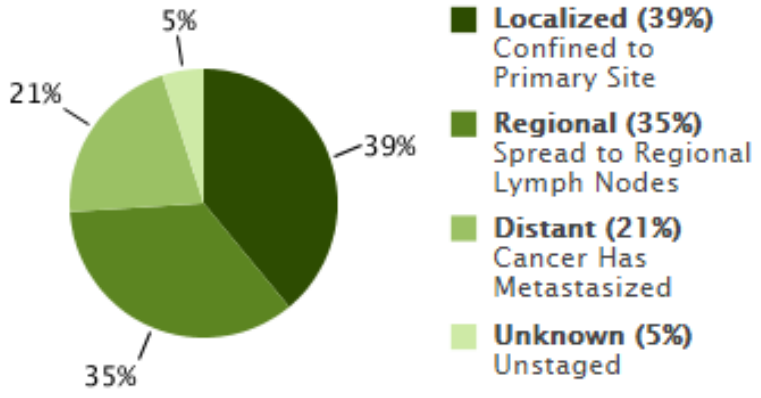
Metastatik Kolon Kanserinde Birinci Basamak Tedavi Seçenekleri

Dr. Deniz Tural
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

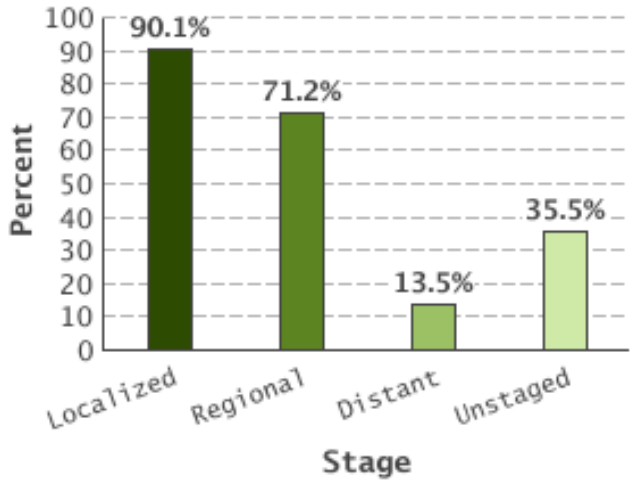
Kolon Kanseri İnsidans ve Mortalite

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

Metastatik Kolon Kanseri

- Kolon kanseri tanısı alan hastaların %50-60 oranında metastaz gelişir
- Metastazın %80-90 unrezektable karaciğer metastazı şeklinde olur
- Sıklıkla metakron metastaz şeklinde, senkron metastaz %20-34 oluşturur, daha kötü prognoza sahip

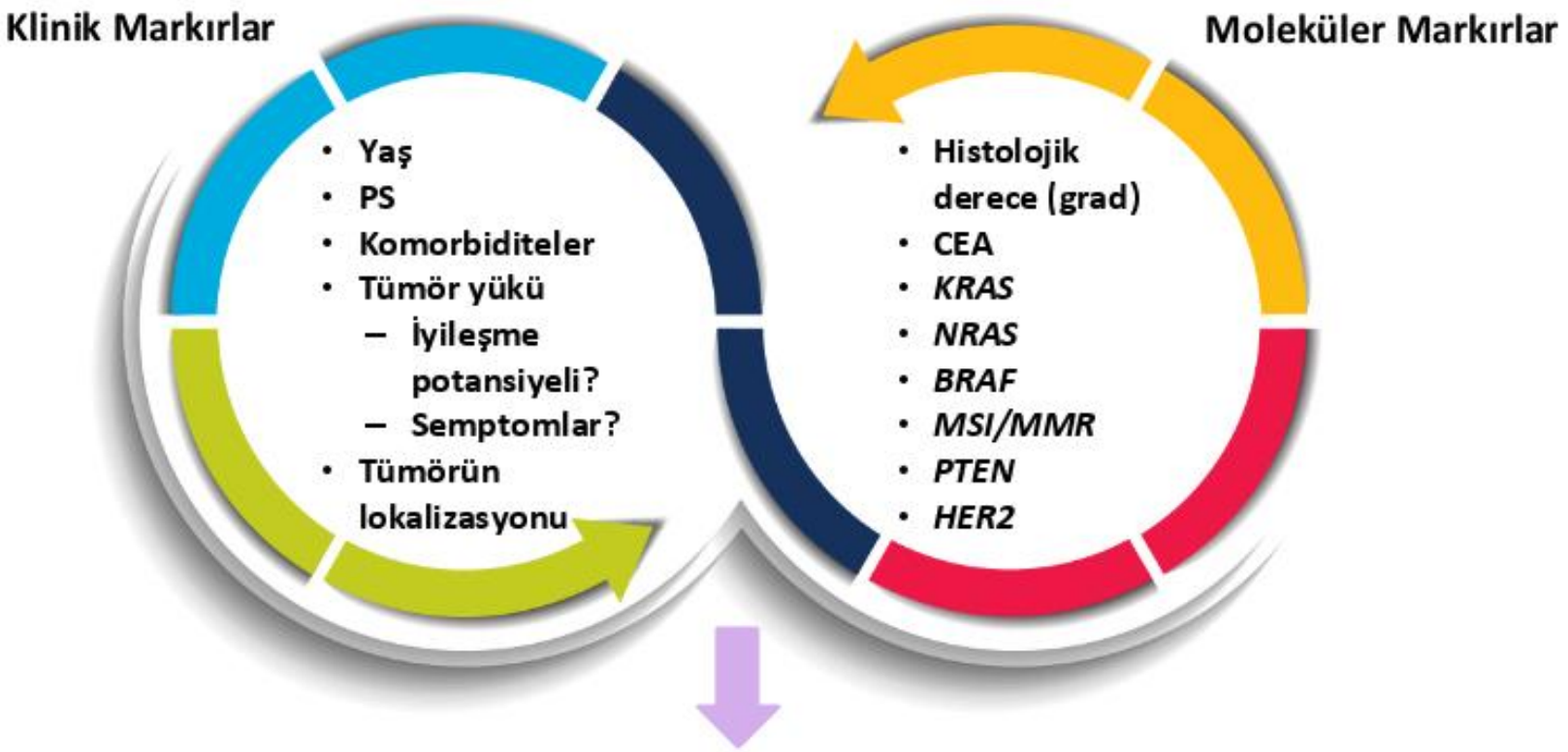
Metastatik Kolon Kanseri Tedavi seçenekleri

Management of mCRC: Goal of Therapy

Cure or Palliation

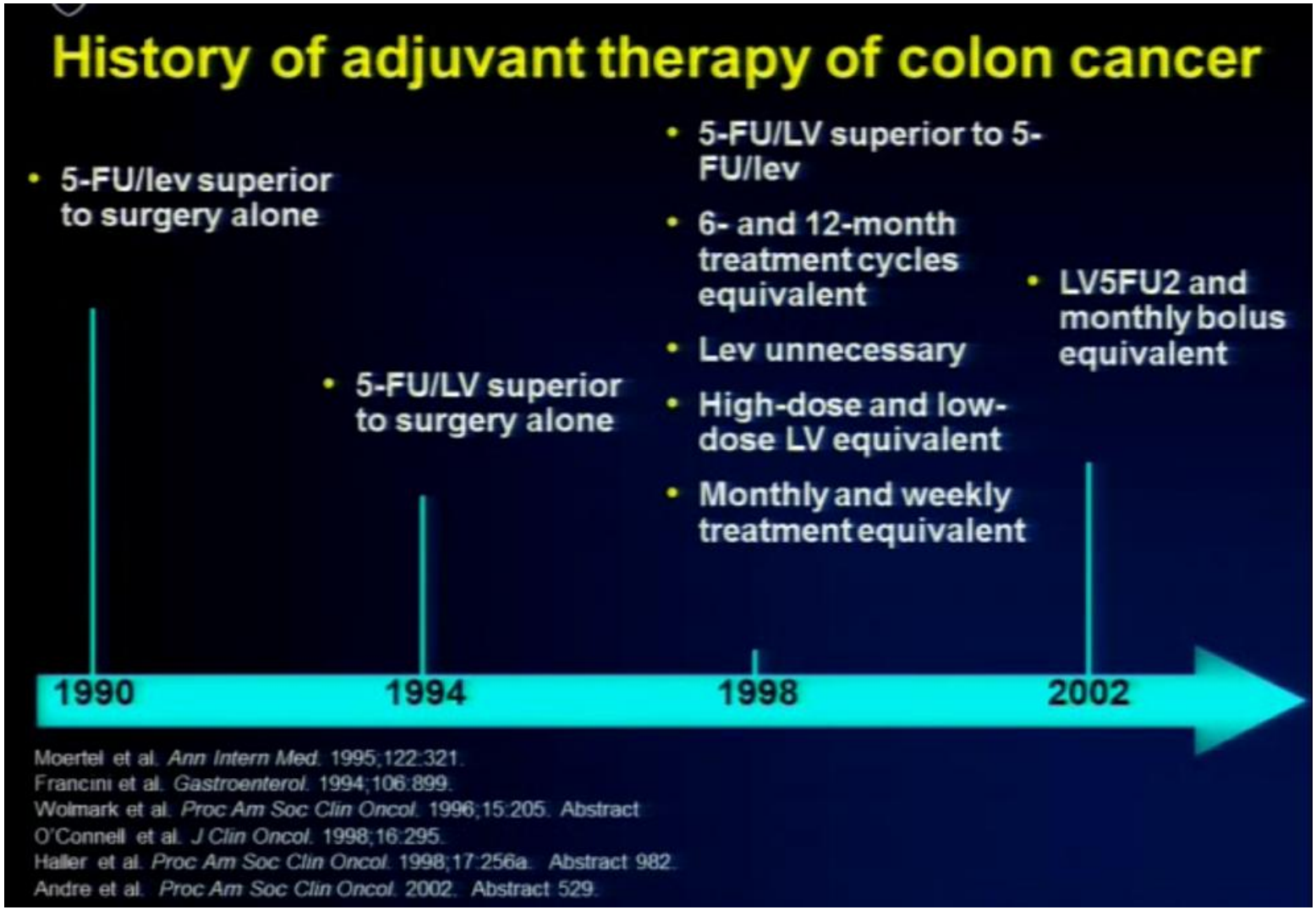
- Extent of disease
- Distribution of disease
- Symptoms related to mCRC
- Co-morbidities
- Patient preference

Metastatik Kolon Kanseri Tedavi seçenekleri



Van Cutsem E vea rk. Ann Oncol. 2016 Aug;27 (8):1386-422

Kolon Kanseri Tedavi



Kolon Kanseri Tedavi

11 Drugs for Colorectal Cancer *Biomarker Driven

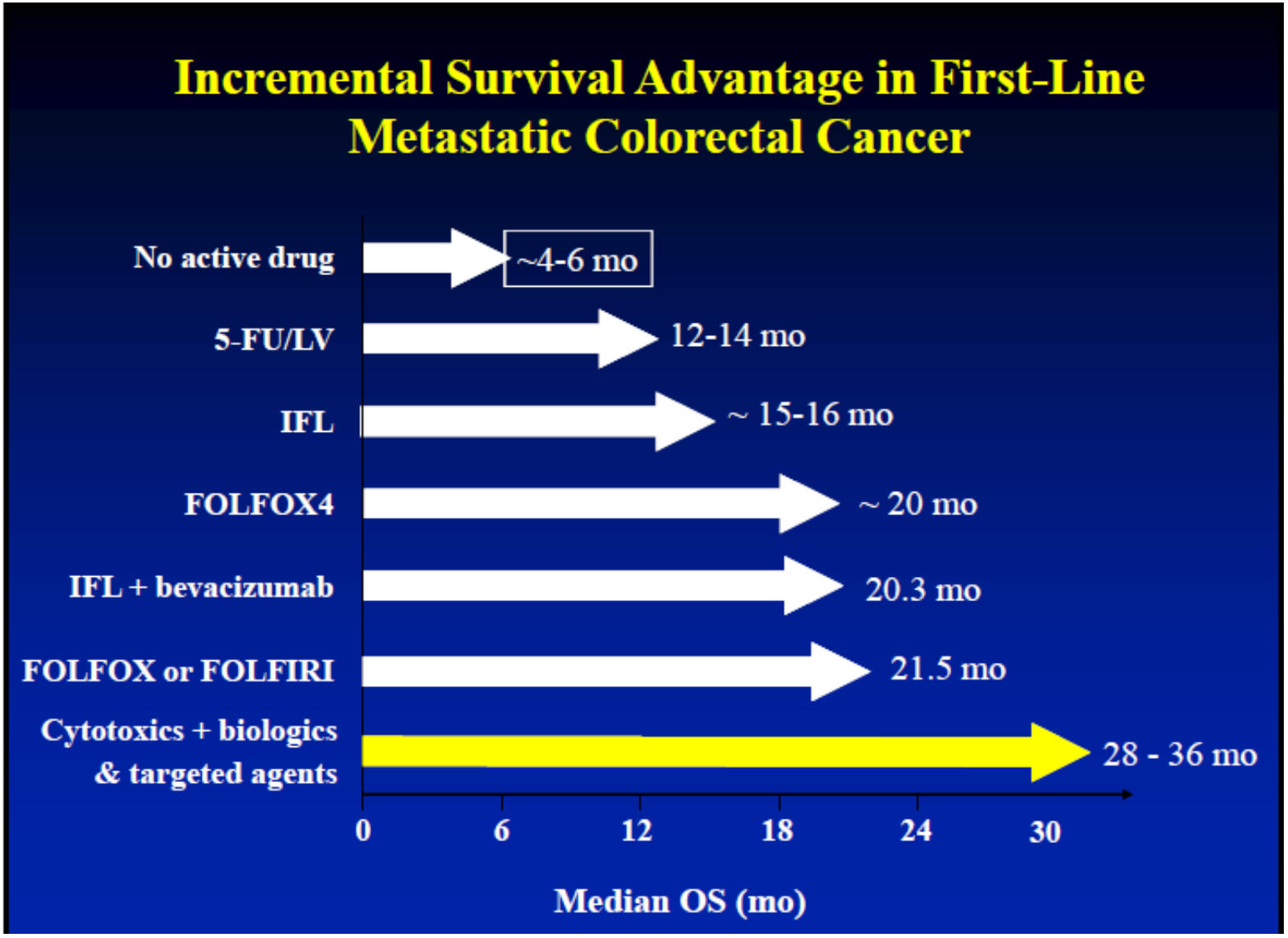
"Cytotoxics"	Mechanism
1. 5-Fluorouracil (5-FU)	-> pyrimidine analog
2. Capecitabine	-> oral 5-FU pro-drug
3. TAS-102	-> oral 5-FU
4. Irinotecan	-> topoisomerase I inhibitor
5. Oxaliplatin	-> 3rd generation platinum

"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

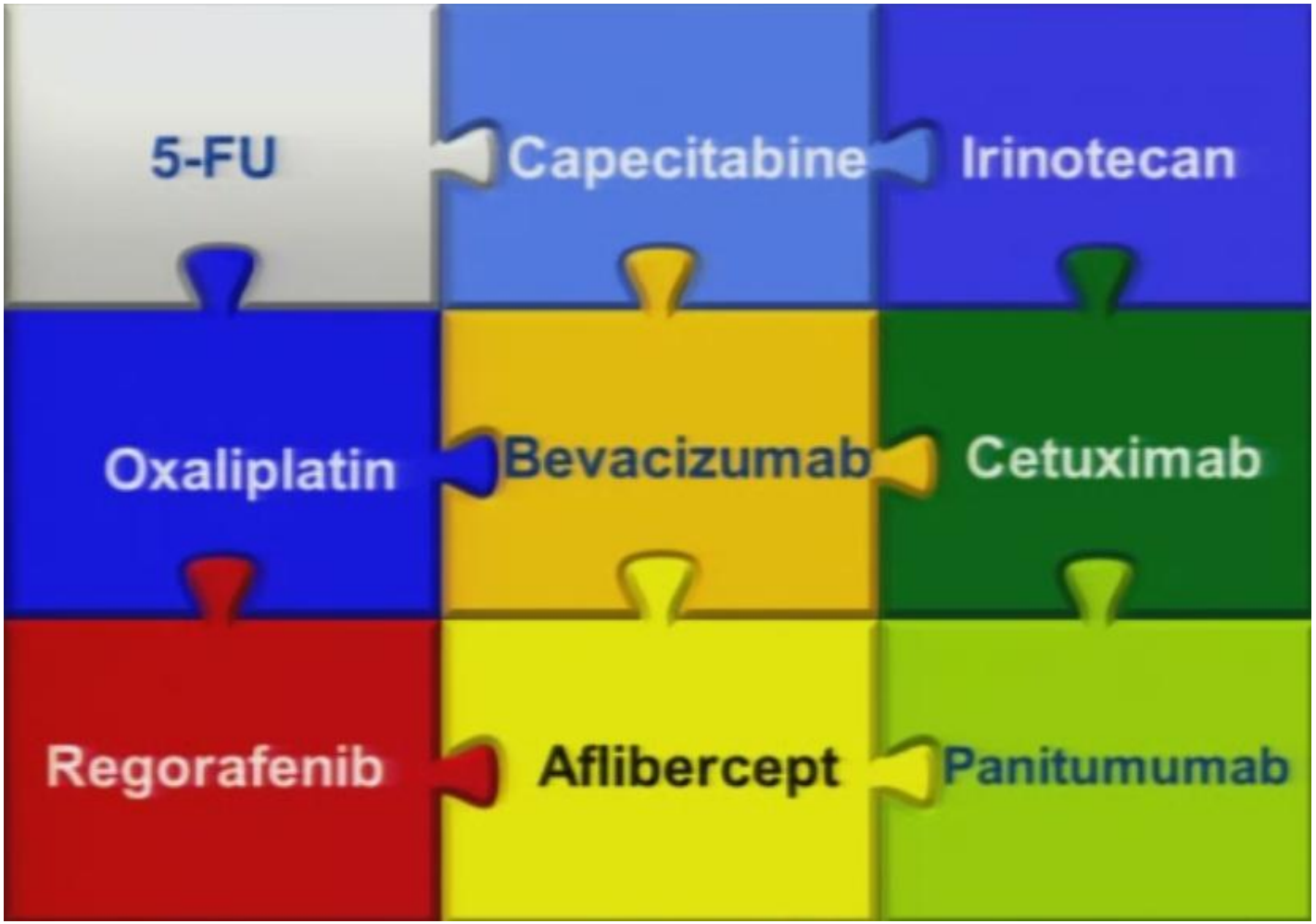
VEGF= Vascular Endothelial Growth Factor

EGFR= Epidermal Growth Factor Receptor

Kolon Kanseri Tedavi



Metastatik Kolon Kanseri Tedavi



Metastatik Kolon Kanseri Tedavi

How are we going to pay for this?

Chemotherapy for Colorectal Cancer (2 weeks)

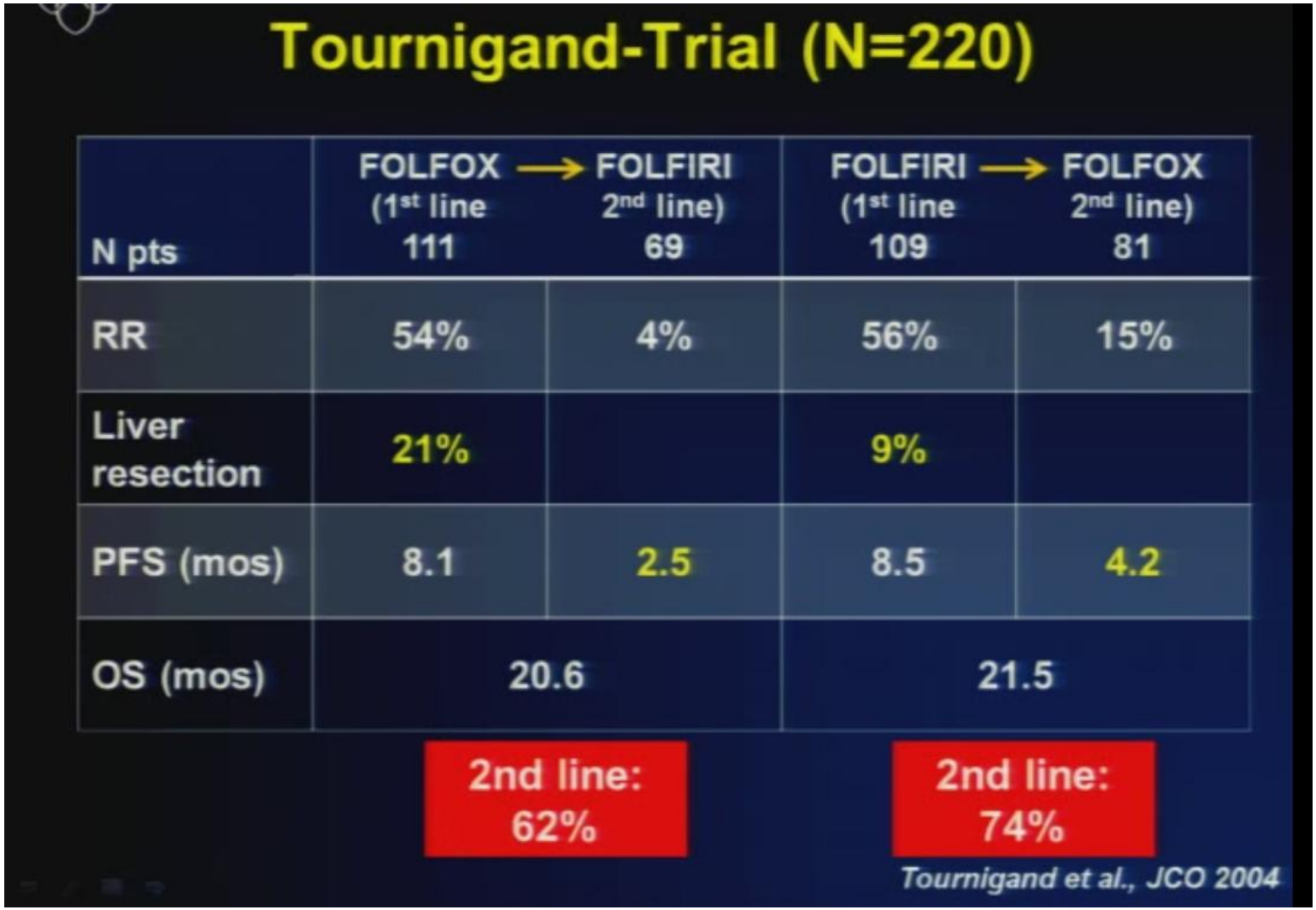
5-FU (500 mg/m^2)	$6
Leucovorin (500 mg/m^2)	$85
Capecitabine (2000 mg/m^2/day)	$3,250
Irinotecan (180 mg/m^2) / generic	$2,300 / $480
Oxaliplatin (85 mg/m^2) / generic	$4,190 / $590
Bevacizumab (5 mg/kg)	$2,560
Cetuximab (250 mg/m^2)	$5,120
Panitumumab (6 mg/kg)	$4,360
Ziv-aflibercept (4 mg/kg)	$5,380
Regorafenib (160 mg, 3/1)	$5,650
Ramucirumab (6mg/kg)	$7,669

1997: 6 months of 5-FU/LV costs ~$500

2013: 24 months therapy with combinations costs >$300,000

Estimates from University of Colorado School of Pharmacy

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

Some Therapy Options for Advanced Colorectal Cancer:

Response rates and survival (targeted agents in yellow)

First Line
- FOLFOX or
- CapeOx or
- FOLFIRI or
- FOLFOXIRI

+/- cetux/pmab (RAS)
+/- bevacizumab

⇒

Second Line
- FOLFOX or
- Irinotecan or
- FOLFIRI

+/- bevacizumab
+/- aflibercept
+/- ramucirumab
+/- cetuximab (RAS)
+/- panitumumab (RAS)

⇒

Third Line
- Irinotecan + cetuximab (RAS)
- cetuximab (RAS)
- panitumumab (RAS)
- regorafenib
- TAS-102

(RAS)= KRAS and NRAS testing

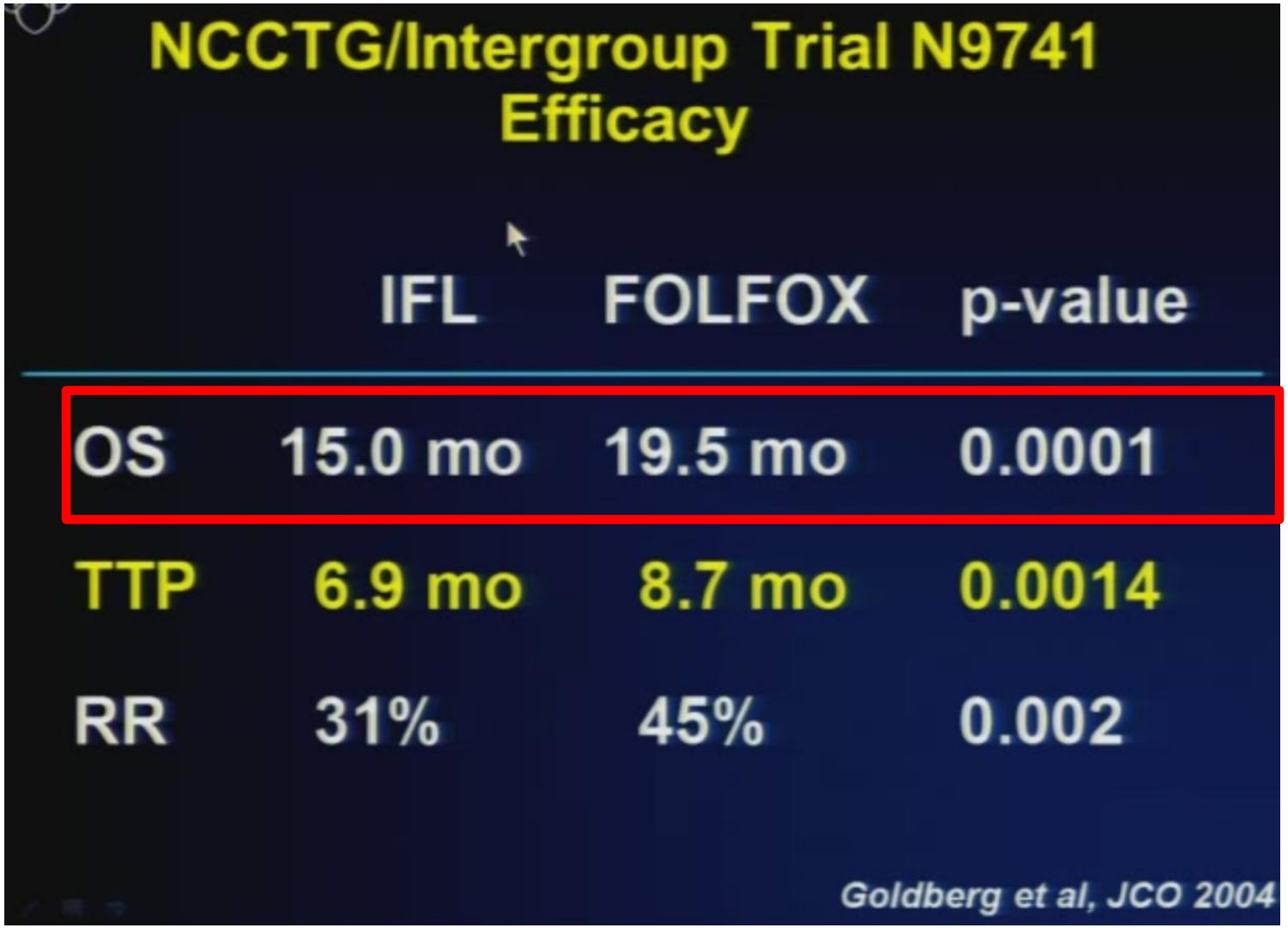
Response Rates in Randomized Trials:

30-70% ⇒ 5-15% ⇒ 10-20%

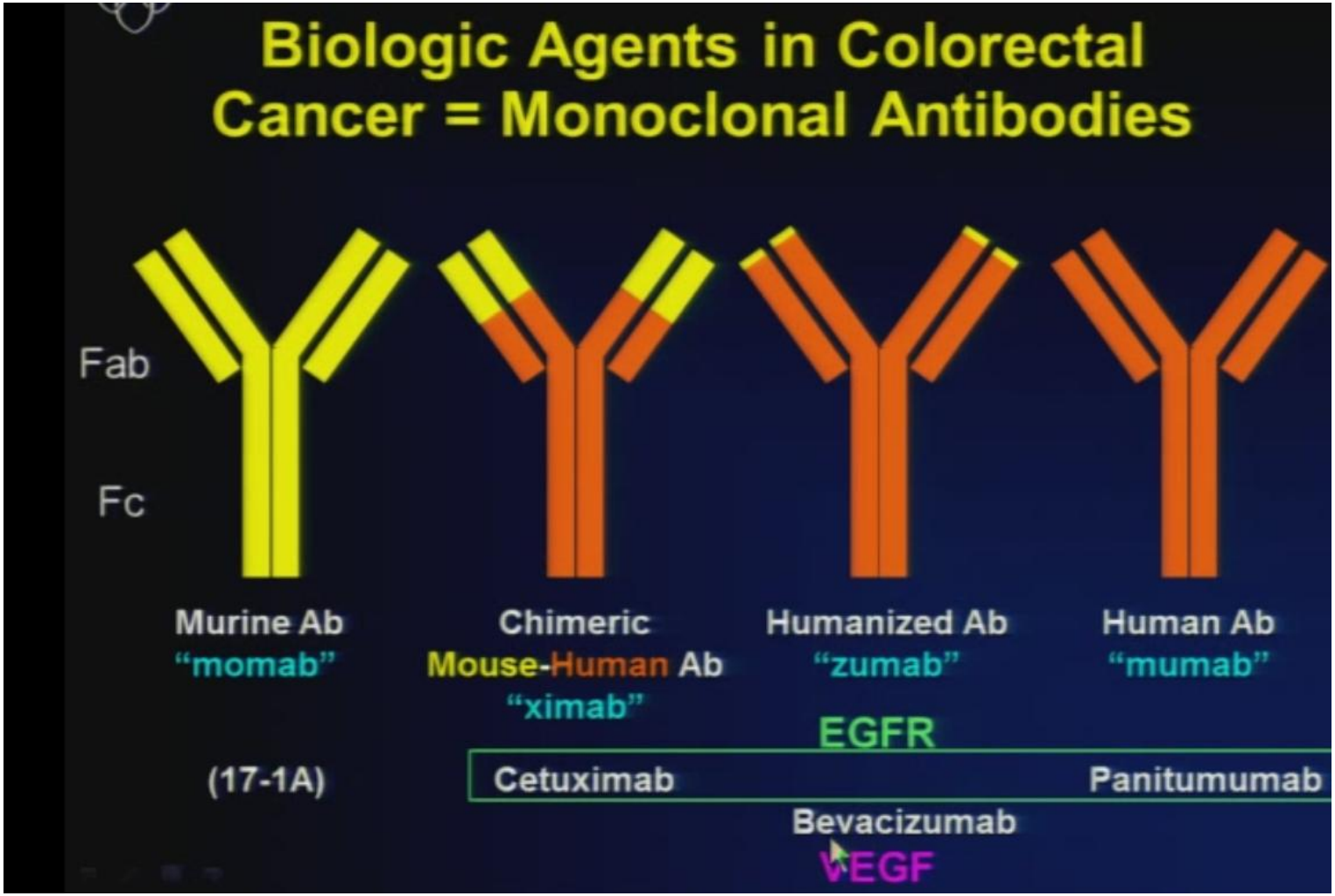
Survival Benefit in Randomized Trials:

Yes ⇒ Yes ⇒ Yes

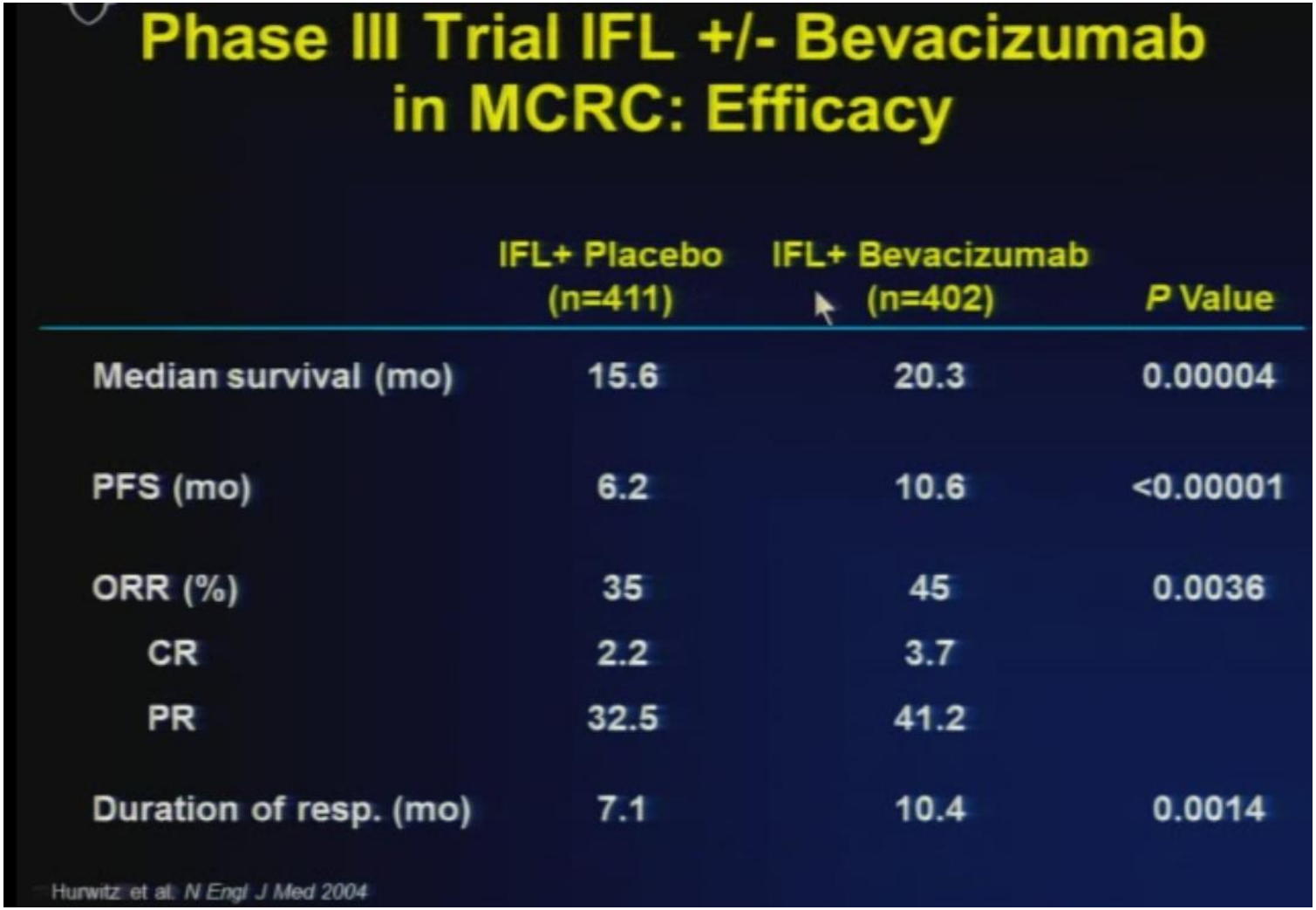
Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



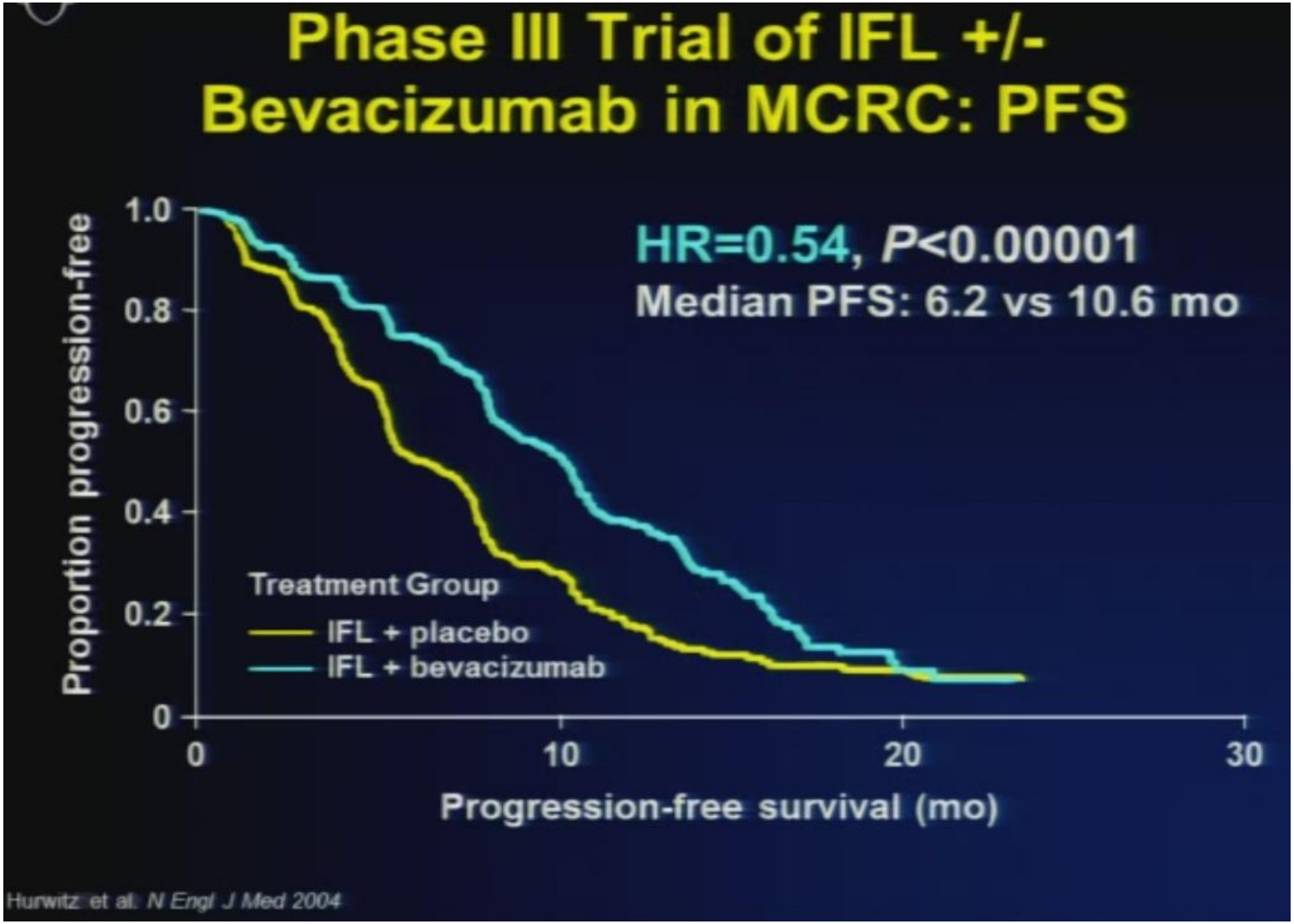
Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



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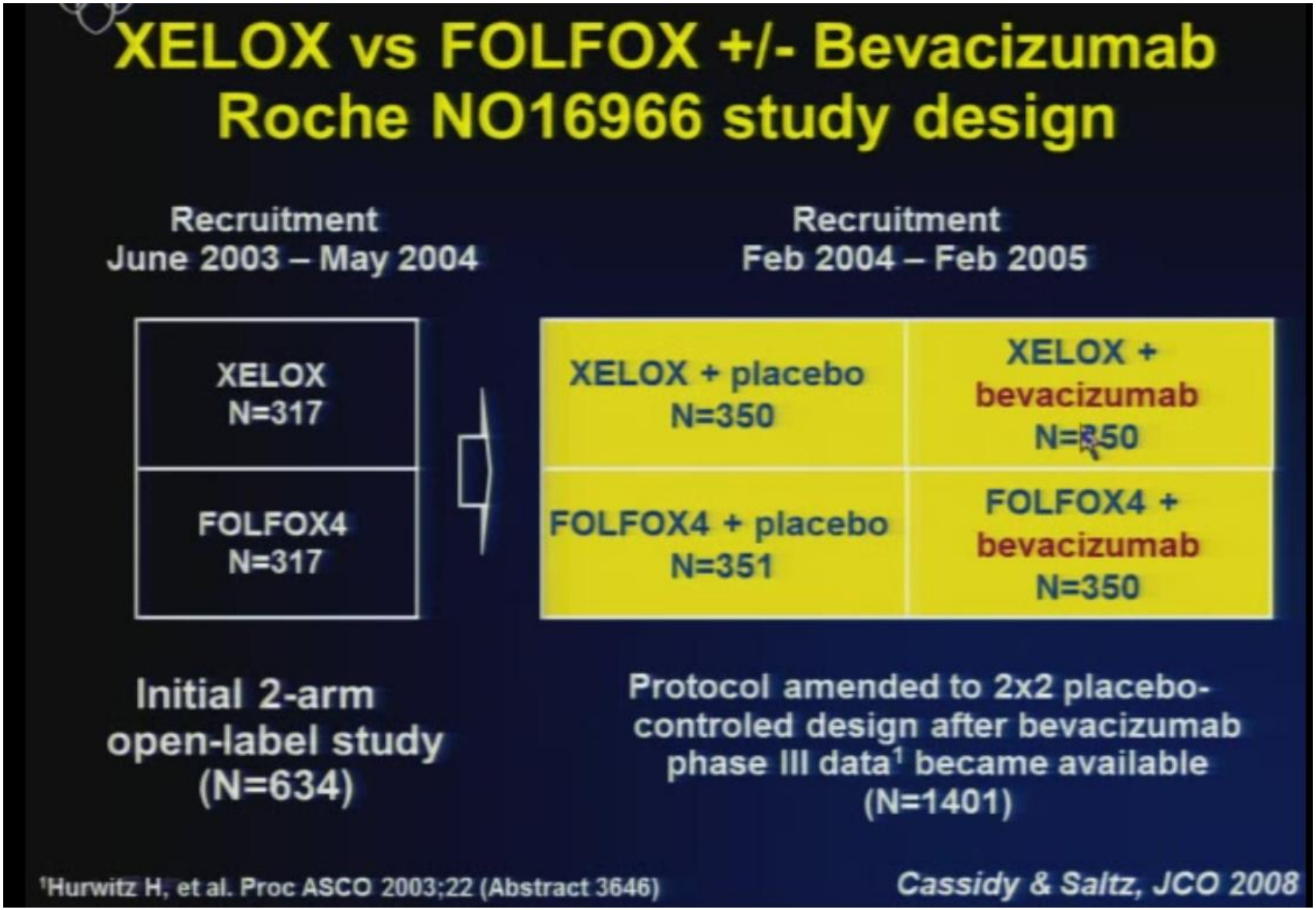

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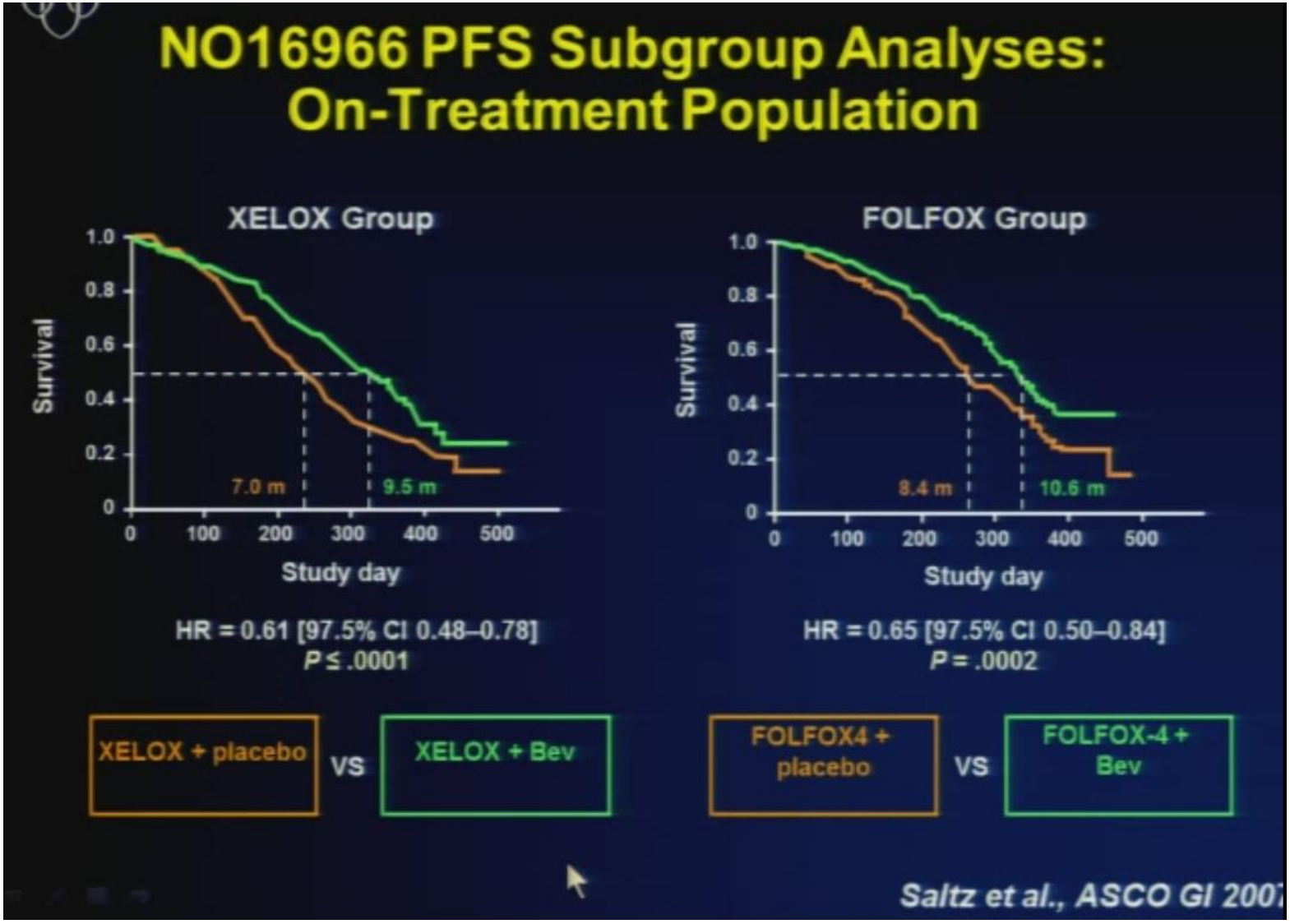

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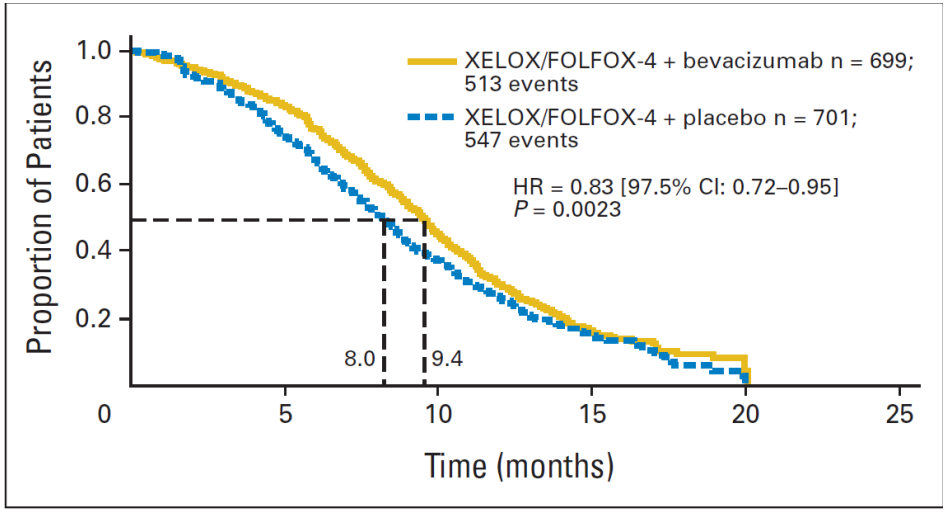


Fig 2. Progression-free survival (intent to treat population). XELOX, capecitabine and oxaliplatin; FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; HR, hazard ratio.

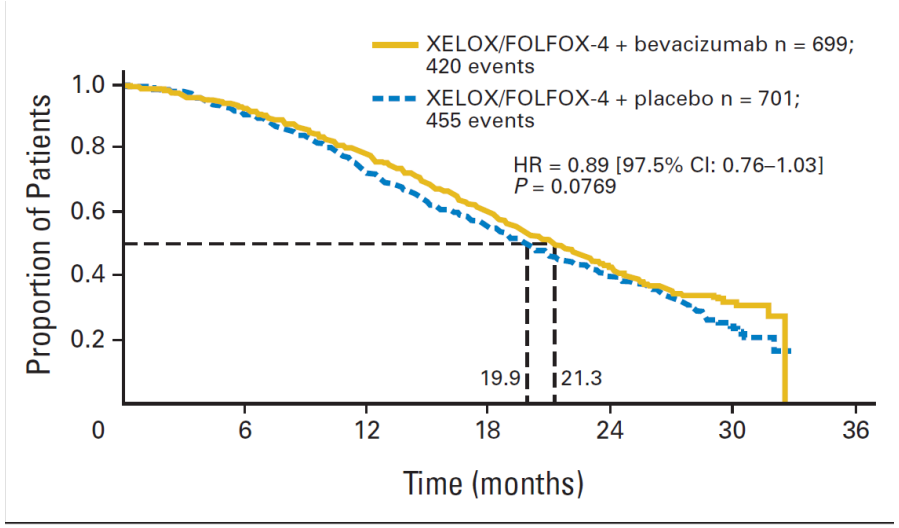
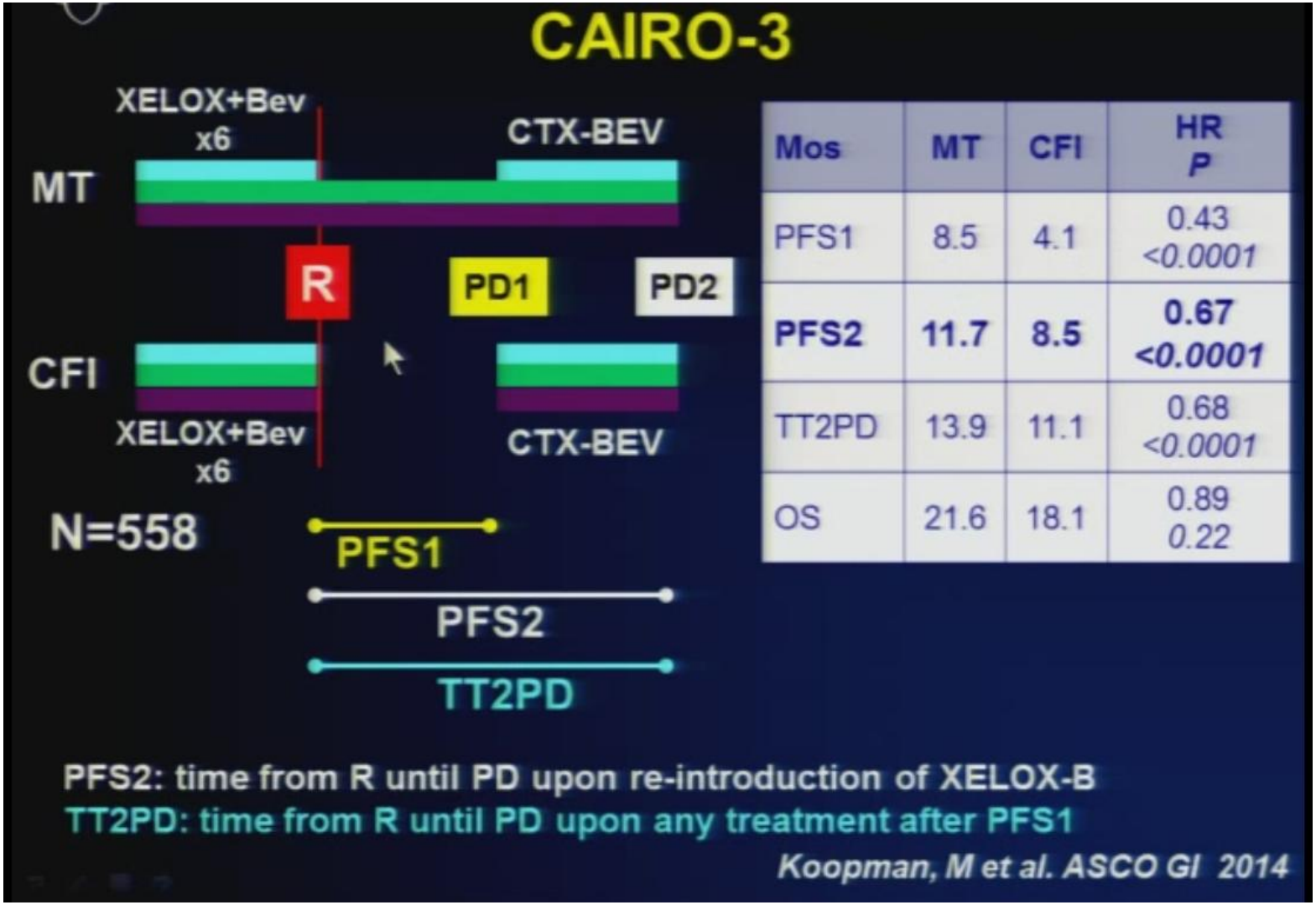


Fig 3. Overall survival (intent to treat population). XELOX, capecitabine and oxaliplatin FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; HR, hazard ratio.

Saltz LB, et al, JCO 2008

Metastatik Kolon Kanserinde Tedavi Seçenekleri



Mos	MT	CFI	HR *P*
PFS1	8.5	4.1	0.43 *<0.0001*
PFS2	**11.7**	**8.5**	**0.67** ***<0.0001***
TT2PD	13.9	11.1	0.68 *<0.0001*
OS	21.6	18.1	0.89 *0.22*

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

Targeting VEGF

First-Line bevacizumab in mCRC, Phase III Trials

Trial Regimen	Response rate (%)		Median PFS or 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/CapeOx + 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.

Metastatik Kolon Kanserinde Tedavi Seçenekleri

Bevacisumab -Metaanaliz

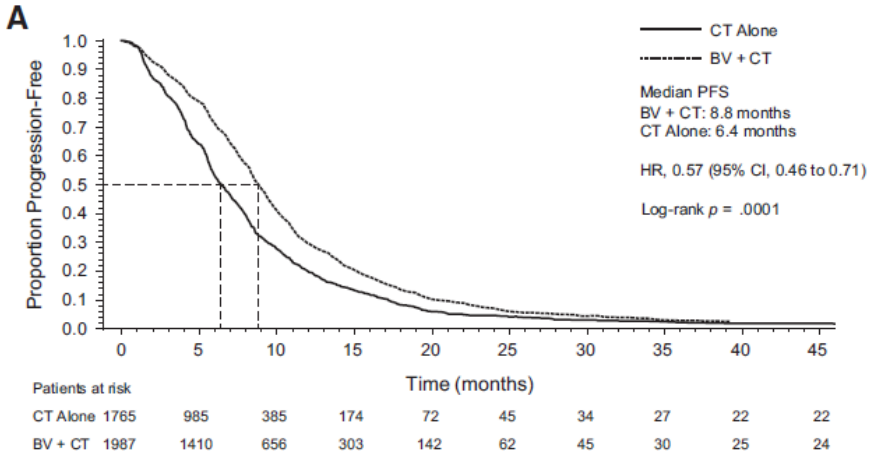
Table 1. Overview of clinical trials included in the analysis

Trial (ClinicalTrials.gov identifier)	Phase	Treatment arms included in the current analysis	Subjects in ITT population	Primary endpoint
First-line mCRC				
AVF2107 (NCT00109070) [1]	III	IFL plus bevacizumab 5 mg/kg	402	OS
		IFL plus placebo	411	
NO16966 (NCT00069095) [4]	III	FOLFOX or XELOX plus bevacizumab 5 or 7.5 mg/kg	699	PFS
		FOLFOX or XELOX plus placebo	701	
ARTIST (NCT00642577) [6]	III	mIFL plus bevacizumab 5 mg/kg	142	PFS, 6-month PFS rate
		mIFL	72	
AVF0780 [16]	II	5-FU/LV plus bevacizumab 5 mg/kg	35	TTP, confirmed response rate
		5-FU/LV plus placebo	36	
AVF2192 (NCT00109226) [2]	II	5-FU/LV plus bevacizumab 5 mg/kg	104	OS
		5-FU/LV plus placebo	105	
AGITG MAX (NCT00294359) [5]	III	Capecitabine plus bevacizumab 7.5 mg/kg with or without mitomycin	315	PFS
		Capecitabine	156	
Second-line mCRC				
E3200 (NCT00025337) [3]	III	FOLFOX plus bevacizumab 10 mg/kg	293	OS
		FOLFOX	292	

Abbreviations: 5-FU/LV, 5-fluorouracil and leucovorin; FOLFOX, infusional 5-FU/LV with oxaliplatin; IFL, bolus 5-FU/LV with irinotecan; ITT, intent-to-treat; mCRC, metastatic colorectal cancer; mIFL, modified infusional 5-FU/LV with irinotecan; OS, overall survival; PFS, progression-free survival; TTP, time to disease progression; XELOX, capecitabine with oxaliplatin.

Hurtwitz HI, et al, Oncologist 2013

Metastatik Kolon Kanserinde Tedavi Seçenekleri



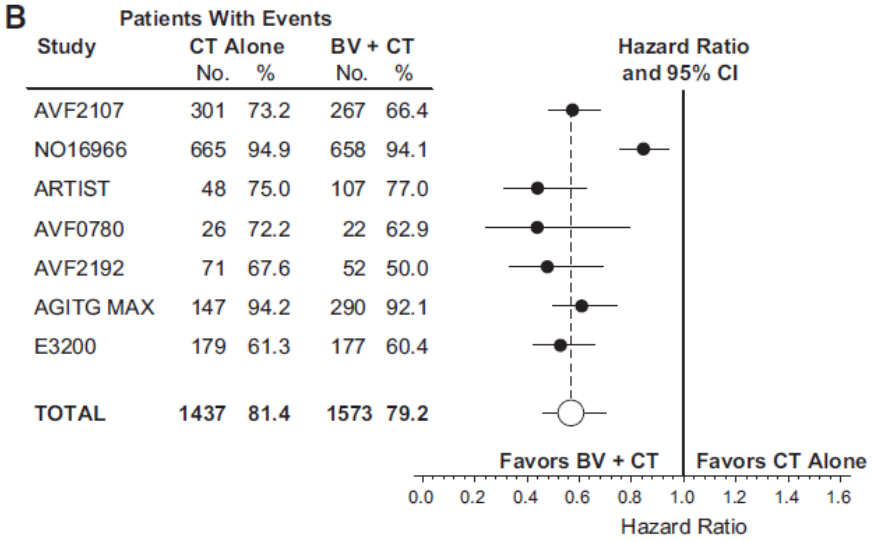
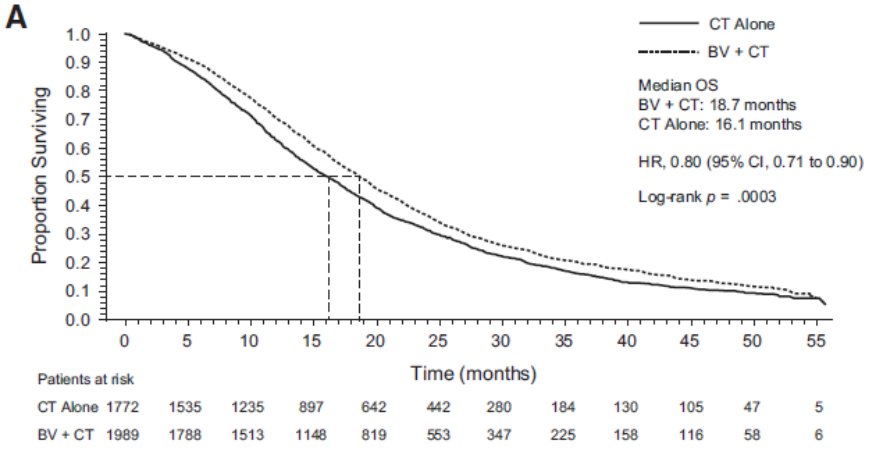


Figure 2. Progression-free survival (PFS) in the overall pooled population and in individual studies (first- and second-line trials of bevacizumab). **(A):** Kaplan-Meier estimate of PFS for the pooled population. **(B):** Forest plot of PFS by study.
Abbreviations: BV, bevacizumab; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival.

Metastatik Kolon Kanserinde Tedavi Seçenekleri



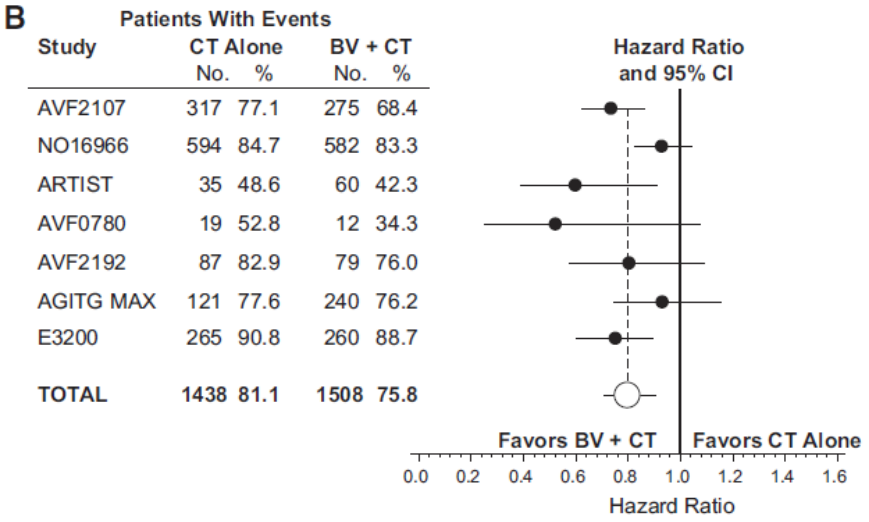


Figure 1. Overall survival (OS) in the overall pooled population and in individual studies (first- and second-line trials of bevacizumab). **(A):** Kaplan-Meier estimate of OS for the overall pooled population. **(B):** Forest plot of OS by study.
Abbreviations: BV, bevacizumab; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival.

Hurtwitz HI, et al, Oncologist 2013

Metastatik Kolon Kanserinde Tedavi Seçenekleri

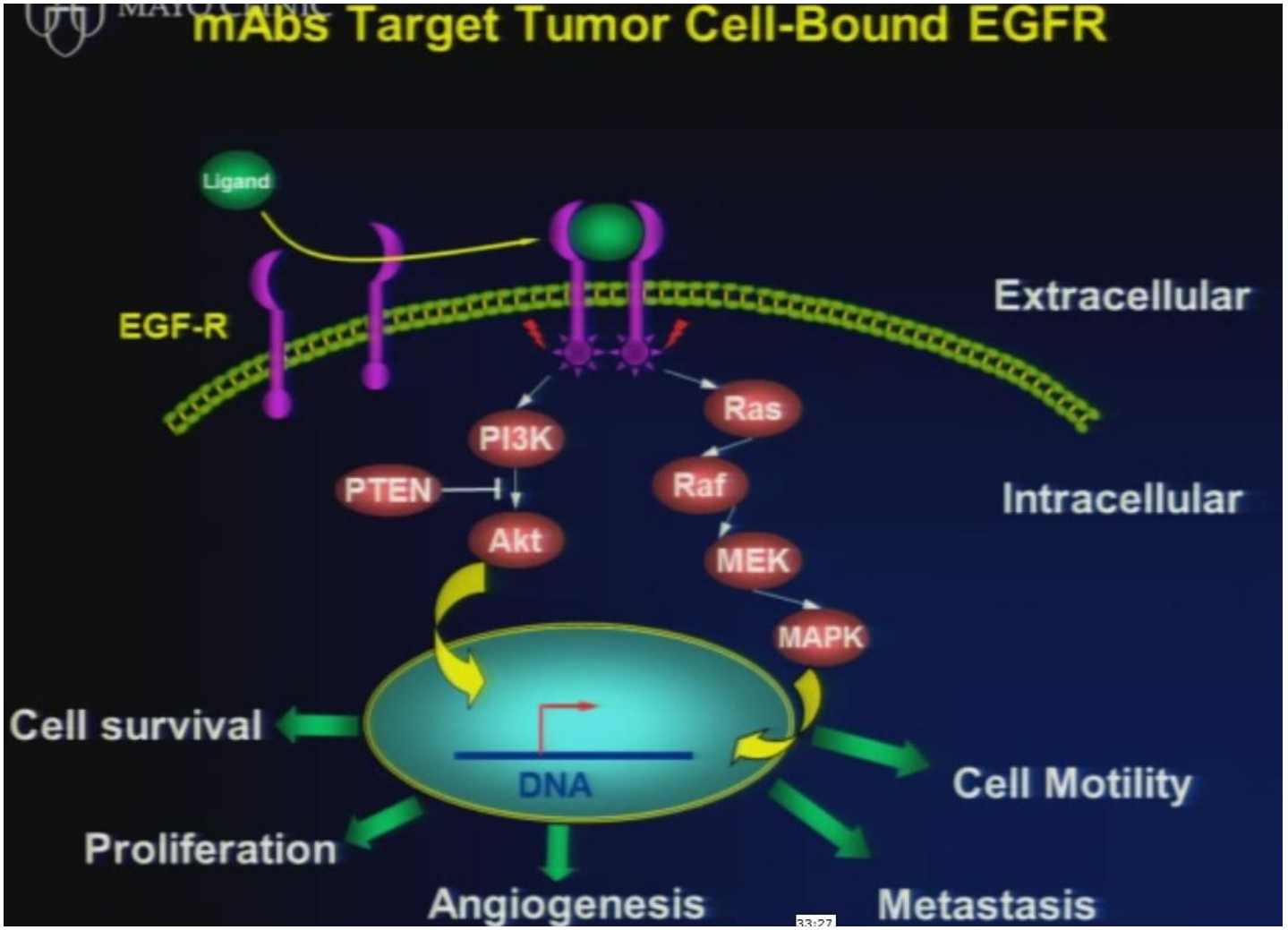
Table 3. Subgroup analyses in the overall pooled population (first- and second-line trials of bevacizumab) and first-line pooled population

	Overall survival			Progression-free survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Overall pooled population (*N* = 3,763)	**0.80**	**0.71–0.90**	**.0003**	**0.57**	**0.46–0.71**	**<.0001**
Irinotecan regimen (*n* = 1,027)	0.71	0.61–0.83	<.0001	0.55	0.47–0.64	<.0001
Oxaliplatin regimen (*n* = 1,985)	0.87	0.79–0.96	.0037	0.77	0.70–0.85	<.0001
Monotherapy (*n* = 751)	0.86	0.72–1.02	.0773	0.56	0.48–0.67	<.0001
Doublets (*n* = 3,012)	0.82	0.76–0.89	<.0001	0.70	0.64–0.76	<.0001
Patients with liver metastases only (*n* = 1,240)	0.84	0.74–0.95	.0066	0.65	0.57–0.74	<.0001
Patients with extensive disease[a] (*n* = 1,279)	0.79	0.70–0.89	.0001	0.66	0.58–0.74	<.0001
Aged <65 yr (*n* = 2,269)	0.80	0.73–0.88	<.0001	0.68	0.62–0.75	<.0001
Aged ≥65 yr (*n* = 1,492)	0.87	0.77–0.97	.0156	0.66	0.59–0.75	<.0001
Aged ≥75 yr (*n* = 426)	0.76	0.62–0.94	.0118	0.55	0.44–0.70	<.0001
ECOG PS 0 (*n* = 2,038)	0.80	0.72–0.89	<.0001	0.67	0.61–0.74	<.0001
ECOG PS ≥1 (*n* = 1,719)	0.85	0.77–0.94	.0020	0.67	0.60–0.75	<.0001
KRAS wild-type patients (*n* = 364)	0.70	0.54–0.91	.0072	0.57	0.45–0.72	<.0001
KRAS mutant patients (*n* = 166)	0.85	0.60–1.22	.3837	0.54	0.38–0.76	.0004
Overall first-line population (*n* = 3,178)	**0.81**	**0.70–0.93**	**.0034**	**0.58**	**0.46–0.73**	**<.0001**
Irinotecan regimen (*n* = 1,027)	0.71	0.61–0.83	<.0001	0.55	0.47–0.64	<.0001
Oxaliplatin regimen (*n* = 1,400)	0.93	0.83–1.04	.1904	0.85	0.76–0.94	.0025
Monotherapy (*n* = 751)	0.86	0.72–1.02	.0773	0.56	0.48–0.67	<.0001
Doublet therapy (*n* = 2,427)	0.84	0.77–0.92	.0003	0.73	0.67–0.80	<.0001
Patients with liver metastases only (*n* = 1,095)	0.87	0.76–1.00	.0449	0.67	0.59–0.77	<.0001
Patients with extensive disease[a] (*n* = 1,049)	0.79	0.69–0.90	.0004	0.67	0.59–0.77	<.0001
Aged <65 yr (*n* = 1,902)	0.82	0.74–0.91	.0002	0.70	0.63–0.78	<.0001
Aged ≥65 yr (*n* = 1,275)	0.88	0.78–1.00	.0524	0.68	0.60–0.78	<.0001
Aged ≥75 yr (*n* = 357)	0.80	0.63–1.00	.0533	0.57	0.45–0.74	<.0001
ECOG PS 0 (*n* = 1,749)	0.81	0.73–0.91	.0004	0.69	0.62–0.77	<.0001
ECOG PS ≥1 (*n* = 1,424)	0.87	0.78–0.98	.0207	0.69	0.61–0.78	<.0001
KRAS wild-type patients (*n* = 364)	0.70	0.54–0.91	.0072	0.57	0.45–0.72	<.0001
KRAS mutant patients (*n* = 166)	0.85	0.60–1.22	.3837	0.54	0.38–0.76	.0004

[a]Patients with metastatic disease in at least one site other than the liver or lung.
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

Hurwitz HI, et al, Oncologist 2013

Metastatik Kolon Kanserinde Tedavi Seçenekleri



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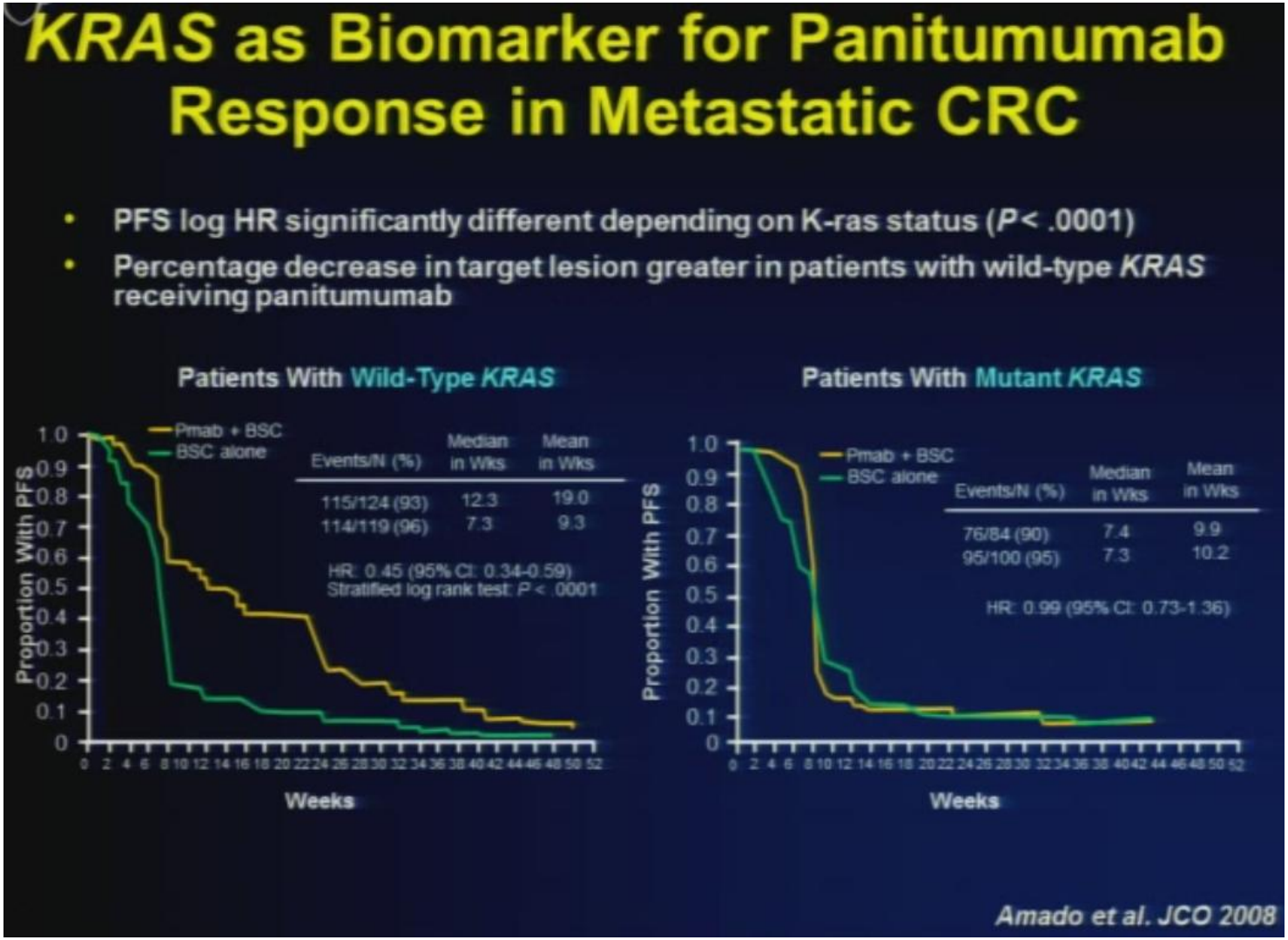

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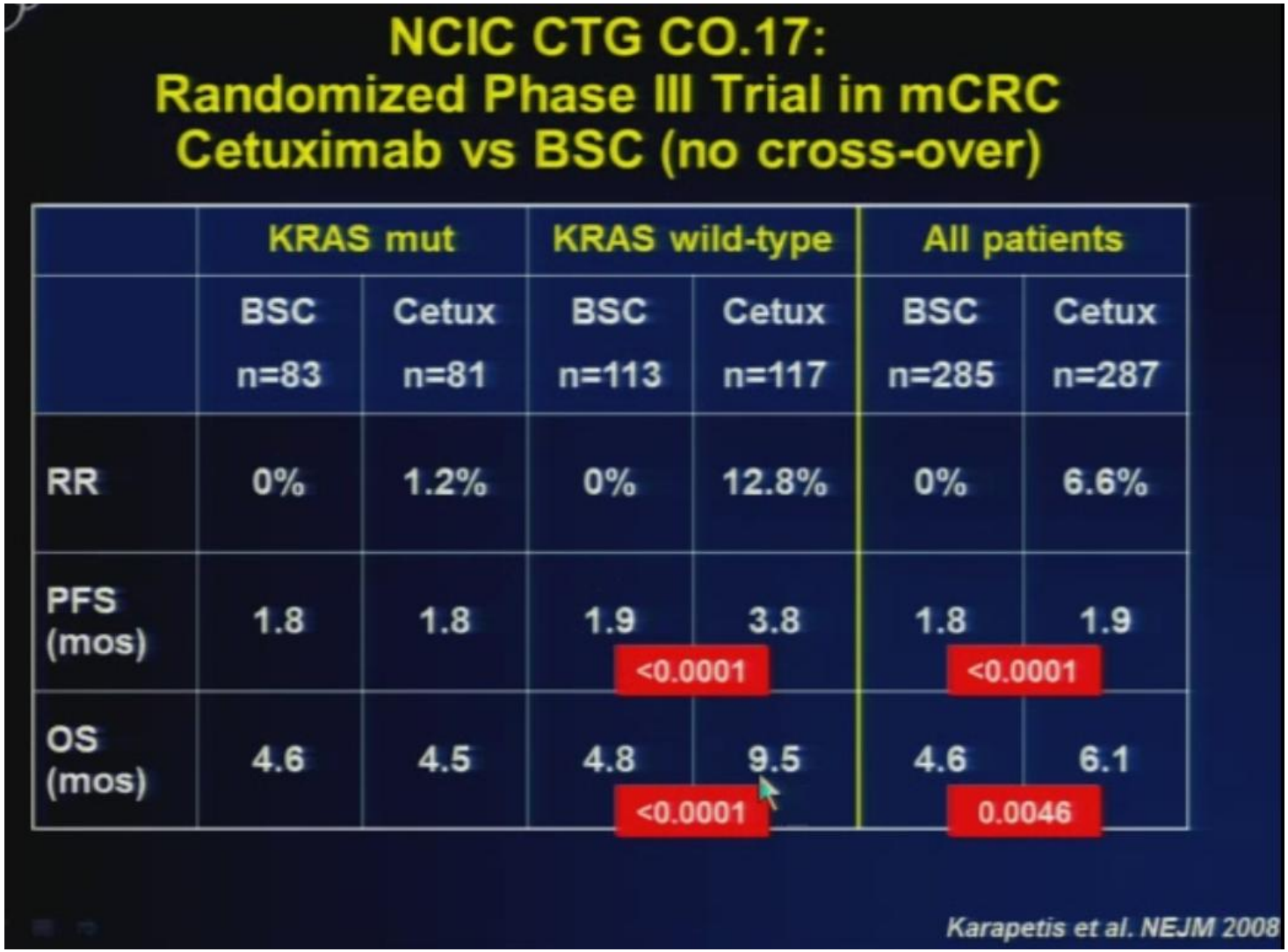
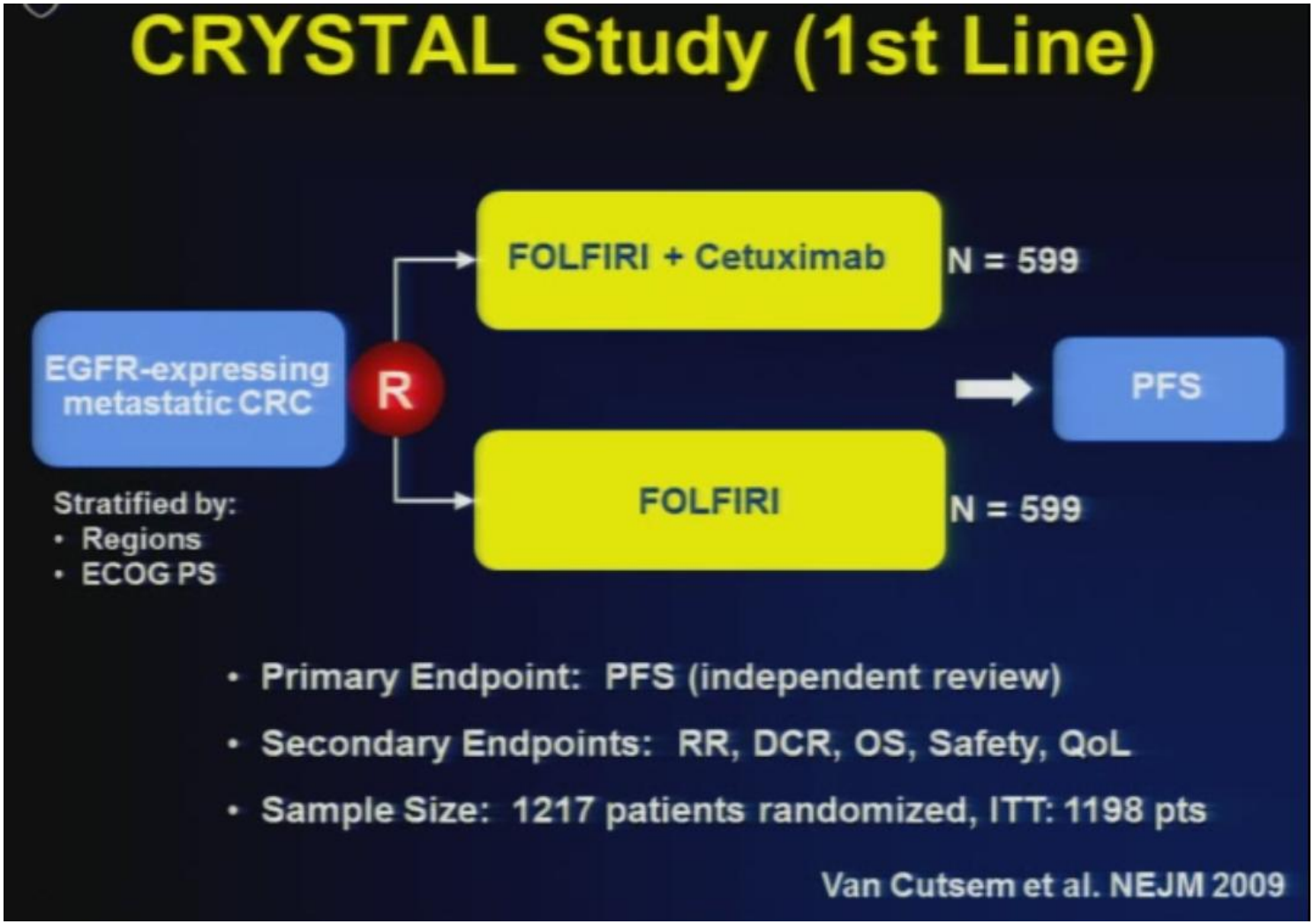


Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

CRYSTAL ÇALIŞMASI

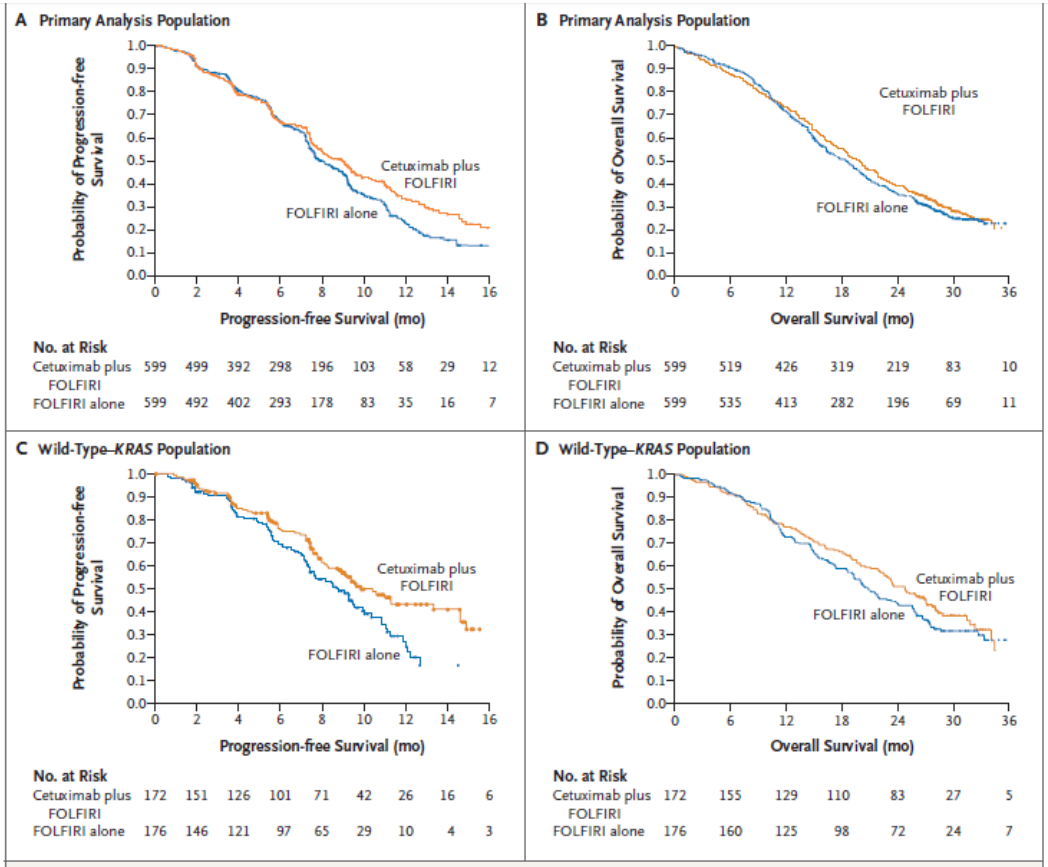
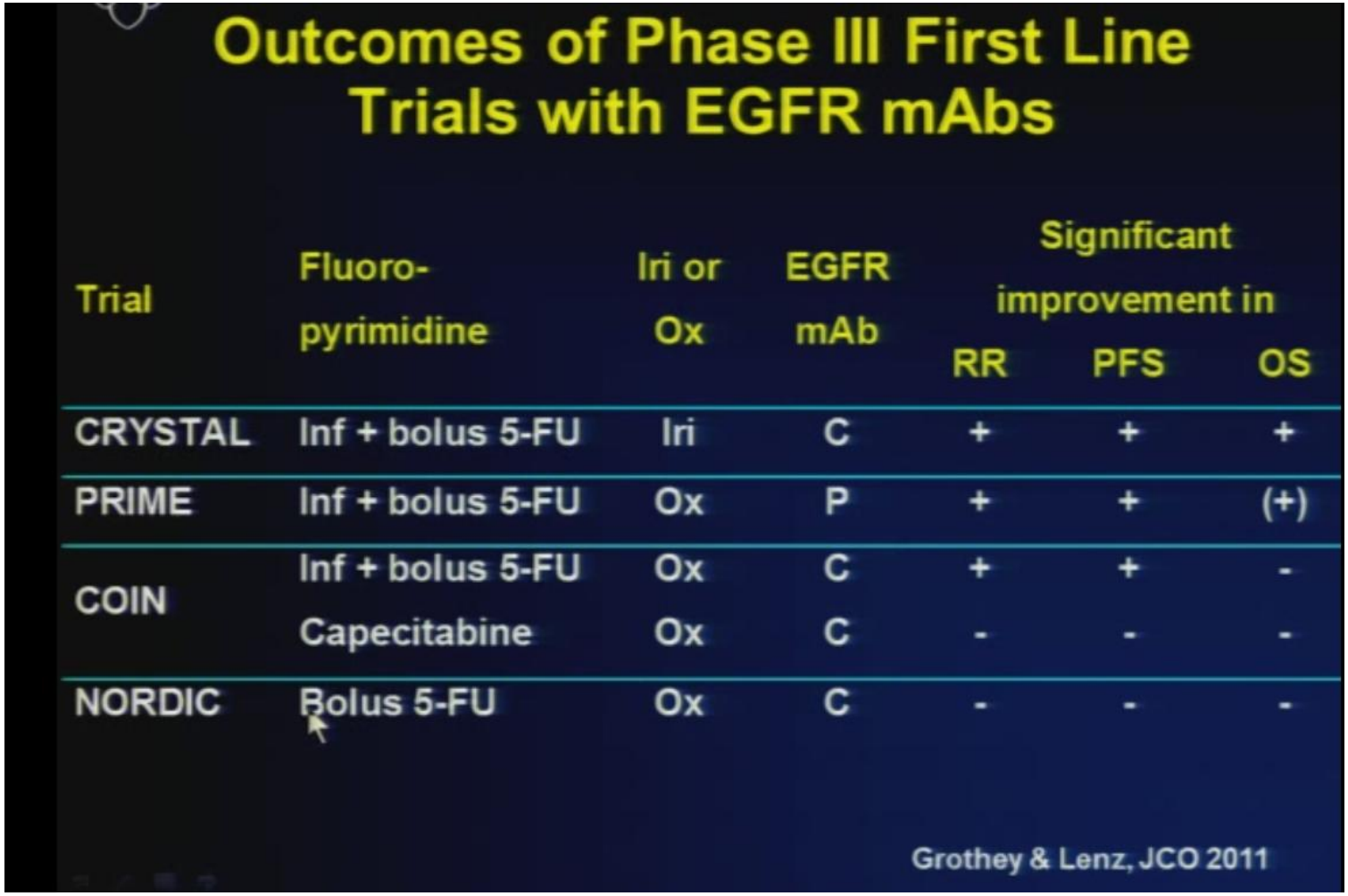


Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival in the Primary Analysis Population and the Wild-Type–*KRAS* Population, According to Treatment Group.

Panel A shows progression-free survival among the 1198 patients in the primary analysis population. The hazard ratio for the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.85 (95% CI, 0.72 to 0.99; P=0.048 by a stratified log-rank test). Median progression-free survival time in the cetuximab–FOLFIRI group was 8.9 months (95% CI, 8.0 to 9.5), as compared with 8.0 months (95% CI, 7.6 to 9.0) in the FOLFIRI group. Panel B shows overall survival among the 1198 patients in the primary analysis population. The hazard ratio for death in the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.93 (95% CI, 0.81 to 1.07; P=0.31 by a stratified log-rank test). The median overall survival in the cetuximab–FOLFIRI group was 19.9 months (95% CI, 18.5 to 21.3), as compared with 18.6 months (95% CI, 16.6 to 19.8) in the FOLFIRI group. Panel C shows progression-free survival among the 348 patients with wild-type–*KRAS* tumors. The hazard ratio for progression in the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.68 (95% CI, 0.50 to 0.94; P=0.02). The median progression-free survival in the cetuximab–FOLFIRI group was 9.9 months (95% CI, 8.7 to 14.6), as compared with 8.7 months (95% CI, 7.4 to 9.9) in the FOLFIRI group. Panel D shows overall survival among the 348 patients with wild-type–*KRAS* tumors. The hazard ratio for death in the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.84 (95% CI, 0.64 to 1.11). The median overall survival in the cetuximab–FOLFIRI group was 24.9 months (95% CI, 22.2 to 27.8), as compared with 21.0 months (95% CI, 19.2 to 25.7) in the FOLFIRI group.

Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri
PRIME çalışması

The NEW ENGLAND JOURNAL of MEDICINE

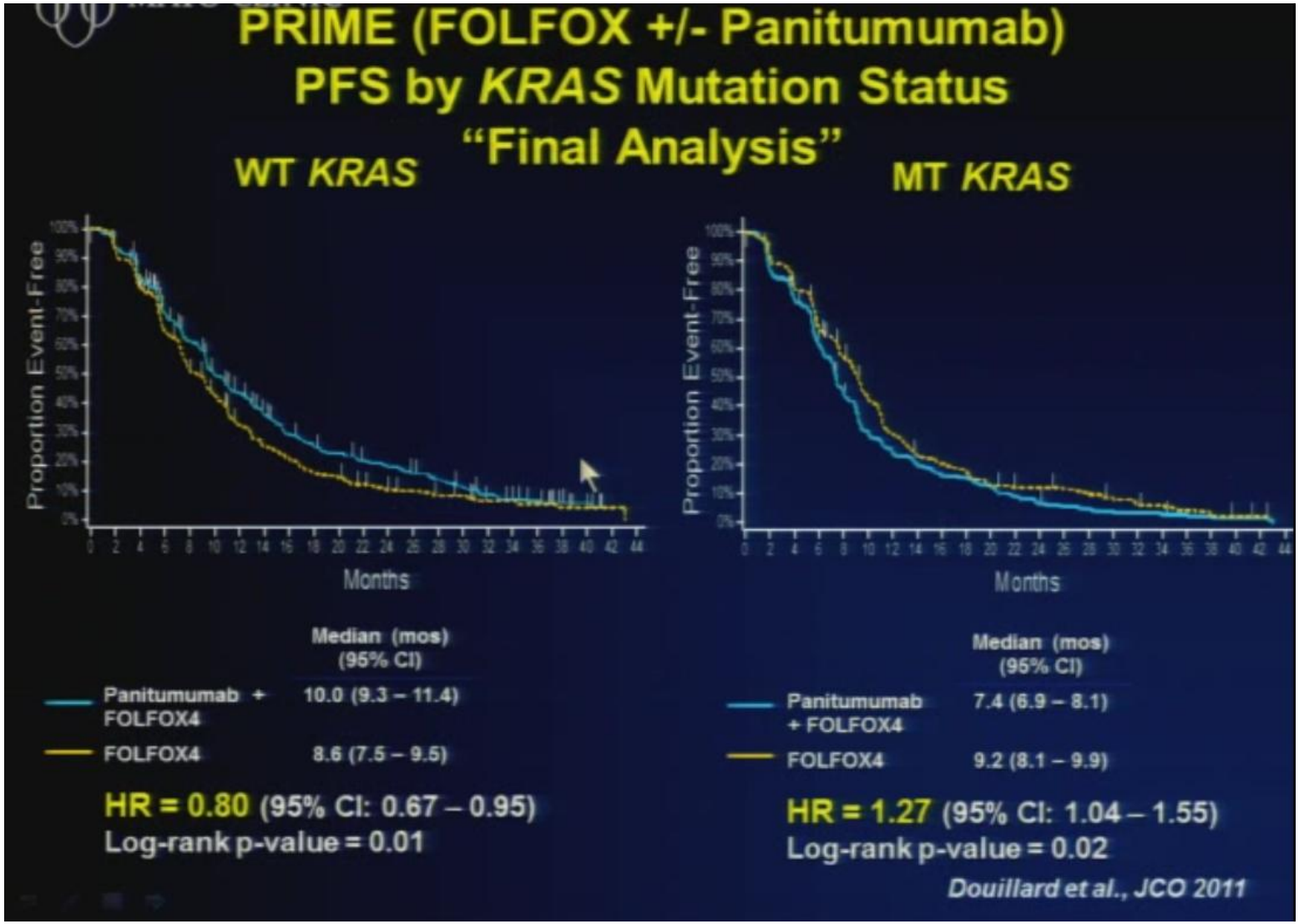
ORIGINAL ARTICLE

Panitumumab–FOLFOX4 Treatment and *RAS* Mutations in Colorectal Cancer

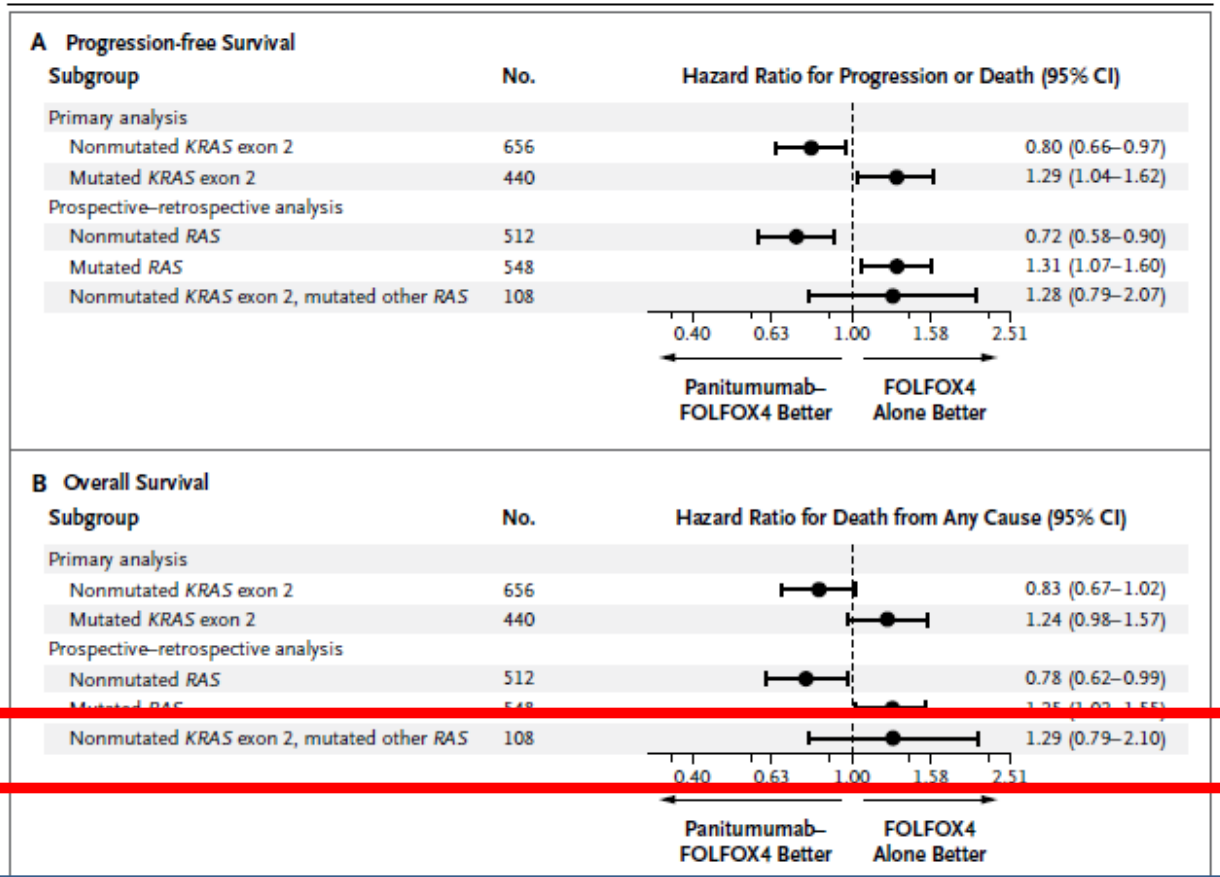
Jean-Yves Douillard, M.D., Ph.D., Kelly S. Oliner, Ph.D., Salvatore Siena, M.D., Josep Tabernero, M.D., Ronald Burkes, M.D., Mario Barugel, M.D., Yves Humblet, M.D., Ph.D., Gyorgy Bodoky, M.D., Ph.D., David Cunningham, M.D., Jacek Jassem, M.D., Ph.D., Fernando Rivera, M.D., Ph.D., Ilona Kocákova, M.D., Ph.D., Paul Ruff, M.D., Maria Błasińska-Morawiec, M.D., Martin Šmakal, M.D., Jean Luc Canon, M.D., Mark Rother, M.D., Richard Williams, M.B., B.S., Ph.D., Alan Rong, Ph.D., Jeffrey Wiezorek, M.D., Roger Sidhu, M.D., and Scott D. Patterson, Ph.D.

ABSTRACT

Metastatik Kolon Kanserinde Tedavi Seçenekleri
PRIME çalışması



Metastatik Kolon Kanserinde Tedavi Seçenekleri
PRIME çalışması

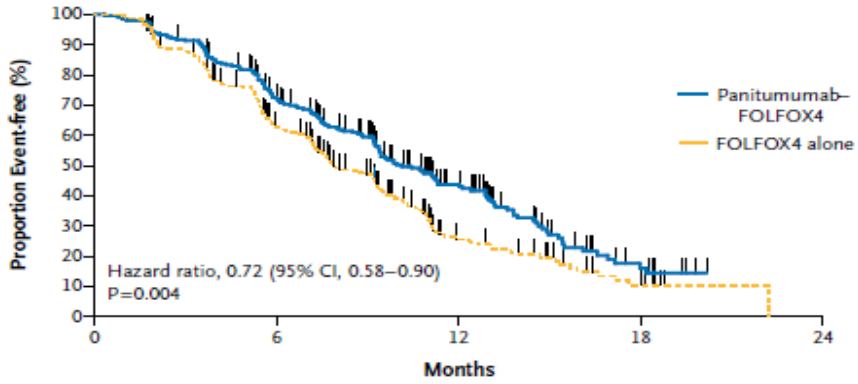


%17 KRAS Mutasyonu dışı RAS mutasyonu saptanmış

Metastatik Kolon Kanserinde Tedavi Seçenekleri
PRIME çalışması

The NEW ENGLAND JOURNAL of MEDICINE

A Progression-free Survival in the Primary-Analysis Population

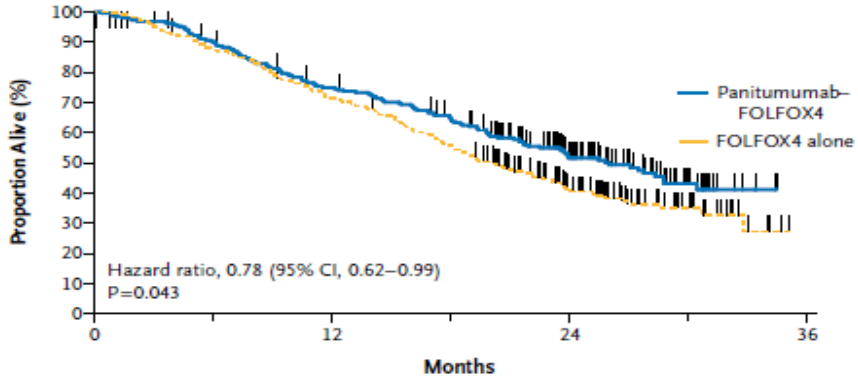


	Events no./total no. (%)	Median Mo (95% CI)
Panitumumab–FOLFOX4	156/259 (60)	10.1 (9.3–12.0)
FOLFOX4 alone	170/253 (67)	7.9 (7.2–9.3)

No. at Risk

Panitumumab–FOLFOX4	259	171	65	10
FOLFOX4 alone	253	140	31	7

B Overall Survival in the Primary-Analysis Population



	Events no./total no. (%)	Median Mo (95% CI)
Panitumumab–FOLFOX4	128/259 (49)	26.0 (21.7–30.4)
FOLFOX4 alone	148/253 (58)	20.2 (17.7–23.1)

No. at Risk

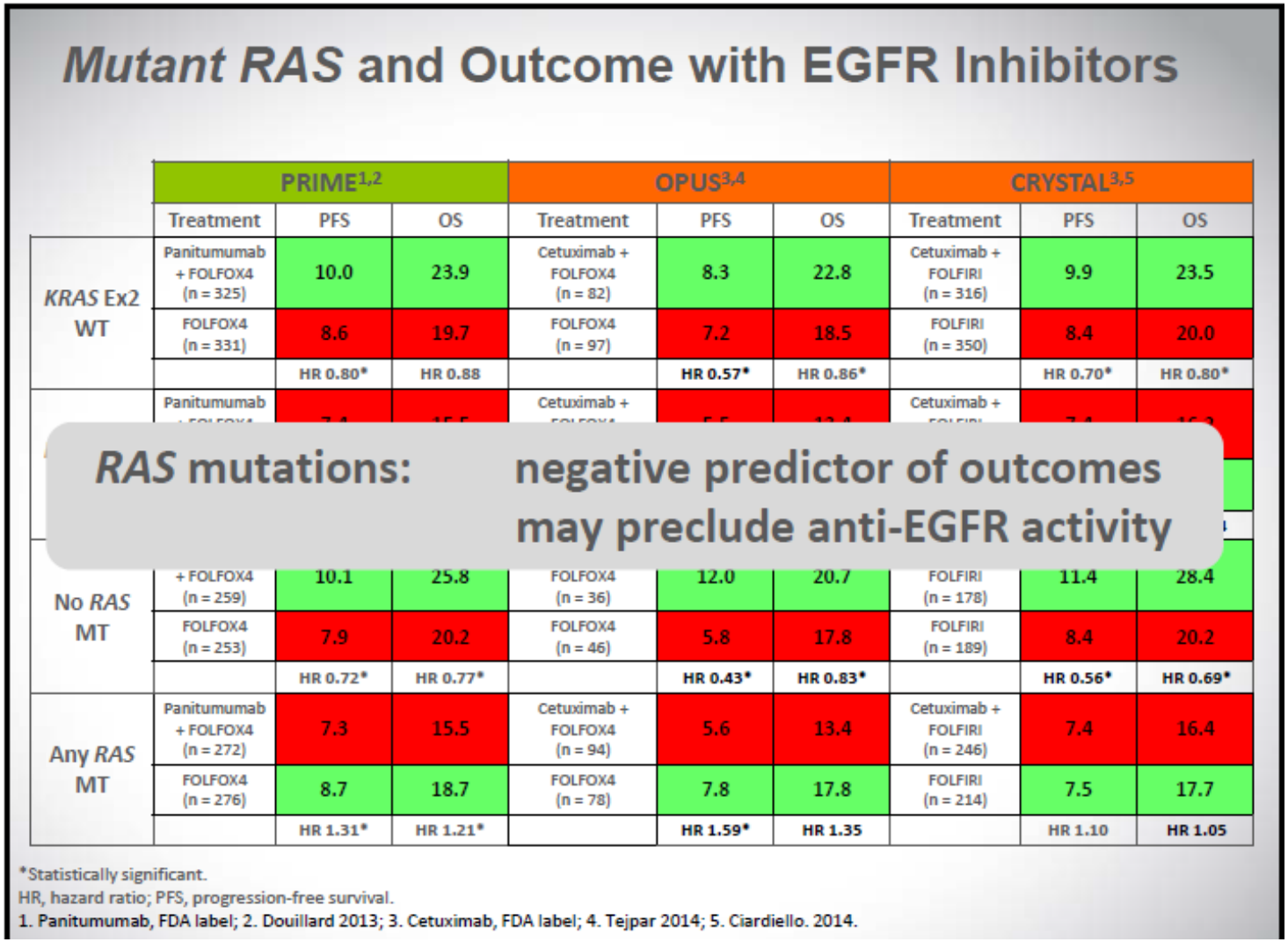
Panitumumab–FOLFOX4	259	189	88	0
FOLFOX4 alone	253	174	65	0

Table 1 Clinical trials of targeted agents in combination with chemotherapy as first-line treatments for metastatic colorectal cancer

Ref.	Year	Population	Patient number	Regimen	Median PFS (mo)	P^1	Median OS (mo)	P^1	Response rate (%)	P^1
CRYSTAL[19]	2009	All	599	FOLFIRI	8.0	0.048	18.6	0.31	38.7	0.0038
			599	FOLFIRI + Cetuximab	8.9		19.9		46.9	
		KRAS WT	350	FOLFIRI	8.4	0.0012	20	0.0093	39.7	< 0.001
		subgroup	316	FOLFIRI + Cetuximab	9.9		23.5		57.3	
		KRAS MT	183	FOLFIRI	7.7	0.26	16.7	0.75	36.1	0.35
		subgroup	214	FOLFIRI + Cetuximab	7.4		16.2		31.3	
OPUS[12]	2009	All	168	FOLFOX4	7.2	0.62	18	0.91	36	0.064
			169	FOLFOX4 + Cetuximab	7.2		18.3		46	
		KRAS WT	97	FOLFOX4	7.2	0.0064	18.5	0.39	34	0.0027
		subgroup	82	FOLFOX4 + Cetuximab	8.3		22.8		57	
		KRAS MT	59	FOLFOX4	8.6	0.0153	17.5	0.2	53	0.029
		subgroup	77	FOLFOX4 + Cetuximab	5.5		13.4		34	
COIN[20]	2011	KRAS WT	367	FOLFOX/XELOX	8.6	0.60	17.9	0.68	57	0.049
		group	362	FOLFOX/XELOX + Cetuximab	8.6		17		64	
		KRAS WT	127	FOLFOX	9.2	0.056	-	-	-	-
		group	117	FOLFOX + Cetuximab	9.0		-		-	
		KRAS WT	240	XELOX	8.0	0.56	-	-	-	-
		group	245	XELOX + Cetuximab	8.4		-		-	
		KRAS MT	268	FOLFOX/XELOX	-	-	14.8	0.8	-	-
		group	297	FOLFOX/XELOX + Cetuximab	-		13.6		-	
NORDIC-VII[21]	2012	All	185	Nordic FLOX (control group)	7.9	-	20.4	-	41	-
			194	FLOX + Cetuximab	8.3	0.31	19.7	0.67	49	0.15
			187	intermittent FLOX + Cetuximab	7.3	NA	20.3	0.79	47	NA
		KRAS WT	97	Nordic FLOX (control group)	8.7	-	22	-	47	-
		subgroup	97	FLOX + Cetuximab	7.9	0.66	20.1	0.48	46	0.89
			109	intermittent FLOX + Cetuximab	7.5	NA	21.4	0.66	51	NA
		KRAS MT	58	Nordic FLOX (control group)	7.8	-	20.4	-	40	-
		subgroup	72	FLOX + Cetuximab	9.2	0.07	21.1	0.89	49	0.31
			65	intermittent FLOX + Cetuximab	7.2	NA	20.5	0.84	42	NA
CALGB/ SWOG[22]	2014	KRAS WT group	578	FOLFIRI or mFOLFOX6 + Cetuximab	10.45	NA	29.93	0.34	-	-
80405 (study is ongoing)			559	FOLFIRI or mFOLFOX6 + Bevacizumab	10.84		29.04		-	
PRIME[9]	2010	KRAS WT	331	FOLFOX4	8.0	0.02	19.7	0.072	48	0.068
		group	325	FOLFOX4 + Panitumumab	9.6		23.9		55	
		KRAS MT	219	FOLFOX4	8.8	0.02	19.3	0.068	40	-
		group	221	FOLFOX4 + Panitumumab	7.3		15.5		40	
Hyman *et al*[37]	2015	BRAF V600	10	Vemurafenib	4.5	-	9.3	-	0	-
		group	27	Vemurafenib + Cetuximab	3.7		7.1		4	
Reidy *et al*[31]	2010	All	23	IMC-A12 (anti-IGF-1R antibody)	5.9	-	5.2	-	0	-
			21	IMC-A12 (anti-IGF-1R antibody) + Cetuximab	6.1		4.5		5	
		KRAS WT group	20	IMC-A12 (anti-IGF-1R antibody) + Cetuximab	9.4		10.9		0	

[1]95%CI. PFS: Progression-free survival; OS: Overall survival; All: All patients group; WT: Wild type; MT: Mutant type; NA: Not available; KRAS: KRAS exon 2, codons 12 and 13; FOLFIRI: Irinotecan, fluorouracil, and leucovorin; FOLFOX: Fluorouracil, leucovorin, and oxaliplatin; XELOX: Capecitabine and oxaliplatin; FLOX: Fluorouracil, leucovorin, and oxaliplatin.

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Mutant RAS and Outcome with EGFR Inhibitors

	PRIME[1,2]			OPUS[3,4]			CRYSTAL[3,5]		
	Treatment	PFS	OS	Treatment	PFS	OS	Treatment	PFS	OS
KRAS Ex2 WT	Panitumumab + FOLFOX4 (n = 325)	10.0	23.9	Cetuximab + FOLFOX4 (n = 82)	8.3	22.8	Cetuximab + FOLFIRI (n = 316)	9.9	23.5
	FOLFOX4 (n = 331)	8.6	19.7	FOLFOX4 (n = 97)	7.2	18.5	FOLFIRI (n = 350)	8.4	20.0
		HR 0.80*	HR 0.88		HR 0.57*	HR 0.86*		HR 0.70*	HR 0.80*
	Panitumumab			Cetuximab +			Cetuximab +		
	+ FOLFOX4 (n = 259)	10.1	25.8	FOLFOX4 (n = 36)	12.0	20.7	FOLFIRI (n = 178)	11.4	28.4
No *RAS* MT	FOLFOX4 (n = 253)	7.9	20.2	FOLFOX4 (n = 46)	5.8	17.8	FOLFIRI (n = 189)	8.4	20.2
		HR 0.72*	HR 0.77*		HR 0.43*	HR 0.83*		HR 0.56*	HR 0.69*
Any *RAS* MT	Panitumumab + FOLFOX4 (n = 272)	7.3	15.5	Cetuximab + FOLFOX4 (n = 94)	5.6	13.4	Cetuximab + FOLFIRI (n = 246)	7.4	16.4
	FOLFOX4 (n = 276)	8.7	18.7	FOLFOX4 (n = 78)	7.8	17.8	FOLFIRI (n = 214)	7.5	17.7
		HR 1.31*	HR 1.21*		HR 1.59*	HR 1.35		HR 1.10	HR 1.05

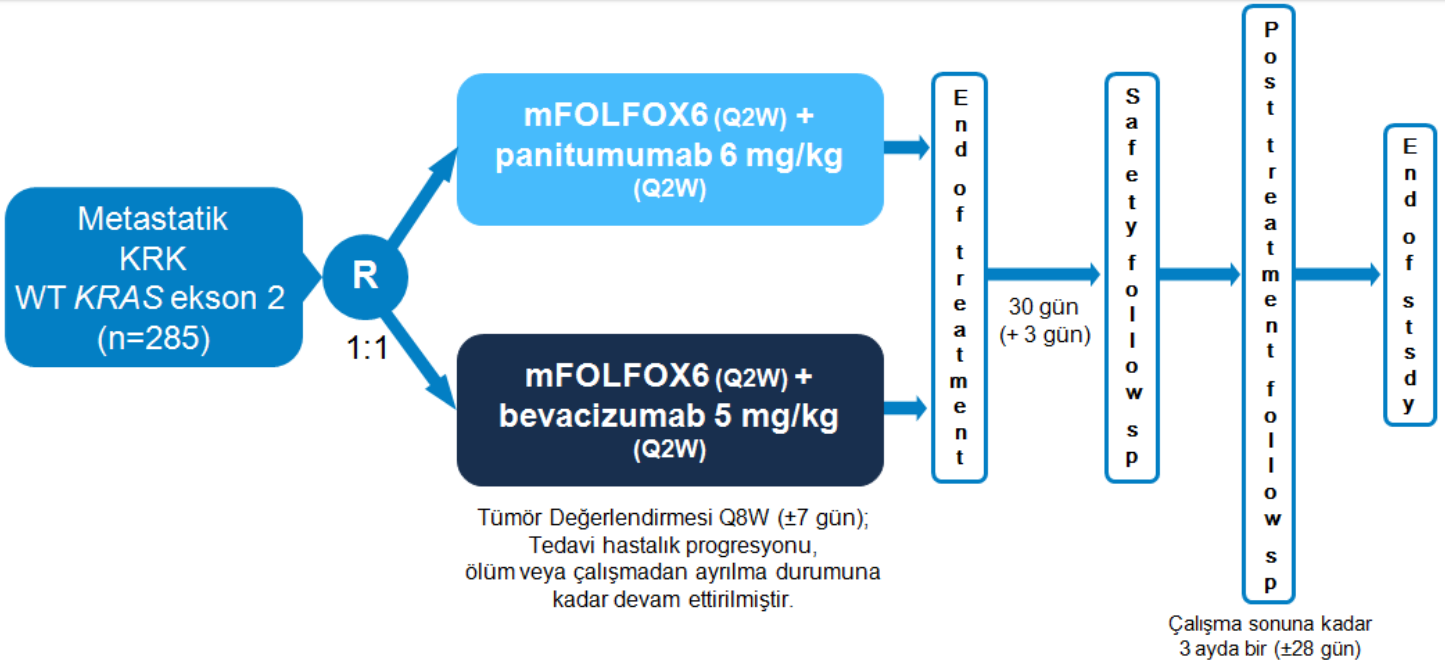
***RAS* mutations: negative predictor of outcomes may preclude anti-EGFR activity**

*Statistically significant.
HR, hazard ratio; PFS, progression-free survival.
1. Panitumumab, FDA label; 2. Douillard 2013; 3. Cetuximab, FDA label; 4. Tejpar 2014; 5. Ciardiello. 2014.

Metastatik Kolon Kanserinde Tedavi Seçenekleri

PEAK çalışması

WT *KRAS* ekson 2 mKRK'nin 1. basamak tedavisinde mFOLFOX6 + panitumumab veya bevacizumab



- Çalışma sonlanım noktaları: PFS (1°); GS, ORR, güvenlilik, araştırma amaçlı biyobelirteç analizi
- Resmi hipotez testi planlanmamıştır.

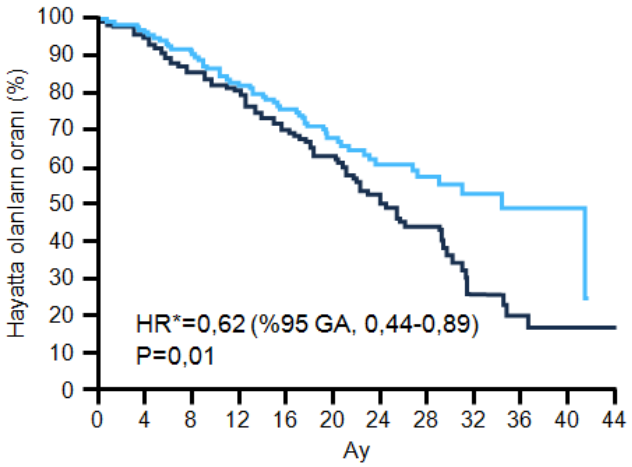
Karthaus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster);
Protocol ID: 20070509; ClinicalTrials.gov tanımlayıcı: NCT00819780.

ORR, objektif yanıt oranı; mFOLFOX6, modifiye FOLFOX6

Metastatik Kolon Kanserinde Tedavi Seçenekleri

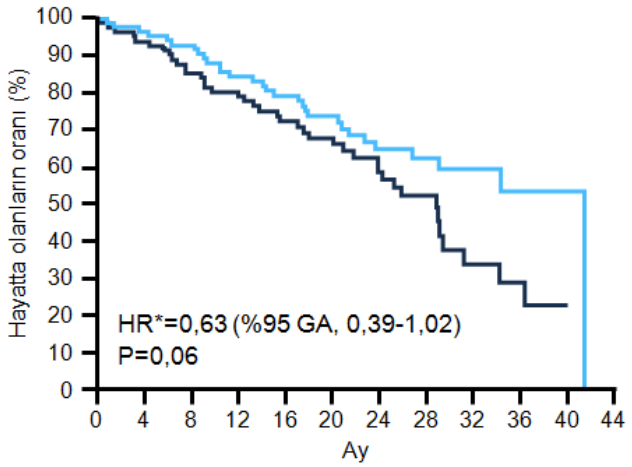
PEAK çalışması
GS (uzun takip analizi)

WT *KRAS* ekson 2



	Olay n (%)	Medyan, ay (%95 GA)
Panitumumab + mFOLFOX6 (n=142)	52 (37)	34,2 (26,6–NR)
Bevacizumab + mFOLFOX6 (n=143)	78 (55)	24,3 (21,0-29,2)

WT *RAS*

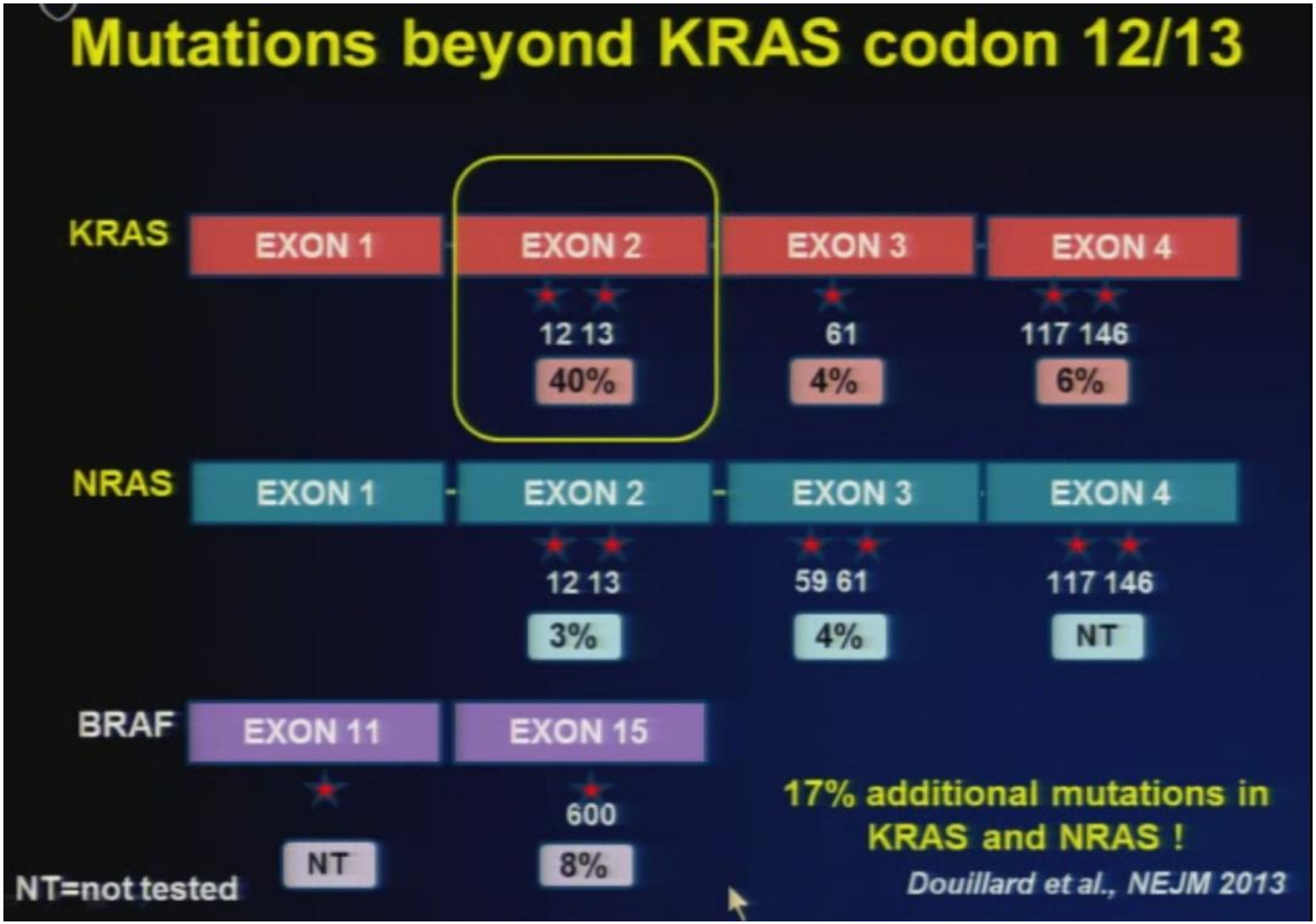


	Olay n (%)	Medyan, ay (%95 GA)
Panitumumab + mFOLFOX6 (n=88)	30 (34)	41,3 (28,8-41,3)
Bevacizumab + mFOLFOX6 (n=82)	40 (49)	28,9 (23,9-31,3)

*Tabakalandırılmış Cox orantılı tehlikeler modeli; Resmi hipotez testi planlanmamıştır; WT *RAS*, WT *KRAS* ve *NRAS* ekson 2/3/4; NR, ulaşılamamıştır.

Karthaus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster).

Metastatik Kolon Kanserinde Tedavi Seçenekleri



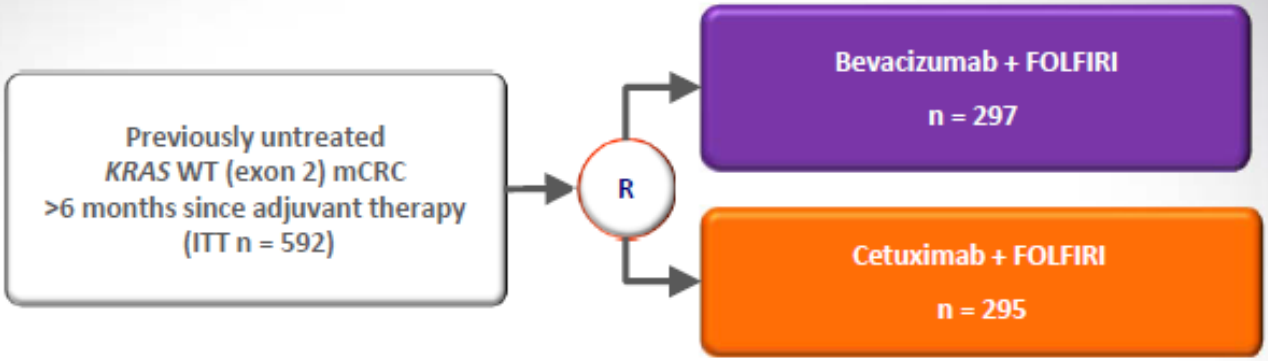
Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

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

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

FIRE-3 Design



- **Primary endpoint**: ORR **(in *KRAS* WT [exon 2])**
- **Secondary endpoints**: OS, PFS, R0 resection rate, safety
- **Exploratory analyses**
  - Extended *RAS* WT (*KRAS/NRAS* WT exon 2, 3, and 4) subpopulation
  - Second-line treatments following progression
  - Tumor location and gender

Results in ITT *KRAS* WT population

- No difference in ORR *(primary endpoint not met)*
- No difference in PFS or R0 resection rate
- OS statistically longer with cetuximab

Heinemann et al, Lancet Oncology, 2014

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

FIRE-3 Secondary Endpoint OS: Cetuximab vs Bevacizumab in *RAS* WT*

OS	Cetuximab + FOLFIRI		Bevacizumab + FOLFIRI		HR (95% CI)	*p* value
	Median, months	95% CI	Median, months	95% CI		
KRAS exon 2 WT (ITT population) (n = 592)[1]	28.7	24.0–36.6	25.0	22.7–27.6	0.77 (0.62–0.96)	0.017
RAS* WT **(n = 400)[2]**	**33.1**	24.5–39.4	**25.0**	23.0–28.1	0.697 (0.54–0.90)	0.0059
Other *RAS* MT (n = 65)[1,3]	16.4	15.9–27.6	20.6	17.0–28.4	1.20 (0.64–2.28)	0.57
All *RAS* MT[2] (n = 188)[2**]	20.2	16.4–23.4	20.6	17.1–26.3	1.05 (0.77–1.44)	0.75

**KRAS/NRAS* exon 2, 3, and 4 WT.
***All *RAS* MT population consists of non-ITT *KRAS* exon 2 MT and ITT other *RAS* MT.
1. Stintzing et al. ECC 2013. Abstract LBA17. 2. Stintzing et al. ESMO 2014. Abstract LBA11. 3. Heinemann et al, Lancet Oncology 2014.

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

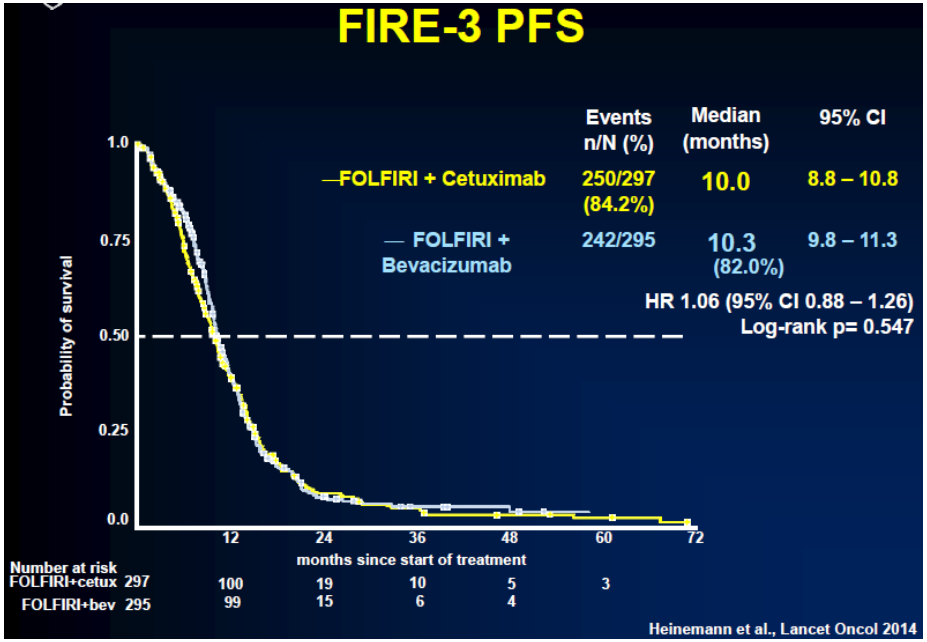
FIRE-3 ORR Primary Endpoint

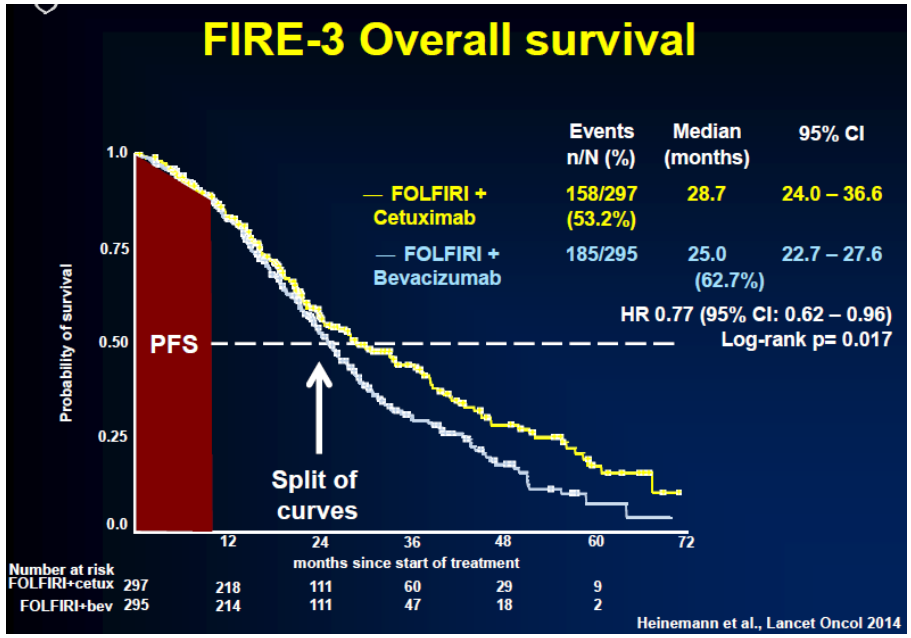
	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab		Odds ratio	p
ORR	%	95%-CI	%	95%-CI		
ITT population (N= 592)	62.0	56.2 – 67.5	58.0	52.1 – 63.7	1.18 0.85-1.64	0.183
Assessable for response (N= 526)	72.2	66.2 – 77.6	63.1	57.1 – 68.9	1.52 1.05-2.19	0.017

p = Fisher's exact test (one-sided)

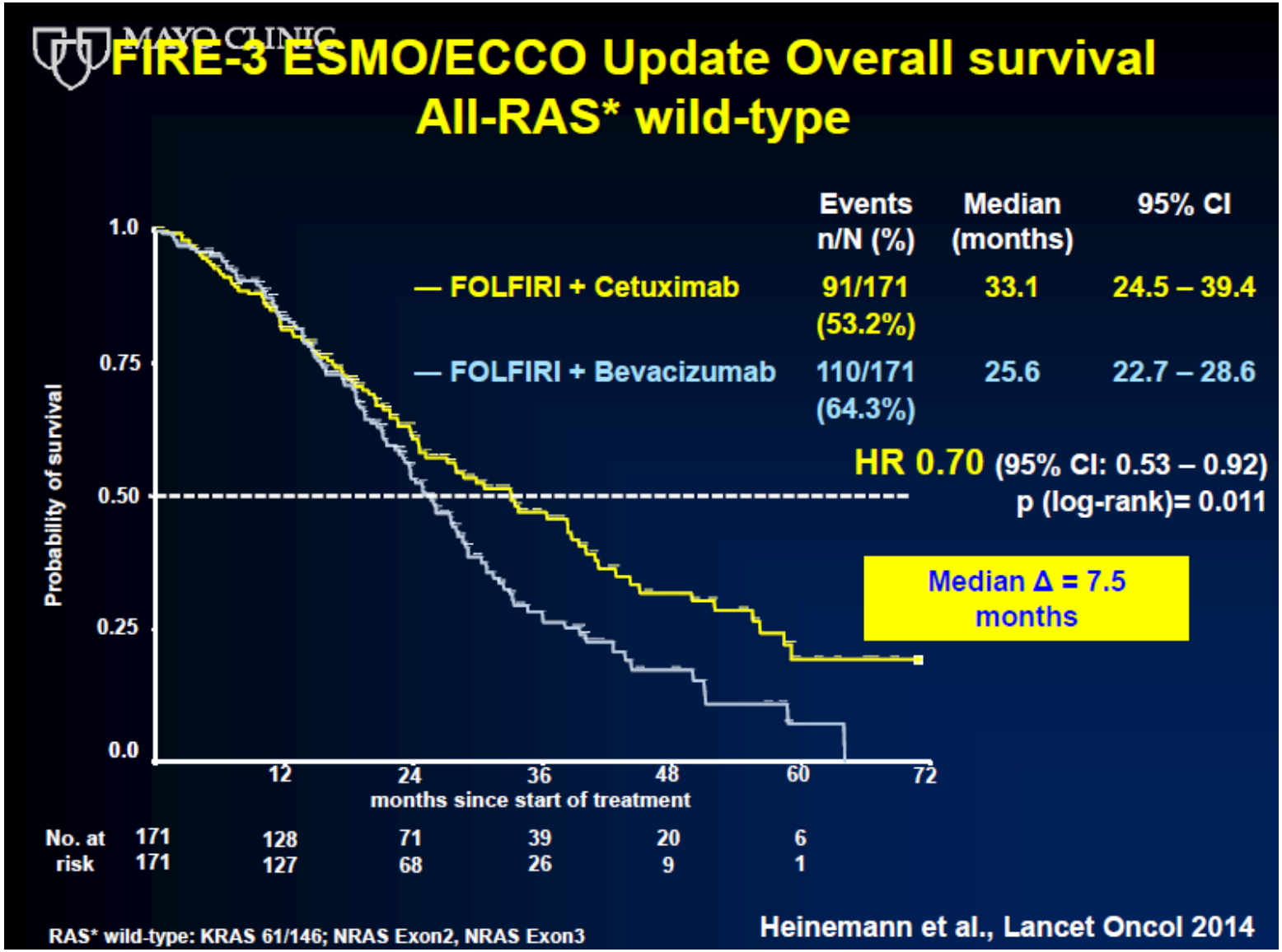
Heinemann et al., Lancet Oncol 2014

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

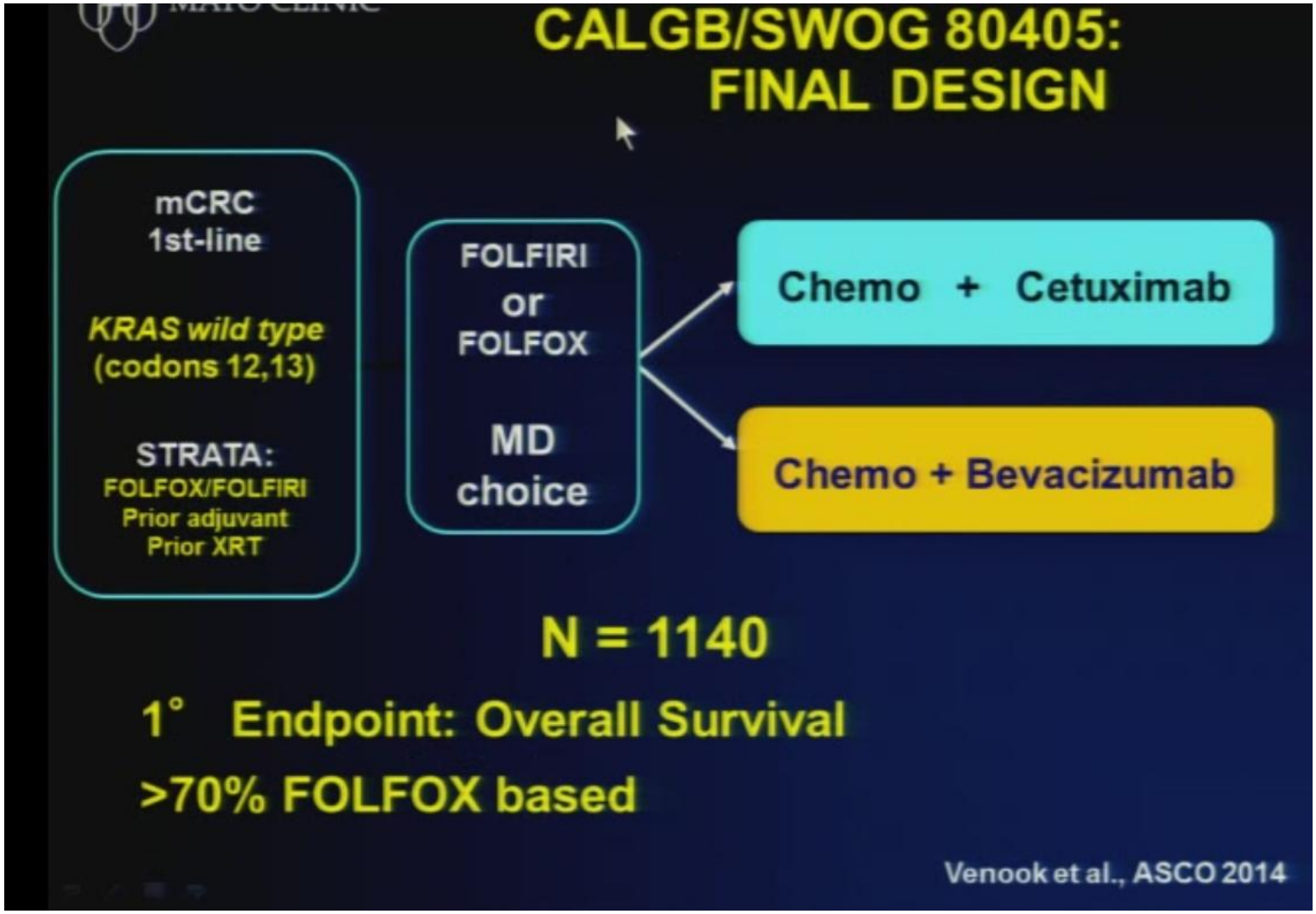




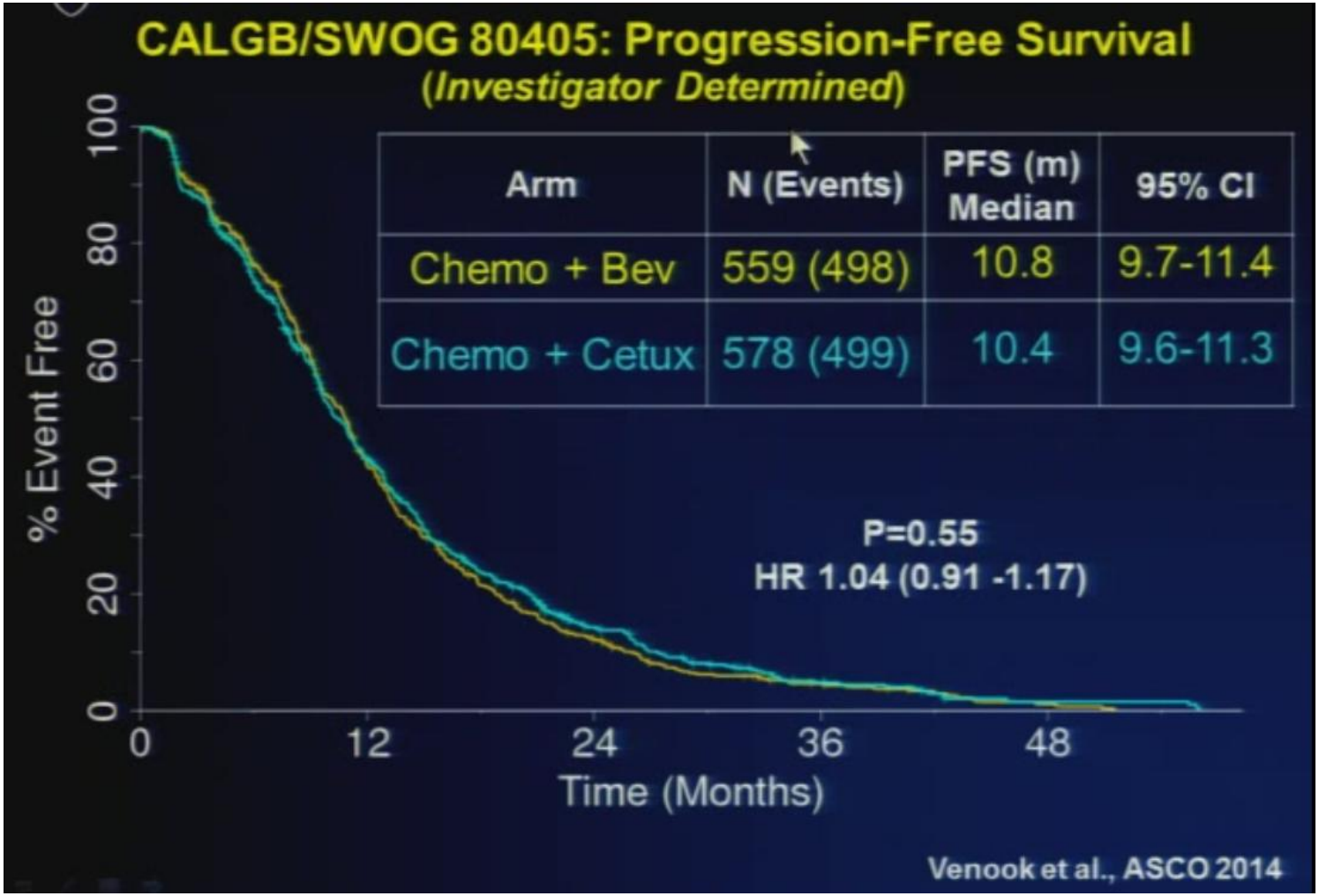
Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



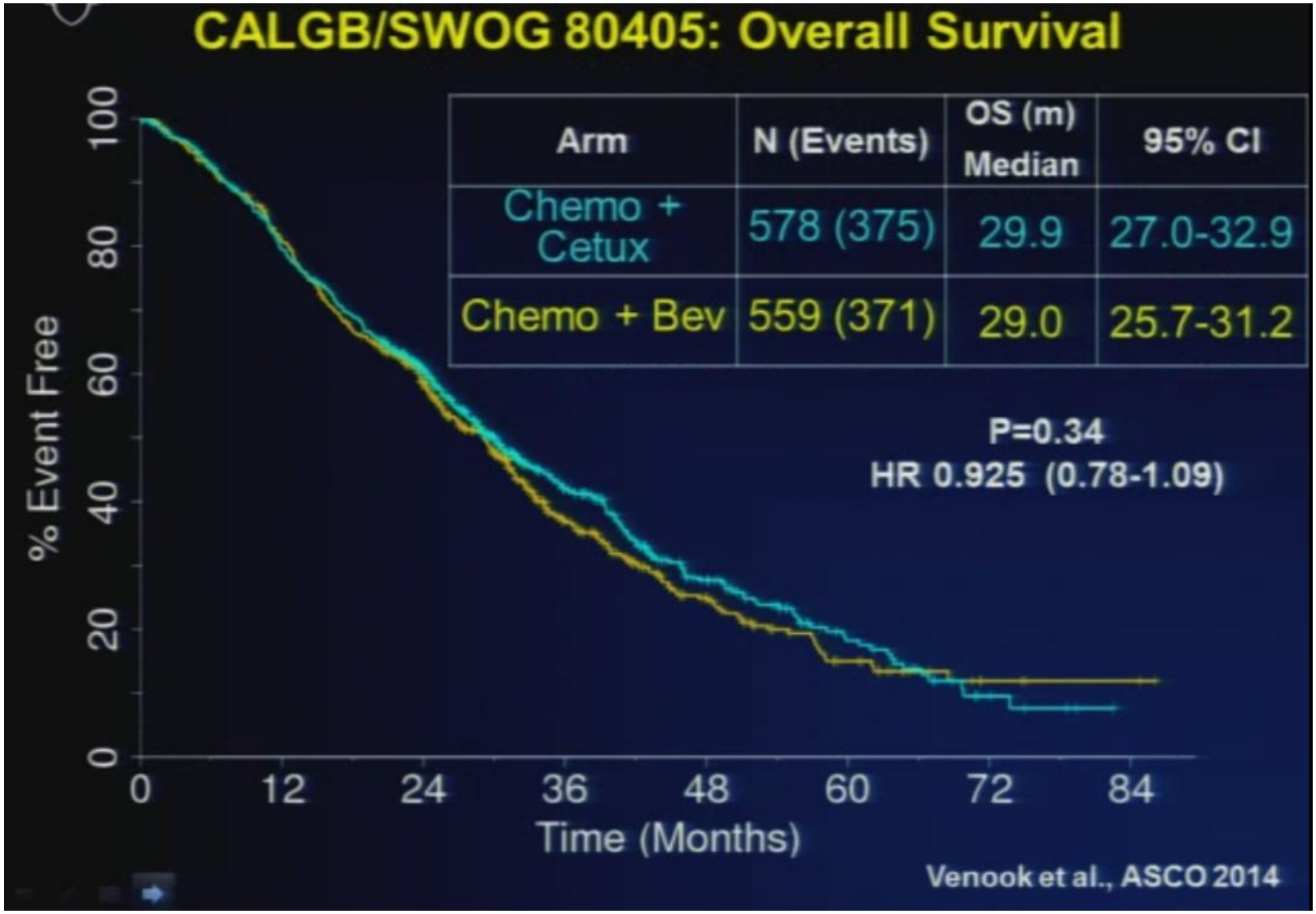
Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

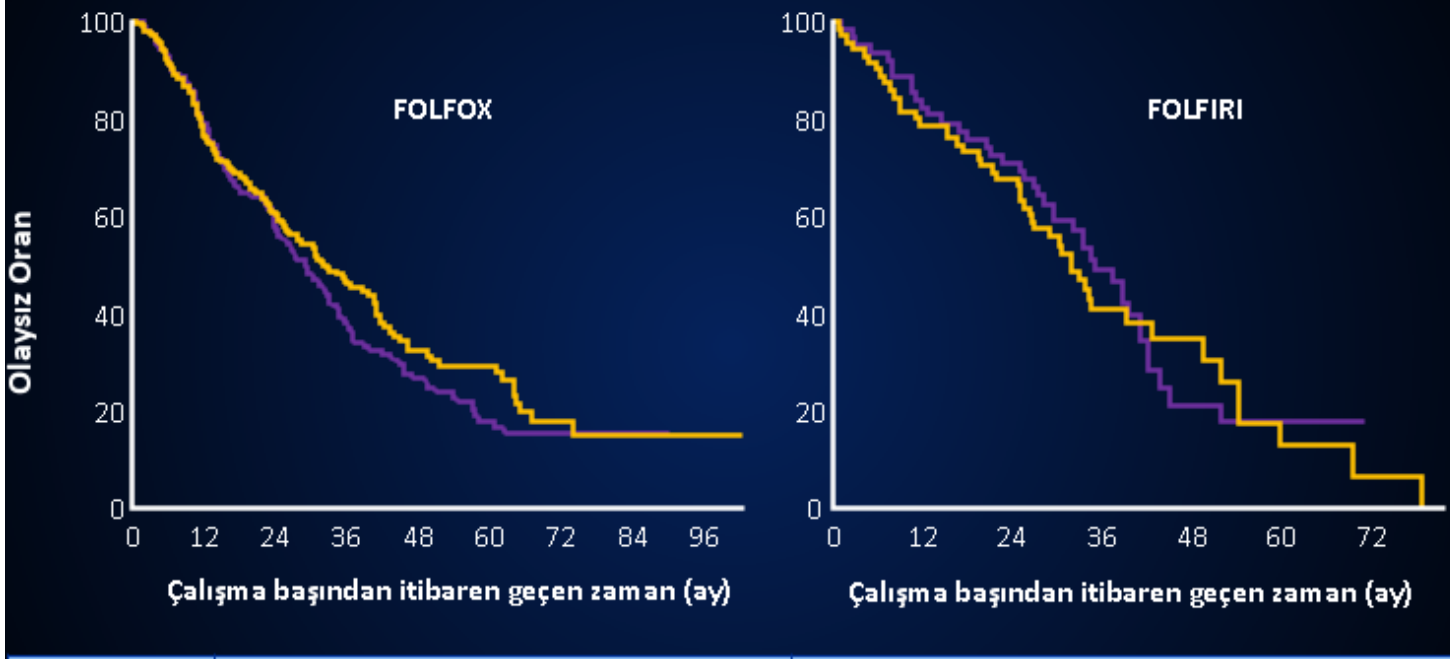


Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

CALGB 80405: Tüm *RAS* WT hastalarda tüm kemoterapi rejimleri ile Setuksimab Bevasizumaba OS üstünlüğü gösterememiştir



	FOLFOX (n = 390)			FOLFIRI (n = 136)		
Kol	medyan (95% CI)	HR (95% CI)	P	medyan (95% CI)	HR (95% CI)	P
Kemo + bev	29.0 (24.0-32.8)	0.86 (0.6-1.1)	.2	35.2 (28.3-41.3)	1.1 (0.7-1.6)	.7
Kemo + cetux	32.5 (26.1-40.4)			32.0 (25.6-42.9)		

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

MAYO CLINIC

FIRE-3 and CALGB/SWOG 80405: Efficacy by *RAS* Status

	FIRE 3 CT + Bev vs CT + Cetux	CALGB/SWOG 80405 CT + Bev vs CT + Cetux
Primary endpoint	Response rate	Overall survival
CT backbone	All FOLFIRI	FOLFOX 74%/FOLFIRI 26%
	(n=295 vs 297)	(n=559 vs 578)
RR, %	58 vs 62 P=0.183	57.2 vs 65.6 P=0.02
PFS, months	10.3 vs 10.0; HR=1.06 (P=0.547)	10.8 vs 10.4; HR=1.04 (P=0.55)
Median OS, months	25.0 vs 28.7 HR=0.77 (*P*=0.017)	29.0 vs 29.9 HR=0.92 (*P*=0.34)
***RAS* WT**	**(n=201 vs 199)**	**(n=256 vs 270)**
RR, %	58.7 vs 65.3; OR=1.33 (*P*=0.18)	53.8 vs 68.6; (*P*<0.01)
PFS, months	10.2 vs 10.3; HR=0.97 (P=0.77)	11.3 vs 11.4; HR=1.1 (P=0.31)
OS, months	**25.0 vs 33.1 HR=0.70 (*P*=0.006)**	**31.2 vs 32.0 HR=0.9 (*P*=0.40)**

Stintzing S, et al. Presented at: ESMO. 2014 (abstr LBA11). Lenz H-J, et al. Presented at: ESMO. 2014 (abstr 501O). Venook. Presented at: WCGC. 2014.

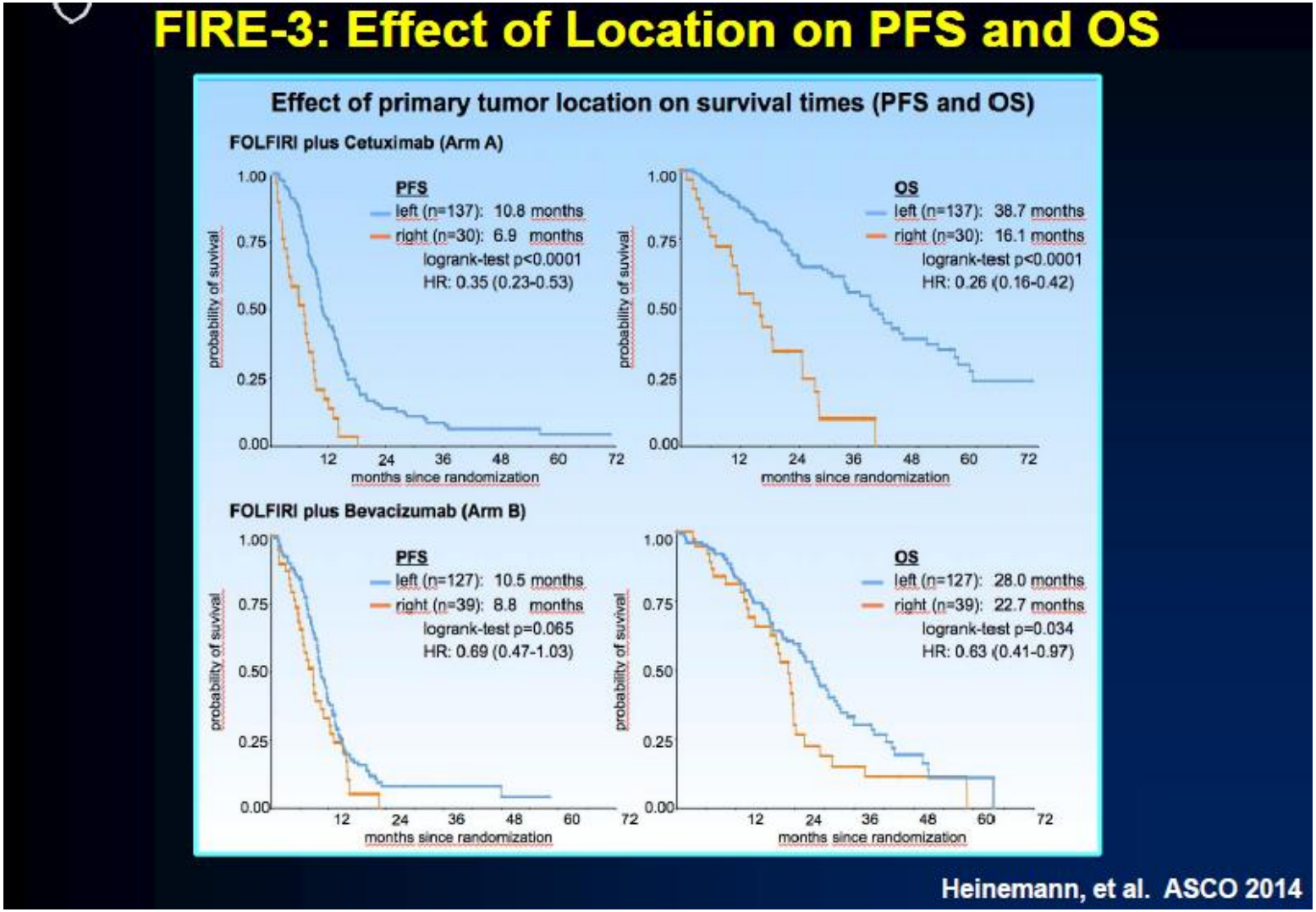
Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

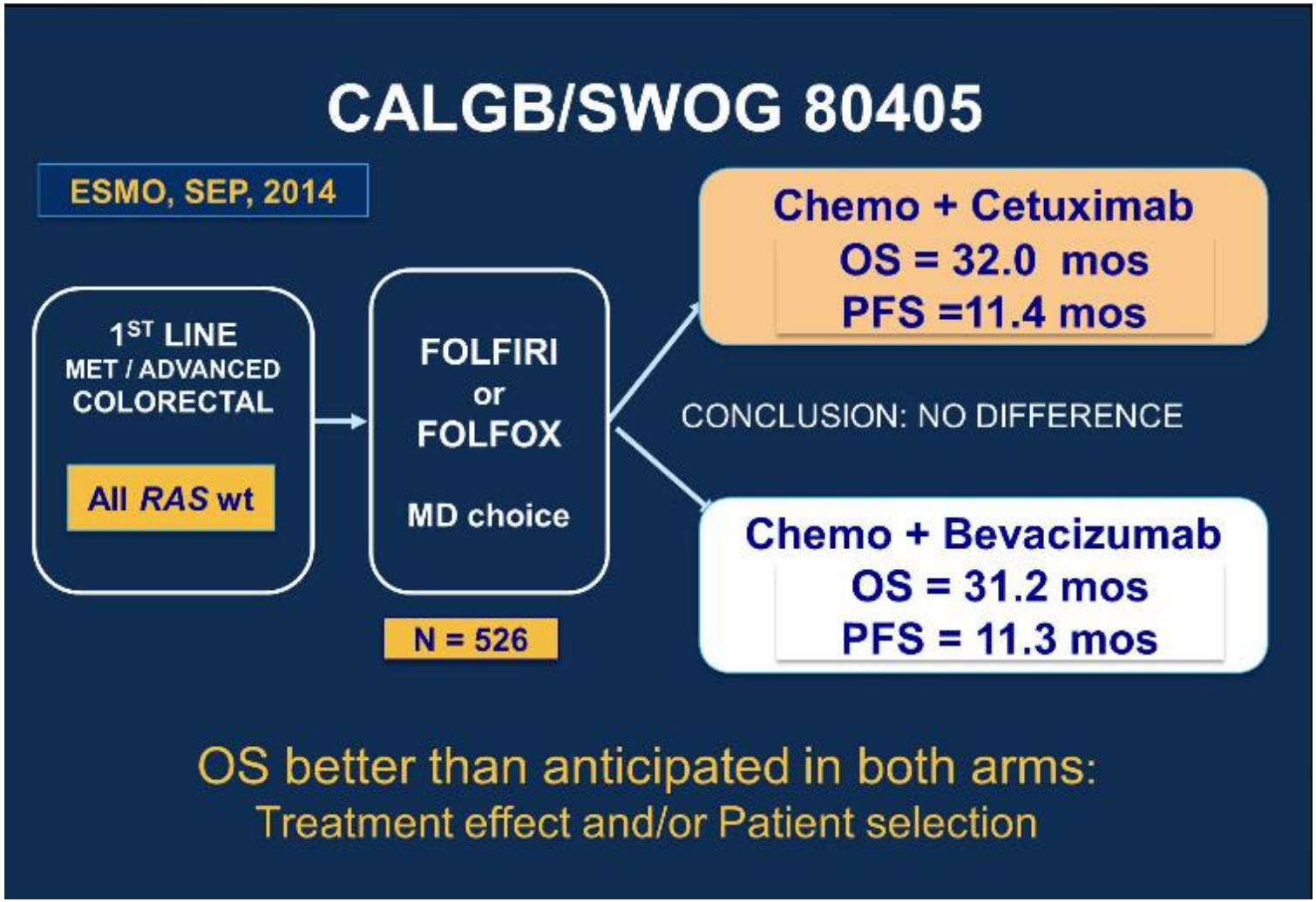
Metastatic Colorectal Cancer: Does Side Matter?

Study	Patients N	Molecular Selection	Treatment	Line of therapy	OUTCOME	RIGHT	LEFT
O'Dwyer JCO 2001 (E2290)	N = 1120	NONE	5FU variations	First line	OS (mos)	10.9	15.8
Brule, EJC 2015 (CO.17)	N =399	*KRAS* wt	BSC v. BSC + CET	Salvage	PFS (mos)	1.9 1.8	1.9 5.4
Loupakis, JNCI 2015	N = 2053	NONE	FOLFIRI/BEV FUOX/BEV IFL/BEV	First line	OS (mos)	24.8 18.0 14.6	42.0 23.0 24.0

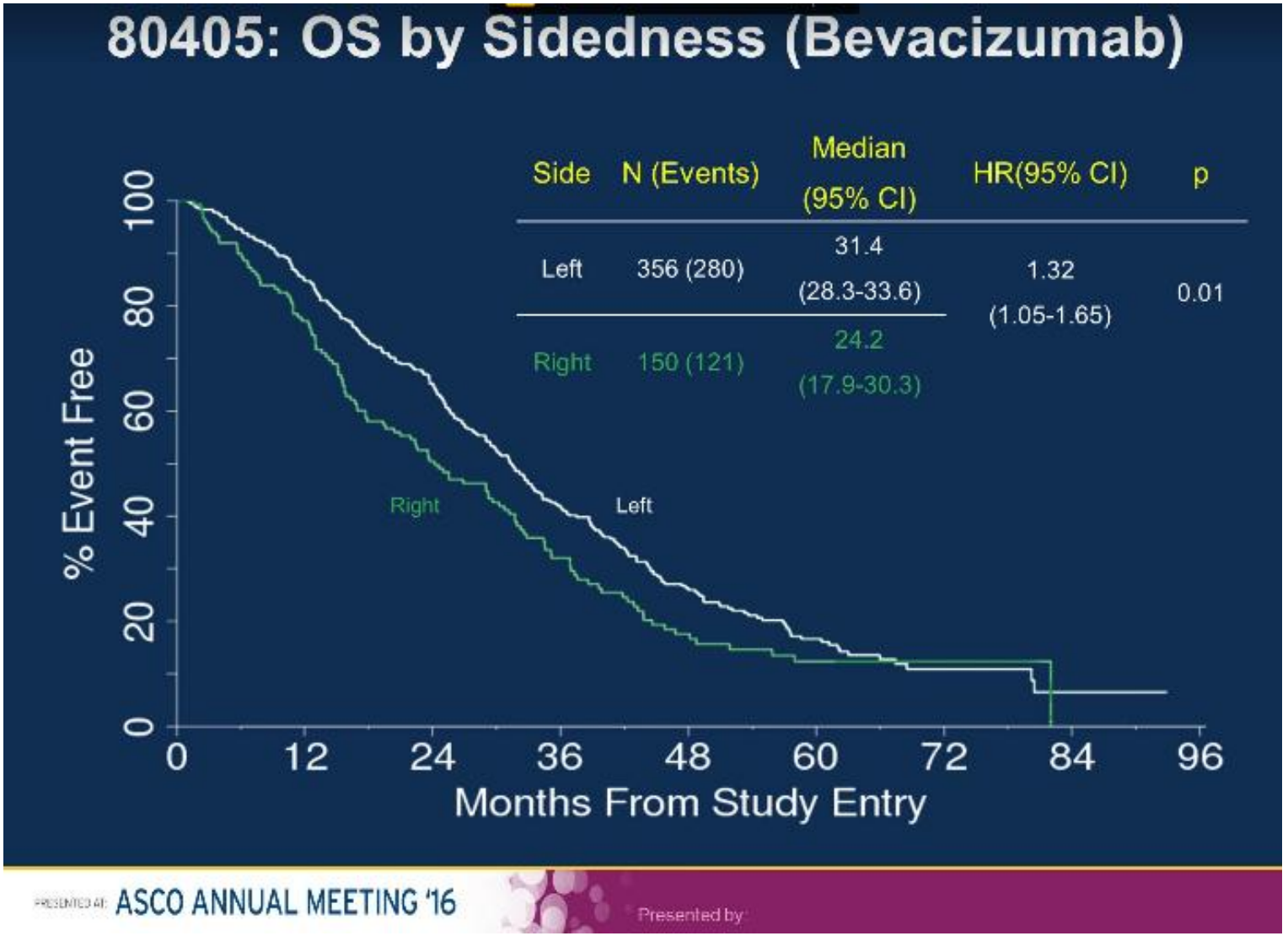
Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



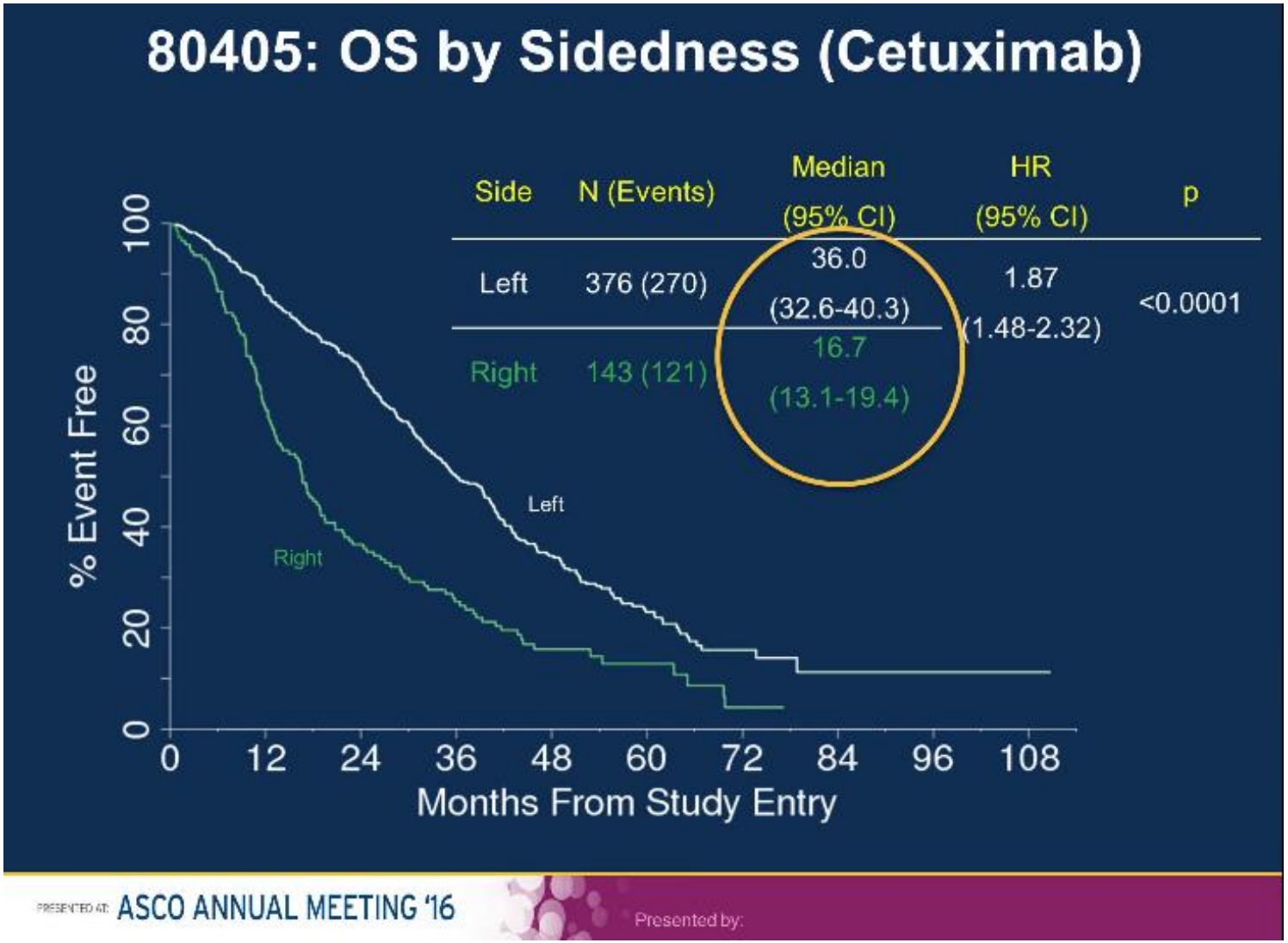
Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

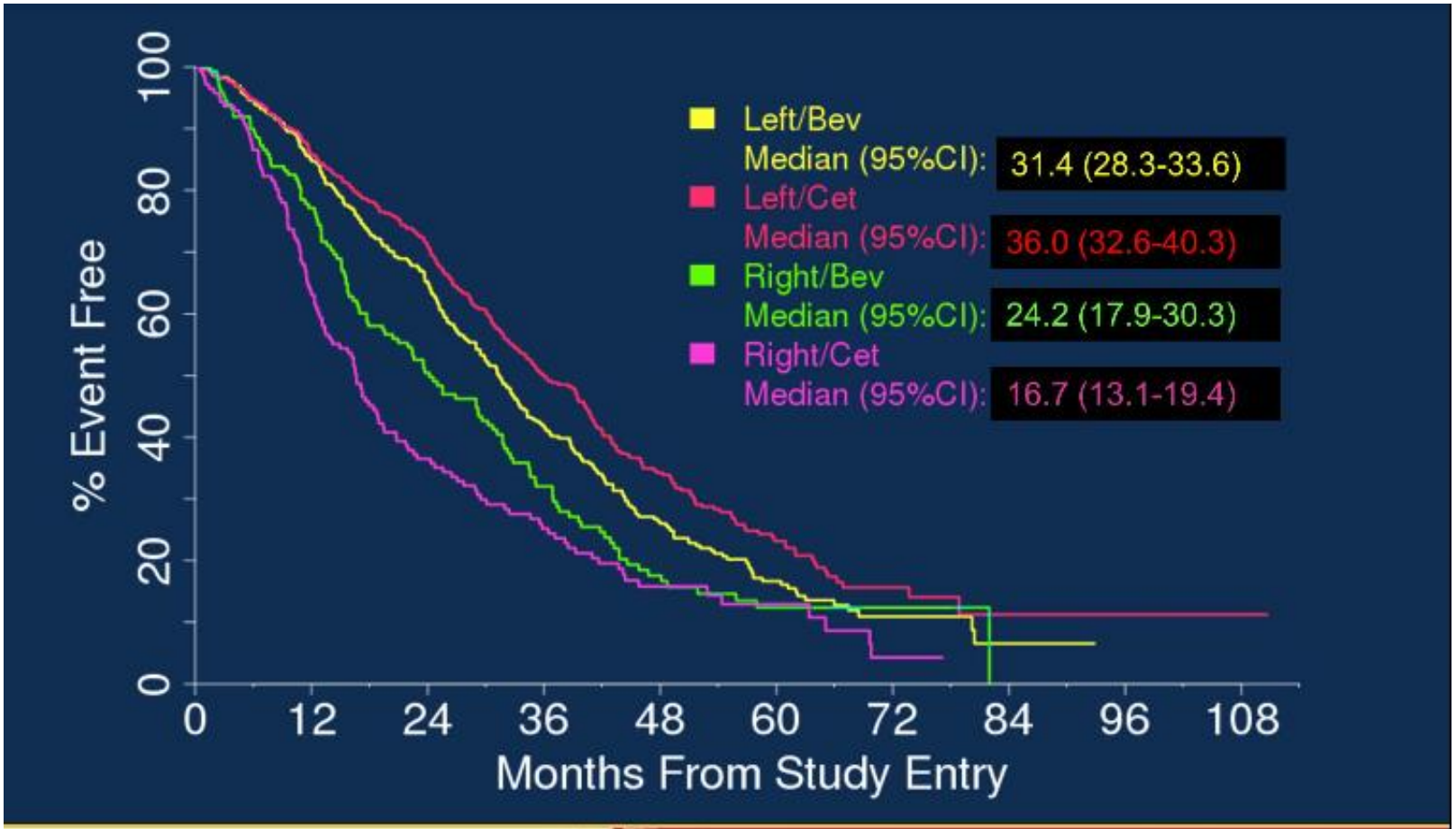
KRAS wt N = 1025	Right 1° Median OS (mos)	Left 1° Median OS (mos)	Hazard Ratio 95% CI (adjusted*)	P (adjusted*)
All pts	19.4	33.3	1.55 (1.32,1.82)	P < 0.0001
Cet	16.7	36.0	1.87 (1.48, 2.32)	P < 0.0001
Bev	24.2	31.4	1.32 (1.05, 1.65)	P = 0.01

19.3 MONTHS IS A BIG DIFFERENCE !!

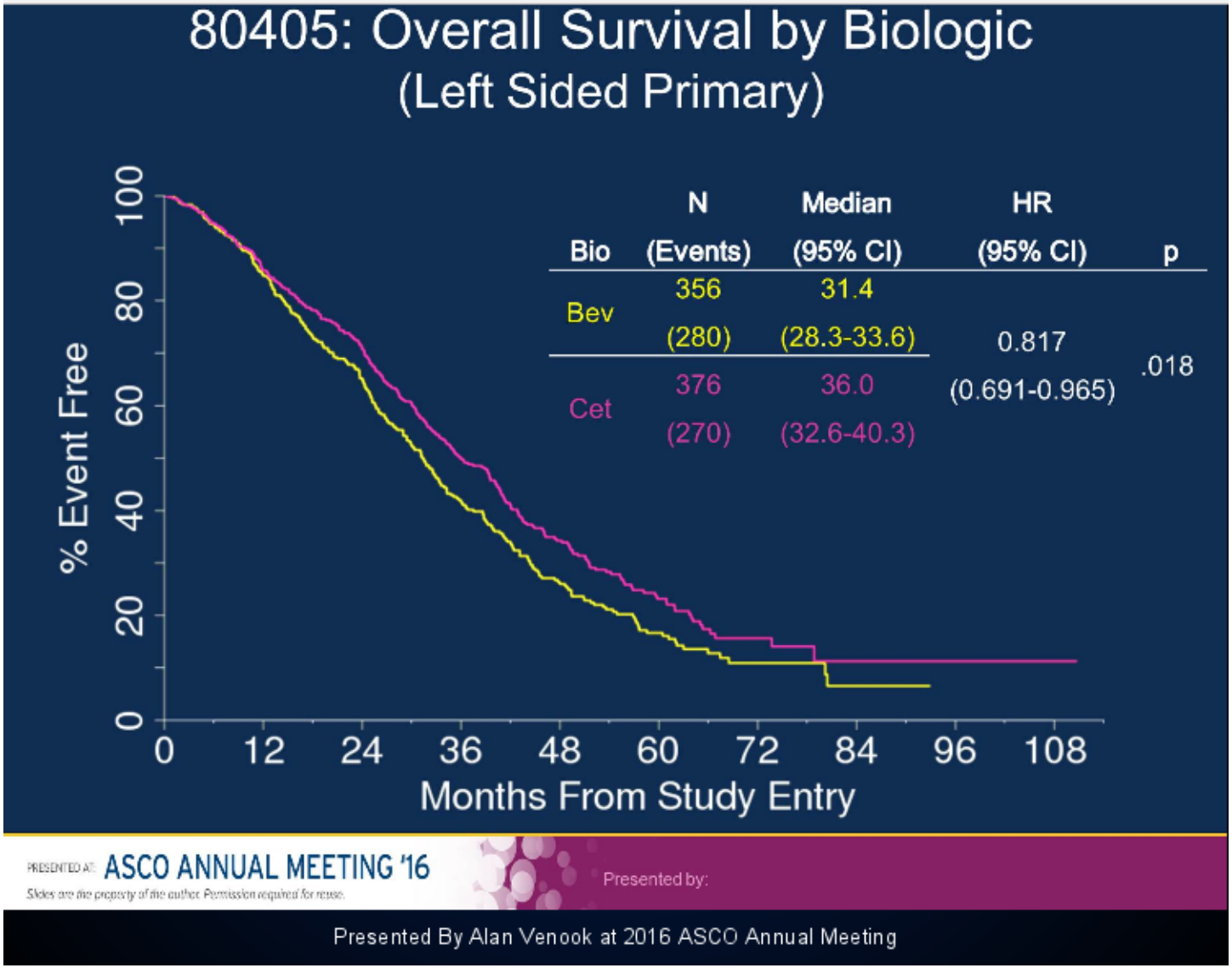
*Adjusted for biologic, protocol chemotherapy, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases

Presented By Alan Venook at 2016 ASCO Annual Meeting

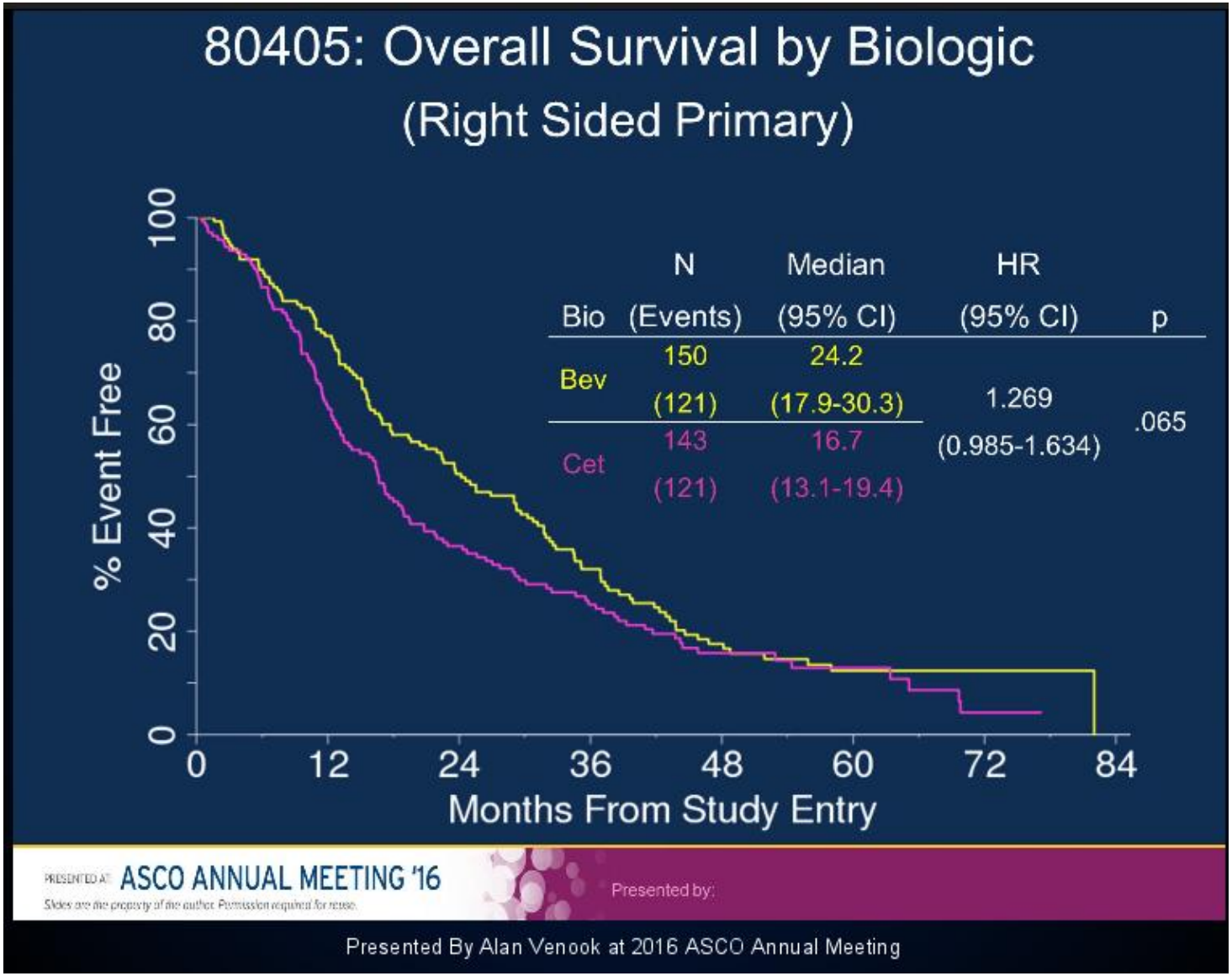
Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

80405: Sidedness is Prognostic
Progression Free Survival (PFS)

All RAS wt N=474	Right 1° Median PFS (mos)	Left 1° Median PFS (mos)	Hazard Ratio Left vs Right 95% CI (adjusted*)	P (adjusted*)
All pts	8.9	11.7	0.81 (0.64, 1.01)	0.06
Cet	7.5	12.7	0.61 (0.45, 0.84)	0.002
BV	10.2	11.2	0.99 (0.71, 1.37)	0.96

*Adjusted for biologic, protocol chemotherapy, prior adjuvant therapy, prior RT, age, sex , synchronous disease, in place primary, liver metastases

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

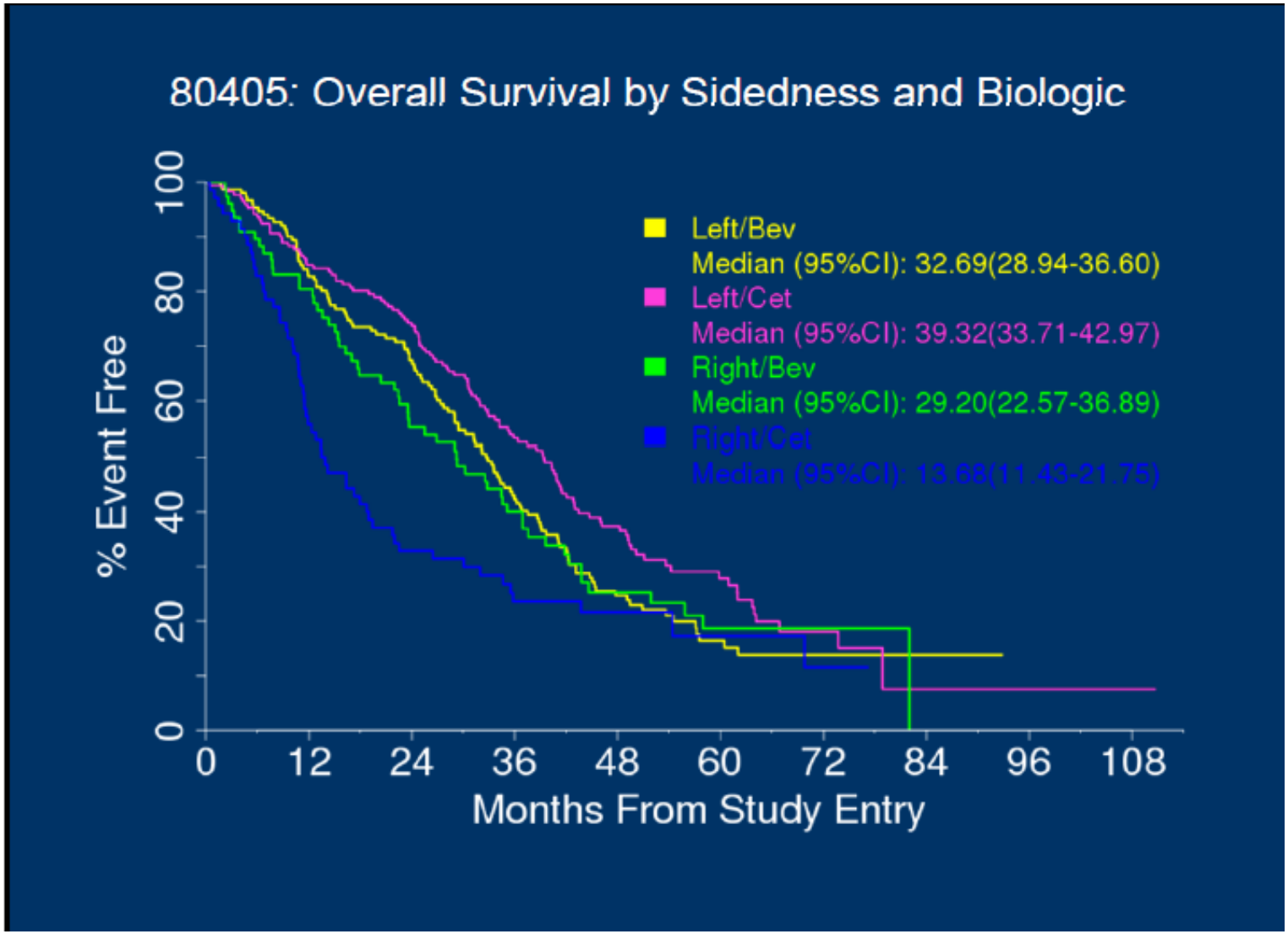
80405: Exploratory Analysis (*wt* v *mut*)

If true, we know less about RAS than we think we do

		Right 1° Median OS (mos)	Left 1° Median OS (mos)	Log Rank p (adjusted*)
	All pts	19.4	33.3	P < 0.0001
KRAS wt N=1025	Cet	**16.7** YES	36.0	P < 0.0001
	Bev	24.2	31.4	P = 0.01
	All pts	23.1	30.3	
*KRAS mut** N=213	Cet	**23.3** NO	27.9	
	Bev	23.0	31.1	

* pre-amendment cohort

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

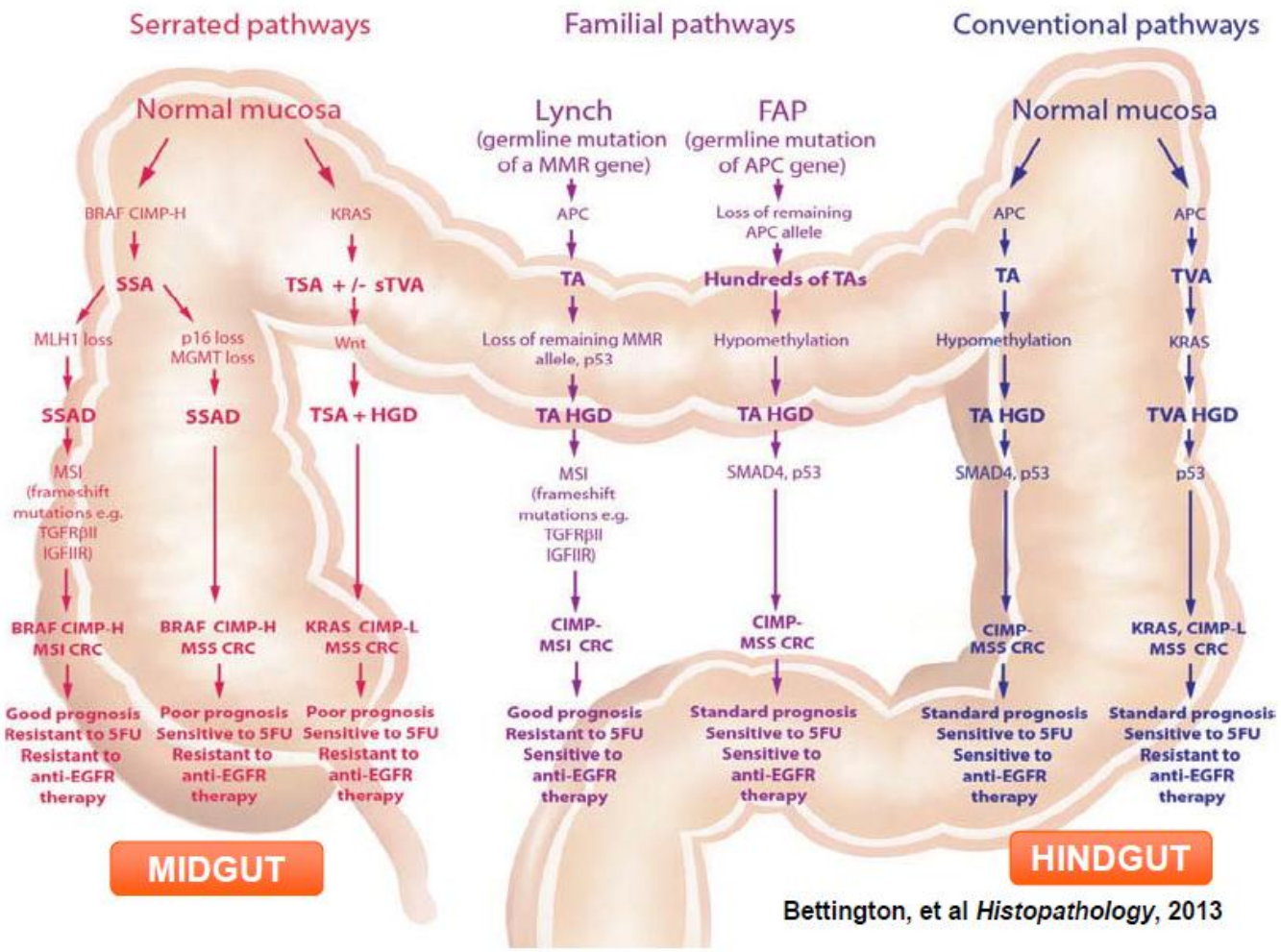
Metastatic Colorectal Cancer: Side Matters

PUBLICATION (Study)	Patients N	Molecular Selection	Treatment	OUTCOME	RIGHT	LEFT
O'Dwyer JCO, 2001 (E2290)	N = 1120	NONE	5FU VARIATIONS	OS (MOS)	10.9	15.8
Brule, Eur J Can, 2015 (CO.17)	N =399	*KRAS* wt	BSC v. BSC + CET	PFS (MOS)	1.9 1.8	1.9 5.4
Loupakis, JNCI, 2015	N = 2053	NONE	FOLFIRI/BEV FUOX/BEV IFL/BEV	OS (MOS)	24.8 18.0 14.6	42.0 23.0 24.0
Moretto, The Oncologist, 2016	N = 75 (R=14; L=61)	RAS, BRAF wt	CET or Irino/CET	RR: PFS:	0% 2.3	41% 6.6
Tejpar, JAMA Onc, 2016, CRYSTAL van Cutsem	N = 367	All RAS wt	FOLFIRI / CET FOLFIRI	RR: OS (MOS):	42.4% 33.3% 18.5 15.0	72.5% 40.6% 28.7 21.7
Tejpar, JAMA Onc, 2016, FIRE-3, Heinemann	N = 333	All RAS wt	FOLFIRI / CET FOLFIRI / BEV	RR: OS (MOS):	52.6% 50.0% 18.3 23.0	68.8% 61.7% 38.3 28.0

Metastatik Kolon Kanserinde Tedavi Seçenekleri

Dr Kimmie Ng: Tedavi kararını etkileyen tüm faktörler dikkate alınmalıdır.

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Bettington, et al *Histopathology*, 2013

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

Prevalence of New RAS Mutations

	New RAS Total[a]	KRAS Exon 3[a] (59, 61)	KRAS Exon 4[a] (117, 146)	NRAS Exon 2[a] (12, 13)	NRAS Exon 3[a] (59, 61)	NRAS Exon 4[a] (117, 146)
OPUS	26.3%	5.9%	9.3%	6.8%	5.1%	0.8%
PICCOLO	9.8%	NR[b]	3.7%[c]	6.3%[d]	NR[b]	NE
20020408	17.6%	4.8%[b]	5.0%	4.2%	3.0%[b]	1.1%
20050181	20.5%	4.6%	7.9%	2.3%	5.8%	0.0%
PRIME	17.4%	3.7%[b]	5.6%	3.4%	4.1%[b]	0.0%
FIRE-3	16.0%	4.3%[b]	4.9%[c]	3.8%	2.0%[b]	0.0%
PEAK	20.1%	4.1%	7.7%	5.4%	5.9%	0.0%
COIN	8.4%	2.1%[b]	NE	0.9%[e]	3.0%[b]	NE
CRYSTAL	14.7%	3.3%	5.6%	3.5%	2.8%	0.9%
SUMMARY[f]	19.9% (16.7%, 23.4%)	4.3% (3.3%, 5.5%)	6.7% (5.7%, 7.9%)	3.8% (3.0%, 4.8%)	4.8% (3.4%, 6.8%)	0.5% (0.2%, 1.2%)

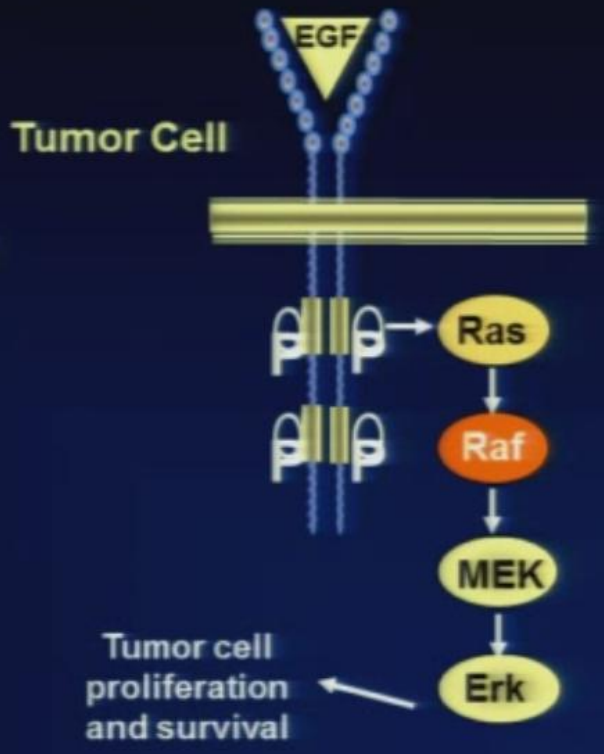
Note: Without this knowledge of new RAS mutations, we would be spending hundreds of millions of dollars likely harming our patients!

Sorich MJ et al. 2014

Metastatik Kolon Kanserinde Tedavi Seçenekleri

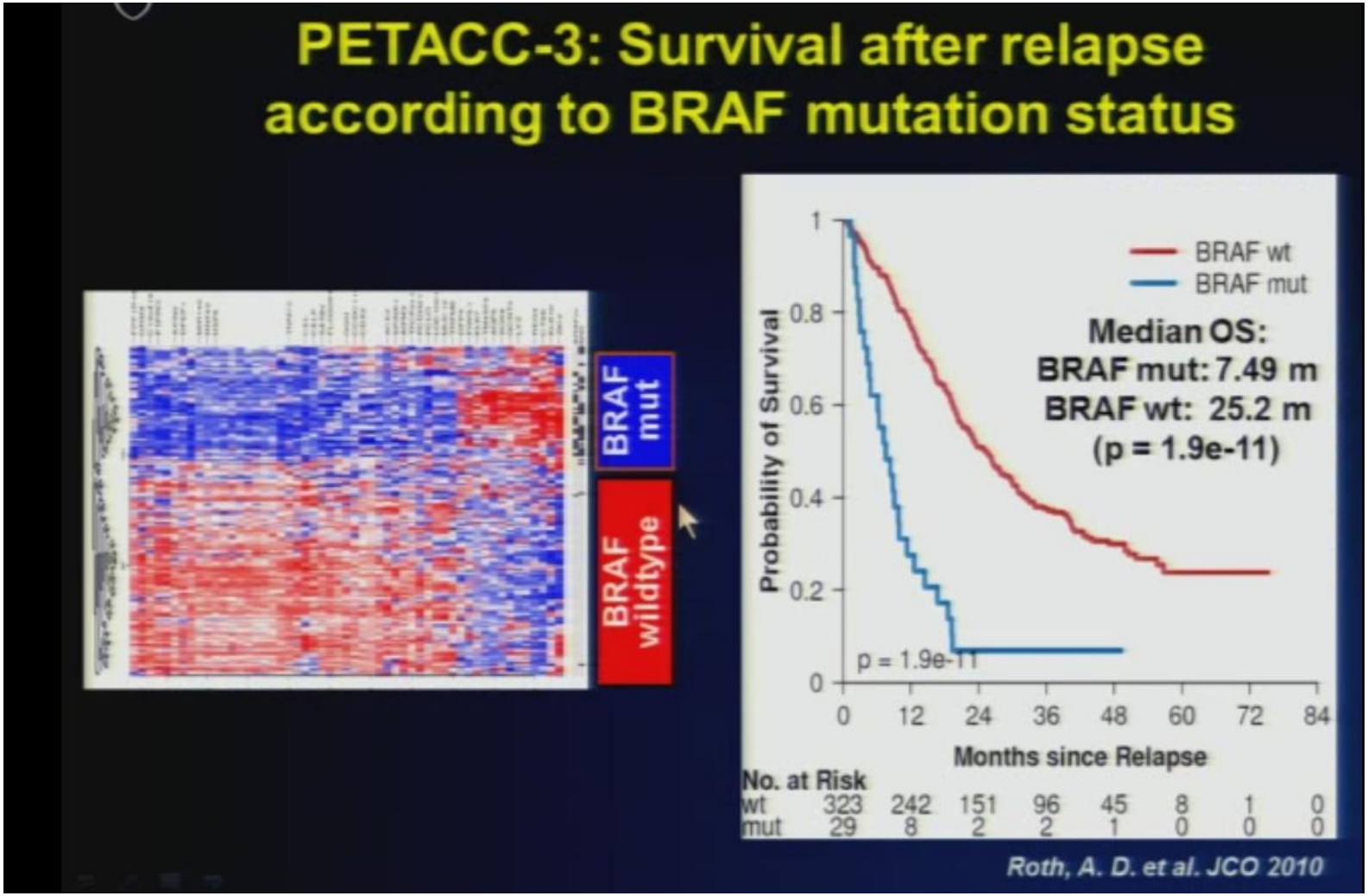
BRAF Mutations in CRC

- BRAF is primary effector of RAS signaling
- BRAF mutations:
  - Occur most frequently in exon 15 (V600E)
  - Found in 4%-14% of patients with CRC
  - Mutually exclusive with RAS mutations



Yarden. *Nat Rev Mol Cell Biol.* 2001;2:127; Di Nicolantonio. *J Clin Oncol.* 2008;26:5705; Artale. *J Clin Oncol.* 2008;26:4217.

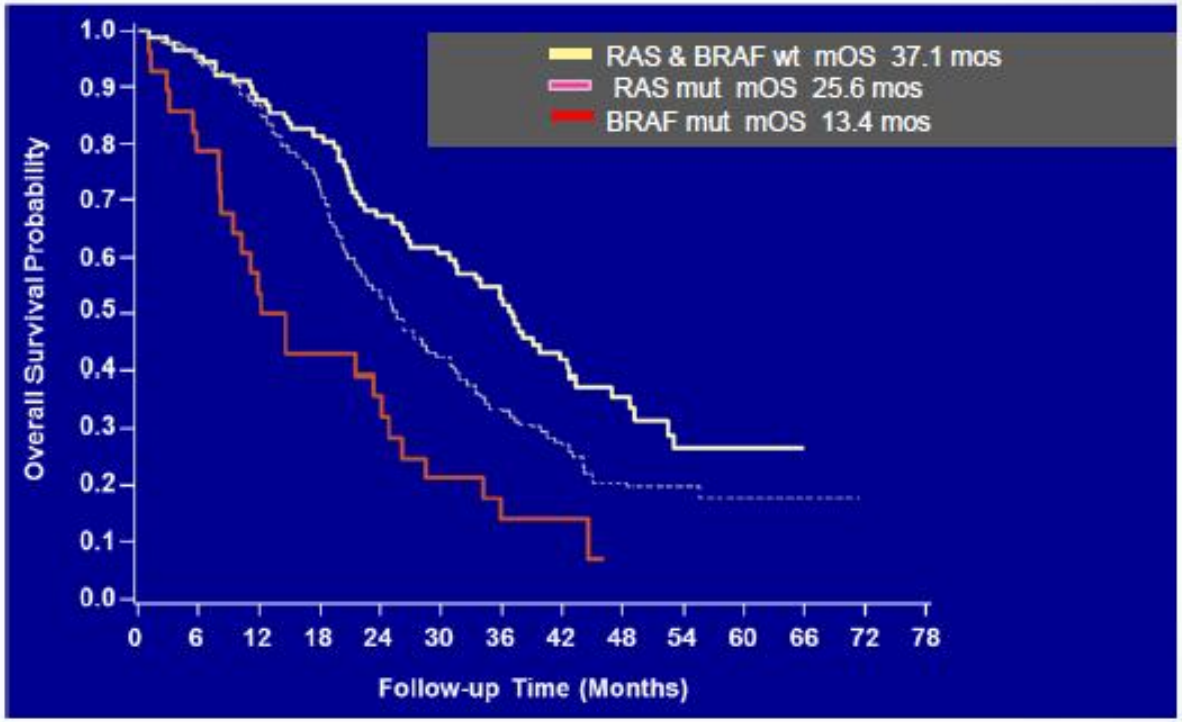
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

BRAFm CRC: Poor Survival

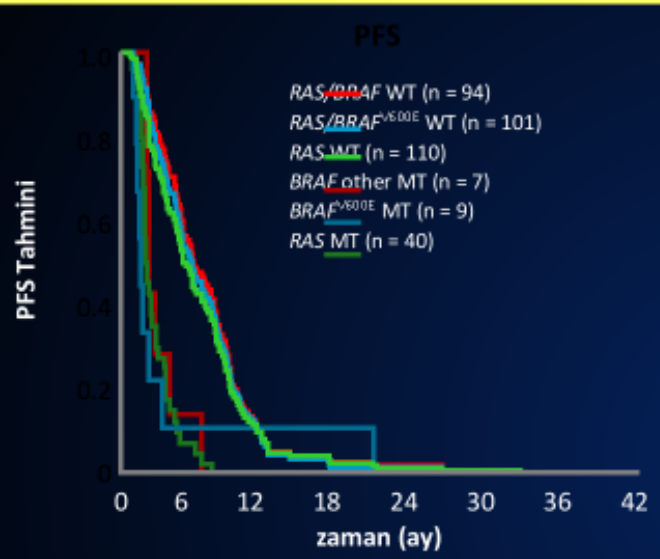
TRIBE

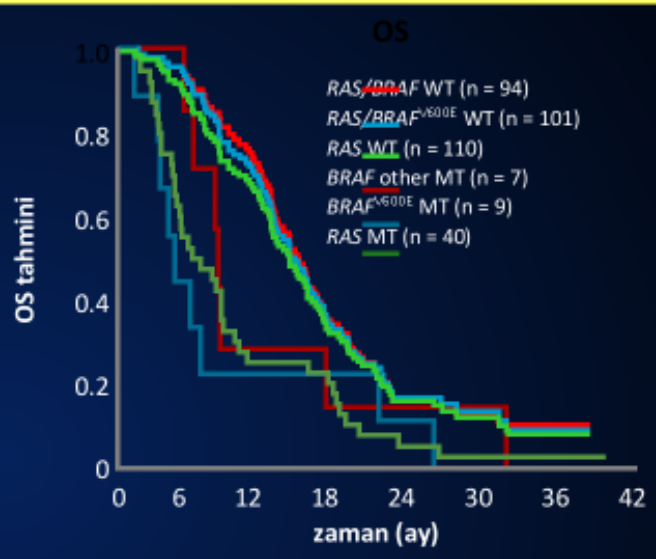


Loupakis F, et al, *J Clin Oncol* 33, 2015 (suppl; abstr 3510).

Metastatik Kolon Kanserinde Tedavi Seçenekleri

BREAC: BRAF mutasyon analizi ile anti-EGFR tedaviye yanıtsızlık gösterilmiştir



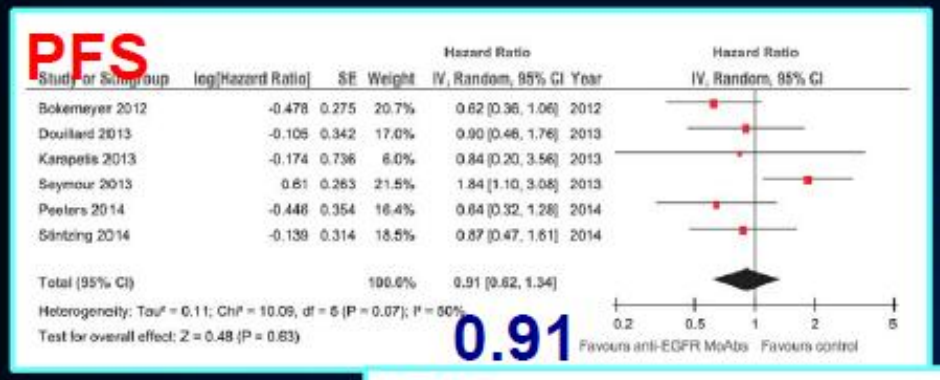


	RAS/BRAF tüm WT (n = 94)	*RAS/BRAF herhangi* MT (n = 56)	*RAS* WT (n = 110)	*RAS/BRAF*^{V600E} WT (n = 101)	*RAS* herhangi MT (n = 40)	*BRAF*^{V600E} MT (n = 9)	*BRAF diğer* MT (n = 7)
medyan PFS, ay	*5.9*	*2.1*	*5.2*	*5.8*	*2.1*	*1.6*	*2.4*
	HR = 3.49 (*P*<.0001)						
medyan OS, ay	*14.5*	*6.4*	*13.9*	*14.3*	*6.3*	*4.6*	*8.1*
	HR = 2.14 (*P*<.0001)						
yanıt oranı, %	*31.9*	*1.8*	*27.3*	*29.7*	*2.5*	*0*	*0*

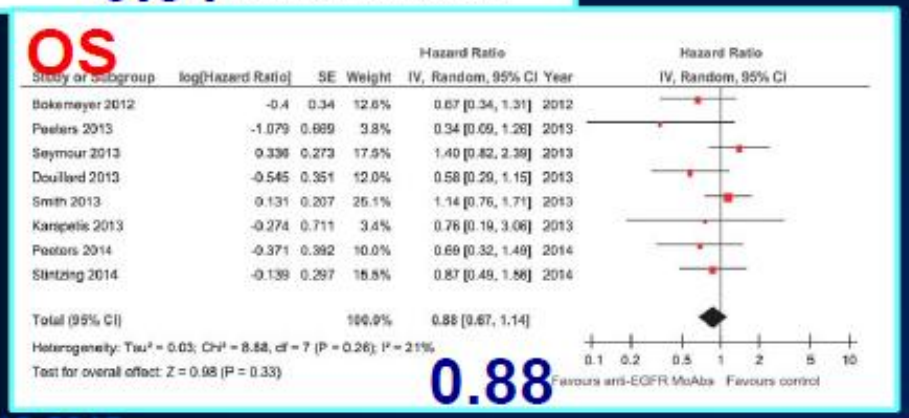
Yuki. 2015.

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

BRAF mut and EGFR mAbs



7 trials
463 pts



Pietrantonio et al., EJC 2015

Metastatik Kolon Kanserinde Tedavi Seçenekleri

GONO ÇALIŞMASI

JOURNAL OF CLINICAL ONCOLOGY

Phase III Trial of Infusional Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan (FOLFOXIRI) Compared With Infusional Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) As First-Line Treatment for Metastatic Colorectal Cancer: The Gruppo Oncologico Nord Ovest

Table 4.

Objective Responses

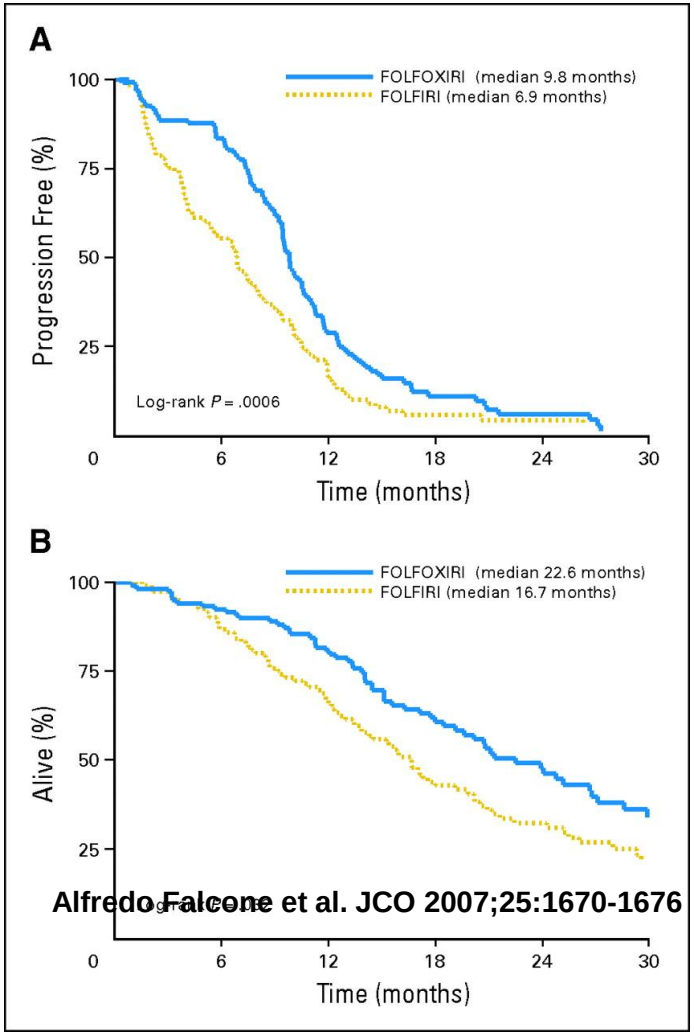
Response	%	
	FOLFIRI (n = 122)	FOLFOXIRI (n = 122)
Investigators assessment		
Complete	6	8
Partial	35	58
Complete + partial	41*	66*
95% CI	0.32 to 0.50	0.56 to 0.74
Stable disease	33	21
Progression	24†	11†
Not assessable	2	2
Externally reviewed		
Complete	6	7
Partial	28	53
Complete + partial	34‡	60‡
95% CI	0.25 to 0.43	0.51 to 0.68
Stable disease	34	21
Progression	24†	11†
Not reviewed	8	8

- Abbreviations: FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan.
- * $P = .0002$.

Metastatik Kolon Kanserinde Tedavi Seçenekleri

GONO ÇALIŞMASI

Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival.



Alfredo Falcone et al. JCO 2007;25:1670-1676

JOURNAL OF CLINICAL ONCOLOGY ASCO

Metastatik Kolon Kanserinde Tedavi Seçenekleri GONO ÇALIŞMASI

Phase III Trial of FOLFOXIRI vs FOLFIRI as First-Line Therapy of Advanced Colorectal Cancer

	FOLFIRI N=122	FOLFOXIRI N=122	*P*-value
RR* (%)	34	60	<0.0001
CR+PR+SD* (%)	68	81	
R0 resection (%) (all patients)	6	15	0.033
R0 resection (%) (liver limited)	12	36	0.017
PFS (mos)	6.9	9.8	0.0006
OS (mos)	16.7†	22.6	0.032

* externally reviewed; †67% 2nd line FOLFOX

Falcone et al. 2007

Metastatik Kolon Kanserinde Tedavi Seçenekleri

TRIBE ÇALIŞMASI

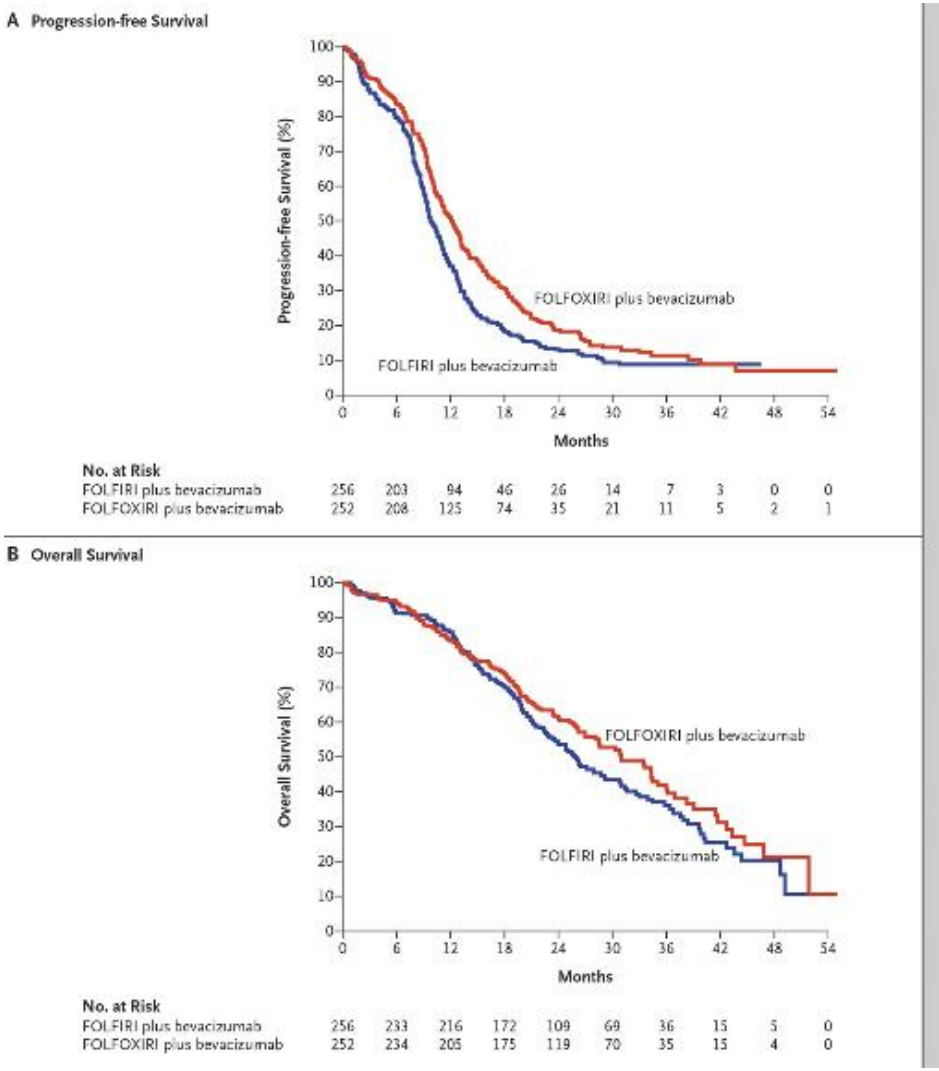


Figure 2. Kaplan–Meier Estimates of Progression-free and Overall Survival, According to Treatment Group.

Median progression-free survival was 9.7 months in the group receiving FOLFIRI plus bevacizumab (control group) and 12.1 months in the group receiving FOLFOXIRI plus bevacizumab (experimental group). Median overall survival was 25.8 months in the control group and 31.0 months in the experimental group.

Metastatik Kolon Kanserinde Tedavi Seçenekleri

TRIBE ÇALIŞMASI

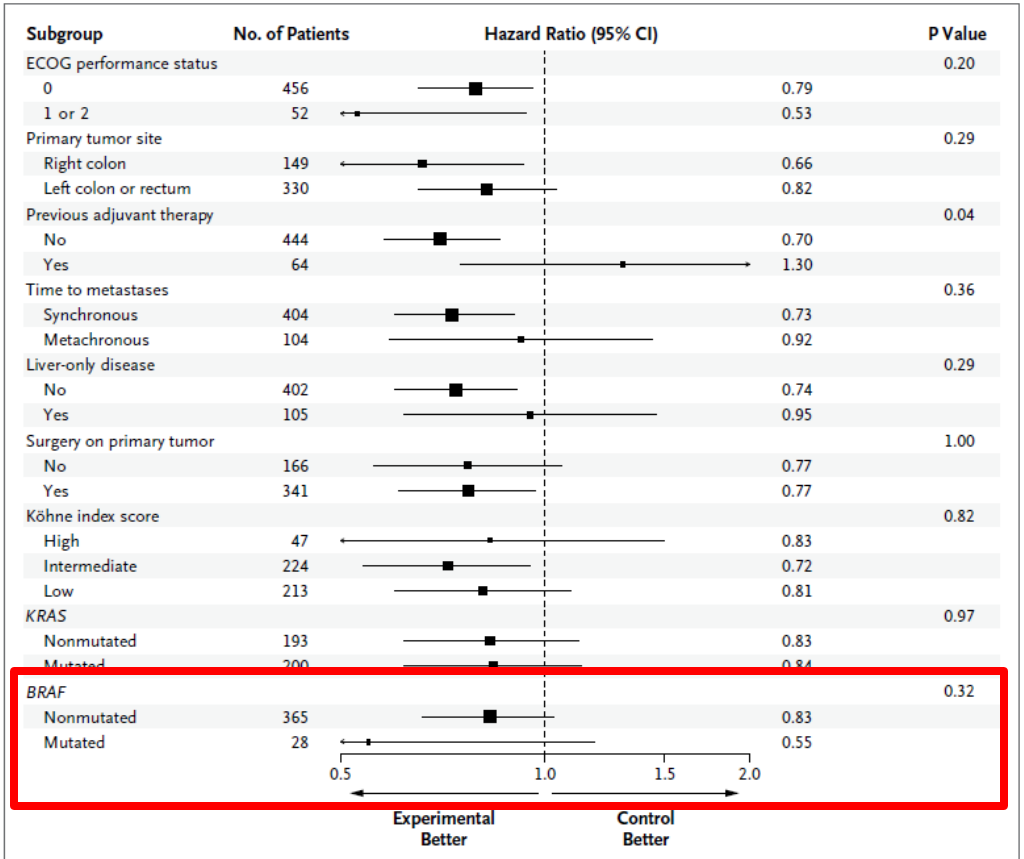
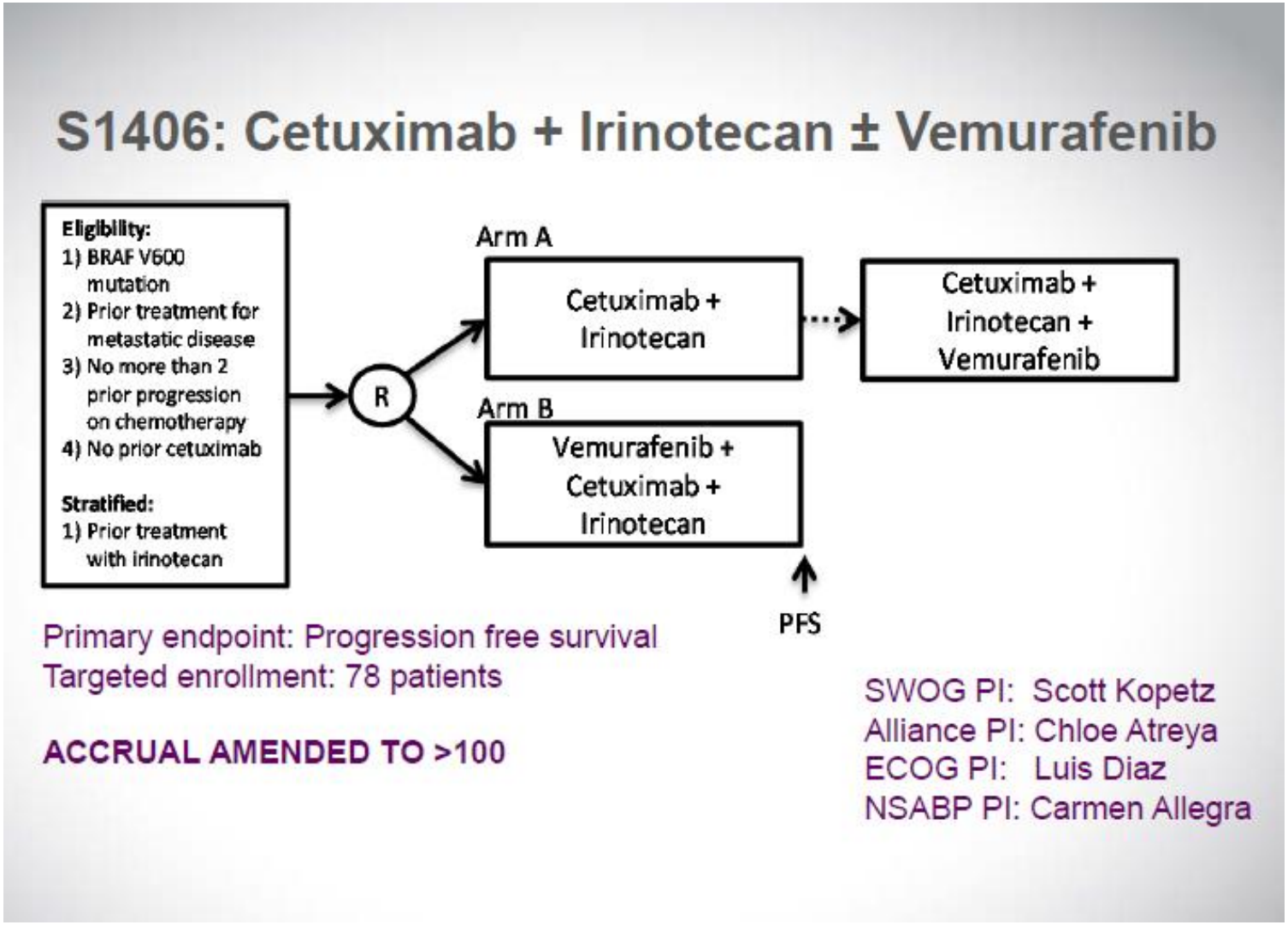


Figure 3. Forest Plot of the Treatment Effect on Progression-free Survival in Subgroup Analyses.

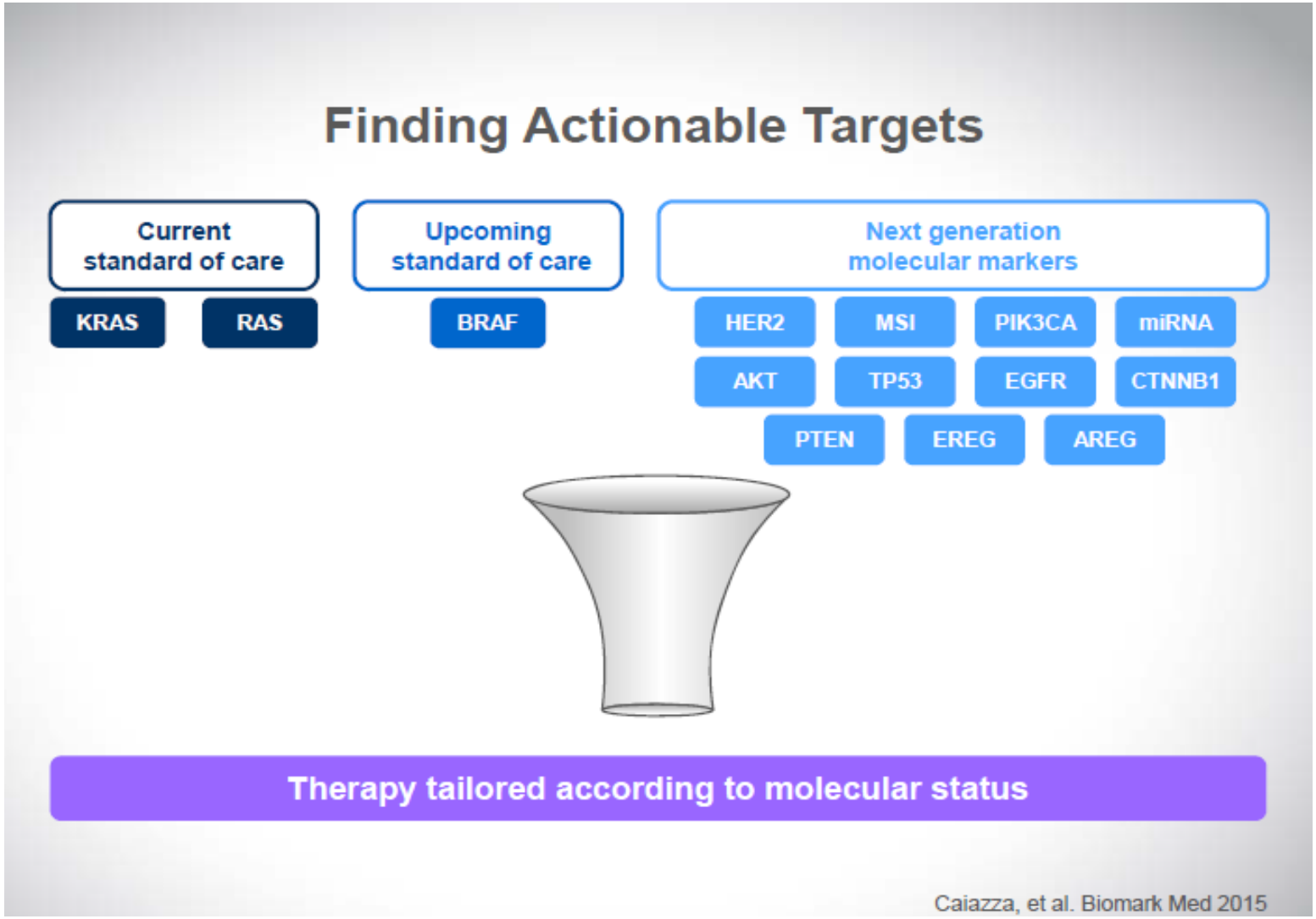
The size of the squares is proportional to the size of the corresponding subgroup. Control denotes FOLFIRI plus bevacizumab, ECOG Eastern Cooperative Oncology Group, and experimental FOLFOXIRI plus bevacizumab.

R0 Rezeksiyon; %15 vs. %12

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

HER2 amplification as a negative predictive biomarker for anti-epidermal growth factor receptor antibody therapy in metastatic colorectal cancer.

Meeting: **2016 ASCO Annual Meeting**
Presenter: **Kanwal Pratap Singh Raghav**

View Poster

Subcategory:
Biomarkers/Epidemiology/Outcomes

Category:
Gastrointestinal (Colorectal) Cancer

Meeting:
2016 ASCO Annual Meeting

Session Type and Session Title:
Poster Discussion Session, Gastrointestinal (Colorectal) Cancer

Abstract Number:
3517

Poster Board Number:
Board #214

Citation:
J Clin Oncol 34, 2016 (suppl; abstr 3517)

Author(s):
Kanwal Pratap Singh Raghav, Michael J. Overman, Ruoxi Yu, Funda Meric-Bernstam, David Menter, Bryan K. Kee, Andrea Muranyi, Shalini Singh, Mark Routbort, Ken Chen, Kenna Rael Shaw, Kandavel Shanmugam, Dipen M. Maru, Marwan Fakih, Scott Kopetz; The University of Texas MD Anderson Cancer Center, Houston, TX; Ventana Medical Systems, Inc., Tucson, AZ; City of Hope, Duarte, CA

Abstract Disclosures

Abstract:

Background: HER2 amplification (HERamp), seen in 5% of KRAS wildtype (WT) metastatic colorectal cancers (mCRC), is associated with resistance to anti-epidermal growth factor receptor antibodies (antiEGFRabs). The purpose of this study was to validate the predictive impact of HERamp in mCRC. **Methods:** We performed systematic analyses of RAS and BRAF WT mCRC patients (pts) across 2 distinct cohorts. We tested HERamp in cohort 1 (N = 97) using immunohistochemistry and dual in-situ hybridization (HERamp: HER2/CEP17 ≥ 2.2). We validated these findings in cohort 2 (N = 99), which comprised of 37 cases of HERamp mCRC pts identified by next-generation sequencing (HERamp: ≥ 4 copies) and 62 HER2 non-amplified (HER2NA) pts treated previously with antiEGFRabs who served as controls. The primary objective was to compare progression-free survival (PFS) in pts treated with antiEGFRabs. PFS and overall survival (OS) were estimated using Kaplan Meier method and compared using log rank test. **Results:** HERamp was seen in 14 (14 %) of RAS/BRAF WT pts in cohort 1. In this cohort, median OS (29.1 v 45.1 months (m), P = 0.78) and PFS on first line therapy without an antiEGFRab (PFS1) (9.7 v 8.4 m, P = 0.70) was similar between HERamp and HER2NA pts. A total of 66 pts in cohort 1 received antiEGFRab after first line therapy. Median PFS on antiEGFRab therapy (PFS2) was significantly shorter in pts with HERamp compared to HER2NA tumors (2.9 v 8.1 m, hazard ratio (HR) 5.0, P < 0.0001). These findings were confirmed in cohort 2, in which 69 pts received antiEGFRab after first line therapy and median PFS2 was significantly shorter for HERamp pts compared to HER2NA pts (2.8 v 9.3 m, HR 6.6, P < 0.0001) with a similar OS (P = 0.86) and PFS1 (P = 0.62). **Conclusions:** HER2 amplification in mCRC is a predictive biomarker for lack of efficacy of antiEGFRab therapy. This magnitude of effect is comparable to RAS mutations; the only other validated predictive biomarker for antiEGFRabs, and affects 1 in 8 patients currently receiving these agents. Patients with RAS/RAF WT mCRC should be screened for HER2 amplification prior to treatment with antiEGFRabs and should be considered for early referral to clinical trials.

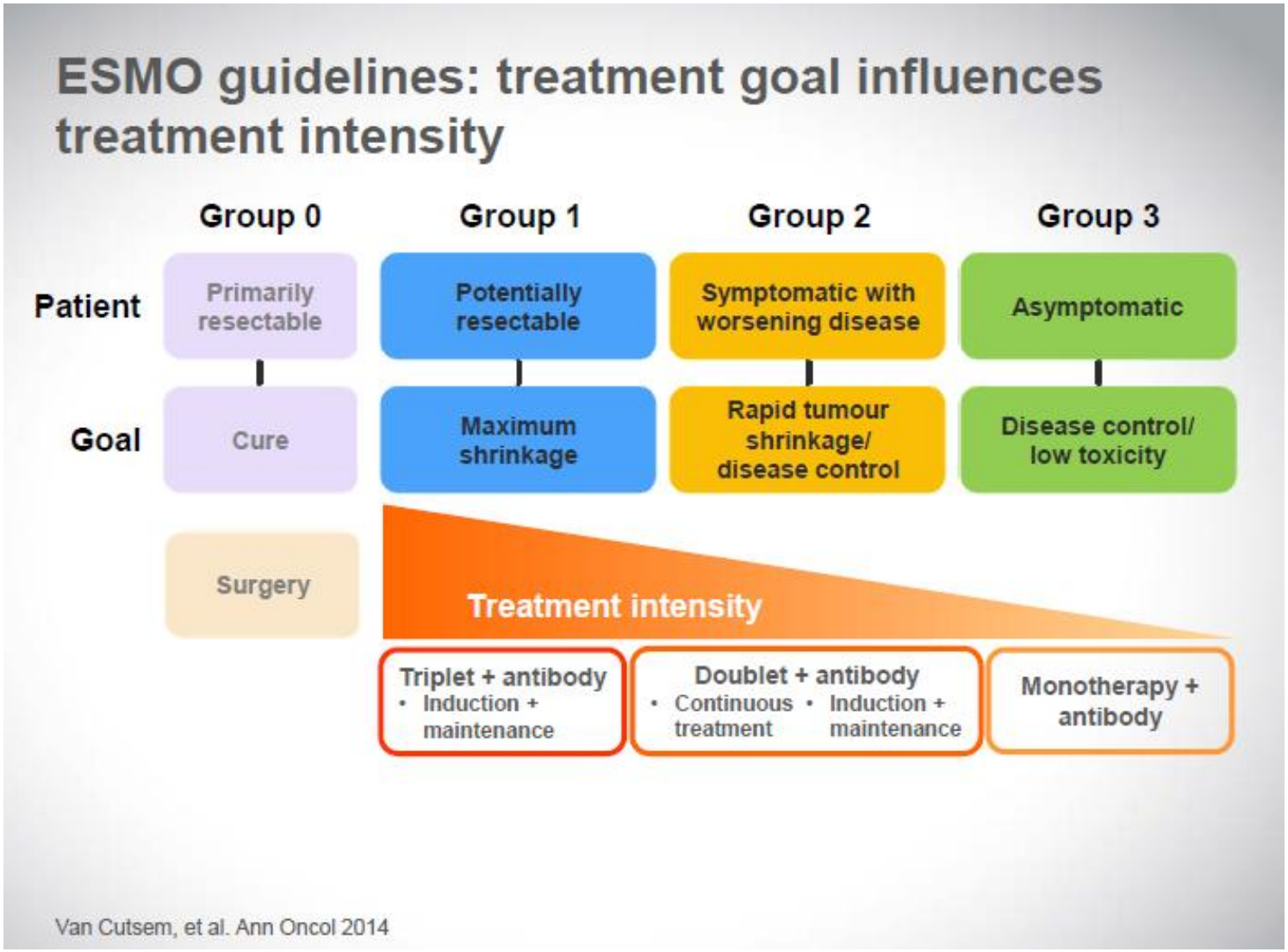
HER2 expresiyonu, %3 oranında tüm kolonda saptanmış. RAS wild typte; %5-14. Anti EGRF tedavisinde dirençle ilişkili olabilir

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri

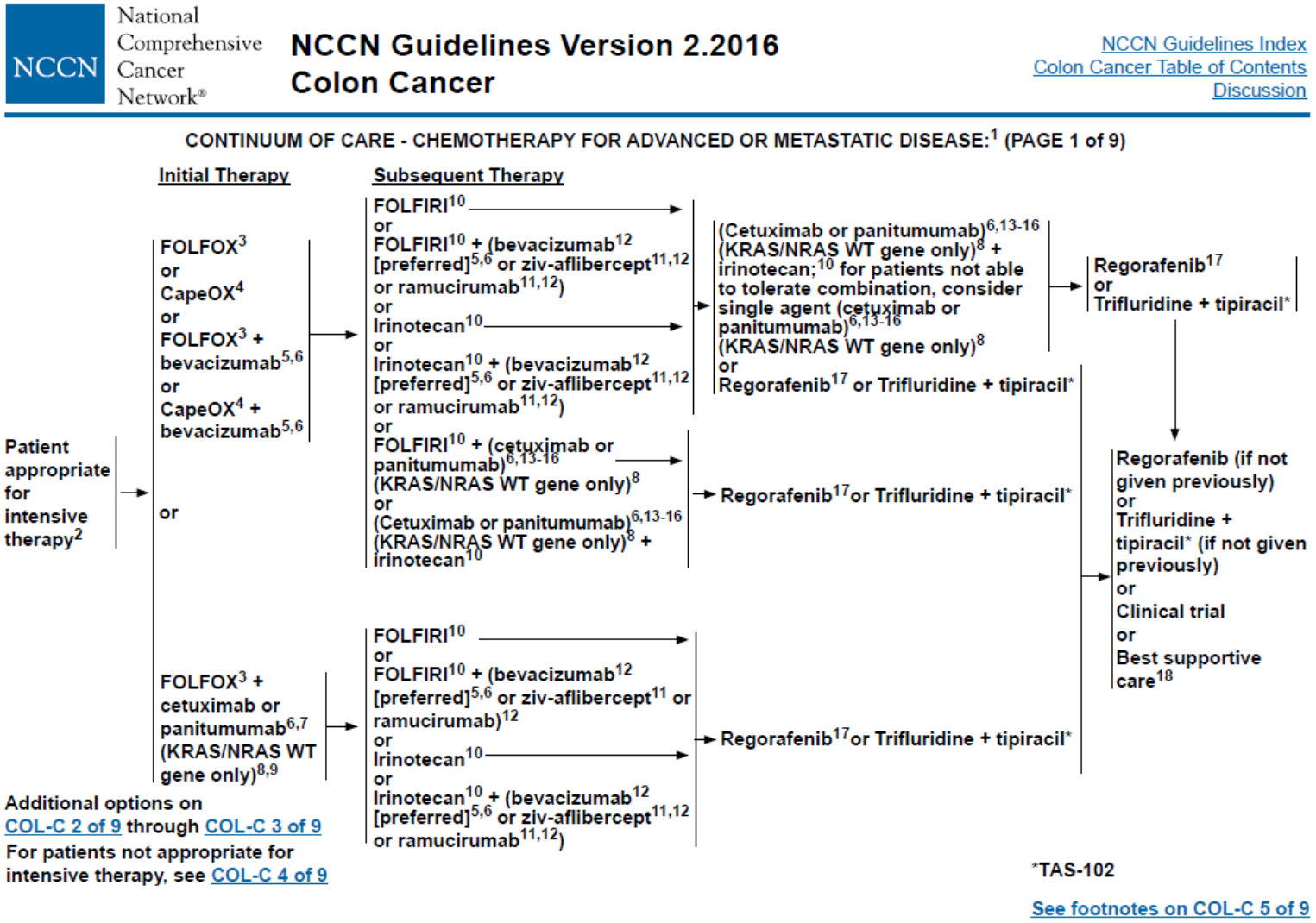
Hangi Hasta Grubunda FOLFORİNOX+/-Bevacizumab

- ❑ Genel durumu iyi, ek hastalığı olmayan, genç hasta popülasyonunda
- ➢ Sınırda rezektable karaciğer metastazı varsa
- ➢ BRAF mutant hastalar

Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



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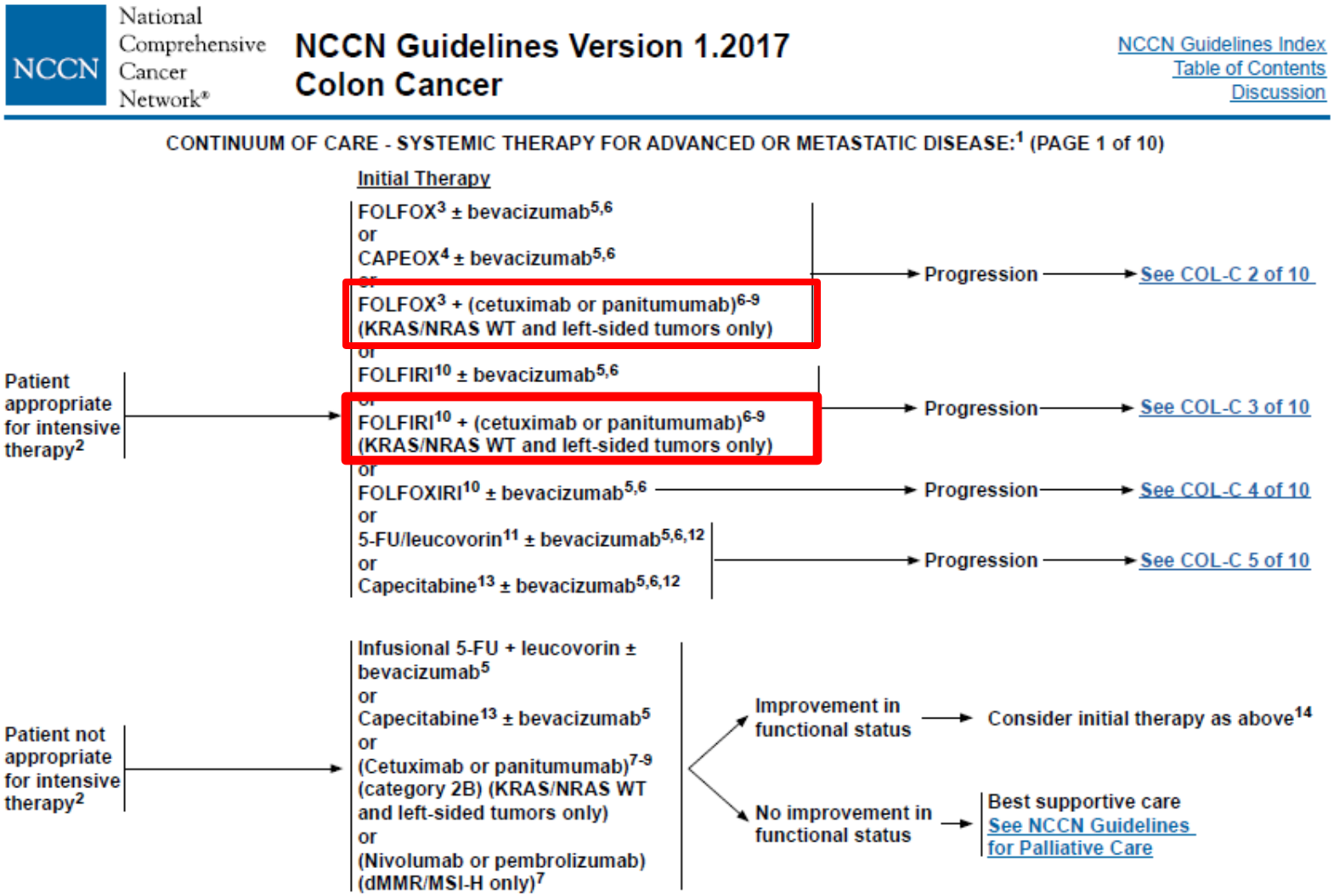
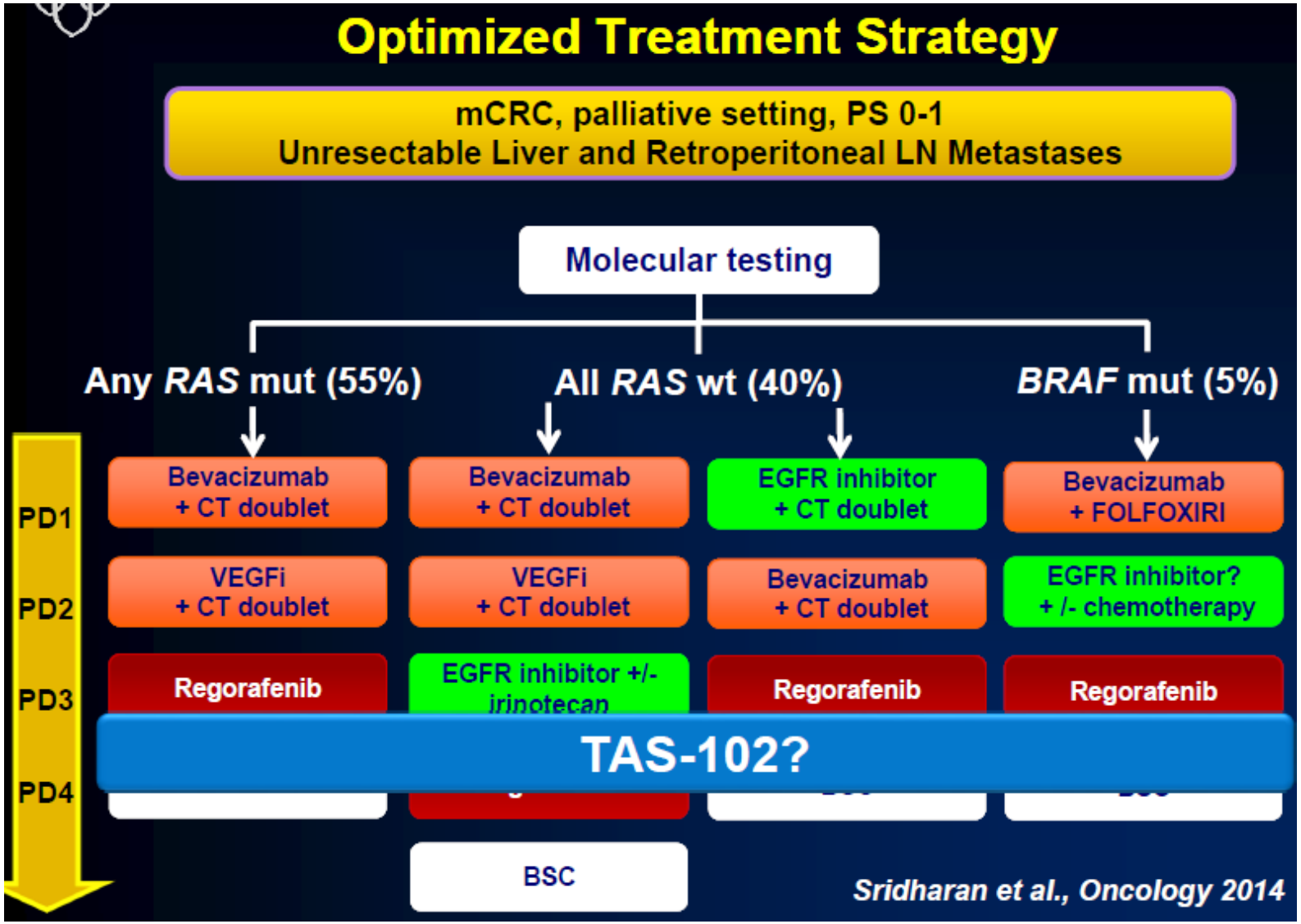
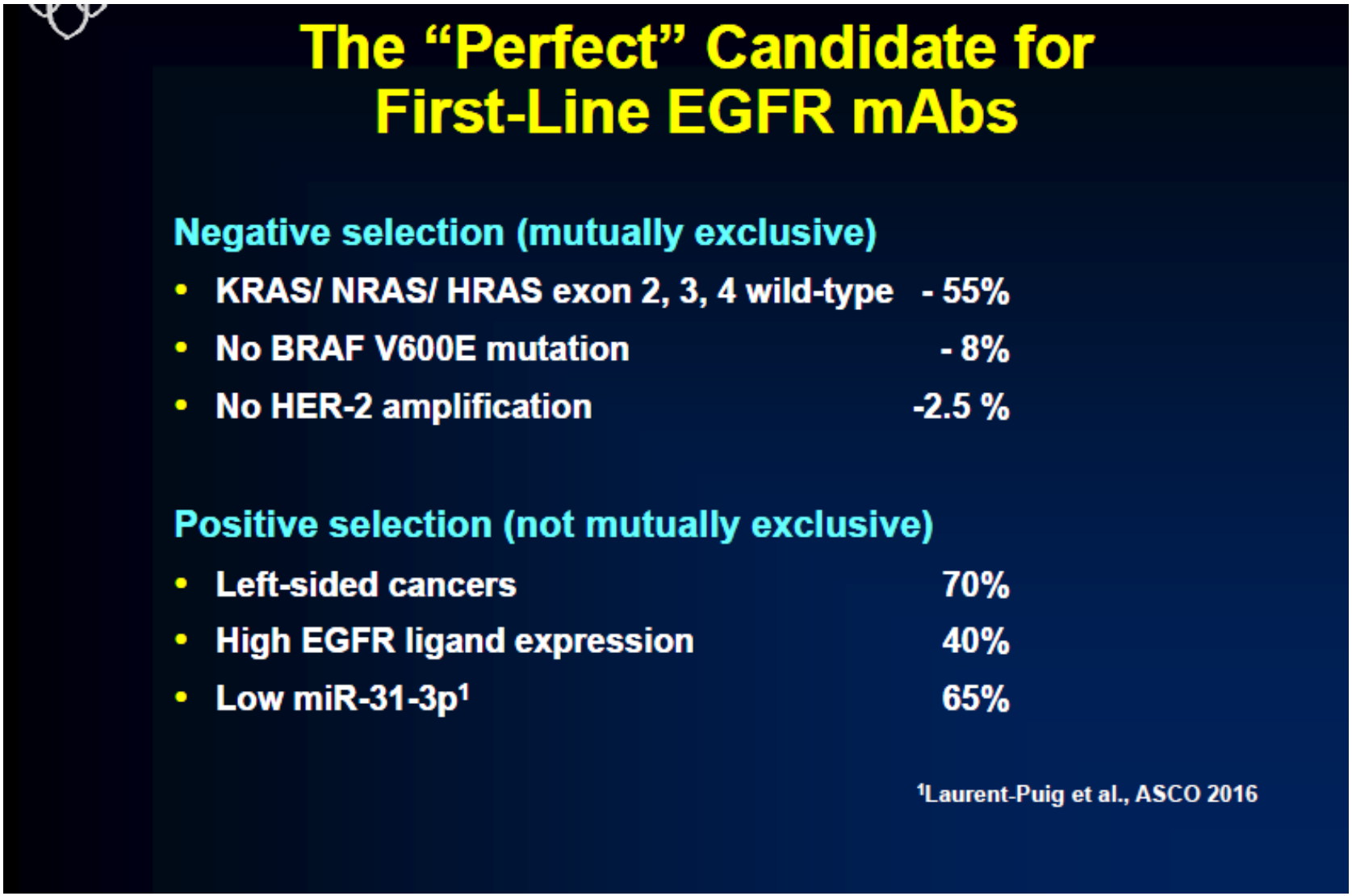


Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



Metastatik Kolon Kanserinde Birinci Basmak Tedavi Seçenekleri



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