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Efficacy of chemoimmunotherapy in a lung adenocarcinoma patient with mutations in the *KRAS* and *STK11*

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ABSTRACT

Immunotherapy is a groundbreaking treatment method when it comes to cancer, and this includes non-small-cell lung cancer (NSCLC). In NSCLC patients, immunotherapy is used in a form of immune checkpoint inhibitors (ICIs), and depending on the proportion of tumor cells with programmed death ligand 1 (PD-L1) expression on them, it can be administered either in monotherapy ($\geq 50\%$) or in combination with chemotherapy ($< 50\%$). In this article, we would like to present a case of a female patient with *Kirsten Rat Sarcoma Virus (KRAS)*-mutated lung adenocarcinoma who was responding to chemoimmunotherapy for a long time despite the presence of co-mutation in the *Serine/Threonine Kinase 11 (STK11)* gene, known to worsen immunotherapy outcomes. In this patient, another mutation was found — in the *nibrin (NBN)* gene, which is of uncertain relevance, but it presumably could be connected to a better outcome as it encodes proteins involved in DNA repair. Deficiency in DNA repair may be marked by homologous recombination deficiency (HRD), and there already exists some evidence of better immunotherapy efficacy in patients with HRD. Considering the above, further investigation and thorough genetic diagnostics in NSCLC patients are required to fully understand the background of immunotherapy response.

Key words: chemotherapy, immunotherapy, lung adenocarcinoma, *KRAS* mutation, *NBN* mutation, *STK11* mutation

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Introduction

The KEYNOTE-024 study demonstrated the efficacy of pembrolizumab monotherapy in patients with programmed death ligand 1 (PD-L1) expression on more than 50% of tumor cells. However, later phase III clinical trials, KEYNOTE-189 and KEYNOTE-407, have proven the efficacy of pembrolizumab in combination with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC), regardless of PD-L1 expression on tumor cells [1]. Therefore, in routine clinical practice, chemoimmunotherapy is used in NSCLC patients with PD-L1 expression on fewer than 50% of tumor

cells and after the exclusion of *Epidermal Growth Factor Receptor (EGFR)* gene mutations as well as *Anaplastic Lymphoma Kinase (ALK)* and *ROS Proto-Oncogene 1 (ROS1)* genes rearrangements. In patients with adenocarcinoma, pembrolizumab in combination with platinum-based chemotherapy and pemetrexed is used. Maintenance therapy with pembrolizumab and pemetrexed might be continued after the end of the first phase of treatment. Currently, new therapeutic options have appeared for NSCLC patients with high (atezolizumab, cemiplimab) and low (atezolizumab in combination with chemotherapy and nivolumab plus ipilimumab in combination with limited chemotherapy) PD-L1 expression.

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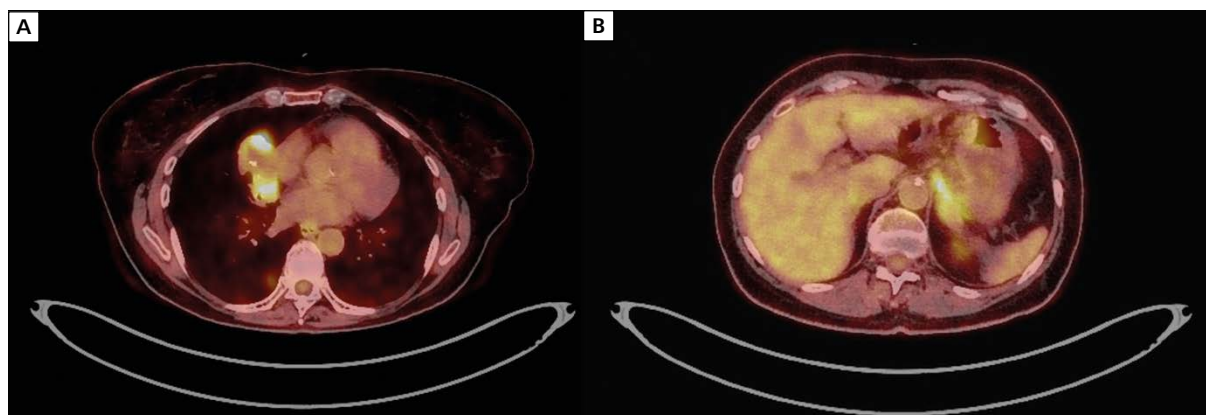


Figure 1. Positron emission tomography–computed tomography (PET-CT) scan images; **A.** An irregular nodal-infiltrative conglomerate in the right pulmonary hilum; **B.** Infiltration between the left adrenal gland and the stomach

The causes of primary and acquired resistance to immunotherapy and chemoimmunotherapy are not fully understood. It seems that they may be related to the molecular status of cancer cells. The presence of mutations in the *EGFR* gene, *ALK*, and *ROS1* gene rearrangements are associated with primary resistance to immunotherapy. These genetic abnormalities usually coexist with the low tumor mutation burden (TMB) in patients, which might be the cause of resistance. On the other hand, the presence of mutations in the *Kirsten Rat Sarcoma Virus (KRAS)* gene, which occurs mainly in smokers, may be associated with high TMB and response to immunotherapy. However, the coexistence of *KRAS* mutations and mutations in suppressor genes, such as *STK11 (Serine/Threonine Kinase 11* also called *Liver Kinase B1, LKB1)*, may result in the lack of response to immunotherapy. Contrarily, the coexistence of mutations in the *KRAS* and *TP53 (tumor protein p53)* genes may increase the effectiveness of immunotherapy [2].

This case report concerns a patient with advanced adenocarcinoma of the lung who benefited from chemoimmunotherapy despite the coexistence of mutations in the *KRAS* gene with the loss of function of two tumor suppressor genes: *STK11* and *nibrin (NBN)*. The patient gave his written consent to participate in the research based on the consent of the local bioethics committee at the Medical University of Lublin (No. KE-0254/160/2021).

Case report

A 69-year-old, non-smoking female patient reported to a pulmonology outpatient clinic due to a persistent dry cough. Chest X-ray, performed in June 2021, revealed infiltration in the area of the right lung hilum. The performance status of the patient was 1 according

to the Eastern Cooperative Oncology Group (ECOG) scale. Hypertension, osteoporosis, and glaucoma were the only comorbidities. Family history included glioblastoma and salivary gland cancer diagnosed in the patient's mother.

In July 2021, a positron emission tomography–computed tomography (PET-CT) was performed. An irregular nodal-infiltrative conglomerate measuring 53 by 35 mm was found in the right pulmonary hilum. (^{18}F) 2-fluoro-2deoxy-D-glucose (^{18}F -FDG) accumulation was uneven and uttermost maximum standardized uptake value (SUV_{max}) was 11.45. In segment 10 of the right lung, a ground glass nodule of 14 mm and SUV_{max} value of 3.2 was visualized (Fig. 1A and 2A).

In addition, there was 45-mm-long infiltration between the left adrenal gland and the stomach with SUV_{max} 5.9 (Fig. 1B and 2C). The stage of the tumor was defined as c.T4N2M1 (stage IV).

Material for pathomorphological examination was collected during bronchoscopy with the endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA). Lung adenocarcinoma (LUAD) was diagnosed in July 2021. Analysis of the basic predictive factors showed no mutations in the *EGFR* gene, no rearrangements in the *ALK* and *ROS1* genes, and PD-L1 expression in 5% of the tumor cells. On this basis, the patient was qualified for chemotherapy with cisplatin and pemetrexed in combination with pembrolizumab immunotherapy based on KEYNOYE 189 study regimen. In the first control computed tomography (CT), partial response was achieved according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The infiltrative-nodal lesion in the left lung hilum decreased to 50 by 20 mm (Fig. 2B). The size of the ground glass nodule did not change. Complete remission was observed in the infiltrative lesion in the abdominal cavity (Fig. 2D). Partial response persisted, and it was

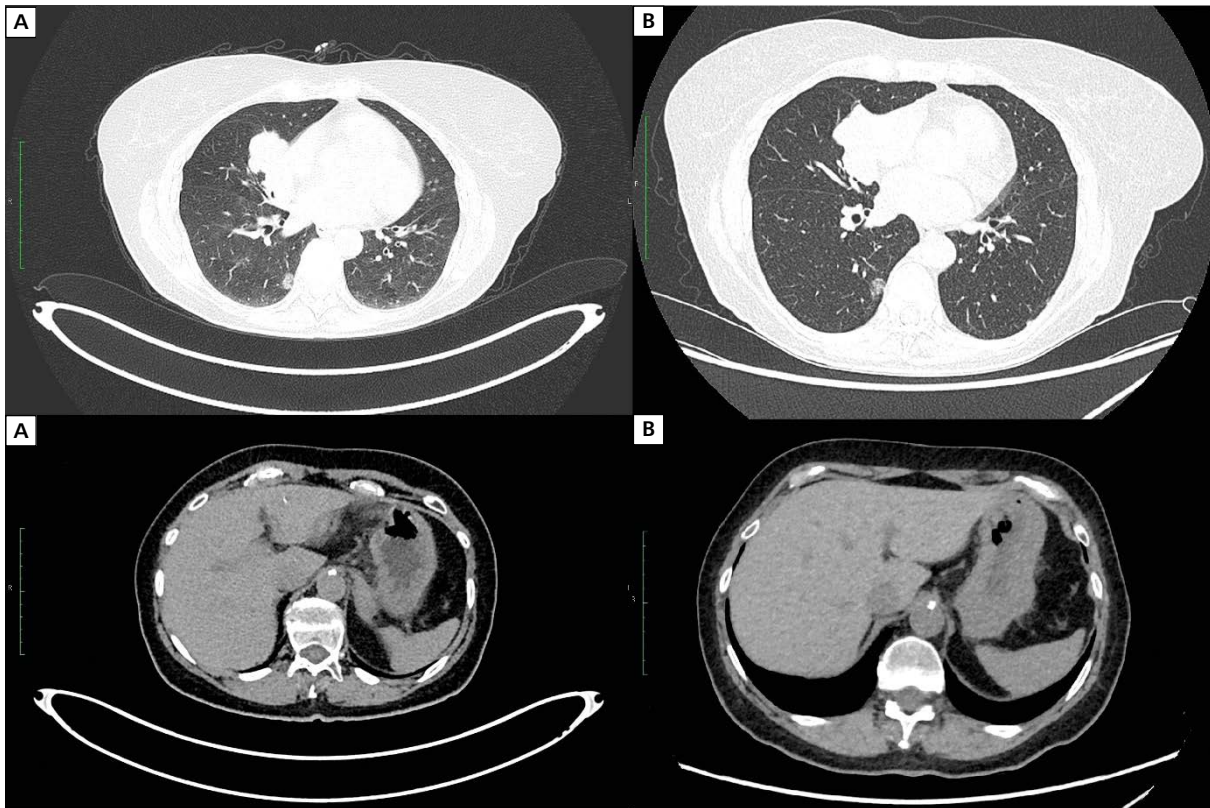


Figure 2. Computed tomography (CT) scan images; **A.** An irregular nodal-infiltrative conglomerate in the right pulmonary hilum; **B.** Partial response of the infiltrative-nodal lesion in the left lung hilum during immunotherapy; **C.** An infiltration between the left adrenal gland and the stomach; **D.** Complete remission of the infiltrative lesion in the abdominal cavity during immunotherapy

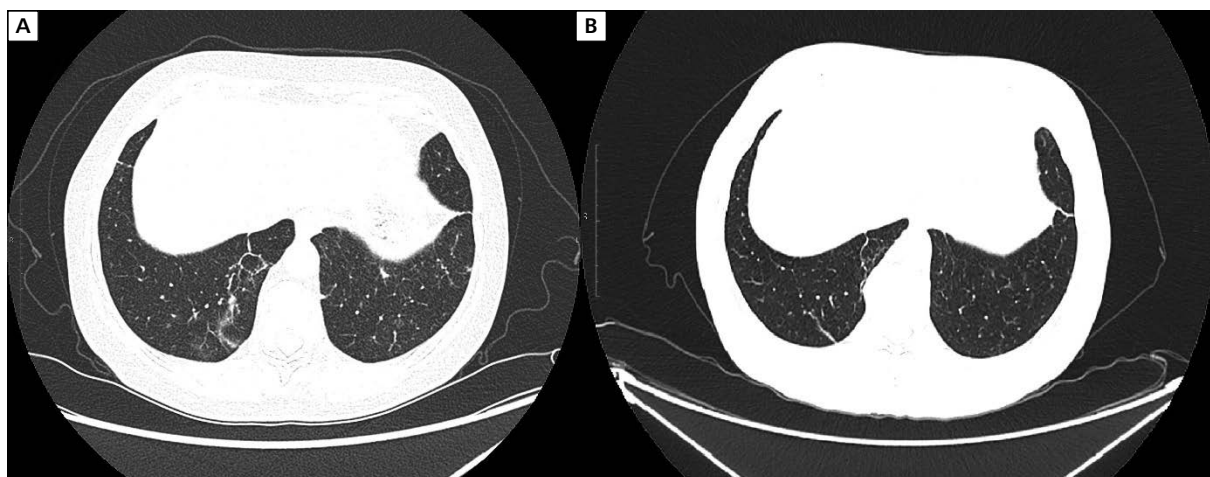


Figure 3. Computed tomography (CT) scan images; **A.** Inflammatory changes in the patient's lungs; **B.** Complete regression of inflammatory lesions

confirmed on subsequent CT scans during maintenance therapy with pemetrexed and pembrolizumab. The partial response continued (last observation in January 2023), resulting in progression-free survival (PFS) of 18 months. Chemotherapy and immunotherapy were very well tolerated.

In April 2022, a control tomography showed inflammatory changes (Fig. 3A) that could be associated with an oligosymptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. The complete regression of these lesions was observed on the next CT performed in July 2022 (Fig. 3B). Suspicion

of Coronavirus Disease 2019 (COVID-19) did not require discontinuation of pembrolizumab and pemetrexed therapy.

During therapy, the patient underwent next-generation sequencing (NGS) using FOUNDATIONONE® CDx assay. Thereby, variants of known pathogenic status were identified in FFPE (Formalin-Fixed Paraffin-Embedded) material from the lung. First, there was a p.Gly12Val (p.G12V, c.35G>T) mutation in the *KRAS* oncogene (NM_004985). The second clinically significant mutation was p.Asp23fs*28 (p.D23fs*28, c.67delG) in the *STK11* gene (NM_000455). The third significant genetic alteration was p.Lys219fs*16 (p.K219fs*16, c.657_661delACAAA) in the *NBN* gene (NM_002485). TMB and microsatellite status in our patient could not be determined.

Discussion

KRAS, *STK11*, and *NBN* genes

The patient's tumor had pathogenic mutations in the *KRAS*, *STK11*, and *NBN* genes. The *KRAS* gene is a member of the RAS family of small guanosine triphosphatases (GTPases), and it is the most frequently mutated oncogenic driver in NSCLC, with the proportion of mutated patients at approximately 30%. *KRAS* gene mutations often occur with co-mutations and are associated with smoking [3]. There are few therapies intended for NSCLC patients with *KRAS* mutations as for a long time an appropriate drug could not be developed. Eventually, adagrasib (accelerated FDA approval) and sotorasib were registered for patients with the *KRAS* p.Gly12Cys (p.G12C, c.34G>T) mutation, which is the most frequent *KRAS* alteration in NSCLC [4–7].

Serine/threonine kinase 11 (STK11) gene encodes STK11 protein (also called LKB1), which is a kinase and acts as a regulator of apoptosis under stress, specifically energy deprivation, and it is considered a tumor suppressor [8]. In NSCLC patients, *STK11* mutations occur alone or, more frequently, as co-mutations with *KRAS* gene mutations. Approximately 8.6% of NSCLC patients without *KRAS* mutation and 25% of *KRAS*-mutated NSCLC patients are carriers of *STK11* mutations [3].

NBN gene encodes nibrin [also called Nijmegen Breakage Syndrome Protein 1 (NBS1)], a protein involved in double-strand DNA breaks (DSBs) recognition and repair. *NBN*-mutated patients suffer from Nijmegen breakage syndrome (NBS), which causes hypersensitivity to ionizing radiation and is characterized by chromosomal instability resulting in developmental disorders, immunodeficiency, and, notably, cancer predisposition [9]. Therefore, as nibrin is involved in homologous recombination (HR) and non-homologous

end joining (NHEJ), the *NBN* gene may be assigned to a group of genes tested when homologous recombination (HR) deficiency (HRD) is assessed [10, 11]. *NBN* mutations are relatively rare in NSCLC patients (< 3%), with the frequency of p.K219fs mutation at 0.16%, and there is no targeted therapy for cancer patients with alterations in this gene. The mutation p.K219fs in the *NBN* gene resulted in the lack of expression of this gene in cancer cells [12, 13]. The presence of this mutation in our patient may explain the occurrence of cancer in her family. However, the presence of a mutation in the *NBN* gene had not been tested in our patient's peripheral blood, and this mutation may only be present in cancer cells [somatic mutation according to the Catalogue of Somatic Mutations in Cancer (COSMIC)].

The efficacy of immunotherapy and chemoimmunotherapy in *KRAS*-, *STK11*-, and *NBN*-mutated NSCLC patients

Due to a lack of *KRAS*-targeted therapy for lung cancer patients, immunotherapy has been commonly used. In general, immune checkpoint inhibitors (ICIs) are effective in this group of patients, but the response depends on the presence of co-mutations, and patients with *STK11* co-mutations have shorter survival and lower response rates than those with *TP53* co-mutations or even those with *KRAS*-mutated *STK11*-wild type. In one of the studies examining ICI effectiveness in NSCLC patients, the overall response rate (ORR) in a *KRAS*- and *STK11*-mutated subgroup was 7.4%, whereas, in a group with *KRAS* and *TP53* mutations, the ORR reached 35.7%. In clinical trials, a combinatorial approach is being investigated. *KRAS* inhibitors are administered with ICIs in ongoing clinical trials (sotorasib in the CodeBreak 101 study, and adagrasib in the KRYSTAL-7 study, both in patients with *KRAS* G12C mutation). Differences in response are probably related to tumor microenvironment (TME) characteristics that are diverse, depending on the alterations occurring. *STK11*-mutated tumors exhibit lower lymphocyte infiltration and lower PD-L1 expression, compared to *TP53*-mutated ones [2].

NBN is one of the proteins involved in the HR mechanism, and HRD sensitizes tumors to poly ADP-ribose polymerase (PARP) inhibitors and platinum-based chemotherapy, but little is known about the predisposition to immunotherapy [14, 15]. A study by Yang et al. [16] included ICI-treated patients (an independent breast cancer cohort), and 11 *in vivo* murine mammary tumor models treated with anti-PD-1/anti-CTLA-4 antibodies. In many cancer types, including LUAD and squamous lung cancer, a high HRD

score was connected to neoantigenesis and a TME well-infiltrated by lymphocytes. Such features indicate that cancer cells may be easily detected, accessible to T cells, and eventually destroyed. Guo et al. [17] conducted an analysis on thousands of patients with 9 types of cancer (including NSCLC). They described that mutations in 7 DNA repair genes, including *NBN* (*ATM*, *ATR*, *POLE*, *ERCC4*, *NBN*, *RAD50*, *PARP1*), were associated with improved overall survival (OS) in patients treated with ICIs ($p < 0.05$ for all genes). Mutations in genes whose products are involved in HR were not associated with worse OS in patients without ICI treatment [17]. Hsiehchen et al. [18] similarly revealed a positive correlation between HR gene mutations (NGS analysis) and OS in ICI-treated patients independently of TMB. *NBN* gene mutations were included in the sequencing procedure. Median OS (mOS) was 41 months in patients with HR gene mutation vs. 16 months in patients without these mutations ($p < 0.001$). Additionally, the authors stated that objective response was more frequently present in patients with mutations in genes involved in HR and NER (nucleotide excision repair) DNA repair mechanisms ($p = 0.041$ for the NSCLC cohort) [18]. Zhou et al. [19] tested ICI therapy in a neoadjuvant regimen in a small cohort of NSCLC patients (13 of them received chemoimmunotherapy with a PD-1 inhibitor, and 1 patient received anti-PD-1 with anti-CTLA-4 immunotherapy). Among those patients, 3 had a major pathological response (MPR), and 3 had a complete pathological response. In patients with MPR, mutations in genes involved in the HR process were enriched, and these findings were then confirmed in public cohorts [19]. In contrast, Kim et al. [20] analysis did not demonstrate that HRD is an effective predictive marker for ICIs in solid tumors, but this study did not include NSCLC patients. Moreover, HRD or HRD scores are often estimated in different ways and thus, studies determining the most efficient method are necessary to verify HRD predictive value.

Several questions still need to be answered. Parkes et al. [21] provide a possible explanation for enhanced anti-tumor response in patients with mutations in DNA damage response (DDR) genes. They have observed that PD-L1 expression ($\geq 1\%$ or $\geq 5\%$) in samples from DDR-deficient breast tumor patients was positively associated with DDR deficiency assay positivity ($p < 0.001$ for both cut-offs). They have also stated that the activation of the innate immune Stimulator of Interferon Genes (STING)-mediated pathway is responsible for chemokine production in response to DNA damage *in vitro*, resulting in an inflammatory TME in DDR deficient breast tumors [21]. This, combined with enhanced PD-L1 expression in those patients and increased neoantigen expression, may lead to stronger immune system activation and anti-tumor

response. Assumably, combining PARP inhibitors and immunotherapy would be a way to intensify this effect. Such a strategy is being investigated in some patients, and Xu et al. [22] described a case of *ROS1*- and *NBN*-mutated patient with long-term response to an ICI — sintilimab (anti-PD-1 antibody) in combination with PARP inhibitor — niraparib after the failure of ROS1 inhibitor therapy.

Conclusions

To conclude, the reported patient with several mutations had a slightly complex genetic background of response to chemoimmunotherapy. Although most of the studies are limited and retrospective, there is some evidence regarding immunotherapy efficacy in NSCLC patients with such mutations. While *KRAS* and *NBN* mutations seem to be favorable, *STK11* alterations are associated with poor immunotherapy outcomes. Additionally, *NBN* mutations are (as the *NBN* gene products are the member of the HR pathway) predictors of good response to platinum-based chemotherapy, which the patient was receiving. HRD is certainly worth considering in terms of immunotherapy outcome prediction, but it requires a standardization process. It is clear that we do not fully understand the immunological and genetic grounds of anti-cancer therapies' effectiveness, and thorough research is crucial to qualify patients properly for treatment.

Ethics statement

The patient gave his written consent to participate in the research based on the consent of the local bioethics committee at the Medical University of Lublin (No. KE-0254/160/2021).

Author contributions

N.K.: article concept, writing, clinical data collection, literature data collection; P.K.: article concept, revising the article; I.C.: clinical data collection; T.J.: clinical data collection; K.W.-K.: writing, and supervising the article; J.M.: revising the article.

All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

Authors declare no conflict of interest.

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