UPDATE IN CANCER THERPAY OF COLO-RECTAL CANCER

ASCO 2022
ESMO 2022

Ahmed Zakari. MD
Associate Professor University of Central Florida, College of Medicine
Medical Director, GastroIntestinal Cancer Program
AdventHealth Cancer Institute

LEARNING OBJECTIVES

- MSI-H (dMMR) Colo-Rectal cancer and ImmunoRx
  - Memorial Sloan Kettering ASCO 2022
  - NICHE-2 Trial ESMO 2022
- Metastatic CRC MSS and IO
- Advanced CRC:
  - Neur 2 Neu (+) : MOUNTAINEER
  - Triplet /Pan Vs Doublet/ Pan for Left sided
- Locally Advanced :
  - Does Neoadjuvant Chemotherapy have role…: OPTICAL Trial
- Circulating Tumor /Free DNA in Early stage Colon Ca: DYNAMIC TRIAL

2022 ASCO ANNUAL MEETING

Late breaking abstract

PD-1 blockade as curative-intent therapy in mismatch repair deficient locally advanced rectal cancer

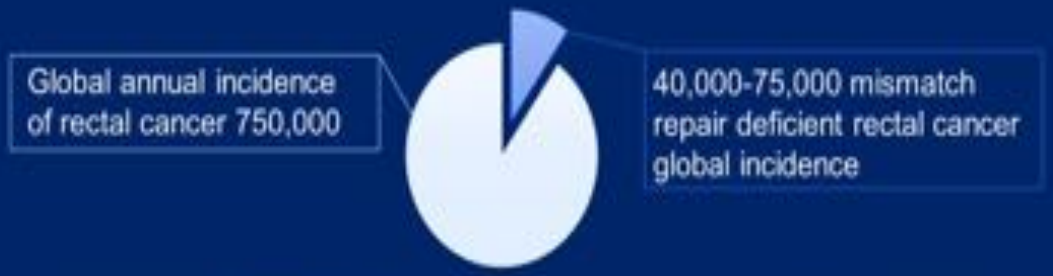
Andrea Cercek, MD
Head, Colorectal Cancer Section
Co-Director Center for Young Onset Colorectal and Gastrointestinal Cancers
Memorial Sloan Kettering Cancer Center

Rectal Cancer

- Therapy for locally advanced rectal cancer has included a combination of chemotherapy, radiation and surgery
- While cure is frequently achieved, radiation and surgery have life-altering consequences
- Following chemotherapy and radiation, a portion become candidates for non-operative management.

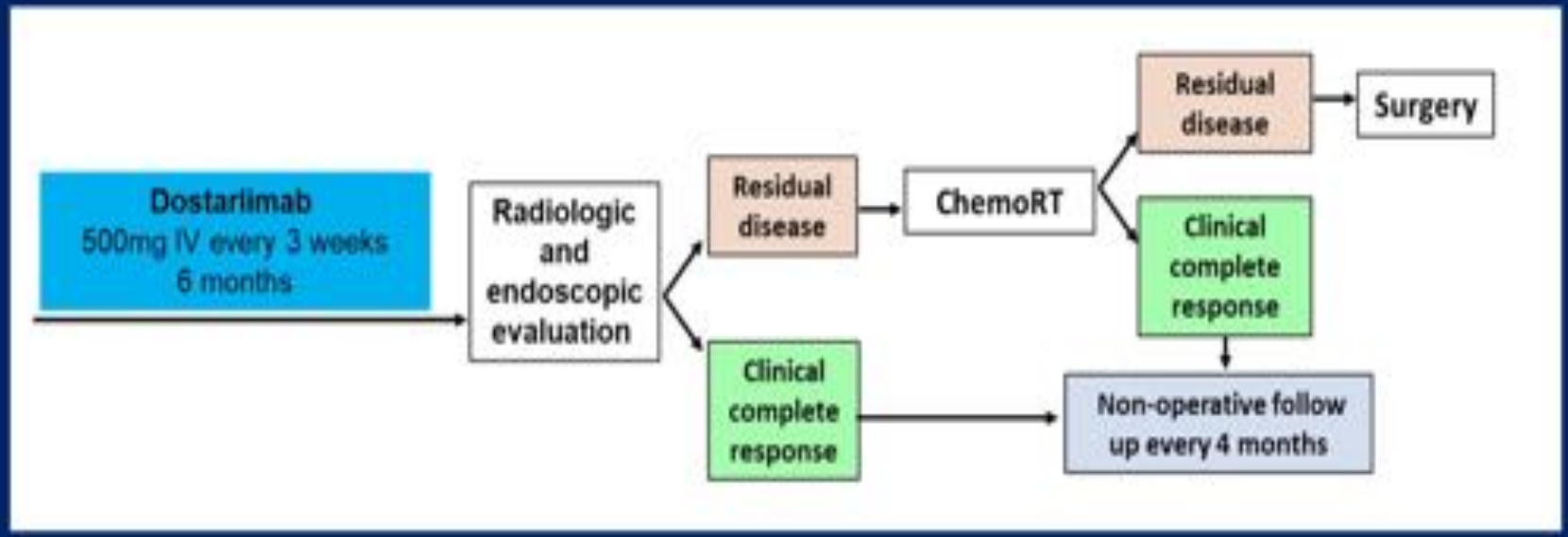
Formijne Jonkers Int J Colorectal Dis 2012
Smith JJ, JAMA Oncol 2019
[illegible] 2014
Garcia-Aguilar J Clin Oncol 2022

Mismatch repair deficient rectal cancer



- Approximately 5-10% of rectal cancers are mismatch repair deficient
- Relatively resistant to chemotherapy
- Checkpoint blockade is highly effective in metastatic mismatch repair deficient cancers with a complete response rate ~10%

Cercek A, Clin Cancer Res 2020
Andre T, N Engl J Med 2020
Le DT, N Engl J Med 2015



Patient population: Stage II and III mismatch repair deficient rectal cancer

Target Enrollment: 30 subjects

Study Design: Simon's two stage minimax design

NCT04165772

Study Objectives

Primary Objectives

- Overall response rate of PD-1 blockade with or without chemoradiation
- Pathologic complete response (pCR) or clinical complete response (cCR) rate at 12 months after PD-1 blockade with or without chemoradiation

Secondary Objective

- Safety and tolerability

Demographic and disease characteristics of the patients at baseline

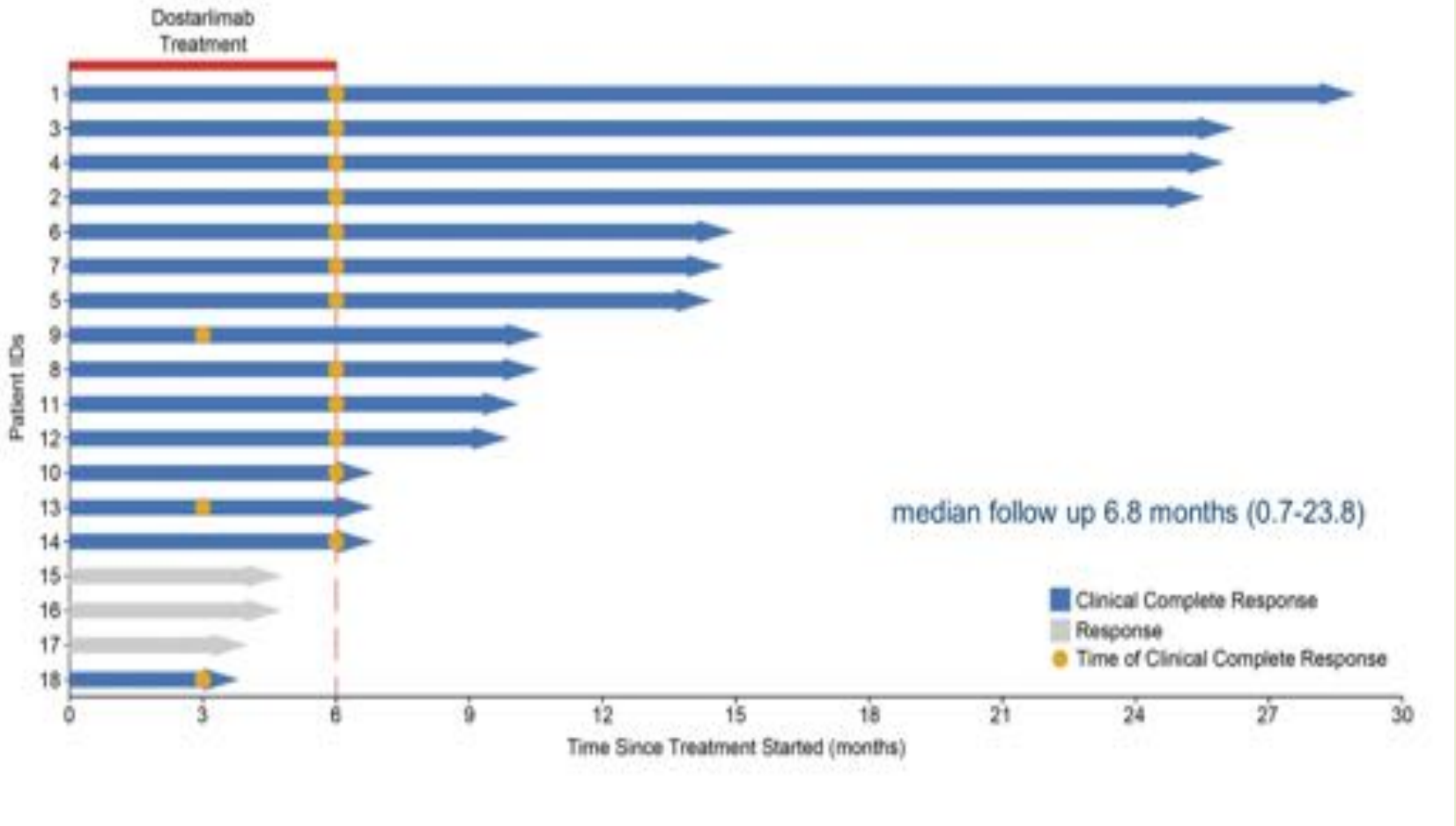
	Value (%)
Sex	
Male	6 (33)
Female	12 (67)
Age, median (range)	54 (26-78)
Race/Ethnicity	
White non-Hispanic	11 (61)
Hispanic	1 (6)
Black or African American	3 (17)
Asian-Far East/Indian Subcontinent	3 (17)
Tumor Staging	
T1/2	4 (22)
T3, T4	14 (78)
Nodal Staging	
Node-positive	17 (94)
Node-negative	1 (6)
Germline Mutation Status n=17	
MSH2, MLH1, MSH6, or PMS2	10 (59)
Negative	7 (41)
BRAF V600E wild type	18 (100)
Tumor Mutational Burden (mut/Mb), mean (range)	67 (36 -106)

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	cCR
2	30	T3	N+	20.5	CR	CR	CR	cCR
3	61	T1/2	N+	20.6	CR	CR	CR	cCR
4	28	T4	N+	20.5	CR	CR	CR	cCR
5	53	T1/2	N+	9.1	CR	CR	CR	cCR
6	77	T1/2	N+	11.0	CR	CR	CR	cCR
7	77	T1/2	N+	8.7	CR	CR	CR	cCR
8	55	T3	N+	5.0	CR	CR	CR	cCR
9	68	T3	N+	4.9	CR	CR	CR	cCR
10	78	T3	N-	1.7	CR	CR	CR	cCR
11	55	T3	N+	4.7	CR	CR	CR	cCR
12	27	T3	N+	4.4	CR	CR	CR	cCR
13	26	T3	N+	0.8	CR	CR	CR	cCR
14	43	T3	N+	0.7	CR	CR	CR	cCR

Duration of response



Conclusion

- This data provides the framework for immuno-ablative therapies
- Highlights the clinical impact of biomarker driven therapy in early-stage disease
- The tumor agnostic mismatch repair deficiency population of early-stage disease has the potential eliminate the need for chemotherapy, radiation and surgery in 3-4% of all cancers
- This has the potential to be translated rapidly into areas around the world without access to modern chemotherapy, radiation and surgery

Where do we go from here ?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Rectal Cancer

NCCN Guidelines Index | Table of Contents | Discussion

CLINICAL STAGE

T3, N any with clear CRM (by MRI)[m]; T1–2, N1–2

TOTAL NEOADJUVANT THERAPY (PREFERRED)

- FOLFOX or CAPEOX (12–16 wk) → Long-course chemo/RT[q,r]: • Capecitabine[p] or infusional 5-FU[p] or Short-course RT[u] → Restaging[c] (best tumor response 8 wk after completion of RT)
- or
- Long-course chemo/RT[q,r]: • Capecitabine[p] or infusional 5-FU[p] or Short-course RT[r,u] → Chemotherapy (12–16 wk): • FOLFOX or CAPEOX → Restaging[c]

PRIMARY TREATMENT

- Transabdominal resection[l,v] → Surveillance (REC-11)
- Resection contraindicated → Systemic therapy[w] (REC-F)

NEOADJUVANT THERAPY

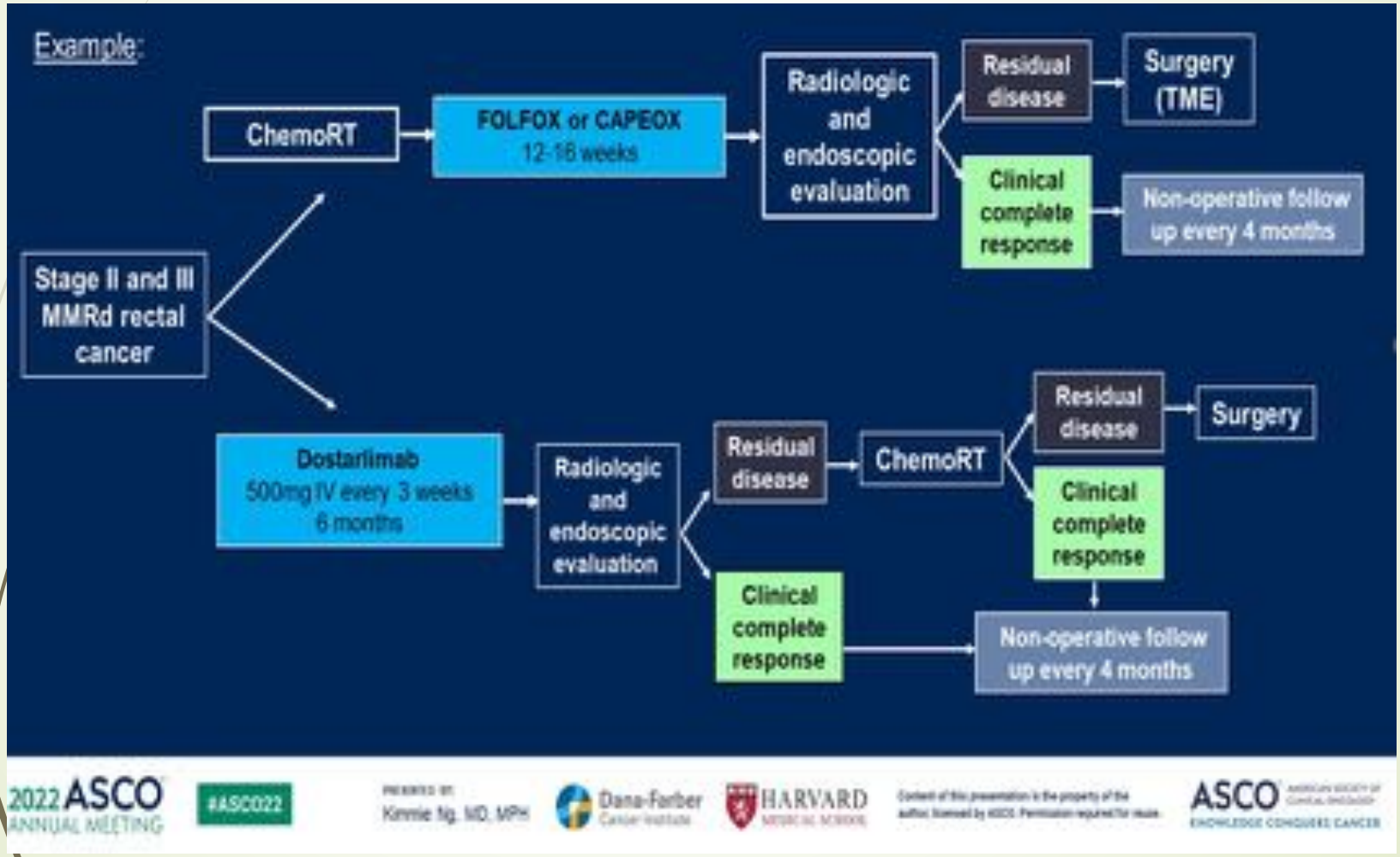
Long-course chemo/RT[q,r]: • Capecitabine[p] or infusional 5-FU[p] or Short-course RT[r,u] → Consider restaging[c] (best tumor response 8 wk after completion of RT)

PRIMARY TREATMENT

- Transabdominal resection[l,v] → **ADJUVANT TREATMENT[c,q,r]**: FOLFOX or CAPEOX (12–16 wk) → Surveillance (REC-11)
- Resection contraindicated → Systemic therapy[w] (REC-F)

No MMR Stratification
No ImmunoRx

Do we really need Randomized Trial to answer this question?



NICHE 2 TRIAL :

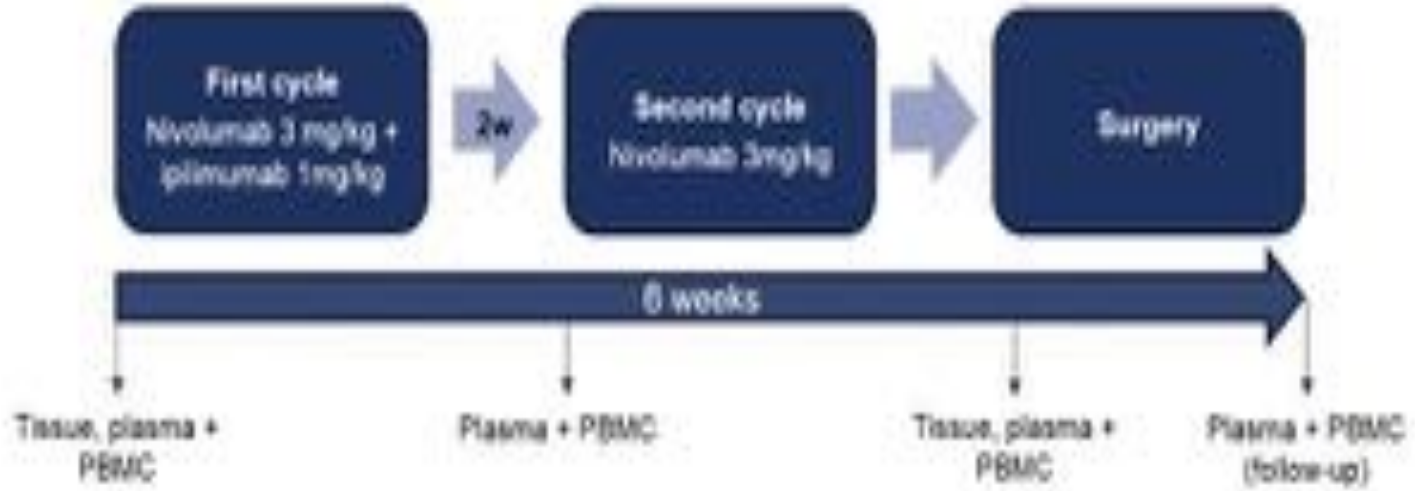
Nivolumab, Ipilimumab & COX2-inhibition in Early Stage Colon Cancer

- 112 patients : Non Met, dMMR , cT3 and/or N+, No perf, No Obstruction
  - Nivo 3 mg/kg plus 1 mg/kg of ipilimumab in the first cycle,
  - then Nivolumab in the second cycle 2 weeks later,
  - followed by surgery within 6 weeks
  - The primary end points of this study :
    - 3-year disease-free survival (DFS) and safety
    - Secondary end points included MPR and cPR
    - Safety and feasibility would be reached if surgery was performed on time, with no more than 2 weeks delay in 95% of patients.
    - A 3-year DFS of 93% would also be deemed successful.

- All patients underwent surgery:
  - All tumor-free resection margins, with 98% of patients undergoing timely surgery
- Pathologic response was defined as 50% or less residual viable tumor (RVT),
  - MPR as 10% or less RVT including tumors with path Response in the primary tumor but RVT in the lymph node
  - pCR as 0% RVT in both the primary tumor and lymph nodes.

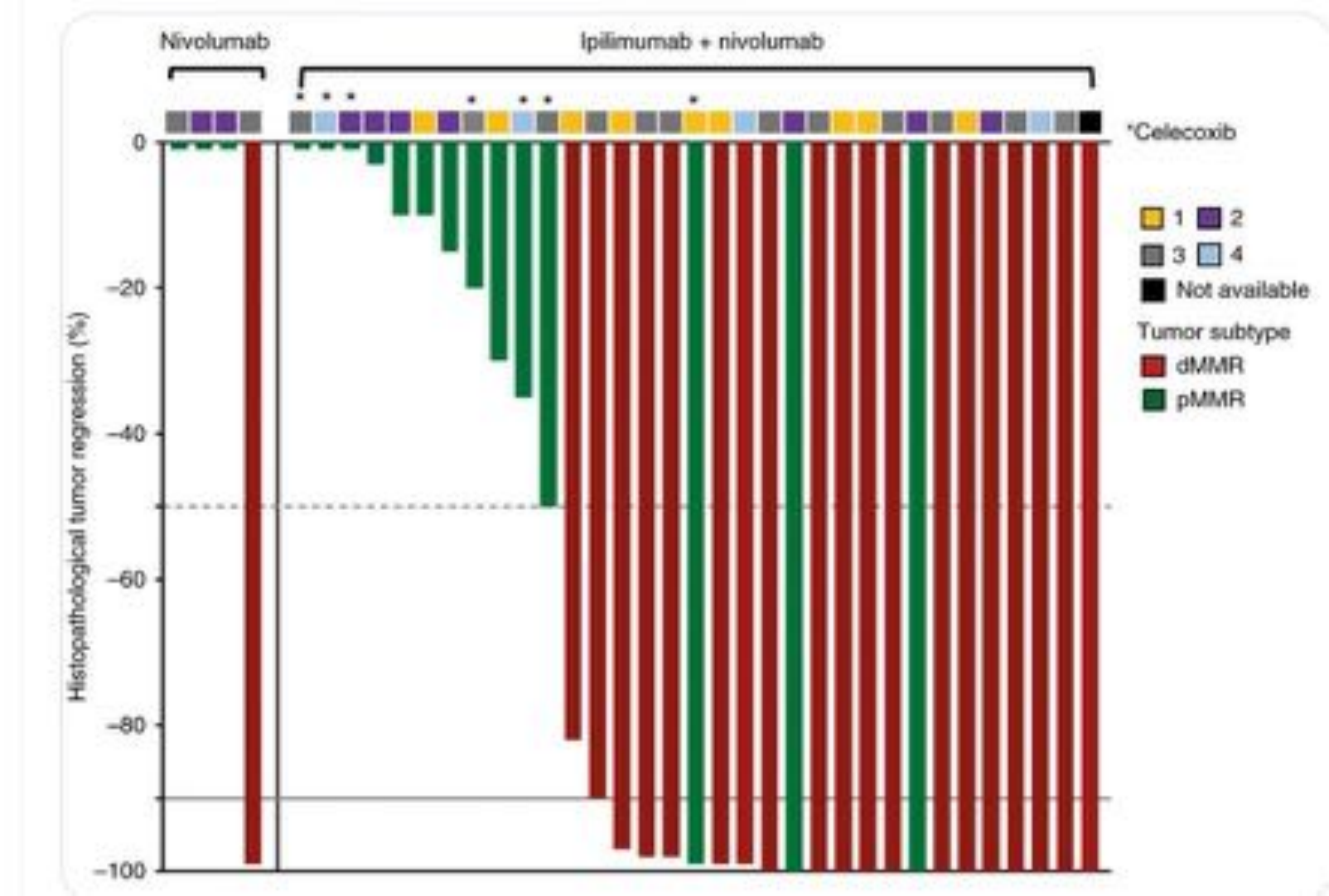
NICHE-2 study design

- Investigator-initiated, non-randomized multicenter* study

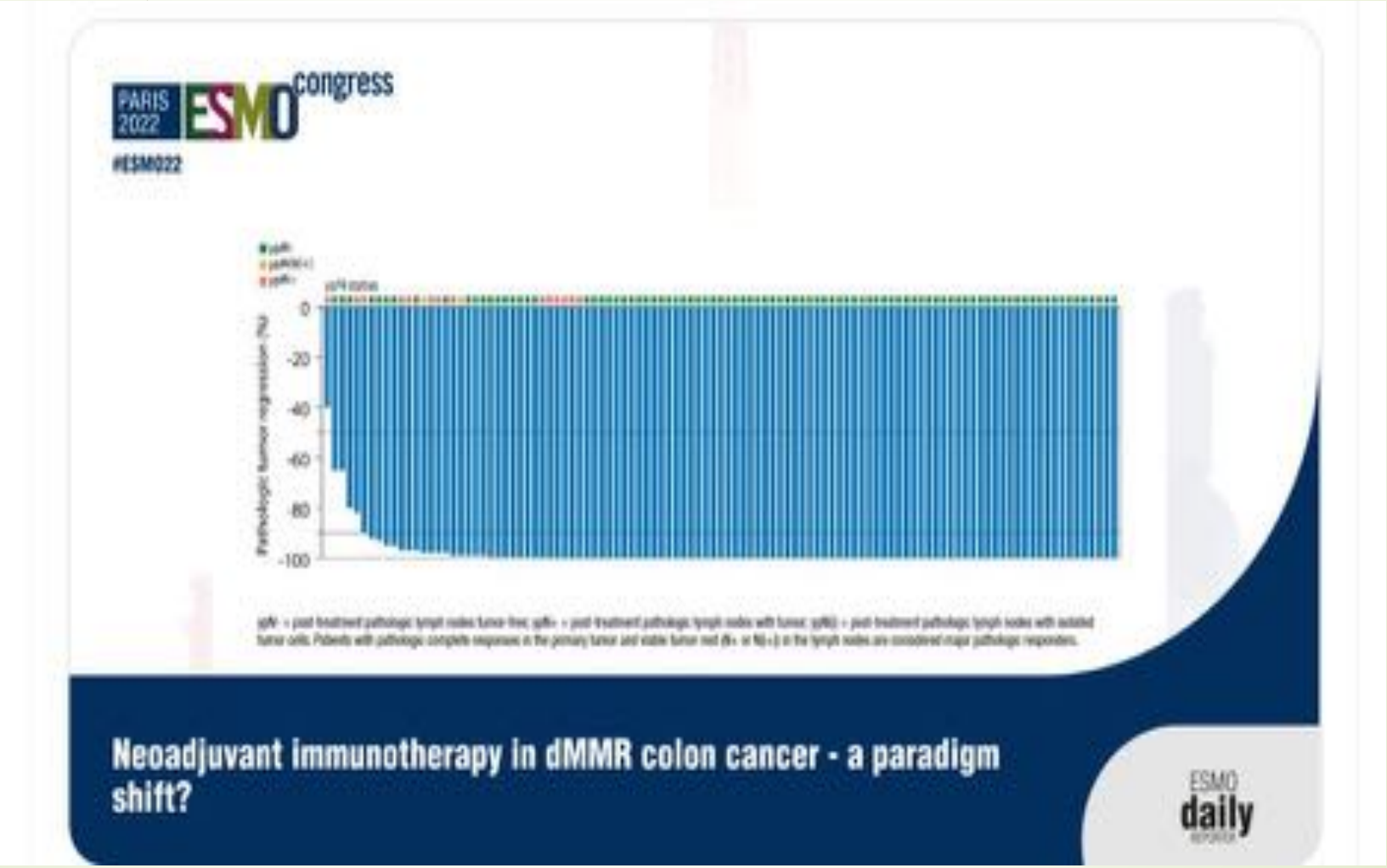


- 107 patients were evaluated for efficacy:
  - 106 patients (99%) showed a pathologic response.
  - MPR was seen in 102 → (95%)
  - pCR in 72 Pt → (67%)
  - Partial pathologic response in 4 (4%) patients.
  - Only 1 patient did not experience pathologic response with 60% RVT upon evaluation
- For the 97 patients in the per protocol population who had Lynch status available
  - 65 had a sporadic dmmR tumor → 58% pCR
  - 32 had Lynch syndrome→ 78% pCR

NICHE 2 TRIAL



NICHE 2 TRIAL



PARIS 2022 ESMO congress

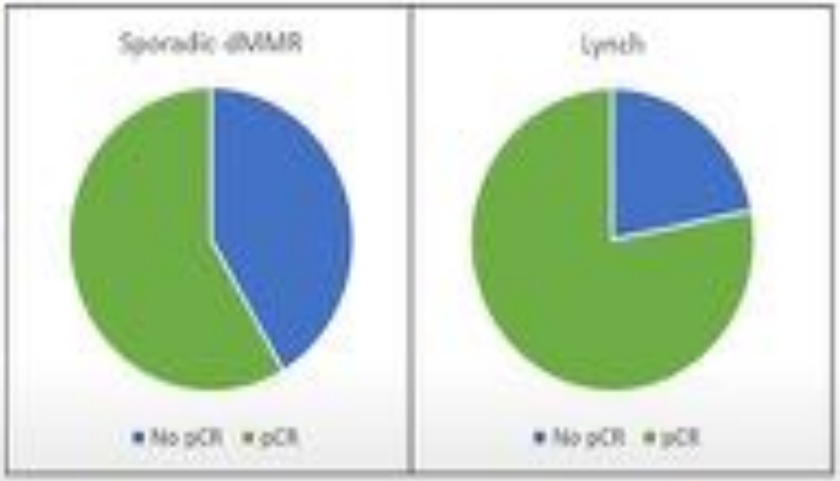
PARIS FRANCE
9-13 SEPTEMBER 2022

esmo.org

pCR rate according in Lynch vs sporadic tumors

	No pCR	pCR	
Sporadic tumor n = 65	27 (42%)	38 (58%)	p = 0.056
Lynch Syndrome n = 32	7 (22%)	25 (78%)	

N totals 97 patients in the per protocol population for whom Lynch status was available at data cut-off



LBA7 - Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study (Myriam Chalabi)

Conclusion Niche 2

- LBA7 - Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: the NICHE-2 study
- Achieved Primary end points:
  - Major Path. Response in 95%
  - Complete Path response in 67%
  - 98% of Patients had undergone surgery , with no major safety challenges
- Historical data in Neoadjuvant CHEMOTHERAPY , the same population had only 7 % of cPR
- The 3 year DFS will be presented in 2023 !!

Metastatic CRC , MSS and Role of Immunotherpay

- Leveraging Targeted or chemotherapy to enhance the efficacy of Immunotherpay in Metastatic CRC with No Loss of MMR Expression (MSS)

- Are we there Yet ??

Background

- Immune checkpoint inhibitors(ICI) targeting programmed death-1 (PD-1) and anti- programmed cell death ligand 1 (PD-L1) have exhibited a durable response in patients with deficient mismatch repair (dMMR)/high levels of microsatellite instability (MSI-H) ~5% of mCRC patients.
- However, microsatellite stable (MSS) tumors represents 95% of mCRC.
- ICI has limited antitumor activity is MSS mCRC due to various reasons including low tumor mutation burden (TMB) and low immune infiltration.

Richard Kim M.D.
References: 1. Ooki A, et al. J Anus Rectum Colon. 2021;5(1):13-24. 2. Llosa NJ, et al. Cancer Discov. 2015;5(1):43-51.

How can we overcome the mechanism of Primary Resistance in pMMR/non-MSI-H CRC

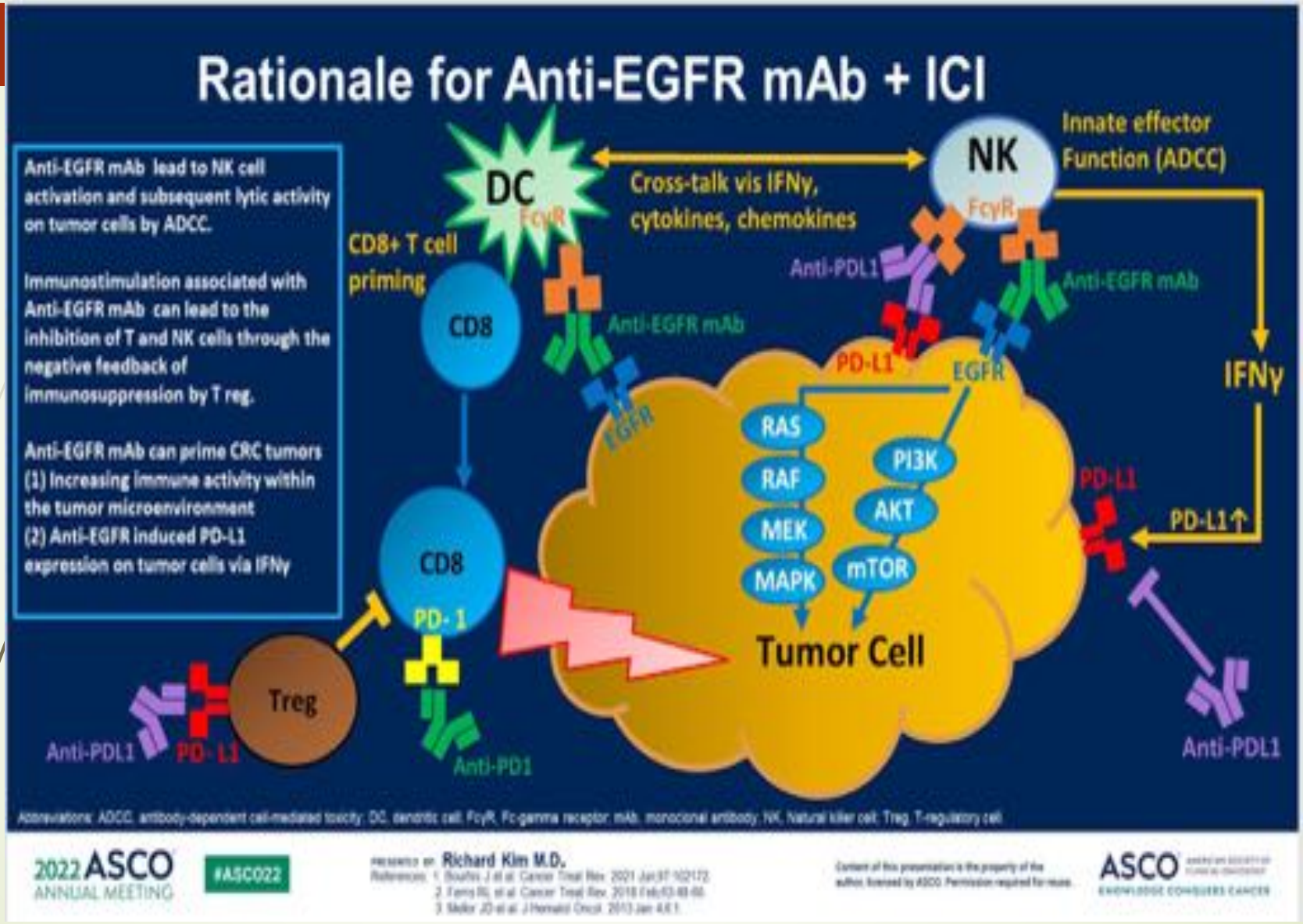
Barriers

- Low Tumor Mutation Burden and Lack of Tumor Antigen.
- VEGF-driven Immunosuppressive TME.
- Immune Tolerance by Liver Metastasis ie. activation of CD8+ T cells and poor CD4+ T cells within the liver may lead to exhaustion or premature death of T cells / lack of dendritic cells.

Goal

- Combine PD-1 blockade with other therapeutic approaches aimed at increasing the immunogenicity of CRC tumors and/or modifying the immunosuppressive TME.

References: 1. Kim CW Te al Cancers (Basel). 2021 Sep 29;13(19):4906



Presented by: Richard Kim M.D.

References: 1. Boutros J et al. Cancer Treat Rev. 2021 Jun;97:102172.
2. Kemp RL et al. Cancer Treat Rev. 2018 Feb;63:48-60.
3. Mellor JD et al. J Hematol Oncol. 2013 Jan 4;6:1.

Rationale for ICI + TKI in CRC with MSS

- MSS colorectal cancer tumor microenvironment hosts more tumor-associated macrophages (TAMs)[1].
- TAMs have been reported to have several protumoral functions, including promotion of angiogenesis and suppression of adaptive immunity[2].
- Tyrosine kinase inhibitors, particularly angiogenesis inhibitors, may decrease TAMs and enhance T cell infiltration and activation along with anti-angiogenesis effect[3,4].
- Multikinase inhibitors may promote DC maturation, T cell priming, activation and differentiation into long-lived memory T cells by increasing tumor antigenicity and tumor immunogenicity[3,4].
- This approach has been successful in certain solid tumors, including endometrial and renal cell carcinoma.

Richard Kim M.D.

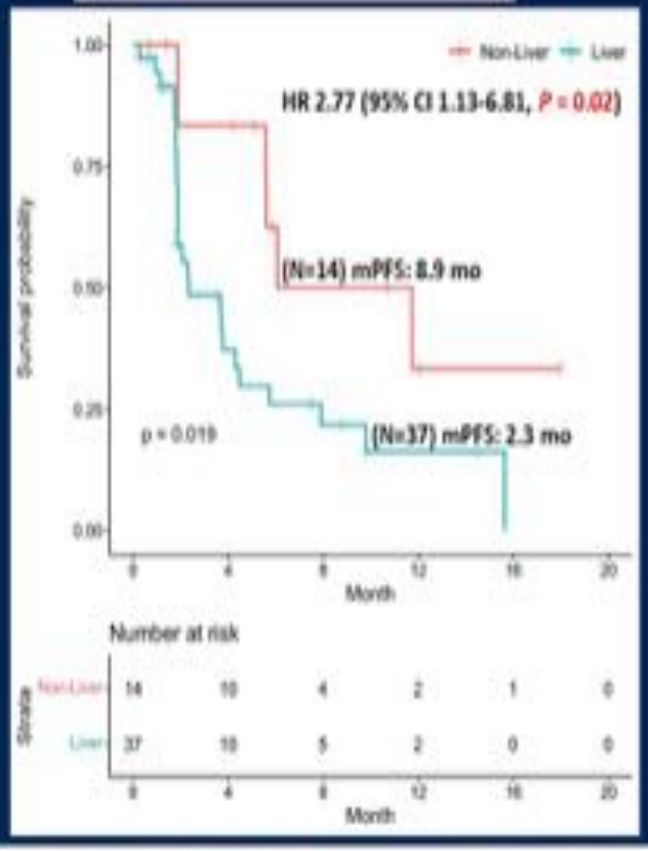
Clinical trials investigating ICIs and TKIs combination in MSS CRC

Phase, Drug	Size, MSI status	ORR	DCR	PFS	OS	Autor, NCT
Phase Ib (REGONIVO), Nivolumab + Regorafenib	25 pts (96% MSS, 4% MSI-H)	36% ORR in MSS subgroup: 33%	N/A	7.9 mo	Not reached	Fukuoka et al. NCT03406871[1]
Phase Ib, Nivolumab + Regorafenib	52 pts (100% MSS) (40 pts were evaluable for efficacy)	8%	63%	4.3 mo	11.1 mo	Kim et al. NCT03712943[2]
Phase II, Nivolumab + Regorafenib	70 pts (100% MSS)	7%	39%	1.8 mo	12.0 mo	Fakih et al. NCT04126733[3]
Phase I/II, Pembrolizumab + Regorafenib	73 pts (100% MSS)	0%	49%	2.0 mo	10.9 mo	Barzi et al. NCT03657641[4]
Phase II (REGOMUNE), Avelumab + Regorafenib	48 pts (100% MSS) (43 pts were evaluable for efficacy)	0%	54%	3.6 mo	10.8 mo	Cousin et al. NCT03475953[5]
Phase II (CAMILLA), Durvalumab + Cabozantinib	36 pts in CRC cohort (100% MSS) (29 pts were evaluable for efficacy)	28%	86%	4.4 mo	9.1 mo	Saeed et al. NCT03539822[6]
Phase II (LEAP -005), Pembrolizumab + Lenvatinib	32 pts in CRC cohort (100% MSS)	22%	47%	2.3 mo	7.5 mo	Gomez-Roca et al. NCT03797326[7]

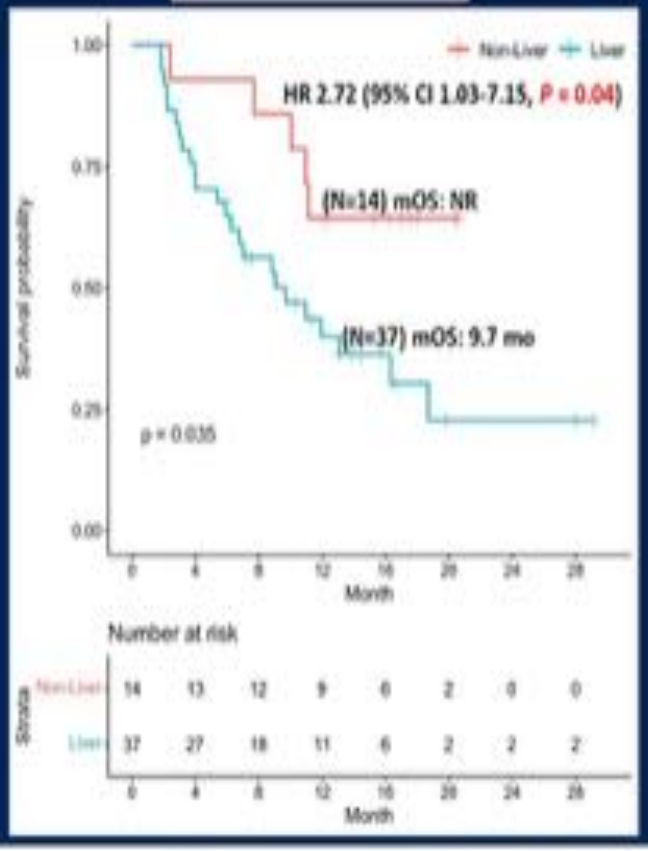
Abbreviation: CRC, Colorectal cancer; DCR, Disease control rate; Mo, Months; MSI-H, Microsatellite instability-high; MSS, Microsatellite stable; ORR, Overall response rate; OS, Overall survival; PFS, Progression-free survival; Pts, Patients; TKI, tyrosine kinase inhibitor.

PFS and OS by Presence and Lack of Liver Metastases in MSS MCRC

Progression Free Survival



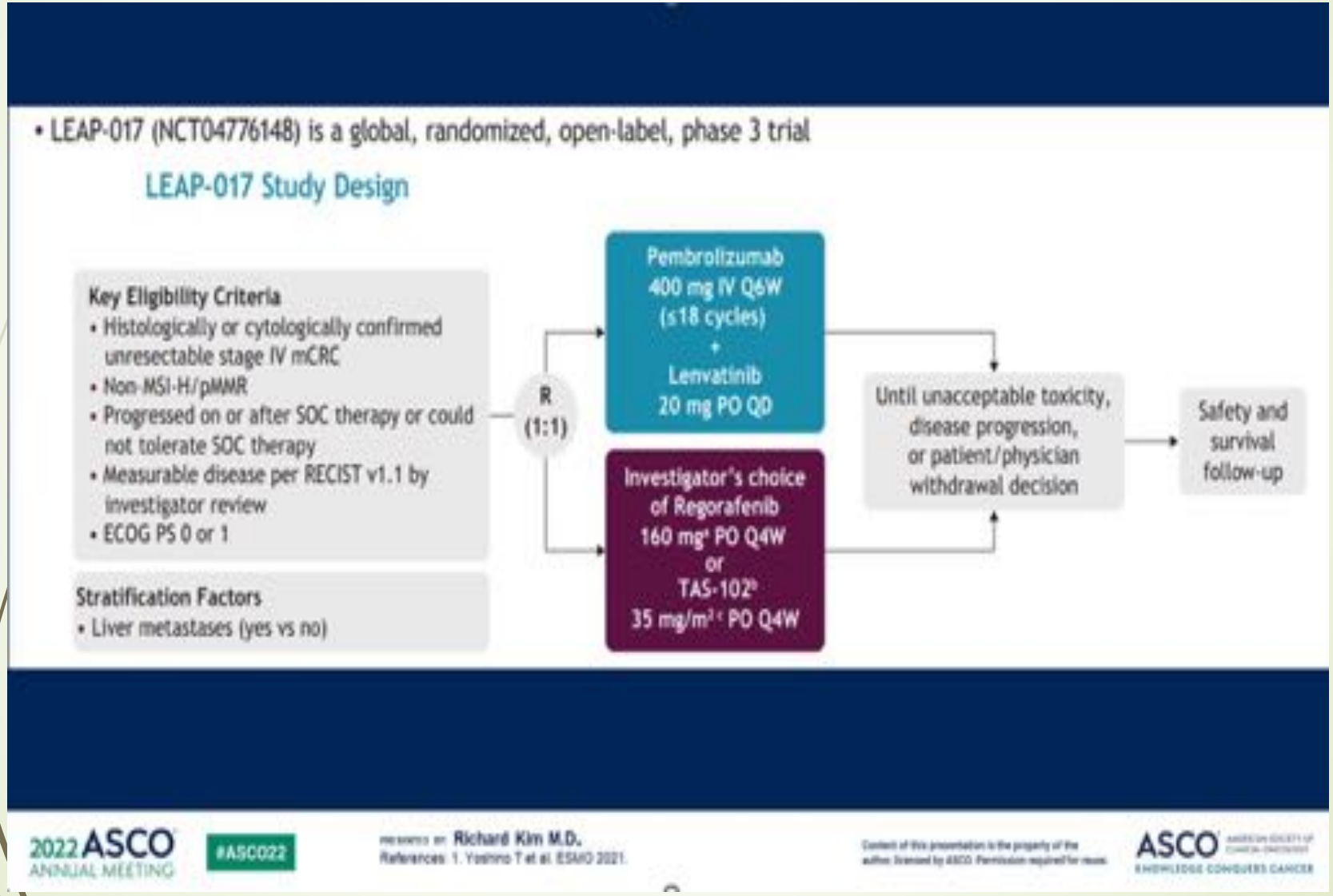
Overall Survival



Richard Kim M.D.

References 1. Kim R et al. EJOC 2022 in press

Future Direction



2022 ASCO ANNUAL MEETING

Abstract #3509: Phase II Study of Nivolumab in combination with FOLFOXIRI/bevacizumab as first-line treatment in patients with Advanced Colorectal Cancer RAS/BRAF mutated (mut) – NIVACOR Trial (GOIRC-03-2018)

Damato A[1], Bergamo F[2], Antonuzzo L[3], Nasti G[4], Pietrantonio F[5], Tonini G[6], Maiello E[7], Bordonaro R[8], Bilancia D[9], Romagnani A[1], Iachetta F[1], Larocca M[1], Maglietta G[10], Normanno N[11], Pinto C[1]

[1]Medical Oncology Unit, Azienda USL-IRCCS Reggio Emilia, Italy; [2]Oncology Unit 1, Istituto Oncologico Veneto-IRCCS Padova, Italy; [3]Clinical Oncology, A.O.U. Careggi Firenze, Italy; [4]Medical Oncology, Addominal Department, National Cancer Institute G. Pascale Foundation, Naples, Italy; [5]Medical Oncology, Istituto Nazionale Tumori Milano, Italy; [6]Policlinico Universitario Campus Bio-Medico, Roma, Italy; [7]Medical Oncology, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; [8]Oncology Unit, ARNAS Garibaldi - Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi, Catania, Italy; [9]Medical Oncology, Azienda Ospedaliera San Carlo, Potenza, Italy; [10]Clinical and Epidemiological Research, Azienda Ospedaliero-Universitaria Parma, Italy; [11]Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori 'Fondazione Giovanni Pascale' IRCCS, Napoli, Italy

NIVACOR Study Design (NCT04072198)

- Phase II, single-arm, multicenter, open-label study

Key Eligibility Criteria:

- Advanced, untreated metastatic colorectal adenocarcinoma
- *RAS/BRAF* mutated
- ECOG 0 or 1
- Regardless of microsatellite status

N=73

FOLFOXIRI[1]
+
Bevacizumab (BEV) 5mg/Kg Q2W
+
Nivolumab (NIV) 240 mg flat dose IV Q2W
for eight cycles

INDUCTION

CR, PR, SD*

Bevacizumab (BEV) 5mg/Kg Q2W
+
Nivolumab (NIV) 240 mg flat dose Q2W
until PD or unacceptable toxicities, or patients/physicians withdrawal decision

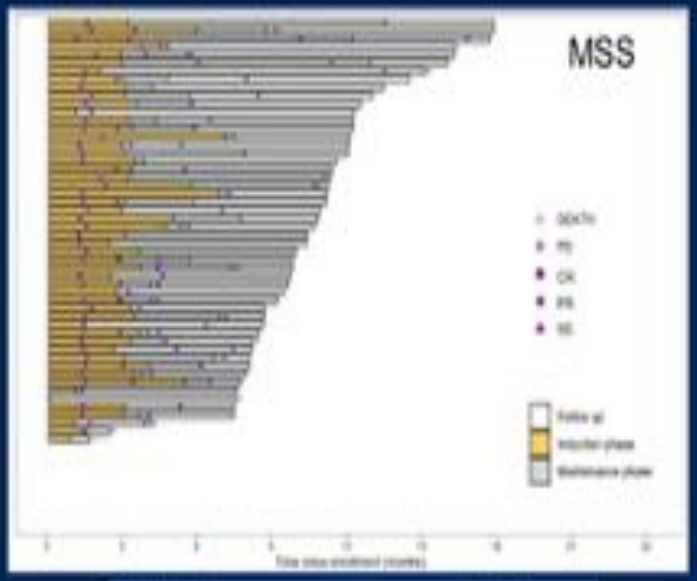
MAINTENANCE

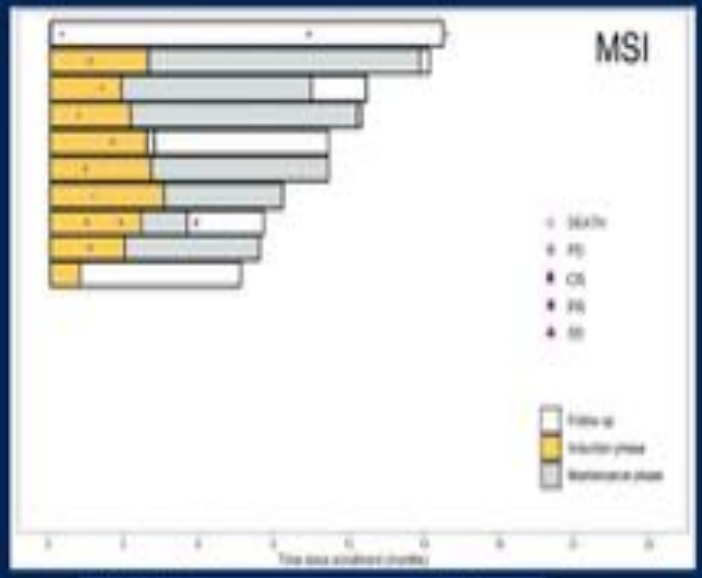
- A'Hern one stage design
- α-error: 0.05, β-error: 0.2
- H_0: ORR=0.66 according to Cremolini C et al.[1] and H_1: ORR=0.80
- Accrual of 73 pts (comprehensive of a 10% drop-out rate) from October 2019 to March 2021.
- At least 56 responses were necessary to not reject the alternative hypothesis

Primary Endpoint: ORR by Investigator (RECIST Criteria v1.1)
Secondary: safety, DCR, DoR, PFS, OS

[1] Cremolini C et al. Lancet Oncol 2015; 16(13):1306-15

Response and Duration of Treatment in MSS and MSI subgroups





Variables	N=52
ORR, %[1]	78.9
DCR, %[1]	96.2
DoR, median (range), months[1]	7.59 (6.21-11.43)

[1]Overall Response rate, [2]Disease control rate, [3]Duration of response

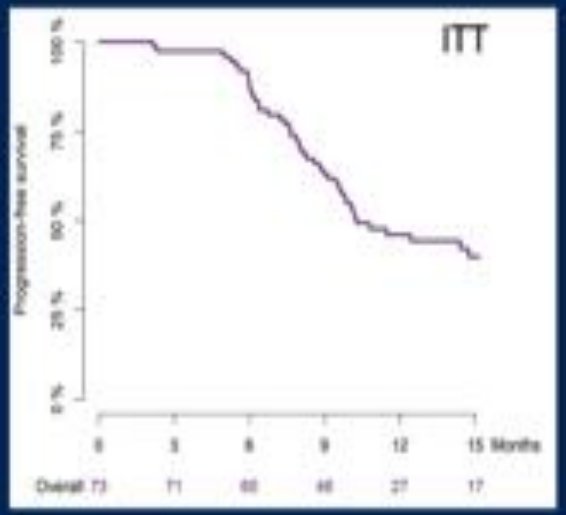
Variables	N=10
ORR, %[1]	70.0
DCR, %[1]	100
DoR, median (range), months[1]	NE (13.5-NE)

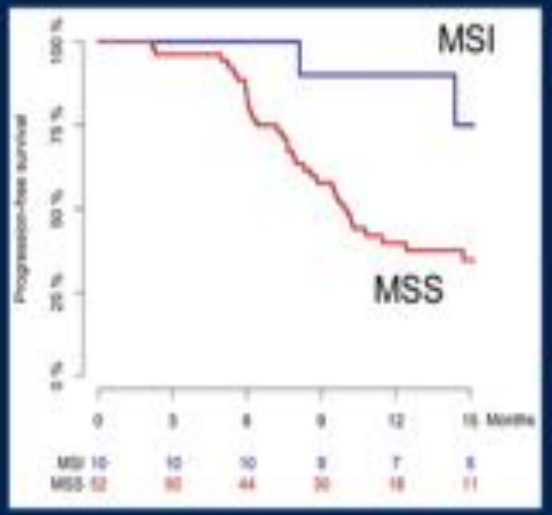
[1]Overall Response rate, [2]Disease control rate, [3]Duration of response

Data cut-off: December 31, 2021

PRESENTED BY: Angela Damato MD, PhD

Progression-free survival in ITT population, MSS, and MSI subgroups





	Overall (n=73)	MSS (n=36/52)	MSI (n=2/10)
Median PFS months (95%CI)	10.1 (9.4 –NE)	9.82 (8.18-15.24)	NE (14.2-NE)

MSS: microsatellite status; MSI: microsatellite instability; PFS: progression-free survival; NE: not estimable

Data cut-off [illegible]

Conclusions

- Immunotherapy in MSS CRC is NOT ready for prime time.
- Current efforts are focused on combination strategies aiming at turning "immune tolerant/cold " tumors into "immune competent/hot " tumors.
- Understanding of mechanisms of immunotherapy resistance and the heterogeneous spectrum of mCRC is needed in order to improve pharmacological strategies to overcome primary resistance to immunotherapy.

LEARNING OBJECTIVES

- MSI-H (dMMR) Colo-Rectal cancer and ImmunoRx
  - Memorial Sloan Kettering ASCO 2022
  - NICHE-2 Trial ESMO 2022
- Metastatic CRC MSS and IO
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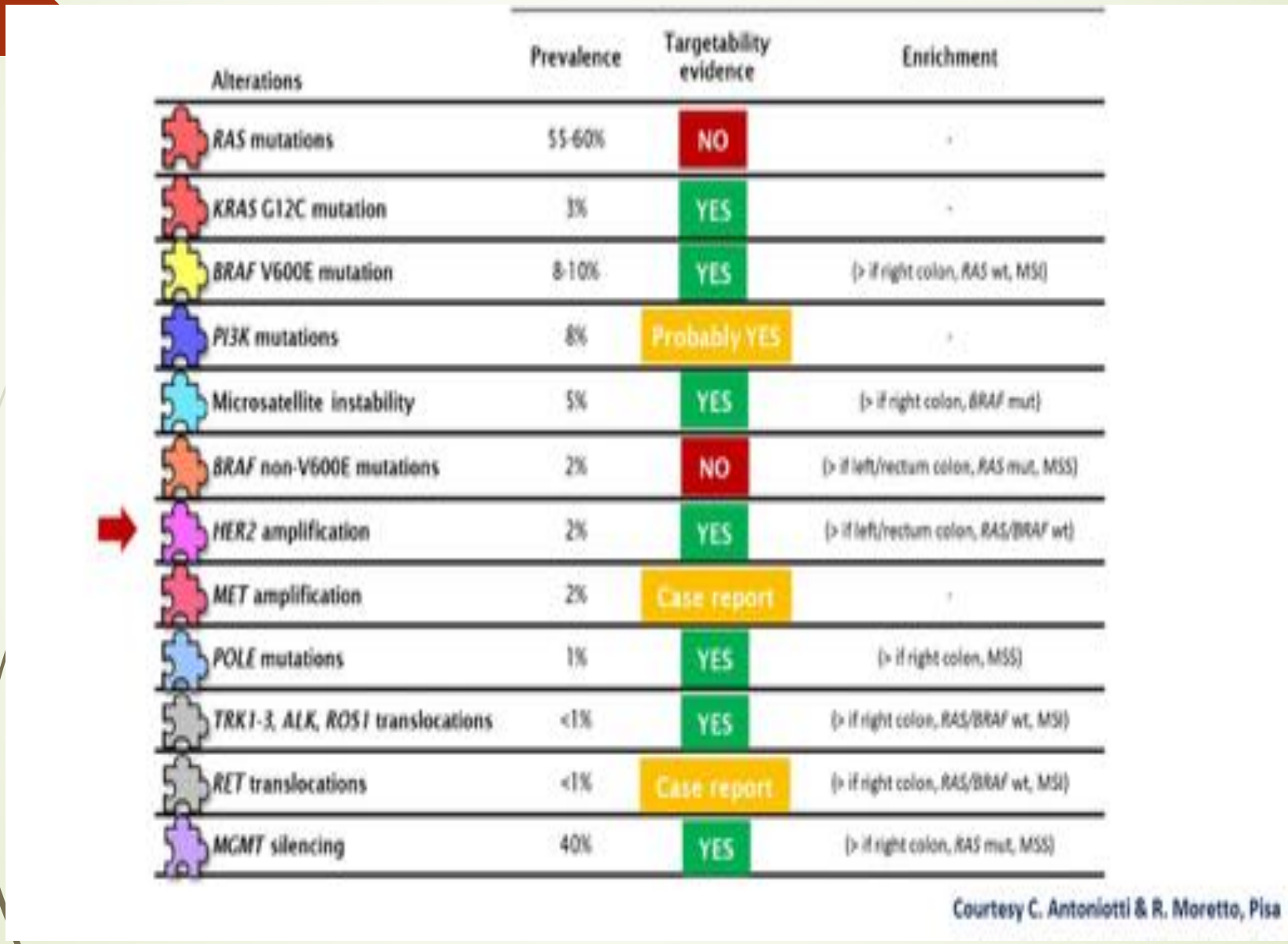


Alterations	Prevalence	Targetability evidence	Enrichment
RAS mutations	55-60%	NO	-
KRAS G12C mutation	3%	YES	-
BRAF V600E mutation	8-10%	YES	(> if right colon, *RAS* wt, MSI)
PI3K mutations	8%	Probably YES	-
Microsatellite instability	5%	YES	(> if right colon, *BRAF* mut)
BRAF non-V600E mutations	2%	NO	(> if left/rectum colon, *RAS* mut, MSS)
HER2 amplification	2%	YES	(> if left/rectum colon, *RAS*/*BRAF* wt)
MET amplification	2%	Case report	-
POLE mutations	1%	YES	(> if right colon, MSS)
TRK1-3, ALK, ROS1 translocations	<1%	YES	(> if right colon, *RAS*/*BRAF* wt, MSI)
RET translocations	<1%	Case report	(> if right colon, *RAS*/*BRAF* wt, MSI)
MGMT silencing	40%	YES	(> if right colon, *RAS* mut, MSS)

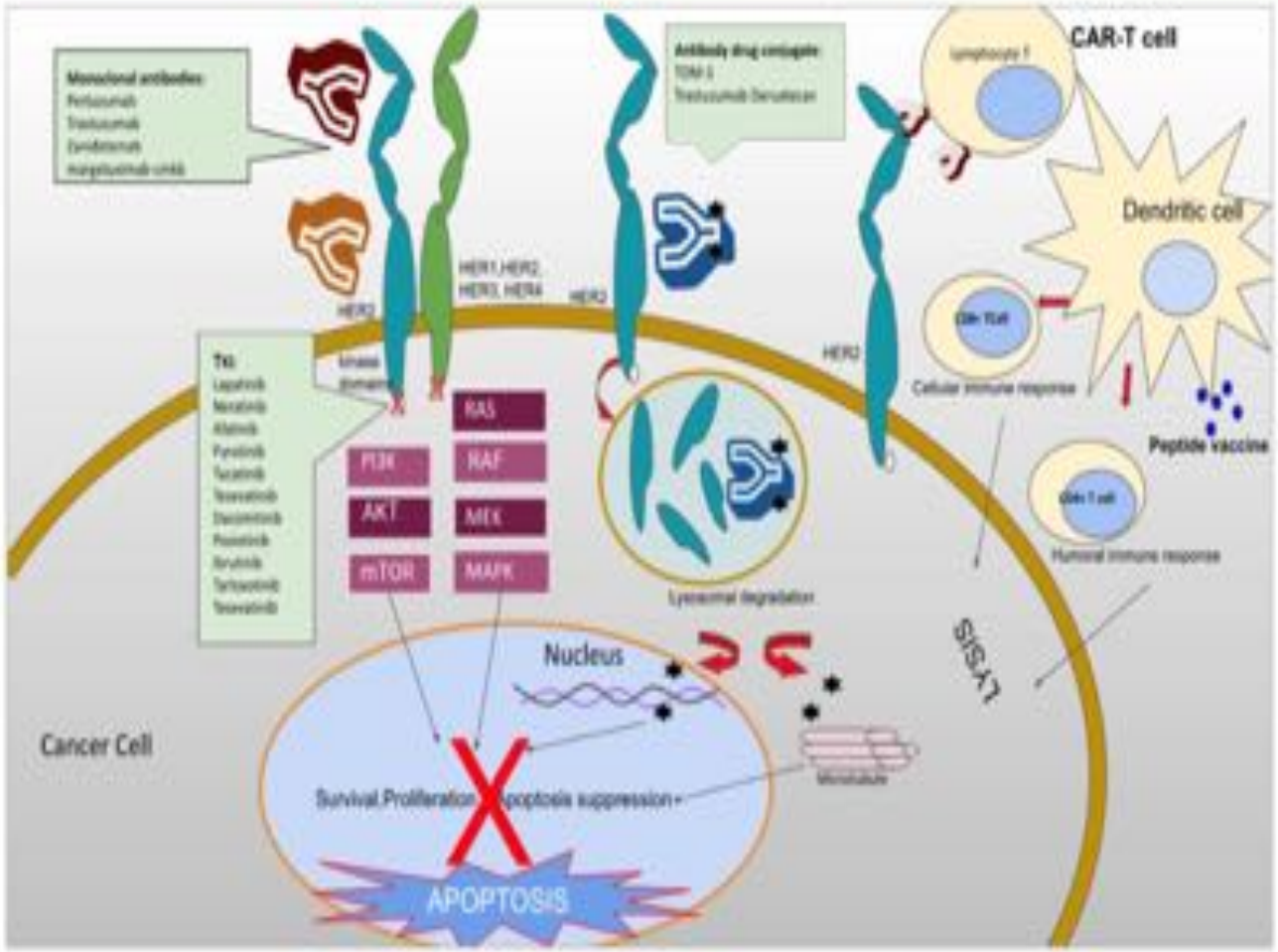
Courtesy C. Antoniotti & R. Moretto, Pisa

Primary analysis of MOUNTAINEER: A phase 2 study of tucatinib and trastuzumab for HER2-positive mCRC

John H. Strickler, Andrea Cercek, Salvatore Siena, Thierry Andre, Kimmie Ng, Eric Van Cutsem, Christina Wu, Andrew Scott Paulson, Joleen M. Hubbard, Andrew L. Coveler, Christos Fountzilas, Adel Kardosh, Pashtoon Murtaza Kasi, Heinz-Josef Lenz, Kristen Ciombor, Elena Elez, David L. Bajor, Michael Stecher, Wentao Feng, Tanios S. Bekaii-Saab

European Society of Medical Oncology World Congress on Gastrointestinal Cancer. Jun 29-Jul 2, 2022. Abstract LBA-2

HER2 inhibitors under investigation



Ahcene Djaballah et al, ASCO Educational Book 2022

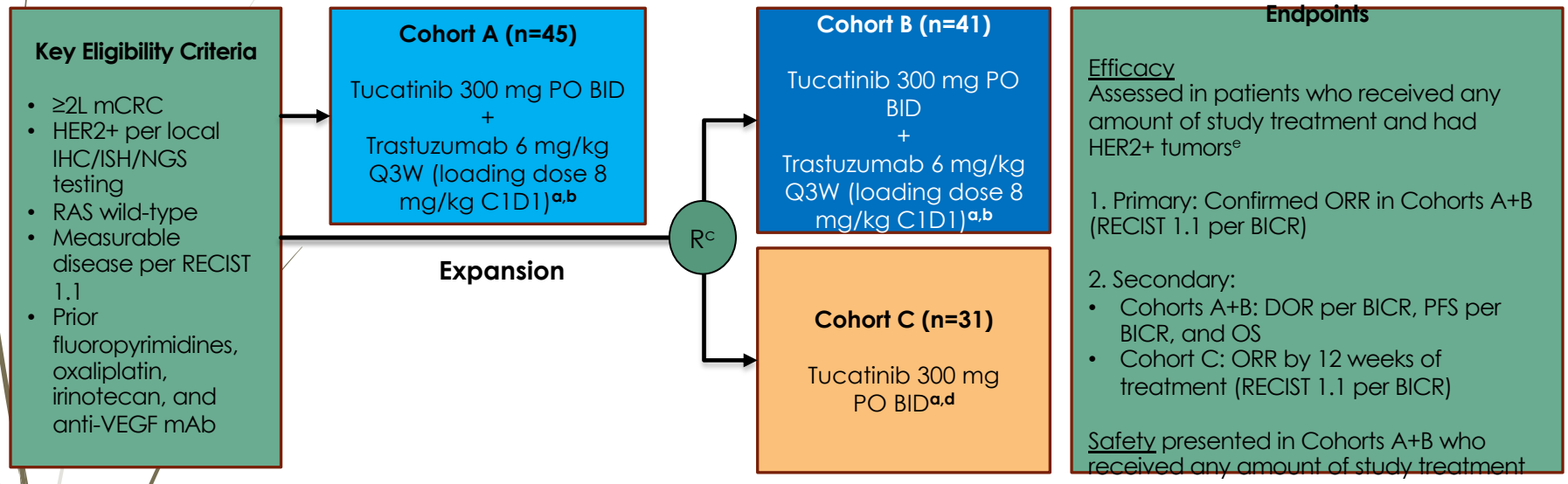
Background

- HER2 amplification/overexpression (HER2+) occurs in ~3%–5% of all patients with mCRC and ~10% of patients with RAS/BRAF wild-type mCRC[1-5]
- Patients with HER2+ mCRC who progress on early lines of chemotherapy regimens receive limited clinical benefit from current standard-of-care treatments[1]
- Tucatinib is a highly selective TKI for HER2 with minimal inhibitory effect on EGFR[3]
  - In patient-derived xenograft models of HER2+ mCRC, tucatinib + trastuzumab showed significantly greater antitumor activity compared with either agent alone
- The MOUNTAINEER trial (NCT03043313) evaluates the efficacy and safety of the investigational combination of tucatinib with trastuzumab in patients with HER2+ and RAS wild-type mCRC[6]

BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; RAS, rat sarcoma virus; TKI, tyrosine kinase inhibitor.

1. Benson et al. J Natl Compr Canc Netw. 2021;19(3):329. 2. Kang et al. J Manag Care Spec Pharm. 2021;S20. 3. Kulukian et al. Mol Cancer Ther. 2020;19:976. 4. Patel et al. J Pers Med. 2019;9. 5. Sartore-Bianchi et al. Oncologist. 2019;24:1395.
6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03043313. Accessed Jun 1, 2022.

MOUNTAINEER: Global, Open-Label, Phase 2 Trial



MOUNTAINEER began as a US Investigator-Sponsored Trial and initially consisted of a single cohort (Cohort A) and was expanded globally to include patients randomised to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C)

Data cut-off for current analysis: March 28, 2022.

a Each treatment cycle is 21 days; b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c Stratification: Left sided tumor primary vs other; d Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a PR or CR by week 12; e Patients had HER2+ tumors as defined by one or more protocol required local tests: IHC 3+ (n=44), amplification by FISH (n=36), or amplification by NGS (n=49)

2L+, second line and later; BICR, blinded independent central review; BID, twice a day; C1D1, cycle 1 day 1; CR, complete response; DOR, duration of response; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; PR, partial response; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; US, United States; VEGF, vascular endothelial growth factor.

https://clinicaltrials.gov/ct2/show/NCT03043313

Tucatinib + Trastuzumab: Efficacy Outcomes

Responses	Tucatinib + Trastuzumab Cohorts A+B n=84
Best overall response per BICR[a], n (%)	
CR	3 (3.6)
PR	29 (34.5)
SD[b]	28 (33.3)
PD	22 (26.2)
Not available[c]	2 (2.4)
cORR per BICR, % (95% CI)[d]	**38.1 (27.7, 49.3)**
cORR per Investigator, % (95% CI)[d]	42.9 (32.1, 54.1)
Median time to objective response per BICR[e], months (range)	2.1 (1.2, 9.8)
DCR[f] per BICR, n (%)	60 (71.4)
Median DOR per BICR, months (95% CI)	**12.4 (8.5, 20.5)**

a Confirmed best overall response assessed per RECIST 1.1; b includes SD and non-CR/non-PD; c includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable; d Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); e Time from the start of study treatment (Cohort A) or date of randomisation (Cohort B) to the first documentation of objective response (CR or PR that is subsequently confirmed); f Defined as sum of CR, PR, and SD

BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

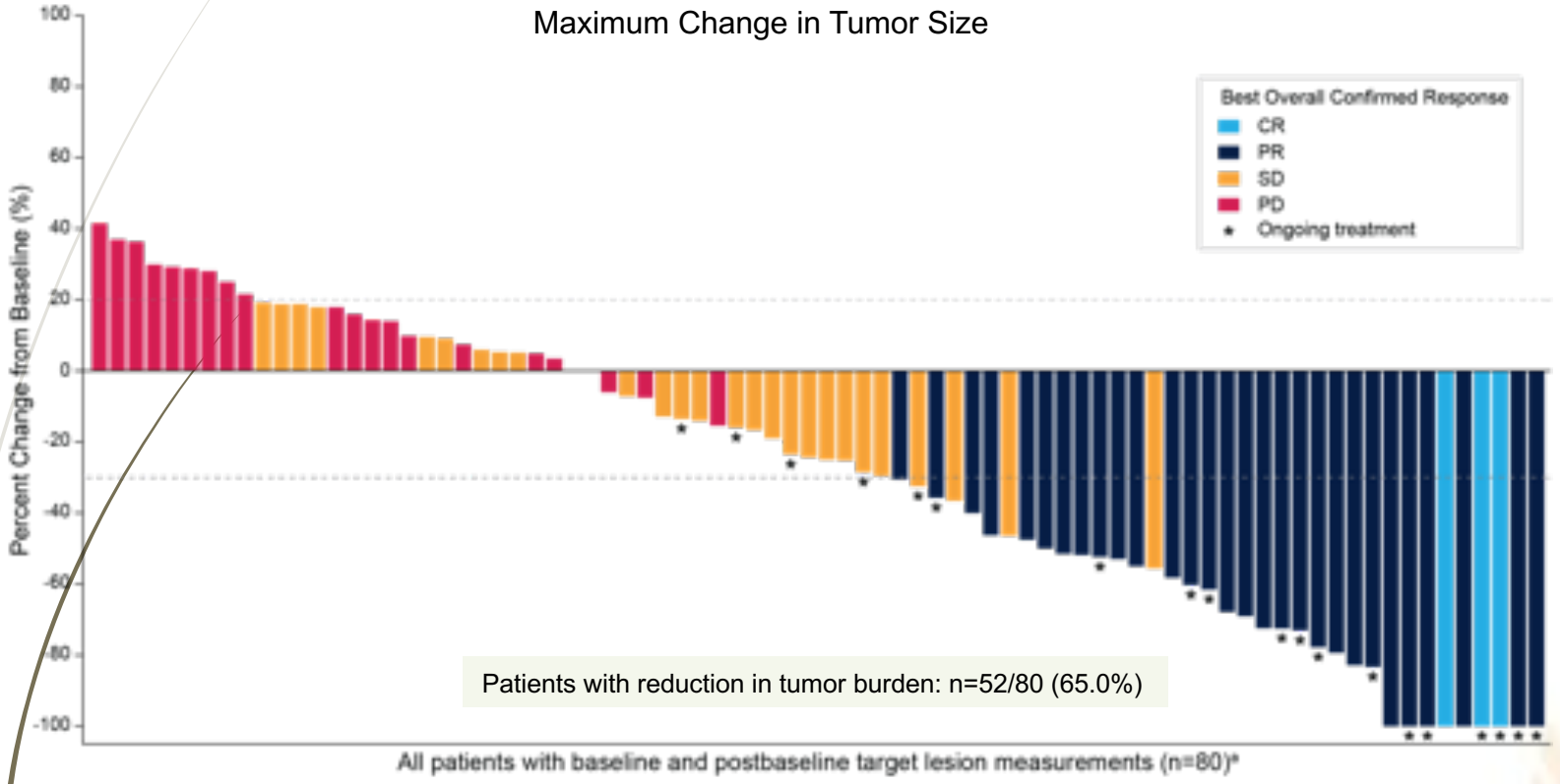
Data cutoff: 28 Mar 2022

Key Baseline Patient Characteristics

Characteristics, n (%)		Tucatinib + Trastuzumab Cohorts A+B n=84[a]	Tucatinib Monotherapy Cohort C n=30[b]
Median age, years (range)		55.0 (24, 77)	59.5 (29, 75)
Sex	Male	51 (60.7)	15 (50.0)
	Female	33 (39.3)	15 (50.0)
ECOG Performance Status	0	50 (59.5)	17 (56.7)
	1	31 (36.9)	13 (43.3)
	2	3 (3.6)	0
Primary tumor site	Left colon and rectum	71 (84.5)	27 (90.0)
	All other primaries	13 (15.5)	3 (10.0)
	Transverse colon	7 (8.3)	0
	Right colon	5 (6.0)	3 (10.0)
	Multiple/overlapping sites	1 (1.2)	0
Stage IV at initial diagnosis		50 (59.5)	19 (63.3)
Patients with liver metastases at study entry		54 (64.3)	15 (50.0)
Patients with lung metastases at study entry		59 (70.2)	20 (66.7)

a Two patients did not have HER2+ disease as specified per protocol and were excluded; b One patient discontinued before receiving treatment
ECOG, Eastern Cooperative Oncology Group.

Tucatinib + Trastuzumab: Change in Tumor Size

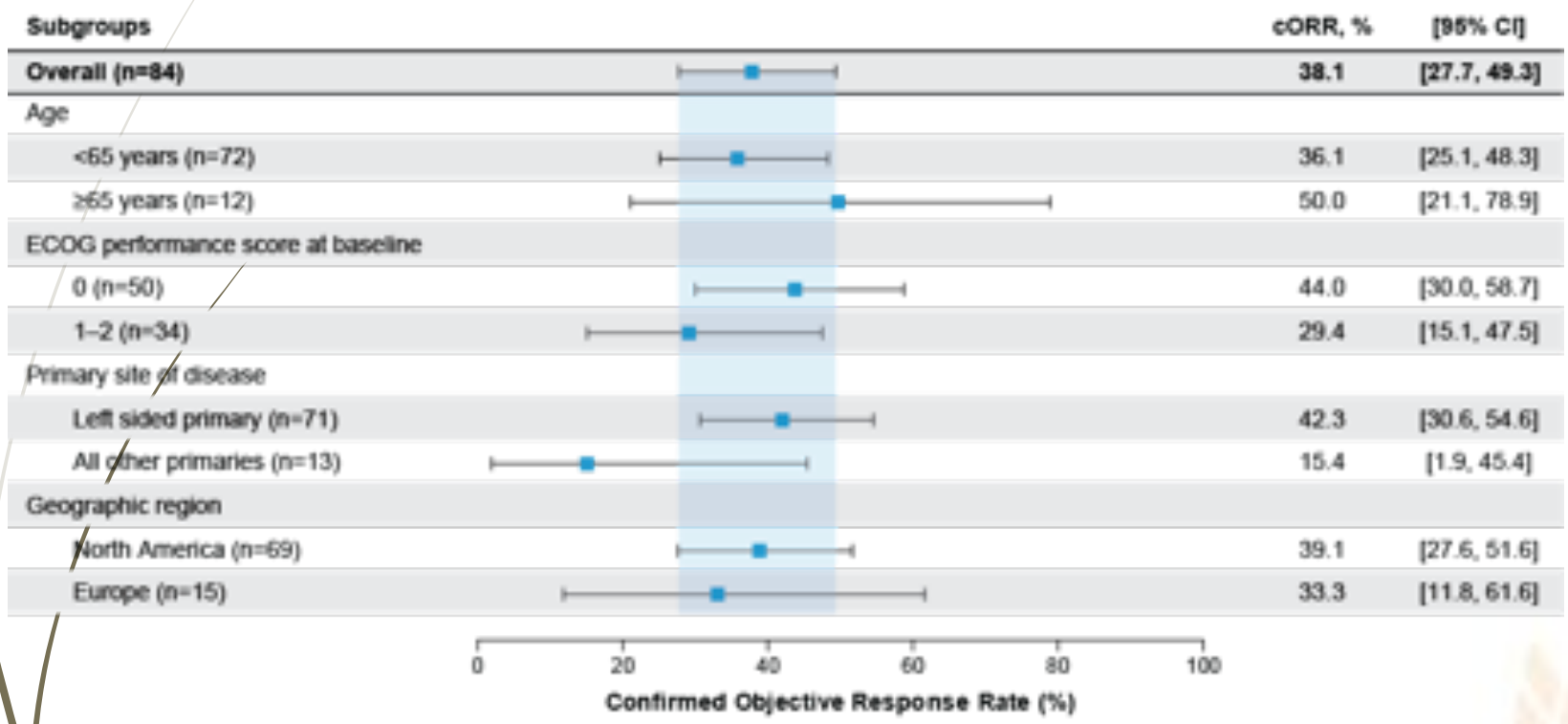


a Four patients who did not have baseline and post-baseline target lesion measurements are excluded

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Data cutoff: 28 Mar 2022

Tucatinib + Trastuzumab: cORR per BICR in Prespecified Subgroups

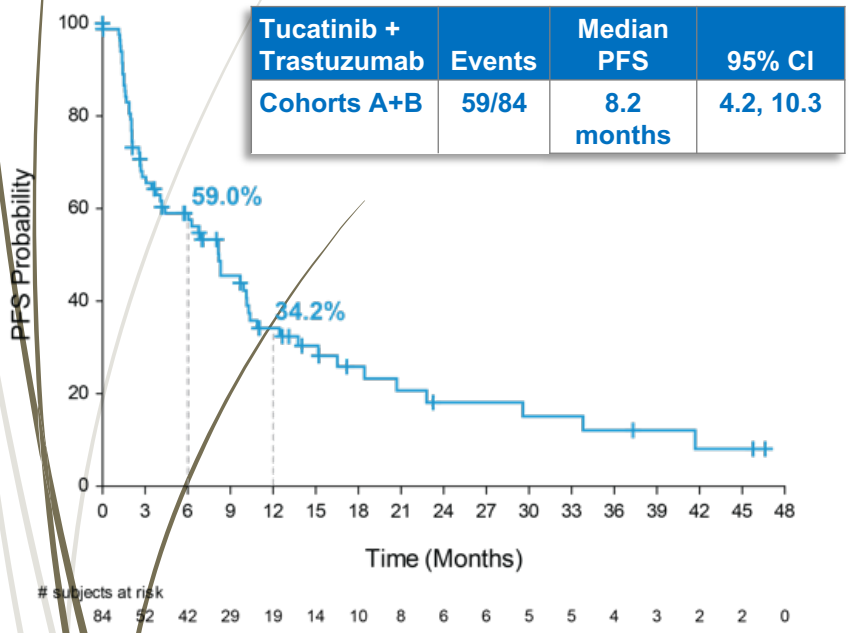


BICR, blinded independent central review; cORR, confirmed objective response rate; ECOG, Eastern Cooperative Oncology Group.
Data cutoff: 28 Mar 2022

Tucatinib + Trastuzumab: PFS and OS

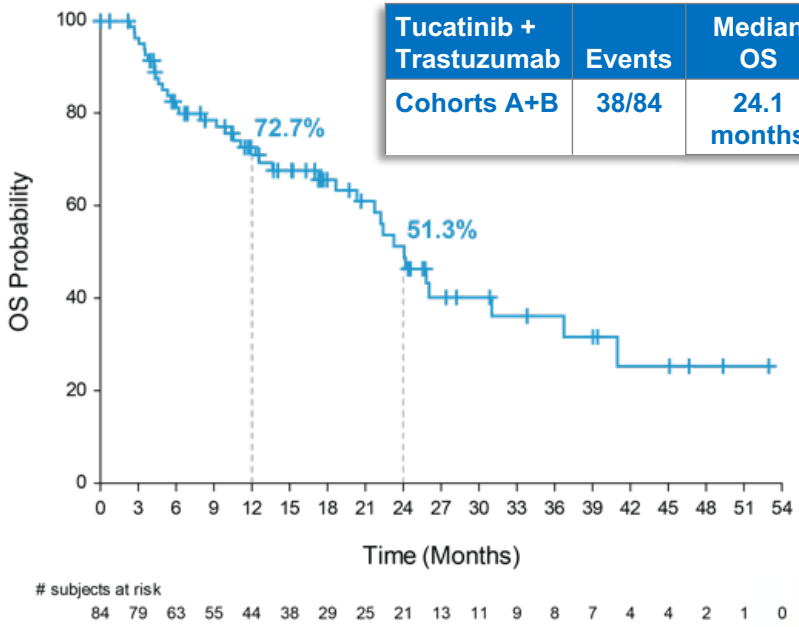
Progression-free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.2 months	4.2, 10.3



Overall Survival

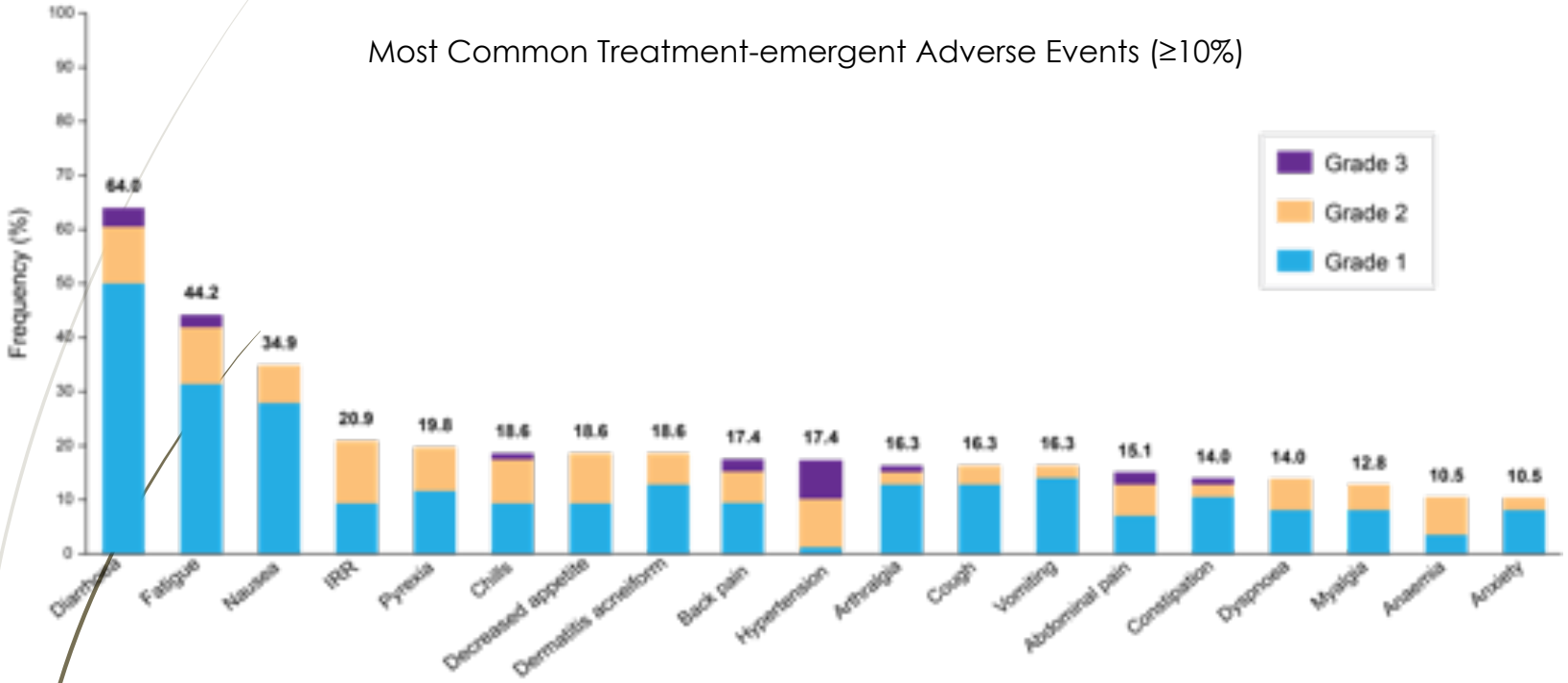
Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	24.1 months	20.3, 36.7



Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

BICR, blinded independent central review; IQR, interquartile range; OS, overall survival; PFS, progressive-free survival.
Data cutoff: 28 Mar 2022

Most Common TEAEs (≥10%) for Tucatinib + Trastuzumab



- Most common tucatinib-related AEs (≥10%): diarrhoea (52.3%), fatigue (29.1%), nausea (18.6%), and dermatitis acneiform (17.4%)
  - Grade ≥3 tucatinib-related AEs (≥2%): alanine aminotransferase increase (2.3%) and diarrhoea (2.3%)

AE, adverse event; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.
Data cutoff: 28 Mar 2022

Conclusions

- In chemotherapy-refractory patients with HER2+ mCRC, tucatinib in combination with trastuzumab demonstrated durable and clinically meaningful antitumor activity
  - Confirmed ORR of 38.1%, DOR of 12.4 months, median PFS of 8.2 months, and median OS of 24.1 months
- Tucatinib + trastuzumab was well tolerated and had low discontinuation rate
  - Diarrhoea was predominately low grade and manageable; no Grade 4 events
  - No deaths resulted from AEs
- Tucatinib in combination with trastuzumab has the potential to become a new standard of care for patients with HER2+ mCRC
- Ongoing phase 3 MOUNTAINEER-03 trial (NCT05253651) will compare tucatinib + trastuzumab + mFOLFOX6 with standard of care

AE, adverse event; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LFT, liver function test; mCRC, metastatic colorectal cancer; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

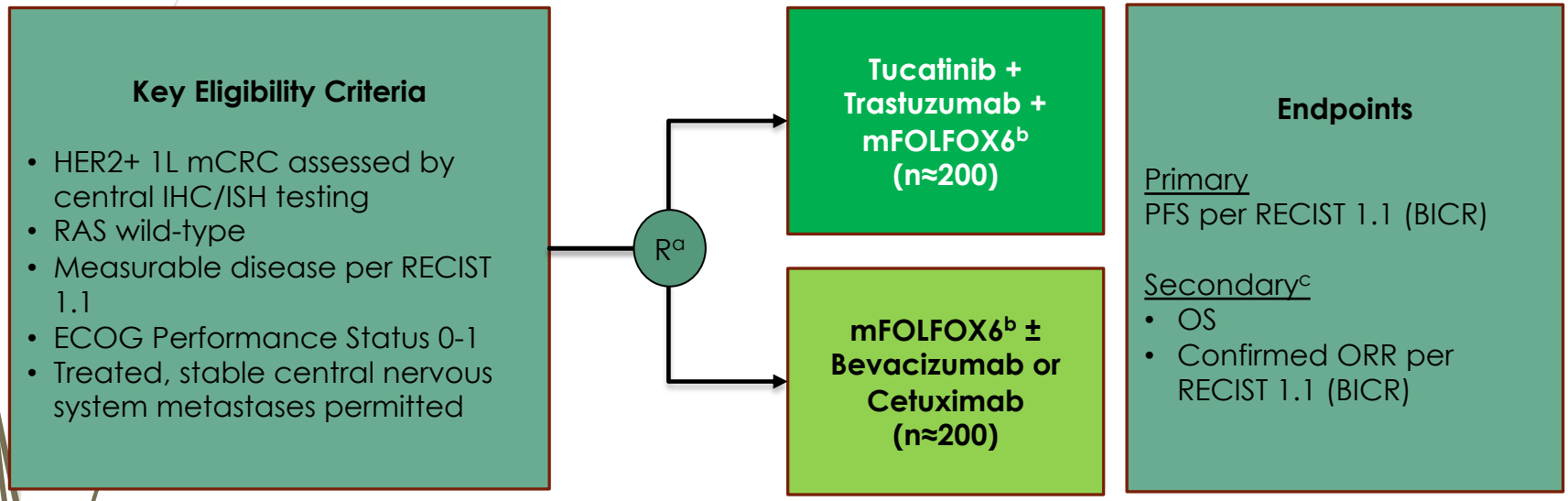
anti-HER2 strategies in HER2+ mCRC: ongoing trials

Study	Phase	N pts	Drugs	Primary endpoint	Country
MOUNTAINEER	II	115	Tucatinib vs Tucatinib + Trastuzumab	ORR	
NCT04430738	I/II	65	Tucatinib + Trastuzumab + FOLFOX/CAPOX	Safety/ORR	
NCT04380012	II	40	Pyrotinib + Trastuzumab	ORR	
MODUL - maintenance	II	-	Trastuzumab + Pertuzumab + Capecitabine	PFS	
NSABP FC-11	II	35	Neratinib + Trastuzumab vs Neratinib + Cetuximab	ORR	
DESTINY-CRC02	II	120 (including *RAS*mut)	T-DXd 5.4 mg/kg vs 6.4 mg/kg	ORR	
SWOG S1613	II	130	Trastuzumab + Pertuzumab vs Cetuximab + Irinotecan	PFS	
MOUNTAINEER-03	III	400	FOLFOX + trastuzumab + tucatinib vs FOLFOX +/- bev or cet	PFS	

Courtesy C. Antoniotti & R. Moretto, Pisa

http://clinicaltrials.gov

MOUNTAINEER-03: Global, Randomised, Open-Label, Phase 3 Trial



a Stratification: Primary tumor sidedness, liver metastases; b Levo-leucovorin may be given in place of leucovorin; c Alpha-controlled

1L, first line; BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors.

https://clinicaltrials.gov/ct2/show/NCT05253651

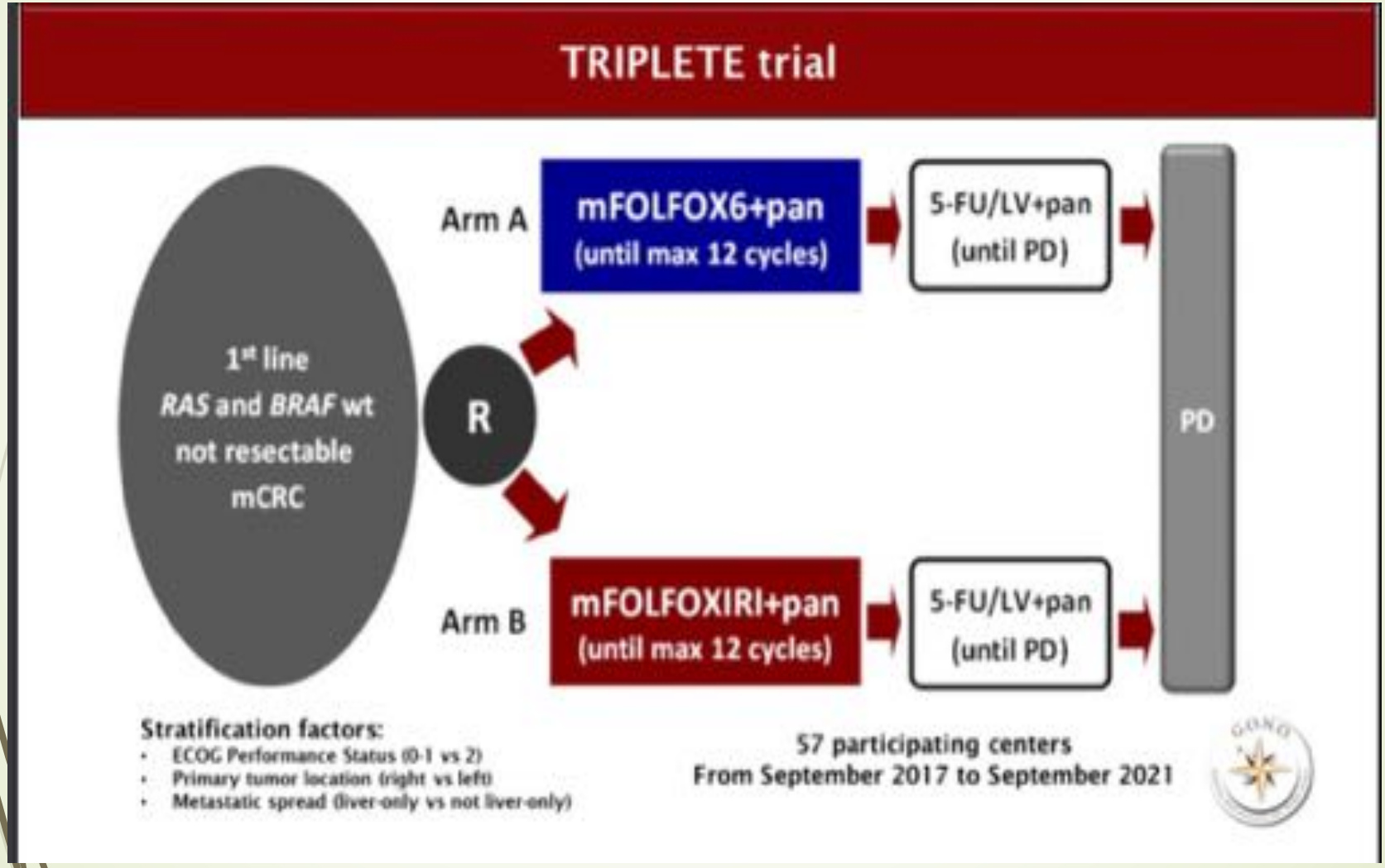
2022 ASCO Annual Meeting

Chicago, 6th June 2022

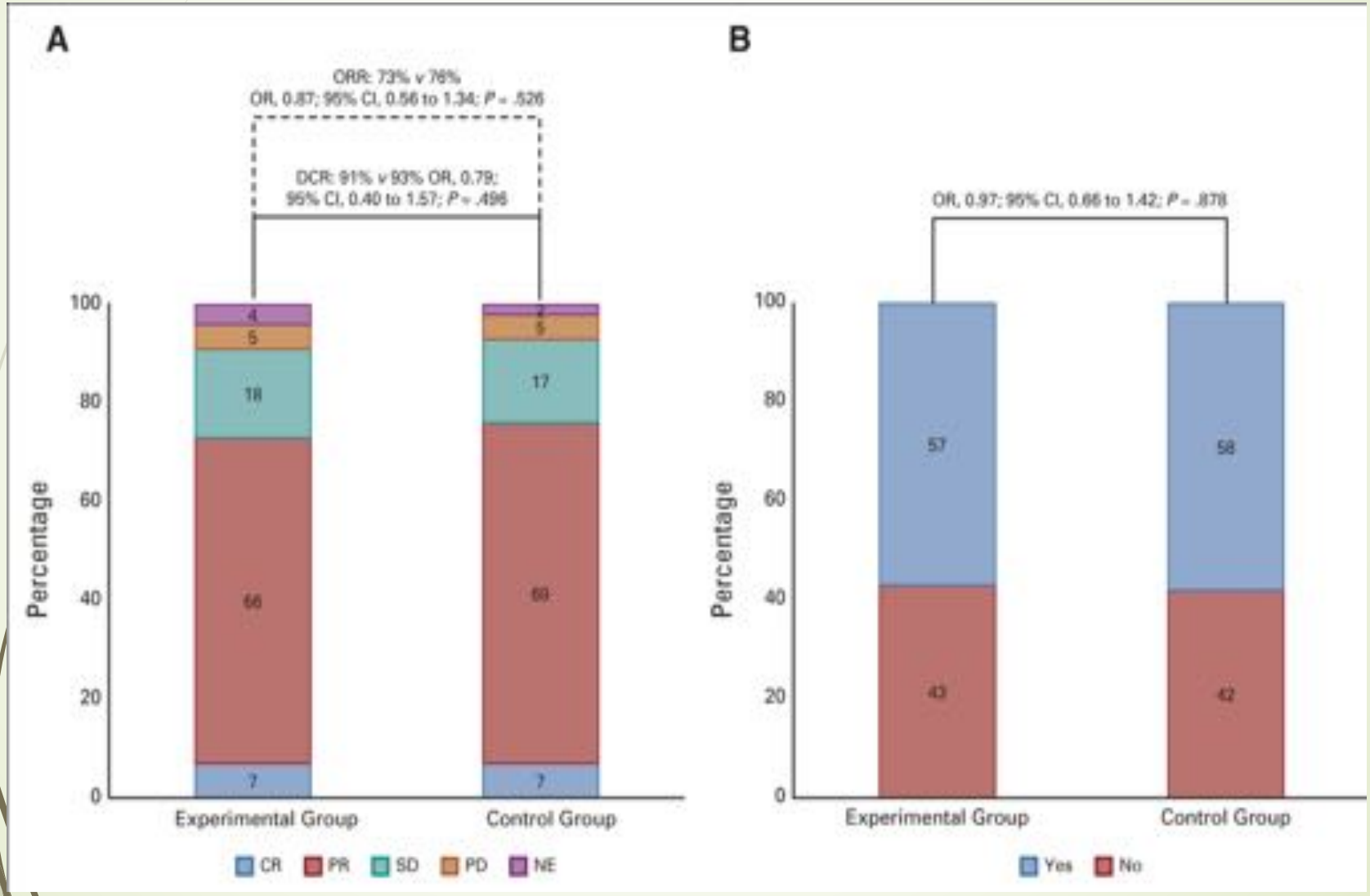
Modified FOLFOXIRI plus panitumumab (mFOLFOXIRI/PAN) versus mFOLFOX6/PAN as initial treatment of patients with unresectable *RAS* and *BRAF* wild-type metastatic colorectal cancer (mCRC): Results of the phase III randomized TRIPLETE study by GONO.

Cremolini C, Rossini D, Lonardi S, Antoniotti C, Pietrantonio F, Marmorino F, Antonuzzo L, Boccaccino A, Randon G, Giommoni E, Pozzo C, Moretto R, De Grandis MC, Viola MG, Passardi A, Buonadonna A, Formica V, Aprile G, Boni L, Masi G

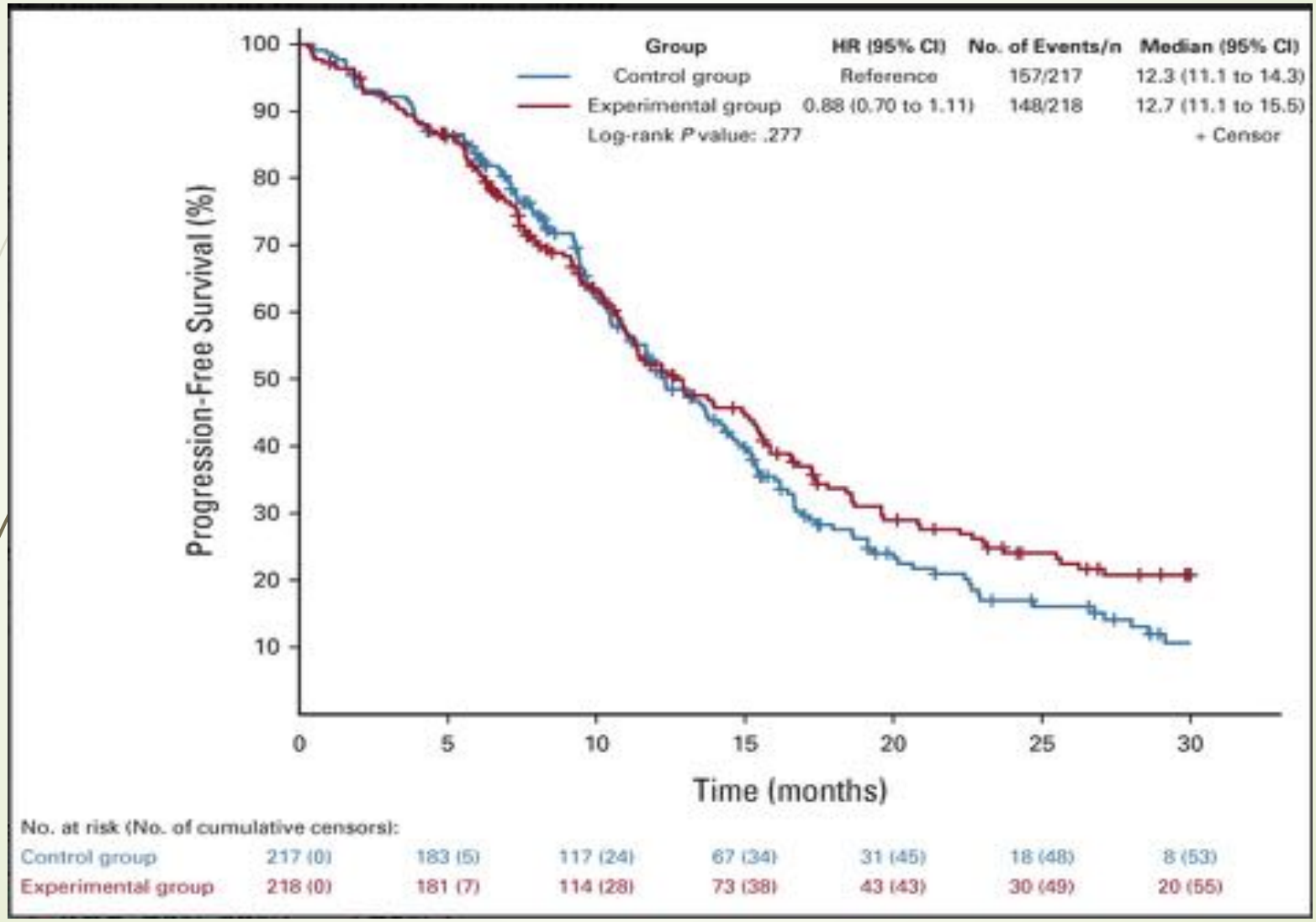
on behalf of the GONO Investigators


TRIPLETE trial
1st line
RAS and BRAF wt
not resectable
mCRC
R
Arm A
mFOLFOX6+pan
(until max 12 cycles)
5-FU/LV+pan
(until PD)
Arm B
mFOLFOXIRI+pan
(until max 12 cycles)
5-FU/LV+pan
(until PD)
PD
Stratification factors:
ECOG Performance Status (0-1 vs 2)
Primary tumor location (right vs left)
Metastatic spread (liver-only vs not liver-only)
57 participating centers
From September 2017 to September 2021

TRIPLETE STUDY GONO



TRIPLETE STUDY GONO



TRIPLETE STUDY / GONO Conclusion

- At a median follow up of 26.5 months:
  - There was no difference in any treatment outcome between the three Vs two-drug regimens objective response rate 73% vs76%;
  - Progression-free survival (median 12.7 and 12.3 month
  - Achievement of R0 resection of metastatic disease 25% and 29%
- Conclusion:
  - Primary End Point was NOT Met: FOLFOXORI/PAN is NOR superior to FOLFIX/PAN
  - High grade G/4 Diarrhea were more seen Triplet

rapid communications

Upfront Modified Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan Plus Panitumumab Versus Fluorouracil, Leucovorin, and Oxaliplatin Plus Panitumumab for Patients With *RAS/BRAF* Wild-Type Metastatic Colorectal Cancer: The Phase III TRIPLETE Study by GONO

Daniele Rossini, MD[1,2]; Carlotta Antoniotti, MD, PhD[1,2]; Sara Lonardi, MD[3]; Filippo Pietrantonio, MD[4]; Roberto Moretto, MD[2]; Lorenzo Antonuzzo, MD, PhD[5]; Alessandra Boccaccino, MD[1,2]; Federica Morano, MD[6]; Marco Brugia, MD[6]; Carmelo Pozzo, MD[7]; Federica Marmorino, MD, PhD[1,2]; Francesca Bergamo, MD[8]; Emiliano Tamburini, MD[9]; Alessandro Passardi, MD[10]; Giovanni Randon, MD[6]; Sabina Murgioni, MD[8]; Beatrice Borelli, MD[1,2]; Angela Buonadonna, MD[11]; Mirella Giordano, PhD[1,2]; Gabriella Fontanini, MD, PhD[12]; Veronica Conca, MD[1,2]; Vincenzo Formica, MD, PhD[13]; Massimo Aglietta, MD[14]; Roberto Bordonaro, MD[15]; Giuseppe Aprile, MD[16]; Gianluca Masi, MD[1,2]; Luca Boni, MD[17]; and Chiara Cremolini, MD, PhD[1,2]

LEARNING OBJECTIVES

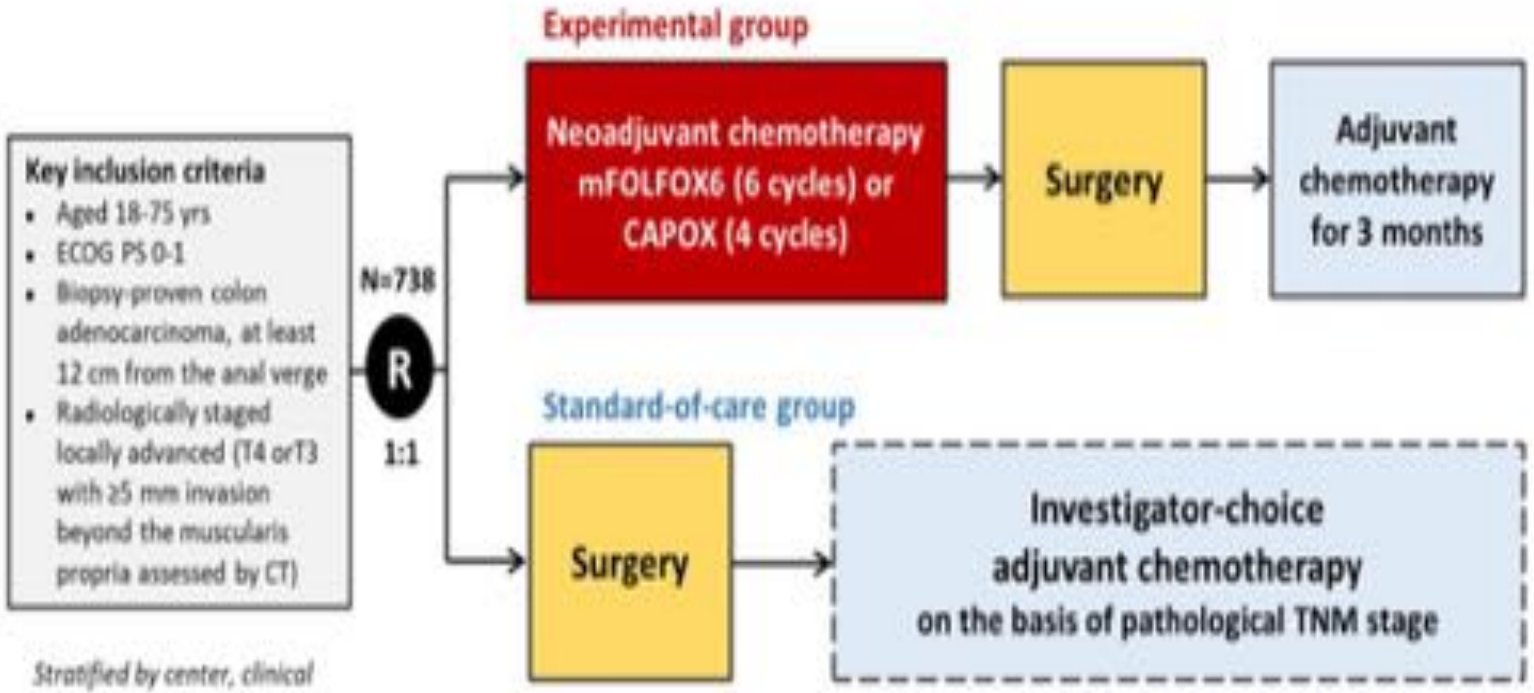
- MSI-H (dMMR) Colo-Rectal cancer and ImmunoRx
  - Memorial Sloan Kettering ASCO 2022
  - NICHE-2 Trial ESMO 2022
- Metastatic CRC MSS and IO
- Advanced CRC:
  - Neur 2 Neu (+) : MOUNTAINEER
  - Triplet /Pan Vs Doublet/ Pan for Left sided
- Locally Advanced :
  - Does Neoadjuvant Chemotherapy have role…: OPTICAL Trial
- Circulating Tumor /Free DNA in Early stage Colon Ca: DYNAMIC TRIAL

Meeting Abstract | 2022 ASCO Annual Meeting I

GASTROINTESTINAL CANCER—COLORECTAL AND ANAL

Perioperative chemotherapy with mFOLFOX6 or CAPOX for patients with locally advanced colon cancer (OPTICAL): A multicenter, randomized, phase 3 trial.

Study Design: Multicenter, Randomized, Phase III Trial (NCT02572141)



Study Endpoints

- **Primary endpoint: 3-year disease-free survival (DFS)**

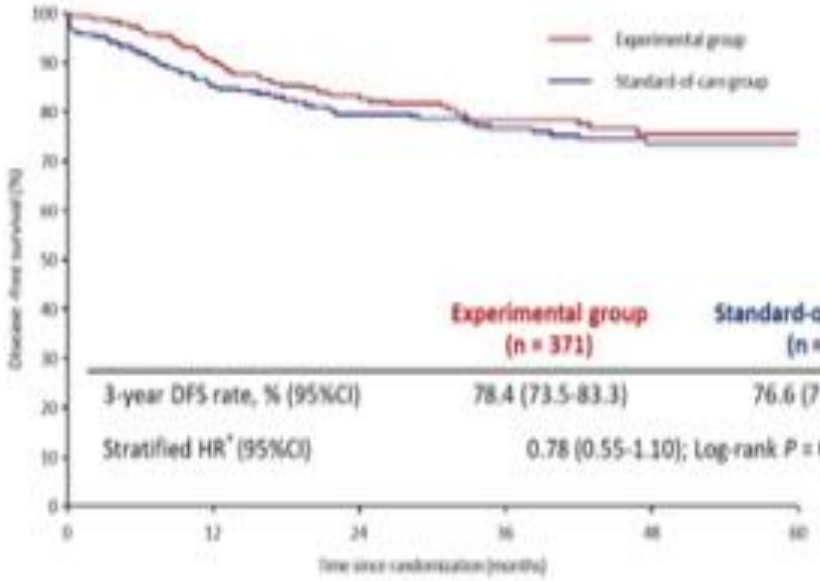
  DFS was defined as the time between randomization and one of the following events, whichever occurred first :

  - Locally progressive disease leading to an unresectable primary tumor
  - An R2 resection for the primary tumor
  - Local recurrence after an R0/1 resection of the primary tumor
  - Distant metastases
  - A new primary colorectal cancer
  - Death from any cause

- **Secondary endpoints:** pathological complete response (pCR), pathological staging, tumor regression grade (AJCC) , overall survival (OS), surgical morbidity and mortality, adverse events with chemotherapy

	Experimental group N(%) (n = 371)	Standard of care group N(%) (n = 373)	*P*
Median age, years (range)	56 (19-75)	56 (22-73)	
Male	215 (58)	223 (60)	
Pathological disease stage			<0.0001
pT0N0M0/ pTisN0M0-stage 0	27 (7)	0 (0)	
Stage I	42 (11)	16 (4)	
Stage II	181 (49)	180 (48)	
Stage III	106 (29)	164 (44)	
Stage IV	7 (2)	13 (4)	
No surgery or missing data	8 (2)	0 (0)	

Disease-Free Survival (DFS) in mITT Population



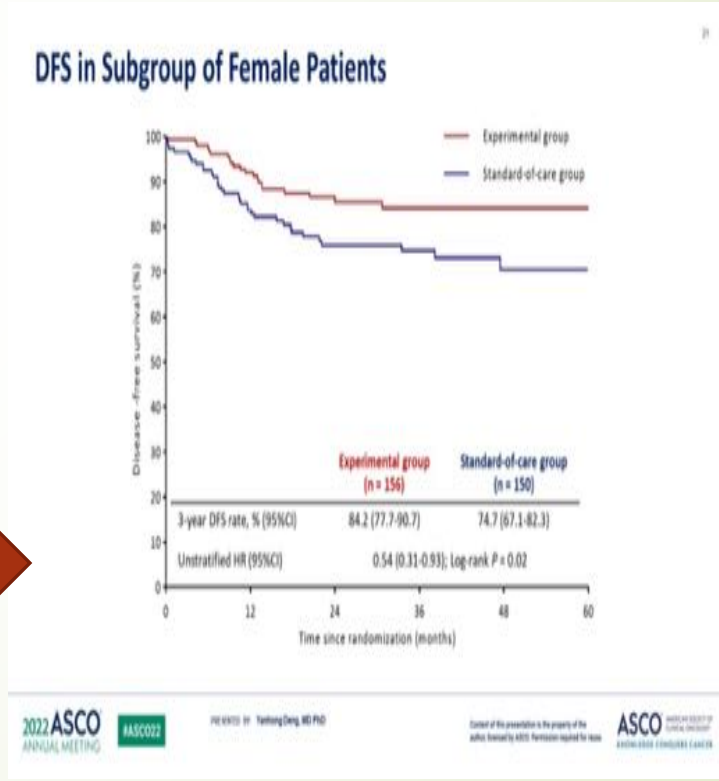
	Experimental group (n = 371)	Standard-of-care group (n = 373)
3-year DFS rate, % (95%CI)	78.4 (73.5-83.3)	76.6 (71.9-81.3)
Stratified HR* (95%CI)	0.78 (0.55-1.10); Log-rank *P* = 0.16	

Number at risk (number censored)						
Experimental group	371 (0)	299 (19)	205 (111)	117 (190)	60 (244)	15 (288)
Standard-of-care group	373 (0)	278 (44)	214 (90)	134 (165)	69 (225)	11 (284)

** Stratified factors included center, clinical T stage (cT3 vs cT4), clinical N stage (cN0 vs cN1-2*

OPTICAL TRIAL
Conclusion

- Difference in 3-year DFS was observed Periop. Group → 78.7% Vs Standard Grp 76.6%
- Did NOT reach statistical significance
- pCR was seen in 7% and 20% downstaged
- Post Hoc



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  - Does Neoadjuvant Chemotherapy have role…: OPTICAL Trial
- Circulating Tumor /Free DNA in Early stage Colon Ca: DYNAMIC TRIAL

CIRCULATING TUMOR DNA stage II Colon cancer

2022 ASCO ANNUAL MEETING

Adjuvant Chemotherapy Guided by Circulating Tumor DNA Analysis in Stage II Colon Cancer

The Randomized DYNAMIC Trial

Jeanne Tie

Peter MacCallum Cancer Centre and Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia

On behalf of the DYNAMIC Investigators

Joshua Cohen, Kamel Lahouel, Serigne Lo, Yuxuan Wang, Rachel Wong, Jeremy Shapiro, Samuel Harris, Adnan Khattak, Matthew Burge, Marion Harris, James Lynam, Louise Nott, Fiona Day, Theresa Hayes, Nickolas Papadopoulos, Cristian Tomasetti, Kenneth Kinzler, Bert Vogelstein, Peter Gibbs

CIRCULATING TUMOR DNA stage II Colon cancer

Background: Stage II Colon Cancer

- **Optimal management continues to be debated**
  - Surgery alone cures > 80%
  - No clear overall survival benefit in adjuvant therapy trials[1-3]
- **Guidelines: consider adjuvant therapy in high-risk patients**[4-6]
  - Definition of high-risk features varies between guidelines
  - Not all high-risk features are equal (e.g., T4 > others)
  - Survival benefit remains modest (< 5%) even in high-risk patients
- **More precise recurrence risk prediction is required to:**
  - Limit adjuvant treatment to well-defined high-risk subset that will potentially benefit
  - Spare treatment in patients with low recurrence risk who are very unlikely to benefit

1. Figueredo et al. Cochrane Database Syst Rev 2008;Cd005390
2. Andre et al. J Clin Oncol 2015;33:4176-87
3. Bockelman et al. Acta Oncol 2015;54:5-16
4. Baxter et al. J Clin Oncol 2022;40:892-910
5. NCCN. Colon Cancer (Version 1, 2022)
6. Argiles et al. Annals of Oncology 2020;31:1291-305

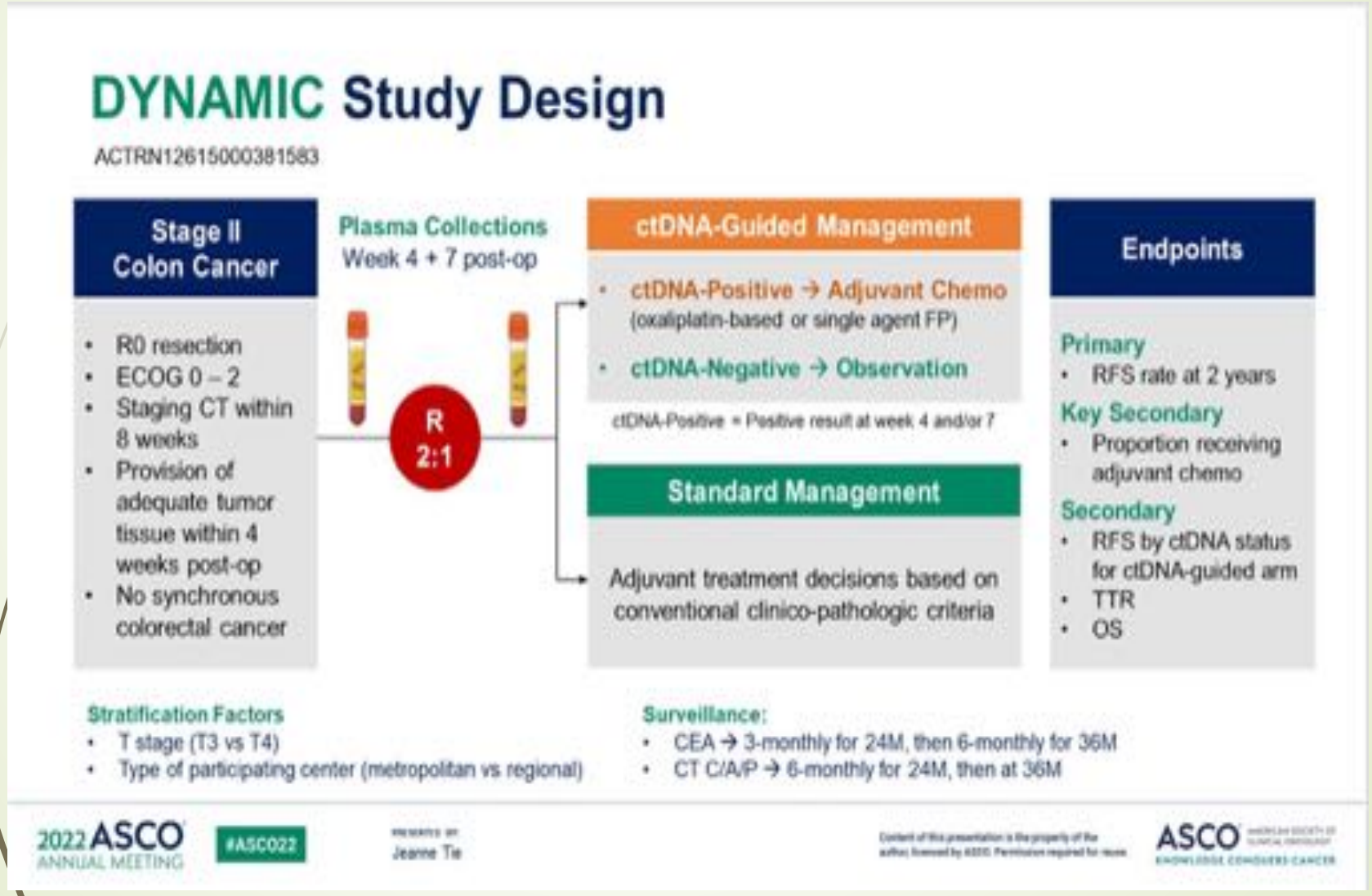
CIRCULATING TUMOR DNA stage II Colon cancer

Background: ctDNA Improves Risk Assessment

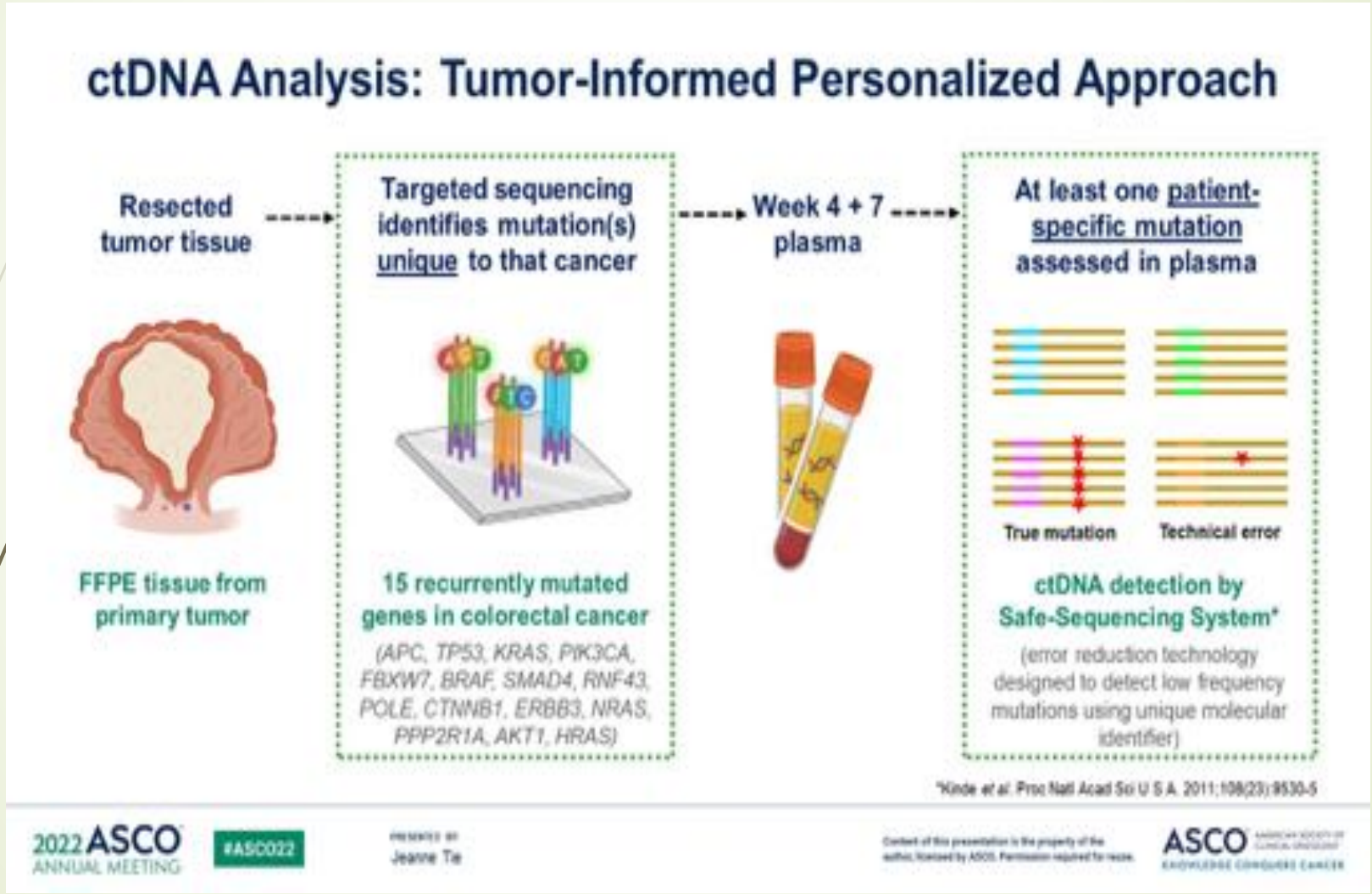
- **ctDNA detects minimal residual disease in solid tumors**
  - ctDNA detection after curative-intent surgery (including stage II colon cancer) → very high recurrence risk (> 80%) without further treatment [1-3]
  - Benefit of adjuvant treatment in ctDNA-positive patients remains unknown
- **DYNAMIC study: randomized phase II trial**
  - Designed to investigate whether a ctDNA-guided approach vs standard approach could reduce the use of adjuvant treatment without compromising recurrence risk

1. Tie et al. Sci Transl Med 2016;8:346ra92 2. Christensen et al. J Clin Oncol 2019;37:1547-57 3. Moding et al. Nat Cancer 2020;1:176-83

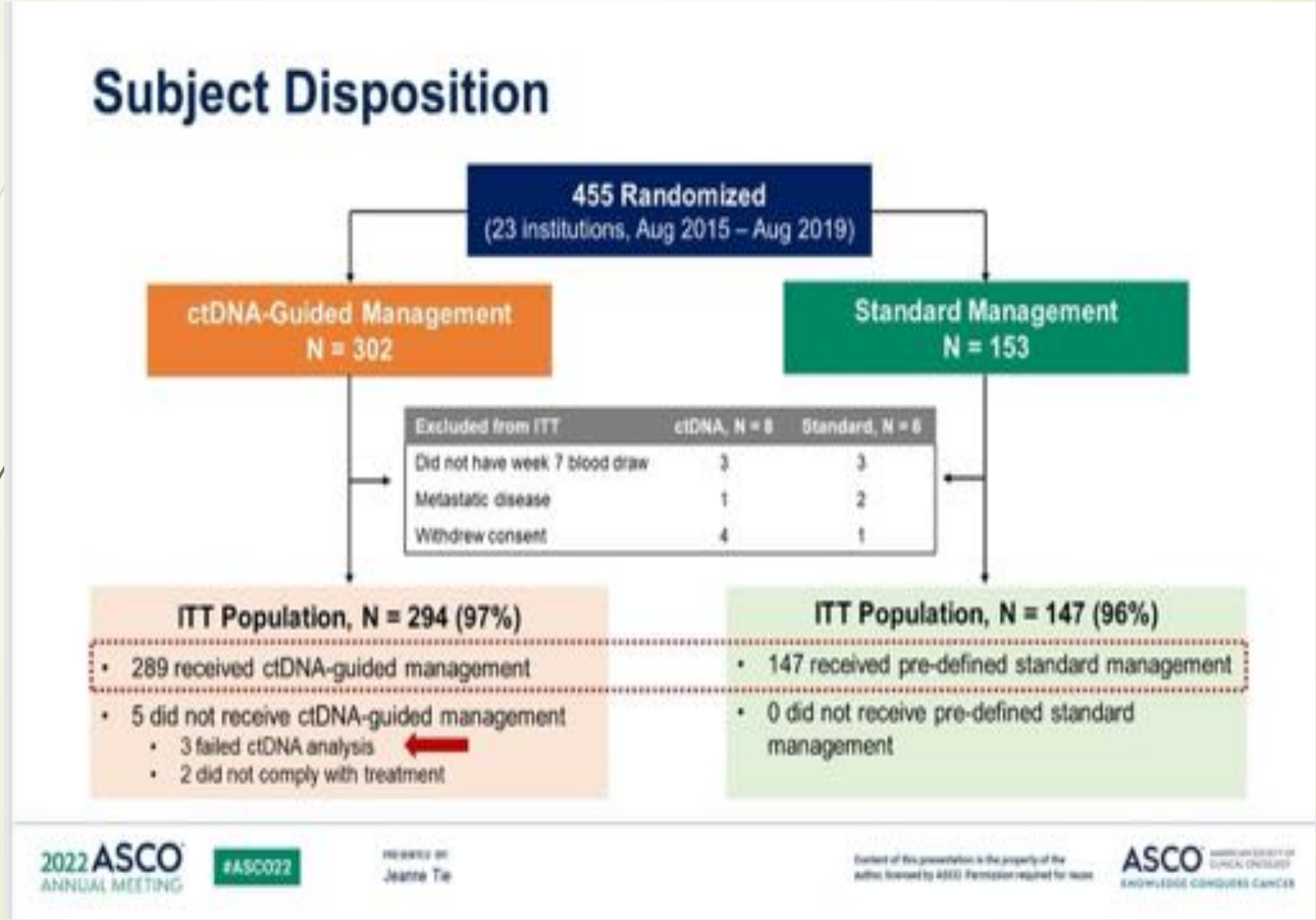
CIRCULATING TUMOR DNA stage II Colon cancer



CIRCULATING TUMOR DNA stage II Colon cancer



CIRCULATING TUMOR DNA stage II Colon cancer

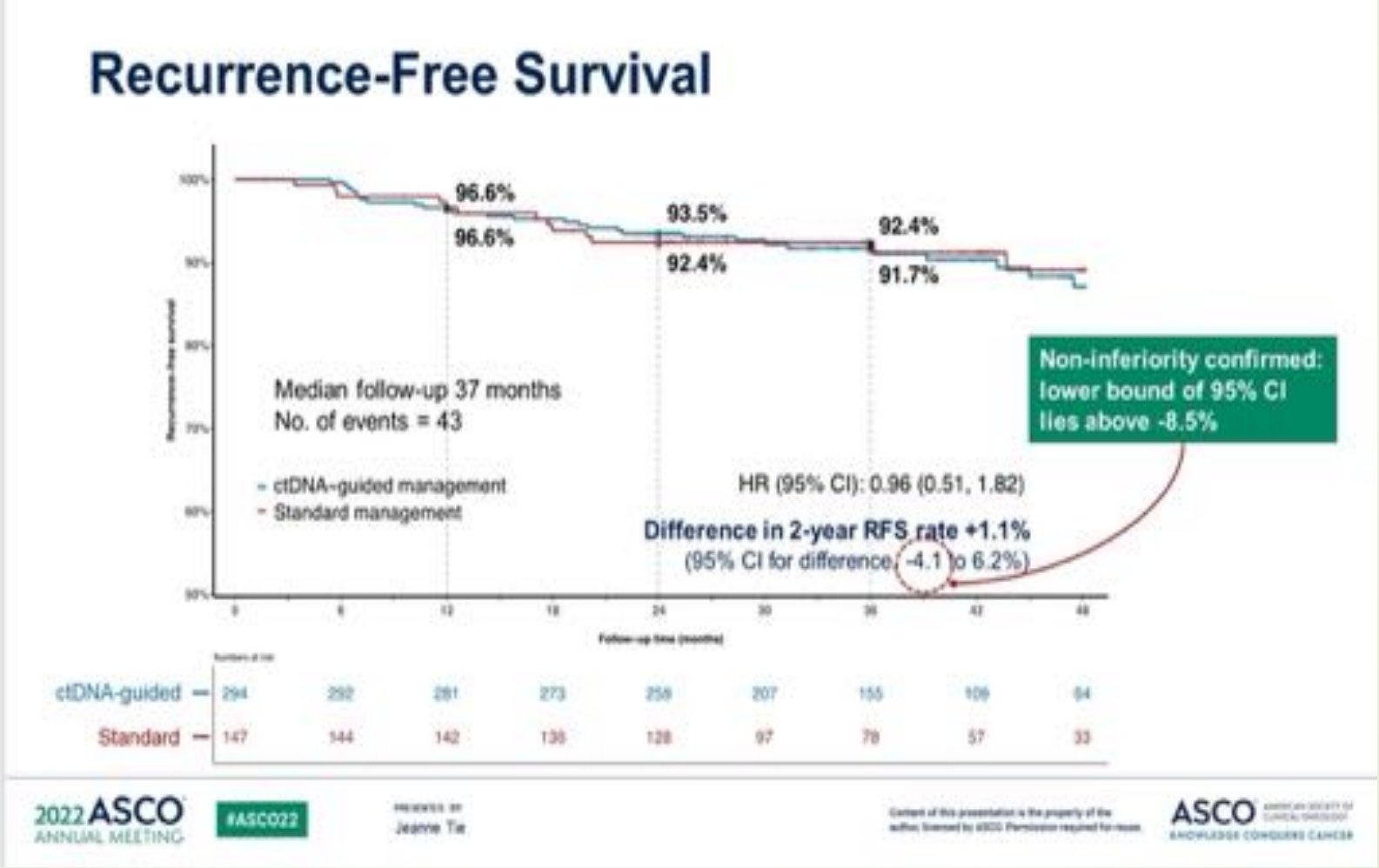


CIRCULATING TUMOR DNA stage II Colon Cancer

Adjuvant Treatment Delivery

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 (15%)	41 (28%)	0.0017
Chemotherapy regimen received, n			
Oxaliplatin-based doublet	28/45 (62%)	4/41 (10%)	
Single agent fluoropyrimidine	17/45 (38%)	37/41 (90%)	<.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

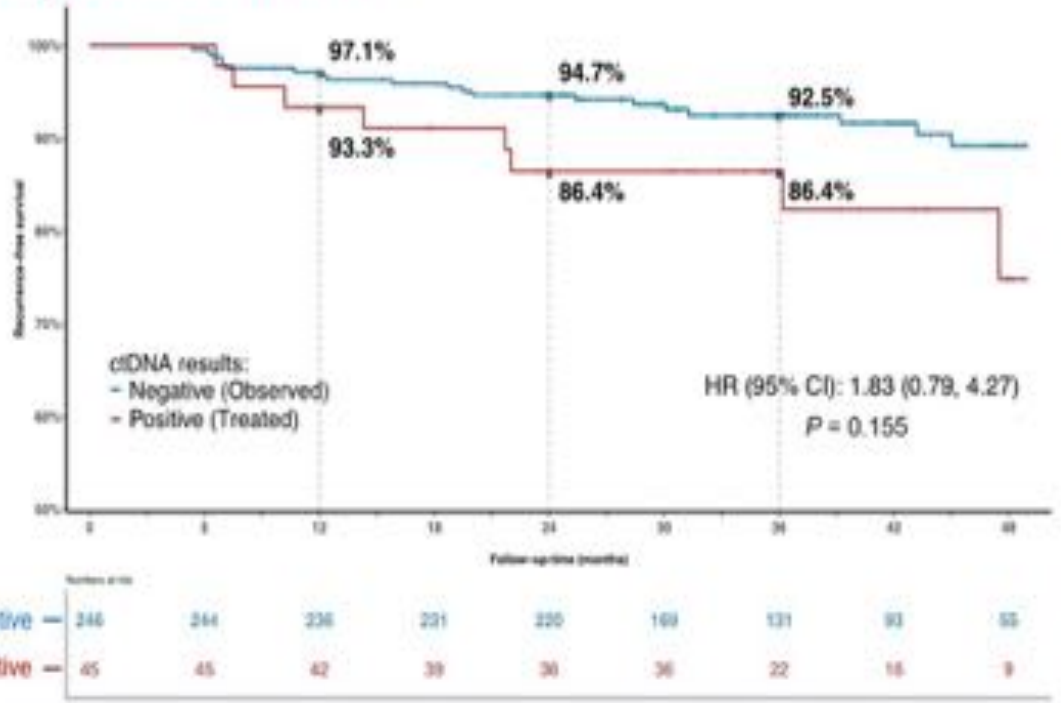
CIRCULATING TUMOR DNA stage II Colon Cancer



CIRCULATING TUMOR DNA stage II Colon cancer

Recurrence-Free Survival: ctDNA-Guided Management

ctDNA Negative vs Positive

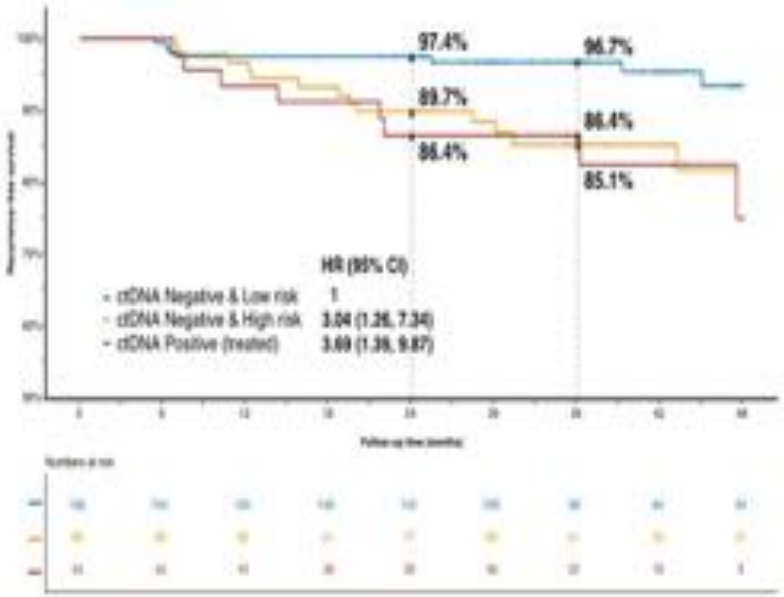


CIRCULATING TUMOR DNA stage II Colon cancer

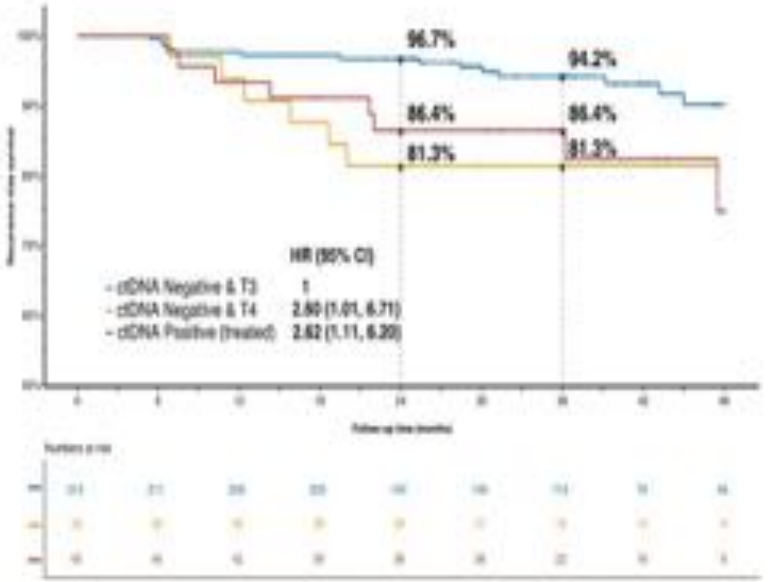
Recurrence-Free Survival: ctDNA-Guided Management

ctDNA, Clinical Risk and T Stage

ctDNA and Clinical Risk



ctDNA and T Stage



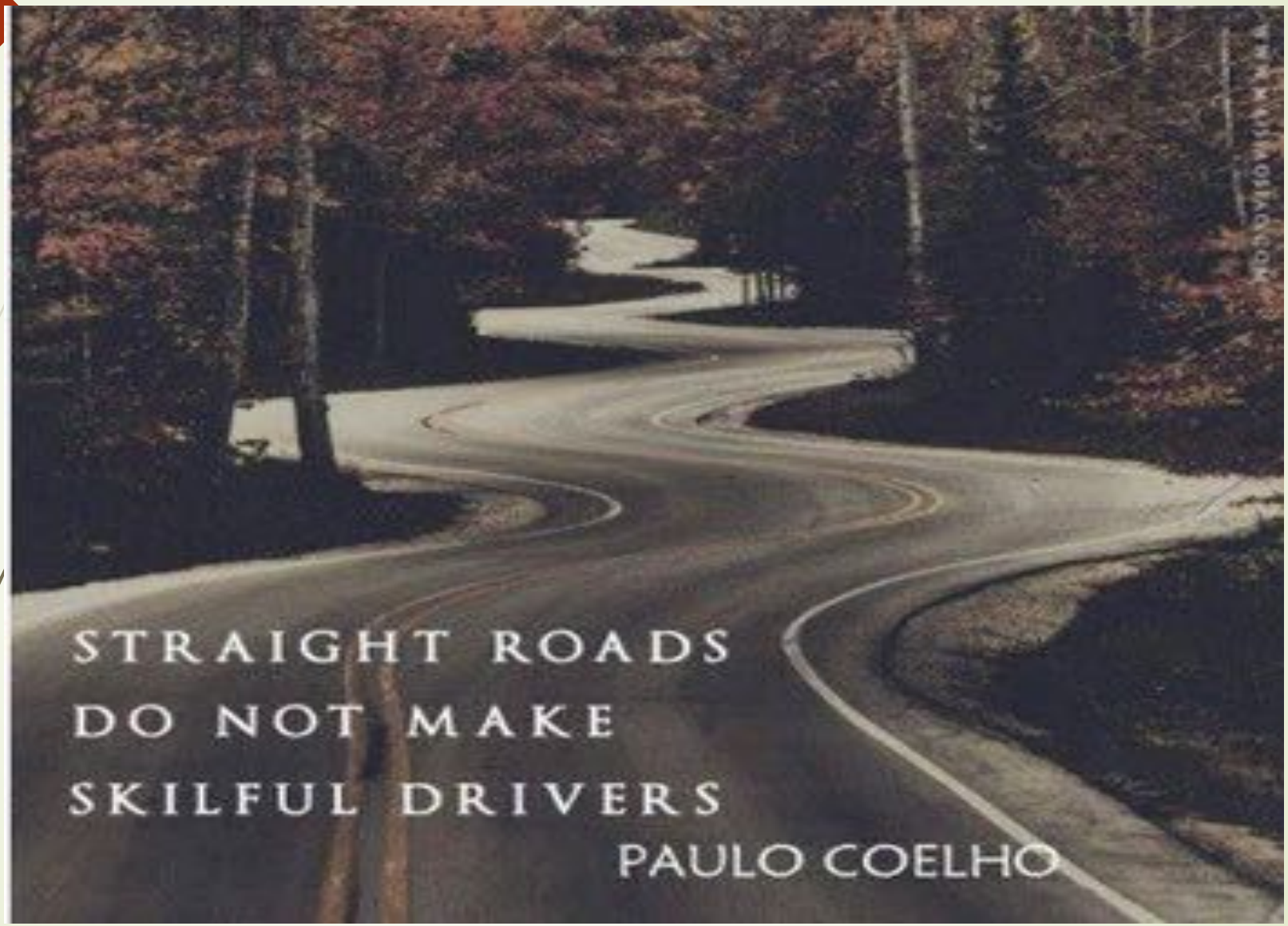
CIRCULATING TUMOR DNA stage II Colon cancer

Summary

- **For patients with stage II colon cancer, a ctDNA-guided approach (treating only patients with a positive ctDNA after surgery) compared to standard-of-care**
  - Substantially reduced the proportion receiving adjuvant chemotherapy (28% → 15%)
  - Did not compromise recurrence-free survival (2-year RFS: 93.5% vs 92.4%)
- **Patients with a positive ctDNA after surgery may derive RFS benefit from adjuvant chemotherapy**
  - Favorable 3-year RFS in patients treated with adjuvant chemotherapy (86.4%) versus low RFS in historical series (< 20%) if untreated
  - Ongoing trials (e.g., COBRA, CIRCULATE, CIRCULATE-PRODIGE) will provide further guidance regarding the optimal use of ctDNA-informed management
- **ctDNA-negative patients have a low recurrence risk without adjuvant chemotherapy**
  - 3-year RFS 92.5% (clinical low risk: 96.7%; T3: 94.2%)

CONCLUSION

- The Management paradigm of Colo-Rectal Cancer is an evolving Process.
- Localized Rectal Cancer MSI-H may benefit from Immunotherapy (Dostarlimab) without need for TNT(Chemotherapy with Radiation / ChemoXRT) Nor Surgery
- Perioperative IO in Locally Advanced Colon cancer MSI-H lead to significant Path response (MPR, CPR)
- Triplet ChemoRx with Panitumumab is No different than Doublet/Pan in Left sided Colon Ca Ras /Raf WT
- Targeting Heur2 Neu in Ras WT Met. CRC is an other pathway to explore in Phase III trials
- Ongoing Trials with focus Met CRC MSS and IO, KRAS G12 C Mut along Anti-EGFR among Others are on the way ….(Never Straight)


STRAIGHT ROADS
DO NOT MAKE
SKILFUL DRIVERS
PAULO COELHO