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UNIVERSITY OF IOWA HOLDEN COMPREHENSIVE CANCER CENTER

University of Iowa Health Care

Colorectal & Anal Cancer

Saima Sharif, MD MS

September 9, 2022

CHANGING MEDICINE.
CHANGING LIVES.®

Disclosure of Conflict of Interest

Saima Sharif, MD, MS has the following relationship to disclose:

- Research funding from GSK
- I have permission from ASCO to use slides from Annual meeting 2022

Learning Objectives

- Updates in Adjuvant treatment of Colon Cancer
  - DYMANIC Trial (LBA #100)
- Updates in Neoadjuvant treatment in Colon Cancer
  - NICHE Trial (#3511)
- Updates in Anal Cancer, metastatic
  - SCARCE PRODIGE 60 Trial (LBA #3508)

2022 ASCO ANNUAL MEETING

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

The Randomized DYNAMIC Trial (LBA 100)

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

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

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

DYNAMIC Study Design

ACTRN12615000381583

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op

R
2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo**
  (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

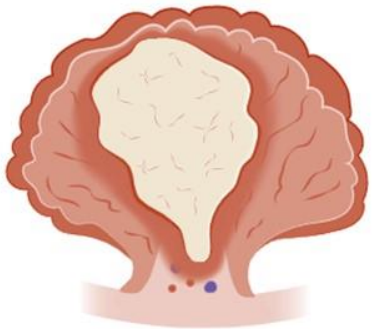
Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

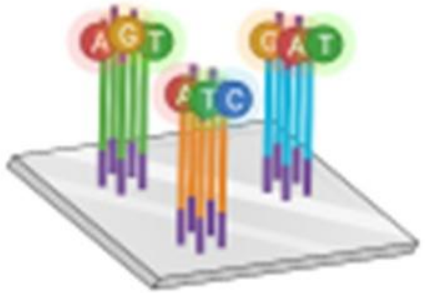
ctDNA Analysis: Tumor-Informed Personalized Approach

Resected tumor tissue



FFPE tissue from primary tumor

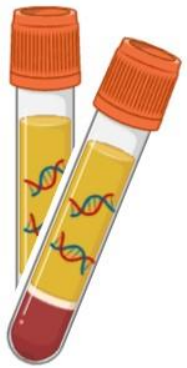
Targeted sequencing identifies mutation(s) unique to that cancer



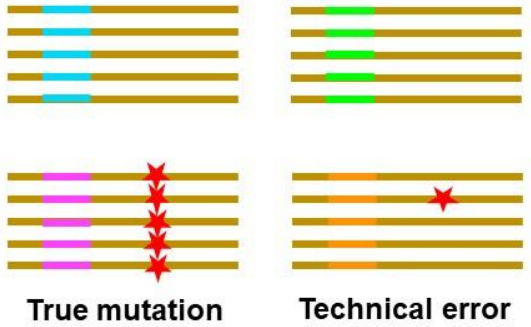
15 recurrently mutated genes in colorecal cancer

(APC, TP53, KRAS, PIK3CA, FBXW7, BRAF, SMAD4, RNF43, POLE, CTNNB1, ERBB3, NRAS, PPP2R1A, AKT1, HRAS)

Week 4 + 7 plasma



At least one patient-specific mutation assessed in plasma



ctDNA detection by Safe-Sequencing System*

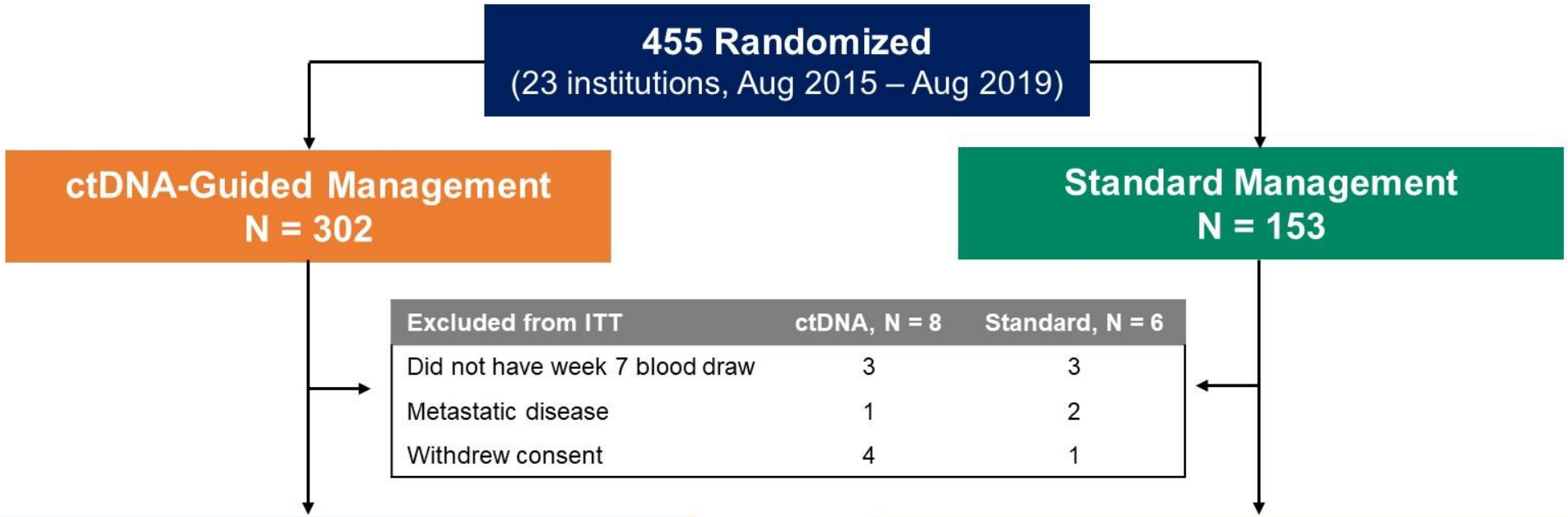
(error reduction technology designed to detect low frequency mutations using unique molecular identifier)

*Kinde *et al*. Proc Natl Acad Sci U S A. 2011;108(23):9530-5

Statistical Considerations

- **Primary Analysis Population: Intention-To-Treat (ITT)**
  - Eligible patients who were randomized and had both blood draws (week 4 and 7)
  - Primary analysis when the last patient reached a minimum follow-up of 2 years
- **Statistics / Sample Size**
  - 80% power, $\alpha = 0.05$, 10% drop-out rate → 450 patients needed to show non-inferiority of 2-year RFS rate with a margin of 8.5%
  - Non-inferiority accepted if lower bound of 95% CI of difference lies above -8.5%
  - Key secondary endpoint: reduction in proportion treated with adjuvant chemotherapy from 30% to 10% (> 99% power, $\alpha = 0.05$)

Subject Disposition



Excluded from ITT	ctDNA, N = 8	Standard, N = 6
Did not have week 7 blood draw	3	3
Metastatic disease	1	2
Withdrew consent	4	1

ITT Population, N = 294 (97%)

- 289 received ctDNA-guided management
- 5 did not receive ctDNA-guided management
  - 3 failed ctDNA analysis
  - 2 did not comply with treatment

ITT Population, N = 147 (96%)

- 147 received pre-defined standard management
- 0 did not receive pre-defined standard management

Baseline Characteristics

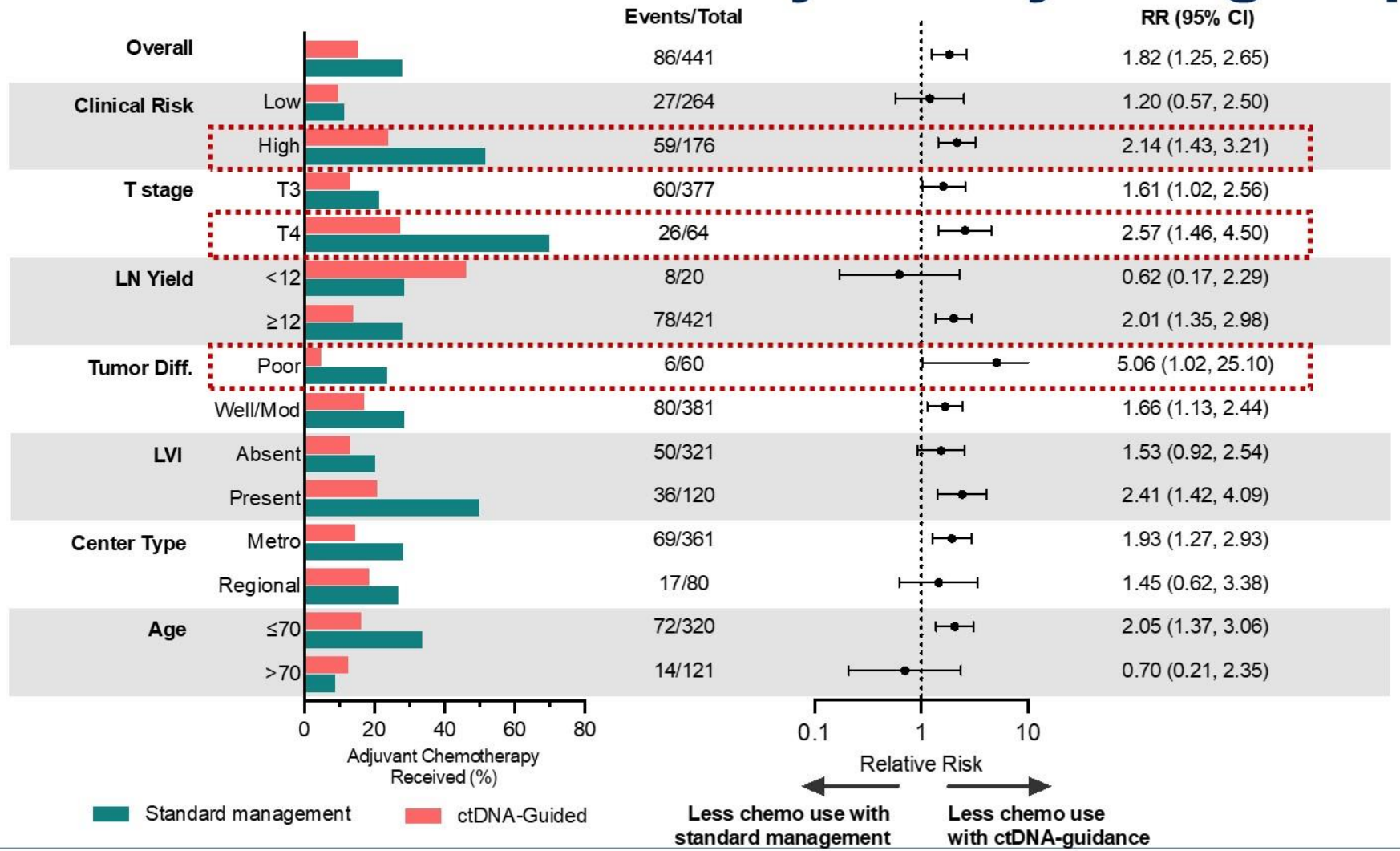
Characteristics	ctDNA-Guided Management N = 294, N (%)	Standard Management N = 147, N (%)
Age, median (range), years	65 (30 , 94)	62 (28 , 84)
Sex, Male	154 (52)	81 (55)
ECOG, 0	226 (77)	124 (84)
Center type, metropolitan	240 (82)	121 (82)
Primary tumor site, left-sided	126 (43)	78 (53)
Tumor stage, T3	250 (85)	127 (86)
Tumor differentiation, poor	43 (15)	17 (12)
Lymph node yield, < 12	13 (4)	7 (5)
Lymphovascular invasion, present	82 (28)	38 (26)
MMR, deficient	59 (20)	27 (18)
Clinical risk group, high*	116 (40)	60 (41)

*High clinical risk = proficient MMR + ≥1 high-risk feature (T4, poor tumor differentiation, <12 lymph node yield, LVI, tumor perforation and/or bowel obstruction)

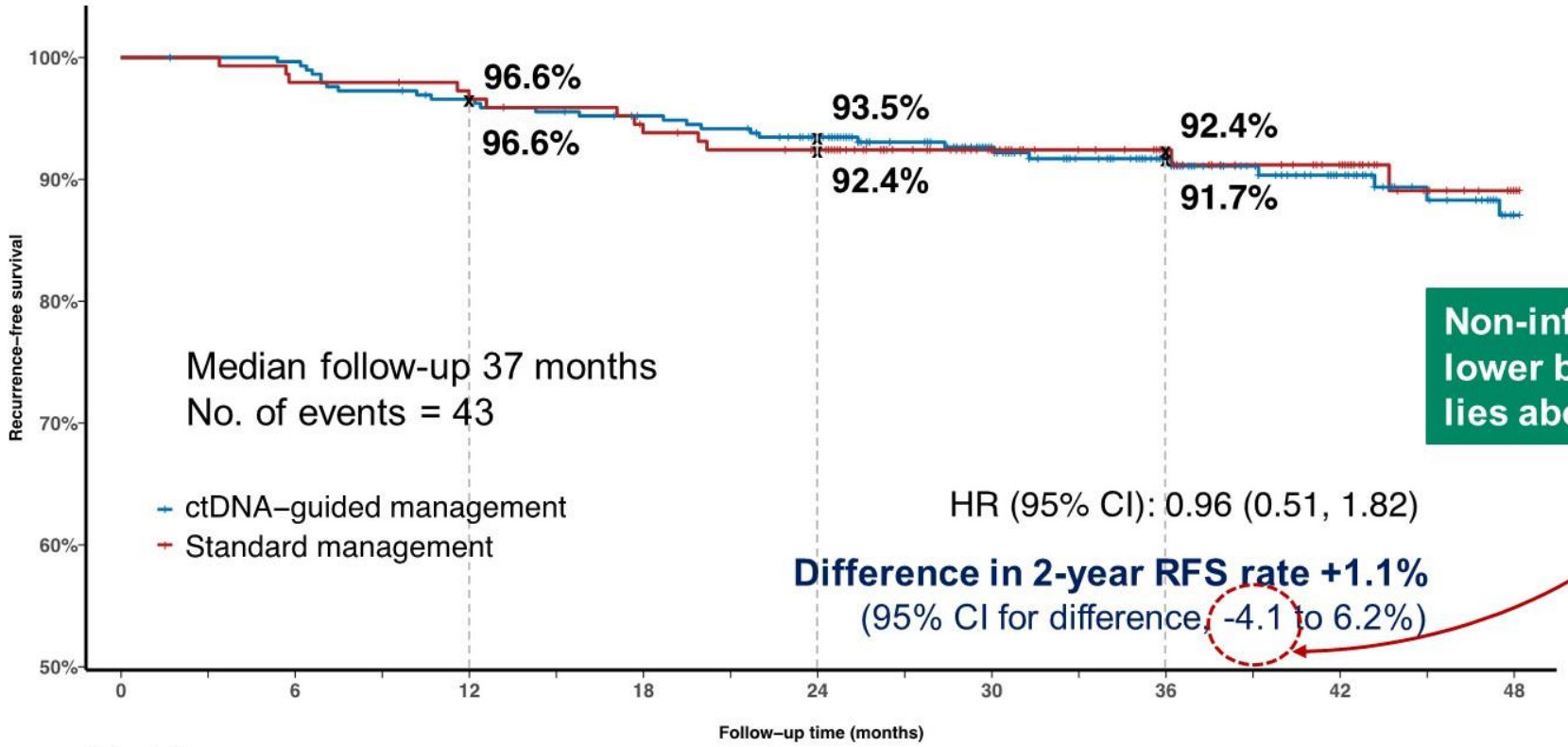
Adjuvant Treatment Delivery

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 Single agent fluoropyrimidine	 28/45 **(62%)** 17/45 **(38%)**	 4/41 **(10%)** 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

Adjuvant Treatment Delivery in Key Subgroups



Recurrence-Free Survival

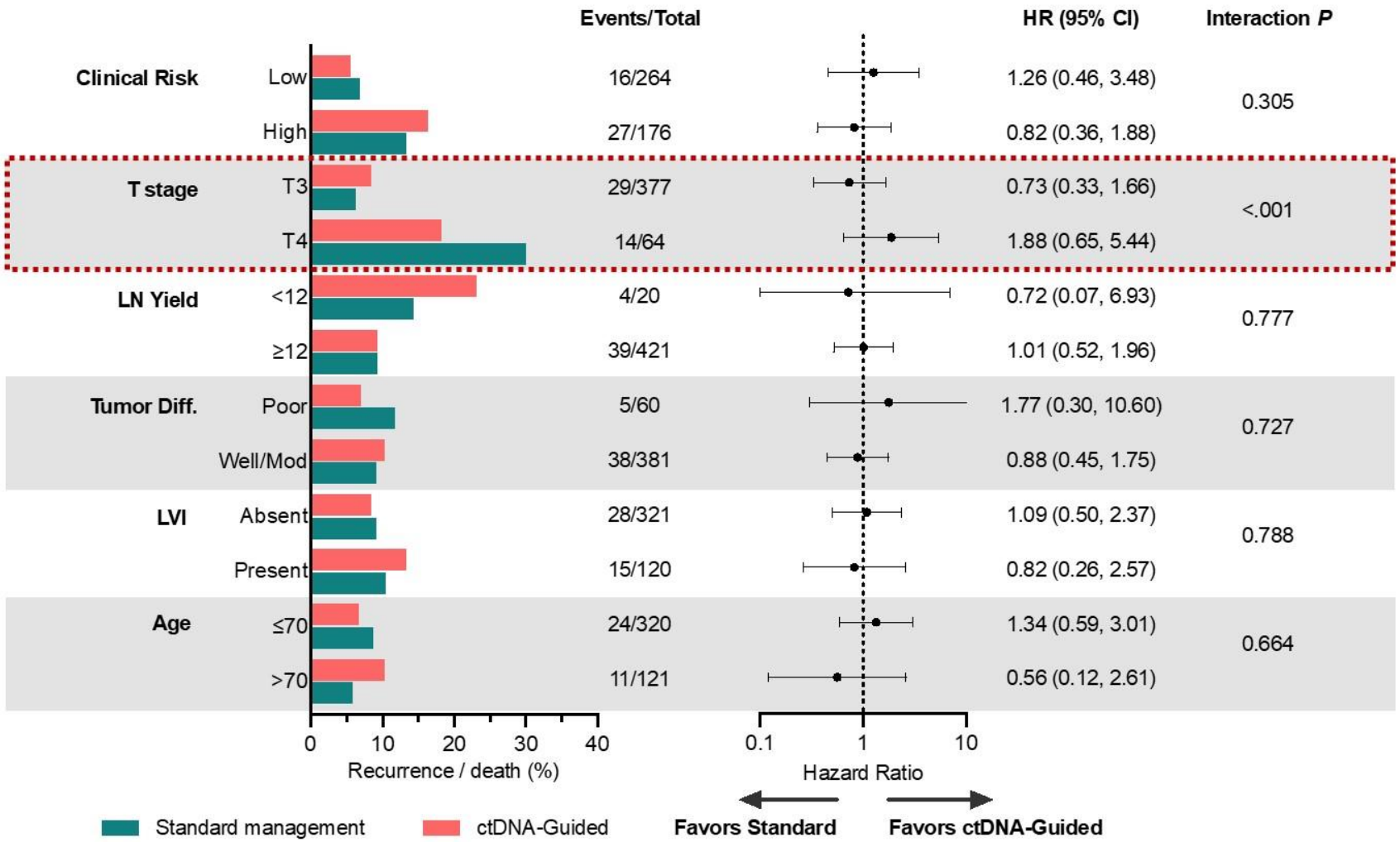


Non-inferiority confirmed: lower bound of 95% CI lies above -8.5%

Numbers at risk

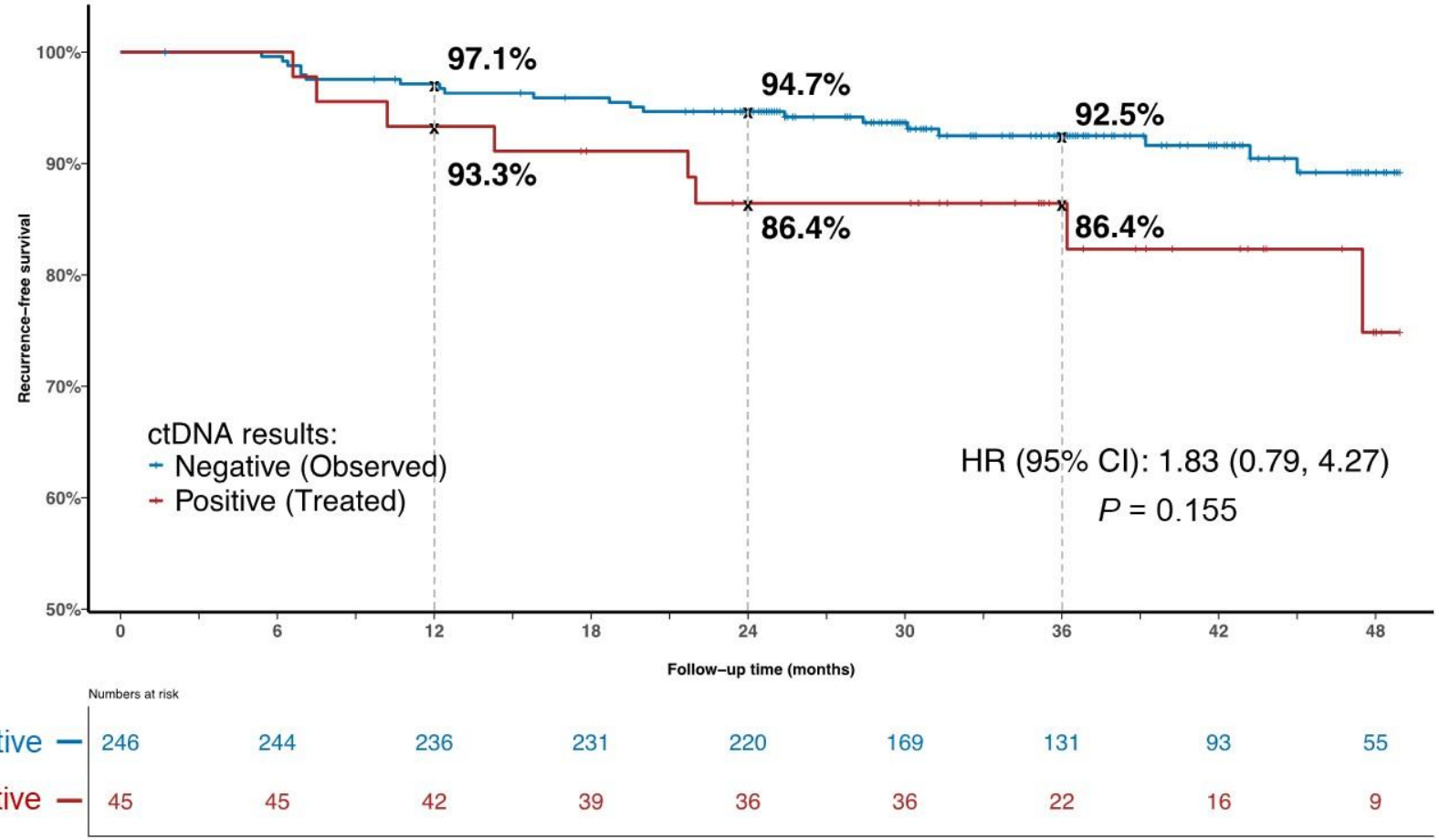
ctDNA-guided	294	292	281	273	259	207	155	109	64
Standard	147	144	142	136	128	97	78	57	33

Recurrence-Free Survival in Key Subgroups



Recurrence-Free Survival: ctDNA-Guided Management

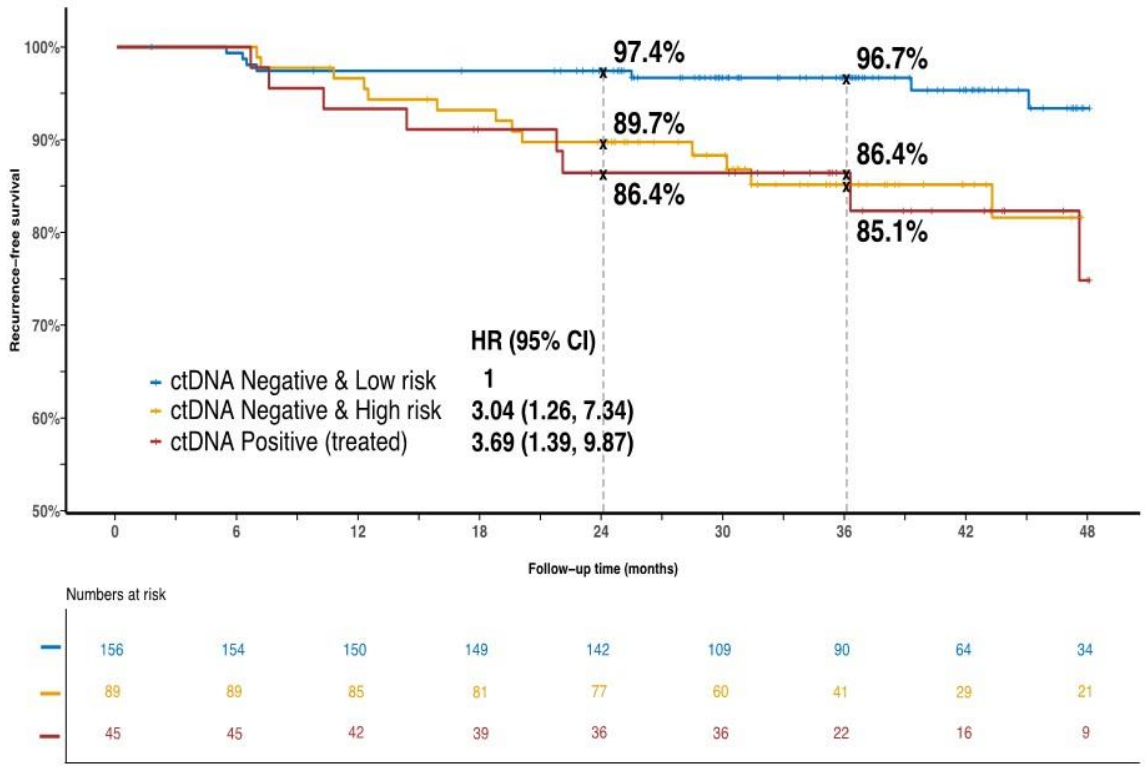
ctDNA Negative vs Positive



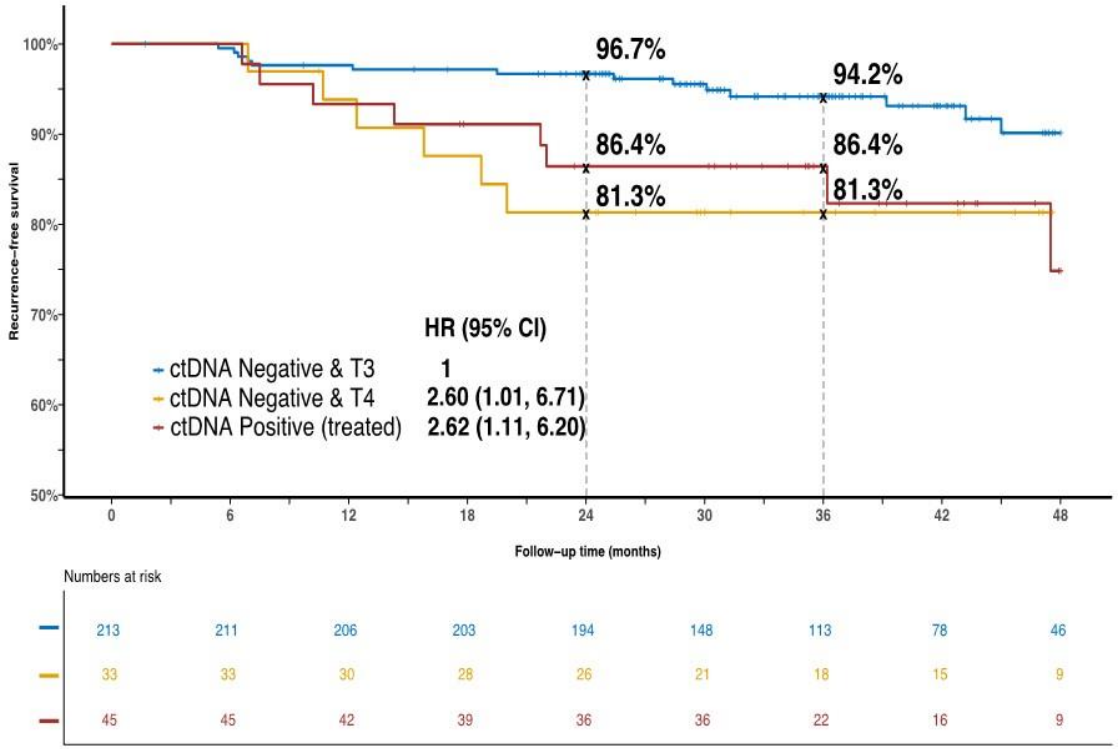
Recurrence-Free Survival: ctDNA-Guided Management

ctDNA, Clinical Risk and T Stage

ctDNA and Clinical Risk



ctDNA and T Stage



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%)

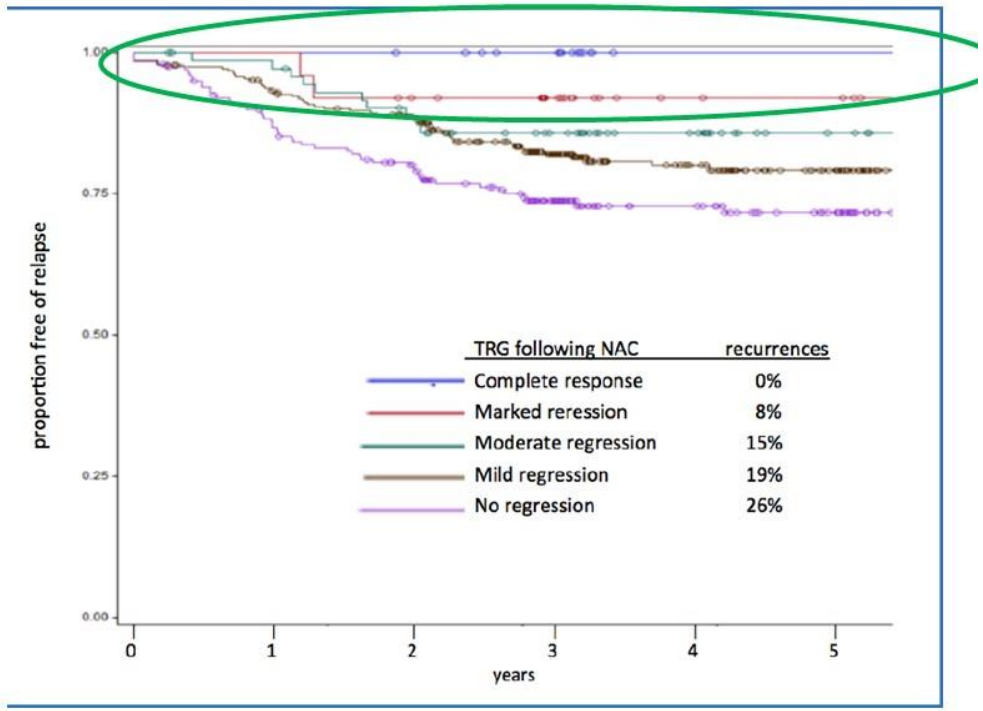
2022 ASCO® ANNUAL MEETING

Neoadjuvant nivolumab, ipilimumab, and celecoxib in MMR-proficient and MMR-deficient colon cancers: Final clinical analysis of the NICHE study.

Y.L. Verschoor, J. van den Berg, G. Beets, K. Sikorska, A. Aalbers, A. van Lent, C. Grootscholten, I. Huibregtse, H. Marsman, S. Oosterling, M. van de Belt, M. Kok, T. Schumacher, M.E. van Leerdam, J.B.A.G. Haanen, E.E. Voest, M. Chalabi

Background

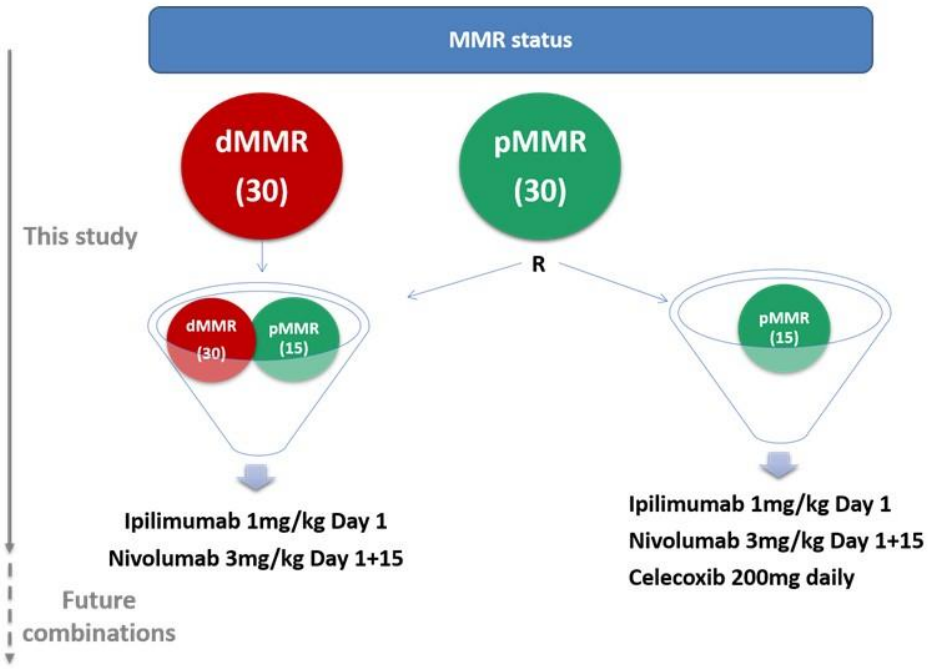
- NICHE was the first neoadjuvant study to show impressive pathologic responses in 100% of dMMR (*n* = 20) and 27% of pMMR colon cancers (*n*= 15)*
- Stark contrast with FOxTROT**: significant pathologic response in a mere 5% of patients with dMMR colon cancer (*n*= 115) after SoC chemotherapy with folfox
  - Good correlation between tumor regression and recurrence risk →
- Here we present final efficacy data for the completed original NICHE study cohorts



*Chalabi et al, Nat Med 2020, ** Morton et al, ESMO 2019

NICHE study design

- Open-label, exploratory study with an adaptive design
- **Study population:** non-metastatic, resectable and previously untreated adenocarcinoma of the colon
- **Original cohorts:** 30 patients with dMMR and 30 with pMMR tumors
- **Treatment** in all patients: nivolumab 3 mg/kg on D1+15 *plus* ipilimumab 1 mg/kg on D1
  - **pMMR cohort:** randomized to additionally receive celecoxib
  - **Surgery within 6 weeks** of registration
- Tumor and normal tissue at baseline and resection, plasma + PBMCs baseline during treatment and follow-up



Baseline characteristics

	dMMR (*n*= 32)	pMMR (*n*= 33) *
Age, median (range)	54 (22-82)	62 (44-77)
Sex		
Male	14 (44%)	18 (55%)
Female	18 (56%)	15 (45%)
Clinical T stage		
T2	6 (19%)	11 (33%)
T3	10 (31%)	19 (58%)
T4	15 (47%)	1 (3%)
Tx	1 (3%)	2 (6%)
Clinical N stage		
N-	7 (22%)	20 (61%)
N+	25 (78%)	13 (39%)
Primary tumor location		
Right colon	20 (62%)	8 (24%)
Left colon	8 (25%)	23 (70%)
Transverse colon	4 (13%)	2 (6%)
Lynch syndrome	13 (41%)	0 (0%)

* Two pMMR patients excluded from efficacy analysis due to not matching inclusion criteria

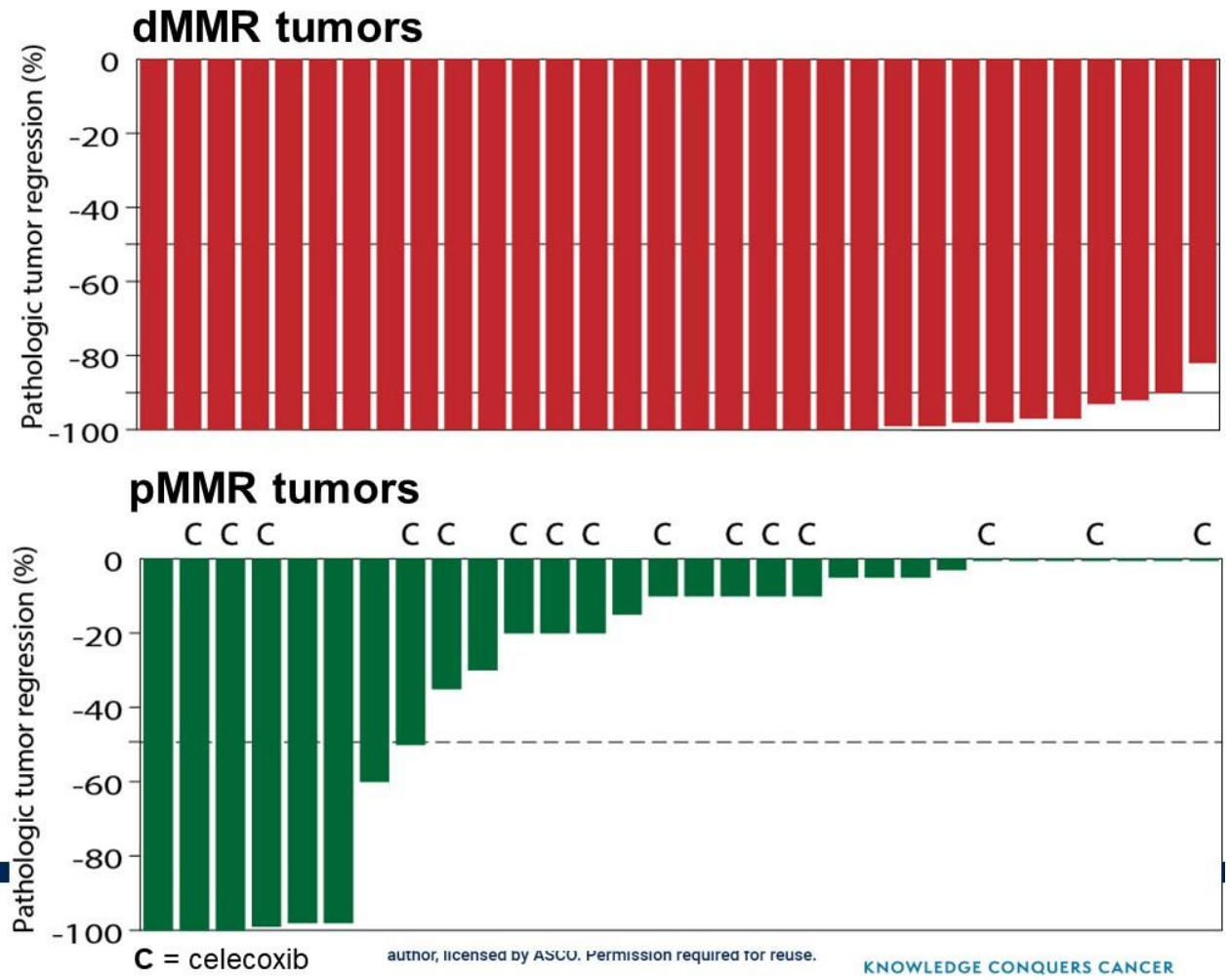
Responses in 29% of pMMR and 100% of dMMR tumors

Pathologic response		dMMR *n*= 32	pMMR *n*= 31
Major (≤10% VTR)		31 (97%)	7 (23%) *
	Complete	22 (69%)	4 (13%) *
Partial (≤50% VTR)		1 (3%)	2 (6%)
Nonresponse (>50% VTR)		0 (0%)	22 (71%)

- **dMMR: 32/32 (100%) responders**
  - Lynch: 13/13 MPR, 12 pCR
  - Non-Lynch: 18/19 MPR, 10 pCR; 1 PR
- **pMMR: 9/31 (29%) responders**

*1 patient has not undergone surgery, now 1 year after treatment completion and no longer evidence of intraluminal or radiological disease, incl neg biopsies

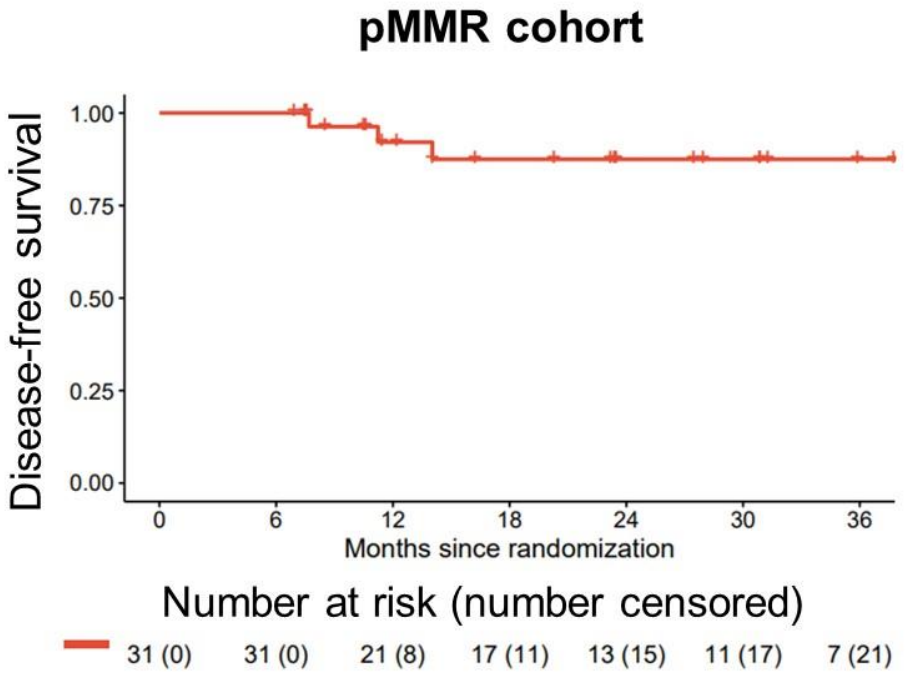
VTR= viable tumor rest; MPR = major pathologic response; pCR = pathologic complete response; PR= partial response



Adjuvant chemotherapy and disease recurrences

- **Adjuvant chemotherapy**
  - 2 dMMR patients with post-treatment positive lymph nodes (1 MPR, 1 PR)
  - 8 pMMR patients (all NR)

- Median follow-up time **pMMR** cohort **28 months**; disease recurrence in 2/31 (6%) patients, both nonresponders*
- Median follow-up time **dMMR** cohort **32 months**: no recurrences to date



* 1 patient had received adjuvant chemotherapy

Future directions

- Response data from the expanded dMMR cohort (*n*=100) expected in Q3 2022
  - Disease-free survival data 2023
- Biomarker analyses, including multiplex imaging, single-cell sequencing and ctDNA dynamics currently underway
- New IO combinations in preparation for both dMMR and pMMR tumors within the NICHE adaptive design
- pMMR cohort with nivolumab plus anti-IL-8 currently ongoing

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Colon Cancer

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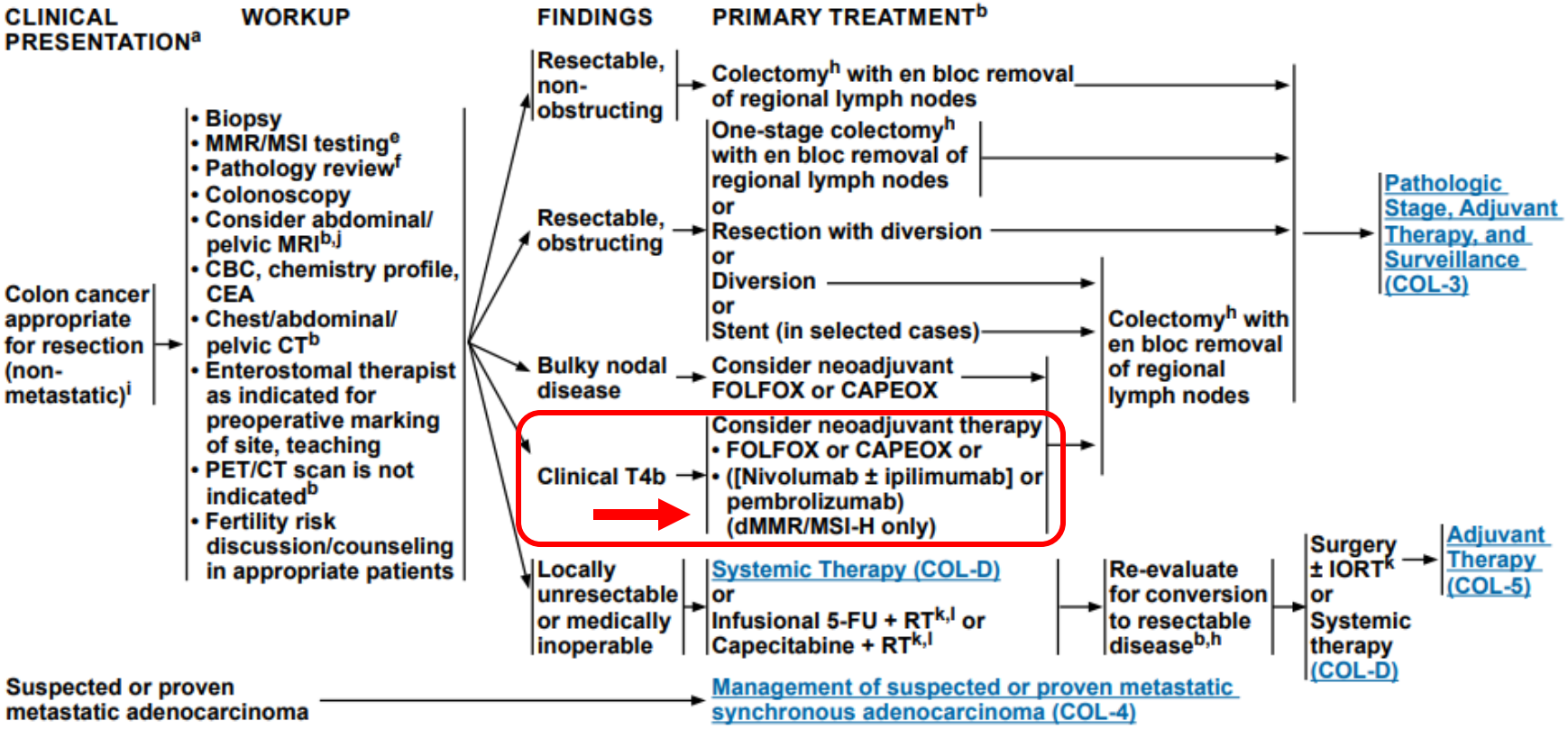
Discussion



[a] All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[b] Principles of Imaging (COL-A).
[e] Principles of Pathologic Review (COL-B 4 of 8) - MSI or MMR Testing.
[f] Principles of Pathologic Review (COL-B) - Colon cancer appropriate for resection, pathologic stage, and lymph node evaluation.
[h] Principles of Surgery (COL-C 1 of 3).
[i] For tools to aid optimal assessment and management of older adults with cancer, see the NCCN Guidelines for Older Adult Oncology.
[j] Consider an MRI to assist with the diagnosis of rectal cancer versus colon cancer (eg, low-lying sigmoid tumor). The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.
[k] Principles of Radiation and Chemoradiation Therapy (COL-E).
[l] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GERCOR

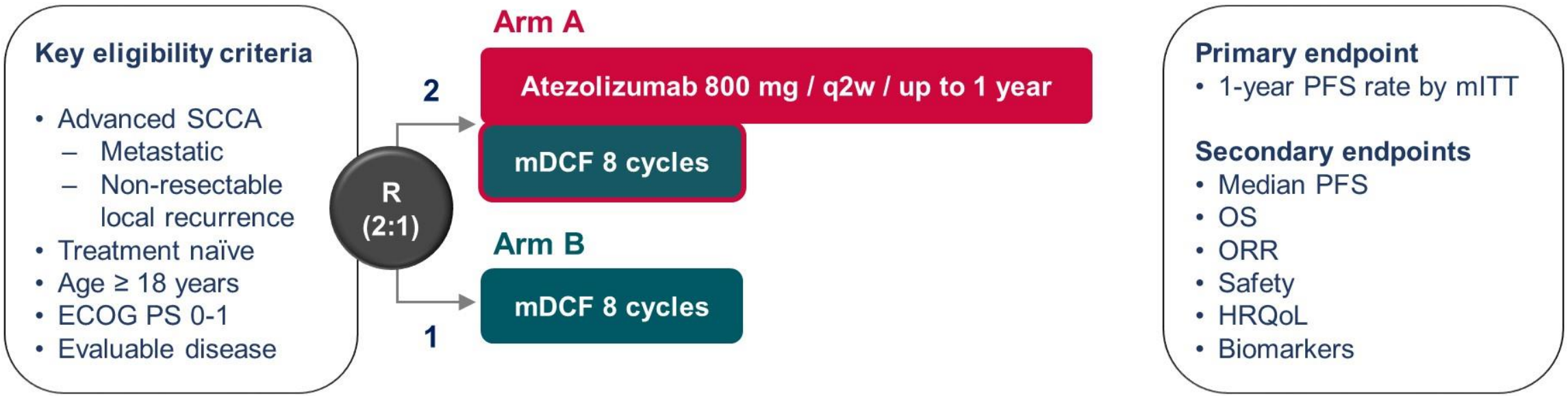
PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

LBA 3508:
Atezolizumab plus modified DCF (docetaxel, cisplatin, and 5-fluorouracil) as first-line treatment for metastatic or locally advanced squamous cell anal carcinoma (SCCA). A SCARCE-PRODIGE 60 randomized phase II study

Stefano Kim,[1] François Ghiringhelli, Christelle de la Fouchardière, Eric François, Denis Smith, Emmanuelle Samalin, Daniel Lopez-Trabada Ataz, Aurélia Parzy, Jérôme Desramé, Nabil Baba Hamed, Bruno Buecher, David Tougeron, Oliver Bouché, Benoist Chibaudel, Farid El Hajbi, Marie-Line Garcia-Larnicol, Aurélia Meurisse, Dewi Vernerey, Simon Pernot, Christophe Borg

[1]Clinical Investigational Center CIC-1403, University Hospital of Besançon; University of Bourgogne-Franche Comté, Besançon, France

SCARCE-PRODIGE 60 Study Design



Stratification: age (<65 vs ≥65 years), stage (synchronous metastatic vs metachronous metastatic vs locally advanced unresectable disease without metastasis)

PRESENTED BY:
Stefano KIM, MD

Baseline patient characteristics (metastatic)

	All (N=76)	Arm A (n=51)	Arm B (n=25)
Number of sites, n (%)			
1	27 (35.5)	14 (27.5)	13 (52.0)
2	27 (35.5)	**21 (41.2)**	6 (24.0)
≥3	22 (28.9)	**16 (31.4)**	6 (24.0)
Metastatic sites, n (%)			
Distant pelvic area	14 (18.4)	**12 (23.5)**	2 (8.0)
Distant lymph node	42 (55.3)	**31 (60.8)**	11 (44.0)
Liver	41 (53.9)	**29 (56.9)**	12 (48.0)
Lung	26 (34.7)	18 (35.3)	8 (32.0)
Bone	9 (11.8)	**7 (13.7)**	2 (8.0)
Skin	2 (2.6)	1 (2.0)	1 (4.0)
Peritoneum	9 (11.8)	4 (7.8)	**5 (20.0)**

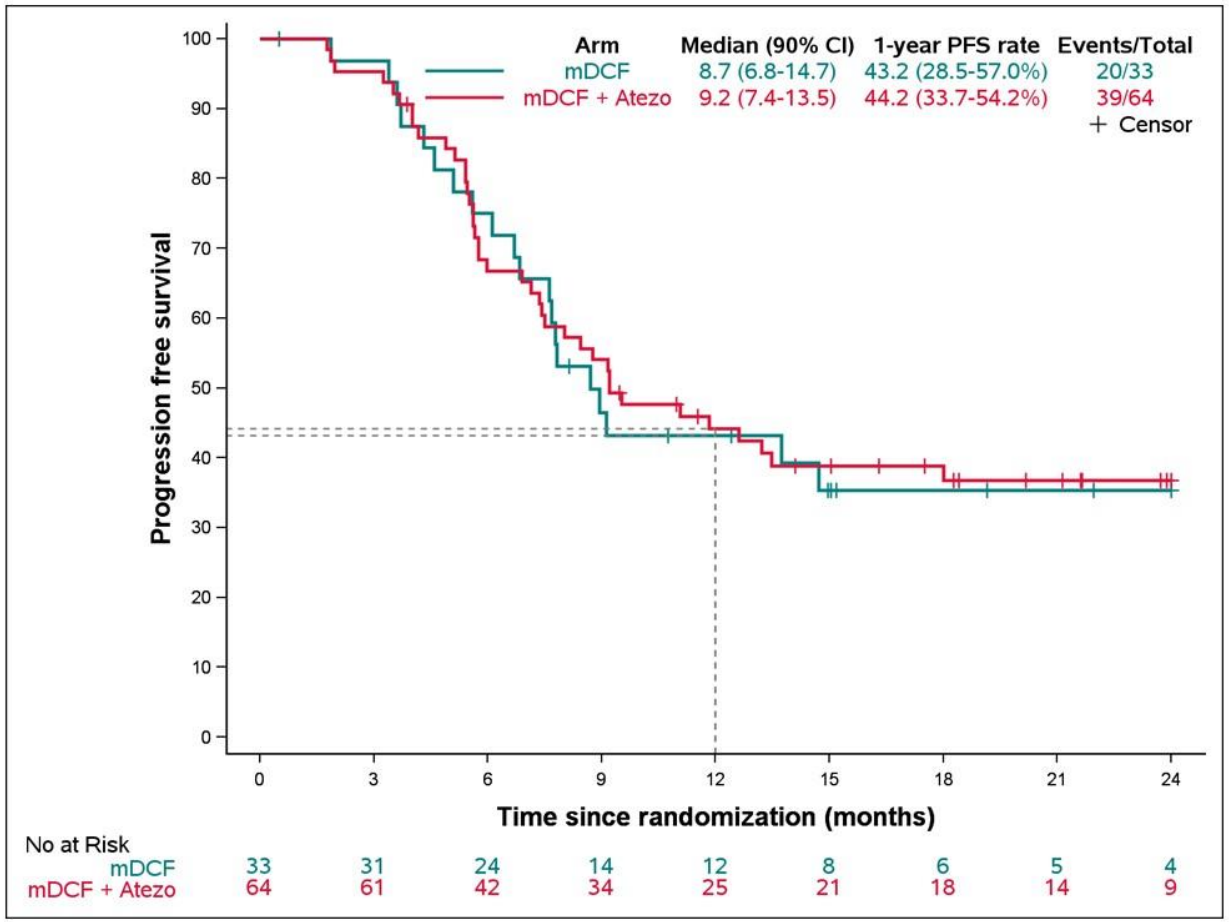
Adverse events (AE) and Serious AE (SAE)

	All (N=97)	Arm A (n=64)	Arm B (n=33)
Grade 3-4 AE, n (%)	48 (51.1)	36 (**59.0**)	12 (**36.4**)
Most frequent (≥ 5%) grade 3-4 AE, n (%)			
Diarrhea	8 (8.5)	7 (**11.5**)	1 (3.0)
Fatigue	7 (7.4)	3 (4.9)	4 (**12.1**)
Anemia	11 (11.7)	10 (**16.4**)	1 (3.0)
Neutropenia	14 (14.9)	9 (14.8)	5 (15.2)
Febrile neutropenia	2 (2.1)	1 (1.6)	1 (3.0)
Treatment-related SAE	20 (20.6)	16 (**25.0**)	4 (12.1)

Primary endpoint – 1-year PFS rate

Arm A

1-year PFS rate: 44.2%
(90% CI 31.7-56.0)



Arm B

1-year PFS rate: 43.2%
(90% CI 25.8-59.4)

Secondary endpoints (investigators' assessment)

	All (N=97)	Arm A (N=64)	Arm B (N=33)	Epitopes-HPV (N=115)[1,2]
Objective response, n (%)	72 (**75.8**)	47 (**74.6**)	25 (**78.1**)	100 (**87.7**)
Complete response	34 (35.8)	19 (30.2)	15 (46.9)	46 (40.3)
Partial response	38 (40.0)	28 (44.4)	10 (31.3)	54 (47.4)
Stable disease	20 (21.1)	14 (22.2)	6 (18.8)	10 (8.8)
Progression disease	3 (3.2)	2 (3.2)	1 (3.1)	4 (3.5)
Missing	2	1	1	0
1-year OS rate, % (95% CI)		**77.7** (68.1-88.7)	**80.8** (68.1-95.9)	**80.8** (73.8-88.3)

[1] Kim, Lancet Oncol 2018
[2] Kim, Ther Adv Med Oncol 2021

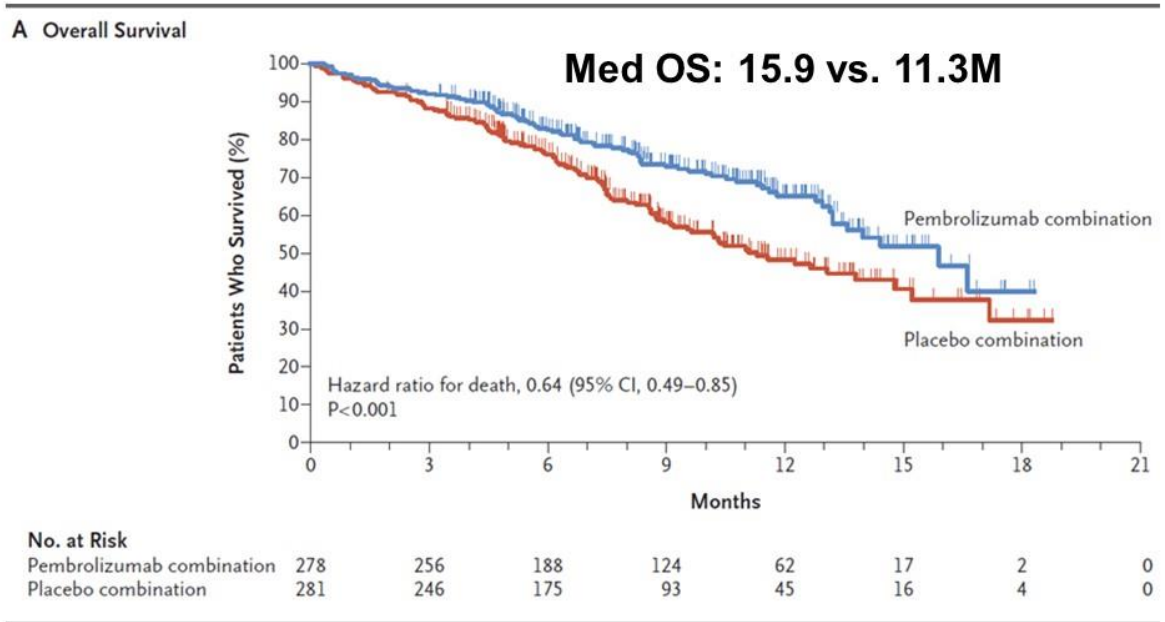
LBA-3508 (SCARCE): Salient Points

- Based on prior phase II studies of IO therapy and Epitopes-HPV02, this was a rational study design
- No statistical difference on subgroup analysis
  - Subtle differences exist between the 2 treatment arms:
    - Investigational arm: Increased sites of met disease
      - Metastatic site matters clinically (ulceration, drainage, pain, etc.,)
  - Increased treatment related SAE's on the investigational arm
- Does this indicate that mDCF is enough?
- Does this indicate there is NO role for IO therapy + chemotherapy in treatment-naïve SCCA patients?
  - Timing of the immunotherapy?
  - Regimen too myelosuppressive? Impact on the tumor microenvironment?

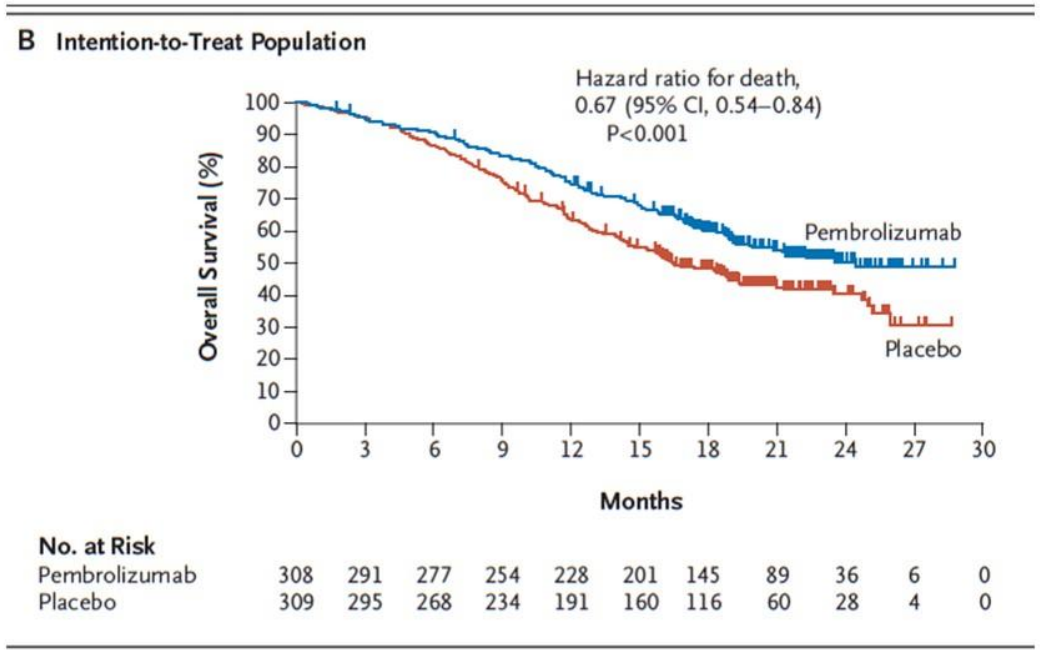
PRESENTED BY:
Cathy Eng, MD, FACP, FASCO

Platinum +/- Immune Checkpoint Inhibitors in Other Squamous Cell Cancers

Phase III: Carboplatin + Paclitaxel (Nab) +/- Pembrolizumab in Squamous NSCLC (KN407)



Platinum +/- Pembrolizumab in Cervical Cancer 24M OS = 50.4% and 40.4%



Paz-Arez et al: NEJM, 2018; Colombo et al: NEJM, 2021

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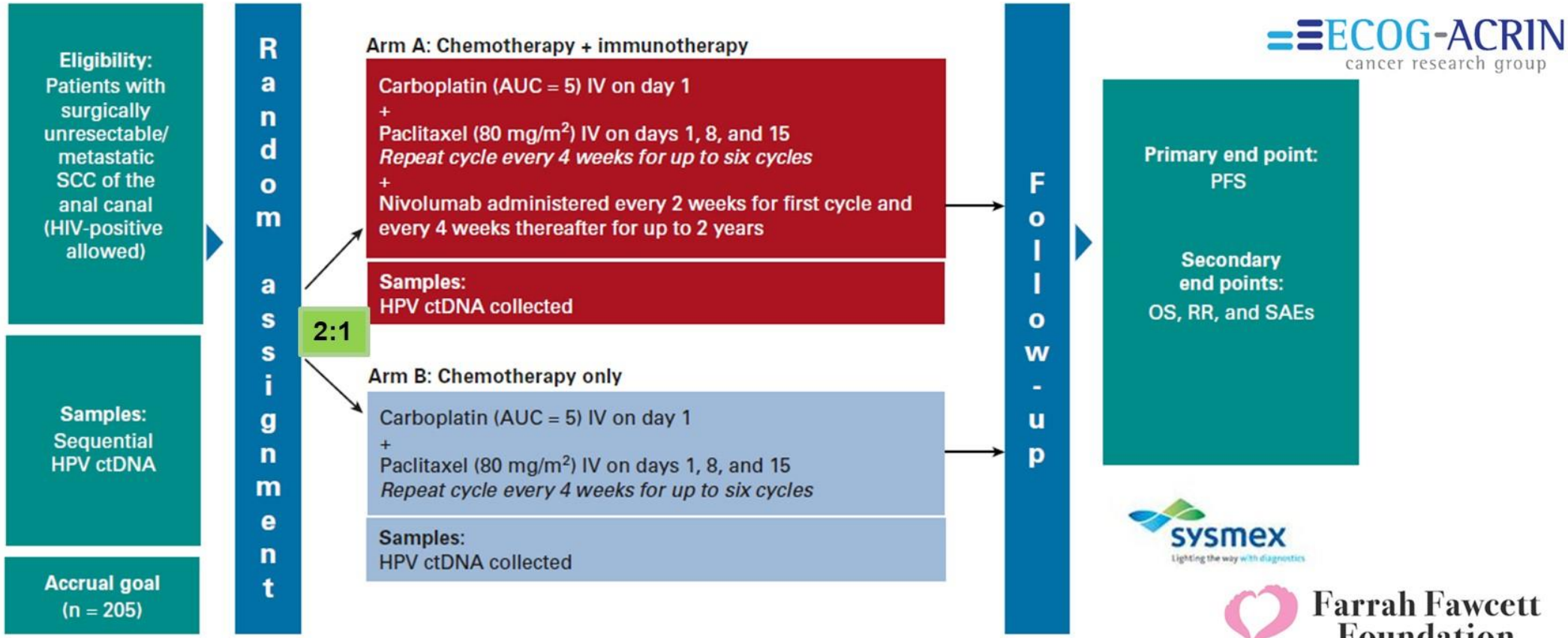
EA2176: Phase 3 Clinical Trial of Carboplatin and Paclitaxel +/- Nivolumab in Treatment-Naive Metastatic Anal Cancer Patients



ECOG-ACRIN cancer research group

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Farrah Fawcett Foundation

PI: C. Eng
Co-PI's: A. Benson, K. Ciombor

Eng et al: JCO, 2022

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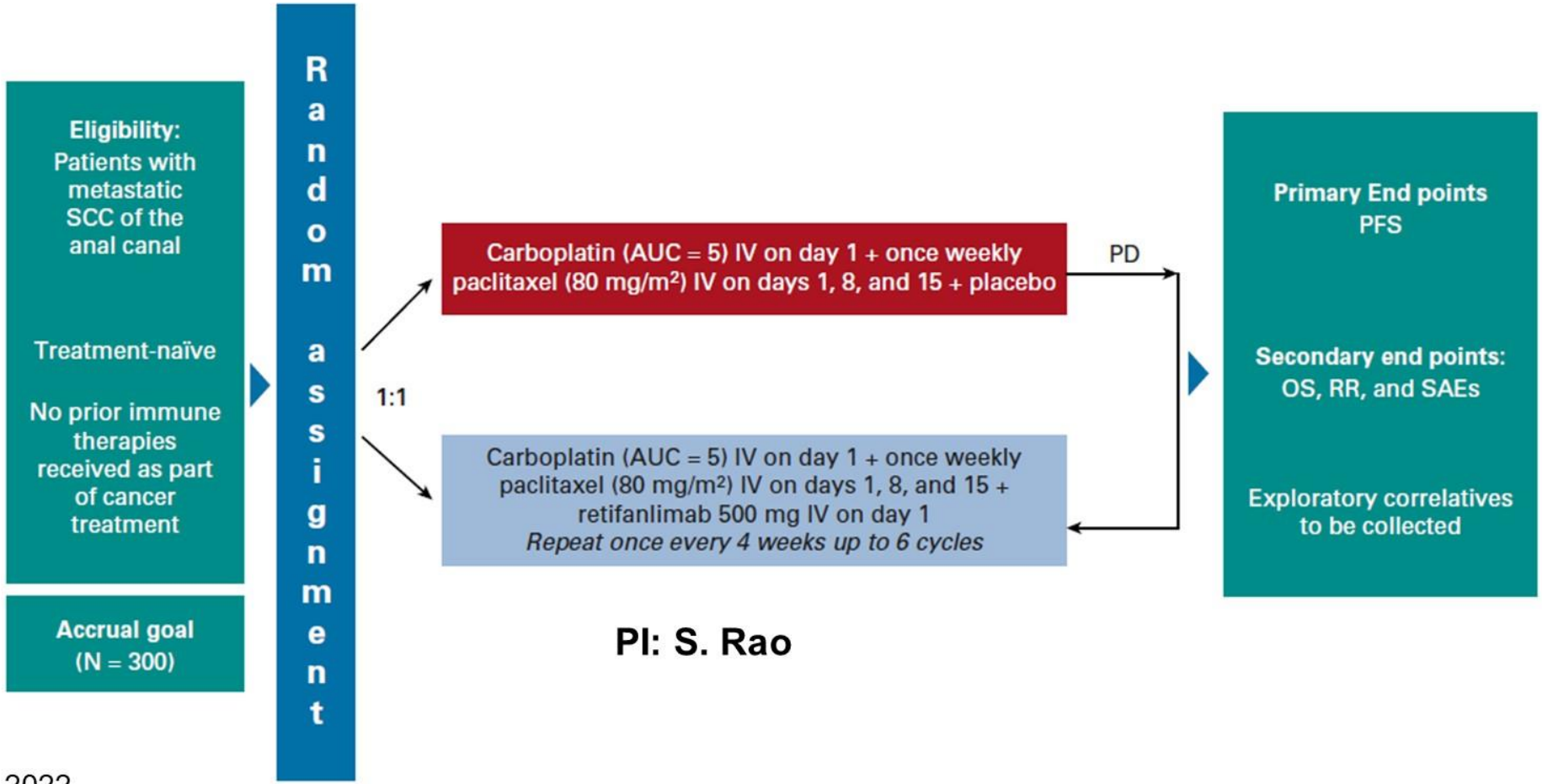
Carboplatin-Paclitaxel With Retifanlimab or Placebo in Participants With Locally Advanced or Metastatic Squamous Cell Anal Carcinoma (POD1UM-303/InterAACT 2)



Eng et al: JCO, 2022

LBA-3508 (SCARCE): Conclusions

- SCARCE did not fulfill its primary endpoint: NO additional benefit was noted for the use of atezolizumab in combination with **mDCF**
- However, mDCF is an option for a disease that has limited treatment choices
- Does this mean there is no role for IO therapy + chemotherapy in treatment naïve patients? **NO**
  - Based on prior studies, there is substantial evidence to support IO therapy in combination with platinum-based therapy
- **Whenever possible enroll onto a clinical trial**
  - This is the **only** way we will make a difference in a rare cancer with a rising incidence

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Learning Objectives (My Conclusions)

- Updates in Adjuvant treatment of Colon Cancer
  - DYMANIC Trial (LBA #100) – potentially practice changing in the near future
- Updates in Neoadjuvant treatment in Colon Cancer
  - NICHE Trial (#3511) – **practice changing**
- Updates in Anal Cancer, metastatic
  - SCARCE PRODIGE 60 Trial (LBA #3508) – **(!!!) please enroll in EA 2176**

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Thank you

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