Metastatik kolon kanseri birden fazla hastalık mı? Moleküler subtip ve tümör lokasyonu tedavi pratiğimizi etkilemeli mi?

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Gençlerle Onkolojiye Bakış Kongresi, 17.2.18, Antalya


1611
1621
1622

PLAN

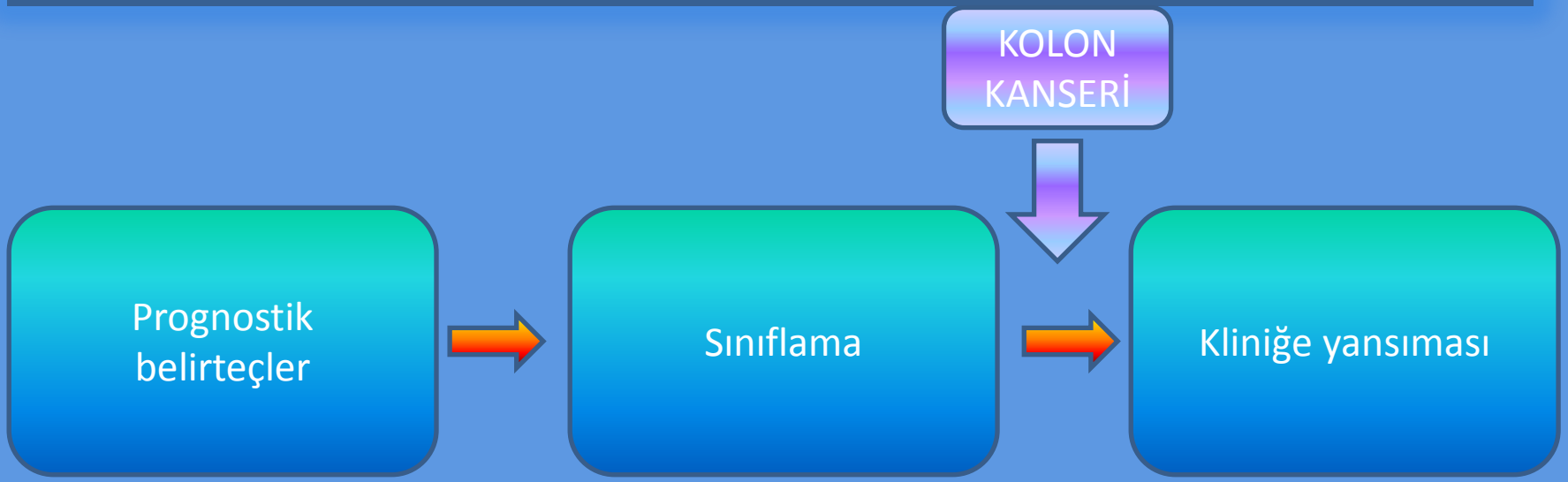
- ✓ Kolon kanseri alt tipleri ve klinik yansımaları
- ✓ Kolon kanseri yerleşim yerinin tedavi kararına etkisi

PLAN

- ✓ **Kolon kanseri alt tipleri ve klinik yansımaları**
- ✓ Kolon kanseri yerleşim yerinin tedavi kararına etkisi

Gençlerle Onkolojiye Bakış Kongresi, 17.2.18, Antalya

Kanser ve subgrup



Neden alt gruplara ayrılıyor?

- ✓ Farklı embriyonel bölgelerden gelişiyor
- ✓ Farklı mekanizmalarla oluşuyor
  - ✓ Mikrosatellit instabilite (%15)
  - ✓ Kromozomal insitabilite (%85)
- ✓ Farklı sebepler;
  - ✓ Sporadik
  - ✓ Ailesel
  - ✓ IBH

Sınıflama

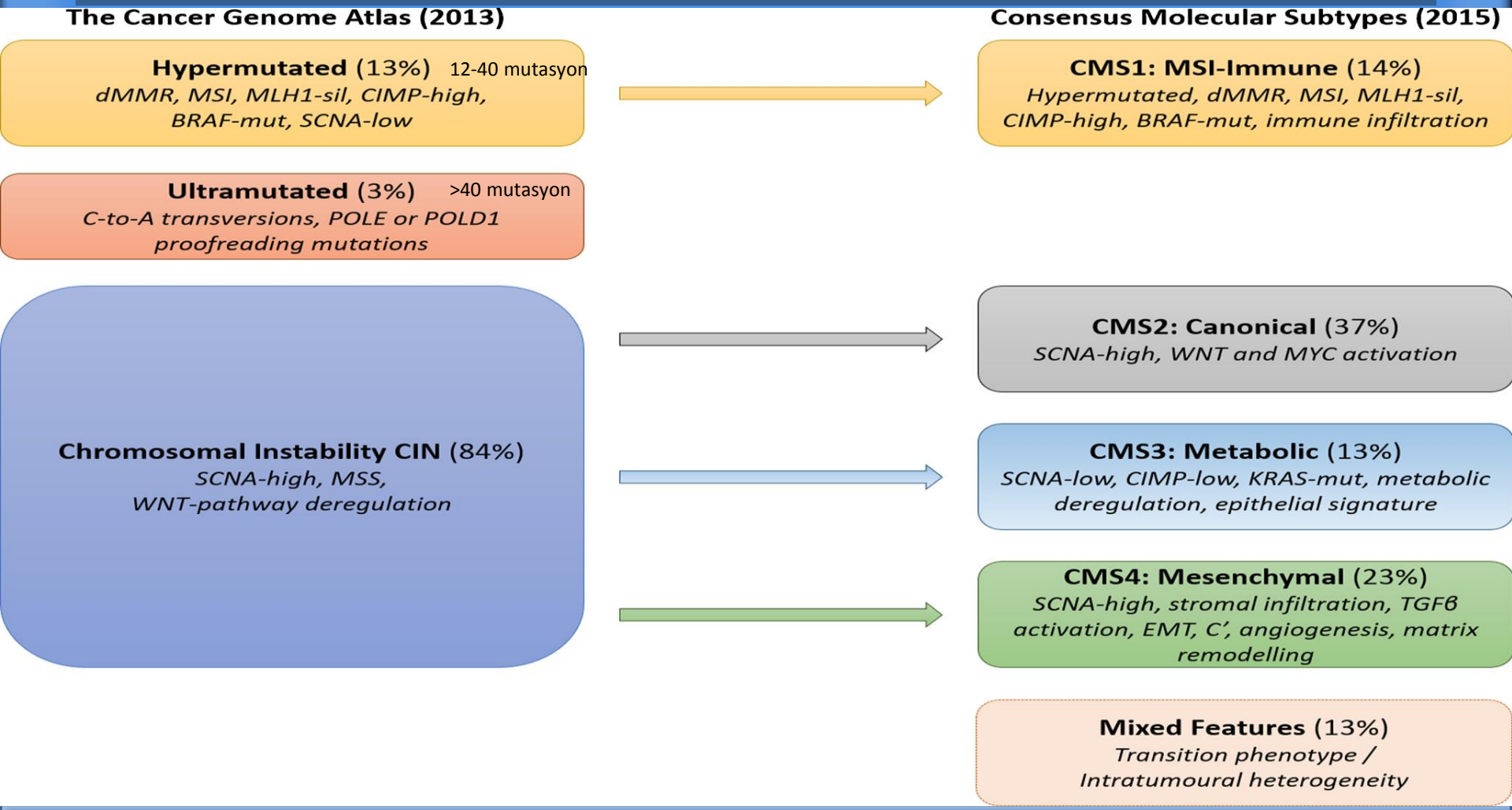
- ✓ DNA temelli
  - ✓ CIN (%85)
  - ✓ MSI (%15)
- ✓ Klinikopatolojik
  - ✓ Serrated pathway
  - ✓ Alternative pathway
  - ✓ Traditional pathway
- ✓ RNA-expresyon temelli
  - ✓ CCS1
  - ✓ CCS2
  - ✓ CCS3

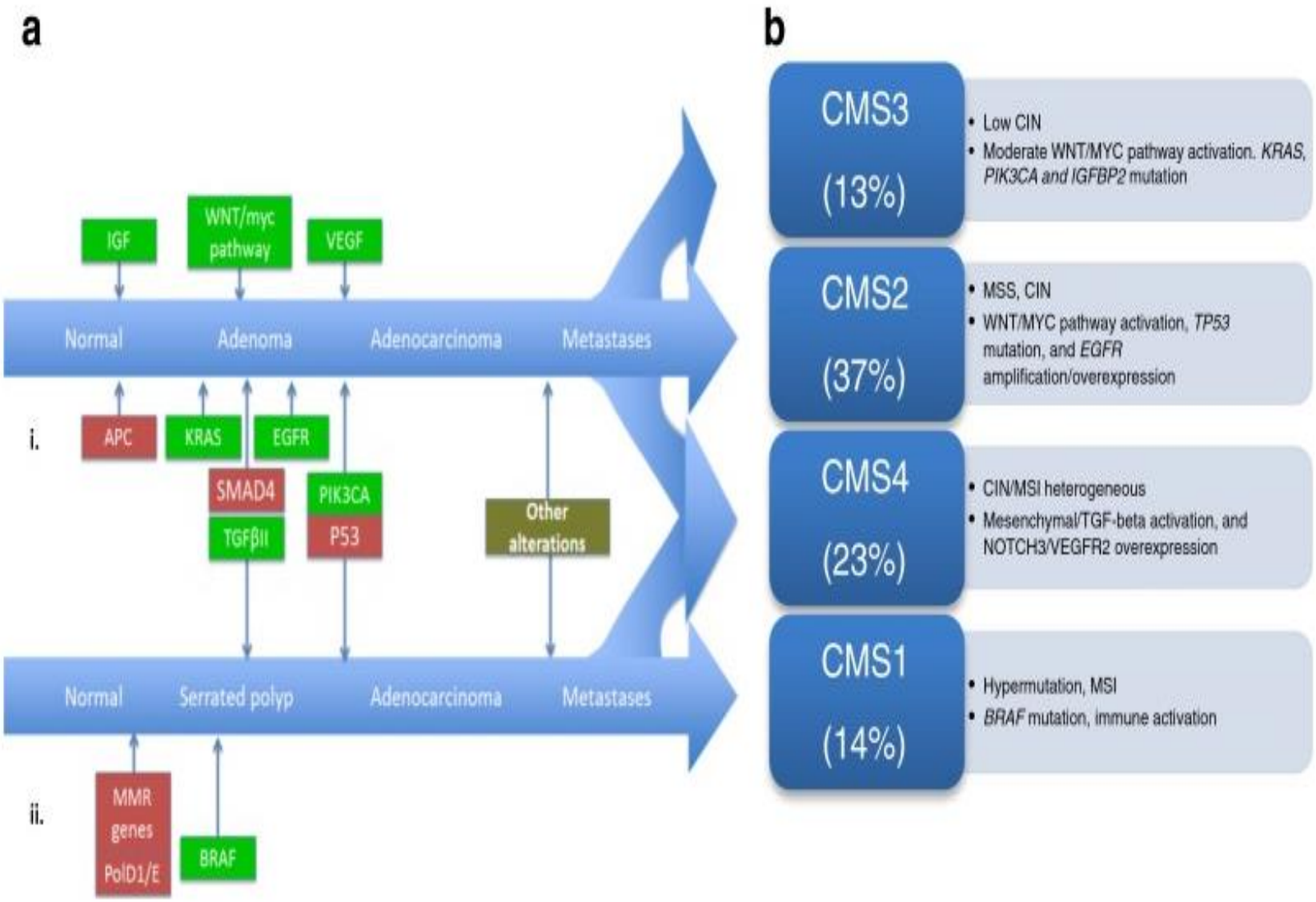
Bu 6 sınıflama çalışması üzerinden 2015 de konsorsiyum

Table 1
Publications used to develop consensus molecular subtypes.

	Patients	Components	Subtypes	Prognosis
Marisa et al. [15]	453 frozen 128 fresh 1058 database	CIN, MSI, CIMP, BRAF, KRAS, Immune, stroma, proliferation, WNT	C1: CIN $_{\text{immune down}}$ C2: dMMR C3: KRASm C4: CSC C5: CIN $_{\text{wnt up}}$ C6: CIN $_{\text{norL}}$	Better prognosis Worse prognosis Worse prognosis
Sadanandam et al. [16]	1290 database 387 fresh	MSI, WNT, mesenchymal, chemokines, interferon, enterocyte, stem cell, differentiation, globlet-specific	Globlet-like Enterocyte Stem-like Inflammatory Transit-amplifying	Best prognosis Worst prognosis
Budinska et al. [18]	1833 database	MSI, CIMP, BRAF, p53, immune, proliferation, stroma, CSC, side	Surface crypt-like Lower crypt-like CIMP-H Mesenchymal Mixed	 Best prognosis Worst prognosis
Schlicker et al. [19]	62 fresh 1600 database	MSI, Immune, Stroma	1.1 Mesenchymal 1.2 1.3 2.1 Epithelial 2.2	Worse prognosis
Roepman et al. [17]	731 fresh	MSI, BRAF, stroma, proliferation, cell type	A B C	 Worst prognosis
De Sousa et al. [20]	1164 database	CIN, MSI, CIMP, BRAF, KRAS, stroma, side	CCS1 CCS2 CCS3	 Worst prognosis

KRK sınıflamaları





a Genetic models of CRC: *i*. Chromosomal Instability; *ii*. Mutator phenotype. Stepwise carcinogenesis occurs due to differing molecular changes in each model. **b** Resulting core genomic subtypes by molecular subtyping. *MMR* mismatch repair, *CIN* chromosomal instability, *MSS* microsatellite stable, *MSI* microsatellite instable

Tümör lokalizasyonu ve alt grup dağılımı

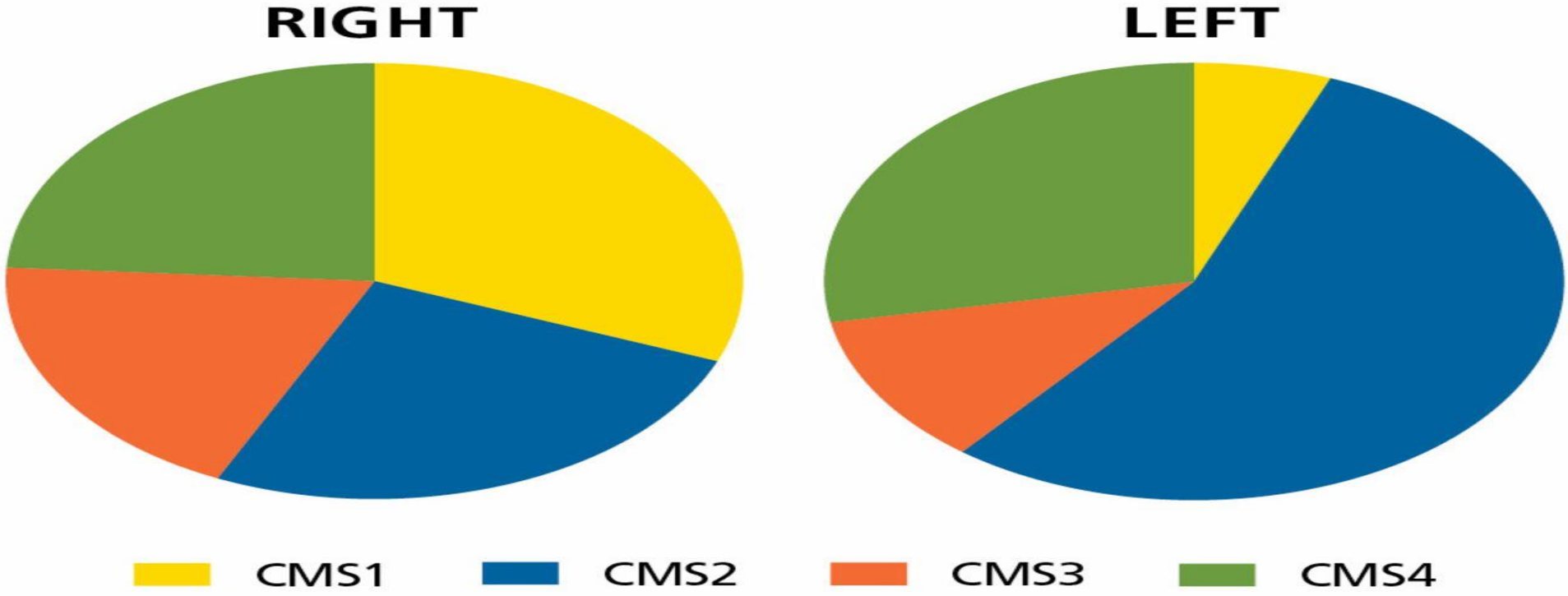
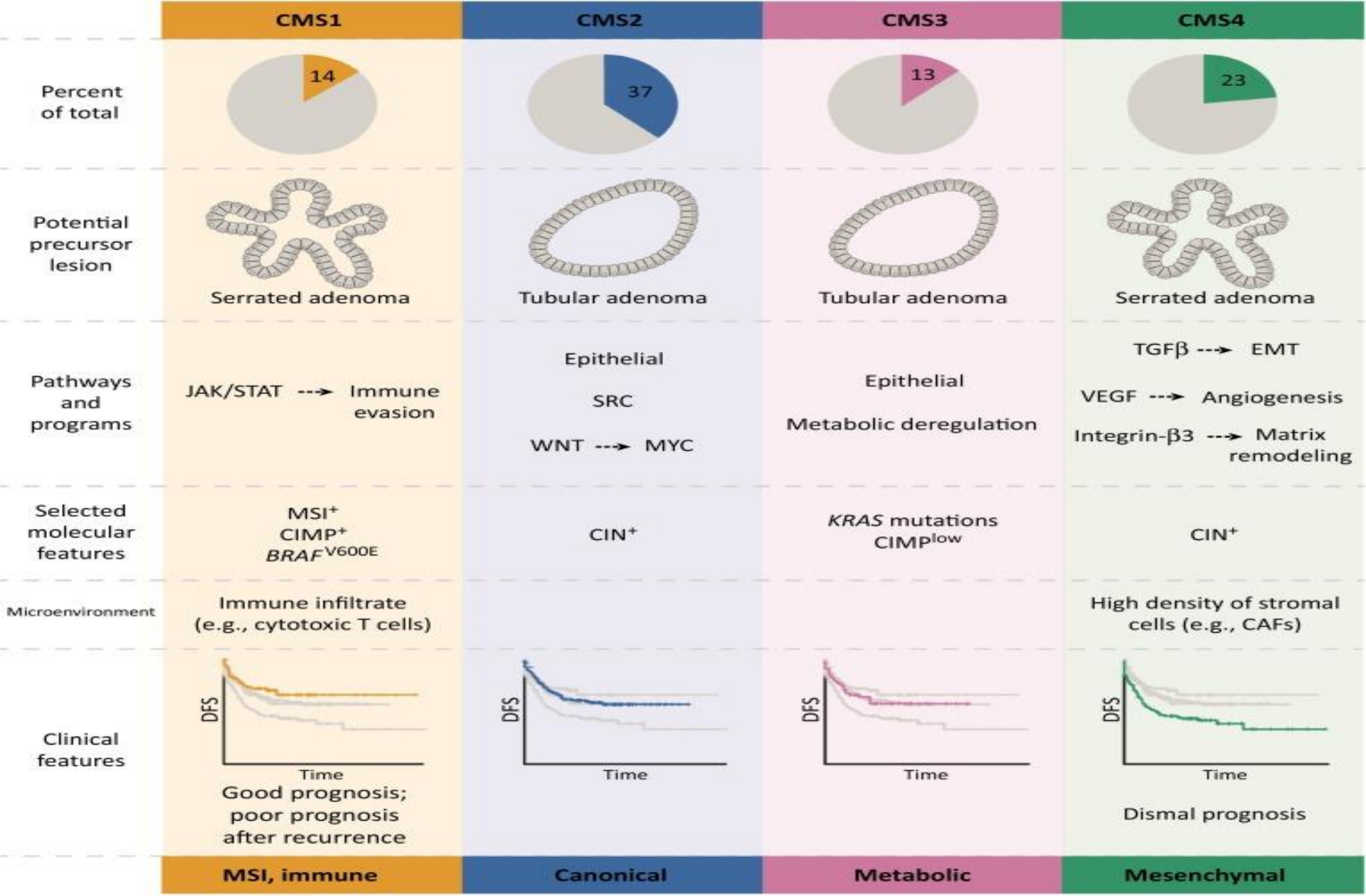


Figure 1. Distribution of CMS by right- and left-sided CRC.[65] Right-side CRC was defined as the cecum through transverse colon, and left-side CRC was defined as the splenic flexure through rectum.
Abbreviations: CMS, consensus molecular subtype; CRC, colorectal cancer.



Trends in Cancer

Table 2
The consensus molecular subtypes of CRC.

	CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
Microsatellite Instability	MSI	MSS	MSS	MSS
CIMP	High	Negative	Low	Negative
SCNA	Normal	High	Low	High
Mutations	BRAF	-	KRAS	-
Immune infiltrate	High	Low	Low	Normal
Stromal Invasion	Normal	Low	Low	High
Epithelial/Mesenchymal	-	Epithelial	Epithelial	Mesenchymal
Pathways	High JAK/STAT	High WNT	High metabolic	High TGFβ/VEGF
Survival	Good Prognosis	-	-	Poor prognosis
Subtypes based on	C2 [15]	C1&C5 [15]	C3 [15]	C4&C6 [15]
	inflammatory [16]	stem-like [16]	enterocyte & TA [16]	stem-like [16]
	CIMP-H [18]	lower crypt-like [18]	surface crypt-like [18]	mesenchymal [18]
	1.2 [19]	2.1 & 2.2 [19]	1.3 [19]	1.1 [19]
	A [17]	B [17]	A/B [17]	C [17]
	CSS2 [20]	CSS1 [20]	CSS1 [20]	CSS3 [20]

CMS1 (immün, %14)

- ✓ Genomik alterasyon: MSI, CpG island metilasyon fenotip (CIMP) ve BRAF mutasyonu (Sporadik MSI hastalarda)
- ✓ MSI-H prognoz>MSS (5 yıllık OS %72 vs 64, BRAF+ ise; %65 vs 46)
- ✓ CIMP-H prognoz>CIMP-L (5 yıllık OS %86 vs 80, BRAF + ise; %74 vs 45)
- ✓ CIMP-H/MSI-H/BRAF+ KRKde intra-tümör inflamasyon artmıştır.

CMS1 (immün)

- ✓ Fenotip:
  - ✓ Tüm hastaların %15'i, Metastatik hastaların %5'i
  - ✓ Sağ taraf, az diff, müsinöz tm, yaşlı bayan
  - ✓ MSI tümörlerdeki iyi prognoz lokal inflamasyon artışı ile ilişkili
  - ✓ MSI tümörlerde sitotoksik T hc ve makrofaj artışı
  - ✓ MSI tm de Thc artışı sağkalım artışı ile ilişkili
  - ✓ Erken evrede iyi prognozla, ileri evrede kötü prognozla ilişkili
  - ✓ Erken evrede adjuvan tedavi yararı, ileri evrede immünoterapi yararını predikte edebilir

Systematic Review of Microsatellite Instability and Colorectal Cancer Prognosis

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From the Section of Cancer Genetics, Institute of Cancer Research, Sutton, UK.

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2303-609/$20.00

DOI: 10.1200/JCO.2005.01.086

ABSTRACT

Purpose

A number of studies have investigated the relationship between microsatellite instability (MSI) and colorectal cancer (CRC) prognosis. Although many have reported a better survival with MSI, estimates of the hazard ratio (HR) among studies differ. To derive a more precise estimate of the prognostic significance of MSI, we have reviewed and pooled data from published studies.

Methods

Studies stratifying survival in CRC patients by MSI status were eligible for analysis. The principal outcome measure was the HR. Data from eligible studies were pooled using standard techniques.

Results

Thirty-two eligible studies reported survival in a total of 7,642 cases, including 1,277 with MSI. There was no evidence of publication bias. The combined HR estimate for overall survival associated with MSI was 0.65 (95% CI, 0.59 to 0.71; heterogeneity $P = .16$; $I^2 = 20\%$). This benefit was maintained restricting analyses to clinical trial patients (HR = 0.69; 95% CI, 0.56 to 0.85) and patients with locally advanced CRC (HR = 0.67; 95% CI, 0.58 to 0.78). In patients treated with adjuvant fluorouracil (FU) CRCs with MSI had a better prognosis (HR = 0.72; 95% CI, 0.61 to 0.84). However, while data are limited, tumors with MSI derived no benefit from adjuvant FU (HR = 1.24; 95% CI, 0.72 to 2.14).

Conclusion

CRCs with MSI have a significantly better prognosis compared to those with intact mismatch repair. Additional studies are needed to further define the benefit of adjuvant chemotherapy in locally advanced tumors with MSI.

RESEARCH BRIEF

The Vigorous Immune Microenvironment of Microsatellite Instable Colon Cancer Is Balanced by Multiple Counter-Inhibitory Checkpoints

Nicolas J. Llosa[1], Michael Cruise[2], Ada Tam[3], Elizabeth C. Wicks[4], Elizabeth M. Hechenbleikner[4], Janis M. Taube[2], Richard L. Blosser[3], Hongni Fan[1], Hao Wang[5], Brandon S. Luber[5], Ming Zhang[6], Nickolas Papadopoulos[6], Kenneth W. Kinzler[6], Bert Vogelstein[6], Cynthia L. Sears[1,7], Robert A. Anders[2], Drew M. Pardoll[1,2,7,8], and Franck Housseau[1]

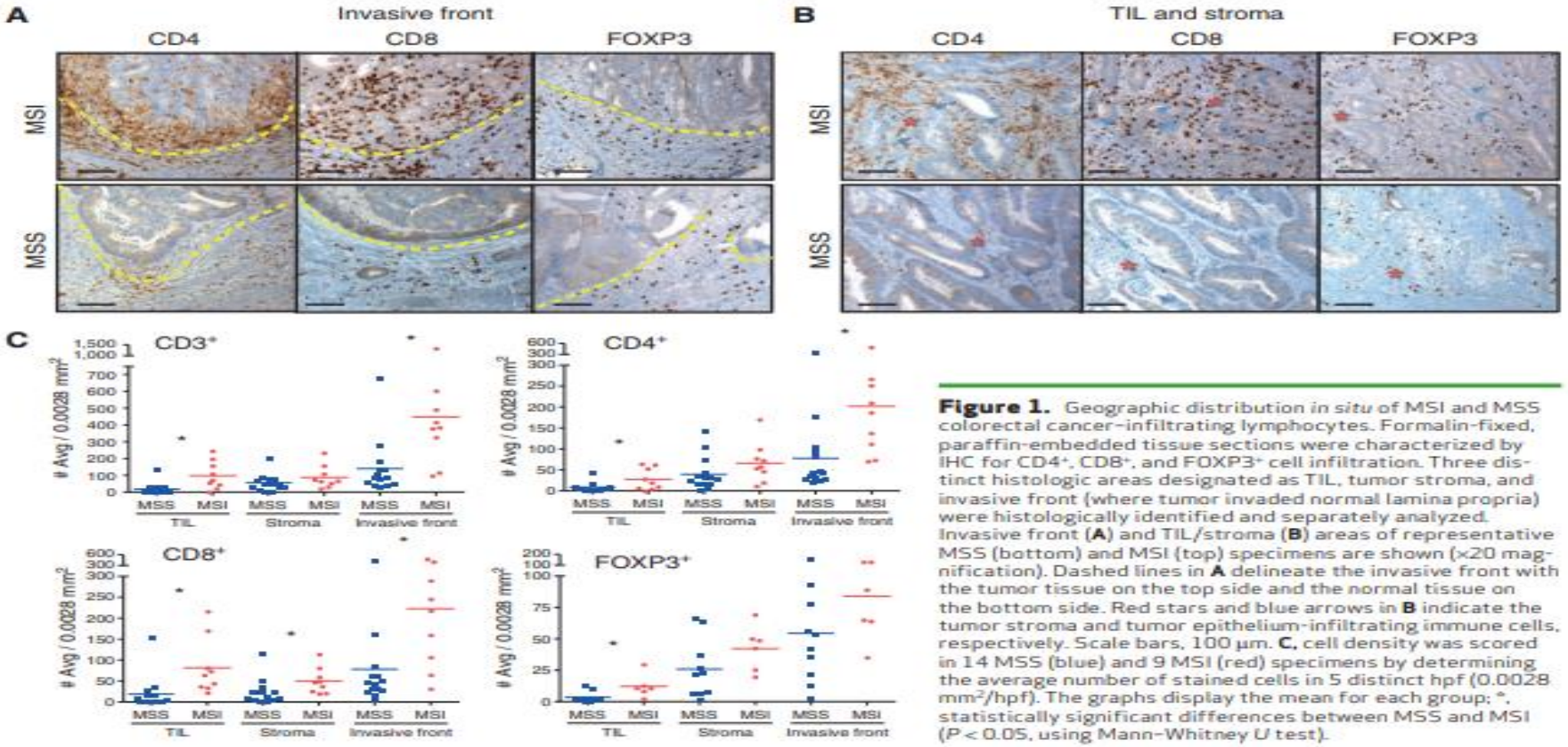

Figure 1. Geographic distribution *in situ* of MSI and MSS colorectal cancer–infiltrating lymphocytes. Formalin-fixed, paraffin-embedded tissue sections were characterized by IHC for CD4+, CD8+, and FOXP3+ cell infiltration. Three distinct histologic areas designated as TIL, tumor stroma, and invasive front (where tumor invaded normal lamina propria) were histologically identified and separately analyzed. Invasive front (**A**) and TIL/stroma (**B**) areas of representative MSS (bottom) and MSI (top) specimens are shown (×20 magnification). Dashed lines in **A** delineate the invasive front with the tumor tissue on the top side and the normal tissue on the bottom side. Red stars and blue arrows in **B** indicate the tumor stroma and tumor epithelium-infiltrating immune cells, respectively. Scale bars, 100 μm. **C**, cell density was scored in 14 MSS (blue) and 9 MSI (red) specimens by determining the average number of stained cells in 5 distinct hpf (0.0028 mm^2/hpf). The graphs display the mean for each group; *, statistically significant differences between MSS and MSI ($P < 0.05$, using Mann–Whitney *U* test).

RESEARCH BRIEF

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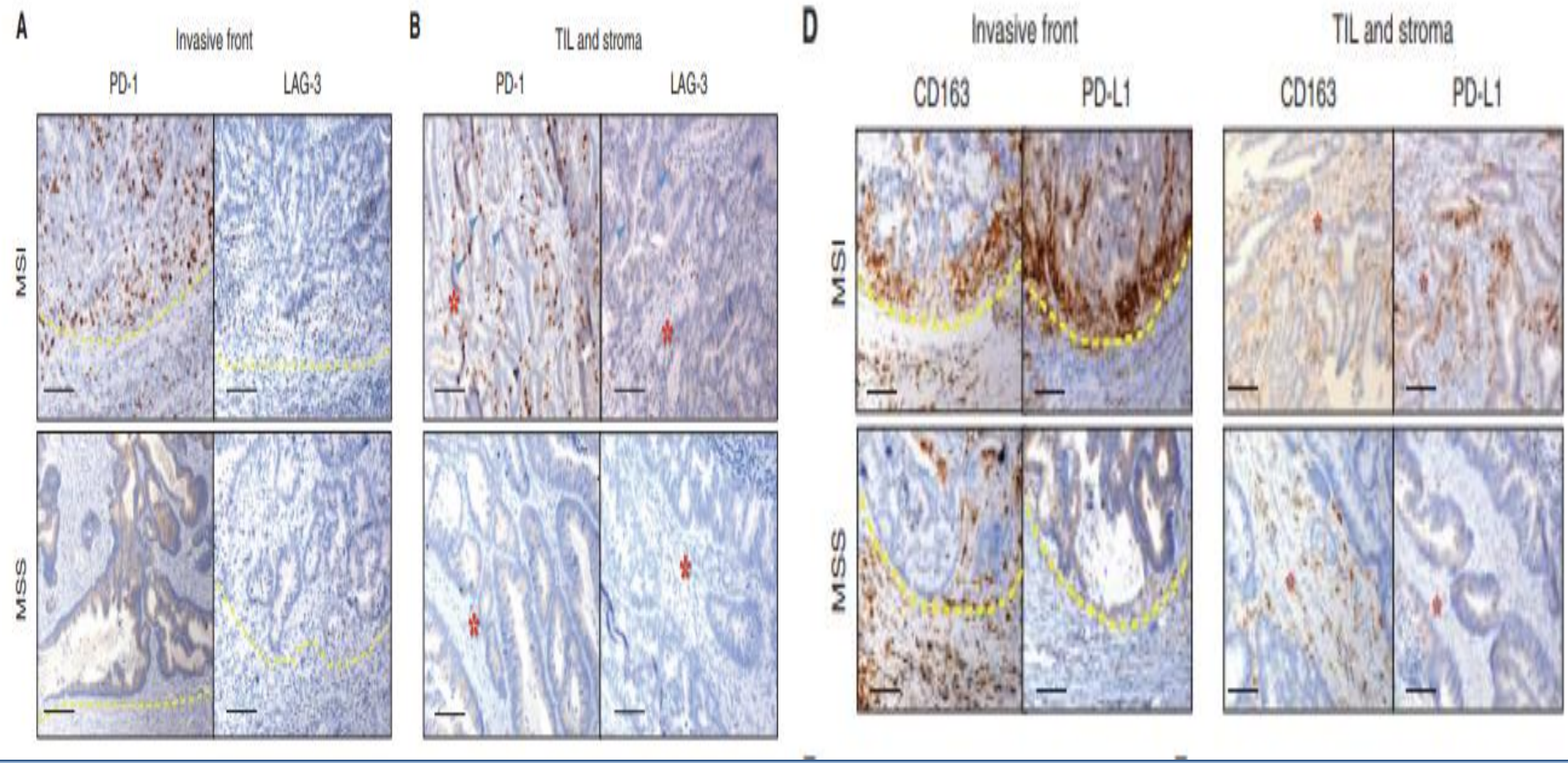


The NEW ENGLAND JOURNAL of MEDICINE

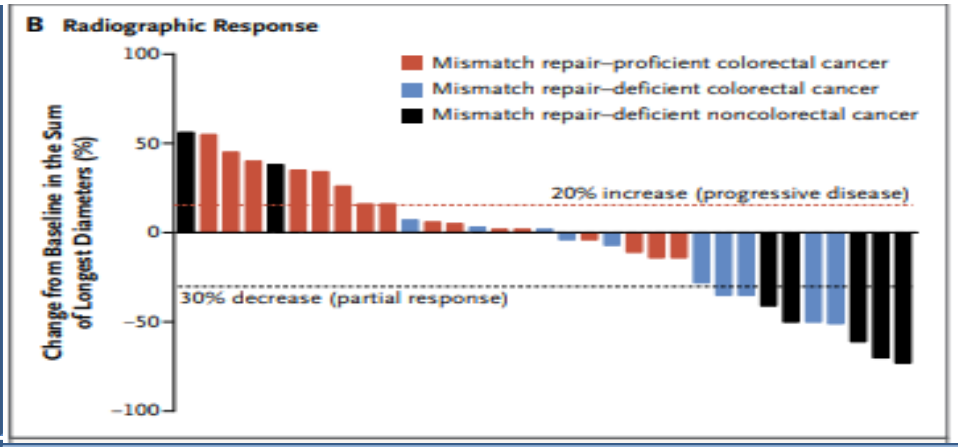
ORIGINAL ARTICLE

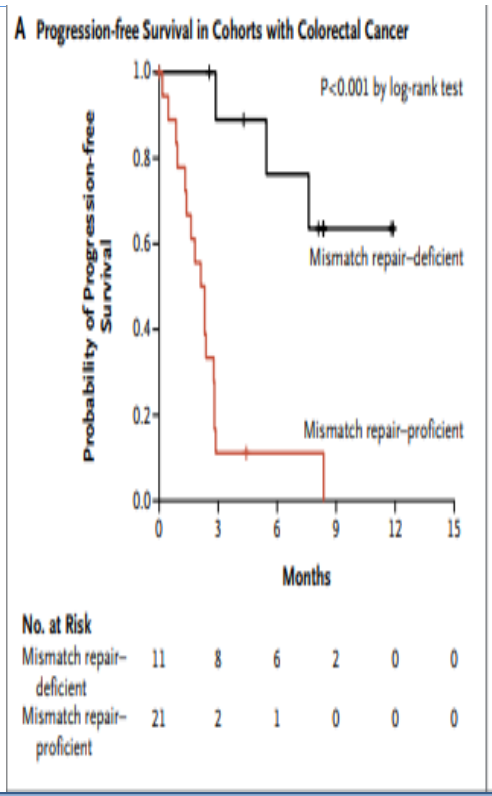
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

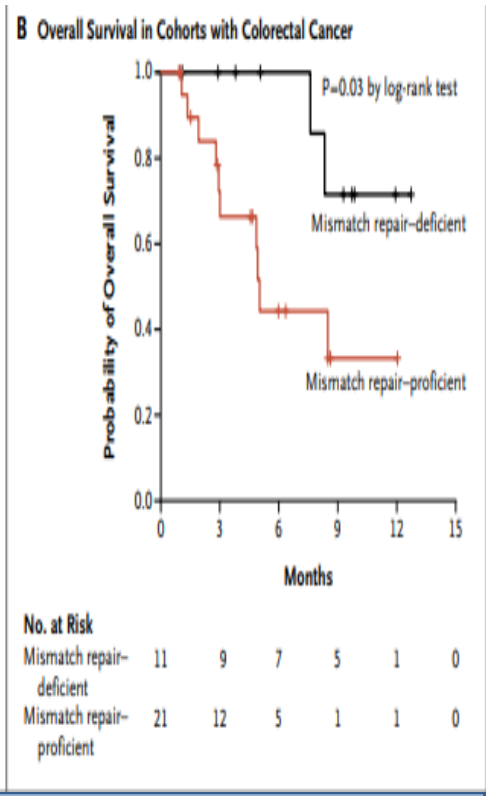
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

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)







ASCO-GI

- ✓ Nivolumab + ipilimumab combination in patients with DNA mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (mCRC): First report of the full cohort from CheckMate-142.
- ✓ Keynote-177: Phase 3, open-label, randomized study of first-line pembrolizumab (Pembro) versus investigator-choice chemotherapy for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal carcinoma (mCRC).

BRAF

ESMO[1]

“Tek başına ya da sitotoksiklerle kombinasyon halinde kullanılan anti-EGFR antikorlarının BRAF mutant tümörü olan hastalara yarar sağlamadığı yönündeki veriler giderek artmaktadır.”

NCCN[2]

“BRAF V600E mutasyonu varlığında, panitumumab ve setuksimabın tek başına tedavi veya sitotoksik kemoterapi ile kombinasyonunda yanıt olasılığının çok düşük olduğu ile ilgili kanıtlar giderek artmaktadır.”

1.Van Cutsem E ve ark. Ann Oncol. 2014 Sep;25 Suppl 3:iii1-9. 2.Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Colon Cancer Version 1.2017.

TABLE

Table 1. Recent Clinical Trials in *BRAF*-Mutant CRC

Regimen	Response Rate, % (No. of Total No.)	Progression-Free Survival, Months	Reference
Singlet or doublet regimens with EK inhibitors			
Vemurafenib	5.0 (1 of 21)	2.1	Kopetz et al., *J Clin Oncol.*, 2015[20]
Dabrafenib	11.0 (1 of 9)	NR	Falchook et al., *Lancet.*, 2012[30]
Encorafenib			t al., ESMO
Dabrafenib a trametinib			, *J Clin Oncol.*,
Doublet regime			
Vemurafenib panitumuma			Clin Can Res.,
Vemurafenib cetuximab			V Engl J Med.,
Encorafenib cetuximab			., ESMO
Dabrafenib a panitumuma			SCO 2015[27]
Triplet regimen			
Dabrafenib a trametinib a panitumumab			SCO 2015[27]
Encorafenib and cetuximab and alpelisib	32.0 (9 of 28)	4.3	Tabernero et al., ESMO 2014[29]
Vemurafenib and cetuximab and irinotecan	35.0 (6 of 17)	7.7	Hong et al., ASCO 2015[28]

Abbreviations: CRC, colorectal cancer; ESMO, European Society for Medical Oncology; NR, not reported; No, number.

Note: ASCO 2015 represents the 2015 Annual Meeting of ASCO, Chicago, IL, May 29 to June 2, 2015; and ESMO 2014 represents the ESMO 2014 Congress, Madrid, Spain, September 26 to 30, 2014.

Ongoing clinical trials for BRAF mutant CRC

Categories	Phase	Study code	Study drug
1. EGFRi+BRAFi+CMT	I	NCT01787500	Irinotecan + Cetuximab with or without Vemurafenib
2. EGFRi+BRAFi+CMT	II/III	NCT02164916 (SWOG 1406)	Irinotecan + Cetuximab with or without Vemurafenib
3. EGFRi+BRAFi+MEKi	I/II	NCT01750918	Panitumumab + Dabrafenib +Trametinib
4. EGFRi+BRAFi+PIK3CAi	II	NCT01719380	Cetuximab + LGX818 (Encorafenib) with or without BYL719 (Alpelisib)
5. EGFRi+ BRAFi+ porcupine inh.	I/II	NCT02278133	Cetuximab + LGX818 (Encorafenib)+ WNT974
6. BRAFi+MEKi+Bcl2i	I/II	NCT01989585	Dabrefenib+Trametinib+Navitoclax
7. EGFRi+BRAFi	I/II	NCT01086267	Cetuximab+BMS-908662 (XL281)
	II	NCT01791309	Panitumumab+ Vemurafenib

CRC=colorectal cancer; EGFR=epidermal growth factor receptor; BRAF= V-raf murine sarcoma viral oncogene honolog B; MEK=mitogen-activated extracellular signaling kinase; PIK3CA= phosphatidylinositol 3-kinase, catalytic subunit alpha; Bcl-2= B-cell lymphoma 2; CMT=chemotherapy; i, inh.= inhibitor

Table 2
The consensus molecular subtypes of CRC.

	CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
Microsatellite Instability	MSI	MSS	MSS	MSS
CIMP	High	Negative	Low	Negative
SCNA	Normal	High	Low	High
Mutations	BRAF	-	KRAS	-
Immune infiltrate	High	Low	Low	Normal
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Subtypes based on	C2 [15] inflammatory [16] CIMP-H [18] 1.2 [19] A [17] CSS2 [20]	C1&C5 [15] stem-like [16] lower crypt-like [18] 2.1 & 2.2 [19] B [17] CSS1 [20]	C3 [15] enterocyte & TA [16] surface crypt-like [18] 1.3 [19] A/B [17] CSS1 [20]	C4&C6 [15] stem-like [16] mesenchymal [18] 1.1 [19] C [17] CSS3 [20]

CMS2 (Canonical, %37)

- ✓ Genomik alterasyon:
  - ✓ Somatik kopya sayısı değişikliği
  - ✓ WNT ve MAPK yolağı
- ✓ Fenotip: Proliferasyon
  - ✓ Artmış proliferasyon (artmış Ki67)
  - ✓ Artmış proliferasyon kötü prognostik
  - ✓ Ki67 B-katenin aktivasyonu göstermek için kullanılabilir
- ✓ Klinik yansıma: --

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The consensus molecular subtypes of CRC.

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	A [17]	B [17]	A/B [17]	C [17]
	CSS2 [20]	CSS1 [20]	CSS1 [20]	CSS3 [20]

CMS3 (Metabolik, %13)

- ✓ Genomik alterasyon:
  - ✓ KRAS mutasyonu %75
  - ✓ Bu grubun çoğu KRAS mutant ancak KRAS mutant hastaların çoğu diğer 3 grupta
- ✓ Fenotip: Metabolik (KRAS mutasyonu ve metabolisma ilişkisi)
  - ✓ Tümör lokalizasyonu, yaş ve cinsiyetle ilişkisiz
- ✓ Klinik yansıma:
  - ✓ Anti EGFR tedaviden yarar görmez

Table 2
The consensus molecular subtypes of CRC.

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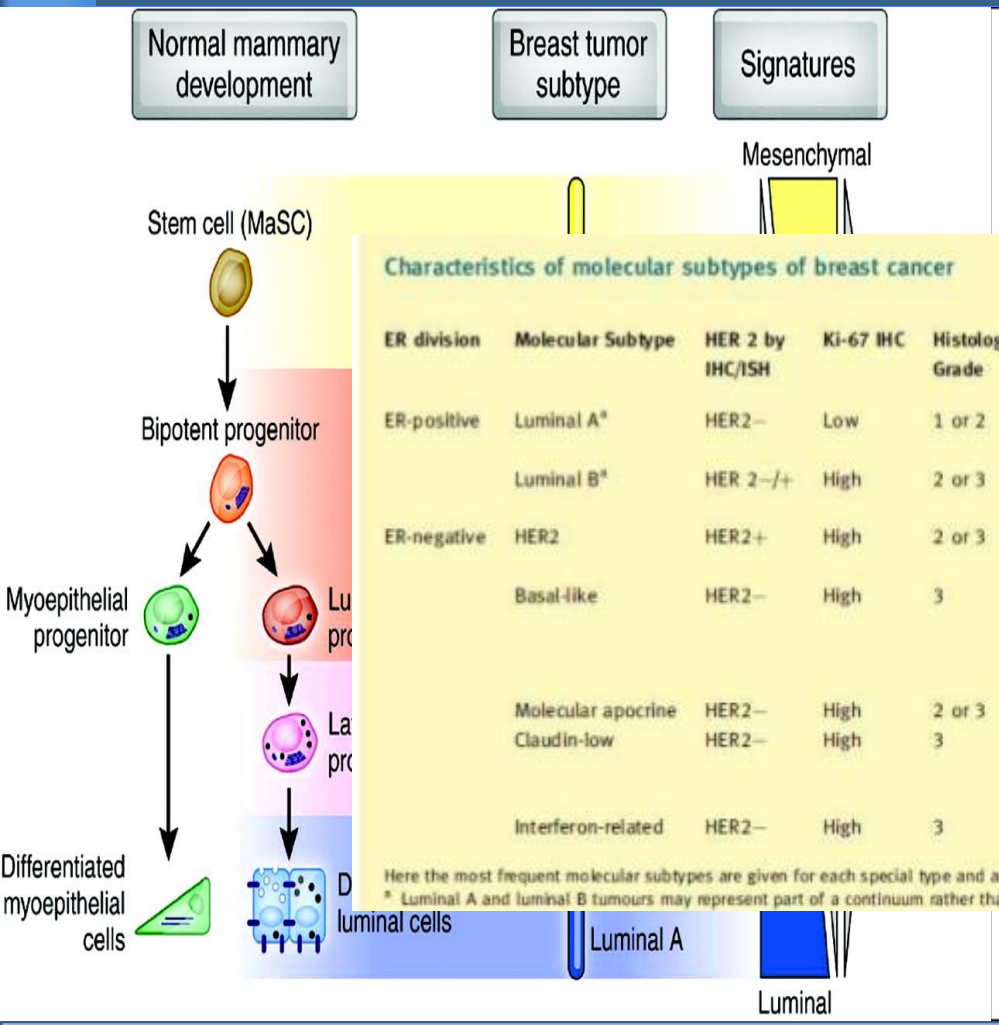
	A [17]	B [17]	A/B [17]	C [17]
	CSS2 [20]	CSS1 [20]	CSS1 [20]	CSS3 [20]

CMS4 (Mezenkimal %23)

- ✓ Genomik alterasyon:
  - ✓ Somatik kopya sayısı alterasyonu (TGFB)
- ✓ Fenotip: Mezenkimal (Stromal invazyon)
  - ✓ Yüksek stromal tümör içeriği prognozu kötü etkiliyor (5 yıllık OS %77 vs %59)
  - ✓ Daha genç ve ileri evre
  - ✓ En kötü prognozlu grup
- ✓ Klinik yansıma:
  - ✓ Anti EGFR tedaviler düşük etkili
  - ✓ Rektum ca RT yanıtları kötü

- ✓ Alt tiplerin belirlenmesi klinik pratikte nasıl yapılabilir?

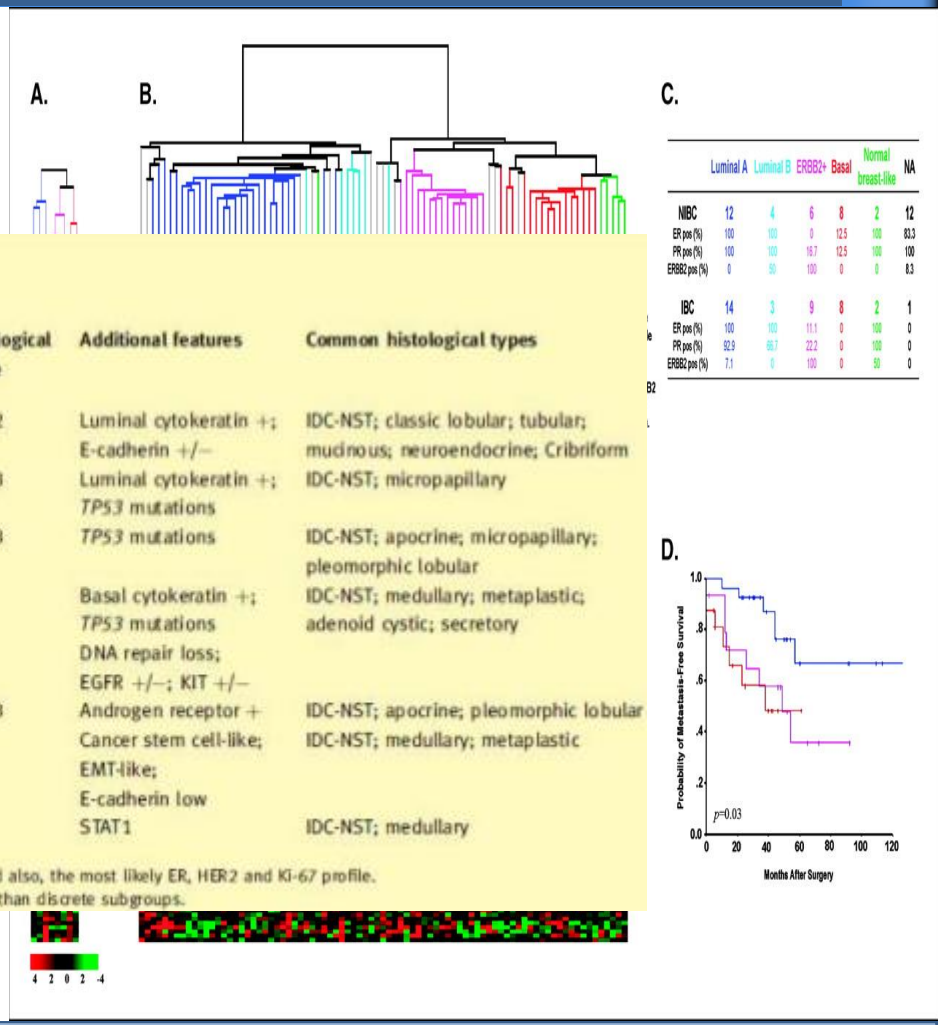
Meme kanseri- alt tipler



Characteristics of molecular subtypes of breast cancer

ER division	Molecular Subtype	HER 2 by IHC/ISH	Ki-67 IHC	Histological Grade	Additional features	Common histological types
ER-positive	Luminal A*	HER2−	Low	1 or 2	Luminal cytokeratin +; E-cadherin +/−	IDC-NST; classic lobular; tubular; mucinous; neuroendocrine; Cribriform
	Luminal B*	HER 2−/+	High	2 or 3	Luminal cytokeratin +; *TP53* mutations	IDC-NST; micropapillary
ER-negative	HER2	HER2+	High	2 or 3	*TP53* mutations	IDC-NST; apocrine; micropapillary; pleomorphic lobular
	Basal-like	HER2−	High	3	Basal cytokeratin +; *TP53* mutations DNA repair loss; EGFR +/−; KIT +/−	IDC-NST; medullary; metaplastic; adenoid cystic; secretory
	Molecular apocrine	HER2−	High	2 or 3	Androgen receptor +	IDC-NST; apocrine; pleomorphic lobular
	Claudin-low	HER2−	High	3	Cancer stem cell-like; EMT-like; E-cadherin low	IDC-NST; medullary; metaplastic
	Interferon-related	HER2−	High	3	STAT1	IDC-NST; medullary

Here the most frequent molecular subtypes are given for each special type and also, the most likely ER, HER2 and Ki-67 profile.
* Luminal A and luminal B tumours may represent part of a continuum rather than discrete subgroups.



Kolon Kanseri-alt tip tahmini

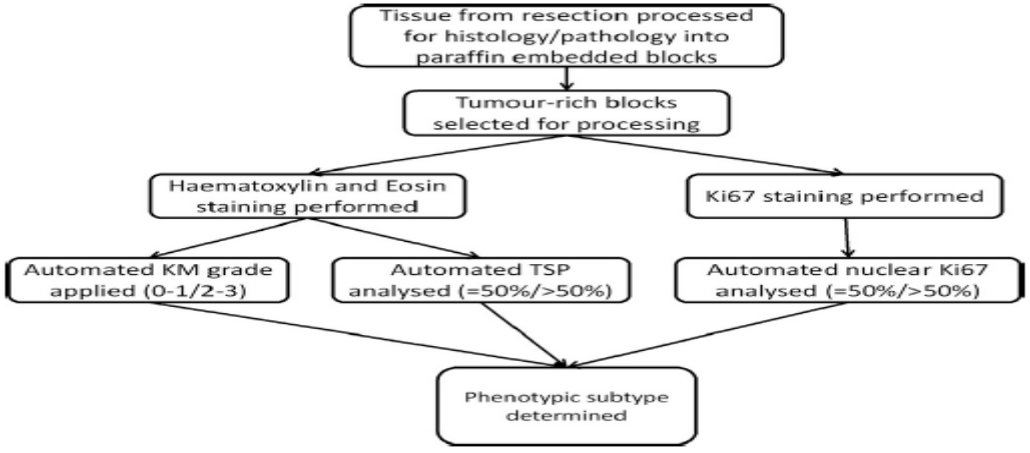


Fig. 2. Flow chart showing biomarker testing that can be utilised in the clinic.

Table 3
Simple IHC-based testing for molecular subtypes of CRC.

	CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
Intra-tumour immune infiltrate (KM grade; 0–1/2–3)	High	Low	Low	Low
Stromal invasion (TSP; ≤50%/>50%)	Low	Low	Low	High
Proliferation rate (Ki76; ≤50%/>50%)	Any	High	Low	Any
Cancer Specific Survival	Best Prognosis	Good Prognosis	Poor Prognosis	Worst Prognosis

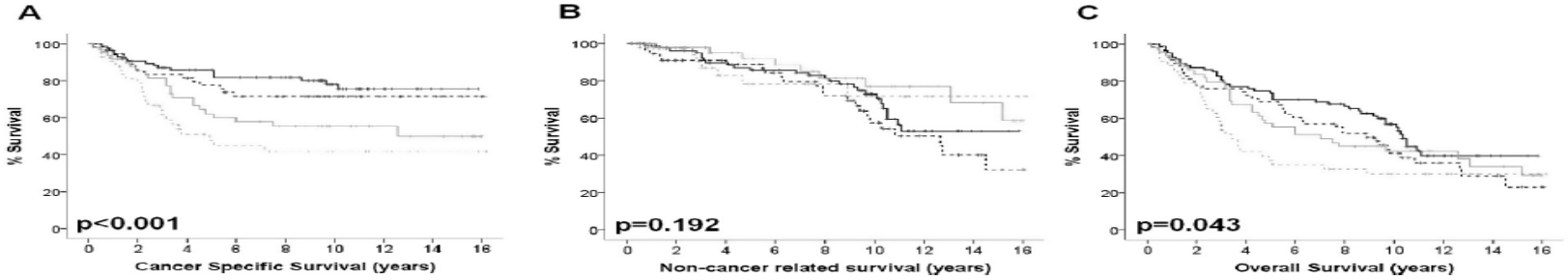


Fig. 1. Phenotypic subtypes predict cancer-specific survival in CRC patients. Kaplan Meier curves showing the association between phenotypic subtypes (MSI Immune (solid black), Canonical (dotted black), Metabolic (solid grey) and Mesenchymal (dotted grey)) and (A) cancer-specific survival, (B) Non-cancer related survival and (C) overall survival in 237 CRC patients.

ASCO Meeting Library

Sign In

Phenotypic subtypes and risk of local recurrence after radical resection for rectal cancer.

Presented Saturday, January 20, 2018

Methods:

From a CRC database, pts with rectal cancer and phenotypic subtyping available were identified. Subtyping was performed based on immune cell infiltrate, stromal volume and tumor proliferation. LR was considered pelvic or peritoneal.

Conclusions:

LR after rectal cancer surgery was associated with the stromal subtype. Validation is needed but pre-treatment tumor subtyping may identify subsets at risk of LR and have implications for patient selection for neoadjuvant therapy.

Kolon Kanseri-alt tip tahmini

ASCO Meeting Library

ColotypeR: A tool to classify colon cancers by consensus molecular subtype and subtype-specific risk of recurrence.

Presented Saturday, January 20, 2018

Results:

In the training set, a 20-gene panel (ColotypeR-CMS) predicts CMS subtype. Mean accuracy for CMS1-4 prediction was 0.87 in AV and 0.81 in COAD. In AV, 5-year RFS is 0.52 (95%CI 0.43 – 0.63) in the predicted CMS4, and 0.70 (95%CI 0.65 – 0.77) in the non-CMS4 samples. The risk of relapse for non-CMS4 samples was refined by a genomic score (ColotypeR-Risk) computed using expression of 25 genes in the training set. ColotypeR-Risk was prognostic of RFS ($p = 0.0004$) among the AV non-CMS4 samples, and also prognostic ($p = 0.0001$) among the stage II non-CMS4 AV samples not treated with chemotherapy. The prognostic significance of ColotypeR-Risk among non-CMS4 samples is independent of tumor location (right or left) and CMS subtype (CMS1-3 or mixed). ColotypeR-Risk was also prognostic of RFS in non-CMS4 samples in COAD ($p = 0.005$).

Conclusions:

ColotypeR identifies the consensus molecular subtypes (CMS1, CMS2, CMS3, CMS4, or mixed), and assesses subtype-specific risk of recurrence of colon cancer. ColotypeR identifies prognostic risk and molecular features that could help guide the management of colon cancer patients.

Devam eden çalışmalar

Table 1 Selected molecular subtypes of colorectal cancer and associated clinical trials utilising targeted agents

Tumour subtype	Investigative strategies	Agents	Phase of trial	Clinicaltrials.gov identifier
Mismatch repair deficient/microsatellite instable	PARP inhibition	Olaparib	II	NCT00912743
	Immune checkpoint inhibition (PD-L1)	Durvalumab (MEDI4736)	II	NCT02227667
	Immune checkpoint inhibition (PD-L1)	Atezolizumab (MPDL3280A)	II	NCT02291289
	Immune checkpoint inhibition (PD-1)	Nivolumab ± Ipilimumab	I/II	NCT02060188
	Immune checkpoint inhibition (PD-1)	Pembrolizumab (MK-3475)	II	NCT02460198
		± standard chemotherapy	III	NCT02563002
RAS mutation	Pan-RAF inhibition	BMS-908662 ± Cetuximab	I/II	NCT01086267
	AKT and MEK inhibition	MK-2206 and AZD6244 (Selumetinib)	II	NCT01333475
	HDAC inhibition	4SC-201 (Resminostat) + FOLFIRI	II	NCT01277406
	ERK inhibition	CC-90003	I	NCT02313012
	NOTCH inhibition	RO4929097 + Cetuximab	I	NCT01198535
	MEK and MET inhibition	PD-0325901 + Crizotinib	I	NCT02510001
	Multikinase inhibition	Regorafenib	II	NCT02175654
	MEK and BCL2 inhibition	Trametinib and Navitoclax (ABT-263)	I/II	NCT02079740
	PI3K and MEK inhibition	BKM120 + MEK162	I	NCT01363232
Resistant to EGFR inhibition	RAF inhibition	BMS-908662 ± Cetuximab	I/II	NCT01086267
	NOTCH inhibition	RO4929097 + Cetuximab	I	NCT01198535
BRAF mutation	PI3K and MEK inhibition	BKM120 + MEK162	I	NCT01363232
		BEZ235 + MEK162	I	NCT01337765
	BRAF, MEK and EGFR inhibition	Trametanib, Dabrafenib + Panitumumab	II	NCT01750918
	RAF inhibition	BMS-908662 ± cetuximab	I/II	NCT01086267
	BRAF and EGFR inhibition	Irinotecan, Cetuximab + Vemurafenib	II	NCT02164916
	BRAF, PI3K and EGFR inhibition	LGX818, BYL719, and Cetuximab	I/II	NCT01719380
	BRAF, WNT and EGFR inhibition	LGX818, WNT974 and Cetuximab	I/II	NCT02278133
	ERK inhibition	BVD-523	I	NCT02313012
	ERK inhibition	CC-90003	I	NCT02313012
PI3K mutation/PTEN depletion	MEK and PI3K/mTOR inhibition	Pimasertib + SAR245409	I	NCT01390818
	AKT and MEK inhibition	MK-2206 and AZD6244 (selumetinib)	II	NCT01333475
HER2 amplification	HER2 dual inhibition	Trastuzumab + Lapatinib	II	EudraCT Number: 2012-002128-33
		Trastuzumab + Pertuzumab	II	
MET amplification	MEK and MET inhibition	PD-0325901 + Crizotinib	I	NCT02510001

FOCUS trial

Table 2 FOCUS4 trial cohorts: an example of a trial designed with treatment stratification based on molecular subtyping within colorectal cancer

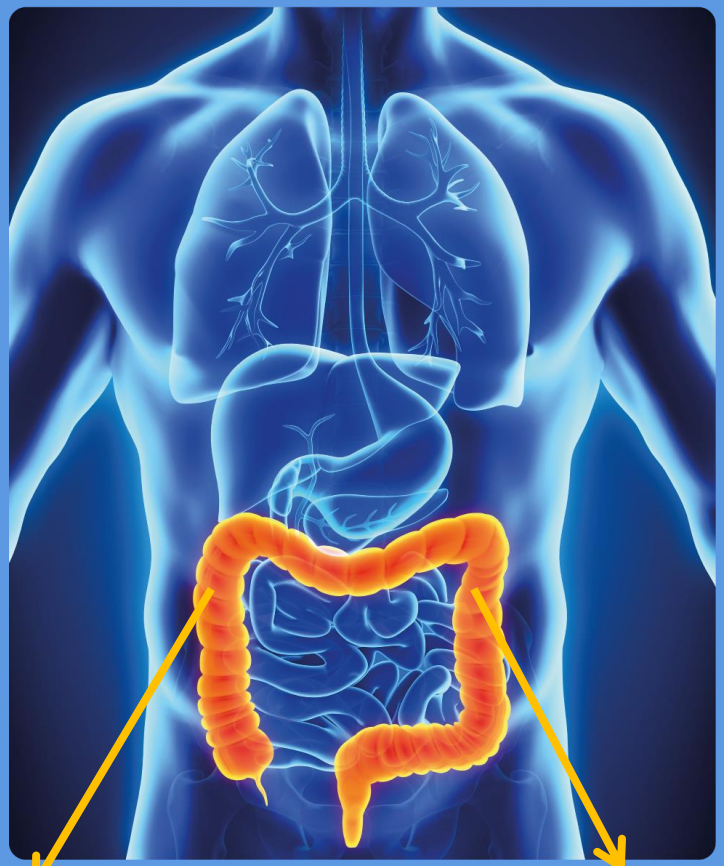
Study arm	Molecular aberration	Treatment
FOCUS-A	BRAF mutation	EGFR/BRAF/MEK inhibitors vs observation
FOCUS-B	PIK3CA mutation	Aspirin vs placebo
FOCUS-C	P53 and RAS dual mutation or H3K36me3 loss	WEE1 inhibitor vs placebo
FOCUS-D	BRAF/RAS/PI3KCA WT and no PTEN loss	HER-1, 2, 3 inhibitor vs placebo
FOCUS-E	Mismatch repair deficiency or POLD1/POLE mutations	PD-L1 inhibitor vs placebo
FOCUS-F	ATM loss	ATR inhibitor vs placebo
FOCUS-N	No other cohort available	Capecitabine vs observation

PLAN

- ✓ Kolon kanseri alt tipleri ve klinik yansımaları
- ✓ **Kolon kanseri yerleşim yerinin tedavi kararına etkisi**

Sağda yerleşimli (proksimal) kolon kanseri

- Kadınlarda daha yaygın[4]
- Mikrosatellit İnstabil[4]
- Midguttan köken alır[4]
- CIMP+, BRAF mutasyonu[4]
- MAPK sinyali, dişli yolak[4]
- Mutajenik CYP450 metabolitler[4]
- HNPCC[4]
- Semptomlar çoğunlukla mikrositik anemi, kilo kaybı gibi küçük semptomlardır[5]
- Kötü prognoz[6]
- CMS1 ve CMS 3[6]
- Safra asidi maruziyeti[6]
- İnvaziv bakteriyel biofilmler[6]



Yağ ▲
Karbonhidrat ▲

Solda yerleşimli (distal) kolon kanseri

- Erkeklerde daha yaygın[4]
- Kromozomal instabilite[4]
- Hindguttan köken alır[4]
- APC, K-RAS, p53 mutasyonları[4]
- EGFR sinyal, Wnt sinyali[4]
- HER1, HER2 amplifikasyonu[4]
- FAP[4]
- Semptomlar çoğunlukla rektal kanama, bağırsak alışkanlığı değişikliği gibi semptomlar olup daha belirgindir[5]
- Normalde daha erken evrede tanı alır[5]
- İyi prognoz[6]
- Tübüler Adenom[6]
- CMS2 ve CMS4[6]
- Yüksek EREG/AREG ekspresyonu[6]

Protein ▲
Et ▲
Kalsiyum ▼

1. Peeters M, ve ark. Drugs 2015;75:731–748.
2. Schwartzberg LS, ve ark. J Clin Oncol. 2014 Jul 20;32(21):2240-7.
3. Carrato A, ve ark. Eur J Cancer. 2017 Aug;81:191-202.
4.https://genderedinnovations.stanford.edu/case-studies/colon.html#tabs-2. Erişim: 16.11.2017.
5. Lee GH, ve ark. Eur J Surg Oncol 2015;41:300–8.
6. Lee MS, ve ark. J Natl Compr Canc Netw 2017;15(3):411–419

Microbiota organization is a distinct feature of proximal colorectal cancers

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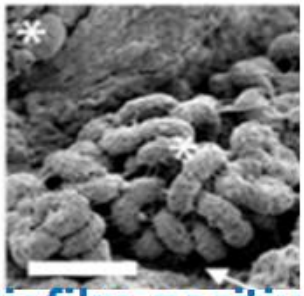
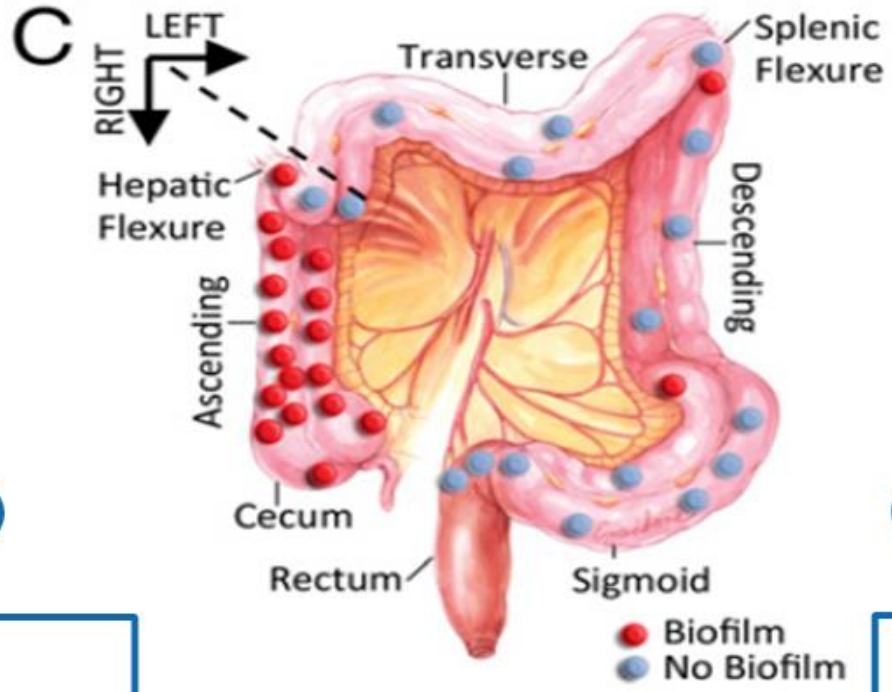
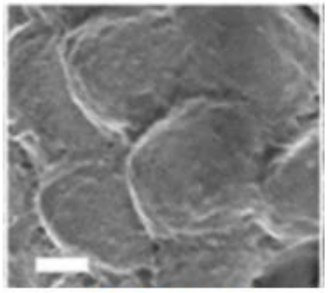


Biofilm-positive right-sided tumor

87% biofilm-positive



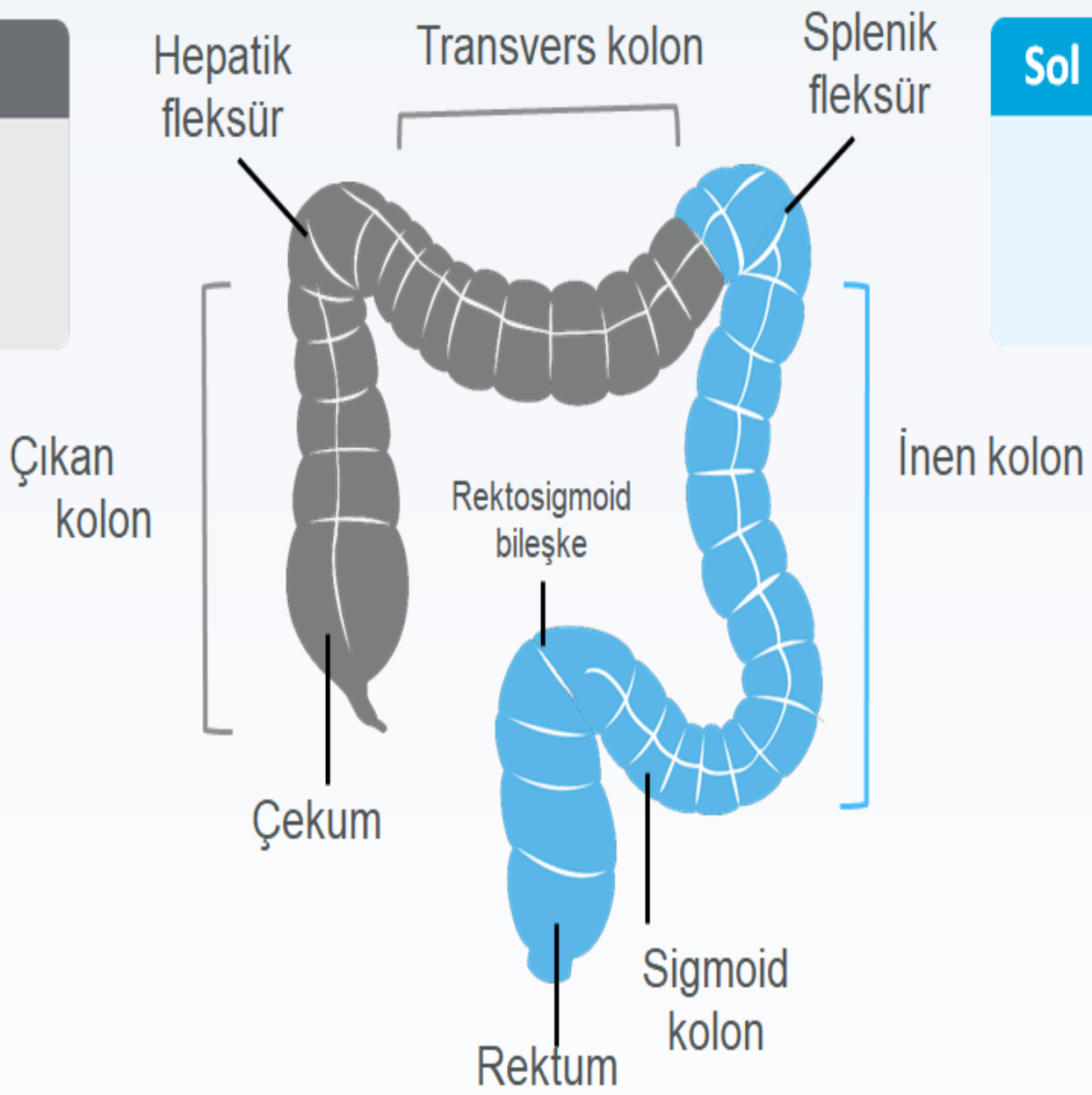


Biofilm-negative left-sided tumor

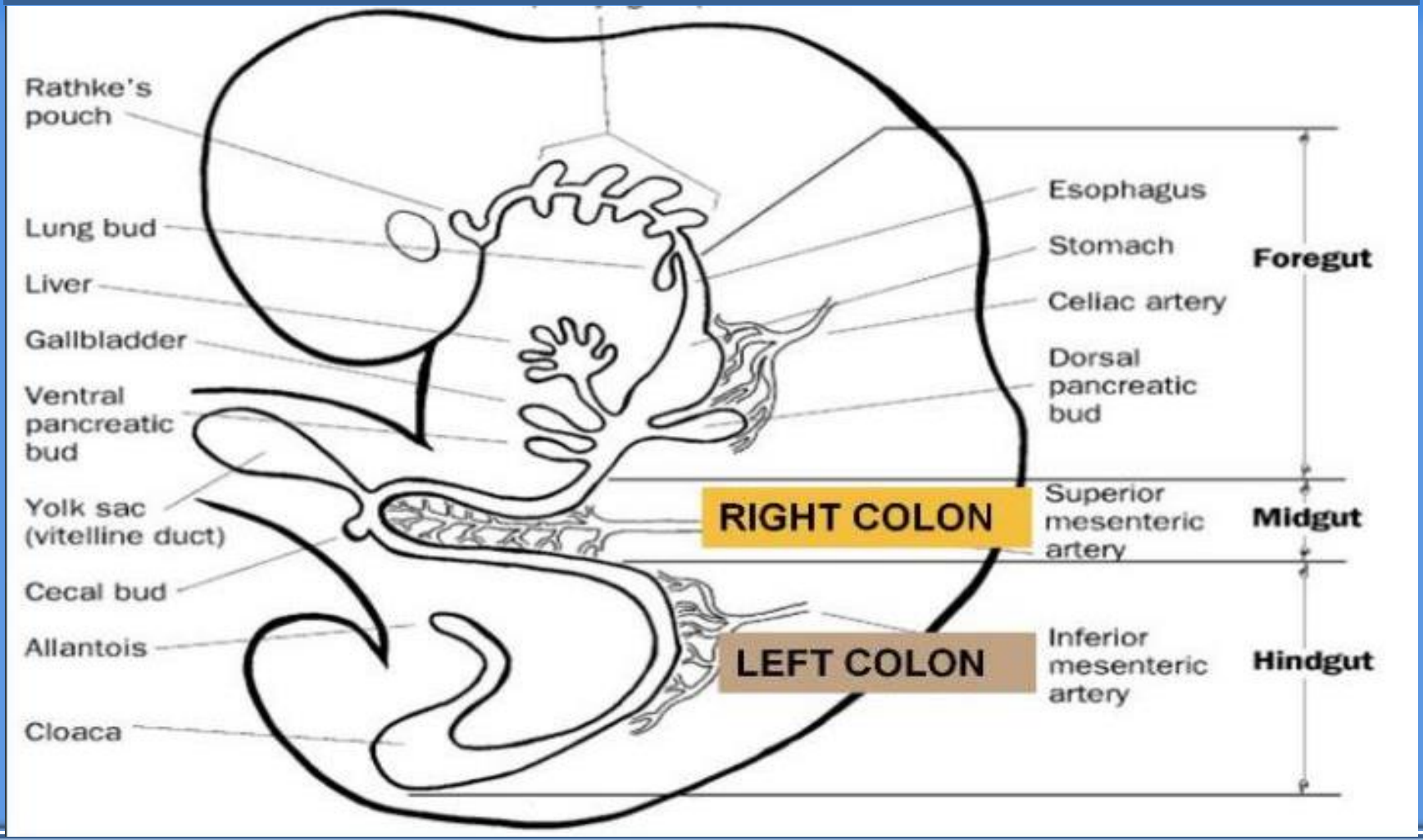
13% biofilm-positive

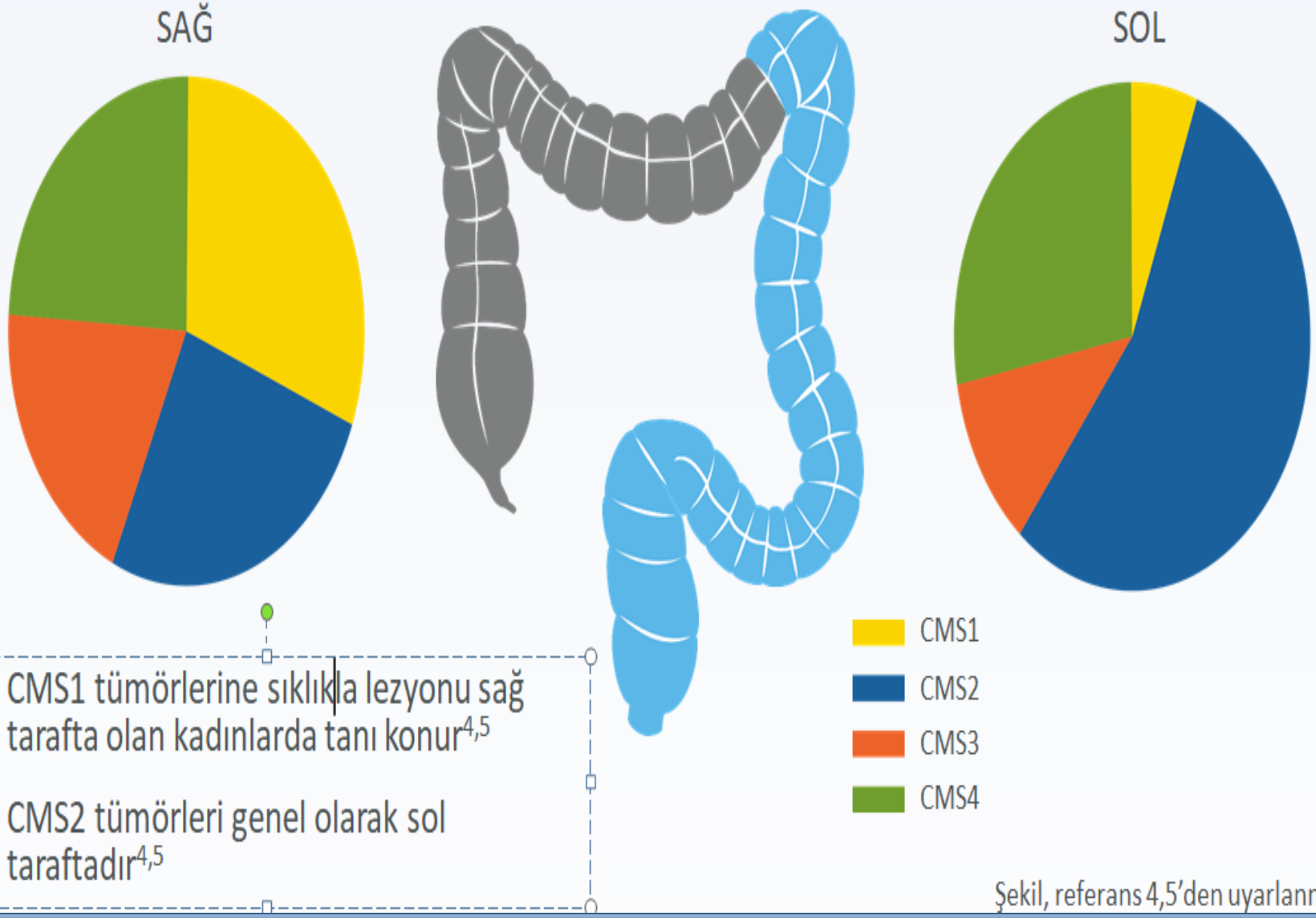
p=0.0001

Sağ kolon	Sol kolorektum
%28[4]	%72[4]



Sağ/sol kolon Embriyolojik Orijin farklı

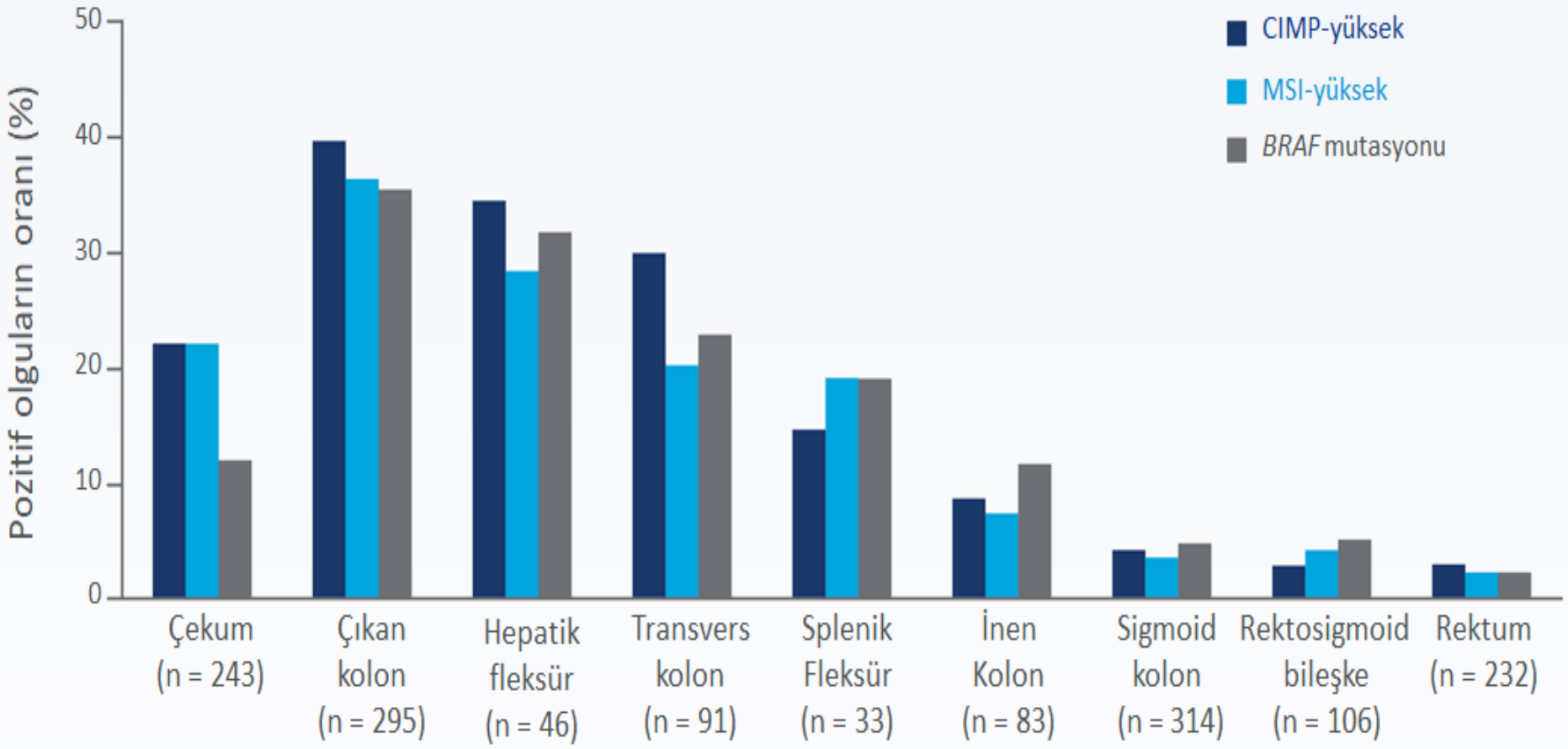




- CMS1 tümörlerine sıklıkla lezyonu sağ tarafta olan kadınlarda tanı konur[4,5]
- CMS2 tümörleri genel olarak sol taraftadır[4,5]

Şekil, referans 4,5'den uyarlanmıştı

Tümör lokalizasyonu ve moleküler özellikler

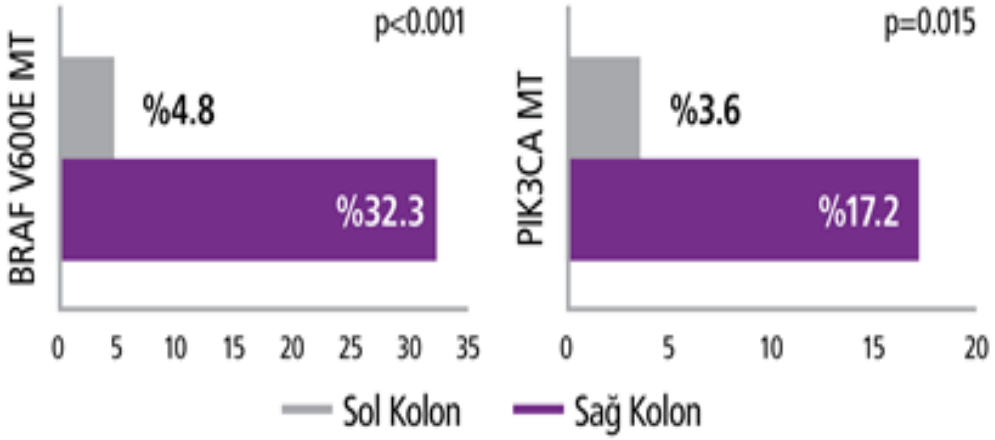


Tümör lokalizasyonu ve moleküler özellikler

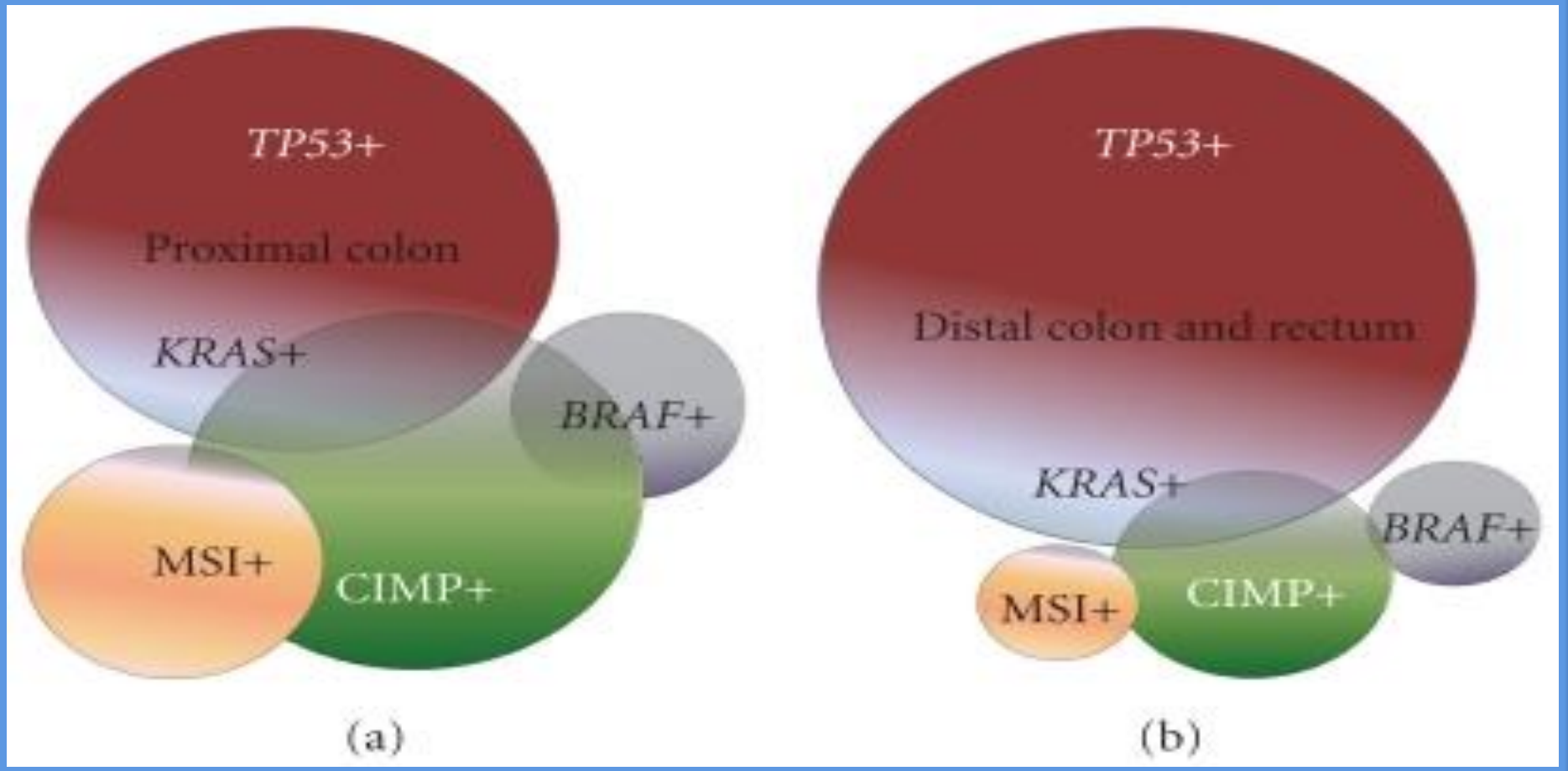
- Sağ kolon yerleşimli RAS WT tümörlerin **%57**'sinde **BRAF veya PIK3CA mutasyonu** bulunmaktadır.[1]

- BRAF V600E ve PIK3CA mutasyonu olan tümörlerin sağ kolon yerleşimli olma olasılığı, sol kolona göre yaklaşık **5-6 kat daha fazladır.**[1]

Tümör yerleşimine göre mutasyon prevalansı[1]



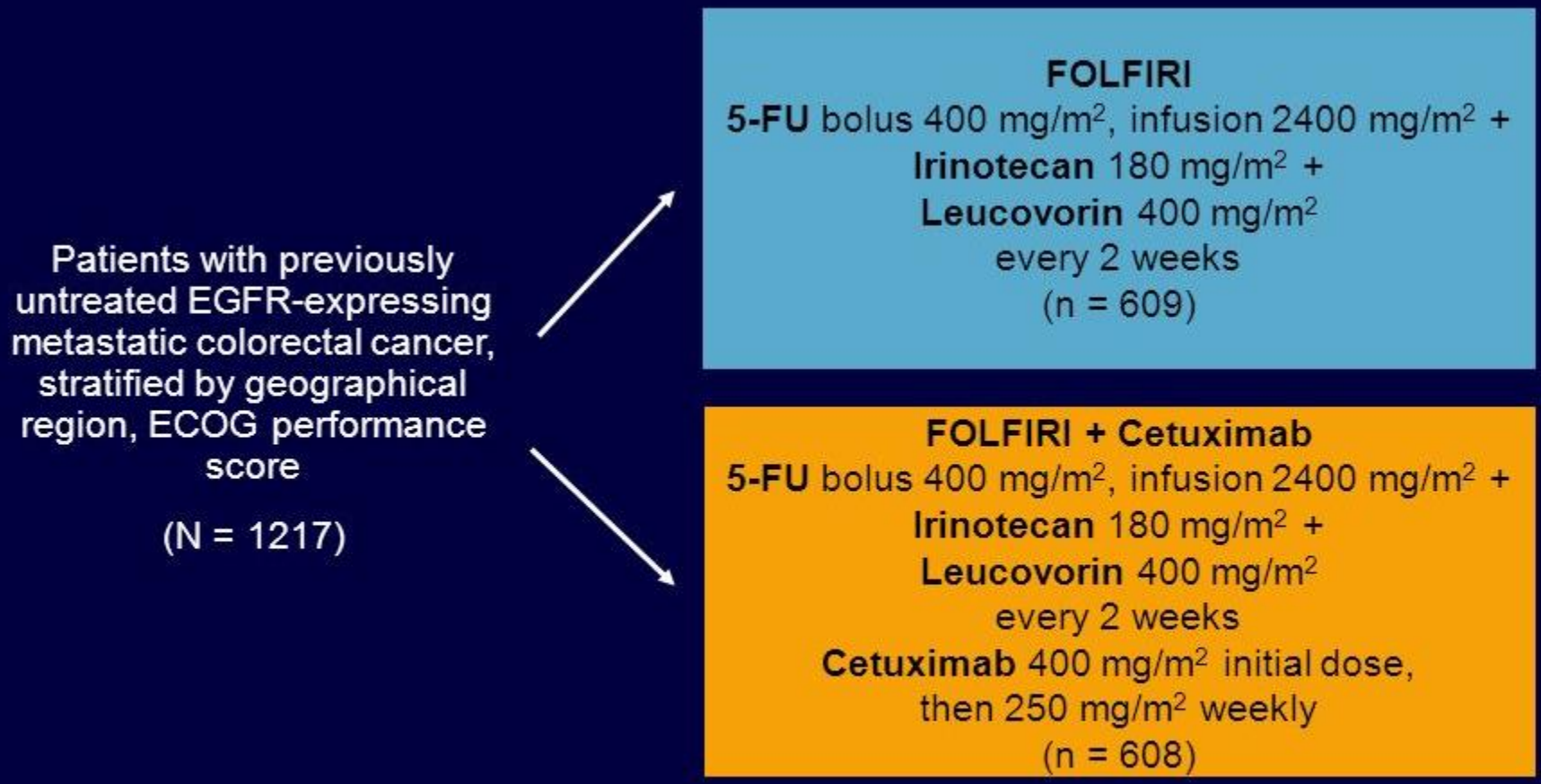
Tümör lokalizasyonu ve moleküler özellikler



- ✓ SAĞ/SOL KOLON tartışması neden tekrar gündeme geldi?
- ✓ RAS wild tip hastalarda metastatik 1. sıra tedavi seçimi

- ✓ Metastatik kolon kanserinde 1. basamakta Anti EGFR ajanların tedaviye eklenmesinin yararı var mıdır?

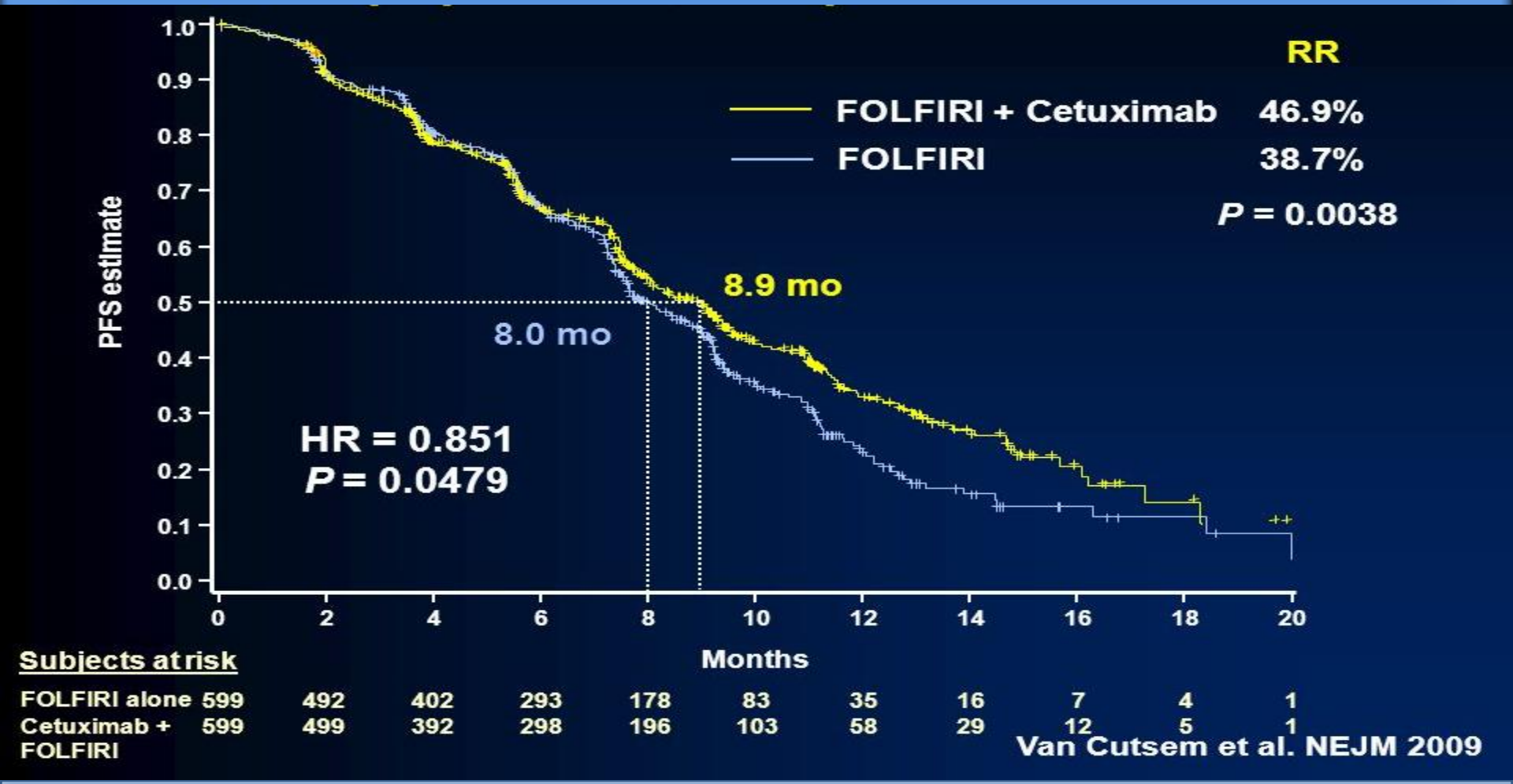
CRYSTAL çalışması



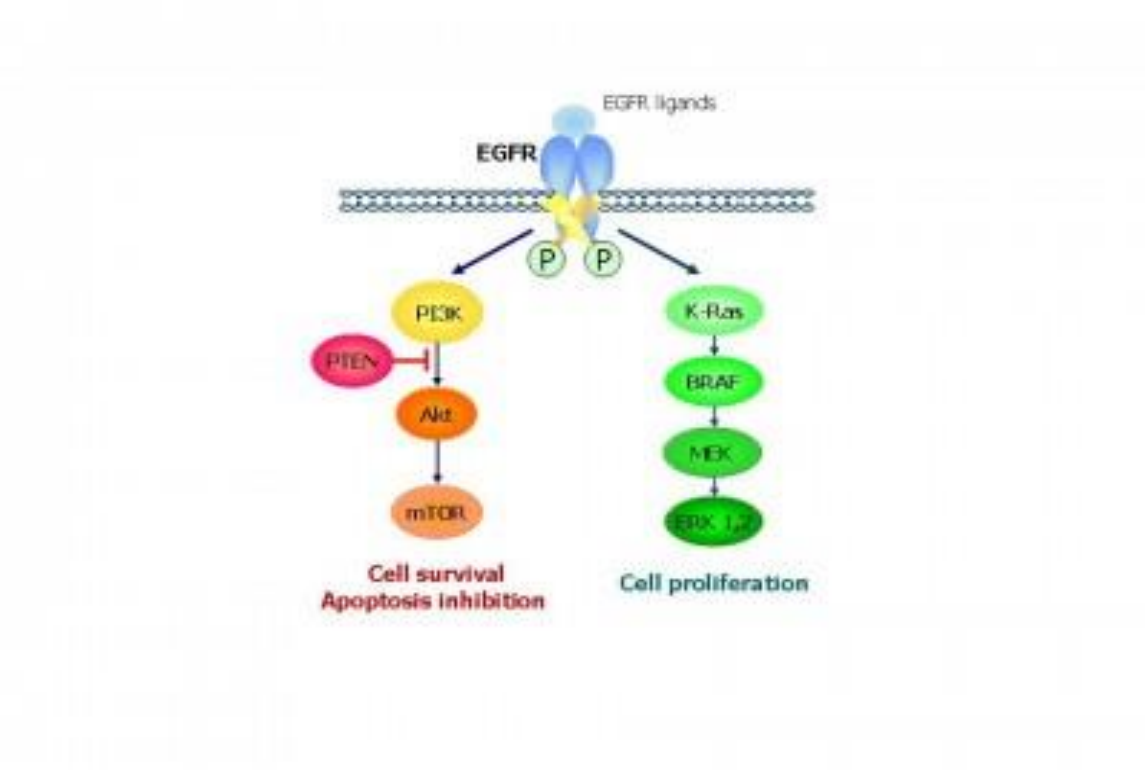
Van Cutsem E, et al. ASCO 2007. Abstract 4000.

clinicaloptions.com/oncology

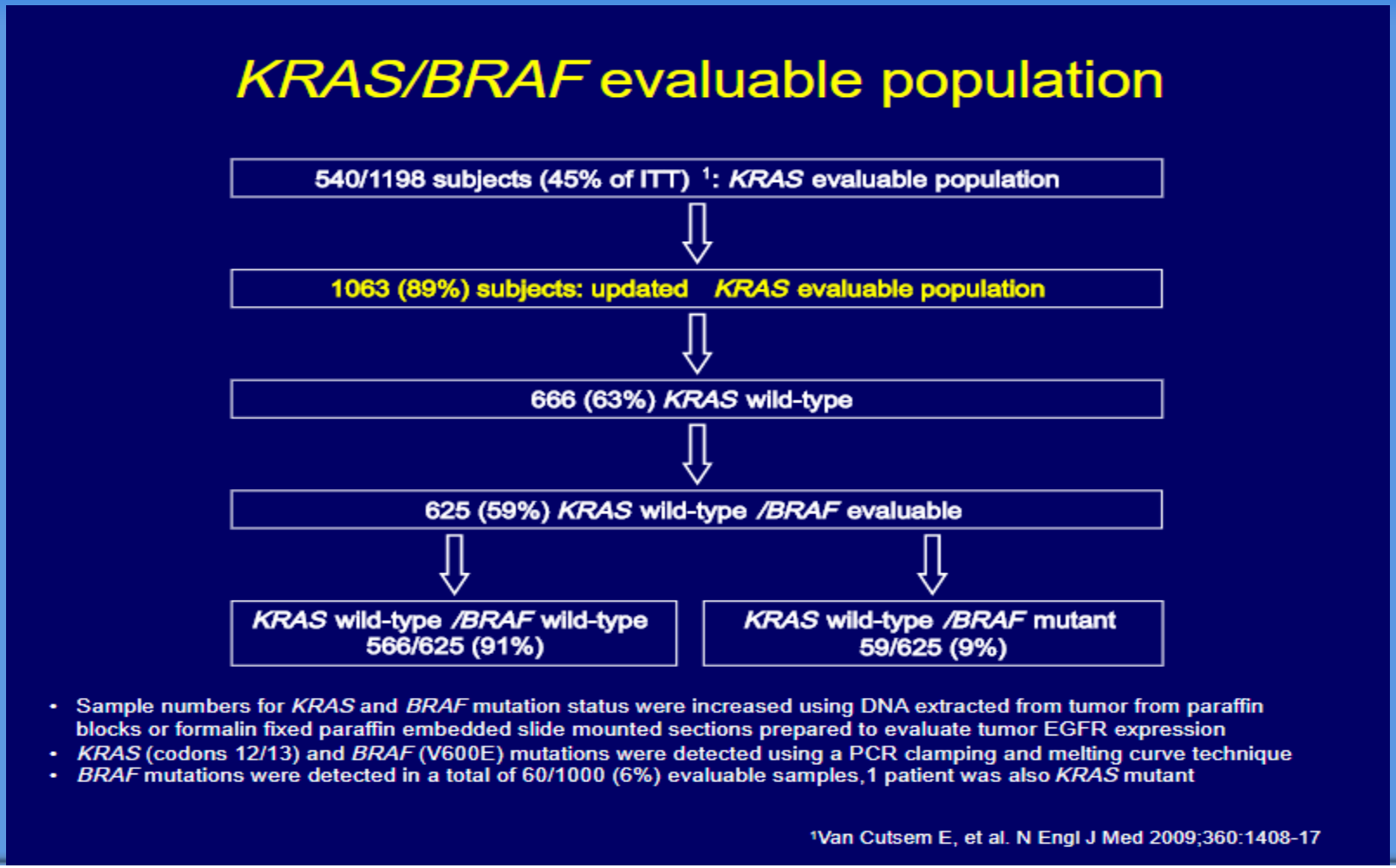
CRYSTAL çalışması



✓ K-RAS mutant hastaları dışlarsak etkin olur mu?



CRYSTAL çalışması



CRYSTAL çalışması

Response in patients with *KRAS* wild-type tumors

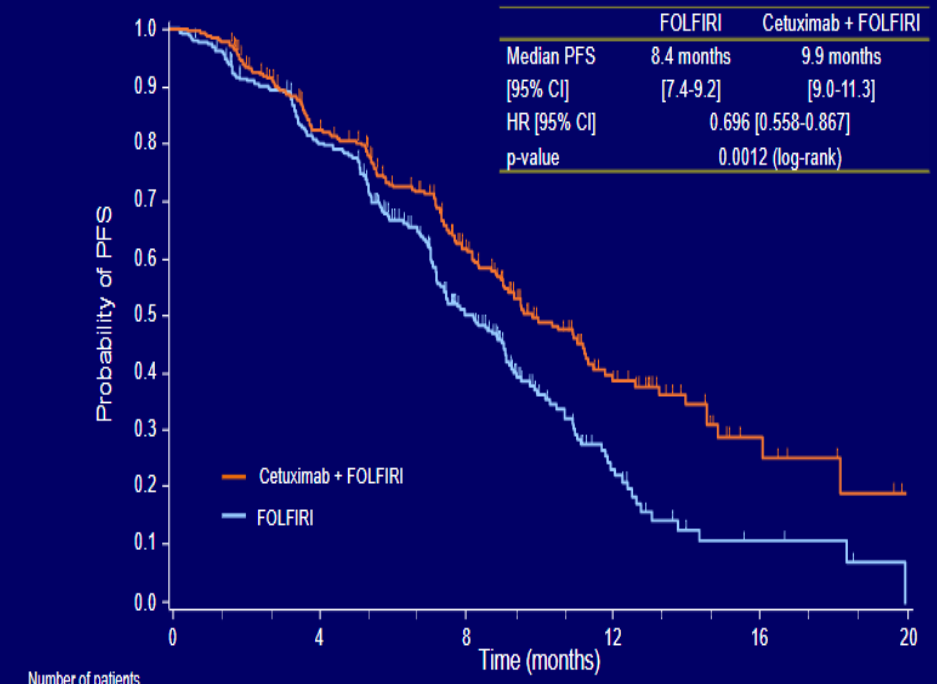
	FOLFIRI (n= 350)	Cetuximab + FOLFIRI (n= 316)
OR rate (%) [95% CI]	39.7 [34.6–45.1]	57.3 [51.6–62.8]
Odds ratio [95% CI]	2.0693 [1.5154–2.8258]	
p-value[a]	<0.0001	

[a]Cochran-Mantel-Haenszel test

CI, confidence interval; OR, best overall response

CRYSTAL çalışması

PFS in patients with *KRAS* wild-type tumors

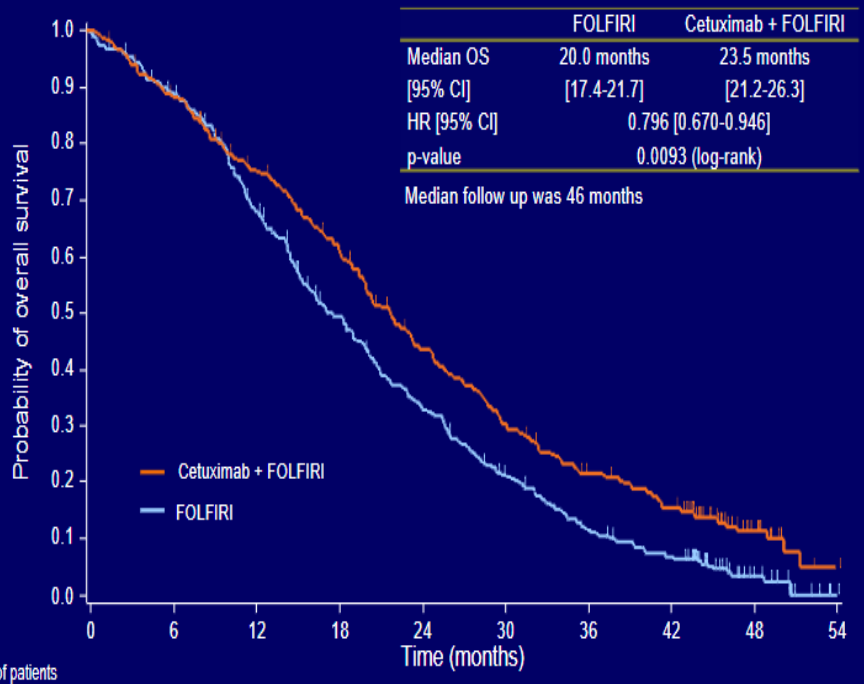


	FOLFIRI	Cetuximab + FOLFIRI
Median PFS	8.4 months	9.9 months
[95% CI]	[7.4-9.2]	[9.0-11.3]
HR [95% CI]	0.696 [0.558-0.867]	
p-value	0.0012 (log-rank)	

Number of patients						
Cetuximab + FOLFIRI	316	227	128	40	8	1
FOLFIRI	350	237	111	22	4	0

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

OS in patients with *KRAS* wild-type tumors



	FOLFIRI	Cetuximab + FOLFIRI
Median OS	20.0 months	23.5 months
[95% CI]	[17.4-21.7]	[21.2-26.3]
HR [95% CI]	0.796 [0.670-0.946]	
p-value	0.0093 (log-rank)	

Median follow up was 46 months

Number of patients										
Cetuximab + FOLFIRI	316	281	237	198	144	108	82	65	21	4
FOLFIRI	350	311	246	179	132	92	64	48	18	2

CI, confidence interval; HR, hazard ratio; OS, overall survival

PRIME
(NCT00364013)

Faz 3
1. Basamak mKRK

R

- Panitumumab + FOLFOX4
- FOLFOX4

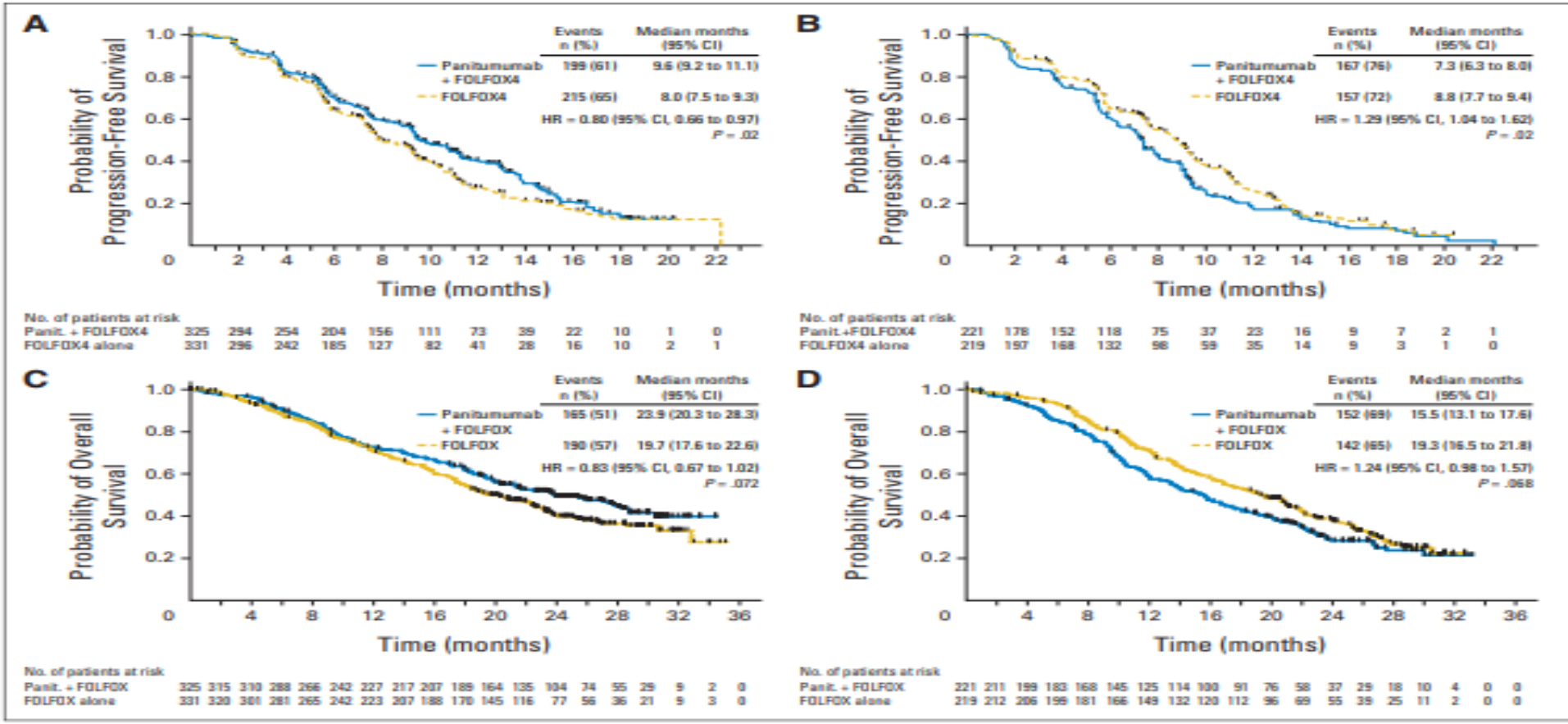


Fig 2. Progression-free survival in patients with (A) wild-type (WT) *KRAS* and (B) mutant (MT) *KRAS*. Overall survival in patients with (C) WT *KRAS* and (D) MT *KRAS*. FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; Panit., panitumumab; HR, hazard ratio.

- ✓ Anti EGFR ajanlar 1. seri tedavide KRAS wild hastalarda Anti VEGF ajanlardan üstün müdür?

PEAK[1]
(faz II)
Herhangi bir hipotez test etmemektedir

Tedavi edilmemiş, unresektabıl KRAS WT mKRK **(n=285)**

R

- Bevasizumab + mFOLFOX6 → PD
- Panitumumab + mFOLFOX6 → PD

FIRE-3[2]
(faz III)
primer sonlanım noktası: **ORR**

Tedavi edilmemiş, unresektabıl KRAS WT mKRK **(n=592)**

R

- Bevasizumab + FOLFIRI → PD
- Setuksimab + FOLFIRI → PD

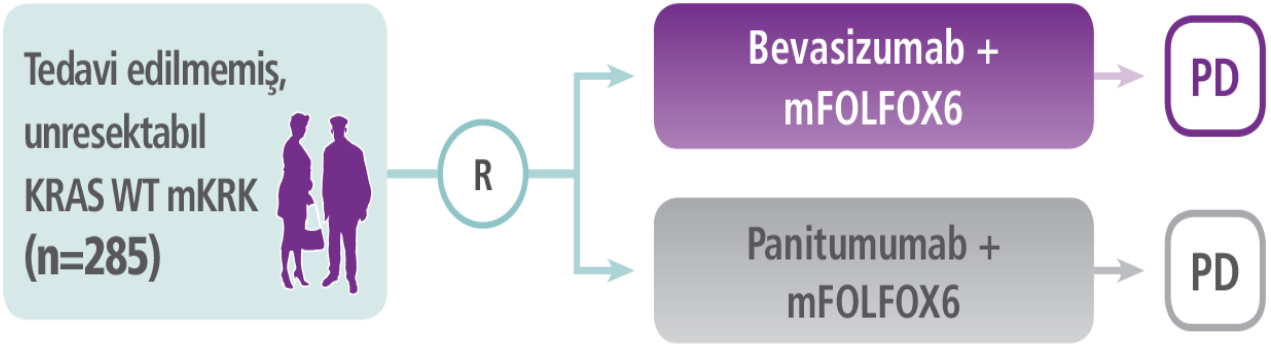
CALGB 80405[3]
(faz III)
primer sonlanım noktası: **OS**

Tedavi edilmemiş, unresektabıl KRAS WT mKRK **(n=1,137)**

R

- Bevasizumab + FOLFOX veya FOLFIRI → PD
- Setuksimab + FOLFOX veya FOLFIRI → PD

PEAK[1]
(faz II)
Herhangi bir hipotez test etmemektedir



WT KRAS ekson 2 ITT grubu[1]

	Bevasizumab + mFOLFOX6 (n=143)	Panitumumab + mFOLFOX6 (n=142)
PFS olayları, n (%)	94 (%66)	90 (%63)
Medyan PFS, ay (%95 GA)	**10.1** (9 - 12.6)	**10.9** (9.4 - 13)
HR (%95 GA)	0.87 (0.65 - 1.17) p=0.353	
ORR, (%) (%95 GA)	57.8 (49.2 - 66)	53.5 (45 - 61.9)
OS olayları, n (%)	78 (%55)	52 (%37)
Medyan OS, ay (%95 GA)	24.3 (21 - 29.2)	34.2 (26.6 - NR)
HR (%95 GA)	0.62 (0.44 - 0.89) p=0.009	

NR: ulaşılamamıştır.

Schwarzberg LS ve ark. J Clin Oncol. 2014 Jul 20;32(21):2240-7.

FIRE-3[2]
(faz III)
primer sonlanım noktası: **ORR**

Tedavi edilmemiş, unresektabıl KRAS WT mKRK **(n=592)**

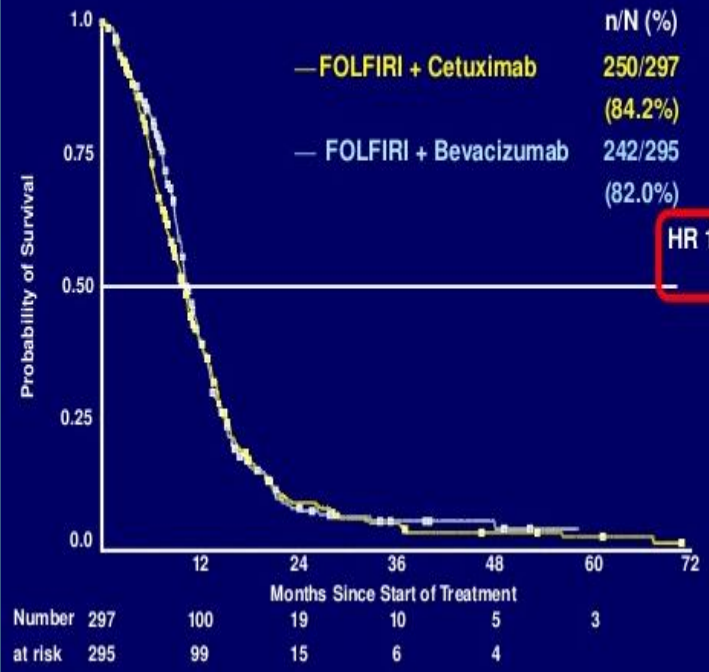
R

- Bevasizumab + FOLFIRI → PD
- Setuksimab + FOLFIRI → PD

FIRE-3 PFS:

	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	250/297 (84.2%)	10.0	8.8 – 10.8
— FOLFIRI + Bevacizumab	242/295 (82.0%)	10.3	9.8 – 11.3

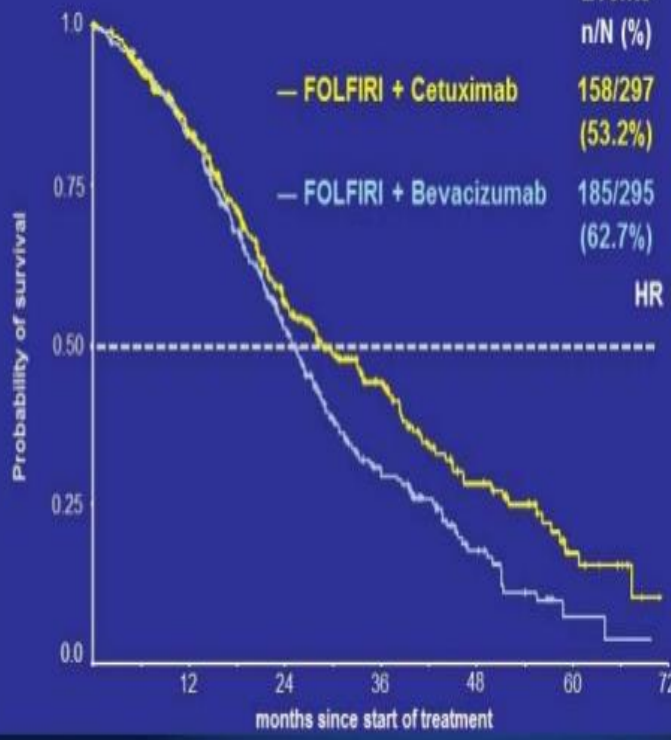
HR 1.06 (95% CI 0.88 – 1.26)
Log-rank *P*= .547



Heinemann V, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract LBA3506.

	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	158/297 (53.2%)	28.7	24.0 – 36.6
— FOLFIRI + Bevacizumab	185/295 (62.7%)	25.0	22.7 – 27.6

HR 0.77 (95% CI: 0.62 – 0.96)
Log-rank p= 0.017



Heinemann V. ASCO 2013. Abstract LBA3506.

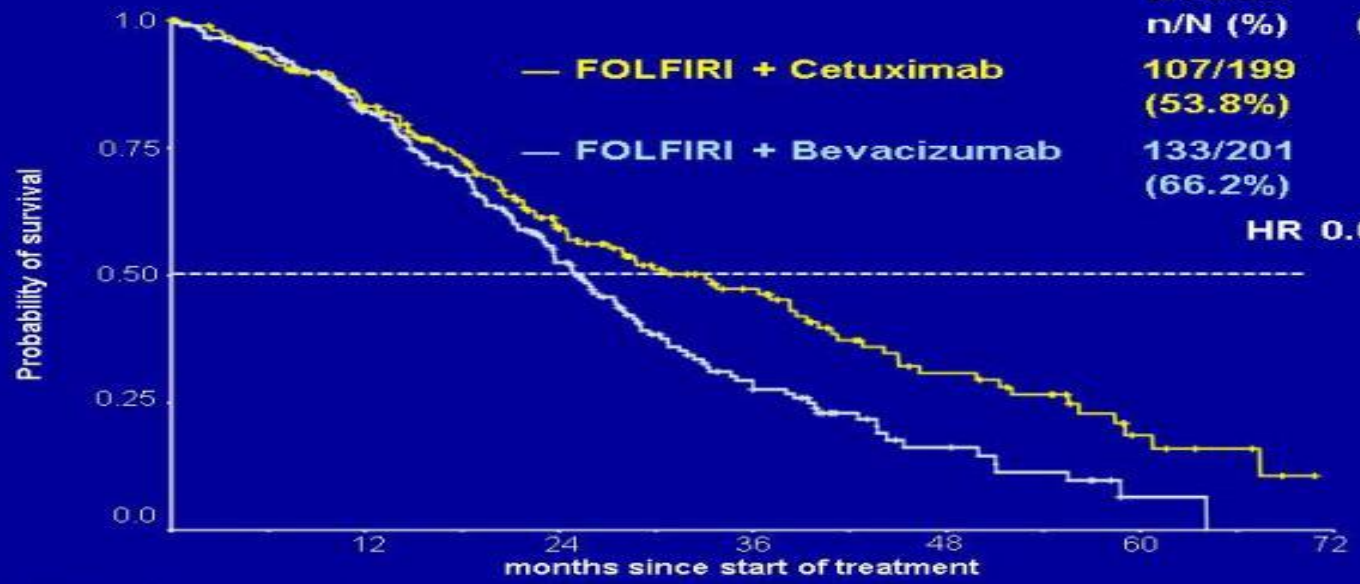
FIRE-3[2]
(faz III)
primer sonlanım noktası: **ORR**

Tedavi edilmemiş, unresektabıl KRAS WT mKRK (n=592)

R

- Bevasizumab + FOLFIRI → PD
- Setuksimab + FOLFIRI → PD

Overall survival
Final RAS* wild-type population



	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	107/199 (53.8%)	33.1	24.5 – 39.4
— FOLFIRI + Bevacizumab	133/201 (66.2%)	25.0	23.0 – 28.1

HR 0.697 (95% CI: 0.54 – 0.90)
p (log-rank)= 0.0059

No. at risk	199	147	79	46	23	7
	201	147	82	34	11	1

* KRAS and NRAS exon 2, 3 and 4 wild-type

CALGB 80405[3]
(faz III)
primer sonlanım noktası: **OS**

Tedavi edilmemiş, unresektabıl KRAS WT mKRK **(n=1,137)**

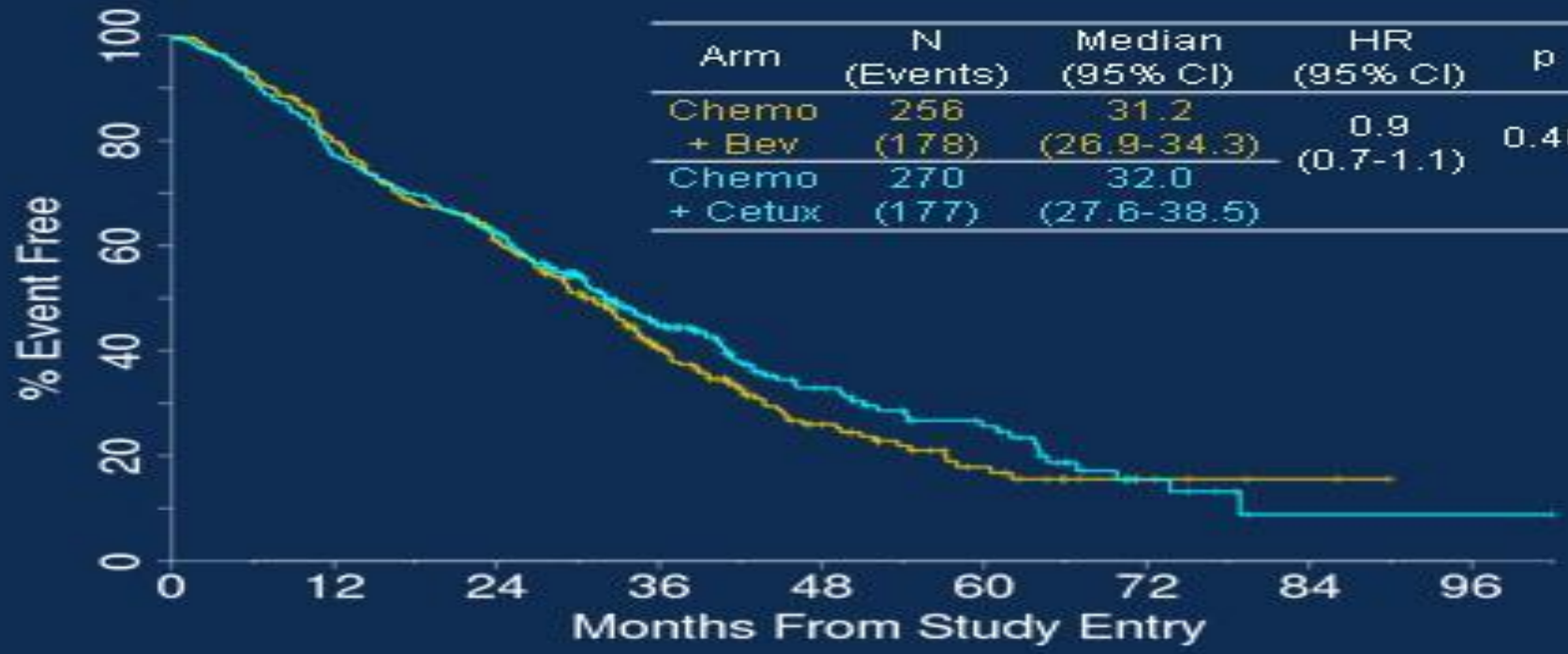
R

Bevasizumab + FOLFOX veya FOLFIRI → PD

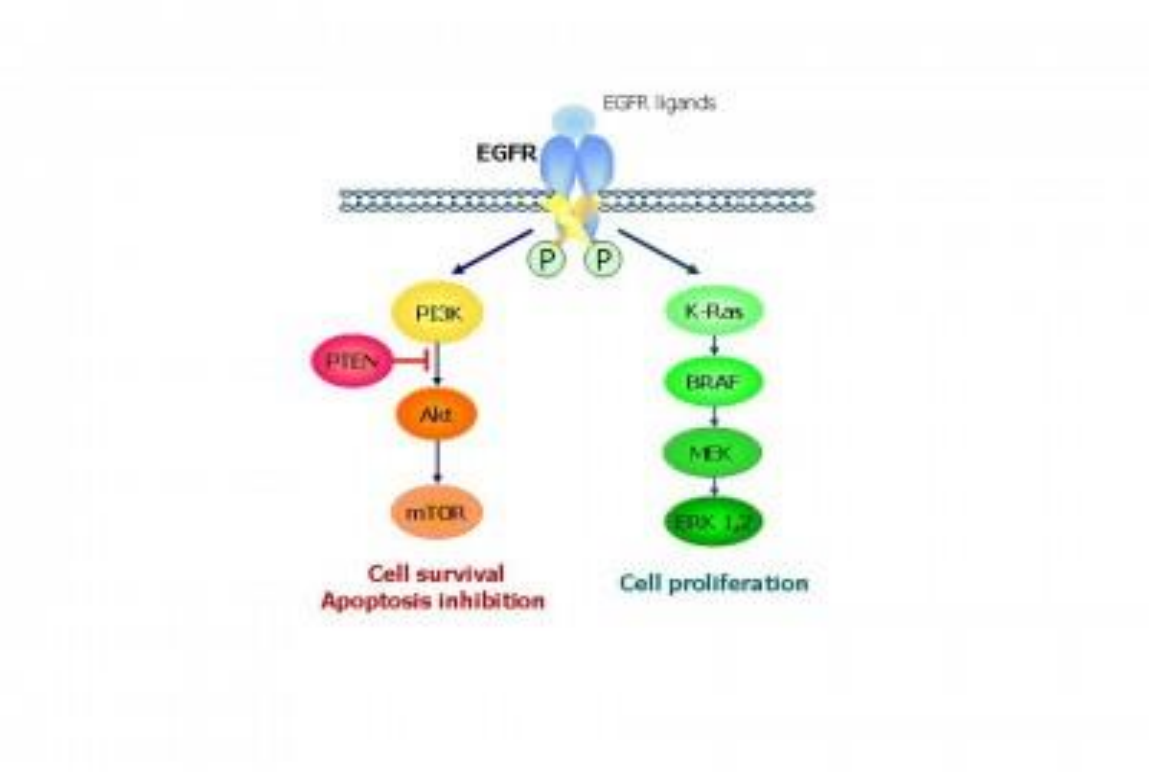
Setuksimab + FOLFOX veya FOLFIRI → PD

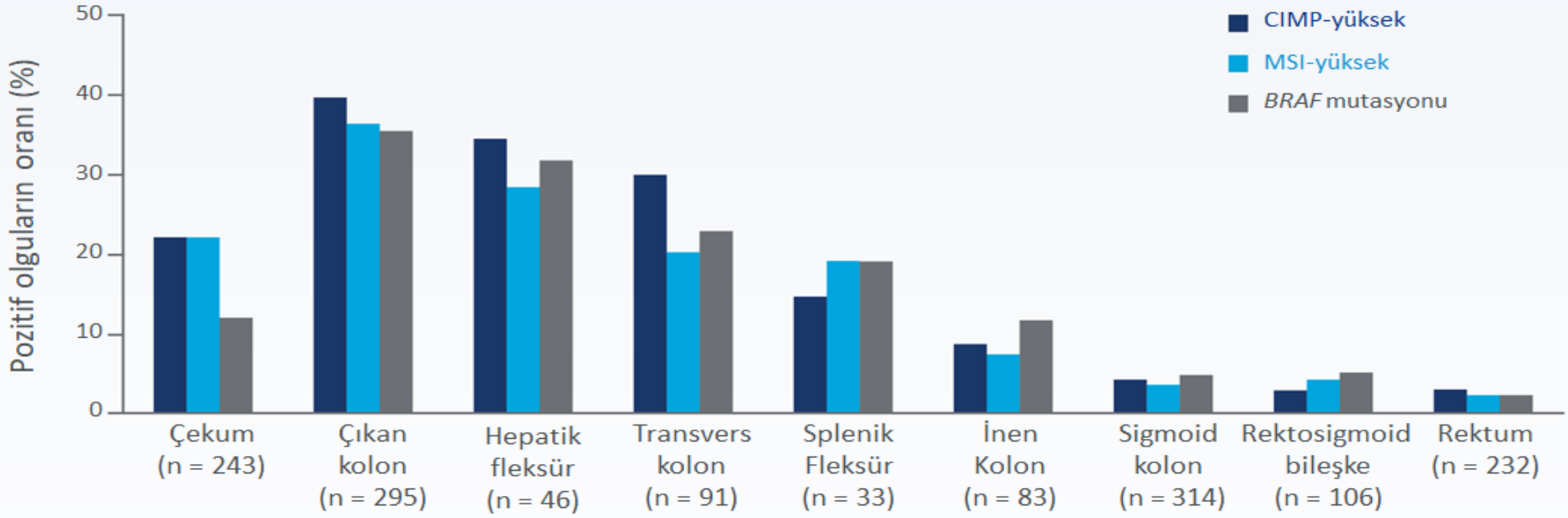
Overall Survival By Arm
(All RAS Wild Type Patients)

Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	256 (178)	31.2 (26.9-34.3)	0.9 (0.7-1.1)	0.40
Chemo + Cetux	270 (177)	32.0 (27.6-38.5)		



- ✓ Tümör yerleşim yerinin AntiEGFR vs AntiVEGF kararı vermede katkısı?

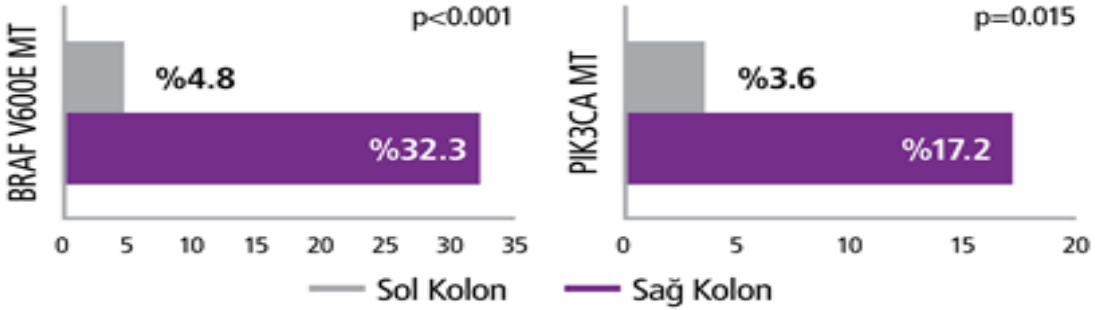




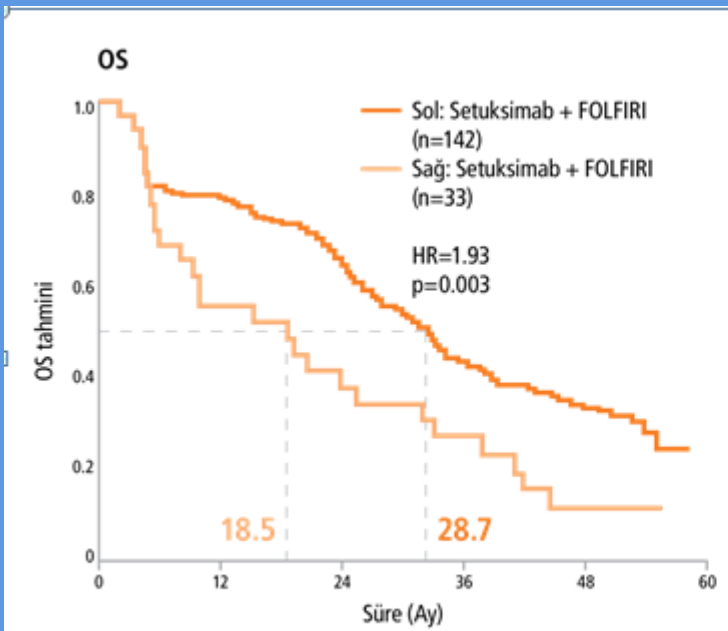
- Sağ kolon yerleşimli RAS WT tümörlerin **%57**'sinde **BRAF veya PIK3CA mutasyonu** bulunmaktadır.[1]

- BRAF V600E ve PIK3CA mutasyonu olan tümörlerin sağ kolon yerleşimli olma olasılığı, sol kolona göre yaklaşık **5-6 kat daha fazladır.**[1]

Tümör yerleşimine göre mutasyon prevalansı[1]

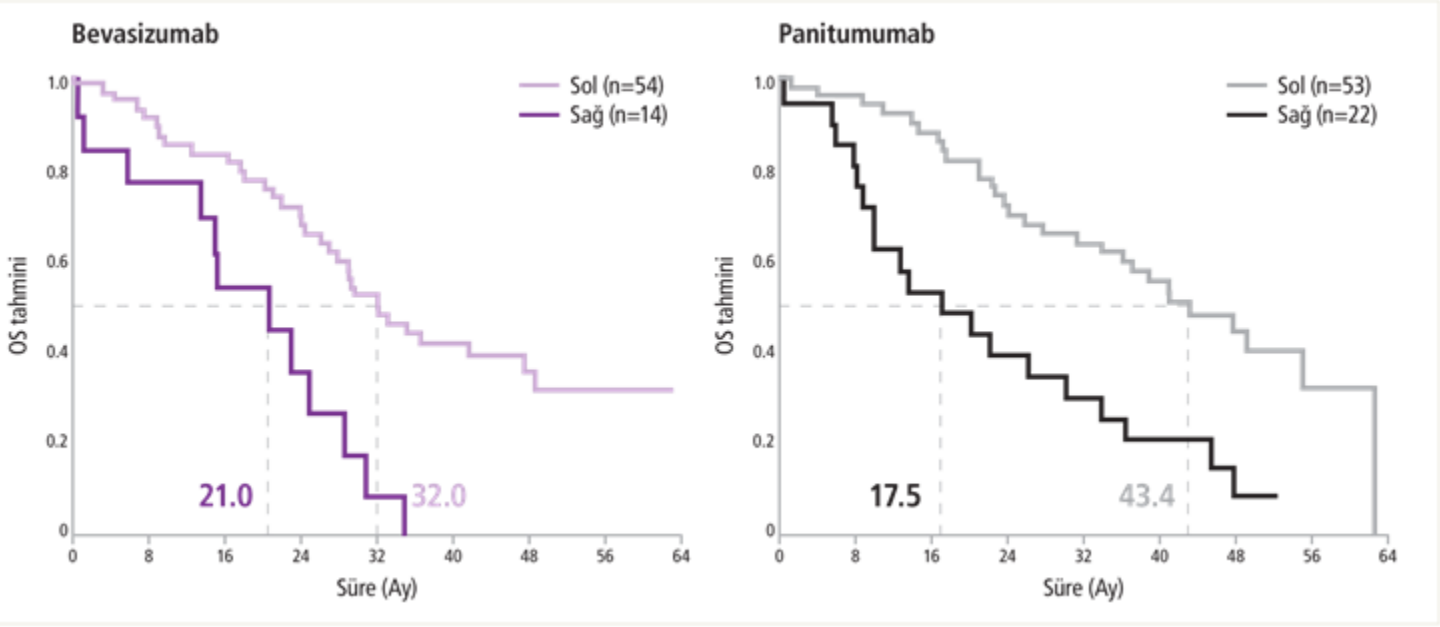


CRYSTAL: Tüm RAS WT Hastalar

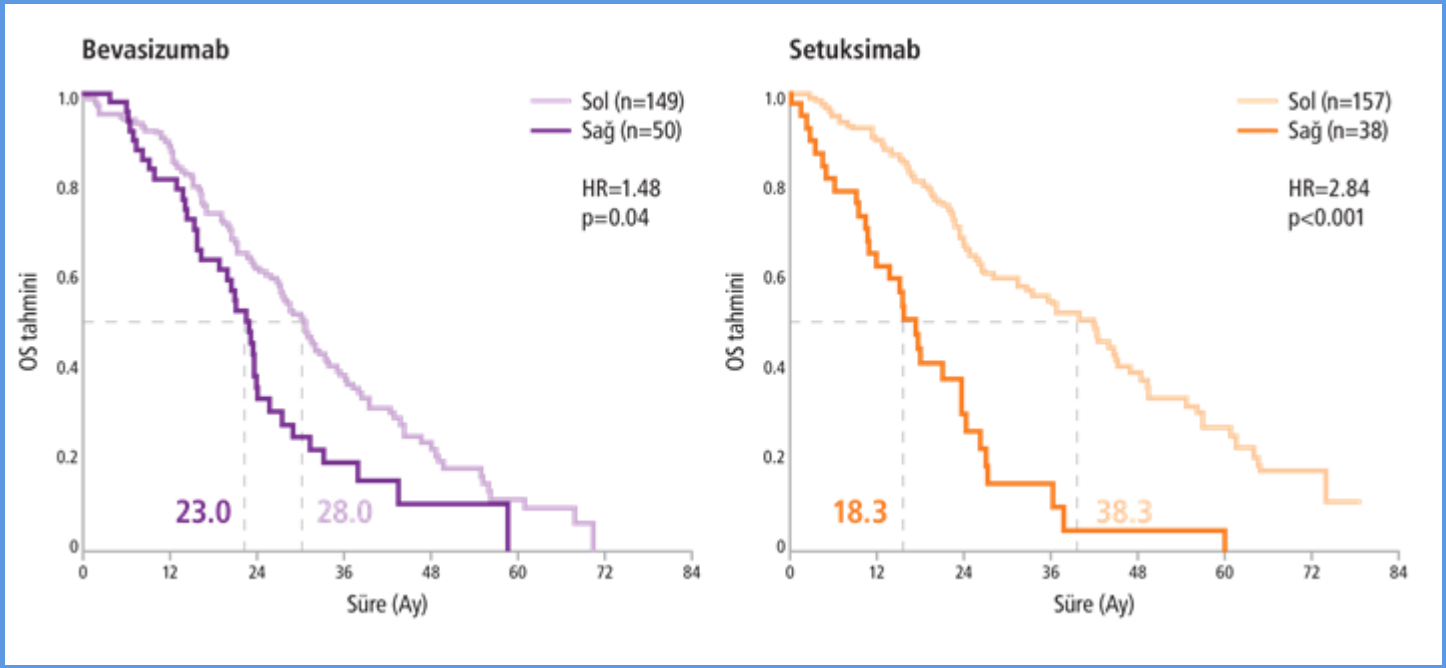


	Setuksimab + FOLFIRI	FOLFIRI	HR (95% GA)
Medyan PFS, Ay			
Sol kolon yerleşimli tümör	12.0	8.9	0.50 (0.34–0.72)
Sağ kolon yerleşimli tümör	8.1	7.1	0.87 (0.47–1.62)
Medyan OS, Ay			
Sol kolon yerleşimli tümör	28.7	21.7	0.65 (0.50–0.86)
Sağ kolon yerleşimli tümör	18.5	15.0	1.08 (0.65–1.81)

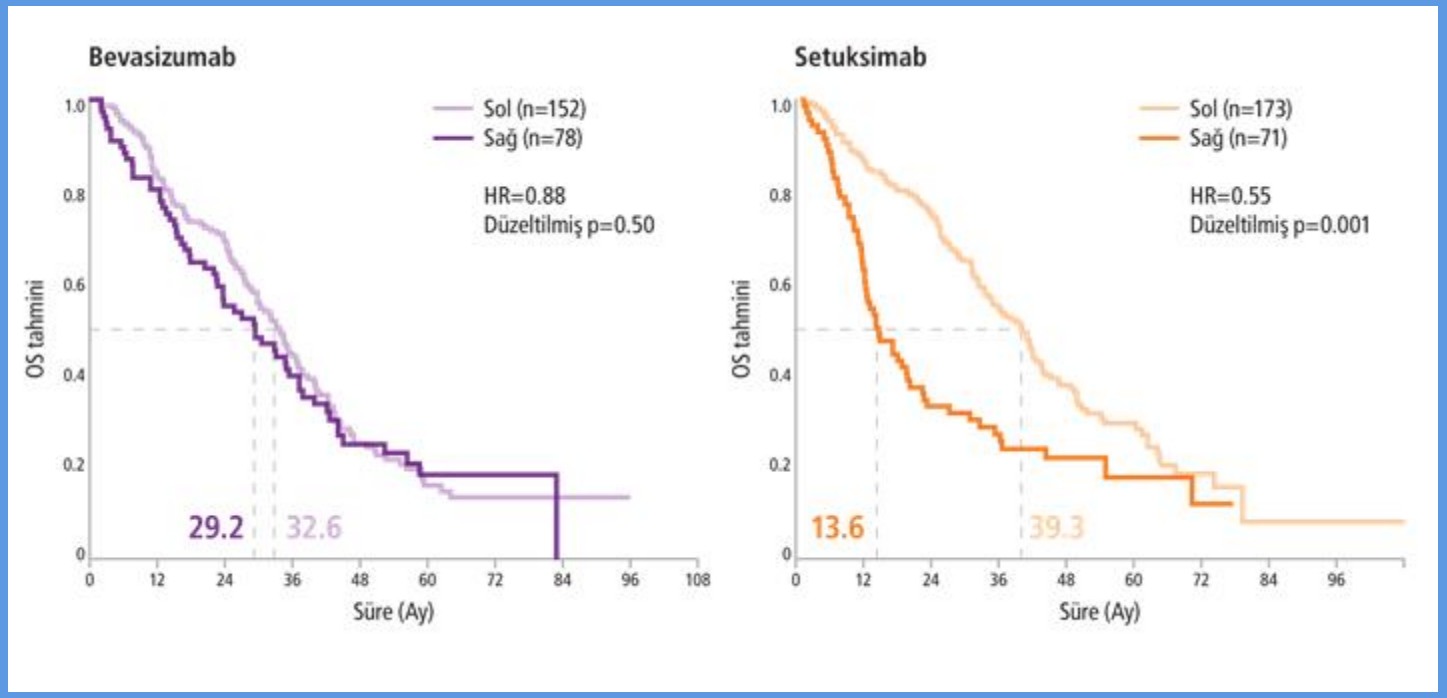
PEAK:RAS WT Hastalar



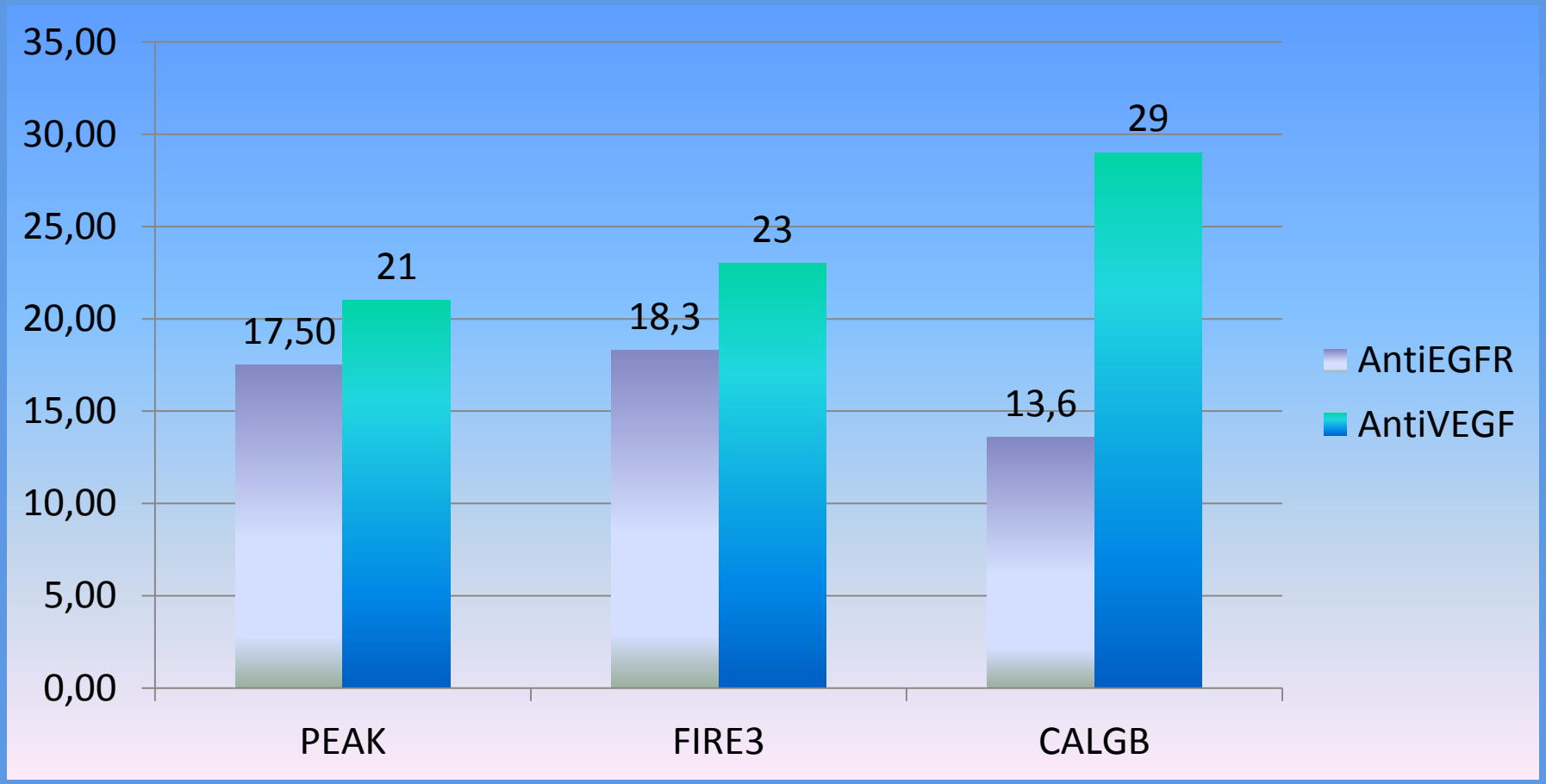
FIRE-3:RAS WT Hastalarda



CALGB:RAS WT Hastalar



Sağ Kolon OS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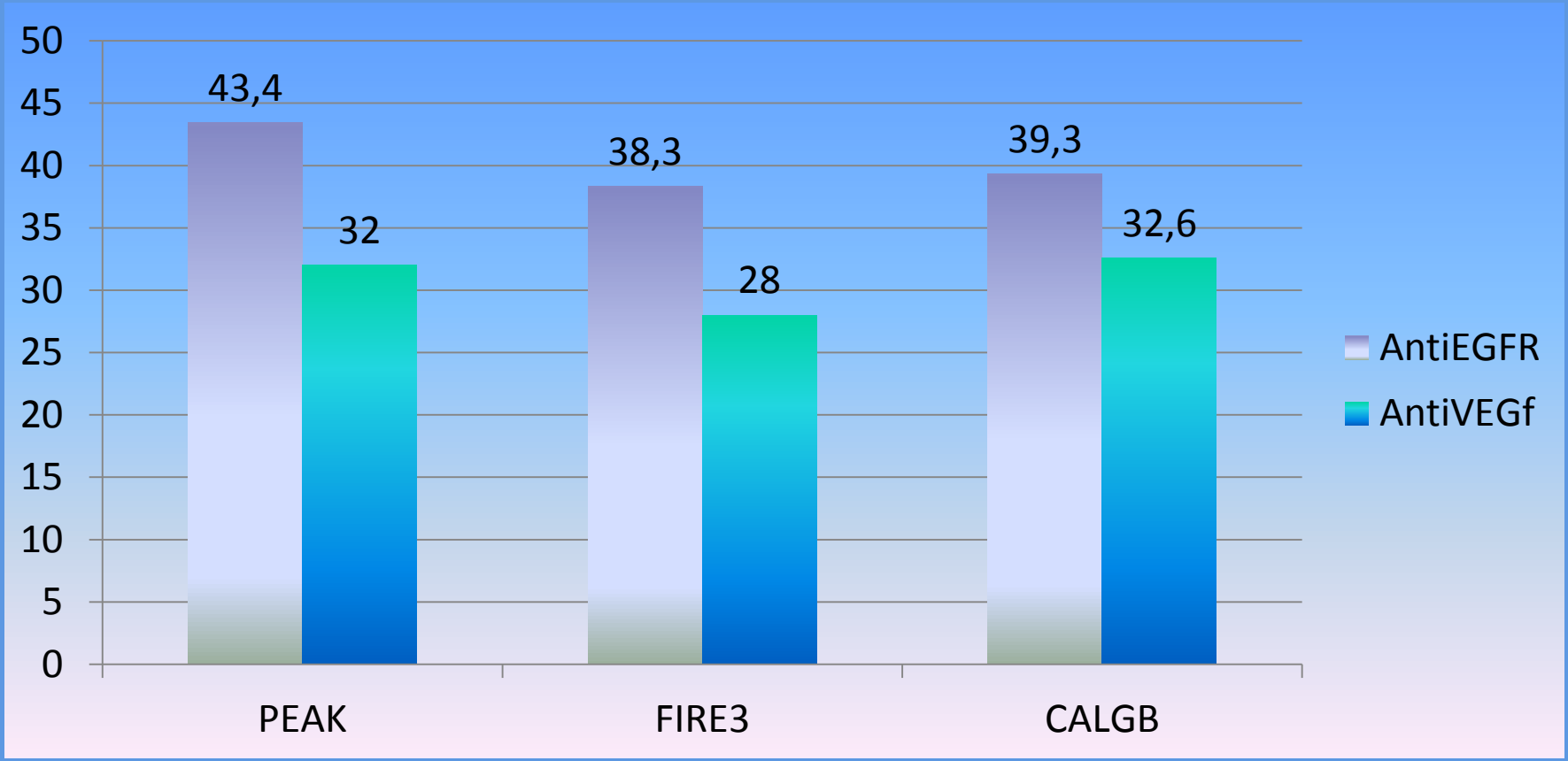
PEAK
FIRE3
CALGB
AntiEGFR
AntiVEGF

Sol Kolon OS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32,6
PEAK
FIRE3
CALGB
AntiEGFR
AntiVEGf

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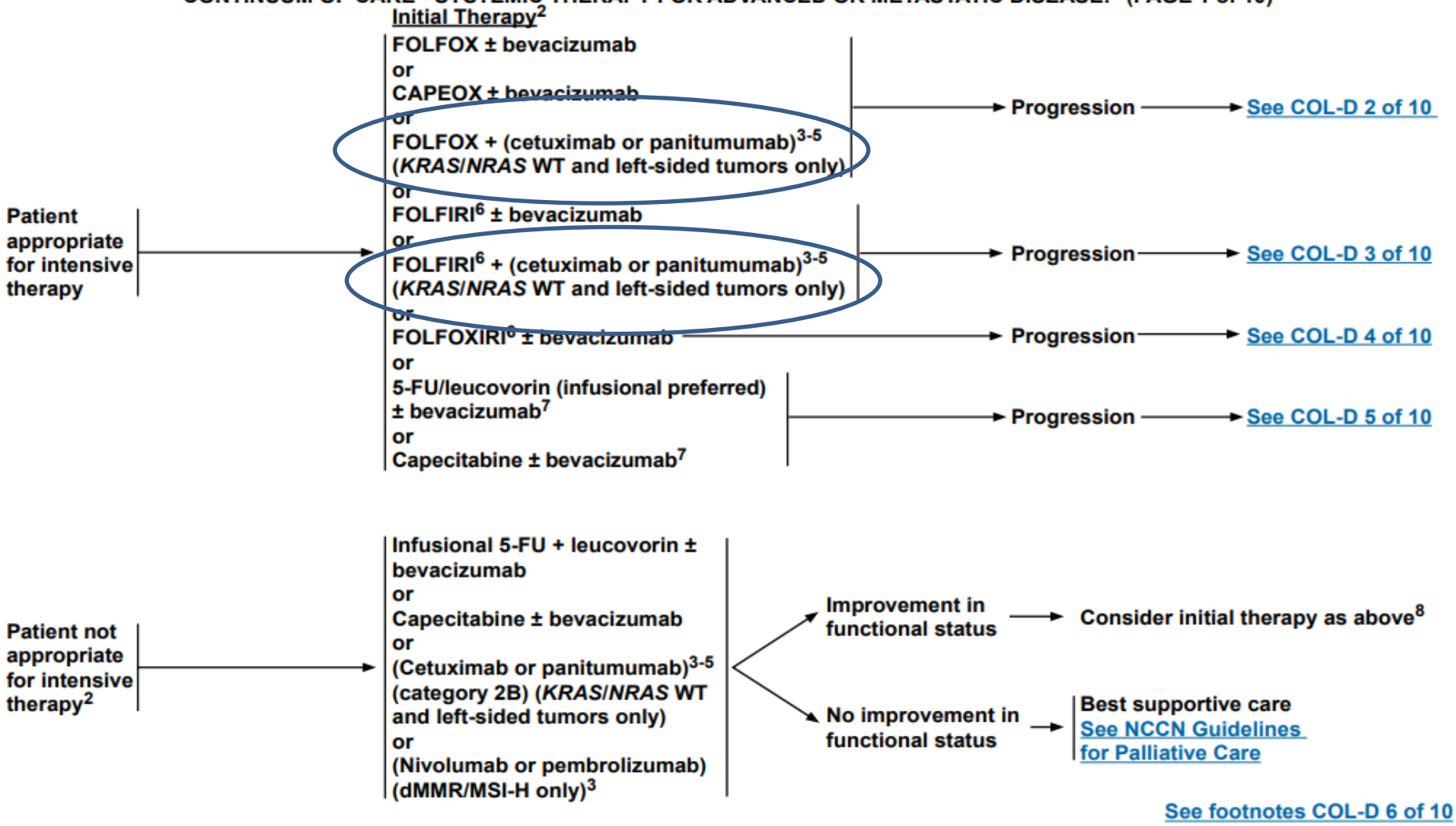
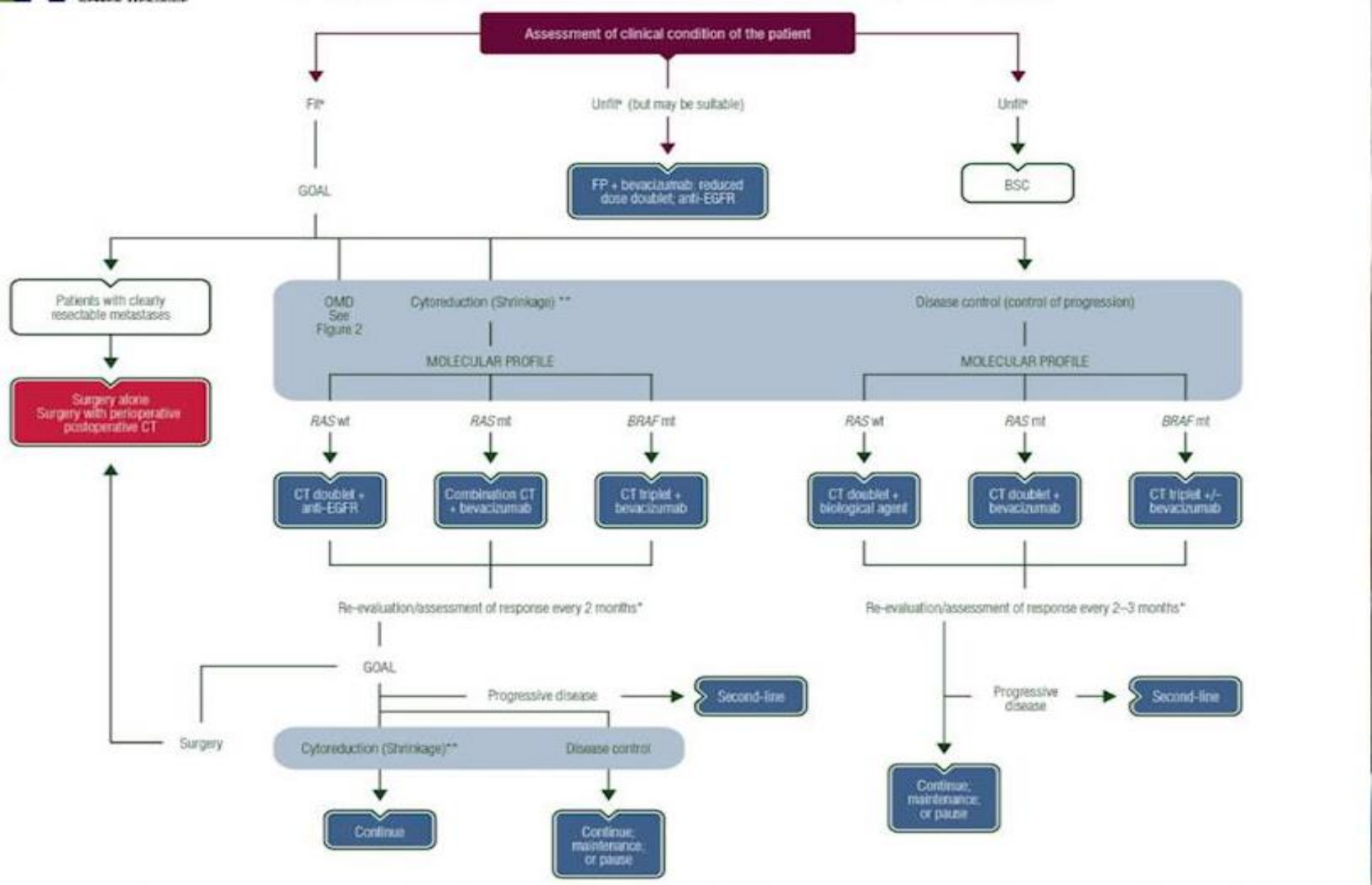
NCCN Guidelines Version 1.2018
Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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



See footnotes COL-D 6 of 10



Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016; Online Ann Oncol, July 2016

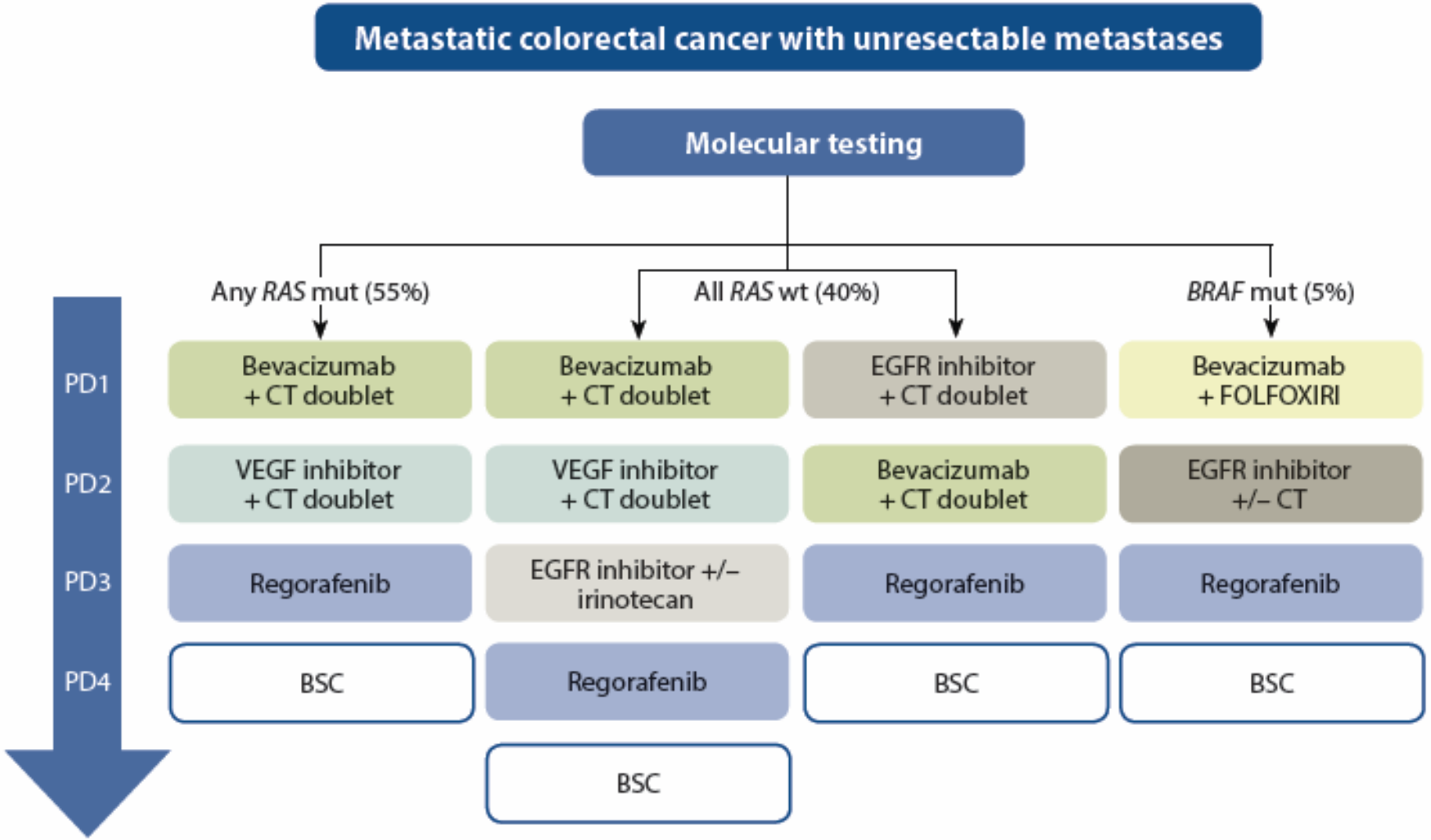
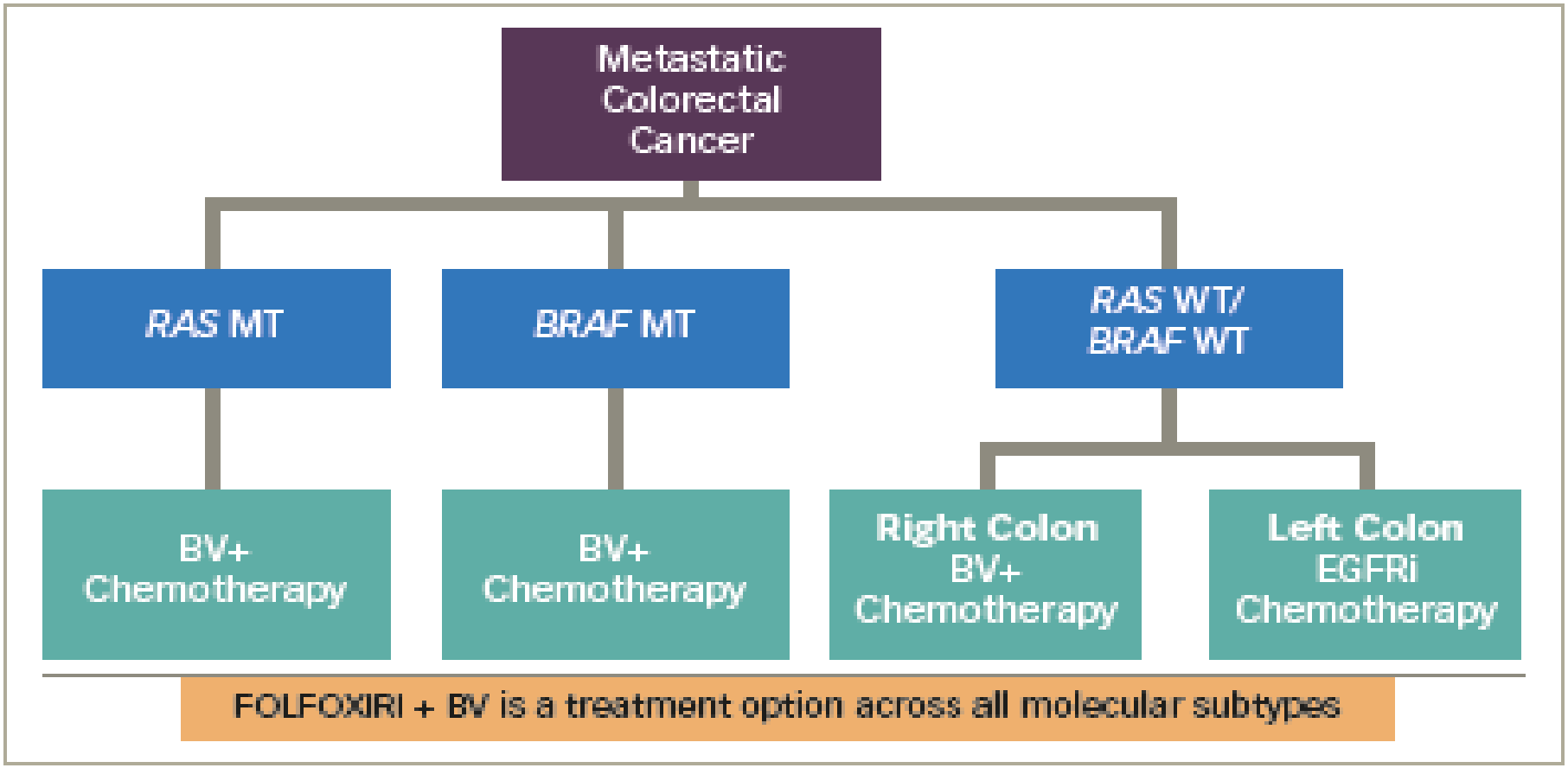


Figure 3: Treatment Algorithm for the Practical Medical Management of mCRC Based on Clinically Relevant Molecular Testing—BSC = best supportive care; CT = chemotherapy; EGFR = epidermal growth factor receptor; mCRC = metastatic colorectal cancer; mut = mutated; PD = progressive disease; VEGF = vascular endothelial growth factor; VEGF inhibitor = bevacizumab or aflibercept; wt = wild-type.

Figure 1: First-line treatment algorithm in good performance patients with metastatic colorectal cancer



MT = mutated; WT = wild-type; BV = bevacizumab; EGFRi = epidermal growth factor receptor inhibitor (cetuximab or panitumumab); FOLFOXIRI = folinic acid, fluorouracil, oxaliplatin, irinotecan.

ASCO GI 2018

Colorectal cancer molecular classification using BRAF, KRAS, microsatellite instability, and CIMP status: Prognostic implications and response to chemotherapy.

Presented Saturday, January 20, 2018

Molecular subtype assay to reveal anti-EGFR response sub-clones in colorectal cancer (CRC).

Presented Saturday, January 20, 2018

Impact of primary tumor side (TS) on outcomes of once-every-2-weeks (q2w) cetuximab + first-line (1L) FOLFOX or FOLFIRI in patients with *RAS* wild-type (wt) metastatic colorectal cancer (mCRC) in the phase 2 APEC trial.

Presented Saturday, January 20, 2018

Gençlerle Onkolojiye Bakış Kongresi, 17.2.18, Antalya

TEŞEKKÜRLER

Gençlerle Onkolojiye Bakış Kongresi, 17.2.18, Antalya