3 QW and 16 mg/kg IV Cycle 4-8 Q3W.
Dexamethasone: 20 mg on day of and day after bortezomib in cycle 1-8 in BVd and DVd regimens.

- **Primary endpoint:** PFS
- **Key secondary endpoints:** OS, DoR, MRD negativity

Hungria V. et al., *NEJM*, 2024.

DREAMM-7: Baseline Patient Characteristics

Baseline characteristics	ITT population	
	BVd (N=243)	DVd (N=251)
Age, median (range), years	65.0 (34-86)	64.0 (32-89)
<65, n (%)	121 (50)	126 (50)
65-<75, n (%)	85 (35)	95 (38)
≥75, n (%)	37 (15)	30 (12)
Male / Female, n (%)	128 (53) / 115 (47)	144 (57) / 107 (43)
White / Black or African American / Other[a] n (%)	206 (85) / 8 (3) / 28 (12)	203 (81) / 12 (5) / 34 (14)
Revised ISS stage at screening[b], n (%)		
I	102 (42)	103 (41)
II	130 (53)	132 (53)
III	9 (4)	14 (6)
Unknown	2 (<1)	2 (<1)
Cytogenetic abnormalities, n (%)		
High risk[c]	67 (28)	69 (27)
Standard risk[d]	175 (72)	175 (70)
Missing or non-evaluable	1 (<1)	7 (3)

Prior treatments, n (%)	ITT population	
	BVd (N=243)	DVd (N=251)
Prior LOT		
1	125 (51)	125 (50)
2 or 3	88 (36)	99 (39)
4+	30 (12)	27 (11)
Prior PI	218 (90)	216 (86)
Prior bortezomib	210 (86)	211 (84)
Prior IMiD	198 (81)	216 (86)
Prior thalidomide	121 (50)	144 (57)
Prior lenalidomide	127 (52)	130 (52)
Refractory to lenalidomide	79 (33)	87 (35)
Prior daratumumab	3 (1)	4 (2)
Prior ASCT	164 (67)	173 (69)

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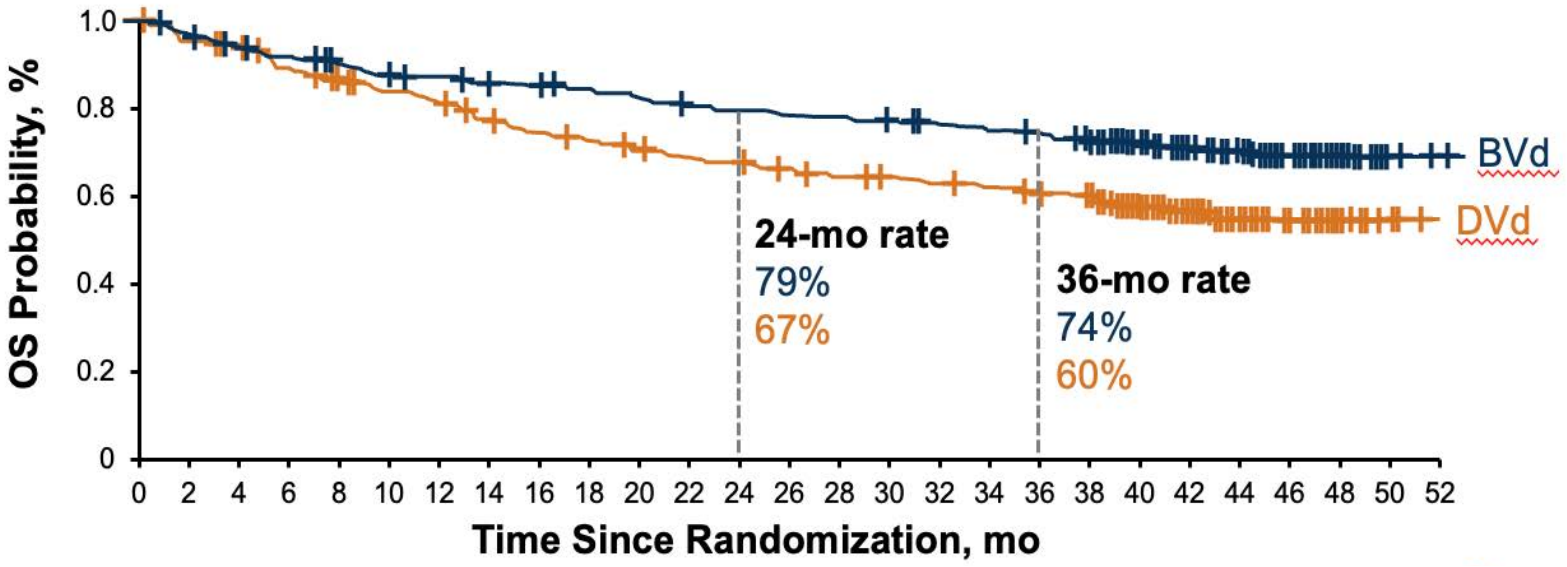
Hungria V. et al., *NEJM*, 2024.

DREAMM-7: PFS and OS



	BVd (N = 243)	DVd (N = 251)
ORR, %	83%	71%
≥CR, %	36%	18%
Median PFS, mo	**36.6**	**13.4**
Median OS, mo	**NR, HR = 0.58; *P* = .0002**	

Median follow-up: 39.4 mo

BelaVd with significant PFS and OS benefit vs DVd

BelaVd approved now in ≥2 prior lines of therapy in US (October, 2025)

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Hungria V. et al., *NEJM*, 2024.
Hungria V. et al, *Lancet Oncology,* 2025

DREAMM-7: MRD and Depth of Response

Responses, % (n/N)	BVd (N = 243)	DVd (N = 251)
≥CR	36 (87/243)	18 (44/251)
≥CR and MRD negativity (10^{-5})	70 (61/87)	59 (26/44)
≥CR and MRD negativity (10^{-6})	45 (39/87)	23 (10/44)
Sustained ≥CR MRD negativity for ≥ 12 mo	57 (35/61)	42 (11/26)

BVd greater than two-fold higher MRD negativity rate compared to DVd arm irrespective of

- **lenalidomide-refractory status**
- **≥1 high-risk cytogenetic features**

Hungria et al. *ASH 2025*, Abstract 2265

DREAMM-8: BelaPd versus PVd

Recruitment period
October 2020 to December 2022

Treatment period
Until PD, death, unacceptable toxicity, end of study, or withdrawal of consent

Eligibility criteria

- Adults with MM
- ≥1 prior line of MM therapy including LEN
- Documented PD during or after their most recent therapy
- No prior treatment with anti-BCMA or pomalidomide; not refractory/intolerant to bortezomib

N=302

1:1 randomization

BPd (Q4W)

Belantamab mafodotin
2.5 mg/kg IV (cycle 1) then 1.9 mg/kg IV Q4W from cycle 2 onward
+
Pomalidomide 4 mg orally on days 1-21 (28-day cycles)
+
Dexamethasone 40 mg[a] on days 1, 8, 15, and 22

PVd (Q3W)

Bortezomib
1.3 mg/m^2 SC on days 1, 4, 8, and 11 of cycles 1-8 then days 1 and 8 (21-day cycles)
+
Pomalidomide 4 mg orally on days 1-14 (21-day cycles)
+
Dexamethasone 20 mg[a] on the day of and day after bortezomib

End-of-treatment visit

Primary endpoint:
PFS (IRC assessed per IMWG)

Key secondary endpoints:
OS, MRD negativity, DOR

Additional secondary endpoints include:
ORR, CRR, ≥VGPR,TTBR, TTR, TTP, PFS2, AEs, ocular findings, HRQOL, and PROs

Stratification[b]:
- Prior lines of treatment (1 vs 2 or 3 vs ≥4)
- Prior bortezomib (yes vs no)
- Prior anti-CD38 therapy (yes vs no)

In the BPd group:

- 53% had received 1 prior LOT
- 90% received prior PI
- 81% were Lenalidomide refractory
- 23% were anti-CD38 refractory

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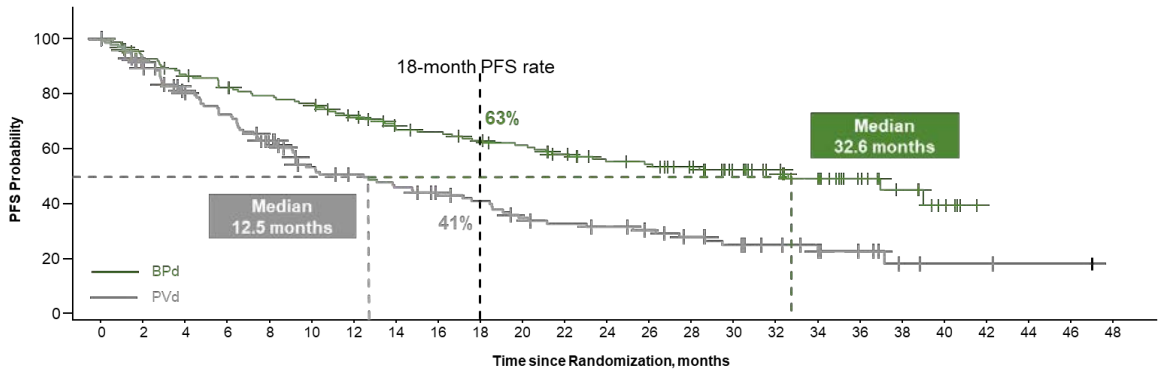
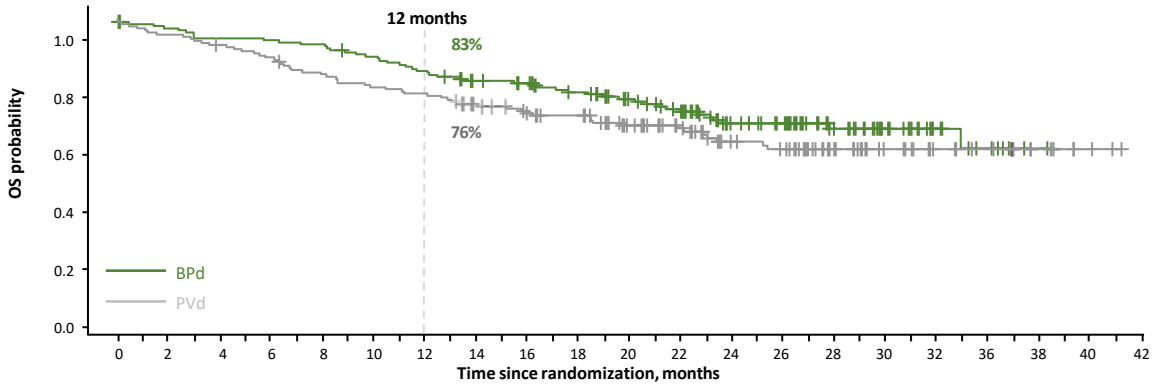
Dimopoulos MA, et al. N Engl J Med. 2024 Aug 1;391(5):408-421

DREAMM-8: PFS and OS

Progression-free Survival



Overall Survival



		BPd (N=155)	PVd (N=147)
PFS	PFS, median (95% CI), months	**32.6 (21.1, NR)**	**12.5 (9.1, 17.6)**
	HR (95% CI)	0.49 (0.35-0.68)	
OS	OS, median (95% CI), months	NR (33.0, NR)	NR (25.2, NR)
	HR (95% CI)‡	0.77 (0.53, 1.14)	

BelaPd with significant PFS benefit versus PVd

BelaPd approved now in European Commission (EC) ≥ 1 line of therapy + lenalidomide exposed (2025)

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Dimopoulos MA, et al. N Engl J Med. 2024 Aug 1;391(5):408-421; Dimopoulos MA , et al EHA 2025.

Keratopathy and Visual Acuity (KVA) Grading Scale

Ophthalmic exam finding graded per KVA	Grade 1	Grade 2	Grade 3	Grade 4
Corneal exam finding	Mild superficial punctate keratopathy (documented worsening from baseline, with or without symptoms)	Any or a combination of: •Moderate superficial punctate keratopathy •Patchy microcyst-like deposits •Peripheral subepithelial haze •New peripheral stromal opacity	Any or a combination of: •Severe superficial punctate keratopathy •Diffuse microcyst-like deposits •Central subepithelial haze •New central stromal opacity	Corneal epithelial defect such as corneal erosion(s) or corneal ulcers
Change in BCVA	Decline from baseline of 1 line on Snellen Visual Acuity	Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	Decline from baseline of >3 lines (and Snellen Visual Acuity not worse than 20/200)	Snellen Visual Acuity worse than 20/200

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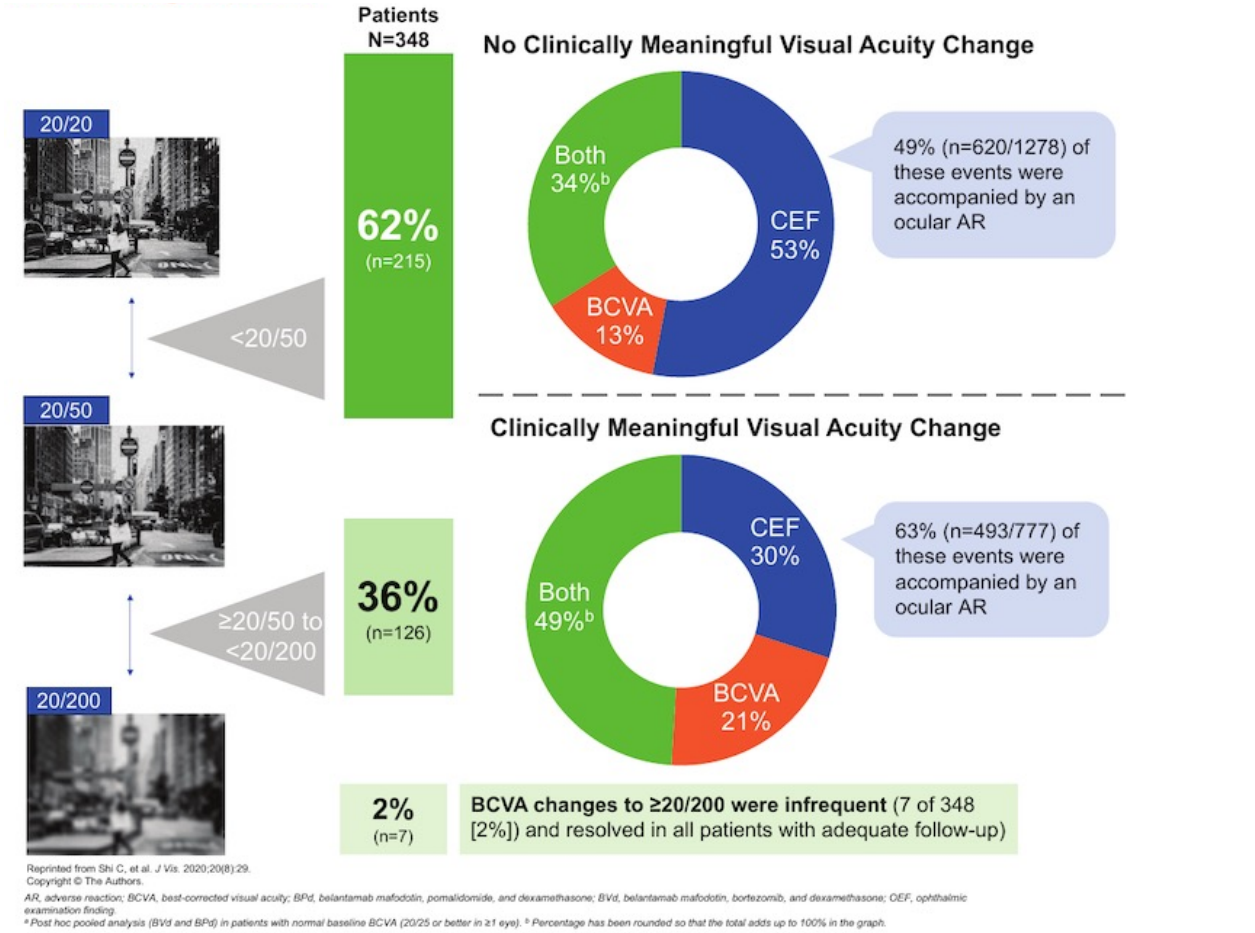
Mateos et al, *Blood Advances*, 2025

Ocular Adverse Events in DREAMM-7 and DREAMM-8

	DREAMM-7 BVd (N=242)	DREAMM-8 BPd (N=150)
Overall grade ≥2 OEFs, n (%)	209 (86)	131 (87)
Time to onset of first grade ≥2 event, median (d)	43	32
Time to resolution of first grade ≥2 event, median (d)	86	109
First event resolved, n (%)	169/209 (81)	113/131 (86)
Occurrences = 1, n (%)	63/209 (30)	36/131 (27)
Occurrences = 2, n (%)	35/209 (17)	20/131 (15)
Occurrences ≥3, n (%)	111/209 (53)	75/131 (57)
Grade ≥2 corneal exam finding, n (%)	198 (82)	120 (80)
Grade ≥2 BCVA change, n (%)	194 (80)	124 (83)



Reprinted from Shi C, et al. *J Vis.* 2020;20(8):29.
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AR, adverse reaction; BCVA, best-corrected visual acuity; BPd, belantamab mafodotin, pomalidomide, and dexamethasone; BVd, belantamab mafodotin, bortezomib, and dexamethasone; OEF, ophthalmic examination finding.

[a] Post hoc pooled analysis (BVd and BPd) in patients with normal baseline BCVA (20/25 or better in ≥1 eye). [b] Percentage has been rounded so that the total adds up to 100% in the graph.

Grade ≥2 Ocular Exam Findings frequency comprised corneal exam findings alone without changes in BCVA

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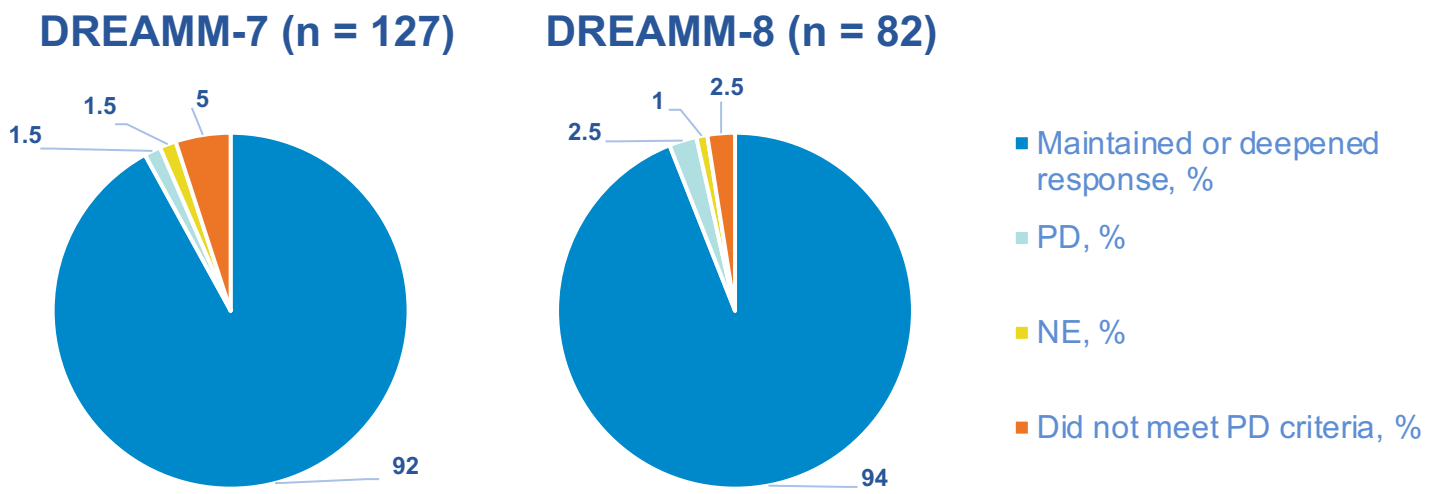
Hajek et al, *EHA,* 2025; Mateos et al, *Blood Advances*, 2025

Belamaf Ocular Adverse Events Managed Effectively with Dose Delays and Dose Reductions

- Ocular events in DREAMM-7 and DREAMM-8 were managed by belamaf dose modifications (dose delays or dose reductions)
- In DREAMM-7 and DREAMM-8, 92% and 94% of patients, respectively, sustained or deepened their response during their first extended dose delay

Last Assessed Response During First Extended Belamaf Dose Delay of >9 Weeks



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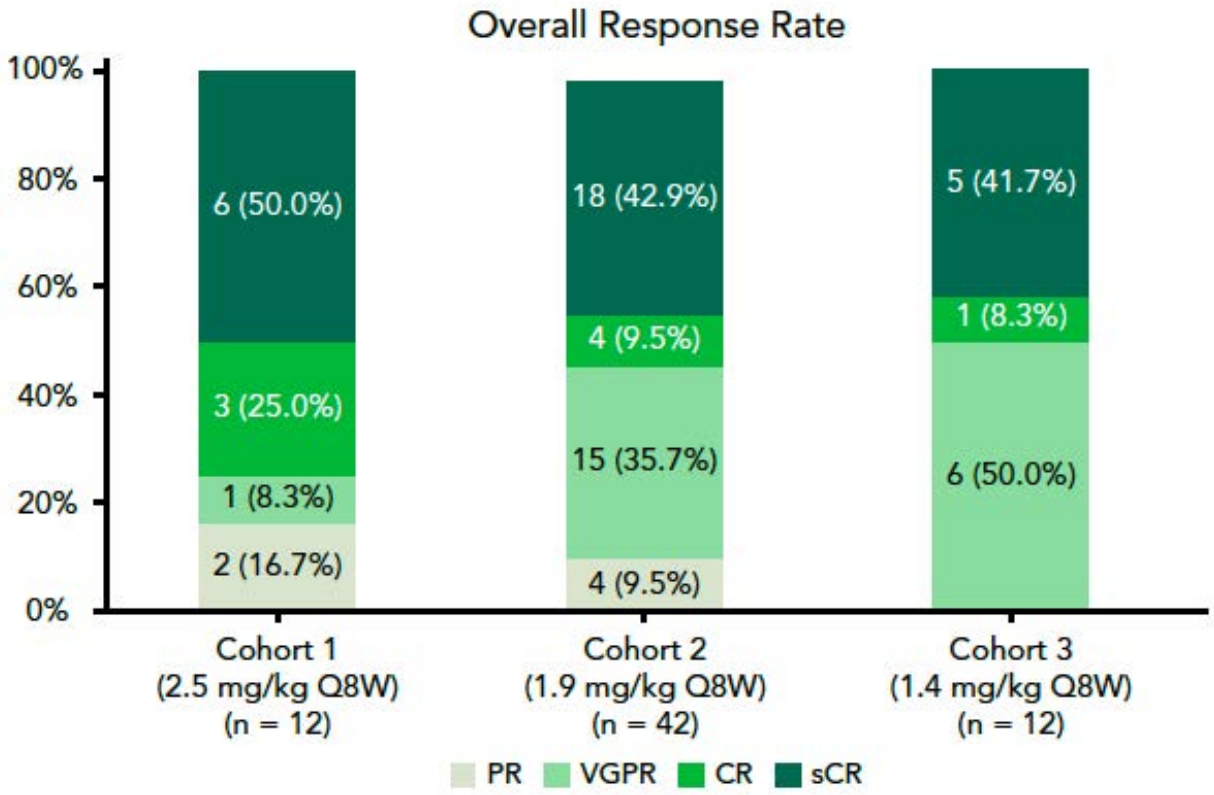
Hajek et al, *EHA,* 2025; Mateos et al, *Blood Advances*, 2025

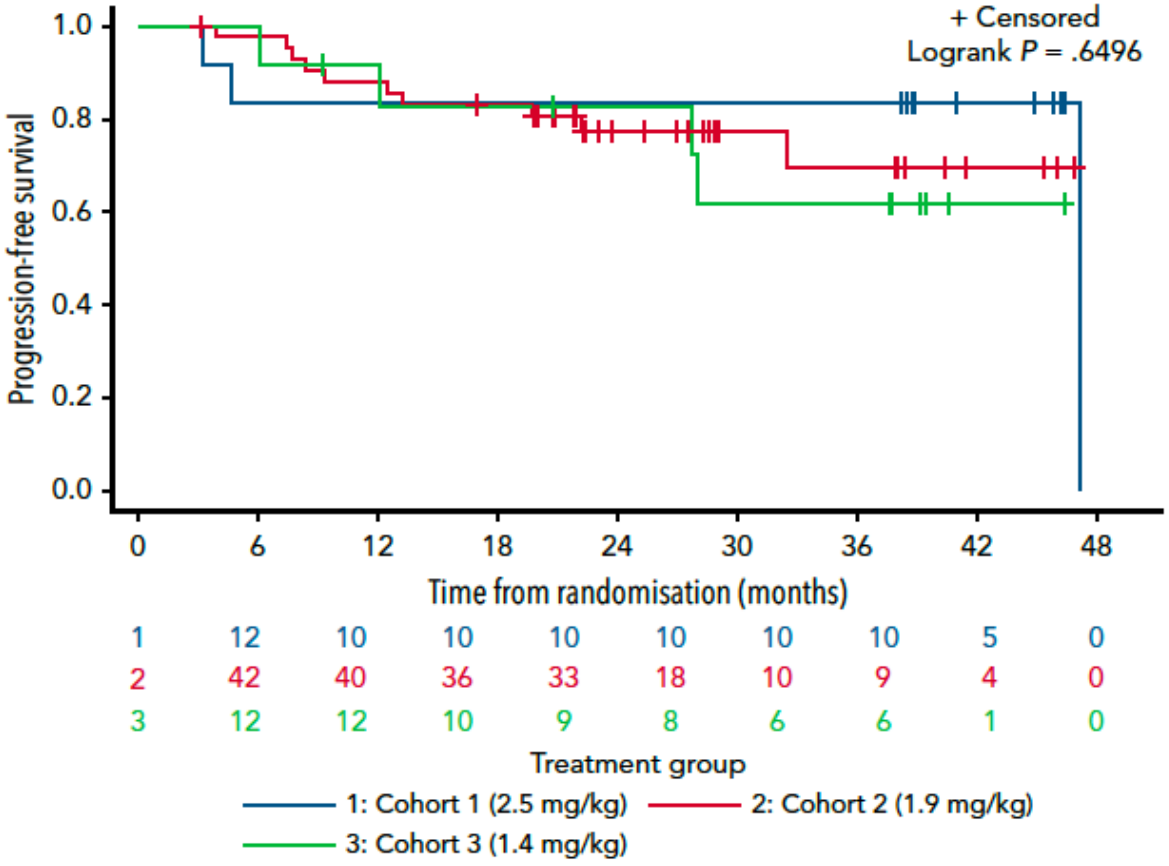
Belamaf Dose Modifications Guidance

Regimen	Severity of OEF	DREAMM-7 BVd (cycle length: 3 wk)	DREAMM-8 BPd (cycle length: 4 wk)
Standard schedule	No finding Grade 1	2.5 mg/kg Q3W	2.5 mg/kg once in cycle 1 followed by 1.9 mg/kg Q4W from cycle 2
Reduced dose level 1	Grade 2 Grade 3	Dose delay until resolution to grade ≤1, then resume at same dose (2.5 mg/kg Q3W or 1.9 mg/kg Q3W) after grade 2 finding or 1.9 mg/kg Q3W after grade 3 finding	Dose delay until resolution of both components to grade ≤1, then 1.9 mg/kg Q8W
	Grade 4	Discontinuation or 1.9 mg/kg Q3W rechallenge after improvement and sponsor approval	-
Reduced dose level 2	Grade 4	NA	Dose delay until KVA grade ≤1, then 1.4 mg/kg Q8W

Mateos et al, *Blood Advances*, 2025

DREAMM-9: Belamaf-Len-Dex in Newly Diagnosed Transplant Ineligible Myeloma





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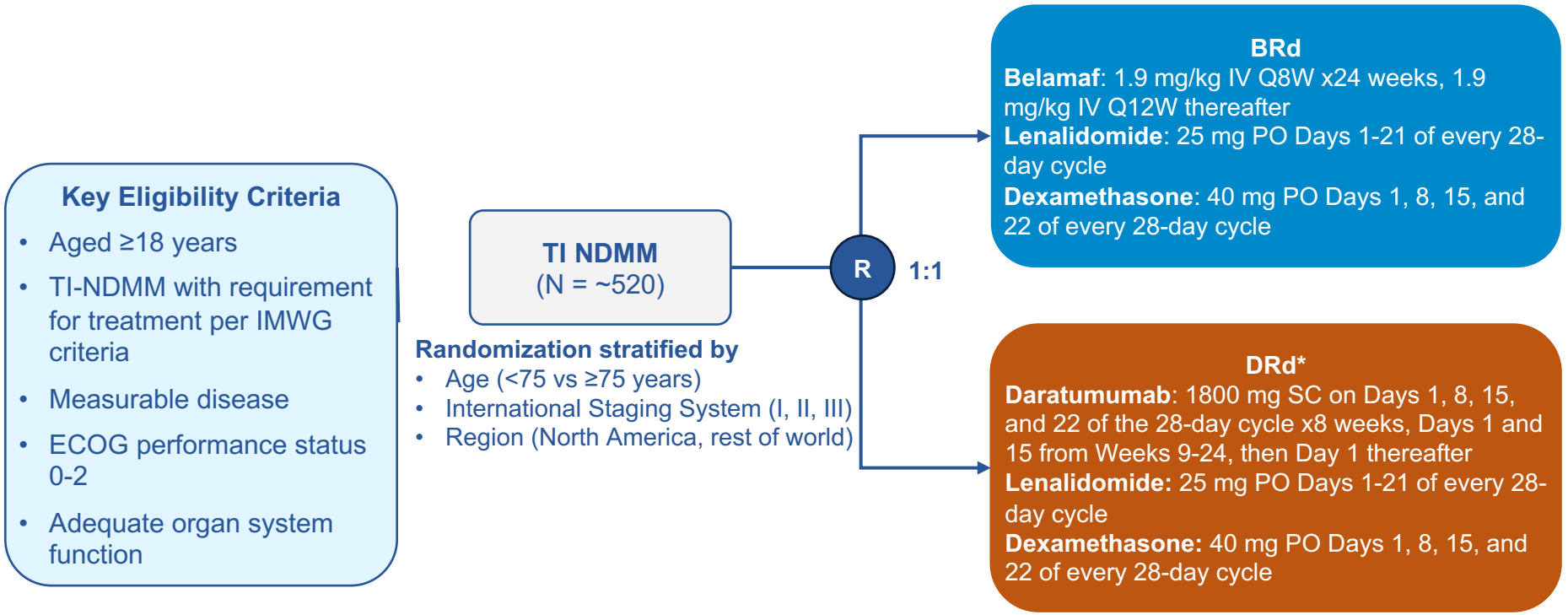
Terpos et al, *Blood, 2026*

DREAMM-10: Belamaf-Rd vs. Dara-Rd in Newly Diagnosed Transplant Ineligible Myeloma



- **Dual primary endpoints:** MRD-negativity rate and PFS
- **Key secondary endpoints:** OS, PFS2

Currently Enrolling!

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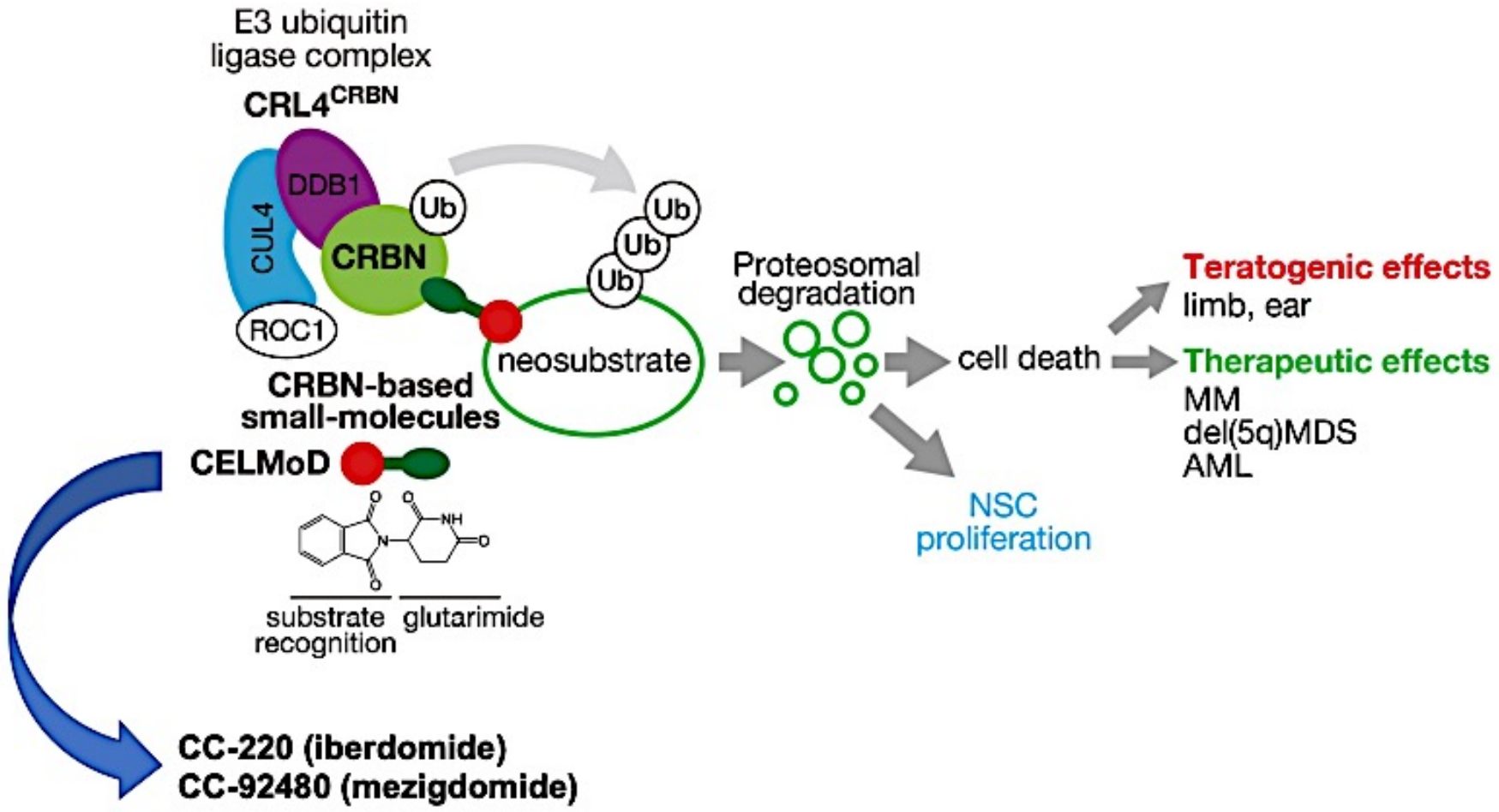
NCT06679101; Lonial S et al. *EHA*, 2025. Abstract PS1793.

Agenda

- Belantamab mafodotin
  - Current application in relapsed/refractory myeloma
  - Management of ocular adverse events
  - Emerging data in newly diagnosed myeloma and ongoing studies

- **CELMoDs**
  - **Iberdomide**
  - **Mezigdomide**

Cereblon E3 Ligase Modulators (CELMoDs)



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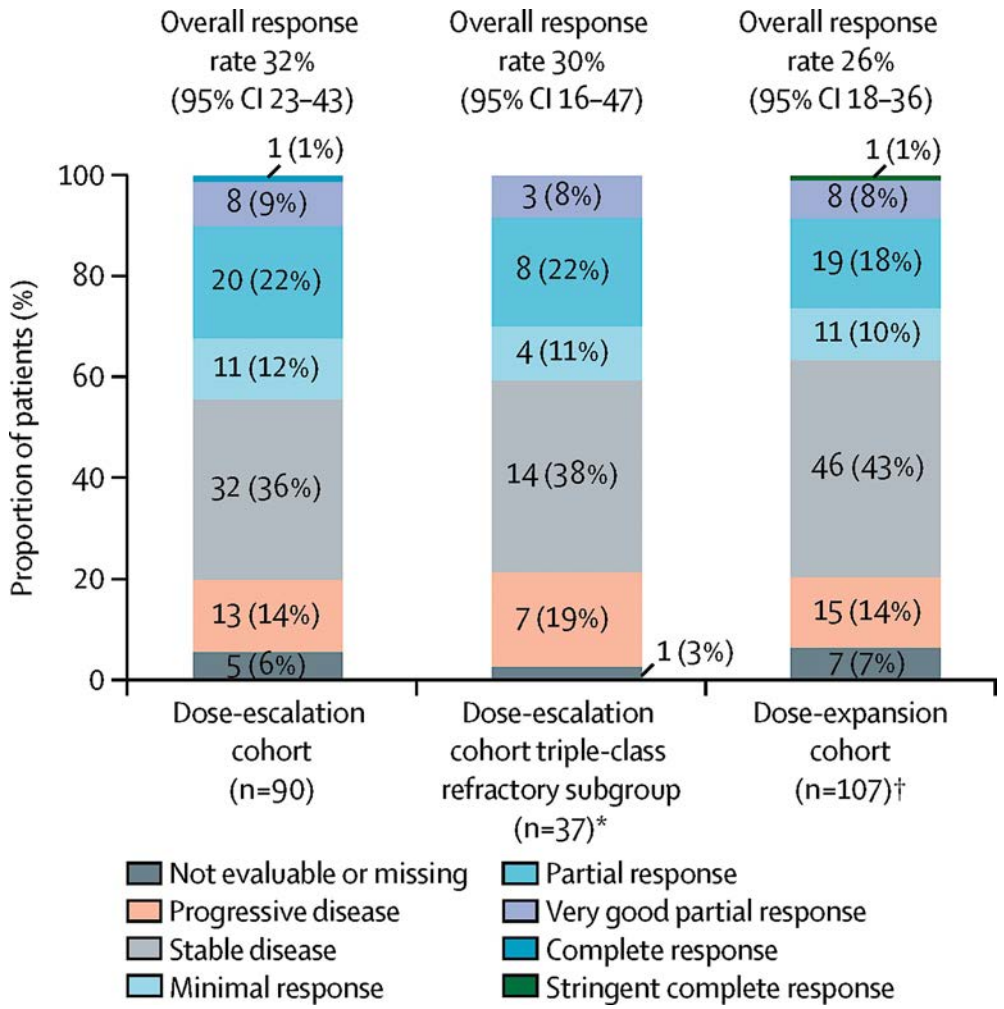
Sato et al, *Front. Cell Dev. Biol*, 2021

Iberdomide + Dex in Late Relapsed/Refractory Myeloma



- At dose-expansion in patients ≥3 lines of prior therapy and and triple-class refractory (N=107)
- ORR 26%
- Median PFS 3 months

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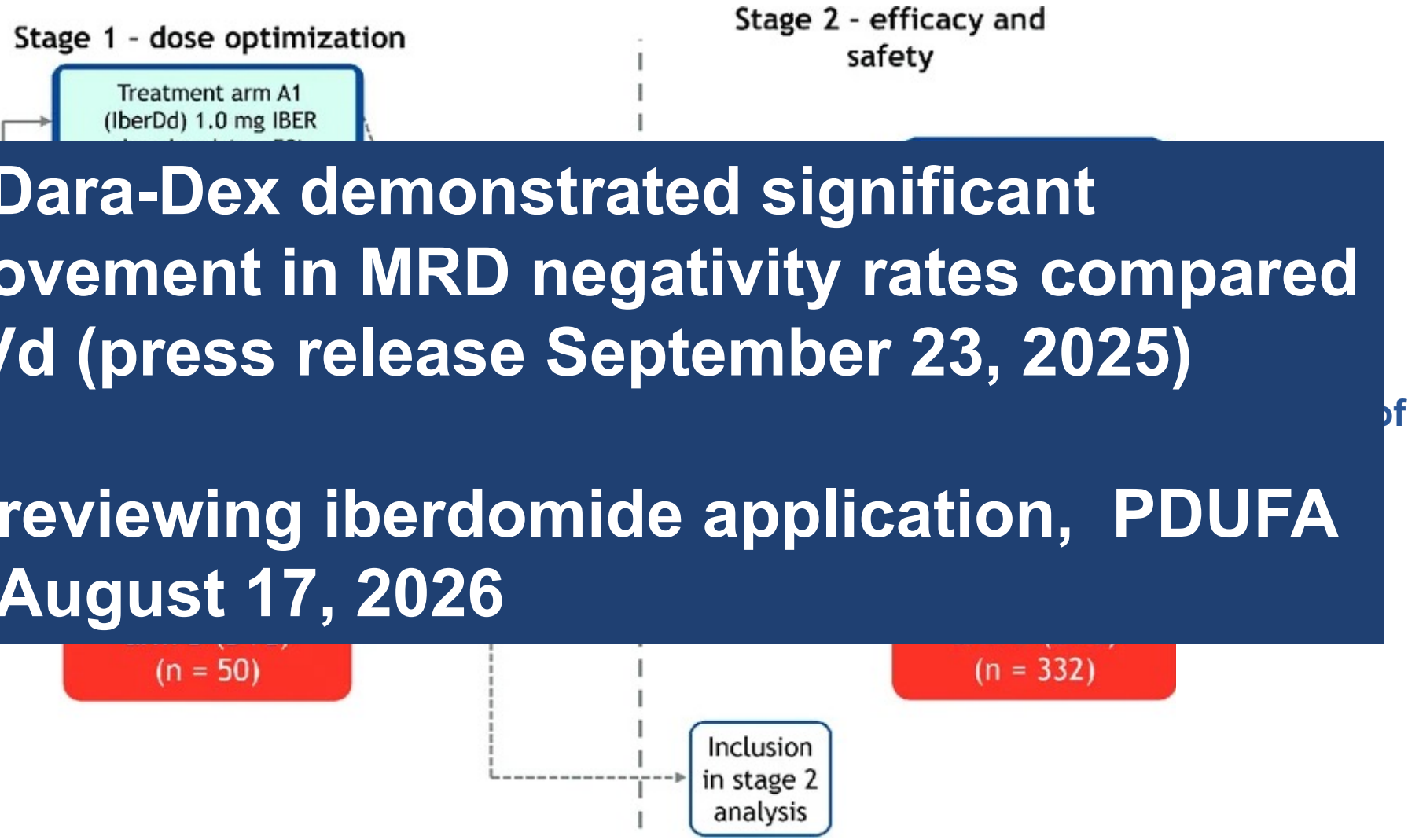
Lonial et al, *Lancet Haematology*, 2022

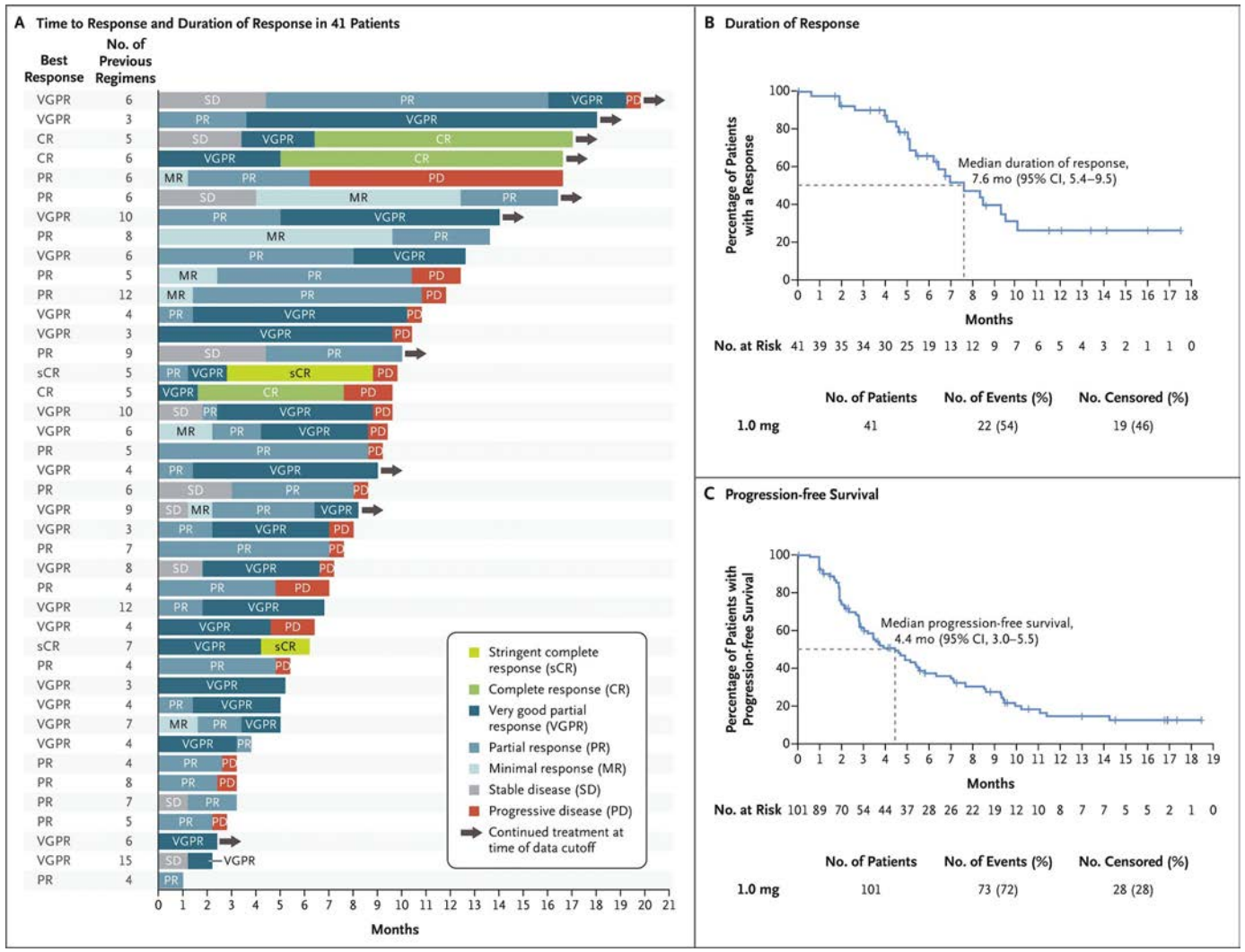
EXCALIBUR-RRMM: Iber-Dara-Dex vs. DVd



- Iber-Dara-Dex demonstrated significant improvement in MRD negativity rates compared to DVd (press release September 23, 2025)
- FDA reviewing iberdomide application, PDUFA date August 17, 2026

Lonial et al, *Future Oncology*, 2025

Mezigdomide + Dex in Late Relapsed/Refractory Myeloma



- Phase 2 (N=101) in patients ≥3 lines of prior therapy and and triple-class refractory
- ORR 41%
- Median PFS 4.4 months

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Richardson et al, *NEJM*, 2023

SUCCESSOR-2: Mezi + Carfilzomib-Dex (Kd) vs. Kd

- ≥1
- Le
  ex
- Pr
  exposure excluded

- **Mezi-KD demonstrated significant improvement in PFS compared to Kd (press release March 9, 2026)**

Summary

- Belantamab mafadotin in combination with bortezomib/dexamethasone (Bela-Vd) approved in US for RRMM ≥2 prior lines of therapy (October, 2025)
  - Signifcant PFS and OS benefit of BelaVd vs. daratumumab, bortezomib, dexamethasone in DREAMM-7 study
  - Ocular adverse events managed effectively with dose delays and dose reductions

- Oral CELMoDs represent next generation IMiDs
  - Iberdomide and Mezigdomide both with positive data in randomized phase 3 studies in combination with other standard agents
  - Iberdomide, daratumumab/dexamethasone under FDA review (PDUFA date in August, 2026) based on EXCALIBUR study

QUESTIONS?

Module 5: Gastroesophageal Cancers

Role of Anti-PD-1/PD-L1- and CLDN18.2-Directed Antibodies in the Management of Gastroesophageal Cancers — Dr Klempner

Management of HER2-Positive Gastroesophageal Cancers — Dr Janjigian

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Module 5: Gastroesophageal Cancers

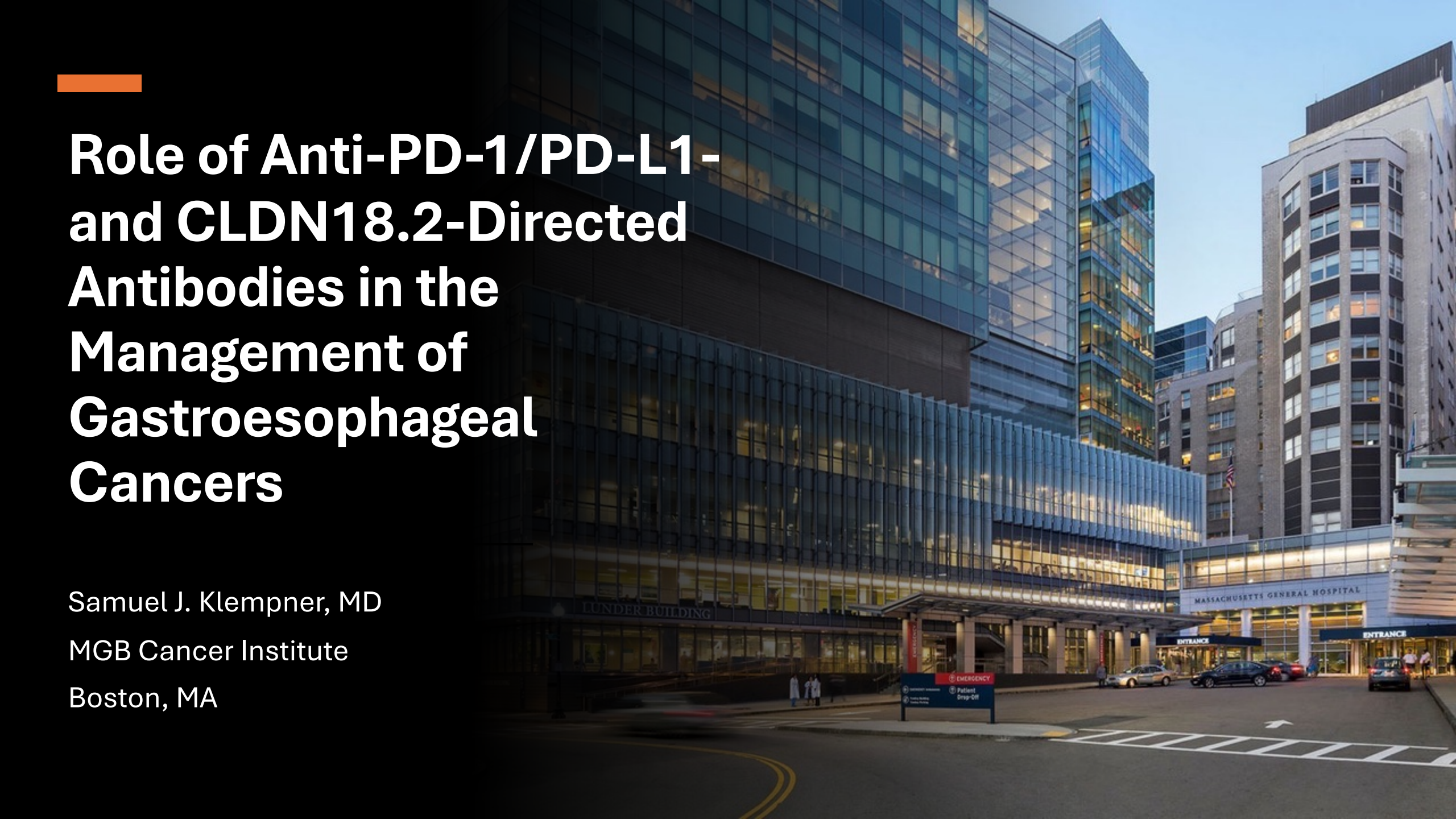
Role of Anti-PD-1/PD-L1- and CLDN18.2-Directed Antibodies in the Management of Gastroesophageal Cancers — Dr Klempner

Management of HER2-Positive Gastroesophageal Cancers — Dr Janjigian

Module 5: Gastroesophageal Cancers

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

Role of Anti-PD-1/PD-L1- and CLDN18.2-Directed Antibodies in the Management of Gastroesophageal Cancers



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Boston, MA

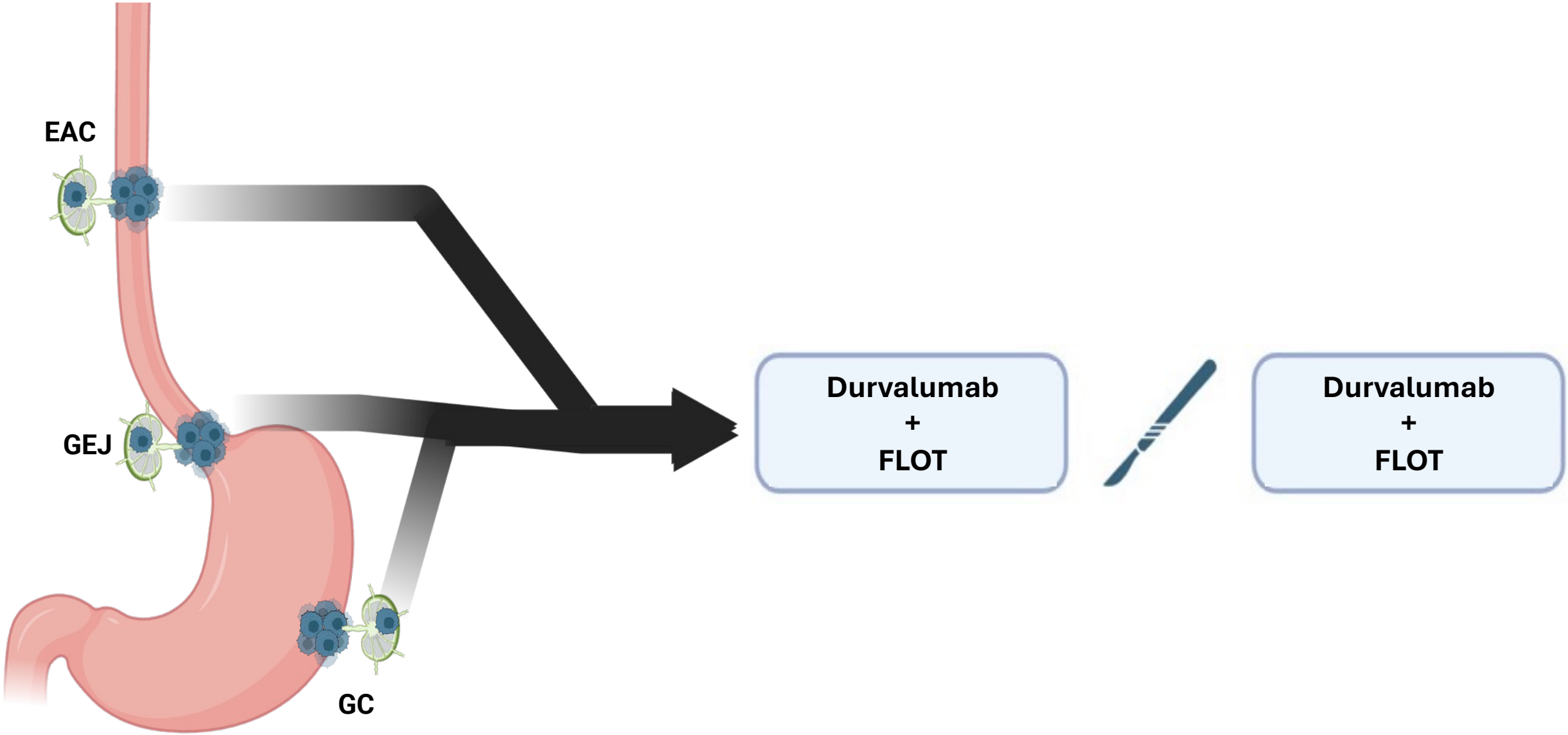
Disclosures

Advisory Committees	Astellas, AstraZeneca Pharmaceuticals LP, BeOne, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology, EsoBiotec, Gilead Sciences Inc, I-Mab Biopharma, Jazz Pharmaceuticals Inc, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Signet Therapeutics, Taiho Oncology Inc
Consulting Agreements	Astellas
Contracted Research	Arcus Biosciences, AstraZeneca Pharmaceuticals LP, I-Mab Biopharma, Mersana Therapeutics Inc, Parabilis Medicines
Data and Safety Monitoring Boards/Committees	Sanofi
Stock OPTIONS — Private Companies	MBrace Therapeutics
Nonrelevant Financial Relationships	Debbie's Dream Foundation, Degregorio Family Foundation, Gastric Cancer Foundation, National Cancer Institute/National Institutes of Health, NCCN (member of Gastric and Esophageal Guidelines Committees), Stand Up 2 Cancer/AACR, Torrey Coast Foundation

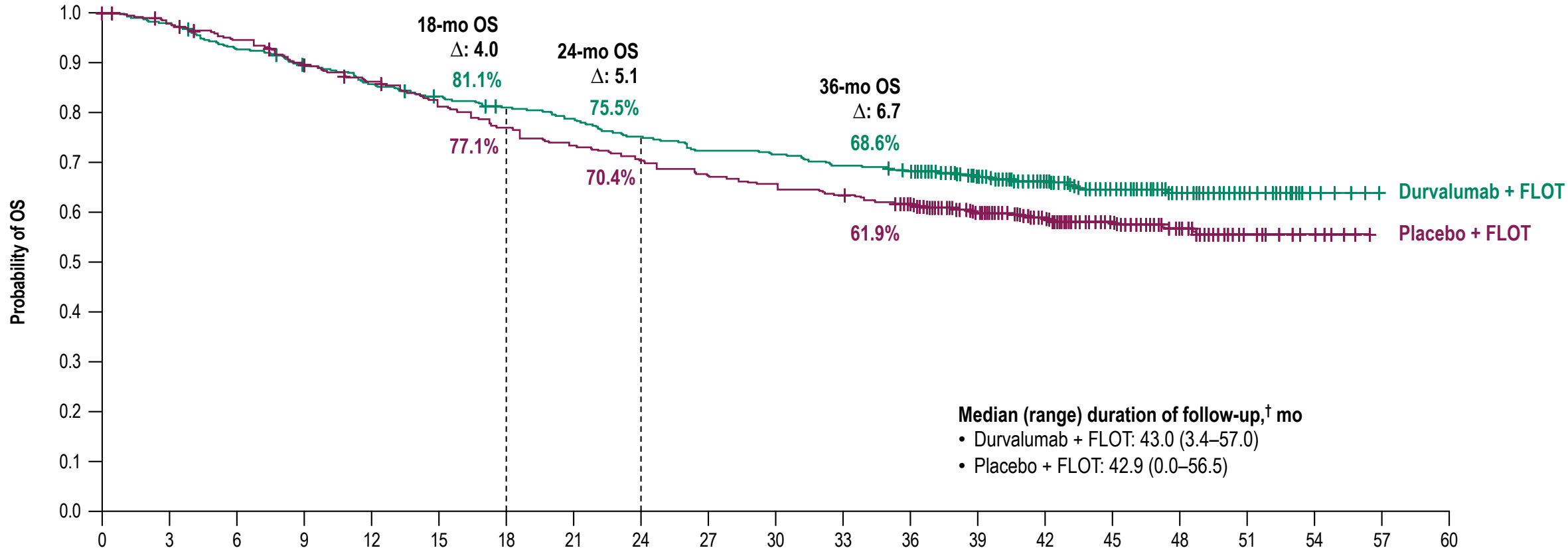
Overview

1. Perioperative Updates
2. Perioperative Subgroups and the Future
3. The Frontline ICI Landscape
4. ILUSTRO: A GLOW-UP for Zolbetuximab
5. Expanding the CLDN18.2 world with ADCs

Non-Metastatic Paradigms: Present



MATTERHORN Overall Survival Data

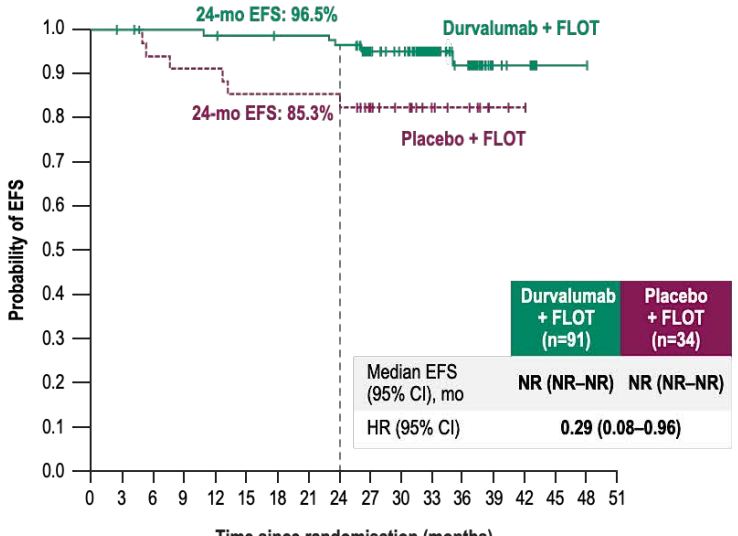


No. of participants at risk																					Total no. of events
Durvalumab + FLOT	474	464	438	422	403	389	377	367	351	338	334	323	316	255	182	112	71	29	6	1	0	160
Placebo + FLOT	474	457	439	414	395	374	355	338	324	310	298	293	278	221	167	99	61	23	7	0	0	192

Tabernero J, et al. ESMO Congress 2025; Berlin, DE. LBA81.

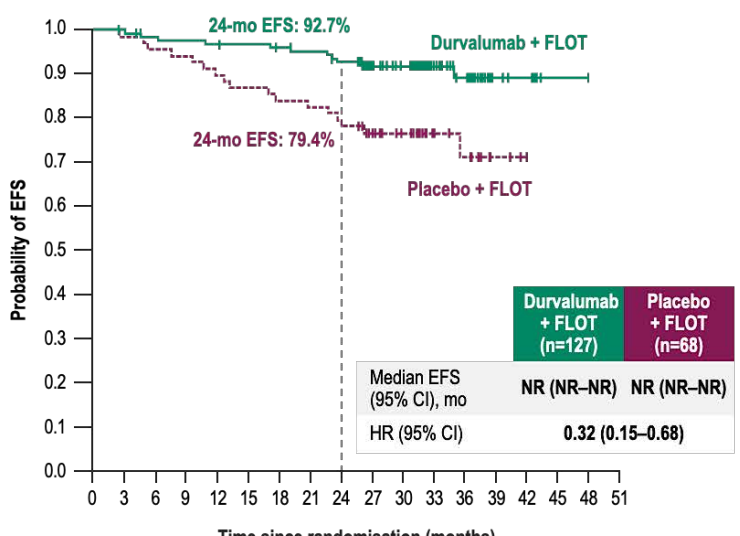
Prognostic Variables in MATTERHORN: Path Response

pCR



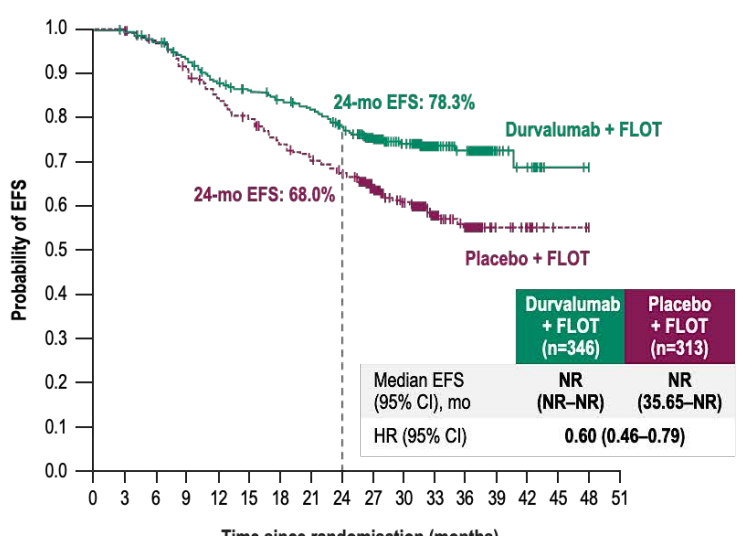
No. of participants at risk																		Total no. of events
Durvalumab + FLOT	91	90	88	88	87	86	85	85	83	68	60	38	27	7	5	1	1	0	5
Placebo + FLOT	34	34	32	31	31	29	29	29	29	23	16	11	8	2	1	0	0	0	6

MPR



No. of participants at risk																		Total no. of events
Durvalumab + FLOT	127	126	122	121	120	119	117	115	111	91	78	45	34	9	6	1	1	0	11
Placebo + FLOT	68	67	65	64	61	59	57	56	54	45	35	19	13	3	1	0	0	0	17

Any pathological response*



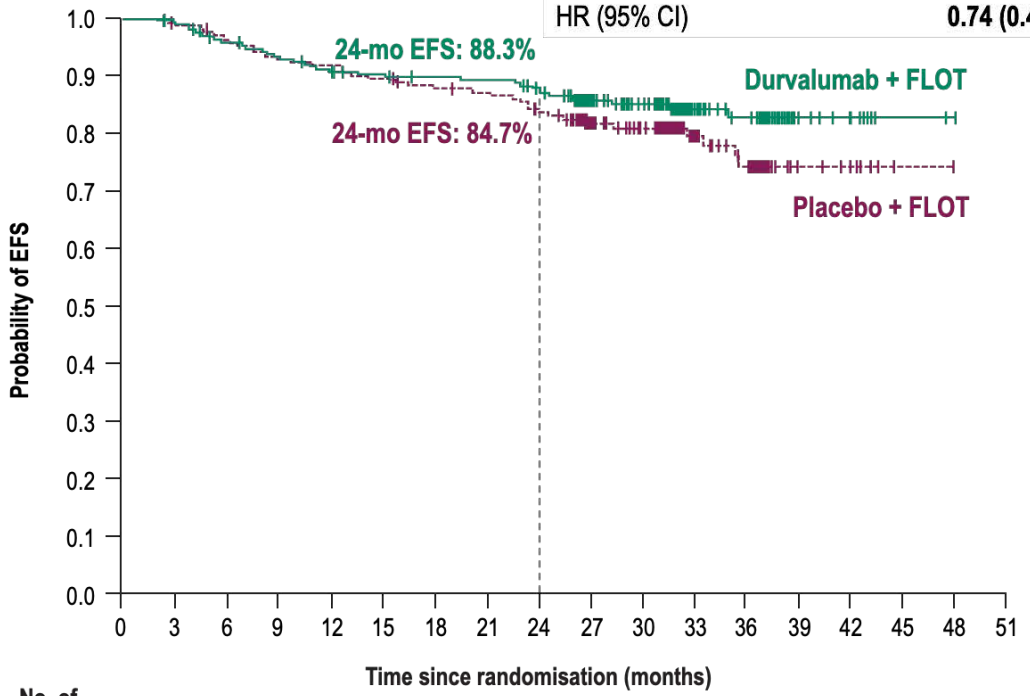
No. of participants at risk																		Total no. of events
Durvalumab + FLOT	346	343	330	314	295	283	273	265	248	201	162	90	75	28	17	2	1	0	87
Placebo + FLOT	313	312	300	279	257	242	224	213	200	160	129	74	54	21	17	2	1	0	123

Tabernero J, et al. ESMO Congress 2025; Berlin, DE. LBA81.

Prognostic Variables in MATTERHORN: Nodal Status

ypN-

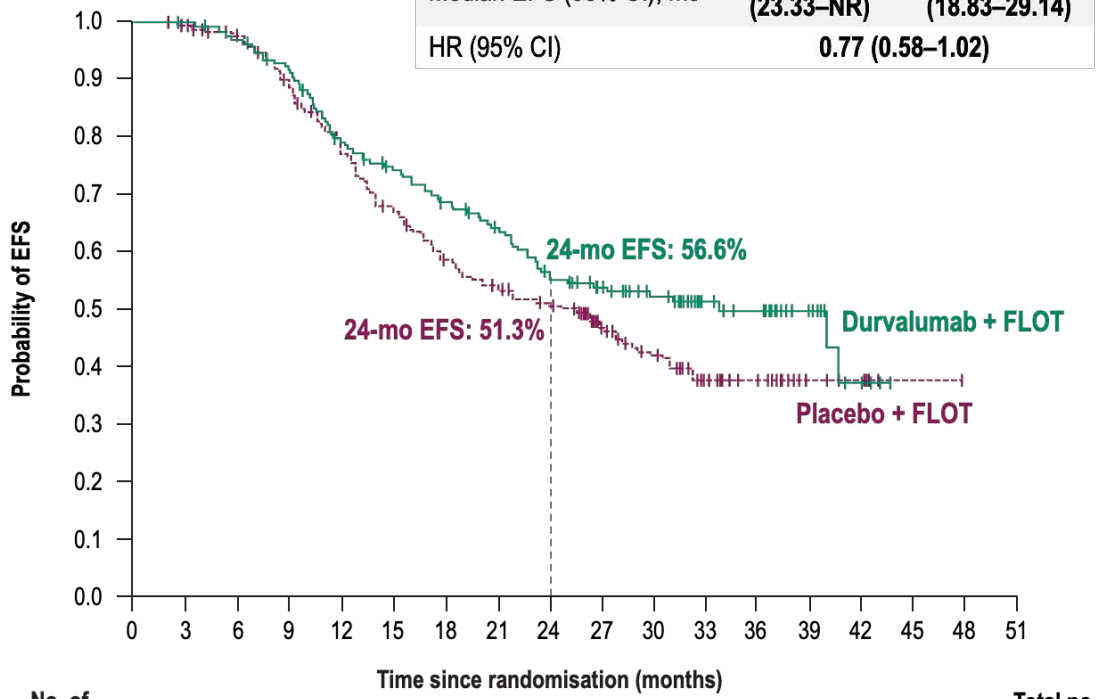
	Durvalumab + FLOT (n=239)	Placebo + FLOT (n=179)
Median EFS (95% CI), mo	NR (NR–NR)	NR (NR–NR)
HR (95% CI)	0.74 (0.46–1.18)	



No. of participants at risk																		Total no. of events
Durvalumab + FLOT	239	237	224	217	211	206	203	202	196	158	123	71	57	19	15	2	1	0	35
Placebo + FLOT	179	178	172	166	163	159	155	152	145	123	99	57	40	16	13	1	1	0	36

ypN+

	Durvalumab + FLOT (n=172)	Placebo + FLOT (n=221)
Median EFS (95% CI), mo	33.84 (23.33–NR)	25.56 (18.83–29.14)
HR (95% CI)	0.77 (0.58–1.02)	



No. of participants at risk																		Total no. of events
Durvalumab + FLOT	172	171	165	154	132	121	110	100	87	72	60	32	28	13	5	0	0	81
Placebo + FLOT	221	218	207	187	161	139	119	108	100	75	59	31	25	10	8	1	0	121

Tabernero J, et al. ESMO Congress 2025; Berlin, DE. LBA81.

We Can Do It! FLOT Delivery in MATTERHORN

Table 1. FLOT treatment delivery

	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)*
Number of neoadjuvant FLOT cycles (Days 1 and 15), n (%)		
Cycle 1 Day 1	475 (100)	469 (100)
Cycle 1 Day 15	469 (98.7)	459 (97.9)
Cycle 2 Day 1	462 (97.3)	452 (96.4)
Cycle 2 Day 15	456 (96.0)	446 (95.1)
Number who received ⩾1 adjuvant FLOT cycle	n=354	n=345
Number of adjuvant FLOT cycles (Days 1 and 15), n (%)		
Cycle 3 Day 1	354 (74.5)	345 (73.6)
Cycle 3 Day 15	341 (71.8)	333 (71.0)
Cycle 4 Day 1	318 (66.9)	319 (68.0)
Cycle 4 Day 15	292 (61.5)	302 (64.4)

Rows are cumulative and participants are included if they have taken treatment up to that number of cycles. If a cycle was prolonged due to toxicity, this was counted as 1 cycle. A cycle was counted if treatment was started, even if the full dose was not delivered.
*Safety analysis set (participants who received ⩾1 dose of study treatment); one participant in the placebo + FLOT arm received a single dose of durvalumab and is, therefore, included in the durvalumab + FLOT arm for the safety analysis.

FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Table 2. FLOT component discontinuation due to AEs by treatment period

	Neoadjuvant		Adjuvant		Overall	
	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)*	Durvalumab + FLOT (n=365)*	Placebo + FLOT (n=351)*	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)*
⩾1 FLOT component discontinuation due to AEs,† n (%)	**31 (6.5)**	**36 (7.7)**	**78 (21.4)**	**53 (15.1)**	**121 (25.5)**	**95 (20.3)**
5-fluorouracil	13 (2.7)	11 (2.3)	40 (11.0)	28 (8.0)	64 (13.5)	42 (9.0)
Oxaliplatin	27 (5.7)	30 (6.4)	70 (19.2)	41 (11.7)	112 (23.6)	81 (17.3)
Docetaxel	21 (4.4)	25 (5.3)	48 (13.2)	30 (8.5)	80 (16.8)	59 (12.6)

*Safety analysis set (participants who received ⩾1 dose of study treatment); one participant in the placebo + FLOT arm received a single dose of durvalumab and is, therefore, included in the durvalumab + FLOT arm for the safety analysis. †Includes discontinuations of 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel.

AE, adverse event; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Table 3. AEs leading to FLOT discontinuation by treatment period

	Neoadjuvant		Adjuvant		Overall	
	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)*	Durvalumab + FLOT (n=365)*	Placebo + FLOT (n=351)*	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)*
⩾1 FLOT component discontinuation due to AEs,† n (%)	**31 (6.5)**	**36 (7.7)**	**78 (21.4)**	**53 (15.1)**	**121 (25.5)**	**95 (20.3)**
Peripheral neuropathy‡	14 (2.9)	16 (3.4)	7 (1.9)	5 (1.4)	25 (5.3)	27 (5.8)
Neutropenia§	1 (0.2)	1 (0.2)	10 (2.7)	7 (2.0)	15 (3.2)	8 (1.7)
Infusion-related reaction	1 (0.2)	0	12 (3.3)	5 (1.4)	13 (2.7)	5 (1.1)
Hypersensitivity‖	2 (0.4)	1 (0.2)	9 (2.5)	6 (1.7)	11 (2.3)	7 (1.5)

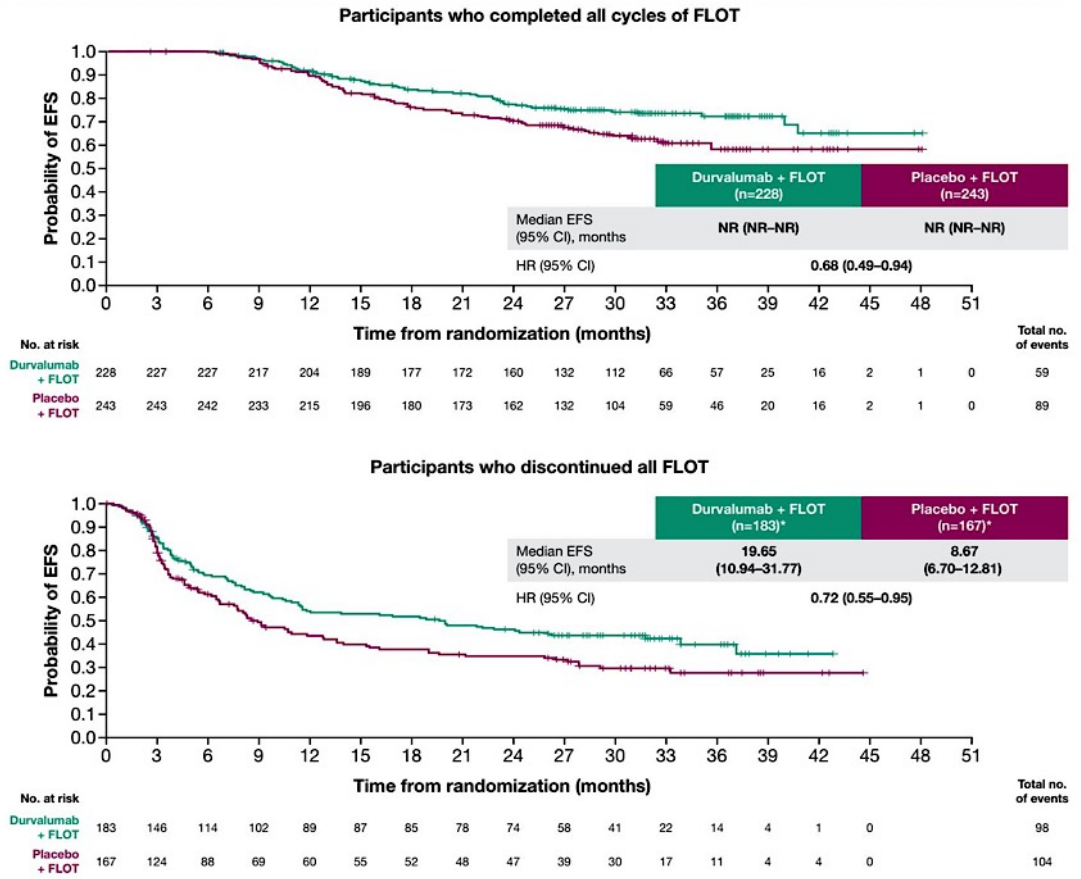
AEs shown are those occurring in ⩾2% of participants in either arm overall.
*Safety analysis set (participants who received ⩾1 dose of study treatment); one participant in the placebo + FLOT arm received a single dose of durvalumab and is, therefore, included in the durvalumab + FLOT arm for the safety analysis. †Includes discontinuations of 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel. ‡Grouped term includes the PTs peripheral sensory neuropathy, neuropathy peripheral, and paresthesia. §Grouped term includes the PTs neutropenia and neutrophil count decreased. ‖Grouped term includes the PTs hypersensitivity and drug hypersensitivity.

AE, adverse event; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; PT, Preferred Term.

Table 4. AEs leading to FLOT discontinuation by FLOT component

	5-fluorouracil		Oxaliplatin		Docetaxel	
	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)*	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)*	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)*
FLOT component discontinuation due to any AE, n (%)	**64 (13.5)**	**42 (9.0)**	**112 (23.6)**	**81 (17.3)**	**80 (16.8)**	**59 (12.6)**
Peripheral neuropathy†	2 (0.4)	1 (0.2)	24 (5.1)	27 (5.8)	11 (2.3)	7 (1.5)
Neutropenia‡	11 (2.3)	5 (1.1)	12 (2.5)	5 (1.1)	14 (2.9)	8 (1.7)
Infusion-related reaction	1 (0.2)	1 (0.2)	11 (2.3)	5 (1.1)	4 (0.8)	1 (0.2)
Hypersensitivity§	2 (0.4)	2 (0.4)	10 (2.1)	5 (1.1)	2 (0.4)	0

Figure 2. EFS by FLOT completion status

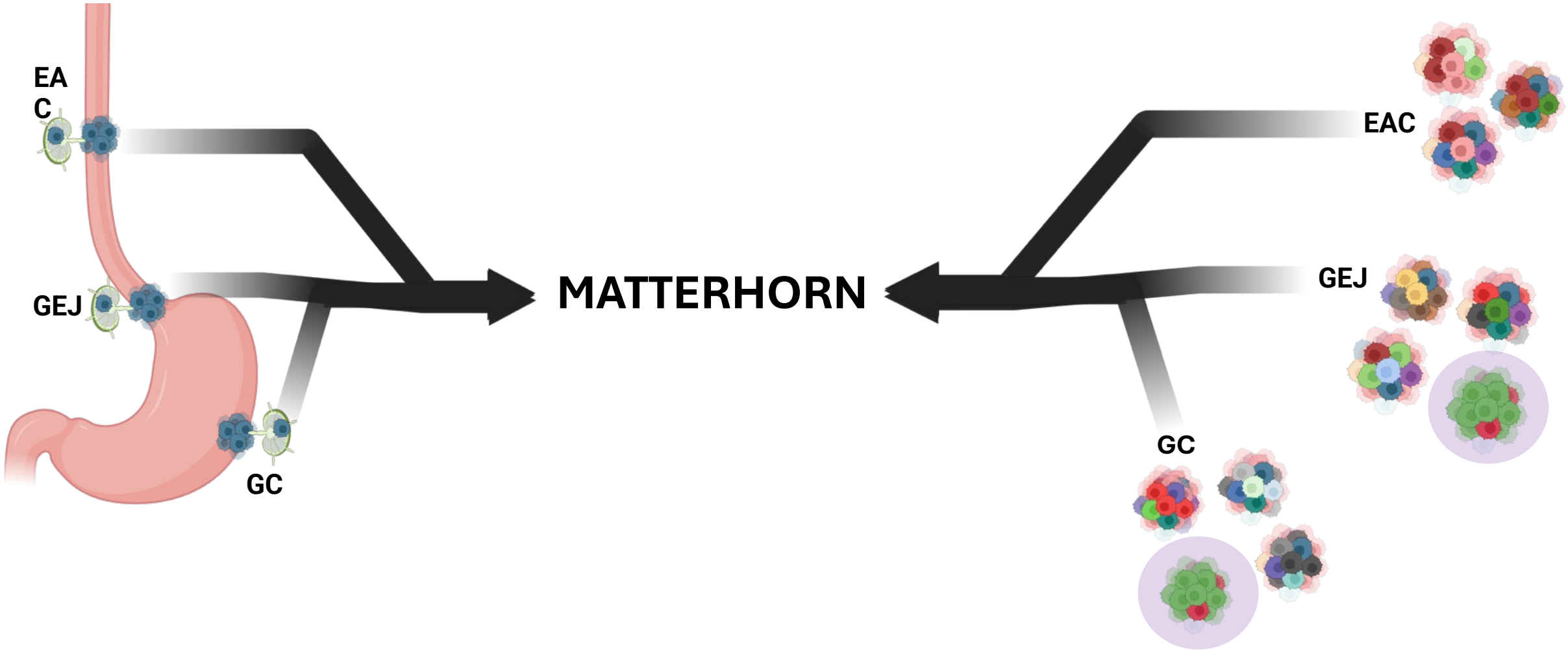


FLOT discontinuation and EFS

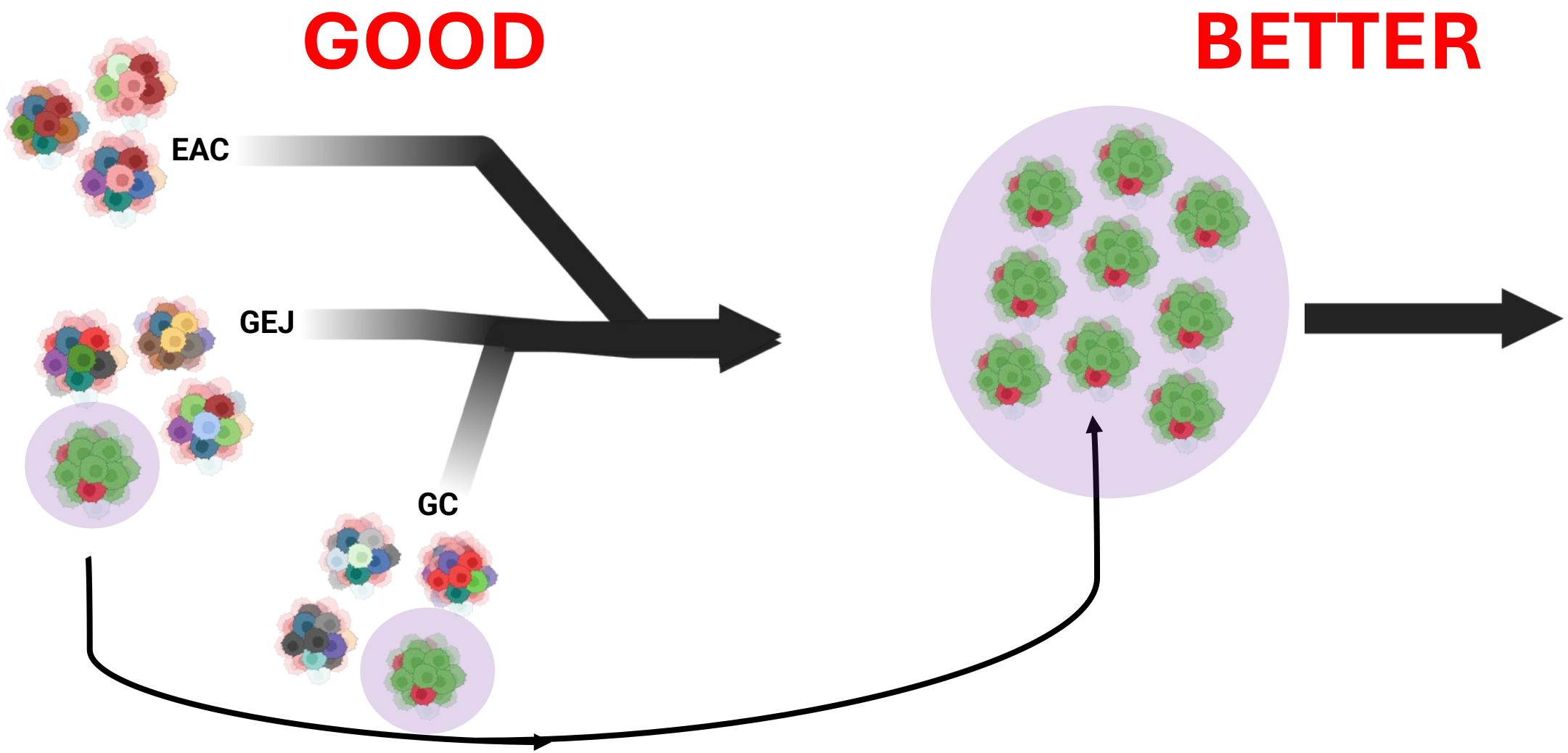
	Durvalumab + FLOT (n=474)	Placebo + FLOT (n=470)	EFS HR (95% CI)
Discontinued any FLOT components, n (%)	246 (51.9)	227 (48.3)	0.68 (0.53–0.88)
Discontinued 1 FLOT component, n (%)	47 (9.9)	45 (9.6)	
Discontinued 2 FLOT components, n (%)	15 (3.2)	15 (3.2)	0.35 (0.16–0.71)†
Discontinued 3 FLOT components, n (%)	1 (0.2)	0	
Discontinued all FLOT, n (%)*	183 (38.6)	167 (35.5)	0.72 (0.55–0.95)

Smyth et al ASCO GI 2026

Non-Metastatic Paradigms: Present



Leveraging Biology to Improve Operable Outcomes: dMMR/MSI-High

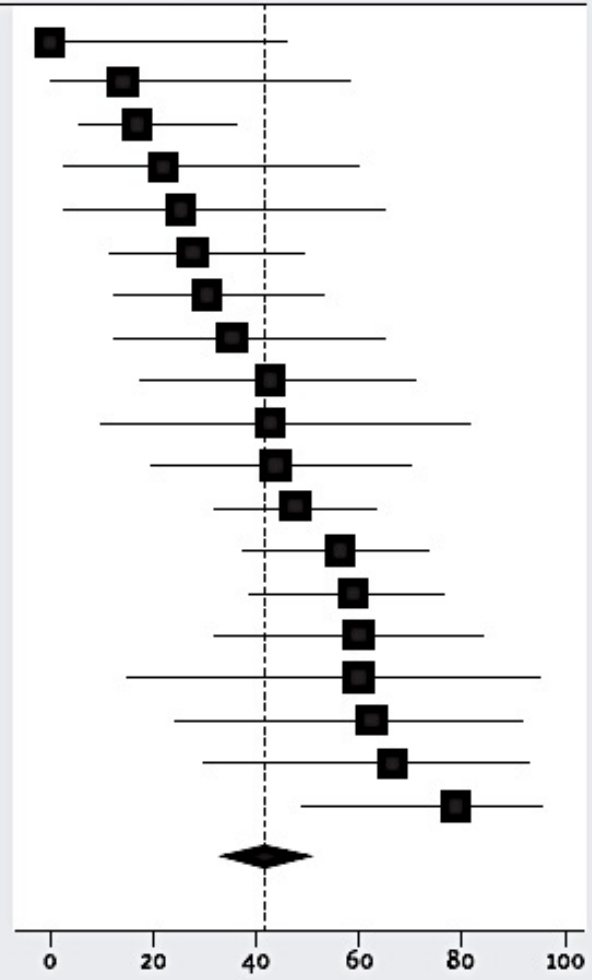


dMMR Data in Operable GEA: PathCR

A Overall pathological complete response (pCR) rate

Study	Event	Total	Prevalence	95% CI
MONEO 2025	0	6	0.00	(0.00–45.93)
Hasegawa 2022	1	7	14.29	(0.36–57.87)
IMHOTEP 2024	5	29	17.24	(5.85–35.77)
Kang 2025	2	9	22.22	(2.81–60.01)
Alcindor 2025	2	8	25.00	(3.19–65.09)
MATTERHORN 2025	7	25	28.00	(12.07–49.39)
Zhang 2024	7	23	30.43	(13.21–52.92)
Tang 2022	5	14	35.71	(12.76–64.86)
Chubenko 2024	6	14	42.86	(17.66–71.14)
Huang 2023	3	7	42.86	(9.90–81.59)
DRAGON IV/CAP 05 2024	7	16	43.75	(19.75–70.12)
Wang 2024	21	44	47.73	(32.46–63.31)
Sun 2024	18	32	56.25	(37.66–73.64)
NEONIPIGA 2022	17	29	58.62	(38.94–76.48)
INFINITY 2024	9	15	60.00	(32.29–83.66)
Shannon 2024	3	5	60.00	(14.66–94.73)
DANTE 2023	5	8	62.50	(24.49–91.48)
Sahvan 2025	6	9	66.67	(29.93–92.51)
NICE 2024	11	14	78.57	(49.20–95.34)
Total (95% CI)	**135**	**314**	**41.87**	**(33.20–51.07)**

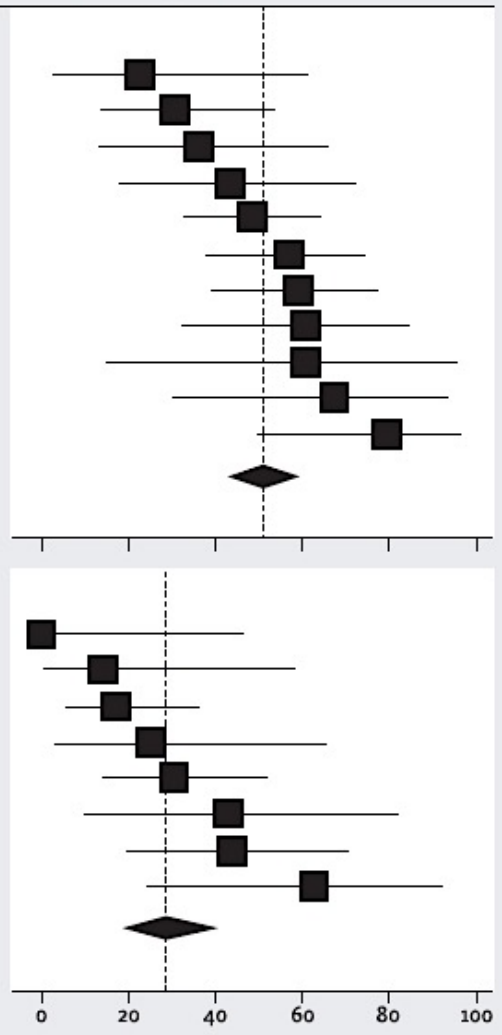
Heterogeneity: $Tau^2 = 0.3445$; $c^2 = 31.45$; df = 18 ($P = 0.0249$); $I^2 = 42.9\%$



PMID: 41687159

dMMR Data in Operable GEA: Duration of ICI and pCR

Study	Event	Total	Prevalence	95% CI
≥3 months				
Kang 2025	2	9	22.22	(2.81–60.01)
Zhang 2024	7	23	30.43	(13.21–52.92)
Tang 2022	5	14	35.71	(12.76–64.86)
Chubenko 2024	6	14	42.86	(17.66–71.14)
Wang 2024	21	44	47.73	(32.46–63.31)
Sun 2024	18	32	56.25	(37.66–73.64)
NEONIPIGA 2022	17	29	58.62	(38.94–76.48)
INFINITY 2024	9	15	60.00	(32.29–83.66)
Shannon 2024	3	5	60.00	(14.66–94.73)
Sahvan 2025	6	9	66.67	(29.93–92.51)
NICE 2024	11	14	78.57	(49.20–95.34)
Total (95% CI)	**105**	**208**	**50.52**	**(42.35–58.67)**
Heterogeneity: $Tau^2 = 0.0759$; $c^2 = 14.31$; df = 10 ($P = 0.1591$); $I^2 = 30.1\%$				
<3 months				
MONEO 2025	0	6	0.00	(0.00–45.93)
Hasegawa 2022	1	7	14.29	(0.36–57.87)
IMHOTEP 2024	5	29	17.24	(5.85–35.77)
Alcindor 2025	2	8	25.00	(3.19–65.09)
MATTERHORN 2025	7	25	28.00	(12.07–49.39)
Huang 2023	3	7	42.86	(9.90–81.59)
DRAGON IV/CAP 05 2024	7	16	43.75	(19.75–70.12)
DANTE 2023	5	8	62.50	(24.49–91.48)
Total (95% CI)	**30**	**106**	**28.40**	**(18.94–40.24)**
Heterogeneity: $Tau^2 = 0.1563$; $c^2 = 8.38$; df = 7 ($P = 0.3003$); $I^2 = 16.5\%$				
Test for subgroup differences: $c^2 = 8.84$; df = 1 ($P = 0.0029$)				



- All patients need MMR/MSI testing
- All dMMR/MSI-high should get neoadj ICI-containing
- Suggestion of higher pCR/MPR with dual ICI and longer neoadj duration

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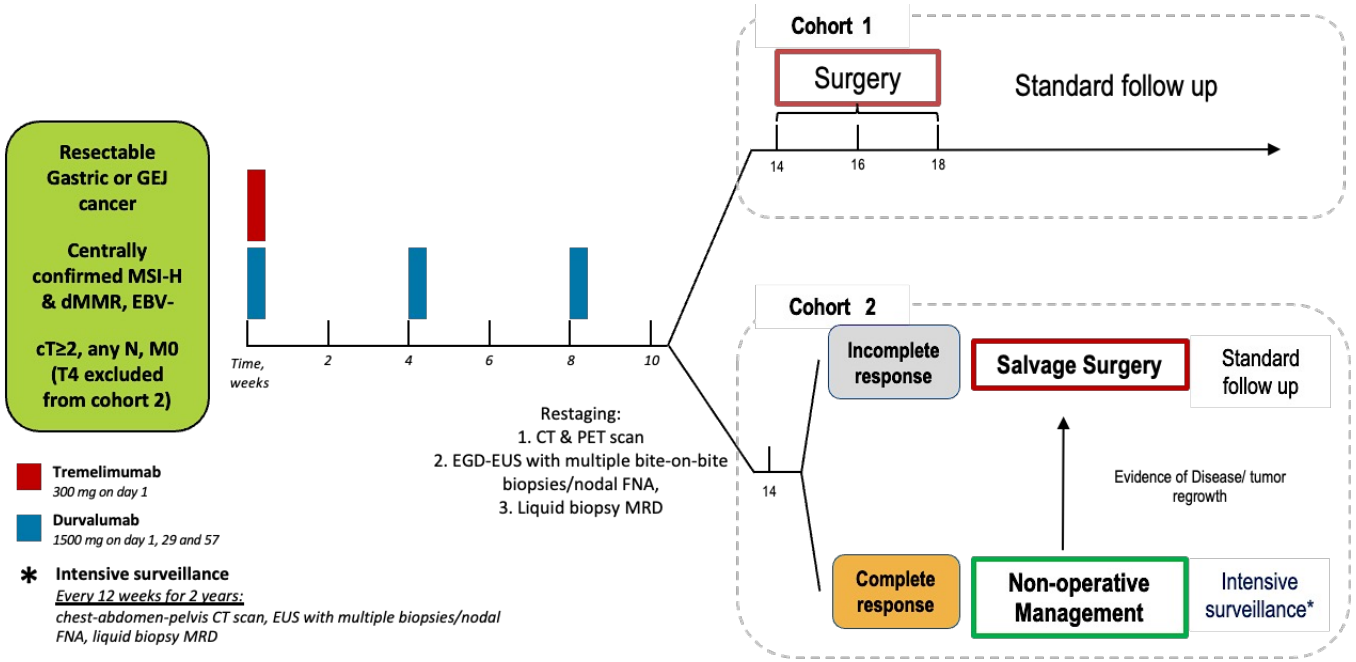
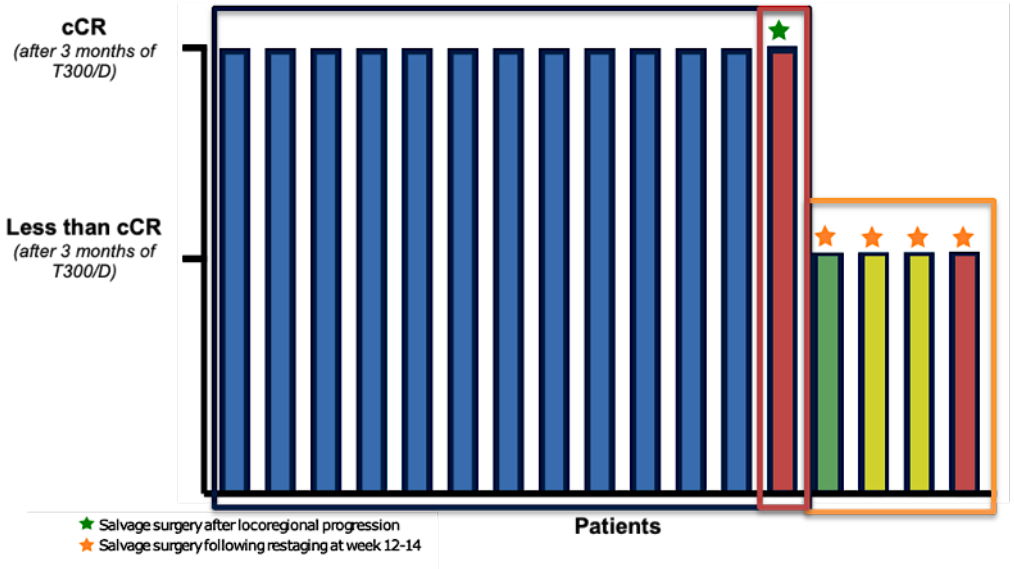
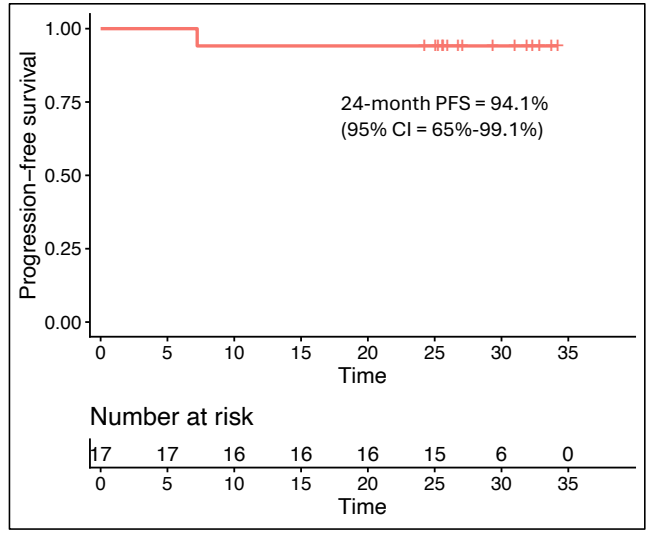
dMMR (and HER2) as non-op Foundation





- Clinical CR rate at 2 years = 71% (primary endpt)
- 24-month PFS = 94.1% (95% CI, 65%-99.1%)*
- 24-month OS = 100%
- 24-month GFS = 70.6% (95% CI, 43.1%-86.6%)*



INFINITY trial, AACR 2026

Overview

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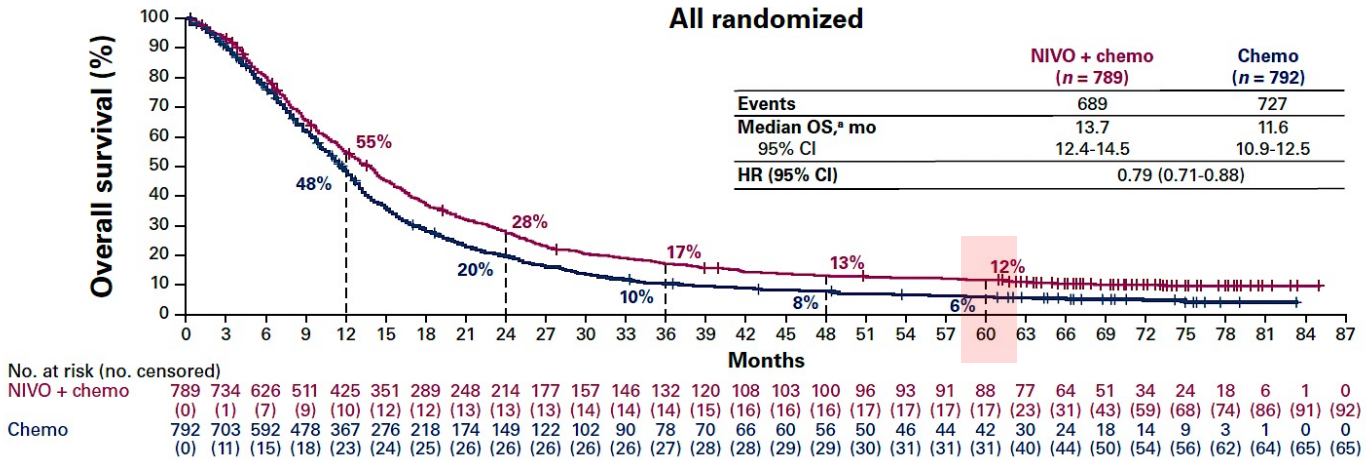
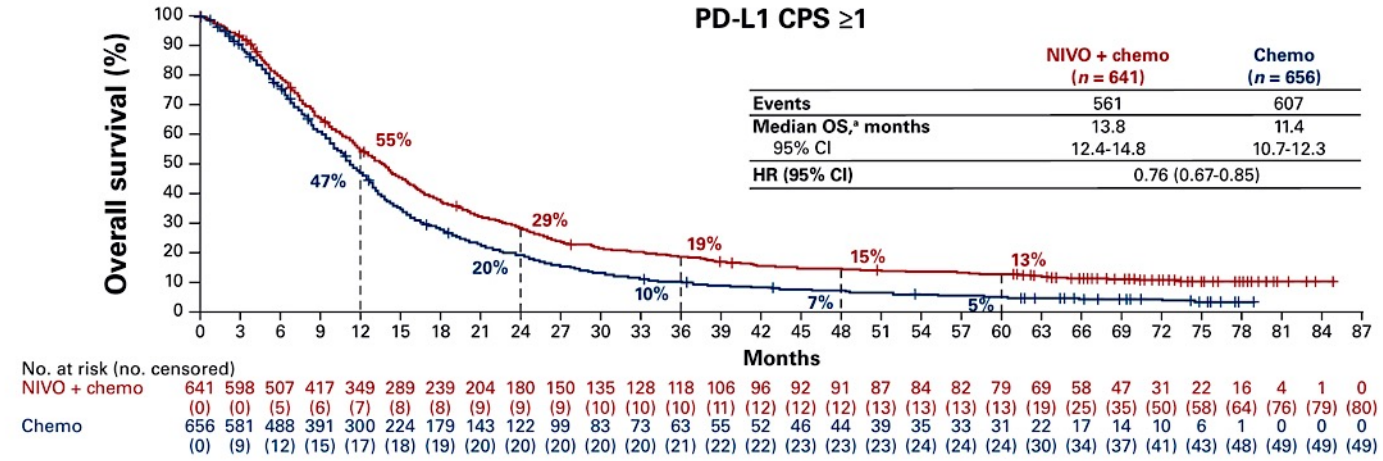
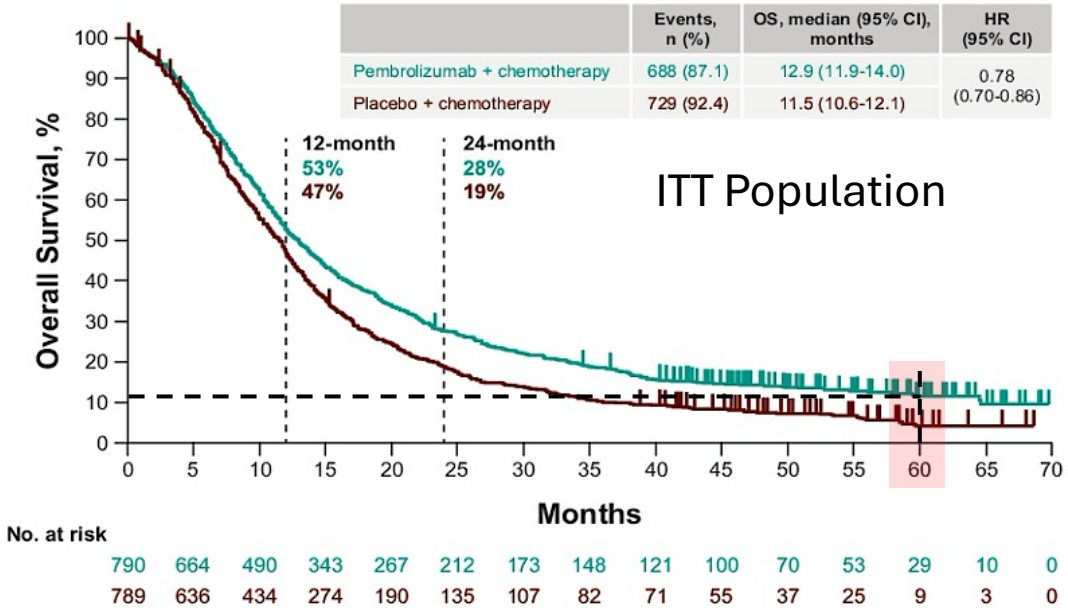
The Frontline ICI Landscape



	NIVO + chemo (*n* = 789)	Chemo (*n* = 792)
Events	689	727
Median OS,[a] mo	13.7	11.6
95% CI	12.4-14.5	10.9-12.5
HR (95% CI)	0.79 (0.71-0.88)	

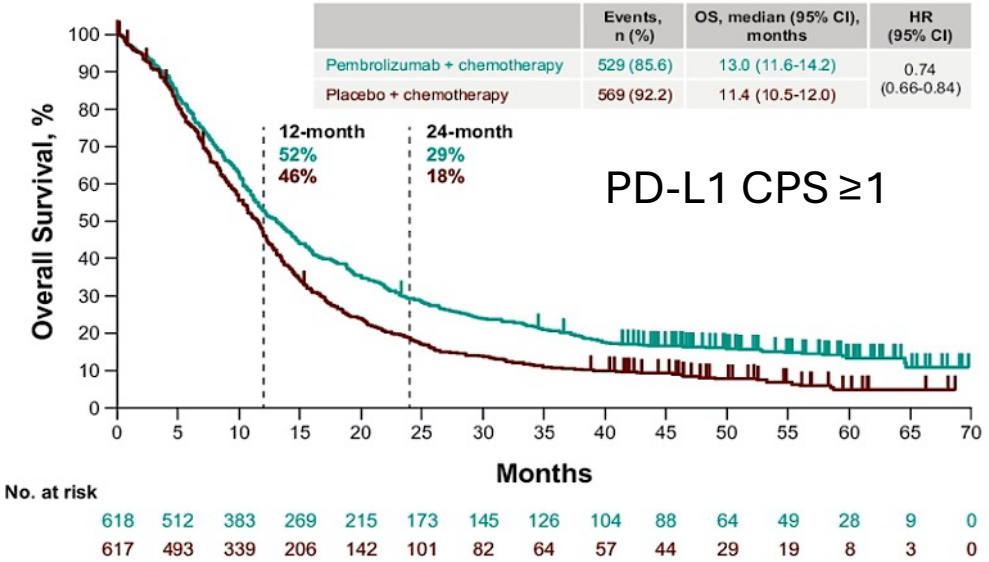


	NIVO + chemo (*n* = 641)	Chemo (*n* = 656)
Events	561	607
Median OS,[a] months	13.8	11.4
95% CI	12.4-14.8	10.7-12.3
HR (95% CI)	0.76 (0.67-0.85)	



	Events, n (%)	OS, median (95% CI), months	HR (95% CI)
Pembrolizumab + chemotherapy	688 (87.1)	12.9 (11.9-14.0)	0.78 (0.70-0.86)
Placebo + chemotherapy	729 (92.4)	11.5 (10.6-12.1)	

ITT Population



	Events, n (%)	OS, median (95% CI), months	HR (95% CI)
Pembrolizumab + chemotherapy	529 (85.6)	13.0 (11.6-14.2)	0.74 (0.66-0.84)
Placebo + chemotherapy	569 (92.2)	11.4 (10.5-12.0)	

PD-L1 CPS ≥1

Janjigian YY et al. Ann Oncol 2026; Rah SY et al. ASCO 2025

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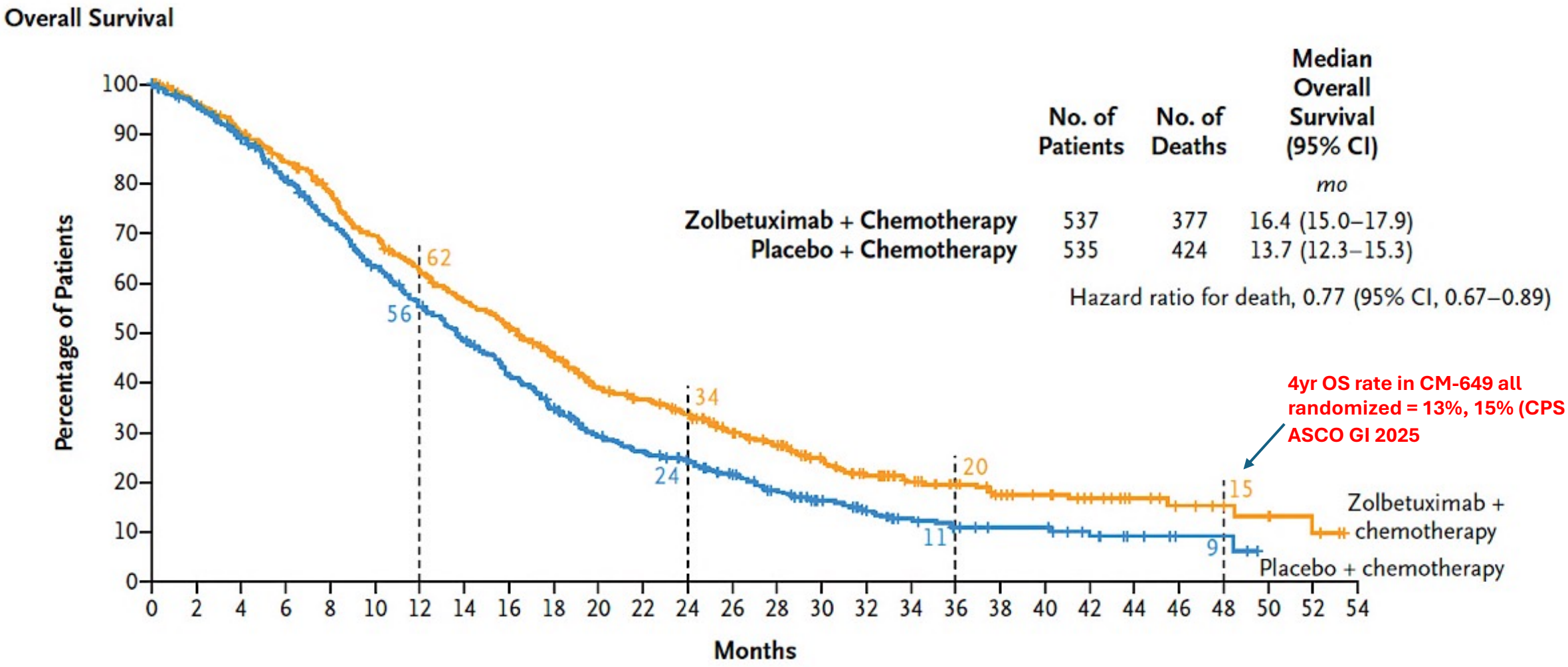
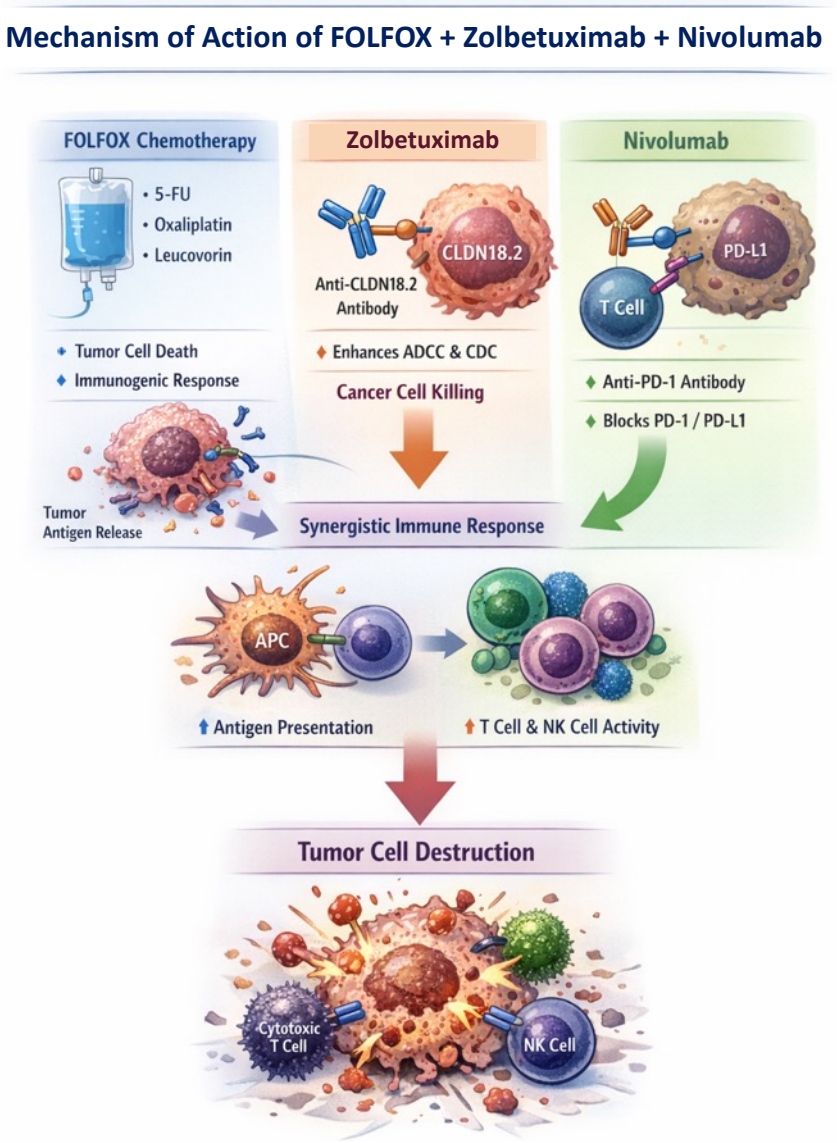
The Benchmark for CLDN18.2 GEA



Shitara K et al. NEJM 2024

Zolbetuximab Gets a GLOW Up: ILUSTRO



Images made with ChatGPT

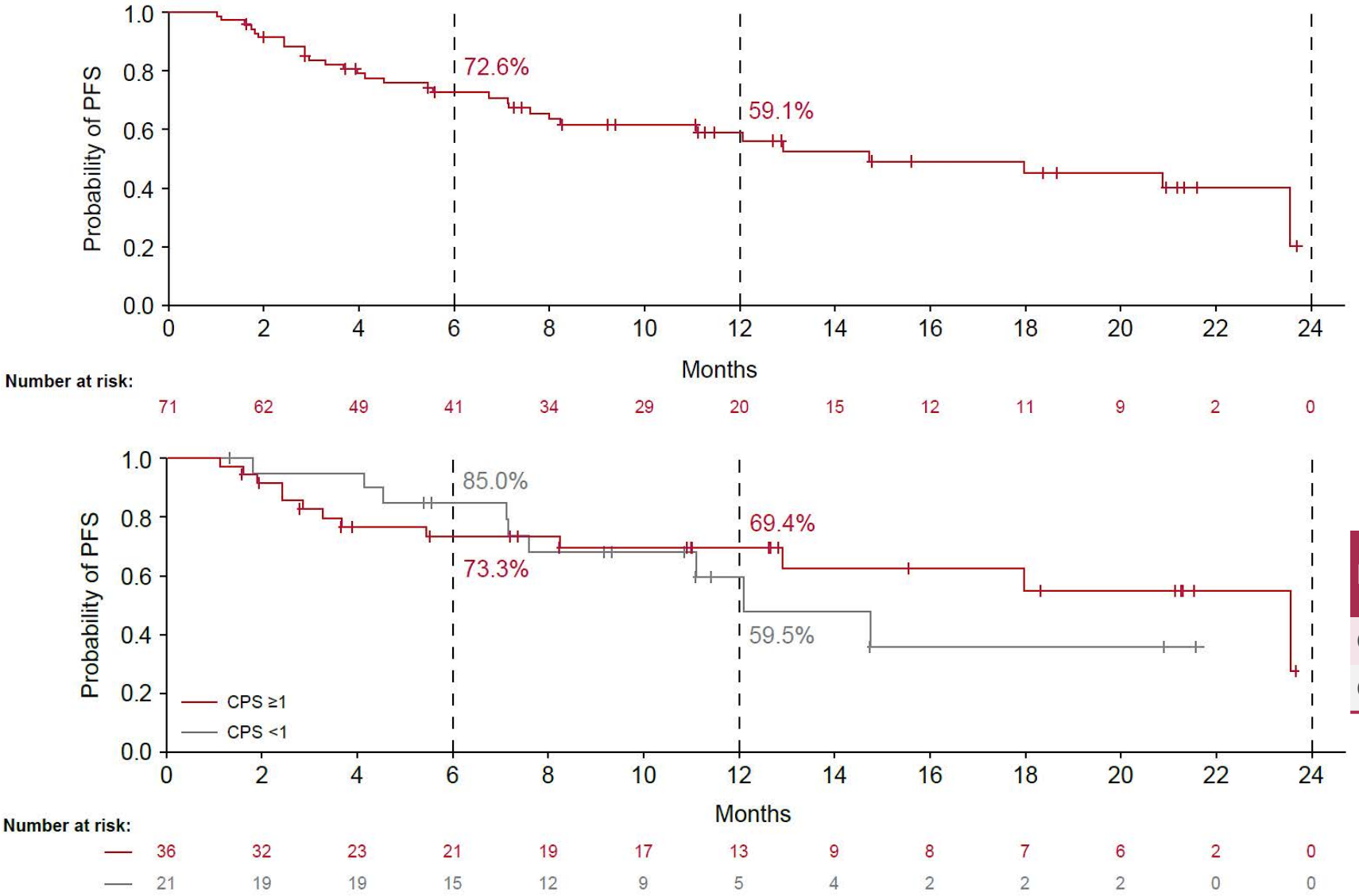
ILUSTRO Population

Parameter[a]		Cohort 4A + 4B (N = 77)
Age, years	Median (range)	61.0 (37.0–86.0)
Sex, *n* (%)	Male Female	48 (62.3) 29 (37.7)
Race, *n* (%)	Asian White	53 (79.1) 14 (20.9)
Previous treatment, *n* (%)	Surgery alone Surgery followed by chemotherapy Chemotherapy followed by surgery	3 (4.3) 3 (4.3) 1 (1.4)
Primary site, *n* (%)	Stomach Gastroesophageal junction	64 (86.5) 10 (13.5)

Parameter[a]		Cohort 4A + 4B (N = 77)
Number of metastatic sites, *n* (%)	0–2 ≥ 3	54 (70.1) 23 (29.9)
Lauren classification, *n* (%)	Diffuse Intestinal Mixed Other	53 (70.7) 10 (13.3) 3 (4.0) 9 (12.0)
ECOG PS, *n* (%)	0 1	51 (66.2) 26 (33.8)
Measurable disease, *n* (%)	Yes No	63 (81.8) 14 (18.2)
CLDN18.2 expression, *n* (%)	High[b] Intermediate[c]	65 (85.5) 11 (14.5)
PD-L1 status, *n* (%)	CPS ≥ 1 CPS < 1	49 (65.3) 26 (34.7)

Shitara K et al. ASCO GI 2026. LBA284

ILUSTRO Outcomes



PFS in Cohort 4B

Events/n (%)	Median PFS, months (95% CI)
31/71 (43.7)	14.8 (8.3–NE)

PFS by PD-L1 in CLDN18.2 High

PD-L1 status	Events/n (%)	Median PFS (months)
CPS ≥ 1	13/36 (36.1)	23.6
CPS < 1	9/21 (42.9)	12.1

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ILUSTRO Safety Profile in Cohorts 4A + 4B

The safety profile was manageable with no unexpected signals

Event, n (%)	Cohort 4A + 4B (N = 77)
TEAEs leading to discontinuation of any study drug	38 (49.4)
TEAEs leading to discontinuation of zolbetuximab	4 (5.2)
TEAEs leading to discontinuation of nivolumab	6 (7.8)
TEAEs leading to discontinuation of mFOLFOX6 component Oxaliplatin Fluorouracil bolus Fluorouracil infusion	 27 (35.1) 20 (26.0) 2 (2.6)
TEAEs leading to dose adjustment of zolbetuximab	3 (3.9)
TEAEs leading to dose adjustment of nivolumab	0
TEAEs leading to dose adjustment of mFOLFOX6 component Oxaliplatin Fluorouracil bolus Fluorouracil infusion	 43 (55.8) 29 (37.7) 36 (46.8)

- The median (range) duration of treatment was 288.5 days (1–1271) for zolbetuximab and 226.0 days (1–872) for nivolumab
- Mean (standard deviation) relative dose intensity of zolbetuximab was 97.1% (11.6) and nivolumab was 97.0% (7.1)

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ILUSTRO TEAEs in ≥20% of Patients in All Treated Patients from Cohorts 4A + 4B

Most common adverse event was nausea; all events were low grade

Event, n (%)	Cohort 4A + 4B (N = 77)	
Any grade Related to any study drug	76 (98.7) 76 (98.7)	
Grade ≥ 3	51 (66.2)	
Serious Related to any study drug	29 (37.7) 18 (23.4)	
TEAEs in ≥ 20% of patients by preferred terms, *n* (%)	**Any grade**	**Grade ≥ 3**
Nausea	62 (80.5)	0
Decreased appetite	56 (72.7)	6 (7.8)
Neutrophil count decreased	35 (45.5)	25 (32.5)
Peripheral sensory neuropathy	35 (45.5)	2 (2.6)
Vomiting	29 (37.7)	3 (3.9)
Diarrhea	28 (36.4)	1 (1.3)
Pyrexia	24 (31.2)	0
Anemia	19 (24.7)	2 (2.6)
Constipation	17 (22.1)	0

Shitara K et al. ASCO GI 2026. LBA284

Managing GI Toxicities from Zolbetuximab/CT

Consensus Guidance for Prevention and Management of Nausea and Vomiting

in Patients Treated With Zolbetuximab + Chemotherapy: A RAND/UCLA Modified Delphi Panel Study

Methods

PANELISTS

15 key external experts who have participated in clinical studies of zolbetuximab plus chemotherapy.

RATING FORM

Over 300 interventions to prevent nausea and vomiting in patients treated with zolbetuximab plus chemotherapy.

2-ROUND DELPHI SURVEY

Panelists reviewed current evidence on the prevention and management of nausea and vomiting, rated appropriateness of interventions using a scale of 1-9 (Round 1), discussed the results virtually, and repeated the rating (Round 2).

Conclusions

The consensus-based guidelines can help guide clinicians to **prevent and manage nausea and vomiting** in patients treated with zolbetuximab plus chemotherapy.

This may help these patients to continue receiving the treatment and **achieve the benefits it offers.**

Results

Round 1 → Discussion of results → Round 2

Consensus was achieved on 210 of 376 **(55.9%)** interventions

Consensus was achieved on 324 of 382 **(84.8%)** interventions

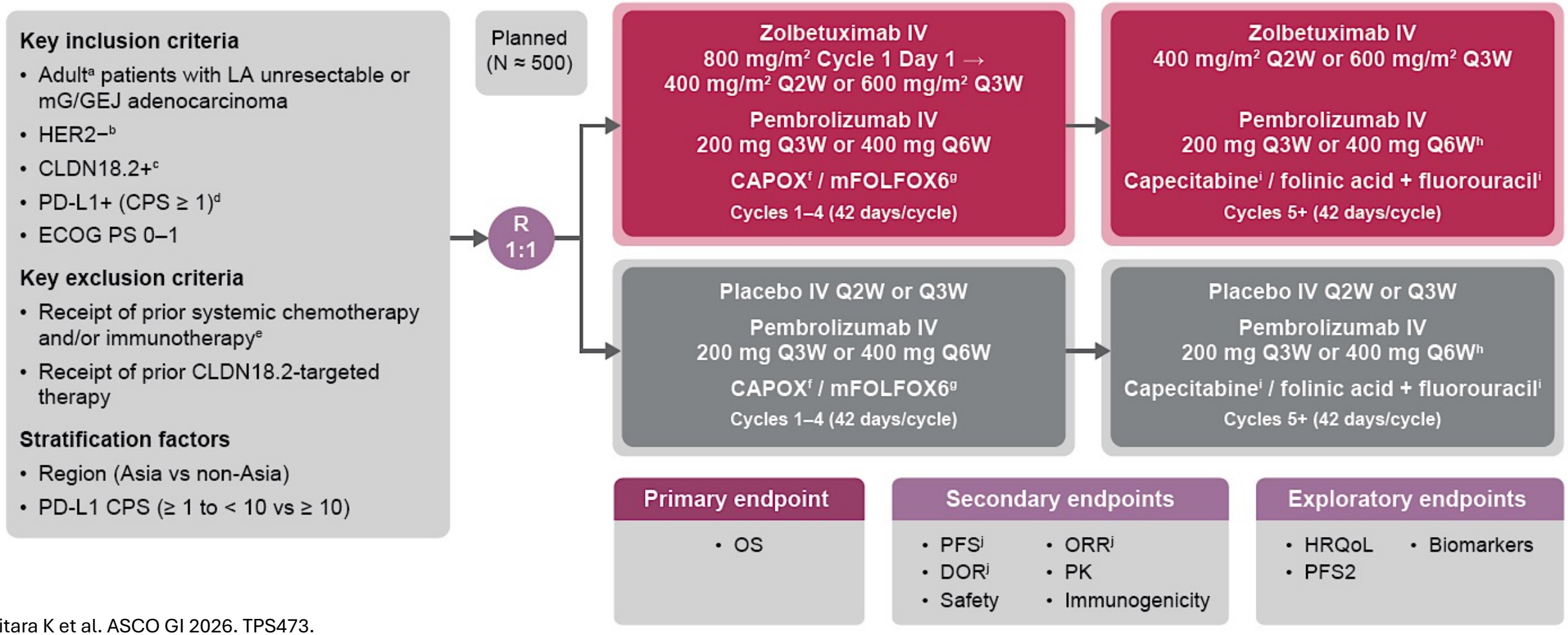
Recommendations from the Delphi panel

- Use NCCN recommended regimens for high-emetic risk prophylactically.
- During infusions, adjust infusion rate, pause the zolbetuximab infusion temporarily, use antiemetic medications not used for prophylaxis, and/or provide intravenous hydration.
- Escalate antiemetics and support before discontinuing zolbetuximab permanently.

Klempner SJ et al. ESMO GI 2025;7:100131.

Phase III Validation: LUCERNA

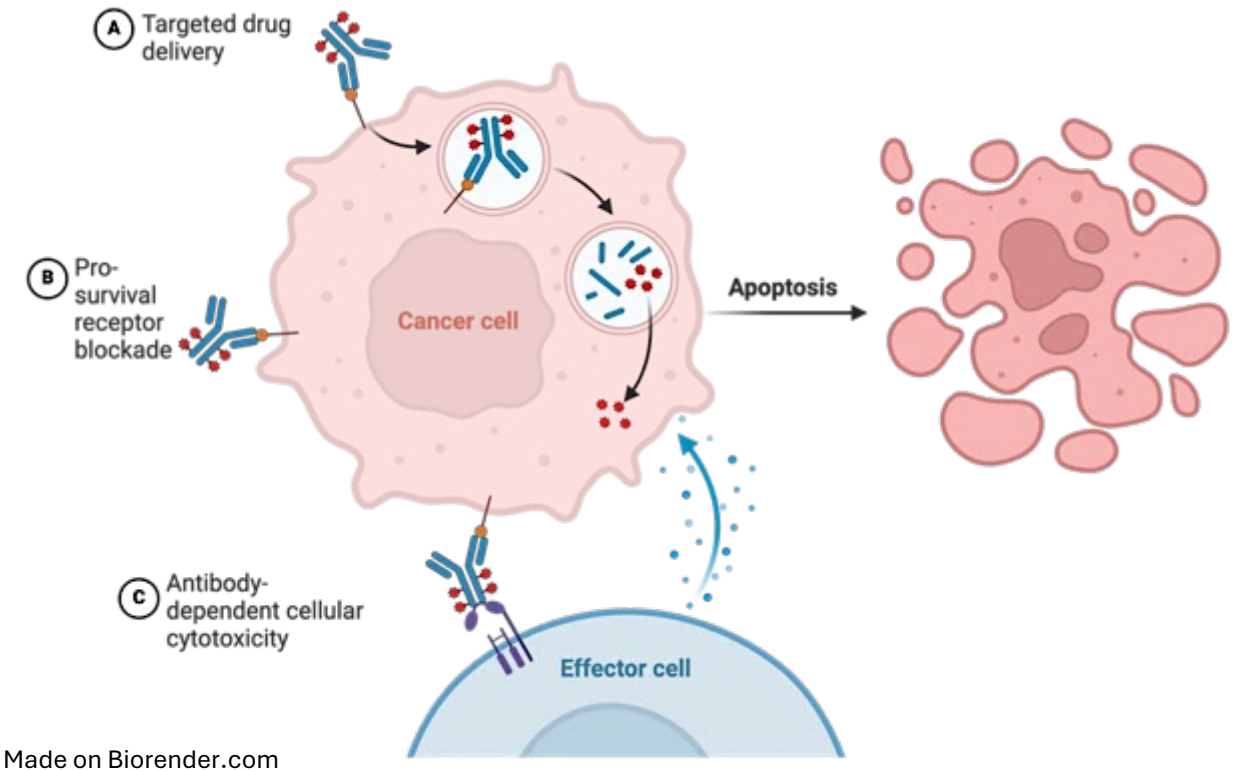
Phase 3 LUCERNA (NCT06901531) Study Design



Shitara K et al. ASCO GI 2026. TPS473.

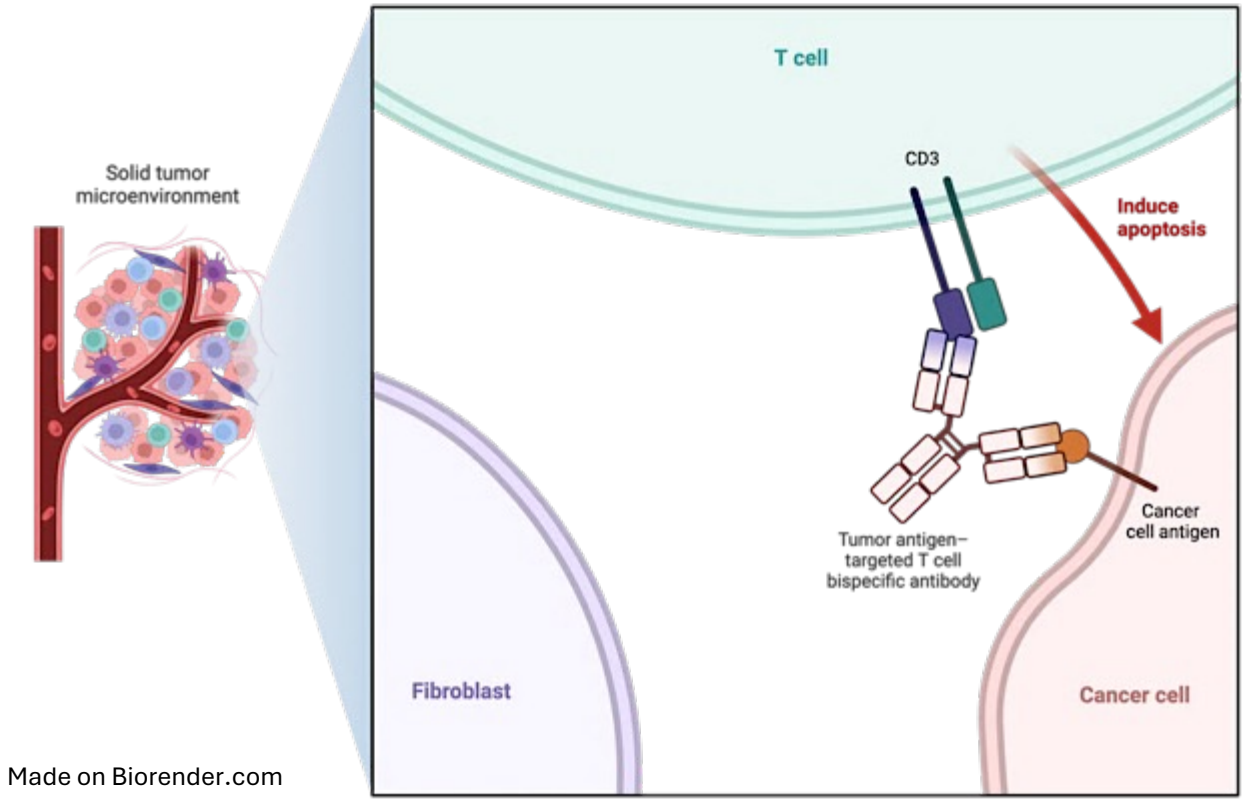
Expanding Beyond Zolbetuximab: Sone-V

Antibody Drug Conjugates



AZD0901 – CLDN18.2 ADC with **MMAE** Payload
EO-3021 – CLDN18.2 ADC with **MMAE** Payload
IBI343 -- CLDN18.2 ADC with **TOPO1** Payload
SHR-A1904 -- CLDN18.2 ADC with **TOPO1** Payload

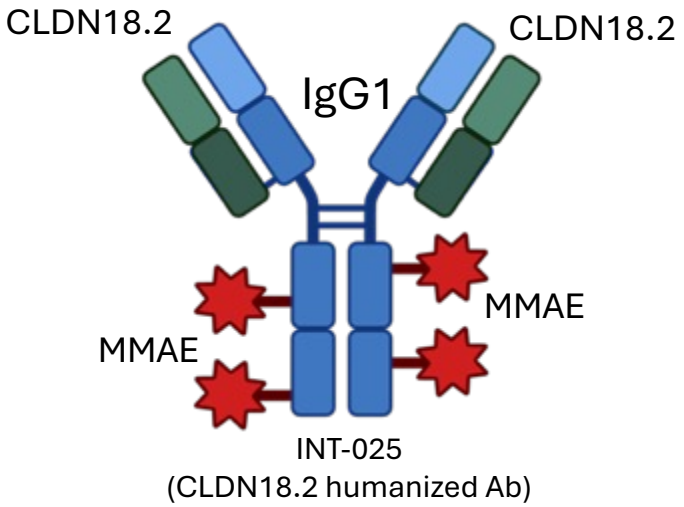
Bispecific Antibodies and BiTEs



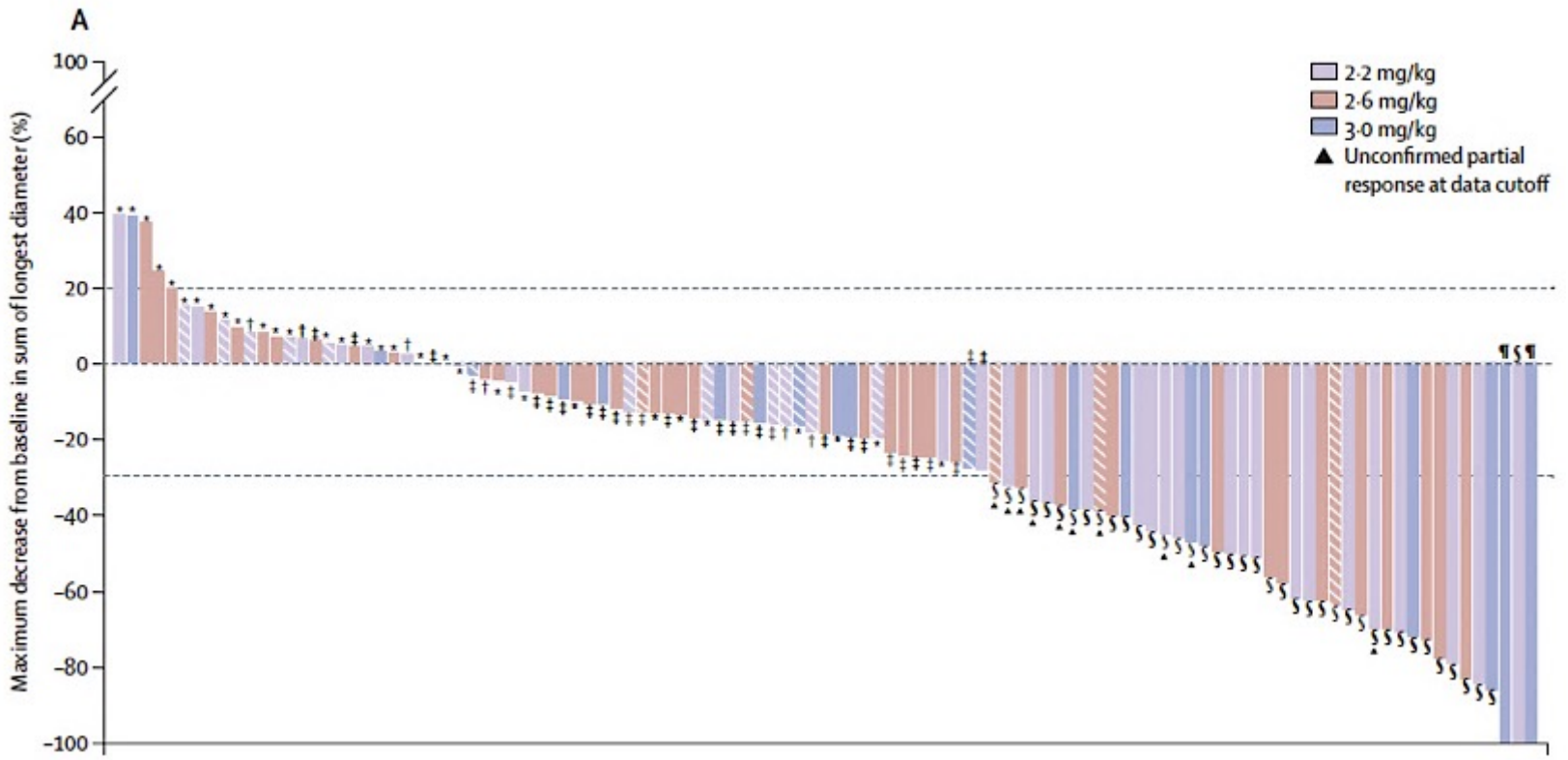
Givastomig – CLDN18.2 x 4-1BB bispecific
PT886 – CLDN18.2 x CD47 bispecific
ASP2138 – CLDN18.2 x CD3 BiTE
AZD5863 -- CLDN18.2 x CD3 BiTE

CLDN18.2 ADC Activity in GC/GEJ: AZD0901

AZD0901
(sonesitatug vedotin, Sone-V)



Global phase III 2L+ CLARITY trial examining AZD0901 vs investigator-choice chemotherapy in CLDN18.2+ GC/GEJ is ongoing (NCT06346392)



Feature	CLDN18.2-high 2.2mg/kg (n = 32)	CLDN18.2-high 2.6mg/kg (n = 45)	CLDN18.2-high 3.0mg/kg (n = 15)	CLDN18.2-high Total (n = 93)
cORR	47%	22%	38%	33%
mPFS	4.8 months	3.3 months	9.9 months	4.8 months
mOS	11.8 months	11.5 months	11.1 months	11.8 months

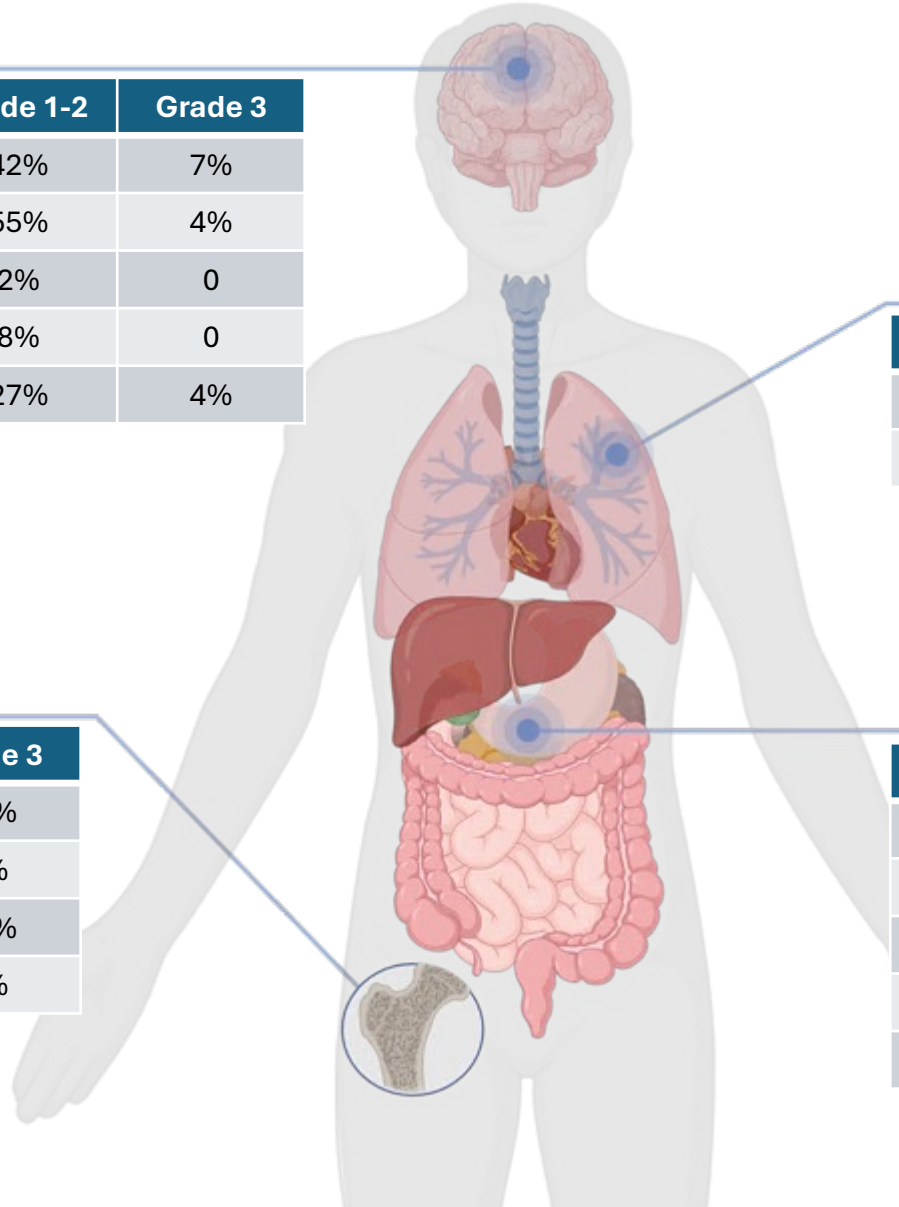
CLDN18.2 ≥2+ in 20% tumor cells = CLDN18.2-high

Ruan DY et al. Lancet Oncology 2025

CLDN18.2 ADC Toxicity in GC/GEJ: AZD0901

General

Toxicity	Grade 1-2	Grade 3
Decr. Appetite	42%	7%
Weight Loss	55%	4%
Fatigue	2%	0
Alopecia	8%	0
Asthenia	27%	4%



Pulmonary

Toxicity	Grade 1-2	Grade 3
Pneumonitis	6%	0
URI	6%	1%

Bone Marrow

Toxicity	Grade 1-2	Grade 3
Anemia	52%	13%
Low PLTs	10%	2%
Neutropenia	33%	16%
Leukopenia	43%	7%

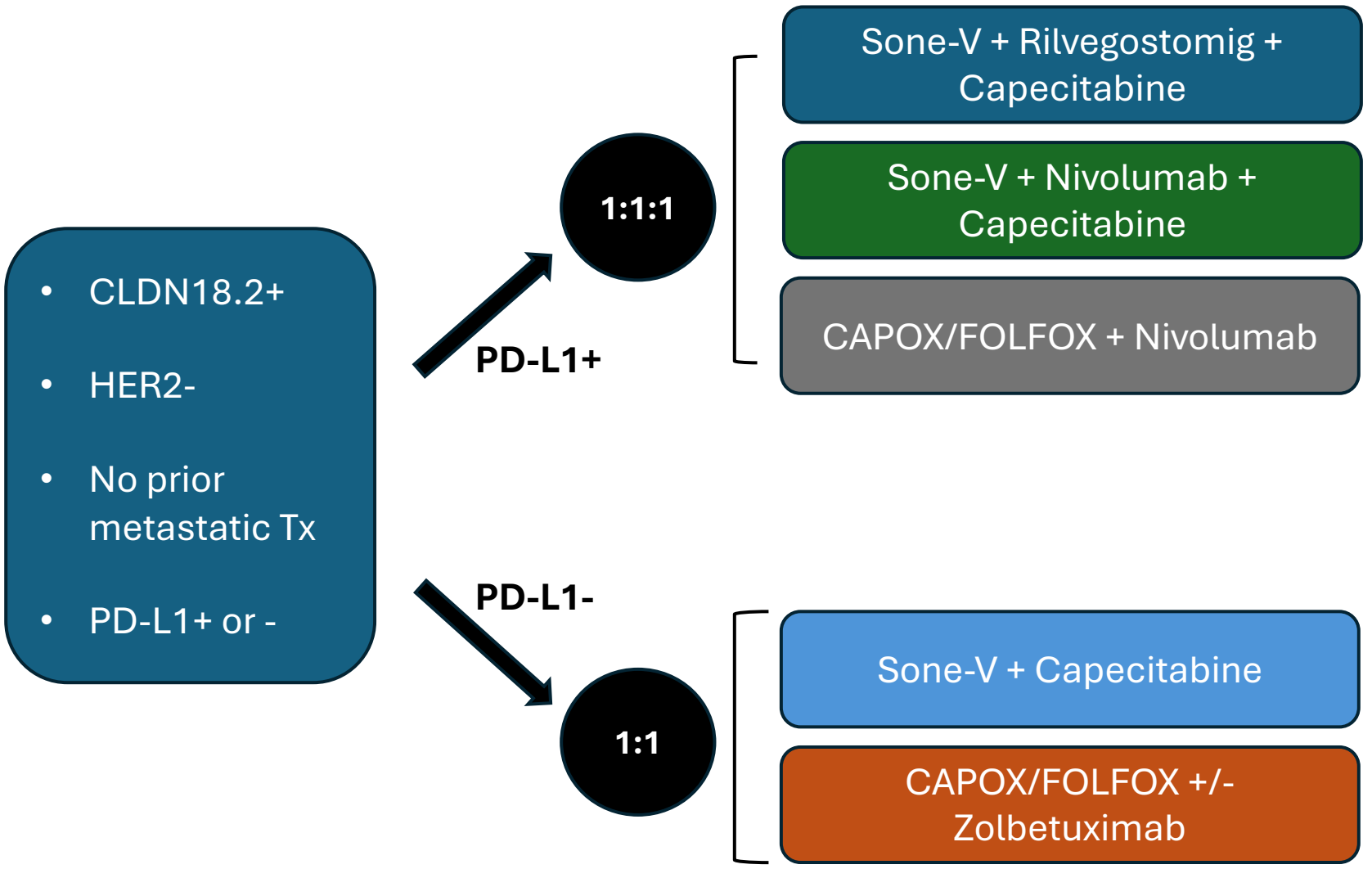
Gastrointestinal

Toxicity	Grade 1-2	Grade 3
Vomiting	46%	10%
Nausea	53%	4%
Diarrhea	19%	1%
Abd. Pain	16%	3%
Constipation	21%	0%

Made on Biorender.com

Ruan DY et al. Lancet Oncology 2025

Will CLDN18.2 ADC Come to 1L?



There are several other global late phase trials in 1L, 2L, 2L+ exploring additional CLDN18.2 directed ADCs

NCT07431281

Summary

1. Emerging data continues to support perioperative D-FLOT as a standard in operable gastroesophageal adenocarcinomas

2. ALL patients should get MMR/MSI testing and non-operative management may be an option in setting of complete clinical response

3. Frontline chemo-immunotherapy is here to stay for PD-L1+ patients

4. Zolbetuximab in combination with FOLFOX and PD-1 represents an encouraging dataset

5. AZD0901 (Sonesitatug vedotin) and other CLDN18.2 targeting ADCs may be coming, and the Phase III CLARITY Gastric-01 is eagerly awaited

QUESTIONS?

Module 5: Gastroesophageal Cancers

Role of Anti-PD-1/PD-L1- and CLDN18.2-Directed Antibodies in the Management of Gastroesophageal Cancers — Dr Klempner

Management of HER2-Positive Gastroesophageal Cancers — Dr Janjigian

Memorial Sloan Kettering Cancer Center

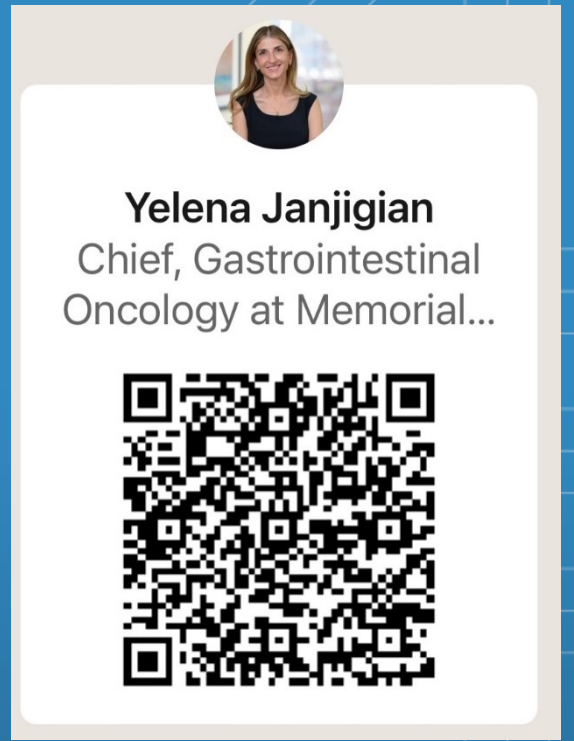
Management of HER2-Positive Gastroesophageal Cancers

Yelena Y. Janjigian, MD
Chief Attending Physician
Carroll and Milton Petrie Chair

Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center

Email: janjigiy@mskcc.org

Saturday April 25th| 10 minutes
11:40am EST



Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Daiichi Sankyo Inc
Consulting Agreements	AbbVie Inc, AlphaSights, Arcus Biosciences, ARS Pharmaceuticals, AskGene Pharma, Astellas, AstraZeneca Pharmaceuticals LP, Basilea Pharmaceutica Ltd, Bayer HealthCare Pharmaceuticals, BeOne, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Cencora, Daiichi Sankyo Inc, Eisai Inc, Geneos Therapeutics, Gilead Sciences Inc, GSK, Guardant Health, HC Wainwright & Co, Health Advances, Imugene, Inspirna, Lilly, Lynx Health, Merck, Merck Serono, Mersana Therapeutics Inc, PeerMD, Pfizer Inc, Sanofi, Seagen Inc, Suzhou Liangyihui Network Technology Co Ltd, Zymeworks Inc
Contracted Research	Arcus Biosciences, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Genentech, a member of the Roche Group, Inspirna, Lilly, Merck, Transcenta
Nonrelevant Financial Relationships	Clinical Care Options, Cycle for Survival, Debbie's Dream Foundation, eChinaHealth, ED Medresources Inc, Fred's Team, HMP, i3Health, Imedex, Mashup Media LLC, Master Clinician Alliance, MJH Life Sciences, National Cancer Institute, OncoDaily (stock options), Paradigm Medical Communications, PeerView, Physician Education Resource (PER), Stand Up 2 Cancer, Talem Health, TotalCME, US Department of Defense, WebMD

KEYNOTE-811 Study Design (NCT03615326)

Phase 3 Randomized, Placebo-Controlled

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

Stratification Factors

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

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

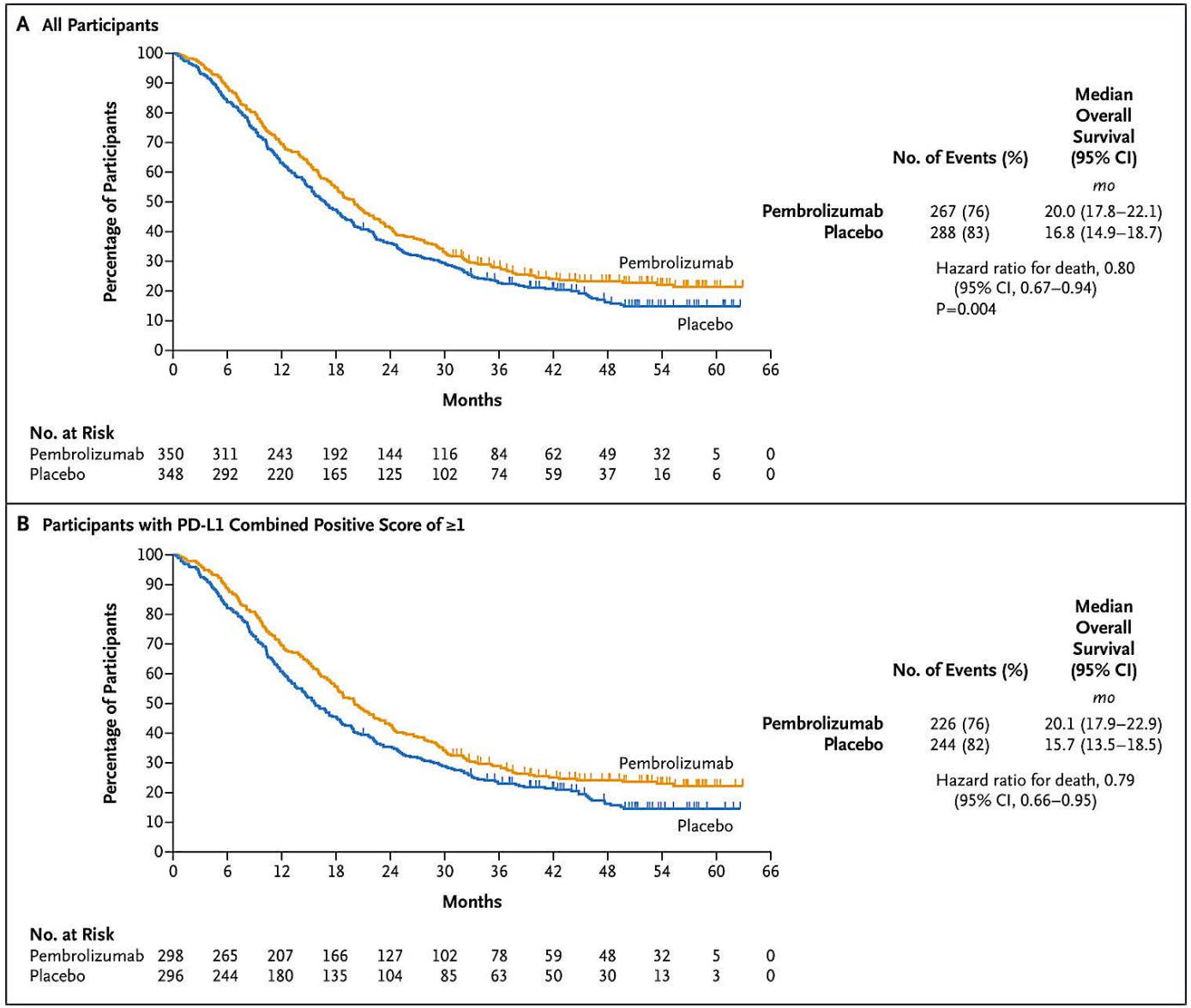
Endpoints

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

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. PFS, ORR, DOR per RECIST by BICR.

Pembrolizumab in HER2-Positive Gastric Cancer

Published September 13, 2024 | N Engl J Med 2024;391:1360-1362 | DOI: 10.1056/NEJMc2408121



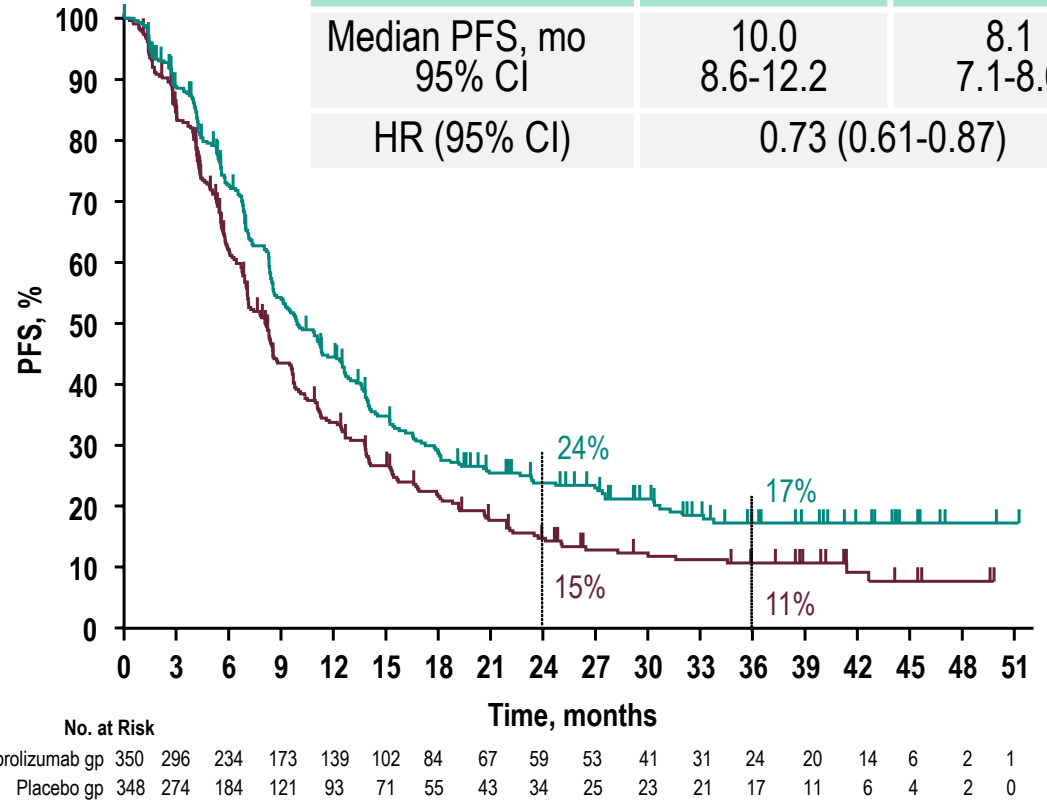
Janjigian NEJM 2024

Progression-Free Survival at IA3: 38.5 months of follow-up[a]

RECIST V1.1, BICR

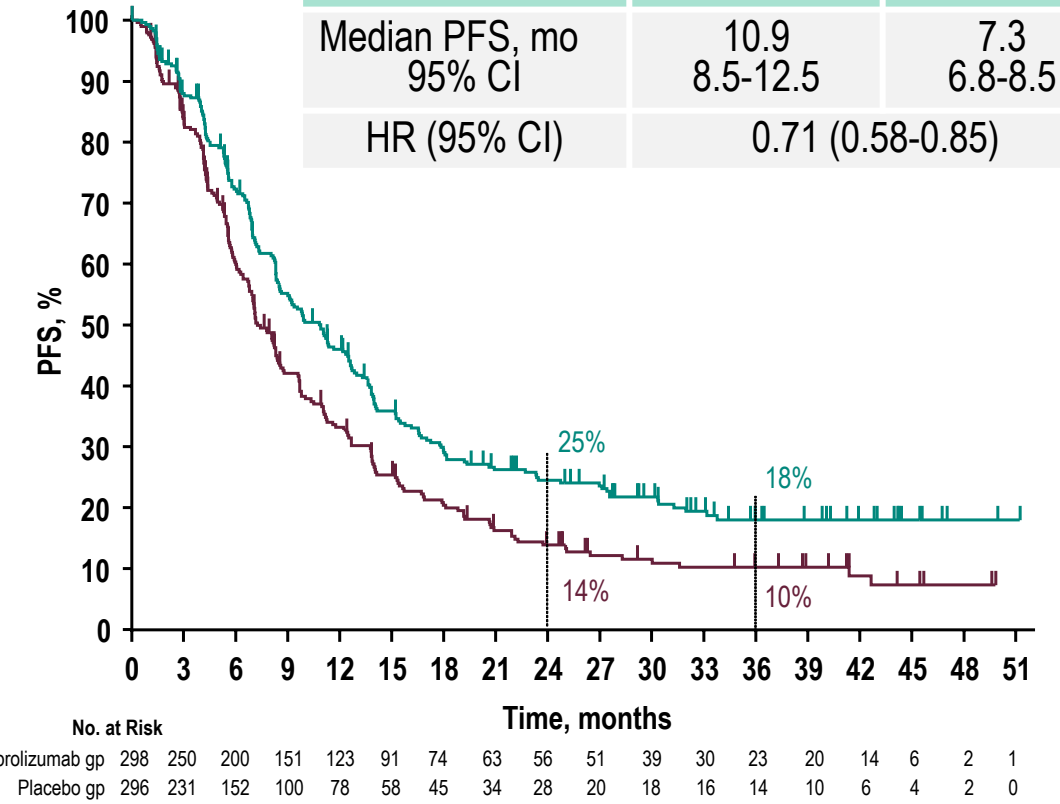
All patients

	Pembro	Placebo
Median PFS, mo 95% CI	10.0 8.6-12.2	8.1 7.1-8.6
HR (95% CI)	0.73 (0.61-0.87)	



PD-L1 CPS ≥1[b]

	Pembro	Placebo
Median PFS, mo 95% CI	10.9 8.5-12.5	7.3 6.8-8.5
HR (95% CI)	0.71 (0.58-0.85)	



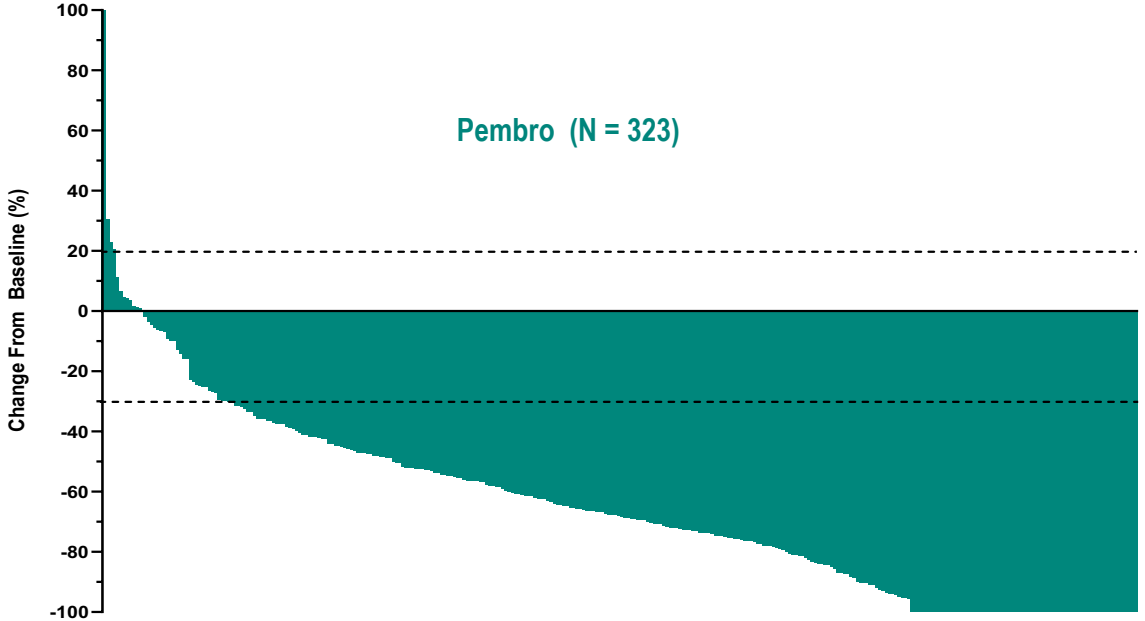
Janjigian NEJM 2024

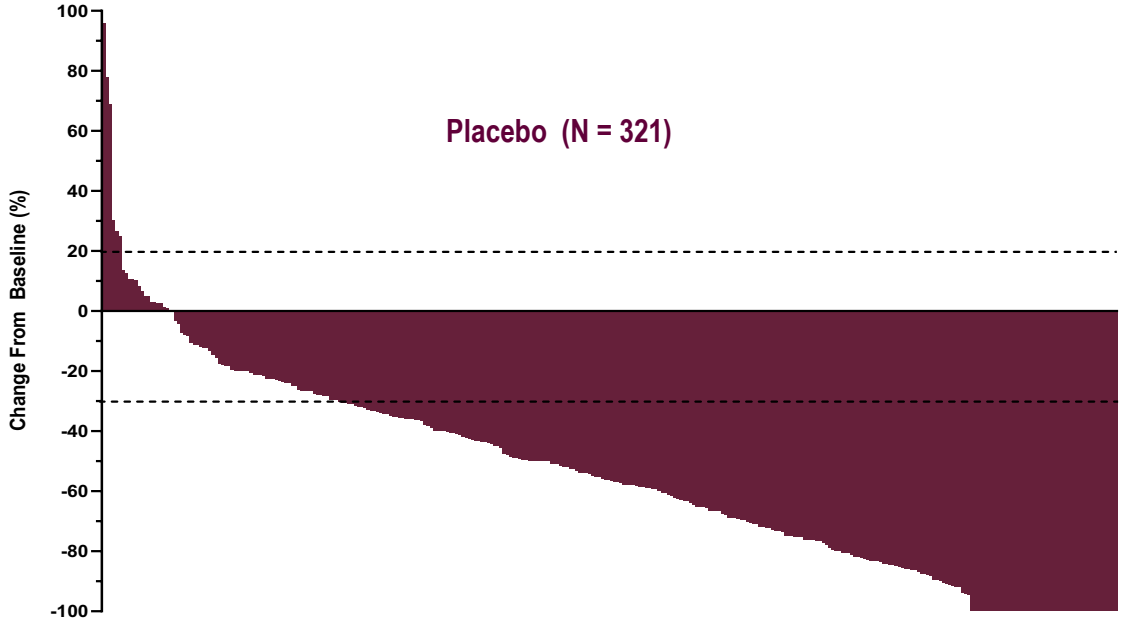
Data cut-off: March 29, 2023. [a]Median follow-up. [b]Not a prespecified endpoint.

Antitumor Response on Pembrolizumab/Trastuzumab/Chemotherapy

Best response, n (%)	Pembro N = 350	Placebo N = 348
CR	**58 (17)**	**39 (11)**
PR	**196 (56)**	**170 (49)**
SD	67 (19)	95 (27)
PD	19 (5)	23 (7)
NE or NA	10 (3)	21 (6)

Response and Duration	Pembro N = 350	Placebo N = 348
ORR, % (95% CI)	73 (68-77)	60 (55-65)
DCR, % (95% CI)	92 (88-94)	87 (83-91)
DOR, median (range), mo	11.3 (1.1+ to 49.7+)	9.5 (1.4+ to 48.7+)





Data cut-off: March 29, 2023. ORR at IA1 was 74% (11% CR) in the pembro gp vs 52% (3% CR) in the pbo gp (ORR difference: 22% [95% CI, 11-34]; P=0.00006). ORR at IA3 in CPS ≥1 was 73% in the pembro gp vs 58% in the pbo gp.
NE, post-baseline assessment not evaluable. NA, no post-baseline assessment available for response evaluation. + indicates no progressive disease at time of last disease assessment.

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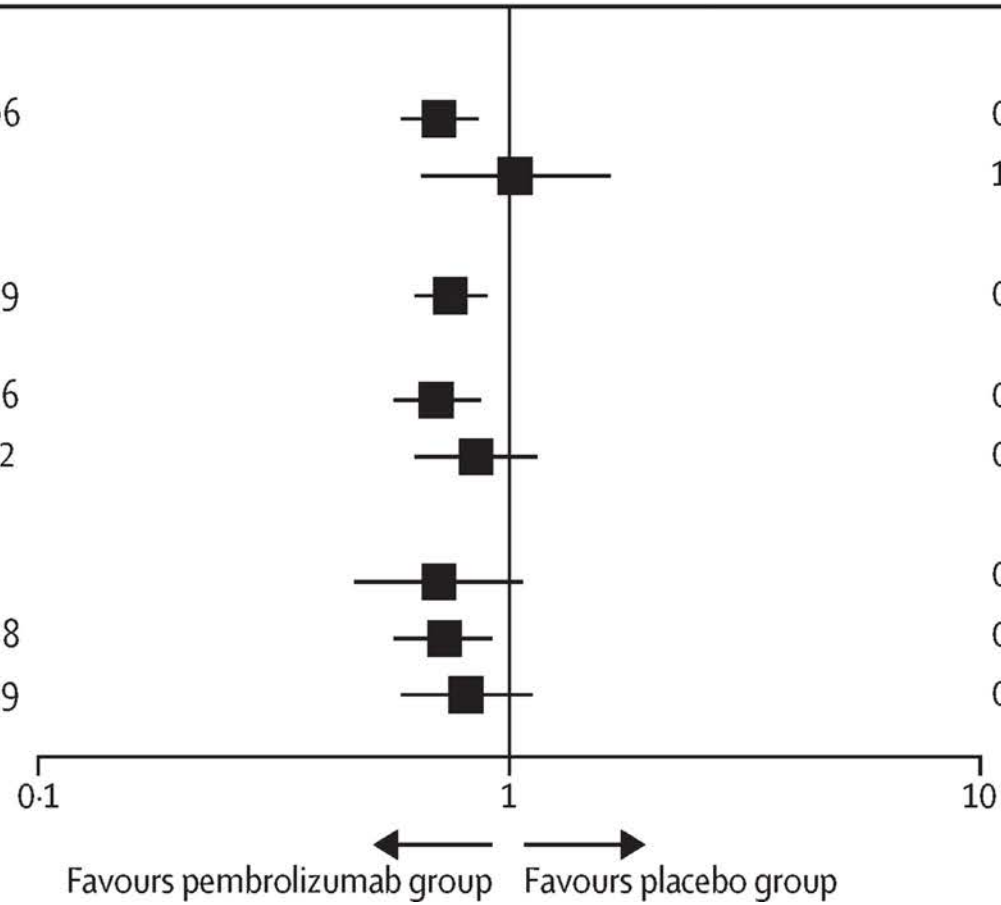
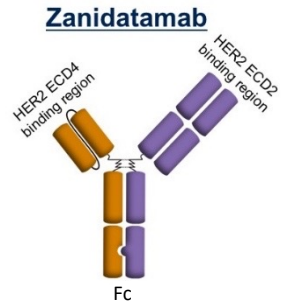
Subgroup analysis- Keynote 811

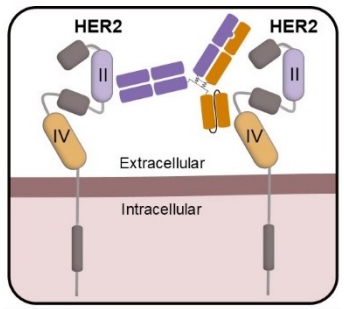
	Events/patients, n/N		HR (95% CI)
	Pembrolizumab group	Placebo group	
PD–L1 status			
CPS≥1	217/298	225/296	0·71 (0·59–0·86)
CPS<1	36/52	36/52	1·03 (0·65–1·64)
MSI status			
Non-high	234/326	244/329	0·75 (0·63–0·90)
Primary tumour location			
Stomach	171/240	173/226	0·70 (0·57–0·87)
Gastro-oesophageal junction	82/110	88/122	0·85 (0·63–1·15)
Histological subtypes			
Diffuse	50/68	44/51	0·71 (0·47–1·07)
Intestinal	136/198	134/188	0·73 (0·57–0·92)
Indeterminate	66/83	83/109	0·81 (0·59–1·12)



Janjigian et al Lancet 2023

HER2-Targeted Biparatopic mAb: Zanidatamab + chemo 1L





- Zanidatamab is a dual HER2-targeted bispecific antibody that drives multiple antitumor MOAs, including[1]:
  - Facilitation of HER2 internalization and subsequent degradation
  - Reduction of HER2 on the cell surface
  - Inhibition of HER2 signaling pathways
  - Activation of immune-mediated effects (CDC, ADCC, and phagocytosis)

Single arm trial: Zanidatamab + clinician's choice of chemotherapy

Zanidatamab[a,b] IV Q3W + CAPOX[c]

Zanidatamab[a,b] IV Q3W + FP[d]

Zanidatamab[b,e] IV Q2W + mFOLFOX6[f]

After the first 25 patients were enrolled and treated, antidiarrheal prophylaxis[g] was added for all subsequent patients

CT/MRI scans Q6W per RECIST v1.1[1]

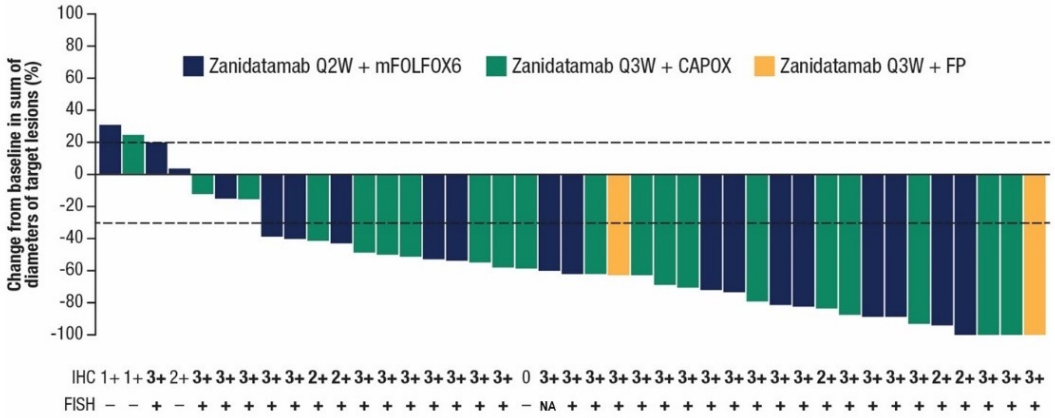
Plasma ctDNA samples at baseline and on treatment using NGS testing (Guardant360)

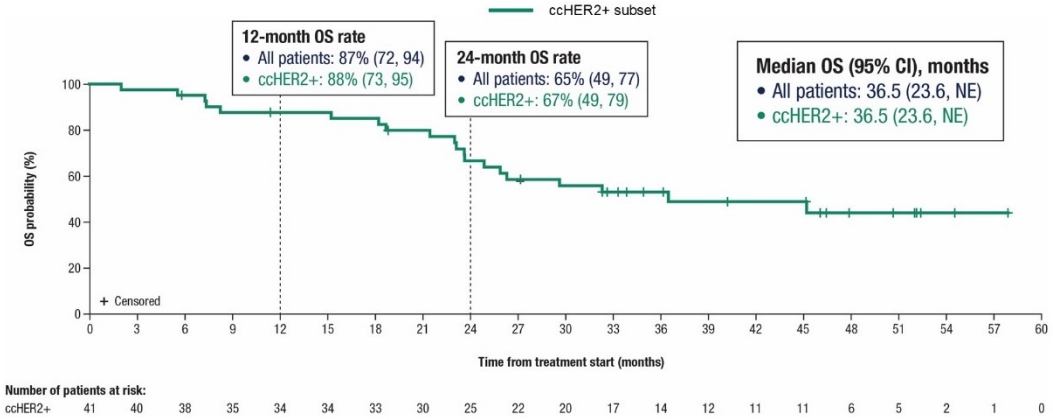
Primary endpoint
- Investigator-assessed confirmed ORR

Select secondary endpoints
- DOR
- PFS
- OS
- Rate and severity of AEs

Exploratory endpoint
- Potential biomarkers for prognostic prediction

	All Patients (N = 42)	ccHER2+ Subset (n = 37)
cORR		
n (%)	32 (76)	31 (84)
95% CI	60, 88	68, 94
cBOR,[a] n (%)		
CR	3 (7)	3 (8)
PR	29 (69)	28 (76)
SD	5 (12)	4 (11)
PD	5 (12)	2 (5)
DCR[b]		
n (%)	37 (88)	35 (95)
95% CI	74, 96	82, 99
CBR[c]		
n (%)	33 (79)	32 (86)
95% CI	63, 90	72, 96





- **Phase 3 HERIZON-GEA-01: 1L chemo + zanidatamab +/- tislelizumab at ASCO GI 2026**

Elimova E, ASCO 2025

HERIZON
GEA-301

HERIZON-GEA-01 Study Design

Global phase 3 trial of zanidatamab + chemotherapy ± tislelizumab vs trastuzumab + chemotherapy in previously untreated patients with HER2+ mGEA

Key Eligibility Criteria

- Age ≥18 years
- Unresectable, locally advanced, recurrent or metastatic GEA
- HER2 IHC 3+ or IHC 2+/ISH+ per central testing
- ECOG PS 0 or 1
- No prior treatment for locally advanced or metastatic disease
- No prior HER2-targeted agents or immunotherapy in any setting

Stratification Factors

- Geographic region
- HER2 status
- ECOG PS

R 1:1:1

N = 914

Arm A: Trastuzumab + chemotherapy[a]

Arm B: Zanidatamab 1800 mg (<70 kg)/2400 mg (≥70 kg) IV Q3W **+ chemotherapy[a]**

Arm C: Zanidatamab 1800 mg (<70 kg)/2400 mg (≥70 kg) IV Q3W **+ tislelizumab[b] + chemotherapy[a]**

Prophylaxis to prevent IRR and diarrhea was mandatory in the zanidatamab-containing arms

CT/MRI[c] Q6W

Dual Primary Endpoints

- PFS (per BICR)
- OS

Select Secondary Endpoints

- cORR (per BICR)
- Frequency and severity of AEs

ClinicalTrials.gov: NCT05152147

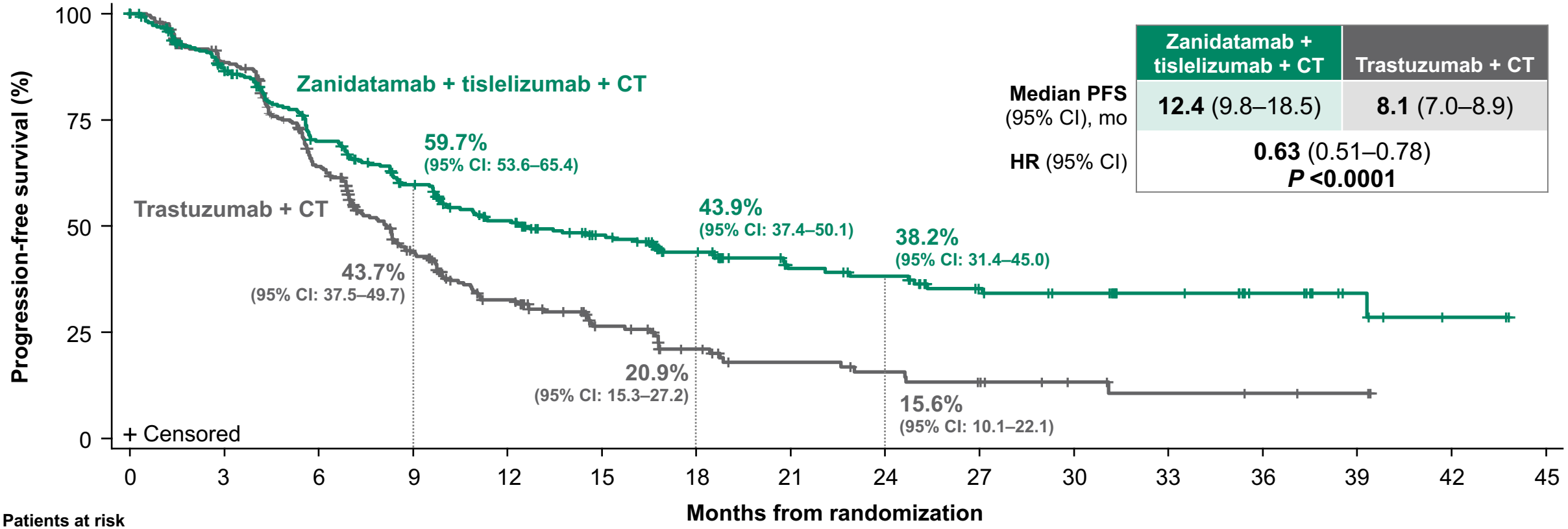
Treatment until disease progression/death/unacceptable toxicity
Chemotherapy could be discontinued after 6 cycles

[a]Physician's choice of capecitabine plus oxaliplatin or 5-fluorouracil plus cisplatin. Chemotherapy was administered for at least 6 cycles or until disease progression, unacceptable toxicity, or another criterion for treatment discontinuation was met.
[b]Tislelizumab 200 mg was administered IV Q3W. [c]CT/MRI scans were performed every 6 weeks for the first 54 weeks, then every 9 weeks.
AE, adverse event; BICR, blinded independent central review; cORR, confirmed objective response rate; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRR, infusion-related reaction; ISH, in situ hybridization; IV, intravenously; mGEA, advanced or metastatic GEA; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomization.

HERIZON
GEA-301

Primary Endpoint: PFS per BICR

Statistically significant and clinically meaningful improvement in PFS with zanidatamab + tislelizumab + CT vs trastuzumab + CT (>4-month prolongation in median PFS)



	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
Median PFS (95% CI), mo	**12.4** (9.8–18.5)	**8.1** (7.0–8.9)
HR (95% CI)	**0.63** (0.51–0.78) ***P* <0.0001**	

Patients at risk

Zani + TIS + CT	302	240	183	147	113	90	65	46	42	30	27	20	13	6	2	0
Tras + CT	308	247	168	97	63	37	23	16	13	10	6	4	3	2	0	

BICR, blinded independent central review; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

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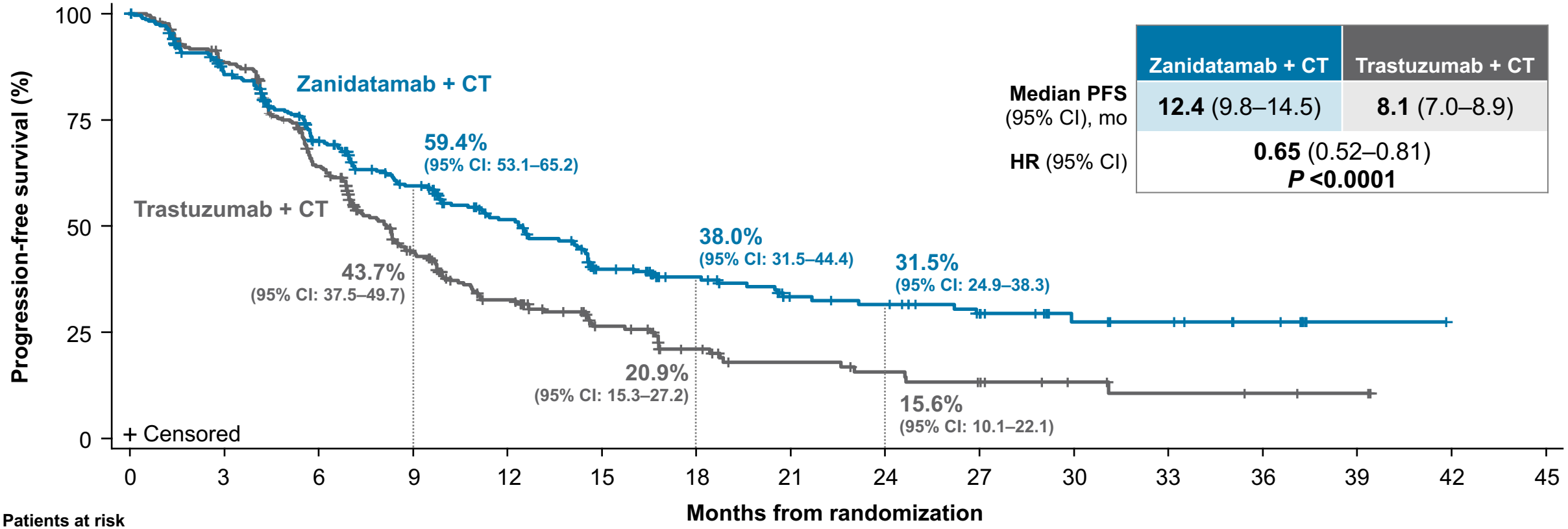
Primary Endpoint: PFS per BICR

Statistically significant and clinically meaningful improvement in PFS with zanidatamab + CT vs trastuzumab + CT (>4-month prolongation in median PFS)



	Zanidatamab + CT	Trastuzumab + CT
Median PFS (95% CI), mo	**12.4** (9.8–14.5)	**8.1** (7.0–8.9)
HR (95% CI)	**0.65** (0.52–0.81) ***P* <0.0001**	

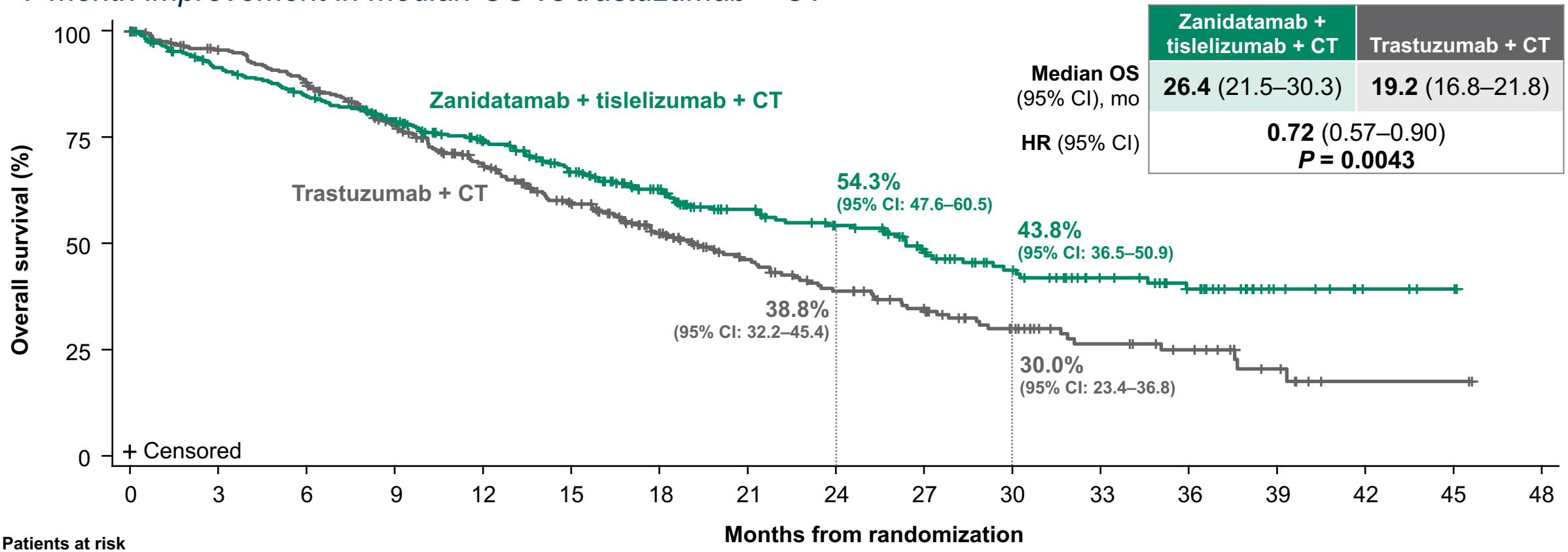
Patients at risk

Zani + CT	304	231	175	137	105	70	53	37	34	26	14	12	8	1	0	
Tras + CT	308	247	168	97	63	37	23	16	13	10	6	4	3	2	0	

BICR, blinded independent central review; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; Tras, trastuzumab; Zani, zanidatamab.

Primary Endpoint: Overall Survival

Zanidatamab + tislelizumab + CT demonstrated a statistically significant and clinically meaningful OS benefit with a >7-month improvement in median OS vs trastuzumab + CT



	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
Median OS (95% CI), mo	**26.4** (21.5–30.3)	**19.2** (16.8–21.8)
HR (95% CI)	**0.72** (0.57–0.90)	
	***P* = 0.0043**	

Patients at risk

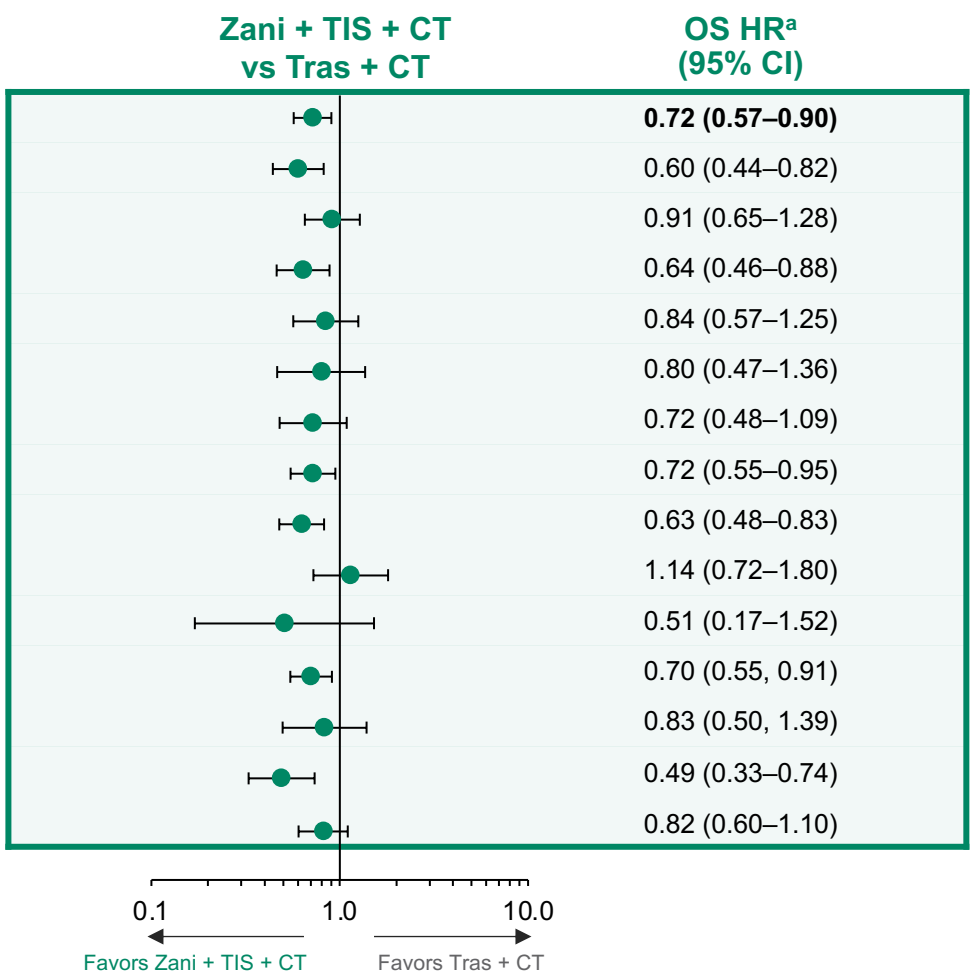
Zani + TIS + CT	302	267	246	222	190	157	125	96	82	64	49	36	27	10	4	2	0
Tras + CT	308	284	261	219	178	140	106	77	61	50	33	22	17	8	2	2	0

CT, chemotherapy; HR, hazard ratio; OS, overall survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

OS in Key Prespecified Subgroups

Improvements in OS occurred across major prespecified subgroups, including regions and PD-L1 TAP scores

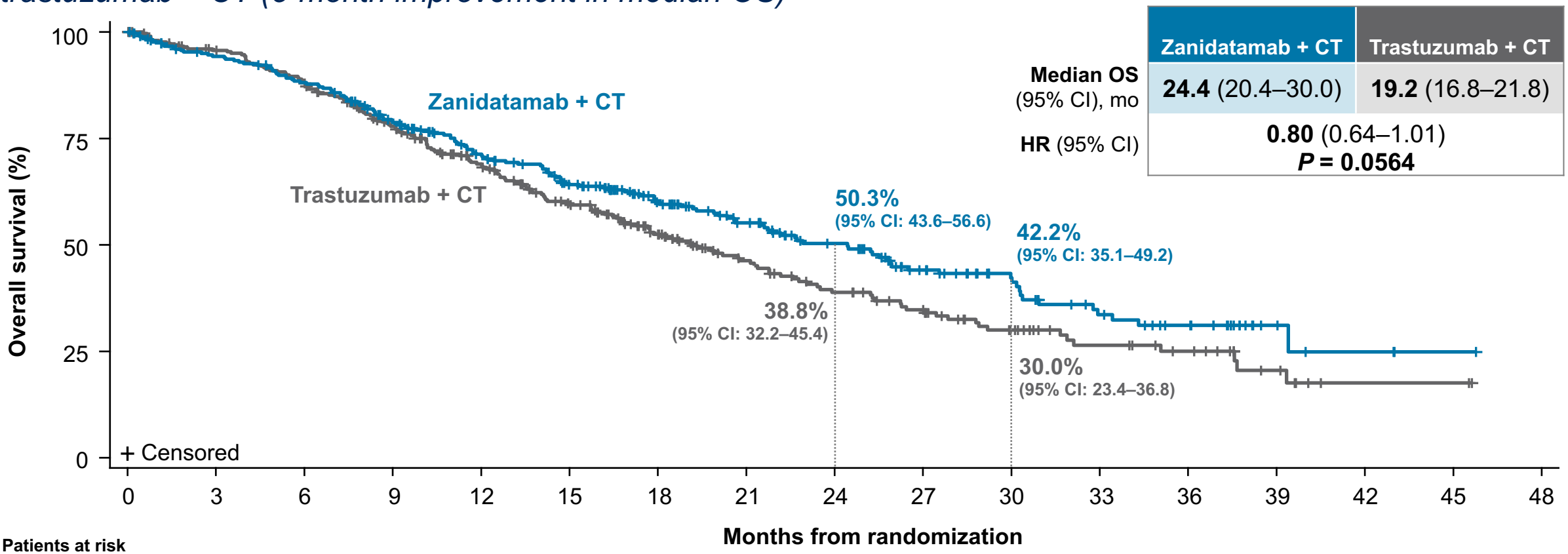
Subgroup	Category	Events/patients: Zanidatamab + tislelizumab + CT	Events/patients: Trastuzumab + CT
All patients		**134/302**	**170/308**
Age, years	<65	68/163	99/162
	≥65	66/139	71/146
Geographic region	Asia	63/159	89/165
	EU/NA	46/95	52/93
	ROW	25/48	29/50
ECOG PS	0	41/121	52/120
	1	92/180	118/188
Anatomical subtype	Gastric	87/208	127/226
	GEJ	42/74	33/60
	Esophageal	5/20	10/22
HER2 status	IHC 3+	106/251	138/255
	IHC 2+/ISH+	28/51	31/52
PD-L1 status	TAP <1%	38/90	65/98
	TAP ≥1%	79/187	92/188



[a]The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; NA, North America; OS, overall survival; PD-L1, programmed death-ligand 1; ROW, rest of world; TAP, tumor area positivity; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Primary Endpoint: Overall Survival

At this interim analysis, there was a strong trend toward significance for OS favoring zanidatamab + CT vs trastuzumab + CT (5-month improvement in median OS)



	Zanidatamab + CT	Trastuzumab + CT
Median OS (95% CI), mo	**24.4** (20.4–30.0)	**19.2** (16.8–21.8)
HR (95% CI)	**0.80** (0.64–1.01) ***P* = 0.0564**	

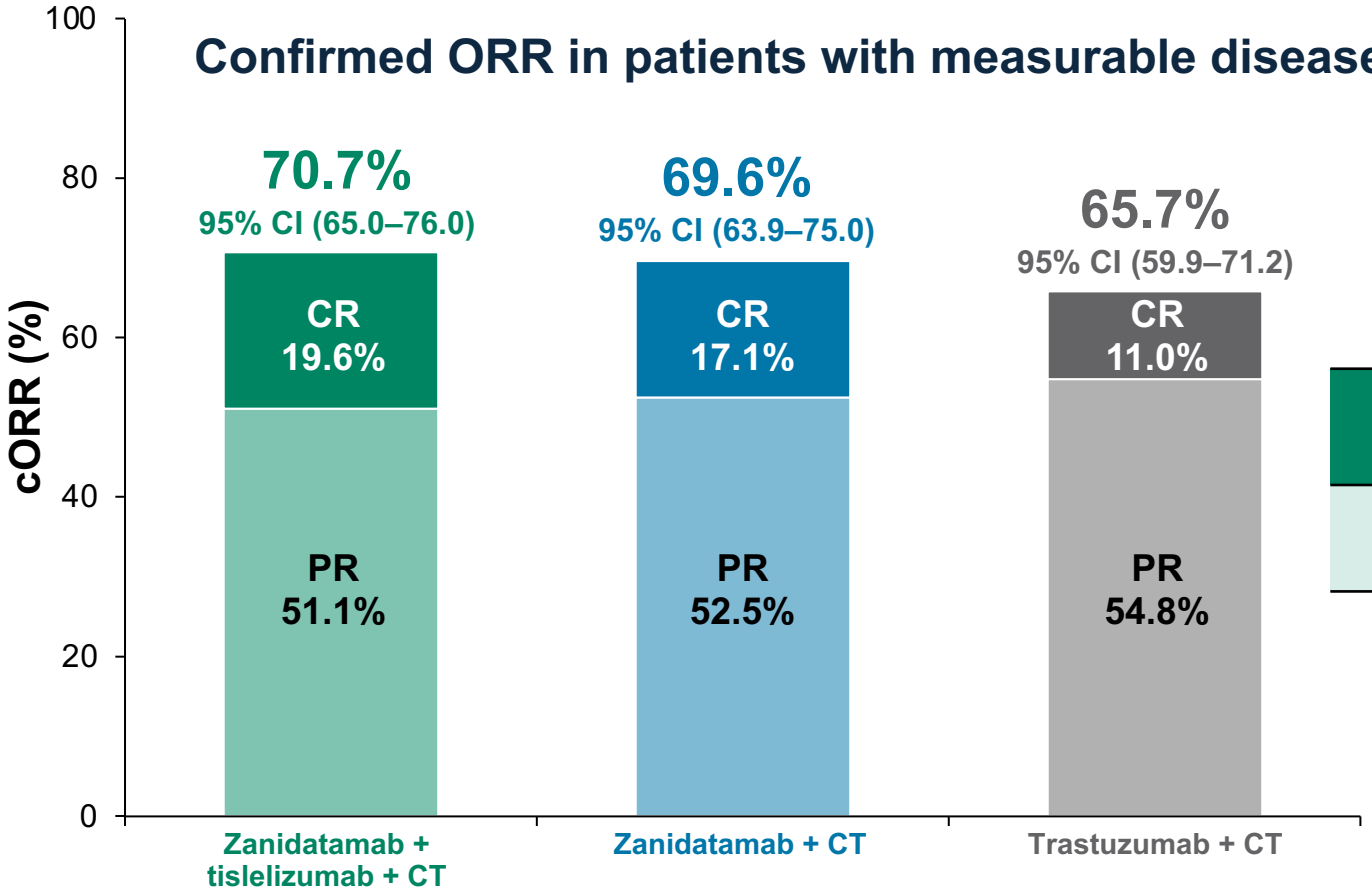
Patients at risk

Zani + CT	304	277	257	222	187	156	121	98	78	56	41	28	21	6	3	1	0
Tras + CT	308	284	261	219	178	140	106	77	61	50	33	22	17	8	2	2	0

CT, chemotherapy; HR, hazard ratio; OS, overall survival; Tras, trastuzumab; Zani, zanidatamab.

Key Secondary Endpoint: Antitumor Activity

Responses were deeper and more durable in the zanidatamab-containing arms vs the trastuzumab + CT arm



Median DOR (95% CI), mo

Zanidatamab + tislelizumab + CT (n = 195)	Zanidatamab + CT (n = 186)	Trastuzumab + CT (n = 198)
20.7 (12.6–37.7)	**14.3** (11.5–21.9)	**8.3** (6.7–9.8)

cORR was defined as the proportion of patients achieving a best overall response of CR or PR, as determined by BICR using RECIST v1.1, with the response confirmed at a subsequent visit ≥28 days after the initial assessment. DOR was assessed among patients with measurable disease at baseline who achieved a confirmed objective response by BICR per RECIST v1.1. The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
BICR, blinded independent central review; cORR, confirmed ORR; CR, complete response; CT, chemotherapy; DOR, duration of response; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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Treatment-Emergent Diarrhea

Treatment-emergent diarrhea generally occurred early in treatment and resolved within 3 weeks, and few patients discontinued zanidatamab due to diarrhea

	Zanidatamab + tislelizumab + CT (n = 294)[a]	Zanidatamab + CT (n = 305)[a]	Trastuzumab + CT (n = 302)
Treatment-related diarrhea, n (%)			
Any grade	240 (81.6)	233 (76.4)	146 (48.3)
Grade ≥3	72 (24.5)	61 (20.0)	39 (12.9)
Treatment-related diarrhea leading to discontinuation, n (%)			
Any component	22 (7.5)	15 (4.9)	5 (1.7)
Zanidatamab or trastuzumab	12 (4.1)	4 (1.3)	0
Tislelizumab	6 (2.0)	—	—
Time to first onset of diarrhea, median (IQR), days			
Any grade	7.0 (14.5)	6.0 (12.0)	10.0 (30.0)
Grade ≥3	16.0 (43.0)	11.0 (23.0)	37.0 (56.0)
Duration of first diarrhea event, median (95% CI), days			
Any grade	14.0 (11.0–18.0)	17.0 (13.0–20.0)	10.0 (7.0–15.0)
Grade ≥3	8.0 (7.0–9.0)	9.0 (6.0–11.0)	9.0 (6.0–12.0)

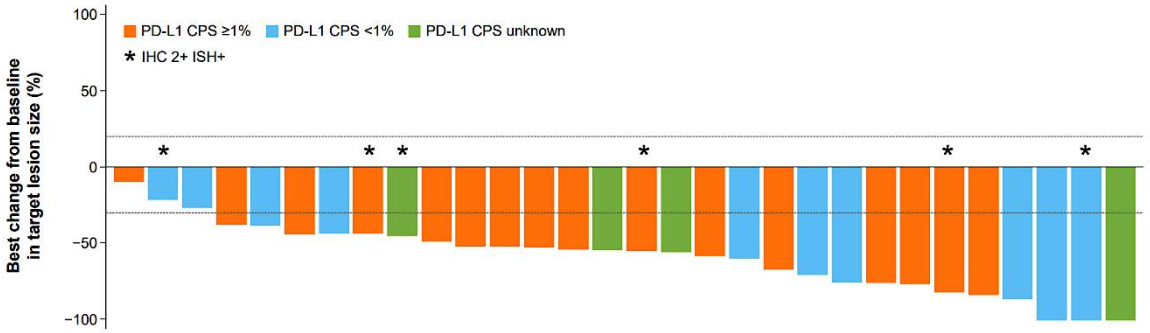
Mandatory diarrhea prophylaxis for patients in the zanidatamab-containing arms
Loperamide (4 mg BID) for the first 7 days of cycle 1 only

[a]Five patients who were assigned to the zanidatamab-tislelizumab-chemotherapy arm did not receive tislelizumab. Data from these patients are summarized in the zanidatamab-chemotherapy arm.
BID, twice daily; CT, chemotherapy; IQR, interquartile range.

DESTINY-Gastric03: 1L T-DXd plus chemo +/- anti-PD1

Trastuzumab Deruxtecan with PD-1 Blockade Safe and Effective

Figure 2. Best percentage change from baseline in the size of target lesion

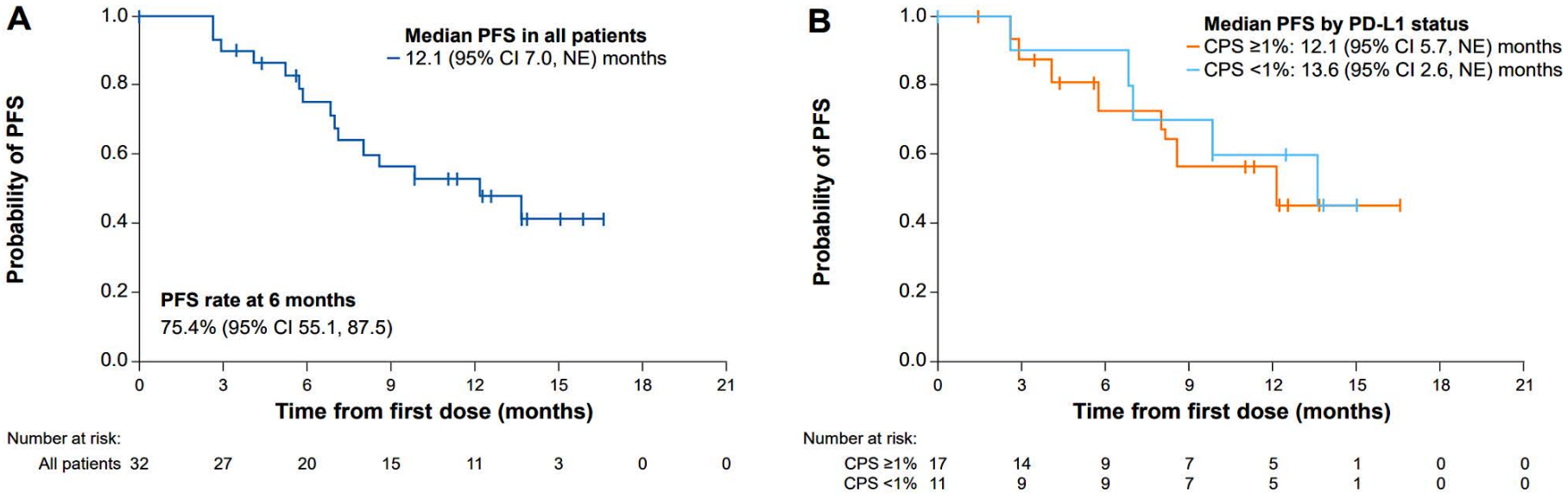


Investigator assessed per RECIST 1.1. Best percentage change is the maximum reduction or minimum increase from baseline in the target lesion size; the dashed lines at −30% and 20% change in target lesion size indicate the thresholds for partial response and progressive disease, respectively. HER2 status based on local test results. PD-L1 status was centrally assessed. Patients with no target lesions at baseline (n=1) or no post-baseline scans (n=1) were not included in the analysis

CPS, combined positive score; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours

AEs, n (%)	Arm F: T-DXd 5.4 mg/kg + FP + pembrolizumab (n=32)
AEs	31 (96.9)
Drug-related AEs*	27 (84.4)
Grade ≥3 AEs	15 (46.9)
Drug-related Grade ≥3 AEs*	11 (34.4)
Most common (≥8%) Grade ≥3 AEs	
Neutrophil count decreased	5 (15.6)
Platelet count decreased	3 (9.4)
Anemia	3 (9.4)

Figure 3. Kaplan-Meier estimates of PFS in all patients (A) and by PD-L1 status (B)



Janjigian et al, ESMO Asia 2025

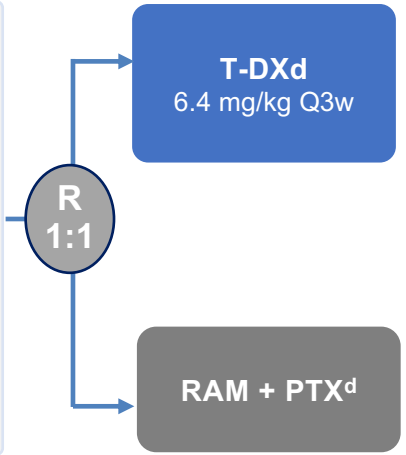
DESTINY-Gastric04 Study:

The world's first randomized, double-blind, controlled Phase III study comparing the efficacy of second-line treatment regimens for HER2+ advanced gastric cancer

Study Design

Patient Population

- HER2+(IHC 3+ or IHC 2+/ISH+)[a] GC/GEJA
- HER2 status confirmed locally or centrally on a recent biopsy obtained after progression on trastuzumab
- ECOG PS 0 or 1
- No clinically active CNS metastases



Primary Endpoint
- OS

Secondary Endpoints
- PFS(INV)
- Confirmed ORR (INV)
- DCR(INV)
- DOR(INV)
- Safety

Exploratory Endpoints
- PROs

Stratification factors
- HER2 status (IHC 3+ vs IHC 2+/ISH+)
- Geography (Asia [excluding mainland China] vs Western Europe vs mainland China / rest of world)
- Time to progression (<6 months vs ≥6 months)

Demographics and Baseline Characteristics

	T-DXd n = 246	RAM + PTX n = 248
Age, median (range), years	63.2 (21.1-84.1)	64.3 (31.9-87.0)
Male, n (%)	187 (76.0)	205 (82.7)
Geography,[a] n (%)		
Asia (excluding mainland China)	57 (23.2)	60 (24.2)
Western Europe	140 (56.9)	139 (56.0)
Mainland China/ROW	49 (19.9)	49 (19.8)
Race, n (%)		
White	116 (47.2)	130 (52.4)
Black/African American	0	2 (0.8)
Asian	101 (41.1)	97 (39.1)
Other	28 (11.4)	19 (7.7)
ECOG PS, n (%)		
0 | 1	97 (39.4) | 148 (60.2)	88 (35.5) | 158 (63.7)
2 | missing	1 (0.4) | 0	1 (0.4) | 1 (0.4)
Primary tumor location, n (%)		
Gastric	153 (62.2)	149 (60.1)
GEJ	93 (37.8)	99 (39.9)

	T-DXd n = 246	RAM + PTX n = 248
HER2 status,[a,b] n (%)		
IHC 2+/ISH+	39 (15.9)	40 (16.1)
IHC 3+	207 (84.1)	208 (83.9)
Time to progression on 1L therapy,[a] n (%)		
<6 months	61 (24.8)	61 (24.6)
≥6 months	185 (75.2)	187 (75.4)
Prior treatment with ICI, n (%)		
Yes	39 (15.9)	38 (15.3)
No	207 (84.1)	210 (84.7)
Metastatic sites, n (%)		
<2	73 (29.7)	75 (30.2)
≥2	173 (70.3)	173 (69.8)
Presence of liver metastases, n (%)	147 (59.8)	158 (63.7)
Presence of brain metastases, n (%)	16 (6.5)	18 (7.3)

T-DXd significantly extended median overall survival to 14.7 months and doubled the 2-year overall survival rate

DESTINY Gastric04

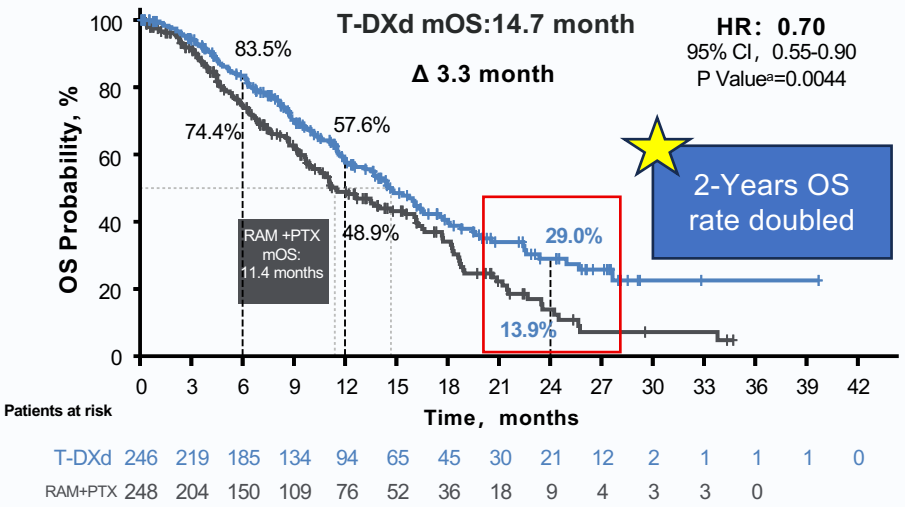
OS

T-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with RAM + PTX in HER2+ GC/GEJA, showing a 30% reduction in risk of death

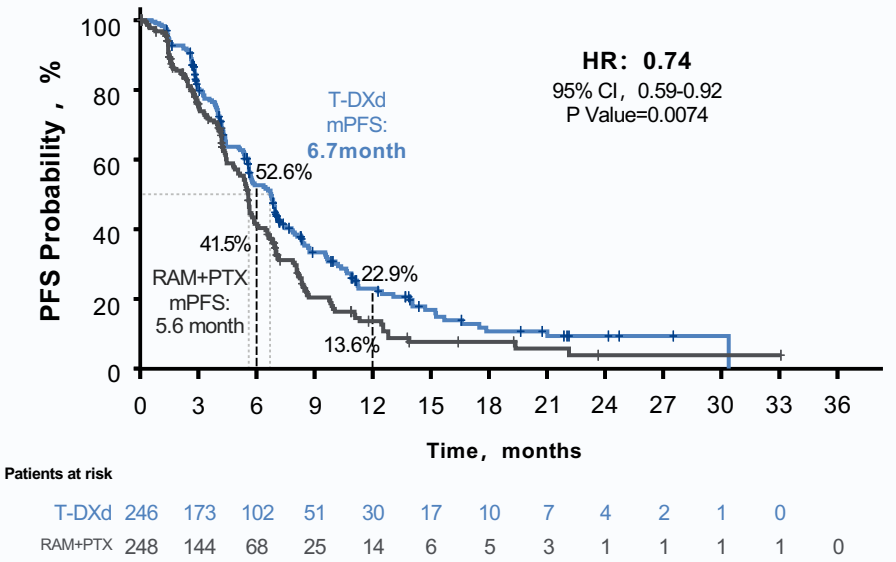
PFS

T-DXd demonstrated a statistically significant improvement in PFS compared with RAM + PTX in HER2+ GC/GEJA, showing a 26% reduction in risk of progression or death

Primary endpoint: OS



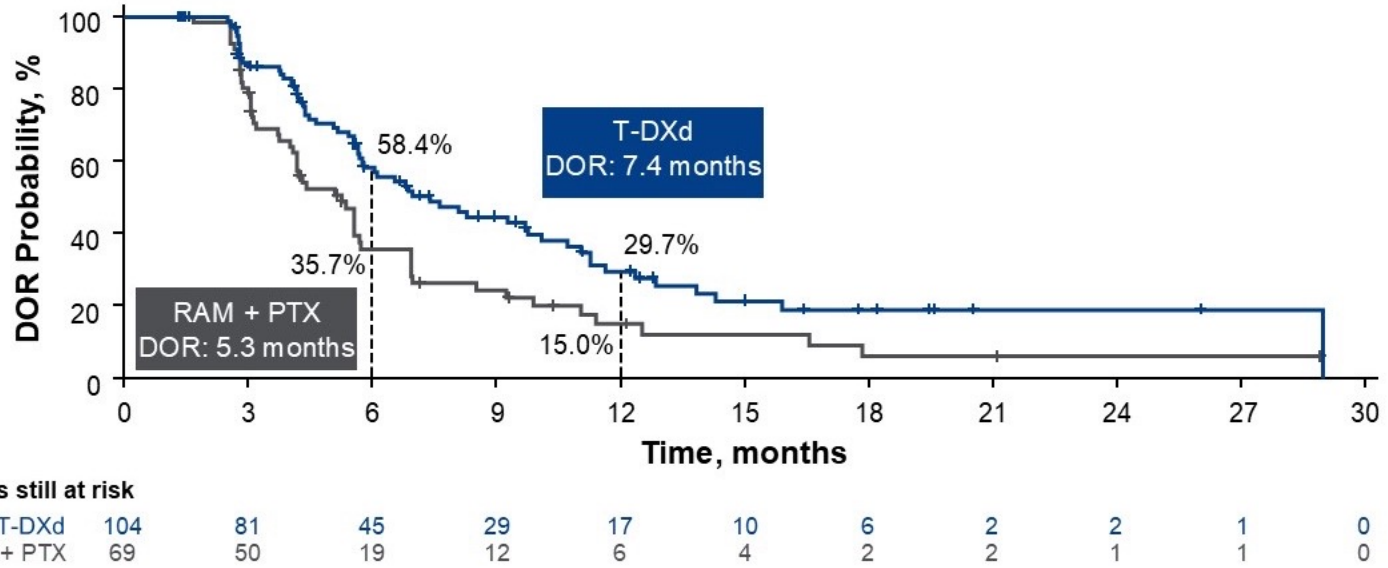
Key Secondary endpoint: PFS (INV)



At DCO (October 24, 2024), the median duration of OS follow-up was 16.8 months for T-DXd and 14.4 months for RAM + PTX

Confirmed ORR and DCR

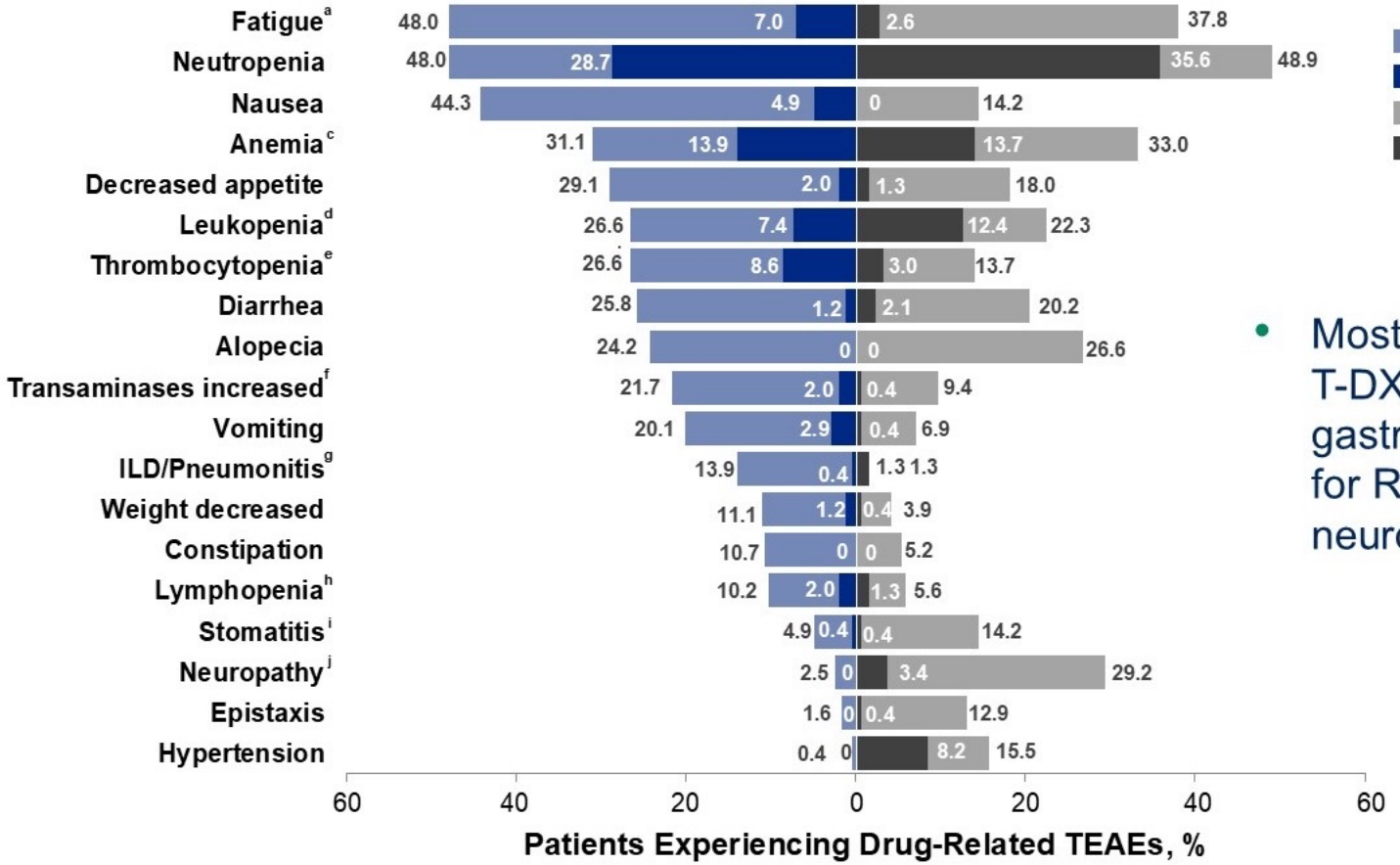
	T-DXd n = 246	RAM + PTX n = 248
Confirmed ORR (95% CI),[c] %	**44.3 (37.8-50.9)**	**29.1 (23.4-35.3)**
P value[d]	0.0006	
Difference (95% CI),[e] %	15.1 (6.1-24.2)	
DOR, median (95% CI), mo	**7.4 (5.7-10.1)**	**5.3 (4.1-5.7)**
DCR (95% CI), %	**91.9 (87.7-95.1)**	**75.9 (70.0-81.2)**
Confirmed BOR, n (%)		
CR[f]	7 (3.0)	3 (1.3)
PR	97 (41.3)	66 (27.8)
SD[g]	112 (47.7)	111 (46.8)
PD	13 (5.5)	22 (9.3)
NE	6 (2.6)	35 (14.8)



The confirmed ORR was 15.1% greater with T-DXd compared with RAM + PTX (*P* = 0.0006), with longer DOR

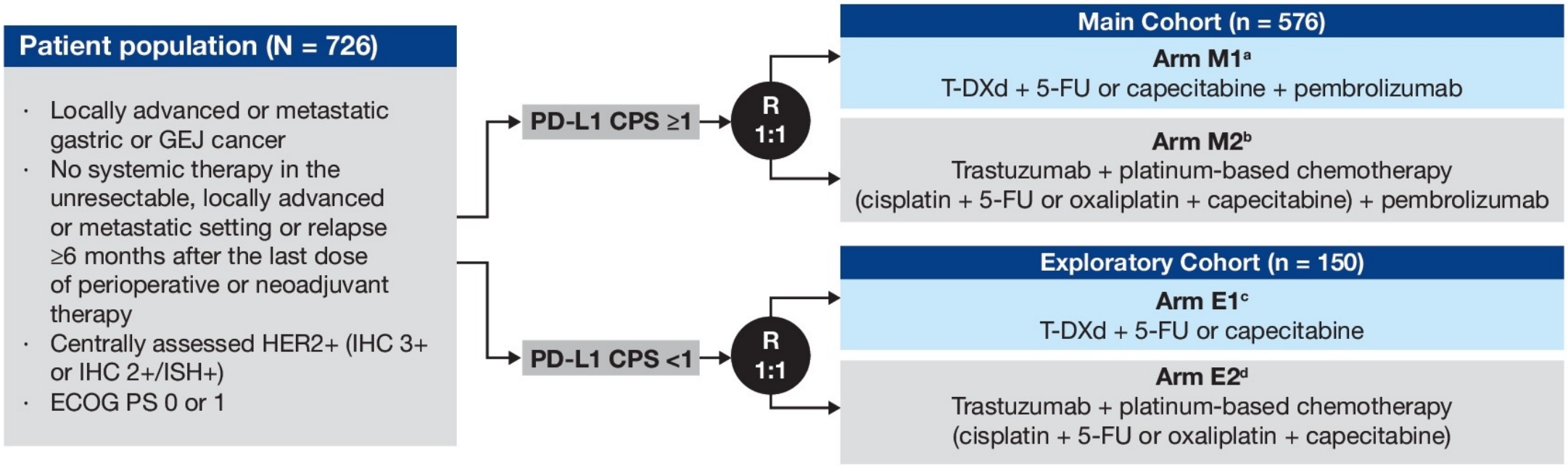
Safety analysis:

The safety profile of trastuzumab deruxtecan 6.4 mg/kg was consistent with previous safety data, with no new safety signals identified



- Most common drug-related TEAEs with T-DXd included fatigue or AEs of gastrointestinal or hematologic nature; for RAM + PTX, they included fatigue, neuropathy, and hematologic AEs

DESTINY-Gastric05: T-DXd plus chemo +/- anti-PD1



[a]T-DXd 5.4 mg/kg IV Q3W on day 1 plus 5-FU 600 mg/m^2/day IV on days 1 to 5 or capecitabine 750 mg/m^2 PO BID on days 1 to 14 plus pembrolizumab 200 mg IV Q3W on day 1.

[b]Trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg IV Q3W plus platinum-based chemotherapy (cisplatin 80 mg/m^2/day IV on day 1 plus 5-FU 800 mg/m^2/day IV on days 1 to 5 or oxaliplatin 130 mg/m^2/day IV on day 1 plus capecitabine 1000 mg/m^2 PO BID on days 1 to 14) plus pembrolizumab 200 mg IV Q3W on day 1.

[c]T-DXd 5.4 mg/kg IV Q3W on day 1 plus 5-FU 600 mg/m^2/day IV on days 1 to 5 or capecitabine 750 mg/m^2 PO BID on days 1 to 14.

[d]Trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg IV Q3W plus platinum-based chemotherapy (cisplatin 80 mg/m^2/day IV on day 1 plus 5-FU 800 mg/m^2/day IV on days 1 to 5 or oxaliplatin 130 mg/m^2/day IV on day 1 plus capecitabine 1000 mg/m^2 PO BID on days 1 to 14).

Shitara K & Janjigian Y, ASCO 2025

ARTEMIDE-Gastric01: study design[1,2]

1L rilvegostomig + T-DXd + fluoropyrimidine in HER2+ / PD-L1 CPS ≥1 GC / GEJC

- Histologically confirmed locally advanced or metastatic GC / GEJC
- No prior systemic treatment
- HER2+ (IHC 3+ or IHC 2+ / ISH+)
- PD-L1 CPS ≥ 1
- WHO or ECOG PS 0 or 1

N=~840

R
1:1:1

Arm A
Rilvegostomig + T-DXd + 5-FU / capecitabine

Arm B
Pembrolizumab + trastuzumab + 5-FU + cisplatin / CAPOX

Arm C
Rilvegostomig + trastuzumab+ 5-FU + cisplatin / CAPOX

Primary endpoints

PFS, OS (Arm A vs Arm B)

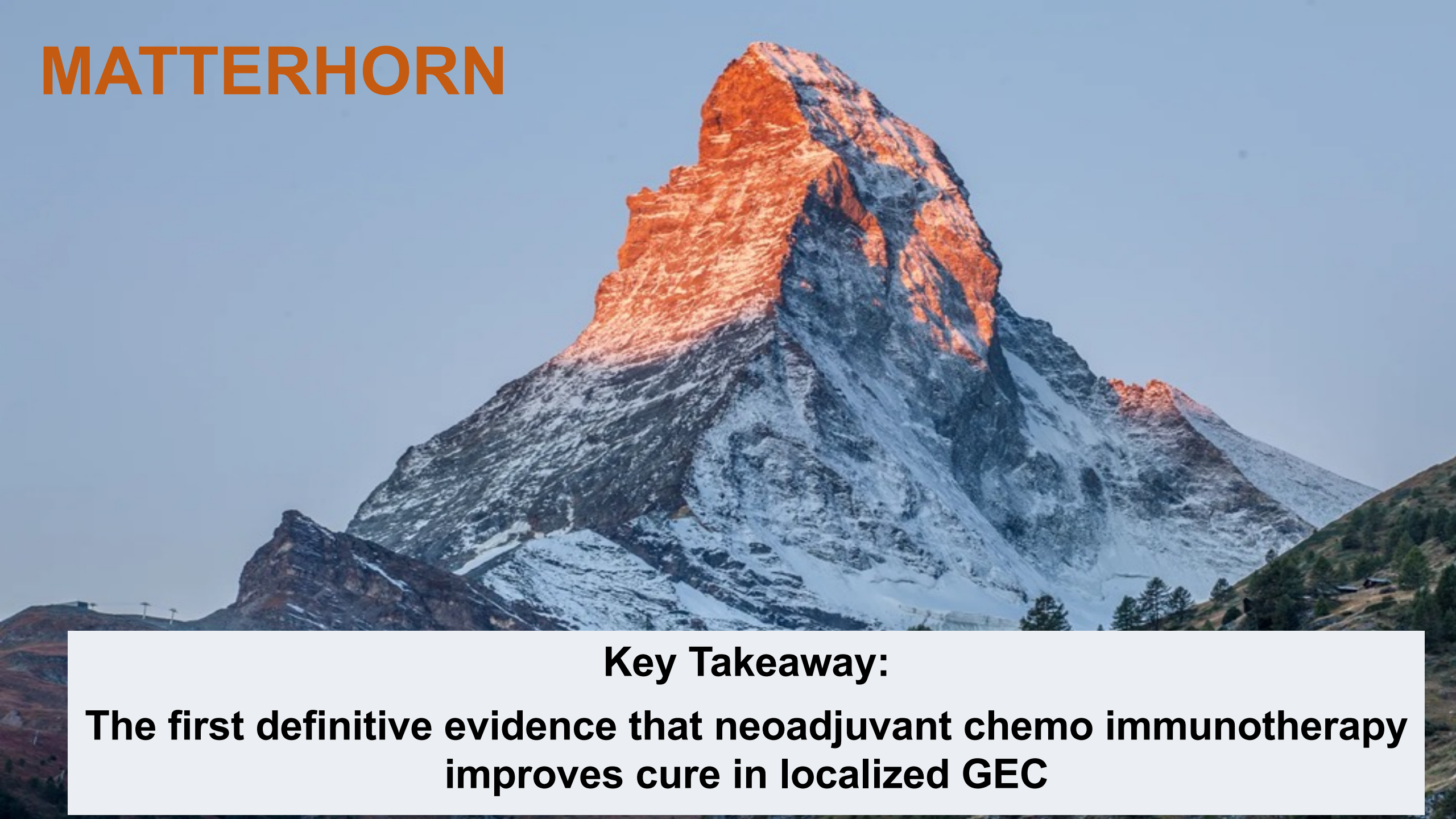
Study design	• Phase 3, randomised global study, N=~840 • Testing of HER2 and PD-L1 for participant selection • Arm A: Rilvegostomig IV Q3W plus T-DXd 5.4 mg/kg IV Q3W plus fluoropyrimidine* • Arm B: Pembrolizumab 200 mg IV Q3W plus trastuzumab 6 mg/kg IV Q3W plus platinum-based chemotherapy† • Arm C: Rilvegostomig IV Q3W plus trastuzumab 6 mg/kg IV Q3W plus platinum-based chemotherapy†
Endpoints	• Primary endpoint (Arm A vs Arm B): PFS (BICR), OS • Key secondary endpoints (Arm C vs Arm B): PFS (BICR), OS • Secondary endpoints: PFS (investigator), ORR (investigator), and DoR (investigator), safety and tolerability, PK, immunogenicity, and PROs

* Investigator's choice of capecitabine 750 mg/m^2 PO BID for 14 days Q3W, OR 5-FU 600 mg/m^2/day IV Q3W. †Investigator's choice of cisplatin 80 mg/m^2 IV (up to 6 cycles) plus 5-FU 800 mg/m^2/day IV Q3W, OR oxaliplatin 130 mg/m^2 IV (up to 8 cycles) plus capecitabine 1000 mg/m^2 PO BID for 14 days Q3W.

1L, first-line; 5-FU, 5-fluorouracil; BICR, blinded independent central review; BID, twice daily; CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; PRO, patient-reported outcome; Q3W, once every 3 weeks; R, randomised; T-DXd, trastuzumab deruxtecan; WHO, World Health Organisation.

1. Xu R-H, et al. Presented at: ASCO Annual Meeting; May 30–June 3, 2025; Chicago, IL, USA. Abstract TPS4204. 2. NIH. NCT06764875. https://www.clinicaltrials.gov/study/NCT06764875. Accessed 26 September 2025.

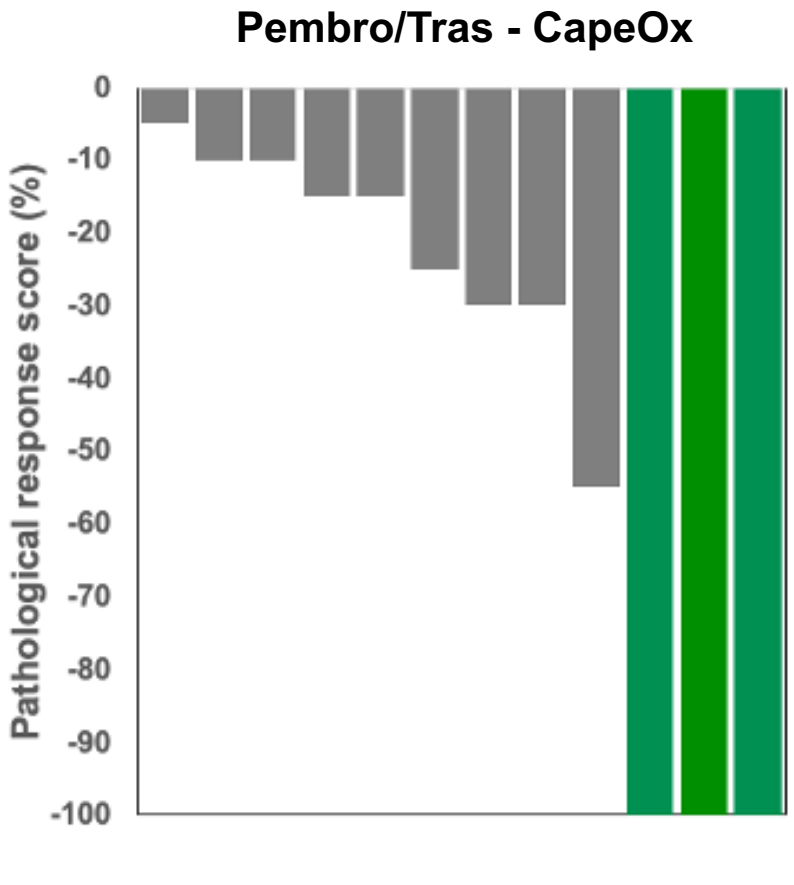
MATTERHORN

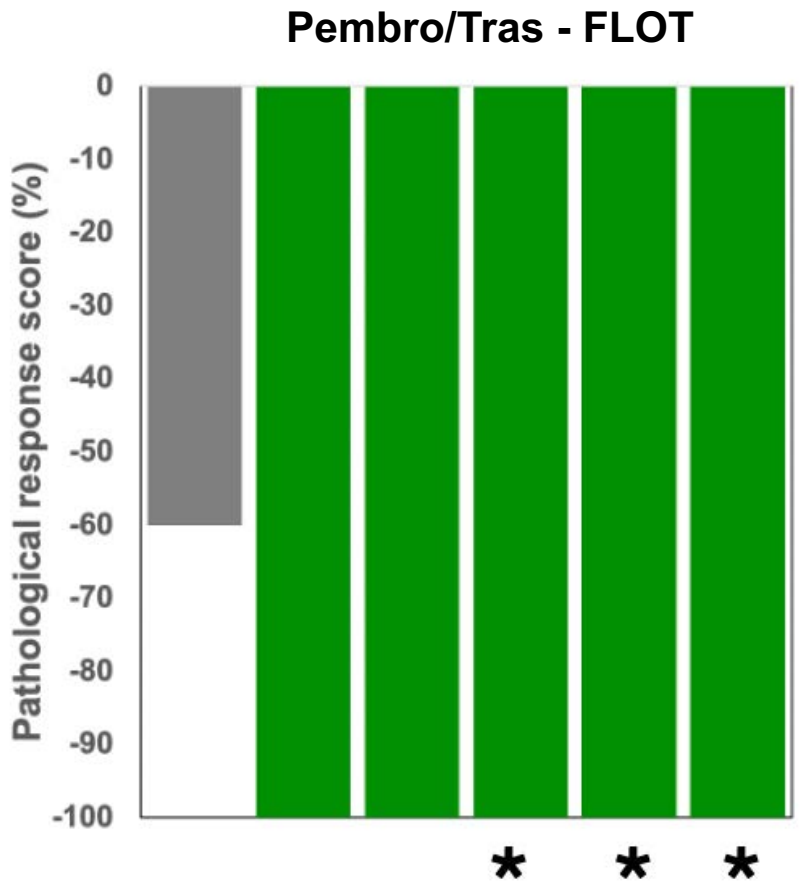


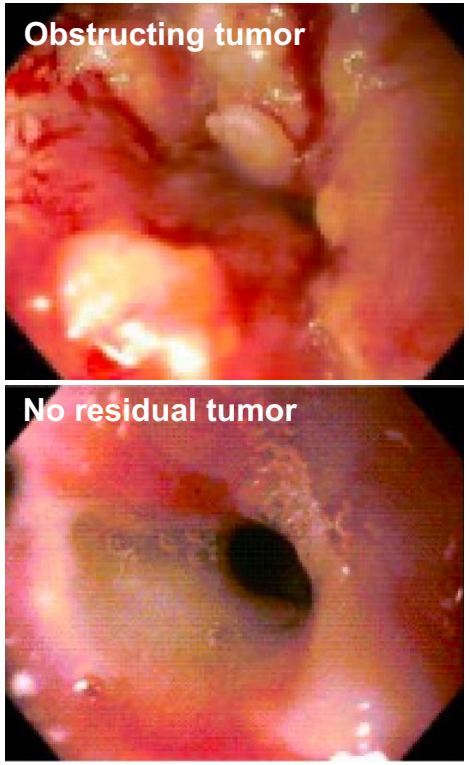
Key Takeaway:

The first definitive evidence that neoadjuvant chemo immunotherapy improves cure in localized GEC

Pembro + trastuzumab + FLOT enables organ preservation







cCR 25% (3/12)

cCR 83% (5/6)

- PD-1 + HER2 targeting can generate clinical complete responses
- Durable disease-free survival observed in cCR patients
- Prospective non-operative management strategies under investigation

Conclusions

- **HER2-positive gastroesophageal cancer therapy is rapidly evolving.**
- **Checkpoint inhibition plus trastuzumab and chemotherapy has improved response depth and outcomes in the first-line setting (KEYNOTE-811).**
- **Next-generation HER2 targeting (e.g., zanidatamab combinations) demonstrates meaningful improvements in PFS and OS versus trastuzumab-based therapy.**
- **Antibody–drug conjugates such as trastuzumab deruxtecan have transformed second-line treatment and are moving earlier in therapy.**
- **Novel combinations integrating HER2 targeting and immunotherapy are redefining first-line treatment strategies.**
- **Increasingly effective systemic therapy raises the possibility of greater cure rates and organ-preserving approaches in localized GEC.**

QUESTIONS?

We are taking a short break!

The program will resume at 1:20 PM ET

Up Next…

Drs Mrinal Gounder and Richard F Riedel discuss the management of desmoid tumors and soft tissue sarcoma

RTP
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TO PRACTICE