Module 6: Desmoid Tumors and Soft Tissue Sarcoma

Desmoid Tumors — Dr Gounder

Soft Tissue Sarcoma — Dr Riedel

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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.

Desmoid Tumors

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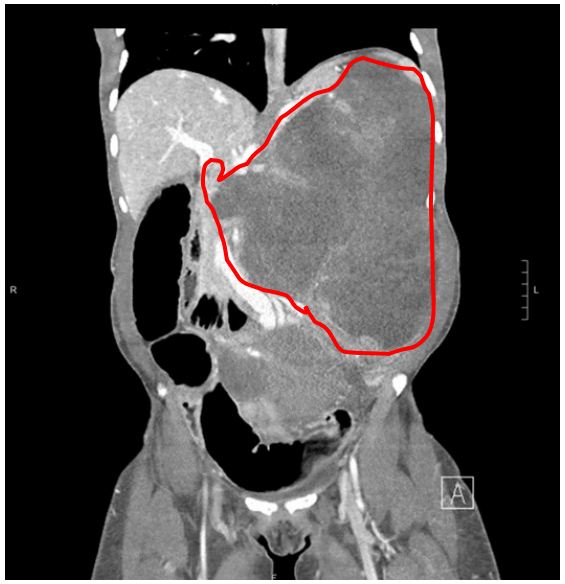
Disclosures

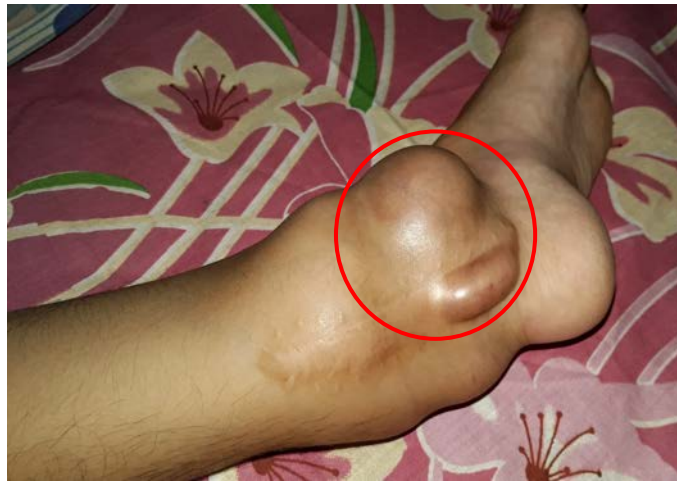
Consulting Agreements	Aadi Bioscience, Avacta Therapeutics, Ayala Pharmaceuticals, Ikena Oncology, Immunome, Ipsen Biopharmaceuticals Inc, Kura Oncology, Orion Corporation, Parabilis Medicines, Rain Oncology, Regeneron Pharmaceuticals Inc, SpringWorks Therapeutics Inc, Syros Pharmaceuticals Inc
Contracted Research	Avacta Therapeutics, Ayala Pharmaceuticals, Ikena Oncology, Immunome, Ipsen Biopharmaceuticals Inc, Kura Oncology, Orion Corporation, Parabilis Medicines, Pyxis Oncology, SpringWorks Therapeutics Inc, Tango Therapeutics, Vivace Therapeutics
Data and Safety Monitoring Boards/Committees	Kura Oncology

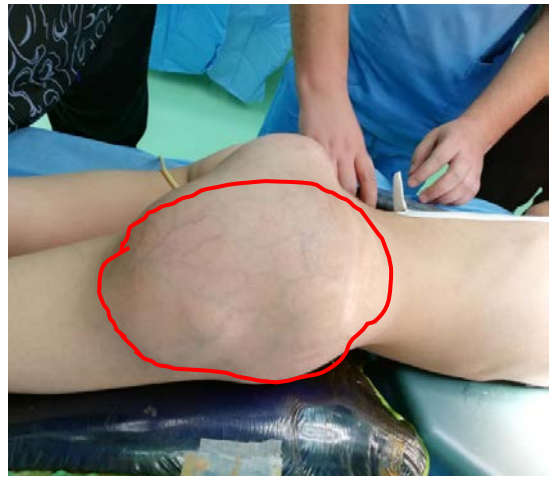
Learning Objectives

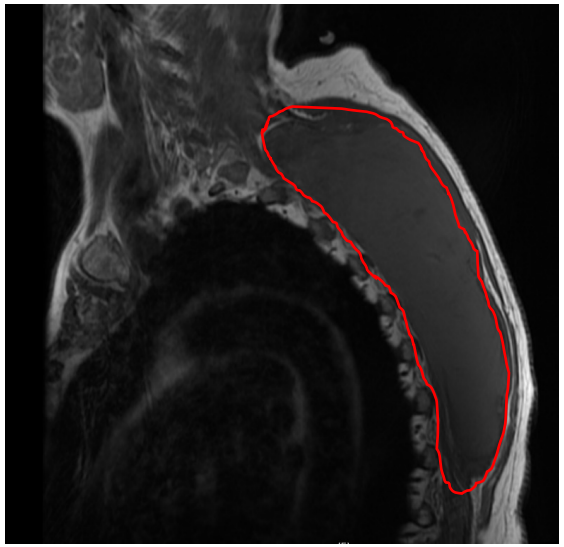
- Apply relevant strategies to address timely diagnosis in patients with desmoid tumors
- Discuss patient selection for systemic treatment based on safety and efficacy data

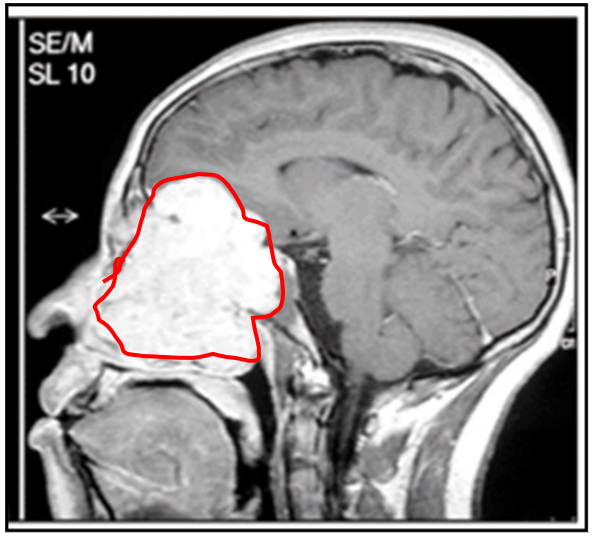
DESMOID TUMORS – Locally aggressive, fibroblastic, connective tissue tumor – rarely fatal

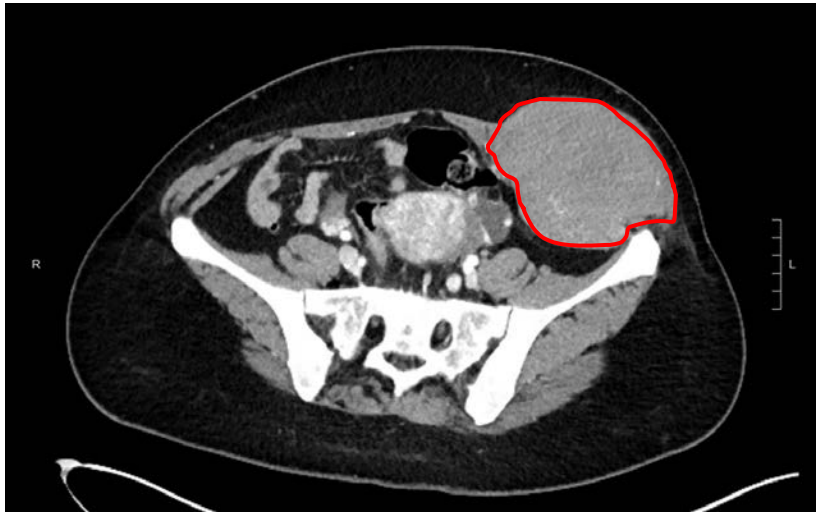




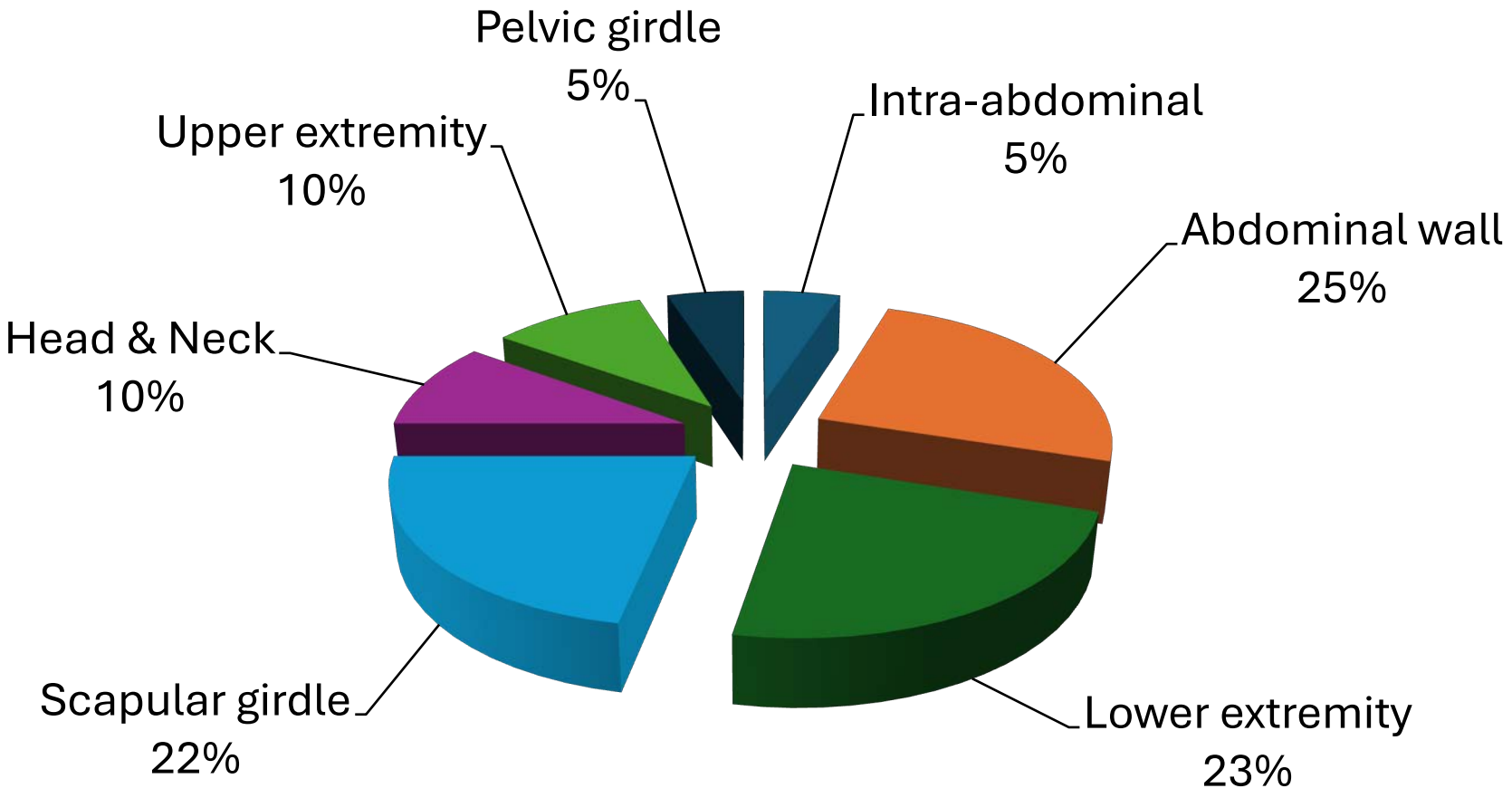








Sites

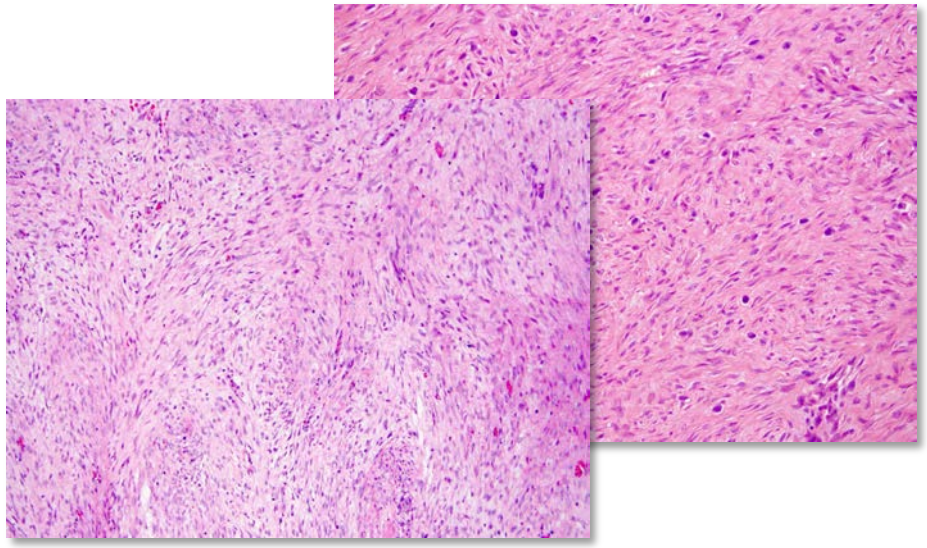

Pelvic girdle
5%
Intra-abdominal
5%
Upper extremity
10%
Abdominal wall
25%
Head & Neck
10%
Scapular girdle
22%
Lower extremity
23%

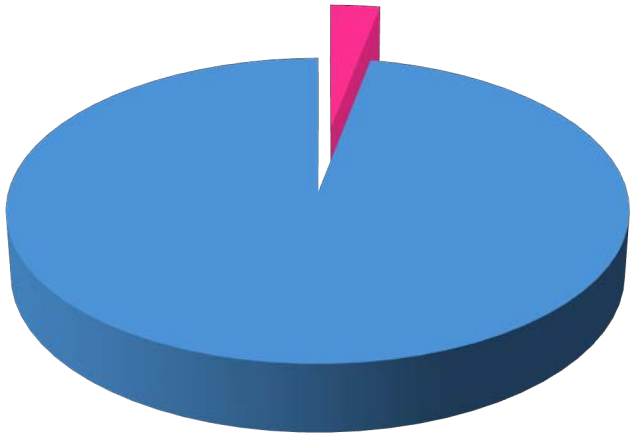
Overview: *Desmoid Tumors (DT)*

- Rare
  - <3% of all soft tissue tumors
  - Incidence 2-4 cases/1,000,000 individuals
- Also known as…
  - Aggressive fibromatosis (AF), Deep fibromatosis, Desmoid-type fibromatosis
- Fibrous tissue proliferation
  - Often indolent
  - Can be locally invasive and aggressive
- No metastatic potential
  - Can be associated with morbidity and mortality

Desmoid Tumor Working Group. *Eur J Cancer*. 2020;127:96-107.

Incidence of Desmoid Tumors Globally





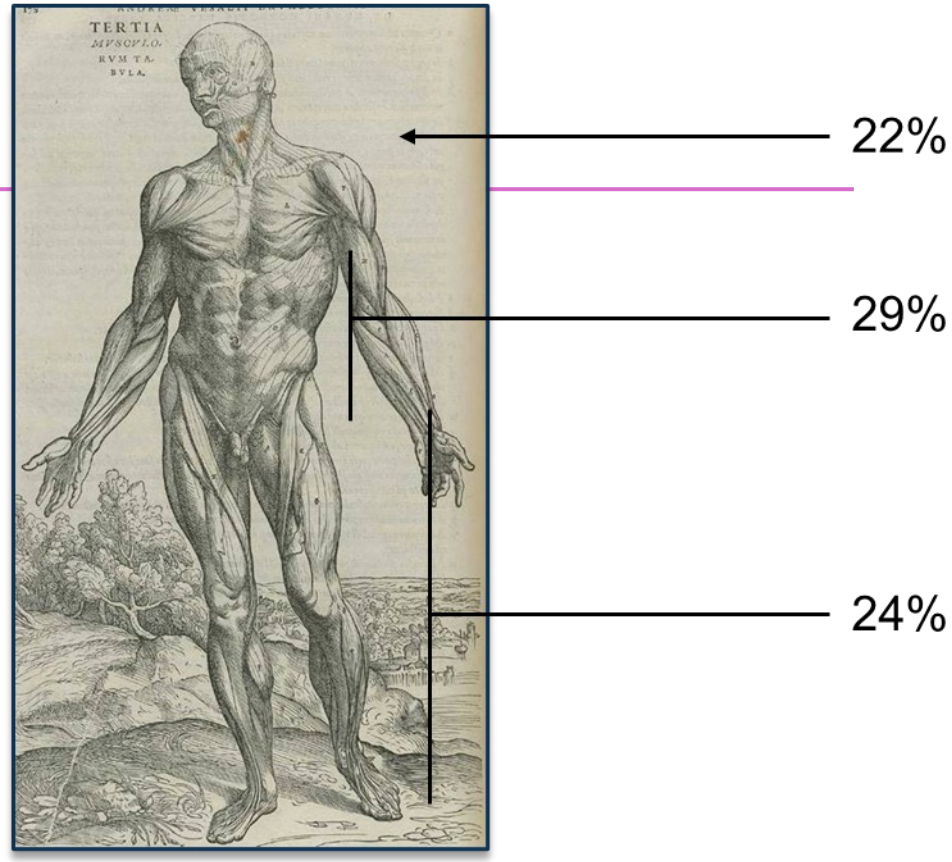
0.5-0.6/100,000/y

Obeidin F, Alexiev B. PathologyOutlines.com website.

Desmoid Tumor Research Foundation.
Desmoid Tumor Foundation of Canada.
Desmoid Tumor Working Group. Eur J Cancer. 2020;127:96-107.

Clinical Presentation

- Varied symptoms
  - Painless or painful
- Vast majority occur spontaneously
  - Association with FAP (Gardner's syndrome)
- Can occur anywhere in the body
  - Palpable mass in the extremities or trunk
  - Intra-abdominal desmoid tumors (FAP)



- Reports of desmoid tumors in conjunctions with pregnancy, breast implants, orthopedic hardware, etc.
- Often misdiagnosed as other sarcomas, leading to poor outcomes due to incorrect management

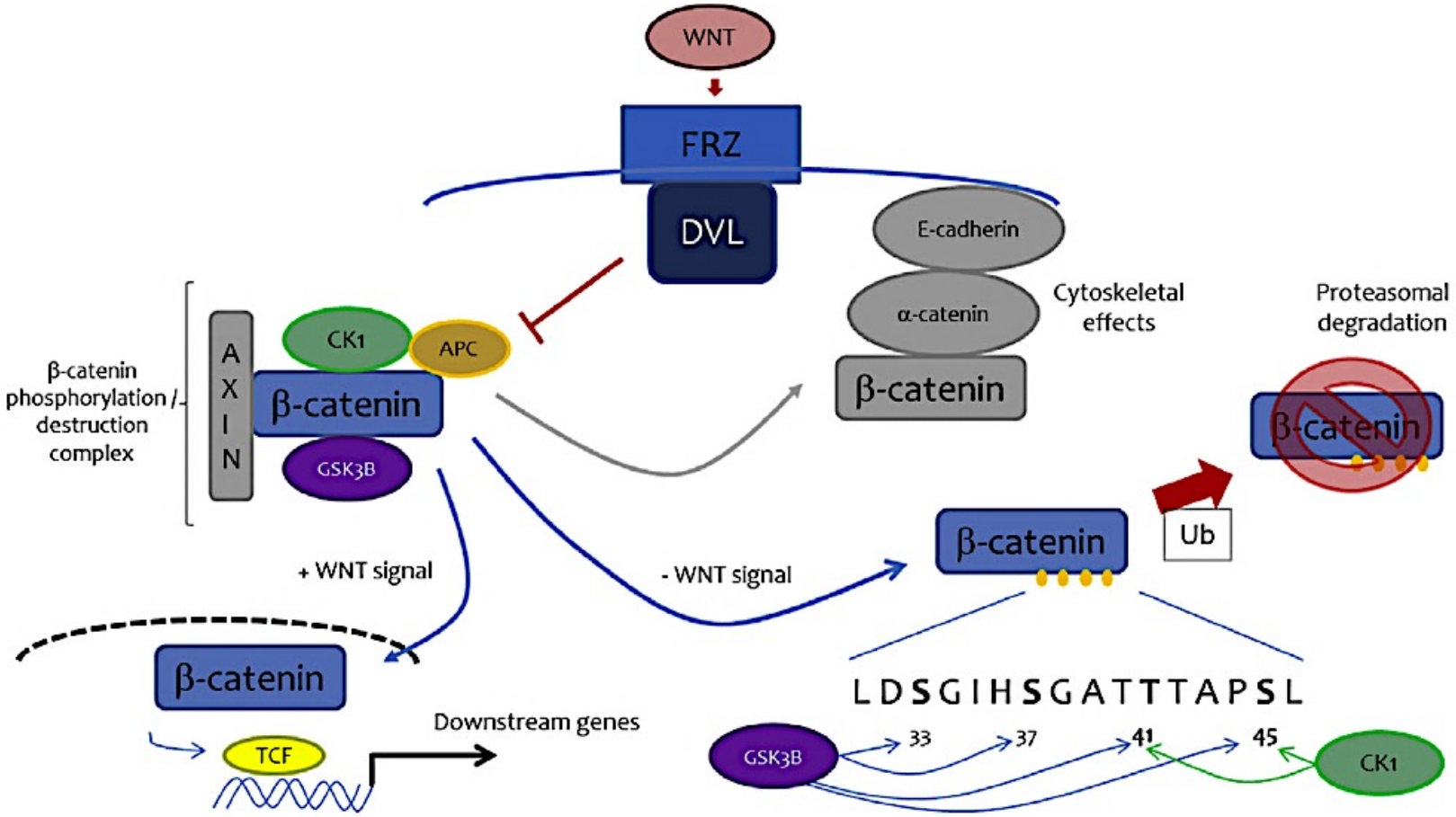
Desmoid Tumor Working Group. *Eur J Cancer*. 2020;127:96-107.

Role of Imaging

- Whole body staging is not necessary
- Ultrasound and PET imaging have limited use
- CT and MRI are the preferred imaging modalities
  - CT for intra-abdominal disease
  - MRI for extra-abdominal/extremity disease

Braschi-Amirfarzan M et al. *Radiographics*. 2016;36(3):767-82.

Either *CTNNB1 (beta-catenin)* <u>or</u> *APC* loss (FAP) mutations

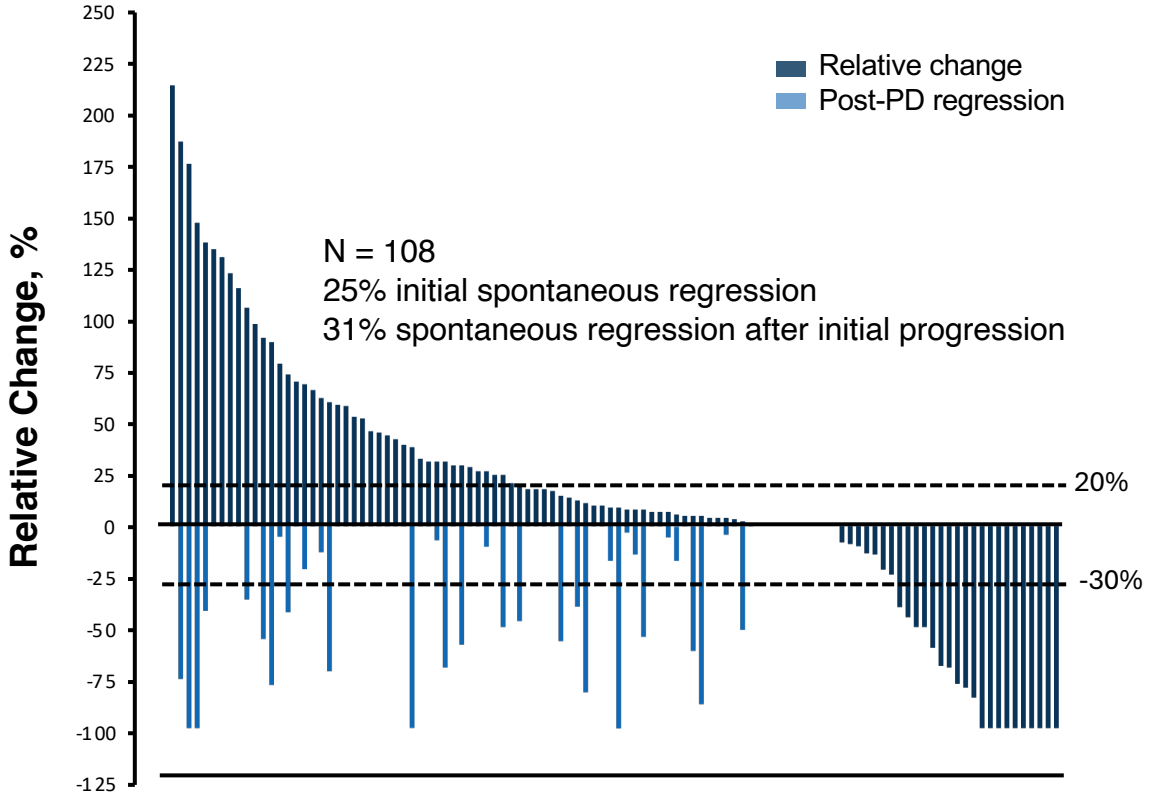


- Both are mediators of the wingless signaling pathway, which gives rise to an uncontrolled proliferation of fibroblasts

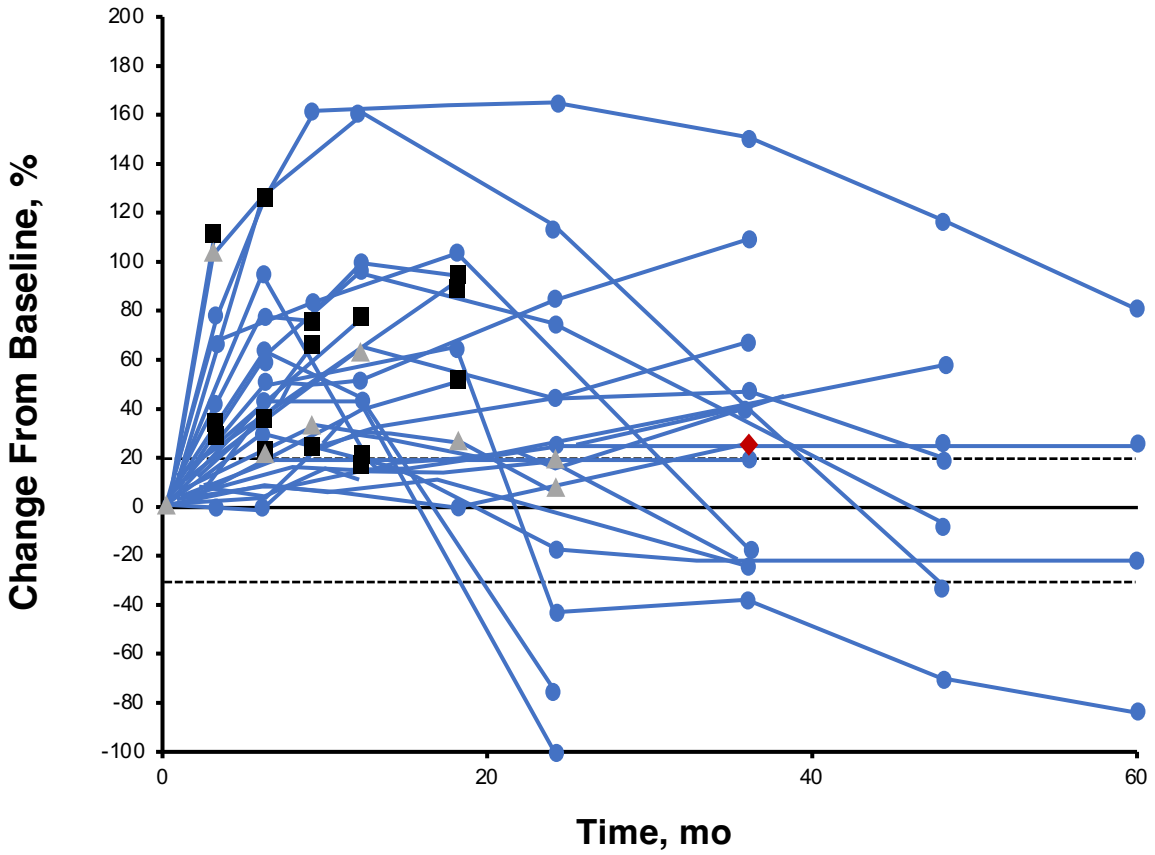
Desmoid Tumor Working Group. Eur J Cancer. 2020 Mar:127:96-107.

Spontaneous Regression After Progression

Italian Observational Study[1]

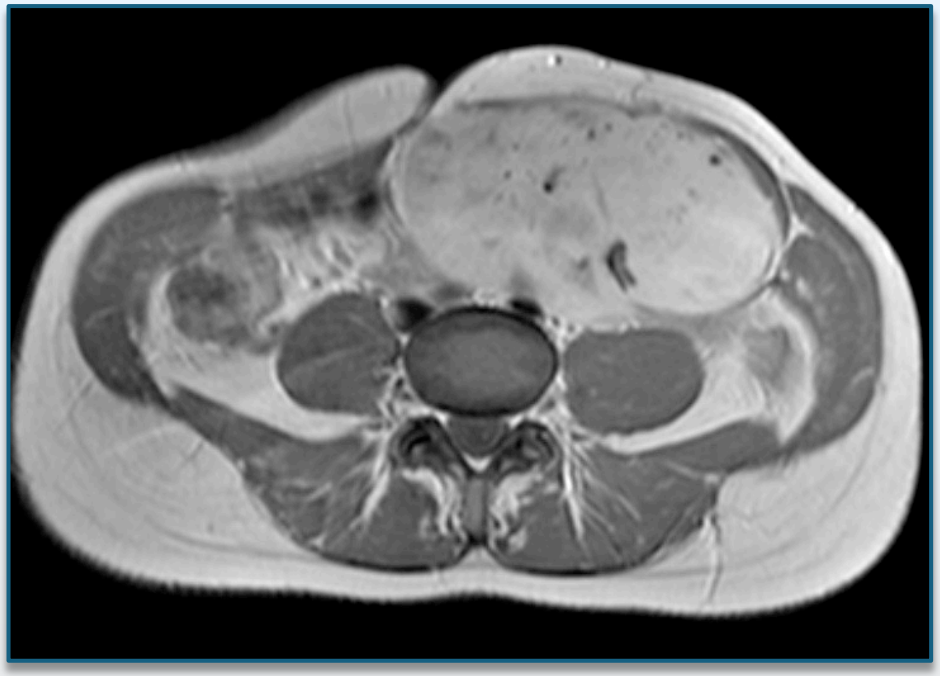


The GRAFITI Study[2]



1. Colombo C et al. *Clin Cancer Res*. 2022;28:4027-4032. 2. Schut AW et al. *Ann Surg*. 2023;277(4):689-696. doi: 10.1097/SLA.0000000000005415.

Criteria for Active Treatment



- ✓ Cosmesis
- ✓ Pregnancy
- ✓ Progression
- ✓ Pain

Surgery in <u>rare</u> cases after tumor board discussion.

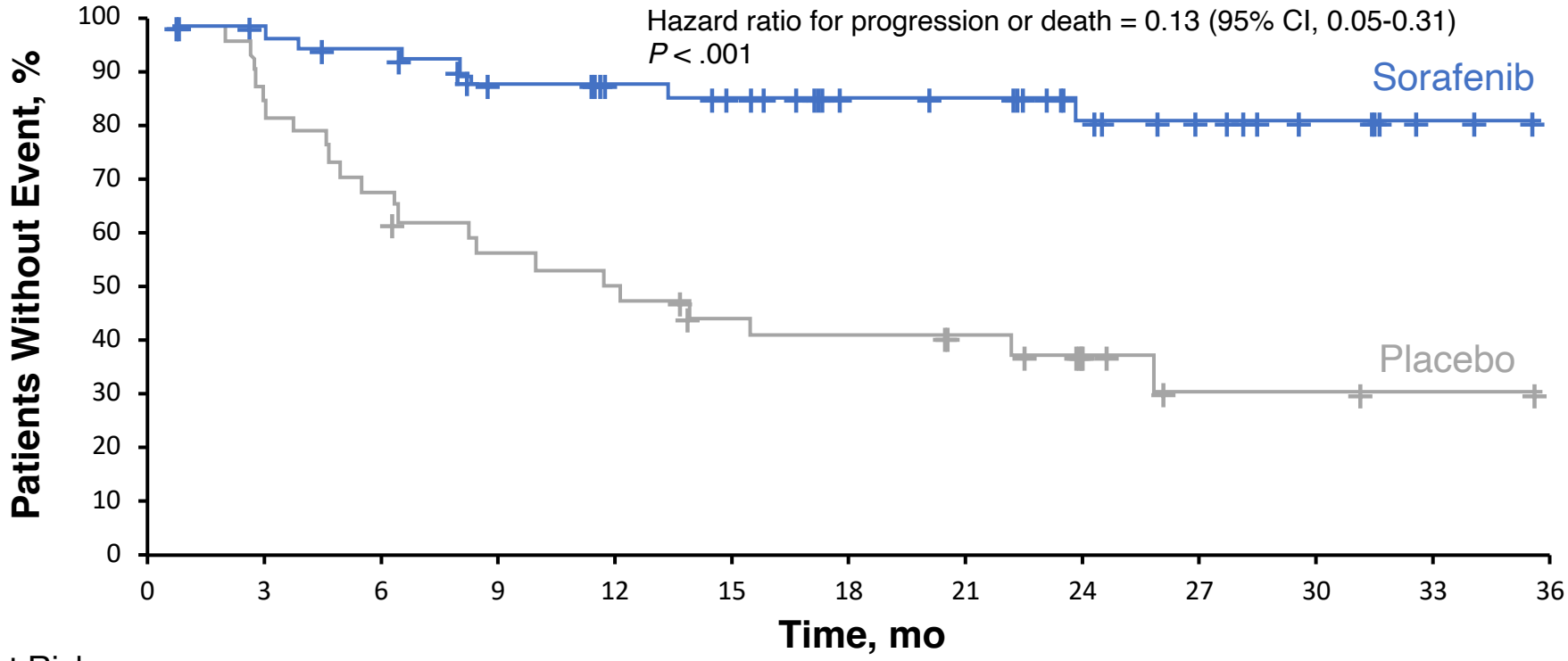
Cytotoxic Chemotherapy
Progressing and/or Symptomatic

- MTX/vinblastine[1]
- MTX/vinorelbine[1,2] or vinorelbine alone[1,3]
- Pegylated liposomal doxorubicin (PLD)[5-7]
- Anthracycline-based regimens[4]

1 Skapek SX et al. *J Clin Oncol.* 2007;25(5):501-6.
2 Weiss AJ et al. *Am J Clin Oncol.* 1999;22(2):193-195.
3 Mir O et al. *J Clin Oncol.* 2016;34(suppl; abstr 11050).
4 De Camargo VP et al. *Cancer.* 2010;116(9):2258-2265.
5 Constantinidou A et al. *Eur J Cancer.* 2009;45(17):2930-2934.
6 Constantinidou A et al. *Acta Oncol.* 2011;50(3):455-461.
7 Pang A et al. *J Clin Oncol.* 2016;34(suppl; abstr 11032).

Phase 3 Randomized Study: *Sorafenib Versus Placebo*

	No. of Patients	No. of Events	Median PFS (95% CI), mo
Sorafenib	49	7	NE (NE-NE)
Placebo	35	22	11.3 (5.7-NE)



No. at Risk													
Sorafenib	49	46	41	36	32	29	23	22	17	14	8	4	3
Placebo	35	28	20	18	15	12	11	10	7	3	3	2	2

Gounder MM et al. *N Engl J Med*.2018;379(25):2417-2428.

Tyrosine Kinase Inhibitors

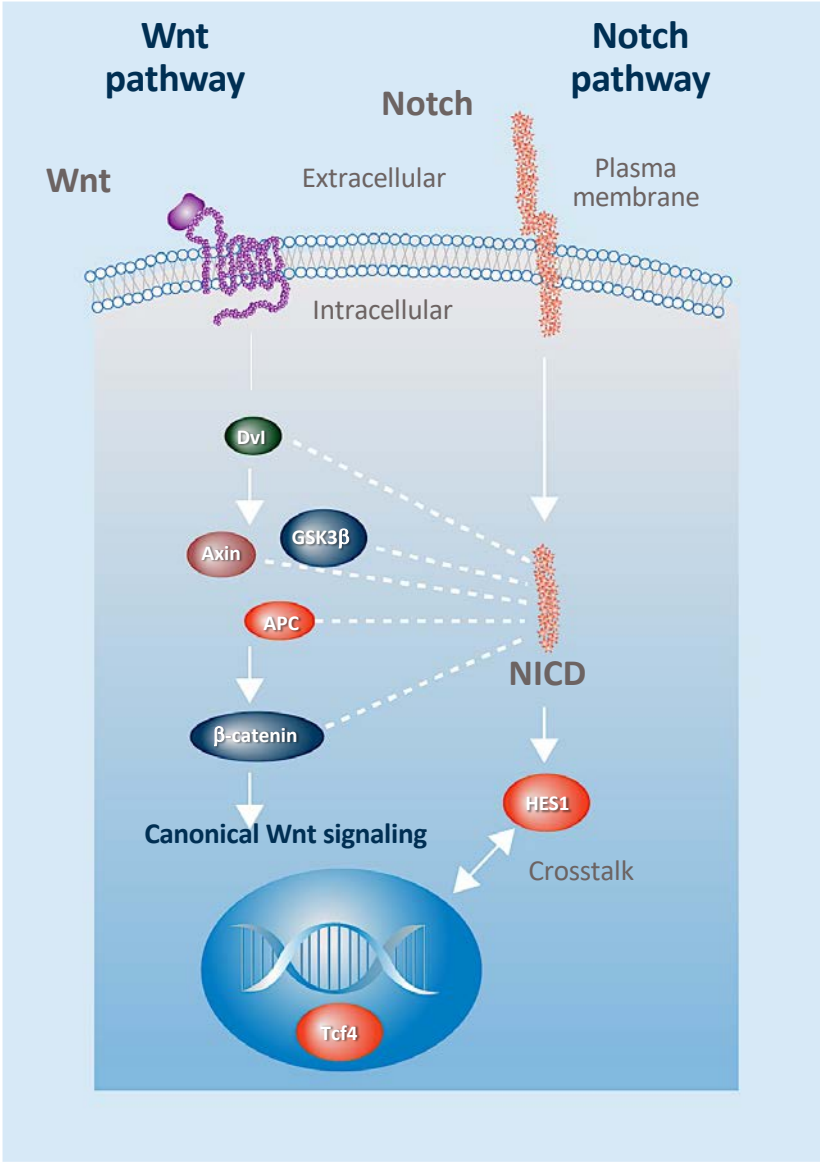
Reference	n	Inclusion Criteria	Treatment Dose, mg	Treatment Duration	ORR, %	6-Month PFS, %	12-Month PFS, %	24-Month PFS, %
Heinrich et al, 2006	19	“Heavily pretreated patients”	Imatinib 800 mg	325 days	16	53	37	NE
Penel et al, 2010	35	“Radiological evidence for PD”	Imatinib 400 mg	1 year	11	80	67	55
Chugh et al, 2010	49	“Locally advanced disease”	Imatinib 200-600 mg	Until PD 9 patients >3 years	6	84	66	NE
Kasper et al, 2017	38	RECIST PD	Imatinib 800 mg	2 years	19	65	59	45
Sorafenib Gounder, 2018	50	“Progressive or symptomatic”	Sorafenib 400 mg	Until PD	33	NE	89	81
Pazopanib Toulmond, ASCO 2018	48	RECIST PD	Pazopanib 800 mg	1 year	37	81	86	NE
Nirogacestat Kummar, 2017	17	“Progressive/ symptomatic”	Nirogacestat 300 mg	Until PD	29	100	100	100

Gamma Secretase Inhibition in Desmoid Tumors

- There is mechanistic rationale for the use of GSIs in DTs because these tumors highly express Notch, which can be blocked by GSIs[5,6]

Nirogacestat is an FDA-approved oral, targeted, and selective gamma secretase inhibitor indicated for adult patients with progressing DTs who require systemic treatment

AL102 is an investigational, oral, potent inhibitor of gamma secretase

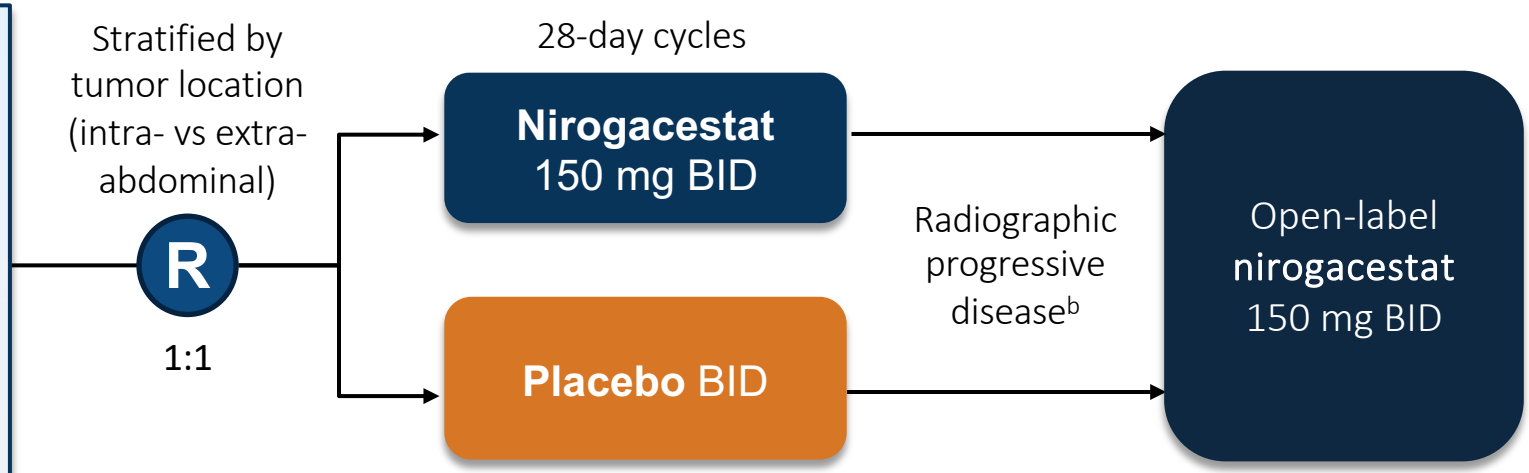


DeFi: Phase 3 Study of Nirogacestat vs Placebo

- Global, randomized, double-blind, placebo-controlled, phase 3 trial comparing the efficacy, safety, and tolerability of nirogacestat vs placebo in adult patients with progressing DTs
- 142 patients randomized across 37 sites in North America and Europe

Adult eligible patients

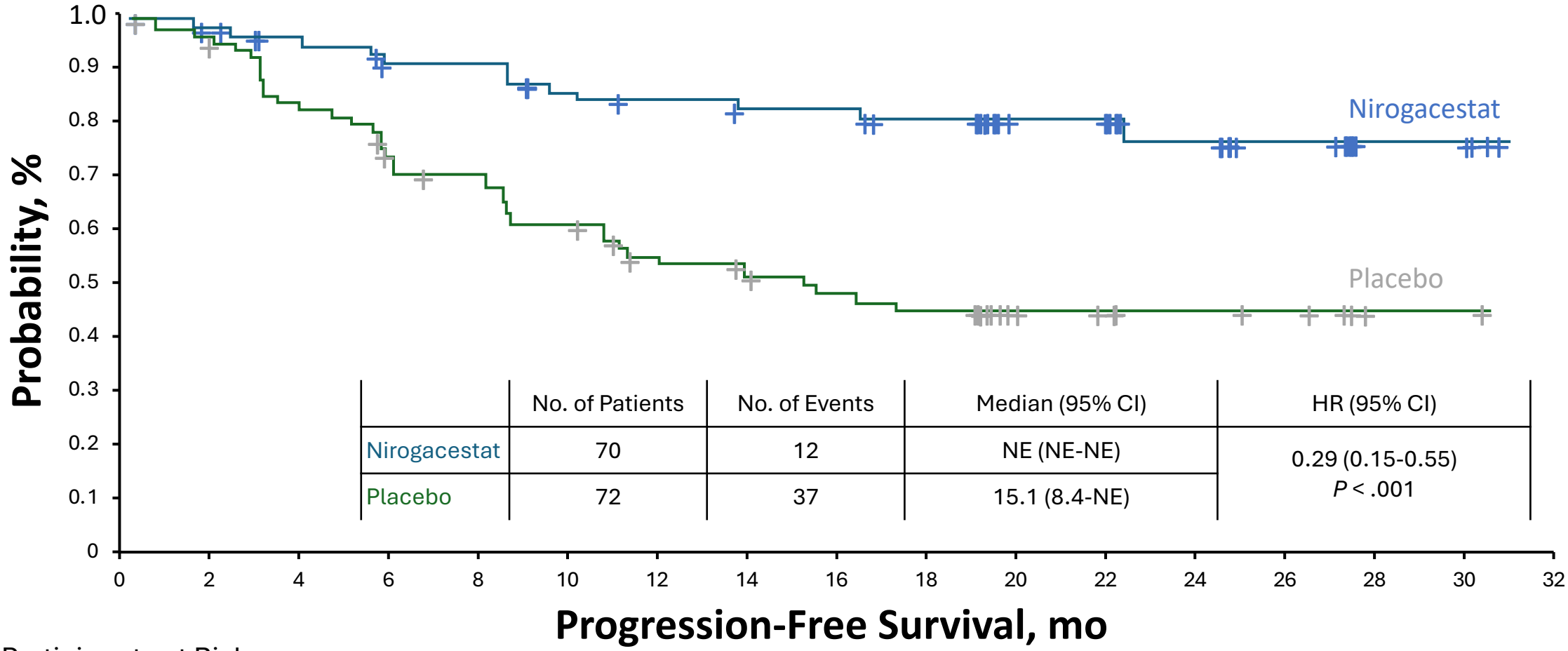
- Histologically confirmed DT with progressive disease per RECIST v1.1[a]
  - Treatment-naive with DT not amenable to surgery, *or*
  - Refractory or recurrent disease (after ≥1 line of therapy)



Primary Analysis Data Cutoff: April 7, 2022

- **Primary endpoint:** PFS[c]
- **Secondary endpoints:** ORR and PROs, including symptom burden, physical/role function, and overall QoL[d]

Nirogacestat Significantly Reduced the Risk of Disease Progression



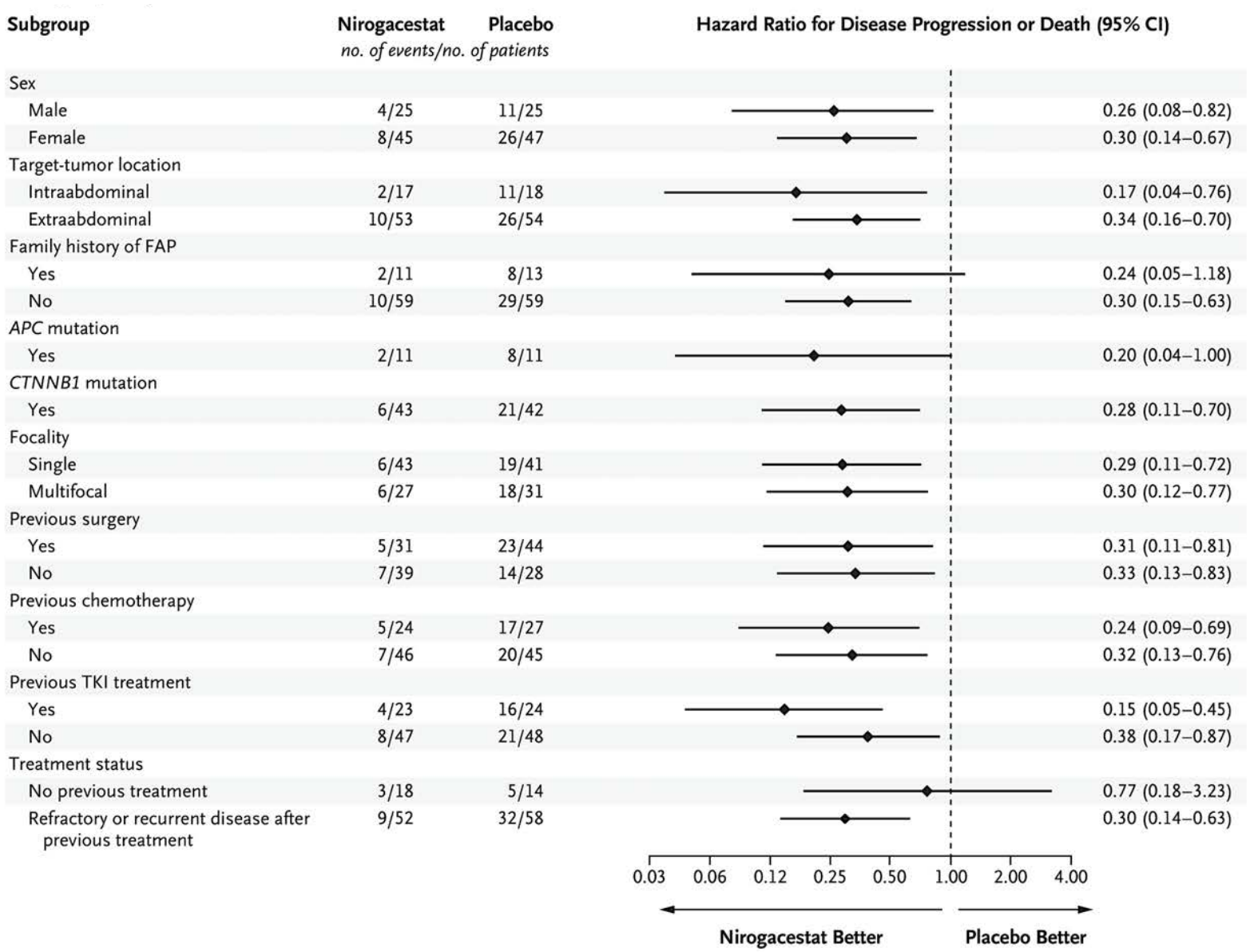
	No. of Patients	No. of Events	Median (95% CI)	HR (95% CI)
Nirogacestat	70	12	NE (NE-NE)	0.29 (0.15-0.55) *P* < .001
Placebo	72	37	15.1 (8.4-NE)	

No. of Participants at Risk

Nirogacestat	70	63	56	52	52	47	46	44	44	41	26	26	17	12	4	4	0
Placebo	72	67	58	47	45	40	32	29	27	25	10	8	6	5	1	1	0

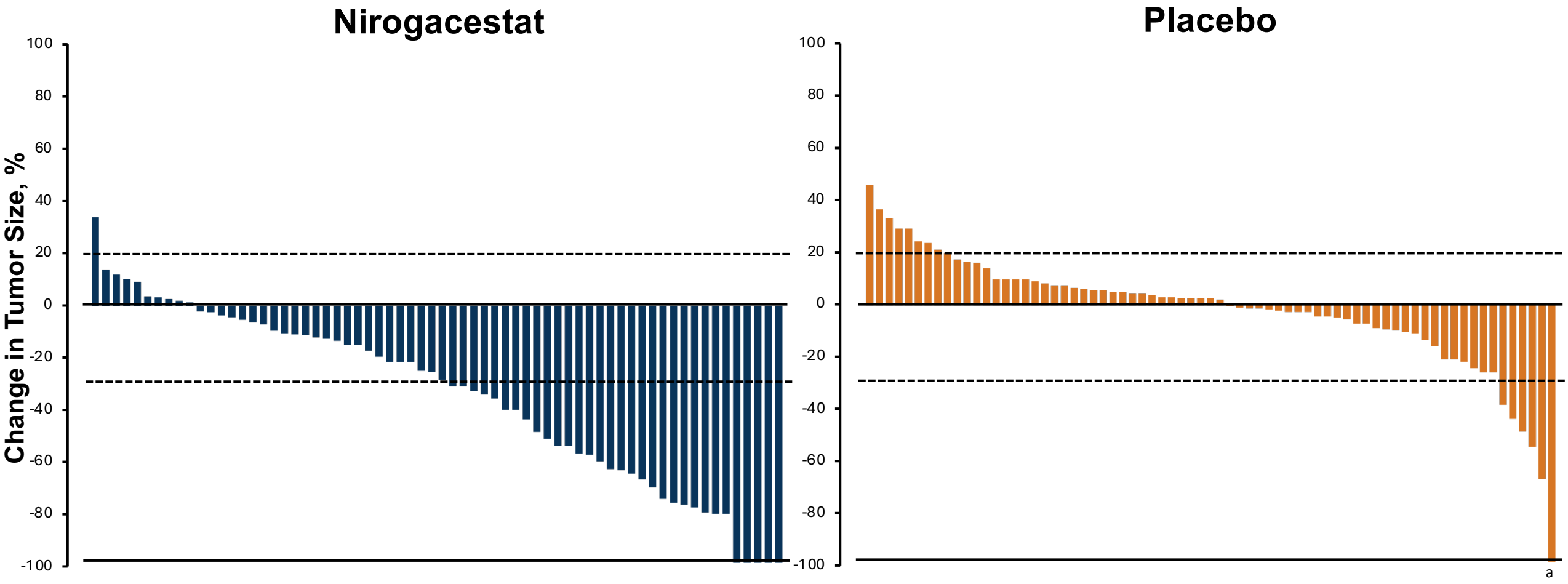
Gounder M et al. NEJM 2023

PFS Benefit With Nirogacestat Was Observed Across Pre-specified Subgroups



Gounder M et al. NEJM 2023

Nirogacestat Resulted in Substantial Reductions in Tumor Size



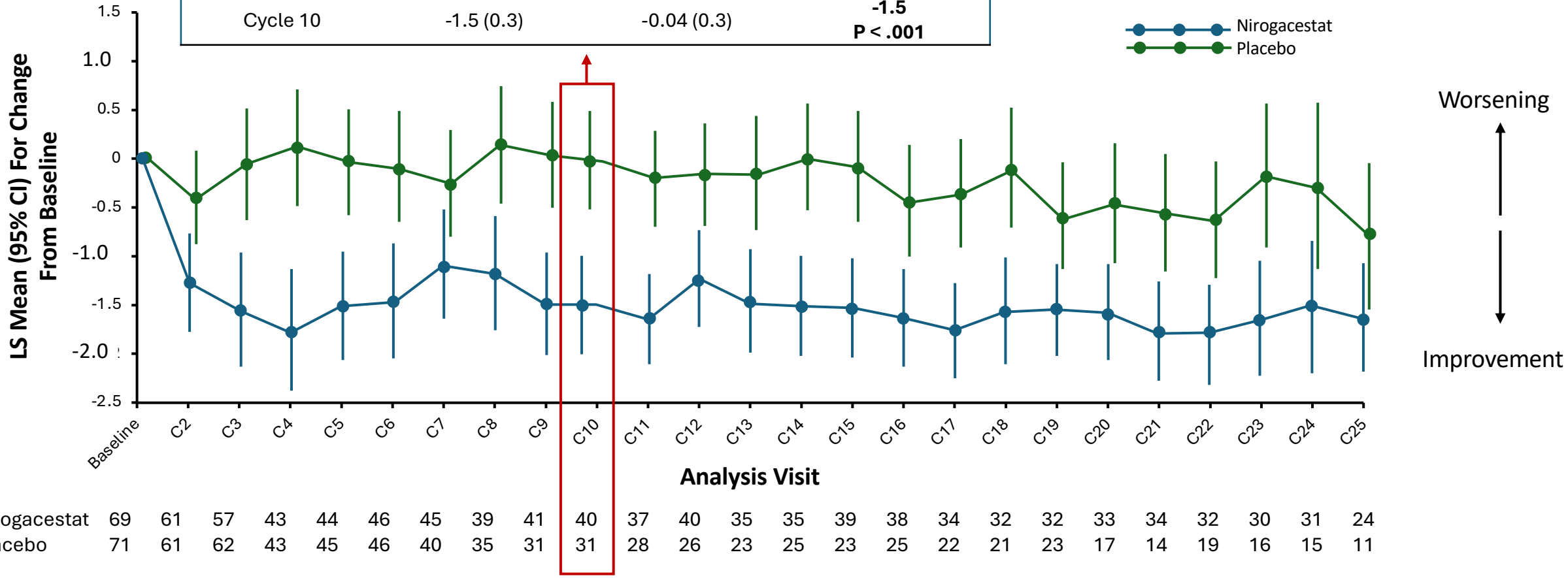
[a] Patient had a complete resolution of the target lesion but still had documented non-target lesion; therefore, not a complete response. Best percent change values are averaged between 2 blinded independent reviewers unless a reader was selected for adjudication, in which case only the adjudicated value is presented.

1. Kasper B et al. ESMO 2022. Abstract LBA2.

Nirogacestat Significantly Reduced Pain

Brief Pain Inventory Short Form: Worst Pain Intensity

LS Mean (SE)	Nirogacestat	Placebo	Difference
Cycle 10	-1.5 (0.3)	-0.04 (0.3)	**-1.5** **P < .001**



Nirogacestat	69	61	57	43	44	46	45	39	41	40	37	40	35	35	39	38	34	32	32	33	34	32	30	31	24
Placebo	71	61	62	43	45	46	40	35	31	31	28	26	23	25	23	25	22	21	23	17	14	19	16	15	11

Mean (SD) baseline scores: nirogacestat, 3.2 (3.26); placebo, 3.3 (3.31). Differences at cycle 10 were statistically significant and clinically meaningful. LS mean change from baseline represents the 7-day average of "worst pain in last 24 hours".

1. Kasper B et al. ESMO 2022. Abstract LBA2.

Nirogacestat Safety Profile

Safety Population, n (%)	Nirogacestat (n = 69)		Placebo (n = 72)	
Duration of study drug exposure, median (range), mo	20.6 (0.3-33.6)		11.4 (0.2-32.5)	
Dose intensity, median (range), mg/d	288.3 (169-300)		300.0 (239-300)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any TEAE	69 (100)	39 (57)	69 (96)	12 (17)
TEAEs of any grade reported in ≥25% of patients in either arm				
Diarrhea	58 (84)	11 (16)	25 (35)	1 (1)
Nausea	37 (54)	1 (1)	28 (39)	0
Fatigue	35 (51)	2 (3)	26 (36)	0
Hypophosphatemia	29 (42)	2 (3)	5 (7)	0
Rash, maculopapular	22 (32)	4 (6)	4 (6)	0
Headache	20 (29)	0	11 (15)	0
Stomatitis	20 (29)	3 (4)	3 (4)	0
TEAEs leading to death	0		1 (1)[a]	
Dose reductions due to TEAEs	29 (42)		0	
Discontinuations due to TEAEs	14 (20)[b]		1 (1)[b]	

- 95% of TEAEs were grade 1 or 2; the first onset of TEAEs in most patients occurred during cycle 1

[a]Death due to sepsis.

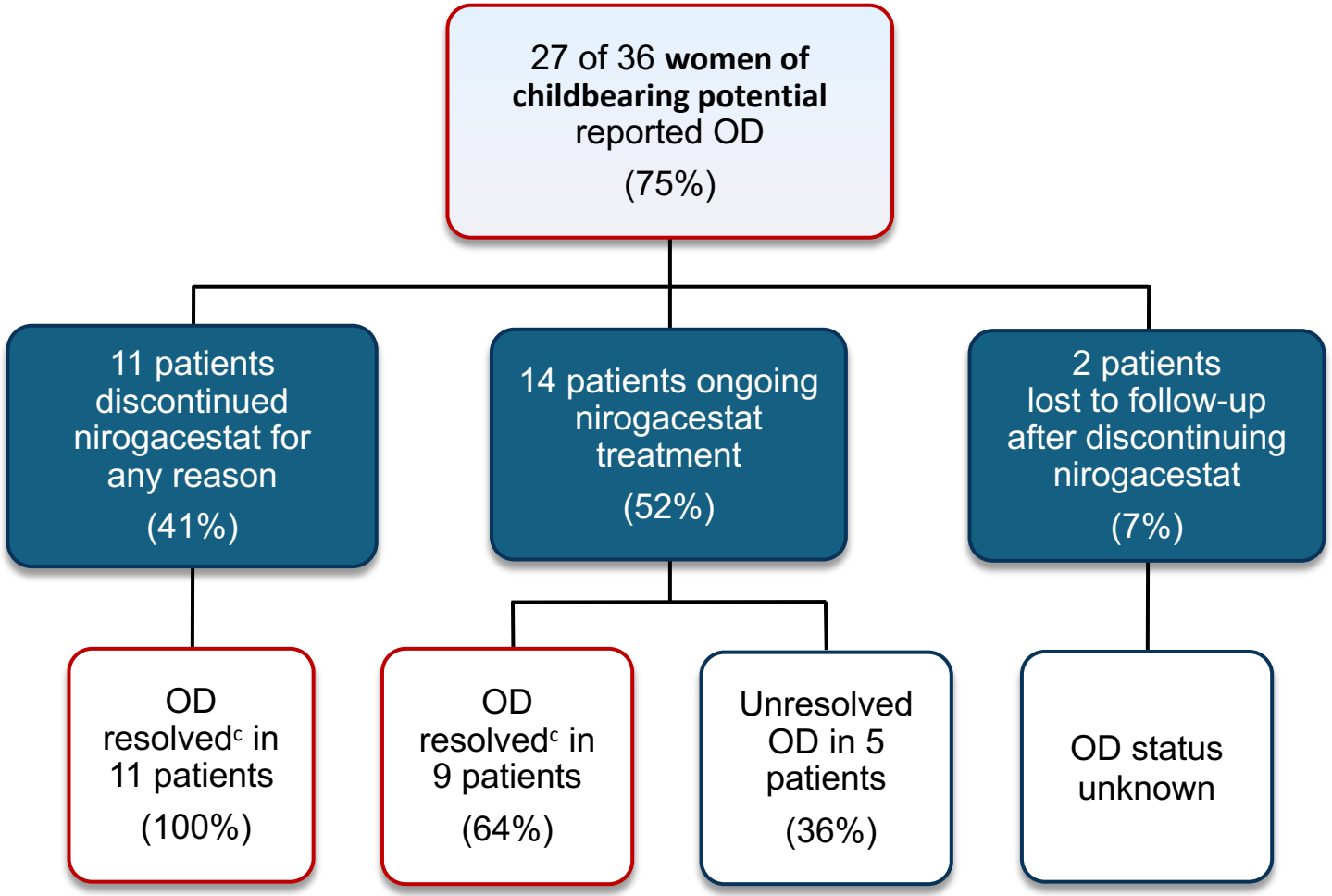
[b]TEAEs leading to discontinuations in ≥1 patient include gastrointestinal disorders (n=5 [4%]), ovarian dysfunction (n=4 [3%]), alanine aminotransferase increase (n=3 [2%]), aspartate aminotransferase increase (n=2 [1%]), and metabolism/nutritional disorders (n=2 [1%]).

TEAE, treatment-emergent adverse event

Kasper B et al. ESMO 2022. Abstract LBA2.

Frequency and Resolution of Ovarian Dysfunction Observed With Nirogacestat

- OD is a composite AE associated with changes in female reproductive hormone levels and clinical manifestations[2,3]
- Protocol-mandated serum hormone collection at baseline and cycles 1, 2, 4, and every 3 thereafter
- Among women of childbearing potential, OD was observed in 75% receiving nirogacestat and 0% receiving placebo
  - Median time to first onset of OD: 8.9 weeks
  - Median duration of OD events: 21.3 weeks

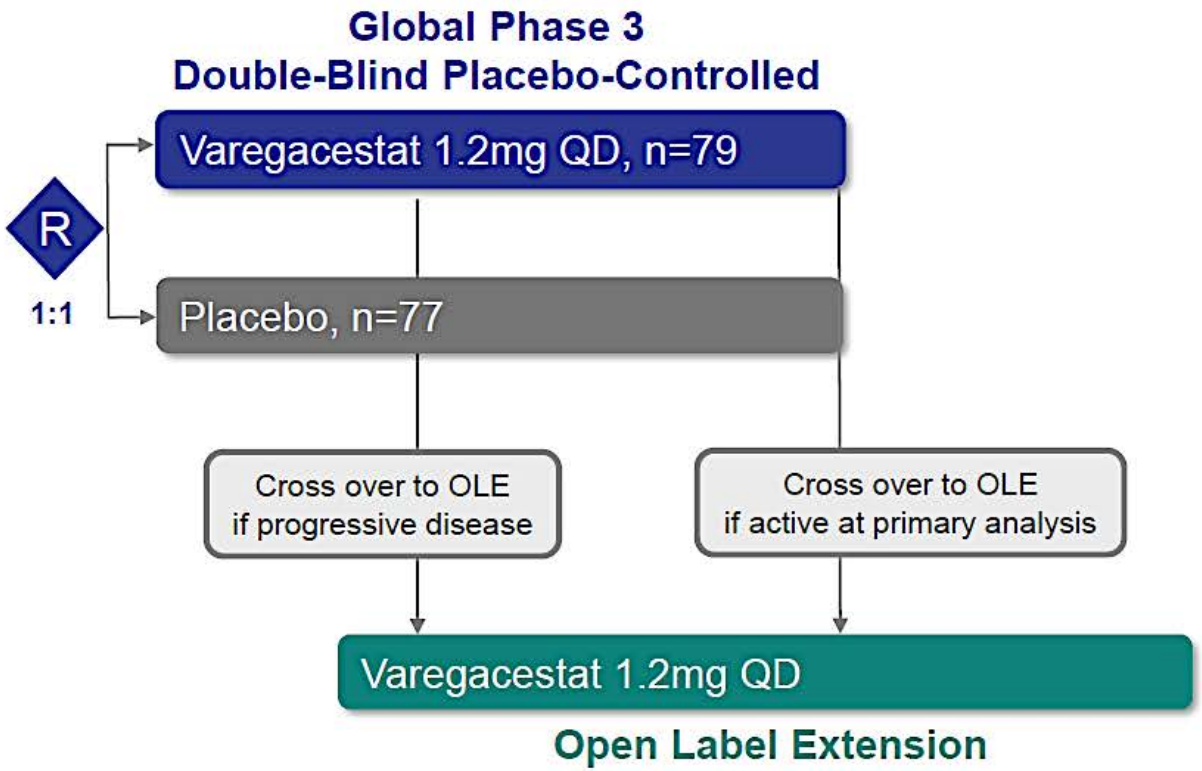


OD, ovarian dysfunction

1. Thurston et al. Obstet Gynecol Clin North Am. 2011;38:489-501.
2. Mauri et al. Front Endocrinol (Lausanne). 2020;11:572388.
3. Kasper B et al. ESMO 2022. Abstract LBA2.

RINGSIDE is the Largest Phase 3 Study in Desmoid Tumors

Design consistent with prior registrational trials



Key Inclusion Criteria

- Progressed within last 12 months[1]
- Treatment naïve or recurrent/refractory disease appropriate for systemic treatment

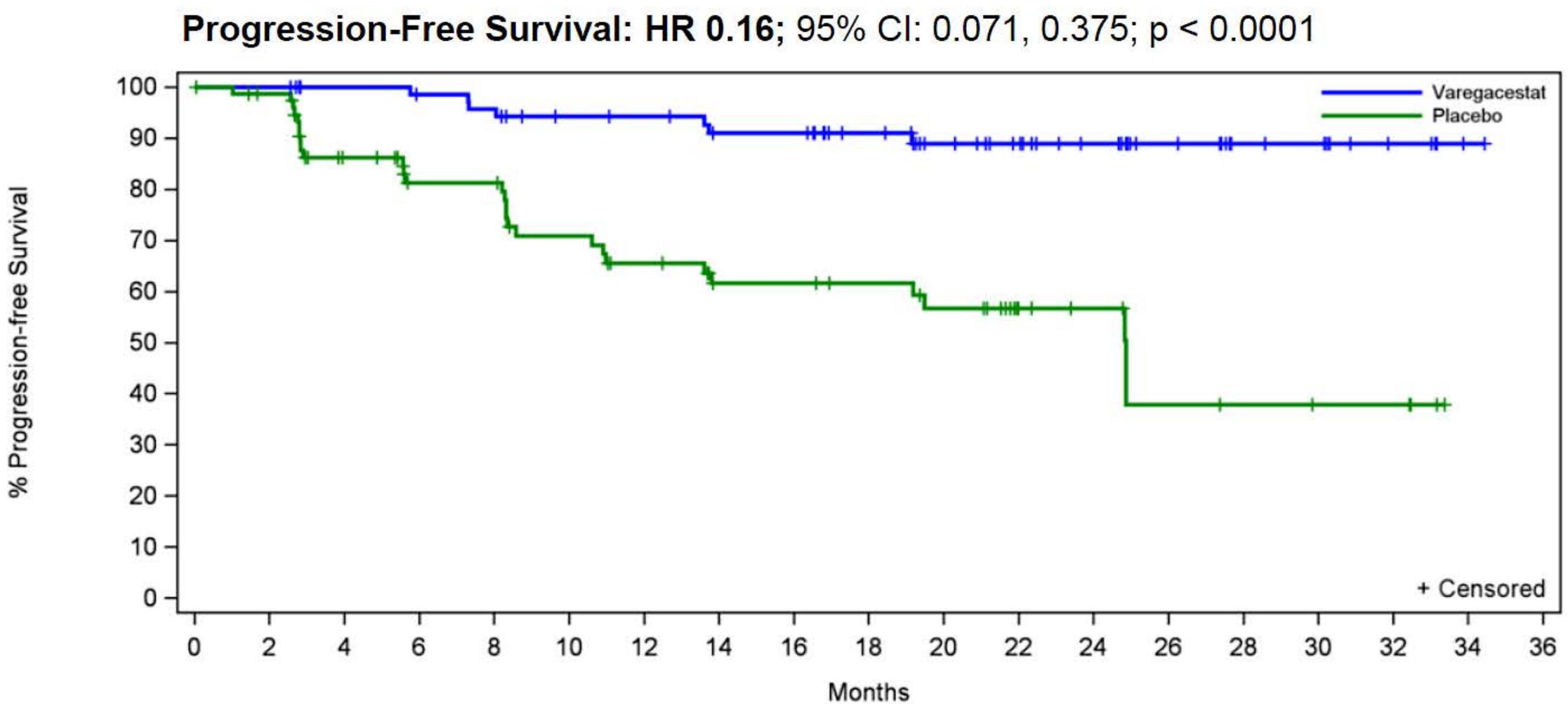
Key Endpoints

- **Primary: Progression-free survival[2] (PFS)**
- Alpha-controlled key secondary
  - **Objective Response Rate**
  - Tumor Volume[3] at Week 24
  - Worst Pain Intensity at Week 12[4]
- Safety and tolerability
- Additional efficacy assessments, including **median best percent change in Tumor Volume[3]**

(1) Progression was defined as ≥20% increase per RECIST v1.1
(2) PFS was defined as time from randomization until the date of assessment of radiographic progression as assessed Blinded Independent Central Review (BICR) based on RECIST v1.1
(3) Measured by T2 weighted MRI or CT per BICR
(4) Measured using Desmoid Tumor Symptom Scale Item 1 from the GOunder/Desmoid Tumor Research Foundation Desmoid Tumor Symptom/Impact Scale (GODDESS)

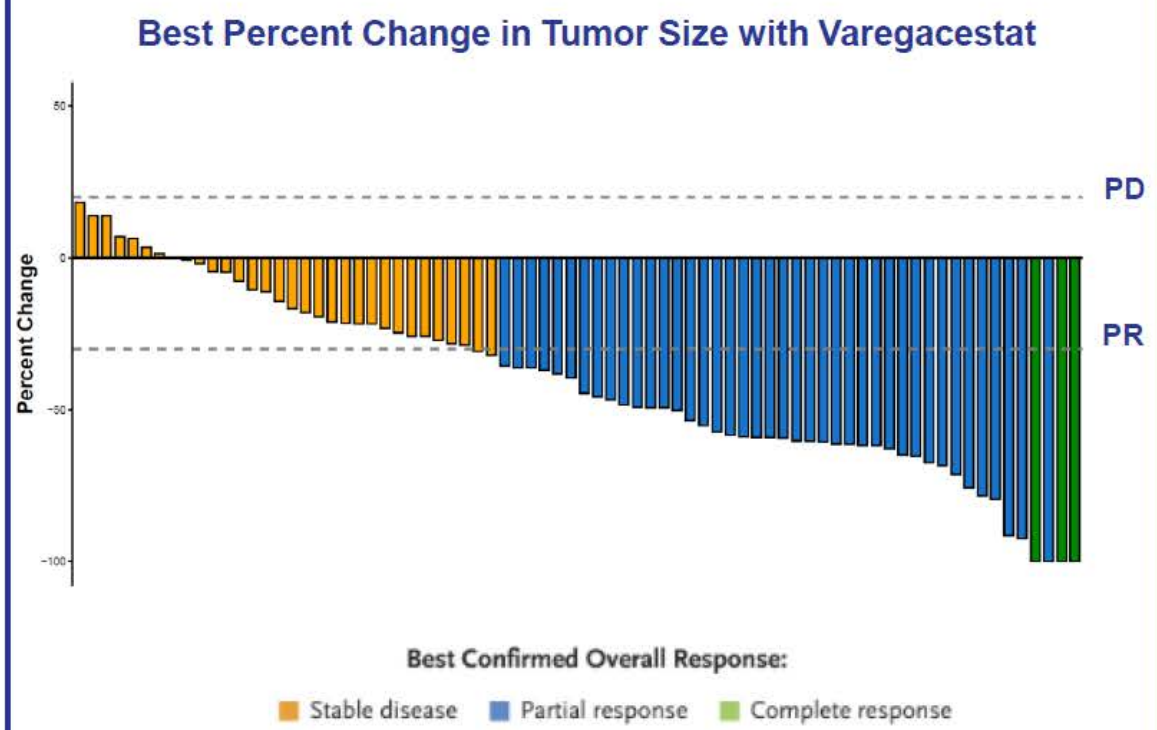
Varegacestat Achieved Primary Endpoint

84% Reduction in the Risk of Progression or Death vs Placebo

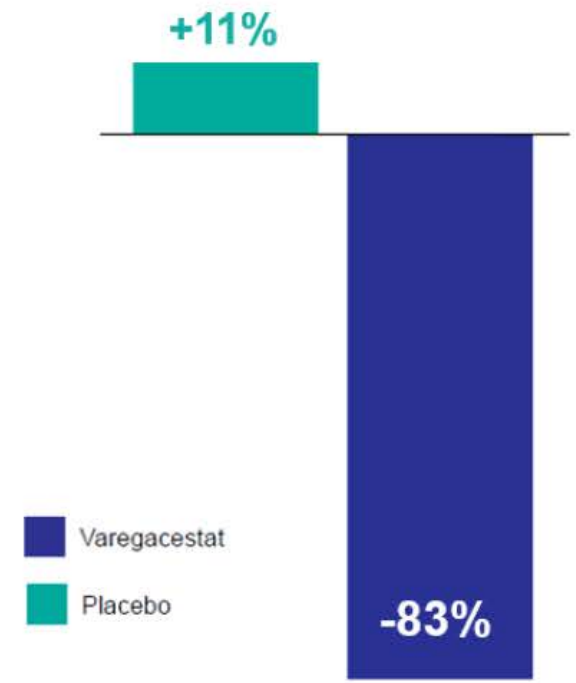


Varegacestat Demonstrates Robust Antitumor Activity

56% ORR With Varegacestat vs 9% With Placebo (p<0.0001)

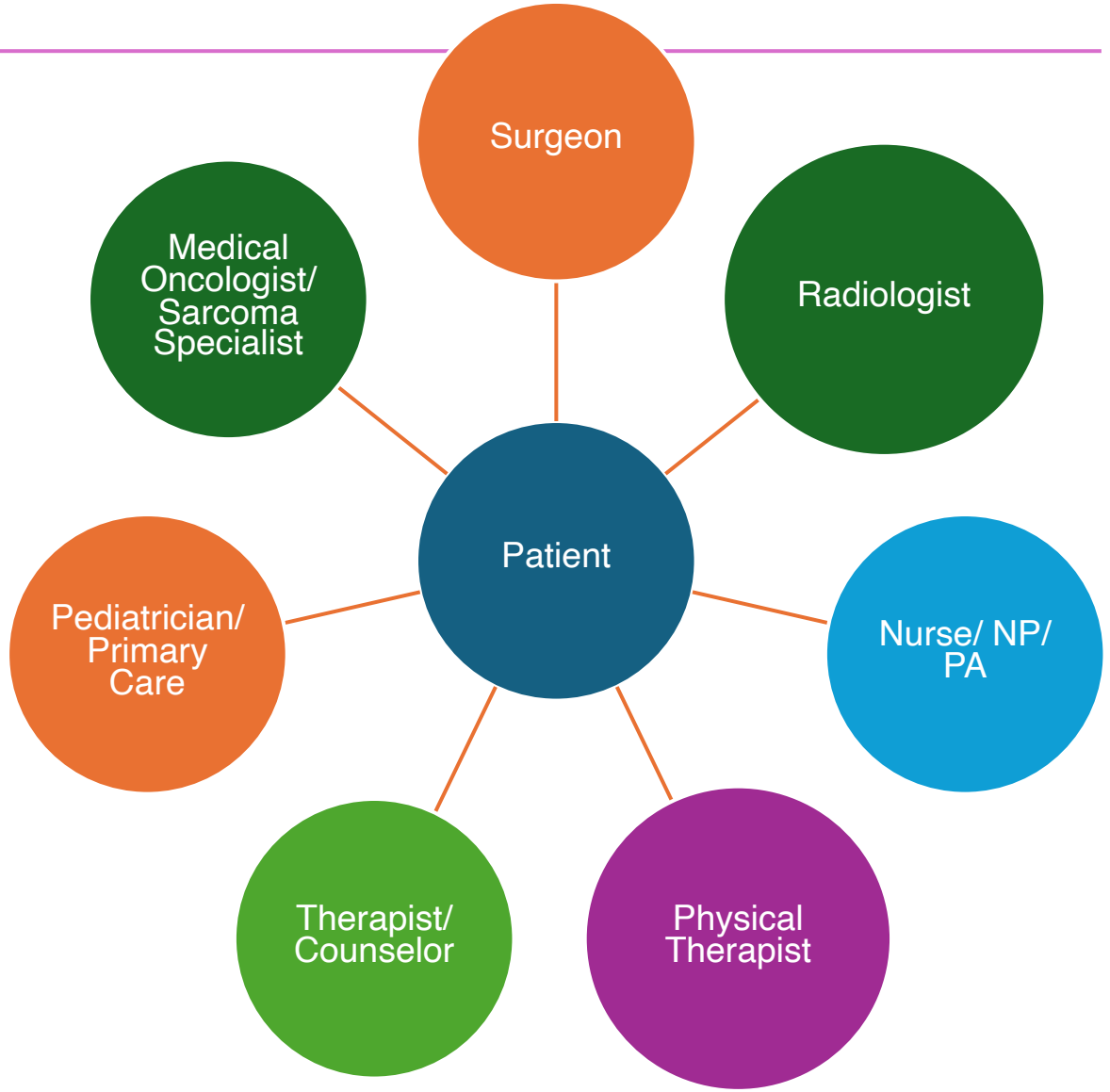


-83% Median Best Percent Change in Tumor Volume With Varegacestat vs +11% With Placebo



The Desmoid Tumor Multidisciplinary Team

- Multidisciplinary care is essential in desmoid tumors
- At various stages in their treatment journey, patient care may involve numerous specialties
- Allied health professionals such as physical therapists, massage therapists, and mental health specialists are particularly important for long-term patient well-being
- Because many patients with desmoid tumors are diagnosed as adolescents, it is important that pediatric providers ensure appropriate transfer of care to adult providers later in life



Desmoid Tumor Working Group. *Eur J Cancer*. 2020;127:96-107.

QUESTIONS?

Module 6: Desmoid Tumors and Soft Tissue Sarcoma

Desmoid Tumors — Dr Gounder

Soft Tissue Sarcoma — Dr Riedel

Soft Tissue Sarcoma (STS)

Fifth Annual National General Medical Oncology Summit

Richard F. Riedel, MD

Duke Cancer Institute

April 25, 2026

DukeHealth

Disclosures

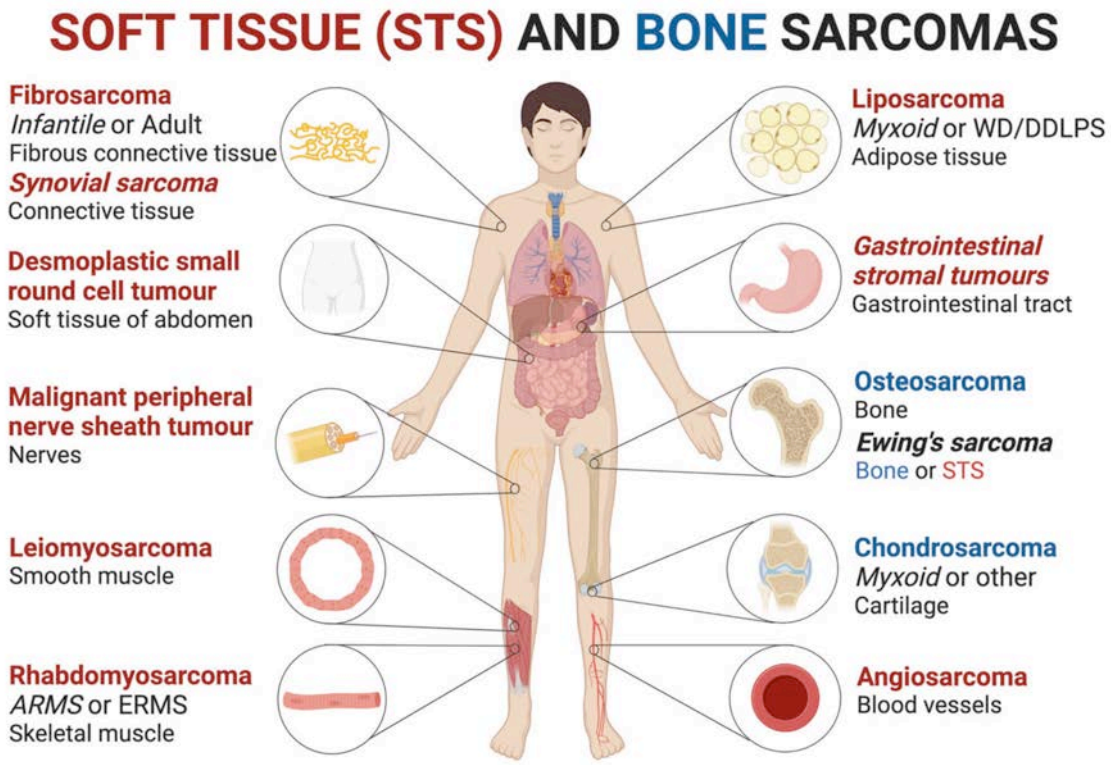
Advisory Committees and Consulting Agreements	Aadi Bioscience, Adaptimmune, Bayer HealthCare Pharmaceuticals, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Cogent Biosciences, Daiichi Sankyo Inc, Deciphera Pharmaceuticals Inc, EMD Serono Inc, GSK, Ipsen Biopharmaceuticals Inc, NANO MRNA, Recordati, Replimune, SpringWorks Therapeutics Inc
Contracted Research	Aadi Bioscience, Adaptimmune, Cogent Biosciences, Daiichi Sankyo Inc, Deciphera Pharmaceuticals Inc, GSK, Inhibrx, Intensity Therapeutics, Kura Oncology, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, TRACON Pharmaceuticals Inc
Nonrelevant Financial Relationships	SARC (Sarcoma Alliance for Research through Collaboration)

Objectives

- Review historical treatment paradigms for advanced soft tissue sarcoma (STS)
- Highlight efficacy and safety findings with *nab*-sirolimus in PEComa
- Introduce key data from trials involving cell-based therapies in STS
  - Afamitresgene autoleucel (afami-cel) and Letetresgene autoleucel (lete-cel)
- Summarize other novel agents in unique STS subtypes

Overview: Sarcomas

- Rare
  - ~15,000 cases/yr
  - 1% of cancer in adults
- Heterogeneous
  - >100 histologic subtypes
- Location
  - 50% Extremities
  - 40% Trunk
  - 10% Head and Neck
- Classification
  - 75% soft tissue
  - 25% bone



Sig Transduct Target Ther **6**, 246 (2021).

Limitations/Challenges

- Rare
- Histologic diversity
- Genetic diversity
- Prognosis remains for poor for patients with metastatic disease
- Suboptimal systemic therapy
  - Number of treatment options are limited
  - Effectiveness of available options is limited
  - Toxicity of our treatments needs to be considered

In my practice*…metastatic (non-GIST) STS

Pre-2012

- 1st line
  - Anthracycline-based
    - Single agent vs Combination
      - + Ifosfamide (Synovial sarcoma)
  - Paclitaxel (Angiosarcoma)
  - Gem/Doce (LMS)
- 2nd line
  - Gemcitabine-based
  - Doxorubicin (if not previously received)
  - Ifosfamide (good PS)
- 3rd line
  - Dacarbazine

Post-2012 through 2019

- 1st line
  - Anthracycline-based
    - Single agent vs. Combination
      - + Ifosfamide (Synovial sarcoma)
  - Paclitaxel (Angiosarcoma)
- 2nd line
  - Gemcitabine-based
  - **Trabectedin (Myxoid liposarcoma)**
- 3rd line
  - **Eribulin (Liposarcoma)**
  - **Trabectedin (LMS/Liposarcoma)**
  - **Pazopanib (non-Liposarcoma)**
- 4th line and later
  - Dacarbazine

* Clinical trial always preferred

Systemic Therapy: Recent Advances

- Histology-specific
  - Pexidartinib[1] in tenosynovial giant cell tumor (TGCT)
  - Ripretinib[2] in 4th line GIST
  - Avapritinib[2] in PDGFR exon 18 mutant positive GIST
  - Tazemetostat[2] in epithelioid sarcoma (withdrawn from market in 2026)
  - *nab*-sirolimus[3] in perivascular epithelioid cell tumor (PEComa)
  - Crizotinib[4] in ALK-positive inflammatory myofibroblastic tumor (IMT)
  - Atezolizumab[4] in alveolar soft part sarcoma (ASPS)
  - Nirogacestat[5] in desmoid tumors
  - Afamitresgene autoleucel (afami-cel)[6] in synovial sarcoma
  - Vimseltinib[7] in TGCT
  - Doxorubicin/Trabectedin in leiomyosarcoma (LMS)
  - Letetresgene autoleucel (lete-cel) in synovial sarcoma and myxoid round cell liposarcoma

1: FDA approved in 2019
2: FDA approved in 2020
3: FDA approved in 2021
4: FDA approved in 2022
5: FDA approved in 2023
6: FDA approved in 2024
7: FDA approved in 2025

Nab-Sirolimus in Malignant Perivascular Epithelioid Cell Tumor (PEComa)

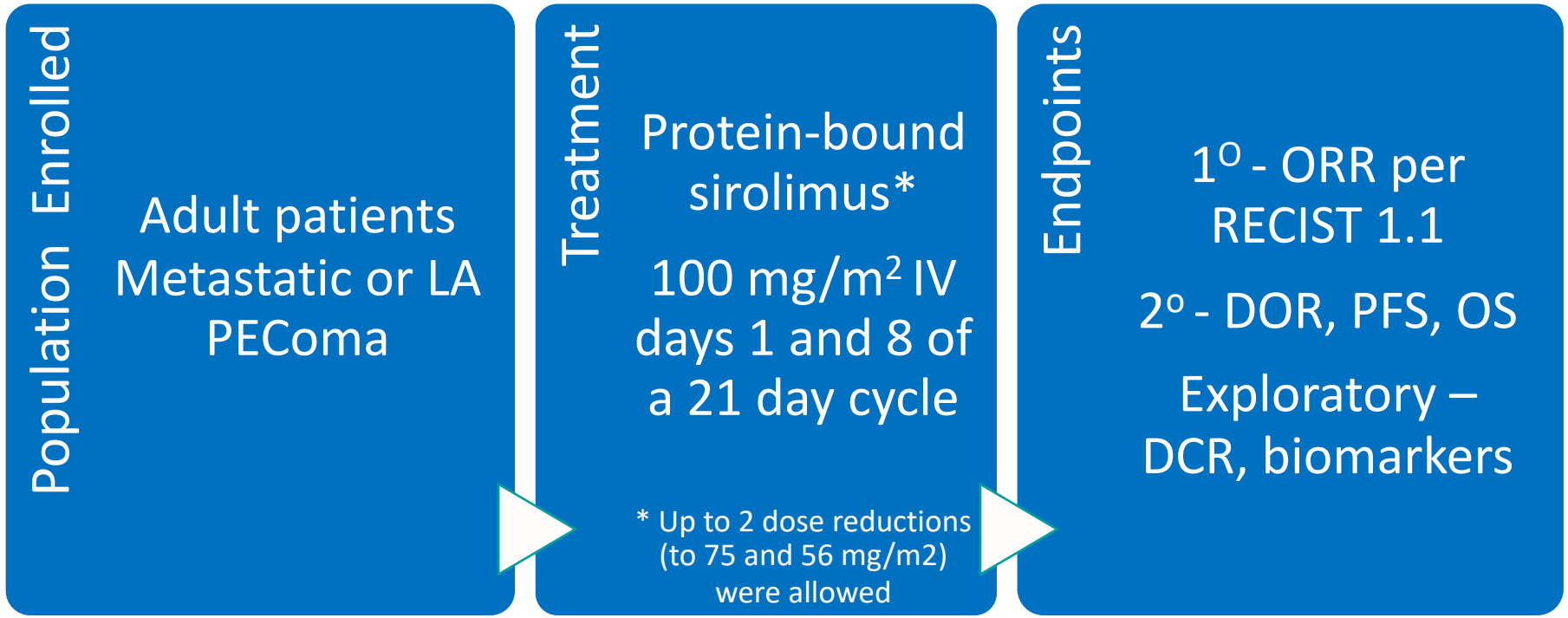
PEComa: Incidence and Presentation

- "Ultra-rare" mesenchymal family of neoplasms
  - Less than 500 cases/year in the U.S.
  - Less aggressive/Benign: Angiomyolipoma (AML), Clear cell sugar tumor of the lung, Lymphangioleiomyomatosis (LAM)
  - More aggressive/Malignant: Epithelioid AML, Malignant PEComa
- Female predominance
- Most common primary sites: kidney, uterus, liver, pancreas
- Prognosis is poor for patient with metastatic disease
- Review of pathology at a center with expertise is critical
  - Morphology is variable and IHC overlaps with other cancers
  - Loss of TSC1/TSC2 (majority) resulting in activation of the mTOR pathway, TFE3 fusion (small subset)

J Clin Oncol. 2010;28(5):835-40.
Pathologe. 2020; 41(Suppl 1): 9–19.
Clin Cancer Res. 2019 Sep 1;25(17):5295-5300.

AMPECT Study: Study Design

- Prospective
- Open-label
- Single arm
- Phase 2 study



LA: locally advanced; ORR: overall response rate; DOR: duration of response; PFS: progression free survival; OS: overall survival; DCR: disease control rate

J Clin Oncol. 2021 Nov 20;39(33):3660-3670.

AMPECT Study: Patient Characteristics

Variable	All Treated Patients (N = 34)
Age, years, median (range)	60 (27-78)
≥ 65 years, No. (%)	15 (44)
Female, No. (%)	28 (82)
Race, No. (%)	
White	24 (71)
Black	3 (9)
Asian	3 (9)
Pacific Islander or Hawaiian	1 (3)
Others or unknown	3 (9)
ECOG 0, No. (%)	26 (76)
ECOG 1, No. (%)	8 (24)
Metastatic, No. (%)	29 (85)
Locally advanced, inoperable, No. (%)	5 (15)
Prior systemic Rx for advanced PEComa,[a] No. (%)	4 (12)

[a] Includes docetaxel, doxorubicin, gemcitabine, ifosfamide, and olaratumab.

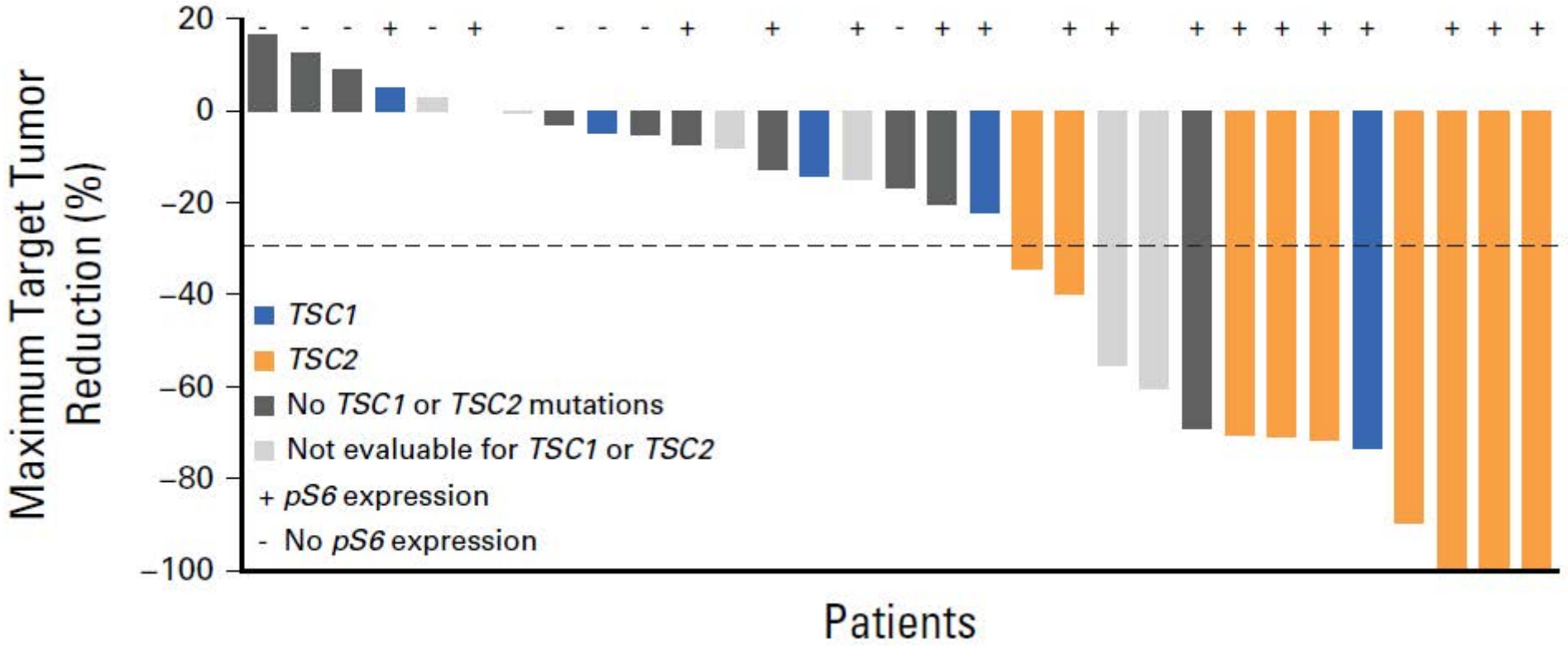
J Clin Oncol. 2021 Nov 20;39(33):3660-3670.

AMPECT Study: Outcomes

	Efficacy Outcome (n=31)
Overall Response Rate, n (%)	**12 (38.7)**
Complete Response (CR), n (%)	2 (6.5)
Partial Response (PR), n (%)	10 (32.3)
Stable Disease (SD), n (%)	16 (51.6)
Progressive Disease (PD), n (%)	3 (9.7)
Disease Control Rate, n (%)	**22 (71.0)**
Median PFS, months (95% CI)	**10.6 (5.5 to 41.2)**
Median OS, months (95% CI)	**53.1 (22.2 to Not reached)**

J Clin Oncol. 2021 Nov 20;39(33):3660-3670.
J Clin Oncol. 2024; 2024 May 1;42(13):1472-1476.

AMPECT Study: Waterfall Plot



J Clin Oncol. 2024; 2024 May 1;42(13):1472-1476.

AMPECT Study: Treatment-related AEs

TRAE	Any Grade ≥ 25%	Grade 3
Patients with any TRAEs, No. (%)	34 (100)	
Hematologic TRAEs		
Anemia[a]	16 (47)	4 (12)
Thrombocytopenia[a]	11 (32)	1 (3)
Nonhematologic TRAEs, No. (%)		
Mucositis[a]	27 (79)	6 (18)
Rash[a]	19 (56)	—
Fatigue	20 (59)	1 (3)
Nausea	16 (47)	—
Diarrhea	13 (38)	—
Weight decreased	13 (38)	—
Hyperglycemia[a]	12 (35)	3 (9)
Hypertriglyceridemia[a]	11 (32)	1 (3)
Hypercholesterolemia[a]	11 (32)	—
Decreased appetite	11 (32)	—
Dermatitis[a]	10 (29)	—
Dysgeusia	10 (29)	—
Headache	10 (29)	—
Peripheral edema	9 (26)	—

J Clin Oncol. 2021 Nov 20;39(33):3660-3670.

AMPECT Study: Summary

- AMPECT study confirmed utility of targeting mTOR pathway, with *nab*-sirolimus, in malignant PEComa
- *nab*-sirolimus has shown clear efficacy with a reasonable side effect profile and no new safety signals

FDA Approved in November 2021 for adult patients with locally-advanced or metastatic malignant PEComa

Cell-based Therapies in Select Sarcoma Subtypes

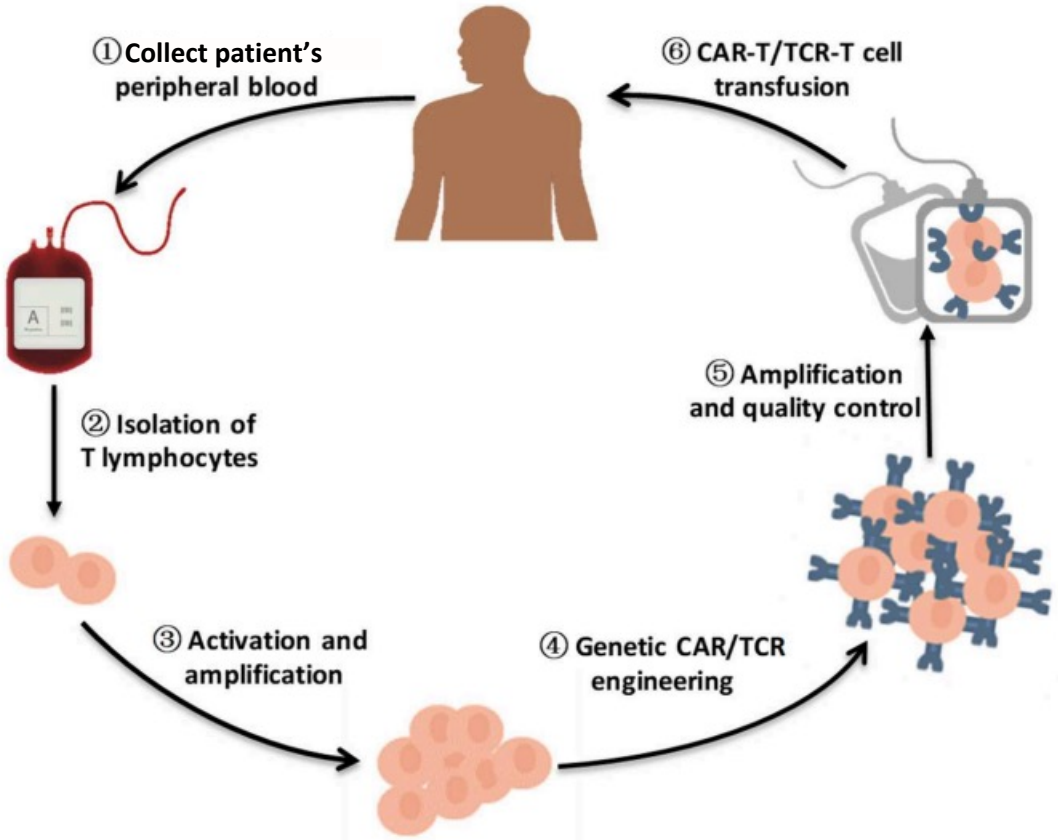
Overview: Synovial Sarcoma and MRCLS

- Rare (~5-10%) histologic subtypes of STS
  - ~800-1000 cases annually
- Translocation Associated Sarcomas
  - Synovial sarcoma - t(X;18), *SS18::SSX* fusion
  - MRCLS – t(12;16), *FUS::DDIT3* fusion
- Majority express tumor associated antigens
  - MAGE-A4
  - NY-ESO

MRCLS: Myxoid/Round Cell Liposarcoma
STS: soft tissue sarcomas

Stat Pearls – Synovial Cell Sarcoma.
https://www.ncbi.nlm.nih.gov/books/NBK587366/
Stat Pearls – Liposarcoma.
https://www.ncbi.nlm.nih.gov/books/NBK538265/

Engineered T-Cell Receptor Cellular Products



Front Immunol. 10:2250.

SPEARHEAD-1 Trial

Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial

Sandra P D'Angelo, Dejka M Araujo, Albiruni R Abdul Razak, Mark Agulnik, Steven Attia, Jean-Yves Blay, Irene Carrasco Garcia, John A Charlson, Edwin Choy, George D Demetri, Mihaela Druta, Edouard Forcade, Kristen N Ganjoo, John Glod, Vicki L Keedy, Axel Le Cesne, David A Liebner, Victor Moreno, Seth M Pollack, Scott M Schuetze, Gary K Schwartz, Sandra J Strauss, William D Tap, Fiona Thistlethwaite, Claudia Maria Valverde Morales, Michael J Wagner, Breelyn A Wilky, Cheryl McAlpine, Laura Hudson, Jean-Marc Navenot, Tianjiao Wang, Jane Bai, Stavros Rafail, Ruoxi Wang, Amy Sun, Lilliam Fernandes, Erin Van Winkle, Erica Elefant, Colin Lunt, Elliot Norry, Dennis Williams, Swethajit Biswas, Brian A Van Tine

Lancet 2024; 403: 1460–71

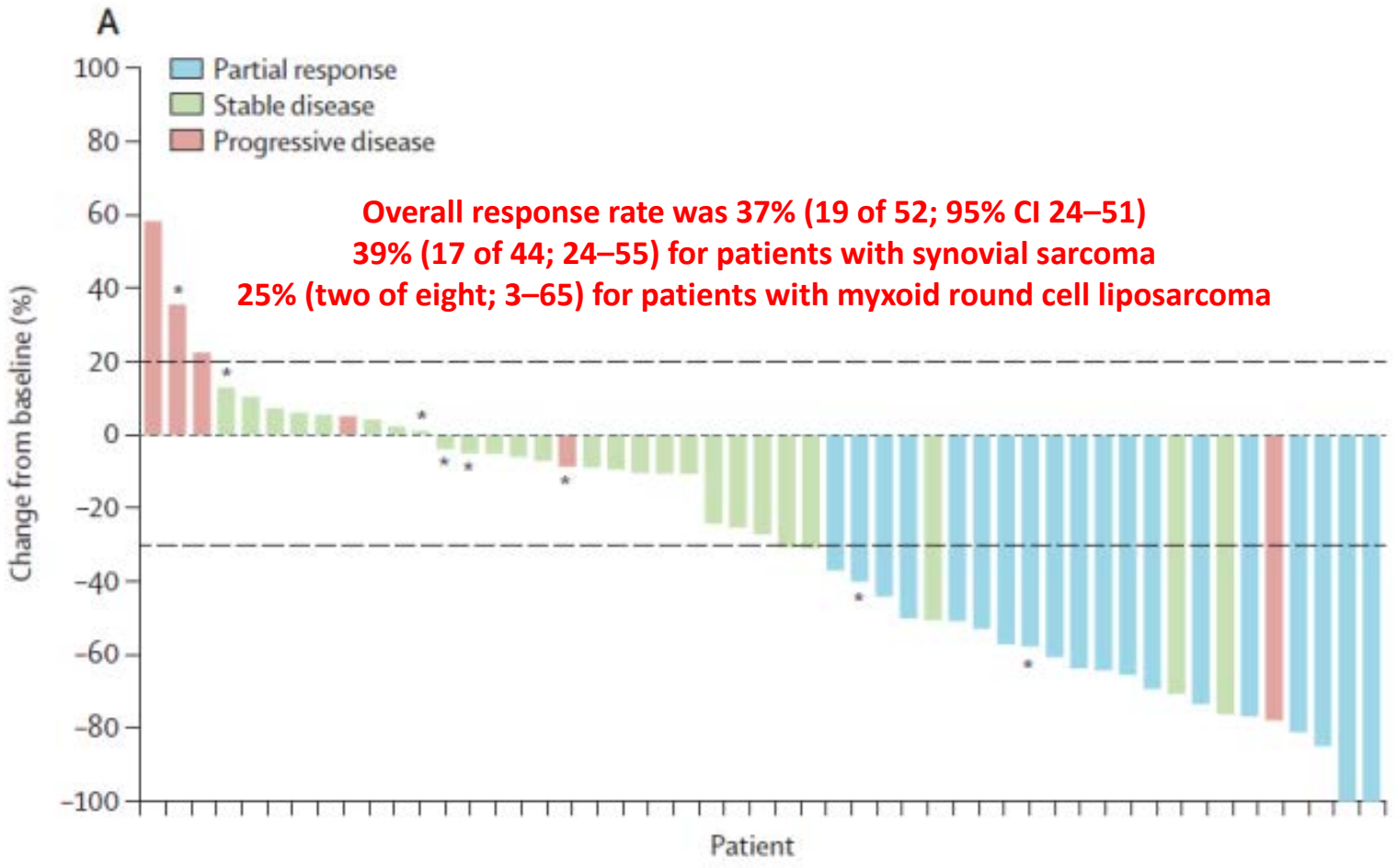
SPEARHEAD-1 Trial: Patient Characteristics*

	Synovial Sarcoma Patients (n=44)
Age, years	40.5 (31.0-46.0)
Male:Female	22 (50%) : 22(50%)
ECOG PS 0-1	43 (97%)
Race Asian Black of African American White	 3 (7%) 2 (5%) 39 (86%)
Prior systemic therapy 1 2 3 ≥4	 7 (16%) 14 (32%) 9 (20%) 14 (32%)

* 52 patients enrolled in total (44 with synovial sarcoma; 8 with myxoid round cell liposarcoma)

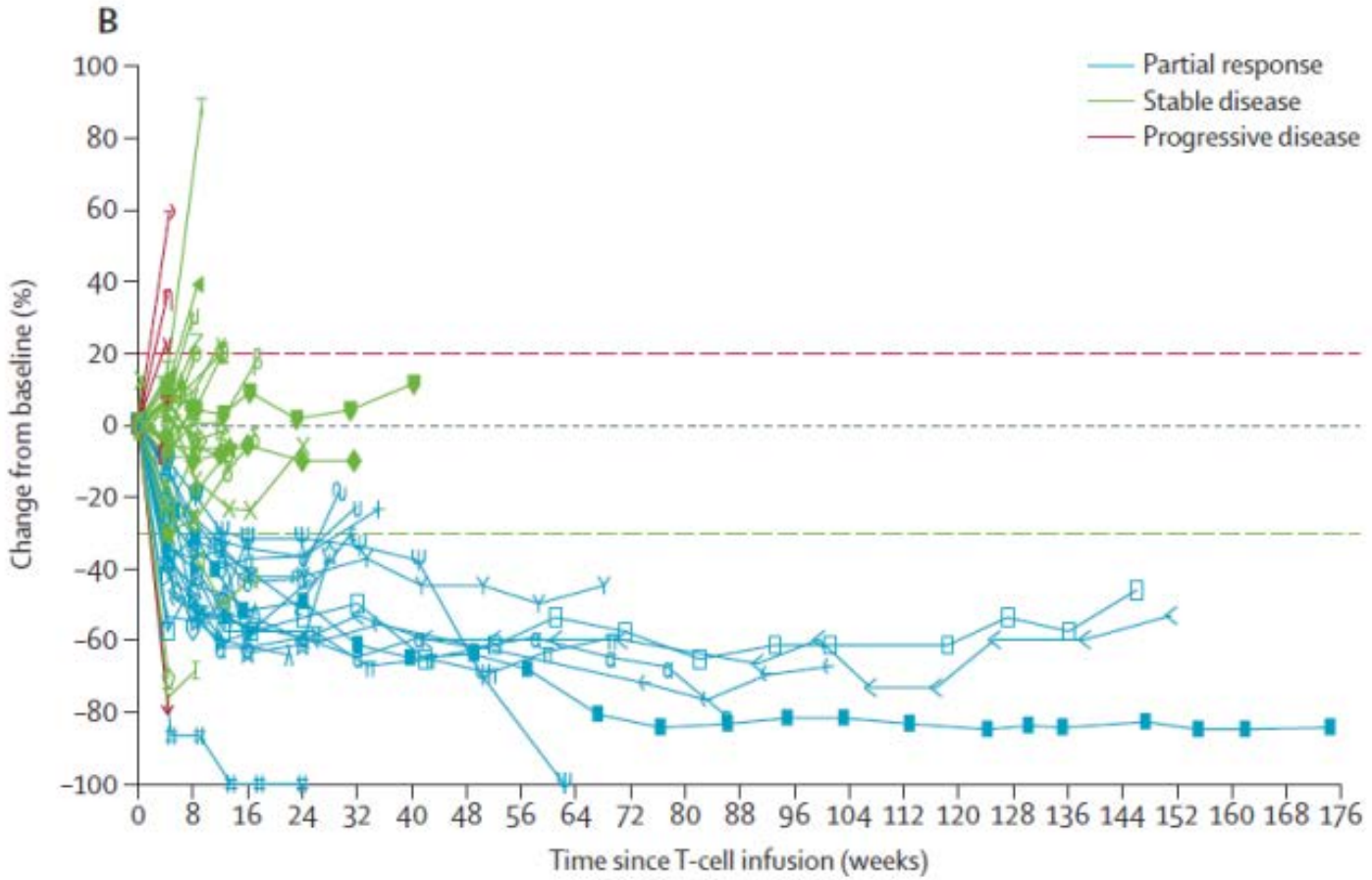
Lancet 2024; 403: 1460–71

SPEARHEAD-1 Trial: Waterfall Plot



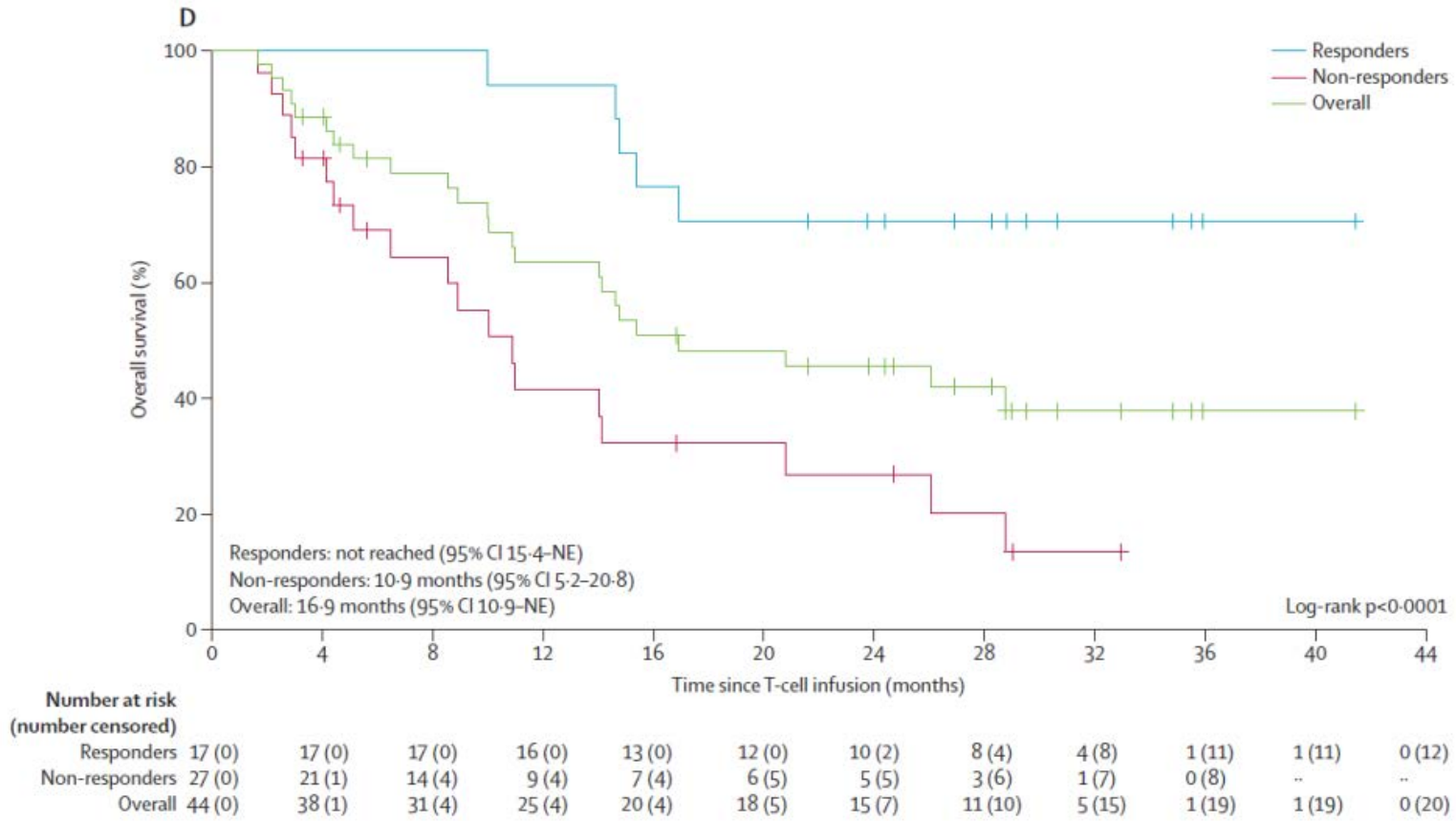
Lancet 2024; 403: 1460–71

SPEARHEAD-1 Trial: Spider Plot



Lancet 2024; 403: 1460–71

SPEARHEAD-1 Trial: Overall Survival



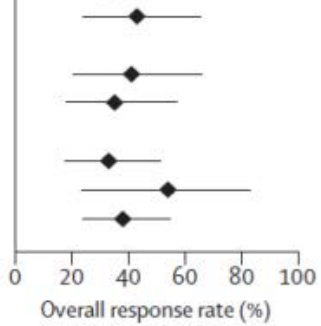
Number at risk (number censored)											
Responders	17 (0)	17 (0)	17 (0)	16 (0)	13 (0)	12 (0)	10 (2)	8 (4)	4 (8)	1 (11)	1 (11)	0 (12)
Non-responders	27 (0)	21 (1)	14 (4)	9 (4)	7 (4)	6 (5)	5 (5)	3 (6)	1 (7)	0 (8)	..	..
Overall	44 (0)	38 (1)	31 (4)	25 (4)	20 (4)	18 (5)	15 (7)	11 (10)	5 (15)	1 (19)	1 (19)	0 (20)

Lancet 2024; 403: 1460–71

SPEARHEAD-1 Trial: Subgroup Analyses

C

	Events/patients	Overall response rate (95% CI)
Bridging therapy		
Yes	4/16	25% (7–52)
No	13/28	46% (28–66)
Baseline sum of longest diameters of target lesions, mm		
≥100	5/21	24% (8–47)
<100	12/22	55% (32–76)
MAGE-A4 expression H score		
<200	4/13	31% (9–61)
≥200	13/31	42% (25–61)
Sex		
Male	6/22	27% (11–50)
Female	11/22	50% (28–72)
Age, years		
<40	7/21	33% (15–57)
≥40	10/23	44% (23–66)
Previous lines of systemic therapy		
≤2	7/21	33% (15–57)
≥3	10/23	44% (23–66)
Dose of transduced T cells administered, $\times 10^9$		
<7	8/19	42% (20–67)
≥7	9/25	36% (18–57)
Any-grade cytokine release syndrome		
Occurred	11/33	33% (18–52)
Did not occur	6/11	55% (23–83)
Overall	**17/44**	**39% (24–55)**



Lancet 2024; 403: 1460–71

SPEARHEAD-1 Trial: Adverse Events (>10%)*

	Grade 1-2	Grade 3	Grade 4	Overall
Cytokine release syndrome	36 (69%)	1 (2%)	0	37 (71%)
Leukopenia	1 (2%)	8 (15%)	5 (10%)	14 (27%)
Pyrexia	10 (19%)	1 (2%)	1 (2%)	12 (23%)
Lymphopenia	0	3 (6%)	6 (12%)	9 (17%)
Nausea	6 (12%)	0	0	6 (12%)
Fatigue	6 (12%)	0	0	6 (12%)
Thrombocytopenia	3 (6%)	1 (2%)	2 (4%)	6 (12%)

* n=52; AEs related to T-cell infusion; No treatment-related deaths

Lancet 2024; 403: 1460–71

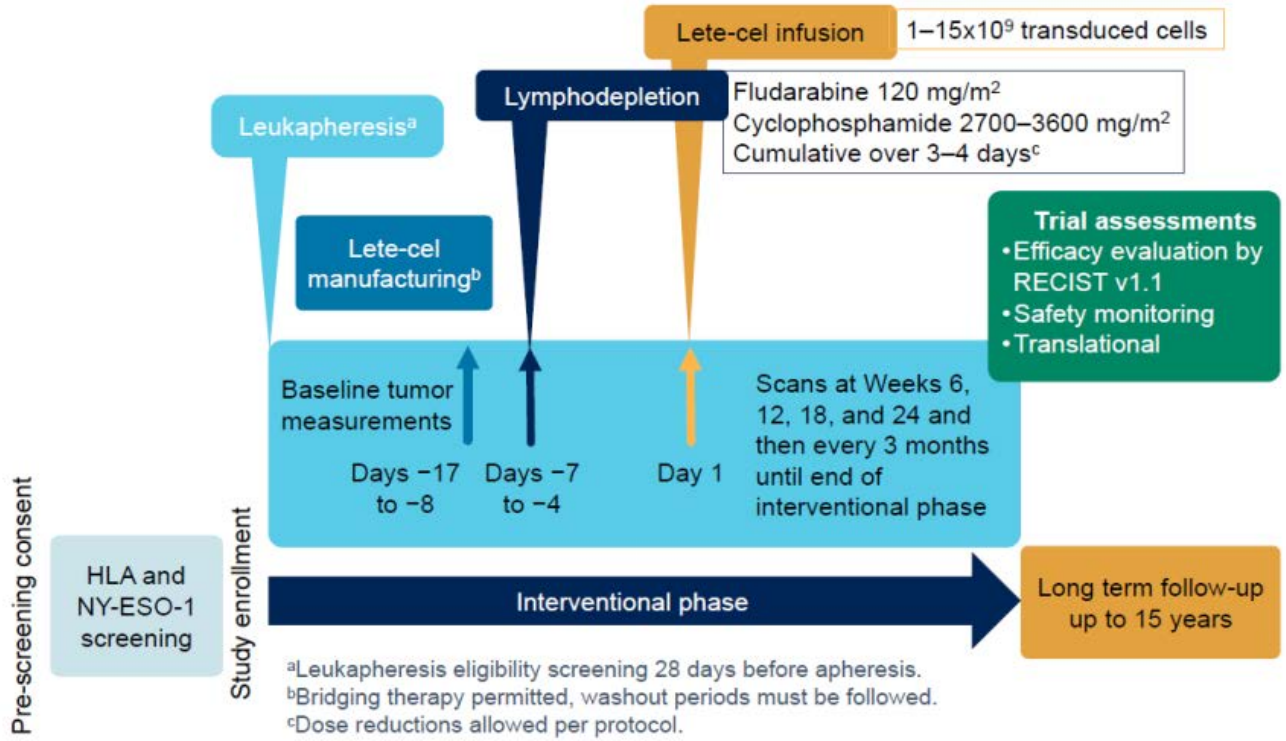
SPEARHEAD-1 Trial: Conclusions

- Engineered TCR strategies targeting MAGE-A4 are feasible and have efficacy
  - *HLA-A*02*$^{+}$-positive patients
- ORR 39% in pretreated synovial sarcoma
- Responses were durable
- Side effect profile is consistent with other cell-based approaches
  - Cytokine release syndrome and cytopenias

FDA granted accelerated approval August 2024

IGNYTE-ESO Trial: Study Schema

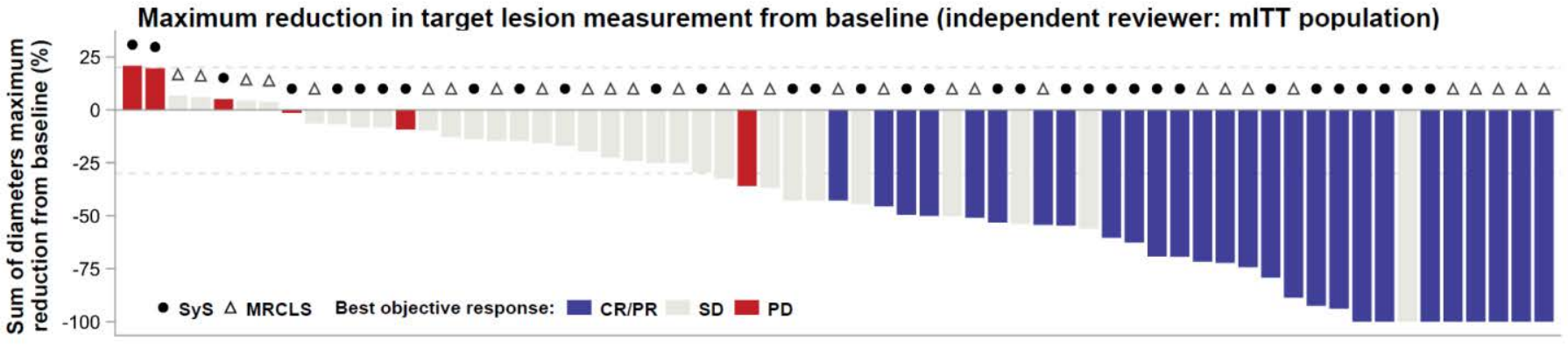
- Letetresgene autoleucel (Lete-cel)
  - TCR recognizing NY-ESO-1 presented by select *HLA-A*02* types
- Open-label, phase 2 study
  - 64 patients in Efficacy Population
    - 34 (53%) with synovial sarcoma, 30 (47%) with MRCLS
    - 63 (98%) with metastatic disease
    - 38 (60%) had 2 or more lines of systemic therapy
  - Primary endpoint: ORR per RECIST



Presented at CTOS 2024 Annual Meeting by Dr. Sandra D'Angelo

IGNYTE-ESO Trial: Waterfall Plot

ORR at Primary Analysis: 42%



Best overall response, n (%)	Overall (N=64)	SyS (n=34)	MRCLS (n=30)
CR	6 (9)	3 (9)	3 (10)
PR	21 (33)	11 (32)	10 (33)
SD	30 (47)	14 (41)	16 (53)
PD	6 (9)	5 (15)	1 (3)
NE	1 (2)	1 (3)	0
ORR [95% CI]	27 (42) [29.9–55.2]	14 (41) [24.6–59.3]	13 (43) [25.5–62.6]

Patient(s) who had a best objective response of NE are not shown in the figure. Data displayed are restricted to patients receiving lete-cel intended commercial supply. Independent reviewer–assessed overall response rate and best response with confirmation (RECIST 1.1 criteria).

Presented at CTOS 2024 Annual Meeting by Dr. Sandra D'Angelo

IGNYTE-ESO Trial: Adverse Events

Lymphodepletion-related AEs in >15% of patients, N=66

Adverse event, n (%)	Any grade	Grade ≥3
Any event	65 (98)	59 (89)
Neutropenia	48 (73)	48 (73)
Thrombocytopenia	42 (64)	32 (48)
Anemia	41 (62)	29 (44)
Leukopenia	32 (48)	31 (47)
Febrile neutropenia	19 (29)	18 (27)
Fatigue	14 (21)	0
Alopecia	13 (20)	0
Diarrhea	13 (20)	0
Decreased appetite	12 (18)	2 (3)
Nausea	12 (18)	0
Aspartate aminotransferase increased	11 (17)	6 (9)
Hypophosphatemia	11 (17)	2 (3)

T cell–related AEs in ≥15% of patients, N=66

Adverse event, n (%)	Any grade	Grade ≥3
Any event	64 (97)	56 (85)
Cytokine release syndrome	61 (92)	8 (12)
Rash (and associated terms)	42 (64)	23 (35)
Neutropenia	30 (45)	28 (42)
Anemia	26 (39)	22 (33)
Thrombocytopenia	23 (35)	20 (30)
Alanine aminotransferase increased	21 (32)	11 (17)
Pyrexia	20 (30)	2 (3)
Aspartate aminotransferase increased	19 (29)	6 (9)
Diarrhea	16 (24)	0
Leukopenia	16 (24)	15 (23)
Nausea	16 (24)	0
Hypophosphatemia	13 (20)	0
Febrile neutropenia	12 (18)	11 (17)
Pruritus	12 (18)	0
Dyspnea	11 (17)	3 (5)
Headache	10 (15)	0

Presented at CTOS 2024 Annual Meeting by Dr. Sandra D'Angelo

IGNYTE-ESO Trial: Conclusions

- Engineered TCR strategies targeting NY-ESO are feasible and have efficacy
  - *HLA-A*02*$^{+}$-positive patients
- ORR 41% in pretreated synovial sarcoma and 43% in MRCLS
- Responses were durable
- Side effect profile is consistent with other cell-based approaches
  - Cytokine release syndrome and cytopenias

To be submitted for FDA consideration

Other Novel Agents and Approaches

- Atezolizumab for Advanced Alveolar Soft Part Sarcoma – *N Eng J Med* 2023
  - ORR 37% (1 CR, 18 PR) in a single-group, phase 2 study
  - FDA approval

- Doxorubicin-Trabectedin with Trabectedin Maintenance in Leiomyosarcoma – *N Eng J Med* 2024
  - Improved PFS and OS compared to doxorubicin alone

- Study of INBRX-109 in Conventional Chondrosarcoma (ChonDRAgon) – Presented at CTOS Nov 2025
  - Improved PFS when compared to placebo

- PEAK Study: Bezuclastinib in combination with sunitinib in GIST – Positive Study/Presentation TBD
  - Improved PFS and ORR when compared to sunitinib (Per Press Release)

Other Novel Agents and Approaches

- EA7222: A Randomized Phase III Trial of Doxorubicin + Pembrolizumab Versus Doxorubicin Alone for the Treatment of Undifferentiated Pleomorphic Sarcoma (UPS) and Related Poorly Differentiated Sarcomas – Accrual ongoing

- Ivosidenib in Participants With Locally Advanced or Metastatic Conventional Chondrosarcoma Untreated or Previously Treated With 1 Systemic Treatment Regimen (CHONQUER) – Accrual ongoing

- A Study to Investigate Efficacy & Safety of Intratumoral INT230-6 Compared to US Standard of Care in Adults with Soft Tissue Sarcomas (INVINCIBLE-3) – Accrual ongoing

- Study of ADI-PEG 20 or Placebo Plus Gemcitabine and Docetaxel in Previously Treated Subjects with Leiomyosarcoma (ARGSARC) – Accrual ongoing

Conclusion

- The treatment landscape for STS is rapidly evolving
  - Histology-specific and/or molecular defined treatment approaches
- Advances, including FDA approvals, are being made in rare histologic subtypes
  - *nab*-sirolimus in PEComa
  - Atezolizumab in alveolar soft part sarcoma (ASPS)
- Cellular based approaches are feasible and efficacious
  - Afamitresgene autoleucel in synovial sarcoma - FDA approved
  - Letetresgene autoleucel in synovial sarcoma and MRCLS
- The future is bright!!!

QUESTIONS?

Module 7: Urothelial Bladder Cancer

Role of Immunotherapeutic Strategies in the Management of Nonmetastatic UBC; Emerging Utility of Circulating Tumor DNA (ctDNA) Evaluation — Dr Friedlander

Other Novel Agents and Strategies for Nonmetastatic and Metastatic UBC — Dr Petrylak

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Research To Practice
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Lecanto, Florida

Module 7: Urothelial Bladder Cancer

Role of Immunotherapeutic Strategies in the Management of Nonmetastatic UBC; Emerging Utility of Circulating Tumor DNA (ctDNA) Evaluation — Dr Friedlander

Other Novel Agents and Strategies for Nonmetastatic and Metastatic UBC — Dr Petrylak

Module 7: Urothelial Bladder 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.

Immunotherapy in the Management of Nonmetastatic UBC and Emerging Utility of Circulating Tumor DNA (ctDNA)

Terence Friedlander, MD
Clinical Professor
Robert and Virginia O'Reilly Family Endowed Chair
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco
Chief of Hematology-Oncology
Zuckerberg San Francisco General Hospital and Trauma Center
San Francisco, California

@DrTFriedlander UCSF

Disclosures

Advisory Committees	Aadi Bioscience, AbbVie Inc, Adaptimmune, Aktis Oncology, Astellas, Bicycle Therapeutics, Bristol Myers Squibb, Gilead Sciences Inc, Merck, Pfizer Inc, Samsung Bioepis
Consulting Agreements	Astellas, EMD Serono Inc, Genentech, a member of the Roche Group
Contracted Research	AbbVie Inc, Bicycle Therapeutics, Flare Therapeutics, Genentech, a member of the Roche Group, Johnson & Johnson, Pfizer Inc

Outline

- NMIBC
  - Rationale for use of BCG + PD-1 immunotherapy
  - Safety and Efficacy from recent Phase III trials (CREST, POTOMAC, ALBAN)
  - Long-term findings with pembrolizumab monotherapy in patients with high-risk BCG-unresponsive NMIBC
- MIBC
  - NIAGARA study of perioperative Platinum + Durvalumab
  - IMvigor011 trial - ctDNA- guided adjuvant Atezolizumab
  - Prognostic and predictive impact of ctDNA in nonmetastatic UBC

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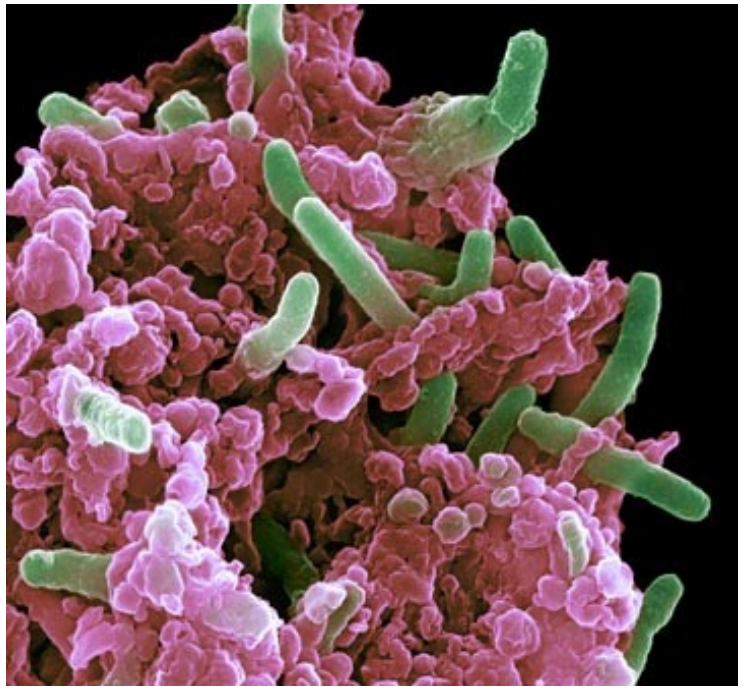
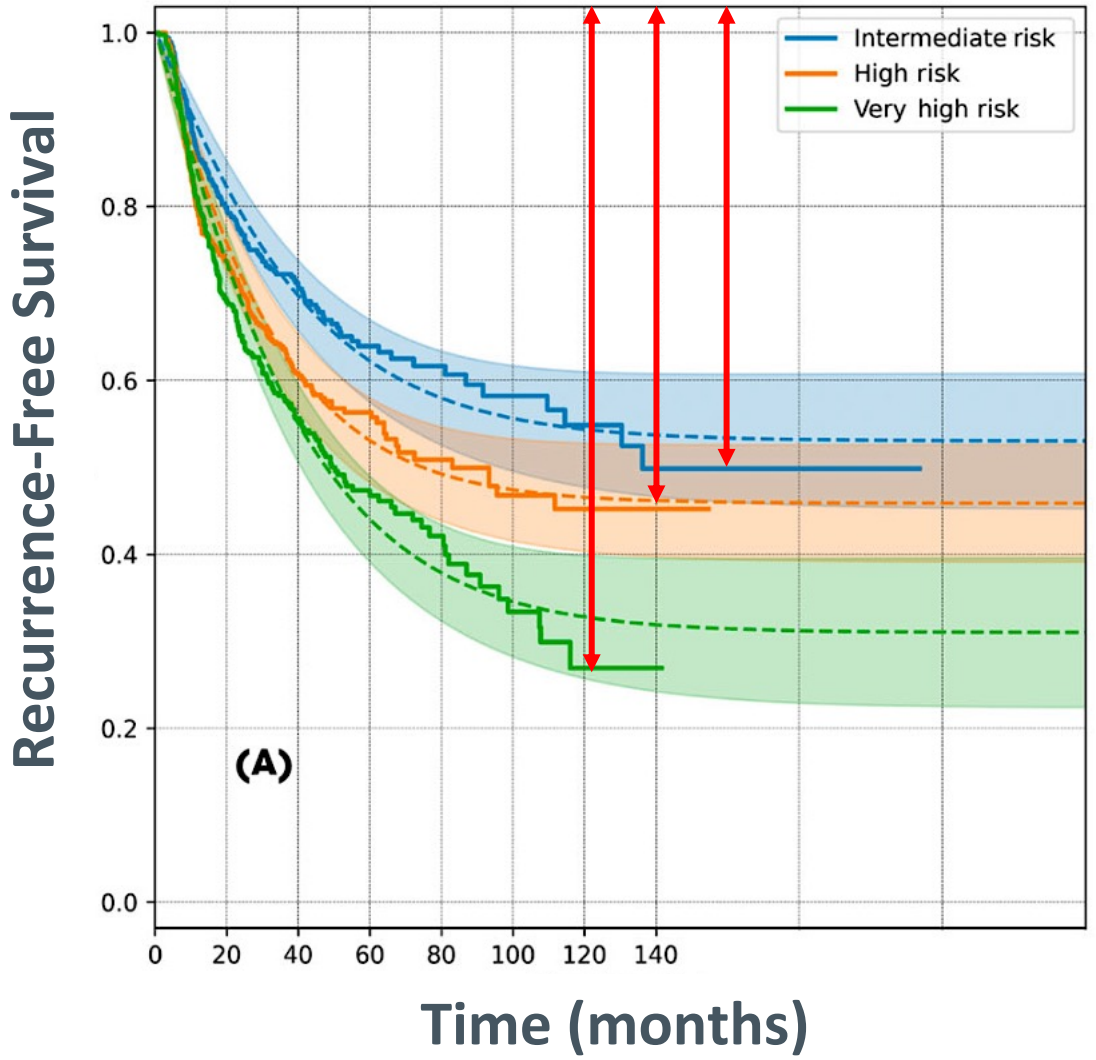
BCG is the Standard of Care for treatment-naïve NMIBC



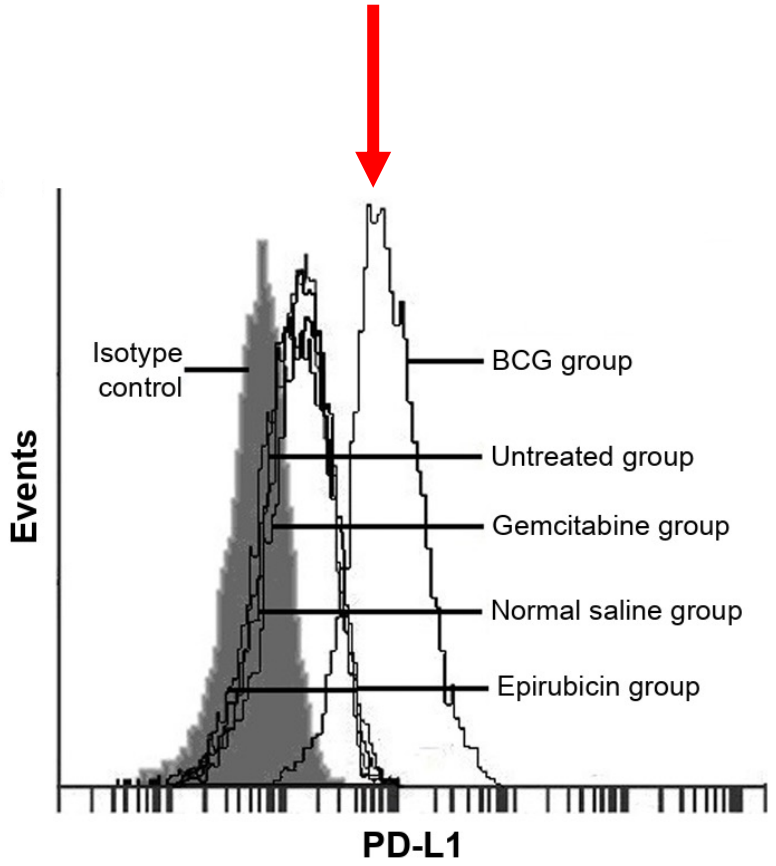


>50% of patients will not be cured!

Nature Medicine 2011, Subiela et al BJUI 2026

Why add PD-1 immunotherapy to BCG?

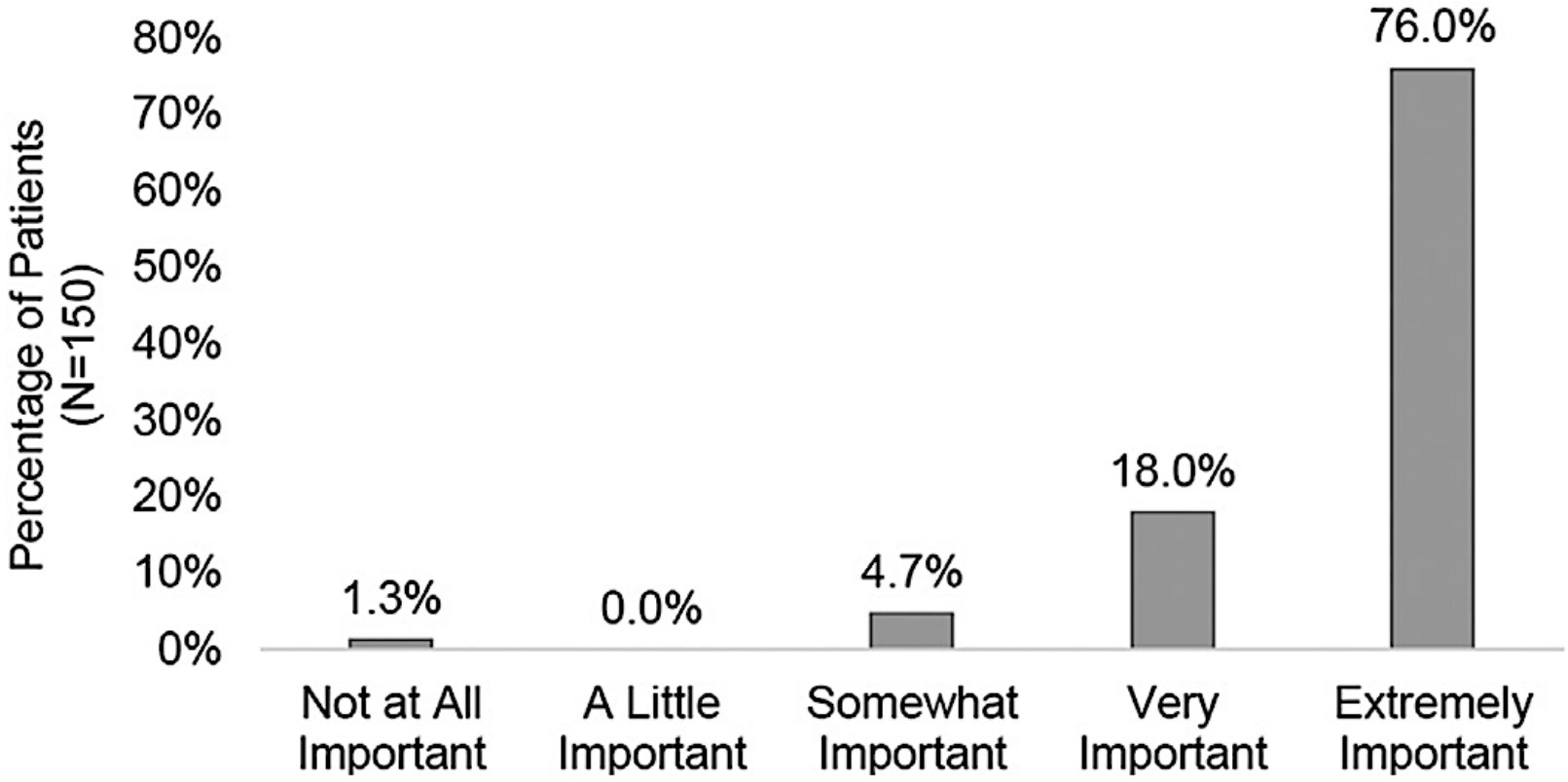
- Immunologically
  - BCG upregulates PD-L1 on tumors and tumor infiltrating lymphocytes (TIL)
    - "Counter-inflammatory response"
  - Resistance associated with T-cell exhaustion
- Clinically
  - Avoids cystectomy (potentially!)
  - Synergy of 2 immunotherapies
    - BCG addresses localized disease
    - PD-1 addresses any disease beyond the urothelium



Wang et al OncoTarg and Therapy 2018, Fukumoto Ann Surg Onc 2018, Hashizume et al Oncotarget 2018, Lim et al Front Immunol 2021

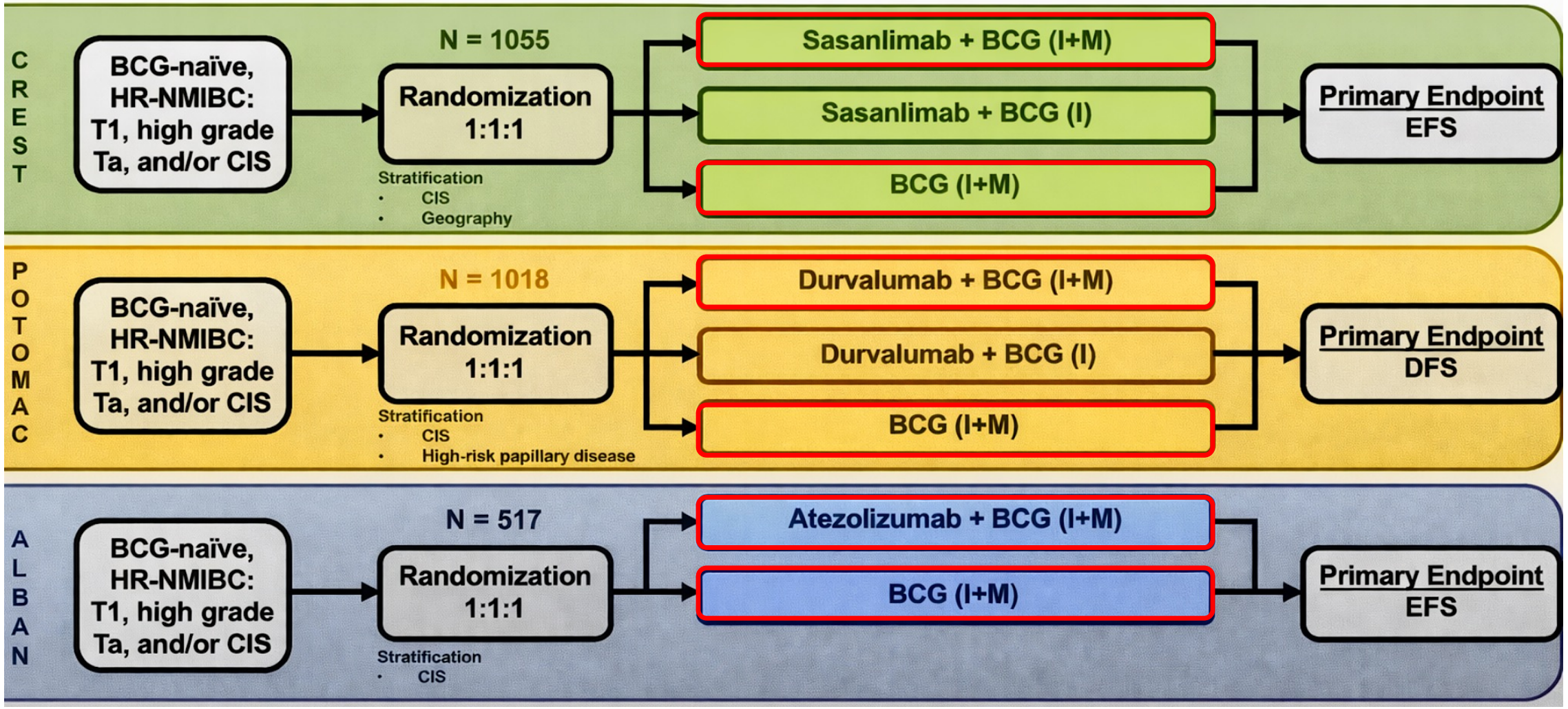
The Patient Perspective?

How important is it to keep the bladder and avoid cystectomy?



Kopenhafer L et al, Urol Oncol 2024

Studies to discuss today



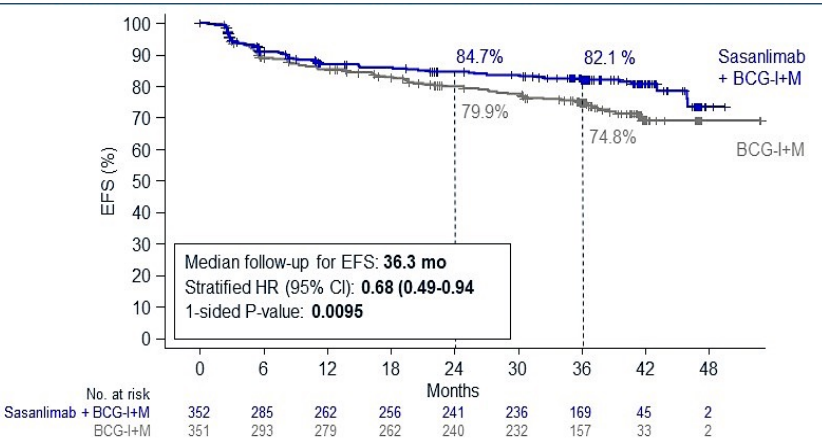
HR-NMIBC = High-risk Non-muscle invasive bladder cancer; I = Induction; M = Maintenance; EFS = Event-free survival; DFS = Disease-free survival

Hahn GU ASCO 2026, Shore NS et al, AUA 2025 / Nat Med 2025;31:2806-14 / De Santis M et al, ESMO 2025 / Lancet 2025;406(10516):2221-2234 / Roupret M et al, ESMO 2025 / Ann Oncol 2026;37(1):44-52

CREST

2 years BCG

2 years Sasanlimab



EFS HR 0.68

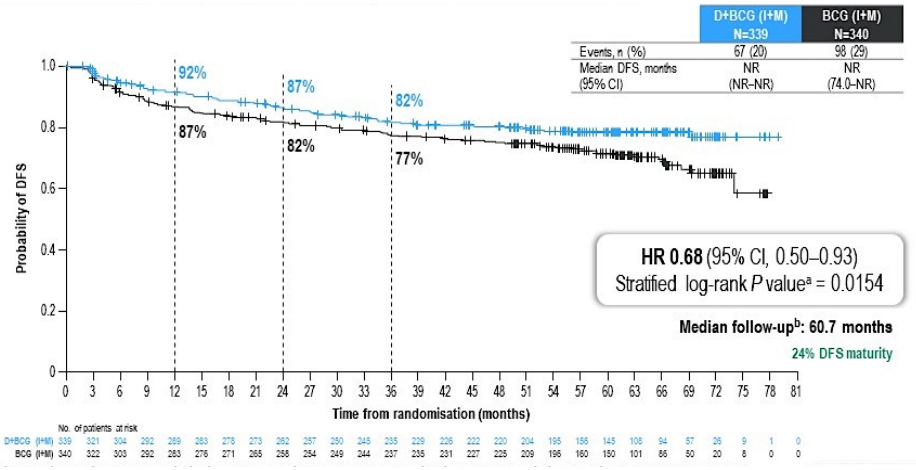
primary endpoint

OS HR 1.13 (0.68-1.87)

POTOMAC

2 years BCG

1-year Durvalumab



EFS HR 0.68

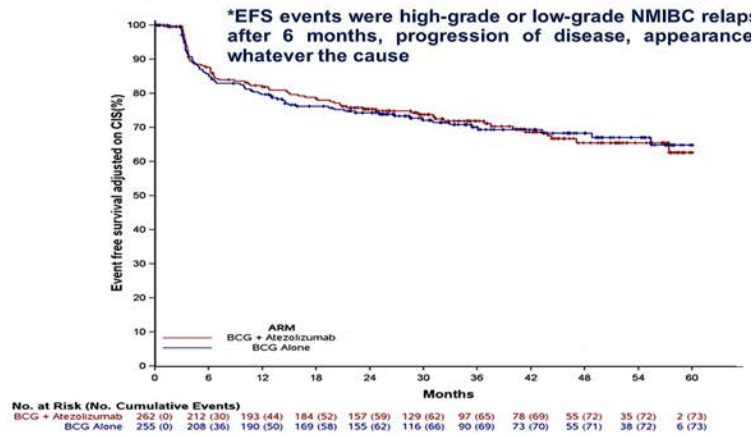
primary endpoint

OS HR 0.8 (0.53-1.20)

ALBAN

1 year BCG

1-year Atezolizumab



EFS HR 0.98

primary endpoint

OS HR 1.73 (0.76-3.92)

Shore NS et al, AUA 2025 / Nat Med 2025, De Santis M et al, ESMO 2025 / Lancet 2025 Roupret M et al, ESMO 2025 / Ann Oncol 2026, Hahn GU ASCO 2026

What explains these differences?

	CREST	**POTOMAC**	**ALBAN**
ICI Agent	Sasanlimab (anti-PD-1)	Durvalumab (anti-PD-L1)	Atezolizumab (anti-PD-L1)
Route of Admin	SubQ	IV	IV
Sample Size	1,055	1,018	517
High risk population (T1 %)?	**Yes** - 58%	**Yes** – 58%	**No** – 39%
Adequate BCG Maintenance?	**Yes** - 2 years	**Yes** - 2 years	**No -** 1 year
Does EFS Definition include low-grade NMIBC or UTUC?	**No**	**No**	**Yes**
Gr 3+ TRAE	29% vs 5.4%	21% vs 4%	23% vs 9%

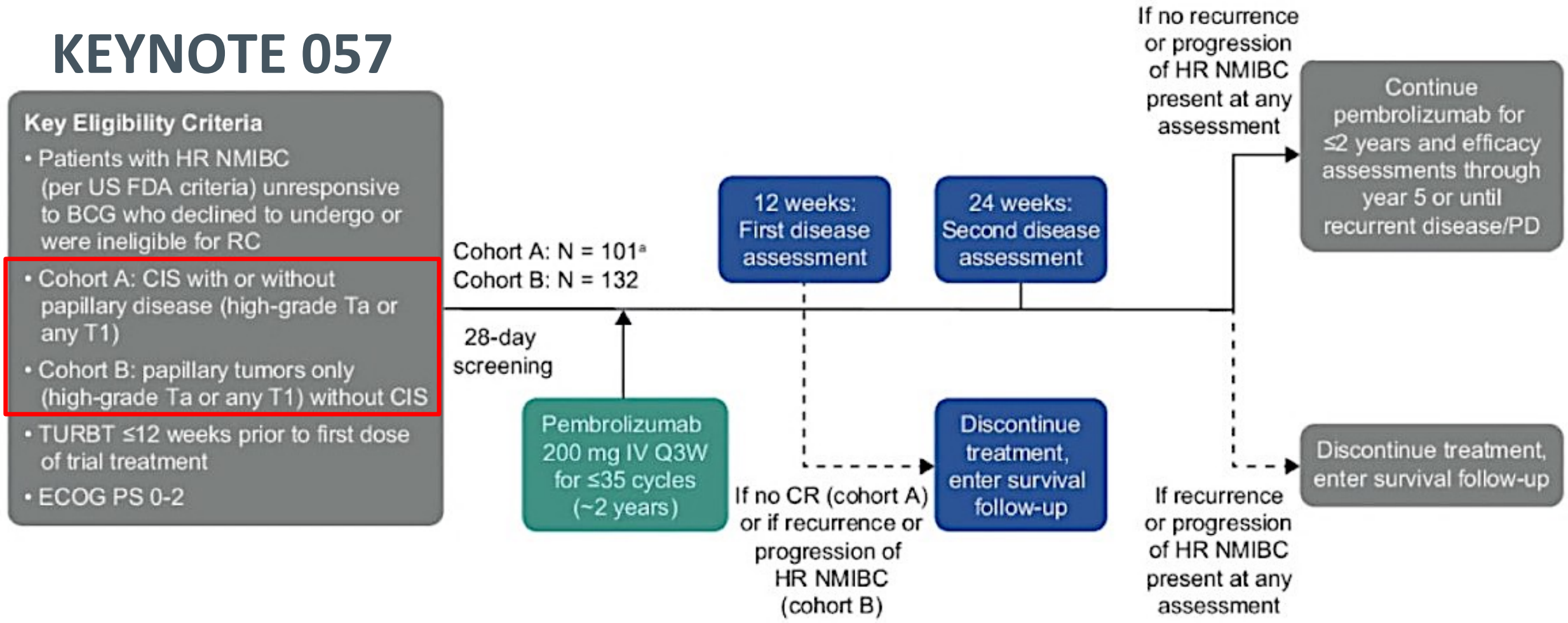
DeSantis et al. ESMO 2025; Powles et al. ASCO 2025; Roupret et al. ESMO 2025; Shore et al AUA 2025

Impact on Practice

- Either Sasanlimab or Durvalumab combined with BCG induction and maintenance **may** become an option for high-risk BCG-naïve NMIBC
  - Benefit mostly in T1 (highest risk) population
  - Awaiting KEYNOTE-676 trial in similar population
- Are autoimmune side effects worth it?
  - How to balance EFS (positive), OS (immature) and Toxicity (real)?
  - Likely will allow some patients to avoid cystectomy
  - But… multiple later-line therapies available for NMIBC
- Who will be giving this therapy? Urologists? Medical Oncologists?

Can we “save” PD-1 for BCG-unresponsive patients?

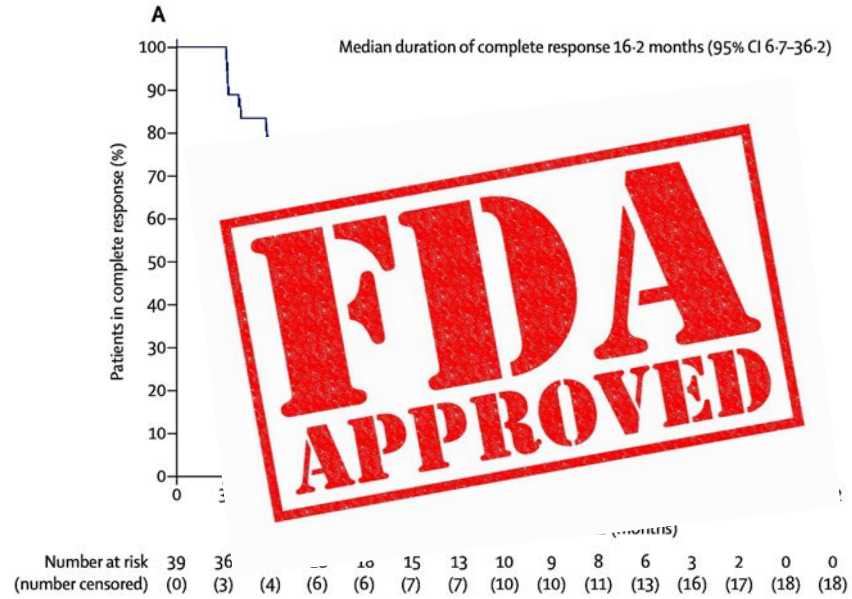
KEYNOTE 057



Li et al ASCO 2024

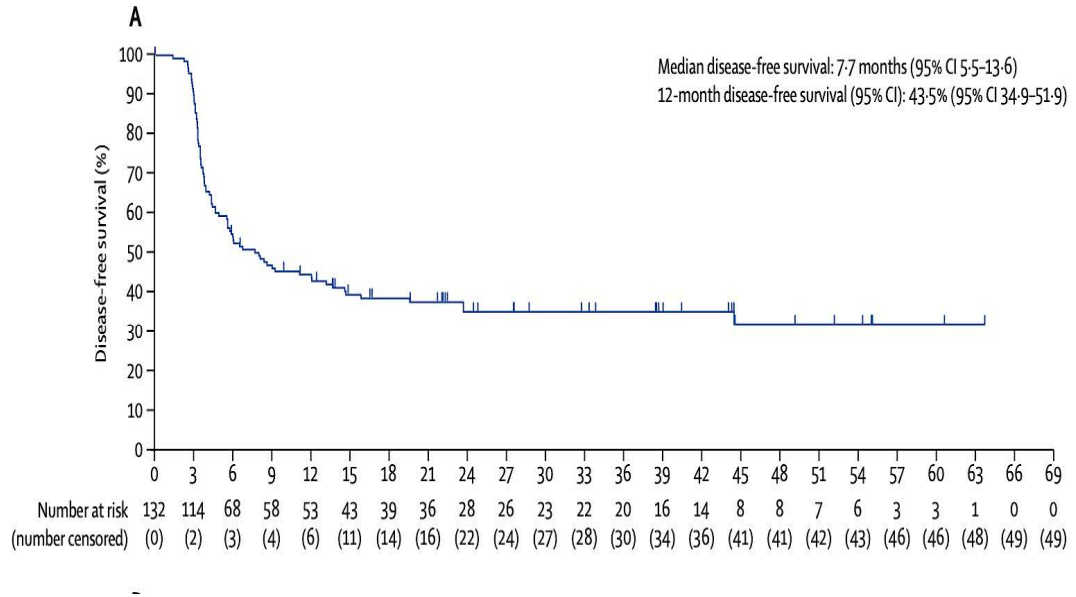
KEYNOTE 057: Pembrolizumab for High-risk (HR) BCG-unresponsive NMIBC

HR NMIBC **with** CIS



- 41% CR rate at 3 months
  - Median duration of CR 16.2 months
  - 9.3% (n=9) remain in CR at 45 months

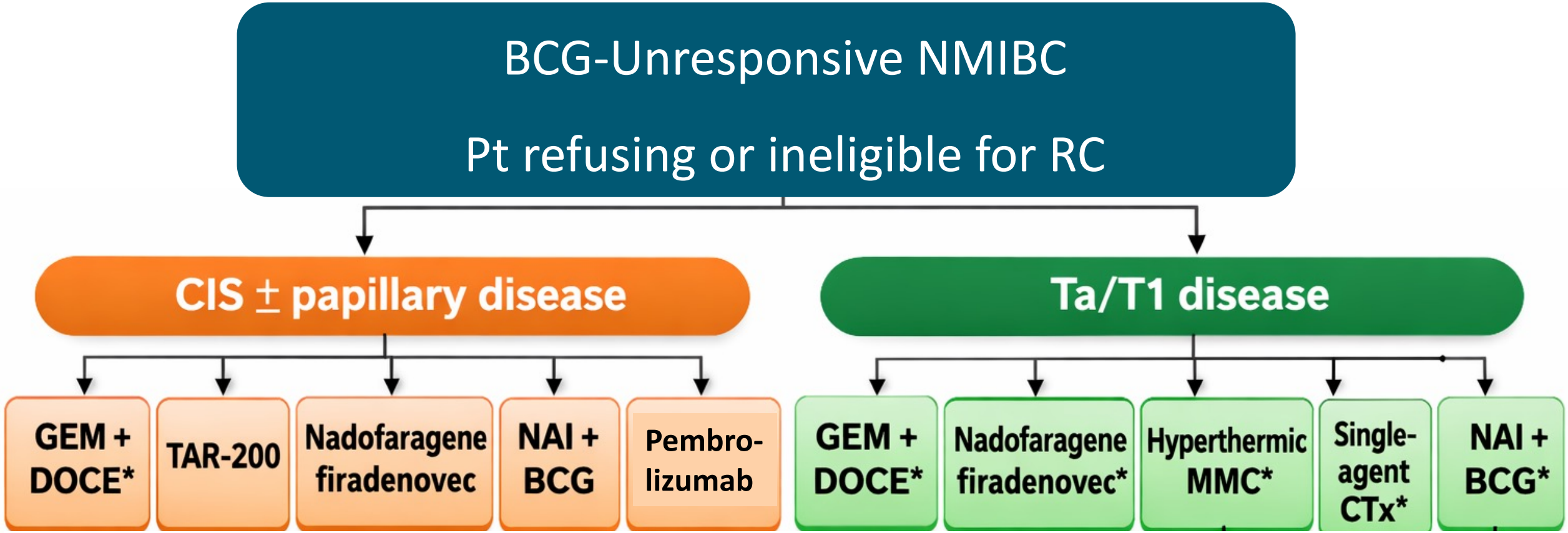
HR NMIBC **without** CIS



- 12 month DFS: 43%
- 36 month DFS: 33%

Balar et al Lancet Onc 2021, Necchi et al Lancet Onc 2024

Many options for BCG-unresponsive NMIBC



Adapted from: Li and International Bladder Cancer Group, Eur Urol, 2024

Many Ongoing Trials

- Treatment naïve vs BCG-resistant
- Multiple Modalities
  - » Intravesical
  - » Systemic
  - » Combinations

Drug	FDA Approval	Study	Mechanism of Action	Number of Pts in Study	Response Rate	Reported Response Duration	Cystectomy free rate
Anktiva (N-803)	Yes	Quilt 3.302	Activation and proliferation of natural killer and CD8 + T cells	CIS (n=83); nonCIS (n=77)	CIS 71%; nonCIS 48%	24 months	CIS 91%; nonCIS 95%
Pembrolizumab	Yes	KEYNOTE-057	Monoclonal antibody binds to PD-1 inhibiting interaction with PD-L1 and PD-L2	96	41%	16.2 months	Not Reported
Atezolizumab	No	SWOG S1605	PD-L1 inhibition	129	27%	6 months	Not Reported
Sasanlimab	No	CREST	Monoclonal antibody binds to PD-1 inhibiting interaction with PD-L1 and PD-L2	Preliminary results not reported	Not yet reported	Not yet reported	Not yet reported
Durvalumab	No	PATAPSCO	Monoclonal antibody binds PD-L1 inhibiting its interaction with PD-1	Preliminary results not reported	Not yet reported	Not yet reported	Not yet reported
Nivolumab	No	CheckMate 9UT	PD-1 immune checkpoint inhibitor	Preliminary results not reported	Not yet reported	Not yet reported	Not yet reported
Nadofaragene Firadenovec	Yes	INSTILADRIN	Recombinant adenovirus vector and polyamide surfactant	157	a) 53% b) 34.2%	a) 9.7 months b) 36 months	Not Reported
CG0070	No	CORE1	Modified adenovirus that induces cell lysis paired with anti PD-1 therapy	35	a) 88% b) 73%	a) 3 months b) 12 months	Not Reported
TARA-002	No	ADVANCED-1	Lyophilized mixture of low-virulence Streptococcus pyogenes cells treated with benzylpenicillin	102	Not reported	Not yet Reported	Not yet reported
Gemcitabine & Docetaxel	No	Retrospective Review	Combination intravesical therapy	276	a) 60% b) 46%	a) 12 months b) 24 months	Not Reported
Cabazitaxel, Gemcitabine, Cisplatin	No	Phase 2 trial	Combination intravesical therapy	Preliminary results not reported	Not yet reported	Not yet reported	Not yet reported
Electromotive Drug Administration	No	Prospective Trial	Intravesical chemotherapy with mild electric current to enhance penetration	26	a) 44% b) 30.4%	a) 12 months b) 18 months	Not Reported
Hyperthermic Intravesical Chemotherapy	No	Retrospective Review	Heated intravesical therapy	56	a) 53% b) 35%	a) 12 months b) 24 months	Not Reported
TAR-200	No	SUNRISE-1 and SUNRISE-2	Investigational drug delivery system; controlled, continuous dose of gemcitabine or cetrelimab	23	Not yet reported	Not yet reported	Not yet reported

Wiesen B, et al Front. Oncol. 2025

Outline

- NMIBC
  - Rationale for use of BCG + PD-1 immunotherapy
  - Safety and Efficacy from recent Phase III trials (CREST, POTOMAC, ALBAN)
  - Long-term findings with pembrolizumab monotherapy in patients with high-risk BCG-unresponsive NMIBC

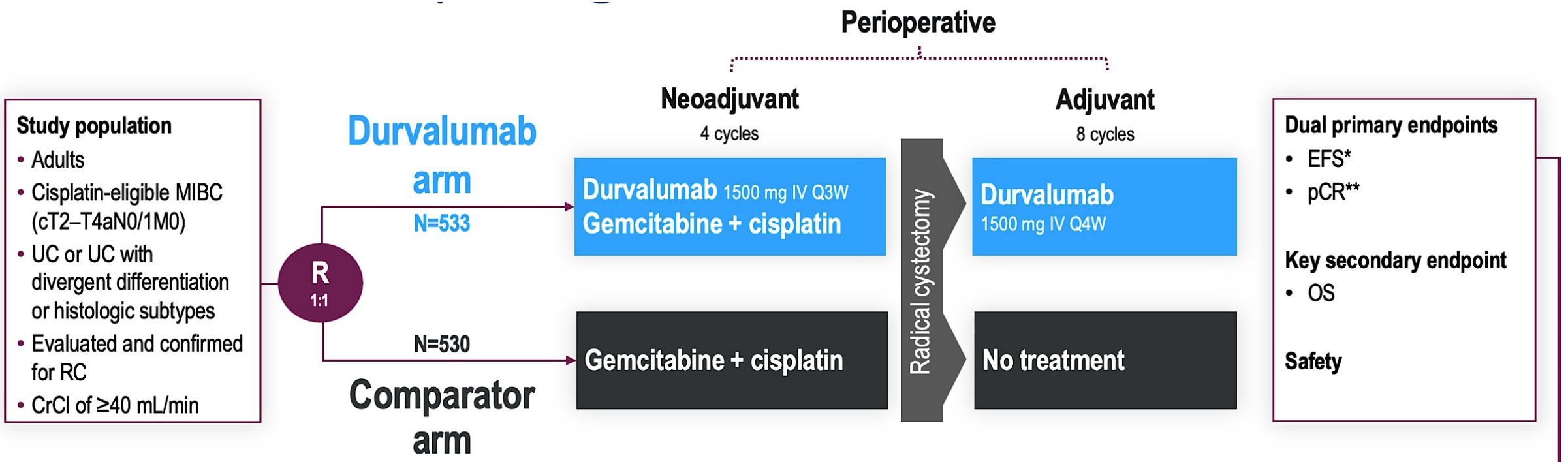
- MIBC
  - NIAGARA study of perioperative Platinum + Durvalumab
  - IMvigor011 trial - ctDNA- guided adjuvant Atezolizumab
  - Prognostic and predictive impact of ctDNA in nonmetastatic UBC

Recent and Ongoing Phase III Neoadjuvant IO-Based Trials in MIBC

	Clinical Trial	N	Treatment Arms	Control Arm
CISPLATIN ELIGIBLE	**KEYNOTE-866**	907	Pembrolizumab + GC	GC
	NIAGARA	1063	Durvalumab + GC	GC
	ENERGIZE	8	Nivolumab + GC	GC
	KEYNOTE-B15/EV-304	784	Pembrolizumab + EV	GC
CISPLATIN INELIGIBLE	**KEYNOTE-905/EV-303**	857	A: Pembrolizumab + EV B: Pembrolizumab mono	RC
	VOLGA	830	A: Durvalumab-Tremelimumab + EV B: Durvalumab + EV	RC

Clinicaltrials.gov

NIAGARA: Study Design



Stratification factors

Clinical tumour stage (T2N0 vs >T2N0)

Renal function (CrCl ≥60 mL/min vs ≥40–<60 mL/min)

PD-L1 status (high vs low/negative expression)

Gemcitabine/cisplatin dosing

CrCl ≥60 mL/min: Cisplatin 70 mg/m² + gemcitabine 1000 mg/m² Day 1, then gemcitabine 1000 mg/m² Day 8, Q3W for 4 cycles

CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m² + gemcitabine 1000 mg/m² Days 1 and 8, Q3W for 4 cycles

EFS was defined as:

- **Progressive disease that precluded RC**
- **Recurrence after RC**
- **Date of expected surgery in patients who did not undergo RC**
- **Death from any cause**

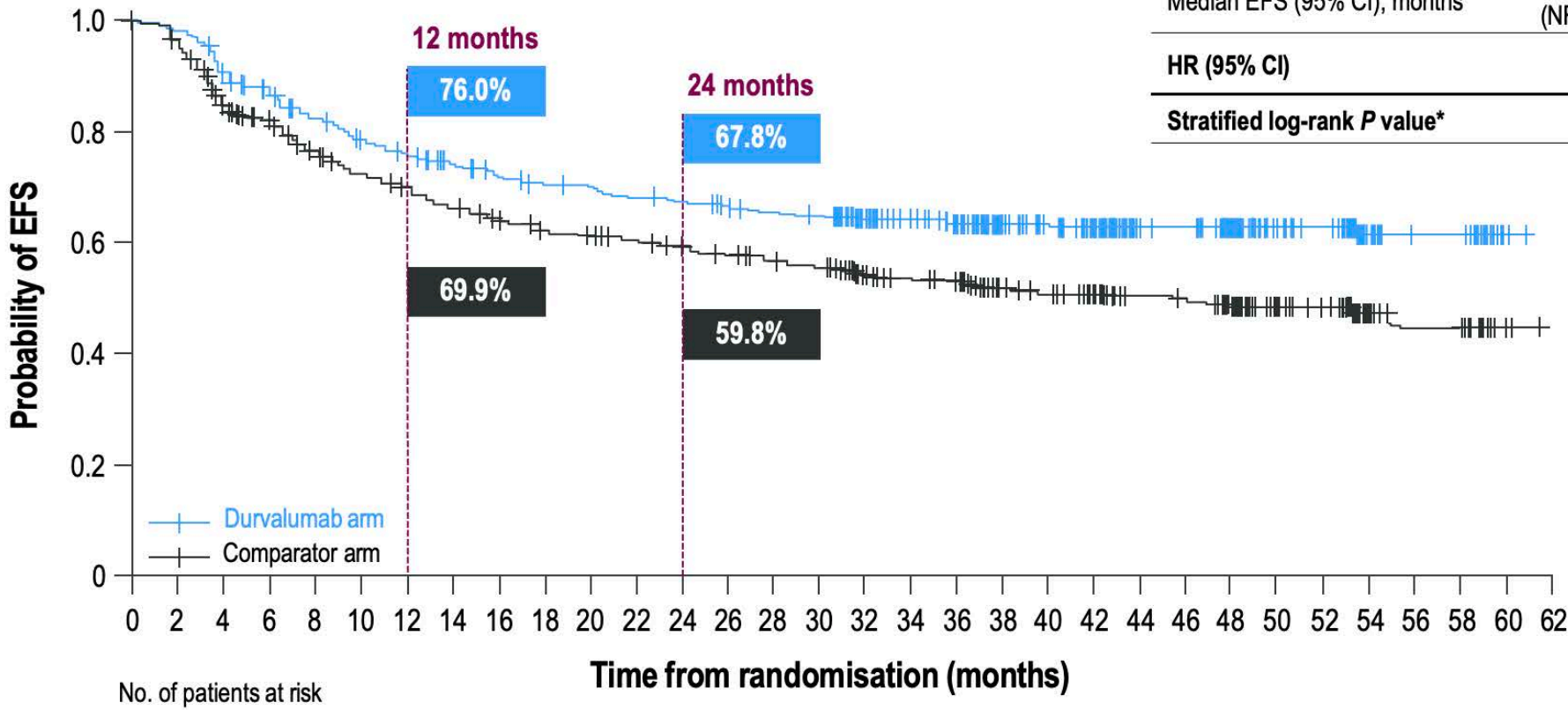
Other endpoints (not reported here): DFS, DSS, MFS, HRQoL, 5-year OS

Powles et al ESMO 2024

*Evaluated by blinded independent central review or central pathology review (if a biopsy was required for a suspected new lesion). **Evaluated by blinded central pathology review.
ClinicalTrials.gov, NCT03732677; EudraCT number, 2018-001811-59. CrCl, creatinine clearance; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival; HRQoL, health-related quality of life; IV, intravenous; MFS, metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomised; RC, radical cystectomy; UC, urothelial carcinoma..

NIAGARA Results Positive

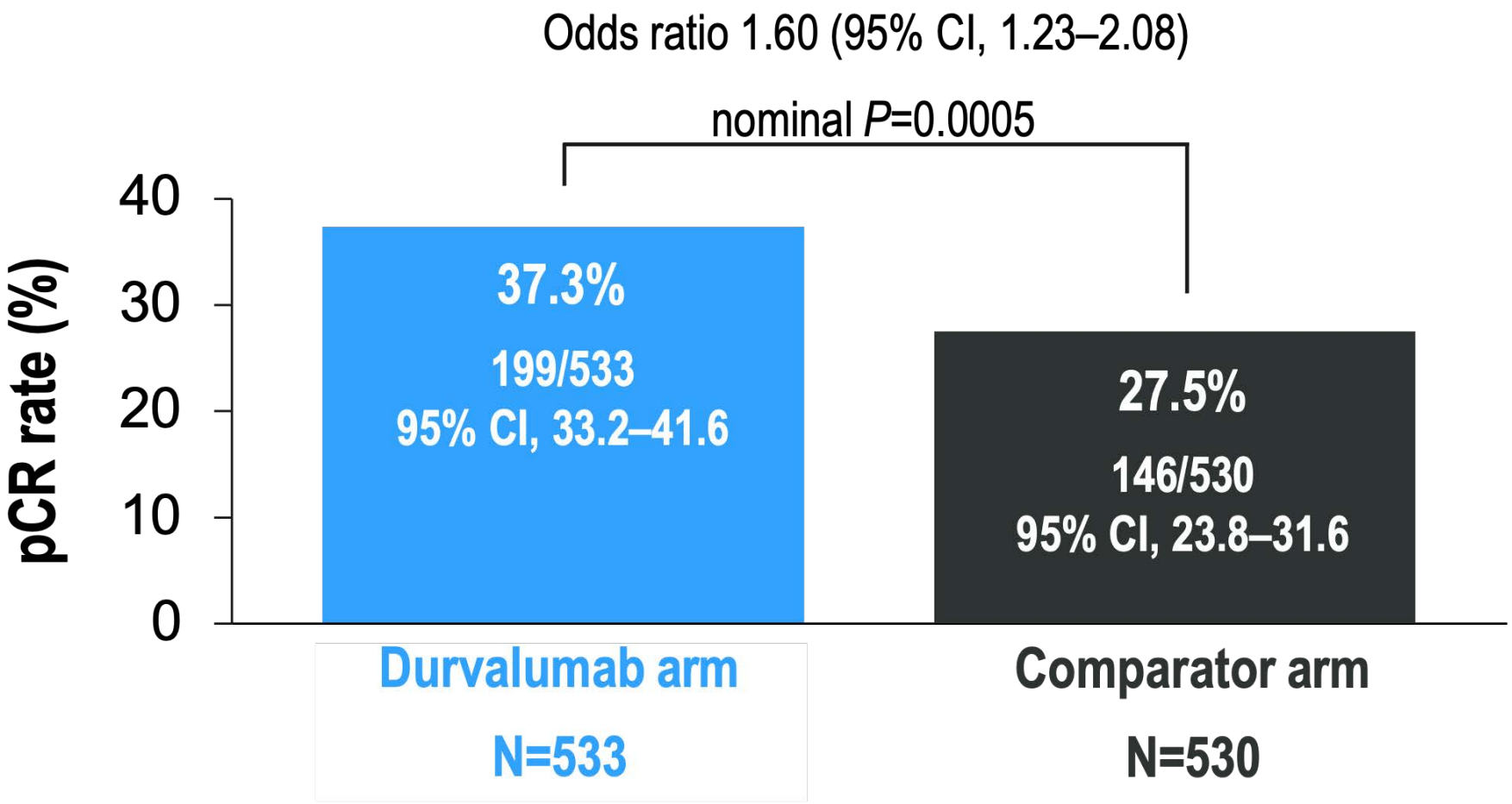
	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS (95% CI), months	NR (NR–NR)	46.1 (32.2–NR)
HR (95% CI)	**0.68 (0.56–0.82)**	
Stratified log-rank *P* value*	**<0.0001**	



Median follow-up in censored patients: 42.3 months (range, 0.03–61.3)

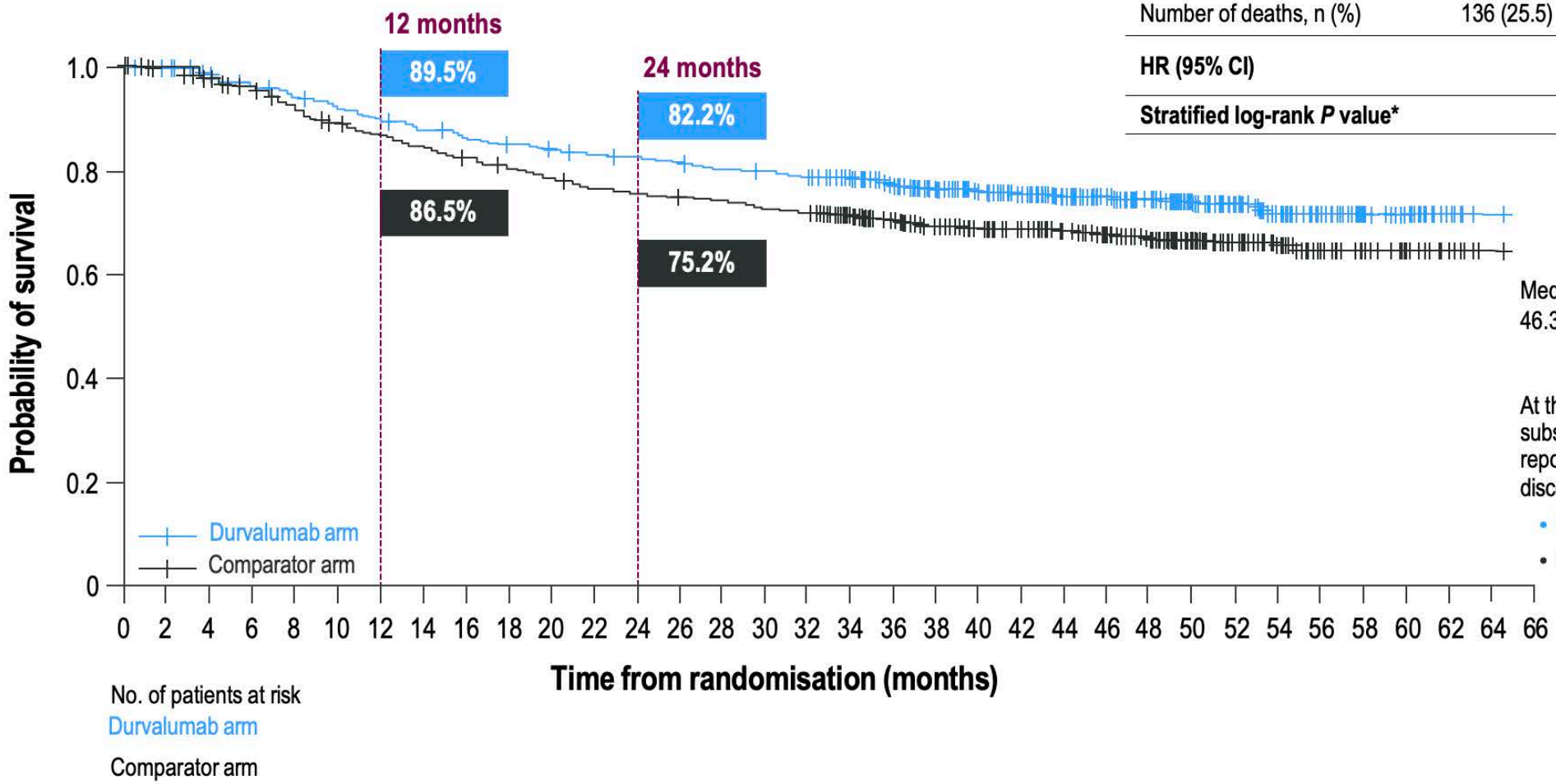
Powles et al ESMO 2024, NEJM 2024

NIAGARA Results Positive



Powles et al ESMO 2024, NEJM 2024

NIAGARA Results Positive



	Durvalumab arm N=533	Comparator arm N=530
Number of deaths, n (%)	136 (25.5)	169 (31.9)
HR (95% CI)	**0.75 (0.59–0.93)**	
Stratified log-rank *P* value*	**0.0106**	

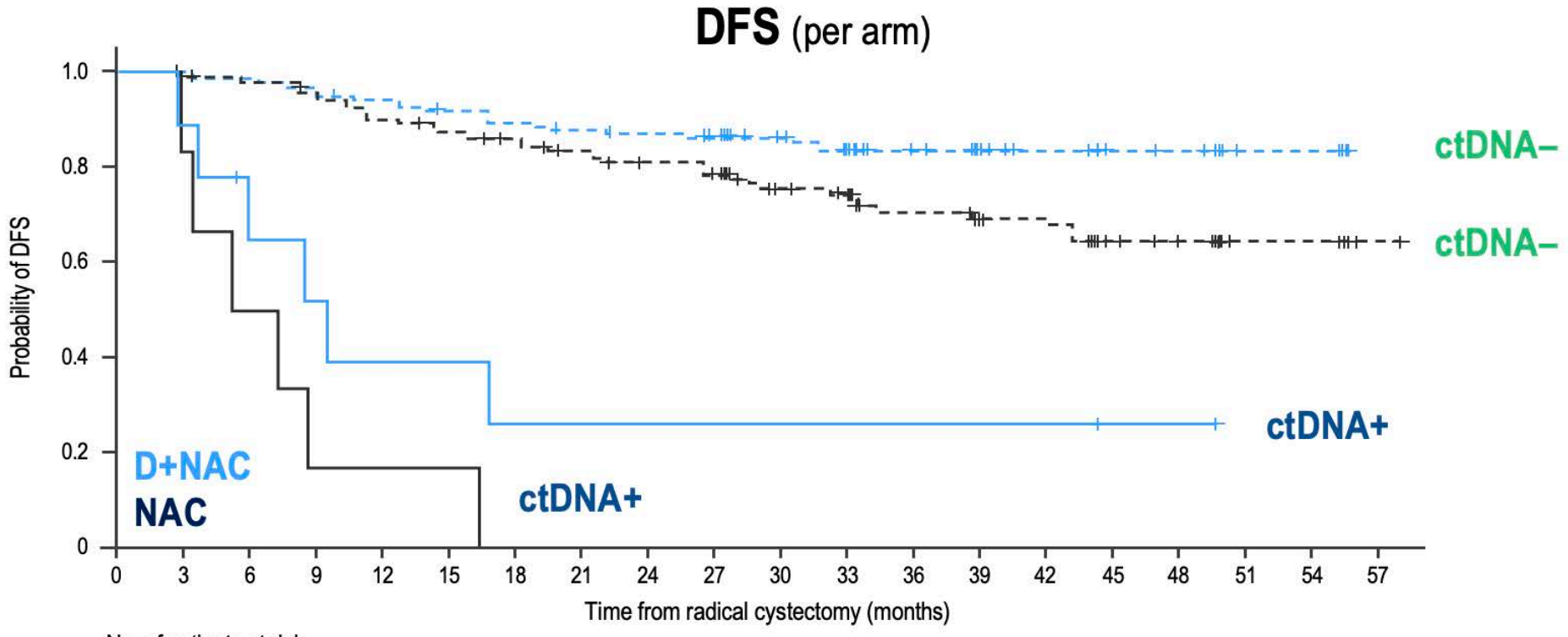
Median follow-up in censored patients: 46.3 months (range, 0.03–64.7)

At the time of this analysis, at least 1 subsequent anti-cancer therapy was reported after treatment discontinuation for:

- 53 patients in the durvalumab arm
- 93 patients in the comparator arm

Powles et al ESMO 2024, NEJM 2024

Prognostic Value of ctDNA



No. of patients at risk

ctDNA– D+NAC	129	129	127	123	121	117	114	111	109	106	95	87	71	49	45	28	27	6	6	0
ctDNA– NAC	126	125	123	118	111	107	102	98	93	89	75	71	56	41	40	23	20	6	6	1
ctDNA+ D+NAC	9	8	6	4	3	3	2	2	2	2	2	2	2	2	2	1	1	0	0	0
ctDNA+ NAC	8	5	3	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

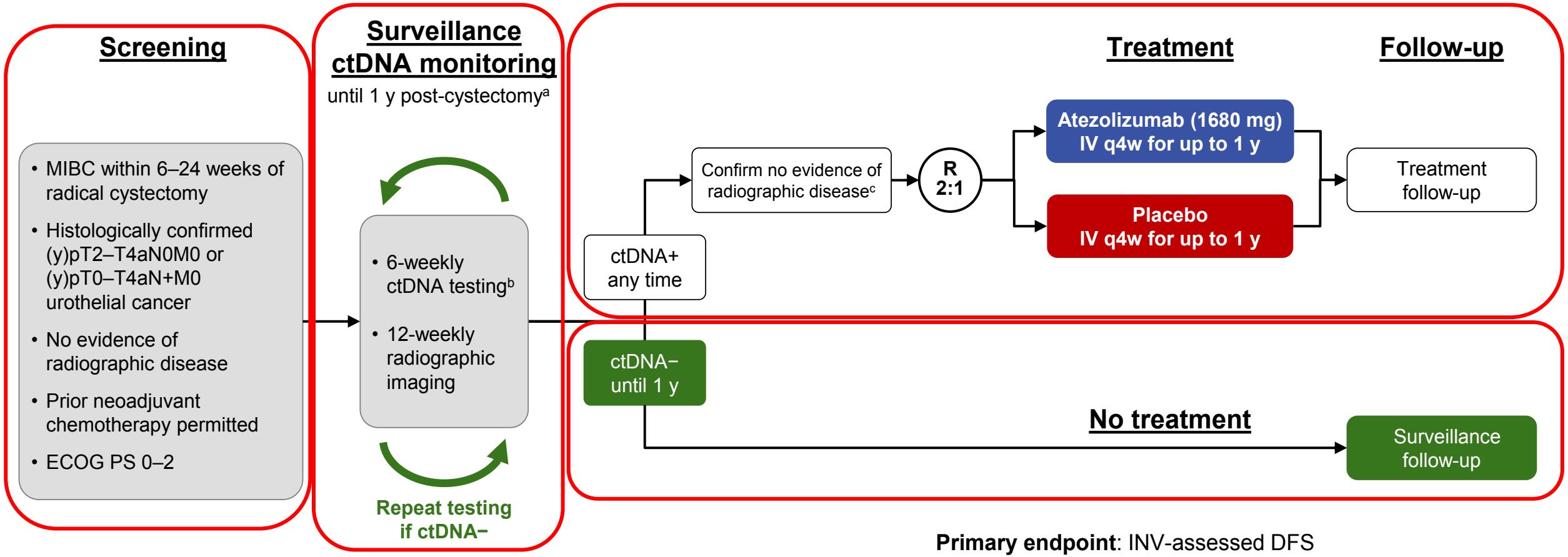
ctDNA–: D+NAC vs NAC	**HR, 0.49** (95% CI, 0.28–0.84)
ctDNA+: D+NAC vs NAC	HR not calculated[a]

Durvalumab arm = D+NAC; Comparator arm = NAC

Powles et al ASCO 2025

[a]Not calculated due to less than 20 events between arms.
BEP, biomarker evaluable population; CI, confidence interval; ctDNA, circulating tumor DNA; D, durvalumab; DFS, disease-free survival; HR, hazard ratio; NAC, neoadjuvant chemotherapy.

IMvigor 011: ctDNA Guided-Adjuvant Therapy



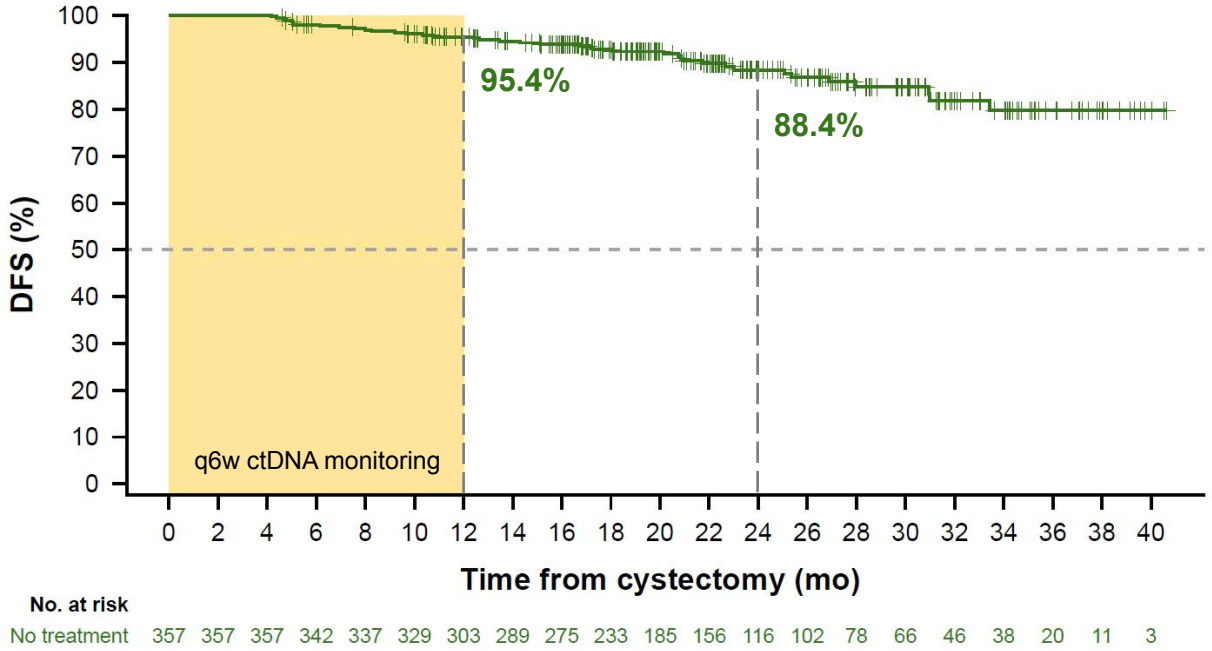
Primary endpoint: INV-assessed DFS
Key secondary endpoint: OS

ClinicalTrials.gov number, NCT04660344. Stratification factors were nodal status (positive vs negative), tumour stage at cystectomy (≤pT2 vs pT3/pT4), PD-L1 status (IC0/1 [<5%] vs IC2/3 [≥5%] by VENTANA SP142 immunohistochemistry assay) and time from cystectomy to first ctDNA+ sample (≤20 weeks vs >20 weeks). [a] Early versions of the protocol included a 21-mo surveillance ctDNA monitoring period.
[b] ctDNA status was determined by the Natera Signatera™ MRD test (outside of mainland China) and by the BGI MRD test (in mainland China). [c] By INV and IRF assessment. ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cells; INV, investigator; IRF, independent review facility; IV, intravenous; mo, month; PD-L1, programmed death-ligand 1; R, randomised; y, year.
Adapted from Powles T, et al. ESMO 2021 (Abstract 3716) with permission.

ctDNA- patients do well without adjuvant therapy

INV-assessed DFS

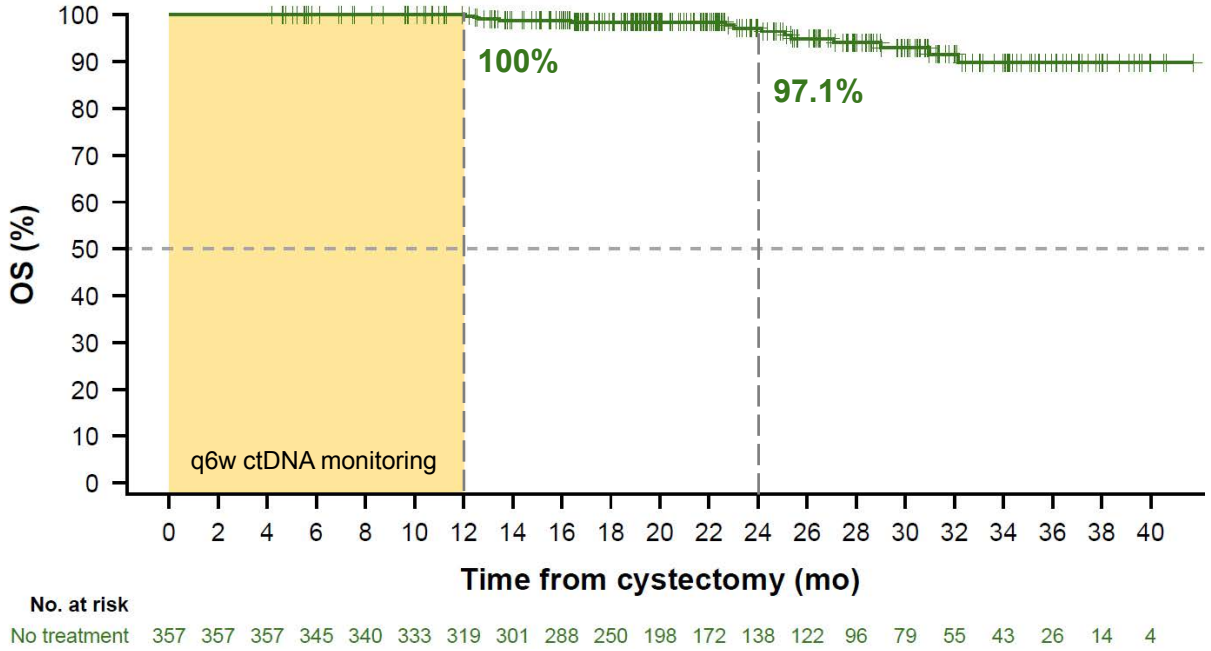
	No treatment (n=357)
Events, n (%)	39 (10.9)
DFS, median (95% CI), mo	NE (NE)



Median follow-up: 21.8 mo from cystectomy

OS

	No treatment (n=357)
Events, n (%)	14 (3.9)
OS, median (95% CI), mo	NE (NE)



8 DFS events were deaths not clearly attributed to disease recurrence

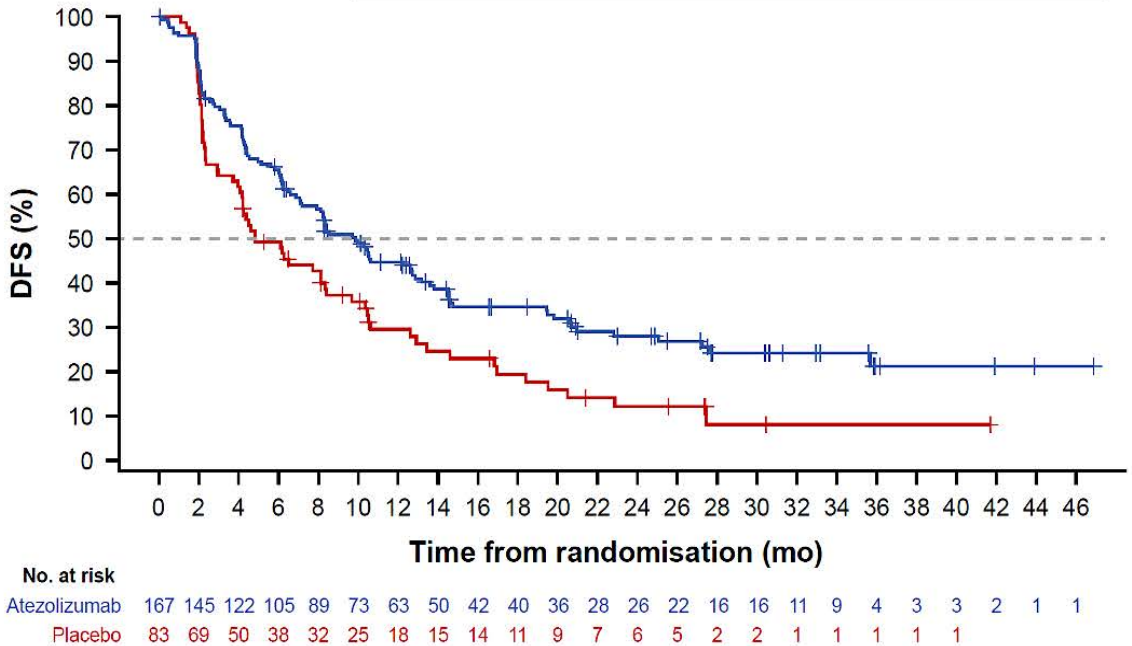
15 patients (4.2%) who experienced disease recurrence during the ctDNA monitoring period were discontinued from the study and censored for OS

Clinical cutoff: 15 June 2025. To be included in the ctDNA− efficacy-evaluable population, patients must have ≥1 negative test result and no positive test result, had ≥1 post-baseline clinical outcome assessment and completed 1 y of surveillance or discontinued from surveillance without a ctDNA+ result. q6w, every 6 weeks

Powles et al ESMO 2025

ctDNA+ patients benefit from adjuvant therapy

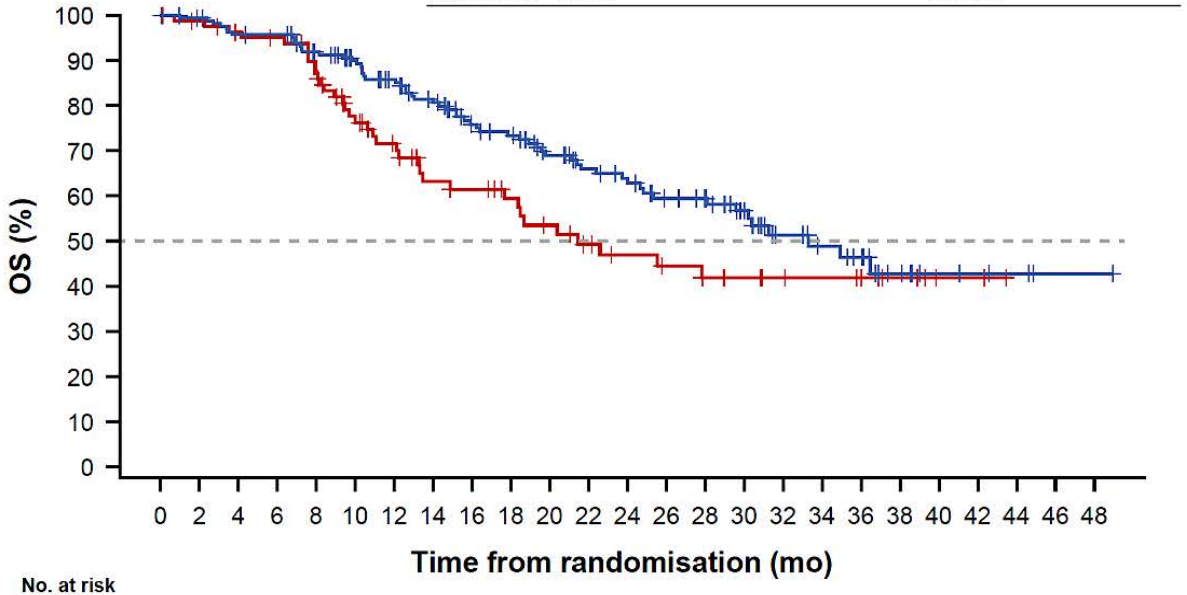
	Atezolizumab (n=167)	Placebo (n=83)
Events, n (%)	112 (67.1)	66 (79.5)
DFS, median (95% CI), mo	9.9 (7.2, 12.7)	4.8 (4.1, 8.3)
Stratified HR (95% CI)	**0.64 (0.47, 0.87)**	
Stratified *P* value	**0.0047**	



No. at risk

Atezolizumab	167	145	122	105	89	73	63	50	42	40	36	28	26	22	16	16	11	9	4	3	3	2	1	1
Placebo	83	69	50	38	32	25	18	15	14	11	9	7	6	5	2	2	1	1	1	1	1			

	Atezolizumab (n=167)	Placebo (n=83)
Events, n (%)	60 (35.9)	36 (43.4)
OS, median (95% CI), mo	32.8 (27.7, NE)	21.1 (14.7,NE)
Stratified HR (95% CI)	**0.59 (0.39, 0.90)**	
Stratified *P* value	**0.0131**	



No. at risk

Atezolizumab	167	162	155	154	143	130	118	108	92	86	75	65	59	51	43	30	23	19	12	7	5	3	2	1	1
Placebo	83	80	76	74	65	53	44	36	34	30	26	21	19	17	15	13	10	10	8	5	2	1			

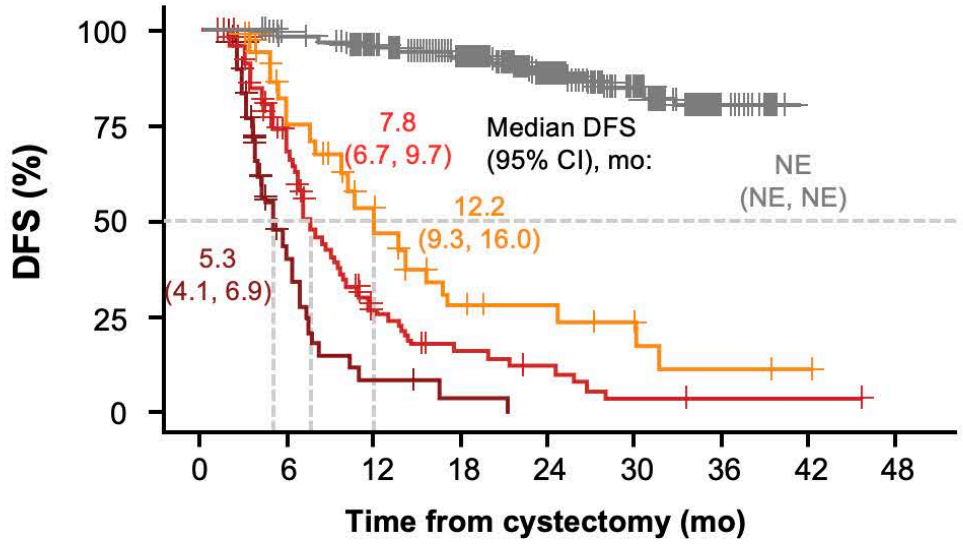
Powles et al ESMO 2025

ctDNA levels matter…

High ctDNA concentration was associated with inferior clinical outcomes

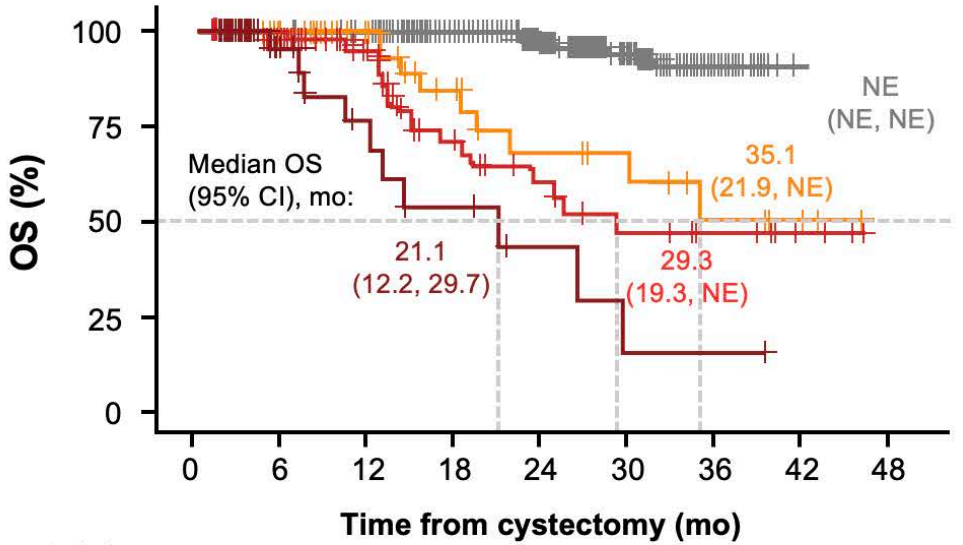
ctDNA+ untreated (n=212)

ctDNA– (n=357)



No. at risk

ctDNA–	357	342	303	233	116	66	20	0	0
≤0.1 MTM/mL	56	39	22	9	7	5	2	1	0
>0.1–≤3 MTM/mL	99	55	18	9	6	2	1	1	0
>3 MTM/mL	57	14	3	1	0	0	0	0	0



No. at risk

ctDNA–	357	345	319	250	138	79	26	0	0
≤0.1 MTM/mL	56	40	30	18	11	9	5	3	0
>0.1–≤3 MTM/mL	99	59	40	23	15	10	7	3	0
>3 MTM/mL	57	18	10	6	3	1	1	0	0

DFS rate, % (no. at risk)

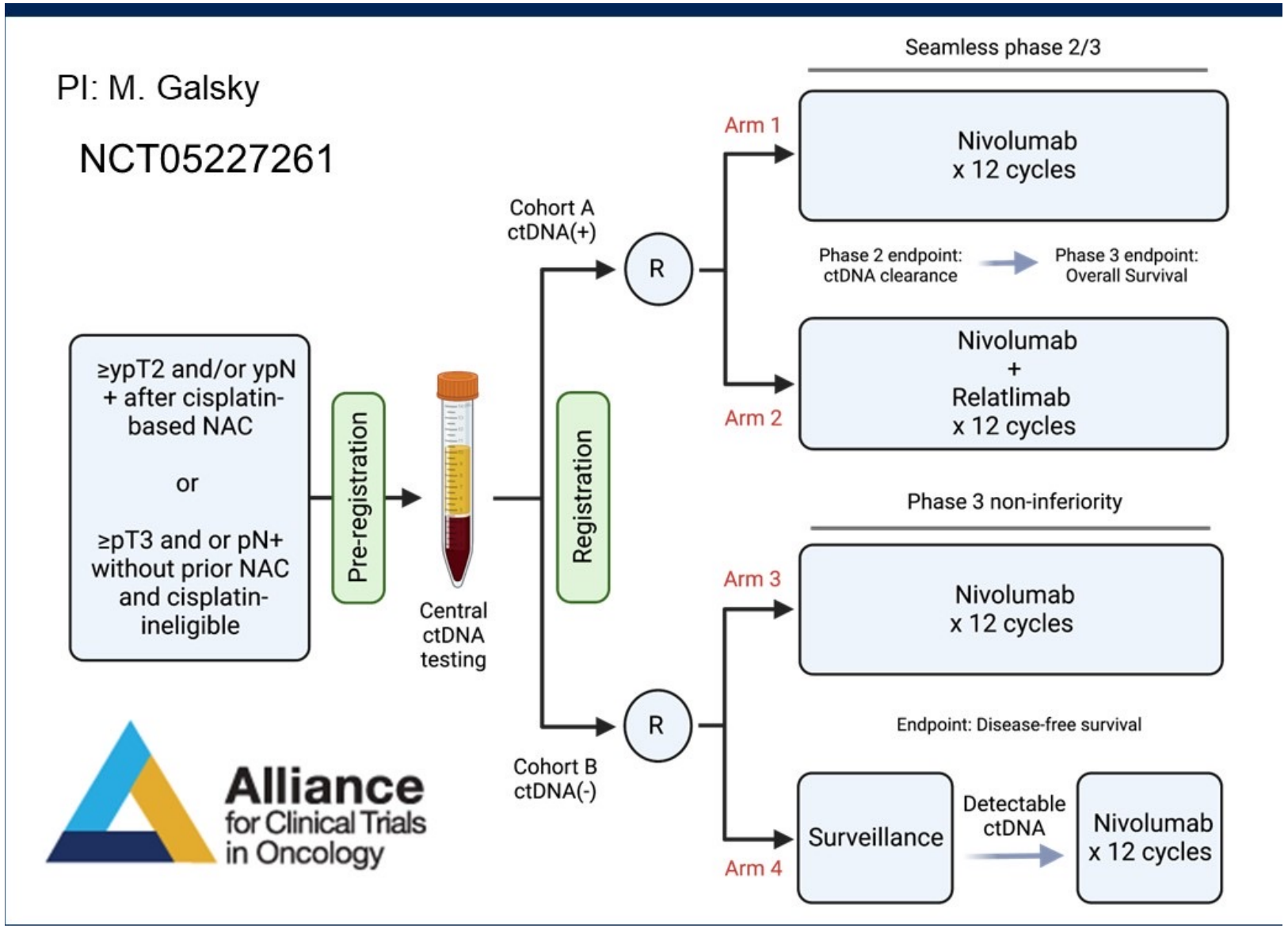
Mo	ctDNA–	≤0.1 MTM/mL	>0.1–≤3 MTM/mL	>3 MTM/mL
6	98.0 (342)	82.1 (39)	71.2 (55)	44.0 (14)
12	95.4 (303)	53.4 (22)	26.6 (18)	9.4 (3)
24	88.4 (116)	28.4 (7)	13.2 (6)	0 (0)

OS rate, % (no. at risk)

Mo	ctDNA–	≤0.1 MTM/mL	>0.1–≤3 MTM/mL	>3 MTM/mL
6	100 (345)	100 (40)	97.2 (59)	95.2 (18)
12	100 (319)	100 (30)	95.0 (40)	76.0 (10)
24	97.1 (138)	67.4 (11)	60.1 (15)	42.6 (3)

Bellmunt et al GU ASCO 2026

In Progress: Alliance A032103 MODERN trial



Galsky et al ASCO 2024

Summary: MIBC

- Combination IO + chemotherapy is effective
  - Durvalumab + Gem/Cis is a Standard of Care for MIBC
  - Is perioperative Enfortumab Vedotin + Pembrolizumab data stronger?
- Tumor-informed cfDNA identifies patients likely to relapse and to benefit from immediate adjuvant therapy
  - Await cfDNA results from EV trials, VOLGA, and others
- cfDNA as a future tool to *personalize treatment strategies*

QUESTIONS?

Module 7: Urothelial Bladder Cancer

Role of Immunotherapeutic Strategies in the Management of Nonmetastatic UBC; Emerging Utility of Circulating Tumor DNA (ctDNA) Evaluation — Dr Friedlander

Other Novel Agents and Strategies for Nonmetastatic and Metastatic UBC — Dr Petrylak

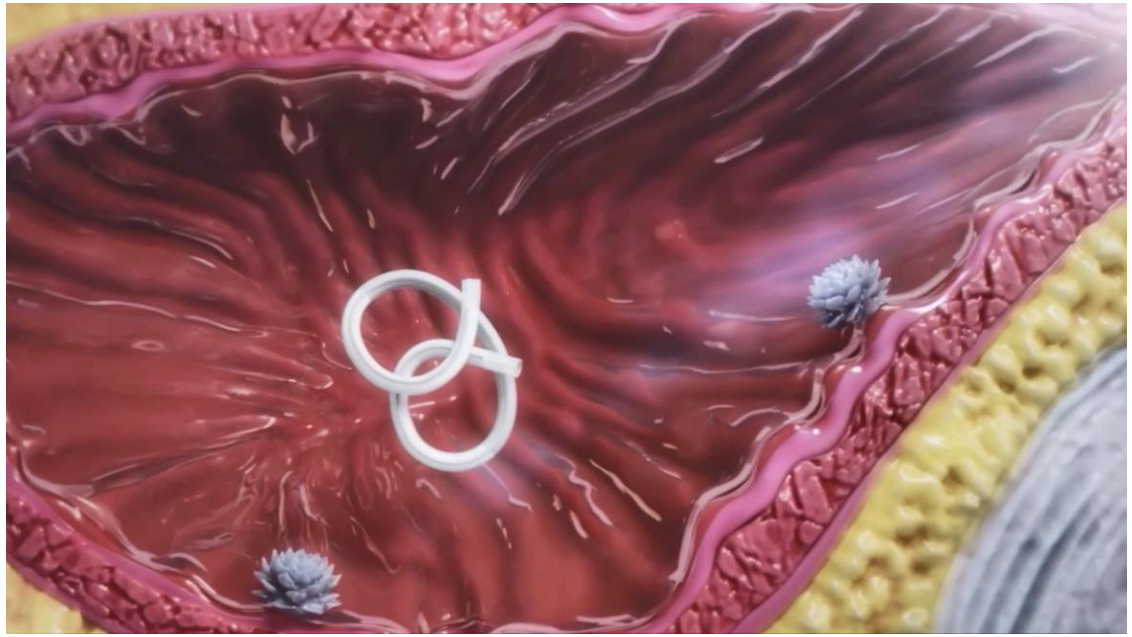
Other Novel Agents and Strategies for Nonmetastatic and Metastatic UBC

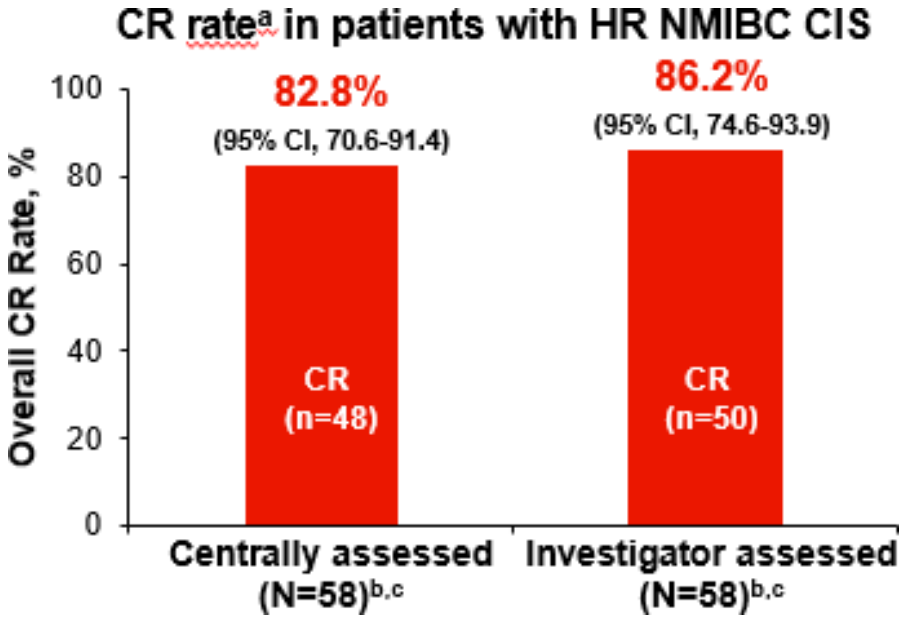
Daniel P. Petrylak, MD
Professor of Medicine and Urology
Division Chief, Genitourinary Cancer
Smilow Cancer Center, Yale University

Disclosures

No relevant conflicts of interest to disclose.

TAR-200: Intravesical Drug Eluting Device-Gemcitabine

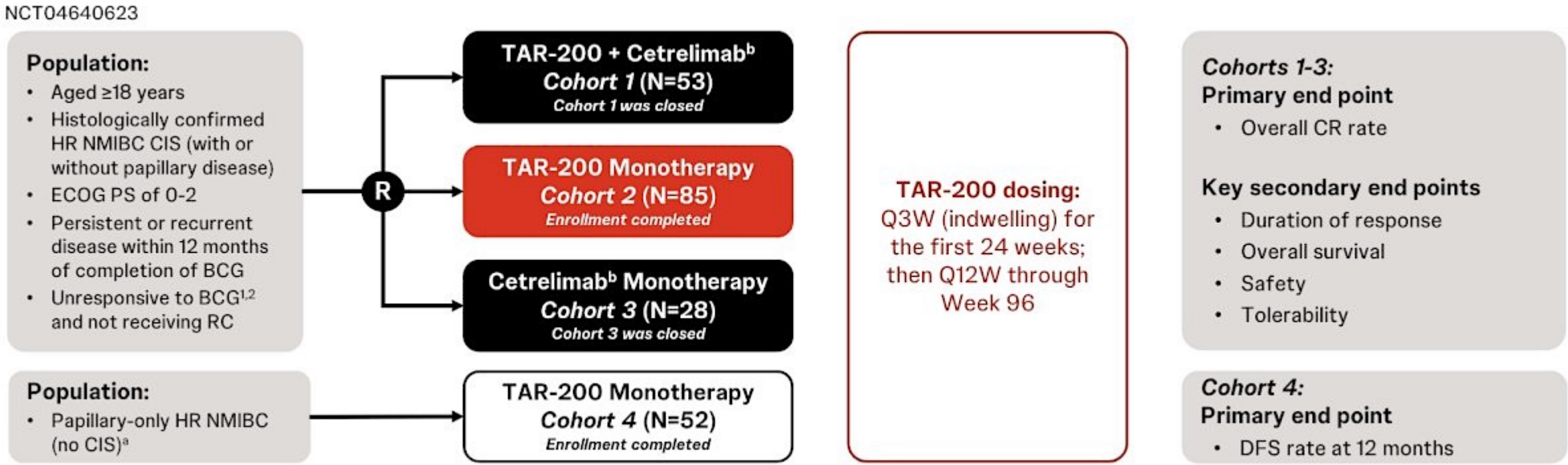




- High CR rate 83% with CIS NMIBC
- Onset of response rapid
  - 98% CRs observed at first assessment on week 12

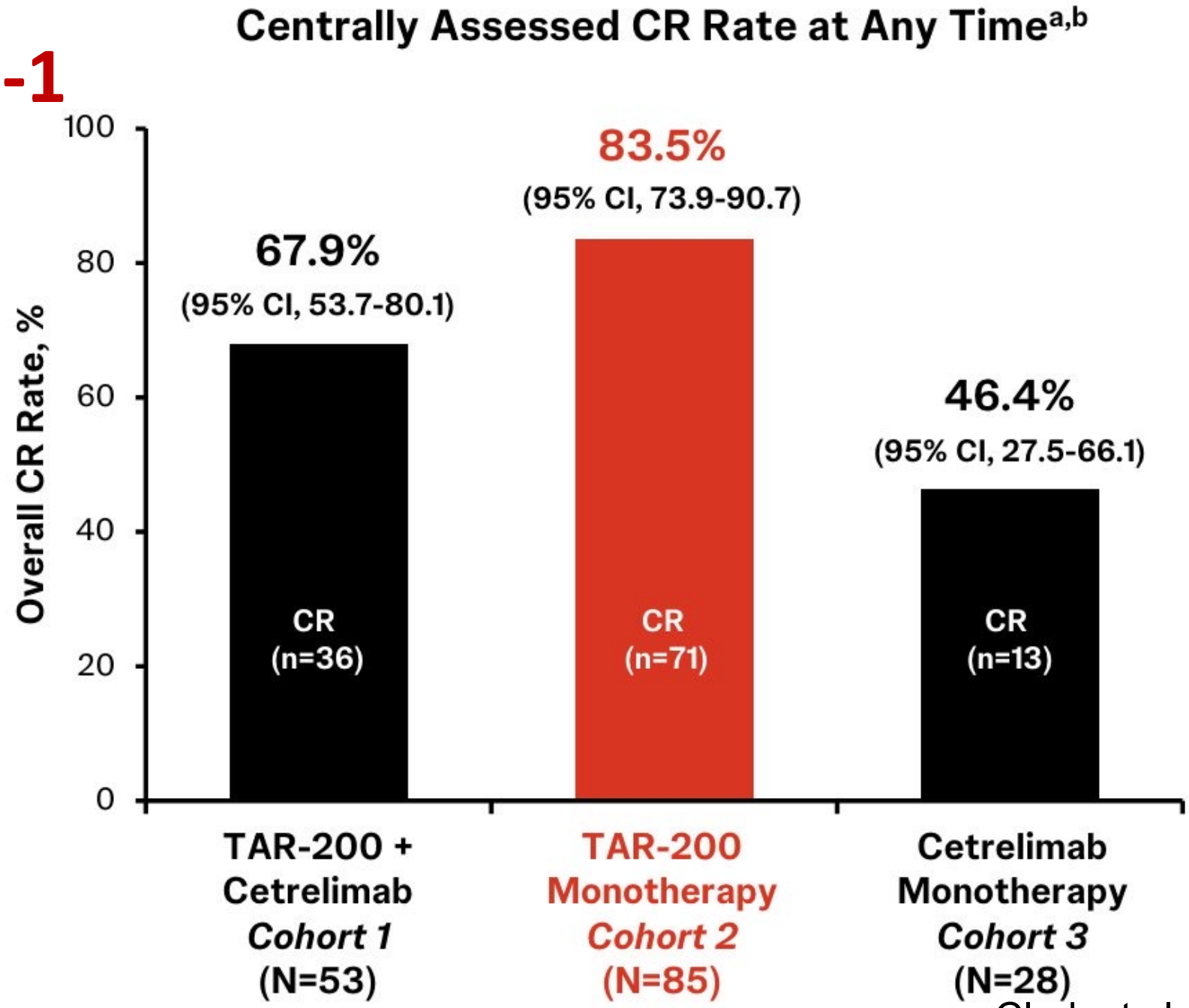
Jacob et al. AUA 2024

TAR-200 ± Cetrelimab and Cetrelimab Alone in BCG-Unresponsive High-Risk NMIBC: Updated Results from SunRISe-1



Clark et al. SESAUA 2025

SunRISe-1



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SunRISe-1

	TAR-200 + Cetrelimab *Cohort 1* (N=53)	TAR-200 Monotherapy *Cohort 2* (N=85)	Cetrelimab Monotherapy *Cohort 3* (N=28)
Estimated 12-month CR rate[c], % (95% CI)	**56.7** (41.2-69.6)	**57.4** (40.6-71.0)	**22.8** (8.6-41.1)
Estimated 12-month DOR rate[c], % (95% CI)	**75.9** (57.5-87.2)	**65.7** (45.2-80.1)	**48.5** (17.9-73.7)
Median follow-up in responders, months (range)	**21.8** (9.2-35.9)	**9.2** (3.7-36.6)	**18.2** (11.3-33.1)
Patients remaining in response, % (n/N)	**75.0** (27/36)	**81.6** (58/71)	**53.8** (7/13)

Clark et al. SESAUA 2025

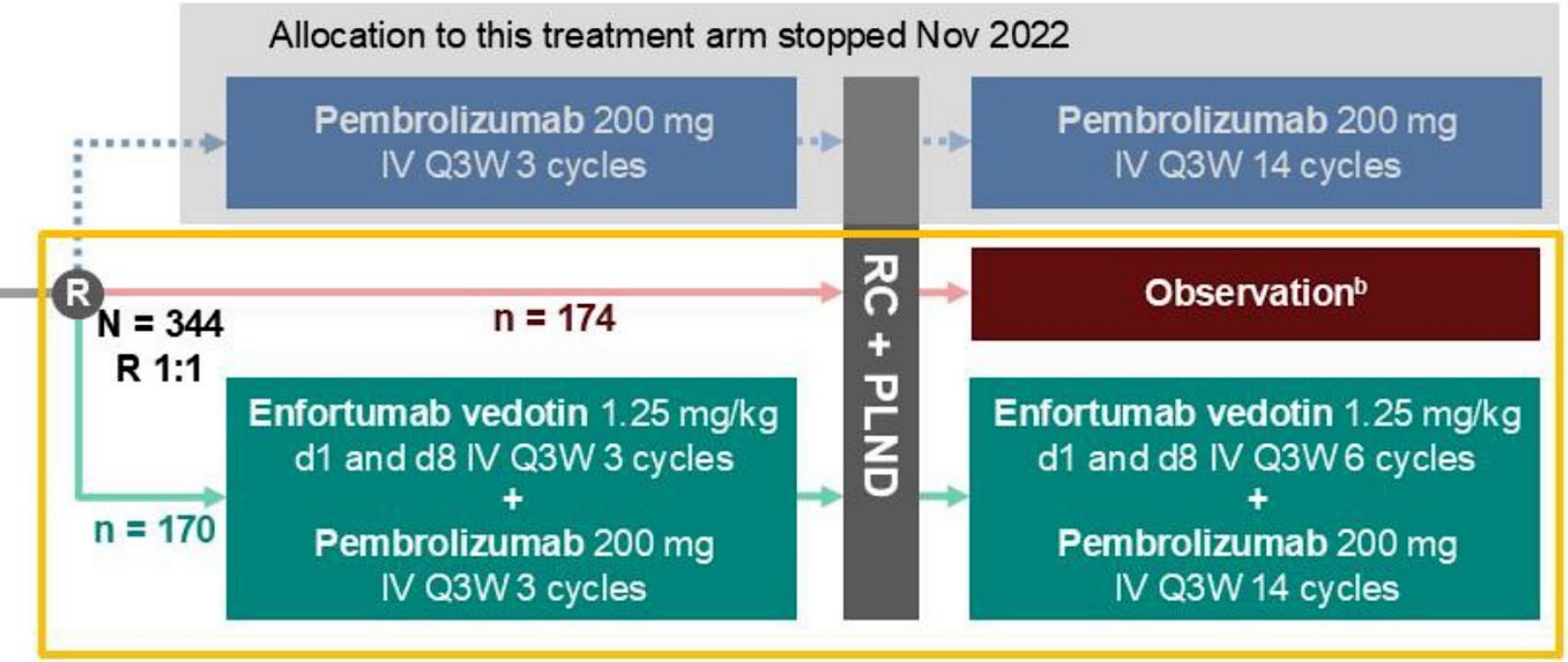
KEYNOTE-905/EV-303 Study (NCT03924895)

Key Eligibility Criteria

- Adults with MIBC
- Clinical stage T2-T4aN0M0 or T1-T4aN1M0 by central assessment
- ≥50% Urothelial histology
- Cisplatin-ineligible per Galsky criteria[a] or cisplatin-declining
- ECOG PS 0-2

Stratification Factors

- Cisplatin ineligibility (ineligible vs. eligible but declining)
- Clinical stage (T2N0 vs. T3/T4aN0 vs. T1-4aN1)
- Region (US vs. EU vs. Most of World)



Primary endpoint: Event-free survival (EFS) by BICR
Key secondary endpoints: OS and pathological complete response (pCR; pT0N0, i.e. absence of viable tumor in examined tissue from surgery) by central pathologist review
Other secondary endpoints include: Safety
Exploratory endpoints include: EFS by pCR status

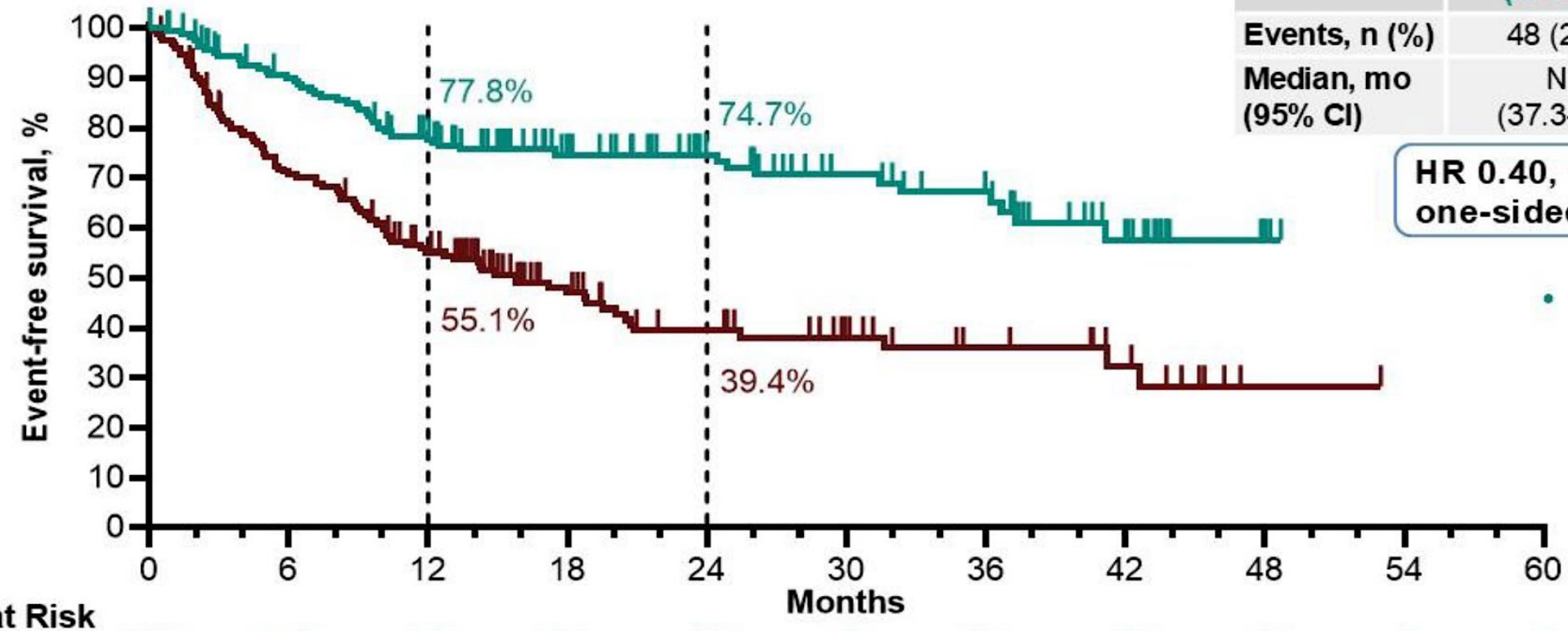
BICR, blinded independent central review; IV, intravenous; Q3W, every 3 weeks. [a]Protocol-defined as having ≥1 of the following: impaired renal function (creatinine clearance 30–59 ml/min), ECOG PS 2, gr ≥2 audiometric hearing loss, or NYHA class III heart failure; [b]As of Nov 2022, adjuvant nivolumab was permitted when clinically indicated and regionally available.

Primary Endpoint: EFS[a] by BICR

ITT Population

	EV + pembro (N = 170)	Control (N = 174)
Events, n (%)	48 (28.2)	95 (54.6)
Median, mo (95% CI)	NR (37.3–NR)	15.7 (10.3–20.5)

HR 0.40, 95% CI 0.28–0.57, one-sided *P* <.0001*



No. at Risk

EV + pembro	170	140	116	73	56	42	35	16	3	0	0
Control	174	116	84	48	33	22	14	9	1	0	0

- 29/174 pts (16.7%) in the control arm received adjuvant nivolumab as of data cutoff per local guidelines/prescribing information

NR, not reached. * denotes statistical significance (one-sided boundary 0.0097). [a]Time from randomization to first occurrence of: radiographic PD precluding surgery; biopsy-proven residual MIBC (pts who did not undergo surgery); gross residual disease post-surgery or newly detected metastatic disease at surgery; local/distant recurrence post-surgery (imaging or biopsy); or death (any cause). Any new high-risk NMIUC was also considered an event. Pts who did not undergo surgery were considered as having an EFS event if they met criteria for EFS events at any point in time or were censored within ≤16 wks from last dose of neoadjuvant therapy or surgery.

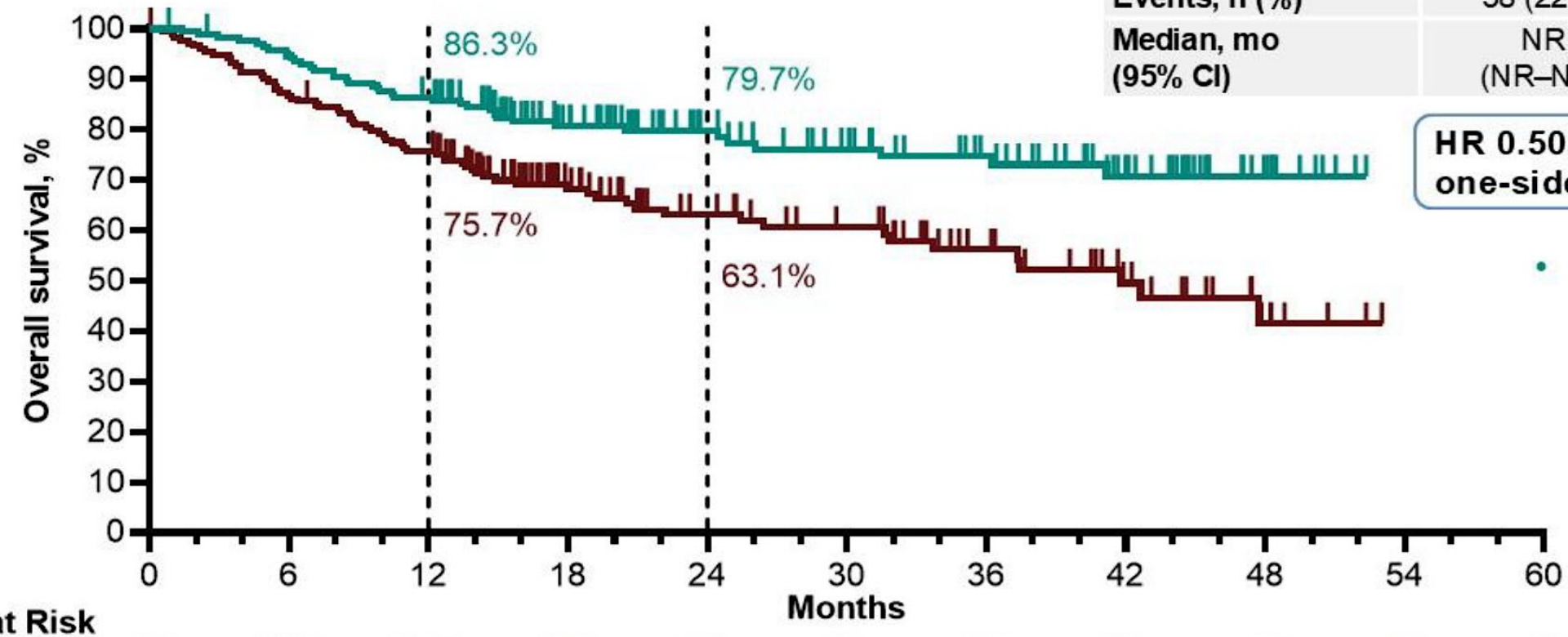
Data cutoff date: 6 June 2025

Key Secondary Endpoint: OS

ITT Population

	EV + pembro (N = 170)	Control (N = 174)
Events, n (%)	38 (22.4)	68 (39.1)
Median, mo (95% CI)	NR (NR–NR)	41.7 (31.8–NR)

HR 0.50, 95% CI 0.33–0.74, one-sided *P* =.0002*



No. at Risk

EV + pembro	170	159	144	94	68	56	45	28	10	0	0
Control	174	150	130	75	54	45	30	18	6	0	0

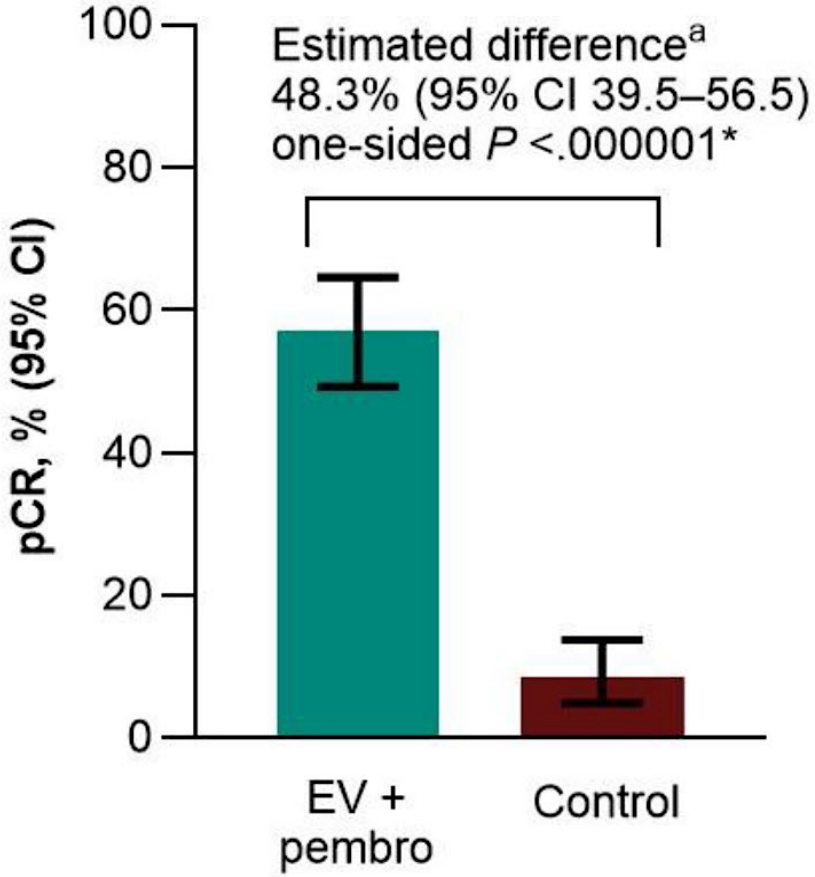
- 8/170 pts (4.7%) in the EV + pembro arm and 46/174 (26.4%) in the control arm received subsequent therapy for recurrent/metastatic disease

NR, not reached. * denotes statistical significance (one-sided boundary 0.00488).

Data cutoff date: 6 June 2025

Key Secondary Endpoint: pCR by Central Pathology Review

ITT Population



	EV + pembro (N = 170)	Control (N = 174)
pCR, n	97	15
pCR rate, % (95% CI)	57.1 (49.3–64.6)	8.6 (4.9–13.8)

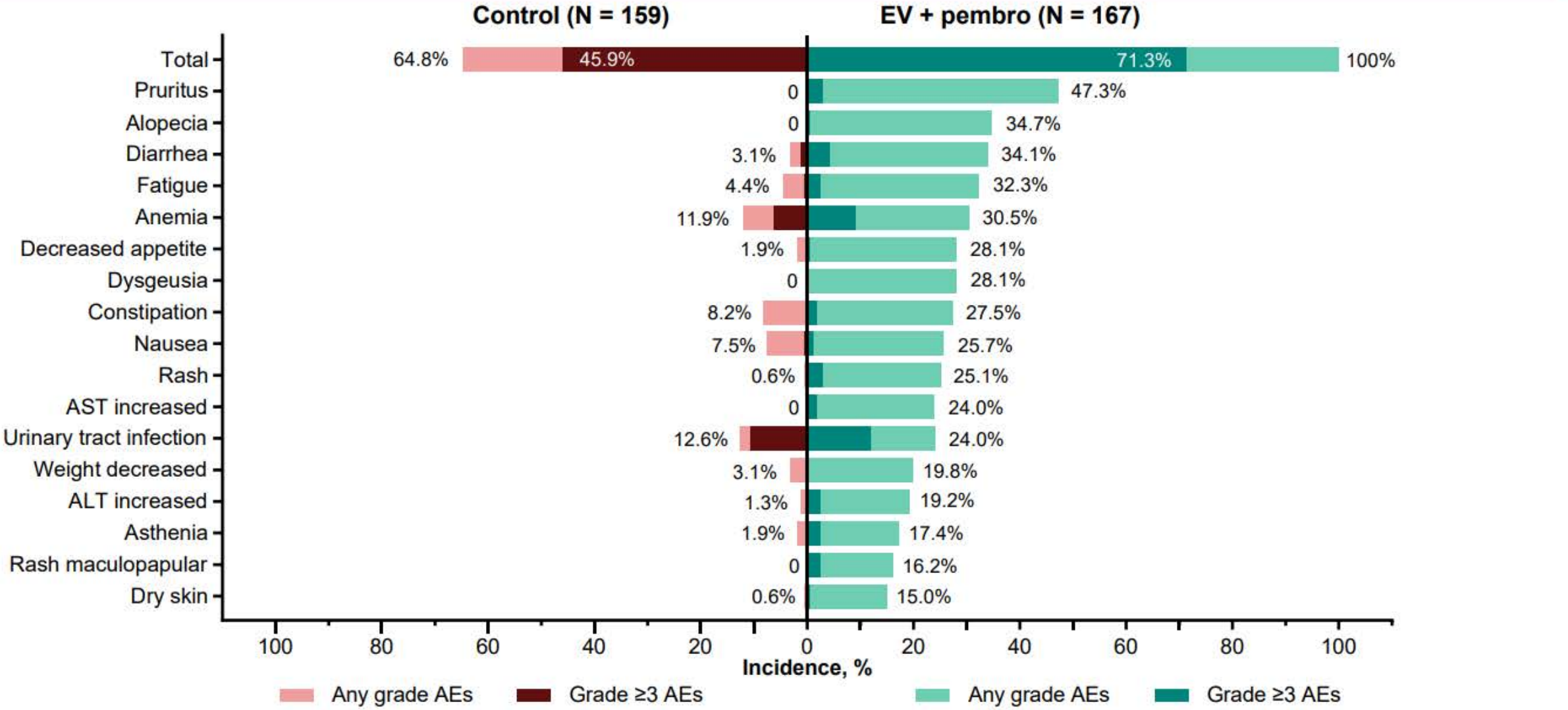
- **pCR:** absence of viable tumor (pT0N0) in examined tissue from RC + PLND
- Pts who did not undergo surgery, including those with clinical complete response after neoadjuvant therapy, were considered non-responders

* denotes statistical significance (one-sided boundary 0.00025).
[a]Based on stratified Miettinen and Nurminen method.

Data cutoff date: 6 June 2025

Common TEAEs[a] (Incidence ≥15%), All Phases of Treatment

Safety Analysis Population

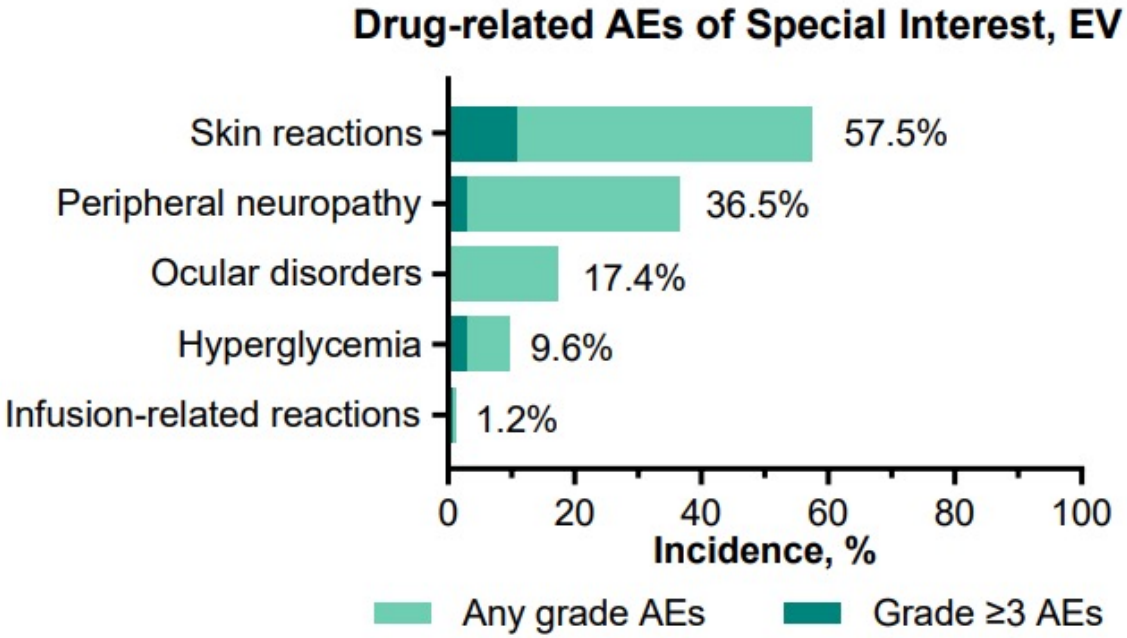


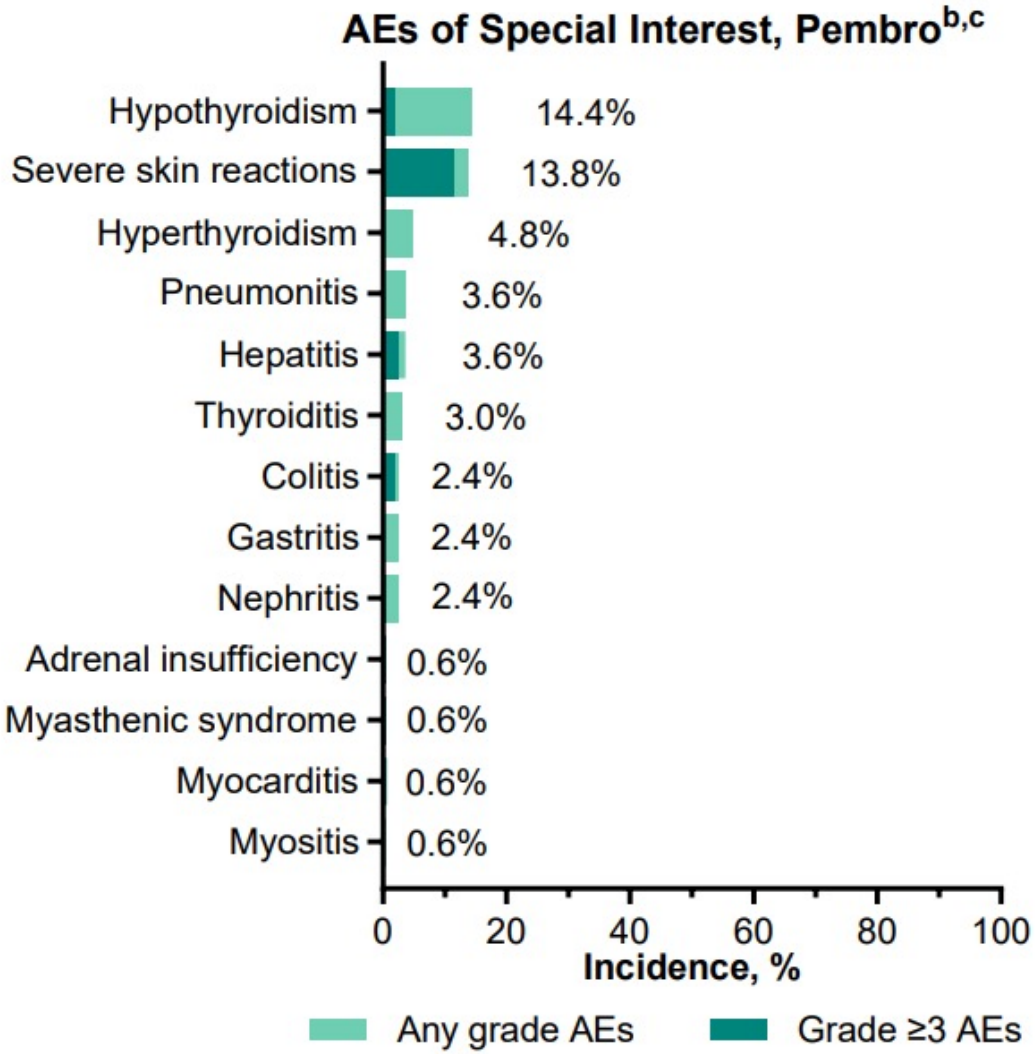
[a]Collected up to 30 days after cessation of study treatment.

Data cutoff date: 6 June 2025

AEs of Special Interest[a]

Safety Analysis Population, EV + Pembro Arm



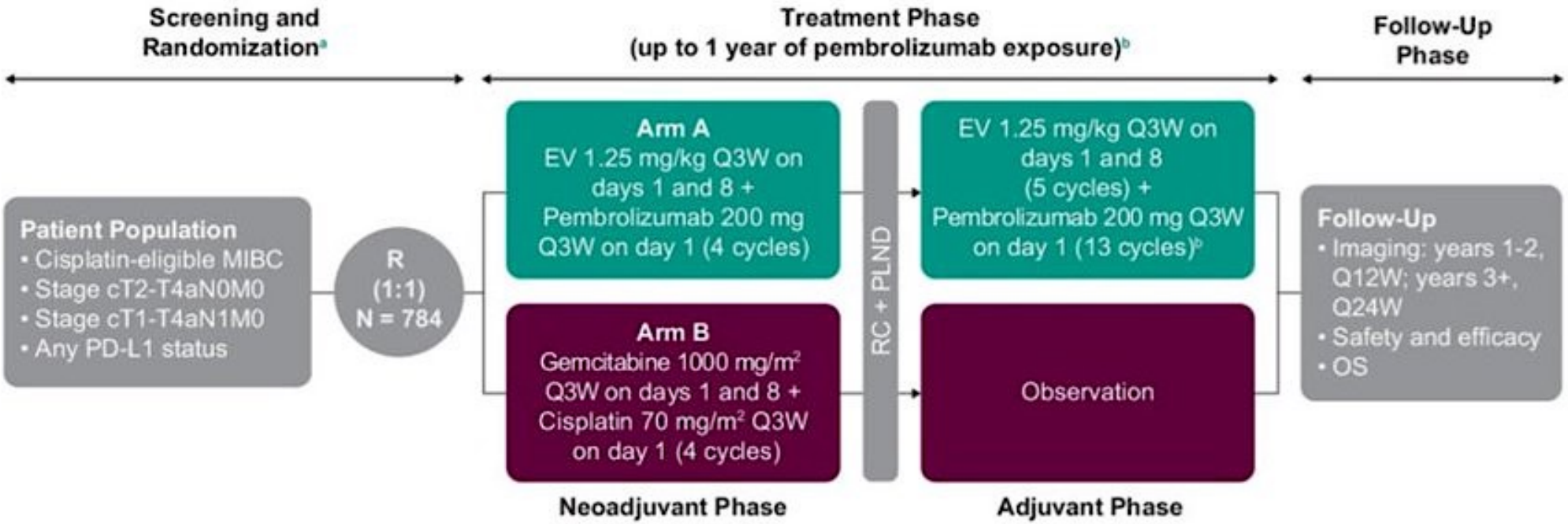


[a]Based on separate prespecified lists of preferred terms (grouped) of known risks associated with EV and pembro treatment. [b]Considered regardless of attribution to study treatment by the investigator. [c]Infusion reactions, reported separately, occurred in 1 pt (0.6%); no grade ≥3 infusion reactions occurred.

Data cutoff date: 6 June 2025

Galsky et al. ASCO GU 2026

EV-304



AE, adverse event; BICR, blinded independent central review; CT, computed tomography; MOW, most of world; MRI, magnetic resonance imaging; Q3W, every 3 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; R, randomization.

[a]All patients will undergo baseline imaging studies (CT or MRI) for clinical staging (evaluated by BICR before randomization) and central pathology confirmation for pathologic stage pT2-T4a or pT1 (only if N1), urothelial histology, and PD-L1 expression.

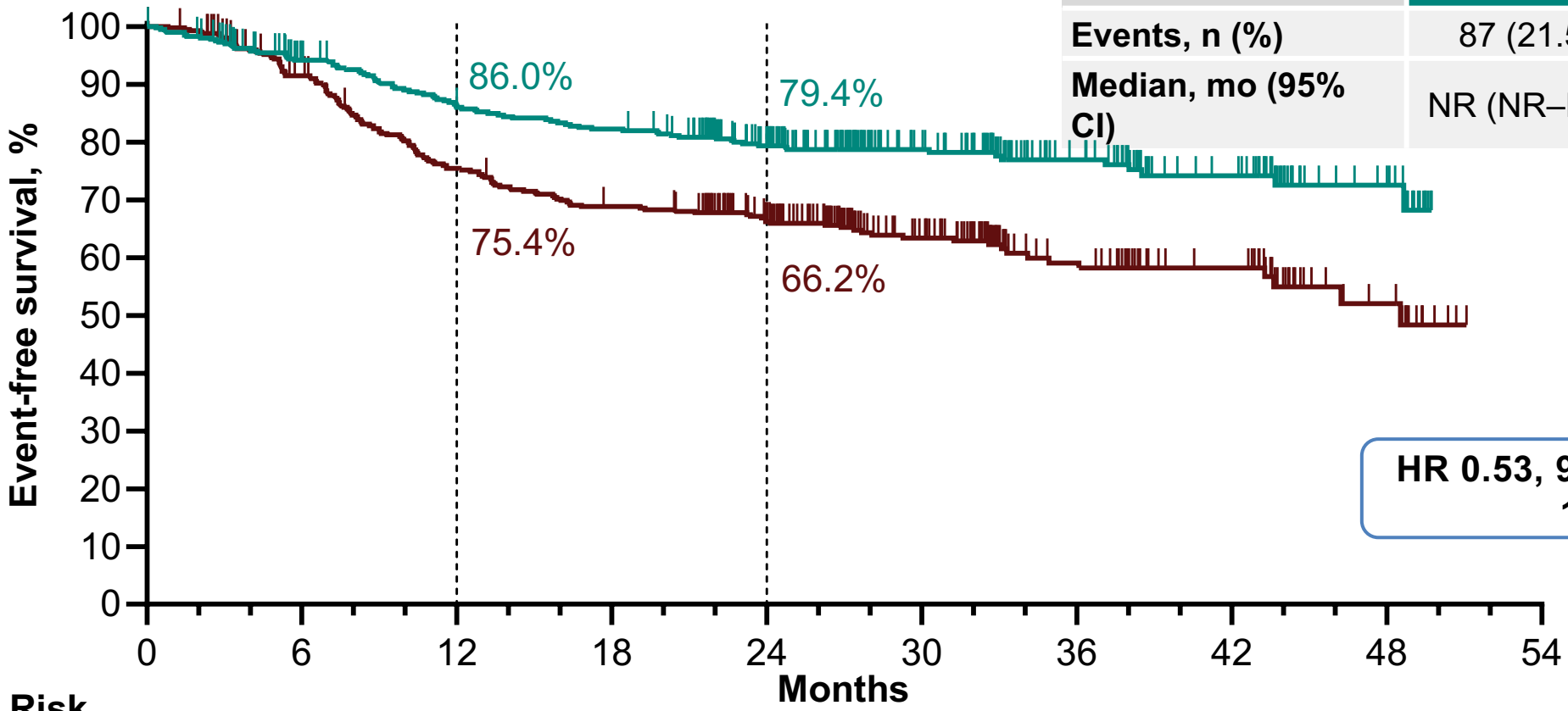
[b]Until unacceptable AEs, intercurrent illness preventing further treatment administration, or investigator or patient decision to withdraw.

[c]CPS is the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Primary Endpoint: EFS by BICR

ITT Population

	EV + pembro N = 405	Cis + gem N = 403
Events, n (%)	87 (21.5)	146 (36.2)
Median, mo (95% CI)	NR (NR–NR)	48.5 (43.3–NR)



HR 0.53, 95% CI 0.41–0.70, 1-sided *P* <.0001*

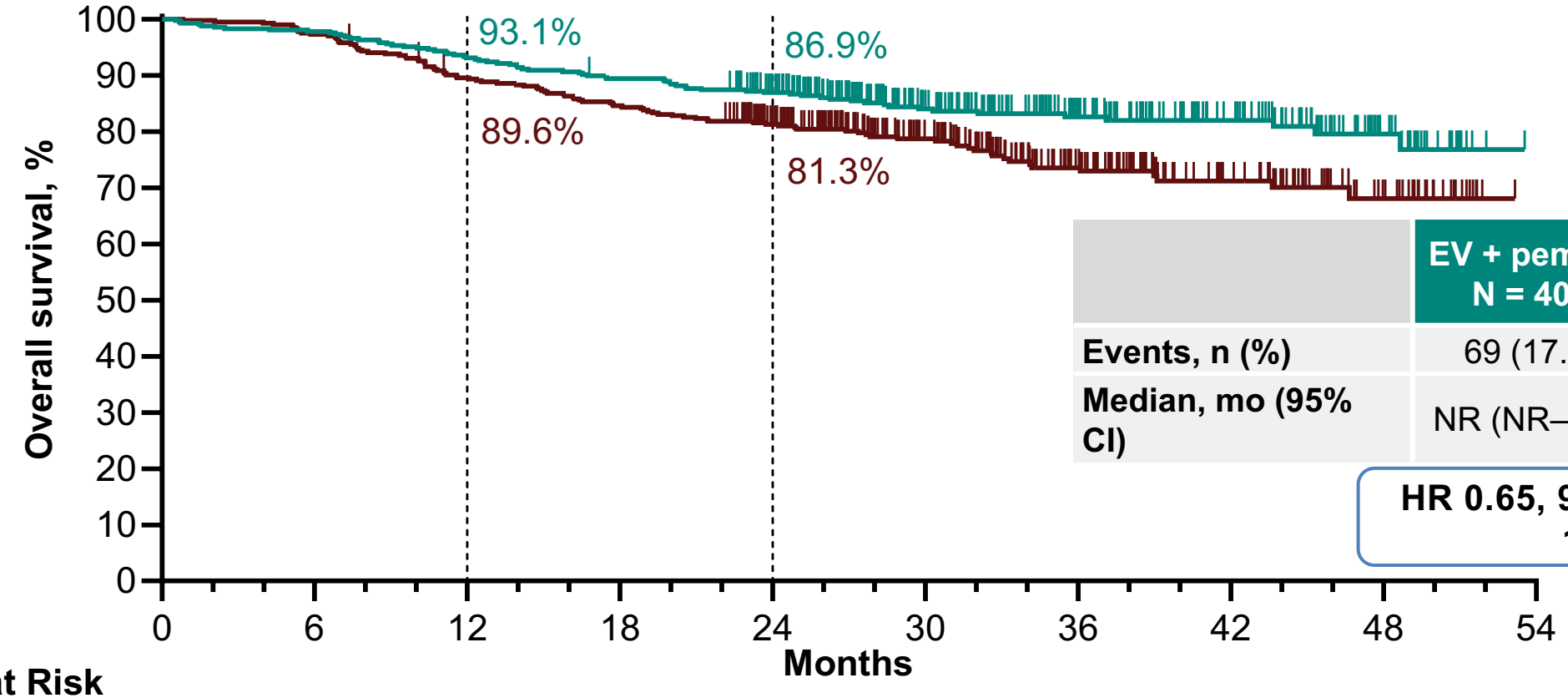
No. at Risk

EV + pembro	405	351	317	303	257	154	100	63	23	0
Cis + gem	403	350	286	259	216	131	70	45	16	0

NR, not reached. * denotes statistical significance (one-sided boundary 0.0082).

Data cutoff date: 27 October 2025

Key Secondary Endpoint: OS
ITT Population



	EV + pembro N = 405	Cis + gem N = 403
Events, n (%)	69 (17.0)	99 (24.6)
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

HR 0.65, 95% CI 0.48–0.89, 1-sided *P* =.0029*

No. at Risk

EV + pembro	405	396	377	361	325	215	142	90	34	0
Cis + gem	403	392	358	338	295	201	119	67	29	0

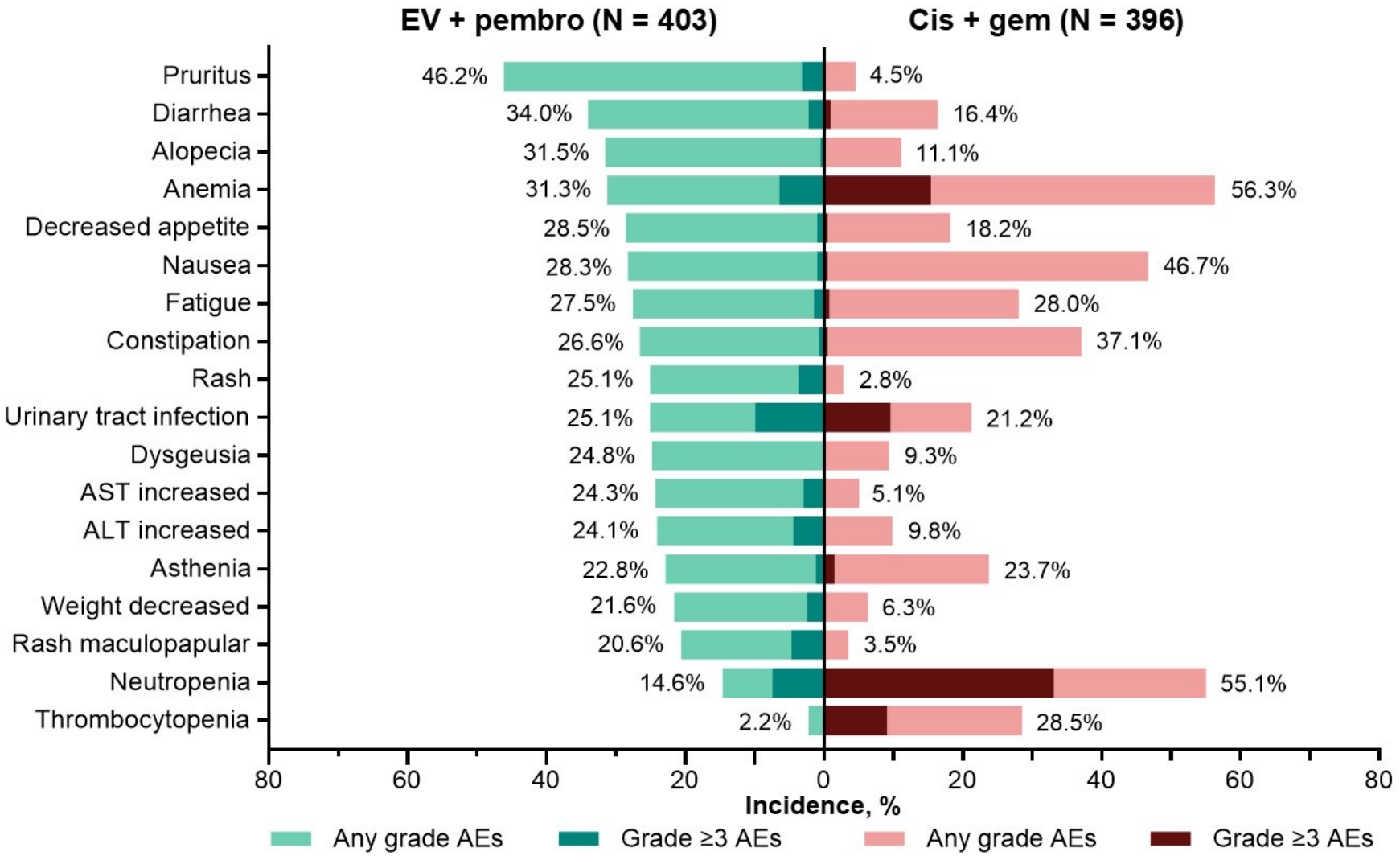
- In total, 44/87 (50.6%) of pts with an EFS event in the EV + pembro arm and 86/146 (58.9%) of pts with an EFS event in the cis + gem arm received any subsequent systemic therapy

NR, not reached. * denotes statistical significance (one-sided boundary 0.0038).

Data cutoff date: 27 October 2025

Common TEAEs[a] (Incidence ≥20% in Either Arm)

Safety Analysis Population, All Phases of Treatment

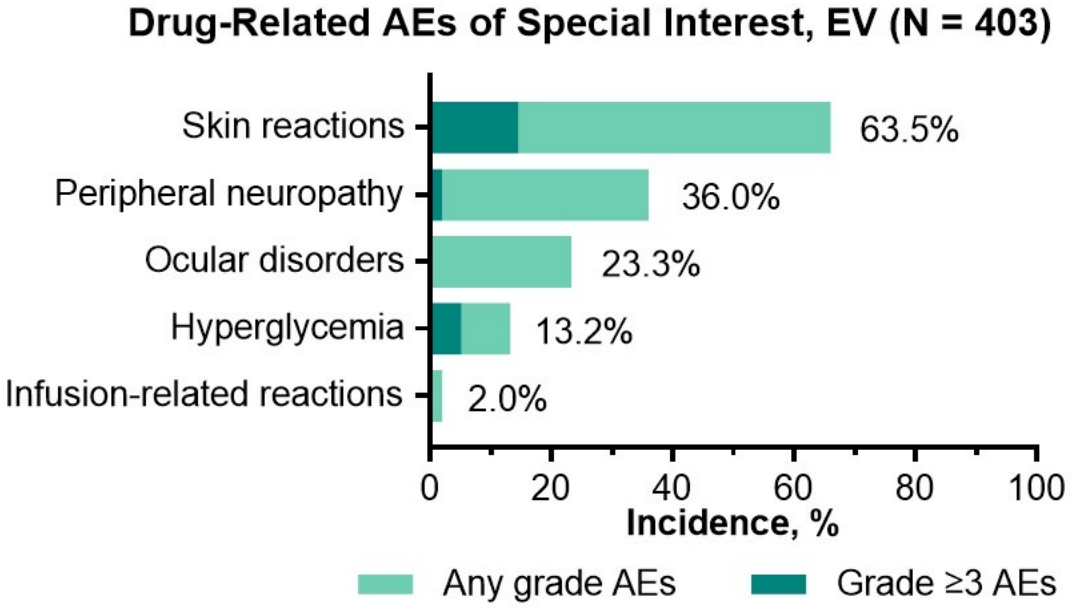


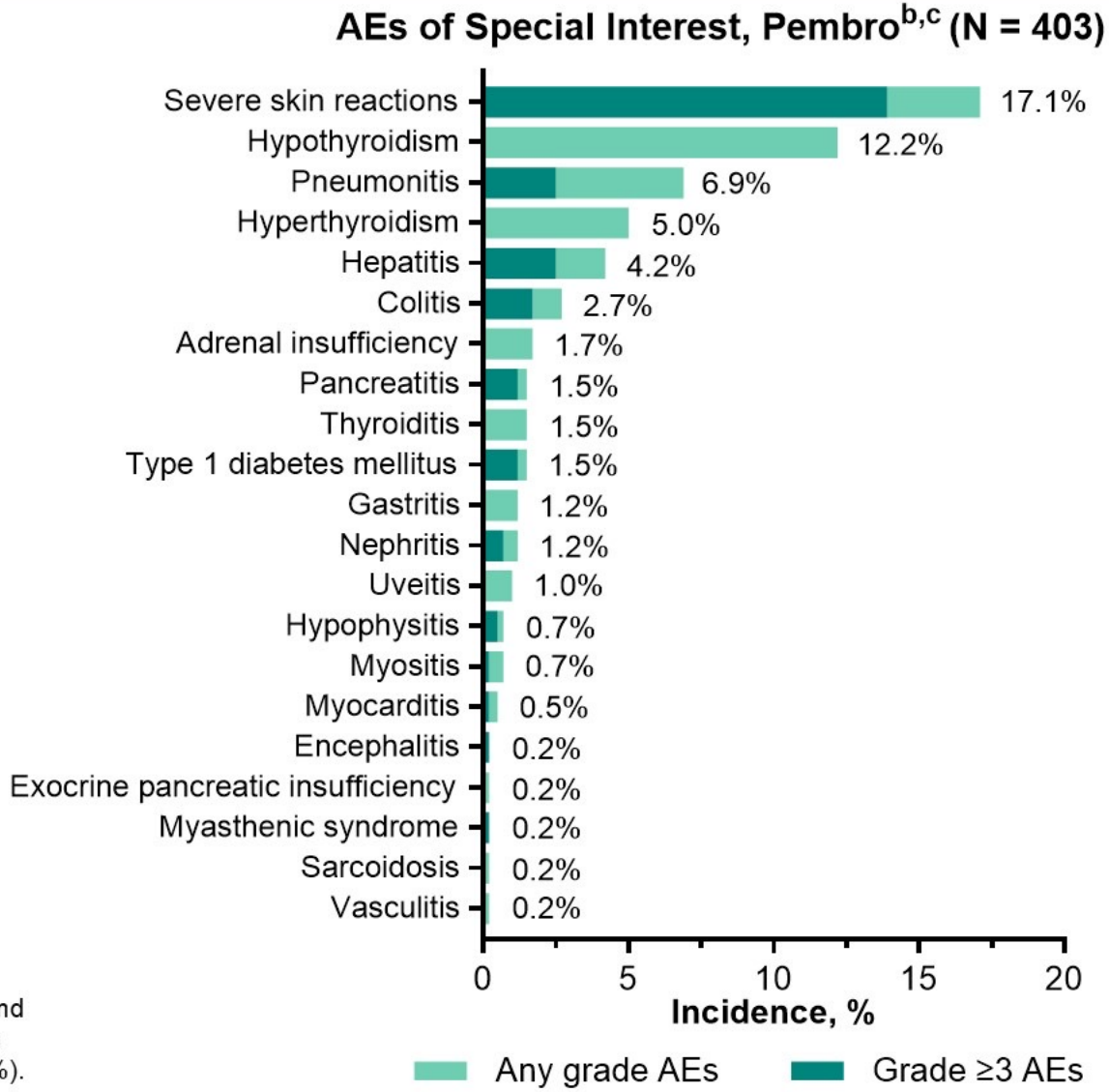
[a]Collected up to 30 days after cessation of study treatment (90 days for serious AEs); EV + pembro reporting window included neoadjuvant, surgery, and adjuvant phases, cis + gem reporting window included neoadjuvant and surgery phases.

Data cutoff date: 27 October 2025

AEs of Special Interest[a]

Safety Analysis Population, EV + Pembro Arm





[a]Based on separate prespecified lists of preferred terms (grouped) of known risks associated with EV and pembro treatment. [b]Considered regardless of attribution to study treatment by the investigator. [c]Infusion reactions, reported separately, occurred in 12 pt (3.0%); grade ≥3 infusion reactions occurred in 3 (0.7%).
Data cutoff date: 27 October 2025

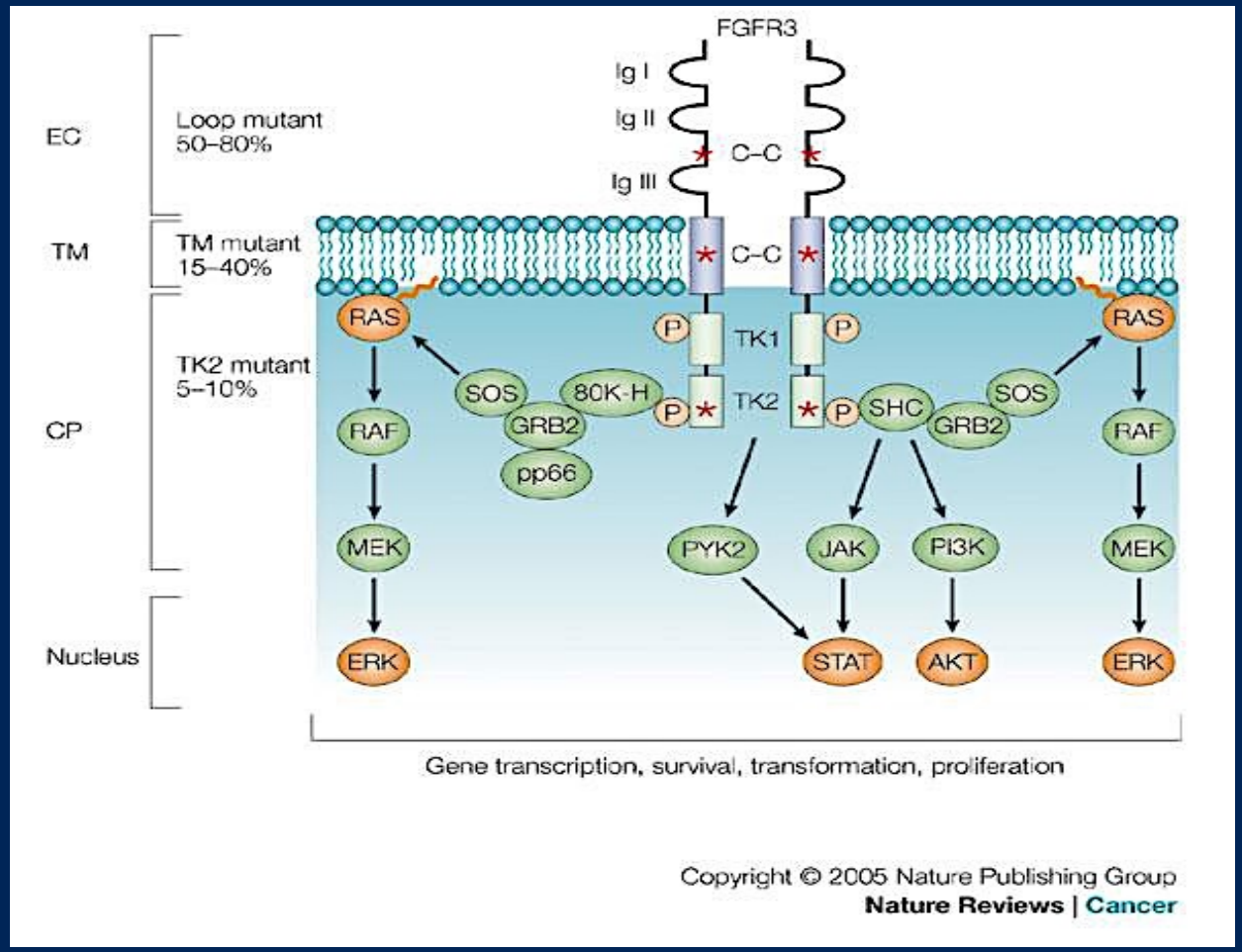
Biomarker Testing in Metastatic Urothelial Cancer

- 761 patients(pts)received post platinum therapy from 4/1/2019 to 9/1/2021
- 343 pts (41%) underwent FGFR testing
- 305 pts had tissue-based testing and 74 had blood-based testing
  - 71 pts (20.7%) had susceptible FGFR alterations
  - 30 pts (30%) received Erdafitinib

Nimgaonkar et al *JAMA Oncol.* 2022;8(7):1070-1072. doi:10.1001/jamaoncol.2022.1167

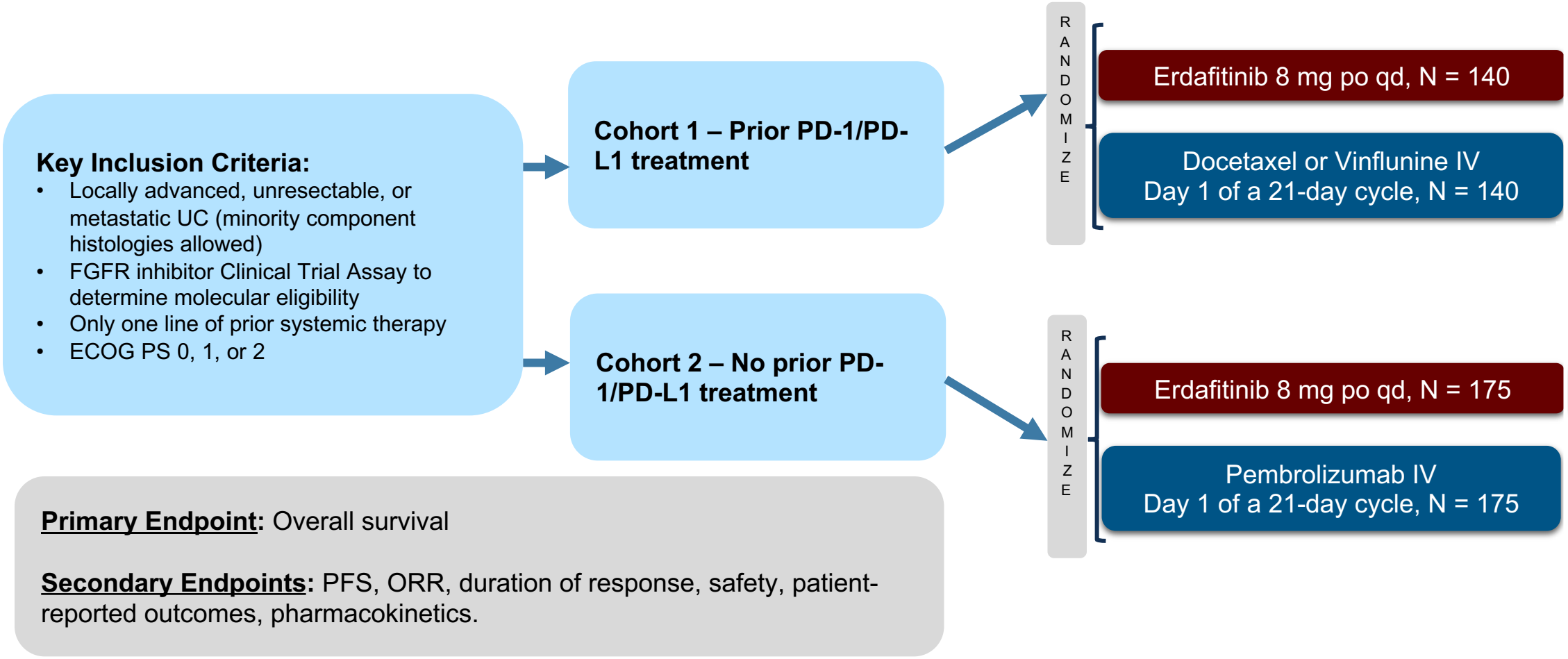
FGFR3—Fibroblast Growth Factor Receptor

- A membrane based TKR involved in cellular proliferation, differentiation, and steroid biosynthesis (*image, right*)[1]
- There are 4 distinct FGFR subtypes
- FGFR mutations and overexpression have been implicated in bladder cancer[2]
- **April 12, 2019** – FDA granted accelerated approval to the FGFR inhibitor erdafitinib for locally advanced/metastatic bladder cancer with a FGFR2 or FGFR3 alteration, that has progressed during or after platinum chemotherapy[3]
- FGFR inhibitors and anti-FGFR ADCs are in ongoing and upcoming trials in advanced UC[4]



1. Wu X-R. *Nat Rev Cancer.* 2005;5:713-725; 2. Turo R, et al. *J Urol.* 2015;193:325-330; 3. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-erdafitinib-metastatic-urothelial-carcinoma; 4. ClinicalTrials.gov.

Phase 3 THOR Trial: Study Design



Loriot Y, et al. *N Engl J Med*. 2023;389(21):1961-1971. NCT03390504.

THOR (Cohort 1): Safety

- 1 treatment-related death in the erdafitinib group (sudden death)
- 11 patients (8.1%) discontinued study treatment with erdafitinib due to treatment-related AEs

AEs occurring in ≥30% (any grade) or ≥5% (grade 3-4) of patients	Erdafitinib (n = 135)	
	Any Grade	Grade 3-4
≥1 treatment-related AE	131 (97.0%)	62 (45.9%)
Hyperphosphatemia	106 (78.5%)	7 (5.2%)
Diarrhea	74 (54.8%)	4 (3.0%)
Stomatitis	62 (45.9%)	11 (8.1%)
Dry mouth	52 (38.5%)	0
PPE syndrome	41 (30.4%)	13 (9.6%)
Onycholysis	31 (23.0%)	8 (5.9%)

AEs of interest	Erdafitinib (n = 135)		Chemotherapy (N = 112)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Nail disorders	90 (66.7%)	15 (11.1%)	6 (5.4%)	0
Skin disorders	74 (54.8%)	16 (11.9%)	14 (12.5%)	0
Eye disorders (excluding central serous retinopathy)	57 (42.2%)	3 (2.2%)	6 (5.4%)	0
Central serous retinopathy	23 (17.0%)	3 (2.2%)	0	0

Loriot Y, et al. *N Engl J Med.* 2023;389(21):1961-1971.

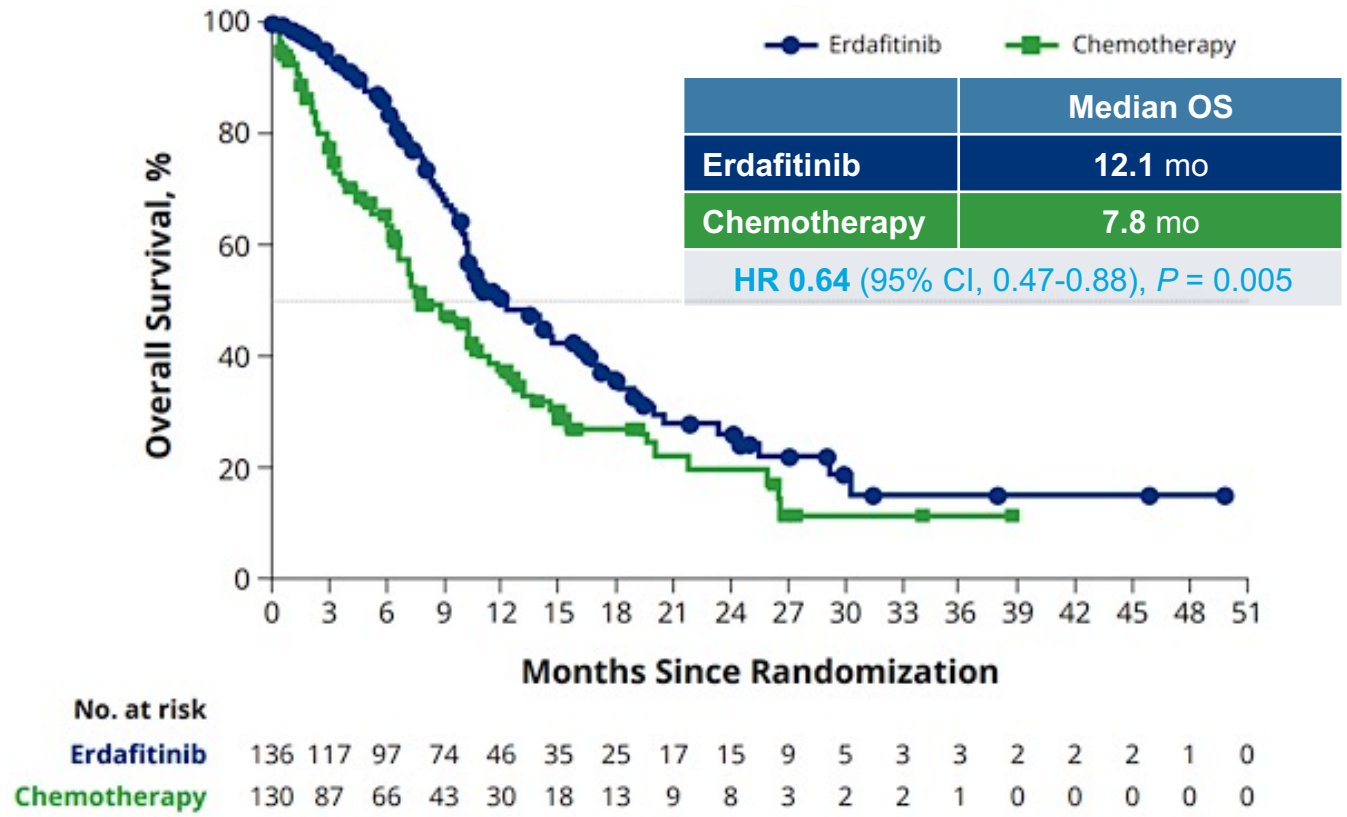
THOR (Cohort 1): Overall Survival

- ~20% of patients with advanced UC have *FGFR* alterations
- Erdafitinib is an oral selective pan-FGFR tyrosine kinase inhibitor

Key eligibility criteria

- Unresectable or metastatic UC
- Progressed on or after ≥1 prior treatment that included an anti–PD-(L)1
- Select *FGFR3/2alt* (mutation/fusion)
- ECOG PS 0-2

Erdafitinib (n = 136)	**Chemo (n = 130)**
8 mg PO once daily; up-titration to 9 mg	Docetaxel or vinflunine every 3 weeks

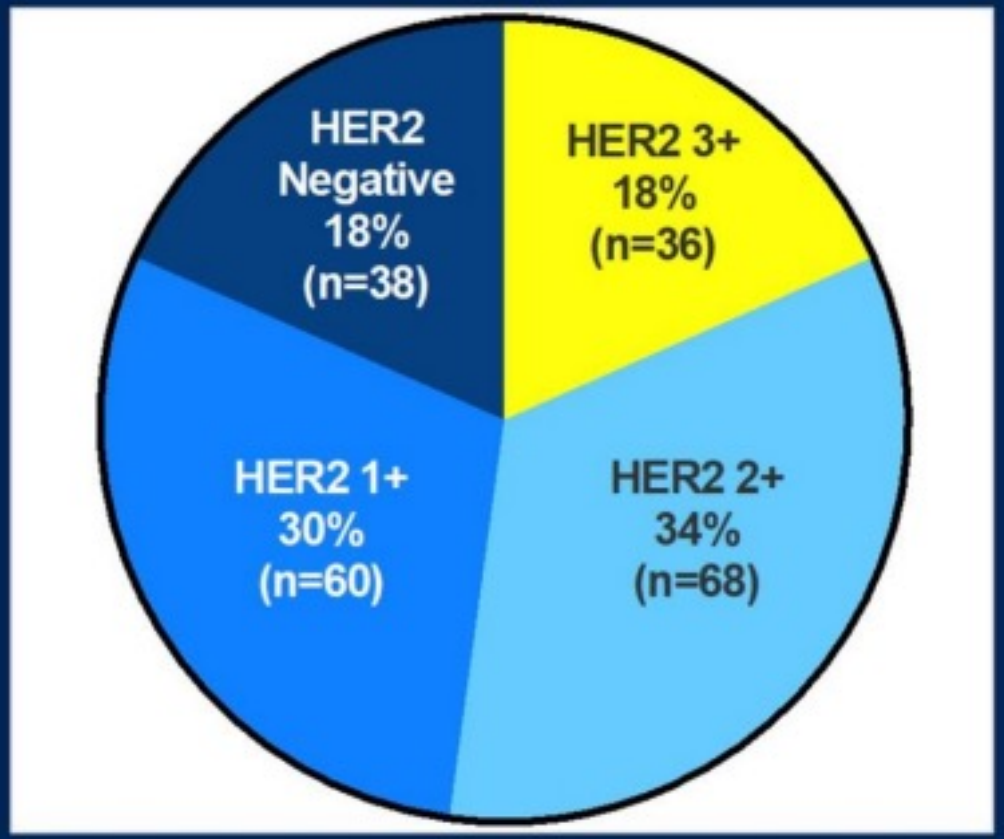


	Median OS
Erdafitinib	**12.1** mo
Chemotherapy	**7.8** mo

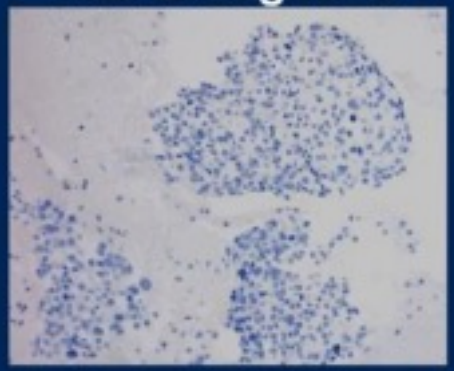
HR 0.64 (95% CI, 0.47-0.88), *P* = 0.005

Loriot Y, et al. *N Engl J Med*. 2023;389(21):1961-1971.

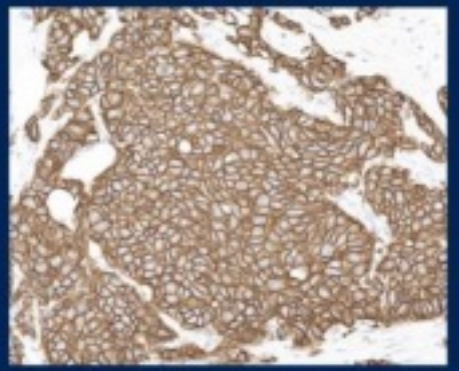
HER2 Expression by IHC



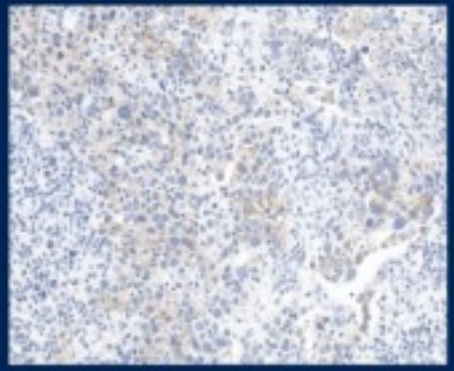
HER2 negative



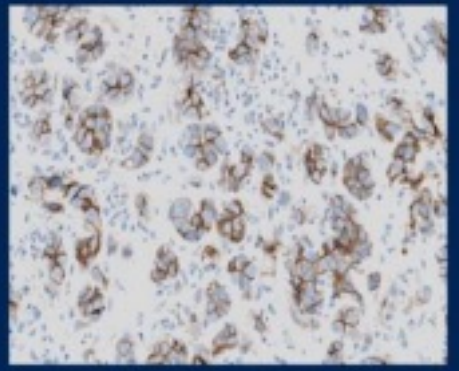
HER2 3+



HER2 1+



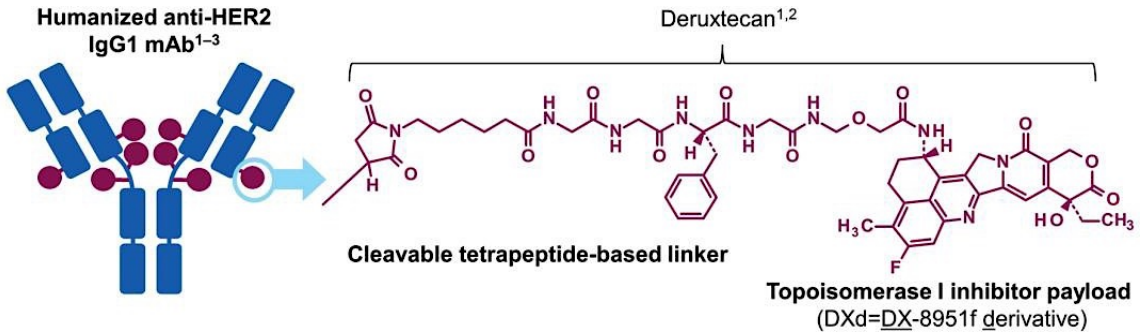
HER2 2+



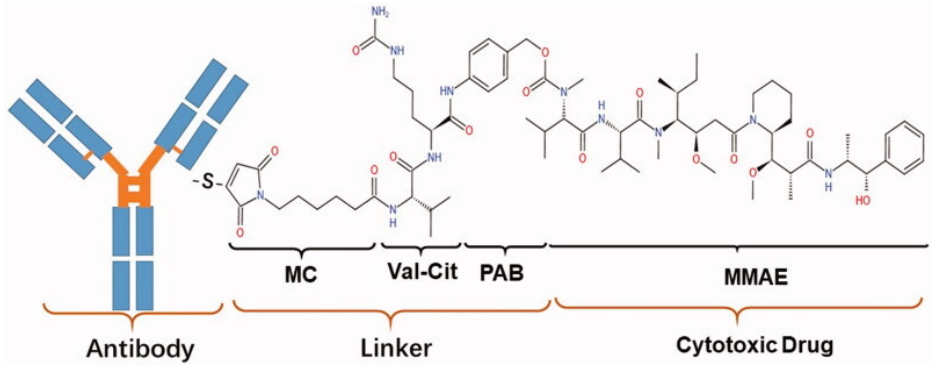
HER2-TARGETED ADCs IN la/mUC

ADC	Target	Linker	Payload	Average DAR	Tumor Types	First Approval Date
Trastuzumab deruxtecan (T-DXd)[1]	HER2	Tetrapeptide-based cleavable	Deruxtecan (topoisomerase I inhibitor)	7-8	Breast cancer, GEJ cancer, NSCLC, Tumor agnostic	Breast cancer: 12/2019 Tumor agnostic: 4/2024
Disitamab vedotin (RC48 or DV)[2]	HER2	Protease cleavable (mc–VC–PABC)	MMAE (microtubule-disrupting agent)	4	Urothelial cancer, GEJ cancer	China: 6/2021 Not yet FDA approved

Trastuzumab deruxtecan (T-DXd)



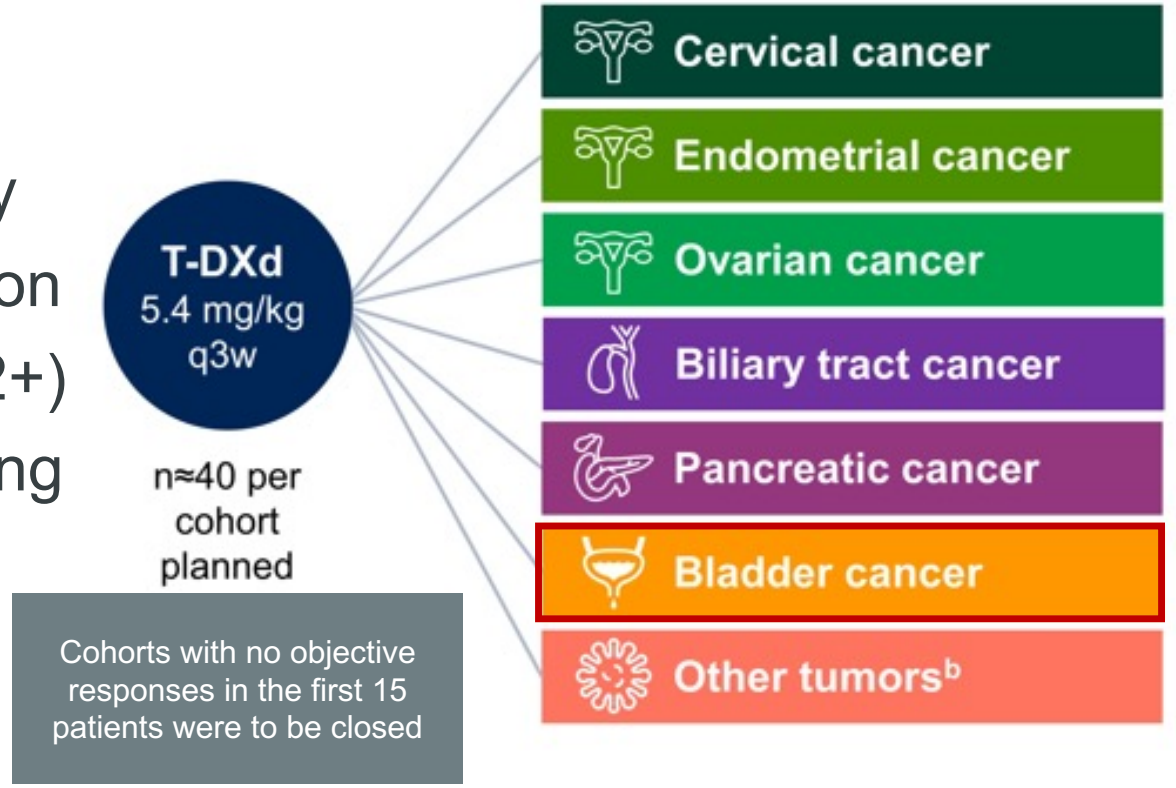
Disitamab vedotin (RC48 or DV)



1. Tarantino P. Nat Rev Clin Oncol. 2023. 2. Shi F. Drug Deliv. 2022. 3. Meric-Bernstam F. ASCO 2023

DESTINY-PanTumor02: Study Design

- Advanced solid tumors not eligible for curative therapy
- 2L patient population
- HER2 (IHC 3+ or 2+)
- Prior HER2-targeting agents allowed
- ECOG PS 0-1



Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

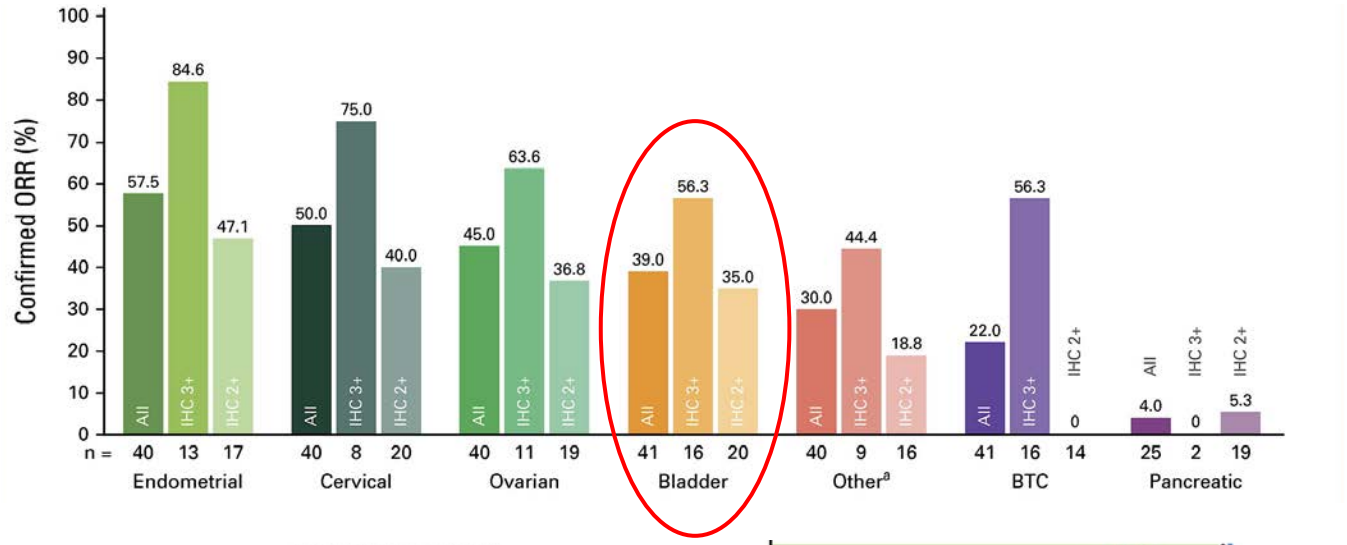
- DOR
- DCR
- PFS
- OS
- Safety

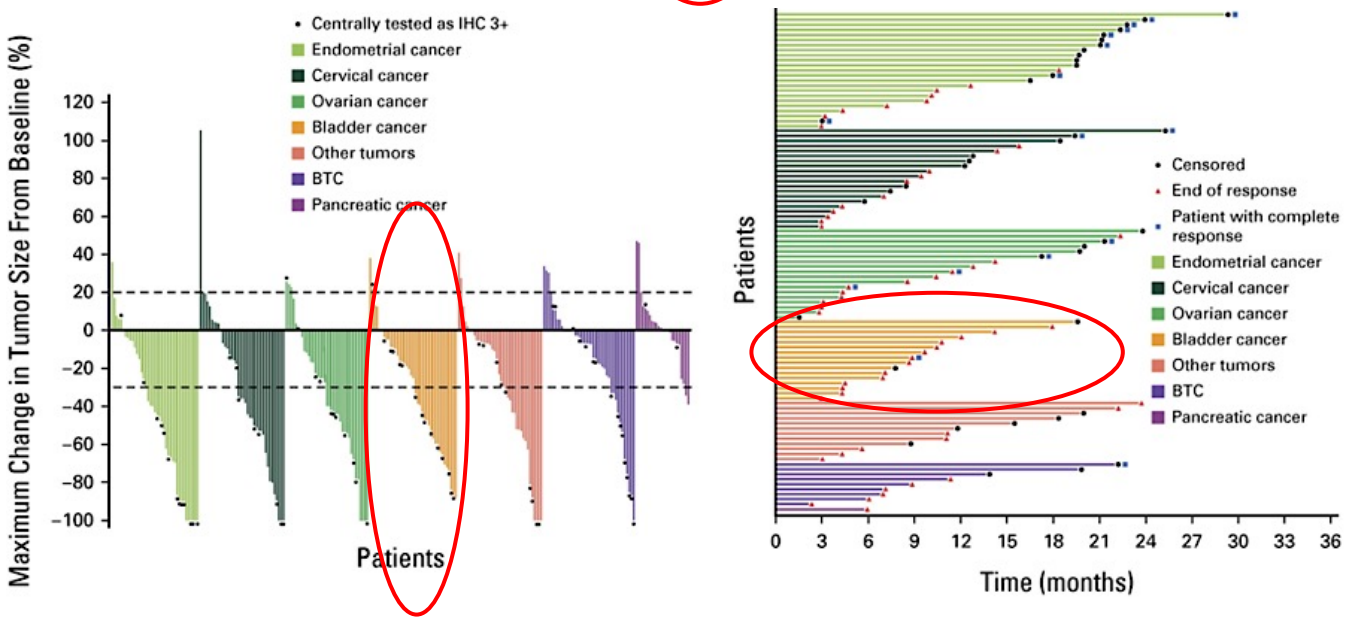
Data cut-off for analysis:

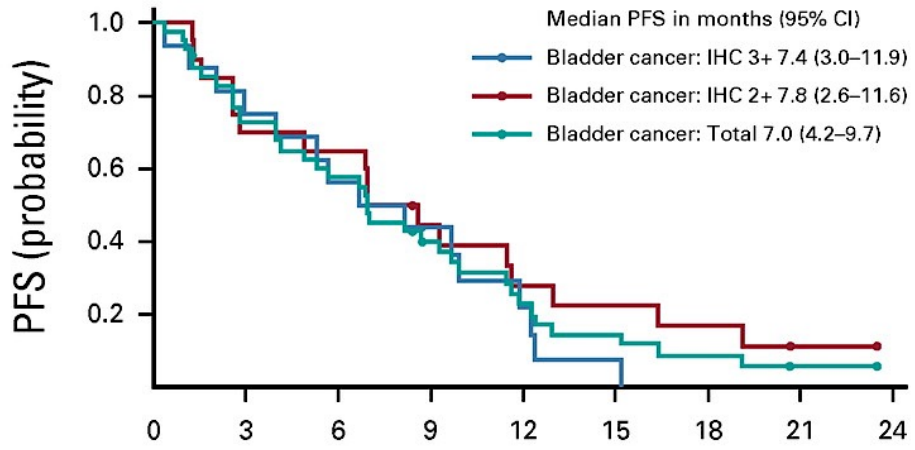
- Nov 16, 2022

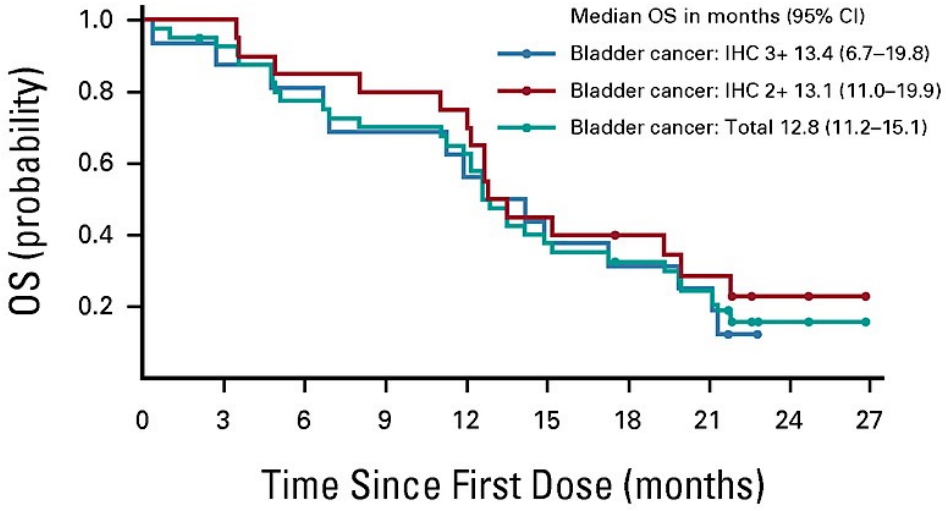
Meric-Bernstam F et al. ASCO 2023; Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

DESTINY-PanTumor02: Efficacy in Bladder Cancer





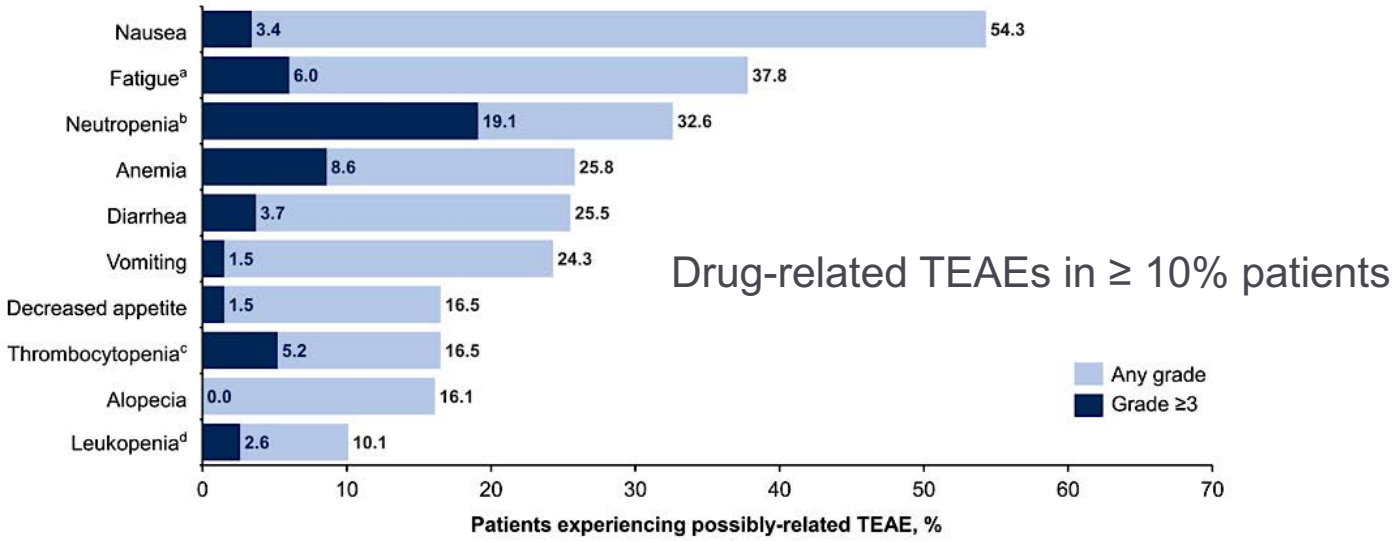




Meric-Bernstam F et al. ASCO 2023; Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

DESTINY-PanTumor02: Safety

n (%) Overall safety summary	All patients (N=267)
Any drug-related TEAEs	225 (84.3)
Drug-related TEAEs Grade ≥3	103 (38.6)
Serious drug-related TEAEs	32 (12.0)
Drug-related TEAEs associated with dose discontinuations	22 (8.2)
Drug-related TEAEs associated with dose interruptions	49 (18.4)
Drug-related TEAEs associated with dose reductions	50 (18.7)
Drug-related TEAEs associated with deaths	2 (0.7)[a]



Drug-related TEAEs in ≥ 10% patients

ILD/pneumonitis adjudicated as T-DXd related	
Grade	All patients, n (%) n = 267
1	6 (2.2)
2	12 (4.5)
3	1 (0.4)
4	0
5	1 (0.4)
Any	20 (7.5)

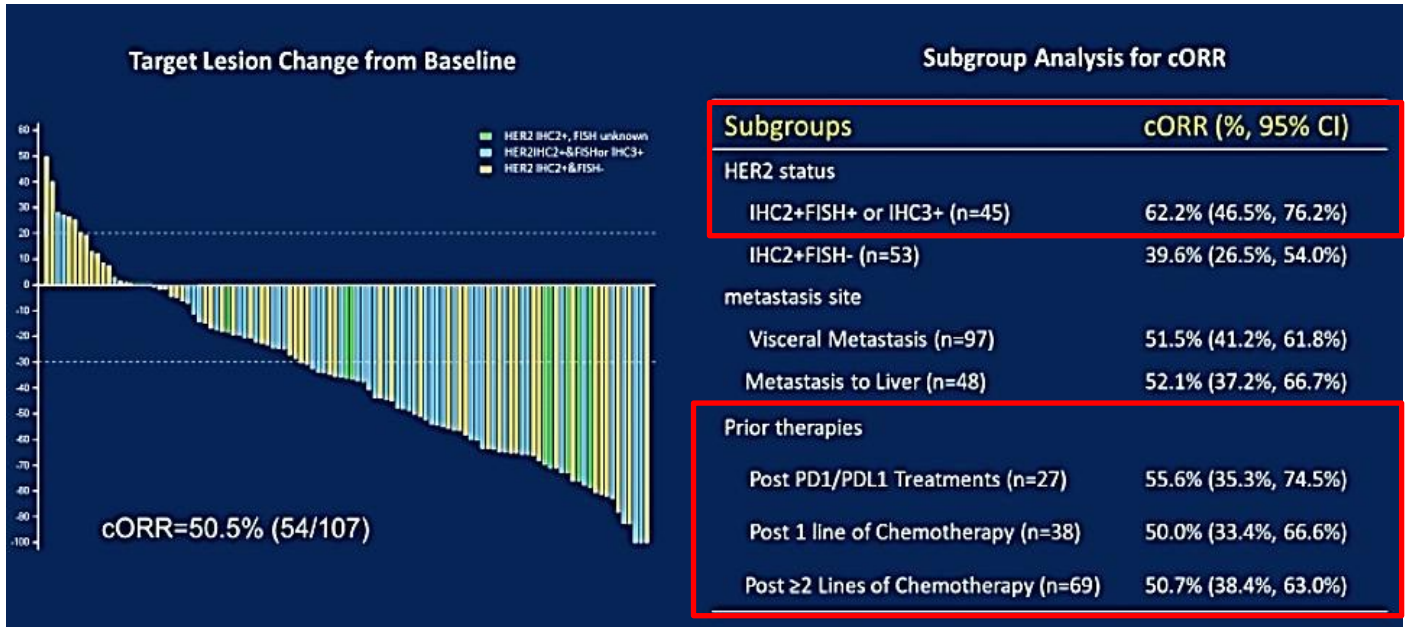
Left ventricular dysfunction	
Grade	All patients, n (%) n = 267
1	1 (0.4)
2	4 (4.5)
3	1 (0.4)
4	0
5	0
Any	7 (2.6)

Meric-Bernstam F et al. ASCO 2023; Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

DISITAMAB VEDOTIN (DV) IN PRE-TREATED la/mUC

Activity in HER2-positive patients (IHC 2+/FISH+ or IHC 3+)

Phase II RC48-C005 & RC48-C009 Trials in China (N=107)[1,2]



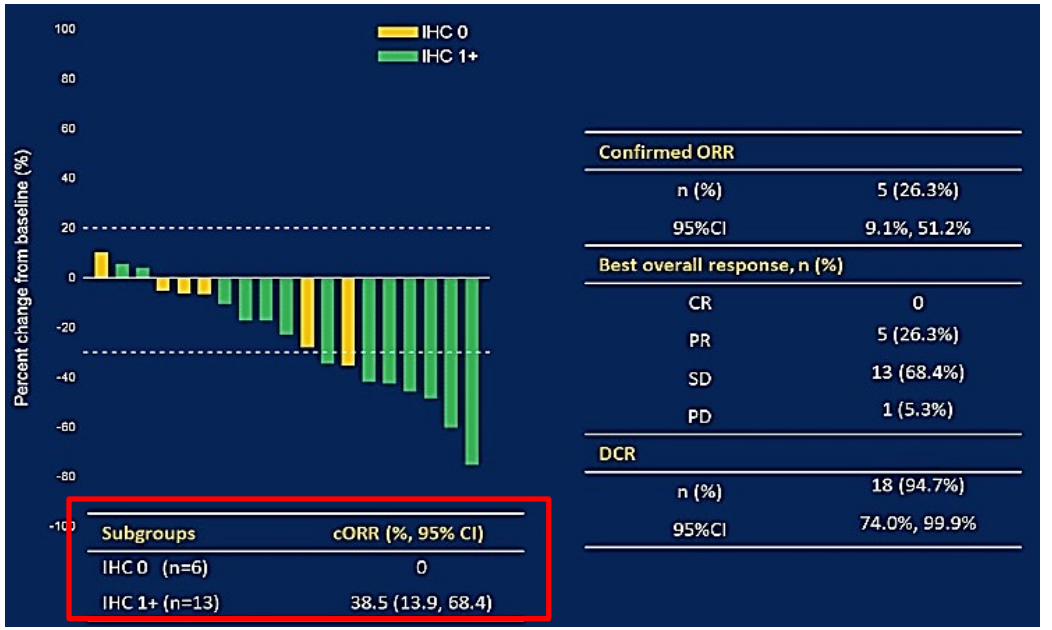
Subgroup Analysis for cORR

Subgroups	cORR (%, 95% CI)
HER2 status	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
metastasis site	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
Prior therapies	
Post PD1/PDL1 Treatments (n=27)	55.6% (35.3%, 74.5%)
Post 1 line of Chemotherapy (n=38)	50.0% (33.4%, 66.6%)
Post ≥2 Lines of Chemotherapy (n=69)	50.7% (38.4%, 63.0%)

mPFS: 5.9 months
mOS: 14.2 months

Activity in HER2-low patients (IHC 0 or 1+)

Phase II RC48-C011 Trial in China (N=19)[3]



Subgroups	cORR (%, 95% CI)
IHC 0 (n=6)	0
IHC 1+ (n=13)	38.5 (13.9, 68.4)

Confirmed ORR	
n (%)	5 (26.3%)
95%CI	9.1%, 51.2%
Best overall response, n (%)	
CR	0
PR	5 (26.3%)
SD	13 (68.4%)
PD	1 (5.3%)
DCR	
n (%)	18 (94.7%)
95%CI	74.0%, 99.9%

mPFS: 5.5 months
mOS: 16.4 months

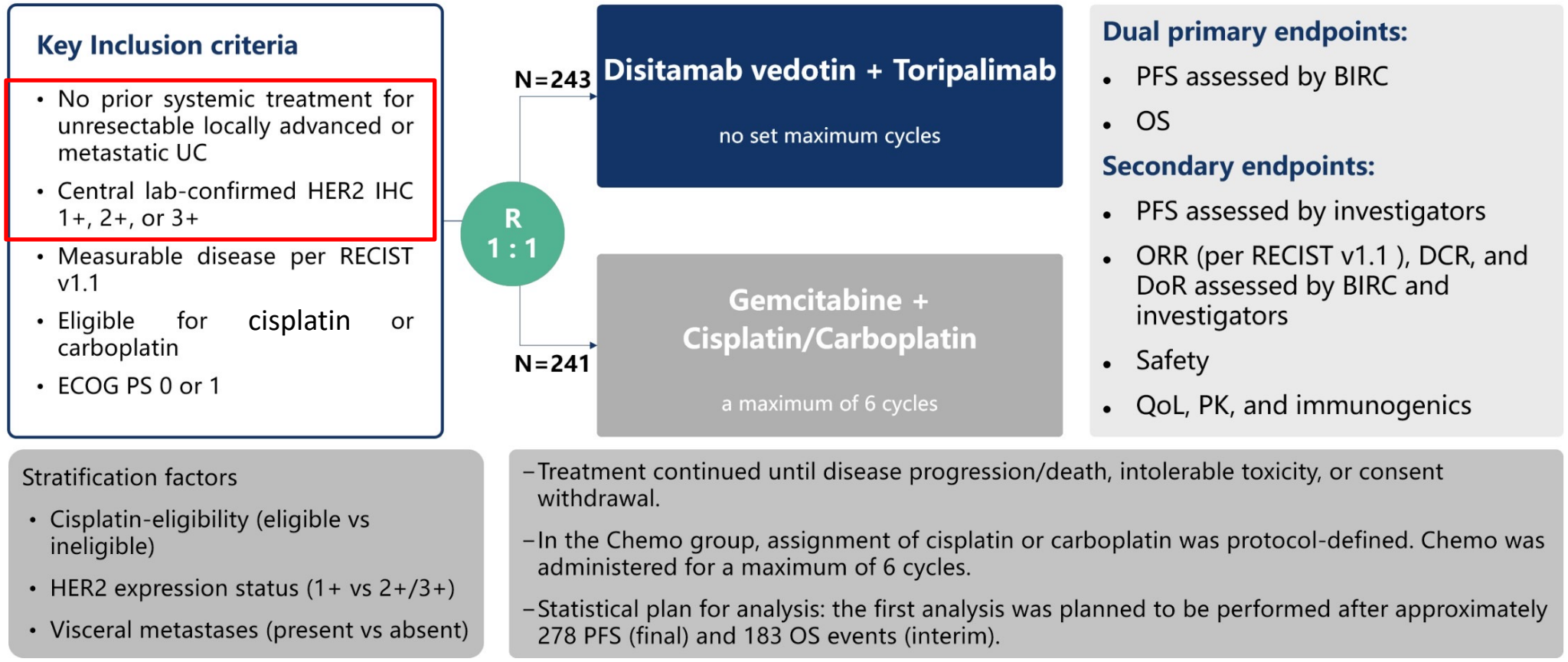
- Promising results from DV trials in China led to breakthrough therapy designation by the FDA in 9/2020
- Phase II & III global registrational studies are accruing (DV monotherapy post-platinum & in combination with ICI)

1. Sheng X. ASCO 2022. Abstract 4520. 2. Sheng X. J Clin Oncol. 2023. 3. Xu H. ASCO 2022. Abstract 4519.

Slide adapted with permission from Vadim Koshkin, MD.

PH III RC48-C016: DV + TORIPALIMAB VS. PBC

RC48-C016 Study Design (NCT05302284)

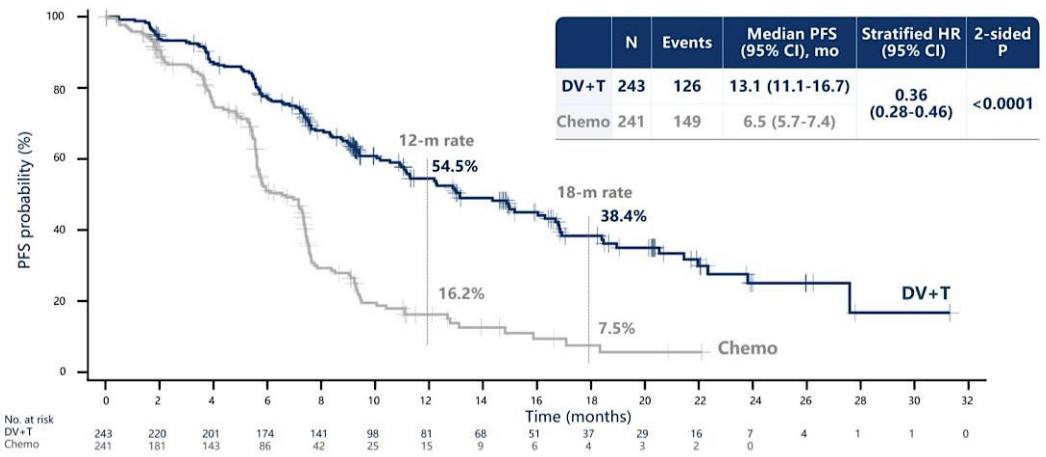


Sheng X. Abstr LBA7. ESMO 2025.

PH III RC48-C016: DV + TORIPALIMAB VS. PBC

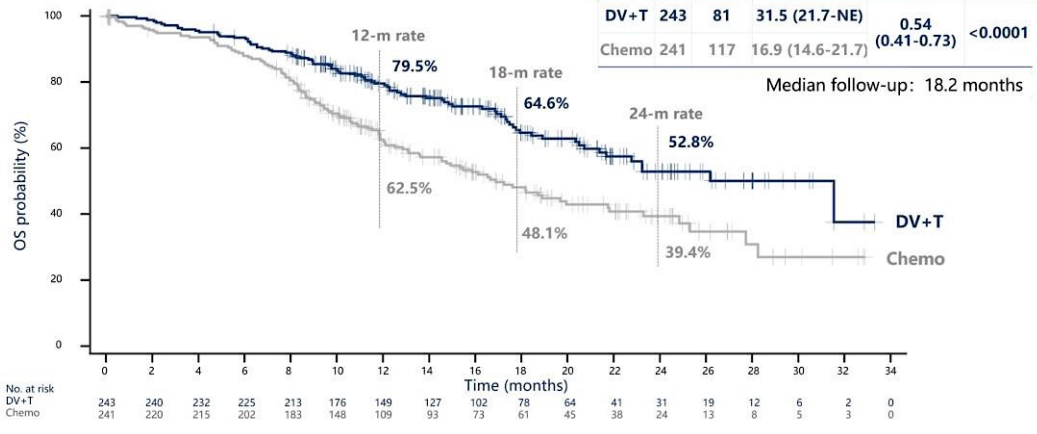
Median follow up: 18.2 months

PFS



	N	Events	Median PFS (95% CI), mo	Stratified HR (95% CI)	2-sided P
DV+T	243	126	13.1 (11.1-16.7)	0.36 (0.28-0.46)	<0.0001
Chemo	241	149	6.5 (5.7-7.4)		

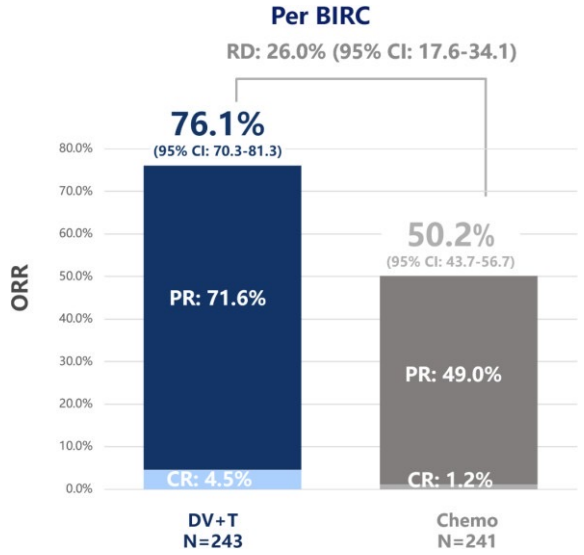
OS



	N	Events	Median OS (95% CI), mo	Stratified HR (95% CI)	2-sided P
DV+T	243	81	31.5 (21.7-NE)	0.54 (0.41-0.73)	<0.0001
Chemo	241	117	16.9 (14.6-21.7)		

Median follow-up: 18.2 months

	DV+T (n=243)	Chemo (n=241)	95% CI	p-value
ORR	76.1%	50.2%	Risk Diff 26.0% (95% CI 17.6-34.1)	N/A
Median DoR, mos	14.6	5.6	DV+T: 11.3-18.7 Chemo: 5.3-5.8	N/A
Median PFS, mos	13.1	6.5	HR 0.36 (95% CI 0.28-0.46)	<0.0001
Median OS, mos	31.5	16.9	HR 0.54 (95% CI 0.41-0.73)	<0.0001



Sheng X. Abstr LBA7. ESMO 2025.

Conclusions

- TAR-200 is a novel delivery system for gemcitabine in non-muscle invasive urothelial cancer
- EVP demonstrates consistent pCR rates of approximately 60% in both cisplatin eligible and ineligible patients
- Second line treatment should be based on biomarker approaches
- Regimens for second line therapy include gemcitabine + cis/carboplatin, FGF targeted therapies and Her-2 neu targeted therapies.

QUESTIONS?

We are taking a short break!

The program will resume at 3:20 PM ET

Up Next…

Drs Adam M Brufsky and Kevin Kalinsky discuss the management of triple-negative breast cancer

RTP
RESEARCH
TO PRACTICE