

## LETTERS TO THE EDITOR

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# Some subgroups might get less benefit from adjuvant olaparib trial in high-risk, HER2-negative and germline BRCA2 BRCA1- or BRCA2-mutated early breast cancer patients

Dear Editor,

BRCA1 or BRCA2 germline mutations are associated with approximately 5% of all breast cancers. Outcome is better for many patients with germline BRCA mutations and early breast cancer receiving standard treatments, but recurrence rates remain high for some patients, so additional or adjuvant, novel targeted treatments are needed. Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, targets DNA repair defects in cancers with BRCA mutations and is approved for BRCA-mutated HER2-negative breast cancer that has metastasized [1]. Tutt et al [2] reported that olaparib given for 52 weeks as adjuvant therapy after neoadjuvant or adjuvant chemotherapy and local therapy resulted in significantly longer survival free of invasive or distant disease than placebo in high-risk, HER2-negative and germline BRCA2 BRCA1- or BRCA2-mutated early breast cancer patients. Almost 81% of all patients in each group were with triple negative breast cancer. The authors did not give detailed information about tumor subtypes. Histologic heterogeneity (metaplastic breast cancer vs. medullary breast cancer vs others) in triple negative breast cancer significantly affect the survival outcome [3]. Therefore, unequal distribution of histologic subtypes in both groups might affect progression-free and overall survival. Secondly, patients

with hormone receptor positive or patients who received previous platinum based chemotherapy seem to get less benefit from adjuvant olaparib treatment. This issue needs further investigation.

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# Association between aspirin use and reduction in risk of triple negative breast cancer: Still debatable issue?

Dear Editor,

Almost 15% of breast cancers are triple-negative (TNBCs), a clinically aggressive molecular subtype with a higher risk of death and an early pattern of metastasis. Aspirin, also known as acetylsalicylic acid, is used widely as an analgesic to relieve pain, as an antipyretic to reduce fever and as an anti-inflammatory medication. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandins and cyclooxygenases (COX-1 and COX-2). Although the benefit of aspirin for ischemic

heart disease is well-known, the suggestion that aspirin could be of benefit against cancer is suggestive. Some epidemiological studies showed that aspirin and other NSAIDs are inversely related to the incidence of various cancers [1]. Hurwitz and colleagues [2] investigated whether age, body mass index, smoking, physical inactivity and family history of cancer modify the effect of daily aspirin use on colorectal, ovarian, breast, endometrial and aggressive prostate cancer risk. They reported that daily aspirin use appears to reduce colorectal cancer risk regardless of other risk factors. Weak or null associations were observed for breast, endometrial,

and aggressive prostate cancer, with no strong effect modification observed. The authors did not mention any association between aspirin use and risk of reduction in specific breast cancer subtypes. Shiao and his colleagues investigated the therapeutic role of antiplatelet (AP) agents (Aspirin/clopidogrel use) in a TNBC population. They reported that antiplatelet agent use improves distant metastases rate (DMR) and disease-free survival (DFS) among a stage II and III TNBC population [3]. Another study evaluated aspirin use and risk of breast cancer in African American women. The authors suggested that current regular aspirin use may be associated with a nearly 20% reduction in risk of ER negative breast cancer and a 30% reduction in risk of TNBC [4]. These findings warrant further studies to confirm the association between aspirin use and TNBC.

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# Vismodegib and radiotherapy combination in treatment of cancer

Dear Editor,

Cancer is a disease that makes universal treatment strategy impossible due to its heterogeneous nature. Functional disorders in regulation of signaling pathways and potential to differentiate from stem cells contribute to cancer development. In addition, these cells are predisposed to resistance against chemotherapy and radiotherapy, and manipulation towards tumor metastasis. Resistance gained by tumor cells makes it difficult to treat cancer. Thus, it becomes important to target stem cells and signaling pathways in the treatment of cancer [1-3].

Hedgehog (Hh) signaling pathway is critical in embryonic life as it plays a role in cellular proliferation and differentiation. In addition, it is inactive in most adult tissues except stem cells which are important in cellular continuity [2,3]. Abnormal activation of Hh signaling pathway causes cancer development. Dysregulated Hh pathway is associated with many types of cancer including skin cancer, breast cancer, lung cancer, neuroblastoma, medulloblastoma, brain and prostate cancers [1-5]. Cellular responses to Hh signaling are regulated by transmembrane proteins termed as Patched-1 (PTCH1) and Smoothened (SMO). PTCH1 serves to suppress SMO activity [1, 2, 4].

Vismodegib (GDC-0449) inactivates SMO molecule that regulates Hh signaling by suppressing the proliferation of tumor cells without impeding normal cell proliferation. It is an Hh pathway inhibitor which is approved for metastatic or locally advanced basal cell carcinoma (BCC) by FDA [1-3]. In a phase II study on 104 patients with locally advanced and metastatic BCC, Sekulic et al found a response rate of 30% in patients with metastatic BCC and 43% in patients with locally advanced BCC [5]. There are case reports supporting radiotherapy (RT) in combina-

tion with vismodegib (VIS) in locally advanced BCC [1]. Tumor was sensitized to radiotherapy by VIS. Currently, there is no randomized-controlled study supporting use of VIS combined with RT in definitive and adjuvant treatment. In a phase I study, LoRusso et al investigated the effectiveness of VIS therapy in solid tumors refractory to available treatments or lacking standard therapy. It was reported that it is safe and effective in the treatment of medulloblastoma and advanced BCC [4]. It was shown that combined use of VIS with chemotherapy had therapeutic potential in cervix cancers with Hh signaling pathway [3]. In another *in vitro* study, it was reported that VIS enhanced the effectiveness of radiation in locally advanced lung cancer.

In conclusion, Hh signaling pathway plays an important role in the development and metastasis of many cancers including BCC, breast, lung, brain, prostate, neuroblastoma and medulloblastoma. In preclinical studies and clinical studies, it is observed that use of Hh signal pathway inhibitors in combination with radiotherapy improves the effectiveness of treatment. There is a need for randomized-controlled studies in this field.

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## Is there any association between human papillomavirus amplification and ductal histology in invasive breast carcinoma?

Dear Editor,

Many studies have evaluated the relation between breast carcinoma and human papillomavirus (HPV) status with highly variable results due to marked heterogeneity in the methodologies used. Although evidence has suggested a role for high-risk HPV in breast cancer, the precise pathogenesis remains unknown [1]. Gao and colleagues [2] investigated HPV amplification in breast benign and malignant lesions by chromogenic *in situ* hybridization (CISH) and the concordance of p16 expression by immunohistochemistry. The presence of HPV6/11 and HPV16/18 in 33 cases of intraductal papilloma, 34 cases of ductal carcinoma *in situ* (DCIS), and 56 cases of invasive breast carcinoma (IBC) was evaluated using matched-background breast parenchyma and breast reduction as control groups. They concluded that HPV infection was detected in both breast lesions and background parenchyma. HPV infection may play a role in the pathogenesis of breast cancer but is not associated with intraductal papilloma. However, the authors did not detail information about histopathology of invasive tumors (lobular vs. ductal). One study showed that HPVs are present in cancers occurring in human nipple milk ducts and that these cancers have the typical histological features of HPV-induced human cancers [3]. It would be expected that HPV might be associated more with ductal histology than with lobular histology. This issue merits further investigation.

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## Association between breast cancer risk factors and tumor subtypes

Dear Editor,

Breast cancer is the most commonly diagnosed cancer in women worldwide and characterized its by molecular and clinical heterogeneity. Five common subtypes of breast cancer include luminal A, luminal B, HER-2 overexpress-

ing, basal-like, and normal breast-like. Although clinical differences between subtypes have been well described in the literature, etiologic heterogeneity has not been fully studied [1]. Lilleborge et al [2] investigated the association between the modifiable factors physical activity, body mass index (BMI), alcohol consumption, tobacco smoking, meno-

pausal hormone therapy (HT) use and the risk of breast cancer among women with a benign lesion, hyperplasia with atypia, or carcinoma *in situ* detected. During follow-up, 274 women with a benign lesion, 34 women with hyperplasia with atypia and 118 women with carcinoma *in situ* were diagnosed with invasive breast cancer. They observed an increased risk of breast cancer associated with use of menopausal hormone therapy for women with a benign or premalignant lesion. Alcohol consumption and tobacco smoking showed increased risk of breast cancer among women with a benign lesion. The authors did not give detailed information about the association between risk factors and invasive breast cancer subtypes. We evaluated the associations between several hormonal and non-hormonal risk factors and molecular subtypes of invasive breast cancer [3]. This cross-sectional study consisted of 1884 invasive female invasive breast cancer cases. We found that reproductive and hormonal characteristics (breastfeeding, parity, age at first full-term birth, hormone replacement therapy) were associated with luminal subtype, compared to nonluminal breast cancer, consistent with previous studies. Obesity and overweight increased the risk of triple negative subtype, particularly in premenopausal women. Older age and use of hormone replacement therapy were related to the risk of HER-2 overexpressing breast cancer. Likewise, Pizzato and colleagues [4] compared selected risk factors with breast cancer subtypes, using a case-case approach in 1321 invasive breast cancers. This case-only study showed that triple negative, compared to luminal A, was negatively associated with higher breast density (BD), while it was positively associated with positive family history of breast cancer, higher education and late age at menarche. Fur-

thermore, this study suggested that luminal BH+(ER+and/or PR+, HER2+), compared to luminal A, was positively associated with higher BD, whereas it was negatively associated with parity. Two clinical studies suggest a significant heterogeneity between breast cancer risk factors and tumor subtypes. This issue merits further investigation.

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## The place of Omalizumab in the treatment of Carboplatin hypersensitivity

Dear Editor,

Carboplatin (CP) is a second generation platinum derivative commonly used in oncology practice. Common side effects are nausea, vomiting and myelosuppression associated with dose. In addition, more specific toxicities, such as hypersensitivity reactions, can be observed in CP. CP, which is used in malignant diseases such as lung, testis and ovarian cancer, has been reported to cause hypersensitivity reaction in 0.5-25% of the patients [1,2].

CP-induced hypersensitivity reaction is often mediated by IgE. Drug antigens bind to high affinity IgE receptors in mast cells and/or basophils to release inflammatory mediators [3-5]. Studies have shown that reactions to CP develop more often after the 6th cycle and the risk of reactions increases rapidly after the 7th and 8th cycles [4]. These reactions can be observed in seconds, but usually occur 30 min after the infusion has started [4,5].

It is known that premedication and / or desensitization methods by reducing the infusion rate in patients with CP-induced hypersensitivity reactions have not always been successful in tolerating the drug. The effectiveness of alternative chemotherapy regimens is also often limited due

to tumor sensitivity/insensitivity, so drug exchange is not readily possible. This may be an important cause of morbidity and mortality for patients. In recent years, anti-IgE treatment (Omalizumab), which is one of the desensitization methods, has started to be tried.

Omalizumab is a DNA-derived, recombinant humanized immunoglobulin G1κ monoclonal antibody that selectively binds to human IgE. It reduces the amount of free IgE and IgE FcεRI required for activation of mast cells and basophils (3,5). Desensitization with Omalizumab, an anti-IgE that has been shown to be safe and efficacious, has been shown in case reports to improve quality of life and possibly survival, since it allows patients to use chemotherapy agents (3). However, there is no sufficient literature information on how much Omalizumab treatment can treat hypersensitivity reactions.

In conclusion, hypersensitivity reactions caused by CP limit its use because of their potential to cause more severe reactions and even death in the next application. CP-induced hypersensitive reactions may help in the treatment of patients who fail Omalizumab's standard desensitization protocols. However, randomized clinical trials are needed to evaluate the efficacy, safety and response to treatment.



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## Taxane use for breast cancer-related lymphoedema risk

Dear Editor,

The association of taxanes with the development of lymphedema in breast cancer patients was reported previously [1]. Martínez-Jaimez and colleagues in their article [2] identified the risk factors for lymphedema following axillary lymph node dissection (ALND) in a European sample and proposed a lymphoedema prediction model for this population. They reported that the factor contributing most to the risk of lymphoedema was the level of lymph node dissection, and the only patient-related factor in the prediction model was body mass index (BMI). The authors suggested that the main risk factors for lymphoedema following breast cancer treatment are the type of surgery, the woman's BMI, adjuvant chemotherapy and postoperative complications. The authors did not give detailed information about chemotherapy schedules. The association of taxanes with the development of peripheral edema was evaluated previously. Taxanes may cause systemic disruption, which could have a longer-term effect on lymphatic function leading to lymphedema in breast cancer patients. Furthermore, Cariate and colleagues [3] in their hypothesis-generating study investigated risk factors for lymphedema with a specific focus on the potential impact of chemotherapy. They found that patients who received adjuvant taxanes were nearly three times more likely to develop lymphedema than patients

who had no chemotherapy. In conclusion, adjuvant or neo-adjuvant taxane use might be considered one of the main risk factors for the risk of lymphedema. This issue merits further investigation.

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## Preference of trastuzumab emtansine as a second or third line treatment in patients with human epidermal growth factor receptor 2 positive metastatic breast cancer refractory to trastuzumab and pertuzumab

Dear Editor,

Trastuzumab-emtansine (T-DM1), a novel drug developed for the treatment of HER2-positive breast cancer, is a human epidermal growth factor receptor (HER2) targeted

antibody drug conjugate, composed of trastuzumab, a stable thioether linker, and the potent cytotoxic agent DM1 (derivative of maytansine). The phase III randomized trial EMILIA has shown that T-DM1 provided objective tumor responses and significantly improved progression-free survival

and overall survival compared to lapatinib and capecitabine combination in HER2-positive metastatic breast cancer patients treated with a prior taxane and trastuzumab regimen [1]. Data about outcome with second-line T-DM1 in trastuzumab plus pertuzumab refractory setting is scarce. Huertes and colleagues [2] evaluated published evidence on the efficacy and prolonged responses with T-DM1 after first-line trastuzumab plus pertuzumab and provided possible factors related to prolonged responses to T-DM1. The total number of patients was 796 (276 of them received pertuzumab). They reported that the efficacy of T-DM1 after a previous pertuzumab treatment was lower than if pertuzumab was not given, although prolonged responses were observed in this setting. The results are more similar to those of TH3RESA trial (very pre-treated population). The authors also concluded that pertuzumab-pretreated patients obtained less long-term benefit with second-line T-DM1 than patients who did not receive pertuzumab and the benefit could be greater if they were administered T-DM1 in third or later lines. Prior treatment with pertuzumab-trastuzumab-based combinations may promote internalization and endocytic destruction of HER2 cell surface receptors. The lack of HER2 receptors, after previous pertuzumab, can block the activity of T-DM1. Therefore, lapatinib or tucatinib-based combinations might be priority

for second-line treatment. In this sense, T-DM-1 might be kept for third-line treatment because of the re-expression of HER2 receptors. This issue warrants further investigation.

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# SARS-CoV-2 influence on renal cell carcinoma patients

Dear Editor,

Coronavirus disease 2019 (COVID-19), a rapidly globally spreading pandemic - characterized by elevated rates of infectivity and mortality - increased the need and pressure for design and development of specific anti-SARS-CoV-2 targeted therapeutic strategies via monoclonal antibodies (mAbs) and also for massive production of safe and effective vaccines. In fact, Coronavirus-related Severe Acute Respiratory Syndrome (SARS-CoV) in 2002/2003, Middle-East Respiratory Syndrome (MERS-CoV) in 2012/2013, and especially the current 2019/2020 Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) affected negatively the national health systems' endurance worldwide. In order to face this emergency situation, many pharmaceutical companies focused on the design and development of efficient vaccines that are considered necessary for providing a level of normalization in totally affected human social-economical activity worldwide. SARS-Cov-2 virus belongs to lineage b of beta-CoVs demonstrating a strong phylogenetic similarity with BatCoV RaTG13 type. Concerning its genomic structure, a large non-segmented, positive-sense RNA molecule of approximately 30 kb has been detected and analyzed in conjunction with the corresponding RNA-dependent RNA-polymerase (RdRp) that is essential for its replication in the cytoplasm of the target epithelial cells. Analyzing SARS-CoV-2 spherical virion's structure (diam~100nm), research groups have confirmed that there are four main proteins including the spike surface glycoprotein (S), the main or matrix protein (M), the envelope protein (E), and finally the nucleocapsid protein (NC). S glycoprotein projections -consisting of two subunits S1/S2- provide a unique crown-like formation (corona) on virion's surface. Concerning their

functional role, S1 represents the main receptor-binding domain (RBD), whereas S2 is involved in the virus-cell membrane fusion mechanism interacting with proteases, such as furin, thrypsin, cathepsin or serino-protease TM-PRSS2. SARS-CoV-2 molecular basis is under investigation by implementing novel, sophisticated multi-omics based techniques [1].

Since early 2020, COVID-19 pandemic has negatively influenced the management of a variety of oncological patients, including breast and pancreatic carcinoma [2,3]. Additionally, the impact of SARS-CoV-2 - mediated clinoco-immunologic implications in renal cell carcinoma (RCC) patients with severe or mild level infection are under investigation [4]. Especially, for the patients that receive specific immune checkpoint inhibitors (ICIs) such as anti-programmed cell death protein-1 (PD-1) there are controversial results regarding the involvement of the virus as a strong or not independent risk factor that modifying the levels of T-cell cytokine production. In conjunction, there is an increased scepticism on the basis of a possible cross-reaction between SARS-CoV-2 spike surface glycoprotein and host cell receptors in patients with ICI therapeutic regimens infected by the virus [5].

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## Some concerns about clinical-pathological characteristics of breast cancer cases detected by chest computed tomography

Dear Editor,

Studies have shown detection rates for incidental malignant breast lesions of 0.3% on unenhanced computed tomography (CT) and 0.6% on contrast-enhanced CTscans. Previous studies have reported a prevalence of malignant breast lesion among incidental findings of up to 28%. Georgieva et al [1] evaluated incidental breast lesions on CT with histopathological correlation. They reported that out of 35.000 chest CT examinations, a total of 31 incidental breast lesions in 27 patients were detected. Among the 31 lesions, 23 were malignant and 8 benign. The malignant lesions included 17 carcinomas and 6 metastases (4 lymphomas and 2 melanomas) [1]. However, the authors did not discuss clinical and pathological characteristics of these 17 breast cancer cases. The mean age of all cases was 70 years. Distribution of histological subtypes were different. HER-2 positive and triple-breast cancer cases [10 patients, (58%)] were higher than hormone-receptor positive cases [7 patients, (42%)]. Breast cancer cases in this study were accepted as interval cancer. One study showed that interval cancers in the trial generally had nonfavorable characteristics as observed in this study [2]. One would expect that

these non-favorable breast cancer patients detected by chest CT scan might lead better survival outcome. This issue merits further investigation.

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