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PIK3CA mutation presence as luminal breast cancer chemo-resistance prognostic marker

Movchan Oleksii Volodimirovich[1], Smolanka Ivan Ivanovich[2], Lyashenko Andriy Oleksandrovich[1], Dosenko Irina Viktorivna[1], Loboda Anton Dmitrovich[1], Ivankova Oksana Mykolaivna[1]

[1] Doctor of the Department of breast cancer and reconstructive surgery, State Non-commercial Enterprise "National Cancer Institute" of the Ministry of Health of Ukraine, Kyiv, Ukraine
[2] Chief of the Department of breast cancer and reconstructive surgery, State Non-commercial Enterprise, National Cancer Institute of the Ministry of Health of Ukraine, Kyiv, Ukraine

ABSTRACT

Breast Cancer (BC) is the major cause of morbidity and mortality among women in Ukraine and throughout the world, is characterized by a diverse set of gene alterations, the interaction between the tumor's molecular and genetic properties and the prognostic and clinical aspects. The National Comprehensive Cancer Network's (NCCN) Clinical Practice Guidelines for Breast Cancer indicate anthracycline with cyclophosphamide and taxane as a recommended Neoadjuvant Chemotherapy (NAC) strategy. Despite advances in disease prognosis and the overall advantages of chemotherapy, BC treatment frequently generates miscellaneous results in various groups. Drug resistance is a significant cause of cancer therapeutic failure. There is critical to investigate additional gene polymorphisms that may affect BC therapy responses. *PIK3CA* mutations are seen in around 25%-45% of BC, and they are more common in Hormone Receptor-Positive (HR^+) patients. Although data have been extensively reported in BC, no study has focused on the molecular characterization and clinical outcome of patients with *PIK3CA*-mutated Chemo-resistant (ChR) BC. According to researches, the oncogenic *PIK3CA* mutation pathway, in conjunction with other pathways, induces tumor aggressiveness and chemo-resistance. Therefore a need to better understand the characteristics of the ChRBC population harboring *PIK3CA* mutations. Resistance to neoadjuvant chemotherapy is related with *PIK3CA* mutations. This biomarker will be studied further for therapeutic utility in the treatment of luminal ChRBC patients. *PIK3CA* mutation was found to be unfavorable in patients with both overall and luminal BC, demonstrating the potential of *PIK3CA* mutation in combination with other multiple gene alterations and their relationships among themselves as detailed prognostic indicators in BC resistance subgroups. When the response to NAC and prognosis of breast cancer-intrinsic subtypes were evaluated, patients with luminal tumors had a lower pathologic complete response rate, but better outcomes than triple negative and HER2 types. Similarly, luminal tumors with *PIK3CA* mutations exhibited chemo-resistance when compared to *PIK3CA* wild-type.

Keywords: chemo-resistance, relapse, luminal breast cancer, *PIK3CA* gene mutations, neoadjuvant chemotherapy, genetic polymorphisms, pathological response, prognosis

Address for correspondence:
Movchan Oleksii Volodimirovich, Department of breast cancer and reconstructive surgery, State Non-commercial Enterprise, National Cancer Institute of the Ministry of Health of Ukraine, Kyiv, Ukraine

E-mail: aleexeymed@gmail.com

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INTRODUCTION

Breast Cancer (BC) is the most common malignancy among women aged 18 to 65. Every year, roughly 1.9 million women are diagnosed with this condition and treated. BC has the greatest incidence of new cases among 154 nations and is the main cause of death in 103 countries [1]. BC incidence is expected to rise by 27% by 2030, based on incident cases in 2023 [2].

Several drugs for the BC treatment are readily accessible. The tumor's characteristics and hormone receptor status, such as estrogen receptor, progesterone receptor, and HER2, as well as the tumor's proliferative index *Ki67*, determine recommendations for more specific treatment options, such as systemic chemotherapy, endocrine therapy, or HER2-targeted therapy, to yield a better disease prognosis [3].

The National Comprehensive Cancer Network's (NCCN) Clinical Practice Guidelines for Breast Cancer indicate anthracycline with cyclophosphamide and taxane as a recommended Neoadjuvant Chemotherapy (NAC) strategy. Despite advances in disease prognosis and the overall advantages of chemotherapy, BC treatment frequently generates miscellaneous results in various groups. Such variations are caused by intrinsic resistance to certain of the medications used [4].

Drug resistance is a significant cause of cancer therapeutic failure. The therapeutic response varies from person to person, owing to genetic variations that might influence treatment effectiveness [5]. Resistance can be explained by a variety of processes, including changes in drug pharmacokinetics, amplification or decrease in cell signaling, changes in pharmacodynamic-related receptor counts, and so on [6]. It is critical to investigate additional gene polymorphisms that may affect BC therapy responses in order to identify drug resistance and provide information that enables the development of personalized medicine, such as phosphatidylinositol 3-kinase/protein kinase b (PI3K/AKT) pathways in cell cycle arrest, which is also considered as an addition to the main chemotherapy regimens such as taxane and thus increases BC patient survival rate [7].

The conversion of phosphatidylinositol 4,5-biphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3) is mediated by phosphatidylinositol 3-kinases (PI3Ks). The PI3Ks of class IA are heterodimers composed of a catalytic subunit (p110) and a regulatory subunit (p85). This subclass of PI3Ks plays an important role in the regulation of cellular activities such as

cell growth and proliferation, metabolism, and migration via the PI3K/AKT/mTOR pathway. Several studies have shown that this pathway is up-regulated in up to 68% of human tumors [8]. PIK3CA mutations are seen in around 25%-45% of BC, and they are more common in Hormone Receptor-Positive (HR^+) patients [9]. The most common PIK3CA mutations are p.E542K and p.E545K in exon 10 (corresponding to the helical domain), and p.H1047R in exon 21 (corresponding to the kinase domain) [10]. PIK3CA mutations have been linked to poor outcomes in individuals with HR^+/Her^{2+} BC, according to couple researches [11].

The most common intrinsic subtype of breast cancer is luminal BC, which accounts for 60%-72% of all BC [12]. Patients with luminal BC have treatment options including chemotherapy and endocrine therapy; however, methods for optimizing remain unclear [13]. Comprehensive genomic BC investigation indicates genetic variability. These genetic traits have recently been linked to therapy effectiveness and prognosis [14].

The *PIK3CA* mutation is the most common molecular abnormality in the PI3K signaling pathway, which is the most frequently in BC altered, that can be therapeutically targeted by small molecules; however, not every patient with *PIK3CA*-mutated BC will benefit from PI3K inhibitors; only a 23% overall response rate was observed among *PIK3CA*-mutated BC patients with this treatment [15].

Although data have been extensively reported in BC, no study has focused on the molecular characterization and clinical outcome of patients with *PIK3CA*-mutated ChRBC. There is therefore a need to better understand the characteristics of the ChRBC population harboring *PIK3CA* mutations.

It is widely established that PI3K pathway activation is a canonical route in various cancer types and a mechanism of resistance to antiendocrine treatment in ER+BC. The U S F ood a nd D rug Administration (FDA) approved alpelizib in combination with fulvestrant on May 24th, 2019, for postmenopausal women and men with hormone receptor HR-positive and HER2-negative, *PIK3CA*-mutant, progressive, or metastatic BC, as detected by FDA-approved testing after progression on or after an endocrine regimen. *PIK3CA* mutation provides resistance to trastuzumab treatment in HER2 tumors [16].

Several genomic investigations have described the importance of *PIK3CA* in BC biology. This shows that other genetic regulators may still be involved in *PIK3CA* mutation and clinical outcome. Oncogenic PI3K signaling might be controlled by the MET axis, the Programmed Death-Ligand 1 (PDL-1) axis, and microsatellite instability caused by mismatch repair deficiency (MSI/dMMR), the modulation of which can contribute to BC therapy [17]. According to researches, the oncogenic *PIK3CA* mutation pathway, in conjunction with other pathways, induces tumor aggressiveness and chemo-resistance [18].

There is pressing needs to find the biomarker in the selection of neoadjuvant therapy in luminal ChRBC patients.

There is insufficient evidence to support the use of immunochemical markers such as Ki67, morphological markers such as Tumor-Infiltrating Lymphocytes (TIL), and genomic profile markers such as the Oncotype DX Recurrence Score to guide clinical decisions for neoadjuvant therapy [19].

Several retrospective investigations have found that individuals with *PIK3CA* mutations are less receptive to preoperative chemotherapy in all subtypes of BC, including HER2-positive and triple-negative [20]. However, this has not been well studied in luminal BC.

The PubMed database and available on Internet was searched for relevant material for this review. The search criteria were "*PIK3CA* mutation, Chemo-resistant luminal breast cancer" with additional filtering for papers published between 2015 and 2023. The search was done in September 2023, and suitable items were manually reviewed. Figure 1 depicts a flowchart for the literature search method.

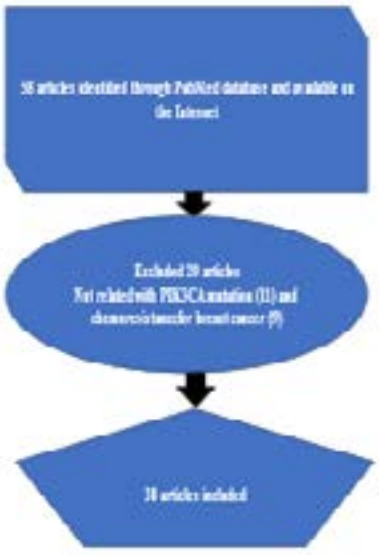

Fig. 1. Flowchart representing the literature search process

LITERATURE REVIEW

The most used methods for PIK3CA mutation detection

High resolution melting analysis, and Sanger sequencing:

Tissue samples of pretreatment core needle biopsy and surgical specimen should be collected in Formalin Fixed, Paraffin Embed-ded (FFPE). The tumors were histologically assessed on hema-toxylin and eosin sections, and the region containing more than 70% of the cancer cells was chosen. Four 4 m thick sections were cut, and the tumor region of each piece was manually dissected with a disposable scalpel. Total DNA was extracted from samples according to the manufacturer's instructions using the QIAamp DNA FFPE kit (Qiagen, Hilden, Germany). High Resolution Melting (HRM) analysis on a LightCycler 480 (Roche Diagnos-tics, Mannheim, Germany) was used to search for mutations in PIK3CA exons 9 and 20 [21].
The primers used for analysis:

Exon 9 F
TGTAAAACGACGGCCAGTGCAATTTCTA-CACGAGATCCTCT;
R
CAGGAAACAGCTATGACCTTTAGCACTTACCTGT-GACTCCA;

Exon 20
F TGTAAAACGACGGCCAGTCTGAGCAAGAG-GCTTTGGAG;
R
CAGGAAACAGCTATGACCTGTGTGGAAGATC-CAATCCA

Following Sanger sequencing, the M13 chimeric primers were employed.

High Resolution Melting (HRM) analysis revealed positive *PIK- 3CA* (exons 9 and 20) Polymerase Chain Reaction (PCR) results, which were sequenced to confirm the presence of mutations using the BigDye Terminator v3.1 cycle sequencing kit (Applied Biosys-tems, Foster City, USA). M13 primers were used for sequencing. The sequencing results were examined using an ABI PRISM 3130 Genetic Analyzer from Applied Biosystems.

Modified PCR technology applying optimized Peptide Nucleic Acid (PNA) probes:

The Maxwell 16 FFPE Purification Kit for DNA (Promega, Madi-son, WI, USA) was used to recover genomic DNA from two slides of 5 m thick FFPE slices. A NanoDrop ND-1000 spectropho-tometer (NanoDrop Technologies, Wilmington, NC, USA) was used to measure their concentration and purity. The average DNA content was 45.27 ng/L (range: 19.50 ng/L-146.70 ng/L), while the estimated 260/280 purity ranged from 1.88 to 3.99. Unless utilized immediately, the DNA samples were kept at 20°C.

PIK3CA variations were altered using the PNAClamp *PIK3CA* Mutation Detection kit (Panagene, Daejeon, Korea), which uses modified PCR methodology with improved Peptide Nucleic Acid (PNA) probes that strongly attach to wild-type DNA templates: E542G 9 Exon 1625A>G; E542V 9 Exon 1625A>T; E542K 9 Exon 1624G>A; E545K 9 exon 1633G>A; E545G 9 Exon 1634A>G; E545D 9 Exon 1635G>T; Q546E 9 Exon 1636C>G; Q546K 9 Exon 1636C>A; Q546P 9 Exon 1637A>C; Q546R 9 Exon 1637A>G; E545A 9 Exon 1634A>C; H1047Y 20 Exon 3139C>T; H1047L 20 Exon 3140A>T; H1047R 20 Exon 3140A>G; C420R 7 Exon 1258T>C.

Those strong attachments to the wild-type DNA templates prevented the wild-type DNA template from being amplified during Polymerase Chain Reaction (PCR), whereas the altered DNA templates were processed for multiplication.

PIK3CA variations were altered using the PNAClamp PIK3CA Mutation Detection kit (Panagene, Daejeon, Korea), which uses modified PCR methodology with improved Peptide Nucleic Acid (PNA) probes that strongly attach to wild-type DNA templates [22].

Next Generation Sequencing (NGS):

Hotspot mutations in exons 2, 5, 10, 14, or 21 of the PIK3CA gene. The All Prep DNA/RNA Mini kit (Qiagen, Hilden, Germany) was used to isolate DNA from frozen core biopsies. The Qubit 2.0 Fluorometer was used to measure DNA (Quant-iTTM dsDNA BR Assay Kit; Thermo Fisher Scientific, Les Ulis, France). Frozen samples were evaluated using a bespoke panel that targeted 59 cancer-related genes with 1200 amplicons. The initial PCR step (17 cycles) was performed with 10 ng of DNA. FuPA enzyme was used to partly digest amplicons to remove extremities corresponding to primer sequences. For variant calling, a depth of coverage of >100 reads is required, with 6% for calling known single nucleotide variants/mutations (with Cosmic ID) and 11% for calling known indels (with Cosmic ID). ANNOVAR and the datasets COSMIC68, dbSNP137, 1000 genomes, ESP6500, and RefGene were used to identify differences in raw readings linked to the reference human genome hg19. Non-synonymous modifications that have not been observed in more than 0.1% of the population (1000 genomes and ESP6500) are considered somatic mutations. Using existing datasets (Cosmic, The Cancer Genome Atlas), a professional molecular biologist detected, categorised, and analyzed all somatic mutations [23].

Determination of PIK3CA mutations on circulating tumor DNA:

Quantified the presence of PIK3CA mutations on circulating DNA who received chemotherapy. DNA extracted from 1 ml–7 ml of EDTA plasma obtained after a double centrifugation. Extraction carried out using a Maxwell® RSC ccfDNA Plasma Kit (Promega, Charbonnières-les-Bains, France). Determination of PIK3CA mutational status carried out, on the one hand, using next-generation sequencing approach based Oncomine™ Pan-Cancer Cell-Free Assay, using the Ion Chef device and S5 sequencer (Thermo Fisher Scientific, Darmstadt, Germany). On the other hand, analyses carried out by Crystal™ Digital™ PCR with the Naica Digital PCR (ddPCR) system (Stilla Technologies, Villejuif, France). Primers and probes designed for

the detection of PIK3CA (NM_006218.3) hotspot mutations p.E542K (c.1624G>A), p.E545K (c.1633G>A), p.H1047R/L (c.3140A>G & c.3140A>T) [24].

The therascreen® *PIK3CA* RGQ PCR Kit (QIAGEN Manchester, Ltd.) has been authorized by the FDA as a companion diagnostic test to identify individuals with *PIK3CA* mutations in tumor tis-sue samples and/or circulating tumor DNA (ctDNA) extracted from plasma samples. If the test for PIK3CA mutations in plasma is negative, patients should be examined for *PIK3CA* mutations in tumor tissue. SOLAR-1 (NCT02437318) was the basis for the approval. It was a phase III, randomized, double-blind, placebo-controlled study of alpelizib plus fulvestrant versus placebo plus fulvestrant in 604 patients with HR-positive, HER2-negative, ad-vanced or metastatic BC whose disease had progressed either after chemotherapy or after taking an aromatase inhibitor [25].

Validation of the Assay for PIK3CA Mutation:

PIK3CA-mutated (A549 cell line) DNA was serially diluted to generate samples containing 100%, 50%, 20%, 10%, 5, and 1% of *PIK3CA*-mutant alleles (E542K and H1047R, respectively), which were then subjected to PNA clamp real-time PCR to inde-pendently determine each detection rate of the diluted *PIK3CA*-mutant alleles. Ct1 values for E542K-mutant alleles should be 12.84, 11.95, 9.83, 8.11, 7.83, and 4.09 for 100^{-}, 5^{-}, 2^{-}, 10^{-}, 5^{-}, and 1% mutant samples, respectively, and 12.75, 12.03, 9.92, 8.39, 7.90, and 5.10 for H1047R-mutant alleles. The PNA clamp real-time PCR test, with a Ct1 cutoff value of 2.0, is capable of detect-ing the PIK3CA mutation in a 1% mutant population (Figure 2) [26].

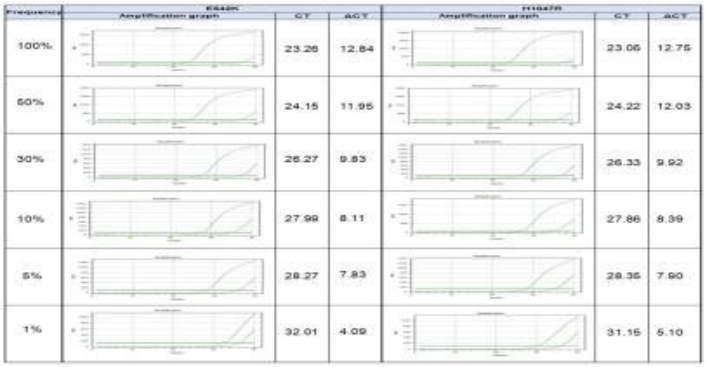

Fig. 2. Validation of detection rate of PIK3CA mutation in serially diluted cell line experiment from 100, 50, 20, 10, 5, to 1% of PIK3CA-mutant alleles

TCGA Dataset Analysis for PD-L1/c-Met/MMR Related to PIK3CA Mutation:

Mutational status of *PIK3CA* gene and mRNA expression profile of 6 genes (PD-L1, MET, MLH1, MSH2, MSH6, and PMS2) could be depicted from the "Breast Invasive Carcinoma" dataset of the TCGA [http://cancergenome.nih.gov/abouttcga (accessed on 27 January 2022)] in cBioPortal [https://www.cbioportal.org/ (accessed on 27 January 2022)].

DISCUSSION

Traditional prognostic factors for breast cancer including tumor size, Lymph Node (LN) involvement, tumor grade, fertile, and even immunehistochemistry status is not enough for successful BC treatment tactics now [27].

There are several treatment options for patients with luminal BC, including surgery, chemotherapy, and endocrine therapy. Study showed that in clinical practice, the *PIK3CA* mutations examina-tion may provide useful information to determine NAC.

According to Hayama S. and colleagues, *PIK3CA* mutations were found in 30.4% of patients prior to therapy. Tumors with *PIK3CA* mutations responded considerably worse than tumors with wild-type *PIK3CA* (p=0.03). The log-rank test revealed no change in RFS between PIK3CA mutant patients and *PIK3CA* wild-type patients (p=0.43). Time to recurrence was predicted by estrogen and progesterone receptors, as well as pathological thera-peutic impact, in the Cox proportional hazards model for recurrence free survival. According to the RECIST standards, the clini-cal response in 40% of patients with mutant *PIK3CA* was without relapse [19].

Exactly the same Hu and colleagues reported, patients after neo-adjuvant chemotherapy, who had tumor with *PIK3CA* mutations showed significantly poorer response than tumor with *PIK3CA* wild-type (RR 11.5% *vs* 34.3%, p=0.03). On the other hand, in the neoadjuvant chemotherapy group, there was no significant difference in pathological therapeutic effect between tumor with PIK3CA mutations and tumor with *PIK3CA* wild-type (RR 7.2% *vs* 12.9%, p=0.54) [28].

Univariate analysis revealed, that only *PIK3CA* mutation status was significantly correlated with the pathological effect of therapy (Odds Ratio 5.26, p=0.04). A meta-analysis of eight retrospective cohort studies found that the group with the *PIK3CA* mutation was more dependent on good clinical outcomes [29]. In contrast, *PIK3CA* mutations were not related with prognosis in a prospec-tive clinical study on adjuvant endocrine treatment [30].

It is hypothesized that the impact of *PIK3CA* mutations on prog-nosis varies by subtype and treatment, with little effect in patients with luminal BC. *PIK3CA* mutations are found in 30%-50% of patients with luminal BC using digital PCR or Next-Generation Sequencing (NGS). Compared to PCR and NGS, the Sanger se-quencing is less sensitive. The High-Resolution Melting (HRM) analysis and Sanger sequencing approach, on the other hand, were beneficial for finding clinically relevant alterations [31].

MAP3K1 mutations were more common in patients with *PIK-3CA* mutations. These mutations are recurring drivers in recurrent BC and are implicated in MEK pathway activation. Other studies have indicated that *MAP3K1* mutations are prevalent in roughly 11% of *PIK3CA*-mutated breast tumors [32].

Avivar-Valderas et al. demonstrated how, in the context of *PIK3CA* mutation, *MAP3K1* loss of function drives resistance to -selective PI3K inhibitors by activating IRS1. It needs to be seen whether *MAP3K1* mutations cause PI3K inhibitor resistance in patients. This discovery might lead to the creation of PI3K and MEK inhibitor combinations. Interestingly, 8% of patients with *PIK3CA* hot area mutations also had another change in the same gene; 4% had a *PIK3CA* amplification, and 6% had a mutation beyond the hot spot regions [33].

PIK3CA mutations have been linked to androgen receptor and apocrine subtype expression in individuals with ChRBC, and are negatively connected to immune system activation and PTEN changes [34]. The PI3K/AKT/PTEN pathway is altered in 35% of BC patients, encouraging the present development of AKT inhibitors in these malignancies. In the metastatic situation, 67% of *PIK3CA* mutations were found in individuals whose initial tumor exhibited HR. Because *PIK3CA*-mutated luminal BC is sensitive to PI3K inhibitors, there is a compelling case for developing PI3K inhibitors in this scenario [35]. These data suggest that further trials that will test PI3K inhibitors in ChBC will have to stratify patients based on HR expression on the primary tumor.

Based on the TCGA database, researchers discovered a substan-tial association between the *PIK3CA* mutation and the signaling pathways of c-Met and dMMR in ChBC, as well as a negative prognostic role for the *PIK3CA* mutant with c-Met and MSI/MMR expression in ChBC. The *PIK3CA* mutation, which ac-counted for roughly 60% of the patient group who received ad-juvant chemotherapy following surgery, was a poor prognostic factor for poorer RFS, particularly in the c-Met-positive, MSS, triple-negative, or younger age onset 50 years subtypes. Because the *PIK3CA* mutation is linked to the success of PI3K inhibi-tors as well as other endocrine or targeted therapies, it is critical to precisely establish the *PIK3CA* mutational status and predict therapeutic benefits in chemo-resistance [36].

ASCO recently endorsed NGS for the discovery of *PIK3CA* mutations in patients with luminal subtype BC to determine therapy eligibility for alpelisib.

The absence of specific clinical or demographic characteristics as-sociated with the presence of the *PIK3CA* mutation among the patients, which was consistent with other studies; any subset of clinicopathological factors is unlikely to indicate a specific group of patients expected to carry the *PIK3CA* mutation, implying that all BC patients should be tested for the *PIK3CA* gene in order to detect the mutation. Alternatively, economic considerations of cost-effective testing are required [37].

FUTURE PERSPECTIVES

Future research will improve the characterization of resistance mechanisms. There are now 26 clinical studies in breast cancer with *PIK3CA* inhibitors listed on clinicaltrials.gov, while funda-mental research uncovers new mechanisms, such as PIM1, which has recently been implicated in resistance to *PIK3CA* inhibitors. Although *PIK3CA* and hormone receptors collaborate in BC re-sistance to conventional treatment. A better characterization of resistance mechanisms is required in order to identify individuals who will benefit from various combinations of medication [38].

CONCLUSIONS

Resistance to neoadjuvant chemotherapy is related with *PIK3CA* mutations. This biomarker will be studied further for therapeutic utility in the treatment of Chemo-resistant luminal breast cancer patients.

PIK3CA mutation was found to be unfavorable in patients with both overall and luminal BC, demonstrating the potential of *PIK-3CA* mutation in combination with other multiple gene alterations and their relationships among themselves as detailed prognostic indicators in BC resistance subgroups.

When the response to neoadjuvant chemotherapy and prognosis of breast cancer-intrinsic subtypes were evaluated, patients with luminal tumors had a lower pathologic complete response rate but better outcomes than triple negative and HER2 types. Similarly, luminal tumors with *PIK3CA* mutations exhibited chemo-resistance when compared to *PIK3CA* wild-type.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Movchan O.V.(MOV), Prof. Smolanka I.I.(SII), Lyashenko A.O. (LAO), Dosenko I.V.(DIV), Loboda A.D (LAD), Ivankova O.M.(IOM).

MOV, SII and LAO: conceptualization, methodology, writing of the original draft; MOV, LAO: project administration, supervision; DIV, LAD, IOM: data collection, feedback, reviewing and making substantive changes. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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