GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

PRACTICE CHANGING STUDIES IN GI CANCERS IN 2018

Fortunato Ciardiello

Professor of Medical Oncology,
Dean, School of Medicine and Surgery,
Department of Precision Medicine,
University of Campania Luigi Vanvitelli, Naples, Italy

CONFLICT OF INTEREST DISCLOSURE

Receipt of honoraria or consultation fees for speaker, consultancy or advisory roles: Amgen, Bayer, Bristol-Myers Squibb, Celgene, Merck Serono, Pfizer, Roche, Servier

Direct research funding as the principal investigator for institutional research projects: Amgen, Bayer, Merck Serono, Roche, Ipsen

Institutional financial interests, financial support for clinical trials or contracted research: Merck Serono, Roche, Symphogen, Array

Leadership Positions in Professional Societies (non financial interests): ESMO Past-President (2018-19), President of the Associazione Italiana di Oncologia Toracica (2018-22)

PRACTICE CHANGING STUDIES IN 2018:

Focus on:

- Adjuvant therapy for pancreatic cancer
- Therapy for chemorefractory metastatic gastric cancer
- Immunotherapy for metastatic colorectal cancer (success and failure)
- Molecular targeted therapy for molecularly selected metastatic colorectal cancer (BRAF mutation as a driver)

What clinical research evidence does really change medical oncology practice?

PRACTICE CHANGING STUDIES IN 2018:

Focus on:

- **Adjuvant therapy for pancreatic cancer**
- Therapy for chemorefractory metastatic gastric cancer
- Immunotherapy for metastatic colorectal cancer (success and failure)
- Molecular targeted therapy for molecularly selected metastatic colorectal cancer (BRAF mutation as a driver)

What clinical research evidence does really change medical oncology practice?

ESMO

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 20, 2018 VOL. 379 NO. 25

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J.-L. Raoul, L. Choné, E. Francois, P. Artru, J.J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, G. Breysacher, F. Di Fiore, C. Cripps, P. Kavan, P. Texereau, K. Bouhier-Leporrier, F. Khemissa-Akouz, J.-L. Legoux, B. Juzyna, S. Gourgou, C.J. O'Callaghan, C. Jouffroy-Zeller, P. Rat, D. Malka, F. Castan, and J.-B. Bachet, for the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group*

ABSTRACT

BACKGROUND

Among patients with metastatic pancreatic cancer, combination chemotherapy with fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) leads to longer overall survival than gemcitabine therapy. We compared the efficacy and safety of a modified FOLFIRINOX regimen with gemcitabine as adjuvant therapy in patients with resected pancreatic cancer.

METHODS

We randomly assigned 493 patients with resected pancreatic ductal adenocarcinoma to receive a modified FOLFIRINOX regimen (oxaliplatin [85 mg per square meter of body-surface area], irinotecan [180 mg per square meter, reduced to 150 mg per square meter after a protocol-specified safety analysis], leucovorin [400 mg per square meter], and fluorouracil [2400 mg per square meter] every 2 weeks) or gemcitabine (1000 mg per square meter on days 1, 8, and 15 every 4 weeks) for 24 weeks. The primary end point was disease-free survival. Secondary end points included overall survival and safety.

RESULTS

At a median follow-up of 33.6 months, the median disease-free survival was 21.6 months in the modified-FOLFIRINOX group and 12.8 months in the gemcitabine group (stratified hazard ratio for cancer-related event, second cancer, or death, 0.58; 95% confidence interval [CI], 0.46 to 0.73; P<0.001). The disease-free survival rate at 3 years was 39.7% in the modified-FOLFIRINOX group and 21.4% in the gemcitabine group. The median overall survival was 54.4 months in the modified-FOLFIRINOX group and 35.0 months in the gemcitabine group (stratified hazard ratio for death, 0.64; 95% CI, 0.48 to 0.86; P=0.003). The overall survival rate at 3 years was 63.4% in the modified-FOLFIRINOX group and 48.6% in the gemcitabine group. Adverse events of grade 3 or 4 occurred in 75.9% of the patients in the modified-FOLFIRINOX group and in 52.9% of those in the gemcitabine group. One patient in the gemcitabine group died from toxic effects (interstitial pneumonitis).

CONCLUSIONS

Adjuvant therapy with a modified FOLFIRINOX regimen led to significantly longer survival than gemcitabine among patients with resected pancreatic cancer, at the expense of a higher incidence of toxic effects. (Funded by R&D Unicancer and others; ClinicalTrials.gov number, NCT01526135; EudraCT number, 2011-002026-52.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Conroy at the Department of Medical Oncology, Institut de Cancérologie de Lorraine, 6 Ave. de Bourgogne, CS 30519, 54519 Vandoeuvre-lès-Nancy CEDEX, France, or at t.conroy@nancy.unicancer.fr.

*A complete list of the investigators in the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2018;379:2395-406.
DOI: 10.1056/NEJMoa1809775
Copyright © 2018 Massachusetts Medical Society.

PRODIGE 24/CCTG PA.6 trial: study design

NCT01526135

- R0 or R1 resected pancreatic cancer
- postoperative CT-scan mandatory
- CA19-9 level < 180 U/mL within 12 weeks after surgery

Stratification:
- center
- resection margin (R0 vs R1)
- CA19-9 level (≤ 90 vs 91-179 U/mL)
- pN0 (< 12 vs ≥ 12 examined nodes) vs pN1

RANDOMIZE

1:1

mFolfirinox

Oxaliplatin 85 mg/m², Leucovorin 400 mg/m²,
Irinotecan 180 mg/m²*, all at D1
Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours
Every 2 weeks; 12 cycles
**Reduced to 150 mg/m² after patient 162*

Gemcitabine

1000 mg/m², qw 3/4 *weeks;*
6 cycles

for both arms:
- 6 months of chemotherapy
- CT scans: every 3 months

Slides are the property of the author, permission required for reuse

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Modified FOLFIRINOX (N=247)	Gemcitabine (N=246)
Age		
Median (range) — yr	63 (30–79)	64 (30–81)
≥70 yr — no. (%)	47 (19.0)	54 (22.0)
Male sex — no. (%)	142 (57.5)	135 (54.9)
WHO performance-status score — no./total no. (%)†		
0	122/245 (49.8)	127/242 (52.5)
1	123/245 (50.2)	115/242 (47.5)
Status of surgical margins — no. (%)‡		
R0	148 (59.9)	134 (54.5)
R1	99 (40.1)	112 (45.5)
Tumor histologic findings — no./total no. (%)		
Ductal adenocarcinoma	244/247 (98.8)	242/245 (98.8)
Nonductal carcinoma	3/247 (1.2)	3/245 (1.2)
Tumor stage — no. (%)§		
I	12 (4.9)	14 (5.7)
IIA	43 (17.4)	47 (19.1)
IIB	183 (74.1)	179 (72.8)
III	1 (0.4)	1 (0.4)
IV	8 (3.2)	5 (2.0)
Lymphovascular invasion — no./total no. (%)	154/209 (73.7)	135/214 (63.1)
Perineural invasion — no. (%)	205/221 (92.8)	207/231 (89.6)
Surgery		
Venous resection — no./total no. (%)	53/245 (21.6)	69/245 (28.2)
Portal-vein resection — no. (%)	32 (13.0)	42 (17.1)
Superior-mesenteric-vein resection — no. (%)	19 (7.7)	25 (10.2)
Arterial resection — no./total no. (%)	8/247 (3.2)	7/245 (2.9)

* Patients in the modified-FOLFIRINOX group received fluorouracil (without bolus), leucovorin, irinotecan, and oxaliplatin. There were no significant differences between the two treatment groups, except for lymphovascular invasion (P=0.02).
† Scores for the World Health Organization (WHO) performance status are assessed on a 5-point scale, with higher numbers indicating greater disability; a score of 0 indicates that the patient is fully active and able to carry on activities without restriction, and a score of 1 that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out light work.
‡ A surgical margin of R0 indicates that no cancer cells were present within 1 mm of all resection margins, and R1 the presence of cancer cells within 1 mm of one or more resection margins.
§ Tumor stage was assessed according to the 2009 tumor–node–metastasis (TNM) classification, 7th edition.[19]

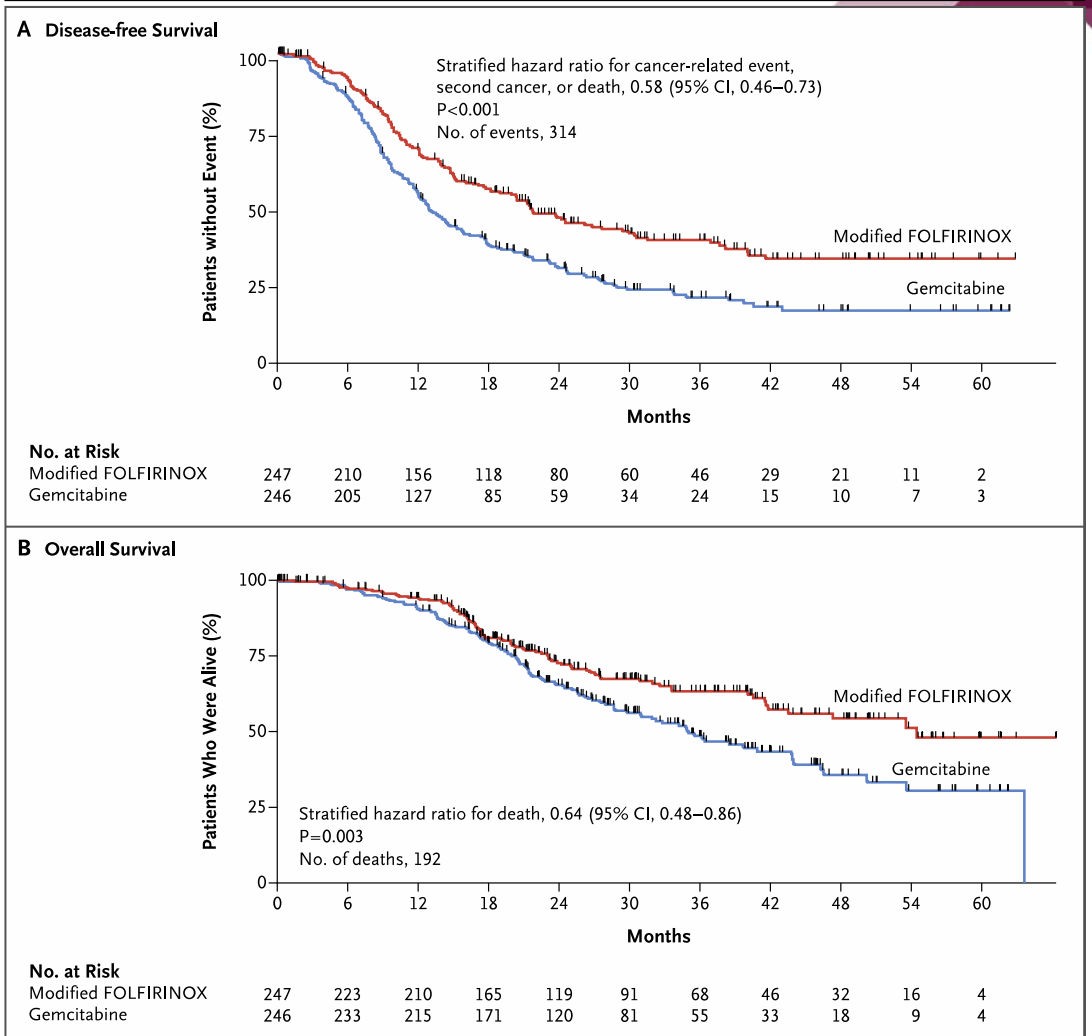


Figure 2. Kaplan–Meier Estimates of Disease-free Survival and Overall Survival in the Intention-to-Treat Population, According to Treatment Group.

The median disease-free survival was 21.6 months in the modified-FOLFIRINOX group, as compared with 12.8 months in the gemcitabine group (Panel A). The median overall survival was 54.4 months in the modified-FOLFIRINOX group, as compared with 35.0 months in the gemcitabine group (Panel B). Tick marks indicate censored data.

Six-month treatment completion

	mFolfirinox No = 238	Gemcitabine No = 243	P
All cycles of chemotherapy	66.4%	79.0%	0.002
Planned administrations	12	18	—
Median No. administrations	12 [1-12]	18 [1-18]	
No. administrations delayed	14.4%	3.9%	< 0.001
Relative dose-intensity > 0.70	48.7%	91.4%	< 0.001
Early stop	80 (33.6%)	51 (21.0%)	0.002
due to :			
- relapse	15 (6.3%)	26 (10.7%)	
- toxicity	21 (8.8%)	11 (4.5%)	
- Principal Investigator's decision	7 (2.9%)	2 (0.8%)	
- patient decision	13 (5.4%)	2 (0.8%)	

Safety: hematologic AEs

Grade 3-4 adverse events, % per patient	mFolfirinox N=238	Gemcitabine N=243	p
Anemia	0.0%	0.4%	1.00
Neutropenia	28.4 %	26.0 %	0.56
G-CSF use	59.9 %	3.7 %	<0.001
Febrile neutropenia	2.9 %	3.7 %	0.65
Lymphopenia	1.3 %	2.9 %	0.34
Thrombocytopenia	1.3 %	4.5 %	0.03

Slides are the property of the author, permission required for reuse.

Safety: main nonhematologic AEs

AE, % per patient	mFolfirinox N=238		Gemcitabine N=243		p-value all grades
	All grades	Grade 3/4	All grades	Grade 3/4	
Diarrhea	84.4 %	18.6 %*	49 %	3.7 %	< 0.001
Sensory peripheral neuropathy	61.2 %	9.3 %	8.7 %	-	< 0.001
Fatigue	84 %	11 %	77.6 %	4.6 %	0.003
Vomiting	46 %	5 %	29 %	1.2 %	< 0.001
Mucositis	33.8 %	2.5 %	14.9 %	0 %	< 0.001
Alopecia	27 %	-	19.5 %	-	0.07
Hand-foot syndrome	5 %	0.4 %	0.8 %	-	0.023

* 8.6% during cycle 1; 6.3% during cycle 2; 3% at cycles 3-5; 1% at cycles 6-12
Grade 3-4 diarrhea is significantly related to a higher number of lymph nodes examined, p = 0.02.

Slides are the property of the author; permission required for reuse.

PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

Conclusions

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

- **Adjuvant chemotherapy with mFOLFIRINOX in resected PC patients is superior to Gem, with significantly improved Disease-Free Survival, Metastasis-free Survival, Specific Survival and Overall Survival**
- **Its superiority is observed in all predefined subgroups**
- **mFOLFIRINOX is more toxic than Gem, but is a safe regimen with manageable toxicities**
- **mFOLFIRINOX should now be considered a new standard of care after pancreatic cancer resection in patients with good performance status, at least in Western countries**

Slides are the property of the author, permission required for reuse.

PRACTICE CHANGING STUDIES IN 2018:

Focus on:

- Adjuvant therapy for pancreatic cancer
- **Therapy for chemorefractory metastatic gastric cancer**
- Immunotherapy for metastatic colorectal cancer (success and failure)
- Molecular targeted therapy for molecularly selected metastatic colorectal cancer (BRAF mutation as a driver)

What clinical research evidence does really change medical oncology practice?

TAS102 GASTRIC STUDY
tags

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
WORLD CONGRESS ON Gastrointestinal Cancer

20–23 June 2018
Barcelona SPAIN

Overall Survival Results from a Phase III Trial of Trifluridine/Tipiracil vs Placebo in Patients with Metastatic Gastric Cancer Refractory to Standard Therapies (TAGS)

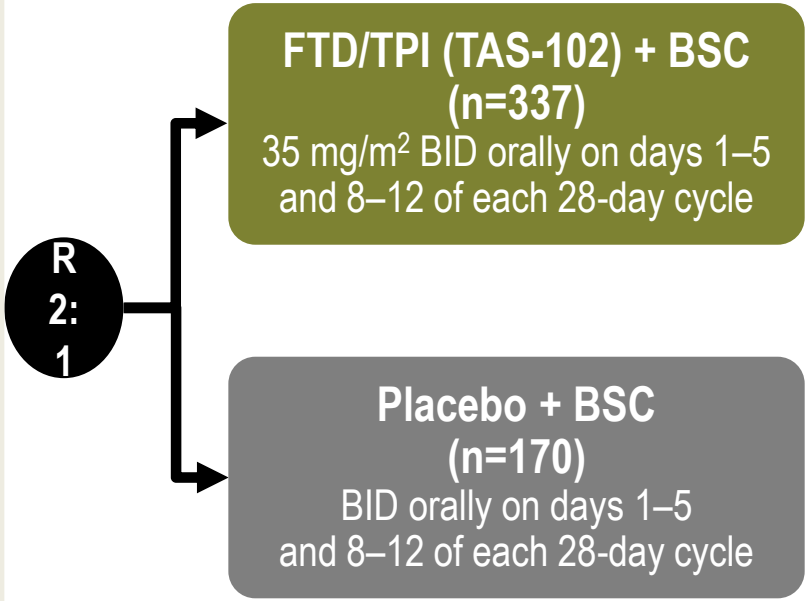
Josep Tabernero,[1] Kohei Shitara,[2] Mikhail Dvorkin,[3] Wasat Mansoor,[4] Hendrik-Tobias Arkenau,[5] Aliaksandr Prokharau,[6] Maria Alsina,[1] Michele Ghidini,[7] Catia Faustino,[8] Vera Gorbunova,[9] Edvard Zhavrid,[10] Kazuhiro Nishikawa,[11] Ayumu Hosokawa,[12] Doina Ganea,[13] Şuayib Yalçın,[14] Kazumasa Fujitani,[15] Giordano D. Beretta,[16] Robert Winkler,[17] Lukas Makris,[18] Toshihiko Doi,[2] David H. Ilson[19]

[1]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [2]National Cancer Center Hospital East, Chiba, Japan; [3]Omsk Regional Clinical Centre of Oncology, Omsk, Russian Federation; [4]The Christie NHS Foundation Trust, Manchester, UK; [5]Sarah Cannon Research Institute, London, UK; [6]Minsk City Clinical Oncology Dispensary, Minsk, Belarus; [7]Azienda Ospedaliera di Cremona, Cremona, Italy; [8]Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal; [9]N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation; [10]Alexandrov National Cancer Centre of Belarus, Minsk, Belarus; [11]Osaka National Hospital, Osaka, Japan; [12]University of Toyoma, Toyoma, Japan; [13]Spitalul Judetean de Urgenta Sfantul Ioan cel Nou Suceava, Suceava, Romania; [14]Hacettepe University, Ankara, Turkey; [15]Osaka General Medical Center, Osaka, Japan; [16]Humanitas Gavazzeni, Bergamo, Italy; [17]Taiho Oncology, Inc., Princeton, NJ, USA; [18]Stathmi, Inc., New Hope, PA, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

TAGS: TAS-102 Gastric Study[a]

Patients with mGC
(including GEJ cancer)
- ≥2 prior regimens:
  - Fluoropyrimidine
  - Platinum
  - Taxane and/or irinotecan
  - HER2 inhibitor, if available, for HER2+ disease
  - Refractory to/intolerant of last prior therapy
- ECOG PS of 0 or 1
- Age ≥18 y (≥20 y in Japan)

Target sample size: 500



End points
- Primary:
  - OS
- Key secondary:
  - PFS, safety
- Other secondary:
  - ORR
  - DCR
  - QOL
  - Time to ECOG PS ≥2

- Treatment until progression, intolerable toxicity, or patient withdrawal
- Multicenter, randomized, double-blind, placebo-controlled, phase III study
  - **Stratification: ECOG PS (0 vs 1), region (Japan vs ROW), prior ramucirumab (yes vs no)**
  - **Sites: 18 countries, 110 sites; enrollment: February 2016 – January 2018**
  - **Data cutoff date: March 31, 2018**
  - **Target 384 events allowed detection of HR for death of 0.70 with 90% power at 1-sided type 1 error of 0.025**

BID, twice daily; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ORR, overall response rate; PFS, progression-free survival; QOL, quality of life; ROW, rest of world; [a]NCT02500043

Baseline Demographic and Disease Characteristics

		FTD/TPI (n=337)	Placebo (n=170)
Age, years; median (range)		64.0 (24–89)	62.5 (32–82)
Gender, %	Male	75	69
Geographic region, %	Japan	14	16
	ROW	86	84
ECOG PS, %	0	36	40
	1	64	60
Primary site, %	Gastric	71	71
	GEJ	29	28
	Both	0	1
Prior gastrectomy, %	Yes	44	44
Number of prior regimens, %	2	37	38
	3	40	35
	≥4	23	27

ITT population

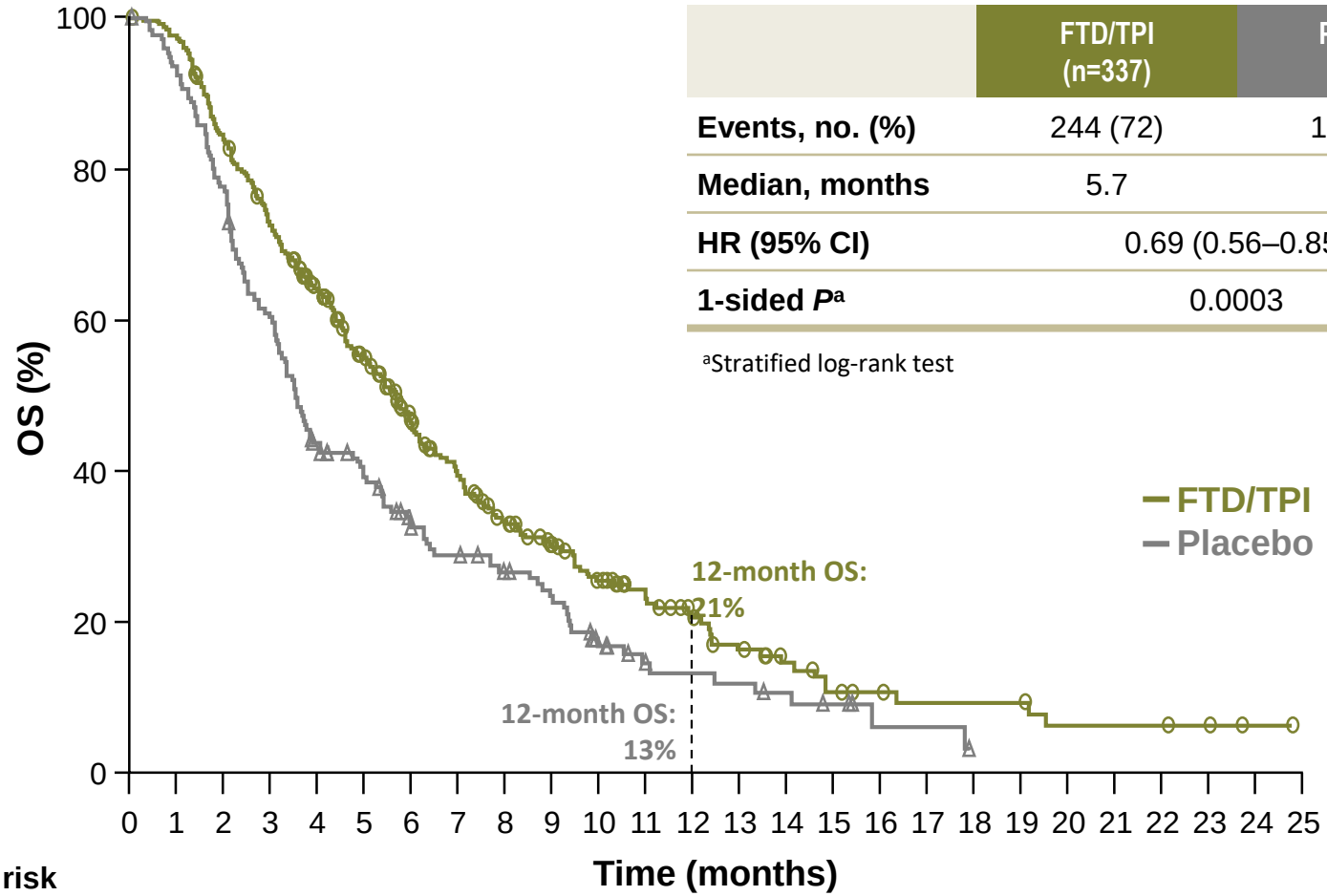
Baseline Disease Characteristics and Post-Study Therapy

		FTD/TPI (n=337)	Placebo (n=170)
Number of metastatic sites, %	1–2	46	42
	≥3	54	58
HER2 status, %	Positive	20	16
	Negative	61	62
	Not assessed	18	22
Prior systemic cancer therapeutic agents, %	Fluoropyrimidine	>99[a]	100
	Platinum	100	100
	Irinotecan[b]	54	58
	Taxane[b]	92	87
	Ramucirumab	34	32
	Anti-HER2 therapy	18	14
	Immunotherapy (anti-PD-1/PD-L1)	7	4
Post-study systemic anticancer therapy, %		25	26

ITT population; PD-1, programmed death-1; PD-L1, programmed death-ligand 1

[a]1 patient did not receive a fluoropyrimidine; [b]All patients received irinotecan or taxane or both

Primary Endpoint – OS

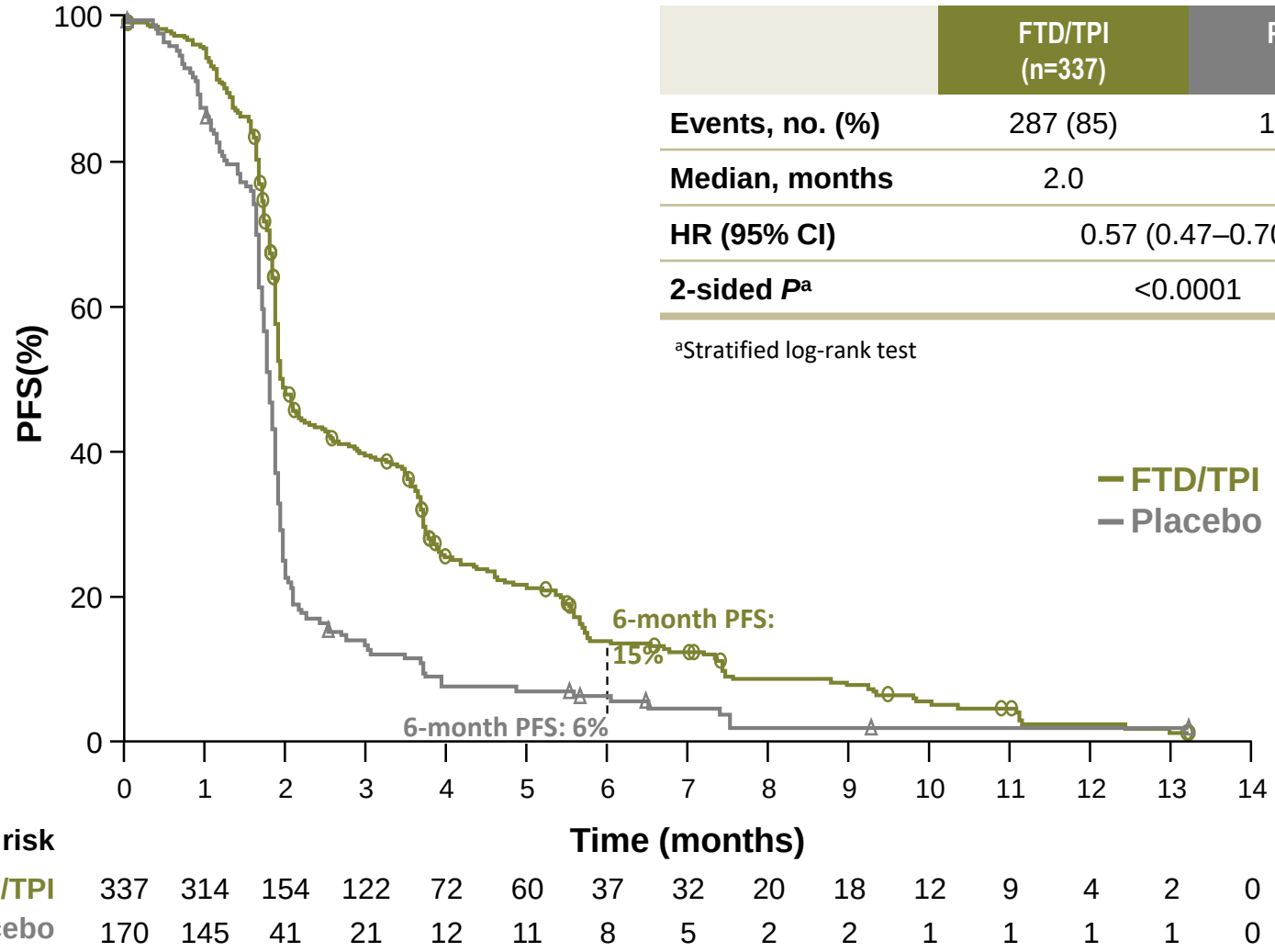


	FTD/TPI (n=337)	Placebo (n=170)
Events, no. (%)	244 (72)	140 (82)
Median, months	5.7	3.6
HR (95% CI)	0.69 (0.56–0.85)	
1-sided *P*[a]	0.0003	

[a]Stratified log-rank test

ITT population

Secondary Endpoint – PFS



	FTD/TPI (n=337)	Placebo (n=170)
Events, no. (%)	287 (85)	156 (92)
Median, months	2.0	1.8
HR (95% CI)	0.57 (0.47–0.70)	
2-sided *P*[a]	<0.0001	

[a]Stratified log-rank test

ITT population

Conclusions

- FTD/TPI showed a clinically meaningful and statistically significant improvement in OS and PFS compared with placebo in heavily pretreated mGC
  - 31% reduction in risk of death (HR, 0.69; 95% CI, 0.56–0.85; *P*=0.0003)
  - 2.1-month improvement in median OS (5.7 vs 3.6 months)
- FTD/TPI showed a predictable and manageable safety profile, consistent with that seen previously in patients with mCRC
  - No new safety signals were observed in patients with mGC
- FTD/TPI represents an effective treatment option with a manageable safety profile for patients with heavily pretreated mGC

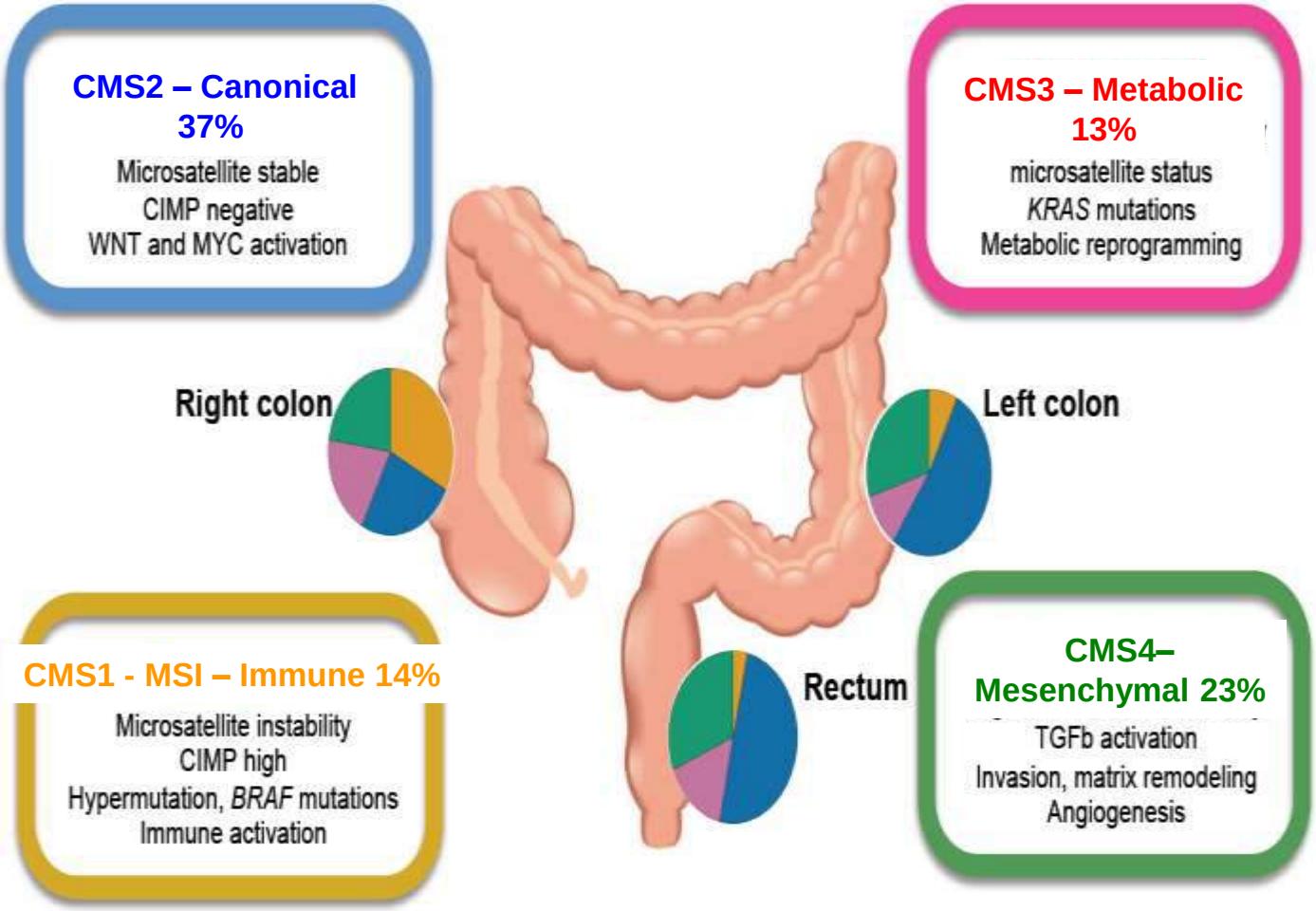
PRACTICE CHANGING STUDIES IN 2018:

Focus on:

- Adjuvant therapy for pancreatic cancer
- Therapy for chemorefractory metastatic gastric cancer
- **Immunotherapy for metastatic colorectal cancer (success and failure)**
- Molecular targeted therapy for molecularly selected metastatic colorectal cancer (BRAF mutation as a driver)

What clinical research evidence does really change medical oncology practice?

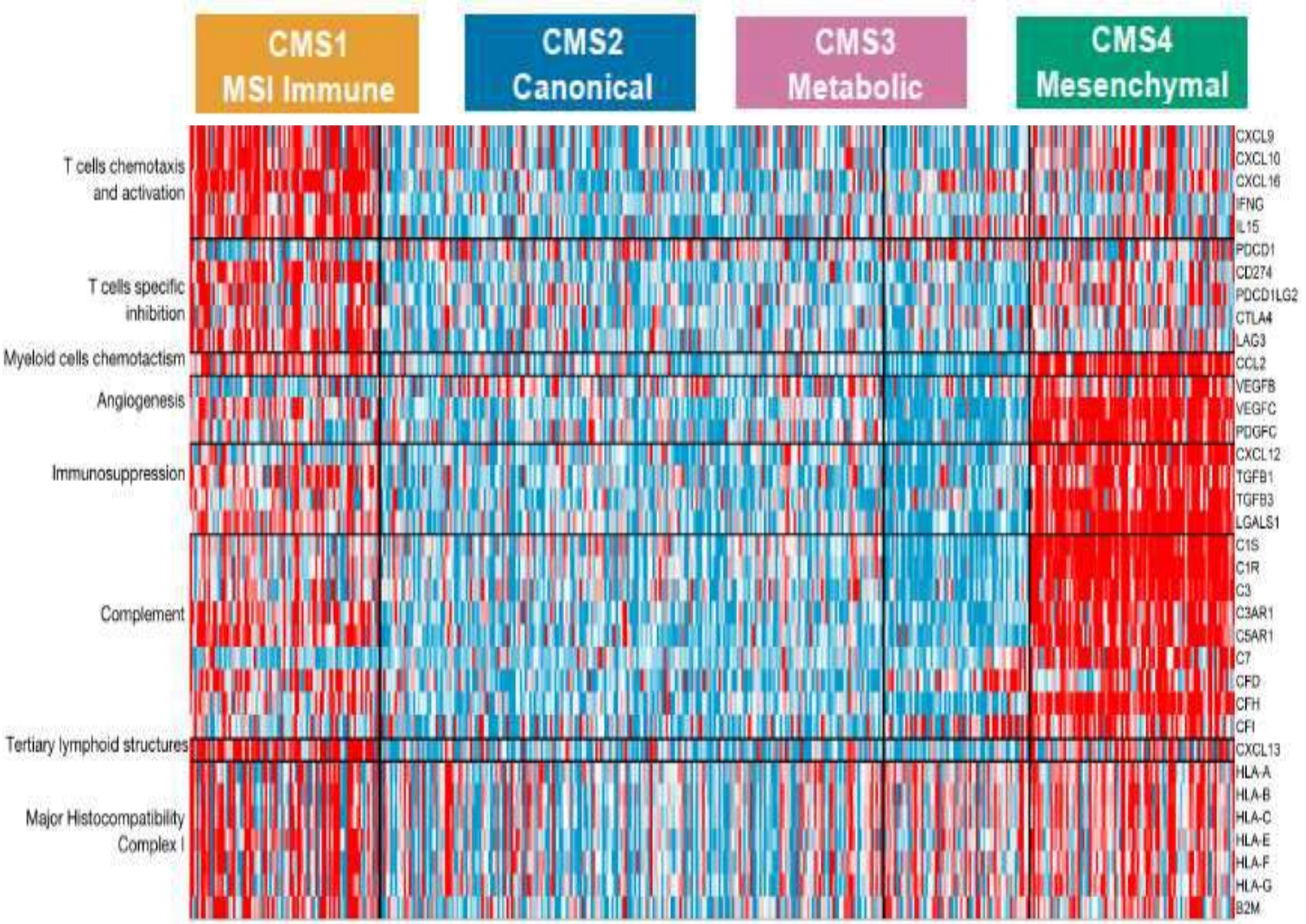
CMS subtypes – clinical and molecular correlates



Guinney J, Dienstmann R et al. Nat Med 2015

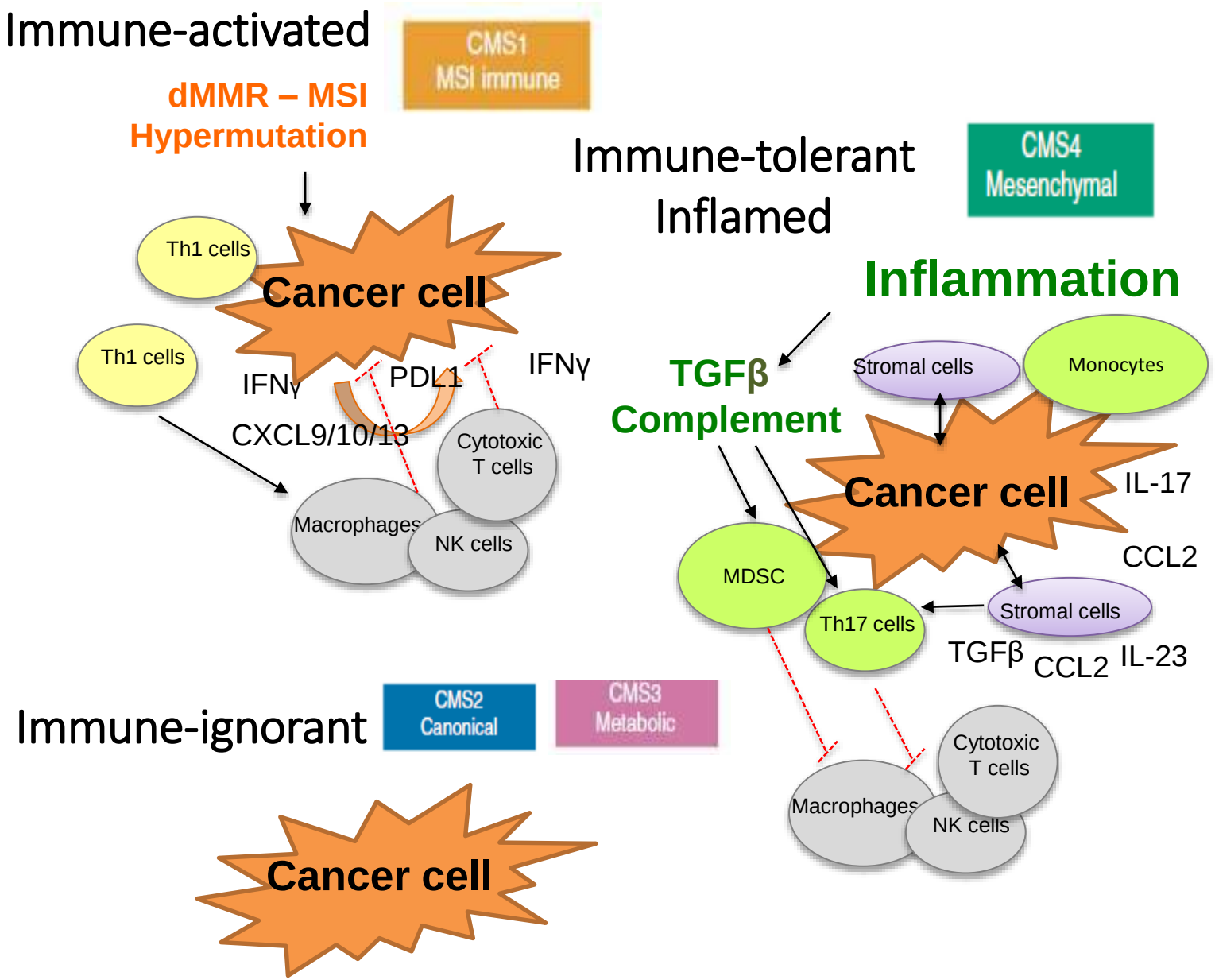
Immune vs Transcriptomic subtypes of CRC

Supervised immune infiltration analysis



Becht E et al, Clin Cancer Res 2016

Immune vs Transcriptomic subtypes of CRC



HIGHLY CONFIDENTIAL

Durable Clinical Benefit With Nivolumab Plus Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer

Heinz-Josef Lenz,[1] Eric Van Cutsem,[2] Maria Luisa Limon,[3] Ka Yeung Mark Wong,[4] Alain Hendlisz,[5] Massimo Aglietta,[6] Pilar García-Alfonso,[7] Bart Neyns,[8] Gabriele Luppi,[9] Dana B. Cardin,[10] Tomislav Dragovich,[11] Usman Shah,[12] Ajlan Atasoy,[13] Roelien Postema,[13] Zachary Boyd,[13] Jean-Marie Ledeine,[13] Michael James Overman,[14] Sara Lonardi[15]

[1]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [2]University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; [3]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [4]Westmead Hospital, Sydney, Australia; [5]Institut Jules Bordet, Brussels, Belgium; [6]Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; [7]Hospital Gral Universitario Gregorio Marañon, Madrid, Spain; [8]University Hospital Brussels, Brussels, Belgium; [9]University Hospital of Modena, Modena, Italy; [10]Vanderbilt – Ingram Cancer Center, Nashville, TN, USA; [11]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [12]Lehigh Valley Hospital, Allentown, PA, USA; [13]Bristol-Myers Squibb, Princeton, NJ, USA; [14]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [15]Istituto Oncologico Vento IOV-IRCSS, Padova, Italy

Presentation number: LBA18_PR

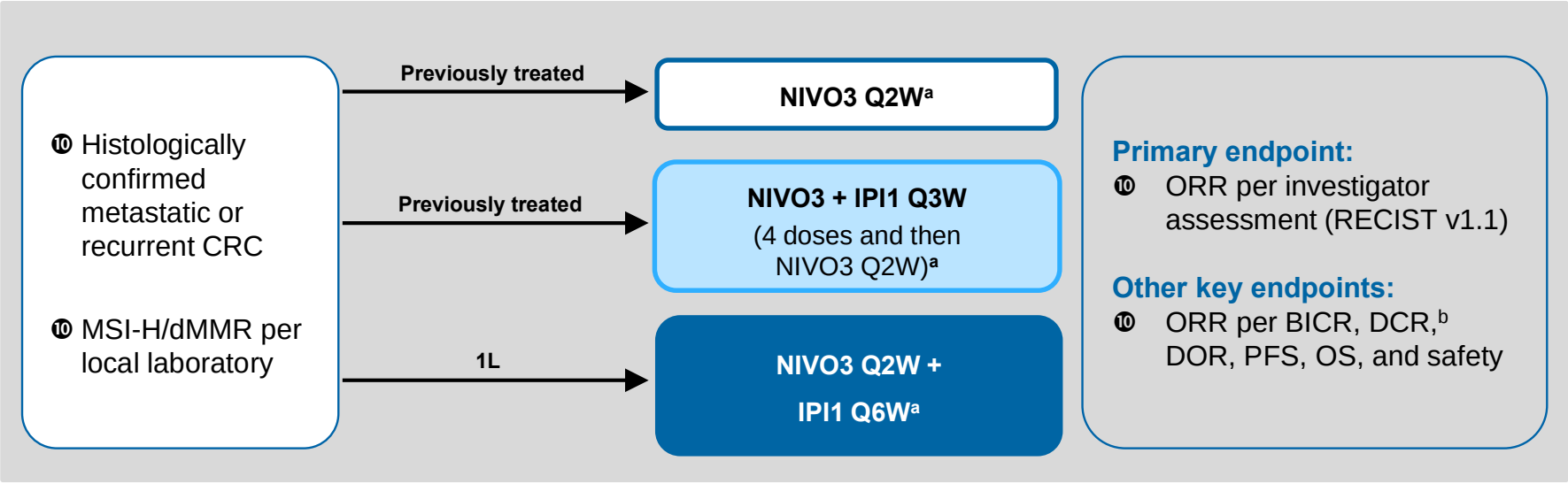
Introduction: CheckMate 142

- In CheckMate 142, nivolumab plus low-dose (1 mg/kg) ipilimumab provided improved clinical benefit relative to nivolumab monotherapy, with a favorable benefit-risk profile, in previously treated patients with MSI-H/dMMR mCRC[a,1]
  - ORR, 55% vs. 31%; 12-month OS rate, 85% vs. 73%, respectively
  - Grade 3–4 TRAEs, 32% vs. 20%; discontinuation due to any grade TRAEs, 13% vs. 7%, respectively
- Based on these results, nivolumab received accelerated FDA approval as a single agent or in combination with ipilimumab in patients with MSI-H/dMMR mCRC who progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan[2]
- Here we report the first results of the efficacy and safety of nivolumab plus low-dose ipilimumab as a 1L therapy for patients with MSI-H/dMMR mCRC from CheckMate 142

[a]Indirect comparisons; CheckMate 142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison
FDA = Food and Drug Administration; ORR = objective response rate; OS = overall survival; TRAEs = treatment-related adverse events
1. Overman MJ, et al. *J Clin Oncol* 2018;8:773–779; 2. OPDIVO® (nivolumab) [prescribing information]. Bristol-Myers Squibb Co., 2018.

CheckMate 142 Study Design

- CheckMate 142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)



- Median follow-up for the 1L nivolumab plus low-dose ipilimumab cohort was 13.8 months (range, 9–19)[c]

[a]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; [b]Patients [illegible] divided by the number of treated patients; [c]Time from first dose to data cutoff

BICR = blinded independent central review; CR = complete response; CRC = colorectal cancer; DCR = disease control rate; DOR = duration of response; IPI1 = ipilimumab 1 mg/kg; NIVO3 = nivolumab 3 mg/kg; PFS = progression-free survival; PR = partial response; Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q6W = once every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

Baseline Characteristics

	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median age (range), years	66 (21–85)
Male, n (%)	23 (51)
ECOG performance status, n (%)	
0	25 (56)
1	20 (44)
Disease stage at diagnosis, n (%)[a]	
I–III	28 (62)
IV	17 (38)
Tumor PD-L1 expression at baseline, n (%)*	
≥ 1%	12 (27)
< 1%	26 (58)
Unknown	7 (16)
Mutation status, n (%)	
BRAF/KRAS wild type	13 (29)
BRAF mutation	17 (38)
KRAS mutation	10 (22)
Unknown	5 (11)
Lynch syndrome,[b] n (%)	
Yes	8 (18)
No	11 (24)
Unknown	26 (58)

*Percentages may not add up to 100% because of rounding
[a]All patients had stage IV disease at study entry; [b]Based on clinical records of patients at sites in countries where this reporting was permitted (excluded Italy)
BRAF = V-Raf murine sarcoma viral oncogene homolog B1; ECOG = Eastern Cooperative Oncology Group; *KRAS* = Kirsten rat sarcoma viral oncogene homolog

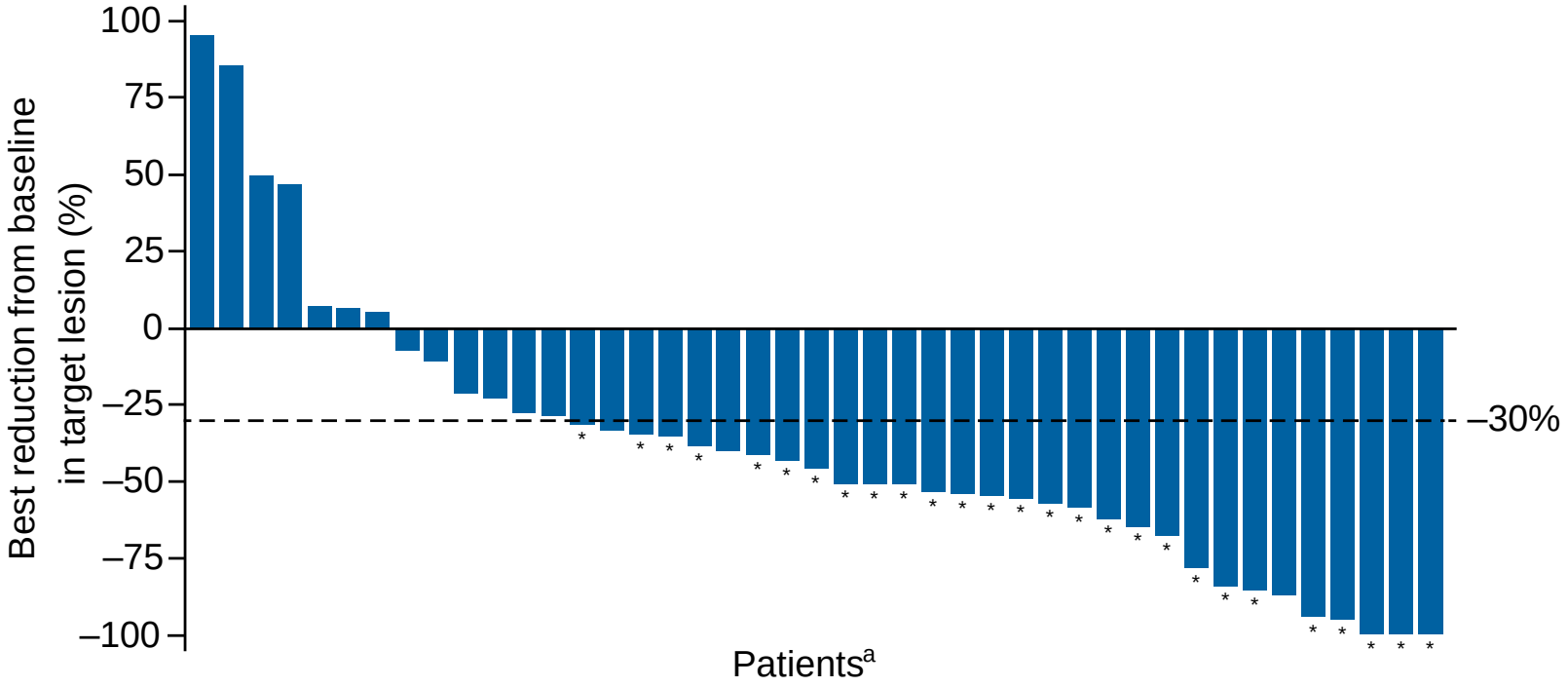
Response and Disease Control

Investigator-assessed	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
ORR[a], n (%)	27 (**60**)
[95% CI]	[44.3, 74.3]
Best overall response, n (%)*	
CR	3 (**7**)
PR	24 (53)
SD	11 (24)
PD	6 (13)
Not determined	1 (2)
DCR[b], n (%)	38 (**84**)
[95% CI]	[70.5, 93.5]

- Responses were observed regardless of tumor PD-L1 expression, *BRAF* or *KRAS* mutation status, or diagnosis of Lynch syndrome
  - The ORR and DCR in patients with a *BRAF* mutation (n = 17) were 71% and 88%, respectively

*Percentages may not add up to 100% because of rounding
[a]Patients with CR or PR divided by the number of treated patients; [b]Patients [illegible]
CI = confidence interval; PD = progressive disease

Best Reduction in Target Lesions

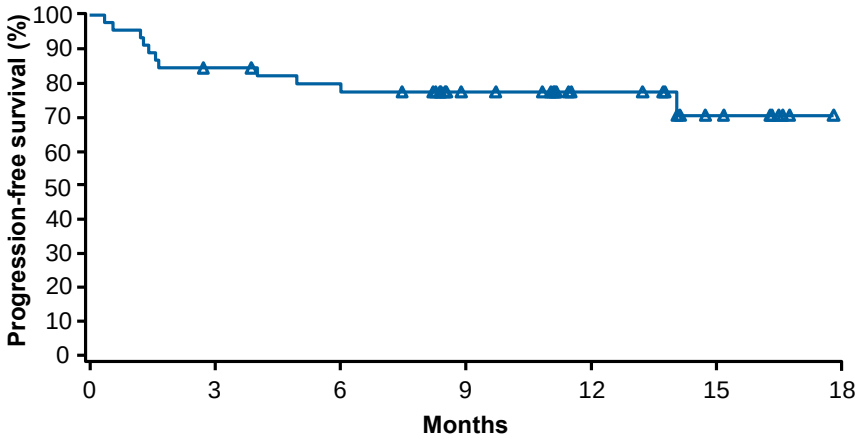


- 84% of patients had a reduction in tumor burden from baseline

*Confirmed response per investigator assessment
[a]Evaluable patients per investigator assessment

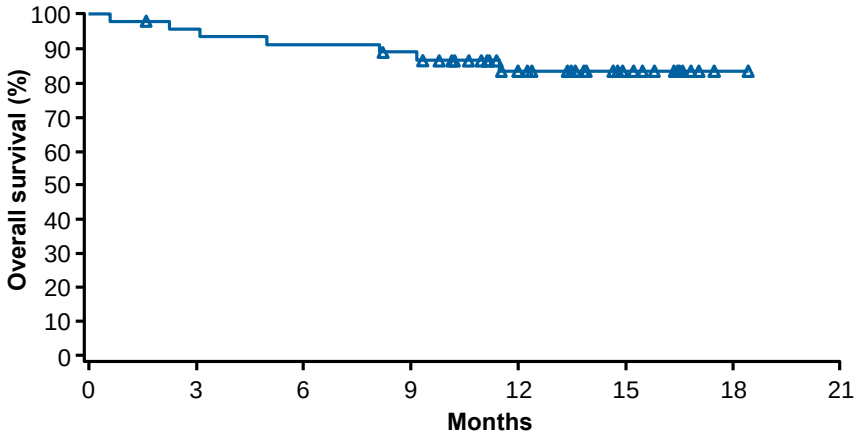
Progression-Free and Overall Survival

PFS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median PFS, months (95% CI)	NR (14.1–NE)
9-mo rate (95% CI), %	77 (62.0–87.2)
12-mo rate (95% CI), %	77 (62.0–87.2)



No. at risk	45	37	34	24	15	7	7

OS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median OS, months (95% CI)	NR (NE)
9-mo rate (95% CI), %	89 (74.9–95.1)
12-mo rate (95% CI), %	83 (67.6–91.7)



No. at risk	45	42	40	38	24	13	1	0

[a]Per investigator assessment.
mo = month; NE = not estimable; NR = not reached

Summary and Conclusions

- Nivolumab (Q2W) plus low-dose ipilimumab (Q6W) demonstrated robust and durable clinical benefit as a 1L treatment for MSI-H/dMMR mCRC
  - High ORR (60%, with 7% CR)
  - Durable responses (median DOR not reached)
  - [illegible]
  - Most patients had a reduction in tumor burden from baseline (84%)
  - Median PFS and OS not reached with a median follow-up of 14 months
  - 12-month PFS and OS rates were 77% and 83%, respectively
- Nivolumab plus low-dose ipilimumab was well-tolerated (grade 3–4 TRAEs, 16%) with a low rate of discontinuation due to TRAEs (7%)
- Nivolumab plus low-dose ipilimumab may represent a new 1L treatment option for patients with MSI-H/dMMR mCRC

But wait for the results of: "KEYNOTE-177, a phase 3, open-label, randomized study of first-line pembrolizumab versus investigator-choice chemotherapy for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal carcinoma (mCRC)".

PRACTICE CHANGING STUDIES IN 2018:

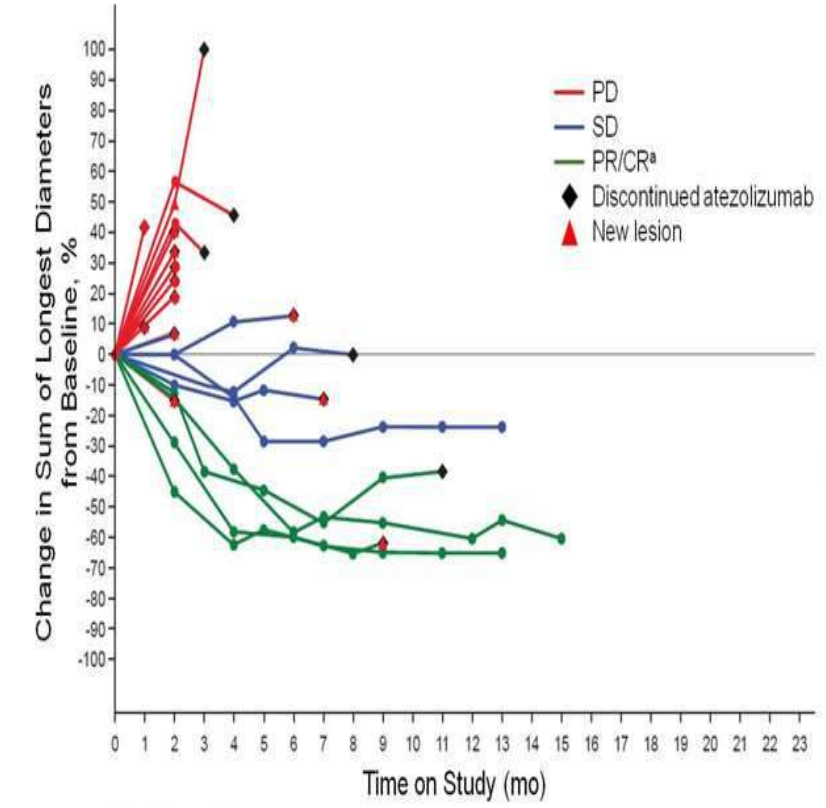
Focus on:

- Adjuvant therapy for pancreatic cancer
- Therapy for chemorefractory metastatic gastric cancer
- **Immunotherapy for metastatic colorectal cancer (success and failure)**
- Molecular targeted therapy for molecularly selected metastatic colorectal cancer (BRAF mutation as a driver)

What clinical research evidence does really change medical oncology practice?

Cobimetinib + Atezolizumab

	KRAS MT CRC	All CRC pts
	N=20	N=23
ORR	20%	17%
CR	0	0
PR	20%	17%
SD	20%	22%
PD	50%	52%
NE	10%	9%
mPFS (m)	2.3 (1.8-9.5)	2.3 (1.8-9.5)
mOS (m)	NE (6.5-NE)	NE (6.5-NE)



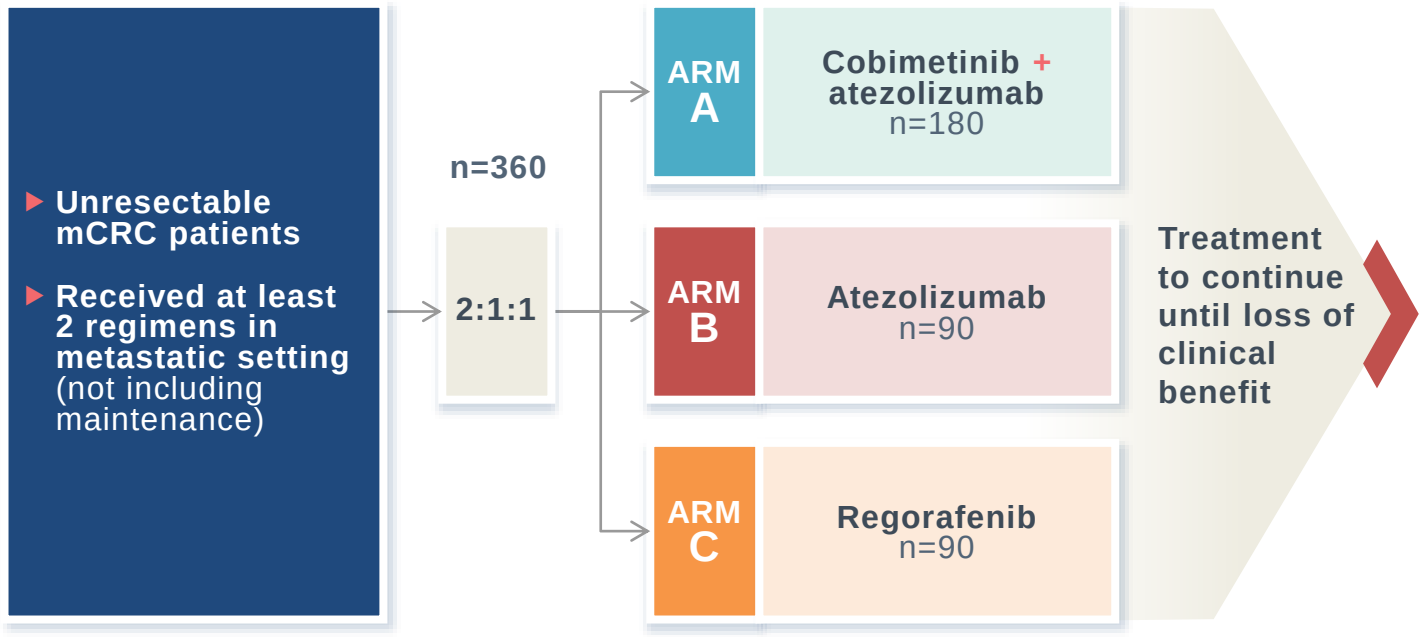
[a]Confirmed per RECIST v1.1. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off February 12, 2016.

Bendell J et al. Proc ASCO 2016

Efficacy and safety results from IMblaze370, a randomised Phase III study comparing atezolizumab + cobimetinib and atezolizumab monotherapy vs regorafenib in chemotherapy-refractory metastatic colorectal cancer

Johanna Bendell,[1] Fortunato Ciardiello,[2] Josep Tabernero,[3] Niall Tebbutt,[4] Cathy Eng,[5] Maria Di Bartolomeo,[6] Alfredo Falcone,[7] Marwan Fakih,[8] Mark Kozloff,[9] Neil H Segal,[10] Alberto Sobrero,[11] Yi Shi,[12] Louise Roberts,[12] Yibing Yan,[12] Ilsung Chang,[12] Anne Uyei,[12] Tae Won Kim[13]

[1] Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [2] Università degli Studi della Campania Luigi Vanvitelli, Napoli, Italy; [3] Vall d'Hebron Institute of Oncology, VHIO, Barcelona, Spain; [4] Medical Oncology, Austin Health, Heidelberg, VIC, Australia; [5] M. D. Anderson Cancer Center, Houston, TX, USA; [6] Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [7] University Hospital of Pisa, Pisa, Italy; [8] City of Hope, Duarte, CA, USA; [9] University of Chicago, Chicago, IL, USA; [10] Memorial Sloan Kettering Cancer Center, New York, NY, USA; [11] IRCCS Ospedale San Martino IST, Genova, Italy; [12] Genentech, Inc., South San Francisco, CA, USA; [13] Asan Medical Center, University of Ulsan, Seoul, South Korea

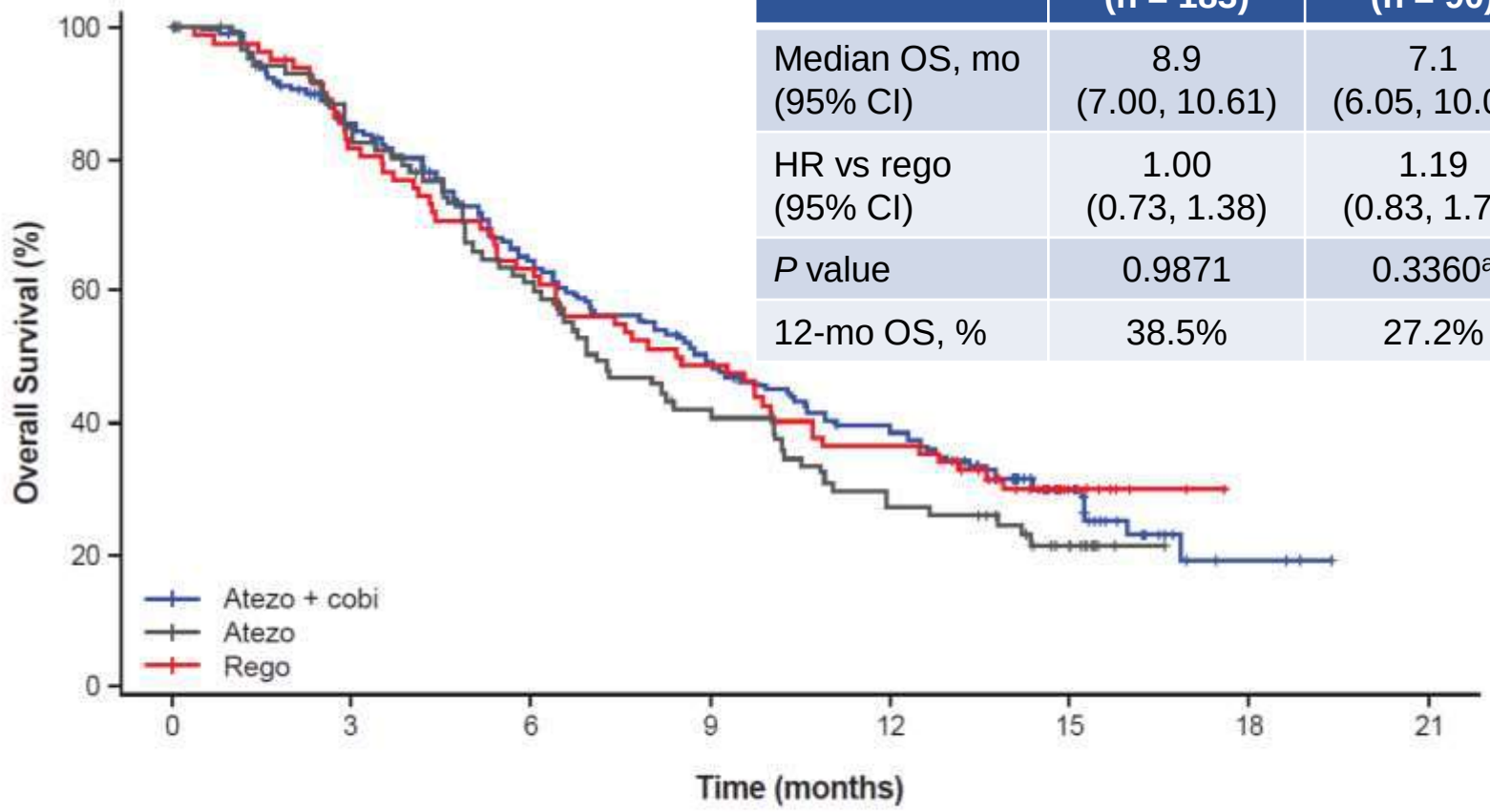


- Stratified by tumor extended *RAS* status and time since diagnosis of first metastasis
- MSI-H capped at approximately 5%
- At least 180 patients with extended *RAS*-mutant tumors to be enrolled

Eng C. et al., Lancet Oncology, 2019, in press

Overall survival

	Atezo + cobi (n = 183)	Atezo (n = 90)	Rego (n = 90)
Median OS, mo (95% CI)	8.9 (7.00, 10.61)	7.1 (6.05, 10.05)	8.5 (6.41, 10.71)
HR vs rego (95% CI)	1.00 (0.73, 1.38)	1.19 (0.83, 1.71)	N/A
P value	0.9871	0.3360[a]	N/A
12-mo OS, %	38.5%	27.2%	36.6%



No. at risk							
Atezo + cobi	183	150	110	83	63	28	3
Atezo	90	73	51	34	22	9	
Rego	90	67	52	40	30	9	

Conclusions

- **IMblaze370 did not meet its primary objective of improvement in OS with atezolizumab + cobimetinib and atezolizumab monotherapy vs regorafenib**
  - **There were no statistically significant differences in OS by clinical or biomarker subgroups, including patients with MSS or extended *RAS* mutation disease**
  - **PFS, ORR, DOR were not improved between the arms**
  - **Efficacy in MSI high disease was not estimable due to limited patient number**
    - **Responses were observed in 2 of 3 patients with atezolizumab + cobimetinib and 1 of 3 with atezolizumab monotherapy**

- **Lack of clinical activity may be due to the immune-excluded phenotype of mCRC**
  - **Simultaneous inhibition of the PD-L1 immune checkpoint and MAPK-mediated immune suppression may not be sufficient to generate anti-tumour immune responses in immune-excluded tumours, such as mCRC**

PRACTICE CHANGING STUDIES IN 2018:

Focus on:

- Adjuvant therapy for pancreatic cancer
- Therapy for chemorefractory metastatic gastric cancer
- Immunotherapy for metastatic colorectal cancer (success and failure)
- **Molecular targeted therapy for molecularly selected metastatic colorectal cancer (BRAF mutation as a disease driver)**

What clinical research evidence does really change medical oncology practice?

688

Gastrointestinal Cancers Symposium (ASCO GI)

[illegible]

Updated Results of the BEACON Colorectal Cancer (CRC) Safety Lead-In: Encorafenib (ENCO) + Binimetinib (BINI) + Cetuximab (CETUX) for *BRAF* [illegible]

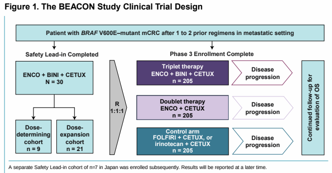
Scott Kopetz,[1] Axel Grothey,[2] Rona Yaeger,[3] Pieter-Jan Cuyle,[4] Sanne Huijberts,[5] Jan H. M. Schellens,[5] Elena Elez,[6] Marwan Fakih,[7] Clara Montagut,[8] Marc Peeters,[9] Jayesh Desai,[10] Takayuki Yoshino,[11] Fortunato Ciardiello,[12] Harpreet Wasan,[13] Victor Sandor,[14] Kati Maharry,[14] Janna Christy-Bittel,[14] Ashwin Gollerkeri,[14] Eric Van Cutsem,[15] Josep Tabernero[16]

[1]UT MD Anderson Cancer Center, Houston, TX, USA; [2]West Cancer Center, University of Tennessee, Germantown, TN, USA; [3]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [4]Imelda Ziekenhuis, Bonheiden, Belgium; [5]The Netherlands Cancer Institute, Amsterdam, the Netherlands; [6]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]City of Hope, Duarte, CA, USA; [8]Department of Medical Oncology, Hospital Universitari del Mar, Barcelona, Spain; [9]Antwerp University Hospital, Edegem, Belgium; [10]Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Walter and Eliza Hall Institute, Parkville, VIC, Australia; [11]National Cancer Center Hospital East, Kashiwa, Japan; [12]University of Campania, Naples, Italy; [13]Hammersmith Hospital, Department of Cancer Medicine, London, UK; [14]Array BioPharma Inc, Boulder, CO, USA; [15]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium; [16]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain*

BACKGROUND

- *BRAF* V600E mutation occurs in up to 15% of patients with metastatic colorectal cancer (mCRC), confers a poor prognosis, and results in worse outcomes with standard-of-care treatments for mCRC.[1-11]
- In a phase 2 study in *BRAF* V600E mCRC, treatment with the anti–epidermal growth factor receptor (EGFR) antibody cetuximab (CETUX) plus the *BRAF* inhibitor encorafenib (ENCO) led to a median progression-free survival (PFS) of 4.2 months, an overall response rate (ORR) of 24%, and a median overall survival (OS) of 9.3 months, which represent improvements in outcomes relative to historic data.[12]
- *BRAF* inhibitors may cause feedback activation of EGFR in *BRAF*-mutant colorectal cancer, leading to continued cell proliferation.[12-14] It is hypothesized that this feedback activation may be overcome by targeting additional points in the pathway, such as MEK.[15,16]
- BEACON CRC (NCT02928224) is a randomized, open-label, 3-arm Phase 3 study evaluating binimetinib (BINI), a MEK inhibitor, plus ENCO and CETUX compared with chemotherapy plus CETUX and ENCO plus CETUX in patients with *BRAF* V600E mCRC after 1 or 2 prior metastatic treatment regimens (Figure 1).[17]
- As part of the BEACON CRC trial, a safety lead-in (SLI) phase was conducted in 30 patients to evaluate the safety and tolerability of the triplet regimen and to assess preliminary efficacy prior to initiating the phase 3 portion of the study.
- Previously reported data showed promising safety in 30 patients treated and efficacy in 29 patients with *BRAF* V600E mCRC.[18]
- Here we report updated safety and efficacy results, including mature OS, from the SLI.

Figure 1. The BEACON Study Clinical Trial Design



A separate Safety Lead-in cohort of n=7 in Japan was enrolled subsequently. Results will be reported at a later time.

OBJECTIVE

Study Population

- All patients who received at least one dose of study drug were included in the safety analyses (n=30).
- For efficacy analyses, all patients with a *BRAF* V600E mutation who received at least one dose of study drug were included.

Endpoints

- The primary endpoint of the SLI was the assessment of safety and tolerability, which included
  - Dose-limiting Toxicities (DLTs);
  - Incidence and severity of AEs and changes in clinical laboratory parameters, vital signs, ECGs, ECHO/MUGA scans, and ophthalmic examinations; and
  - Incidence of dose interruptions, dose modifications, and discontinuations.
- Efficacy endpoints included
  - Confirmed Overall Response Rate (ORR; per RECIST v1.1)
  - Duration of Response (DOR)
  - Progression Free Survival (PFS),
  - Time to Response (TTR), and
  - Overall Survival (OS)
- Radiographic assessment of tumor response and progression was determined locally by the investigator.
- Blinded central review of radiographically determined tumor response was also conducted retrospectively and reported.
- Pharmacokinetic endpoints were also evaluated and will be presented elsewhere.

METHODS

- All patients in the SLI received ENCO 300 mg once daily, BINI 45 mg twice daily, and CETUX at the standard weekly dose (400 mg/m², then 250 mg/m² once weekly)
- Safety data were reviewed by an independent data monitoring committee during the dose-determining cohort before proceeding to dose expansion and then following the completion of dose expansion (after enrollment of a total of 30 patients in the SLI).
- Efficacy was assessed on the basis of radiological imaging (eg, computed tomography, magnetic resonance imaging, x-ray, whole-body bone scans)
- Tumor response was determined by the investigator according to RECIST, version 1.1
  - Tumor assessment was performed every 6 weeks from the first dose for the first 24 weeks and then every 12 weeks until disease progression, withdrawal of consent for treatment, initiation of subsequent anticancer therapy, or lost to follow-up

Key Inclusion Criteria

- Patients ≥18 years of age with confirmed mCRC.
- Presence of a *BRAF* V600E mutation in tumor tissue as detected by central testing or by polymerase chain reaction (PCR) or next-generation sequencing (NGS) per local testing. Patients could enroll based on local determination of *BRAF* V600E mutation, however, confirmation by a central laboratory was required for all patients within 30 days of starting treatment.
- Progression after 1 to 2 prior regimens in the metastatic setting.
- Eligible to receive CETUX per local label with regard to tumor RAS status.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Key Exclusion Criteria

- Patients were excluded if they had previous treatment with any RAF or MEK inhibitor, cetuximab, panitumumab, or other EGFR inhibitor; symptomatic brain metastasis or leptomeningeal disease.

RESULTS

Patients

- From November 1, 2016, to April 24, 2017, a total of 30 patients were treated in the SLI portion of BEACON (Table 1).
  - The median age of the patients was 59 years (range, 38–77 years).
- 60% of patients had received 1 prior line of therapy, and 40% of patients received 2 prior lines of therapy.
  - 43% had received prior irinotecan.
- At the time of data cut-off (September 2, 2018), 6 patients remained on treatment.

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Patients (N=30)
BRAF V600E mutation, n (%)[a]	29 (97)
Male sex, n (%)	13 (43)
Race, n (%)	
White	29 (97)
Black or African American	1 (3)
Age, median (range), years	59 (38–77)
ECOG PS 0, n (%)	17 (57)
Location of primary tumor, n (%)	
Left side	9 (30)
Right side	18 (60)
Unknown	3 (10)
No. of organs with ≥2 / metastasis, n (%)	22 (73)
Metastatic site locations, n (%)	
Liver	20 (67)
Lymph nodes	15 (50)
Peritoneum	11 (37)
Lung	9 (30)
Other	15 (50)
Resection of primary tumor, n (%)	
Yes	21 (70)
No	9 (30)
No. of prior systemic therapies, n (%)[b]	
1	18 (60)
2	12 (40)
Received prior irinotecan, n (%)	13 (43)
MSI-H, n (%)[c]	1 (3)
CEA, median (range) at baseline, μg/mL	28 (1–3,434)

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability high. [a]1 patient had a non-V600E *BRAF* mutation. [b]Includes prior systemic therapies in the metastatic setting only. [c]Based on immunohistochemical assessment of MLH1 and MSH6.

Safety Profile

- All 30 patients received at least 1 drug treatment and were assessed for safety (Table 2).
- No unexpected toxicities occurred with this new triplet combination since the previous data analysis.
- DLTs were observed in 5 of 30 patients and have been reported previously.[18]
- A total of six (20%) patients had at least one drug discontinued due to AEs.
  - One (3%) discontinued all three drugs due to grade 2 fatigue;
  - Two (7%) discontinued binimetinib alone due to increased blood creatinine (n=1) and retinal detachment (n=1);
  - Two (7%) discontinued cetuximab alone due to an allergic reaction; and
  - One (3%) discontinued both encorafenib and binimetinib due to increased blood bilirubin.
    - The patient received a dose of cetuximab two weeks following discontinuation of encorafenib and binimetinib and then discontinued study treatment completely two weeks later due to clinical progression.
  - There were five (17%) on-treatment deaths, all due to disease progression.

RESULTS (continued)

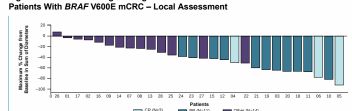
Table 2. [illegible] of Causality

[illegible]	Any Grade	[illegible]
Diarrhea	23 (77)	1 (3)
Dermatitis acneiform	20 (67)	0
Fatigue	19 (63)	4 (13)
Nausea	19 (63)	2 (7)
Vomiting	15 (50)	2 (7)
Dry skin	15 (50)	0
Anemia	12 (40)	3 (10)
Decreased appetite	12 (40)	2 (7)
Abdominal pain	11 (37)	1 (3)
Increased creatinine kinase	11 (37)	3 (10)
Pyrexia	11 (37)	0
Dyspnea	10 (33)	2 (7)
Constipation	9 (30)	0
Arthralgia	8 (27)	0
Creatine increased	8 (27)	0
Skin fissure	8 (27)	0
Vision blurred	8 (27)	0
Increased aspartate aminotransferase	6 (20)	3 (10)
Asthenia	6 (20)	0
Malaise	6 (20)	1 (3)
Myalgia	6 (20)	0
PPED syndrome	6 (20)	0
Rash maculopapular	6 (20)	0
Urinary tract infection	5 (17)	3 (10)

Efficacy

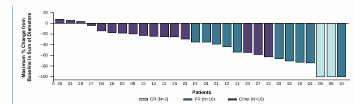
- Efficacy was evaluated in n=29 patients with *BRAF* V600E mutations
  - A non-V600 *BRAF* mutation (G466V) was identified in 1 patient, who was excluded from the efficacy analysis.
  - Median time of 7.9 months (range, 1.0–21.4 months) on study treatment (Table 3).
- Confirmed ORR by local assessment was 48% (14/29 patients), including complete responses (CRs) in 3 patients (Figure 2A). The duration of response per Kaplan-Meier estimate was ≥6 months in 43% of responders.
  - ORR in patients with 1 previous line of therapy, 59% (10/17; 8 partial responses [PRs] and 2 CRs)
  - ORR in patients with 2 previous lines of therapy, 33% (4/12; 3 PRs and 1 CR)
- Confirmed ORR by central assessment was 41% (12/29 patients) with 2 patients reported as CR; Figure 2B). The duration of response was ≥6 months in 73% of responders.
  - ORR in patients with 1 previous line of therapy, 53% (9/17; 8 partial responses [PRs] and 1 CRs)
  - ORR in patients with 2 previous lines of therapy, 25% (3/12; 2 PRs and 1 CR)

Figure 2A. Best Percentage Change in Tumor Measurements From Baseline in Patients With *BRAF* V600E mCRC – Local Assessment



One patient was without a postbaseline sum of diameters (not presented). Colors represent best response (confirmed). Patients with CR, defined as the disappearance of all target lesions, can have pathological lymph node metastases present; target or nontarget lymph node metastases must have reduction in short axis to < 10 mm. One patient had SD that was too early for assessment and was classified as NE. NE, not evaluable.

Figure 2B. Best Percentage Change in Tumor Measurements From Baseline in Patients With *BRAF* V600E mCRC – Central Assessment



One patient was without a postbaseline sum of diameters (not presented). Colors represent best response (confirmed). Patients with CR, defined as the disappearance of all target lesions, can have pathological lymph node metastases present; target or nontarget lymph node metastases must have reduction in short axis to < 10 mm. One patient had SD that was too early for assessment and was classified as NE. NE, not evaluable.

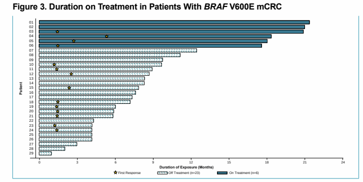
Table 3. [illegible]

[illegible]	Patients (N = 29)[b]	
	Local Assessment	Central Assessment
Overall Response Rate		
(CR + PR) [95% CI]	14 (48) [29–68%]	12 (41) [24–61%]
Complete Response (CR)	3 (10)	2 (7)
Partial Response (PR)	11 (38)	10 (34)
Stable Disease (SD)	13 (45)	13 (45)
Progressive Disease (PD)	0	0
Not Evaluable (NE)[c]	2 (7)	4 (14)

[a]Response confirmed per Response Evaluation Criteria in Solid Tumors, version 1.1. [b]Patients with *BRAF* V600E mutations only. [c]Nonresponders per intent-to-treat analysis. CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; NE, Not Evaluable

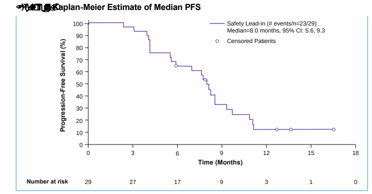
- Median duration of response was 5.5 months (95% CI, 4.1 months–not reached [NR]) per local assessment and 8.2 months (95% CI, 2.8 months–NR) per central assessment (Figure 3).

Figure 3. Duration on Treatment in Patients With *BRAF* V600E mCRC



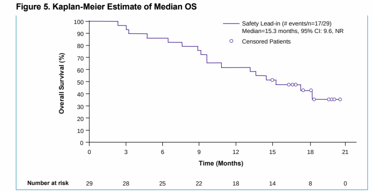
- The median follow-up time for survival was 18.2 months.
- Median PFS was 8.0 months (95% CI, 5.6–9.3 months) per local assessment (Figure 4)

[illegible] Kaplan-Meier Estimate of Median PFS



- The median OS was 15.3 months (95% CI, 9.6 months–NR) (Figure 5)
  - 6-month OS; 86.2% (67.3–94.6)
  - 12-month OS; 62.1% (42.1–76.9)

Figure 5. Kaplan-Meier Estimate of Median OS



CONCLUSIONS

- ENCO and BINI combined with CETUX has a manageable toxicity profile, with efficacy exceeding historic data in patients with *BRAF* V600–mutant mCRC
- Median OS was 15.3 months (95% CI, 9.6–not reached), with median duration of follow-up of 18.2 (16.6–19.8) months
- Overall response rate by central assessment was consistent with local assessment
- The confirmed ORR and median PFS remain unchanged from the previous report (ORR, 48% [95%CI, 29.4–67.5]; PFS, 8.0 mo [95% CI, 5.6–9.3 mo] - Local Assessment)
  - Historic standards of care have generally demonstrated ORRs <10%, median PFS rates of ≈2 months, and median OS times of 4–6 months
- Common AEs were similar to those previously reported with other *BRAF*, MEK, and EGFR inhibitors and included gastrointestinal and skin toxicities
  - Only one patient discontinued treatment with all drugs due to an adverse event
  - The rate of grade 3/4 skin toxicities continues to be lower than generally observed with CETUX in mCRC
- On the basis of results from the BEACON SLI, the randomized phase 3 portion of the study was initiated and is currently ongoing
- If the data are consistent with the SLI, the results of the phase 3 BEACON CRC study could establish this regimen as a new standard of care for patients in this setting

REFERENCES

1. Loupakis F, et al. *Br J Cancer.* 2009;101:715-721.
2. Tie J, et al. *Int J Cancer.* 2011;128:2075-2084.
3. De Roock W, et al. *Lancet Oncol.* 2010;11:753-762.
4. Morris V, et al. *Clin Colorectal Cancer.* 2014;13:164-171.
5. Giantonio BJ, et al. *J Clin Oncol.* 2007;25:1539-1544.
6. Haller DG, et al. *J Clin Oncol.* 2008;26:4544-4550.
7. Iwamoto S, et al. *Ann Oncol.* 2015;26:1427-1433.
8. Peeters M, et al. *Ann Oncol.* 2014;25:107-116.
9. Sobrero AF, et al. *J Clin Oncol.* 2008;26:2311-2319.
10. Tabernero J, et al. *Lancet Oncol.* 2015;16:499-508.
11. Van Cutsem E, et al. *J Clin Oncol.* 2012;30:3499-3506.
12. Van Cutsem E, et al. *World GI oral presentation.* 2018.
13. Corcoran RB, et al. *Cancer Discov.* 2012;2:227-235.
14. Prahallad A, et al. *Nature.* 2012;483:100-103.
15. Planchard D, et al. *Lancet Oncol.* 2016;17:984-993.
16. Corcoran RB, et al. *Ann Oncol.* 2016;27(suppl 6) [abstract 4550].
17. https://www.clinicaltrials.gov/ct2/show/NCT02928224. Accessed November 15, 2018.
18. Van Cutsem E, et al. *J Clin Oncol.* 2018;36(suppl 4S) [abstract 627].

Acknowledgments

[illegible] and Pierre Fabre. [illegible]

This study is sponsored by Array BioPharma Inc.

Available at: www.arraybiopharma.com

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission froam ASCO® and the author of this poster.

Van Cutsem E. et al., Journal of Clinical Oncology, 2019, in press

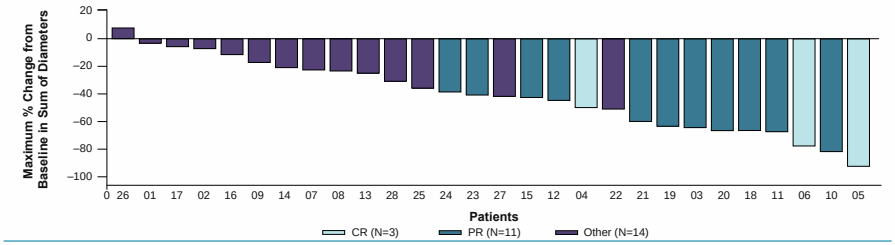
Table 2. [illegible] of Causality

[illegible]	Any Grade	[illegible]
Diarrhea	23 (77)	1 (3)
Dermatitis acneiform	20 (67)	0
Fatigue	19 (63)	4 (13)
Nausea	19 (63)	2 (7)
Vomiting	15 (50)	2 (7)
Dry skin	15 (50)	0
Anemia	12 (40)	3 (10)
Decreased appetite	12 (40)	2 (7)
Abdominal pain	11 (37)	1 (3)
Increased creatinine kinase	11 (37)	3 (10)
Pyrexia	11 (37)	0
Dyspnea	10 (33)	2 (7)
Constipation	9 (30)	0
Arthralgia	8 (27)	0
Creatine increased	8 (27)	0
Skin fissure	8 (27)	0
Vision blurred	8 (27)	0
Increased aspartate aminotransferase	6 (20)	3 (10)
Asthenia	6 (20)	0
Malaise	6 (20)	1 (3)
Myalgia	6 (20)	0
PPED syndrome	6 (20)	0
Rash maculopapular	6 (20)	0
Urinary tract infection	5 (17)	3 (10)

Efficacy

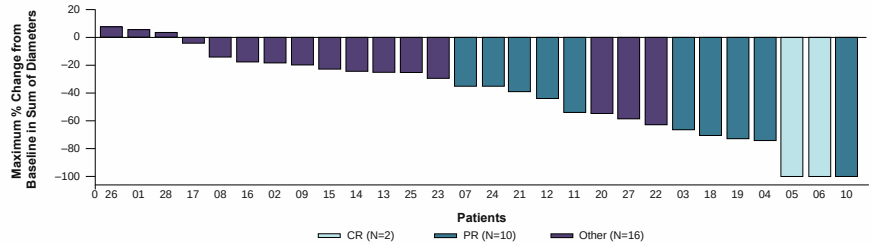
- Efficacy was evaluated in n=29 patients with *BRAF* V600E mutations
  - A non-V600 *BRAF* mutation (G466V) was identified in 1 patient, who was excluded from the efficacy analysis.
  - Median time of 7.9 months (range, 1.0–21.4 months) on study treatment (Table 3).
- Confirmed ORR by local assessment was 48% (14/29 patients), including complete responses (CRs) in 3 patients (Figure 2A). The duration of response per Kaplan-Meier estimate was ≥6 months in 43% of responders.
  - ORR in patients with 1 previous line of therapy, 59% (10/17; 8 partial responses [PRs] and 2 CRs)
  - ORR in patients with 2 previous lines of therapy, 33% (4/12; 3 PRs and 1 CR)
- Confirmed ORR by central assessment was 41% (12/29 patients) with 2 patients reported as CR; Figure 2B). The duration of response was ≥6 months in 73% of responders.
  - ORR in patients with 1 previous line of therapy, 53% (9/17; 8 partial responses [PRs] and 1 CRs)
  - ORR in patients with 2 previous lines of therapy, 25% (3/12; 2 PRs and 1 CR)

Figure 2A. Best Percentage Change in Tumor Measurements From Baseline in Patients With *BRAF* V600E mCRC – Local Assessment



One patient was without a postbaseline sum of diameters (not presented). Colors represent best response (confirmed). Patients with CR, defined as the disappearance of all target lesions, can have pathological lymph node metastases present; target or nontarget lymph node metastases must have reduction in short axis to < 10 mm. One patient had SD that was too early for assessment and was classified as NE. NE, not evaluable.

Figure 2B. Best Percentage Change in Tumor Measurements From Baseline in Patients With *BRAF* V600E mCRC – Central Assessment



One patient was without a postbaseline sum of diameters (not presented). Colors represent best response (confirmed). Patients with CR, defined as the disappearance of all target lesions, can have pathological lymph node metastases present; target or nontarget lymph node metastases must have reduction in short axis to < 10 mm. One patient had SD that was too early for assessment and was classified as NE. NE, not evaluable.

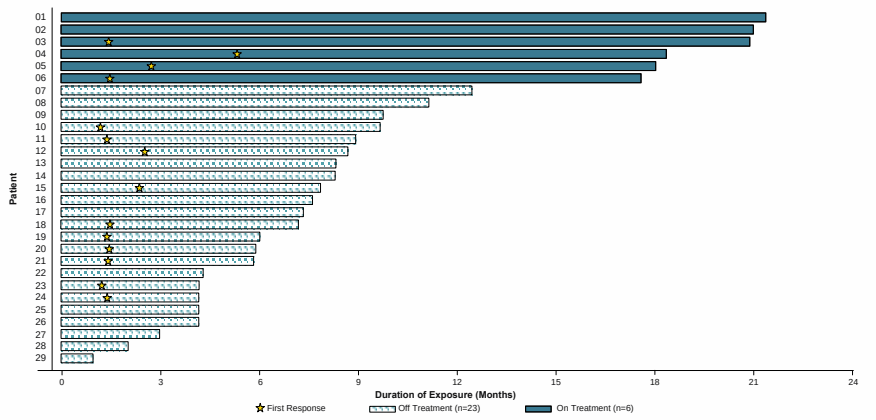
Table 3. [illegible]

[illegible]	Patients (N = 29)[b]	
Overall Response Rate	Local Assessment	Central Assessment
(CR + PR) [95% CI]	14 (48) [29–68%]	12 (41) [24–61%]
Complete Response (CR)	3 (10)	2 (7)
Partial Response (PR)	11 (38)	10 (34)
Stable Disease (SD)	13 (45)	13 (45)
Progressive Disease (PD)	0	0
Not Evaluable (NE)[c]	2 (7)	4 (14)

[a]Response confirmed per Response Evaluation Criteria in Solid Tumors, version 1.1. [b]Patients with *BRAF* V600E mutations only. [c]Nonresponders per intent-to-treat analysis. CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; NE, Not Evaluable

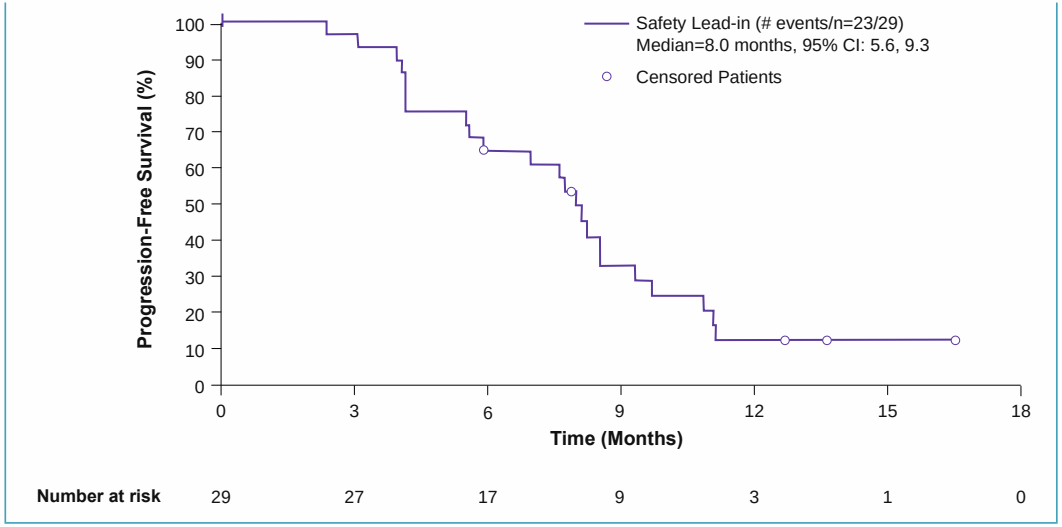
- Median duration of response was 5.5 months (95% CI, 4.1 months–not reached [NR]) per local assessment and 8.2 months (95% CI, 2.8 months–NR) per central assessment (Figure 3).

Figure 3. Duration on Treatment in Patients With *BRAF* V600E mCRC



- The median follow-up time for survival was 18.2 months.
- Median PFS was 8.0 months (95% CI, 5.6–9.3 months) per local assessment (Figure 4)

Kaplan-Meier Estimate of Median PFS



- The median OS was 15.3 months (95% CI, 9.6 months–NR) (Figure 5)
  - 6-month OS; 86.2% (67.3–94.6)
  - 12-month OS; 62.1% (42.1–76.9)

Figure 5. Kaplan-Meier Estimate of Median OS

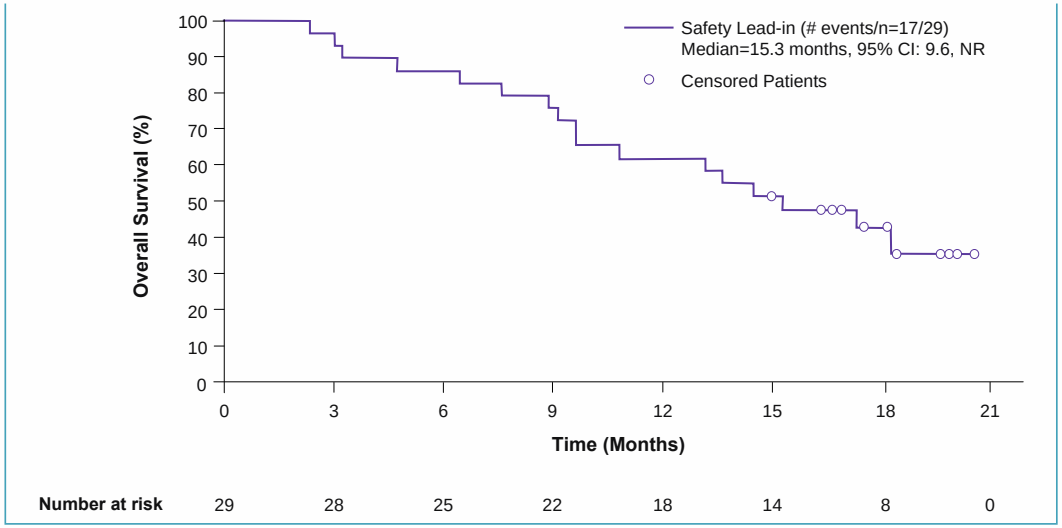
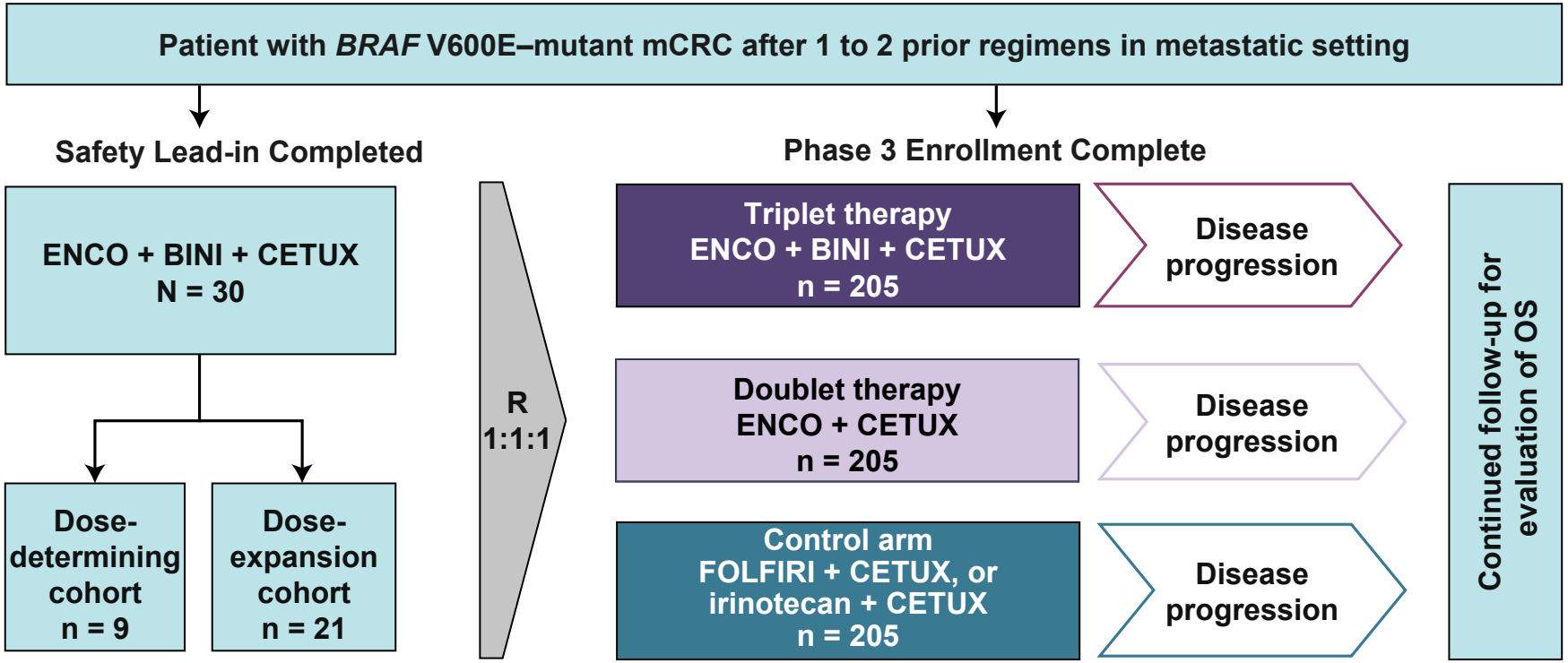



Figure 1. The BEACON Study Clinical Trial Design