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LETTERS TO THE EDITOR

Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: is it too early to reach conclusion?

Dear Editor,

Breast cancer is the most common cancer in women worldwide. Understanding the biology of this tumor is a prerequisite for selecting an appropriate treatment. Cell cycle alterations are seen in many cancers, such as breast cancer. Newly popular targeted agents in breast cancer are cyclin-dependent kinase inhibitors (CDKIs) (palbociclib, ribociclib, abemaciclib) which are agents inhibiting the function of cyclin-dependent kinases (CDKs) [1]. On October 12th 2021, the United States Food and Drug Administration (FDA) approved abemaciclib in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), node-positive, early breast cancer at high risk of recurrence and a Ki-67 score of ≥20% as determined by an FDA-approved test. A pivotal adjuvant trial concluded that abemaciclib + endocrine therapy significantly improved invasive disease-free survival (IDFS) in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative, node-positive, high-risk early breast cancer, with an acceptable safety profile [2]. At the additional follow-up analysis, with 27 months median follow-up and 90% of patients off treatment, IDFS ($p<0.0001$) and distant relapse-free survival (DRFS) ($p<0.0001$) benefit was maintained. However, median follow-up time is still quite short for a study of ER+ adjuvant therapy, where the majority of recurrences and deaths occur after 5 years in many studies. Furthermore, this class of cyclin-dependent kinase 4 and 6 is likely cytostatic, rather than cytocidal. It means that it blocks cell proliferation rather than leading to cell senescence and apoptosis. Overall survival was a secondary outcome measure for the monarchE study [2] . This survival information was not included in the recent study, due to immaturity of the data. Whether the survival curves for combination therapy will come together with those for endocrine therapy alone once patients stop taking the drug is still common concern and needs to be investigated.

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Regular daily weighted Hula-Hooping might reduce central adiposity leading to decreased pre- and postmenopausal breast cancers risk

Dear Editor,

Adiposity is commonly measured through body mass index (BMI), which represents adipose tissue and lean mass. Higher BMI is associated with increased postmenopausal breast cancer risk. Waist circumference (WC) and waist-to-hip ratio (WHR) are often used to measure central obesity, characterized by high levels of visceral adipose tissue (VAT). Central adiposity may be particularly relevant to breast cancer development as VAT may be more metabolically active than subcutaneous adipose tissue (SAT). Houghton et al [1] examined whether WC, hip circumference (HC), or WHR were associated with incident invasive breast cancer (overall and by tumor subtype), independent of BMI according to

menopause status. They reported that central adiposity was positively associated with pre- and postmenopausal breast cancers independent of BMI. Therefore, strategies for reducing central adiposity are major concerns. Hula-hooping is an ancient type of dance, which has recently experienced a comeback in the form of aerobic core training. Beneficial metabolic effects in obese subjects is unknown. One study compared the effects of weighted hula-hooping and walking in obese subjects. They found that 6 weeks of hula-hooping for an average duration of 13 min per day sig¬nificantly decreased waist circumference and body fat in the android region and increased trunk muscularity compared to a period of walking in a group of overweight subjects [2]. Furthermore, excess total body fat and abdominal adipose tissue are recognized risk factors for metabolic diseases but also for some types of cancers, including breast cancer. Obesity stimulates cancer progression through chronic, low-grade inflammation in white adipose tissue. One study showed that a 16-week aerobic and resistance exercise in¬tervention attenuates adipose tissue inflammation in obese postmenopausal breast cancer survivors [3]. We previously suggested that weighted Hula-Hooping as an exercise type may decrease breast cancer recurrence by decreasing abdominal fat and in¬creasing trunk muscularity in obese postmenopausal breast cancer survivors [4]. Taken all together, regular daily weighted Hula-Hooping exercise might reduce central adiposity leading to decrased pre- and postmenopausal breast cancers risk. This issue merits further investigation.

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SARS-CoV-2 implication in retinoblastoma

Dear Editor,

Intraocular malignancies are rare in childhood, and for this reason early diagnosis and early treatment implementation modifies positively the prognosis of the corresponding patients. Among them, retinoblastoma (Rb) -although the most common primary malignant intraocular carcinoma in children- is a rare type developed histo-pathologically by abnormal immature cells of retina, the light-detecting tissue of the eye responsible for light and color recognition. Concerning its genetic signature, Rb suppressor gene demonstrates a sporadic and also hereditary (germinal) pattern caused by a congenital mutation in the chromosome 13 gene 13q14 (retinoblastoma protein). It seems - as it happens in other malignancies including breast and pancreatic carcinoma- that pandemics like coronavirus-related have negatively influenced the management of a variety of oncological patients [1,2]. Specific studies on retinoblastoma patients have concluded that delay in optimal and timely management leads to prolonged treatment interruptions, permanent default, and even death in children, especially in countries with vast, uncontrolled populations [3]. 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. SARS-Cov-2 virus belongs to lineage b of beta-CoVs, demonstrating a strong phylogenetic similarity with Bat-CoVRaTG13 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 (Rd-Rp) 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 the 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 TMPRSS2. SARS-CoV-2 molecular basis is under investigation by implementing novel, sophisticated multi-omics based techniques. Concerning the influence of SARS-CoVs' specific genomic sequences in Rb gene, some molecular studies have already revealed crucial interactions with an endoribonuclease, the Nsp15 [4]. An *in vitro* analysis showed that retinoblastoma protein-binding motif (LXCXE/D) exists in the majority of Nsp15 altered cases of severe acute respiratory syndromes mediated by Covs. Additionally, mutations in the Rb-binding motif modify the corresponding expression of the sNsp15 in cells leading to an increased abundance of Rb in the cytoplasm, but also decrease overall levels of Rb. Similarly, SARS-CoVs' well conserved open reading frames (ORFs) are involved in Rb abnormal expression. A molecular study showed that ORF7a overexpression down regulated the mRNA transcription and expression of

cyclin D3 leading to decreased activity of cyclin D/cdk4/6 by inhibiting Rb phosphorylation. These aberrations block cell cycle progression at G0/G1 phase.

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Synchronous breast cancer metastases both to parotid and thyroid glands: a rare presentation

Dear Editor,

Metastasis to the salivary gland is rare. The parotid is the most commonly involved site among the salivary glands. Breast cancer metastasis to the parotid gland has been rarely reported in the literature, and relatively few case reports have described the imaging findings [1, 2]. The thyroid is a rare site for distant metastases from breast carcinoma. The incidence of thyroid metastases in fine needle aspiration biopsy (FNAB) was less than 0.2% [3]. A 59-year-old female patient was diagnosed with locally advanced left breast cancer with luminal B subtype in May 2011. She received four cycles of neoadjuvant cyclophosphamide-epiribucin-5-fluorouracil chemotherapy regimen and underwent left modified radical mastectomy with stage pT1N3M0 disease. She then received two cycles of adjuvant doxorubicin and docetaxel and subsequent adjuvant radiotherapy. She was on adjuvant letrozole treatment for about 6 years. Due to increased tumor marker levels, PET-CT scan and neck MRI were performed and showed nodules both in the right parotid gland and thyroid. FNAB and trucut biopsy from thyroid and parotid, respectively, revealed metastatic breast cancer with luminal B subtype in both sites in December 2020. She then started fulvestrant and palbociclib. On her last visit in October 2021, PET-CT scan showed no evidence of metastases. She is still continuing to receive fulvestrant and palbociclib. We reported a case of synchronous breast cancer metastases both to the parotid and the thyroid glands for the first time in the literature which highlights that thyroid and parotid metastases should be considered in a patient with thyroid and parathyroid lesions in combination with a history of breast carcinoma.

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P53/MDM-2 gene alterations in laryngeal squamous cell carcinoma

Dear Editor,

Cell cycle deregulation leads progressively normal epithelia to their neoplastic transformation. P53 is a key regulator of the genome stability and function. The gene is located on the short (p) arm of chromosome 17 at position 13.1 (17p13.1) encoding a nuclear phosphoprotein with a molecular mass of 53 kDa acting as a transcrip-

tion factor that negatively regulates cell proliferation. It is also involved in a significant number of cell signaling pathways including cell cycle, programmed cell death, and DNA repair. Murine double minute 2 (MDM2), a proto-oncogene (12q14.3) encoding a nuclear-localized E3 ubiquitin ligase, acts as a major negative regulator in p53-MDM2 auto-regulatory pathway. MDM2 directly binds to p53 and represses its transcriptional activity and promotes p53 proteasomal degradation. Aberrant p53/MDM2 over expression is a frequent observation in breast carcinomas [1]. Gene amplification is the major mechanism of MDM2 deregulation and overexpression in breast carcinoma correlated with aggressive phenotype [2]. Concerning laryngeal squamous cell carcinoma (LSCC), a study group co-analyzing the expression patterns of p53, its upstream regulator MDM2, and also p21/WAF molecule concluded that p53 mainly and MDM2 aberrant expression could be used as markers for inferior and worse prognosis (overall survival), respectively [3]. Interestingly, specific genetic imbalances (gene polymorphisms) regarding MDM2 gene seem to be associated to increased risk for LSCC onset. A study group implemented a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) protocol for the detection of specific MDM2 polymorphisms (MDM2 rs769412 and MDM2 rs937283). They observed that both of the analyzed polymorphisms were correlated with high susceptibility to LSCC rise and progression, especially in sub-groups of patients with a history of chronic alcohol consumption [4]. Similarly, another study group based on a combination of pyrosequencing and enzyme-linked immunosorbent assay (ELISA) analyzed the status of a specific single-nucleotide polymorphism (SNP) 309T/G SNP in the promoter region of MDM2 and measured MDM2 plasma levels, respectively [5]. They observed that the MDM2 SNP309 G allele acts as a significant LSCC and vocal leukoplakia inhibition genetic marker in the Chinese population, whereas GT type patients correlated with a lower plasma MDM2 level than the TT genotypes. In these patients, a low stage and metastatic potential was also observed. The previous referred molecular data show that deregulation of p53/MDM2 pathway is critical for LSCC rise and progression involved in the early genomic instability of normal laryngeal epithelia. In this model of gene co-reaction, a suppressor gene (p53) is downregulated combined with an oncogene (MDM2) overactivation.

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Solitary radius metastasis in a breast cancer patient: a rare presentation

Dear Editor,

Breast cancer is the most common cancer in women worldwide. Bone is the most frequent site of distant metastasis from breast cancer and accounts for the highest proportion of first site relapse in patients with breast cancer [1]. One study evaluated the incidence and distribution of bone metastases in breast cancer. The authors found that the most frequent site was the spine, including thoracic spine (63.6%) and lumbar spine (53.8%). The second commonly metastatic site was ribs (57.4%), followed by pelvis (54.1%) and sternum (44.34). The least affected site of bone metastases were ulna and radius (0.3%) [2]. However,one case with solitary metastasis to radius was reported in the literature [3]. Here, we present the second breast cancer patient having solitary metastasis to radius in the literature. A 55-year-old woman was diagnosed with right invasive breast ductal carcinoma and she underwent right modified radical mastectomy with stage T2N2M0 and luminal subtype B in December 2014 and then she received adjuvant chemotherapy of four cyles of adriamycin-cyclophosphamide, followed by 12 weeks of paclitaxel and furthermore she received adjuvant radiotherapy. She was with adjuvant endocrine treatment with letrozole for about 7.5 years. For the last 2 months, she suffered from right arm pain and right upper extremity MRG clearly showed destructive-lytic lesion 4.5 cm in size, located at the proximal radius in October 2021 and further imaging with PET-CT scan showed solitary right lytic-expansile-destructive lesion observed in the proximal radius with higher FDG uptake. Furthermore, biopsy taken from the right radius showed metastatic breast cancer with luminal B subtype. Currently, she will receive palliative radiotherapy to the radius together with fulvestrant, ribociclib and denosumab.

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Triple negative apocrine breast cancer with atypical metastatic presentations

Dear Editor,

Invasive apocrine carcinoma is a rare breast cancer that is frequently triple negative. Little is known about the characteristics of its molecular subtypes. Apocrine carcinoma, a subtype of invasive ductal carcinoma of the breast, also expresses androgen receptor (AR). Triple-negative apocrine adenocarcinomas have a modestly improved long-term survival when compared with triple-negative invasive ductal cancers [1,2]. A 48-year-old woman was diagnosed with left breast triple-negative apocrine carcinoma and underwent left modified radical mastectomy with stage T2N2M0 disease in January 2008. Her tumor expressed androgen receptor (AR) and Ki 67 was 10% as well. She received four cycles of adriamycin-cyclophosphamide followed by four cylcles of docetaxel. She then received adjuvant radiotherapy. She was on remission. BRCA status was not known at that time. She came to the clinic with right axillary lymphadenopathy in May 2013. Trucut biopsy showed metastatic triple-negative apocrine breast cancer with AR expression. Metastatic work-up did not reveal metastasis including right breast other than right axillary lymph node. Then she received 4 cyles of docetaxel and capecitabine followed by radiotherapy to right axillary region with complete remission. Surgery was not performed at all. While she was in remission for about 8 years, due to CA 125 and CEA tumor marker elevation, detailed metastatic work-up was performed showing metastatic left pleural metastatic nodules in November 2021. Trucut biopsy reported again metastatic triple-negative apocrine breast cancer with AR expression. Weekly paclitaxel was planned to be initiated. In conclusion, patients with triple-negative apocrine carcinoma had a better prognosis than patients with triple-negative breast cancer, and chemotherapy was associated with survival advantage in triple-negative apocrine carcinoma patients [3].

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Microsatellite instability in oral squamous cell carcinoma

Dear Editor,

Microsatellites are referred to repetitive nucleotide sequences including usually 1 to 5 base pairs repeated for 15-30 times which are normally relatively stable. Thousands of microsatellites are detectable throughout the human genome. In fact, during DNA replication accumulation of them forms a small loop in any of two strands. Insertion or deletion of these repeated nucleotide chains are identified also inside the introns of the genes. For all these molecular reasons, Microsatellite instability (MSI) is a biomarker for detecting DNA MMR deficiency in CRCs and also in a variety of malignancies of different histogenetic origin [1]. Among the genetic mechanisms that provide a stable

micro-environment inside the molecule, DNA mismatch repair system (DNA MMR) plays a leading role. Humanized homologues of DNA MMR main genes are located on chromosomes 2, 3, 5 and 7 including MLH1, MSH2, MSH3, GTBP/MSH6, PMS1 and PMS2 [2]. Specific genomic alterations –germline mutations, accompanied usually by allelic loss (loss of heterozygosity -LOH), or epigenetic changes such as promoter hypermethylation- in the MMR genes lead to loss of their expression affecting their function in repairing the corresponding base to base errors. In contrast to colon adenocarcinoma, there are limited data regarding DNA MMR and MSI in oral cavity carcinomas. Two independent study groups were based on patients with different ethnicity (Korean vs Asian Indians) exploring specific genetic polymorphism of the hMLH1gene. They reported that hypermethylation of the hMLH1 gene may be the principal inactivating mechanism in oral cancer with MSI in HPV related lesions and also that the hMLH1 -93 A>G polymorphism is associated with the higher risk of tobacco-related OSCC could be useful in screening population at a higher risk [3,4]. Hypermethylation of hMLH1 and hMSH2 might play a role in oral carcinogenesis and may be correlated with a tendency to develop multiple oral malignancies. Furthermore, expression of hMLH1, hPMS2, and hMSH2 genes seem to be related progressively with oral epithelial dysplasia and squamous cell carcinoma. Immunohistochemical analyses showed that reduced expression of these markers was correlated with dysplasia to carcinoma progression and also with the grade of the carcinomas (poorly differentiated from well-differentiated) [5]. Identification of specific gene deregulation mechanisms regarding DNA MMR genes is a significant issue for understanding their altered protein expression. Reduced expression levels of these markers are correlated with MSI both in oral cavity carcinomas. hMLH1 is a crucial gene for both of them and its abnormal expression and function influences the progression and the biological behavior in these malignancies.

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Isolated contralateral axillary lymph node recurrence in breast cancer

Dear Editor,

Isolated breast cancer metastasis to contralateral supraclavicular lymph node (CSM) without metastases to any other distant organ is currently assigned M1 status (stage IV) instead of N3 (stage III). Lymph node metastases in the contralateral axilla is consindered to be a locoregional spread of the tumor from the index breast via lymphatics rather than hematogenous spread [1]. Isolated CSM in breast cancer patients should not be classified as stage IV disease. Likewise, contralateral axillary nodal metastases (CAM) are classified as stage IV disease, although many centers treat CAM with curative intent. One study showed that CAM patients who received multi-modal therapy with curative intent may have overall survival (OS) more comparable to locally advanced breast cancer patients (LABC) than metastatic patients [2]. A 48-year-old woman was diagnosed with LABC right invasive ductal breast cancer carcinoma (cT3N2M0) with luminal B subtype in May 2015 and received neo-adjuvant chemotherapy of four cyles of adriamycin-cyclophosphamide followed by 12 weeks of paclitaxel and then she underwent right modified radical mastectomy with stage pT1N2M0 disease and luminal subtype B in December 2015 and then she started to receive adjuvant radiotherapy and adjuvant tamoxifen and ovarian function suppression. On routine follow-up, left supraclavivular lymphadenopathy was detected in breast ultrasonography in November 2021 and fine needle aspiration from lymphadenopathy showed atypical suspicious malignant cells while PET-CT scan showed only metastatic supraclavicular lymphadenopathy and 5 CSMs were excised with 5 nodal metastases-one with extracapsular extension with luminal B subtype in December 2021 and letrozole plus ribociclip were initiated and radiotherapy to left SCMs was planned as well. Furthermore, next generation and PD-L1 determination were ordered. Oligometastatic breast cancer, typically defined as the presence of 1-5 metastases, represents an intermediate state between locally advanced and widely metastatic disease. Emerging research suggests that oligometastatic cancer has a unique molecular signature distinct from widely metastatic disease, and that it carries a better prognosis. Owing to its more limited capacity for

widespread progression, oligometastatic disease may benefit from aggressive ablative therapy to known metastases. Options for ablation include surgical excision, radiofrequency ablation, and hypofractionated image-guided radiotherapy (HIGRT) [3,4]. Therefore, for this specific patient, we try to initiate aggressive local treatment concurrent with systemic treatment.

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