Clinical Experience with SMARCA4-*mutated* NSCLC

Dr. Adam Schoenfeld
Memorial Sloan Kettering Cancer Center

Learning Objectives

- How is SMARCA4-*mutated* advanced NSCLC treated today?
- What has been our clinical experience in treating these patients?
- Where would a SMARCA2 degrader fit in clinical practice? How could it change SoC?
- Where is the unmet need greatest in the treatment of advanced NSCLC?

SMARCA4 mutations occur in ~10% of all NSCLC and to varying degrees across other cancers

NSCLC: 10%

Squamous cell lung: 8%

Esophageal: 8%

Colorectal: 6%

Gastric: 8%

Pancreatic: 3%

Endometrial: 13%

Urinary: 9%

Types of mutations:

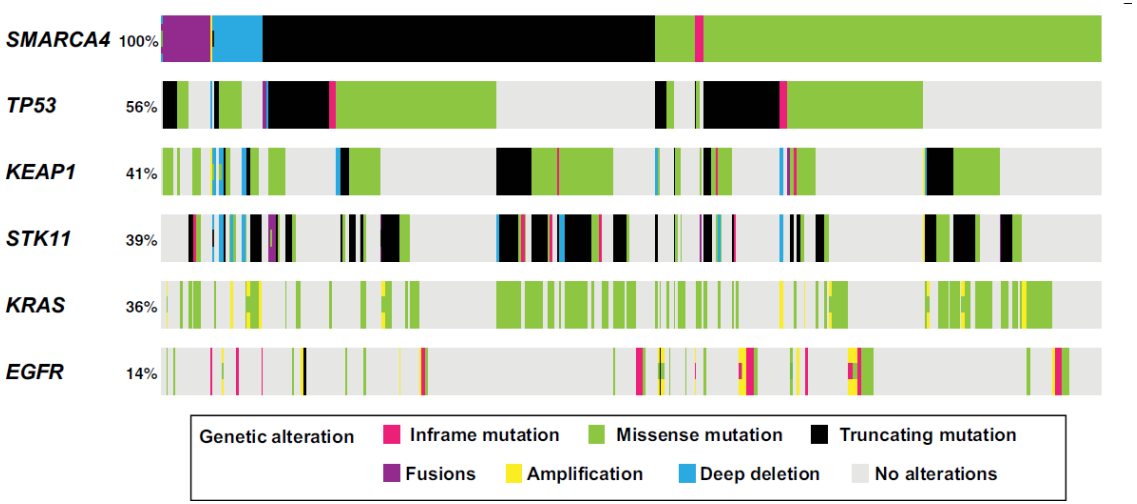
Class I (Loss-of-function)

Class II (Missense, other)

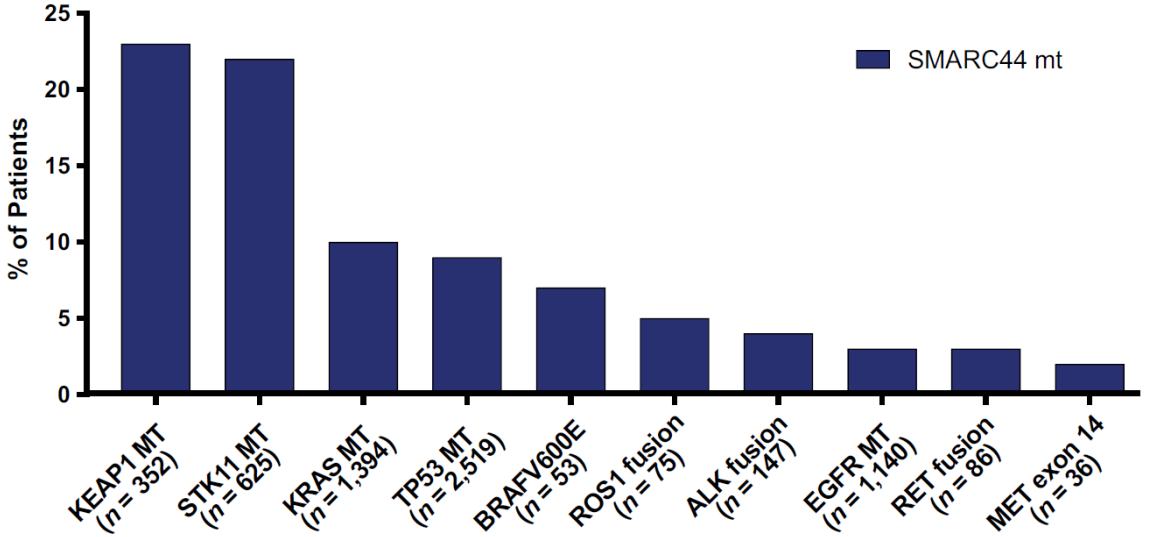
[1]Dagogo-Jack et al. Journal of Thoracic Oncology. 2020 Foundation Medicine dataset

SMARCA4 mutations are sometimes concurrent with other driver oncogenes

Most Frequent Co-Occurring Mutations



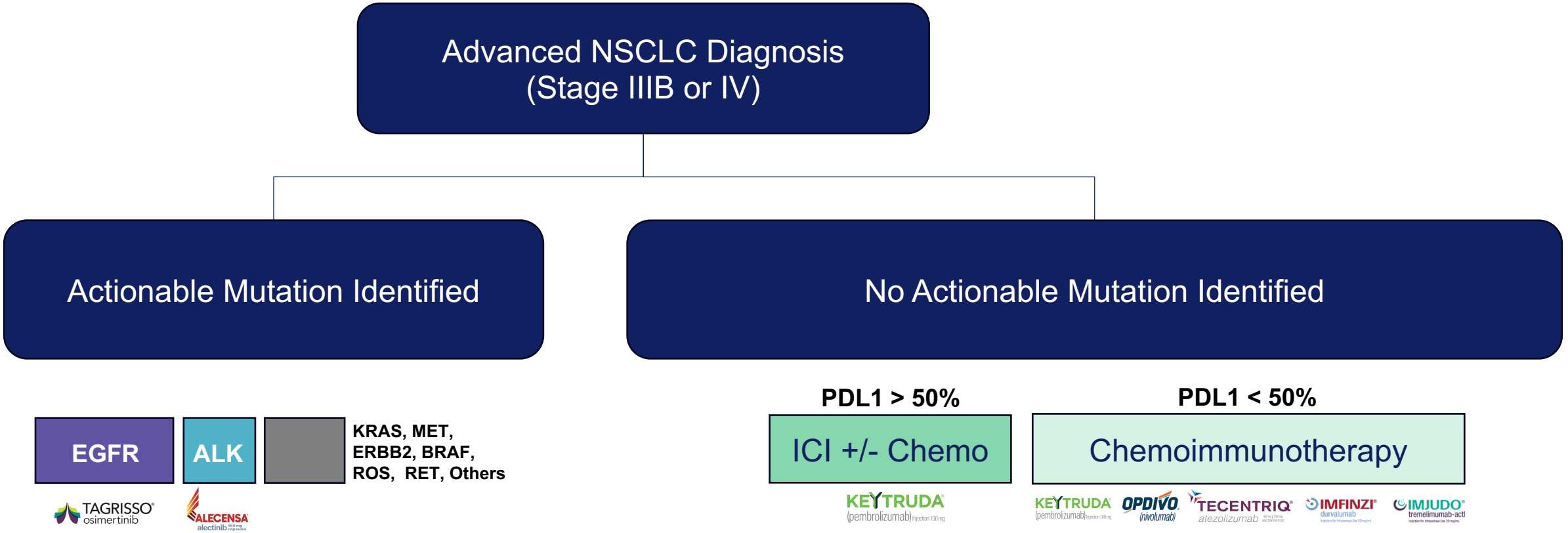
Distribution of *SMARCA4* Mutation by Commonly Altered Gene Subgroup



Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708.

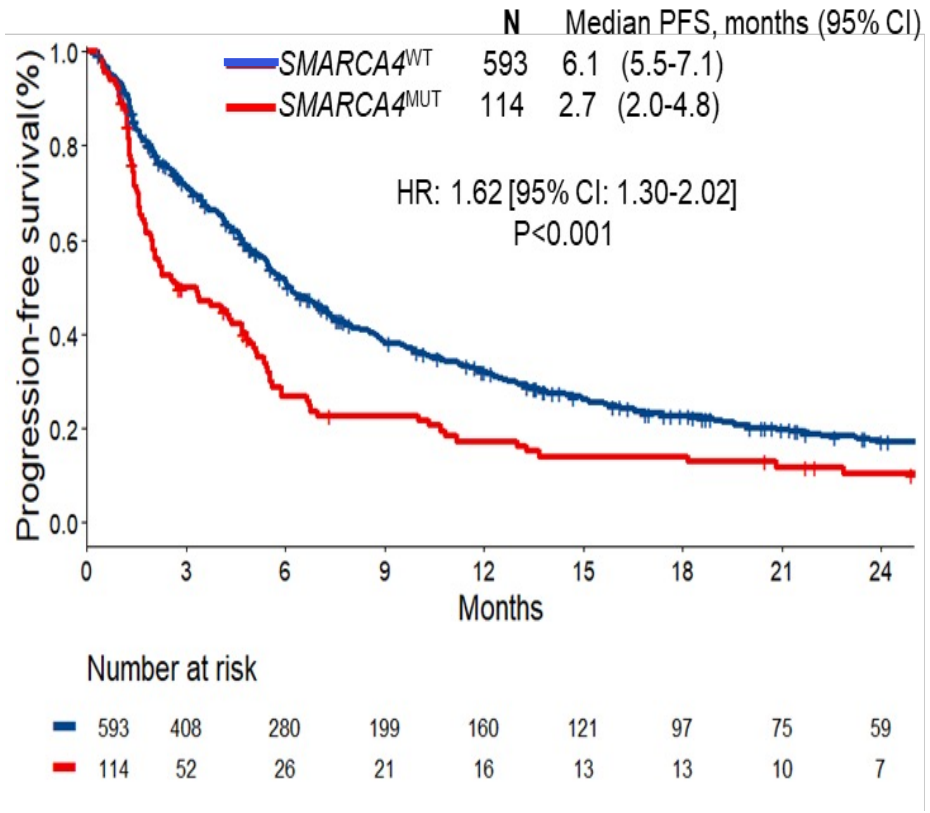
Prelude THERAPEUTICS

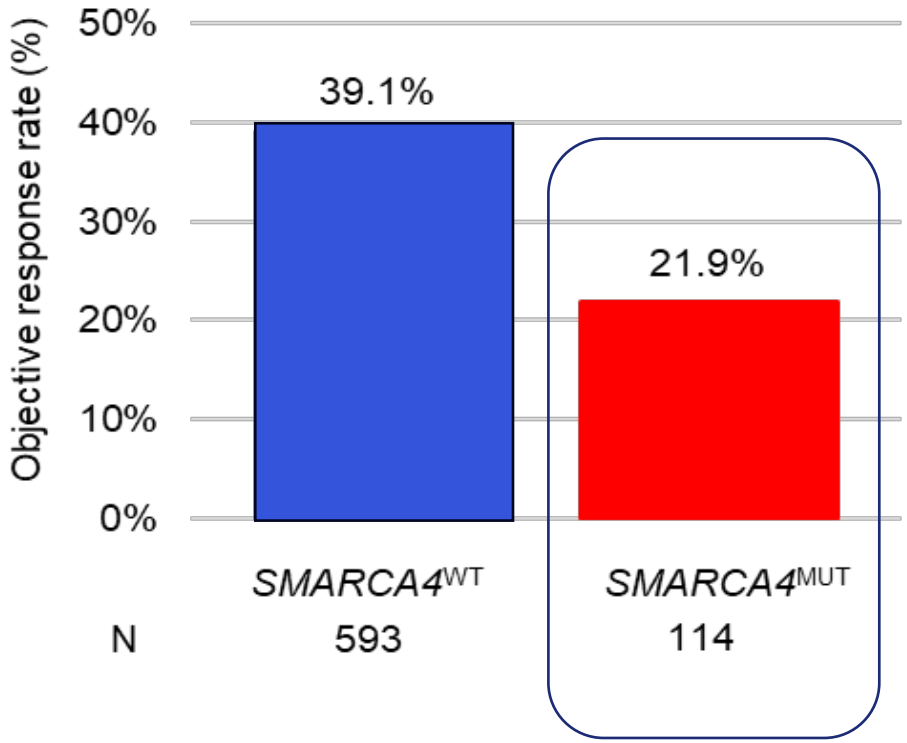
Majority of advanced NSCLC patients are currently treated with chemoimmunotherapy



Note: Simplified schematic based on current ESMO and NCCN Clinical Practice Guidelines and current clinical experience at MSKCC

SMARCA4-*mutated* NSCLC patients have significantly worse prognosis





Alessi JV, et al. Clinicopathologic and genomic factors impacting efficacy of first-line chemoimmunotherapy in advanced non-small cell lung cancer (NSCLC). J Thorac Oncol. 2023 Feb 10:S1556-0864(23)00121-1. doi: 10.1016/j.jtho.2023.01.091. PMID: 36775193 (attached).

Prelude THERAPEUTICS

Impact of SMARCA4 mutations on clinical outcomes for NSCLC patients

Key Eligibility:

- Patients with SMARCA4 alteration on MSK-IMPACT
- SMARCA4 IHC was performed on all patients with tissue available
- Retrospective review
- Patients with SMARCA4 wildtype status used as a comparator group

Class 1 Alterations*
Likely oncogenic/oncogenic variants

Class 2 Alterations
Missense mutations
Variants of unknown significance

Outcomes:

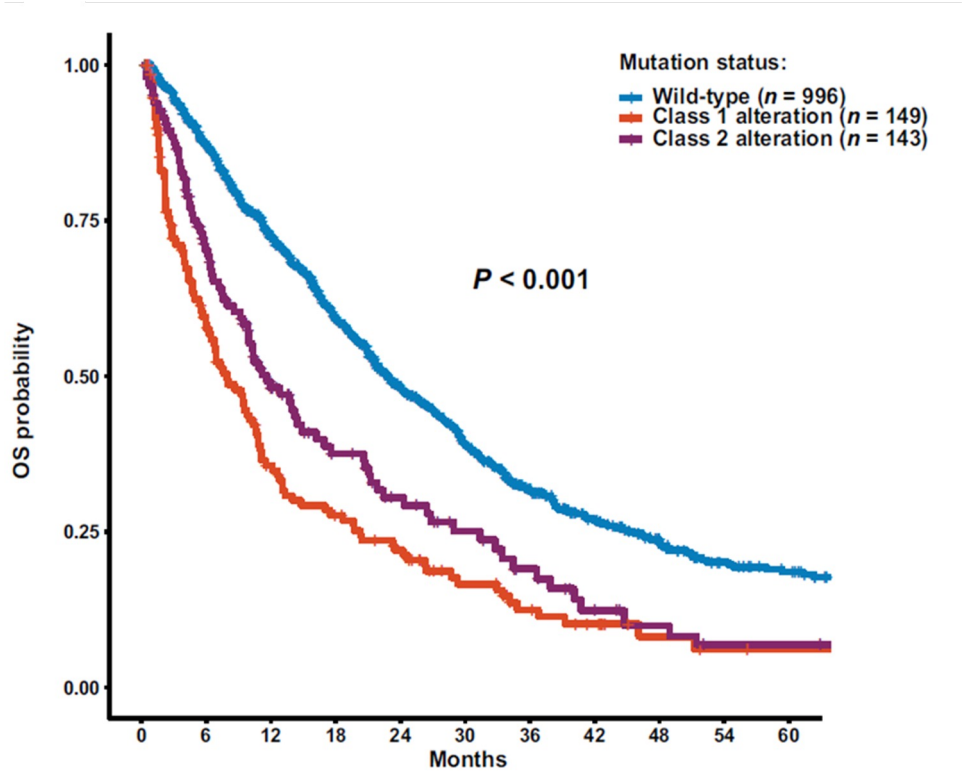
- Genomic relationships
- Protein expression
- Overall survival
- Outcomes on ICIs

* Class 1 includes chromosomal rearrangements, truncating mutations, and likely oncogenic variants as determined by Oncokb

Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708.

SMARCA4-*mutated* NSCLC patients (Class I & II) associated with worse prognosis

OS Among All Patients



N = 1288	Hazard Ratio	95% CI	p value
SMARCA4 mutation type			<0.001
Wild type	--	--	
Class 2	2.01	1.58, 2.55	
Class 1	1.59	1.25, 2.04	
Sex			0.2
Female	--	--	
Male	1.12	0.95, 1.31	
Age (10 years)	1.22	1.13, 1.32	<0.001
Smoking status			0.005
Never smoker	--	--	
Former light (<15 pack-year)	1.58	1.23, 2.03	
Former heavy (>15 pack year)	1.21	0.96, 1.51	
Current smoker	1.27	0.96, 1.69	
Histology			<0.001
Adenocarcinoma	--	--	
Non-adenocarcinoma	1.79	1.38, 2.33	
Tumor mutation burden (TMB)	0.98	0.97, 0.99	<0.001
STK11			<0.001
Negative	--	--	
Positive	1.52	1.23, 1.88	
KEAP1			0.036
Negative	--	--	
Positive	1.26	1.02, 1.55	

Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708.

Substantial unmet need in the treatment of patients with SMARCA4-*mutated* NSCLC

FIRST LINE

Chemoimmunotherapy[1]

ORR	< 25%
mOS	< 12 months

SECOND LINE

Chemotherapy[2]

ORR	< 15%
mOS	< 8 months

Response rates are less than 25% and expected median OS is less than a year

Even greater unmet need in 2nd line where fewer effective treatment options are available

[1] Response Rate and Survival Data: Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708
[2] Second line estimates based on docetaxel label and clinical experience

There is high unmet need in NSCLC for patients with SMARCA4 mutations

- In NSCLC, SMARCA4 mutations are observed in ~10% of cases and are associated with more aggressive and invasive disease and shorter survival
- The majority of these patients are not eligible for other targeted therapies, and therefore are typically treated with chemoimmunotherapy combinations
- In patients with metastatic NSCLC, SMARCA4 mutations (both Class I & II) have been associated with poor prognosis when given first-line chemo-immunotherapy
- The unmet need is even greater in 2L NSCLC where few treatment options are approved

Key Takeaways