Metastatik Kolorektal Kanserde Optimal Tedavi

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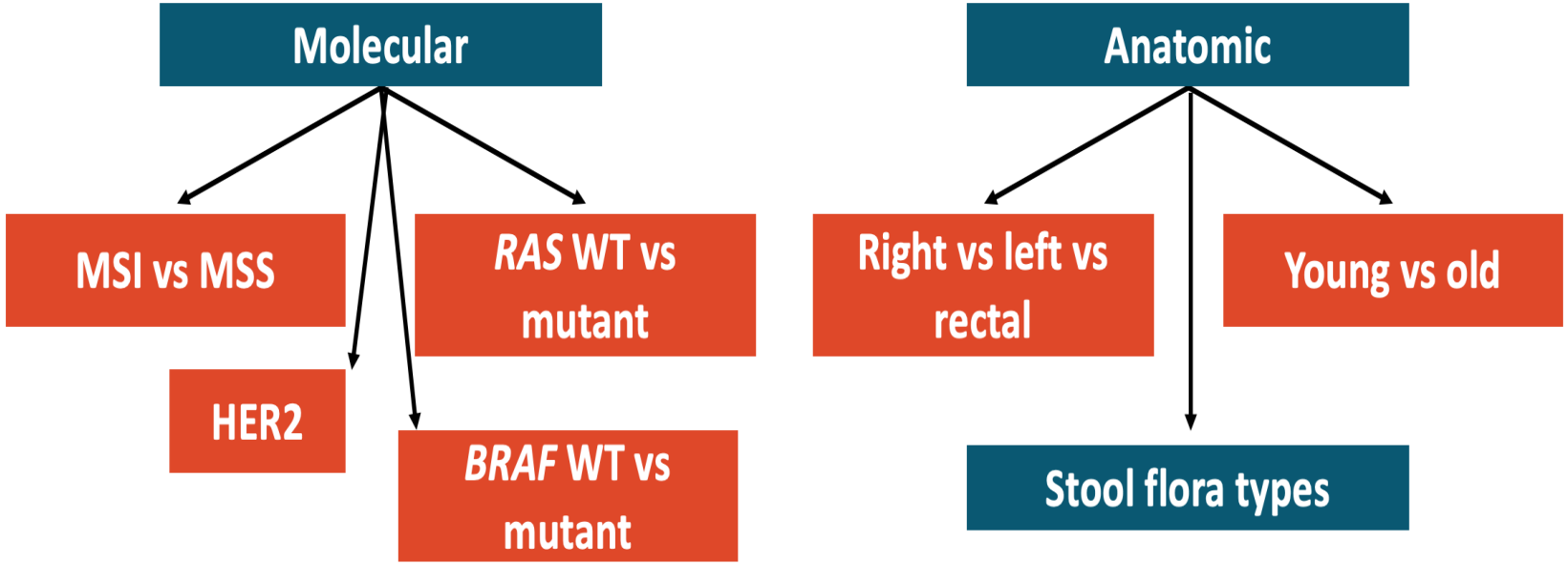
Sunum Planı

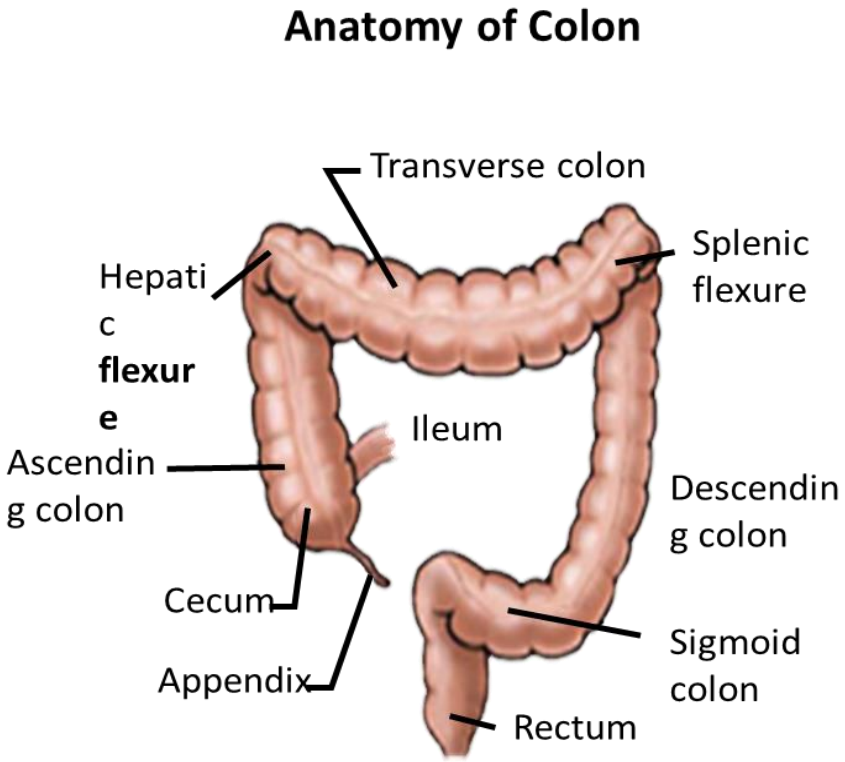
- mKRK'lerde Sistemik Tedavi Algoritması
  - Anatomik yerleşim prediktif midir?
    - Sağ vs Sol mKRK'de tedavi önerileri
  - Moleküler belirteçler prediktif midir?
    - Ras-Wt/Mt
    - BRAF-Mt
    - Her-2 ekspresyon (+)
    - MSI-H/MSS
    - NTRK-1,2,3 gen füzyon (+)
- KC/AC metastaz ve primer odak cerrahisi ve HiPEC/SRC'den söz edilmeyecektir

KRK Heterojen Bir Hastalıktır



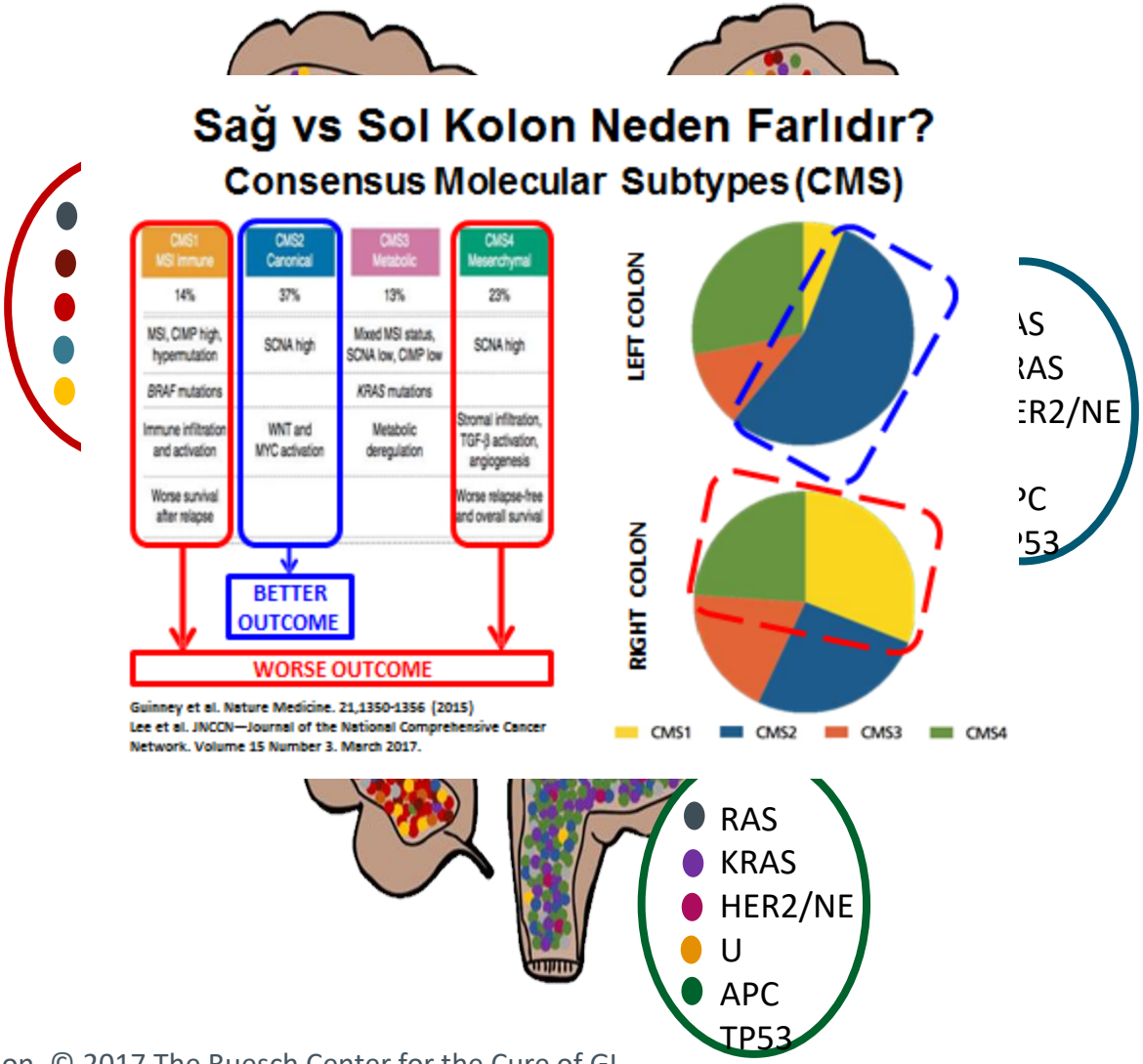
Sağ/Sol Kolon Ca TEDAVİ FARKLILIĞI RASYONELİ

- Embriyonel orijinleri farklıdır
- Mikrobiata farklıdır
- Pre-neoplastik lezyonlar farklıdır
- Moleküler patogenetikleri farklıdır



1. Guinney. Nat Med. 2015;21:1350. 2. Dienstmann. Nat Rev Cancer. 2017;17:79.
3. O'Dwyer. JCO. 2001;19:2413. 4. Loupakis. J Natl Cancer Inst. 2015;107:dju427.

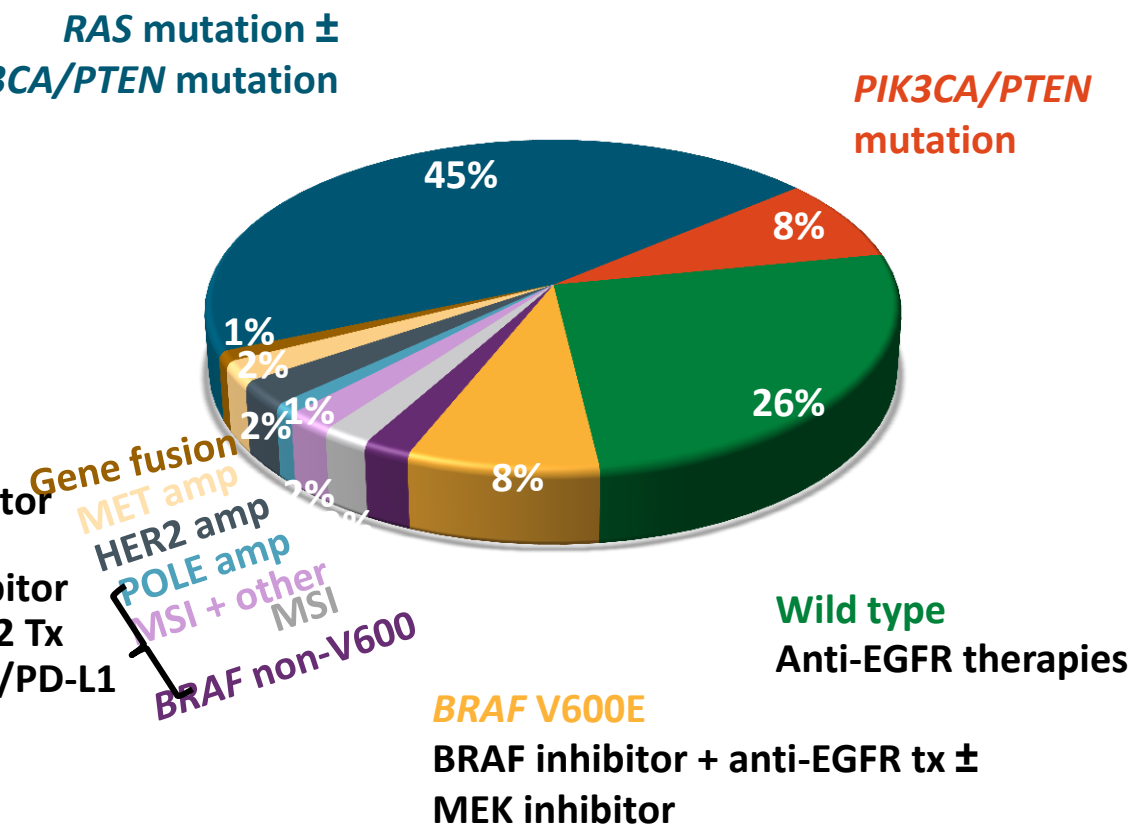
Sağ vs Sol Kolon Arasında Moleküler Heterojenite Vardır



KRK'da Biyomarkır Testleri

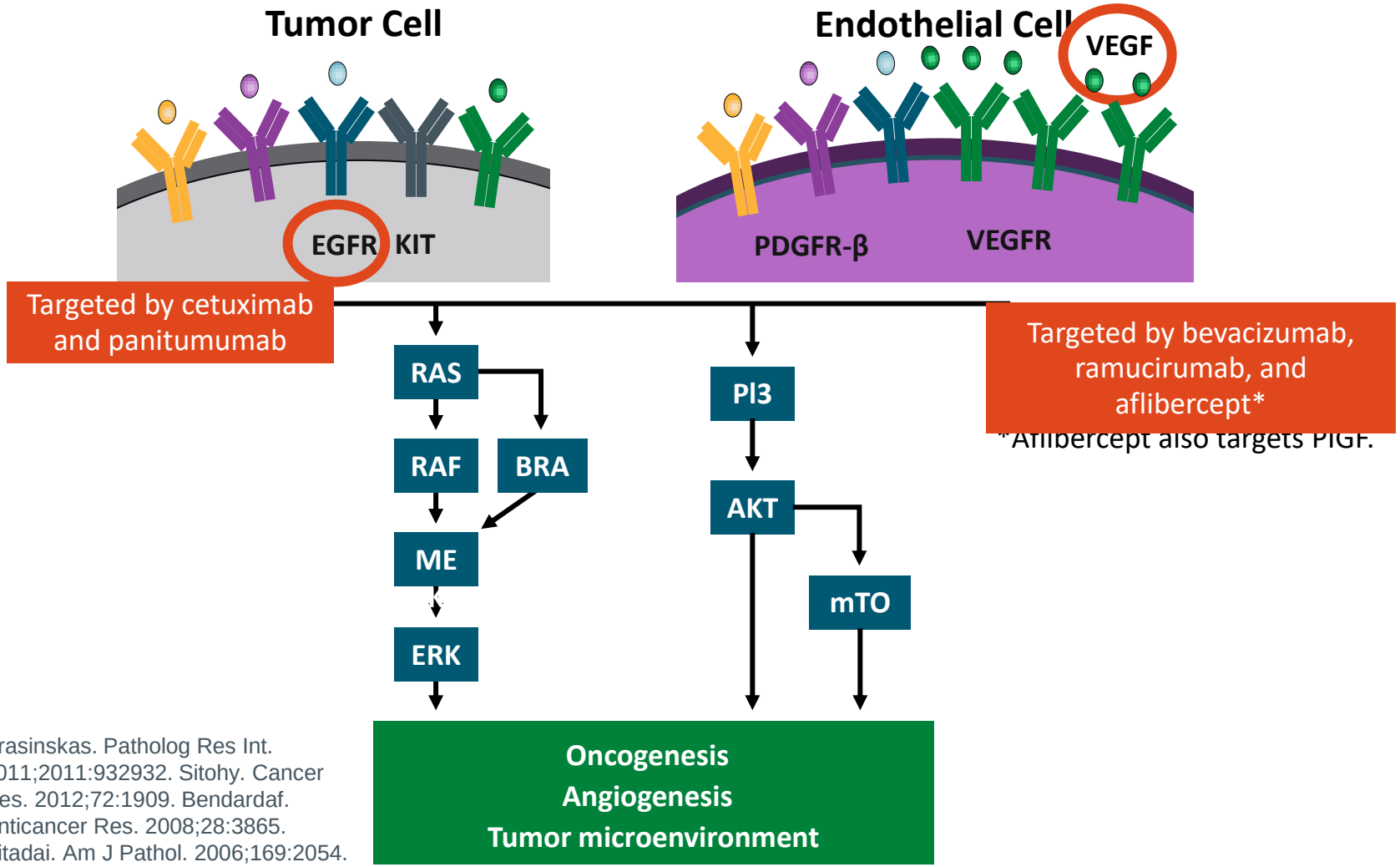
- **For all colon cancers:**
  - MMR
  - Microsatellite stability
- **Metastatic disease:**
  - *RAS*
  - *BRAF*
  - *HER2*
  - *dMMR*
  - *NTRK-1,2,3*

Molecular Classification of CRC and Associated Targeted Therapies



Dienstmann. Am Soc Clin Oncol Educ Book. 2018;38:231.

EGFR and VEGFR Growth Signaling Pathways



Krasinskas. Patholog Res Int. 2011;2011:932932. Sitohy. Cancer Res. 2012;72:1909. Bendardaf. Anticancer Res. 2008;28:3865. Kitadai. Am J Pathol. 2006;169:2054. Jayson. JCO. 2005;23:973.

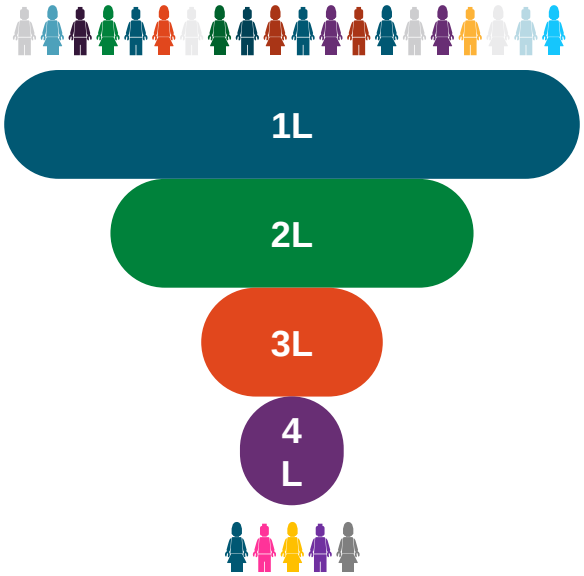
mKRK'da Tedavi Seçiminde Belirleyici Faktörler?

Patient characteristics

- Comorbidities
- Prior adjuvant treatment
- Age
- Performance status

Molecular characteristics

- RAS
- BRAF
- MSI-high
- HER2



Tumor characteristics

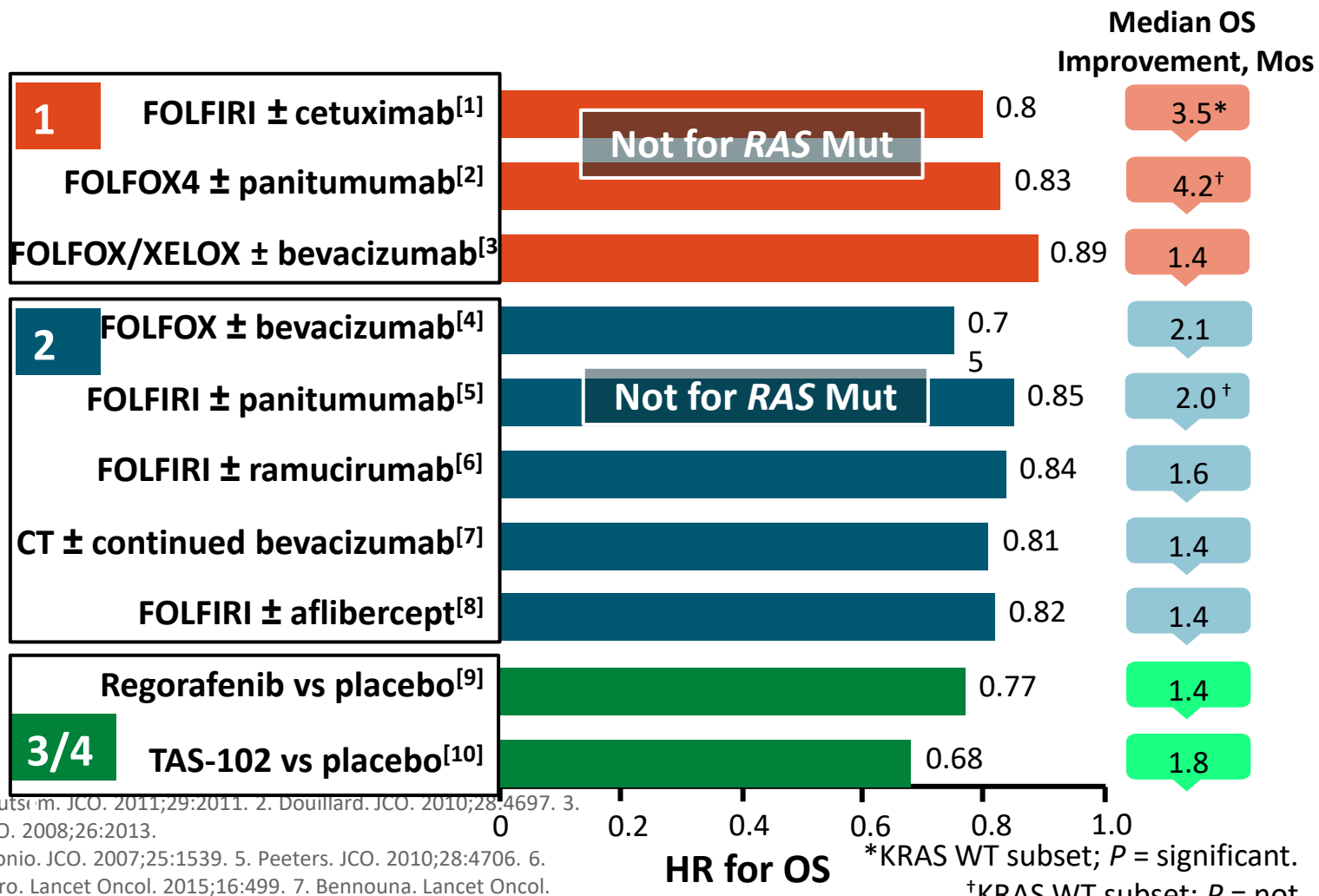
- Tumor burden
- Resectability
- Tumor location

Patient preference

- Quality of life
- Toxicity profile

Therapy tailored according to individual patient needs

Önerilebilecek Çoklu Tedavi Seçenekleri



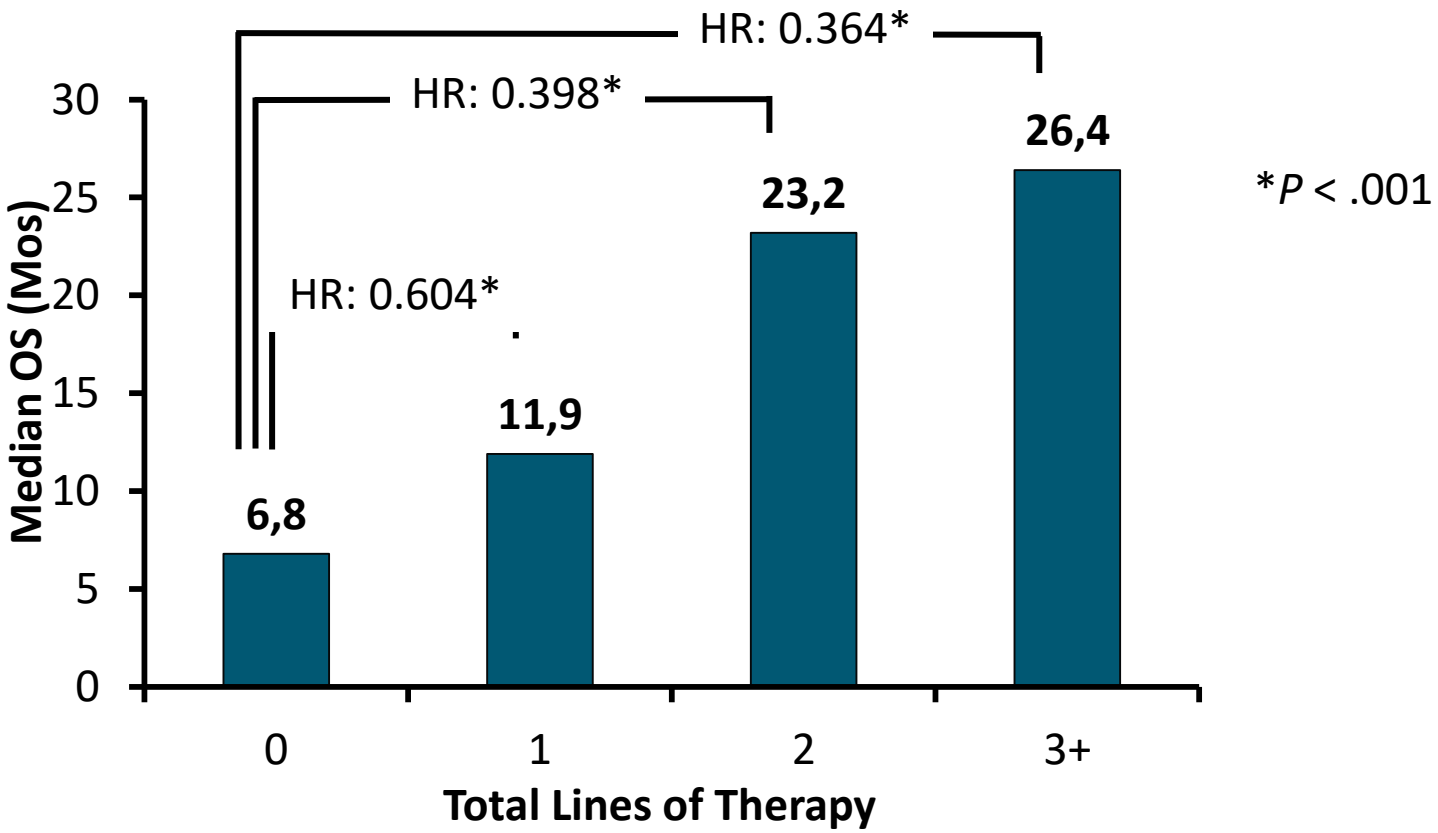
*KRAS WT subset; *P* = significant.
†KRAS WT subset; *P* = not significant.

1. Van Cutsem. JCO. 2011;29:2011. 2. Douillard. JCO. 2010;28:4697. 3. Saltz. JCO. 2008;26:2013.
4. Giantonio. JCO. 2007;25:1539. 5. Peeters. JCO. 2010;28:4706. 6. Tabernero. Lancet Oncol. 2015;16:499. 7. Bennouna. Lancet Oncol. 2013;14:29. 8. Van Cutsem. JCO. 2012;30:3499.
9. Grothey. Lancet. 2013;381:303. 10. Mayer. NEJM. 2015;372:1909.

Uygulanan Tedavi Sıra Sayısı ile mOS Artar

- Patients should be exposed to all active and approved agents during treatment

SEER Medicare Database Analysis for mCRC (2003-2007; N = 5129)



Hanna. ASCO GI 2014. Abstr 559.

Metastatik Sağ Kolon vs Sol Kolon Tdv?

- <u>Genellikle Uygulanan Kemoterapi Rejimleri</u>
  - FOLFOX/mFOLFOX6
  - FOLFIRI
  - CAPEOX
  - 5-FU/LV// Kapesitabin
  - FOLFOXIRI

± Biyolojik Ajan

Sağ Kolon: FOLFOX-BEVA/FOLFIRI-BEVA/FOLFOXIRI-BEVA

https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

Version 4.2020

RAS-WT, Microsatellite-Stable mCRC

Mutant *RAS* and Outcome With EGFR Inhibitors

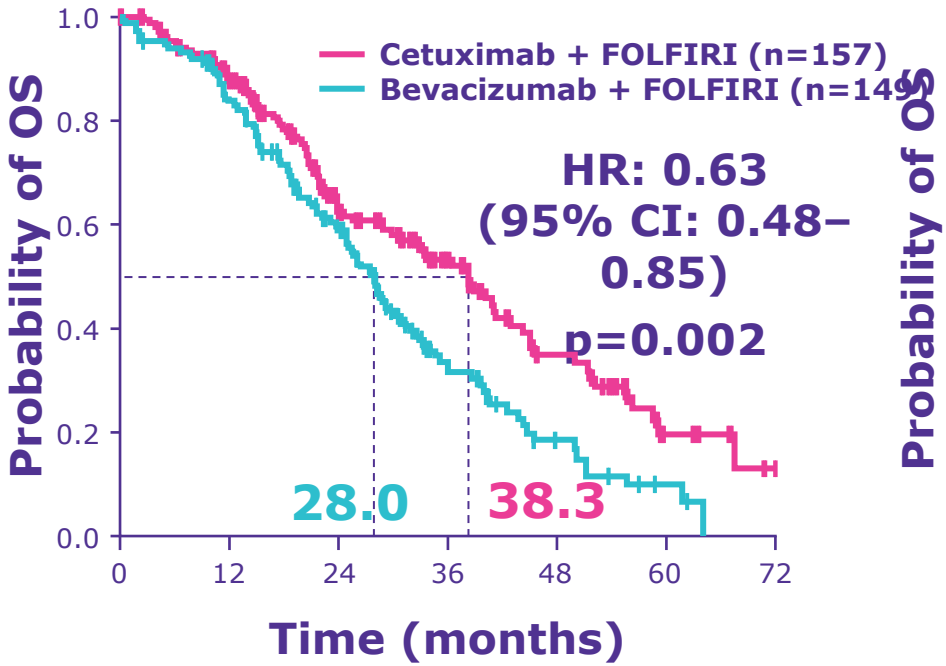
	PRIME[1,2]			OPUS[3,4]			CRYSTAL[5,6]		
	Treatment	PFS	OS	Treatment	PFS	OS	Treatment	PFS	OS
***KRAS* Ex2 WT**	Panitumumab + FOLFOX4 (n = 325)	**10.0**	**23.9**	Cetuximab + FOLFOX4 (n = 82)	**8.3**	**22.8**	Cetuximab + FOLFIRI (n = 316)	**9.9**	**23.5**
	FOLFOX4 (n = 331)	**8.6**	**19.7**	FOLFOX4 (n = 97)	**7.2**	**18.5**	FOLFIRI (n = 350)	**8.4**	**20.0**
		HR 0.80*	**HR 0.88**		**HR 0.57***	**HR 0.86***		**HR 0.70***	**HR 0.80***
***KRAS* Ex2 MT**	Panitumumab + FOLFOX4 (n = 221)	**7.4**	**15.5**	Cetuximab + FOLFOX4 (n = 77)	**5.5**	**13.4**	Cetuximab + FOLFIRI (n = 214)	**7.4**	**16.2**
	FOLFOX4 (n = 219)	**9.2**	**19.2**	FOLFOX4 (n = 59)	**8.6**	**17.5**	FOLFIRI (n = 183)	**7.7**	**16.7**
		HR 1.27*	**HR 1.17**		**HR 1.72***	**HR 1.29**		**HR 1.17**	**HR 1.04**
No *RAS* MT	Panitumumab + FOLFOX4 (n = 259)	**10.1**	**25.8**	Cetuximab + FOLFOX4 (n = 38)	**12.0**	**19.8**	Cetuximab + FOLFIRI (n = 178)	**11.4**	**28.4**
	FOLFOX4 (n = 253)	**7.9**	**20.2**	FOLFOX4 (n = 49)	**5.8**	**17.8**	FOLFIRI (n = 189)	**8.4**	**20.2**
		HR 0.72*	**HR 0.77***		**HR 0.53***	**HR 0.94***		**HR 0.56***	**HR 0.69***
Any *RAS* MT	Panitumumab + FOLFOX4 (n = 272)	**7.3**	**15.5**	Cetuximab + FOLFOX4 (n = 92)	**5.6**	**13.5**	Cetuximab + FOLFIRI (n = 246)	**7.4**	**16.4**
	FOLFOX4 (n = 276)	**8.7**	**18.7**	FOLFOX4 (n = 75)	**7.8**	**17.8**	FOLFIRI (n = 214)	**7.5**	**17.7**
		HR 1.31*	**HR 1.21***		**HR 1.54***	**HR 1.29**		**HR 1.10**	**HR 1.05**

RAS-WT, Microsatellite-Stable mCRC: Anatomik Yerleşim Önemli midir?

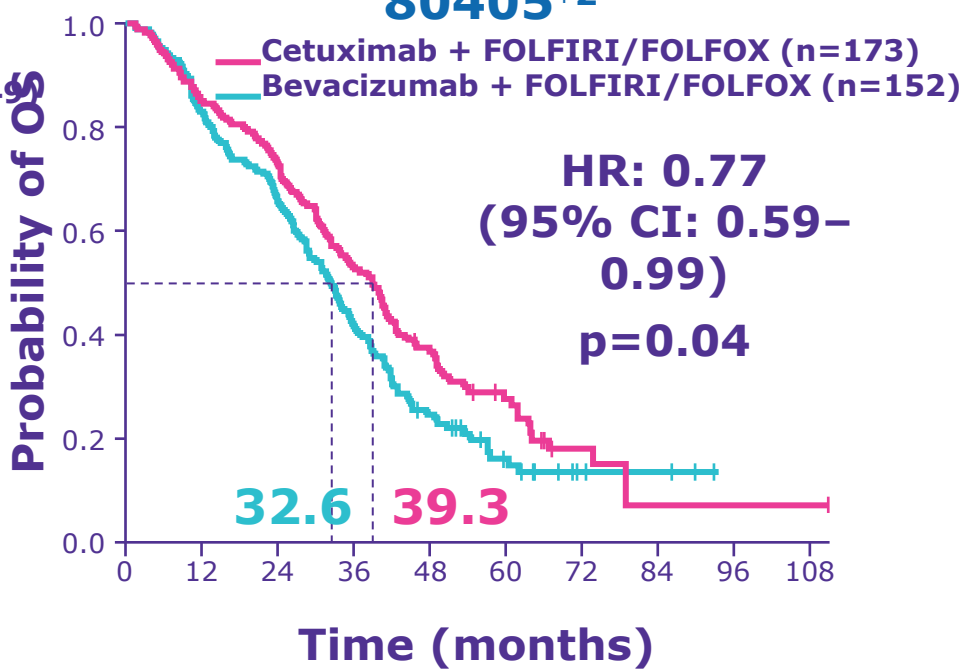
In left-sided RAS wt mCRC, cetuximab + CT has consistently shown a survival benefit vs bevacizumab + CT[1,2]

Retrospective subanalyses

OS in FIRE-3*[1]



OS in CALGB/SWOG 80405[†2]

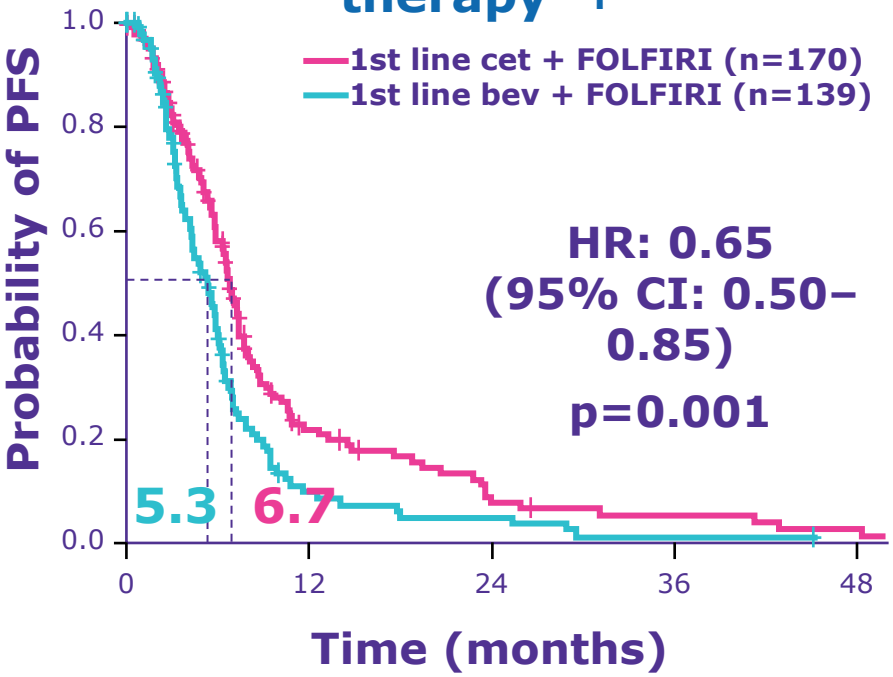


*FIRE-3 did not meet its primary endpoint of significantly improving overall response rate (ORR) based on investigators' read in patients with KRAS (exon 2) wt mCRC.[3] †The CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving overall survival in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC[4]

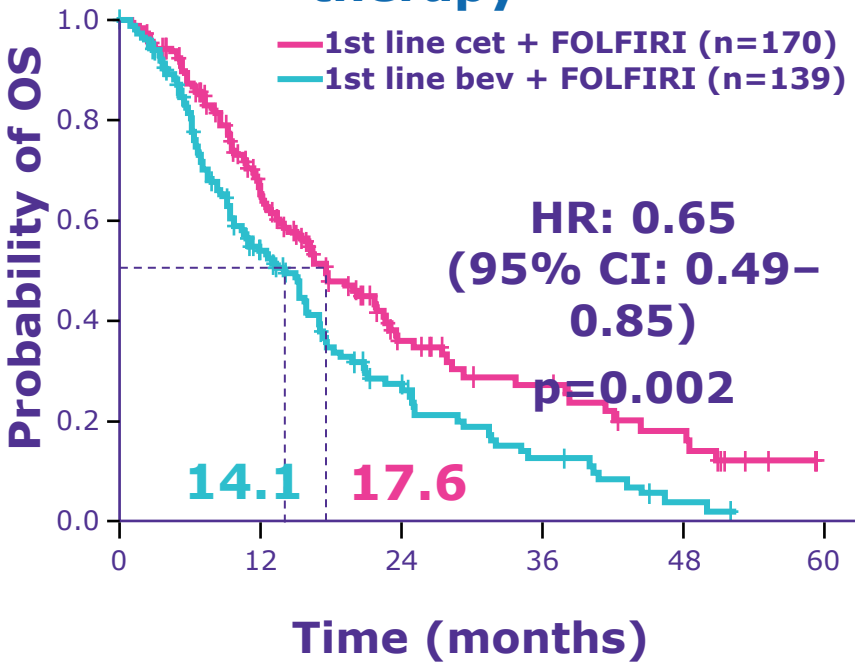
1. Tejpar S, et al. JAMA 2017;3:194–201;
2. Venook AP, et al. ESMO 2016. Special Session;
3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075;
4. Venook A, et al. JAMA. 2017;317:2392-2401.

In FIRE-3, 2nd line OS and PFS were longer after 1st line cetuximab + FOLFIRI than bevacizumab + FOLFIRI in left-sided RAS wt mCRC

PFS from start of 2nd line therapy*†[1]



OS from start of 2nd line therapy*†[1]



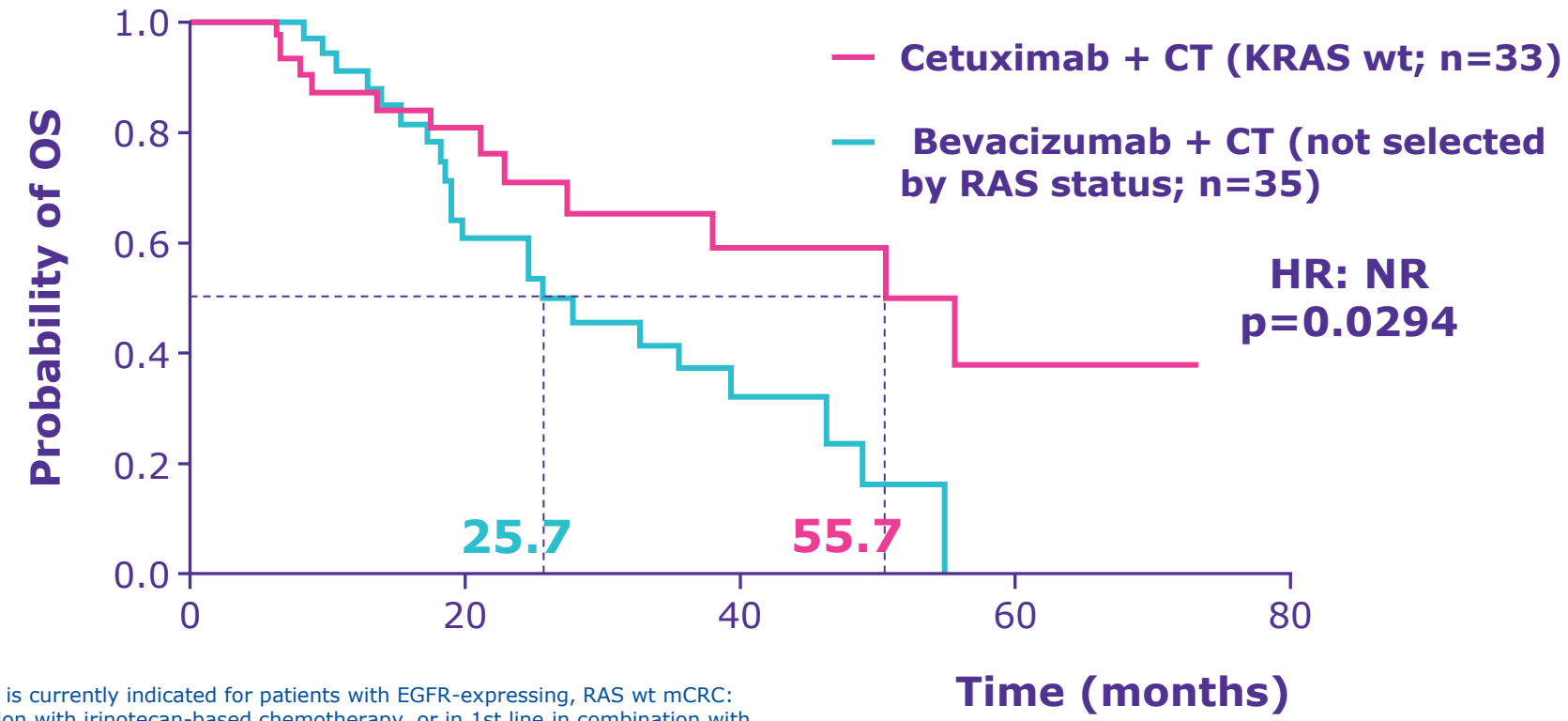
1st line cetuximab may sensitize tumors to subsequent anti-VEGF therapy[2]

*FIRE-3 did not meet its primary endpoint of significantly improving overall response rate (ORR) based on investigators' read in patients with KRAS (exon 2) wt mCRC.[3] †2nd line therapy was defined as any new anticancer drug administered for mCRC following 1st line therapy.

1. Modest DP, et al. ASCO 2017 (Abstract No. 3525);
2. Wainberg ZA, Drakaki A. Expert Opin Biol Ther 2015;15:1205–1220;
3. Heinemann V et al. Lancet Oncol 2014;15:1065–1075.

Real world data have confirmed the OS benefit of cetuximab + CT over bevacizumab + CT in left-sided tumors*[1]

Japanese single centre, retrospective case-control study*†



*Cetuximab is currently indicated for patients with EGFR-expressing, RAS wt mCRC: in combination with irinotecan-based chemotherapy, or in 1st line in combination with FOLFOX, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. †In this Japanese single-institution, retrospective, case-control study, all Erbitux-treated patients had KRAS wt mCRC, whereas those who received bevacizumab had KRAS wt or KRAS mt tumor status.[1] Cetuximab should not be used in the treatment of CRC patients whose tumors have RAS mutations or for whom RAS tumor status is unknown[2]

1. Sagawa T, et al. ASCO GI 2017 (Abstract No. 711);
2. Erbitux SmPC, June/2014.

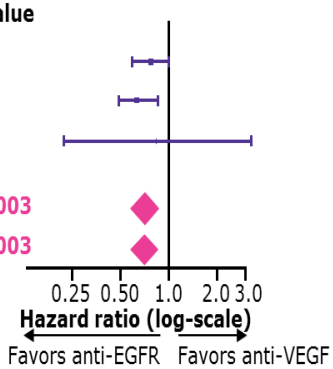
Meta-analyses support the preferential use of anti-EGFR + CT over bevacizumab + CT for LS tumors

Holch meta-analysis of OS[1]

1st line CT + anti-EGFR vs CT + bevacizumab in patients with LS tumors*

Study	n	Weight (%)	OS HR	95% CI	p-value
CALGB/SWOG 80405	325	53.8	0.77	(0.59–0.99)	
FIRE-3	306	44.2	0.63	(0.48–0.85)	
PEAK	107	2	0.84	(0.22–3.27)	
Summary (FE)			**0.71**	**(0.58–0.85)**	**0.0003**
Summary (RE)			**0.71**	**(0.58–0.85)**	**0.0003**

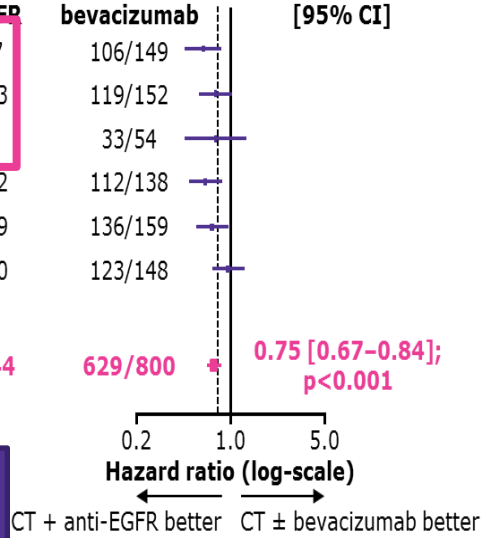
Heterogeneity: I^2 = 0%, 95% CI = (0–95.1%)
p-value = 0.575 (χ^2 test)



Arnold meta-analysis of OS[2]

1st/2nd line CT + anti-EGFR vs CT ± bevacizumab in patients with LS tumors*

Category	No. deaths/no. entered CT + anti-EGFR	No. deaths/no. entered CT ± bevacizumab	HR interaction [95% CI]
FIRE-3	86/157	106/149	
CALGB/SWOG 80405	119/173	119/152	
PEAK	29/53	33/54	
CRYSTAL	102/142	112/138	
PRIME	126/169	136/159	
20050181	129/150	123/148	
Total	**591/844**	**629/800**	**0.75 [0.67–0.84]; p<0.001**



86% of LS anti-EGFR + CT-treated patients in the head-to-head trials vs bevacizumab + CT received cetuximab + CT

FE, fixed-effects model; RE, random-effects model
*FIRE-3 did not meet its primary endpoint of significantly improving ORR in patients with KRAS (exon 2) wt mCRC based on investigators' read;[3] the OS benefit of cetuximab plus chemotherapy vs bevacizumab plus chemotherapy demonstrated for patients with RAS wt mCRC in the FIRE-3 study[4] could not be confirmed in the CALGB/SWOG 80405 study[5]

1. Holch JW, et al. Eur J Cancer 2017;70:87–98;
2. Arnold D, et al. Ann Oncol 2017; epub Apr 12. doi: 10.1093/annonc/mdx175;
3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075;
4. Stintzing S, et al. Lancet Oncol 2016;17:1426–1434;
5. Venook A, et al. JAMA. 2017;317:2392-2401.

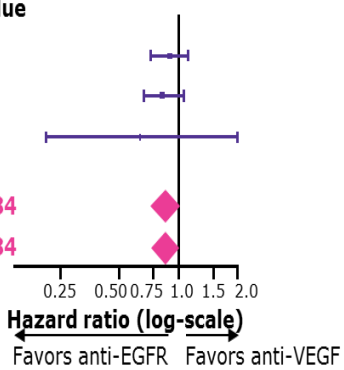
Meta-analyses support the preferential use of anti-EGFR + CT over bevacizumab + CT for LS tumors

Holch meta-analysis of PFS[1]

1st line CT + anti-EGFR vs CT + bevacizumab in patients with LS tumors*

Study	n	Weight (%)	PFS HR	95% CI	p-value
FIRE-3	306	48.9	0.9	(0.71–1.14)	
CALGB/SWOG 80405	325	48.9	0.84	(0.66–1.06)	
PEAK	107	2.2	0.65	(0.21–2)	
Summary (FE)			**0.86**	**(0.73–1.02)**	**0.084**
Summary (RE)			**0.86**	**(0.73–1.02)**	**0.084**

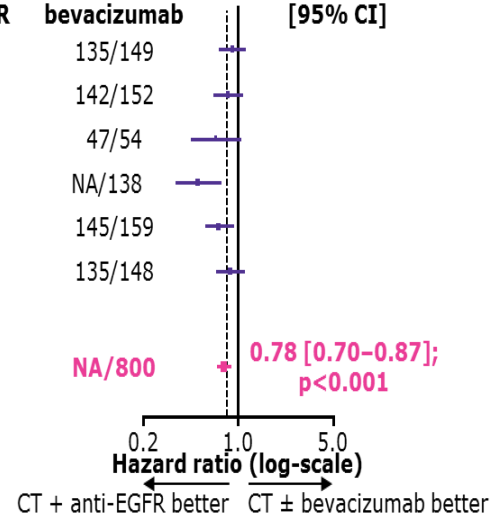
Heterogeneity: I^2 = 0%, 95% CI = (0–97.2%)
p-value = 0.813 (χ^2 test)



Arnold meta-analysis of PFS[2]

1st/2nd line CT + anti-EGFR vs CT ± bevacizumab in patients with LS tumors*

Category	No. events/no. entered CT + anti-EGFR	No. events/no. entered CT ± bevacizumab	HR interaction [95% CI]
FIRE-3	131/157	135/149	
CALGB/SWOG 80405	156/173	142/152	
PEAK	43/53	47/54	
CRYSTAL	NA/142	NA/138	
PRIME	146/169	145/159	
20050181	140/150	135/148	
Total	**NA/844**	**NA/800**	**0.78 [0.70–0.87]; p<0.001**



FE, fixed-effects model; RE, random-effects model
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1. Holch JW, et al. Eur J Cancer 2017;70:87–98;
2. Arnold D, et al. Ann Oncol 2017; epub Apr 12. doi: 10.1093/annonc/mdx175;
3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075;
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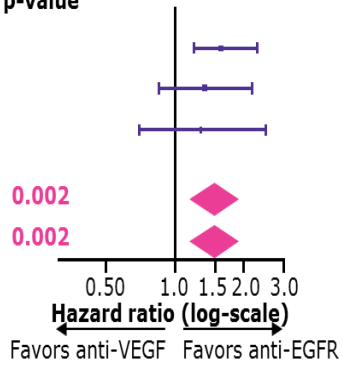
Meta-analyses support the preferential use of anti-EGFR + CT over bevacizumab + CT for LS tumors

Holch meta-analysis of ORR[1]

1st line CT + anti-EGFR vs CT + bevacizumab in patients with LS tumors*

Study	n	Weight (%)	ORR	95% CI	p-value
CALGB/SWOG 80405	325	57.7	1.6	(1.2–2.3)	
FIRE-3	306	27.3	1.37	(0.85–2.19)	
PEAK	107	15.1	1.3	(0.7–2.5)	
Summary (FE)			**1.49**	**(1.16–1.9)**	**0.002**
Summary (RE)			**1.49**	**(1.16–1.9)**	**0.002**

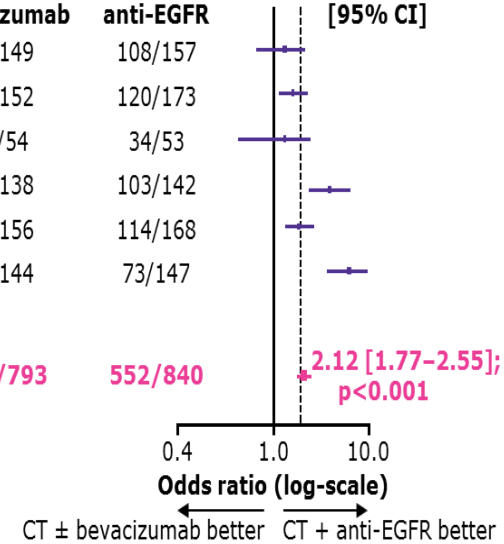
Heterogeneity: I^2 = 0%, 95% CI = (0–88%)
p-value = 0.786 (χ^2 test)



Arnold meta-analysis of ORR[2]

1st/2nd line CT + anti-EGFR vs CT ± bevacizumab in patients with LS tumors*

Category	No. response/no. entered CT ± bevacizumab	No. response/no. entered CT + anti-EGFR
FIRE-3	92/149	108/157
CALGB/SWOG 80405	88/152	120/173
PEAK	31/54	34/53
CRYSTAL	56/138	103/142
PRIME	82/156	114/168
20050181	19/144	73/147
Total	**368/793**	**552/840**



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1. Holch JW, et al. Eur J Cancer 2017;70:87–98;
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3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075;
4. Stintzing S, et al. Lancet Oncol 2016;17:1426–1434;
5. Venook A, et al. JAMA. 2017;317:2392-2401.

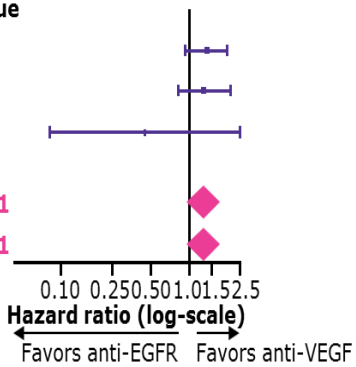
No significant difference in OS for CT + anti-EGFR vs CT ± bevacizumab for RS tumors

Holch meta-analysis of OS[1]

1st line CT + anti-EGFR vs CT + bevacizumab in patients with RS tumors*

Study	n	Weight (%)	OS HR	95% CI	p-value
CALGB/SWOG 80405	149	59.5	1.36	(0.93–1.99)	
FIRE-3	88	37.6	1.31	(0.81–2.11)	
PEAK	36	2.9	0.45	(0.08– 2.49)	
Summary (FE)			**1.3**	**(0.97–1.74)**	**0.081**
Summary (RE)			**1.3**	**(0.97–1.74)**	**0.081**

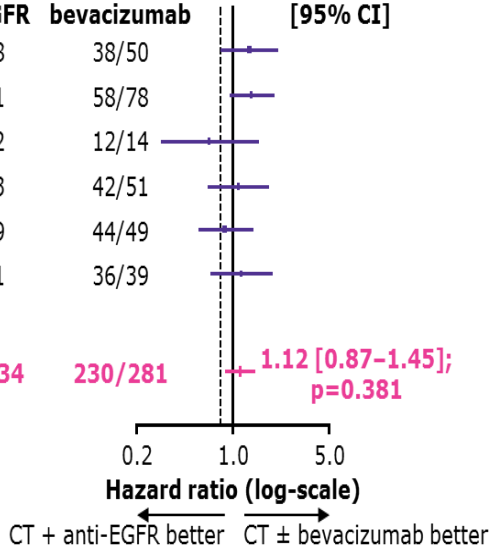
Heterogeneity: I^2 = 0%, 95% CI = (0–99.4%)
p-value = 0.468 (χ^2 test)



Arnold meta-analysis of OS[2]

1st/2nd line CT + anti-EGFR vs CT ± bevacizumab in patients with RS tumors*

Category	No. deaths/no. entered CT + anti-EGFR	No. deaths/no. entered CT ± bevacizumab	HR interaction [95% CI]
FIRE-3	31/38	38/50	
CALGB/SWOG 80405	56/71	58/78	
PEAK	19/22	12/14	
CRYSTAL	26/33	42/51	
PRIME	34/39	44/49	
20050181	28/31	36/39	
Total	**194/234**	**230/281**	**1.12 [0.87–1.45]; p=0.381**



FE, fixed-effects model; RE, random-effects model
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1. Holch JW, et al. Eur J Cancer 2017;70:87–98;
2. Arnold D, et al. Ann Oncol 2017; epub Apr 12. doi: 10.1093/annonc/mdx175;
3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075;
4. Stintzing S, et al. Lancet Oncol 2016;17:1426–1434;
5. Venook A, et al. JAMA. 2017;317:2392-2401.

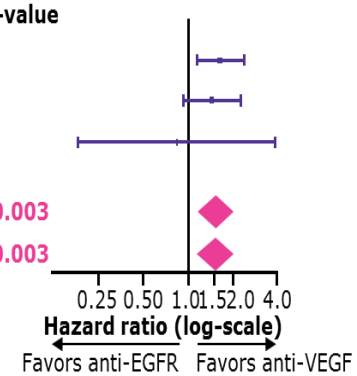
No PFS benefit for CT + anti-EGFR vs CT ± bevacizumab for RS tumors

Holch meta-analysis of PFS[1]

1st line CT + anti-EGFR vs CT + bevacizumab in patients with RS tumors*

Study	n	Weight (%)	PFS HR	95% CI	p-value
CALGB/SWOG 80405	149	59	1.64	(1.15–2.36)	
FIRE-3	88	37.7	1.44	(0.92–2.26)	
PEAK	36	3.3	0.84	(0.18–3.79)	
Summary (FE)			**1.53**	**(1.16–2.01)**	**0.003**
Summary (RE)			**1.53**	**(1.16–2.01)**	**0.003**

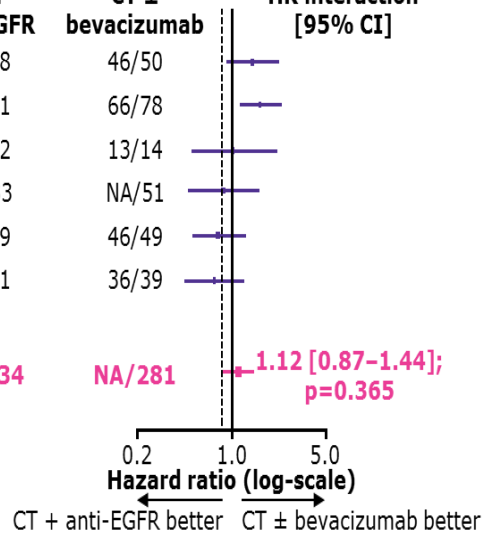
Heterogeneity: I^2 = 0%, 95% CI = (0–98.3%)
p-value = 0.668 (χ^2 test)



Arnold meta-analysis of PFS[2]

1st/2nd line CT + anti-EGFR vs CT ± bevacizumab in patients with RS tumors*

Category	No. events/no. entered: CT + anti-EGFR	No. events/no. entered: CT ± bevacizumab	HR interaction [95% CI]
FIRE-3	35/38	46/50	
CALGB/SWOG 80405	67/71	66/78	
PEAK	21/22	13/14	
CRYSTAL	NA/33	NA/51	
PRIME	34/39	46/49	
20050181	28/31	36/39	
Total	**NA/234**	**NA/281**	**1.12 [0.87–1.44]; p=0.365**



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4. Stintzing S, et al. Lancet Oncol 2016;17:1426–1434;
5. Venook A, et al. JAMA. 2017;317:2392-2401.

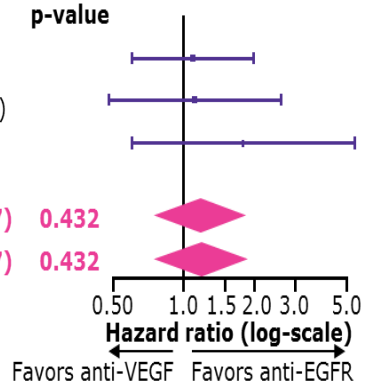
Cetuximab + CT is effective in patients with RS tumors: ORR numerically favors anti-EGFR + CT over bevacizumab + CT

Holch meta-analysis of ORR[1]

1st line CT + anti-EGFR vs CT + bevacizumab in patients with RS tumors*

Study	n	Weight (%)	ORR	95% CI	p-value
CALGB/SWOG 80405	149	55.2	1.1	(0.6–2)	
FIRE-3	88	28.2	1.11	(0.48–2.59)	
PEAK	36	16.6	1.8	(0.6–5.4)	
Summary (FE)			**1.2**	**(0.77–1.87)**	**0.432**
Summary (RE)			**1.2**	**(0.77–1.87)**	**0.432**

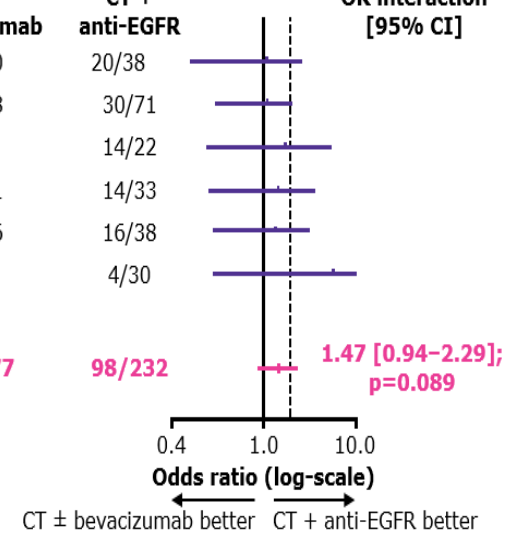
Heterogeneity: I^2 = 0%, 95% CI = (0–94.2%)
p-value = 0.728 (χ^2 test)



Arnold meta-analysis of ORR[2]

1st/2nd line CT + anti-EGFR vs CT ± bevacizumab in patients with RS tumors*

Category	No. response/no. entered: CT ± bevacizumab	No. response/no. entered: CT + anti-EGFR	OR interaction [95% CI]
FIRE-3	25/50	20/38	
CALGB/SWOG 80405	31/78	30/71	
PEAK	7/14	14/22	
CRYSTAL	17/51	14/33	
PRIME	16/46	16/38	
20050181	1/38	4/30	
Total	**97/277**	**98/232**	**1.47 [0.94–2.29]; p=0.089**



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1. Holch JW, et al. Eur J Cancer 2017;70:87–98;
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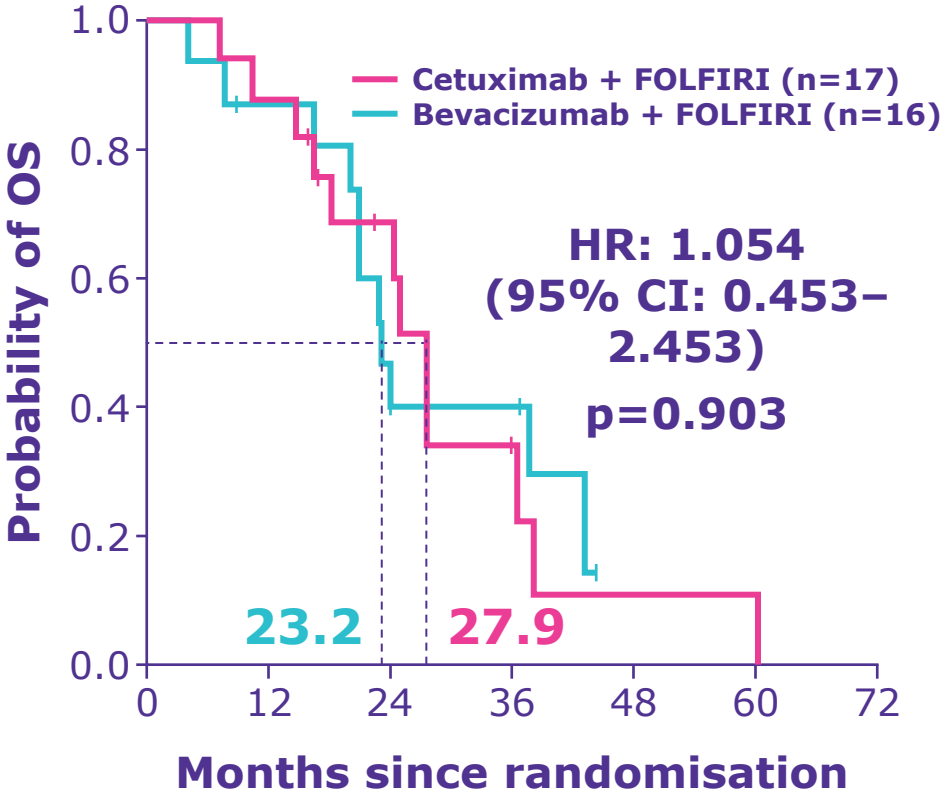
4. Stintzing S, et al. Lancet Oncol 2016;17:1426–1434;
5. Venook A, et al. JAMA. 2017;317:2392-2401.

Patients with RS tumors who have ETS ≥20% have similar outcomes with cetuximab + CT to bevacizumab + CT[1]

Sub-analysis of FIRE-3 in patients with RS tumors and ETS ≥20%*[1]



	Cetuximab + FOLFIRI (n=17)	Bev + FOLFIRI (n=16)	HR/OR* (p-value)
Median PFS, months	7.8	13.4	1.72 (p=0.14)
Median DpR, %	58	41	N/A (p=0.30)
ORR, %	88	94	0.5 (p=0.99)

DpR, depth of response (maximum shrinkage measured from baseline); ETS, early tumor shrinkage
*FIRE-3 did not meet its primary endpoint of significantly improving ORR in patients with KRAS (exon 2) wt mCRC based on investigators' read.[2]

1. Holch JW, et al. ASCO 2017 (Abstract No. 3586);
2. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075.

ESTER: therapeutic intensification by FOLFIRINOX and cetuximab in the 1st line of treatment for patients with metastatic colorectal cancer RAS wild-type

Samalin et al. (Abstract P-099)

Background:

- Triplet CT is a viable option for patients with metastatic colorectal cancer who are suitably fit and motivated[1,2]
  - 1st-line efficacy of anti-EGFR + triplet CT in mCRC has been demonstrated in several Phase II studies[3–5] and continues to be investigated[6–8]

This study: retrospectively analyzed results from three clinical trials and individual medical records to assess the efficacy of cetuximab + FOLFIRINOX[9]

Study design:[9]

Retrospective analysis of:

- **Three clinical trials**
- **Individual records**

→ **RAS wt mCRC receiving 1L cetuximab* + FOLFIRINOX*** (N=70)

Primary endpoint: PFS

Secondary endpoints: 9-month PFS rate, ORR (RECIST v1.1), OS, safety

1. Cremolini C, et al. Lancet Oncol 2015;16:1306–15;
2. Loupakis F, et al. N Engl J Med 2014;371:1609–18;
3. Cremolini C, et al. JAMA. 2018;4:529–36;
4. Modest DP, et al. ASCO 2019 (Abstract 3530);
5. Geissler M, et al. ASCO 2019 (Abstract 3511);
6. EU Clinical Trials Register. Clinical trials. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-004849-11/DE. (last accessed July 2019);
7. Clinicaltrials.gov. NCT02515734. Available at: https://clinicaltrials.gov/ct2/show/NCT02515734. (last accessed July 2019);
8. Clinicaltrials.gov. NCT01802645. Available at: https://clinicaltrials.gov/ct2/show/NCT01802645. (last accessed July 2019);
9. Samalin E, et al. WCGC 2019 (Abstract P-099).

ESTER: therapeutic intensification by FOLFIRINOX and cetuximab in the 1st line of treatment for patients with metastatic colorectal cancer RAS wild-type

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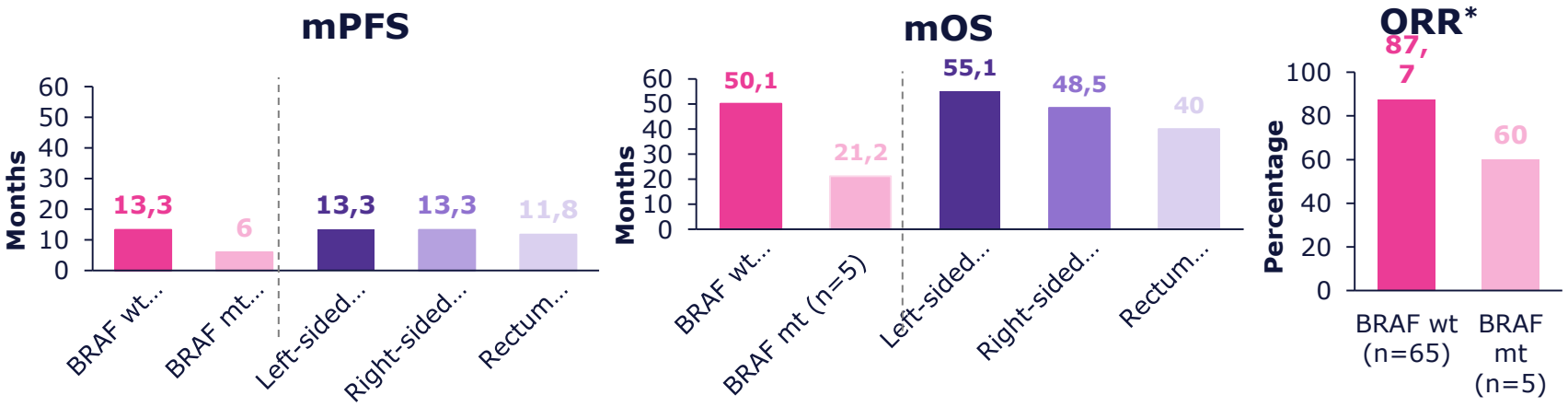


Authors conclusions:

- Therapeutic intensification with cetuximab + FOLFIRINOX for patients with initially unresectable RAS wt mCRC is feasible and efficient
- Other prospective studies are needed to confirm the efficacy of this combination, especially in BRAF mt mCRC

Response rates, %	
ORR	85.7
CR	20.0
PR	65.7
SD	7.1
PD	2.9

Safety (Grade 3/4 AEs, ≥10 %), %	
Diarrhea	31.4
Neutropenia	21.4
Fatigue	20.0
Oxaliplatin-related neuropathy	14.3

*Results by tumor location not reported.
AEs, adverse events; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Samalin E, et al. WCGC 2019 (Abstract P-099).

mFOLFOXIRI ± cetuximab as conversion therapy (FOCULM)

ASCO GI; Hu H, et al. Abstract No. 99 (slide 1/1)

FOCULM was a non-randomized, open-label, multicentre Phase II trial[1]

RAS/BRAF wt patients with unresectable liver metastases

1L mFOLFOXIRI + QW cetuximab (n=67)

1L mFOLFOXIRI (n=34)

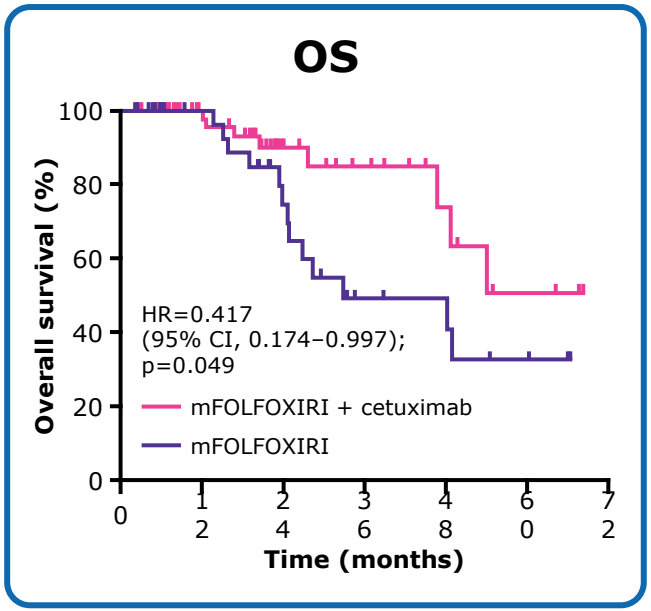
Until PD, resectability, intolerability or completion of 12 cycles

Primary endpoint: rate of no evidence of disease (NED)

Secondary endpoints: ORR, local or ablative treatment rate, resection rate, OS, PFS and safety

Results

Outcome	mFOLFOXIRI + cetuximab (n=67)	mFOLFOXIRI (n=34)	p-value
Rate of NED, n (%)	45 (67)	13 (38)	0.005
ORR, n (%)	64 (96)	26 (77%)	0.004
Overall resection rate, n (%)	31 (46)	10 (29)	0.103
R0 resection rate, n (%)	23 (34)	7 (21)	0.153
mPFS, months (CI)	15.5 (13.2–	14.2 (11.0–	0.246



Authors' conclusions

mFOLFOXIRI + cetuximab significantly improved the rate of NED, ORR, OS and deep tumor shrinkage and is therefore an effective conversion regimen in this patient population

DpR, depth of response; NED, no evidence of disease; ORR, overall response rate; OS, overall survival; QW, weekly; mPFS, median progression-free survival; PD, disease progression

1. Clinicaltrials.gov. NCT02063529. Available from: https://clinicaltrials.gov/ct2/show/NCT02063529. Last accessed: February 2020.

What are consensus molecular subtypes?

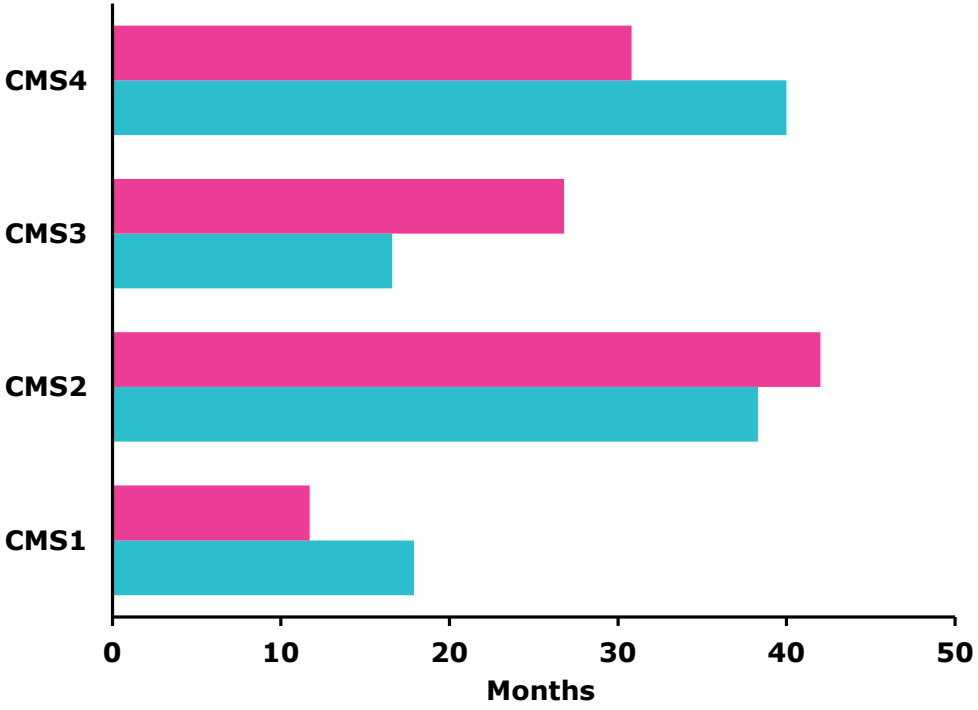
- Consensus molecular subtypes (CMS) refer to a signature biology or gene expression pattern[1,2]
- Retrospective analyses from FIRE-3* and CALGB/SWOG 80405† indicate a prognostic role for CMS and suggest CMS may be predictive for response to targeted therapies and/or chemotherapy; however, this role is poorly understood[3,4]
- CMS are not currently used to guide treatment decisions in clinical practice, likely owing to their complexity[5]

CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		KRAS mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Right-sided tumors; mucinous histology		75% RAS mt (often combined with PIK3CA mt); no association with location	EMT signature
FIRE-3: mOS 14.8 months CALGB/SWOG 80405: 15.0 months	FIRE-3: mOS 31.9 months CALGB/SWOG 80405: 40.3 months	FIRE-3: mOS 18.7 months CALGB/SWOG 80405: 24.3 months	FIRE-3: mOS 24.8 months CALGB/SWOG 80405: 31.4 months

CIMP, CpG island methylator phenotype; CMS, consensus molecular subtypes; EMT, epithelial-mesenchymal transition MSI, microsatellite instability high; ORR, overall response rate; SCNA, somatic copy number alteration; TGF-β, transforming growth factor beta.
*FIRE-3 did not meet its primary endpoint of significantly improving ORR based on investigators' read in patients with KRAS (exon 2) wt mCRC;[6]
†CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving overall survival in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC.[7]

Retrospective analyses from FIRE-3* and CALGB/SWOG 80405† suggest that CMS may influence the efficacy of cetuximab + CT[1,2]

mOS with cetuximab + CT 1st-line treatment in RAS wt mCRC[1,2]



FIRE-3 – 100% of patients received **FOLFIRI**[3]

CALGB/SWOG 80405 – 73.7% of patients received **FOLFOX**[4]

? Could differences in mOS by CMS reflect interactions between cetuximab and the CT backbone?

CT, chemotherapy; mOS, median overall survival; ORR, overall response rate.
*FIRE-3 did not meet its primary endpoint of significantly improving ORR based on investigators' read in patients with KRAS (exon 2) wt mCRC;[3]
†CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving overall survival with cetuximab + CT vs bevacizumab + CT in patients with KRAS (exon 2) wt mCRC.[4]

1. Lenz HJ, et al.JCO 2019; doi.org/10.1200/JCO.18.02258;
2. Messersmith WA. Discussant – Making Sense of Consensus; Molecular Subtypes session at ASCO 2017;
3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075;
4. Venook AP, et al. JAMA 2017;317:2392–2401.

What might be the optimal combinations for 1st-line therapy by CMS status?

The longest mOS is achieved with 1st-line cetuximab + CT in 3 out of 4 CMS groups

	CALGB/SWOG 80405[1*] 73.7% of patients received FOLFOX[2]		FIRE-3[3†] 100% of patients received FOLFIRI[4]	
	mOS (months)			
	Cetuximab arm	Bevacizumab arm	Cetuximab arm	Bevacizumab arm
CMS1	11.7	22.5	17.9	13.1
CMS2	42.0	36.0	38.3	29.1
CMS3	26.8	15.1	16.6	18.6
CMS4	30.8	32.7	40.1	21.1

Best combination?[5]

- Bevacizumab + FOLFOX
- Cetuximab + FOLFOX/FOLFIRI
- Cetuximab + FOLFOX
- Cetuximab + FOLFIRI

Cetuximab + CT may be the best therapy choice for CMS2, CMS3 and CMS4, accounting for ~86% of patients[5]

CT, chemotherapy; mOS, median overall survival.
*CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving overall survival in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC.[2] †FIRE-3 did not meet its primary endpoint of significantly improving overall response rate (ORR) based on investigators' read in patients with KRAS (exon 2) wt mCRC.[4]

1. Lenz HJ, et al. JCO 2019; doi.org/10.1200/JCO.18.02258;
2. Venook AP, et al. JAMA 2017;317:2392–2401;
3. Messersmith WA. Discussant – Making Sense of Consensus; Molecular Subtypes session at ASCO 2017;
4. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075;
5. Aderka D, et al. Lancet Oncol 2019;20:e227–283.

CALGB/SWOG 80405: Sonuç/Öneri

KRAS-WT mKRK'lerde primer tümör yerleşimi prognostiktir

- PFS, OS süreleri Solda vs Sağ kolon tümörüne göre daha uzundur

Tümör yerleşimi biyolojik ajanlara cevapta prediktirftir

- İlk sırada KT+Ctx (vs KT-Beva) ile tedavi edilen sol kolon tümörlerinde OS süreleri belirgin daha uzundur
- Sağ kolon yerleşimli tümörler il sırada KT-Beva (vs KT-Ctx) ile tedavi edildiklerinde daha fazla yarar görürler
- Biyomarkırların tanımlanması ile anatomik yerleşim yerine kişisel tedavilerin oluşturulmasında daha belirleyici olacaktır

Venook AP, et al. ASCO 2016. Abstract 3504.

Randomized phase 3 study of panitumumab with FOLFOX4 compared to FOLFOX4 alone as first-line treatment in patients with metastatic colorectal cancer: the PRIME trial

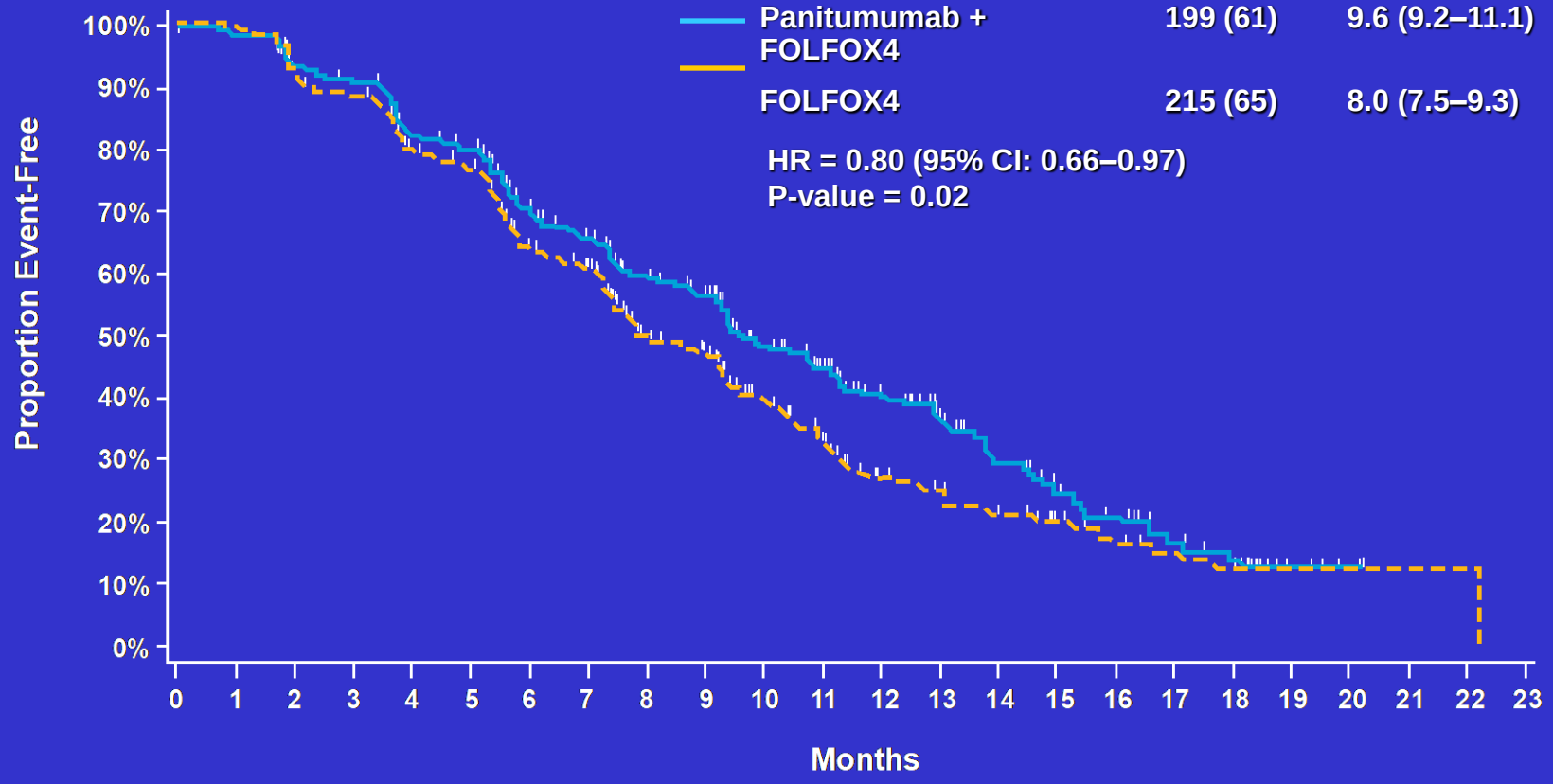
S. Siena,[1] J. Cassidy,[2]
J. Tabernero,[3] R. Burkes,[4] M.E. Barugel,[5]
Y. Humblet,[6] D. Cunningham,[7]
F. Xu,[8] J. Gansert,[8] J.Y. Douillard[9]

[1]Ospedale Niguarda Ca' Granda, Milan, Italy; [2]The Beatson West Of Scotland Cancer Centre, Glasgow, United Kingdom; [3]Vall d'Hebron University Hospital, Barcelona, Spain; [4]Mount Sinai Hospital, Toronto, Canada; [5]Hospital de Gastroenterología, Buenos Aires, Argentina; [6]Centre du Cancer de l'Université Catholique de Louvain, Brussels, Belgium; [7]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [8]Amgen Inc., Thousand Oaks, California, [9]Centre René Gauducheau, Nantes, France;

WT *KRAS*: Progression-Free Survival

	Events n (%)	Median (95% CI) months
Panitumumab + FOLFOX4	199 (61)	9.6 (9.2–11.1)
FOLFOX4	215 (65)	8.0 (7.5–9.3)

HR = 0.80 (95% CI: 0.66–0.97)
P-value = 0.02

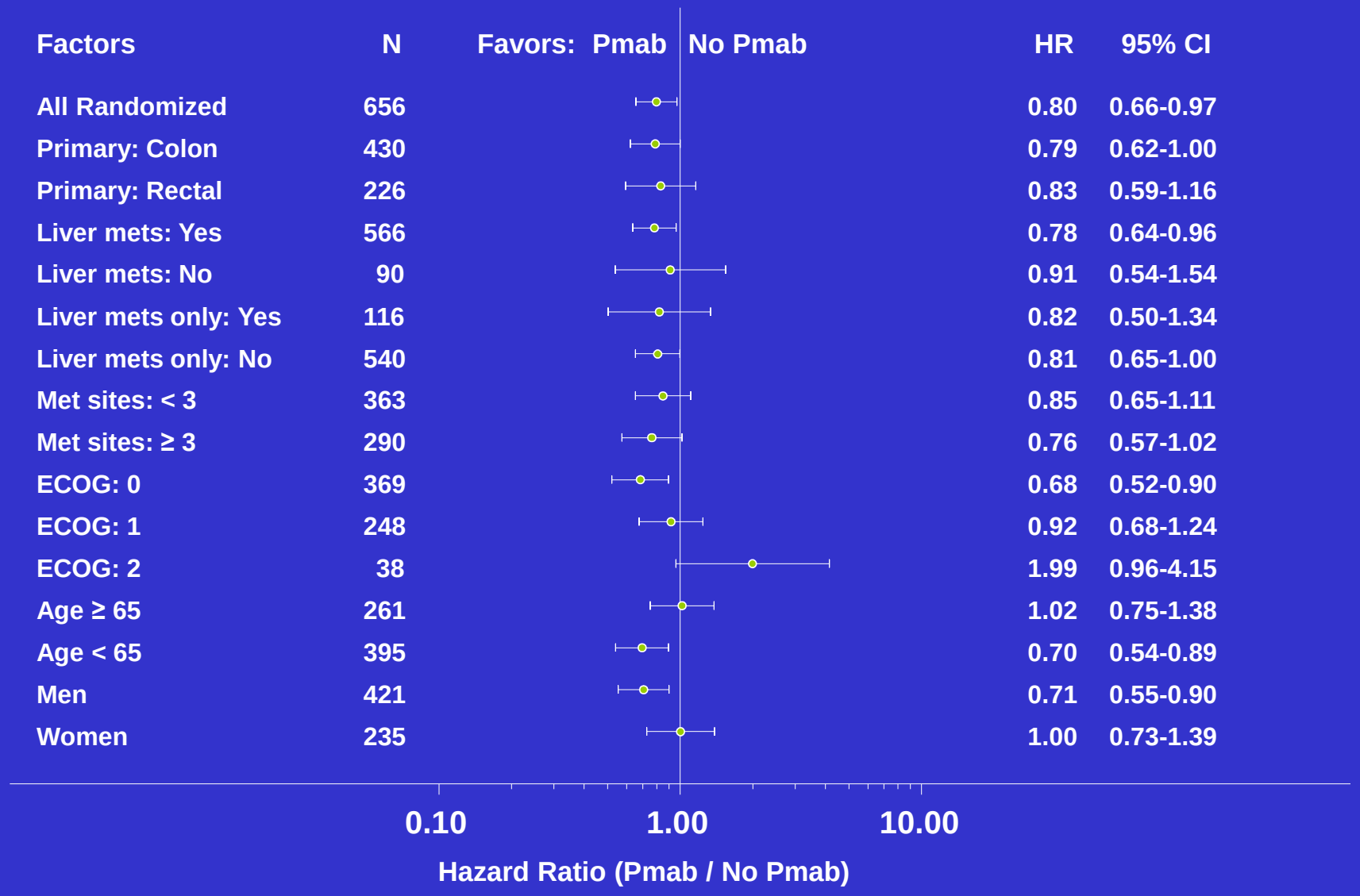


Patients at risk:

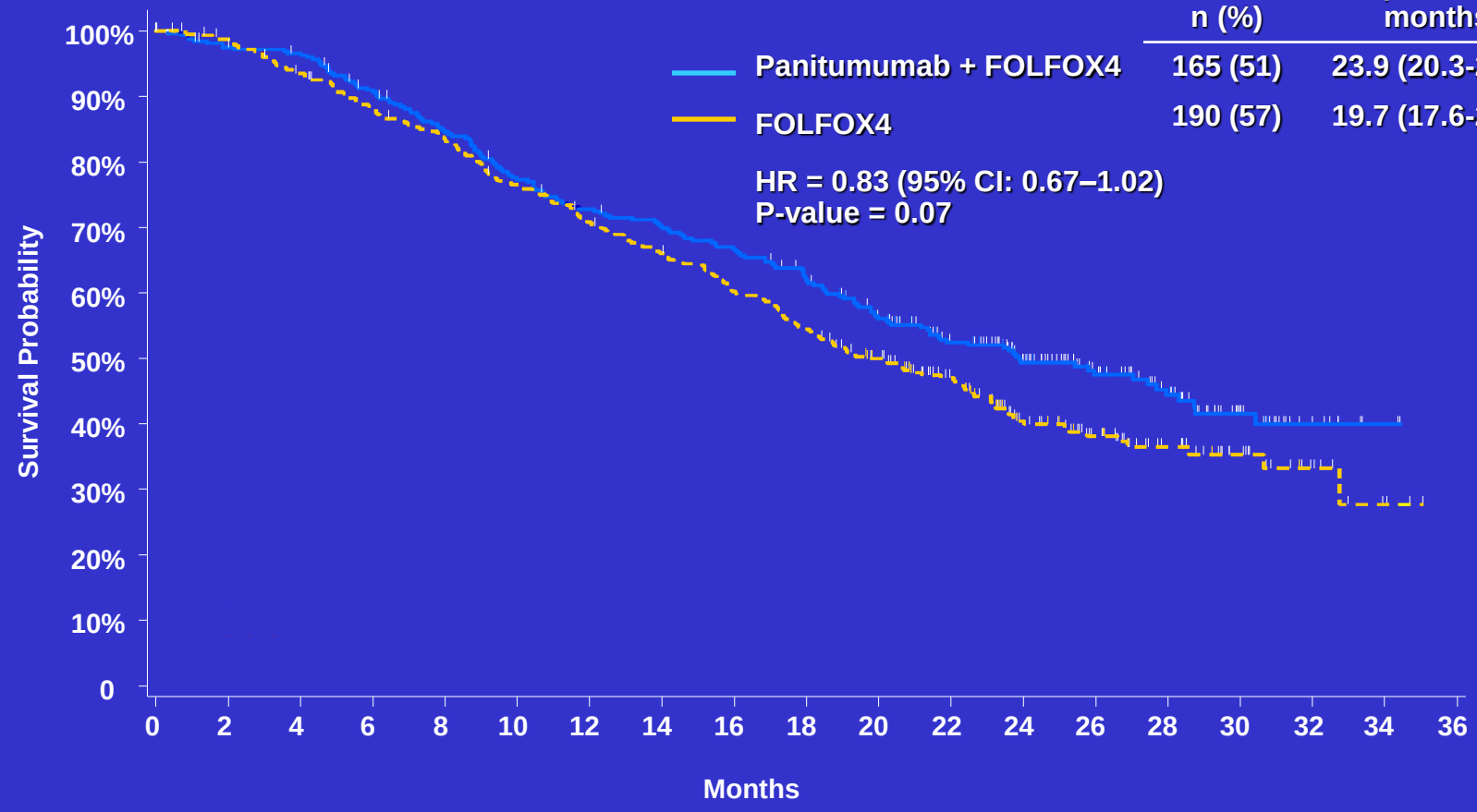
Panitumumab+FOLFOX4	325	313	294	284	254	243	204	187	156	145	111	94	73	57	39	28	22	14	10	4	1	0	0	0
FOLFOX4 alone	331	321	296	281	242	231	185	172	127	113	82	65	41	36	29	22	16	12	10	2	1	1	1	0

WT *KRAS*: Subgroup Analyses for PFS

Factors	N	HR	95% CI
All Randomized	656	0.80	0.66-0.97
Primary: Colon	430	0.79	0.62-1.00
Primary: Rectal	226	0.83	0.59-1.16
Liver mets: Yes	566	0.78	0.64-0.96
Liver mets: No	90	0.91	0.54-1.54
Liver mets only: Yes	116	0.82	0.50-1.34
Liver mets only: No	540	0.81	0.65-1.00
Met sites: < 3	363	0.85	0.65-1.11
Met sites: ≥ 3	290	0.76	0.57-1.02
ECOG: 0	369	0.68	0.52-0.90
ECOG: 1	248	0.92	0.68-1.24
ECOG: 2	38	1.99	0.96-4.15
Age ≥ 65	261	1.02	0.75-1.38
Age < 65	395	0.70	0.54-0.89
Men	421	0.71	0.55-0.90
Women	235	1.00	0.73-1.39



WT *KRAS*: Overall Survival



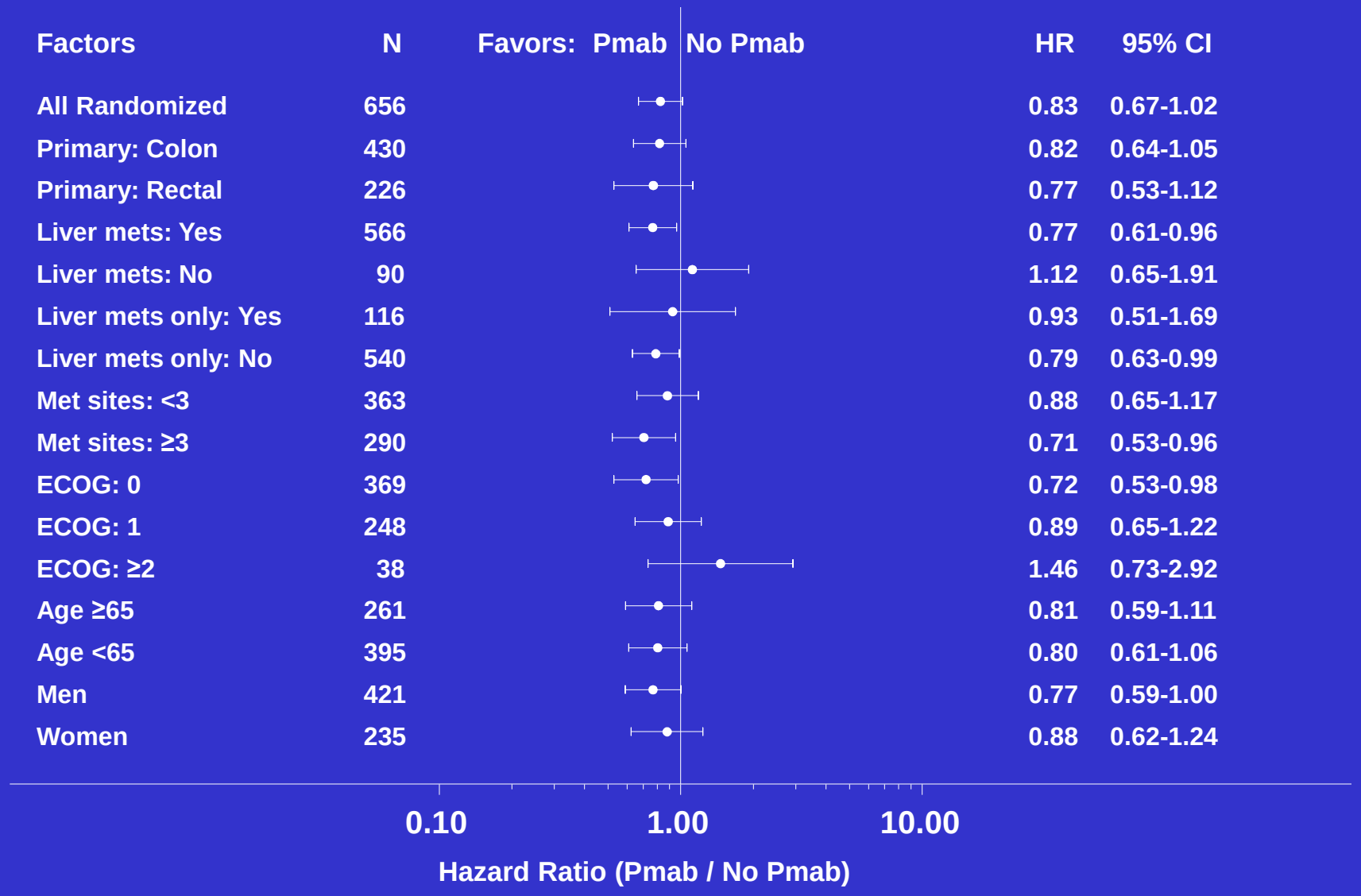
	Events n (%)	Median (95% CI) months
Panitumumab + FOLFOX4	165 (51)	23.9 (20.3-28.3)
FOLFOX4	190 (57)	19.7 (17.6-22.6)

Patients at risk:

Panitumumab+FOLFOX4	325	315	310	288	266	242	227	217	207	189	164	135	104	74	55	29	9	2	0
FOLFOX4 alone	331	320	301	281	265	242	223	207	188	170	145	116	77	56	36	21	9	3	0

WT *KRAS*: Subgroup Analyses for OS

Factors	N	HR	95% CI
All Randomized	656	0.83	0.67-1.02
Primary: Colon	430	0.82	0.64-1.05
Primary: Rectal	226	0.77	0.53-1.12
Liver mets: Yes	566	0.77	0.61-0.96
Liver mets: No	90	1.12	0.65-1.91
Liver mets only: Yes	116	0.93	0.51-1.69
Liver mets only: No	540	0.79	0.63-0.99
Met sites: <3	363	0.88	0.65-1.17
Met sites: ≥3	290	0.71	0.53-0.96
ECOG: 0	369	0.72	0.53-0.98
ECOG: 1	248	0.89	0.65-1.22
ECOG: ≥2	38	1.46	0.73-2.92
Age ≥65	261	0.81	0.59-1.11
Age <65	395	0.80	0.61-1.06
Men	421	0.77	0.59-1.00
Women	235	0.88	0.62-1.24



WT *KRAS*: Objective Response

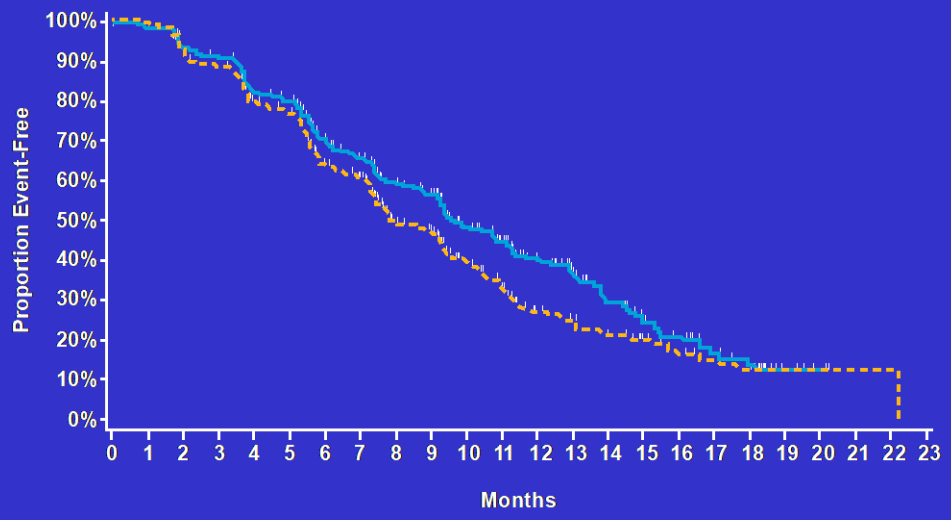
	Central Review	
	Panitumumab + FOLFOX4 (n = 317)[1]	FOLFOX4 (n = 323)[1]
Objective response rate, % (95% CI)[2]	55 (50–61)	48 (42–53)
Complete response, %	0	0.3
Partial response, %	55	47
Stable disease, %	30	36
Progressive disease, %	7	11

[1]Included only patients with baseline measurable disease per central review
[2]P = 0.068 (descriptive); exact test of stratified odds ratio

All responses were confirmed no earlier than 28 days after the response criteria were first met

PFS by *KRAS* Mutation Status

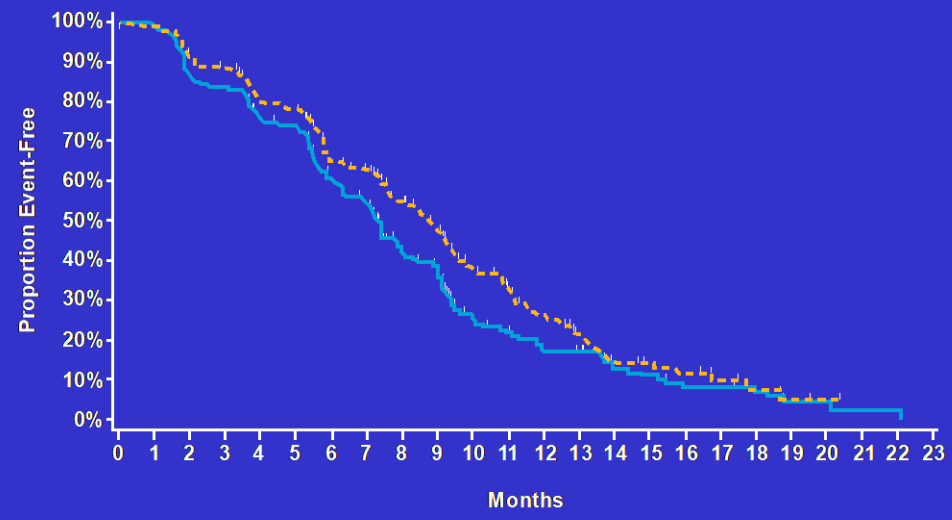
WT *KRAS*



	Events n (%)	Median (95% CI) months
Panitumumab + FOLFOX4	199 (61)	9.6 (9.2–11.1)
FOLFOX4	215 (65)	8.0 (7.5–9.3)

HR = 0.80 (95% CI: 0.66–0.97)
P-value = 0.02

MT *KRAS* : Detrimental etki

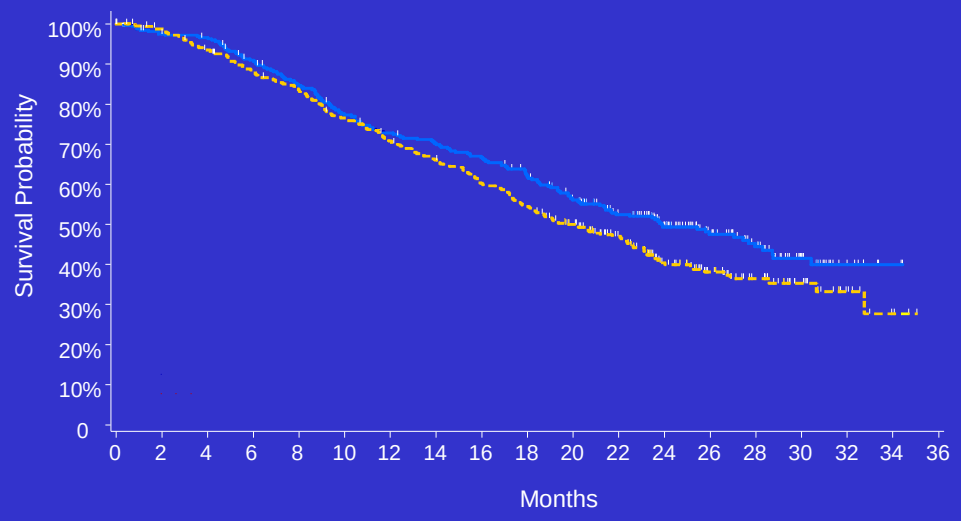


	Events n (%)	Median (95% CI) months
Panitumumab + FOLFOX4	167 (76)	7.3 (6.3–8.0)
FOLFOX4	157 (72)	8.8 (7.7–9.4)

HR = 1.29 (95% CI: 1.04–1.62)
P-value = 0.02

OS by *KRAS* Status

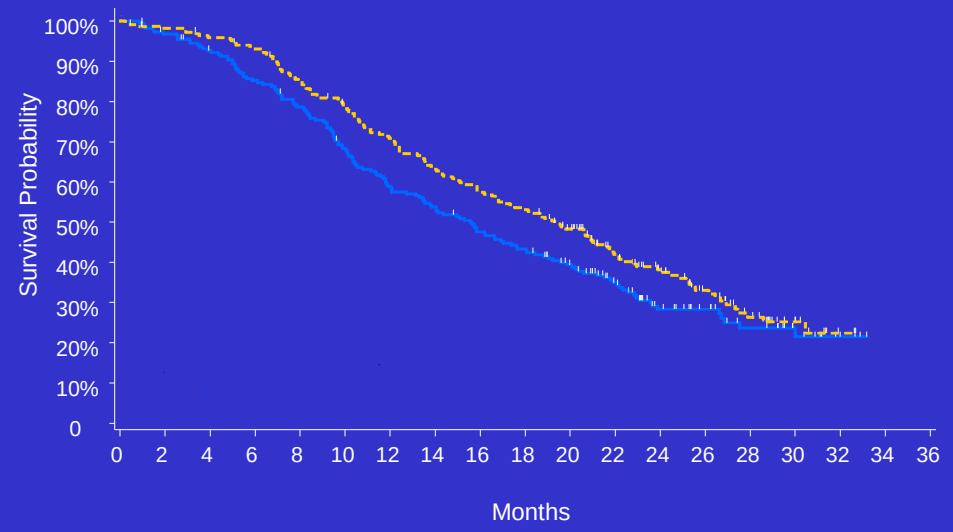
WT *KRAS*



	Events/n (%)	Median months
Panitumumab+ FOLFOX4	165 (51)	23.9 (20.3-28.3)
FOLFOX4	190 (57)	19.7 (17.6-22.6)

HR = 0.83 (95% CI: 0.67–1.02)
P-value = 0.07

- **MT *KRAS* : Detrimental etki**



	Events/n (%)	Median months
Panitumumab+ FOLFOX4	152 (69)	15.5 (13.1-17.6)
FOLFOX4	142 (65)	19.3 (16.5-21.8)

HR = 1.24 (95% CI: 0.98–1.57)
P-value = 0.07

Conclusions

- In this large randomized phase 3 trial, results were prospectively analyzed according to tumor *KRAS* status – an important predictive biomarker for EGFR tx in 1st-line mCRC
- In patients with WT *KRAS* tumors:
  - panitumumab significantly improved PFS when added to FOLFOX4 (median 9.6 vs 8.0 mo; HR = 0.80, p = 0.02)
  - A favorable effect on OS was observed, although it did not reach statistical significance (median 23.9 vs 19.7 mo; HR = 0.83, p = 0.072).
  - Response rates were higher in patients who received panitumumab (55% vs 48%)
- In patients with MT *KRAS* tumors, outcomes were inferior for panitumumab + FOLFOX4 vs FOLFOX4 alone (mechanism unknown)
- Panitumumab was well-tolerated when administered with FOLFOX4
  - The AE profile was as expected for an anti-EGFR antibody
  - Grade 3/4 panitumumab-related infusion reactions were rare: (n = 2/539)

LBA20: TRIBE2: a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts) – Cremolini C, et al

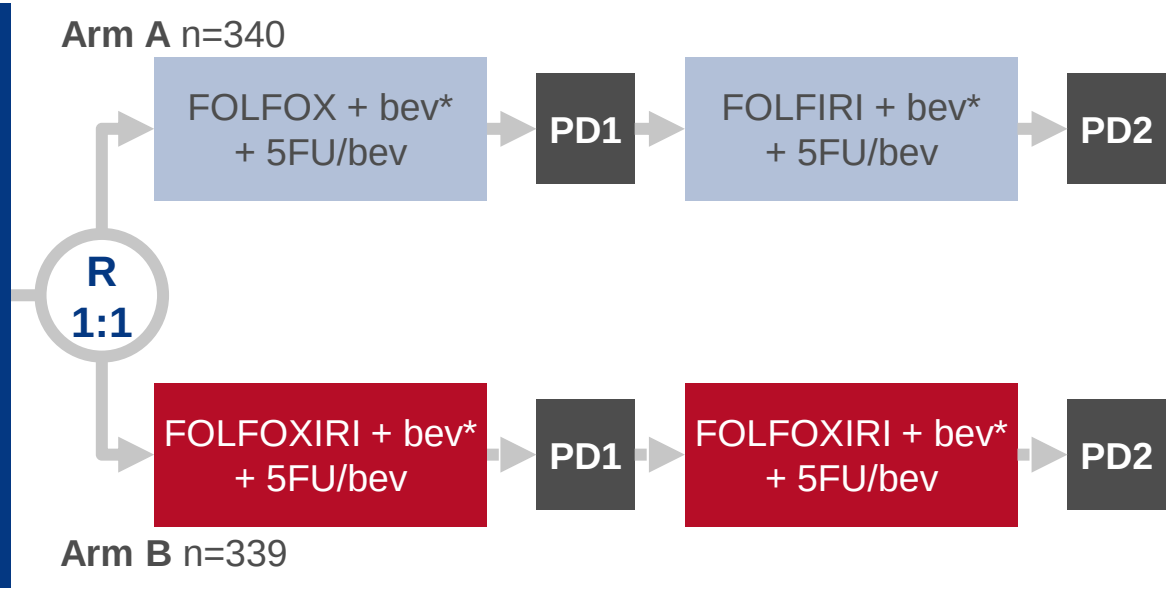
Study objective

- To assess whether three active chemotherapy agents (triplet FOLFOXIRI) upfront is more beneficial than a pre-planned sequential strategy in 2 subsequent lines of therapy (FOLFOX – FOLFIRI) combined with sustained antiangiogenic treatment

Key patient inclusion criteria

- Unresectable (locally assessed) mCRC not pre-treated for metastasis
- No adjuvant oxa-containing CT
- Adjuvant fluoropyrimidine permitted if completed >6 months before relapse
- ECOG PS ≤2 (or PS =0 if 71–75 years of age)

(n=679)



PRIMARY ENDPOINT

- PFS2

SECONDARY ENDPOINT

- PFS1

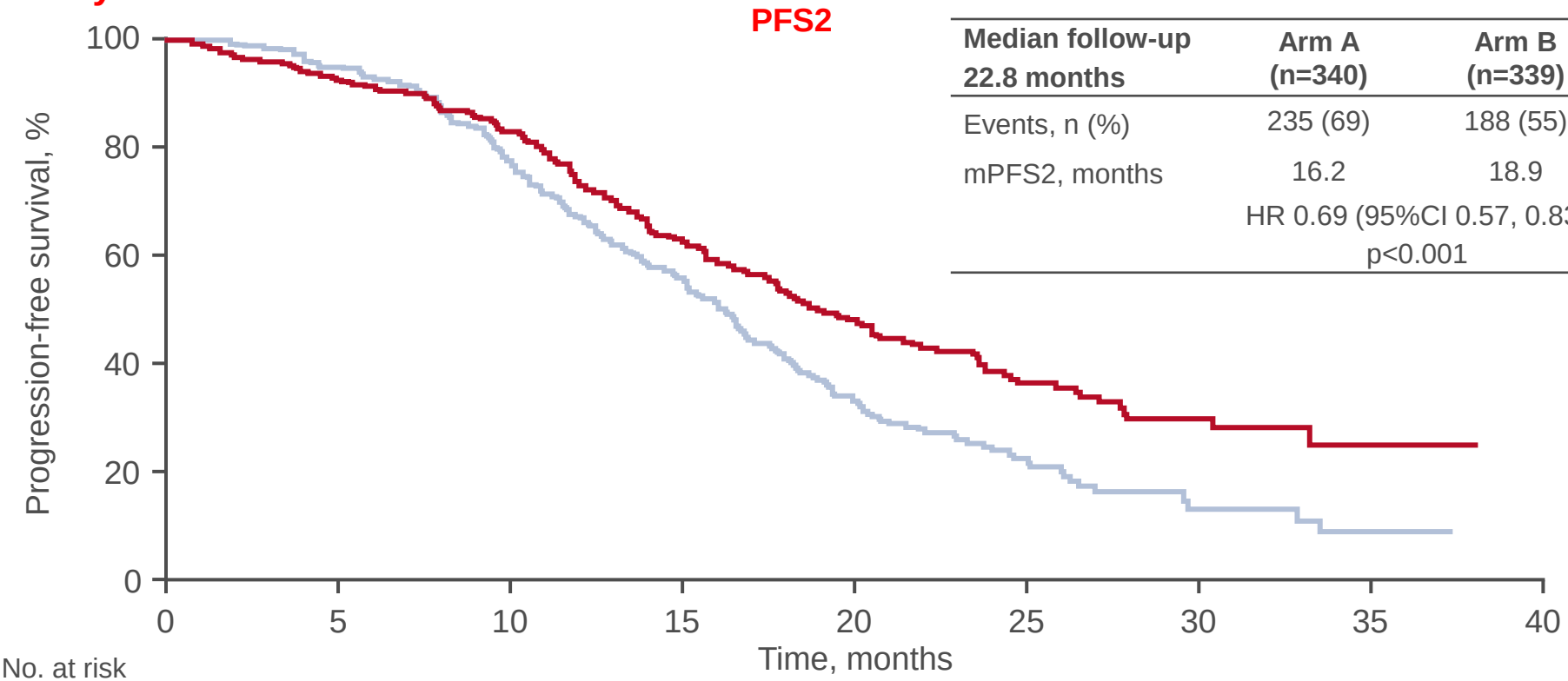
*Up to 8 cycles

Cremolini C, et al. Ann Oncol 2018;29(suppl 5):abstr LBA20

LBA20: TRIBE2: a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts) – Cremolini C, et al

Key results

- **FOLFOXIRI/bevacizumab followed by the reintroduction of the same agents after PD was superior to pre-planned sequential strategy of FOLFOX/bevacizumab followed by FOLFIRI/bevacizumab**



Median follow-up 22.8 months	Arm A (n=340)	Arm B (n=339)
Events, n (%)	235 (69)	188 (55)
mPFS2, months	16.2	18.9
	HR 0.69 (95%CI 0.57, 0.83) p<0.001	

No. at risk

Arm A	340	319	253	167	73	29	7	2	0
Arm B	339	313	273	181	101	48	21	3	0

Cremolini C, et al. Ann Oncol 2018;29(suppl 5):abstr LBA20

LBA20: TRIBE2: a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts) – Cremolini C, et al

Key results (cont.)

- **1L FOLFOXIRI/bevacizumab was associated with a higher response rate than FOLFOX/bevacizumab** (61% vs. 50%; p=0.005) and a longer PFS (12.0 vs. 9.9 months, HR 0.73 [95%CI 0.62, 0.87]; p<0.001)
- OS results are immature (around 40% of events)
- AEs were similar between the two treatment groups, but compared with FOLFOX/bevacizumab, 1L FOLFOXIRI/bevacizumab was associated with a higher incidence of diarrhoea (5% vs. 17%), neutropenia (21% vs. 50%) and febrile neutropenia (3% vs. 7%)
- In total, 86% and 74% of patients received treatment after progression on FOLFOX/bevacizumab and FOLFOXIRI/bevacizumab, respectively

Cremolini C, et al. Ann Oncol 2018;29(suppl 5):abstr LBA20

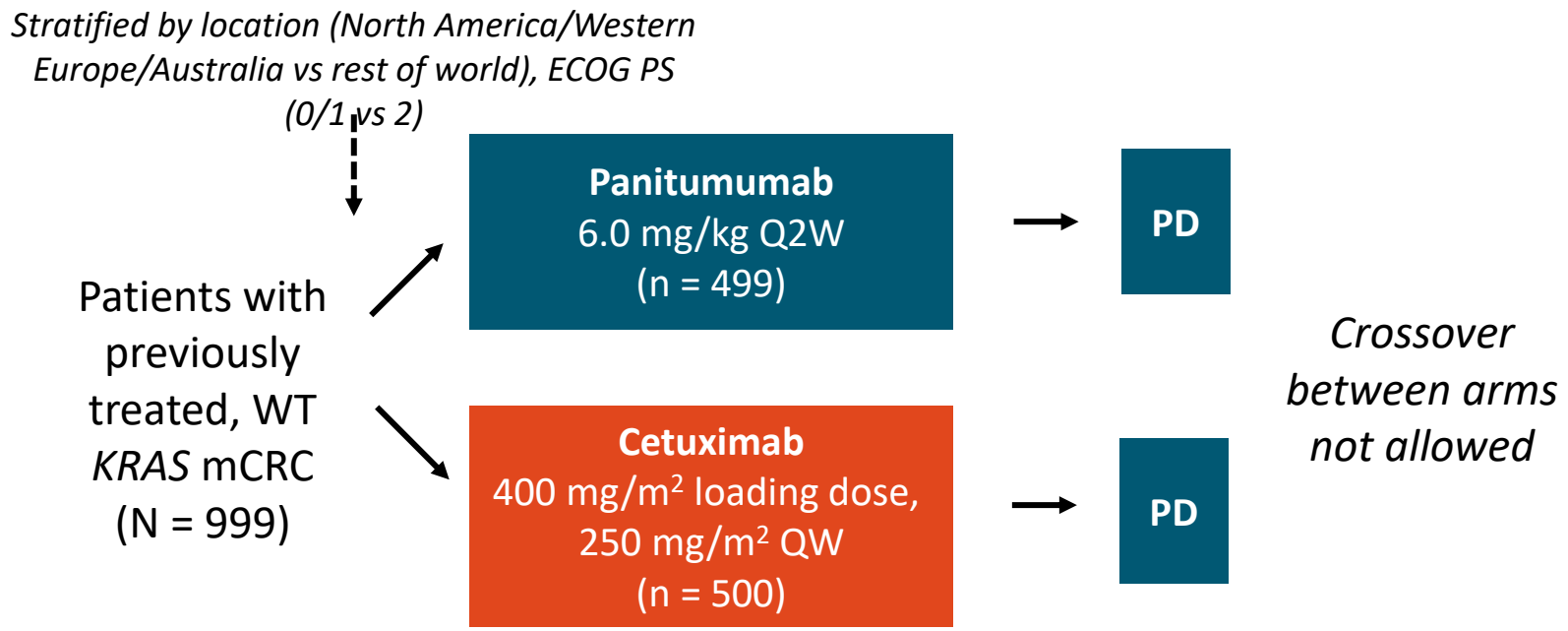
LBA20: TRIBE2: a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts) – Cremolini C, et al

Conclusions

- In patients with **unresectable mCRC, FOLFOXIRI/bevacizumab was superior to a pre-planned strategy of sequential exposure of the same agents**
- 1L treatment with FOLFOXIRI/bevacizumab does not compromise the feasibility and the efficacy of therapies after progression
- The **findings of this study for FOLFOXIRI/bevacizumab are comparable to those of the previous phase III TRIBE study**

Cremolini C, et al. Ann Oncol 2018;29(suppl 5):abstr LBA20

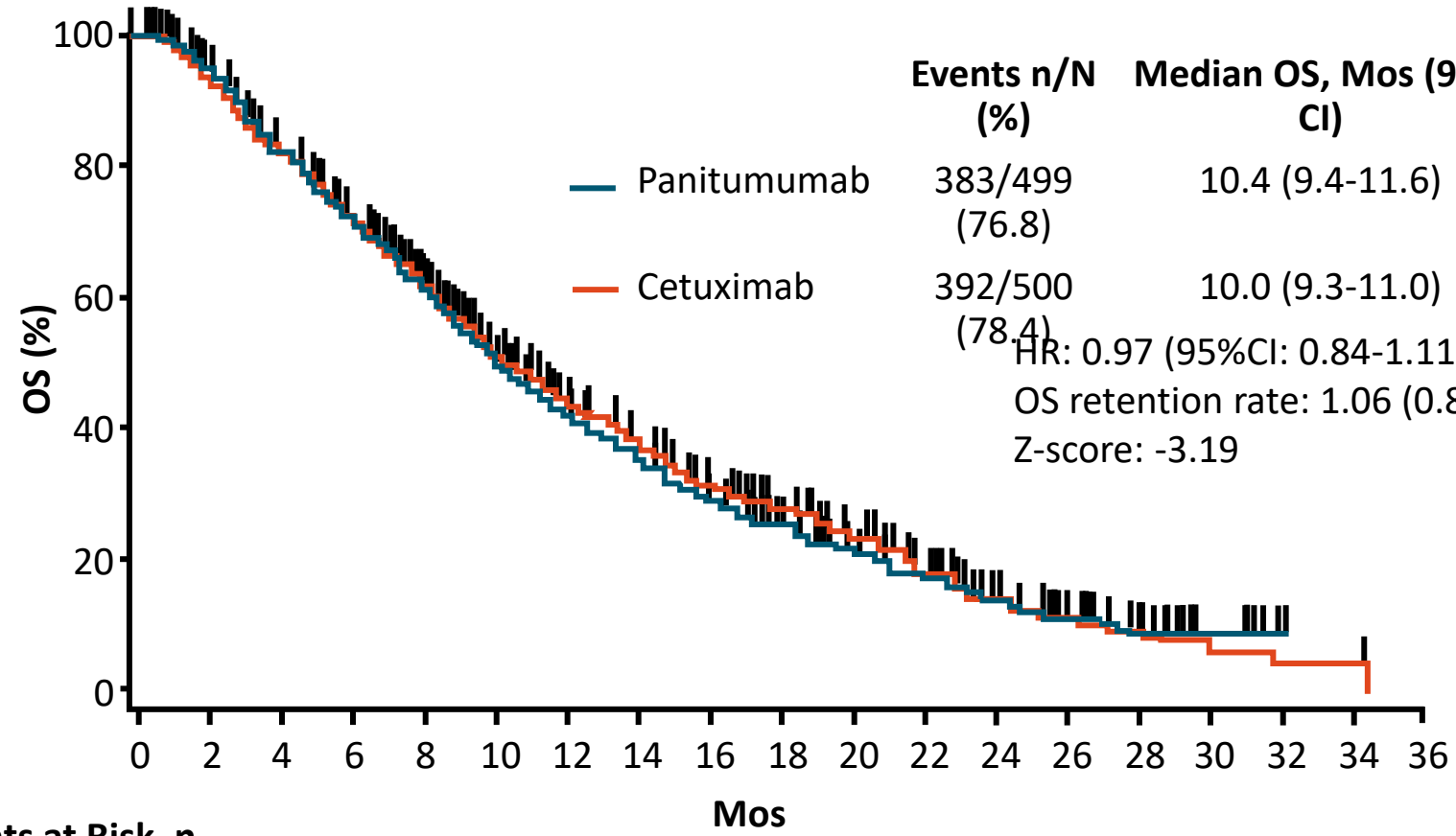
Phase III ASPECCT: Panitumumab vs Cetuximab in KRAS-WT mCRC



- Primary endpoint: OS

Price. Lancet Oncol. 2014;15:569.

Phase III ASPECCT: OS



	Events n/N (%)	Median OS, Mos (95% CI)
Panitumumab	383/499 (76.8)	10.4 (9.4-11.6)
Cetuximab	392/500 (78.4)	10.0 (9.3-11.0)

HR: 0.97 (95%CI: 0.84-1.11; *P* = .0007

OS retention rate: 1.06 (0.82-1.30)

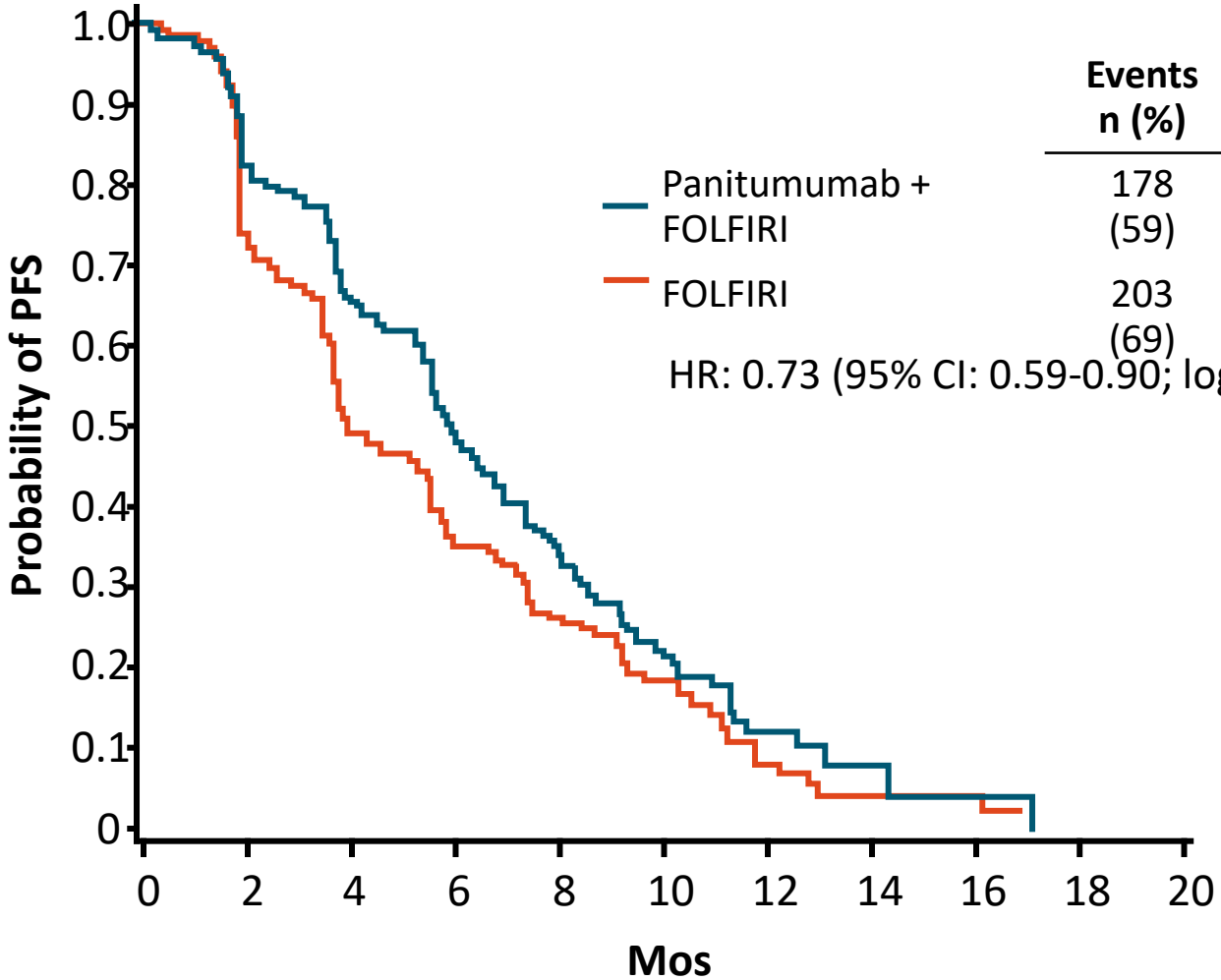
Z-score: -3.19

Patients at Risk, n

Cetuximab	500	462	398	349	283	221	181	151	122	94	70	54	37	24	16	8	1	0	0
Panitumumab	499	456	399	345	286	224	185	156	124	98	76	48	32	22	12	3	2	2	0

Price. Lancet Oncol. 2014;15:569.

Second-line ± Panitumumab in *KRAS* WT mCRC: PFS

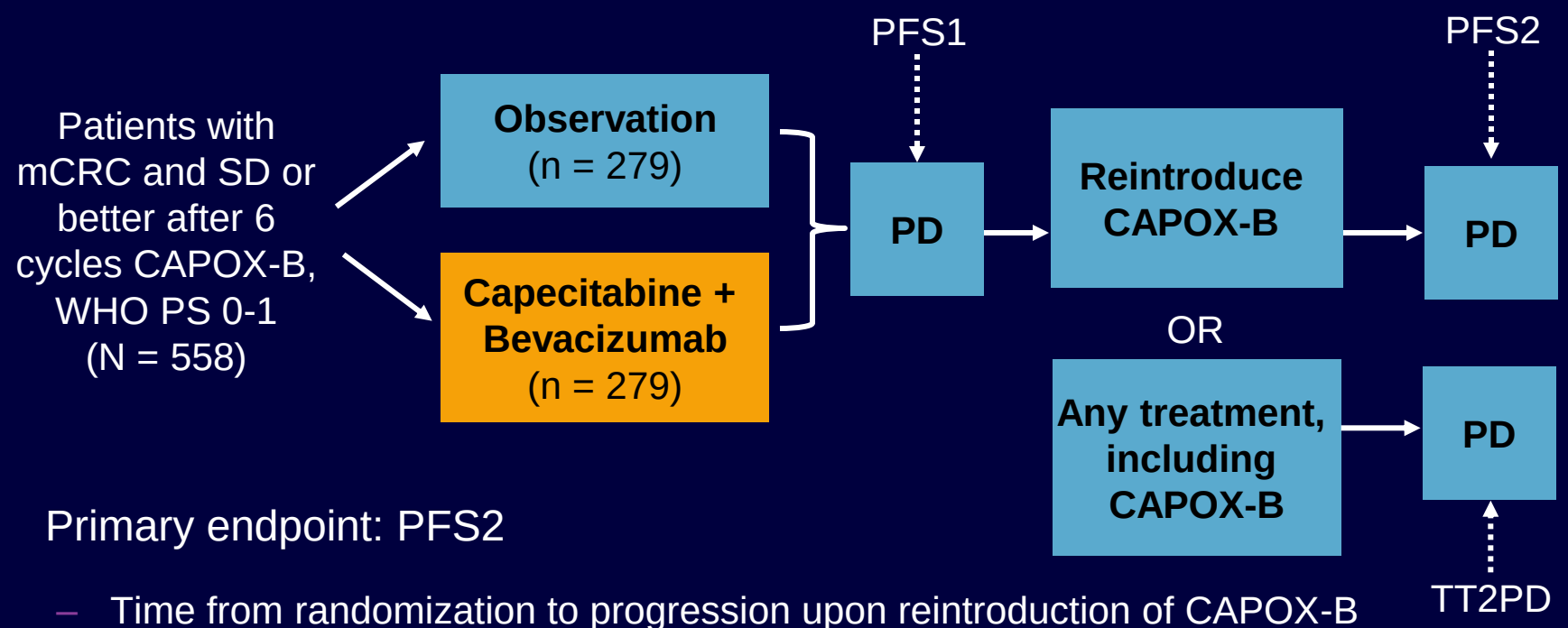


	Events n (%)	Median, Mos (95% CI)
Panitumumab + FOLFIRI	178 (59)	5.9 (5.5-6.7)
FOLFIRI	203 (69)	3.9 (3.7-5.3)

HR: 0.73 (95% CI: 0.59-0.90; log-rank *P* = .004)

Peeters. JCO. 2010;28:4706.

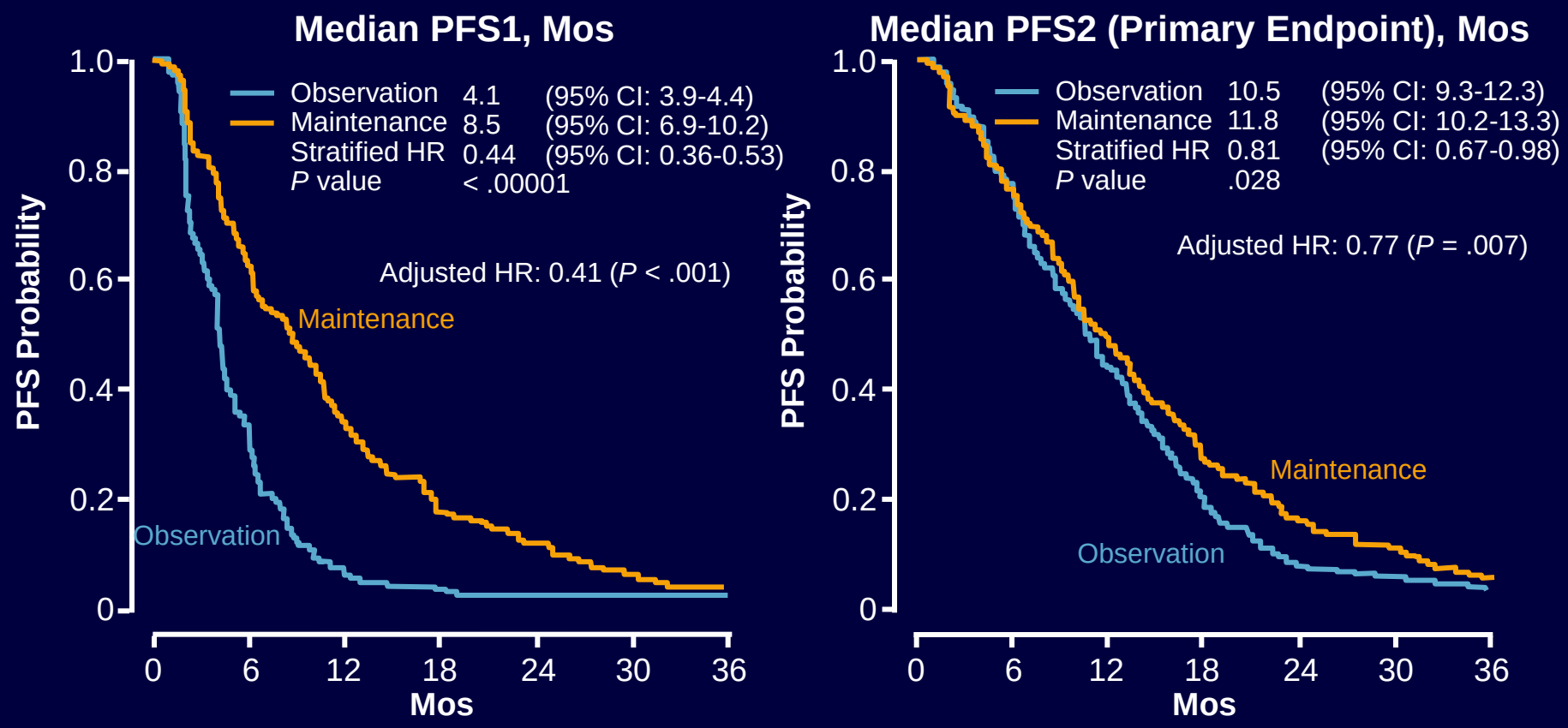
Phase III CAIRO-3 Trial: Maintenance Capecitabine + Bev vs Obs in mCRC



- Primary endpoint: PFS2
  - Time from randomization to progression upon reintroduction of CAPOX-B
  - PFS2 considered equal to PFS1 in patients who do not receive CAPOX-B again (for any reason)
- Median follow-up: 40 mos

Koopman M, et al. ASCO 2013. Abstract 3502. Used with permission.

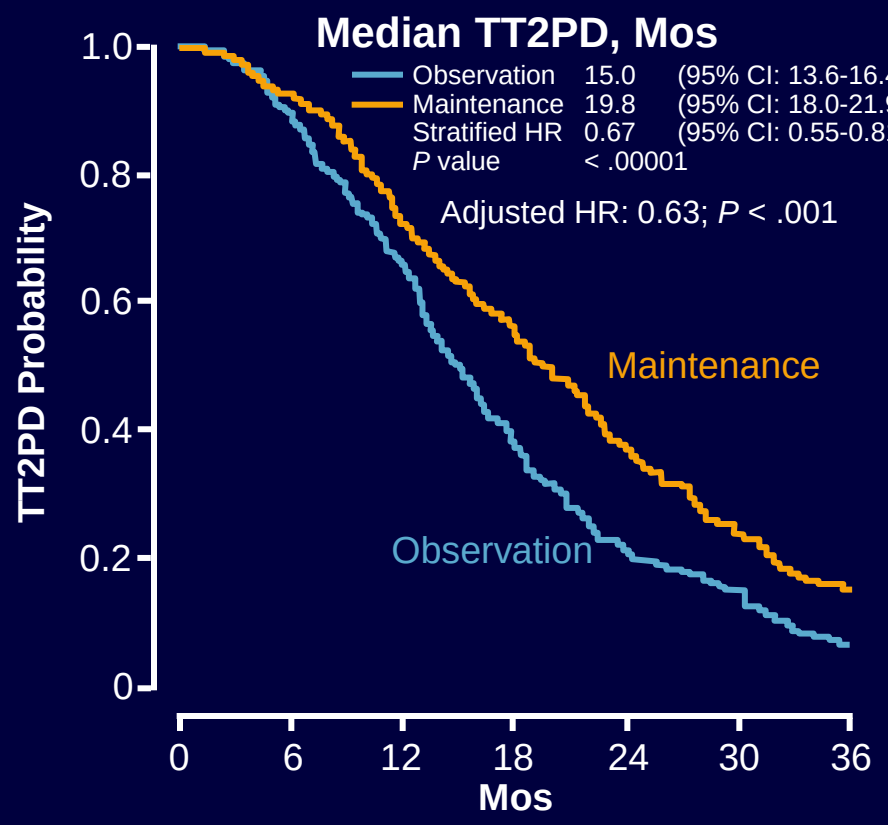
CAIRO-3 Trial of Maint Capecitabine + Bev vs Obs in mCRC: PFS Results

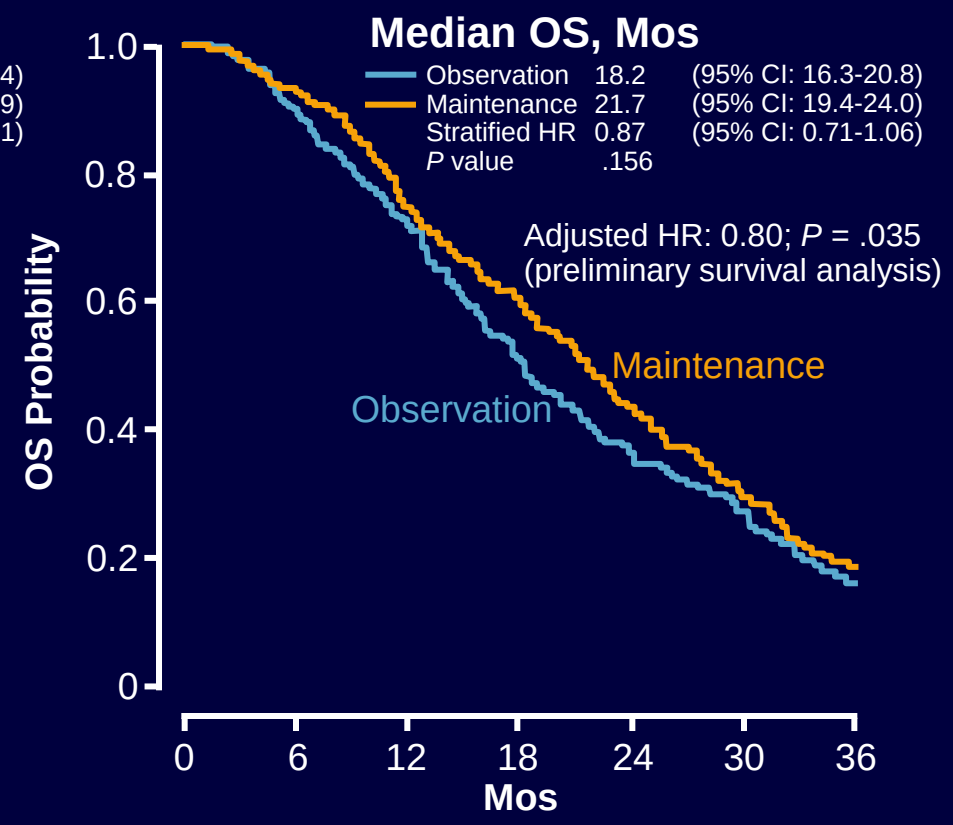


Maintenance treatment with capecitabine + bev after 6 cycles CAPOX-B significantly prolongs PFS1 and PFS2

Koopman M, et al. ASCO 2013. Abstract 3502. Used with permission.

CAIRO-3 Trial of Maint Capecitabine + Bev vs Obs in mCRC: TT2PD and OS Results





Maintenance treatment with capecitabine + bev after 6 cycles CAPOX-B significantly prolongs TT2PD and OS

Koopman M, et al. ASCO 2013. Abstract 3502. Used with permission.

CAIRO-3 Trial of Maint Capecitabine + Bev vs Obs in mCRC: Conclusions

- Maintenance with capecitabine + bevacizumab after 6 cycles CAPOX-B is feasible and significantly prolongs both PFS1 and PFS2 in patients with mCRC
  - Median PFS1: 8.5 mos with maintenance vs 4.1 mos with observation
  - Median PFS2: 11.8 mos with maintenance vs 10.5 mos with observation
- Maintenance treatment also significantly prolongs time to second progression
  - Median TTP2: 19.8 mos with maintenance vs 15.0 mos with observation
- OS benefit emerged in adjusted preliminary analysis
  - Median OS: 21.7 mos with maintenance vs 18.2 mos with observation
  - Time on treatment relevant to OS

Koopman M, et al. ASCO 2013. Abstract 3502. Used with permission.

Phase III SAKK 41/06 Study: Bev vs No Bev After First-line Chemo-Bev in mCRC

Stratified by response during first-line Tx (CR/PR vs SD), duration of first-line Tx (16-20 vs 21-24 wks), type of chemo (fluoropyrimidine ± irinotecan or oxaliplatin), metastatic burden (1 vs multiple organs)

Patients with mCRC who received first-line chemo + bev for 4-6 mos, have ≥ SD, WHO PS 0-1 (N = 262)

→ **Bev 7.5 mg/kg q3w** (n = 131) → ***PD***

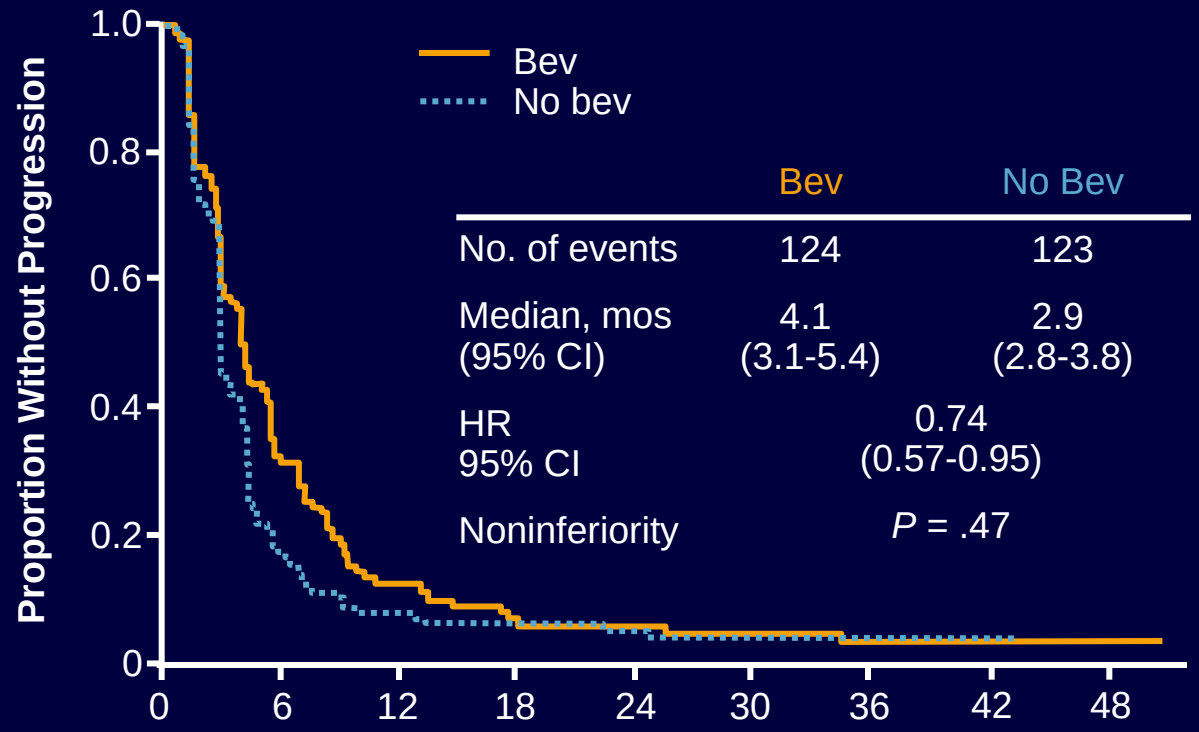
→ **No antitumor treatment** (n = 131)

- Primary endpoint: TTP (measured by CT q6w until PD)
- Secondary endpoints: PFS, TTNT, OS, bev-related toxicity, treatment costs

Koeberle D, et al. ASCO 2013. Abstract 3503. Used with permission.

SAKK 41/06 Study of Bev vs No Bev After First-line Chemo-Bev in mCRC: TTP

- Noninferiority of bev vs no bev could not be demonstrated (HR: 0.74)

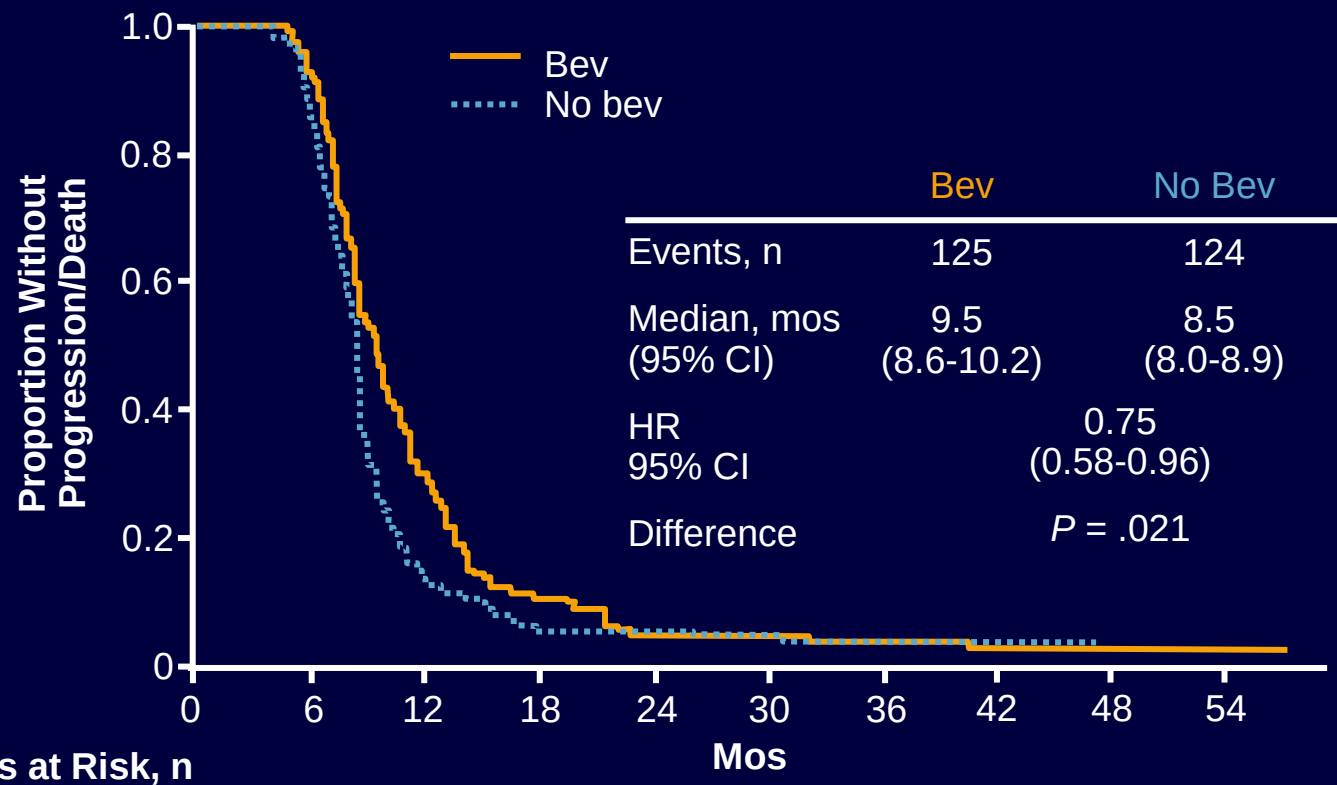


	Bev	No Bev
No. of events	124	123
Median, mos (95% CI)	4.1 (3.1-5.4)	2.9 (2.8-3.8)
HR 95% CI	0.74 (0.57-0.95)	
Noninferiority	*P* = .47	

Pts at Risk, n									
Bev	131	40	14	8	6	5	3	2	1
No bev	131	22	10	7	5	1	1	1	0

Koeberle D, et al. ASCO 2013. Abstract 3503. Used with permission.

SAKK 41/06 Study of Bev vs No Bev After First-line Chemo-Bev in mCRC: PFS

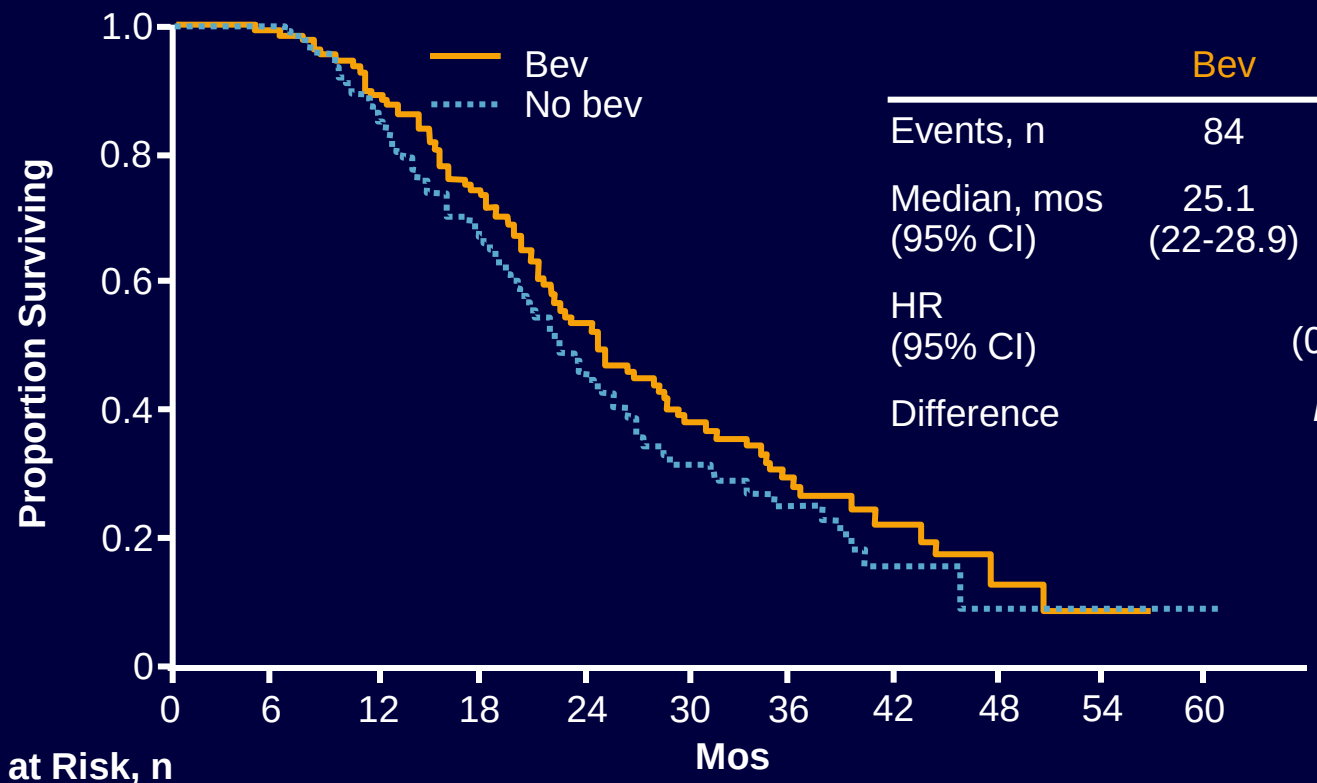


	Bev	No Bev
Events, n	125	124
Median, mos (95% CI)	9.5 (8.6-10.2)	8.5 (8.0-8.9)
HR 95% CI	0.75 (0.58-0.96)	
Difference	*P* = .021	

Pts at Risk, n										
Bev	131	122	40	13	6	6	5	3	2	1
No bev	131	116	18	8	7	4	1	1	0	0

Koeberle D, et al. ASCO 2013. Abstract 3503. Used with permission.

SAKK 41/06 Study of Bev vs No Bev After First-line Chemo-Bev in mCRC: OS



	Bev	No Bev
Events, n	84	84
Median, mos (95% CI)	25.1 (22-28.9)	22.8 (20.3-26.1)
HR (95% CI)	0.83 (0.61-1.12)	
Difference	*P* = .218	

Pts at Risk, n											
Bev	131	130	115	86	52	33	22	10	3	1	0
No bev	131	131	107	76	44	25	13	6	1	1	1

Koeberle D, et al. ASCO 2013. Abstract 3503. Used with permission.

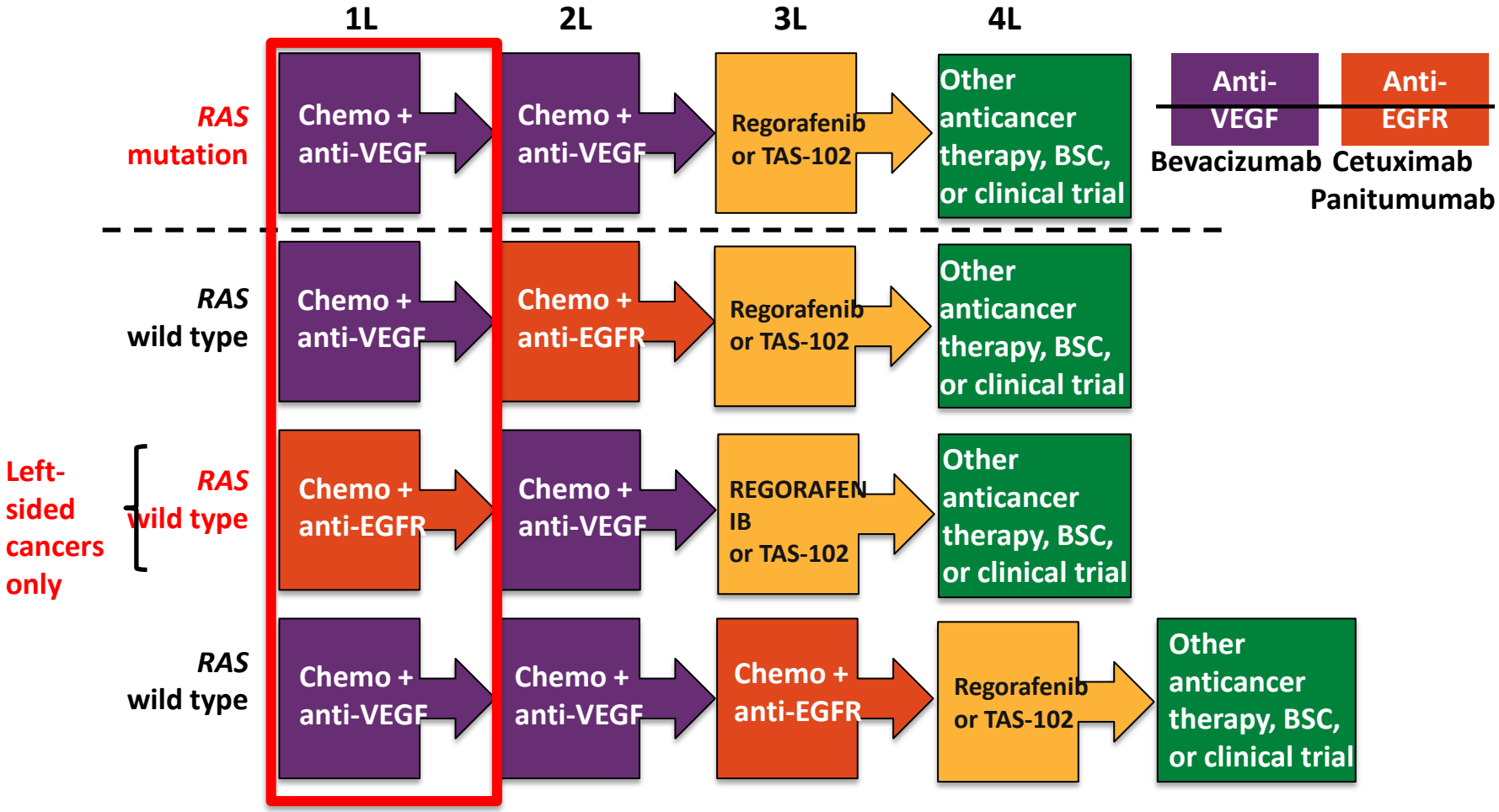
Bev vs No Bev After First-line Chemo-Bev in mCRC: Conclusions

Continuing bev (vs no bev) did not provide significant benefit after first-line chemotherapy + bevacizumab in patients with mCRC:

- TTP not significantly different with or without continued bevacizumab
  - Median TTP: 5 wks longer with bevacizumab continuation vs no treatment
- OS not significantly different with or without continued bevacizumab
  - Median OS: 25.1 mos with bevacizumab vs 22.8 mos without bevacizumab
- PFS not significantly different with or without continued bevacizumab
  - Median PFS: 9.5 mos with bevacizumab vs 8.5 mos without bevacizumab

Koeberle D, et al. ASCO 2013. Abstract 3503. Used with permission.

mKRK İlk Sıra Tedavi Önerisi Treatment



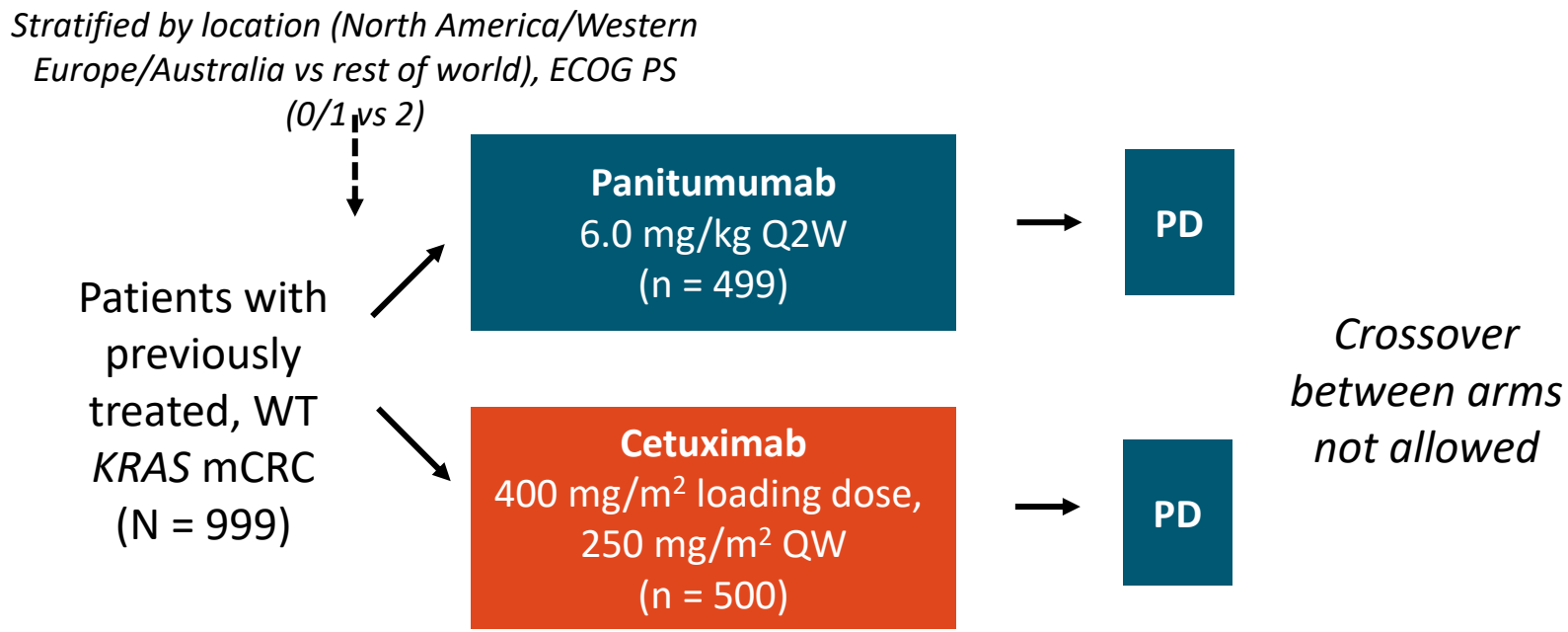
van Cutsem. Ann Oncol. 2016;27:1386.

İkinci Sıra Tedavide Belirleyici Faktörler

- Daha önce VEGF veya EGFR inhibitörü almış olmak
- VEGF inhibitörü tedavisi altında ilk 6 ayda progresyon gelişmesi
- Daha önce VEGF inh. almışsa, > 3 ay idameden sonra
- Tümörün moleküler ve genetic fenotipi nasıl? Molecular and genetic phenotype of tumor (MSI, *BRAF*, *HER2* ekspresyonu/amp)
- Tedavi toksisite profili değerlendirilmeli

Refrakter *RAS*-WT mCRC

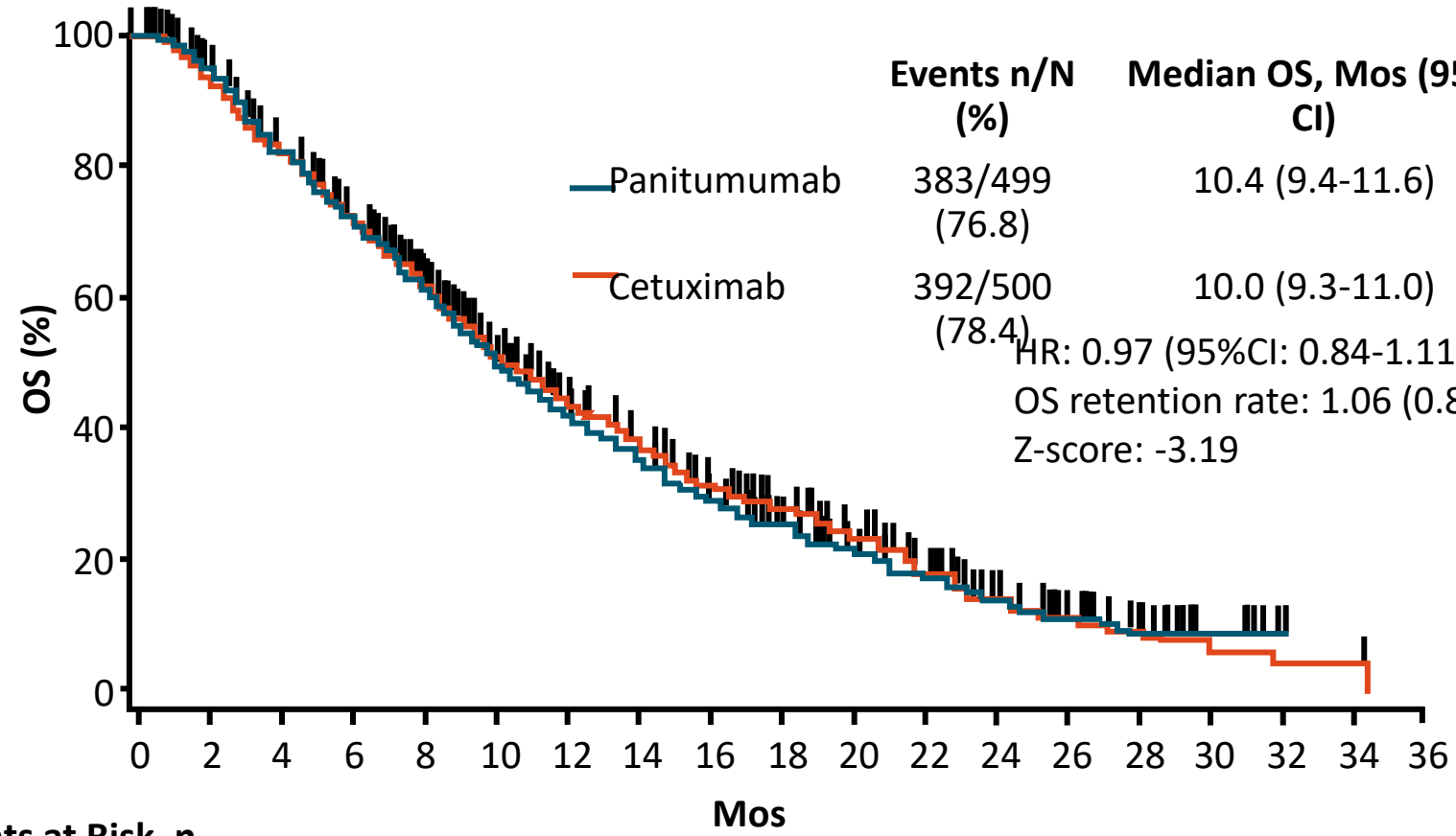
Phase III ASPECCT: Panitumumab vs Cetuximab in KRAS-WT mCRC



- Primary endpoint: OS

Price. Lancet Oncol. 2014;15:569.

Phase III ASPECCT: OS



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Cetuximab	392/500 (78.4)	10.0 (9.3-11.0)

HR: 0.97 (95%CI: 0.84-1.11; *P* = .0007

OS retention rate: 1.06 (0.82-1.30)

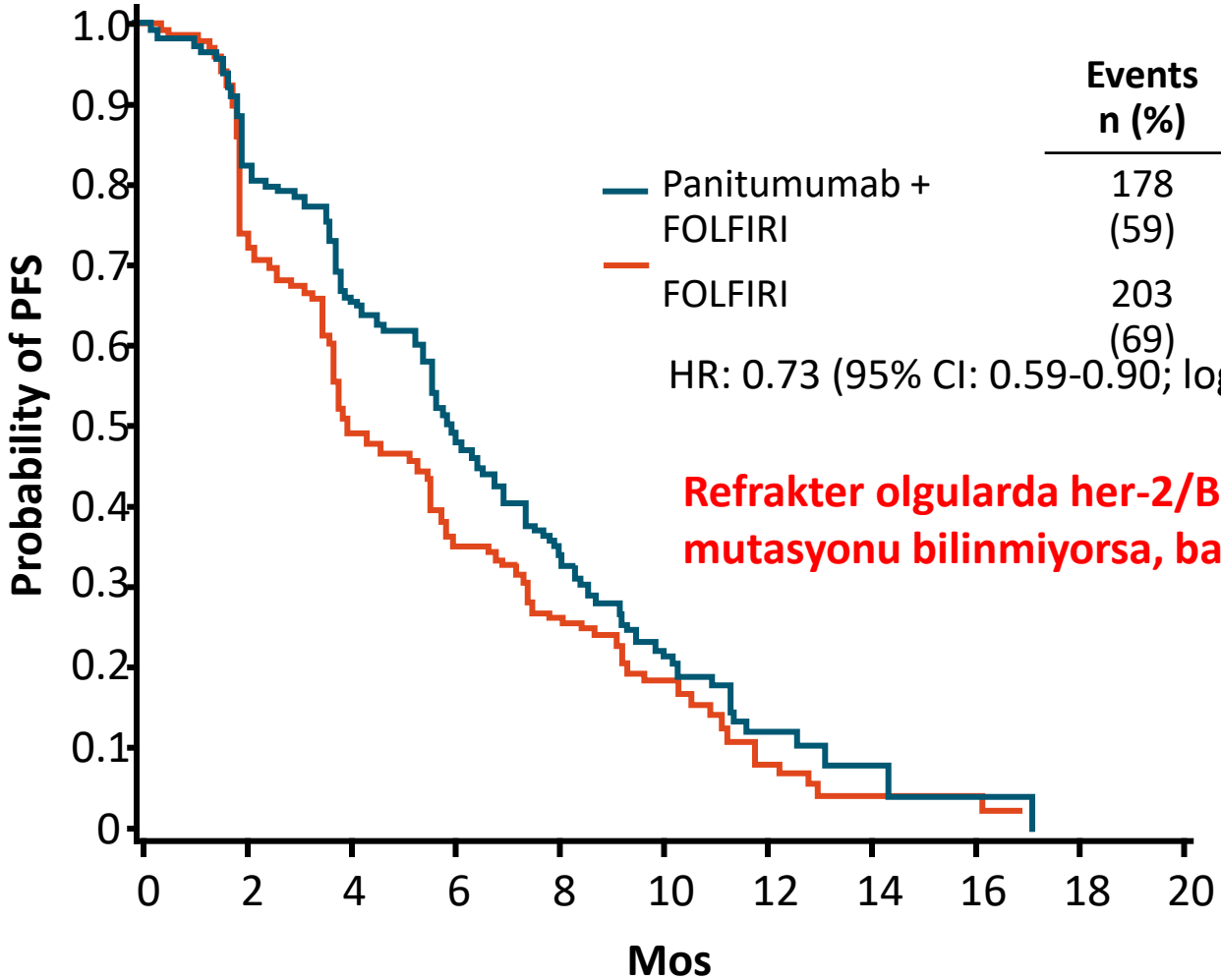
Z-score: -3.19

Patients at Risk, n

Cetuximab	500	462	398	349	283	221	181	151	122	94	70	54	37	24	16	8	1	0	0
Panitumumab	499	456	399	345	286	224	185	156	124	98	76	48	32	22	12	3	2	2	0

Price. Lancet Oncol. 2014;15:569.

Second-line ± Panitumumab in *KRAS* WT mCRC: PFS



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FOLFIRI	203 (69)	3.9 (3.7-5.3)

HR: 0.73 (95% CI: 0.59-0.90; log-rank *P* = .004)

Refrakter olgularda her-2/BRAF mutasyonu bilinmiyorsa, bakılmalı!!

Peeters. JCO. 2010;28:4706.

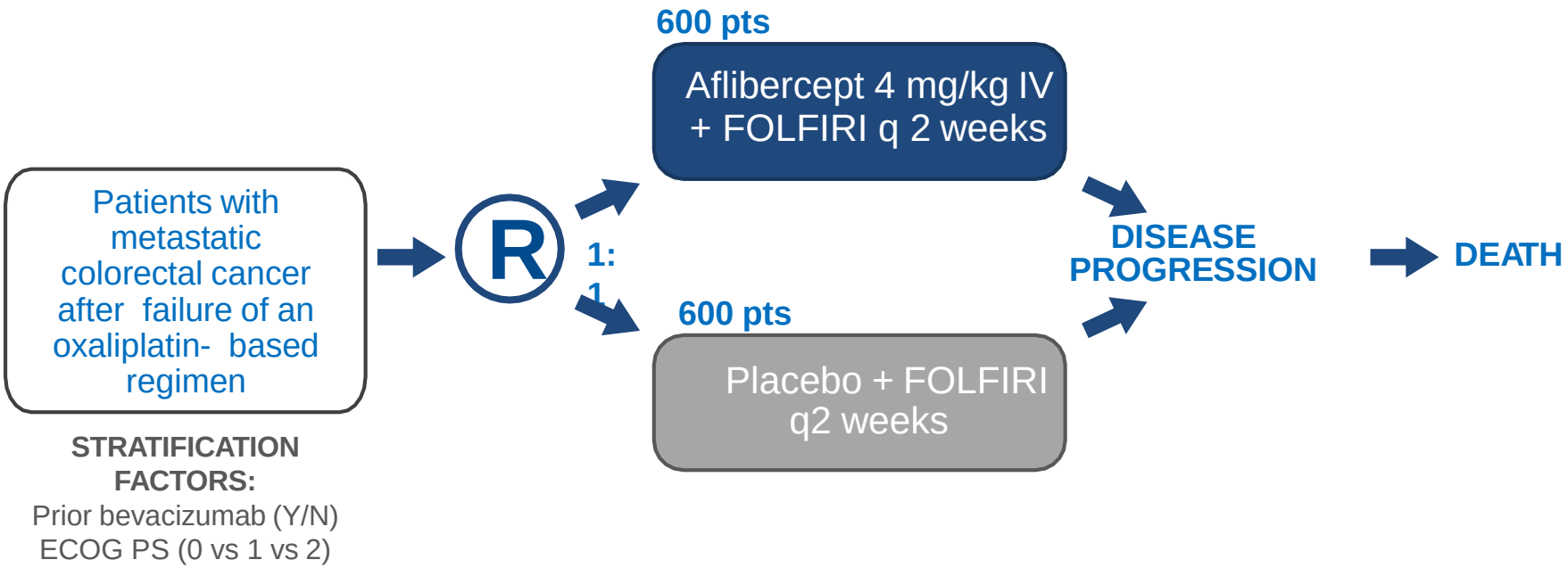
Second-line *RAS*-Mutated mCRC «Önceki Sırada Beva Almış»

Beva Tedavisi Altında Progresyonda VEGF İnhibisyonu ?

Agent	Bevacizumab		Ziv-aflibercept		Ramucirumab	
Trial	TML[1]		VELOUR[2]		RAISE[3]	
First line	Chemo + BEV		FP + Oxali ± BEV		FP + Oxali + BEV	
Second line	Chemo + BEV (n = 409)	Chemo (n = 410)	FOLFIRI + AFL (n = 612)	FOLFIRI + Pbo (n = 614)	FOLFIRI + RAM (n = 536)	FOLFIRI + Pbo (n = 536)
Median OS, mos	11.2	9.8	13.5	12.1	13.3	11.7
	HR: 0.81 *P* = .0062		HR: 0.82 *P* = .0032		HR: 0.84 *P* = .022	
Median PFS, mos	5.7	4.1	6.9	4.7	5.7	4.5
	HR: 0.68 *P* < .0001		HR: 0.76 *P* < .0001		HR: 0.79 *P* = .0005	
RR, %	5.4	3.9	19.8	11.1	13.4	12.5

1. Bennouna. Lancet Oncol. 2013;14:29. 2. van Cutsem. JCO. 2012;30:3499. 3. Tabernero. Lancet Oncol. 2015;16:499.

Phase III: Velour Trial:



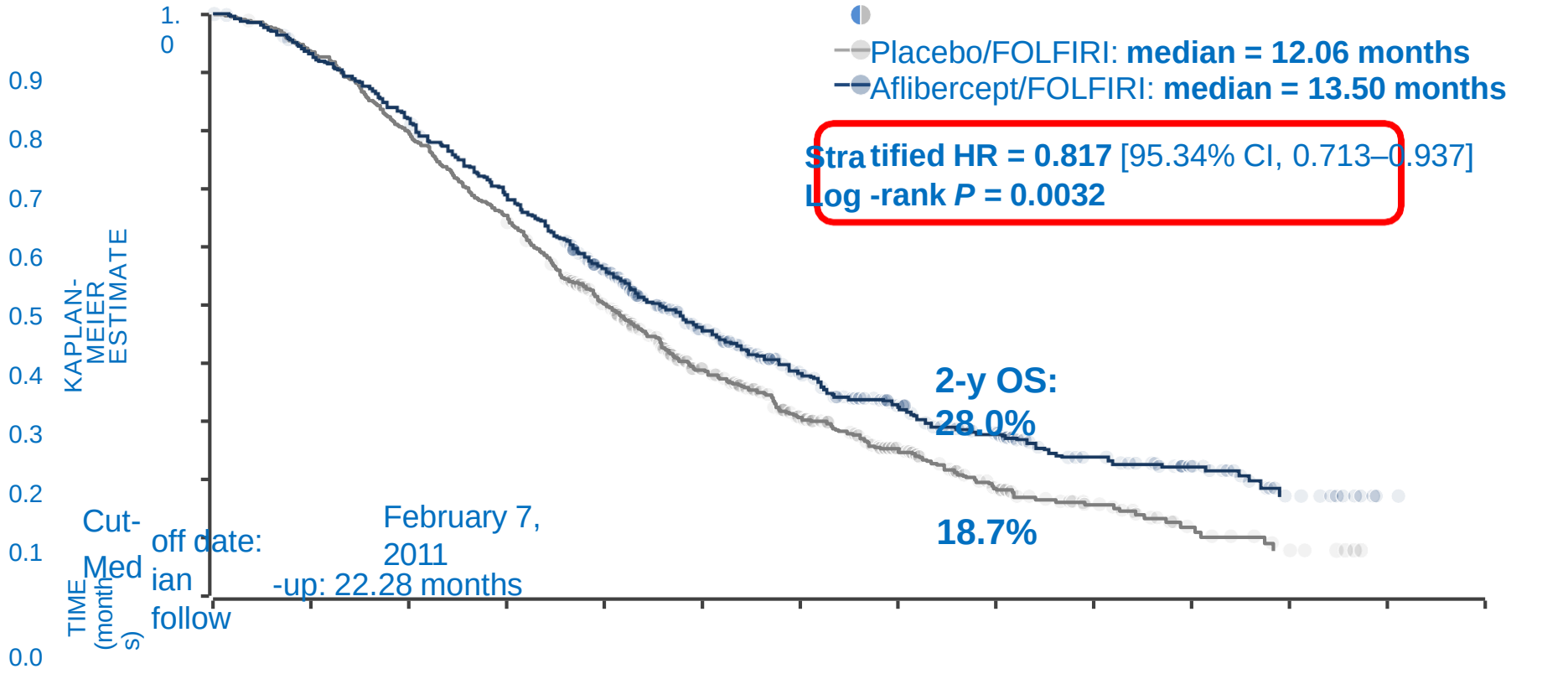
PRIMARY ENDPOINT: OS

SECONDARY ENDPOINTS:
ORR, PFS, safety, PK

Clinicaltrials.gov. NCT00561470. Van Cutsem, et al. J Clin Oncol. 2012 Oct 1;30(28):3499-506.

VELOUR: Overall Survival ITT Population

Censor

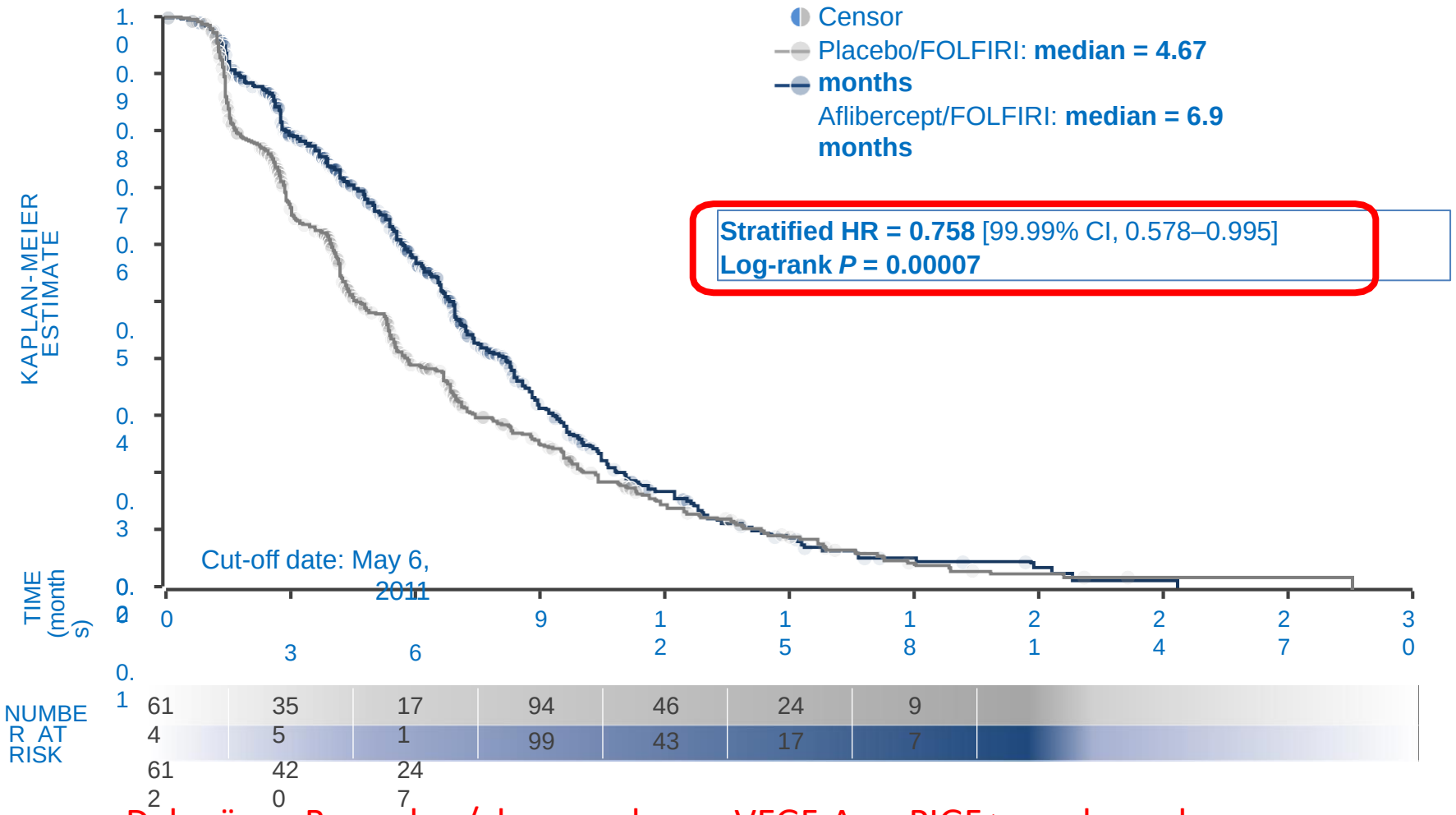


NUMBER AT RISK													
614	573	485	401	286	193	131	87	51	31	14			
612	566	498	416	311	216	148	104	75	49	33			
SURVIVAL PROBABILITY													
		9.1%		50.3%		30.9%		18.7%		12.0%			
		1.9%		56.1%		38.5%		28.0%		22.3%			

Clinicaltrials.gov. NCT00561470. Van Cutsem, et al. J Clin Oncol. 2012 Oct 1;30(28):3499-506.

VELOUR: PFS ITT Population,

Independent Review Committee



Daha önce Beva alsın/almasın plazma VEGF-A ve PIGF > medyan olan hastalarda OS daha uzun saptanmış

Clinicaltrials.gov. NCT00561470. Van Cutsem, et al. J Clin Oncol. 2012 Oct 1;30(28):3499-506.

Phase III RAISE Study: Second-Line Ramucirumab/FOLFIRI vs FOLFIRI

Stratified by geographic region, KRAS mutation status, TTP after start of first-line therapy

Patients with CRC and progression during or within 6 months of first-line bevacizumab, oxaliplatin, and a fluoropyrimidine (N = 1072)

Ramucirumab 8 mg/kg + **FOLFIRI** q2w per cycle (n = 536)

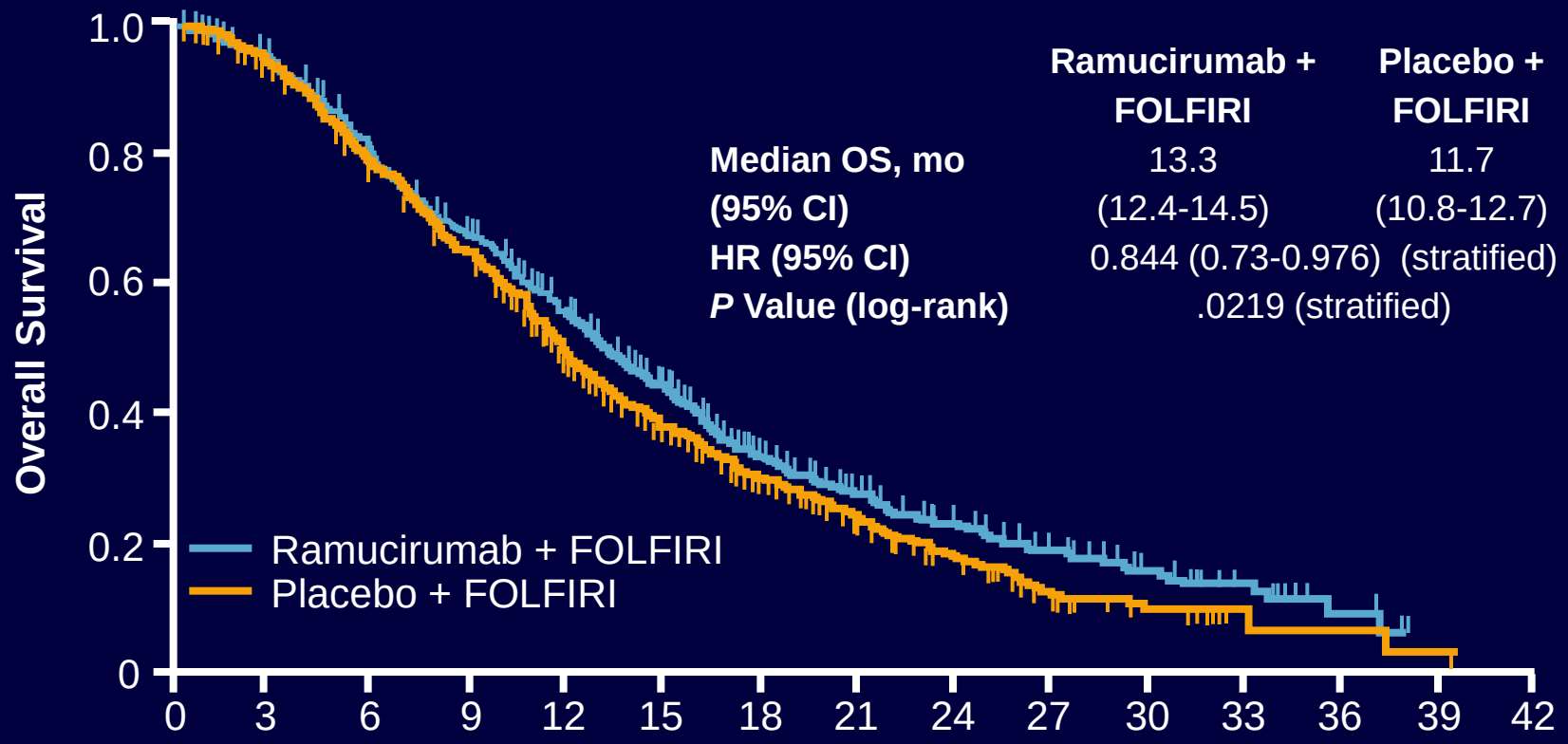
Placebo + **FOLFIRI** q2w per cycle (n = 536)

Treat until PD or unacceptable toxicity

- Ramucirumab: anti-VEGFR2 antibody
- Primary endpoint: OS

Tabernero J, et al. Lancet Oncol. 2015;16:499-508.

Second-Line Ramucirumab/FOLFIRI vs FOLFIRI (RAISE): Overall Survival

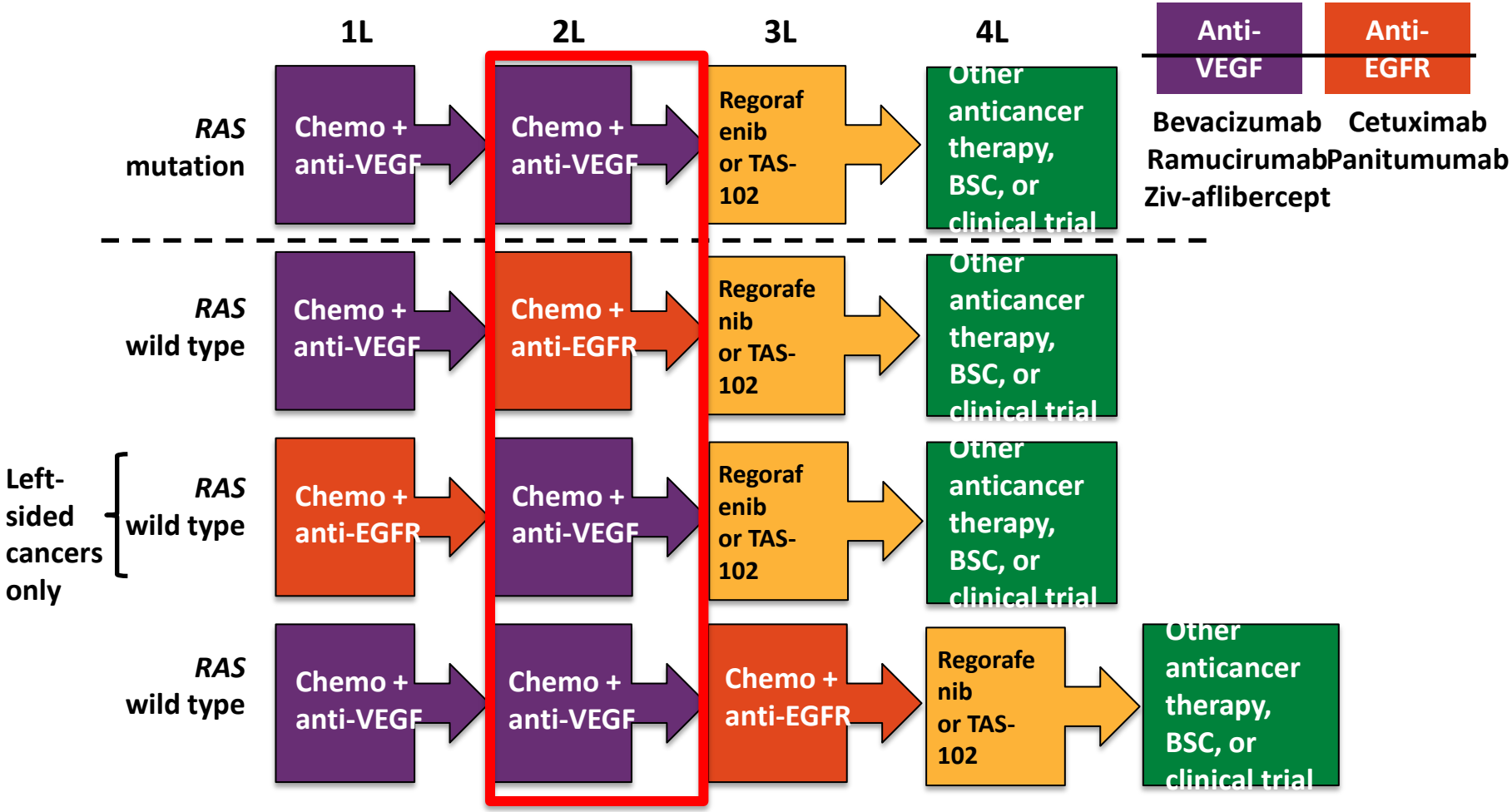


	Ramucirumab + FOLFIRI	Placebo + FOLFIRI
Median OS, mo	13.3	11.7
(95% CI)	(12.4-14.5)	(10.8-12.7)
HR (95% CI)	0.844 (0.73-0.976) (stratified)	
***P* Value (log-rank)**	.0219 (stratified)	

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

Tabernero J, et al. Lancet Oncol. 2015;16:499-508.

mKRK İkinci Sıra Tedavi Önerisi



van Cutsem. Ann Oncol. 2016;27:1386.

mKRK Tümörleri Üçüncü Sıra Tedavi Seçenekleri

- **Regorafenib**

VEGF, KIT, PDGF, RET, BRAF inhibitörü

- **TAS-102**

Trifluridine Tipiracil

CORRECT: Regorafenib vs Placebo + BSC After Progression

- Multicenter, randomized, double-blind, placebo-controlled phase III trial

Randomized 2:1

Stratified by previous VEGF-targeting agents, time from diagnosis of mCRC, geographic region

Patients with mCRC who progressed on or within 3 mos of previous therapy; ECOG PS 0-1 (N = 760)

Regorafenib 160 mg PO QD Wks 1-3 of 4-wk cycle + **BSC** (n = 505)

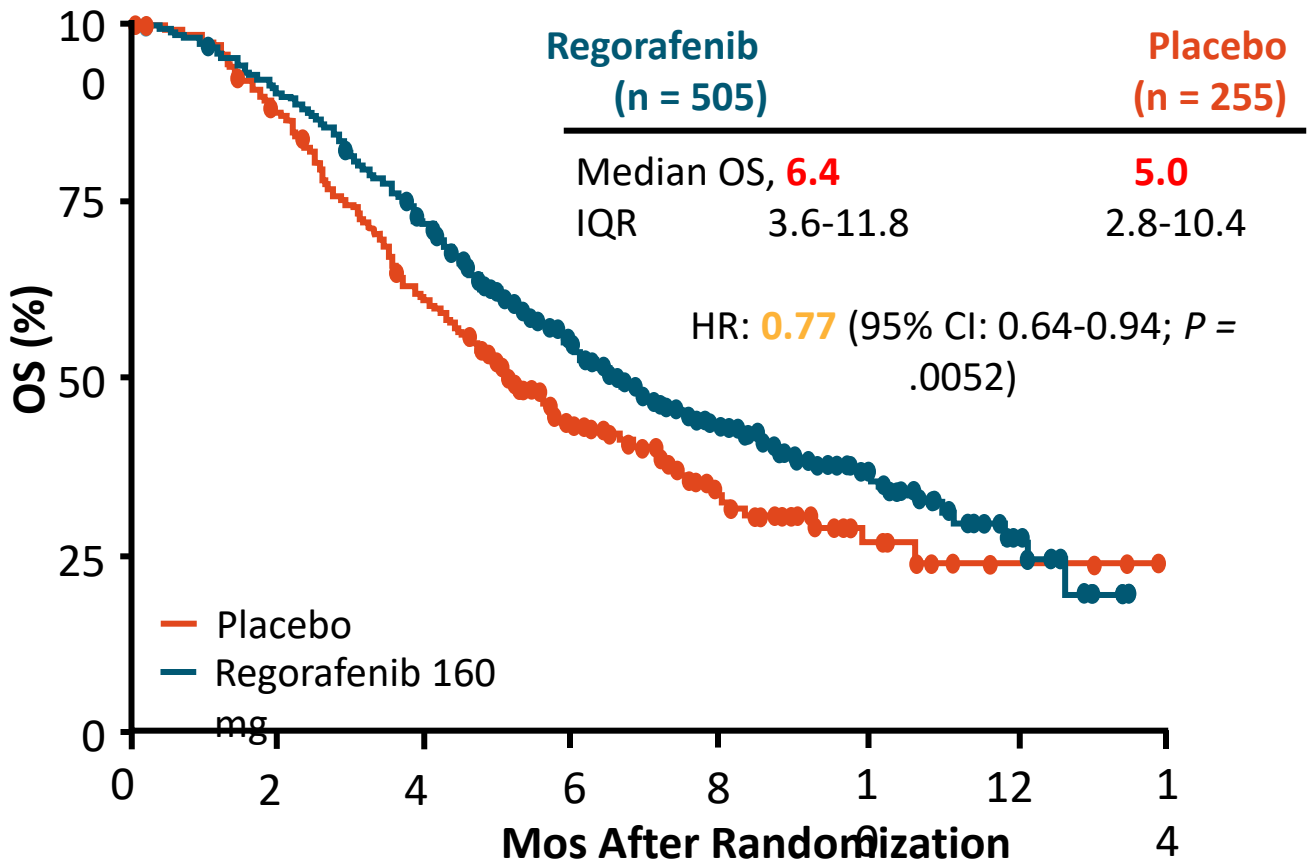
Placebo QD Wks 1-3 of 4-wk cycle + **BSC** (n = 255)

No crossover allowed

- Primary endpoint: OS; secondary endpoints: PFS, ORR, DCR; tertiary endpoints: DoR/SD, QoL, PK, biomarkers

Grothey. Lancet. 2013;381:303.

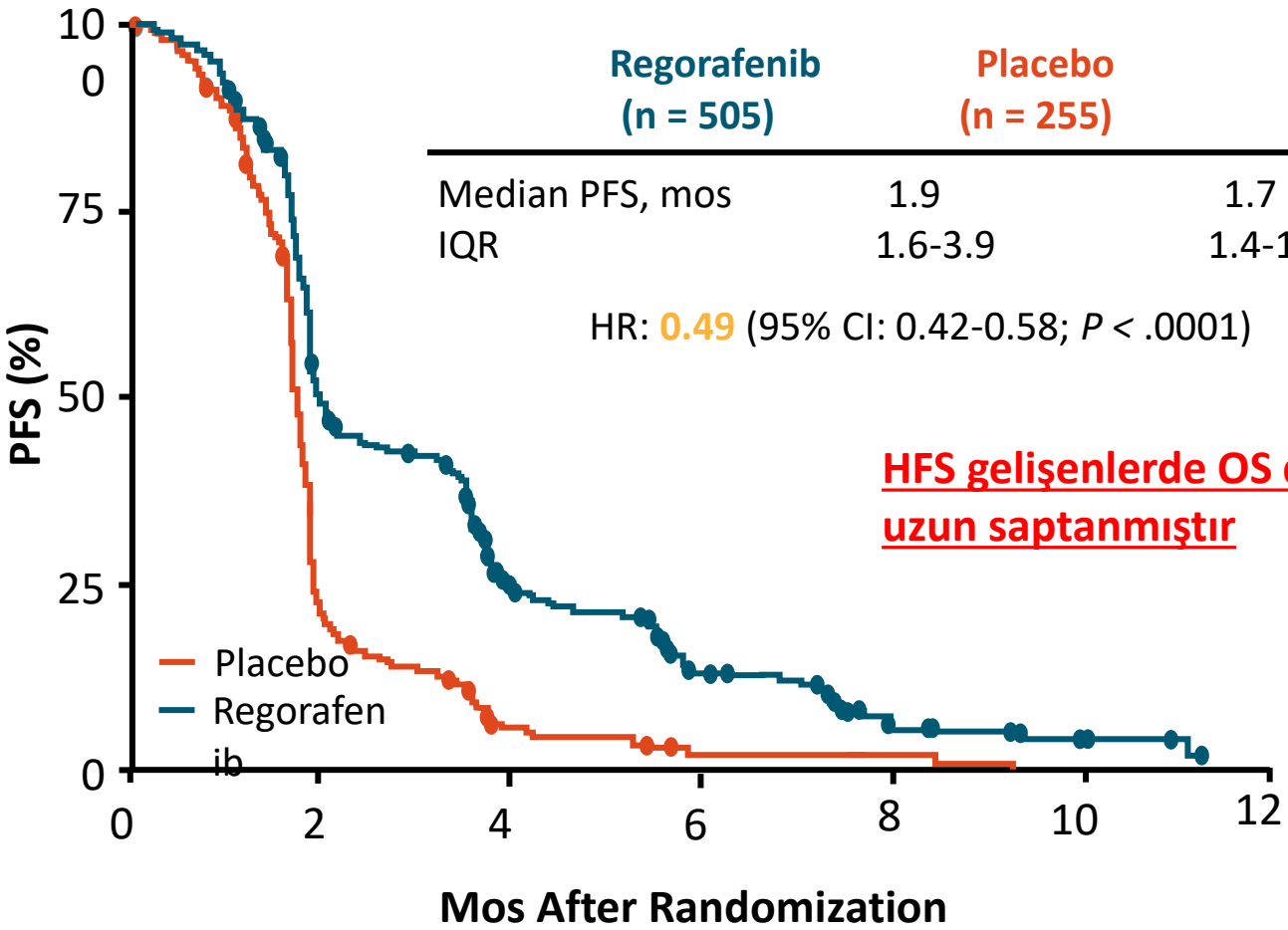
CORRECT: OS (Primary Endpoint)



- Primary endpoint met prespecified stopping criteria at second interim analysis ($P \leq .009279$)

Grothey. Lancet. 2013;381:303.

CORRECT: PFS



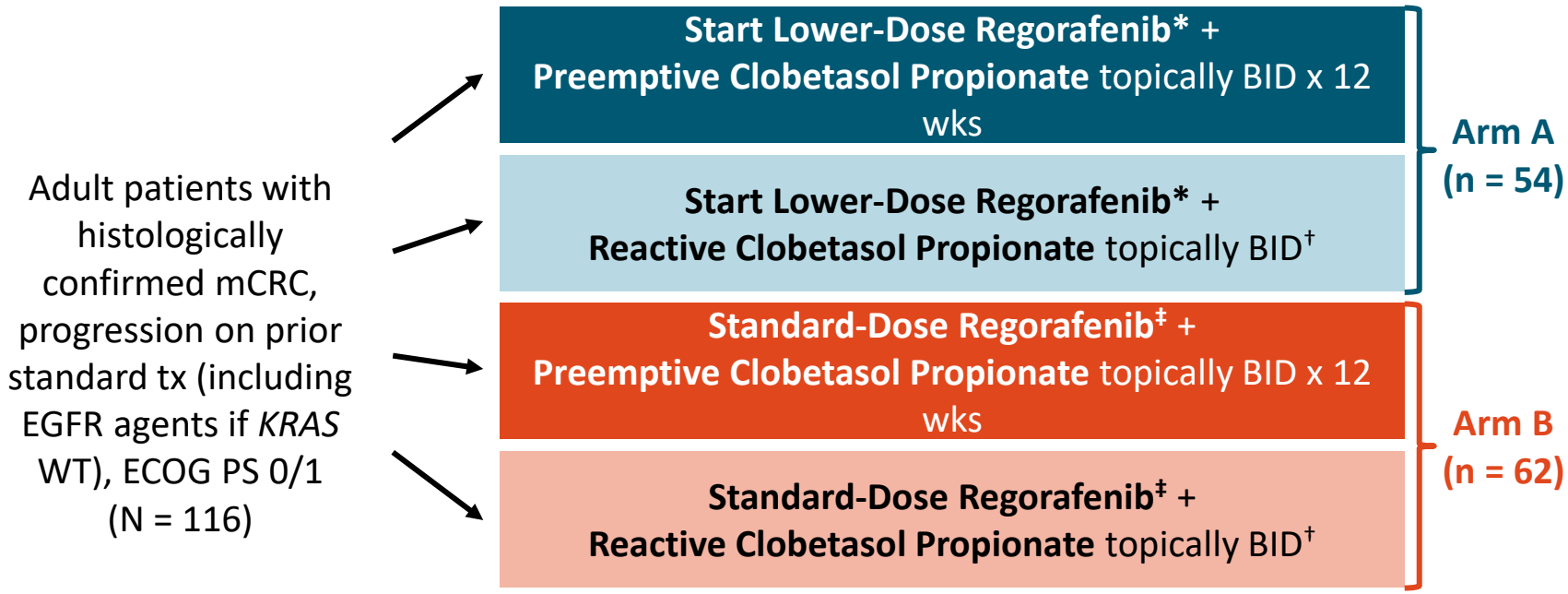
	Regorafenib (n = 505)	Placebo (n = 255)
Median PFS, mos	1.9	1.7
IQR	1.6-3.9	1.4-1.9

HR: 0.49 (95% CI: 0.42-0.58; *P* < .0001)

HFS gelişenlerde OS daha uzun saptanmıştır

Grothey. Lancet. 2013;381:303.

ReDOS: Phase II Study Design



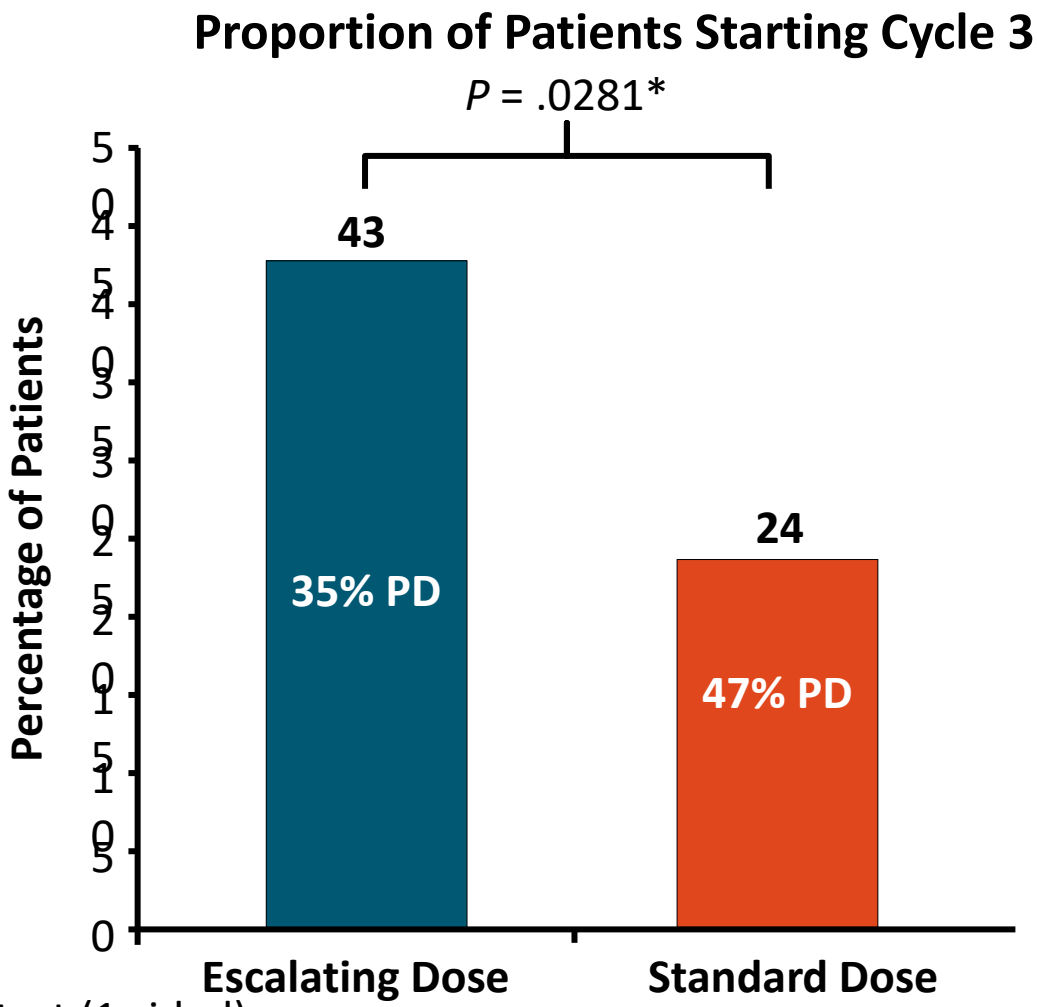
*Regorafenib initiated at 80 mg QD for Wk 1; 120 mg QD for Wk 2; 160 mg QD for Wk 3 of Cycle 1.
†Administered by physician discretion on occurrence of grade ≥ 1 palmar–plantar erythrodysesthesia syndrome.
‡Regorafenib standard dose: 160 mg PO QD on Days 1-21 of 28-day cycles.

Primary endpoint: proportion of patients completing 2 cycles and initiating cycle 3 in arms A and B

Secondary endpoints: OS, PFS, TTP

Bekaii-Saab. ESMO GI 2018. Abstr O-014.

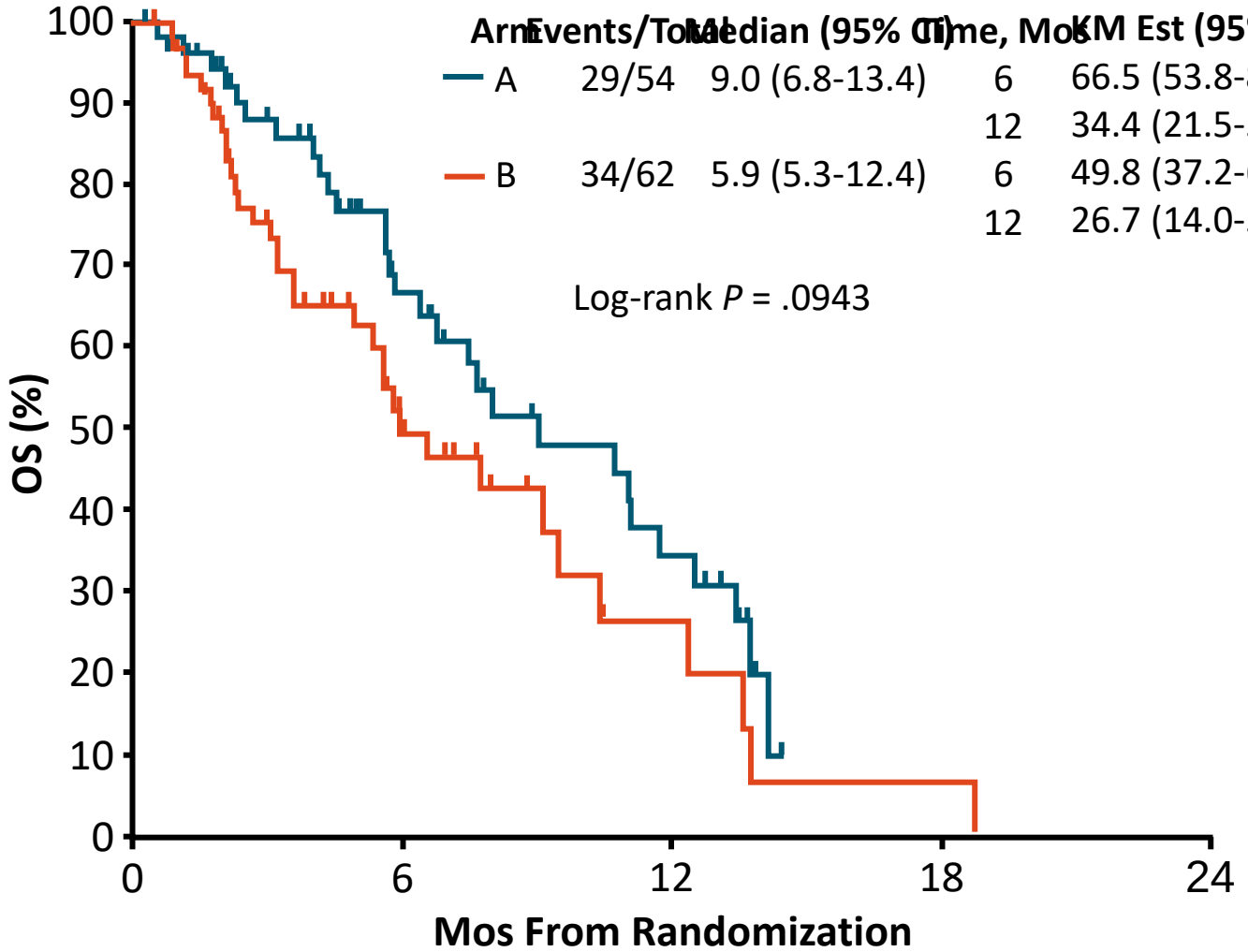
ReDOS: Primary Endpoint



*Fisher's exact test (1 sided).

Bekaii-Saab. ESMO GI 2018. Abstr O-014.

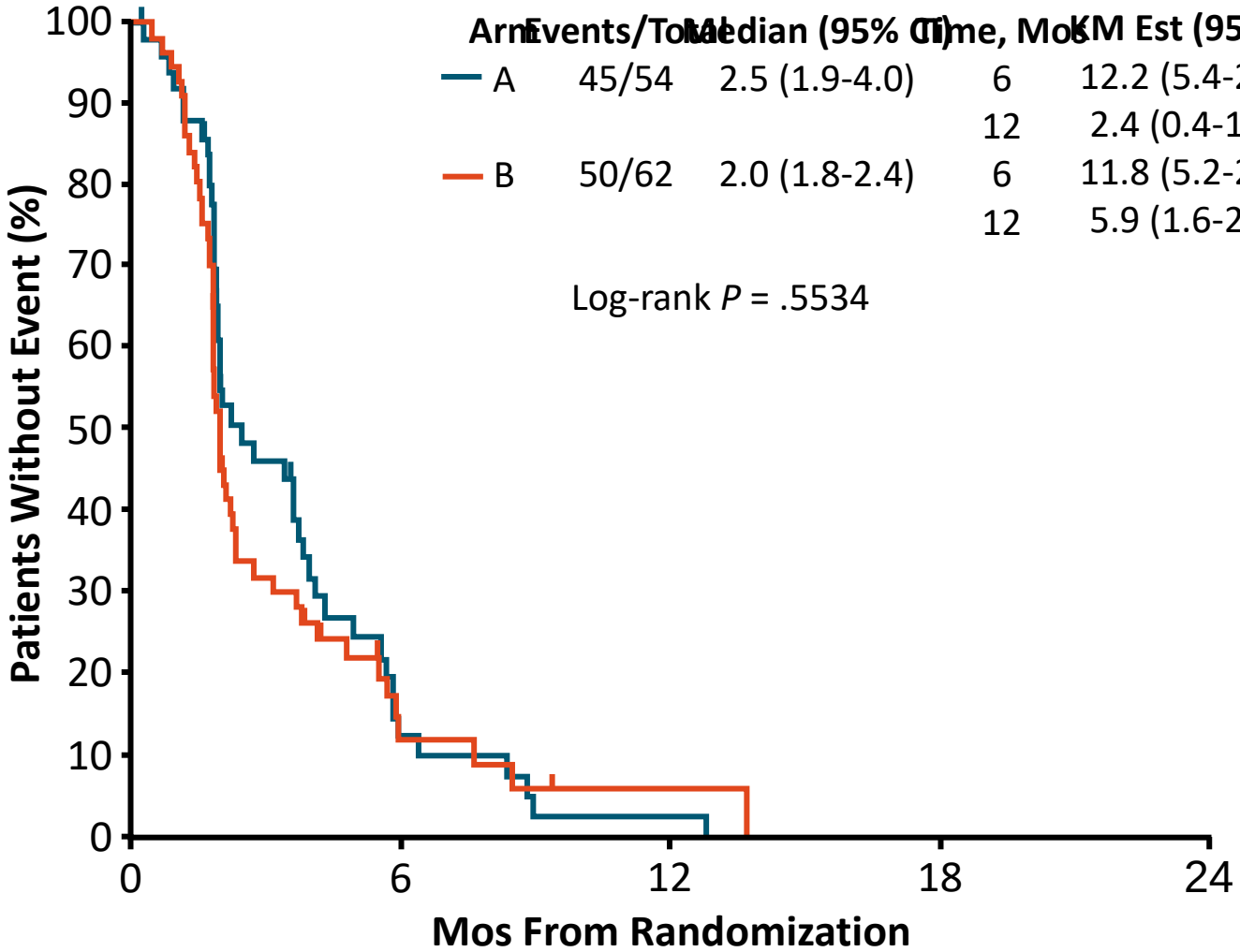
ReDOS: Overall Survival



Arm	Events/Total	Median (95% CI)	Time, Mos	KM Est (95% CI)	HR (95% CI)
A	29/54	9.0 (6.8-13.4)	6	66.5 (53.8-82.2)	0.65 (0.39-1.08)
			12	34.4 (21.5-55.2)	
B	34/62	5.9 (5.3-12.4)	6	49.8 (37.2-66.8)	Reference
			12	26.7 (14.0-51.1)	

Bekaii-Saab. ESMO GI 2018. Abstr O-014.

ReDOS: PFS (Secondary Endpoint)



Arm	Events/Total	Median (95% CI)	Time, Mos	KM Est (95% CI)	HR (95% CI)
A	45/54	2.5 (1.9-4.0)	6	12.2 (5.4-27.0)	0.89 (0.59-1.33)
			12	2.4 (0.4-16.9)	
B	50/62	2.0 (1.8-2.4)	6	11.8 (5.2-26.6)	Reference
			12	5.9 (1.6-21.0)	

Log-rank *P* = .5534

Bekaii-Saab. ESMO GI 2018. Abstr O-014.

Phase II ReDOS Study: AEs Occurring in ≥ 4% of Patients

	Escalating Dose (n = 54)		Standard Dose (n = 62)	
AE, n (%)	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	**7 (13.0)**	**0**	**11 (17.7)**	**0**
PPES	**8 (14.8)**	**0**	**10 (16.1)**	**0**
Abdominal pain	9 (16.7)	0	4 (6.5)	0
Hypertension	**4 (7.4)**	**0**	**9 (14.5)**	**0**
Hyponatremia	2 (3.7)	1 (1.9)	4 (6.5)	1 (1.6)
Bilirubin increased	2 (3.7)	0	5 (8.1)	0
Alkaline phosphatase increased	3 (5.6)	0	1 (1.6)	1 (1.6)
AST increased	1 (1.9)	0	4 (6.5)	0
Dehydration	0	0	5 (8.1)	0
Dyspnea	1 (1.9)	1 (1.9)	3 (4.8)	0
Lymphocyte count decreased	4 (7.4)	0	0	0
Maculopapular rash	0	0	3 (4.8)	0

Bekaii-Saab. ESMO GI 2018. Abstr O-014.

TAS-102
Trifluridine Tipiracil

RECOURSE: TAS-102 in mCRC With ≥ 2 Prior Lines of Standard Chemotherapy

Randomized 2:1; stratified by KRAS status (WT vs mutant), time between first diagnosis of metastases and randomization (< vs ≥ 18 mos), region (Japan vs US/Europe/Australia)

Patients with mCRC and ≥ 2 prior lines of standard chemotherapy, ECOG PS 0/1 (N = 800)

TAS-102 35 mg/m^2 PO BID, D1-5 and 8-12 Q4W + **Best Supportive Care** (n = 534)

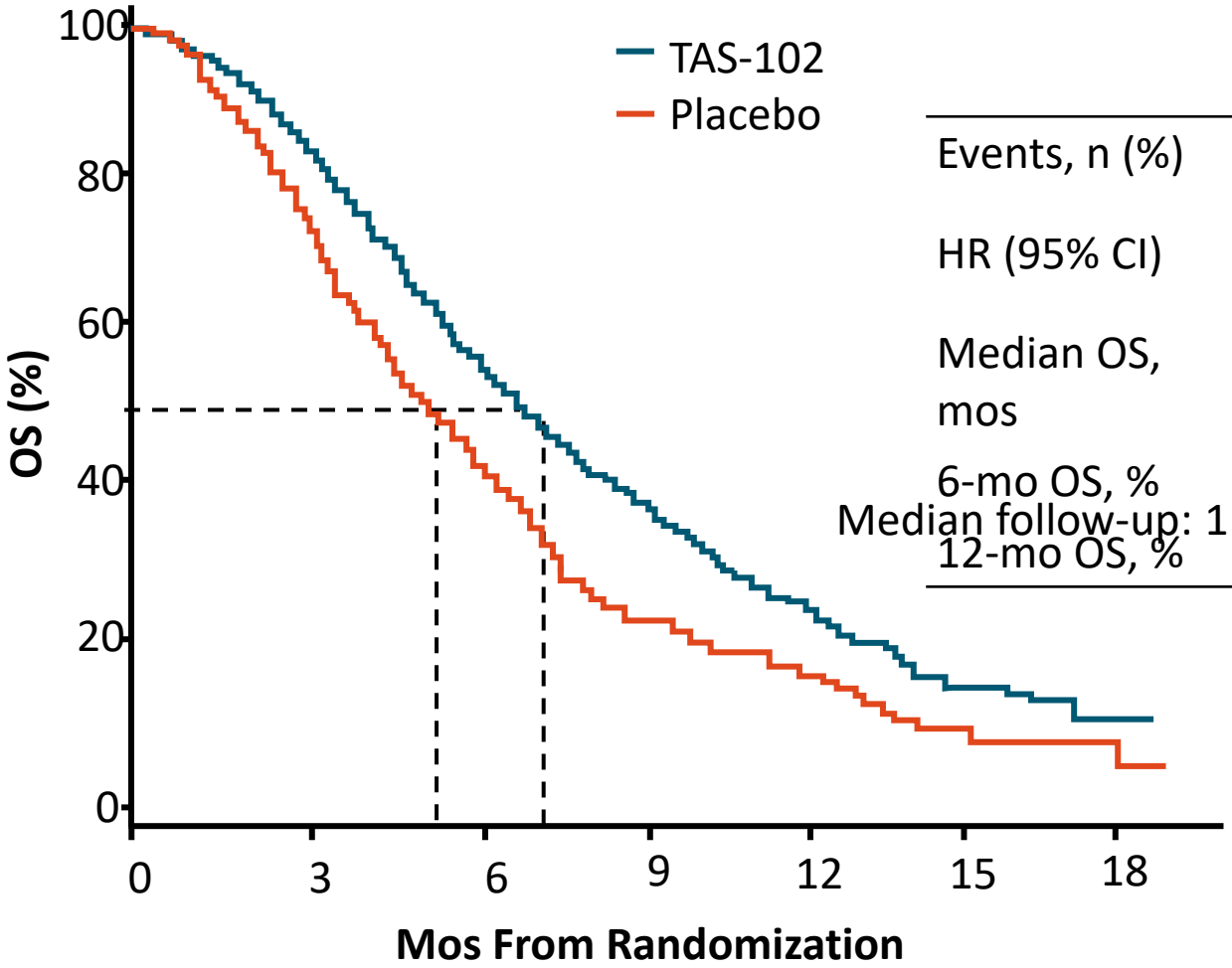
Placebo PO BID, D1-5 and 8-12 Q4W + **Best Supportive Care** (n = 266)

Treat until PD, unacceptable toxicity, or death

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, DCR, safety, TTF, DoR, subgroup by KRAS (OS and PFS)

Mayer. NEJM. 2015;372:1909.

RECOURSE: OS

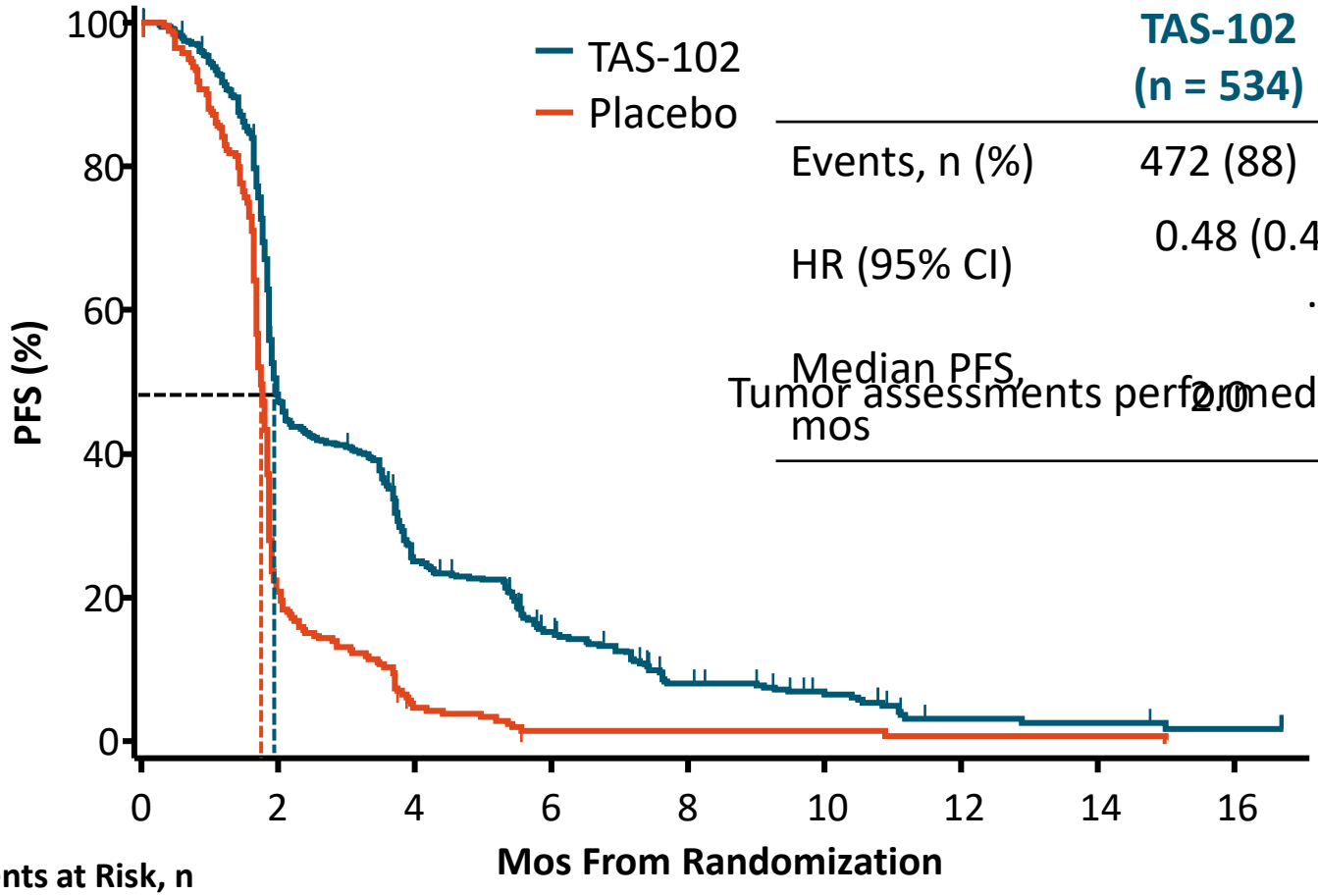


	TAS-102 (n = 534)	Placebo (n = 266)
Events, n (%)	364 (68)	210 (79)
HR (95% CI)	0.68 (0.58-0.81); *P* < .001	
Median OS, mos	7.1	5.3
6-mo OS, %	58	44
12-mo OS, %	27	18

Median follow-up: 11.8 mos

Mayer. NEJM. 2015;372:1909.

RECOURSE: PFS



	TAS-102 (n = 534)	Placebo (n = 266)
Events, n (%)	472 (88)	251 (94)
HR (95% CI)	0.48 (0.41-0.57); *P* < .001	
Median PFS, mos	2.0	1.7

Tumor assessments performed every 8 wks

Patients at Risk, n

TAS-102	534	238	121	66	30	18	5	4	2
Placebo	266	51	10	2	2	2	1	1	0

Mayer. NEJM. 2015;372:1909.

Comparison of Regorafenib, TAS-102 After mCRC Progression

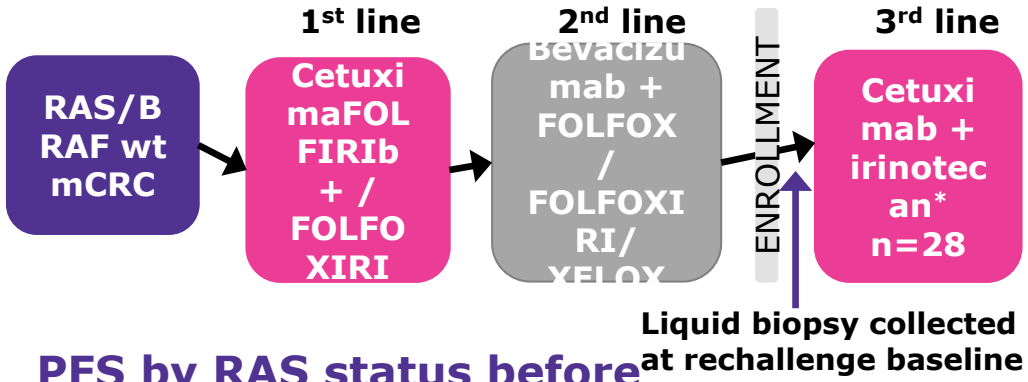
Agent	Regorafenib				TAS-102			
Trial	CORRECT[1]		CONCUR[2]		RECOURSE[3]		TERRA[4]	
Prior biologics	100% BEV 100% EGFR mAbs		60%		100% BEV 53% EGFR mAbs 18% Prior Rego		20% BEV 18% EGFR mAbs	
	Rego (n = 505)	**BSC + PL** (n = 255)	**Rego** (n = 136)	**BSC + PL** (n = 68)	**TAS-102** (n = 534)	**BSC + PL** (n = 266)	**TAS-102** (n = 271)	**BSC + PL** (n = 135)
Median OS, mos	6.4	5.0	8.8	6.3	7.1	5.3	7.8	7.1
	HR: 0.77 *P* = .0052		**HR: 0.55** *P* = .0002		**HR: 0.68** *P* <.0001		**HR: 0.79** *P* = .0035	
Median PFS, mos	1.9	1.7	3.2	1.7	2.0	1.7	2.0	1.8
	HR: 0.49 *P* < .0001		HR: 0.31 *P* < .0001		HR: 0.48 *P* < .0001		HR: 0.43 *P* < .0001	
RR, %	1.0	0.4	4.4	0	1.6	0.4	1.1	0

- Main adverse events: hand-foot skin reaction, fatigue (regorafenib); neutropenia, GI toxicities, fatigue (TAS-102)

1. Grothey. Lancet. 2013;381:303. 2. Li. Lancet Oncol. 2015;16:619. 3. Meyer. NEJM. 2015;372:1909. 4. Kim. ESMO 2016. Abstr 465PD.

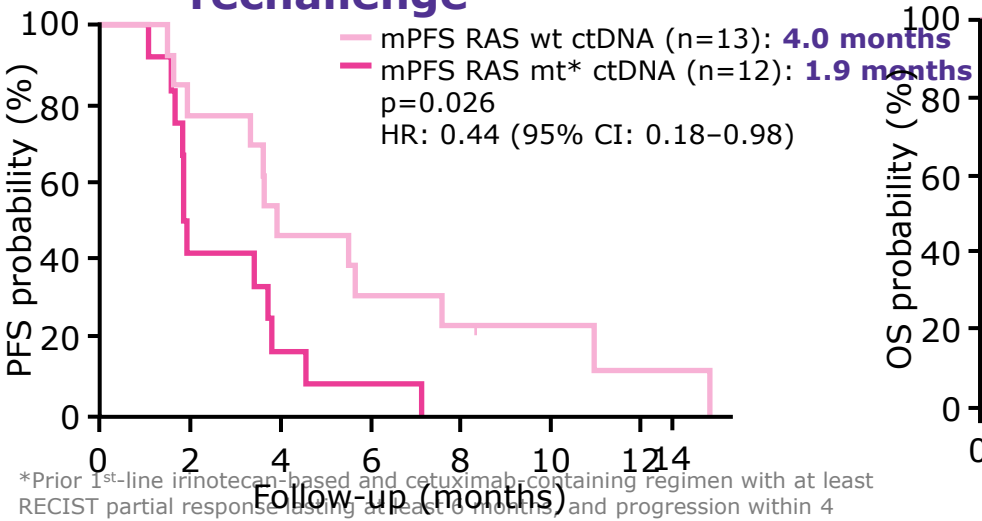
The CRICKET trial further demonstrated the potential of cetuximab rechallenge in RAS wt/BRAF wt mCRC

Phase II, multicentre, single-arm study[1]

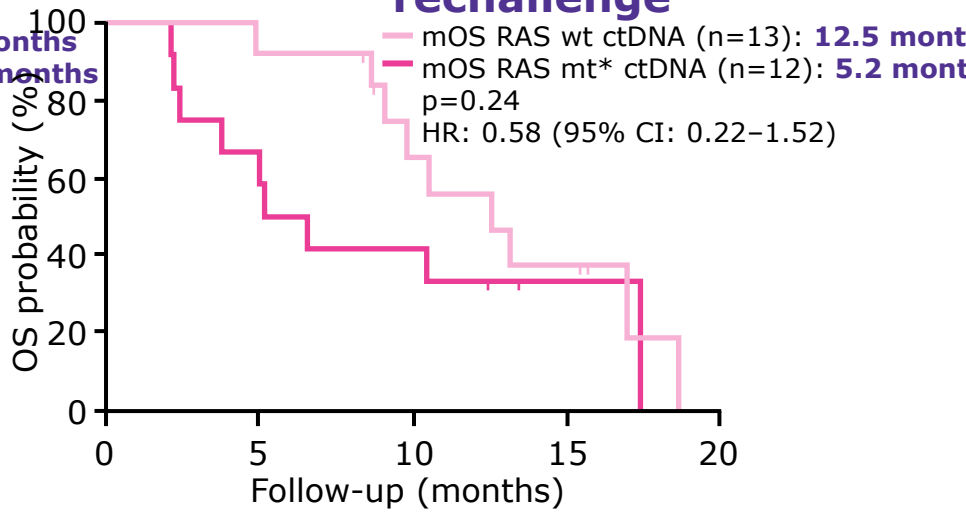


- **Primary endpoint met: ORR: 21% (6/28)†**
- **Secondary endpoint met: DCR: 54% (15/28)**
- RAS mutations were found in ctDNA collected at the rechallenge baseline in 12 of 25 patients (48%)
- No RAS mutations were found in patients who achieved a PR during rechallenge

PFS by RAS status before rechallenge[1]



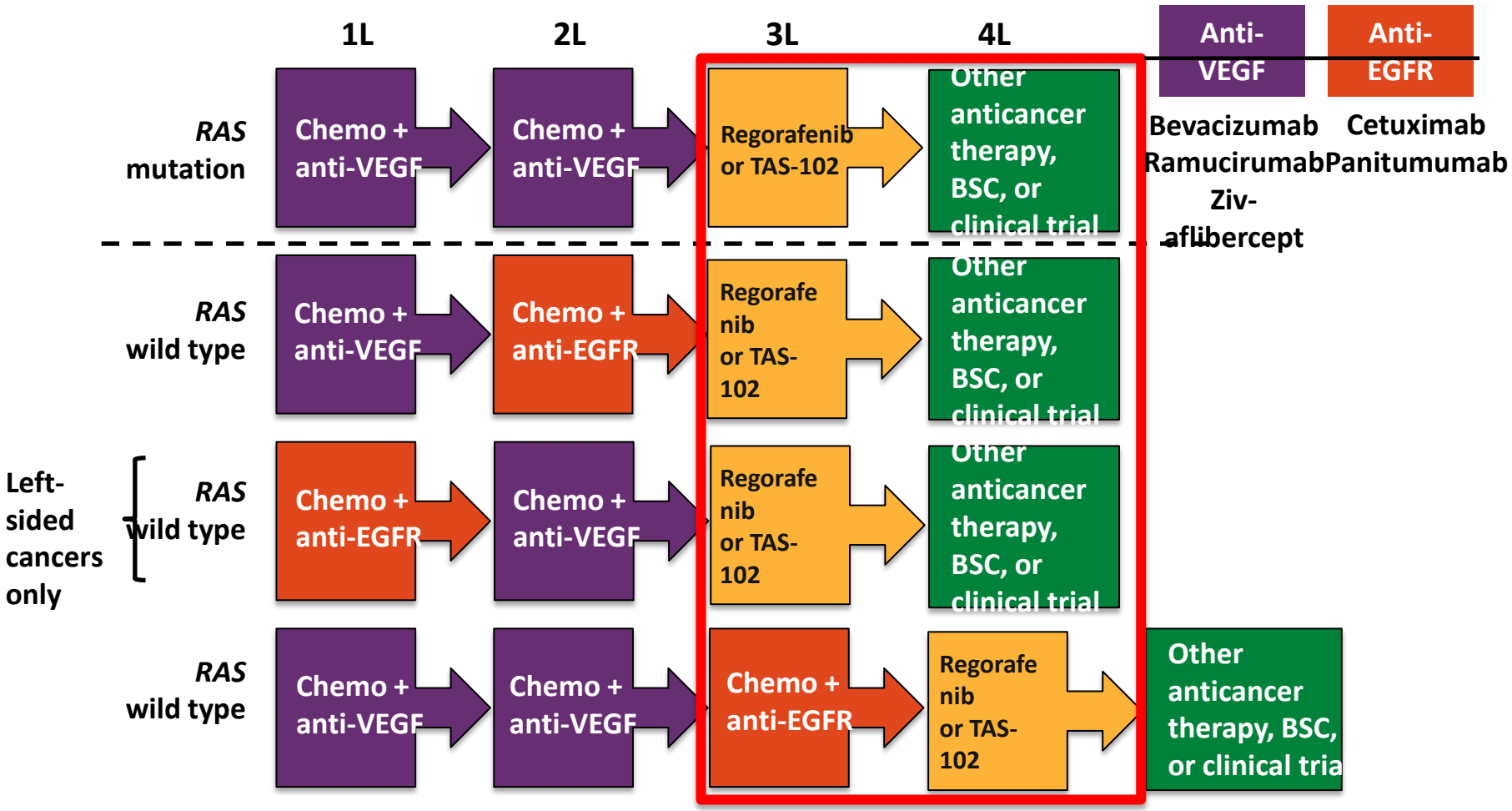
OS by RAS status before rechallenge[1]



*Prior 1st-line irinotecan-based and cetuximab-containing regimen with at least RECIST partial response lasting at least 6 months, and progression within 4 weeks after the last administration of cetuximab, prior 2nd-line oxaliplatin-based and bevacizumab-containing treatmentCetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown; †Two (7%) patients had unconfirmed partial response.
CI, confidence interval; HR, hazard ratio; ctDNA, circulating DNA.

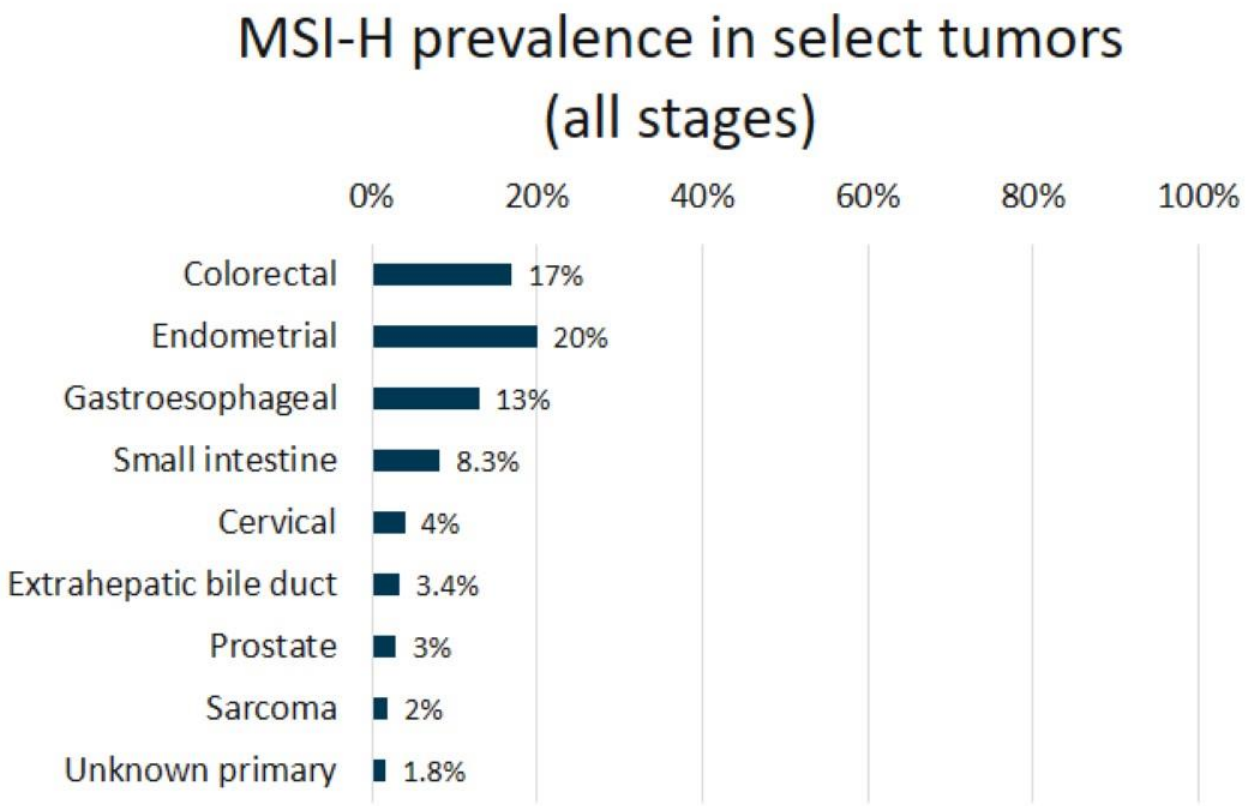
1. Cremolini C, et al. JAMA Oncol 2019;5:343–350.

mKRK Üçüncü Sıra Tedavi Önerisi Treatment



van Cutsem. Ann Oncol. 2016;27:1386.

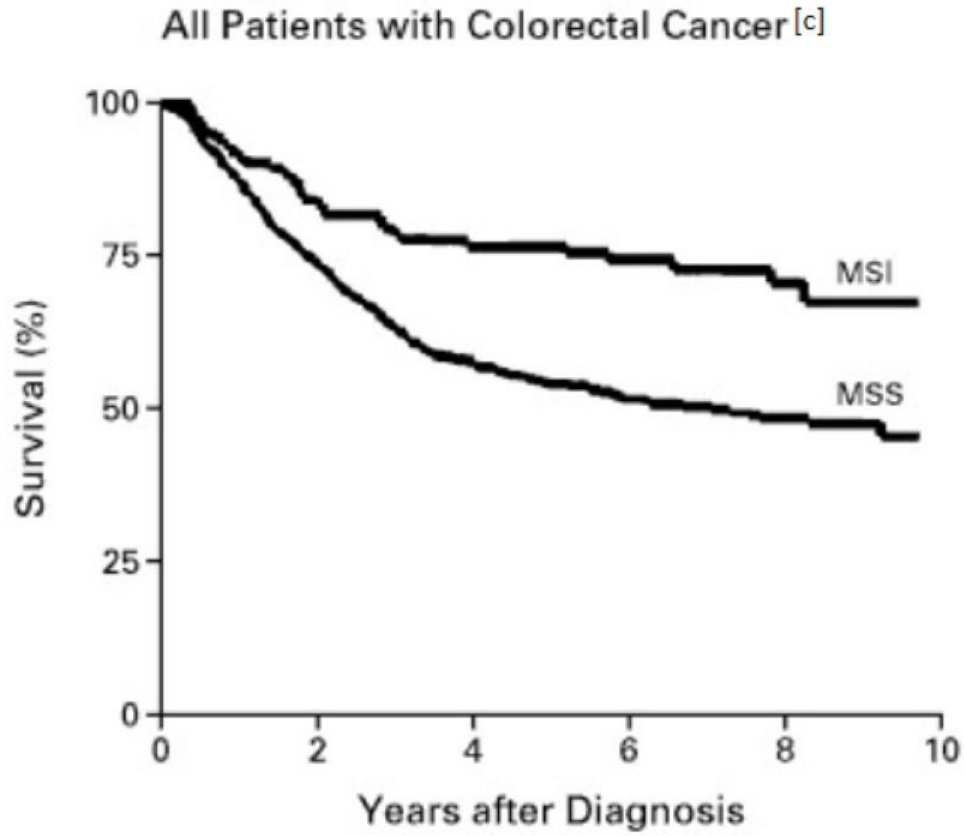
Microsatellite Instability in Cancer



Luchini C, et al. *Ann Oncol.* 2019. [Epub ahead of print]

Prognostic Impact of Microsatellite Instability in CRC

- MSI-H status varies by tumor stage[a,b]:
  - Stage I: 14.1%
  - Stage II: 17.5%
  - Stage III: 13.5%
  - Stage IV: 3.5%-5.5%



No. at Risk

MSI	102	86	78	53	29	0
MSS	485	358	280	183	75	0

a. Koopman M, et al. *Br J Cancer.* 2009;100(2):266-273; b. Samowitz WS, et al. *Cancer Epidemiol Biomarkers Prev.* 2001;10(9):917-923; c. Gryfe R, et al. *N Engl J Med*. 2000;342(2):69-77.

Contrasting Pembrolizumab With Standard Later-Line Therapies

Outcome	CORRECT Trial[a] (N = 753)		RECOURSE Trial[b] (N = 800)		¥KEYNOTE-164[c] (N = 63)
	Regorafenib (n = 500)	Placebo (n = 253)	TAS-102 (n = 534)	Placebo (n = 266)	Pembrolizumab
ORR, %	1.0	0.4	1.6	0.4	32
mPFS, mo	1.9	1.7	2.0	1.7	4.1
mOS, mo	6.4	5.0	7.1	5.3	NR*

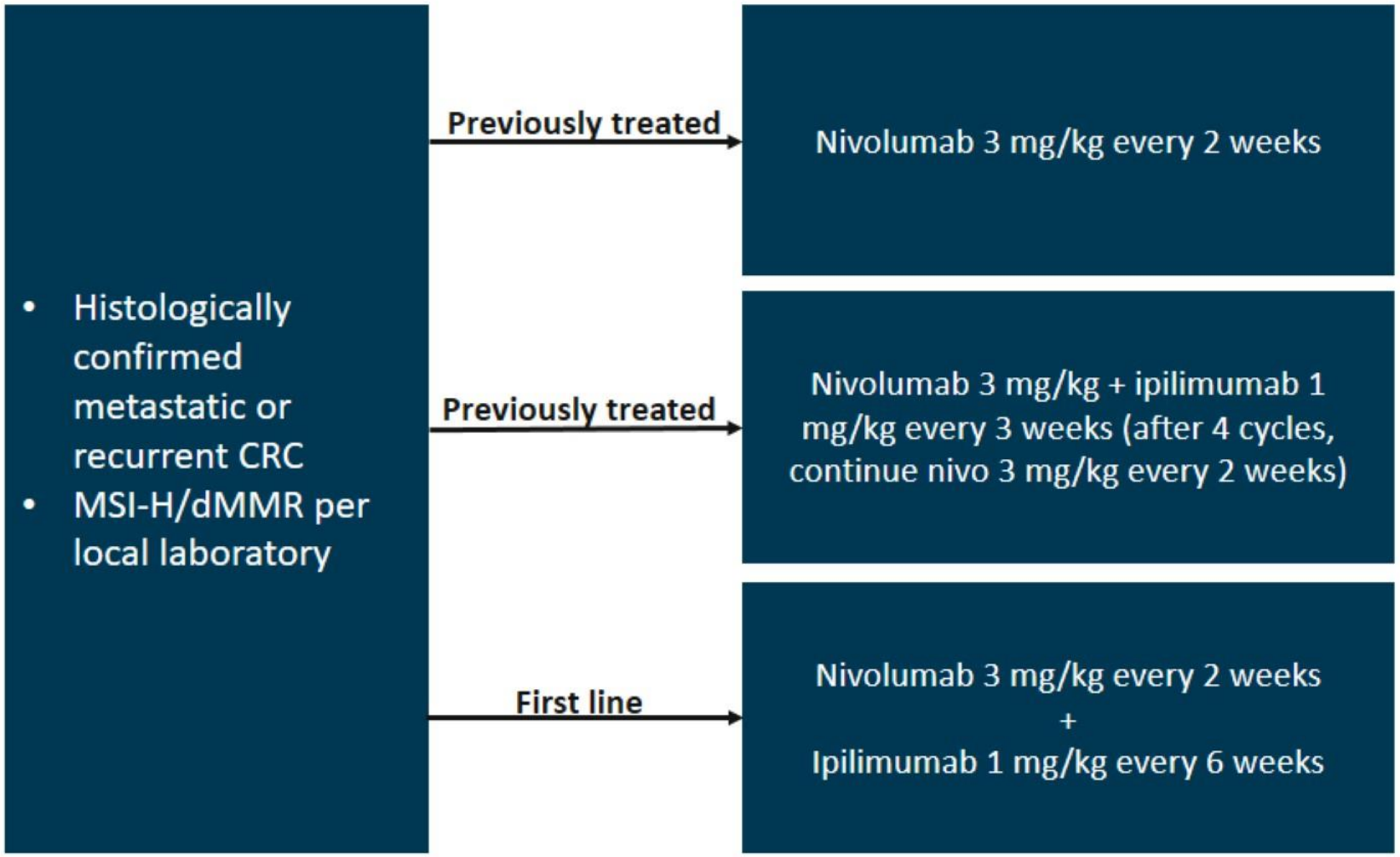
*12.6 median duration of follow-up; 12-month OS rate was 76%.

¥ En az iki sıra tedavi almış hastalarda Pembrolizumab monoterapi

a. Grothey A, et al. *Lancet*. 2013;381(9863):303-312.
b. Mayer RJ, et al. *N Engl J Med*. 2015;372(20):1909-1919.
c. Le D, et al. *Ann Oncol*. 2018;29(suppl 5). Abstract O-021.

CheckMate-142

What Is the Optimal Immunotherapy Approach for MSI-H CRC?



Lenz HJ, et al. *Ann Oncol.* 2018;29(suppl 8). Abstract LBA18_PR.

CheckMate 142
Single-Agent Nivolumab in MSI-H CRC

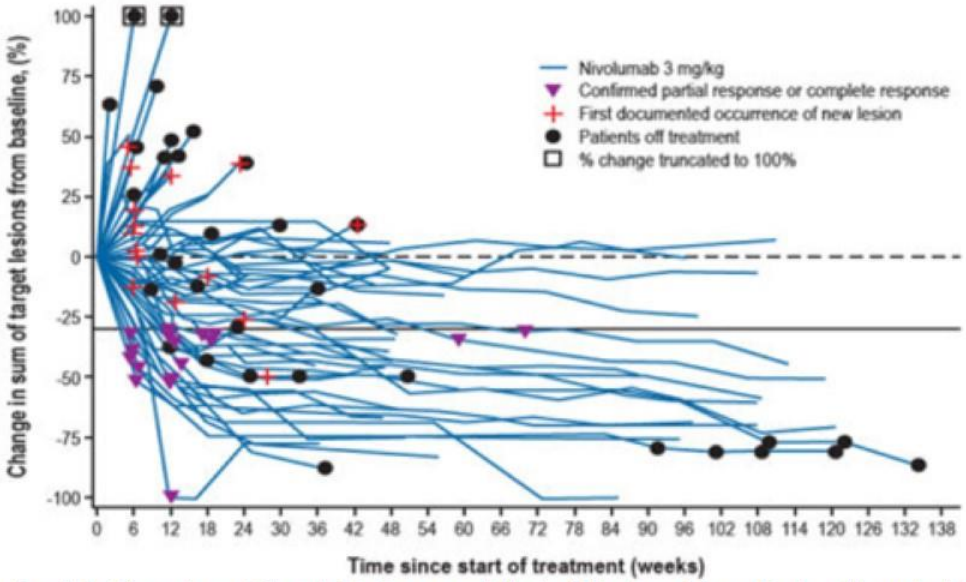
- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory

Previously treated → Nivolumab

Previously treated → Nivolumab + ipilimumab

First line → Nivolumab + ipilimumab

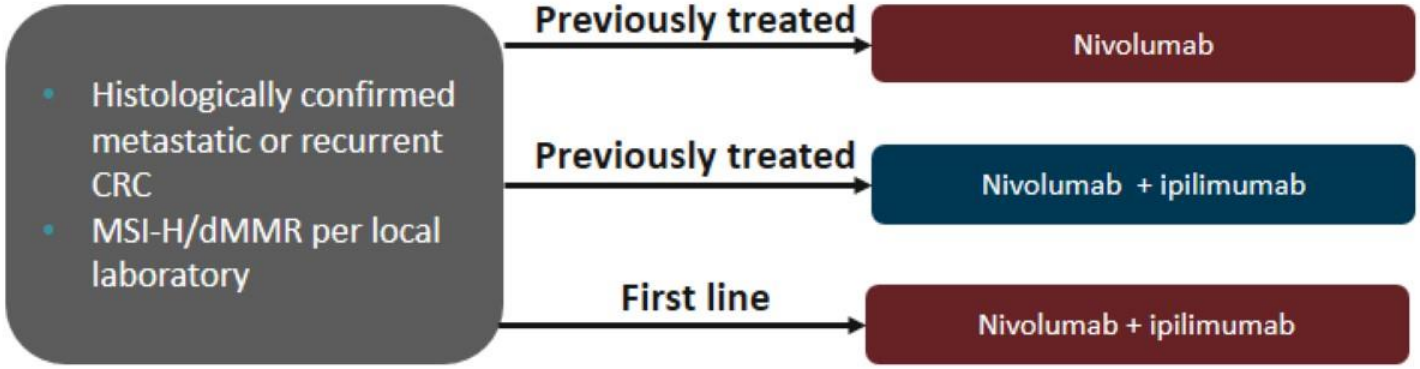
Endpoint	Nivolumab (N = 74)
ORR, %	31.1
DCR, %	68.9
mDoR, mo	NR



Reprinted from Lancet Oncol, 18, Overman MJ, et al,Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study, 1182-1191, 2017, with permission from Elsevier.

Overman MJ, et al. *Lancet Oncol*. 2017;18(9):1182-1191.

CheckMate-142 Nivolumab-Ipilimumab Combination Results



Endpoint	Nivolumab + ipilimumab (N = 119)
ORR, %	55
12-wk DCR, %	80
mDoR, mo	NR
6-mo DoR, %	83%

Overman MJ, et al. *J Clin Oncol.* 2018;36(8):773-779.

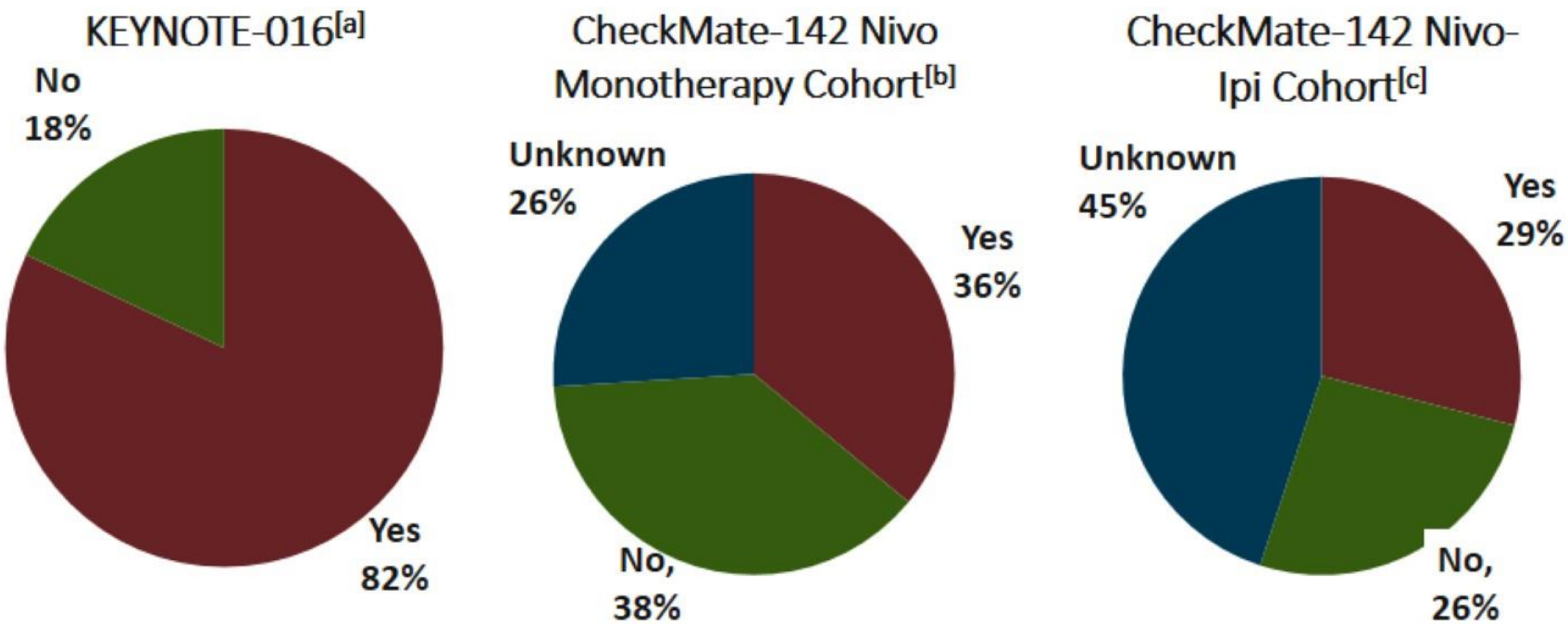
Single-Agent or Combination Immunotherapy?

- Need to consider the following:
  - Toxicity profiles
  - Drug availability
  - Limited, non-randomized data to date
  - Patient preference

AE, %	Nivo[a]		Nivo-Ipi[b]	
	Grade 1/2	Grade ≥ 3	Grade 1/2	Grade ≥ 3
Any event	48.6	20.3	41	32
Diarrhea	20.3	1.4	20	2
Fatigue	21.6	1.4	16	2
Pruritis	13.5	0	15	2
Pyrexia	5.4	0	15	0
Increased AST	6.8	0	7	8
Hypothyroidism	9.5	0	13	1
Nausea	9.5	0	12	1
Increased ALT	4.1	1.4	5	7
Rash	10.8	0	9	2

a. Overman MJ, et al. *Lancet Oncol*. 2017;18(9):1182-1191.
b. Overman MJ, et al. *J Clin Oncol*. 2018;36(8):773-779.

Does It Matter Whether MSI-H Status Is Germline or Somatic?

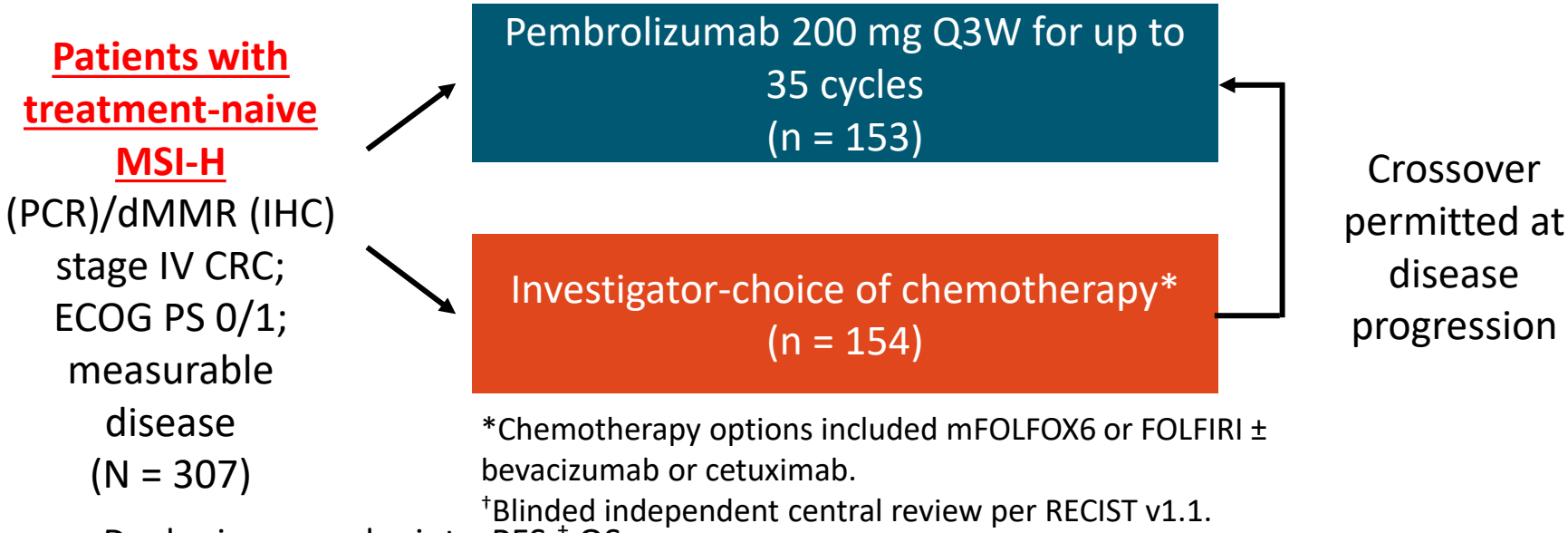


Responses observed with immune checkpoint inhibitors in MSI-H CRC regardless of Lynch syndrome status[a-c]

a. Le DT, et al. *N Engl J Med*. 2015;372:2509-2520; b. Overman MJ, et al. *Lancet Oncol*. 2017;18(9):1182-1191; c. Overman MJ, et al. *J Clin Oncol.* 2018;36(8):773-779.

KEYNOTE-177: First-line Pembrolizumab vs Chemotherapy for MSI-H/dMMR mCRC

- Randomized, open-label phase III trial



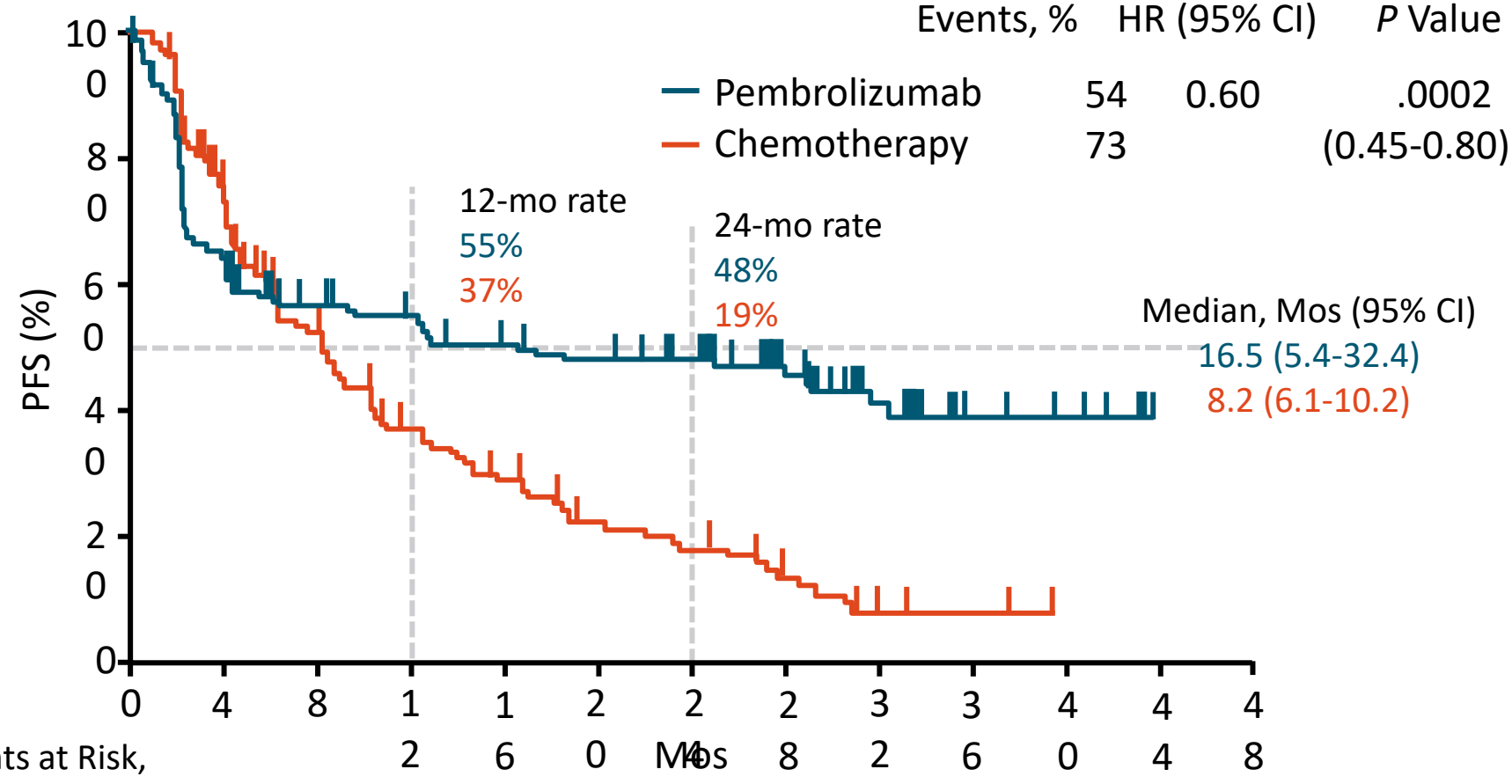
*Chemotherapy options included mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab.
†Blinded independent central review per RECIST v1.1.

- Dual primary endpoints: PFS,† OS
  - Trial positive if pembrolizumab superior to chemotherapy for either primary endpoint
- Secondary endpoints: ORR,† safety

- Data cutoff: February 29, 2020
- Median follow-up: 28.4 mos in pembrolizumab arm, 27.2 mos in comparator arm

Andre. ASCO 2020. Abstr LBA4.

KEYNOTE-177: PFS (Primary Endpoint; ITT)



Patients at Risk,

155	153	96	77	72	64	60	55	37	20	7
154	150	100	68	43	33	22	18	11	4	3

Andre. ASCO 2020. Abstr LBA4. Reproduced with permission.

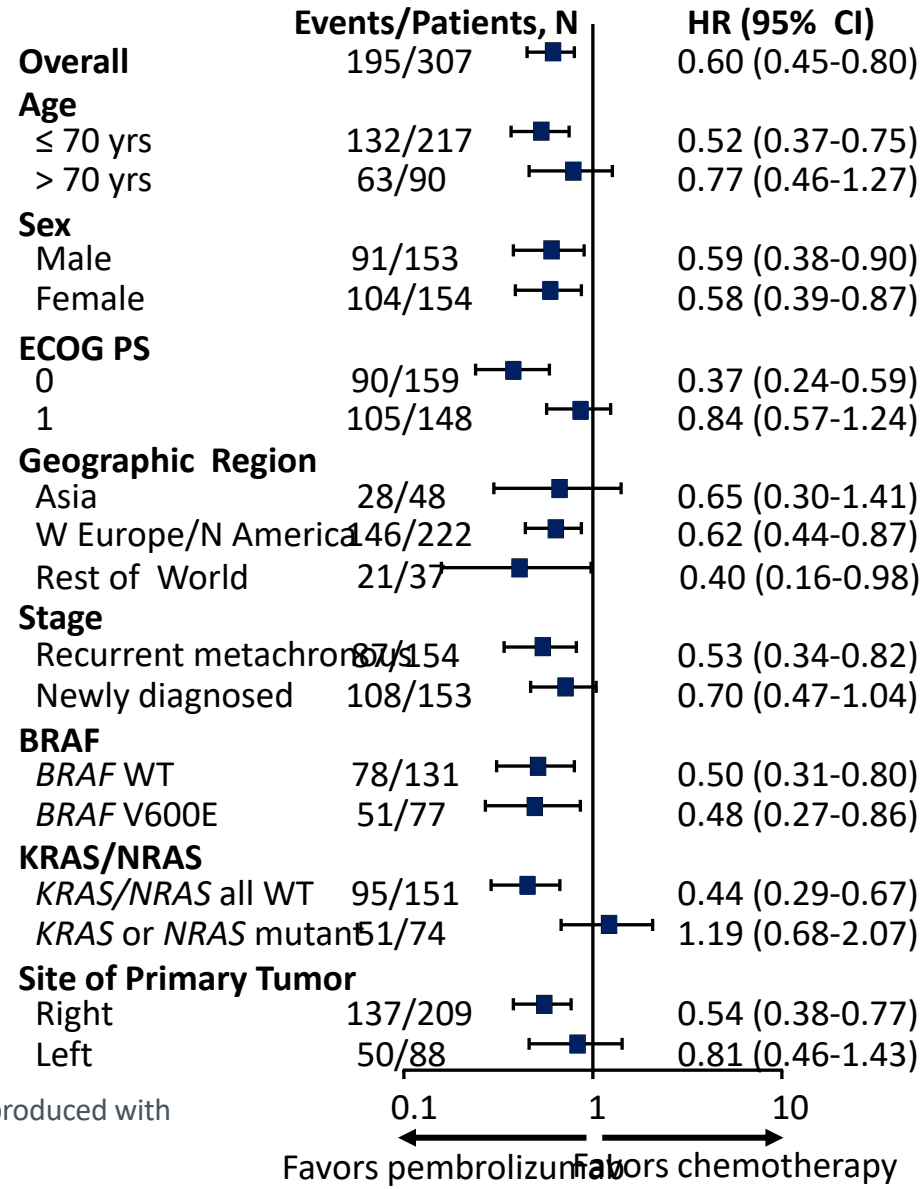
KEYNOTE-177: Response

Efficacy Outcomes (ITT)	Pembrolizumab (n = 153)	Chemotherapy (n = 154)	*P* Value
ORR, %	43.8	33.1	.0275
DCR (CR + PR + SD), %	64.7	75.3	
Best overall response, %			
▪ CR	11.1	3.9	
▪ PR	32.7	29.2	
▪ SD	20.9	42.2	
▪ PD	29.4	12.3	
▪ Not evaluable	2.0	1.3	
▪ No assessment	3.9	11.0	
Median time to response, mos (range)	2.2 (1.8-18.8)	2.1 (1.7-24.9)	

- 36% of patients in chemotherapy arm crossed over to receive pembrolizumab; 23% received anti–PD-1/PD-L1 therapy outside of study
- OS analysis ongoing

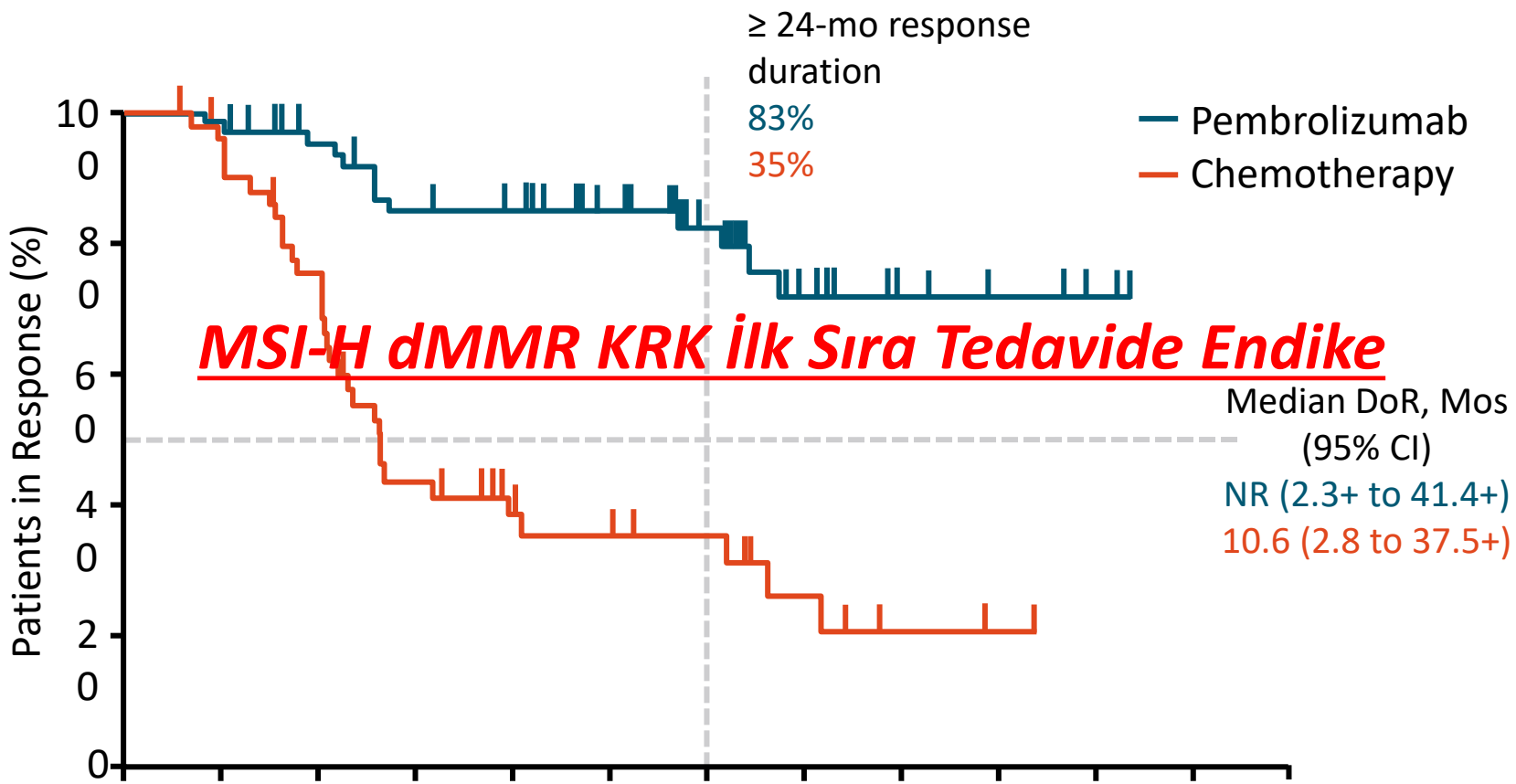
Andre. ASCO 2020. Abstr LBA4.

KEYNOTE-177: PFS Subgroup Analysis



Andre. ASCO 2020. Abstr LBA4. Reproduced with permission.

KEYNOTE-177: Duration of Response



MSI-H dMMR KRK İlk Sıra Tedavide Endike

Patients at Risk,

67	64	57	50	48	41	29	13	6	4
62	60	50							
51	48	35	19	13	11	9	5	2	1
0	0	0							

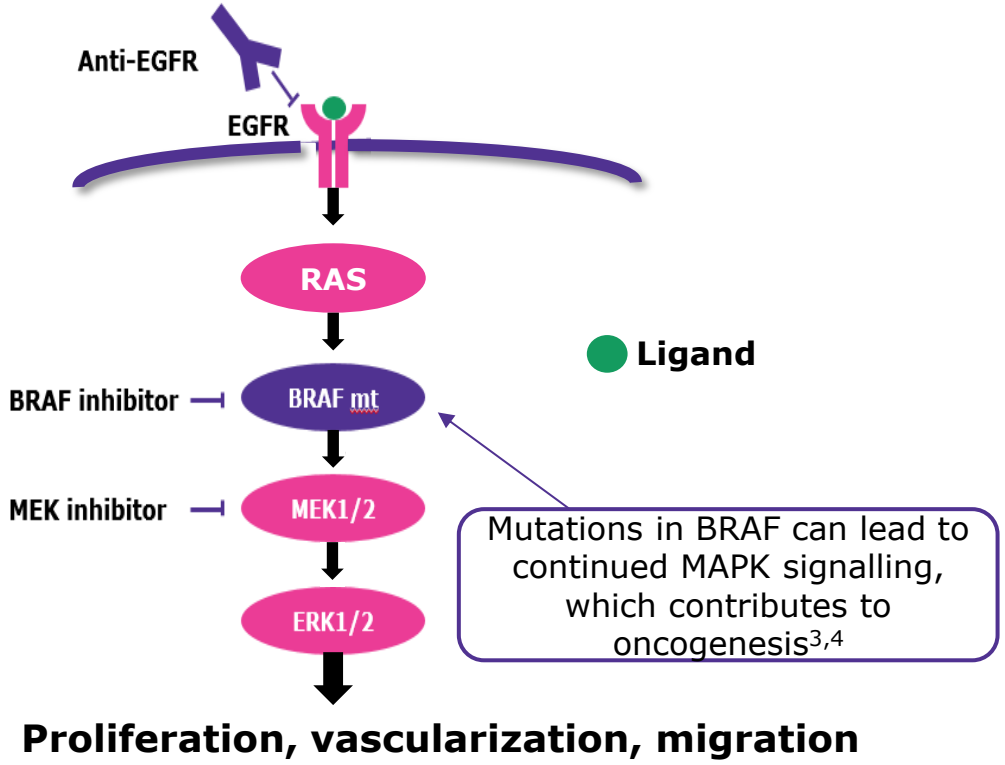
Andre. ASCO 2020. Abstr LBA4. Reproduced with permission.

The biological rationale for multi-targeted inhibition in BRAF mt mCRC

EGFR signalling pathways[2]

Multi-targeted therapy:

- Cetuximab (an anti-EGFR)
- Encorafenib (a BRAF inhibitor)
- Binimetinib (a MEK inhibitor)



CT, chemotherapy; MAPK, mitogen activated protein kinase.

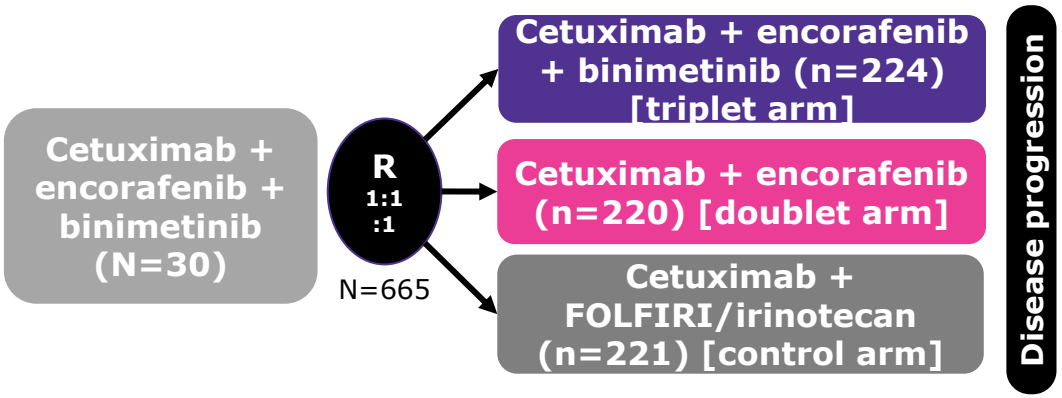
2. Leto SM, et al. J Mol Med 2014;92:709–722;
3. Thiel A and Ristimäki A. Front Oncol 2013;3:281;
4. Hall RD and Kudchadkar RR. Cancer Control 2014;21:221–230.

BEACON is a randomized, open-label, 3-arm, multicenter Phase III study

STUDY DESIGN[5,6,7]

Key inclusions: RAS wt, **BRAF V600E mCRC; 1–2 lines of prior treatment in metastatic setting**

Key exclusions: Previous treatment with RAF, MEK or EGFR inhibitors; symptomatic brain metastases or leptomeningeal disease



Co-primary endpoints:

- OS of triplet vs control (all randomized patients)
- ORR of triplet vs control (blinded central review in the first 331 randomized patients)

Secondary endpoints:

- OS in doublet vs control and triplet vs doublet
- Comparison of PFS, ORR, DOR and time to response across arms
- Safety

Primary analysis presented at WCGC 2019 confirmed that the study had met its primary endpoints[5]. An additional 6 months of data were presented at ASCO 2020[8]

400mg/m^2 cetuximab was given on Day 1 followed by 250 mg/m^2 q1w; 300 mg encorafenib was given q1d PO; 45 mg binimetinib was given BID PO; the control arm received FOLFIRI (irinotecan 180 mg/m^2 i.v on Days 1 and 15, FA 400mg/m^2 on Days 1 and 15, 5-FU 400 mg/m^2 i.v on Day 1 and 15, then 1200mg/m^2/d 2 days continuous infusion) or irinotecan (180 mg/m^2 i.v on days 1 and 15).
BID, twice daily; DLT, dose-limiting toxicity; DOR, duration of response; FA, folinic acid; PO, per os; QD, daily; Q1, weekly.

5. Kopetz S, et al. N Engl J Med 2019;1632–1643;
6. Tabernero S, et al. ESMO 2019 (Abstract No. LBA32);
7. Array BioPharma Inc. Protocol v6.0, 2018;
8. Kopetz S, et al. ASCO 2020 (Abstract No. 4001).

There were significantly more patients with baseline characteristics indicative of poor prognosis in the triplet vs doublet arm

Baseline characteristics[5,6]

Characteristic	Triplet (n=224)	Doublet (n=220)	Control (n=221)
Female, %	53	48	57
Age, median (range)	62 (26–85)	61 (30–91)	60 (27–91)
ECOG PS 0, n (%)	116 (52)	112 (51)	108 (49)
Location of primary tumor,* n (%)			
Left (includes rectum)	79 (35)	83 (38)	68 (31)
Right	126 (56)	110 (50)	119 (54)
≥3 organs involved, n (%)	110 (49)	103 (47)	98 (44)
Presence of liver metastases, n (%)	144 (64)	134 (61)	128 (58)
Prior lines of therapy, n (%)			
1	146 (65)	146 (66)	145 (66)
>1	78 (35)	74 (34)	76 (34)
MSI-H,† n (%)	22 (10)	19 (9)	12 (5)
CEA >5 ug/L, n (%)	179 (80)	153 (70)	178 (81)
CRP >10 mg/L, n (%)	95 (42)	79 (36)	90 (41)

*Remaining patients had their primary tumor either in the left and the right, or it was unknown; †Based on assessment by PCR; MSI status was missing in 23% of patients.

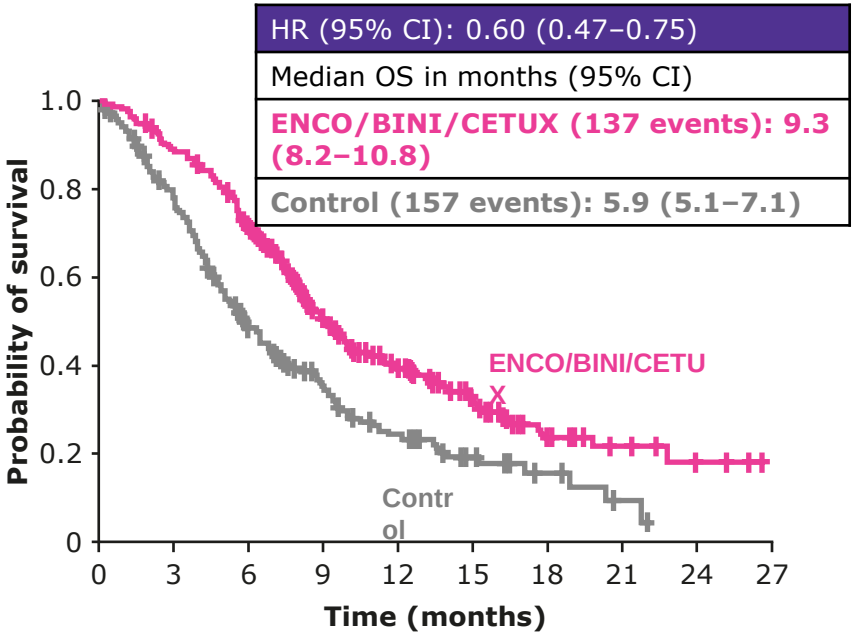
Highlighted characteristics were significantly more predominant in the triplet vs doublet arm ($p<0.0001$)[5,6]

Additionally, the number of patients with ≥2 prior regimens for metastatic disease were significantly higher in the triplet vs doublet arm ($p=0.0493$; not shown in table)[6]

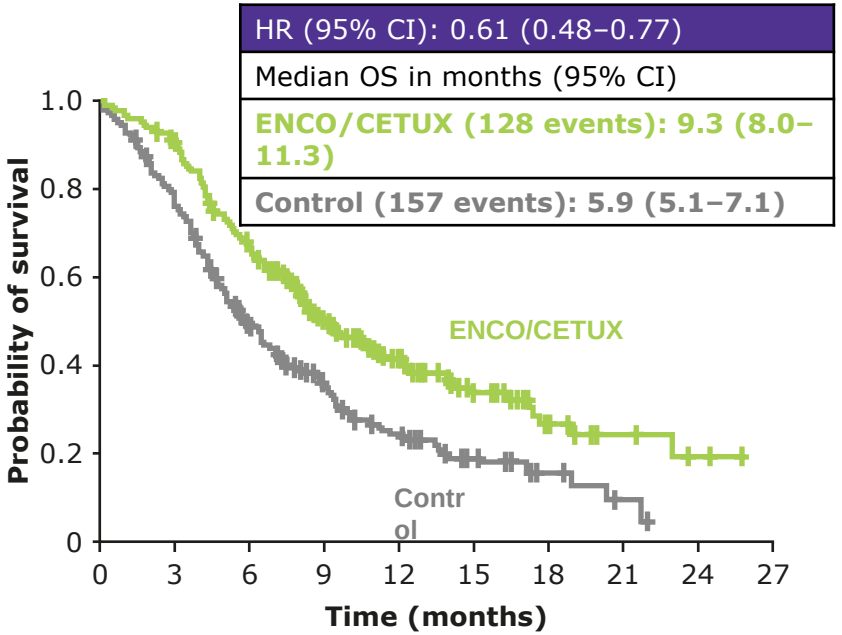
5. Kopetz S, et al. N Engl J Med 2019;1632–1643;
6. Tabernero S, et al. ESMO 2019 (Abstract No. LBA32).

Triplet* and doublet† therapy significantly improved OS vs control

Co-primary endpoint: OS triplet vs control[8]



Secondary endpoint: OS doublet vs control[8]



Co-primary endpoint: ORR[8]

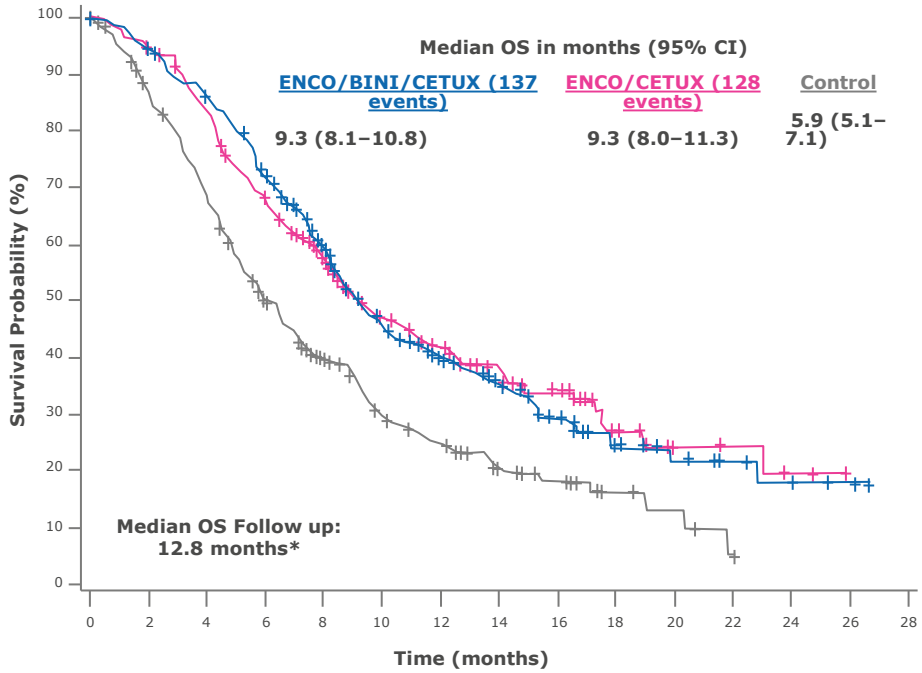
	Triplet (n=224)	Doublet (n=220)	Control (n=221)
ORR, % 95% CI	**27** (21, 33)	**20** (15, 25)	**2** (<1, 5)

*Encorafenib + cetuximab + binimetinib; †Encorafenib + cetuximab.
CI, confidence interval; HR, hazard ratio; ORR, overall response rate; OS, overall survival.

8. Kopetz S, et al. ASCO 2020 (Abstract No. 4001).

Triplet* and doublet† therapy significantly improved OS vs control

OS of triplet, doublet and control[8]



ENCO/BINI/CETUX	224	211	191	157	109	71	56	40	27	15	10	7	4	2	0
ENCO/CETUX	220	206	181	143	105	70	47	33	26	13	7	5	2	0	0
Control	221	183	142	98	65	42	33	18	13	6	4	1	0	0	0

- **First line?: ANCHOR, f-2, In patients with BRAF V600E-mutant mCRC, 1L treatment with encorafenib + binimetinib + cetuximab demonstrated clinical activity and was well-tolerated**
- e

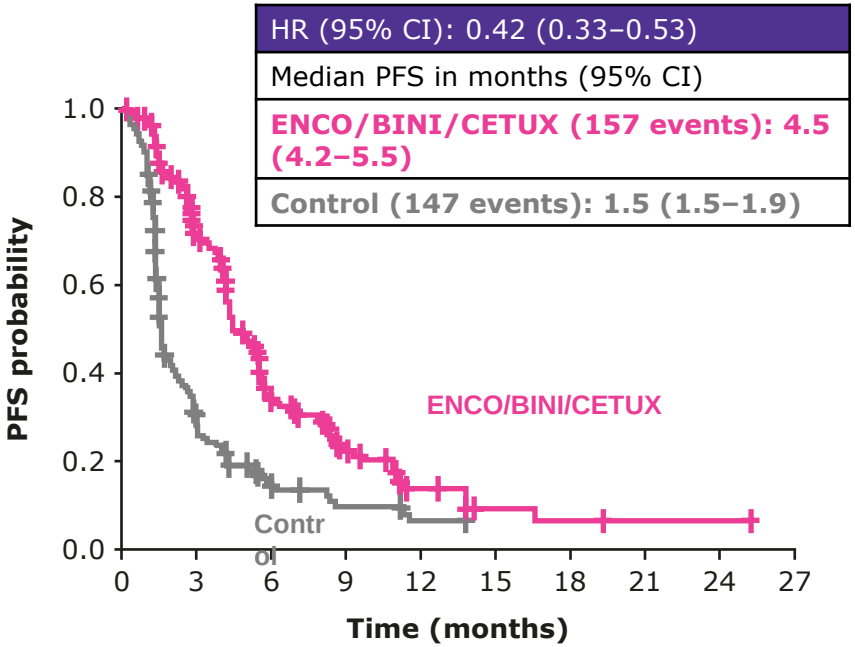
*Encorafenib + cetuximab + binimetinib; †Encorafenib + cetuximab.
CI, confidence interval; OS, overall survival.

8. Kopetz S, et al. ASCO 2020 (Abstract No. 4001).

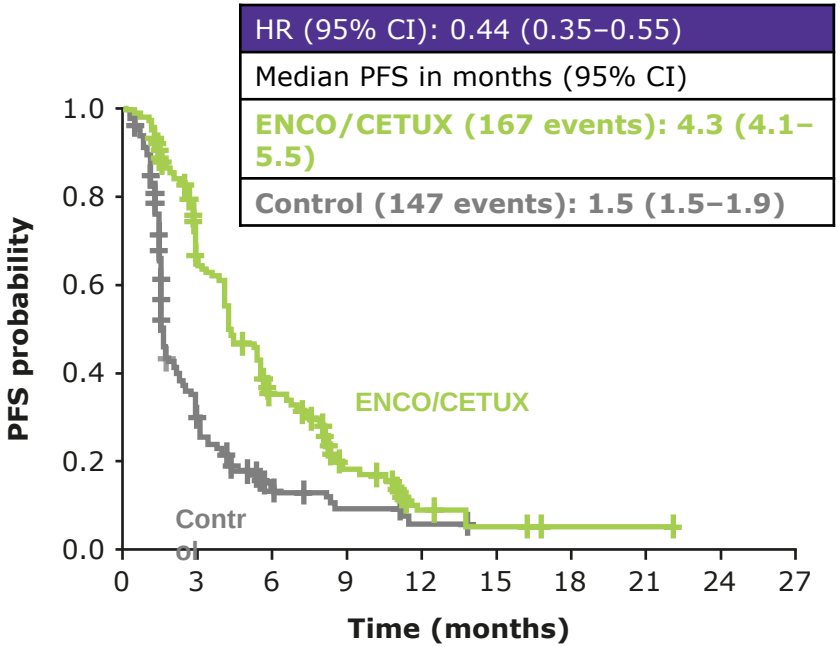
Triplet* and doublet† therapy significantly improved PFS vs control

Secondary endpoint: PFS analysis (N=665)[8]

PFS: triplet vs control[8]



PFS: doublet vs control[8]



The approvals of cetuximab + encorafenib were based on positive results from the BEACON trial. The FDA and EMA approved encorafenib in combination with cetuximab as the addition of binimetinib did not seem to provide significant additional benefit[1,5,11]

*Encorafenib + cetuximab + binimetinib; †Encorafenib + cetuximab.
CI, confidence interval; HR, hazard ratio; PFS, progression free survival; OS, overall survival.

8. Kopetz S, et al. ASCO 2020 (Abstract No. 4001).

HERACLES: Trastuzumab + Lapatinib for Previously Treated mCRC

- Multicenter, open-label phase II trial

Patients with HER2+/*KRAS* exon 2 WT metastatic CRC; PD on/within 6 mos of approved standard treatment for CRC*; ECOG PS 0-1 (N = 27)

→ **Trastuzumab** at 4 mg/kg loading dose then 2 mg/kg IV QW + **lapatinib** 1000 mg PO QD on 21-d cycles

→ *Until PD, unacceptable toxicity, consent withdrawal, or investigator decision*

- Primary endpoint: ORR; secondary endpoints: PFS, safety
- Exploratory endpoints: molecular determinants of response, resistance to study therapies

Best Response, n (%)	Patients (N = 27)
ORR	8 (30)
▪ CR	1 (4)
▪ PR	7 (26)
SD ≥ 16 wks*	8 (30)
SD < 16 wks	4 (15)

DCR 59%

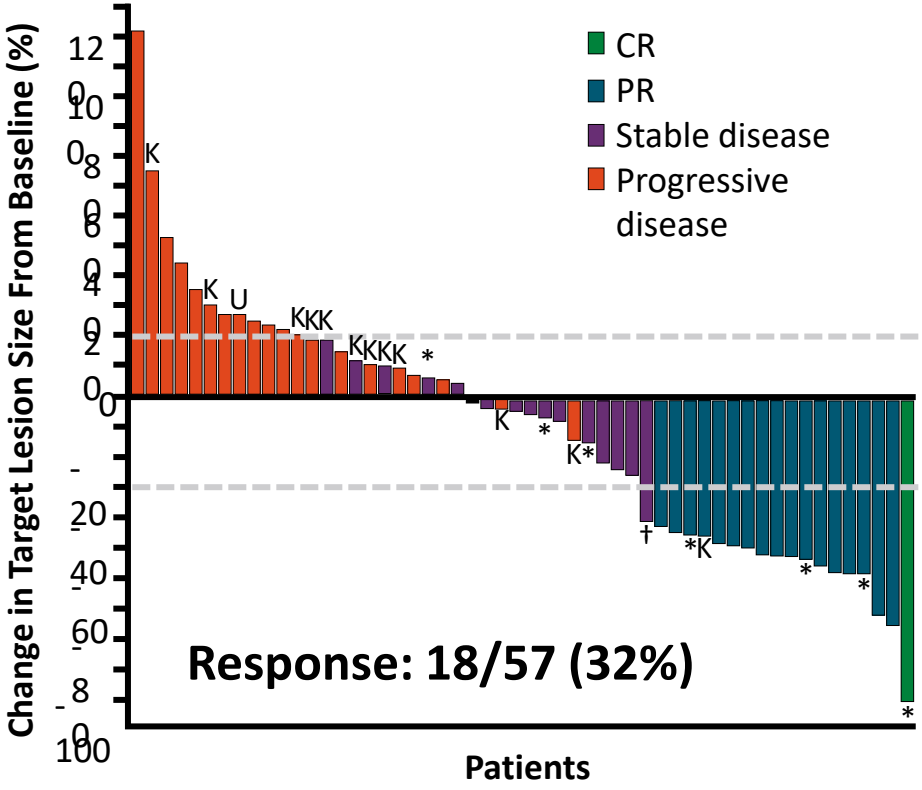
*Regimens containing fluoropyrimidines, oxaliplatin, irinotecan, cetuximab, or panitumumab ± anti-angiogenic agents.

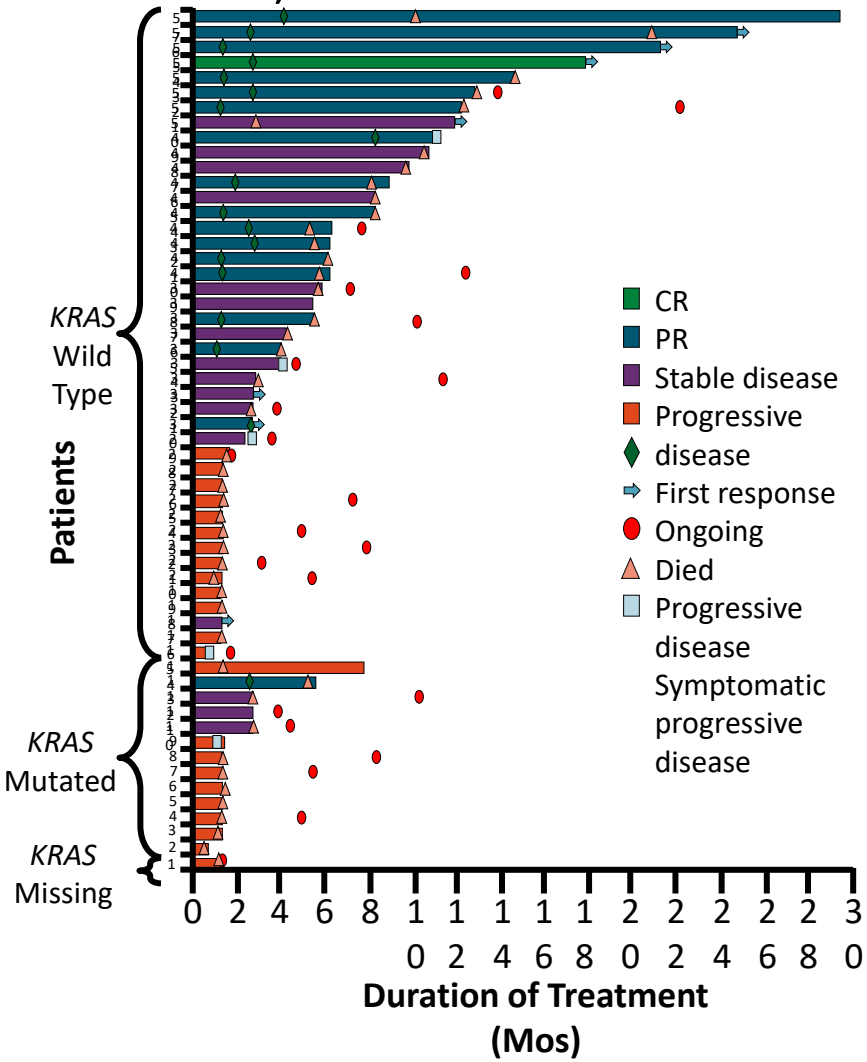
- Primary endpoint met in advance with 8/27 objective responses (per protocol, 6/27 needed to declare the study positive)

Sartore-Bianchi. Lancet Oncol. 2016;17:738.

MyPathway: Trastuzumab + Pertuzumab for HER2+ Metastatic CRC

- Open-label phase IIa basket study (n = 57 with CRC)



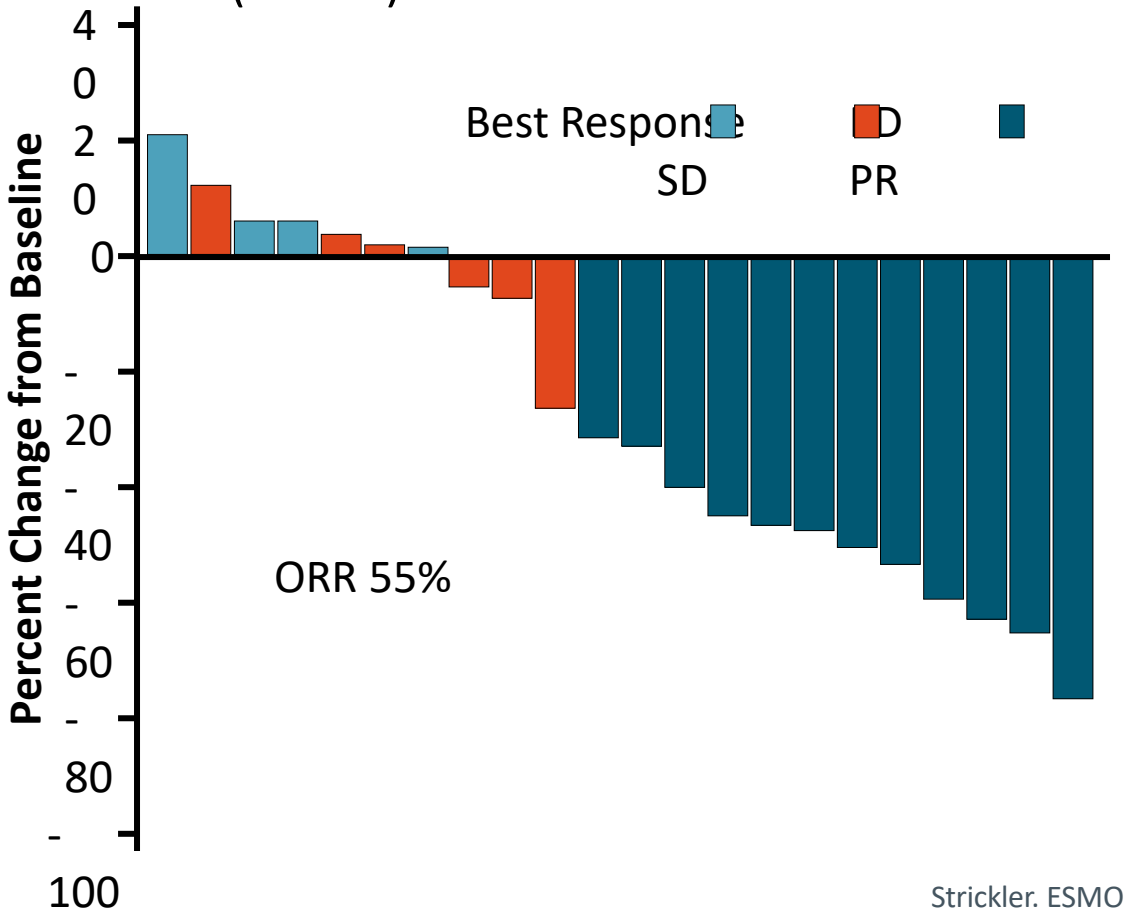


K, KRAS mutated. U, KRAS status unknown. *Treatment ongoing.

Merik-Bernstam. Lancet Oncol. 2019;20:518.

MOUNTAINEER: Tucatinib + Trastuzumab in *HER2*-Amplified mCRC

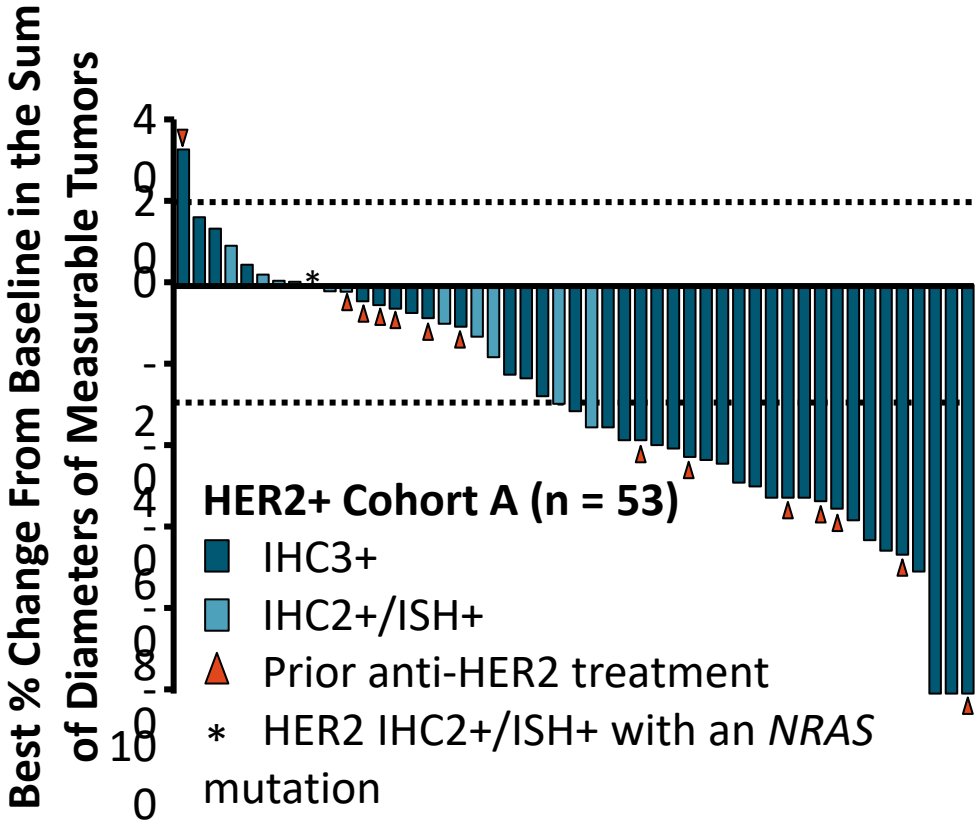
- Open-label, single-arm phase II study of tucatinib + trastuzumab for patients with previously treated, *RAS*-WT, *HER2*-amplified, metastatic or unresectable CRC (N = 26)



Strickler. ESMO 2019. Abstr 4795.

DESTINY-CRC01: Trastuzumab Deruxtecan for Patients With HER2-Expressing Metastatic Colorectal Cancer

- Open-label, multicohort phase II trial of T-DXd for patients with unresectable/metastatic RAS/BRAF wild type CRC; received ≥ 2 previous regimens; cohort A: HER2 positive (IHC 3+ or IHC 2+/ISH+); cohort B: HER2 IHC2+/ISH-; cohort C: HER2 IHC 1+ (N = 78)



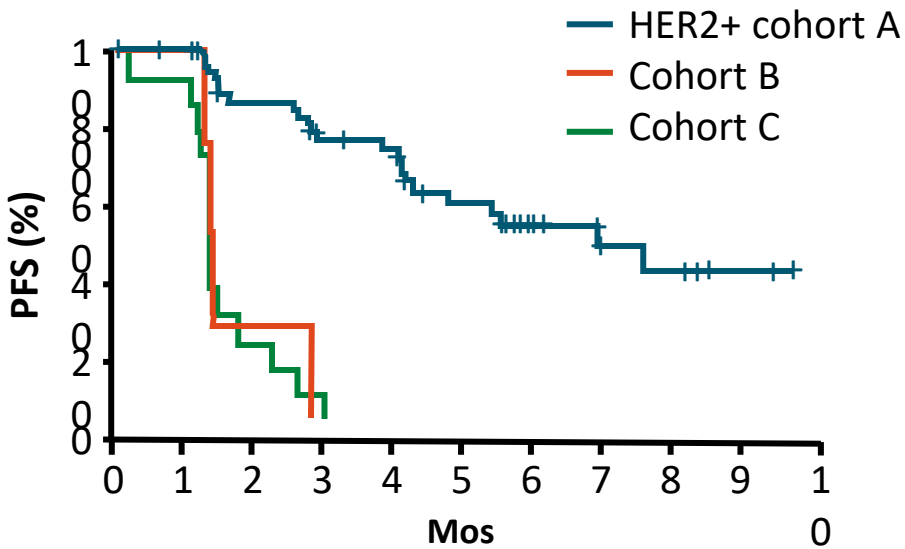
Response, n (%)	HER2+ Cohort A (n = 53)
Confirmed ORR by ICR (primary endpoint)	24 (45.3)
▪ CR	1 (1.9)
▪ PR	23 (43.4)
▪ SD	20 (37.7)
▪ PD	5 (9.4)
▪ NE	4 (7.5)*
DCR, %	83.0
Median DoR, mos	NR

Siena. ASCO 2020. Abstr 4000. NCT03384940.

DESTINY-CRC01: PFS and OS by Cohort

PFS

Median PFS in Cohort A: 6.9 mos

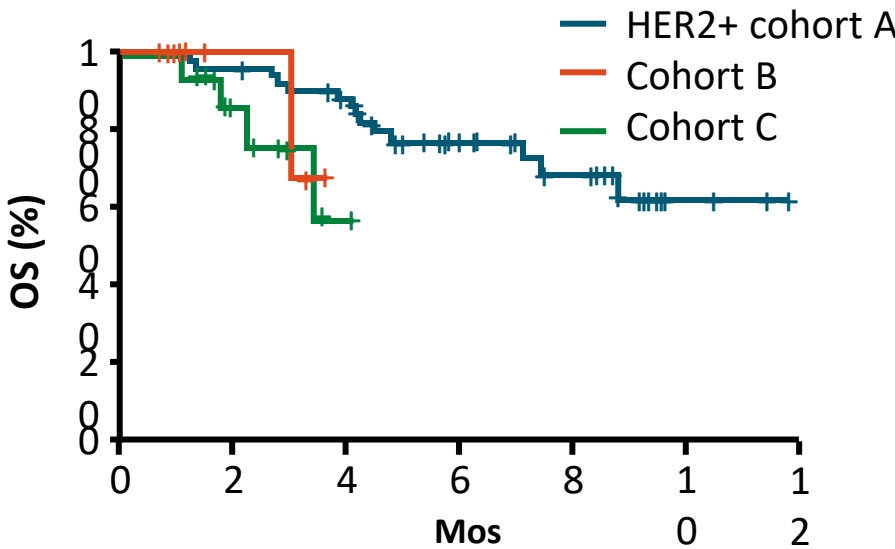


Patients at Risk, n

Cohort A	53	50	42	35	33	21	11	7	6	2	0
Cohort B	7	6	1	0	0	0	0	0	0	0	0
Cohort C	18	13	3	1	0	0	0	0	0	0	0

OS

Median OS in any Cohort: NR

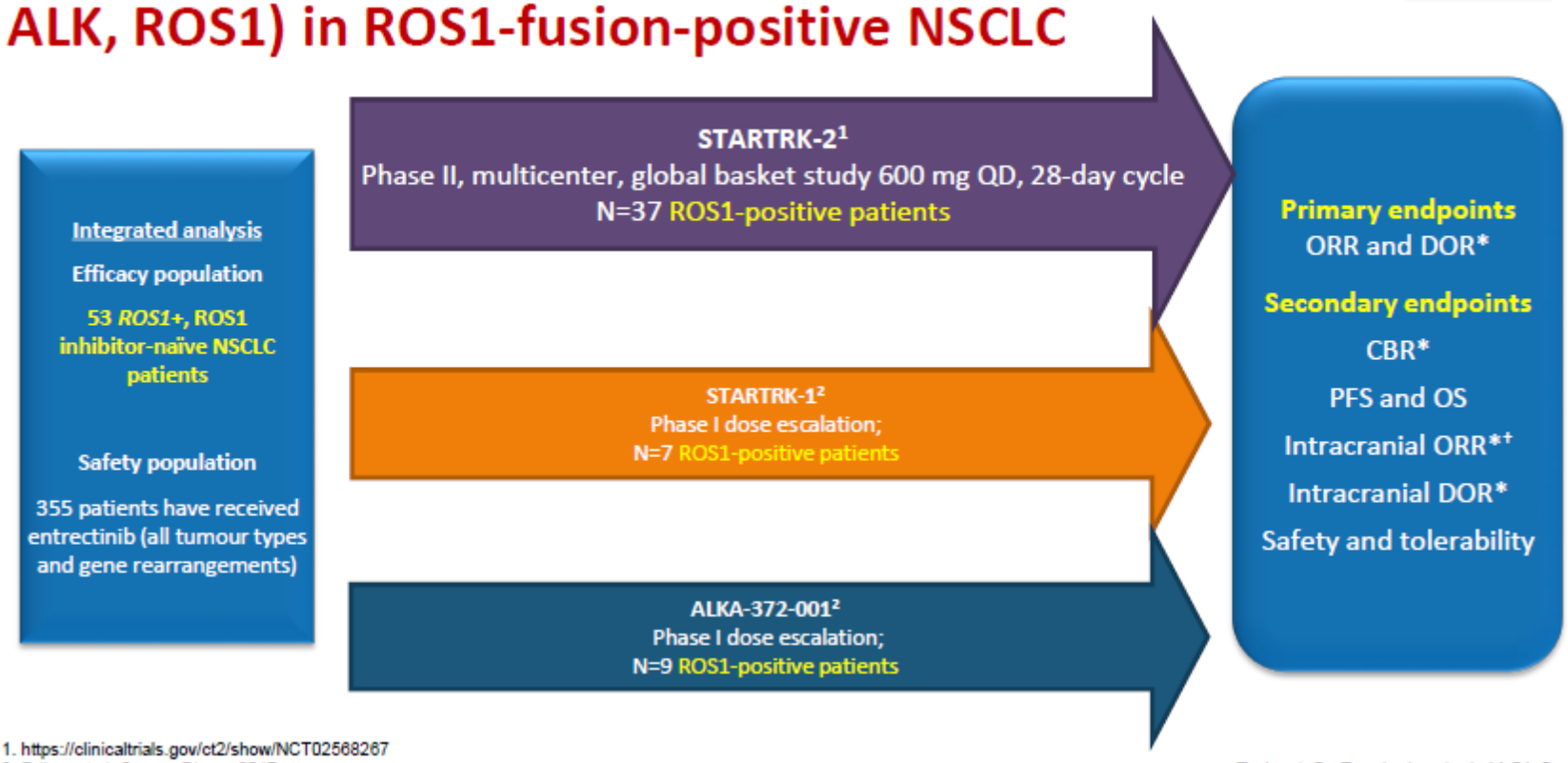


Patients at Risk, n

Cohort A	53	49	42	23	14	4	0
Cohort B	7	3	0	0	0	0	0
Cohort C	18	9	1	0	0	0	0

Siena. ASCO 2020. Abstr 4000.

Pooled analysis of three studies: entrectinib (NTRK, ALK, ROS1) in ROS1-fusion-positive NSCLC



1. https://clinicaltrials.gov/ct2/show/NCT02568267
2. Drilon, et al. Cancer Discov 2017

Robert C. Doebele et al, IASLC

First-generation TRK inhibitors are active in TRK fusion-positive cancers

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

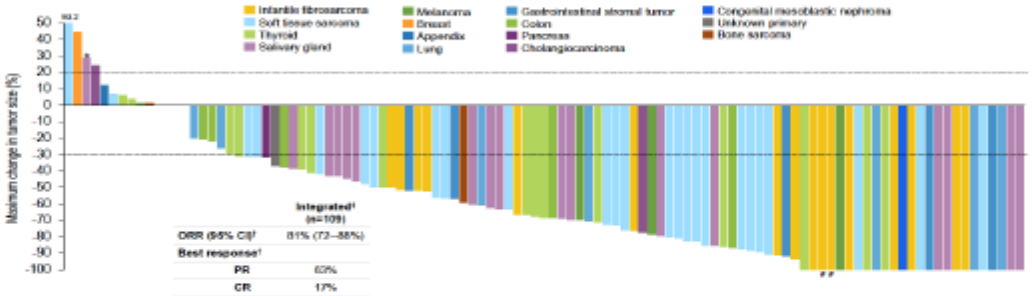
Larotrectinib

ORR 81%

(95% CI 72-88%, n=109)

Median DoR not reached

Median PFS not reached



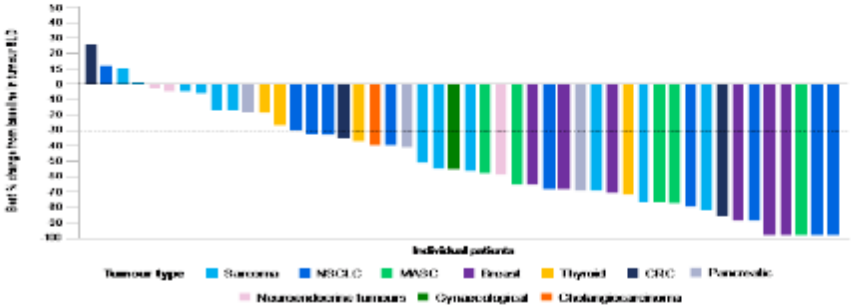
Entrectinib

ORR 57%

(95% CI 43-71%, n=54)

Median DoR 10 mos

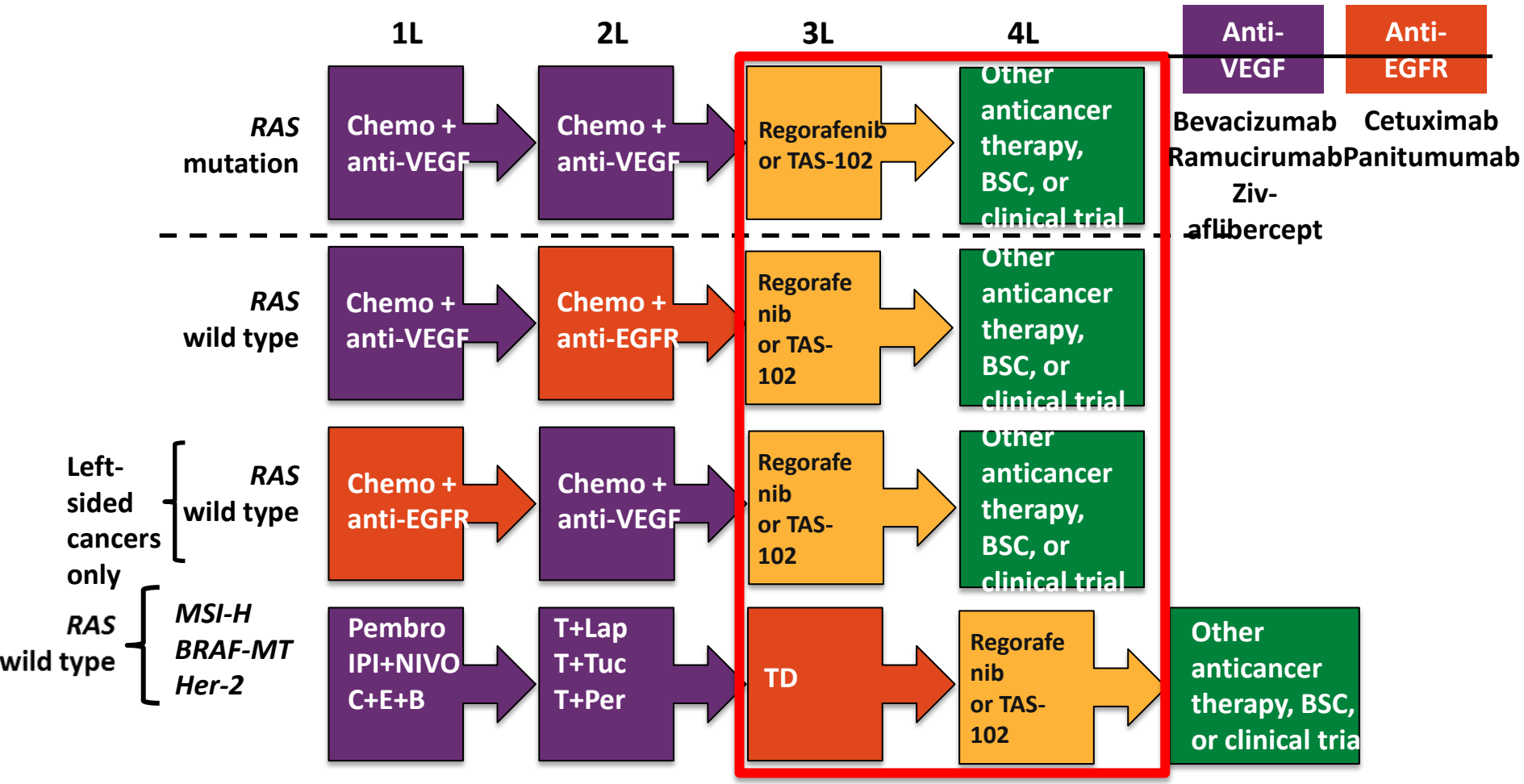
Median PFS 11 mos



Lassen et al, ESMO 2018; Demetri et al, ESMO 2018

A.Drilon

mKRK Üçüncü Sıra Tedavi Önerisi Treatment



C: Cetixumab, E: Encorafenib, T: Trastuzumab, Lap: Lapatinib, Per: Pertuzumab, Tuc: Tucatinib,TD: Trastuzumab Deruxtecan

SAbrInIz İçiN TeşEkkürLer