UPDATES IN COLORECTAL CANCER

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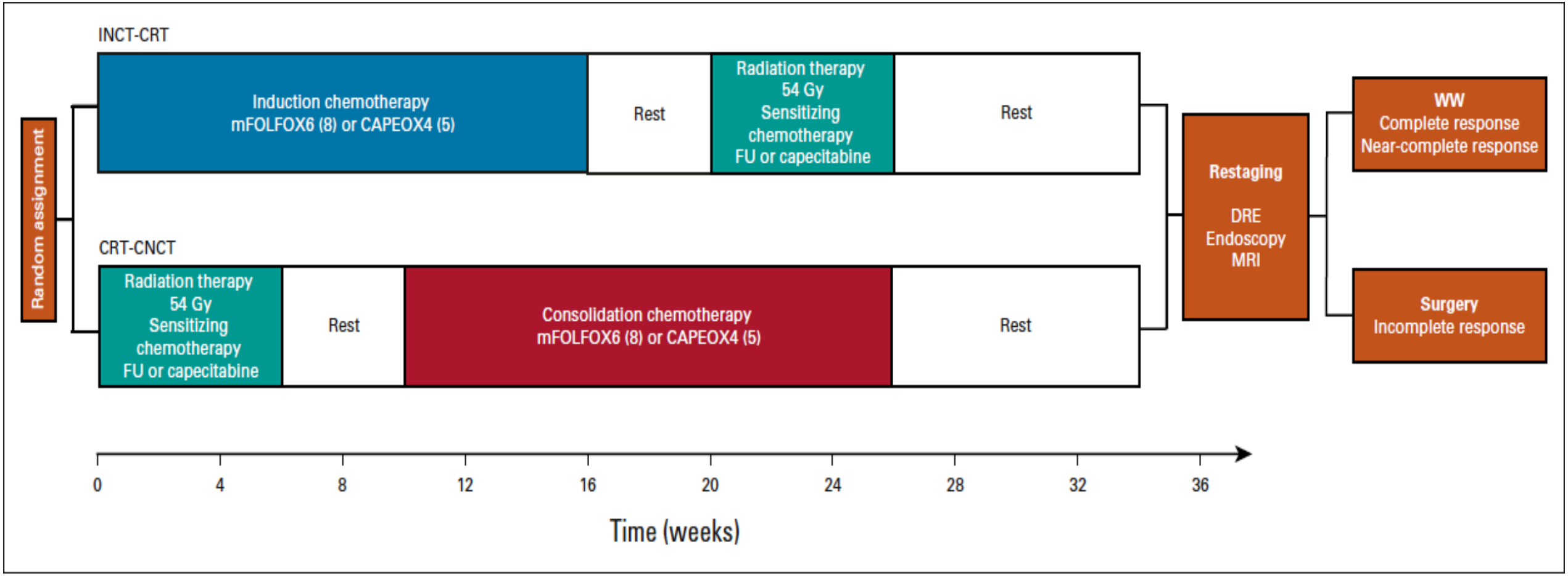
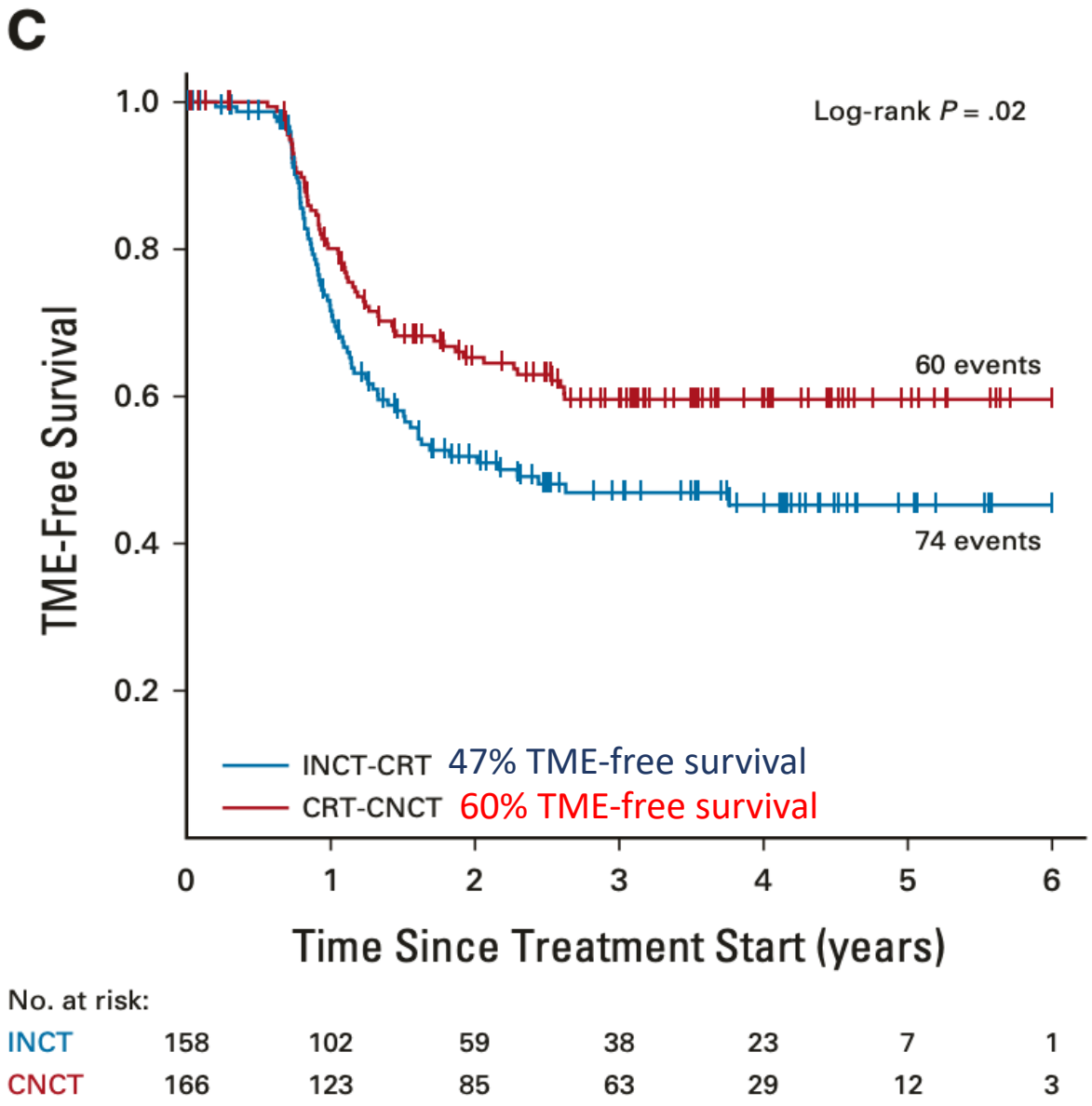
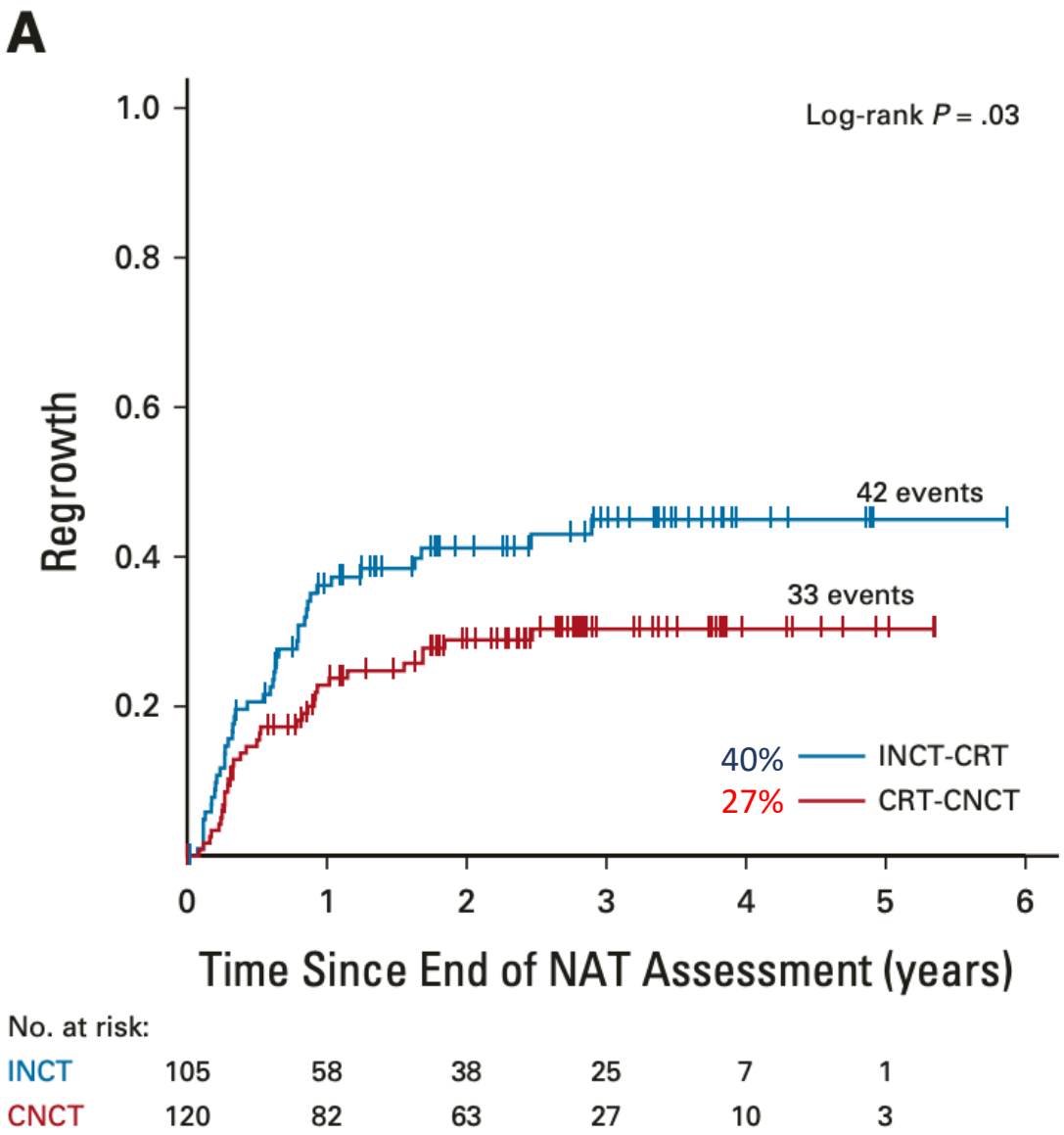
Neoadjuvant treatment of rectal cancer

OPRA Phase II Randomized Trial



Garcia-Aguilar J, et al. *J Clin Oncol* 2022





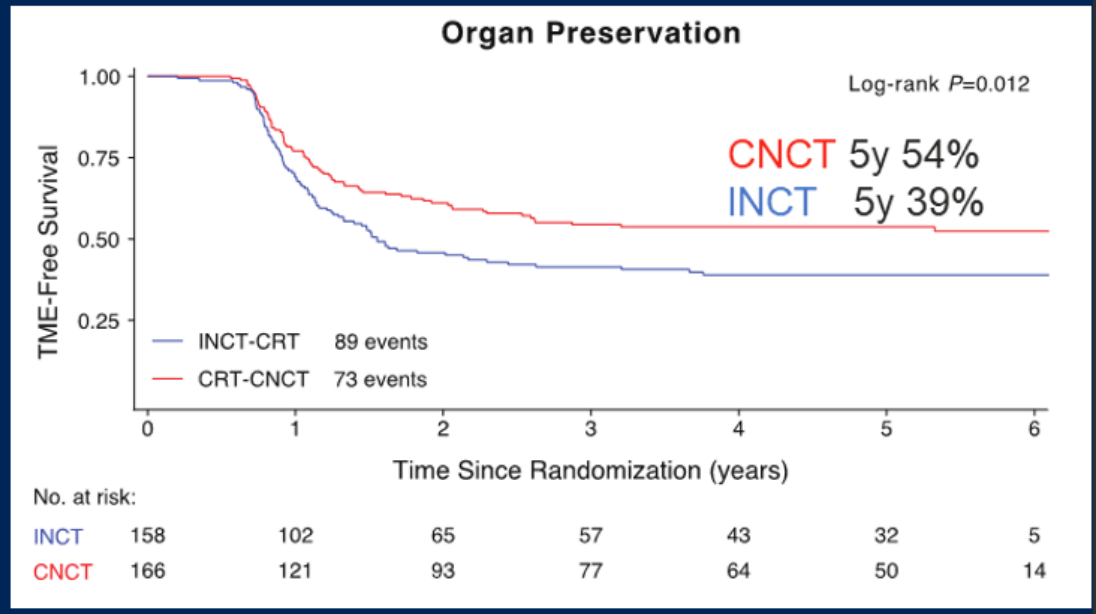
Garcia-Aguilar J, et al. *J Clin Oncol* 2022

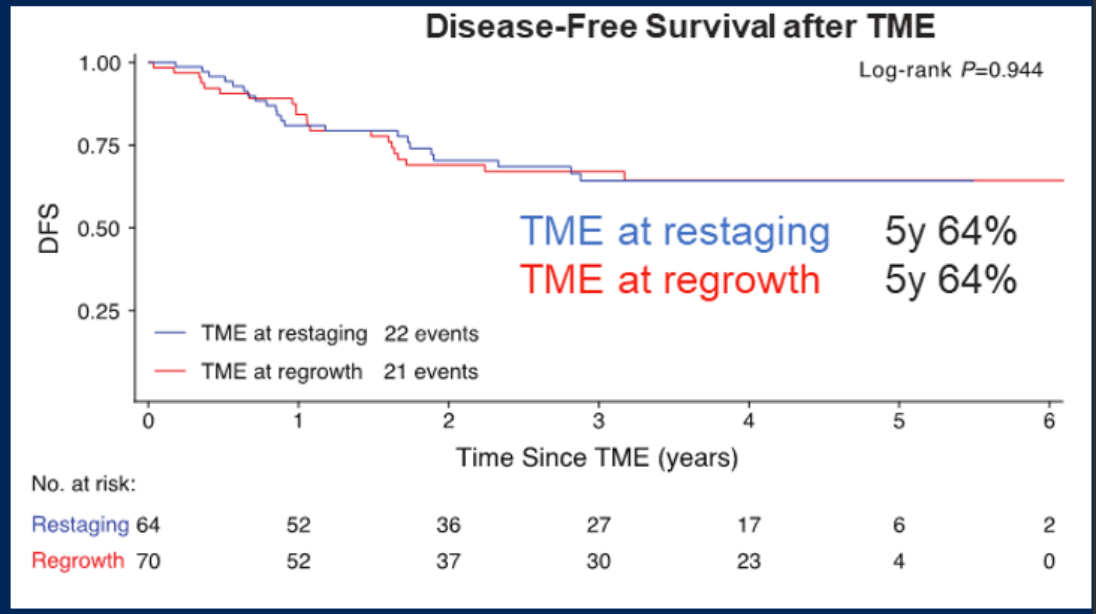
Unanswered Questions from 2022

- Do patients who develop regrowth and require salvage TME do worse than those treated with upfront TME (i.e., do we miss the window for cure)
- Updated (5-year) organ preservation (TME-free survival) between INCT-CRT and CRT-CNCT
- What is the timing of Regrowth (i.e., when can we stop surveillance)

Median follow-up 5.1 years

- 225/304 (74%) were offered WW:
  - Similar rates for INCT and CNCT
- 81 (36%) developed a regrowth:
  - 44% of INCT patients.
  - 29% of CNCT patients.
- No difference in DFS between TME at restaging vs. at regrowth
- 94% of regrowths occurred within 2 years and 99% occurred within 3 years





Take Home Points

- Nearly half of rectal cancer patients preserve their rectum at 5 years, higher rates of organ preservation in patients treated with CRT-CNCT.

- The majority of tumor regrowths occur in the first 2 years, suggesting that a close follow-up in this period is critical.

- Salvage TME for tumor regrowth offers similar outcomes to immediate TME.

Surveillance following non-operative management

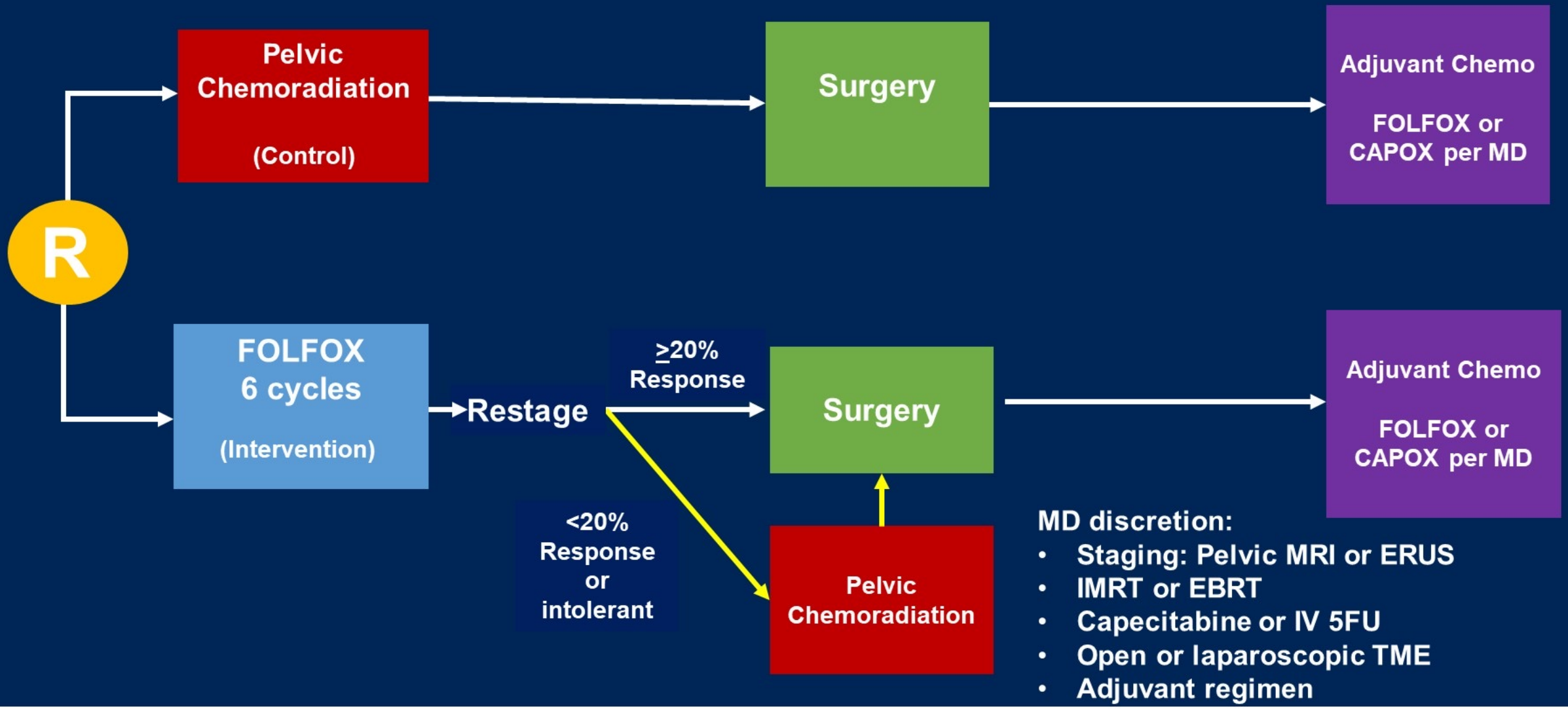
- History and physical examination every 3–6 months for 2 years and then every 6 months for a total of 5 years
- CEA every 3-6 months for 2 years, then every 6 months for a total of 5 years
- DRE and proctoscopy or flexible sigmoidoscopy every 3–4 months for 2 years, then every 6 months for a total of 5 years
- MRI rectum every 6 months for at least 3 years
- CT chest/abdomen every 6 months for years 1 and 2. CT chest/abdomen annually for years 4 and 5 with inclusion of pelvis.
- Colonoscopy at 1 year following completion of therapy
  - If advanced adenoma, repeat in 1 year
  - If no advanced adenoma, repeat in 3 years, then every 5 years

Timing of Assessment for cCR

- INCT:
  - Assessment should be performed no earlier than 8 weeks (we prefer 12 weeks) after completion of radiotherapy to allow time for delayed response to radiation.

- CNCT:
  - Assessment should be completed within a month of completion of chemotherapy.

PROSPECT Study Full Schema



PROSPECT Main Eligibility Criteria

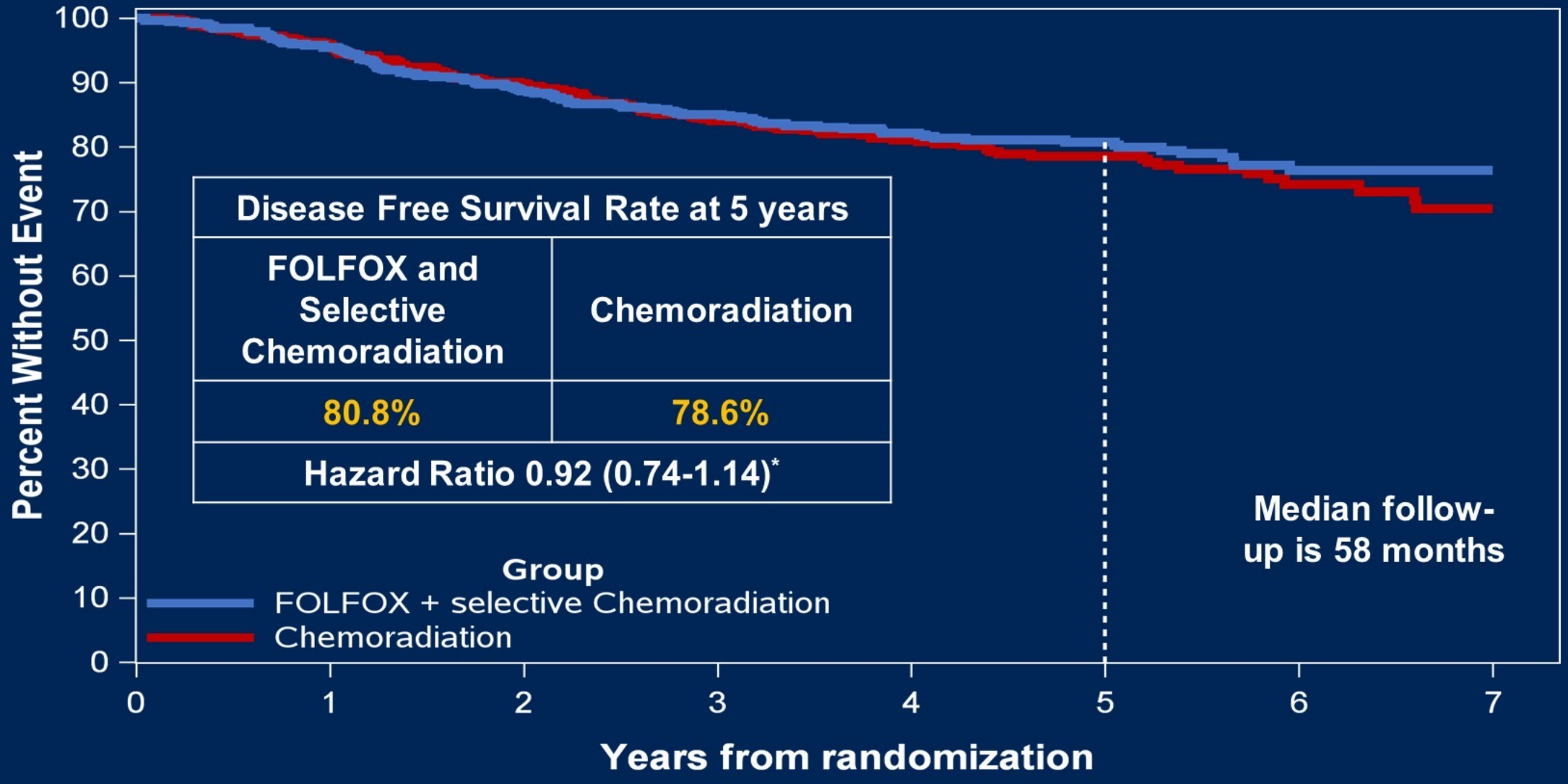
Inclusion:

- Clinical Stage T2N+, T3N-, T3N+
- Chemoradiation is indicated
- Candidate for sphincter-sparing surgery

Exclusion:

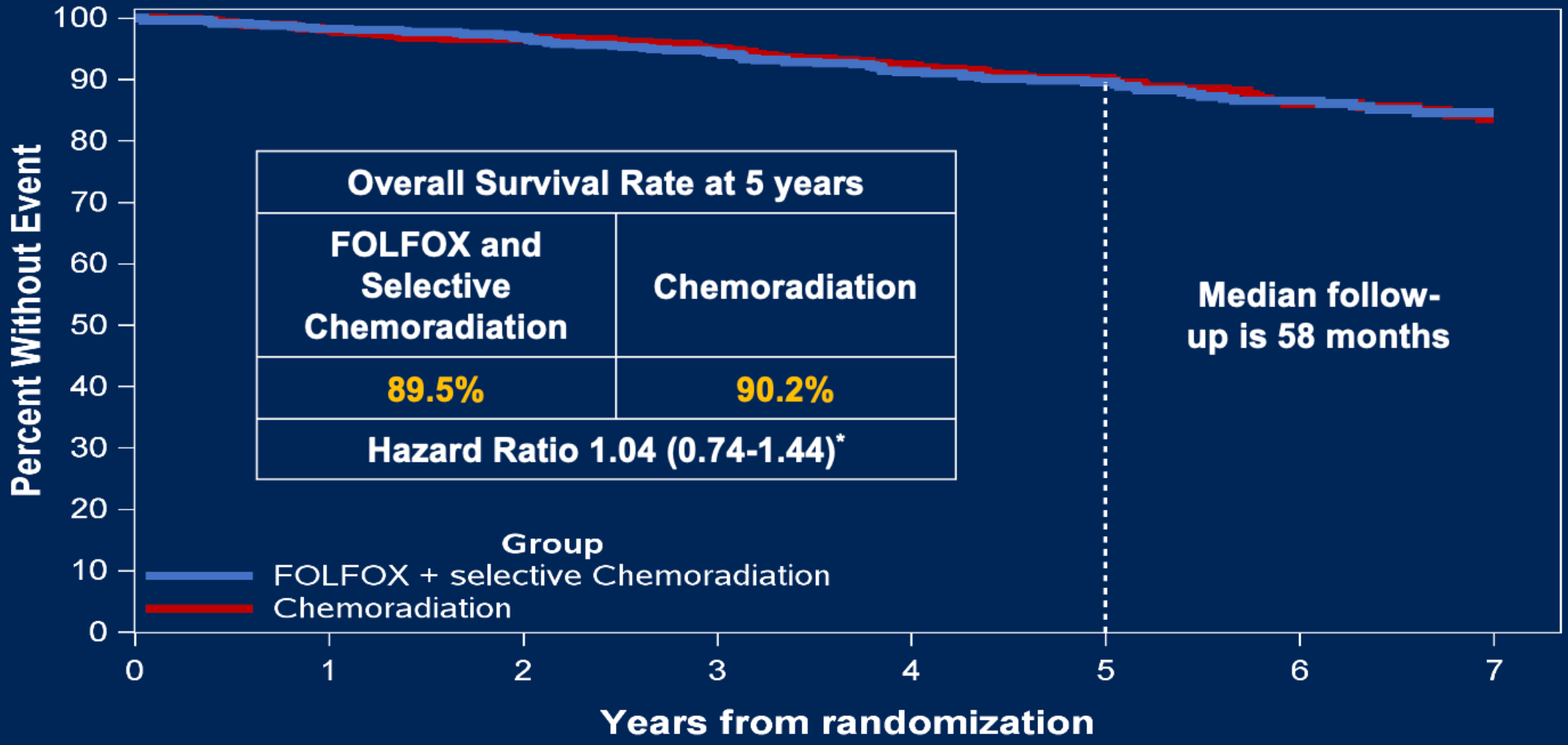
- Tumor requiring an APR
- cT4 tumor
- ≥ 4 pelvic lymph nodes ≥ 1cm in short axis

PROSPECT: Disease Free Survival



*Two-sided 90.2% confidence interval

PROSPECT: Overall Survival



Overall Survival Rate at 5 years	
FOLFOX and Selective Chemoradiation	Chemoradiation
89.5%	90.2%
Hazard Ratio 1.04 (0.74-1.44)*	

585	565	551	531	429	287	212	120
543	527	513	486	380	273	182	107

*Two-sided 95% confidence interval

Surgical and Pathologic Endpoints

Secondary endpoints in participants who completed Surgery	FOLFOX and Selective Pelvic Chemoradiation N=535	Pelvic Chemoradiation N=510
Complete (R0) Rectal Resection	99%	97%
Low Anterior Resection Rate	98%	98%
Pathologic Complete Response	22%	24%
Positive Radial margin	1.2%	1.5%

Use of Pelvic Chemoradiation in patients randomized to FOLFOX

9% (53/585) of participants randomized to FOLFOX received neoadjuvant chemoradiation either because:

Restaging demonstrated clinical response <20% or

They did not tolerate at least 5 cycles of FOLFOX

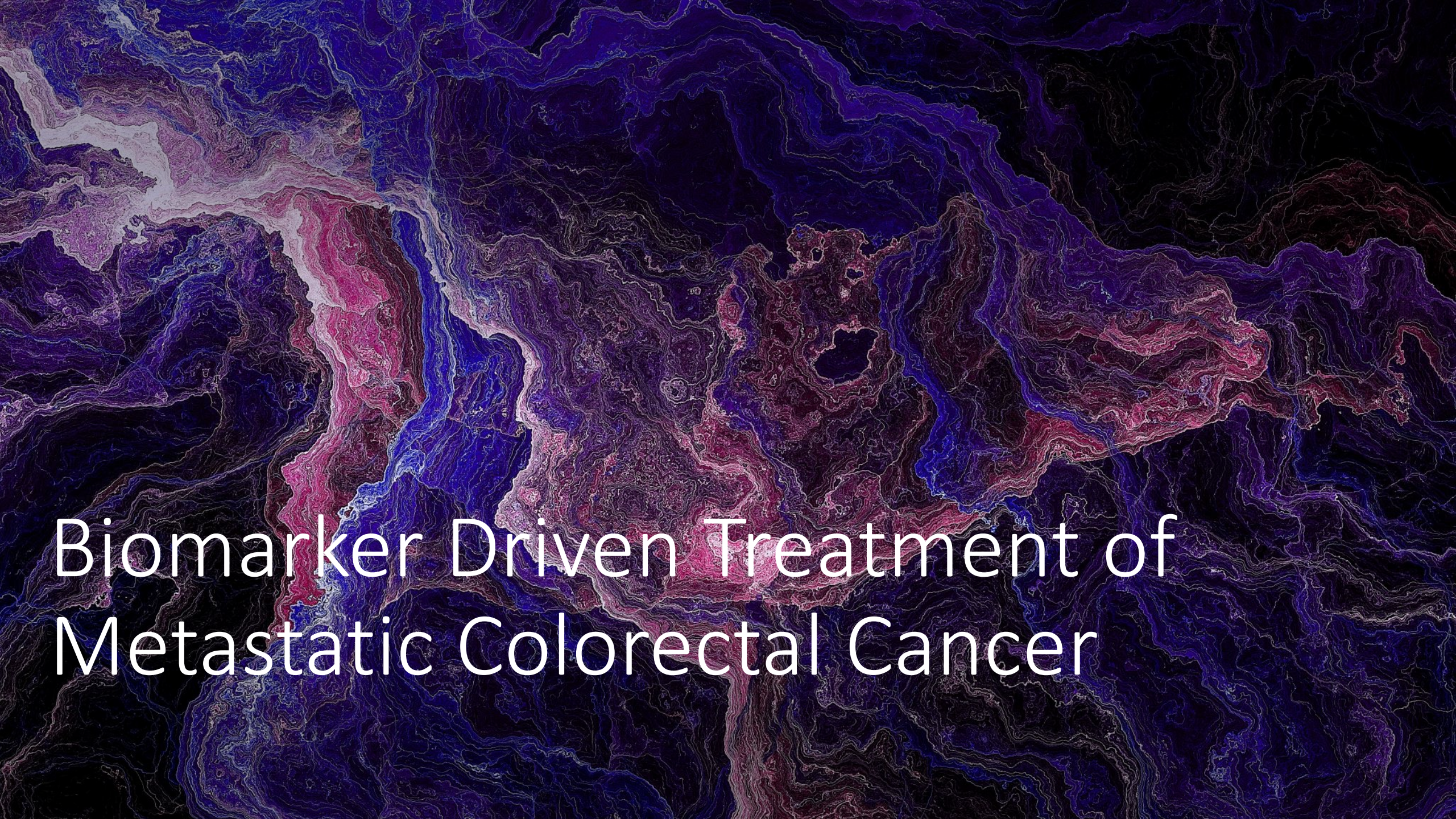
PRESENTED BY: Deb Schrag MD MPH FASCO

PROSPECT Trial Conclusion

Neoadjuvant FOLFOX, with only selective use of pelvic chemoradiation, is a safe and effective treatment option for patients with cT2N+, cT3N-, or cT3N+ rectal cancer

Remaining Questions for Non-Operative Management

- What are the long-term DFS and OS outcomes?
- Does NOM result in improved functional outcomes and QoL?
- Are there biomarkers (i.e. ctDNA, radiomics) that can better predict who may achieve pCR?
- What is the optimal surrogate endpoint for clinical trials of NOM?
- Is a NOM strategy feasible in the community setting?


Biomarker Driven Treatment of
Metastatic Colorectal Cancer

Targeting KRAS G12C Mutations: Adagrasib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated *KRAS* G12C

Rona Yaeger, M.D., Jared Weiss, M.D., Meredith S. Pelster, M.D., Alexander I. Spira, M.D., Ph.D., Minal Barve, M.D., Sai-Hong I. Ou, M.D., Ph.D., Ticiana A. Leal, M.D., Tanios S. Bekaii-Saab, M.D., Cloud P. Paweletz, Ph.D., Grace A. Heavey, B.A., James G. Christensen, Ph.D., Karen Velastegui, B.Sc., Thian Kheoh, Ph.D., Hirak Der-Torossian, M.D., and Samuel J. Klempner, M.D.

KRYSTAL-1

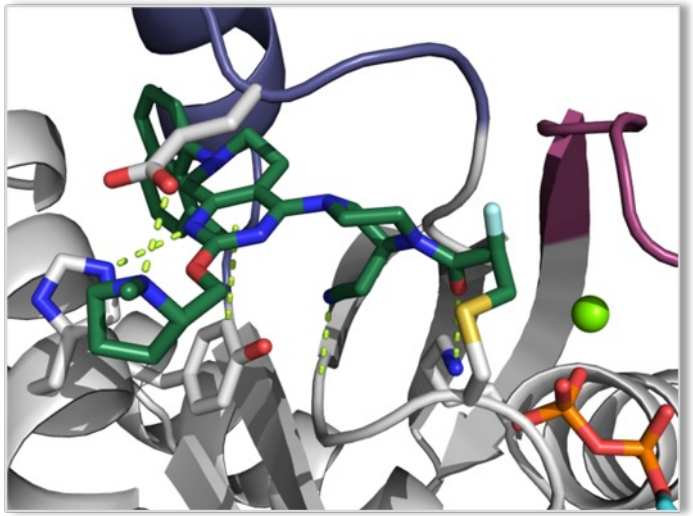
Yaeger, NEJM 2023

Targeting KRAS G12C Mutations: Adagrasib

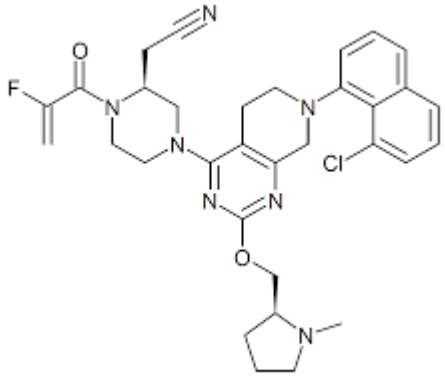
- $KRAS^{G12C}$ mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinoma), 3-4% of CRC, and 1-2% of several other cancers[1-3]

- Adagrasib is a covalent inhibitor of $KRAS^{G12C}$ that irreversibly and selectively binds $KRAS^{G12C}$ in its inactive, GDP-bound state[4]

- Adagrasib was optimized for desired properties of a $KRAS^{G12C}$ inhibitor:
  - Potent covalent inhibitor of $KRAS^{G12C}$ (cellular IC_{50}: ~5 nM)
  - High selectivity (>1000X) for the mutant $KRAS^{G12C}$ protein vs wild-type KRAS
  - Favorable PK properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution

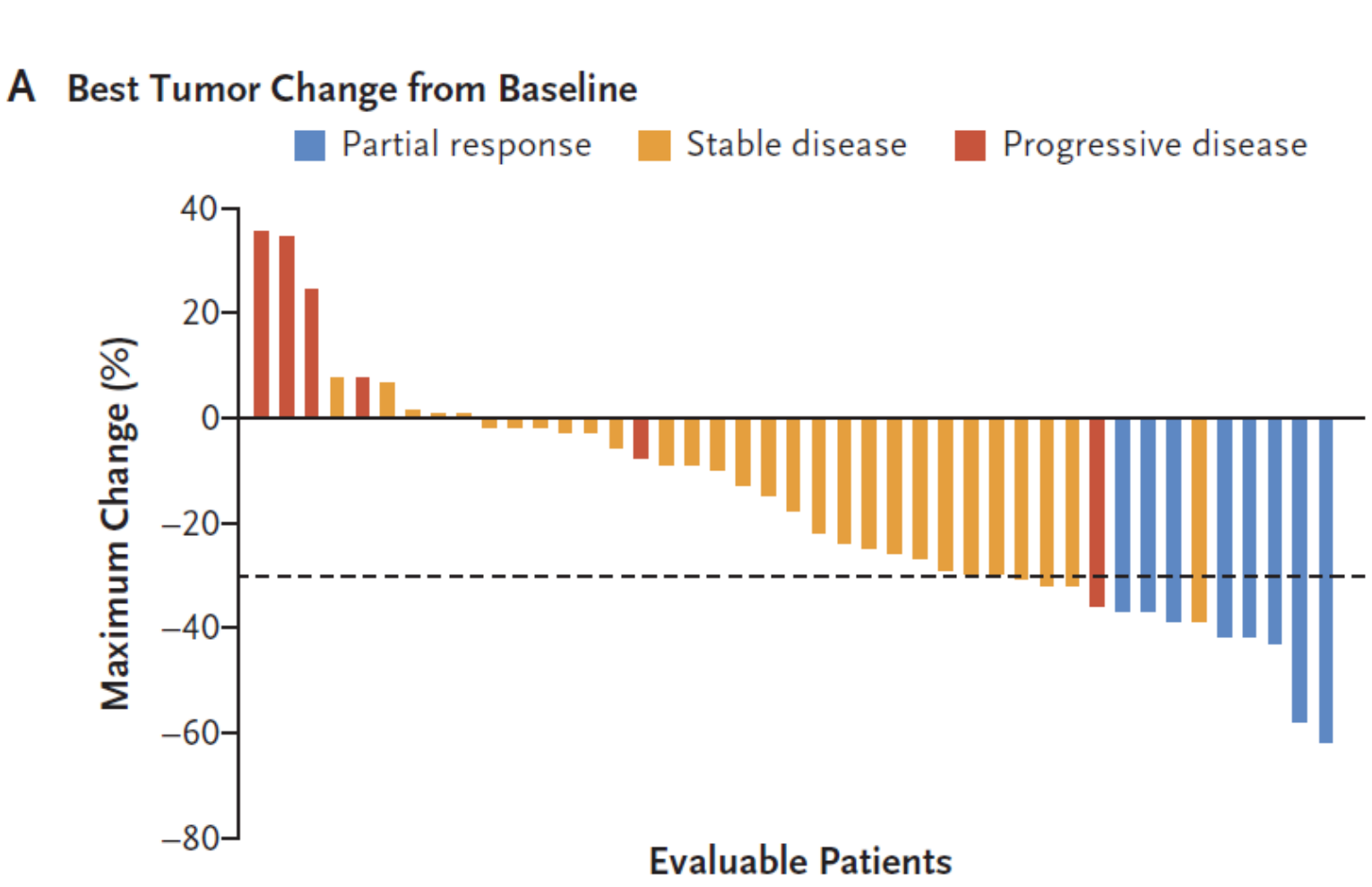


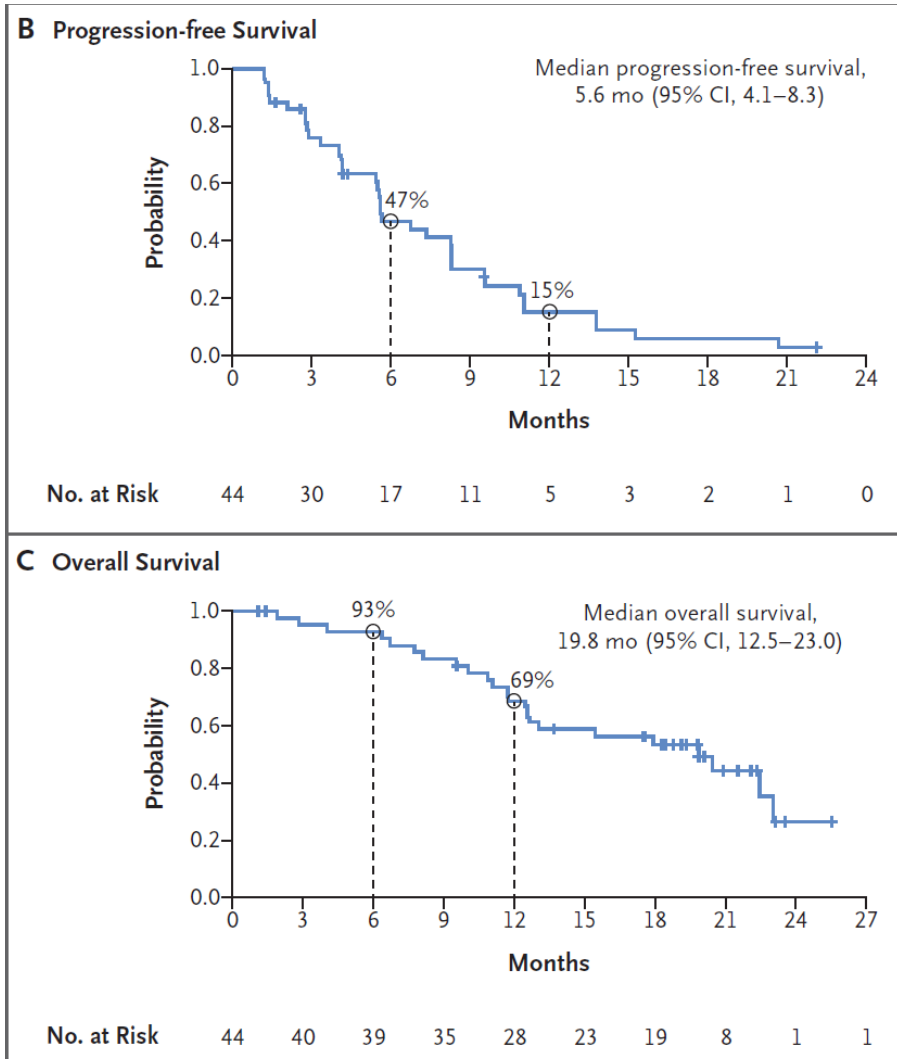
Adagrasib Crystal Structure



1. Zehir A, Benayed R, Shah RH, et al. *Nat Med*. 2017;23(6):703–713. 2. Schirripa M, Nappo F, Cremolini C, et al. *Clin Colorectal Cancer*. 2020;S1533-0028(20)30067-0. 3. NIH TCGA: The Cancer Genome Atlas. 4. Hallin J, Engstrom LD, Hargis L, et al. *Cancer Discov*. 2020;10(1): 54-71.

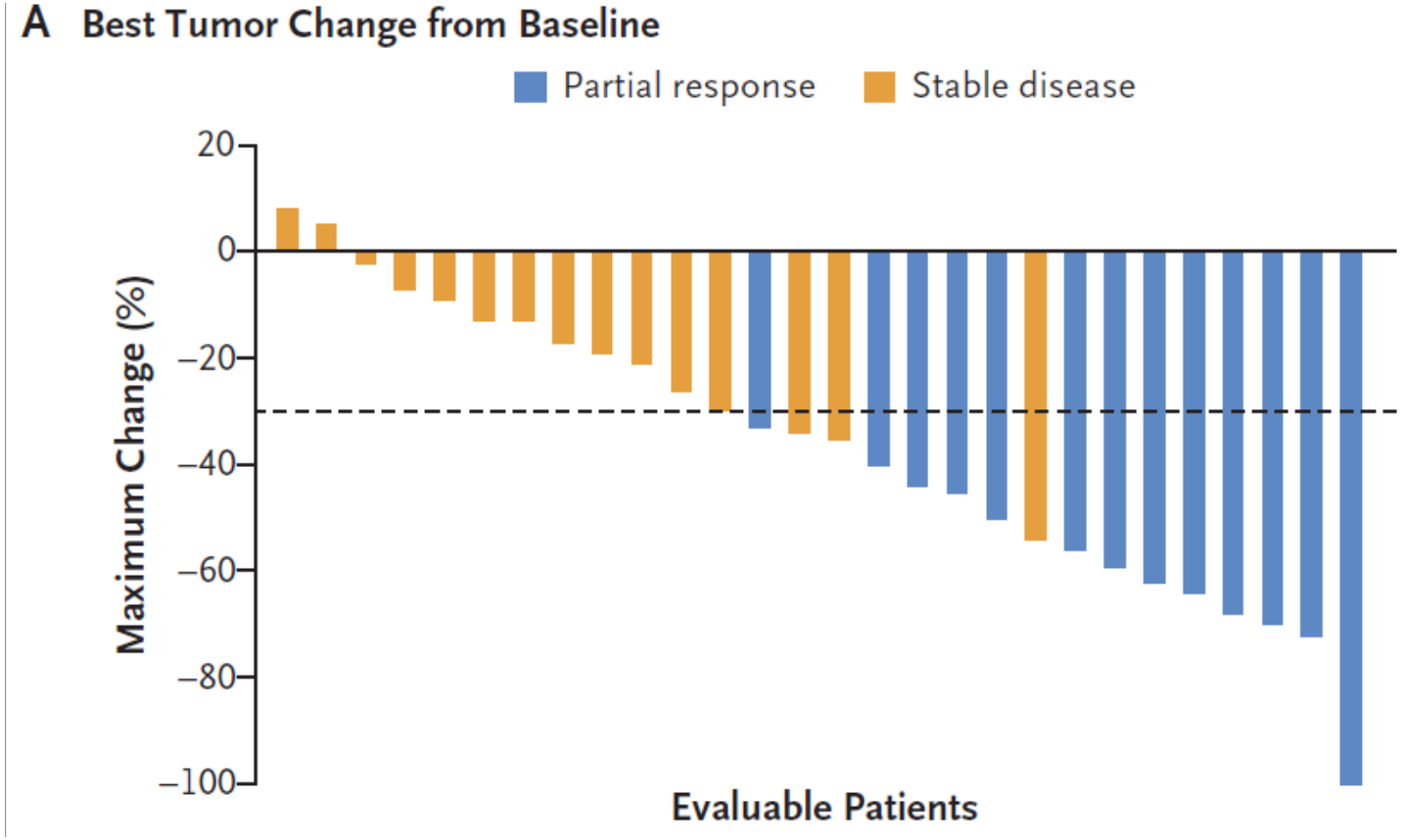
Targeting KRAS G12C Mutations: Adagrasib

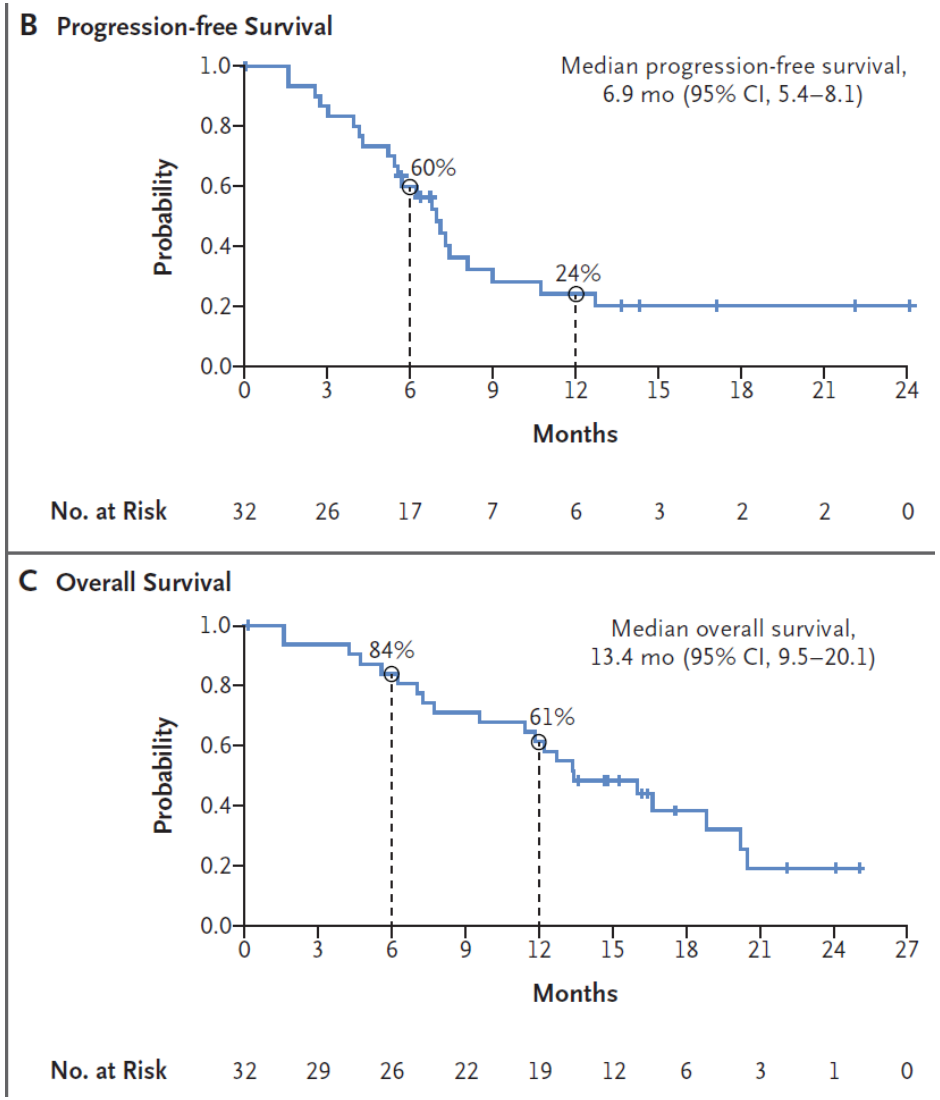




Yaeger, NEJM 2023

Adagrasib and Cetuximab





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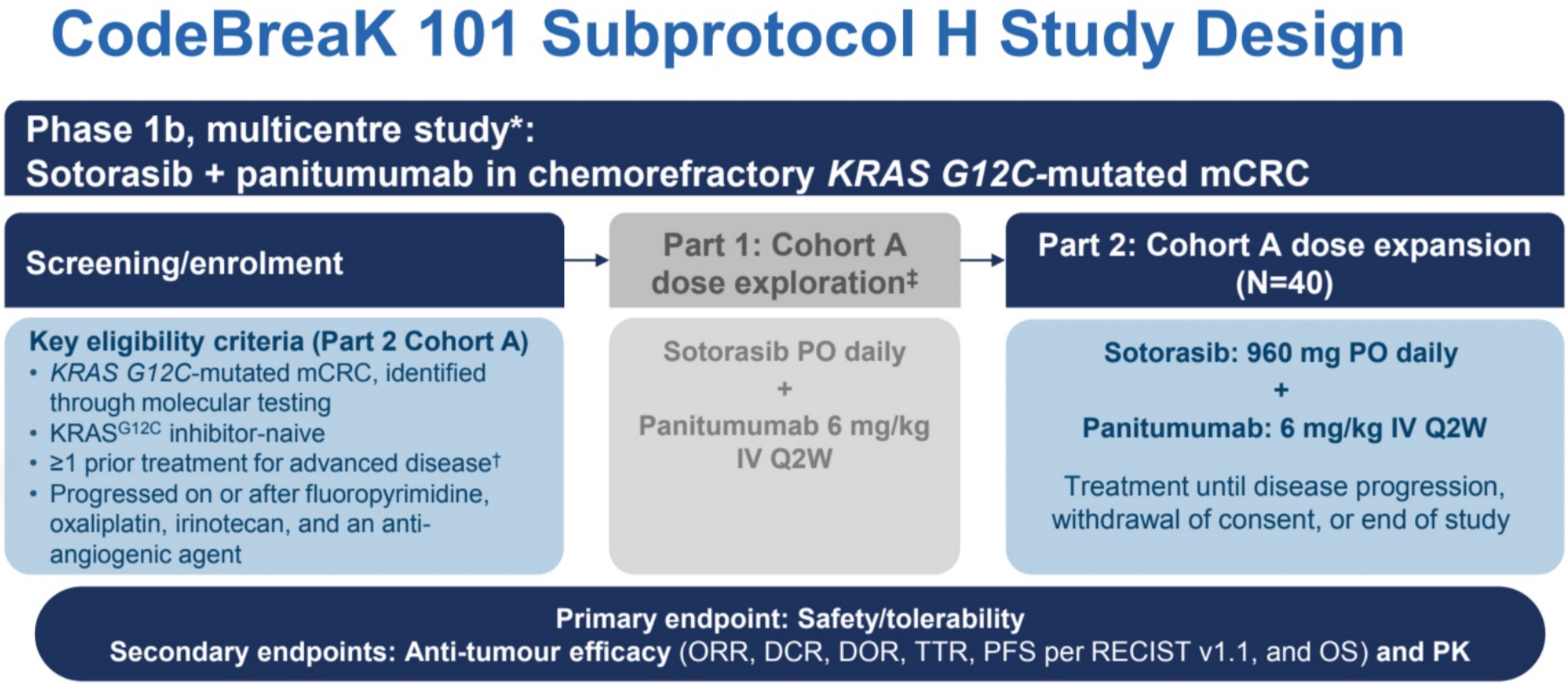
Targeting KRAS G12C Mutations: Adagrasib

Table 2. Overall Summary of Clinical Activity.*

Variable	Adagrasib Monotherapy (N = 43)†	Adagrasib plus Cetuximab (N = 28)‡
Objective response§		
Per blinded independent central review — no. of patients	10	13
% (95% CI)	23 (12–39)	46 (28–66)
As confirmed by investigator — no. of patients	8	13
% (95% CI)	19 (8–33)	46 (28–66)
Best overall response — no. (%)		
Complete response	0	0
Partial response	8 (19)	13 (46)
Stable disease	29 (67)	15 (54)
Progressive disease	6 (14)	0
Not evaluable	0	0
Median duration of response — mo	4.3	7.6
95% CI	2.3–8.3	5.7–NE
Median progression-free survival — mo¶	5.6	6.9
95% CI	4.1–8.3	5.4–8.1
Median overall survival — mo¶	19.8	13.4
95% CI	12.5–23.0	9.5–20.1

Yaeger, NEJM 2023

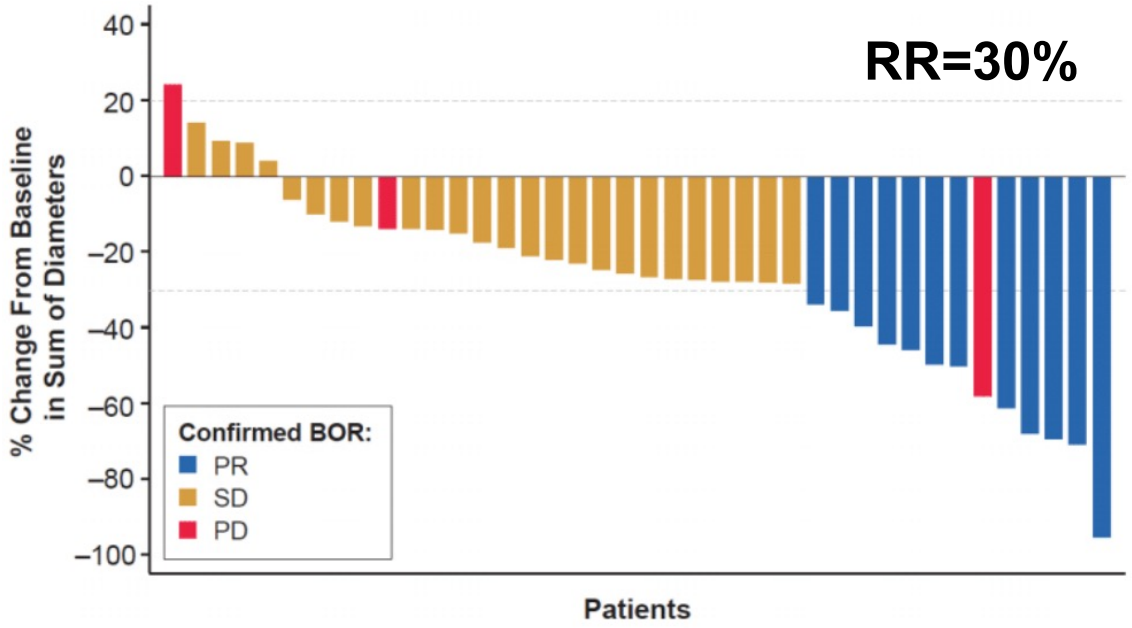
Targeting KRAS G12C Mutations: Sotorasib

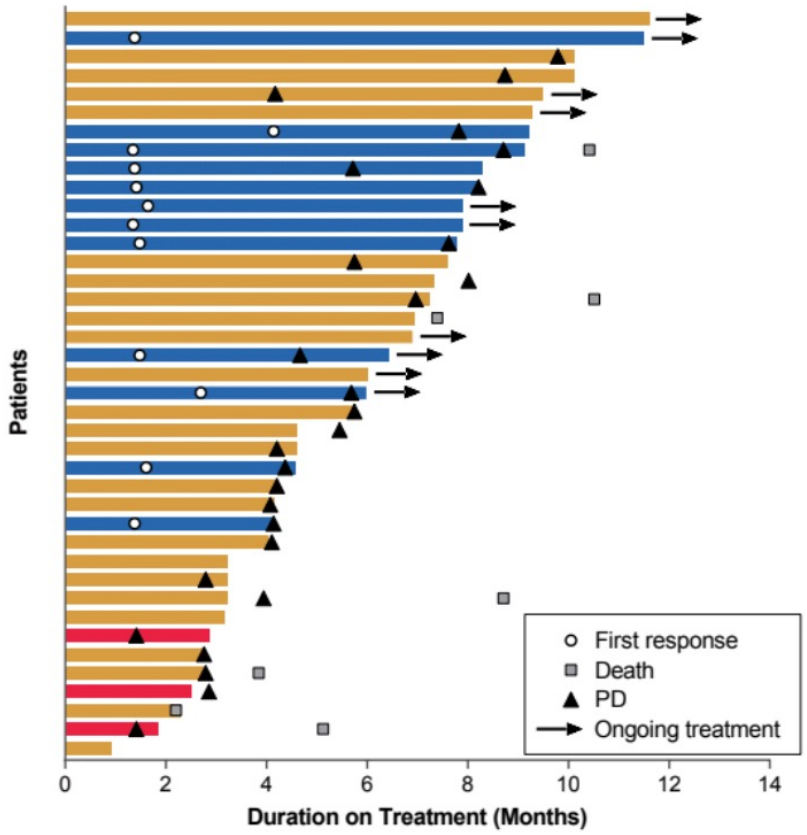


Kuboki, ESMO 2022

Targeting KRAS G12C Mutations: Sotorasib/Pmab

Tumour Response





- Reduction in RECIST target lesions observed in 88% of patients
- Median (range) duration of treatment was 5.9 (0.5, 11.3) months, with 25% of patients remaining on treatment

Kuboki, ESMO 2022

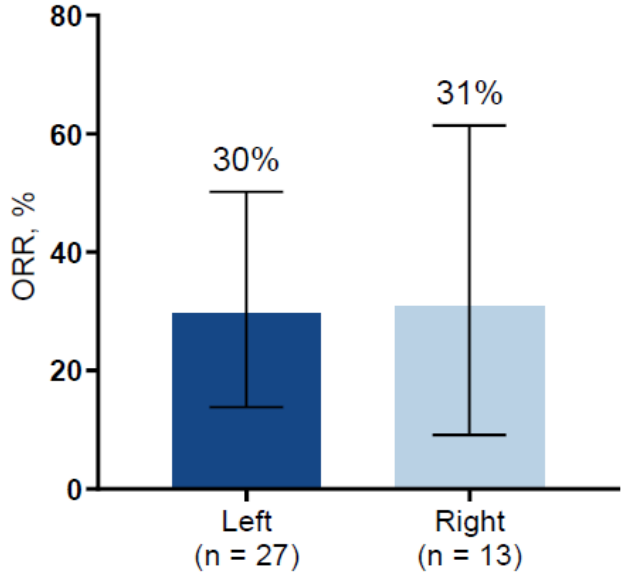
Targeting KRAS G12C Mutations: Sotorasib/Pmab

Efficacy

Response by investigator assessment	N = 40 n (%)
ORR confirmed (95% CI)	**12 (30)** (16.6, 46.5)
Complete response	0
Partial response	12 (30)
Stable disease*	25 (63)
Progressive disease	3 (8)
DCR (95% CI)	**37 (93)** (79.6, 98.4)

Data cutoff: June 24, 2022.
*Minimum requirement for stable disease was 5 weeks.
DCR, disease control rate; mCRC, metastatic colorectal cancer; ORR, objective response rate.

ORR subgroup analysis by primary tumour location

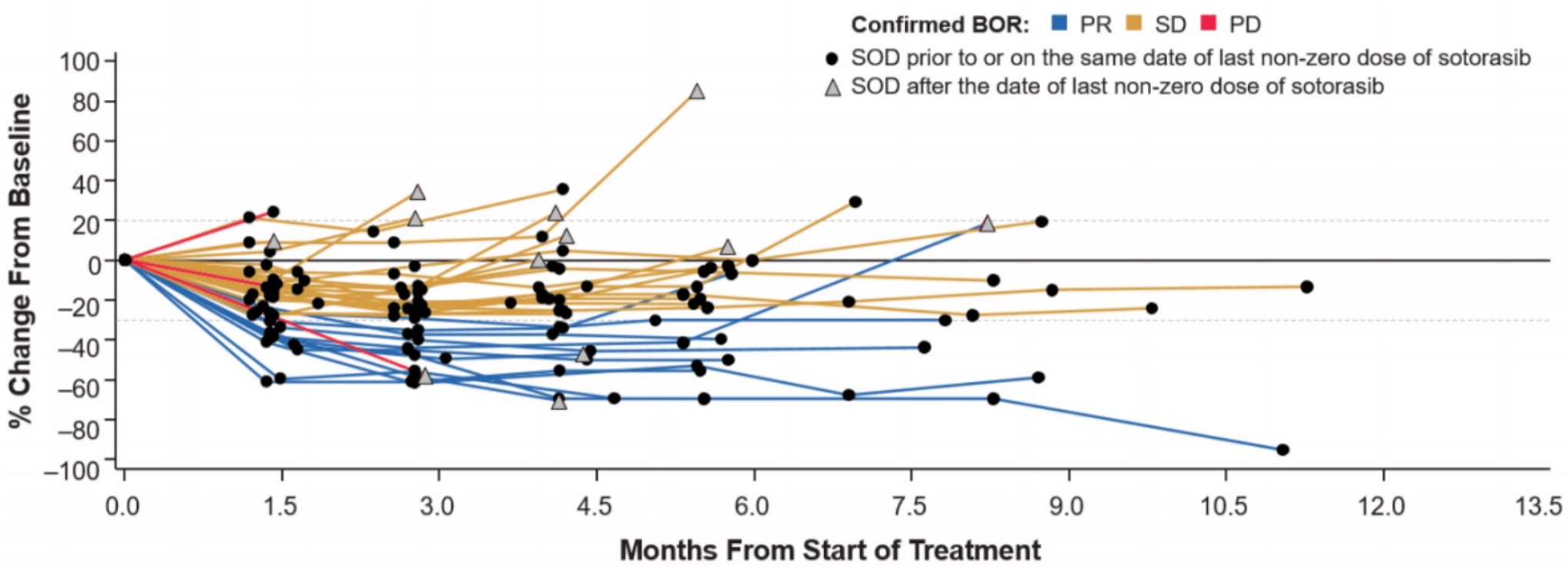


- **30% confirmed response rate for sotorasib + panitumumab in patients with chemorefractory mCRC, with disease control rate of 93%**
- **No obvious differences in response based on tumour location**

Kuboki, ESMO 2022

Targeting KRAS G12C Mutations: Sotorasib/Pmab

Change in Target Lesions Over Time



Median duration of response was 4.4 months (range, 2.8–7.4 months)

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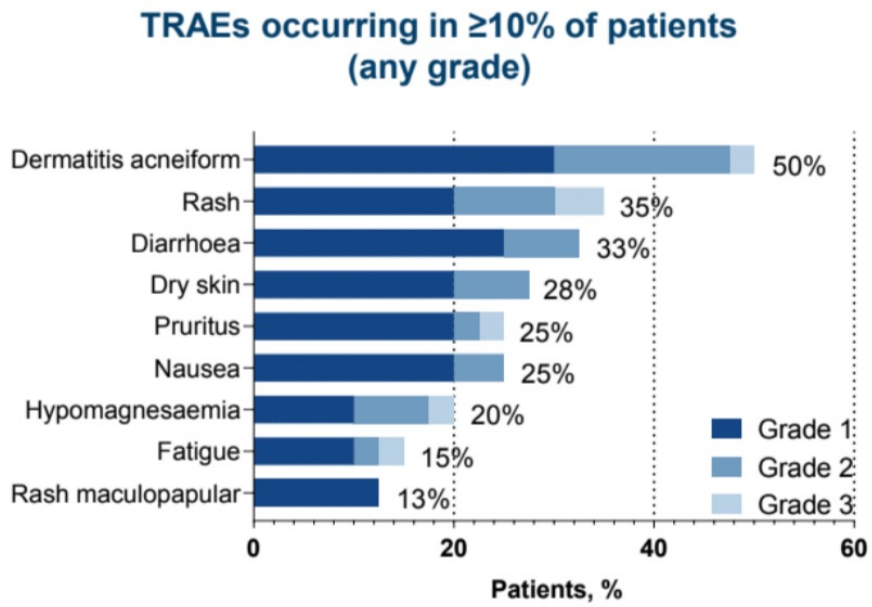
Targeting KRAS G12C Mutations: Sotorasib/Pmab

Treatment-Related Adverse Events (TRAEs)

TRAE	N = 40 n (%)
TRAE, any grade	37 (93)
Attributed to sotorasib	26 (65)
Attributed to panitumumab	37 (93)
Grade 3 TRAE*	9 (23)
Grade 4 TRAE	0
Fatal TRAE	0
TRAE leading to dose interruptions/reductions	
Attributed to sotorasib	6 (15)
Attributed to panitumumab	10 (25)
TRAE leading to discontinuation of either drug	0



Data cutoff: June 24, 2022.
*Grade 3 TRAEs were rash (n=2, 5%), anaemia, fatigue, peripheral oedema, cellulitis, pustular rash, salmonellosis, skin infection, hypomagnesaemia, malignant neoplasm progression, pulmonary embolism, dermatitis acneiform, and pruritus (n=1 patient each, 3%).

- **Sotorasib/panitumumab was well tolerated; no TRAEs resulted in discontinuation of either drug**
- **TRAEs were consistent with known safety profiles of the individual drugs**

Kuboki, ESMO 2022

Targeting KRAS G12C in Colorectal Cancer

Conclusions:

- $KRAS^{G12C}$ mutations act as oncogenic drivers and occur in approximately 3-4% of CRC
- Adagrasib and sotorasib are oral KRAS inhibitors
  - **Sotorasib** was FDA approved on 5/28/2021 for >2L locally advanced or metastatic non-small cell lung cancer (NSCLC) with a G12C mutation; FDA also approved QIAGEN therascreen® K-RAS RGQ PCR kit for use in tissue, and the Guardant360® CDx for use in plasma, as companion diagnostics
  - **Adagrasib** was approved 12/12/2022 for the same indication "as determined by an FDA-approved test"
- Both agents has shown activity in mCRC, with higher response rates when combined with an EGFR-targeting mAb (limited number of patients)
  - 30% response rate with **sotorasib/Pmab** in G12C-mutated ≥3L mCRC (10% monotherapy)
  - 46% response rate with **adagrasib/Cmab** in G12C-mutated ≥3L mCRC* (20% monotherapy)

*no available standard-of-care treatment (or were ineligible or declined treatment)

Comparing the KRAS G12C mCRC trials

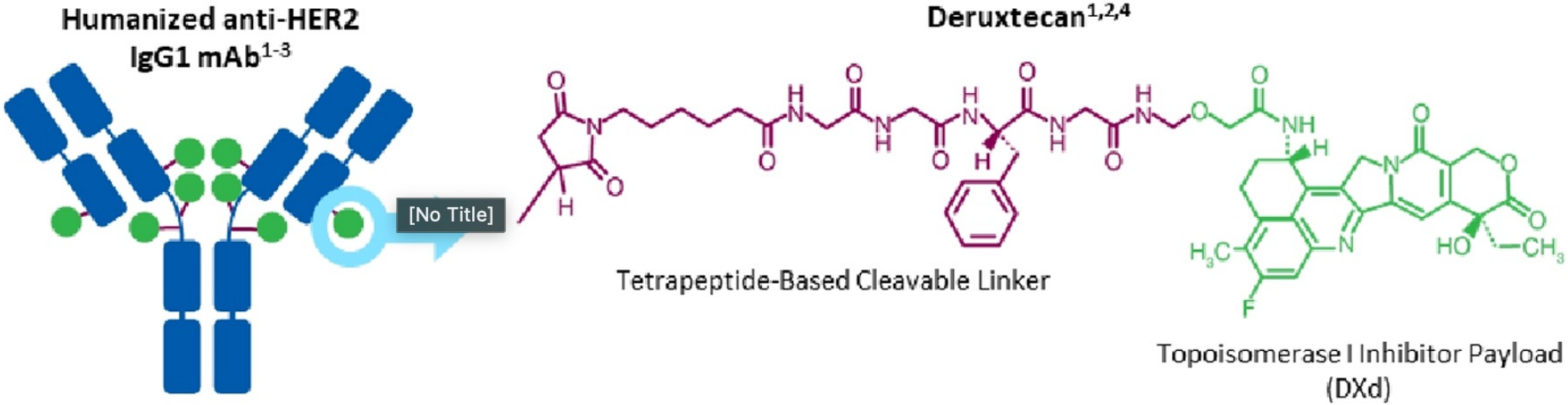
- The small number of patients in the two studies does not allow cross comparison
  - In the CodeBreaK100 trial, 100% of patients treated with sotorasib monotherapy received oxaliplatin, irinotecan, and a fluoropyrimidine prior to study enrollment, whereas 77% of the adagrasib monotherapy population were exposed to all three drugs
  - CodeBreaK100 was enriched with patients who had prior exposure to trifluridine and/or regorafenib (44%) in comparison to the adagrasib monotherapy population in KRYSTAL-1 (23%).
- Higher rate of gastrointestinal toxicity than sotorasib monotherapy, which led to a higher rate of treatment interruptions and dose reductions (45% for adagrasib and 18% for sotorasib).
- **KRYSTAL-10** (NCT04793958) is a second-line phase III trial comparing adagrasib/cetuximab with standard second-line chemotherapy
- **CodeBreaK300** (NCT05198934) is a third-line phase III trial comparing low-dose sotorasib plus panitumumab vs standard-dose sotorasib (960 mg daily) plus panitumumab vs regorafenib or trifluridine.

https://ascopost.com/issues/february-10-2023

Trastuzumab Deruxtecan-nxkio (DS-8201)

fam-trastuzumab deruxtecan-nxkio (T-DXd): (DS-8201) antibody-drug conjugate consisting of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor.

FDA-approved 1/15/2021 for "adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen"



Siena, ASCO 2020

NCT03384940

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)

Patients

- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- RAS/BRAF wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

T-DXd 6.4 mg/kg q3w

Cohort A (n = 53)
HER2 Positive (IHC 3+ or IHC 2+/ISH+)

A futility monitoring was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C

Cohort B (n = 7)
HER2 IHC 2+/ISH−

Cohort C (n = 18)
HER2 IHC 1+

Primary endpoint

- Confirmed ORR by independent central review (ICR) in Cohort A

Data cutoff: August 9, 2019

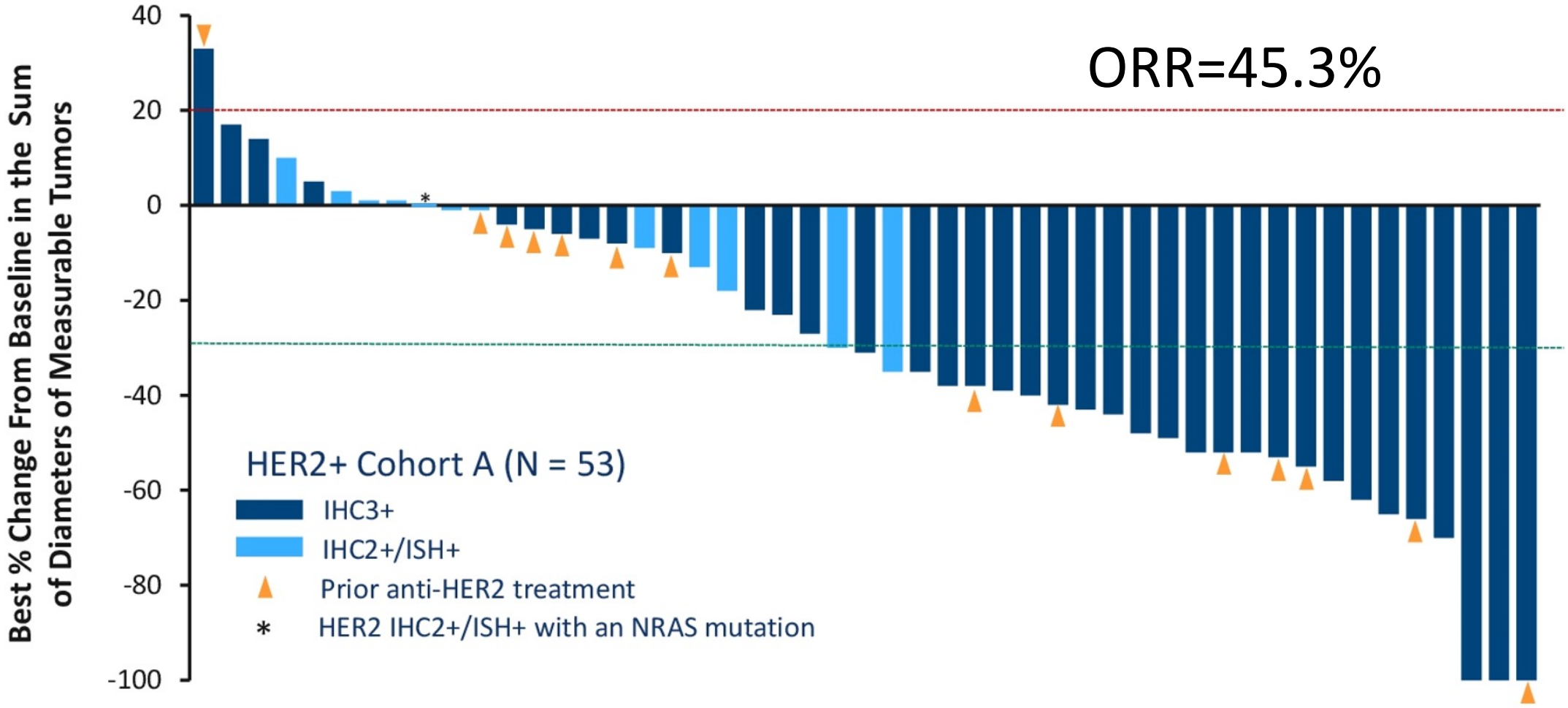
- 38.5% (30/78) remained on treatment
- 61.5% discontinued, primarily for progressive disease (41.0%) and clinical progression (9.0%)

Siena, ASCO 2020

NCT03384940

DESTINY-CRC01 Cohort A

Best Change in Tumor Size



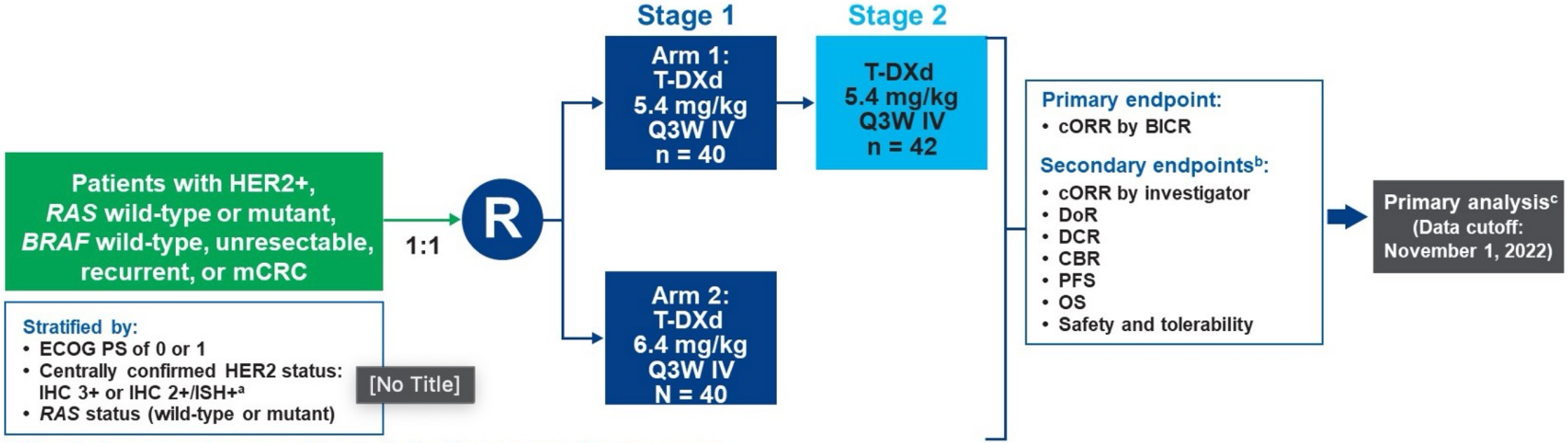
Siena, ASCO 2020

NCT03384940

DESTINY-CRC02 Study Design

A randomized, blinded, 2-stage, 2-arm, multicenter, global, phase 2 study (NCT04744831)

- Stage 1 (randomized) was followed by Stage 2 (nonrandomized), which enrolled an additional 42 patients



This study was not powered to statistically compare the two arms.

BICR, blinded independent central review; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Both investigators and patients were blind to treatments.
[a]HER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay (IUO). [b]Exploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator. [c]Primary analysis occurred ≥6 months after the last patient had been enrolled or when all patients discontinued from the study, whichever was earlier.

PRESENTED BY: Kanwal Raghav, MD

DESTINY-CRC01

(Yoshino, Nat Com 2023)

Table 1 | Patient demographics and baseline characteristics

Baseline characteristic	HER2 IHC 3 + or IHC 2 + /ISH + Cohort A *n* = 53	HER2 IHC 2 + / ISH − Cohort B *n* = 15	HER2 IHC 1 + Cohort C *n* = 18	Overall *N* = 86
Median age	57.0 (27–79)	62.0 (37–78)	58.5 (43–79)	58.5 (27–79)
Sex				
Female	28 (52.8)	5 (33.3)	7 (38.9)	40 (46.5)
Male	25 (47.2)	10 (66.7)	11 (61.1)	46 (53.5)
Region				
Europe	28 (52.8)	9 (60.0)	9 (50.0)	46 (53.5)
Asia	15 (28.3)	3 (20.0)	8 (44.4)	26 (30.2)
North America	10 (18.9)	3 (20.0)	1 (5.6)	14 (16.3)
ECOG PS				
0	37 (69.8)	8 (53.3)	9 (50.0)	54 (62.8)
1	16 (30.2)	7 (46.7)	8 (44.4)	31 (36.0)
2	0	0	1 (5.6)	1 (1.2)
Primary tumor site[a]				
Left	47 (88.7)	14 (93.3)	17 (94.4)	78 (90.7)
Right	6 (11.3)	1 (6.7)	1 (5.6)	8 (9.3)
Microsatellite status[b]				
MSI-H	0	0	0	0
MSS	43 (81.1)	14 (93.3)	12 (66.7)	69 (80.2)
Unknown	10 (18.9)	1 (6.7)	6 (33.3)	17 (19.8)
***RAS* wild-type**[b,c]	52 (98.1)	14 (93.3)	18 (100)	84 (97.7)
***BRAF* wild-type**[b,d]	53 (100)	15 (100)	17 (94.4)	85 (98.8)
HER2 status[e]				
IHC 3+	40 (75.5)	0	0	40 (46.5)
IHC 2+	13 (24.5)	15 (100)	0	28 (32.6)
IHC 1+	0	0	18 (100)	18 (20.9)
ISH+	52 (98.1)[f]	0	4 (22.2)	56 (65.1)
ISH−	0	15 (100)	14 (77.8)	29 (33.7)

DESTINY-CRC02

(Raghav, ASCO 2023)

		5.4 mg/kg T-DXd n = 82	6.4 mg/kg T-DXd n = 40
Median follow-up, mo (range)		8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median DoR by BICR, mo (95% CI)		5.5 (4.2-8.1)	5.5 (3.7-non-evaluable)
Median PFS, mo (95% CI)		5.8 (4.6-7.0)	5.5 (4.2-7.0)
Best overall response by BICR in subgroups, n/N (%) [95% CI]			
Prior anti-HER2 therapy		7/17 (41.2) [18.4-67.1]	4/10 (40.0) [12.2-73.8]
	HER2 IHC 3+	30/64 (46.9) [34.3-59.8]	10/34 (29.4) [15.1-47.5]
	HER2 IHC 2+/ISH+	1/18 (5.6) [0.1-27.3]	1/6 (16.7)
	RAS wt	27/68 (39.7) [28.0-52.3]	11/34 (32.4) [17.4-50.5]
	*RAS*m	4/14 (28.6)[a] [8.4-58.1]	0/6

RAS MT patients included

[a]All *RAS*m responders were IHC 3+.

Note: full slide deck send to panel members

Efficacy Results

	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
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**3[illegible] (37.8) [27.3-49.2]**	**1[illegible] (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; mo, month; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease; T-DXd, trastuzumab deruxtecan.

TEAEs in ≥20% of Patients[a]

n (%)	T-DXd 5.4 mg/kg Q3W Total N = 83[b]		T-DXd 6.4 mg/kg Q3W Stage 1 N = 39	
	Any-grade	Grade ≥3	Any-grade	Grade ≥3
Any TEAEs	82 (98.8)	41 (49.4)	39 (100)	23 (59.0)
Nausea	48 (57.8)	7 (8.4)	22 (56.4)	0
Fatigue[c]	38 (45.8)	8 (9.6)	18 (46.2)	2 (5.1)
Neutropenia[d]	25 (30.1)	14 (16.9)	18 (46.2)	11 (28.2)
Decreased appetite	25 (30.1)	2 (2.4)	6 (15.4)	0
Anemia[e]	22 (26.5)	8 (9.6)	16 (41.0)	9 (23.1)
Thrombocytopenia[f]	21 (25.3)	5 (6.0)	14 (35.9)	5 (12.8)
Alopecia	20 (24.1)	0	11 (28.2)	0
Constipation	20 (24.1)	0	5 (12.8)	0
Diarrhea	19 (22.9)	2 (2.4)	11 (28.2)	0
Vomiting	17 (20.5)	4 (4.8)	3 (7.7)	0

Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.
Febrile neutropenia occurred in 1 patient in both Stage 1 (grade 3) and Stage 2 (grade 1) treated with T-DXd 5.4 mg/kg and 1 patient treated with T-DXd 6.4 mg/kg (grade 4)
[a]Based on the total population treated with T-DXd 5.4 mg/kg. [b]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [c]Fatigue includes the preferred terms asthenia, fatigue, malaise and lethargy. [d]Neutropenia includes the preferred terms neutrophil count decreased and neutropenia. [e]Anemia includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [f]Thrombocytopenia includes the preferred terms platelet count decreased and thrombocytopenia.

Adjudicated Drug-Related ILD/Pneumonitis by Independent Adjudication Committee

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
Any grade	4 (9.8)	3 (7.1)	7 (8.4)	5 (12.8)
Grade 1	1 (2.4)	0	1 (1.2)	2 (5.1)
Grade 2	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	1 (2.6)[b]

ILD, interstitial lung disease; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.
[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

DESTINY-CRC01 and –CRC02

- The **5.4 mg/kg dose level** is more efficacious and better tolerated (compared to 6.4 mg/kg); **RR= 47%** in HER2 IHC 3+ staining.
- The RR dropped to 1/18 (5%) in patients with IHC 2+/ISH+ patients.
- Reponses were seen in 4/14 patients (28%) of patients with **KRAS MT** diseases; responding patients had her2 3+ staining
- Responses were seen in 7/17 patients (41%) of patients with **prior HER2-directed therapies**.
- ILD/Pneumonitis seen in ~8% patients, mostly grade 2.
- Likely will be added to NCCN guidelines, and language regarding “forgo HER2 testing if RAS MT” will be removed.

Other HER2 ADC’s in development: A166, XMT-1522, MEDI-4276, ARX788, RC48-ADC, BAT8001 and PF-06804103

THANK YOU!

Cancer Center

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