Keck School of Medicine of USC

CARIS PRECISION ONCOLOGY ALLIANCE

Genomic analysis of esophageal carcinoma (EC) identifies recurrent mutations in histone methyltransferases as a distinctive subset

Jingyuan Wang[1], Joanne Xiu[2], MatthewOberley[2], Francesca Battaglin[1], Hiroyuki Arai[1], Shivani Soni[1], Wu Zhang[1], Richard M. Goldberg[3], Anthony F. Shields[4], Axel Grothey[5], Jimmy J. Hwang[6], John L. Marshall[7], Igor Astaturov[8], Benjamin A. Weinberg[7], Emil Lou[10], Michael J Hall[11], Rachna T. Shroff[12], Moh'd Khushman[13], Mohamed E. Salem[14], Davendra P.S. Sohal[15], Aaron J. Scott[12], Sanjay Goel[16] and Heinz-Josef Lenz[1]

[1] University of Southern California, Los Angeles, California [2] Caris Life Sciences, Phoenix, Arizona, USA.[3] West Virginia University Cancer Institute, Morgantown, West Virginia.[4] Karmanos Cancer Institute, Wayne State University, Detroit, Michigan.[5] West Cancer Center and Research Institute, Germantown, TN.[6] Levine Cancer Institute, North Carolina [7] Georgetown University Medical Center, Washington, D.C.[8] Fox Chase Cancer Center, Philadelphia, Pennsylvania.[9] University of Miami/Sylvester Comprehensive Cancer Center, Miami, Florida [10] University of Minnesota, Minneapolis, Minnesota [11]Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA. [12] Division of Hematology/Oncology, University of Arizona Cancer Center, Tucson, AZ.[13] Mitchell Cancer Institute, University of South Alabama.[14] Levine Cancer Institute, Carolinas HealthCare System, Charlotte, North Carolina.[15] Cleveland Clinic, Cleveland, Ohio [16] Rutgers Cancer Institute of New Jersey, New Brunswick, NJ.

Abstract ID: 379

wangjy_2015pku@163.com

Introduction

Histone-lysine N-methyltransferase 2 (KMT2) family proteins methylate lysine 4 on the histone H3 tail at important regulatory regions in the genome and thereby impart crucial functions through modulating chromatin structures and DNA accessibility[1], which is associated with tumorigenesis and immune tolerance, indicating its possible correlation with the efficacy of immunotherapy.

Recurrent mutations of *KMT2* have been identified in EC, but data addressing the molecular features of *KMT2* mutated (MT) EC are lacking. We aimed to understand the molecular profile of *KMT2*-MT EC.

Methods

A total of 787 oesophageal carcinoma [adenocarcinoma (EAC), N=604; squamous cell carcinoma (ESCC), N=183] were analyzed using next-generation sequencing (NGS) and immunohistochemistry (Caris Life Sciences, Phoenix, AZ).

Tumor mutational burden (TMB) was calculated based on somatic nonsynonymous mutations, and mismatch repair deficiency (dMMR)/microsatellite instability-high (MSI-H) status was evaluated by a combination of IHC, Fragment analysis and NGS.

For PD-L1 expression, PD-L1 SP142 clone was used. PD-L1 positivity was defined as TPS≥1.

Immune-related overall survival (irOS) was defined as the time from initial immunotherapy treatment to the day of death or the end of follow-up.

[1] Oncogene 2021, 40, 4894-4905

Results

Fig1. KMT2 mutations in oesophageal carcinoma [adenocarcinoma (EAC), N=604; squamous cell carcinoma (ESCC), N=183].

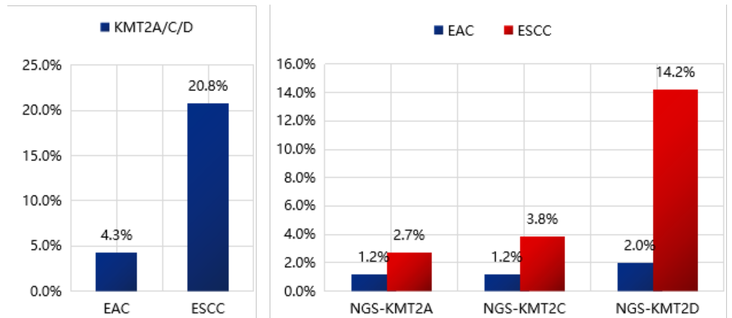


Fig2. Mutational landscape of KMT2-MT EA patients, compared with KMT2-WT EA patients. However, in ESCC there were no significant differences in gene mutations between the KMT2-MT and WT groups.

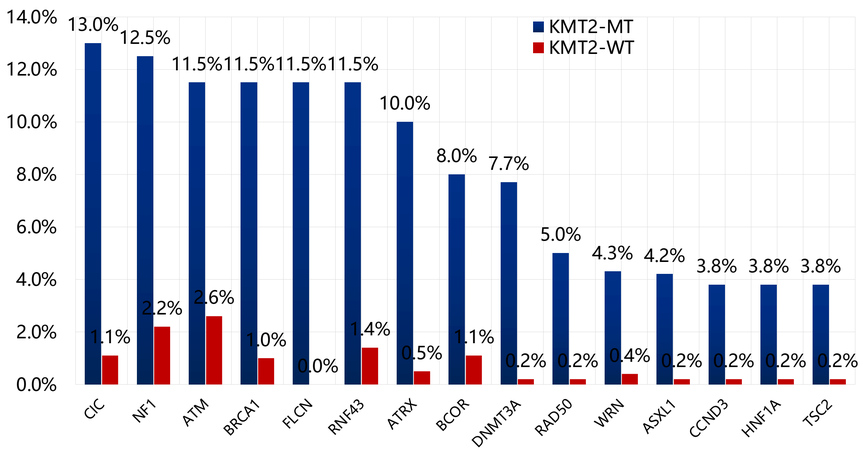


Fig3. TMB in EAC and ESCC with KMT2-MT, compared with KMT2-WT EA patients.

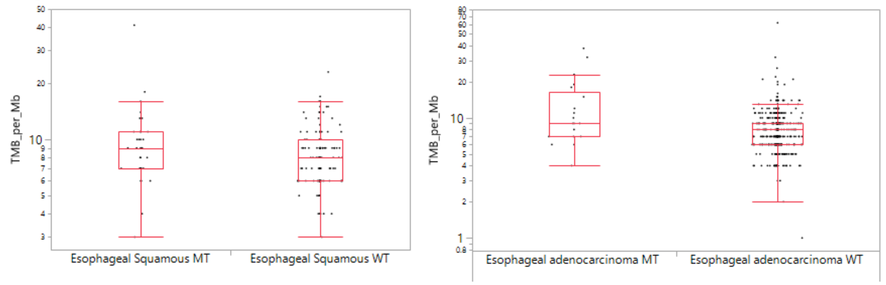


Fig4. Immune-related markers in EAC and ESCC with KMT2-MT, compared with KMT2-WT patients.

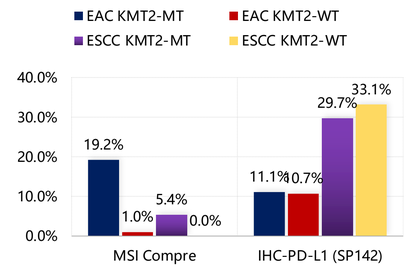
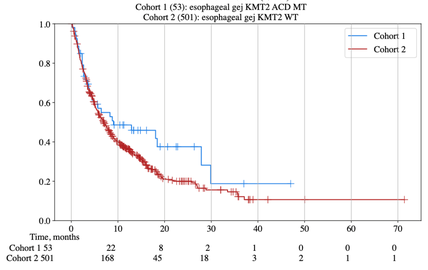


Fig5. KMT2 mutations on irOS in EC patients.



Conclusion

This is the largest study to investigate the distinct genomic landscapes between KMT2-MT and WT EC to date. Our data showed the KMT2-MT EC has a distinctive genetic profile, indicated by higher TMB, and higher frequency of dMMR/MSI-H and gene mutations involved in DDR and epigenetic regulation. Understanding these molecular characteristics may be informative in the development of effective treatment strategies in KMT2-MT EC.