

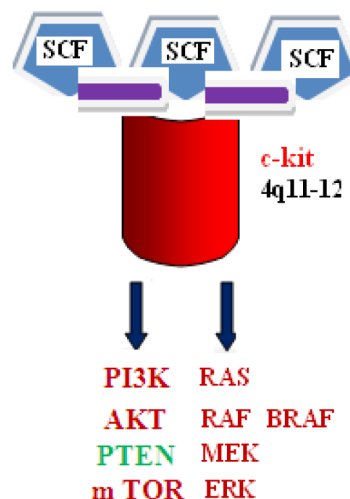
## LETTERS TO THE EDITOR

# c kit in oral mucosal melanoma

Dear Editor,

Among head and neck malignancies, primary mucosal melanoma is an extremely aggressive tumor with fatal prognosis. This malignancy arises from melanocytes located in the mucosal epithelium of the oral cavity, nasal and also paranasal areas and its etiology is unknown. Compared to cutaneous melanoma, this malignancy demonstrates some similarities but also distinct histo-morphological features and genetic profile [1]. Referring to its pathogenesis, cigarette consumption seems to be a risk factor, although there are limited and sometimes controversial data. In contrast to cutaneous melanoma, there is no evidence that ultra-violet radiation is a predominant factor. Based on multiple and extensive molecular analyses, BRAF (V-RAF murine sarcoma viral oncogene homolog B), MEK (mitogen-activated protein kinase kinase), N-RAS and also bcr-abl/c-kit/platelet-derived growth factor receptor (PDGF-R) oncogenes overactivation via point mutations composes a significant molecular landscape in oral mucosal melanoma (OMM) tissues [2].

C-kit gene (cytogenetic band: 4q11-12) encodes for the human homolog of the proto-oncogene c-kit. C-kit was first identified as the cellular homolog of the feline sarcoma viral oncogene v-kit. Multiple transcript variants encoding different isoforms have been found for this gene. The protein acts as a transmembrane receptor tyrosine kinase (RTK), especially as a type-3 cell-surface receptor for MGF (mast cell growth factor). Its normal activation - due to cytokine stem cell factor (SCF) ligand-high affinity binding dimerization and phosphorylation - regulates a cataract of sub-membranous cytoplasmic reactions involving molecules of different signaling transduction pathways (RAS/RAF-MEK-ERK/MAPK, PI3K/AKT/PTEN/mTOR) (Figure 1). A variety of normal functions including cell survival, proliferation, hematopoiesis, stem cell maintenance, gametogenesis, mast cell, interstitial cells of Cajal development, and melanogenesis are mediated by the c-kit protein. Somatic (missense) mutations in the corresponding gene are associated with gastrointestinal stromal tumors (GISTs), mast cell disease, acute myelogenous leukemia, piebaldism and also other sarcomas. Concerning OMM, harbored KIT mutations are detected in 7.0 to 20% of analyzed cases (exons 9,11,13, and 17), a significant percentage compared to cutaneous melanoma, in which approximately 3 to 15% malignant tissues are found to be c-Kit-mutant [3]. Among the latter, increased percentages implicate acral skin disease (palms, soles and nail bed). According to published combined c-kit molecular (polymerase chain reaction-PCR) and immunohistochemical analyses, increased protein expression in atypical melanocytes suggests the role of c-kit in the early stage of OMM tumorigenesis. Based on this observation, c-kit protein expression correlated with activating mutations indicating the pertinent role of the pro-



**Figure 1.** c-kit - SCF ligand binding dimerization and phosphorylation- regulates a cataract of sub-membranous cytoplasmic reactions involving molecules of different signaling transduction pathways including RAS/RAF-MEK-ERK/MAPK, PI3K/AKT/PTEN/mTOR (reddish/maroon molecules: oncogenes, green: suppressor genes, purple lines: dimerization of stem cell factor-SCF (blue) ligands).

tooncogene KIT in the tumorigenesis of OMM [4]. Despite the obvious progress in detecting activating c-kit mutations in OMM, its impact in handling the corresponding patients based on targeted therapeutic anti-kit agents seems to be poor. In contrast to increased response rates (up to 80%) to imatinib mesylate - a selective inhibitor targeting c-Kit, Abl and PDGFR- observed in GISTs patients, in c-Kit-mutant melanoma the response rate to imatinib is only 30%. A major genetic factor that negatively influences response rates and also recurrence of the malignancy in OMM seems to be the elevated percentage of activating mutations, especially in exon 11 variant (~34% of c-Kit mutations) [5]. Besides imatinib, c-Kit inhibitor resistance is observed also in other novel agents such as sunitinib, dasatinib and nilotinib, reflecting poor sensitivity of the malignancy.

## References

1. Ascierto PA, Accorona R, Botti G et al. Mucosal melanoma of the head and neck. *Crit Rev Oncol Hematol* 2017;112:136-52.
2. Hsieh R, Nico MM, Camillo CM, Oliveira KK, Sanguenza M, Lourenço SV. Mutational Status of NRAS and BRAF Genes and Protein Expression Analysis in a Series of Primary Oral Mucosal Melanoma. *Am J Dermatopathol* 2017;39:104-10.

3. Lyu J, Wu Y, Li C et al. Mutation scanning of BRAF, NRAS, KIT, and GNAQ/GNA11 in oral mucosal melanoma: a study of 57 cases. *J Oral Pathol Med* 2016;45:295-301.
4. Rivera RS, Nagatsuka H, Gunduz M et al. C-kit protein expression correlated with activating mutations in KIT gene in oral mucosal melanoma. *Virchows Arch* 2008;452:27-32.
5. Karimkhani C, Gonzalez R, Dellavalle RP. A review of novel therapies for melanoma. *Am J Clin Dermatol* 2014;15:323-37.

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## Aromatase inhibitors might be more effective when they are given 2-3 months later after the administration of luteinizing hormone-releasing hormone agonists in younger premenopausal breast cancer patients

Dear Editor,

Aromatase inhibitors (AIs) and luteinizing hormone-releasing hormone (LHRH) agonists are effective in hormone receptor-positive premenopausal breast cancer patients. Adjuvant exemestane + LHRH analogs seem to work better than tamoxifen + LHRH analogs in high-risk and young women. The degree of ovarian suppression is important for AIs activity. Specifically, monitoring estradiol upon AI treatment might be useful in young breast cancer patients who did not receive adjuvant chemotherapy [1]. In clinical practice, AIs are given concomitantly with LHRH analogs. However, ovarian suppression might not be at satisfactory level at which AIs work efficiently. They even might stimulate LHRH with increasing estrogen levels. Taken all together, it is more rationale to give AIs 2-3

months later after the administration of LHRH agonists in younger premenopausal breast cancer patients.

### References

1. Torrisi R, Rota S, Losurdo A, Zuradelli M, Masci G, Santoro A. Aromatase inhibitors in premenopause: Great expectations fulfilled? *Crit Rev Oncol Hematol* 2016;107:82-9.

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## Bevacizumab, temsirolimus with or without cetuximab: combinational treatment against patients with advanced HNSCC

Dear Editor,

Overexpression of the epidermal growth factor receptor (EGFR) is a common characteristic of head and neck squamous cell carcinomas (HNSCC). There remain numerous unanswered questions regarding the optimal use of cetuximab in HNSCC, including patient selection, its mechanisms of action and resistance, the effect of human papillomavirus status on outcomes, its role when combined with induction chemotherapy or adjuvant radiation, and optimal management of skin toxicity and hypersensitivity reactions. In addition, a variety of other anti-EGFR agents are currently under investigation in clinical trials in different HNSCC therapeutic settings [1]. On the other hand, the function of PI3K-AKT-mTOR molecular signal

transduction pathway, via interactions with growth factor receptors, plays a crucial role in regulating normal squamous cell growth. The deregulation of the mTOR pathway participates significantly in the development of HNSCC [2].

Recently, Liu et al. [3] made a very interesting report on the treatment of advanced malignancies treated with the combination of the anti-VEGF binding monoclonal antibody bevacizumab, anti-EGFR monoclonal antibody cetuximab, and the mTOR inhibitor temsirolimus. They have stated that this combination exhibited activity against HNSCC but generated a more toxic profile. The reported HNSCC patients received the combination after failure of prior administration of 2-3 lines with cytotoxic regimens and reached at 54% best response but suffered from considerable incidence of grade 3-4 toxicities. Also, it was indicated that

this is the first study to evaluate the combination of bevacizumab, temsirolimus and cetuximab in patients with HNSCC and other advanced malignancies and treatment with this combination was based on previous experience and logical assumptions of synergistic effects. Of the 8 HNSCC patients evaluable one partial response (PR) and one stable disease (SD) were confirmed in two patients previously treated with cetuximab and one PR in a patient previously naive to cetuximab. Toxicity was significant in the different dosing schemes studies, especially at 10mg/kg of bevacizumab plus 5mg of temsirolimus and 100 or 75 mg/m<sup>2</sup> of cetuximab. This report was a valuable investigation. However we would like to contribute with some earlier clinical results, rather the first published, on bevacizumab and temsirolimus combinational treatment in patients with advanced HNSCC previously treated unsuccessfully with cetuximab and multiple cytotoxic drug combinations [4].

Bozec et al. [5] previously reported that mTOR inhibition with temsirolimus exhibits synergistic antiproliferative effects when administered in combination with irradiation, anti-EGFR (cetuximab) and anti-angiogenic (bevacizumab) therapies in HNSCC xenografts. In a previously published work [4] the clinical benefit of the combination of temsirolimus and bevacizumab was demonstrated for the first time. The drug combination *in vitro* against the A431 human squamous epidermoid carcinoma cell line, as well as *in vivo* on the treatment of A431 xenograft on Nu/Nu\*nuBR mice resulted in significant additive and synergistic cytostatic activity. Further the treatment with the combination of two patients with chemoresistant, multi-treated HNSCC (including prior cetuximab with chemotherapy) as biweekly bevacizumab (6mg/kg) plus temsirolimus (25mg) showed significant results since both patients achieved a PR and progression-free survival of more than 9 months with no significant hematological or non-hematological toxicities. This is in contrast to the published results from Liu et al., where the triplet was associated with significantly more toxic effects at the reported different dosing schemes and it seems that a comparable efficacy can be achieved with less toxicity using only temsirolimus plus bevacizumab after cetuximab.

To date, we have used this combination in similar patients with acceptable and promising results, thus we believe that this combination is worth of further investigation in patients with either locoregional nonmetastatic HNSCC or as first line treatment in recurrent or metastatic setting.

## References

1. Cohen RB. Current challenges and clinical investigations of epidermal growth factor receptor (EGFR)- and ErbB family-targeted agents in the treatment of head and neck squamous cell carcinoma (HNSCC). *Cancer Treat Rev* 2014;40:567-77. doi: 10.1016/j.ctrv.2013.10.002.
2. Mastronikolis NS, Tsiambas E, Papadas TA et al. mTOR deregulation in oral cavity squamous cell carcinoma. *JBUON* 2017;22:610-3.
3. Liu X, Kambrick S, Fu S et al. Advanced malignancies treated with a combination of the VEGF inhibitor bevacizumab, anti-EGFR antibody cetuximab, and the mTOR inhibitor temsirolimus. *Oncotarget* 2016;7:23227-38. doi: 10.18632/oncotarget.7594
4. Trafalis DT, Aliferis C, Dalezis P, Geromichalos G, Sitaras NM. Indications for an alternative effective treatment of head and neck squamous cell carcinoma with temsirolimus plus bevacizumab: from bench to bedside? *Anticancer Drugs* 2012;23:874-82.
5. Bozec A, Etienne-Grimaldi MC, Fischel JL et al. The mTOR- targeting drug temsirolimus enhances the growth-inhibiting effects of the cetuximab-bevacizumab- irradiation combination on head and neck cancer xenografts. *Oral Oncol* 2011;47:340-4.

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## HPV DNA methylation in cervical and head and neck carcinomas

Dear Editor,

Human papillomavirus (HPV) involvement in cervical and head and neck squamous cell carcinomas (HNSCC) development and progression represents a classical example of viral-mediated carcinogenesis. Initially in both pathological entities, High Risk (HR) HPV subtypes initially act as a simple (episomal) viral infection in target cells [1]. Persistent infection leads to a HPV-DNA integration into the host cell genome resulting to aberrant oncogene E6/E7 expression. Inactivation of p53 and Rb suppressor genes are the main genetic abnormalities correlated with HPV E6/E7 increased production, respectively. Besides genetic events including gross chromosome and specific gene aberrations, new molecular approaches, such as epigenetic changes based on promoter methylation and miRNAs ex-

pression have also been implemented in analyzing HPV-positive and HPV-negative HNSCC tumor tissues [2]. DNA methylation drives numerous cancer-related genes to their silencing, modifying also cell cycle checkpoint regulation, signal transduction, cell adhesion, angiogenesis and apoptosis. CpG island methylation is closely related to biochemical modifications of histone proteins by interacting with Methyl-CpG-binding domain protein 2 (MBD2) and DNA methyltransferases (DNMTs). In cancer cells, abnormal DNMTs expression negatively affects intra-nuclear instability. Concerning DNA methylation as a multi-step process, crucial role plays a complex reaction of DNA methyltransferases (DNMTs), including *de novo* (DNMT3A and DNMT3B) and maintenance (DNMT1) enzymes. CpG island insertion induces normal methylation of gene promoters. Hypermethylation of DNA in gene promoter seg-

ments and also overall hypomethylation are epigenetic changes that have been frequently detected in human solid malignancies, triggering a cataract of chain reactions due to disorganization of this critical for gene activity region.

Molecular studies analyzing HPV DNA-triggered epigenetic changes have shown that methylation at CpG sites in the 3'LCR of HPV16 could be an early genetic event affecting critically E2 protein activity when episomal HPV DNA is present [3]. Interestingly, another study group observed that regarding this specific gene promoter segment HPV16 was correlated with a higher methylation at all CpG sites compared to HPV18 and HPV45 regions [4]. They also showed different molecular patterns based on the presence and disruption of intact E1/E2 at all CpG sites. In fact, disruption of E1/E2 was more frequently found in HPV45 and HPV18 compared to HPV16 DNA. Additionally, concomitant disruption of E1/E2 was most frequent in HPV45. Mechanisms of aberrant methylation have also been identified in HNSCCs. It is also known that HPV-positive oral squamous cell carcinomas (OSSC) demonstrate a better phenotype and prognosis status than the corresponding HPV-negative cases [5]. Based on these molecular differences regarding methylation status, patients with OSSC are characterized by specific genetic signatures profiles eligible for personalized targeted therapeutic strategies.

## References

1. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol* 2010;11:781-9.
  2. Kalfert D, Pesta M, Kulda V et al. MicroRNA profile in site-specific head and neck squamous cell cancer. *Anticancer Res* 2015;35:2455-63.
  3. Leung TW, Liu SS, Leung RC, Chu MM, Cheung AN, Ngan HY. HPV 16 E2 binding sites 1 and 2 become more methylated than E2 binding site 4 during cervical carcinogenesis. *J Med Virol* 2015;87:1022-33.
  4. Amaro-Filho SM, Pereira Chaves CB, Felix SP et al. HPV DNA methylation at the early promoter and E1/E2 integrity: a comparison between HPV16, HPV18 and HPV45 in cervical cancer. *Papillomavirus Res* 2018;5:172-9.
  5. van Kempen PM, Noorlag R, Braunius WW, Stegeman I, Willems SM, Grolman W. Differences in methylation profiles between HPV-positive and HPV-negative oropharynx squamous cell carcinoma: a systematic review. *Epigenetics* 2014;9:194-203.
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# Retesting HER2 status in axillary node metastases has important potential as a guide to subsequent therapy after pathologic complete eradication of cytologically proven hormone receptor positive and HER2-negative primary breast cancer following neoadjuvant treatment

Dear Editor,

Estrogen receptor (ER), progesterone receptor (PR), and HER2/neu are the most important tissue markers in the management of breast cancer in the (neo) adjuvant settings and in the setting of metastatic disease. Many studies have demonstrated a discordance of expression between primary breast cancer and synchronous axillary metastases. High HER2 concordance between primary breast cancer and axillary lymph node metastases has been demonstrated in many studies; in the discordant cases, it is more frequent to have HER2-positive metastases with negative primary tumors than the opposite [1-3]. Specifically, retesting HER2 status in axillary node metastases is important potential as a guide to subsequent therapy after pathologic complete eradication of cytologically proven hormone receptor positive and HER2-negative primary breast cancer following neoadjuvant treatment. If axillary lymph node metastases are HER2-positive, then anti-HER-2 treatment should come into play. This issue merits further investigation.

## References

1. Rossi S, Basso M, Strippoli A et al. Hormone Receptor Status and HER2 Expression in Primary Breast Cancer Compared With Synchronous Axillary Metastases or Recurrent Metastatic Disease. *Clin Breast Cancer* 2015;15:307-12.
2. Li P, Liu T, Wang Y, Shao S et al. Influence of neoadjuvant chemotherapy on HER2/neu status in invasive breast cancer. *Clin Breast Cancer* 2013;13:53-60.
3. Hennessy BT, Hortobagyi GN, Rouzier R et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. *J Clin Oncol* 2005;23:9304-11.

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## Chromosomal instability mapping in meningioma

Dear Editor,

Extensive epidemiological studies have shown that -among primary central nervous system neoplasms - meningiomas represent the most common type in adults worldwide. Their histological substrate is the arachnoid cap cells of the meninges on the periphery of the brain. Brain tissue invasion is the most critical histopathological evidence of aggressive biological behavior of the tumor. Furthermore, meningiomas' extra-cranial metastatic potential is low and their metastatic activity and penetration is extremely rare [1]. Novel and sophisticated molecular techniques based on next-generation whole-genome sequencing analyses have screened significant series of meningiomas and detected gross chromosomal and specific gene aberrations (rearrangements/intra- or inter- translocations, gains, frame-shift deletions/insertions, point-driver mutations or in-frame fusions) which also reflect their grades of differentiation (grades I-III). According to their histo-genetic features, deletion (loss of heterozygosity) or mutation on chromosome 22 and especially in the 22q11.21-13.33 band which encodes for neurofibromatosis 2 (NF2) is involved in grade I meningiomas rise and progression. Additionally, PIK3CA, KLF4, CHEK2, POLR2A, SUFU, SMARCB1, AKT1, SMO, NOTCH2, and also TRAF7 genes demonstrate specific mutations or deletions in them. These genomic variants are correlated with specific pathological sub-types including clear cell and rhabdoid variants, respectively. Interestingly, anatomical location of meningiomas seems to be associated also with specific gene alterations. A subgroup of them which carries TRAF7/AKT1 and SMO mutations, rise on the anterior fossa, median middle fossa, or anterior calvarium, and most of them were meningothelial or transitional meningiomas [2]. The majority of them - including the NF2 gene - are tumor suppressor genes which are deleted in meningiomas, whereas gene amplification mechanism is prominent in the rest of them which act as oncogens. Furthermore, germline mutations have been identified implicating chromatin remodeling complex subunit (SMARCB1) [3]. Numerical imbalances affect also other chromosomes besides chromosome 22. Fragment deletions have been detected on chromosome 1p and also 2q33-q35. Regional amplifications occur on chromosome 6p21-p22 and also on chromosomal

13q33, 17 and 19. In conjunction to chromosomal and gene instability described above, meningiomas are characterized by a broad spectrum of somatic single nucleotide variants, demonstrating specific single nucleotide polymorphism [4]. Chromosome 1, 3, 9 and 19 were found to be frequent carriers regarding these polymorphisms. In higher grades (II-III) meningiomas, involvement of human telomerase catalytic protein subunit (h-TERT) and also SMARCE1 and BAP1 mutations combined or not with NF2 loss/mutation have been identified. Finally, concerning epigenetic alterations, abnormal methylation profiles seem to be associated with specific phenotypes of the neoplasm combined or not with chromosome 22 monosomy and NF2 mutations [5].

### References

1. Du Y, Lu T, Huang S, Ren F, Cui G, Chen J. *Cancer Commun (Lond)*. 2018;4:16-22.
2. Yuzawa S, Nishihara H, Tanaka S. Genetic landscape of meningioma. *Brain Tumor Pathol* 2016;33:237-47.
3. Smith MJ. Germline and somatic mutations in meningiomas. *Cancer Genet* 2015;208:107-14.
4. Tang M, Wei H, Han L et al. Whole-genome sequencing identifies new genetic alterations in meningiomas. *Oncotarget* 2017;8:17070-80.
5. Bi WL, Prabhu VC, Dunn IF. High-grade meningiomas: biology and implications. *Neurosurg Focus* 2018;44:E2-6.

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## Role of mTOR signaling pathway proteins and proteins influencing mTOR pathway in resistance to radiotherapy in prostate cancer

Dear Editor,

Novel therapeutic strategies targeting specific signaling pathways and immunotherapy have been investigated in aggressive prostate cancer. In previous studies, it was found that mammalian target of rapamycin (mTOR) signaling pathway is an attractive target in the treatment of prostate cancer. The mTOR protein is a serine/threonine kinase bound to PI3K. Recent findings showed that mTOR

pathway is activated in several cellular processes [1-3].

In previous studies, it was found that mTOR pathway is important in the development of prostate cancer. When compared to low-grade prostate cancer (Gleason  $\leq 7$ ), pAKT is often increased in high-grade prostate cancers (Gleason  $\geq 8$ ) and it was shown that this is correlated to increased mTOR activity. It was found that PTEN loss or PI3K/AKT pathway activation is common in invasive and metastatic prostate cancer. It was also reported that PTEN loss and

AKT activation changed the cellular response in the treatment with maximal androgen blockade and that it was an important marker for castration-resistant prostate cancer development [1-4].

In recent studies, it was found that mTOR pathway play a role in the resistance to radiotherapy in prostate cancer. However, there is no sufficient data on this role. In a cell culture study, Ni et al. emphasized that the epithelial cell adhesion molecule (EpCAM), also known as CD326, has an important role in prostate cancer proliferation, invasion and chemoradiation resistance related to PI3K/Akt/mTOR pathway activation and that it is a novel therapeutic target for sensitization of prostate cancer cells to chemoradiotherapy [1]. In a cell culture study, Yao et al. investigated the role of platelet activating factor receptor (PAFR) in the progression of prostate cancer and development of radioresistance. The authors suggested that PAFR causes radioresistance via the mTOR pathway [3]. In another study, it was emphasized that continuous activation of PI3K/Akt/mTOR pathway causes radioresistance [4].

In previous studies, it was shown that mTOR signaling pathway proteins (p-mTOR, AKT, PIK3CA, 4E-BP1, p-P70S6K) and proteins interacting with this pathway (E-Cadherin, PTEN, Stathmin-1, CYP4z1, Hey2) can be targets for cancer treatment. These observations triggered growing scientific and clinical interest on mTOR signaling pathway. Many preclinical and clinical studies investigated several agents that inhibit PI3K itself or downstream effectors (AKT1, PDK1 and mTOR). In experimental studies and clinical trials, it was shown that mTOR inhibitors have anti-proliferative and anti-angiogenic activities in breast, lung, neuroendocrine and gastric cancer as well as in lymphoma [1-3].

In conclusion, PI3K/PTEN/AKT signaling pathway is often dysregulated in prostate cancer. These pathways

are important in metastasis and the development of radioresistance. Thus, identification and characterization of interplay among signaling pathways used to predict cases with radioresistance will allow developing novel strategies that can be used against these targets. Treatments targeting mechanisms involved in mTOR pathway may also be effective in prostate cancer.

## References

1. Ni J, Cozzi P, Hao J et al. Epithelial cell adhesion molecule (EpCAM) is associated with prostate cancer metastasis and chemo/radioresistance via the PI3K/Akt/mTOR signaling pathway. *Int J Biochem Cell Biol* 2013;45:2736-48.
2. Chang L, Graham PH, Hao J et al. Emerging roles of radioresistance in prostate cancer metastasis and radiation therapy. *Cancer Metastasis Rev* 2014;33:469-96. (Review).
3. Yao B, Liu B, Shi L et al. PAFR selectively mediates radioresistance and irradiation-induced autophagy suppression in prostate cancer cells. *Oncotarget* 2017;8:13846-54.
4. Chang L, Graham PH, Ni J et al. Targeting PI3K/Akt/mTOR signaling pathway in the treatment of prostate cancer radioresistance. *Crit Rev Oncol Hematol* 2015;96:507-17 (Review).

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