

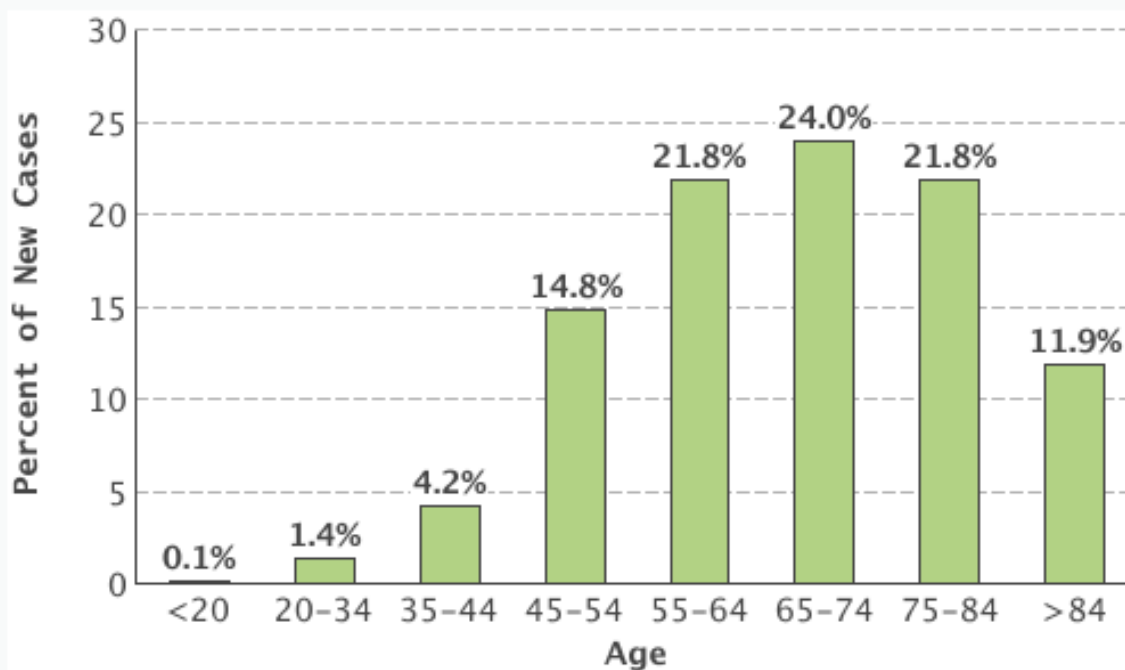
# Metastatik Kolon Kanserinde İlk Basamak Tedavi Sonrası Progresyon Gösteren Hastalarda Tedavi Seçenekleri

Dr. Deniz Tural

Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi  
Tıbbi Onkoloji

# Kolon Kanseri İnsidans ve Mortalite

Percent of New Cases by Age Group: Colon and Rectum Cancer



Colon and rectum cancer is most frequently diagnosed among people aged 65-74.

Median Age  
At Diagnosis

68

SEER 18 2009-2013, All Races, Both Sexes

# Kolon Kanseri İnsidans ve Mortalite

Common Types of Cancer	Estimated New Cases 2016	Estimated Deaths 2016
1. Breast Cancer (Female)	246,660	40,450
2. Lung and Bronchus Cancer	224,390	158,080
3. Prostate Cancer	180,890	26,120
<b>4. Colon and Rectum Cancer</b>	<b>134,490</b>	<b>49,190</b>
5. Bladder Cancer	76,960	16,390
6. Melanoma of the Skin	76,380	10,130
7. Non-Hodgkin Lymphoma	72,580	20,150
8. Thyroid Cancer	64,300	1,980
9. Kidney and Renal Pelvis Cancer	62,700	14,240
10. Leukemia	60,140	24,400

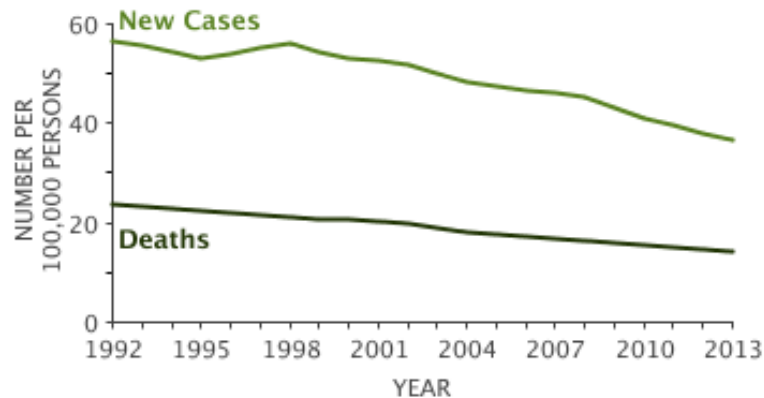
Colon and rectum cancer represents 8.0% of all new cancer cases in the U.S.



In 2016, it is estimated that there will be 134,490 new cases of colon and rectum cancer and an estimated 49,190 people will die of this disease.

# Kolon Kanseri İnsidans ve Mortalite

Estimated New Cases in 2016	134,490
% of All New Cancer Cases	8.0%
Estimated Deaths in 2016	49,190
% of All Cancer Deaths	8.3%



Percent Surviving 5 Years
<b>65.1%</b>
2006-2012

**Number of New Cases and Deaths per 100,000:** The number of new cases of colon and rectum cancer was 41.0 per 100,000 men and women per year. The number of deaths was 15.1 per 100,000 men and women per year. These rates are age-adjusted and based on 2009–2013 cases and deaths.

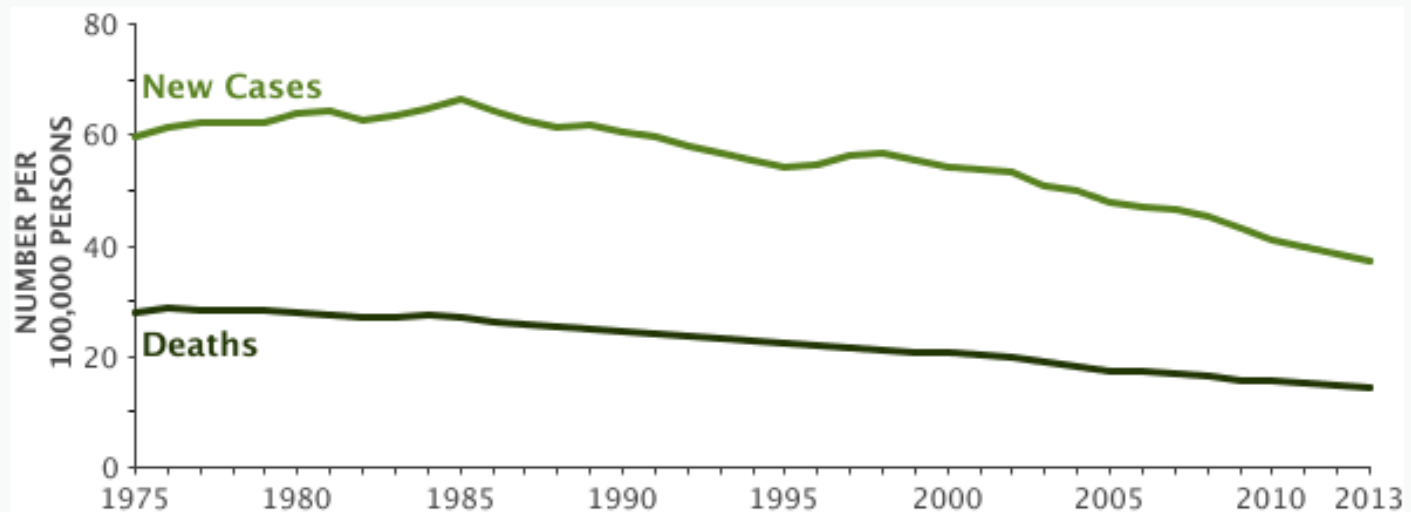
**Lifetime Risk of Developing Cancer:** Approximately 4.5 percent of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime, based on 2010–2012 data.

**Prevalence of This Cancer:** In 2013, there were an estimated 1,177,556 people living with colon and rectum cancer in the United States.

# Kolon Kanseri İnsidans ve Mortalite

## New Cases, Deaths and 5-Year Relative Survival

[View Data Table](#)



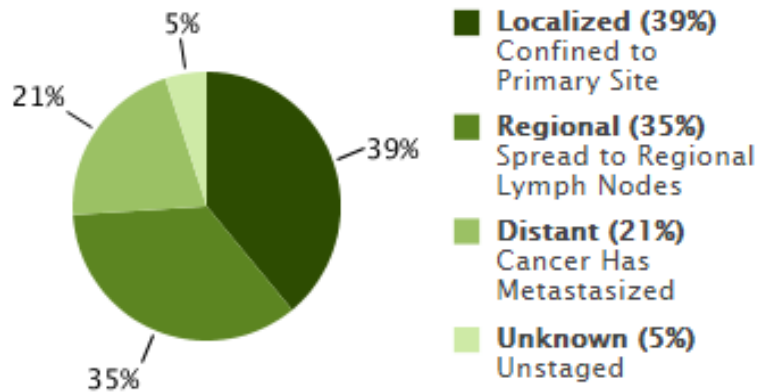
Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	48.6%	51.2%	58.1%	60.8%	59.7%	64.8%	65.7%	67.2%

SEER 9 Incidence & U.S. Mortality 1975-2013, All Races, Both Sexes. Rates are Age-Adjusted.

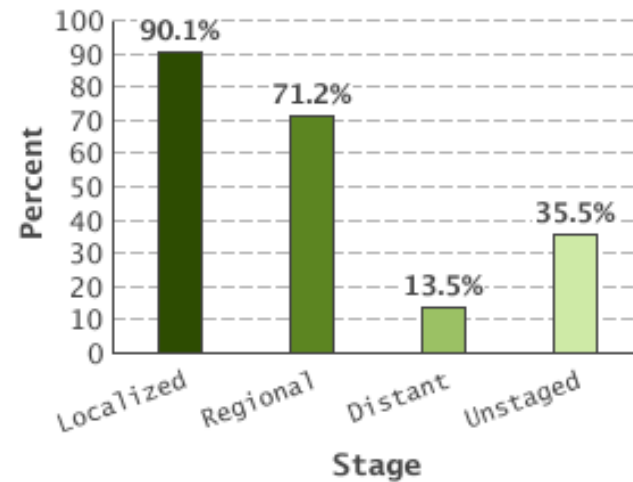
# Kolon Kanseri İnsidans ve Mortalite

## Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Colon and Rectum Cancer

Percent of Cases by Stage



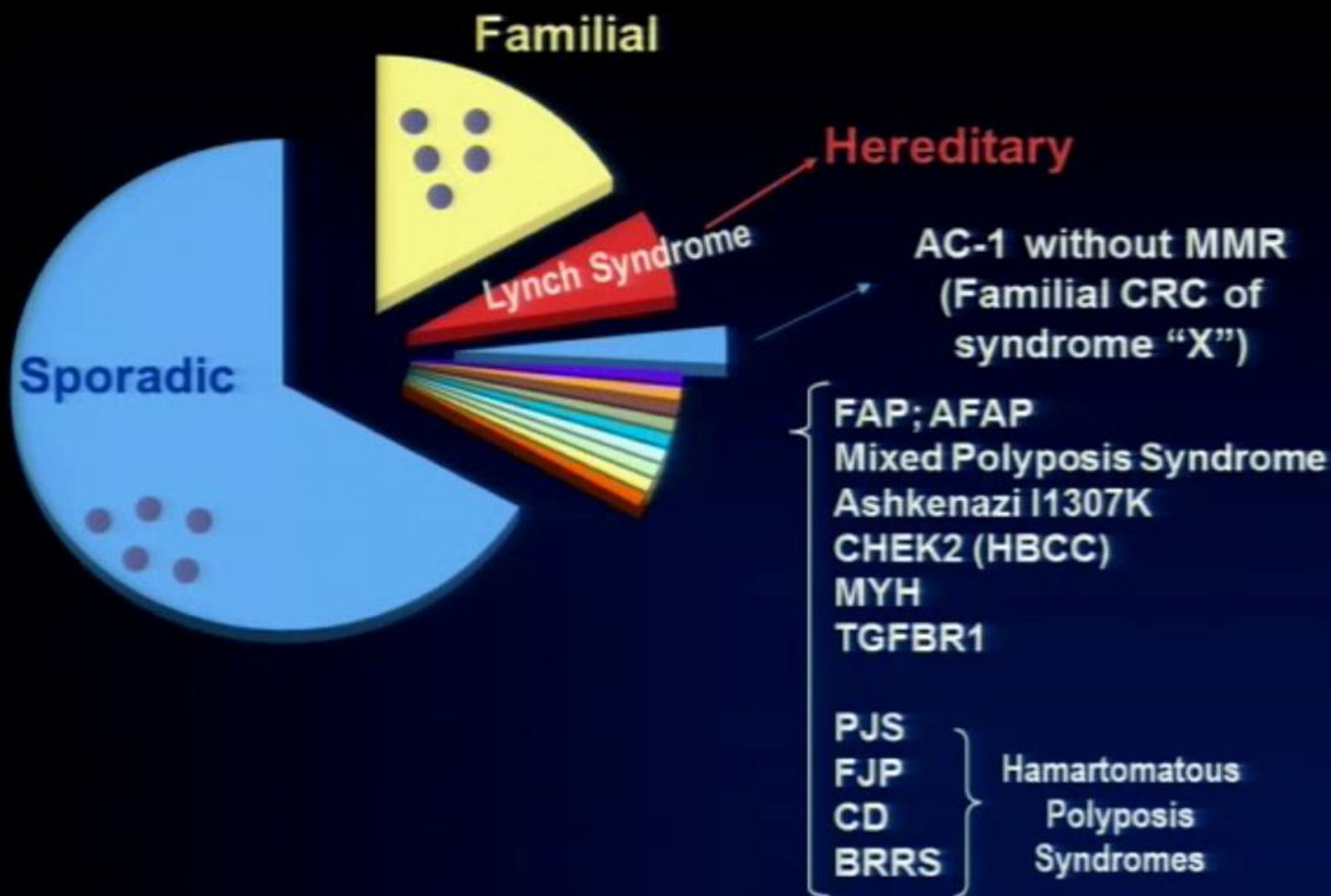
5-Year Relative Survival



SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

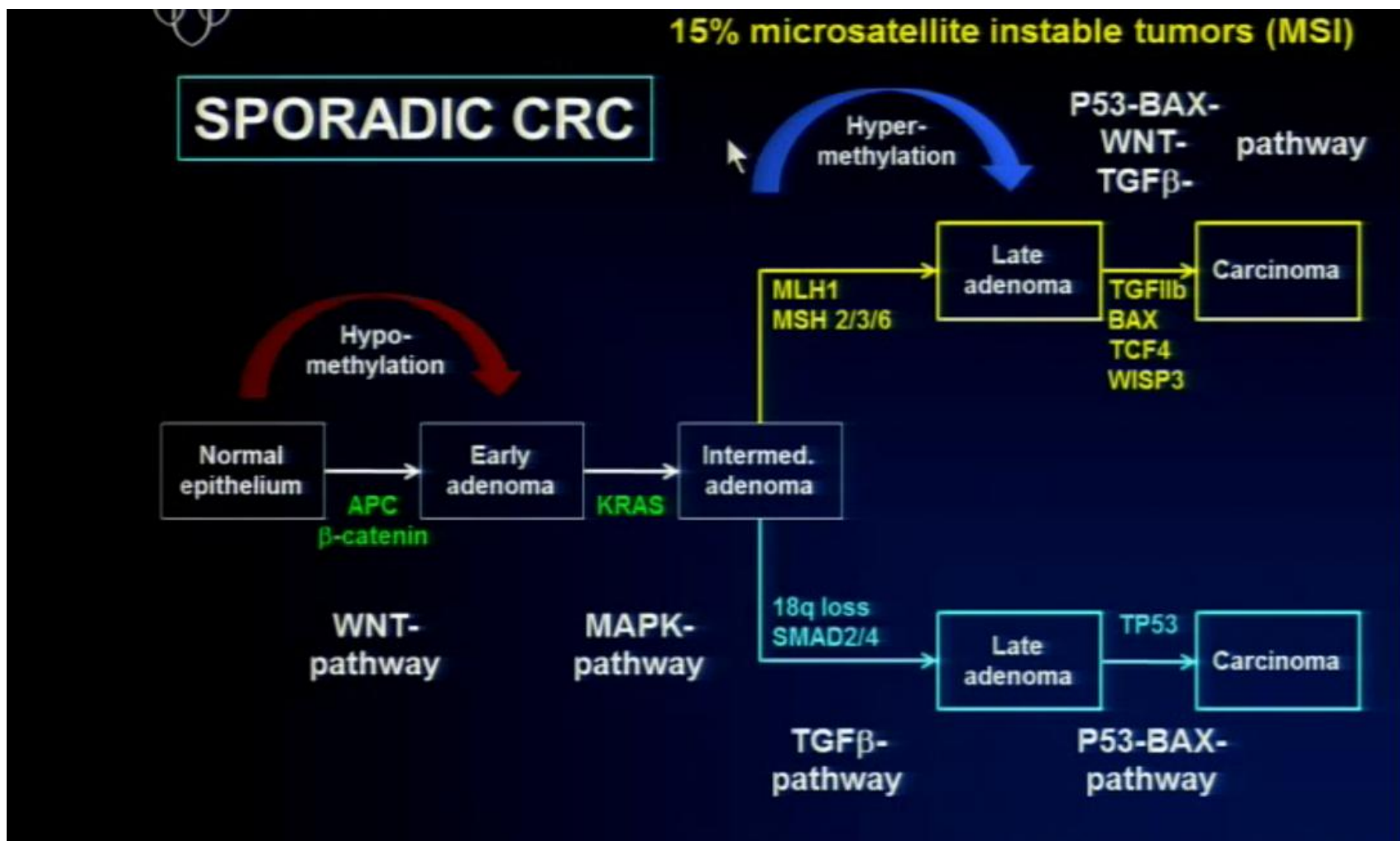
# Kolon Kanseri

## Genetik ve Risk Faktörleri



# Kolon Kanseri

## Genetik ve Risk Faktörleri





# Kolon Kanseri Tedavi

## History of adjuvant therapy of colon cancer

- 5-FU/lev superior to surgery alone

- 5-FU/LV superior to surgery alone

- 5-FU/LV superior to 5-FU/lev

- 6- and 12-month treatment cycles equivalent

- Lev unnecessary

- High-dose and low-dose LV equivalent

- Monthly and weekly treatment equivalent

- LV5FU2 and monthly bolus equivalent

1990

1994

1998

2002

Moertel et al. *Ann Intern Med.* 1995;122:321.

Francini et al. *Gastroenterol.* 1994;106:899.

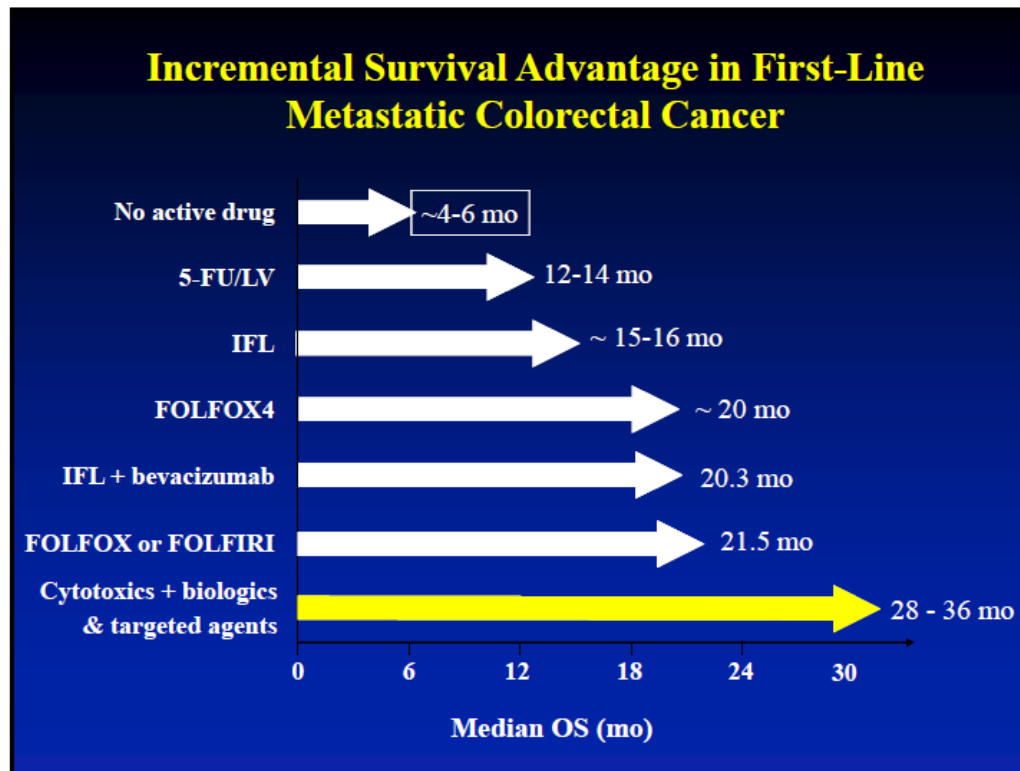
Wolmark et al. *Proc Am Soc Clin Oncol.* 1996;15:205. Abstract

O'Connell et al. *J Clin Oncol.* 1998;16:295.

Haller et al. *Proc Am Soc Clin Oncol.* 1998;17:256a. Abstract 982.

Andre et al. *Proc Am Soc Clin Oncol.* 2002. Abstract 529.

# Kolon Kanseri Tedavi



# Kolon Kanseri Tedavi

## Some Therapy Options for Advanced Colorectal Cancer:

Response rates and survival (targeted agents in yellow)

### First Line

- FOLFOX or  
- CapeOx or  
- FOLFIRI or  
- FOLFOXIRI  
+/- **cetux/pmab** (RAS)  
+/- **bevacizumab**



### Second Line

- FOLFOX or  
- Irinotecan or  
- FOLFIRI  
+/- **bevacizumab**  
+/- **afibercept**  
+/- **ramucirumab**  
+/- **cetuximab** (RAS)  
+/- **panitumumab** (RAS)



### Third Line

- Irinotecan +  
**cetuximab** (RAS)  
- **cetuximab** (RAS)  
- **panitumumab** (RAS)  
- **regorafenib**  
- **TAS-102**

(RAS)= KRAS and NRAS testing

### Response Rates in Randomized Trials:

**30-70%**



**5-15%**



**10-20%**

### Survival Benefit in Randomized Trials:

**Yes**

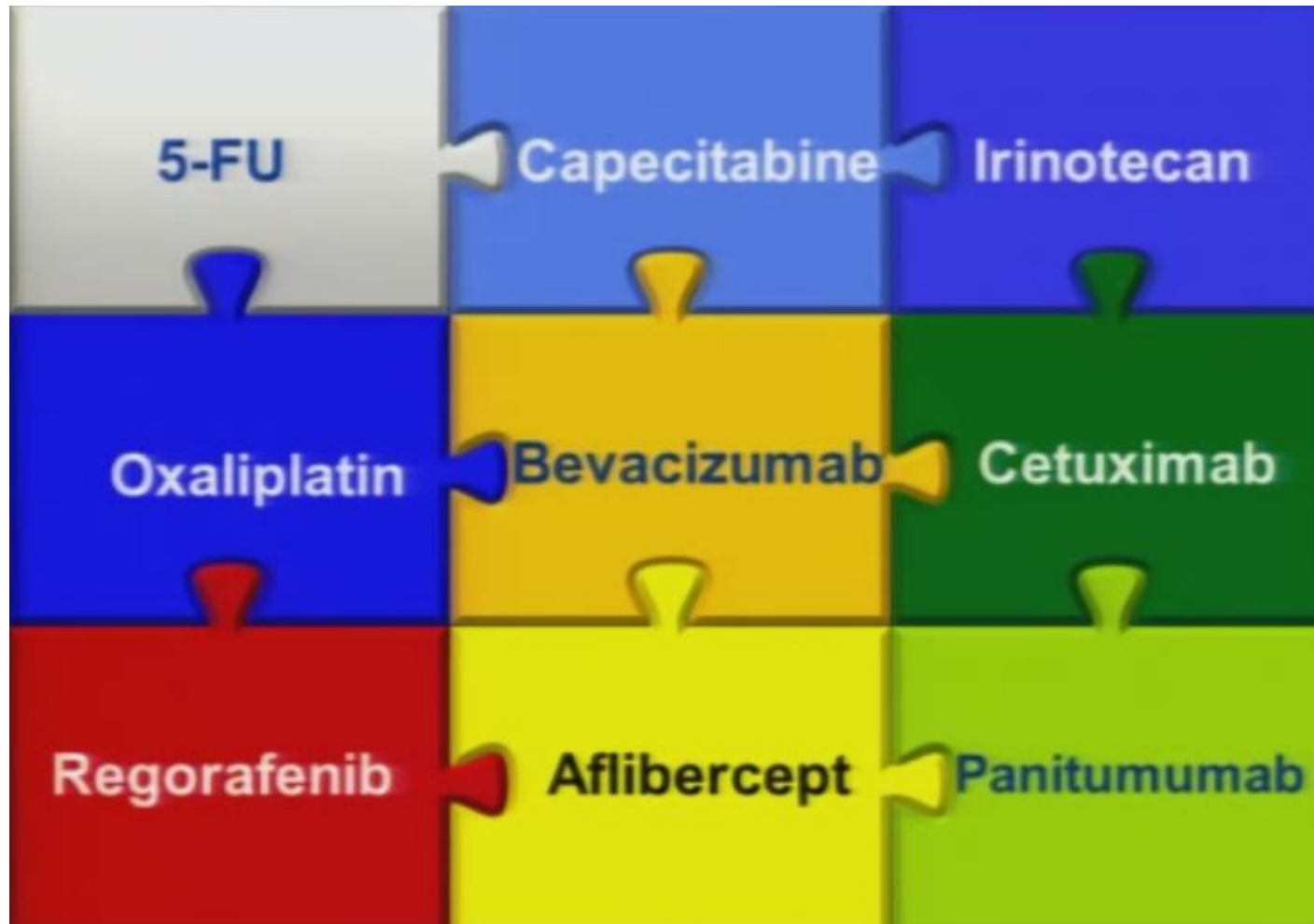


**Yes**



**Yes**

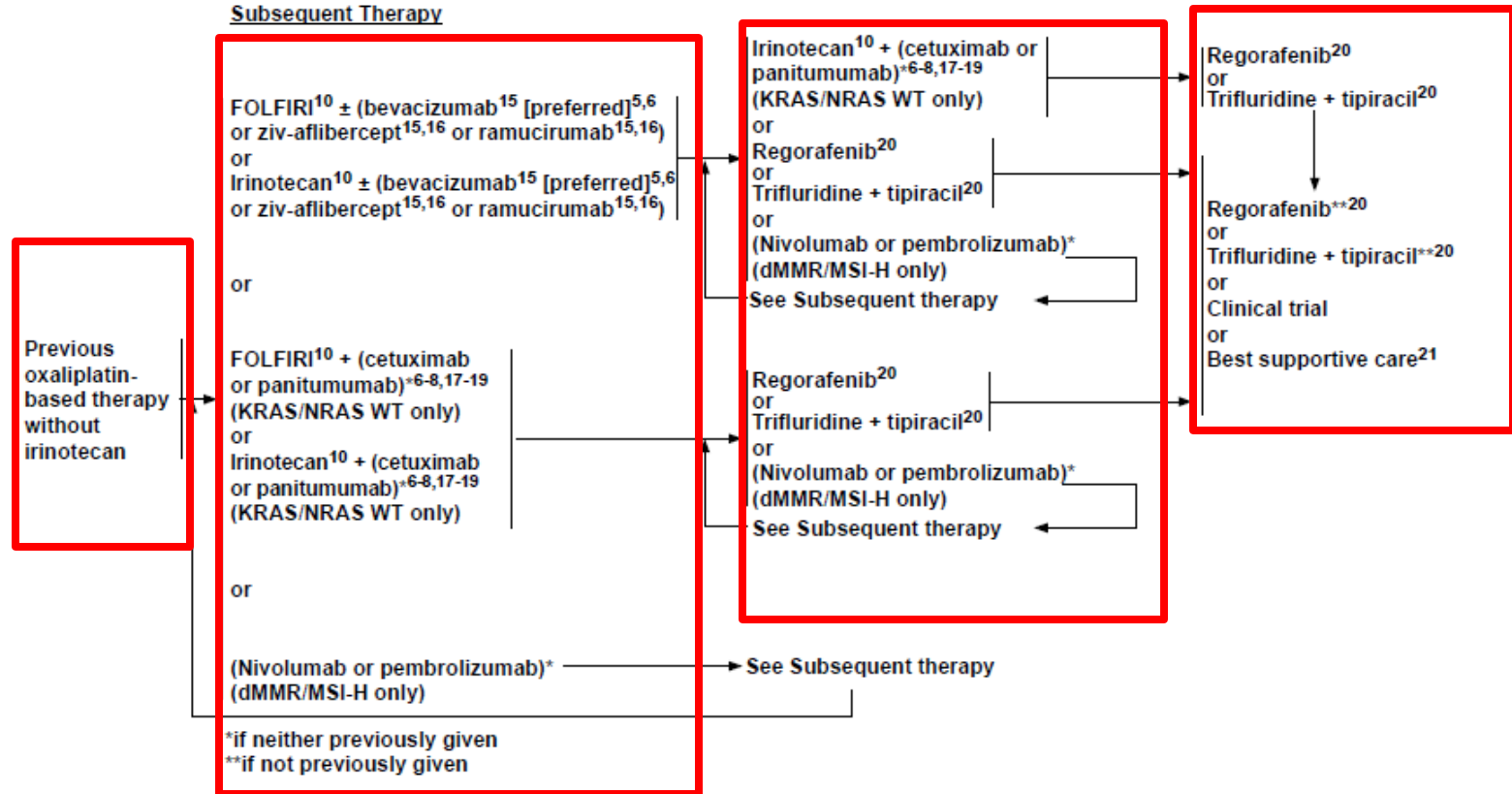
# Metastatik Kolon Kanseri Tedavi



# Metastatik Kolon Kanseri Tedavi

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 2 of 10)

Subsequent Therapy



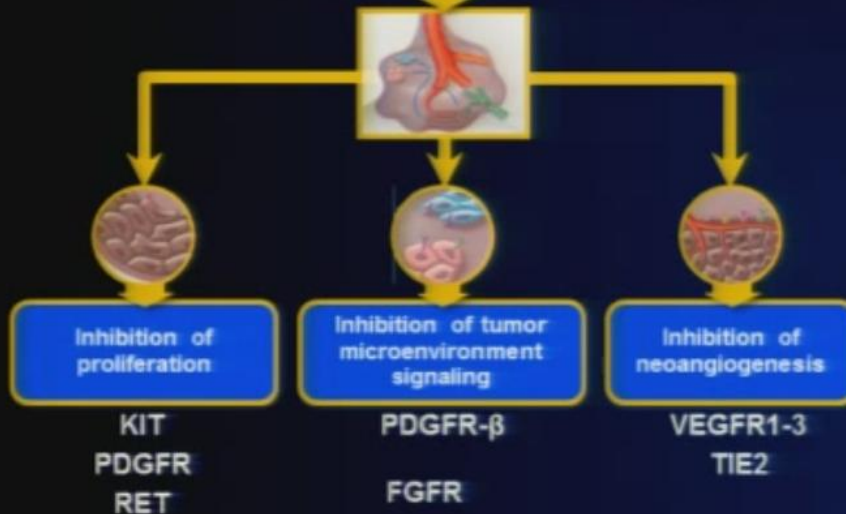
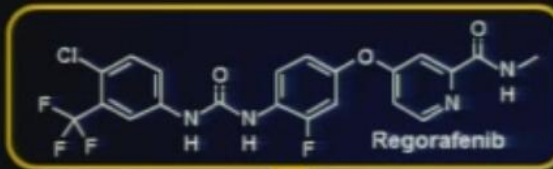
[See footnotes COL-C 6 of 10](#)

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



# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## Regorafenib (BAY 73-4506), an Oral Multikinase Inhibitor Targeting Multiple Tumor Pathways



Biochemical Activity	Regorafenib IC <sub>50</sub> mean ± SD nmol/l (n)
VEGFR1	13 ± 0.4 (2)
Murine VEGFR2	4.2 ± 1.6 (10)
Murine VEGFR3	46 ± 10 (4)
TIE2	311 ± 46 (4)
PDGFR-β	22 ± 3 (2)
FGFR1	202 ± 18 (6)
KIT	7 ± 2 (4)
RET	1.5 ± 0.7 (2)
RAF-1	2.5 ± 0.6 (4)
B-RAF	28 ± 10 (6)
B-RAF <sup>V600E</sup>	19 ± 6 (6)

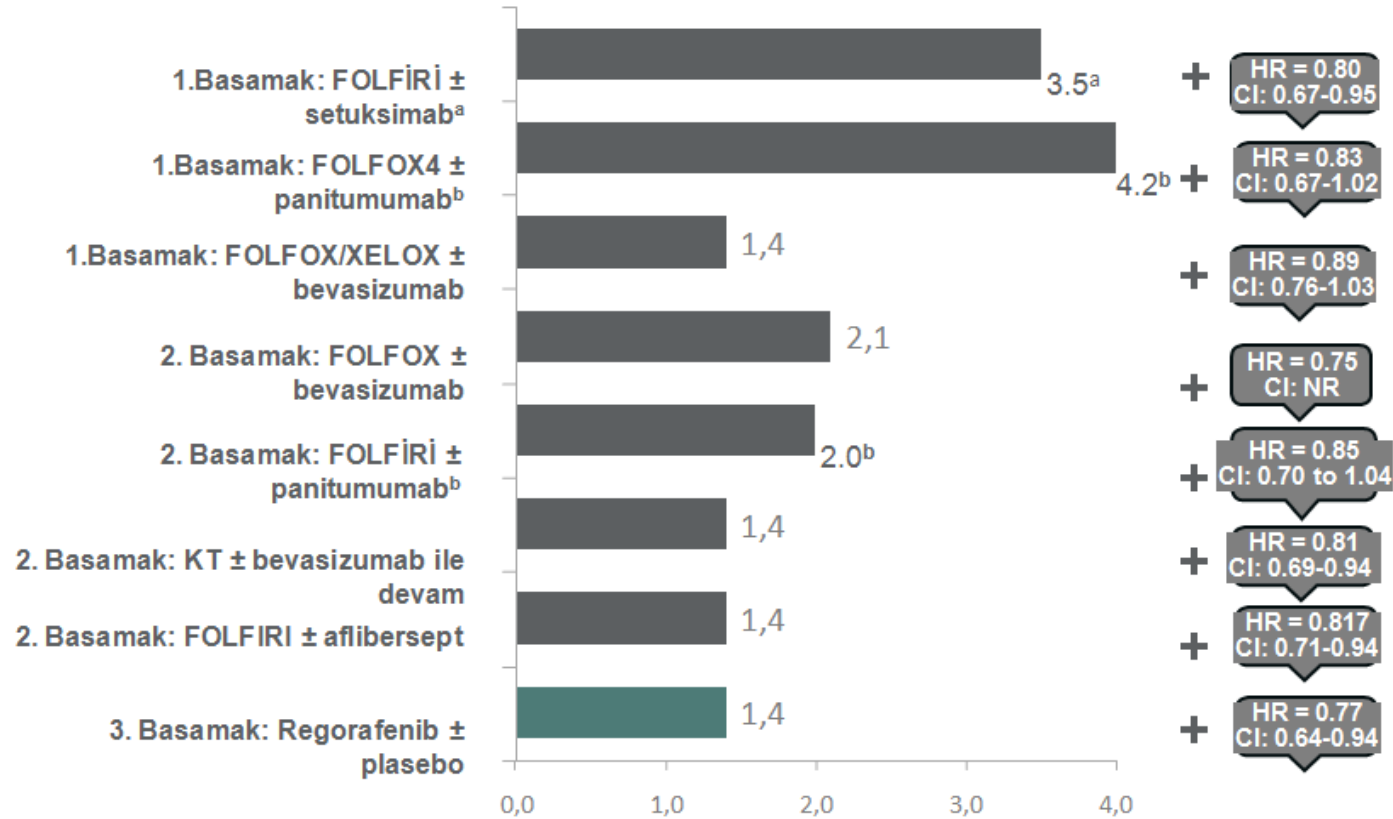
Wilhelm SM, et al. *Int J Cancer*. 2011;129(1):245-255.

Mross K, et al. *Clin Cancer Res*. 2012;18(9):2658-2667.

Strumberg D, et al. *Expert Opin Invest Drugs*. 2012;21(6):879-889.



# Metastatik Kolon Kanserinde Tedavi Seçenekleri



<sup>a</sup>KRAS WT subset; *P* value = not significant.

<sup>b</sup>KRAS WT subset; *P* value = significant.

Medyan Genel Sağlıkım Farkı (Ay)



# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## Regorafenib Faz III Çalışmaları

CORRECT  
CONCUR

### Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial

Wallerby M, et al. *Lancet* 2015; 385: 1731-42. doi:10.1016/S0140-6736(15)00050-9

**Summary**  
Background: To explore options available for patients with metastatic colorectal cancer who progress after all approved standard therapies, we compared regorafenib monotherapy with placebo in a randomised phase 3 trial to assess the maximum tolerable regorafenib dose in these patients.

**Methods:** We did the trial at 33 centres in 16 countries. Patients with documented metastatic colorectal cancer and progression during or within 3 months after the last standard therapy were randomised (by a 2:1 ratio) to compare regorafenib monotherapy (at and increasing doses) with placebo. The primary endpoint was overall survival. Secondary endpoints were progression-free survival, time to next anti-neoplastic therapy, and quality of life. The trial was registered at ClinicalTrials.gov number NCT01328532.

**Findings:** Between April 20, 2012, and March 22, 2015, 952 patients were randomised. 748 patients were randomised to receive regorafenib (n=498) or placebo (n=254), and 204 patients assigned treatment regorafenib 160 mg (placebo n=102) completed the study analysis. The primary endpoint of overall survival was not a predefined secondary endpoint; data cutoff was on July 21, 2015. Median overall survival was 4.2 months in the regorafenib group versus 3.4 months in the placebo group (hazard ratio 1.17; 95% CI 1.04 to 1.32; p=0.007). Secondary endpoints showed no statistically significant differences between regorafenib and placebo. The most common adverse events of grade three or higher related to regorafenib were hand-foot skin reaction (31 patients, 7%), fatigue (16, 3%), diarrhoea (16, 3%), hypertension (16, 3%), and rash or dermatitis (12, 3%).

**Interpretation:** Regorafenib is the first endothelin-receptor antagonist with overall benefits in metastatic colorectal cancer which has progressed after all standard therapies. The present study provides evidence for a continuing role of targeted treatment after disease progression, with regorafenib offering a potential new line of therapy in this heterogeneous population.

**Funding:** Bayer Healthcare Pharmaceuticals.

**Introduction:** Worldwide, each 2.2 million people are diagnosed with and die from colorectal cancer each year. In fact, 9% of patients develop metastases and most of these patients have unresectable tumours. Targeted therapies for these patients include chemotherapy based on fluoropyrimidines, oxaliplatin, and irinotecan used in combination with anti-epidermal and anti-vascular endothelial growth factor antibodies. In addition to EGFR and VEGFR tyrosine kinase inhibitors, targeting epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and other tyrosine kinase receptors has been shown to improve progression-free survival in patients who have disease progression despite all currently available therapies. In some early phase studies, progression-free survival was significantly improved in patients who received regorafenib compared with placebo. In a phase III study, regorafenib, given at a dose of 160 mg once daily for the first 3 weeks of each 4-week

Articles



Articles

### Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial

Wallerby M, et al. *Lancet* 2015; 385: 1743-52. doi:10.1016/S0140-6736(15)00051-7

**Summary**  
Background: In the international randomised phase 3 CORRECT trial (NCT01328532), regorafenib significantly improved overall survival versus placebo in patients with treatment-refractory metastatic colorectal cancer. We did the CONCUR trial to assess regorafenib in a broader population of Asian patients with refractory metastatic colorectal cancer who were unable to tolerate standard treatment. Patients had to have an Eastern Cooperative Oncology Group performance status of 1 or 2 (regardless of age), and adequate liver, renal, and cardiac function, without other successful medical disorders. We randomised Asian patients 2:1 with a comprehensive assessment of baseline for the study to receive regorafenib plus best supportive care (placebo plus best supportive care) or placebo plus best supportive care. The primary endpoint was overall survival. Secondary endpoints were progression-free survival, time to next anti-neoplastic therapy, and quality of life. The trial was registered at ClinicalTrials.gov number NCT01328532.

**Methods:** In this randomised, double-blind, placebo-controlled, parallel-group phase 3 trial, Asian patients with previously treated metastatic colorectal cancer who had received at least two previous systemic lines or were unable to tolerate standard treatment. Patients had to have an Eastern Cooperative Oncology Group performance status of 1 or 2 (regardless of age), and adequate liver, renal, and cardiac function, without other successful medical disorders. We randomised Asian patients 2:1 with a comprehensive assessment of baseline for the study to receive regorafenib plus best supportive care (placebo plus best supportive care) or placebo plus best supportive care. The primary endpoint was overall survival. Secondary endpoints were progression-free survival, time to next anti-neoplastic therapy, and quality of life. The trial was registered at ClinicalTrials.gov number NCT01328532.

**Findings:** Between April 20, 2012, and July 4, 2015, we randomised 242 patients and randomised 160 patients to receive regorafenib plus best supportive care (n=107) or placebo plus best supportive care (n=135). In the regorafenib group, median overall survival was 4.2 months (95% CI 3.7-4.7) versus 3.4 months (95% CI 3.0-3.9) in the placebo group. Progression-free survival was 4.2 months (95% CI 3.7-4.7) versus 3.4 months (95% CI 3.0-3.9) in the placebo group. Secondary endpoints showed no statistically significant differences between regorafenib plus best supportive care and placebo plus best supportive care. The most common adverse events were hand-foot skin reaction (22 patients, 14%), fatigue (16 patients, 10%), diarrhoea (16 patients, 10%), hypertension (16 patients, 10%), and rash or dermatitis (12 patients, 8%).

**Interpretation:** This phase 3 trial is the second to show an overall survival benefit with regorafenib compared with placebo in patients with treatment-refractory metastatic colorectal cancer, substantiating the role of regorafenib as an important treatment option for patients whose disease has progressed after standard treatment. In this trial, providing standard treatment plus regorafenib was not associated with improved survival. Adverse events were generally consistent with the known side profile of regorafenib in this setting.

**Funding:** Bayer Healthcare Pharmaceuticals.

**Introduction:** There is a need for therapies that improve the survival of colorectal cancer patients who have disease progression despite all currently available therapies. In some early phase studies, progression-free survival was significantly improved in patients who received regorafenib compared with placebo. In a phase III study, regorafenib, given at a dose of 160 mg once daily for the first 3 weeks of each 4-week

Articles



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# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## Gerçek Yaşam Verileri

CONSIGN  
REBECCA

Annals of Oncology (Supplement 4): 1171-1173, 2015  
doi:10.1093/annonc/mdv025

### abstracts

**1171-1173** **Results from the large, open-label phase 3b CONSIGN study of regorafenib in patients with previously treated metastatic colorectal cancer**

E. Van Cutsem<sup>1</sup>, F. Ciardiello<sup>2</sup>, J.P. Selig<sup>3</sup>, R. Hoffhans<sup>4</sup>, U. Wenz<sup>5</sup>, M. Gossens<sup>6</sup>, A. Drouot<sup>7</sup>, A. Meyer<sup>8</sup>, J. Krawinkel<sup>9</sup>, J. D'Amico<sup>10</sup>, A. Barbiere<sup>11</sup>

<sup>1</sup>European Cancer Institute, University Hospital Louvain, Louvain-la-Neuve, Belgium; <sup>2</sup>Università di Bari, Bari, Italy; <sup>3</sup>University of Toronto, Toronto, Canada; <sup>4</sup>University of Cologne, Cologne, Germany; <sup>5</sup>University of Turin, Turin, Italy; <sup>6</sup>University of Padua, Padua, Italy; <sup>7</sup>University of Pisa, Pisa, Italy; <sup>8</sup>University of Bari, Bari, Italy; <sup>9</sup>University of Bari, Bari, Italy; <sup>10</sup>University of Bari, Bari, Italy; <sup>11</sup>University of Bari, Bari, Italy

**Background:** Regorafenib is an oral multikinase inhibitor that targets tumor angiogenesis, oncogenes, and the tumor microenvironment. The CONSIGN (phase 3b) trial showed that regorafenib significantly improved overall survival (OS) and quality of life (QoL) in patients with previously treated metastatic colorectal cancer (mCRC) and is the only agent approved in this setting. CONSIGN (NCT01288386) was initiated to allow patients with mCRC access to regorafenib before reaching end-of-trials and to characterize the safety of regorafenib in a large cohort of patients (primary objective).

**Methods:** CONSIGN was a prospective, open-label, single-arm study carried out at 108 sites in 15 countries. Patients with mCRC who progressed after approved standard therapies and had an ECOG performance status (PS) of 0-1 received regorafenib 160 mg once daily for the first 2 weeks of each 4-week cycle. Treatment was continued until disease progression, death, or withdrawal from the treatment because of progression was at the investigator's discretion. The primary endpoint was safety. Progression-free survival (PFS) (per investigator assessment) was the only efficacy variable assessed.

RESEARCH ARTICLE

Open Access



## Survival, safety, and prognostic factors for outcome with Regorafenib in patients with metastatic colorectal cancer refractory to standard therapies: results from a multicenter study (REBECCA) nested within a compassionate use program

Antoine Adenis<sup>1,2\*</sup>, Christelle de Fouchardiere<sup>2</sup>, Bernard Paule<sup>3</sup>, Pascal Burini<sup>4</sup>, David Touzeau<sup>5</sup>, Jennifer Waller<sup>6</sup>, Louis-Marie Dourthe<sup>7</sup>, Pierre-Luc Esenne<sup>8</sup>, Laurent Mineur<sup>9</sup>, Stéphanie Olsani<sup>10</sup>, Jean-Marc Philip<sup>11</sup>, Andrew Kramar<sup>12</sup> and Thierry André<sup>1\*</sup>

### Abstract

**Background:** Randomized trials have shown a survival benefit for regorafenib over placebo in patients with metastatic colorectal cancer (mCRC) that progressed after standard therapies. We evaluated survival and safety outcomes in patients treated with regorafenib in a real-life setting.

**Methods:** REBECCA is a cohort study nested within a compassionate use program designed to evaluate survival, safety, and potential prognostic factors for outcome associated with regorafenib in patients with mCRC refractory to standard therapies. Treatment effects according to various patient and tumour characteristics were evaluated using univariate and multivariate Cox proportional hazards regression models.

**Results:** Of 1178 patients in the compassionate use program, 654 were in the full analysis set. Median follow-up was 165 months. Median survival was 5.6 months. The 12-month survival rate was 22%. Survival was independently and unfavourably affected by the following variables: poor performance status, short time from initial diagnosis of metastases to the start of regorafenib, low initial regorafenib dose, >5 metastatic sites, presence of liver metastases, and KRAS mutations. We identified prognostic groups of patients with low, intermediate, and high risk of death, with a median survival of 9.2, 5.2, and 2.5 months, respectively. Five-hundred-seventy-four patients (80.1%) experienced at least one regorafenib-related adverse event, most commonly, fatigue, hand-foot skin reaction, diarrhea, anorexia, arterial hypertension, and mucositis.

**Conclusion:** The safety and efficacy profile of regorafenib in REBECCA are similar to those in randomized trials. Our prognostic model identified subgroups of mCRC patients who derived a minimal and maximum benefit from regorafenib.

**Trial registration:** ClinicalTrials.gov NCT0130477.

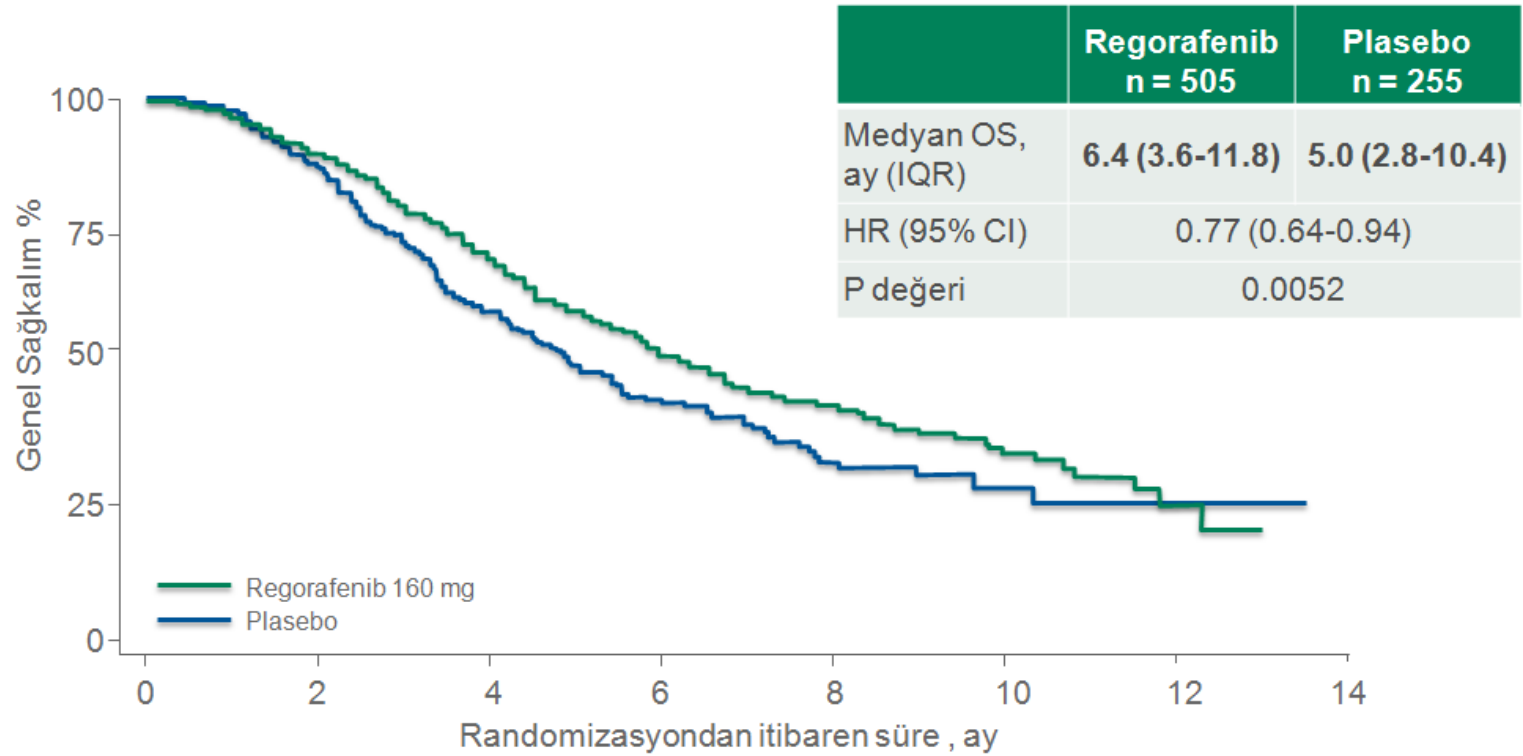
**Keywords:** Colorectal cancer; Metastatic disease; Regorafenib; Antiangiogenic; Cohort study

# Metastatik Kolon Kanserinde Tedavi Seçenekleri CORRECT Çalışması

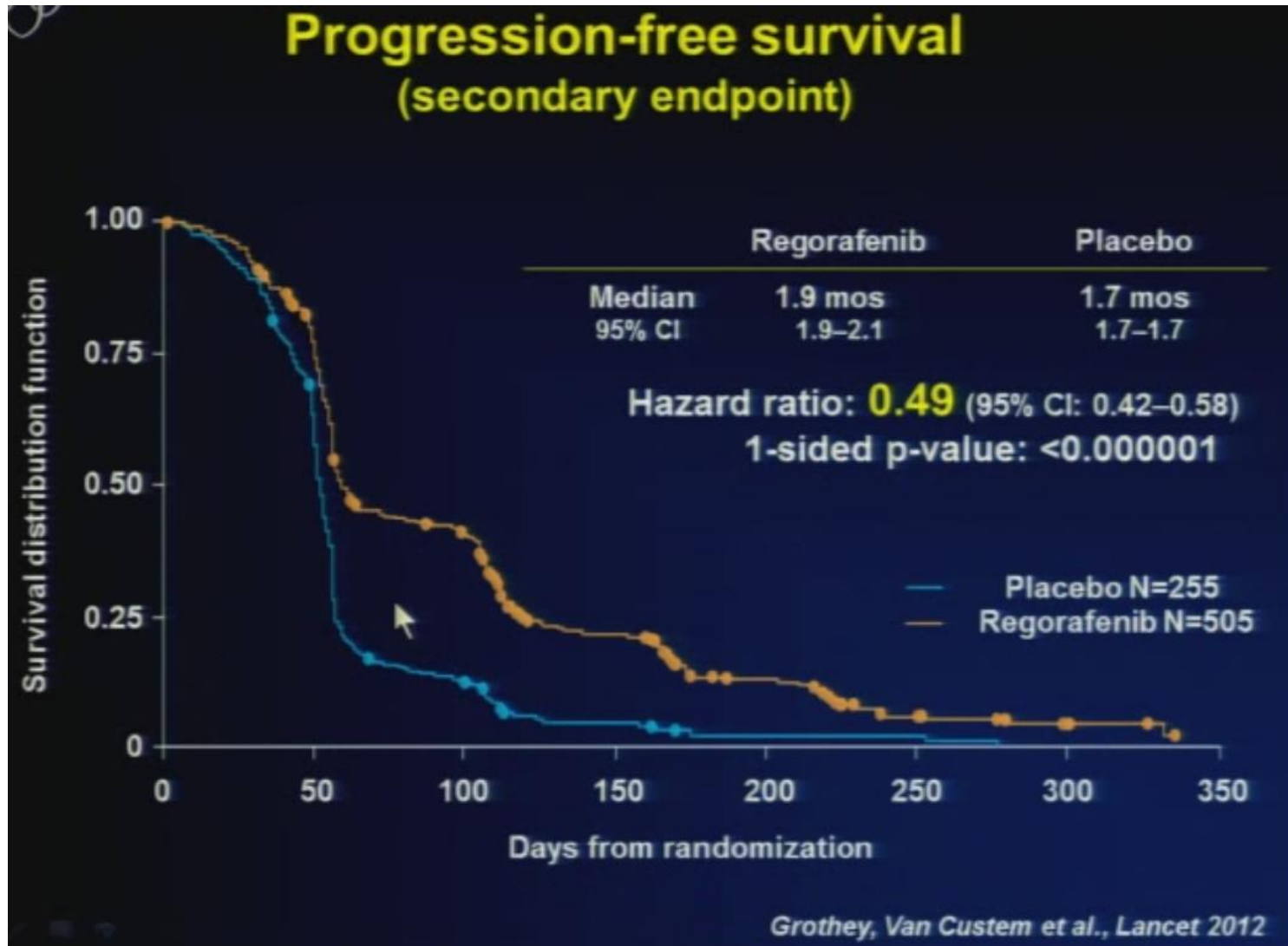
	Regorafenib (N=505)	Plasebo (N=255)
Medyan yaş (yıl [IQR])	61 (54-67)	61 (54-68)
Cinsiyet		
Erkek	311 (%62)	153 (%60)
Kadın	194 (%38)	102 (%40)
İrk		
Beyaz	392 (%78)	201 (%79)
Siyah	6 (%1)	8 (%3)
Asyalı	76 (%15)	35 (%14)
Other or not specified	31 (%6)	11 (%4)
Bölge		
NA, WE, IS, AU	420 (%83)	212 (%83)
Asya	69 (%14)	35 (%14)
Doğu Avrupa	16 (%3)	8 (%3)
<b>ECOG performans durumu</b>		
<b>0</b>	<b>265 (%52)</b>	<b>146 (%57)</b>
<b>1</b>	<b>240 (%48)</b>	<b>109 (%43)</b>
Primer hastalık yeri <sup>a</sup>		
Kolon	323 (%64)	172 (%68)
Rektum	151 (%30)	69 (%27)
Kolon ve Rektum	30 (%6)	14 (%5)
KRAS mutasyon <sup>b</sup>		
Yok	205 (%41)	94 (%37)
Var	273 (%54)	157 (%62)
Bilinmiyor	27 (%5)	4 (%2)

	Regorafenib (N=505)	Plasebo (N=255)
BRAF mutasyonu <sup>c</sup>		
Yok	322/336 (%96)	163/166 (%98)
Var	14/336 (%4)	3/166 (%2)
Histoloji (>2%)		
Adenokarsinom	493 (%98)	245 (%96)
<b>Önceki sistemik antikanser tedavileri (metastaz tanısından önce ve sonra)</b>		
<b>1-2<sup>d</sup></b>	<b>135 (%27)</b>	<b>63 (%25)</b>
<b>3</b>	<b>125 (%25)</b>	<b>72 (%28)</b>
≥4	245 (%49)	120 (%47)
Öncesinde bevasizumab	505 (%100)	255 (%100)
Progresyon nedeniyle tedaviyi bırakma		
Floroprimidin	421 (%83)	221 (%87)
Bevasizumab	403 (%80)	214 (%84)
İrinotekan	405 (%80)	214 (%84)
Oksaliplatin	278 (%55)	160 (%63)
Panitumumab veya setuximab veya her ikisi	219 (%43)	107 (%42)
Metastaz tanısından itibaren geçen süre		
Medyan (ay, [IQR])	31.0 (20.6-43.3)	29.9 (20.2-46.4)
<18 ay	91 (%18)	49 (%19)
≥18 ay	414 (%82)	206 (%81)

# Metastatik Kolon Kanserinde Tedavi Seçenekleri CORRECT Çalışması



# Metastatik Kolon Kanserinde Tedavi Seçenekleri



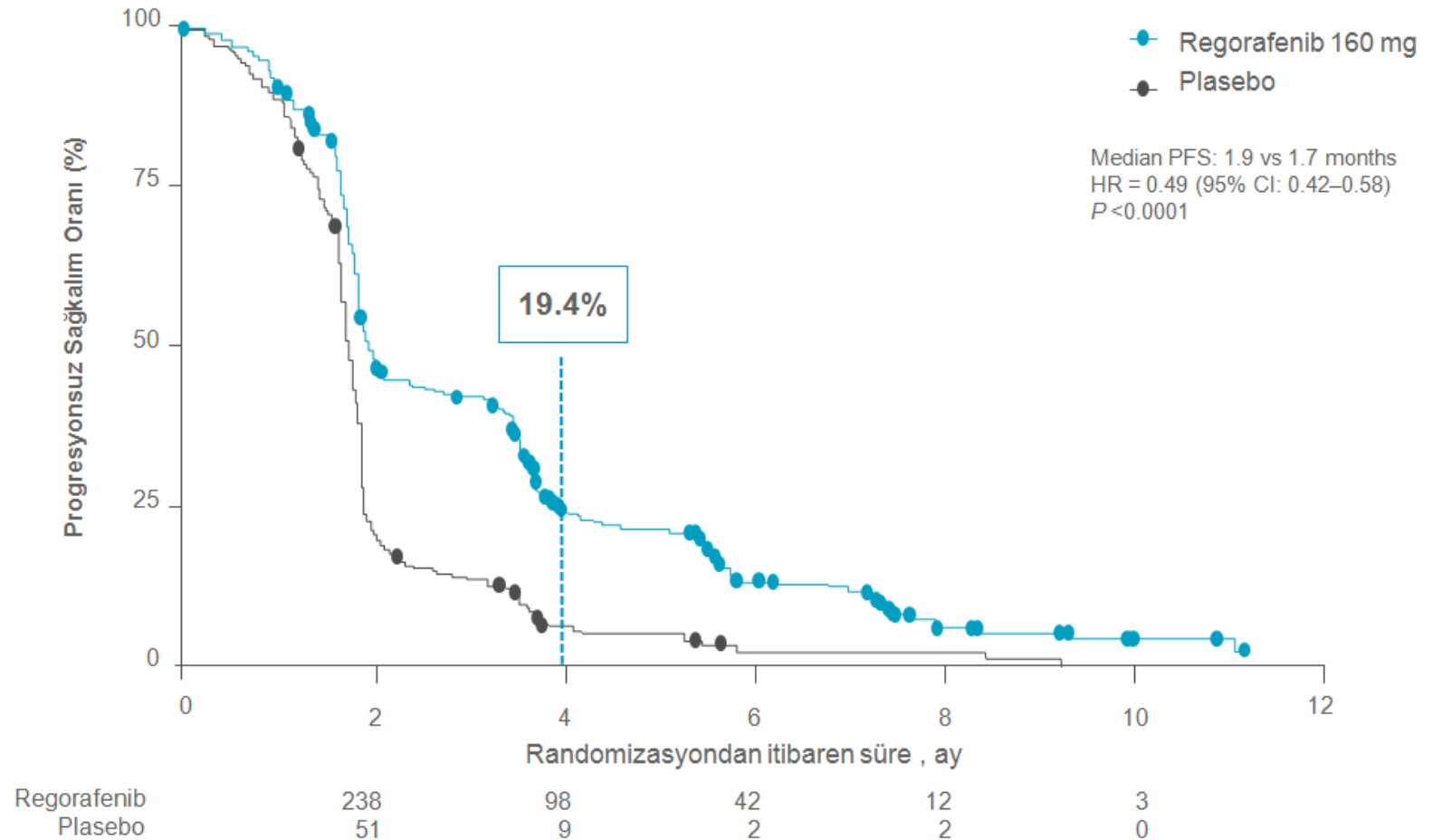
# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## CORRECT ALT GRUP

ALTGRUP	N	Regorafenib Lehine	Plasebo Lehine	HR	95% CI
Tüm Hastalar	760			0.774	0.636-0.942
Cinsiyet					
Erkek	464			0.773	0.599-0.998
Kadın	296			0.751	0.552-1.022
Yaş					
<65 yaş	475			0.716	0.561-0.914
≥65 yaş	285			0.856	0.614-1.193
Bölge					
Kuzey Amerika, Batı Avrupa, İsrail, Avustralya	632			0.768	0.622-0.948
Asya	104			0.790	0.429-1.456
Doğu Avrupa	24			0.694	0.195-2.466
Başlangıç ECOG PS					
0	411			0.702	0.530-0.929
1	349			0.773	0.586-1.020
Primer hastalık yeri					
Kolon	495			0.703	0.557-0.887
Rekum	220			0.953	0.633-1.436
Kolon ve rektum	44			1.091	0.441-2.697
İlk metastaz tanısından randomizasyona kadar geçen süre					
<18 ay	140			0.816	0.532-1.251
≥18 ay	620			0.760	0.609-0.948
Önceki antikanser tedaviler					
Floroprimidin, oksaliplatin, irinotekan, bevasizumab	375			0.825	0.625-1.089
Floroprimidin, oksaliplatin, irinotekan, bevasizumab, anti-EGFR	385			0.710	0.538-0.938
Metastatik KRK önceki tedavi serileri					
≤3	395			0.788	0.599-1.038
>3	365			0.747	0.564-0.988
KRAS mutasyonu (hasta kayıtlarına göre)					
Yok	299			0.653	0.476-0.895
Var	430			0.867	0.670-1.123

0.0 0.5 1.0 1.5 2.0 2.5 3.0

# Metastatik Kolon Kanserinde Tedavi Seçenekleri CORRECT ALT GRUP





# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## CORRECT Yan Etki Yönetimi

CORRECT çalışmasındaki hastaların  $\geq$  %10'da görülen ilaca bağlı AO'lar

Advers Olaylar	STIVARGA® (160 mg) + EDT (n=500)			Plasebo + EDT (n=253)		
	Tüm Gradlar	Grad 3	Grad 4	Tüm Gradlar	Grad 3	Grad 4
Tümü	%93	%51	%3	%61	%12	%2
Yorgunluk	%47	%9	<%1	%28	%5	<%1
El ayak deri reaksiyonu	%47	%17	0	%8	<%1	0
Diyare	%34	%7	<%1	%8	%1	0
Anoreksi	%30	%3	0	%15	%3	0
Ses değişiklikleri	%29	<%1	0	%6	0	0
Hipertansiyon	%28	%7	0	%6	%1	0
Oral mukozit	%27	%3	0	%4	0	0
Döküntü ve deskuamasyon	%26	%6	0	%4	0	0
Bulantı	%14	<%1	0	%11	%0	0
Kilo kaybı	%14	0	0	%2	0	0
Ateş	%10	%1	0	%3	0	0

- CORRECT çalışmasında Stivarga ile tedavi edilmiş hastaların %18'i, plasebo kolundaki hastaların da %13'ü tedavi ilişkili AO'lar nedeniyle tedaviyi bırakmıştır.



# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## CORRECT Yan Etki Yönetimi

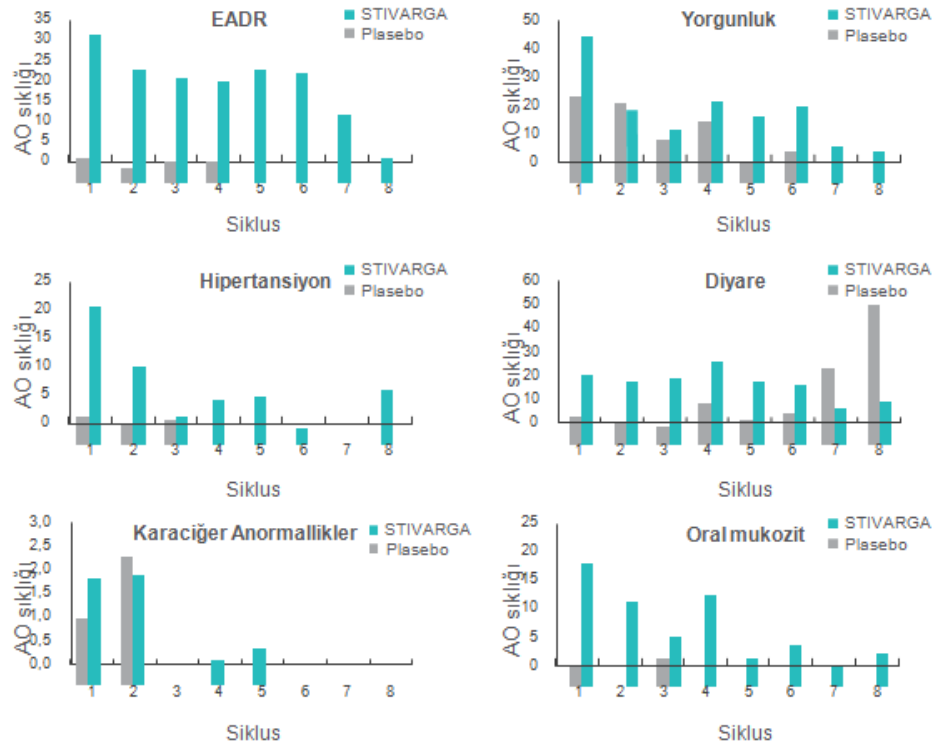
### CONCUR çalışmasındaki hastaların $\geq$ %10'da görülen AO'lar

Advers Olaylar	STIVARGA® (160 mg) + BSC (n=136)			Plasebo + BSC (n=68)		
	Tüm Gradlar	Grad 3	Grad 4	Tüm Gradlar	Grad 3	Grad 4
Palmar-plantar eritrodisestezi	%74.3	%16.2	--	%5.9	0	--
Kan bilirubin artışı	%48.5	%7.4	%4.4	%20.6	%4.4	0
ALT yükselmesi	%31.6	%8.1	0	%17.6	%1.5	0
Diyare	%29.4	%2.2	0	%7.4	%1.5	0
Ses değişikliği/kısıklığı	%28.6	%0.7	--	0	0	--
Hipertansiyon	%25.0	%11.8	0	%5.9	%4.4	0
Yorgunluk	%22.1	%2.9	--	%10.3	%1.5	--
Hipokalemi	%13.2	%5.9	0	0	0	0
Hipofosfatemi	%11.8	%8.8	0	0	0	0
Döküntü, makülo-papüler	%11.8	%4.4	--	%1.5	0	0
Platelet düşüşü	%11.8	%2.9	%0.7	%1.5	0	0
Akyuvar düşüşü	%10.3	%2.2	0	0	0	0

- CONCUR çalışmasında Stivarga ile tedavi edilmiş hastaların %14'ü, plasebo kolundaki hastaların da %6'sı tedavi ilişkili AO'lar nedeniyle tedaviyi bırakmıştır.

# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## CORRECT Yan Etki Yönetimi



- CORRECT çalışmasındaki hasta popülasyonunda EADR, hipertansiyon ve oral mukozitin insidansı ve şiddeti zaman içinde artmamıştır.<sup>2</sup>
- Stivarga ilişkili AO'lar kemoterapilerle ilişkili diğer AO'lar gibi kümülatif değildir.<sup>2</sup>

# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## CORRECT Yan Etki Yönetimi

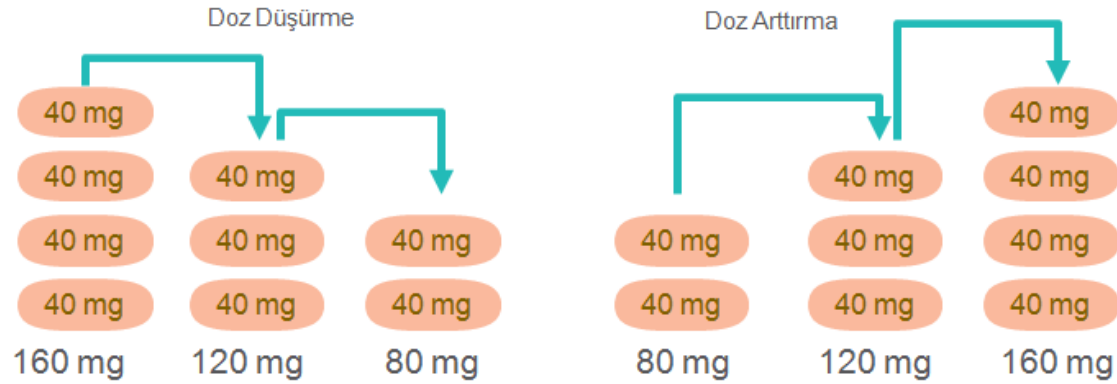
- Stivarga'nın potansiyel yan etkileri hakkında hastaya bilgi verilmeli<sup>1,2</sup>
- Hastalar advers olayları önlemek ve gelişme ihtimaline en aza indirmek için eğitilmeli<sup>2</sup>
- Monitörize edilebilmeleri için semptomları olursa sağlık çalışanlarına haber vermeli<sup>1,2</sup>

### Bilgilendir-eğit-önle-monitörize et<sup>1,2</sup>

Saçılmış AO'lar	Tedaviye başlamadan önce	Her siklus için önerilen takip sıklığı (haftalık)*															
		1. Siklus				2. Siklus				3. Siklus				4. Siklus			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
El ayak deri reaksiyonu	Tüm vücut cilt muayenesi yaptır, hastayı EADR önlenmesi konusunda eğit	Haftalık				Haftalık				Aylık				Aylık			
Döküntü	Döküntü olma ihtimaline karşı hastayı bilgilendir	Haftalık				Haftalık				Aylık				Aylık			
Hipertansiyon†	Kan basıncını ölç ve yükselirse kontrol et	Haftalık				Haftalık				Aylık				Aylık			
Karaciğer fonksiyon bozukluğu (AST, ALT ve bilirubin)	AST,ALT ve bilirubin seviyelerine bak	1. ve 3. hafta				1. ve 3. hafta				Aylık				Aylık			
Yorgunluk	Yorgunluk gelişme ihtimali, yorgunluğun hayat kalitesi ve günlük aktiviteler üzerindeki olumsuz etkileri hakkında bilgi ver	Haftalık				Haftalık				2 haftada 1				2 haftada 1			

# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## CORRECT Yan Etki Yönetimi

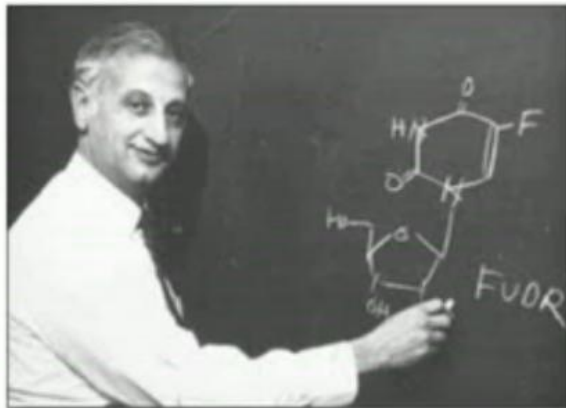
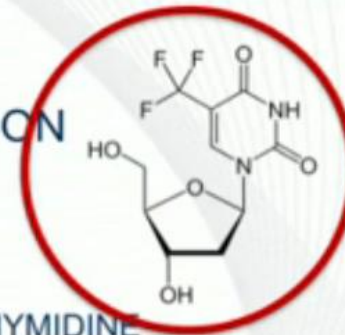


- Hekimin kararı ile AO'ların stabilize olması halinde 160mg'lık doza tekrar çıkılabilir.
- Bireysel güvenliliğe ve tolerabiliteye bağlı olarak ilacın kullanımına ara verilmesi ve/veya dozun azaltılması gerekebilir.
- Doz modifikasyonları 40 mg'lık (bir tablet) doz adımları şeklinde uygulanır.
- En düşük önerilen günlük doz **80 mg'dır**.
- Maksimum günlük doz **160 mg'dır**.

# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## TAS-102

A NOVEL ANTI-METABOLITE COMBINATION  
("Teaching an old dog new tricks")

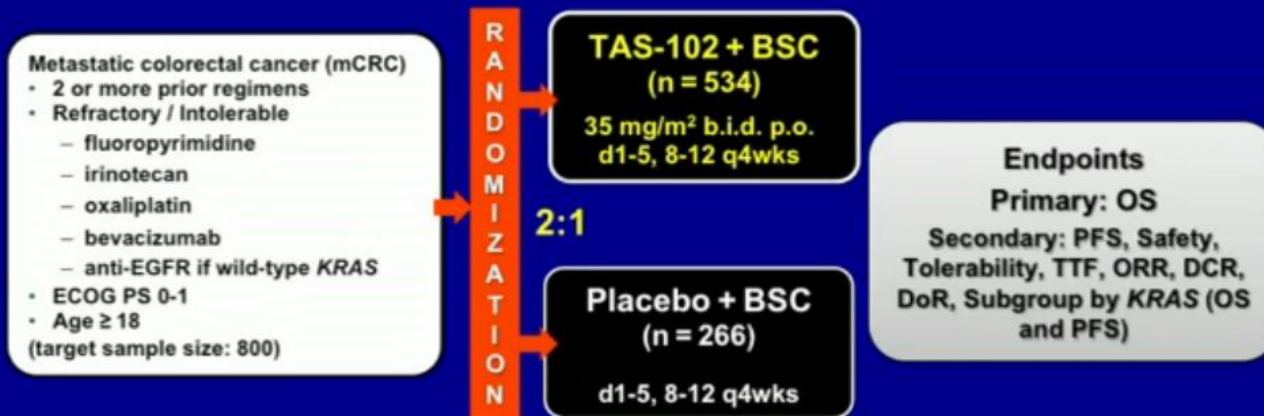


CHARLES HEIDELBERGER

- TRI-FLUORO-THYMIDINE
  - A fluoropyrimidine nucleoside
- Synthesized in 1964
- $T_{1/2} = 12$  minutes
- TF-MP inhibits TS
- TF-TP incorporated into DNA
- Active in 5FU resistant cell lines
- Extensive first pass hepatic metabolism by Thymidine Phosphorylase
- Combined with TPI (Thymidine Phosphorylase Inhibitor, tipiracil)
- Effective oral dosing, BID

# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## Global Randomized Phase III study RECURSE: Refractory Colorectal Cancer Study (NCT01607957)



- Treatment continuation until progression, intolerant toxicity or patient refusal
- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification: *KRAS* status, time from diagnosis of metastatic disease, geographical region
- Sites: 13 countries, 114 sites
- Enrollment: June 2012 to October 2013

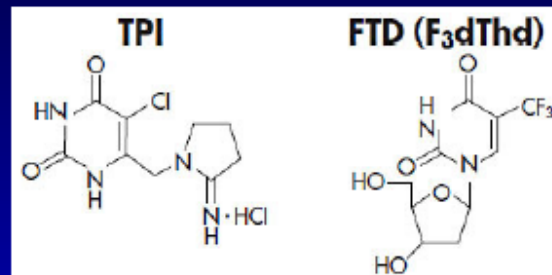


# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## TAS102: RECOURSE

Combination of two agents:

- **Trifluridine** (FTD), a nucleoside analog activated by thymidine kinase
- **Tipiracil hydrochloride** (TPI), a thymidine phosphorylase inhibitor which inhibits metabolism of trifluridine; also **has anti-angiogenic properties** via PDGF inhibition.

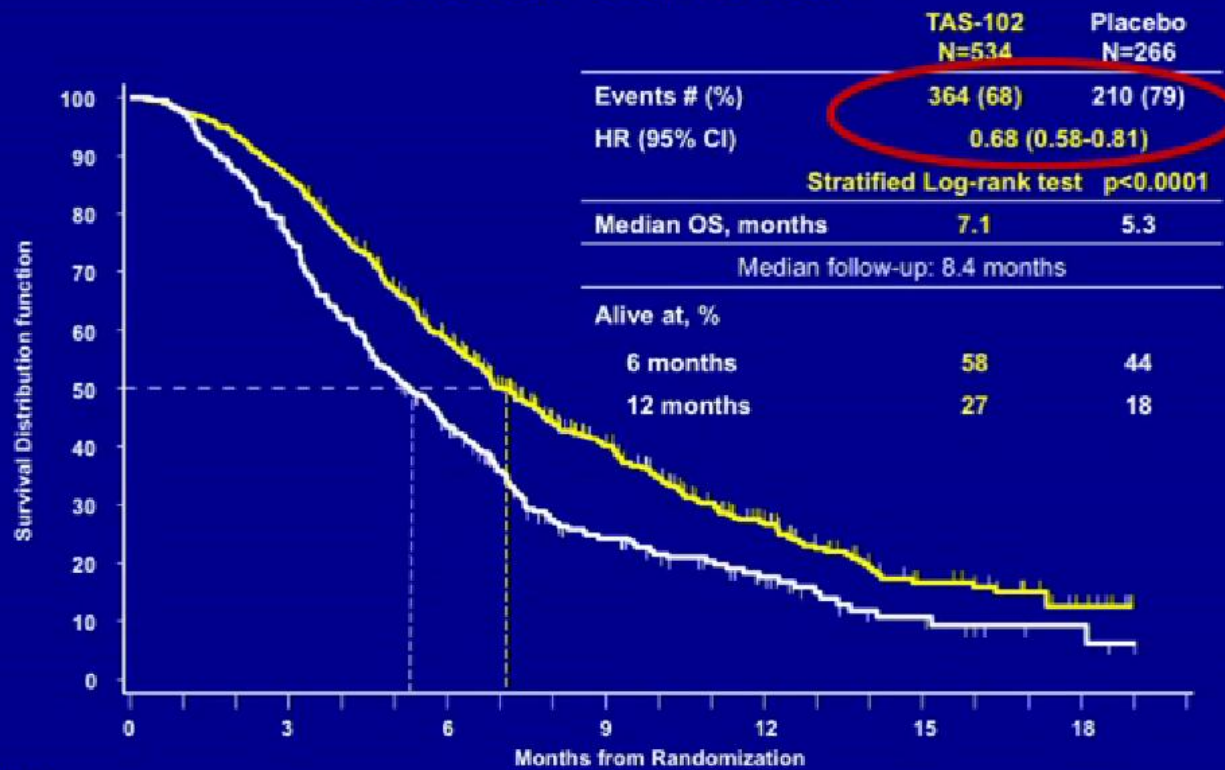


### RECOURSE trial

- global phase III trial conducted in 13 countries at 114 centres
- mCRC refractory to all standard therapies (including EGFR-targeting mAb for KRAS WT patients)
- Randomized 2:1 to **TAS-102** (534 patients), 35 mg/m<sup>2</sup> BID on Days 1- 5 and 8-12 of each 28-day cycle, or **placebo** (266 patients)
- The primary endpoint was **overall survival**.

# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## Overall Survival

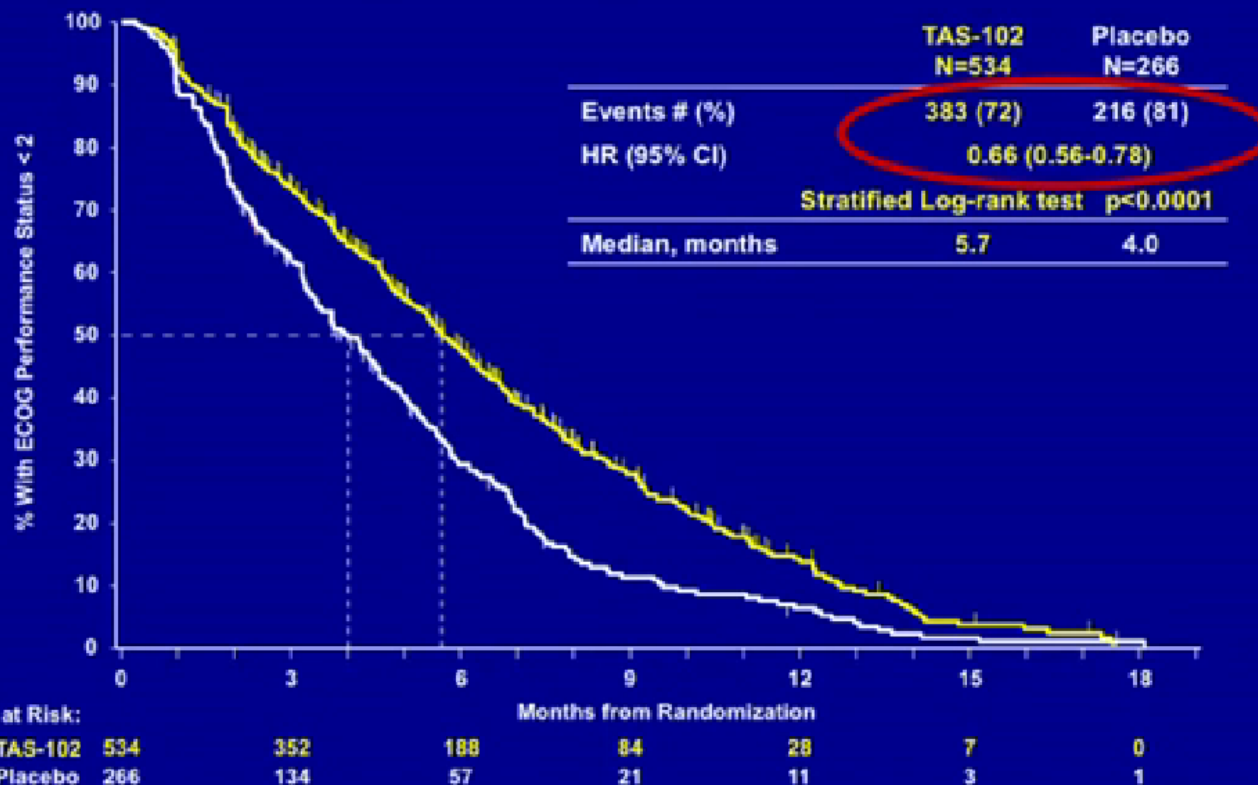


N at Risk:		0	3	6	9	12	15	18
TAS-102	534	459	294	137	64	23	7	
Placebo	266	198	107	47	24	9	3	



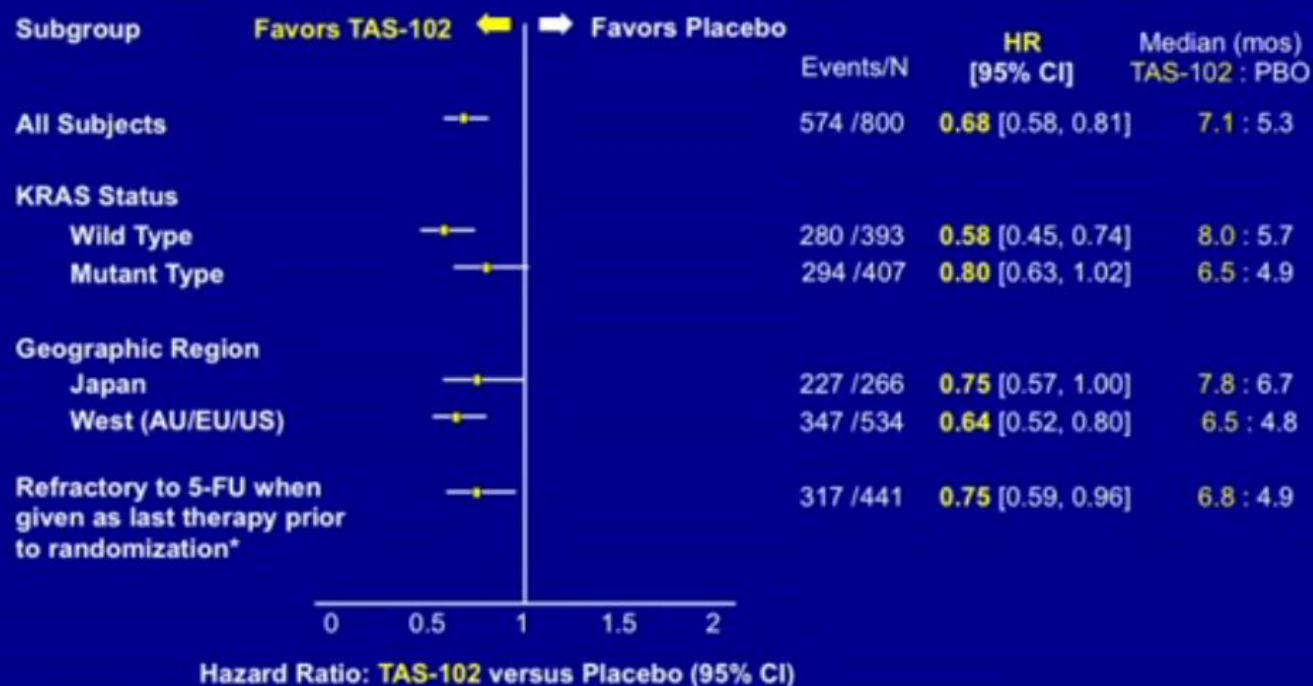
# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## Time to ECOG PS $\geq$ 2 (Intent-to-treat population)



# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## Key Subgroup Analysis of OS



\*Not prespecified subgroup

# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## TAS-102 RECURSE: Toxicity

Mayer, NEJM 2015

Event	TAS-102 (N= 533)		Placebo (N= 265)	
	Any Grade	Grade $\geq 3$	Any Grade	Grade $\geq 3$
Nausea	258 (48)	10 (2)	63 (24)	3 (1)
Vomiting	148 (28)	11 (2)	38 (14)	1 (<1)
Decreased appetite	208 (39)	19 (4)	78 (29)	13 (5)
Fatigue	188 (35)	21 (4)	62 (23)	15 (6)
Diarrhea	170 (32)	16 (3)	33 (12)	1 (<1)
Abdominal pain	113 (21)	13 (2)	49 (18)	10 (4)
Fever	99 (19)	7 (1)	37 (14)	1 (<1)
Asthenia	97 (18)	18 (3)	30 (11)	8 (3)
Events associated with fluoropyrimidine treatment — no. (%)				
Febrile neutropenia	20 (4)	20 (4)	0	0
Stomatitis	43 (8)	2 (<1)	17 (6)	0
Hand-foot syndrome	12 (2)	0	6 (2)	0
Cardiac ischemia†	2 (<1)	1 (<1)	1 (<1)	1 (<1)
Laboratory abnormalities — no./total no. (%)§				
Neutropenia	353/528 (67)	200/528 (38)	2/263 (<1)	0
Leukopenia	407/528 (77)	113/528 (21)	12/263 (5)	0
Anemia	404/528 (77)	96/528 (18)	87/263 (33)	8/263 (3)
Thrombocytopenia	223/528 (42)	27/528 (5)	21/263 (8)	1/263 (<1)

# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## TAS-102 Toxicity

- Mainly Hematologic (Grade 3)

	Grade 3 (%)	Grade 4 (%)
Leukopenia	19	3
Neutropenia	27	11
Anemia	18	-
Thrombopenia	4.5	0.5

- Minimal Non-hematologic toxicity

**Table 1. Demographic and Baseline Characteristics of the Patients.\***

Characteristic	Mismatch Repair–Deficient Colorectal Cancer (N=11)	Mismatch Repair–Proficient Colorectal Cancer (N=21)	Mismatch Repair–Deficient Noncolorectal Cancer (N=9)	P Value†
Median age (range) — yr	46 (24–65)	61 (32–79)	57 (34–92)	0.02
Sex — no. (%)				0.72
Female	5 (45)	8 (38)	4 (44)	
Male	6 (55)	13 (62)	5 (56)	
Race — no. (%)‡				0.66
White	8 (73)	17 (81)	8 (89)	
Black	1 (9)	3 (14)	0	
Other	2 (18)	1 (5)	1 (11)	
ECOG performance status — no. (%)§				0.07
0	0	6 (29)	2 (22)	
1	11 (100)	15 (71)	7 (78)	
Cancer type — no. (%)				>0.99
Colon	9 (82)	18 (86)	0	
Rectal	2 (18)	3 (14)	0	
Ampullary or cholangiocarcinoma	0	NA	4 (44)	
Endometrial	0	NA	2 (22)	
Small bowel	0	NA	2 (22)	
Gastric	0	NA	1 (11)	
Histologic grade — no. (%)				0.20
Well or moderately differentiated	7 (64)	18 (86)	4 (44)	
Poorly differentiated	4 (36)	3 (14)	3 (33)	
Other	0	0	2 (22)	
Stage IV cancer — no. (%)	11 (100)	21 (100)	9 (100)	>0.99
Liver metastases — no. (%)	6 (55)	11 (52)	6 (67)	>0.99
Median time since initial diagnosis (range) — mo	31 (6–95)	58 (27–192)	23 (2–105)	0.07
Previous therapies — no. (%)				0.89
1	0	0	1 (11)	
2	3 (27)	4 (19)	5 (56)	
3	3 (27)	5 (24)	1 (11)	
>4	5 (45)	12 (57)	2 (22)	
Detected germline mutation or known Lynch syndrome — no. (%)				<0.001
Yes	9 (82)	0	4 (44)	
No	2 (18)	21 (100)	4 (44)	
Unknown	0	0	1 (11)	
BRAF wild type — no. (%)				0.64
Yes	8 (73)	11 (52)	4 (44)	
No	0	1 (5)	0	
Unknown	3 (27)	9 (43)	5 (56)	
KRAS wild type — no. (%)				0.72
Yes	6 (55)	13 (62)	4 (44)	
No	5 (45)	8 (38)	1 (11)	
Unknown	0	0	4 (44)	

\* NA denotes not applicable.

† P values are for the comparison between the cohort with mismatch repair–deficient colorectal cancer and the cohort with mismatch repair–proficient colorectal cancer.

‡ Race was self-reported.

§ Eastern Cooperative Oncology Group (ECOG) performance status is a measure of a patient's ability to perform activities of daily living; values range from 0 to 5, with higher scores indicating greater impairment.

# Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi

## PD-1 BLOCKADE IN MISMATCH-REPAIR DEFICIENCY

**Table 2. Objective Responses According to RECIST Criteria.**

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

\* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.

† One patient had a partial response at 12 weeks.

‡ Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.

§ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.

¶ The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair–proficient colorectal cancer.

# Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterpi

## PD-1 blockade in mismatch repair deficient colorectal cancer

### Study Design

#### Colorectal Cancers

Cohort A  
**Deficient in  
Mismatch Repair  
(n=28)**

Cohort B  
**Proficient in  
Mismatch Repair  
(n=25)**

#### Non-Colorectal Cancers

Cohort C  
**Deficient in  
Mismatch Repair  
(n=30)**

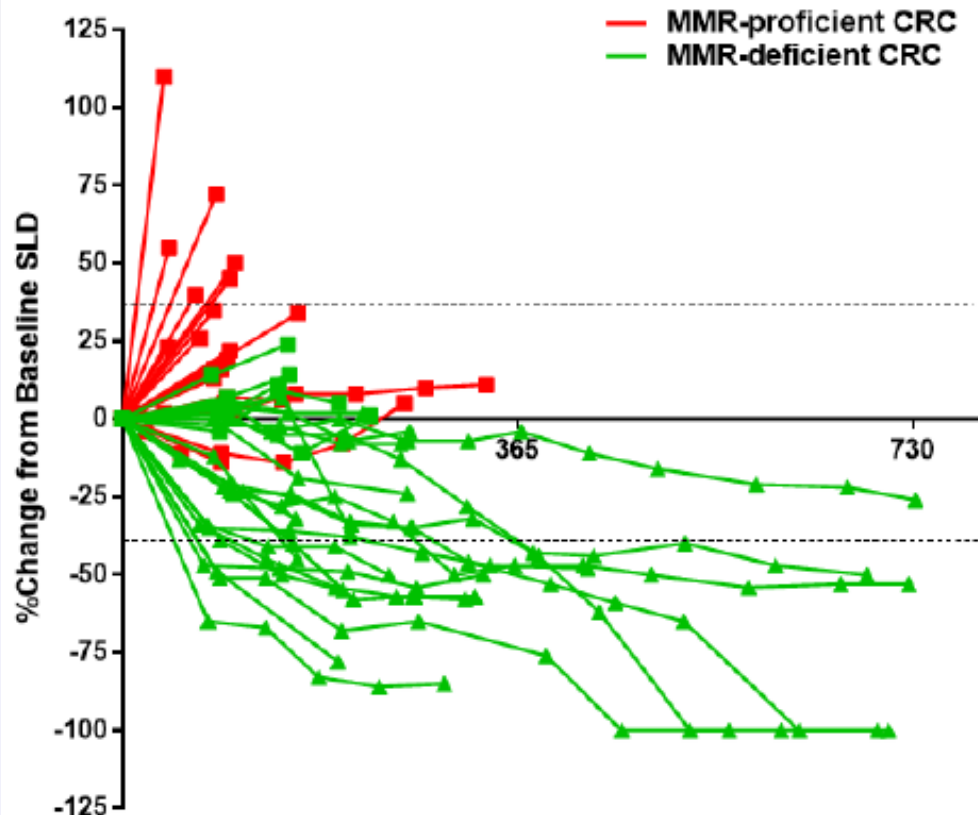
- 
- Anti-PD1 (pembrolizumab) – 10 mg/kg every 2 weeks
  - Here they updated from the original 13 CRC Cohort A patients reported at ASCO 2015/NEJM 2015

# Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi

## PD-1 in MSI-H mCRC

Le, ASCO 2016

### Radiographic Response



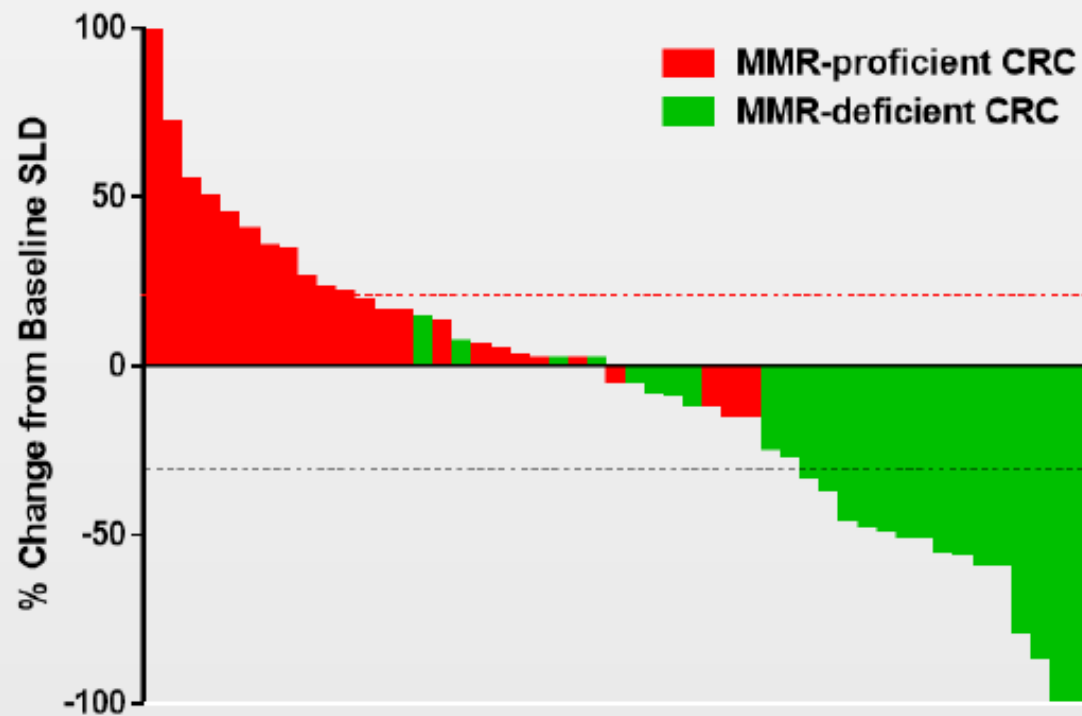


# Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi

## PD-1 in MSI-H mCRC

Le, ASCO 2016

### Best Radiographic Response

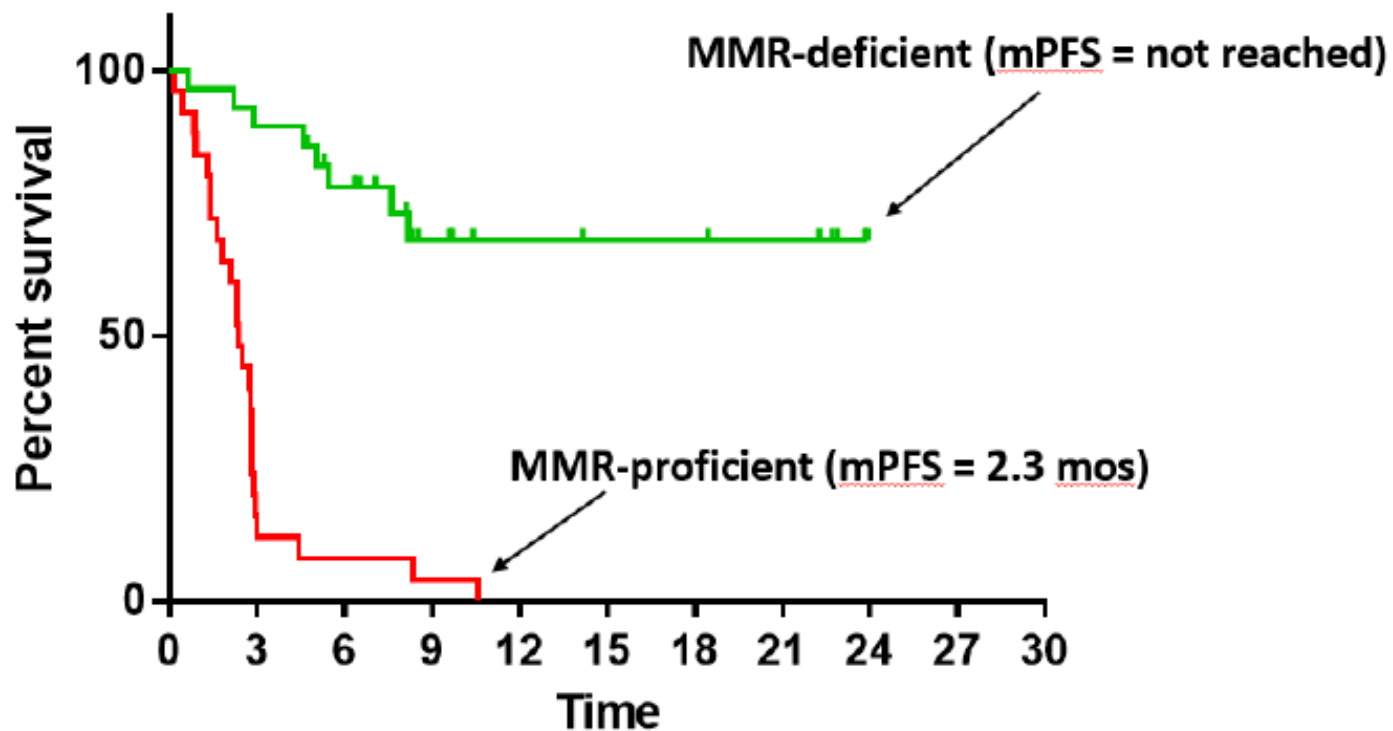


# Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi

## PD-1 in MSI-H mCRC

Le, ASCO 2016

### Progression-free Survival



# Metastatik Kolon Kanserinde Tedavi Seçenekleri- İmmünoterapi

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## Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results.

**Subcategory:**  
Advanced Disease

**Category:**  
Gastrointestinal (Colorectal) Cancer

**Meeting:**  
2016 ASCO Annual Meeting

**Session Type and Session Title:**  
Oral Abstract Session, Gastrointestinal (Colorectal) Cancer

**Abstract Number:**  
3501

**Citation:**  
J Clin Oncol 34, 2016 (suppl; abstr 3501)

**Author(s):**

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**Abstract Disclosures**

### ASSOCIATED PRESENTATION



Meeting: 2016 ASCO Annual Meeting  
Presenter: **Michael J. Overman**

[View Video](#)

### ASSOCIATED SLIDES

**Nivolumab ± Ipilimumab in Treatment of Patients With Metastatic Colorectal Cancer With and Without High Microsatellite Instability: CheckMate 142 Interim Results**

**Michael Overman**, Scott Kopetz, Ray McDermott, Joseph Leach, Sara Lonardi, Heinz-Josef Lenz, Michael A. Morse, Jayesh Desai, Andrew Hill, Michael D. Axelson, Rebecca Anne Moss, Chen-Sheng Lin, Monica Goldberg, Thierry Andre; The University of Texas MD Anderson Cancer Center, Houston, TX; St Vincent's University Hospital, Dublin, Ireland; Allina Health System, Minneapolis, MN; Istituto Oncologico Veneto IOV-IRCCS, Padova, Italy; University of Southern California, Los Angeles, CA; Duke University Office of Research Administration, Durham, NC; Royal Melbourne Hospital, Melbourne, Australia; Tasman Oncology Research Pty Ltd, Southport, Queensland, Australia; Bristol-Myers Squibb, Princeton, NJ; Hôpital Saint Antoine, Paris, France

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— ASCO ANNUAL MEETING '16

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# Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi

## Author(s):

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## Abstract Disclosures

## Abstract:

**Background:** Evidence supports use of nivolumab (N) in MSI-H mCRC. N, a fully human anti-PD-1 mAb and ipilimumab (I), a humanized anti-CTLA-4 mAb, have favorable safety & efficacy in other tumors. CheckMate-142, a phase 2 study, evaluates N ± I in pts with mCRC, MSI-H and non-MSI-H. **Methods:** Pts had ECOG PS 0–1, and intolerance/progression on ≥ 1 tx. MSI-H pts received N 3 mg/kg q2 wk (N3) or N 3 mg/kg + I 1 mg/kg q3 wk (N3+I) × 4 doses followed by N3 until disease progression (PD) or other discontinuation. Initial evaluation of N+I at 3 doses was completed in non-MSI-H pts. Primary endpoint was investigator-reported ORR by RECIST 1.1; other endpoints were safety, OS, and PFS. **Results:** 33 (N3) and 26 (N3+I) MSI-H pts, and 3 (N1+I1), 10 (N1+I3), and 10 (N3+I1) non-MSI-H pts were enrolled. 82% (N3) and 92% (N3+I) of MSI-H and 100% of non-MSI-H pts had ≥ 2 prior regimens. 15% (N3) and 25% (N3+I) of MSI-H pts had known BRAF V600E. 17 (52%; N3) and 19 (73%; N3+I) MSI-H pts remain on tx. Efficacy results are shown in the Table. In MSI-H pts, tx-related adverse events (TRAEs) occurred in 26 (79%; N3) and 22 pts (85%; N3+I); most common were diarrhea and fatigue (27% each; N3) and diarrhea (46%; N3+I). Grade 3–4 TRAEs occurred in 7 (N3) and 8 pts (N3+I). One pt on N3 had a Grade 5 TRAE (sudden death). In non-MSI-H pts median (95% CI) PFS was 1.4 mo (1.2–1.9; pooled N+I). **Conclusions:** N and N+I were well tolerated in most pts and demonstrated encouraging clinical activity and survival in MSI-H mCRC. This study is ongoing. Clinical trial information: [NCT02060188](#)

## MSI-H<sup>a</sup> efficacy.

	N3 (n = 33)	N3+I1 (n = 26)
ORR, n (%)	9 (27)	4 (15)
CR	0	0
Confirmed PR	9 (27)	4 (15)
SD	8 (24)	17 (65)
PD	11 (33)	3 (12)
Not determined/not reported	5 (15)	2 (8)
Median duration of response (95% CI), mo	NR (4.2–NE)	NR (NE–NE)
Median PFS (95% CI), mo	5.3 (1.4–NE)	NR (NE–NE)
4-mo PFS rate, <sup>b</sup> %	55	80
Median OS (95% CI), mo	16.3 (8.3–NE)	NR (NE–NE)
5-mo OS rate, <sup>c</sup> %	75	100

NR, not reached; NE, not estimable <sup>a</sup>By local screen <sup>b</sup>PFS Kaplan-Meier plot estimate, N3 = 17/33 events, N3+I1 = 4/26 events <sup>c</sup>PFS Kaplan-Meier plot estimate, N3 = 11/33 events, N3+I1 = 0/26 events

# Metastatik Kolon Kanseri Tedavi

NCCN

National  
Comprehensive  
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## NCCN Guidelines Version 1.2017 Colon Cancer

were 78% (95% CI, 40–97), 11% (95% CI, 1–35), and 67% (95% CI, 22–96), respectively. These results indicate that MSI is a predictive marker for the effectiveness of pembrolizumab across tumor types. Furthermore, the median PFS and OS were not reached in the arm with dMMR colorectal cancer and were 2.2 and 5.0 months, respectively, in the MMR-proficient colorectal cancer group (HR for disease progression or death, 0.10;  $P < .001$ ).

Nivolumab is another humanized IgG4 PD-1 blocking antibody, with FDA indications in melanoma and non-small cell lung cancer.<sup>785</sup>

Nivolumab was studied with or without ipilimumab in patients with metastatic colorectal cancer in a phase II trial.<sup>786</sup> The median PFS was 5.3 months (95% CI, 1.4–not estimable) in the MMR-deficient patients who received nivolumab monotherapy, not reached in the MMR-deficient patients who received nivolumab plus ipilimumab, and 1.4 months (95% CI, 1.2–1.9) in the pooled MMR-proficient group.

Based on these data, the panel recommends pembrolizumab or nivolumab as treatment options in patients with metastatic MMR-deficient colorectal cancer in second- or third-line therapy. Patients progressing on either of these drugs should not be offered the other. Additional clinical trials are ongoing to confirm the benefit of these drugs in this setting.

*Cetuximab or Panitumumab vs. Bevacizumab*  
The randomized, multicenter, phase III trial compared first-line oxaliplatin-based therapy plus bevacizumab or FOLFIRI plus panitumumab in the primary endpoint of PFS between the bevacizumab arm vs. panitumumab arm (9.2 months vs. 9.2 months; 95% CI, 0.68–1.50;  $P = .97$ ).

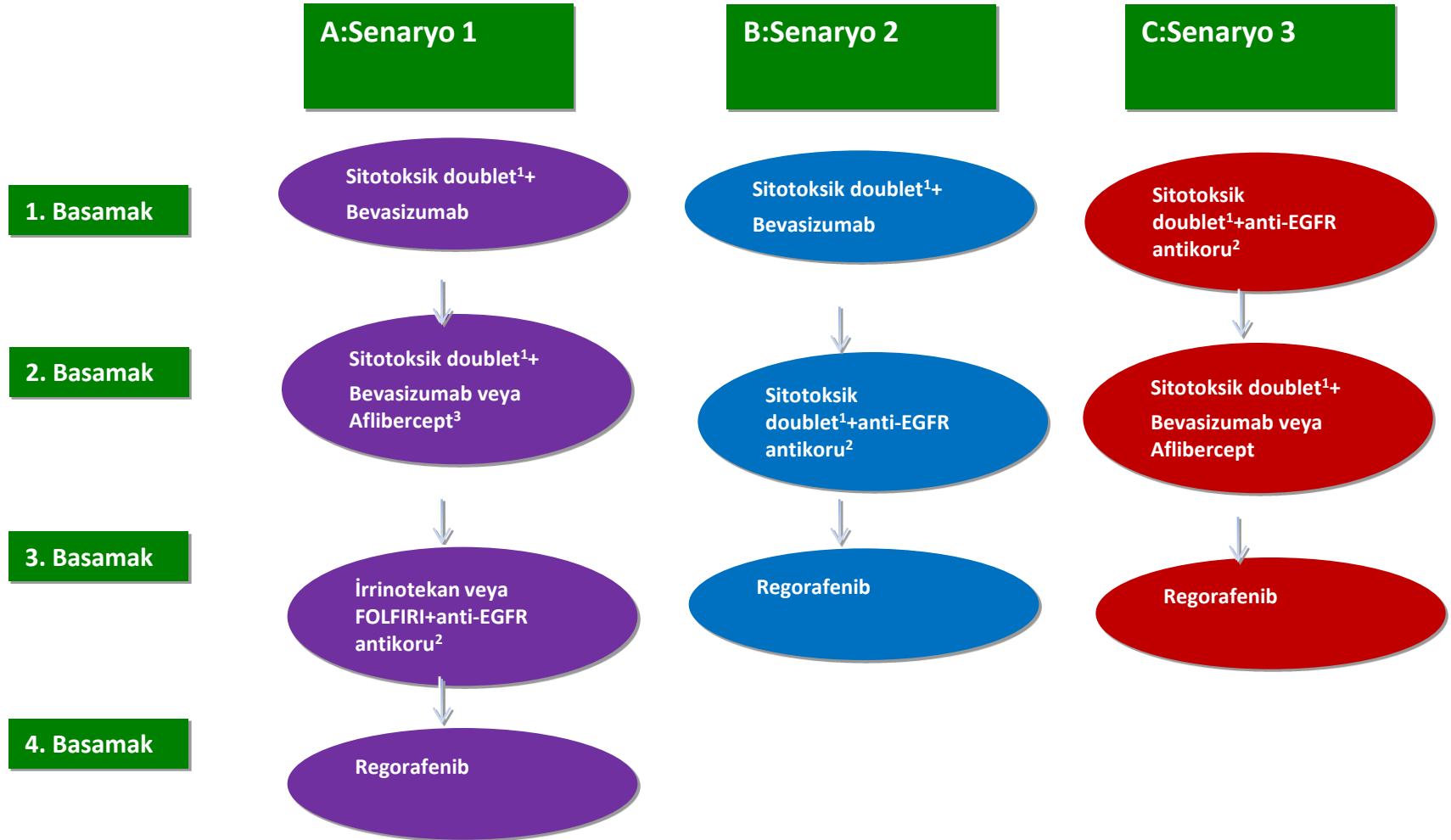
### Workup and Management of Symptomatic Metastases

The workup for patients in whom metastatic colorectal adenocarcinoma from the large bowel is suspected should include a total CEA determination, biopsy if indicated, and contrast-enhanced CT of the chest, abdomen, and pelvis. Contrast should be considered if CT is equivocal. The panel recommends tumor *KRAS/NRAS* genotyping for metastatic disease and consideration of targeted therapy for patients with *KRAS/NRAS* wild-type tumors. *Role of KRAS, NRAS, and BRAF S*

The panel strongly discourages the use of routine staging, baseline imaging, or routine

# Metastatik Kolon Kanserinde Tedavi Seçenekleri

## ESMO TEDAVİ REHBERİ



1. Sitotoksik doublet: fluoropirimidin + oksaliplatin veya irrinotekan; 2. Ras wild tip; 3. Yalnızca FOLFIRI ile kombinasyonda Aflibercept