

SITC/World Immunotherapy Council's Young Investigator Symposium

Genomic Instability, Tumor Mutation Burden and Biomarkers in Lung Cancer and other solid tumors

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The OHIO State University James Cancer Center



Disclosure

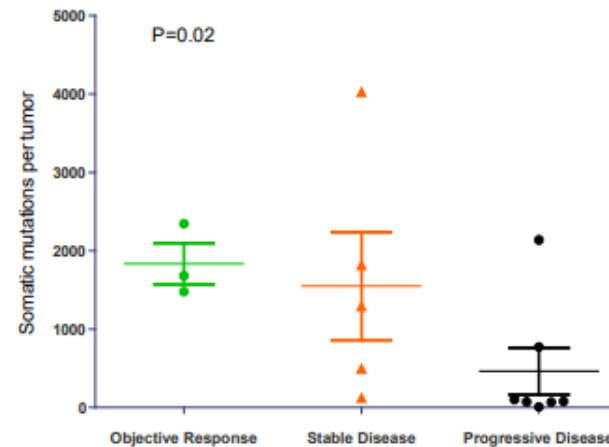
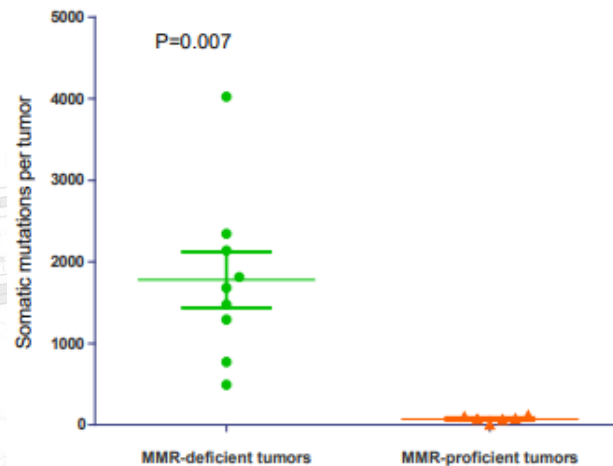
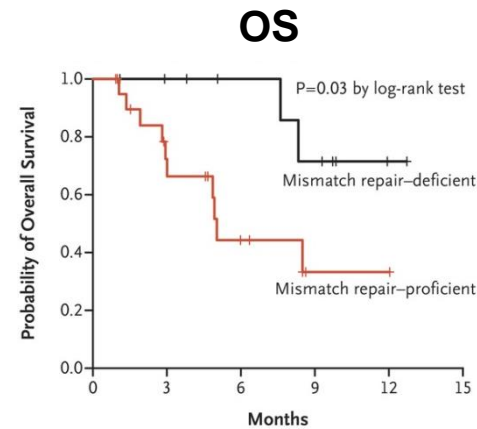
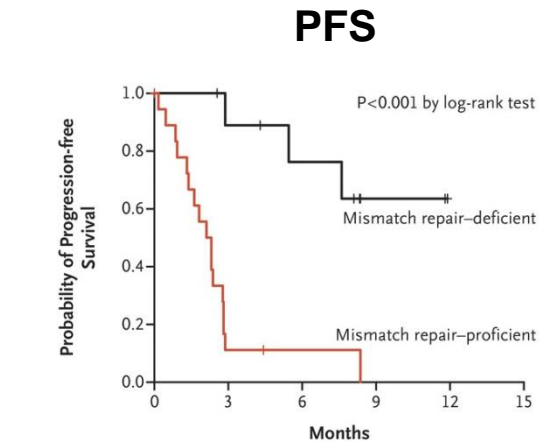
- Clinical trial and research funding as investigator or institutional support
 - BMS, Merck, Adapimmune, Iovance, Mirati, Genentech, Amgen, GSK
- Advisor/Consultant – Perthera, BMS, Geneplus

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Genomic Instability (MMRd), TMB and ICB outcomes



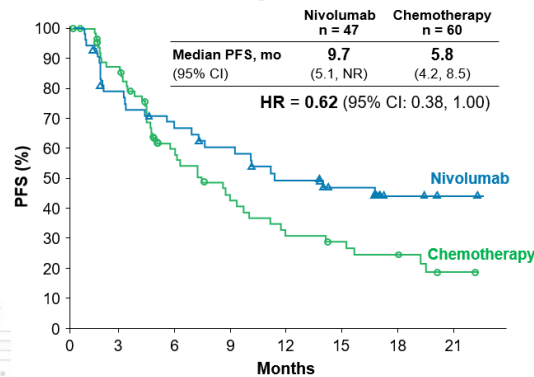
Le et al, *N Engl J Med* 2015; 372:2509-2520

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TMB and ICB outcomes in NSCLC

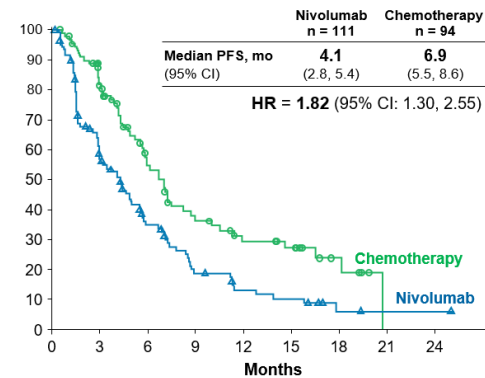
PFS - NSCLC

High TMB



PFS - NSCLC

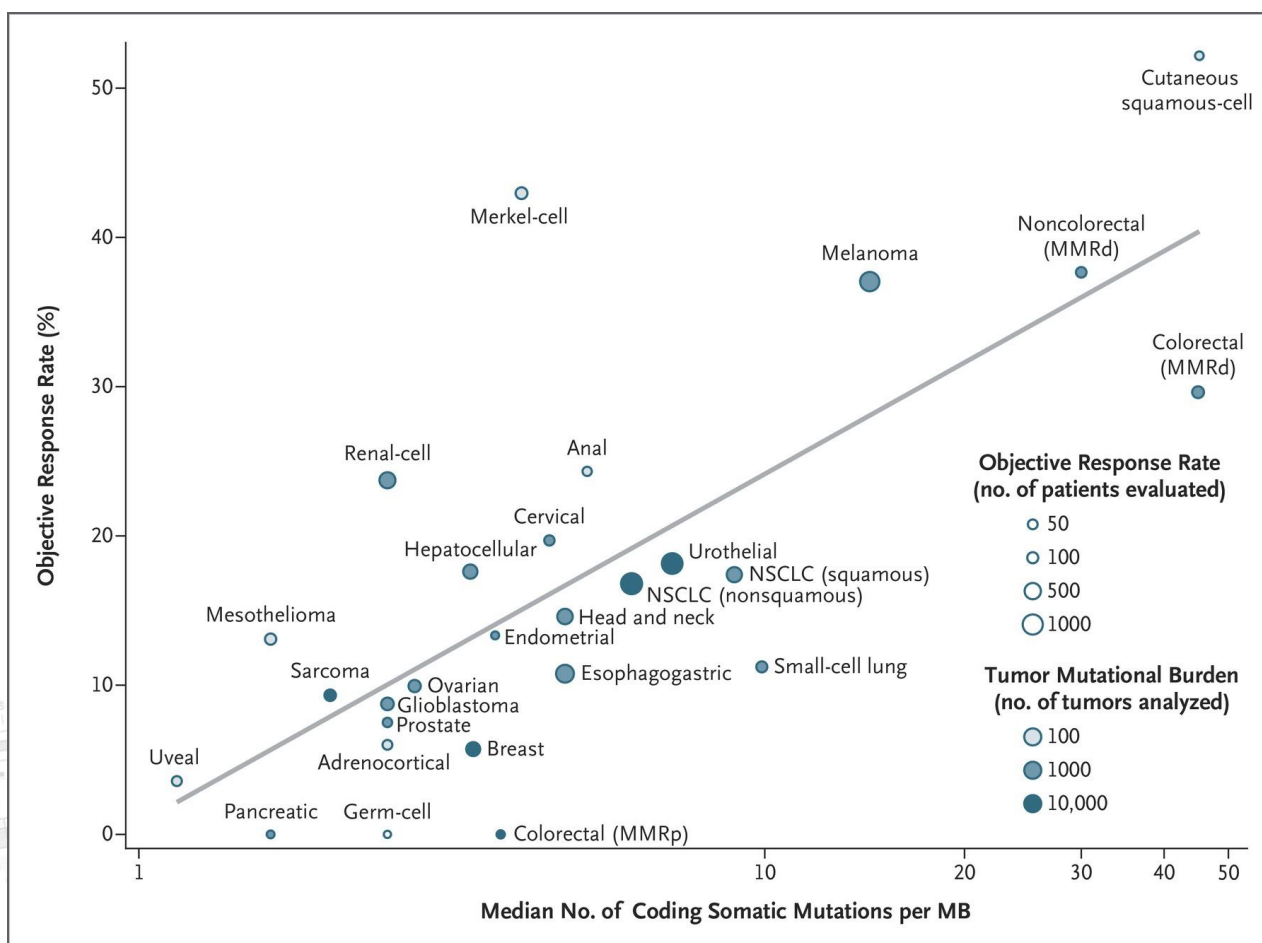
Low/medium TMB



Carbone et al. *N Engl J Med.* 2017;376:2415–2426

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Response to immune checkpoint blockade vs TMB

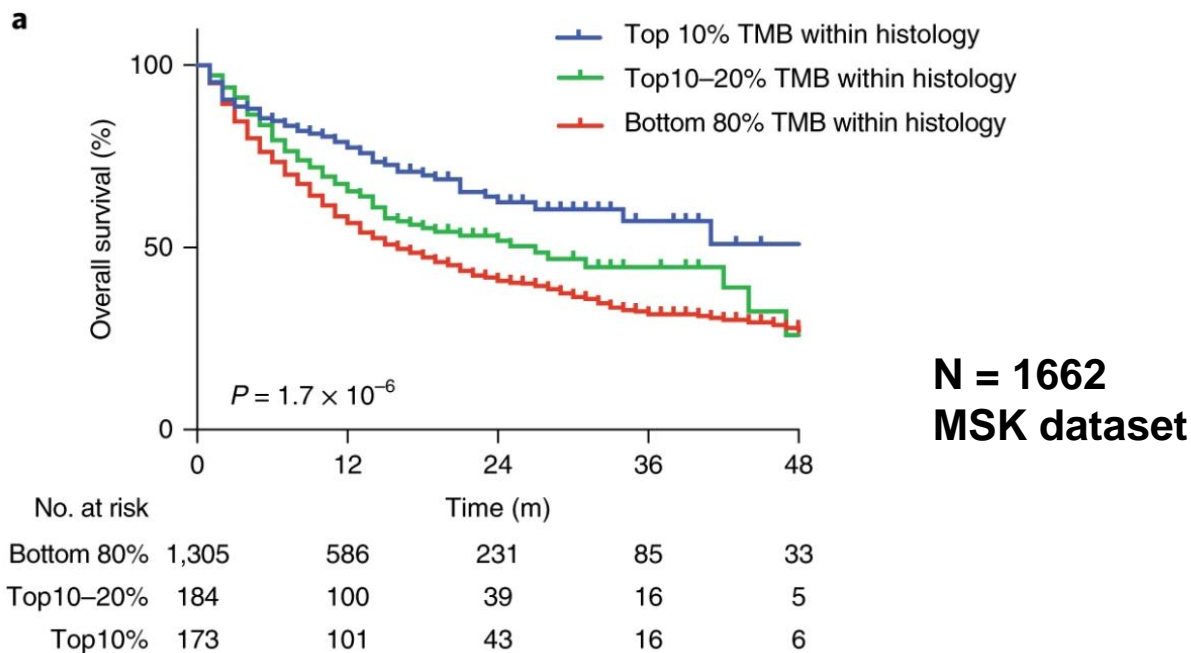


N =27 cancers

Yarchoan M, Hopkins M, Jaffee EM *N Engl J Med*, 2017.

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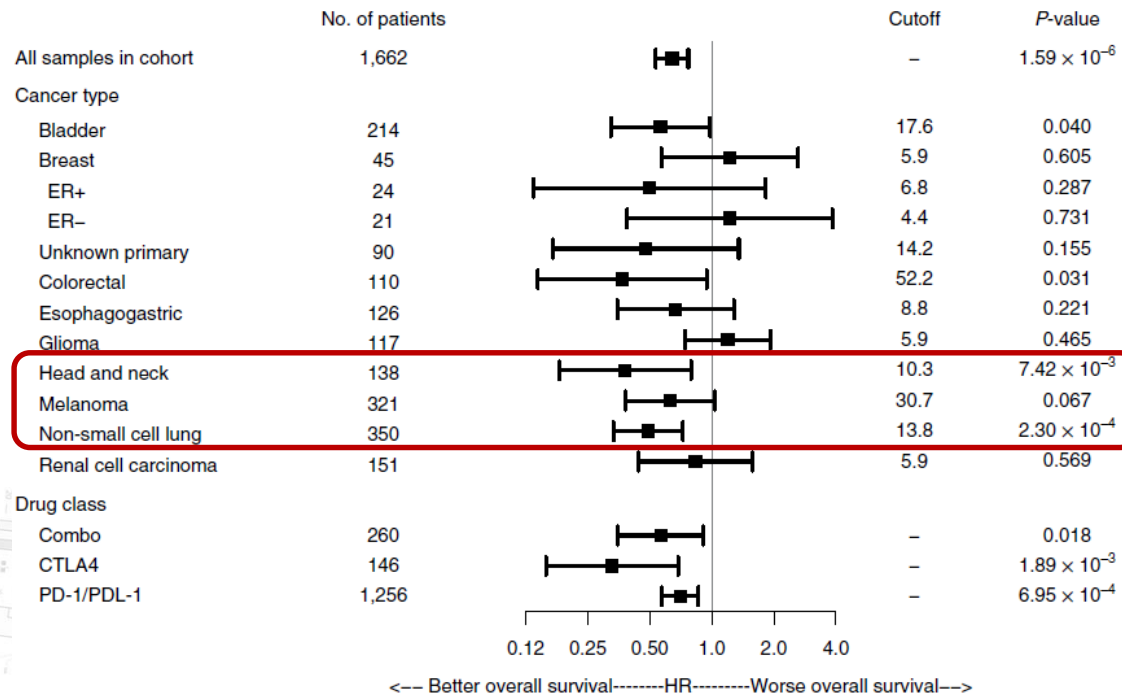
Overall survival vs TMB across cancer types



Nat Genet. 2019 Feb;51(2):202-206

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Effect of nonsynonymous mutational load on overall survival after ICB



Nat Genet. 2019 Feb;51(2):202-206

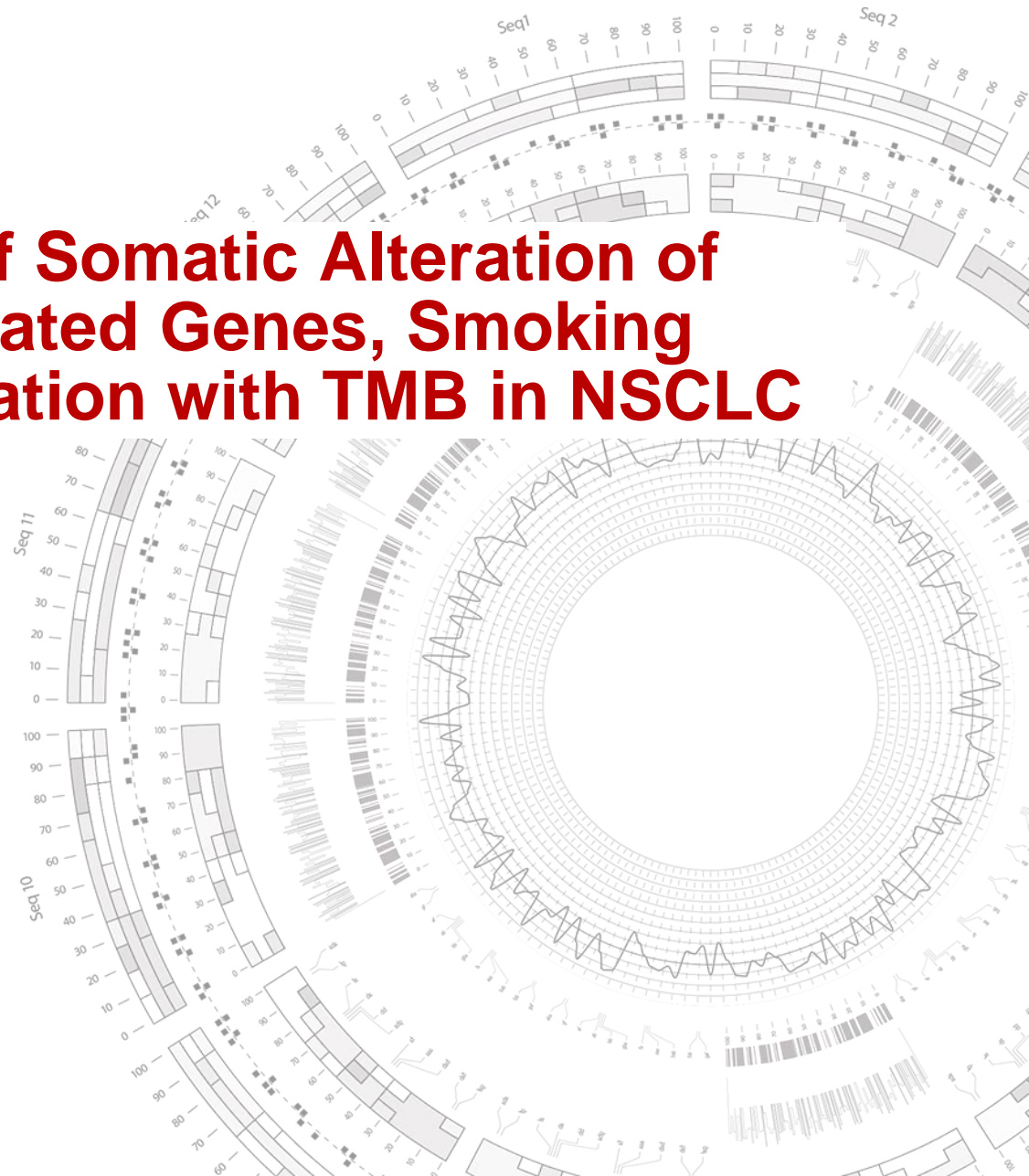
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The Landscape of Somatic Alteration of DNA Integrity-Related Genes, Smoking and Their Association with TMB in NSCLC

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We examined 182 DNA repair genes in 15 repair pathways in TCGA lung dataset

BER	NER	DR	MMR	HR	NHEJ	FA	Conserved DR
21	30	3	13	21	8	17	16
APEX1 (APE1) APEX2 APLF (C2ORF13) LIG3, MBD4 MPG MUTYH (MYH) NEIL1, NEIL2 NEIL3 NTHL1 (NTH1) OGG1 PARP1 (ADPRT) PARP2 (ADPRTL2) PNKP SMUG1 TDG UNG XRCC1 PARP3 (ADPRTL3)	CETN2, FBL3 (FBXL2), RAD23A, RAD23B, RPA1, RPA2, RPA3, XPA, XPC, ERCC6 (CSB) ERCC8 (CSA), MMS19, UVSSA (KIAA1530), XAB2 (HCNP), CCNH, CDK7 DDB1, DDB2 (XPE), ERCC1, ERCC2 (XPD) ERCC3 (XPB) ERCC4 (XPF) ERCC5 (XPG) GTF2H1, GTF2H2 GTF2H3, GTF2H4 GTF2H5 (TTDA) LIG1, MNAT1	ALKBH3 (DEPC1) ALKBH2 (ABH2) MGMT (AGT)	MLH1 MLH3 MSH2 MSH3 MSH4 MSH5 MSH6 PMS1 PMS2 PMS2L3 (PMS5) DUT NUDT1 (MTH1) RRM2B (p53R2)	BRCA1 DMC1 EME1 (MMS4L) EME2 GEN1 GIYD1 (SLX1A) GIYD2 (SLX1B) MRE11A MUS81 NBN (NBS1,RAD21) RAD50, RAD51 RAD51B, RAD51D RAD52 RAD54B RAD54L SHFM1 (DSS1) SMC6L1 XRCC2, XRCC3	DCLRE1C (Artemis) LIG4 NHEJ1 (XLF, Cernunnos) PRKDC (DNA-PK) SIRT1 XRCC4 XRCC5 (Ku80) XRCC6 (Ku70)	BRCA2 (FANCD1) BRIP1 (FANCI) BTBD12 (SLX4) (FANCP) FAAP20 (C1orf86) FAAP24 (C19orf40) FANCA FANCB FANCC FANCD2 FANCE FANCF FANGC (XRCC9) FANCI (KIAA1794) FANCL FANCM PALB2 (FANCN) RAD51C (FANCO)	ATR CHEK1 CHEK2 CLK2 HUS1 MDC1 PER1 RAD1 RAD17 (RAD24) RAD9A RIF1 RRM1 RRM2 TOPBP1 TP53 TP53BP1 (53BP1)
Defective in Disease	Repair Crosslink	Chromatin structure	Polymerase	Nuclease	Ubiquitination	Other	Total
5	2	3	15	8	11	9	182 genes
ATM BLM RBBP8 (CtIP) RECQL4 WRN	TDP1 TDP2 (TTRAP)	CHAF1A (CAF1) H2AFX (H2AX) SETMAR (METNASE)	MAD2L2 (REV7) PCNA, POLB POLD1, POLE POLG, POLH POLI (RAD30B) POLK (DINB1) POLL, POLM POLN (POL4P) POLQ REV1L (REV1) REV3L (POLZ)	APTX (aprataxin) ENDOV EXO1 (HEX1) FAN1 (MTMR15) FEN1 (DNase IV) SPO11 TREX1 (DNase III) TREX2	HLTF (SMARCA3) RAD18, RNF168 RNF4, RNF8 SHPRH SPRTN (c1orf124) UBE2A (RAD6A) UBE2B (RAD6B) UBE2N (UBC13) UBE2V2 (MMS2)	DCLRE1A (SNM1) DCLRE1B (SNM1B) HELQ (HEL308) OBF2B (SSB1) PRPF19 (PSO4) RDM1 (RAD52B) RECQL (RECQ1) RECQL5 RPA4	

Wood RD et al., *Sicence* 291 (2001) and *Mutation Res.* 577, 275 (2005)
DNA Repair and Mutagenesis, 2nd edition (ASM Press, Washington, DC)
Lange SS et al, *Nature Reviews Cancer* 11, 96 (2011)

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Legend
 Loss of function mutations
 Other mutations
 Deep copy number deletions

Lung Adenocarcinoma
 N Tumors: 400 200 0

Lung Squamous Cell Carcinoma
 N Tumors: 0 200 400

Genome Stability Pathway

Other conserved DNA damage response genes

Nucleotide excision repair

Fanconi Anemia

DNA polymerases

Base excision repair

Sensitivity to DNA damaging agents

Homologous recombination

Mismatch excision repair

Non-homologous end-joining

Other DNA repair genes

Ubiquitination and modification

Editing and processing nucleases

Chromatin structure and modification

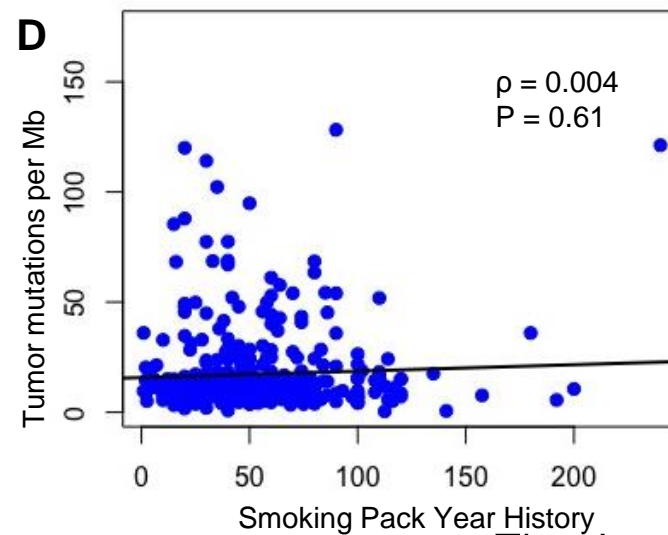
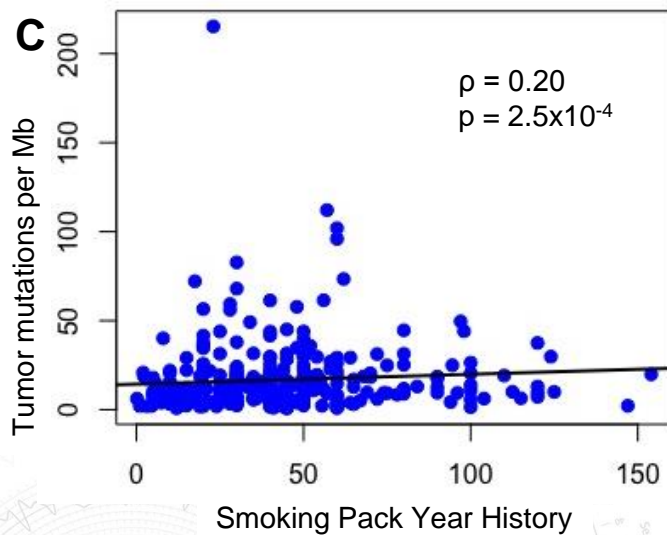
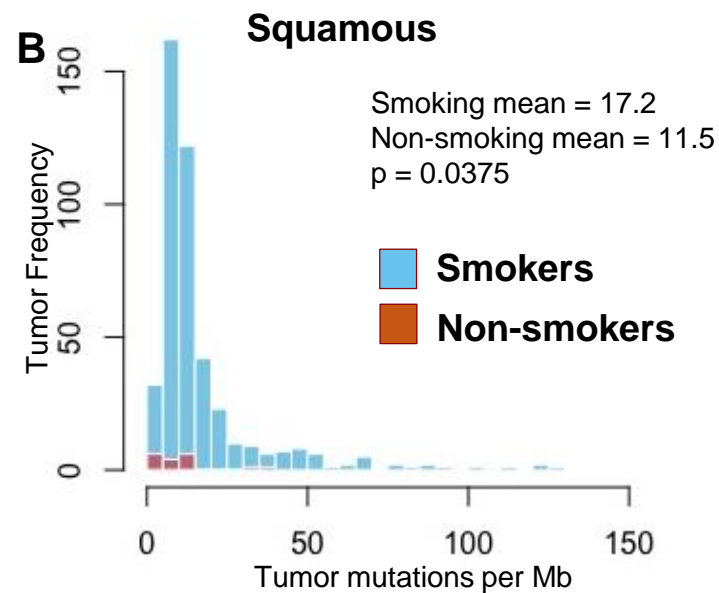
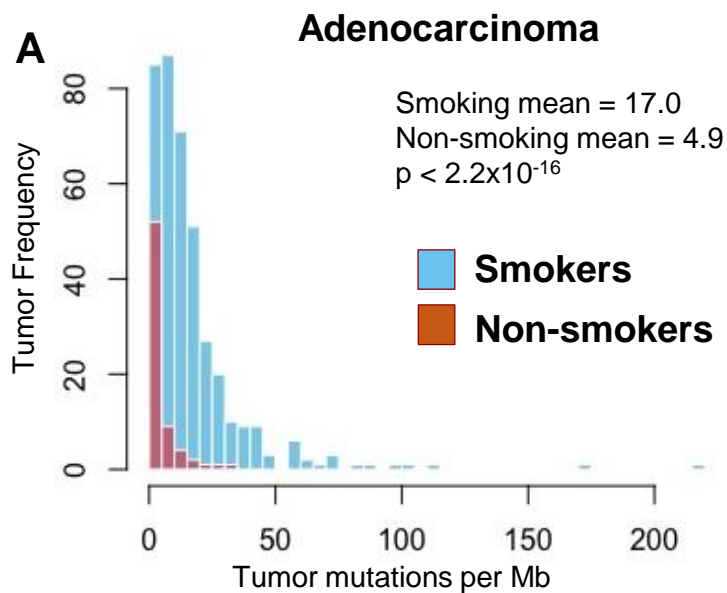
Direct reversal of damage

Modulation of nucleotide pools

Repair of DNA-topoisomerase crosslinks

Landscape of
 alteration of
 genome stability
 related genes
 and pathways in
 NSCLC

Sharpnack MF, ..., He K. in submission



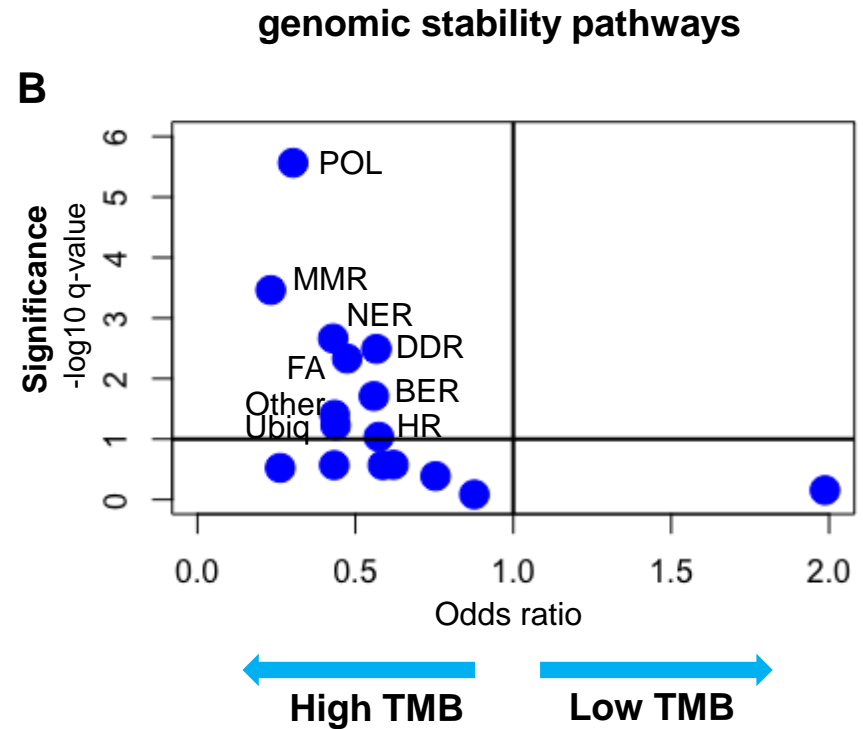
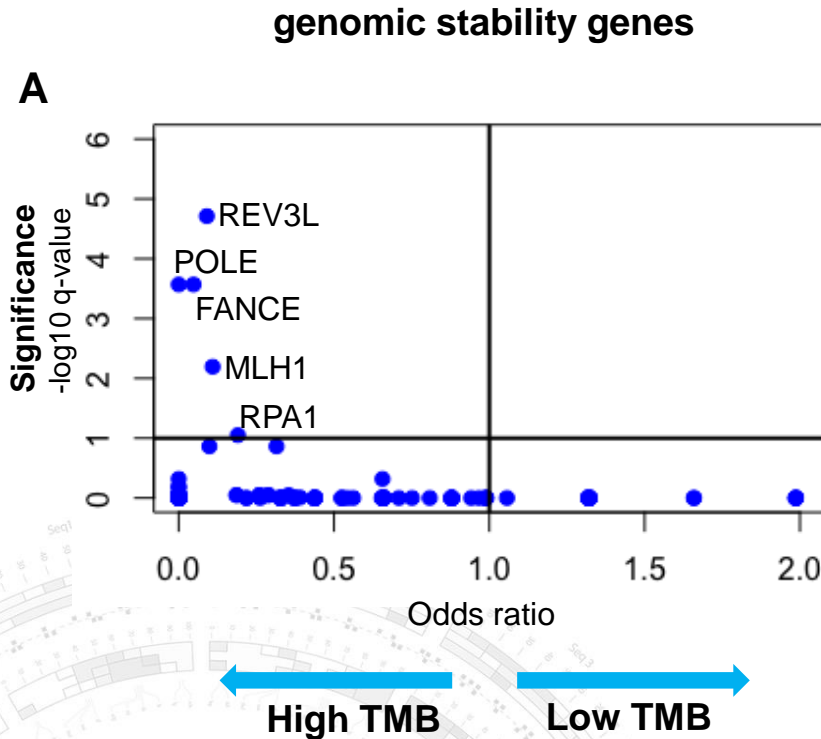
Sharpnack MF, ..., He K. in submission



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Inactivation of genomic stability related genes and pathways vs TMB in NSCLC



Sharpnack MF,, He K. in submission

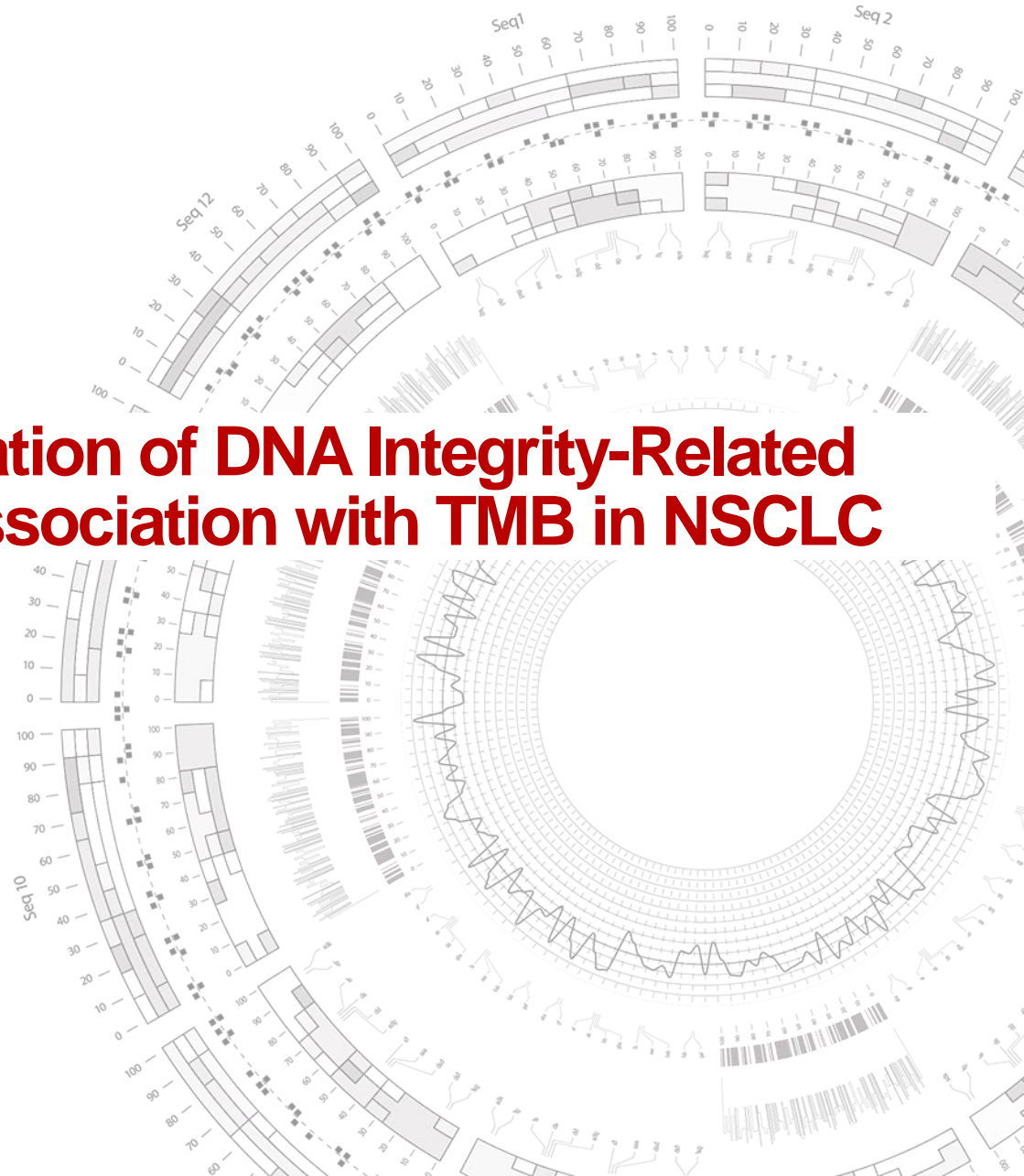
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The Germline Alteration of DNA Integrity-Related Genes and Their Association with TMB in NSCLC

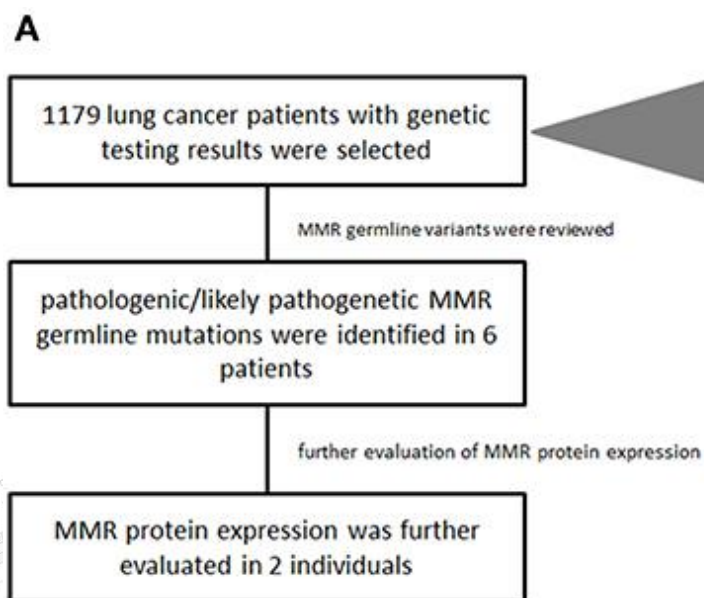
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Germline Mismatch Repair Gene Mutations in Chinese NSCLC With Paired Tumor-Normal NGS



B

Clinicopathologic Characteristics	
Characteristics	N(%)
Median diagnosis age, years (range)	60 (16-87)
Gender	
Male	711 (60.4%)
Female	464 (39.5%)
Histology subtype	
Adenocarcinoma	912 (77.4%)
Squamous	121 (10.3%)
SCLC	29 (2.5%)
Other NSCLC	29 (2.5%)
NA	88 (7.5%)
Clinical stage	
I/II	77 (6.5%)
III	141 (12.0%)
IV	959 (81.3%)
NA	2 (0.2%)
Smoking history	
Never smokers	406 (34.4%)
Smokers	428 (36.3%)
NA	345 (29.2%)

Sun et al, *Front. Oncol.*, 26 June 2019

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Baseline Characteristics and Genetic Testing Results of Lung Cancer Patients with Germline MMR Mutations

Case	Age range at diagnosis	Smoking status	Family history	Histological subtype	Sample type	Germline mutation	TMB (mut/Mb)	MSI	MMR expression	Genes with somatic mutations
1	60–65	NS	Mother, colon cancer	ADC	PB	<i>MSH2</i> NM_000251.2, c.340delG, p.E114Rfs*60	1	N/A	Intact	<i>MAP2K2, GNAS</i>
2	70–75	NS	No	ADC	PB	<i>PMS2</i> NM_000535.5, c.943C>T, p.R315*	1	MSS (PCR)	Intact	<i>PTCH1</i>
3	70–75	NS	No	ADC	FFPE	<i>PMS2</i> NM_000535.5 c.1053delG, p.L351Ffs*5	5	MSS (NGS)	N/A	<i>GNAS, EGFR, MTOR, CUL3, CREBBP, FGFR4, ABCB1</i>
4	55–60	NS	Mother, colon cancer	ADC	FFPE	<i>MSH6</i> NM_000179.2 c.3118T[3>1], p.F1040*	4	MSS (NGS)	N/A	<i>MLL3, EGFR, TP53, RB1, NXF5, CBL</i>
5	65–70	S	No	NSCLC	FFPE	<i>MSH6</i> NM_000179.2 c.4001G>A p.R1334Q	6	MSS (NGS)	N/A	<i>IGF1R, TP53, ARID2, XRCC3, MET, SLC34A2, LRP1B, DICER1</i>
6	75–80	S	Brother, gastric cancer	SCC	FFPE	<i>MSH6</i> NM_000179.2 c.2552_2553dupGC, p.K852Afs*17	8	MSS (NGS)	N/A	<i>ALK, LRP1B, TP53, DNMT3A, HRAS, DDR2, NTM, TCF7L2, POLE</i>

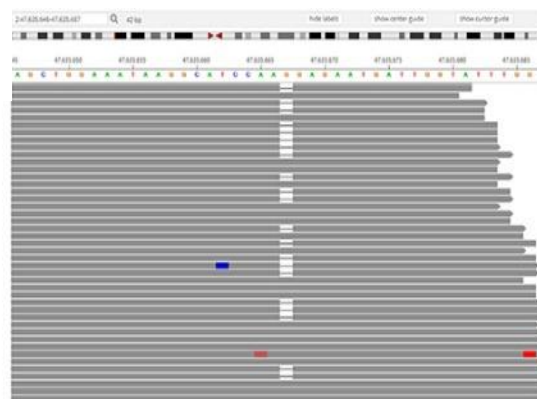
NS, never-smoker; S, smoker; ADC, adenocarcinoma; NSCLC, non-small-cell lung cancer; SCC, squamous-cell carcinoma; PB, peripheral blood; FFPE, formalin fixation and paraffin embedding tissue; TMB, tumor mutation burden; MSI, microsatellite instability; MSS, microsatellite stable; N/A, not available.

Sun et al, *Front. Oncol.*, 26 June 2019

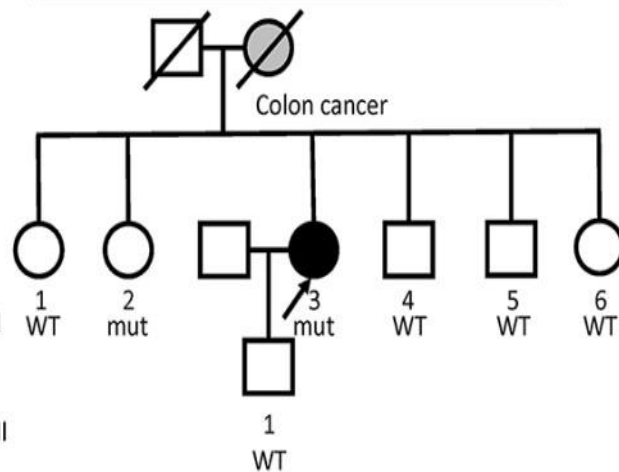
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Germline Mutations Identified in Patients and Their Family Members 1.

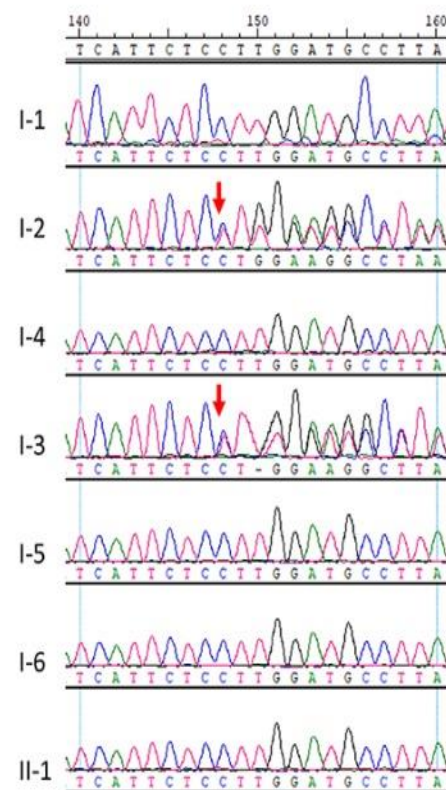
A



B



C



Sun et al, Front. Oncol., 26 June 2019

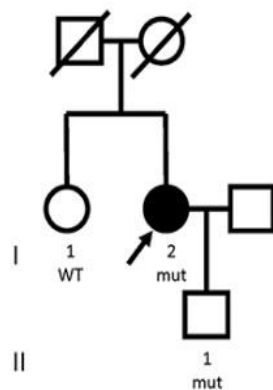
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Germline Mutations Identified in Patients and Their Family Members 2.

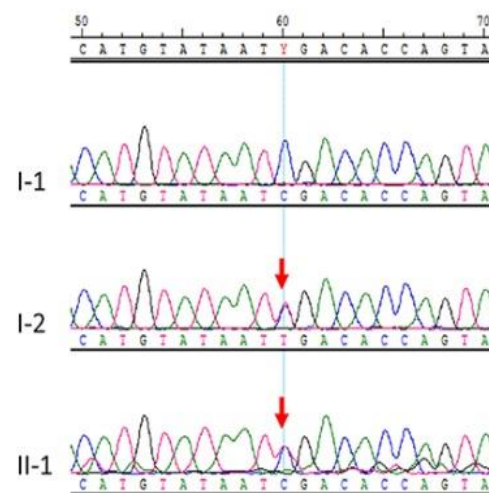
A



B



C



Sun et al, Front. Oncol., 26 June 2019

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Clinical Characteristics of Lung Cancer Patients with Germline Mutation Detected on Routine NGS at OSU

Year	Age	Sex	Histology	Stage	Smoking history	Other cancer	Germline mutation	Other somatic gene alteration	Targeted therapy	Response
2014	37	F	Ad	IA	Former smoker (2 pack year)	No	<i>BRCA2</i>	not evaluated	—	—
2014	72	F	Ad	IV	Former smoker	Breast cancer Lung cancer	<i>EGFR</i> T790M	<i>EGFR</i> G719S	Rociletinib	SD
2015	69	F	Ad	IIIA	Former smoker	Breast cancer Uterine cancer	<i>BRCA2</i>	<i>EGFR</i> L858R	—	—
2015	50	F	SCLC	IA	Never smoker	Breast cancer	<i>TP53</i> Y236* <i>PARK2</i> Q347*	<i>FGFR2</i> amplification	—	—
2016	34	F	Ad	IV	Former smoker	No	<i>BRCA2</i> L3061*	<i>MET</i> 3028+2T>C (splice site mutation)	Crizotinib	PR
2016	44	F	Ad	IV	Never smoker	Orbital Rhabdomyosarcoma	<i>TP53</i>	<i>ALK</i> fusion	Crizotinib	PR
2017	62	F	SCLC	IV	Former smoker	Breast cancer	<i>BRCA1</i>	not evaluated	—	—

Abbreviations: F, Female; Ad, Adenocarcinoma; SCLC, Small Cell Lung Cancer; SD, Stable Disease; PR, Partial Response

Shukuya et al, J Thorac Oncol. 2018 Feb;13(2)

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Case:

A 34 year old female former smoker with lung adenocarcinoma (metastatic pleural effusion) patient with *BRCA2* L3061*.

She has no personal or family history of breast or ovarian cancer. She was treated with pleural catheter placement, four cycles of carboplatin plus pemetrexed followed by two cycles of maintenance pemetrexed, and four doses of nivolumab. She had germline genetic testing which confirmed the *BRCA* mutation.

Foundation ACT
Blood Sample

Adenocarcinoma of Lung

Alterations	Mutation allele frequency
<i>BRCA2</i> L3061*	50.7%
<i>MET</i> 3028+2T>C (splice site mutation)	0.19%

Shukuya et al, J Thorac Oncol. 2018 Feb;13(2)

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Germline Mutations in DNA Integrity-Related Genes and Other Genes in Pan-Cancers

Identification GPV Using Matched Tumor-Normal Sequencing in Pan-Cancer Patients in China

1. Surveyed the germline variants in 7363 Chinese patients across more than 18 diverse cancer types.
2. Germline variants in 62 cancer-susceptibility genes were called from a 1021 gene NGS panel analyzing matched normal DNA.
3. Investigated the germline mutations in DNA integrity-related genes and their impacts on somatic mutation landscape.

Sharpnack M,....., He K, ASCO 2018, manuscript in submission

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Summary

1. Inactivation selected DNA instability related genes and pathways are associated with increased TMB in NSCLC
2. Smoking is not a sufficient substitute biomarker for TMB in NSCLC.
3. PGVs in MMR genes were detected in 6/1,179 NSCLC patients. All of them are heterozygous and MSS. TMB was 4.5 muts/MB. Testing of family members identified new Lynch syndrome cases in two first-degree relatives.
4. Targeted matched tumor-normal NGS reveals PGVs commonly exist in patients with cancers of diverse tissue origin, which is valuable in therapeutic interventions and genetic risk analysis.
5. We are creating a multivariate model of tumor mutation burden and studying the potential role as therapeutic biomarkers of immune checkpoint inhibition in NSCLC.

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Acknowledgments

- The patients and families who made clinical trials and studies possible.
- OSU James Thoracic Oncology Center: David P. Carbone, MD, PhD, Director, and others.
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- Bioinformatics: Kun Huang, PhD (IU);
- Other Collaborators: Renhua Guo, MD, Nangjing, Geneplus, Beijing, China; James Herman, MD (UPMC), and others
- Appreciate CAHON support!

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Thank you!



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