Proto-oncogene HRAS transcript level predicts overall survival in locally advanced colorectal cancer

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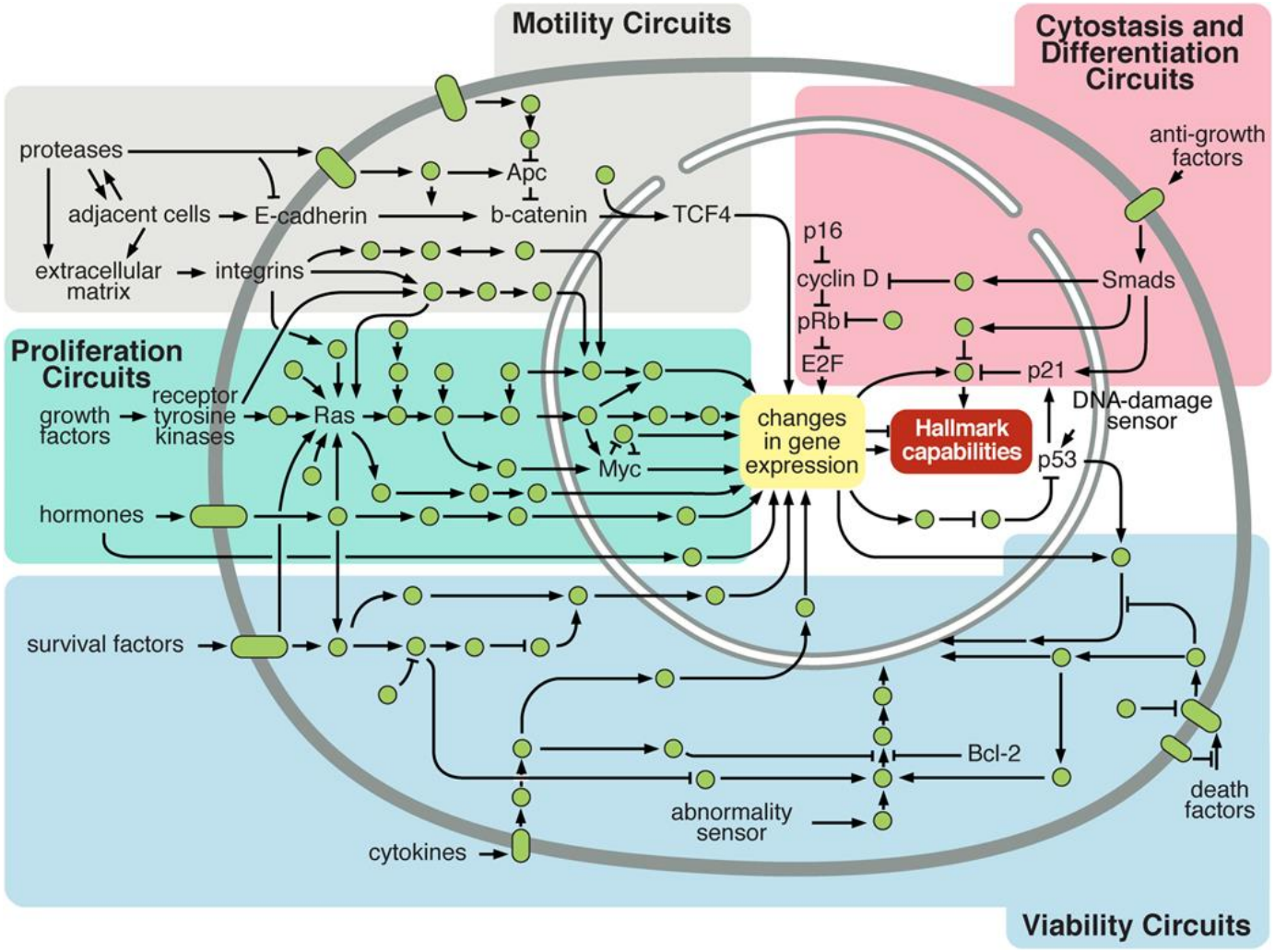
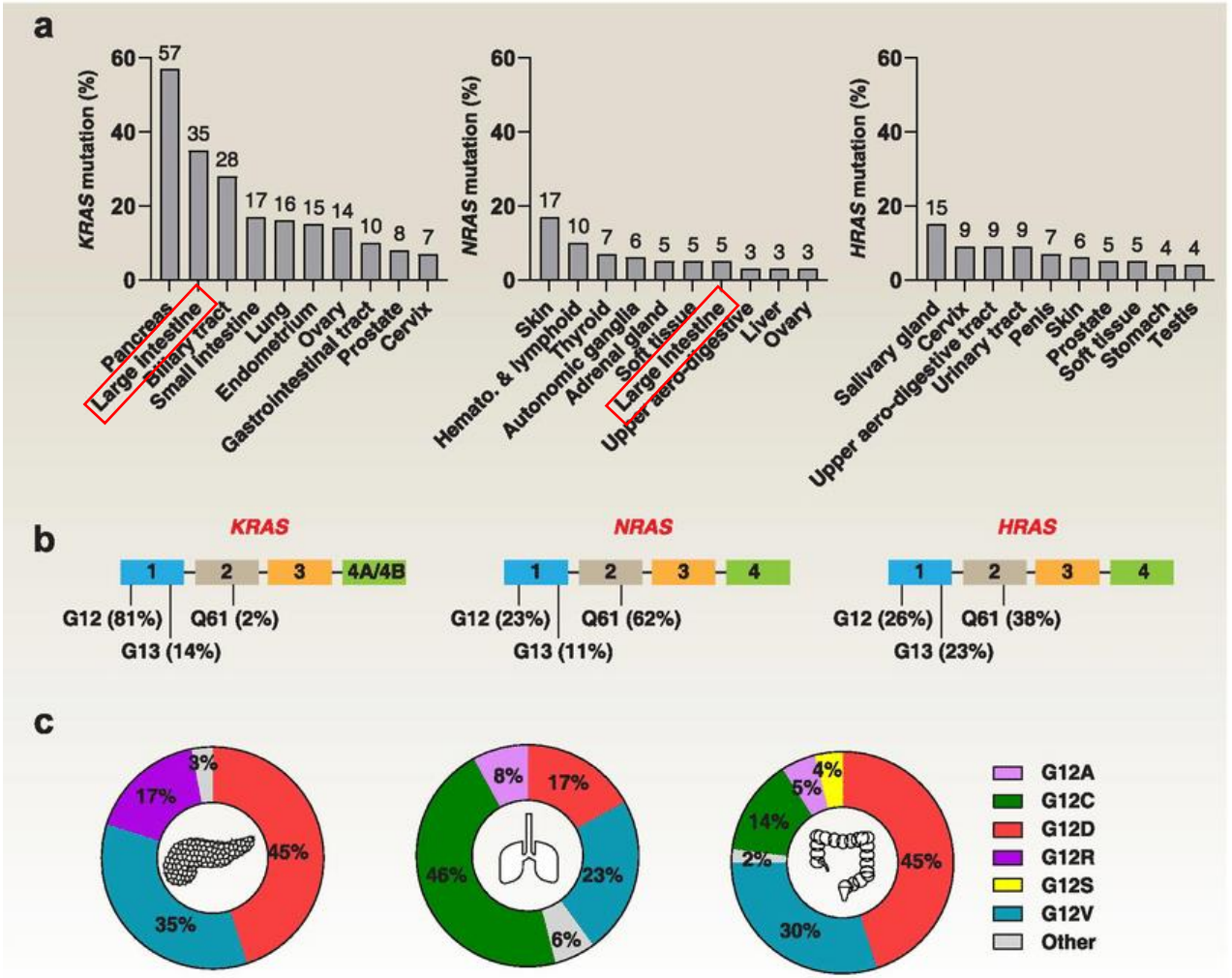
“I have no conflict of interest to declare”

RAS pathway lies at the core of oncogenic circuitry



Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646-74

RAS pathway activity is prognostic in colorectal cancer, although clinical significance of HRAS remains obscure in colorectal cancer



Tang D, Kroemer G, Kang R. Oncogenic KRAS blockade therapy: renewed enthusiasm and persistent challenges. Mol Cancer. 2021 Oct 4;20(1):128

RNA-Seq database of 734 locally advanced colorectal cancer cases were retrieved, batch-corrected, and retrospectively reviewed

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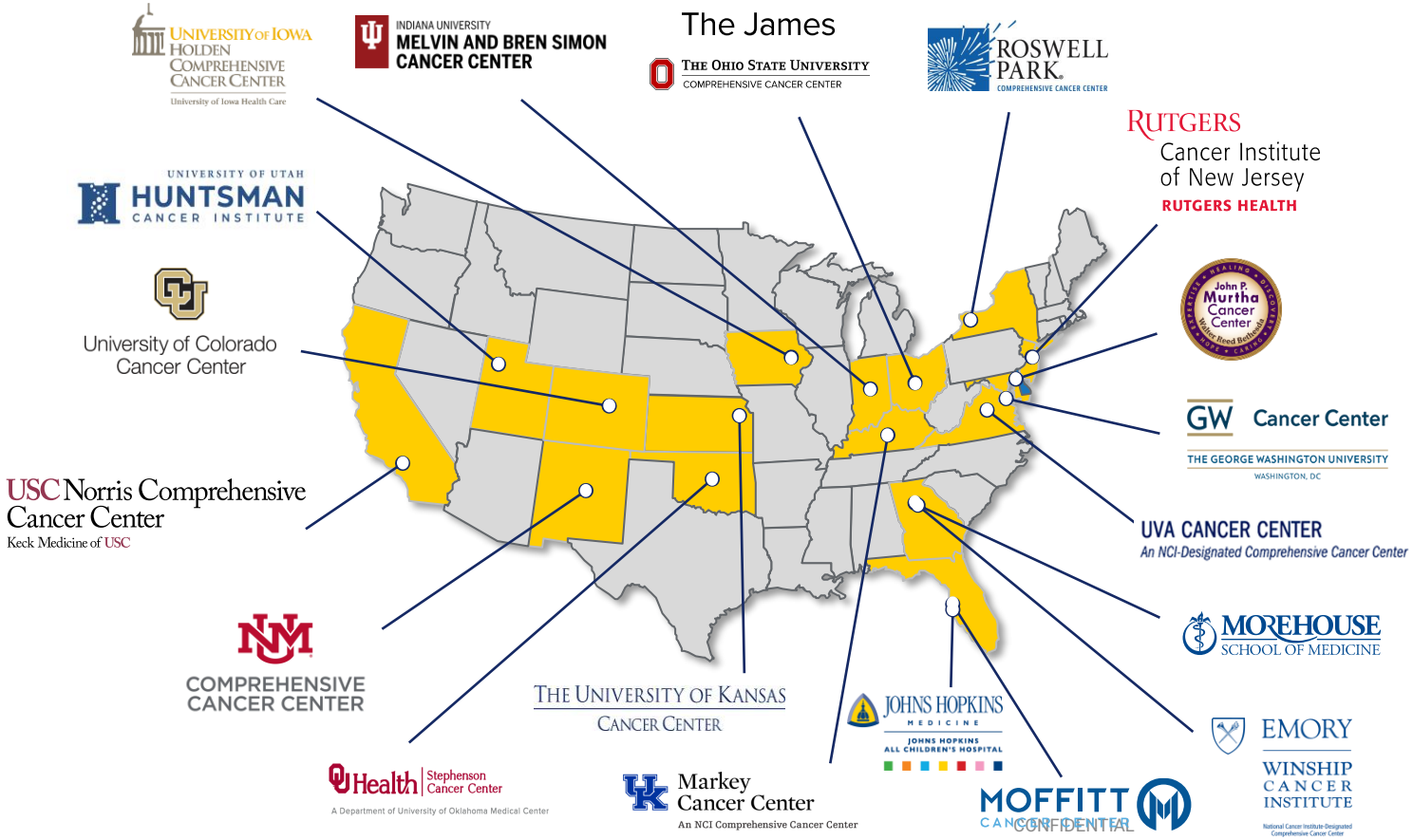
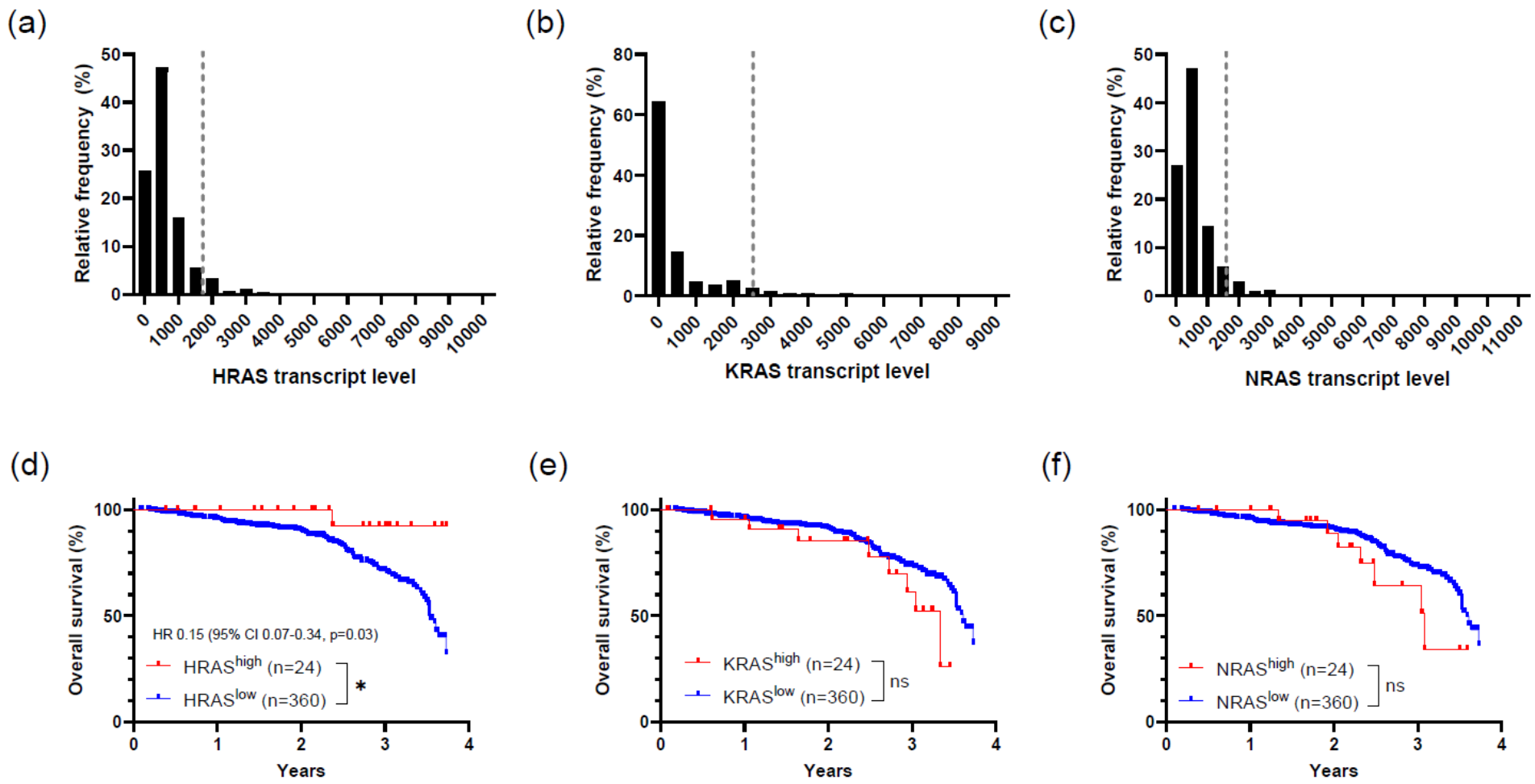


CONFIDENTIAL

High mRNA expression of HRAS, but not KRAS or NRAS, is associated with superior overall survival in locally advanced colorectal cancer

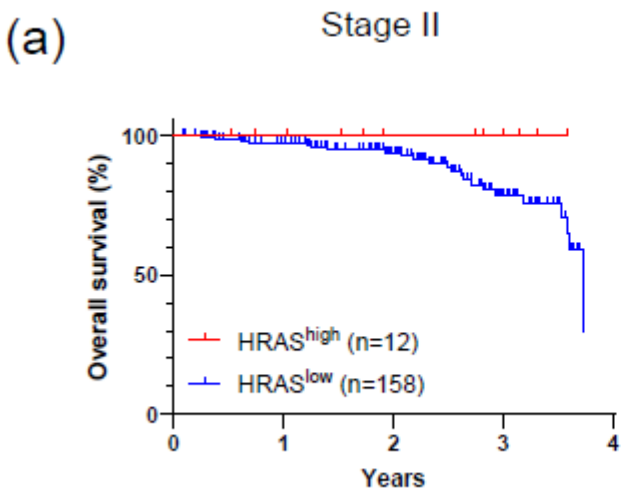


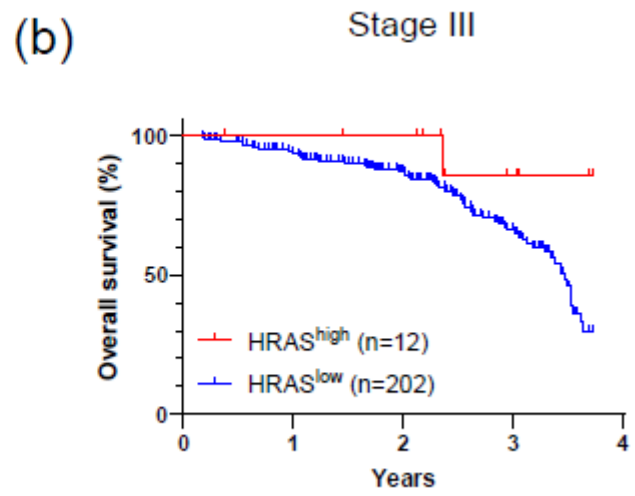
Cox regression analysis suggest TNM stage II and MSI-H status also associated with superior OS

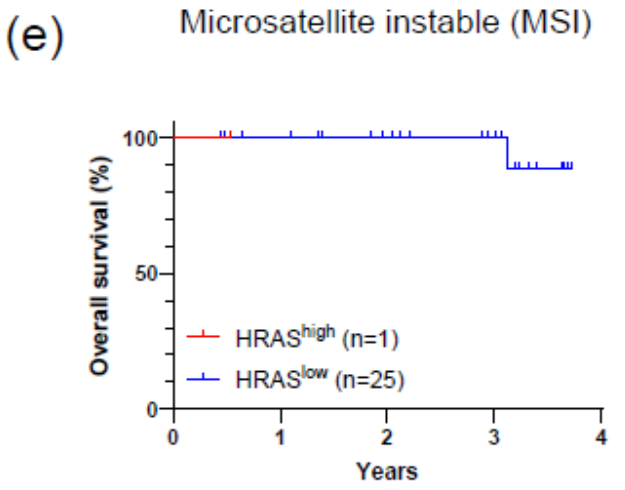
Table 1. Cox regression analysis on overall survival of locally advanced colorectal cancer at 4 years

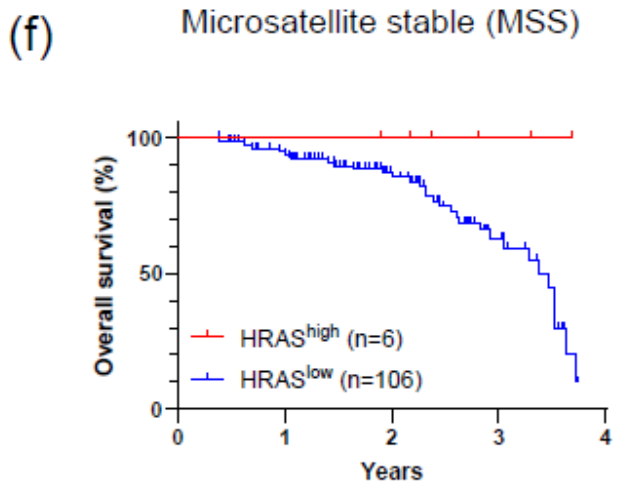
Variable	HR	95% CI	*p* value
Gender (Male vs. Female)	1.491	0.9692 to 2.318	0.0714
Peri-operative 5-FU	1.056	0.6844 to 1.623	0.8038
KRAS pathologic mutation (codon 12, 13, 61)	1.338	0.8626 to 2.060	0.1886
BRAF mutation (any)	0.8749	0.4166 to 1.655	0.7011
NRAS mutation (any exon mutation)	2.316	0.5588 to 6.401	0.162
Pathological TNM stage (Stage II vs. III)	0.4765	0.2856 to 0.7686	0.0032 (*)
Tumor sidedness (Left vs. Right)	1.069	0.6838 to 1.678	0.7715
HRAS transcript level (High vs. Low)	0.1302	0.007357 to 0.5932	0.0436 (*)
Microsatellite (Instable vs. stable)	0.08938	0.005011 to 0.4191	0.0177 (*)
(*) indicate p value < 0.05			

However, TNM stage and microsatellite status does not seem to influence the high HRAS expression-associated OS benefit

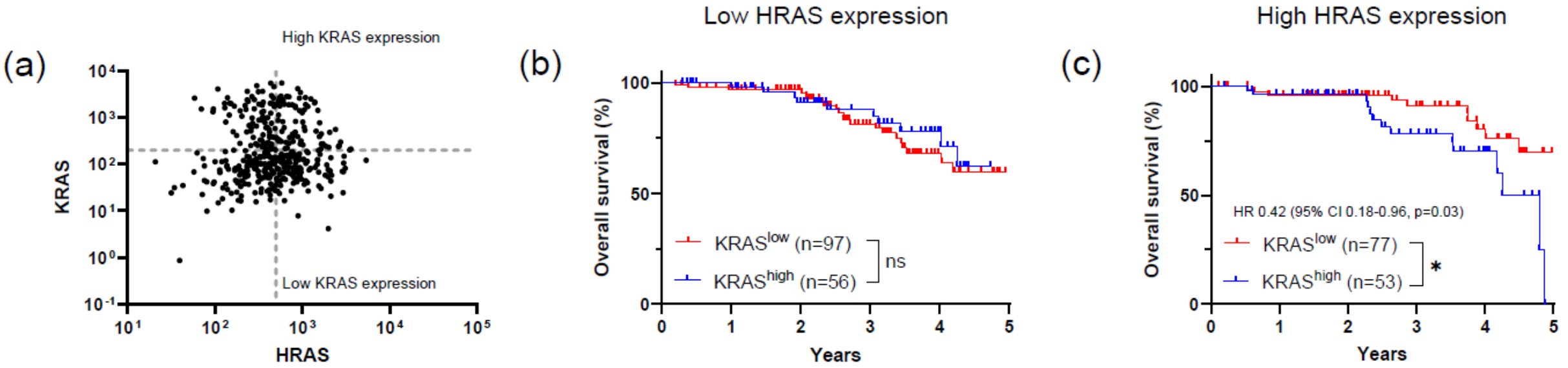








The OS benefit of high HRAS mRNA expression is pronounced in patients with low KRAS mRNA expression



Only the patients with KRAS(-); BRAF(-); NRAS(-) genotypic background are included in this analysis

Cox regression analysis of the sub-group expressing high HRAS suggests right-sided primary disease may also be associated with superior OS

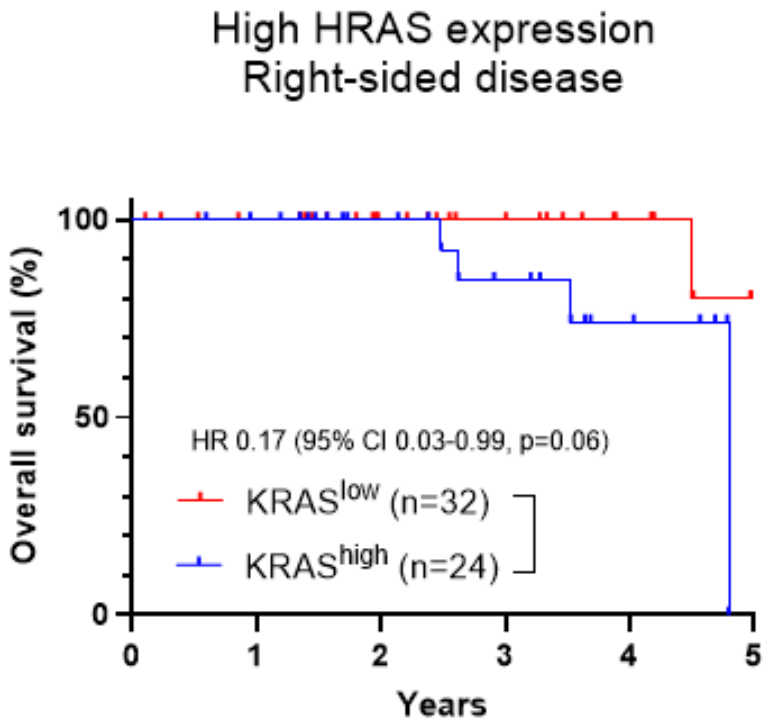
Table 2. Cox regression analysis on overall survival of locally advanced colorectal cancer with high HRAS transcript expression in KRAS(-);BRAF(-);NRAS(-) genotypic background at 5 years

Variable	HR	95% CI	*p* value
Gender (Male vs. Female)	0.7576	0.3004 to 1.895	0.5508
Peri-operative 5-FU	0.6898	0.2328 to 1.932	0.4865
Pathological TNM stage (Stage II vs. III)	0.5689	0.1733 to 1.635	0.3143
Tumor sidedness (Left vs. Right)	2.776	0.9825 to 9.119	0.0671
KRAS transcript level (High vs. Low)	2.166	0.9195 to 5.266	0.0789
NRAS transcript level (High vs. Low)	1.038	0.3945 to 3.072	0.9418
Microsatellite (Instable vs. stable)	1.581E-11	N/A	>0.9999
(*) indicate *p* value < 0.05			

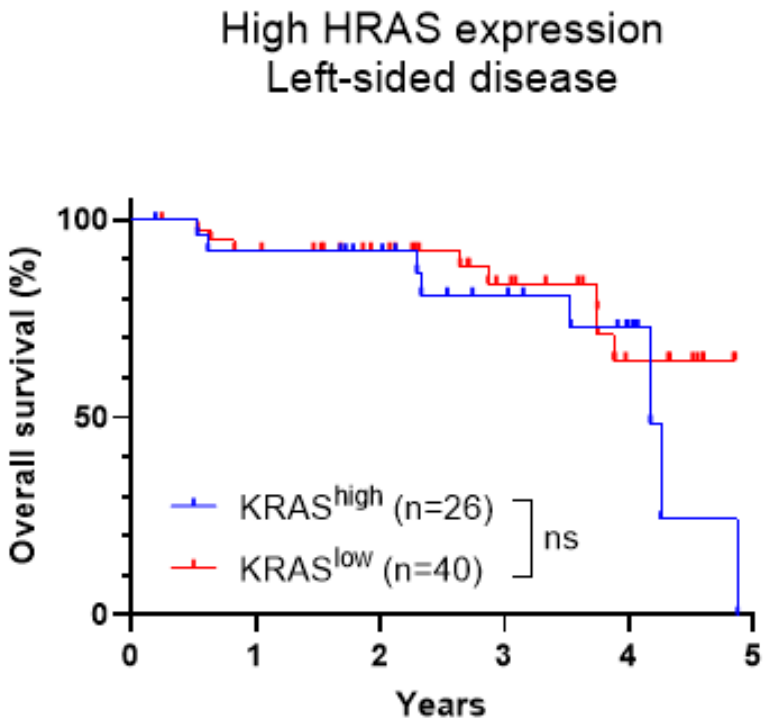
Only the patients with KRAS(-); BRAF(-); NRAS(-) genotypic background are included in this analysis

The OS benefit of high HRAS mRNA expression is most pronounced in patients with (1) low KRAS mRNA expression with (2) right-sided primary disease

(a)



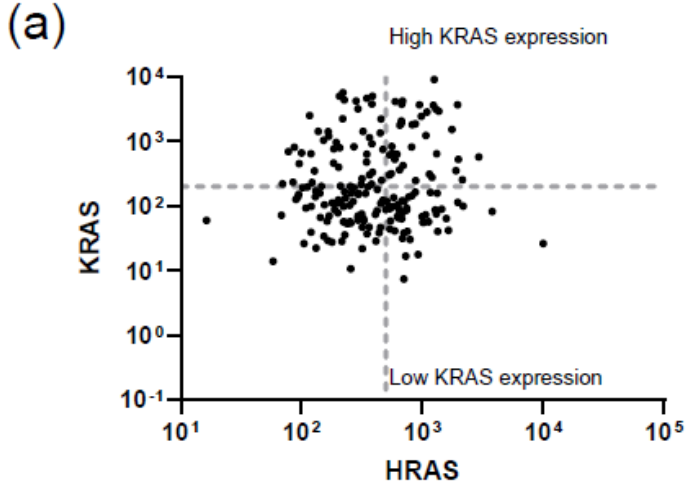
(b)

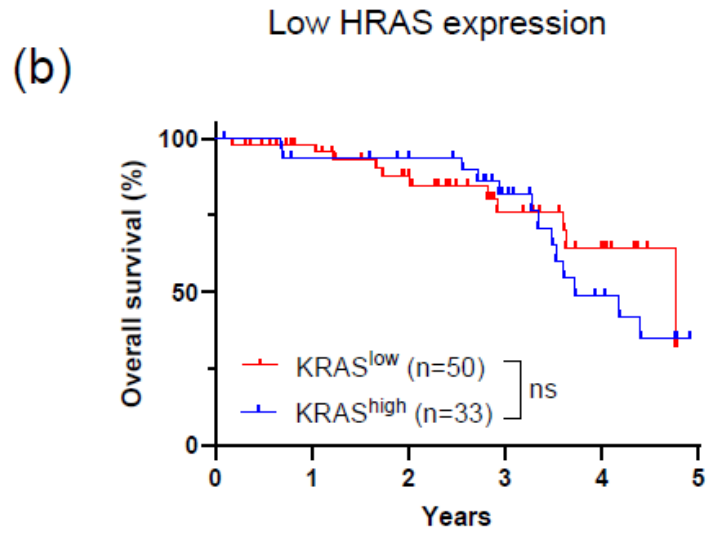


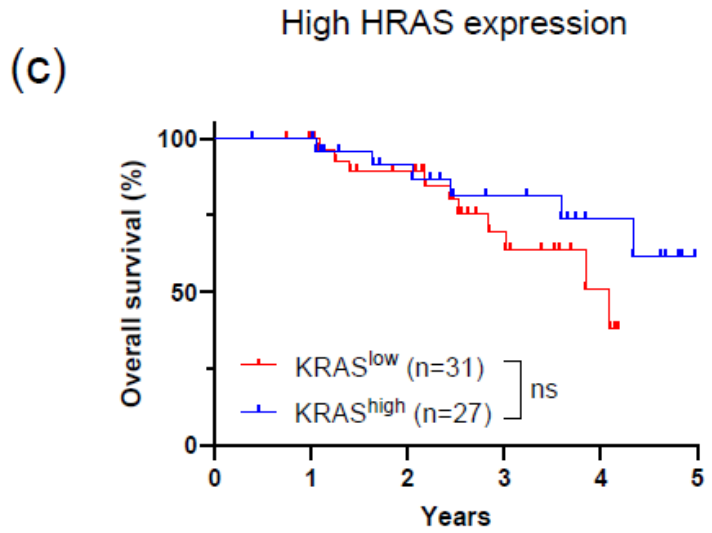
Only the patients with KRAS(-); BRAF(-); NRAS(-) genotypic background are included in this analysis

The OS benefit of high HRAS mRNA expression is no longer obvious in patients with low KRAS mRNA expression with pathologic KRAS mutations (codon 12, 13 and 61)

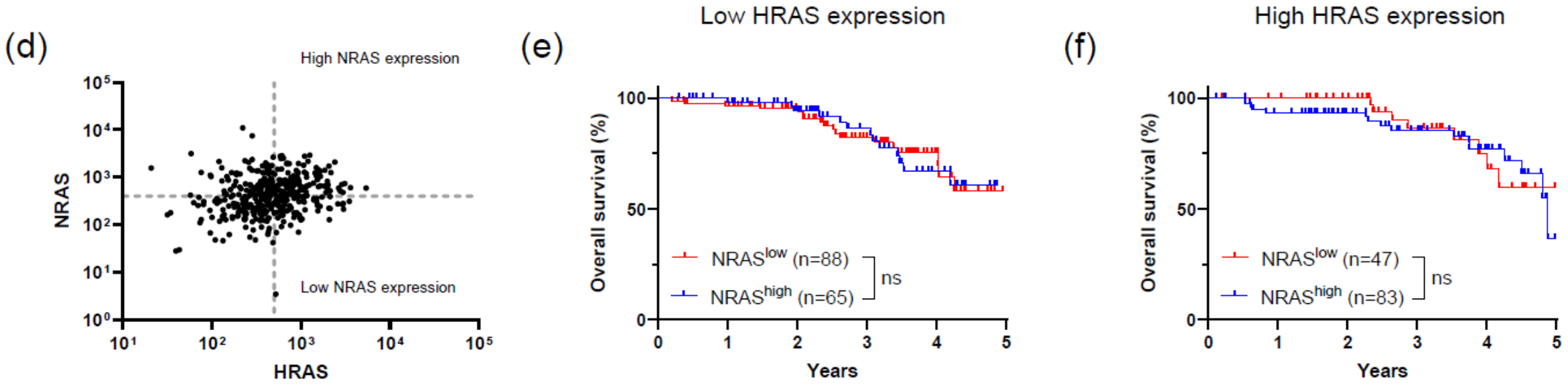
KRAS(+)
BRAF(-)
NRAS(-)







The OS benefit of high HRAS mRNA expression is <u>not</u> NRAS expression dependent



Only the patients with KRAS(-); BRAF(-); NRAS(-) genotypic background are included in this analysis

Conclusion

- Contrary to the notion that RAS family genes are proto-oncogenic, we propose that HRAS transcript level may be a novel biomarker for superior OS in locally advanced CRC

- The high HRAS-associated OS benefit was most pronounced in patients expressing low KRAS transcript levels in the absence of pathologic KRAS mutations

- We speculate that HRAS, when expressed at high levels, may counteract the proto-oncogene KRAS but not oncogene KRAS at the transcript level

Antagonistic interaction between the RAS family genes has been previously reported in a KRAS-mutated lung cancer mouse model study using CRISPR/Cas9 gene-editing system

nature cell biology

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Multiplexed screens identify RAS paralogues HRAS and NRAS as suppressors of KRAS-driven lung cancer growth

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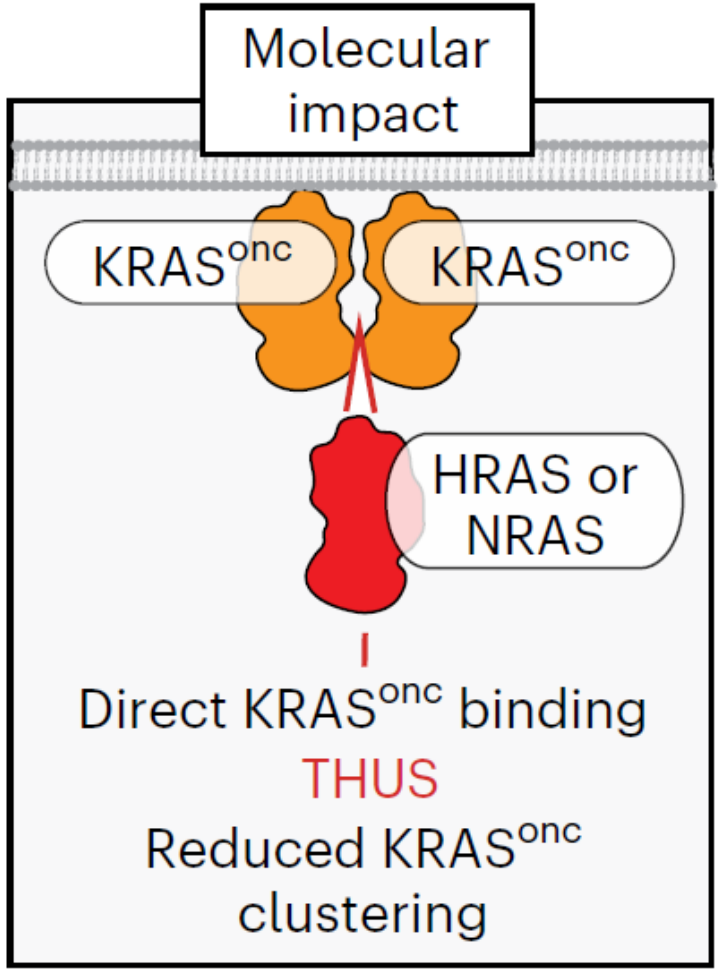
Check for updates

Rui Tang[1,10], Emily G. Shuldiner[2,10], Marcus Kelly[3,4], Christopher W. Murray[3], Jess D. Hebert[1], Laura Andrejka[1], Min K. Tsai[1,3], Nicholas W. Hughes[1], Mitchell I. Parker[5,6], Hongchen Cai[1], Yao-Cheng Li[7], Geoffrey M. Wahl[7], Roland L. Dunbrack[5], Peter K. Jackson[3,4], Dmitri A. Petrov[2,3,8] & Monte M. Winslow[1,3,9]



Thank you

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