METASTATİK MİDE KANSERİNDE YENİLİKLER

Dr. Erkan DOĞAN
İstanbul Yeni Yüzyıl Üniversitesi
Gaziosmanpaşa Hastanesi
Tıbbi Onkoloji BD

Mide Kanseri: Epidemioloji

- Dünyada en sık 5. hastalık
- Kansere Bağlı ölümlerin 3. sıklıktaki sebebi

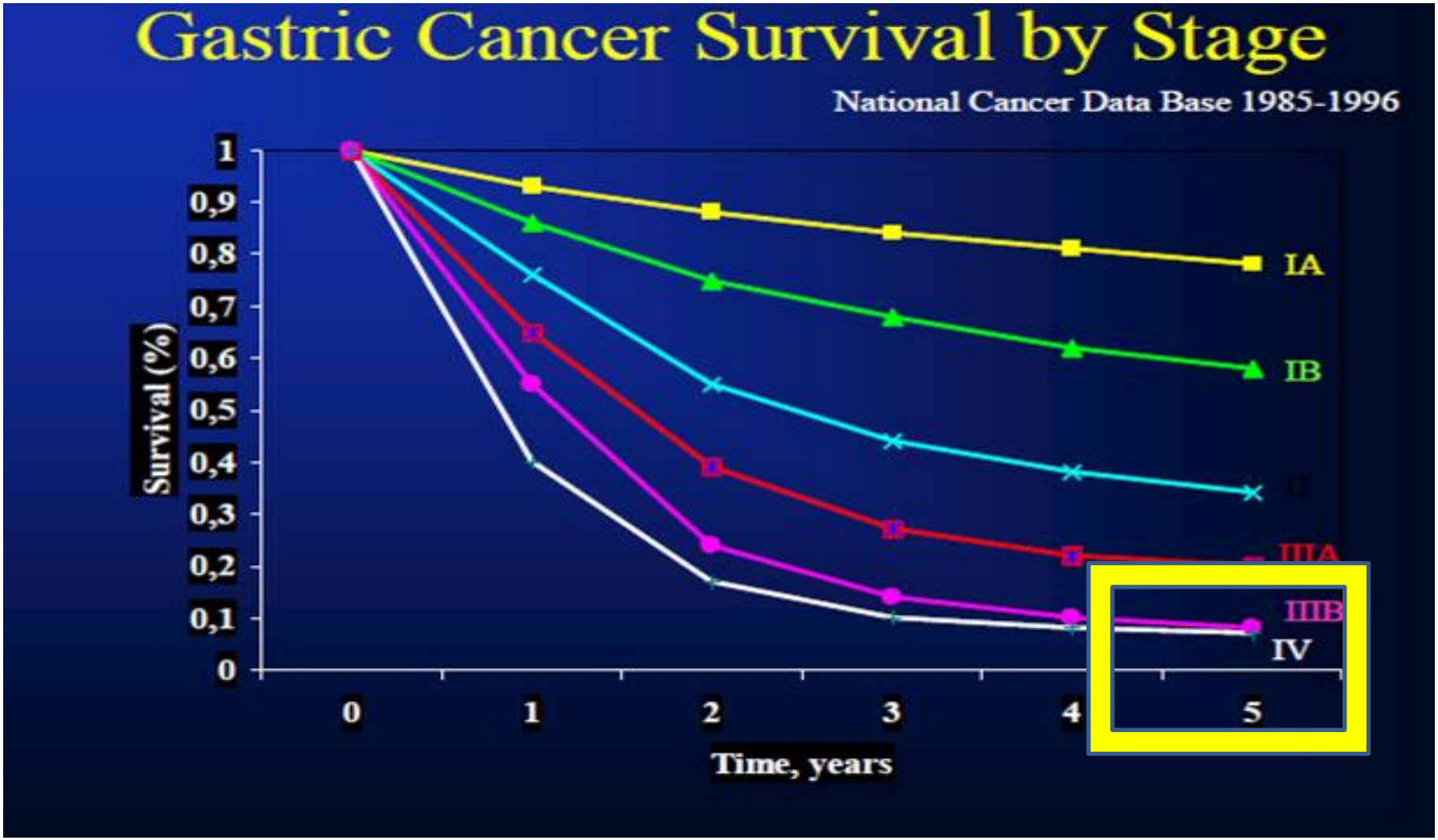
*Globocan 2012 verileri

Mide Kanseri: Epidemiyoloji

- Mide Ca'nın %50 si tanı anında metastatiktir*
- Ayrıca %40-60'ı radikal cerrahi sonrası nüks eder*
- Hastalardan 1. basamak tedavi alanların yaklaşık %40-75'i 2. basamak kemoterapi alabiliyorlar. Bunlarında %50'si kemoterapiye dirençli oluyor.

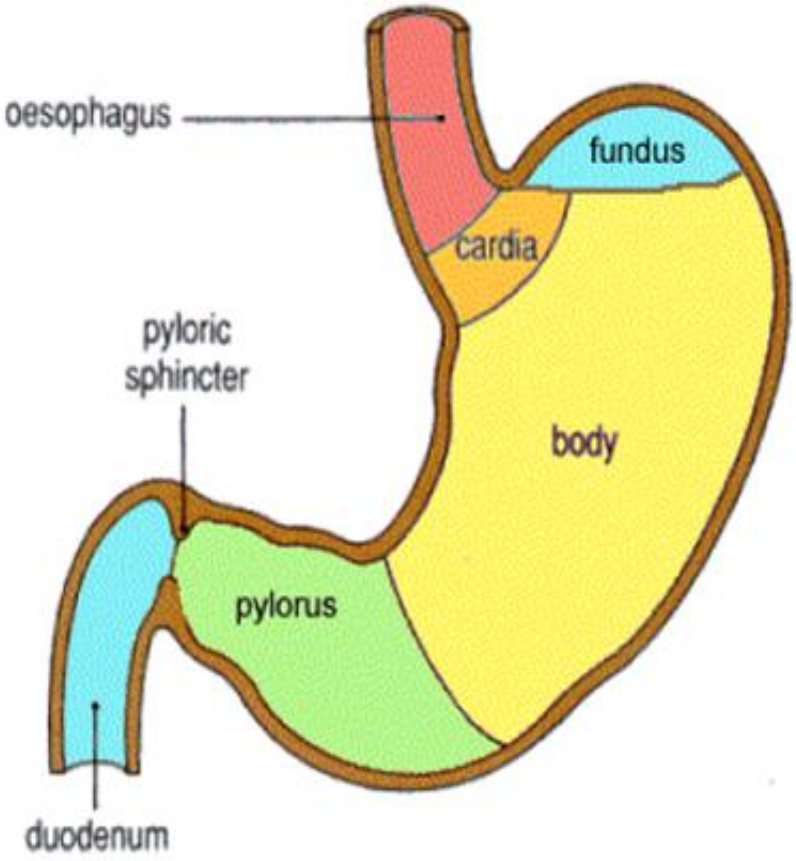
*Van Cutsem E. Ethal. Gastric Cancer. Lanset. 2016

Metastatik Mide Kanseri Evrelere Göre Sağkalım



Mide Kanseri; Ne tip bir hastalık Tedavi etmeye çalışıyoruz ?

- Histologic
  - Intestinal vs Diffuse
- Anatomic
  - GEJ vs body vs pylorus
- Geographic
  - East vs West
- Molecular
  - MSI vs MSS, ERBB2+ , PD1,PDL1…



Mide Kanseri; Ne tip bir hastalık Tedavi etmeye çalışıyoruz ?

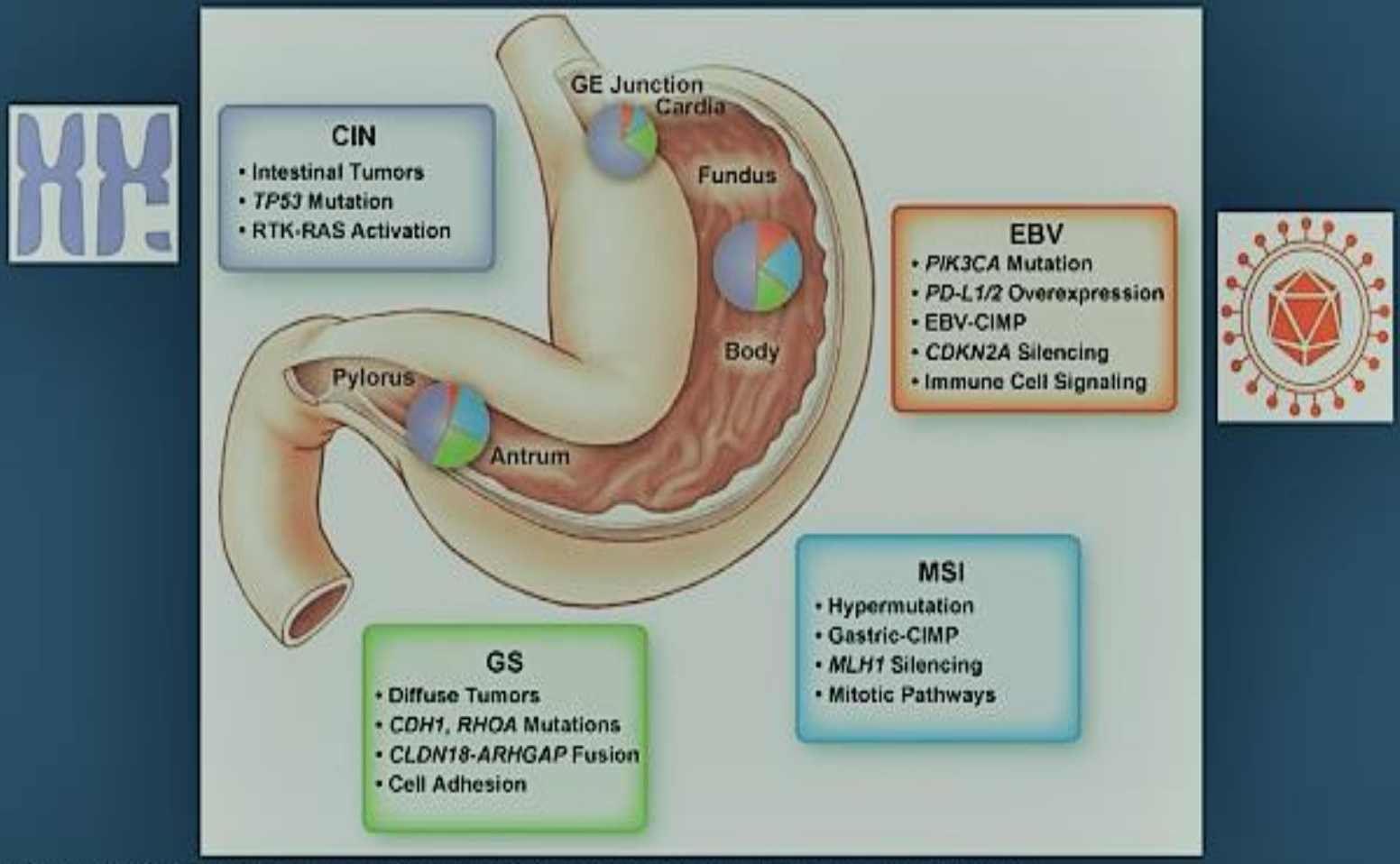
- Histologic
  - Intestinal vs Diffuse

Mide kanseri oldukça heterojen .

Temel tedavi yaklaşımımız ne; Hala "One size fit all" mı ?

  - East vs West
- Molecular
  - MSI vs MSS, ERBB2+ , PD1,PDL1…

MİDE KANSERİ MOLEKÜLER ALT TİPLERİ



CIN=chromosome instability; EBV=Epstein-Barr virus; GS=genomically stable; MSI=microsatellite instability

The Cancer Genome Atlas Research Network. Nature 2014.

GENOMİC ANALİZİN SONUÇLARI

- Mide Ca tek bir hastalık değil
  - Alt tipleri var
- Tedaviye cevaptaki farklılıkların ve prognozdaki farklılıkların sebebi bu farklı genetik alt tipler olabilir
- Farklı molelükler tetikleyiciler (diver) rol oynuyor
- Farklı hedefe yönelik ajanlar var !!!!!!

Advanced gastric cancer

Locally advanced unresectable

Survival: median 11 months if left untreated

median 14 months if treated

Aim of treatment: tumor shrinkage to obtain resectability; survival similar to initially resectable tumor

Preferred regimen: triplet including docetaxel or epirubicin

Metastatic

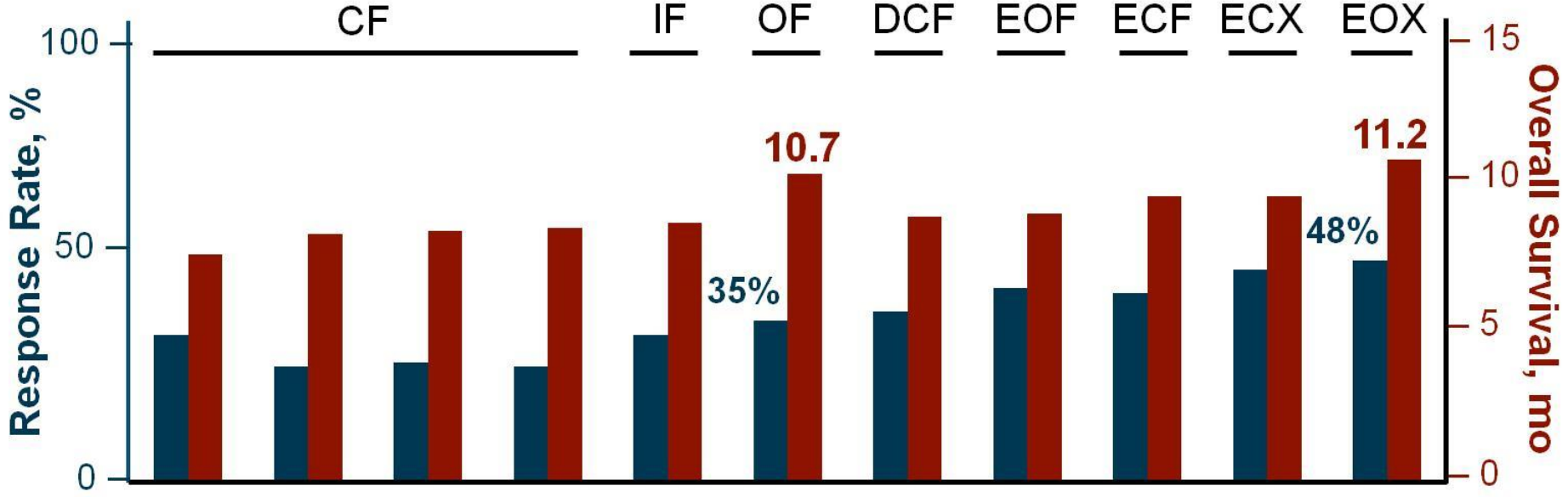
Survival: median 3 months if left untreated

median 9-11 months if treated

Aim of treatment: symptoms palliation, QoL, prolonged survival

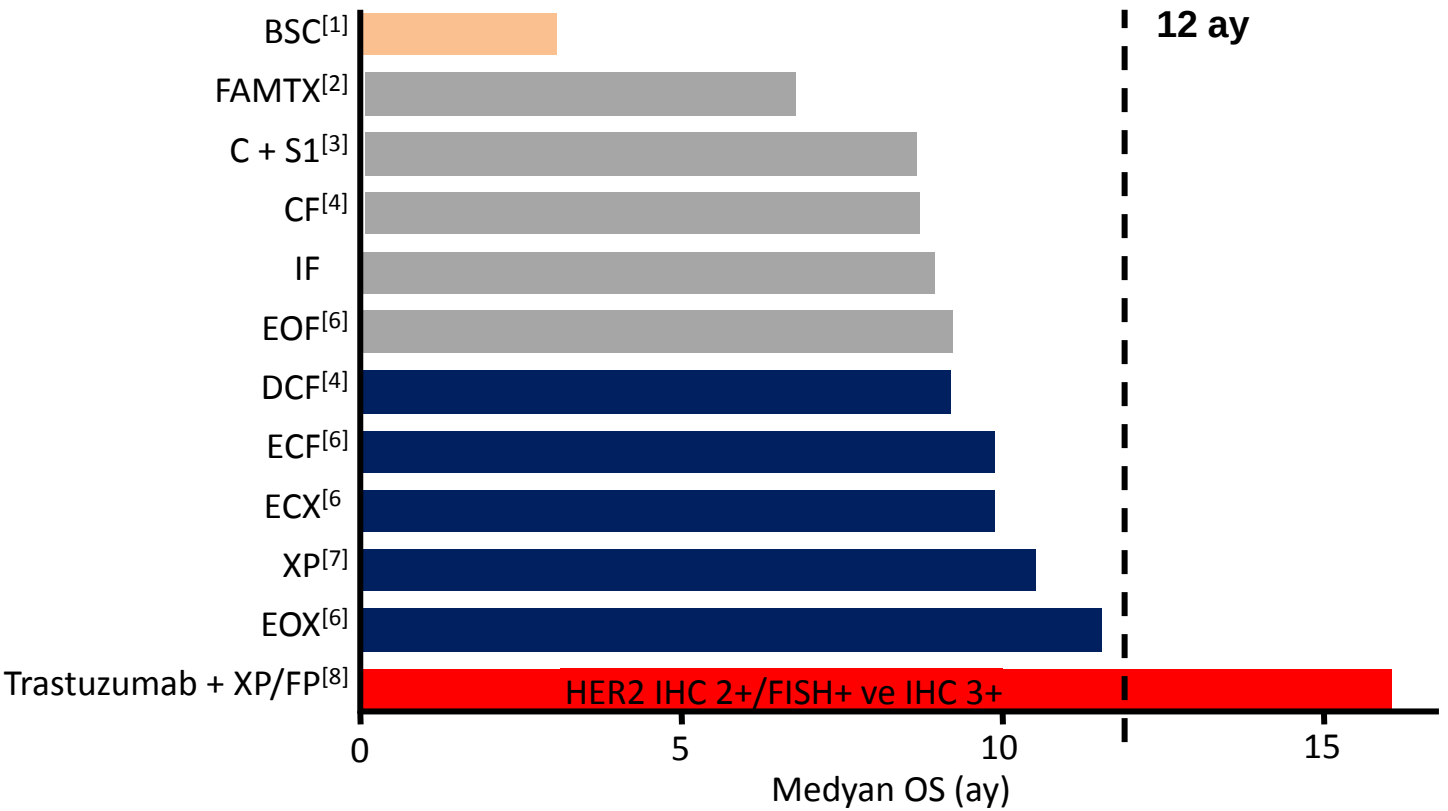
Preferred regimen: fluoropyrimidine/platinum agent doublet (e.g. FOLFOX)

Chemotherapy Regimens for Metastatic Esophagogastric Cancer



Ajani JA, et al. *J Clin Oncol.* 2010;28:1547-1553[21]; Al-Batran SE, et al. *J Clin Oncol.* 2008;26:1435-1442[22]; Boku N, et al. *Lancet Oncol.* 2009;10:1063-1069[23]; Dank M, et al. *Ann Oncol.* 2008;19:1450-1457[24]; Okines AF, et al. *Ann Oncol.* 2009;20:1529-1534[25]; Van Cutsem E, et al. *J Clin Oncol.* 2006;24:4991-4997.[26]

Metastatik Mide Kanserinde Tedavi Tiplerine Bağlı Medyan Genel Sağkalım



1. Murad AM, et al. Cancer. 1993;72:37-41. 2. Vanhoefer U, et al. J Clin Oncol. 2000;18:2648-2657.
3. Ajani JA, et al. J Clin Oncol. 2010;28:1547-1553. 4. Van Cutsem E, et al. J Clin Oncol. 2006;24:4991-4997.
5. Dank M, et al. Ann Oncol. 2008;19:1450-1457. 6. Cunningham D, et al. N Engl J Med. 2008;358:36-46.
7. Kang YK, et al. Ann Oncol. 2009;20:666-673. 8. Bang YJ, et al. Lancet. 2010;376:687-697.

Metastatik Mide Kanserinde

1. Basamak Tedavi

HER2 NEGATİF

Table 1 Major randomised phase III trials of first-line chemotherapy in advanced gastric cancer.

Author (year)	Study intervention	Number of patients	Primary endpoint	ORR (%)	Median PFS/FFS/TTP (months)	Median OS (months)
Webb *et al* (1997)[18]	ECF vs FAMTX	274	OS	45 vs 21 (p=0.0002)	FFS 7.4 vs 3.4 (p=0.00006)	8.9 vs 5.7 (p=0.0009)
Van Cutsem *et al* (2006)[19]	DCF vs CF	445	TTP	37 vs 25 (p=0.01)	TTP 5.6 vs 3.7 (HR 1.47, p<0.001)	9.2 vs 8.6 (HR 1.29, p=0.02)
Cunningham *et al* (2008)[24]	ECF vs ECX vs EOF vs EOX	1002	OS*	40.7 vs 46.4 vs 42.4 vs 47.9 (NS)	PFS 6.2 vs 6.7 6.5 vs 7.0 (NS)	9.9 vs 9.9 vs 9.3 vs 11.2 (HR 0.80, p=0.02)†
Dank *et al* (2008)[29]	IF vs CF	333	TTP	31.8 vs 25.8 (NS)	TTP 5.0 vs 4.2 (NS)	9 vs 8.7 (NS)
Al-Batran *et al* (2008)[27]	FLO vs FLC	220	PFS	24.5 vs 34.8 (NS)	PFS 5.8 vs 3.9 (NS)	10.7 vs 8.8 (NS)
Kang *et al* (2009)[25]	CX vs CF	316	PFS‡	46 vs 32 (p=0.020)	PFS 5.6 vs 5.0 (HR 0.81, p<0.001)‡	10.5 vs 9.3 (HR 0.85, p<0.008)‡
Koizumi *et al* (2008)[31]	CS1 vs S1	305	OS	54 vs 31 (p=0.002)	PFS 6.0 vs 4.0 (HR, p<0.0001)	13 vs 11 (HR 0.77, p=0.04)
Ajani *et al* (2010)[33]	CS1 vs CF	1053	OS	29.1 vs 31.9 (NS)	PFS 4.8 vs 5.5 (NS)	8.6 vs 7.9 (NS)
Yamada *et al* (2014)[69]	OXS1 vs CS1	685	PFS, OS§	55.7 vs 52.2 (HR NR)	PFS 5.5 vs 5.4 (HR 1.004, p=0.0044)	14.1 vs 13.1 (HR 0.958, p = NR)
Guimbaud *et al* (2014)[10]	FOLFIRI vs ECF	416	TTF¶	39.2 vs 37.8 (NS)	TTF 5.3 vs 5.8 (NS)	9.5 vs 9.7 (NS)
Wang *et al* (2016)[70]	mDCF vs CF	243	PFS	48.7 vs 33.9 (p=0.0244)	PFS 7.2 vs 4.9 (HR 0.58, p=0.0008)	10.2 vs 8.5 (HR 0.71, p=0.0319)

*Noninferiority for the triplet therapies containing capecitabine as compared with fluorouracil and for those containing oxaliplatin as compared with cisplatin.
†EOX vs ECF.
‡Noninferiority of CX versus CF.
§Noninferiority in PFS for OXS1 compared with CS1; relative efficacy in OS between OXS1 and CS1.
¶TTF was significantly longer with FOLFIRI than with ECX (5.1 v 4.2 months; P= 0.008).
CF, cisplatin and fluorouracil; CS1, cisplatin and S1; CX, cisplatin and capecitabine; DCF, docetaxel, cisplatin and fluorouracil; ECF, epirubicin, cisplatin and fluorouracil; ECX, epirubicin, cisplatin, and capecitabine; EOF, epirubicin, oxaliplatin and fluorouracil; EOX, epirubicin, oxaliplatin and capecitabine; FAMTX, fluorouracil, doxorubicin and methotrexate; FFS, failure free survival; FLC, fluorouracil, leucovorin and cisplatin; FLO, fluorouracil, leucovorin and oxaliplatin; FOLFIRI, fluorouracil, leucovorin and irinotecan; IF, irinotecan and fluorouracil; mDCF, modified docetaxel, cisplatin and fluorouracil. ORR, overall response rate; NR, not reported; NS: not significant; OS, overall survival; OXS1, oxaliplatin and S1; PFS, progression free survival; TTP, time to progression.

Metastatik Mide Kanserinde
1. Basamak Tedavi
HER2 POZİTİF

Mide Kanserinde HER2 Pozitifliği

- Mide kanserinde HER2 pozitiflik oranı %7-34 arasında bildirilmiştir.

- Ortalama Her2 pozitifliği: %12-15

- Mide kanserinde HER 2 pozitifliğinin;
  - ✓ önemli bir biyomarker olduğu,
  - ✓ tümör gelişiminde önemli yeri olduğu,
  - ✓ Agresif seyirle ilişkili olduğu gösterilmiştir.

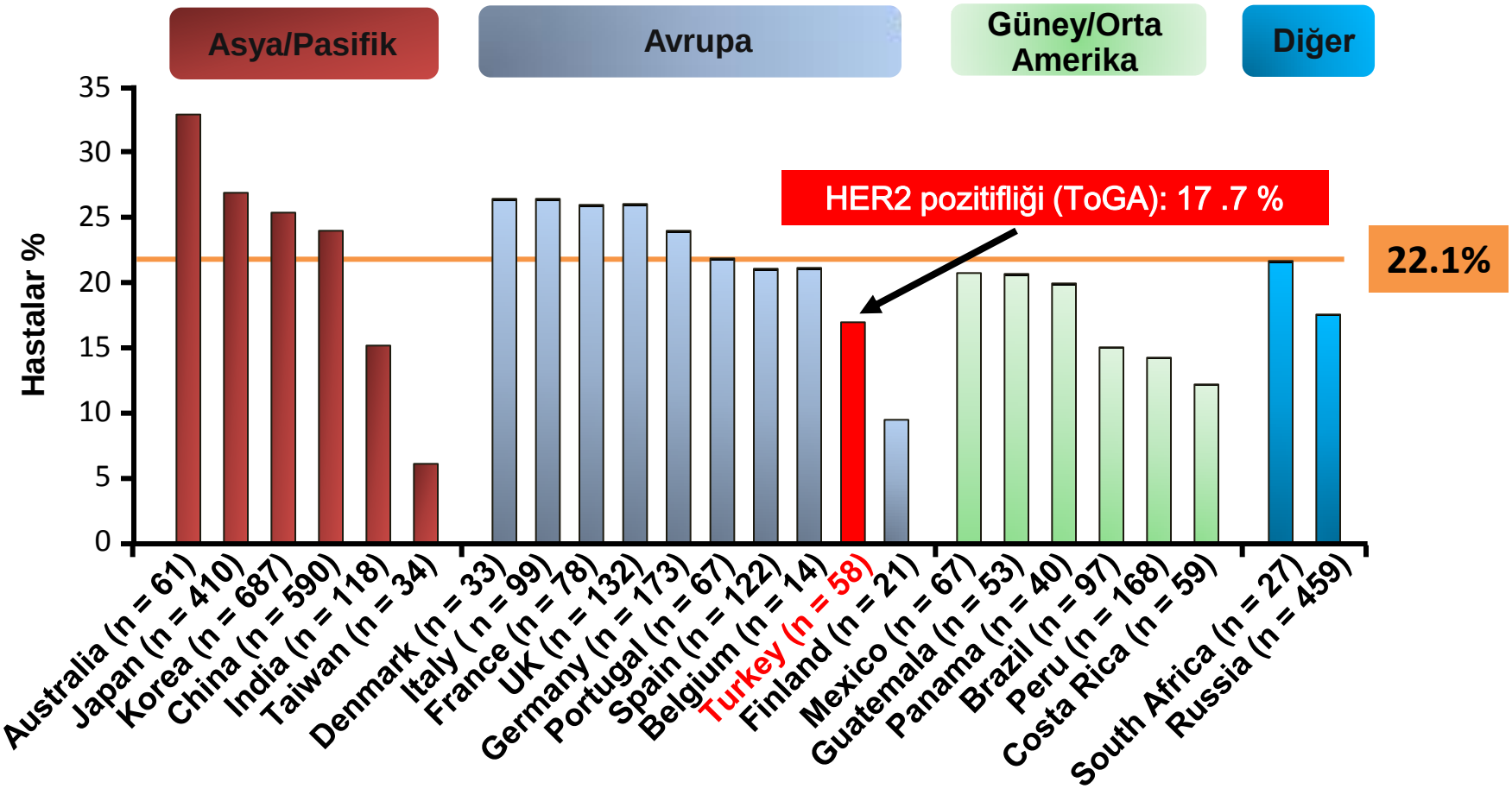
Bang YJ, et al. Lancet. 2010;376:687-697.

HER2 Pozitif İlerlemiş Gastrik yada Gastro-özefageal Bileşke Kanserinin Tedavisi İçin Tek Başına Kemoterapi ve Kemoterapi ile Kombinasyon Halinde Trastuzumab Kullanımının Karşılaştırılması (ToGA): Faz III, Açık Etiketli, Randomize Kontrollü Çalışma

Yung_Jue Bang, Eric Van Cutsem, Andrea Fevereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Tarah Satoh, Giuseppe Aprile, Evgeny Kulilov, Julie Hill, Michaela Lehle, Josef Rüschoff, Yoon-Koo Kang

Bang YJ, et al. Lancet. 2010;376:687-697.

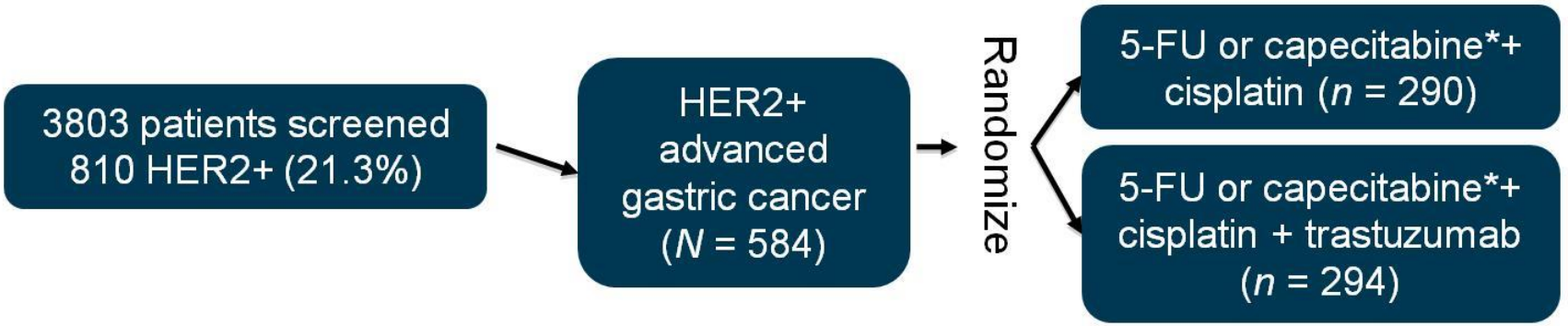
ToGA: HER2 pozitifliği



Bang YJ, et al. ASCO 2009. Abstract 4556.

The ToGA Study: Targeting the HER2 Protein

Phase 3, Randomized, Open-Label, International, Multicenter Study



Regimen	Dose
Capecitabine	1000 mg/m^2 BID days 1 to 14 every 3 weeks × 6 cycles
5-FU	800 mg/m^2/day continuous IV infusion days 1 to 5 every 3 weeks × 6 cycles
Cisplatin	80 mg/m^2 IV infusion day 1 every 3 weeks × 6 cycles
Trastuzumab	8 mg/kg IV LD followed by 6 mg/kg every 3 weeks until PD/UT/WC

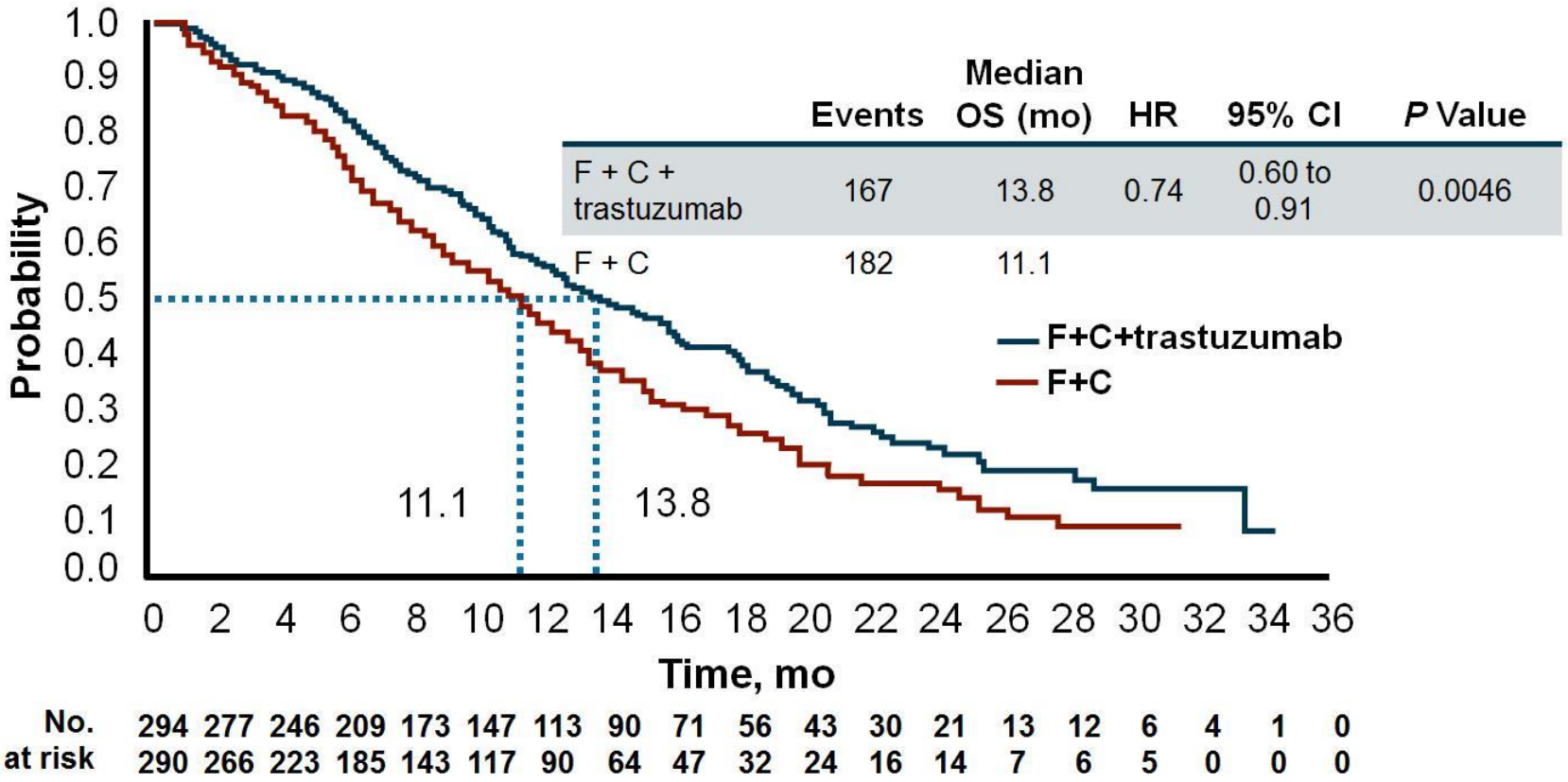
Primary End Point	Secondary End Points
OS	PFS TTP ORR CBR DOR QOL Safety Pain intensity Analgesic consumption Weight change Pharmacokinetics

*Chosen at investigator's discretion.

Van Cutsem E, et al. *J Clin Oncol*. 2009;27:18s.[19]

The ToGA Study: OS

- ToGA Primary End Point: OS

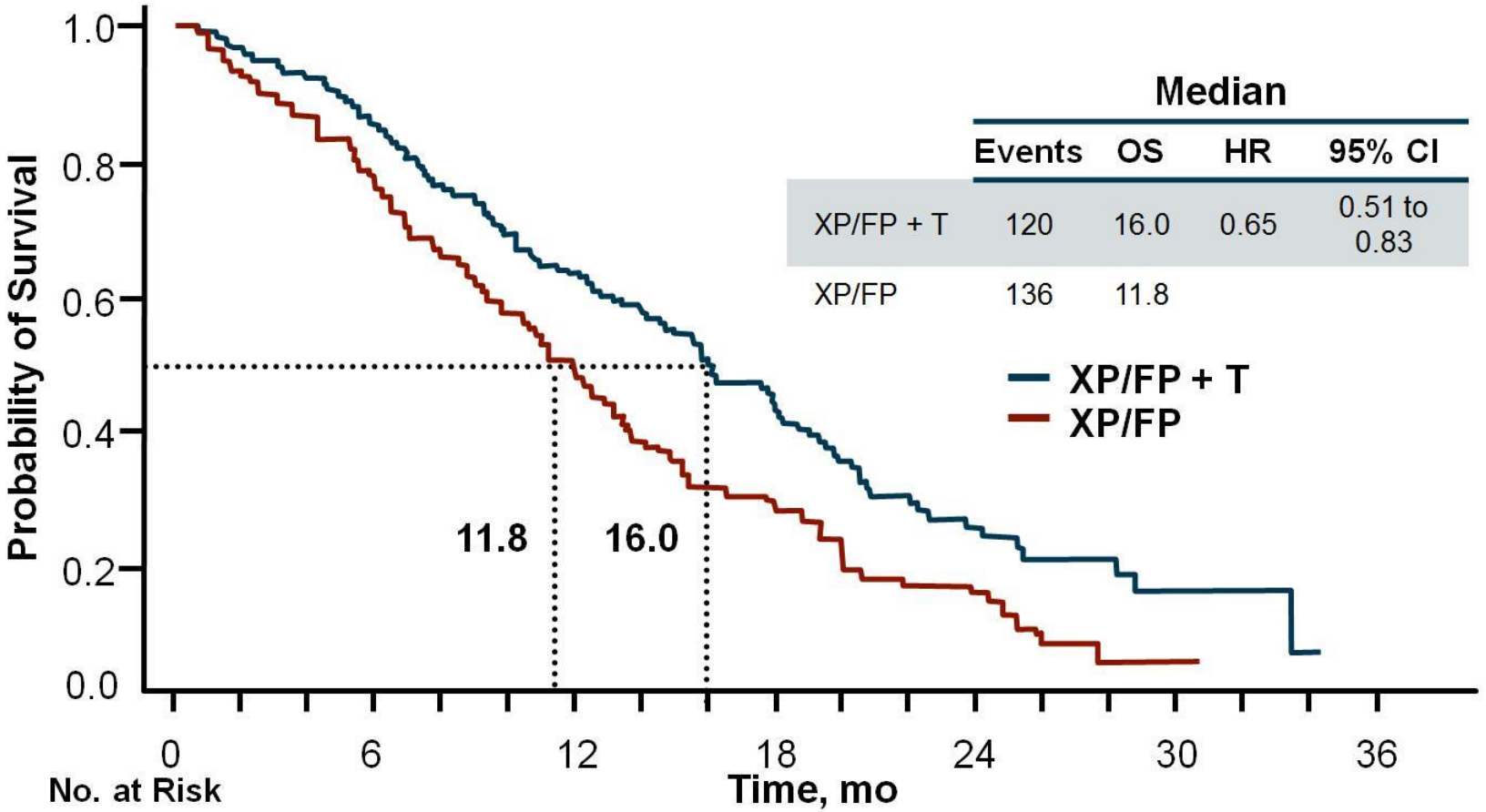


	Events	Median OS (mo)	HR	95% CI	*P* Value
F + C + trastuzumab	167	13.8	0.74	0.60 to 0.91	0.0046
F + C	182	11.1			

F = fluoropyrimidine (either fluorouracil or capecitabine), C = cisplatin

Reproduced from Bang YJ, et al. *Lancet.* 2010;376:687-697. ©2010 with permission from Elsevier.[20]

OS in Patients With IHC 2+/FISH+ or IHC 3+: (Exploratory Analysis)



	Median			
	Events	OS	HR	95% CI
XP/FP + T	120	16.0	0.65	0.51 to 0.83
XP/FP	136	11.8		

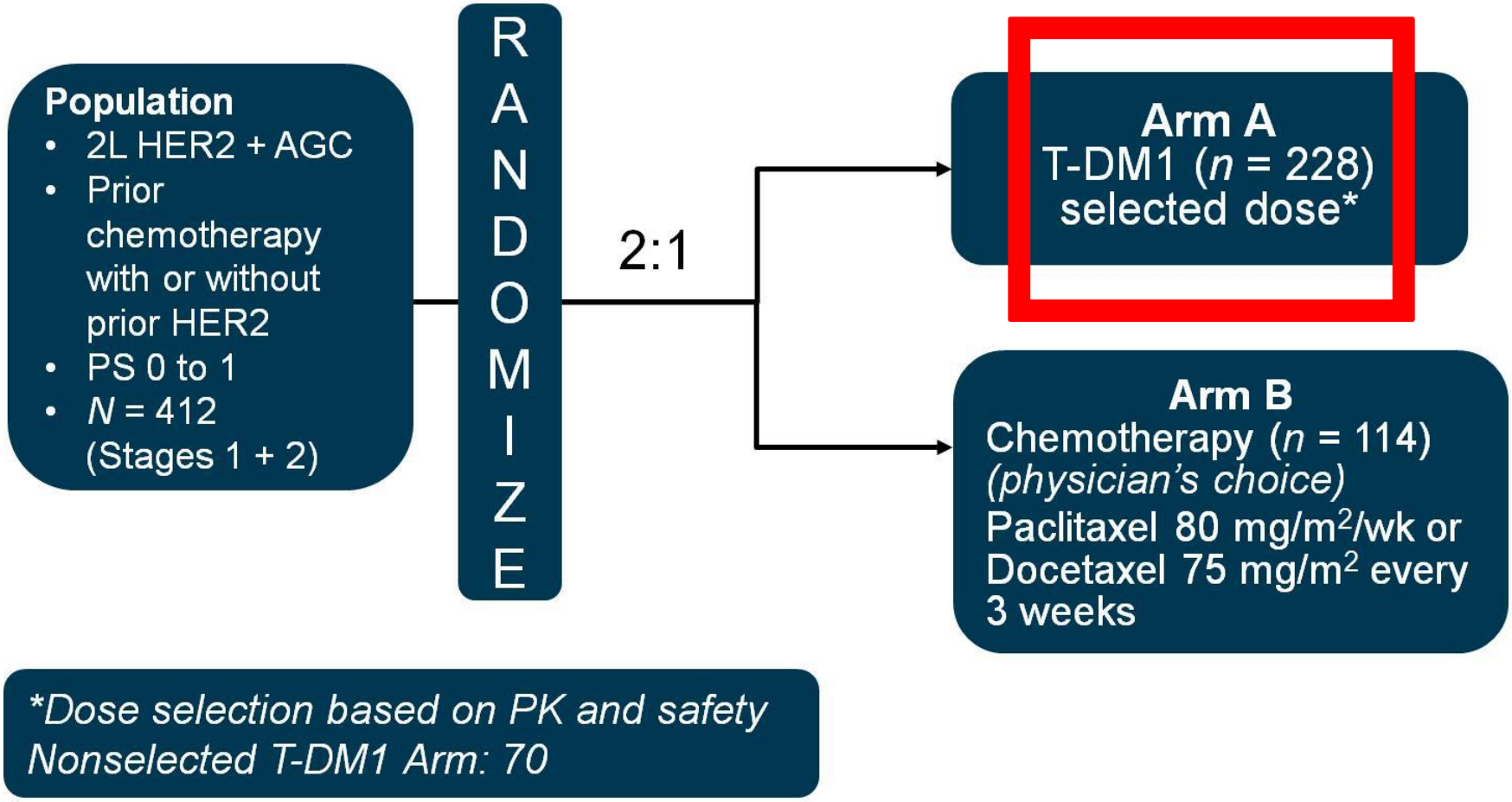
No. at Risk

XP/FP + T	228	218	196	170	142	122	100	84	65	51	39	28	20	12	11	5	4	1	0
XP/FP	218	198	170	141	112	96	75	53	39	28	20	13	11	4	3	3	0	0	0

Reproduced from Bang YJ, et al. *Lancet.* 2010;376:687-697. ©2010 with permission from Elsevier.[20]

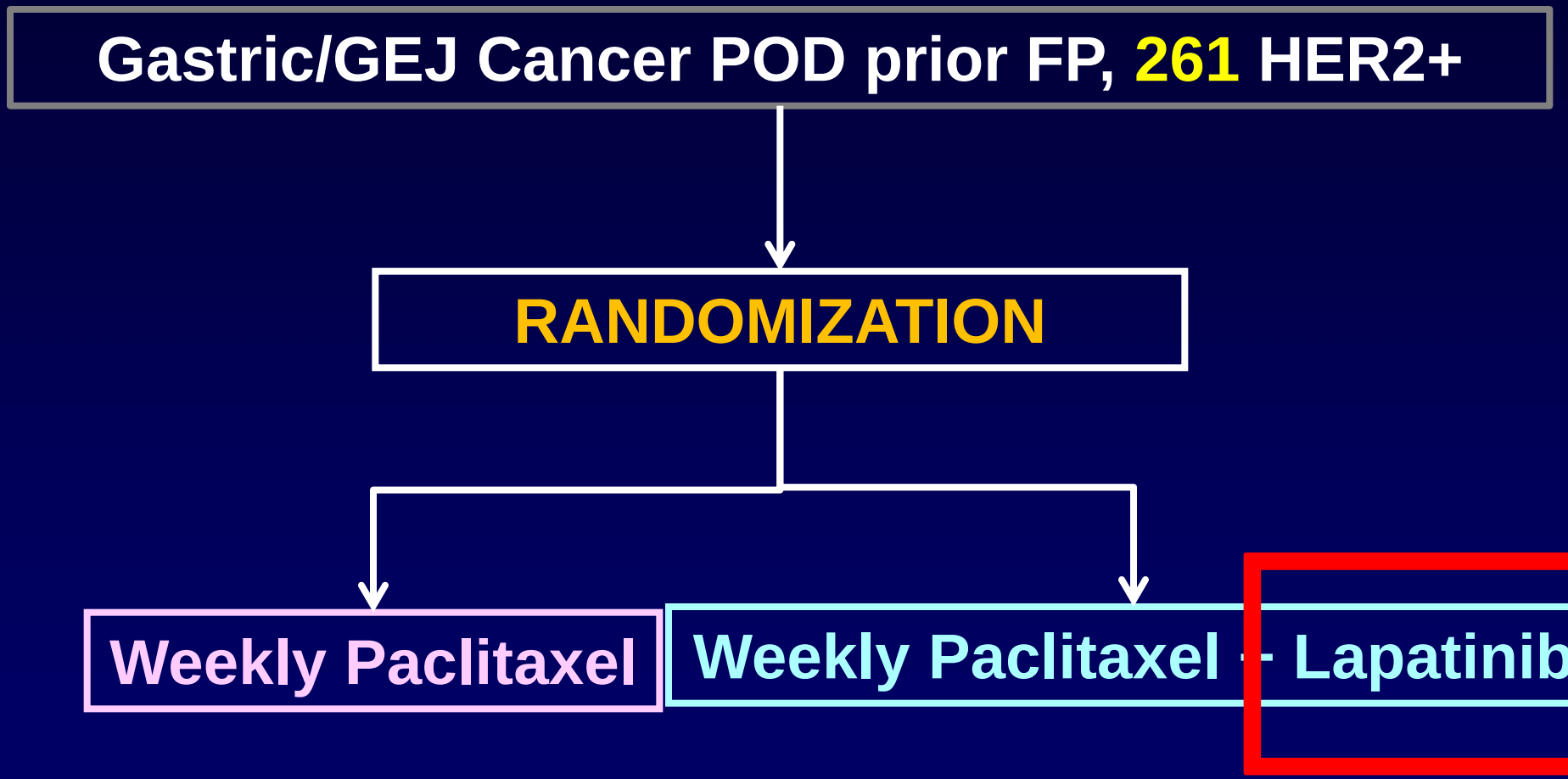
GATSBY ÇALIŞMASI: MİDE KANSRİNDE TRASTUZUMAB EMTAMSİNE

GATSBY: Adaptive Phase 2/3 Study
Design in Previously Treated HER2+ AGC



ClinicalTrials.gov Website [31]

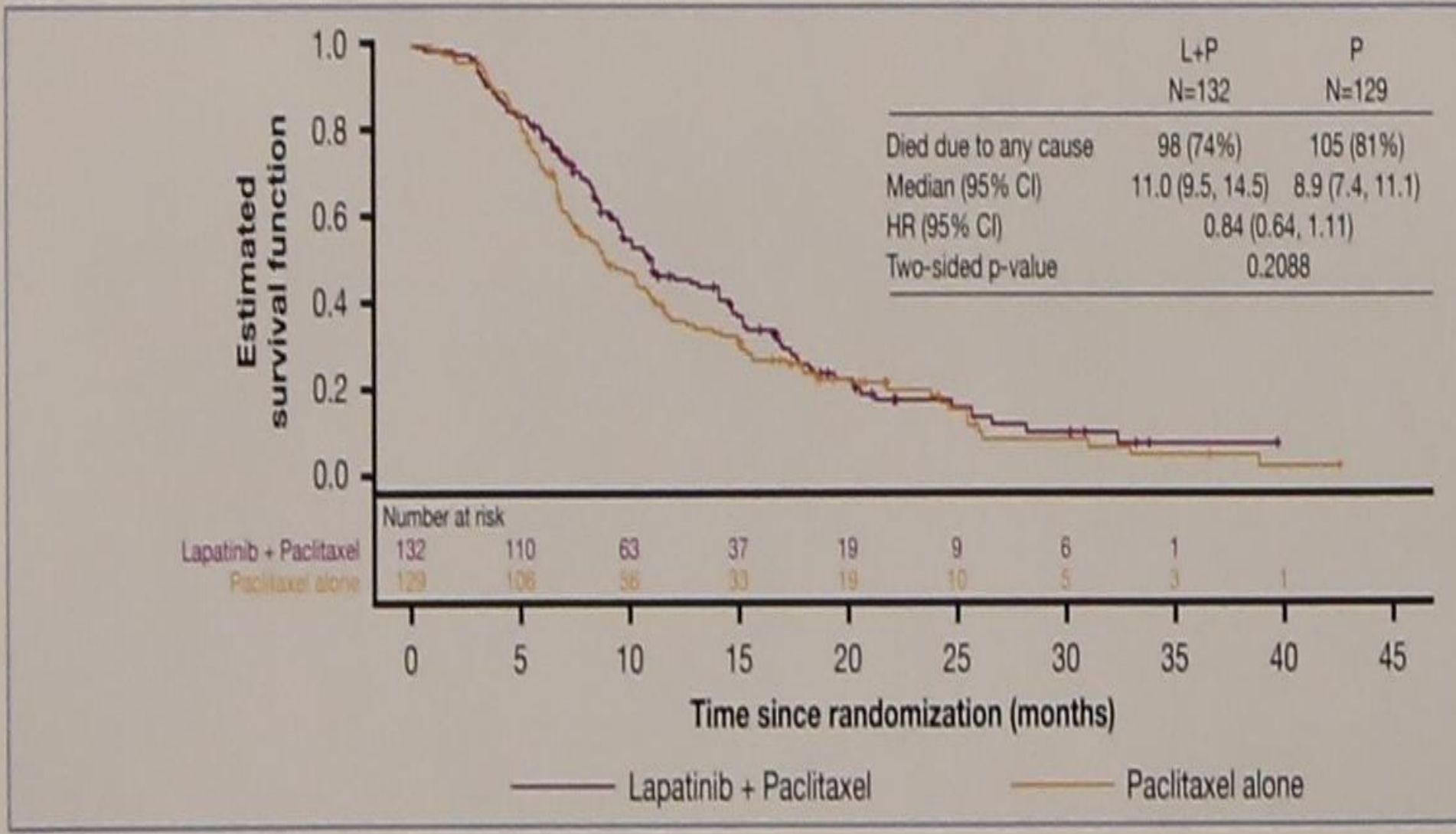
TYTAN Trial: Gastric Cancer



Bang YJ, et al. J Clin Oncol. 2012;30(15S): Abstract 11

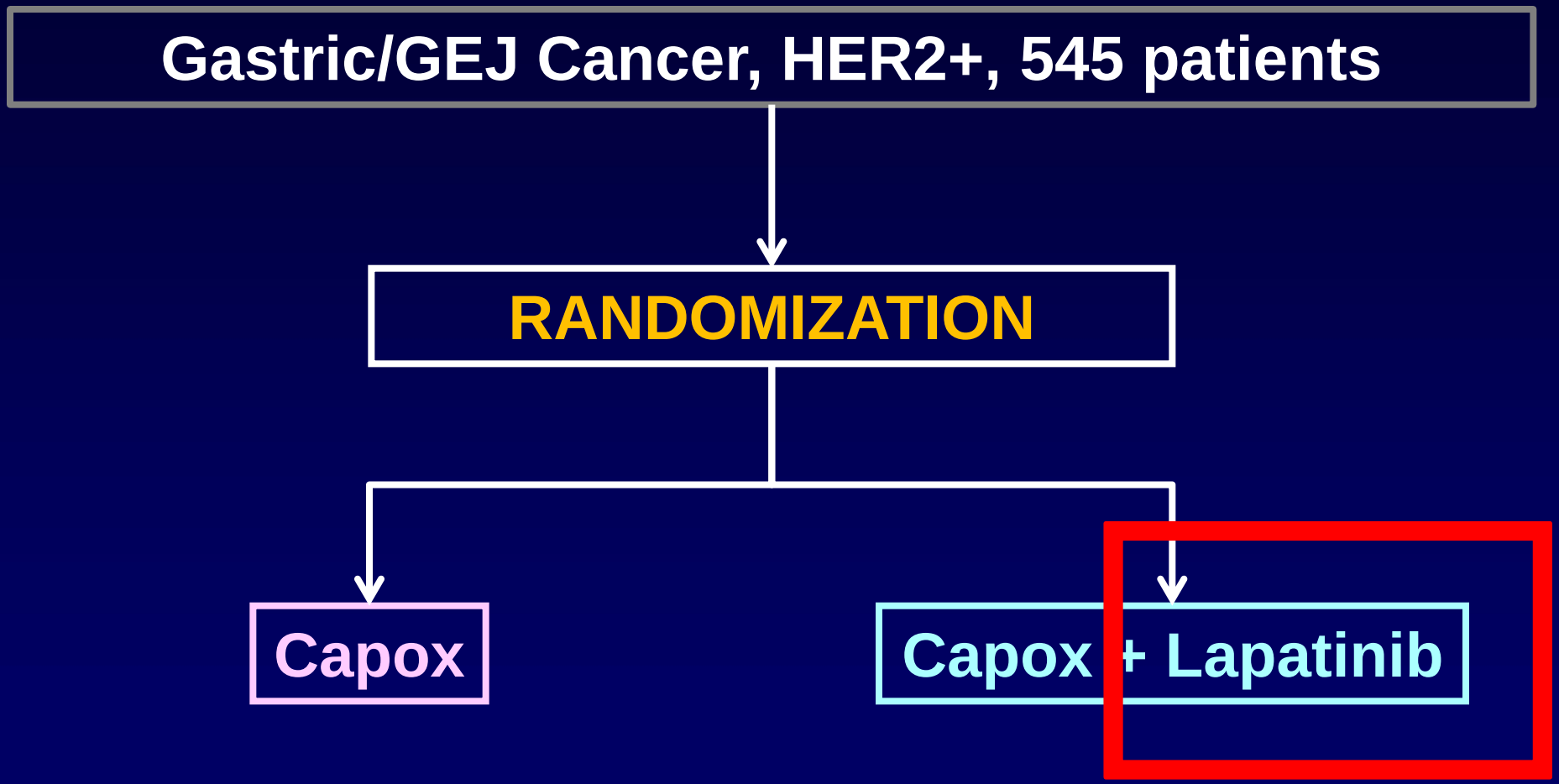
TYTAN Trial: OS

Figure 2. Plot of Kaplan-Meier OS curves (intent-to-treat [ITT] population)



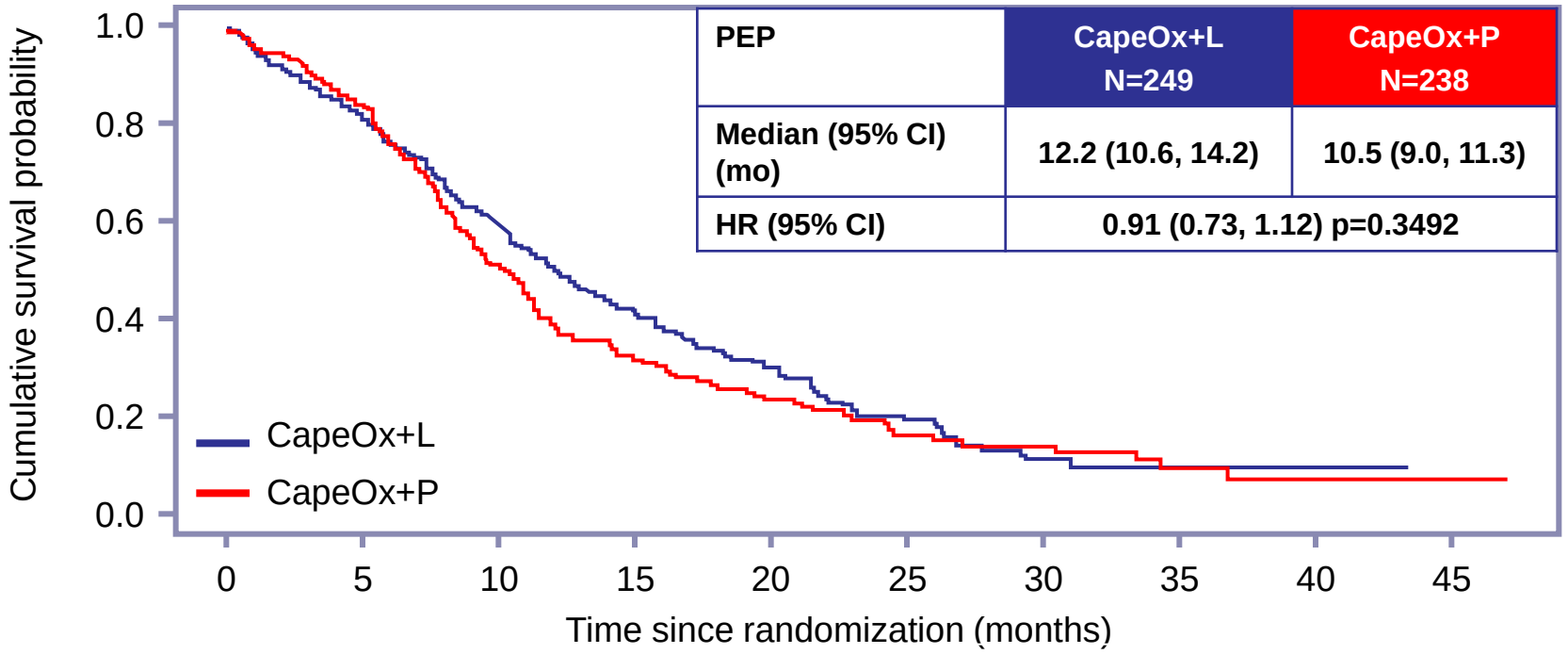
CI, confidence interval; HR hazard ratio

LOGIC Trial: Gastric Cancer



Hecht JR, et al. *J Clin Oncol.* 2013;31(Suppl):Abstract LBA4001

LOGIC Primary Endpoint: Overall Survival



PEP	CapeOx+L N=249	CapeOx+P N=238
Median (95% CI) (mo)	12.2 (10.6, 14.2)	10.5 (9.0, 11.3)
HR (95% CI)	0.91 (0.73, 1.12) p=0.3492	

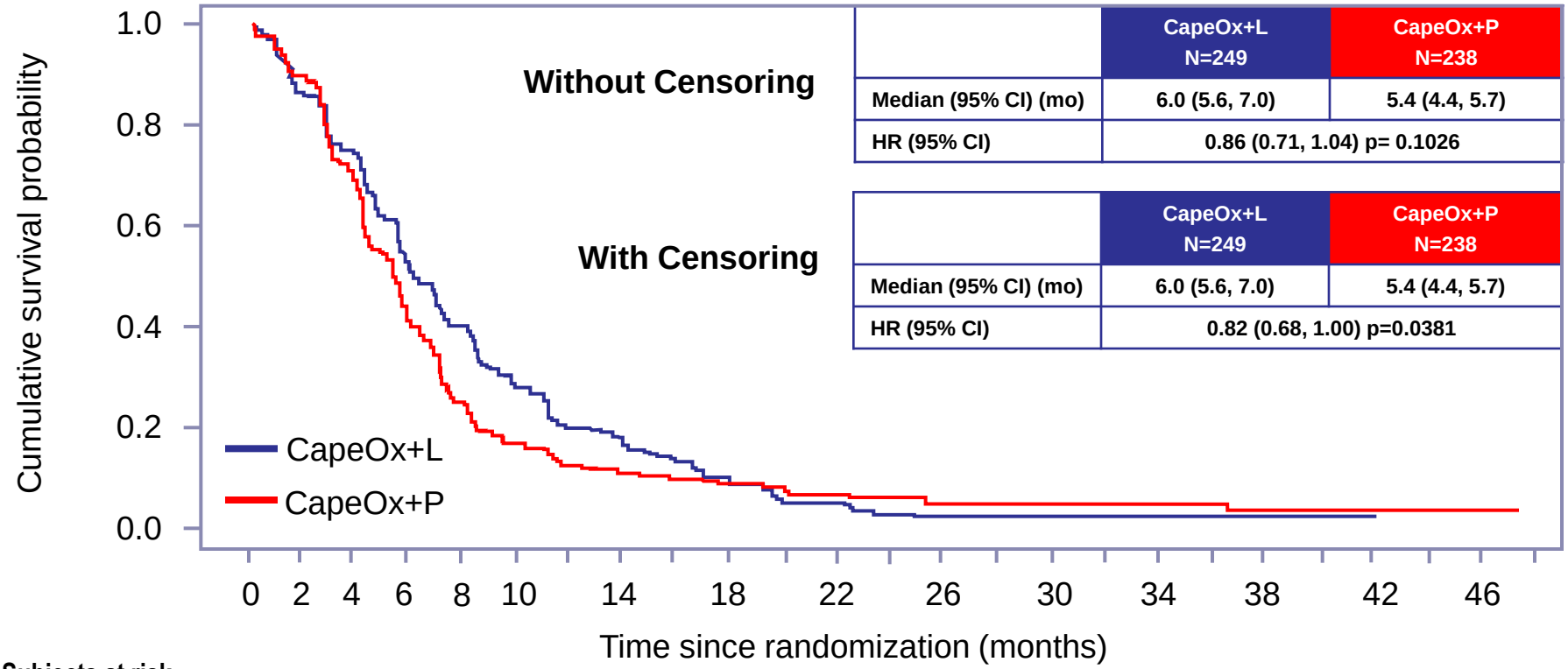
Subjects at risk

CapeOx+L	249	199	133	83	47	24	9	3	3	
CapeOx+P	238	189	106	53	34	17	11	7	2	2

ITT analysis HR 0.91

Presented at ASCO 2013

LOGIC Progression Free Survival (PFS)



	CapeOx+L N=249	CapeOx+P N=238
Median (95% CI) (mo)	6.0 (5.6, 7.0)	5.4 (4.4, 5.7)
HR (95% CI)	0.86 (0.71, 1.04) p= 0.1026	

	CapeOx+L N=249	CapeOx+P N=238
Median (95% CI) (mo)	6.0 (5.6, 7.0)	5.4 (4.4, 5.7)
HR (95% CI)	0.82 (0.68, 1.00) p=0.0381	

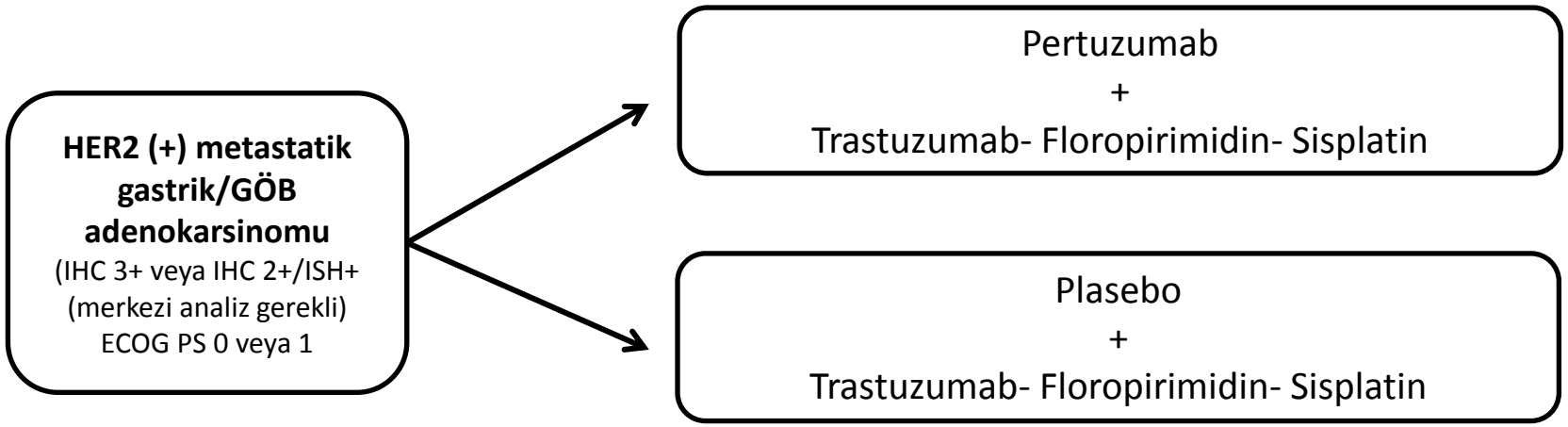
Subjects at risk

CapeOx+L	249	212	180	121	95	63	43	35	27	17	9	9	5	4	4	3	2	1	1	1	1	0	0	0	0
CapeOx+P	238	205	157	91	54	36	25	20	18	15	11	9	7	6	6	6	5	4	3	2	1	1	1	1	0

Note: The curve displayed represents data without censoring

JACOB Çalışması

HER-2 Pozitif metastatik gastroözafageal bileşke veya gastrik kanser hastalarında trastuzumab ve kemoterapi ile kombinasyon halinde verilen **pertuzumabın** *etkililiğinin ve güvenliliğinin değerlendirildiği randomize faz III çalışma*



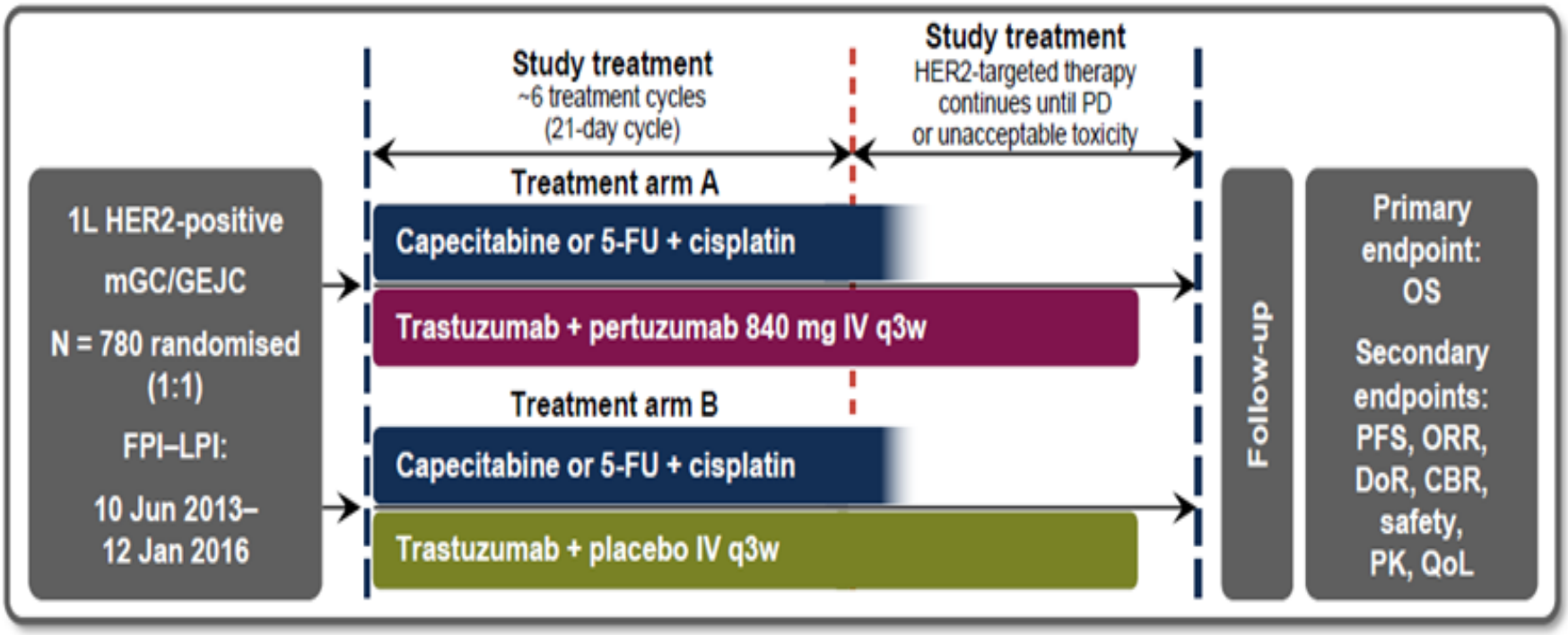
Primer sonlanım noktası: OS

Sekonder sonlanım noktaları: PFS, ORR, DoR, CBR, Güvenlilik, Farmakokinetik, QoL

Kapesitabin: Üç haftada bir 1-15 günler arası 2 dozda 1000 mg/m^2, 6 siklus
Florourasil: Üç haftada bir 800 mg/m^2/24 saat iv infüzyon (120 saat), 6 siklus
Sisplatin: Üç haftada bir 80 mg/m^2 , 6 siklus
Trastuzumab: 8 mg/kg yükleme; 6 mg/kg idamePertuzumab: Üç haftada bir 840 mg

www.clinicaltrials.gov/ NCT01774786

JACOB: Study design



Key eligibility criteria:
- HER2-positive mGC/GEJC
- IHC 3+ or IHC 2+ and ISH-positive (central testing required)
- ECOG PS 0 or 1

Stratification factors:
- Geographical region (Asia [excluding Japan], Japan, North America/Western Europe/Australia, South America/Eastern Europe)
- Prior gastrectomy (yes/no)
- HER2 IHC 3+ vs IHC 2+/ISH-positive

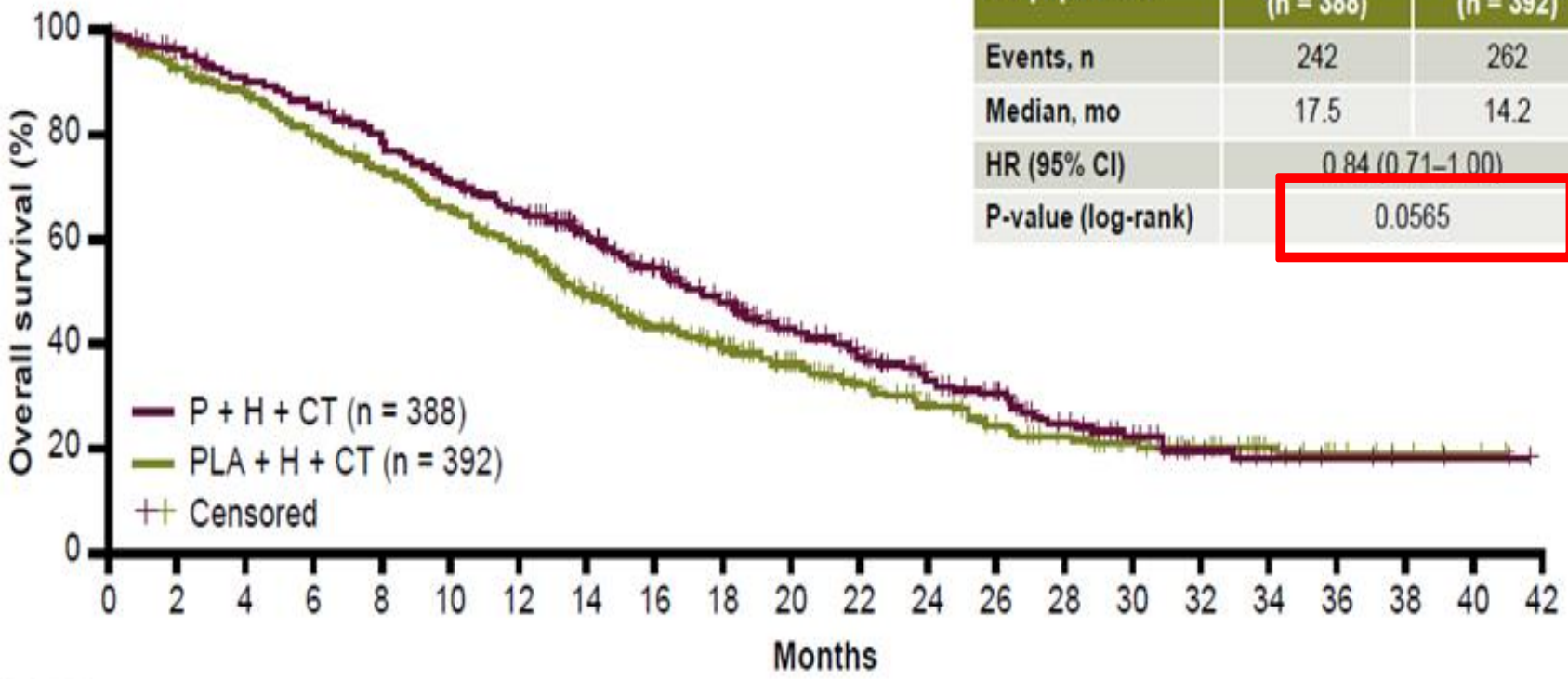
1L, first-line; 5-FU, 5-fluorouracil; CBR, clinical benefit rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FPI, first patient in; IHC, immunohistochemistry; ISH, in situ hybridisation; IV, intravenous; LPI, last patient in; mGC/GEJC, metastatic gastric or gastro-oesophageal junction cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; QoL, quality of life.

Tabernero J et al. 6160

Overall survival

16% reduction in risk of death and 3.3 month increase in median OS; did not reach statistical significance

ITT population	P + H + CT (n = 388)	PLA + H + CT (n = 392)
Events, n	242	262
Median, mo	17.5	14.2
HR (95% CI)	0.84 (0.71–1.00)	
P-value (log-rank)	0.0565	



No. at risk

P + H + CT 388	363	342	323	297	266	243	209	175	149	114	92	67	54	36	27	16	10	6	4	3
PLA + H + CT 392	359	339	306	279	252	221	175	143	118	95	76	60	47	38	31	23	14	7	4	2

Stratified HR.
Median duration of survival follow-up: P + H + CT = 24.4 months (min–max, 22.3–26.1); PLA + H + CT = 25.0 months (min–max, 22.3–28.9).
CI, confidence interval; CT, chemotherapy; H, trastuzumab; HR, hazard ratio; P, pertuzumab; PLA, placebo.

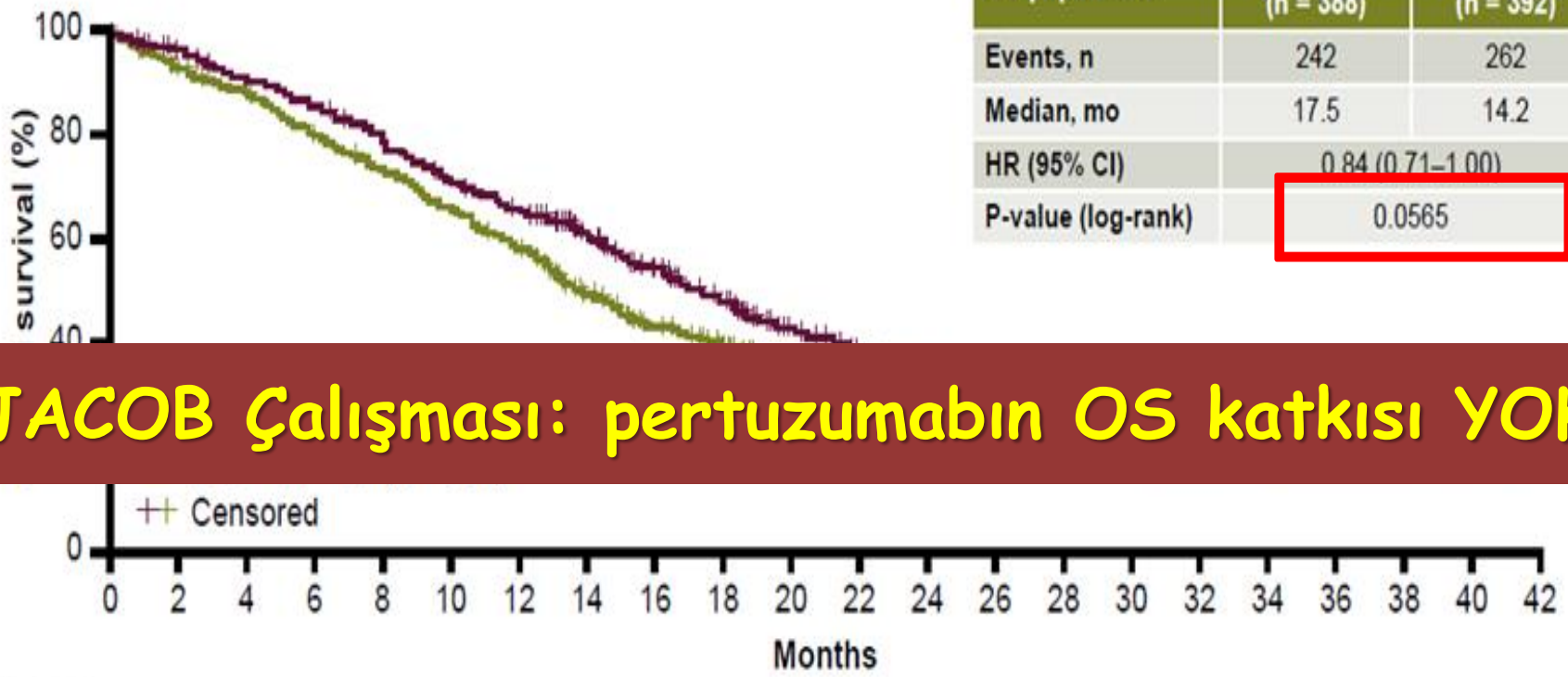
MADRID 2017 ESMO congress

Tabernero J et al. 6160

Overall survival

16% reduction in risk of death and 3.3 month increase in median OS; did not reach statistical significance

ITT population	P + H + CT (n = 388)	PLA + H + CT (n = 392)
Events, n	242	262
Median, mo	17.5	14.2
HR (95% CI)	0.84 (0.71–1.00)	
P-value (log-rank)	0.0565	



JACOB Çalışması: pertuzumabın OS katkısı YOK !!

No. at risk

P + H + CT 388	363	342	323	297	266	243	209	175	149	114	92	67	54	36	27	16	10	6	4	3
PLA + H + CT 392	359	339	306	279	252	221	175	143	118	95	76	60	47	38	31	23	14	7	4	2

Stratified HR.
Median duration of survival follow-up: P + H + CT = 24.4 months (min–max, 22.3–26.1); PLA + H + CT = 25.0 months (min–max, 22.3–28.9).
CI, confidence interval; CT, chemotherapy; H, trastuzumab; HR, hazard ratio; P, pertuzumab; PLA, placebo.

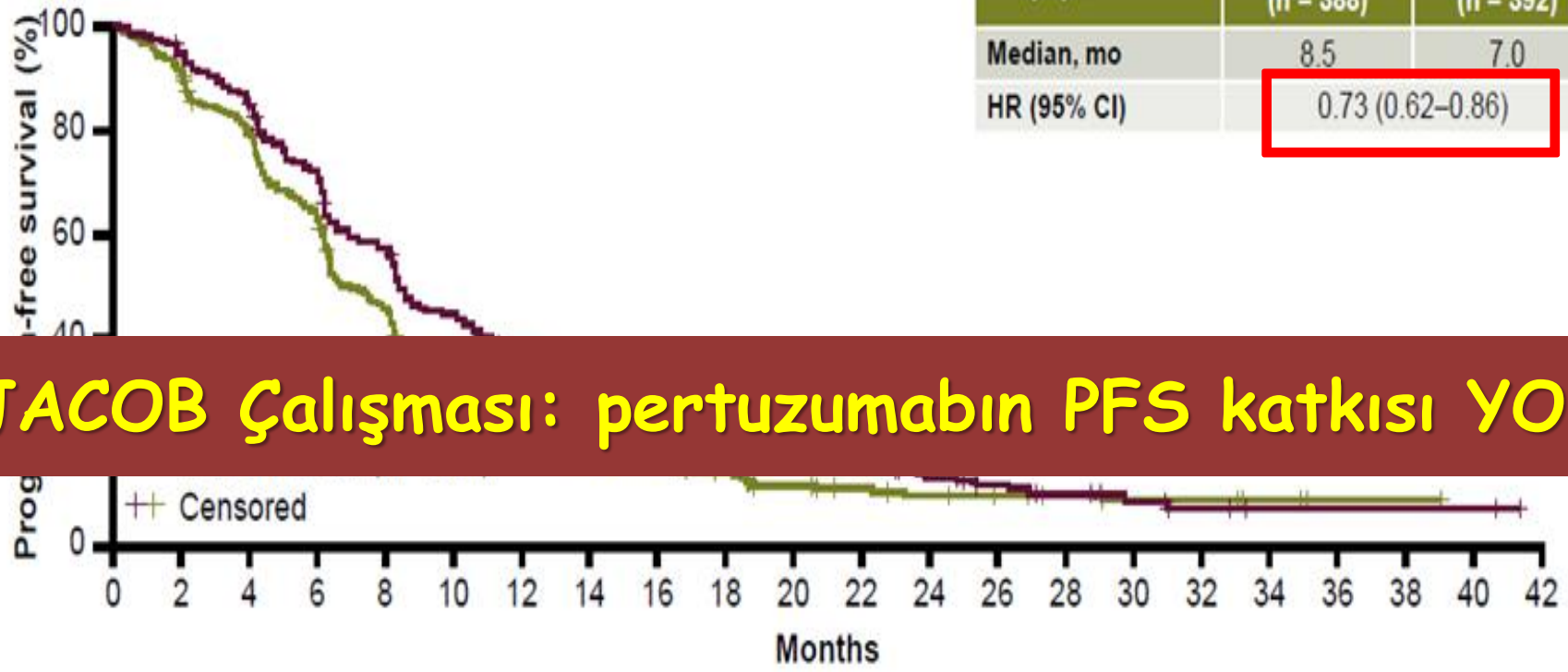
MADRID 2017 ESMO congress

Tabernero J et al. 6160

Progression-free survival

27% reduction in risk of progression or death;
cannot conclude statistical significance due to hierarchical testing

ITT population	P + H + CT (n = 388)	PLA + H + CT (n = 392)
Median, mo	8.5	7.0
HR (95% CI)	0.73 (0.62–0.86)	



JACOB Çalışması: pertuzumabın PFS katkısı YOK !!

No. at risk

P + H + CT 388	354	320	267	213	165	135	104	80	67	50	36	26	18	14	7	4	2	2	2	2
PLA + H + CT 392	349	301	242	172	120	85	67	51	35	27	21	17	15	12	8	7	4	1	1	

Stratified HR. Progression-free survival was investigator-assessed.
CI, confidence interval; CT, chemotherapy; H, trastuzumab; HR, hazard ratio; P, pertuzumab; PLA, placebo.

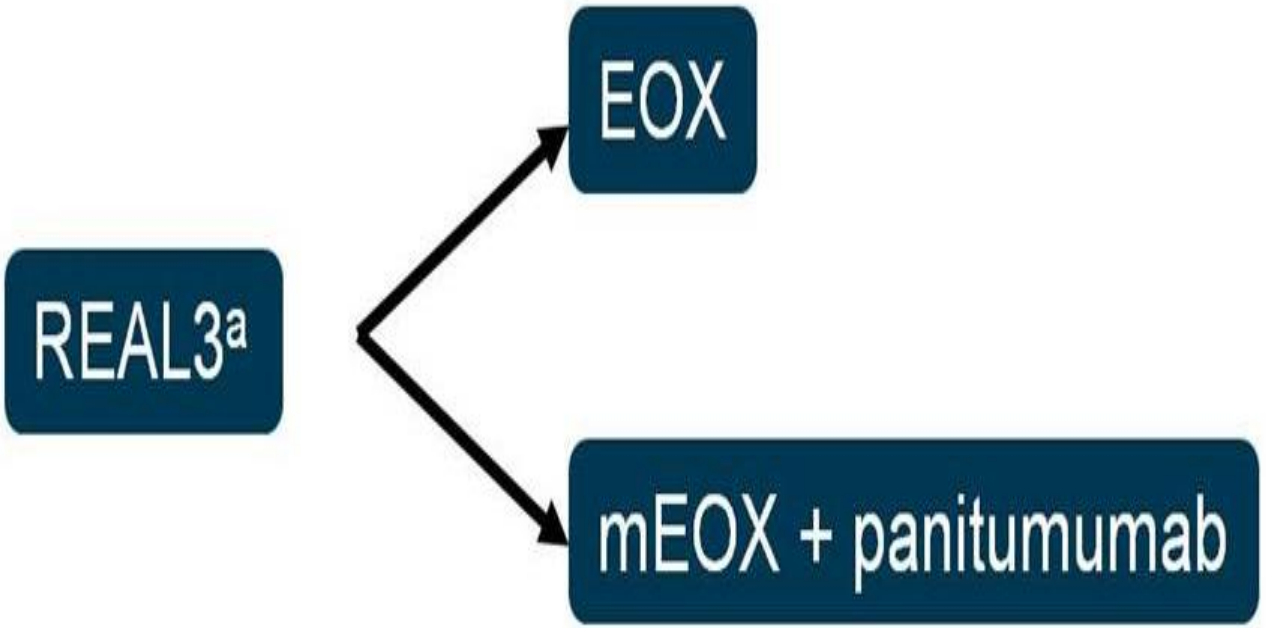
MADRID 2017 ESMO congress

Tabernero J et al. 6160

Mide Ca: EGFR İnhibitörleri ???

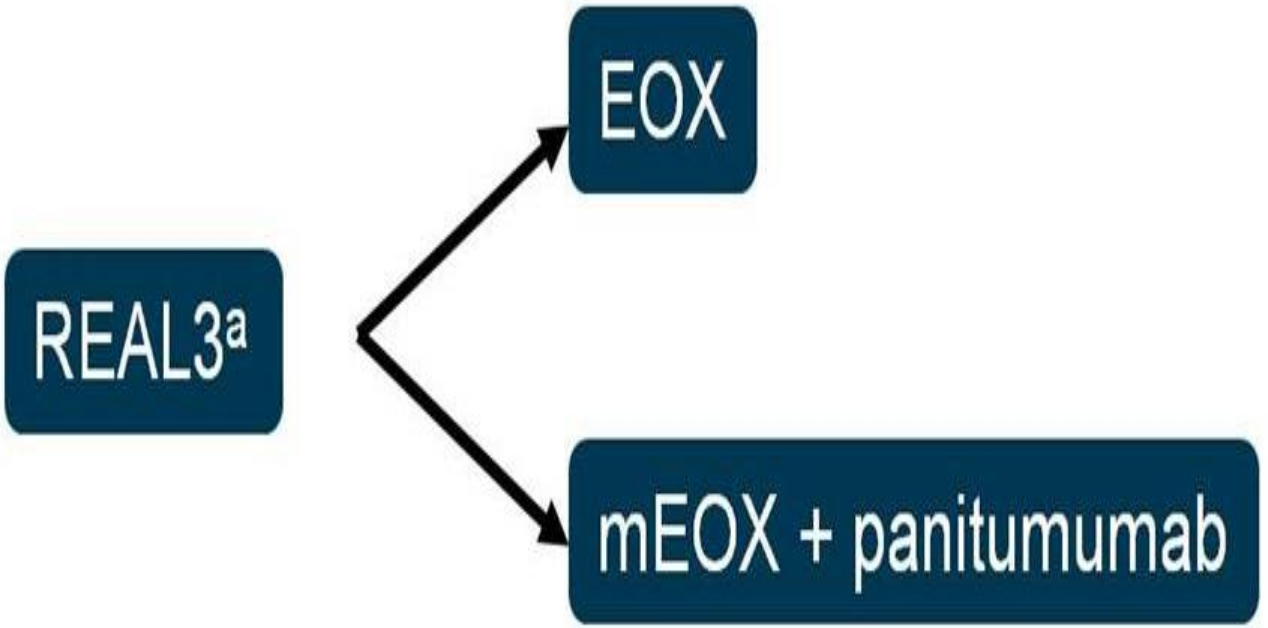
- Panitumumab
- Setuksimab

FAZ 3 -REAL3 Çalışması: Mide Ca'da Setuksimabın katkısı ???



Waddell TS et al. JCO, 2012

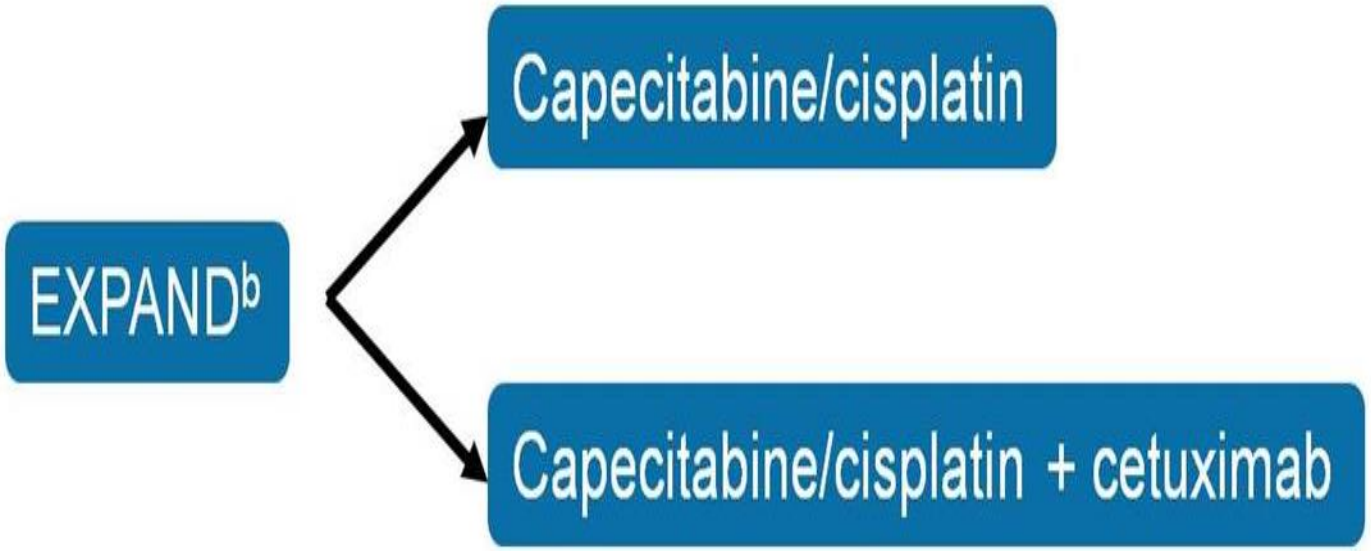
FAZ 3 -REAL3 Çalışması: Mide Ca'da Setuksimabın katkısı ???



REAL3 Çalışması: panitumumabın OS katkısı YOK !!

Waddell TS et al. JCO, 2012

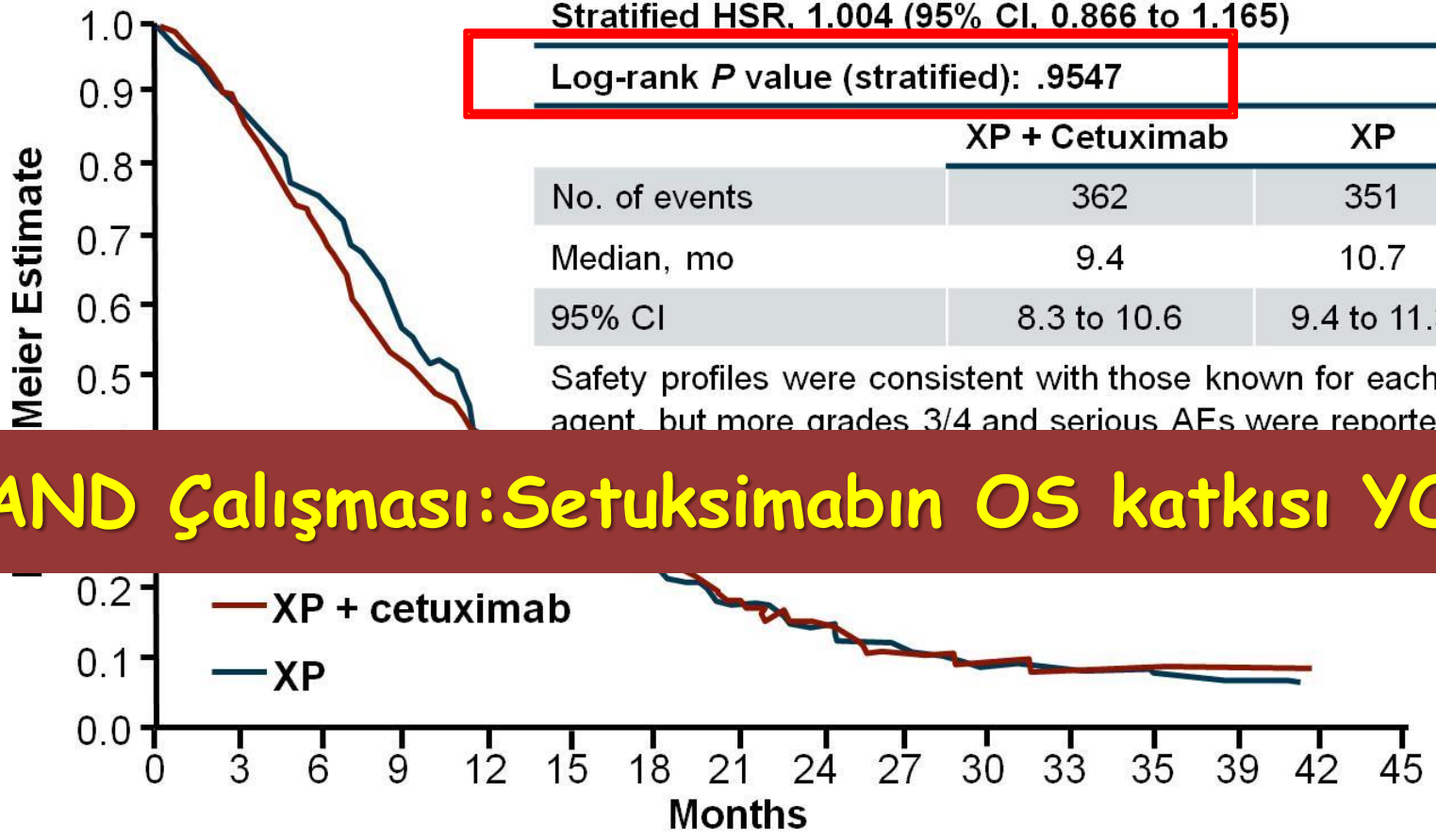
EXPAND Çalışması: Mide Ca'da Setuksimabın katkısı ?????



a. Waddell TS, et al. *J Clin Oncol*. 2012;30.[33]

b. Lordick F, et al. ESMO 2012 Congress. Abstract LBA3.[34]

EXPAND Study: OS



Stratified HSR, 1.004 (95% CI, 0.866 to 1.165)

Log-rank *P* value (stratified): .9547

	XP + Cetuximab	XP
No. of events	362	351
Median, mo	9.4	10.7
95% CI	8.3 to 10.6	9.4 to 11.3

Safety profiles were consistent with those known for each agent, but more grades 3/4 and serious AEs were reported

EXPAND Çalışması:Setuksimabın OS katkısı YOK !!

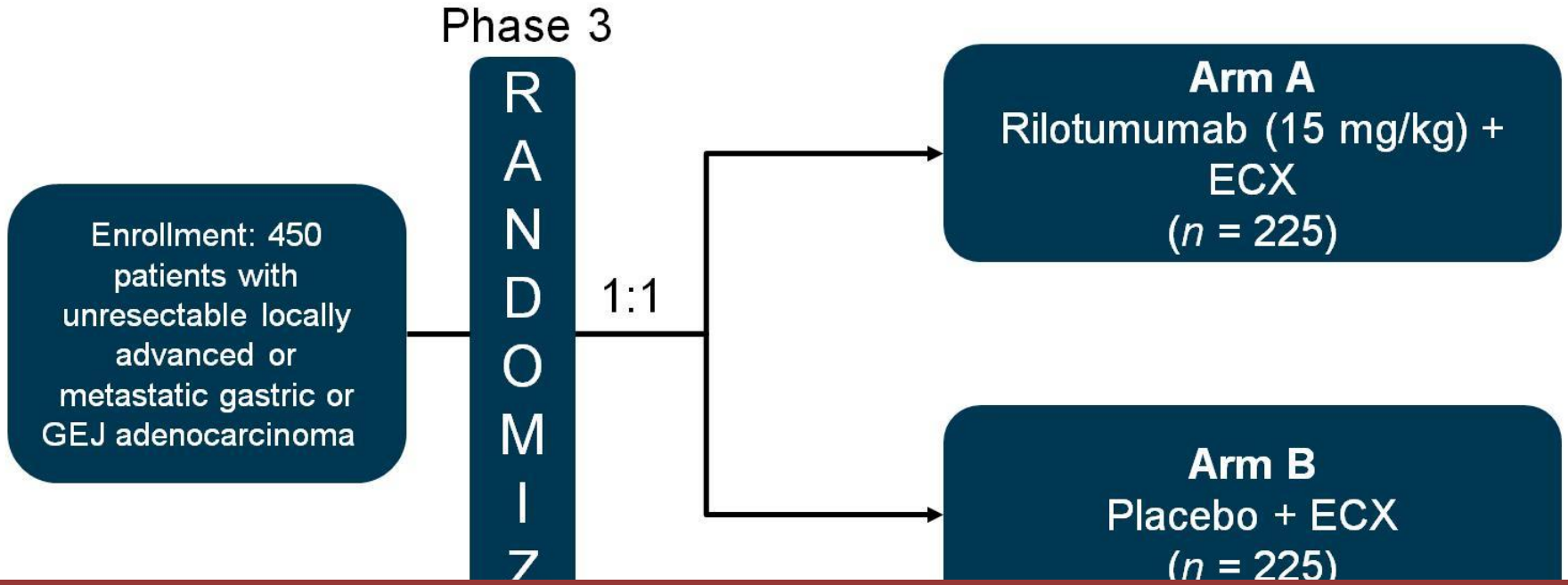
XP + cetuximab	455	382	298	224	171	129	91	51	27	16	14	12	5	2	1	0
XP	449	379	314	238	169	119	77	39	26	18	15	14	5	1	0	0

XP = capecitabine and cisplatin.

Lordick F, et al. ESMO Congress 2012. Abstract LBA3.[34]

Rilotumumab in Gastric Cancer

Phase 3: RILOMET



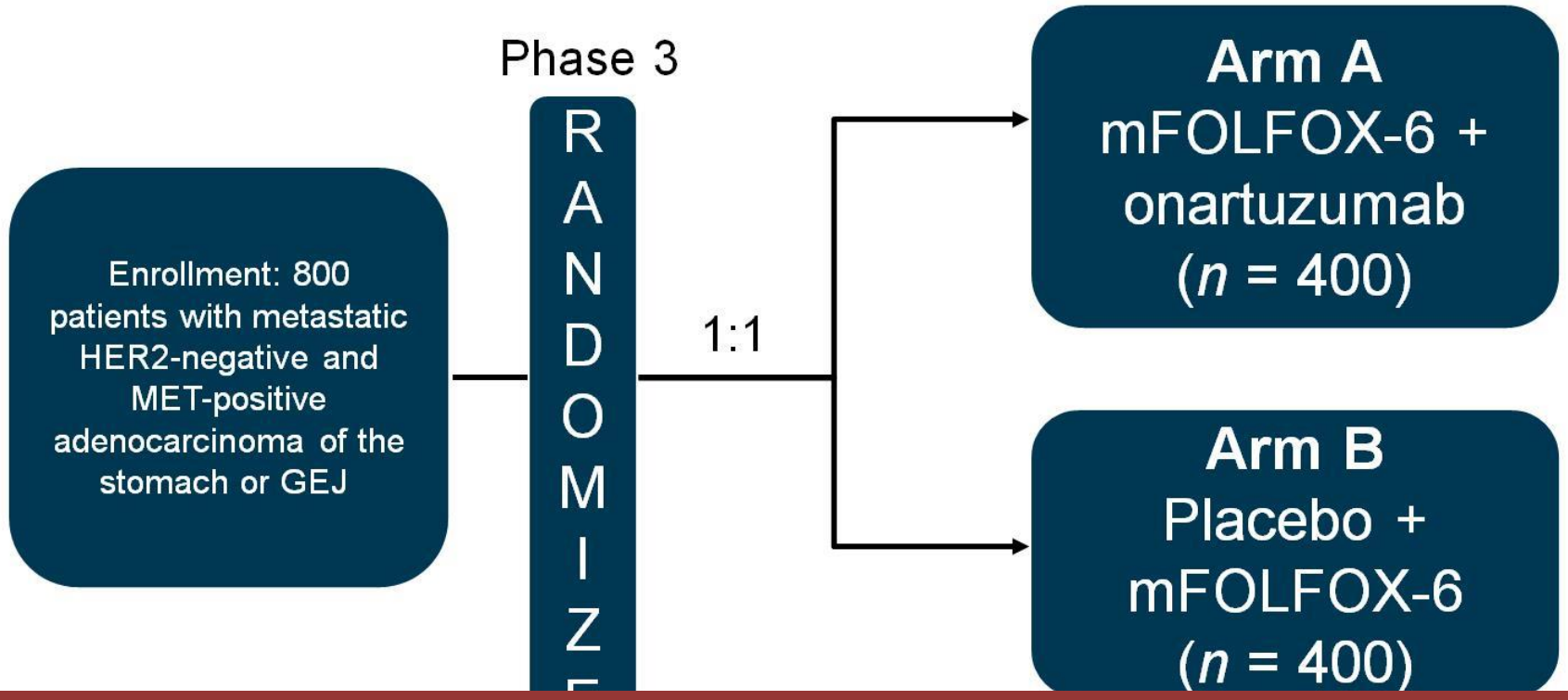
Rilotumumabın OS katkısı YOK !!

Stratification Factors
ECOG PS 0 vs 1
LA vs Metastatic
Tumor MET-positive on IHC
Her2 negative

E: Epirubicin: 50 mg/m^2 IV, day 1
C: Cisplatin: 60 mg/m^2 IV, day 1
X: Capecitabine: 625 mg/m^2 BID orally, days 1 to 21

Cunningham D, et al. *J Clin Oncol*. 2013.[12]

Onartuzumab: METGASTRIC



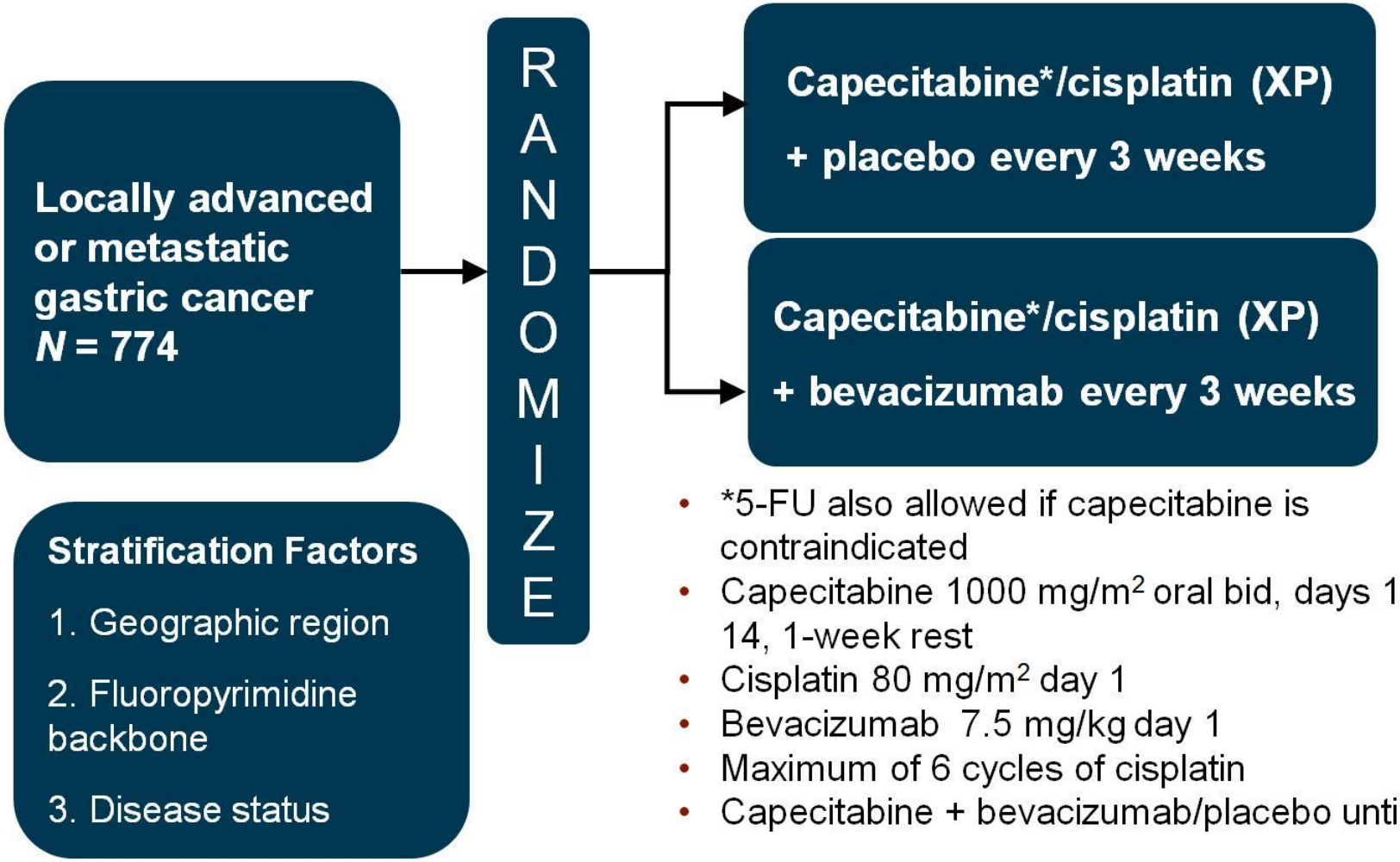
Metgastric Çalışması: Onartuzumabın OS katkısı YOK !!

Stratification Factors
Tumor classified as **both** HER2 negative **and** MET positive

- Maximum of 12 cycles of mFOLFOX-6

Cunningham D, et al. *J Clin Oncol*. 2013.[13]

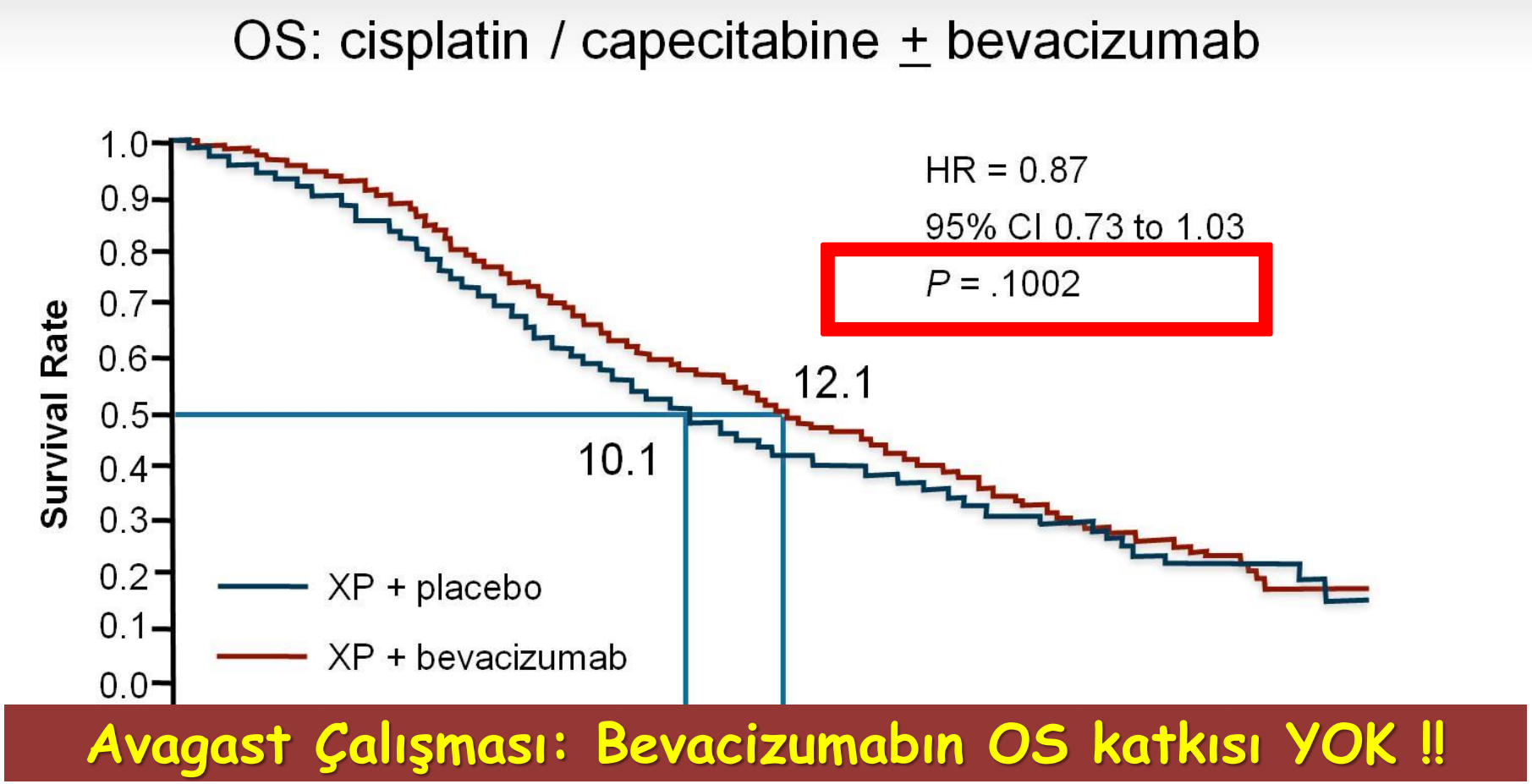
AVAGAST: A Randomized Double-blind Placebo-controlled Phase 3 Study



*Starting dose of bevacizumab/placebo: 30 minutes, subsequent doses: 15 minutes.

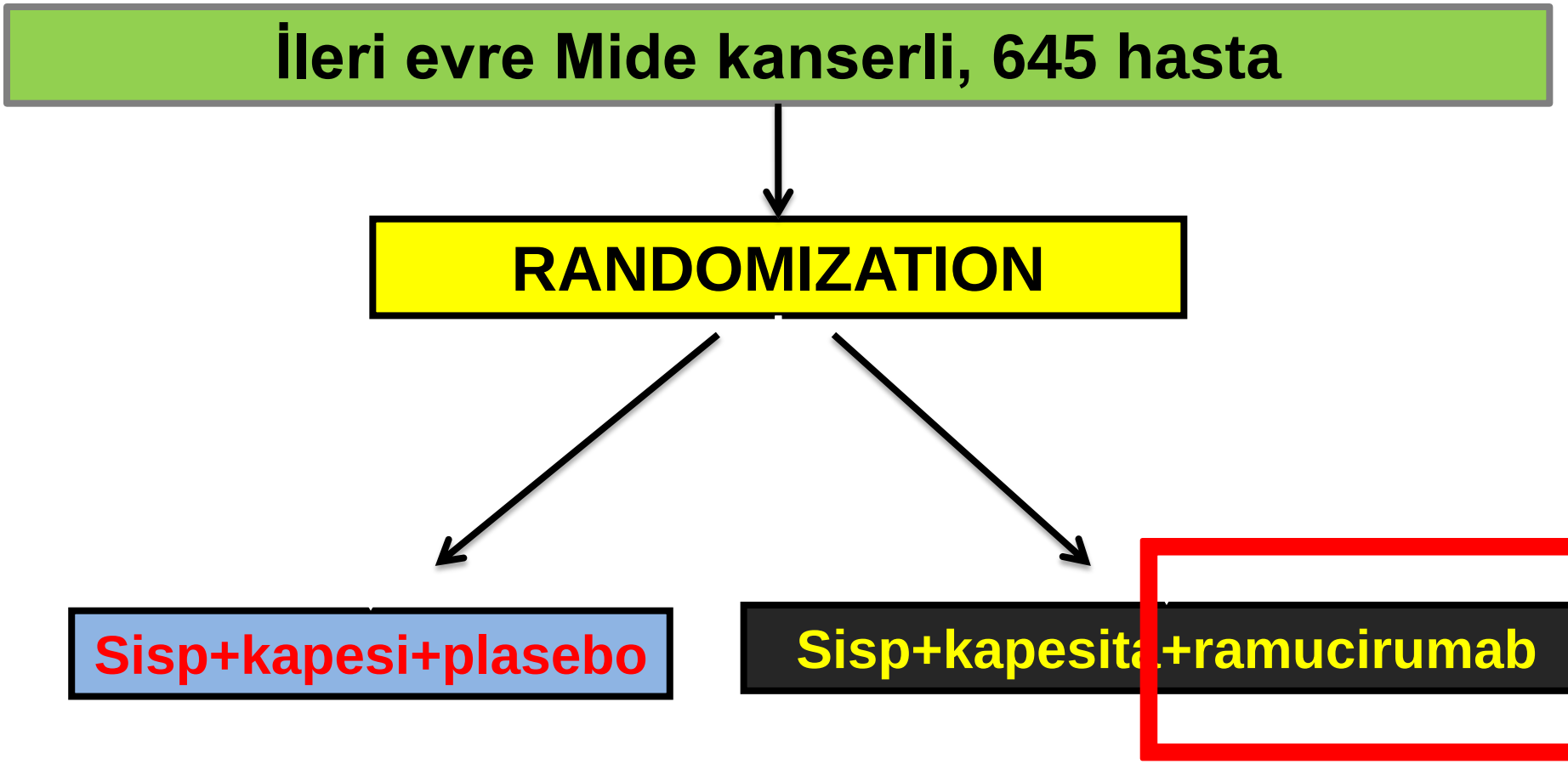
Shah MA, et al. *J Clin Oncol*. 2012;30[43]

AVAGAST: OS



Shah MA, et al. *J Clin Oncol*. 2012;30[43]; figure courtesy of Manish A. Shah, MD.

RAİNFALL Trial: 1.Basamakta Ramucirumab



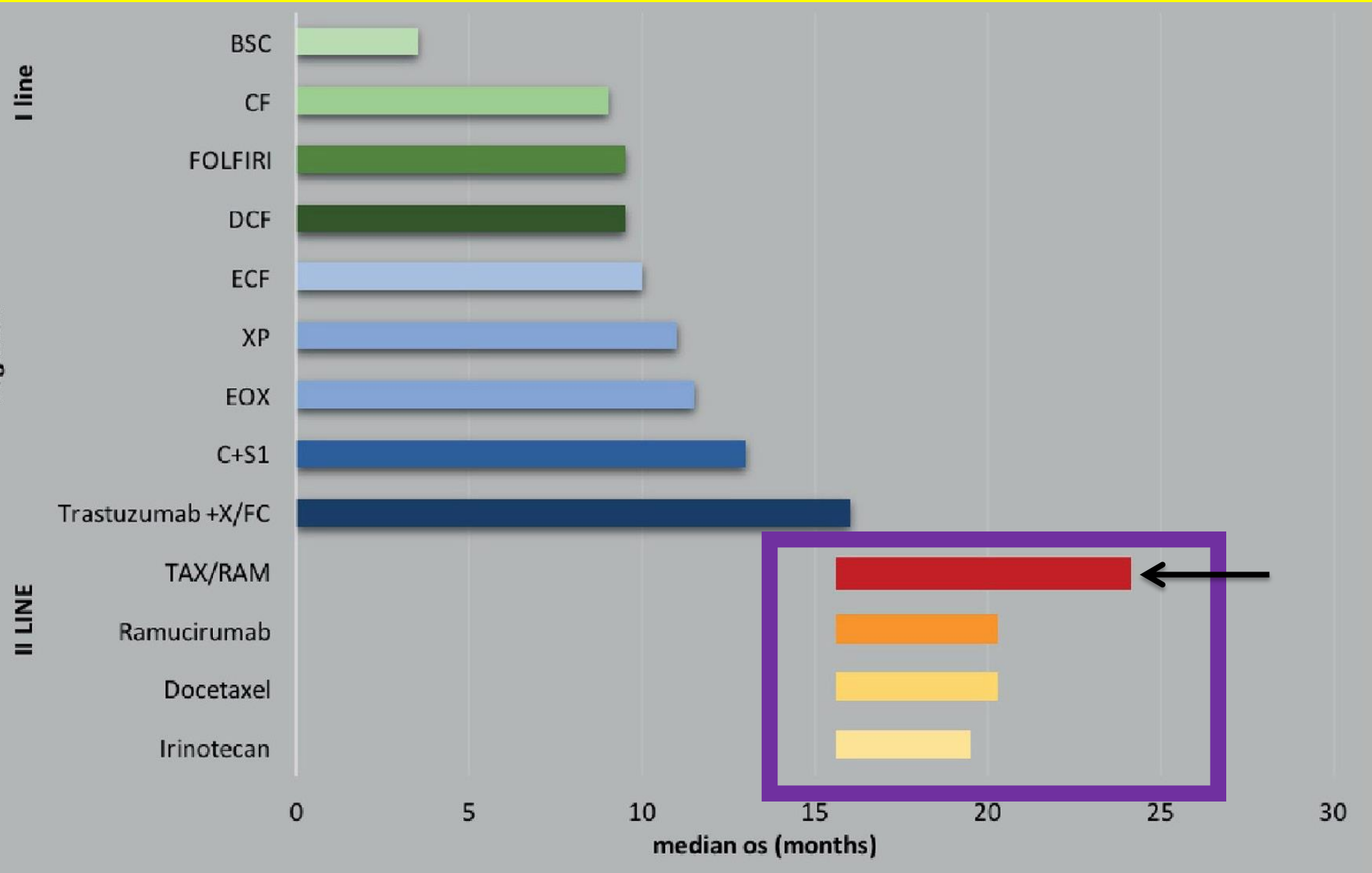
RAİNFALL Sonuçlar

- Çalışma, **Primer sonlanım noktası** olan PFS yi karşıladı.
- Median PFS için Hazard oranı 0,75 (p= 0,011)
- Median PFS, 5.72 aya karşılık 5,39 ay, 9 gün !!!
- **Median Genel sağkalım 11,7 aya karşılık 10,74 ay Hazard oran 0,96, (p=0,68) !!!!!**
- **ORR %41 vs %36, fark yok**

Araştırmacının Yorumu: güncel partiğimizi değiştirmeyecek

MİDE KANSERİNDE 2. BASAMAK TEDAVİNİN SAĞKALIMA KATKISI VAR MI ?

Median OS by chemotherapy regimen in the first- and the second-line setting for advanced gastric cancer



Mide Kanserinde 2. Basamak Tedavi

Table 2 Major randomised phase III trials of second-line treatments in advanced gastric cancer.

Trial	Study intervention	Number of patients	Median PFS (months)	Median OS (months)	Grade ≥3 AEs in the experimental arm
AIO*	Irinotecan + BSC vs BSC	40	2.6 vs NR	4.0 vs 2.4 HR 0.48, p=0.012	Diarrhoea 26%, leucopenia 21%, febrile neutropenia 16%
Kang *et al*[14]	Docetaxel or irinotecan vs BSC	202	NR	5.3 vs 3.8 HR 0.65, p=0.007†	Anaemia 31%, fatigue 18%, neutropenia 17%
WJOG 4007[48]	Paclitaxel vs irinotecan	219	3.6 vs 2.3	9.5 vs 8.4 HR 1.13, p=0.38	Neutropenia 39.1%, anaemia 30%, anorexia 17.3%
COUGAR-02[15]	Docetaxel + BSC vs BSC	168	NR	5.2 vs 3.6 HR 0.67, p=0.01	Neutropenia 15%, infection 19%, febrile neutropenia 7%
REGARD[16]	Ramucirumab + BSC vs BSC	355	2.1 vs 1.3	5.2 vs 3.8 HR 0.77, p=0.047	Hypertension 8%, fatigue 6%, abdominal pain 6%
RAINBOW[17]	Ramucirumab + paclitaxel vs paclitaxel	665	4.4 vs 2.8	9.6 vs 7.4 HR 0.87, p=0.017	Neutropenia 41%, leucopenia 17%, hypertension 14%

*Prematurely closed due to poor patients accrual.

†No OS difference between docetaxel (5.2 moths) and irinotecan (6.5 months).

AIO, Arbeitsgemeinschaft Internistische Onkologie; AE: adverse event; BSC: best supportive care; NR: not reported.

Mide Kanserinde 2. Basamak Tedavi: everolimus

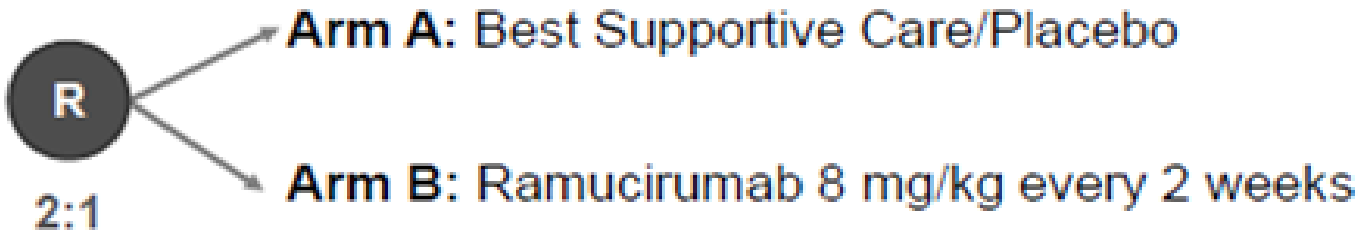
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Gastric cancer: Second line chemotherapy trials comparing BSC versus active treatment

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	Gain in median survival
Thuss-Patience, et al.[1]	2011	40 1:1	Irinotecan	0.48	0.0023	2.4 months
Kang, et al.[2]	2012	193 2:1	Irinotecan Docetaxel	0.65	0.004	1.3 months
Ford, et al.[3]	2014	168 1:1	Docetaxel	0.67	0.01	1.6 months
Otshu, et al[4]	2013	656 2:1	Everolimus	0.90	0.124	0.9 months
Fuchs, et al[5]	2014	355 2:1	Ramucirumab	0.77	0.047	1.4 months

1. Thuss-Patience PC, et al. Eur J Cancer 2011;47:2306–2314. 2. Kang JH, et al. J Clin Oncol 2012;30:1513–1518.
3. Ford HE, et al. Lancet Oncol 2014;15:78–86. 4. Otshu A. et al. J Clin Oncol 2013;31:3935–3943. 5. Fuchs CS, et al. Lancet

Mide Kanseri 2. Basamak Tedavi REGARD çalışması, Ramucirumab VS BSC

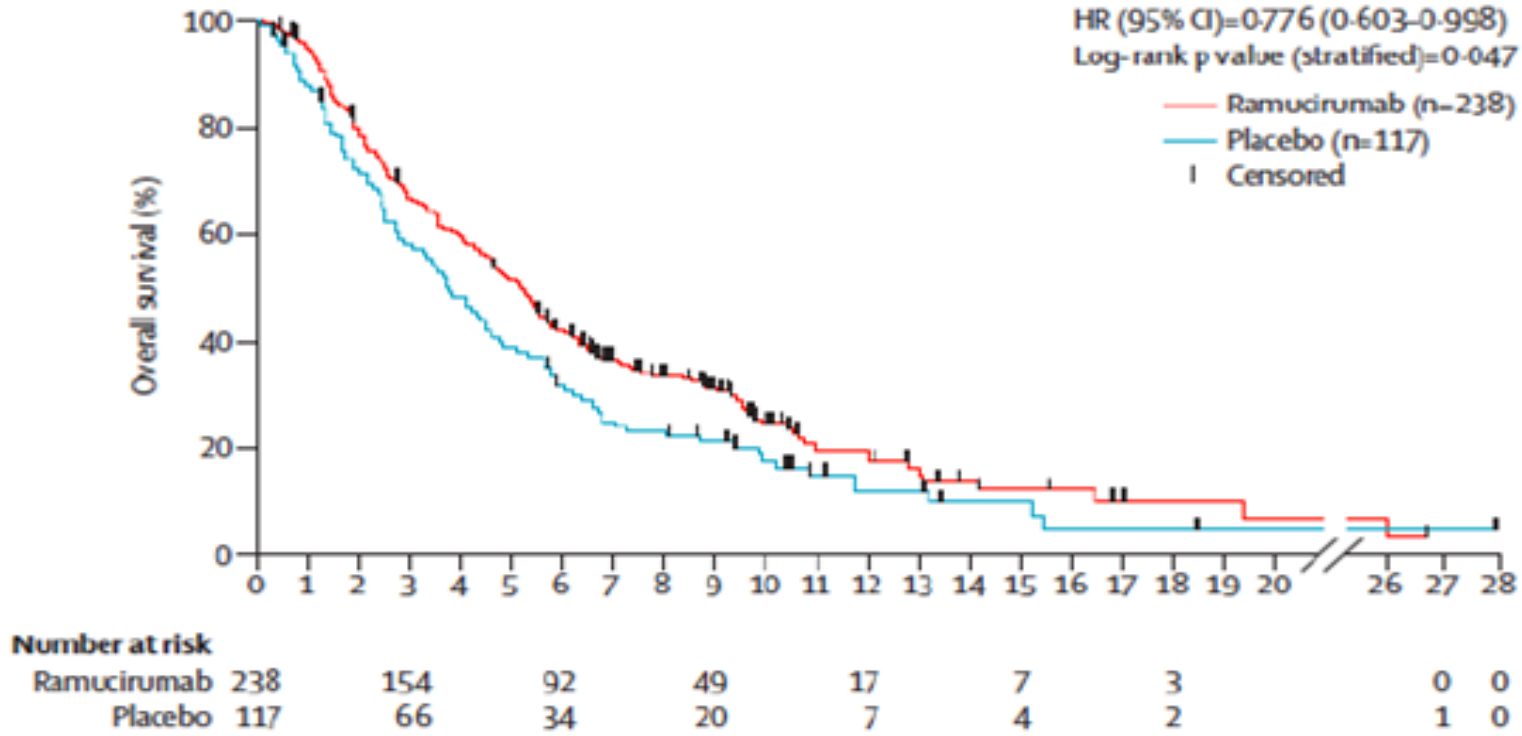


Main aim: Overall survival

- Stratification by:
  - Weight Loss: < or > 10%
  - Site: Oesophagus *vs.* junction *vs.* gastric
  - Geographic region
- 615 patients needed to show a HR of 0.71 in favour of ramucirumab with two-sided alfa 0.05 and 90% power

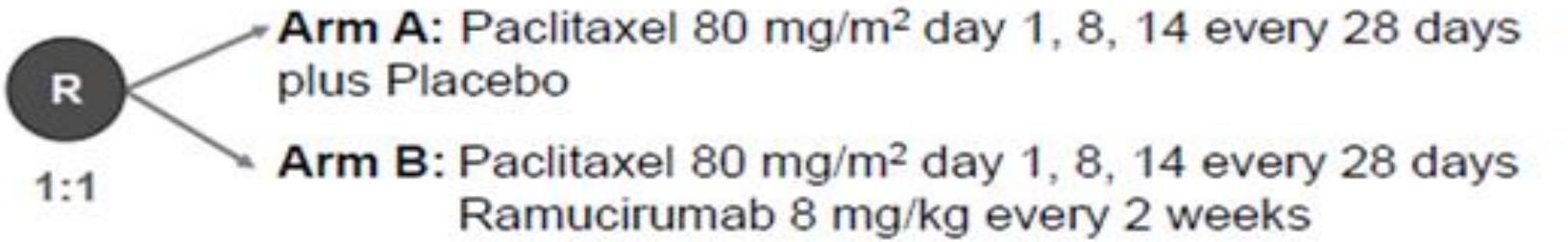
Fuchs CS, *et al.* Lancet 2014;383:31–39.

REGARD çalışması, Ramucirumab VS BSC
Ramucirumab ile OS avantajı sağlanıyor



Reprinted from Fuchs CS, *et al.* Lancet Oncol 2014;383:31–39; © (2005) with permission from Elsevier

2. Basamak Tedavide Tek ajan aktif tedavi ile Aktif Ajan + Monoklonal Ab karşılaştıran Çalışma, RAİNBOW Study

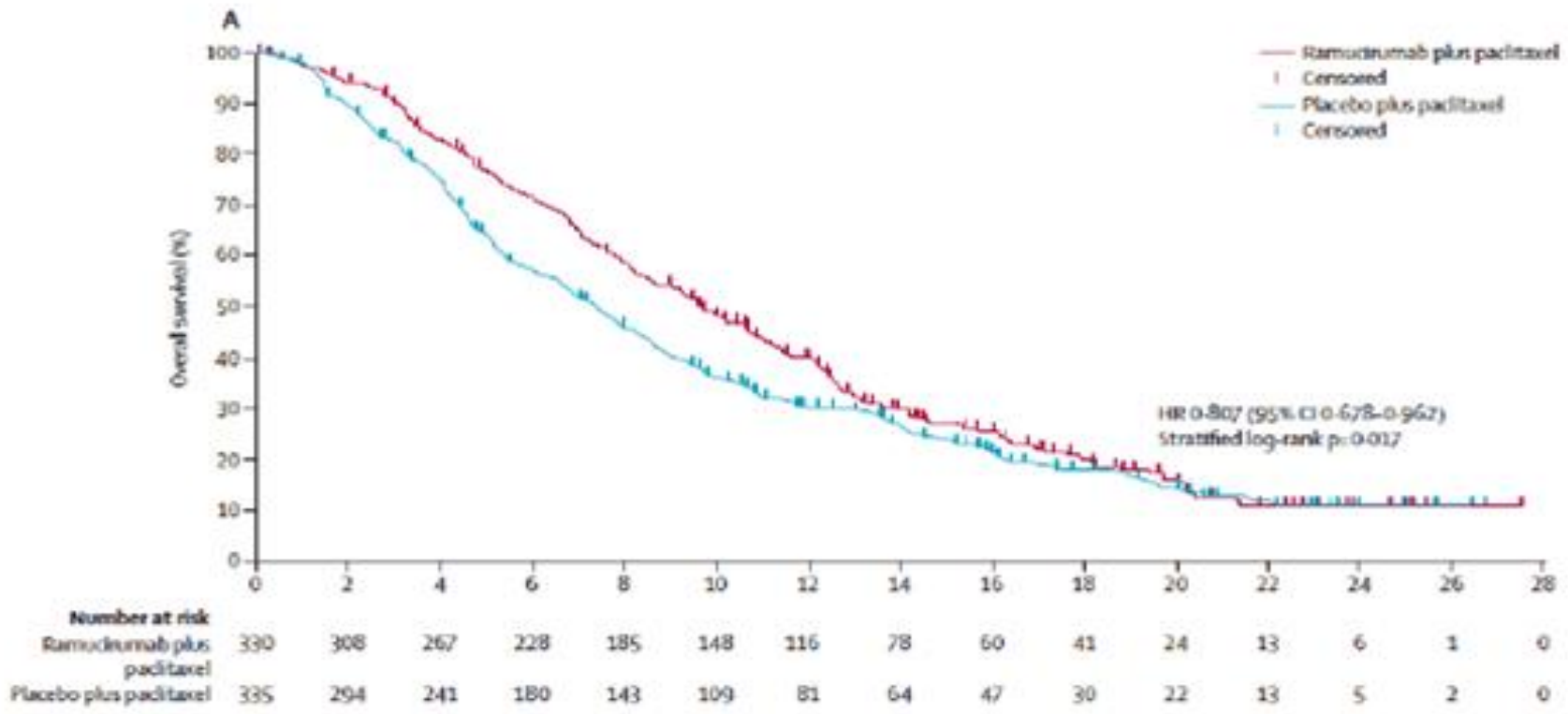


Main aim: Overall survival

- Stratification by:
  - Measurable *vs.* non-measurable
  - Time to progression after first line: < or > 6 month
  - Geographic region
- 663 patients needed to show a HR of 0.75 in favour of paclitaxel+ramucirumab with two-sided alfa 0.05 and 90% power

Wilke HJ, *et al.* Lancet Oncol 2014;15:1224–1235.

RAİNBOW Study, Pakli+Ramucirumab lehine OS avantajı !!!!



Wilke HJ, *et al.* Lancet Oncol 2014;15:1224–1235; © (2005) with permission from Elsevier

MİDE KANSERİNDE 3. BASAMAK TEDAVİNİN SAĞKALIMA KATKISI VAR MI ?

Mide Kanserinde 3. Basamak Tedavi

İntergrate trial phase II		Regoragefnib versus placebo	0.40 (<0.001)	PFS: 2,6 vs 0,9
Advanced gastric cancer – third line				
Li et al. [34] (Apatinib)	271	Apatinib + BSC versus BSC	0.71 (0.0149)	OS: 6.5 versus 4.7 PFS: 2.6 versus 1.8
Kang et al. [46] (ONO-4538-12, ATTRACTION-2)	493	Nivolumab versus Placebo	0.63 (<0.0001)	OS: 5.26 versus 4.14

HR, Hazard ratio; OS, Overall survival; CX, Cisplatin and Capecitabine; CF, Cisplatin and 5-FU; PFS, Progression-free survival; BSC, Best supportive c

[1]Hazard ratio reduced to 0.8 on follow-up analysis.

INTEGRATE Study

- 150 Adults
- Histologically confirmed gastroesophageal cancer
- Measurable metastatic or locally advanced disease
- Refractory to first- or second-line chemotherapy or for whom second line is not appropriate

RANDOMIZE

2:1

Arm A Regorafinib (*n* = 100)
orally
once daily on days 1 to 21 of each 28-day cycle plus best supportive care

Arm B Placebo (*n* = 50)
4 × tablets orally, once daily on days 1 to 21 of each 28-day cycle plus best supportive care

Stratification Factors
- Lines of prior chemotherapy for advanced disease (1 vs 2)
- Geographic region

Targets
- 90% power at 5% significance to reject null hypothesis of PFS rate ≤50%, compared with PFS rate of ≥66%

End point
- PFS
- OS

Pavlick N et al. *J Clin Oncol* 2013; 31 (suppl):abstract TPS4157[56]

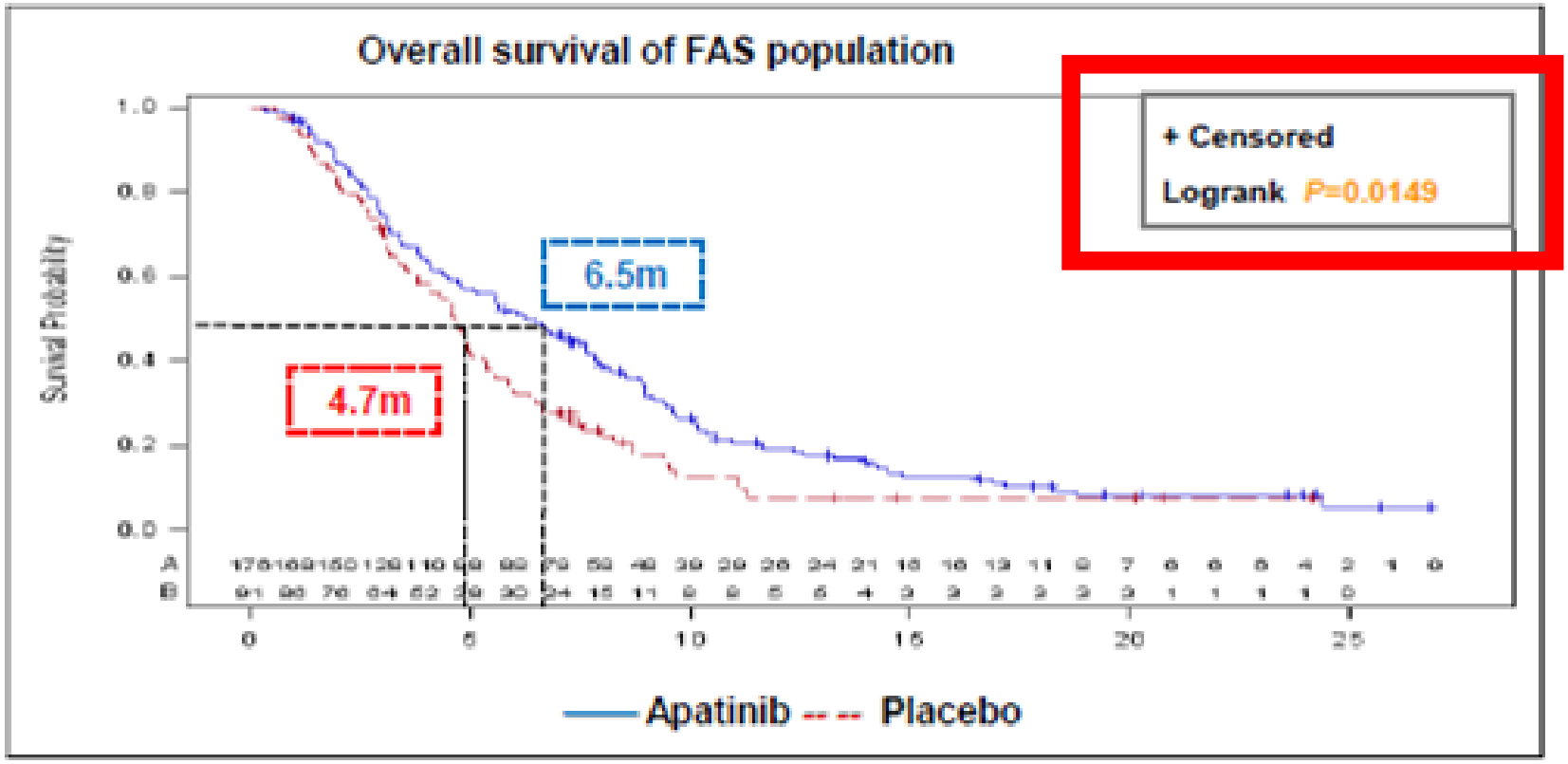
3. Basamak Tedavi Apatinib VS Placebo

- Design: Multicenter, randomized, double-blind, placebo-controlled clinical trial

- 1 treatment cycle = 28 days
- Stratification factor: Number of metastatic sites (≤ 2 vs. >2)

Li J, *et al*. J Clin Oncol 2016;34:1458-1464.

Apatinib 3. Basamak tedavide Sağkalım avantajı Sağlıyor



Group	n	mOS (95% CI), months	P value	HR (95%CI)
Apatinib	176	6.5 (4.8–7.6)	0.0149	0.709 (0.537–0.937)
Placebo	91	4.7 (3.6–5.4)		

Li J, *et al.* J Clin Oncol 2016:34:1458-1464.

Metastatik Mide Kanserinde İmmunoterapiler

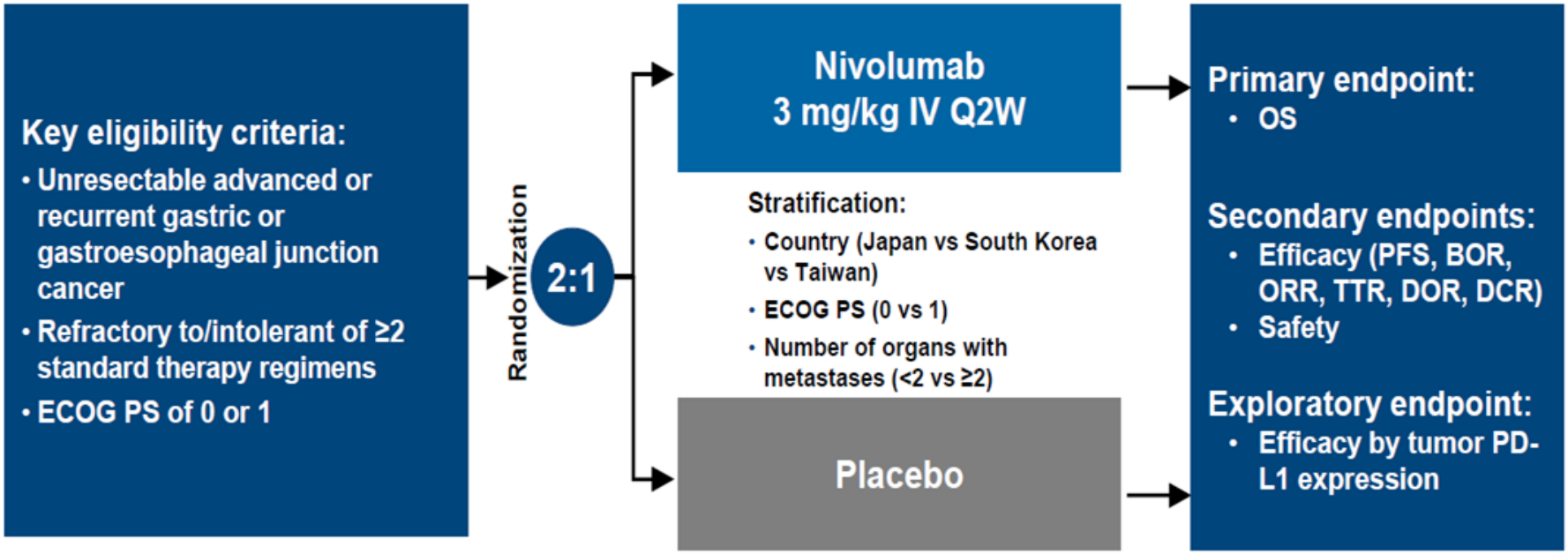
Study	Phase	Trial population	*n*	ORR (%)	6 m PFS (%)	6 m OS (%)	12 m PFS (%)	12 m OS (%)	Median OS (m)	Median PFS (m)	Ref
KEYNOTE-012	Ib	Advanced GC	39	22	26	66	NR	42	11.4	1.9	43
KEYNOTE-028	Ib	Advanced esophageal	23	30	30	NR	21.7	NR	NR	NR	55
CheckMate-032 N 3 mg/kg	I/II	Advanced GC	59	14	18	49	7	36	5	1.3	52
CheckMate-032 N 3mg/kg, I 1mg/kg	I/II	Advanced GC	52	10	9	43	NR	NR	4.6	1.6	52
CheckMate-032 N 1mg/kg, I 3mg/kg	I/II	Advanced GC	49	26	18	54	18	34	6.9	1.5	52
JAVELIN	Ib	Advanced GC/GEJ, second line	62	9.7	NR	NR	NR	NR	NR	1.5	56
Tremelimumab	II	Advanced GC, esophageal	18	5	NR	NR	NR	33	4.8	2.8	73
ONO-4538	III	>2 prior lines, gastric, GEJ	493	11.2	NR	46.4	7.6	26.6	5.32	1.6	54

Notes: Data reflect updates through ASCO GI 2017. For the JAVELIN study, only the second line subgroup is reported.

Abbreviations: GC, gastric cancer; GEJ, gastroesophageal junction; N, nivolumab; I, ipilimumab; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; m, months; NR, not reported; ASCO, American Society of Clinical Oncology.

ATTRACTION-02 ÇALIŞMASI
Nivolumab VS Placebo

Study design of ATTRACTION-02



- Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug
- Retrospective determination of tumor PD-L1 expression, defined as positive if staining in ≥1% (or ≥5%) of tumor cells, was performed in a central laboratory using immunohistochemistry (28-8 pharmDx assay) for patients with available tumor samples

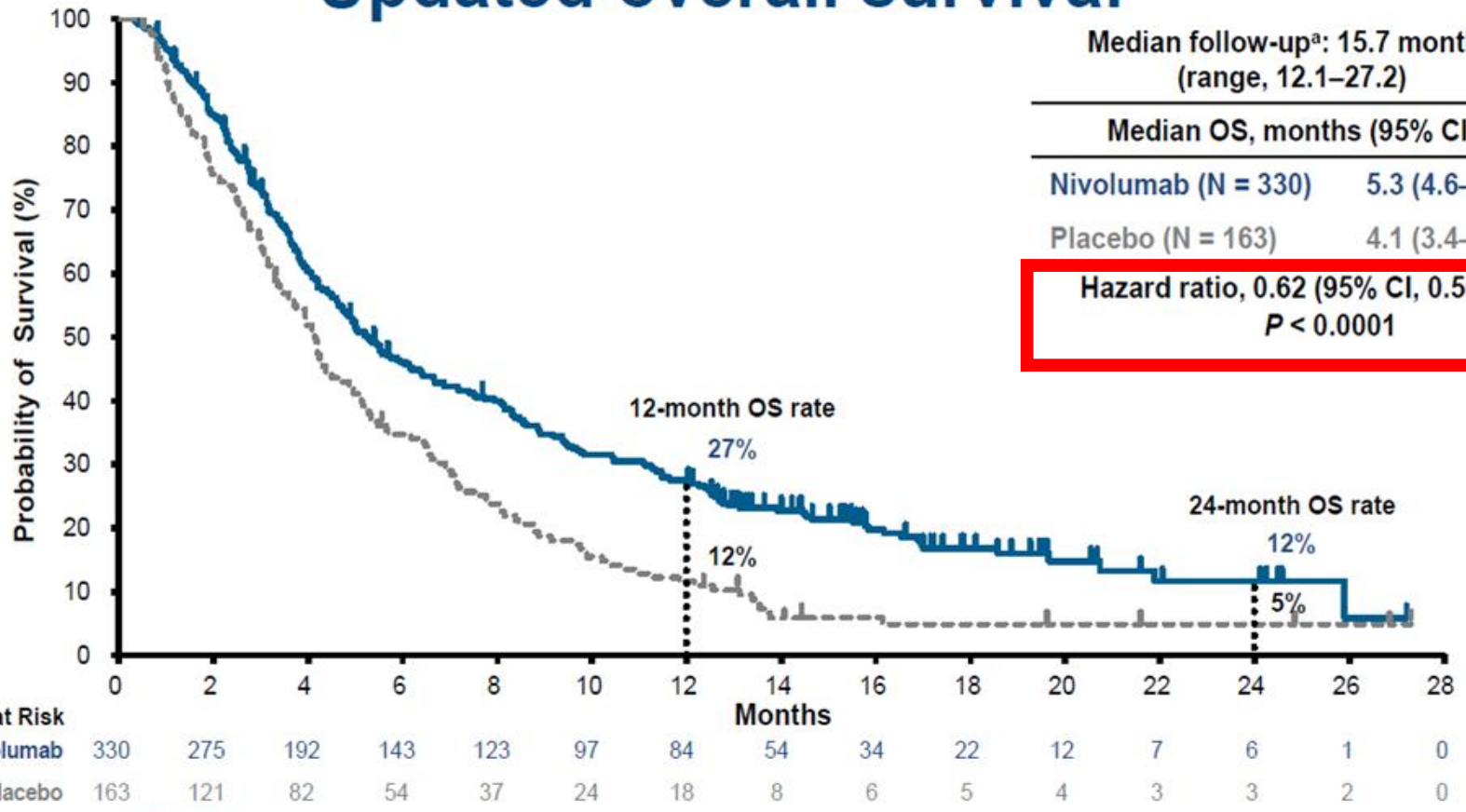
MADRID 2017 ESMO congress

Boku N et al. 6160

ATTRACTION-02 ÇALIŞMASI
Nivolumab VS Placebo

ATTRACTION-02

Updated overall survival



Median follow-up[a]: 15.7 months (range, 12.1–27.2)

Median OS, months (95% CI)	
Nivolumab (N = 330)	5.3 (4.6–6.4)
Placebo (N = 163)	4.1 (3.4–4.9)

Hazard ratio, 0.62 (95% CI, 0.50–0.76)
P < 0.0001

MADRID 2017 ESMO congress

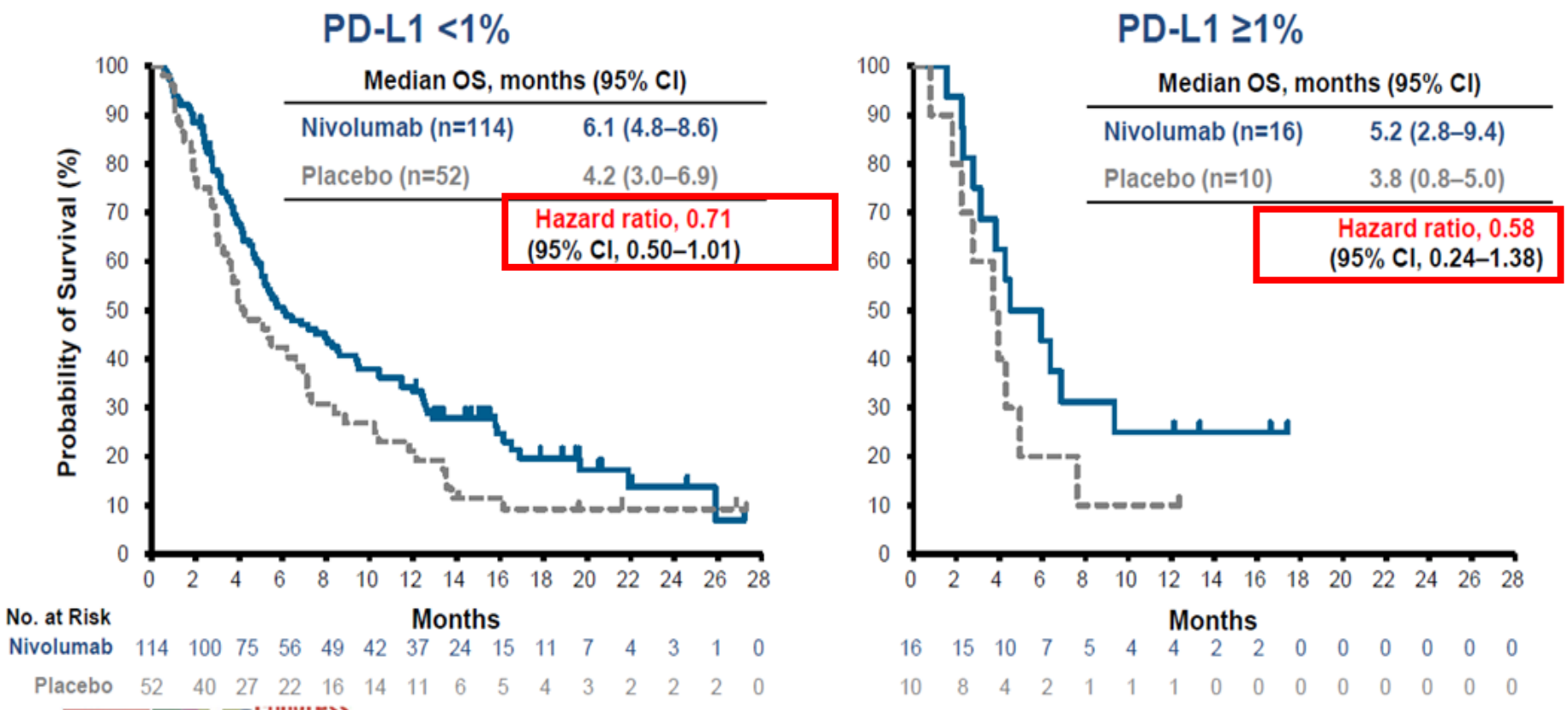
[a]Time from first dose to data cut-off for surviving patients

Boku N et al. 6160

ATTRACTION-02 ÇALIŞMASI
Nivolumab VS Placebo

ATTRACTION-02

Overall survival by PD-L1 expression <1% vs ≥1%



MADRID 2017 ESMO Congress

PD-L1 evaluable patients (N=192)

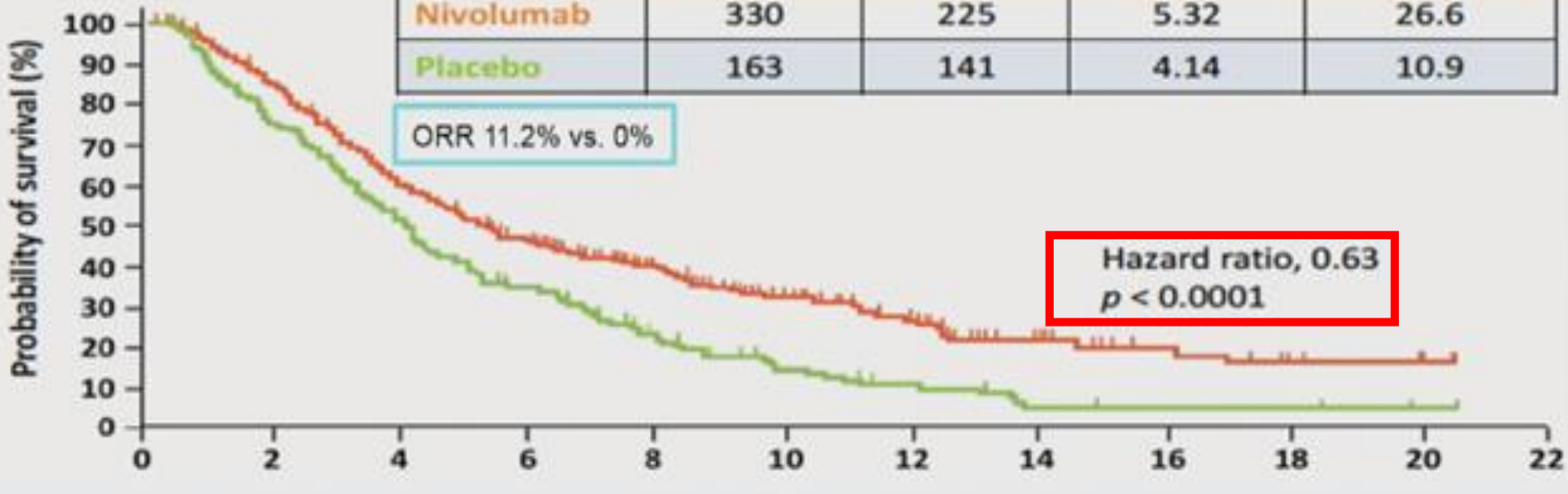
Boku N et al. 6160

ATTRACTION-02 ÇALIŞMASI
Nivolumab VS Placebo

ATTRACTION 2: Phase III of NIVOLUMAB vs. Placebo in G/GEC

	Patients, n	Events, n	Median OS, months	12-month OS rate, %
Nivolumab	330	225	5.32	26.6
Placebo	163	141	4.14	10.9

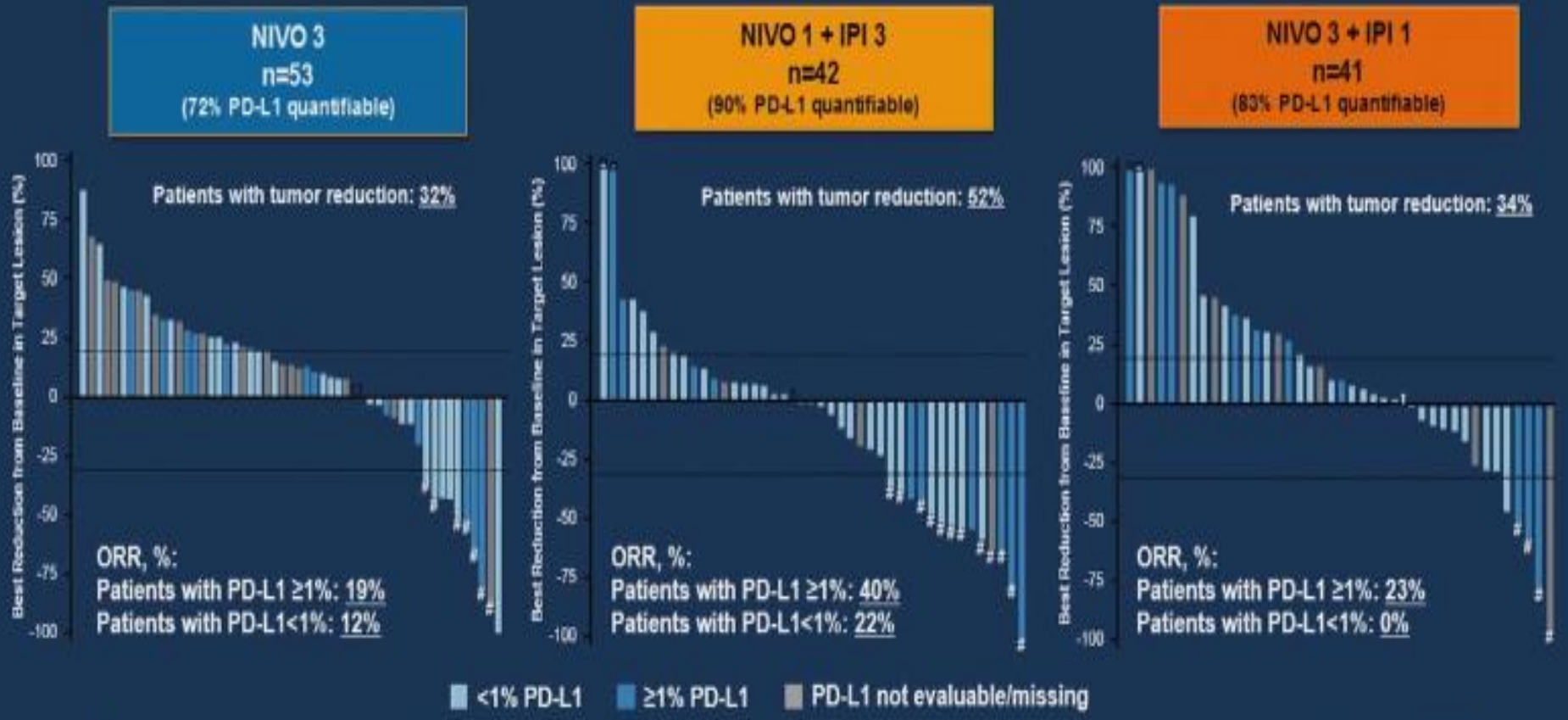
ORR 11.2% vs. 0%



At risk:												
Nivolumab	330	275	193	142	95	57	39	19	10	5	3	0
Placebo	163	121	82	53	32	16	10	4	3	3	1	0

Kang et al . ASCO GI 2017

Nivolumab ± ipilimumab in patients with advanced/metastatic chemotherapy-refractory gastric, esophageal, or gastroesophageal junction cancer: CheckMate 032 study

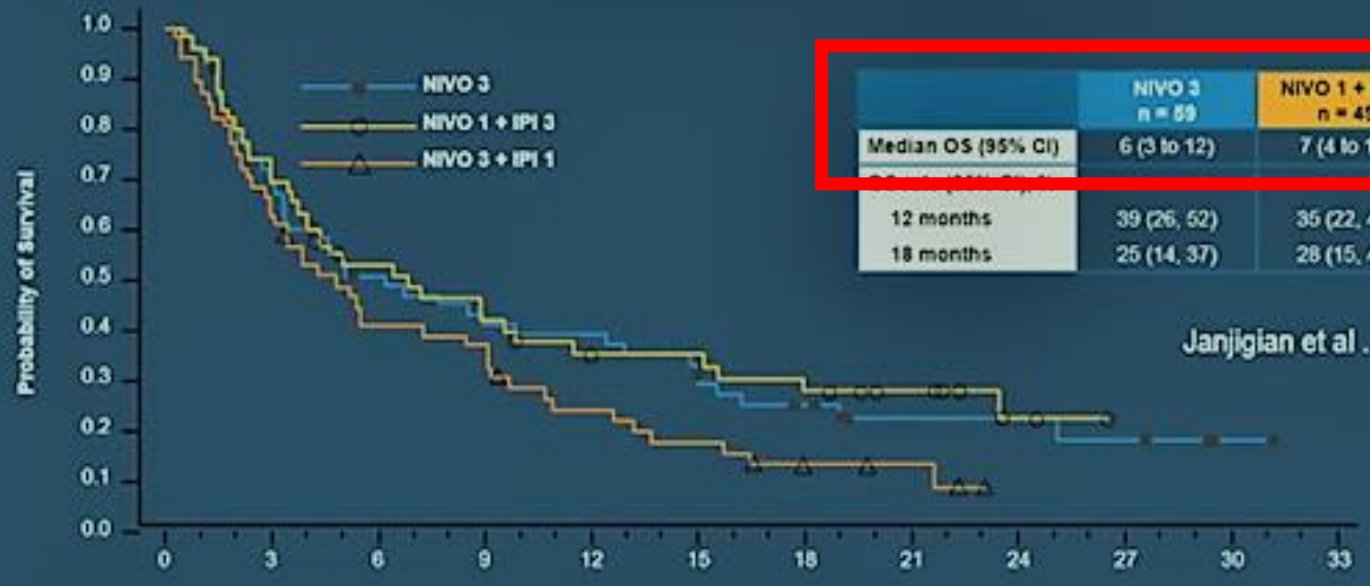


- Responses to nivolumab alone and in combination with ipilimumab were observed regardless of PD-L1 tumor expression

Janjigian et al . Abs 4016. ASCO 2017

Checkmate-032 Study:
Nivo ya İpi eklenmesinin etkisi ?

Overall Survival



	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
Median OS (95% CI)	6 (3 to 12)	7 (4 to 11)	5 (3 to 8)
12 months	39 (26, 52)	35 (22, 49)	24 (13, 37)
18 months	25 (14, 37)	28 (15, 41)	13 (5, 24)

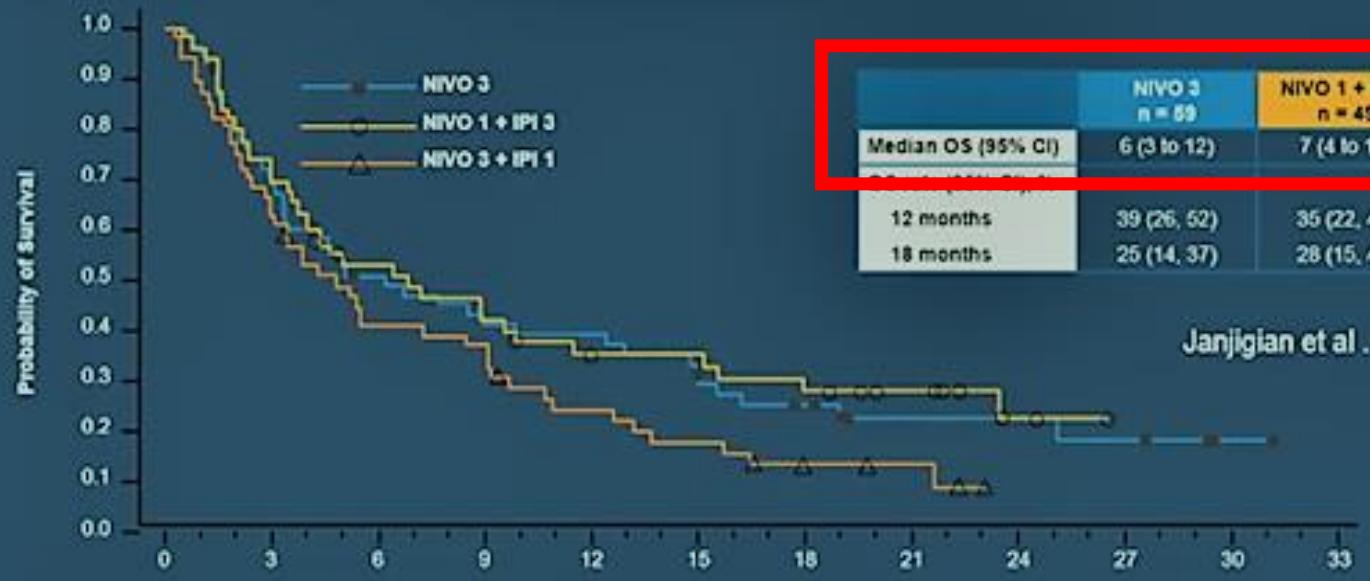
Janjigian et al . Abs 4016. ASCO 2017

At risk:												
NIVO 3	59	40	26	21	20	15	11	5	5	4	1	0
NIVO 1 + IPI 3	49	35	24	19	14	14	11	8	3	0	0	0
NIVO 3 + IPI 1	52	33	20	18	11	8	4	3	0	0	0	0

Median follow-up was 28 months in NIVO 3, 24 months in NIVO 1 + IPI 3, and 22 months in NIVO 3 + IPI 1

Checkmate-032 Study:
Nivo ya İpi eklenmesinin etkisi ?

Overall Survival



	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
Median OS (95% CI)	6 (3 to 12)	7 (4 to 11)	5 (3 to 8)
12 months	39 (26, 52)	35 (22, 49)	24 (13, 37)
18 months	25 (14, 37)	28 (15, 41)	13 (5, 24)

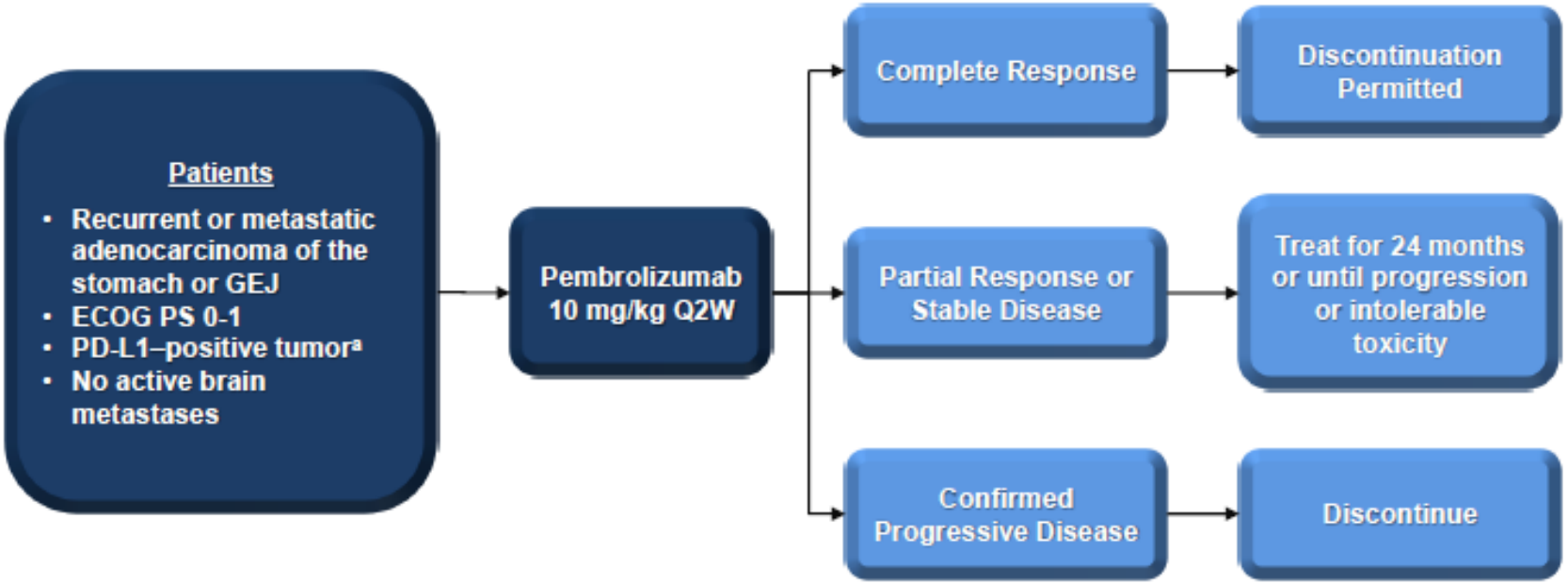
Janjigian et al . Abs 4016. ASCO 2017

OS katkısı YOK !! Toksisite artıyor !!!!

NIVO 1 + IPI 3	49	35	24	19	14	14	11	8	3	0	0	0
NIVO 3 + IPI 1	52	33	20	18	11	8	4	3	0	0	0	0

Median follow-up was 28 months in NIVO 3, 24 months in NIVO 1 + IPI 3, and 22 months in NIVO 3 + IPI 1

Mide Kanserinde Pembrolizumab: KEYNOTE-12 çalışması

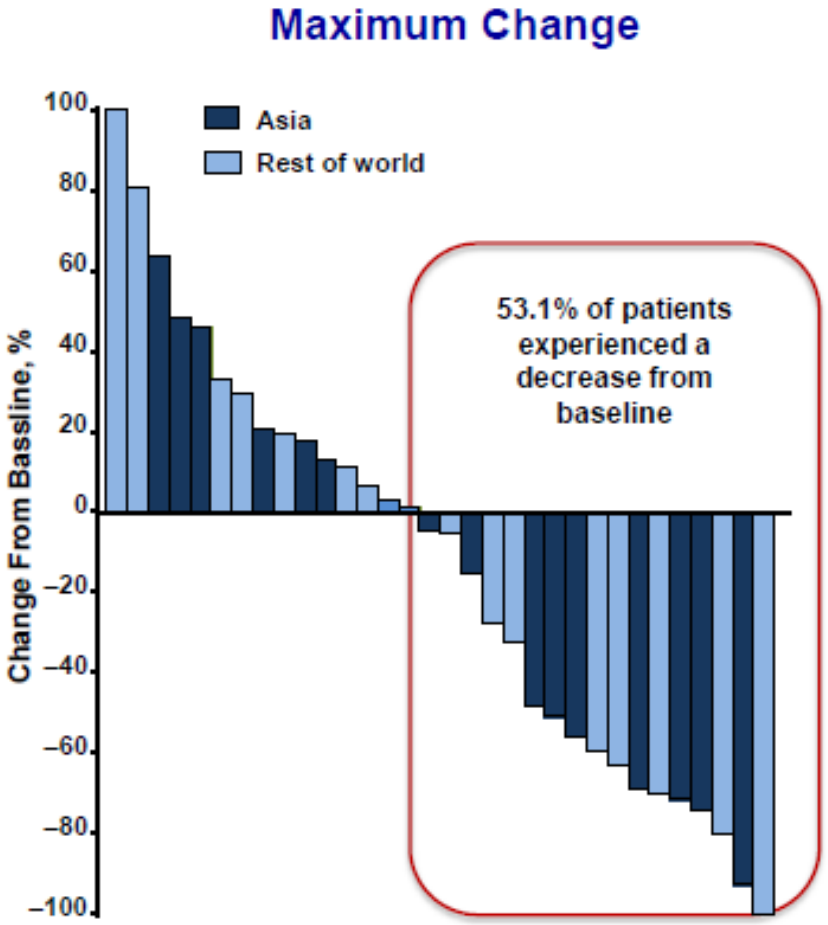


Screening: 65 of 162 (40%) patients assessed for PD-L1 expression had PD-L1-positive tumors
Patients: 19 patients from Asia and 20 patients from the rest of the world
Treatment: 10 mg/kg IV Q2W
Response assessment: Performed every 8 weeks per RECIST v1.1 by central radiology review

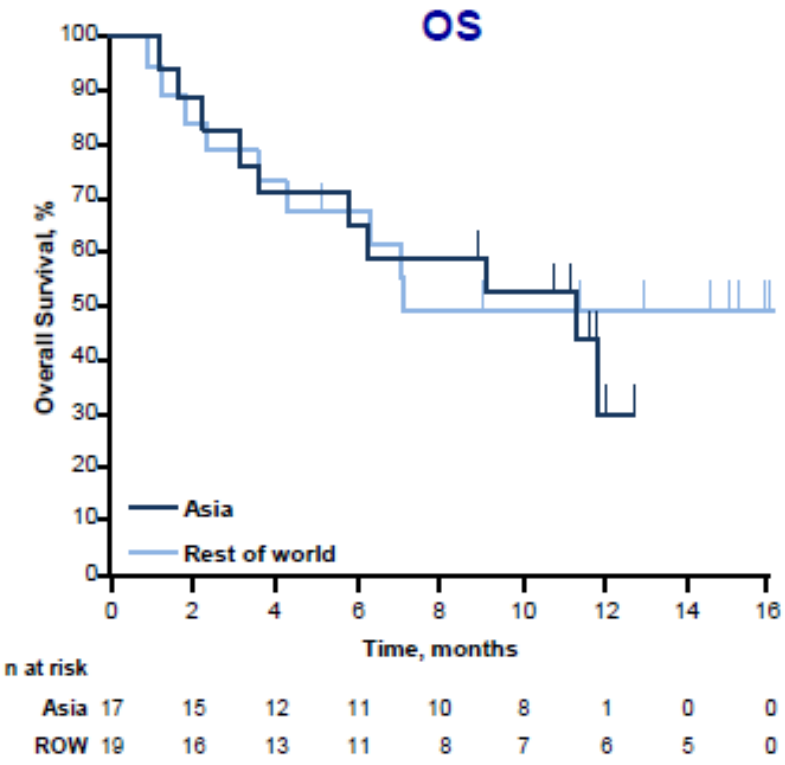
[a]Assessed in archival tumor samples using a prototype IHC assay (22C3 antibody). Positivity defined as PD-L1 staining in stroma or ≥1% of tumor cells.

Muro K et al. Lancet Oncol 2016

KEYNOTE-012: Gastric Cancer Cohort



ORR, % (95% CI): 22.2 (10.1, 39.2)



- Total population
  - 6-month OS rate: 66%
  - Median OS: 11.4 months (95% CI, 5.7-NR)

Muro K et al. Lancet Oncol 2016

Mide Kanserinde Pembrolizumab: KEYNOTE-12 çalışması

- 2 ve daha fazla basamak kemoterapi aldıktan sonra progrese olan hastalarda pemmrolizumab verildi
- OS 11,4 ay
- PFS 1,9 ay
- ORR % 22 ile

önemli bir etkinlik ve yönetilebilir bir güvenlik profili göstermiştir

Mide Kanserinde Pembrolizumab: Keynote-061 ve 062

- Pembrolizumabın 3. basamakta etkinliğinin gösterilmesiyle 2. basamak Keynote-061 ve

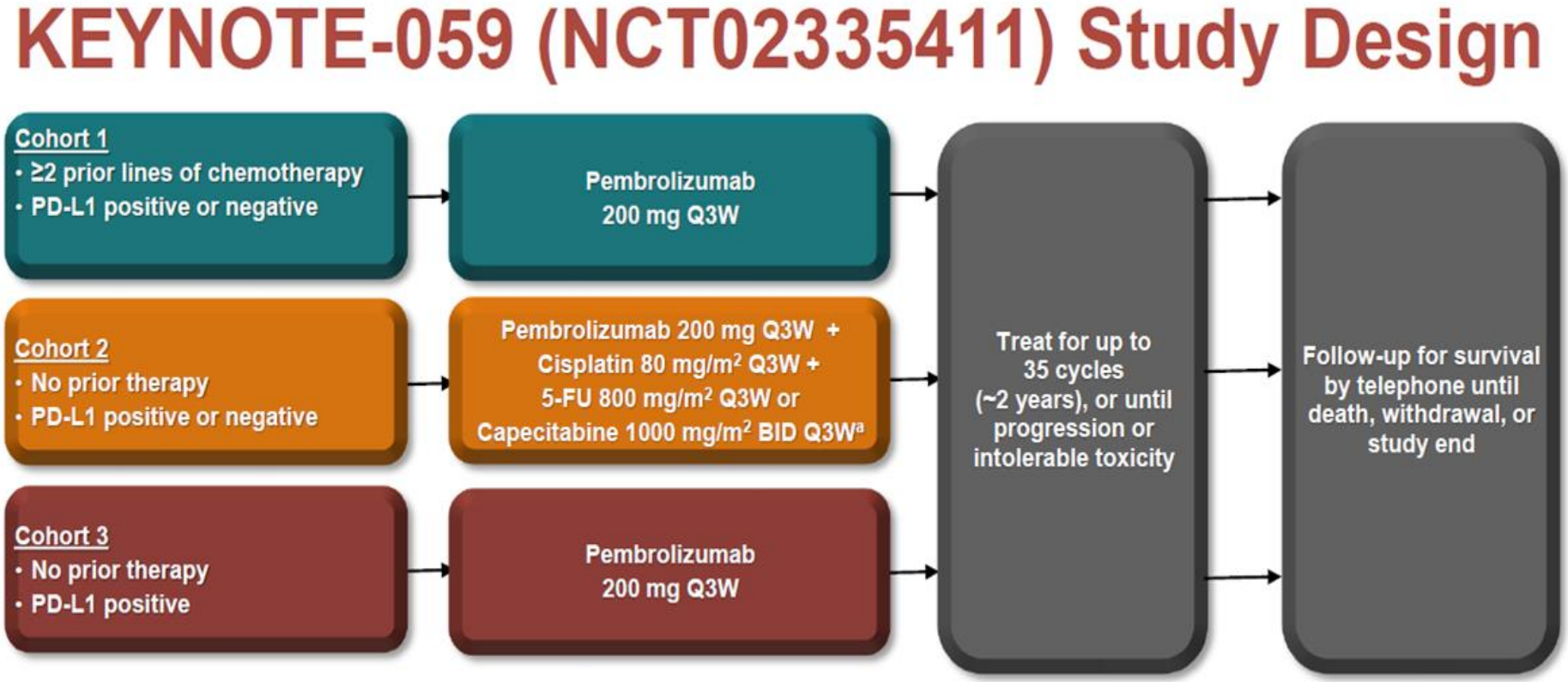
  1. basamak Keynote-062 çalışmalar dizayn edilip başlatıldı.

- Keynote-061 update verileri açıklandı,
- Keynote-062 halen devam etmekte

Mide Kanserinde Pembrolizumab: Faz 3 Keynote-61 çalışması Updated Verileri

- 2. basamak, platin-fluoroprimin sonrası progrese
- PD-L1 exprese eden Mide ve bileşke tümörü olan 592 hasta
- Primer sonlanım noktası olan OS yi ve PFS'yi karşılamadı HR : 0,82

Mide Kanserinde Pembrolizumab: Faz II KEYNOTE-059 çalışması



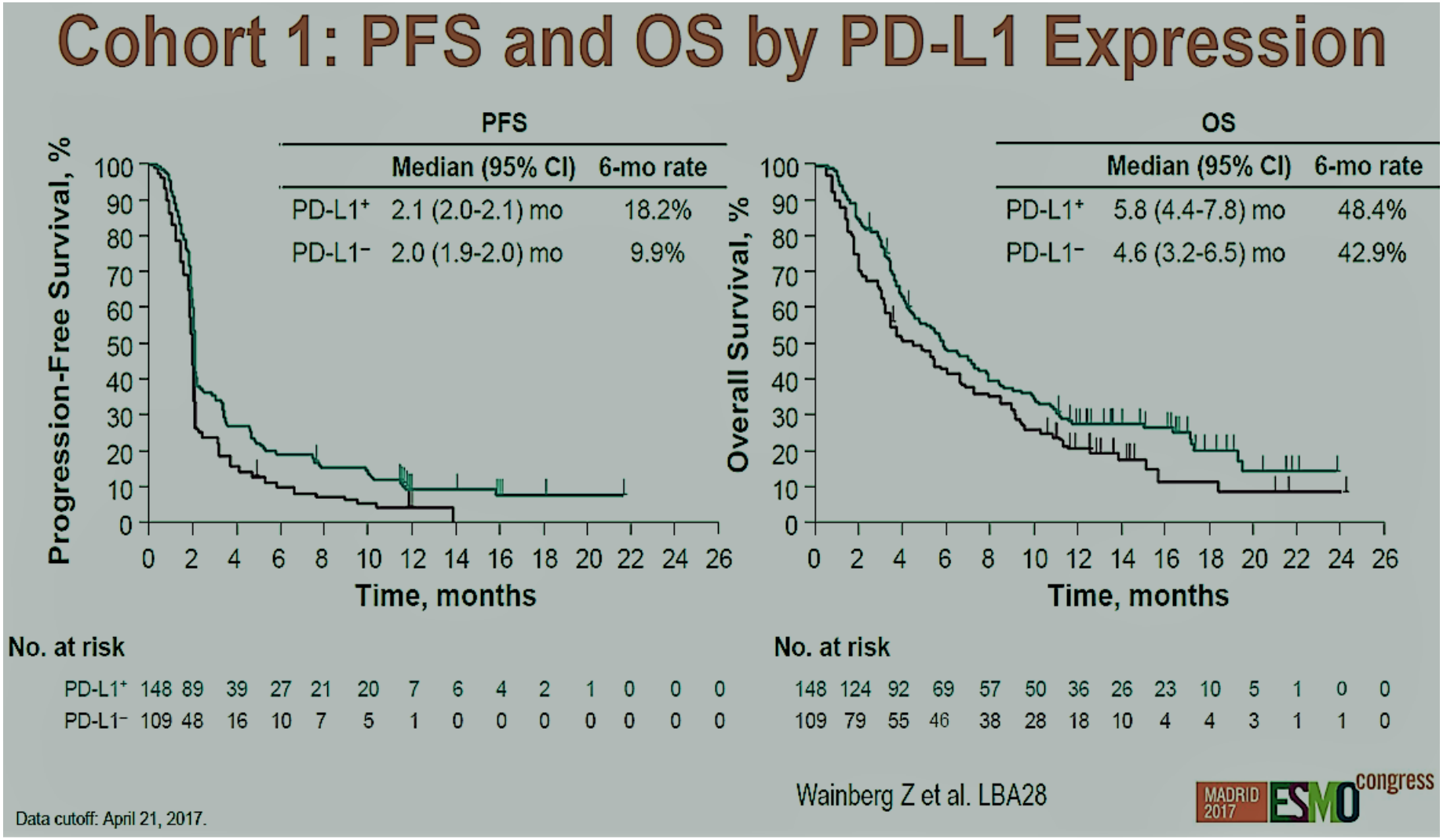
Response assessment per RECIST v1.1: First scan 9 weeks after cycle 1, then every 6 weeks for year 1 and every 9 weeks thereafter
Primary endpoints: Safety (all cohorts); ORR by central review per RECIST v1.1 (cohort 1: all patients and patients with PD-L1–positive expression); ORR by central review per RECIST v1.1 (cohort 3)
PD-L1 positive was defined as combined positive score (CPS) ≥1 (previously reported as and equivalent to CPS ≥1%), where CPS = ratio of PD-L1–positive cells[b] (tumor cells, lymphocytes, and macrophages) to the total number of tumor cells ×100

[a]Capecitabine was administered only in Japan.
[b]PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA).

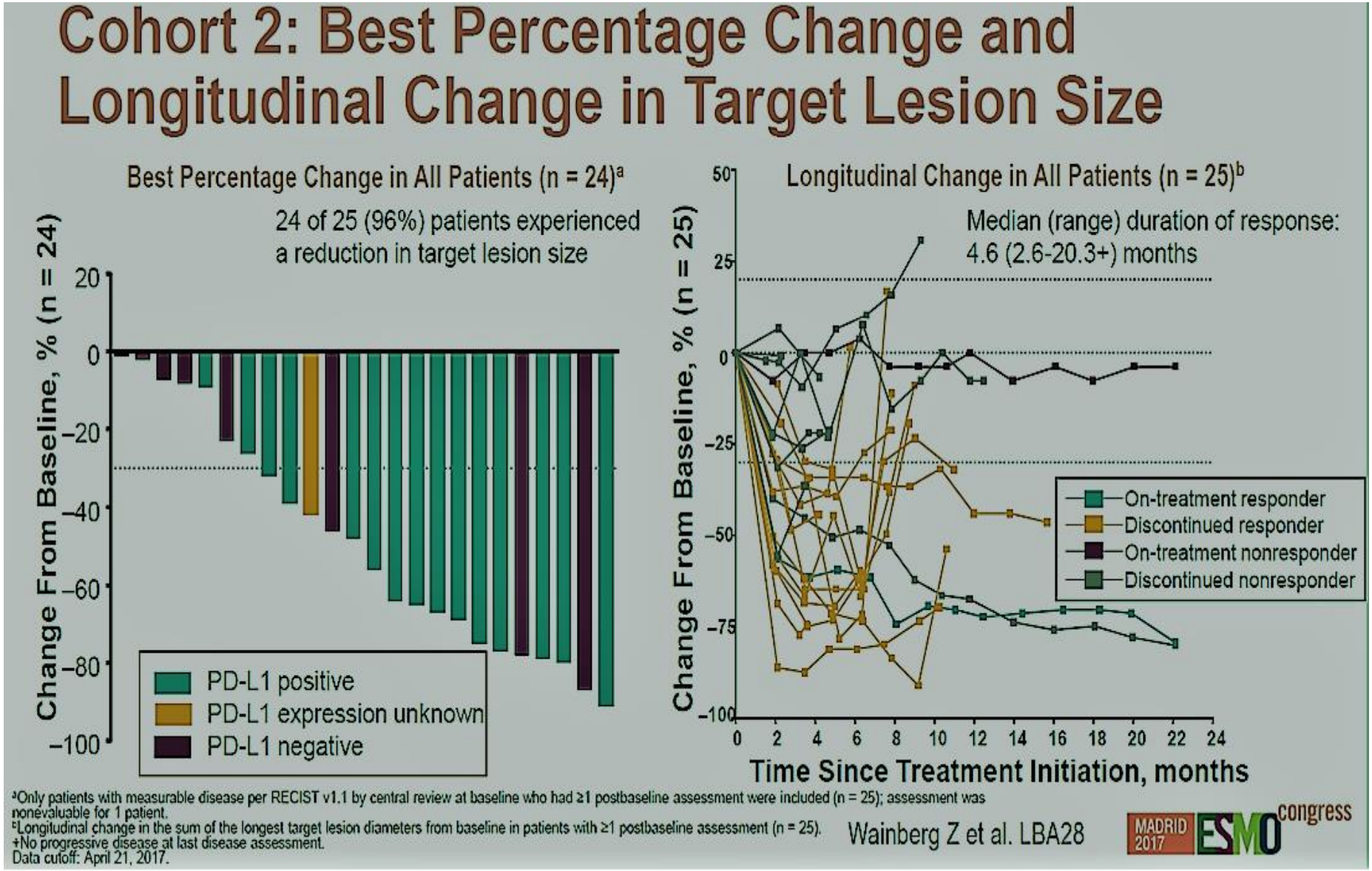
Wainberg Z et al. LBA28

MADRID 2017 ESMO congress

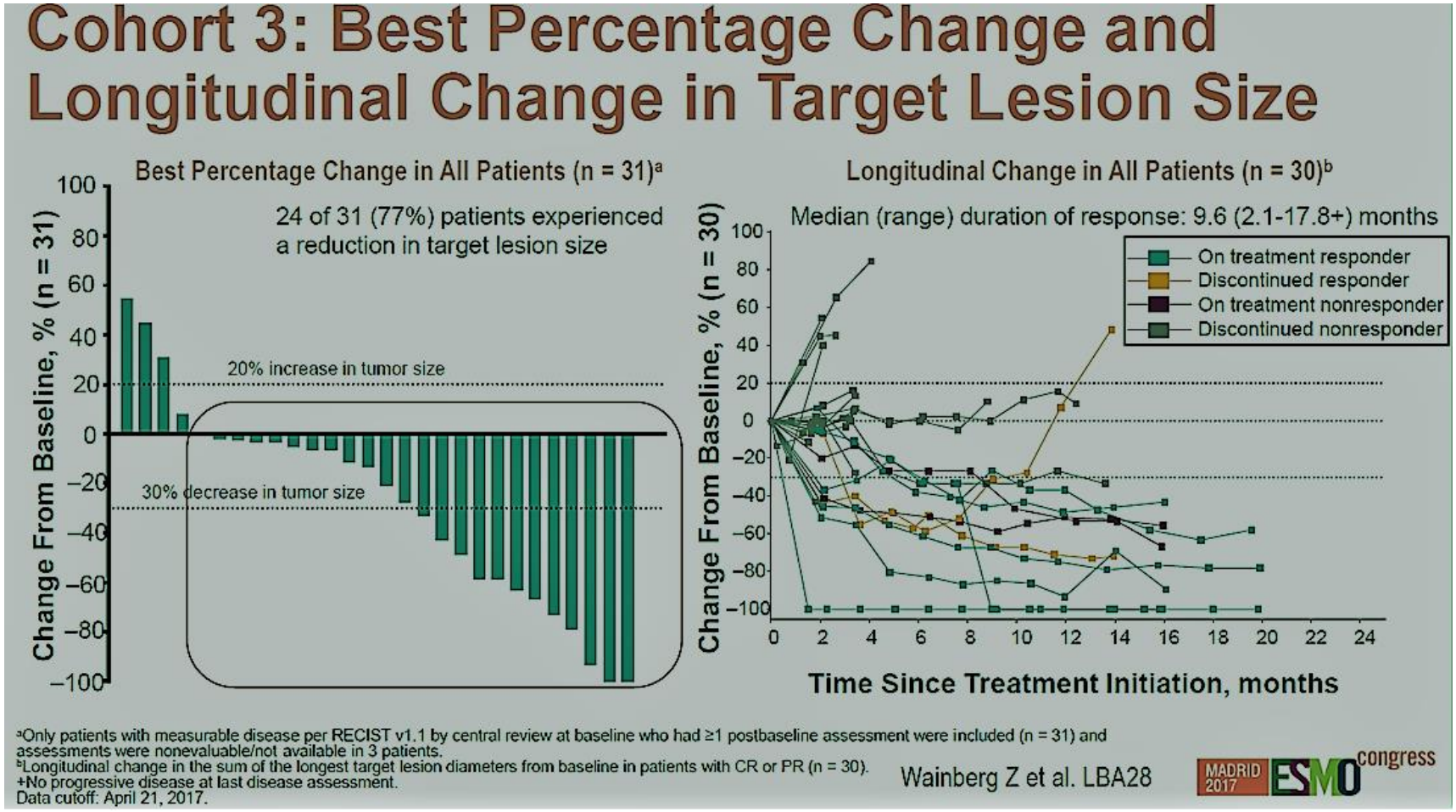
KEYNOTE-059 çalışması: Cohort 1,



KEYNOTE-059 çalışması: Cohort 2,



KEYNOTE-059 çalışması: Cohort 3,



Mide Kanserinde Pembrolizumab Faz II KEYNOTE-059 çalışması: Pembrolizumab

- Bu çalışmayla **pemrolizumab,**

  fluoropirimidin ve plantinli tedaviler içeren 2 veya daha fazla basamak tedavi alıp progrese olan nüks, lokal ileri ve metastatik mide kanserinde **ONAY aldı.**

Summary slide : Immunotherapy in Advanced Gastro-Esophageal Cancer

- Is this practice changing?
  - CheckMate 032 Broadens promising data from ATTRACTION by including a non-Asian population.
  - KEYNOTE-059 (Pembrolizumab) confirms this as well
  - Not yet for CTLA4 inhibitors +/- PD1 inhibitors
- What are the take home points?
  - Nivolumab and Pembrolizumab should be considered for patients with refractory disease
  - PDL1 staining should not be performed or used to select candidate patients (or may be if MSI-ve and considering moving up the line)
- Additional research is needed:
  - Role of CTLA4 +/- PD1 inhibitors (ongoing)
  - Moving immunotherapy to earlier lines of therapy (+/- other modalities)
  - Better understand better the molecular subtypes that benefit from immunotherapy

Ongoing Phase III Clinical Studies

Line	Study	N	Treatment Arms	Primary EP	
1st Line	KEYNOTE-062 NCT02494583 (TPS 4138)	750	Pembrolizumab 200mg Q3W vs Pembro + Cisplatin + 5-FU/CPC vs Placebo + Cisplatin + 5-FU/CPC	OS PFS (RECIST 1.1)	CG & CUGE PS 0-1, PD-L1+/HER2- Stratification: Europe/North America/Australia vs Asia vs ROW RECIST 1.1 & irRECIST
Maintenance	JAVELIN Gastric 100 NCT02625610 (TPS 4134)	666	FOLFOX/XELOX x12 weeks, thereafter: Avelumab 10mg/kg Q2W vs Continuation FOLFOX/XELOX	OS PFS (from random)	CG & CUGE, PS 0-1, PD-L1+ Exclusion HER2+ RECIST 1.1
2nd Line	KEYNOTE-061 NCT02370498 (TPS 4137)	720	Pembrolizumab 200mg Q3W vs Paclitaxel	PFS (RECIST 1.1) OS in PD-L1+	CG & CUGE, PS 0-1 No molecular selection RECIST 1.1 & irRECIST
3rd Line	JAVELIN Gastric 300 NCT02625623 (TPS4135)	330	Avelumab 10mg/kg Q2W + BSC vs Paclitaxel/Irinotecan/BSC	OS (negative)	CG & CUGE, PS 0-1 No molecular selection Stratification: Asia vs non Asia Exclusion of previous immunotherapy RECIST 1.1

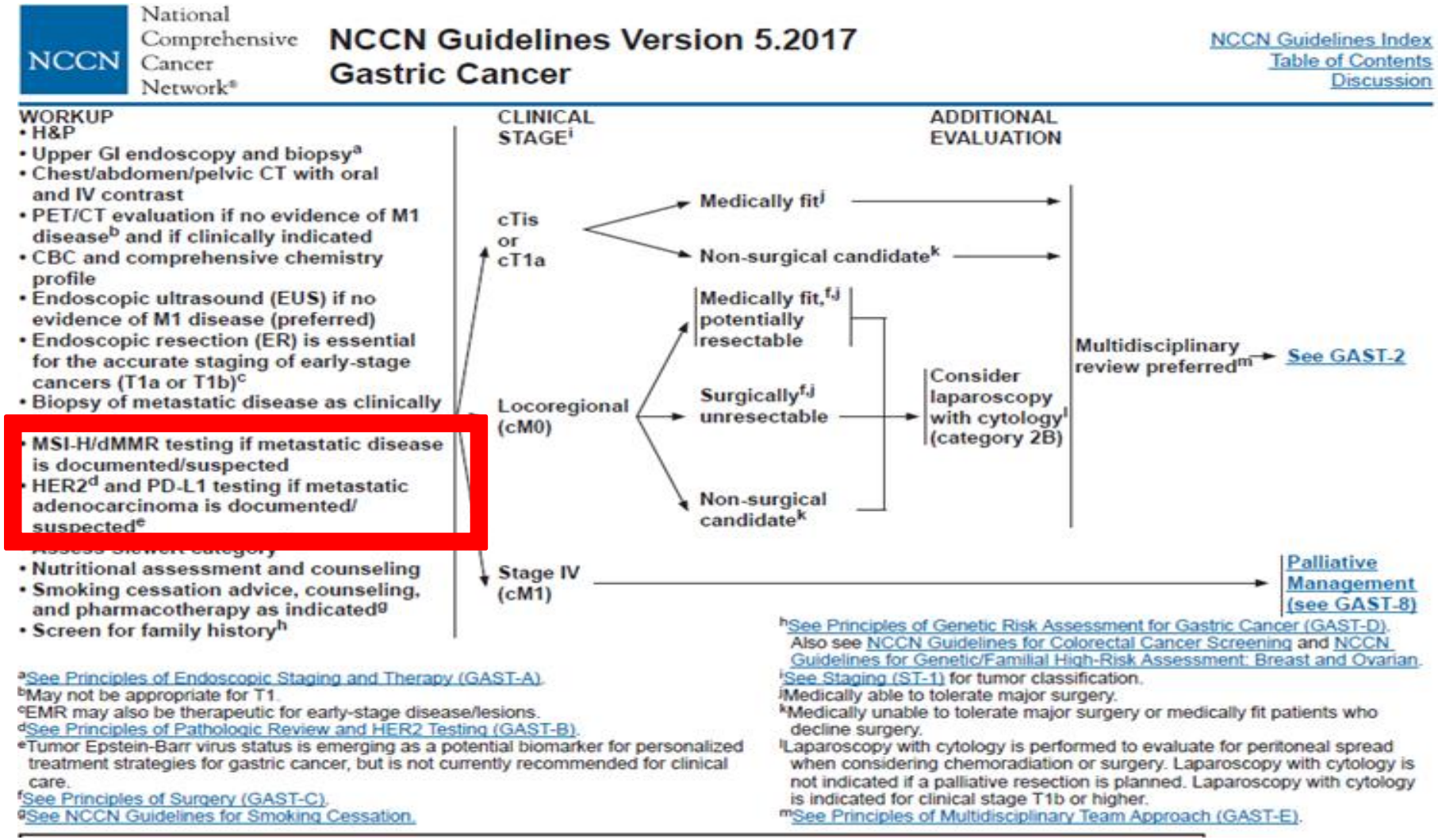
İleri evre Mide Kanserinde sadece Trastuzumab ve ramucirumab genel sağkalımı arttıran biyolojik ajanlardır

These agents yielded negative results in phase 3 trials:

Pathway	1st-line	2nd-line
Angiogenesis	bevacizumab	
EGFR	panitumumab, cetuximab	gefitinib
HER2	lapatinib	lapatinib, T-DM1
MET	onartuzumab, rilotumumab	
MTOR		everolimus

MET	Onartuzumab	METGASTRIC	•NEGATİF
	Rilotumumab	RILOMET	•NEGATİF
HER2	Pertuzumab	JACOB	•NEGATİF
	T-DM1	GATSBY	•NEGATİF
	Trastuzumab	TOGA	•POZİTİF
EGFR	Panitumumab	REAL3	•NEGATİF
	Cetuximab	EXPAND	•NEGATİF
Angiogenesis	Ramucirumab	REGARD	•POZİTİF
		RAINBOW	•POZİTİF
	Regorafenib	INTEGRATE	•NEGATİF
Angiogenesis	Ramucirumab	RAİNFALL	•POZİTİF

Klavuzlar ne diyor ? NCCN



Klavuzlar ne diyor ?

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2017
Gastric Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

- Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.
- Trastuzumab should be added to chemotherapy for HER2 overexpressing metastatic adenocarcinoma.
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.[1]
- Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Perioperative chemotherapy,[2,3] or postoperative chemotherapy plus chemoradiation[4] is the preferred approach for localized gastric cancer.
- Postoperative chemotherapy is recommended following primary D2 lymph node dissection.[5,6] (See Principles of Surgery [GAST-C])
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.

Klavuzlar ne diyor ?

NCCN Comprehensive Cancer Network®

NCCN Guidelines Version 5.2017
Gastric Cancer

NCCN

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

- Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma (See Principles of Pathologic Review and HER2 Testing [GAST-B])
  - Combination with fluoropyrimidine and cisplatin (category 1)[13]
  - Combination with other chemotherapy agents (category 2B)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy

Two-drug cytotoxic regimens are preferred because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

- Preferred Regimens:
  - Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin[14-17] (category 1)
  - Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[15,18,19]
- Other Regimens:
  - Paclitaxel with cisplatin or carboplatin[20-22]
  - Docetaxel with cisplatin[23,24]
  - Fluoropyrimidine[16,25,26] (fluorouracil† or capecitabine)
  - Docetaxel[27,28]
  - Paclitaxel[29,30]
  - Fluorouracil†,* and irinotecan[31]
  - DCF modifications
    - Docetaxel, cisplatin, and fluorouracil†,[32]
    - Docetaxel, oxaliplatin, and fluorouracil[33]
    - Docetaxel, carboplatin, and fluorouracil (category 2B)[34]
  - ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[35]
  - ECF modifications (category 2B)[3,4]
    - Epirubicin, oxaliplatin, and fluorouracil
    - Epirubicin, cisplatin, and capecitabine
    - Epirubicin, oxaliplatin, and capecitabine

Second-Line or Subsequent Therapy

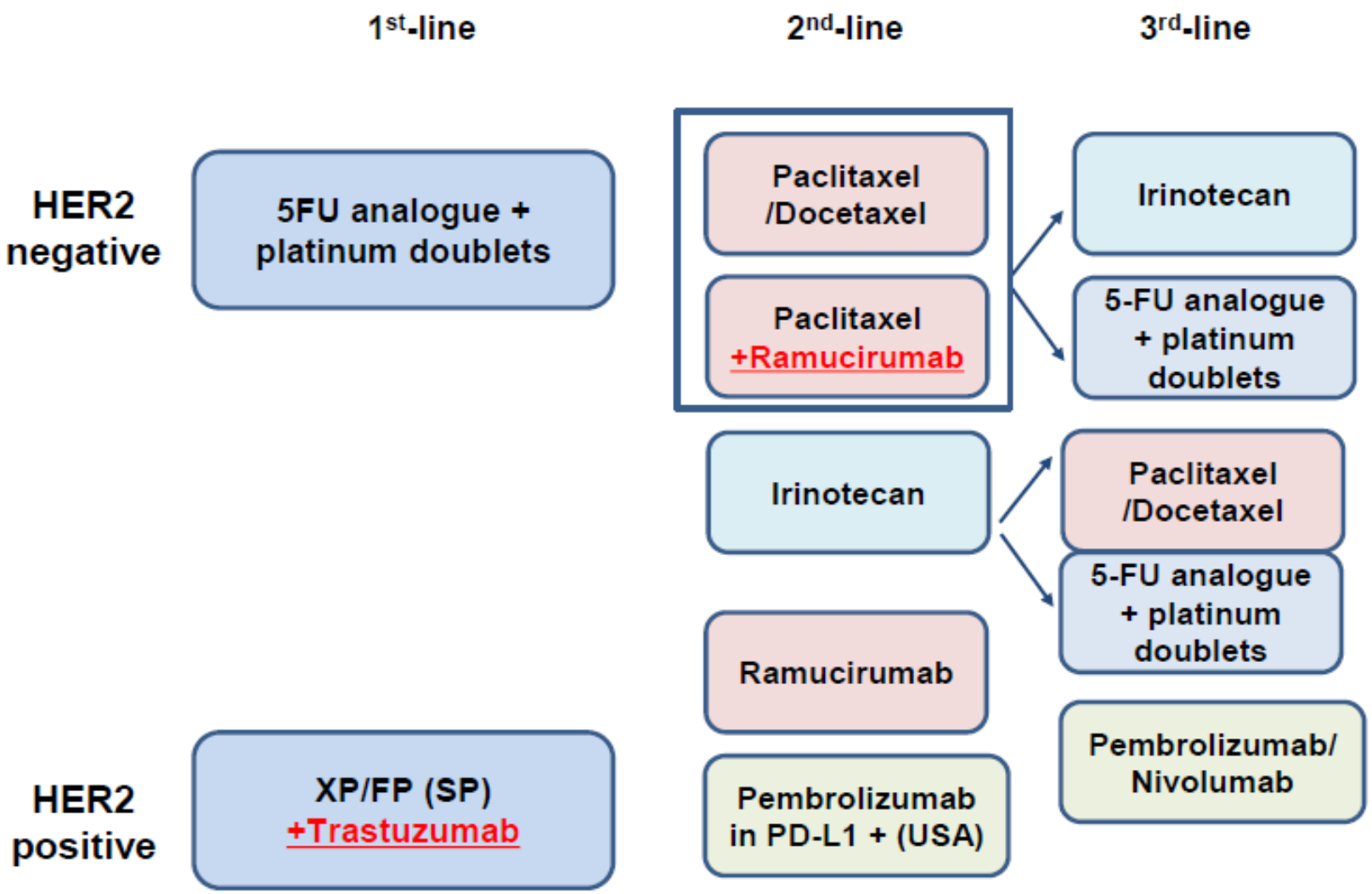
Dependent on prior therapy and PS:

- Preferred Regimens:
  - Ramucirumab and paclitaxel (category 1)[36]
  - Docetaxel (category 1)[27,28]
  - Paclitaxel (category 1)[29,30,37]
  - Irinotecan (category 1)[37-40]
  - Ramucirumab (category 1)[41]
  - Fluorouracil†,* and irinotecan[38,42,43]

  (if not previously used in first-line therapy)
- Other Regimens:
  - Irinotecan and cisplatin[18,44]
  - Pembrolizumab
    - For second-line or subsequent therapy for MSI-H or dMMR tumors[45,46]
    - For third-line or subsequent therapy for PD-L1 positive adenocarcinoma[47,**]
  - Docetaxel and irinotecan[48] (category 2B)

†Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see Discussion
*Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
**Pembrolizumab is approved for patients with gastric tumors with PD-L1 expression levels ≥ 1 as determined by an FDA-approved test.

Metastatik Mide Kanserinde Tedavi Algoritması



Sabrınız için Teşekkürler !!!