Best of ASCO® Gastroenterology Cancer Abstracts

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CRC- More is not always better

Abstracts- LBA1
3507

2

Prospective Pooled Analysis of Six Phase III Trials Investigating Duration of Adjuvant Oxaliplatin-based therapy (3 vs. 6 months) for Patients with Stage III Colon Cancer: The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration

Qian Shi, Alberto F. Sobrero, Anthony F. Shields, Takayuki Yoshino, James Paul, Julien Taieb, Ioannis Souglakos, Rachel Kerr, Roberto Labianca, Jeffrey A. Meyerhardt, Franck Bonnetain, Toshiaki Watanabe, Ioannis Boukovinas, Lindsay A. Renfro, Axel Grothey, Donna Niedzwiecki, Valter Torri, Thierry Andre, Daniel J. Sargent, Timothy Iveson

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Background and Rationale

- Current standard of care for stage III colon cancer patients: six months of oxaliplatin-based treatment
  - FOLFOX, CAPOX
- Oxaliplatin is associated with cumulative dose-dependent neurotoxicity
  - 12.5% grade 3 neuropathy with 6 months of FOLFOX

    Andre et al. J Clin Oncol 2009;27:3109-3116
- Shorter duration treatment without loss of efficacy would be of benefit to patients and health care resources

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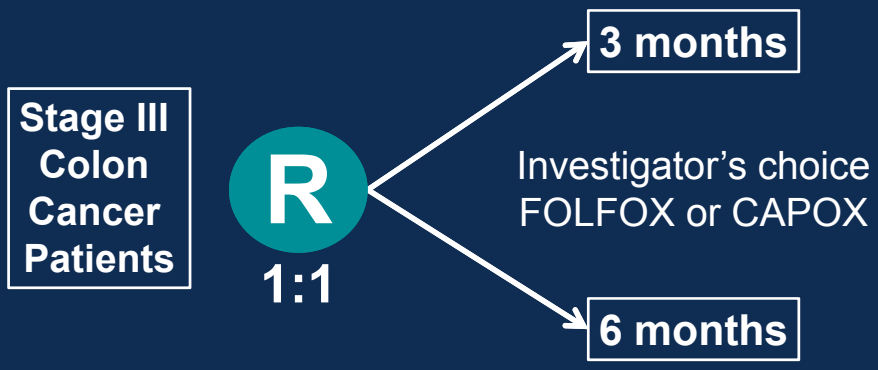
Presented by: Qian Shi, PhD on behalf of IDEA collaborators

Study Schema

Total planned accrual ≥ 10,500



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

IDEA Trials Summary

Trial	Regimen(s)	Stage III Colon Cancer Patients*	Enrolling Country
TOSCA	CAPOX or FOLFOX4	2402	Lwdo
SCOT	CAPOX or mFOLFOX6	3983	XN/#Ghqp dun/#Vsdlq/# Dxvwudld/#Vzhghq/#Qhz #]hdodqg
IDEA France	CAPOX or mFOLFOX6	2010	France
C80702	mFOLFOX6	2440	XV/#Fdqdgd
HORG	CAPOX or FOLFOX4	708	Greece
ACHIEVE	CAPOX or mFOLFOX6	1291	Japan

*Only stage III colon cancer patients were included in the pooled primary analysis

Statistical Design

- **Primary Endpoint: Disease-free survival (DFS)**
  - Time from date of randomization (enrollment) to the earliest date of relapse, secondary colorectal primary tumor, or death due to all causes
- **Primary Analysis Population: Modified Intent-To-Treat**
  - Randomized and received any dose of treatment
  - Analysis according to patients' original randomization assignment
- DFS Hazard ratio (HR; 3m vs. 6m) and two-sided 95% confidence interval (CI) were estimated by Cox model **stratified by study**
- **Pre-planned Subgroup Analyses: By regimen and T/N stage**

Rationale for Non-inferiority Margin

Historical Data from MOSAIC

5FU/LV + Oxaliplatin vs. 5FU/LV

24% relative risk reduction

IDEA Consensus (Oncologists and Patient Advocates)

Oxaliplatin-based Treatment: **3m vs. 6m**

12% relative risk increase (upper 95% CI)

→ **NI Margin: DFS HR = 1.12**

Andre et al. N Engl J Med 2004; Andre et al. Curr Colorectal Cancer Rep 2013

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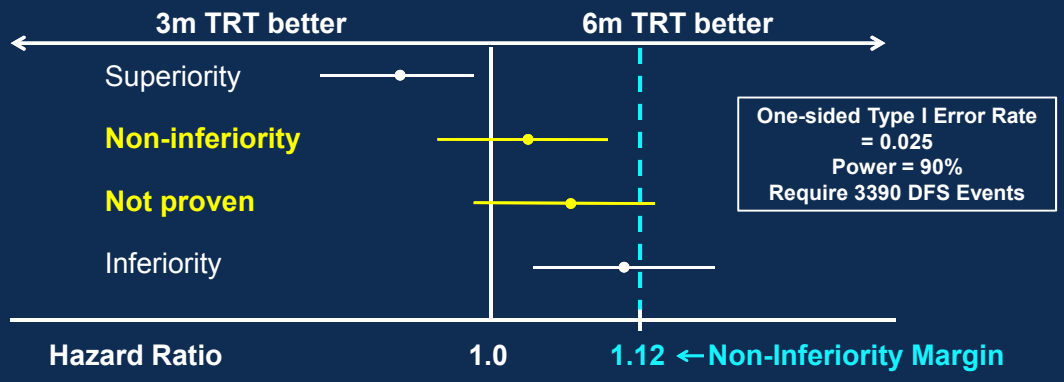
Non-inferiority Hypothesis Testing

Statistical Conclusions Under Different Scenarios



TRT: treatment

Piaggio et al. JAMA 2012;308(24):2594-2604

Results: mITT Population

N patients	12,834
Total DFS events	3,263 (96% of planned)
ECOG PS 0 / 1	79% / 21%
N1 / N2	72% / 28%
T1-2	13%
T3	66%
T4	21%
FOLFOX / CAPOX	60% / 40%

Data frozen on Feb 1st, 2017

Patient Characteristics by Study

Sdwlhqw#Fkdudfwhulvwlfv	WRVFD +Q@5735,	VFRW +Q@6<;6,	IGHD#Iudqfh +Q@5343,	F;3:35 +Q@5773,	KRUJ +Q@:3;,	DFKIHYH +Q@45<4,
P hgldq#Djh/#hduv	97	98	97	94	9:	99
HFRJ#SV- 3 4	<8(8(		:7(58(	:4(5;(	;5(4;(	
W7	45(	5<(	4;(	48(	47(	5;(
Q#Vwdjh Q4 Q5	:6(5:(	9<(64(	:8(58(		9:(66(	
P hgldq#iroorz 0xs wlp h/#p	95	6:	84	68	7;	6:
p						

Treatment Compliance

Treatment Compliance	FOLFOX		CAPOX	
	3m Arm	6m Arm	3m Arm	6m Arm
Total no. weeks received treatment Median (Q1-Q3)	12 (12-12)	24 (20-24)	12 (12-12)	24 (18-24)
Reached the planned last cycle[1]	90%	71%	86%	65%
% of dose actually delivered, Mean (Standard Deviation)				
5FU[2]	92.4 (22.7)	81.6 (26.6)	---	---
Capecitabine	---	---	91.2 (23.5)	78.0 (29.4)
Oxaliplatin	91.4 (19.9)	72.8 (25.6)	89.8 (21.7)	69.3 (28.3)

[1] 1% of patients assigned to 3m treatment (both FOLFOX and CAPOX) received > 3m of treatment; [2] combining infusion and bolus

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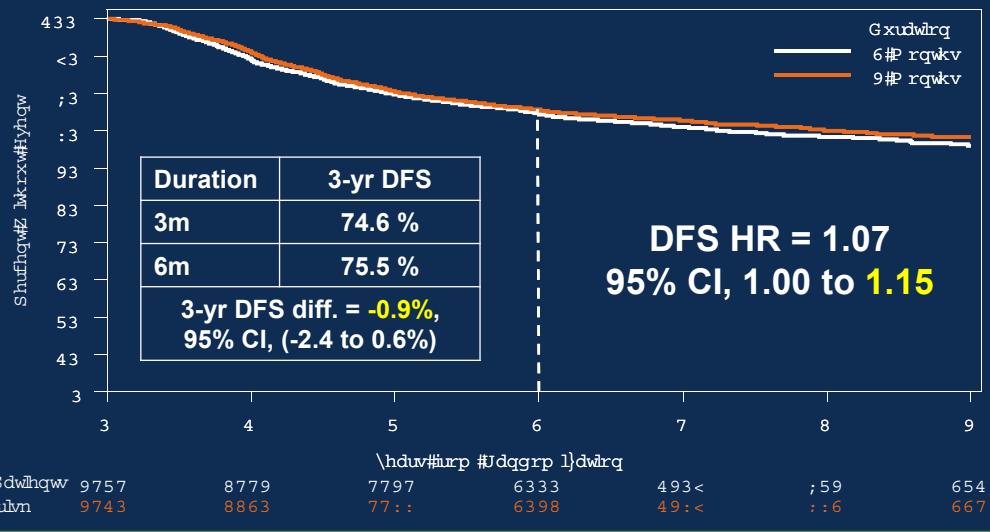
Adverse Events

Dgyhuvh#Hyhqw	IROIR [6p Dup	IROIR [9p Dup	IROIR [s0ydoxh[4]	FDSR [6p Dup	FDSR [9p Dup	FDSR [s0ydoxh[4]
R yhudoo						
G2	65(	65(	?13334	**41%**	**48%**	?13334
G3-4	6;(	8:(		**24%**	**37%**	
Q hxurwr{lflw						
G2	47(	**32%**	?13334	**12%**	69(	?13334
G3-4	6(	**16%**		**3%**	<(	
G lduukhd						
G2	**11%**	**13%**	?13334	**10%**	46(	31344:
G3-4	**5%**	**7%**		**7%**	<(	

[1]Chi-squared test for trend; Total of 19 grade 5 events; Adverse events only collected on first 617 patients enrolled to SCOT trial

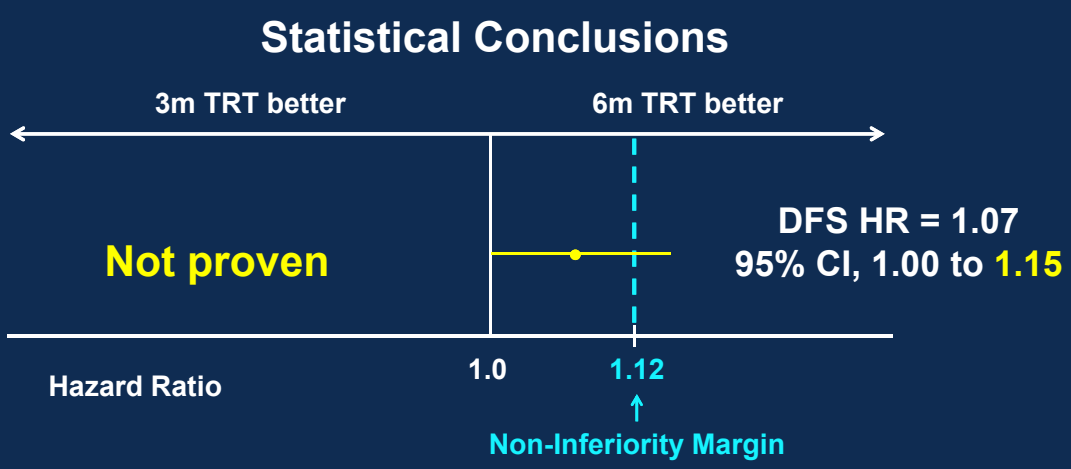
Primary DFS Analysis (mITT)



Duration	3-yr DFS
3m	74.6 %
6m	75.5 %
3-yr DFS diff. = -0.9%, 95% CI, (-2.4 to 0.6%)	

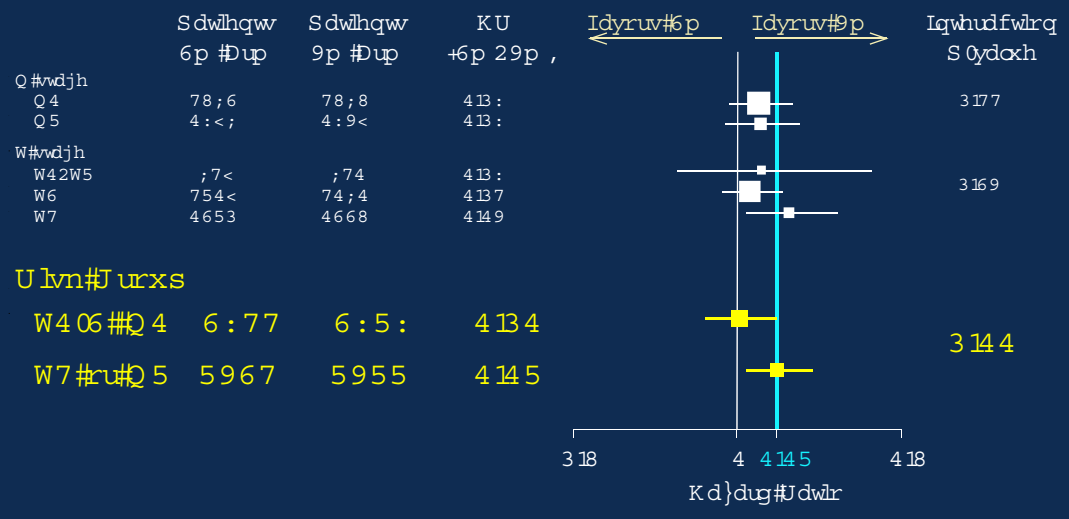
DFS HR = 1.07
95% CI, 1.00 to 1.15

Primary DFS Analysis (mITT), cont.



TRT: treatment

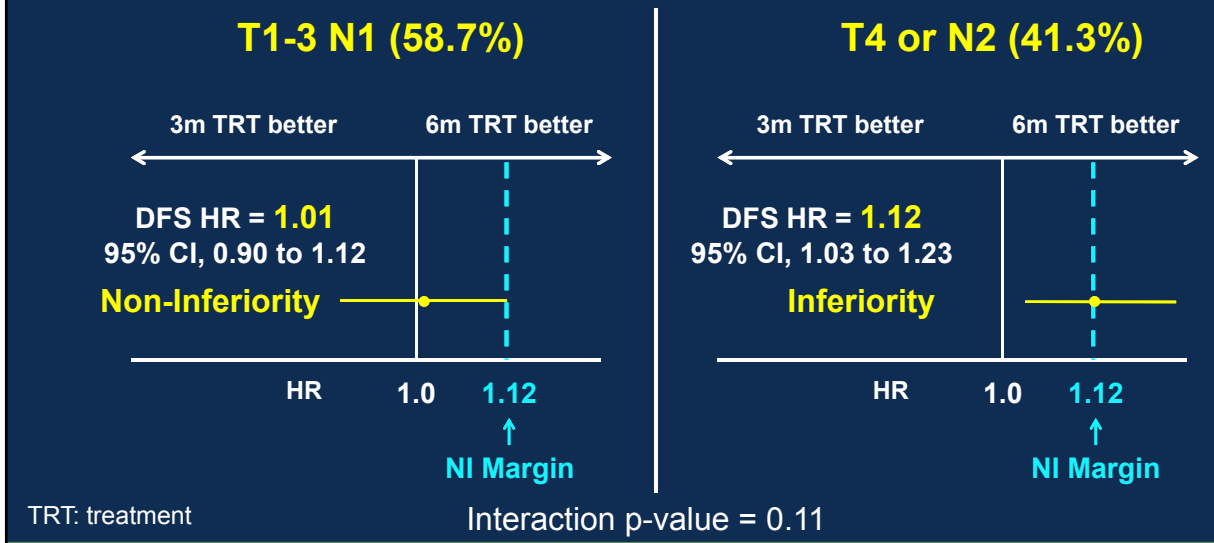
DFS Comparison by Stage, cont.



Analysis by Risk Groups and Regimens

- Large difference in overall prognosis observed between (T1-3 N1) and (T4 or N2) cancers
  - 3 year DFS Δ 20%
  - ➢ Analysis of 3m vs 6m adjuvant therapy for these groups
- Two different adjuvant regimens used, FOLFOX and CAPOX
  - Preplanned analysis of 3m vs 6m based on regimen

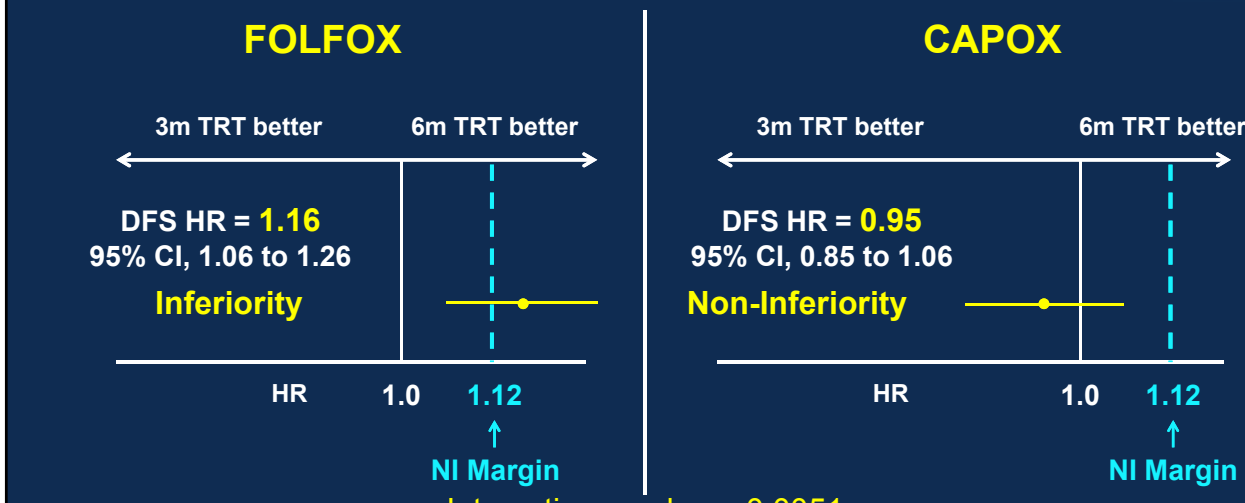
DFS Comparison by Risk Groups, cont.



TRT: treatment

Interaction p-value = 0.11

DFS Comparison by Regimen, cont.

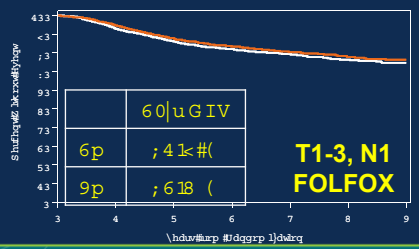


TRT: treatment

Interaction p-value = 0.0051

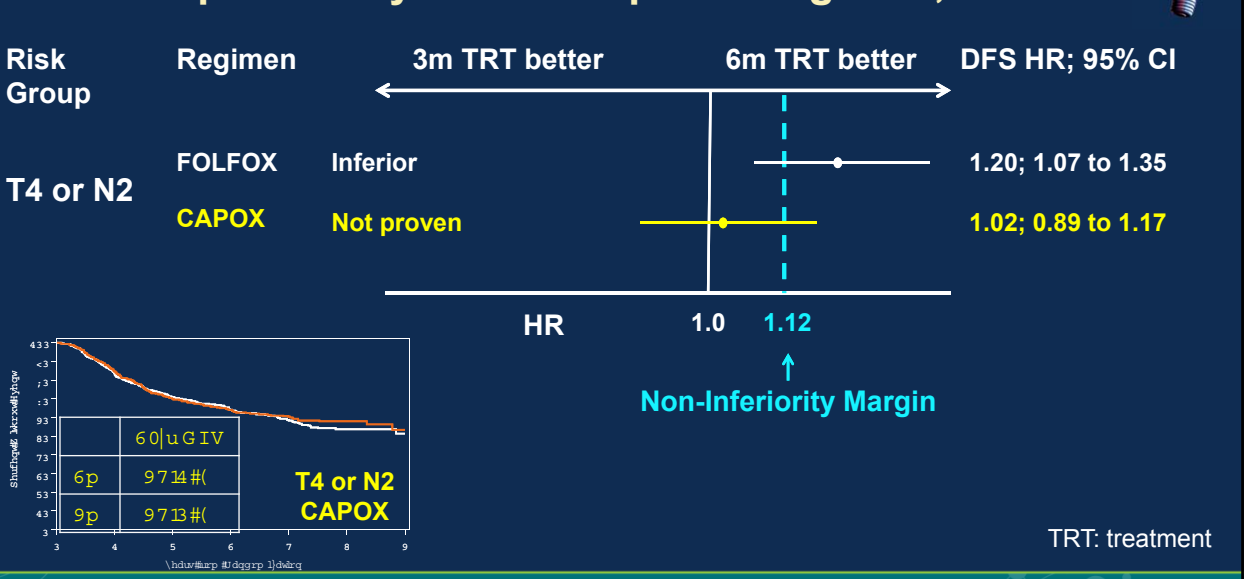
DFS Comparison by Risk Group and Regimen

Risk Group	Regimen		DFS HR; 95% CI
T1-3 N1	FOLFOX	Not proven	1.10; 0.96 to 1.26
	CAPOX	Non-Inferior	0.85; 0.71 to 1.01



TRT: treatment

DFS Comparison by Risk Group and Regimen, cont.



TRT: treatment

Summary

- 3m (vs. 6m) treatment: higher treatment compliance
- 3m (vs. 6m) treatment: substantially lower (G2+) neurotoxicity
  - FOLFOX: 17% vs. 48%
  - CAPOX: 15% vs. 45%
- The DFS non-inferiority of 3m oxaliplatin-based adjuvant therapy was not established in overall stage III colon cancer
- However, results comparing DFS between 3m and 6m treatment depend on risk groups and regimen

Considerations by IDEA collaborators

- The trade-off between potential loss of DFS benefit and reduced (neuro)toxicity should be considered in the clinical decision-making regarding treatment duration
- Although 3-year DFS is a validated surrogate endpoint of OS, long term OS data are needed to show the robustness of the results
- As each IDEA trial treated varying proportions of patients with CAPOX (0 to 75%), the regimen duration interaction likely produced the differential outcomes observed across individual studies

Considerations, cont.

- IDEA was not designed to compare DFS between regimens, and patients were not randomized between regimens. Hence there is potential selection bias affecting DFS comparison between FOLFOX and CAPOX
- Difference in schedule and delivery methods of chemotherapy components may explain the different performance between the two regimens
  - Further investigations needed

IDEA Clinical Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer

Risk group	Recommended duration of adjuvant therapy	
	3 months	6 months
W4 06 #Q 4	———	
(~60% of stage III)		
W7#dqg2ru#Q 5	———	
(Or other high-risk factors)		

Duration of therapy determined by
- tolerability of therapy
- patient preference
- assessment of risk of recurrence
- Regimen (CAPOX vs FOLFOX)

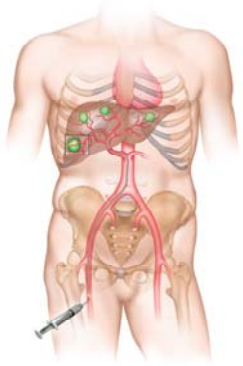
Overall survival analysis of the FOXFIRE prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer

Professor Ricky Sharma
Chair of Radiation Oncology, University College London, United Kingdom

on behalf of the FOXFIRE, SIRFLOX and FOXFIRE-Global Investigators

Selective Internal Radiation Therapy (SIRT)

- SIRT involves injection of millions of yttrium-90 labelled resin microspheres directly in to the blood supply of primary or secondary liver tumors
  - A single large radiation dose
  - FDA approved in 2002 for unresectable liver tumors
  - Supported by NCCN Guidelines (Category 2A) and ESMO Guidelines (II,B)
  - Commissioned in several countries for mCRC patients refractory to chemotherapy



Hendlisz A et al. *J Clin Oncol* 28: 3687-3694, 2010.
NCCN Guidelines: Rectal Cancer v1.2017.
NCCN Guidelines: Colon Cancer v1.2017
Van Cutsem E et al. *Ann Oncol* 27: 1386-1422, 2016

Three prospective randomized studies planned for combined analysis of overall survival

Study name	Geographic region	Recruitment completed	Patients recruited
SIRFLOX	ANZ, EME, USA	2013	530
FOXFIRE	UK	2014	364
FOXFIRE Global	ANZ, AP, EME, USA	2014	209
		Total recruitment	**1,103**

Virdee PS et al. *JMIR Res Protocol* 28: e43, 2017

Key eligibility criteria

- Adenocarcinoma of the colon or rectum
- Liver metastases not surgically resectable or ablatable
- Eligible for systemic chemotherapy as first-line treatment for metastatic CRC
- WHO Performance Status 0 – 1
- Limited extra-hepatic metastases
- Permitted to have primary tumor in situ
- No evidence of ascites, cirrhosis, portal hypertension

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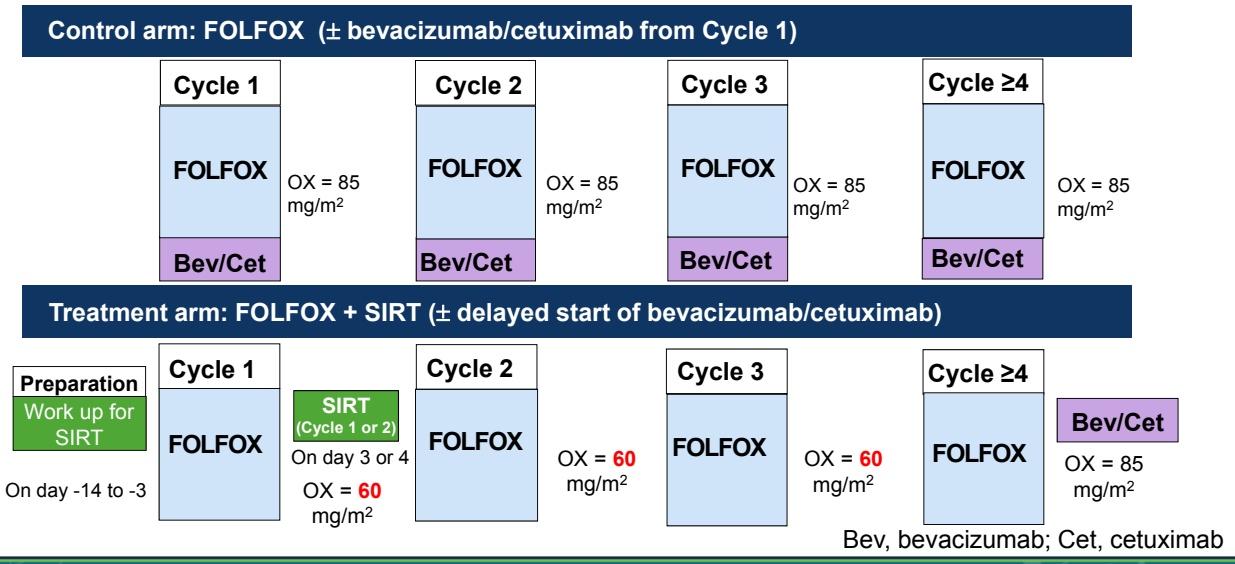
Treatment schedule



Bev, bevacizumab; Cet, cetuximab

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Study endpoints

Primary endpoint

- Overall survival *(time from randomization to all-cause death)*

Secondary endpoints

- PFS at any site (independent central imaging review)
- Liver-specific PFS (independent central imaging review)
- Objective tumor response rate at any site (RECIST v1.0)
- Hepatic resection rate
- Toxicity & safety (NCI CTCAE v3.0)
- Health-related quality of life

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Patient characteristics

Characteristic	Chemo (n = 549)	Chemo+SIRT (n = 554)
Median age in years (range)	63 (23 – 89)	63 (28 – 90)
Male	65.8%	65.5%
WHO performance status 0 1	63.2% 36.4%	63.9% 35.7%
Extra-hepatic metastases	34.8%	35.9%
>25% liver involvement	30.6%	32.3%
Intent to treat with biologicals	54.5%	53.8%
Synchronous presentation with liver mets	86.5%	87.2%
Primary tumor in situ	55.0%	50.2%

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Treatment characteristics

Characteristic	Chemo (n = 549)	Chemo+SIRT (n = 554)
Did not receive SIRT: Total	-	**8.5%**
Reasons in FOXFIRE:		
• Clinical deterioration	-	(33.3%)
• Aberrant vascular anatomy/lung shunting	-	(40.0%)
• Withdrew consent to SIRT	-	(20.0%)
Cycles of oxaliplatin received at full protocol dose	49.1%	43.8%
Median (IQR) number of cycles of FOLFOX chemotherapy	12 (7-13)	12 (7-15)
Patients receiving bevacizumab	**46.6%**	**35.6%**
Patients receiving cetuximab	1.6%	0.7%

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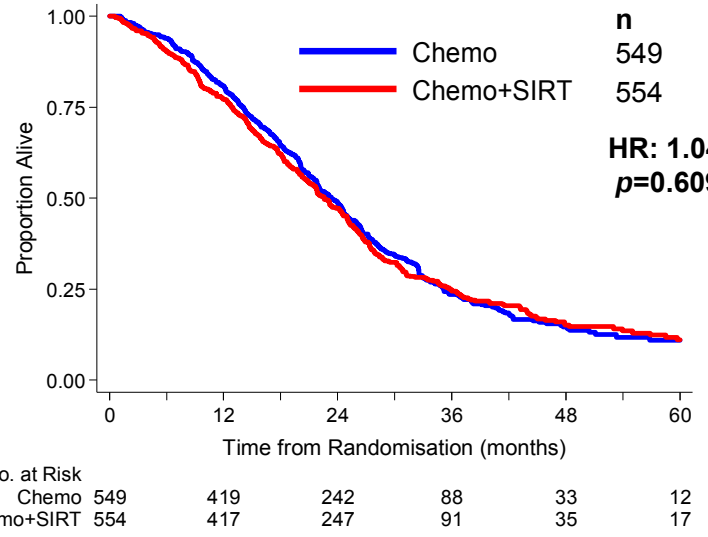
Overall survival (n=1103)



	n	Events	Median
Chemo	549	411	23.3 months
Chemo+SIRT	554	433	22.6 months

HR: 1.04 (95% CI: 0.90–1.19)
***p*=0.609**

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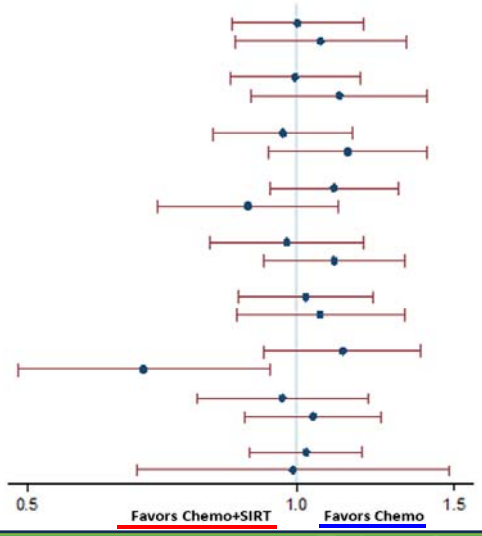
Treatment effect on OS within subgroups

Subgroup	n	Events	HR (95% CI)
Liver-only	713	525	1.00 (0.85 - 1.19)
Liver-dominant	390	319	1.07 (0.85 - 1.33)
Liver involvement ≤ 25%	754	545	1.00 (0.84 - 1.18)
Liver involvement > 25%	347	297	1.12 (0.89 - 1.41)
Age < 65 years	623	470	0.97 (0.81 - 1.16)
Age ≥ 65 years	479	374	1.14 (0.93 - 1.41)
Male	724	556	1.11 (0.94 - 1.31)
Female	378	288	0.88 (0.70 - 1.12)
No primary tumor in situ	521	390	0.98 (0.80 - 1.19)
Primary tumor in situ	580	453	1.10 (0.92 - 1.33)
WHO performance status 0	701	514	1.03 (0.86 - 1.22)
WHO performance status 1	398	328	1.07 (0.86 - 1.32)
Primary tumor location - left	540	389	1.14 (0.93 - 1.39)
Primary tumor location - right	179	147	0.67 (0.48 - 0.92)
Bevacizumab received	465	336	0.97 (0.78 - 1.20)
Bevacizumab not received	638	508	1.04 (0.87 - 1.24)
Synchronous disease	958	739	1.02 (0.89 - 1.18)
Metachronous disease	139	101	0.99 (0.66 - 1.48)



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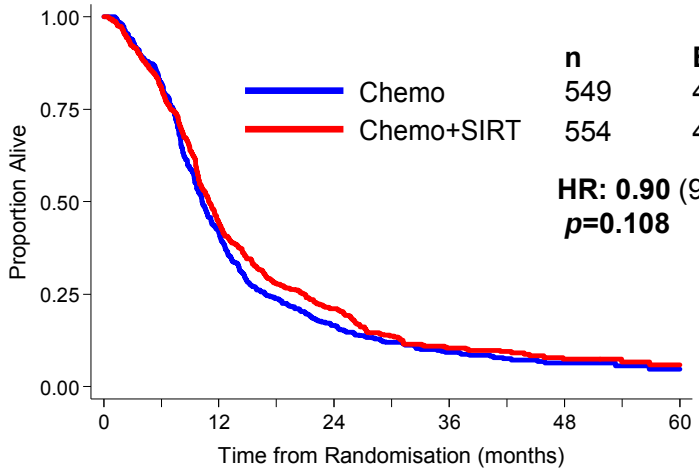
Progression-free survival



	n	Events	Median
Chemo	549	467	10.3 months
Chemo+SIRT	554	474	11.0 months

HR: 0.90 (95% CI: 0.79–1.02)
***p*=0.108**

No. at Risk

Chemo	549	209	78	37	14	6
Chemo+SIRT	554	229	104	37	15	7

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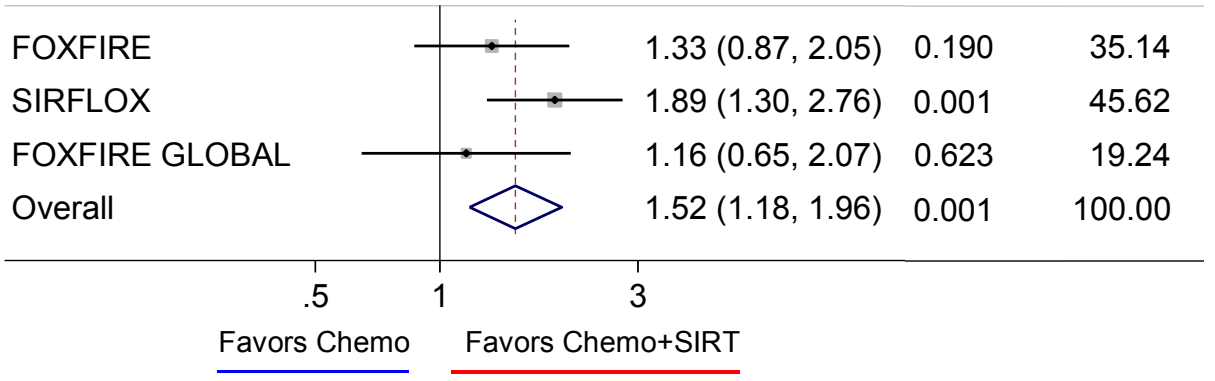
Best radiological response by study



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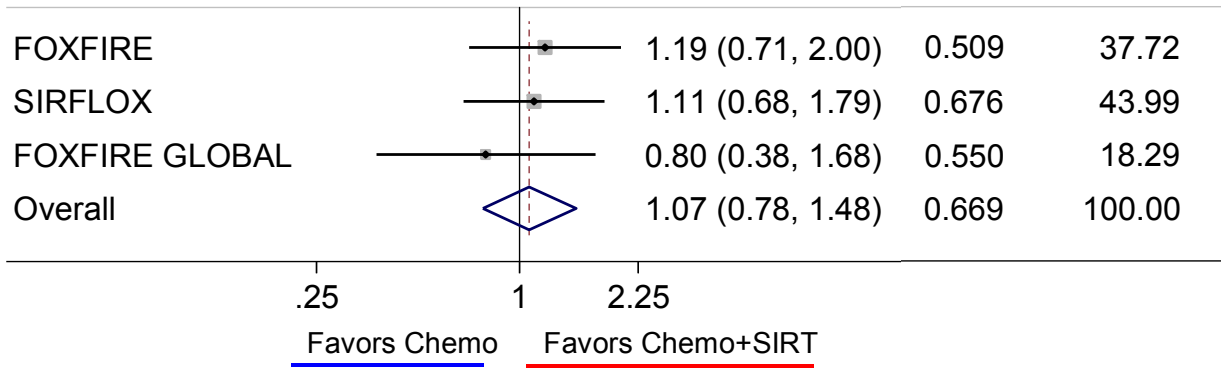
Resection rate



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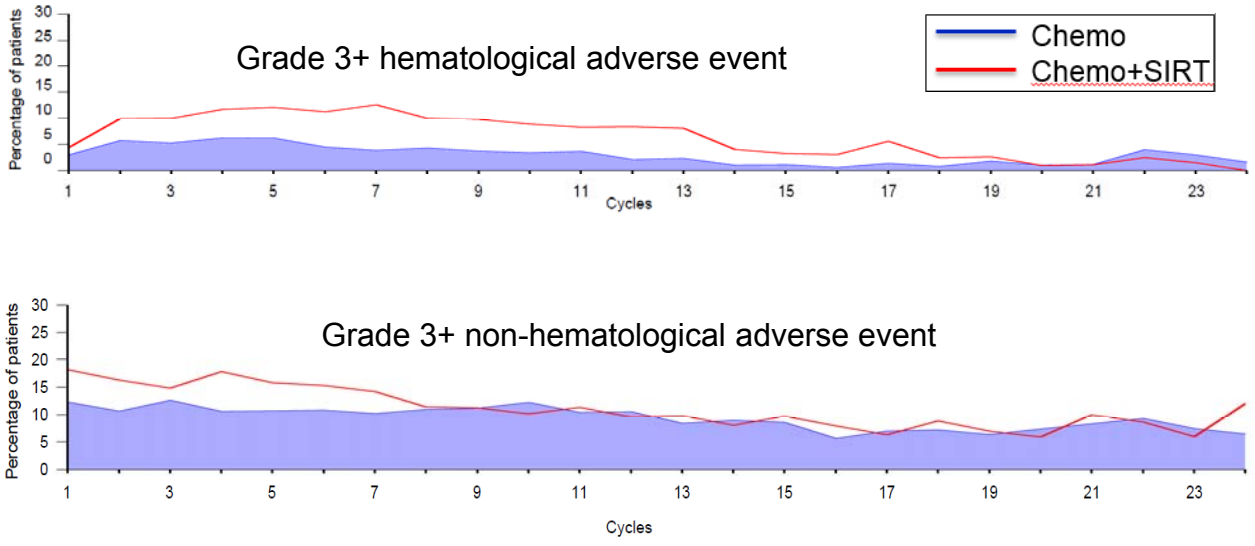
Selected all-cause adverse events (safety population)

Adverse events	Chemo (n = 571)	Chemo+SIRT (n = 507)
All patients any grade	99.6%	99.8%
All patients grade ≥3	**66.5%**	**74.0%**
All patients grade 5	1.9%	2.0%
Hematological (grade ≥3)		
Neutropenia	**24.2%**	**36.7%**
Febrile neutropenia	**2.8%**	**6.5%**
Thrombocytopenia	**1.2%**	**7.7%**
Leukopenia	**2.3%**	**5.9%**
Non-hematological (grade ≥3)		
Fatigue	**4.9%**	**8.5%**
Abdominal pain	**2.3%**	**6.1%**
Diarrhea	6.5%	6.7%
Peripheral neuropathy	**5.8%**	**3.6%**
Radiation hepatitis	-	0.8%

Grade 3+ adverse events per cycle of chemotherapy



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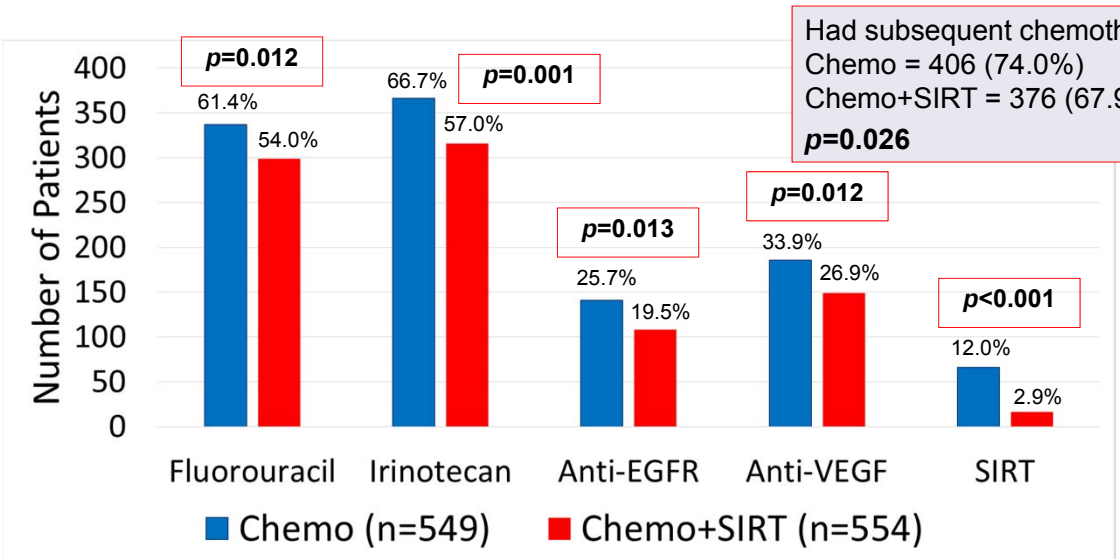
Post-protocol systemic treatment or SIRT



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Conclusions

- Addition of SIRT to FOLFOX first-line chemotherapy in patients with liver-only or liver-dominant mCRC did not improve OS or PFS
- Significant benefit in liver-specific PFS and radiological response rate was achieved by the addition of SIRT
- Toxicity was higher in FOLFOX+SIRT group, particularly hematological
- FOLFOX+SIRT patients were less likely to receive bevacizumab and to receive subsequent post-protocol systemic therapy
- Liver metastases from right-sided primary merit evaluation in other datasets as a subgroup who may derive additional clinical benefit from SIRT

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BRAF mutated CRC, finally good news!

Abstract 3505

Randomized trial of irinotecan and cetuximab with or without vemurafenib in *BRAF*-mutant metastatic colorectal cancer (SWOG S1406)

Scott Kopetz,[1] Shannon McDonough,[2] Heinz-Josef Lenz,[3] Anthony Maglioccо,[4] Chloe Atreya,[5] Luis A. Diaz Jr.,[6] Carmen Allegra,[7] Kanwal Raghav,[1] Van Morris,[1] Stephen Wang,[8] Christopher Lieu,[9] Katherine A. Guthrie,[2] Howard S. Hochster[10]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Fred Hutchinson Cancer Research Center, Seattle, WA; [3]USC Norris Comprehensive Cancer Center, Los Angeles, CA; [4]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [5]University of California, San Francisco, San Francisco, CA; [6]Memorial Sloan Kettering Cancer Center, NewYork, NY; [7]University of Florida, Gainesville, FL; [8]Kaiser Permanente, Sacramento, CA; [9]University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO; [10]Yale Cancer Center, New Haven, CT

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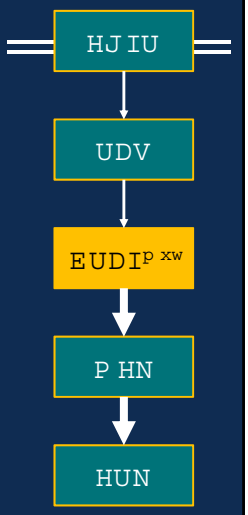
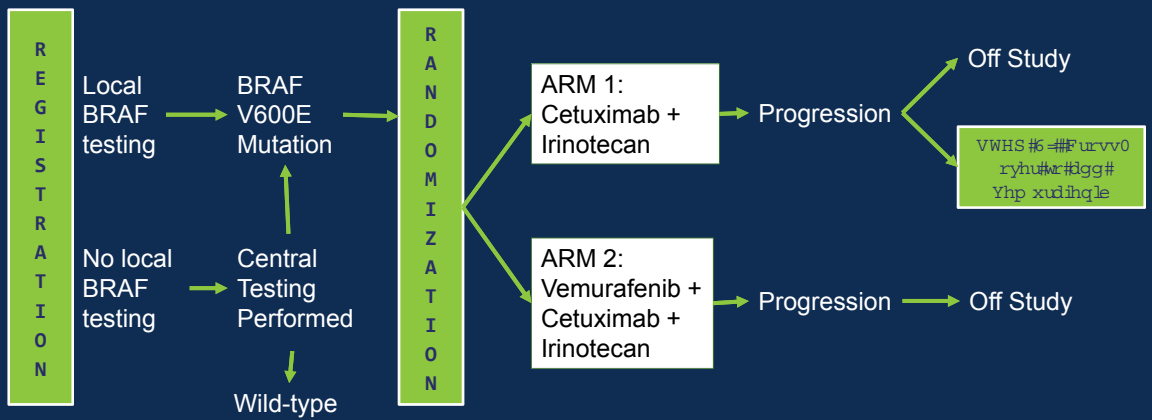
Introduction

- $BRAF^{V600E}$ mutations are present in 7% of mCRC
  - Associated with aggressive biology, short OS, and limited response to standard chemotherapy[1]
- $BRAF^{V600E}$ mutation results in constitutive activation of MAPK signaling.
- Vemurafenib is a $BRAF^{V600}$-specific inhibitor
- However, limited activity with single agent BRAF inhibition with vemurafenib[2] or with cetuximab-based standard of care chemotherapy[3-4]



[1]Morris et al Clin Colorectal Cancer '14, [2]Kopetz et al JCO '15, [3]Pietrantonio et al Eur J Cancer '15, [4]Rowland et al Br J Cancer '15

Study Design



Vemurafenib 960mg PO bid continuous
Cetuximab 500mg/m2 IV q2weeks
Irinotecan 180mg/m2 IV q2weeks

Presented by: Scott Kopetz, MD, PhD

Key inclusion and exclusion criteria

Inclusion Criteria

- Measurable or non-measurable metastatic disease
- BRAF V600E mutation and have tissue available for central BRAF V600E testing
- Extended RAS wild type
- Must have had one or two prior regimens of systemic chemotherapy for metastatic disease or locally advanced, unresectable disease
- Performance status of 0 or 1

Exclusion Criteria

- Prior cetuximab or panitumumab
- Prior BRAF or MEK inhibitor
- Chemotherapy within 14 days of registration

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Objectives

Primary Objective:

- Progression-free survival

Key Secondary Objectives:

- Frequency and severity of treatment-related toxicity
- Overall survival
- Overall response rate, including confirmed and unconfirmed, complete and partial response in the subset of patients with measurable disease

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Demographics

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Grade 3/4 Adverse Events

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*Seven patients did not start treatment, primarily due to decline in PS before treatment initiated, and are not included in the safety cohort.
*Median duration of treatment is 47 days and 88 days

April 18. 2017 data cutoff

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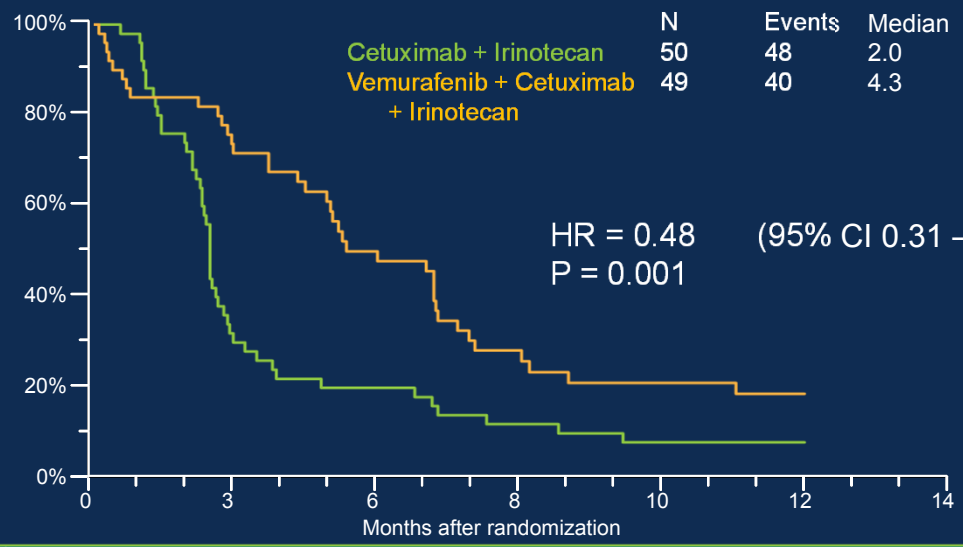
Primary Endpoint: Progression-free survival



	N	Events	Median	95% Conf Int
Cetuximab + Irinotecan	50	48	2.0	(1.8 – 2.1)
Vemurafenib + Cetuximab + Irinotecan	49	40	4.3	(3.6 – 5.7)

HR = 0.48 (95% CI 0.31 – 0.75)
P = 0.001

April 18. 2017 data cutoff
7.3 months of median follow up

Response Rate

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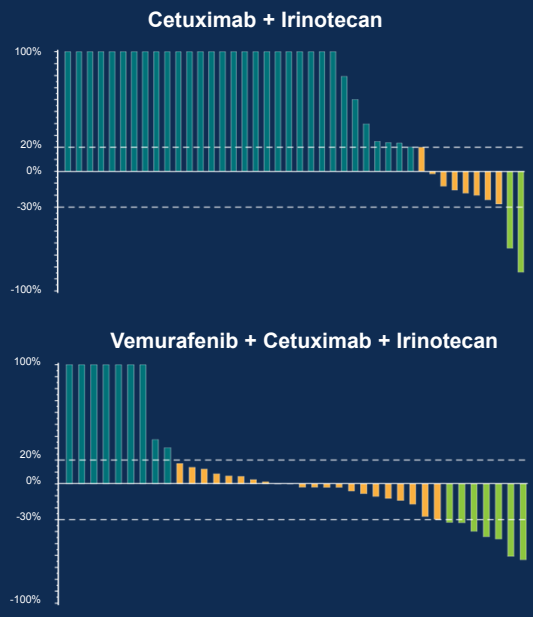
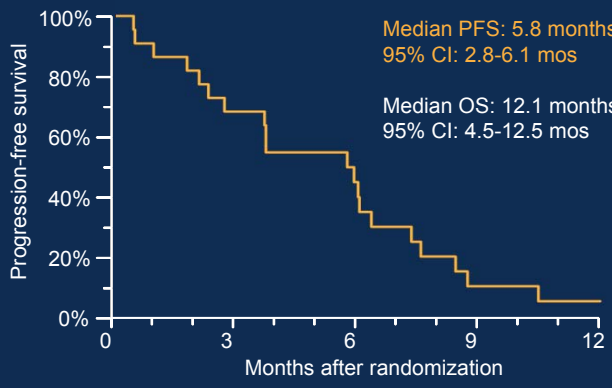


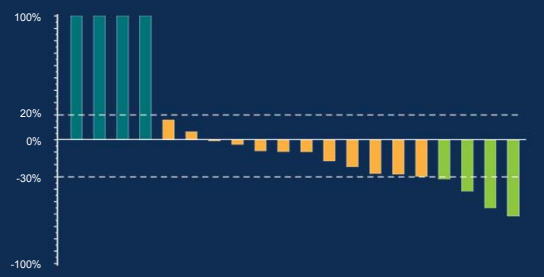
Crossover to VIC after progression

- Patients with radiographically documented progression on IC crossed over to receive VIC
- 48% of patients treated on IC arm crossed over



Median PFS: 5.8 months
95% CI: 2.8-6.1 mos

Median OS: 12.1 months
95% CI: 4.5-12.5 mos



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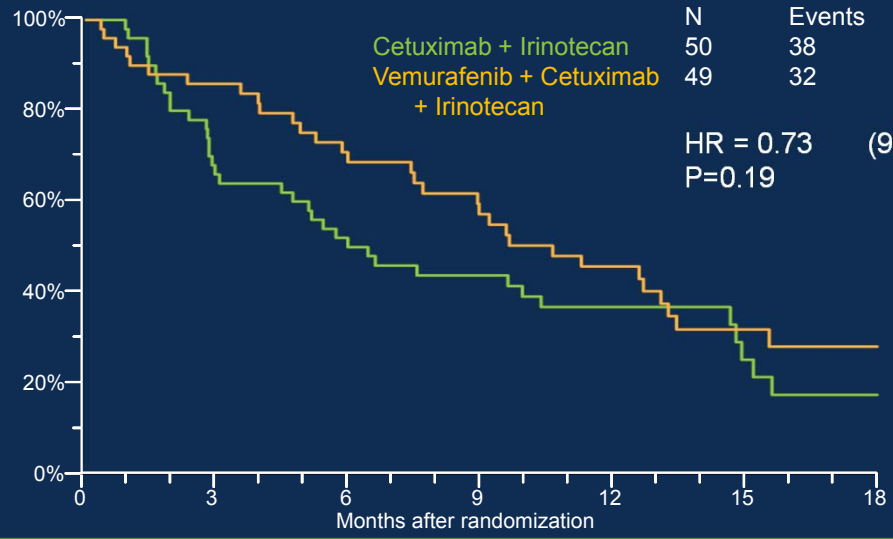
Secondary Endpoint: Overall Survival



Cetuximab + Irinotecan
Vemurafenib + Cetuximab + Irinotecan

	N	Events	Median	95% Conf Int
Cetuximab + Irinotecan	50	38	5.9	(3.0 – 9.9)
Vemurafenib + Cetuximab + Irinotecan	49	32	9.6	(7.5 – 13.1)

HR = 0.73 (95% CI 0.45 – 1.17)
P=0.19

April 18. 2017 data cutoff

Conclusions

- The combination of vemurafenib, cetuximab, and irinotecan (VIC) met its primary endpoint demonstrating improved progression-free survival in patients with $BRAF^{V600E}$ CRC
- Activity of VIC combination did not differ by prior irinotecan, MSI status, PIK3CA mutations, or sidedness.
- Addition of Vemurafenib to IC showed activity even after progression on IC.
- Overall survival showed a trend that VIC decreased risk of death compared to IC. This analysis is limited by a high rate of crossover to VIC after progression on IC.
- VIC represents a new treatment for metastatic $BRAF^{V600E}$ colorectal cancer.

EMORY WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

A New Standard in Biliary Tract Cancer
Abstract 4006

Adjuvant capecitabine for biliary tract cancer: the BILCAP randomized study

Primrose JN, Fox RP, Palmer D, Prasad R, Mirza D, Anthony A, Corrie P, Falk S, Wasan H, Ross P, Wall L, Wadsley J, Evans J, Stocken D, Praseedom R, Cunningham D, Garden OJ, Stubbs C, Valle JW and Bridgewater J on behalf of the BILCAP investigators

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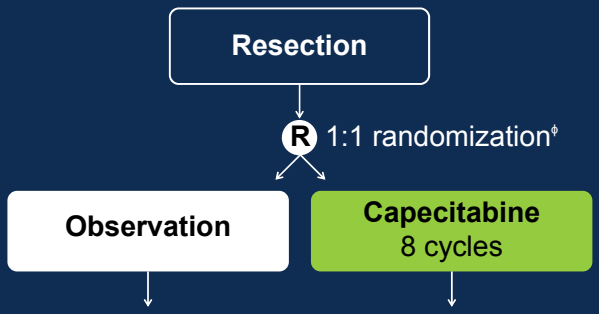
Study overview

BILCAP

- Two arm, open label, randomized, controlled clinical trial

Interventions
- Observation
- Capecitabine (1250mg/m^2) twice a day on day 1 to 14 of a 3 weekly cycle for 24 weeks (8 cycles)

Outcome measures
- Primary; overall survival (OS)
- Secondary;
  - Relapse free survival (RFS)
  - Toxicity
  - Quality of life*
  - Health economics



Primary analysis after a minimum 2 year follow-up

*EORTC QLQ-C30 & LMC-21 (latter for patients with colorectal liver metastasis)
♦Minimized on surgical centre, tumour site, type of resection (RO/RI) & performance status (ECOG PS 0-2)

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Patient selection

Main inclusion criteria

- Histologically confirmed;
  - Intrahepatic cholangiocarcinoma (CC)
  - Hilar CC
  - Muscle invasive gallbladder cancer
  - Lower common bile duct CC
- Radical & macroscopically complete surgery
- ECOG performance status ≤ 2
- Adequate renal, haematological & liver function

Main exclusion criteria

- Pancreatic or ampullary cancer
- Mucosal (T1a) gallbladder cancer
- Incomplete recovery from previous surgery
- Previous chemotherapy or radiotherapy for biliary tract cancer

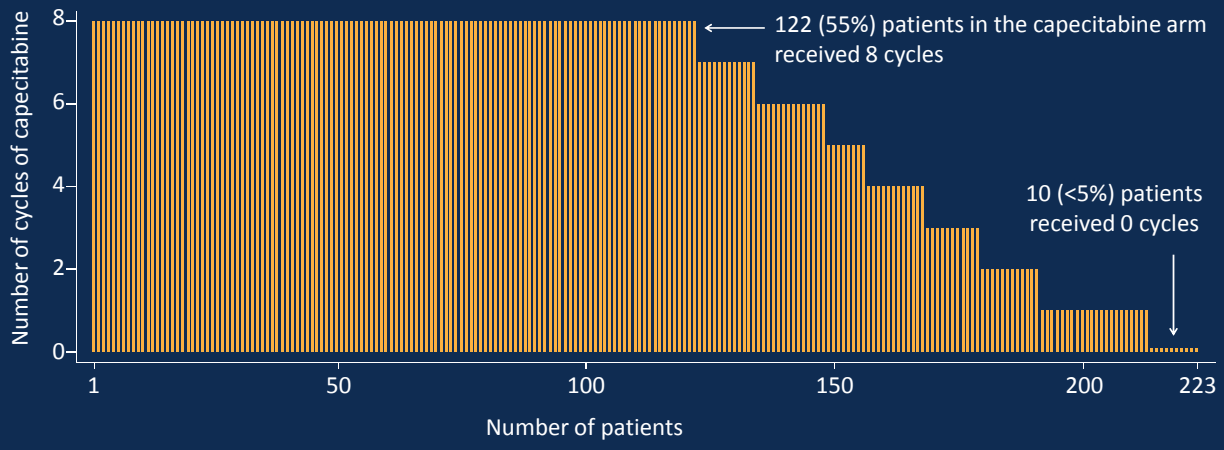
Baseline characteristics

		Observation arm (n=224)	Capecitabine arm (n=223)
Gender	Male	113 (50%)	111 (50%)
Age	Median years (inter-quartile range)	64 (55-69)	62 (55-68)
Tumour site	Intrahepatic CC	41 (18%)	43 (19%)
	Hilar CC	63 (28%)	65 (29%)
	Muscle invasive gall bladder carcinoma	40 (18%)	39 (17%)
	Lower common bile duct CC	80 (36%)	76 (34%)
Resection status	R0	140 (63%)	139 (62%)
	R1	84 (38%)	84 (38%)
ECOG performance status	0	101 (45%)	100 (45%)
	1	116 (52%)	116 (52%)
	2	7 (3%)	7 (3%)
Tumour size	Median mm (inter-quartile range)	25 (20-44)	25 (19-45)
Lymph node status	N0	108 (48%)	100 (45%)
	N1	102 (46%)	108 (48%)
	NX	14 (6%)	15 (7%)

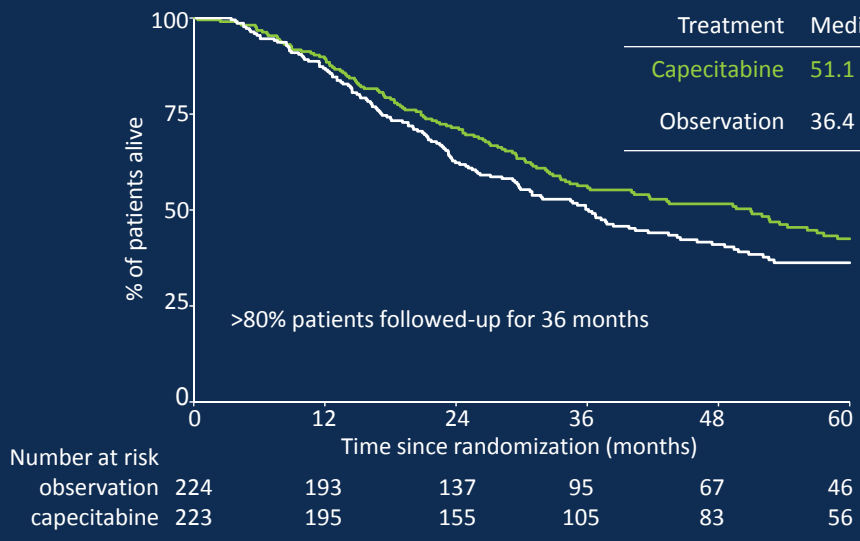
Values shown are n (%) for categorical data, and median (IQR) for continuous measures

Treatment compliance

- Median capecitabine dose was 1250mg/kg twice daily (IQR 1061 - 1250mg/kg)



OS in the ITT population



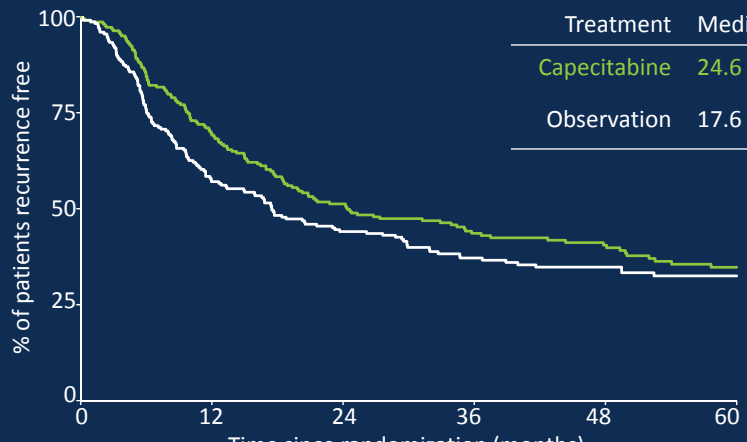
Treatment	Median OS (95% CI)	HR (95% CI)
Capecitabine	51.1 months (34.6-59.1)	0.81 (0.63-1.04) p=0.097
Observation	36.4 months (29.7-44.5)	

Sensitivity analyses

Adjusting for further prognostic factors (nodal status, disease grade, gender)

HR 0.70 (95% CI 0.55-0.91) p=0.007

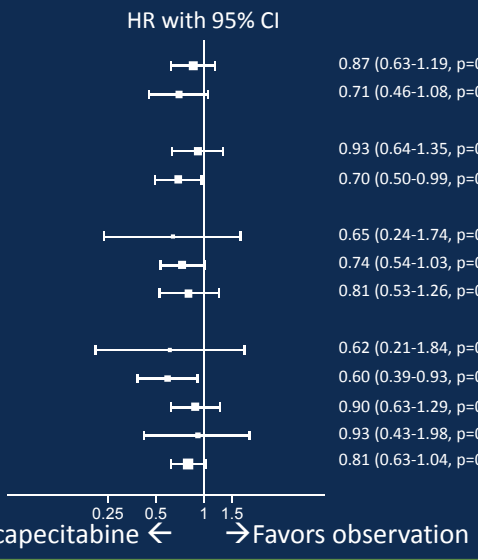
RFS in the ITT population



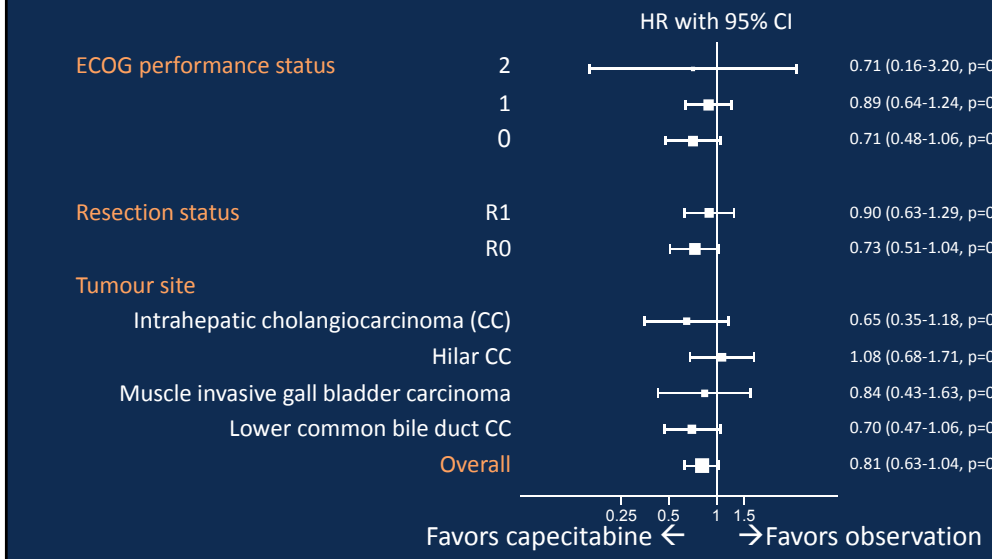
Treatment	Median RFS (95% CI)	HR (95% CI)
Capecitabine	24.6 months (18.9-36.7)	0.76 (0.58-0.99) p=0.039
Observation	17.6 months (12.8-27.6)	

Number at risk						
observation	224	126	92	67	52	37
capecitabine	223	148	108	78	62	43

Sub-group analyses; OS



Sub-group analyses; OS



Toxicity

Toxicity type	All grades n	All grades %	Grades 1 & 2 n	Grades 1 & 2 %	Grades 3&4 n	Grades 3&4 %
Fatigue	175	82	159	75	16	8
Plantar palmar erythema	174	82	130	61	44	21
Diarrhoea	137	64	121	57	16	8
Nausea	108	51	106	50	2	1
Mucositis/stomatitis	96	45	94	44	2	1
Vomiting	50	24	49	23	1	0.5
Neutropenia	49	23	45	21	4	2
Bilirubin	45	21	42	20	3	1
Thrombocytopenia	26	12	25	12	1	0.5
Alopecia	20	9	20	9	0	0

- Safety population* n=213 patients

Serious adverse events

- 93 SAEs reported
- ≥1 SAE in 69 (32%) of all patients
- Capecitabine arm; 64 in 47 patients
- Observation arm; 29 in 22 patients (of which 3 resulted in death)

Serious adverse reactions

- Capecitabine arm; 33 in 30 patients

*conditional on receiving capecitabine

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Conclusions

BILCAP

- Capecitabine as adjuvant improves OS in patients with resected biliary tract cancer from 36 to 51 months and should become standard of care in this setting
- Capecitabine toxicity was modest
- QoL was not reduced
- Capecitabine should be the control arm in future adjuvant trials in patients with biliary tract cancer

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Immune therapy in Gastric Cancer
Abstract: 4014

Nivolumab ± Ipilimumab in Patients With Advanced/Metastatic Chemotherapy-Refractory Gastric, Esophageal, or Gastroesophageal Junction Cancer: CheckMate 032 Study

Yelena Y. Janjigian,[1] Patrick A. Ott,[2] Emiliano Calvo,[3] Joseph W. Kim,[4] Paolo A. Ascierto,[5] Padmanee Sharma,[6] Katriina Peltola,[7] Dirk Jaeger,[8] Jeffrey Evans,[9] Filippo de Braud,[10] Ian Chau,[11] Marina Tschaika,[12] Christopher T. Harbison,[12] Weiguo Cai,[12] Johanna Bendell,[13] Dung T. Le[14]

[1]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Dana-Farber Cancer Institute, Boston, MA; [3]START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; [4]Yale Cancer Center, New Haven, CT; [5]Istituto Nazionale Tumori IRCCS, Naples, Italy; [6]The University of Texas MD Anderson Cancer Center, Houston, TX; [7]Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; [8]National Center for Tumor Diseases, University Hospitals Heidelberg, Heidelberg, Germany; [9]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK; [10]Fondazione IRCCS Istituto Tumori Milano, University of Milan, Milan, Italy; [11]Royal Marsden Hospital, London and Surrey, UK; [12]Bristol-Myers Squibb, Princeton, NJ; [13]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [14]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17

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Background

- Nivolumab improved OS vs placebo in Asian patients with gastric/GEJ cancer with ≥ 2 prior treatments (ATTRACTION-2 phase 3 study)[1]
  - **27% vs 11% of patients alive at 1 year (HR, 0.63; *P* < 0.0001)**
- Nivolumab alone or in combination with ipilimumab led to encouraging results in a similar population of Western patients (CheckMate 032 phase 1/2 study)[2,3]
- Here we present **longer-term updated survival, efficacy, and safety** data from **CheckMate 032**

GEJ, gastroesophageal junction.

1. Kang YK, et al. ASCO-GI 2017 [abstract 2]; 2. Janjigian YY, et al. ASCO 2016 [abstract 4010]; 3. https://clinicaltrials.gov/ct2/show/study/NCT01928394 (Accessed April 21, 2017).

Checkmate 032 EG Cohort

Western patients with advanced/metastatic EG cancer with progression on ≥1 prior chemotherapy
N = 160

Nivolumab 3 mg/kg IV Q2W (NIVO 3)	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W* (NIVO 1 + IPI 3)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W* (NIVO 3 + IPI 1)
Median (range) follow-up, mo†: 28 (17 to 35)	24 (21 to 33)	22 (19 to 25)

Primary endpoint:
- ORR per RECIST v1.1

Secondary endpoints:
- OS, PFS, TTR, DOR
- Safety

Exploratory endpoint:
- PD-L1 tumor expression (Dako 28-8 pharmDx assay)

DOR, duration of response; EG, esophagogastric (including gastric/esophageal/gastroesophageal junction cancer); TTR, time to response.
* Nivolumab + ipilimumab administered for 4 cycles followed by nivolumab 3 mg/kg IV Q2W.
† Time from first dose to data cut-off; follow-up was shorter for patients who died prior to data cut-off.

Baseline Characteristics

Patients, n (%)	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
Age, median (range), years	60 (29 to 80)	53 (27 to 77)	58 (19 to 81)
≥65 years	17 (29)	10 (20)	17 (33)
Male	45 (76)	34 (69)	45 (87)
Race			
White	56 (95)	46 (94)	50 (96)
Black	3 (5)	1 (2)	1 (2)
Asian/other	0	2 (4)	1 (2)
Primary site			
Gastric	19 (32)	22 (45)	18 (35)
GEJ/esophageal	40 (68)	27 (55)	34 (65)
Number of prior regimens			
0	0	1 (2)	0
1	10 (17)	6 (12)	16 (31)
2	**20 (34)**	**19 (39)**	**16 (31)**
3	**19 (32)**	**11 (22)**	**13 (25)**
>3	**10 (17)**	**12 (24)**	**7 (13)**
PD-L1 tumor expression, n/N (%)*			
≥1%	16/42 (38)	10/42 (24)	13/43 (30)
<1%	**26/42 (62)**	**32/42 (76)**	**30/43 (70)**

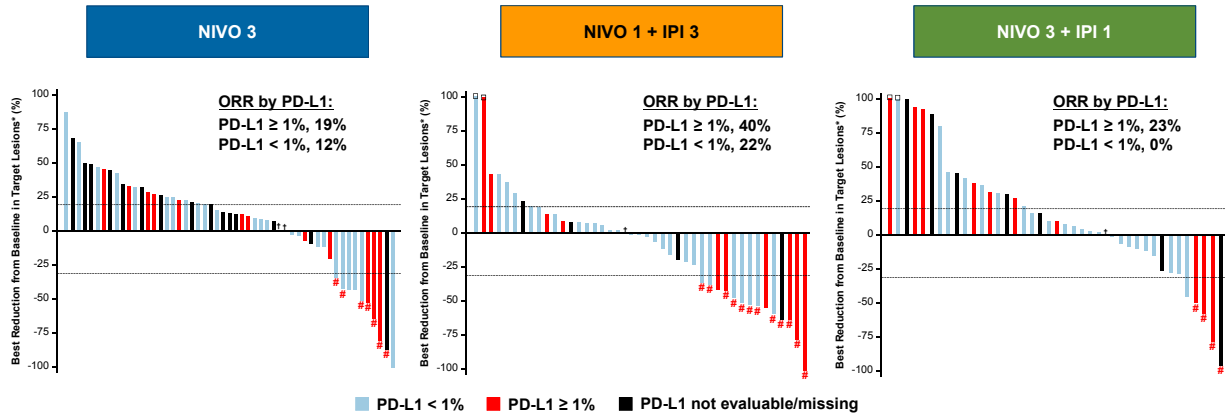
* PD-L1 tumor expression rates reported according to the number of patients with quantifiable samples. PD-L1 was quantifiable in 71%, 86%, and 83% of patients in the NIVO 3, NIVO 1 + IPI 3, and NIVO 3 + IPI 1 treatment groups, respectively.

Objective Response

	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
ORR, n (%)*	**7 (12)**	**12 (24)**	**4 (8)**
[95% CI]	[5, 23]	[13, 39]	[2, 19]
BOR, n (%)*			
Complete response	1 (2)	1 (2)	0
Partial response	6 (10)	11 (22)	4 (8)
Stable disease	12 (20)	8 (16)	15 (29)
Progressive disease	34 (58)	23 (47)	24 (46)
Not evaluable	6 (10)	6 (12)	9 (17)
DCR, n (%)†	19 (32)	20 (41)	19 (37)
Median TTR (range), months	1.6 (1.2 to 4.0)	2.7 (1.2 to 14.5)	2.6 (1.3 to 2.8)
Median DOR (95% CI), months	7.1 (3.0, 13.2)	7.9 (2.8, NE)	NR (2.5, NE)

BOR, best objective response; DCR, disease control rate; NR, not reached, NE, not estimable.
* Investigator review.
† Patients with a BOR of complete response, partial response, or stable disease.

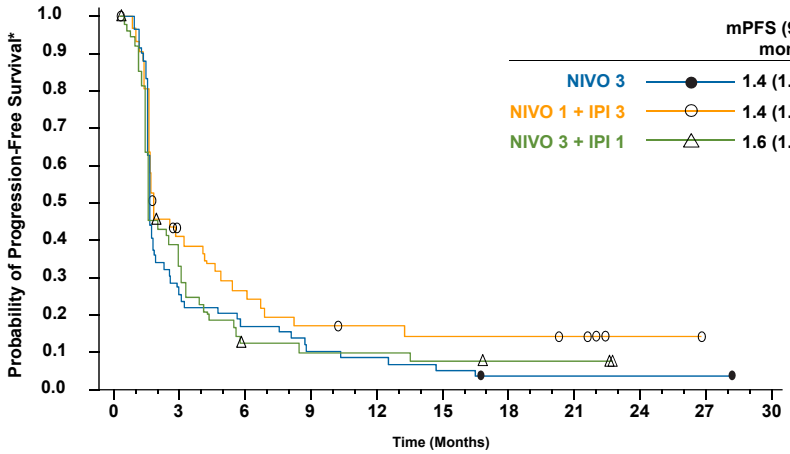
Best Reduction in Target Lesions



- Responses were observed regardless of PD-L1 expression

* Investigator review.
# Patients with confirmed response (complete or partial response).
† Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥1% (NIVO 3, n=2; NIVO 3 + IPI 1, n=1) and 1 patient with PD-L1 <1% (NIVO 1 + IPI 3).
□ change truncated to 100%

Progression-Free Survival



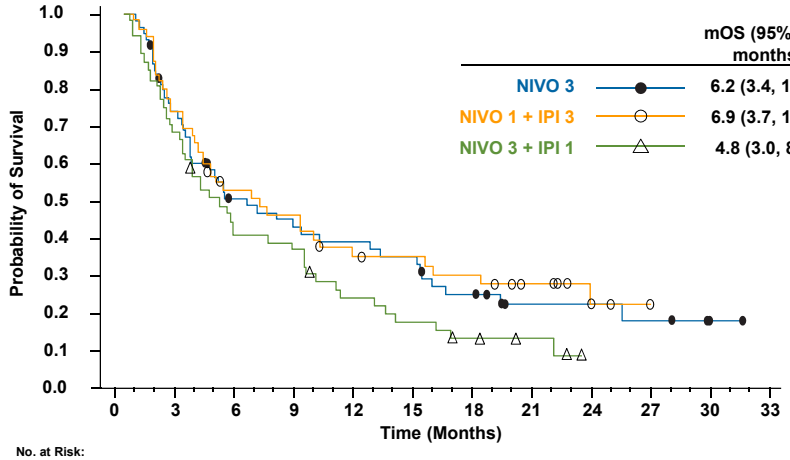
	mPFS (95% CI), months	6-month PFS rate, %	12-month PFS rate, %
NIVO 3	1.4 (1.2, 1.5)	17	8
NIVO 1 + IPI 3	1.4 (1.2, 3.8)	24	17
NIVO 3 + IPI 1	1.6 (1.4, 2.6)	12	10

No. at Risk:

NIVO 3	59	13	10	6	5	3	1	1	1	1	0
NIVO 1 + IPI 3	49	16	10	7	6	5	5	4	1	0	0
NIVO 3 + IPI 1	52	13	5	4	4	3	2	2	0	0	0

mPFS, median PFS
* Investigator review.

Overall Survival



	mOS (95% CI), months	12-month OS rate, %	18-month OS rate, %
NIVO 3	6.2 (3.4, 12.4)	39	25
NIVO 1 + IPI 3	6.9 (3.7, 11.5)	35	28
NIVO 3 + IPI 1	4.8 (3.0, 8.4)	24	13

No. at Risk:

NIVO 3	59	40	26	21	20	15	11	5	5	4	1	0
NIVO 1 + IPI 3	49	35	24	19	14	14	11	8	3	0	0	0
NIVO 3 + IPI 1	52	33	20	18	11	8	4	3	0	0	0	0

mOS, median OS.

Treatment-Related Adverse Events

Patients, n (%)	NIVO 3 n = 59		NIVO 1 + IPI 3 n = 49		NIVO 3 + IPI 1 n = 52	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAE	41 (69)	10 (17)	41 (84)	23 (47)	39 (75)	14 (27)
Serious TRAEs	**6 (10)**	**3 (5)**	**21 (43)**	**17 (35)**	**13 (25)**	**9 (17)**
TRAEs leading to treatment discontinuation	2 (3)	2 (3)	10 (20)	10 (20)	7 (13)	5 (10)
TRAEs in ≥15% of patients in any treatment arm						
ALT increased	5 (8)	2 (3)	8 (16)	7 (14)	5 (10)	2 (4)
AST increased	7 (12)	3 (5)	8 (16)	5 (10)	2 (4)	1 (2)
Decreased appetite	9 (15)	0	5 (10)	0	3 (6)	0
Diarrhea	9 (15)	1 (2)	15 (31)	7 (14)	5 (10)	1 (2)
Fatigue	20 (34)	1 (2)	14 (29)	3 (6)	10 (19)	0
Pruritus	10 (17)	0	9 (18)	1 (2)	12 (23)	0
Rash	5 (8)	0	10 (20)	0	8 (15)	0

- One grade 5 TRAE was reported (tumor lysis syndrome in a patient treated with NIVO 3 + IPI 1)

TRAE, treatment-related adverse event.

Conclusions

- Nivolumab alone or in combination with ipilimumab demonstrates clinical activity in patients with chemotherapy-refractory EG cancer irrespective of PD-L1 status
- Safety profile is consistent with prior reports[1-4]
- Nivolumab alone and in combination with ipilimumab are being investigated in phase 3 studies in patients with advanced EG cancer

1. Janjigian YY, et al. ASCO 2016 [abstract 4010]; 2. Larkin J, et al. *N Engl J Med.* 2015;373:23-34; 3. Wolchok JD, et al. *N Engl J Med.* 2013;369:122-133; 4. Antonia SJ, et al. *Lancet Oncol.* 2016;17:883-895.