

CGSI 2026

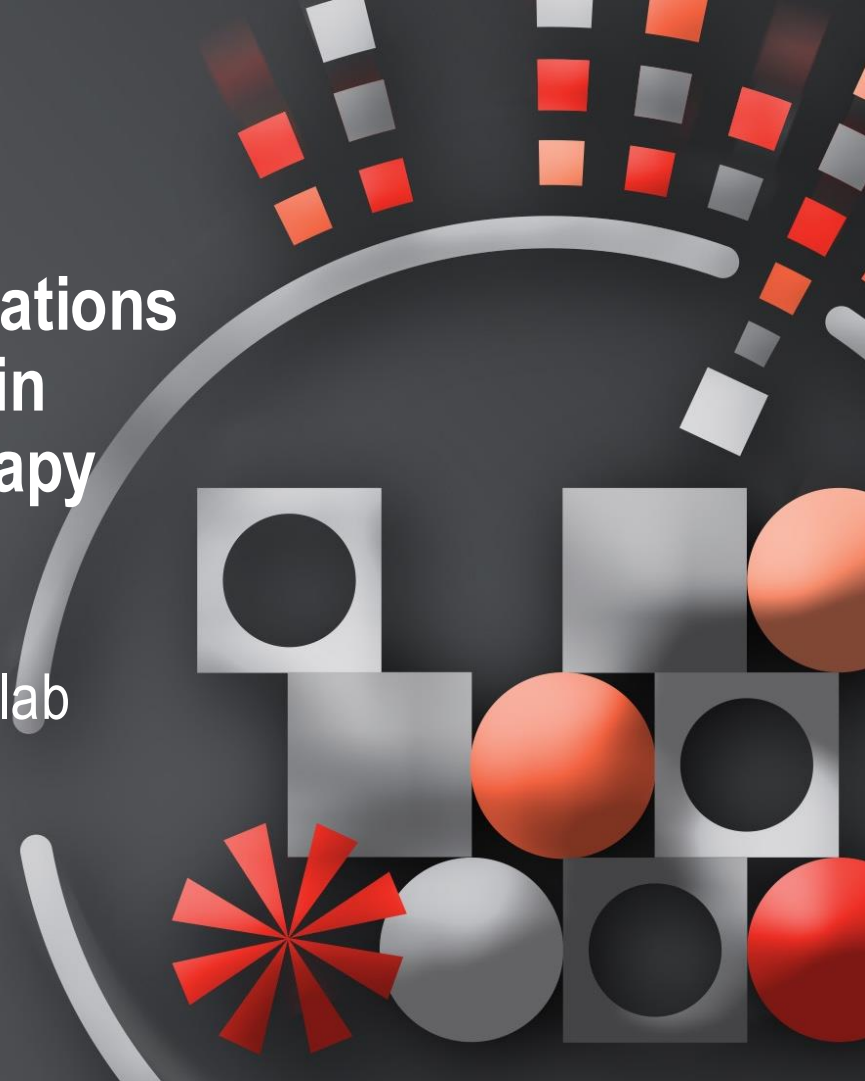
Bidirectional Prognostic Associations of Subclonal Mutation Fraction in Patients Receiving Immunotherapy

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THE UNIVERSITY OF TEXAS
MDAnderson
Cancer Center

Making Cancer History®



MD Anderson ICB clinical trials on low-TMB malignancy - advanced prostate cancer



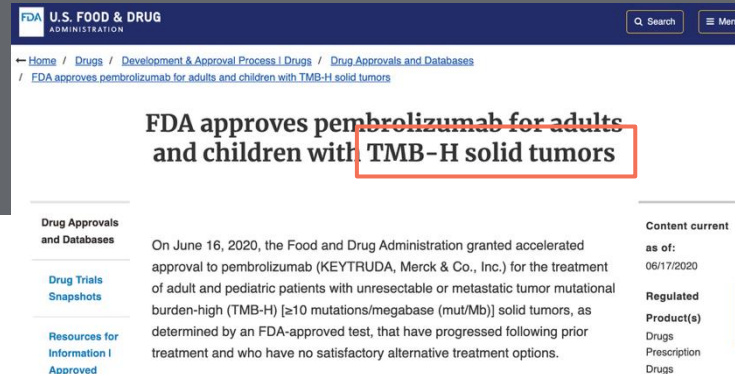
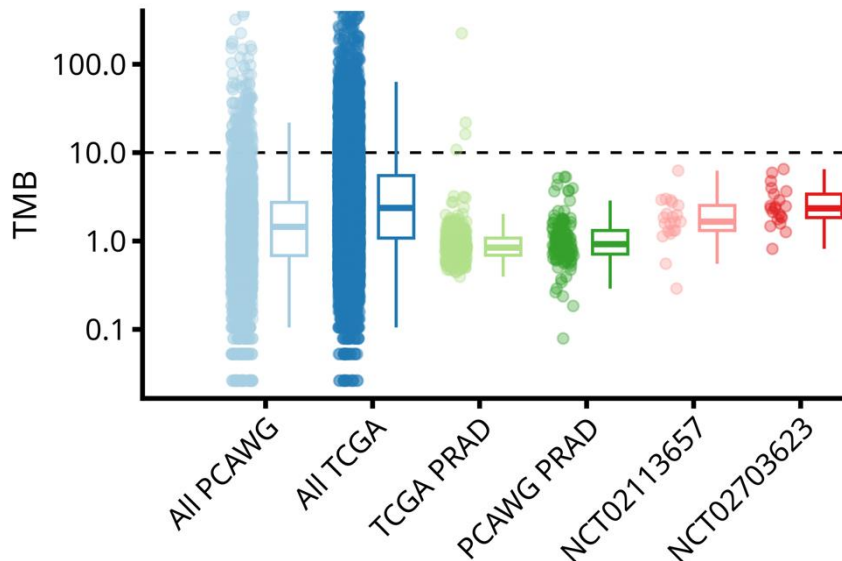
Ana Aparicio



Sumit Subudhi



Pam Sharma



- Immune checkpoint blockade (ICB) therapy is effective in 25-40% of immune-hot (high TMB) cancers.
- Patients with immune-cold (low TMB) cancers still respond to ICB but the molecular underpinnings are largely unknown.

Two MD Anderson trials provide a cohort for studying ICB outcomes in low-TMB prostate cancer



Ana Aparicio

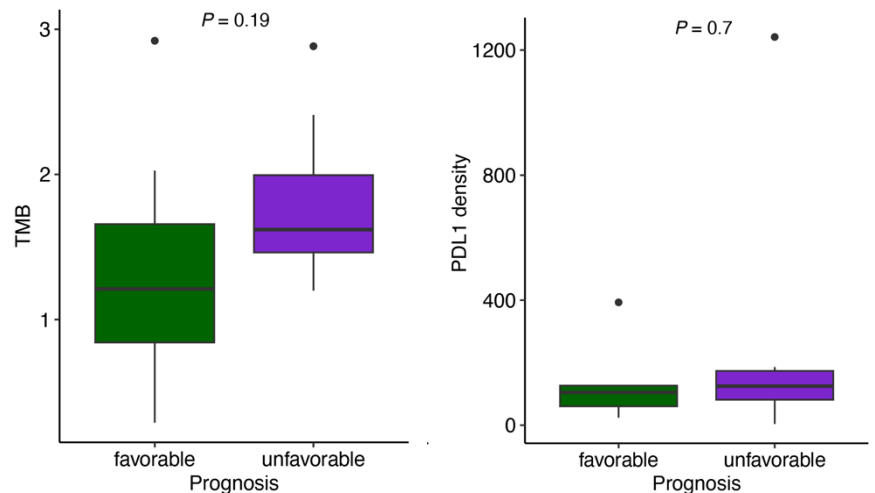
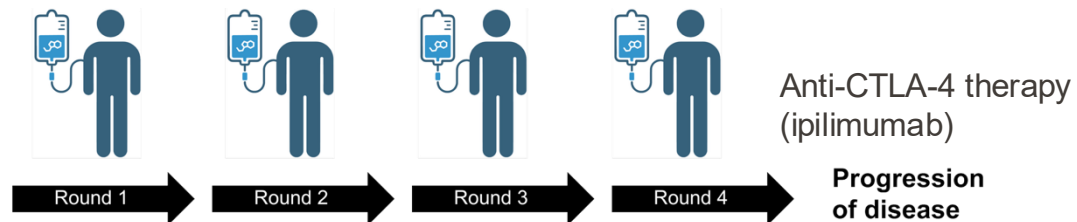


Sumit Subudhi

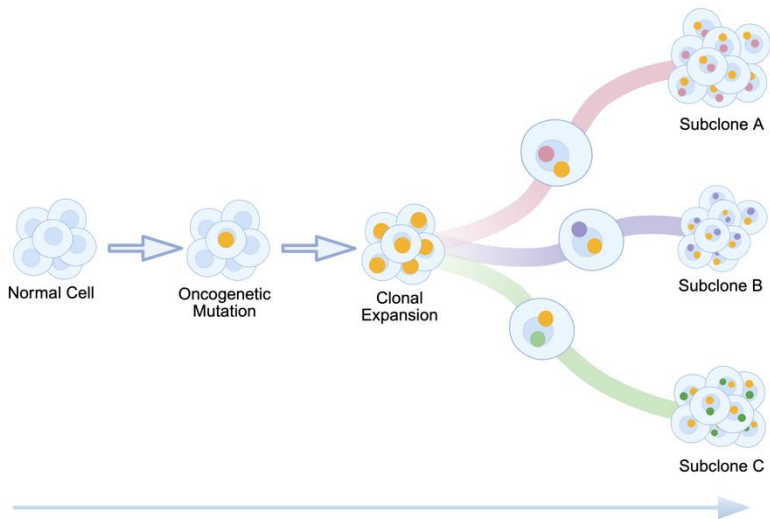


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NCT02703623 Arm 2B
(n=64) ApA + IPI
NCT02113657 (n=30) IPI



Tumors with the same TMB can have different clonal architectures



Clonal mutation = 5, subclonal mutation = 1
TMB = 6



Clonal mutation = 2, subclonal mutation = 4
TMB = 6

subclonal Mutation Fraction (sMF) =

$$\frac{\text{No. of subclonal variants}}{\text{No. of variants}}$$

sMF, but not TMB, stratifies progression-free survival after ICB



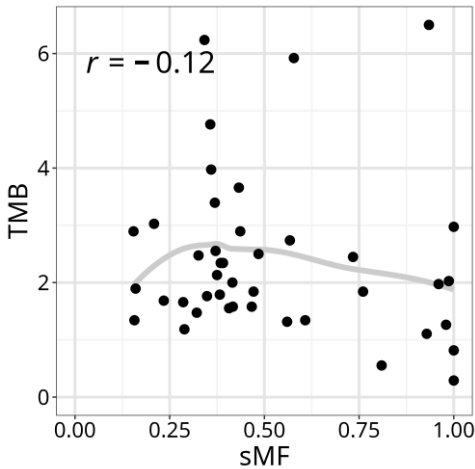
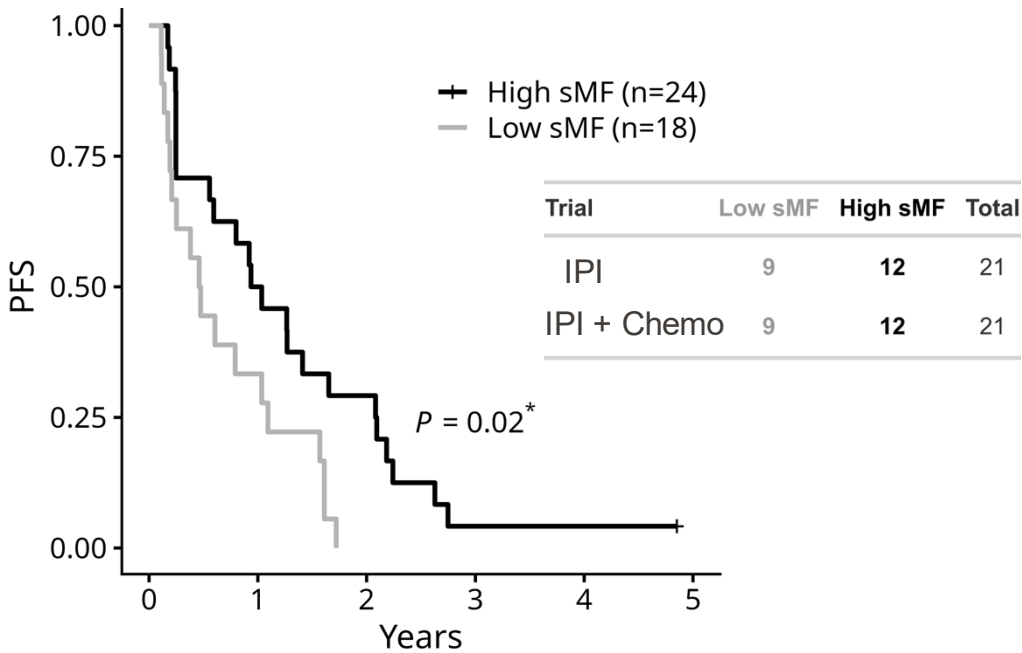
Ana Aparicio



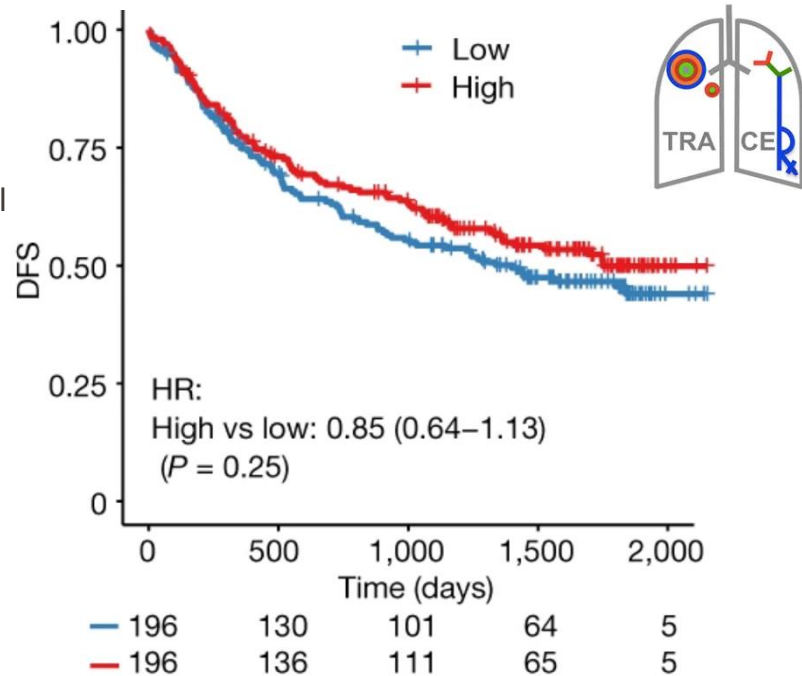
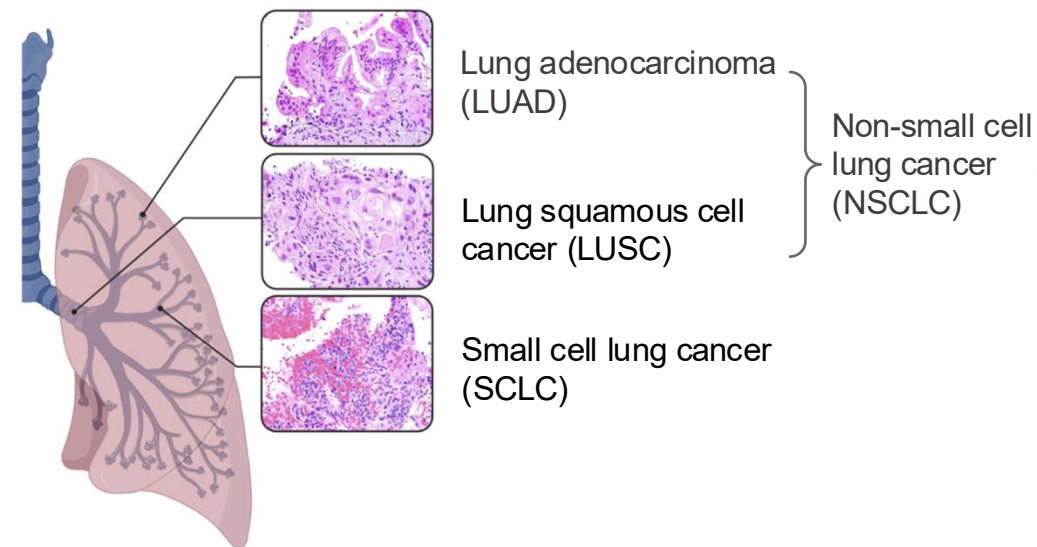
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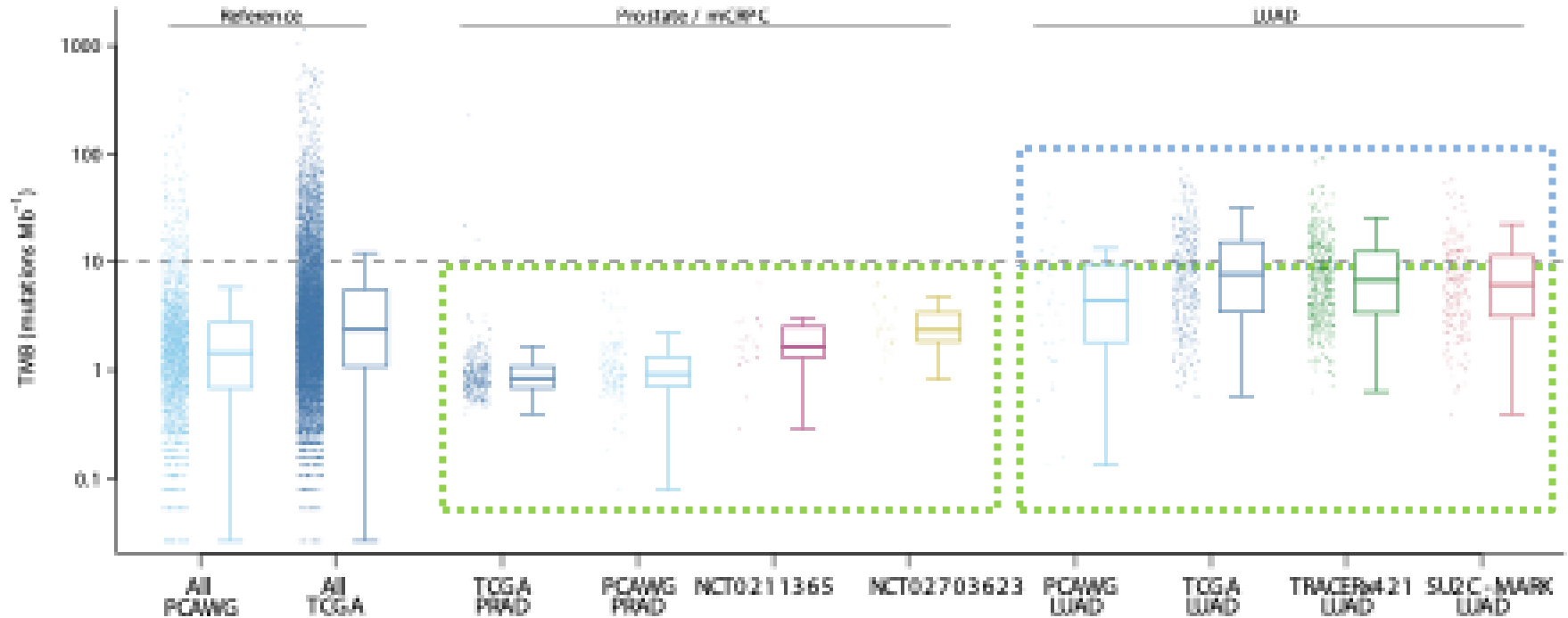


Prior work found no significant overall prognostic association for sMF



Frankell et al., *Nature* 2023

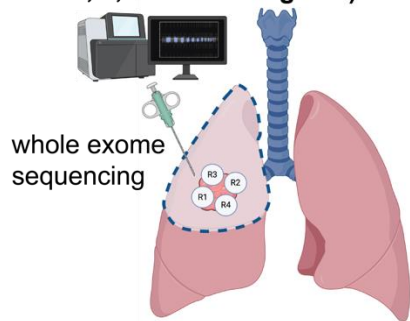
Coding TMB varies substantially across cancer types



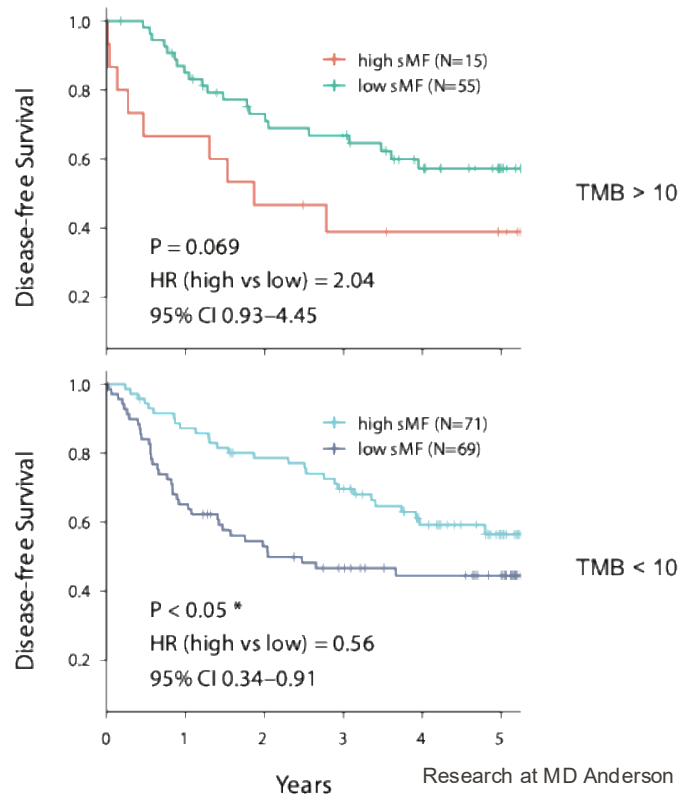
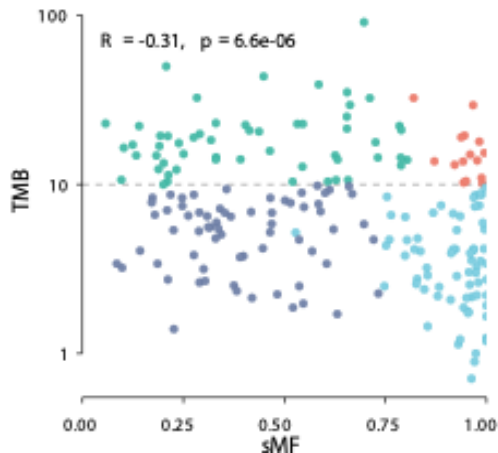
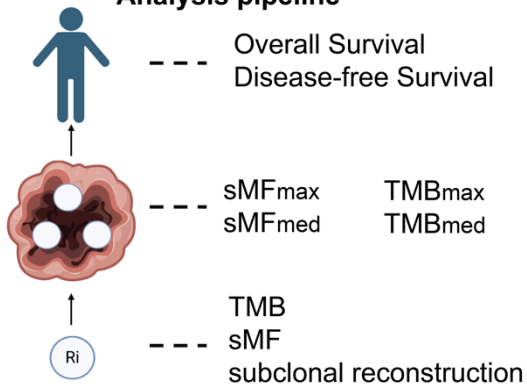
sMF shows opposite prognostic associations across coding-TMB strata in TRACERx421 LUAD



TRACERx421 multi-region study of NSCLC
(421 patients, 1,644 tumor regions)



Analysis pipeline



Multivariable analysis supports a significant interaction between TMB and sMF



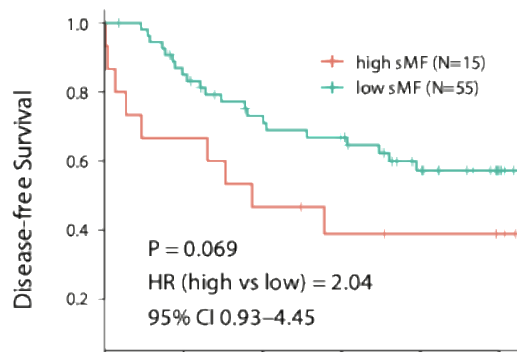
age	(N=212)	1.04 (1.01 - 1.07)		0.003 **
pTNM_stage	IA (N=53)	reference		
	IB (N=55)	2.07 (1.00 - 4.29)		0.05
	IIA (N=33)	3.98 (1.74 - 9.10)		0.001 **
	IIB (N=25)	2.07 (0.82 - 5.24)		0.123
	III (N=46)	4.03 (1.85 - 8.80)		<0.001 ***
pack_years	(N=212)	1.00 (0.99 - 1.01)		0.439
Adjuvant	No adjuvant (N=140)	reference		
	Adjuvant (N=72)	1.42 (0.82 - 2.46)		0.212
SCNA.ITH	low (N=114)	reference		
	high (N=97)	0.76 (0.47 - 1.24)		0.277
gd_status	No GD (N=60)	reference		
	Subclonal GD (N=36)	0.84 (0.40 - 1.75)		0.639
	Clonal GD only (N=115)	0.67 (0.37 - 1.23)		0.195
RecentSubclExpansionScore	low (N=113)	reference		
	High (N=99)	1.57 (0.98 - 2.53)		0.063

TMB	low (N=140)	reference		
	high (N=72)	0.55 (0.31 - 0.98)		0.041 *
sMF	low sMF (N=126)	reference		
	high sMF (N=86)	0.47 (0.24 - 0.92)		0.027 *
TMB.sMF.Interaction	(N=212)	4.03 (1.55 - 10.51)		0.004 **

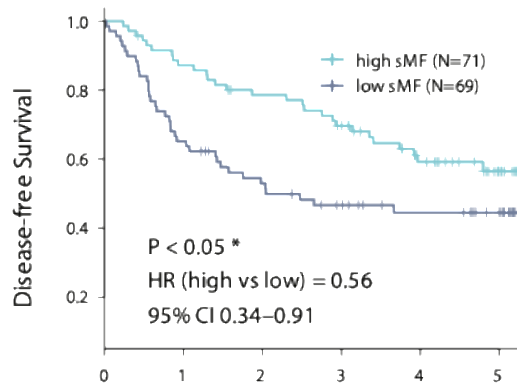
Events: 96; Global p-value (Log-Rank): 1.4638e-06

AIC: 926.12; Concordance Index: 0.72

0.2 0.5 1 2 5 10



TMB > 10



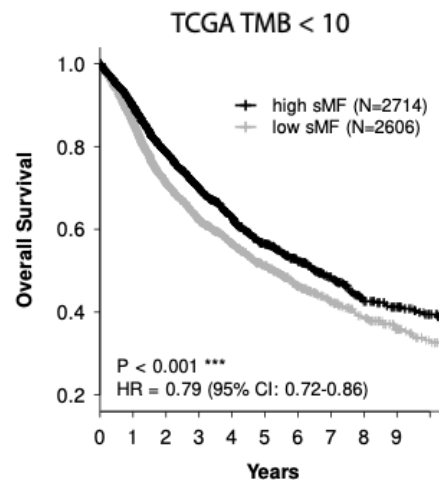
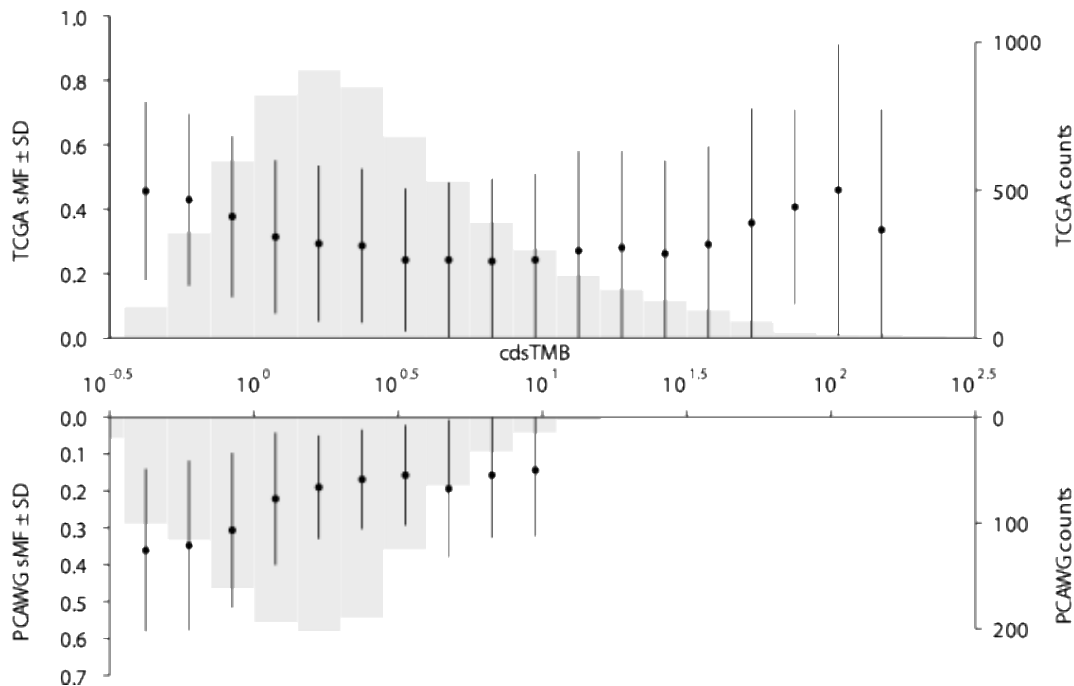
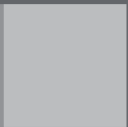
TMB < 10

Years

Research at MD Anderson

9

Pan-cancer analyses support a TMB-dependent association between sMF and survival



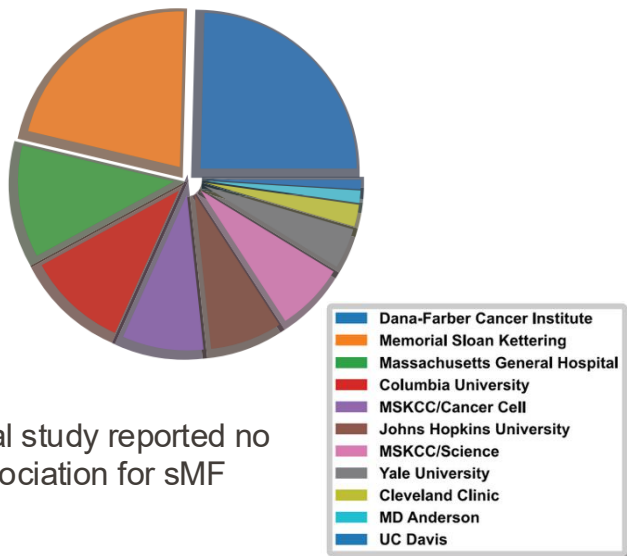
sMF is associated with immunotherapy outcomes in LUAD



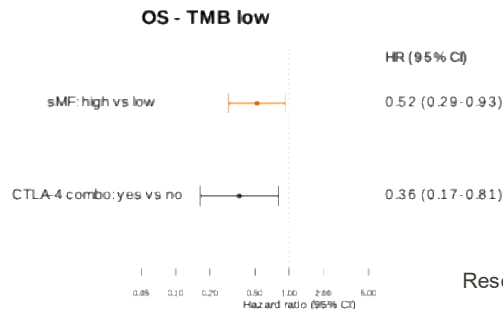
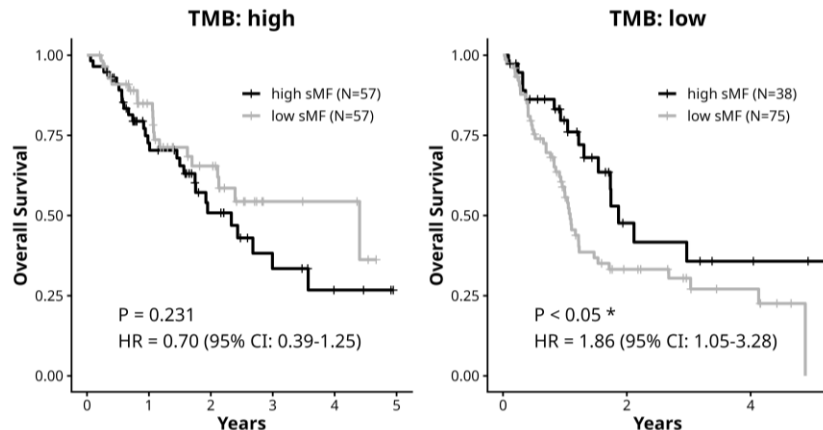
Stand Up To Cancer-Mark Foundation (SU2C-MARK) NSCLC cohort

- Anti-PD-(L)1 or Anti-PD-(L)1 + Anti-CTLA4

WES samples institutions



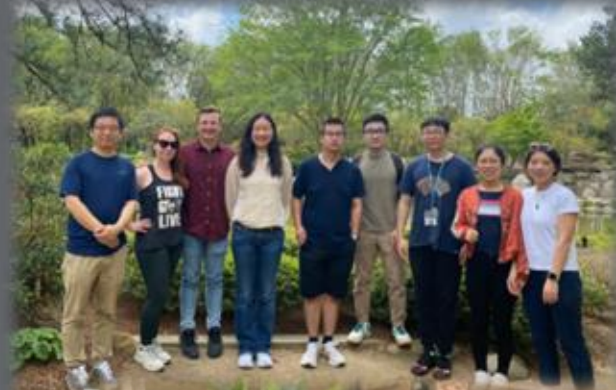
The original study reported no overall association for sMF



Takeaway

- The prognostic association of sMF is bidirectional and depends on TMB.
- High sMF may identify a subgroup of patients with low-TMB tumors who experience favorable outcomes after ICB.





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MDACC Cancer Moonshot Platforms



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