

**CRITICAL REVIEW OF ATEZOLIZUMAB IN PATIENTS WITH
ADVANCED NON-SMALL CELL LUNG CANCER****Nandipalli Vineetha*, Addanki Anusha**

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ABSTRACT

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related mortality worldwide and is frequently diagnosed at an advanced stage with a poor prognosis. Immunotherapy targeting the programmed death ligand-1 (PD-L1) pathway has emerged as a significant advancement in NSCLC treatment. Atezolizumab, a monoclonal antibody against PD-L1, has demonstrated promising clinical outcomes in patients with previously treated NSCLC. This critical review evaluates the TAIL study, which assessed the safety and effectiveness of atezolizumab in clinically diverse NSCLC patients, including those with poor prognostic factors and comorbidities who were commonly excluded from earlier clinical trials. The TAIL study was a prospective, phase III/IV, single-arm, multicentre trial involving patients with advanced or metastatic NSCLC who had previously received platinum-

based chemotherapy. Participants received intravenous atezolizumab every three weeks until disease progression or unacceptable toxicity. The study findings indicated that atezolizumab was safe and well-tolerated, with manageable rates of serious and immune-related adverse events. Efficacy outcomes showed improvements in overall survival and progression-free survival, particularly among patients with PD-L1 expression. The study also highlighted that patients with baseline comorbidities and poor prognostic factors experienced safety outcomes similar to those in populations included in earlier pivotal trials. Although the study lacked a comparator group and had limitations related to its open-label design, the findings support the role of atezolizumab as an effective immunotherapeutic option for advanced NSCLC. Further

controlled studies are required to confirm long-term comparative benefits in broader patient populations.

KEYWORDS: Non-small cell lung cancer, NSCLC, Atezolizumab, PD-L1, Immunotherapy, Lung cancer, Monoclonal antibody, TAIL study, Advanced cancer, Immune checkpoint inhibitor.

BACKGROUND

Lung cancer is Primarily of two categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Non-small cell pathology accounts for about four out of five cases of lung cancer. Based on cell type, NSCLC is further divided into 3 subtypes: glandular (adeno), squamous cell, and large cell (Tan, 2022). Although the three subtypes have distinct clinical features, the treatment approaches remain the same. According to Global Cancer Statistics 2020, lung cancer is the leading cause of death due to cancer worldwide (Sung et al., 2021). The prognosis of lung cancer is poor. Most cases are identified and confirmed at a progressive and inoperable stage. More than 50% of lung cancer patients die within one year after diagnosis (Zappa & Mousa, 2016). Cigarette smoking is the most common causative agent for lung cancer. Since 1990, the incidence of lung cancer has been increasing, after cigarettes became the top manufactured tobacco product (Hecht, 1999). Treatment of NSCLC depends on the stage. Treatment for stage I, II, or III NSCLC include an intent to cure approach with surgical resection, chemotherapy and radiation. Treatment for advanced disease (stage IV or metastatic NSCLC) mainly involves integrating targeted therapy with inhibitors of specific mutations into the treatment plan (Duma et al., 2019). Immunotherapy with atezolizumab is indicated for patients with NSCLC whose tumours have high expression of programmed cell death ligand 1 (PD-L1) ($\geq 50\%$ of tumour cells). The FDA waved the green light for atezolizumab in October 2016, under the trade name TECENTRIQ, as a single-agent treatment or in addition to platinum-based cancer treatment in patients with NSCLC who experienced progression of lung carcinoma after being treated with platinum-based anti-cancer drugs (Rittmeyer et al., 2017; Centre for Drug Evaluation and Research, 2016). In October 2021, the FDA again approved atezolizumab as supportive therapy for stage II and IIIA NSCLC as intravenous injections at a dose of 840 mg once in 14 days, 1200 mg once in 21 days, or 1680 mg once in 28 days for up to 1 year (Centre for Drug Evaluation and Research, 2021).

INTRODUCTION

NSCLC comprises about 85%-90% of all lung cancers. PD-L1 expression is prevalent in about 25%-60% of NSCLC patients (Yu et al., 2016). PD-L1 is an immune checkpoint protein expressed by cancer cells to evade anti-tumour responses. PD-L1, upon interaction with PD-1, inhibits the innate cytotoxic T-cell response by inhibiting T-cell propagation and survival, along with inducing apoptosis in tumour-specific T-cells (Ohaegbulam et al., 2015; Han et al., 2020; Wang et al., 2020). Immune therapy with antibodies that inhibit PD-L1 binding to PD-1 has been associated with improved survival in patients with lung cancer (Brahmer et al., 2012). Atezolizumab is an IgG1 monoclonal antibody that can stop PD-L1 from binding to PD-1. Unlike anti-PD-1 antibodies, atezolizumab directly targets PD-L1, maximising anti-tumour responses and minimising autoimmunity. Additionally, atezolizumab stimulates the silenced immune cells to destroy tumour cells (Chen et al., 2012).

Anti-PD1/PD-L1 therapy has been regarded as the gold standard for first- or second-line therapy in stage III-IV NSCLC (invasion into adjacent tissue and distant spread to other organs) over the last ten years (Dantoing et al., 2021). Multiple clinical trials demonstrated greater efficacy with atezolizumab compared with chemotherapy (Herbst et al., 2020; Rittmeyer, 2017). An open-label randomised controlled trial was conducted to compare atezolizumab with docetaxel in patients previously diagnosed with and treated for NSCLC (OAK phase 3 study). This study suggested that atezolizumab was associated with significantly longer overall survival than docetaxel (13.8 vs 9.6 months) in the intention-to-treat population. Similar results were found in patients whose cancer cells expressed PD-L1 on $\geq 1\%$ of cells, defined as the TC1/2/3 or IC1/2/3 subgroups, with an overall survival of 15.7 months in the atezolizumab group and 10.3 months in the docetaxel group. Interestingly, patients whose cells exhibited low PD-L1 levels also benefited more from atezolizumab than from docetaxel (overall survival: 12.6 months vs 8.9 months, respectively). Maximum benefit with atezolizumab was observed in patients whose cancer cells showed high PD-L1 expression, with an overall survival of 20.5 months compared with 8.9 months in the docetaxel group (Rittmeyer, 2017). Clinical trials involving atezolizumab (Rittmeyer, 2017; Herbst, 2020) and other immunotherapies, including Nivolumab (Brahmer et al., 2015; Borghaei et al., 2015), Pembrolizumab (Leighl et al., 2019), excluded patients with uncontrolled concomitant diseases, significant cardiovascular disease within three months before randomisation, severe infections within 4 weeks prior to randomisation, and patients who had taken oral or intravenous antibiotics within 2 weeks before randomisation were

excluded. These conditions are common in patients with NSCLC and comprise about 25%-40% of cases. The current clinical trial under review, TAIL (NCT03285763) (Ardizzoni et al., 2021), evaluated the effectiveness and safety of atezolizumab in patients with NSCLC who had poor prognostic factors, as mentioned above, and who were excluded from earlier clinical trials.

Research question

Is atezolizumab safe and effective in a population of patients diagnosed and previously treated for NSCLC with varied symptomology and other comorbidities, as well as patients who were fulfilling the exclusion criteria for previous pivotal clinical studies? Population with varied symptomatology refers to patients with NSCLC who have risk factors generally associated with poor prognosis and were generally excluded from previous studies, including the OAK phase 3 trial.

The safety of atezolizumab was evaluated using the incidence of serious adverse events (SAEs) and immune-related adverse events (irAEs), which are declared to be associated with the treatment. Efficacy was evaluated using overall survival (OS), progression-free survival (PFS), and objective response rate (ORR), as determined by the primary researcher.

Clinical trial

The TAIL study was a prospective phase III/IV study conducted across 112 sites in 24 countries, including Italy, Spain, China, Mexico, Greece, Switzerland, the USA and the UK. Patient enrolment for the study took place between October and December 2018. A total of 619 patients were enrolled in the study after screening 765 patients for inclusion and exclusion criteria (see Figure 1). The inclusion criteria for the TAIL study were: patients aged 18 years or older with NSCLC at the adjacent invasion or distant spread stage, and patients who had previously received platinum-based anticancer treatment. Exclusion criteria were “symptomatic CNS metastases, spinal cord compression, prior treatment with a checkpoint inhibitor other than anti-PD-1 therapy”. As mentioned earlier, the TAIL study included a clinically diverse population that would have been excluded in the OAK criteria, which were as follows: patients with leptomeningeal disease, malignancies other than NSCLC, uncontrolled pleural effusion, pericardial effusion and ascites. In the OAK study, patients with autoimmune diseases or those previously treated with docetaxel, anti-PD-L1, or anti-PD-1 were also excluded.

TAIL was a single-arm study; therefore, all enrolled patients received the same treatment. Of the 619 patients, 4 died before receiving treatment. In contrast, the remaining 615 received 1200 mg IV atezolizumab every 21 days until evidence of tumour progression as per Response Evaluation Criteria in Solid Tumours V.1.1 (RECIST 1.1), severe toxicity, or withdrawal from the study.

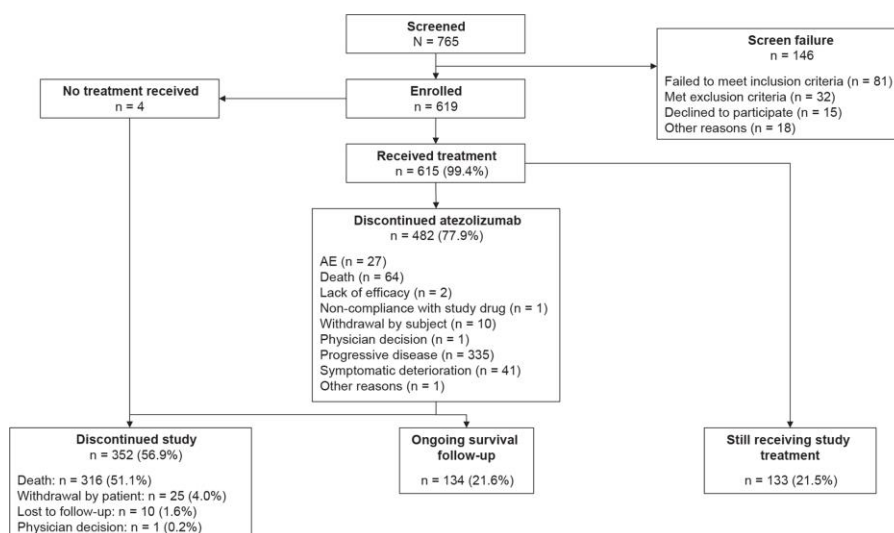


Figure 1: Patient Disposition.

Safety outcomes

Discontinuation of atezolizumab treatment was seen in 77.9% of the participants (n=482). The reason for discontinuation was either disease progression (54.1%; n=335) or death (10.3%; n=64). About 7.8% of the total participants experienced treatment-related SAEs, and 8.3% experienced treatment-related irAEs. A subgroup analysis was conducted for patients who satisfied the inclusion and exclusion criteria of the OAK study, described in TAIL as the OAK-like population (n=406). The occurrence of treatment-related SAEs was similar in both overall study participants and OAK-like study participants (7.8% vs 7.1%) (see Figure 2). The most frequent SAEs include pneumonitis (1.6%), infusion-related reaction (0.8%), pyrexia (0.7%), colitis (0.5%), pericarditis (0.5%), asthenia (0.3%) and diarrhoea (0.3%). The occurrence of treatment-related irAEs was also similar among overall study participants and OAK-like study participants (8.3% vs 8.6%) (see Figure 2). The most frequent treatment-related irAEs include pneumonitis (2.9%), hypothyroidism (1.1%), rash (1.1%), colitis (0.7%), and hyperthyroidism (0.7%).

Findings from safety outcomes suggest that having NSCLC with poor prognostic risk factors does not affect the safety profile of atezolizumab. According to the OAK selection criteria,

about one-third (n=209) of patients would not have been included in the present TAIL study. Despite including these patients, no change in the safety of atezolizumab was observed; no new treatment-related SAEs or irAEs were identified among the clinically diverse NSCLC patients.

Efficacy outcomes

The efficacy of atezolizumab was evaluated based on OS, PFS and objective response rate. The average OS rate was 11.1 months, the PFS rate was 2.7 months, and the objective response rate was 11.1% in the overall population. The overall survival rate was higher in the OAK-like population, i.e., 13.7 months. The median PFS and the ORR in the OAK-like population were not reported.

The efficacy findings from the TAIL study suggest that overall survival with atezolizumab is lower in patients with NSCLC who have baseline comorbidities than in those without any (TAIL population vs OAK-like population).

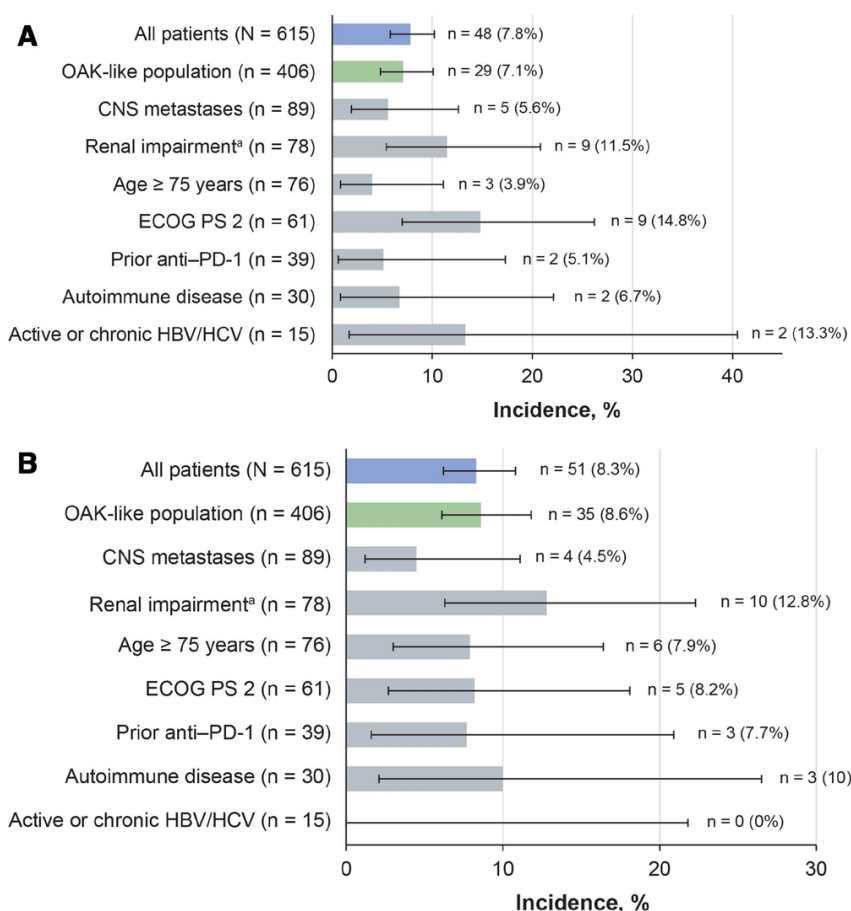


Figure 2: Incidence of SAEs and irAEs associated with treatment in the overall population and subgroups.

Arguments

The authors of the TAIL study state that the clinically diverse population included in the study closely resembles a real-world patient population with NSCLC at a stage of local invasion or distant spread who have previously received platinum-based anticancer therapy. Because this study included patients with conditions/stages of disease that could result in a bad prognosis, those normally excluded in pivotal trials, about 30% additional patients met the inclusion criteria. The effectiveness and adverse event profiles were similar in the overall and OAK-like population. No real-world studies were found reporting the efficacy and safety of atezolizumab in patients with NSCLC. However, when other immune checkpoint inhibitors were compared, the findings from the TAIL study were consistent with the real-world setting. Crino et al. reported in 2019 the effectiveness and tolerability of nivolumab in an Italian cohort of patients diagnosed with NSCLC. The median OS was 7.9 months, and ORR was 18%. About 76% (281 of 371 patients) discontinued the treatment, of which 59% of patients discontinued due to disease progression and 24% were due to death (Crinò et al., 2019).

Strengths

The main strength of the TAIL study is its broad inclusion criteria, which enabled the description of efficacy and safety outcomes in a real-world-like setting. This study demonstrated that additional comorbidities that contribute to a poor prognosis do not affect the overall efficacy and safety of atezolizumab. Subgroup analysis in the OAK-like population is an additional strength, enabling a direct comparison between the population with poor prognostic risk factors and that without them.

Limitations

The main limitation of the TAIL study was its single-arm design. Therefore, there was no direct comparator for the effectiveness and tolerability of atezolizumab versus control in patients with NSCLC. The study's sample size was relatively small, limiting the ability to draw meaningful conclusions in a real-world setting. Moreover, because the study design was an open-label phase III/IV trial, the results, including the incidence of AEs, SAEs, and irAEs, may be uncontrolled and prone to overly optimistic bias (Kahan et al., 2014).

CONCLUSION

The findings from the TAIL study suggest that atezolizumab is safe and effective in patients with non-small cell lung cancer at a stage of local invasion or metastasis who have received

treatment with platinum-based anti-cancer therapy before. The efficacy and safety outcomes with atezolizumab are similar in patients with NSCLC having other comorbidities that lead to poor prognosis at baseline as compared to patients without poor prognostic risk factors. The findings from the TAIL study are similar to those of real-world studies that evaluated other immune checkpoint inhibitors. Atezolizumab is effective across all subgroups diagnosed with NSCLC.

However, comparison of atezolizumab with a placebo or no-drug group was not possible due to the lack of a comparator group. Future studies may focus on reporting comparative outcomes with atezolizumab versus a control group in patients with NSCLC.

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