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REVIEW ARTICLE

Rovalpituzumab Tesirine: A Novel DLL3-Targeting Antibody–Drug Conjugate

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Abstract

Small cell lung cancer (SCLC) comprises about 15% of all cases of lung cancer. In recent years, owing to a change in the epidemiology of smoking habits, the incidence of the tumor has decreased; however, it remains a significant challenge to global health. While the tumor has a favorable initial response to chemoradiation, relapse is invariable, and second-line regimens may be intolerable given the severity of side effects. For patients with tumors resistant to second-line regimens, no current standard regimens exist. Rovalpituzumab tesirine is a novel antibody–drug conjugate, targeting delta-like protein 3, fundamental in the downstream cellular signaling for proliferation and apoptosis. This drug is reported to have shown promise in pre-clinical and phase I trials. It appears effective in decreasing tumor burden and is reported to be well tolerated, albeit with a significant adverse effect profile. Currently, it is being studied as part of initial and subsequent line chemotherapeutic regimens; it remains to be seen if this is a viable option in the treatment of SCLC. This may add to the agents that can be used against SCLC, and help improve outcomes.

Key Points

Rovalpituzumab tesirine is a novel antibody–drug conjugate that targets the delta-like 3 (DLL3) protein, a surface protein on neoplastic cells, and delivers a cytotoxic payload upon ingestion.

Pre-clinical and clinical experience has shown some clinical efficacy in reducing disease burden, especially in patients who have experienced multiple relapses.

While reported as having a manageable side effect profile, the agent has shown significant adverse events in both phase I and phase II studies, and appears to have limited tolerability.

The agent is a step forward in the development of novel therapies, and ongoing clinical trial data will be instrumental in determining how this agent affects clinical practice.

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1 Introduction

Small cell lung cancer (SCLC) comprises about 15% of all cases of lung cancer in the United States. Although the incidence of this disease has decreased lately, it still remains a significant challenge to practicing oncologists [1]. SCLC is characterized by rapid growth and early dissemination and is frequently metastatic at diagnosis. Platinum-based combination chemotherapy remains the backbone of treatment. Various regimens that can be utilized include carboplatin-etoposide, cisplatin-etoposide, carboplatin-irinotecan and cisplatin-irinotecan [2]. The response rate with these platinum doublets is more than 60% in the first-line setting [3]. Although the tumor is highly responsive to chemotherapy and radiotherapy initially, it almost invariably relapses within a year. Treatment is often challenging at relapse, especially in those with relapses within 6 months. For this subset of patients, oral topotecan is favored, with improved survival and quality of life. This finding was demonstrated in a phase III trial where oral topotecan was compared with best supportive care [4]. However, the overall response rate was very low (7% but 44% with stable disease) and median survival was 26 weeks [4]. Other systemic treatment options include irinotecan, paclitaxel, docetaxel, temozolomide, vinorelbine, oral etoposide, gemcitabine, bendamustine and nivolumab with or without ipilimumab [5]. However, response rates with these agents are not exciting and they do come with a toxicity profile that is prohibitive in patients with declining performance status owing to disease progression. There is therefore an unmet need for additional therapeutic options in patients with SCLC resistant to second-line regimens [6]. In recent years, there has been a significant amount of interest in the development of newer, more efficient drugs with fewer systemic side effects. Antibody–drug conjugates (ADCs) are one such class; they employ an antibody directed towards a specific cancer cell antigen, delivering the cytotoxic compound to neoplastic cells while relatively sparing healthier non-cancerous cells. Rovalpituzumab is a novel ADC with activity against SCLC.

2 Pathophysiology and Pharmacology

Rovalpituzumab tesirine is a novel ADC that targets delta-like 3 (DLL3), an inhibitory ligand of the Notch signaling pathway. The Notch signaling pathway in mammalian cells is fundamental for differentiation, proliferation and apoptotic cellular programs [7]. Notch activation has been implicated in the oncogenic pathogenesis of multiple malignancies such as T-cell lymphoma; chronic lymphocytic leukemia; breast cancer; osteogenic sarcoma; cervical; head and neck; endometrial; renal; lung; pancreatic, gastrointestinal and hepatocellular cancer; and medulloblastoma [8]. However, it appears that Notch can also behave as a tumor suppressor in neuroendocrine cells and some other cell lines [9]. DLL3 inhibits the Notch pathway, and in healthy cells, is localized to intracellular membranes. DLL3 is expressed on the surface of neoplastic neuroendocrine cells in contrast to healthy cells, including 80% of SCLC. Activation of the ligand results in rapid internalization and attachment to the NOTCH1 protein, signaling the deactivation of the pathway [10].

Rovalpituzumab exploits the DLL3 ligand by binding to and delivering a cytotoxic payload (tesirine) to cells expressing the receptor. It comprises a humanized monoclonal antibody against DLL3 linked to a pyrrolobenzodiazepine dimer toxin referred to as D6.5 (similar to an anthracycline) via a dipeptide linker. Upon internalization, the D6.5 moiety is released and causes DNA damage, which is inhibitory to the proliferation of tumor cells overexpressing the target receptor.

3 Pharmacokinetics and Metabolism

Rovalpituzumab has a drug-to-antibody ratio of 2. It shows roughly linear pharmacokinetics, with dose-proportional increases in exposure and a half-life of around 10–14 days. Steady-state concentrations were achieved in three to four cycles for 3-weekly administration and two to three cycles for 6-weekly administration [12]. The pharmacokinetics of total antibody (conjugated, partly deconjugated, and fully deconjugated ADC) and ADC were correlated (Pearson correlation coefficient 0.94), with full antibody exposures roughly 5–25% higher than those associated with ADCs across cohorts with no dose dependence. Circulating amounts of the DNA cross-linking agent SC-DR002 were not measurable (only seven of 427 samples from 26 patients had levels above the lower limit of detection of 40 pg/mL). No anti-therapeutic antibodies against rovalpituzumab tesirine were detected.

4 Pre-clinical and Clinical Experience

As previously stated, DLL3 expression occurs on the cellular surface in SCLC and large cell neuroendocrine tumors (LNECs) but not healthy tissue. Rovalpituzumab was shown in preclinical trials to be active in patient-derived xenograft tumors with DLL3 expression. Models were found to rapidly debulk, attributed to the expression of DLL3 and the cytotoxic activity of the internalized molecule. The response was sustained, possibly due to the active targeting of tumor

initiator cells. It should also be noted that rovalpituzumab was effective in tumor cells in vitro that were otherwise refractory to carboplatin plus etoposide, indicating that there may be a role for rovalpituzumab in patients with refractory disease [11].

This finding was the basis for conducting a first-in-human trial, enlisting 74 patients with recurrent SCLC to determine dosing for phase II clinical studies. Each patient had previously been treated with either one or two chemotherapeutic regimens, including a platinum-based agent. Nine patients were excluded, for multiple reasons, and 65 were available for analysis owing to multiple reasons. Twenty-nine individuals had a high rate of DLL3 expression, defined as > 50% of tumor burden with immunohistochemically confirmed surface expression. Median survival in patients treated with rovalpituzumab was 4.6 months and 2.7 months in patients without DLL3 expression, as compared to 5.8 months in patients with DLL3 expression. Of 29 assessable patients who were defined as DLL3-high, ten (35%) had a confirmed objective response, and 26 (90%) achieved disease control. Of ten assessable patients with low DLL3 expression, none had an objective response and six (60%) achieved disease control. One-year survival was reported at 18%, with patients expressing DLL3 doing better at 32%, while none of the DLL3- low patients survived at the 1-year mark.

In a separate analysis, groups were stratified according to chemotherapy-sensitive status. One-year overall survival was 21% in patients with resistant/refractory disease, 29% in the DLL3-high patients, and 0% in the DLL3-low patients. One-year overall survival was 17% in patients with chemotherapy-sensitive disease, 33% in DLL3-high patients, and 23% in DLL3-low patients [12].

Based on the findings of this trial, it appears that rovalpituzumab may be useful in producing and sustaining response in SCLC that has failed to respond to traditional chemotherapeutic regimens. However, the effects are modest at best in tumor response and lesser still in disease-free survival [13]. It is also important to note that although tumor shrinkage was favorable in the subjects involved in the study, the trial itself was not designed to prove efficacy.

The results obtained through preclinical trials and those reported by Rudin et al. [12] sparked significant interest to justify multiple clinical trials to study the effects of rovalpituzumab. One such trial is the TRINITY trial, an open-label, single-arm, phase II study evaluating the efficacy, safety and pharmacokinetics of this agent as third-line therapy in SCLC patients.

The preliminary results of this trial add to the literature on rovalpituzumab tesirine. The results are somewhat encouraging regarding the efficacy of the agent in a population of patients for whom no other therapy currently exists. The principal participants of the study were patients who have failed at least two lines of chemotherapy and included some who had failed more than five. For these patients, no recommended therapeutic option exists, and this trial aimed to investigate the efficacy of this agent in producing clinical and radiographic response to therapy. In patients with high DLL3 expression, the investigator-assessed response was around 29% for a median duration of 4.1 months. However, independent reviewer-assessed response was much lower at only 16%. Care must be taken while interpreting these interim results, and more data are required before definitive appraisal can be made.

5 Safety Profile

In the dose-finding study [12] referred to earlier, rovalpituzumab was described to be well tolerated at doses sufficient to produce encouraging antitumor activity. However, several significant toxicities have been reported in the same, and careful consideration of these is required to guide objective appraisal. Grade 4 thrombocytopenia, defined as a life-threatening decrease in platelet count (less than 25000/mm^3) indicating the need for urgent reversal was a significant dose-limiting adverse reaction. Hepatotoxicity was also noted to be a significant dose-limiting reaction. Both occurred at dosages of 0.8 mg/kg every week [12]. A serious complication in the form of a capillary leak syndrome was also encountered, which led to the development of multiple serosal effusions, cardiac tampnade, pulmonary edema, hypoalbuminemia and hemoconcentration, and presented itself as a potentially life-threatening therapeutic challenge. The phase I trial also documents the development of severe acute renal dysfunction in about 1% of the patients and resultant death of one participant

In addition, photosensitive eruptions and other skin reactions were also noted. Less severe but frequently noted adverse effects encountered included anemia, arthralgias, dyspnea, erythema, fatigue, maculopapular rashes, nausea, pancytopenia, pleural effusions, and peripheral edema, among others.

This trend was also observed in the preliminary results of the phase II TRINITY trial, where a large proportion of participants experienced at least one adverse event.

The most commonly reported events were fatigue and photosensitivity, occurring in more than 30% of patients; pleural effusions and peripheral edema occurred in about one-fourth of the patient population. Severe events in the form of grade 3/4 events were not as frequent; however, they did occur in a concerning number of patients, with thrombocytopenia in 15%, photosensitivity in 7% and pleural effusions in 7%. Data regarding dose limitation and mortality remain to be published; however, the significant side effect profile at this early stage remains a concern for many clinicians.

6 Dosage and Administration

The maximum tolerated dosage of rovalpituzumab tesirine was 0.4 mg/kg every 3 weeks, and the recommended phase 2 dose and schedule were 0.3 mg/kg every 2 weeks [12]. In the expansion cohorts of the study, 60 assessable patients were treated at active dose levels (0.2–0.4 mg/kg every 3 or 6 weeks) producing significant antitumor effects. Dosage information from the phase II study is awaited.

7 Summary and Future Directions

Multiple experimental drugs are currently being investigated in the management of SCLC [14]. Rovalpituzumab appears to be a new tool. Presently, it is being studied as a first-line treatment for extensive-stage SCLC with DLL3 expression [14]. It is also being studied as a subsequent treatment for disease that has failed to respond to platinum-based chemotherapy, where its efficacy will be compared to topotecan, an established subsequent chemotherapeutic agent, in the TAHOE trial [15].

While this agent's performance as a third-line treatment in SCLC with DLL3 expression [16] remains lackluster, it is premature to predict how this ADC will affect clinical practice. However, it appears that we may be on the threshold to efficiently develop effective treatment options for a very grim malignancy.

Compliance with Ethical Standards

Conflict of interest Bilal H. Lashari has no conflict of interest. Yazhini Vallatharasu has no conflict of interest. Lakshmi Kolandra has no conflict of interest. Mohsin Hamid has no conflict of interest. Dipesh Uprety has no conflict of interest.

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