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

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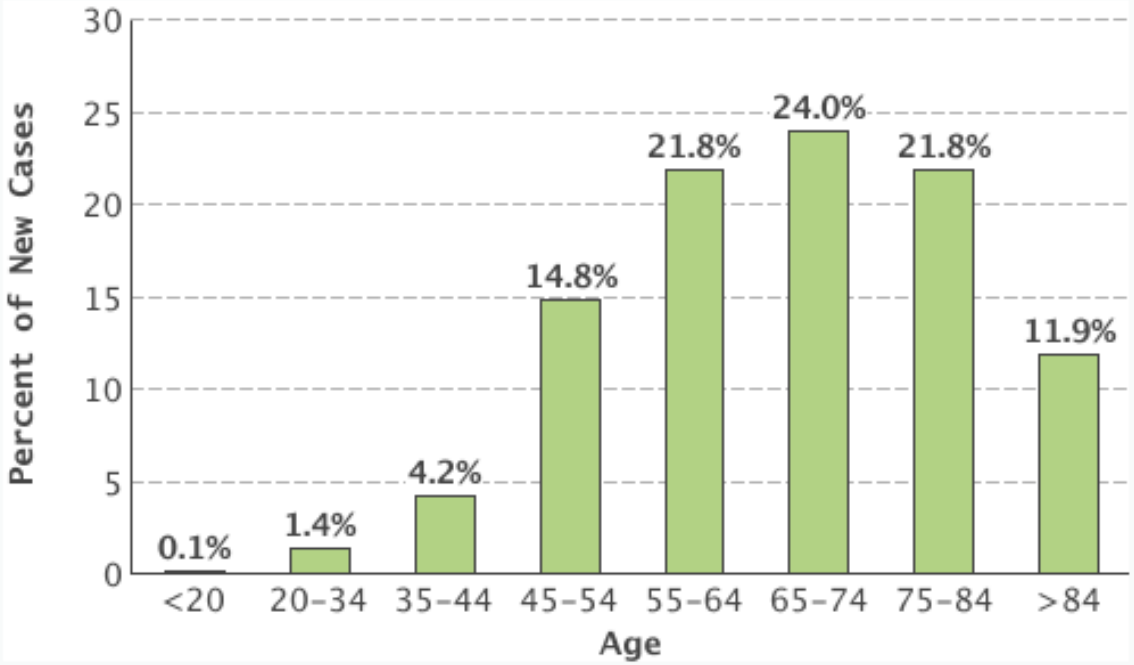
Tıbbi Onkoloji

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

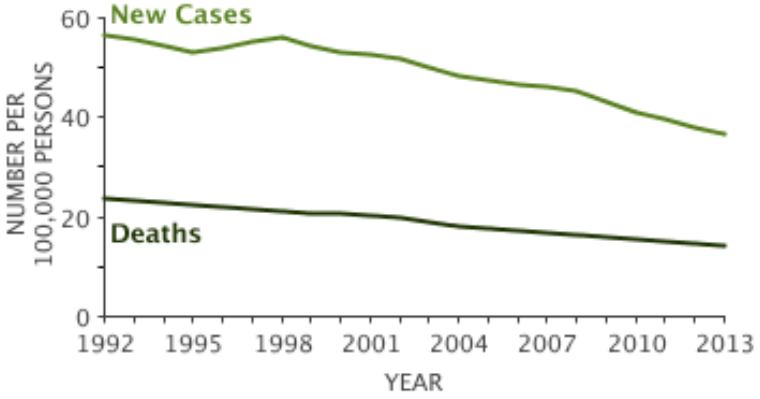
Colon and rectum cancer represents 8.0% of all new cancer cases in the U.S.

8.0%

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.

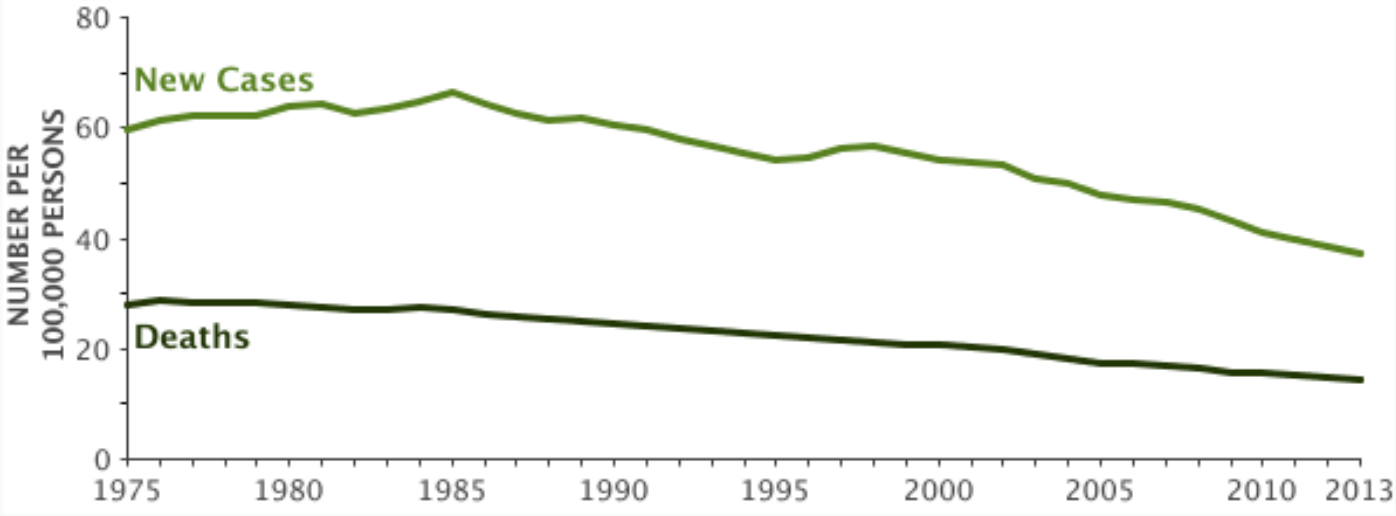
Lifetime Risk of Developing Cancer: Approximately 4.5 percent of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime, based on 2010–2012 data.

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



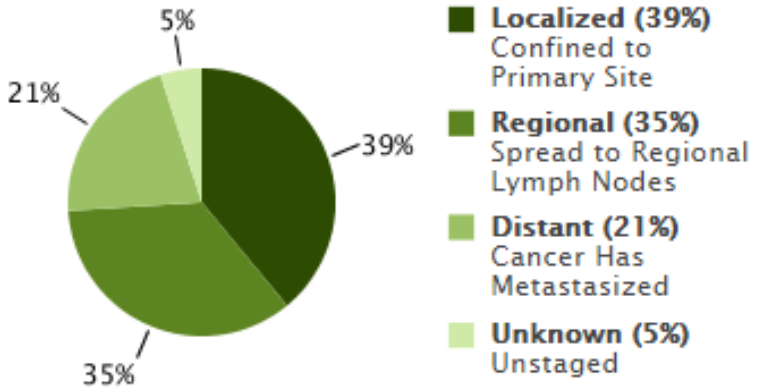
Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	48.6%	51.2%	58.1%	60.8%	59.7%	64.8%	65.7%	67.2%

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

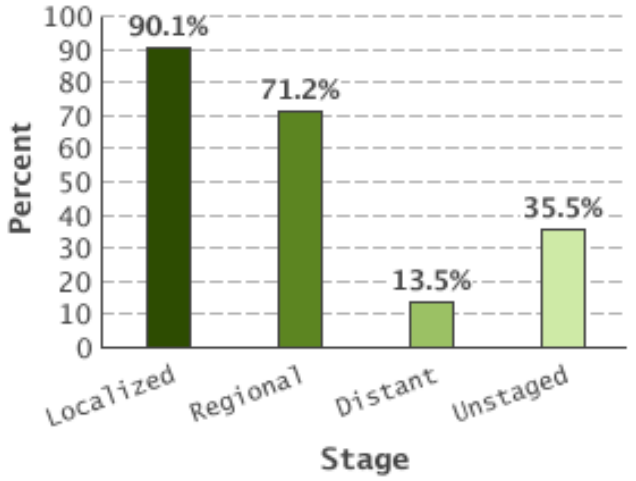
Kolon Kanseri İnsidans ve Mortalite

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

Percent of Cases by Stage

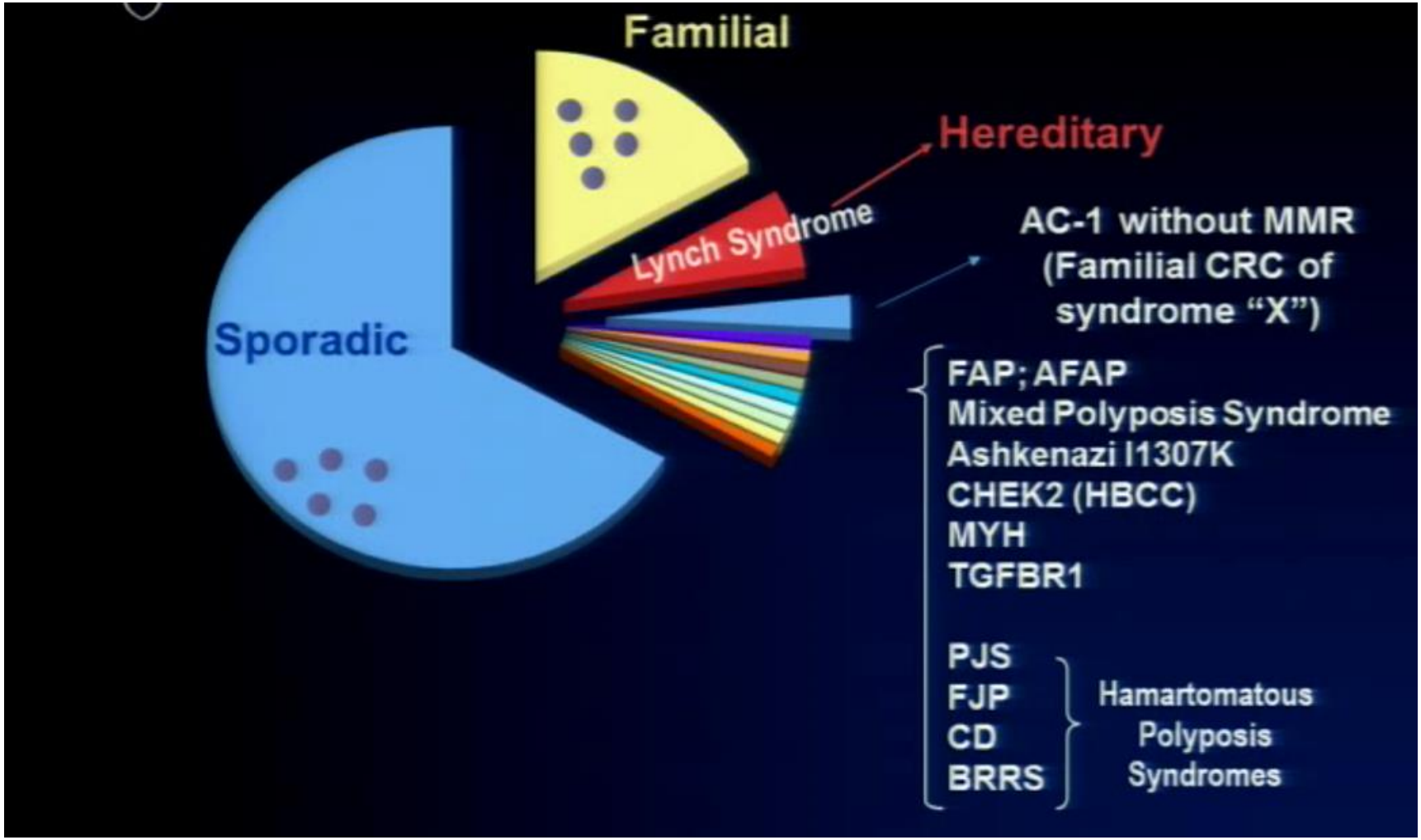


5-Year Relative Survival

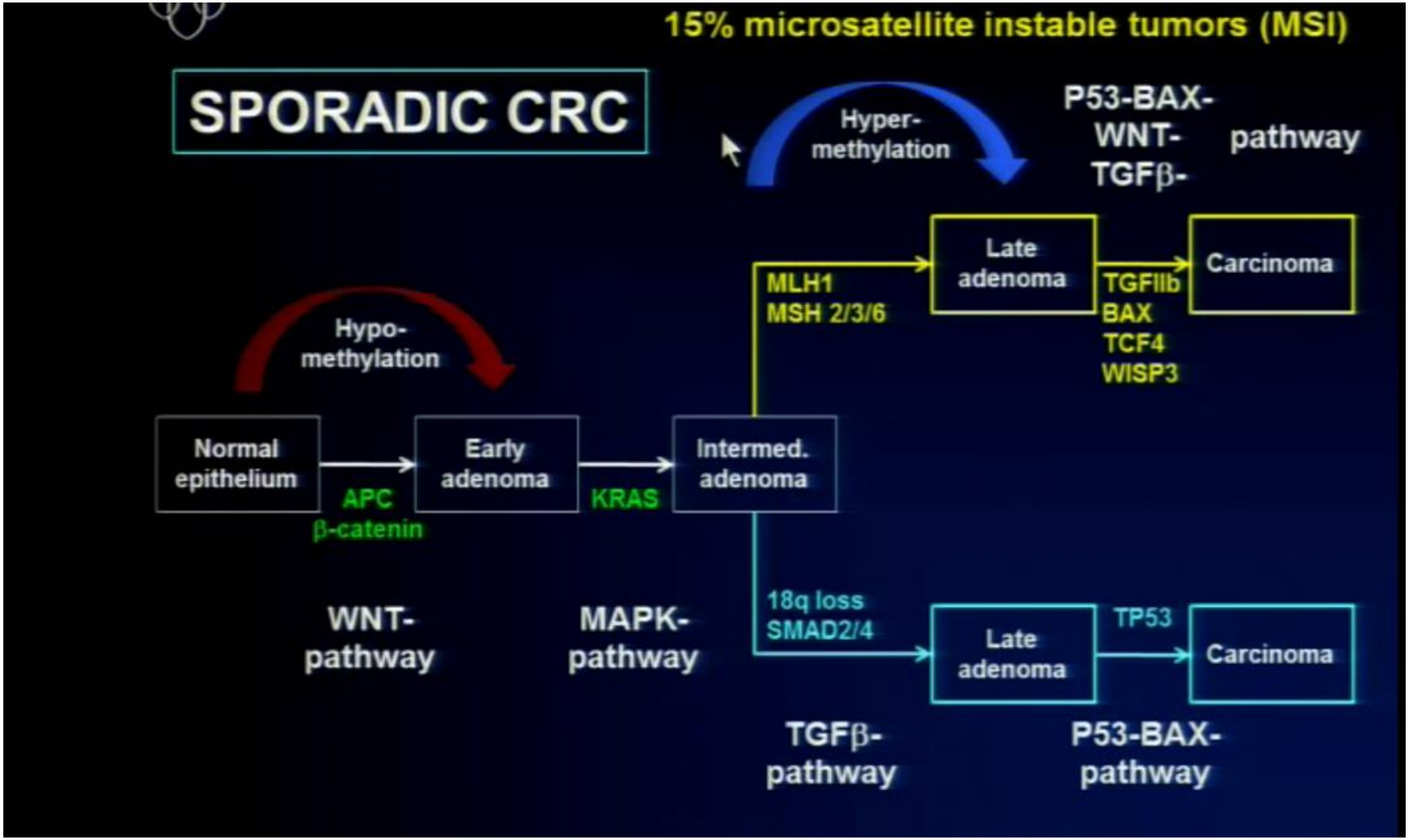


SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

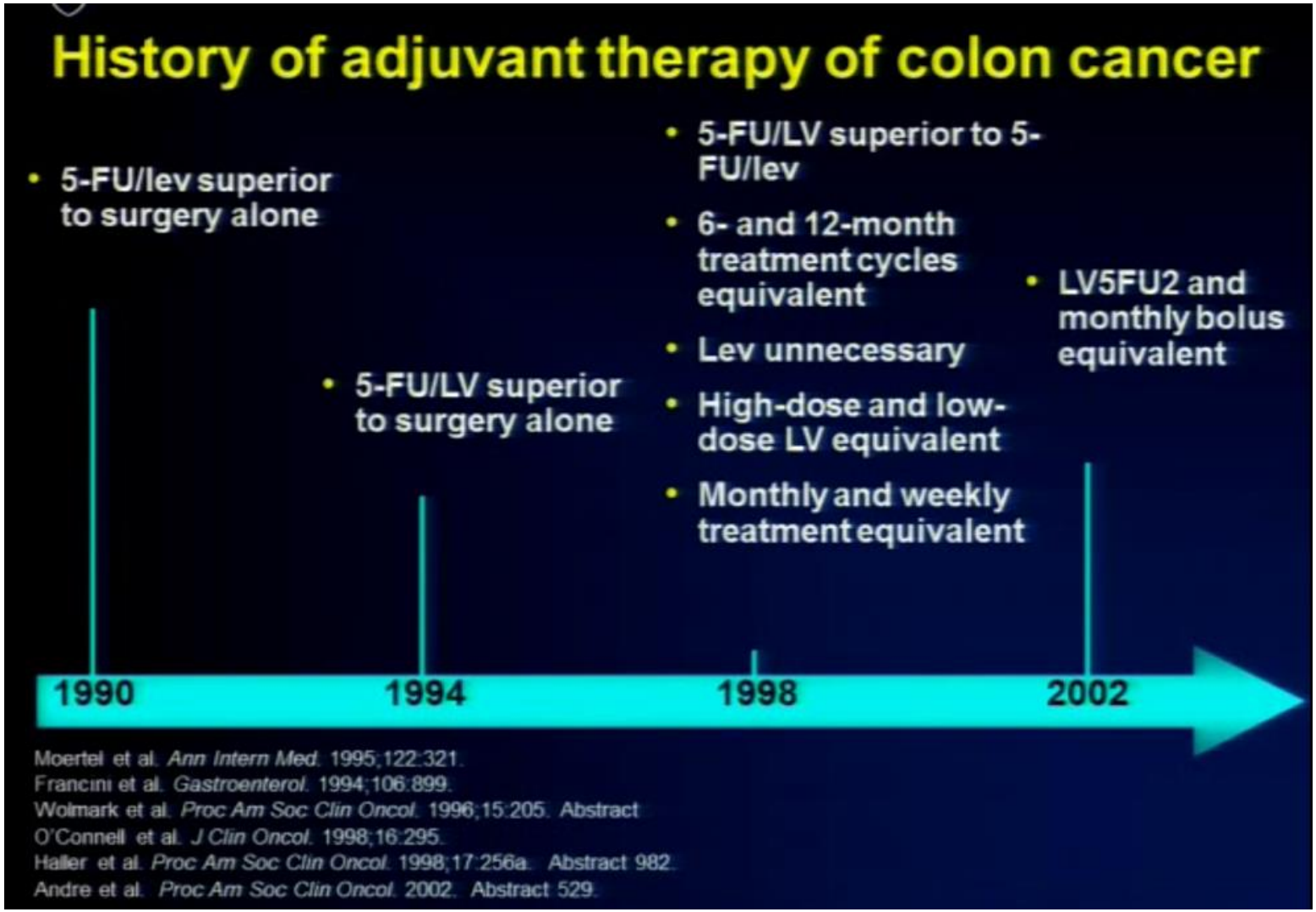
Kolon Kanseri
Genetik ve Risk Faktörleri



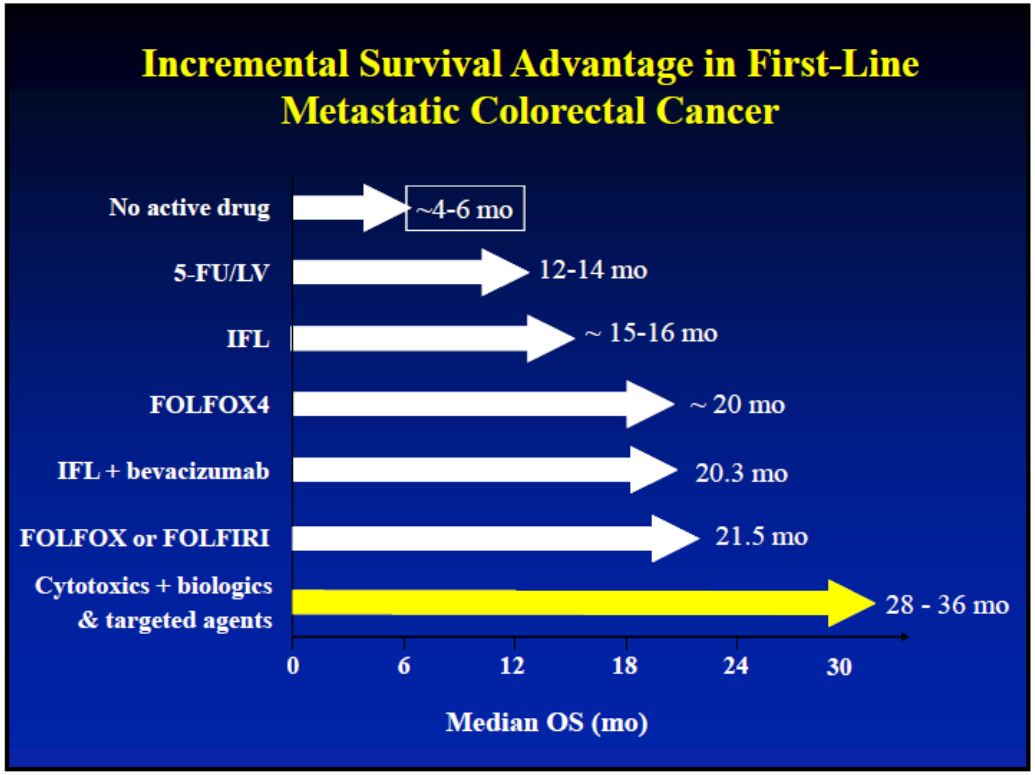
Kolon Kanseri
Genetik ve Risk Faktörleri



Kolon Kanseri Tedavi



Kolon Kanseri Tedavi



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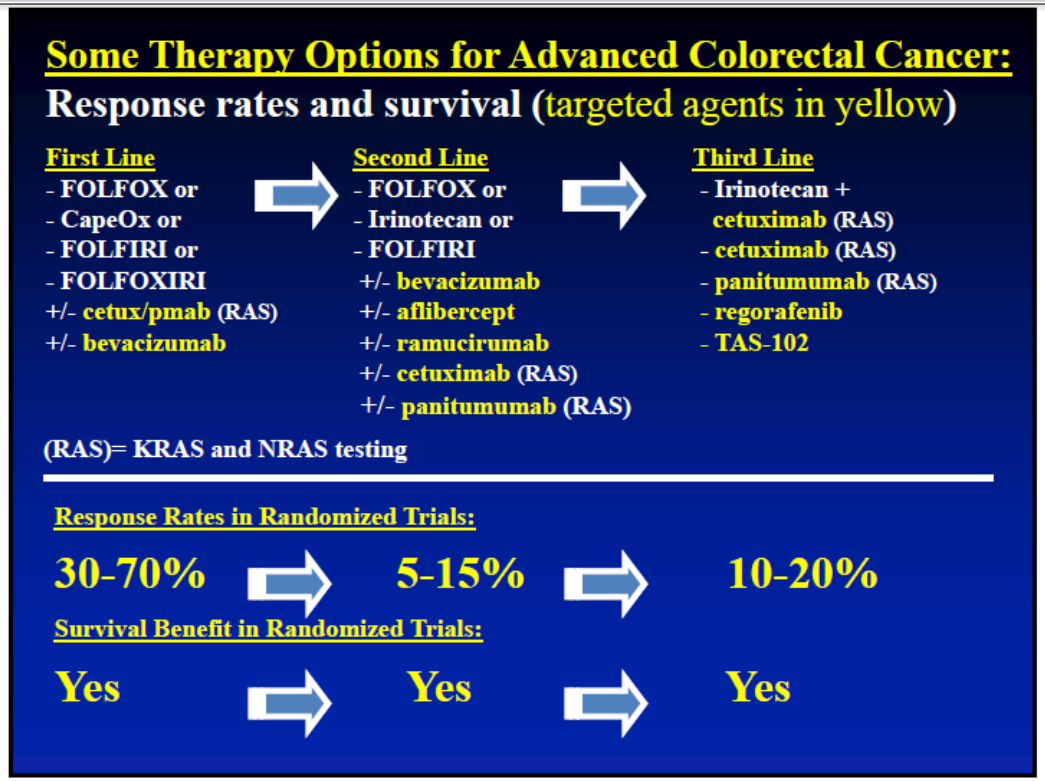
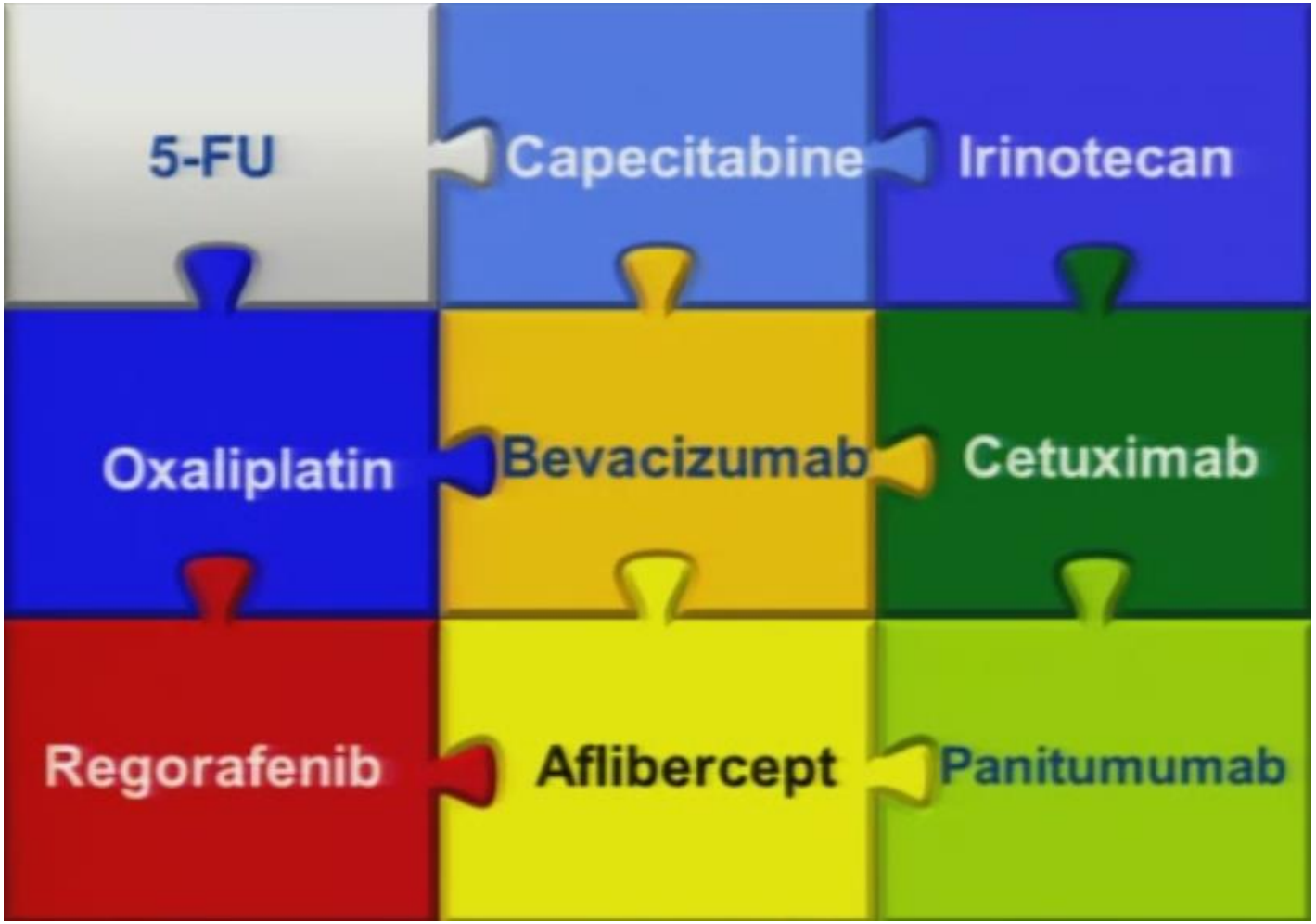


Metastatik Kolon Kanseri Tedavi

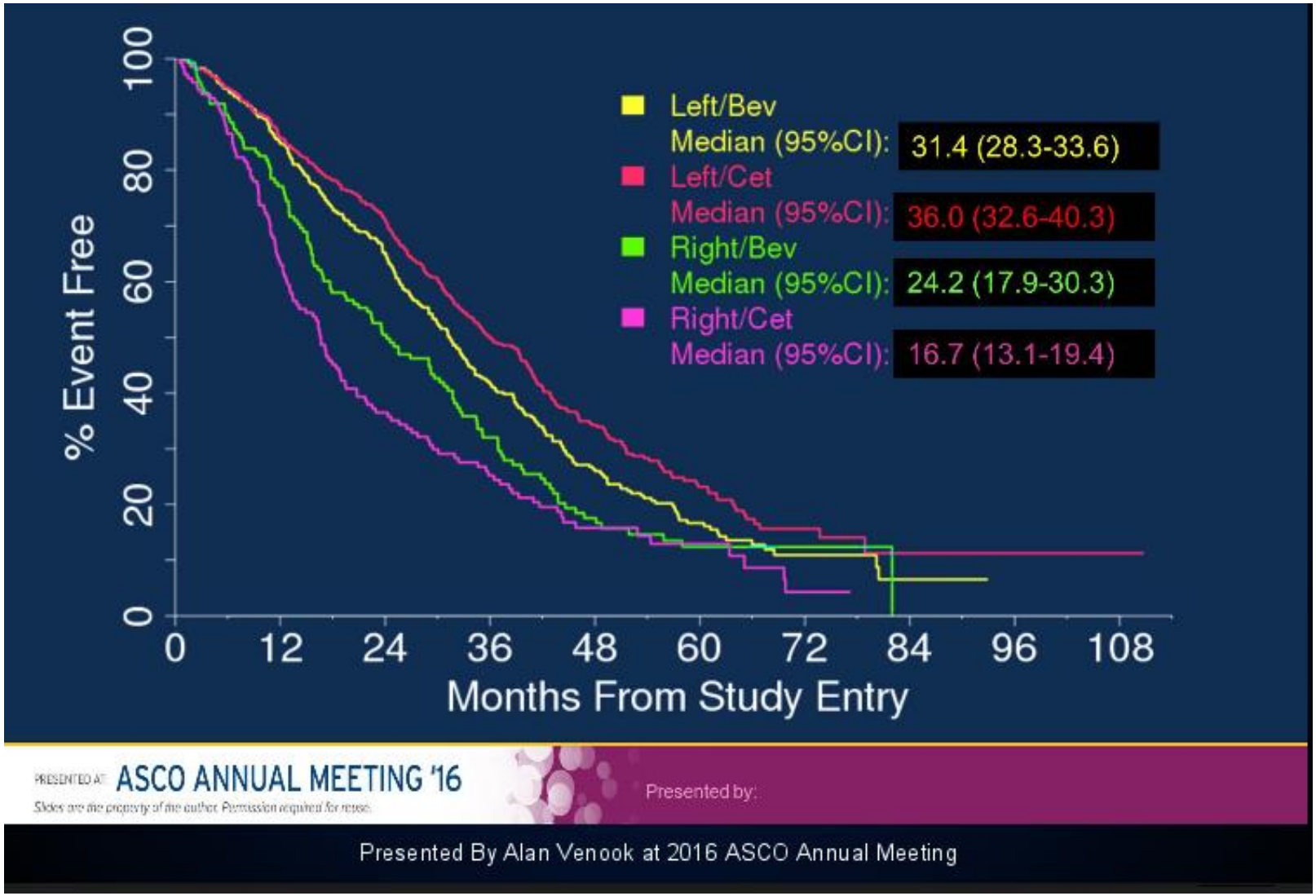


Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

Çalışma	Medyan OS (mo)	Medyan PFS (mo)	Medyan ORR (%)
PEAK[1] (faz II) (KRAS WT) Hipotez test edilmemiştir			
Bevasizumab + mFOLFOX6 (n = 143)	**24.3** HR = 0.62 P = .009	**10.1** HR = 0.87 P = .353	**54.0**
Panitumumab + mFOLFOX6 (n = 142)	**34.2**	**10.9**	**58.0**
FIRE-3[2] (faz III) (KRAS WT) primer sonlanım noktası: ORR			
Bevasizumab + FOLFIRI (n = 295)	**25.0** HR = 0.77 P = .017	**10.3** HR = 1.06 P = .547	**58.0** HR = 1.18 P = .183
Setuksimab + FOLFIRI (n = 297)	**28.7**	**10.0**	**62.0**
CALGB 80405[3] (faz III) (KRAS WT) primer sonlanım noktası: OS			
Bevasizumab + FOLFOX veya FOLFIRI (n = 559)	**29.0** HR = 0.92 P = .34	**10.8** HR = 1.04 P = .55	**57.2** P = .02
Setuksimab + FOLFOX veya FOLFIRI (n = 578)	**29.9**	**10.4**	**65.6**

1.Schwarzberg LS ve ark. J Clin Oncol. 2014 Jul 20;32(21):2240-7. 2.Heinemann V ve ark. Lancet Oncol 2014; 15 : 1065–75. 3.Lenz ve ark. ESMO 2016. Right or left metastatic colon cancer: will the side change your treatment?

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Kolon Kanseri Tedavi

2nd Line Colorectal Cancer

QUESTION

What is the best 2nd line chemotherapy option for this patient?

1) FOLFIRI/ziv-aflibercept
2) FOLFIRI/ramucirumab
3) FOLFIRI/bevacizumab

Kolon Kanseri Tedavi

11 Drugs for Colorectal Cancer *Biomarker Driven

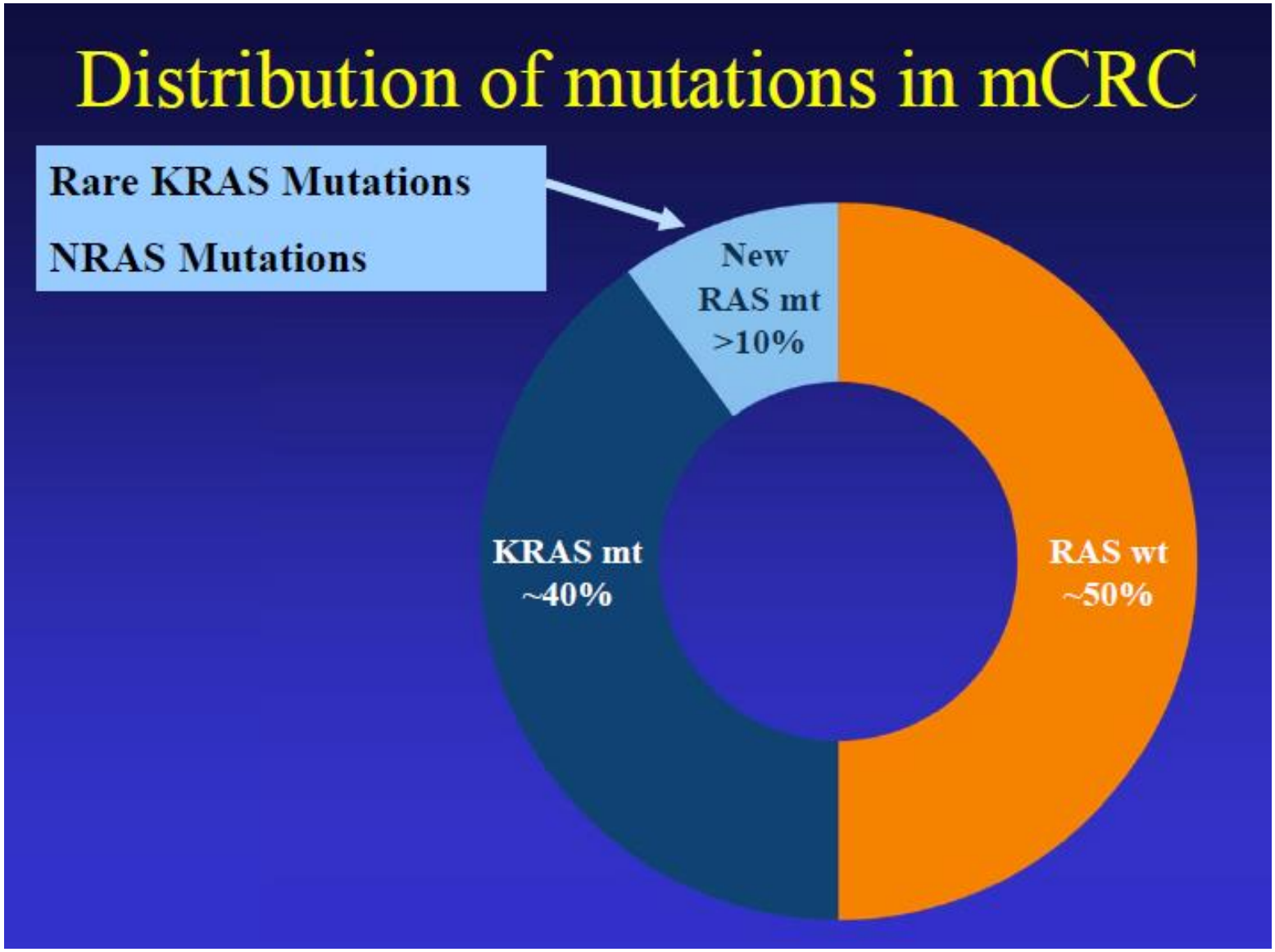
"Cytotoxics"	Mechanism
1. 5-Fluorouracil (5-FU)	-> pyrimidine analog
2. Capecitabine	-> oral 5-FU pro-drug
3. TAS-102	-> oral 5-FU
4. Irinotecan	-> topoisomerase I inhibitor
5. Oxaliplatin	-> 3rd generation platinum

"Biologics/Targeted"	Mechanism
1. Cetuximab	-> antibody against EGFR
2. Panitumumab	-> antibody against EGFR
3. Bevacizumab	-> antibody against VEGF
4. Aflibercept	-> dummy VEGF receptor
5. Regorafenib	-> tyrosine kinase inhibitor
6. Ramucirumab	-> antibody against VEGFR2

VEGF= Vascular Endothelial Growth Factor

EGFR= Epidermal Growth Factor Receptor

Metastatik Kolon Kanseri Tedavi



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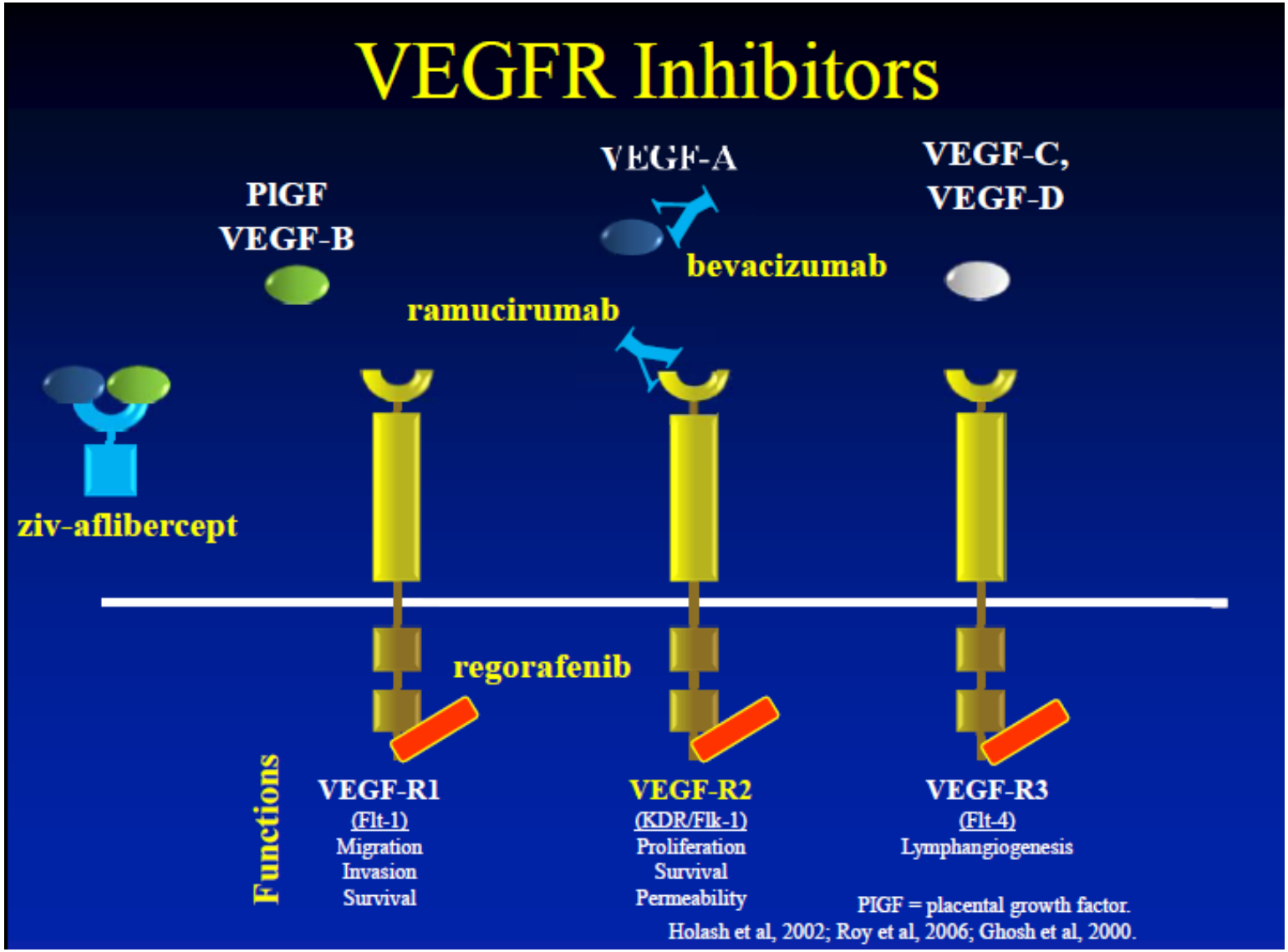

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Targeting VEGF

First-Line Bevacizumab in mCRC, Phase III Trials

Trial Regimen	Response rate (%)		Median OS (mo)	
	CT	CT + bev	CT	CT + bev
AVF2107g IFL (n = 411) vs IFL + bev (n = 402)	35	45	6.2	10.6
NO16966 FOLFOX/CAPEOX (n = 701) vs FOLFOX/CAPOX + bev (n = 699)	49	47	8.0	9.4
BICC-C: FOLFIRI (n = 144) vs FOLFIRI + bev (n = 57)	47	58	23.1	28.0
BICC-C mIFL (n = 141) vs mIFL + bev (n = 60)	43	53	17.6	19.2
AVEX (pt > 70 years) Bev + cape (n = 140) vs cape (n = 140)	10%	19%	16.8	20.8

CT, chemotherapy; OS, overall survival; bev, bevacizumab; cape, capecitabine.

Hurwitz, et al. *N Engl J Med*. 2004;350:2335. Saltz, et al. *J Clin Oncol*. 2008;26:2013. Fuchs CS, et al. *J Clin Oncol*.2008;26(4):689-90. Fuchs CS, et al. *J Clin Oncol*. 2007;25(30):4779-86. Cunningham D, et al. *Lancet Oncol*. 2013;14:1077-1085.

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VEGF-Targeted Agents in 2nd mCRC

Modest improvements in PFS and OS, even in patients with prior exposure to bevacizumab.

Hazard Ratios (HR) for OS are 0.81 (bevacizumab), 0.82 (ziv-aflibercept), 0.84 (ramucirumab). Remarkably similar.

	TML			VELOUR			RAISE		
	CT (N=410)	CT + bevacizumab (N=409)	HR (*P* value)	FOLFIRI (N=187)	FOLFIRI + ziv-aflibercept (N=186)	HR (*P* value)	FOLFIRI (N=525)	FOLFIRI + ramucirumab (N=525)	HR (*P* value)
m**OS**, mos	**9.8**	**11.2**	0.81; *P*=0.02	**11.7**	**12.5**	0.86; *P*=NR	**11.7**	**13.3**	0.84; *P*=0.02
m**PFS**, mos	**4.1**	**5.7**	0.68; *P*<0.001	**3.9**	**6.7**	0.66; *P*=NR	**4.5**	**5.7**	0.79; *P*=0.0005

Bennouna et al. Lancet Oncol 2013; Van Cutsem et al. J Clin Oncol 2012; Tabernero et al. Lancet Oncol 2015

PFS = progression-free survival; OS = overall survival

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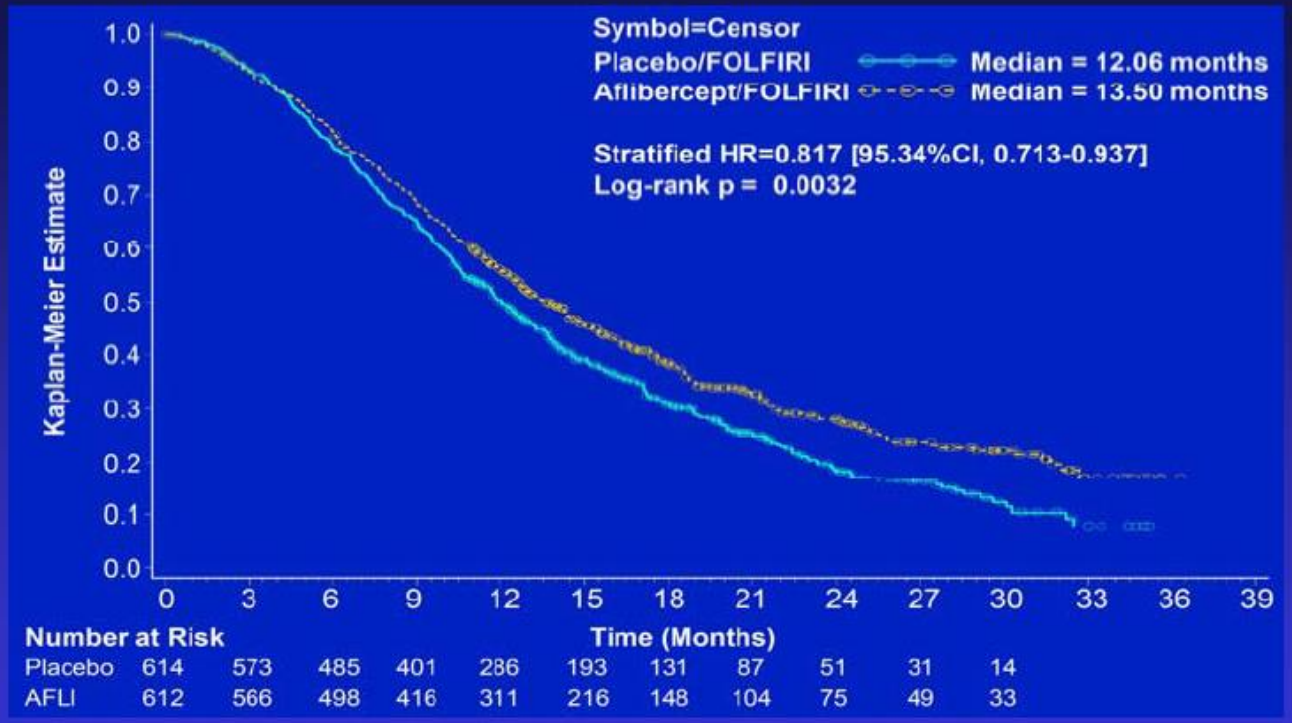
"VELOUR" trial: Overall Survival



Cut-off date = February 7, 2011; Median follow-up = 22.28 mos

Van Cutsem et al, 2011.

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VELOUR

VOLUME 30 · NUMBER 28 · OCTOBER 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen

Eric Van Cutsem, Josep Tabernero, Radek Lakomy, Hans Prenen, Jana Prausová, Teresa Macarulla, Paul Ruff, Guy A. van Hazel, Vladimir Moiseyenko, David Ferry, Joe McKendrick, Jonathan Polikoff, Alexia Tellier, Rémi Castan, and Carmen Allegra

Önceden OKSALİPLATİN temelli rejim ile tedavi edilmiş mKRK hastaları ile yürütülen Faz III randomize çalışmada FOLFİRİ rejimine AFLİBERSEPT eklenmesi sağkalımı arttırır

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Example of side effect profile

Safety Population, % of patients	Placebo, N = 605		Ziv-aflibercept N = 611	
Adverse Event	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Diarrhea	56.5	7.8	69.2	19.3
Neutropenia**	56.3	29.5	67.8	36.7
Complicated neutropenia		2.8		5.7
Asthenic conditions (HLT)	50.2	10.6	60.4	16.9
Stomatitis & ulceration (HLT)	34.9	5.0	54.8	13.7
Thrombocytopenia**	33.8	1.7	47.4	3.3
Infections (SOC)	32.7	6.9	46.2	12.3
Decrease appetite	23.8	1.8	31.9	3.4
Weight decreased	14.4	0.8	31.9	2.6
Palmar plantar erythrodysaesthesia	4.3	0.5	11.0	2.8
Skin hyperpigmentation	2.8	0	8.2	0
Dehydration	3.0	1.3	9.0	4.3

PL: 12.1% AFL: 26.6%

AEs leading to treatment discontinuation

Van Cutsem et al, 2011.

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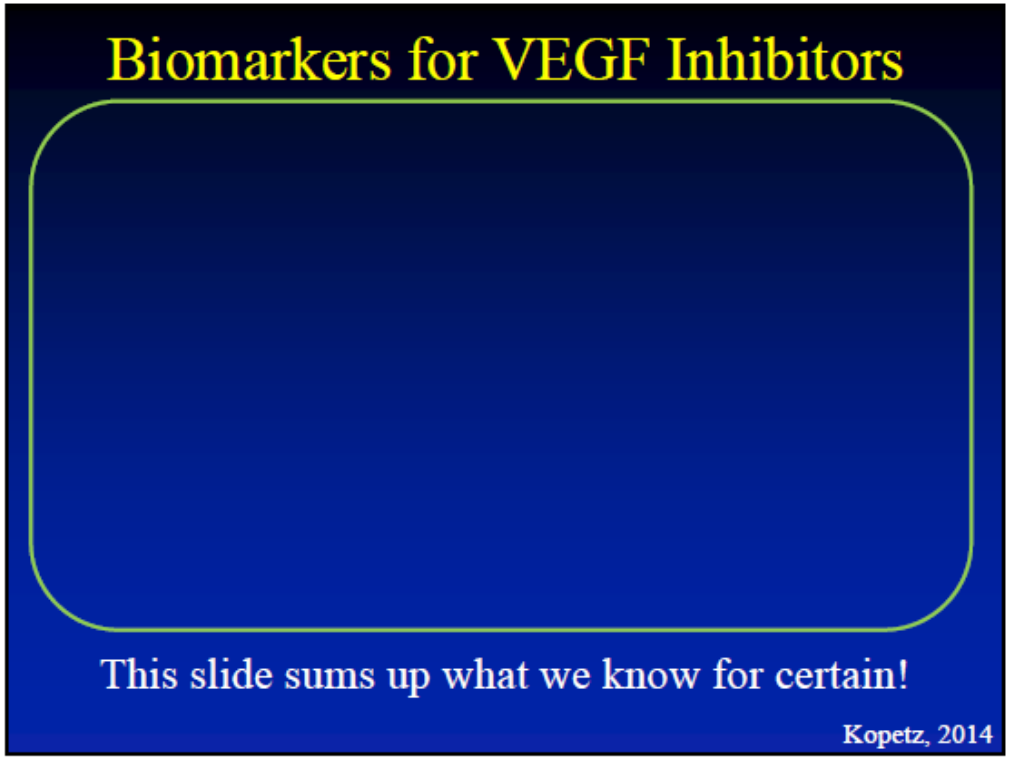

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VELOUR: BEV kullanmış olan/olmayan hastalarda OS ve PFS yararı

	BEVASİZUMAB (+)			BEVASİZUMAB (-)		
	PLS/FOLFIRI (N=187)	AFL/FOLFIRI (N=186)	Δ	PLS/FOLFIRI (N=427)	AFL/FOLFIRI (N=426)	Δ
OS (ay) (%95.34 GA)	11.7 (9.8-13.8)	12.5 (10.8-15.5)	0.8	12.4 (11.2-13.5)	13.9 (12.7-15.6)	1.5
PFS (ay) (%99.99 GA)	3.9 (2.9-5.4)	6.7 (4.8-8.7)	2.8	5.4 (4.2-6.7)	6.9 (5.8-8.2)	1.5

OS **ve** ***PFS*** **düzelmesi açısından bevasizumab kullanmış olan ve olmayan hasta alt gruplarında anlamlı fark bulunmamıştır** ***(sırasıyla p=0.567 ve p=0.196)***

Tabernero et al. Eur J Cancer. 2014;50:320-331.

Kolon Kanseri Tedavi

VELOUR trial biomarkers update: Impact of RAS, BRAF, and sidedness on aflibercept activity.

Abstract 3538

Pratyaksha Wirapati , Valentina Pomella, Ben Vandenbosch, Peter Kerr, Evaristo Maiello, Grahame Mark Jeffery, Razvan-Ovidiu D. Curca, Meinolf Karthaus, John A. Bridgewater, Anca C. Mihailov, Igor Kiss, Sandra Merino, Joseph James McKendrick, Zacharenia Saridaki, Xavier JA Sagaert, Sabine Tejpar. Swiss Institute of Bioinformatics, Lausanne, Switzerland; University of Leuven, Leuven, Belgium; Almac Diagnostics, Craigavon, Northern Ireland; U.O. Oncologia, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; Christchurch Hospital, Christchurch, NZ; County Emergency County Hospital Alba Iulia, Romania; Klinikum Neuperlach, Dept Hematology and Oncology, Städt. Klinikum München, Germany, Germany; University College London Cancer Institute, London, United Kingdom; C.F. Clinical Hospital Cluj-Napoca, Romania; Masaryk Memorial Cancer Institute, Brno, Czech Republic; Hospital Universitari de Sant Joan de Reus, Tarragon, Spain; Monash University Melbourne Australia; Asklepios Oncology Unit, Heraklion, Crete, Greece; University Hospitals Leuven Dept of Pathology, Leuven, Belgium; University Hospital Leuven, KUL, Leuven, Belgium. Contact: sabine.tejpar@uzleuven.be

ABSTRACT

Background: Addition of (ziv)-aflibercept (A) to FOLFIRI in second-line therapy for metastatic colorectal cancer (CRC) has been shown to be beneficial in phase III VELOUR trial (NCT00561470). A retrospective follow-up study (NCT01754272) was undertaken to acquire tumor samples for biomarker analyses and identify subgroups of patients with differential treatment effects. The primary results assessing efficacy according to well-established CRC subgroups defined by RAS, BRAF status and sidedness are reported here.

Methods: Tissue specimens were collected for 666 patients from 1226 ITT pts. Suitable specimens were assayed for somatic mutation using NGS targeting extended RAS and BRAF genes. NGS assays with no missing values were obtained for 482 pts. Affymetrix gene chip technology was used for whole-transcriptome profiling; sidedness was extracted from available pathological reports. Differences between subgroups were assessed by interaction analysis.

Results: The treatment effects on overall survival (OS) for the 482 pts is still significant HR = 0.80 (CI 0.65-0.99), and similar to the ITT (n = 1226) results (HR = 0.82, CI 0.71-0.93). Two established ways of defining mutations (traditional KRAS exon 2 and extended RAS using NGS) show a trend for a differential effect across mutation groups.(see table for OS). Interestingly, BRAF mutants (which are all RAS wild type) show a trend for better outcome Same is seen for PFS and RR. Sidedness did not affect efficacy (HR: 0.83 (0.63- 1.1) for left and HR: 0.83 (0.54-1.3) for right)

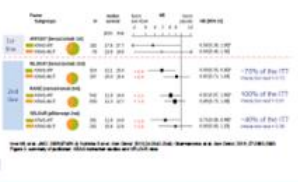
Conclusions: None of the mutations subgroup results shows significant interaction, although the ratios of treatment HR favor RAS wild types. Similar trends were observed in published trials with bevacizumab or ramucirumab.

INTRODUCTION and METHODS

- The phase 3 VELOUR trial showed that aflibercept added to FOLFIRI significantly improved overall survival [OS], PFS and ORR compared with FOLFIRI alone [median OS: 13.50 vs 12.06 months (HR=0.817; IC95%: 0.713-0.937; p=0.0032); median PFS: 6.90 vs 4.67 months (HR=0.758; IC95%: 0.661-0.869; p=0.00007); ORR: 19.8% vs 11.1% (p<0.001)] in mCRC patients previously treated with an oxaliplatin-containing regimen.[1]
- A follow-up non-interventional study (NCT01754272) was undertaken to acquire archived tumor materials, with the purpose of identifying subgroups of patients with differential treatment effects.
- **Methods**: Archived tissue specimens (FFPE blocks) from participating centers world-wide were collected in a centralized pathology facility. Specimens with suitable quality and quantity were assayed using next-generation sequencing (NGS) targeted at KRAS, NRAS and BRAF genes. Based on the mutations, the patients were classified into four groups (with no overlap): KRAS exon 2 ("KRASex2"), other KRAS and NRAS mutations ("newRAS"), BRAF V600E ("BRAF") and double wild-type absent in all aforementioned RAS or BRAF mutations ("WT").
- Affymetrix gene chip technology was used for whole-transcriptome profiling. Here we present the results of two signatures: the "BRAF-like" and "RAS-like signatures, that were derived on external datasets and applied to VELOUR. Patients are dichotomized into "mutant-like" or "wild-type-like", based on cutoff that puts 55% of the patient as "KRAS-mutant-like" and 7% "BRAF-mutant-like", based on the frequencies of respective mutations in DNA data.

1. Van Cutsem E et al. J Clin Oncol. 2012 Oct 1;30(28):3499-506

Definition of VELOUR biomarker population



RESULTS

- The treatment effects on overall survival for the biomarker subpopulation (n=482, or 39.3% of original ITT, n=1226) is still significant (HR=0.80 (CI 0.65-0.99), p = 0.043), and similar to the ITT results (HR=0.82, (CI 0.71-0.93), p = 0.0031). Pretreatment rates with bevacizumab and patient demographics are similar except for fewer samples from America in the biomarker group.
- Figure 1 shows summary results of treatment effects on OS under various subgroupings. The treatment effect of the original trial is shown on the first line (ITT:all). The second line shows the summaries of the subset where DNA data are available versus those that are not, showing that the biomarker subset has representative baseline HR. The subsequent subdivisions ("mutation", "KRAS" and so on) are all pertaining to those with DNA available. The vertical dashed line is aligned with the HR of the samples with available DNA.
- In the comparison of the four mutation classes, we see the trend of WT and BRAF mut having better HR than the total, while newRAS and KRASex2 are worse, as also reflected by the differences in the median survival. However, the confidence intervals are wide (none of the subgroups are significant on its own) and the global interaction test is also not significant (p = 0.22).
- Pairwise comparisons for several ways to define mutation groups also show no significant interaction except for BRAF mutant versus others for OS. The treatment HR's for BRAF are not significant due to small number, but the magnitude and direction is consistent to those of other studies. The Kaplan-Meier curves in figure 2 highlight the treatment effects of aflibercoet on BRAF mutants.

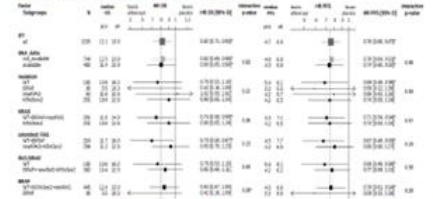


Figure 1. : Treatment effects on OS and PFS , subgrouped by DNA mutations. (*) indicates significant p-value (0.05 for HR, 0.1 for interaction). Cox regression models stratified by ECOG status and prior bevacizumab were used to obtain HR and interaction tests

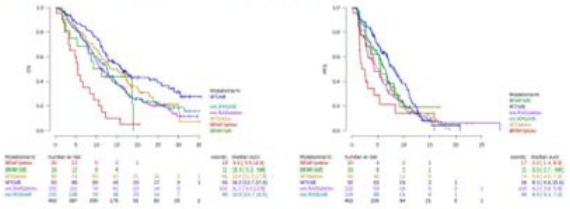


Figure 2. :Kaplan-Meier curves for OS and PFS , subgrouped by DNA mutations. 'extRAS' is a pool of KRAS exon 2 and new RAS mutation. See figure 1 for detailed survival analysis.

- For RAS mutants, there is a consistent trend of quantitative reduction of effects, although the interaction tests are not significant. The ratio of OS hazard ratios (RoHR) of mutant relative to wild-type for KRASex2 is 1.21 (95%CI: 0.74 – 1.96; p=0.45), and 1.39 (95%CI: 0.90 – 2.13; p= 0.13) for extRAS respectively, indicating a potential loss of 20 to 40% of the positive aflibercept effect, not reaching statistical significance.
- Similar studies have been reported for KRAS exon2 and other antiangiogenic drugs, summarized in figure3

Additional exploratory results

- Although RAS mutations are a validated biomarker for anti-EGFR therapy, not RAS mutation itself but some associated characteristic may drive the association observed here . Further investigation is needed to pinpoint the optimal definition for the subgroup with reduced efficacy. We complemented our DNA analysis by RNA based characterization of RAS and BRAF likeness which captures downstream pathway activation regardless of mutation status. RNA profiling showed 78% concordance between the KRAS-like signature and extended-RAS status; while 91% agreement is found between BRAF-like and BRAF mutation status.
- Fig 4. Of note the subset of patients available for this RNA signature, (n=439, with only n=363 overlapping with the subset with available DNA data) is not representative any more of the ITT in terms of treatment effects: HR in the population with RNA samples available is 0.92 (95%CI: 0.74 – 1.16) versus HR=0.82 (95%CI: 0.71 -0.93) in the ITT population. Thus, caution must be exercised not to interpret the treatment effects as absolute, but only to observe the relative effect sizes between RNA subgroups.
- The BRAF-like and KRAS-like groups show differential effects similar to the corresponding DNA mutations (more efficacy in KRAS-WT-like and BRAF-mutant-like). Significant interactions are seen for KRAS-like status for all OS, PFS and ORR. BRAF-like signature shows trends in the same direction, but lack significant due to very small (7%) mutant-like subgroup. Further validation of this is needed.

Figure 4 : Treatment effects on OS and PFS, subgrouped by RNA signatures

CONCLUSIONS

- This retrospective biomarker analyses tested RAS and BRAF defined patient subgroups for differential treatment effects.
- Our data suggest that aflibercept could have a specific beneficial effect in BRAF mutant patients. This is the first randomized trial with an antiangiogenic drug to show a BRAF biomarker/drug interaction. BRAFmut pt numbers remain small and these results need further validation in similar trials to inform clinical practice
- RAS defined subgroups show no significant interaction, although the ratios of treatment HR favor RAS wild types. Similar trends were observed in published trials with bevacizumab or ramucirumab for KRAS mut and merit further investigation.
- Left versus right side origin of tumors has no effect on aflibercept efficacy. For OS: left HR = 0.86 [0.64 – 0.15], right HR = 0.85 (0.53 -1.35), interaction p-value = 0.96. For PFS: left HR = 0.74 (0.46 – 1.00), right HR = 0.70 (0.42 – 1.15), interaction p-value = 0.69.

ACKNOWLEDGMENTS

- Sanofi supported this ISS
- We thank all the investigators and patients of the original trial and particularly those investigators that contributed to sample collection

Kolon Kanseri Tedavi

RAS Alt Popülasyonuna karşı VELOUR ITT

	N	GSK		PFS		RR	
		Plasebo	Aflibersept	Plasebo	Aflibersept	Plasebo	Aflibersept
VELOUR ITT	1226	12.1	13.5	4.7	6.9	11.8%	19.9%
Tam biyobelirteç popülasyonu	482	11.4	12.9	4.3	6.8	12.4%	19.3%
Ras wt	218	11.7 (10.1 – 15.9)	16.0 (12.7 – 22.8)	4.5 (3.9 – 5.8)	7.7 (6.7 – 9.7)	10.9 (5.34 – 19.1)	28.6 (18.6 – 38.2)
HR (%95 CI)		**0.70 (0.50 – 0.97)**		**0.67 (0.49 – 0.93)**		**3.63 (1.56 – 8.43)**	
Ras mutant	264	11.2 (9.9 – 13.8)	12.6 (10.7 – 14.5)	4.2 (3.9 – 5.9)	6.5 (5.4 – 7.2)	13.6 (7.8 – 21.5)	12.7 (7.14 – 20.4)
HR (%95 CI)		**0.93 (0.7-1.23)**		**0.80 (0.60 – 1.07)**		**0.94 (0.43 – 2.07)**	
Etkileşim testi		0.13		0.29		0.03	

Wirapati P et al. *Ann Oncol.* 2017;28(suppl 3; abstract and oral LBA-005); Van Cutsem E et al. J Clin Oncol. 2012;30:3499–3506.

Kolon Kanseri Tedavi

BRAF Alt Popülasyonuna karşı VELOUR ITT

	N	GSK		PFS		RR	
		Plasebo	Aflibersept	Plasebo	Aflibersept	Plasebo	Aflibersept
VELOUR ITT	1226	12.1	13.5	4.7	6.9	11.8%	19.9%
Tam biyobelirteç popülasyonu	482	11.4	12.9	4.3	6.8	12.4%	19.3%
BRAF wt	446	12.4 (10.7 – 15.1)	13.0 (12.4 – 15.9)	4.5 (4.1 – 5.8)	6.9 (6.2 – 7.7)	14.0% (9.1 – 20.3)	23.5% (16.9 – 31.1)
HR (%95 CI)		**0.84 (0.67 – 1.05)**		**0.76 (0.61 – 0.94)**		**1.76 (0.99 – 3.14)**	
BRAF mutant	36	5.5 (3.5 – 10.6)	10.3 (5.3 – NA)	2.2 (1.4 – 8.3)	5.5 (2.7 – NA)	15.4% (1.9 - 45.5)	30.0% (6.7 – 65.2)
HR (%95CI)		**0.42 (0.16-1.09)**		**0.59 (0.22 – 1.58)**		**1.26 (0.14 – 11.01)**	
Etkileşim testi		0.08		0.29		0.98	

Wirapati P et al. *Ann Oncol.* 2017;28(suppl 3; abstract and oral LBA-005; Van Cutsem E et al. *J Clin Oncol.* 2012;30:3499–3506.

Kolon Kanseri Tedavi

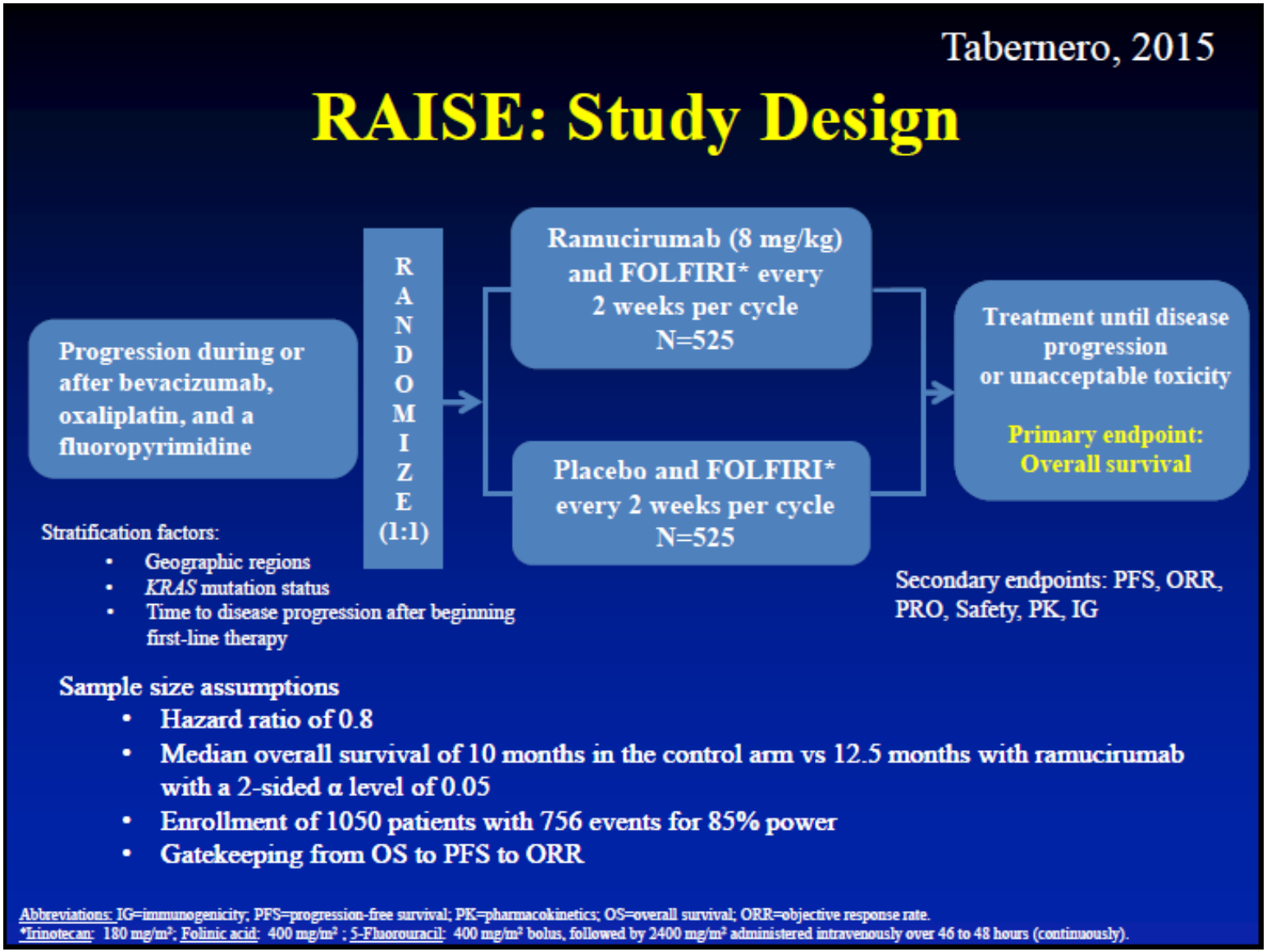
Tümör lokasyonu: Sola karşı Sağ

- Tümörlerin sol veya sağ taraf kaynaklı olmasının, afliberseptin etkililiği üzerinde herhangi bir etkisi yoktur.

	GSK	PFS
Sol	HR 0.86 (0.64-1.15)	0.74 (0.46-1.00)
	Etkileşim p-değeri=0.96	
Sağ	HR 0.85 (0.53-1.35)	0.70 (0.42-1.15)
	Etkileşim p-değeri=0.69	

Wirapati P et al. *Ann Oncol.* 2017;28(suppl 3; abstract and oral LBA-005).

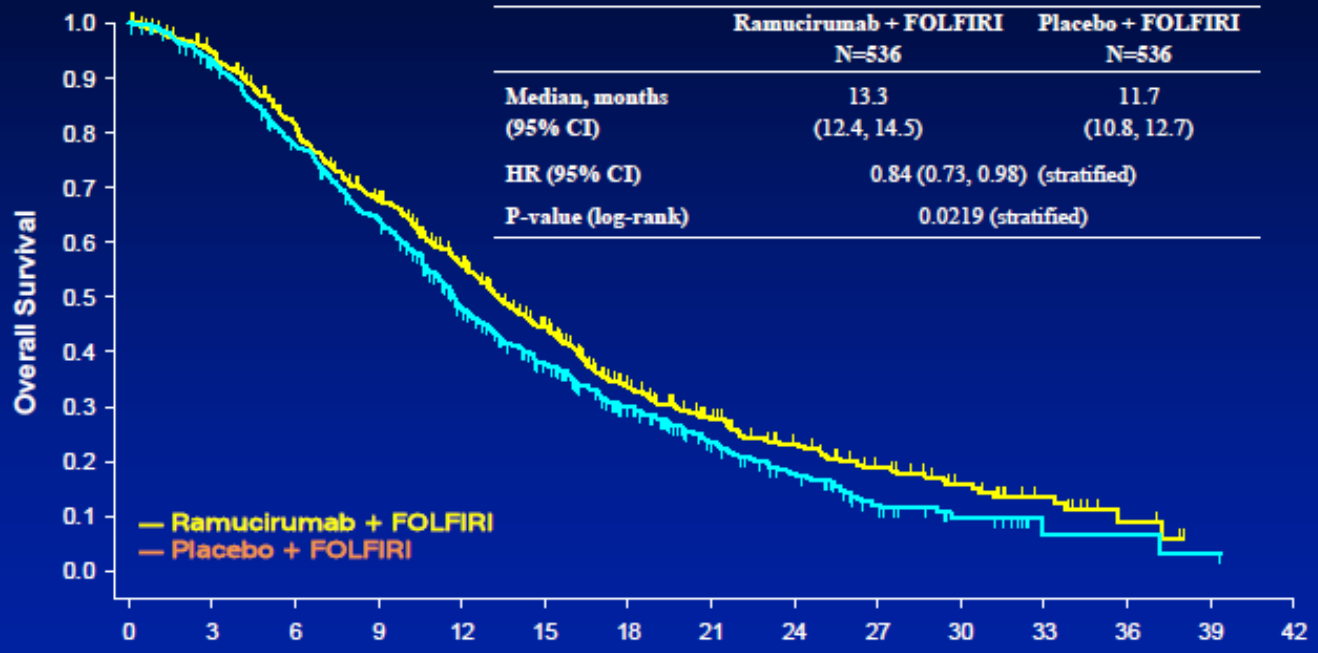
Kolon Kanseri Tedavi



Kolon Kanseri Tedavi

RAISE Overall Survival: HR=0.84

Note: survival in control arm was higher than expected



	Ramucirumab + FOLFIRI N=536	Placebo + FOLFIRI N=536
Median, months (95% CI)	13.3 (12.4, 14.5)	11.7 (10.8, 12.7)
HR (95% CI)	0.84 (0.73, 0.98) (stratified)	
P-value (log-rank)	0.0219 (stratified)	

Patients at Risk

Ram + FOLFIRI	536	497	421	345	269	195	114	78	53	34	22	12	4	0	0
Placebo + FOLFIRI	536	486	400	329	228	166	108	66	44	22	10	2	2	1	0

Tabernero, 2015

Abbreviations: CI=confidence interval; HR=hazard ratio; Ram=ramucirumab.

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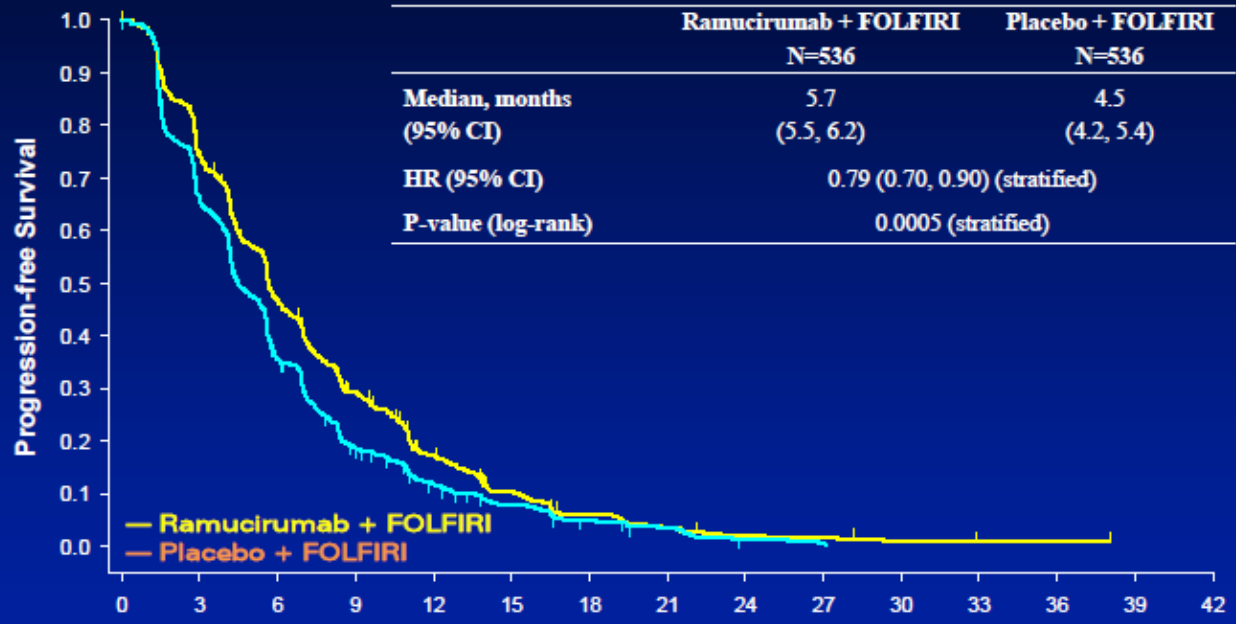
RAISE: Progression-free Survival



	Ramucirumab + FOLFIRI N=536	Placebo + FOLFIRI N=536
Median, months (95% CI)	5.7 (5.5, 6.2)	4.5 (4.2, 5.4)
HR (95% CI)	0.79 (0.70, 0.90) (stratified)	
P-value (log-rank)	0.0005 (stratified)	

Patients at Risk

Ram + FOLFIRI	536	381	234	142	77	38	20	11	6	5	2	1	1	0	0
Placebo + FOLFIRI	536	345	182	92	52	31	17	10	3	1	0	0	0	0	0

Tabernero, 2015

Abbreviations: CI=confidence interval; HR=hazard ratio; Ram=ramucirumab.

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RAISE: Tumor Response

	Ramucirumab + FOLFIRI N=536 %	Placebo + FOLFIRI N=536 %	P-value
Response rate (CR+PR)	13.4	12.5	0.6336
Disease control rate (CR+PR+SD)	74.1	68.8	0.0587
Complete response (CR)	0	0.4	
Partial response (PR)	13.4	12.1	
Stable disease (SD)	60.6	56.3	
Progressive disease (PD)	16.2	25.0	
Not done or unknown	9.7	6.2	

Tumor assessments based on RECIST 1.1.

Tabernero, 2015

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Treatment-emergent Adverse Events (All Grades 20% or Higher, or Grade 3–5 5% or Higher in Either Treatment Arm)

Preferred Term	Any Grade				Grade ≥3			
	Ramucirumab + FOLFIRI N=529		Placebo + FOLFIRI N=528		Ramucirumab + FOLFIRI N=529		Placebo + FOLFIRI N=528	
	n	%	n	%	n	%	n	%
Any TEAE	522	98.7	519	98.3	418	79.0	329	62.3
Neutropenia	*311*	*58.8*	*241*	*45.6*	*203*	*38.4*	*123*	*23.3*
Fatigue	*305*	*57.7*	*275*	*52.1*	*61*	*11.5*	*41*	*7.8*
Diarrhea	316	59.7	271	51.3	57	10.8	51	9.7
Hypertension	136	25.7	45	8.5	57	10.8	15	2.8
Stomatitis	163	30.8	110	20.8	20	3.8	12	2.3
Abdominal pain	*140*	*26.5*	*139*	*26.3*	*18*	*3.4*	*19*	*3.6*
Thrombocytopenia	*150*	*28.4*	*72*	*13.6*	*16*	*3.0*	*4*	*0.8*
Vomiting	154	29.1	144	27.3	15	2.8	13	2.5
Nausea	262	49.5	271	51.3	13	2.5	14	2.7
Decreased appetite	198	37.4	144	27.3	13	2.5	10	1.9
Anemia	*86*	*16.3*	*110*	*20.8*	*8*	*1.5*	*19*	*3.6*
Constipation	151	28.5	120	22.7	5	0.9	8	1.5
Peripheral edema	108	20.4	48	9.1	1	0.2	0	
Epistaxis	177	33.5	79	15.0	0		0	
Alopecia	155	29.3	165	31.3	0		0	

- The febrile neutropenia rate (any grade) was 3.6% in ramucirumab patients and 2.7% in placebo patients.

Italicized terms are consolidated adverse event category comprising synonymous MedDRA preferred terms.

Tabernero, 2015

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3rd Line Colorectal Cancer

QUESTION

What is the best 3rd line chemotherapy option for this patient?

1) TAS-102
2) regorafenib
3) EGFR inhibitor (cetuximab or panitumumab)

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NCIC CO.17 Trial: Overall Survival Difference with EGFR-targeting mAb

-Published in the NEJM since this was the only study to show an OS difference (no cross-over)

- Pretreated with 5-FU, oxaliplatin, irinotecan

Previously treated metastatic colorectal cancer

N=572

→ **Cetuximab 250 mg/m² weekly (1st dose 400) & Best Supportive Care**

→ **Best Supportive Care**

Karapetis et al. NEJM 2008; 359(17):1757-1765

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NCIC CO.17 Trial

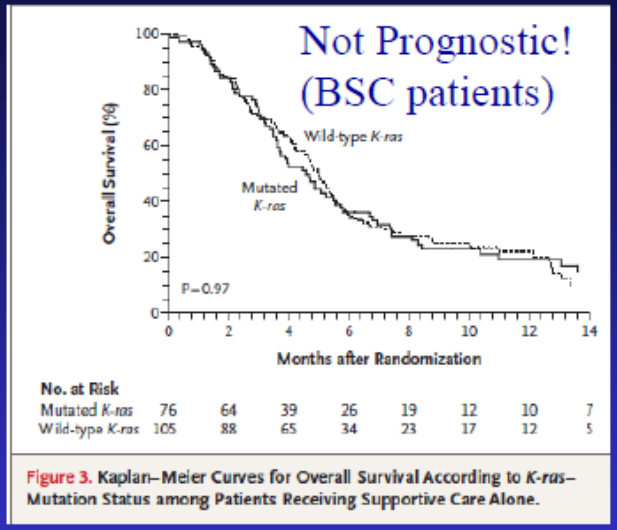
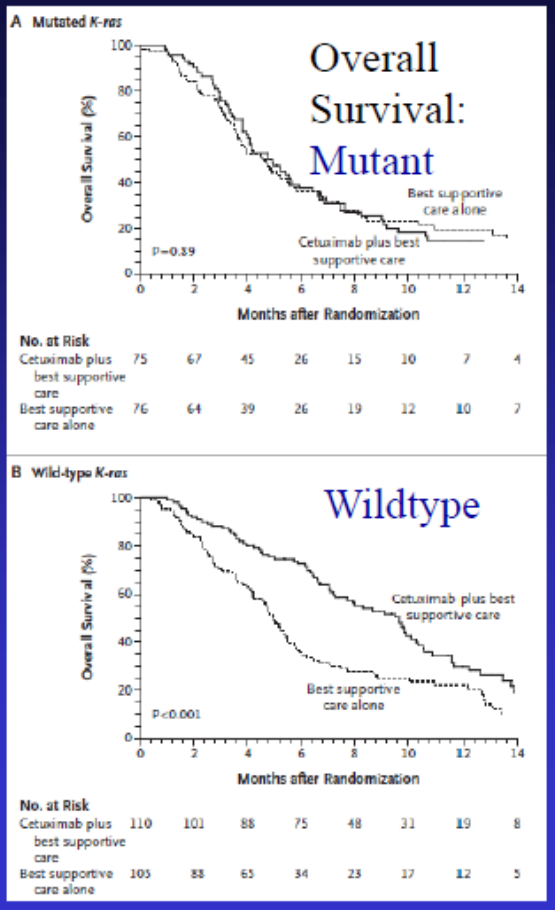


Figure 3. Kaplan–Meier Curves for Overall Survival According to *K-ras*–Mutation Status among Patients Receiving Supportive Care Alone.

Key Points:

- KRAS not prognostic
- Benefit confined to KRAS WT (wild-type)

Karapetis et al. NEJM 2008; 359(17):1757-1765



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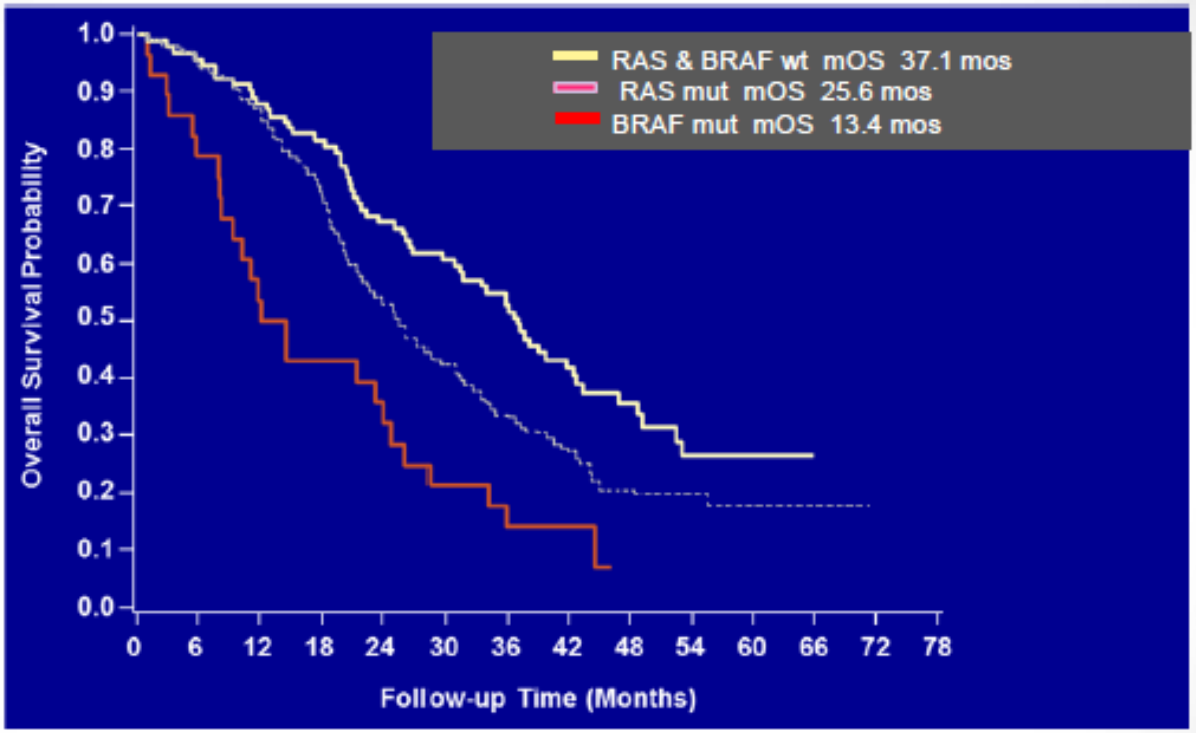
BRAFm CRC: Poor Survival

TRIBE



Loupakis F, et al, *J Clin Oncol* 33, 2015 (suppl; abstr 3510).

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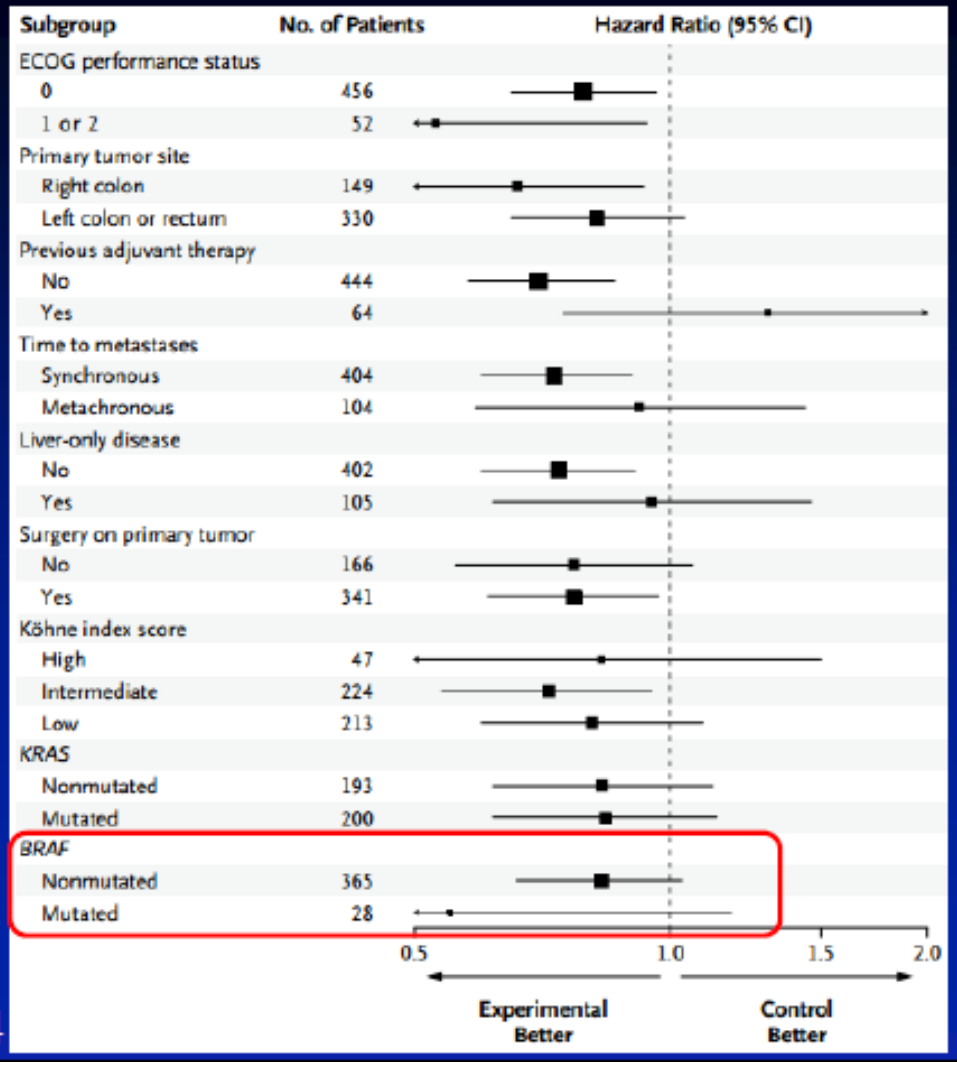
FOLFOXIRI and BRAF: PFS



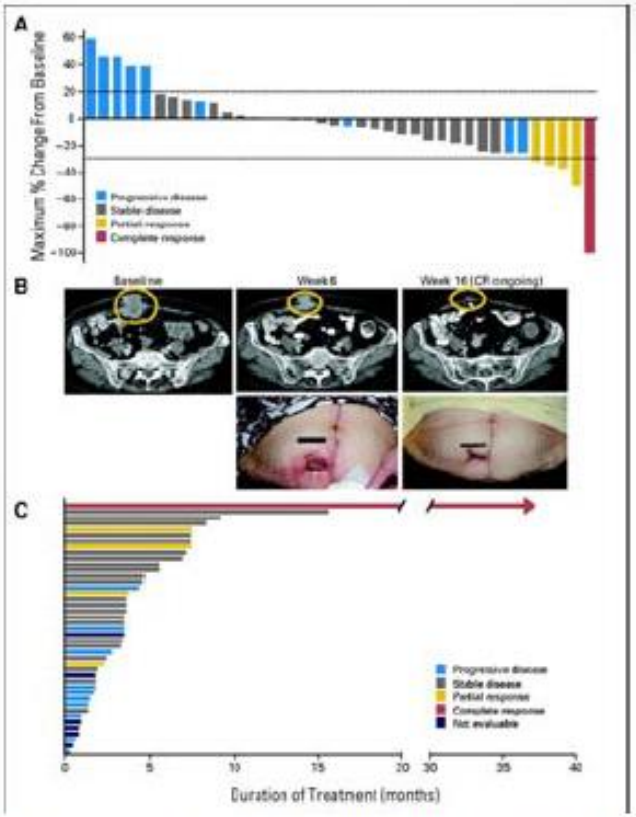
Caution: Based on only 28 patients

Loupakis, NEJM 2014

Kolon Kanseri Tedavi

Combined BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600-mutant colorectal cancer

(A) Waterfall plot of maximum percent reduction in target lesion size by RECIST. Horizontal lines at + 20% and − 30% denote boundaries of stable disease.

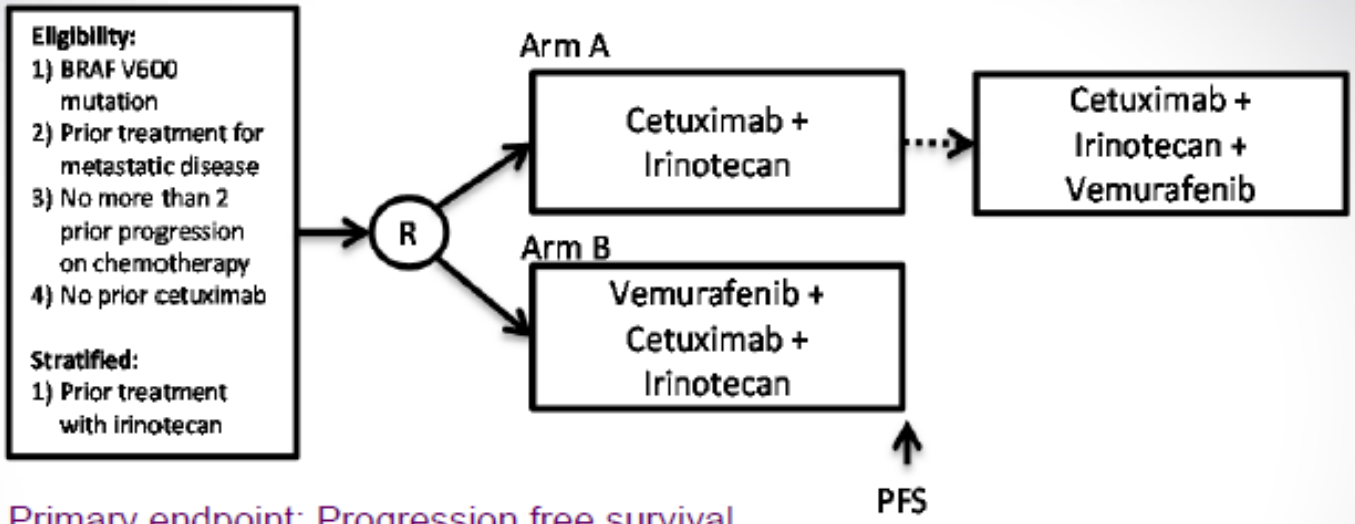


Ryan B. Corcoran et al. JCO doi:10.1200/JCO.2015.63.2471

JOURNAL OF CLINICAL ONCOLOGY ASCO

Kolon Kanseri Tedavi

S1406: Cetuximab + Irinotecan ± Vemurafenib

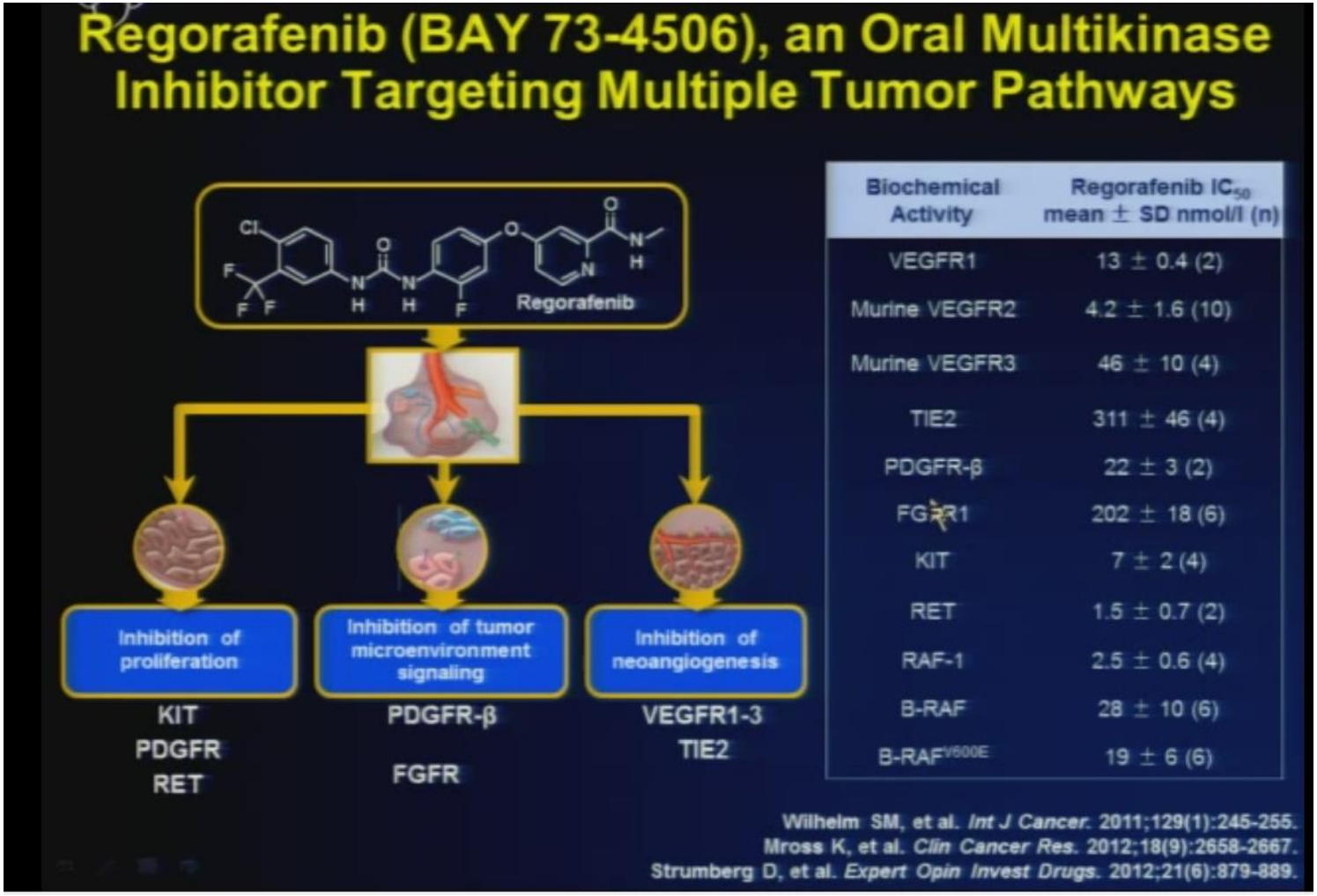


Primary endpoint: Progression free survival
Targeted enrollment: 78 patients

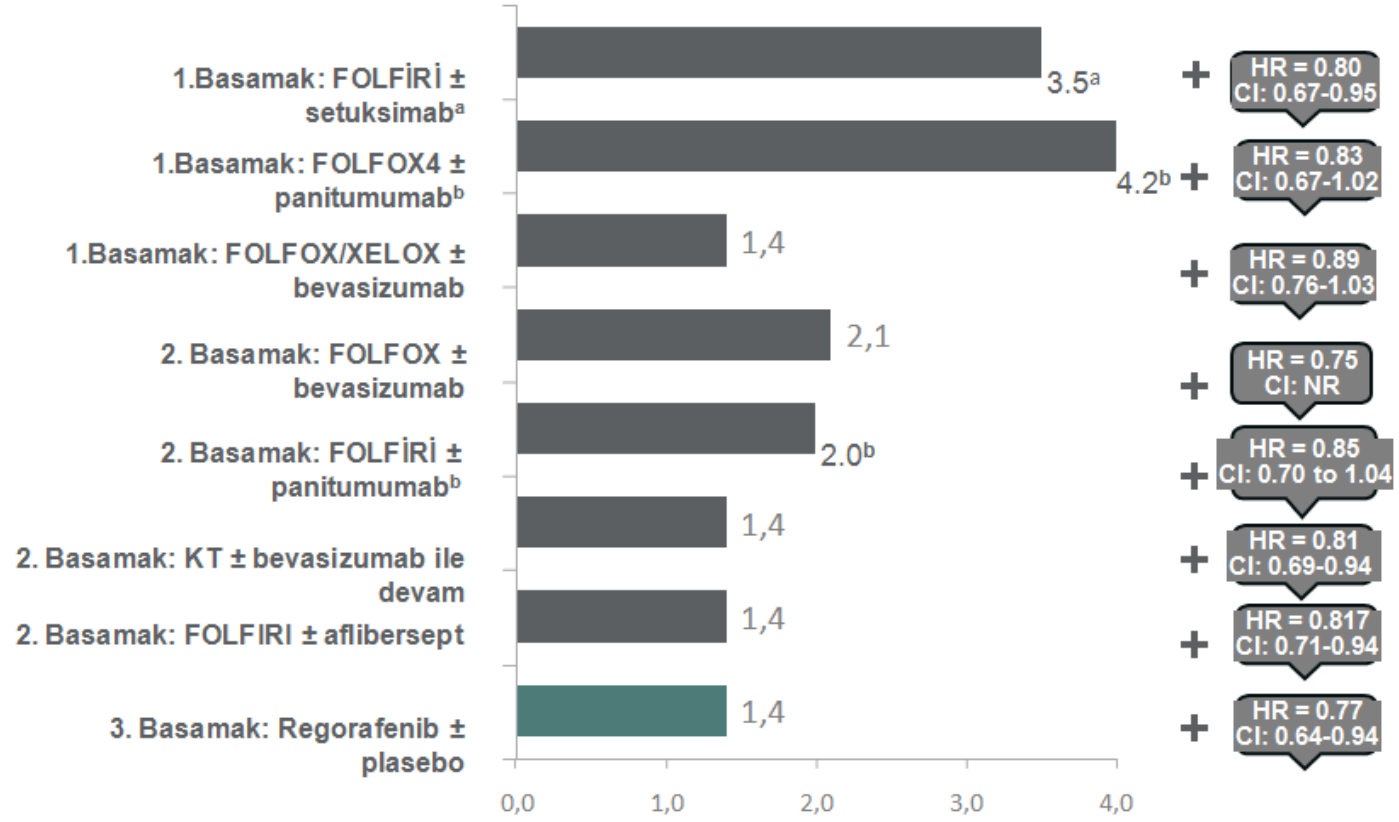
ACCRUAL AMENDED TO >100

SWOG PI: Scott Kopetz
Alliance PI: Chloe Atreya
ECOG PI: Luis Diaz
NSABP PI: Carmen Allegra

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

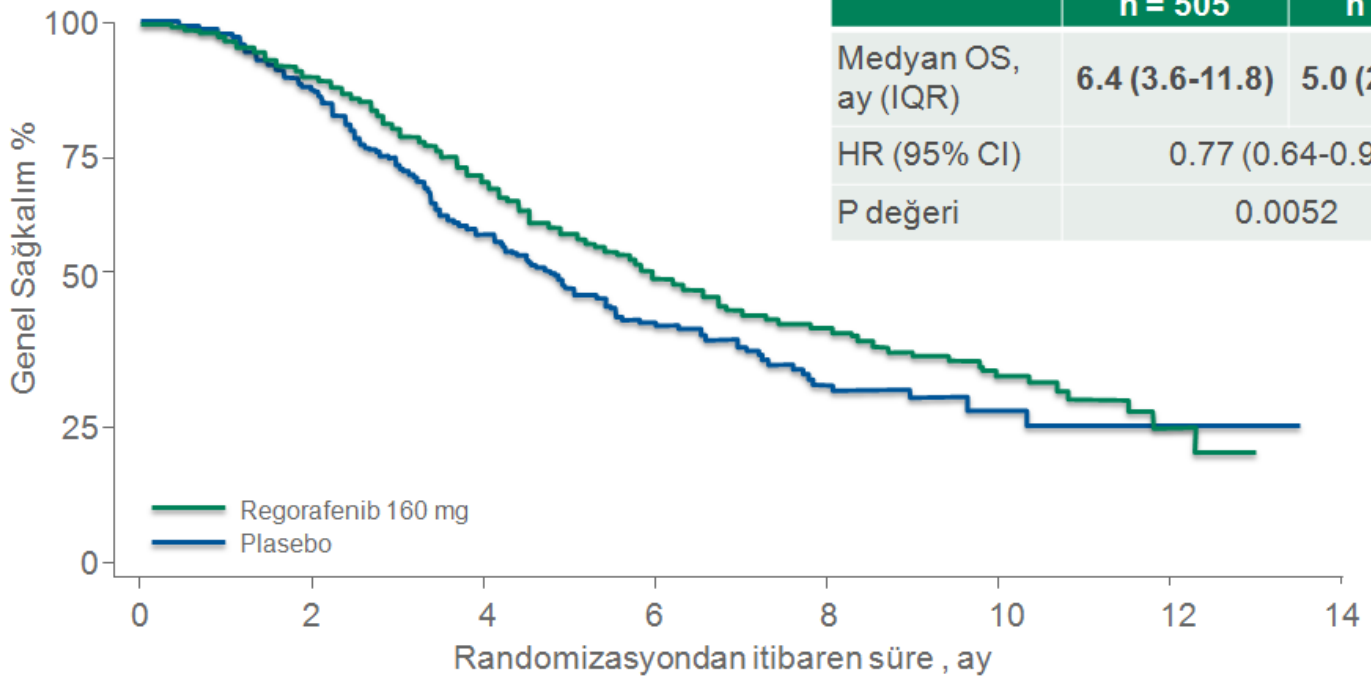
Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial

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
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
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

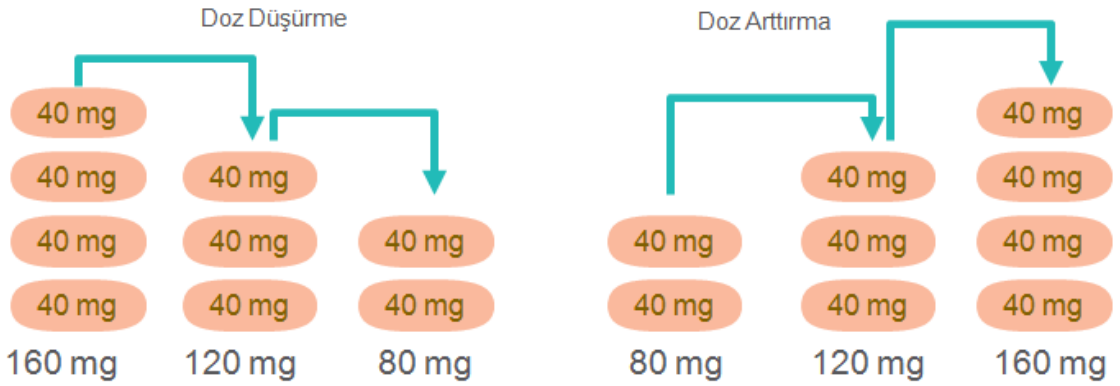
- Stivarga'nın potansiyel yan etkileri hakkında hastaya bilgi verilmeli[1,2]
- Hastalar advers olayları önlemek ve gelişme ihtimaline en aza indirmek için eğitilmeli[2]
- Monitörize edilebilmeleri için semptomları olursa sağlık çalışanlarına haber vermeliler[1,2]

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



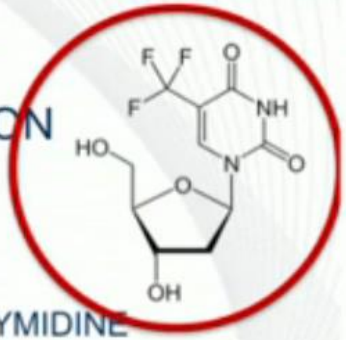
- Hekimin kararı ile AO'ların stabilize olması halinde 160mg'lık doza tekrar çıkılabilir.
- Bireysel güvenliliğe ve tolerabiliteye bağlı olarak ilacın kullanımına ara verilmesi ve/veya dozun azaltılması gerekebilir.
- Doz modifikasyonları 40 mg'lık (bir tablet) doz adımlarışeklinde uygulanır.
- En düşük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

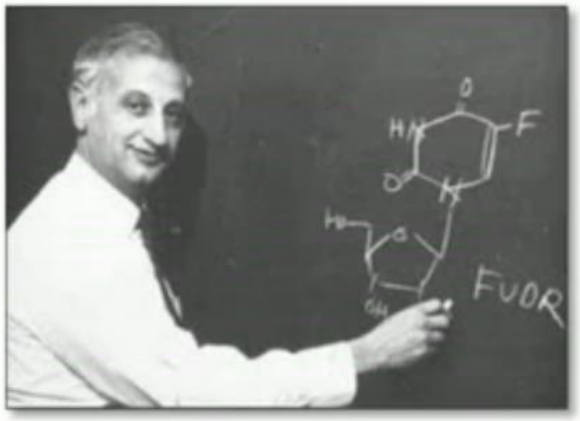
Stivarga 40 mg film kaplı tablet, Kısa Ürün Bilgisi, 18.05.2015, Türkiye

Metastatik Kolon Kanserinde Tedavi Seçenekleri

TAS-102

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

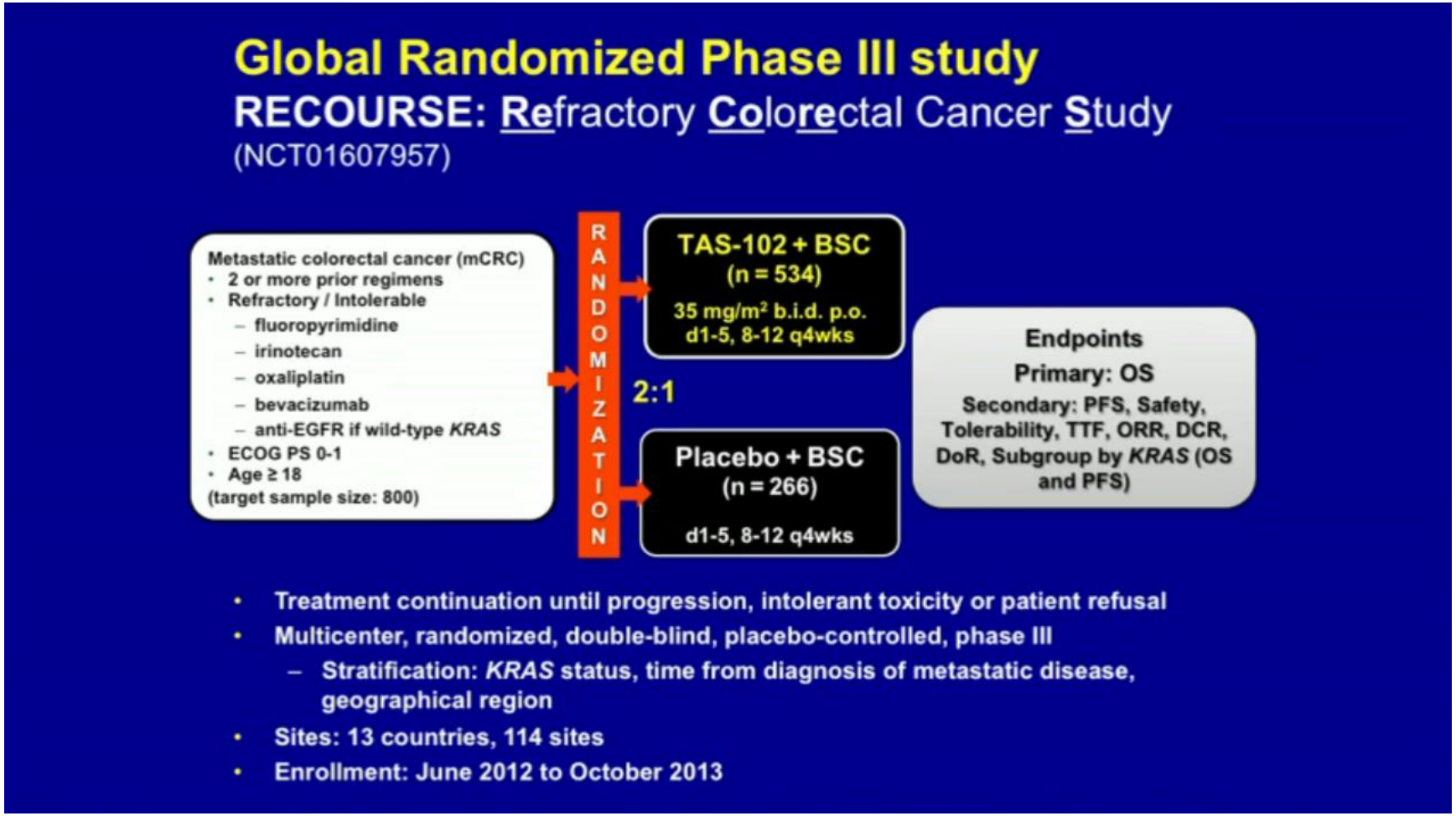




CHARLES HEIDELBERGER

- 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

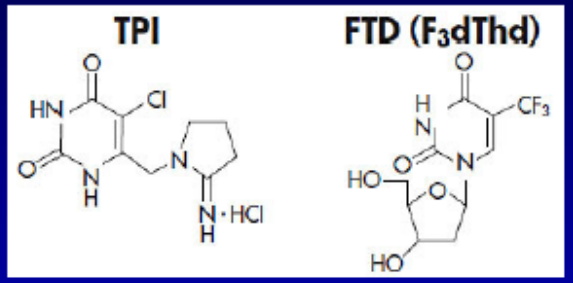


Metastatik Kolon Kanserinde Tedavi Seçenekleri

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.

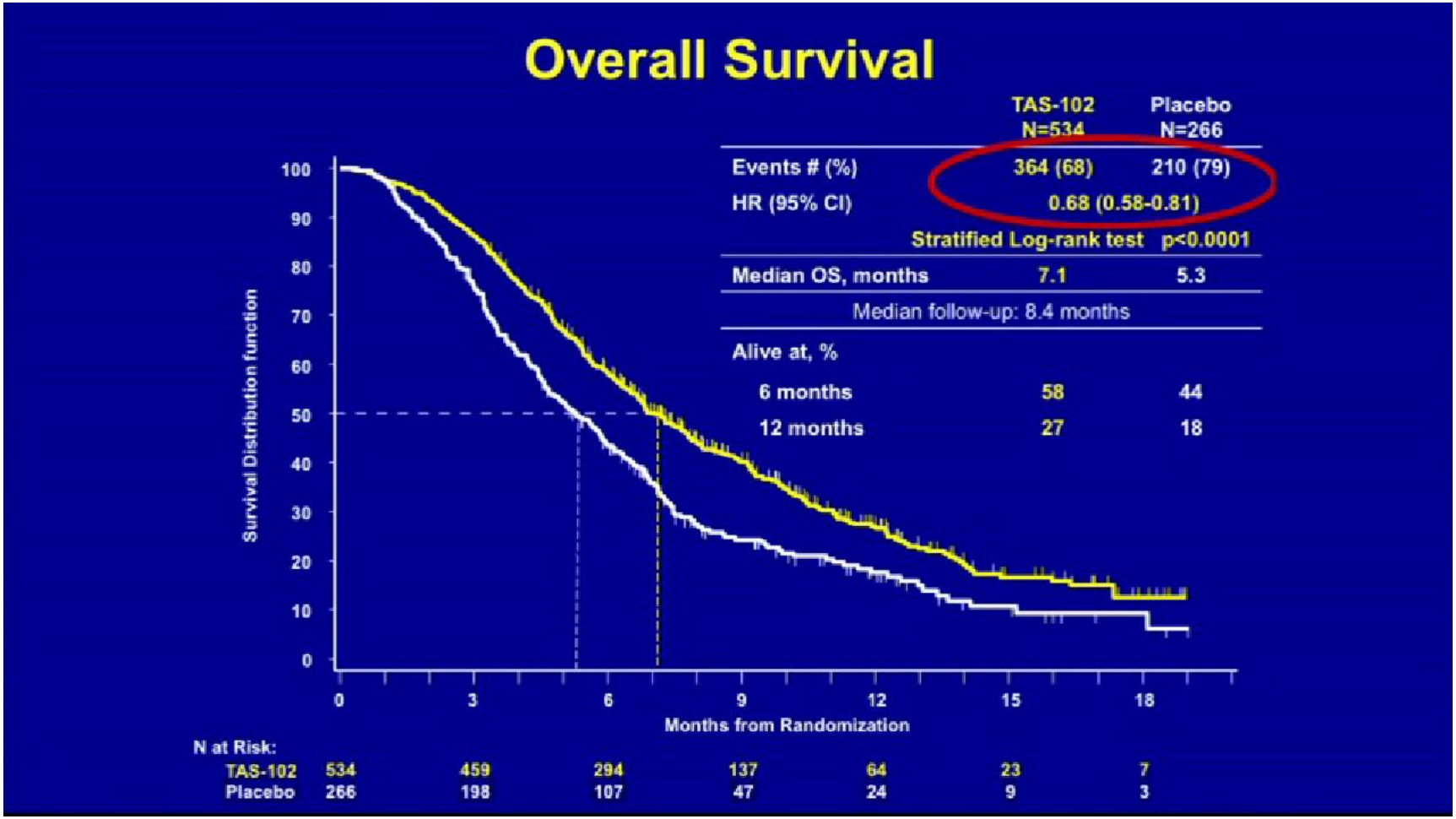


RECOURSE trial

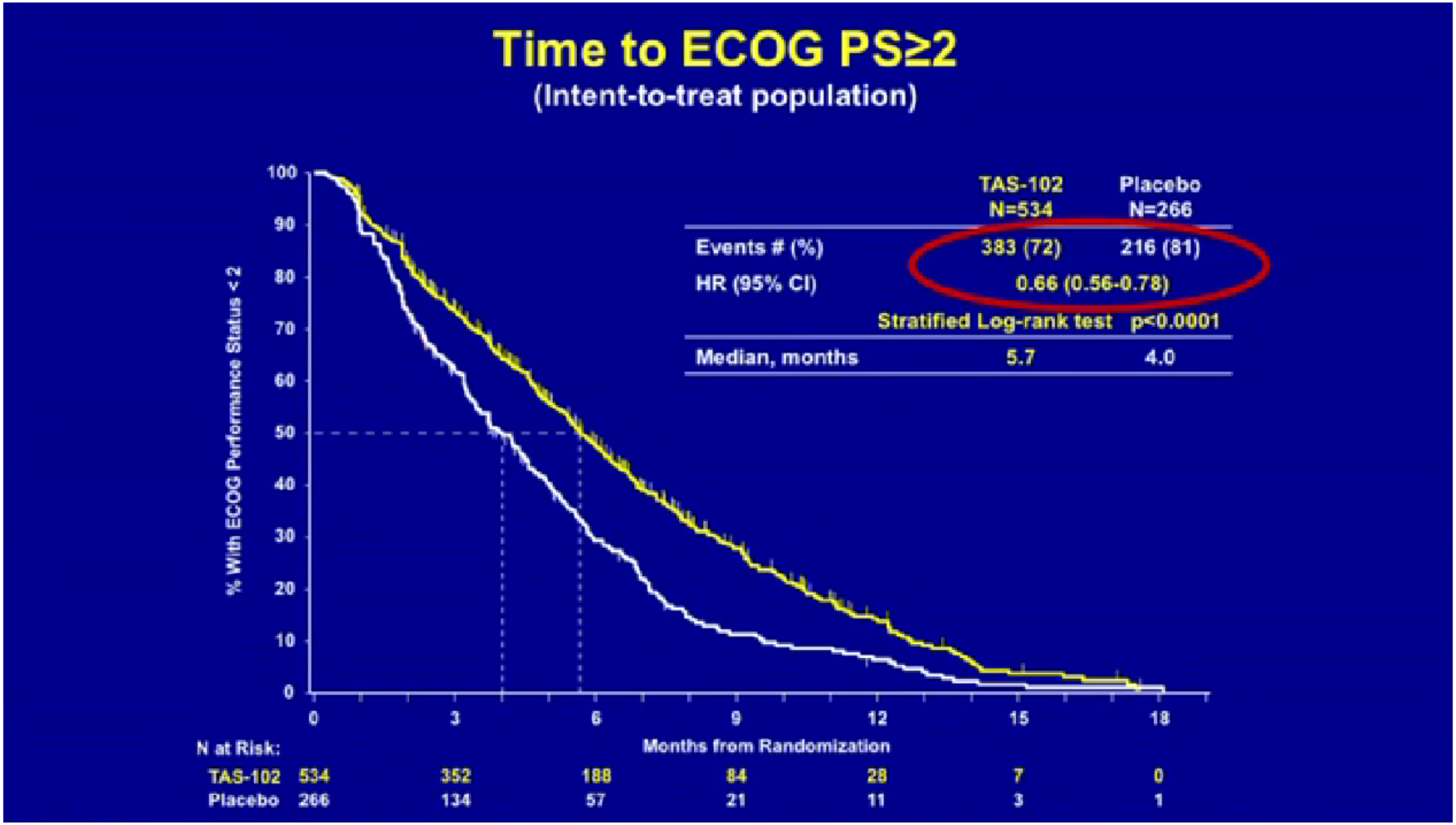
- global phase III trial conducted in 13 countries at 114 centres
- mCRC refractory to all standard therapies (including EGFR-targeting mAb for KRAS WT patients)
- Randomized 2:1 to TAS-102 (534 patients), 35 mg/m2 BID on Days 1- 5 and 8-12 of each 28-day cycle, or placebo (266 patients)
- The primary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

Mayer, NEJM 2015

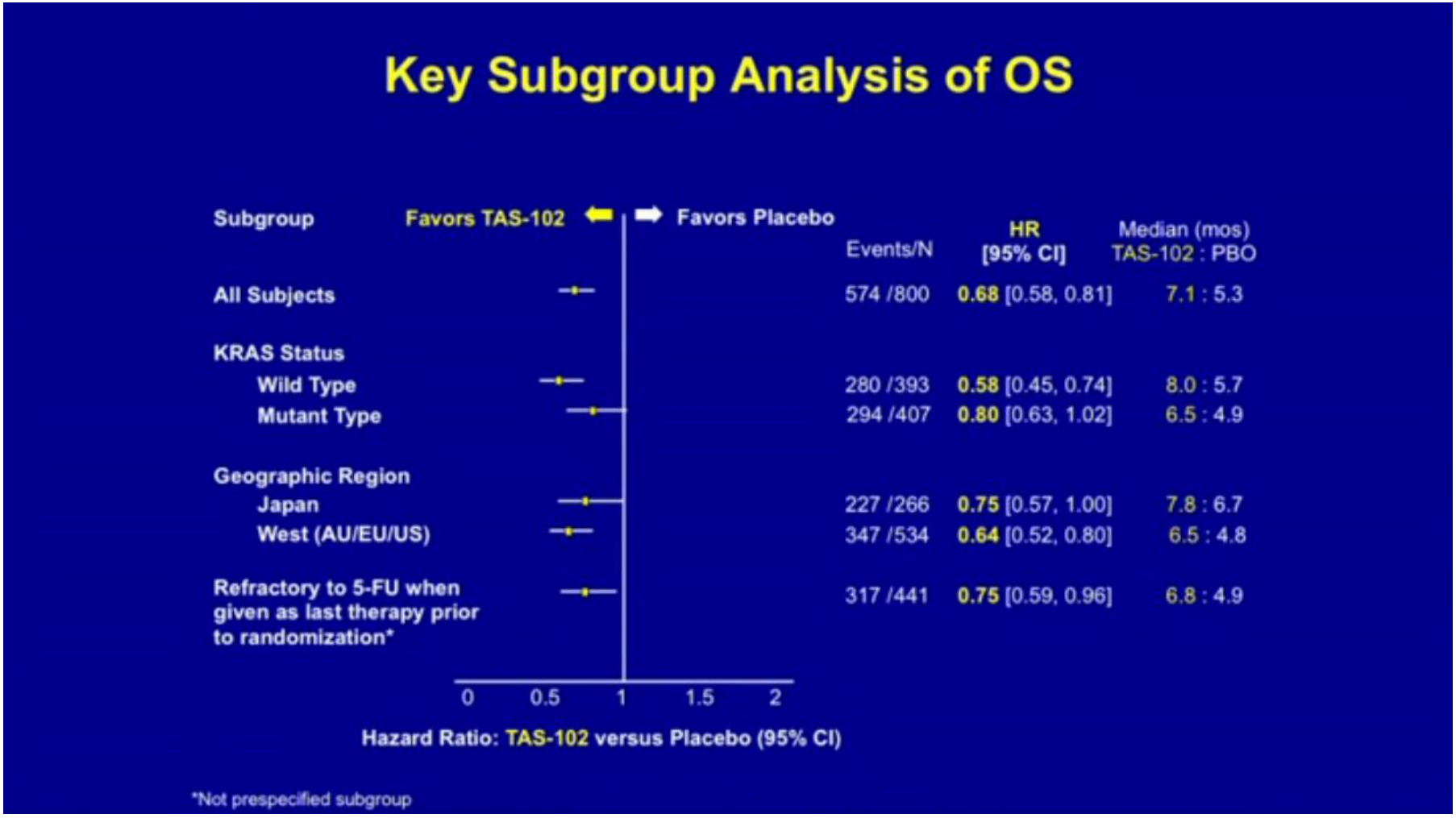
Metastatik Kolon Kanserinde Tedavi Seçenekleri



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)

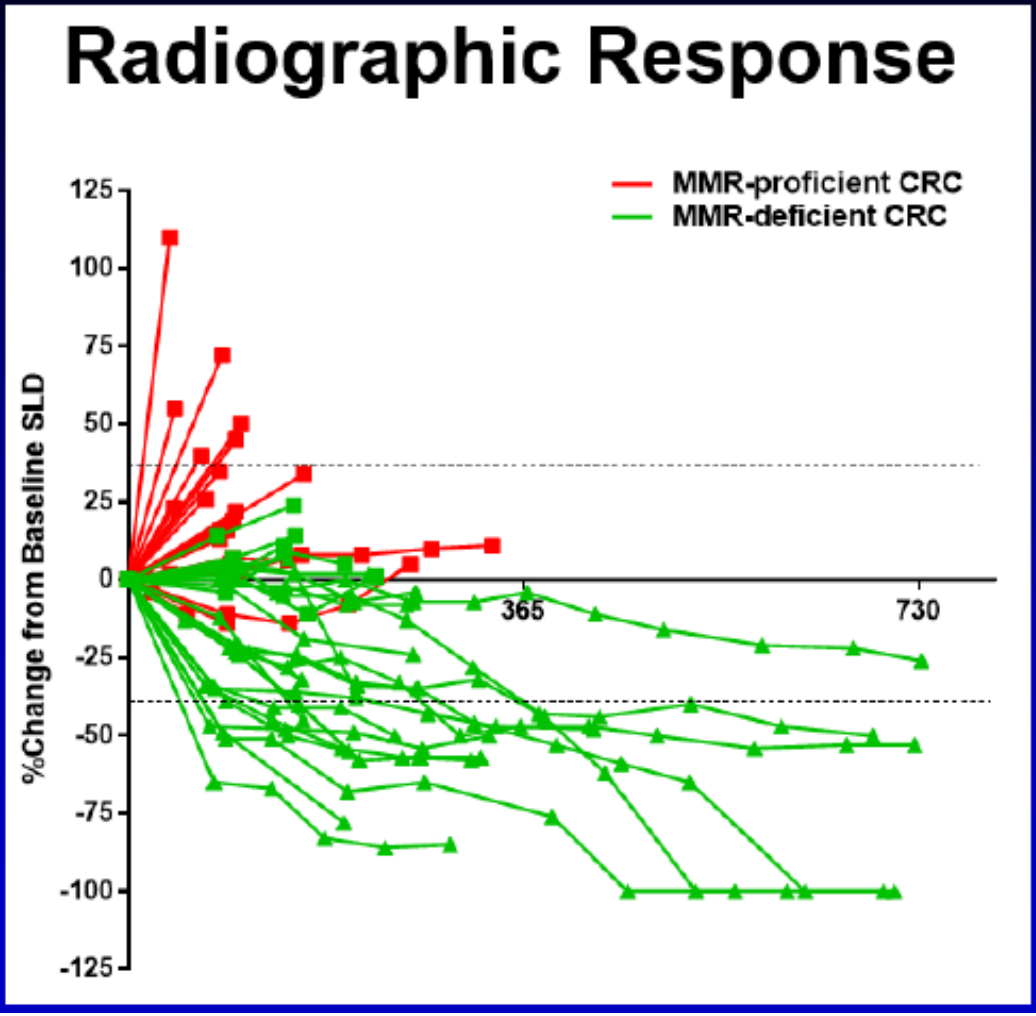
- Anti-PD1 (pembrolizumab) – 10 mg/kg every 2 weeks
- Here they updated from the original 13 CRC Cohort A patients reported at ASCO 2015/NEJM 2015

Le, ASCO 2016

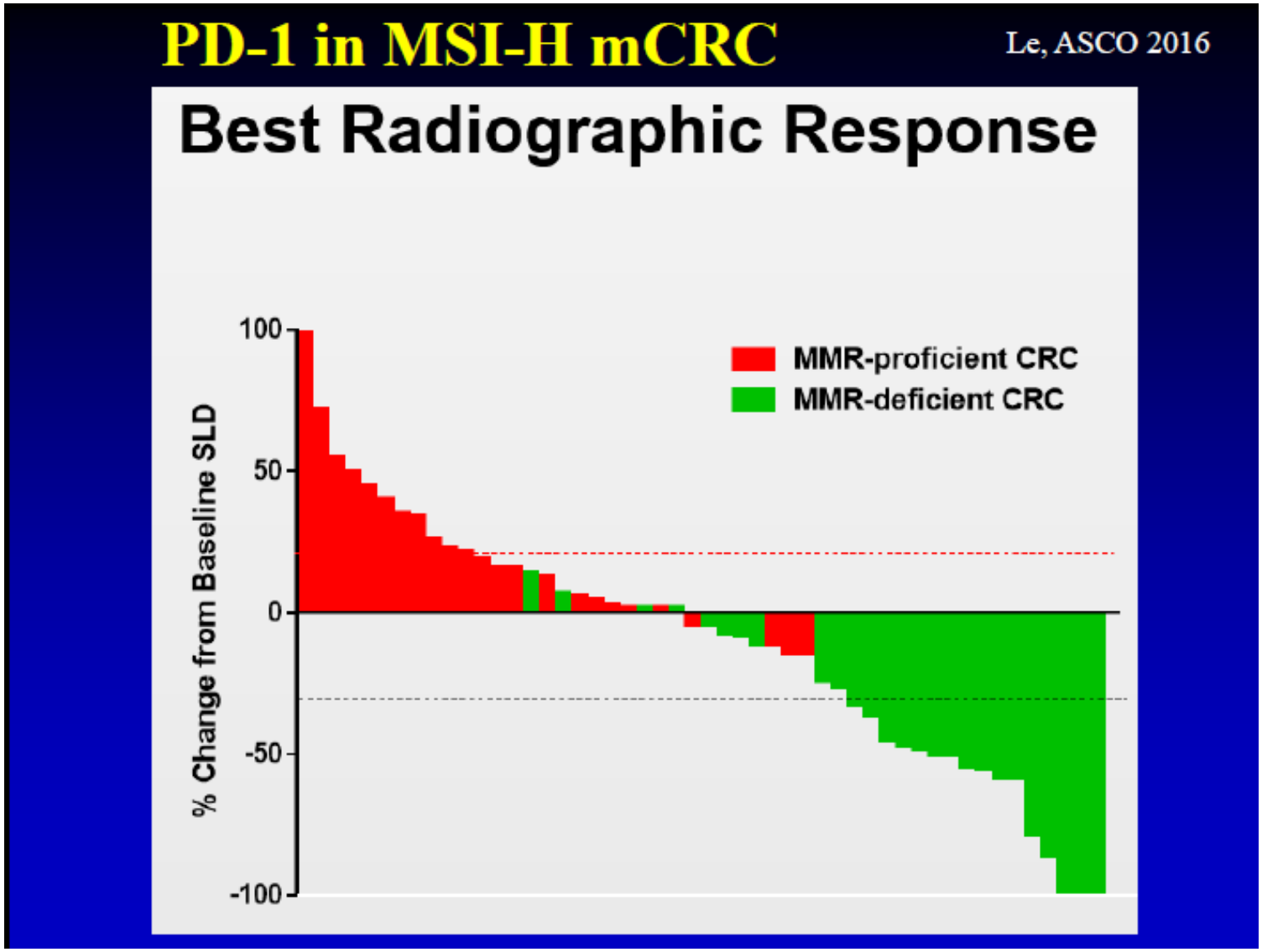
Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi

PD-1 in MSI-H mCRC

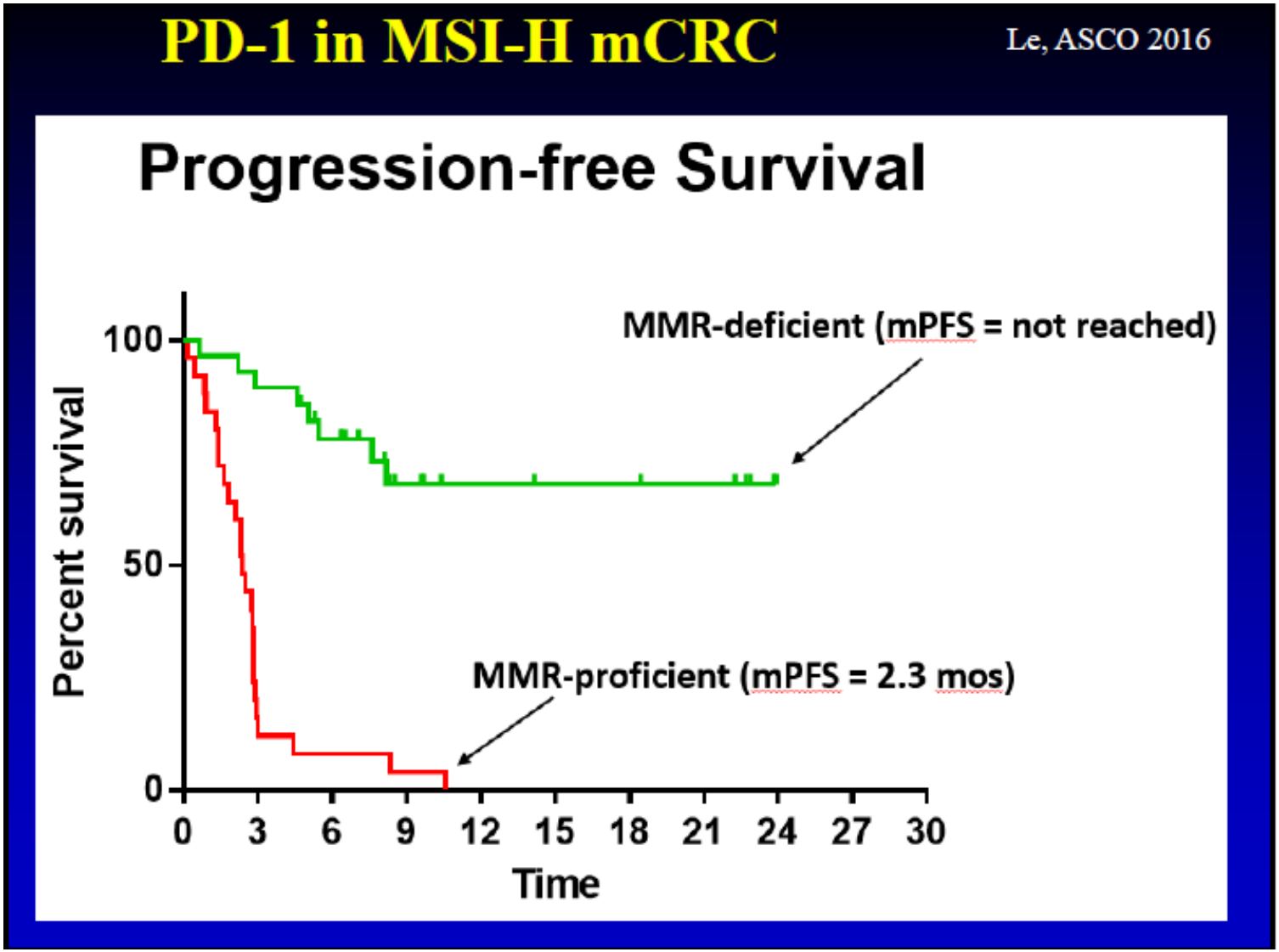
Le, ASCO 2016



Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi



Metastatik Kolon Kanserinde Tedavi Seçenekleri-İmmünoterapi



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

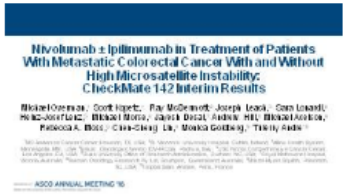
Abstract Disclosures

ASSOCIATED PRESENTATION

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

View Video

ASSOCIATED SLIDES



View Slides

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

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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

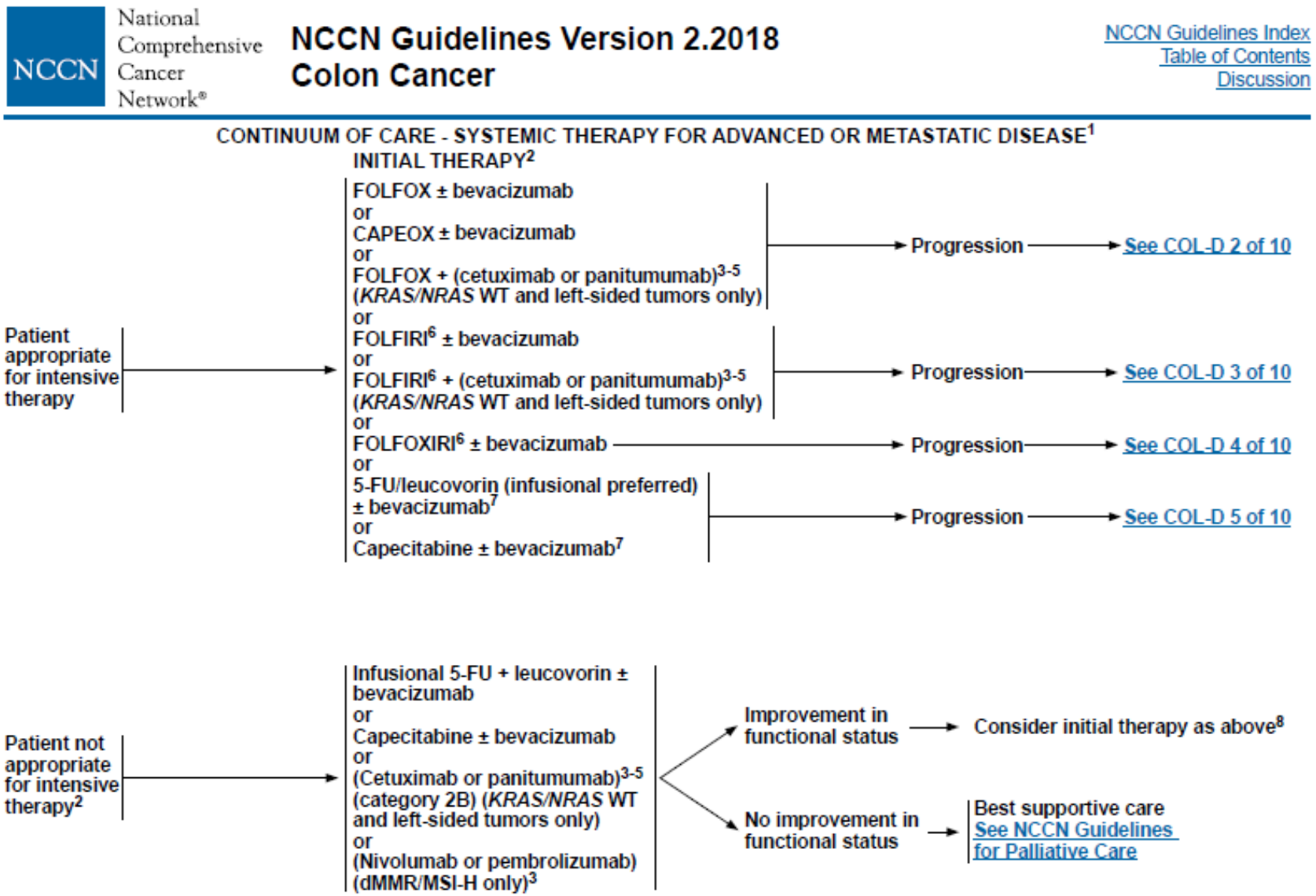
The randomized, multicenter, phas
patients with *KRAS* wild-type tumo
line oxaliplatin-based therapy plus
bevacizumab or FOLFIRI plus pani
in the primary endpoint of PFS betv
panitumumab arm vs. 9.2 months i
95% CI, 0.68–1.50; $P = .97$).

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

Kolon Kanseri Tedavi



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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[1]

Previous oxaliplatin-based therapy without irinotecan

SUBSEQUENT THERAPY[2]

FOLFIRI[6] or irinotecan[6]
or
FOLFIRI[6] + (bevacizumab[9] [preferred] or ziv-aflibercept[9,10] or ramucirumab[9,10])
or
Irinotecan[6] + (bevacizumab[9] [preferred] or ziv-aflibercept[9,10] or ramucirumab[9,10])

or

FOLFIRI[6] + (cetuximab or panitumumab)*[3,4,11] (*KRAS/NRAS* WT only)
or
Irinotecan[6] + (cetuximab or panitumumab)*[3,4,11] (*KRAS/NRAS* WT only)
or
Irinotecan[6] + (cetuximab or panitumumab)*[3] + vemurafenib (*BRAF* V600E mutation positive)
or

(Nivolumab or pembrolizumab)* (dMMR/MSI-H only) → See Subsequent therapy

Irinotecan[6] + (cetuximab or panitumumab)*[3,4,11] (*KRAS/NRAS* WT only)
or
Regorafenib[12]
or
Trifluridine + tipiracil[12]
or
(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)

See Subsequent therapy

Regorafenib[12]
or
Trifluridine + tipiracil[12]
or
(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)

See Subsequent therapy

Regorafenib[12]
or
Trifluridine + tipiracil[12]

Regorafenib**[12]
or
Trifluridine + tipiracil**[12]
or
Best supportive care

*if neither previously given
**if not previously given

See footnotes COL-D 6 of 10

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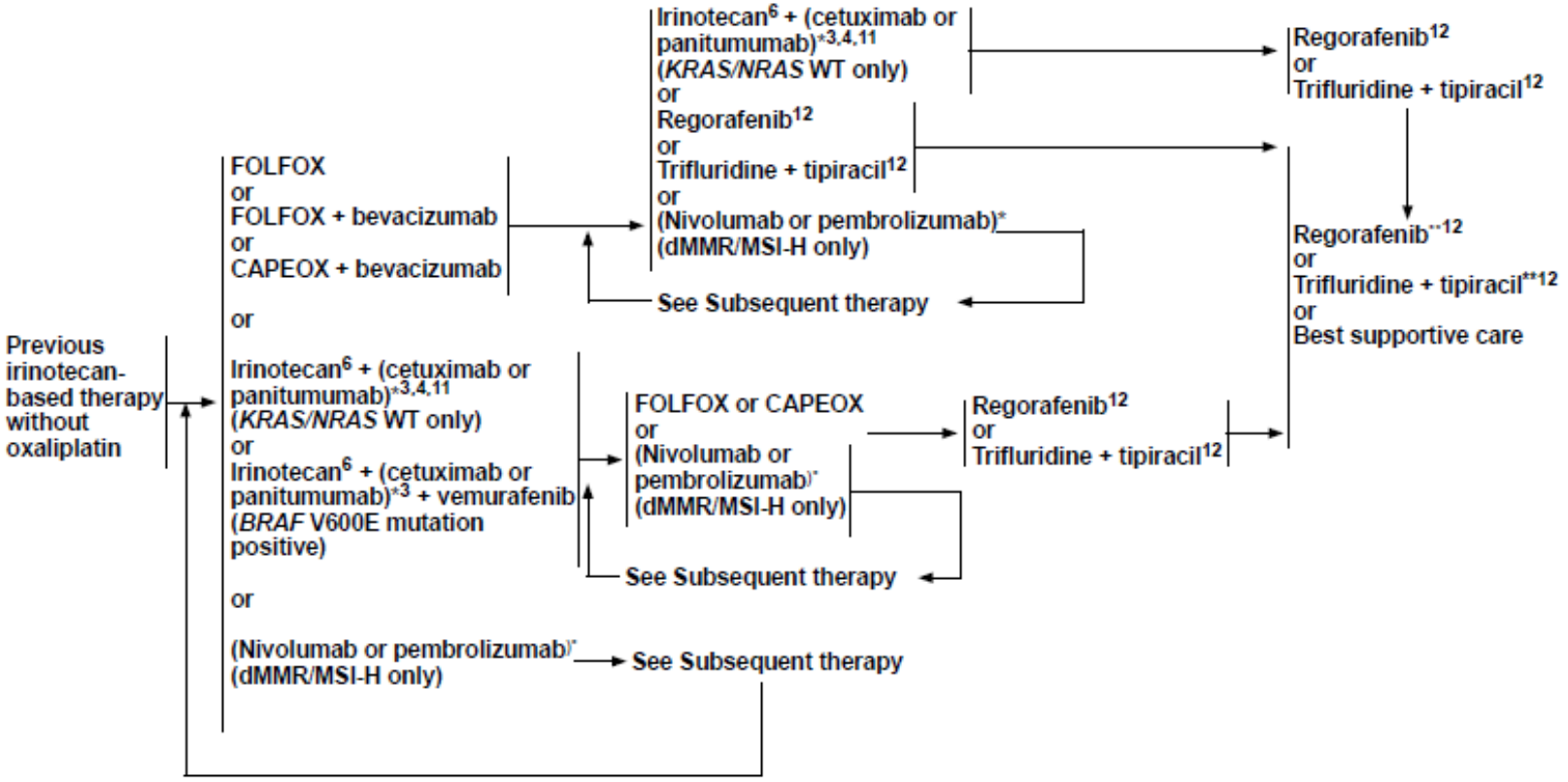
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[1]



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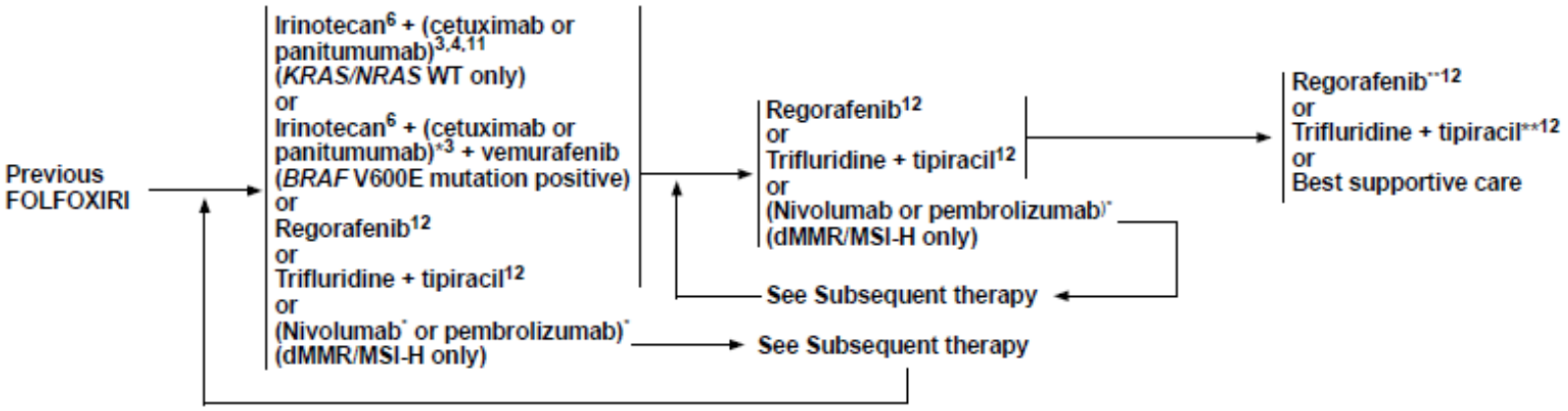
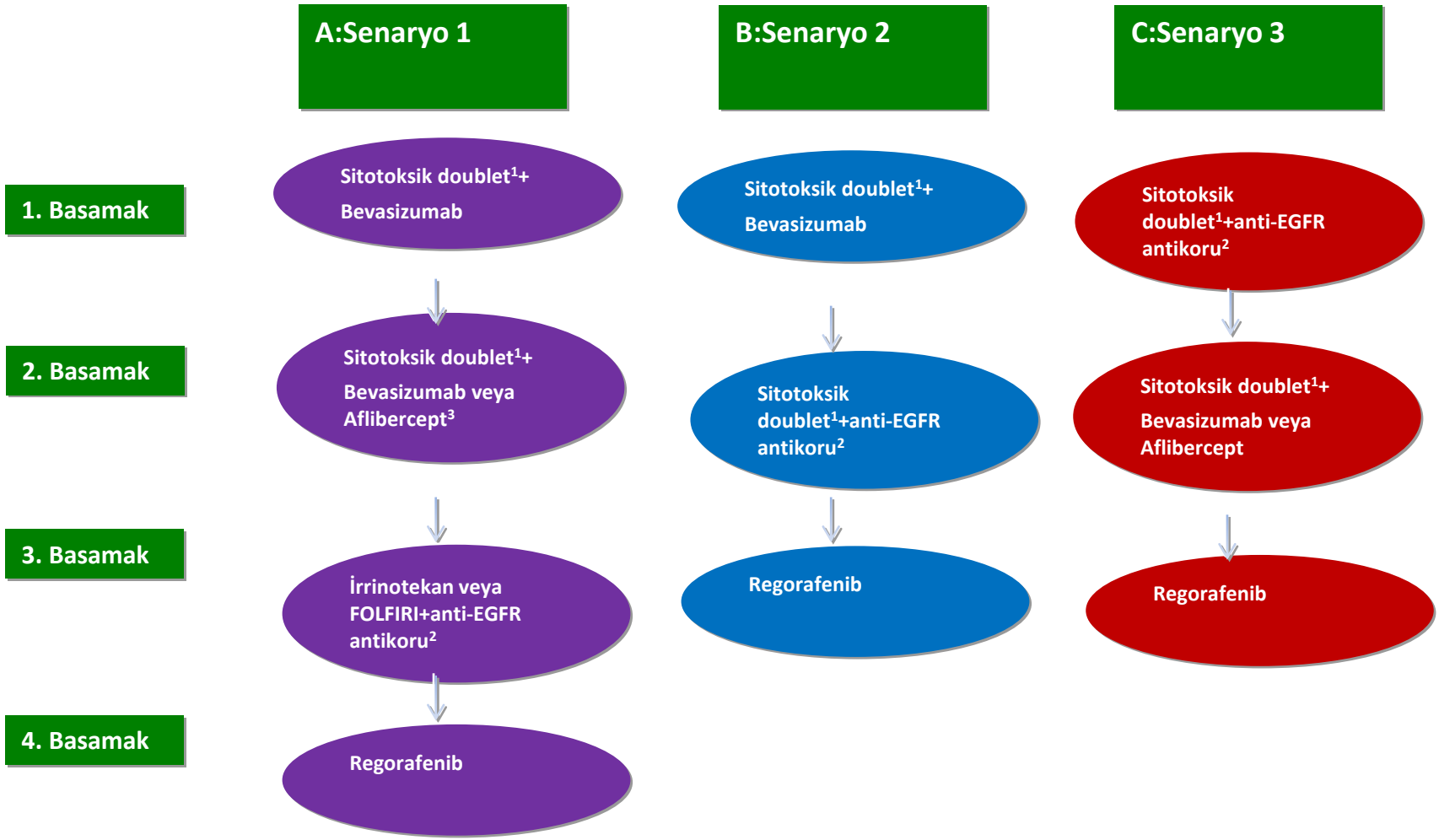
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[1]

SUBSEQUENT THERAPY[2]



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**