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

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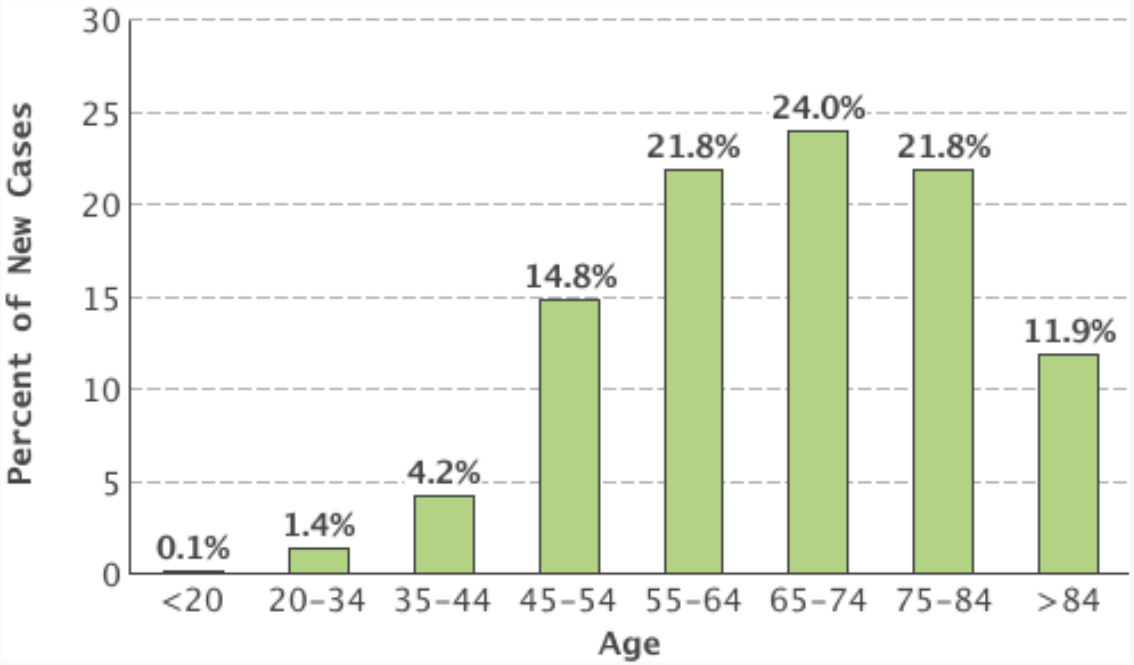
Tıbbi Onkoloji

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

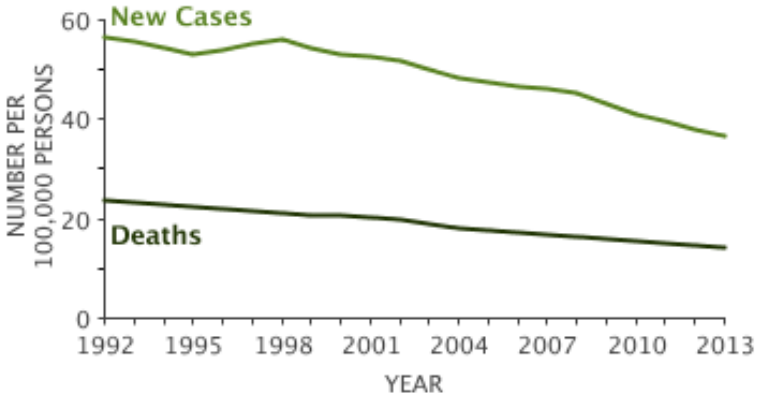
	Common Types of Cancer	Estimated New Cases 2016	Estimated Deaths 2016
1.	Breast Cancer (Female)	246,660	40,450
2.	Lung and Bronchus Cancer	224,390	158,080
3.	Prostate Cancer	180,890	26,120
4.	**Colon and Rectum Cancer**	**134,490**	**49,190**
5.	Bladder Cancer	76,960	16,390
6.	Melanoma of the Skin	76,380	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
65.1%
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.

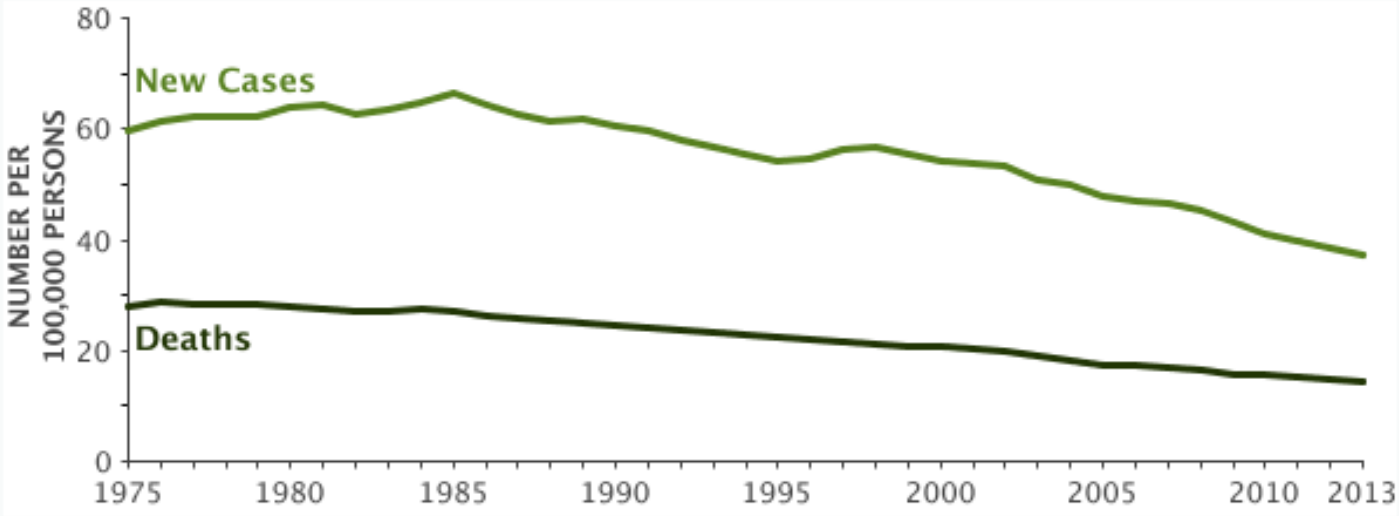
Lifetime Risk of Developing Cancer: Approximately 4.5 percent of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime, based on 2010–2012 data.

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

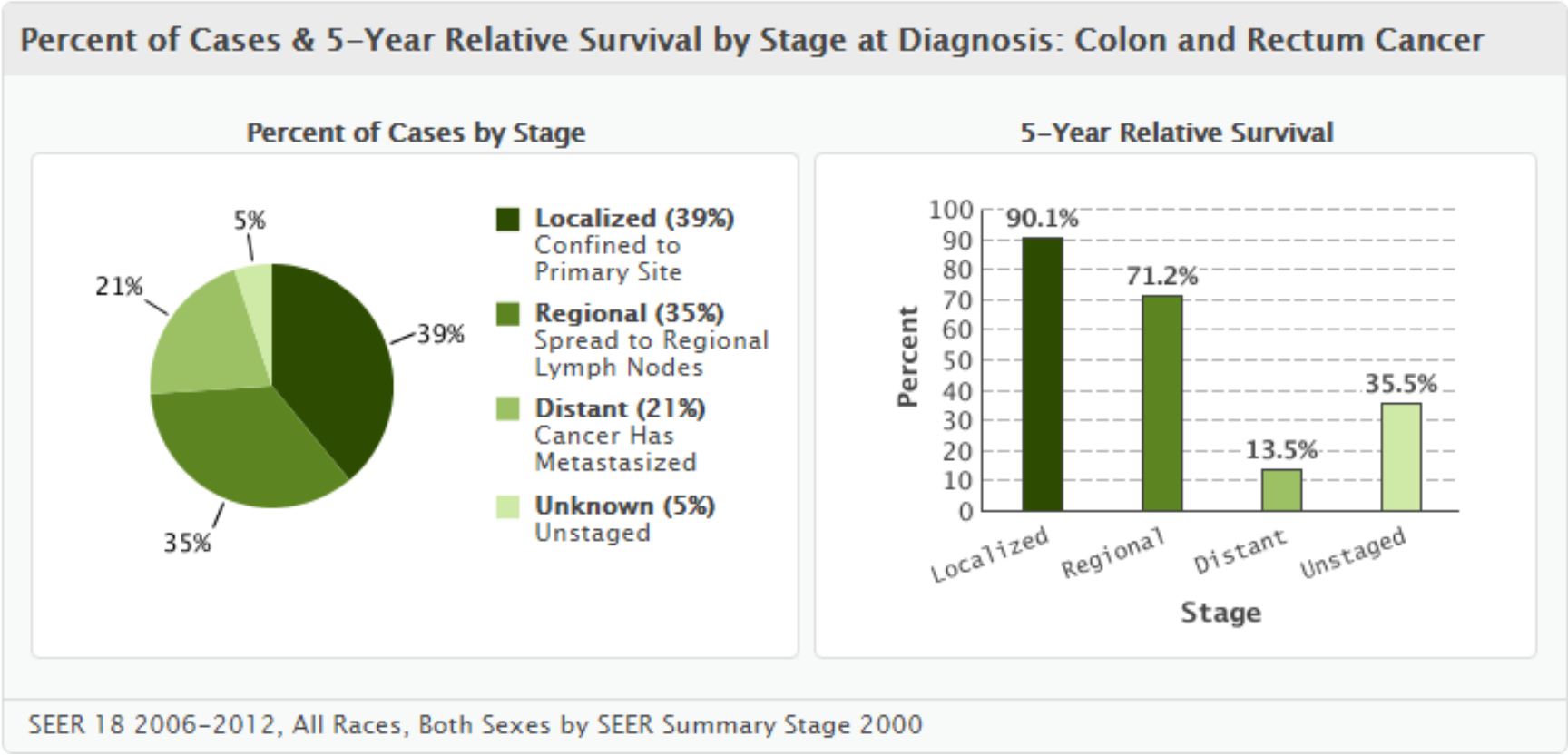
View Data Table



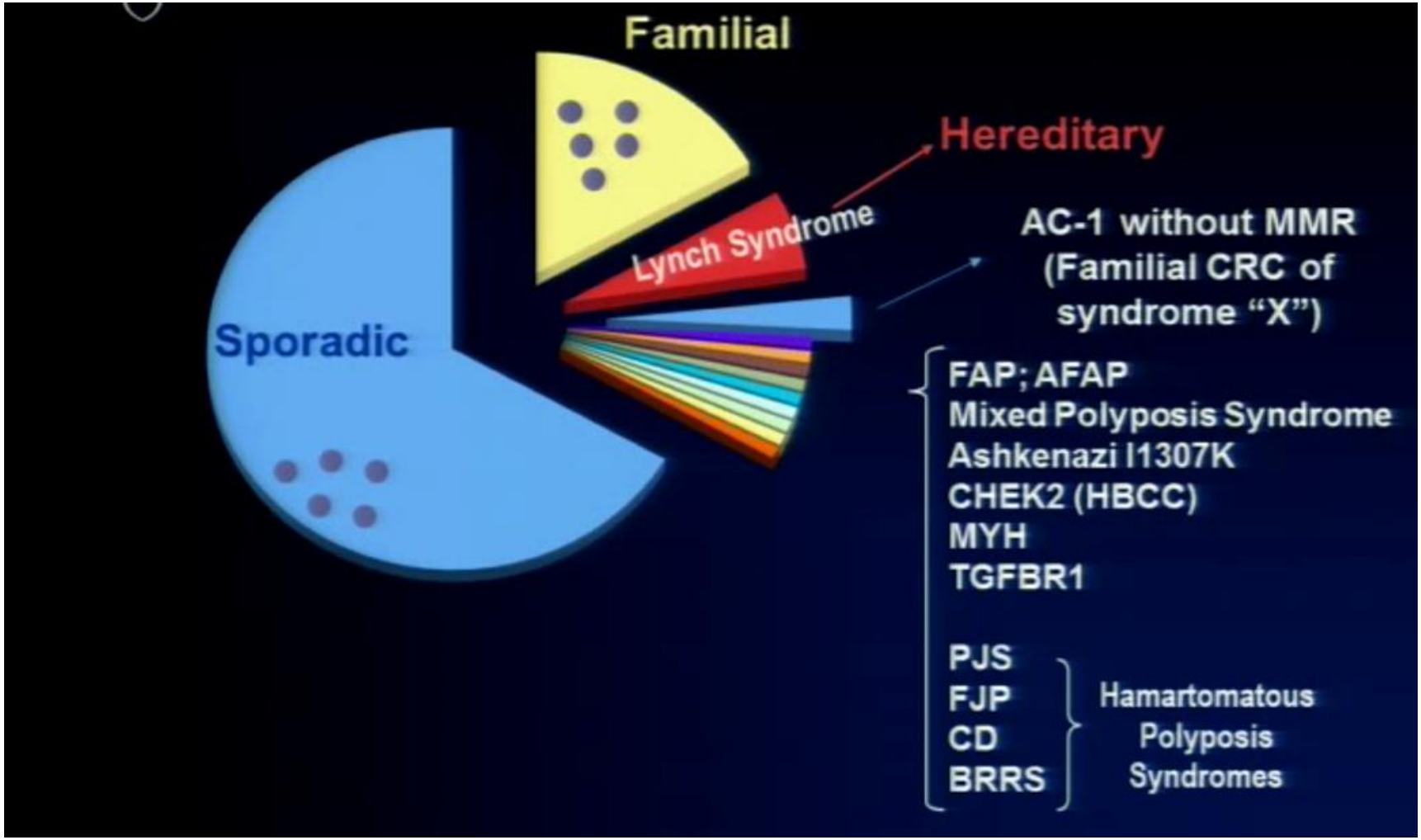
Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	48.6%	51.2%	58.1%	60.8%	59.7%	64.8%	65.7%	67.2%

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

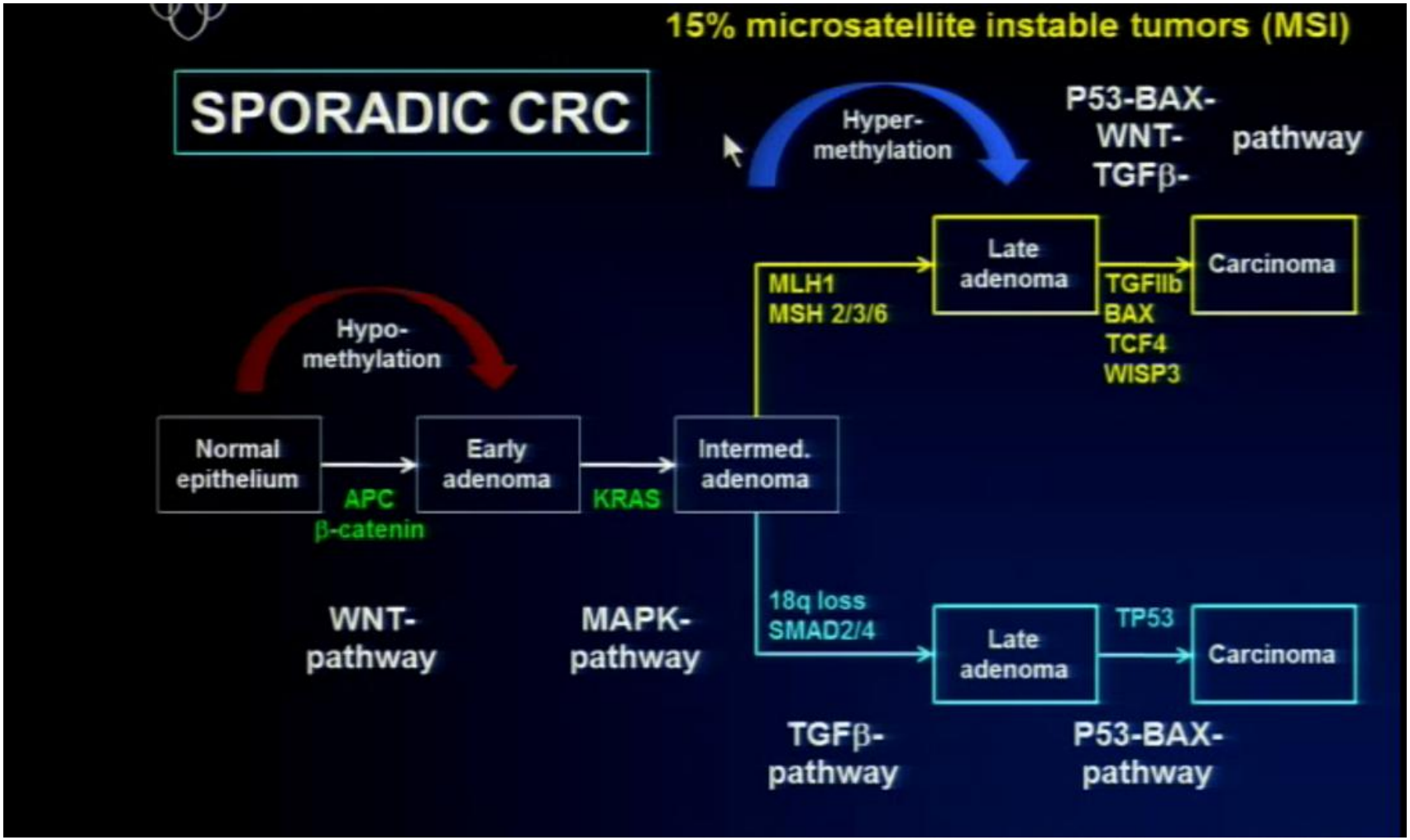
Kolon Kanseri İnsidans ve Mortalite



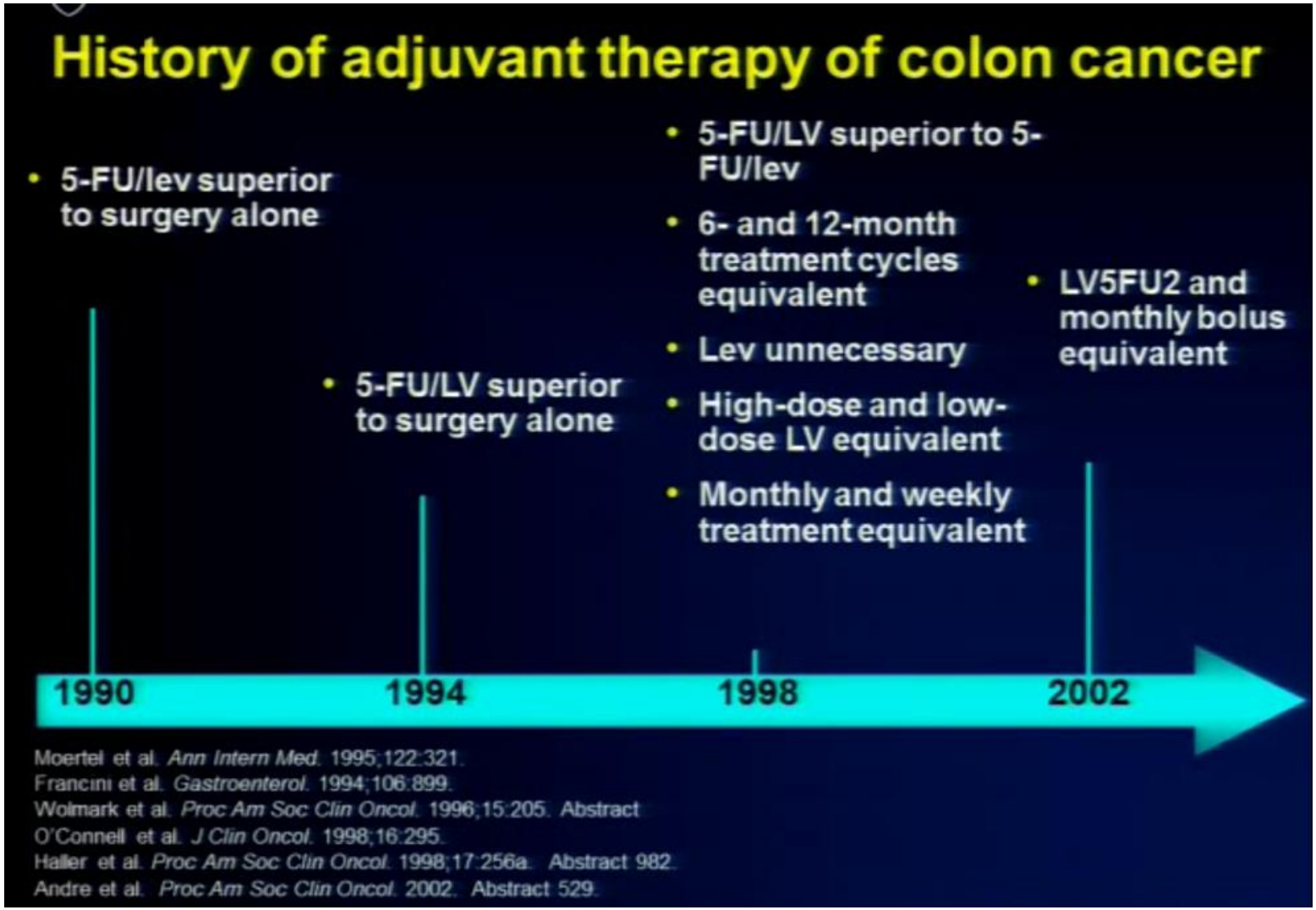
Kolon Kanseri
Genetik ve Risk Faktörleri



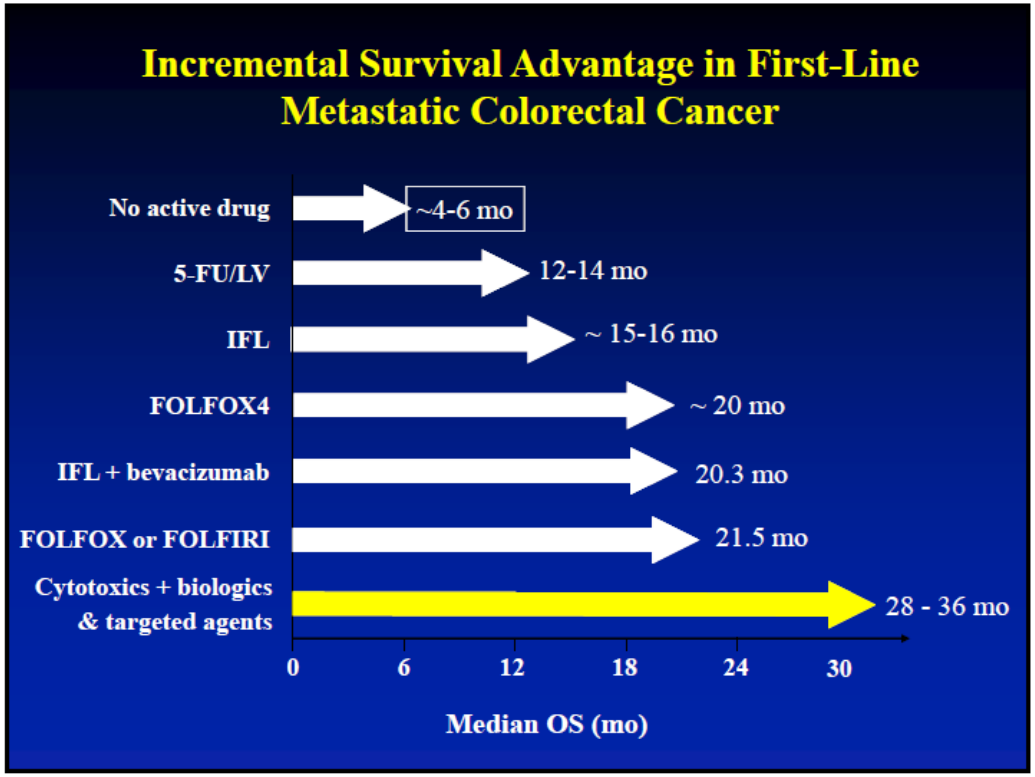
Kolon Kanseri
Genetik ve Risk Faktörleri



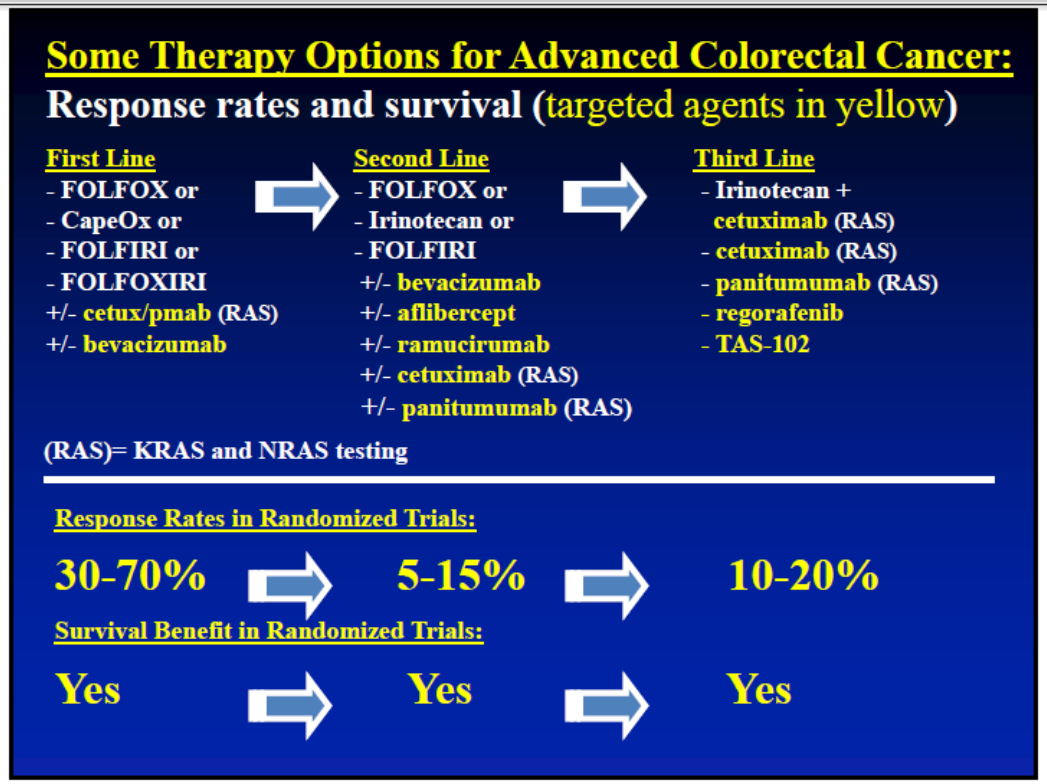
Kolon Kanseri Tedavi



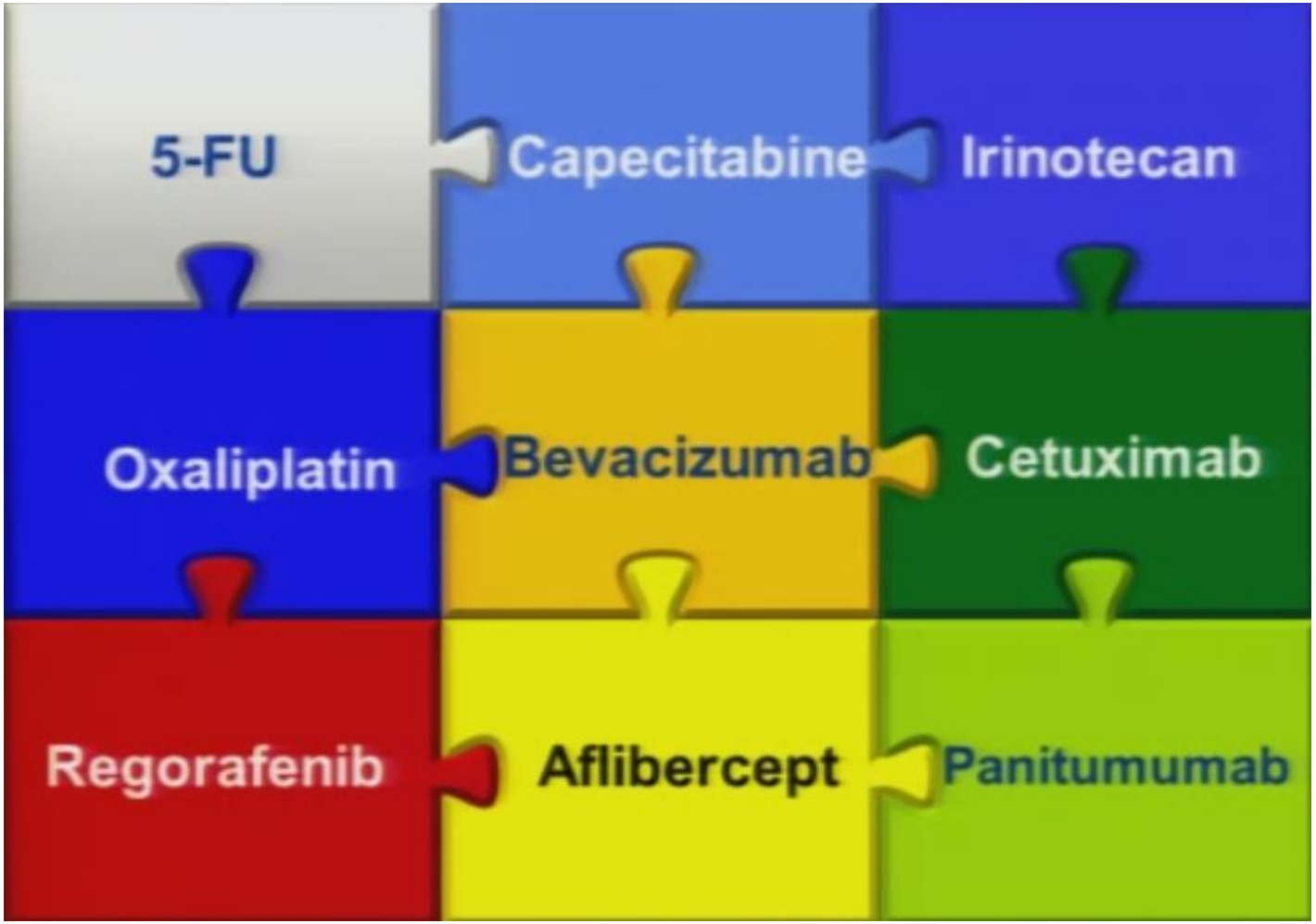
Kolon Kanseri Tedavi



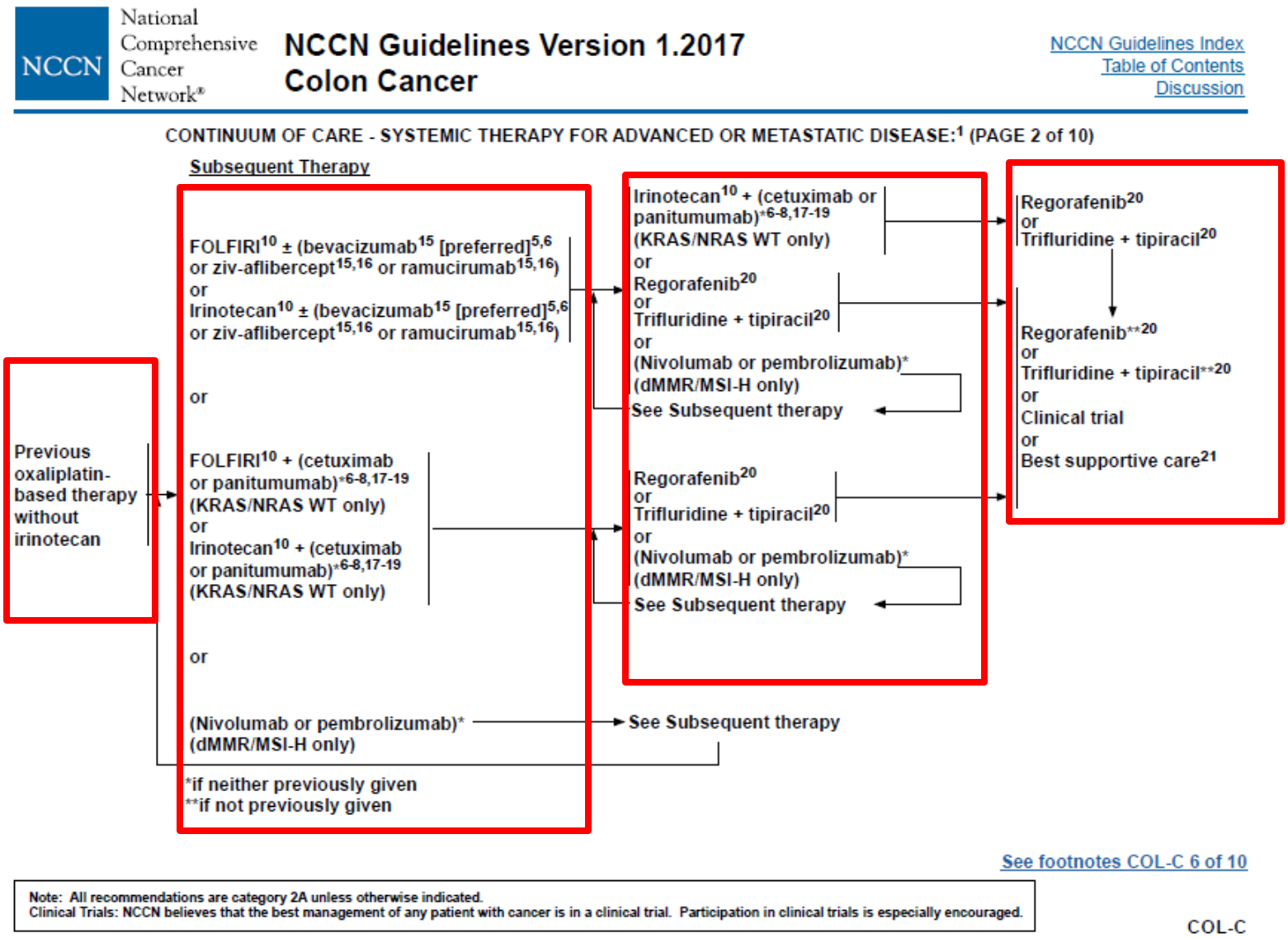
Kolon Kanseri Tedavi



Metastatik Kolon Kanseri Tedavi



Metastatik Kolon Kanseri Tedavi



Metastatik Kolon Kanseri Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Colon Cancer

NCCN Guidelines Index
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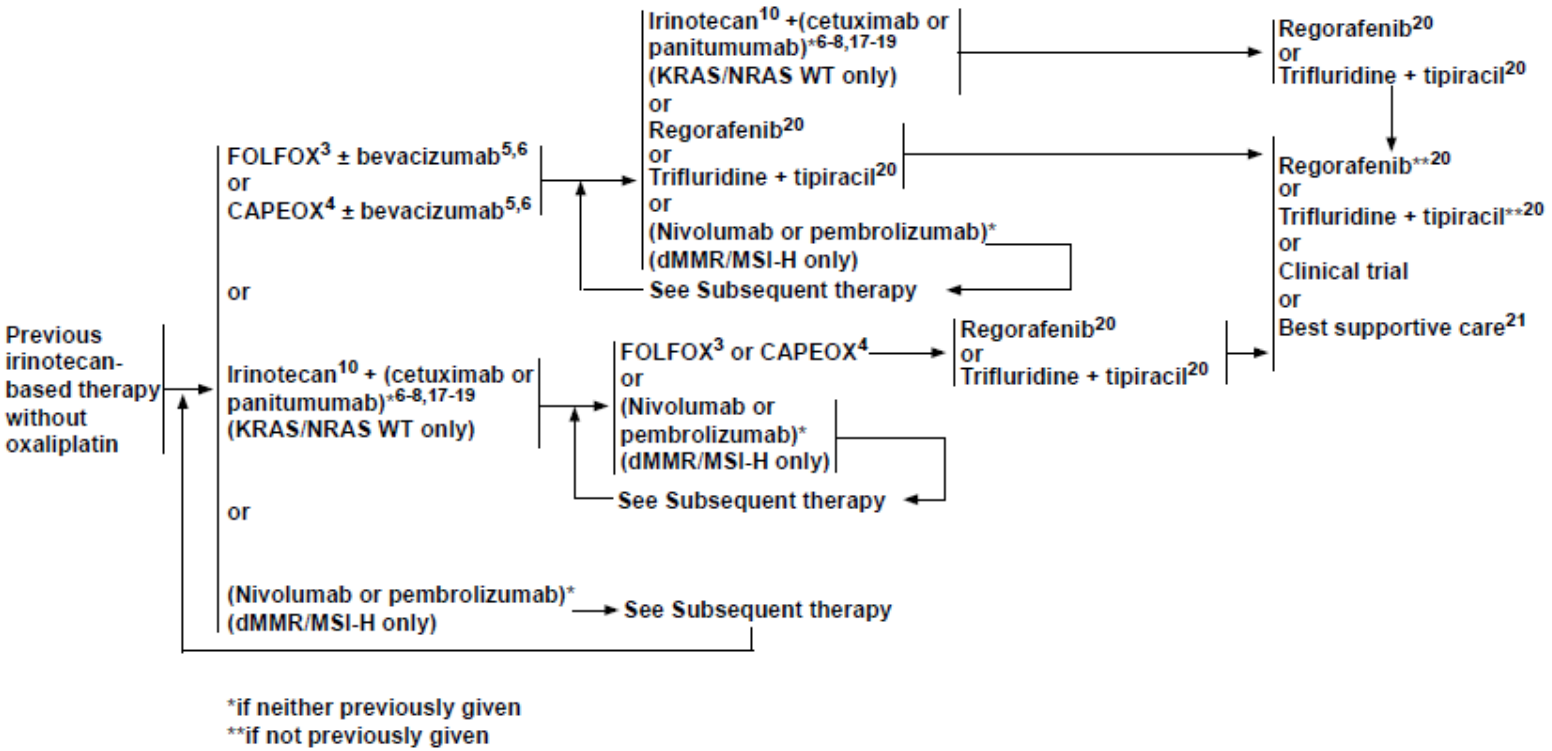
Discussion

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 3 of 10)

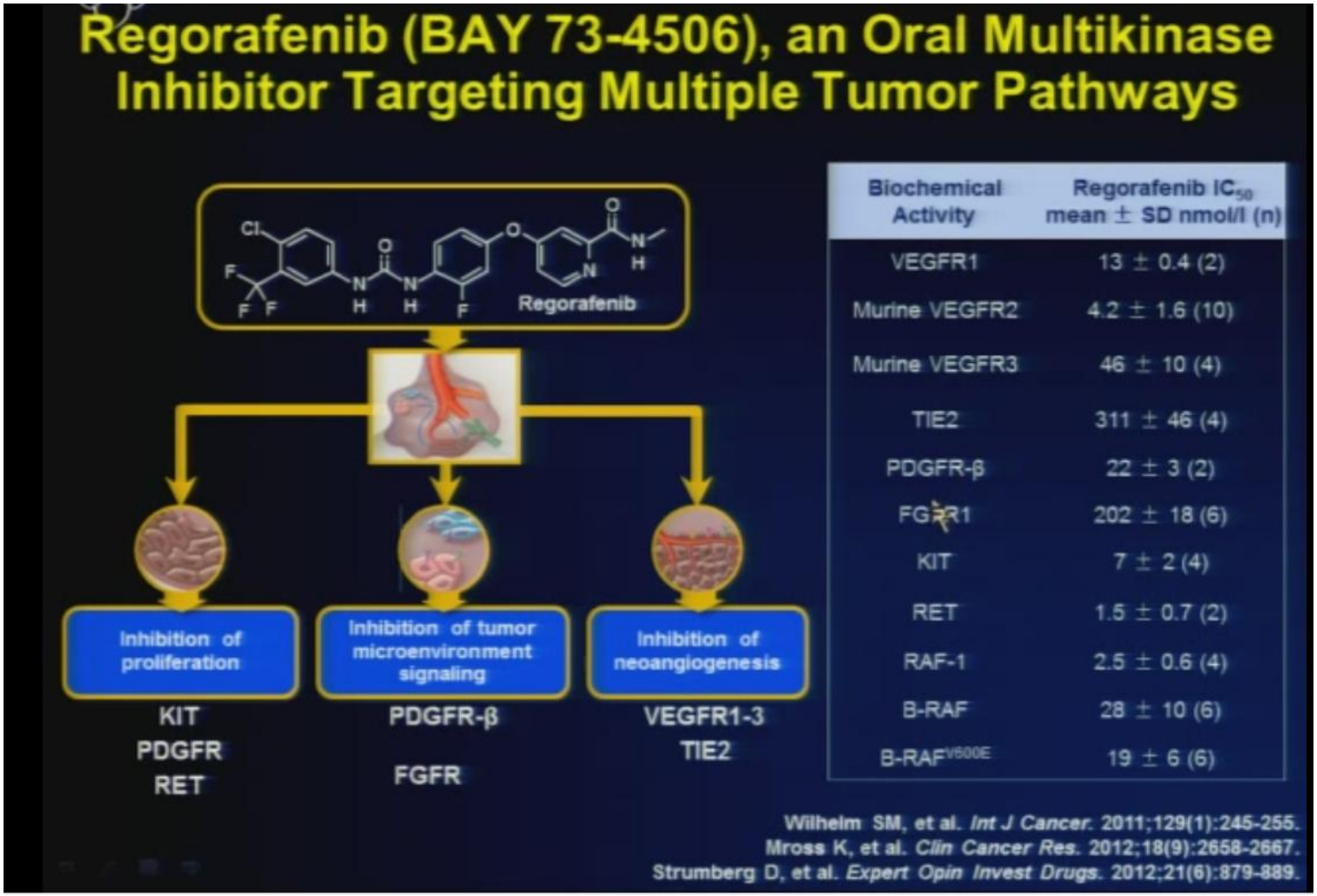


*if neither previously given
**if not previously given

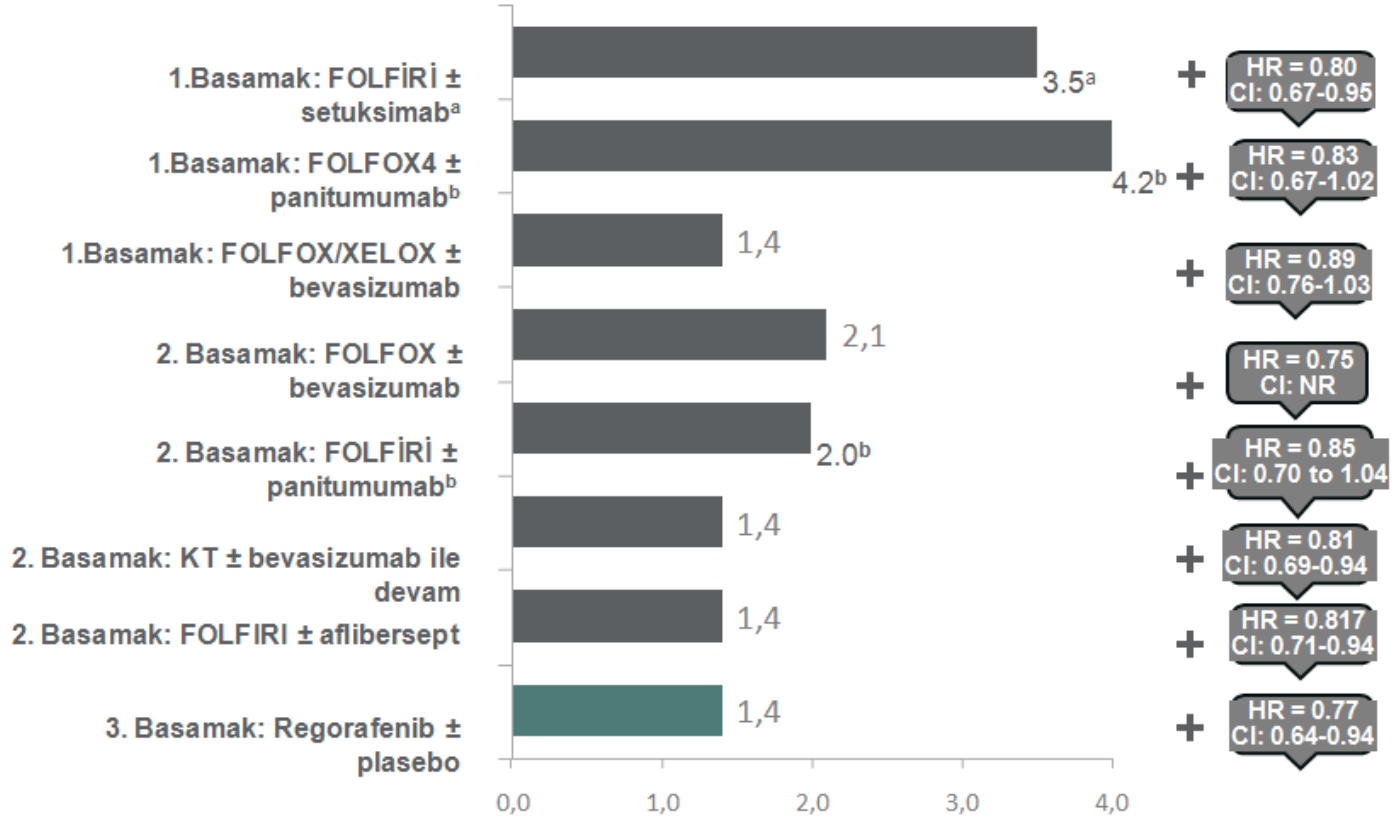
See footnotes COL-C 6 of 10

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



Metastatik Kolon Kanserinde Tedavi Seçenekleri



[a]KRAS WT subset; *P* value = not significant.
[b]KRAS WT subset; *P* value = significant.

Saltz LB, et al. J Clin Oncol. 2008;26(12):2013-2019; Douillard, J-Y, et al. J Clin Oncol. 2010;28(31):4697-4705; Van Cutsem E, et al. J Clin Oncol. 2011;29(15):2011-2019; Van Cutsem E, et al. J Clin Oncol. 2012;30(28):3499-3506; Arnold D, et al. J Clin Oncol. 2012;30(suppl): abstract CRA3503; Giantonio BJ, et al. J Clin Oncol. 2007;25(12)1539-1544; Peeters M, et al. J Clin Oncol . 2010;28:4706-4713; Grothey A, Van Cutsem E, et al. Lancet. 2013;381:303-312.

Metastatik Kolon Kanserinde Tedavi Seçenekleri

Regorafenib Faz III Çalışmaları

CORRECT
CONCUR

Articles

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

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

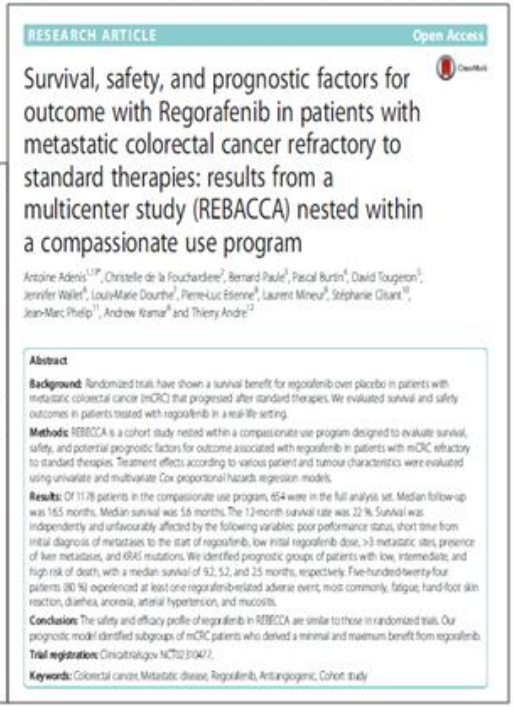
Metastatik Kolon Kanserinde Tedavi Seçenekleri

Gerçek Yaşam Verileri

CONSIGN
REBECCA

abstracts

LBA – 08 **Results from the large, open-label phase 3b CONSIGN study of regorafenib in patients with previously treated metastatic colorectal cancer**



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 (REBACCA) nested within a compassionate use program

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 16.5 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, >3 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-twenty-four patients (80 %) 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 NCT02314roll.

Keywords: Colorectal cancer, Metastatic disease, Regorafenib, Antiangiogenic, Cohort study

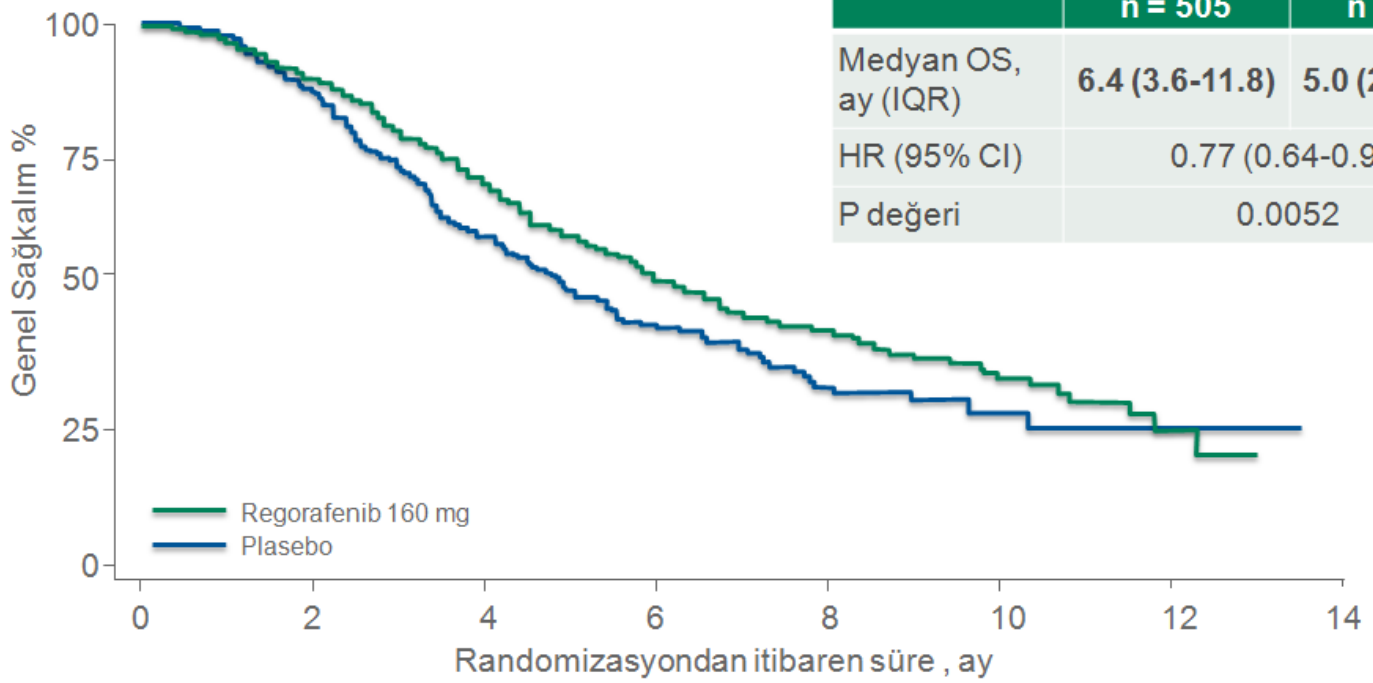
Metastatik Kolon Kanserinde Tedavi Seçenekleri
CORRECT Çalışması

	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)
Irk		
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)
ECOG performans durumu		
0	**265 (%52)**	**146 (%57)**
1	**240 (%48)**	**109 (%43)**
Primer hastalık yeri[a]		
Kolon	323 (%64)	172 (%68)
Rektum	151 (%30)	69 (%27)
Kolon ve Rektum	30 (%6)	14 (%5)
KRAS mutasyon[b]		
Yok	205 (%41)	94 (%37)
Var	273 (%54)	157 (%62)
Bilinmiyor	27 (%5)	4 (%2)

	Regorafenib (N=505)	Plasebo (N=255)
BRAF mutasyonu[c]		
Yok	322/336 (%96)	163/166 (%98)
Var	14/336 (%4)	3/166 (%2)
Histoloji (>2%)		
Adenokarsinom	493 (%98)	245 (%96)
Önceki sistemik antikanser tedavileri (metastaz tanısından önce ve sonra)		
1-2[d]	**135 (%27)**	**63 (%25)**
3	**125 (%25)**	**72 (%28)**
≥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)

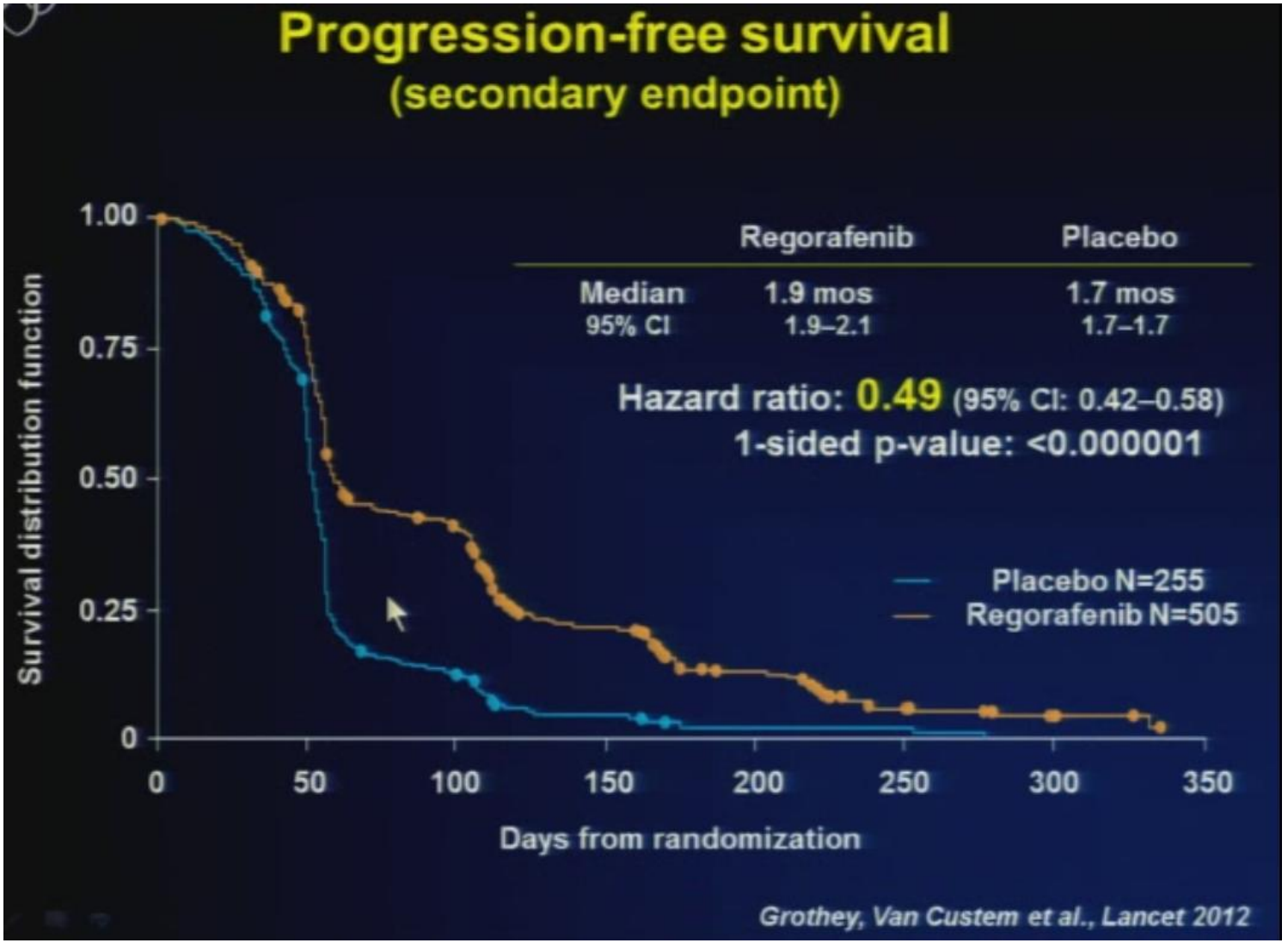
Metastatik Kolon Kanserinde Tedavi Seçenekleri
CORRECT Çalışması

	Regorafenib n = 505	Plasebo n = 255
Medyan OS, ay (IQR)	**6.4 (3.6-11.8)**	**5.0 (2.8-10.4)**
HR (95% CI)	0.77 (0.64-0.94)	
P değeri	0.0052	



Grothey A, et al. Lancet. 2013;381:303-312.

Metastatik Kolon Kanserinde Tedavi Seçenekleri

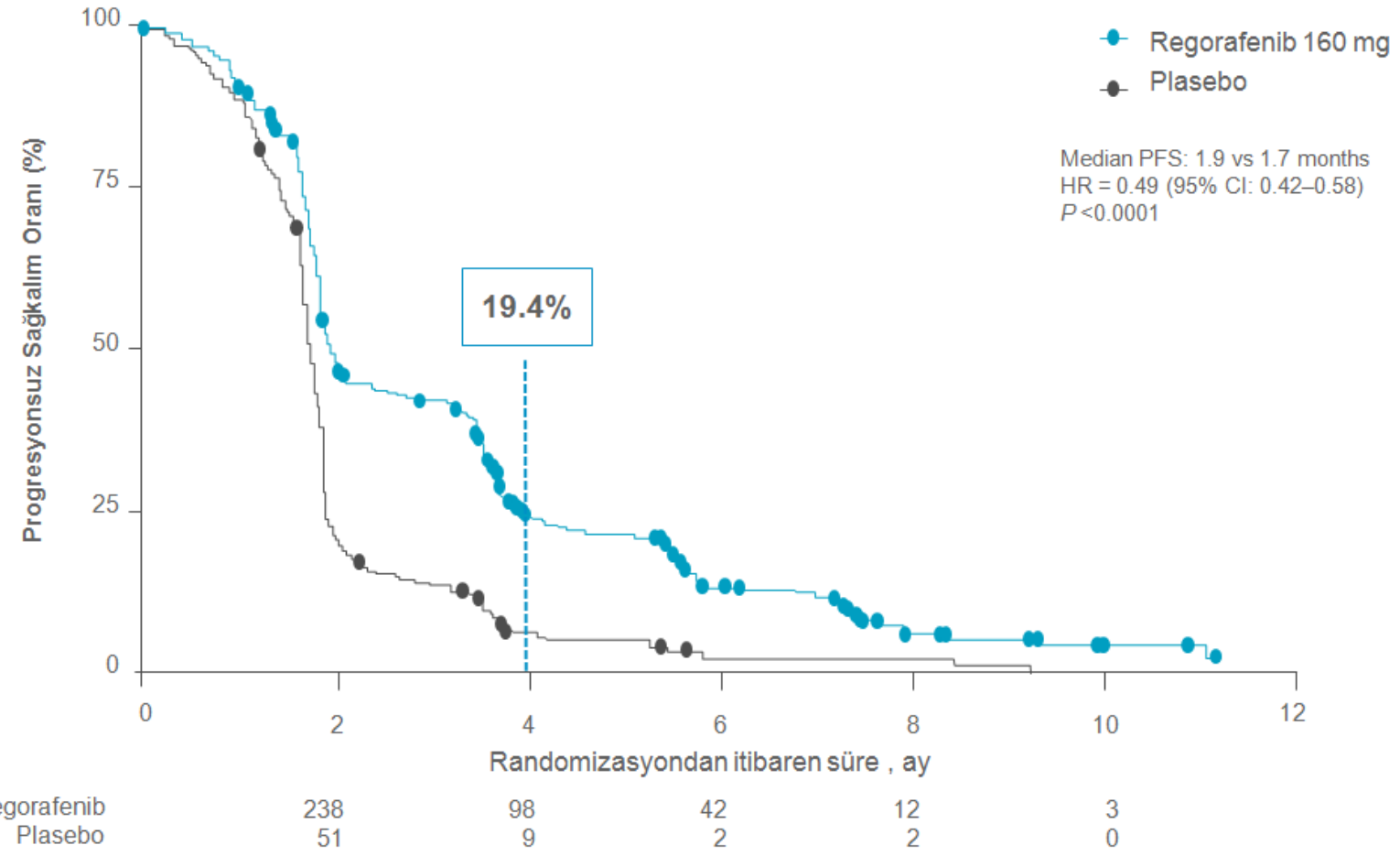


Metastatik Kolon Kanserinde Tedavi Seçenekleri
CORRECT ALT GRUP

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

Grothey A, et al. Lancet. 2013;381:303-312.

Metastatik Kolon Kanserinde Tedavi Seçenekleri
CORRECT ALT GRUP



Grothey A, Van Cutsem E, et al. Lancet. 2013;381(9863):303-312; Grothey A, et al. ASCO GI 2015. Abstract 710.

Metastatik Kolon Kanserinde Tedavi Seçenekleri
CORRECT Yan Etki Yönetimi

CORRECT çalışmasındaki hastaların ≥ %10'da görülen ilaca bağlı AO'lar

	STIVARGA® (160 mg) + EDT (n=500)			Plasebo + EDT (n=253)		
Advers Olaylar	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.

Grothey A et al. Lancet. 2013;381:303-312.

Metastatik Kolon Kanserinde Tedavi Seçenekleri
CORRECT Yan Etki Yönetimi

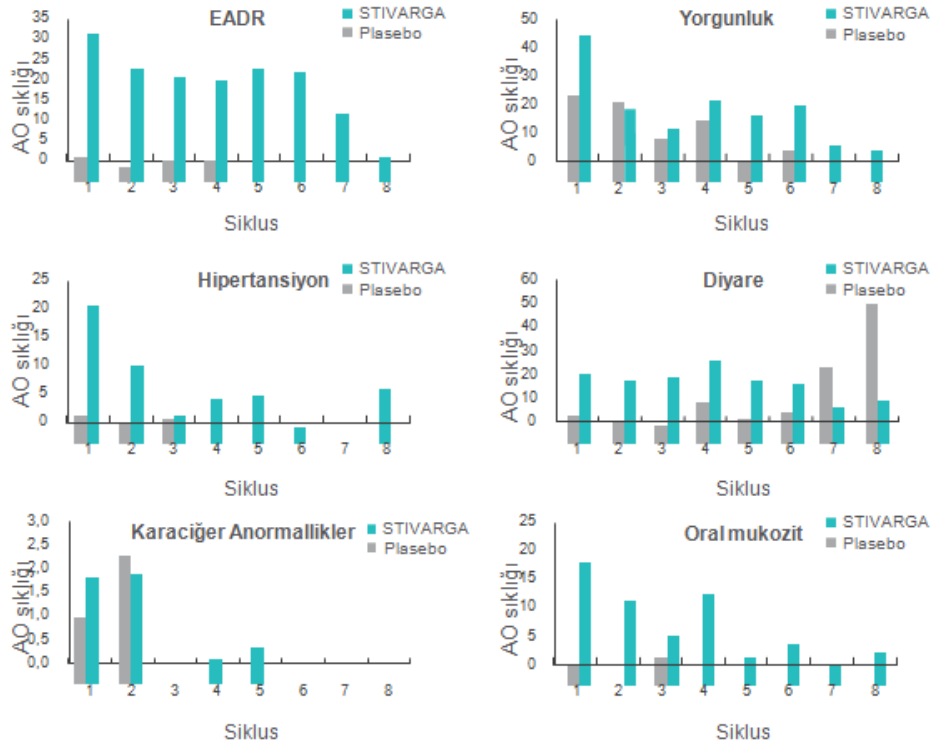
CONCUR çalışmasındaki hastaların ≥ %10'da görülen AO'lar

	STIVARGA® (160 mg) + BSC (n=136)			Plasebo + BSC (n=68)		
Advers Olaylar	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.

Jin, et al. Lancet Oncol 2015; 16: 619-29.

Metastatik Kolon Kanserinde Tedavi Seçenekleri
CORRECT Yan Etki Yönetimi



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

1. Grothey A et al. Lancet. 2013;381:303-312. 2. Khan G et al. Cancer Manage Res. 2014;6:93-103.

Metastatik Kolon Kanserinde Tedavi Seçenekleri
CORRECT Yan Etki Yönetimi

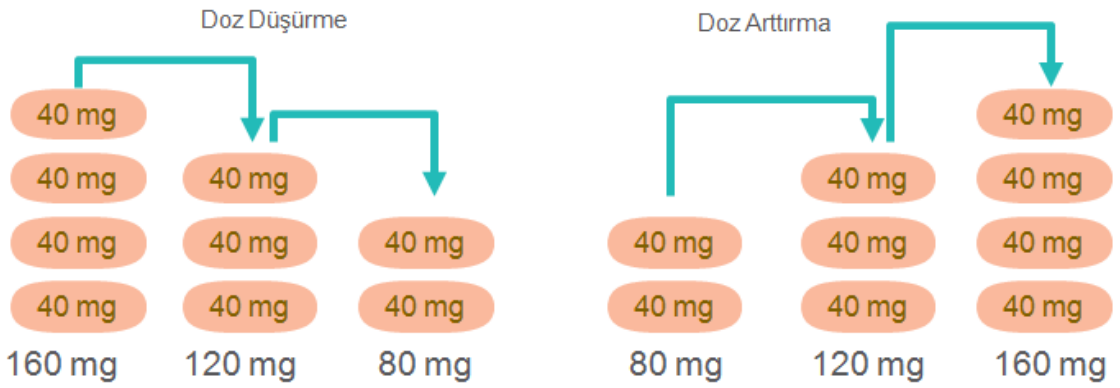
- Stivarga'nın potansiyel yan etkileri hakkında hastaya bilgi verilmeli[1,2]
- Hastalar advers olayları önlemek ve gelişme ihtimaline en aza indirmek için eğitilmeli[2]
- Monitörize edilebilmeleri için semptomları olursa sağlık çalışanlarına haber vermeliler[1,2]

Bilgilendir-eğit-önle-monitörize et[1,2]

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			

1. Grothey A et al. Oncologist. 2014;19:1-12. 2. De Wit M et al. Support Care Cancer. 2014;22:837-846.

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 adımlarışeklinde uygulanır.
- En düşük önerilen günlük doz **80 mg'dır.**
- Maksimum günlük doz **160 mg'dır.**

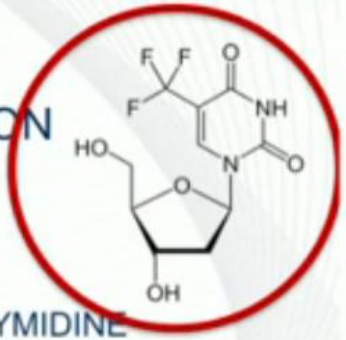
Stivarga 40 mg film kaplı tablet, Kısa Ürün Bilgisi, 18.05.2015, Türkiye

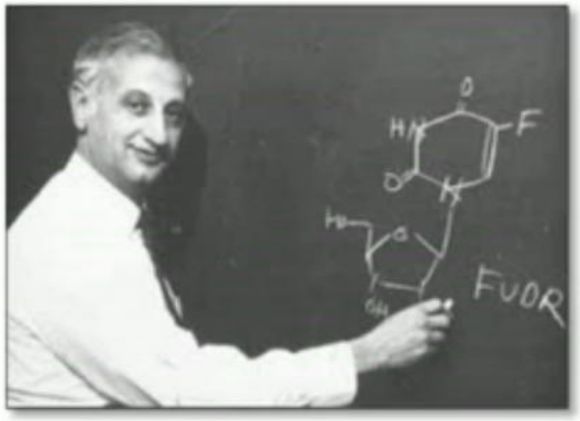
Metastatik Kolon Kanserinde Tedavi Seçenekleri

TAS-102

A NOVEL ANTI-METABOLITE COMBINATION

("Teaching an old dog new tricks")

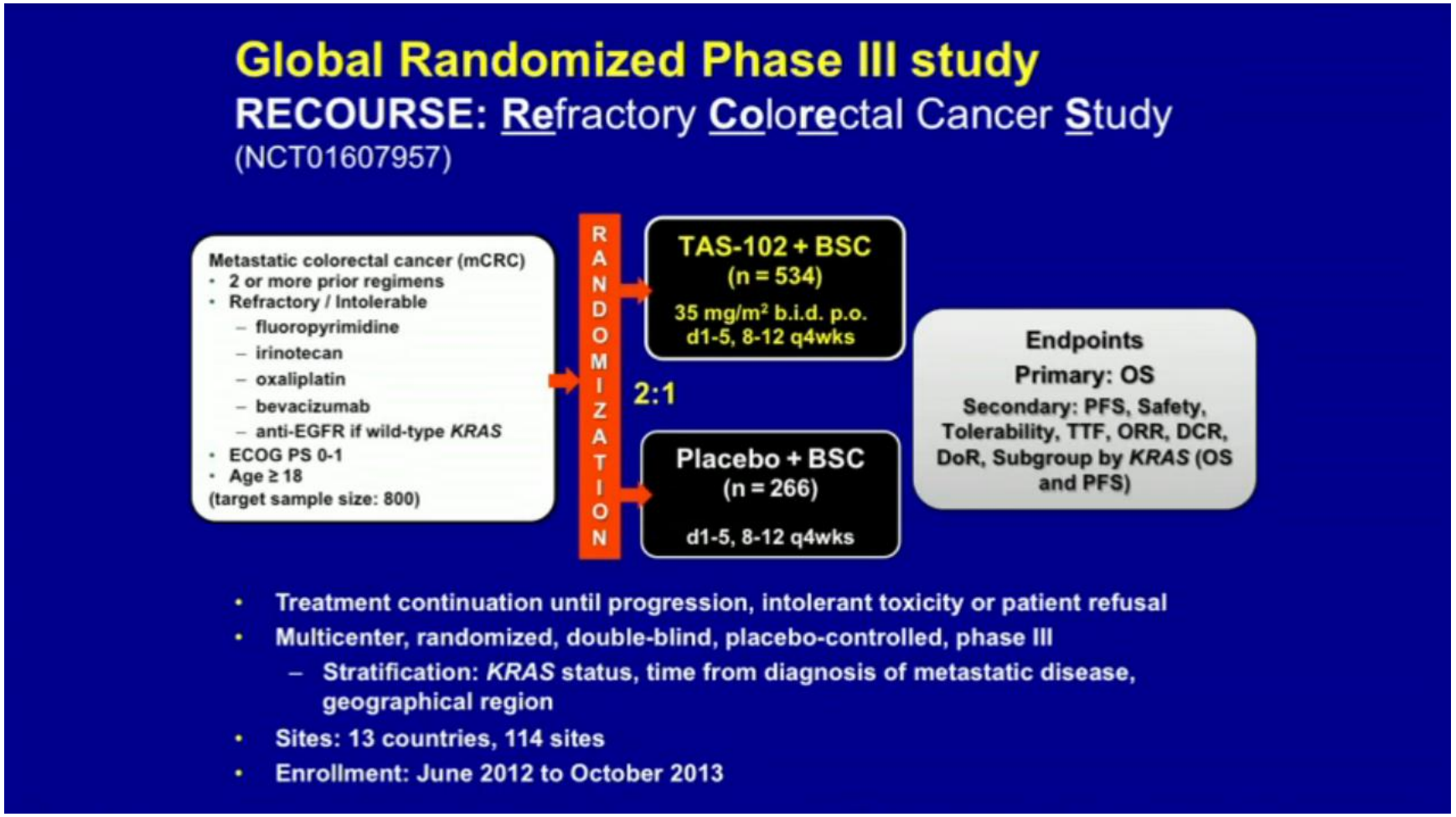




CHARLES HEIDELBERGER

- TRI-FLUORO-THYMIDINE
  - A fluoropyridimine 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

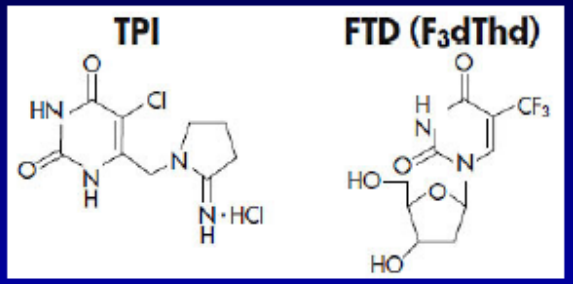


Metastatik Kolon Kanserinde Tedavi Seçenekleri

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.

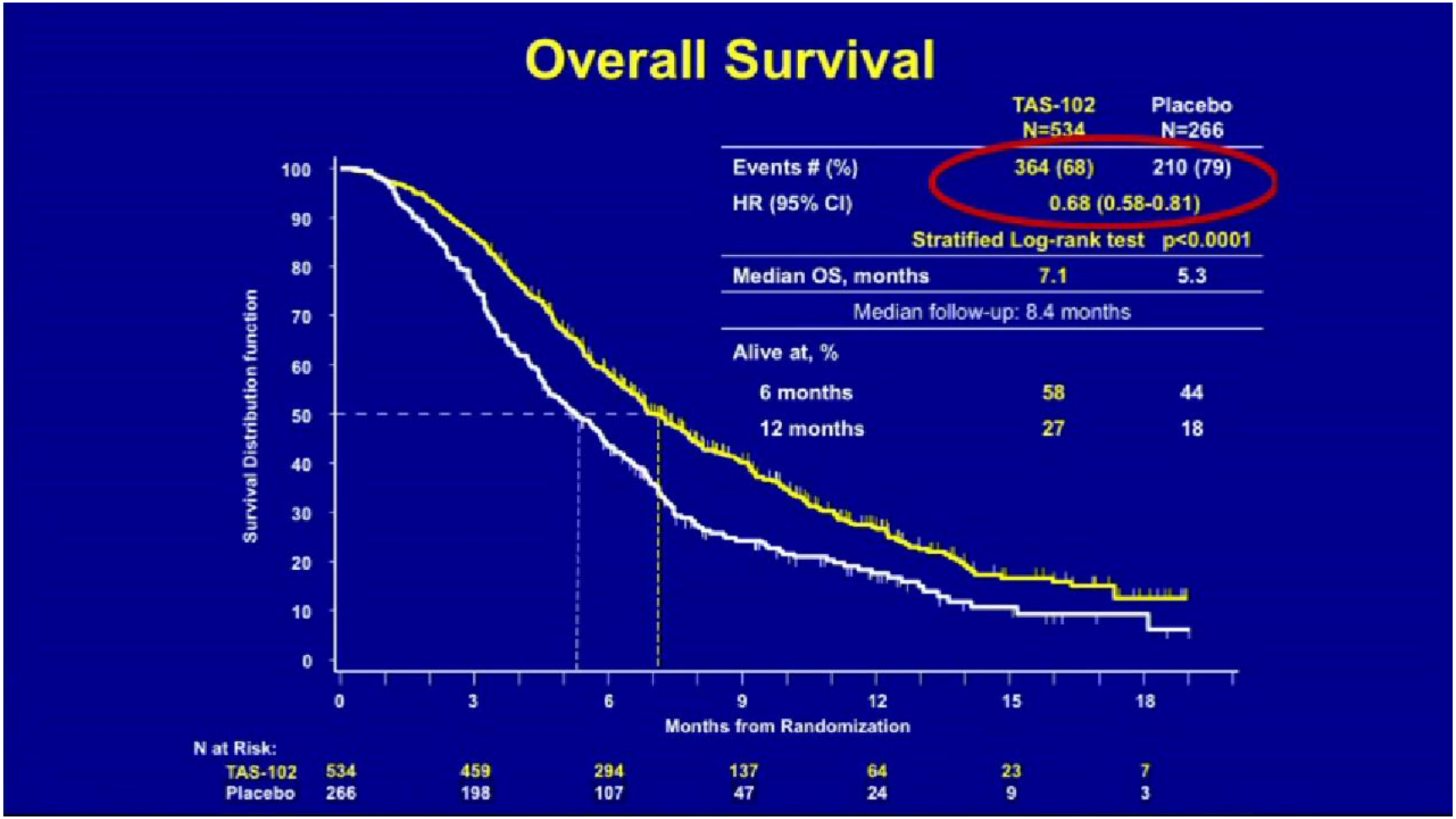


RECOURSE trial

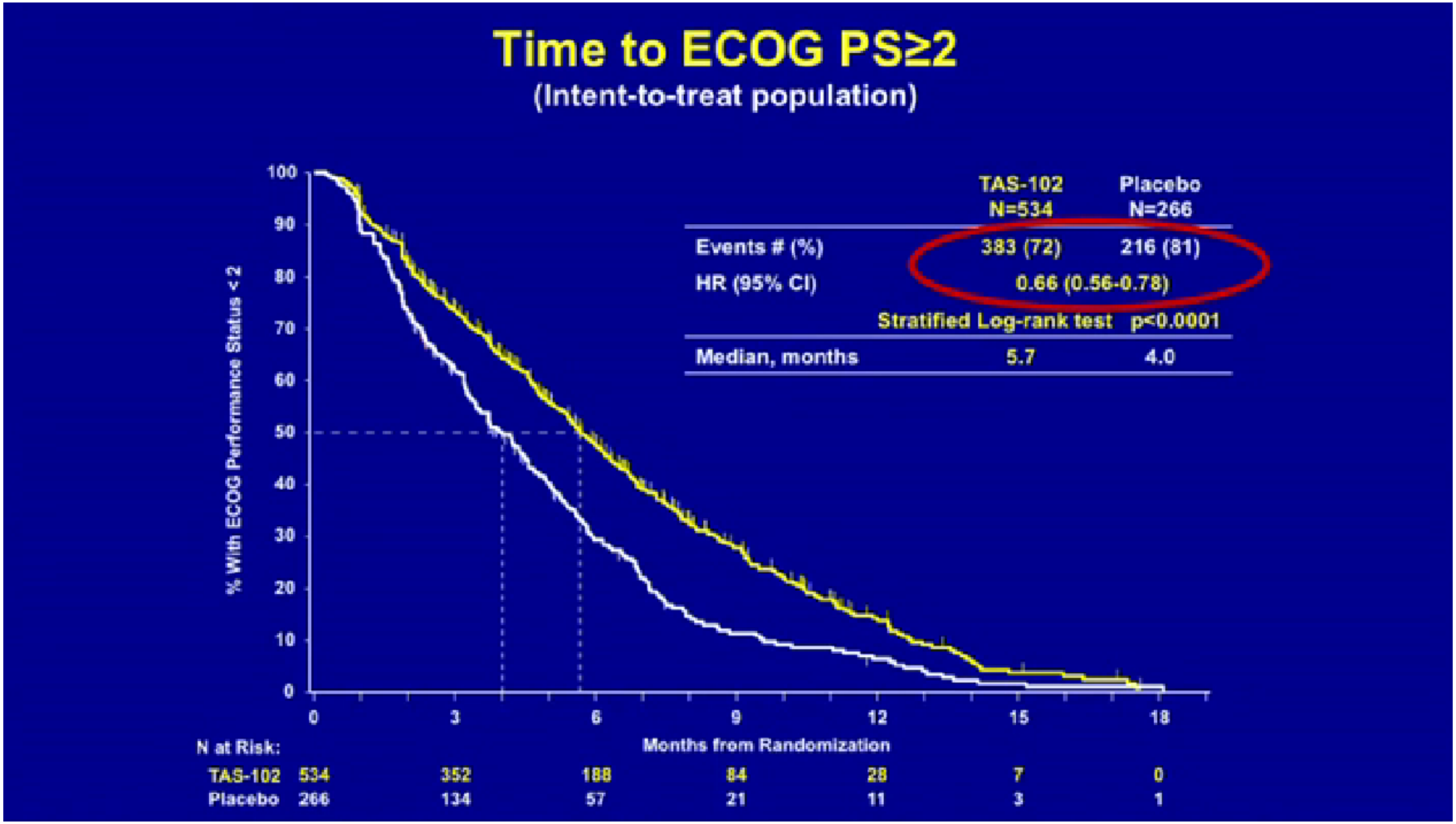
- global phase III trial conducted in 13 countries at 114 centres
- mCRC refractory to all standard therapies (including EGFR-targeting mAb for KRAS WT patients)
- Randomized 2:1 to TAS-102 (534 patients), 35 mg/m2 BID on Days 1- 5 and 8-12 of each 28-day cycle, or placebo (266 patients)
- The primary endpoint was overall survival.

Mayer, NEJM 2015

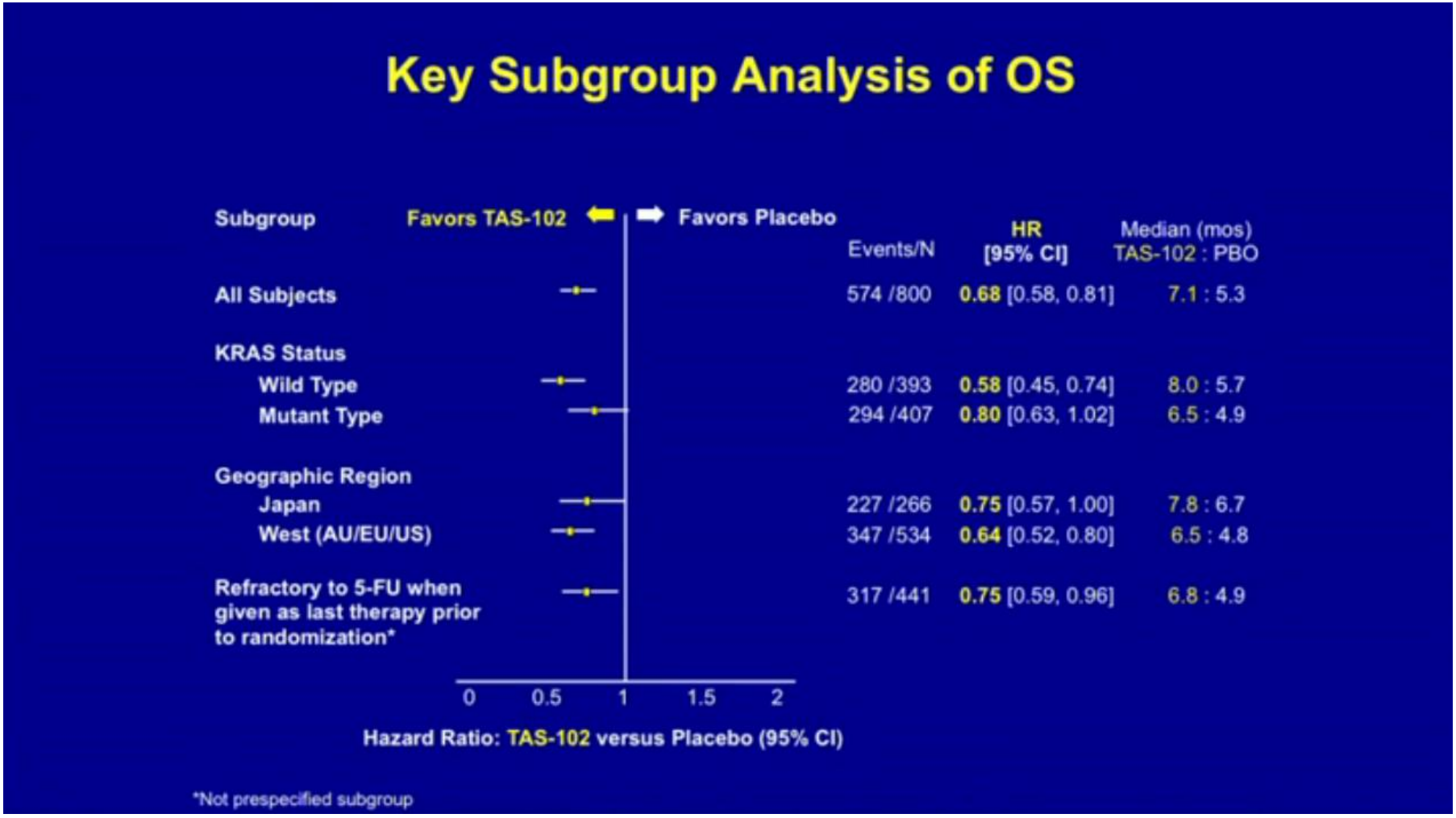
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

TAS-102 RECOURSE: Toxicity

Mayer, NEJM 2015

Event	TAS-102 (N=533)		Placebo (N=265)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥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

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		Non-Colorectal Cancers
Cohort A Deficient in Mismatch Repair (n=28)	Cohort B Proficient in Mismatch Repair (n=25)	Cohort C Deficient in Mismatch Repair (n=30)

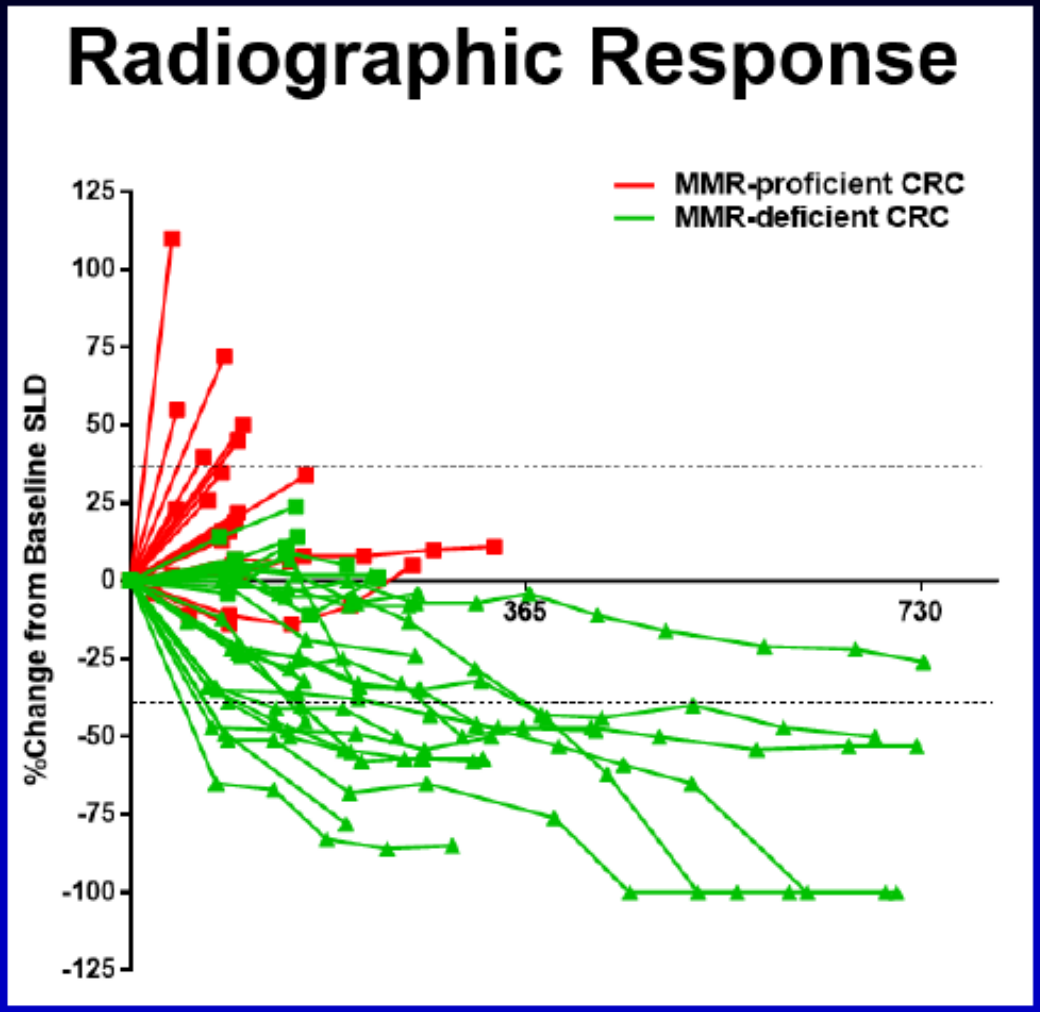
- Anti-PD1 (pembrolizumab) – 10 mg/kg every 2 weeks
- Here they updated from the original 13 CRC Cohort A patients reported at ASCO 2015/NEJM 2015

Le, ASCO 2016

Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi

PD-1 in MSI-H mCRC

Le, ASCO 2016



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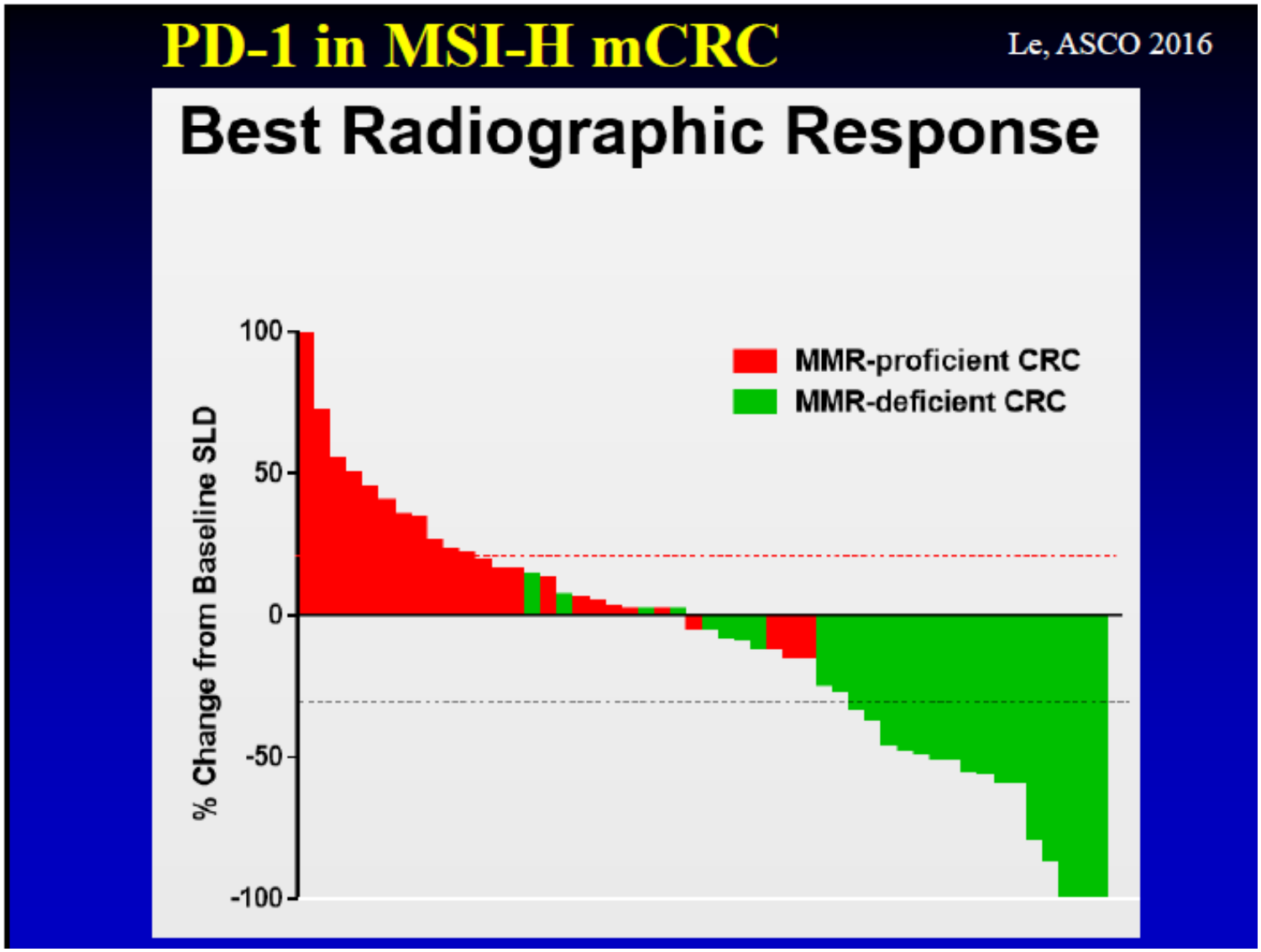

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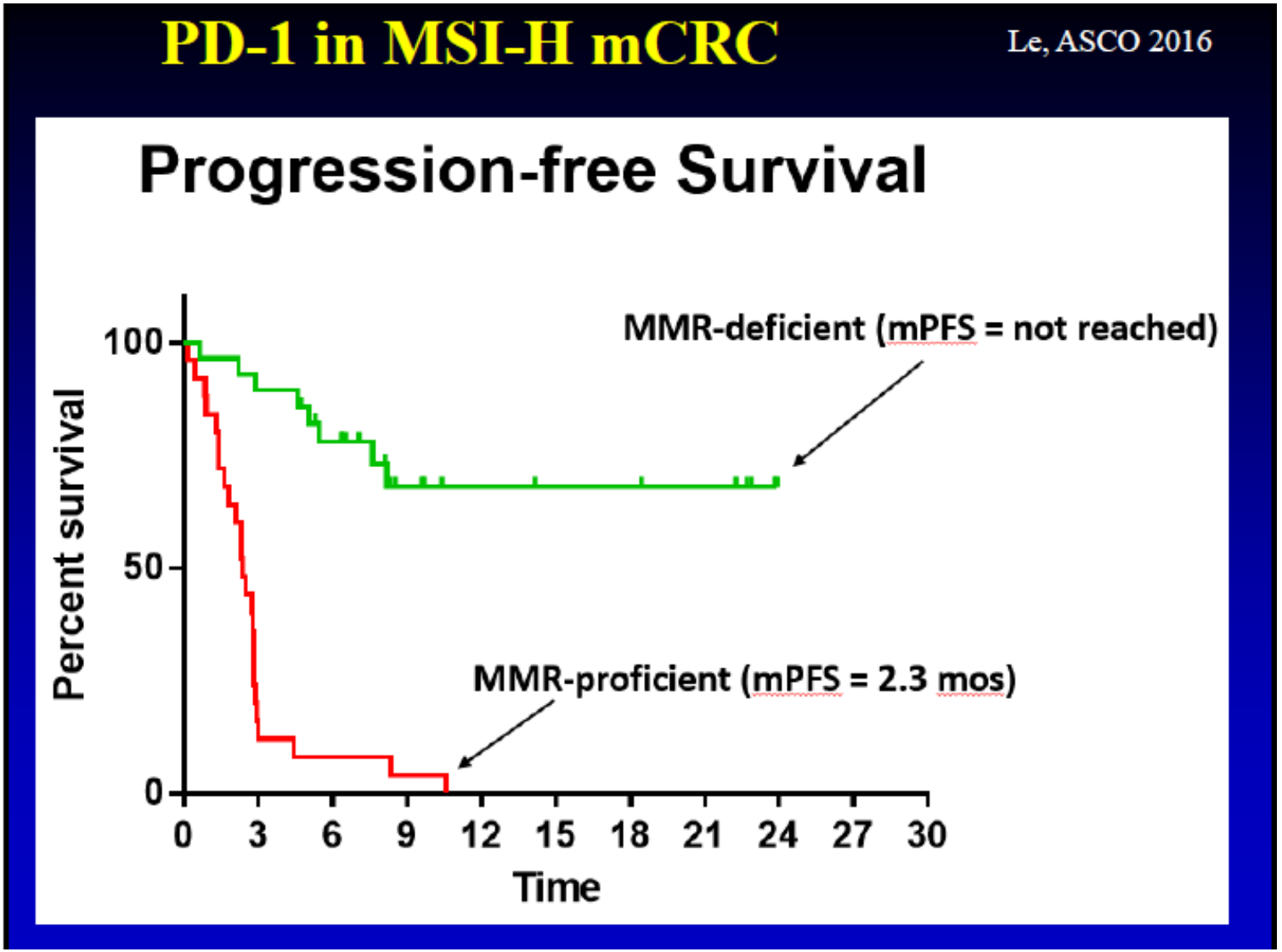

Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi

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):
Michael J. Overman, Scott Kopetz, Raymond S. 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-IRCSS, 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

Abstract Disclosures

ASSOCIATED PRESENTATION

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

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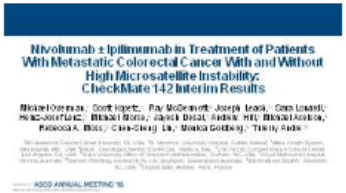
ASSOCIATED SLIDES



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Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi

Author(s):
Michael J. Overman, Scott Kopetz, Raymond S. 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-IRCSS, 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

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+I1) x 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+I1) 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+I1) of MSI-H and 100% of non-MSI-H pts had ≥ 2 prior regimens. 15% (N3) and 25% (N3+I1) of MSI-H pts had known BRAF V600E. 17 (52%; N3) and 19 (73%; N3+I1) 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+I1); most common were diarrhea and fatigue (27% each; N3) and diarrhea (46%; N3+I1). Grade 3–4 TRAEs occurred in 7 (N3) and 8 pts (N3+I1). 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[a] 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,[b] %	55	80
Median OS (95% CI), mo	16.3 (8.3–NE)	NR (NE–NE)
5-mo OS rate,[c] %	75	100

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

Metastatik Kolon Kanseri Tedavi

National Comprehensive Cancer Network®

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.[785] Nivolumab was studied with or without ipilimumab in patients with metastatic colorectal cancer in a phase II trial.[786] 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. Be
The randomized, multicenter, phas
patients with *KRAS* wild-type tumo
line oxaliplatin-based therapy plus
bevacizumab or FOLFIRI plus pani
in the primary endpoint of PFS betv
panitumumab arm vs. 9.2 months i
95% CI, 0.68–1.50; $P = .97$).

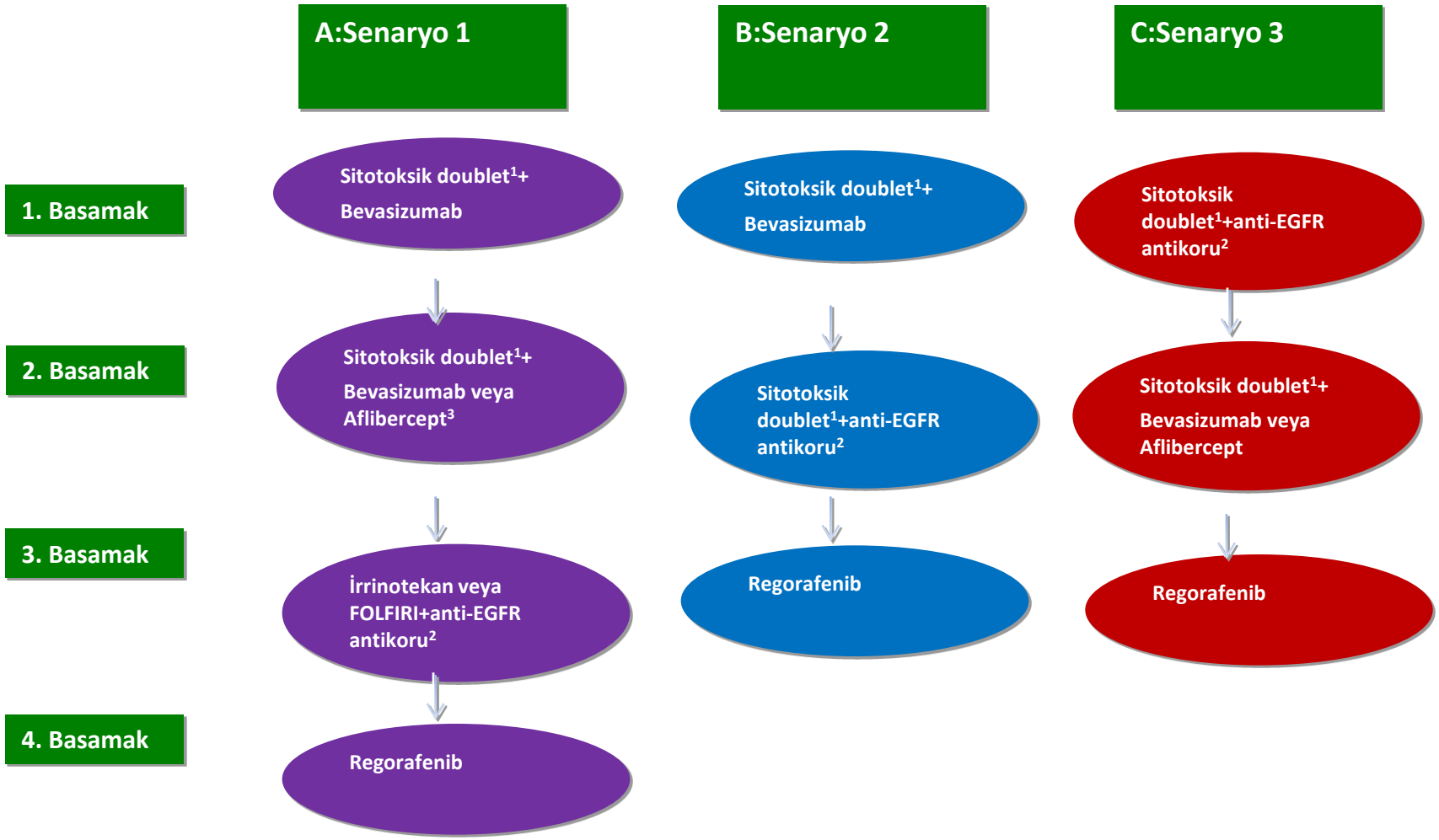
Workup and Management of Syr

The workup for patients in whom m
adenocarcinoma from the large bo
is suspected should include a total
CEA determination, biopsy if indica
contrast of the chest, abdomen, an
contrast should be considered if C
recommends tumor *KRAS/NRAS* g
metastatic disease and considerati
patients with *KRAS/NRAS* wild-typ
Role of KRAS, NRAS, and BRAF S

The panel strongly discourages the
staging, baseline imaging, or routir

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**