Editorial

MetaLanc9 as a novel biomarker for non-small cell lung cancer: promising treatments via a PGK1-activated AKT/mTOR pathway

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Non-small cell lung cancer (NSCLC) is still challenging in terms of screening and treatment approaches (1). In Europe, Latin-America and US, NSCLC is among the most common diseases for both men and women (2). Despite recent advances in terms of systemic treatment modalities (3,4), the prognosis is still poor (5). Epidermal growth factor receptor and *ALK/EML4* fusion are consolidated as important predictive biomarkers for advanced NSCLC (6). Recently, Yu *et al.* (7) published an interesting article addressing the potential role of MetaLnc9, which it was related to lung cancer metastasis by stimulating the PGK1-Activated AKT/mTOR pathway. In this manuscript, they reported that the elevated expression of MetaLnc9 in human NSCLC specimens was correlated with poor prognosis, promoting migration and invasion of NSCLC cells *in vitro*, and enhancing lung metastasis formation *in vivo*. The authors postulated that MetaLnc9 might work as an AKT/mTOR pathway activator. Furthermore, they showed that high levels of MetaLnc9 in lung cancer tissues are correlated with poor tumor TNM stage and tumor metastasis. The RNA expression of MetaLnc9 was up-regulated in 61.6% (45/73) of NSCLC cases. Thus, it could be considered as a clinical biomarker for the prognosis of NSCLC (7). Despite this interesting conclusion, the article sample are very small and without enough statistical power. In addition, it was not performed correlation of MetaLnc9 expression with others confounding predictive biomarkers, such as *EGFR* mutation, *EML4/ALK* fusion and *ROS1* expression.

Taking those results in account, inhibition of mTOR pathway could represent a promising approach to improve the outcomes of advanced NSCLC through the use of mTOR inhibitors (everolimus, deforolimus, ridaforolimus, temsirolimus). In 2007, Milton *et al.* reported an interesting phase I trial that accessed the role of everolimus, a mTOR inhibitor, and gefitinib in ten patients with advanced NSCLC. The maximum tolerated dose (MTD) recommended was everolimus 5 mg with gefitinib 250 mg, both daily. Two partial radiological responses were identified among the eight response-evaluable patients (8). Thus, these reported results might suggest the potential role of mTOR pathway and MetaLnc9 expression in the NSCLC setting. In 2008, another phase I trial (9) evaluated deforolimus, another mTOR inhibitor, in advanced solid

tumors in thirty-two patients who received at least one dose of deforolimus, which dose ranged from 3 to 28 mg per day. The MTD was 18.75 mg/d. Interesting, in this study toxicity profile was an important issue since three dose-limiting grade 3 toxicity events were reported. The common drug-related adverse events reported were reversible mouth sores and rash. Also, four patients presenting with different histology, non-small-cell lung cancer, mixed mullerian tumor (carcinosarcoma), renal cell carcinoma, and Ewing sarcoma, experienced confirmed partial response (PR). Further, three others patients had no significant tumor shrinkage (9). In addition to this scenario, others mTOR inhibitors, such as temsirolimus (10) and ridaforolimus (11), also demonstrated their benefits for advanced NSCLC in phase I trials. In 2012, Reungwetwattana *et al*. addressed, in a phase II trial (12), 52 advanced NSCLC patients treated with temsirolimus 25 mg intravenous 30 minutes infusion weekly, each 4 weeks. Unfortunately, 33 patients experienced significant grade 3 or grade 4 adverse events, such as dyspnea (12%), fatigue (10%), hyperglycemia (8%), hypoxia (8%), nausea (8%) and rash (6%). In additional, this study suggested a clinical benefit rate of 35%. There were four patients who presented a confirmed PR and 14 patients who presented stable disease (SD) for over 8 weeks. Furthermore, Reungwetwattana's study showed a 24-week progression-free-survival (PFS) rate of 25%; and median PFS and overall survival (OS) of 2.3 and 6.6 months, respectively. Moreover, there were identification of p70s6 kinase, phospho-p70s6 kinase, Akt, phospho-Akt expression in the studied samples, which it could be useful for further exploration of novel biomarkers in a near future. The authors concluded that temsirolimus might be given as a single agent for treatment of advanced NSCLC, with good tolerability and significant clinical benefit. Despite of this, those hypotheses are still premature and need to be assessed for further larger validation, since it was not the main end-point of their study. However, as a take-home-message, it is important to enhance the patient tailoring thorough effective surrogate biomarkers to improve the efficacy of temsirolimus in advanced NSCLC.

Actually, it is possible to find in the literature interesting studies accessing the role of everolimus in combination with erlotinib (13) and docetaxel (14). Despite the acceptable tolerability, the best selection type of patient who would benefit from these approaches is currently not known. Furthermore, temsirolimus (15) and everolimus (3) were evaluated as a radiosensitizing drug for the locally-advanced NSCLC radical treatment setting. The results were interesting in terms of PR for those patients, who presented reasonable MTD and toxicities. Taking all those features in account, MetaLnc9 could also represent an interesting predictive biomarker to tailor mTOR inhibitors in future clinical trials, since it is closely related to lung cancer aggressiveness. However, further research is still warranted to validate this biomarker in a clinical effective setting for NSCLC. In addition to the best evidence, the retrospectively analysis of the clinical trials tumor specimens would also be helpful in this search for the best NSCLC screening and treatment.

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Footnote

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