

## Ramucirumab: a promising development in advanced non-small cell lung cancer

The VEGF pathway is a critical target for anti-angiogenic therapy in advanced non-small cell lung cancer (NSCLC). Bevacizumab, a monoclonal antibody targeting VEGF-A, is the only anti-angiogenic agent approved for first-line use in combination with platinum-based chemotherapy. Ramucirumab is another monoclonal antibody that specifically binds to the extracellular domain of the main angiogenic receptor VEGFR-2 on endothelial cells. Clinical development of ramucirumab demonstrated promising activity and a tolerable safety profile in combination with first-line chemotherapy in advanced NSCLC. Recently, the REVEL Phase III trial, including both squamous and nonsquamous carcinoma, demonstrated that the addition of ramucirumab to standard second-line docetaxel provided a significant improvement of overall survival, providing an evidence for VEGFR-targeted antiangiogenic therapy in advanced NSCLC.

**Keywords:** angiogenesis • bevacizumab • non-small cell lung cancer • ramucirumab • VEGF • VEGFR-2

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths in the world. A majority of patients have stage IV disease at diagnosis and therefore are not treated with curative intent. However, even though the outcome remains poor, the past 10 years have seen considerable advances in stage IV NSCLC based on the development of treatment tailored to the molecular characteristics of the individual tumor. The discovery that some NSCLC, mainly adenocarcinomas, depend on a single genetic abnormality led to the concept of ‘oncogenic addiction’, meaning that tumor growth and survival result from a single driver oncogene [1]. The identification of EGFR mutations [2] and anaplastic lymphoma kinase (ALK) rearrangements [3] allowed the development of tyrosine kinase inhibitors specifically targeting the mutated proteins. The introduction of the anti-EGFR agents gefitinib and erlotinib and the ALK-targeted agent crizotinib has changed the natural history of NSCLC in patients whose tumors have the relevant

molecular abnormalities and has significantly improved prognosis [4,5].

Nevertheless, oncogenesis arising from on a targetable molecular abnormality affects only a minority of NSCLC patients. These are mainly nonsmokers or former light smokers. For the majority of patients, who are mostly smokers, first-line treatment of advanced NSCLC continues to be built around third-generation platinum-based chemotherapy [6]. The introduction of pemetrexed in the first-line setting for nonsquamous cell carcinoma [7] and maintenance strategies for patients with controlled disease after induction chemotherapy provided significant but small survival improvements [8,9]. The development of second-line therapy also produced an overall survival benefit [10,11], mainly due to the prolongation of disease control. However, there have been no significant advances in the second-line NSCLC setting since 2005.

The concept of therapy targeting tumor angiogenesis offered the possibility of

Virginie Avrillon<sup>1</sup> &  
Maurice Pérol<sup>\*1</sup>

<sup>1</sup>Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France  
\*Author for correspondence:  
maurice.perol@lyon.unicancer.fr

enhancing the benefits of chemotherapy in advanced NSCLC [12]. The most clinically relevant anti-angiogenic agents target the VEGF pathway, either by preventing VEGF from binding to its receptors on endothelial cells or by inhibiting the VEGF receptors (VEGFR) themselves. The addition of bevacizumab, a monoclonal antibody specifically binding to circulating VEGF-A, to standard first-line carboplatin-paclitaxel chemotherapy in nonsquamous cell carcinoma demonstrated a significant survival advantage [13]. However, bevacizumab is currently the only US FDA-approved anti-angiogenic therapy in NSCLC and its use is limited to first-line therapy of advanced disease.

Ramucirumab is a promising monoclonal antibody that binds specifically to the extracellular domain of VEGFR-2, preventing binding of the ligand. It now has robust Phase III evidence of efficacy. This article summarizes the development of ramucirumab in advanced NSCLC.

### Targeting the VEGF pathway in advanced NSCLC

Advances in the field of cancer cell biology have led to a better understanding of cancer cell characteristics [14]. The ability of the tumor to sustain angiogenesis is key to its survival and therefore an important target in cancer drug development. Tumor growth beyond 1–2 mm requires the development of new vessels and depends on activation of an ‘angiogenesis switch’ by oncogenes that respond to hypoxia by secreting angiogenic factors. Neoangiogenesis is complex, involving multiple growth factors and receptors on tumor cells, endothelial cells, pericytes and the tumor stroma. The activation, proliferation and migration of endothelial cells reliant on pro-angiogenic factors lead to the creation of new vessels. However, these vessels have important structural and functional abnormalities, among which is increased permeability. These new vessels facilitate the systemic circulation of tumor cells, either directly or by lymphangiogenesis [15,16].

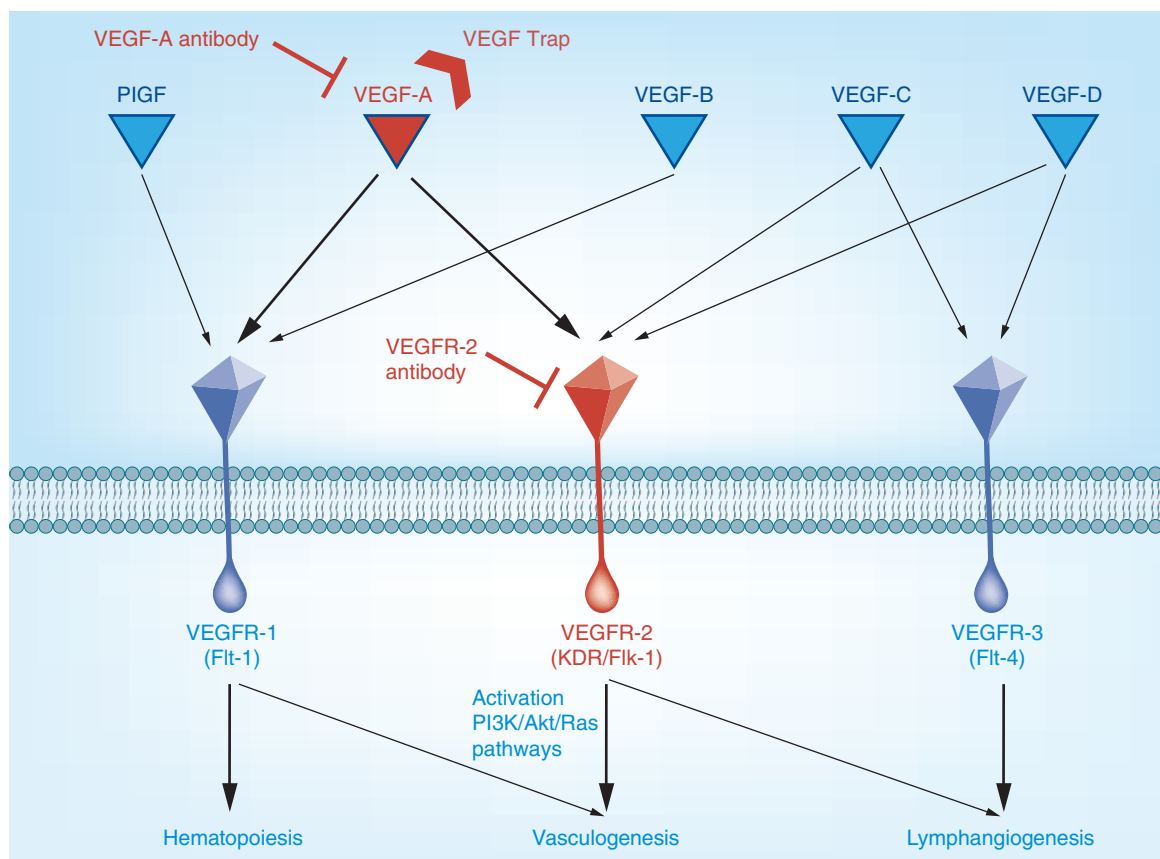
VEGF and its receptors play a crucial role in both physiological and pathological angiogenesis [17]. VEGF expression is triggered during the early phase of tumor growth by tumor hypoxia and activation of oncogenes such as *K-Ras*, *HER2* and *EGFR*. It is also released from the extracellular matrix by proteolytic enzymes. The VEGF family has six members – VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placenta growth factor (PlGF) – with several isoforms for each member [17]. There are three tyrosine kinase VEGF receptors, VEGFR-1 (Flt-1), VEGFR-2 (KDR) and VEGFR-3 (Flt-4) expressed on endothelial cells with a dimerization occurring after VEGF binding.

Several studies have suggested that the different subtypes of VEGF and receptor have distinct roles. VEGF-A is the most directly pro-angiogenic factor through its binding to VEGFR-2 (also called KDR) which is mainly expressed on endothelial cells. This leads after dimerization and autophosphorylation of tyrosine residues to activation of the *PI3K*, *Akt* and *Ras* pathways and promotion of endothelial cell growth and migration. VEGF-A also increases vessel permeability and plays an important role in mobilization of endothelial progenitor cells from the bone marrow to distant tumor sites. Hence VEGFR-2 is the main angiogenic driver. VEGFR-1, on the other hand, seems to have an inhibitory action (Figure 1) but might also lead to induction of matrix metalloproteinases, regulation of hematopoiesis and recruitment of monocytes.

In addition to the classical VEGF receptors, neuropiline receptors 1 and 2 (NRP-1 and -2), devoid of tyrosine kinase activity, might play a co-receptor role for some VEGF-A isoforms and therefore modulate its binding on VEGFR-1 and VEGFR-2 [18]. VEGF-C and VEGF-D can bind to VEGFR-3 (Flt-4), which appears to be involved in the lymphangiogenesis process [18,19].

Most clinically developed antiangiogenic agents have targeted the VEGF pathway using one of two approaches [20]. The first is to prevent VEGF-A binding to its receptors. Bevacizumab is a recombinant humanized monoclonal antibody against VEGF-A. Its development was restricted to nonsquamous lung carcinoma because of the occurrence of pulmonary hemorrhage, due to tumor necrosis, in patients with squamous carcinoma [21]. The addition of bevacizumab to first-line platinum-based chemotherapy consistently resulted in an improvement of response rate and of progression-free survival. A positive impact on overall survival was only seen in combination with carboplatin–paclitaxel combination [13,22]. However, meta-analyses of randomized trials assessing bevacizumab in combination with chemotherapy demonstrated a small but significant overall survival (OS) benefit [23].

The safety profile of bevacizumab in advanced nonsquamous NSCLC showed that hypertension and proteinuria (mostly grade 1–2) were common side effects, and also suggested a small increase in the rate of arterial thromboembolic events. Pulmonary hemorrhage was rare, but patients with tumor invading major vessels were excluded from clinical trials. Bevacizumab is currently the only approved antiangiogenic agent in nonsquamous NSCLC when given in combination with first-line chemotherapy. It is also approved as maintenance therapy in patients with controlled disease at the end of chemotherapy. Nevertheless, none of the clinical studies conducted in various tumor types could identify any predictive factors for treatment selection.



**Figure 1. The vascular epithelial growth factor pathway.** Mechanism of activation of VEGF receptor family by the different ligands and tyrosine kinase activation pathway, with the different mechanism of action of antiangiogenic agents.

PIGF: Placental growth factor; TKIs: Tyrosine kinase inhibitors.

Aflibercept is a recombinant human fusion protein designed to bind with high affinity to VEGF-A and -B isoforms and to placental growth factor-1 and -2. Despite an improvement in response rate and progression-free survival (PFS) when given in combination with docetaxel (compared with docetaxel alone) in second-line advanced nonsquamous lung carcinoma, aflibercept failed to demonstrate an OS benefit [24]. To date, no anti-VEGF agent has been approved in the second-line treatment of advanced NSCLC.

The second widely used approach to inhibiting the VEGF pathway is to block signal transmission following activation of endothelial VEGF receptors, particularly VEGFR-2 which binds VEGF-A, -C and -D. Several multitargeted receptor tyrosine kinase inhibitors as sunitinib, sorafenib, axitinib, pazopanib, etc. block VEGF receptor signal transduction, and some are already approved for renal cell and hepatocellular carcinoma. Certain of these tyrosine kinase inhibitors also target PDGFRs or FGFRs involved in tumor angiogenesis. However, clinical trials that have assessed these compounds in advanced NSCLC (either in combination with chemotherapy in first-line treatment or as a single agent in the second- or third-line

setting) have failed to demonstrate any significant or clinically relevant improvement in response rate, PFS or OS. This is true of sorafenib [25,26], vandetanib [27,28], sunitinib [29], motesanib [30] and cediranib [31]. Moreover, such studies have shown significant toxicities, and even a deleterious impact on OS for patients with squamous cell carcinoma [25].

A third way to target the VEGF pathway is to use a monoclonal antibody to block the extracellular domain of VEGF-receptors. This approach differs from the inhibition of tyrosine kinases since it prevents the activation of still inactive receptors. Ramucirumab (IMC-1121B; ImClone System, Inc.) is a fully human monoclonal antibody of the immunoglobulin G subclass 1 that specifically binds to the extracellular domain of VEGFR-2 with high affinity (dissociation constant of ~ 50 pM, half maximal inhibitory concentration [IC<sub>50</sub>] of 0.8–1.0 nM) [32,33]. Ramucirumab was designed to bind to a VEGFR-2 epitope and so prevents the activation of the receptor by all VEGF ligands and subsequent intracellular signal transduction [33]. Ramucirumab is being developed in several solid tumors. This review focuses on advanced NSCLC.

### Preclinical data & Phase I study

DC 101, the murine version of ramucirumab, was used in preclinical xenograft studies to assess its ability to block VEGFR-2 and subsequent signaling pathways in endothelial cells [32,34–37]. Mouse models demonstrated that DC101 prevented VEGF binding to VEGFR-2 and led to blockade of VEGFR signaling and to significant antiangiogenic and antitumor activity, both as single agent and in combination with cytotoxic therapies [32,34–37]. Toxicity studies in animals indicated a good safety profile.

Thirty-seven patients with various advanced solid malignancies were included in the ramucirumab Phase I study [33]. Patients were treated with weekly 2–16 mg/kg. Pharmacokinetic studies showed dose-dependent elimination and a nonlinear exposure indicating a saturation of ramucirumab clearance at doses exceeding 8 mg/kg. Given that the primary mechanism for drug elimination is receptor-mediated clearance, this suggests that all VEGFR-2 are blocked by ramucirumab at this dose. The ramucirumab half-life at steady state ranged from 200 to 300 h at doses of 8–16 mg/kg, with a large interpatient variability. Minimum ramucirumab concentrations exceeded the target concentration of  $\geq 20 \mu\text{g/ml}$  at all doses.

Pharmacodynamic studies showed a consistent increase in VEGF-A (1.5–3.5-fold higher than pretreatment values) concentrations that persisted for the duration of ramucirumab administration. In contrast, soluble VEGFR-1 and VEGFR-2 concentrations decreased immediately after ramucirumab administration, independently of the dose level. DCE-MRI with full kinetic modeling was available in 13 patients, showing decreased tumor perfusion and vascularity in 9 of 13, including 4 of 6 patients receiving 2- or 3-week doses.

The toxicity profile was similar to that of other agents targeting the VEGF-VEGFR axis. The most frequently reported serious adverse events, irrespective of their relation to ramucirumab, included hypertension (13.5%), abdominal pain (10.8%), anorexia,

vomiting, increased blood alkaline phosphatase, headache, proteinuria, dyspnea and deep vein thrombosis (DVT) (each in 5.4% of patients). Hypertension was the most common treatment-related side effect (grade 3 hypertension occurring in five patients). This was linked to both weekly and cumulative dose but (except in one patient) was easily manageable with oral anti-hypertensives. The dose limiting toxicities (DLTs) during the first 4-week cycle included grade 3 hypertension and DVT, each in one patient; other DLTs were grade 3 proteinuria and grade 3 vomiting, each in one patient during subsequent cycles. The maximum tolerated dose (MTD) was therefore determined as being 13 mg/kg with a weekly schedule. These results were pooled with those from another Phase I study assessing an every 2- and 3-week treatment schedule [38], leading to a 10 mg/kg every 3 weeks or a 8 mg/kg every 2 weeks schedule as optimal regimens for Phase II and III further studies.

Ramucirumab exhibited some single agent anticancer activity in this Phase I study with four patients (15% of those with measurable disease) having a partial response (in melanoma, ovarian cancer, uterine leiomyosarcoma and gastric cancer) and 62% stable disease as best response [33,38].

### Clinical development of ramucirumab in advanced NSCLC

The development of ramucirumab in advanced NSCLC is summarized in Table 1. Ramucirumab has been assessed in combination with cytotoxic chemotherapy in the first- and second-line treatment of advanced NSCLC in both nonsquamous and squamous histologies.

#### First-line therapy

Two Phase II trials have been conducted in first-line advanced NSCLC; all histological subtypes were eligible. The first study was an open-label, one arm trial assessing the combination of ramucirumab

Table 1. Overview of clinical development of ramucirumab in advanced non-small cell lung cancer.

Treatment line	Methodology	Treatment	Primary endpoint	Results
First line	NTC00735696 Phase II, single arm	Carboplatin-paclitaxel + ramucirumab	PFS at 6 months	Final results available
	NTC01160744 Randomized Phase II stratified by histology, open label	Nonsquamous carcinoma: Carbo/cisplatin + pemetrexed ± ramucirumab	PFS	Final results available
		Squamous carcinoma: Carbo/cisplatin + gemcitabine ± ramucirumab	PFS	Ongoing study
Second line	NTC01168973 REVEL Phase III, double blind	Docetaxel + ramucirumab vs docetaxel + placebo	OS	Final results available

OS: Overall survival; PFS: Progression-free survival.

with paclitaxel and carboplatin. Eligible patients had untreated stage IV NSCLC without blood vessel involvement, history of hemoptysis or tumor cavitation; and an ECOG PS of 0 or 1. Those with treated brain metastases were permitted. Patients received ramucirumab (10 mg/kg), paclitaxel (200 mg/m<sup>2</sup>) and carboplatin (AUC6) on day 1 of each 3-week cycle. The primary end point was PFS at 6 months; the secondary endpoints were safety profile, objective response rate (ORR) and OS rate at 1 year, the duration of response, pharmacokinetic profile and immunogenicity of ramucirumab [39].

Forty patients were included: 25 were female, 85% had adenocarcinoma and the median age was 59 years. The main adverse events were fatigue (53%), peripheral neuropathy (33%), nausea (28%), epistaxis (23%) and myalgia (23%). Twenty percent (8/40) patients experienced treatment-related serious adverse events and these included two cases of febrile neutropenia. Hypertension was observed in 15%, proteinuria in 10% and arterial thromboembolic events in 5%. Three patients (7.5%) experienced mild hemoptysis.

The PFS rate at 6 months was 59% (95% CI: 41.3–72.9%), with a median PFS of 7.9 months. The ORR was 55% (95% CI: 38.5–70.7%) with a disease control rate (DCR) of 90%. Median OS was 16.85 months with a 1-year OS rate of 74.6% (95% CI: 57.9–85.4%) [39]. These results compare favorably with those obtained with bevacizumab in combination

with carboplatin-paclitaxel but must take into account the Phase II setting and the favorable prognostic characteristics of the patients [39].

The second study was a randomized, open-label Phase II trial assessing the addition of ramucirumab to first line platinum-based chemotherapy, with patients stratified by histology (nonsquamous vs squamous cell carcinoma) [40]. For squamous cell carcinoma, the backbone chemotherapy was cisplatin or carboplatin combined with gemcitabine; accrual to this cohort has been completed but the study is ongoing. The final results of the nonsquamous cell carcinoma cohort were presented at the 2013 World Conference of Lung Cancer [40]. Chemotherapy consisted of cisplatin or carboplatin plus pemetrexed followed by pemetrexed maintenance treatment after 4–6 cycles of induction chemotherapy. In the experimental arm, ramucirumab was continued in combination with pemetrexed during the maintenance phase. Eligibility criteria were similar to those of the previous trial, except for PS 2 patients that were eligible at the beginning of the study (later amended to PS 0–1 only patients). The primary endpoint was PFS.

One-hundred-and-forty patients were enrolled (Table 2). Prognostic factors were well balanced between the two arms except for a higher proportion of females in the experimental arm (48 vs 37%). The majority of patients (87%) had adenocarcinoma and were PS 0–1 [40]. There was a small but nonsignificant

**Table 2. Main results of the randomized Phase II trial evaluating the addition of ramucirumab to cisplatin or carboplatin-pemetrexed chemotherapy in advanced nonsquamous cell lung carcinoma<sup>†</sup>.**

	Control	Ramucirumab	Log-rank p-value
N (ITT population)	71	69	
Male	63%	52%	
Adenocarcinoma	87%	87%	
PS 2	6%	7%	
Cisplatin	30%	30%	
Age ≥ 65	48%	46%	
Complete response	0 (0.0)	0 (0.0)	
Partial response	26 (36.6%)	30 (43.5%)	
Stable disease	25 (35.2%)	30 (43.5%)	
Disease control rate	51 (71.8%)	60 (87.0%)	p = 0.031
Median PFS months	5.6	7.2	
HR for PFS	0.75 90% CI: 0.55, 1.03		p = 0.1318
Median OS months	10.4	13.9	
HR for OS	1.03 90% CI: 0.74, 1.42		p = 0.8916

HR: Hazard ratio; ITT: Intention to treat; OS: Overall survival; PFS: Progression-free survival; PS: Performance status.  
Adapted from [39]



increase in hematological toxicity in the ramucirumab arm (35.8 vs 23.2% of patients experienced neutropenia [all grades] but only 20.9 vs 18.8% were grade  $\geq 3$ ). The only significant difference in treatment-related adverse events was in hypertension which affected 17.9% of patients in the ramucirumab arm (grade  $\geq 3$  in 9%). There were no cases of pulmonary hemorrhage. The addition of ramucirumab to chemotherapy resulted in a nonsignificant improvement of PFS (median of 7.2 vs 5.6 months) and OS (median 13.9 vs 10.4 months). This was consistent with an improvement of response and disease control rates (Table 2) [40]. This Phase II study provided a good signal of ramucirumab activity in combination with chemotherapy and suggested a favorable toxicity profile similar to that of other anti-VEGF agents.

### Second-line therapy

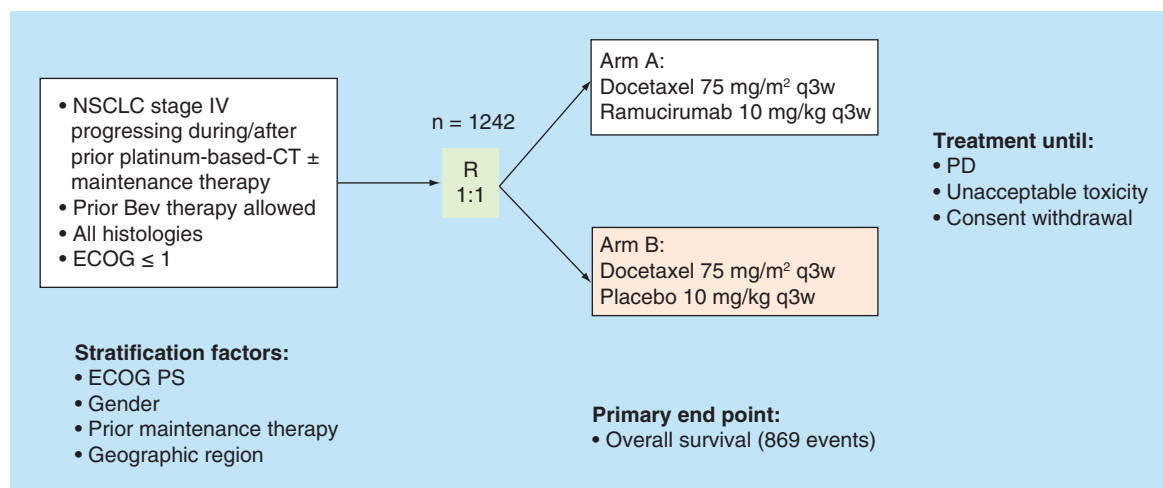
The pivotal 'REVEL' Phase III (Figure 2) study was designed to compare the efficacy and safety of ramucirumab given in combination with docetaxel versus docetaxel plus placebo as second-line therapy [41]. Eligible patients had advanced NSCLC with progressive disease after one previous first-line chemotherapy, with or without maintenance therapy or prior bevacizumab. All tumor histologies, including squamous cell carcinoma, were included. Patients with evidence of major blood vessels invasion or recent hemoptysis history were not eligible. Patients were randomized 1:1 and stratified by PS (0 vs 1), gender, geographic region and prior maintenance treatment. Treatment was continued in both arms until evidence of progressive disease or unacceptable toxicity. It was possible to prolong treatment with ramucirumab or placebo as a single agent after discontinuation of docetaxel. The primary

endpoint was OS. Secondary endpoints included response rate, PFS, safety and quality of life assessments. Between December 2010 and January 2013, 1253 patients were included. The study met its primary endpoint by demonstrating a significant improvement in overall survival (HR: 0.86; 95% CI: 0.75–0.98;  $p = 0.023$ ) with a median overall survival of 10.5 months in the ramucirumab plus docetaxel arm and 9.1 months in the docetaxel plus placebo arm. There was a consistent improvement in the response rate (22.9% in the ramucirumab plus docetaxel arm vs 13.6% in the placebo plus docetaxel arm) and in PFS (HR: 0.76; 95% CI: 0.68–0.86;  $p < 0.0001$ ) with a median PFS of 4.5 months in the ramucirumab plus docetaxel arm compared with 3.0 months in the placebo plus docetaxel group. The magnitude of benefit was consistent in the majority of patient subgroups, including squamous and nonsquamous carcinomas. The most common grade 3 or 4 adverse events were neutropenia in 49% of patients in the ramucirumab group versus 40% in the control arm with febrile neutropenia in 16% versus 10%, respectively. Grade 3 or 4 hypertension occurred in 6% of patients in the treatment group versus 2% in the controls. There was no increase in the incidence of gastrointestinal bleeding, pulmonary hemorrhage or hemoptysis in the ramucirumab arm, including patients with squamous cell carcinoma [42].

Therefore, REVEL is the first study since a decade to demonstrate a significant improvement of patients survival over chemotherapy alone in second-line therapy of advanced NSCLC.

### Conclusion & future perspective

Ramucirumab is a monoclonal antibody specifically targeting VEGFR-2 which prevents the binding of



**Figure 2. Design of the REVEL pivotal Phase III trial.**

CT: Chemotherapy; ECOG: Eastern cooperative oncology group; PS: Performance status; N: Number; NSCLC: Non-small-cell lung cancer; PD: Progressive disease; q3w: Every three weeks; R: Randomize

all VEGF isoforms. Its long plasma half-life allows prolonged VEGFR-2 inhibition with 2–3 weekly administration. In the second-line treatment of advanced gastric cancer, it improved overall survival, both as single agent [43] and in combination with paclitaxel [44,45]. The toxicity profile of ramucirumab is similar to that of other anti-VEGF therapies, and it did not have a negative impact on quality of life in Phase III studies in gastric cancer.

Studies in NSCLC included all histologies, although patients with tumors invading blood vessels or with cavitation were excluded. These have shown promising activity and a good tolerability profile in combination with first-line chemotherapy in non-squamous cell carcinoma. Results in squamous cell carcinoma are pending. The pivotal REVEL study conducted in the second-line setting met its primary endpoint, demonstrating a significantly extended OS when ramucirumab was added to docetaxel. More data are needed to evaluate the role of ramucirumab in the first-line treatment of NSCLC, especially in squamous cell carcinoma, and its potential as a

maintenance agent after discontinuation of chemotherapy. Several Phase III trials in NSCLC and other tumor types are ongoing.

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#### Executive summary

##### Targeting the VEGF pathway in advanced non-small cell lung cancer

- Angiogenesis is a critical target in cancer treatment.
- The VEGF-A/VEGFR-2 axis is the main angiogenic driver.
- One promising approach is to block activation of VEGFR-2 by using ramucirumab, a monoclonal antibody specifically designed to bind to the receptor's extracellular domain.

##### Preclinical & Phase I data

- Preclinical data confirm the ability of ramucirumab to block VEGFR-2 signaling in the endothelial cell.
- The Phase I study showed a good safety profile, inhibition of angiogenesis and antitumor activity.

##### Clinical development of ramucirumab in advanced non-small cell lung cancer

- In the first-line setting, ramucirumab plus paclitaxel and carboplatin provide results that are similar to bevacizumab plus the platinum combination.
- In combination with carbo- or cisplatin plus pemetrexed for nonsquamous cell carcinoma, ramucirumab showed in the first-line setting an improvement of objective response rate and progression-free survival, with a favorable toxicity profile similar to that of other anti-VEGF agents.
- In the second-line setting, the REVEL Phase III study demonstrates a statistically significant improvement in OS and progression-free survival when ramucirumab plus docetaxel is compared against docetaxel plus placebo, regardless of histology. This is the first trial to show an overall survival benefit in second-line non-small cell lung cancer since 2005.

##### Future perspective

- In first line setting, ramucirumab might be developed in squamous cell carcinoma, subject to the results of Phase II squamous cohort.
- In second line therapy, the positive results of the pivotal REVEL study might lead to the approval of ramucirumab in combination with docetaxel.
- REVEL provides the first rationale for anti-angiogenic treatment beyond first-line therapy in advanced non-small cell lung cancer.

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