



Third line scenario in advanced non-small cell lung cancer: is the anti-angiogenetic strategy the only actor up to now?

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Lung cancer is the leading cause of cancer-related deaths worldwide. Among all the different types, non-small cell lung cancer (NSCLC) accounts for 80–85% and most patients (70%) are diagnosed at advanced disease (1). In the last decade, targeted therapies for patients with epidermal growth factor receptor (EGFR) activating mutations and anaplastic lymphoma kinase (ALK) or ROS1 rearrangements, together with immunotherapy have modified therapeutic landscape in metastatic NSCLC (2).

Improvements in clinical outcomes make the third (or further) lines of therapy a reality for an increasing number of patients. A recent systematic review has evaluated real-world treatment patterns and clinical outcomes for patients receiving second and third-line therapy for advanced NSCLC. In this analysis approximately 30% of patients received a third-line. Treatment decision is based on age, performance status (PS), comorbidity, previous treatments, molecular and safety profile from previous lines of therapy, as well as patient preference. Chemotherapy (50%) and targeted therapy (40%) were the most used third-line regimens. Monotherapy with docetaxel, gemcitabine, vinorelbine, pemetrexed or erlotinib represented the most common therapeutic options. Four of 12 studies included in this review reported overall survival (OS) data in third-line treatment. The median (95% CI) OS from start of third-line ranged from 3.8 (95% CI, 2.6–5.4) months to 12.0 (95% CI, 9.3–14.2) months (3).

Overall, the role of third line and the best approach in this setting remain unclear. No standard of care or specific guidelines are currently available for the systemic treatment in those patients who have failed two therapy regimens and a

small number of phase II/III clinical trials are available in this setting. Among these, some are investigating targeted agents such as EGFR tyrosine kinase inhibitors (TKIs) (osimertinib, erlotinib) (4,5), immune checkpoint inhibitors (durvalumab) (6) and next generation anti-angiogenetic agents.

No doubts about the potential role of anti-angiogenetic compounds in the anticancer therapy scenario: tumour angiogenesis plays a central role in cancer development, invasion, progression and metastatic dissemination. Several molecular drivers and signalling pathways are involved in tumour angiogenesis. The pro-angiogenic factors include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and the angiopoietins. VEGF is the most extensively studied and stimulates angiogenesis, primarily through activation of vascular endothelial growth factor receptor-2 (VEGFR-2), which are both commonly expressed in NSCLC (7). Angiogenesis inhibition in the treatment of NSCLC has utilized two main strategies: monoclonal antibodies targeting VEGF (bevacizumab) or VEGFR (ramucirumab) and the small molecule TKIs (nintedanib) inhibiting multiple angiogenic and proliferative pathways. Bevacizumab is approved in the first-line treatment of non-squamous NSCLC in combination with platinum chemotherapy (8). Ramucirumab and nintedanib are approved in different countries in second line in combination with docetaxel for advanced NSCLC (9) and non-squamous NSCLC, respectively (10). The possible benefits of other small molecule TKIs such as anlotinib (11), apatinib (12) and fruquintinib are currently under investigation.

Fruquintinib is a novel receptor TKI inhibiting

VEGFRs 1/2/3. Its antitumor efficacy was demonstrated in several human tumor xenograft models (13). In clinical development this molecule has been evaluated within a phase II study in combination with gefitinib in first-line setting for advanced NSCLC patients with EGFR activating mutation. Preliminary results of this study were highlighted in an oral presentation at the 18th World Conference on Lung Cancer: among 17 evaluable patients, 13 (76.5%) achieved partial response (PR) and 4 (23.5%) a stable disease (SD), meaning 100% disease control rate (DCR) with a reasonable safety profile (14).

In the paper of Lu and colleagues published on *Journal of Clinical Oncology*, the authors evaluate the efficacy and safety of fruquintinib in patients with advanced, pre-treated non-squamous NSCLC with progressive disease after at least two lines of therapy. In this multicenter phase II study, 91 patients were randomized (2:1) to fruquintinib (5 mg once daily in 4 weeks cycle of 3 weeks of treatment) or placebo plus best supportive care (BSC) (15). Treatment could be continued until disease progression, intolerable toxicity or study withdrawal. Tumour response was performed using Response Evaluation Criteria in Solid Tumors version 1.1. Patients were stratified according to EGFR mutation status (mutated *vs.* wild type *vs.* unknown). The primary end point was progression free survival (PFS) evaluated by blinded image central review (BICR) and secondary end points were investigator-evaluated PFS, OS, overall response rate (ORR), DCR and safety. The study showed a median PFS equal to 3.8 months in the experimental arm *vs.* 1.1 months in placebo arm by BICR (HR: 0.34; 95% CI: 0.20–0.57; $P < 0.001$) and investigator's assessment. The median OS was 7.7 and 9.7 months in the fruquintinib and placebo group (HR: 0.70; 95% CI: 0.43–1.15; $P = 0.152$), respectively. The 3- and 6-months survival rates were 90.2% *vs.* 73.3% for 3 months and 67.2% *vs.* 58.8% for 6 months in the fruquintinib and placebo group, respectively.

Subgroup analyses showed that median OS was higher with fruquintinib than with placebo in patients with EGFR mutation (8.4 *vs.* 5.5 months, HR 0.58, $P = 0.11$). The ORR (13.1% *vs.* 0%; $P = 0.041$), as well as DCR (60.7% *vs.* 13.3%; $P < 0.01$), was higher in the experimental arm than in placebo group. Despite the small sample size does not allow a definitive conclusion, the crosstalk between VEGF and EGFR pathways has been demonstrated by preclinical studies. For example, cells with an EGFR mutation express higher levels of VEGF and VEGF is down regulated by EGFR inhibition (16). In xenograft models, acquired

resistance to cetuximab, a monoclonal antibody targeting EGFR, was associated with increased VEGF levels and increased tumour angiogenesis *in vivo* (17). These studies suggest that dual blockade of the VEGF and EGFR pathways leads to an increasing or synergistic activity. Clinical significance of this approach is under investigation in several trials in patients with metastatic EGFR-mutated NSCLC. The combination studies with erlotinib and bevacizumab have shown synergic effects on inhibiting tumour growth and improving OS (18).

In the study of Lu and colleagues, in terms of safety, the more common grade 3 or 4 adverse events (AEs) were hypertension (8.2%), hand foot syndrome (4.9%), proteinuria (4.9%) and fatigue (83.3%). Based on the results, the authors concluded that in third and fourth line fruquintinib was superior to placebo with a safe toxicity profile in advanced non-squamous NSCLC.

The authors should be recognized for having designed a study in an advanced line of treatment and, in a therapeutic scenario completely oriented towards immunotherapy and targeted therapy, to have done it with an anti-angiogenic drug.

Some aspects in this trial should be discussed. Patient enrolled are not exactly representing the real-world population: they were only Asians, with a good PS (ECOG 0-1) and without brain metastases that is uncommon for such heavily pre-treated patients. Even if the eligibility criteria list did not include patients with brain metastases, in fruquintinib arm 11.5% of cases already presented brain dissemination at baseline. In this subgroup PFS and OS benefits have not been described though the small sample sizes do not allow a conclusive evaluation.

Furthermore, some key considerations need to be addressed regarding previous treatments. A relevant percentage of patients did not receive the treatment currently considered the standard of care. This is only partially linked to the historical period of the enrollment in which some therapeutic options were not yet available in clinical practice. Nowadays, on the basis of guidelines, molecular testing is mandatory for all patients with advanced NSCLC to choose the optimal treatment. Patients with molecular alteration in EGFR, ALK and ROS1 benefit from targeted therapies in the first-line setting and in subsequent lines. In patients with no known driver mutations or with wild-type tumours, immunotherapy with checkpoint inhibitors has revolutionized treatment. In this trial, approximately half the patients in each treatment group harboured EGFR mutations, but 30% of cases have not been exposed to EGFR TKIs. None of them has been

screened for one of the most important mechanism of resistance to EGFR TKI therapy which is the substitution of threonine to methionine (T790M) on exon 20 of the EGFR gene, occurring in 49% to 60% of patients. The screening for ALK/ROS1 alterations has not been performed in the trial population and none of the patients received immunotherapy in first and/or second line.

Finally, some limitations need to be considered looking at the way in which the assessment of fruquintinib benefit was done. The drug was only compared with placebo that could be an acceptable comparison in “*non-oncogene addicted*” patients or in a situation in which all the standard therapeutic options have been explored, which is not the case for this trial.

Subgroup analyses of OS showed non-significant trends in favour of fruquintinib for all subgroups except for patients with a time start of primary therapy <9 months (TSPT). A shorter TSPT may be used in clinical trials as a marker for poorer prognosis. Potential outcome advantage with fruquintinib confirms results already seen in REVEL and Lume-Lung 1 trials, concerning the subgroup of patients with aggressive or refractory disease to first-line therapy (9,10). Globally, clinical and preclinical evidences suggest that tumours with rapid progression would be more likely to be dependent on angiogenic pathways for growth and survival (19).

In the heavily pretreated NSCLC patients, the aim of treatment after second line is to further achieve a disease control and to improve quality of life (QoL) with minimal toxicity. The safety profile of fruquintinib reported by Lu and colleagues was acceptable and consistent with other anti-angiogenetic agents. For sure, this is a crucial aspect to be included in a full assessment of the benefit-risk profile of a drug, particularly in the approach of heavily pretreated patients. QoL measurement is among the criteria taken into account by the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) for a proper evaluation of the benefit of a compound, but no information in this context has been collected in the trial.

The optimal treatment strategy for patients with metastatic NSCLC is currently characterized by a continuous evolution. Despite great improvements deriving from growing knowledges in precision medicine, in immunotherapy and from the introduction of several options in different lines of therapy, there is still the need to ameliorate the therapeutic algorithm both for oncogene addicted and for non- oncogene addicted ones. The anti-angiogenetic drugs are not yet fully exploited in pulmonary oncology and several clinical trials are

currently ongoing (*Table 1*).

An interesting and very actual field of research is also the evaluation of synergy mechanisms between the anti-angiogenetic compound and immunotherapy. The preclinical rationale is very strong: VEGF, for instance, promotes tumoral immune escape favoring inhibitory immune cell subsets, such as T regulatory cells (T Regs) and myeloid-derived suppressor cells (MDSCs) and suppression of dendritic cell maturation (20). Different clinical trials are evaluating the combined use of immunotherapy including programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors with agents targeting VEGF/VEGFR pathway. Some promising results have already been presented showing a significant OS benefit with atezolizumab plus carboplatin/paclitaxel (CP) and bevacizumab compared to CP plus bevacizumab in first line non-squamous NSCLC without safety signals (21).

Data currently available on fruquintinib are limited. The pivotal phase III FALUCA trial completed its enrollment in February 2018. Five hundred and twenty-seven Chinese NSCLC patients, who have failed two lines of systemic chemotherapy, were randomized to receive fruquintinib or placebo (NCT02691299). Randomization was stratified by EGFR/ALK status and history of treatment by VEGF inhibitors. Some information about the molecule could be acquired from the application in another malignant disease. The FRESCO study, a phase III Chinese trial in patients with metastatic colorectal cancer, describes an advantage of fruquintinib compared to placebo in the third (or further) setting in terms of OS (22).

The historical issue in dealing with the anti-angiogenetic compound and to optimize their application has always been the lack of a predictive marker and, now more than ever, this would be necessary in the context of modern medicine. At the same time, several challenges involving the anti-angiogenetic approach in the management of advanced NSCLC remain to be solved to select the most appropriate timing, best sequence and the optimal treatment schedules.

In conclusion, it was an interesting choice to explore the potential role of anti-angiogenetic agents in third-line treatment in advanced NSCLC. Anti-angiogenetic strategy can potentially play a role in this setting, in which many efforts are currently focused on optimizing the sequencing strategies with TKI (in oncogene addicted disease) or improving immunotherapy approach ameliorating knowledges in the most adequate therapeutic algorithm. Some questions about the anti-angiogenetic agents' efficacy as monotherapy or as part of a multimodal treatment are

Table 1 Ongoing trials evaluating combination strategy with antiangiogenic agents in advanced NSCLC

ClinicalTrials.gov identifier	Phase of study	Setting	Investigational agents	Comparator	Comments
Antiangiogenic agents in combination with immune checkpoint inhibitors					
NCT02681549	II	>1 st line; BM positive NSCLC	Bevacizumab + pembrolizumab	None	Prior IO not allowed
NCT02443324	I	≥1 st line	Ramucirumab + pembrolizumab	None	–
NCT03377023	I/II	≥1 st line	Nintedanib + nivolumab + ipilimumab	None	Treatment naive or prior IO allowed
NCT02856425	I	1 st line; active BM-negative	Nintedanib + pembrolizumab	None	–
Antiangiogenic agents in combination with tyrosine kinase inhibitors					
NCT02971501	II	≥2 nd line; EGFR-positive and BM positive NSCLC	Bevacizumab + osimertinib	None	Prior chemotherapy or prior IO allowed
NCT02521051	I/II	≥1 st line; ALK-positive and BM positive NSCLC	Bevacizumab + alectinib	None	–
NCT02411448	III	1 st line; EGFR-positive NSCLC	Ramucirumab + erlotinib	Erlotinib + placebo	–
NCT02856425	I	1 st line; active BM-negative NSCLC	Nintedanib + pembrolizumab	None	–

BM, brain metastases; IO, immunotherapy.

still opened. Clinical and translational researches are needed to obtain more consistent data in a precision medicine prospective.

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Footnote

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the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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