LETTER to the EDITOR

# Circulating Tumor BRAF Mutation and Personalized Thyroid Cancer Treatment

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## Dear Editor

Thyroid cancer is an important malignancy with relatively high incidence among women in middle east (Larijani et al., 2005; Larijani et al., 2004; Mohagheghi et al., 2009) and many part of the world (Salim et al., 2010) like Iran (Sanii et al., 2012; Haghpanah et al., 2006). The incidence has been increasing with rate of up to 3% in countries that reliable cancer registry exits (Morris et al., 2016; Reynolds et al., 2005).

In spite of good prognosis of differentiated thyroid carcinoma (DTC), about five to ten percent of patients will develop metastasis and fail to respond to radioactive iodine (RAI), and other traditional therapies (Chen et al., 2009). The lack of effective therapies for DTC, resistant to radioiodine and traditional therapies, is now being overcome by the development of targeted novel compounds (Antonelli, 2014) in the context of personalized treatment. There is strong believe that ctDNA results will be an additional tool while tumor biopsy will remain the gold standard, as it yields important information about tumor type, morphology and origin of tumor, genetic or epigenetic alterations (Saffar et al., 2013; Mohammadi-asl et al., 2011; Sanii et al., 2012). It is still under the debate that circulating tumor markers will take the place of standard tissue biopsy or will support it to guide us to the more effective interventions?

BRAFV600E mutation leading to excessive activation of the MAPK pathway accounts for 90% of all cancer-related BRAF mutations and is found in about half of all papillary thyroid cancers (29-69%) and one fourth of anaplastic thyroid cancers (10-35%) (Xing et al., 2013b; Bible and Ryder, 2016). BRAF mutation is completely related to tumors resistance in respond to the first line of treatment which is radioactive iodine (RAI) (Xing et al., 2013a). Vemurafenib is an orally bioavailable, ATP-competitive, small-molecule inhibitor of BRAF kinase with the potential of antineoplastic activity. It selectively binds to the ATP-binding site of BRAF kinase and inhibits its activity, which may result in an inhibition of an over-activated MAPK signaling pathway downstream in BRAFV600Ekinase-expressing tumor cells and a reduction in tumor cell proliferation (Information, (accessed Aug. 20, 2016)). Vemurafenib (Zelboraf; Plexxikon/Roche, with molecular formula:C23H18ClF2N3O3S) joins other multi-targeted kinase inhibitors (MKIs) (Sorafenib, Lenvatinib) and lead to more effective treatment of patients (Brose et al. ; Bollag et al., 2012).

The published result related to a phase II clinical study in Philadelphia illustrated treating metastatic thyroid cancer patients with the targeted therapy of Vemurafenib to establish the activity of Vemurafenib in patients with BRAFV600E-positive papillary thyroid (Brose et al.). Their study was on a total of 51 papillary thyroid cancer patients between January 2011 and January 2013 and established that "Vemurafenib showed antitumor activity in patients with progressive, BRAFV600E-positive papillary thyroid cancer refractory to radioactive iodine who had never been treated with a multi-kinase inhibitor. As such, this agent represents a potential new treatment option for these patients"(Brose et al.).

Recent developments in DNA-sequencing and molecular genetics technologies provide an extraordinary ability to characterize the genetic alterations and pathways in tumors comprehensively and make it possible to develop therapies based on the genetic makeup of each tumor (Stratton, 2011; Khatami et al., 2017). The large-scale drug screening that incorporates genomic and gene expression data is another breakthrough to identify drug response biomarkers that could inform optimal application of cancer drugs (Garnett et al., 2012; Yang et al., 2013; Girotti et al., 2016). It is a common knowledge that a small piece of a tumor receiving after tissue biopsy doesn't represent the whole tumor, let alone metastases. Liquid biopsy, which is a diagnostic concept, opens a new perspective for real time monitoring of cancer as whole and and tumor evaluation tumor at molecular level (Pantel and Alix-Panabieres, 2013). Liquid biopsy is defined as circulating tumor cells (CTCs) and fragments of circulating tumor DNA (ctDNA) shed into the bloodstream from primary and metastatic tumor deposits (Ozkumur et al., 2013). Using of ctDNA is superior as a non-invasive and cost effective solution to identify reliable biomarkers for measuring tumor growth, metastasis and response to treatments (Qin et al., 2016). To date, liquid biopsies have generated a lot of excitement since they can provide a non-invasive tool on state of cancer progression, providing opportunity to manage the best effective (Karachaliou et al., 2015). In addition to present evidences about stage and spread, liquid biopsies can be used to observe the special effects of cancer treatment, give an early notice about possible recurrence and offer clues to the reasons for treatment resistance (Karachaliou et al., 2015). Liquid biopsies could be used to guide cancer treatment strategy and perhaps even screen for tumors that are not yet visible on imaging (Karachaliou et al., 2015). It has been shown

that a higher percentage of mutant BRAFV600 in cfDNA is completely related to the shorter survival in advanced cancer (Turski et al., 2016), specially in the way of BRAF inhibitor treatment strategies (Turski et al., 2016).

Take advances in molecular genetics technology into consideration, evaluation and characterization of circulating tumor markers can be the best alternative for real-time tumor tracking. There is a big hope that in the near future liquid biopsy will have a great progress in cancer diagnosis and now is the exact time to focus on CTCs and ctDNA as a circulating tumor biomarker specifically in personalization of cancer treatment.

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