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Biomarkers: when to test, what to test and what are the consequences?

by Dr. Thomas Winder, Dr. Andrea Sartore-Bianchi and Dr. Yu Sunakawa

Biomarkers: when to test, what to test and what are the consequences?

BY

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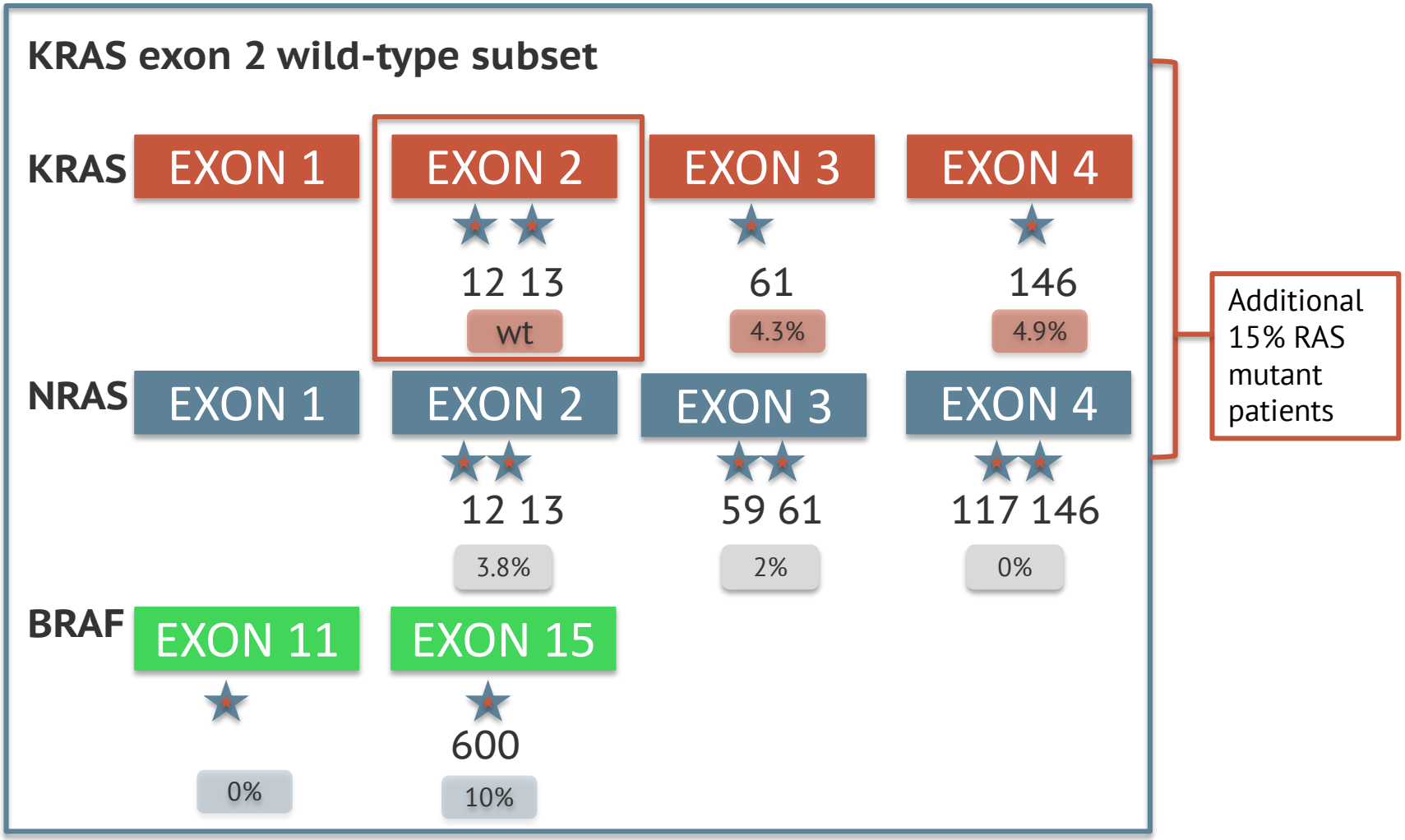
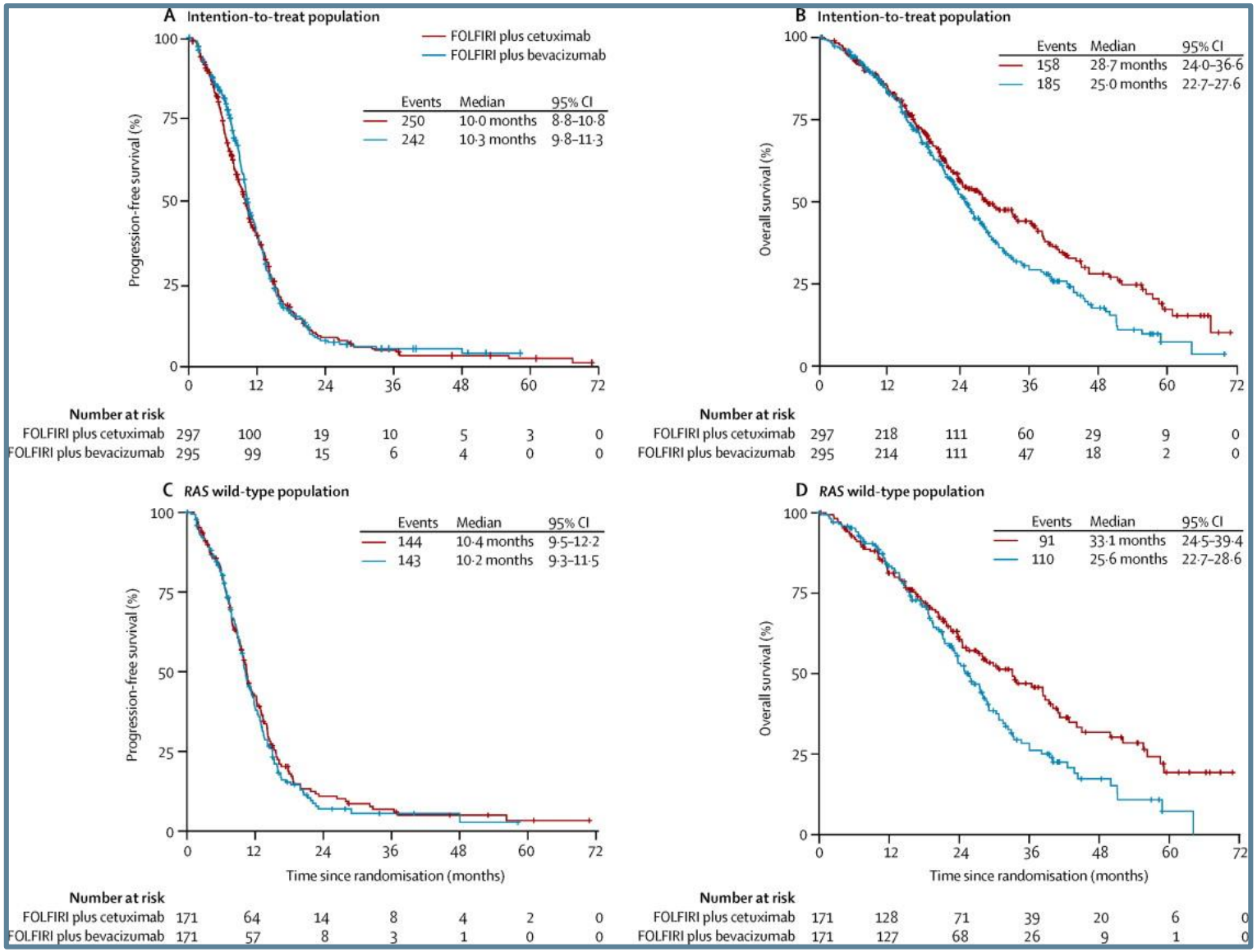
RAS TESTING

FIRE-3-TRIAL: RAS ANALYSIS



FIRE-3-TRIAL: RAS ANALYSIS

OVERALL SURVIVAL ANALYSIS

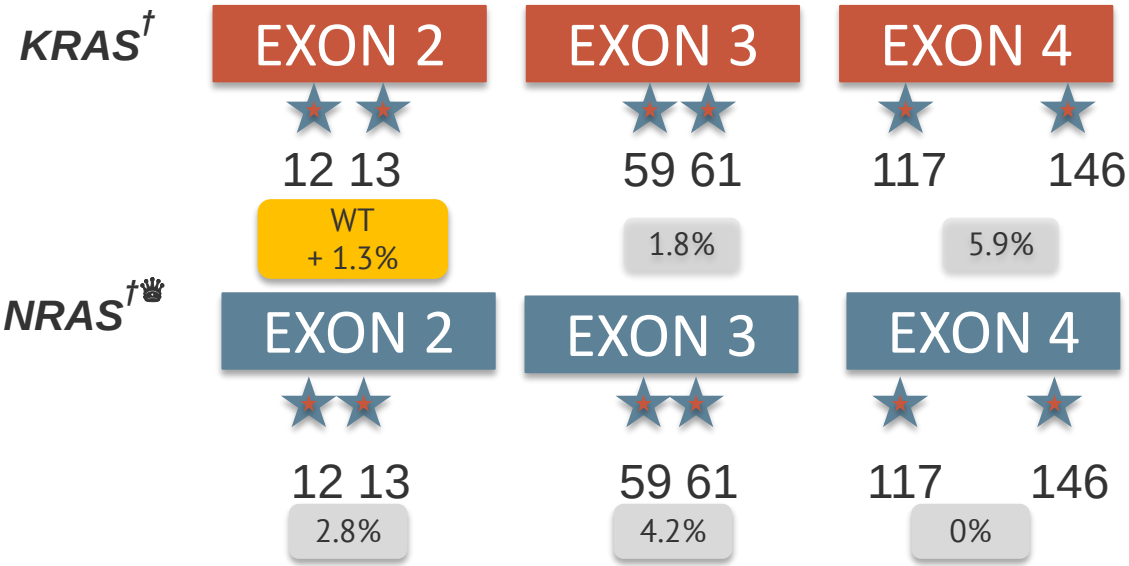


Heinemann V et al. Lancet Oncol. 2014 Sep;15(10):1065-75.

CALGB/SWOG 80405-TRIAL RAS ANALYSIS

RAS mutations: CALGB/SWOG 80405

670/1137 patients (59%) with KRAS codon 12/13 WT tumours evaluable
621/1137 analysed (55%) analysed
95/621 (15.3%) patients new ras mutation identified

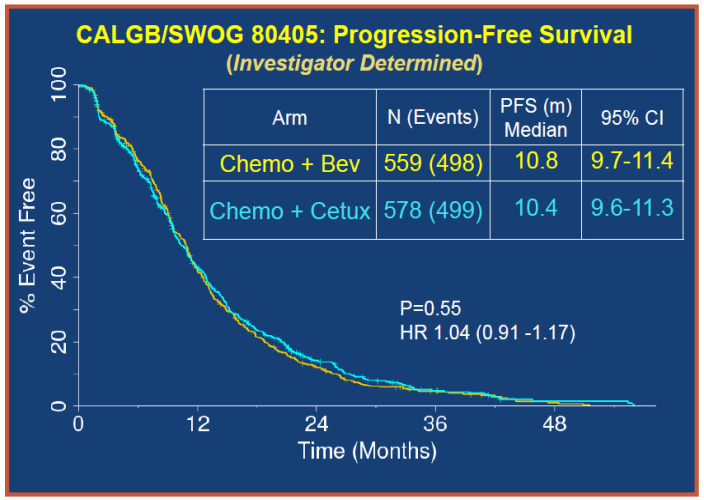


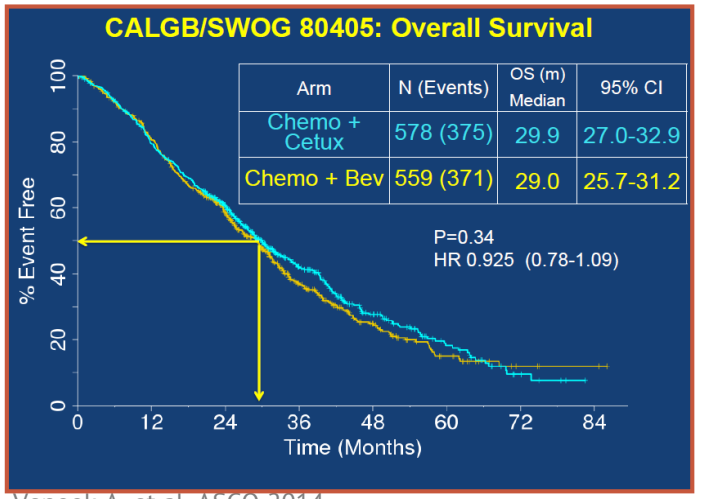
†Percentage relate to fraction of *RAS* evaluable patients with mutations in particular exons;

♛One patients had a mutation at both NRAS EXON1 codon12 and NRAS EXON3 codon61

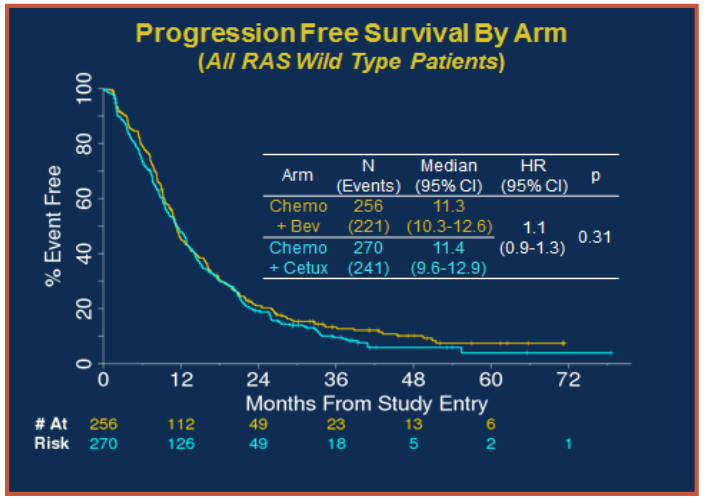
Lenz HJ, et al. ESMO 2014

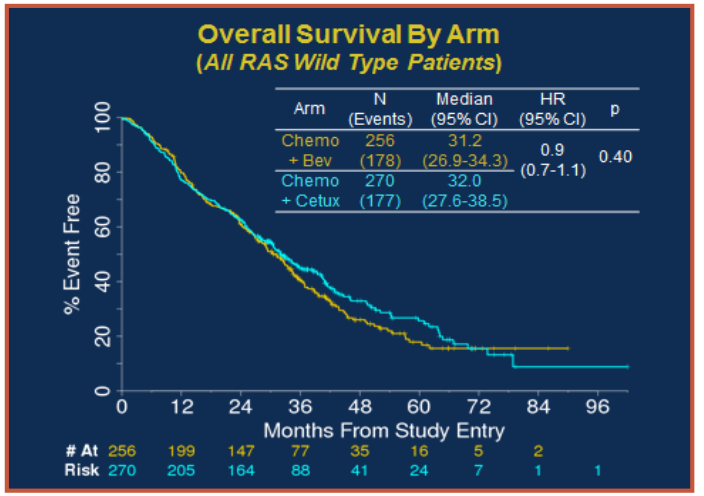
CALGB/SWOG80405-TRIAL RAS ANALYSIS
OVERALL SURVIVAL ANALYSIS





Venook A, et al. ASCO 2014





Lenz HJ, et al. ESMO 2014

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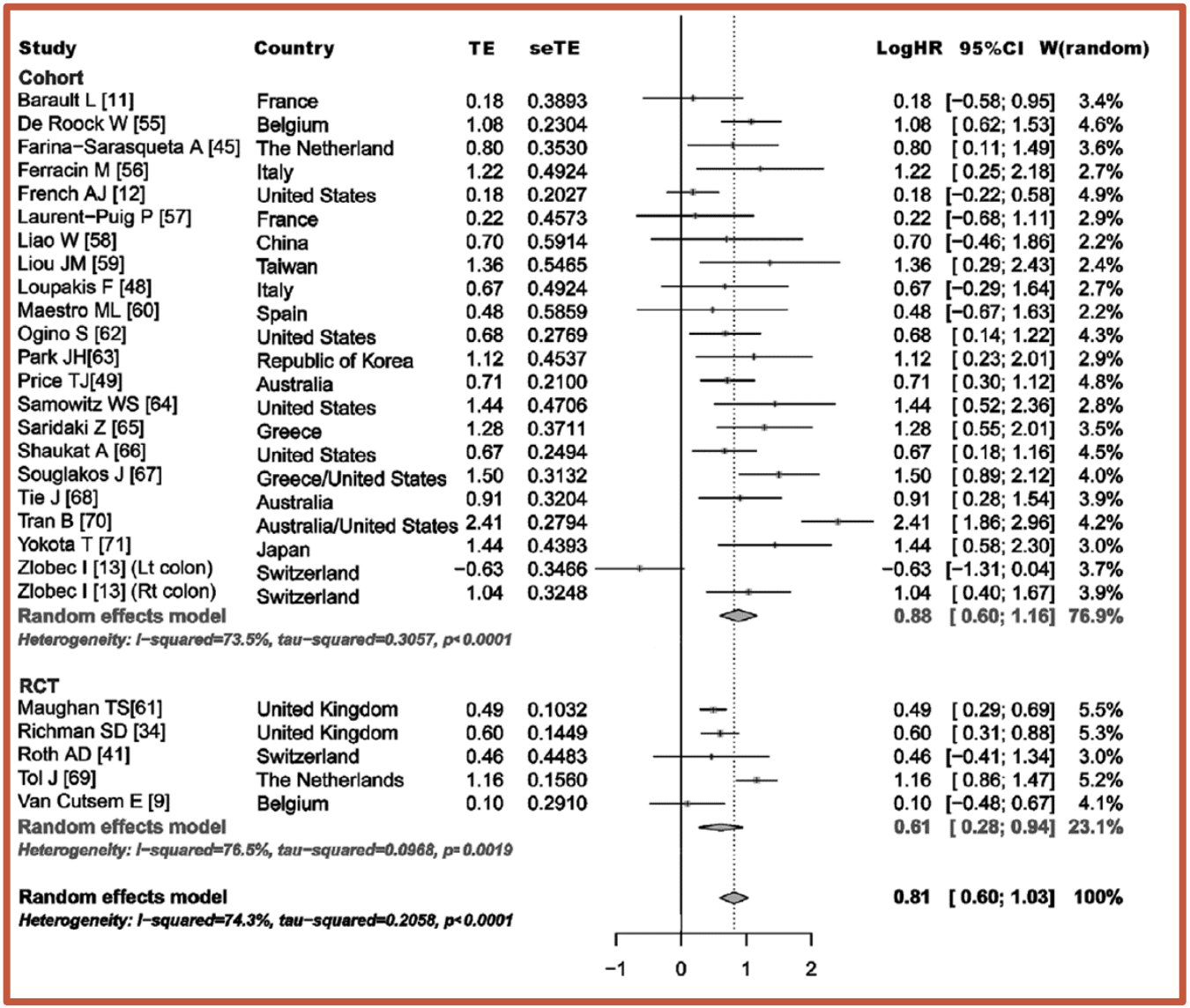
BRAF V600E TESTING

THE PROGNOSTIC VALUE OF *BRAF* MUTATION IN CRC AND MELANOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS



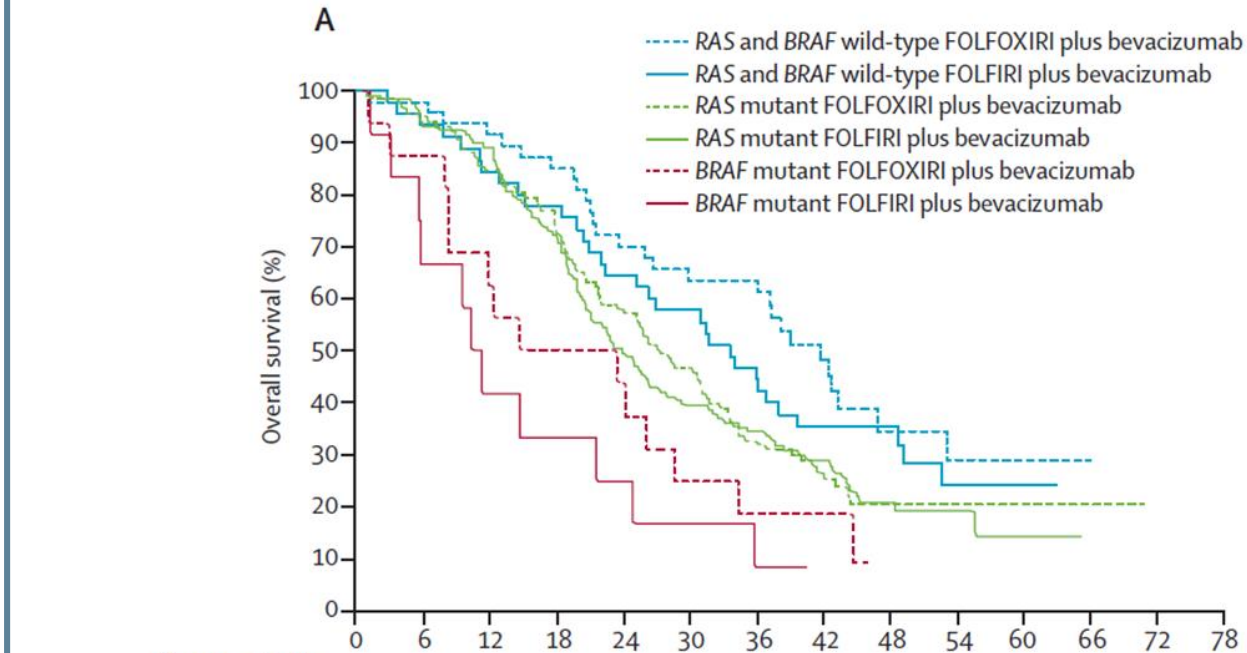
Safaee Ardekani G, PLoS One 2012

TRIBE STUDY

OS DEPENDENT ON MOLECULAR SUBGROUPS AND TREATMENT

FOLFOXIRI - Bevacizumab
BRAF mt median OS 19 months
(n=16)

FOLFIRI - Bevaciczumab
BRAF mt median OS 10.7 months
(n=12)



Number at risk														
RAS and *BRAF* wild-type FOLFOXIRI plus bevacizumab	48	46	43	40	32	29	26	17	8	5	3	0	0	0
RAS and *BRAF* wild-type FOLFIRI plus bevacizumab	45	42	38	35	29	26	20	14	10	5	1	0	0	0
RAS mutant FOLFOXIRI plus bevacizumab	117	111	99	85	67	54	36	20	13	8	3	2	0	0
RAS mutant FOLFIRI plus bevacizumab	119	111	106	85	58	47	40	27	13	7	1	0	0	0
BRAF mutant FOLFOXIRI plus bevacizumab	16	14	10	8	7	4	3	3	0	0	0	0	0	0
BRAF mutant FOLFIRI plus bevacizumab	12	8	5	4	3	2	1	0	0	0	0	0	0	0

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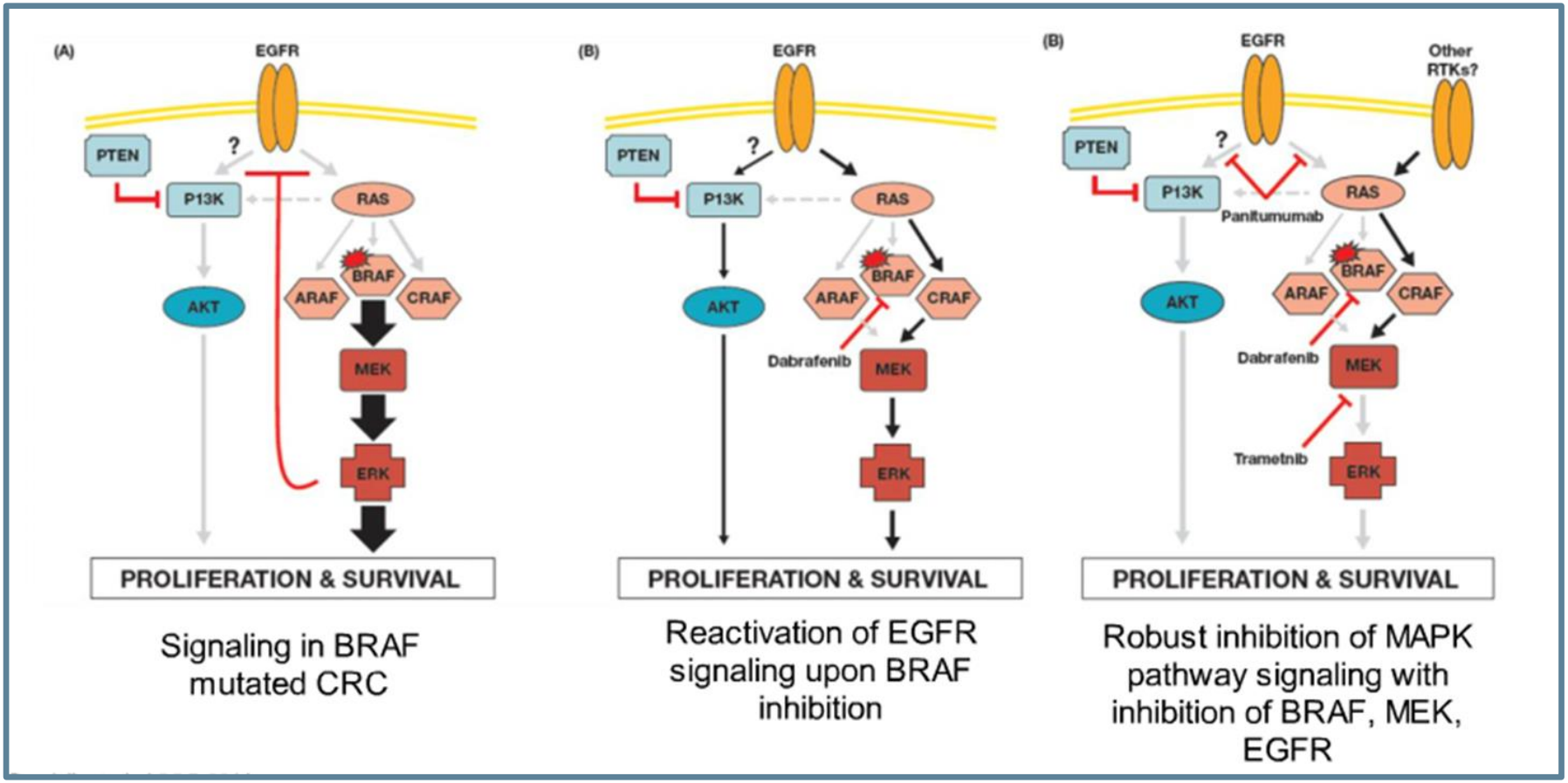
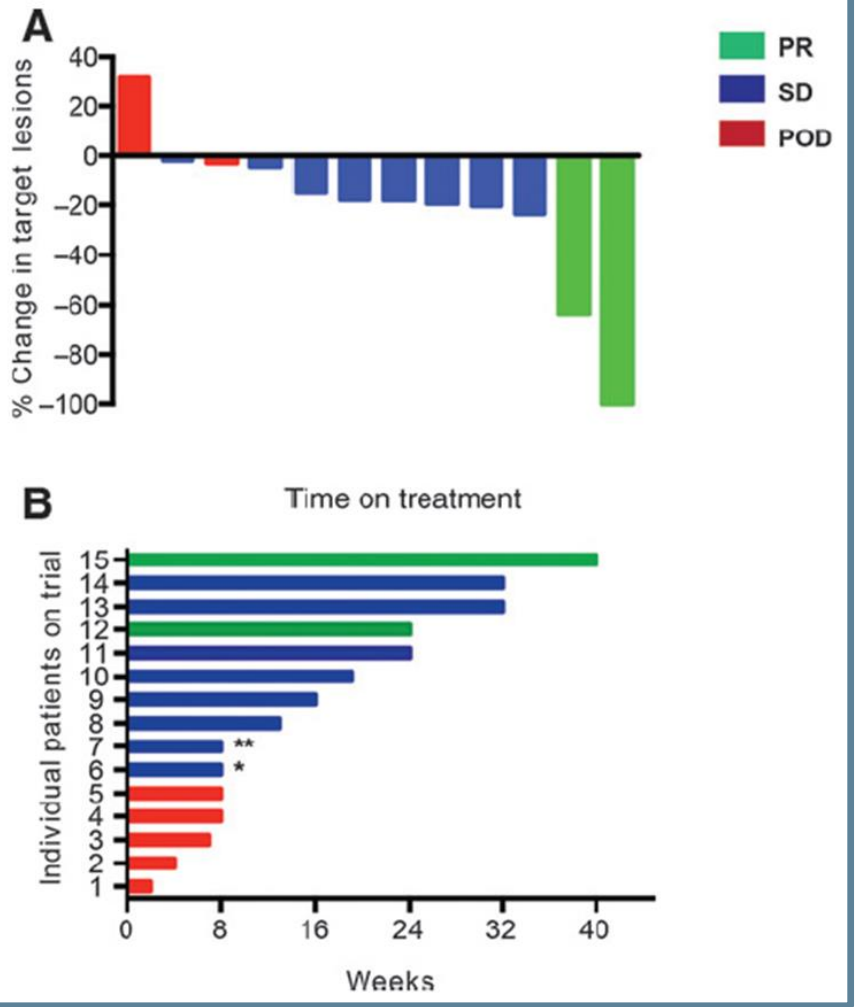
Cremolini C et al. Lancet Oncol. 2015 Oct;16(13):1306-15.

MOLECULAR MECHANISMS UNDERLYING RESISTANCE TO BRAF-DIRECTED SINGLE INHIBITION IN mCRC



Prahallad Nature 2012; Corcoran, Cancer Discovery 2012; Coffee EM, CCR 2013; Mao M CCR, 2013

PILOT TRIAL OF COMBINED BRAF AND EGFR INHIBITION IN *BRAF*-MUTANT mCRC PATIENTS

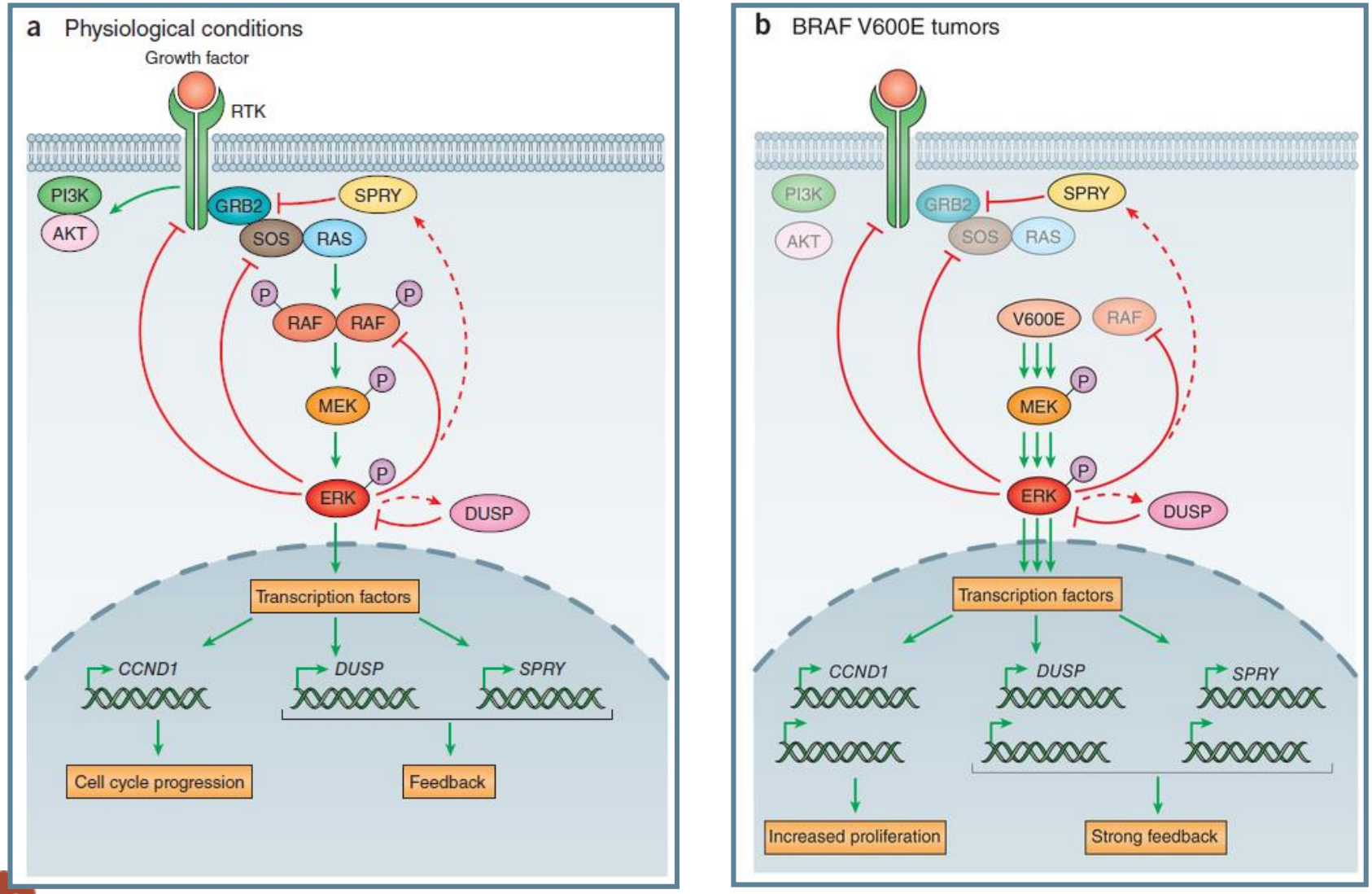


Adverse event	Grade 1	Grade 2	Grade 3–4
Rash acneiform	6 (40%)	2 (13%)	0
Fatigue	4 (27%)	0	1 (7%)
Alkaline phosphatase elevation	0	2 (13%)	3 (20%)
Arthralgias	2 (13%)	2 (13%)	0
Dry skin/xerosis	4 (27%)	0	0
AST/ALT elevation	0	0	3 (20%)[a]
Photosensitivity	2 (13%)	1 (7%)	0
Nausea	1 (7%)	1 (7%)	0
Erythema multiforme	2 (13%)	0	0
Pruritis	2 (13%)	0	0
Rash maculopapular	2 (13%)	0	0
Neutropenia	0	0	1 (7%)
Keratosis	0	1 (7%)	0
Palmar-plantar erythrodysesthesia syndrome	0	1 (7%)	0
Weight loss	0	1 (7%)	0
Alopecia	1 (7%)	0	0
Diarrhea	1 (7%)	0	0
Hypomagnesemia	1 (7%)	0	0
Nasal vestibulitis	1 (7%)	0	0

[a]Grade 4 AST/ALT elevations were noted twice in the same patient, occurring after initial treatment and on rechallenge with vemurafenib.

Yaeger et al. Clin Cancer Res 2015

TREATMENT OPTIONS IN BRAF MUTANT mCRC PATIENTS



Lito P et al. Nature Medicine 19,1401–1409 (2013)

HER2 TESTING

DUAL INHIBITION OF THE HER2 PATHWAY IN mCRC: HERACLES TRIAL

849 patients with mCRC KRAS exon 2 WT

- 803 HER2-negative

46 HER2+ (5.4%)

- 22 not eligible because PS ≥ 2 or tumor-related comorbidities

24 enrolled

- 1 too early for safety & efficacy assessment

23 evaluable for response

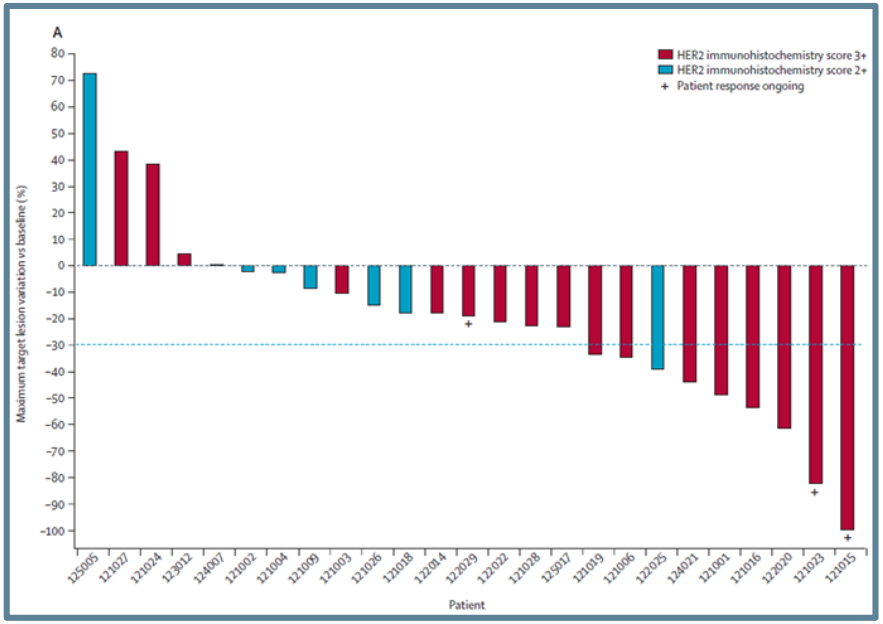
Therapy with:
- Trastuzumab 1v 4mg/kg load and then 2mg/kg/qw
- Lapatinib po 1000 mg/qd

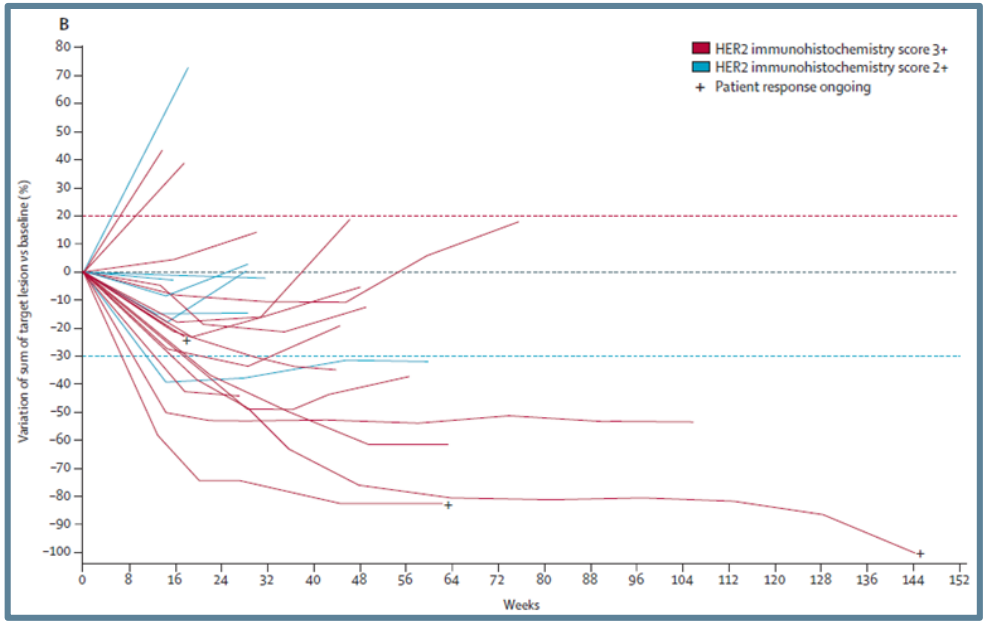
→ PD re-biopsy if possible

Failure of previous fluoropyrimidins, oxaliplatin, irinotecan, cetuximab or panitumumab; prior Bevacizumab, aflibercept and regorafenib allowed but not mandatory

Sartore-Bianchi A et al. Lancet Oncol. 2016 Apr 20. pii: S1470-2045(16)00150-9.

DUAL INHIBITION OF THE HER2 PATHWAY IN mCRC: HERACLES TRIAL





Sartore-Bianchi A et al. Lancet Oncol. 2016 Apr 20. pii: S1470-2045(16)00150-9.

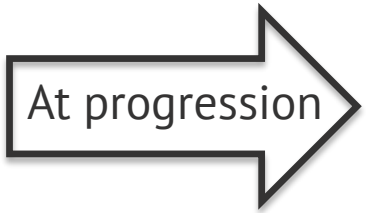
OVERCOMING RESISTANCE TO HER2-TARGETED THERAPY

HERACLES-RESCUE

HER2 AMPLIFICATION FOR COLO-RECTAL CANCER ENHANCED STRATIFICATION RECHALLENGE WITH HER2 SELECTIVE CYTOTOXIC UPTAKE OF EMTANSINE

HER2 positive mCRC patients

HERACLES TRIAL – COHORT A
lapatinib + trastuzumab
RECRUITMENT CLOSED
EudraCT 2012–002128-33



HERACLES RESCUE TRIAL
trastuzumab-emtansine (T-DM1)
3,6 mg/kg q3wks
RECRUITMENT OPEN (N 13)
EudraCT 2015-003275-30

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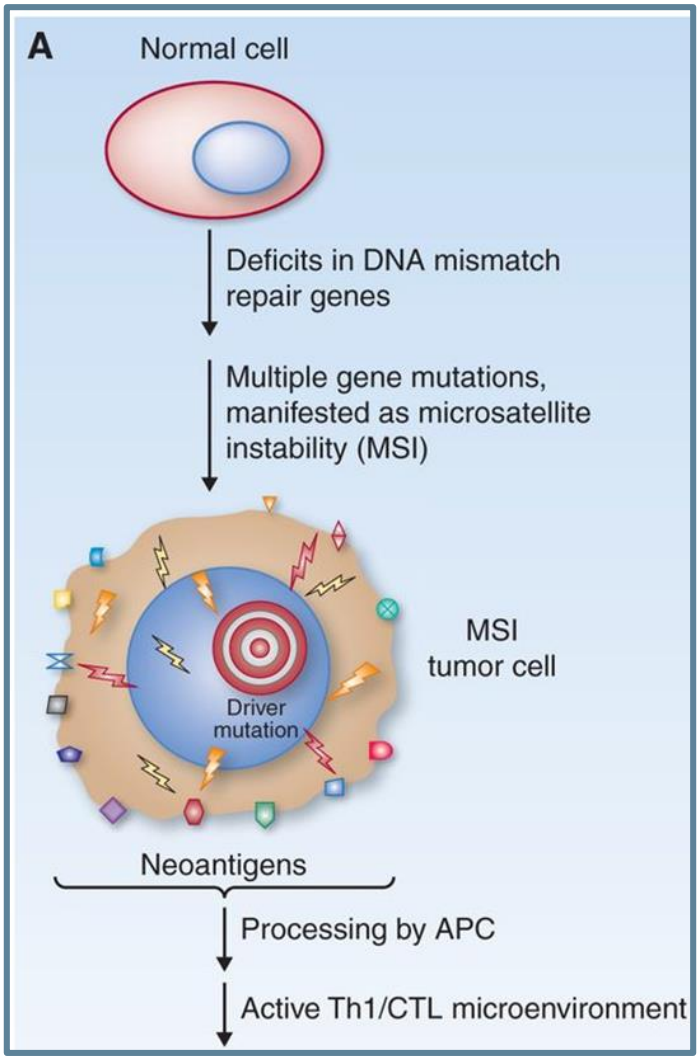
Siena S, 2016 ASCO GI Symposyum - Abstract #160132 Poster #TPS774

MSI TESTING

MSI AND IMMUNOTHERAPY IN CRC



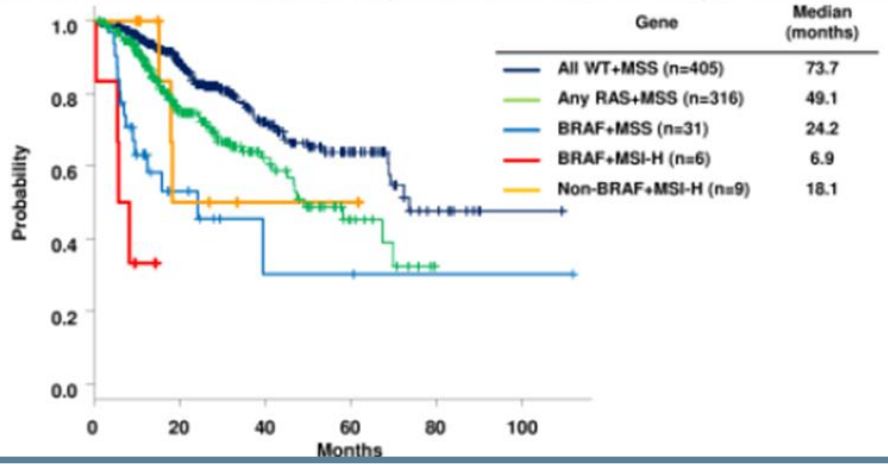
Yanping Xiao, and Gordon J. Freeman Cancer Discovery 2015;5:16-18

MSI STATUS AND CANCER-RELATED GENOME ALTERATIONS IN JAPAN

Table 2. Patients characteristics

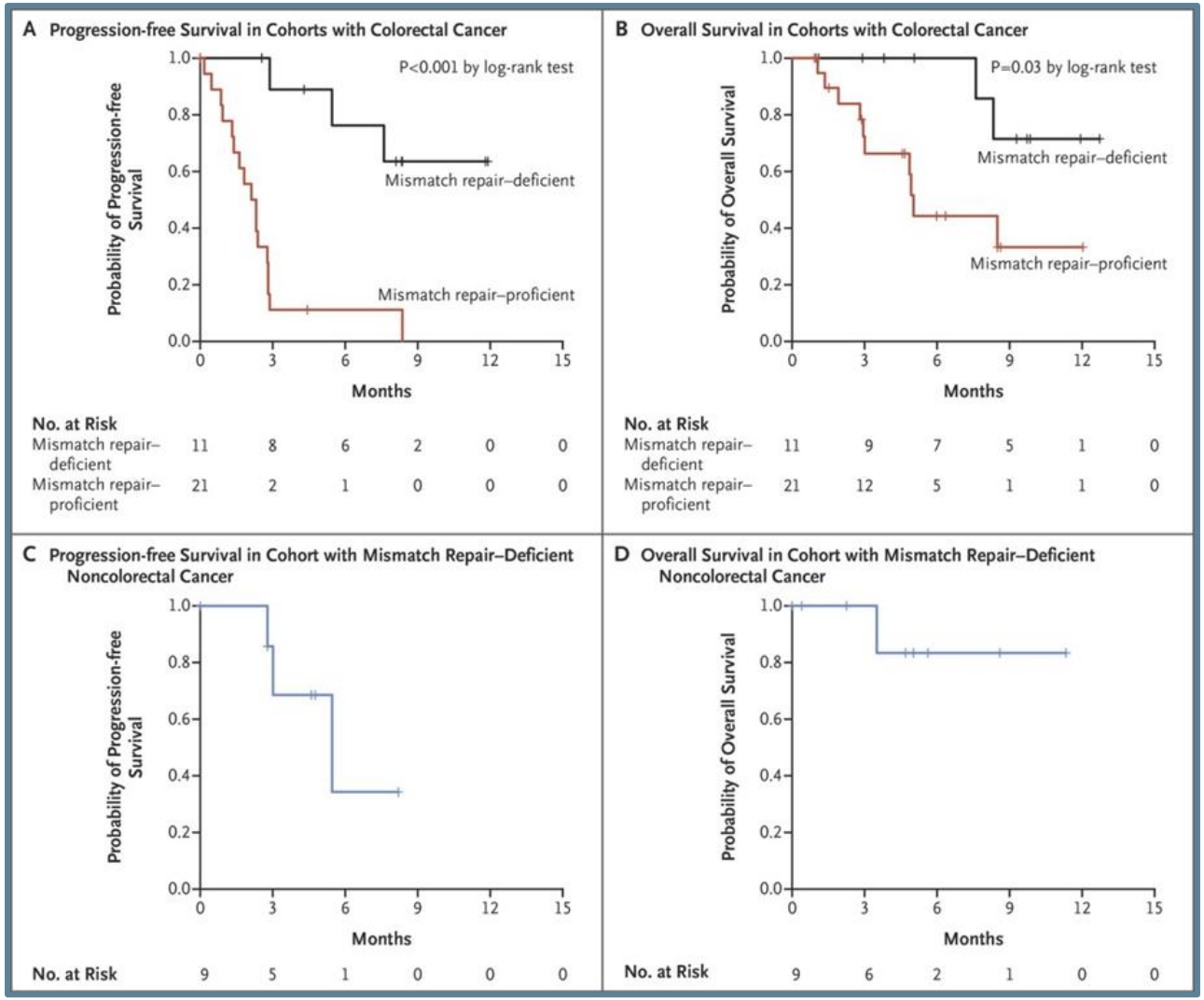
		All WT + MSS (n=423)	Any RAS + MSS (n=330)	BRAF + MSS (n=31)	BRAF + MSI-H (n=6)	Non-BRAF + MSI-H (n=9)
Gender, N(%)	Male	271 (64)	184 (56)	17 (55)	2 (33)	7 (78)
	Female	152 (36)	146 (44)	14 (45)	4 (67)	2 (22)
Age	Median (range)	65 (17-86)	66 (25-88)	64 (32-81)	72 (50-79)	47 (29-72)
Histological type	Tub1, tub2	385 (91)	300 (91)	21 (68)	4 (67)	7 (78)
	Por1, por2	24 (6)	15 (5)	8 (26)	1 (17)	1 (11)
	Pap, muc, sig	12 (3)	9 (3)	2 (6)	1 (17)	1 (11)
	Other	2 (0)	6 (2)	0 (0)	0 (0)	0 (0)
Origin of tumor samples	Right colon	60 (14)	79 (24)	16 (52)	4 (67)	4 (44)
	Left colon	133 (31)	73 (22)	6 (19)	1 (17)	3 (33)
	Rectum	155 (37)	127 (38)	4 (13)	0 (0)	0 (0)
	Other (including metastasis)	75 (18)	51 (15)	5 (16)	1 (17)	2 (22)
PIK3CA	Mutation	25 (6)	41 (12)	1 (3)	0 (0)	2 (22)
	Wild	398 (94)	289 (88)	30 (97)	6 (100)	7 (78)

Figure 3. Overall survival from 1st-line (N=767, patients who received systemic chemotherapy)



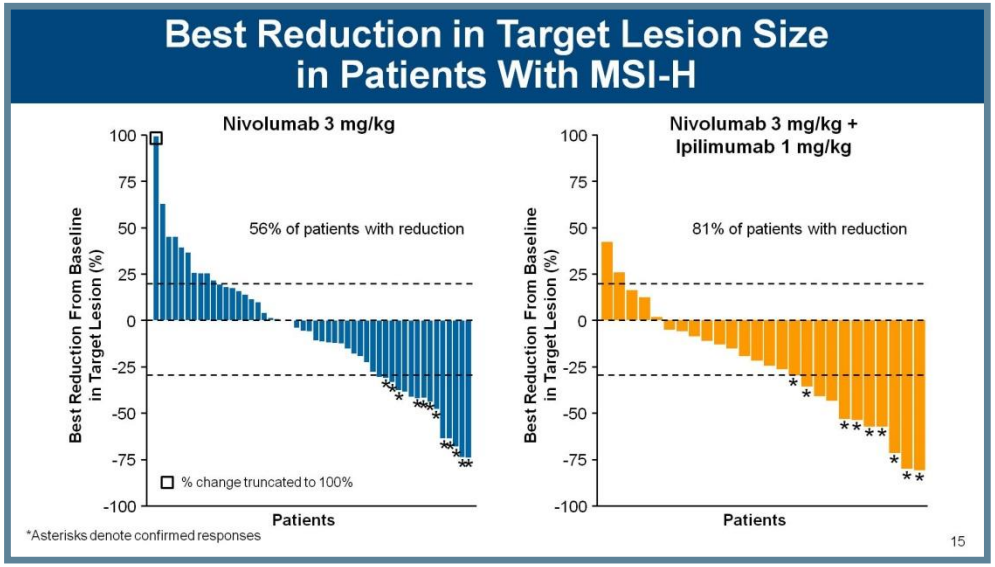
Kajiwara T, et al: ASCO 2016 #3573

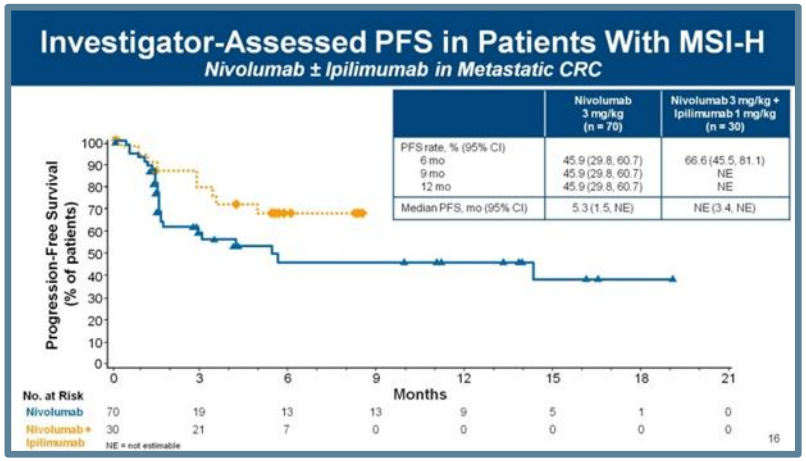
CLINICAL BENEFIT OF PEMBROLIZUMAB TREATMENT ACCORDING TO MISMATCH-REPAIR STATUS

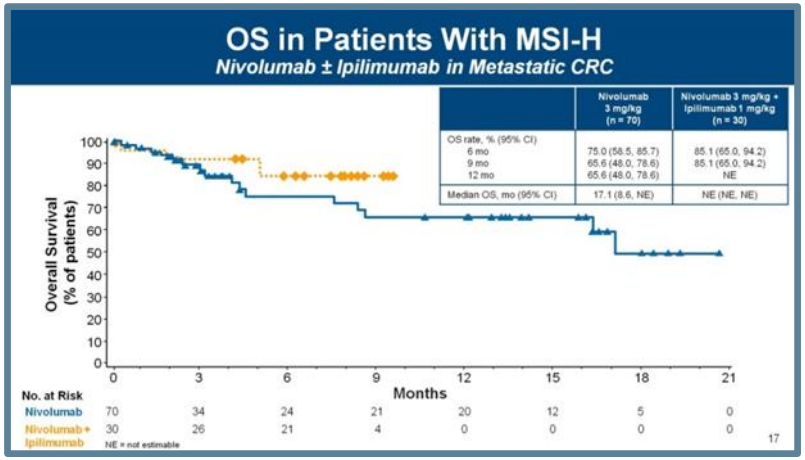


Le DT et al: ASCO 2015 LBA #100. Le DT et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1500596

EFFICACY DATA OF NIVOLUMAB ± IPILIMUMAB ACCORDING TO MISMATCH-REPAIR STATUS







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Overman N, et al: ASCO 2016 #3501


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