MEDICAL SCIENCE MONITOR

EDITORIAL

e-ISSN 1643-3750
© Med Sci Monit, 2021; 27: e934854
DOI: 10.12659/MSM.934854

Received: 2021.09.20
Accepted: 2021.09.21
Available online: 2021.09.22
Published: 2021.09.27

Editorial: Global Regulatory Initiatives Deliver Accelerated Approval of the First Bispecific Therapeutic Monoclonal Antibody for Advanced Non-Small Cell Lung Cancer (NSCLC)

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Conflict of interest: None declared

Abstract The coronavirus disease 2019 (COVID-19) pandemic has affected the number of completed clinical trials, particularly in oncology. Between 80-85% of all lung cancers are non-small cell lung cancer (NSCLC), and of these, between 2-3% have an EGFR exon 20 insertion, which is associated with increased cell proliferation, metastasis, and a lack of response to chemotherapy and epidermal growth factor receptor (EGFR) inhibitors. Until this year, there were no available targeted therapies for advanced NSCLC with this genetic subtype. However, in May 2021, the US Food and Drug Administration (FDA) granted accelerated approval for amivantamab-vmjw (Rybrevant®), a bispecific monoclonal antibody, targeting activating and resistant EGFR and MET mutations and amplifications. This FDA approval was for adult patients with locally advanced metastatic NSCLC, with disease progression on or following platinum-based chemotherapy. The FDA also approved the Guardant360® companion diagnostic, a next-generation sequencing platform for circulating tumor DNA (ctDNA), which is a liquid biopsy assay. In 2019, Project Orbis was launched by the FDA Oncology Center of Excellence as a global collaborative review program to facilitate rapid global access for patients to innovative cancer therapies. This Editorial aims to highlight how global regulatory initiatives from the FDA have delivered accelerated approval of the first bispecific therapeutic monoclonal antibody, amivantamab-vmjw (Rybrevant®), and a companion diagnostic for patients with advanced NSCLC with an EGFR exon 20 insertion.

Keywords: **Editorial • Non-Small Cell Lung Cancer, NSCLC • Targeted Therapy • Monoclonal Antibody • EGFR • MET**

In 2020, data from the World Health Organization (WHO) International Agency for Research on Cancer (IARC) reported that lung cancer was the second most commonly diagnosed malignancy and confirmed that the global incidence has been increasing annually [1]. In the year before the coronavirus disease 2019 (COVID-19) pandemic, there were 2.2 million new cases of lung cancer diagnosed globally, which represented approximately 11.4% of the total global healthcare cancer burden, and there were 1.8 million lung cancer deaths [1]. Histologically, non-small cell lung cancer (NSCLC) includes adenocarcinoma, squamous cell carcinoma, and adenosquamous carcinoma [2]. Treatment of advanced NSCLC requires the sequential use of combined systemic therapy to prolong overall survival (OS) and maintain the quality of life for patients [2]. Two decades ago, driver mutations in the epidermal growth factor receptor (EGFR) mutation in NSCLC were identified [3]. Several drug development programs were initiated to target EGFR mutations in advanced NSCLC [3].

In 2006, the most extensive biomarker study was conducted using human tumor tissue to identify EGFR mutations in patients with advanced NSCLC [4]. The IRESSA Survival Evaluation in Lung Cancer (ISEL) phase 3 trial heralded the start of the global initiative for targeted therapy and personalized medicine, or precision medicine, in patients with advanced NSCLC [4]. ISEL compared the tyrosine kinase inhibitor, gefitinib, with placebo in 1,692 patients with refractory advanced NSCLC [4]. The results showed that the EGFR gene copy number was a predictor of clinical benefit [4]. During the following decade, increasing numbers of biomarkers were identified in NSCLC that targeted specific drugs or a dependent factor associated with the tumor [5]. Initially, these targeted drugs were small-molecule tyrosine kinase inhibitors or monoclonal antibodies against a specific receptor [5]. Early targeted therapies in advanced NSCLC were directed to EGF/EGFR, HER2, VEGF/VEGFR, ALK, BRAF, KRAS, MEK, and MET [5].

Following the early targeted approaches to tumor biomarkers in NSCLC, it was clear that accurate and standardized

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companion diagnostics to identify gene mutations and tumor cell protein expression was required [5]. Companion diagnostic testing is now a mandatory requirement for clinical decisions in targeted therapy for NSCLC [6]. The challenges of increasingly complex companion diagnostic testing, which now includes molecular testing, could be too complicated or expensive for use in routine diagnostic laboratories [6]. These challenges have been overcome by developing commercial companion diagnostic kits, which now require regulatory approval and use in an accredited diagnostic laboratory [6]. Future developments of companion diagnostic testing and approvals may include tests for resistance and drug toxicity biomarkers and tests that predict drug efficacy in NSCLC [6]. During the past decade, there have been increasing regulatory approvals for therapeutic monoclonal antibodies in NSCLC [6]. Early approvals for targeted therapy in advanced NSCLC have included cetuximab, bevacizumab, nivolumab, and pembrolizumab, which all rely on companion diagnostics to identify the therapeutic target in tumor tissue [6].

During 2020 and 2021, the COVID-19 pandemic has profoundly affected clinical research, drug development, and clinical trials, particularly in oncology [7,8]. A US adult Cancer Center Network reported a 50% reduction in patient enrolment for clinical trials [7]. In 2020, a survey conducted by the American Society of Clinical Oncology (ASCO) showed that almost 60% of clinical trial units suspended activity [8]. However, a recent development in personalized monoclonal antibody therapy in oncology has been developing bispecific monoclonal antibodies that bind to two distinct epitopes on the human cancer cell [9]. Between 80-85% of all lung cancers are NSCLC, and of these, between 2-3% have an EGFR exon 20 insertion, which is associated with rapid cell proliferation, invasion, and metastasis and a lack of response to chemotherapy or EGFR inhibitors [10]. Until May 2021, there were no available targeted therapies for advanced NSCLC with this genetic subtype [10].

Amivantamab (JNJ-61186372) is an EGFR and MET bispecific monoclonal antibody that targets activating and resistant EGFR and MET mutations and amplifications [10,11]. Amivantamab has shown preclinical activity in models of tyrosine kinase inhibitor-sensitive EGFR-mutated NSCLC and a first-in-human clinical study in patients with advanced NSCLC [10-12]. In May 2021, the US Food and Drug Administration (FDA) granted accelerated approval for amivantamab-vmjw (Rybrevant®) (Janssen Biotech, Inc., Horsham, PA, USA.) [13,14]. The approval was for adult patients with locally advanced metastatic non-small cell lung cancer (NSCLC), with disease progression on or following platinum-based chemotherapy, identified as having mutations in the EGFR gene exon 20 insertion [13,14]. The indication was approved under the FDA accelerated approval program and is based on the overall response rate (ORR) and duration of response [13,14]. The continued approval of amivantamab-vmjw (Rybrevant®) for this indication is contingent on verifying clinical benefit to patients in future confirmatory clinical trials [13,14].

Also, in May 2021, the FDA approved the Guardant360® companion diagnostic (Guardant Health, Inc. Redwood City, CA, USA), which is a next-generation sequencing platform for a cell-free circulating tumor DNA (ctDNA), or a liquid biopsy assay [15]. The Guardant360® companion diagnostic is reported to be comparable to standard tissue biopsy in the detection biomarkers in advanced NSCLC, has a rapid turnaround time, and can test multiple patient samples [15].

FDA approval for amivantamab-vmjw (Rybrevant®) was based on the safety and efficacy findings from the CHRYSALIS clinical trial (NCT02609776) [10]. CHRYSALIS was a multicenter, multicohort, open-label, non-randomized clinical trial [10]. The efficacy of amivantamab-vmjw (Rybrevant®) was evaluated in 81 patients with advanced NSCLC and included once-weekly intravenous therapy for four weeks, followed by treatment every two weeks [10]. The main efficacy outcome measures in the CHRYSALIS trial were the ORR, which was evaluated by a blinded independent central review (BICR), and duration of response [10]. The trial findings showed an ORR of 40% (95% CI, 29-51%) and a median response duration of 11.1 months [10]. The most common adverse reactions in ≥20% of trial participants were rash, musculoskeletal pain, nausea, and fatigue [10]. The recommended dose for amivantamab-vmjw (Rybrevant®) is 1,050 mg for patients with a baseline body weight of <80 kg, and 1,400 mg for patients with body weight ≥80 kg, given for four weeks, followed by every two weeks, until disease progression or until patients experience unacceptable toxicity [16].

During 2020 and 2021, the COVID pandemic has affected patient recruitment to clinical trials and has caused delays, particularly for clinical trials in oncology [7,8]. The FDA review under Project Orbis was an important factor in the rapid approval process for this new bispecific therapeutic monoclonal antibody [17]. In 2019, Project Orbis was launched by the FDA Oncology Center of Excellence, a global collaborative review program to facilitate rapid global access for patients to innovative cancer therapies [17,18]. The Project Orbis initiative aims for concurrent regulatory submission, review, and regulatory decisions for clinically important marketing applications from participating partner countries [17]. The first action of Project Orbis commenced in September 2019 between the US FDA, the Australian Therapeutic Goods Administration, and Health Canada [17]. Project Orbis was developed to provide an international framework for concurrent submission and review of oncology therapeutics [17]. Current Project Orbis partners include Australia, Brazil, Canada, Switzerland, and Singapore, with the FDA acting as a coordinator [17]. Between June 2019 to June 2020, Project Orbis reviewed 60 oncology marketing

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applications that resulted in 38 approvals [17]. New active substances, or new molecular entities (NMEs), comprised 28% of the marketing applications [17]. Also, from February 2018, the FDA initiated the Real-Time Oncology Review (RTOR) pilot project to facilitate earlier submission of topline oncology study results and datasets to accelerate an earlier start to the application review process [17]. Between February 2018 to April 2020, RTOR supported the submission and review of approvals for 20 oncology drug applications, which all received priority review, and 45% of applications received breakthrough therapy designation status [17]. RTOR was integrated with other review programs that included Assessment Aid and Project Orbis [17].

Comprehensive clinical trials in oncology often involve patients in several countries, with the safety and effectiveness findings leading to drug approvals in the US. The Project Orbis collaboration between international regulators may have an impact at this time as it facilitates earlier access to therapeutics for cancer patients in countries where there could be regulatory delays [17]. Future drug development in oncology and other therapeutic areas at this challenging time might benefit from global treatment standards, improved design of clinical trials, international collaboration, and communication on clinical data relevant to the regulatory applications under review [17].

The FDA collaborated with the Brazilian Health Regulatory Agency (ANVISA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) for the review of amivantamab-vmjw (Rybrevant®), which is also undergoing application reviews by other regulatory agencies [13,14]. Because of these initiatives, this application was approved by the FDA two months ahead of the initial approval target [17,18]. Future expansion of recent FDA programs, such as Project Orbis, to include more countries and review more regulatory applications could offset the delays in approvals during the COVID-19 pandemic.

Conclusions

The recent regulatory approval of amivantamab-vmjw (Rybrevant®), an EGFR and MET bispecific monoclonal antibody, and the Guardant360® companion diagnostic, herald a new era in targeted therapy for patients with advanced NSCLC. When the COVID-19 pandemic has delayed clinical trials and regulatory approvals in oncology, recent global initiatives developed by the FDA helped accelerate the approval of amivantamab-vmjw (Rybrevant®) for patients with advanced NSCLC and mutations in the EGFR gene exon 20 insertion. Future expansion of recent FDA programs, such as Project Orbis, to include more countries and review more regulatory applications could help offset the delays in approvals associated with the ongoing COVID-19 pandemic.

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