Case Report

# The influence of *STK11* mutation on acquired resistance to immunotherapy in advanced non-small cell lung cancer with Lynch syndrome: a case report and literature review

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**Abstract:** Immune checkpoint inhibitors (ICI) monotherapy or combination therapies have become increasingly popular in patients with advanced non-small cell lung cancer (NSCLC). However, there are still many unknowns concerning the predictive bio-markers and resistance mechanisms to immunotherapy. Patients with primary tumor *STK11* mutation reportedly to have a lower response rate than the *STK11* wild-type and possibly a primary resistance mechanism to ICIs. However, there is presently no data regarding the contribution of *STK11* to acquired resistance to ICIs. Herein we report on a patient who was diagnosed with advanced lung squamous cell carcinoma accompanied by Lynch syndrome. The patient developed an *STK11* mutation after receiving pembrolizumab as a first-line treatment. Programmed death ligand 1 (PD-L1) was highly expressed (50%) in the biopsy. *HRAS* Q61L and *TP53* R158L were mainly detected. Unexpectedly, the patient carried an *MSH6* heterozygous germline mutation, and was classified as proficient mismatch repair (pMMR). The patient subsequently received pembrolizumab (200 mg, ivgtt, q3w) as first line therapy and achieved stable disease (SD) as the best response. After eight treatment cycles, the patient suffered disease progression (PD), and an *STK11* frameshift mutation was newly identified in his plasma circulating tumor deoxyribonucleic acid (ctDNA). This case study suggests that *STK11* could contribute to pembrolizumab acquired resistance. Furthermore, the patient was also diagnosed with Lynch syndrome, which rarely occurs in lung cancer.

**Keywords:** Immunotherapy resistance; *STK11*; *MSH6*; Lynch syndrome; case report

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## Introduction

Over the past decade, immune checkpoint inhibitors (ICIs) have changed the treatment paradigm for non-small cell lung cancer (NSCLC). Some characteristics have been investigated as positive predictive biomarkers for ICI therapy, including programmed death ligand 1 (PD-L1), microsatellite instability-high (MSI-H), tumor mutational burden (TMB), and human leukocyte antigen (HLA). Moreover, a segment of patients is unable to respond well to programmed cell death protein (PD-1)/PD-L1 inhibitors. Previous research has suggested that *EGFR* mutations, *ALK* fusion, *STK11* mutations, and loss of *PTEN* are related to poor response (1-4). However, the existence of acquired resistance mechanisms remains unclear. Although colorectal cancer with Lynch syndrome might respond well to ICIs (5), the effectiveness of ICIs in lung cancer is uncertain due to the distant relationship between lung cancer and Lynch syndrome (6). In this paper, we report a patient diagnosed with advanced lung squamous cell carcinoma with a background of Lynch syndrome and high

PD-L1 expression. Pembrolizumab monotherapy was administered as a first-line treatment and successfully reduced the tumor size. However, the disease progressed, and an *STK11* frameshift mutation was found in the patient's plasma circulating tumor deoxyribonucleic acid (ctDNA) 6 months later. This case raises a few important questions that deserve further investigation: (I) could *STK11* contribute to immunotherapy's acquired resistance mechanism? (II) Does Lynch syndrome play a role in this case? We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1639).

## Case presentation

A 76-year-old Chinese male presented with a cough and bloody sputum in November 2017. He had a 50-year smoking history and a family history of gastric cancer (brother) and colon cancer (sister). He had no previous history of other disease. The image results during diagnosis and immunotherapy were shown in *Figure 1*. Computed tomography (CT) of the chest showed masses in the upper lobe and hilar of right lung, accompanied by mediastinal lymphadenopathy (*Figure 1A*). There were no other signs of distant metastasis observed by positron emission tomography–CT (PET-CT). Bilateral bronchial abnormalities were found by fibrobronchoscopy, and squamous cell carcinomas were identified by the lower left and upper right lung biopsies (*Figure 2A*). PD-L1 was highly expressed (50%) in bilateral lung biopsies, which were elucidated by immunohistochemistry (IHC) using an anti-PD-L1 antibody (22C3) (*Figure 2B*). Next-generation sequencing (NGS) using 1,021 cancer-related genes (Appendix 1) was performed on the tissue. Ten mutations including *HRAS* c.182A>T (p.Q61L) (allele fraction/AF, 41.2%) and *TP53* c.473G>T (p.R158L) (AF, 68.0%) were detected (*Table 1*), and *STK11* was identified as wild-type. There was no targetable variation, and the tumor mutational burden (TMB) was 8.0Muts/Mb, which was rated as low (from the Geneplus database). Unexpectedly, one heterozygous germline mutation, *MSH6* c.2552_2553dupGC (p.K852Afs*17), was detected in the white blood cells (*Table 1*, *Figure 3*). However, the IHC results suggested normal expression of MLH1, MSH2, MSH6 and PMS2 in his tumor biopsy, and it was classified as proficient mismatch repair (pMMR) (*Figure 4*). Based on the hereditary aspect of Lynch syndrome, genetic counseling for his daughter and granddaughter found an equivalent mutation sequence in *MSH6*.

The patient was diagnosed with stage IV right lung squamous cell carcinoma (cT3N3M1a). Pembrolizumab (200 mg, ivgtt, q3w), a monoclonal anti-programmed cell death protein 1 (PD-1) antibody, was commenced in November 2017. After four pembrolizumab cycles, chest CT showed that the right hilar mass had decreased by approximately 22%, and the lymph nodes were unchanged (*Figure 1B*). The Response Evaluation Criteria in Solid Tumours (RECIST, v1.1) efficacy evaluation indicated stable disease (SD). However, disease progression (PD) occurred shortly after eight pembrolizumab cycles had been administered (*Figure 1C*). The plasma ctDNA test at PD revealed nine somatic mutations, and an *STK11* c.613delG (p.A205Rfs*82) (AF, 1.1%) frameshift mutation was newly identified compared with the primary tissue (*Table 1*, *Figure 5*). Common terminology criteria for adverse events (CTCAE) assessment revealed grade 1 hepatic injury due to pembrolizumab treatment. The toxicity and side effects were tolerable. Subsequently, the patient received chemotherapy with albumin-bound paclitaxel.

This study was approved by the ethics committee of West China Hospital of Sichuan University (No.587, 2018). All procedures performed in this study involving human participants were following the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

## Discussion

ICI monotherapy or combination therapies have demonstrated survival advantage in patients with advanced NSCLC (2,7,8). Predictive biomarkers for immunotherapy are still under exploring. Retrospective analysis has suggested that high PD-L1 expression and MSI-H were associated with a higher objective response rate (ORR) to PD-1/PD-L1 inhibitors (9), however *ALK* rearrangement and *EGFR* mutation usually does not benefit from immunotherapy (10). Loss of *PTEN*, *JAK1/2*, and amplification of *MDM2/4* are been reportedly associated with anti-PD-1/PD-L1 resistance or hyperprogressors in other tumors (11-13).

*STK11* is an onco-suppressor gene that is frequently inactivated in 8% of NSCLCs (14). Koyama *et al.* demonstrated reduced expression of PD-L1 in a genetically engineered murine model (GEMM) of *KRAS*-driven/*STK11*-deficient NSCLC compared to *KRAS*-driven/

 

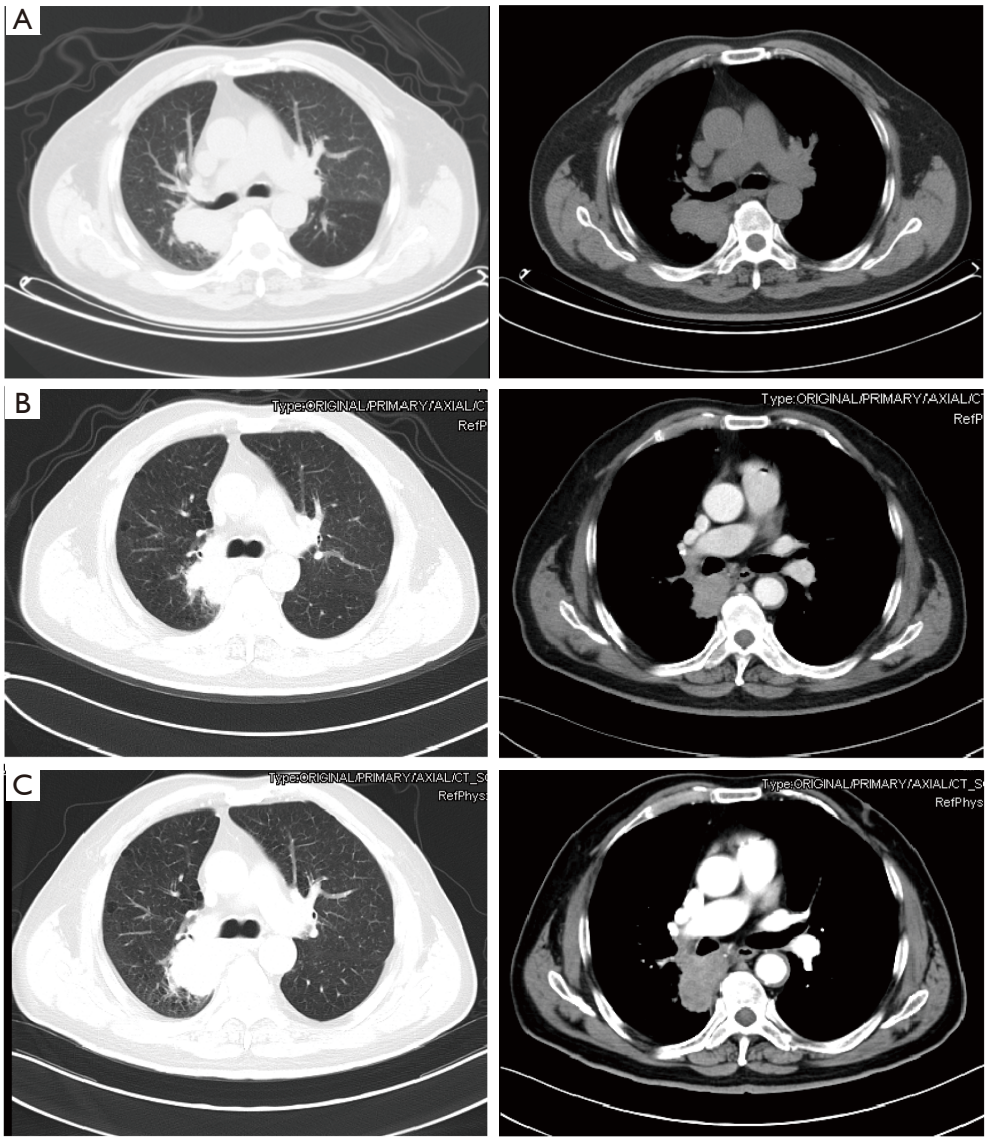


**Figure 1** Chest computed tomography (CT) images. (A) Before pembrolizumab; (B) four cycles of pembrolizumab, efficacy evaluation was SD (stable disease); (C) eight cycles of pembrolizumab, efficacy evaluation was PD (disease progression).

*STK11*-normal status, and *STK11*-deficient tumors were found to be resistant to the anti-PD-1 antibody (15). *STK11*-inactivating mutations can modulate the immune milieu of the lung tumor microenvironment, and offer specific implications for addressing *STK11*-mutated tumors with PD-1-targeting antibody therapies (16). Targeted NGS results from 240 NSCLC patients who were treated with a PD-1/PD-L1 antibody suggested that *STK11* variants were significantly enriched in the no durable benefit (NDB) group compared to the non-ICI NSCLC group (17). The studies above suggest primary (early) resistance to immunotherapy in patient with an *STK11* mutation. This raises a question regarding whether the *STK11* mutation might be one of the acquired (late) resistance mechanism of immunotherapy. Truncating mutations of *B2M* and *JAK1/2* have been distinguished as acquired resistance factors of PD-1 blockade immunotherapy in melanoma (13). However, in this case, *STK11* was a newly identified mutation in the patient's plasma, which was not found in the primary tissue. Thus, the relationship between *STK11* mutation and acquired resistance to pembrolizumab in NSCLC requires further research.

 

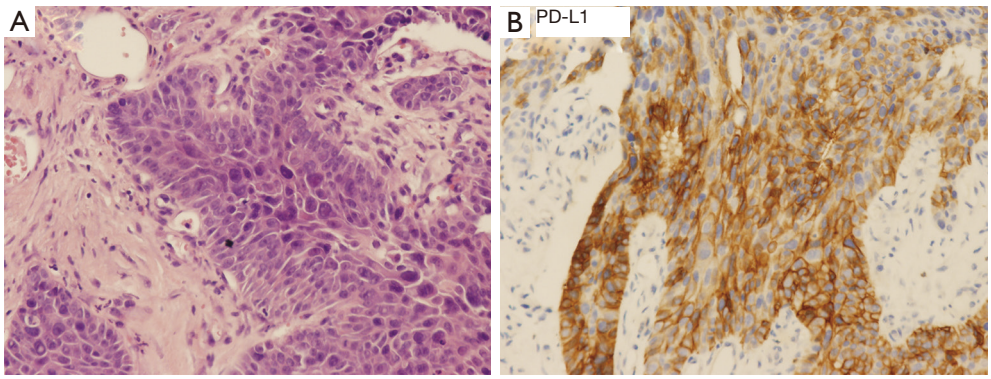


**Figure 2** Pathology images of HE and PD-L1 expression. (A) Hematoxylin and eosin (HE) of tumor (×200); (B) immunohistochemical (IHC) of PD-L1 expression (×200).

**Table 1** Somatic mutation and germline mutation in tissue, ctDNA and white blood cells

| Gene | cHGVS | pHGVS | Allele frequency | |
|---|---|---|---|---|
| | | | Pre-pembrolizumab (tissue) | Post-pembrolizumab (plasma) |
| *ALK* | c.1648-1G>T | – | 40.20% | 2.40% |
| *LRP1B* | c.11131G>T | p.V3711F | 36.60% | 2.10% |
| *LRP1B* | c.12037C>A | p.L4013M | 36.80% | 2.00% |
| *TP53* | c.473G>T | p.R158L | 68.00% | 1.80% |
| *DNMT3A* | c.1803G>A | p.W601* | 38.20% | 1.70% |
| *HRAS* | c.182A>T | p.Q61L | 41.20% | 1.60% |
| *DDR2* | c.1005_1006delGGinsTT | p.V336L | 35.90% | 1.40% |
| *STK11* | c.613delG | p.A205Rfs*82 | ND | 1.10% |
| *DNMT3A* | c.2204A>G | p.Y735C | ND | 0.80% |
| *NTM* | c.719C>T | p.T240I | 38.20% | ND |
| *TCF7L2* | c.1259G>C | p.R420P | 1.50% | ND |
| *POLE* | c.1736G>T | p.R579L | 1.20% | ND |
| *MSH6* | c.2552_2553dupGC | p.K852Afs*17 | Germline mutation, heterozygous | |

ctDNA, circulating tumor deoxyribonucleic acid; ND, not detected.

Hereditary nonpolyposis colorectal cancer (HNPCC), also called Lynch syndrome, is an autosomal dominant familial cancer syndrome caused by MMR gene germline mutation. MMR gene "second-hit" has been frequently found in Lynch syndrome-related cancers, and mostly with MSI-H (18). Furthermore, colorectal cancer with MSI-H has shown a superior response to immunotherapy (5). Although an *MSH6* germline mutation was identified in this NSCLC patient, the MMR proteins were normally expressed. However, whether there is any correlation between Lynch syndrome and lung cancer remains unclear as the data regarding Lynch syndrome and lung cancer is limited. The patient had a family history of gastric and colon cancers, which are related to Lynch syndrome. Considering that Lynch syndrome increases the risk of developing various cancers, the patient should monitor for a second tumor, and family members who have *MSH6* germline mutation should pay attention to cancer screenings.

Our study describes a high PD-L1 expression NSCLC

 

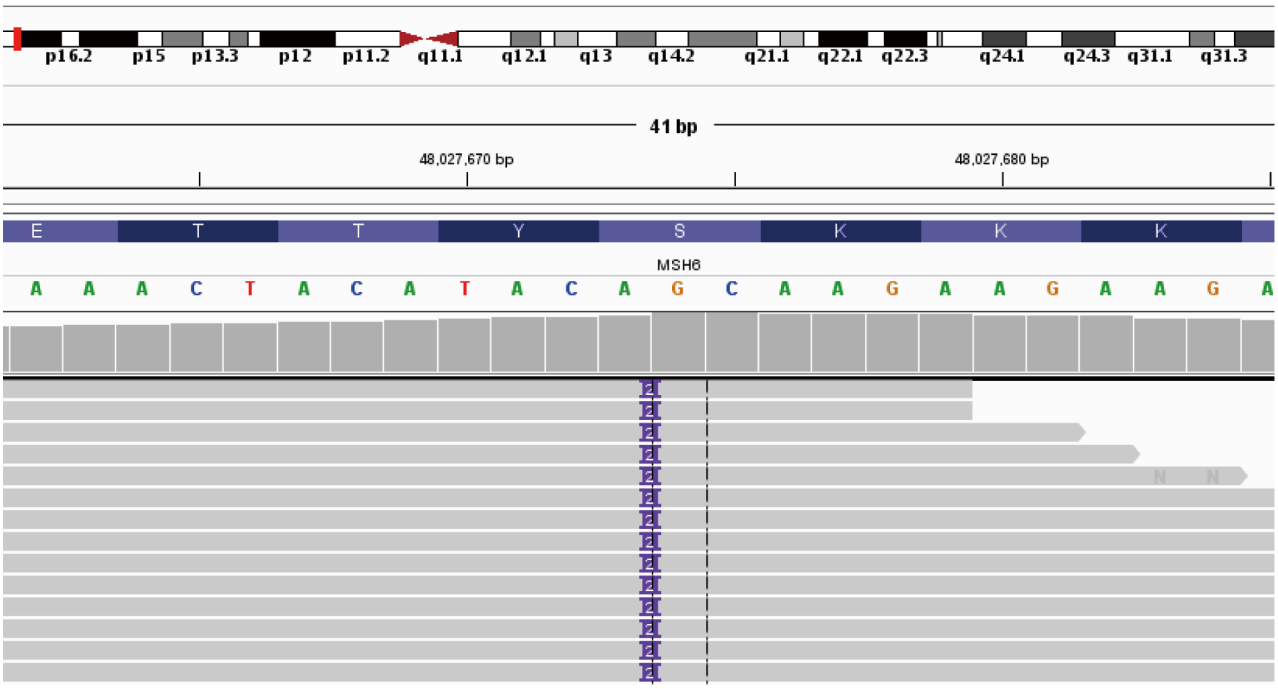


**Figure 3** Schematic representation of *MSH6* c.2552_2553dupGC (p.K852Afs*17) germline mutation in the patient, patient's daughter and patient's granddaughter.

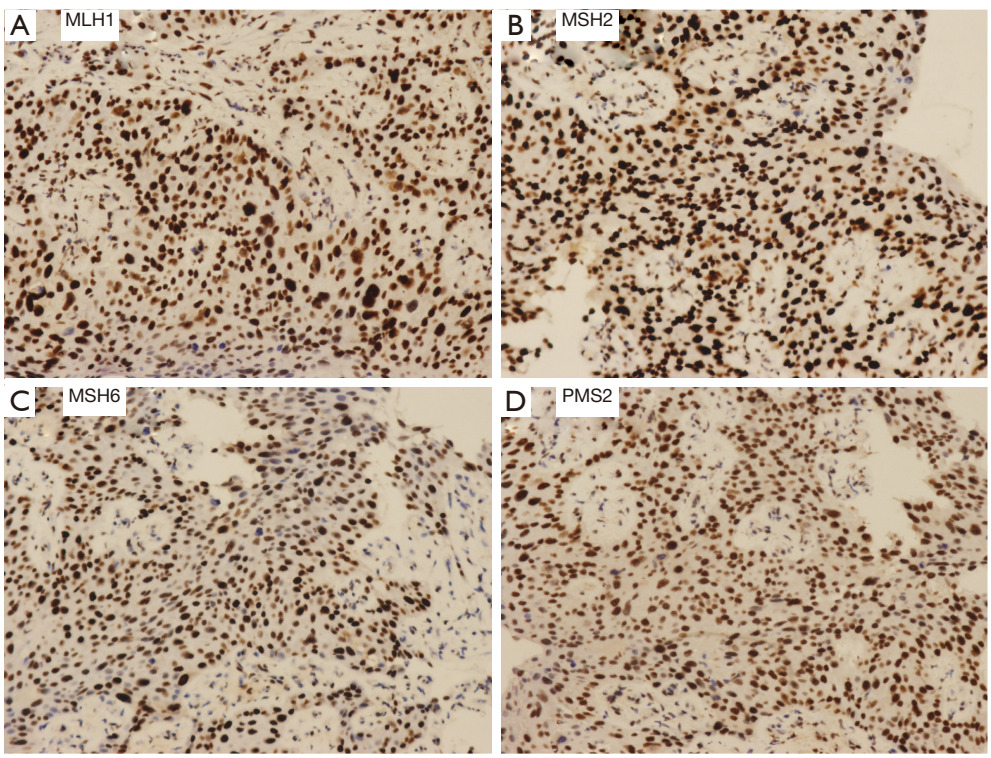


**Figure 4** Pathology images of mismatch repair proteins. Immunohistochemical (IHC) of (A) MLH1, (B) MSH2, (C) MSH6, and (D) PMS2 expression (×200).

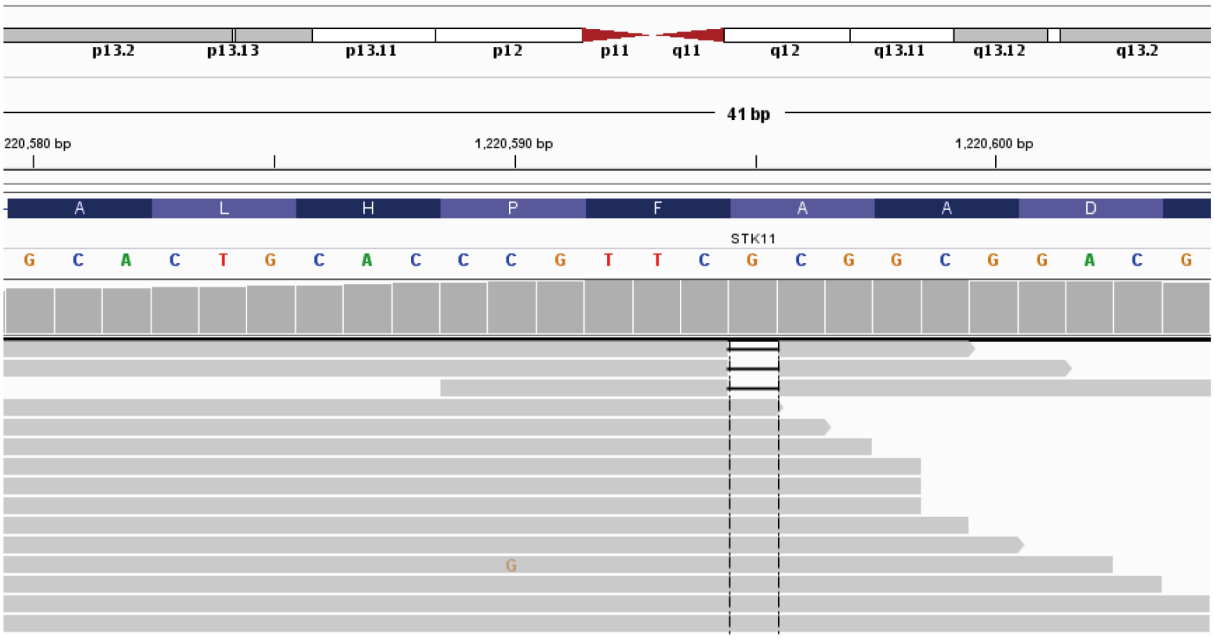


**Figure 5** Schematic representation of *STK11* c.613delG (p.A205Rfs*82) somatic mutation in the patient's plasma after pembrolizumab treatment.

patient with an *MSH6* germline mutation, who was treated with pembrolizumab as first-line therapy. The patient's disease progressed in 6 months. An *STK11* frameshift mutation was newly-discovered in his plasma by NGS. Moreover, the coincidental discovery of Lynch syndrome added complexity to clinical diagnosis and treatment. The impact of *STK11*, Lynch syndrome, and PD-L1 expression on the efficiency of PD-1 inhibitors requires further discussion and research.

## Conclusions

At present, there are too many unknowns in cancer immunotherapy. This case provided one possibility that *STK11* frameshift mutations may contribute to pembrolizumab secondary resistance. Dynamic gene surveillance in plasma might contribute to efficacy prediction during cancer immunotherapy. Given its scarcity, lung cancer with Lynch syndrome is rarely reported, however, the correlation between them requires further research.

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## Footnote

*Reporting Checklist*: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-1639

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1639). The authors have no conflicts of interest to declare.

*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committee of West China Hospital of Sichuan University (No.587, 2018). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.



 

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## Appendix 1 1,021 cancer-related gene panel which used to detect genetic variation by next-generation sequencing in tissue and plasma ctDNA samples

*All exons*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *ABL1* | *ABL2* | *ACVR1B* | *AKT1* | *AKT2* | *AKT3* | *ALK* | *APC* | *AR* | *ARAF* |
| *ARID1A* | *ARID1B* | *ARID2* | *ASXL1* | *ATM* | *ATR* | *ATRX* | *AURKA* | *AURKB* | *AXIN1* |
| *AXIN2* | *AXL* | *B2M* | *BAP1* | *BARD1* | *BCL2* | *BCL2L1* | *BCOR* | *BLM* | *BMPR1A* |
| *BRAF* | *BRCA1* | *BRCA2* | *BRD4* | *BRIP1* | *BTK* | *C11orf30* | *CASP8* | *CBFB* | *CBL* |
| *CCND1* | *CCND2* | *CCND3* | *CCNE1* | *CD274* | *CDC73* | *CDH1* | *CDK12* | *CDK4* | *CDK6* |
| *CDK8* | *CDKN1A* | *CDKN1B* | *CDKN2A* | *CDKN2B* | *CDKN2C* | *CEBPA* | *CHEK1* | *CHEK2* | *CIC* |
| *CREBBP* | *CRKL* | *CSF1R* | *CTCF* | *CTNNA1* | *CTNNB1* | *CUL3* | *CYLD* | *DAXX* | *DDR1* |
| *DDR2* | *DICER1* | *DNMT3A* | *EGFR* | *ELAC2* | *EME2* | *EP300* | *EPAS1* | *EPCAM* | *EPHA2* |
| *EPHA3* | *EPHA5* | *EPHB2* | *EPHB6* | *ERBB2* | *ERBB3* | *ERBB4* | *ERCC1* | *ERCC3* | *ERG* |
| *ERRFI1* | *ESR1* | *EXT1* | *EXT2* | *EZH2* | *FAM123B* | *FAM175A* | *FANCA* | *FANCC* | *FANCD2* |
| *FANCG* | *FANCM* | *FAS* | *FAT1* | *FAT2* | *FBXW7* | *FCGR2A* | *FCGR3A* | *FGFR1* | *FGFR2* |
| *FGFR3* | *FGFR4* | *FH* | *FLCN* | *FLT1* | *FLT3* | *FLT4* | *FOXA1* | *FOXL2* | *FOXP1* |
| *FUBP1* | *GAB2* | *GALNT12* | *GATA3* | *GNA11* | *GNAQ* | *GNAS* | *GRIN2A* | *HDAC1* | *HDAC4* |
| *HGF* | *HNF1A* | *HOXB13* | *HRAS* | *HSP90AA1* | *IDH1* | *IDH2* | *IFNG* | *IFNGR1* | *IGF1R* |
| *IL7R* | *INPP4B* | *IRF2* | *IRS2* | *JAK1* | *JAK2* | *JAK3* | *KDM5A* | *KDM5C* | *KDM6A* |
| *KDR* | *KEAP1* | *KIT* | *KRAS* | *LRP1B* | *MAP2K1* | *MAP2K2* | *MAP2K4* | *MAP3K1* | *MAPK1* |
| *MAX* | *MCL1* | *MDM2* | *MDM4* | *MED12* | *MEN1* | *MET* | *MITF* | *MLH1* | *MLH3* |
| *MLL* | *MLL2* | *MLL3* | *MPL* | *MRE11A* | *MS4A1* | *MSH2* | *MSH3* | *MSH6* | *MTOR* |
| *MUTYH* | *MYC* | *MYCL1* | *MYCN* | *MYD88* | *NBN* | *NCOR1* | *NDUFA13* | *NF1* | *NF2* |
| *NOTCH1* | *NOTCH2* | *NOTCH3* | *NOTCH4* | *NPM1* | *NRAS* | *NSD1* | *NTHL1* | *NTRK1* | *NTRK3* |
| *PALB2* | *PAX5* | *PBRM1* | *PCK1* | *PDCD1LG2* | *PDGFRA* | *PDGFRB* | *PDK1* | *PHF6* | *PIK3CA* |
| *PIK3CB* | *PIK3CG* | *PIK3R1* | *PIK3R2* | *PMS1* | *PMS2* | *POLD1* | *POLE* | *POT1* | *PPM1D* |
| *PRKAR1A* | *PTCH1* | *PTCH2* | *PTEN* | *PTPN11* | *RAD50* | *RAD51* | *RAD51B* | *RAD51C* | *RAD51D* |
| *RAF1* | *RARA* | *RB1* | *RBM10* | *RET* | *RHEB* | *RHOA* | *RICTOR* | *RINT1* | *RNASEL* |
| *RNF43* | *ROS1* | *RPS6KB1* | *RUNX1* | *SDHA* | *SDHAF2* | *SDHB* | *SDHC* | *SDHD* | *SERPINB3* |
| *SERPINB4* | *SETD2* | *SLX4* | *SMAD2* | *SMAD4* | *SMARCA4* | *SMARCB1* | *SMARCE1* | *SMO* | *SOX2* |
| *SOX9* | *SRC* | *STAG2* | *STAT3* | *STK11* | *SUFU* | *SYK* | *TBX3* | *TCF7L2* | *TET2* |
| *TGFBR2* | *TMEM127* | *TMPRSS2* | *TNFAIP3* | *TOP1* | *TOP2A* | *TP53* | *TP73* | *TSC1* | *TSC2* |
| *VEGFA* | *VHL* | *WT1* | *XPO1* | *XRCC2* | *XRCC3* | *ZFHX3* | *ZMAT3* | | |

*Introns, promotor, rearrangement point regions*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *ALK* | *BCL2L11* | *BRAF* | *BRCA1* | *BRD4* | *CD74* | *EGFR* | *EML4* | *ERG* | *ETV6* |
| *EZR* | *FGFR1* | *FGFR2* | *FGFR3* | *KIF5B* | *KIT* | *MAML2* | *MET* | *MSH2* | *MYC* |
| *MYCL1* | *NCOA4* | *NOTCH2* | *NTRK1* | *NTRK2* | *NTRK3* | *PDGFRA* | *PMS2* | *PPARG* | *RAF1* |
| *RET* | *ROS1* | *RSPO2* | *SLC34A2* | *TERT* | *TFE3* | *TMPRSS2* | *TPM3* | | |


http://dx.doi.org/10.21037/apm-20-1639

***Partial exons***

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *ABCA13* | *ABCB1* | *ABCC1* | *ABCC11* | *ABCC2* | *ABCG2* | *ACACA* | *ACIN1* | *ACTB* | *ACTG1* |
| *ACTG2* | *ACVR2A* | *ACVRL1* | *ADAM29* | *ADAMTS5* | *ADCY1* | *AFF1* | *AFF2* | *AFF3* | *AFF4* |
| *AHNAK* | *AKAP9* | *ALB* | *AMOT* | *ANGPT1* | *ANK3* | *ANKRD27* | *ANKRD30A* | *ANKRD30B* | *ANKRD36B* |
| *APEX1* | *APOBEC3B* | *ARAP3* | *ARFGEF1* | *ARFGEF2* | *ARHGAP26* | *ARHGAP29* | *ARHGAP35* | *ARID4B* | *ARNT* |
| *ASCL4* | *ASH1L* | *ASMTL* | *ASPM* | *ASTN1* | *ASXL2* | *ATIC* | *ATP12A* | *ATP11B* | *ATP1A1* |
| *ATP2B3* | *BAZ2B* | *BBS9* | *BCAS1* | *BCL11A* | *BCL11B* | *BCL2A1* | *BCL2L11* | *BCL3* | *BCL9* |
| *BCLAF1* | *BCORL1* | *BCR* | *BIRC2* | *BIRC3* | *BMPR2* | *BNC2* | *BPTF* | *BRD2* | *BRD3* |
| *BRSK1* | *BRWD1* | *BTLA* | *BUB1* | *C15orf23* | *C15orf55* | *C1QA* | *C1S* | *C3orf70* | *C7orf53* |
| *C8orf34* | *CACNA1D* | *CACNA1E* | *CADM2* | *CAMTA1* | *CAPN7* | *CARD11* | *CASP1* | *CASQ2* | *CBLB* |
| *CBR1* | *CBR3* | *CCDC168* | *CCNA1* | *CCNB3* | *CCT3* | *CCT5* | *CCT6B* | *CD22* | *CD33* |
| *CD5L* | *CDA* | *CDH11* | *CDH18* | *CDH23* | *CDK13* | *CHD1* | *CHD1L* | *CHD3* | *CHD4* |
| *CHD6* | *CHD8* | *CHD9* | *CHFR* | *CHI3L1* | *CHN1* | *CIITA* | *CKS1B* | *CLCC1* | *CLDN18* |
| *CLP1* | *CLSPN* | *CLTC* | *CNOT3* | *CNOT4* | *CNTN1* | *CNTN5* | *CNTNAP1* | *CNTNAP5* | *COL1A1* |
| *COL2A1* | *COL5A1* | *COL5A2* | *COL5A3* | *COPS2* | *CPS1* | *CREB3L1* | *CRIPAK* | *CRLF2* | *CRNKL1* |
| *CRTC1* | *CRYBG3* | *CSF1* | *CSF3R* | *CSMD1* | *CSMD3* | *CSNK1A1* | *CSNK1G3* | *CSNK2A1* | *CTLA4* |
| *CTNNA2* | *CTNND1* | *CUX1* | *CYBA* | *CYP19A1* | *CYP1B1* | *CYP1A1* | *CYP2A13* | *CYP2C19* | *CYP2C8* |
| *CYP2D6* | *CYP3A4* | *CYP3A5* | *DCC* | *DDX3X* | *DDX5* | *DEK* | *DHX35* | *DHX9* | *DIAPH1* |
| *DIS3L2* | *DLC1* | *DMD* | *DNAH6* | *DNAJC11* | *DNM2* | *DNMT1* | *DOCK2* | *DOCK7* | *DOT1L* |
| *DPYD* | *DRGX* | *DTX1* | *DUSP22* | *DYSF* | *EBF1* | *ECT2L* | *EEF1A1* | *EGR3* | *EIF2AK3* |
| *EIF2C3* | *EIF3A* | *EIF4G3* | *ELF1* | *ELF3* | *ELF4* | *ELL* | *ELMO1* | *ELN* | *EMID2* |
| *EPC1* | *EPHA1* | *EPHA4* | *EPHA7* | *EPHB1* | *EPHB4* | *EPOR* | *EPPK1* | *EPS15* | *ERBB2IP* |
| *ERCC2* | *ESR2* | *ETS1* | *ETV1* | *ETV5* | *ETV6* | *EWSR1* | *EZR* | *F8* | *FAM131B* |
| *FAM135B* | *FAM157B* | *FAM22A* | *FAM46C* | *FAM5C* | *FAP* | *FASLG* | *FAT3* | *FAT4* | *FCGR1A* |
| *FCGR2B* | *FCRL4* | *FGF10* | *FGF14* | *FGF23* | *FGF3* | *FGF4* | *FGF6* | *FKBP5* | *FLG* |
| *FLI1* | *FLNC* | *FMN2* | *FMR1* | *FN1* | *FNDC4* | *FOXA2* | *FOXO3* | *FOXQ1* | *FRG1* |
| *FRMPD4* | *FUS* | *FXR1* | *FYN* | *FZD1* | *G3BP1* | *G3BP2* | *GABRA6* | *GATA2* | *GFRAL* |
| *GIGYF1* | *GKN2* | *GLB1L3* | *GLI1* | *GLI2* | *GLI3* | *GMPS* | *GNA12* | *GNA13* | *GNG2* |
| *GPC3* | *GPR124* | *GPX1* | *GRB7* | *GRM3* | *GSK3B* | *GSTM5* | *GSTP1* | *GUSB* | *H3F3A* |
| *H3F3C* | *HCLS1* | *HCN1* | *HDAC9* | *HECW1* | *HERC2* | *HEY1* | *HIP1* | *HIST1H1C* | *HIST1H1D* |
| *HIST1H1E* | *HIST1H2AC* | *HIST1H2AG* | *HIST1H2AL* | *HIST1H2AM* | *HIST1H2BC* | *HIST1H2BD* | *HIST1H2BJ* | *HIST1H2BK* | *HIST1H2BO* |
| *HIST1H3B* | *HIST1H4I* | *HLF* | *HMCN1* | *HNRPDL* | *HOXA11* | *HOXA13* | *HOXA3* | *HOXA9* | *HOXC13* |
| *HOXD11* | *HOXD13* | *HSD3B1* | *HSD3B2* | *HSP90AB1* | *HSPA8* | *HSPD1* | *HSPH1* | *ICK* | *IFITM1* |
| *IFITM3* | *IGF2* | *IGF2R* | *IGLL5* | *IGSF10* | *IKBKE* | *IKZF1* | *IKZF2* | *IKZF3* | *IL1RAPL1* |
| *IL21R* | *IL6* | *IL6ST* | *IMPG1* | *ING1* | *INHBA* | *INPP4A* | *INPP5D* | *INPPL1* | *IRF4* |
| *IRF6* | *ITGB3* | *ITK* | *ITSN1* | *JARID2* | *KALRN* | *KAT6A* | *KAT6B* | *KCNJ5* | *KCNQ2* |
| *KDM2B* | *KDM3B* | *KEL* | *KIF5B* | *KLB* | *KLF4* | *KLHL6* | *KLK1* | *KRTAP5-5* | *L3MBTL1* |
| *LAMA2* | *LCP1* | *LEF1* | *LGALS8* | *LIFR* | *LPHN2* | *LPP* | *LRP2* | *LRP4* | *LRP5* |
| *LRP6* | *LRRC7* | *LRRK2* | *LYN* | *LZTS1* | *MACF1* | *MAD1L1* | *MAGI2* | *MAGOH* | *MAML2* |
| *MAML3* | *MAP3K13* | *MAPK3* | *MCC* | *MCM3* | *MDH2* | *MECOM* | *MEF2C* | *MGA* | *MIB1* |
| *MIOS* | *MKI67* | *MKL1* | *MLL4* | *MLLT3* | *MLLT6* | *MMP2* | *MMP11* | *MN1* | *MNDA* |
| *MNX1* | *MPO* | *MSH4* | *MSN* | *MSR1* | *MTHFR* | *MTRR* | *MUC5B* | *MYB* | *MYBL2* |
| *MYH10* | *MYH11* | *MYH14* | *MYH9* | *MYO3A* | *NAP1L1* | *NAV3* | *NBPF1* | *NCAM2* | *NCF2* |
| *NCF4* | *NCK1* | *NCOA2* | *NCOR2* | *NCSTN* | *NDRG1* | *NEB* | *NFATC4* | *NFE2L2* | *NFE2L3* |
| *NIN* | *NKX3-1* | *NLRC3* | *NOD1* | *NOS3* | *NQO1* | *NR1I2* | *NR2F2* | *NR4A2* | *NRP2* |
| *NRXN1* | *NTM* | *NTRK2* | *NUMA1* | *NUP107* | *NUP210* | *NUP98* | *OBSCN* | *OGDH* | *OMD* |
| *OPCML* | *OR11G2* | *OR2T4* | *OR4A15* | *OR4C6* | *OR5L2* | *OR6F1* | *P2RY8* | *P4HB* | *PABPC1* |
| *PABPC3* | *PAG1* | *PAK1* | *PAK3* | *PARK2* | *PARP1* | *PASK* | *PAX3* | *PAX7* | *PBX1* |
| *PC* | *PCDH18* | *PCLO* | *PCSK6* | *PCSK7* | *PDCD1* | *PDCD11* | *PDE4DIP* | *PDGFB* | *PDILT* |
| *PER1* | *PGR* | *PHF1* | *PIK3C2A* | *PIK3C2B* | *PIK3C2G* | *PIK3R3* | *PIP5K1A* | *PKD1L2* | *PKHD1* |
| *PLAC8* | *PLAG1* | *PLCB1* | *PLCG1* | *PLCG2* | *PLK1* | *PLXNA1* | *PLXNB2* | *POLQ* | *POLR2B* |
| *POM121* | *POM121L12* | *POTEG* | *POU2AF1* | *PPP1R17* | *PPP2R1A* | *PPP6C* | *PRAM1* | *PRDM1* | *PRDM16* |
| *PREX2* | *PRF1* | *PRKAA1* | *PRKCB* | *PRKCI* | *PRKDC* | *PRRX1* | *PRX* | *PSG2* | *PSIP1* |
| *PSMB1* | *PSMB5* | *PTGS1* | *PTGS2* | *PTK2* | *PTPN13* | *PTPN2* | *PTPRB* | *PTPRD* | *PTPRF* |
| *PTPRJ* | *PTPRK* | *PTPRO* | *PTPRT* | *PTPRU* | *RAB35* | *RAC1* | *RAC2* | *RAD21* | *RAD54B* |
| *RANBP2* | *RASA1* | *RASGRP1* | *RBL1* | *RECQL4* | *REL* | *RELN* | *RFC1* | *RGS3* | *RHOH* |
| *RHOT1* | *RIT1* | *RNF213* | *ROBO1* | *ROBO2* | *ROBO3* | *ROCK1* | *RPGR* | *RPL22* | *RPTOR* |
| *RSPO2* | *RSPO3* | *RUNX1T1* | *RUNX2* | *RXRA* | *RYR1* | *RYR2* | *SBDS* | *SCUBE2* | *SEC31A* |
| *SEMA3A* | *SEMA3E* | *SEMA6A* | *SERP2* | *SERPINA7* | *SETBP1* | *SETDB1* | *SF1* | *SF3A1* | *SF3A3* |
| *SF3B1* | *SFPQ* | *SGCZ* | *SH3PXD2A* | *SHH* | *SI* | *SIN3A* | *SLC16A1* | *SLC1A2* | *SLC22A16* |
| *SLC22A18* | *SLC22A2* | *SLC22A3* | *SLCO1B3* | *SLIT1* | *SLIT2* | *SMAD3* | *SMC1A* | *SMC1B* | *SMURF2* |
| *SNCAIP* | *SNTG1* | *SNX29* | *SOD2* | *SOS1* | *SOX10* | *SOX17* | *SPEN* | *SPOP* | *SPRR3* |
| *SPSB4* | *SPTA1* | *SRD5A2* | *SRGAP1* | *SRGAP3* | *SRSF2* | *SRSF7* | *SSX1* | *STAG1* | *STAT1* |
| *STAT5A* | *SUCLG1* | *SUCLG2* | *SULT1A1* | *SUZ12* | *SVEP1* | *SYNCRIP* | *SYNE1* | *TAF1* | *TAF15* |
| *TAF1L* | *TAL1* | *TBL1XR1* | *TBX15* | *TBX22* | *TCEB1* | *TCERG1* | *TCF12* | *TCF3* | *TCF4* |
| *TCL1A* | *TCP11* | *TEC* | *TENM3* | *TERT* | *TFDP1* | *TFDP2* | *TFE3* | *TGFBR1* | *TGFBR3* |
| *TGM2* | *THBS1* | *THBS2* | *THRAP3* | *TJP1* | *TLE1* | *TLL2* | *TLR4* | *TLX3* | *TMEM132D* |
| *TNN* | *TNPO1* | *TOP2B* | *TP53BP1* | *TP63* | *TPM3* | *TPR* | *TRAF5* | *TRERF1* | *TRIM24* |
| *TRIM58* | *TRIO* | *TRPC5* | *TRRAP* | *TSHR* | *TSHZ2* | *TSHZ3* | *TTF1* | *TTL* | *TUBA3C* |
| *TUBB3* | *TUSC3* | *TXNIP* | *TYMS* | *TYR* | *TYRP1* | *U2AF1* | *UBE2D2* | *UBR5* | *UGT1A1* |
| *UMPS* | *UPF3B* | *USH2A* | *USP6* | *USP8* | *VDAC2* | *VEZF1* | *VIM* | *WASF3* | *WDR90* |
| *WDTC1* | *WHSC1* | *WHSC1L1* | *WIPF1* | *WNK1* | *WNT5A* | *WSCD2* | *WWOX* | *WWP1* | *WWP2* |
| *XBP1* | *XPC* | *XRCC1* | *YBX1* | *YY1AP1* | *ZBTB16* | *ZC3H11A* | *ZFP36L1* | *ZFP36L2* | *ZFPM2* |
| *ZIC3* | *ZNF217* | *ZNF384* | *ZNF521* | *ZNF638* | *ZNF750* | *ZNF804B* | *ZNF814* | | |


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