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LETTERS TO THE EDITOR

ALK inhibitors and cranial radiotherapy in brain metastasis from NSCLC

Dear Editor,

In recent years, an increasing number of studies using molecular techniques have detected some mutations in lung cancer, providing promising results regarding targeted therapies. There are many studies suggesting that Echinoderm microtubule-associated protein-like4 anaplastic lymphoma kinase (EML4-ALK) gene translocation has prognostic value could guide to individualized therapies in lung adenocarcinoma [1-4].

In 2009, in a a phase I/II study testing the oral c-met/ALK inhibitor crizotinib, on non-small cell lung cancer (NSCLC), higher response and survival rates were observed (XALKORI). The authors reported one-year response rate of 57% and progression-free survival (PFS) of 72% at 6 months. However, resistance develops within one year in the majority of the patients that responded to crizotinib and recurrences were generally seen in the brain and liver. It was suggested that the higher recurrence in the brain might be due to inability to pass through the blood-brain barrier and the nature of tumor in ALK-positive NSCLC [2,3].

In recent publications, it was suggested that second-generation ALK inhibitors can be alternative to local ablative therapy in both intracranial and extra-cranial metastases. Phase I/II studies on this topic are ongoing but treatment response is unknown in cranial metastasis [2,3]. Yoshide et al. reported that the incidence of brain metastasis was higher in ALK-positive NSCLC patients treated with crizotinib when compared to EGFR mutation-positive NSCLC patients treated with gefitinib and erlotinib [1]. A review by Dempke et al. has shown that long-term response was achieved by ALK inhibitors in asymptomatic brain metastasis arising from NSCLC. However, the authors emphasized the need for larger phase II studies to precisely define the activities and therapeutic effectiveness of these agents [3]. Currently, there is limited data about the effectiveness of ALK inhibitors in the treatment of brain metastasis from NSCLC. This is likely due to exclusion of patients with brain metastasis in the majority of phase II studies. It is now unclear which strategy is optimal, since there is no phase III study comparing whole brain radiotherapy (WBRT) plus EGFR and WBRT plus ALK inhibitors. In a study, Johung et al. evaluated the clinical response and toxicity in patients receiving ALK inhibitor plus radiotherapy (WBRT or stereotactic radiosurgery/SRS). The authors found median overall survival 49.5 months and median intracranial PFS 11.9 months in patients receiving combined therapy, concluding that concurrent use of ALK inhibitors and radiotherapy improves survival [4].

In cranial metastasis from lung adenocarcinomas, the combined use of ALK inhibitors with local ablative therapies provides more favorable and promising results when compared to WBRT and/or SRS. Further studies are needed to identify patients who may benefit from targeted therapies.

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Cancer stem cells in oral squamous cell carcinoma

Dear Editor,

Extensive genetic analyses have shown that cancer is a clonal disease. Concerning solid tumors (breast, head and neck carcinomas, colon, lung etc), a variety of gene functional and numerical imbalances in crucial molecular pathways such as cell cycle regulation, signaling transduction, apoptosis or angiogenesis have been identified and explained at the basis of cell malignant transformation [1]. Cell malignant transformation is mediated by an aberrant gene expression, including predominantly oncogenes' up-regulation combined with suppressor genes' downregula-

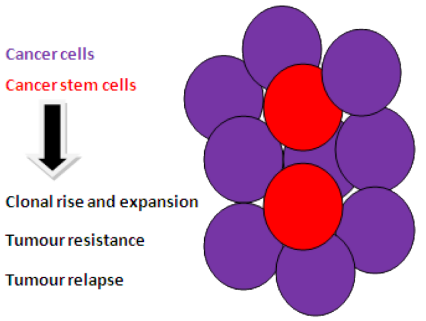

Figure 1. Schematic configuration of cancer stem cells inside the tumor micro-environment

tion that lead to cell cycle deregulation. Cancer genome consists of all genetic alterations that modify the normal DNA/m RNA sequences, triggering a cataract of molecular reactions inside and outside the nucleus microenvironment. Furthermore, malignancies are characterized by an inner clonal rise, intra-tumor heterogeneity and dormancy. Based on some carcinogenetic models, inside carcinoma core, there are specific cells that induce the progression of malignancy. According to some genetic hypotheses, cancer cells could arise from stem cells or from progenitor cells or from a severe dedifferentiation of mature differentiated normal cells [2]. The hierarchical stem cell model of malignant solid tumors rise and development is common in all these hypotheses.

Cancer stem cells (CSCs) demonstrate a similar to normal stem cells activity and the ability to self-renewal. They act as progenitor cells inside the malignant mass exposing their tumorigenic potential. They are also responsible for developing clonal expansion of the malignancy [3]. CSCs formulate a distinct cell pool which is involved in metastatic process and also in carcinoma relapse/recurrence after chemo-targeted therapeutic regimens application in eligible - based on molecular criteria - patients (Figure 1). Concerning head and neck squamous cell carcinomas (HNSCCs), recently published molecular studies based on cluster analyses on cancer cell lines using bio-informatics tools have shown that sub-populations of cancer cells acting as CSCs demonstrated increased levels of aldehyde dehydrogenase 'bright' activity ($ALDH^{br}$). Additionally, deregulation of the cell cycle and cell differentiation combined with signaling pathways alterations was correlated to this specific immunophenotype in oral squamous cell carcinoma (OSCC) [4]. In conjunction to this protein marker, the phenomenon of field cancerization in OSCC is under investigation [5]. It refers to the presence of CSCs local small subpopulations in areas adjacent to the primary malignancy microenvironment correlated to metastatic migration, tumor recurrence and even the birth of second primary tumors.

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Concurrent administration of aromatase inhibitors with chemotherapy might show better outcome in high risk hormone-receptor positive early-stage breast cancer patients

Dear Editor,

Adjuvant chemotherapy (CT) and endocrine therapy (ET) are administered sequentially in patients with hormone-receptor positive breast cancer. However, optimal timing (concurrent vs sequential administration) for the integration of these adjuvant treatments has not been investigated in detail. Concurrent administration might avoid the harmful effect of delay in the administration of ET. However, the cytocidal effects of various alkylating agents are inhibited in the presence of tamoxifen and preclinical studies demonstrated a possible negative interaction between tamoxifen and CT, when administered concurrently [1]. Large randomized study showed a superiority of sequential as compared to concurrent administration of CT and tamoxifen, then it was recommended that tamoxifen should be started after CT [2]. However, there are no data available about the interaction between aromatase inhibitors and cytotoxic drugs in hormone-receptor positive early-stage breast cancer. A recent meta-analysis showed no association between the timing of administration of adjuvant CT and ET and disease-free survival and overall survival in breast cancer patients. In this meta-analysis, data about aromatase inhibitors were not included [3]. I propose

that concurrent administration of aromatase inhibitors with CT might show better outcome in high risk hormone-receptor positive early-stage breast cancer patients. This issue merits further investigation.

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Could PTEN be a biomarker in head and neck cancers subjected to radiotherapy as similar to HPV?

Dear Editor,

Currently, many genetic alterations have been defined in cancers. Some of these alterations are detected early and are associated to tumor onset, while others are detected late and account for disease progression. It is unknown whether genetic and epigenetic oncogenic alterations in PTEN occur early or late. Based on preclinical data, loss of PTEN activity is anticipated in tumors [1-3].

Localized on chromosome 10, PTEN's product is a protein with lipid phosphatase characteristics. PTEN is a most important tumor suppressor that limits the activity of PI3K/Akt signaling pathway. Loss of PTEN activity causes PIP3 accumulation and activation of Akt pathway, resulting in cell proliferation, inhibition of apoptosis, increased tumor angiogenesis and increased cell motility and metastasis. Even a 20% decrease in PTEN expression is sufficient enough for cancer development. Somatic deletions and/or mutations of PTEN gene is commonly seen in some types of tumors, while they are less frequent in some others. Tumors associated with frequent somatic mutation include endometrial cancer, malignant melanoma, breast cancer, high-grade glioblastoma and prostate cancer [2-5].

There are limited literature data about the role of loss in PTEN expression on resistance related to radiotherapy and radiosensitivity, comprising unclear and contradictory results. In a cell culture study by Zhang et al., it was suggested that PTEN- cells were more resistant to radiation than PTEN+ cells in nasopharyngeal cells in clone formation analysis. The authors suggested that characteristics of cancer cells resistant to radiation are regulated by PTEN and suggested that the deleted phosphatase and tensine homolog of PTEN tumor suppressor gene plays role in stem cell regeneration [4]. Snietura et al. suggested that PTEN could be prognostic and predictive marker in patients that received radiotherapy for neck and head tumors. Again, they suggested that PTEN expression is associated to favorable outcome after accelerated postoperative radiotherapy when compared to conventional fractionation [2]. In the study by Pattje et al., it was reported that PTEN expression increased local failure in squamous cell cancers of head and neck which were treated with postoperative radiotherapy [3]. Yang et al. reported that local recurrence risk may be higher in PTEN-negative patients than PTEN-positive patients with early stage laryngeal cancer [5]. Horn et al. showed that PTEN expression is higher in HPV-positive oropharyngeal tumors [1]. In many studies, PTEN expression is associated to better prognosis in breast cancer, astrocytoma, cervix, prostate and colorectal cancers treated in combination with radiotherapy [1,2,5].

In conclusion, it is important to identify novel biomarkers such as PTEN which could lead to the development of novel therapeutic strategies. Stimulation of PTEN activity by any means induces apoptosis, suppresses tumor growth and prevents metastasis by abolishing Akt activity.

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Adding anthracycline plus cyclophosphamide to adjuvant paclitaxel plus trastuzumab might be more reasonable in stage I hormone receptor negative HER-2 positive breast cancer patients

Dear Editor,

Patients with small, low grade, early HER2-amplified breast cancer (particularly ER-positive tumors) have a relatively better prognosis, and hence, adjuvant therapy should be planned considering the risk/benefit ratio. Due to the risk of cardiotoxicity of anthracyclines, other chemotherapy regimens were administered in this group of patients. Favorable efficacy and safety results with weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by 9 months of trastuzumab monotherapy (APT trial) have been reported in two different studies [1,2]. NCCN guideline also approves for the use of this regimen for stage I HER-2 positive disease regardless of hormone receptor status [3]. However, hormone receptor negative, HER2-positive constitute a more aggressive disease than hormone receptor positive HER2-positive patients at stage I. Although no literature data exist to support this hypothesis, among our 83 node negative, HER-2 positive cases, significantly more cases with hormone receptor negative disease developed recurrences with APT trial during longer follow-up [2]. Therefore, our recommendation for hormone receptor negative HER-2 positive stage I cases might be more feasible to add adriamycin and cyclophosphamide before APT trial. This issue merits further investigation.

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Correlation of tumor biology and optimal colorectal liver metastasis resection margin: Existing evidence and future directions

Dear Editor,

Surgical management of stage IV colorectal cancer with liver metastases has evolved significantly during the last 3 decades. Colorectal liver metastases (CRLM) historically were associated with a poor prognosis and resection was offered to selected patients. A step-wise approach as orchestrated by a multidisciplinary tumor board in combination with advances in targeted systemic agents and evolution of surgical techniques has remarkably transformed prognosis.

Widespread interest has focused on optimizing surgical procedures as well as in identifying prognostic and predictive factors for recurrence to modify concurrent therapies [1]. Morphologic tumor factors of primary colorectal malignancy, timing of presentation, size and number of metastases, serum tumor markers and surgical factors such as margins and extent of resection have been evaluated extensively; yet consistent reliable predictions of outcome remain elusive. Several recent reports have identified specific factors of tumor biology, which may influence optimal resection [2].

The presence of mutant-specific DNA from metastatic satellite foci around the margins of dominant hepatic metastasis has been investigated. According to a study, the presence of micrometastases within 4mm of the tumor margin correlated with a marginal decrease in disease-free survival (DFS), but not overall survival (OS) [3]. Another study confirmed mutant-specific DNA in metastatic foci adjacent to CRLM and interestingly showed such findings were limited to within 4mm of the metastases in patients who had an objective response to neoadjuvant treatment [4]. Others have shown that positive resection margins were more frequently encountered in patients with RAS-mutant than RAS-wild type cancers, probably as a result of infiltrative and/or migratory tumor specific growth pattern. Although the local recurrence rates were not addressed, a wider 10mm resection margin for patients with RAS-mutant type CRLM was proposed [2]. Further independent evaluation of the relationship between resection margin width of KRAS status and long-term outcomes has shown that in patients with KRAS wild-type cancers a 1-4mm margin correlated with improved OS compared to a R1 resection and a >4mm margin did not confer additional survival benefit. In contrast, a ≥10mm margin in patients with KRAS mutant-type cancers was not associated with improved survival compared to R1 resection [5].

The clinical impact of these biologic markers remains unknown. Although interesting results are shown, there are limitations: retrospective data collection, unknown KRAS

status prior to CRLM resection, primary origin of KRAS status, colorectal vs. metastasis and other undetailed tumor and patient factors. The evidence is compelling to evaluate KRAS status before hepatic resection of CRLM to determine its operative utility. Moreover, the difference in parenchymal transection technique, the assessment of which clearly influences the results of the measure of gross resection margins must be addressed. Although margins exceeding 1 or 1.5cm would be ideal, this is improbable given that liver-sparing hepatectomy is promoted widely. Finally, patterns of intrahepatic recurrence should be assessed. In the setting of recent studies reporting critical correlation between tumor biology, recurrence and survival rates, implementation of evidence-based and clinically applicable recommendations in the standard surgical practice is of paramount importance.

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