REVIEW

Spotlight on ramucirumab in the treatment of nonsmall cell lung cancer: design, development, and clinical activity

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Abstract: The vascular endothelial growth factor (VEGF) and receptor is a therapeutic target because of the importance of this pathway in carcinogenesis. This pathway regulates and promotes angiogenesis as well as increases endothelial cell proliferation, permeability, and cancer survival. Ramucirumab is a new fully human monoclonal antibody that targets the VEGF receptor-2, an important key receptor implicated in angiogenesis. Ramucirumab has been approved for the treatment of second-line advanced or metastatic non-small cell lung cancer (NSCLC) in combination with the chemotherapy agent docetaxel. This was based on the result of the randomized trial REVEL of 1,253 patients with metastatic NSCLC previously treated with a platinum-based combination therapy. The authors observed a significant improvement in overall survival (OS) with an acceptable toxicities profile. In this study, patients were randomized to receive ramucirumab plus docetaxel or placebo with docetaxel. The combination of docetaxel and ramucirumab showed an improved OS (hazard ratio [HR]: 0.86; 95% CI: 0.75, 0.98). Median OS was 10.5 months in the ramucirumab arm versus 9.1 months in the placebo arm. Regarding side effects, the toxicity described on the ramucirumab arm were principally diarrhea, fatigue, and neutropenia. The most common (5%) adverse reactions of grade 3 and 4 in the ramucirumab arm were fatigue, neutropenia, febrile neutropenia, leukopenia, and hypertension. Adding ramucirumab to docetaxel improves QoL of patients, and does not impair symptoms or functioning. There are currently several trials in progress evaluating the effects of ramucirumab in combination with other drugs in patients with advanced NSCLC.

Keywords: ramucirumab, NSCLC, antiangiogenesis, VEGF-targeted therapy, pretreated

Introduction

Lung cancer is one of the leading causes of cancer death in developed countries. More than 85% of patients are classified as non-small cell lung cancer (NSCLC). Most patients are diagnosed in advanced stage (85% of cases), and for patients with distant metastases, longterm overall survival (OS) is <5%.[1] The standard treatment for metastatic NSCLC in first-line consists of combination therapy with platinum plus a third generation chemotherapy agent. The recommended first-line treatment for nonsquamous metastatic NSCLC could be pemetrexed plus cisplatin or the antiangiogenic agent bevacizumab in combination with carboplatin and paclitaxel.[2,3] Patients with squamous cell histology were excluded for bevacizumab therapy, based on several events of severe pulmonary hemorrhage in previous trials with the combination of bevacizumab and chemotherapy.[3]

Today, the current standard of care for patients with advanced nonsquamous metastatic NSCLC or non-smoker patients with squamous histology, should be to perform tumor evaluation of epidermal growth factor receptor (EGFR) mutations and rearrangements

of anaplastic kinase lymphoma (ALK).[4] If positive for EGFR or ALK, the standard of treatment is with EGFR or ALK tyrosine kinase inhibitors.[4] Two PD-1 inhibitors (nivolumab and pembrolizumab) and PD-L1 inhibitor (atezolizumab), are currently approved for the treatment of previously treated advanced NSCLC. These drugs were approved based on randomized phase III trials and showed significant benefit in overall survival compared with docetaxel after progression to a platinum-based chemotherapy.[5]

Angiogenesis is essential in the process of tumor growth, proliferation, and metastasis. Tumor angiogenesis pathways are important therapeutic targets in many malignant tumors, including NSCLC.[6] Tissue hypoxia is one of the principal stimulants of angiogenesis, which leads to overproduction of proangiogenic factors. The vascular endothelial growth factor (VEGF) family (VEGF-(A–D) and placental growth factor) are important proangiogenic protein factors. Of these, VEGF-A is primarily responsible for vessel formation in adult tissues.[7] VEGF binds to a family of transmembrane receptor tyrosine kinases called receptors (VEGFRs with three isoforms VEGFR-[1–3]).[8] VEGF binds to VEGFR-1; however, its primary effects on angiogenesis are mediated principally by VEGFR-2, involved in endothelial cell proliferation and migration.[9] VEGF binds to VEGFR-2, leading to endothelial proliferation, differentiation, permeability, migration, and generation of new blood vessels.[10] Tumor angiogenesis is characterized by the formation of abnormal vessels, with permeability altered. These characteristics lead to tumor growth and decreased drug delivery due to changes in the permeability of the tumor vasculature.[11]

Ramucirumab (Cyramza™, IMC-1121B; Eli Lilly and Company, Indianapolis, IN, USA) provides a different mechanism of action compared to bevacizumab, which binds with high affinity to the extracellular domain of the VEGFR-2 receptor.[12] Ramucirumab is a recombinant human monoclonal antibody of the G1-class immunoglobulin that binds to VEGFR-2 and blocks the activation of this receptor. However, bevacizumab binds to VEGF and avoids the interaction of this ligand with both VEGFR-1 and VEGFR-2 receptors. VEGFR-2 is overexpressed in the vasculature of several human cancers. Ramucirumab binds VEGFR-2 and inhibits responses resulting from the activation of VEGFR-2 by VEGF-A and VEGF-C. The first approval of ramucirumab by the US Food and Drug Administration (FDA) was for the treatment of patients with metastatic gastric/gastroesophageal junction carcinoma.[13]

Ramucirumab has been evaluated for patients with advanced or metastatic NSCLC in two Phase II trials as first-line therapy in combination with standard chemotherapy and in a Phase III trial as a second-line treatment in combination with docetaxel.[14–16]

Recently, nintedanib, a small molecule inhibitor tyrosine kinase of VEGFR, PDGFR, and FGFR, was registered by European Medicines Agency in combination with docetaxel in the second-line of NSCLC treatment.[17]

Chemistry and action

Ramucirumab is a human monoclonal antibody G1 immunoglobulin with molecular weight of 147 kDa of the recombinant compound. The chemical structure comprises two identical heavy chains of 446 amino acids and two identical light chains of 214 amino acids.[18,19] It inhibits angiogenesis by binding specifically to the extracellular domain of VEGFR-2 inhibiting binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D.[18] The maximal mean inhibitory concentration for the interaction of VEGF-A and VEGFR-2 is 0.8–1 nM.[20] The antigen-binding fragment (Fab) of ramucirumab binds to the end of domain 3 near the N-terminus of the VEGFR-2 receptor.[21] The affinity of ramucirumab to this portion of VEGFR-2 is approximately eight to nine times greater than that of the natural VEGF binding.[22]

Pharmacokinetics

The pharmacokinetic profile of ramucirumab was derived from two Phase I clinical trials.[18,23] In the first one, 37 patients with different advanced solid tumors were treated with weekly ramucirumab and doses escalating from 2 to 16 mg/kg, 1 hour of infusion.[18] In the second one, 25 patients were treated with ramucirumab 6–10 mg/kg administered every 2 weeks and 12–20 mg/kg every 3 weeks.[23] Both trials found high interpatient variability in the pharmacokinetic parameters.[18,23]

In the first trial, a target trough concentration of ≥20 μg/mL was reached following all doses.[17] The terminal half-life ranged from 200 to 300 hours for doses given weekly and 110–160 hours for doses administered every 2–3 weeks.[18,23] In the first trial, authors observed that the half-life, the maximum concentration (C_{max}), and the area under the concentration–time curve (AUC) increased disproportionately with increasing doses.[18] However, in the second trial, the C_{max} and AUC increased as expected with increases in dosage.[23]

Characteristics of patients including age, sex, and race had no significant impact on the pharmacokinetics of ramucirumab.[24] Renal or mild hepatic impairment function did not significantly alter the concentration at steady state. There is no formal pharmacokinetic analysis in patients with severe hepatic function alteration. However, increased encephalopa-

thy, ascites, or hepatorenal syndrome was described in patients with cirrhosis treated with ramucirumab. No significant drug interactions with any of the approved drug combinations resulting in changes to the exposure of ramucirumab.

Pharmacodynamics

Ramucirumab has a higher binding affinity for the extracellular domain of VEGFR-2 in respect to the natural VEGF-A ligand. In both Phase I trials, after drug administration, VEGF-A concentrations increased and remained elevated for at least 7 days.[18,23] VEGF-A levels rose 1.5–3.5 times higher than basal levels[18] and 2–8 times higher, respectively, in both trials, regarding the dose on ramucirumab.[23] In contrast, in both trials VEGFR-2 concentrations decreased after ramucirumab administration; however, VEGFR-1 only decreased after treatment in the first Phase I trial.[18]

Results in dynamic contrast-enhanced magnetic resonance imaging (MRI) parameters demonstrated a decline in several parameters (area under the signal-intensity curve, volume of extravascular extracellular space, and uptake rate constant), indicating an antiangiogenic response based on decreased tumor perfusion and vascularity in nine of 13 patients (69%)[18] and four of nine patients (67%), respectively.[23]

Immunogenicity

Antiramucirumab antibodies were not detected in the first Phase I trial, with 26 patients included.[18] However, in the second Phase I trial, with 25 patients evaluated, three patients developed antiramucirumab antibodies;[23] two patients before the second cycle and the third patient discovered at follow-up after receiving 6 mg/kg every 2 weeks. However, the antibodies detected were not neutralizing.

Efficacy of ramucirumab in NSCLC clinical trials
Phase II trials

Two different open-label Phase II trials have evaluated ramucirumab as a first-line treatment option in combination with chemotherapy. The first study proposed to evaluate the efficacy and safety of the combination of ramucirumab 10 mg/kg intravenously (IV) plus carboplatin (AUC 6) and paclitaxel (200 mg/m²), every 21 days. Principal inclusion criteria were: nonpreviously treated advanced NSCLC, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, and adequate hepatic and renal function.[14]

The primary objective was 6-months (m) progression-free survival (PFS) rate, and secondary objectives were response rate (RR), PFS, OS, safety, pharmacokinetic parameters, and

potential biomarkers of benefit to ramucirumab. Forty patients were enrolled, with a median age of 59.5 years (range: 35–78 years), 82.5% stage IV, 85% adenocarcinoma histology subtype and 92.5% Caucasian. PFS rate at 6 m was 59% (95% CI: 41.3%–72.9%). Fifteen patients (37.5%) had disease progression at 6 m from the starting of therapy. The median PFS was 7.8 m (95% CI: 5.4–9.8) and the median OS 16.8 m (95% CI: 14.8–28.5 m). After 3 years, at the time of data cutoff, 14 patients (35%) were still alive. In respect to response, one patient (2.5%) had a complete response (CR) and 21 patients (52.5%) partial response (PR), with OR (CR+PR) of 55% (95% CI: 38.5%–70.7%) and the disease control rate (DCR [CR+PR+stable disease]) of 90% (95% CI: 76.3%–97.2%).[14]

Biomarkers were analyzed in 22 patients. The results showed that patients who had the single-nucleotide polymorphism rs2981582 on the *FGFR-2* gene were significantly associated with improvement in OS (*P*=0.0059), PFS (*P*=0.0429), and RR (*P*=0.0392). However, high serum IL-6 levels were associated with decreases in PFS (*P*=0.0038) and OS (*P*=0.0029).[14]

The second study was a randomized Phase II trial comparing the combination of pemetrexed (500 mg/m²) and platinum chemotherapy (carboplatin AUC 6 or cisplatin 75 mg/m²) versus the same schema plus ramucirumab 10 mg/kg IV every 21 days. One hundred and thirty six patients were included in the trial, with very similar inclusion criteria to the previous study except for the histology (only nonsquamous NSCLC was allowed) and ECOG PS of 0–2. The principal outcome was PFS. Secondary end points included OS, RR, DCR, and safety.[15]

Patient characteristics were similar between the groups except for a higher percentage of females in the ramucirumab arm (47.8% vs 36.6%). Most patients were nonsmoking (77.5% in ramucirumab vs 84.1% in control arm), Caucasians (91.5% in ramucirumab vs 87% in control arm), ECOG PS of 0–1 (91.5% ramucirumab arm vs 92.8% in control arm), and diagnosed with adenocarcinoma histology subtype (87.3% in ramucirumab vs 87% in control arm). In respect to the efficacy, the median PFS was 7.2 m for the ramucirumab arm (90% CI: 5.8–8.4 m) versus 5.6 m (90% CI: 4.0–5.7 m for the docetaxel arm), although this difference was not statistically significant (hazard ratio [HR]: 0.75 [90% CI: 0.55–1.03; *P*=0.132]). In the ramucirumab arm, median OS was improved compared with the control group, 13.9 m (90% CI: 10.0–17.8 m) vs 10.4 m (90% CI: 8.2–15.9 m), but without a statistically significant difference (HR: 1.03 [90% CI: 0.74–1.42; *P*=0.892]). In respect to the response, in the ramucirumab group, one patient (1.4%) had a CR, 33 patients (47.8%) PR, and 25 patients (36.2%) stable disease; compared to the control group with 27 patients

(38%) with PR and 23 patients (32.4%) with stable disease. The authors found a statistically significant difference in the DCR in the ramucirumab arm (85.5% [90% CI: 78.5%–92.5%] ramucirumab vs 70.4% [90% CI: 61.5%–79.3%], P=0.032) for the docetaxel arm.[16]

Phase III trial

The only Phase III trial was the REVEL study.[16] It was a randomized, double-blind, placebo-controlled trial of patients with advanced NSCLC after progression to one prior chemotherapy treatment with platinum-based therapy for metastatic disease. All patients received docetaxel (75 mg/m^2) IV once every 3 weeks and were randomized to receive ramucirumab (10 mg/kg) or placebo. Stratification criteria were ECOG PS of 0 versus 1, sex, maintenance therapy in previous line, and region (East Asia vs rest of the world). Inclusion criteria included stage IV NSCLC and ECOG PS of 0–1. Prior bevacizumab therapy was allowed. All histologic subtypes (including squamous cell) were allowed; however, for central mediastinal masses (<3 cm from the carina) independent of histology, or squamous cell histology, it was necessary to perform an MRI of the chest or IV contrast CT scan to exclude major airway or blood vessel trunk invasion by cancer.[16]

The primary endpoint was OS. Secondary objectives were PFS and RR. The trial was designed with 85% power to demonstrate an HR of 0.816, corresponding to an improvement in median OS from 7.5 m in the control arm to 9.2 m in the ramucirumab arm. Type I error was to be controlled at a one-sided P value of <0.025 using the stratified log-rank test.

A total of 1,825 patients were screened at 216 sites worldwide; 572 patients were excluded (486 did not meet study criteria, 71 decided not to participate, nine died, and six were excluded for other reasons). The intention-to-treat population consisted of 1,253 patients randomly allocated to ramucirumab plus docetaxel (n=628) or placebo plus docetaxel (n=625). There were 912 patients with nonsquamous cell histology, 328 with squamous cell histology, and 13 with unknown histology. EGFR mutation status was known for only 437 patients (36%); of these, 33 (8%) had tumors harboring an EGFR mutation. The median duration of treatment was 4.5 months (range: 0.7–27) for ramucirumab plus docetaxel and 3.8 months (range: 0.7–30) for placebo plus docetaxel. Overall, baseline demographic and stratification factors were similar between the two treatment arms. There were fewer never-smokers in the ramucirumab arm versus the placebo arm (17% vs 23%). The proportion of elderly patients (age 65 years or older) was 38% in the ramucirumab arm and 35% in the placebo arm.[16]

The RR was higher in the ramucirumab arm (23% vs 14%, odds ratio [OR] 1.89 [95% CI: 1.41–2.54; P<0.0001]). Three patients (0.5%) had a CR and 144 patients (22.5%) had a PR in the experimental arm versus two (0.3%) CR and 83 (13.3%) PR in the arm without ramucirumab. DCR was evaluated and the results showed a statistically significantly higher DCR with ramucirumab (64%) in respect to the control group (53%) (OR 1.60 [95% CI: 1.28–2.01; P<0.0001]).[16]

Median PFS was also significantly higher in the ramucirumab group (4.5 m [95% CI: 4.2–5.4 m]) in respect to the control group (3 m [95% CI: 2.8–3.9 m]), HR: 0.76 (95% CI: 0.68–0.86; P<0.0001). These results were similar in the different subgroups of patients after accounting for baseline characteristics, including histology.[15]

OS was significant improved in patients treated in the group with ramucirumab. The median OS was 10.5 m versus 9.1 m (HR: 0.86; 95% CI: 0.75–0.98; P=0.024). Patients with nonsquamous histology and patients who responded to the first-line platinum therapy had clear significant benefit with ramucirumab (HR: 0.83 [95% CI: 0.71–0.97]) and (HR: 0.84 [95% CI: 0.71–0.99]) respectively, and a trend toward improved OS was observed in patients with squamous cell histology (HR: 0.88 [95% CI: 0.69–1.13]). The benefit with ramucirumab was also maintained in patients previously treated with a taxane or bevacizumab. In respect to the small group of patients with EGFR mutation (n=33), authors observed a trend toward improved OS with ramucirumab in this subgroup. In patients 65 years or older, ramucirumab did not appear to have benefit in PFS or OS.[16]

NCT01703091 was a Japanese study with a very similar design to the REVEL trial. The study consisted of a Phase II, randomized, placebo-controlled study evaluating the efficacy and safety of ramucirumab 10 mg/kg or placebo in combination with docetaxel 60 mg/m^2 in 157 Japanese patients with stage IV NSCLC, whose disease has progressed during or after one platinum-based chemotherapy regimen. Patients who received previous EGFR-tirosin-kinase inhibitor (TKI) monotherapy for EGFR mutation-positive NSCLC in addition to platinum-based chemotherapy participated as a separate, exploratory population. Primary endpoint was PFS and secondary outcomes included OS, RR and safety. Median PFS was longer in the ramucirumab arm, 5.22 m (95% CI: 3.5–6.9), than in the placebo arm; 4.21 m (95% CI: 2.8–5.6); HR: 0.83 (95% CI: 0.59–1.16). Median OS was 15.15 m (95% CI: 12.4–26.5) with ramucirumab and 14.6 m (95% CI: 11.9–24.4) with placebo ; HR: 0.86 (95% CI: 0.56–1.32). Objective RR (28.9% vs 18.5%) and DCR (78.9% vs 70.4%) were numerically greater with ramucirumab than with pla-

cebo. The results of second-line ramucirumab-docetaxel were not statistically significant because of the low number of patients included, but it showed numerically improved PFS similar to that seen in the REVEL trial with a manageable safety profile in Japanese patients with NSCLC. In the exploratory population of EGFR mutation-positive patients with prior EGFR-TKI treatment, median PFS (5.65 m vs 4.37 m), ORR (44.4% vs 41.2%), and DCR (88.9% vs 76.5%) were numerically greater with ramucirumab than with placebo.[25]

Several studies of small molecule inhibitors of VEGFRs have been associated with benefits in PFS but not in OS in NSCLC. One study of particular relevance is the LUME-Lung 1 study, in which 1314 patients were randomized to receive docetaxel plus nintedanib or docetaxel plus placebo. The study did meet its primary endpoint and median PFS was significantly improved in the nintedanib group; 3.4 m (95% CI: 2.9–3.9) vs 2.7 m (2.6–2.8); HR: 0.79, 95% CI: 0.68–0.92, P=0.0019. However, unlike the REVEL study, an OS benefit was not found in the global study population; 10.1 m (95% CI: 8.8–11.2) vs 9.1 m (8.4–10.4); HR: 0.94, 95% CI: 0.83–1.05, P=0.2720. A hierarchical statistical analysis showed an OS benefit in the adenocarcinoma subpopulation; median OS 12.6 m (95% CI: 10.6–15.1) vs 10.3 m (95% CI: 8.6–12.2); HR: 0.83; 95% CI: 0.70–0.99, P=0.0359. A special observation was that maximum benefit in OS in the nintedanib group was observed for patients with adenocarcinoma histology who progressed within 9 months after start of first-line treatment; median OS 10.9 m (95% CI: 8.5–12.6) vs 7.9 m (6.7–9.1); HR: 0.75 (95% CI: 0.60–0.92) P=0·0073.[26]

These data were similarly observed in the REVEL trial, where in patients with time >9 months from the start of the first-line of treatment, the OS benefit with the combination of ramucirumab was not significant; HR: 0.95 (95% CI: 0.75–1.2). However, in patients with time <9 months from the beginning of the first-line of treatment, the OS benefit with the combination of ramucirumab was statistically significant; HR: 0.75 (95% CI: 0.64–0.88).[16]

However, with the introduction of immunotherapy, controversies arise about which patients would benefit best with immunotherapy or with the combination of docetaxel plus antiangiogenic drug. This adds another factor of complexity in clinical decisions. Two PD-1 inhibitors are currently approved for the treatment of metastatic NSCLC patients and progression on or after platinum-based chemotherapy: nivolumab and pembrolizumab. Nivolumab was studied in two Phase III trials, one in patients with squamous histology (Checkmate 017)[27] and the other with nonsquamous histology (Checkmate 057).[28] In patients with squamous histology the

median OS was significantly longer with nivolumab compared with docetaxel (9.2 m vs 6.0 m; HR: 0.59, 95% CI: 0.44–0.79, P<0.001) and PD-L1 expression was not predictive.[27] In adenocarcinoma patients, the median OS was 12.2 m with nivolumab compared with 9.4 m with docetaxel (HR: 0.73, 95% CI: 0.59–0.89, P=0.002). However, at the interim analysis, PD-L1 appeared to be strong predictive with benefit to nivolumab.[28] In the Phase III trial (KEYNOTE-010), patients with previously treated NSCLC with PD-L1 in ≥1% of tumor cells (IHC 22C3 anti-human PD-L1 antibody assay) were randomly assigned to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg or docetaxel 75 mg/m². OS was significantly longer for pembrolizumab 2 mg/kg (10.4 m) versus docetaxel (8.5 m; HR: 0.71, 95% CI: 0.58–0.88, P=0.0008) and for pembrolizumab 10 mg/kg (12.7 m) versus docetaxel (HR: 0.61, 95% CI: 0.49–0.75, P<0.0001).[29]

Safety of ramucirumab in NSCLC clinical trials
Phase II trials

In the Phase II trial of ramucirumab in combination with paclitaxel and carboplatin in first line therapy, adverse drug reactions (ADRs) were reported in 34 patients (85%). Most of the side effects were of grade 2 or 3 (Common Terminology Criteria for Adverse Events, CTCAE). The most frequent toxicities consisted of: nausea, neuropathy, asthenia, myalgia, and bleeding (epistaxis). Grade 3 side effects were described in 10 patients (25%) and included fatigue, anorexia, peripheral neuropathy, constipation, anemia, thrombocytopenia, neutropenia/febrile neutropenia, dyspnea, and hypertension. Grade 4 toxicity was reported in five patients (12.5%) and included neutropenia, febrile neutropenia, thrombocytopenia, and pulmonary embolism. Thirteen patients (32.5%) discontinued treatment due to ADRs, secondary to neutropenia, fatigue and infusion-related reactions (not attributed to ramucirumab).[14]

In the Phase II trial of ramucirumab in combination with pemetrexed and platinum in first-line therapy, toxicity was similar between the two groups. More patients discontinued at least one drug of treatment in the ramucirumab arm (n=22, 32.8%) in respect to the control arm (n=14, 20.3%). Grade 3 thrombocytopenia was the cause of discontinuation in three patients (4.5%) in the ramucirumab arm. The most frequent toxicities in the ramucirumab arm included: fatigue, anorexia, peripheral edema, back pain, headache, neutropenia, thrombocytopenia, bleeding (epistaxis), insomnia, and dyspnea. In this trial, the grade 3 toxicities described in ≥10% of patients were nausea, thrombocytopenia, neutropenia, and hyperten-

sion. These toxicities occurred more frequently in the ramucirumab arm. No difference in deaths during the trial was observed between the arms; three (4.5%) in the ramucirumab arm (multiorgan failure, myocardial infarction, and sudden death) and five (7.2%) in the control group (lung embolism, respiratory failure, cardiorespiratory arrest, hemothorax and myocardial infarction).[15]

Phase III trials

Of the 1,245 patients in the REVEL study, evaluated for toxicity, the most frequent side effects occurring in ≥5% of patients, with a ≥2% increase in the ramucirumab group were: asthenia, hypertension, peripheral edema, lacrimation, mucositis, neutropenia, febrile neutropenia, thrombocytopenia, and bleeding (epistaxis). Dose delays and dose reductions were higher in the ramucirumab group compared with the placebo arm; 42% vs 32%, and 29% vs 21%, respectively.[16]

Authors did not find differences in the serious adverse events (SAEs) between the arms; 43% in the ramucirumab group versus 42% in the placebo arm. The most common SAEs in the ramucirumab arm were: febrile neutropenia (14%), pneumonia (6%), neutropenia (5%), diarrhea (2%), dehydration (2%), and mucositis (2%). No differences were observed in deaths (31 deaths in the ramucirumab group compared with 35 deaths in the control arm).[16]

A safety comparative analysis was performed in the elderly population. Authors observed a slightly higher adverse events rate and grade 3 side effects between the ramucirumab (84%) versus placebo (78%) arms in patients ≥65 years, and slightly higher rate of deaths; 8% versus 4%. The mean relative dose intensity was similar between younger and older patients for both drugs. The causes of death for patients ≥65 years were attributed to pulmonary embolus, pneumonia, respiratory failure, hemoptysis, cardiac arrest, sepsis, disease progression, and cause not specified. In any case, apparent lack of efficacy of ramucirumab in this subpopulation does not appear to be explained by this slight increase in deaths.[16]

Dose adjustments were performed most frequently in patients treated with ramucirumab (n=204, 33%, versus n=139, 23%). The most common side effects requiring dose adjustments were neutropenia (n=77, 12% vs n=55, 9%), febrile neutropenia (n=44, 7% vs n=28, 5%), and asthenia (n=54, 9% vs n=34, 6%). Bleeding toxicity (predominantly epistaxis) occurred twice as often in the ramucirumab group (29% vs 15%), but severe bleeding was similar in incidence between the arms (2.4% vs 2.3%), including pulmonary hemorrhages (7.8% vs 7.4%). Gastrointestinal hemorrhages were slightly higher in the ramucirumab arm (2.7% vs 1.6%).

As expected, the incidence of hypertension was higher in the ramucirumab arm (n=68, 11% vs n=30, 5%).[16]

Meta-analysis

A recent meta-analysis has evaluated the incidence and relative risk of hemorrhagic events in cancer patients treated with ramucirumab in Phase II and III trials. A total of 4963 patients with various solid tumors from 11 trials were selected. The overall incidences of all-grade and high-grade hemorrhagic events were 27.6% (95% CI: 18.7%–36.5%) and 2.3% (95% CI: 1.3%–3.2%), respectively. In consideration of low-grade hemorrhagic events, the RR was significantly increased for ramucirumab (RR, 2.06; 95% CI: 1.85–2.29, $P<0.001$), but not for high-grade hemorrhagic events (RR, 1.19, 95% CI: 0.80–1.76, $P=0.39$). The conclusion was that hemorrhagic events associated with ramucirumab were modest and manageable.[30]

A recent meta-analysis based on Phase II and III trials with a variety of solid tumors has investigated hypertension associated with use of ramucirumab. A total of 2,649 patients were included. The incidence of all grade and high-grade hypertension associated with ramucirumab was 16.4% (95% CI: 11.9%–22.3%) and 9.8% (95% CI: 7.2%–13.0%), respectively. In respect to the control group, patients treated with ramucirumab had an increased risk of developing any-grade (RR: 2.28, 95% CI: 1.61–3.24, $P<0.001$) and high-grade (RR: 3.59, 95% CI: 2.32–5.53, $P<0.001$) hypertension.[31]

Another meta-analysis from six trials including 4579 patients with a variety of solid malignancies, has evaluated risk of gastrointestinal perforation associated with ramucirumab. The RR of gastrointestinal perforation associated with ramucirumab was 2.56 (95% CI: 1.29–5.09; $P=0.007$), with an incidence of 1.5% (95% CI: 1.1%–2.1%) and a mortality of 29.8% (95% CI: 14.9%–50.7%).[32]

Quality of life

The only trial that has evaluated quality of life (QoL) in lung cancer treated with ramucirumab was the Phase III REVEL trial. QoL was assessed by the Lung Cancer Symptom Scale (LCSS) and clinician-reported functional status. LCSS and ECOG PS data were collected at baseline, every 3-week cycle and at the 30-day follow-up after the last dose. The primary analysis compared time to deterioration (TtD) between the two arms for all individual items and summary scores, defined as increase from baseline by ≥15 mm. Also, TtD to ECOG PS ≥2 was analyzed. LCSS compliance was 75% and well balanced between the arms. The mean baseline LCSS total score was 27.3 mm in the ramucirumab arm and 29.6 mm in

the control arm. At 30-day follow-up, mean LCSS total score was 32 and 32.5, respectively. The TtD for all LCSS scores was similar between treatment arms. TtD to PS ≥2 was also similar between arms (HR: 1.03 [95% CI: 0.85, 1.26], *P*=0.743). The conclusion was that adding ramucirumab to docetaxel did not impair patient QoL, symptoms, or functioning.[33]

Ongoing trials

There are currently several trials in progress, evaluating the effects of ramucirumab in combination with other drugs in patients with advanced NSCLC.

The NCT02082210 is a dose escalation Phase I trial. The purpose of this study is to find a recommended schedule and dose range for LY2875358 when given with ramucirumab that may be safely given to participants with advanced cancer, including gastric adenocarcinoma, gastroesophageal junction adenocarcinoma, hepatocellular cancer, renal cell carcinoma, and NSCLC. In Part A of this study, escalating doses of LY2875358 will be given in combination with a fixed dose of ramucirumab to evaluate the safety of the combination. The protocol consisted on dose escalation of LY2875358 administered IV, on days 1 and 15 every 28-day cycle in combination with a fixed dose of ramucirumab administered IV on days 1 and 15 every 28 day cycle. After a recommended schedule and dose range of LY2875358 and ramucirumab has been established, Part B of the study will confirm safety and to see how well certain tumors respond to the combination of study drugs. The average amount of time in the study is expected to be about 6 months and estimated enrollment to be 100 patients. Primary end points including safety and secondary objectives are RR, pharmacokinetic parameters, PFS, and quality of life.

NCT02079636 is a Phase Ib study of LY2835219 (abemaciclib) in combination with multiple single agent options, including pemetrexed, gemcitabine, ramucirumab, and LY3023414 for patients with stage IV NSCLC. The main purpose of this study is to evaluate the safety and tolerability of abemaciclib in combination with other drugs in advanced NSCLC patients. Primary end point was to find dose limiting toxicity. Secondary objectives were pharmacokinetics, response, PFS and quality of life. The experimental arm abemaciclib + ramucirumab consisted on abemaciclib given orally every 12 hours on days 1 through 21 of a 21-day cycle in combination with 10 mg/kg ramucirumab IV on day 1, or ramucirumab alone at the same doses. Participants may continue to receive treatment until discontinuation criteria are met.

In respect to the combination of ramucirumab and TKIs in EGFR mutation, the RELAY study (NCT02411448) consists of a Phase Ib/III study of the combination of ramucirumab with erlotinib in first line stage IV NSCLC with activating epidermal growth factor receptor (EGFR). The trial will assess safety, tolerability, and efficacy. In part A (Phase Ib), 12 patients will receive oral erlotinib 150 mg/day plus ramucirumab 10 mg/kg every 2 weeks. The principal objective is dose-limiting toxicity, assessed during the first 4 weeks of treatment. In part B (Phase III), ~450 patients will be included and all of them treated with erlotinib, and they will be randomized to ramucirumab or placebo every 2 weeks until disease progression or unacceptable toxicity. The principal end points are PFS and safety. Secondary objectives include: OS, RR, DCR, duration of response, pharmacokinetic parameters, immunogenicity and quality of life.[34] NCT02789345 is an open-label, multicenter, Phase I study with expansion cohorts of ramucirumab or necitumumab in combination with osimertinib in patients with advanced T790M-positive EGFR-mutant NSCLC after progression on first-line EGFR TKI therapy. The main objective is dose limiting toxicities (DLTs) and secondary outcome measures: pharmacokinetics, ORR, DCR, Duration of Response (DoR), PFS and OS. Ramucirumab is given IV on day 1 every 2 weeks (q2w) and osimertinib 80 mg is given orally daily during each 14-day cycle.

In respect to the combination of ramucirumab and immunotherapy, antiangiogenic agents can stimulate the immune system and these two types of drugs could operate synergistically in the treatment against cancer, without a significant increase in toxicity. VEGF signaling may attenuate the antitumor response in different ways. VEGF decreases lymphocyte trafficking across endothelia to the tumor by inhibiting lymphocyte adhesion to activated endothelial cells, through defects in endothelial intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and Fas ligand. Although, VEGF has a systemic effect on immune-regulatory cell function through multiple mechanisms, including the induction and proliferation of inhibitory immune-cell subsets, such as T-regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs).[35] The NCT02443324 Phase I trial will evaluate the safety of the combination of ramucirumab with pembrolizumab in several types of advanced cancers, including NSCLC. The principal objective is dose-limiting toxicities and secondary end points include RR, DCR, duration of response, PFS, time to first response, OS, and pharmacokinetic parameters. Preliminary results from the DLT part of the study

have shown no unexpected toxicities. No DLTs were reported in patients with NSCLC.[36]

The main purpose of the ongoing NCT02572687 study is to evaluate the safety of ramucirumab plus MEDI4736 in participants with locally advanced and unresectable or metastatic gastrointestinal or thoracic malignancies including gastric or gastroesophageal junction (GEJ) adenocarcinoma, NSCLC, or hepatocellular carcinoma (HCC). In Phase Ia (DLT phase), ramucirumab plus MEDI4736 IV is given every 3 weeks (q3w) of a 21-day treatment cycle. Participants may continue to receive study treatment until discontinuation criteria are met. In Phase Ib (expansion phase), ramucirumab plus MEDI4736 will be given IV q3w. Participants may continue to receive study treatment until discontinuation criteria are met.

Conclusion

Drugs targeting the VEGF pathway have been developed in recent years for several types of tumors and represent an important advance in the treatment of cancer, since one of the most important mechanisms in the process of tumor progression, and acquisition of evolutionary advantages is based on the process of angiogenesis and cell proliferation.

Ramucirumab offers a very innovative mechanism of action with regard to antiangiogenic therapies previously developed, since it is specifically directed against the receptor VEGFR-2, key to the process of angiogenesis. Currently, ramucirumab has been approved for several indications in gastrointestinal tumors, and specifically, in lung cancer, it has recently been approved for the treatment of advanced second-line NSCLC in combination with chemotherapy, specifically, docetaxel. The approval was achieved thanks to the data from the clinical trial REVEL. This study is a clinical Phase III trial, with an appropriate statistical design, in which a statistically significant benefit in its primary objective was observed. The experimental arm had improved OS of 1.4 months and toxicity was acceptable, with similar grade 3-4 toxicity with respect to the control arm and without deterioration in the quality of life of patients. Although these data are encouraging in the improvement of the overall prognosis of the natural history of advanced NSCLC, however, many questions remain about the utility of this agent in this context.

For example, the benefit of adding ramucirumab to docetaxel in elderly patients is not clear. Patients whose tumors carry genomic alterations of ALK or EGFR must have progression to EGFR or ALK therapy before receiving treatment with ramucirumab, and the number of patients included in the study is very low to be able to obtain clear conclusions. Ongoing clinical trials will give us more information about these issues.

However, with the good current data of immunotherapy, the main question with respect to the indication of the anti-angiogenic therapies (both ramucirumab and nindetanib) in combination with docetaxel in the second line of the advanced NSCLC, will be to establish what subgroup of patients will be most beneficial with immunotherapy or with anti-angiogenic therapies. Nivolumab and pembrolizumab have provided data of benefit in OS with docetaxel monotherapy, with less toxicity profile, and have positioned themselves as a standard for second-line in this setting. This adds another factor of complexity in clinical decisions. In second-line advanced NSCLC, there is no face to face comparison of checkpoints inhibitors to the combination of docetaxel and antiangiogenic agents and no projected new trials with this methodology in the near future. Actually, the selection of post-platinum treatments depends for each patient on several parameters, including performance status, age, corticosteroids use or other contra-indication to immunotherapy, PD-L1 expression or tumor mutational status, and as the hot topic, aggressiveness of the disease with threatening metastatic sites or response and time to progression on first-line therapy. However, availability of the drugs often remains the main decisive consideration. Probably, the role of anti-PD1/PD-L1 agents in the second-line treatment algorithm for advanced NSCLC will likely become the principal options, even in situations where the clinical decision is difficult, relegating docetaxel in combination with an anti-angiogenic drug to the third-line setting, although there are no available data to assess the potential use of ramucirumab plus docetaxel after anti-PD-1 or PD-L1 therapy.

However, availability of the drugs often remains the main decisive consideration, and in determinate algorithms, there are several recommendations that suggest that the use of one strategy against another in specific patients will depend on the evaluation combining pathological factors, specifically, the expression of PD-L1 determined by immunohistochemistry, together with clinical factors.

Moreover, the available data seem to reveal that patients with rapid progression receive little benefit from immunotherapy, with an ORR of 8%–10% with nivolumab and pembrolizumab,[27–29] mainly in patients with low PD-L1 expression. However, angiogenesis inhibitors, such as ramucirumab or nindedanib, seem to work better, specifically in this subgroup which gains the greatest benefit, principally, patients with time <9 months from the beginning of the first line of treatment. This is the subgroup of patients in whom the combination of docetaxel and antiangiogenic drugs may have more benefit than immunotherapy.

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Disclosure

The authors report no conflicts of interest in this work.

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