Advancements in Gastrointestinal Health – A Comprehensive Update

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Esophageal Squamous Cell Carcinoma

- **SKYSCRAPER - 08**: Phase III study of first-line tiragolumab + atezolizumab and chemotherapy in patients with advanced esophageal SCC

GEJ/Gastric Adenocarcinoma

- **GLOW**: Zolbetuximab + CAPOX in CLDN 18.2 positive advanced gastric and GEJ cancer
- **DESTINY - Gastric 02**: TDxd in patients in the USA and Europe with HER2-positive advanced gastric or GEJ cancer with disease progression on or after a trastuzumab-containing regimen

Pancreatic Cancer

- **NAPOLI-3:** Phase 3 study NALIRIFOX versus gemcitabine + nab-paclitaxel in treatment-naïve patients with metastatic pancreatic cancer
- **ALPACA:** Alternating application of gemcitabine/nab-paclitaxel and Gem monotherapy or continuous application of Gem/nab-Pac after induction treatment for first-line treatment of metastatic pancreatic cancer

Neuroendocrine Tumors

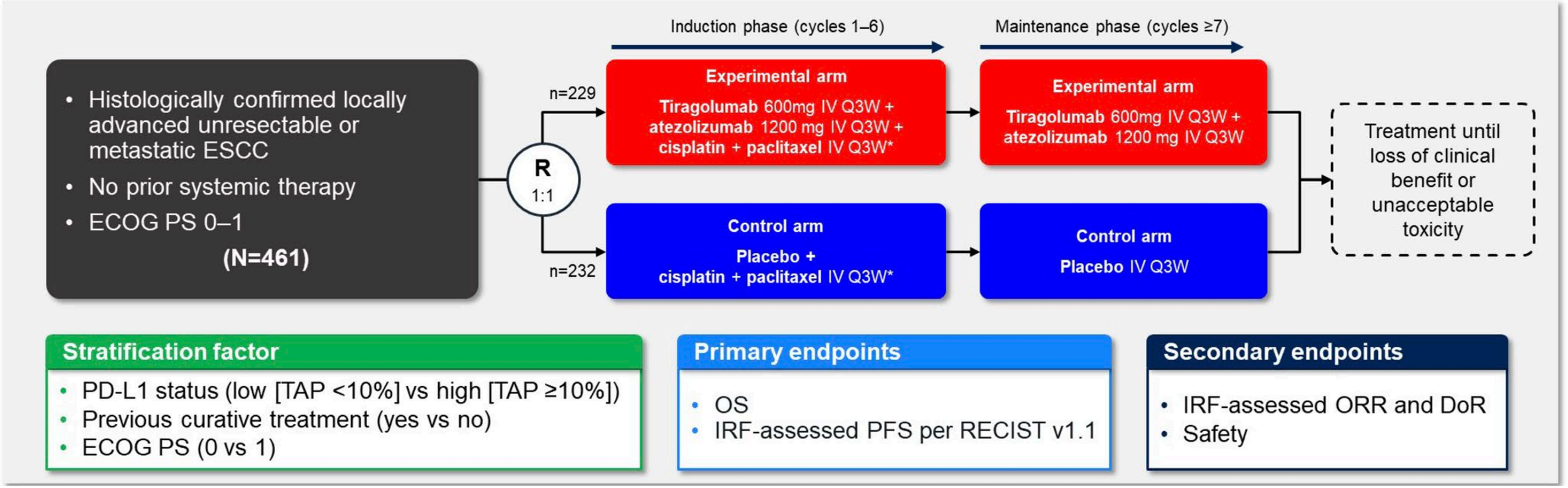
- **NETTER 2**: ^{177}Lu-DOTATATE in newly diagnosed patients with advanced grade 2 and grade 3, well-differentiated gastroenteropancreatic neuroendocrine tumors

Colorectal Cancer

- **PROSPECT**: A randomized phase III trial of neoadjuvant chemoradiation versus neoadjuvant FOLFOX chemotherapy with selective use of chemoradiation, followed by total mesorectal excision for treatment of locally advanced rectal cancer.
- **FRESCO 2**: Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer
- **Updates on role of ctDNA from GI ASCO 2024**

SKYSCRAPER-08: a phase III, randomized, double-blind, placebo-controlled study of first-line tiragolumab + atezolizumab and chemotherapy in patients with esophageal squamous cell carcinoma

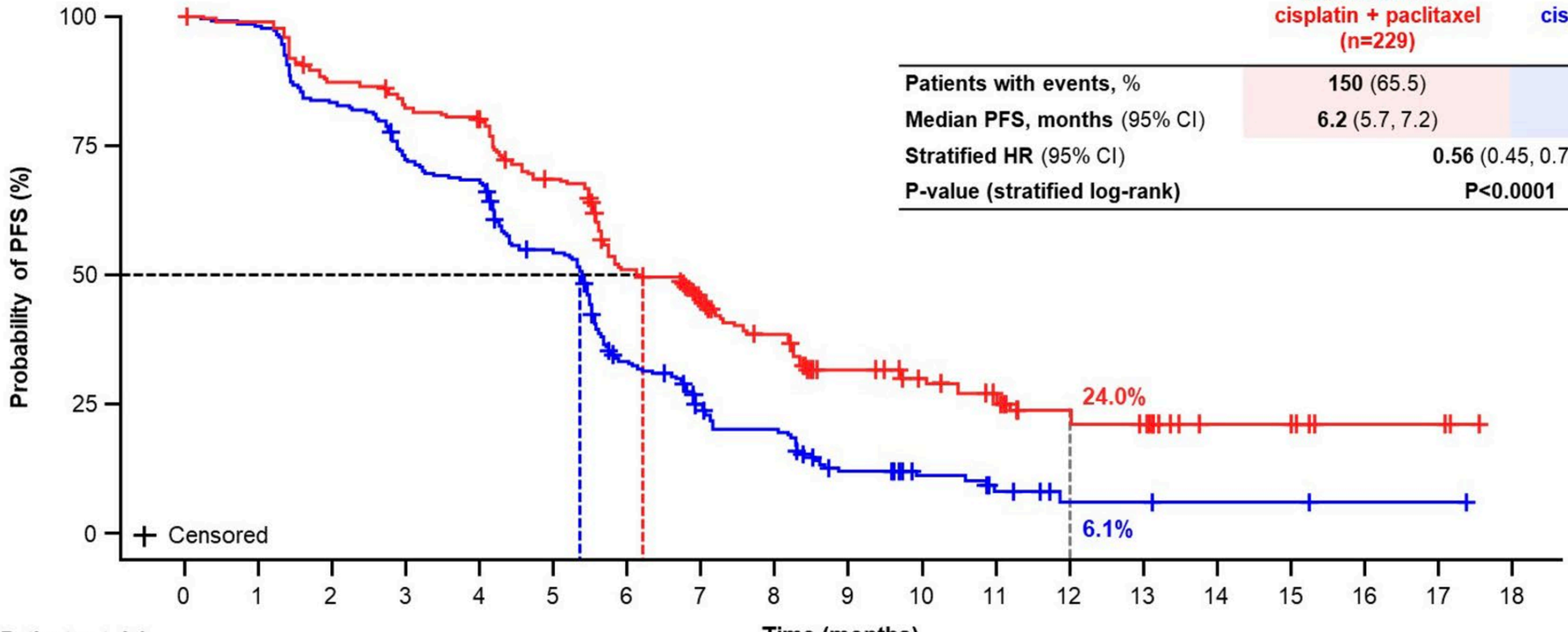
- Patients were enrolled across Asia at 67 centers in mainland China, Hong Kong, Taiwan, South Korea, and Thailand



Chih-Hung Hsu, et al. Journal of Clinical Oncology 2024 42:3_suppl, 245-245

IRF-assessed PFS per RECIST v1.1 (primary endpoint)

	Tiragolumab + atezolizumab + cisplatin + paclitaxel (n=229)	Placebo + cisplatin + paclitaxel (n=232)
Patients with events, %	**150** (65.5)	**193** (83.2)
Median PFS, months (95% CI)	**6.2** (5.7, 7.2)	**5.4** (4.4, 5.5)
Stratified HR (95% CI)	**0.56** (0.45, 0.70)	
P-value (stratified log-rank)	**P<0.0001**	



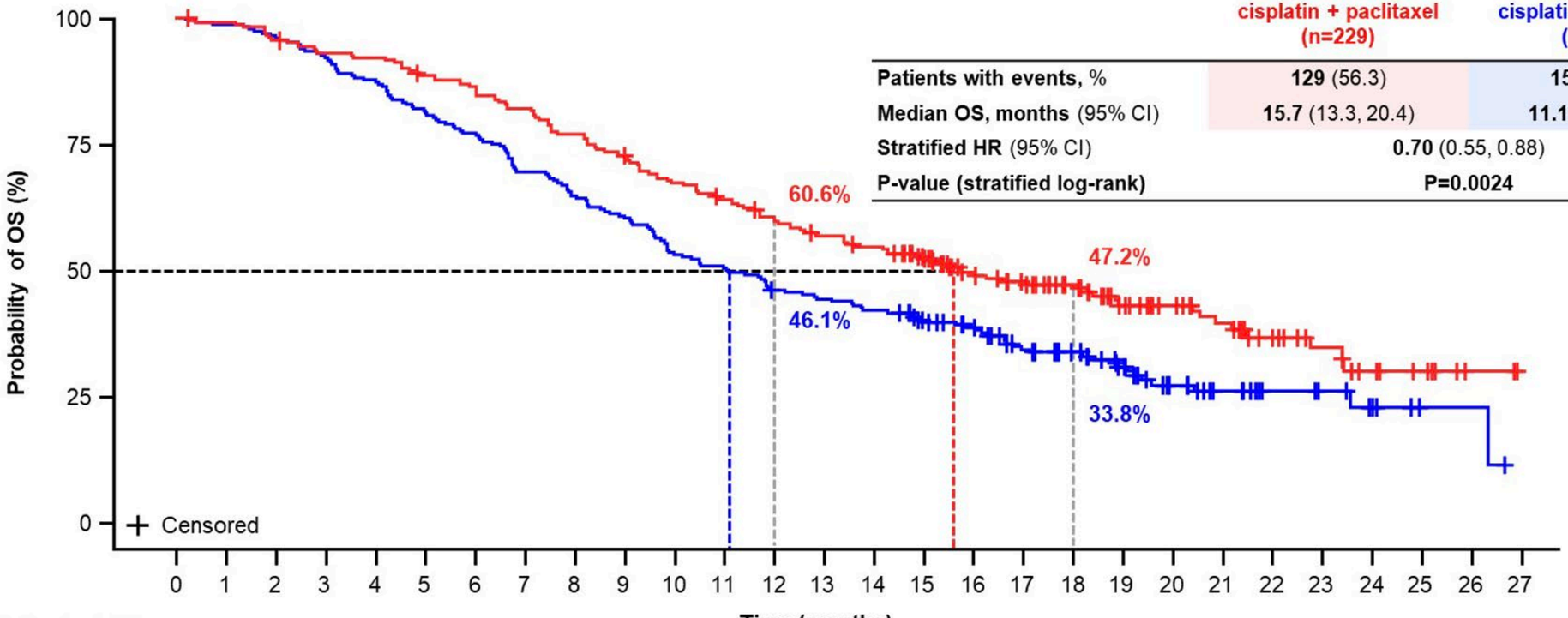
Patients at risk

Tira + atezo + cisplatin + paclitaxel	229	222	194	182	176	148	107	82	64	40	32	26	18	15	7	7	3	3	NE
Placebo + cisplatin + paclitaxel	232	224	190	164	155	119	69	48	38	18	12	7	3	3	2	2	1	1	NE

Chih-Hung Hsu, et al. Journal of Clinical Oncology 2024 42:3_suppl, 245-245

Final analysis of OS (primary endpoint)

	Tiragolumab + atezolizumab + cisplatin + paclitaxel (n=229)	Placebo + cisplatin + paclitaxel (n=232)
Patients with events, %	**129** (56.3)	**158** (68.1)
Median OS, months (95% CI)	**15.7** (13.3, 20.4)	**11.1** (9.6, 13.6)
Stratified HR (95% CI)	**0.70** (0.55, 0.88)	
P-value (stratified log-rank)	**P=0.0024**	



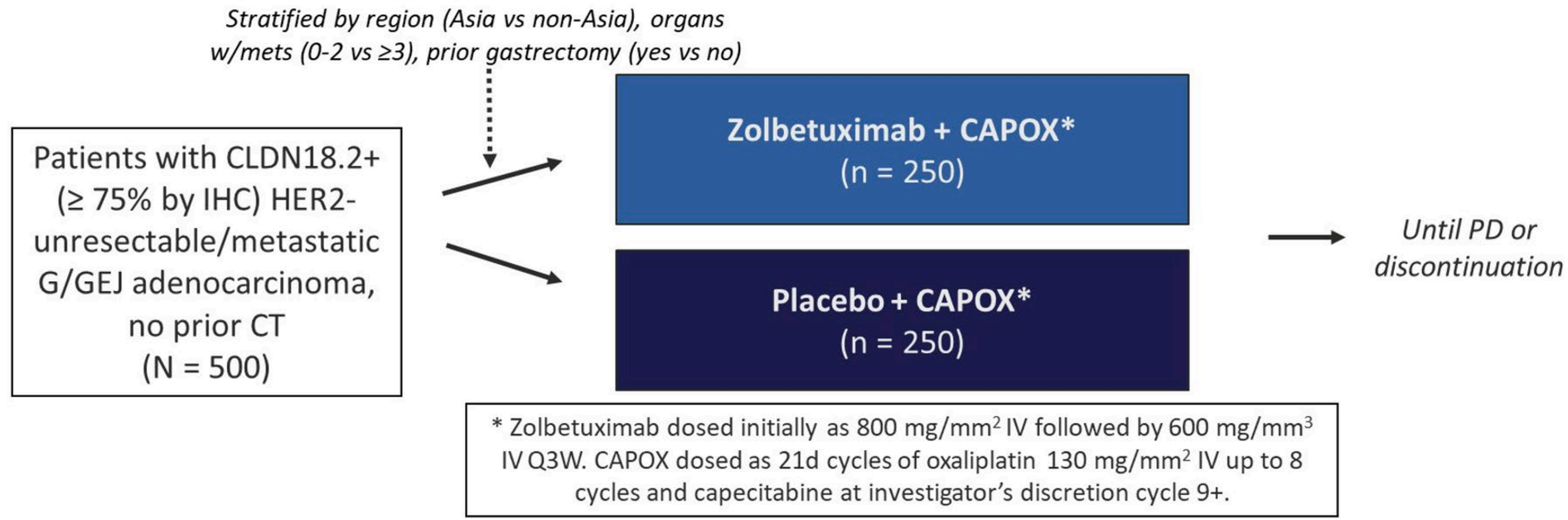
Patients at risk

Tira + atezo + cisplatin + paclitaxel	229	226	218	211	209	200	195	184	174	164	151	143	134	125	119	105	87	78	64	49	41	32	23	16	10	7	2	NE
Placebo + cisplatin + paclitaxel	232	225	219	210	200	183	174	157	146	137	120	115	103	99	94	83	75	59	52	39	26	18	11	9	7	3	2	NE

Chih-Hung Hsu, et al. Journal of Clinical Oncology 2024 42:3_suppl, 245-245

GLOW: Zolbetuximab + CAPOX in CLDN18.2+ G/GEJ Cancer

- Global, double-blind, placebo-controlled, randomized phase III study

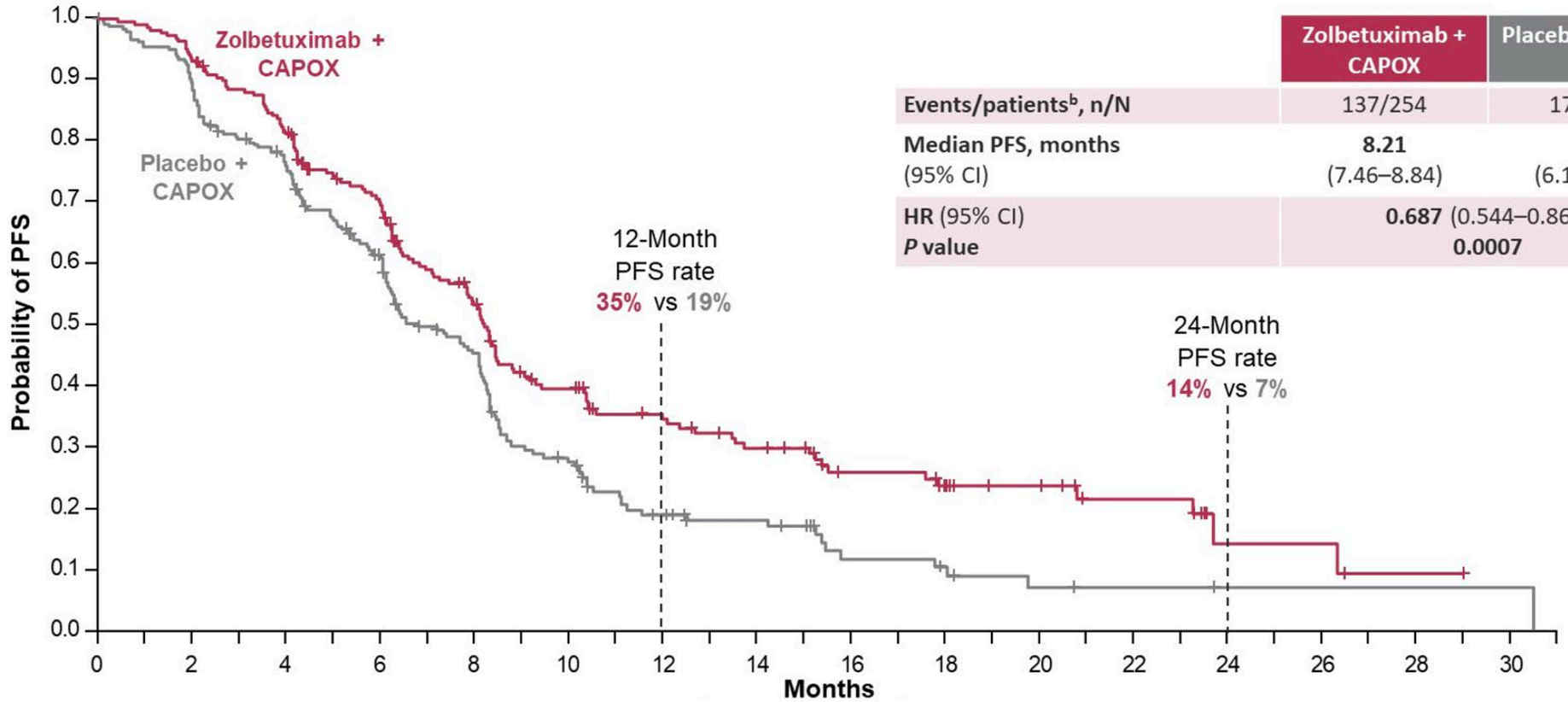


Primary endpoint: IRC-assessed PFS

Secondary endpoints: OS, ORR, DOR, safety, PK, QoL

Shah. et al. Nat Med 2023.

Primary End Point: PFS by Independent Review Committee



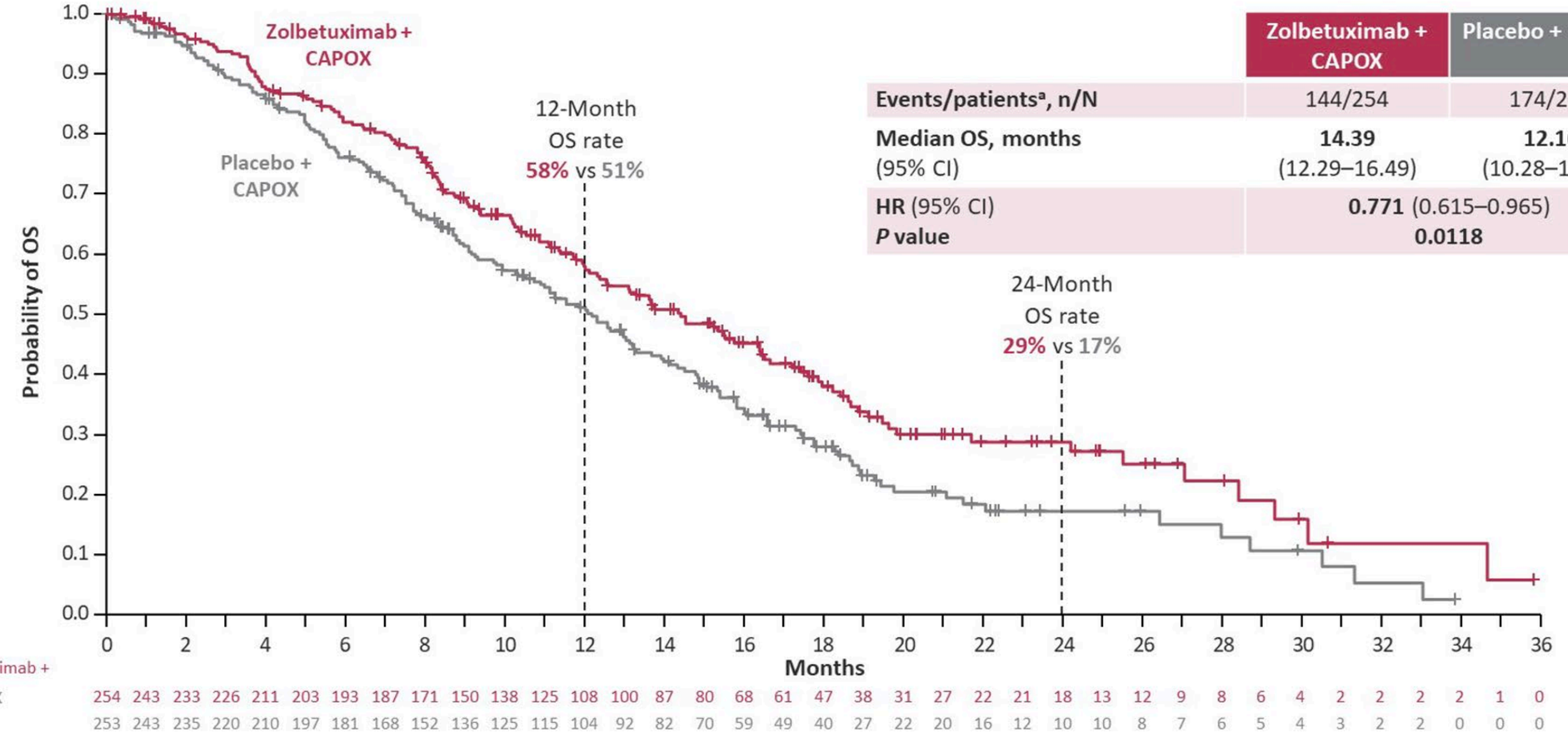
	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[b], n/N	137/254	172/253
Median PFS, months (95% CI)	**8.21** (7.46–8.84)	**6.80** (6.14–8.08)
HR (95% CI)	**0.687** (0.544–0.866)	
***P* value**	**0.0007**	

No. at Risk

Zolbetuximab + CAPOX	254	223	205	187	171	141	132	104	91	66	61	47	45	41	37	35	24	24	19	14	14	9	9	9	3	3	3	1	1	1	0	0
Placebo + CAPOX	253	233	215	188	175	146	127	93	84	48	43	30	24	19	19	17	9	9	7	5	4	2	2	2	1	1	1	1	1	1	1	0

Shah, et al. Nat. Med. 2023

Key Secondary End Point: OS

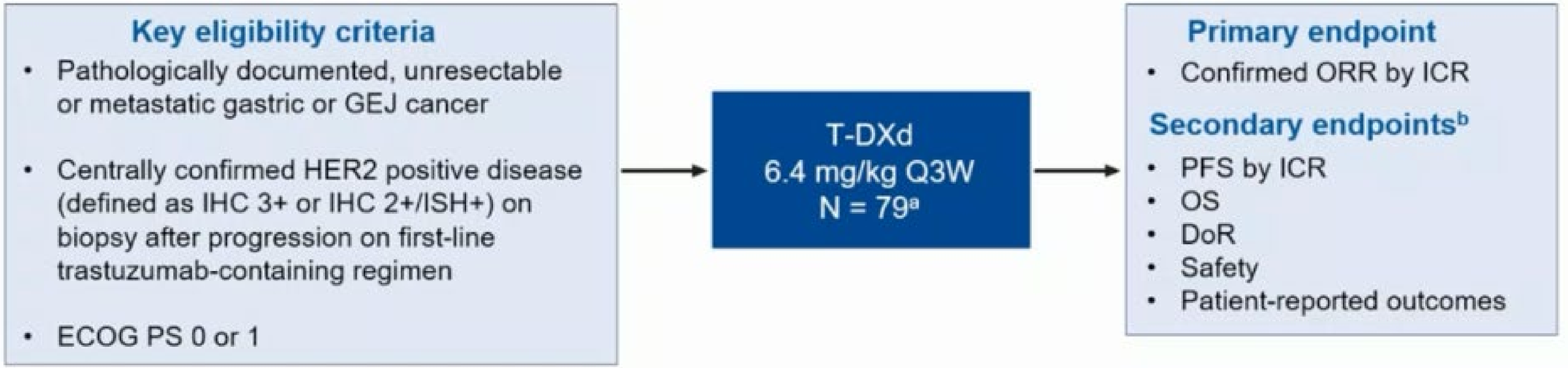


	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[a], n/N	144/254	174/253
Median OS, months (95% CI)	**14.39** (12.29–16.49)	**12.16** (10.28–13.67)
HR (95% CI)	**0.771** (0.615–0.965)	
***P* value**	**0.0118**	

Shah, et al. Nat. Med. 2023

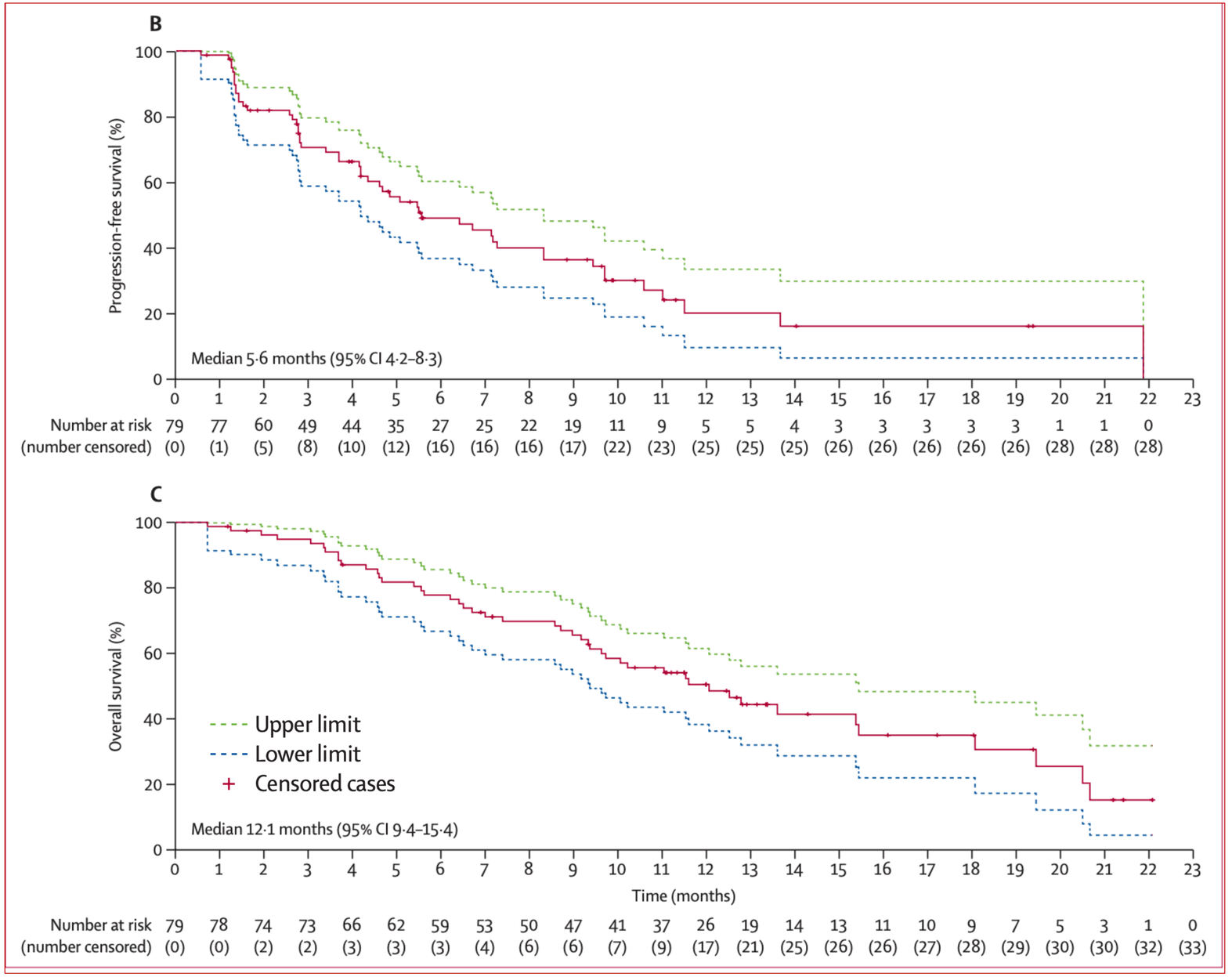
DESTINY-Gastric02 Study Design

An open-label, multicenter phase 2 study in Western patients with HER2+ gastric or GEJ cancer who had progressed on a trastuzumab-containing regimen (NCT04014075)



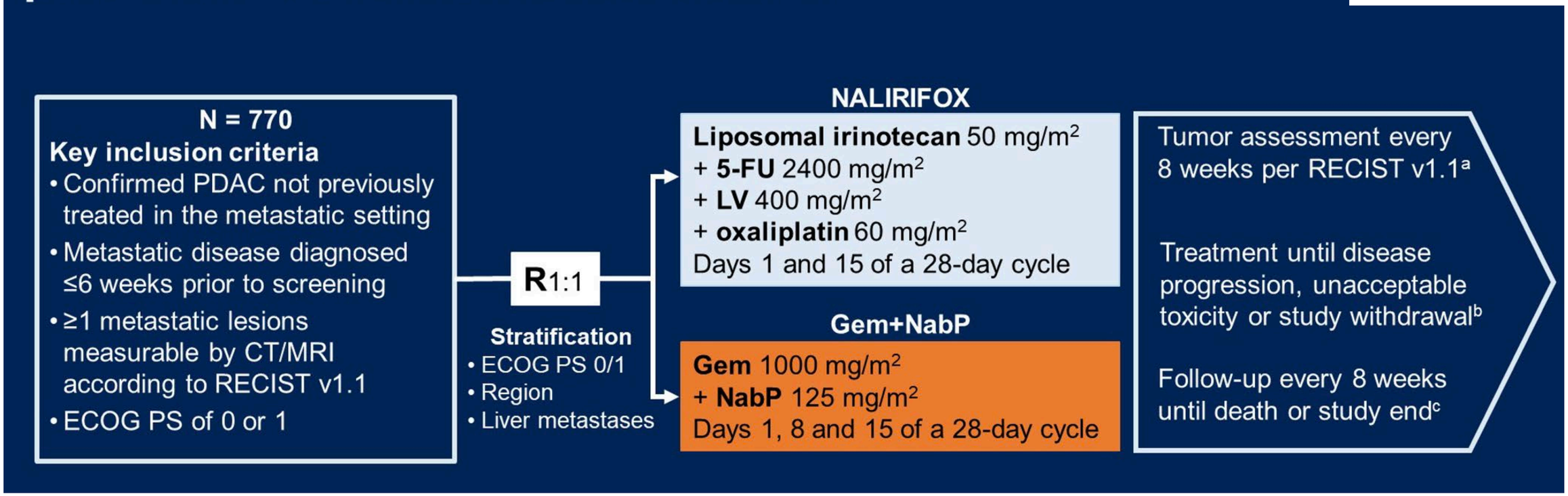
A high proportion of patients receiving trastuzumab deruxtecan in this study reached the primary endpoint of confirmed objective response rate by independent central review (33 [42%; 95% CI 30·8–53·4] of 79; Nov 8, 2021 data cutoff)

Van Cutsem E et. al, Lancet Oncol. 2023 Jul;24(7):744-756. doi: 10.1016/S1470-2045(23)00215-2. Epub 2023 Jun 14. PMID: 37329891.



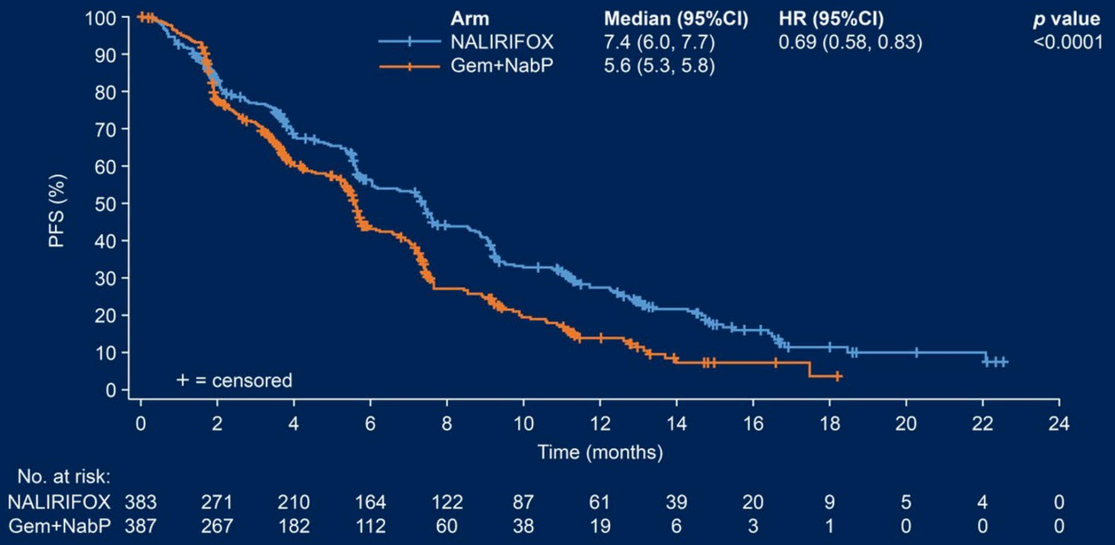
Van Cutsem E et. al, Lancet Oncol. 2023 Jul;24(7):744-756. doi: 10.1016/S1470-2045(23)00215-2. Epub 2023 Jun 14. PMID: 37329891.

NAPOLI 3: A randomized, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma

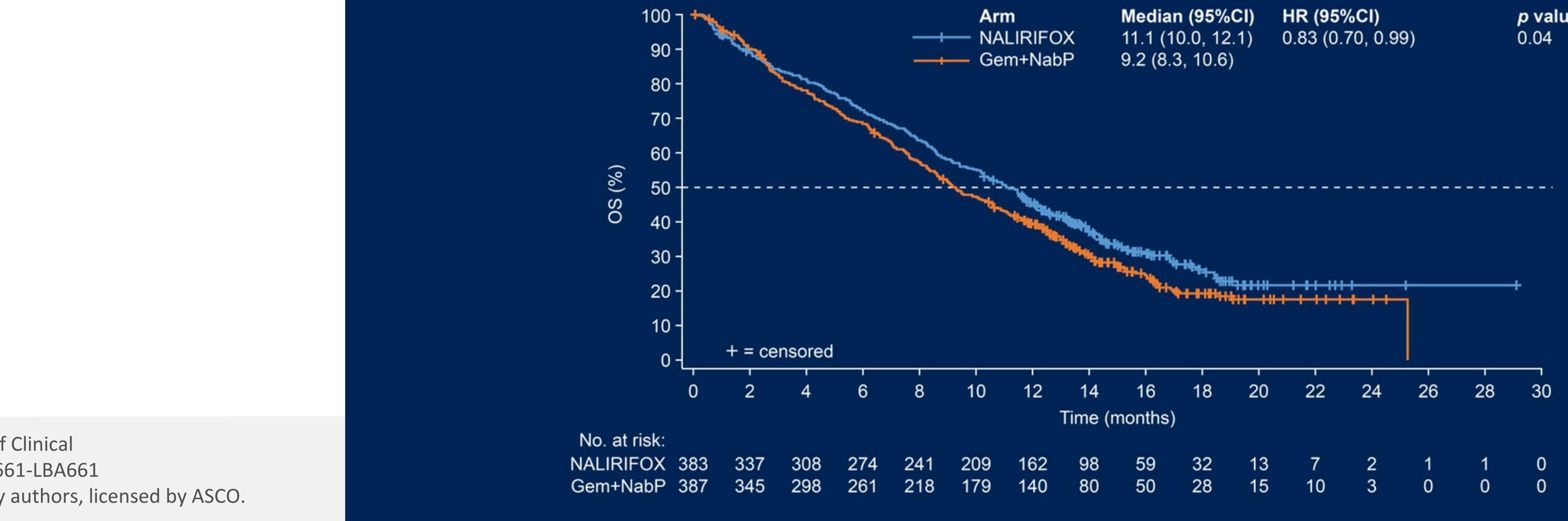


Zev A. Wainberg, et al. Journal of Clinical Oncology 2023 41:4_suppl, LBA661-LBA661

NAPOLI 3: mPFS per investigator (ITT population)



NAPOLI 3: mOS (ITT population)



Zev A. Wainberg, et al. Journal of Clinical Oncology 2023 41:4_suppl, LBA661-LBA661

FDA approves irinotecan liposome for first-line treatment of metastatic pancreatic adenocarcinoma

On February 13, 2024, the Food and Drug Administration approved irinotecan liposome (Onivyde, Ipsen Biopharmaceuticals, Inc.) with oxaliplatin, fluorouracil, and leucovorin, for the first-line treatment of metastatic pancreatic adenocarcinoma.

View full prescribing information for Onivyde.

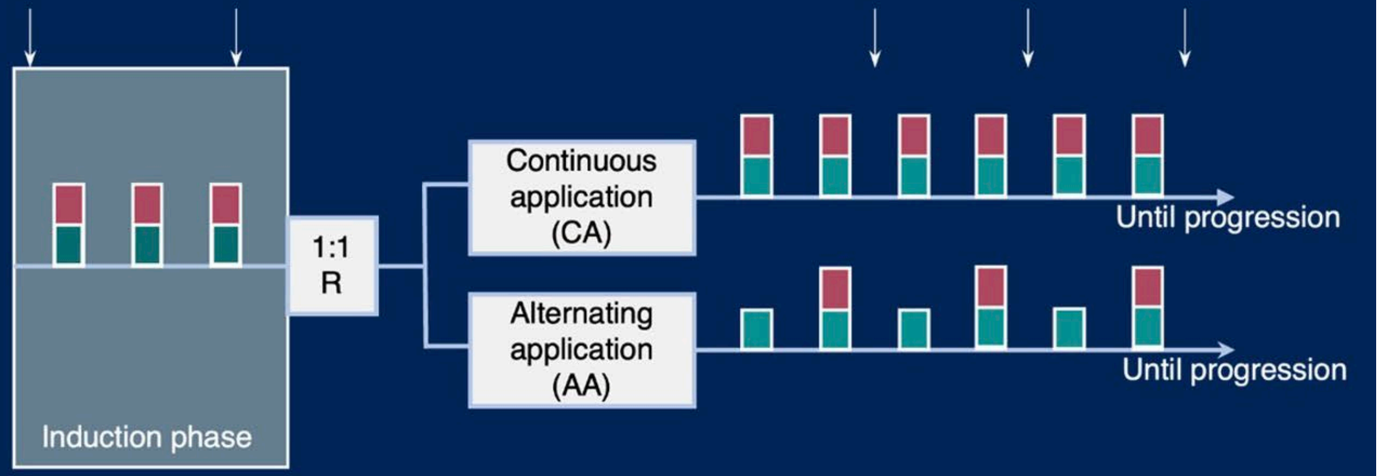
Efficacy was evaluated in NAPOLI 3 (NCT04083235), a randomized, multicenter, open-label, active-controlled trial in 770 patients with metastatic pancreatic adenocarcinoma who had not previously received chemotherapy in the metastatic setting. Randomization was stratified by region, liver metastases, and ECOG performance status. Patients were randomized (1:1) to receive one of the following treatments:

Alternating Gemcitabine/nab-Paclitaxel and Gemcitabine Versus Continuous Gemcitabine/nab-Paclitaxel after Induction Treatment of Metastatic Pancreatic Cancer: The Randomized ALPACA Trial (AIO-PAK-0114)

n = 325

Key inclusion criteria:

- Age ≥18 years
- Confirmed PDAC not previously treated in the metastatic setting
- ≥1 lesion measurable by CT/MRI according to RECIST v1.1
- KPS of 70-100%



Stratification factors:
KPS 70-80% vs. 90-100%
Presence vs. no presence of liver metastasis

nab-Paclitaxel 125 mg/m² on days 1, 8, 15 of a 28-day cycle

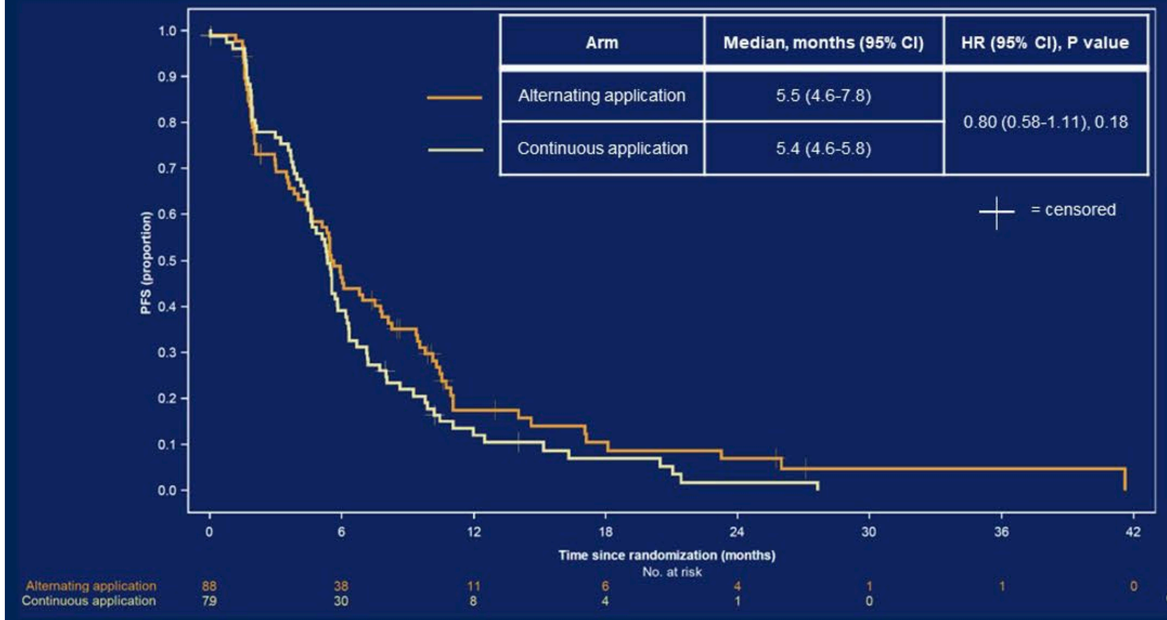
Gemcitabine 1000 mg/m² on days 1, 8, 15 of a 28-day cycle

CT/MRI

Klara Dorman, et al. Journal of Clinical Oncology 2024 42:3_suppl, 605-605

ALPACA: Survival (Full Analysis Set)

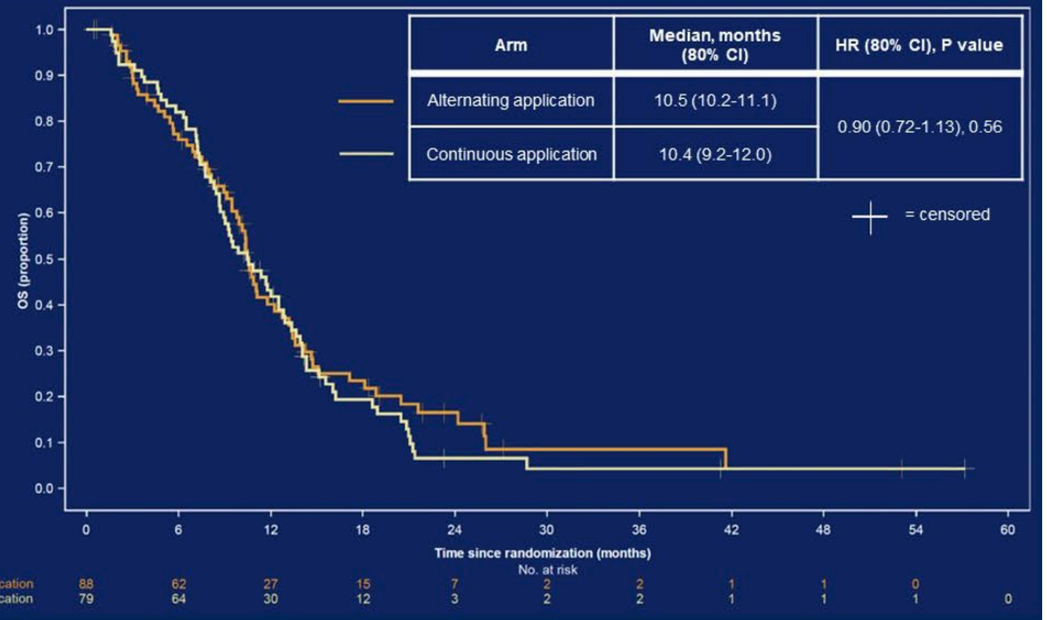
Progression-free survival (PFS)



Arm	Median, months (95% CI)	HR (95% CI), P value
Alternating application	5.5 (4.6-7.8)	0.80 (0.58-1.11), 0.18
Continuous application	5.4 (4.6-5.8)	

= censored

Overall survival (OS)

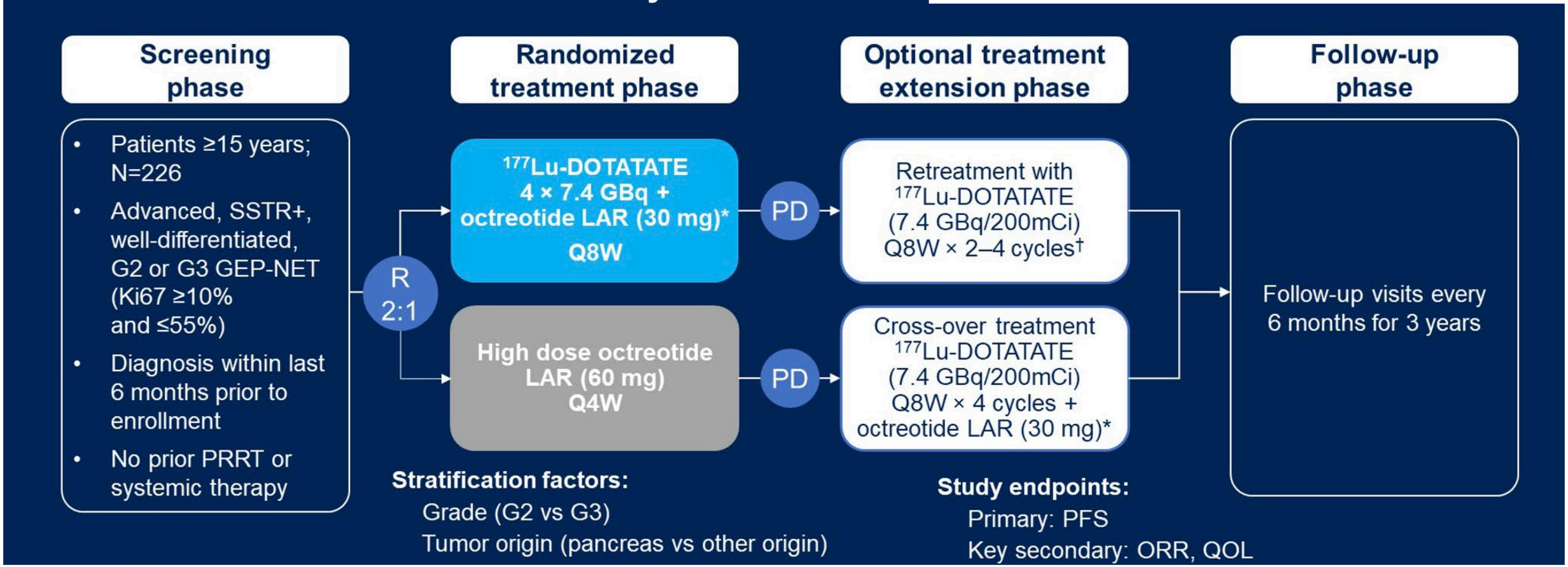


Arm	Median, months (80% CI)	HR (80% CI), P value
Alternating application	10.5 (10.2-11.1)	0.90 (0.72-1.13), 0.56
Continuous application	10.4 (9.2-12.0)	

= censored

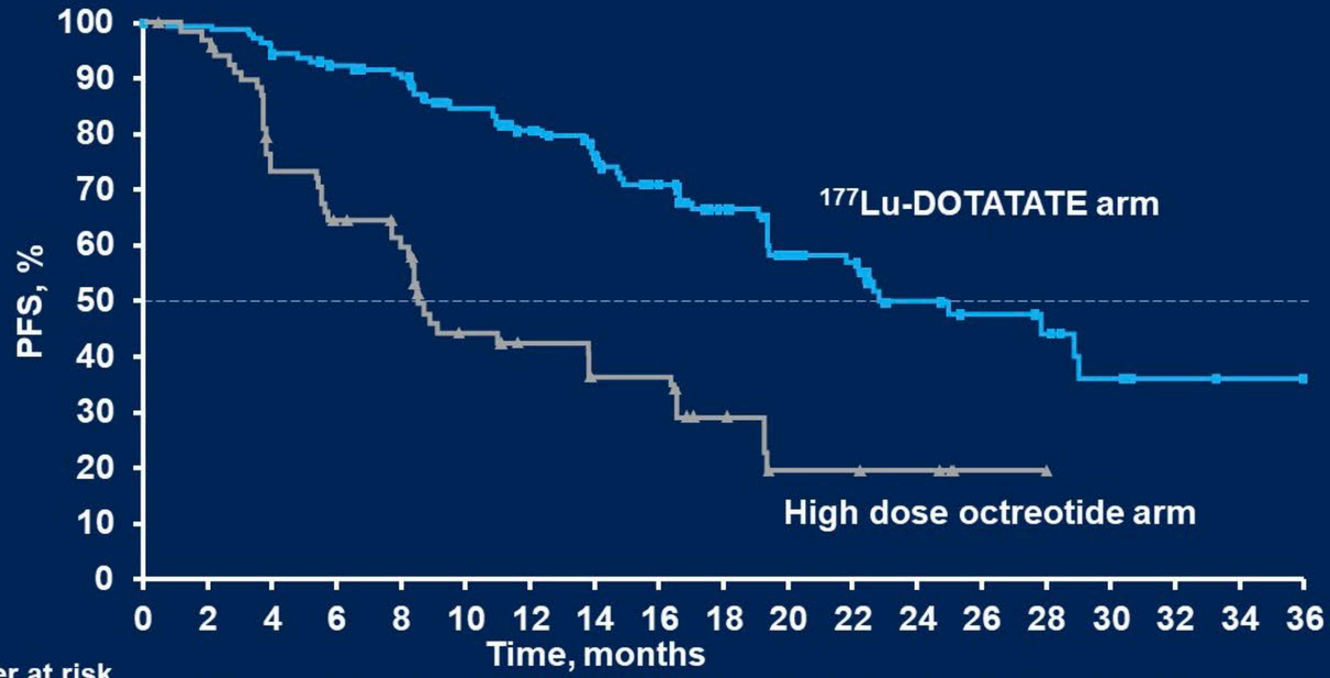
Klara Dorman, et al. Journal of Clinical Oncology 2024 42:3_suppl, 605-605

Efficacy and Safety of [^{177}Lu]Lu-DOTA-TATE in Newly Diagnosed Patients with Advanced Grade 2 and Grade 3, Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: Primary Analysis of the Phase 3 Randomized NETTER-2 Study



Simron Singh, et al. Journal of Clinical Oncology 2024 42:3_suppl, LBA588-LBA588

^{177}Lu-DOTATATE showed significant improvement in primary PFS endpoint



Number at risk																			
^{177}Lu-DOTATATE	151	143	138	129	125	104	92	80	68	53	41	37	23	19	13	9	4	2	0
High dose octreotide	75	67	49	42	37	24	21	16	16	10	5	5	4	1	1	0	0	0	0

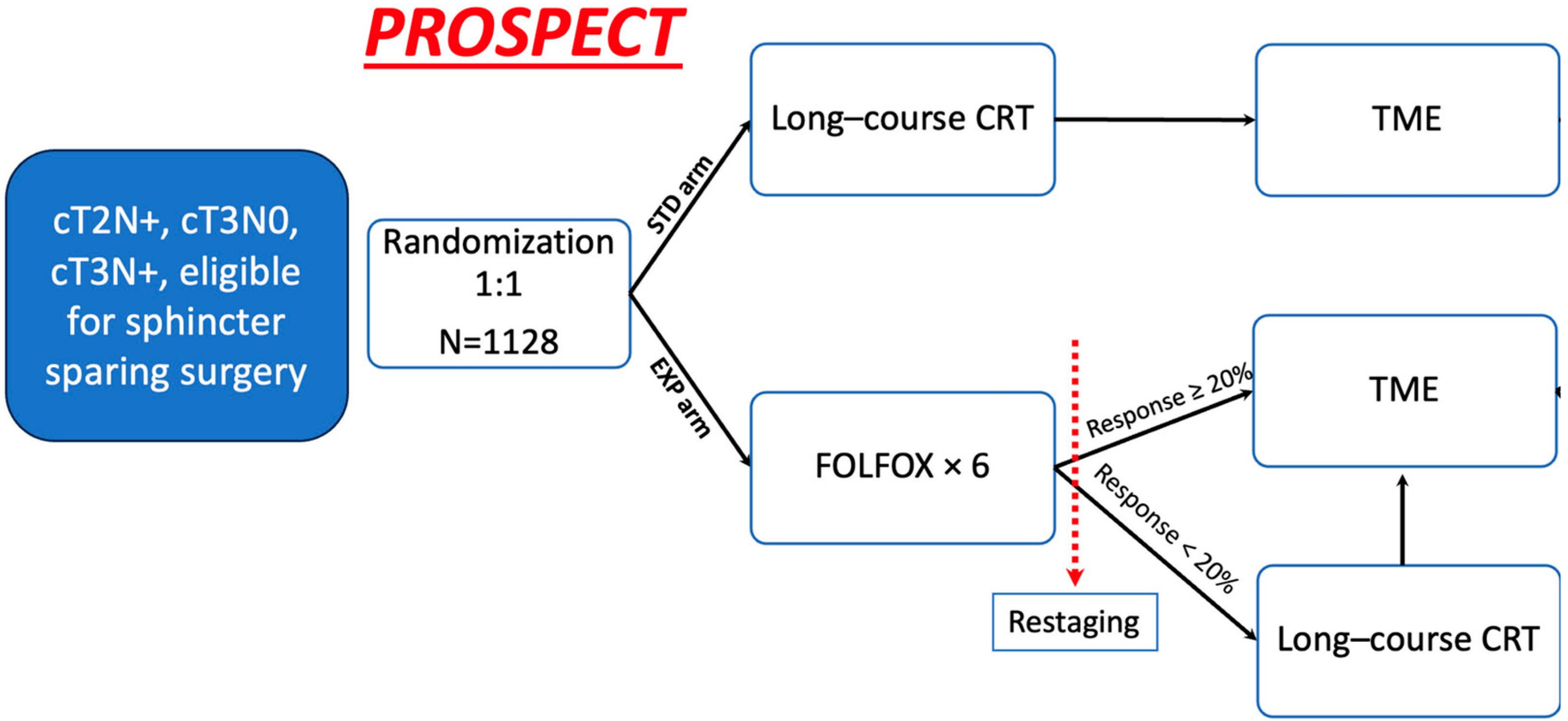
	^{177}Lu-DOTATATE arm n=151	High dose octreotide arm n=75
PFS median, months (95% CI)	**22.8** (19.4, NE)	**8.5** (7.7, 13.8)
Stratified HR (95% CI)	**0.276 (0.182, 0.418)**	
p-value	**<0.0001**	
Number of events, n (%)	55 (36)	46 (61)
Progression	47 (31)	41 (55)
Death	8 (5)	5 (7)

72% reduction in the risk of disease progression or death in the ^{177}Lu-DOTATATE arm versus the high dose octreotide arm

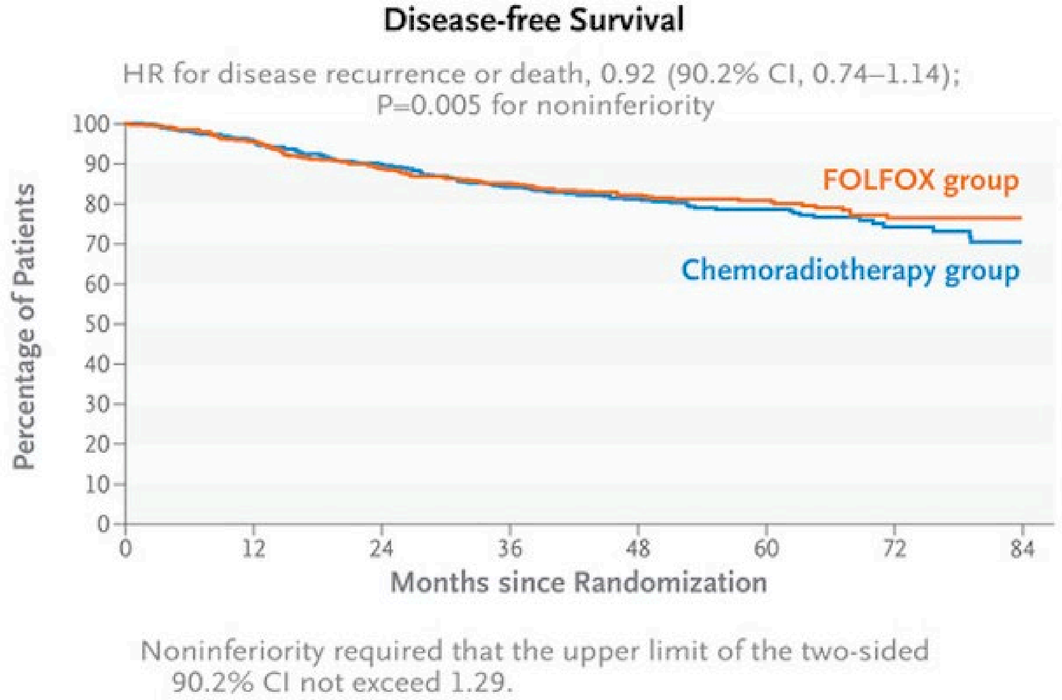
PFS centrally assessed according to RECIST 1.1
CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

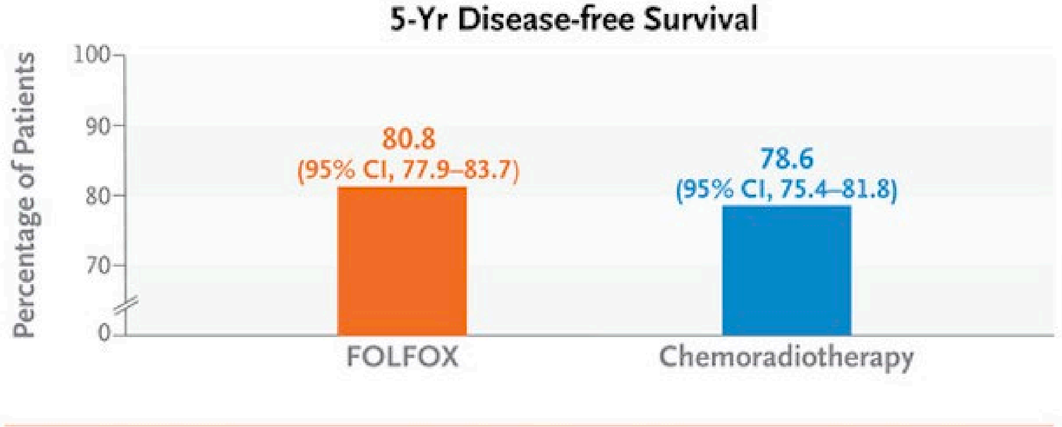
Simron Singh, et al. Journal of Clinical Oncology 2024 42:3_suppl, LBA588-LBA588

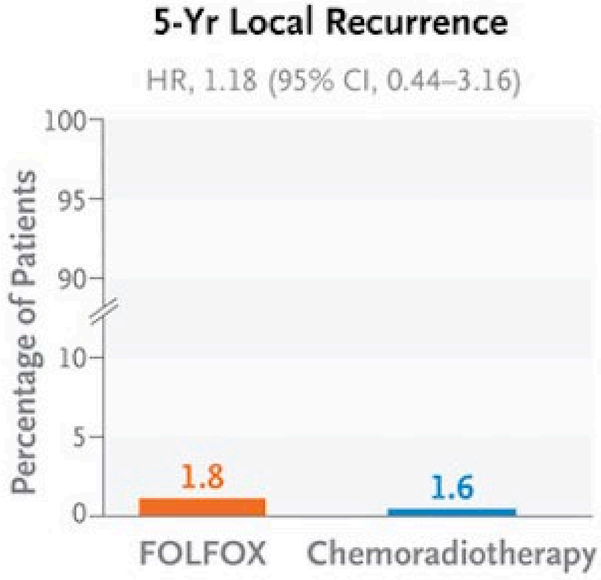
PROSPECT: A randomized phase III trial of neoadjuvant chemoradiation versus neoadjuvant FOLFOX chemotherapy with selective use of chemoradiation, followed by total mesorectal excision (TME) for treatment of locally advanced rectal cancer (LARC) (Alliance N1048).

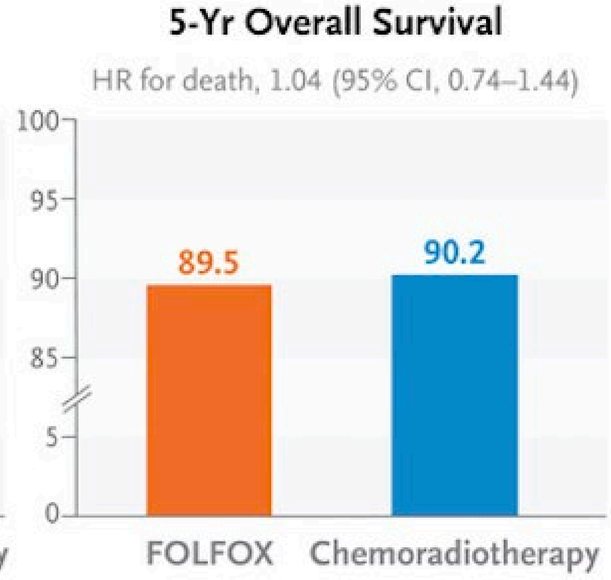


Schrag et al. N Engl J Med 2023;389:322-334
Dapra V et al. *Int. J. Mol. Sci.* 2023, *24*, 12159.









CONCLUSIONS

In patients with locally advanced rectal cancer amenable to sphincter-sparing surgery, neoadjuvant FOLFOX chemotherapy with selective use of chemoradiotherapy was noninferior to neoadjuvant chemoradiotherapy for disease-free survival, and nearly 90% of patients in the FOLFOX group were able to avoid chemoradiotherapy.

Schrag et al. N Engl J Med 2023;389:322-334

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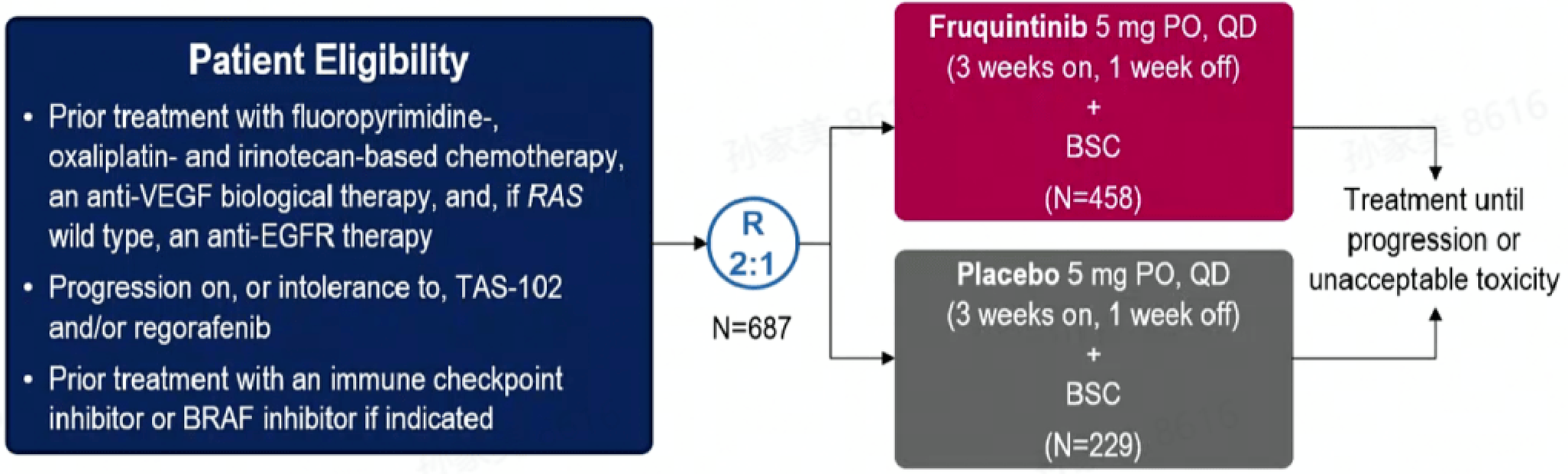
Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study

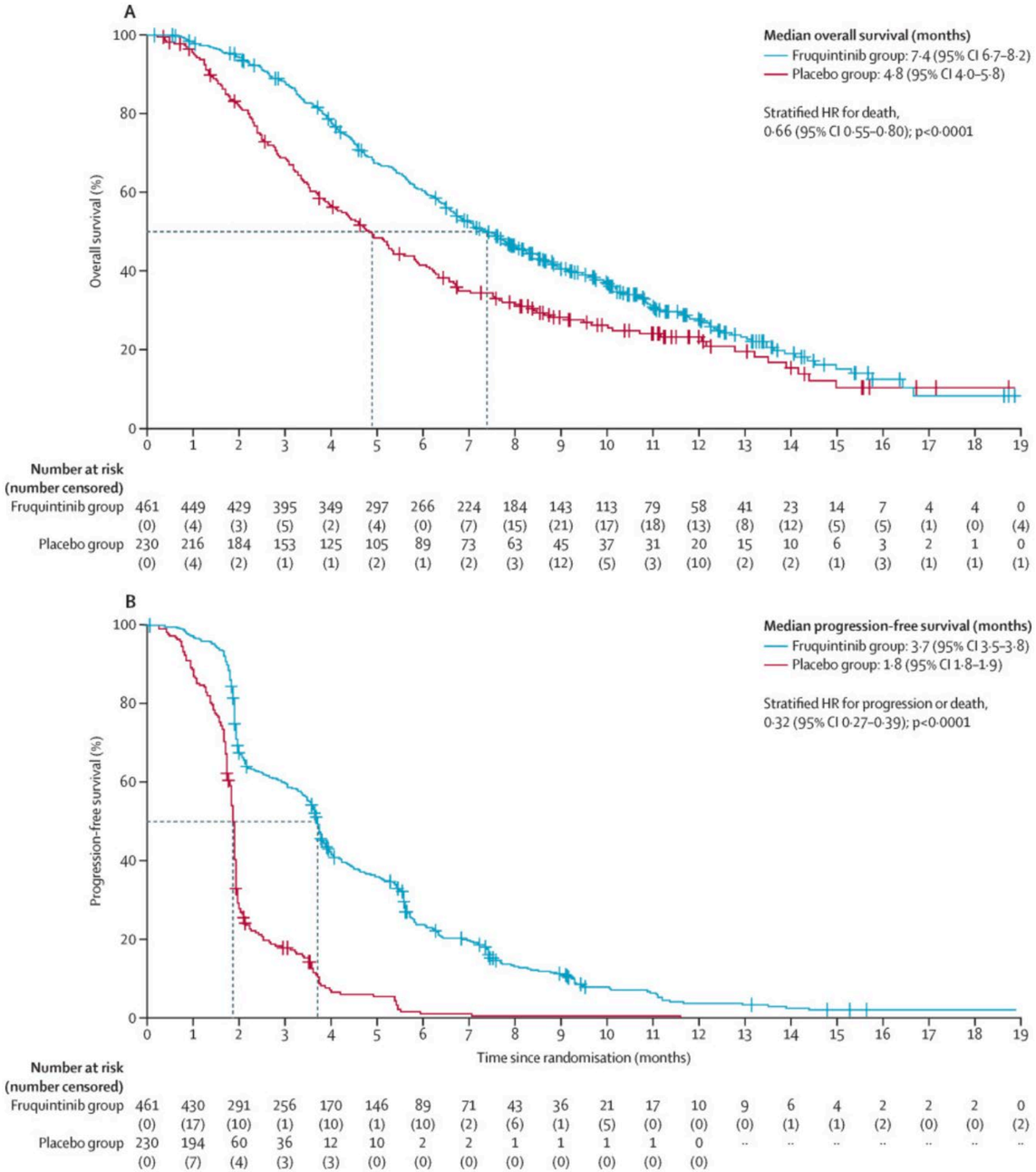


Stratification Factors

- Prior therapy (TAS-102 vs regorafenib vs TAS-102 and regorafenib)
- *RAS* mutational status (wild-type vs mutant)
- Duration of metastatic disease (≤18 months vs >18 months)

Note: To ensure the patient population is reflective of clinical practice, the number of patients treated with prior regorafenib was limited to 344 patients (50%)

Dasari A, et al. Lancet. 2023 Jul 1;402(10395):41-53. doi: 10.1016/S0140-6736(23)00772-9. Epub 2023 Jun 15. PMID: 37331369.



Dasari A, et al. Lancet. 2023 Jul 1;402(10395):41-53. doi: 10.1016/S0140-6736(23)00772-9. Epub 2023 Jun 15. PMID: 37331369.

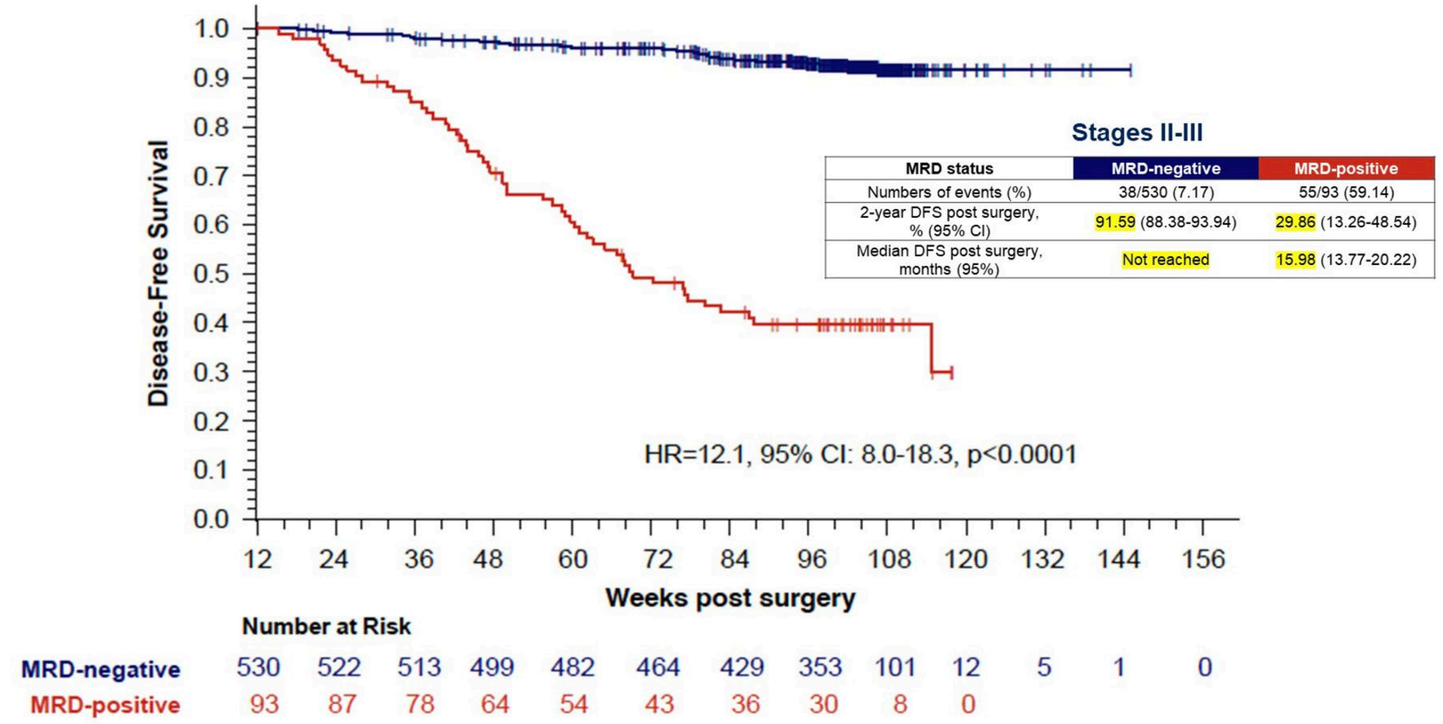
FDA approves fruquintinib in refractory metastatic colorectal cancer

On November 8, 2023, the Food and Drug Administration approved fruquintinib (Fruzaqla, Takeda Pharmaceuticals, Inc.) for adult patients with metastatic colorectal cancer (mCRC) who received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy.

Role of ctDNA in Colorectal Cancer – Updates from GI ASCO 2024

Circulating tumor DNA (ctDNA) for informing adjuvant chemotherapy (ACT) in stage II/III colorectal cancer (CRC): Interim analysis of BESPOKE CRC study

ctDNA-positivity at MRD time point is predictive of inferior DFS



MRD window:
2-12 weeks post-surgery, before the start of adjuvant chemotherapy (ACT)

Surveillance window: >2 weeks post-ACT or >12 weeks post-surgery if on observation

Pashtoon Murtaza Kasi et al. Journal of Clinical Oncology 2024 42:3_suppl, 9-9

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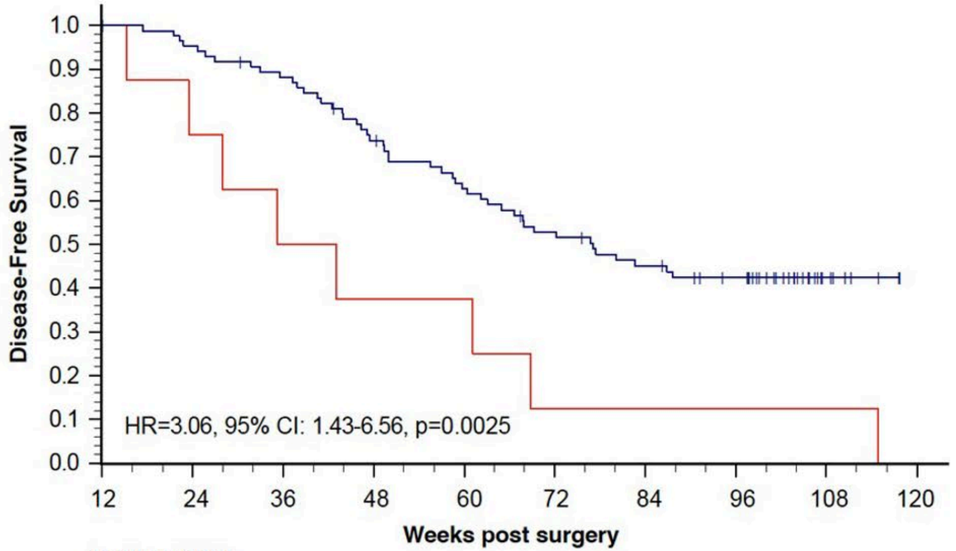
Benefit from ACT observed in MRD-positive but not MRD-negative patients

MRD-positive patients

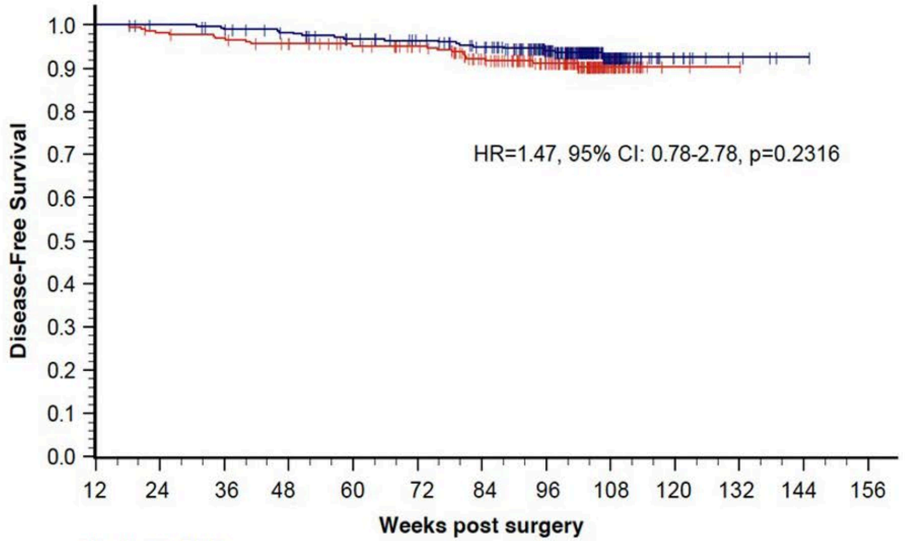


Number at Risk

ACT	85	80	72	56	48	39	32	18	2	0
Observation	8	6	4	3	2	1	1	1	0	

Adjuvant strategy	ACT	Observation
Numbers of events (%)	47/85 (55.29)	8/8 (100)
2-year DFS post surgery, % (95% CI)	42.44 (31.55-52.91)	12.50 (0.66-42.27)
Median DFS post surgery, months (95%)	17.78 (14.37-not reached)	7.52 (3.52-15.88)

MRD-negative patients



Number at Risk

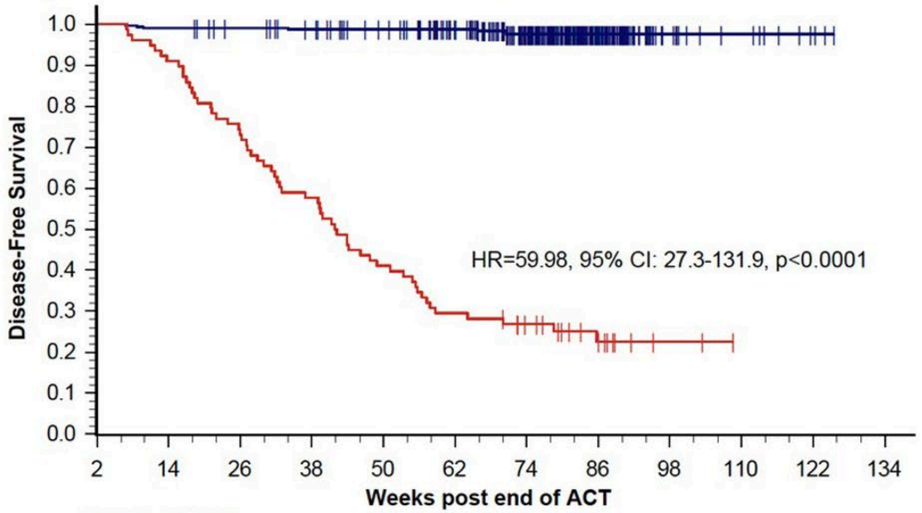
ACT	296	293	288	281	271	263	251	207	61	10	4	1	0
Observation	234	229	225	218	211	201	178	146	40	2	1	0	

Adjuvant strategy	ACT	Observation
Numbers of events (%)	18/296 (6.08)	20/234 (8.55)
2-year DFS post surgery, % (95% CI)	93.70 (90.03-96.05)	90.39 (85.38-93.75)
Median DFS post surgery, months (95%)	Not reached	Not reached

PRESENTED BY: Pashtoon Kasi, MD

ctDNA-positivity during surveillance is predictive of inferior DFS regardless of adjuvant therapy (ACT or observation)

Patients receiving ACT

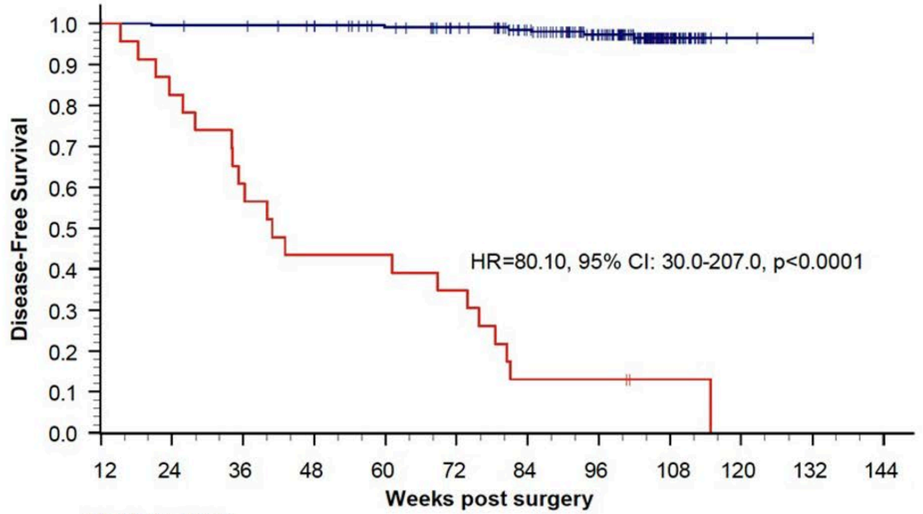


Number at Risk

ctDNA-negative	329	326	321	315	305	278	213	87	16	9	3	0
ctDNA-positive	78	71	57	45	32	23	17	8	2	0		

ctDNA status (surveillance)	ctDNA-negative	ctDNA-positive
Numbers of events (%)	7/329 (2.13)	59/78 (75.64)
2-year DFS post end of ACT, % (95% CI)	97.58 (94.96-98.84)	22.56 (13.49-33.08)
Median DFS post end of ACT, months (95%)	Not reached	9.70 (7.43-12.32)

Patients on observation



Number at Risk

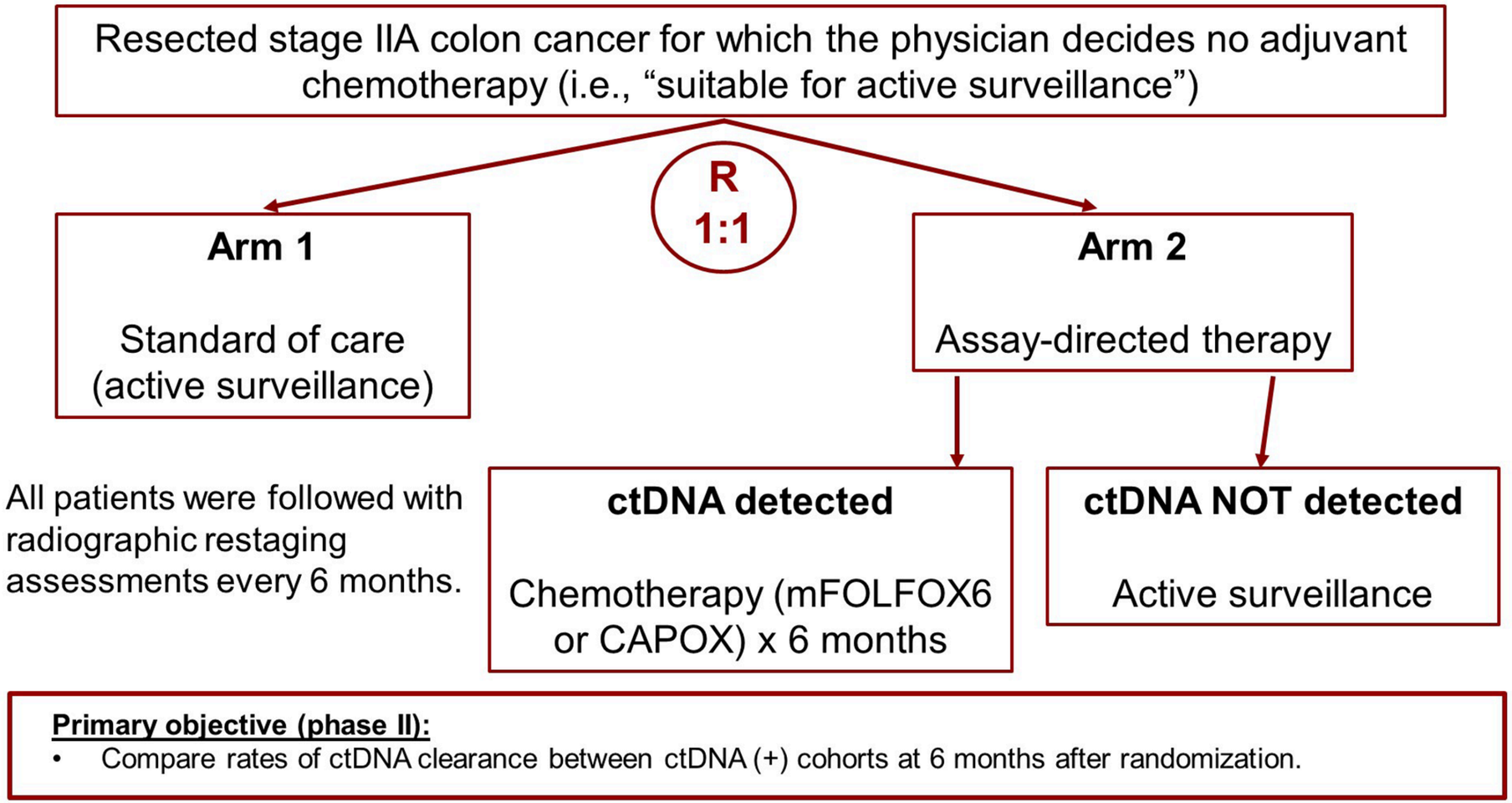
ctDNA-negative	225	224	223	219	211	201	183	151	42	2	1	0
ctDNA-positive	23	19	14	10	10	8	3	3	1	0		

ctDNA status (surveillance)	ctDNA-negative	ctDNA-positive
Numbers of events (%)	6/225 (2.67)	21/23 (91.30)
2-year DFS post surgery, % (95% CI)	96.60 (92.44-98.49)	13.04* (3.27-29.72)
Median DFS post surgery, months (95%)	Not reached	9.44 (7.86-17.03)

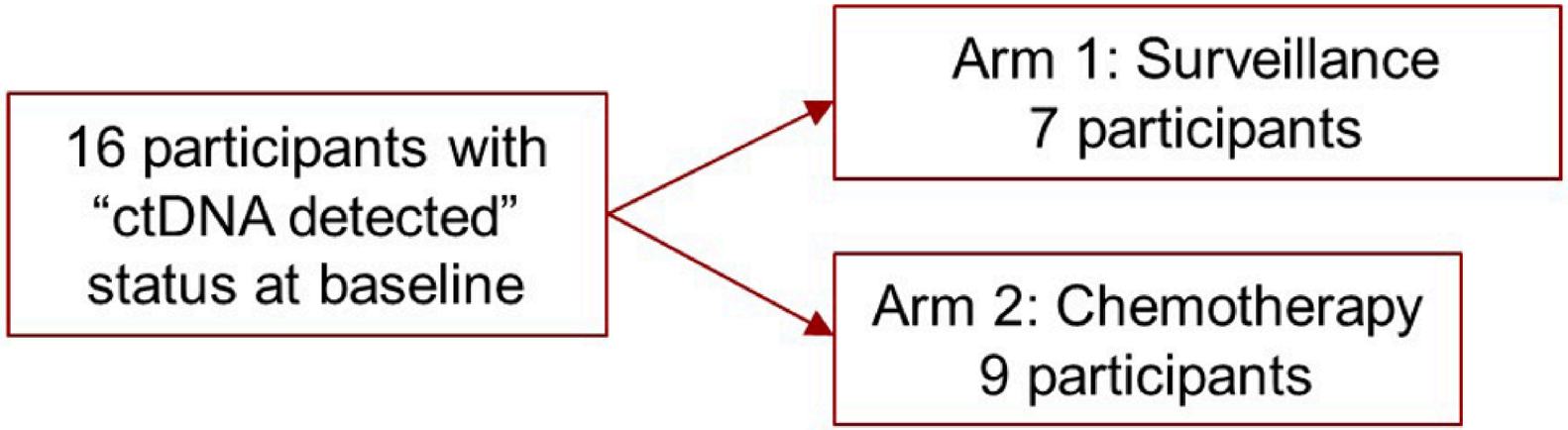
*Most recurrences occurred within the1st year.

PRESENTED BY: Pashtoon Kasi, MD

Phase II results of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA) phase II/III study



Van K Morris et al. Journal of Clinical Oncology 2024 42:3_suppl, 5-5



Clearance of ctDNA at 6 months among ctDNA(+) participants at baseline was observed in:

- **Arm 1 (surveillance):** 3 of 7 (43%, 95% CI 10 - 82%) participants
- **Arm 2 (chemotherapy):** 1 of 9 patients (11%, 95% CI 0.3 - 48%) participants

Study was discontinued early due to futility.

Take Home Points on ctDNA in Colorectal cancer

Given the poor prognostic risk of positive ctDNA and early data on improvement in short-term outcomes with adjuvant chemotherapy, consider use of a positive ctDNA test to escalate treatment in Stage II/III colorectal cancer patients.

We do *not* have enough evidence at this time to use a negative ctDNA test to de-escalate therapy.

Use of ctDNA for monitoring cancer recurrence requires shared decision-making with the patient.

Thank You

West Virginia Oncology Society