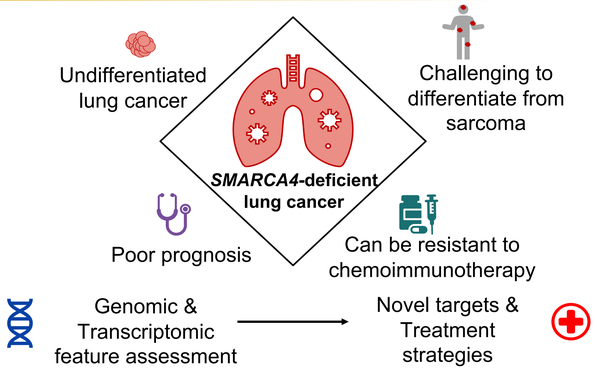
2022 ASCO Abstract 3118

Genomic landscape of *SMARCA4*-deficient lung tumors by clinical RNA sequencing

Brian Pham[1*], Weijie Ma[1], S. Greg Call[2], Arya Ashok[2], Elizabeth Mauer[2],Elham Kamangar[3], Tianhong Li[1]

[1]Division of Hematology/Oncology, Department of Internal Medicine, University of California Davis School of Medicine, University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA; [2]Tempus Labs, Inc., Chicago, IL, USA; [3]Department of Pathology and Laboratory Medicine, University of California Davis School of Medicine, Sacramento, CA, USA

INTRODUCTION



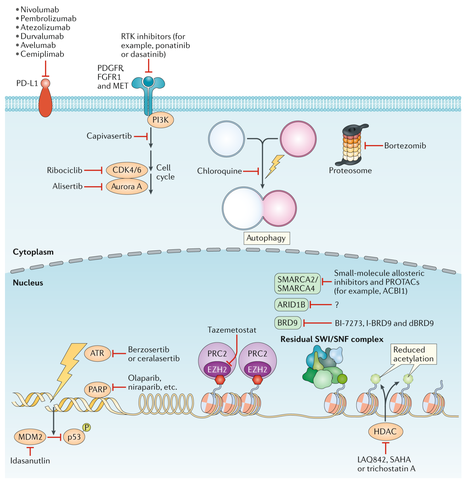
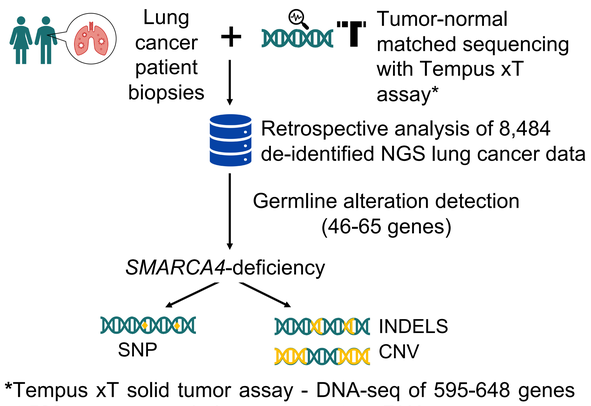


Fig 1: Therapeutic opportunities of SWI/SNF complex[1]

1. Mittal, P., Roberts, C.W.M. The SWI/SNF complex in cancer — biology, biomarkers and therapy. Nat Rev Clin Oncol 17, 435–448 (2020). https://doi.org/10.1038/s41571-020-0357-3

METHODS



*Tempus xT solid tumor assay - DNA-seq of 595-648 genes at 500x coverage; whole-exome capture RNA-seq

Statistical significance was determined using Fisher's exact tests and Wilcoxon rank-sum tests.

SUMMARY

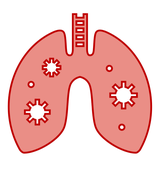
SMARCA4-deficiency was detected in 370 (4.4%) lung tumors.
This study reveals the **unique genomic and transcriptional characteristics of *SMARCA4*-deficient lung tumors**.

SMARCA4-deficient vs *SMARCA4*-WT tumor

More male patients (63% vs 49%, p<0.001)

Diagnosed at younger ages (64 vs 68 years, p <0.001)

High Tumor Mutational Burden (34% vs 15%, p<0.001)



Enrichment of unique somatic and germline mutations

Reduced expression of specific genes (*SMARCA4*, *PD-L1*)

Reduced CD4+ T cell infiltration

RESULTS

Cohort Demographics

Characteristics	SMARCA4 - wild type (n=8114)	*SMARCA4*-deficient (n=370)	Overall (n=8484)
Age at Diagnosis Median (IQR)	68 (61, 75)	64 (58, 71)	68 (61, 75)
Gender			
Male	3957 (49%)	232 (63%)	4189 (49%)
Race			
White	4553 (81%)	208 (84%)	4761 (81%)
Black or African American	654 (12%)	28 (11%)	682 (12%)
Asian	221 (3.9%)	2 (0.8%)	223 (3.8%)
Other race	187 (3.3%)	9 (3.6%)	196 (3.3%)
Unknown	4917	242	5159
Ethnicity			
Not Hisp. or Latino	2986 (93%)	123 (96%)	3109 (94%)
Hisp. or Latino	211 (6.6%)	5 (3.9%)	216 (6.5%)
Unknown	5159	4917	242

Table 1. Characteristics of the patient cohort analyzed. SMARCA4-deficiency was detected in 370 (4.4%) tumors. *SMARCA4*-deficient tumors included more male patients (63% vs 49%, p<0.001) and younger age at diagnosis (median 64 vs 68 years, p <0.001).

Immune Biomarkers	*SMARCA4* – wild type (n=8114)	*SMARCA4* – deficient (n=370)	Overall (n=8484)
TMB-H	1015 (15%)	125 (34%)	1140 (16%)
Unknown	1142	5	1147
MSI-H	40 (0.5%)	3 (0.8%)	43 (0.5%)
Unknown	170	1	171
PD-L1 Positive	2166 (54%)	91 (44%)	2257 (53%)
Unknown	4068	164	4232

Table 2. Immune biomarker characteristics. *SMARCA4*-deficient tumors had high tumor mutational burden (TMB-H, ≥10 mutations per megabase) (34% vs 15%, p<0.001), and fewer patients with positive PD-L1 immunohistochemical staining (44% vs 54%, p=0.009) compared to *SMARCA4* wild-type tumors.

Somatic Landscape

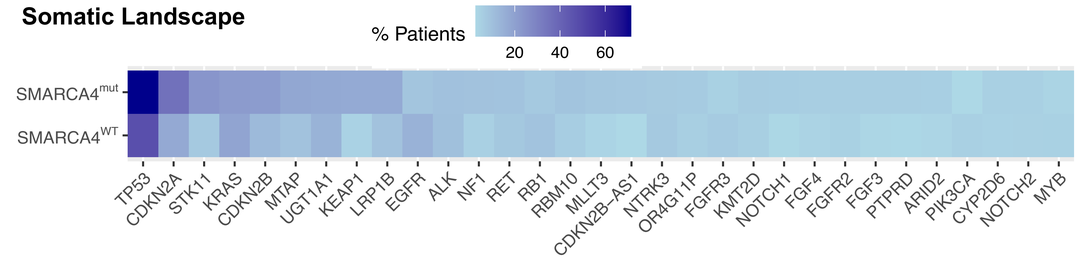


Fig 2: Somatic Landscape of *SMARCA4*-deficient tumors. *SMARCA4*-deficient tumors showed enrichment for somatic mutations in *TP53* (71% vs 47%, q<0.001), *STK11* (24% vs 7.3%, q<0.001), *KEAP1* (17% vs 4.5%, q<0.001), and *CDKN2A* (36% vs 17%, q<0.001) compared to wild-type. Note - the heatmap represents % of patients with a pathogenic/likely pathogenic mutation and/or copy number alteration. Copy number alterations were defined as losses (copy number 0) or amplifications (copy number >=8)

Germline Mutation

Characteristic	*SMARCA4* – wild type (n=8114)	*SMARCA4* – deficient (n=370)
MUTYH	88(1.1%)	8 (2.2%)
ATM	49 (0.6%)	4 (1.1%)
MSH6	3 (<0.1%)	2 (0.5%)

Table 3: Incidental Germline Landscape of *SMARCA4*-deficient tumors. Tumor normal-match sequencing identified incidental germline mutations in *MUTYH* (2.2%), *ATM* (1.1%), and *MSH6* (0.5%) for *SMARCA4*-deficient tumors.

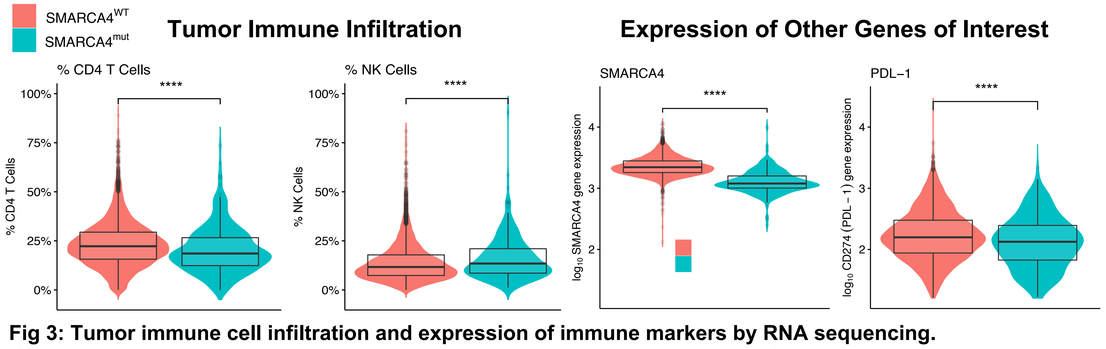


Fig 3: Tumor immune cell infiltration and expression of immune markers by RNA sequencing. RNA-seq analysis revealed that *SMARCA4*-deficient tumors had reduced infiltration of CD4+ T cells (19% vs 22%, p<0.001), increased infiltration of %NK cells of all immune cells: (median 13% vs. 12%, p=0.001), reduced RNA expression *SMARCA4* log10 gene expression: (median 3.08 vs. 3.34, p<0.001), PDL-1 log10 gene expression: (median 2.12 vs. 2.19, p<0.001) compared to *SMARCA4*-wilt type lung tumors .

Acknowledgements: We thank Amrita Iyer, from the Scientific Communications team at Tempus for visualization and poster review. This work was supported by the Tempus Discovery Program and the Personalized Cancer Therapy Gift Fund (TL).

Correspondence: thli@ucdavis.edu