# ASCO GI

San Francisco 2020

# Pro: The Colorectal Cancer Screening Age Should Be Lowered!

## GI Cancer Symposium, San Francisco
## January 2020

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Presented By Uri Ladabaum at 2020 Gastrointestinal Cancer Symposium

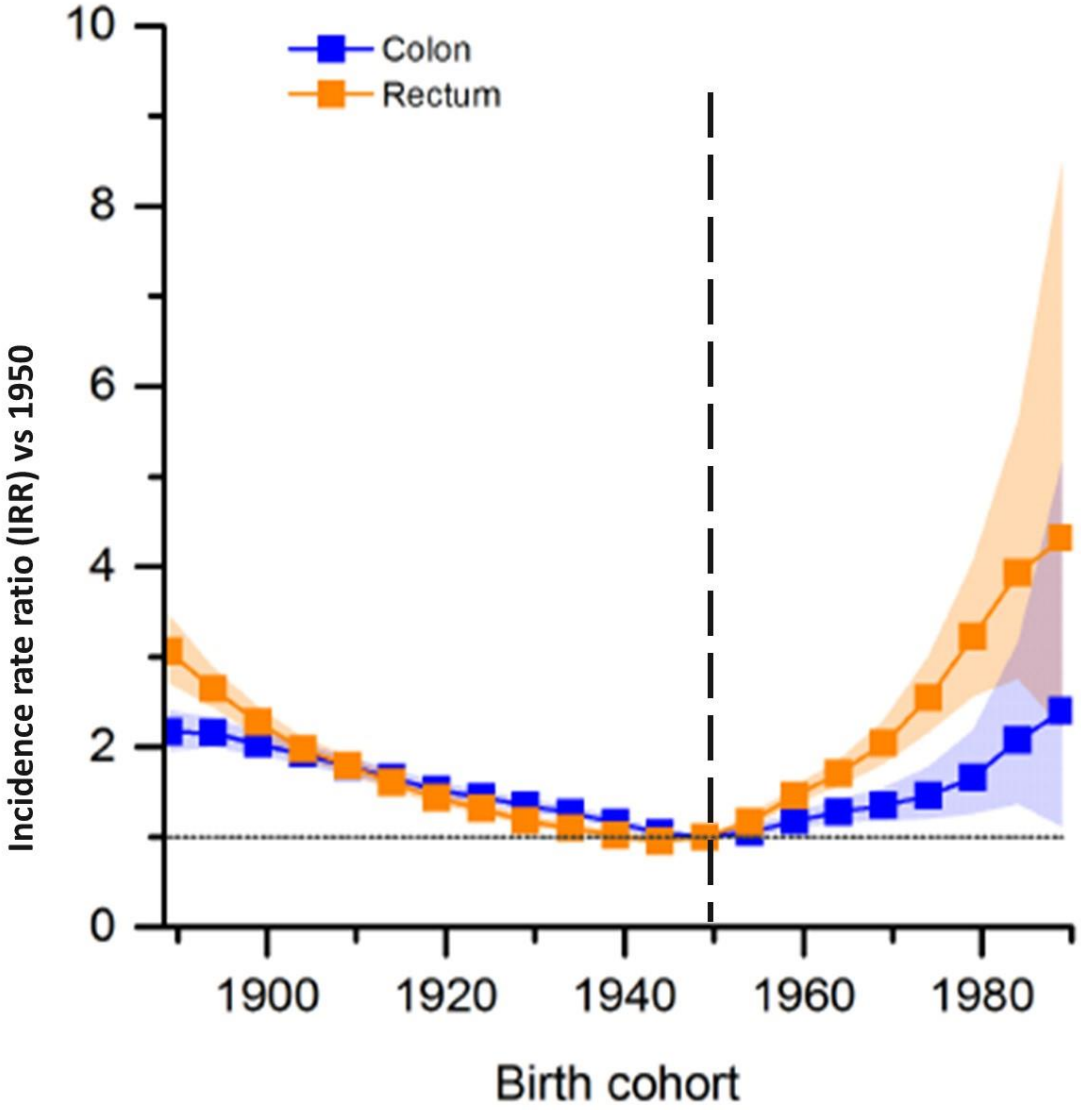
# Why this debate?

- CRC incidence increasing in younger persons
- *"ACS recommends that adults aged 45 years and older with an average risk of CRC undergo regular screening…"*
  - Disease burden
  - Modeling
  - Expect that screening performance <50 ≈ 50+

STANFORD
SCHOOL OF MEDICINE

Wolfe et al., CA Cancer J Clin 2018;68:250
Peterse et al., Cancer 2018;124:2964-2973

# Increasing CRC risk under age 50

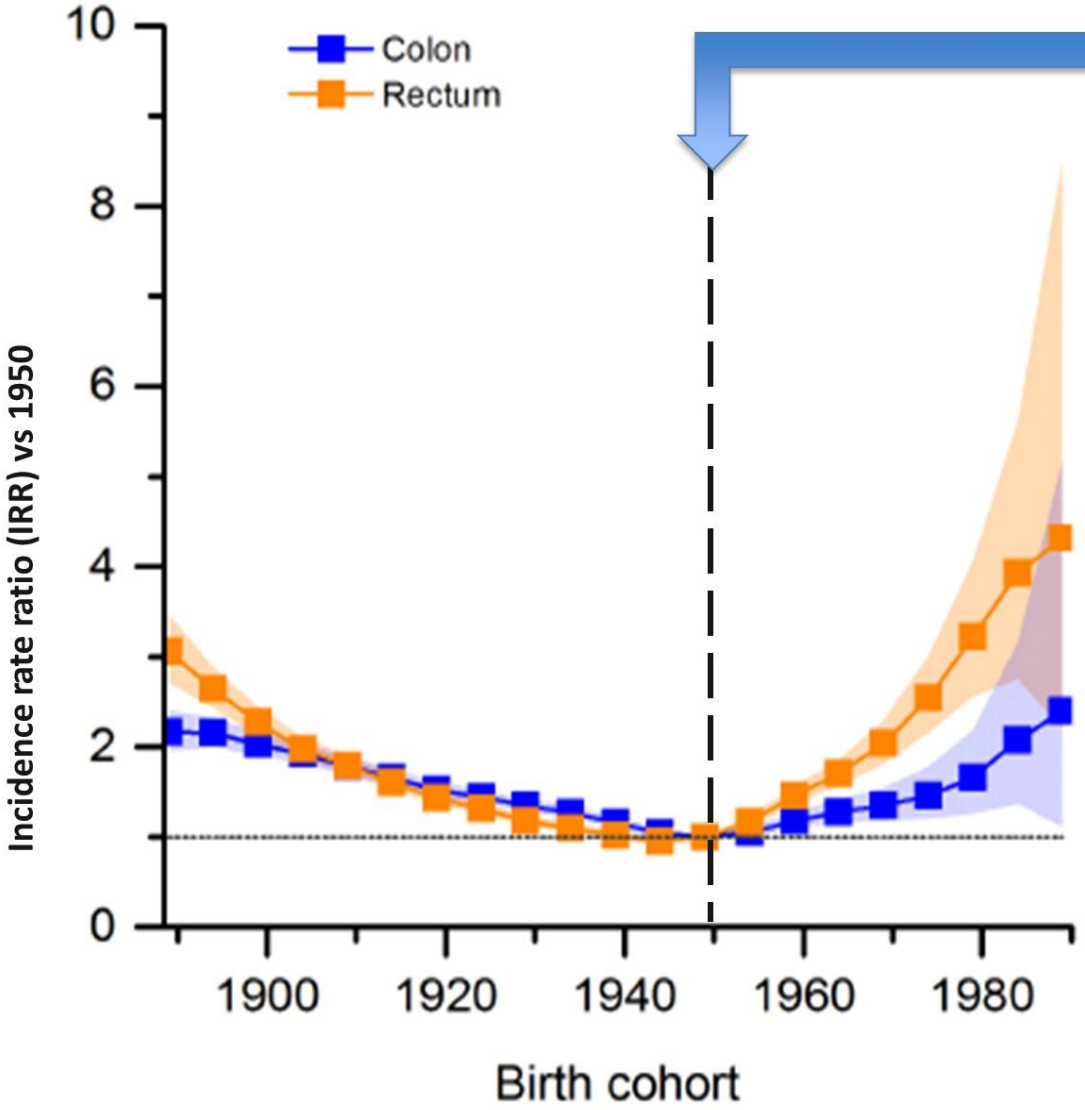



**Rectum: IRR=4.3**
**(95% CI, 2.2-8.5)**

**Colon: IRR=2.4**
**(95% CI, 1.1-5.2)**

Siegel et al., JNCI 2017;109(8)

# Increasing CRC risk under age 50

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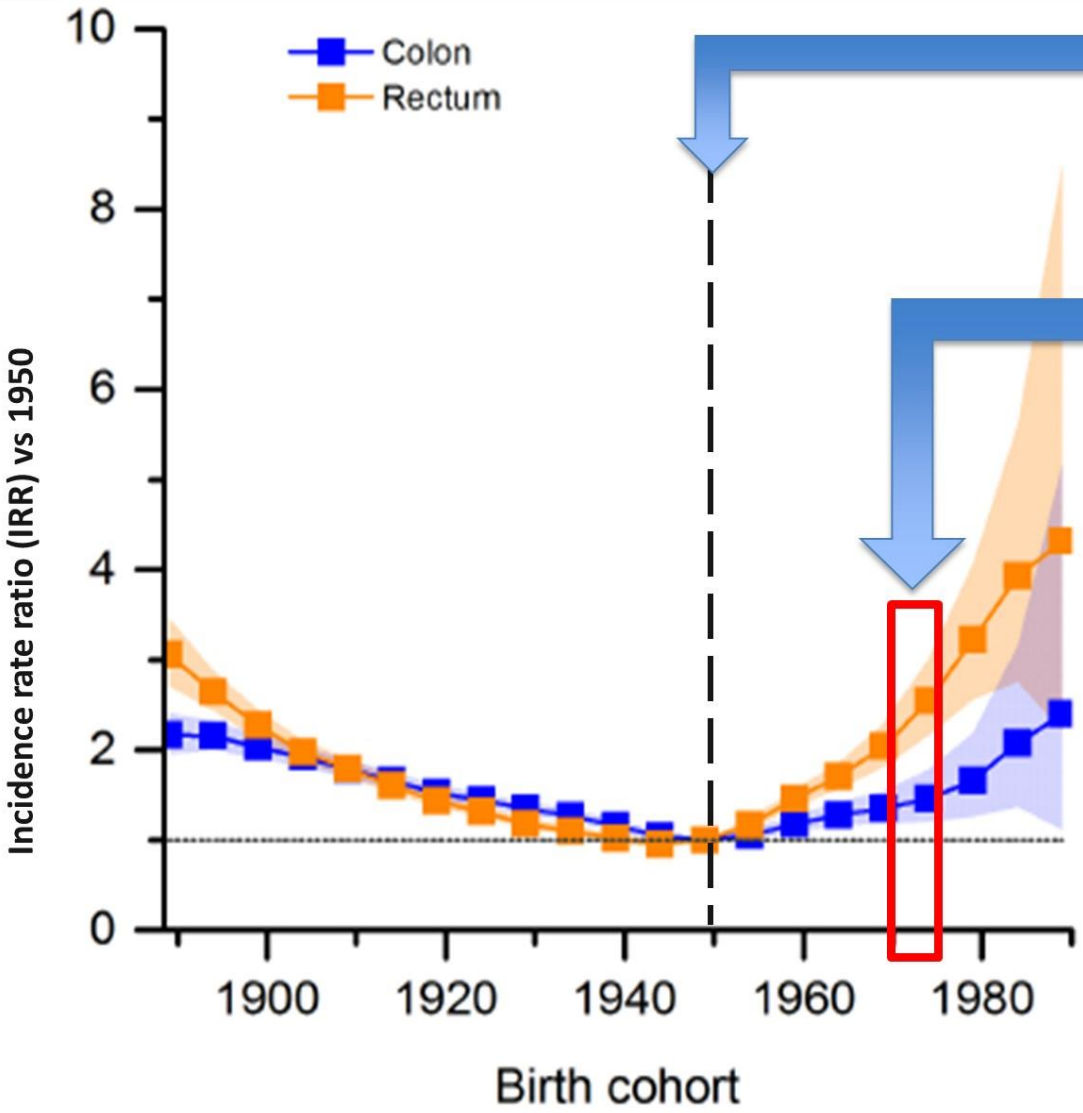
# Increasing CRC risk under age 50



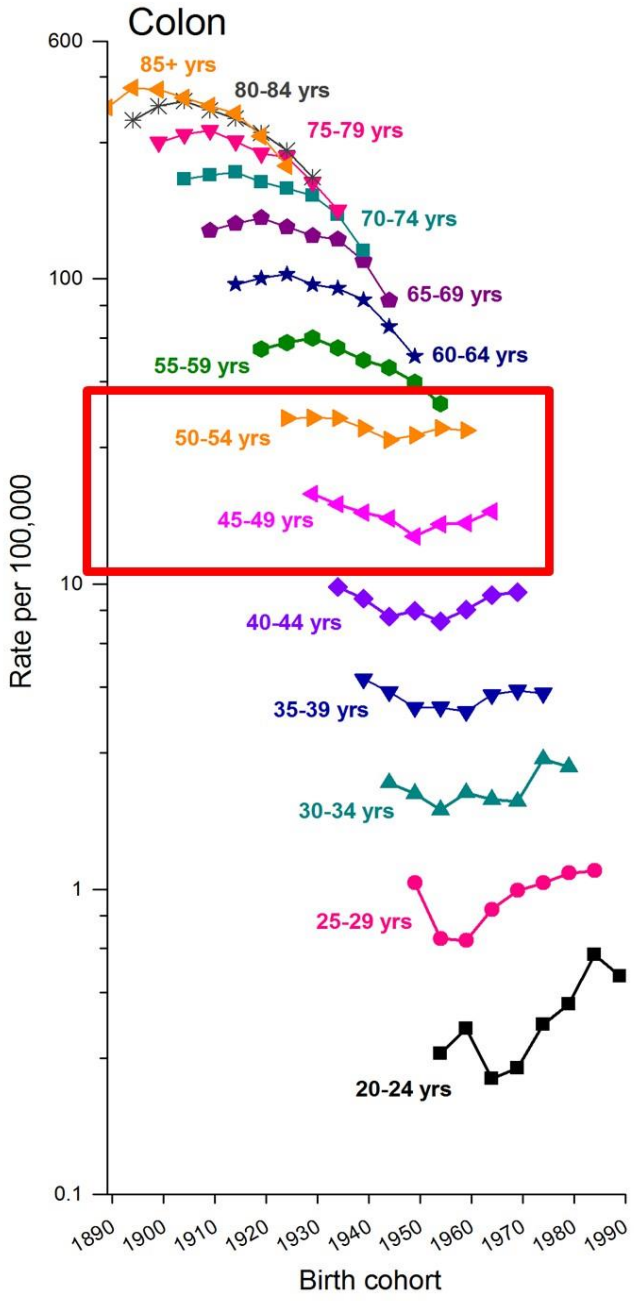

**50 year-olds in 2000**

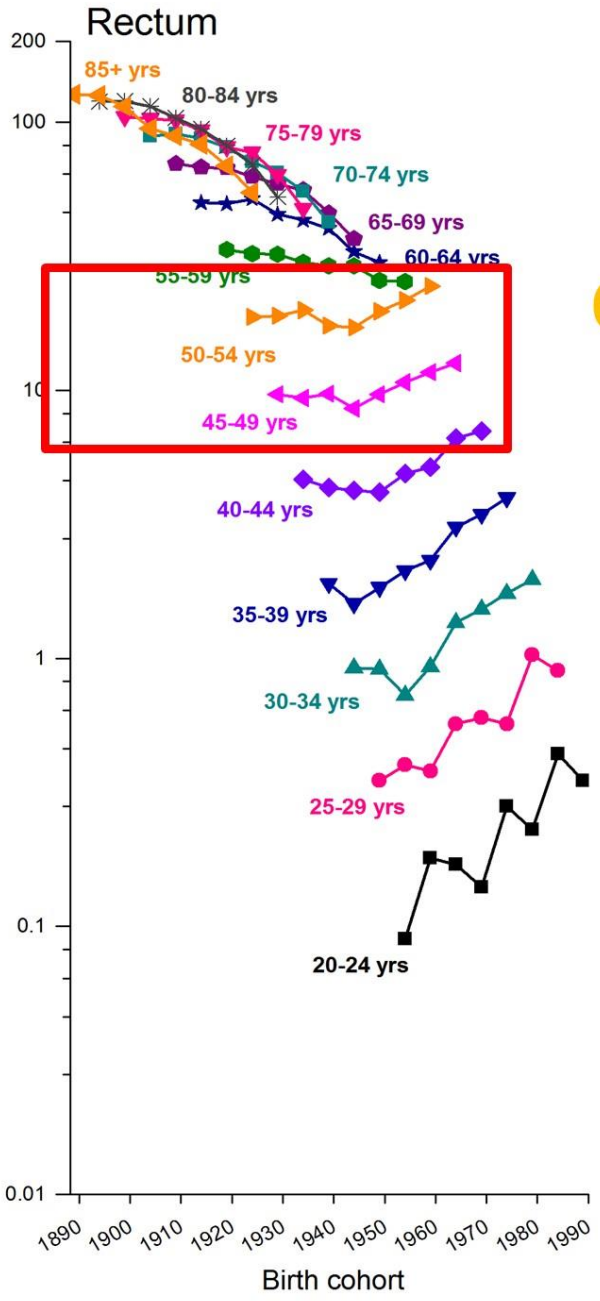
**45-49 year-olds TODAY in 2020**

**Rectum: IRR=4.3 (95% CI, 2.2-8.5)**

**Colon: IRR=2.4 (95% CI, 1.1-5.2)**

Siegel et al., JNCI 2017;109(8)




ORANGE

PINK

Siegel et al., JNCI 2017;109(8)

# Encorafenib plus Cetuximab With or Without Binimetinib for BRAF V600E–Mutant Metastatic Colorectal Cancer: Quality of Life Results from a Randomized, 3-Arm, Phase 3 Study vs. the Choice of Either Irinotecan or FOLFIRI plus Cetuximab (BEACON CRC)

Scott Kopetz, Axel Grothey, Eric Van Cutsem, Rona Yaeger, Harpreet Wasan, Takayuki Yoshino, Jayesh Desai, Fortunato Ciardiello, Fotios Loupakis, Yong Sang Hong, Neeltje Steeghs, Tormod Kyrre Guren, Hendrik-Tobias Arkenau, Pilar Garcia-Alfonso, Ashwin Gollerkeri, Kati Maharry, Janna Christy-Bittel, Christopher Keir, Michael Pickard, and Josep Tabernero

BEACON CRC: **B**inimetinib, **E**ncorafenib, **A**nd **C**etuximab C**O**mbi**N**ed to Treat *BRAF*-mutant **C**olo**R**ectal **C**ancer

PRESENTED AT: Gastrointestinal Cancers Symposium



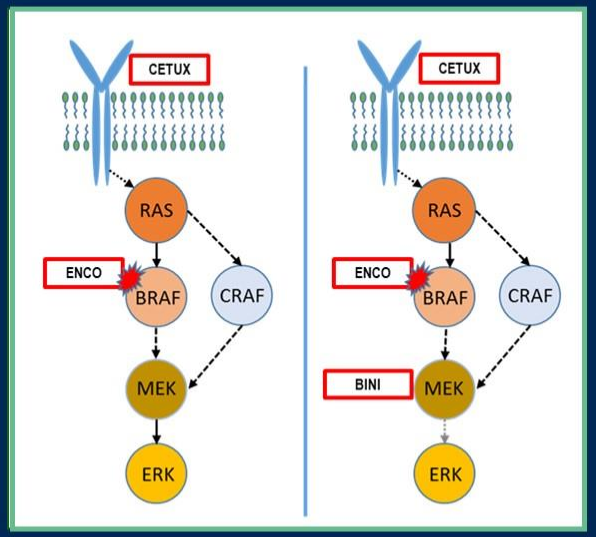
PRESENTED BY: Scott Kopetz, MD

#GI20

# MAPK Pathway Inhibition in *BRAF*-mutant CRC

- *BRAF*$^{V600}$ mutation occurs in 10%–15% of patients and confers a poor prognosis[1-3]
- BRAF inhibitors alone are ineffective due to the feedback activation of EGFR, leading to continued cell proliferation[4-6]
  - Feedback may be overcome by targeting multiple pathway nodes, ie BRAF/MEK/EGFR
  - Preclinically, addition of MEK inhibitor improved outcomes
- In the BEACON CRC safety-lead in study, the triplet regimen of Encorafenib (ENCO) + Binimetinib (BINI) + Cetuximab (CETUX) had manageable safety profile and encouraging activity in patients with *BRAF*$^{V600E}$ mCRC[7]

**MAPK Signaling in Colorectal Cancer[8]**




CETUX=cetuximab; EGFR=epidermal growth factor receptor; ENCO=encorafenib; MAPK=mitogen-activated protein kinase; mCRC=metastatic colorectal cancer; PFS=progression-free survival; ORR=objective response rate; OS=overall survival.

1. De Roock W, et al. *Lancet Oncol*. 2010;11(8):753. 2. Sorbye H, et al. PLoS One. 2015;10:e0131046. 3. Loupakis F, et al. *Br J Cancer*. 2009;101:715. 4. Kopetz S, et al. *J Clin Oncol*. 2017;35(15):3505. 5. Corcoran RB, et al. *Cancer Disc*. 2012;2(3):227. 6. Prahallad A, et al. *Nature* 2012;100:100. 7. Van Cutsem E, et al. J Clin Oncol. 2019 Jun 10;37(17):1460-1469. 8. Adapted From: Strickler JH. *Cancer Treat Rev*. 2017; 60:109.





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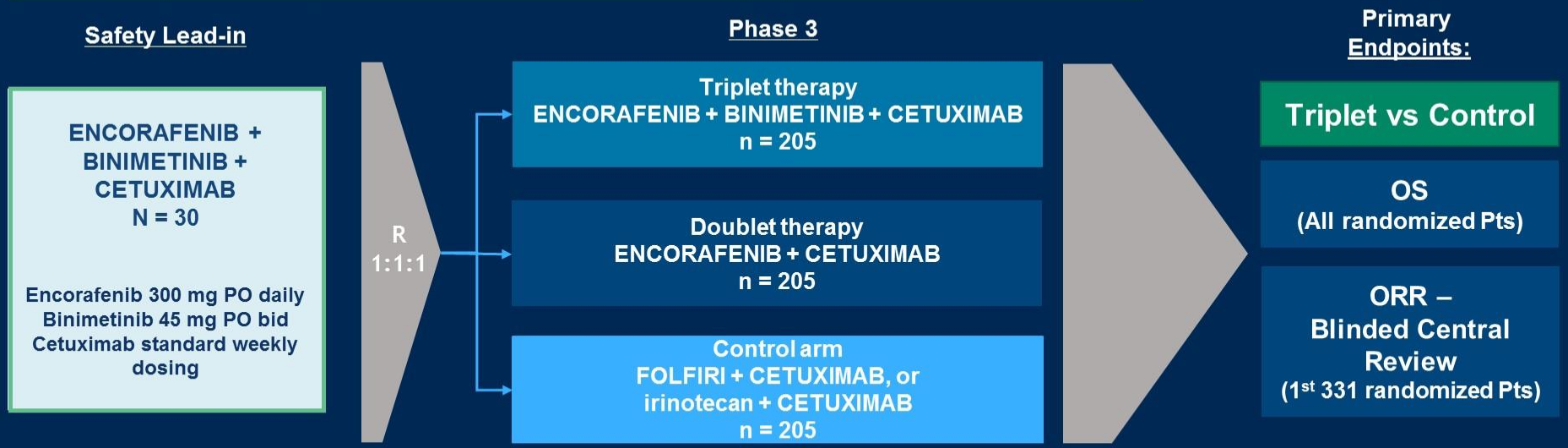
# Study Design

Patients with *BRAF*$^{V600E}$ mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor




Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

**Secondary Endpoints:** Doublet vs Control and Triplet vs Doublet - OS & ORR, PFS, Safety, QOL

**QOL Assessments:** EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer, EuroQol 5D5L, and Patient Global Impression of Change.





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# Baseline Patient Characteristics

| CHARACTERISTIC | Triplet N=224 | Doublet N=220 | Control N=221 |
|---|---|---|---|
| Female | 53% | 48% | 57% |
| Age, median (range), years | 62 (26, 85) | 61 (30, 91) | 60 (27, 91) |
| ECOG PS 0 | 52% | 51% | 49% |
| Location of primary tumor* | | | |
| Left colon (includes rectum) | 35% | 38% | 31% |
| Right colon | 56% | 50% | 54% |
| ≥3 organs involved | 49% | 47% | 44% |
| Presence of liver metastases | 64% | 61% | 58% |
| Prior lines of therapy | | | |
| 1 | 65% | 66% | 66% |
| >1 | 35% | 34% | 34% |
| MSI-H† | 10% | 9% | 5% |
| CEA Baseline Value > 5 ug/L | 80% | 70% | 81% |
| CRP Baseline Value > 10mg/L | 42% | 36% | 41% |
| FACT-C Total Score, median (range) | 97 (36, 134) | 96 (27, 135) | 98 (29, 134) |
| EORTC QLQ-C30 Global Health Status, median (range) | 67 (0, 100) | 67 (0, 100) | 67 (0, 100) |
| EQ- 5D-5L Visual Analog Scale, median (range) | 70 (20, 100) | 70 (0, 100) | 70 (10, 100) |
| PGIC, median (range) | 4 (1, 7) | 4 (1, 7) | 4 (1, 7) |

Abbreviations: CEA, carcinoembryonic antigen; CRP, c-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSI-H, microsatellite instability high (abnormal high); FACT-C, Functional Assessment of Cancer Therapy – Colorectal (version 4); EORTC QLQ-C30, European Organization for Research and Treatment of Cancer core quality-of-life Questionnaire (version 3.0); EQ-5D-5L-EuroQol-5D-5L; PGIC, Patient Global Impression of Change. Baseline characteristics are summarized for all 665 randomized patients. †Based on assessment by polymerase chain reaction. MSI status is missing in 23% of patients. *Remaining patients had primary tumor in both left and right sides of colon and those with unknown location of primary tumor.

Kopetz et al. N Engl J Med 2019; 381:1632-1643





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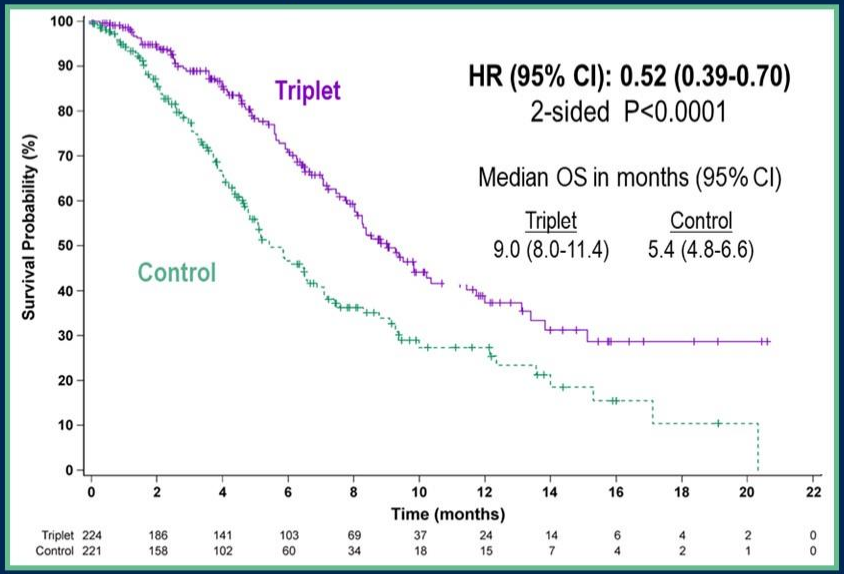
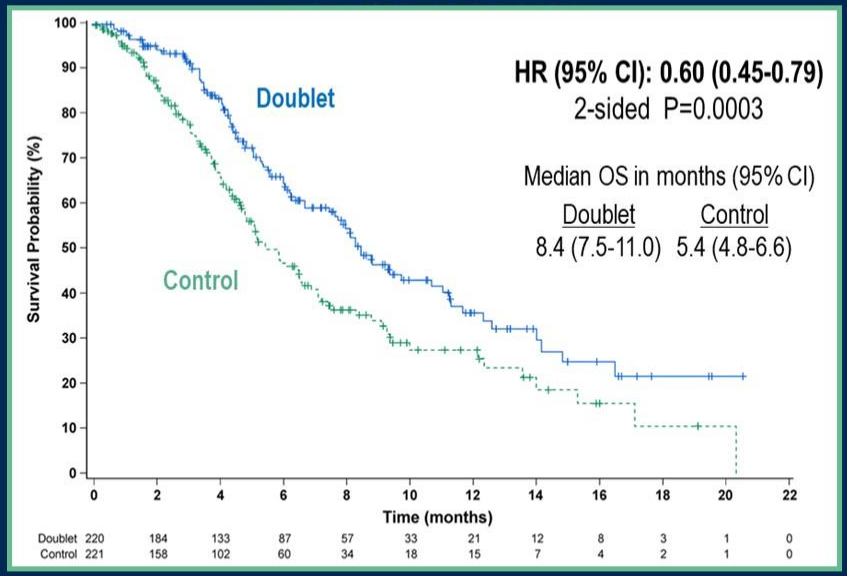
# Primary Overall Survival and Objective Response Rate

## Triplet vs Control*




## Doublet vs Control*




## Objective Response Rate (First 331 Randomized Patients)

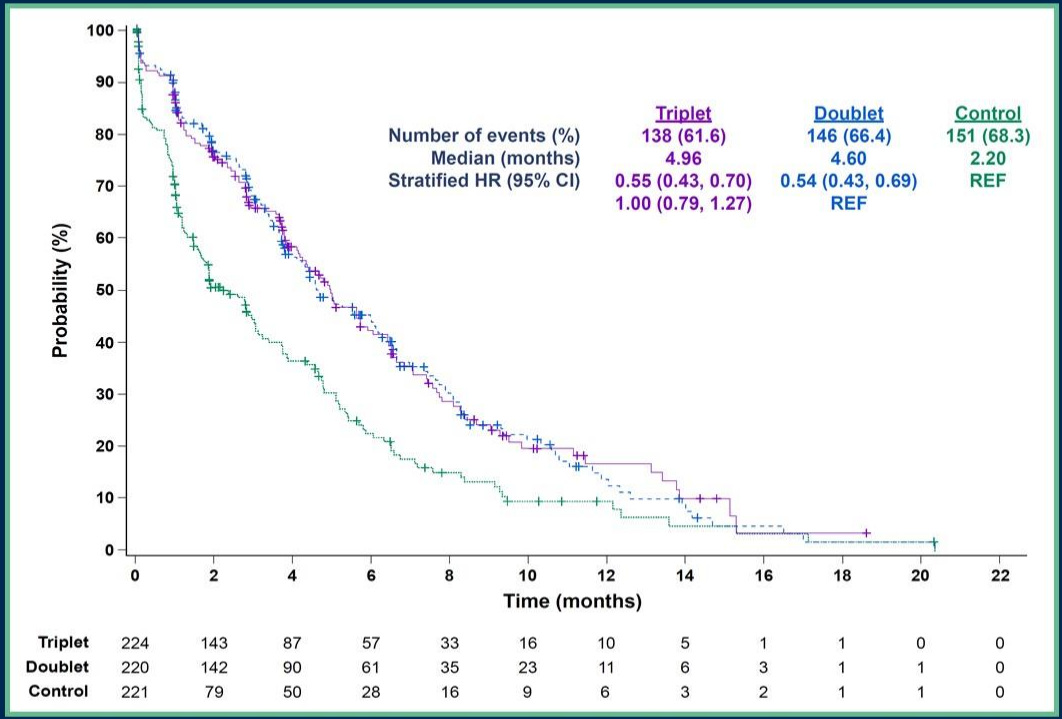
| Confirmed Response by blinded central review | Triplet N=111 | Doublet N=113 | Control N=107 |
|---|---|---|---|
| **Objective Response Rate** | **26%** | **20%** | **2%** |
| 95% (CI) | (18%, 35%) | (13%, 29%) | (<1%, 7%) |
| p-value vs. Control | <0.0001 | <0.0001 | |

*Overall survival analysis conducted in all randomized patients.

Kopetz et al. N Engl J Med 2019; 381:1632-1643

# Maintenance of Quality of Life: EORTC QLQ-C30

## Time to Definitive Deterioration in EORTC QLQ-C30 Global Health Status*




* The time to definitive deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% worsening relative to Baseline of the corresponding scale score with no later improvement above this threshold observed during the course of the study or death due to any cause.





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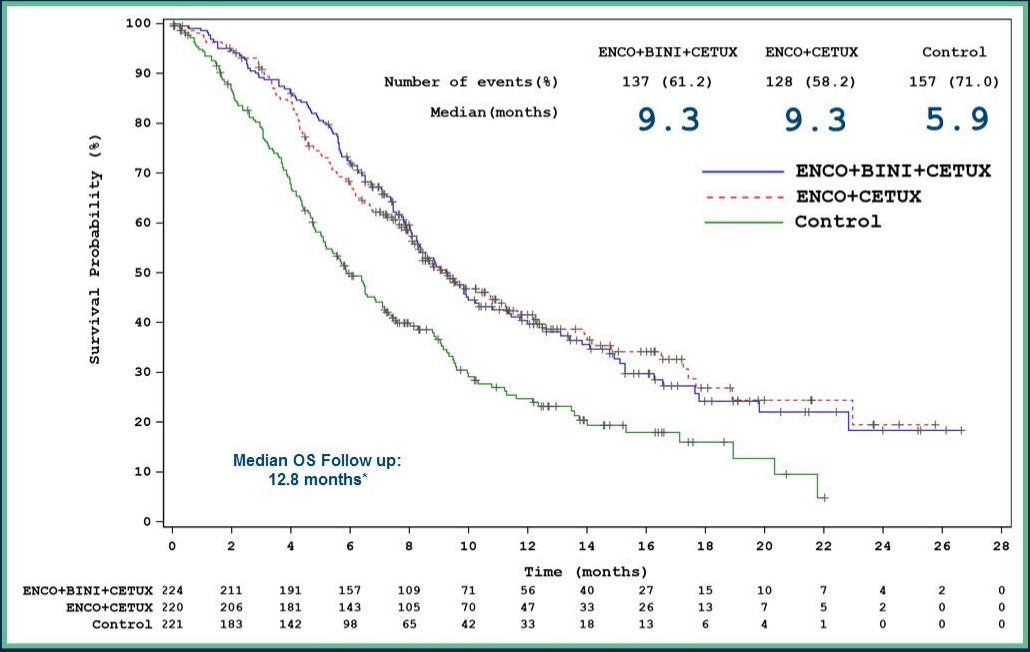
# BEACON CRC: Updated Analysis

- In this updated analysis of BEACON CRC (which includes ORR for all randomized patients (additional 364 patients) and 6 months additional follow-up):
  - The triplet and doublet demonstrated improved OS and ORR in patients with BRAF V600E-mutant mCRC when compared with current standard of care chemotherapy

**The full updated BEACON results with subgroup analysis will be submitted to a future congress**

## Overall Survival




## Objective Response Rate

| Confirmed Response by blinded central review | Triplet N=224 | Doublet N=220 | Control N=221 |
|---|---|---|---|
| **Objective Response Rate** | **27%** | **20%** | **2%** |
| 95% (CI) | (21%, 33%) | (15%, 25%) | (<1%, 5%) |
| p-value vs. Control | <0.0001 | <0.0001 | |





Presented By Scott Kopetz at 2020 Gastrointestinal Cancer Symposium

Gastrointestinal Cancers Symposium
ACCELERATING PERSONALIZED CARE

# Nivolumab + Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/DNA Mismatch Repair Deficient Metastatic Colorectal Cancer: Clinical Update

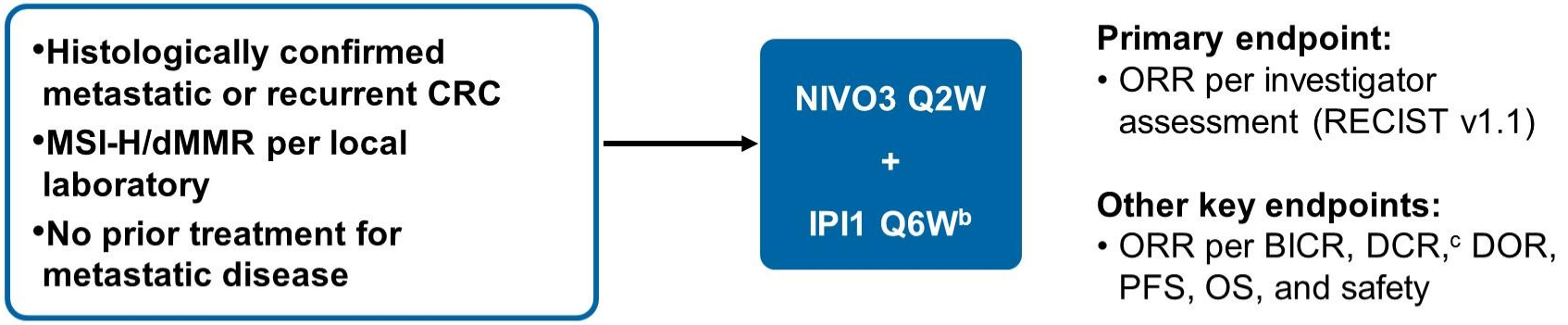
Heinz-Josef Lenz,[1] Sara Lonardi,[2] Vittorina Zagonel,[2] Eric Van Cutsem,[3] Maria Luisa Limon,[4] Ka Yeung Mark Wong,[5] Alain Hendlisz,[6] Massimo Aglietta,[7] Pilar García-Alfonso,[8] Bart Neyns,[9] Andrea Spallanzani,[10] Dana B. Cardin,[11] Tomislav Dragovich,[12] Usman Shah,[13] Ajlan Atasoy,[14*]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

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

*Presentation Number A2*

# CheckMate 142 NIVO3 + IPI1 1L Cohort Study Design

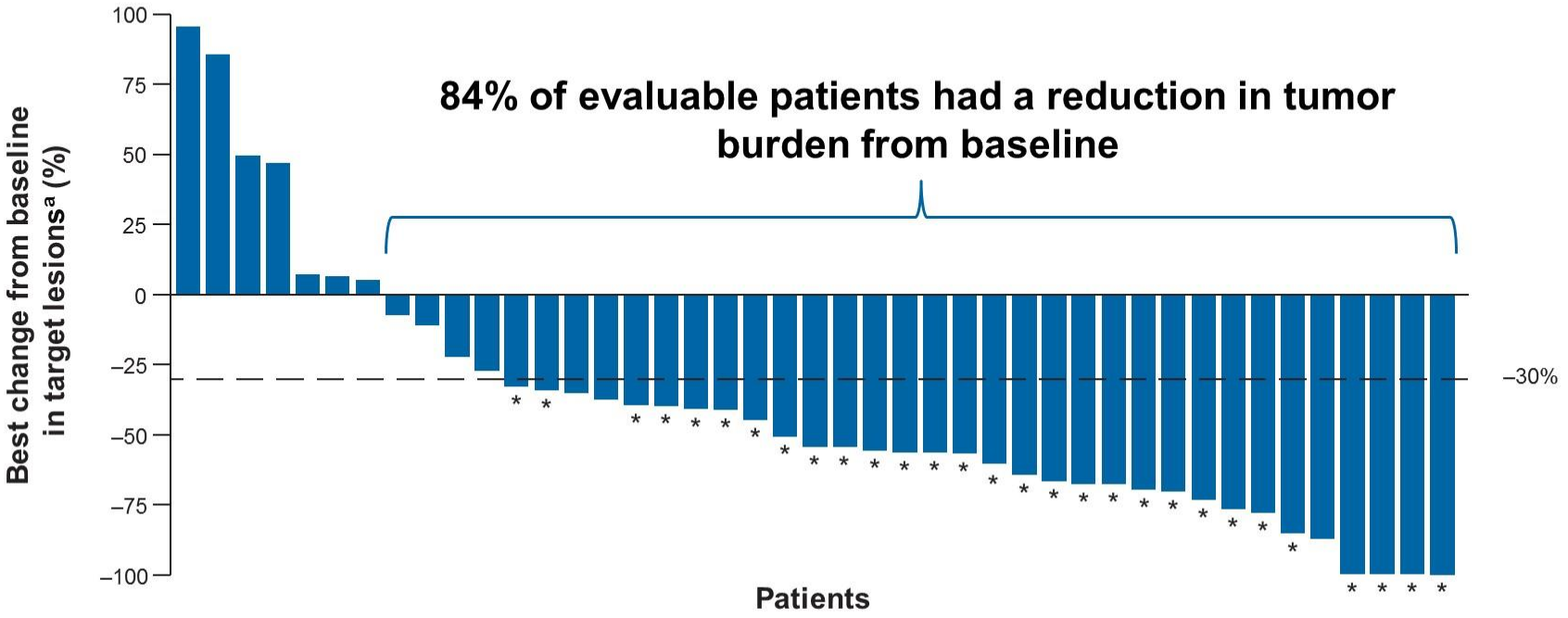
- CheckMate 142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC[a]




- Median duration of follow-up (defined as time from first dose to data cutoff) was 19.9 months (range, 15.1–24.6)

[a]ClinicalTrials.gov number, NCT02060188; [b]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; [c]Patients with a CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients.
BICR, blinded independent central review; CRC, colorectal cancer; DCR, disease control rate; IPI1, ipilimumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

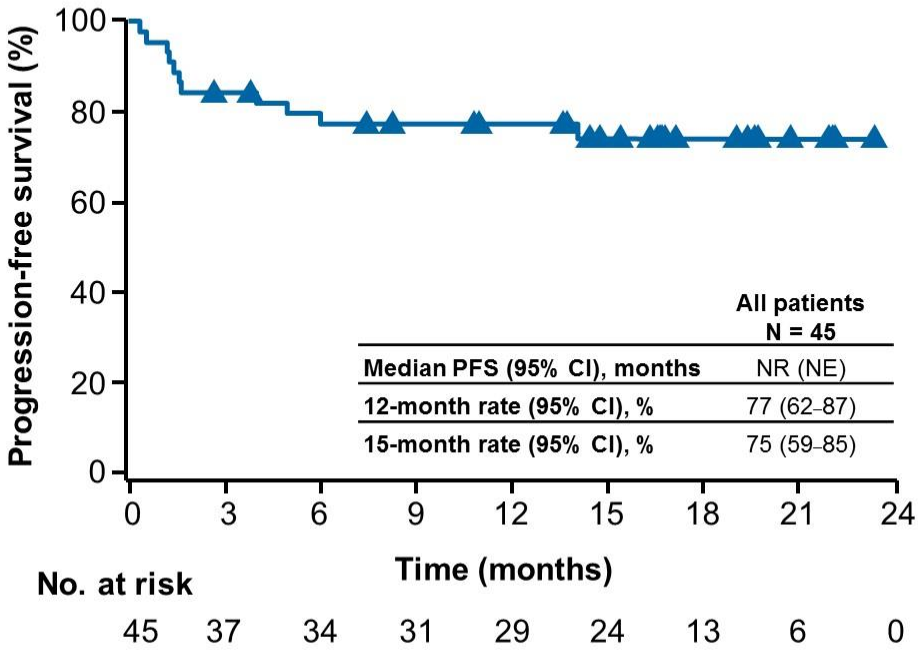
# Best Change From Baseline in Target Lesions



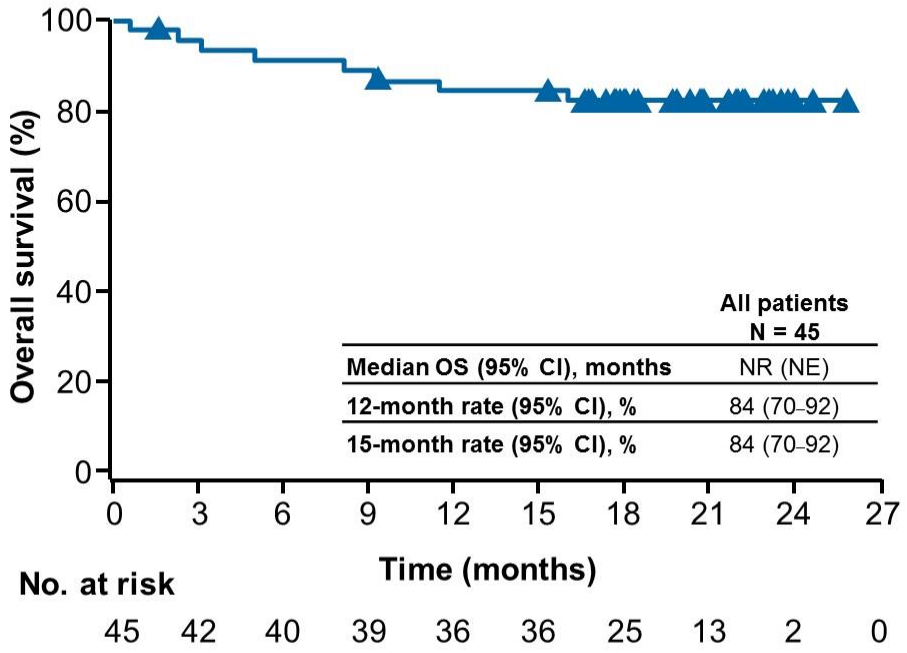

*Confirmed response per investigator assessment.
[a]Evaluable patients per investigator assessment.

# Progression-Free and Overall Survival

## Progression-free survival[a]




## Overall survival




[a]Per investigator assessment.
NE, not estimable.

# Pembrolizumab for Advanced Anal Squamous Cell Carcinoma: Results From the Phase 2 KEYNOTE-158 Study

Aurelien Marabelle,[1] Philippe Cassier,[2] Marwan Fakih,[3] Tormod Guren,[4] Antoine Italiano,[5] Steven Kao,[6] Dorte Nielsen,[7] Paolo Ascierto,[8] Giovanni Mendonca Bariani,[9] Armando Santoro,[10] Jamil Asselah,[11] Anthony El-Khoueiry,[12] Kristen Spencer,[13] Shunji Takahashi,[14] Arkendu Chatterjee,[15] Fan Jin,[15] Kevin Norwood,[15] Jean-Pierre Delord[16]

[1]Gustave Roussy, INSERM U1015, Villejuif, France; [2]Centre Léon Bérard, Lyon, France; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]Oslo University Hospital, Oslo, Norway; [5]Institut Bergonie , Bordeaux, France; [6]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [7]Herlev Hospital, University of Copenhagen, Copenhagen, Denmark ; [8]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; [9]Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil ; [10]Humanitas Clinical and Research Hospital, IRCCS, Humanitas University, Milan, Italy; [11]McGill University, Montreal, QC, Canada; [12]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [13]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [14]Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]Institut Claudius Regaud IUCT-Oncopole, Toulouse, France

Presented By Aurelien Marabelle at 2020 Gastrointestinal Cancer Symposium

# Background

- Outcomes in advanced Anal Squamous Cell Carcinoma (ASCC) are poor
  - InterAACT study (N = 45): first-line carboplatin + paclitaxel provided response rate of 59%, mPFS of 8.1 mo, and mOS of 20 mo[1]
- Second-line systemic treatments are limited to combination chemotherapy regimens (including carboplatin + paclitaxel if not received first-line), followed by anti–PD-1 treatment as preferred subsequent therapy[2,3]
- Pembrolizumab demonstrated acceptable antitumor activity and safety as monotherapy in patients with PD-L1–positive (defined by CPS ≥1) advanced anal carcinoma in the phase 1b multicohort KEYNOTE-028 study, after a median follow-up of 10.6 mo (N = 25)[4]
  - ORR in patients with ASCC (n = 24): 17% (95% CI, 5.0–37)
  - Median DOR for the cohort was not reached (range, <0.1+ to 9.2+ mo)

DOR, duration of response; mOS, median overall survival; mPFS, median progression free survival.

1. Rao S, et al. *Ann Oncol*. 2018;29(suppl 8): abstract LBA21. 2. Eng C, et al. *Am Soc Clin Oncol Educ Book*. 2019; 39:216-225. 3. NCCN Guidelines. Anal carcinoma, version 1.2020. Available at: https://www.nccn.org. 4. Ott PA, et al. *Ann Oncol*. 2017;28(5):1036-1041.

# KEYNOTE-158 (NCT02628067)
## ASCC Cohort

**Key Eligibility Criteria**

- Progression on or intolerance to ≥1 line of standard therapy for unresectable and/or metastatic disease
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- Provision of a tumor sample for biomarker assessment
  - Any PD-L1 status permitted[a]
    - PD-L1–positive defined as PD-L1 CPS ≥1
    - PD-L1–negative defined as PD-L1 CPS <1

**Pembrolizumab**
**200 mg IV Q3W**

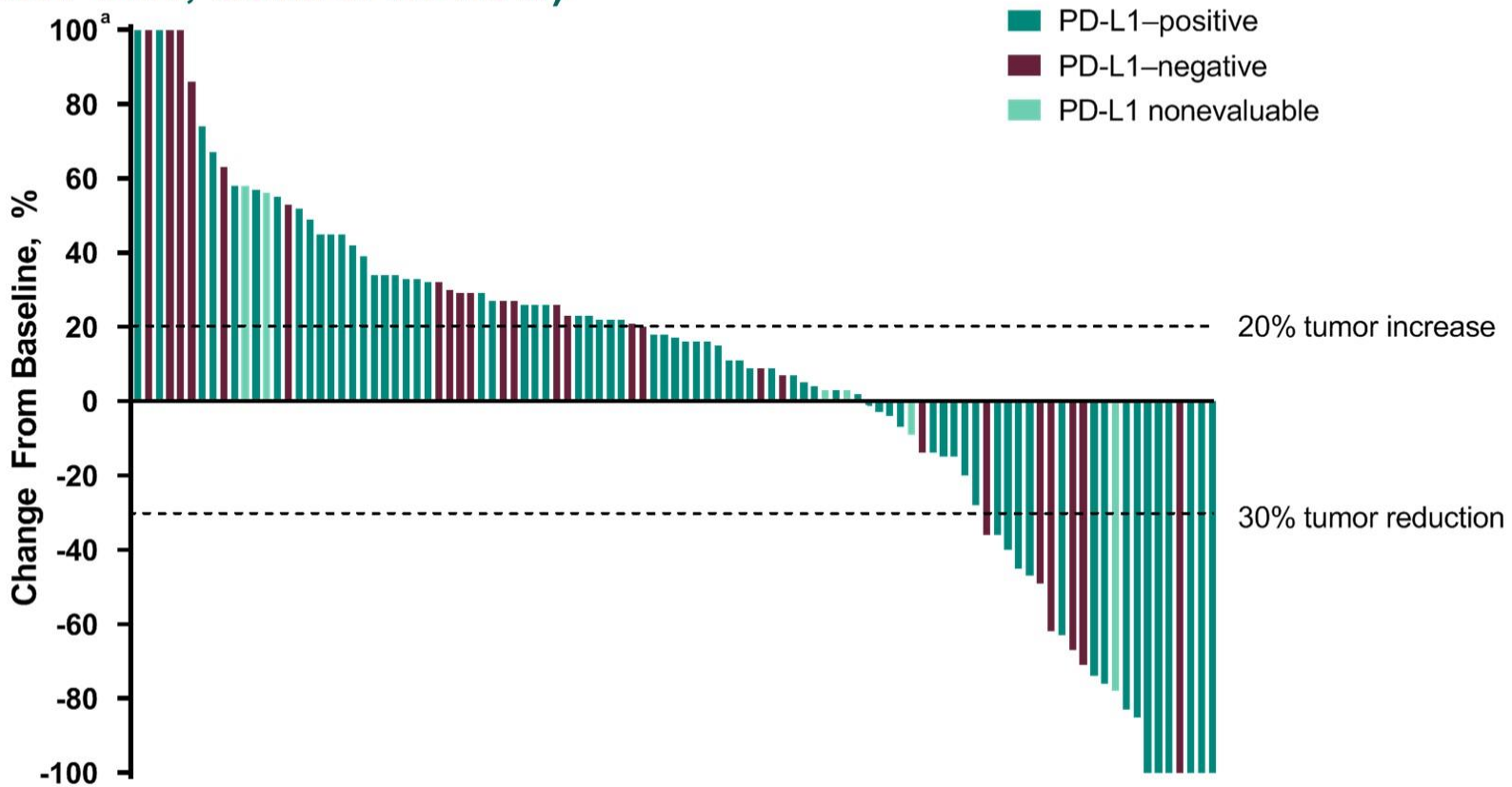
**For 35 cycles (approximately 2 years) or until disease progression,[b] intolerable toxicity, investigator decision, or patient withdrawal**

**Primary endpoint:** ORR (RECIST v1.1, central review), including in biomarker-selected subgroups
**Secondary endpoints:** DOR, PFS (RECIST v1.1, central review), OS, and safety

Response assessed every 9 weeks for 12 months; then every 12 weeks thereafter

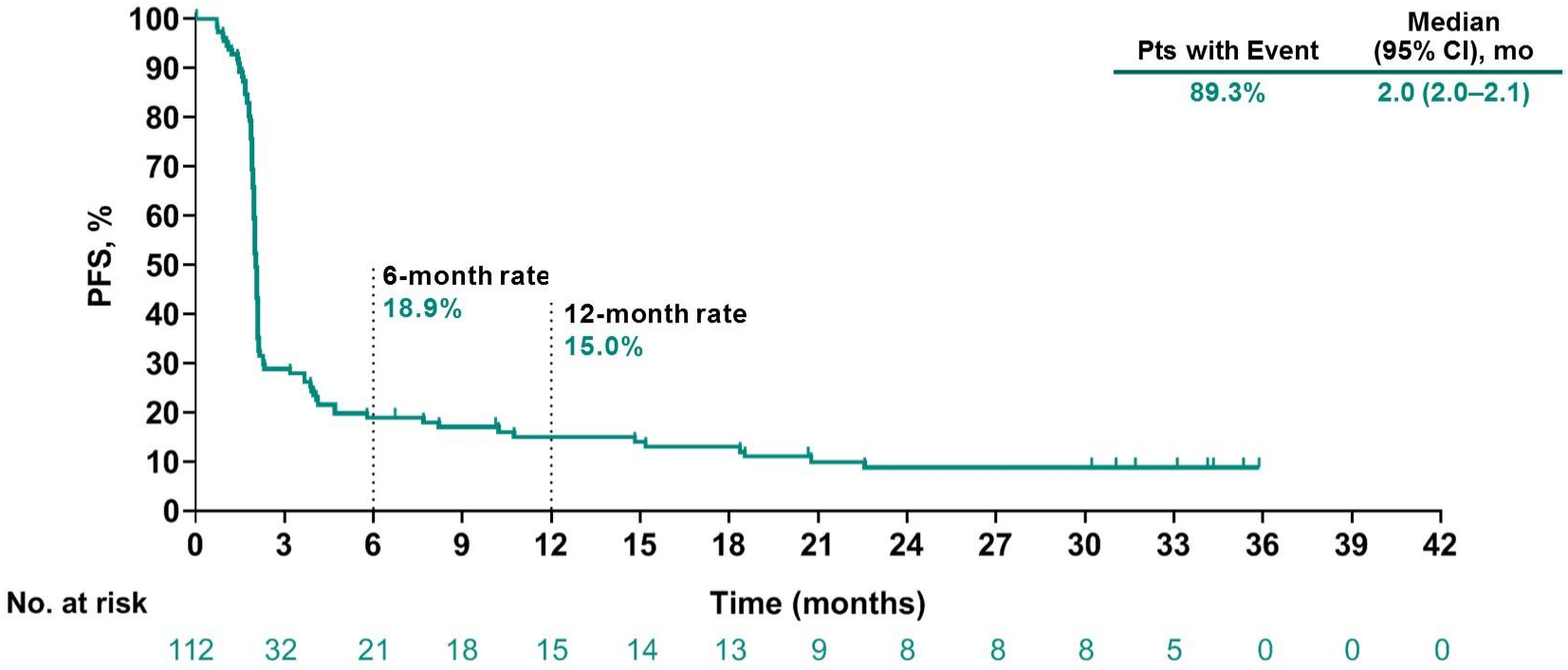
CPS, combined positive score; IV, intravenous.
[a]PD-L1 status assessed centrally using PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA).
[b]Clinically stable patients with radiologic progression could remain on treatment until progression was confirmed on subsequent imaging assessment.

# Best percentage change from baseline in target lesion size
## (RECIST v1.1, Central Review)




[a]Percentage changes from baseline >100% are presented as 100%.
Data cutoff date: June 27, 2019.

# Progression-Free Survival
## (RECIST v1.1, Central Review)




Data cutoff date: June 27, 2019.

## Summary

- Pembrolizumab demonstrated antitumor activity, durable response, and encouraging OS, with manageable safety in patients with previously treated ASCC, regardless of PD-L1 status
  - ORR of 10.7% (PD-L1–positive, 14.7%; PD-L1–negative, 3.3%)
  - Median DOR not reached (range, 6.0+ to 33.9+ mo)
  - Median OS,11.9 mo (95% CI, 9.1–14.9); 12-mo OS rate, 49.1%

- Safety profile was consistent with that previously observed for pembrolizumab in patients with advanced solid tumors