Lung Cancer 120 (2018) 62–69

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

# Antiangiogenic therapy for patients with aggressive or refractory advanced non-small cell lung cancer in the second-line setting

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ARTICLE INFO

*Keywords:*
Angiogenesis
Non-small-cell lung cancer
Ramucirumab
Nintedanib
Immunotherapy

ABSTRACT

A majority of patients with advanced or metastatic non-small cell lung cancer (NSCLC) will experience disease progression after first-line therapy. Patients who have advanced NSCLC that is especially aggressive, which is defined as disease that rapidly progresses on first-line treatment or disease that is refractory to first-line treatment, have a critical unmet medical need. These patients have a poor prognosis in the second-line setting. Several studies have recently shown that treatment with an antiangiogenic therapy may benefit these patients. This review summarizes the approved antiangiogenic therapies for the treatment of patients with advanced NSCLC in the second-line setting, specifically focusing on the outcomes from subgroups of patients with rapidly progressing or refractory disease. Several antiangiogenic agents, as monotherapy or in combination with other treatments, have been or are currently being studied in patients with advanced NSCLC. Antiangiogenics that are approved for use in patients with advanced NSCLC are limited to bevacizumab in combination with chemotherapy (nonsquamous NSCLC), ramucirumab in combination with docetaxel (all histologies), and nintedanib in combination with docetaxel (adenocarcinoma histology). This review focuses on the efficacy, safety, and quality of life outcomes in the subpopulation of patients with rapidly progressing or refractory NSCLC treated with approved antiangiogenic therapies in the second-line setting. We also discuss the impact of newly approved immunotherapy agents on the outcomes of patients with aggressive or refractory disease. Studies in progress and planned future research will determine if combination treatment with antiangiogenics and immunotherapies will benefit patients with aggressive, advanced NSCLC.

## 1. Antiangiogenic therapy in non-small cell lung cancer (NSCLC)

Antiangiogenic targeted therapy is an area of active research in which numerous agents have been studied and have been shown to be effective for many tumor types including NSCLC. Angiogenesis is frequently upregulated in malignant solid tumors and is critical for tumor

*Abbreviations:* CI, confidence interval; DCR, disease control rate; DOC, docetaxel; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HR, hazard ratio; ITT, intent to treat; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD-BRPT, progressive disease as best response to prior therapy; PD-1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TSPT, time since start of prior therapy; TTPFL, time to progression on first-line therapy; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor

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https://doi.org/10.1016/j.lungcan.2018.03.025
Received 14 December 2017; Received in revised form 23 March 2018; Accepted 26 March 2018

growth, proliferation, and metastasis [1]. The vascular endothelial growth factors (VEGF)-A, −B, −C, and −D, and their transmembrane tyrosine kinase receptors, vascular endothelial growth factor receptors (VEGFR)-1, −2, and −3, are important proangiogenic factors in normal and malignant tissues. Vessel formation in adult tissues is primarily mediated by VEGF-A, and downstream proangiogenic activity is mainly facilitated through interactions with VEGFR-2 [2–4]. Overexpression of VEGF proteins occurs in most tumors and is associated with increased risk of recurrence, metastasis, and death [5]. Platelet-derived growth factor and fibroblast growth factor pathways are also implicated in the regulation of angiogenesis [6]. Several antiangiogenic agents combined with chemotherapy have demonstrated clinical activity by targeting VEGF ligands or receptors with monoclonal antibodies or through tyrosine kinase inhibitors (TKIs) that block downstream proangiogenic pathways [7]. A select few of these combinations have demonstrated improved efficacy and acceptable toxicity in randomized trials that have led to their approval for treating patients with advanced NSCLC in the first- and/or second-line setting [8–10].

Until recently, standard first-line treatment for advanced nonsquamous NSCLC consisted of combination therapy with platinum plus a third-generation chemotherapy agent with or without bevacizumab [11]. However, efficacy for these combinations plateaued in fit patients for objective response rates (ORRs) (approximately 25%–35%), time to progression (4–6 months), median overall survival (OS) (8–10 months), 1-year survival rates (30%–40%), and 2-year survival rates (10%–15%) [11].

Single-agent first-line immunotherapy treatment with pembrolizumab has recently been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for patients with advanced NSCLC and ≥50% of tumor cells expressing the programmed death receptor ligand 1 (PD-L1), as it demonstrated improved progression-free survival (PFS) and OS when compared with platinum-containing chemotherapy [12]. In addition, KEYNOTE-021 (Clinicaltrials.gov identifier NCT02039674) led to the FDA accelerated approval of first-line carboplatin-pemetrexed-pembrolizumab in nonsquamous NSCLC patients, irrespective of PD-L1 status determined by immunohistochemistry [13]. Recent advances have improved clinical outcomes for patients with tumors harboring targetable driver aberrations; however, only a small proportion (< 20%) of patients with advanced NSCLC present with these abnormalities (e.g., epidermal growth factor receptor, anaplastic lymphoma kinase, ROS proto-oncogene 1 rearrangements) [7]. Additionally, intrinsic or acquired resistance to some targeted TKIs is increasingly problematic [14].

The first and only antiangiogenic therapy approved in the first-line setting for advanced NSCLC is bevacizumab (Avastin™, Genentech, Inc., San Francisco, CA, USA). Bevacizumab is a humanized monoclonal antibody that targets VEGF-A, inhibiting interactions with VEGFR-1 and VEGFR-2. Bevacizumab was approved in combination with paclitaxel-carboplatin for first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC based on results from a large randomized phase 3 study [10]. It is now a standard first-line treatment option for qualified patients with advanced nonsquamous NSCLC and no actionable biomarkers [11].

## 2. Efficacy of antiangiogenics as second-line treatment in patients with aggressive or refractory disease

Regardless of the initial treatment, most patients with advanced NSCLC experience relapse and disease progression [15]. A subpopulation of immediate concern and clinical need is patients who have advanced NSCLC that is especially aggressive, which is usually defined as disease that rapidly progresses on first-line treatment or disease that is refractory to first-line treatment. These patients have a poor prognosis in the second-line setting.

While many antiangiogenic agents, as monotherapy or in combination with chemotherapy, immunotherapy, or targeted TKIs, have been studied in the second-line setting for patients with advanced or metastatic NSCLC, currently, only ramucirumab (independent of histology) or nintedanib (adenocarcinoma histology only) in combination with docetaxel have received FDA and/or EMA approval based on outcomes from large phase 3 studies [8,9]. In addition, post-hoc analyses have been performed in trials to assess outcomes in patients with aggressive NSCLC.

This review focuses on the efficacy and safety outcomes of approved antiangiogenic treatments in the second-line setting in patients with advanced NSCLC that is aggressive or refractory to first-line therapy.

### 2.1. Ramucirumab

Ramucirumab (Cyramza™, IMC-1121B; Eli Lilly and Company, Indianapolis, IN, USA) is a recombinant human monoclonal $IgG_1$ antibody with high affinity for the extracellular domain of VEGFR-2, inhibiting ligand binding (VEGF-A, −C, and −D) and activation of downstream proangiogenic pathways [16,17]. In REVEL (Clinicaltrials.gov identifier NCT01168973), a large phase 3 trial of ramucirumab plus docetaxel or placebo plus docetaxel, patients with advanced NSCLC who had progressed on first-line platinum-based therapy and were treated with ramucirumab had improved OS (10.5 *vs.* 9.1 months; hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.75–0.98; $P = 0.023$), PFS (4.5 *vs.* 3.0 months; HR 0.76, 95% CI 0.68–0.86; $P < 0.001$), and ORR (23% *vs.* 14%; odds ratio [OR] 1.89, 95% CI 1.41–2.54; $P < 0.0001$) compared with patients treated with placebo with a manageable safety profile [8]. This trial included patients with nonsquamous as well as squamous histologies and even patients with prior bevacizumab exposure. These results led to the FDA and EMA approval of ramucirumab plus docetaxel for previously treated advanced NSCLC regardless of histology [18].

Recent analyses of prespecified and exploratory subgroups from the REVEL study suggested that the benefit of ramucirumab plus docetaxel also applies to patients with aggressive or refractory NSCLC regardless of histology [19]. In multiple subgroup analyses, patients with aggressive or refractory disease were defined in several ways based on known poor prognostic factors for advanced NSCLC. These included (1) a prespecified analysis of patients who had a duration of < 9 months from the start of first-line therapy to the start of second-line therapy, e.g., time since start of prior therapy (TSPT) [8,19]; (2) an exploratory analysis of patients who were refractory to first-line therapy, defined as those with progressive disease as best response to prior therapy (PD-BRPT) [19]; and (3) an exploratory analysis of patients with a rapid time to progression on first-line therapy (TTPFL) within 9, 12, and 18 weeks [20].

In a prespecified REVEL analysis, patients with < 9 months TSPT had balanced baseline characteristics and postdiscontinuation therapy between treatment arms. Outcomes were improved for patients in the ramucirumab arm versus those in the control arm. Similar OS results were observed across histology subgroups (Fig. 1A) [8,19]. In particular, patients in the nonsquamous subgroup with TSPT < 9 months had a median OS of 9.7 versus 6.9 months (HR 0.70, 95% CI 0.58–0.85), patients in the adenocarcinoma subgroup had a median OS of 9.7 versus 7.0 months (HR 0.71, 95% CI 0.57–0.89), and patients in the squamous subgroup had a median OS of 8.9 versus 7.2 months (HR 0.84, 95% CI 0.63–1.14) (Fig. 1A) [8,19].

In an exploratory REVEL analysis, patients with refractory disease, defined as PD-BRPT, in the ramucirumab plus docetaxel arm versus the placebo plus docetaxel arm had significantly improved PFS (4.0 *vs.* 2.5 months; HR 0.71, 95% CI 0.57–0.88; $P = 0.0021$), ORR (22.5% *vs.* 12.6%; $P = 0.014$), and disease control rate (DCR; 52.2% *vs.* 42.3%; $P = 0.049$) independent of histology. There was also a 2-month difference in median OS (8.3 *vs.* 6.3 months; HR 0.86, 95% CI 0.68–1.08). Overall treatment effects were consistent with those observed in the intent-to-treat (ITT) population (Fig. 1B) [8,19].

Another exploratory subgroup analysis of the REVEL study included