Editorial

Angiogenesis and lung cancer: ramucirumab prolongs survival in 2nd-line metastatic NSCLC

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Abstract: In the REVEL trial, ramucirumab, a monoclonal antibody to VEGFR-2, improved overall survival in combination with docetaxel compared to docetaxel alone in the second-line setting of non-small cell lung cancer (NSCLC). Along with bevacizumab and nintedanib, ramucirumab is the third anti-angiogenic agent that has yielded positive overall survival results in a phase III trial of patients with advanced NSCLC. Given the lack of effective therapies in the relapsed setting and the disappointing results of many other VEGF-targeted agents in lung cancer, the results from REVEL are encouraging. One of the major remaining hurdles is the identification of reliable predictive biomarkers in order to predict which patients are most likely to benefit from anti-angiogenic therapies. Despite the positive results seen in REVEL, the exact role of ramucirumab in the treatment paradigm of lung cancer remains to be seen given the modest survival benefit of 1.4 months and the lack of predictive biomarkers at this time.

Keywords: Angiogenesis; ramucirumab; lung cancer; VEGF; docetaxel

Submitted Sep 09, 2014. Accepted for publication Sep 10, 2014.
doi: 10.3978/j.issn.2218-6751.2014.09.05
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2014.09.05

The REVEL trial, a randomized phase III study of ramucirumab, a VEGFR-2 monoclonal antibody, combined with docetaxel versus docetaxel (plus placebo) for second-line treatment of non-small cell lung cancer (NSCLC), was presented at the 2014 Annual ASCO Meeting with positive results. The study met its primary endpoint, demonstrating improvement in median overall survival in the ramucirumab arm (1). Previously, the United States FDA had granted approval for ramucirumab given as monotherapy for second-line treatment of advanced gastric and gastro-esophageal junction cancer based upon a survival benefit seen when compared to best supportive care in the REGARD trial (2). In that trial, median overall survival was 5.2 months in patients receiving ramucirumab compared to 3.8 months in those receiving placebo (HR, 0.776; P=0.047), with higher rates of hypertension seen in the ramucirumab patients (16% *vs*. 8%). Similarly, the REVEL investigators reported an overall survival (OS) improvement for 2nd line advanced stage NSCLC patients also receiving docetaxel, 10.5 months for ramucirumab versus 9.1 months for placebo (HR, 0.86; P=0.023) (3). Notably, the trial included those patients with both squamous and non-squamous histologies, a significant difference from other trials looking at VEGF pathway targeted agents in NSCLC, which have excluded squamous histology patients. Based upon this data, the investigators concluded that ramucirumab is the first new therapy for previously treated NSCLC to improve overall survival in a large phase III randomized trial with an active comparator. Although the survival benefit of 1.4 months remains small, the results from REVEL are nonetheless encouraging and provide hope for the discovery of novel targeted agents that can impact survival in patients with progressive metastatic NSCLC. One of the major challenges is that we have yet to establish which patients are most likely to benefit from anti-angiogenic therapies with the identification of reliable predictive biomarkers.

Angiogenesis clearly plays an important role in tumor growth and survival, and with the results of the REVEL trial, we now have three anti-angiogenic agents that have yielded positive OS results in phase III trials of patients with

advanced NSCLC. In ECOG 4599, the monoclonal antibody to VEGF, bevacizumab, demonstrated an OS benefit when added to carboplatin/paclitaxel (12.3 *vs*. 10.3 months; HR, 0.79; P=0.003) when given as frontline treatment in patients with non-squamous metastatic NSCLC (4). More recently, in LUME-lung 1, nintedanib, an oral angiokinase inhibitor to VEGFR1-3, fibroblast growth factor receptors (FGFR) 1-3, and platelet-derived growth factor receptors (PDGFR) alpha and beta, showed an OS benefit when added to docetaxel as second-line treatment in the subset of patients with adenocarcinoma histology (12.6 *vs*. 10.3 months; HR, 0.83; P=0.0359) (5). Though the study showed a PFS benefit in all histologies, when evaluating the total population of patients in LUME-lung 1 (all histologies), there was no difference in OS between the two groups (10.1 *vs*. 9.1 months; HR, 0.94; P=0.2720) and the survival benefit was seen only on exploratory analysis of patients with adenocarcinoma most refractory to first-line treatment. Of the three studies, REVEL was the only one to show a survival benefit across all histologies, particularly in the squamous cell patient population. These results from REVEL are particularly encouraging given the challenges of treating squamous cell histology NSCLC. A lack of specific driver mutations amenable to treatment with approved targeted agents, and the higher frequency of centrally located tumors in proximity to large blood vessels and airways with risk of hemoptysis and bleeding, have slowed progress in the treatment of this subset of NSCLC patients (6). In REVEL, benefits were also seen in the secondary endpoints of median progression-free survival (PFS) (11.1% ramucirumab *vs*. 6.7% placebo) and overall response rate (ORR) (22.9% ramucirumab *vs*. 13.6% placebo). Although the study population in the REVEL trial was broader in comparison to currently approved anti-angiogenic therapies in NSCLC (4), the fact that >60% of patients were younger than 65 years of age and that the study excluded performance status 2 or greater patients and those with major blood vessel encasement or invasion and cavitation may ultimately limit the generalizability of the results from REVEL. Nonetheless, the positive results from REVEL are noteworthy given the lack of other more effective targeted therapies in the squamous cell subtype of patients and in the second-line NSCLC patient population who generally have poor outcomes with current available therapies.

One of the major reasons for the lack of survival benefit seen in prior trials of anti-angiogenic therapies in NSCLC is felt to be related to the absence of clinically meaningful anti-angiogenic biomarkers. It is notable that several of the previously published studies of anti-angiogenic therapies in NSCLC involved small molecular inhibitors of VEGFRs, including nintedanib in LUME-lung 1, and most of these studies demonstrated benefits in PFS but not in OS when evaluating the overall study population. When placed into this context, the survival benefit, however modest, seen with bevacizumab and now with ramucirumab can be seen as remarkable. The REVEL investigators performed biomarker assessments with patient blood and plasma and archival tumor tissue, which are ongoing and may provide additional insight into which patients are expected to best respond to ramucirumab and other anti-angiogenic treatments. Given the dynamic process of angiogenesis in tumor growth and development, the identification of plasma biomarkers for the anti-angiogenic therapies has not been straightforward or easily achievable and remains a major hurdle in better understanding the true benefit of these drugs in the treatment spectrum of NSCLC.

Interestingly, there was no significant increase in grade 3 risk of hemorrhage seen in those patients receiving ramucirumab. This is in contrast to earlier trials of agents like bevacizumab and VEGFR-TKIs in which toxicity, especially hemorrhage, was higher in squamous histology patients. Patients treated with ramucirumab did experience more bleeding events of any grade (29% *vs*. 15%), with epistaxis being the most common event (19% with ramucirumab *vs*. 6% with placebo). The most common grade 3 or worse adverse events noted in the ramucirumab treated patients were neutropenia (49% in the ramucirumab group *vs*. 40% in the control group), febrile neutropenia (16% *vs*. 10%), fatigue (14% *vs*. 10%), leucopenia (14% *vs*. 12%), and hypertension (6% *vs*. 2%) (1). Toxicities were overall manageable with dose adjustments and supportive care and there was no difference in the number of deaths from adverse events noted between the two groups. Additionally, the study included data regarding quality of life, which is especially important in the second-line setting where the overall goal is palliation. Approximately 50% of patients in each arm provided data on global quality-of-life at the 30 day follow-up with no difference in time to deterioration between the two treatment groups (HR, 1.0; P=0.99) (3). The manageable safety profile and the lack of detriment in global quality-of-life further support the benefits seen in the efficacy endpoints with ramucirumab.

Overall, the positive results from the REVEL study appear promising and further exploration is warranted of this novel anti-angiogenic agent in the treatment of NSCLC patients. Though it will likely play some role, it is

unclear exactly how ramucirumab will fit into the treatment paradigm of NSCLC given the modest benefit in OS seen, and it is hoped that further biomarker analyses will help elucidate which patients are most likely to benefit from this and other anti-angiogenic treatments.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Das M, Wakelee H. Angiogenesis and lung cancer: ramucirumab prolongs survival in 2nd-line metastatic NSCLC. Transl Lung Cancer Res 2014;3(6):397-399. doi: 10.3978/j.issn.2218-6751.2014.09.05

