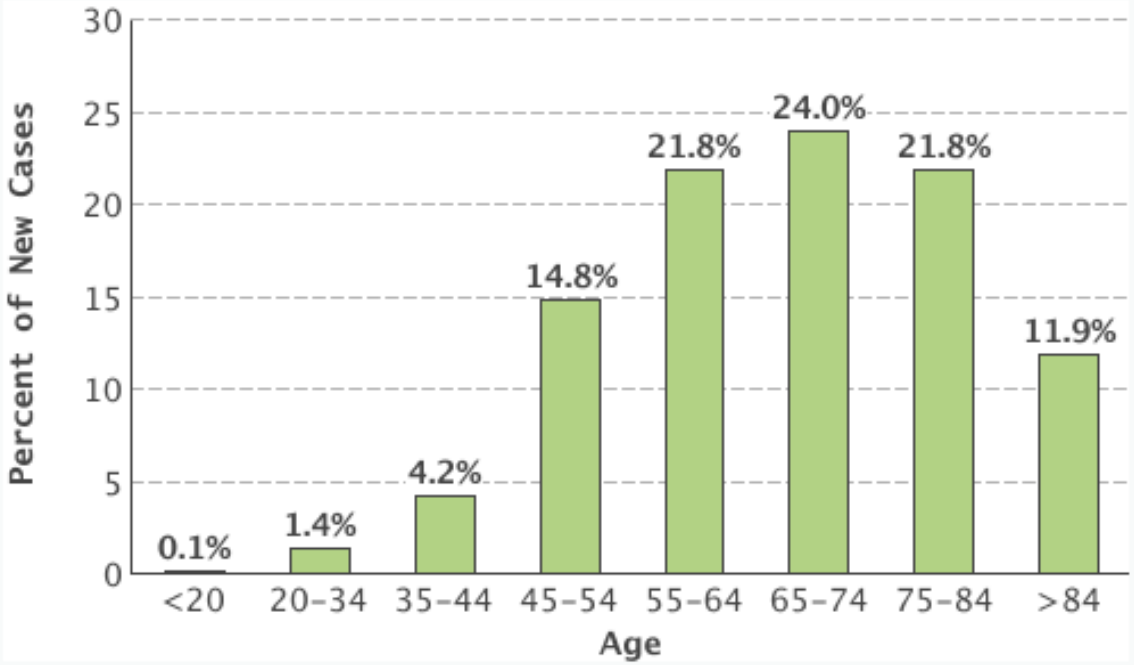
Metastatik Kolon Kanserinde Tedavi Seçenekleri

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

Kolon Kanseri İnsidans ve Mortalite

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



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

Median Age At Diagnosis

68

SEER 18 2009–2013, All Races, Both Sexes

Kolon Kanseri İnsidans ve Mortalite

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

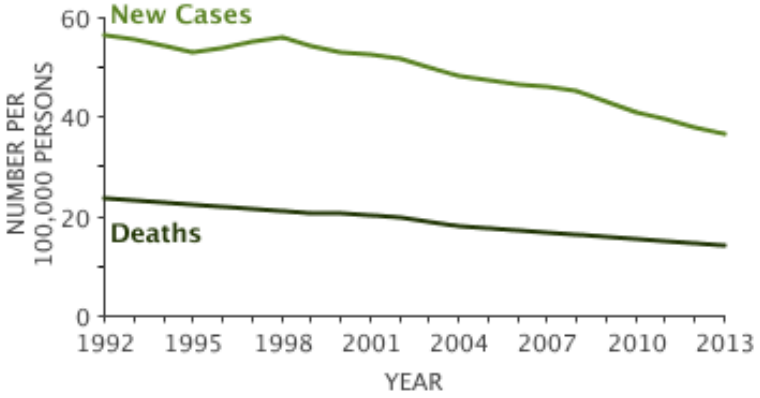
Colon and rectum cancer represents 8.0% of all new cancer cases in the U.S.

8.0%

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

Kolon Kanseri İnsidans ve Mortalite

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



Percent Surviving 5 Years
65.1%
2006–2012

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

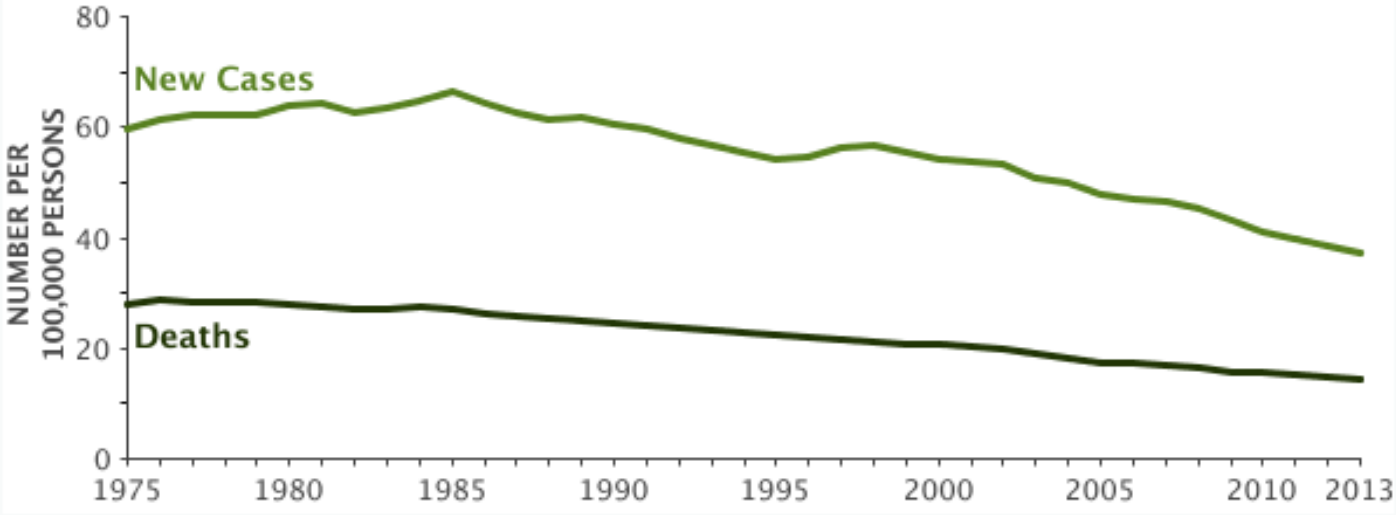
Lifetime Risk of Developing Cancer: Approximately 4.5 percent of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime, based on 2010–2012 data.

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

Kolon Kanseri İnsidans ve Mortalite

New Cases, Deaths and 5-Year Relative Survival

View Data Table



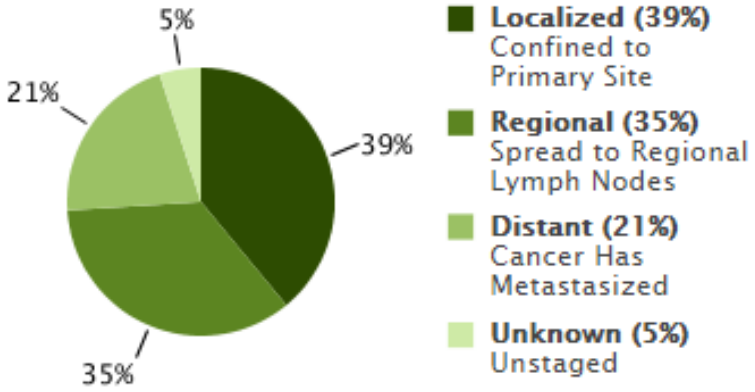
Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	48.6%	51.2%	58.1%	60.8%	59.7%	64.8%	65.7%	67.2%

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

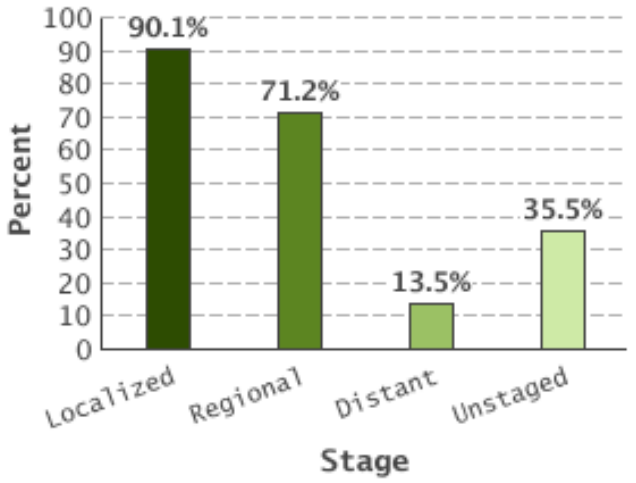
Kolon Kanseri İnsidans ve Mortalite

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

Percent of Cases by Stage

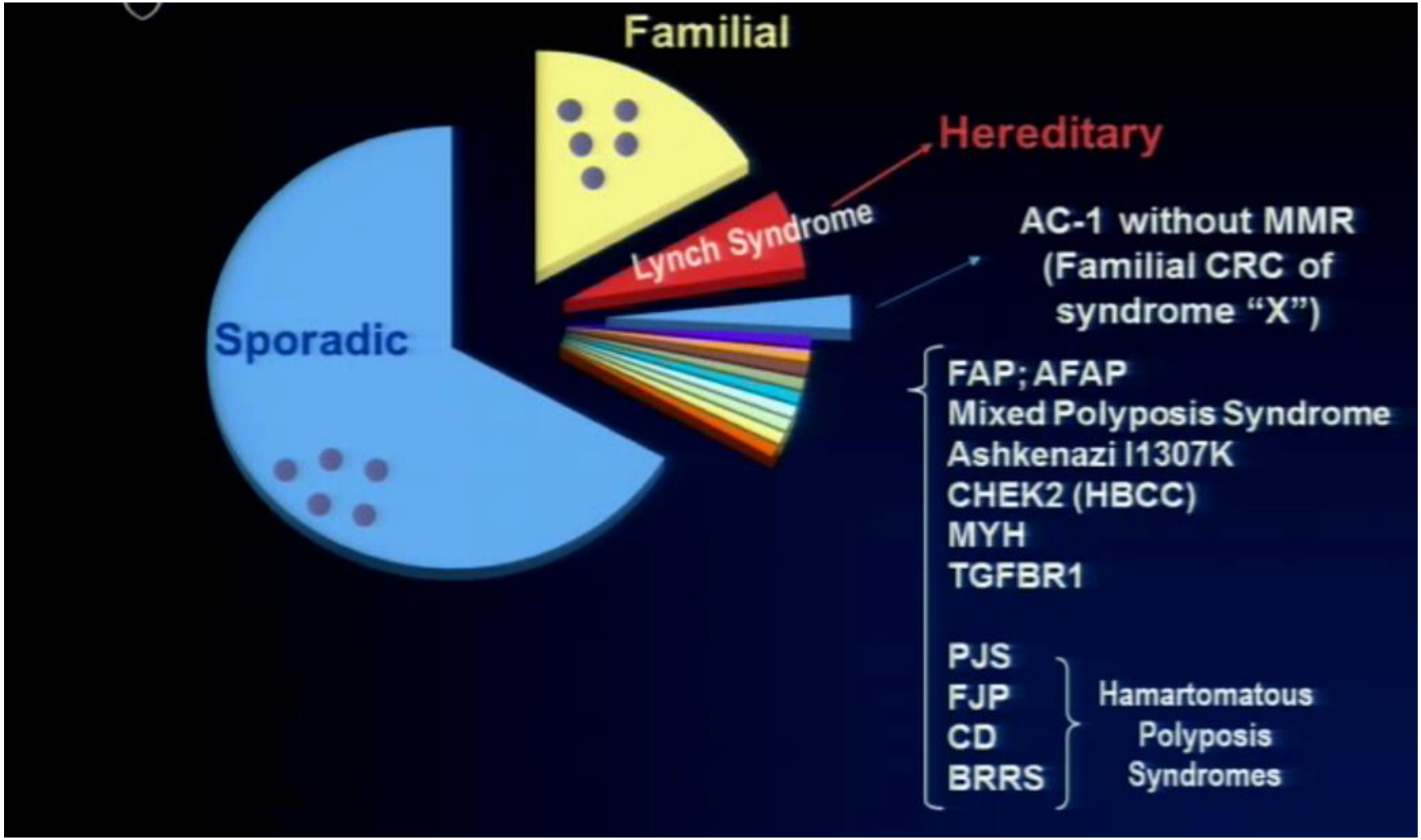


5-Year Relative Survival



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

Kolon Kanseri
Genetik ve Risk Faktörleri



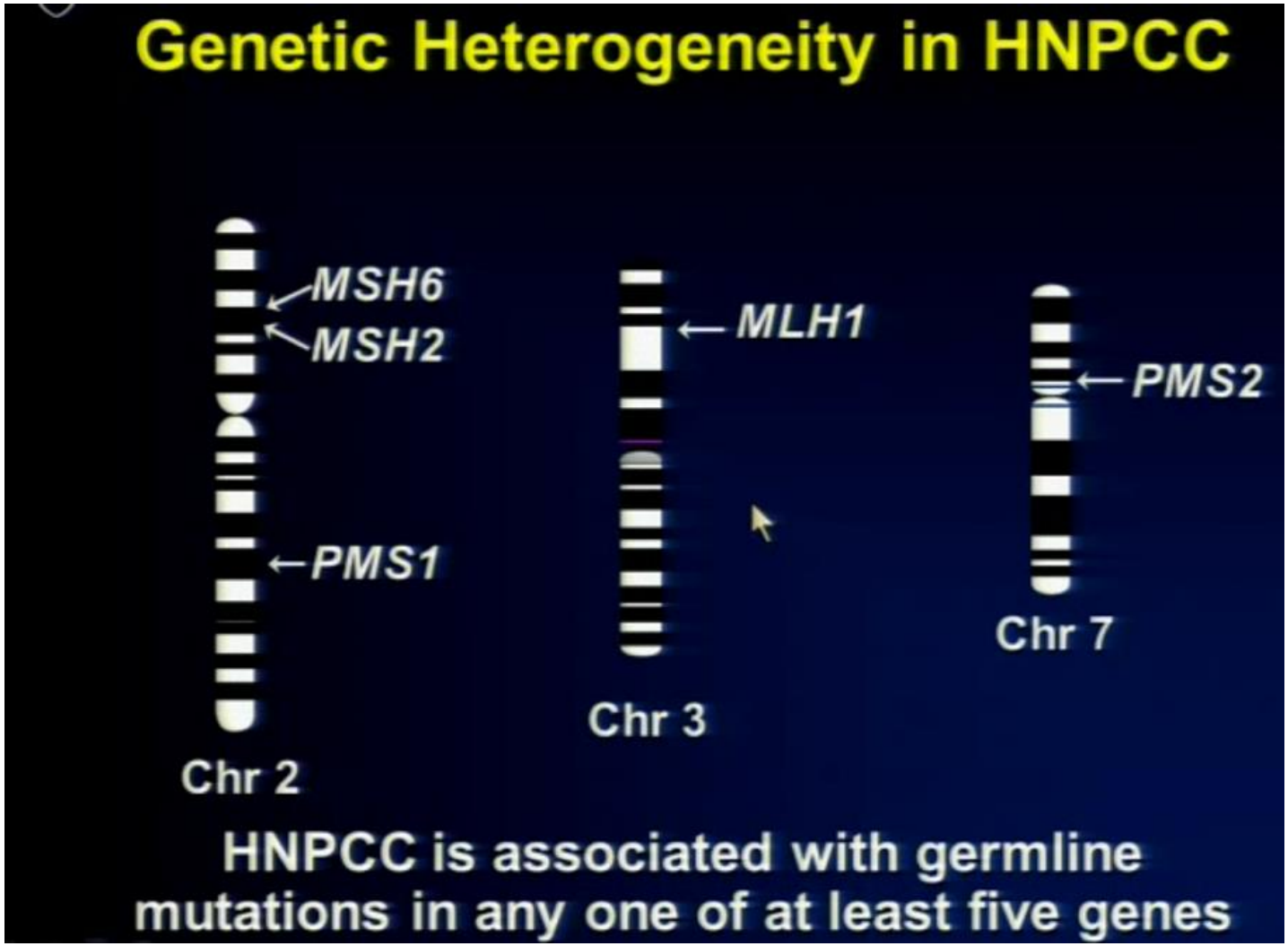
Kolon Kanseri
Genetik ve Risk Faktörleri

Annual worldwide incidence of CRC is 1,023,152*:

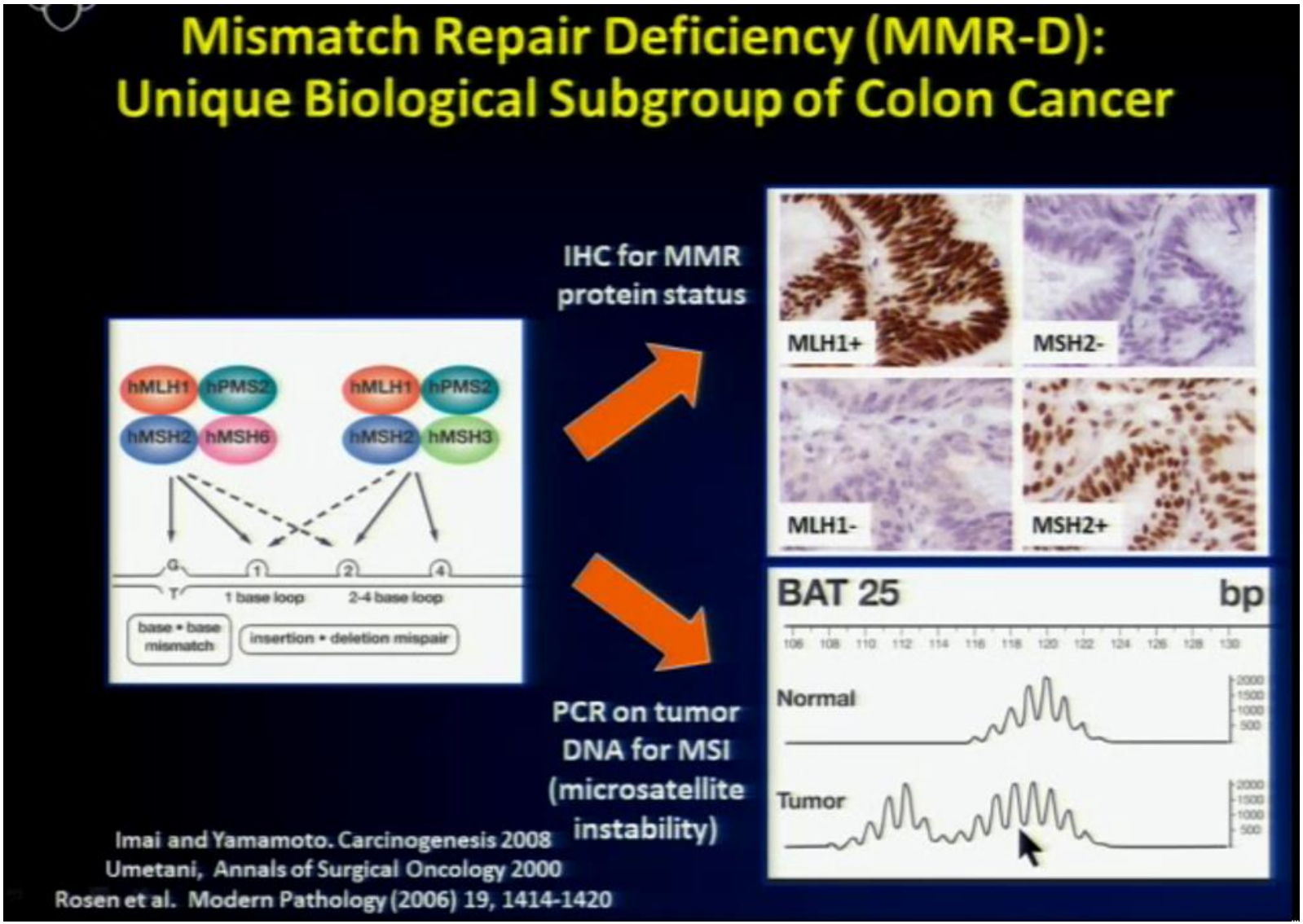
- Lynch syndrome (LS) accounts for ≈ 2-5% (20,460-51,160 cases).
- < 1% (10,230 cases) constitute FAP.
- ≈ 20% (204,630 cases) are familial (2 or more first-degree relatives with CRC.

*International Agency for Research on Cancer. Globocan 2002. Available at: http://www-dep.iarc.fr/.

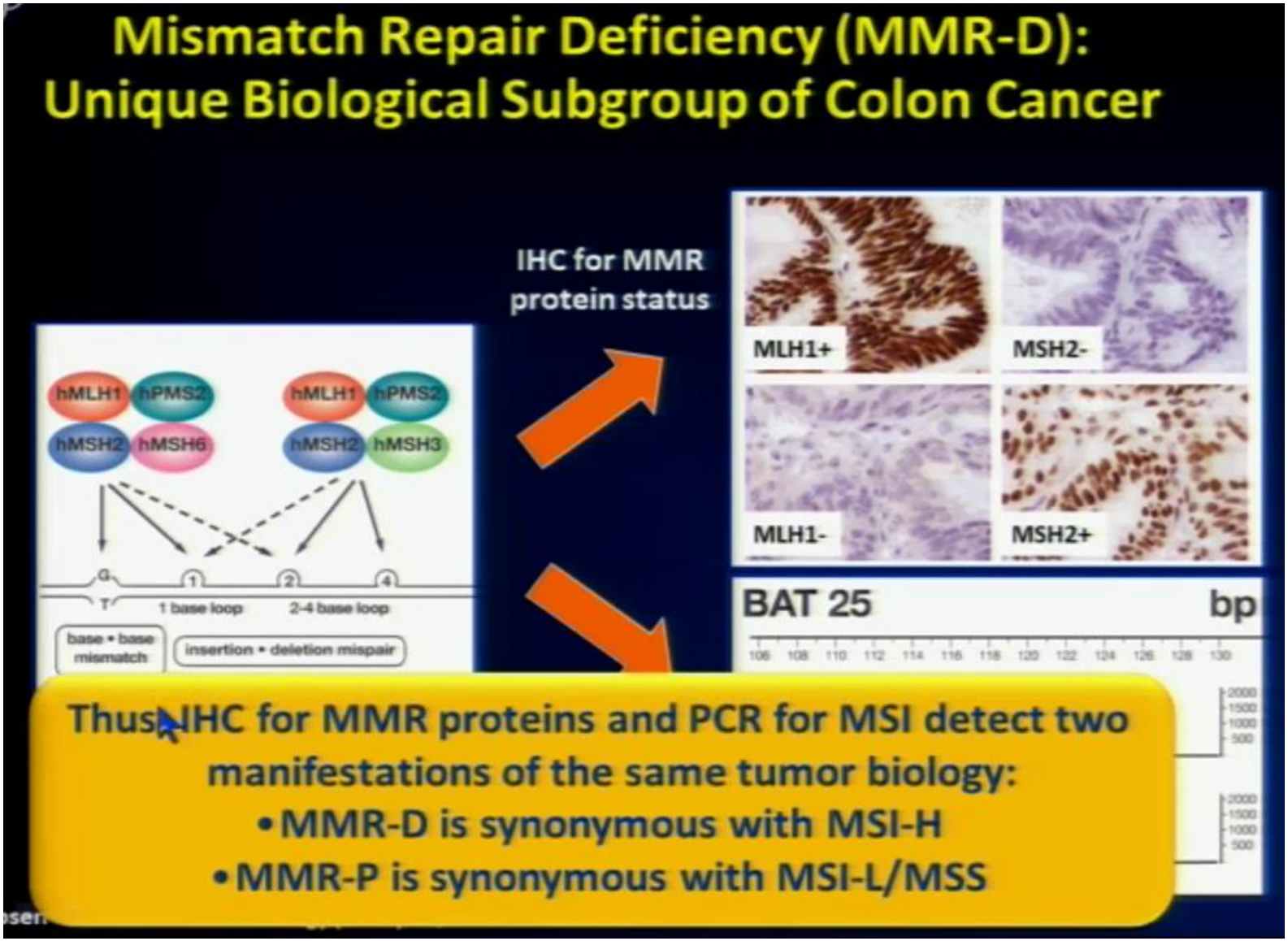
Kolon Kanseri
Genetik ve Risk Faktörleri



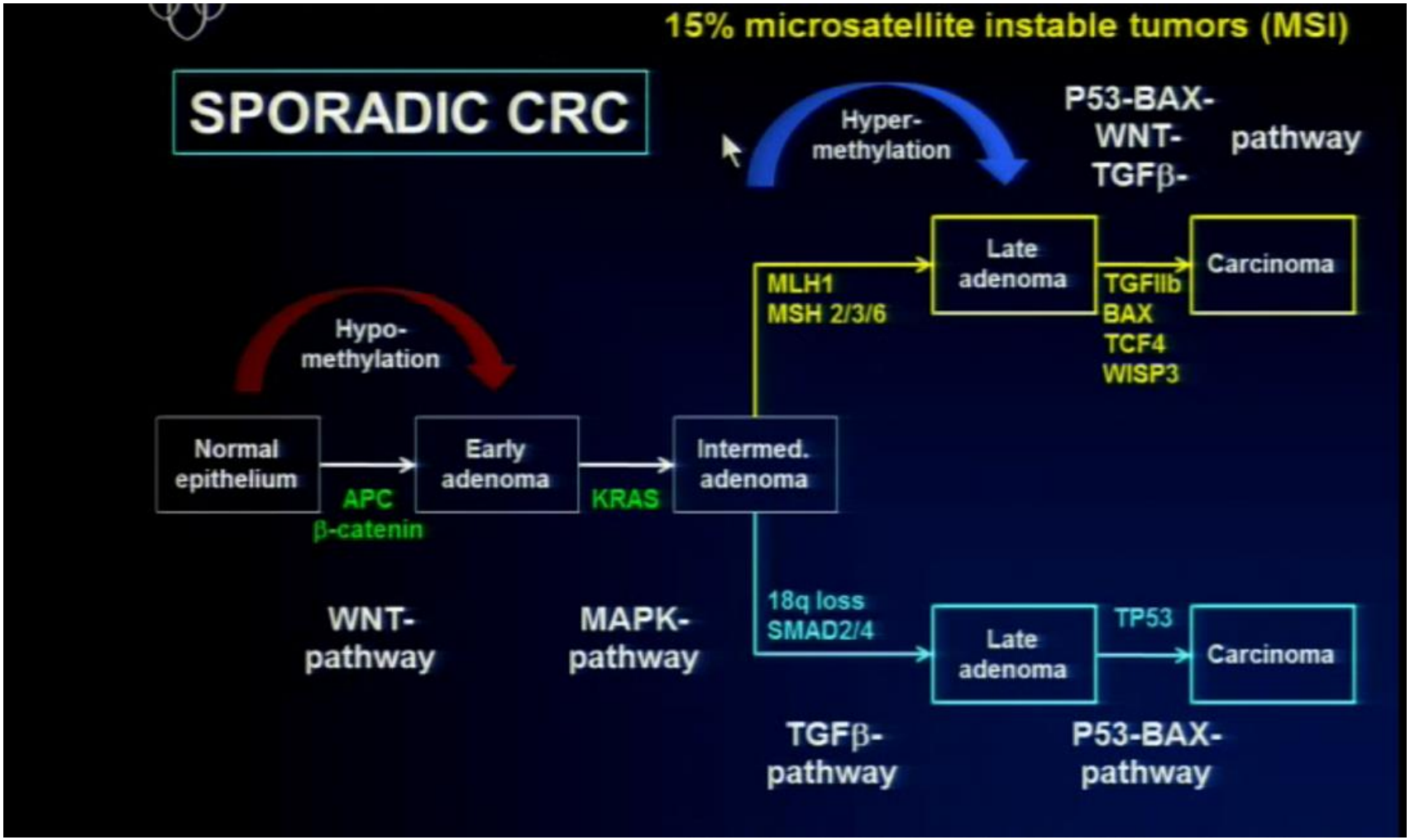
Kolon Kanseri
Genetik ve Risk Faktörleri



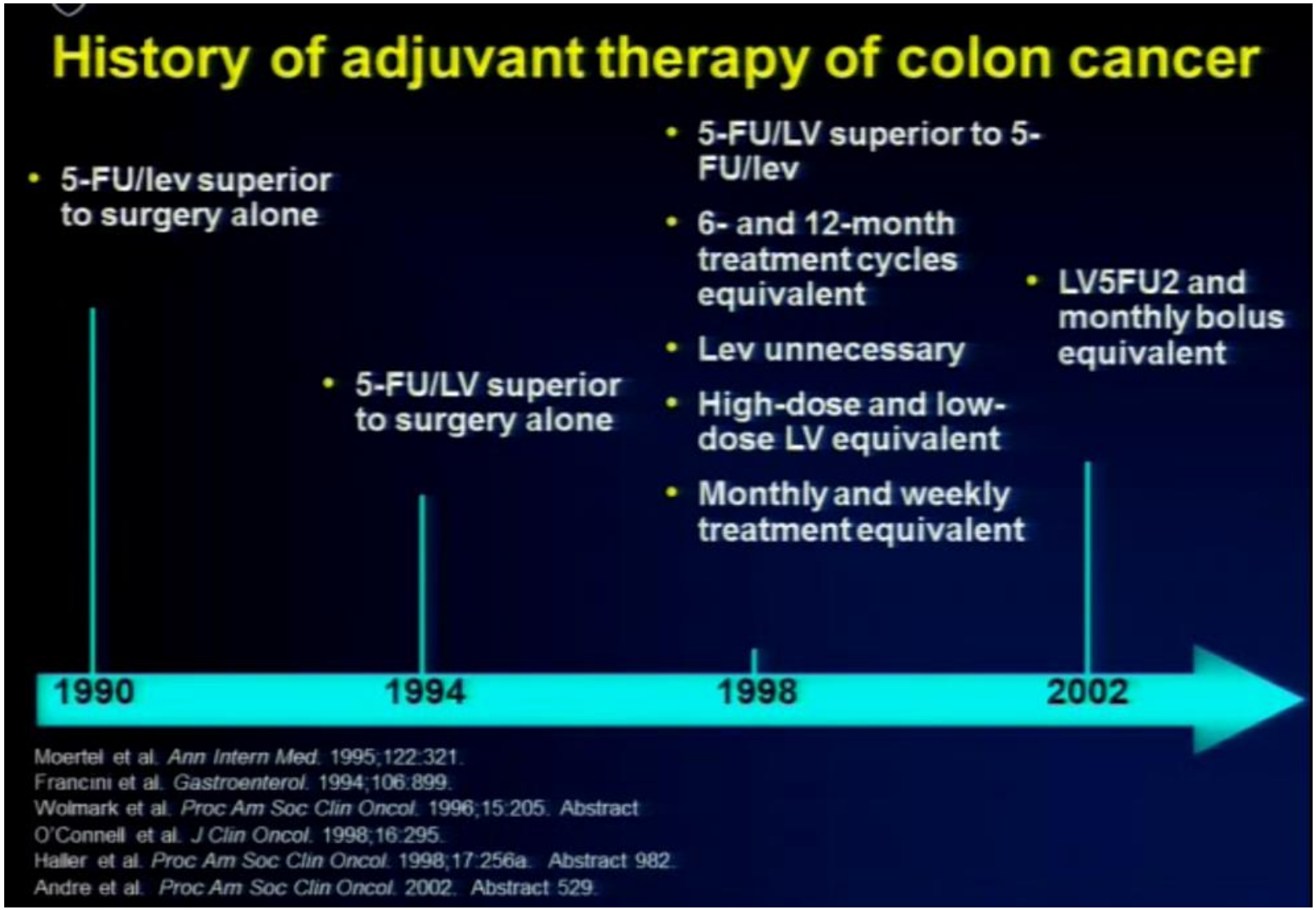
Kolon Kanseri
Genetik ve Risk Faktörleri



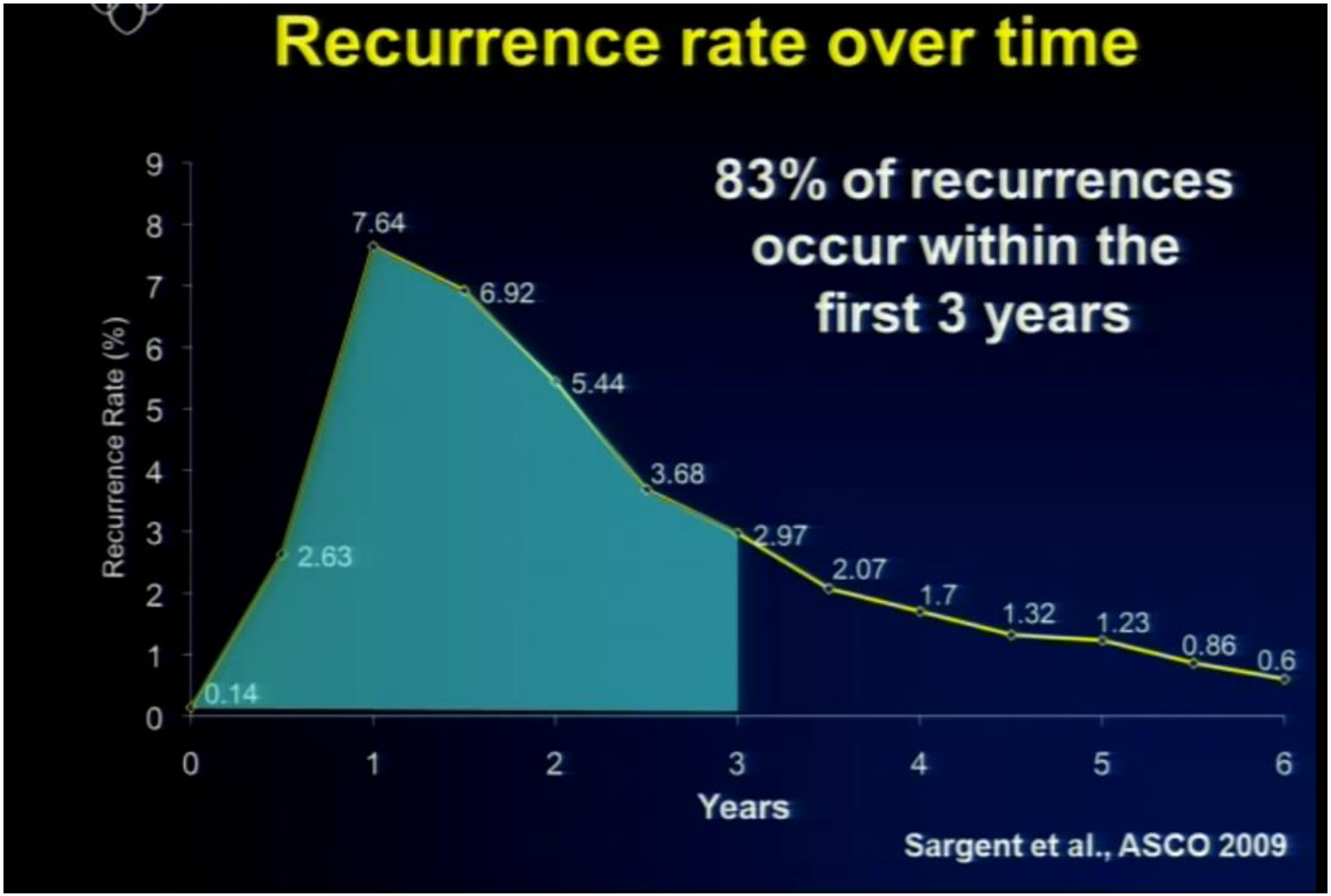
Kolon Kanseri
Genetik ve Risk Faktörleri



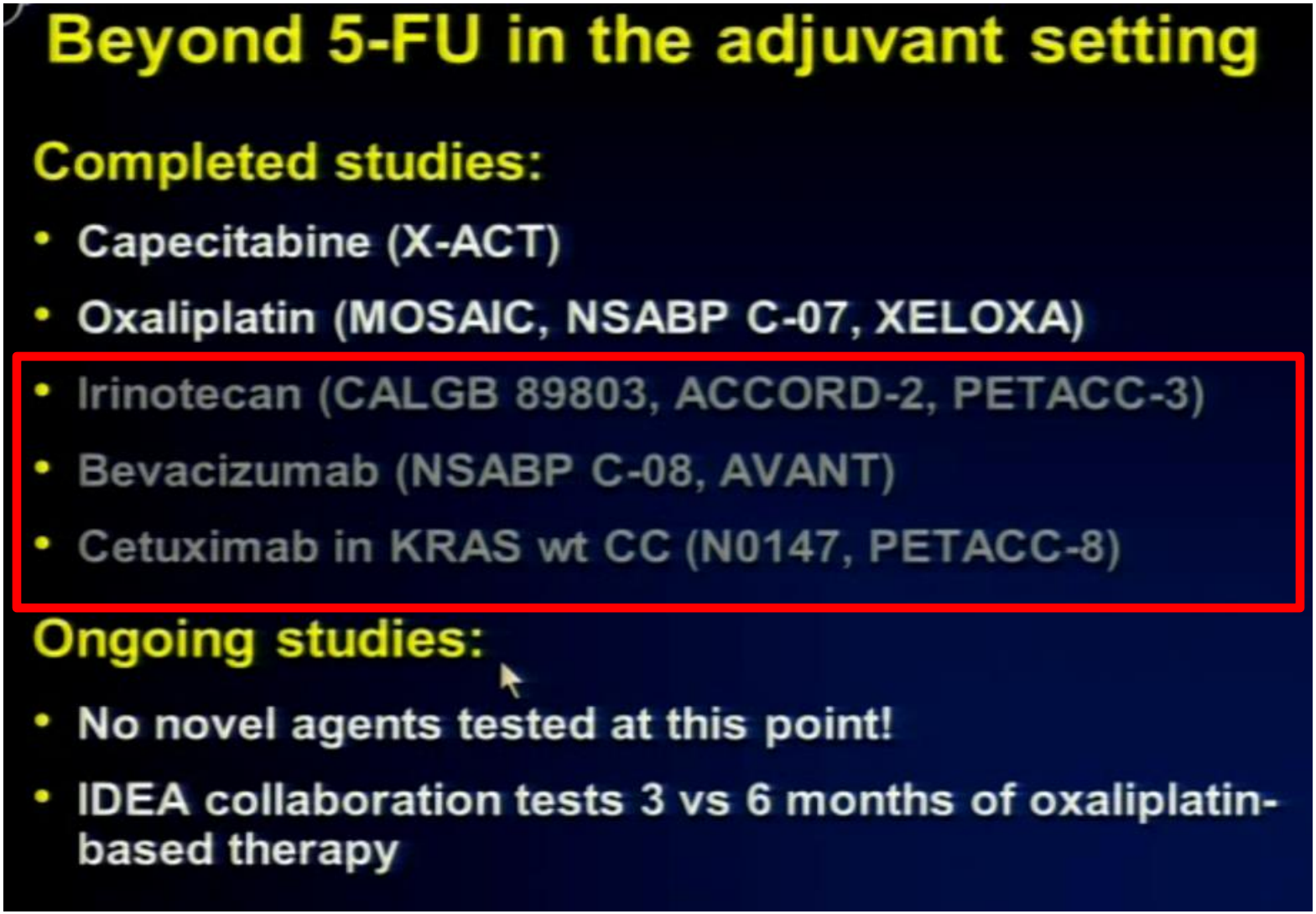
Kolon Kanseri Tedavi



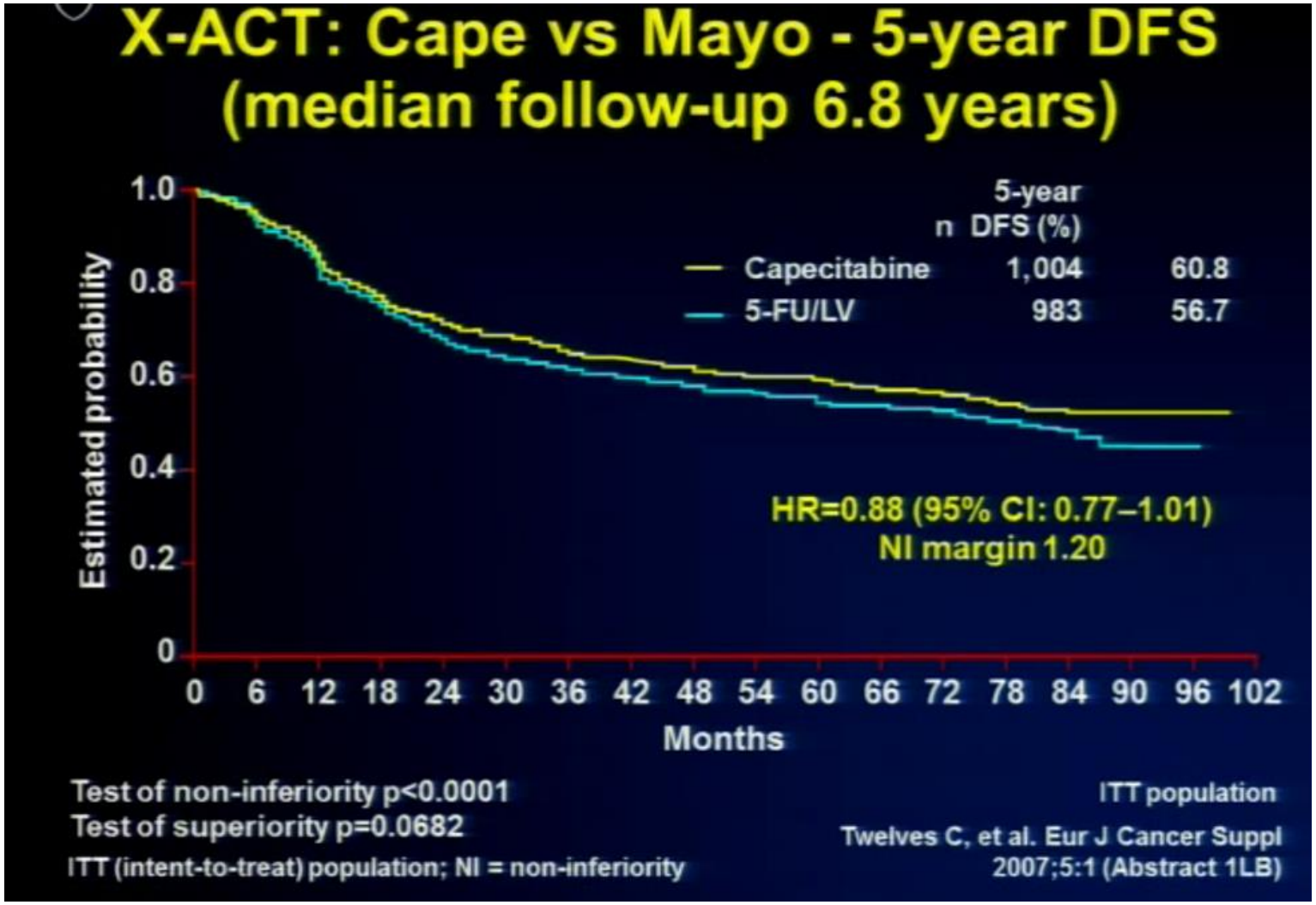
Kolon Kanseri Tedavi



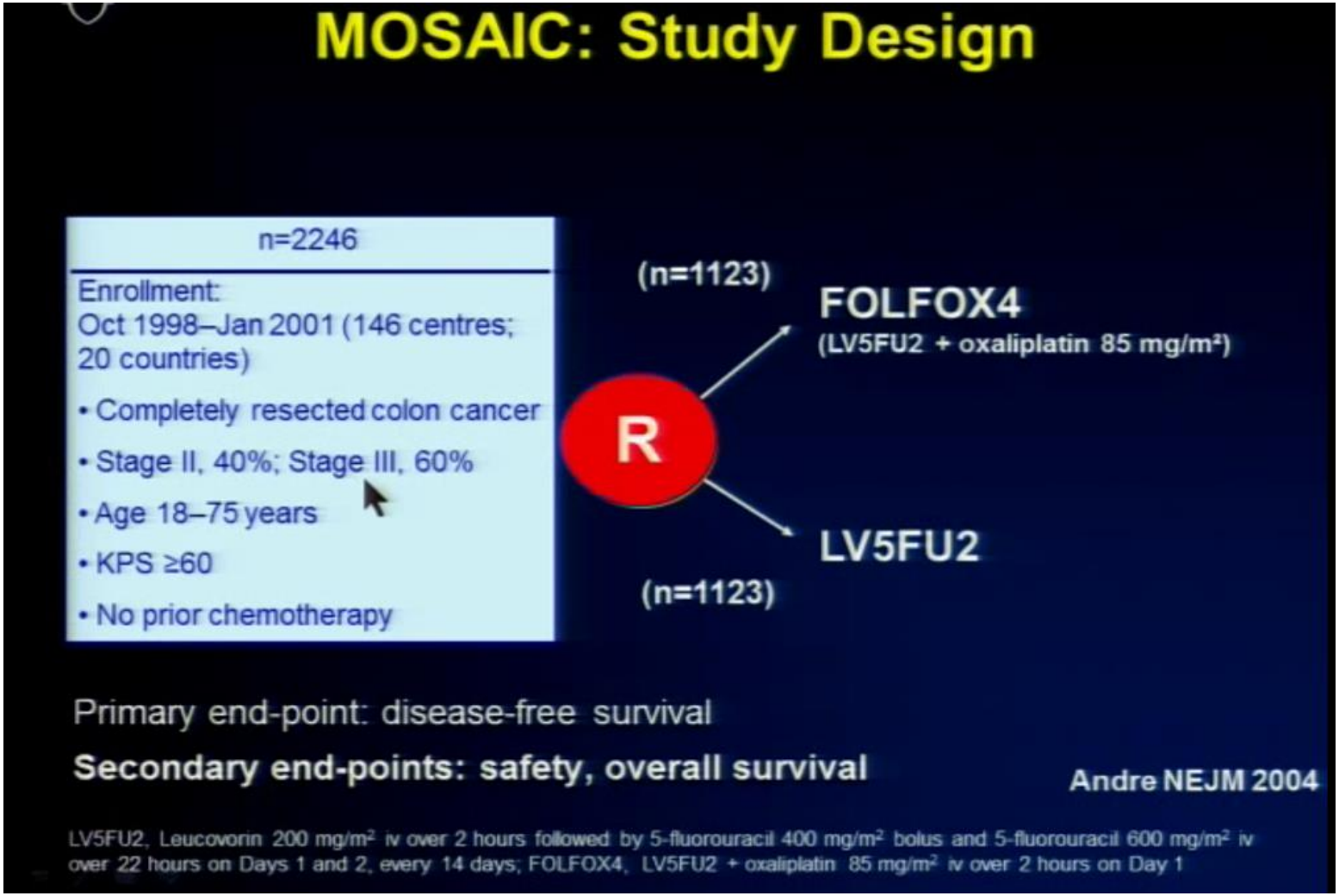
Kolon Kanserinde Adjuvan Tedavi Seçenekleri



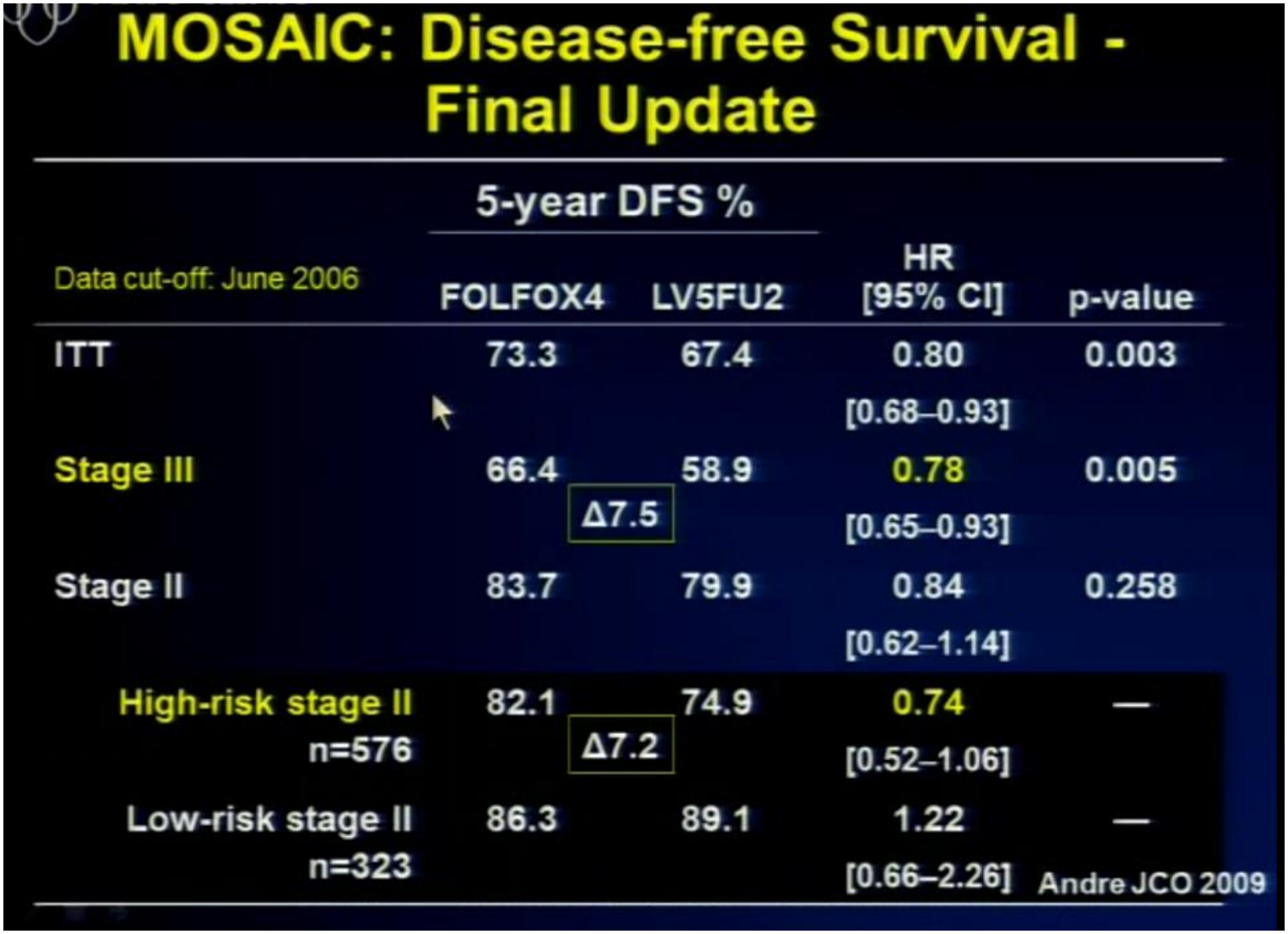
Kolon Kanserinde Adjuvan Tedavi Seçenekleri



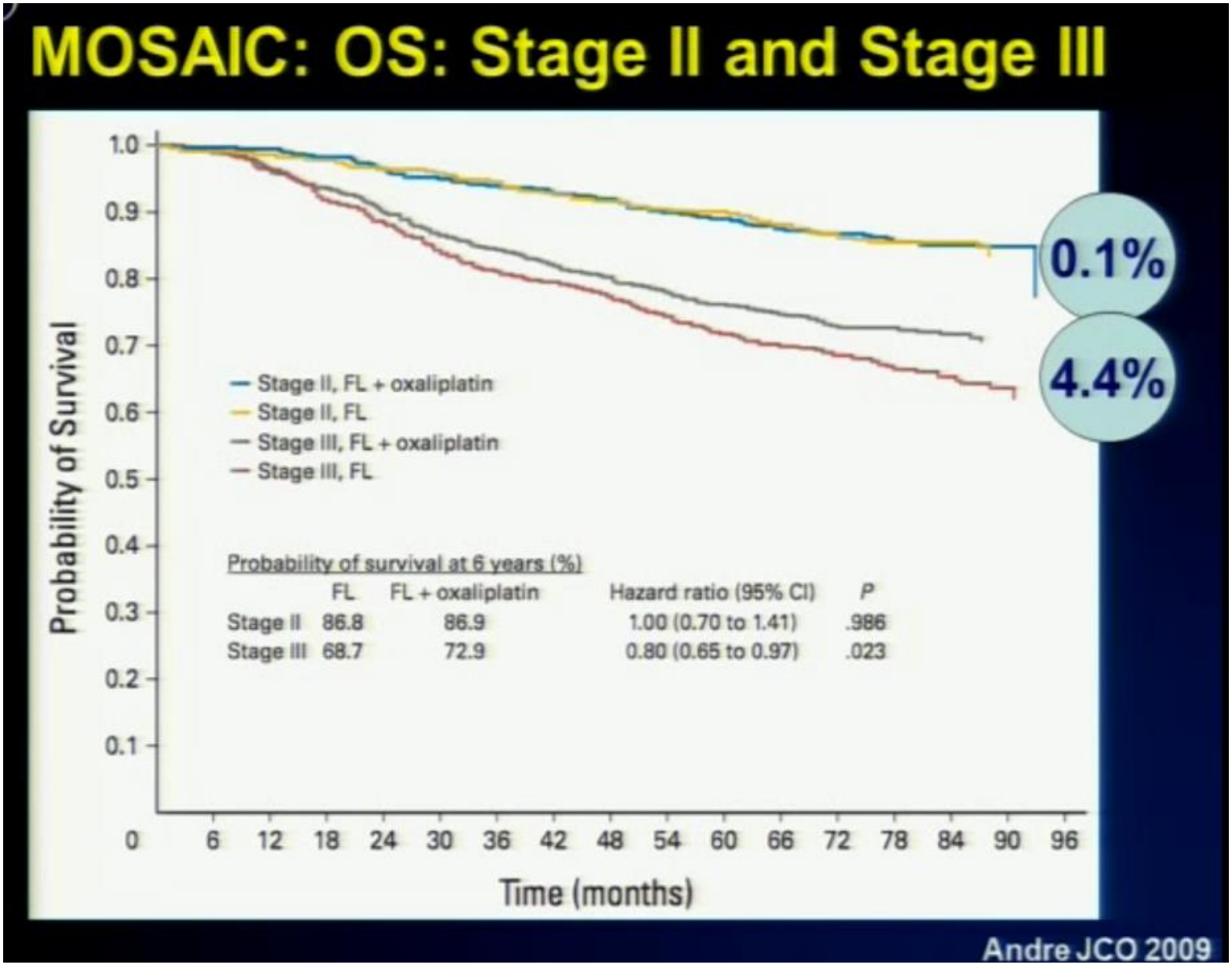
Kolon Kanserinde Adjuvan Tedavi Seçenekleri



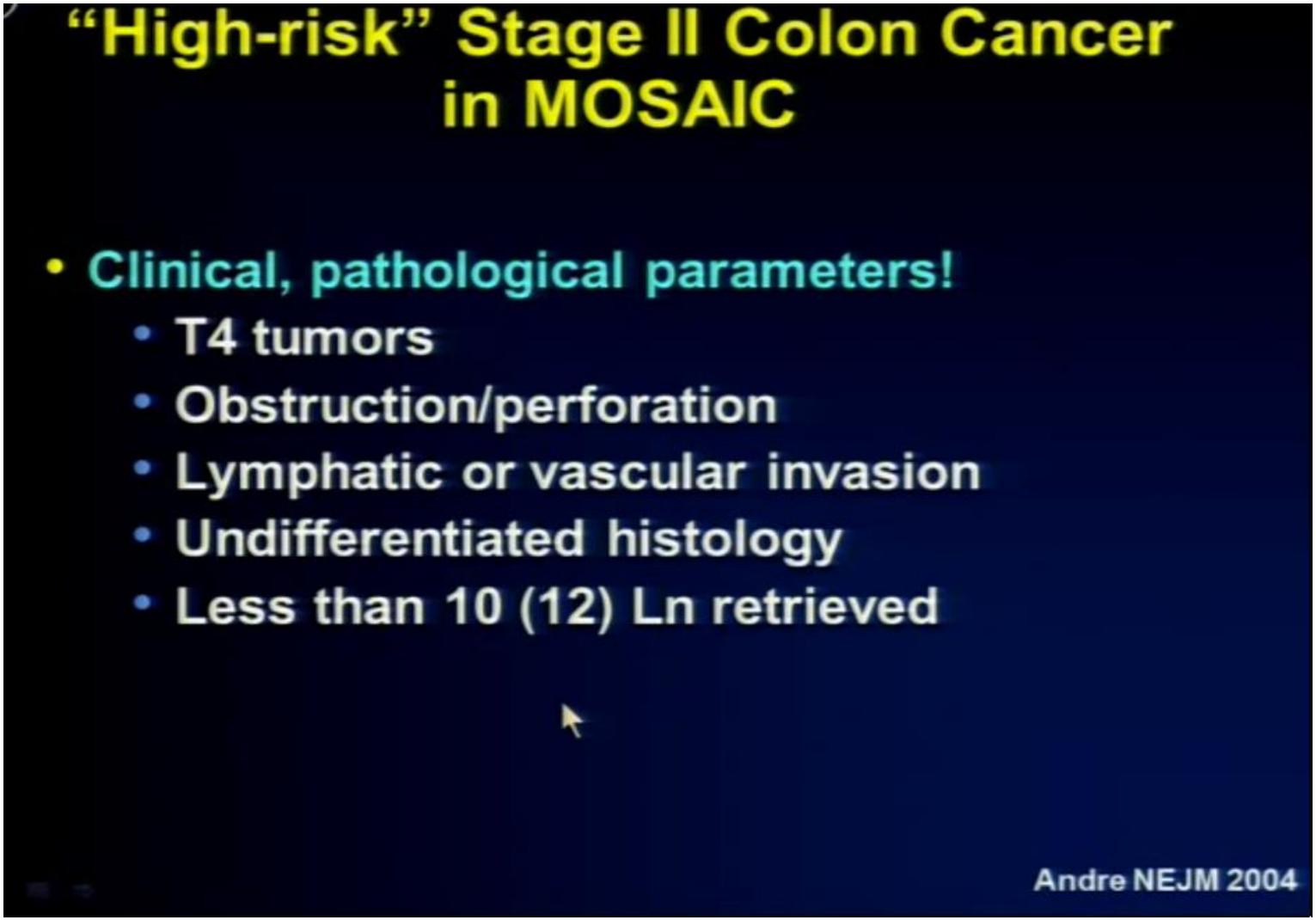
Kolon Kanserinde Adjuvan Tedavi Seçenekleri



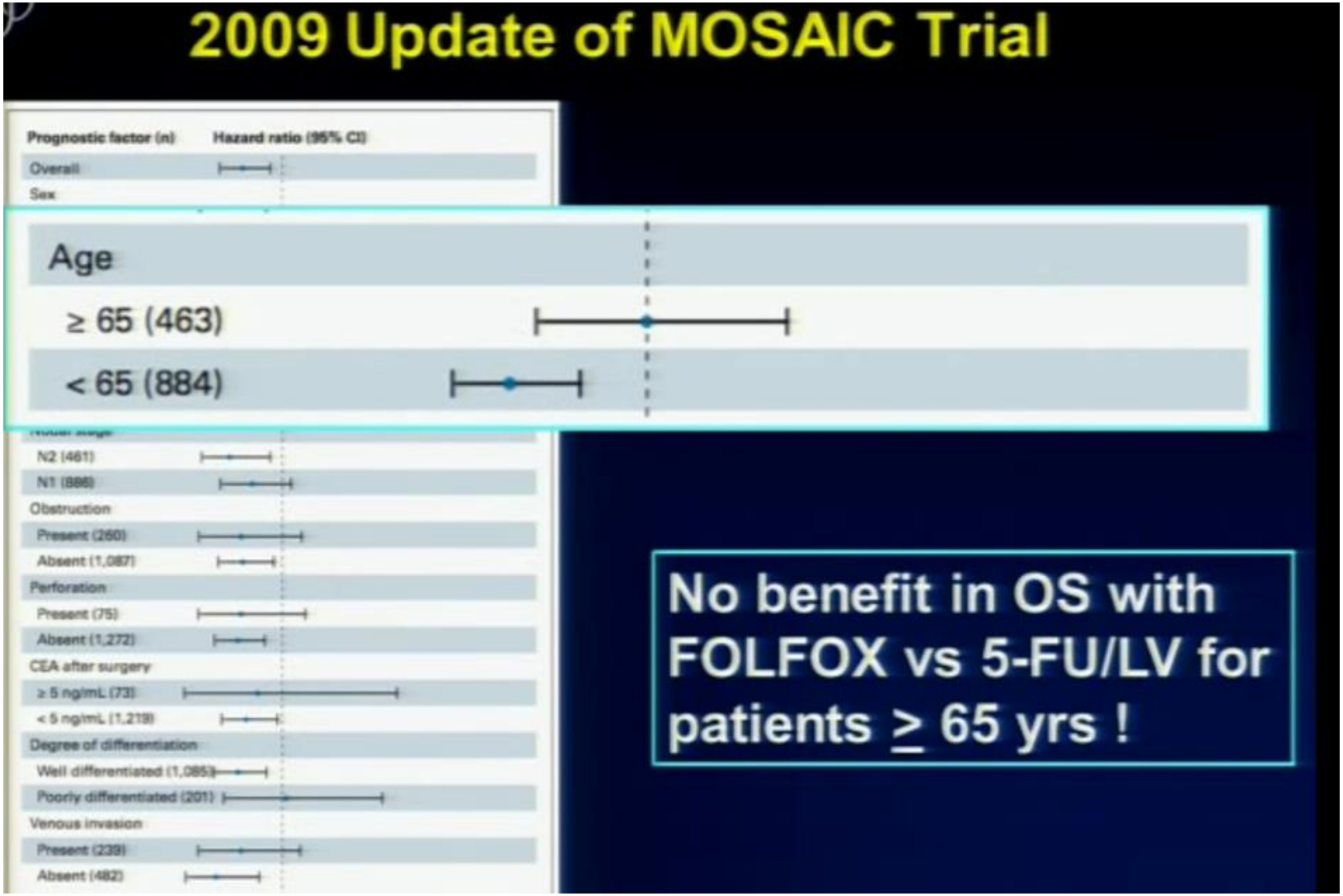
Kolon Kanserinde Adjuvan Tedavi Seçenekleri



Kolon Kanserinde Adjuvan Tedavi Seçenekleri



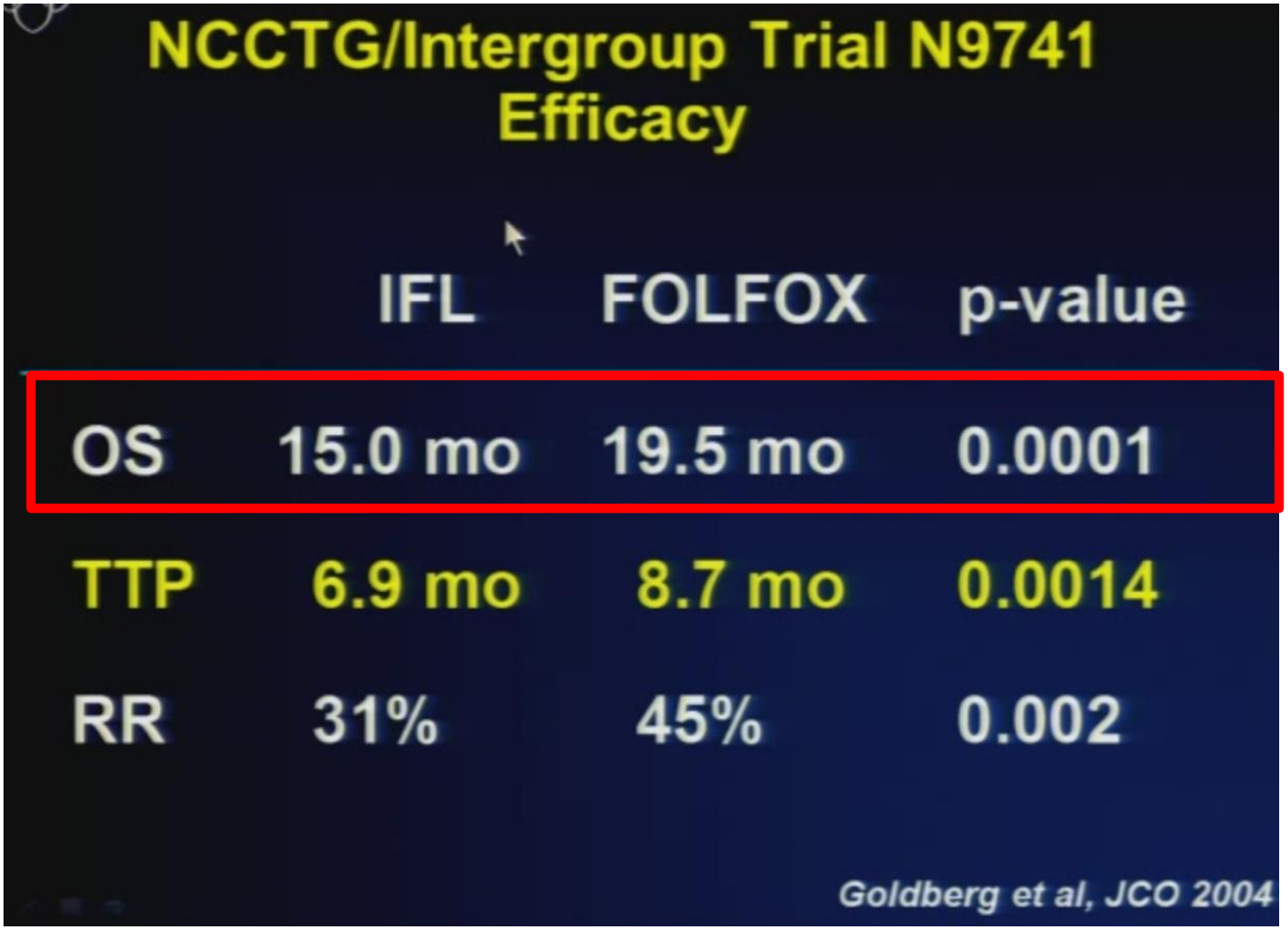
Kolon Kanserinde Adjuvan Tedavi Seçenekleri



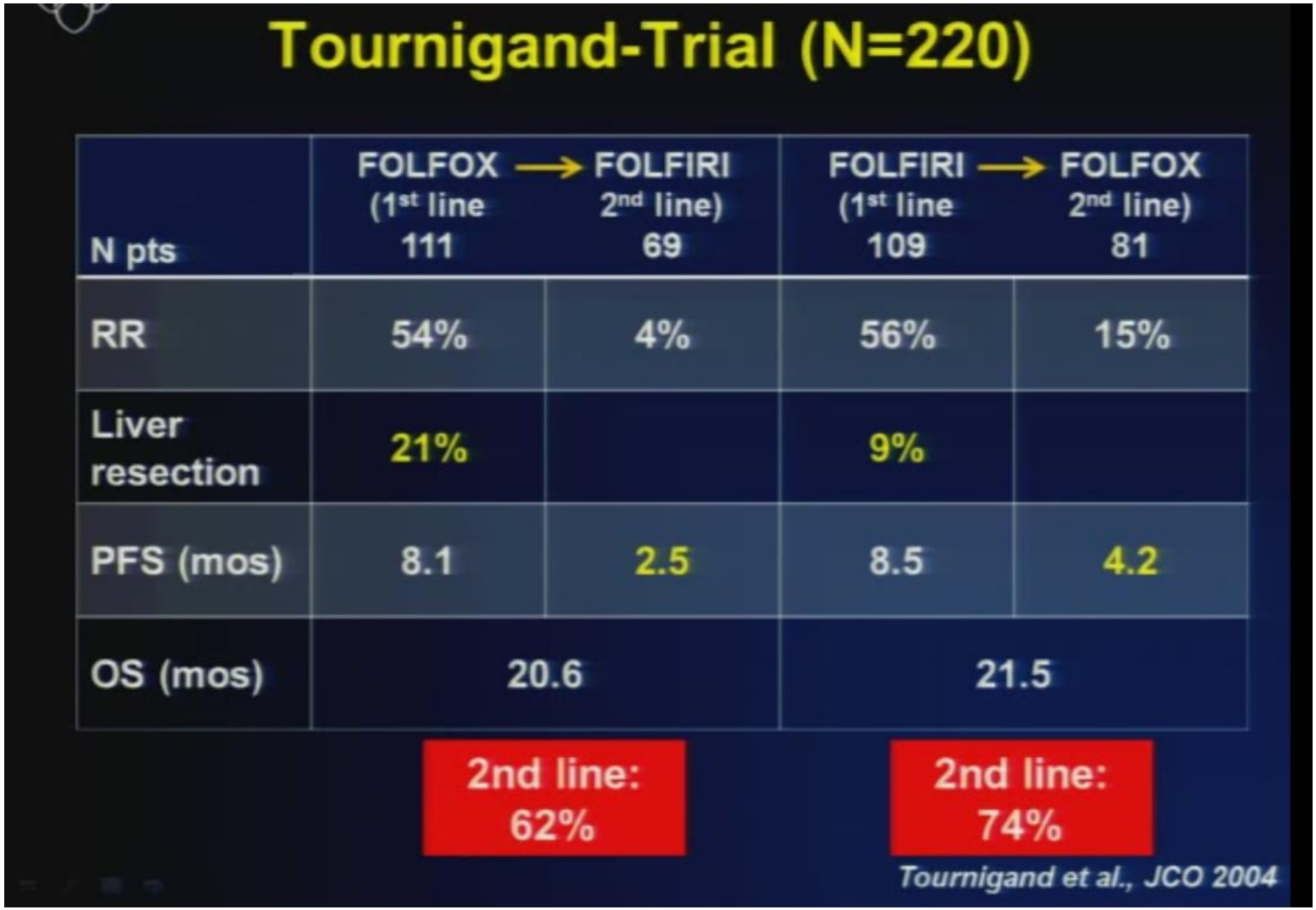
Metastatik Kolon Kanseri Tedavi

- 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

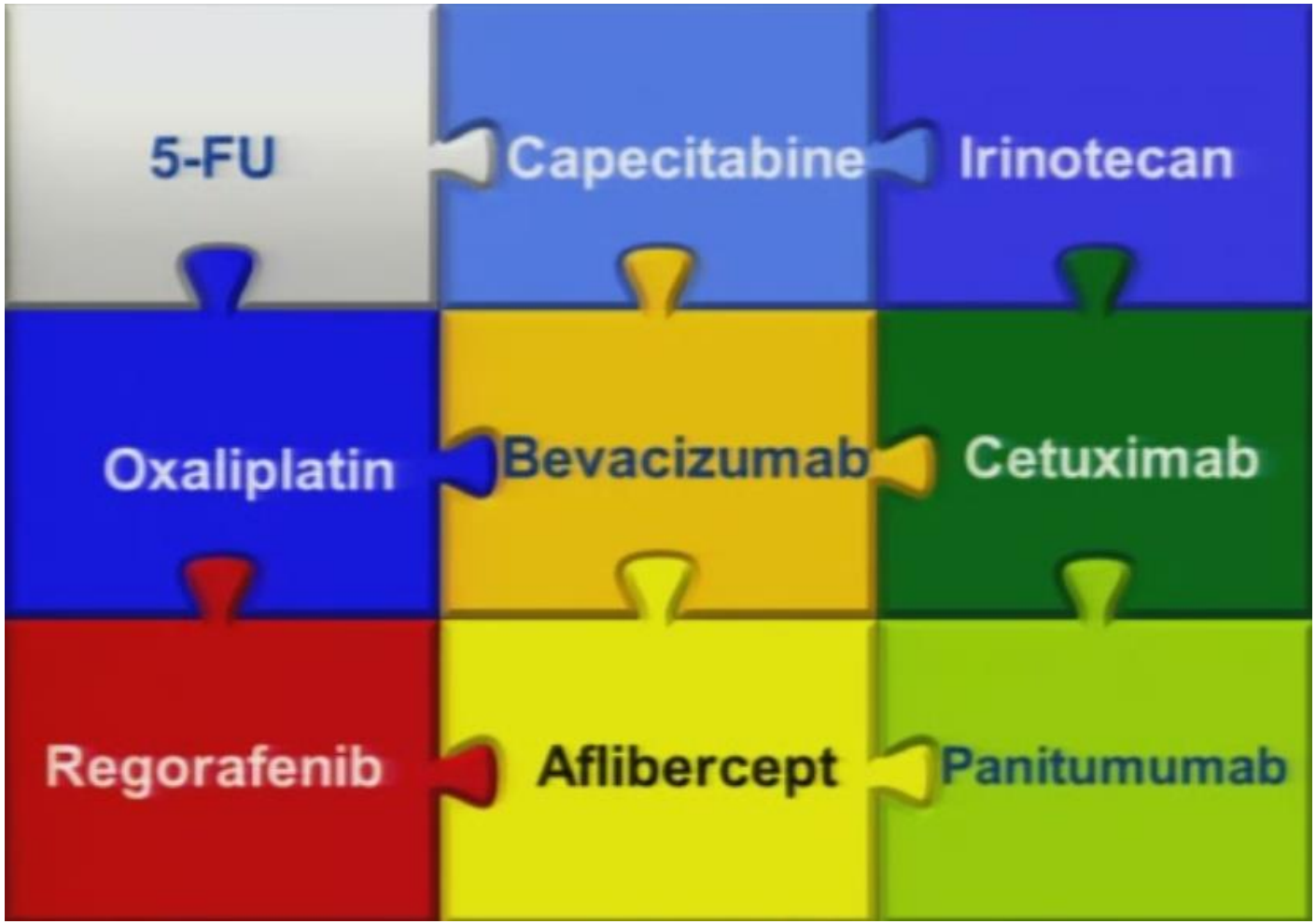
Metastatik Kolon Kanseri Tedavi



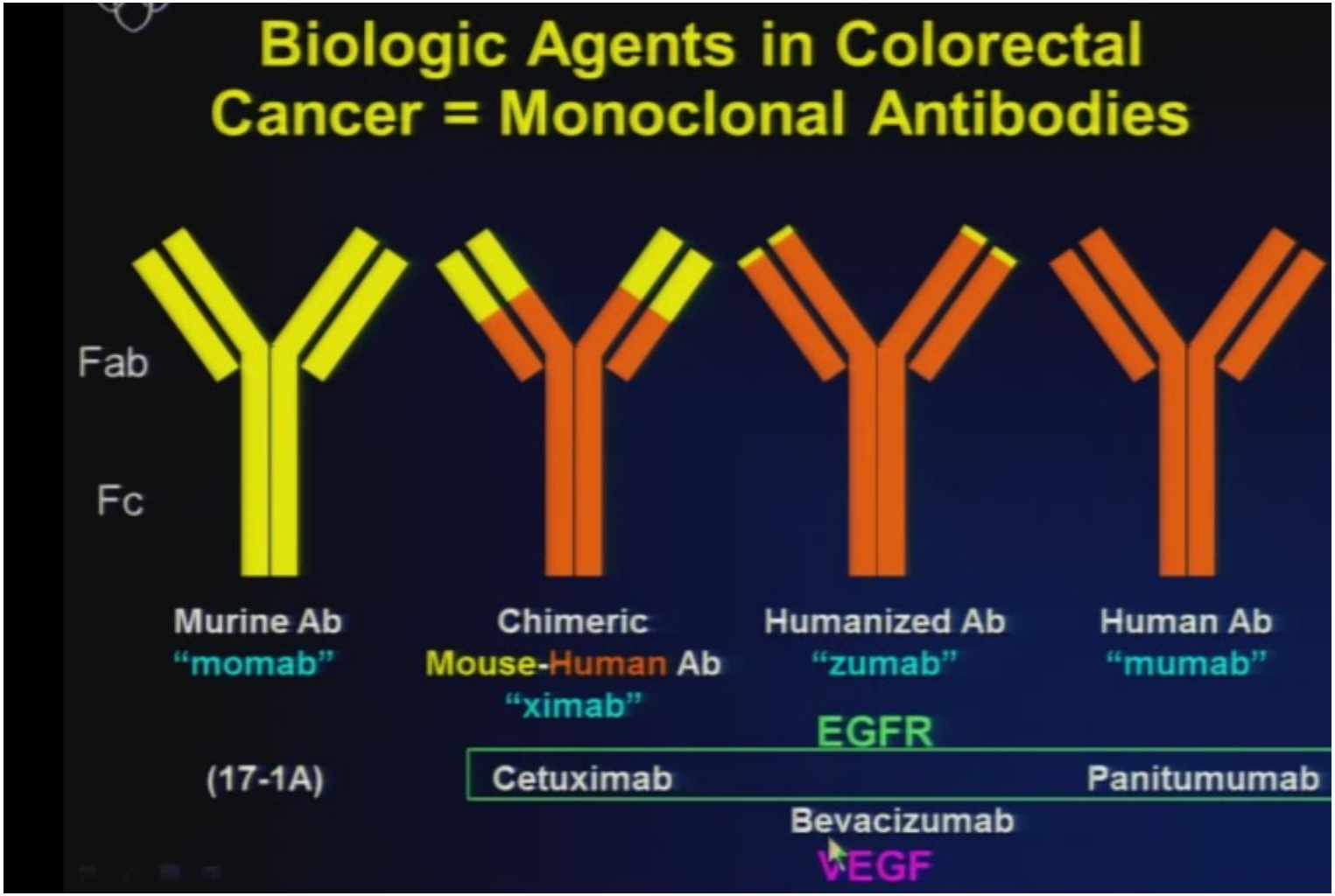
Metastatik Kolon Kanserinde Tedavi Seçenekleri



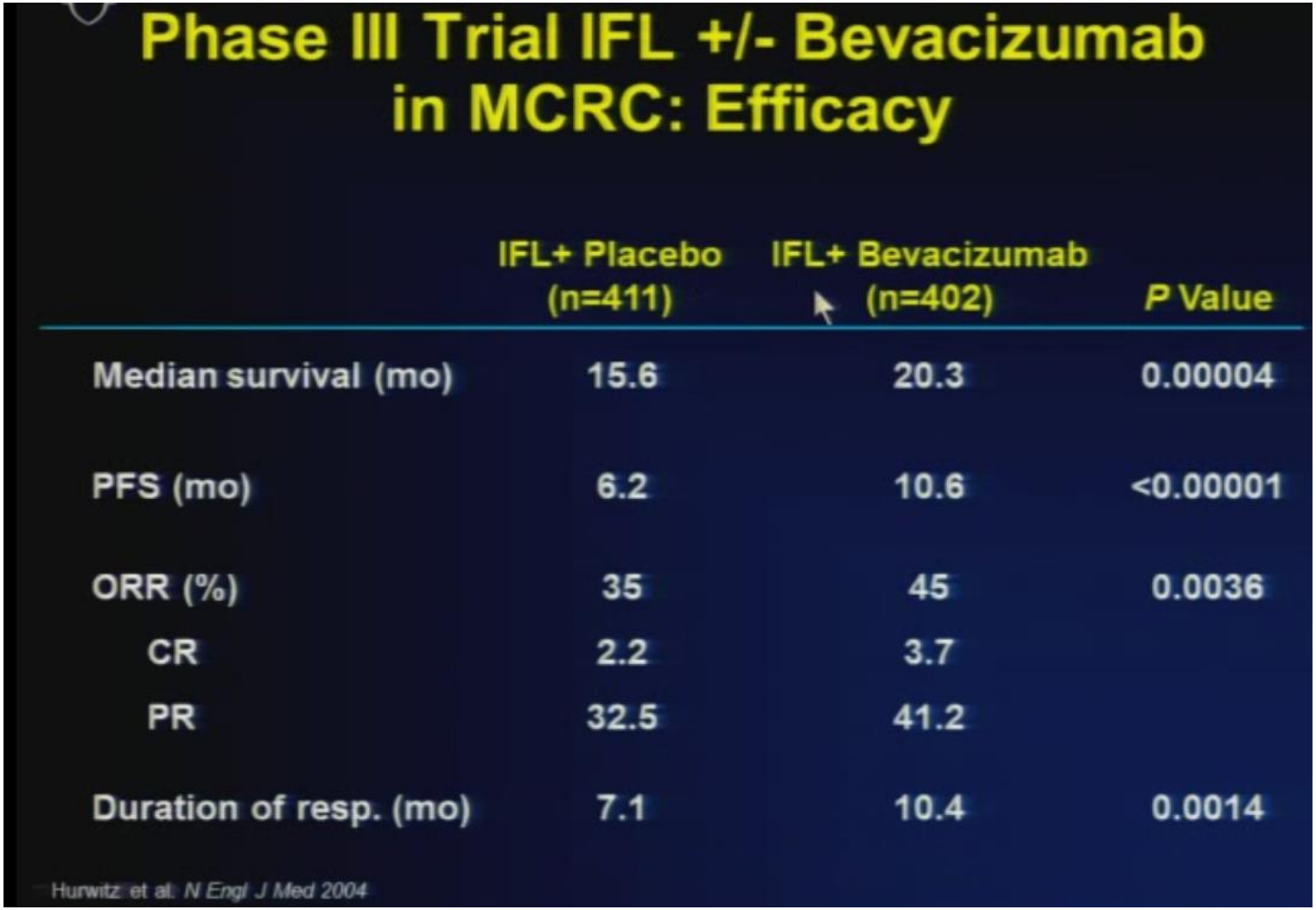
Metastatik Kolon Kanseri Tedavi



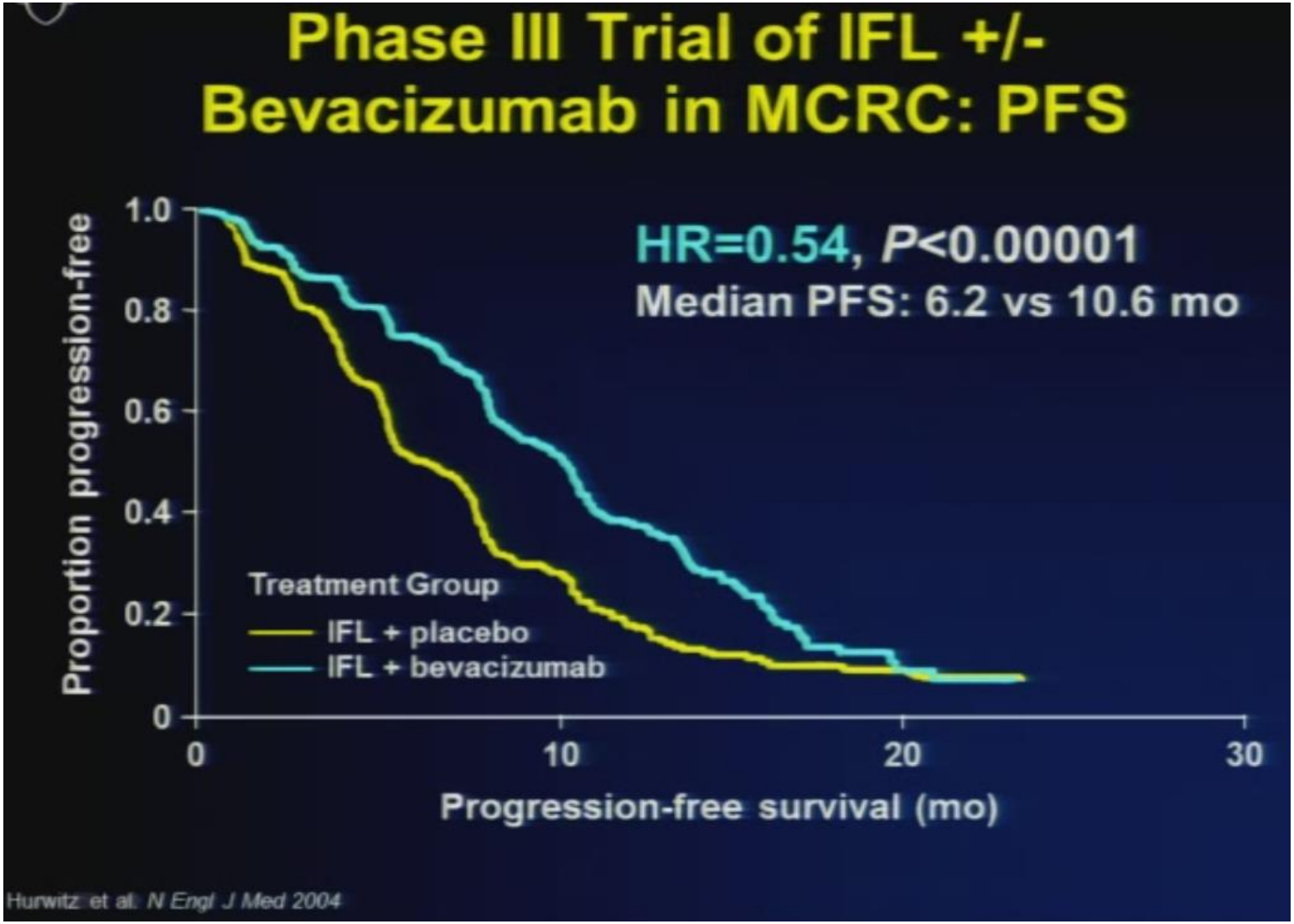
Metastatik Kolon Kanserinde Tedavi Seçenekleri



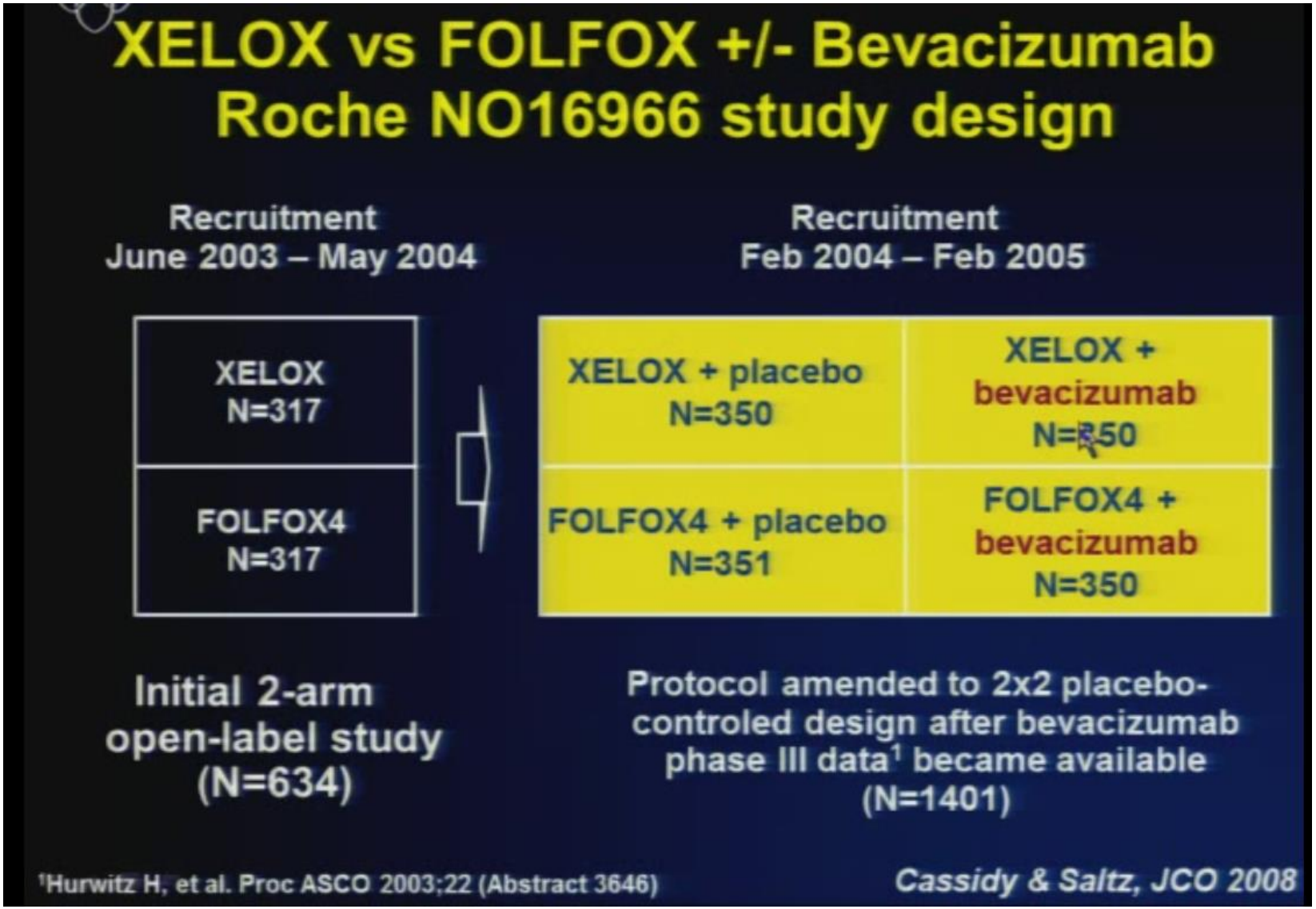
Metastatik Kolon Kanserinde Tedavi Seçenekleri



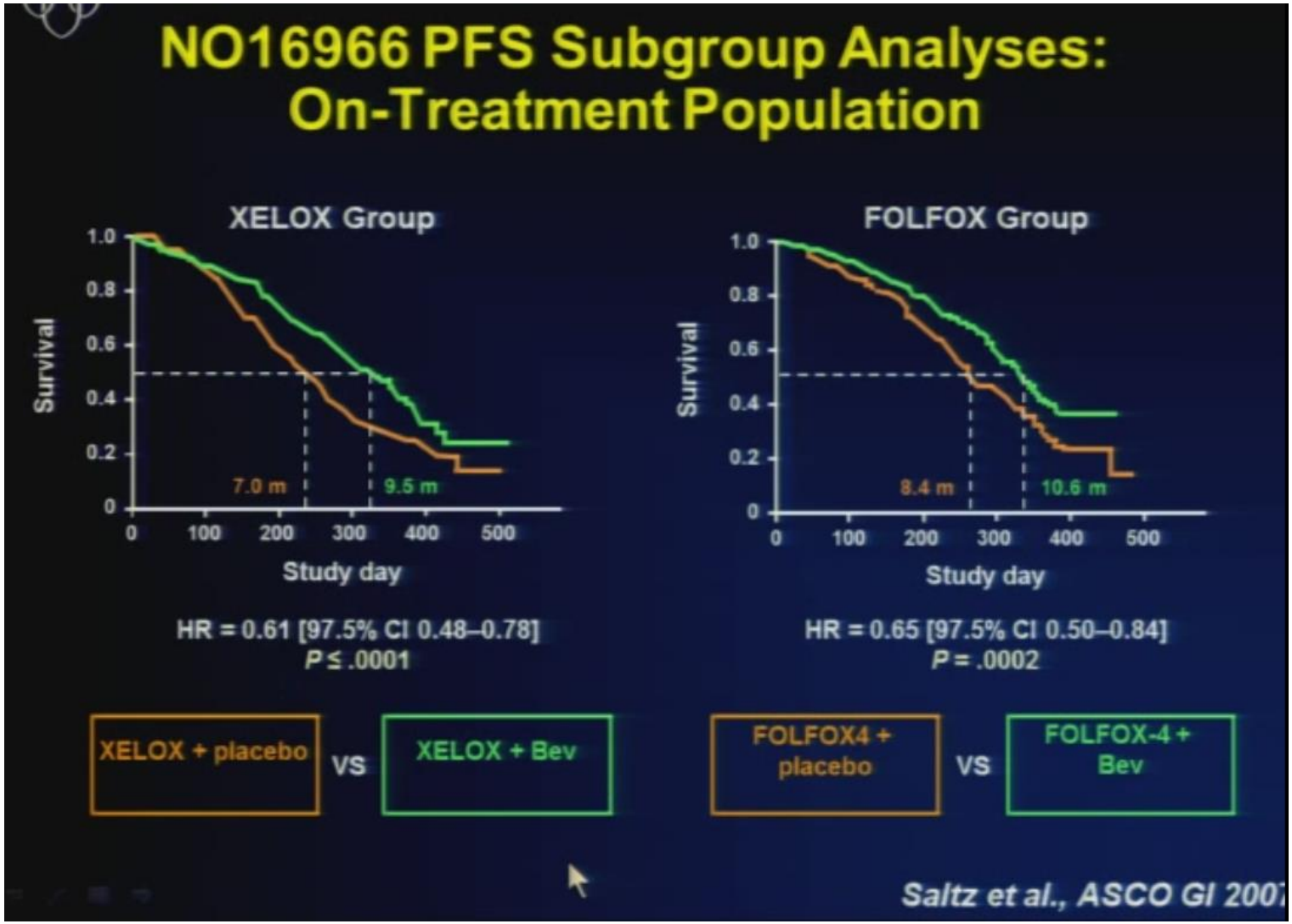
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

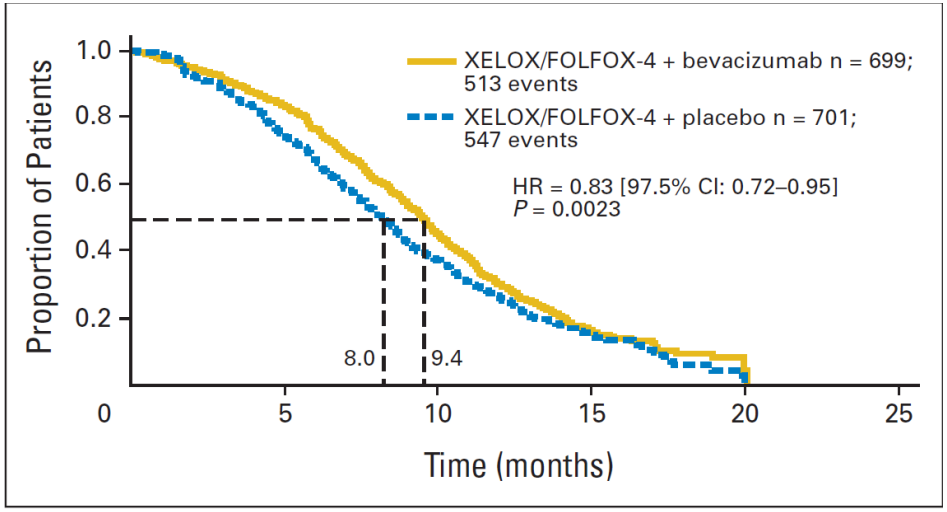


Fig 2. Progression-free survival (intent to treat population). XELOX, capecitabine and oxaliplatin; FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; HR, hazard ratio.

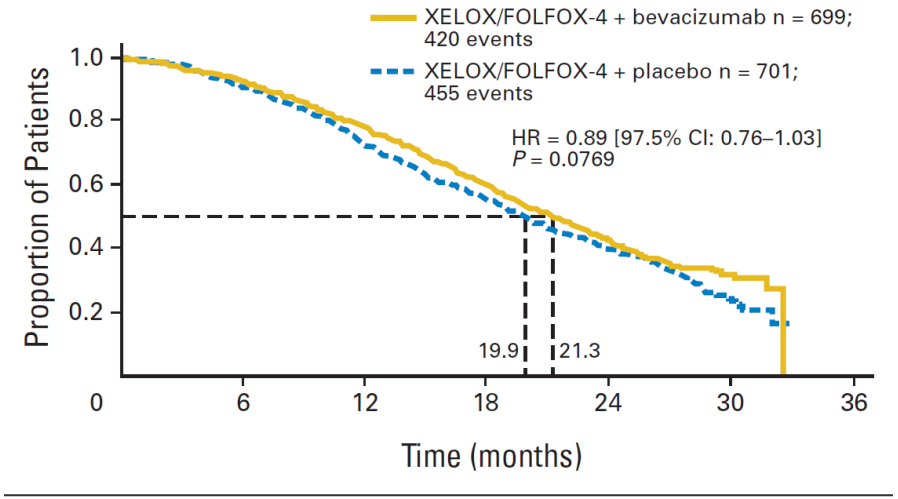
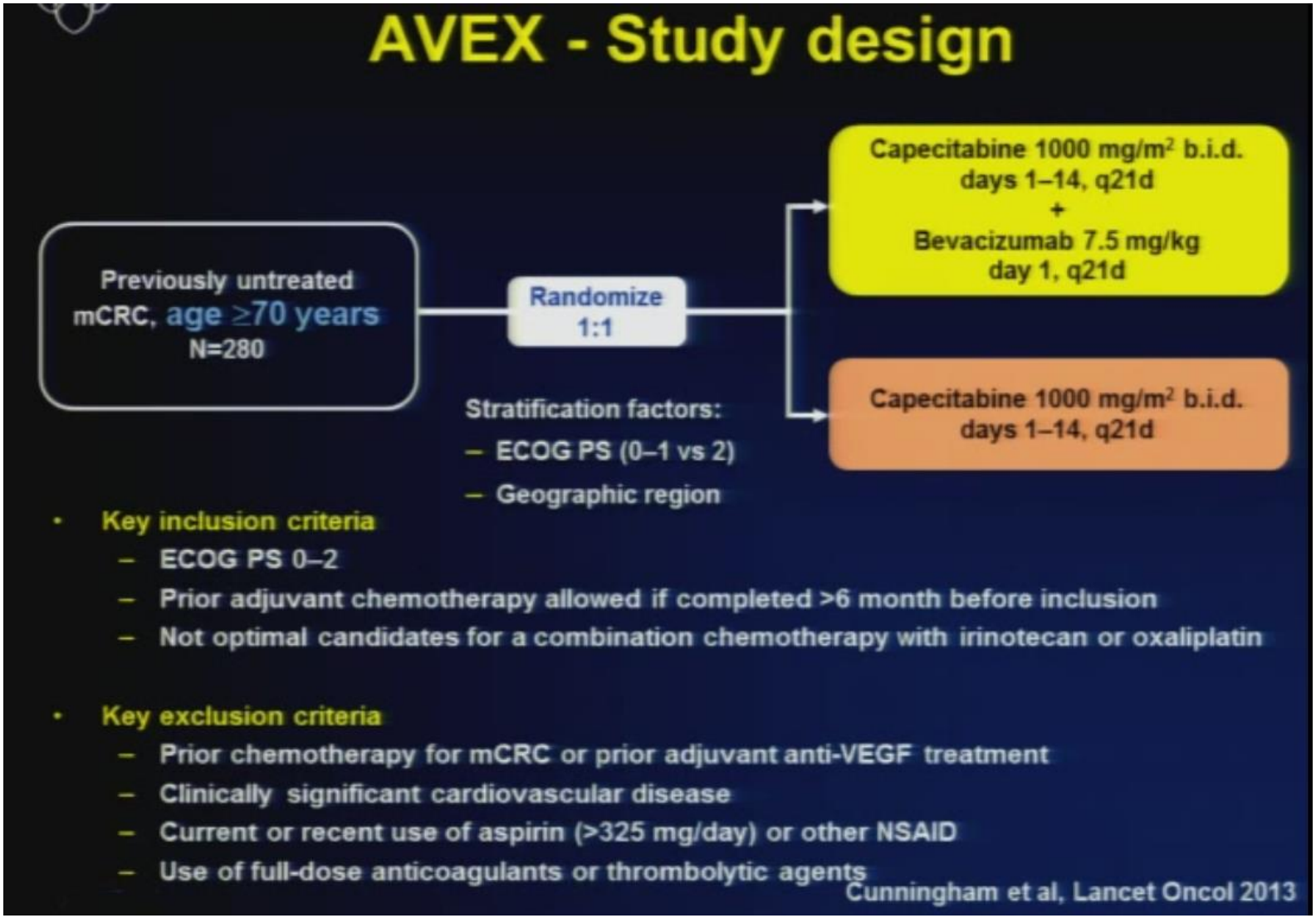


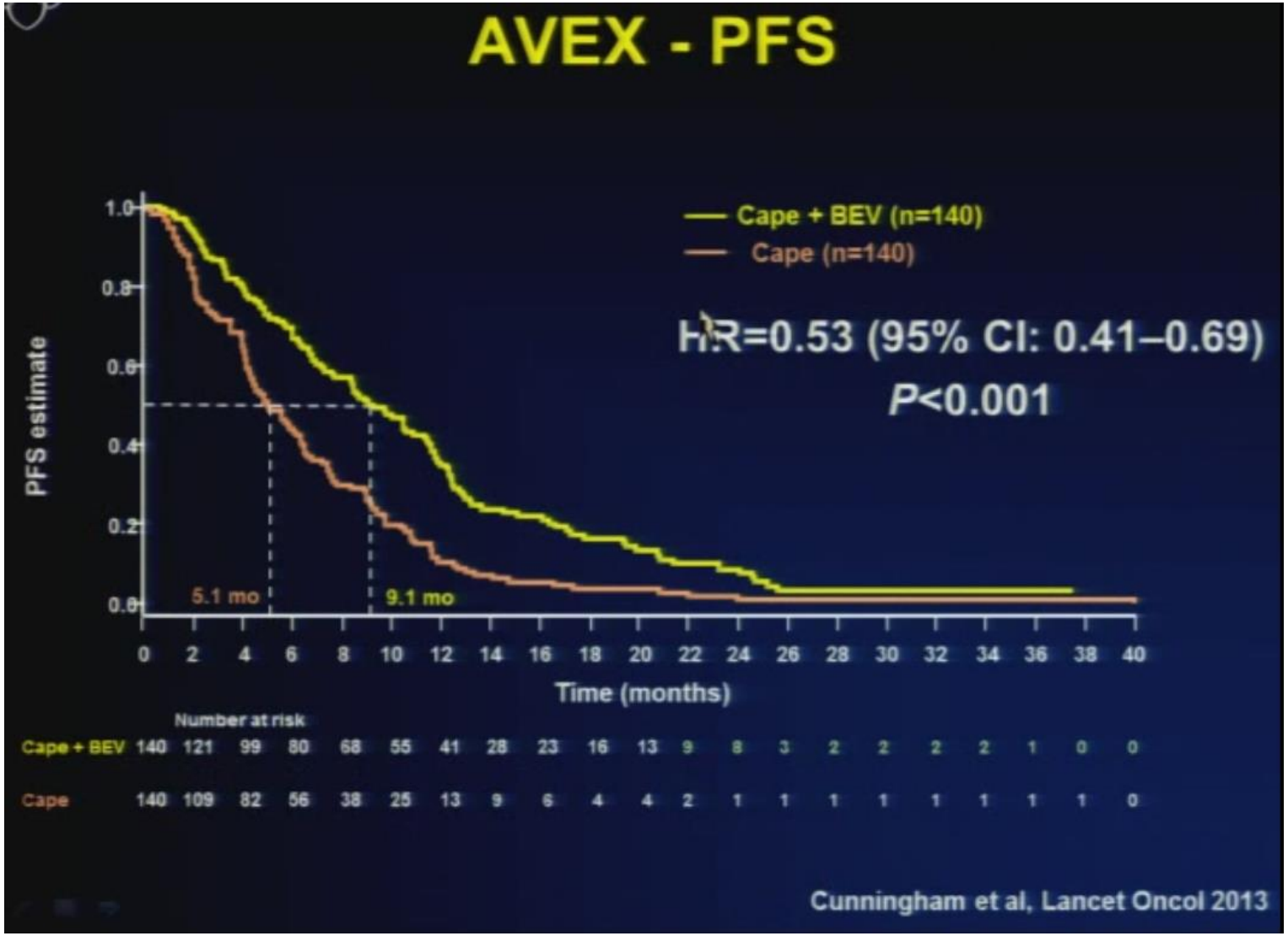
Fig 3. Overall survival (intent to treat population). XELOX, capecitabine and oxaliplatin FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; HR, hazard ratio.

Saltz LB, et al, JCO 2008

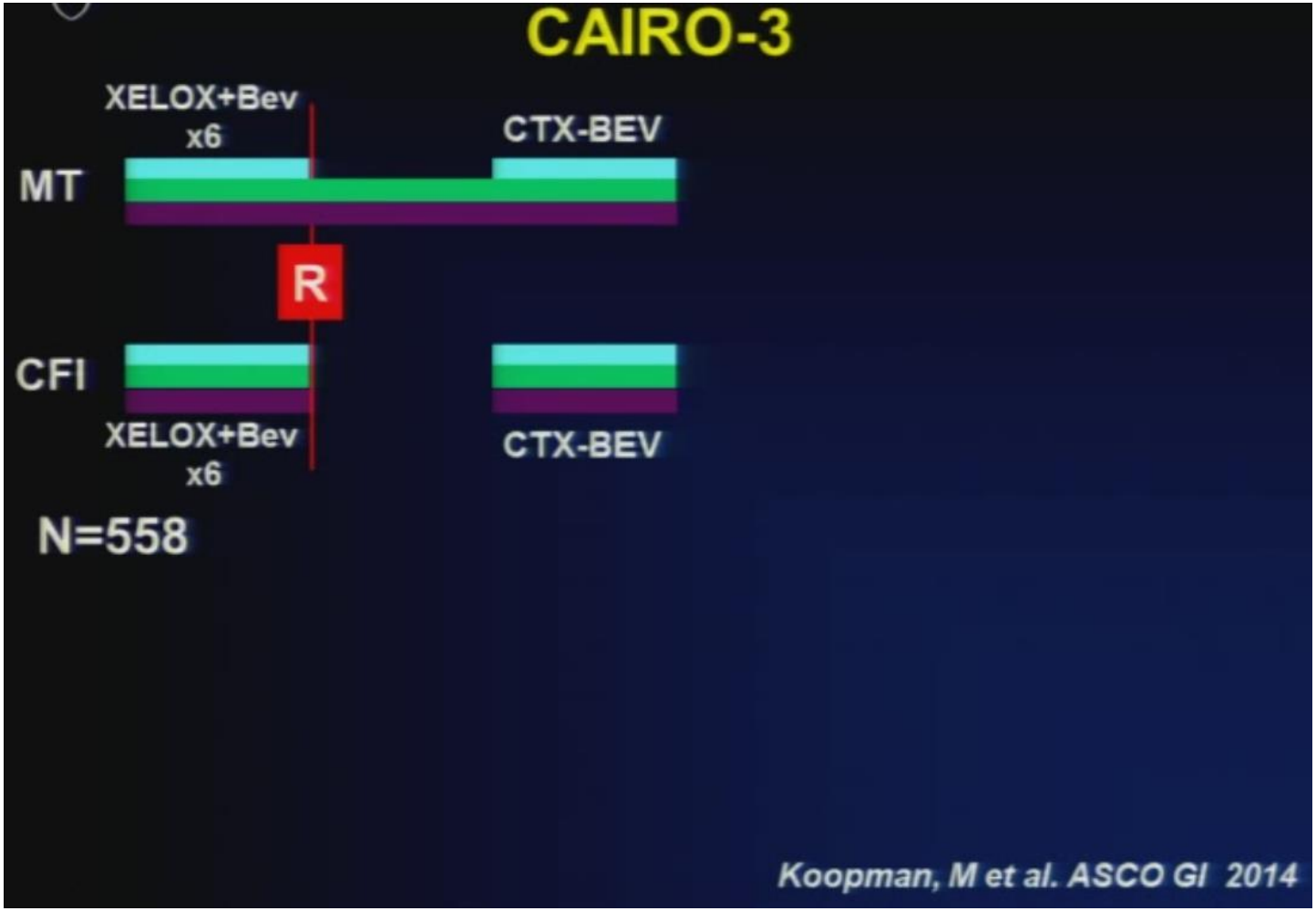
Metastatik Kolon Kanserinde Tedavi Seçenekleri



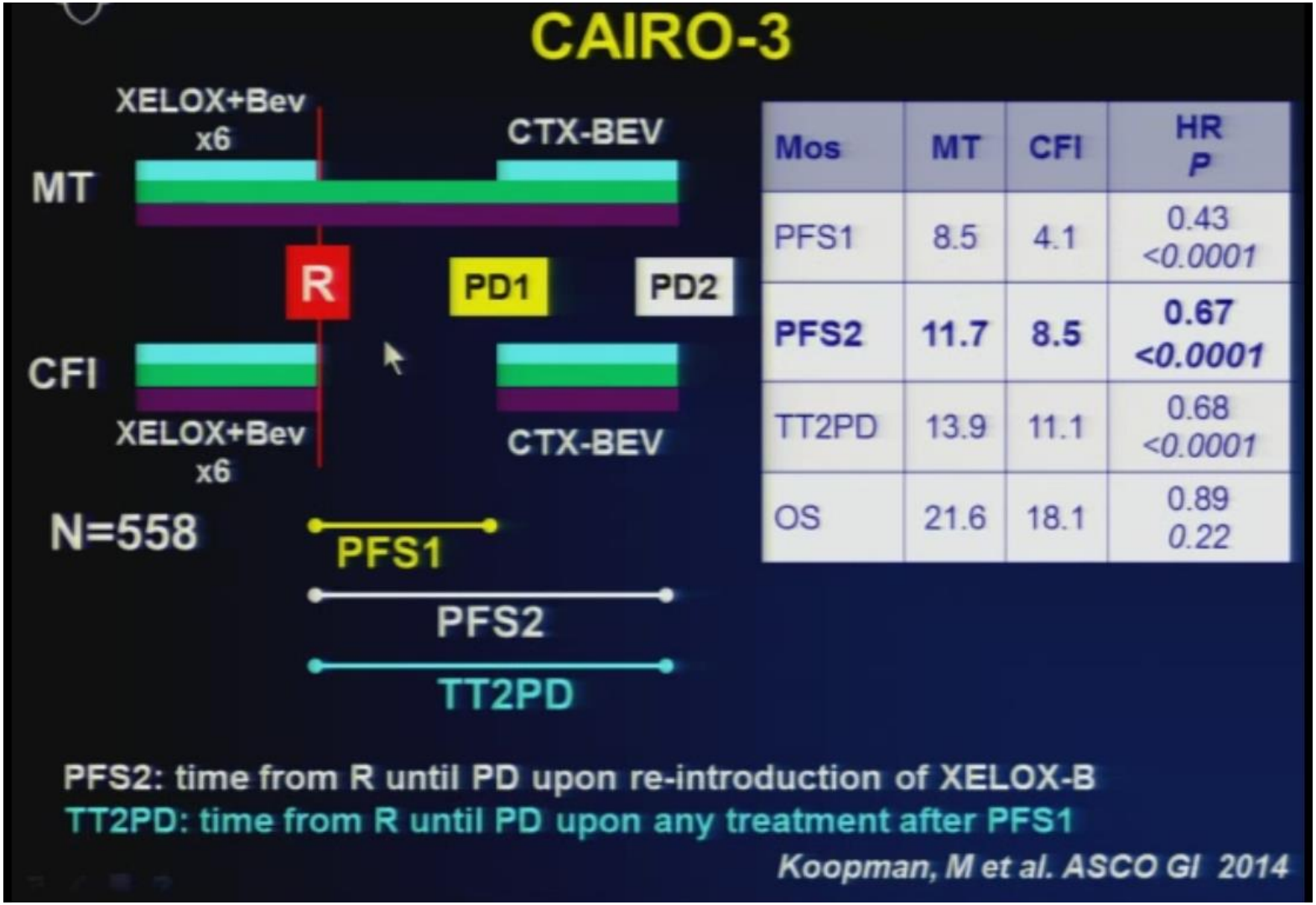
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

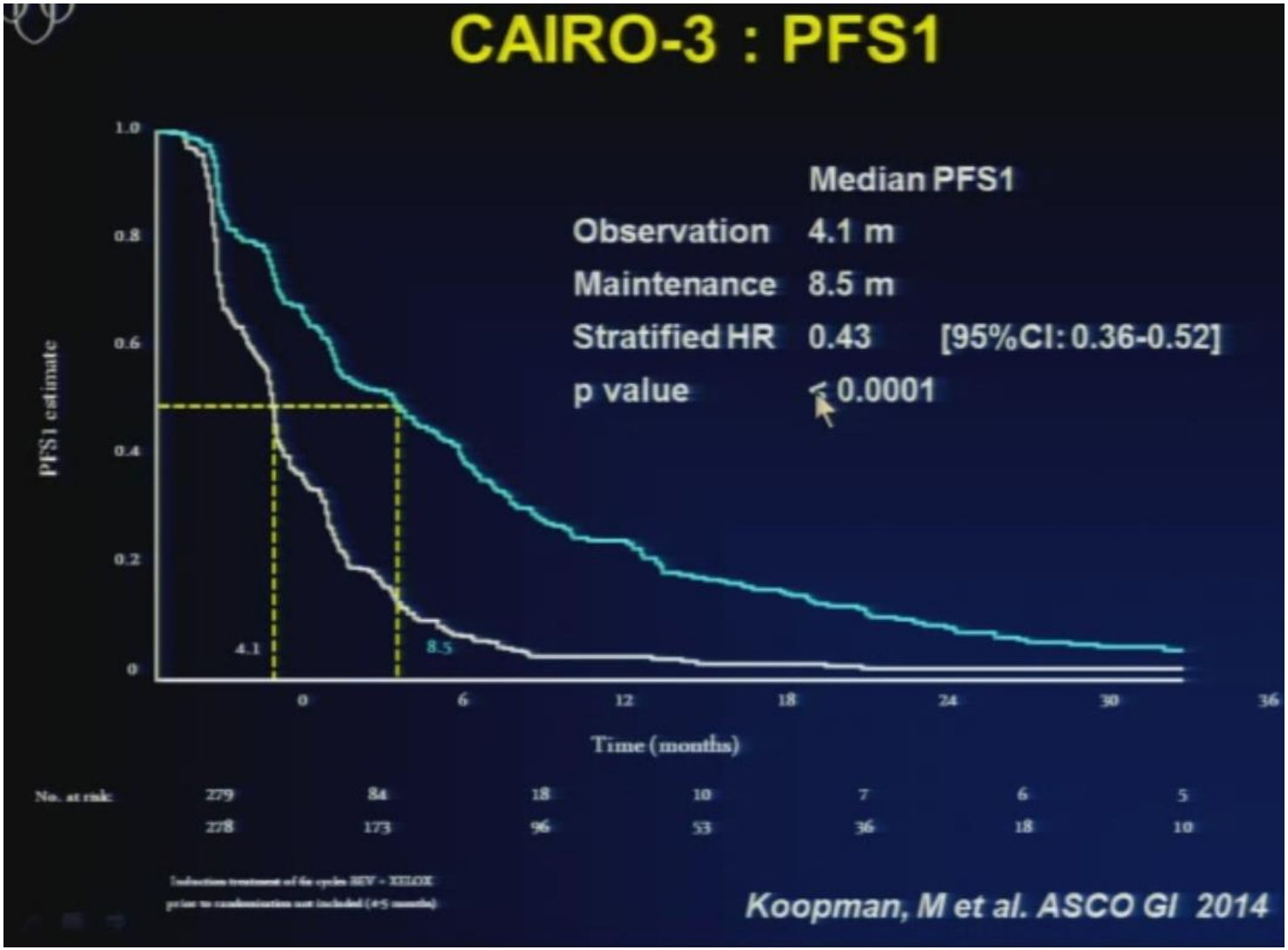


Metastatik Kolon Kanserinde Tedavi Seçenekleri



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 Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri
Bevasizumab İdame Tedavi

Trial	Maintenance Regimen	medyan PFS, Mos	*P* değeri	medyan OS, Mos	*P* değeri
STOP and GO[1]					
▪ Experimental 0.100	Bevasizumab+XELOX	8.3	0.002	20.2	
▪ Control	Bevasizumab+Xeloda	11		23.8	
MACRO[2]					
▪ Experimental	CAPOX-B	10.4	.38	23.2	.65
▪ Control	Bevasizumab	9.7		19.99	
CAIRO-3[3]					
▪ Experimental	CAPOX-B	11.7*	< .0001	21.6	.22†
▪ Control	Observation	8.5*		18.1	
SAKK 41/06[4]					
▪ Experimental	Bevasizumab	9.5	.021	25.1	.218
▪ Control	Observation	8.5		22.8	
AIO 0207[5]					
▪ Experimental	FP + Bev/Bev	6.2/4.2	< .0001	23.8/26.2	.70
▪ Control	Observation	3.6		23.1	

1. Stop and Go Yalcın et.al. Oncology 2013 2. Diaz-Rubio E, ve ark. Oncologist. 2012;17:15-25. 3. Koopman M, ve ark. ASCO 2014. Abstract 3504. 4. Koeberle D, ve ark. ASCO 2013. Abstract 3503. 5. Arnold D, ve ark. ASCO 2014 Abstract 3503.

Metastatik Kolon Kanserinde Tedavi Seçenekleri

Bevacisumab -Metaanaliz

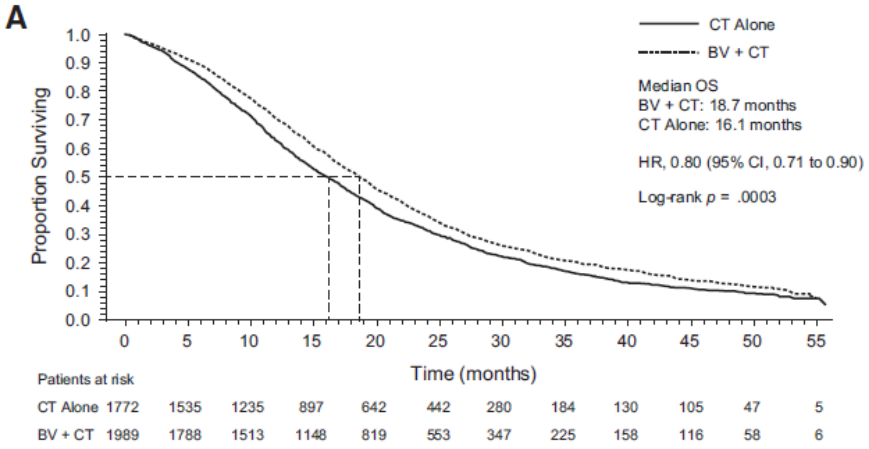
Table 1. Overview of clinical trials included in the analysis

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



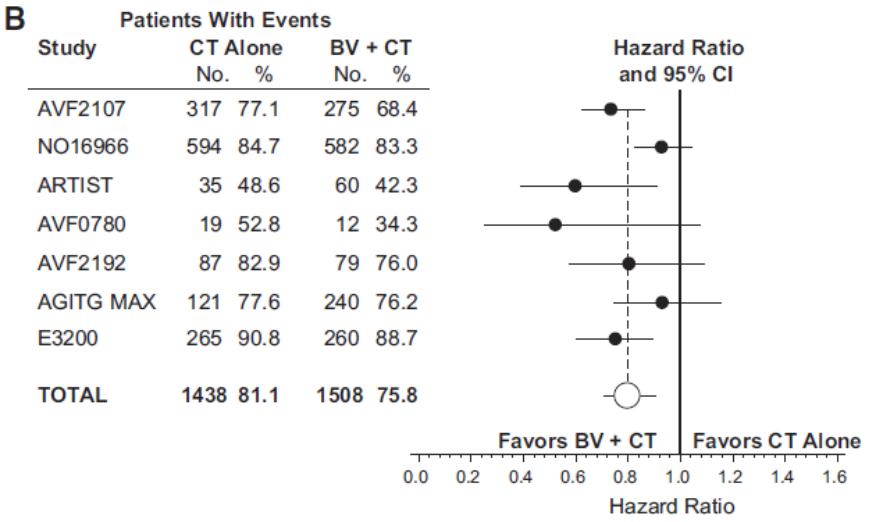
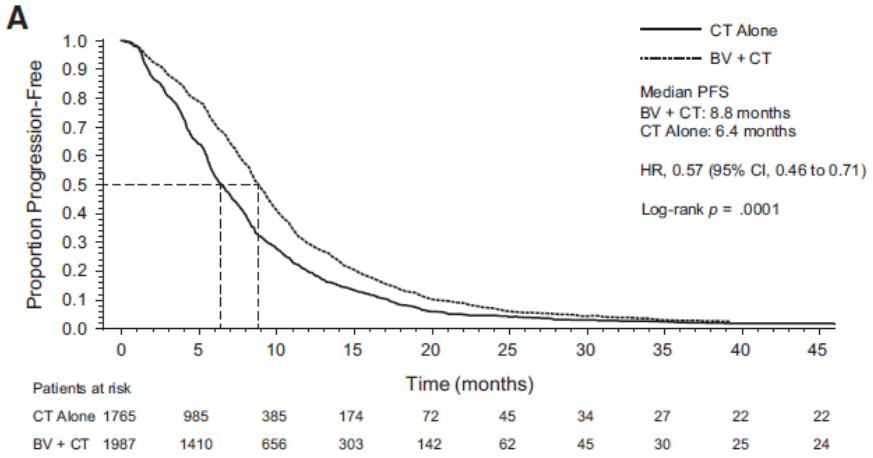


Figure 1. Overall survival (OS) in the overall pooled population and in individual studies (first- and second-line trials of bevacizumab). **(A):** Kaplan-Meier estimate of OS for the overall pooled population. **(B):** Forest plot of OS by study.
Abbreviations: BV, bevacizumab; CI, confidence interval;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

Hurtwitz HI, et al, Oncologist 2013

Metastatik Kolon Kanserinde Tedavi Seçenekleri



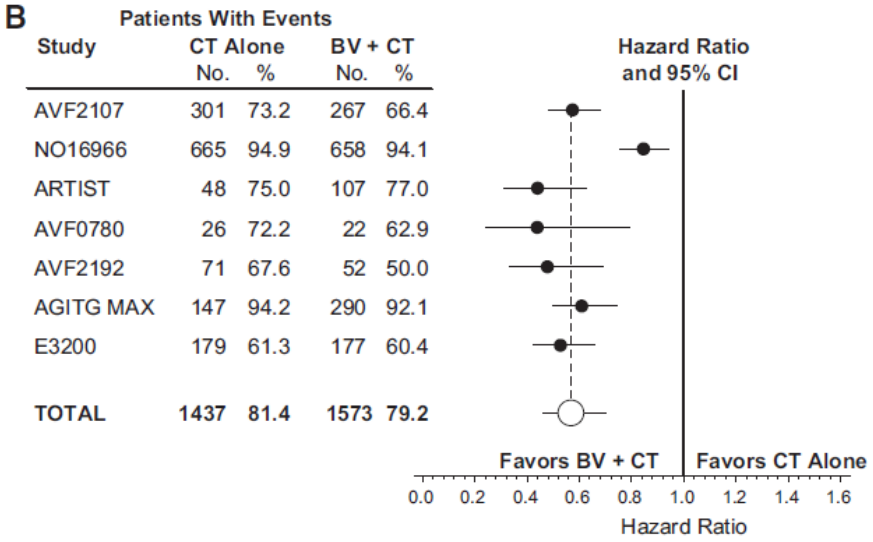


Figure 2. Progression-free survival (PFS) in the overall pooled population and in individual studies (first- and second-line trials of bevacizumab). **(A):** Kaplan-Meier estimate of PFS for the pooled population. **(B):** Forest plot of PFS by study.
Abbreviations: BV, bevacizumab; CI, confidence interval;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

Metastatik Kolon Kanserinde Tedavi Seçenekleri

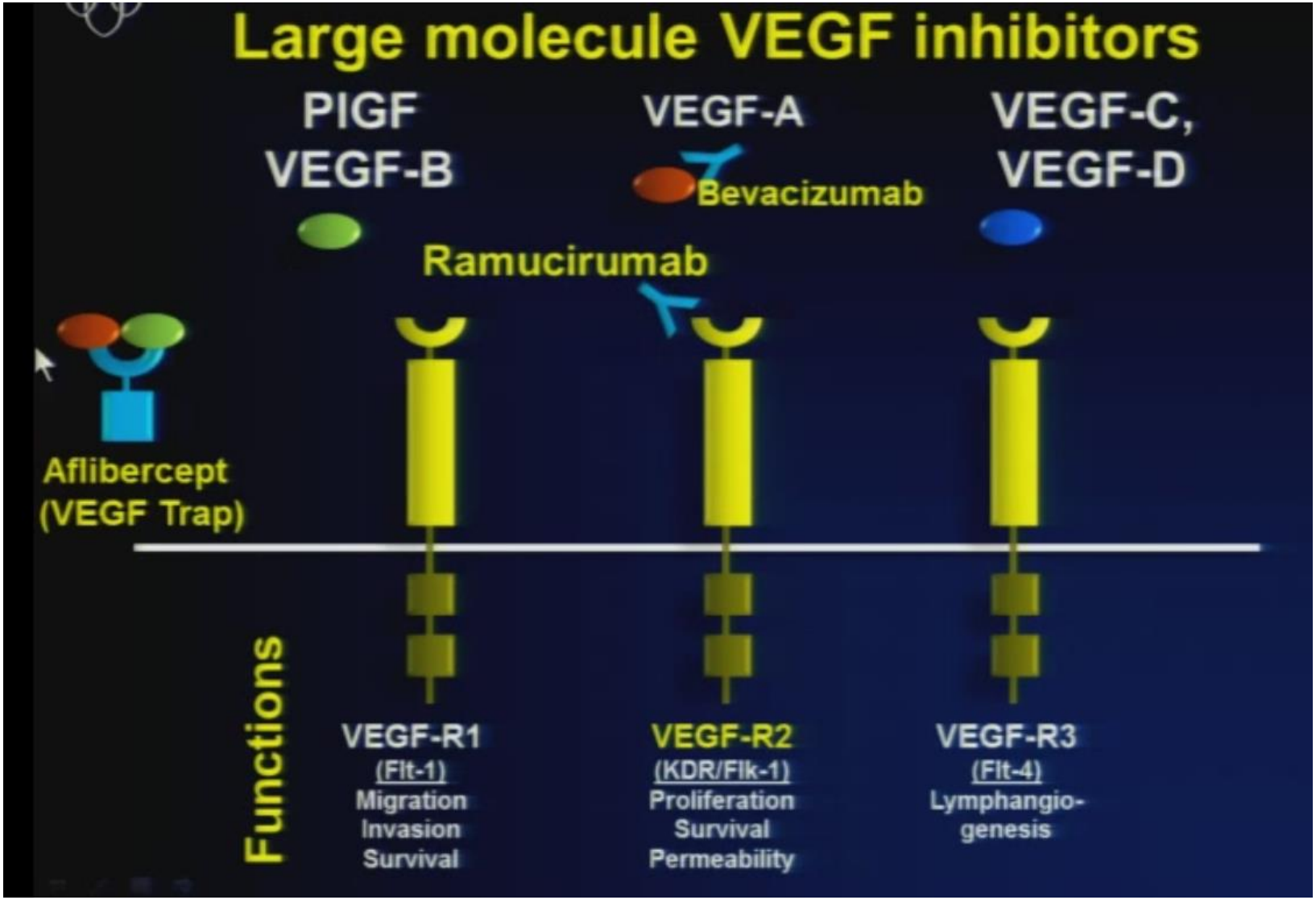
Table 3. Subgroup analyses in the overall pooled population (first- and second-line trials of bevacizumab) and first-line pooled population

	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

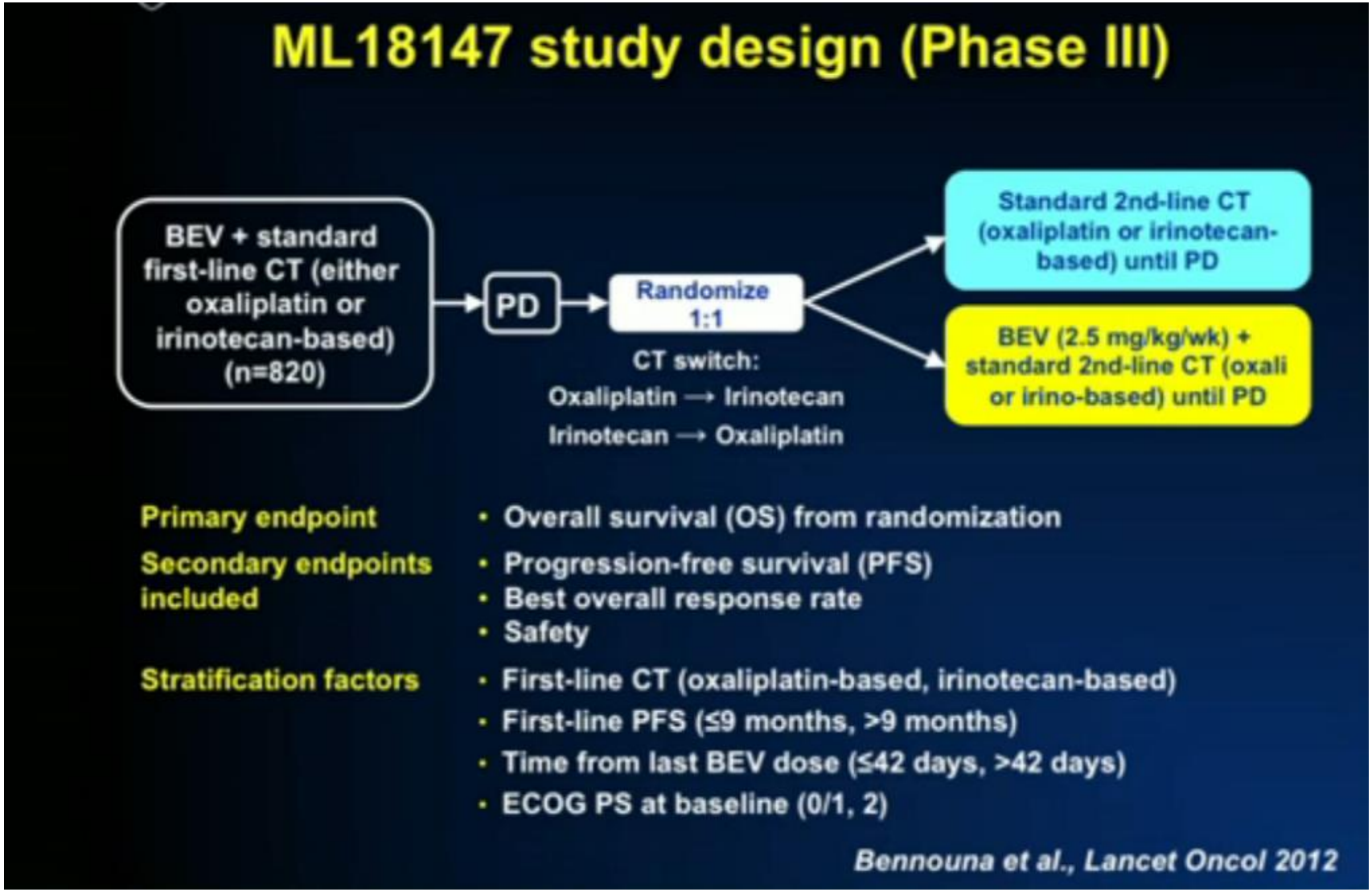
[a]Patients with metastatic disease in at least one site other than the liver or the lung.
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

Hurtwitz HI, et al, Oncologist 2013

Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | 23168366[uid] | Search

Create RSS Create alert Advanced Help

Abstract Send to:

Lancet Oncol. 2013 Jan;14(1):29-37. doi: 10.1016/S1470-2045(12)70477-1. Epub 2012 Nov 16.

Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial.

Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, von Moos R, Viéitez JM, Bouché O, Borg C, Steffens CC, Alonso-Orduña V, Schlichting C, Reyes-Rivera I, Bendahmane B, André T, Kubicka S; ML18147 Study Investigators.

Collaborators (230)

Abstract

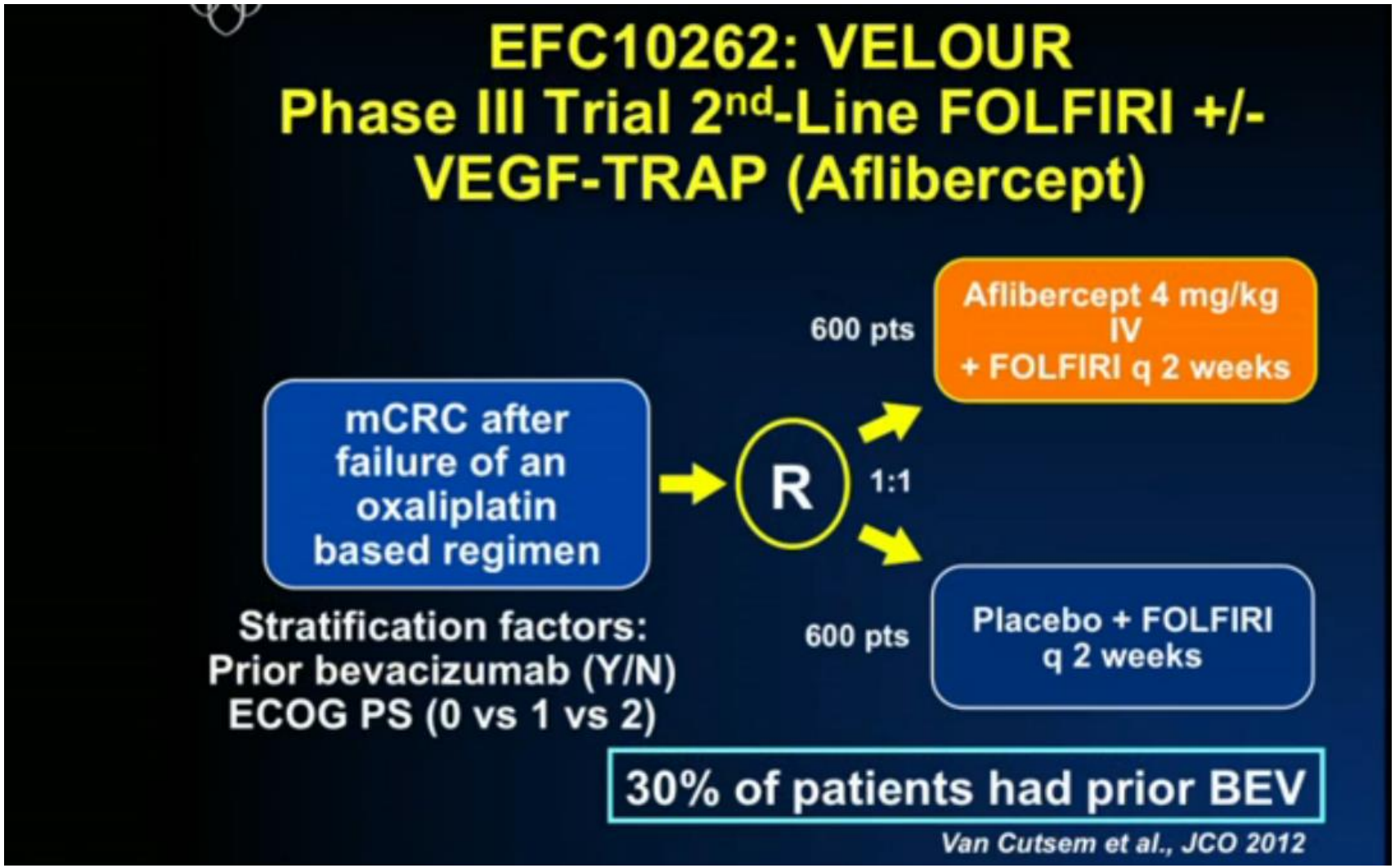
BACKGROUND: Bevacizumab plus fluoropyrimidine-based chemotherapy is standard treatment for first-line and bevacizumab-naive second-line metastatic colorectal cancer. We assessed continued use of bevacizumab plus standard second-line chemotherapy in patients with metastatic colorectal cancer progressing after standard first-line bevacizumab-based treatment.

METHODS: In an open-label, phase 3 study in 220 centres in Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, the Netherlands, Norway, Portugal, Saudi Arabia, Spain, Sweden, and Switzerland, patients (aged ≥18 years) with unresectable, histologically confirmed metastatic colorectal cancer progressing up to 3 months after discontinuing first-line bevacizumab plus chemotherapy were randomly assigned in a 1:1 ratio to second-line chemotherapy with or without bevacizumab 2·5 mg/kg per week equivalent (either 5 mg/kg every 2 weeks or 7·5 mg/kg every 3 weeks, intravenously). The choice between oxaliplatin-based or irinotecan-based second-line chemotherapy depended on the first-line regimen (switch of chemotherapy). A combination of a permuted block design and the Pocock and Simon minimisation algorithm was used for the randomisation. The primary endpoint was overall survival, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00700102.

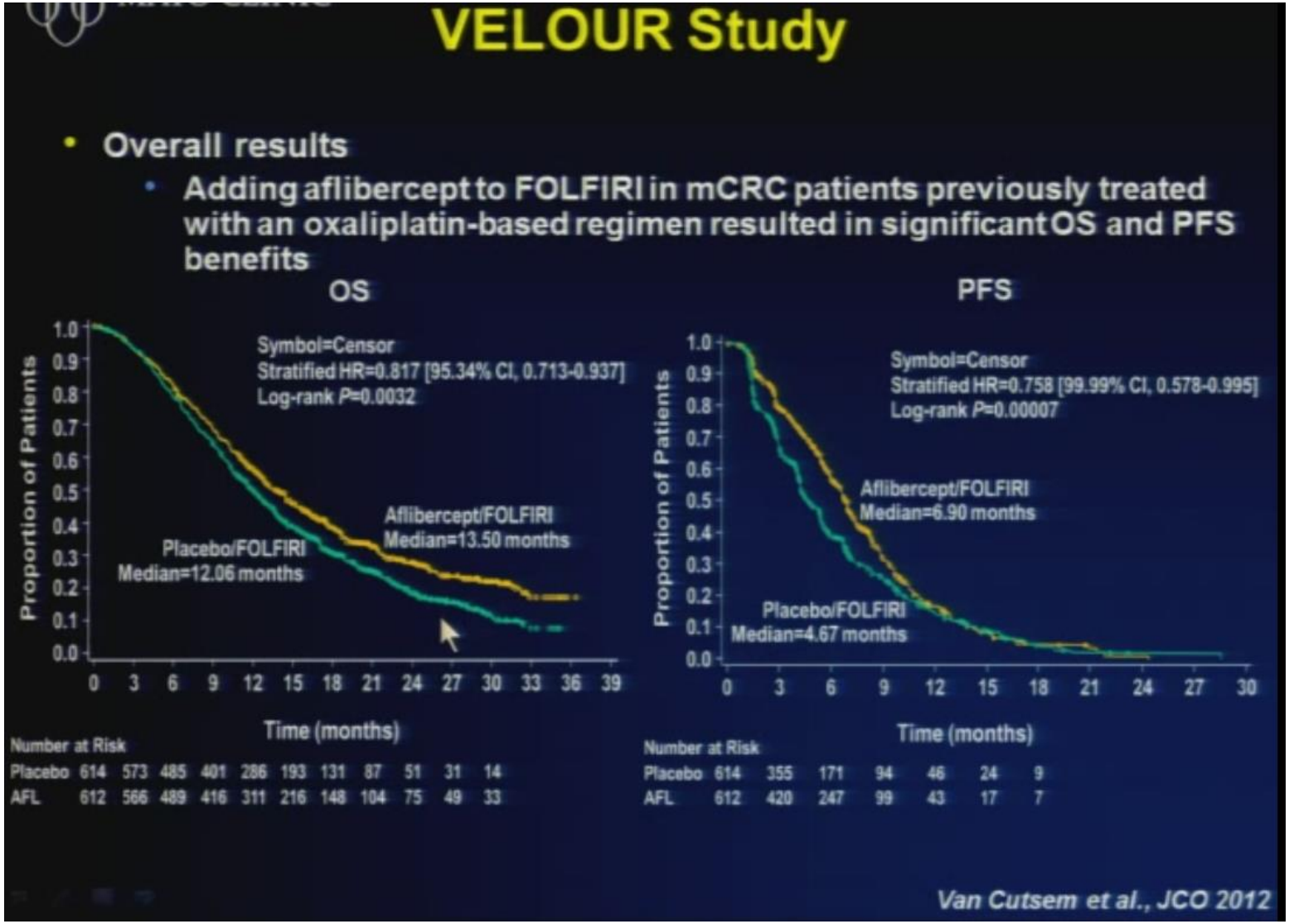
FINDINGS: Between Feb 1, 2006, and June 9, 2010, 409 (50%) patients were assigned to bevacizumab plus chemotherapy and 411 (50%) to chemotherapy alone. Median follow-up was 11·1 months (IQR 6·4-15·6) in the bevacizumab plus chemotherapy group and 9·6 months (5·4-13·9) in the chemotherapy alone group. Median overall survival was 11·2 months (95% CI 10·4-12·2) for bevacizumab plus chemotherapy and 9·8 months (8·9 -10·7) for chemotherapy alone (hazard ratio 0·81, 95% CI 0·69-0·94; unstratified log-rank test p=0·0062). Grade 3-5 bleeding or haemorrhage (eight [2%] vs one [<1%]), gastrointestinal perforation (seven [2%] vs three [<1%]), and venous thromboembolisms (19 [5%] vs 12 [3%]) were more common in the bevacizumab plus chemotherapy group than in the chemotherapy alone group. The most frequently reported grade 3-5 adverse events were neutropenia (65 [16%] in the bevacizumab and chemotherapy group vs 52 [13%] in the chemotherapy alone group), diarrhoea (40 [10%] vs 34 [8%], respectively), and asthenia (23 [6%] vs 17 [4%], respectively). Treatment-related deaths were reported for four patients in the bevacizumab plus chemotherapy group and three in the chemotherapy alone group.

INTERPRETATION: Maintenance of VEGF inhibition with bevacizumab plus standard second-line chemotherapy beyond disease progression has clinical benefits in patients with metastatic colorectal cancer. This approach is also being investigated in other tumour types, including metastatic breast and non-small cell lung cancers.

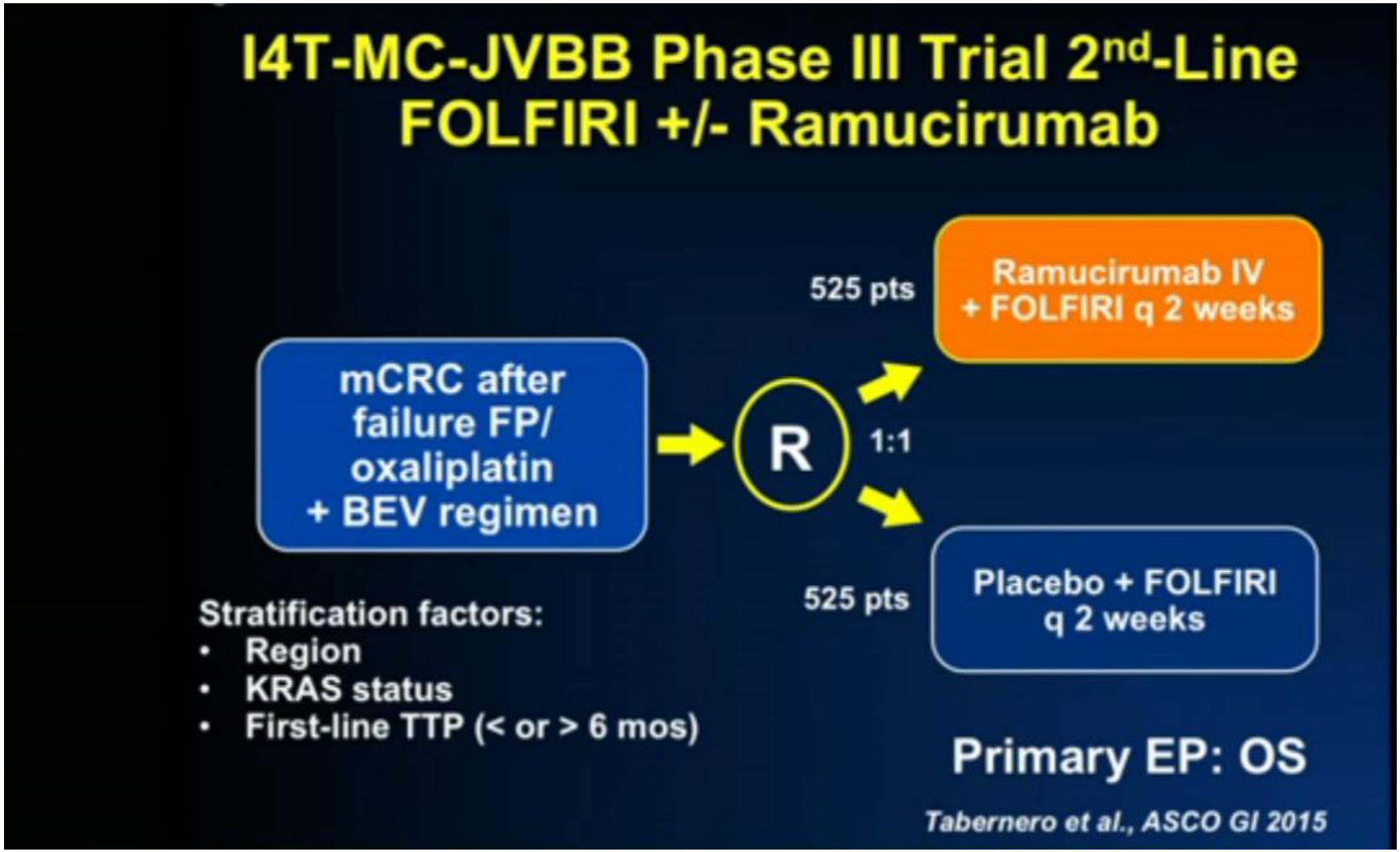
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



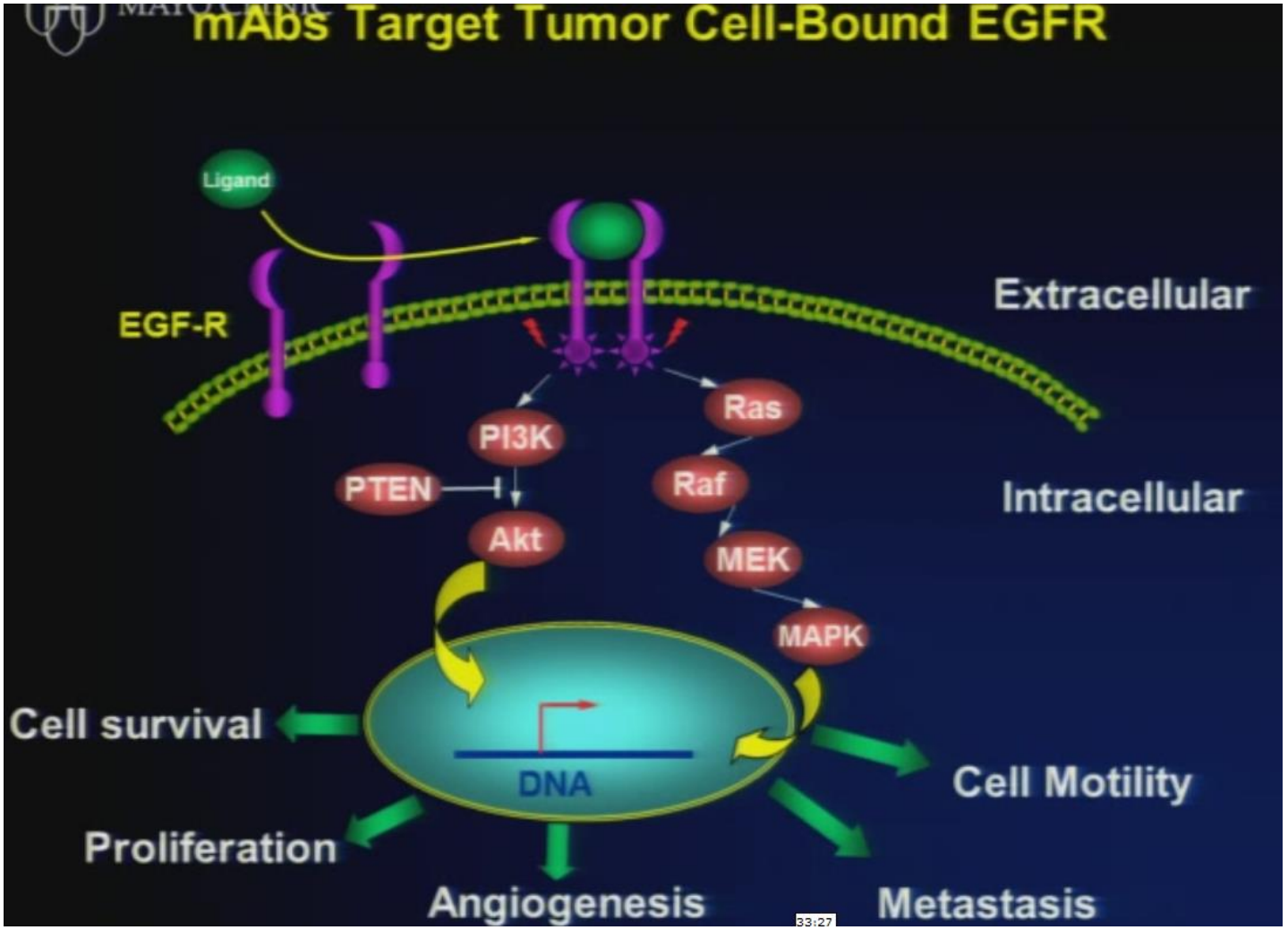
Metastatik Kolon Kanserinde Tedavi Seçenekleri

Comparison of Phase III Trials

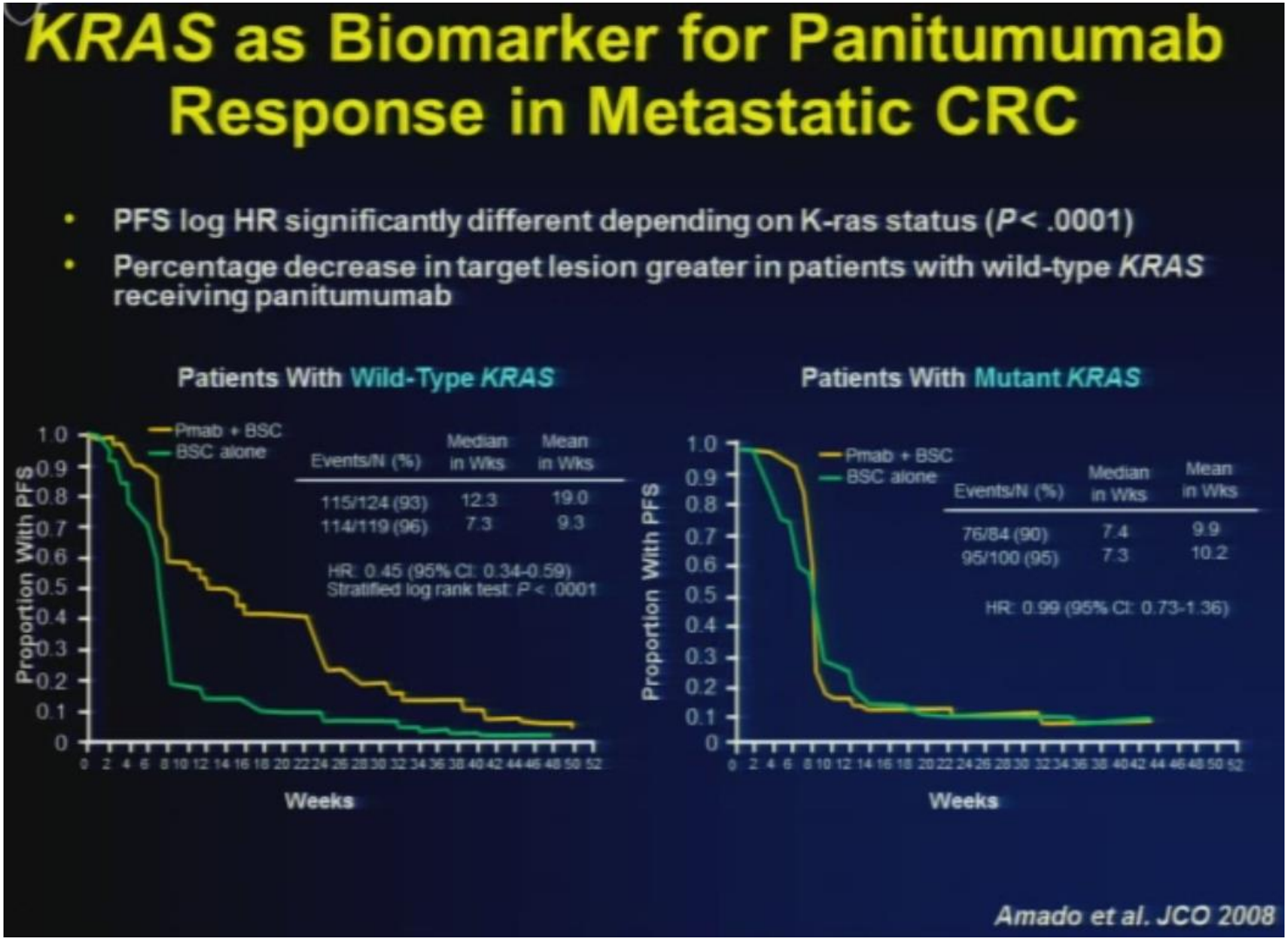
Agent	Bevacizumab		Aflibercept		Ramucirumab	
Study	TML		VELOUR		RAISE	
1st-Line Tx	Chemo+BEV		FP-Oxali+/- BEV		FP-Oxali+BEV	
	Ctx-BEV	**Ctx**	**FOLFIRI + AFL**	**FOLFIRI + PL**	**FOLFIRI + RAM**	**FOLFIRI + PL**
N pts	409	410	612	614	536	536
mOS (mos)	11.2	9.8	13.5	12.1	13.3	11.7
	HR 0.81 p=0.0062		HR 0.82 p=0.0032		HR 0.84 p=0.022	
mPFS (mos)	5.7	4.1	6.9	4.7	5.7	4.5
	HR 0.68 p<0.0001		HR 0.76 p=0.00007		HR 0.79 p=0.0005	
RR (%)	5.4	3.9	19.8	11.1	13.4	12.5

Bennouna et al., Lancet Oncol 2012
van Cutsem et al., JCO 2012
Tabernero et al., ASCO GI 2015;Abstract 512

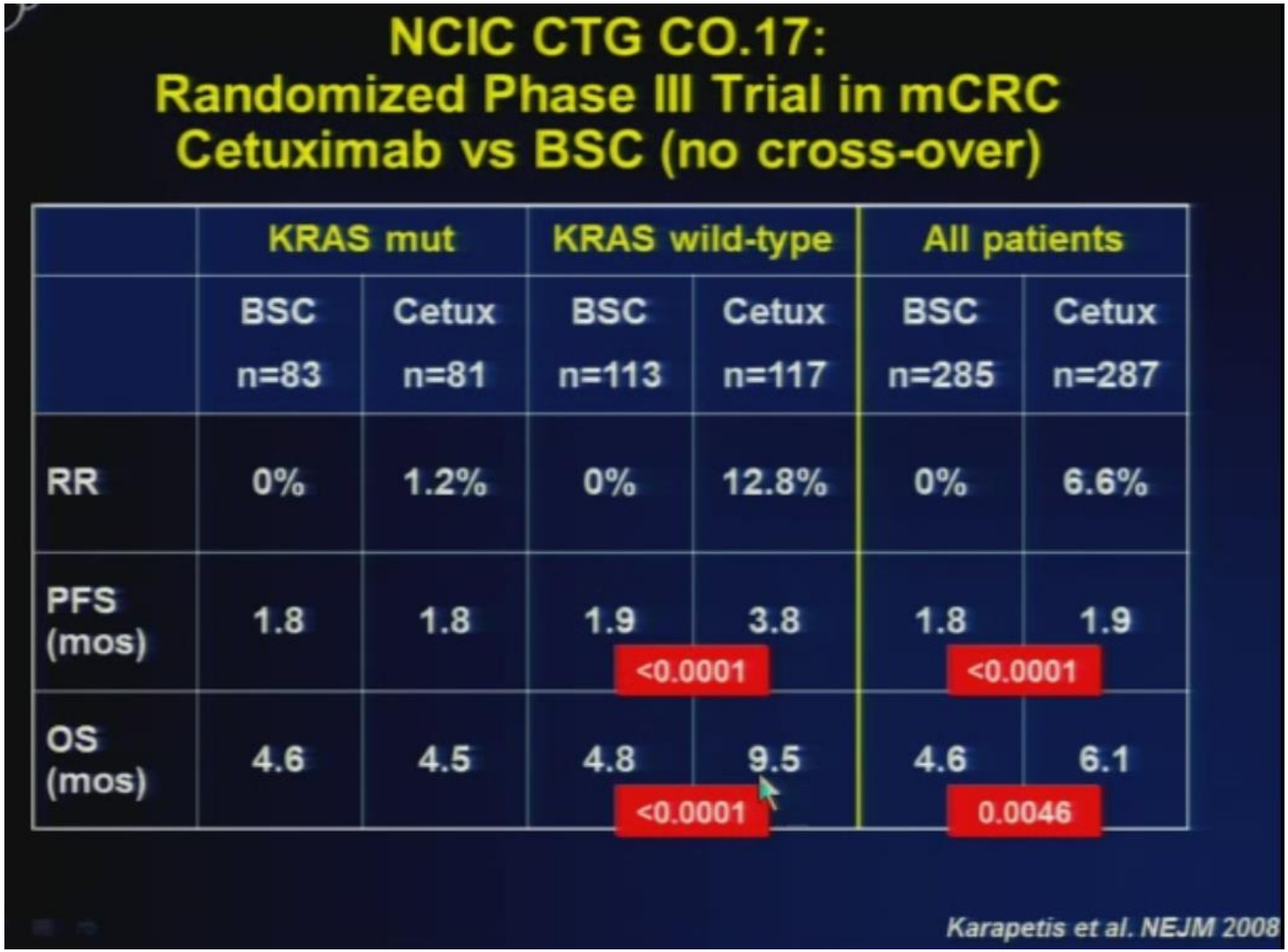
Metastatik Kolon Kanserinde Tedavi Seçenekleri



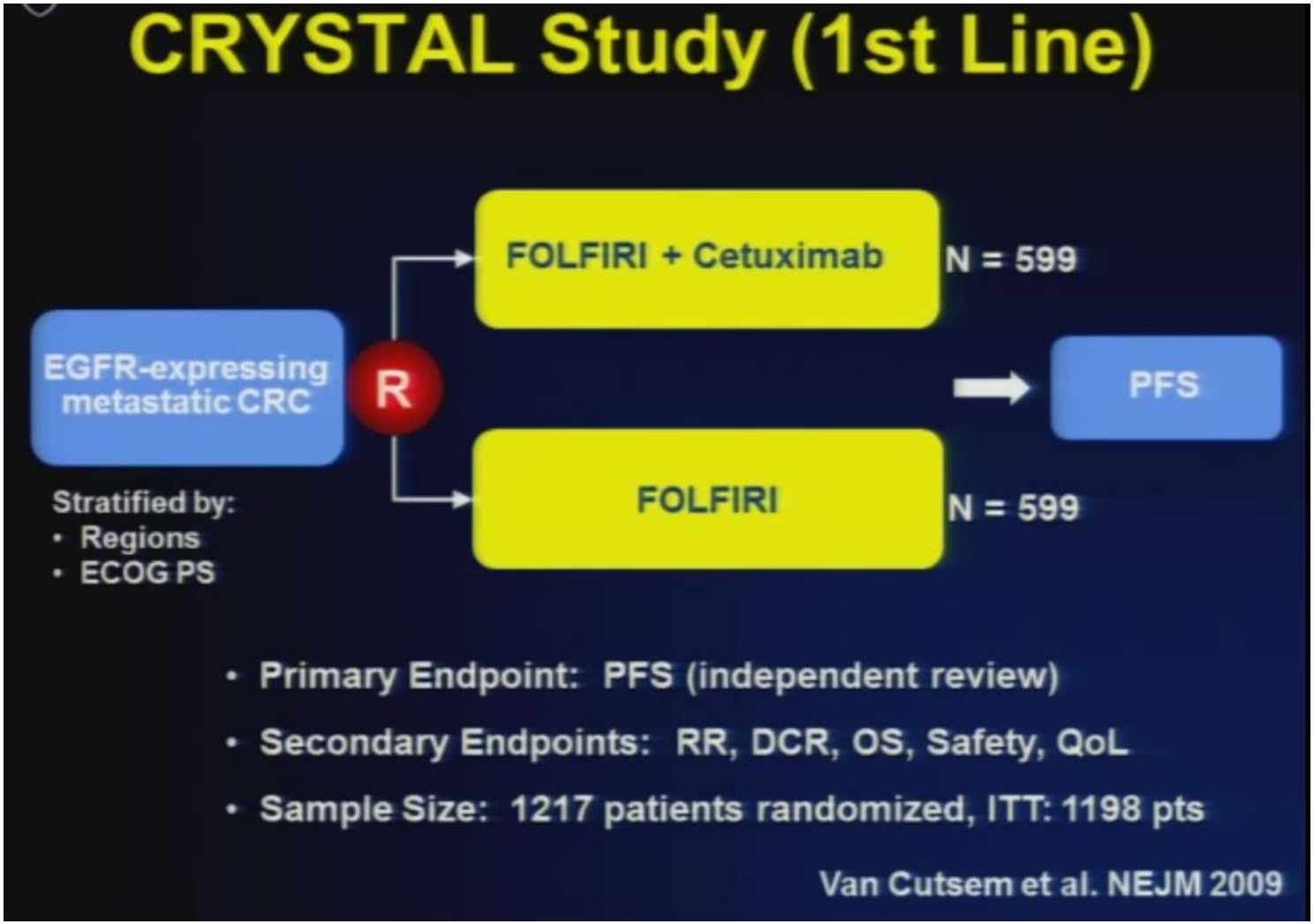
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

CRYSTAL ÇALIŞMASI

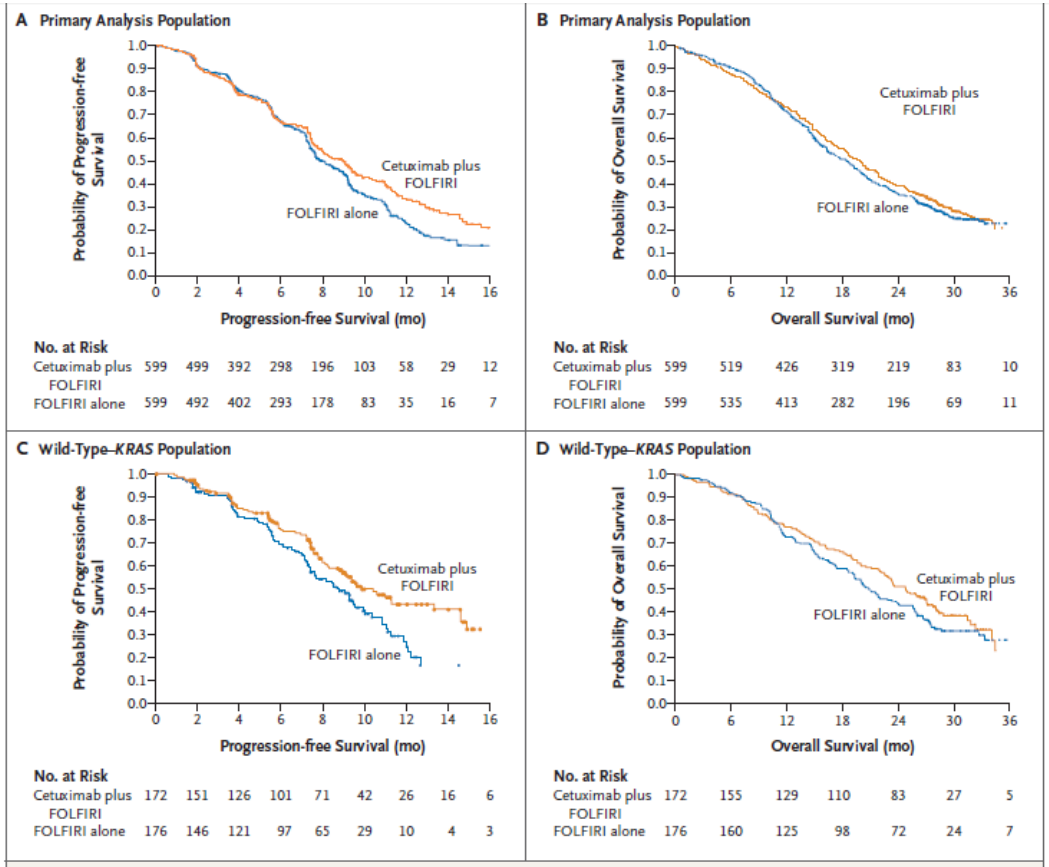
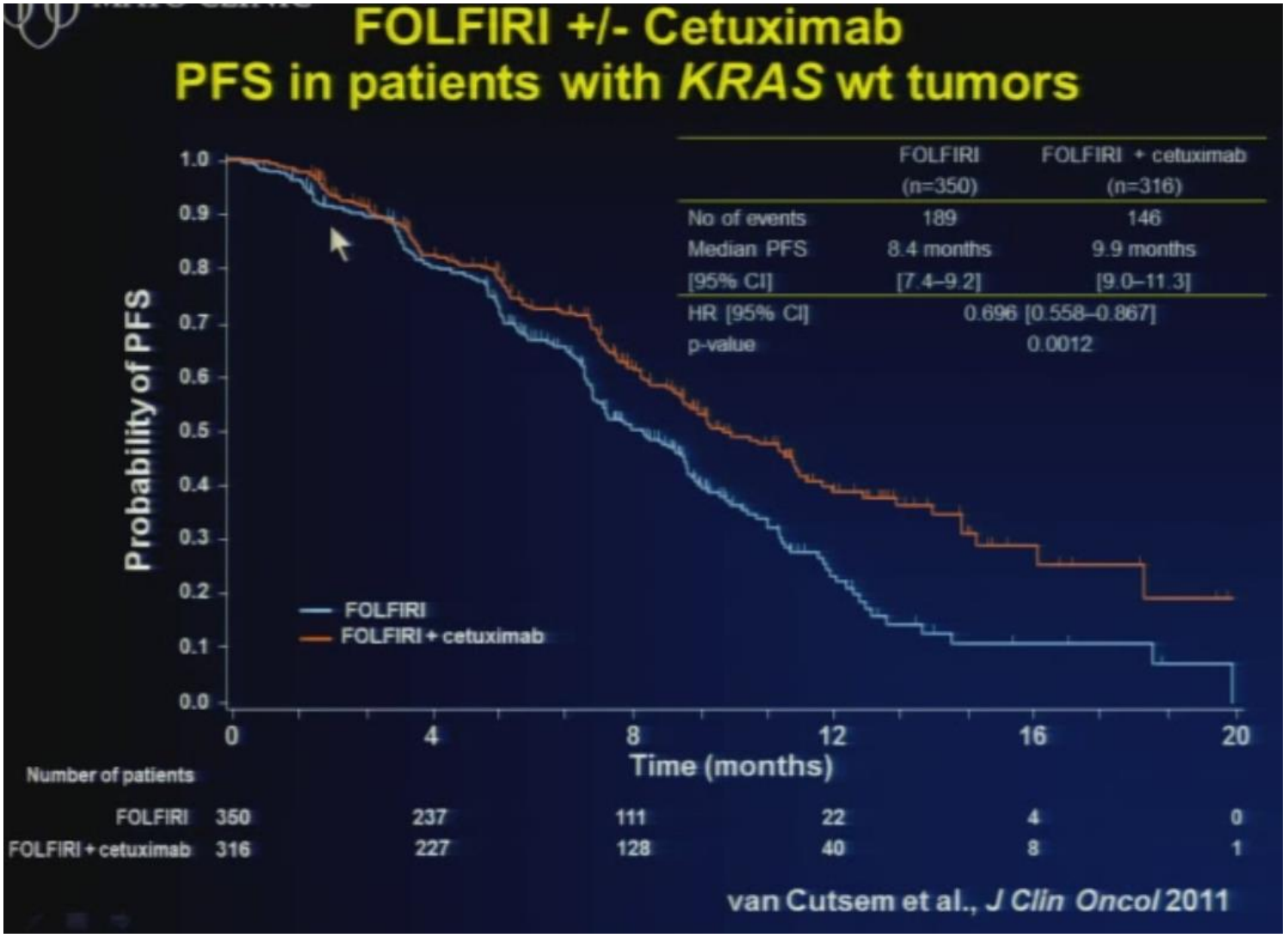


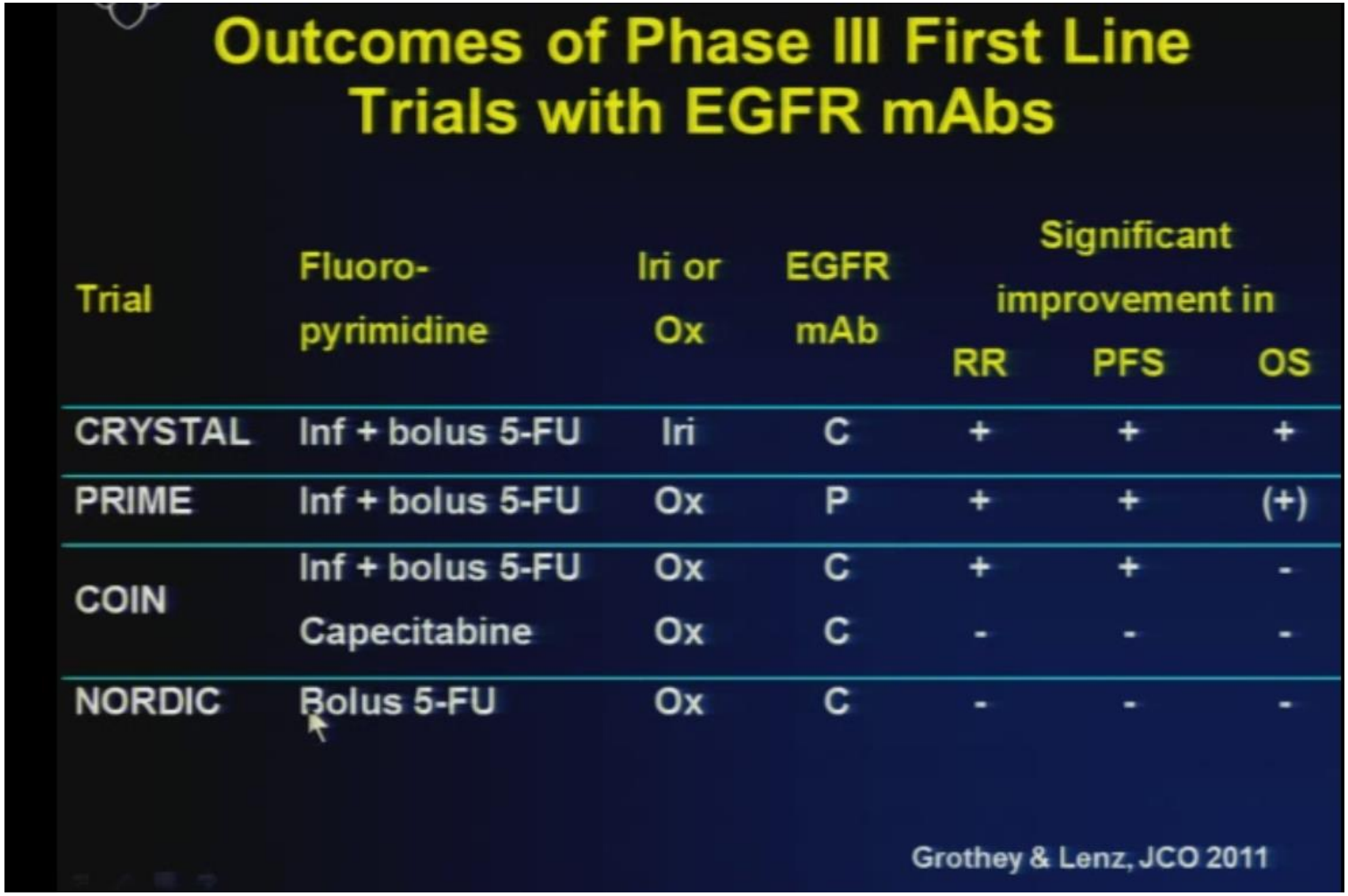
Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival in the Primary Analysis Population and the Wild-Type–*KRAS* Population, According to Treatment Group.

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



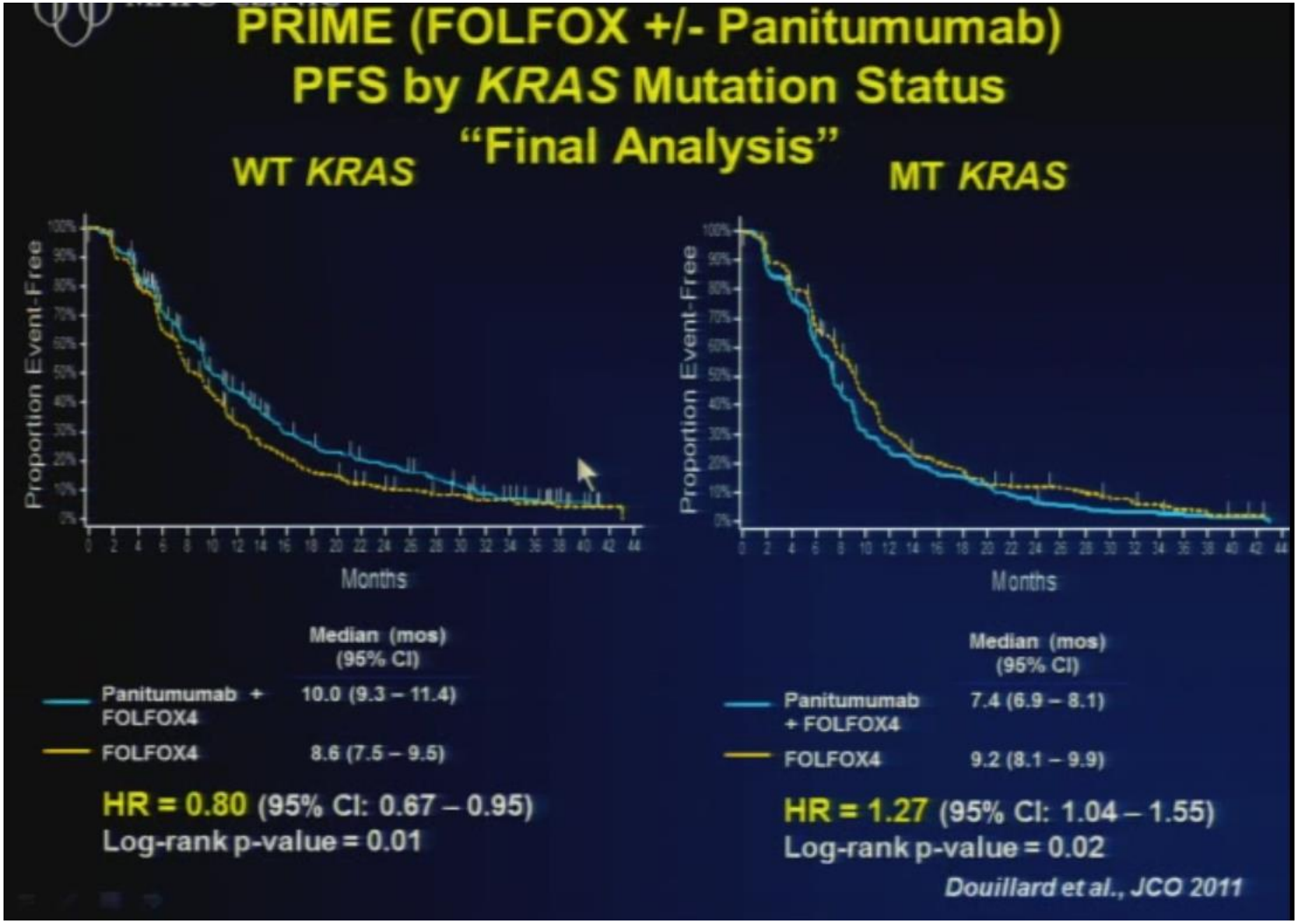
Trial	Fluoro-pyrimidine	Iri or Ox	EGFR mAb	Significant improvement in RR	PFS	OS
CRYSTAL	Inf + bolus 5-FU	Iri	C	+	+	+
PRIME	Inf + bolus 5-FU	Ox	P	+	+	(+)
COIN	Inf + bolus 5-FU	Ox	C	+	+	-
	Capecitabine	Ox	C	-	-	-
NORDIC	Bolus 5-FU	Ox	C	-	-	-

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[8]	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	

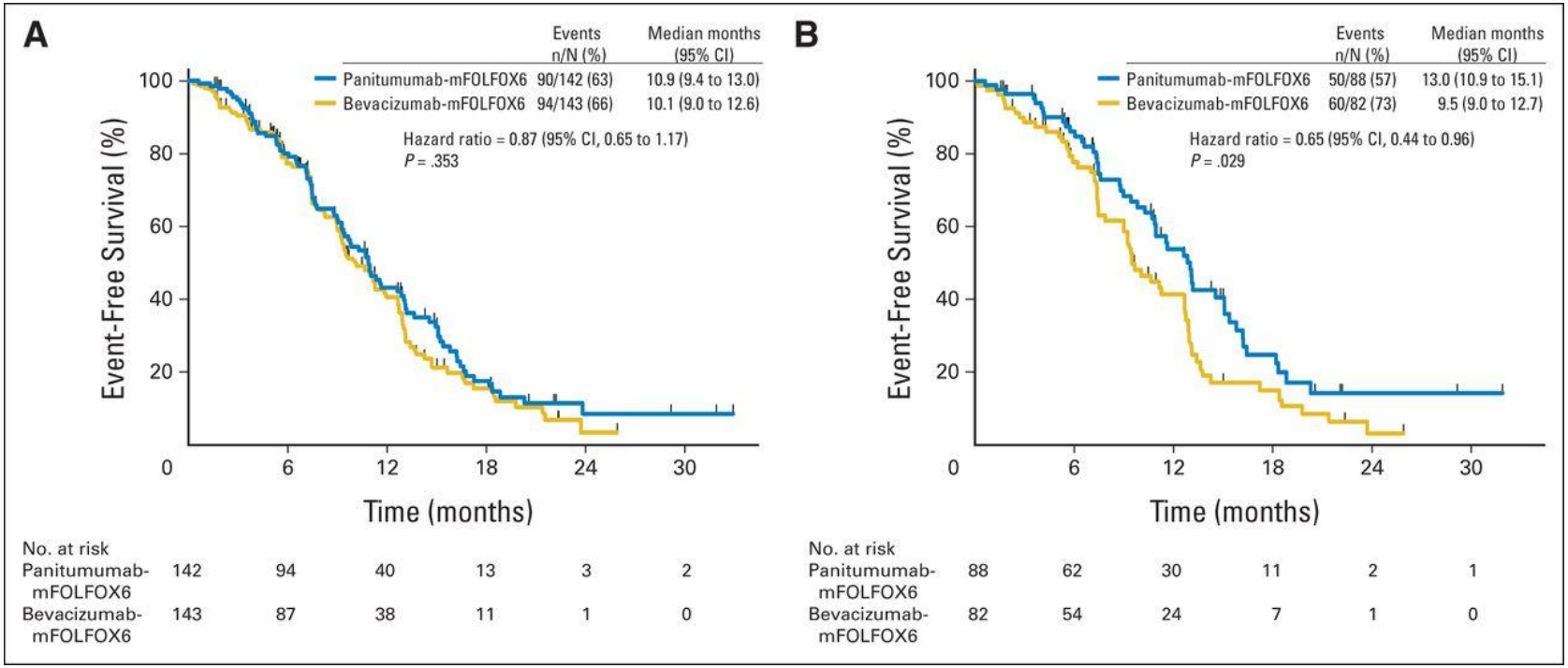
[1]95%CI. PFS: Progression-free survival; OS: Overall survival; All: All patients group; WT: Wild type; MT: Mutant type; NA: Not available; KRAS: KRAS exon 2, codons 12 and 13; FOLFIRI: Irinotecan, fluorouracil, and leucovorin; FOLFOX: Fluorouracil, leucovorin, and oxaliplatin; XELOX: Capecitabine and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

Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

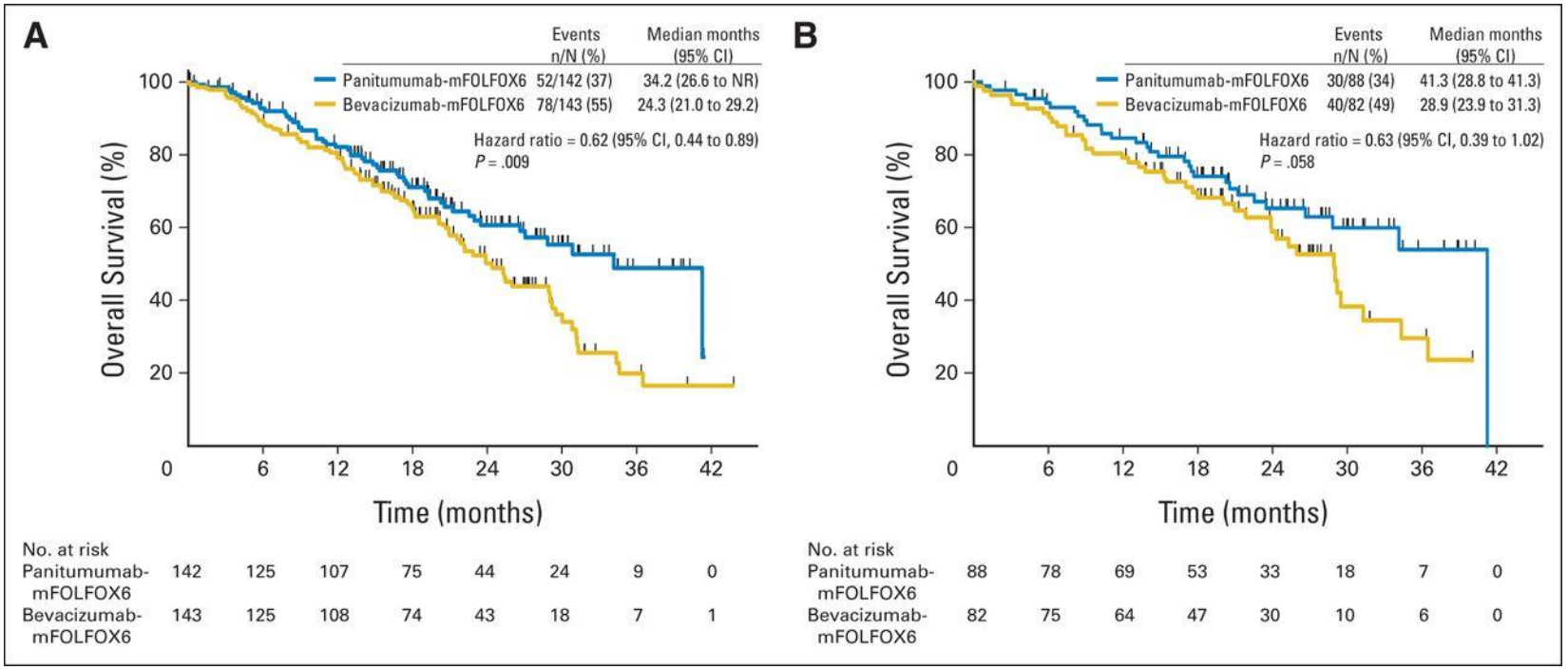
Progression-free survival in (A) wild-type (WT) KRAS exon 2 intent-to-treat group and (B) extended WT RAS subgroup.



Lee S. Schwartzberg et al. JCO 2014;32:2240-2247

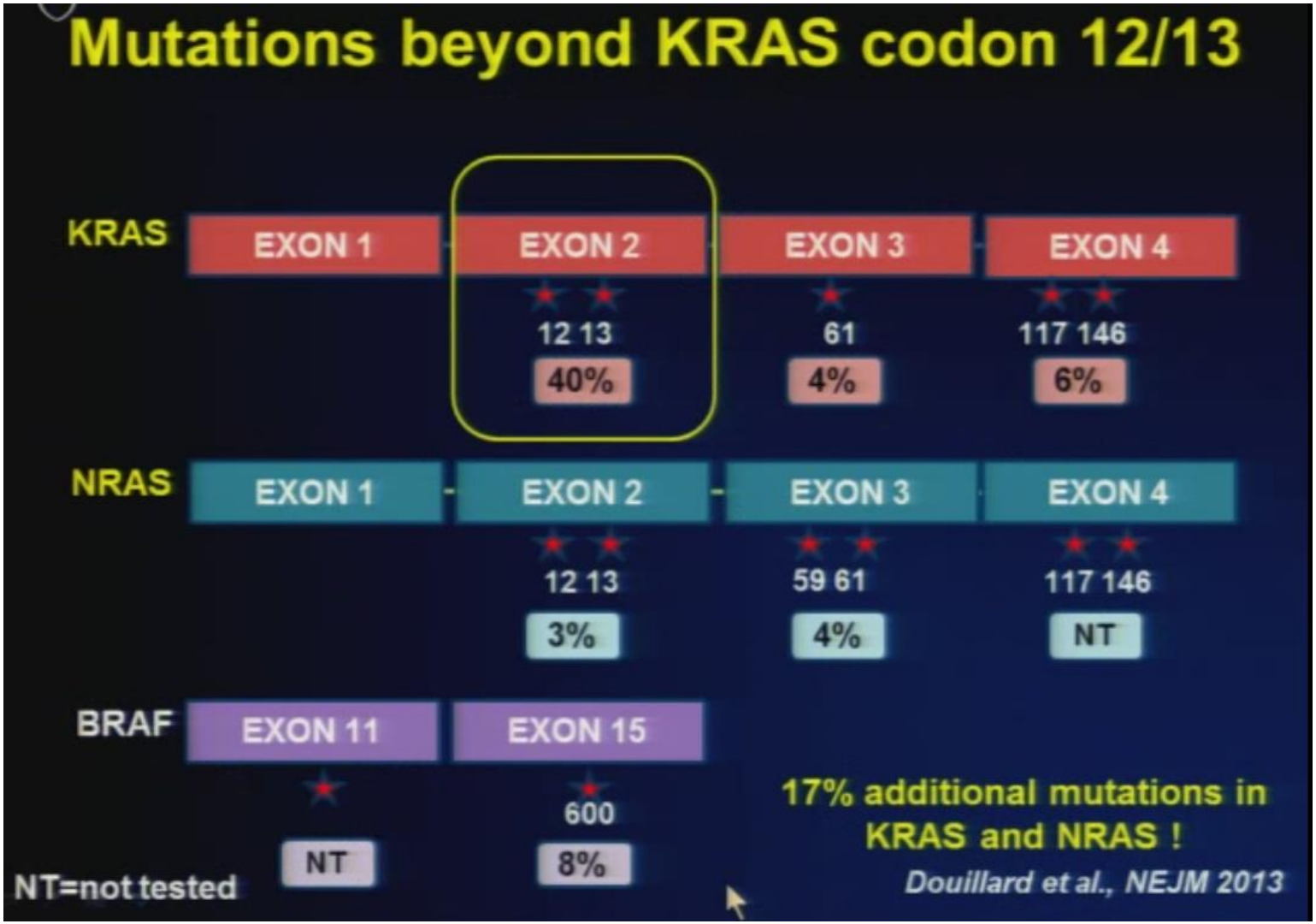
Metastatik Kolon Kanserinde Tedavi Seçenekleri

Overall survival in (A) wild-type (WT) KRAS exon 2 intent-to-treat group and (B) extended WT RAS subgroup.

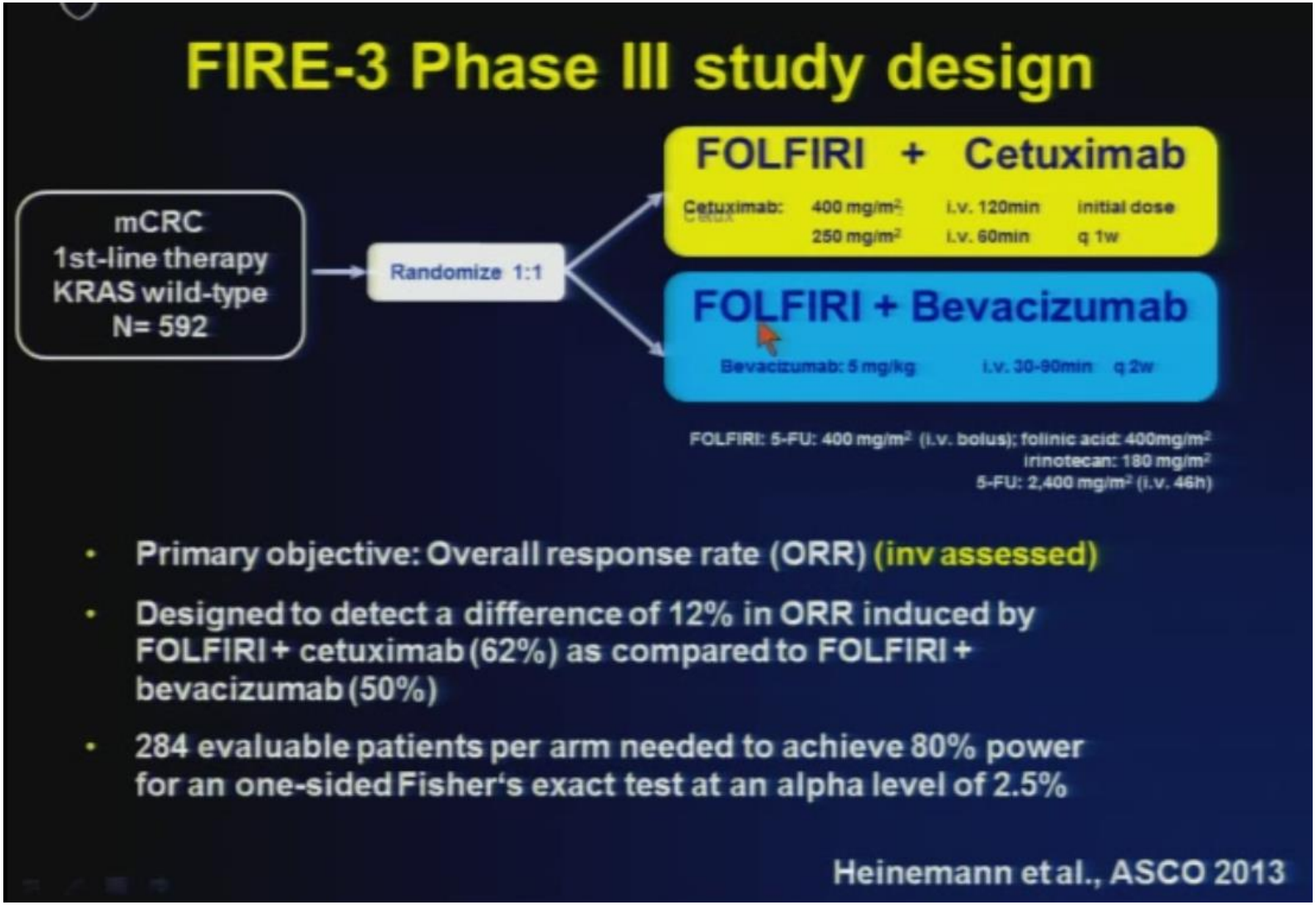


Lee S. Schwartzberg et al. JCO 2014;32:2240-2247

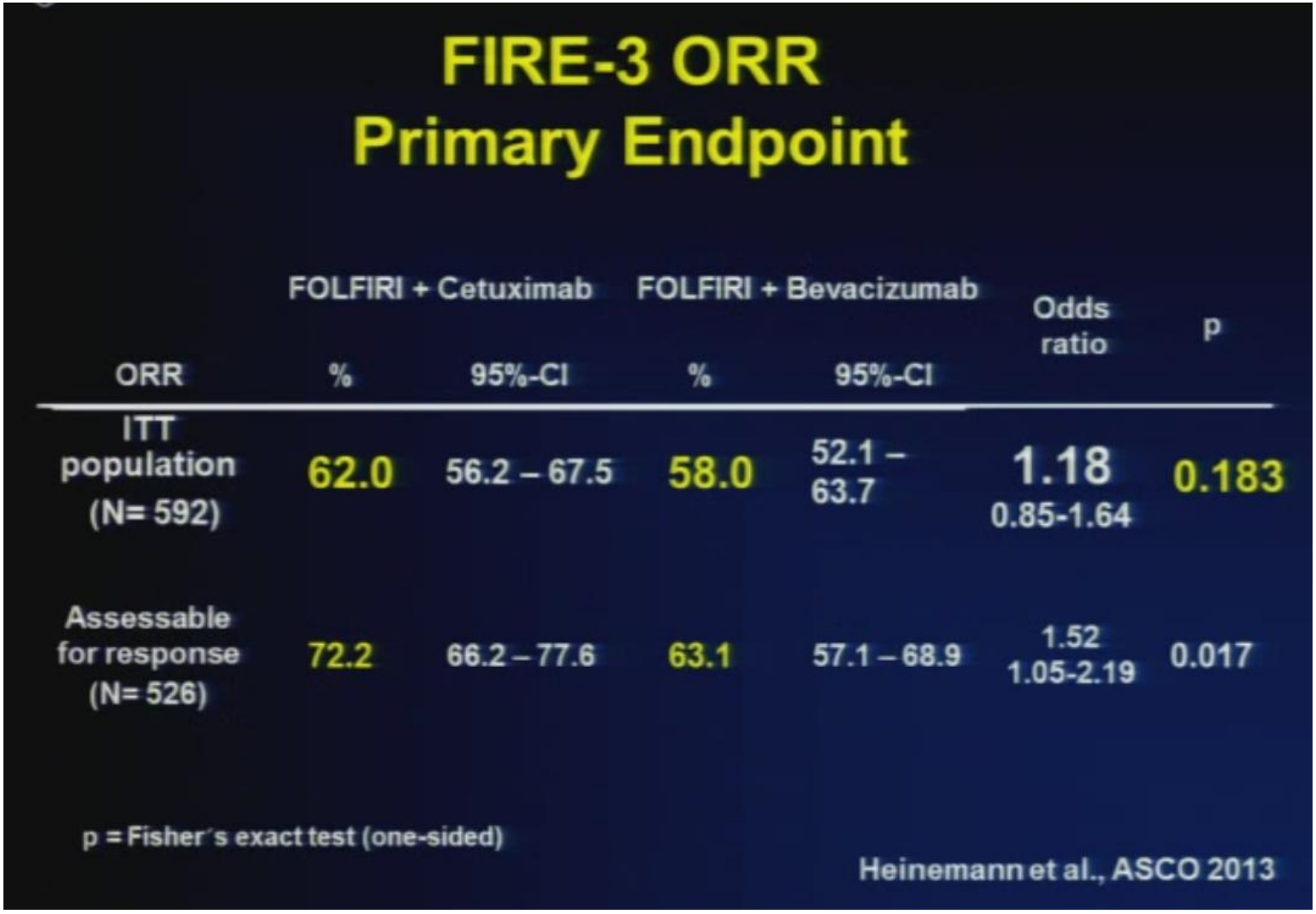
Metastatik Kolon Kanserinde Tedavi Seçenekleri



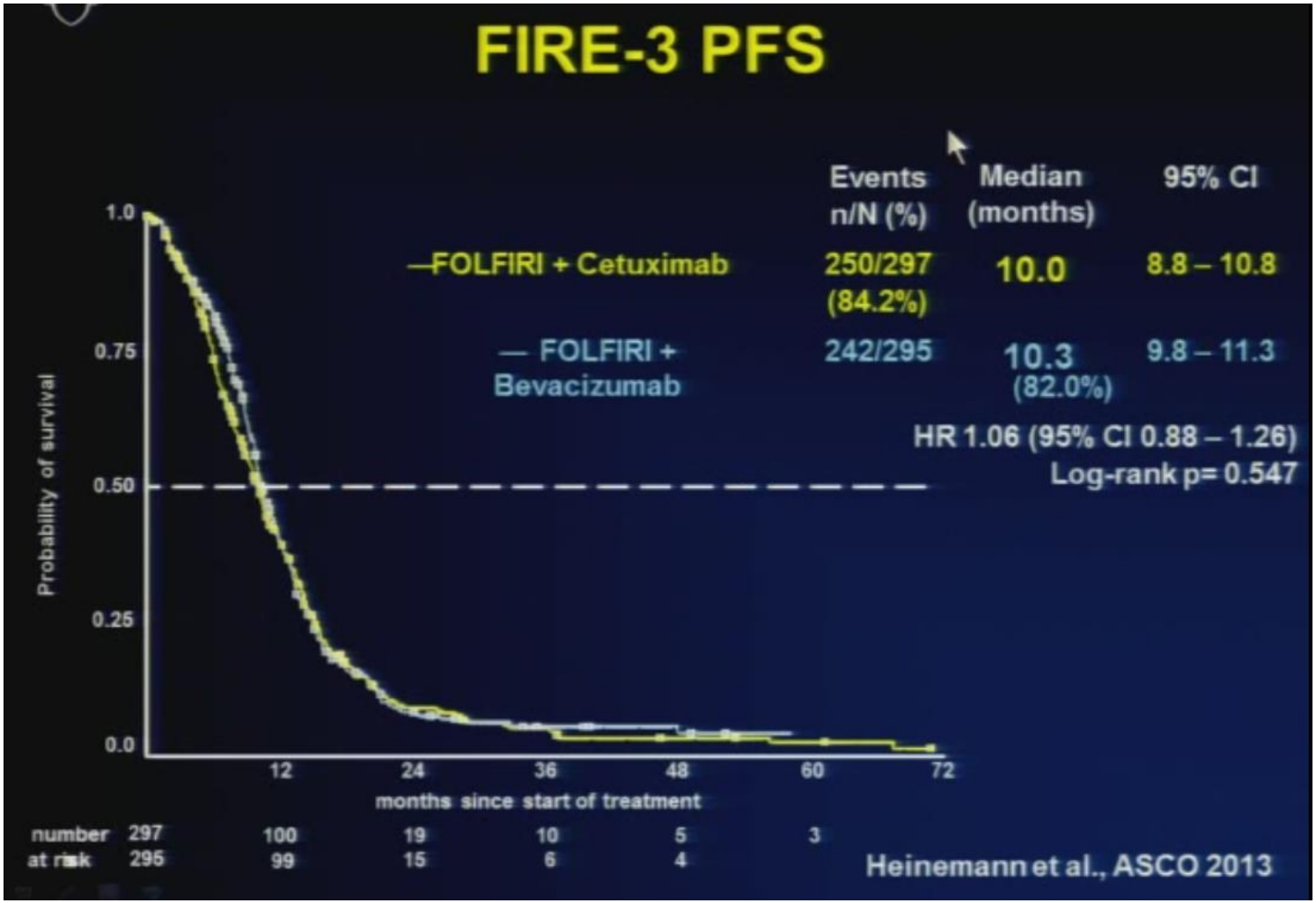
Metastatik Kolon Kanserinde Tedavi Seçenekleri



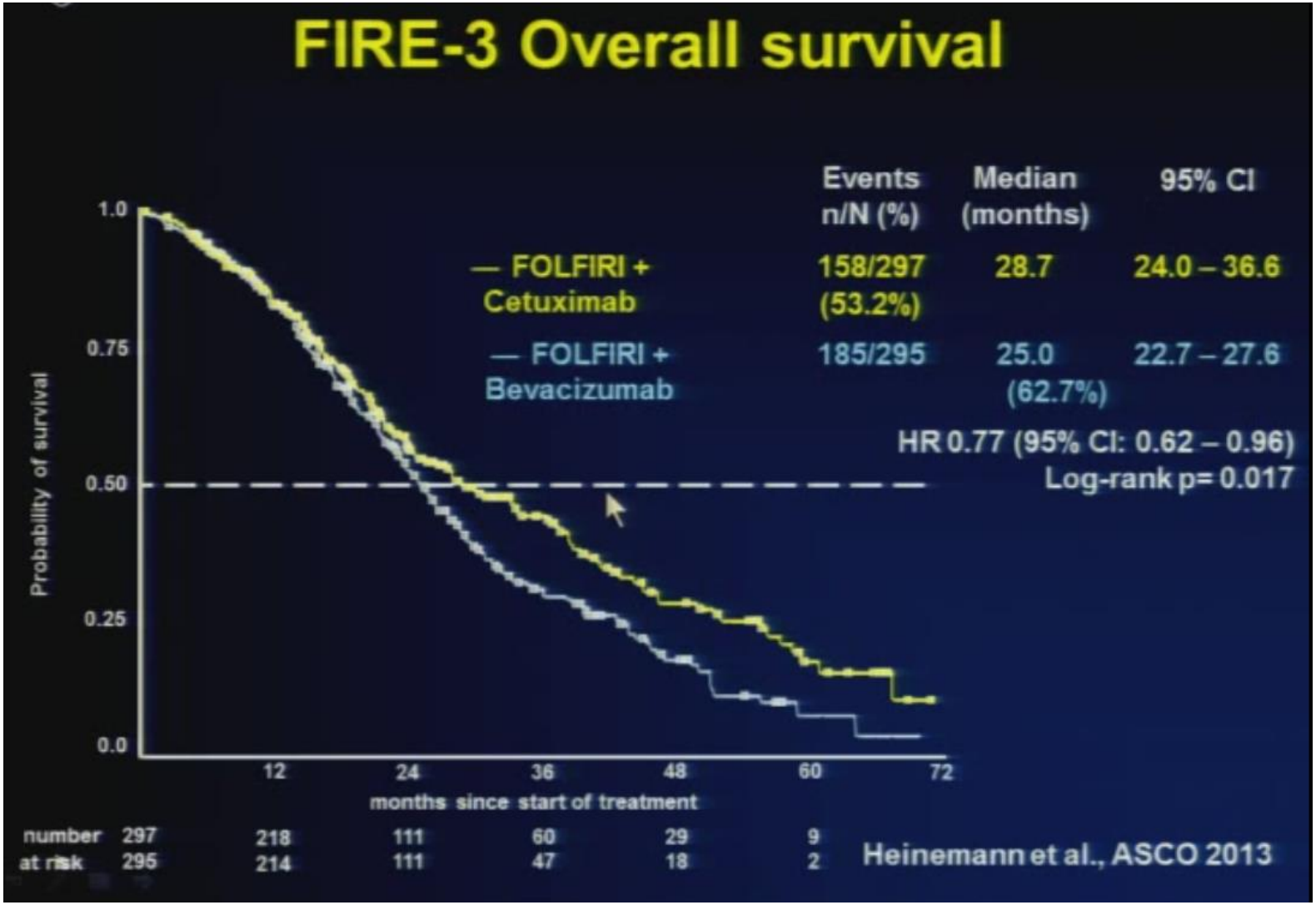
Metastatik Kolon Kanserinde Tedavi Seçenekleri



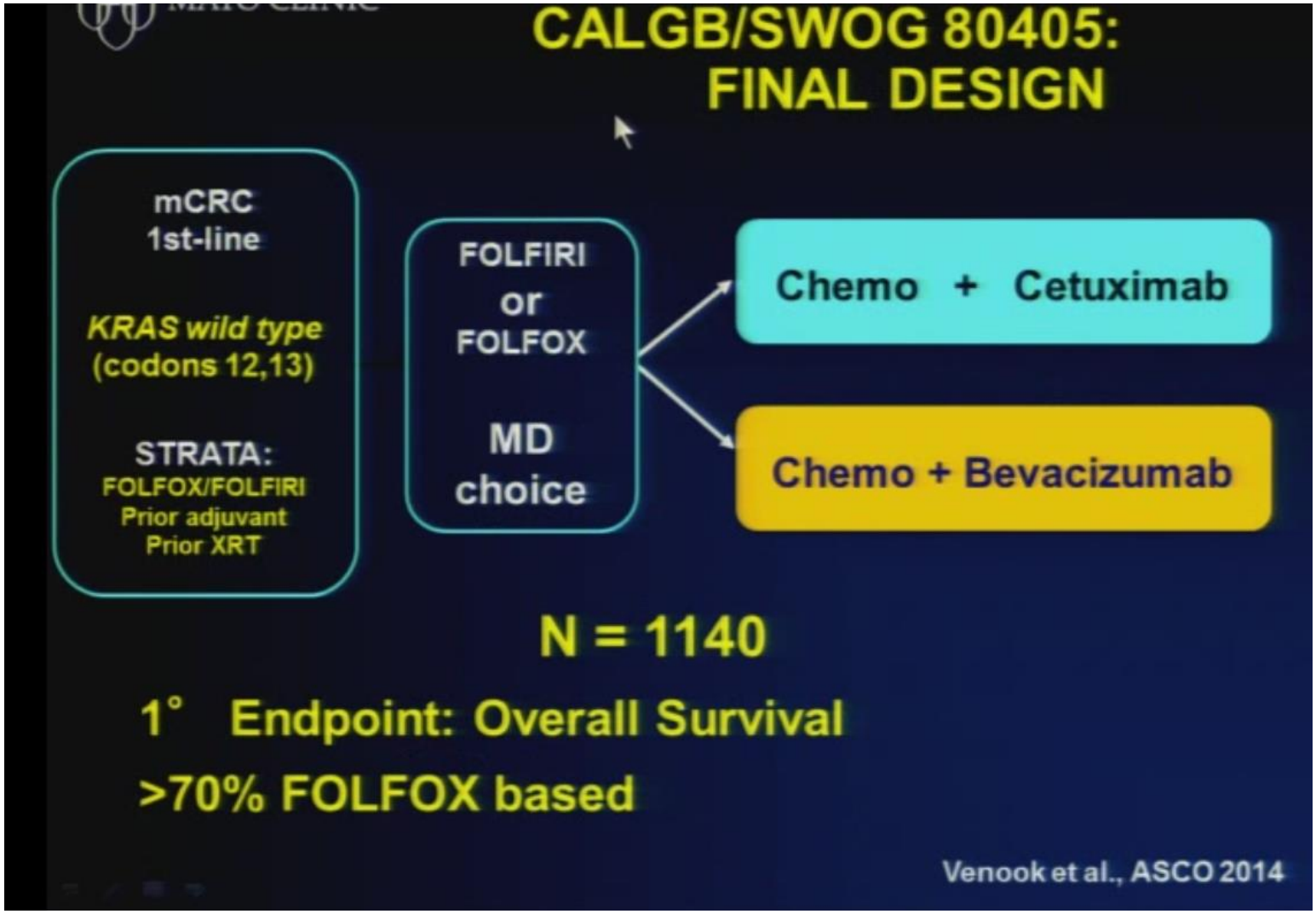
Metastatik Kolon Kanserinde Tedavi Seçenekleri



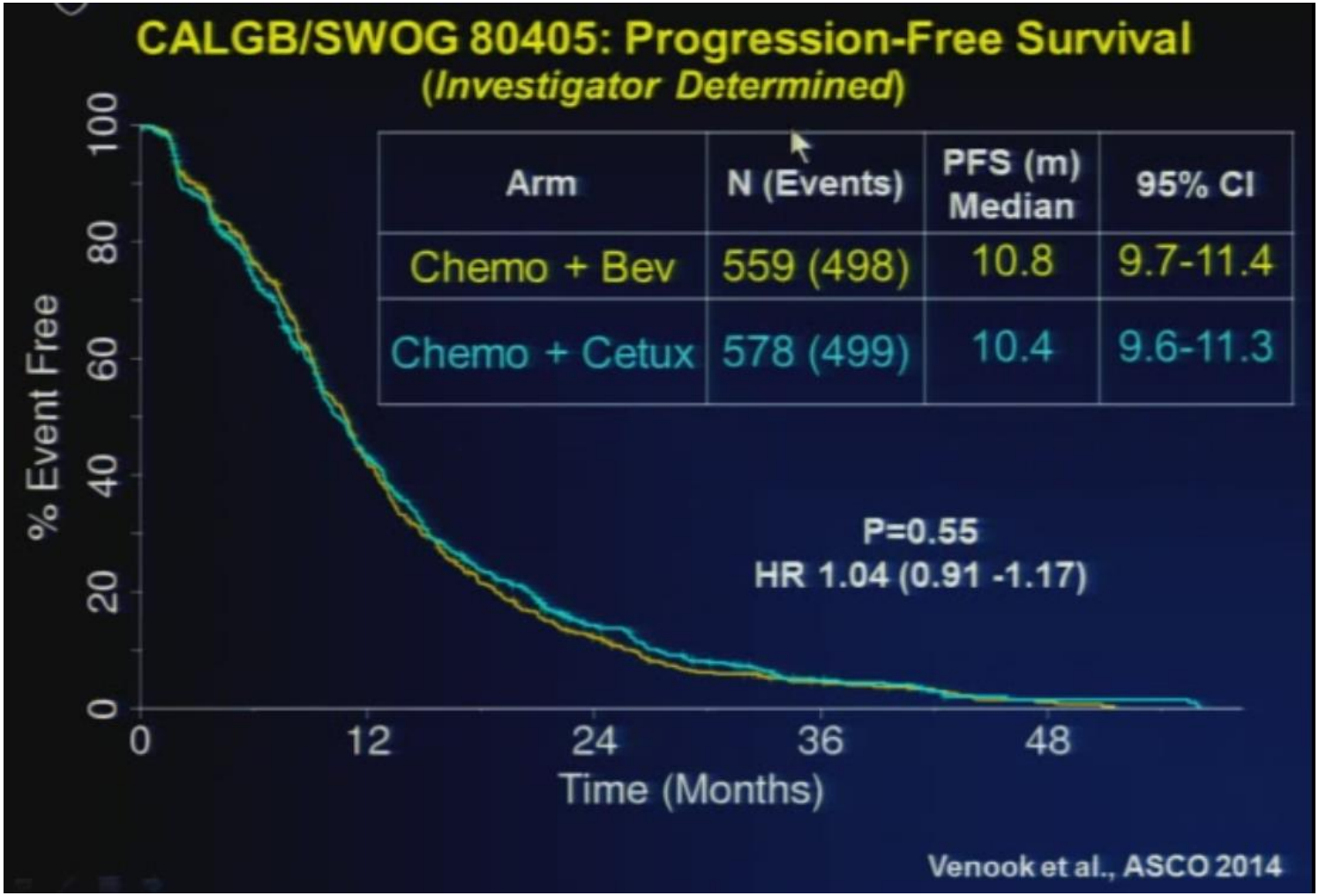
Metastatik Kolon Kanserinde Tedavi Seçenekleri



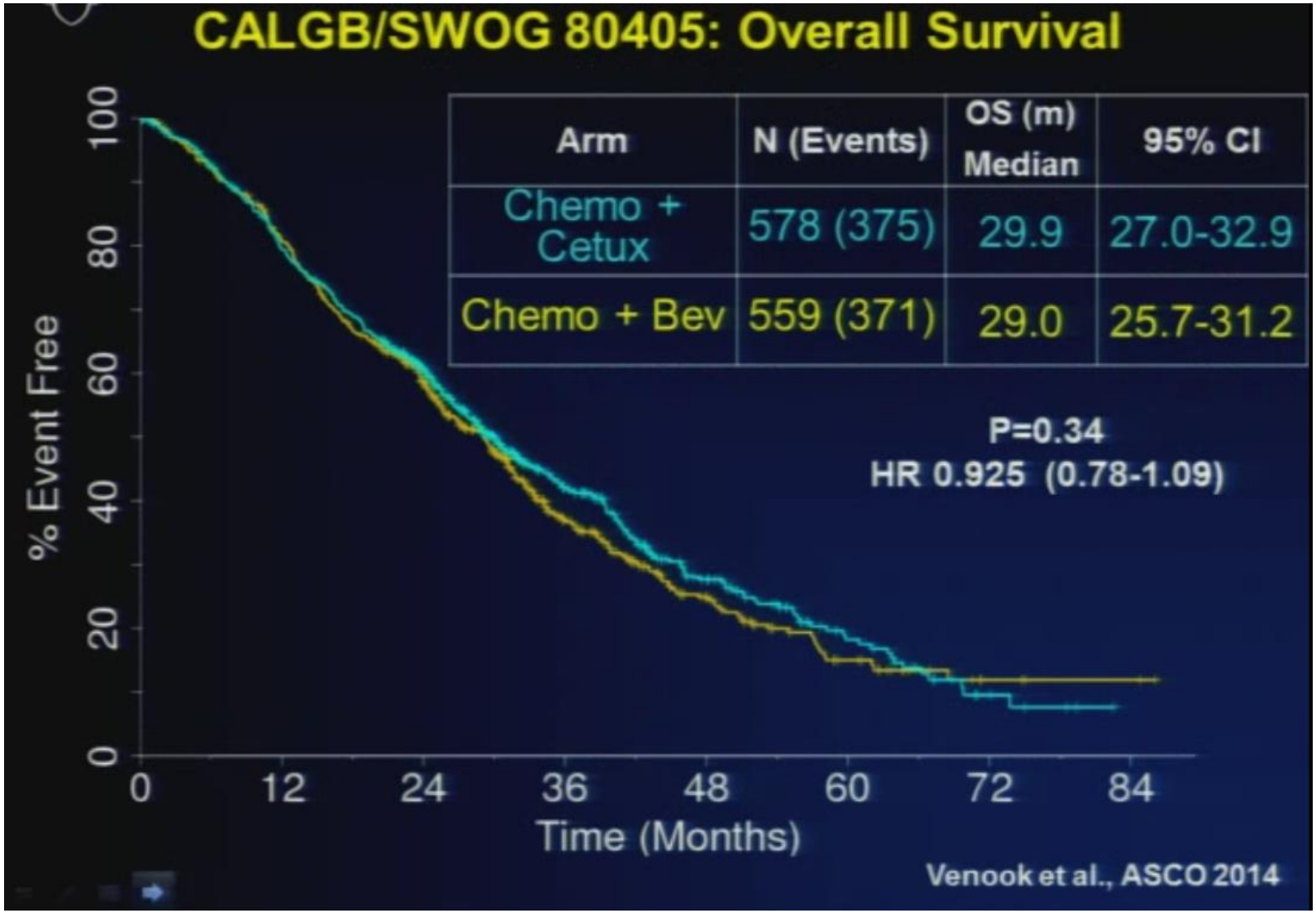
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



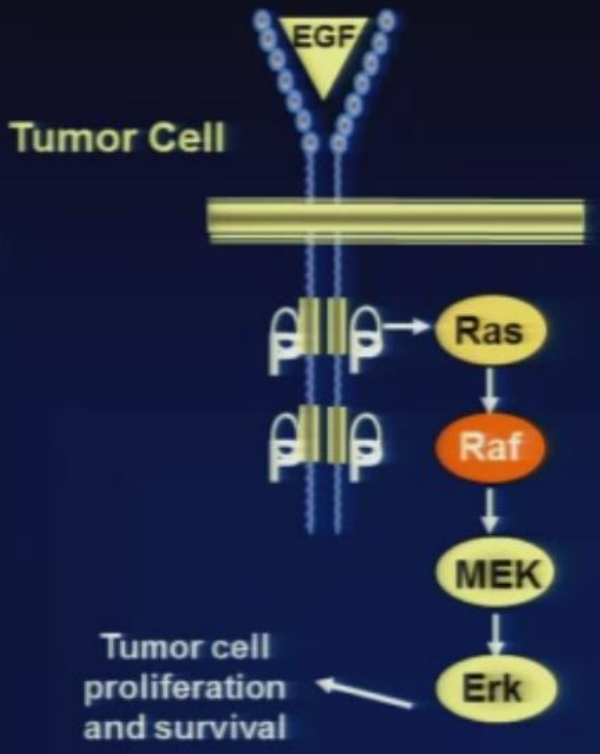
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

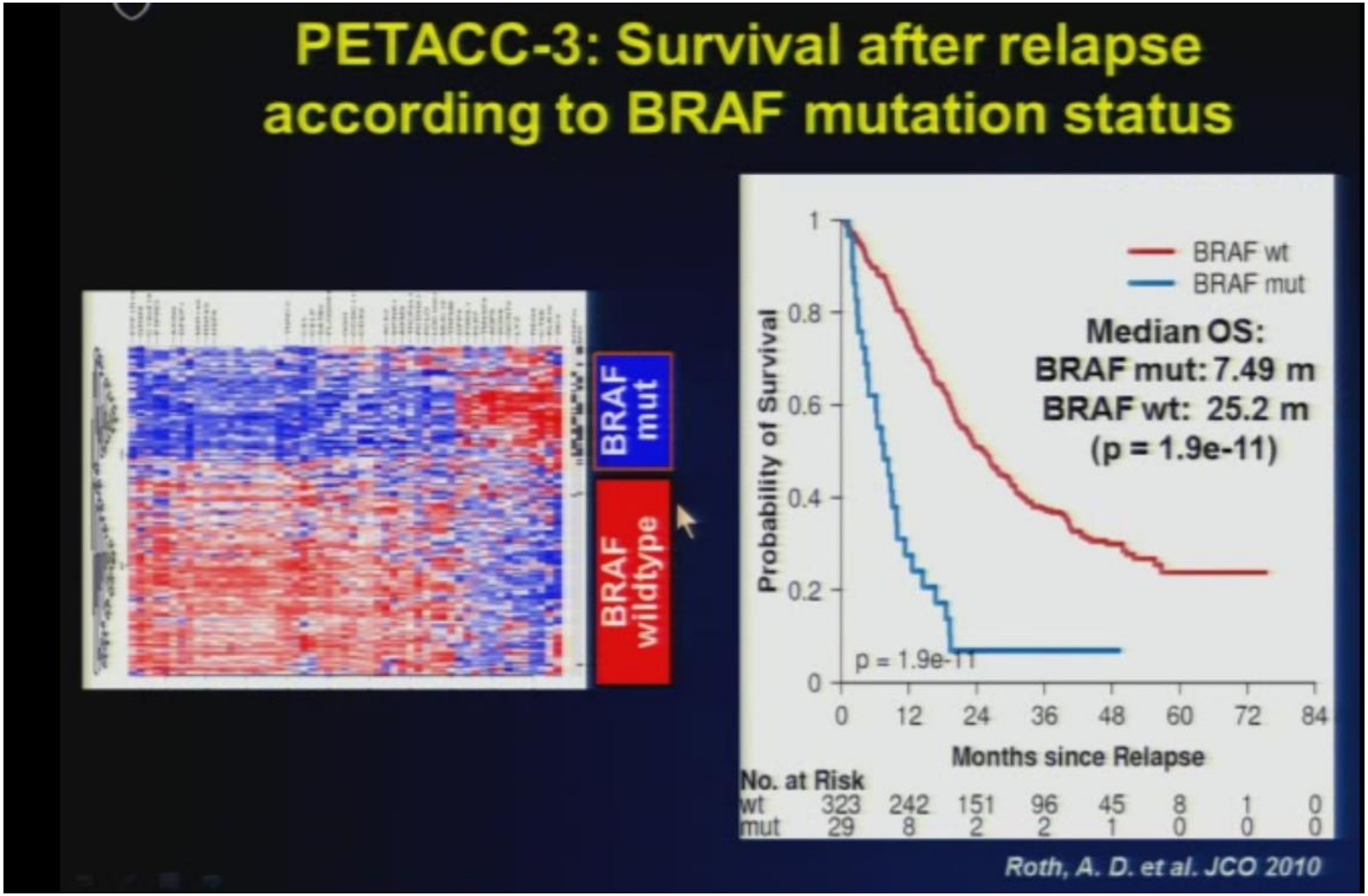
BRAF Mutations in CRC

- 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

GONO ÇALIŞMASI

JOURNAL OF CLINICAL ONCOLOGY JOURNAL OF CLINICAL ONCOLOGY CAL 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

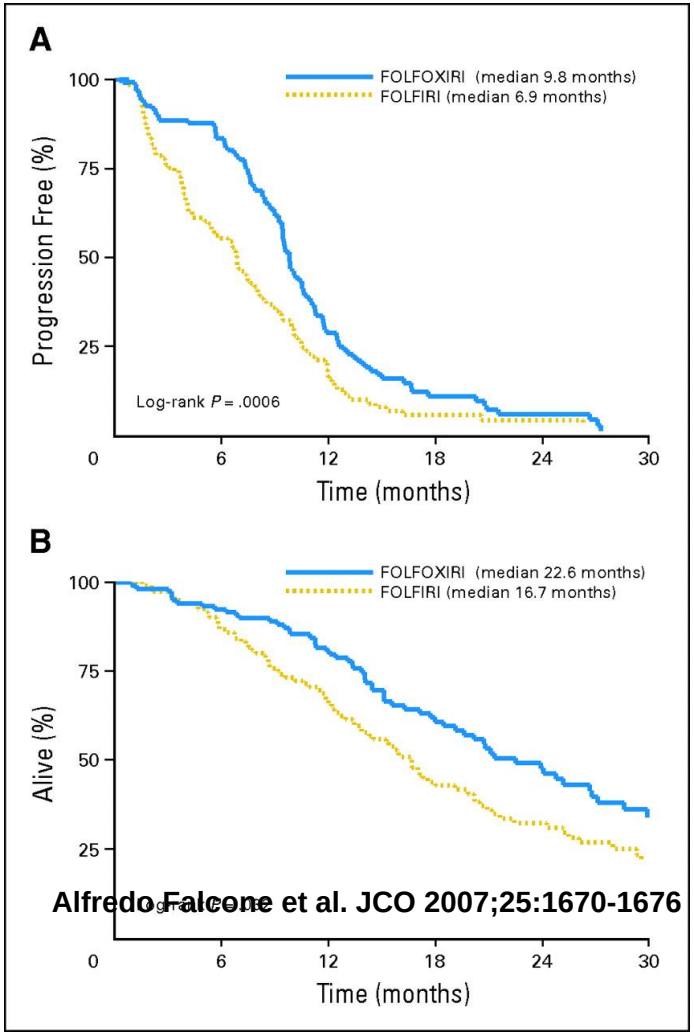
Response	%	
	FOLFIRI (n = 122)	FOLFOXIRI (n = 122)
Investigators assessment		
Complete	6	8
Partial	35	58
Complete + partial	41*	66*
95% CI	0.32 to 0.50	0.56 to 0.74
Stable disease	33	21
Progression	24†	11†
Not assessable	2	2
Externally reviewed		
Complete	6	7
Partial	28	53
Complete + partial	34‡	60‡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

TRIBE ÇALIŞMASI

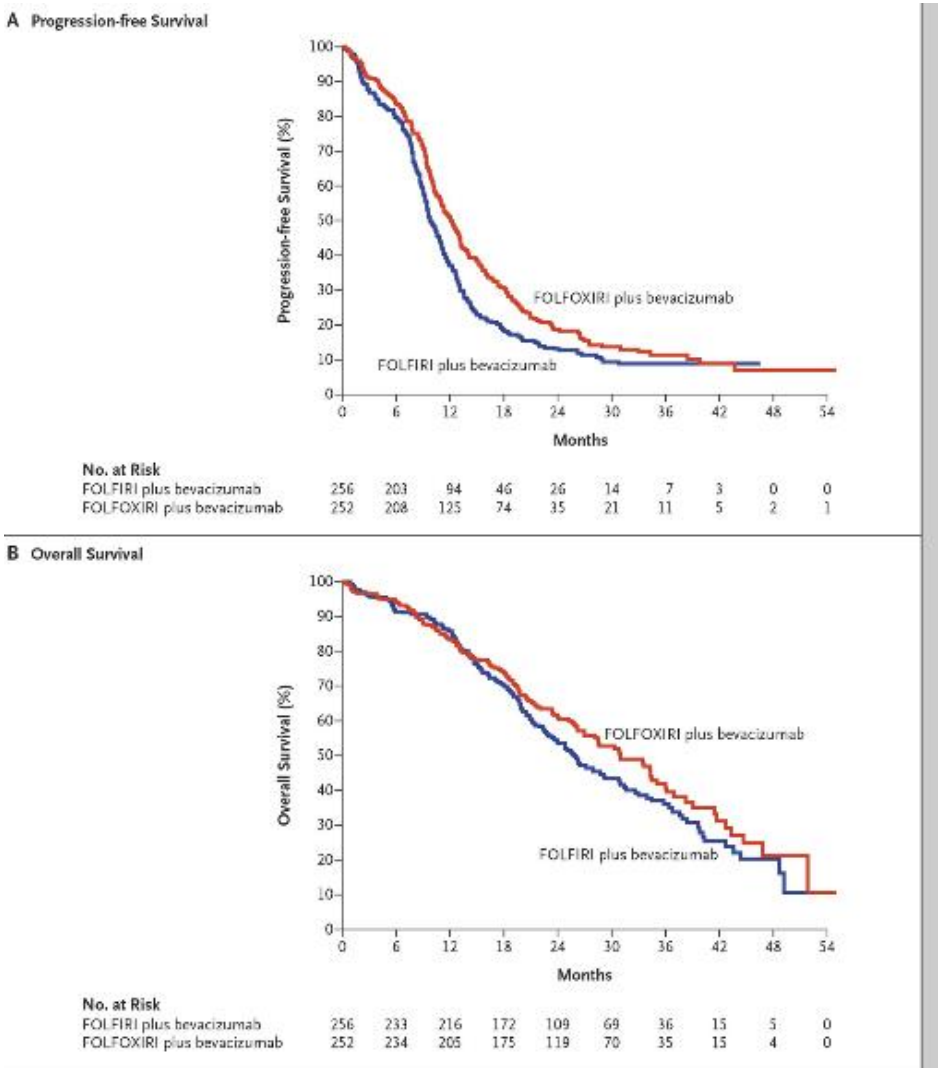


Figure 2. Kaplan–Meier Estimates of Progression-free and Overall Survival, According to Treatment Group.

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

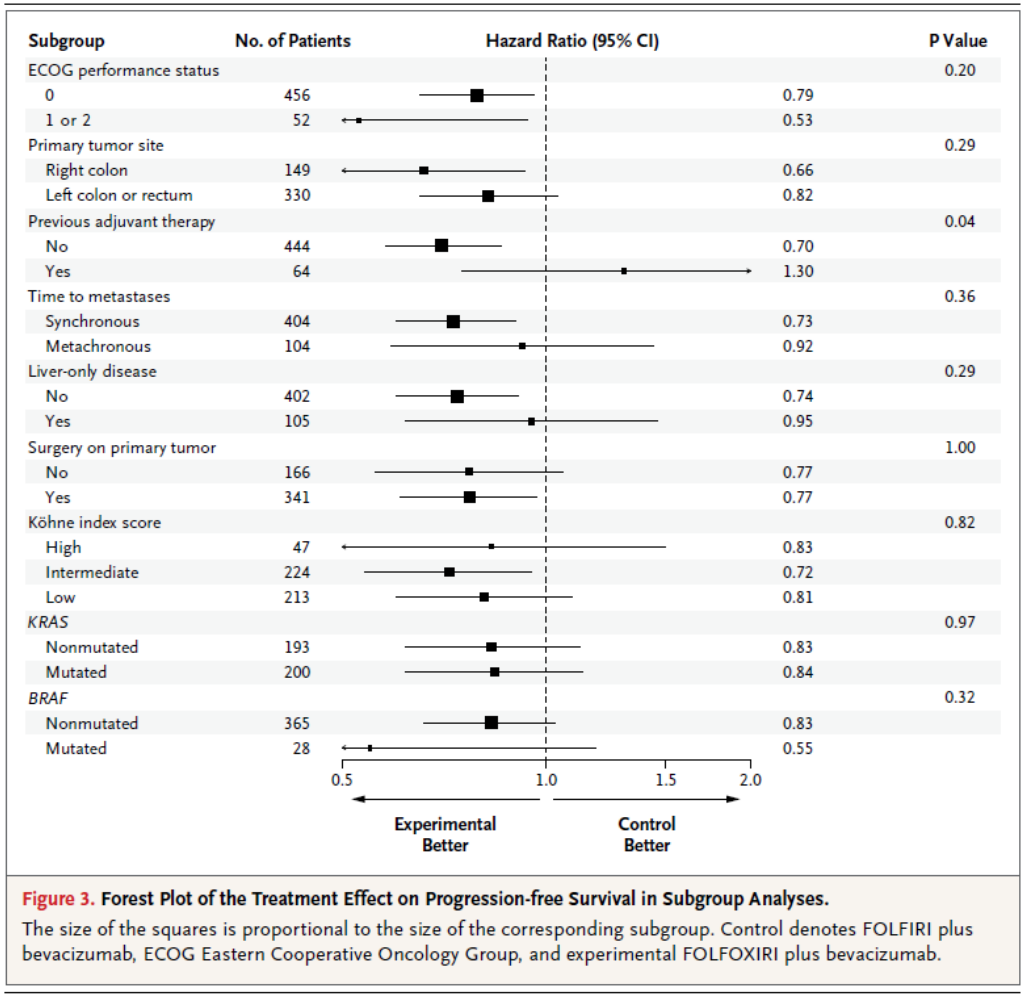


Figure 3. Forest Plot of the Treatment Effect on Progression-free Survival in Subgroup Analyses.

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.

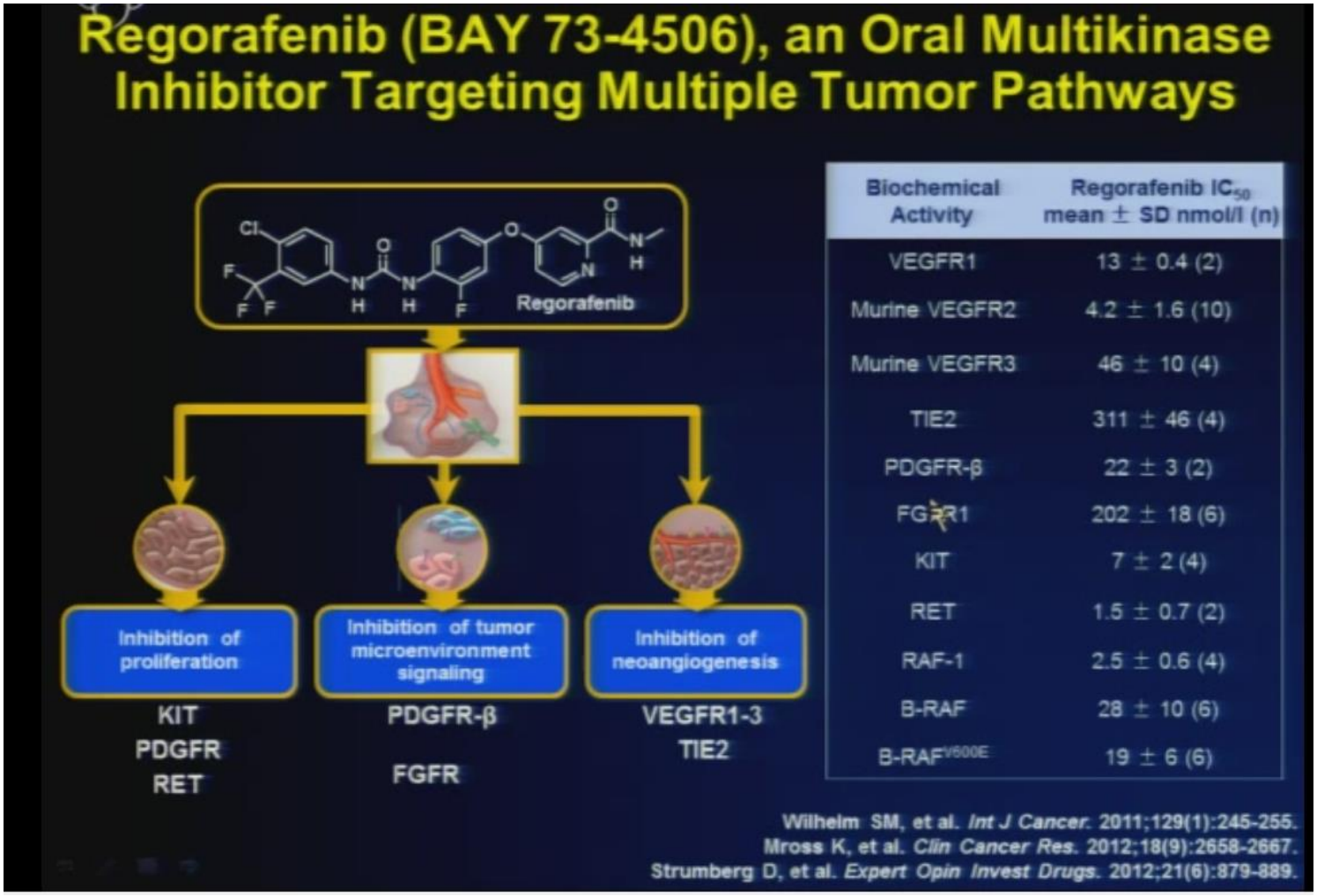
R0 Rezeksiyon; %15 vs. %12

Metastatik Kolon Kanserinde Tedavi Seçenekleri

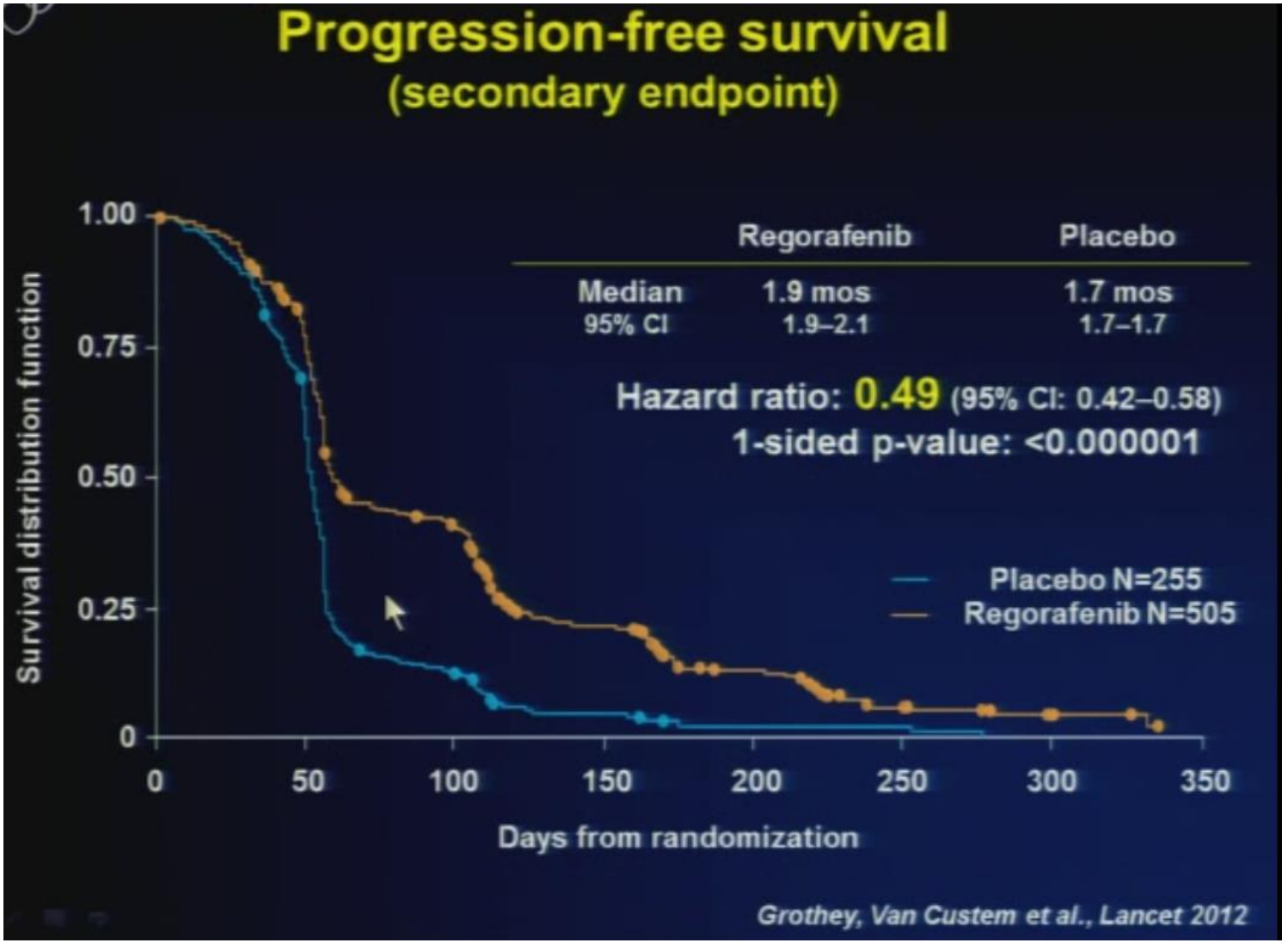
Hangi Hasta Grubunda FOLFORİNOX+/-Bevacizumab

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

Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

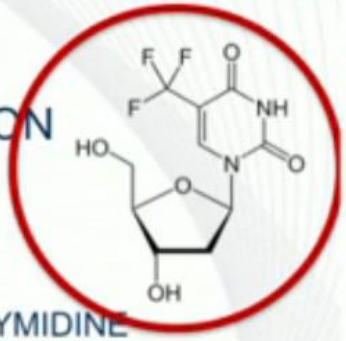


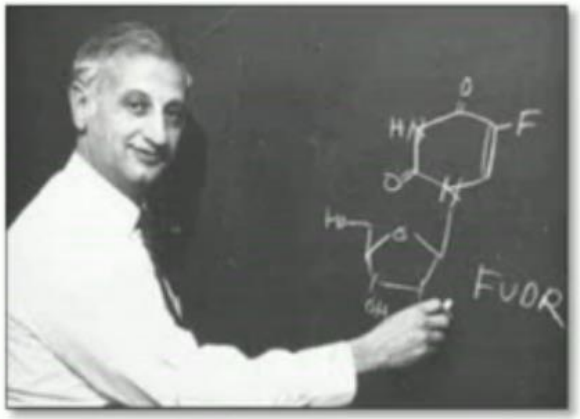
Metastatik Kolon Kanserinde Tedavi Seçenekleri

TAS-102

A NOVEL ANTI-METABOLITE COMBINATION

("Teaching an old dog new tricks")

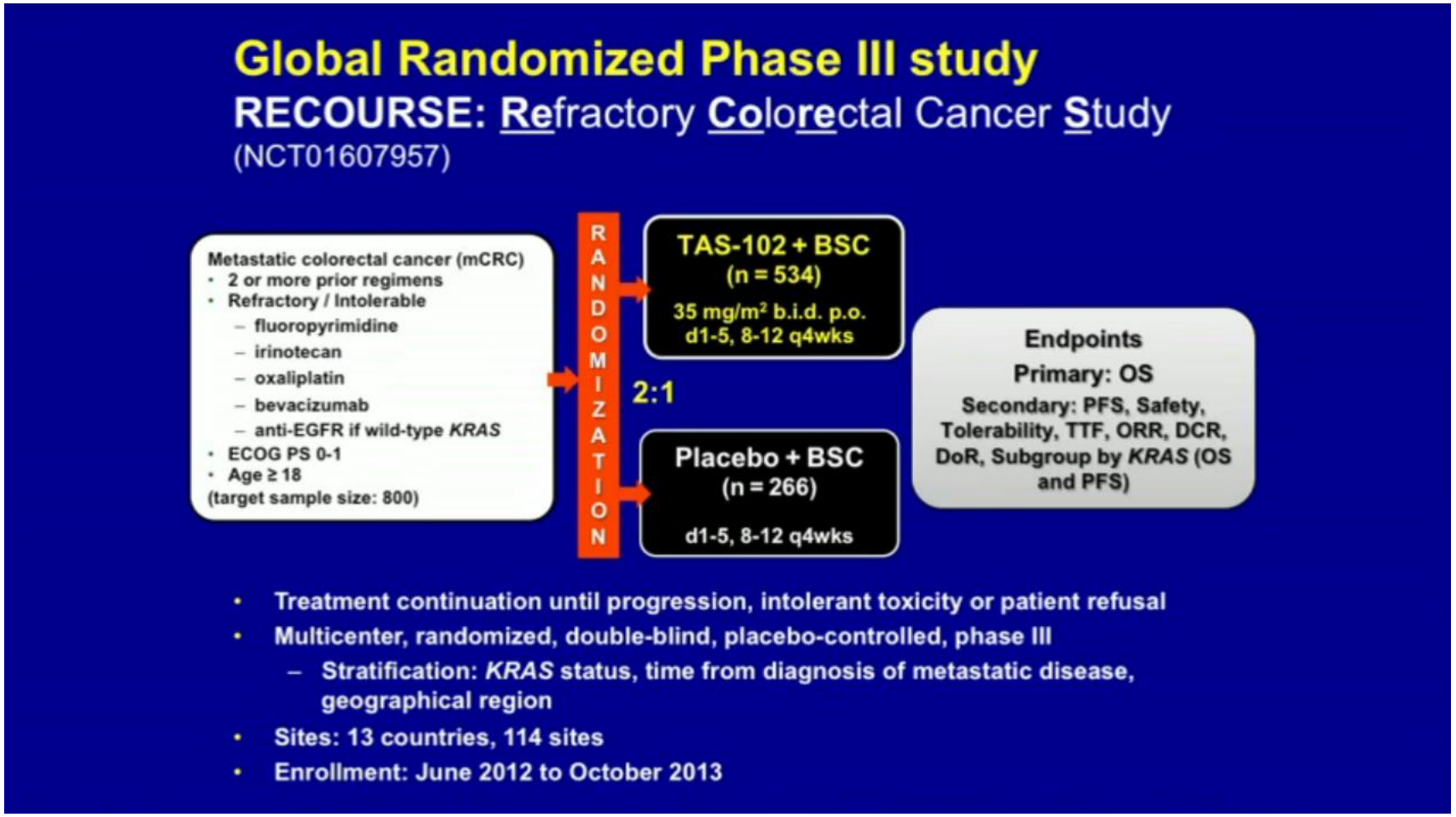




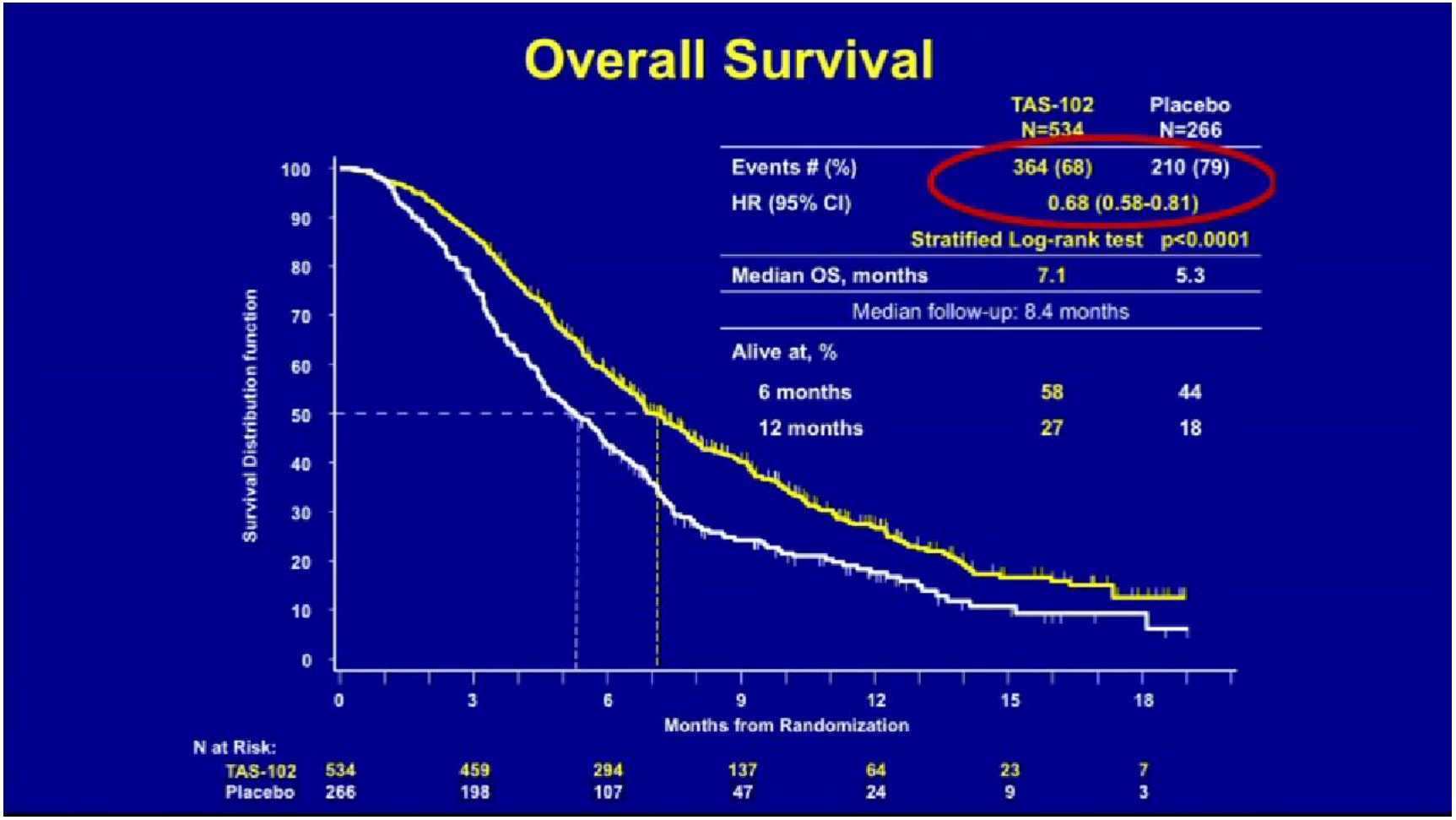
CHARLES HEIDELBERGER

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

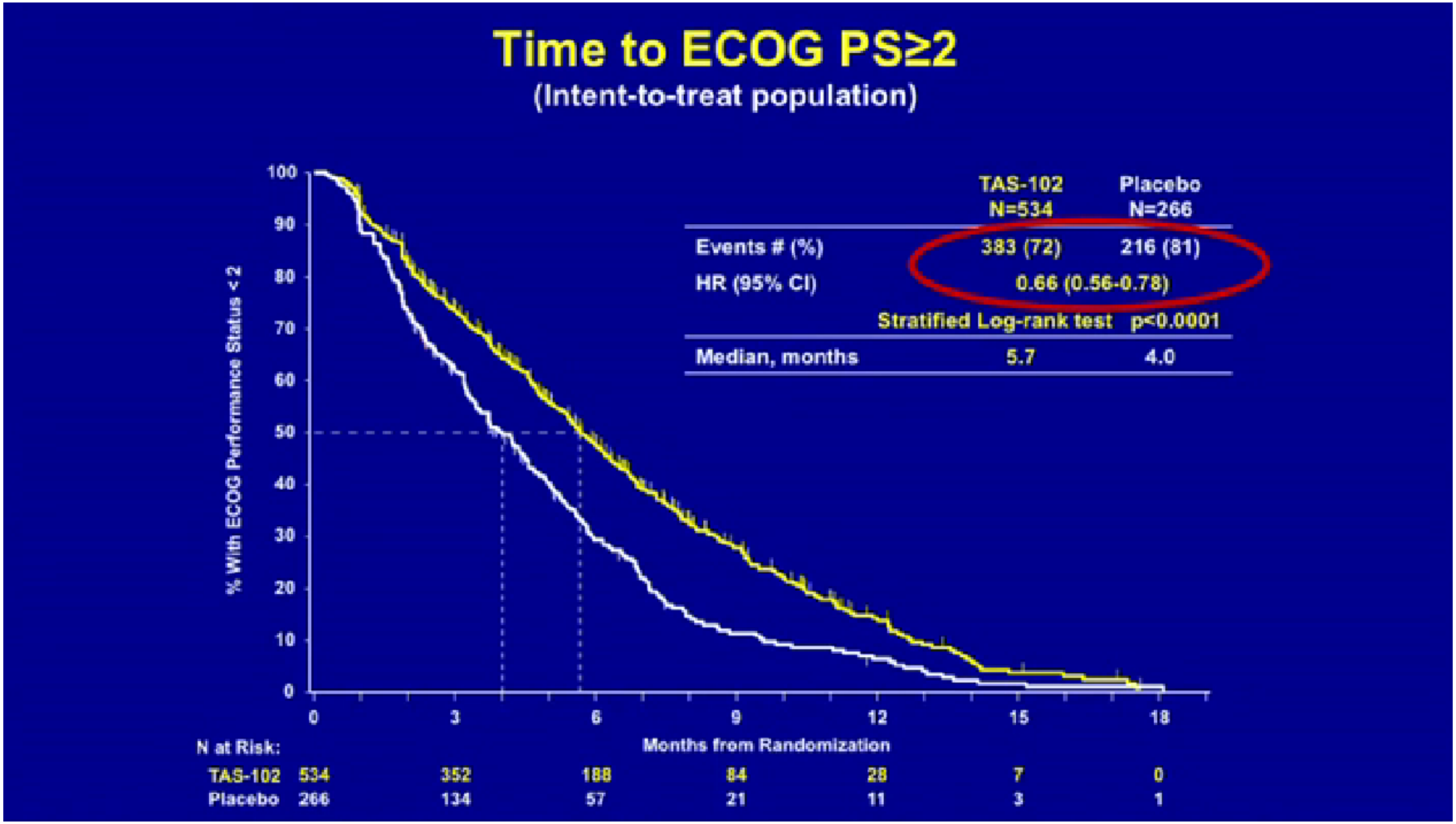
Metastatik Kolon Kanserinde Tedavi Seçenekleri



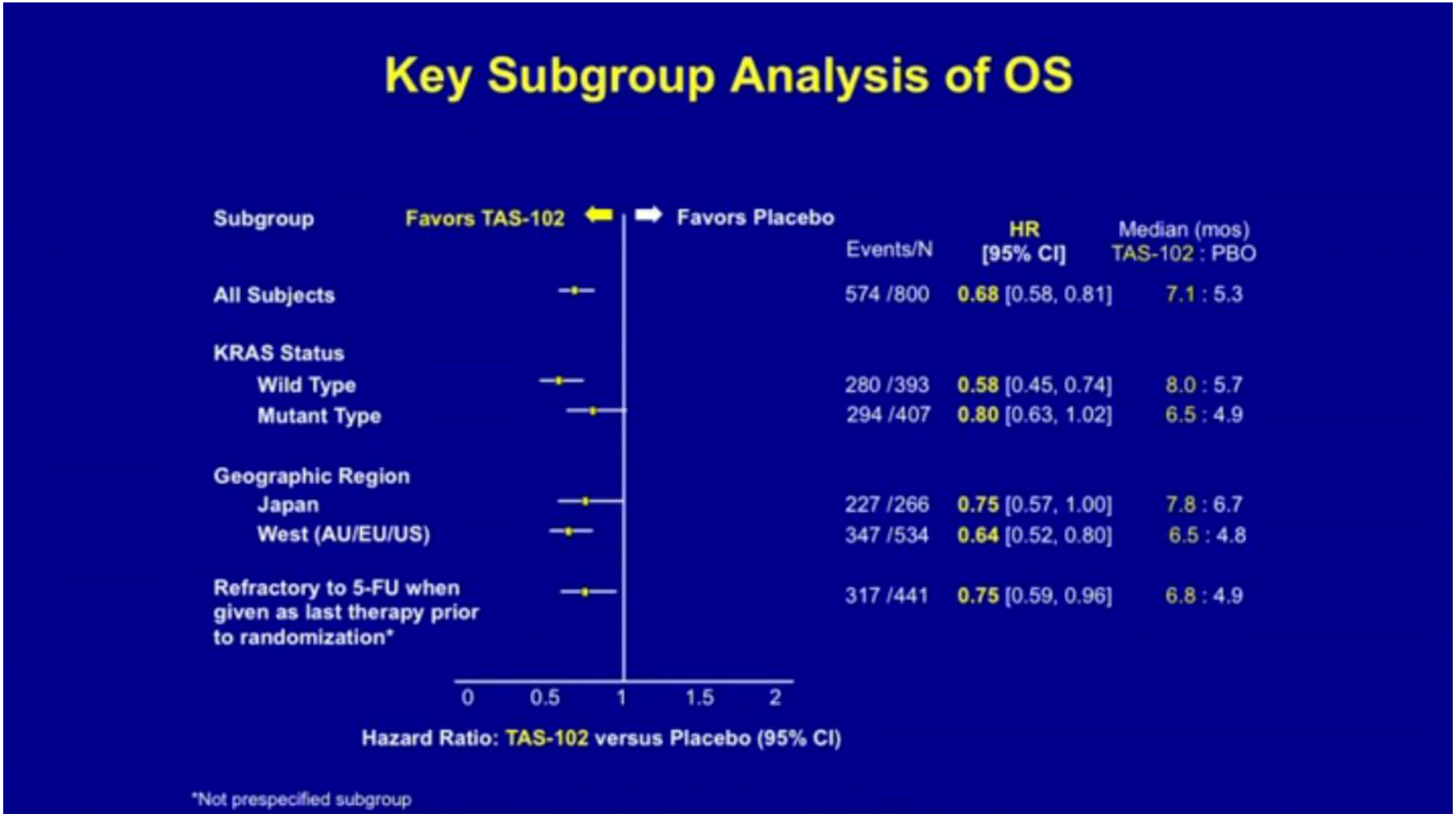
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri

TAS-102 Toxicity

- Mainly Hematologic (Grade 3)

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

- Minimal Non-hematologic toxicity

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

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

* NA denotes not applicable.
† P values are for the comparison between the cohort with mismatch repair–deficient colorectal cancer and the cohort with mismatch repair–proficient colorectal cancer.
‡ Race was self-reported.
§ Eastern Cooperative Oncology Group (ECOG) performance status is a measure of a patient's ability to perform activities of daily living; values range from 0 to 5, with higher scores indicating greater impairment.

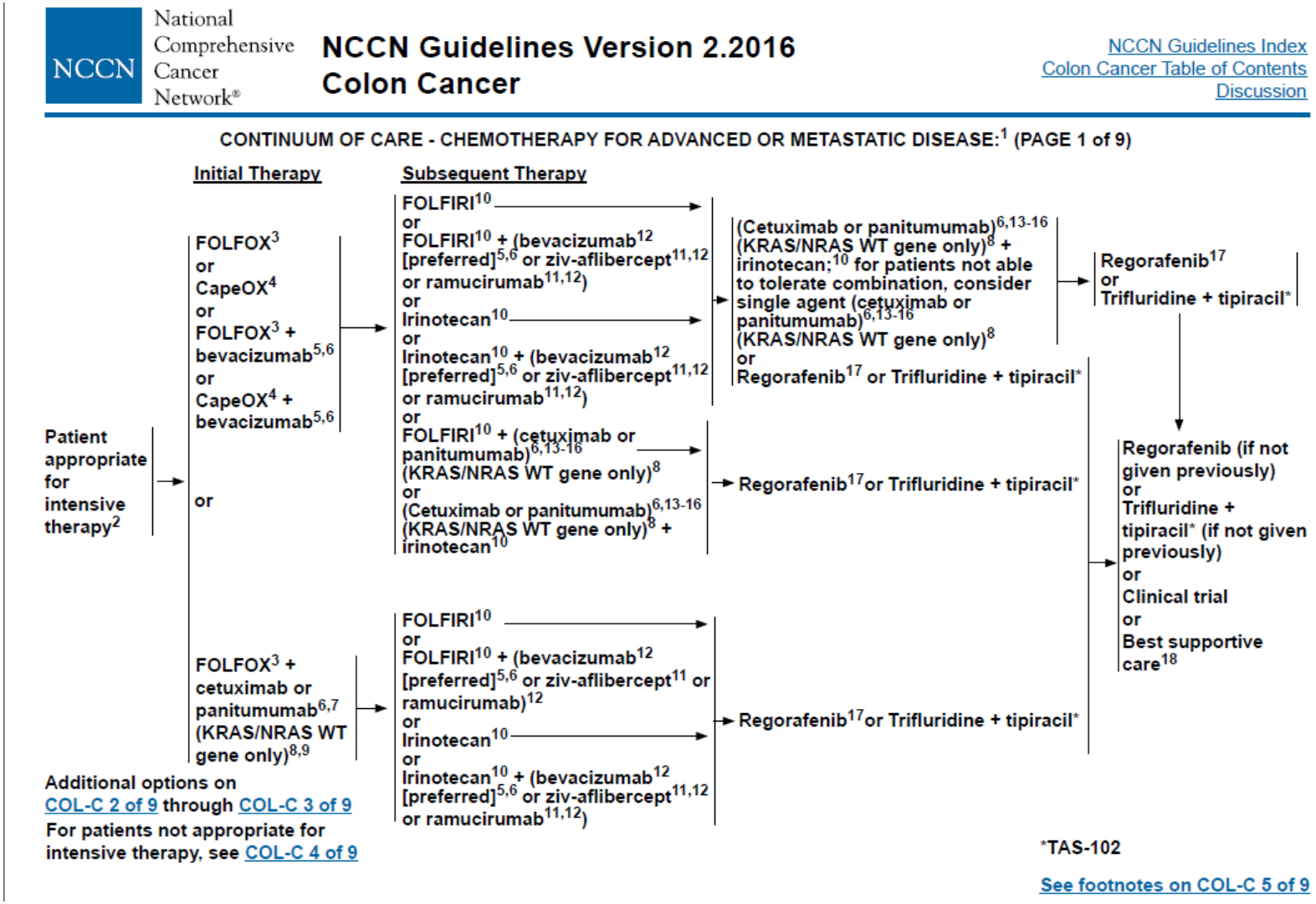
Metastatik Kolon Kanserinde Tedavi Seçenekleri

Table 2. Objective Responses According to RECIST Criteria.

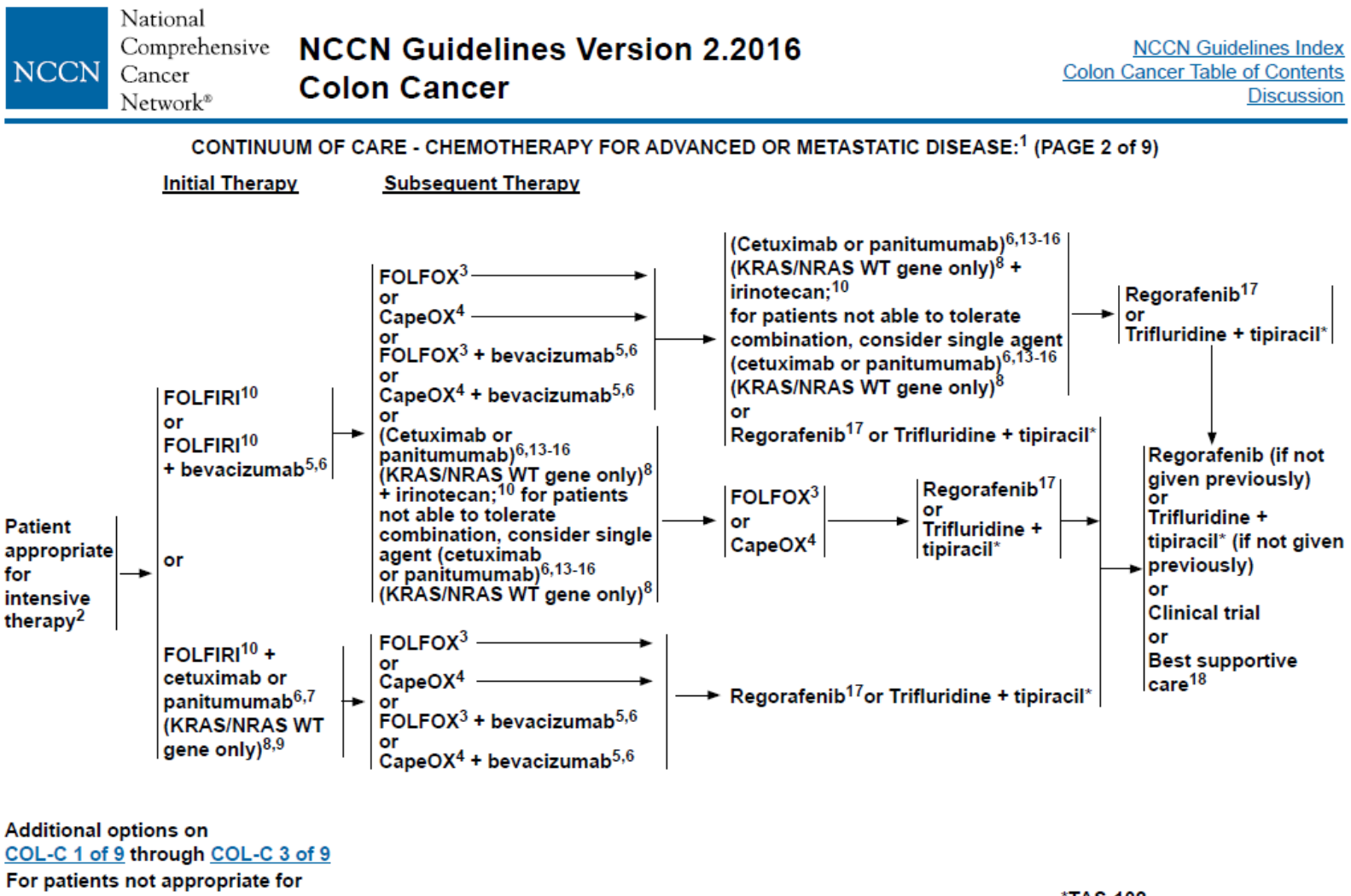
Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2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

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.
† One patient had a partial response at 12 weeks.
‡ Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.
§ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.
¶ The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair–proficient colorectal cancer.

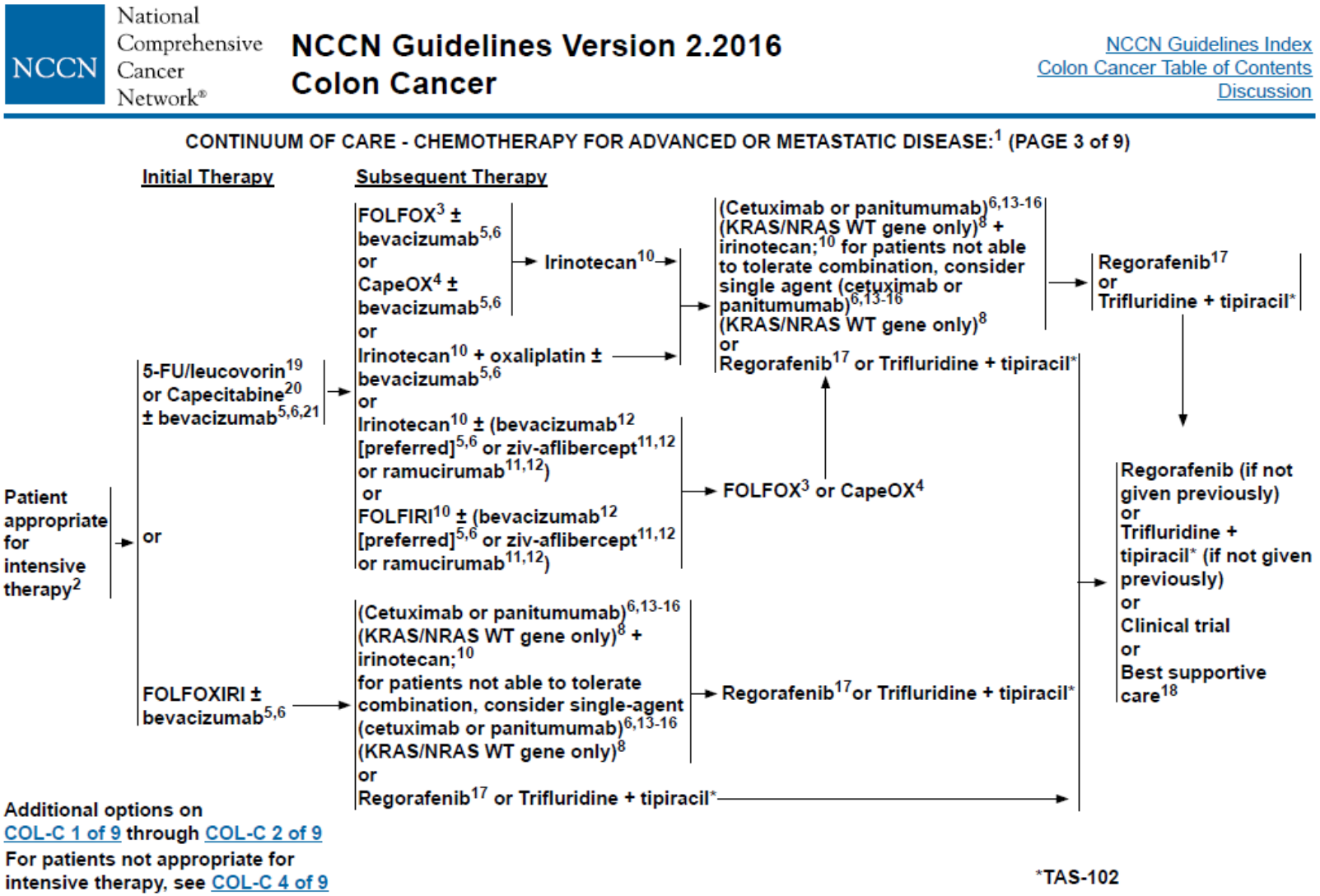
Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



Metastatik Kolon Kanserinde Tedavi Seçenekleri



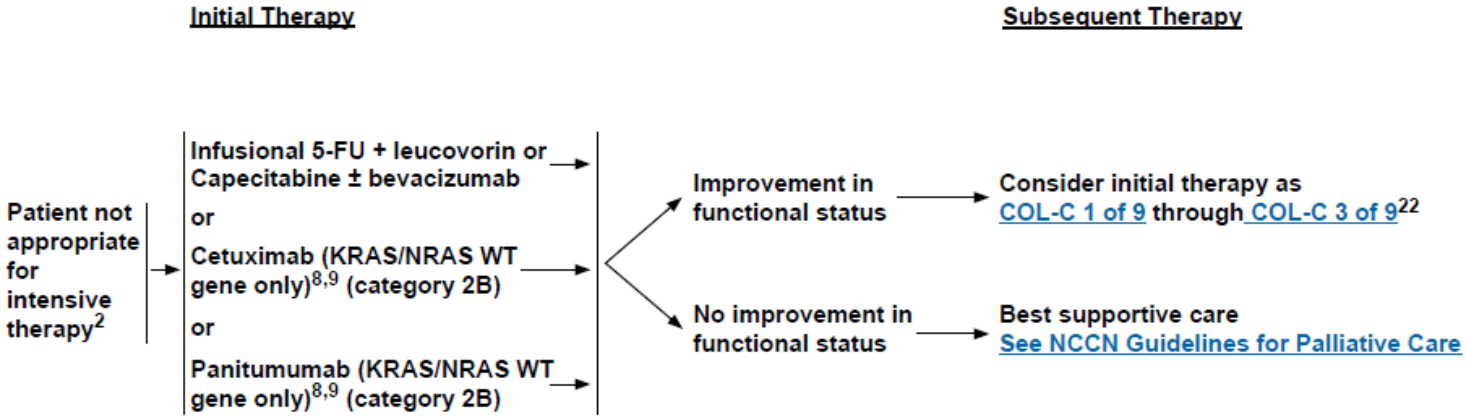
Metastatik Kolon Kanserinde Tedavi Seçenekleri

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Colon Cancer

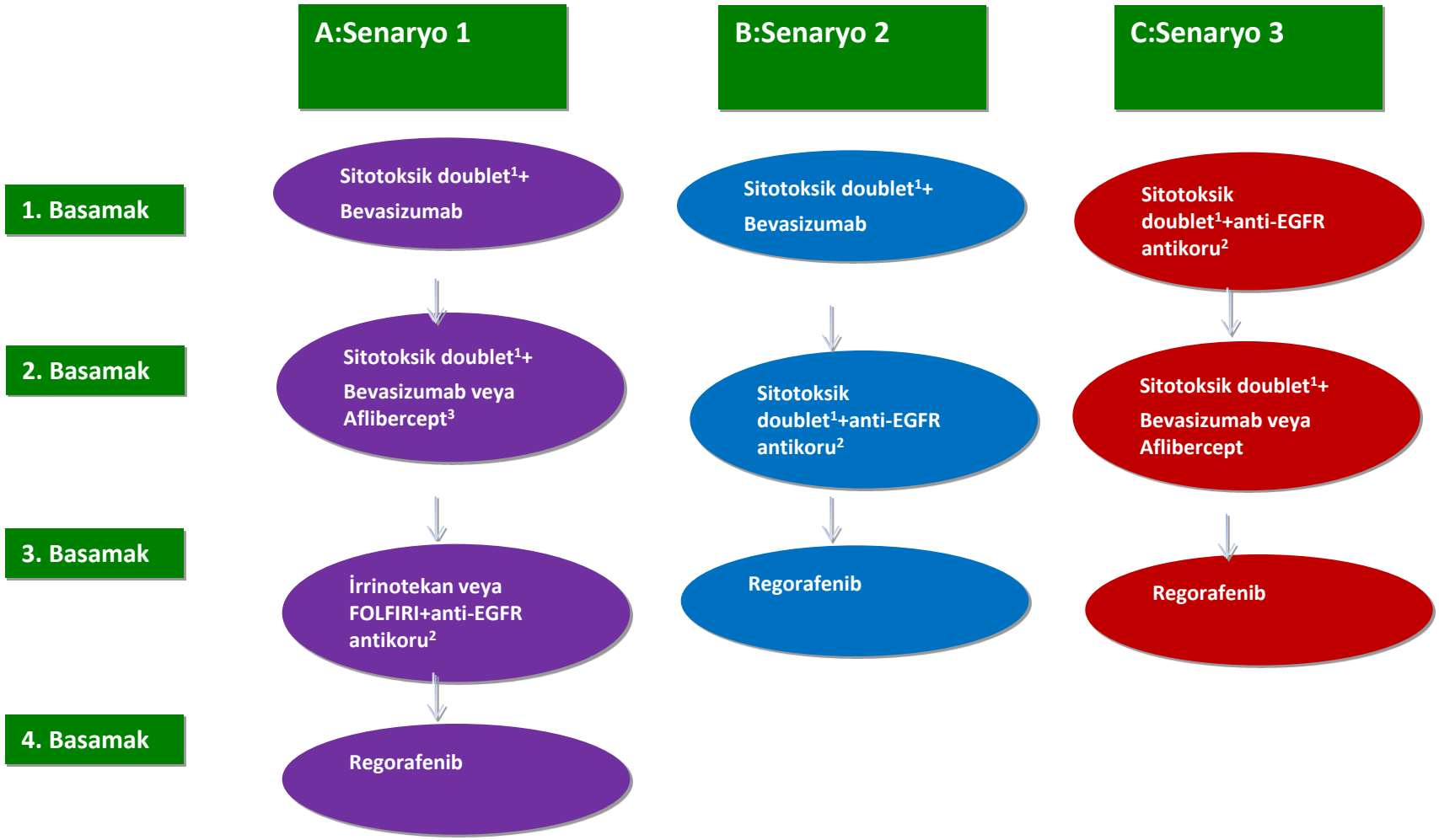
NCCN Guidelines Index
Colon Cancer Table of Contents
Discussion

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 4 of 9)



Metastatik Kolon Kanserinde Tedavi Seçenekleri

ESMO TEDAVİ REHBERİ



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