Verona, 14 Giugno 2019

Highlights: Colorectal Cancer

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AGENDA

- **Early stages:**

-adjuvant CT

-molecular signature

-neoadjuvant CT

- **mCRC:**

triplet/bev vs doublet/bev

ACCENT
Adjuvant Colon Cancer Endpoints Group

Re-evaluating Disease-Free Survival as an Endpoint versus Overall Survival in Stage III Adjuvant Colon Cancer Trials with Chemotherapy +/- Biologics: An Updated Surrogacy Analysis Based on 15,719 Patients from the ACCENT Database

Qian Shi, Aimery De Gramont, Jesse G. Dixon, Jun Yin, Eric Van Cutsem, Julien Taieb, Steven R. Alberts, Norman Wolmark, Hans-Joachim Schmoll, Leonard B. Saltz, Richard M. Goldberg, Rachel Kerr, Sara Lonardi, Takayuki Yoshino, Greg Yothers, Axel Grothey, Thierry Andre, and Mohamed E. Salem

on behalf of Adjuvant Colon Cancer ENdpoinTs (ACCENT) Group

Abstract 3502

The standard end point 5y OS is a long period to wait before concluding that a regimen is effective

Is 3y DFS really a surrogate endpoint for OS in the current era?

It was already established that 3y DFS is a valid surrogate marker for 5y OS

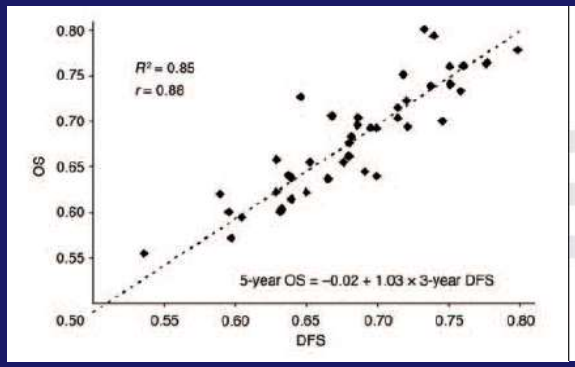


Table 3. Predicted OS Hazard Ratios Based on DFS Hazard Ratios

Observed DFS Hazard Ratio	Predicted OS	
	Hazard Ratio	95% PI*
0.50	0.57	0.49 to 0.65
0.60	0.65	0.58 to 0.73
0.70	0.74	0.68 to 0.81
0.80	0.83	0.77 to 0.90
0.90	0.92	0.86 to 0.99
1.0	1.01	0.95 to 1.08

Abbreviations: OS, overall survival; DFS, disease-free survival.
*95% prediction intervals (PIs) based on a trial of 2,000 patients.

Sargent et al. JCO 2005 ; Sargent et al. JCO 2007; Sargent et al. EJC 2011

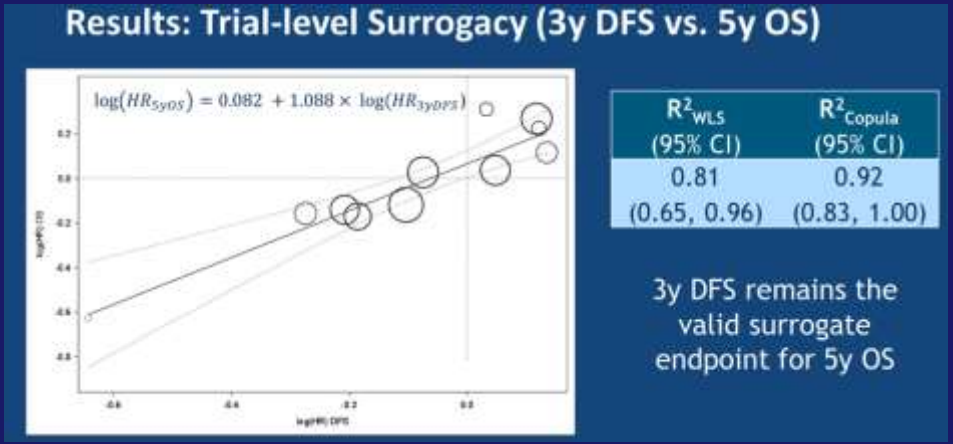
This analysis was needed because…

- **Extended survival after recurrence reduces reliability of 3y DFS as surrogate of 5y OS in a simulation study**

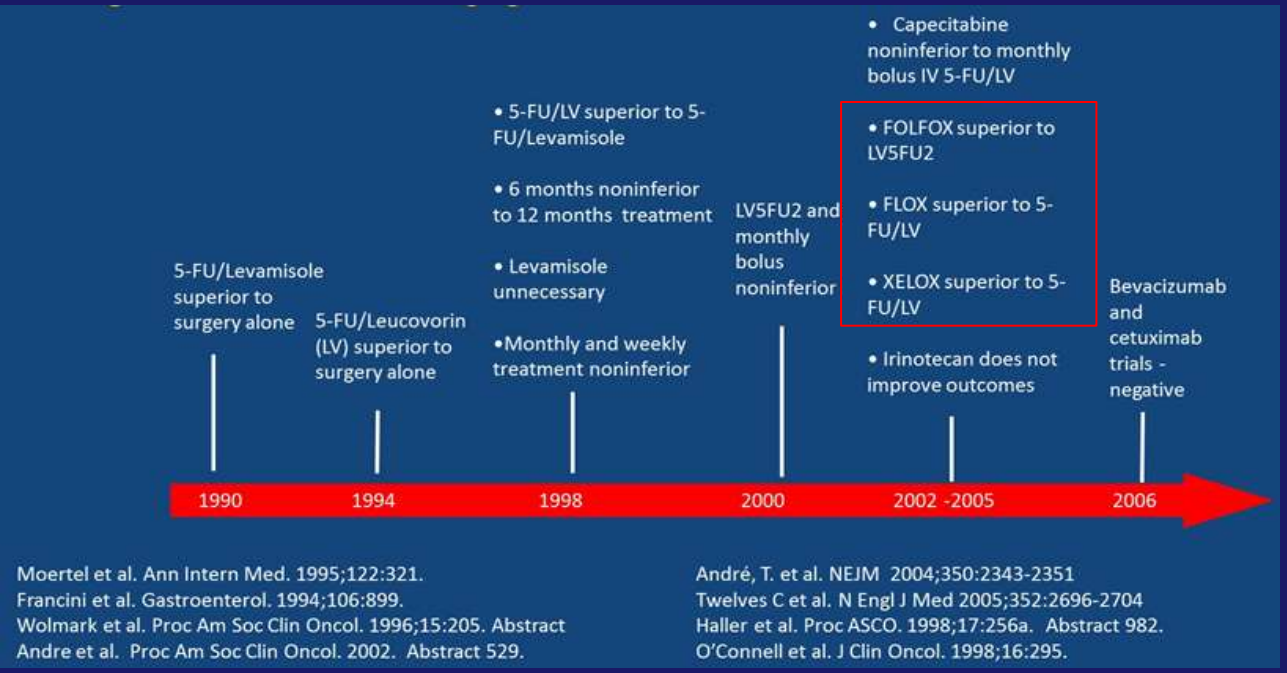
  (de Gramont et al. JCO 2010)

- **FOLFOX treated colon cancer showed improved survival after recurrence and OS for stage III colon cancer patients over years**

  (Salem et al. ASCO GI 2018)



Adjuvant Therapy for Colon Cancer



Moertel et al. Ann Intern Med. 1995;122:321.
Francini et al. Gastroenterol. 1994;106:899.
Wolmark et al. Proc Am Soc Clin Oncol. 1996;15:205. Abstract
Andre et al. Proc Am Soc Clin Oncol. 2002. Abstract 529.

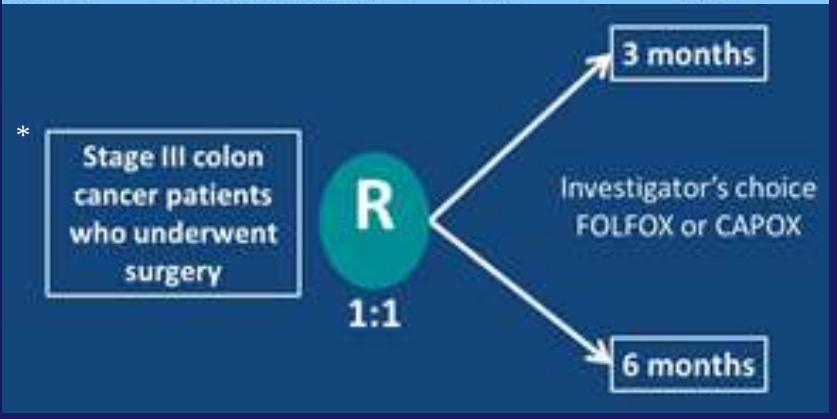
André, T. et al. NEJM 2004;350:2343-2351
Twelves C et al. N Engl J Med 2005;352:2696-2704
Haller et al. Proc ASCO. 1998;17:256a. Abstract 982.
O'Connell et al. J Clin Oncol. 1998;16:295.

Incidence of Neurosensory Symptoms during Treatment and Follow-up after FOLFOX

Andre et al J Clin Oncol. 2009 Jul 1;27(19):3109-16.

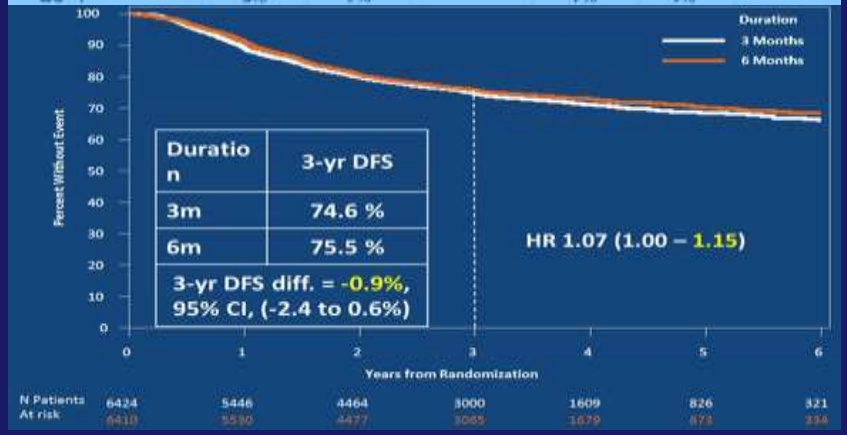
International Duration Evaluation of Adjuvant Therapy Study (IDEA)

Trial	Regimen(s)	Stage III Colon Cancer Pts*	Enrolling Country
TOSCA	CAPOX or FOLFOX4	2402	Italy
SCOT	CAPOX or mFOLFOX6	3983	UK, Denmark, Spain, Australia, Sweden, New Zealand
IDEA France	CAPOX or mFOLFOX6	2010	France
C80702	mFOLFOX6	2440	US, Canada
HORG	CAPOX or FOLFOX4	708	Greece
ACHIEVE	CAPOX or mFOLFOX6	1291	Japan



***Several trials included additional features (e.g., the inclusion of patients with stage II or rectal cancers)**

	FOLFOX			CAPOX		
Adverse Events	3m Arm	6m Arm	p-value†	3m Arm	6m Arm	p-value†
Overall						
G2	32%	32%	<.0001	41%	48%	<.0001
G3-4	38%	57%		24%	37%	
Neurotoxicity						
G2	14%	32%	<.0001	12%	36%	<.0001
G3-4	3%	16%		3%	9%	
Diarrhea						
G2	11%	13%	<.0001	10%	13%	0.0117
G3-4	5%	7%		7%	9%	

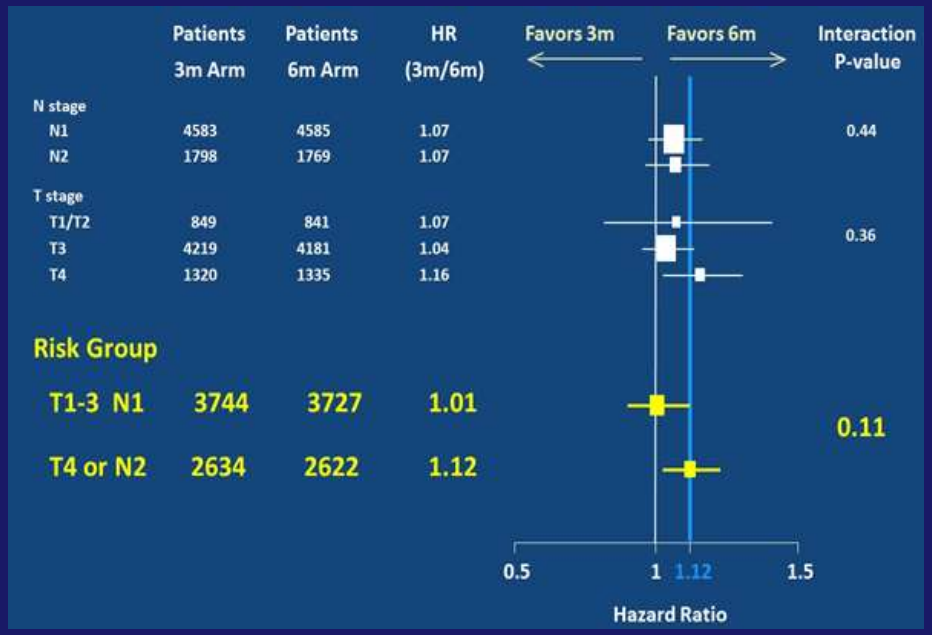


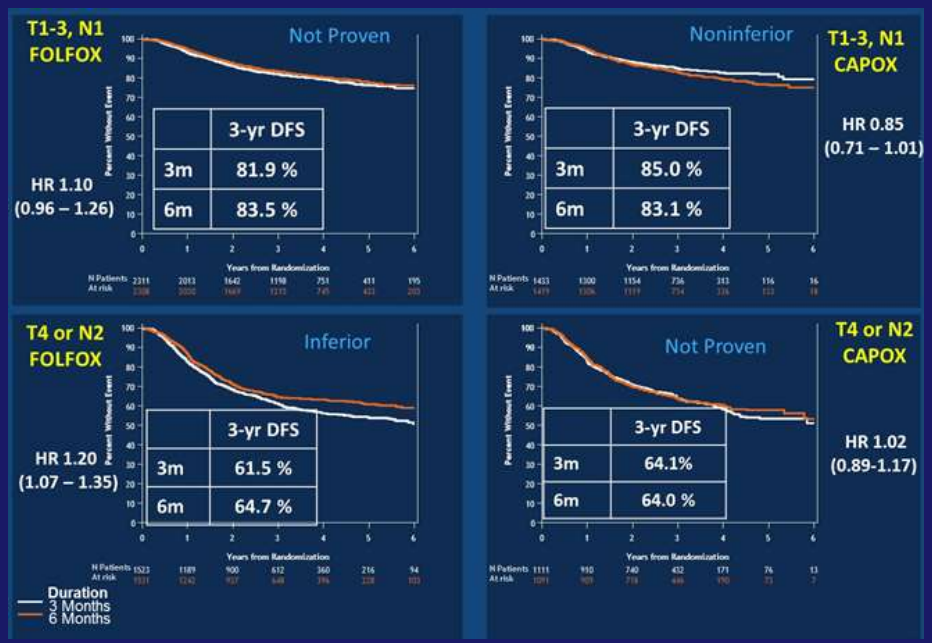
- **Noninferiority of 3m vs 6m could be claimed if the upper limit of the two-sided 95% CI of the HR did not exceed 1.12**

Grothey et al. NEJM 2018

*I*nternational *D*uration *E*valuation of *A*djuvant Therapy Study (IDEA)

DFS Comparison by Risk Groups





IDEA was not able to compare CAPOX and FOLFOX

Grothey et al. NEJM 2018

IDEA: Would we feel differently when the studies began reporting out individually?

Trial	Regimen(s)	Stage III Colon Cancer Pts*	Enrolling Country
TOSCA	CAPOX or FOLFOX4	2402	Italy
SCOT	CAPOX or mFOLFOX6	3983	UK, Denmark, Spain, Australia, Sweden, New Zealand
IDEA France	CAPOX or mFOLFOX6	2010	France
C80702	mFOLFOX6	2440	US, Canada
HORG	CAPOX or FOLFOX4	708	Greece
ACHIEVE	CAPOX or mFOLFOX6	1291	Japan

Study Design

Objective: DFS
Time from randomization to date of disease relapse, 2nd CRC primary or death from any cause

Accrual goal 1,000 patients

Accrual Period: April 2009 to October 2015

*Investigator's choice, no randomization
#T4, obstruction/perforation, EMVI, undifferentiated carcinomas

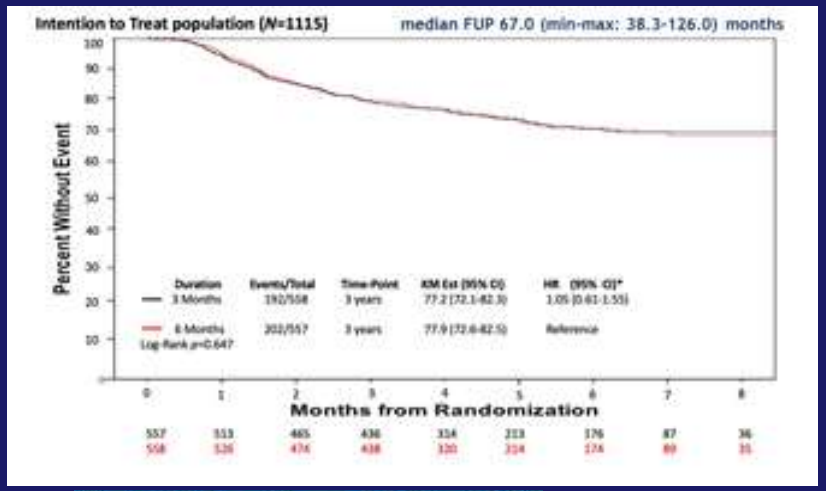
Statistical Considerations

- HORG-IDEA had a target accrual of 1.000 patients within the IDEA collaboration
- No formal statistical calculation for number of patients was applied
- Due to lack of statistical power of HORG-IDEA for non-inferiority analysis, current report focuses on superiority analysis using a non prespecified, descriptive methodology

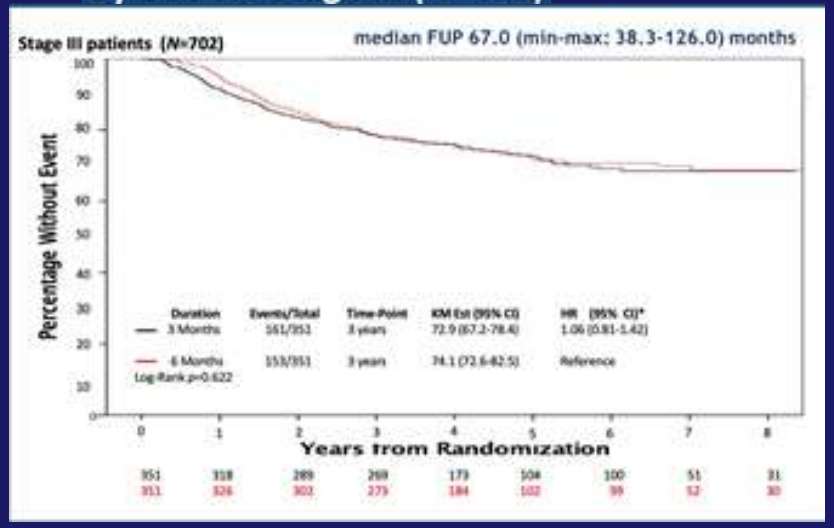
Adverse Events

	3M (%)	6M (%)	*p*-value
Any	20	32	0.037
Neutropenia	11	14	0.482
Febrile Neutropenia	1.4	1.2	0.517
Fatigue	2.8	6.0	0.002
Nausea	1.4	1.8	0.603
Diarrhea	5	8	0.019
Maximum Neuropathy During Treatment			
0-1	70	44	0.004
2	24	35	
3-4	6	21	
Residual Neuropathy at last follow-up visit			
2	1.3	4	<0.001
3	0.2	1.1	<0.001

3y-DFS for the mITT population (N=1115)



3y-DFS for Stage III (N=413)



3y-DFS according to stage and regimen

Results consistent with IDEA:

- **3m of CAPOX appears to be as good as 6m of CAPOX**
- **3m of FOLFOX carries too much risk of inferiority**

Prospective pooled analysis of four randomised trials investigating duration of adjuvant oxaliplatin-based therapy (3 vs 6 months) for patients with high-risk stage II colorectal cancer: The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration

Timothy J. Iveson, Alberto F. Sobrero, Takayuki Yoshino, Ioannis Sougklakos, Fang-Shu Ou, Jeffrey P. Meyers, Qian Shi, Mark P. Saunders, Roberto Labianca, Takeharu Yamanaka, Ioannis Boukovinas, Niels H. Hollander, Valter Torri, Kentaro Yamazaki, Vassilis Georgoulias, Sara Lonardi, Andrea Harkin, Gerardo Rosati, James Paul

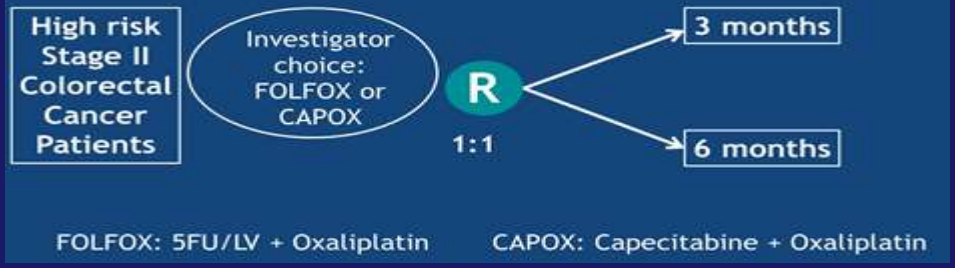
Abstract 3501

IDEA: Would we able to extend the same observations to patients with high risk stage 2 disease?

Trial	Regimen(s)	HR stage II Colorectal Cancer Patients	Enrolling Country
TOSCA	CAPOX or FOLFOX4	1268	Italy
SCOT	CAPOX or mFOLFOX6	1078*	UK, Denmark, Spain, Australia, Sweden
HORG	CAPOX or FOLFOX4	413	Greece
ACHIEVE2	CAPOX or mFOLFOX6	514	Japan

*Included 130 rectal patients

Study Schema



FOLFOX: 5FU/LV + Oxaliplatin CAPOX: Capecitabine + Oxaliplatin

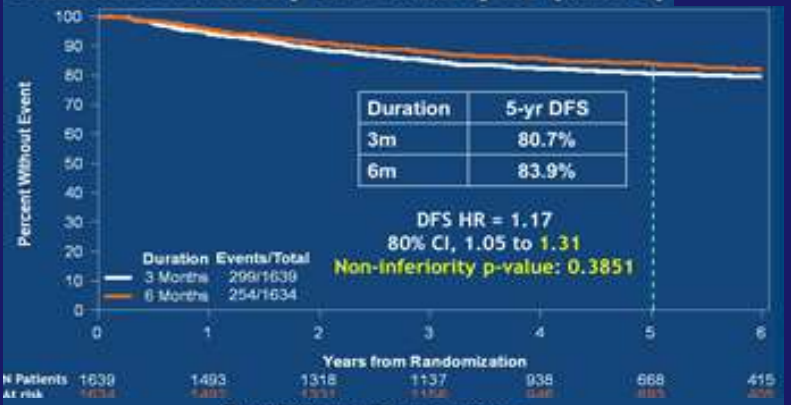
Definition of High Risk Stage II Disease

- T4
- Poorly differentiated
- Invasion (vascular/lymphatic/perineural)
- Inadequate nodal harvest (<10 SCOT, <12 TOSCA, HORG, ACHIEVE)
- Obstruction
- Perforation

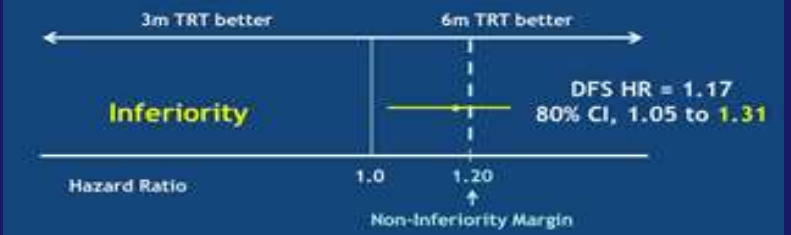
Adverse Events

	FOLFOX			CAPOX			Overall		
Adverse Events	3m Arm	6m Arm	p-value	3m Arm	6m Arm	p-value	3m Arm	6m Arm	p-value
Overall									
G2	33%	36%	<0.0001	35%	47%	<0.0001	34%	42%	<0.0001
G3-5*	31%	51%		22%	32%		26%	40%	
Neurotoxicity									
G2	9%	26%	<0.0001	14%	29%	<0.0001	12%	28%	<0.0001
G3-4	1%	9%		2%	8%		1%	8%	
Diarrhea									
G2	7%	12%	0.0031	7%	12%	0.0026	7%	12%	0.0002
G3-5*	4%	6%		5%	7%		5%	7%	

Results: Primary DFS Analysis (mITT)



Statistical Conclusions

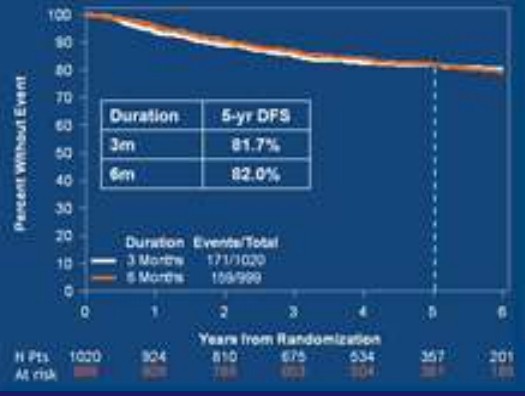


Rationale for Non-Inferiority Margin

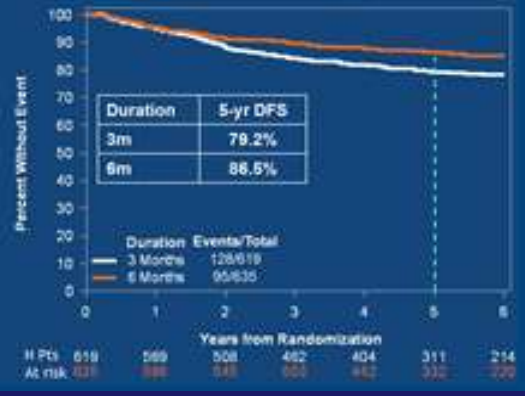
- MOSAIC study: 5yr DFS in high risk stage II colon cancer patients was improved from 74.6% to 82.3% by adding oxaliplatin to LV5FU2
  - HR = 0.72, 95% CI, 0.50 to 1.02
  - Absolute increase: 7.7%
- Clinically meaningful inferiority in patients with stage II disease: HR ≥ 1.2 (i.e. Non-inferiority margin = 1.2 – equivalent to maintaining 60% of benefit from adding oxaliplatin to LV5FU2)

Results: DFS Comparison by Regimen

CAPOX



FOLFOX



- **Overall non-inferiority not shown for 3m treatment for high risk stage II disease**
- **Similar regimen effect seen as in stage III disease**

Association of Colon Cancer Molecular Signatures with Prognosis and Oxaliplatin Prediction-Benefit in the MOSAIC Trial (Multicenter International Study of Oxaliplatin/ 5FU-LV in the Adjuvant Treatment of Colon Cancer)

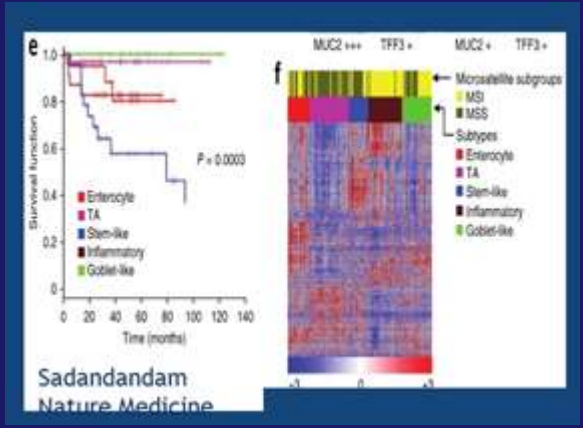
Katherine L. Pogue-Geile, Thierry André, Nan Song, Corey Lipchik, Ying Wang, Rim S. Kim, Huichen Feng, Patrick G. Gavin, Jean-Luc Van Laethem, Ashok Srinivasan, Tamas Hickish, Samuel A. Jacobs, Josep Tabernero, Peter C. Lucas, Aimery De Gramont, Norman Wolmark, Jean-François Flejou, Soonmyung Paik

Abstract 3503

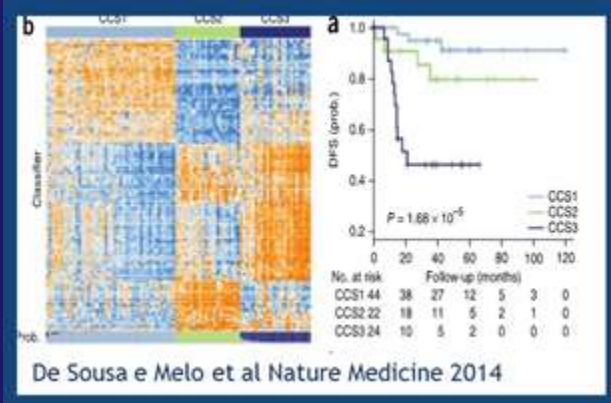
Surrogate markers are desperately needed in adjuvant therapy

Should we move to a new era of molecularly defined subsets?

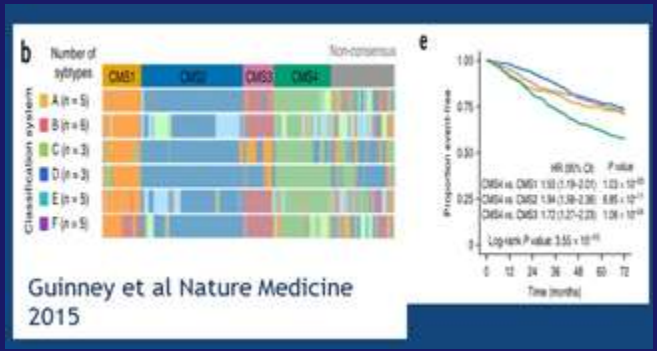
CRCAmplifier Subsets: Gene Expression Profiling



CSS: Colon Cancer Subtypes: CCS1-3



Consensus Molecular Subtypes: CMS1-4



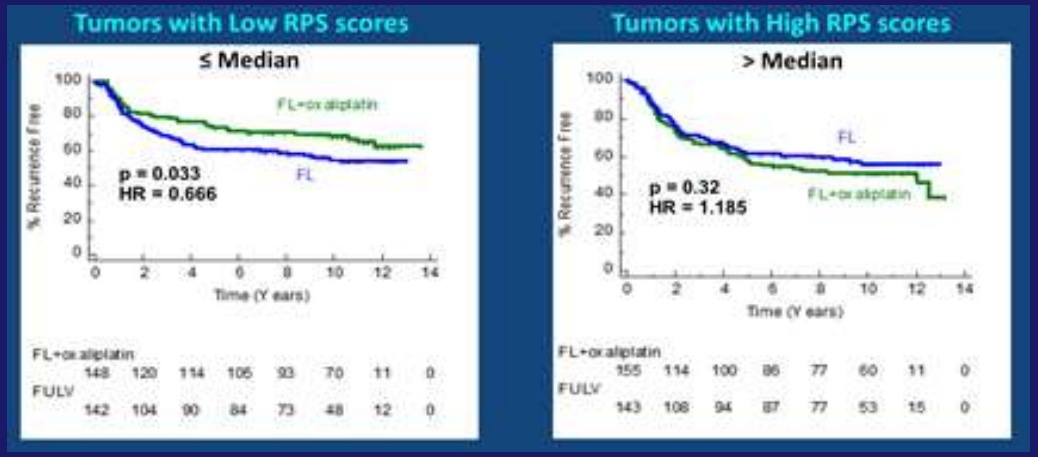
- **The current gene expression profiles may be good prognostic tools but they are an incosistent predictive tool**

- **These tools were developed independent of the mechanisms of action of 5-FU and Oxaliplatin**

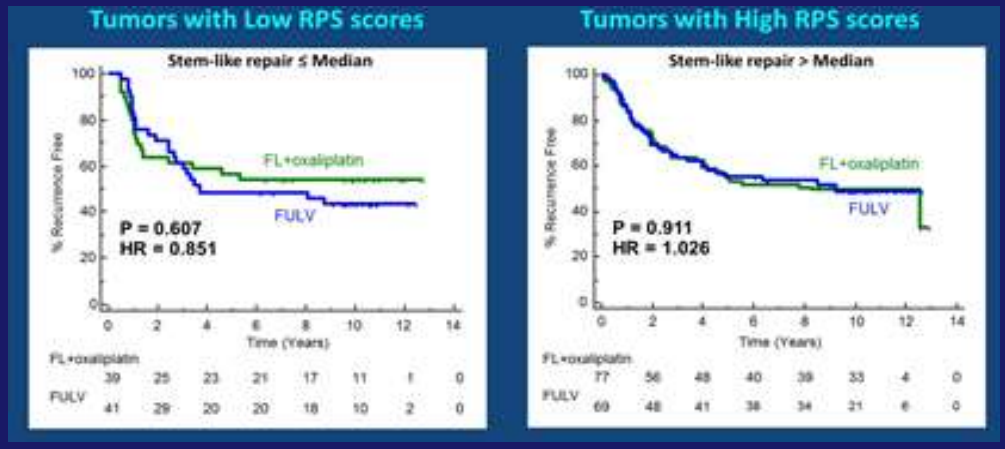
Sadandandam et al. Nature Medicine 2013;
De Sousa e Melo et al. Nature Medicine 2014;
Guinney et al. Nature Medicine 2015

- **Recombination Proficiency Score (RPS): uses expression of 4 genes involved in DNA repair pathway presence (RF1,PARI, RAD51 and Ku80).** Pitroda et al. STM 2014
- **High expression yelds low RPS signaling error-prone repair processes and lethality to DNA damaging agents i.e. predictive for platinums**

Stage III with low RPS scores received oxaliplatin benefit



Stem-like tumors with low RPS scores did not receive oxaliplatin benefit



CANCER RESEARCH UK

NHS National Institute for Health Research

UNIVERSITY OF BIRMINGHAM

BCTU Birmingham Clinical Trials Unit

yorkshire cancer research

UNIVERSITY OF LEEDS

BOBBY MOORE FUND

ECMC

NCRI National Cancer Research Institute

FOxTROT:

an international randomised controlled trial in 1052 patients evaluating neoadjuvant chemotherapy for colon cancer.

On behalf of the FOxTROT collaborative group

Abstract 3504

Should be considered neoadjuvant therapy in localized colon cancer?

Why consider neoadjuvant therapy in localized colon cancer

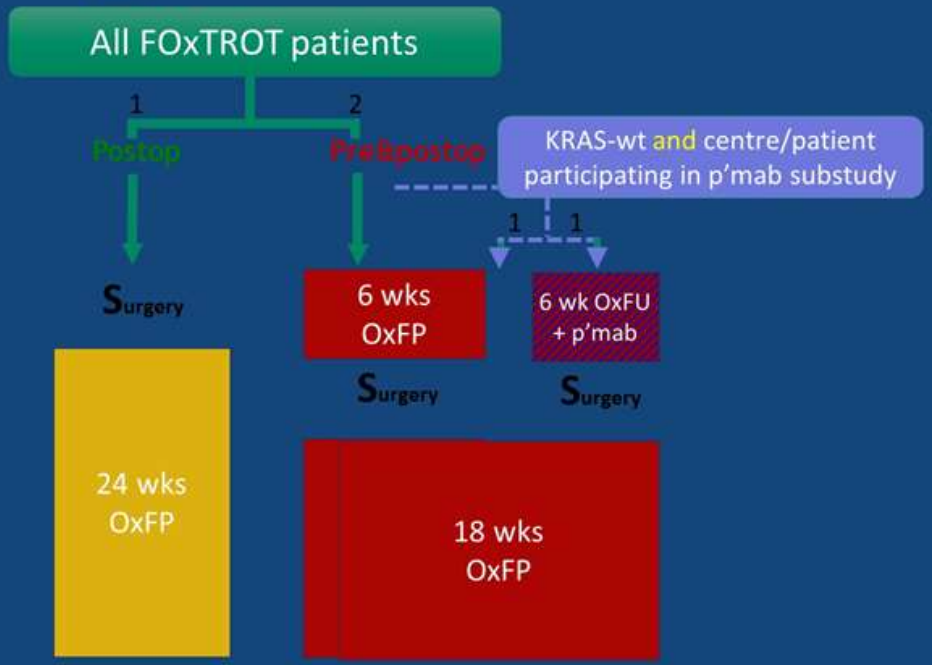
Advantages

- Response might reduce the risk of incomplete surgical resection
- Address micrometastatic disease early
- Pathologic response may be early surrogate endpoint for survival and opportunity to personalise
- Facilitates translational studies

Disadvantages

- Delay surgery
- Risk of progression prior to surgery
- Potential for increased surgical complications
- Potential for overtreatment

Trial Design



- **Primary question: does preoperative chemotherapy increase the cure rate?**
  - Primary outcome: relapse/persistent disease out to 2 yrs
    - 1050 patients, 80% power for a 25% reduction at p<0.05 (eg 32% to 24%)
  - Secondary outcomes: downstaging; tumour regression; curative (R0) resection rate; perioperative safety

The patients

All baseline characteristics were well-balanced between treatment arms

	n=1052
Age	Median 65 yrs (IQR 57-70); 28% ≥70yrs
Sex M:F	64:36
WHO PS 0 : 1 : 2	76% : 22% : 1%
Primary location in colon	49% right : 51% left
Predicted T-stage from CT scan	75% rT4/T3$_{\geq 5mm}$: 25% rT3$_{<5mm}$

The in-trial choices

	pre&post n=698	post n=354	total n=1052
Chemotherapy schedule			
OxMdG (= mFOLFOX)	72%	72%	72%
OxCap (= XelOx)	28%	28%	28%
Planned total chemotherapy duration			
24 weeks	94%	94%	94%
12 weeks	6%	6%	6%

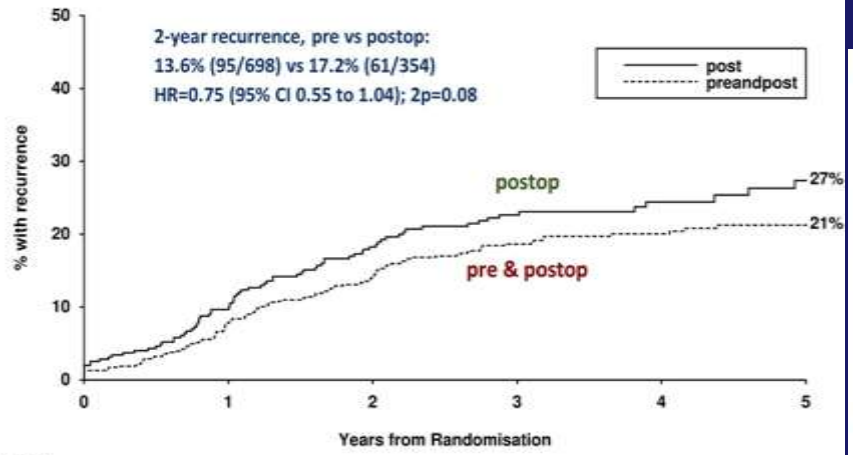
Perioperative Complications

	Pre&post n=682	Post n=350	
Wound infection	8.5%	8.9%	p=0.85
Bronchopneumonia	1.8%	3.1%	p=0.16
PE ± DVT	1.6%	0.6%	p=0.18
Anastomotic leak or intra-abdo abscess	4.7%	7.4%	p=0.07
complication requiring further surgery	4.3%	7.1%	p=0.05
complication prolonging hospital stay	11.6%	14.3%	p=0.22
Death within 30 days	0.6%	0.6%	p=0.98

Safety conclusion: Preop chemotherapy did not increase surgical morbidity:
in fact there were fewer major surgical complications.

Primary outcome: 2-year efficacy

Recurrence – by treatment allocation



At risk:

post	354	303	245	180	107	64
preandpost	698	618	541	375	224	144

Completeness of resection

Local pathologist score*	neoadjuvant chemotherapy n=689	Straight to surgery n=353	
Did not			
Surgery			
R2 – m			
R1 - microscopically incomplete	4.2%	8.8%	(MH)
R0 - microscopically complete	93.1%	88.4%	

Risk of undergoing surgery without achieving R0:

R1, R2 or no resection: **4.8%** vs **11.1%**

*concordance of local vs central assessment of resection margins = 99% (n=904)

Tumour stage/size at surgery

Local pathology	neoadj. chemo n=682	Straight to surgery n=347	
pT0	4.1%	0%	p<0.0001 (MH)
pT1 / pT2	11.7%	5.8%	
pT3	63.7%	64.5%	
pT4	20.5%	29.8%	

Nodal stage at surgery

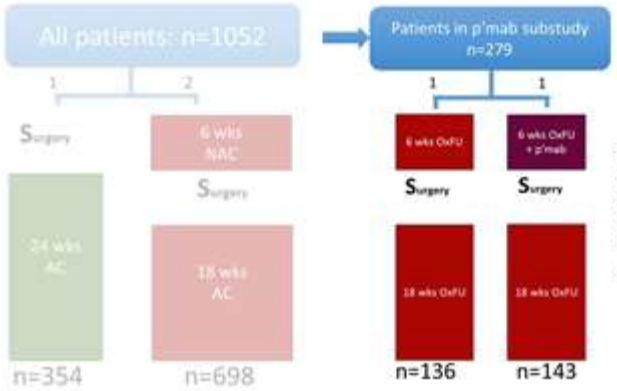
Local pathology	Neoadjuvant chemotherapy n=682	straight to surgery n=346	
pN0	59.4%	48.8%	p<0.0001 (MH)
pN1 (1-3 nodes)	25.4%	25.1%	
pN2 (≥4 nodes)	15.2%	25.9%	
Apical node positive	3.8%	7.5%	p=0.013

This is not practice changing in terms of standard of care, but promising as a treatment option

Efficacy conclusion:

- Trend toward improved 2-year relapse rate, which reached target HR but not predetermined significance: HR=0.75 (0.55-1.04), p=0.08
- Significant down-staging and reduced risk of incomplete resection

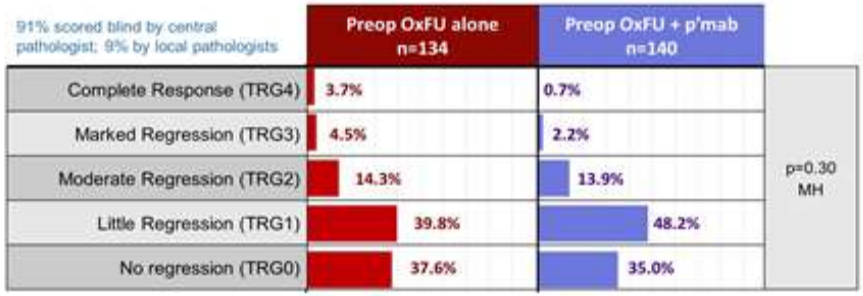
Sensitivity analysis - to assess impact of panitumumab



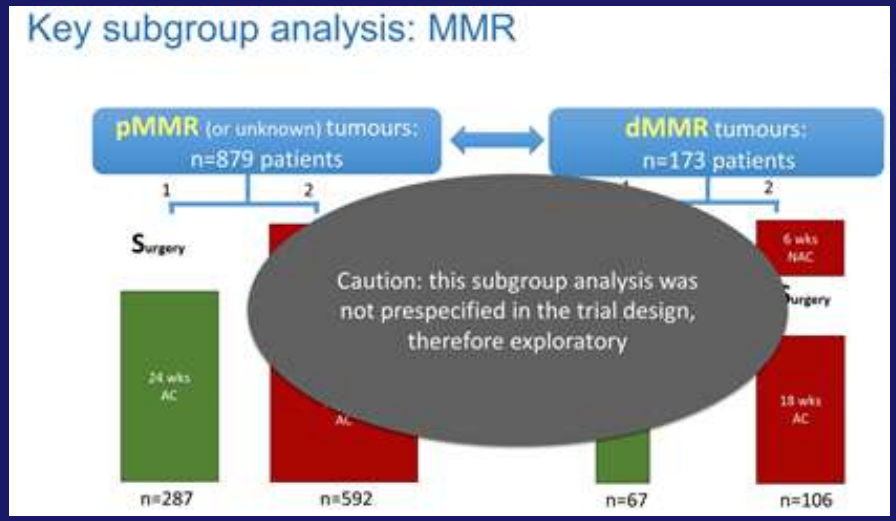
To determine whether p'mab has contributed to the efficacy of preop therapy

Effect of panitumumab

Adding panitumumab to NAC did not increase the observed rate of tumour regression



Key subgroup analysis: MMR



Subgroup analysis conclusion:

- dMMR tumours: no regression in most (but some pCRs); no benefit seen at 2 years.
- pMMR tumours: borderline significant impact on 2-year endoint.

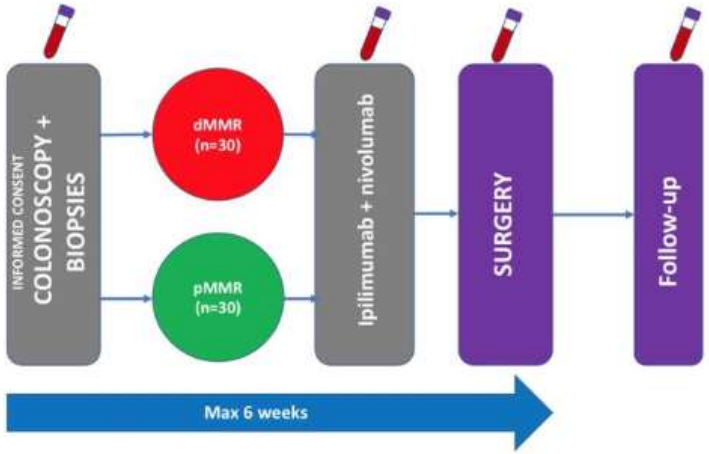
NB exploratory analysis; interaction not significant: interpret with caution.

Neoadjuvant Checkpoint Inhibition in Localized Colon Cancer

NICHE – pre-operative adaptive design

Primary objective:
- safety/feasibility

Secondary objectives:
- efficacy
- associations between response and
  - tumor mutational burden (TMB)
  - interferon $(IFN)_\gamma$ gene signatures
  - T-cell infiltration
  - TCR clonality



efficacy - major response in 100% of dMMR tumors

dMMR (n=7)		
Pre-treatment clinical stage	**Pathological stage at resection**	**Residual vital tumor**
cT2N2a	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT3N0	ypT0N0	0 %
cT3N2a	ypT1N0	1 %
cT4aN2a	ypT2N0	2 %
cT4aN1a	ypT3N1	2 %

pMMR (n=8)		
Pre-treatment clinical stage	**Pathological stage at resection**	**Residual vital tumor**
cT3N1a	ypT3N2	85 %
cT3N0	ypT3N0	90 %
cT2N0	ypT3N1	90 %
cT2N0	ypT3N0	90 %
cT3N1b	ypT3N1	90 %
cT3N1b	ypT3N2	95 %
cT3N0	ypT3N0	100%
cT2N0	ypT2N0	100 %

Neoadjuvant Checkpoint Inhibition in Localized Colon Cancer

ISTITUTO NAZIONALE TUMORI IRCCS – Fondazione Pascale

SCITO

NICOLE (NIvolumab in locally advanced COLon cancEr)

"Preoperative Nivolumab in patients with locally advanced colon cancer (T3 or T4): a window-of-opportunity study."

PI: A. Avallone; Coord. Translational Studies: A. Budillon; Steering committee P.A. Ascierto, P. Delrio, G. Botti, I. Galon

Objectives

PRIMARY

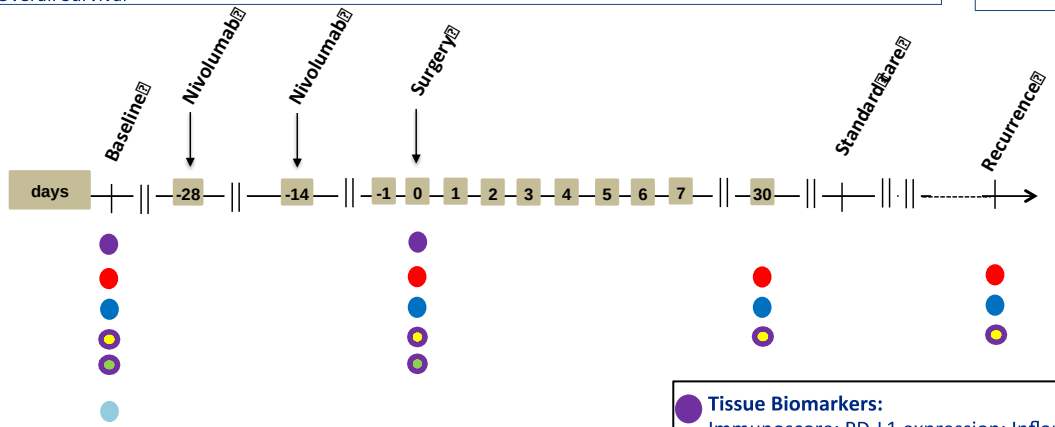
-To determine the feasibility of Nivolumab in the preoperative setting in patients with T3-T4 colon cancer.
-To determine the degree of pathologic regression.
-To determine molecular and immunophenotypic changes in tumor and peripheral blood evaluating several biomarkers.

SECONDARY

-Objective Tumor Response Rate (ORR)
-Metabolic Response by FDG-PET
-Postoperative complications (within 60 days from surgery)
-Relapse-Free Survival
-Overall Survival

Eligibility

Patients diagnosed with histologically confirmed adenocarcinoma of colon with staging of locally advanced (T3 or T4) an no prior treatments (chemotherapy, radiation or surgery). Locally advanced colon cancer must be documented by spiral or multidetector computed tomography (CT) scan.



- Tissue (tumor and normal)
- Blood for Biomarkers
- Blood count, Biochemistry, electrolyte, coagulation and Urinalysis
- TAC t.b.
- PET-FDG.
- Faeces collection (Microbiome and Metabolomic profiling)

- ***A total of 22 patients will receive nivolumab at a flat dosage of 240 mg every two weeks prior to planned surgery.***
- ***Postoperatively, standard adjuvant chemotherapy will be administered in pathological III-stage and at investigator discretion in pathological II-stage.***

Tissue Biomarkers:
Immunoscore; PD-L1 expression; Inflammatory response; T-cell receptor (TCR) Sequencing/Gene Expression analysis. Colorectal cancer immune gene signature by Nanostring MSI and RAS/Braf status; Tumor mutational burden

Blood Biomarkers:
Circulating cytokines and chemokines profiling; Myeloid-derived suppressors cells and immune cell subtypes expression and lymphocyte activation; Metabolomic profiling;

NRG ONCOLOGY

Advancing Research. Improving Lives.™

NIH NATIONAL CANCER INSTITUTE

NRG-GI002: A Phase II Clinical Trial Platform using Total Neoadjuvant Therapy (TNT) in Locally-advanced Rectal Cancer: First Experimental Arm Initial Results

Thomas J. George,[1,2] Greg Yothers,[1,3] Theodore S. Hong,[1,4] Marcia M. Russell,[1,5] Y. Nancy You,[6] William Parker,[1,7] Samuel A. Jacobs,[1,8] Peter C. Lucas,[1,3] Marc Jeffrey Gollub,[9] William A. Hall,[1,10] Lisa A. Kachnic,[1,11] Namrata Vijayvergia,[1,12] Norman Wolmark[1,13]

on behalf of TNT Investigators and Patient Partners

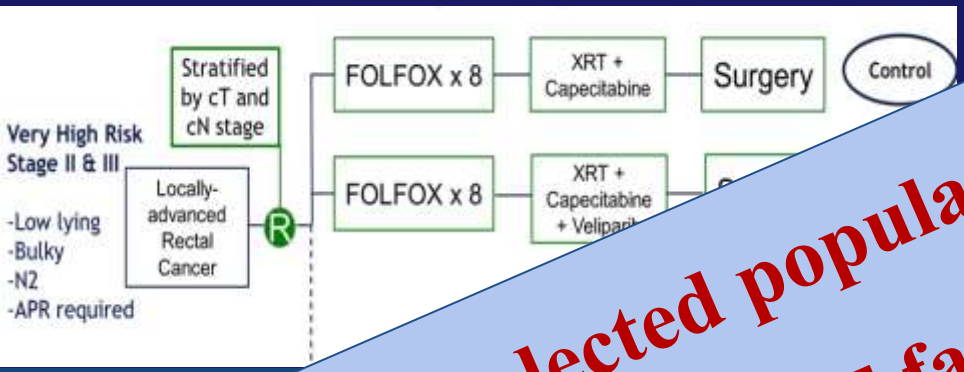
[1]NRG Oncology; [2]University of Florida Health Cancer Center, Gainesville, FL; [3]University of Pittsburgh, Pittsburgh, PA; [4]Massachusetts General Hospital, Boston, MA; [5]VA Greater Los Angeles Healthcare System, and David Geffen School of Medicine at UCLA, Los Angeles, CA; [6]University of Texas MD Anderson Cancer Center, Houston, TX; [7]McGill University Health Centre, Montréal, QC; [8]University of Pittsburgh Cancer Institute, Pittsburgh, PA; [9]Memorial Sloan Kettering Cancer Center, New York, NY; [10]Medical College of Wisconsin, Milwaukee, WI; [11]Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, TN/SWOG; [12]Fox Chase Cancer Center, Philadelphia, PA/EGOG-ACRIN; [13]Allegheny Health Network Cancer Institute, Pittsburgh, PA

Abstract 3505

NCT02921256

Locally advanced rectal cancer comprises a heterogeneous group of tumors in which outcomes vary significantly.

Does intensified neoadjuvant therapy offer advantage in high risk rectal cancer?



In a unselected population the addition of veliparib to CRT failed and led to more toxicity

Started chemoRT	82 (91.1)	167 (93.8)
Completed chemoRT per protocol	57 (69.5)	129 (72.5)
Reasons for discontinuation		
refusal		
		140 (78.6)

		Veliparib	p-value
	12.6 (95%CI: 9.8-15.3)	13.7 (95%CI: 10.2-17.2)	p=0.69

...trolling for stratification variables and SSS candidacy (p=0.78)

Available Secondary Endpoints			
pCR	21.6%	33.8%	p=0.14
R0 Resection	85.1%	83.1%	P=0.82
cCR	28.2%	33.3%	p=0.60
SSS	52.5%	59.3%	p=0.43

Median follow-up among the 161 pts with follow-up and randomized to the Veliparib comparison is 14.5 mos at the time of analysis.

Neoadj...

- Neoadju... account p... stage
- It has been s... score)
  - Validated usi...
  - Analyzed in CA...
    - HR was 4.670 ...
- So, if we lower NA...
  - But the score was ... if we have a TNT ap...

...and/or OS ...have the same impact

George T, et al Curr Colorectal Cancer Rep. 2015;
Fokas E, et al Ann Oncol. 2018 Jul 1;29(7):1521-152...

DFS and OS not available

AGENDA

- **Early stages:**

-adjuvant CT

-surrogate markers

-neoadjuvant CT

- **mCRC:**

- **triplet/bev vs doublet/bev**

GRUPO DE TRATAMIENTO
DE LOS TUMORES DIGESTIVOS

Randomized Phase III Study comparing FOLFOX + Bevacizumab vs FOLFOXIRI + Bevacizumab as 1st line treatment in patients with metastatic colorectal cancer with ≥3 baseline circulating tumor cells The VISNU 1 trial

Javier Sastre, Jose M. Vieitez, Auxiliadora Gomez-España, Silvia Gil, Antonieta Salud, Begoña Graña, Pilar Garcia-Alfonso, Eva Martinez, Guillermo A. Quintero, Juan J. Reina-Zoilo, Encarnación González-Flores, Mercedes Salgado, Carmen Guillen, Rocio Garcia-Carbonero, Maria J. Safont, Adelaida La Casta, Beatriz García-Paredes, Rafael Lopez, Enrique Aranda, Eduardo Diaz-Rubio.

On behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

Abstract 3507

What is the ideal population to use FOLFOXIRI + Bevacizumab?

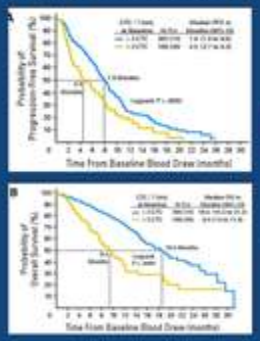
Rationale

- FOLFOXIRI plus bevacizumab has demonstrated a PFS and OS benefit compared with FOLFIRI plus bevacizumab[1,2] in first-line mCRC.
- The ideal population to use triplet drug + bevacizumab combination is not well defined.
- Baseline CTC count ≥ 3 has been defined as a poor prognostic factor[3,4,5,6].
- In the MACRO trial[5], patients with ≥ 3 CTCs at baseline treated with CAPOX + Bevacizumab had a PFS of 7.8 mo.

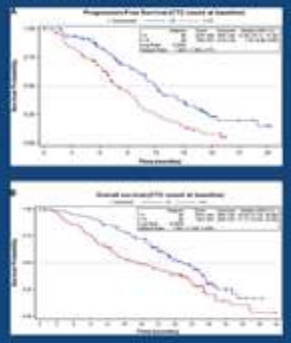
[1]Loupakis F *et al.* HEJN 2014
[2]Cremolini C *et al.* Lancet 2015
[3]Van Cutsem E *et al.* ESMO practice guidelines 2016
[4]Cohen SJ *et al.* J Clin Oncol. 2008
[5]Sastre J *et al.* The Oncologist 2012
[6]Tol J, *et al.* Ann Oncol 2010

≥ 3 Circulating Tumor Cells is an Adverse Feature

Cohen prospective cohort mCRC



MACRO Trial: CapeOX-bev



	≥3 vs <3 CTC at Baseline	
	HR PFS	HR OS
Cohen cohort N=413	1.74 (1.33-2.26)	2.45 (1.77-3.39)
MACRO trial N=180	1.94 (1.38-2.77)	1.62 (1.15-2.35)

Cohen S, et al. JCO 2008
Sastre J, et al. Oncologist 2012

VISNU-1: Study Design

- Open, multicenter phase III trial in mCRC patients with ≥ 3 CTCs at baseline.

mCRC
≤70 y
ECOG 0-1
(349 pts)

R

Stratification:
KRAS (Ex.2,3) mut/WT
Organs affected 1 vs >1

mFOLFOX6 + BEV
Bevacizumab 5 mg/kg D1
Oxaliplatin 85 mg/m² D1
LV 400 mg/m² D1
5-FU 400 mg/m² bolus D1
5-FU 2400 mg/m² 46h CI

FOLFOXIRI + BEV
Bevacizumab 5 mg/kg D1
Irinotecan 165 mg/m² D1
Oxaliplatin 85 mg/m² D1
LV 400 mg/m² D1
5-FU 3200 mg/m² 48h CI

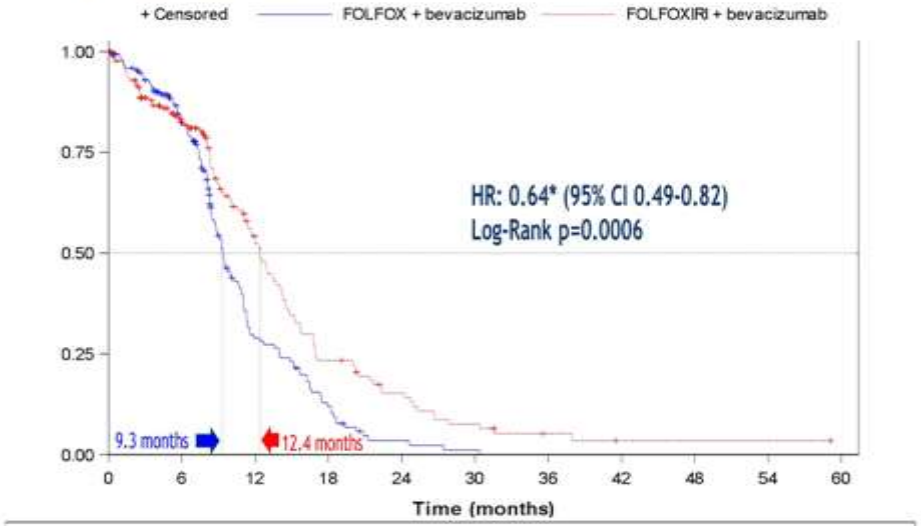
- Accrual: 50 months.
  October 2012-November 2016.
- Data base cut-off: November 2018.
- Tumor evaluations every 12 weeks.
- Protocol amended to add recommended prophylactic GCS-F in the FOLFOXIRI+BEV arm (after 63 pts included).

Every 2 w until PD, unacceptable toxicity or withdrawal of IC

Primary endpoint: efficacy in terms of PFS.

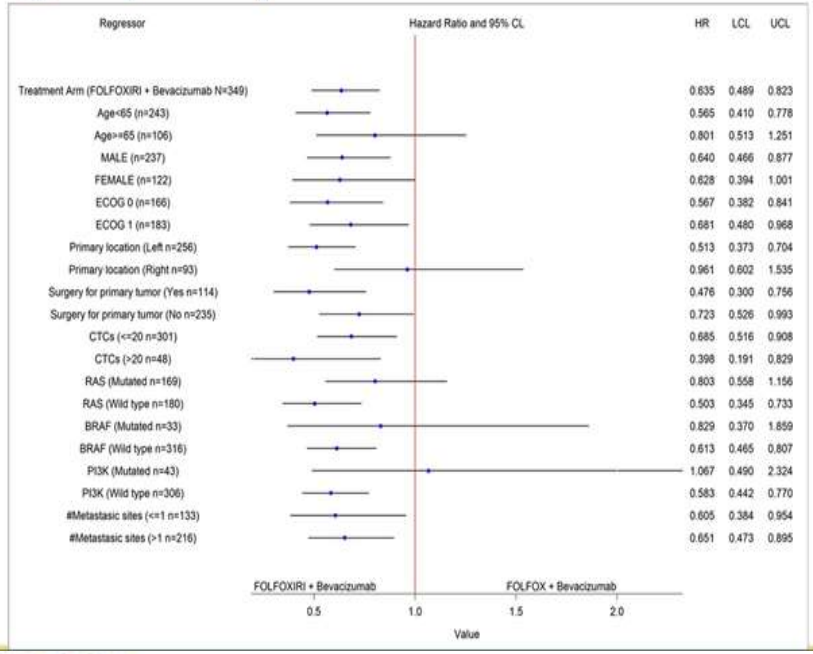
Secondary endpoints: OS; ORR; Resection rate and safety analysis

PFS by treatment arm



* Cox model proportional hazard assumption is not met

PFS Subgroup analysis



	FOLFOXIRI-bev N=172	FOLFOX-bev N=177	HR, 95% CI
PFS	12.4m	9.3m	0.64 (.49-.82)
OS	22.3m	17.6m	0.84 (.66-1.06)
RR	59%	52%	

Safety analysis

- Safety analysis was presented at ASCO 2018.

Grade ≥3 treatment-related AEs N (%)13	FOLFOX+BEV (N=177)	FOLFOXIRI+BEV (N=170)	X^2 p value
Grade ≥3	119 (67)	133 (78)	0.022
Asthenia	12 (7)	27 (16)	0.007
Diarrhea	10 (6)	35 (21)	<0.001
Febrile neutropenia	4 (2)	16 (9)	0.004
Neutropenia	46 (26)	59 (35)	0.077
Mucositis	7 (4)	15(9)	0.063
Neurotoxicity	42 (24)	32 (19)	0.265
Hypertension	8 (4)	7 (4)	0.854
Bowel perforation	7 (4)	4 (2)	0.396
Deaths associated to treatment-related AEs	6 (3)	8 (5)	0.553

Grade ≥3 treatment related AEs (asthenia, diarrhea, and febrile neutropenia) were more frequent in the FOLFOXIRI+BEV group.

- **Survival shorter in pts with high CTCs**
- **Benefit from FOLFOXIRI consistent with other studies**
- **CTCs are prognostic, not predictive of greater benefit from FOLFOXIRI**

2019 ASCO Annual Meeting

Chicago, 31st May – 4th June 2019

Updated results of TRIBE2, a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable mCRC

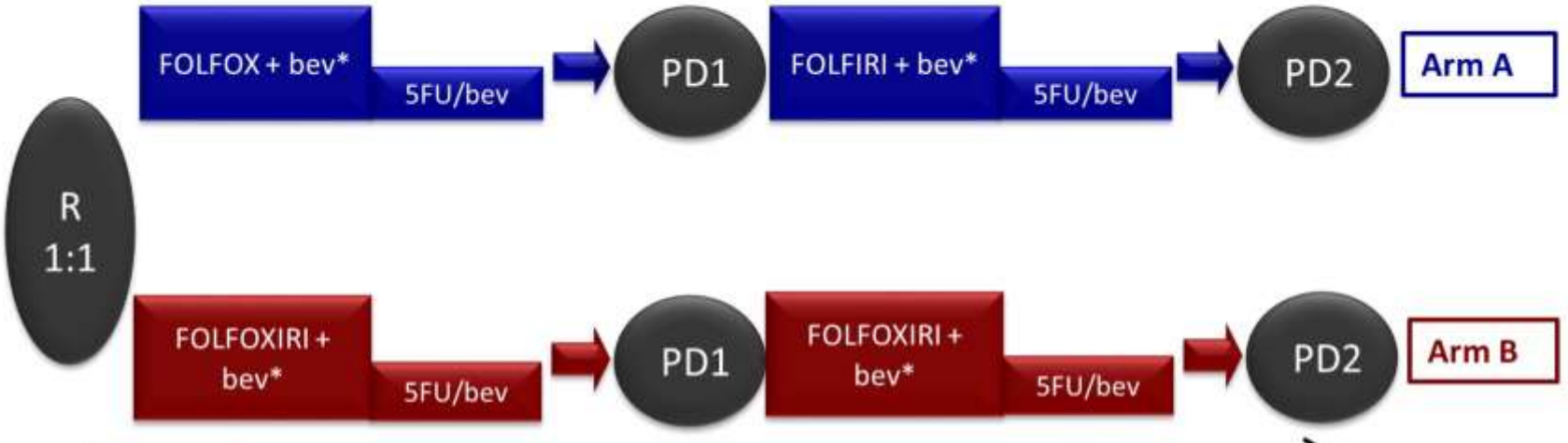
C. Cremolini, C. Antoniotti, S. Lonardi, D. Rossini, F. Pietrantonio, S.S. Cordio, F. Bergamo, F. Marmorino, E. Maiello, A. Passardi, G. Masi, E. Tamburini, D. Santini, R. Grande, A. Zaniboni, C. Granetto, S. Murgioni, G. Aprile, L. Boni, A. Falcone

on behalf of the GONO Investigators

Abstract 3508

What is the advantage of Triplet/Bevacizumab versus a sequential strategy of doublet/Bevacizumab?

TRIBE2: Study design



PRIMARY ENDPOINT: Progression Free Survival 2

SECONDARY ENDPOINTS

1st Progression Free Survival → 2nd Progression Free Survival

- **RECIST Response Rate in 1st and 2nd line**
- **Resection Rate**
- **Safety profile in 1st and 2nd line**
- **Overall Survival**

* Up to 8 cycles

Key eligibility criteria

- Histologically proven adenocarcinoma
- Unresectable (locally assessed) mCRC not pre-treated for mets
- Measurable disease according to RECIST v1.1
- Age 18-75
- ECOG PS ≤ 2 (ECOG PS = 0 if age = 71-75 years)
- Adjuvant oxa-containing chemotherapy NOT allowed
- Adjuvant fluoropyrimidine monotherapy allowed if more than 6 months elapsed between the end of adjuvant and first relapse
- Adequate bone marrow, liver and renal functions

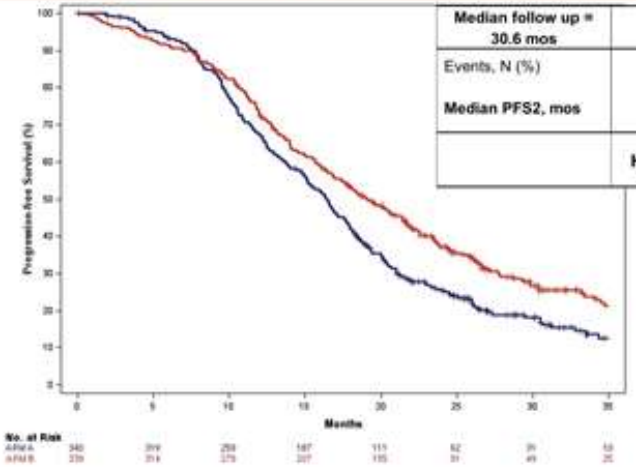
Patients' characteristics – ITT population

	N=679	
Characteristic, % patients	Arm A N = 340	Arm B N = 339
Sex (M / F)	61 / 39	54 / 46
Median Age (range)	61 (30 – 75)	60 (33 – 75)
ECOG PS (0 / 1-2)	85 / 15	86 / 14
Synchronous Metastases (Y / N)	89 / 11	89 / 11
Prior Adjuvant CT (Y / N)	2 / 98	2 / 98
Number Metastatic Sites (1 / >1)	38 / 62	45 / 55
Liver Only Disease (Y / N)	29 / 71	32 / 68
Primary Tumor Side (right / left)	38 / 62	38 / 62
RAS/BRAF (*RAS* mut / *BRAF* mut / wt / NE)	65 / 10 / 20 / 5	63 / 10 / 22 / 5
Right AND/OR *RAS/BRAF* mut / Left AND *RAS/BRAF* wt / NA	79 / 16 / 5	78 / 17 / 5

1st line – Response and Resection Rate

	FOLFOX + bev N = 340	FOLFOXIRI + bev N = 339	OR [95%CI], p
Complete Response	4%	3%	
Partial Response	46%	59%	
Response Rate	50%	62%	1.61 [1.19-2.18], p=0.002
Stable disease	40%	29%	
Progressive Disease	7%	4%	
Not Assessed	3%	5%	
R0 Resection Rate	12%	17%	1.55 [1.00-2.39], p=0.047
Liver-limited subgroup	*N=97*	*N=108*	
R0 Resection Rate	28%	38%	1.59 [0.88-2.86], p=0.124

Primary endpoint: Progression Free Survival 2



Median follow up = 30.6 mos	Arm A N = 340	Arm B N = 339
Events, N (%)	272 (80%)	242 (71%)
Median PFS2, mos	17.5	19.1
	HR = 0.74 [95% CI: 0.62-0.88] p<0.001	

March 1 2019

PFS2 events, n=514

76%

1st line - Safety Profile

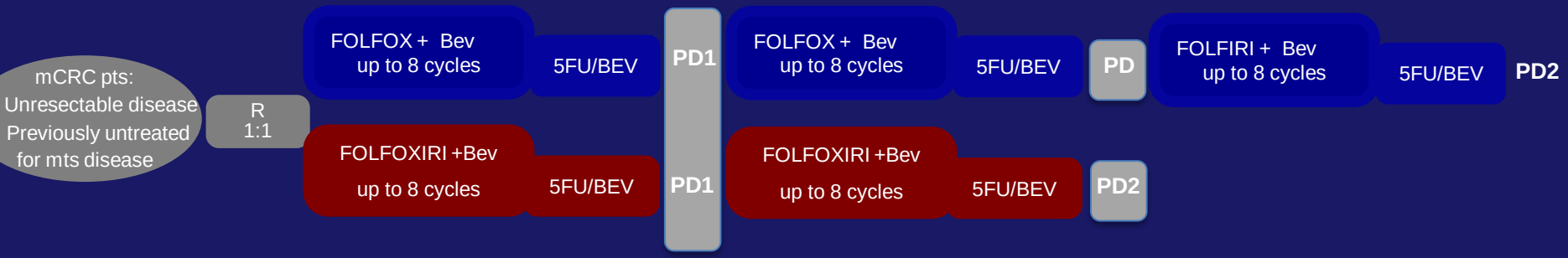
G3/4 adverse events, % patients	FOLFOX + bev N = 336	FOLFOXIRI + bev N = 336	p
Nausea	3	6	0.140
Vomiting	2	3	0.419
Diarrhea	5	17	<0.001
Stomatitis	3	5	0.299
Neutropenia	21	50	<0.001
Febrile neutropenia	3	7	0.050
Neurotoxicity	1	2	0.505
Asthenia	6	7	0.633
Hypertension	10	7	0.223
Venous thromboembolism	6	4	0.204

	FOLFOXIRI-bev N=339	Sequential doublet-bev N=340	
PFS2	19.1m	17.5 m	HR 0.74 (.62-.88)
PFS1	12.0m	9.8 m	HR 0.75 (.63-.88)
OS	27.6m	22.6 m	HR 0.81 (.67-.98)
RR	62%	50% (FOLFOX-bev)	
2nd line RR	19%	12%	
2nd line PFS	6.2 m	5.6 m	HR .87 (.73-1.04)

- **The primary endpoint was met!**
- **Reproducibly efficacy**
- **Not appropriate for all patients**

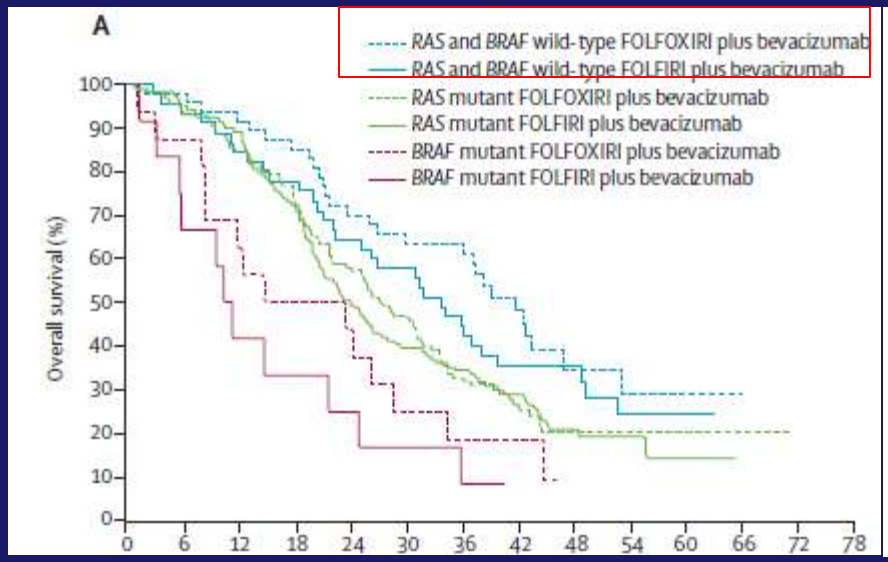
(***older , less robust pts, previous adjuvant oxaliplatin***)

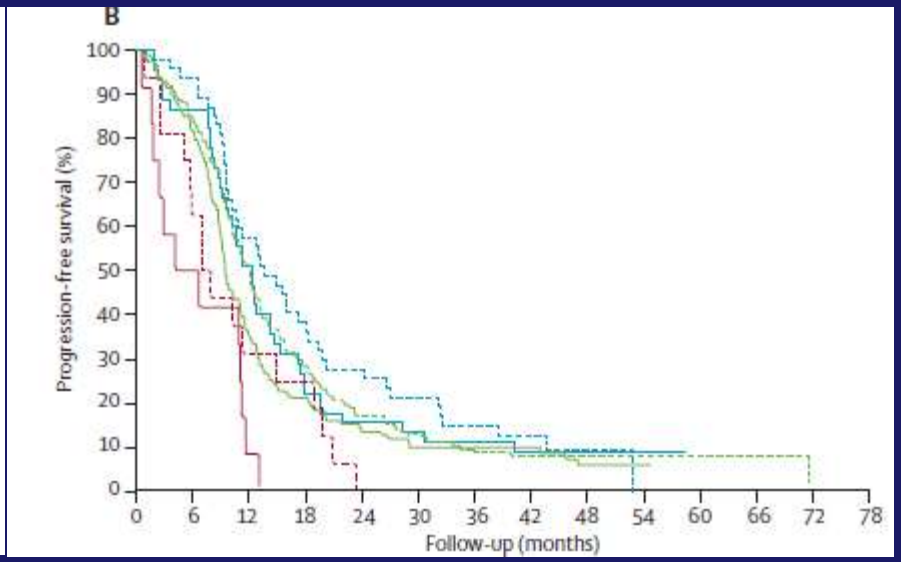
Would have been the results the same if…



What is the ideal population to use FOLFOXIRI + Bevacizumab?

TRIBE TRIAL





Cremolini et al. Lancet Oncology 2015

Thank You
for your attention