Montefiore
THE UNIVERSITY HOSPITAL

Montefiore Einstein
Comprehensive Cancer Center

Clinical Updates: Practice Changing Data From 2023 – Colon & Prostate Cancers

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Montefiore Einstein Comprehensive Cancer Center

Medical Oncology

5th Annual LEAD2023 Enriching Experiences for Women in Hematology & Oncology

University of Nebraska Medical Center

Bio Ascend™

Prostate Cancer

Localized Prostate Cancer

Abstract 5002 (GU ASCO)

Impact of the PSA nadir as a prognostic factor after radiation therapy for localized prostate cancer

Abstract 5011 (GU ASCO)

Do bone scans over-stage disease compared to PSMA PET?

Metastatic Castrate resistant

Abstract 5066 (GU ASCO)

Enzalutamide vs abiraterone in patients with without prostate cancer with and type 2 diabetes mellitus

Abstract 5004 (ASCO 2023) TALAPRO-2

First-Line Talazoparib /Enzalutamide Excels in Patients With *BRCA*-Mutated mCRPC

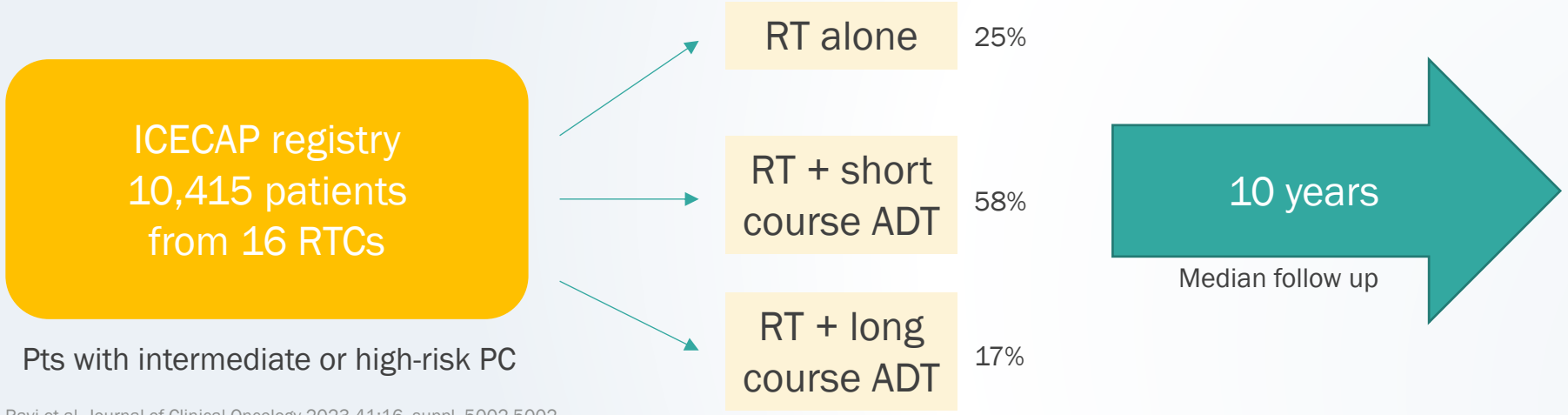
TRINTON-3

Rucaparib versus physicians choice in patients with chemotherapy-naïve mCRPC with BRCA1/2 or ATM alterations

Prognostic impact of PSA nadir ≥0.1 ng/mL within 6 months after completion of radiotherapy for localized prostate cancer

Identify an early surrogative measures to predict long term outcomes such as:

- Prostate cancer-specific survival (PCSS)
- Metastasis-free survival (MFS)
- Overall survival (OS)



Ravi et al, Journal of Clinical Oncology 2023 41:16_suppl, 5002-5002

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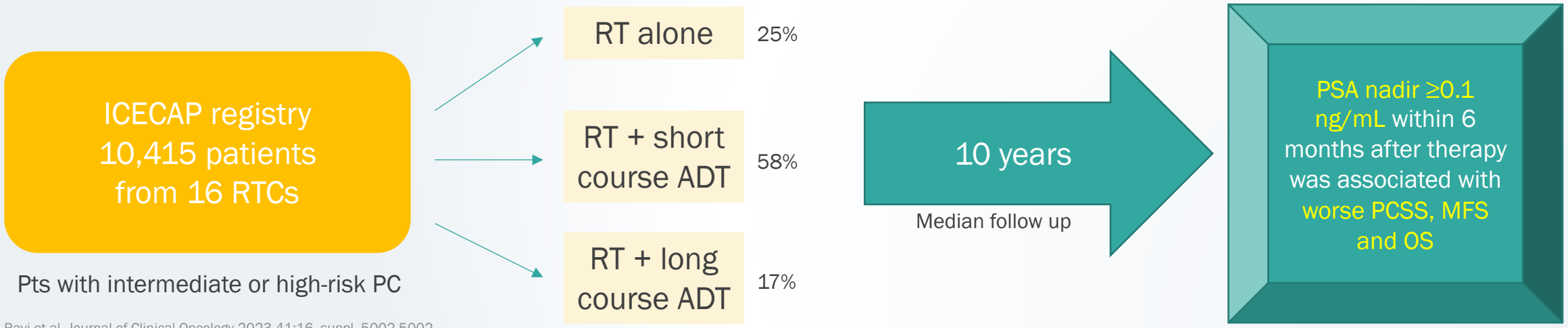

Ravi et al, Journal of Clinical Oncology 2023 41:16_suppl, 5002-5002

Do bone scans over-stage disease compared to PSMA PET? An international multicenter retrospective study with blinded independent readers. Abstract 5011

167 pts were included

- 77 patients with prostate cancer were at the initial staging
- 60 pts had biochemical recurrence
- 30 pts had castrate resistance disease

Pts were imaged with Bone scan and PSMA PET within 100 days

Each study was interpreted by three blinded readers.

Endpoints:

- Positive predictive value (PPV)
- Negative predictive value (NPV)
- specificity for bone scans

Wolfgang et al, Journal of Clinical Oncology 2023 41:16_suppl, 5011-5011

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- Negative predictive value (NPV)
- specificity for bone scans

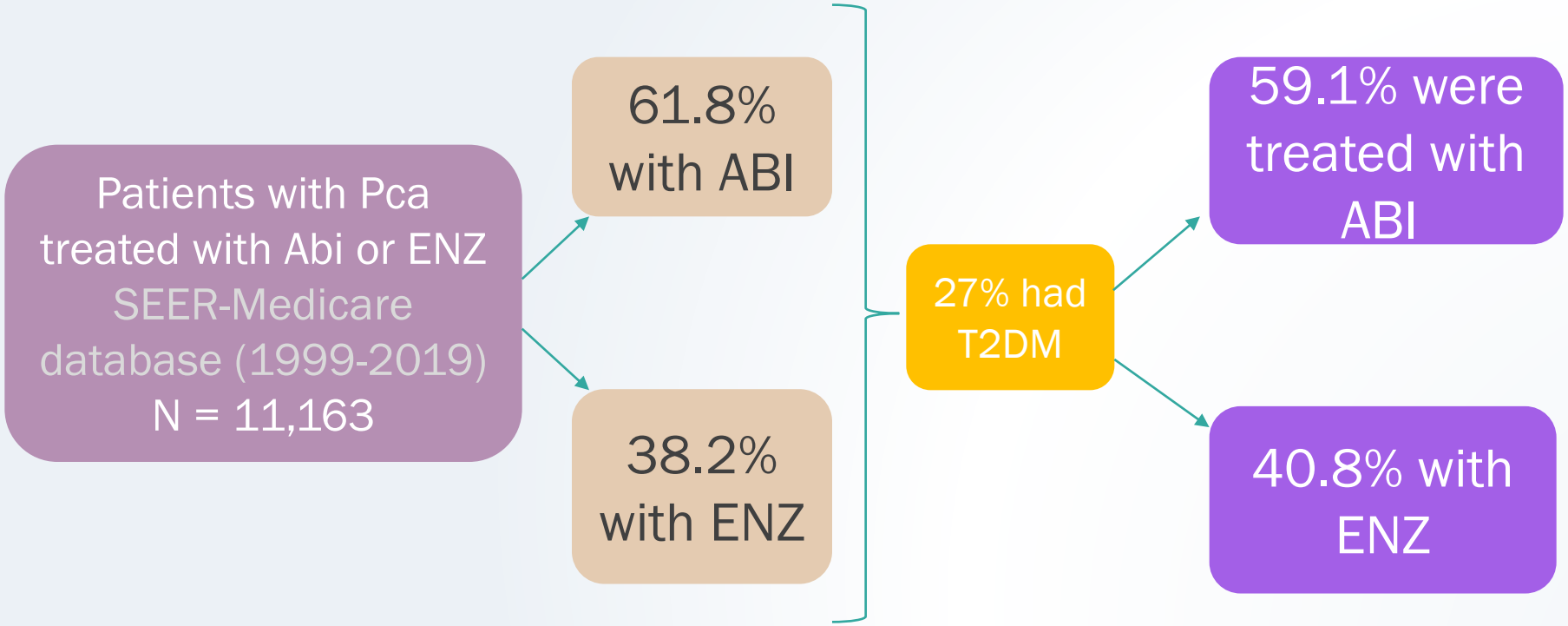
RESULTS

In patients at initial staging,
PPV: 0.43 [0.26,0.63]
NPV: 0.94 [0.85,0.98], and
specificity 0.80 [0.68,0.88].

At initial staging 57% of positive bone scans were false positive.

Wolfgang et al, Journal of Clinical Oncology 2023 41:16_suppl, 5011-5011

Enzalutamide (ENZ) vs Abiraterone (ABI) in patients with prostate cancer with and without type 2 diabetes mellitus. Abstract 5066



Shaver et al, Journal of Clinical Oncology 2023 41:16_suppl, 5066-5066

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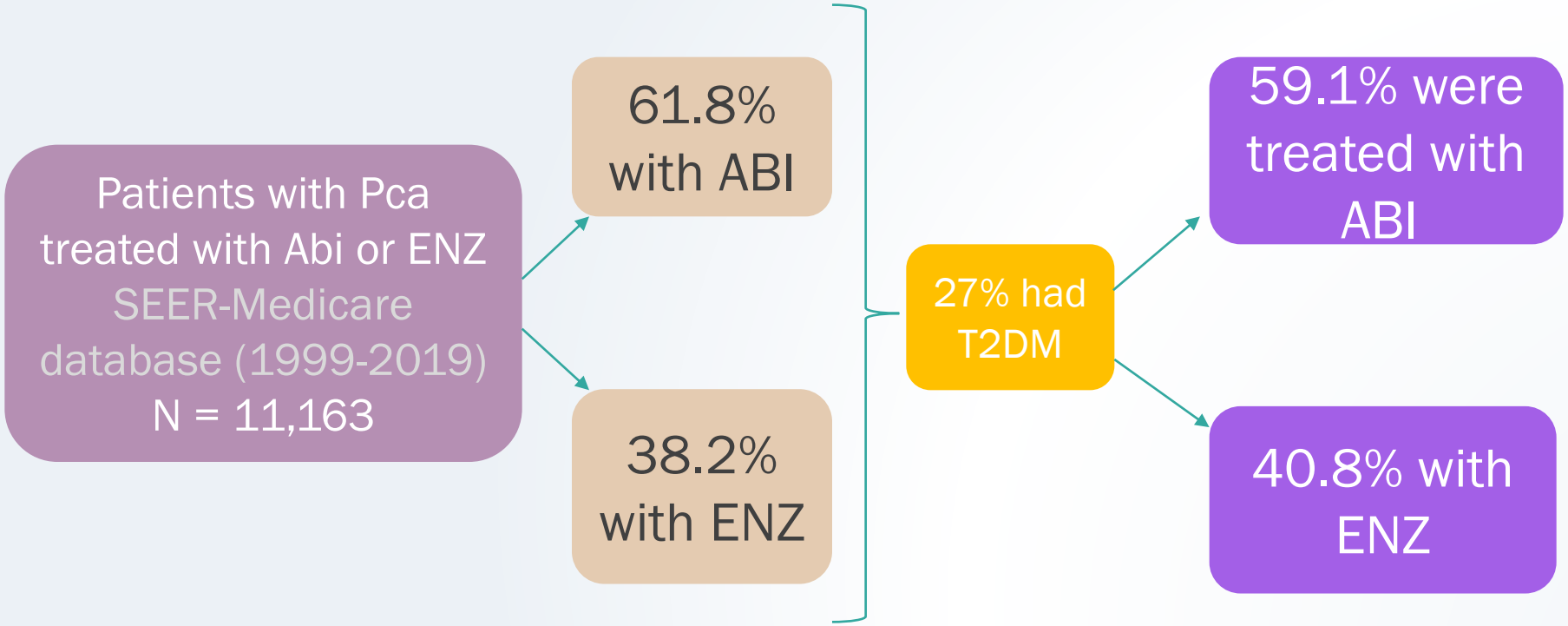

RESULTS

The rate of Acute Care Utilization was 43% higher among those treated with ABI compared to ENZ (IRR 1.43; 95% CI 1.28, 1.61).

Shaver et al, Journal of Clinical Oncology 2023 41:16_suppl, 5066-5066

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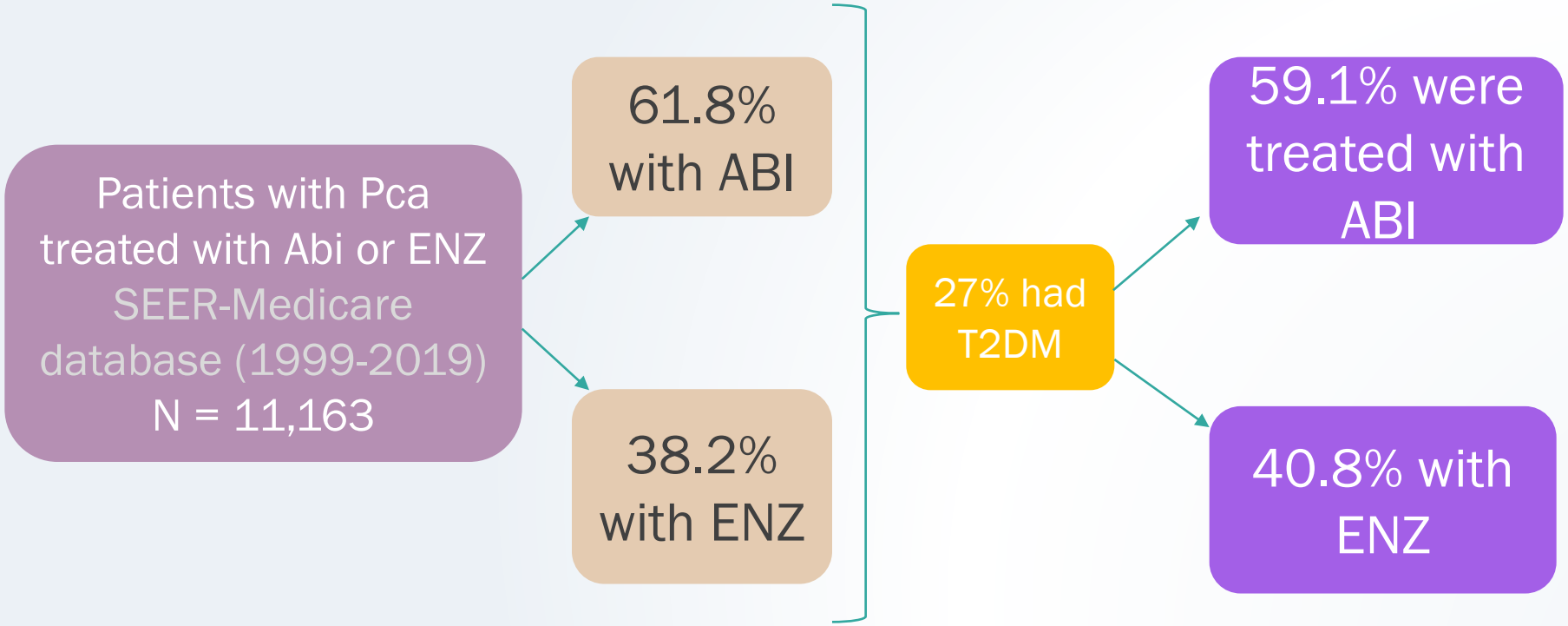


RESULTS

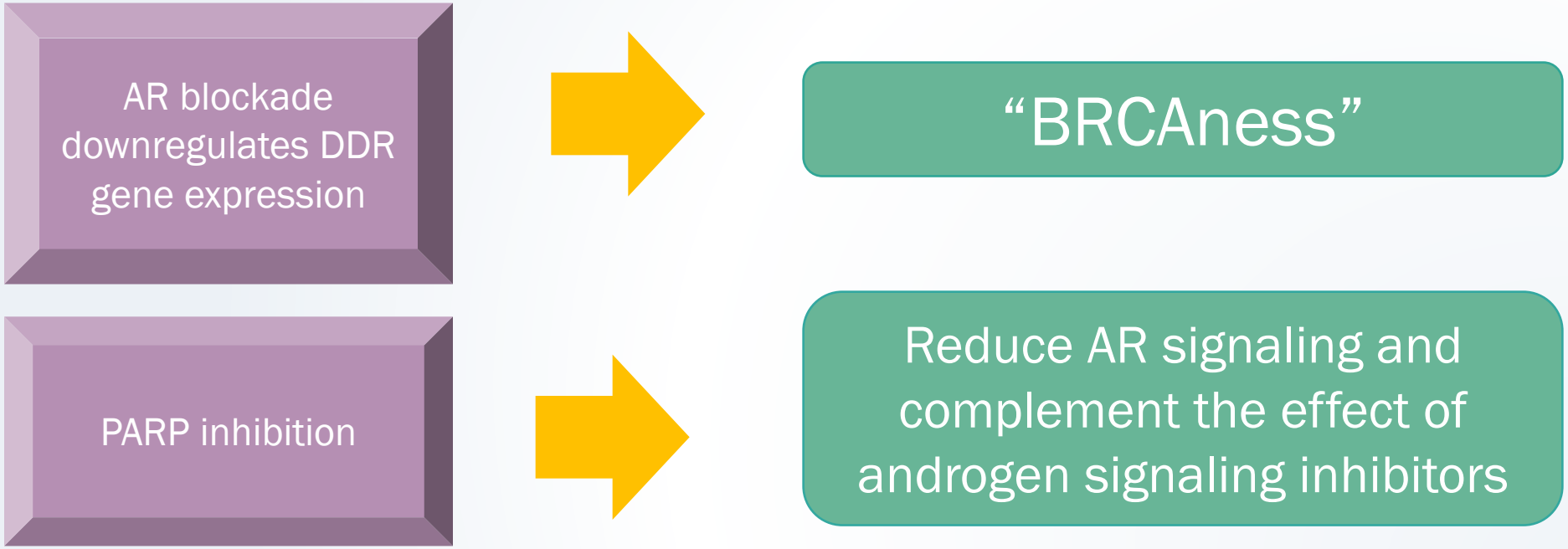
The rate of Acute Care Utilization was 43% higher among those treated with ABI compared to ENZ (IRR 1.43; 95% CI 1.28, 1.61).

Conclusion: Compared to those without T2DM those with T2DM had more ACU, regardless of medication, with a higher rate in the ABI than ENZ group.

Shaver et al, Journal of Clinical Oncology 2023 41:16_suppl, 5066-5066

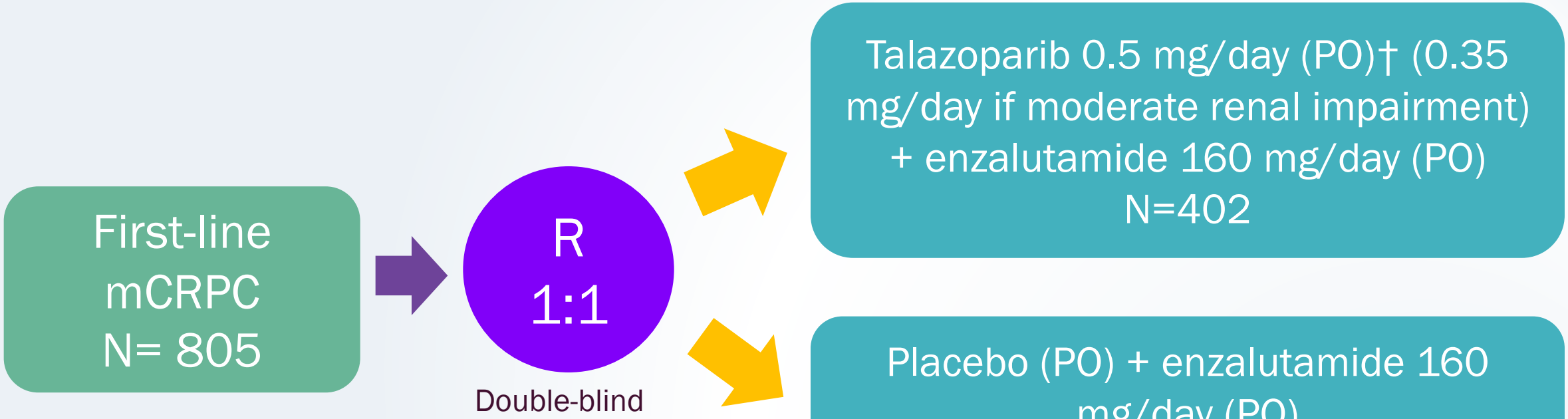
PARP inhibition beyond DDR (DNA damage repair) alteration

Preliminary studies suggest the potential for PARP inhibitors to target tumors regardless of DDR alteration status when combined with an androgen receptor signaling inhibitor.



Asim M, Tarish F, Zecchini HI et al. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. Nat Commun 8(1), 374–374 (2017)

Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomized, placebo-controlled, phase 3 trial



Stratification:

- Previous treatment with abiraterone or taxane-based chemotherapy for CSPC
- DDR alteration status (deficient vs nondeficient/unknown)

Agarwal et al, Lancet. 2023 Jul 22;402(10398)

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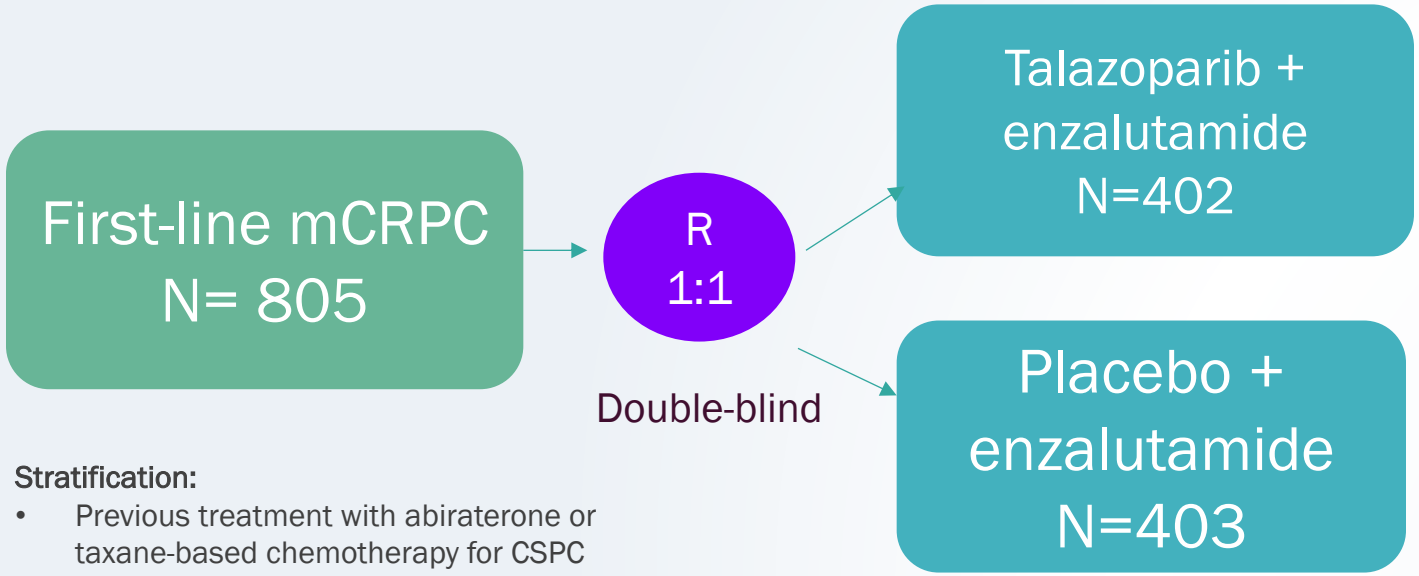


Stratification:

- Previous treatment with abiraterone or taxane-based chemotherapy for CSPC
- DDR alteration status (deficient vs nondeficient/unknown)

Primary endpoint:

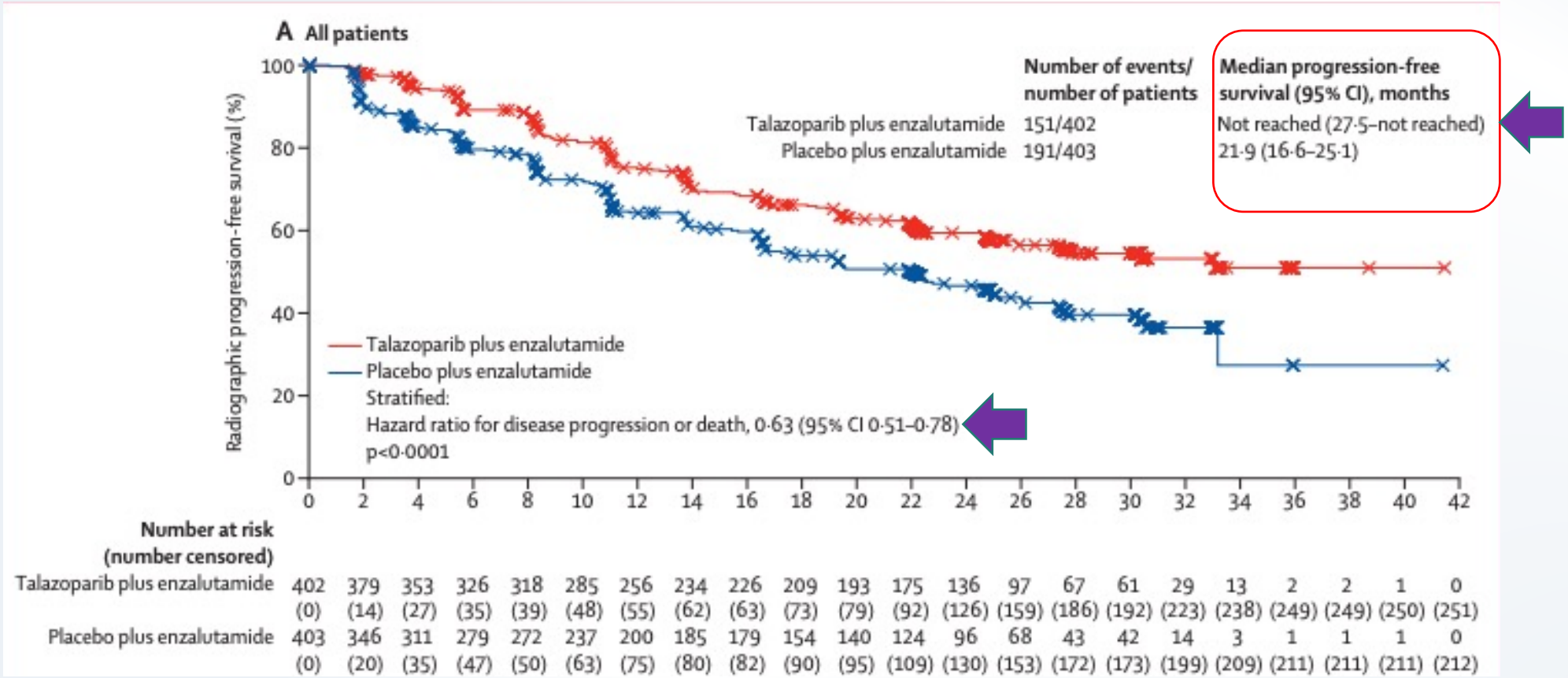
- rPFS by BICR per RECIST 1.1 (soft tissue disease) and PCWG3 (bone disease) in all-comers (Cohort 1) and in patients with DDR alterations (Cohort 2)

Secondary endpoint:

OS, ORR, duration of soft tissue response, time to PSA progression, PSA response, in all-comers and in patients with DDR alterations

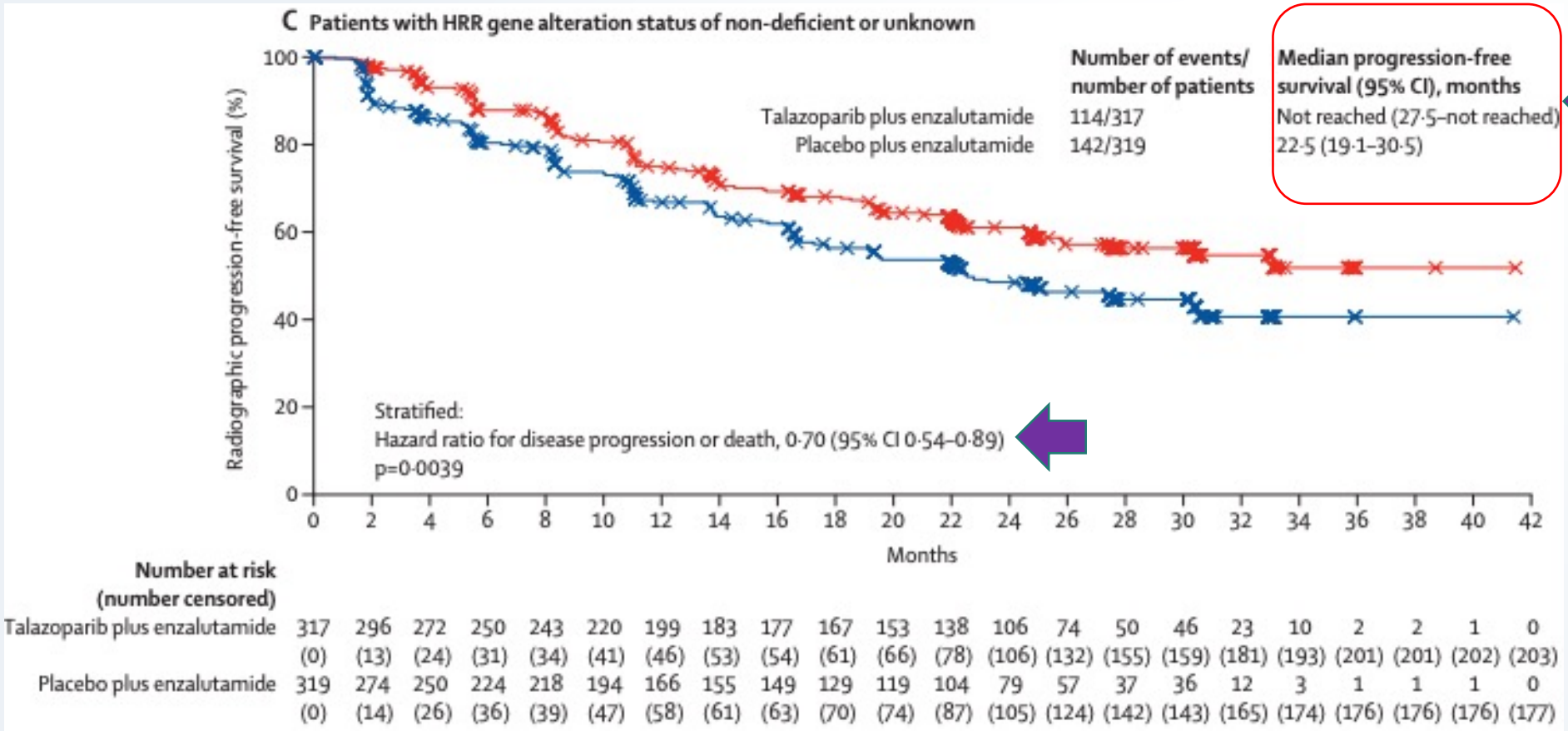
Agarwal et al, Lancet. 2023 Jul 22;402(10398)

Results for TALAPRO-2



Agarwal et al, Lancet. 2023 Jul 22;402(10398)

Patients with non-deficient or unknown HHR gene alteration



Agarwal et al, Lancet. 2023 Jul 22;402(10398)

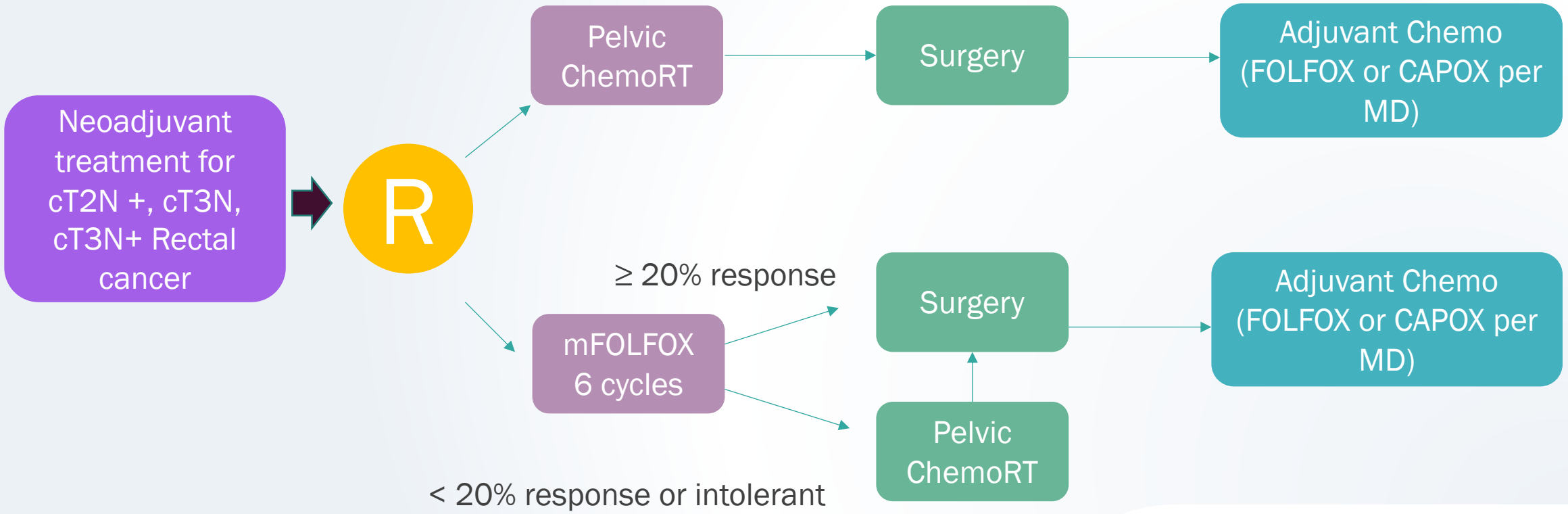
Highlight for Colorectal Cancer in 2023

- **PROSPECT trial**: Neoadjuvant chemoradiation vs FOLFOX With Selective Chemoradiation for Locally Advanced Rectal Cancer

- Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified metastatic colorectal cancer (mCRC). **Phase 2 DESTINY-CRC02 study**

PROSPECT: Neoadjuvant chemoradiation vs FOLFOX With Selective Chemoradiation for Locally Advanced Rectal Cancer

Recruitment 2012-2018 from 264 practice sites in the USA, Canada and Switzerland



Eligibility Criteria

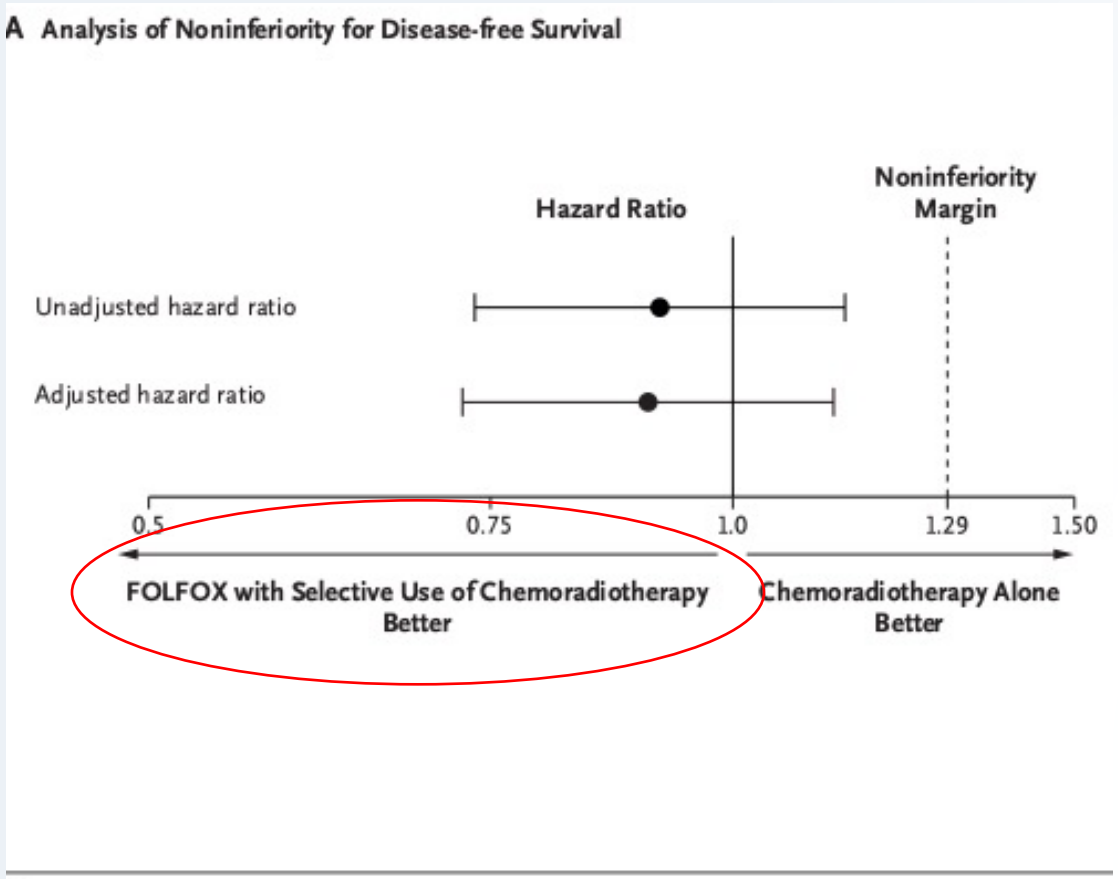
Inclusion criteria	Exclusion criteria
• cT2N+, T3N-, T3N+ • ChemoRT is indicated • Candidate for sphincter-sparing surgery	• Tumor requiring APR • cT4 Tumor • > 4 pelvic lymph nodes

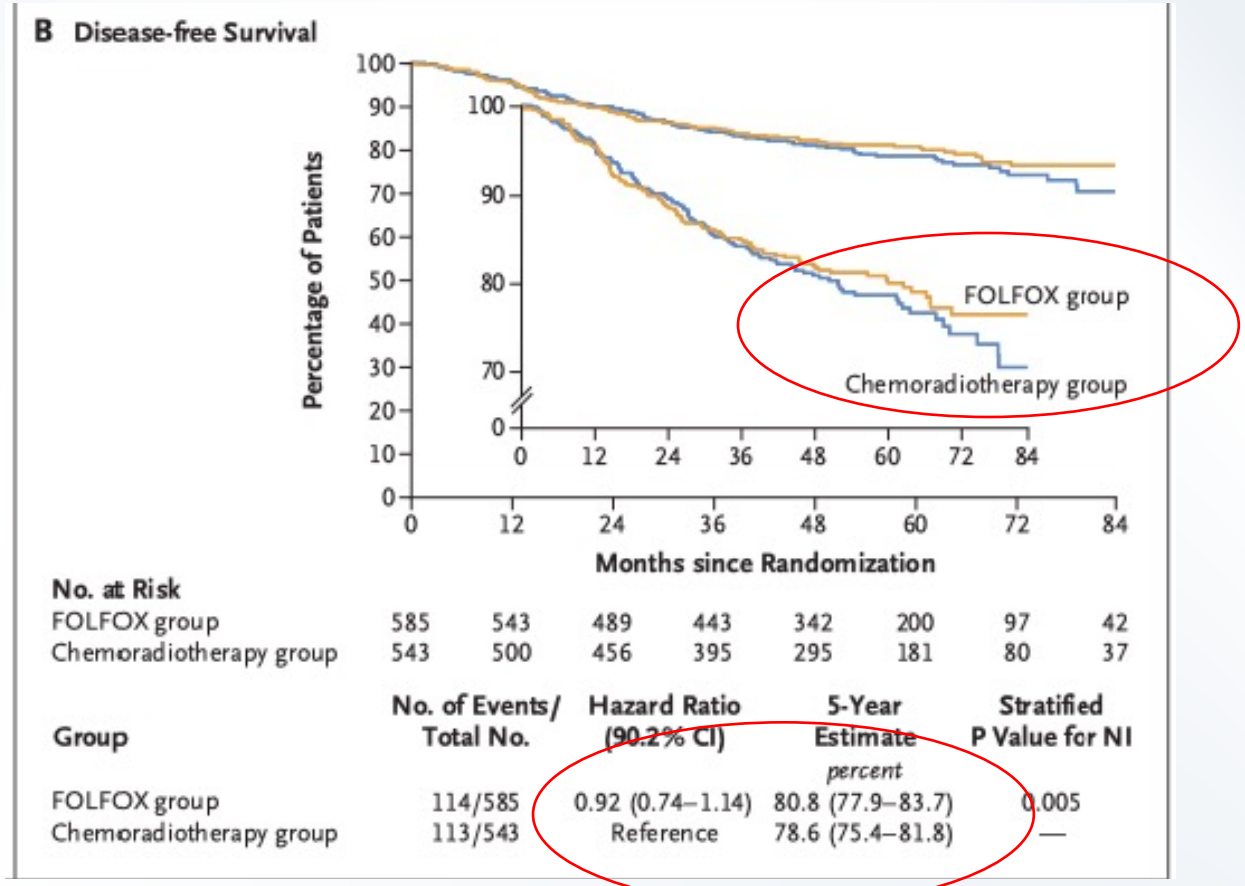
Endpoints

Primary → DFS

Secondary → Time to local recurrence, OS, R0 resection, complete pathologic response, Toxicity, QoL

Primary Endpoint





Secondary Endpoints

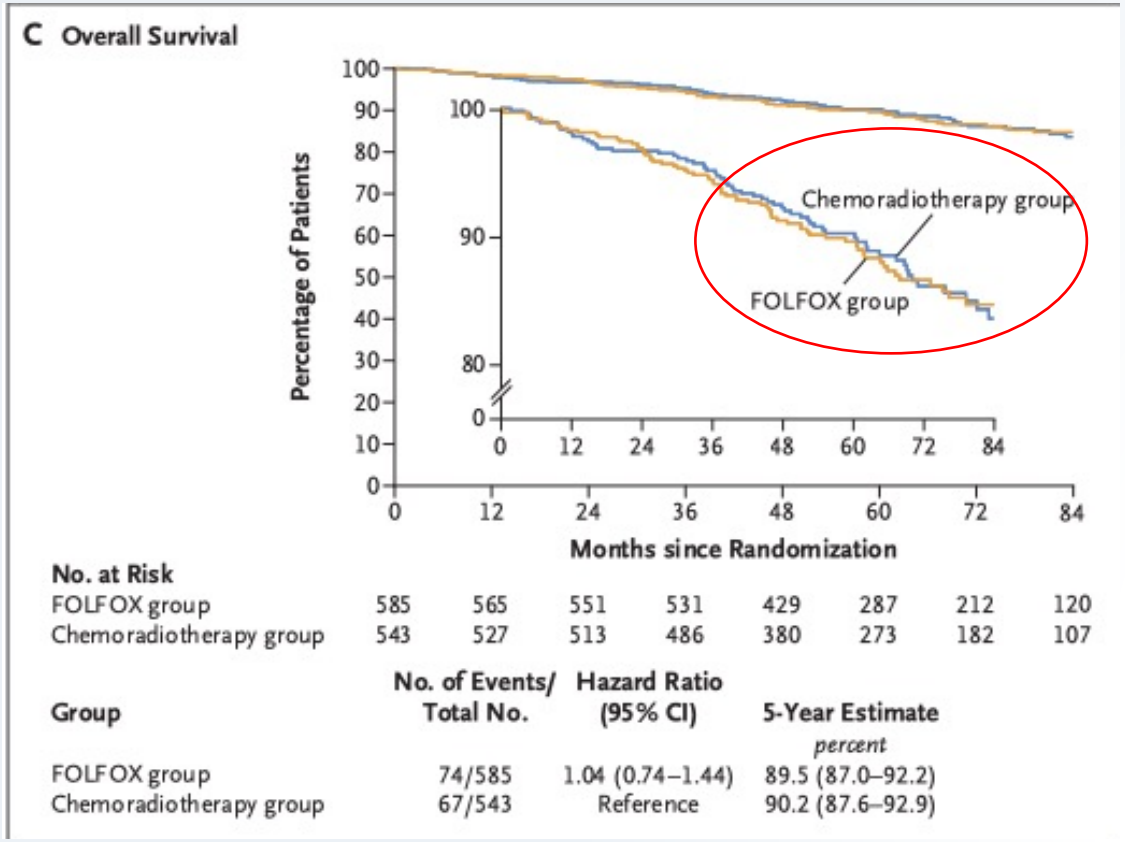


Table. Summary of Efficacy Results

Outcomes	FOLFOX with selective 5-FU CRT (585 patients)	5-FU CRT, (543 patients)
5-year disease-free survival, % (90.2% CI)	80.8 [77.9, 83.7]	78.6 [75.4, 81.8]
	HR 0.92 [0.74, 1.14] stratified noninferiority $P = .0051$	
5-year overall survival, % (95% CI)	89.5 [87.0, 92.2]	90.2 ([87.6, 92.9]
	HR 1.04 [0.74, 1.44]	
5-year local recurrence-free survival, % (95% CI)	9 events	7 events
	98.2 [97.1, 99.4]	98.4 [97.3, 99.6]
	HR 1.18 [0.44, 3.16]	
Surgical and pathological endpoints		
Number completing surgery	535	510
Complete (R0) rectal resection	98.9%	97.1%
Pathologic complete response	21.9%	24.3%
Low anterior resection rate	97.6%	98.0%
Positive radial margin	1.2%	1.5%

Keypoints:

- PROSPECT trial demonstrate that neoadjuvant FOLFOX with selective use of 5-FU chemoradiotherapy (5-FU CRT) was noninferior to 5-FU CRT in participants with locally advanced rectal cancer.

- 2 strategies achieve nearly identical outcomes.

- At 5 years, DFS, OS rates are SIMILAR.

Keypoints:

- PROSPECT trial demonstrate that neoadjuvant FOLFOX with selective use of 5-FU chemoradiotherapy (5-FU CRT) was noninferior to 5-FU CRT in participants with locally advanced rectal cancer.

- 2 strategies achieve nearly identical outcomes.

- At 5 years, DFS, OS rates are SIMILAR.

Most patients with intermediate risk rectal cancer can receive curative-intent treatment without pelvic chemoRT.

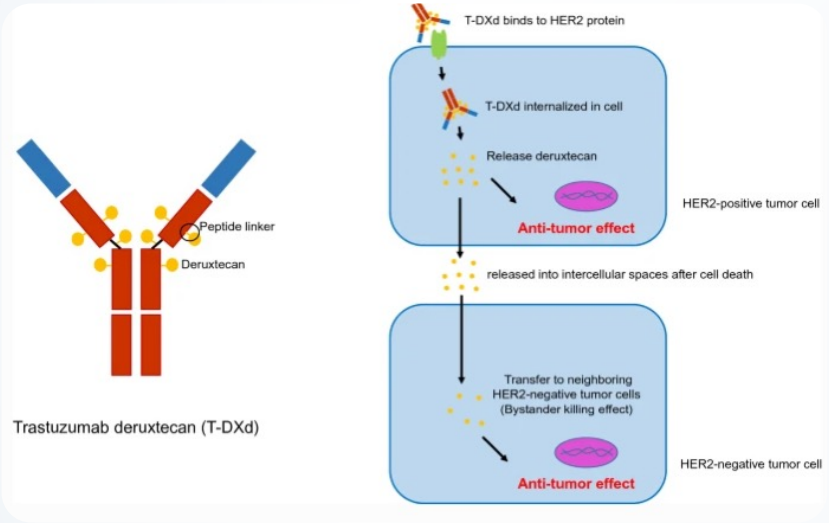
Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified metastatic colorectal cancer (mCRC)

HER 2+ mCRC

- HER2+ (IHC 3+ or IHC 2+/ISH+) mCRC constitutes 2-3% of mCRC and it links with resistant to EGFR target therapy.
- Recent evidence has shown that HER2-targeted therapies is a promising approach for this subset mCRC

Antibody-drug conjugate, humanized with 3 components

T-DXd



Humanized anti-Her-2 igG1 monoclonal antibody

Topoisomerase I inhibitor payload

Tetrapeptide-based cleavage linker

Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified metastatic colorectal cancer (mCRC)

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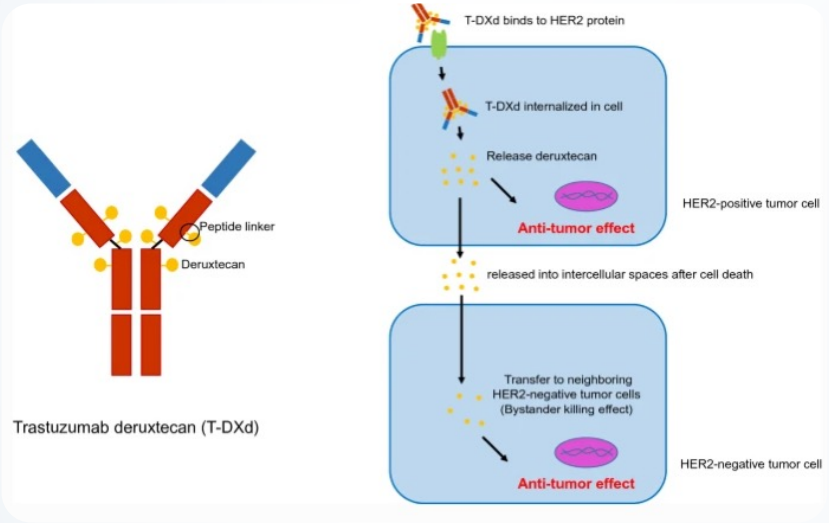
Antibody-drug conjugate, humanized with 3 components

T-DXd

T-DXd 6.4mg/kg Q3w showed antitumor anticity, in DESTINY-CRC01 → efficacy and safety of TDXd 5.4mg/kg and 6.4mg/kg



- Humanized anti-Her-2 igG1 monoclonal antibody
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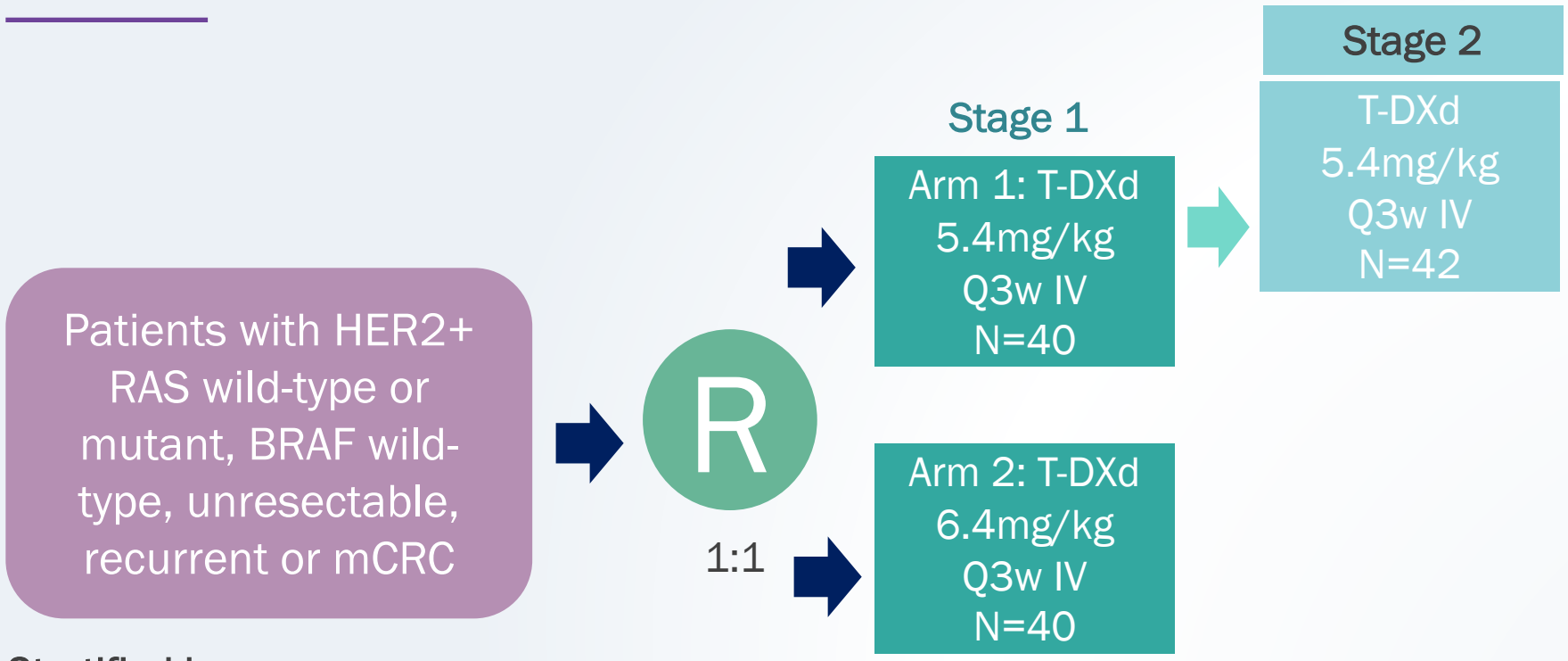
Phase 2 DESTINY-CRC02 study



Stratified by:

- ECOG PS 0 or 1
- Centrally confirmed HER 2 status: IHC 3 or IHC 2 ISH +
- RAS status (wild type or mutant)

Primary Endpoint

- cORR by BICR

Secondary endpoints

- cORR by investigator
- DoR
- DCR
- PFS
- OS
- Safety and tolerability

Raghav et al, Journal of Clinical Oncology 2023 41:16_suppl, 3501-3501

Phase 2 DESTINY-CRC02 study

Baseline Characteristics

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median age, years (range)	58.2 (26-78)	60.6 (30-84)	59.1 (26-84)	62.3 (35-81)
Sex, n (%)				
Male	21 (52.5)	24 (57.1)	45 (54.9)	19 (47.5)
Region, n (%)				
Asia-Pacific	25 (62.5)	22 (52.4)	47 (57.3)	24 (60.0)
US	5 (12.5)	1 (2.4)	6 (7.3)	2 (5.0)
Europe	10 (25.0)	19 (45.2)	29 (35.4)	14 (35.0)
HER2 status, n (%)				
IHC 3+	32 (80.0)	32 (76.2)	64 (78.0)	34 (85.0)
IHC 2+/ISH+	8 (20.0)	10 (23.8)	18 (22.0)	6 (15.0)
ECOG PS, n (%)				
0	22 (55.0)	24 (57.1)	46 (56.1)	22 (55.0)
1	18 (45.0)	18 (42.9)	36 (43.9)	18 (45.0)
***RAS* status, n (%)**				
Wild-type	34 (85.0)	34 (81.0)	68 (82.9)	34 (85.0)
Mutant	6 (15.0)	8 (19.0)	14 (17.1)	6 (15.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.

Raghav et al, Journal of Clinical Oncology 2023 41:16_suppl, 3501-3501

Baseline Characteristics (cont.)

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
HER2/*RAS* status, n (%)				
IHC 2+ ISH+/wild-type	7 (17.5)	5 (11.9)	12 (14.6)	6 (15.0)
IHC 2+ ISH+/mutant	1 (2.5)	5 (11.9)	6 (7.3)	0
IHC 3+/wild-type	27 (67.5)	29 (69.0)	56 (68.3)	28 (70.0)
IHC 3+/mutant	5 (12.5)	3 (7.1)	8 (9.8)	6 (15.0)
Liver metastases at baseline, n (%)	29 (72.5)	30 (71.4)	59 (72.0)	26 (65.0)
CNS metastases at baseline, n (%)	3 (7.5)	0	3 (3.7)	1 (2.5)
Primary tumor site, n (%)				
Left colon[a]	32 (80.0)	29 (69.0)	61 (74.4)	34 (85.0)
Rectum	15 (37.5)	12 (28.6)	27 (32.9)	19 (47.5)
Right colon[b]	8 (20.0)	13 (31.0)	21 (25.6)	6 (15.0)

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Prior Treatment

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median prior lines of systemic therapy, n (range)	4 (1-12)	3 (1-7)	3 (1-12)	4 (1-8)
Systemic chemotherapy, n (%)	**40 (100)**	**42 (100)**	**82 (100)**	**40 (100)**
Irinotecan	39 (97.5)	40 (95.2)	79 (96.3)	40 (100)
Fluoropyrimidines[a]	40 (100)	42 (100)	82 (100)	40 (100)
Oxaliplatin	40 (100)	41 (97.6)	81 (98.8)	40 (100)
Anti-EGFR, n (%)	29 (72.5)	28 (66.7)	57 (69.5)	31 (77.5)
Anti-HER2, n (%)	**11 (27.5)**	**6 (14.3)**	**17 (20.7)**	**10 (25.0)**
HER2 TKI[b]	6 (15.0)	4 (9.5)	10 (12.2)	7 (17.5)
Anti-HER2 antibodies[c]	10 (25.0)	6 (14.3)	16 (19.5)	10 (25.0)
Anti-VEGF, n (%)	36 (90.0)	38 (90.5)	74 (90.2)	38 (95.0)
Regorafenib and tipiracil/trifluridine, n (%)	20 (50.0)	14 (33.3)	34 (41.5)	13 (32.5)
Other systemic therapy, n (%)	5 (12.5)	6 (14.3)	11 (13.4)	10 (25.0)

5FU, fluorouracil; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
[a]Includes 5FU, capecitabine, S1, or tegafur. [b]Includes tucatinib and lapatinib. [c]Includes trastuzumab, trastuzumab duocarmazine, trastuzumab emtansine, pertuzumab, and zanidatamab (ZW25).

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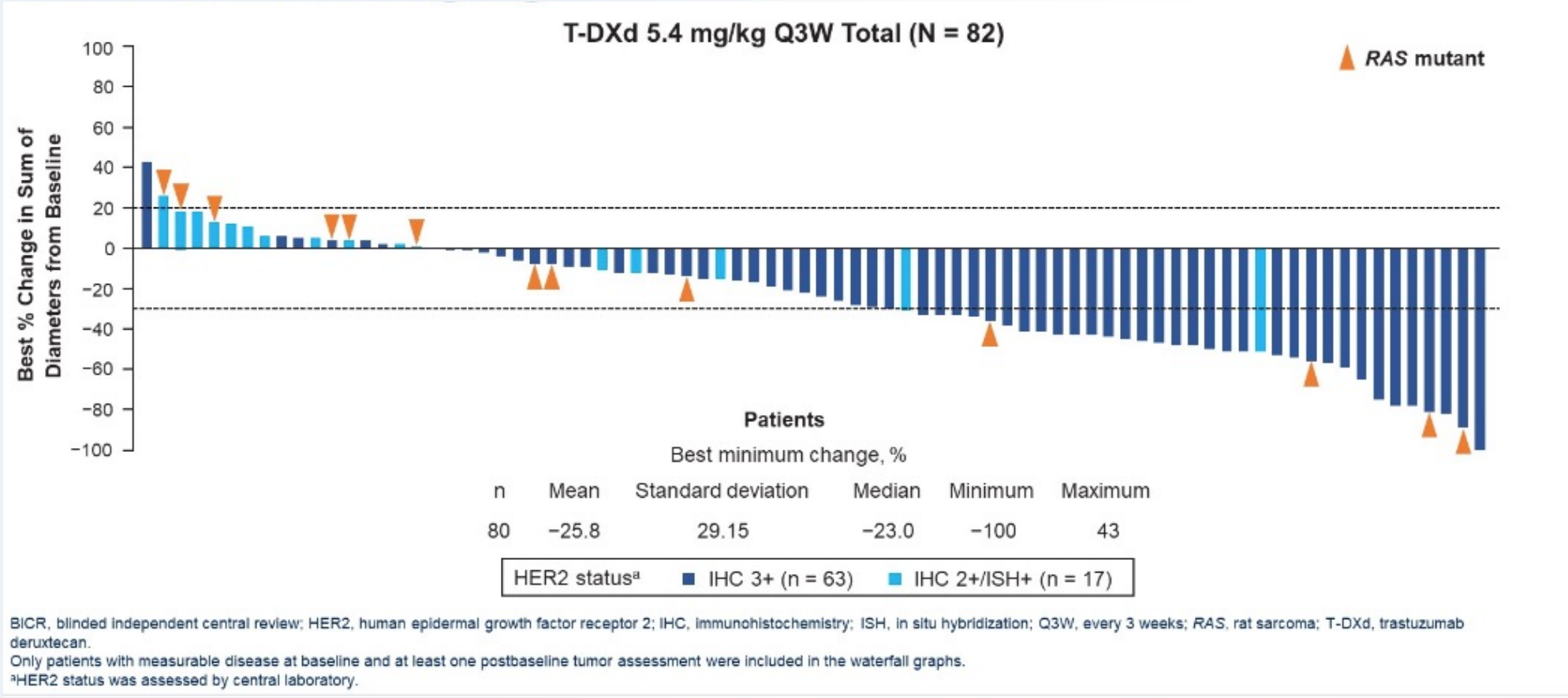
Best Percentage Change in Sum of Diameters by BICR for T-DXd 5.4 mg/kg



BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.
[a]HER2 status was assessed by central laboratory.

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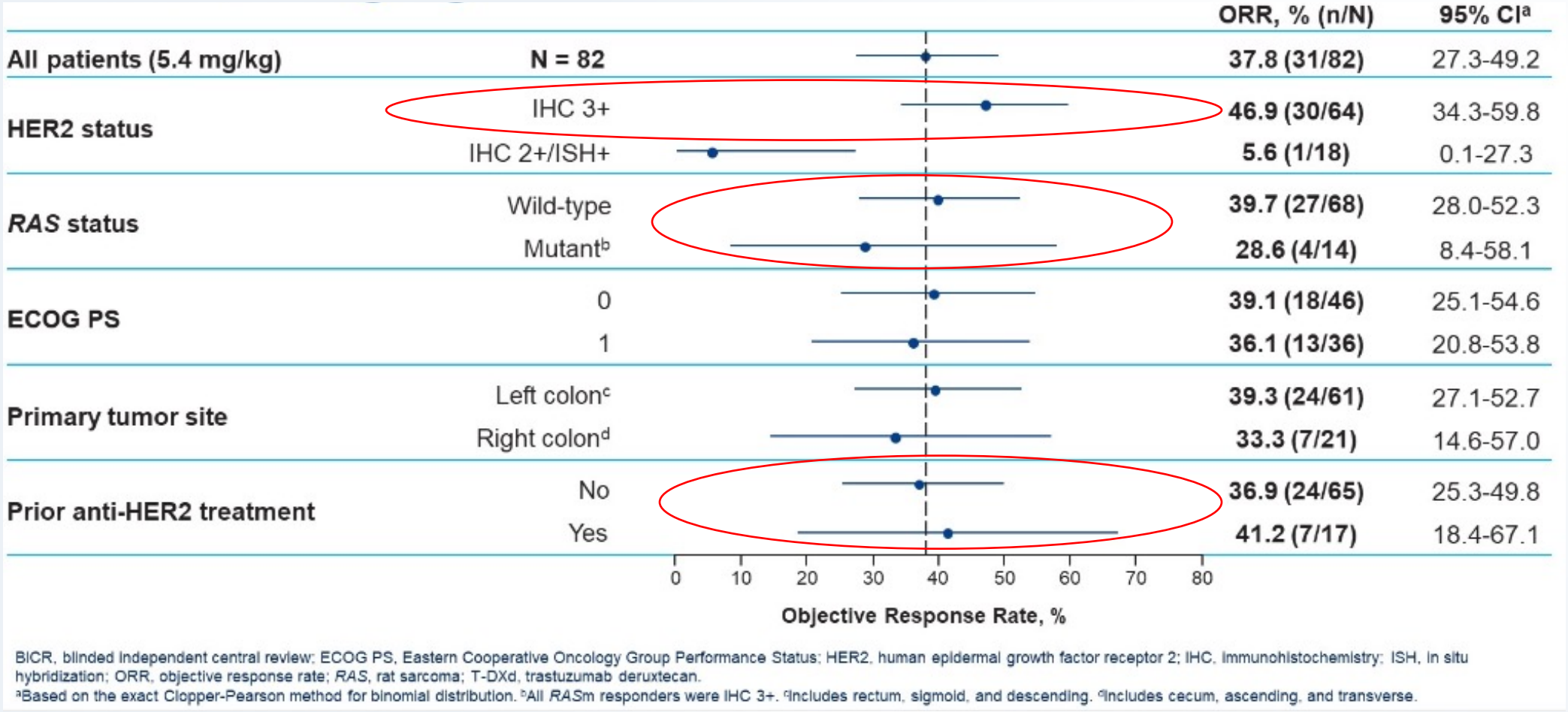
Best Overall Response by BICR by Subgroup With T-DXd 5.4 mg/kg



BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All *RAS*m responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.

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Take Home message HER-2+ mCRC

- HER-2 amplification SHOULD be tested in conjunction with RAS, BRAF, MSI status
- 20% of patients with HER-2 amplification, will have RAS mutation
- HER 2 amplification does drive EGFR inhibitor resistance in metastatic CRC

Thank you!