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Final results from TAIL: updated long-term efficacy of atezolizumab in a diverse population of patients with previously treated advanced non-small cell lung cancer

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ABSTRACT

In patients with previously treated advanced or metastatic non-small cell lung cancer (NSCLC), atezolizumab therapy improves survival with manageable safety. The open-label, single-arm phase III/IV TAIL study (NCT03285763) evaluated atezolizumab monotherapy in patients with previously treated NSCLC, including those with Eastern Cooperative Oncology Group performance status of 2, severe renal impairment, prior anti-programmed death 1 therapy, autoimmune disease, and age ≥75 years. Patients received atezolizumab intravenously (1200 mg) every 3 weeks. At data cut-off for final analysis, the median follow-up was 36.1 (range 0.0–42.3) months. Treatment-related (TR) serious adverse events (SAEs) and TR immune-related adverse events (irAEs) were the coprimary endpoints. Secondary endpoints included overall survival (OS), progression-free survival (PFS), overall response rate, and duration of response. Safety and efficacy in key patient subgroups were also assessed. TR SAEs and TR irAEs occurred in 8.0% and 9.4% of patients, respectively. No new safety signals were documented. In the overall population, median OS and PFS (95% CI) were 11.2 months (8.9 to 12.7) and 2.7 months (2.3 to 2.8), respectively. TAIL showed that atezolizumab has a similar risk-benefit profile in clinically diverse patients with previously treated NSCLC, which may guide treatment decisions for patients generally excluded from pivotal clinical trials.

BACKGROUND

Immune checkpoint inhibitor (CPI) therapies, including anti-programmed death-ligand 1 (PD-L1)/programmed death 1 (PD-1) monotherapies, are among the second-line treatment choices for patients with non-small cell lung cancer (NSCLC) after progression on chemotherapy.[1 2] Atezolizumab is an anti–PD-L1 monoclonal antibody that inhibits PD-L1-PD-1 and PD-L1-B7-1 signaling. As a result of the pivotal Phase III OAK trial, atezolizumab monotherapy is approved for patients with previously treated NSCLC.[3] In the OAK trial, the median overall survival (OS) was 13.8 months in the atezolizumab arm compared with 9.6 months in the docetaxel arm.[3]

Patients with complex comorbidity, low-performance status (PS) autoimmune disease (AID) or active/chronic viral diseases are often excluded from pivotal clinical trials.[3–5] Since they account for 25% to 40% of patients with NSCLC, more information on these populations is required to help guide immunotherapy treatment options.[1 6–8] The phase III/IV TAIL trial included patients with prior anti-PD-1 therapy, asymptomatic central nervous system (CNS) metastases, autoimmune disease (AID), Eastern Cooperative Oncology Group (ECOG) PS of 2, renal impairment, positive for HIV+, and active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.[1]

The final results from TAIL (data cut-off: June 26, 2021) include 24 months of additional follow-up from the previously reported primary analysis of TAIL (data cut-off: June 4, 2019).[1] The final safety and efficacy data from the overall population and selected subgroups are reported.

METHODS

TAIL (NCT03285763) is a phase III/IV, open-label, single-arm, multicenter trial in patients with stage III/IV NSCLC with disease progression following standard chemotherapy.[1] Patients received atezolizumab (1200 mg) intravenously on day 1 of each

21-day cycle until radiographic disease progression per Response Evaluation Criteria in Solid Tumors 1.1. Eligibility criteria included any PD-L1 status, prior anti-PD-1 therapy, ECOG PS 2, severe renal impairment, treated or untreated asymptomatic CNS metastases, AID, HIV+, or active/chronic HBV/HCV. Exclusion criteria included CPI therapies other than anti-PD-1, prior CD137 agonist treatments, renal disorders requiring dialysis or transplant, symptomatic CNS metastases, spinal cord compression, or significant cardiovascular disease. The primary endpoint was safety, measured by incidence of treatment-related (TR) serious adverse events (SAEs) and TR immune-related adverse events (irAEs) (AEs of special interest requiring corticosteroid treatment ≤30 days of onset). AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0. The key secondary endpoint was OS; other secondary endpoints included progression-free survival (PFS), overall response rate, and duration of response. Safety and efficacy were evaluated in enrolled patients who received ≥1 atezolizumab dose, including in key patient subgroups. Final analysis was approximately 30 months after the last patient was enrolled. Incidence and 95% Clopper-Pearson CI were used to summarize TR SAEs and TR irAEs. Time-to-event data for median OS, PFS, duration of response, and 3-year OS were calculated using the Kaplan-Meier method. The 95% CI for survival was calculated using Greenwood's formula (SAS V.9.4).

RESULTS

Initially, 619 patients were enrolled between October 25, 2017 and December 26, 2018. Four patients died before starting treatment, leaving 615 patients who received atezolizumab monotherapy, described as the overall population. At final data cut-off, the median survival follow-up was 36.1 (range 0.0–42.3) months. The OAK-like subgroup included approximately 69% of the overall population (n=424). At baseline, 31% of the overall population would have been ineligible for the OAK trial,[3] including 90 patients with asymptomatic CNS metastases (14.6%), 79 with renal impairment (12.8%, estimated glomerular filtration rate <60 mL/min/1.73 m^2), 61 with ECOG PS of 2 (9.9%), 40 who received prior anti-PD-1 therapy (6.5%), 30 with AID (4.9%), and 14 with active/chronic HBV/HCV (2.3%).

At cut-off, the median duration of atezolizumab treatment in the safety population was 3.15 (range 0–42.3) months, with a median of 5.0 (range 1–60) cycles. In the overall population, 77% of patients died, compared with 72% in the OAK-like subgroup. TR SAEs occurred in 8.0% (95% CI 6% to 10%), TR AEs and TR death occurred in 55% and 1.3% of the overall population, respectively. In the OAK-like subgroup, TR SAEs, TR AEs, and TR death occurred in 8.0% (95% CI 5.6% to 11%), 57%, and 1.2% of patients, respectively (online supplemental table 1). Grade 3/4 AEs occurred in 34% of overall and 33% of OAK-like patients. The second coprimary endpoint of TR irAEs occurred in 9.4% (95% CI 7% to 12%) of overall and 9.7% (95% CI 7% to 12.9%) of OAK-like patients. TR AEs of special interest occurred in 30% of overall and 33% of OAK-like patients (online supplemental table 1).

The overall population 3-year OS rate was 19.6% (95% CI 16.4% to 23.1%), the median OS was 11.2 (95% CI 8.9 to 12.7) months (figure 1A), and the median PFS was 2.7 (95% CI 2.3 to 2.8) months (online supplemental table 2). In the OAK-like subgroup, the 3-year OS rate was 25.4% (95% CI 21.1% to 29.9%), the median OS was 14.4 (95% CI 12.2 to 15.6) months (figure 1B), and the median PFS was 2.9 (95% CI 2.8 to 4.1 months) (online supplemental table 2). Median OS of patients with squamous and non-squamous histology was 12.5 (95% CI 8.9 to 14.1) months and 10.4 (95% CI 8.4 to 12.6) months, respectively (figure 1C).

Patients with renal impairment (11.9 months; 95% CI 8.5 to 15.3), age ≥75 years (11.8 months; 95% CI 7.9 to 14.7), and active/chronic HBV/HCV (14.7 months; 95% CI 3.4 to 26.4) had a median OS similar to the overall and OAK-like populations (figure 1D–F). Patients with ECOG PS 2 (3.5 months; 95% CI 1.9 to 5), asymptomatic CNS metastases (5.1 months; 95% CI 3.9 to 8.1), prior anti-PD-1 treatment (5.8 months; 95% CI 3.3 to 11.5), and AID (10.1 months; 95% CI 6.5 to 14.1) had a median OS shorter than the overall and OAK-like populations (figure 1G–J). In the biomarker-evaluable population, patients with PD-L1 expression on ≥1% of tumor cells had median OS of 15.5 (95% CI 14.2 to 21.7) months, compared with 11.7 (95% CI 7.9 to 13.7) months in the PD-L1-negative population (<1% tumor cell expression) (figure 1K).

DISCUSSION AND CONCLUSION

The phase III/IV TAIL trial results are generally consistent with published data related to CPI use in special interest populations.[1 4–6 8 9] Results from the primary TAIL analysis were evaluated 5 months after the last patient was enrolled,[1] while the final analysis occurred approximately 30 months after final enrolment. Based on the updated results, the primary and secondary endpoints confirmed the safety and efficacy profile of atezolizumab monotherapy from OAK and the primary TAIL analysis.[1 3]

Just under one-third of patients enrolled in the TAIL study would have been excluded from OAK, primarily due to ≥1 factors (eg, prior anti-PD-1 therapy, ECOG PS 2, severe renal impairment, asymptomatic CNS metastases, AID, HIV+, or active/chronic HBV/HCV). Even with these groups, the percentage of AEs that were grade 3/4 and SAEs in the overall population (34%) was comparable with that in the OAK-like subgroup (33%).

Even though TAIL is a single-arm study, the final efficacy results of the OAK-like subgroup and the OAK trial are similar.[9] The 3-year OS rate of the overall population was 19.6%, while the OAK-like subgroup 3-year OS rate was 25.4%. This is similar to what was observed in OAK, where the 3-year OS rate was 21%.[9] For patients ≥75 years

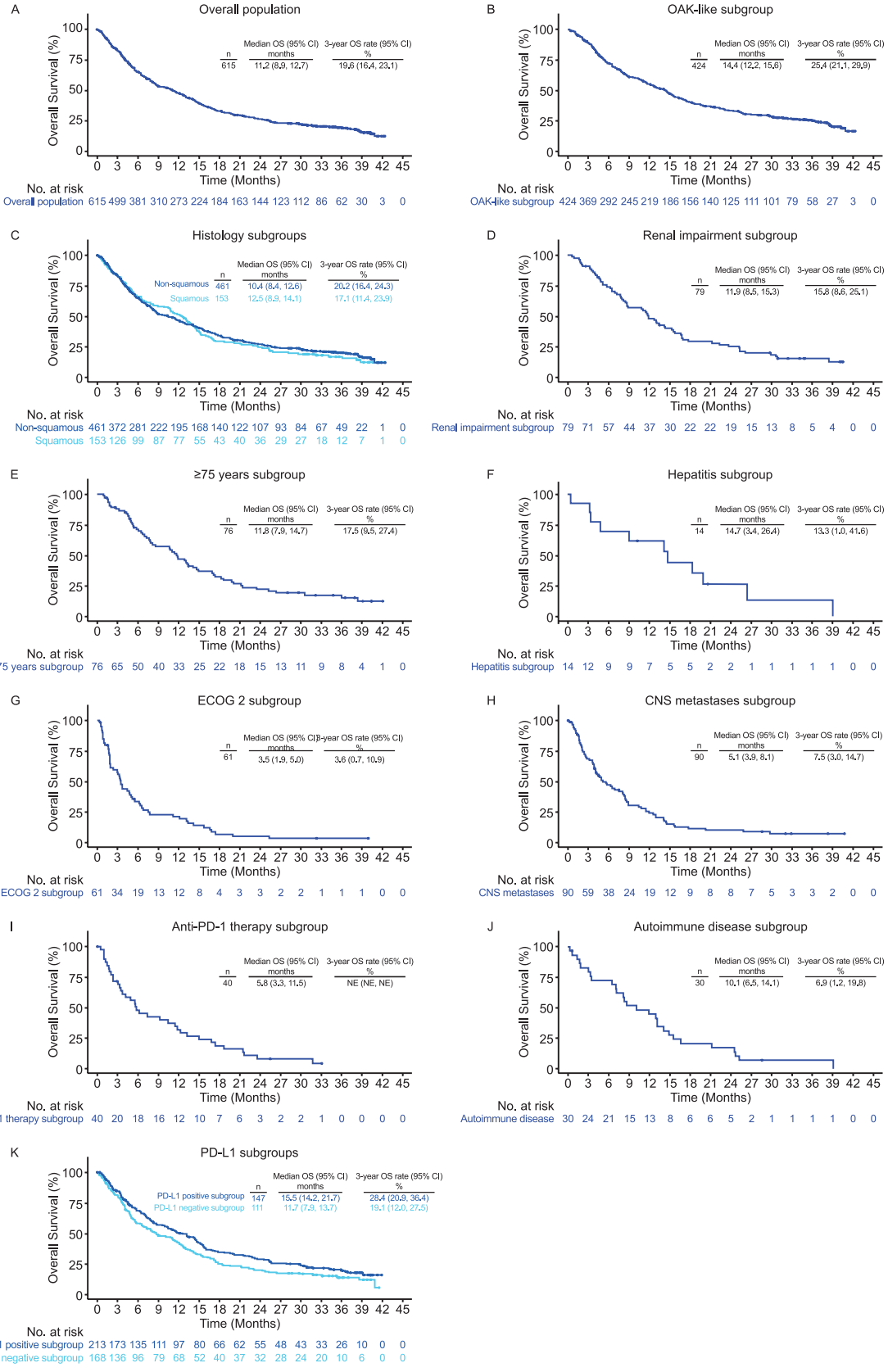

Figure 1 Kaplan-Meier analysis of overall survival (OS) in (A) the overall population; (B) the OAK-like subgroup; and (C) patients with squamous and non-squamous histology, (D) with renal impairment (eGFR of <60 mL/min/1.73 m^2), (E) aged <75 and ≥75 years, (F) with active or chronic hepatitis B virus or hepatitis C virus, (G) with Eastern Cooperative Oncology Group performance status (ECOG PS) of 2, (H) with asymptomatic central nervous system (CNS) metastases, (I) with prior anti-PD-1 therapy and (J) with autoimmune disease, (K) Kaplan-Meier analysis of OS in the biomarker evaluable population with ≥1% (positive) and <1% (negative) PD-L1 expression on tumor cells. eGFR, estimated glomerular filtration rate.

and those with renal impairment, the 3-year OS rate and median OS were similar to the overall population and OAK-like subgroup. Exceptions to the overall population 3-year OS rate or median OS were observed in the ECOG PS 2, prior PD-1 therapy, asymptomatic CNS metastases, and autoimmune subgroups. At 3.6%, patients with ECOG PS 2 had the lowest 3-year OS rate among key subgroups. This is similar to the phase II CheckMate 171 trial of nivolumab in patients with previously treated squamous NSCLC.[10] Although, TAIL and Checkmate 171 support the use of CPIs in the ECOG PS 2 population, neither trial explains why this population seems to be less responsive to anti-PD-L1/PD-1 treatments. It could be that this difficult-to-treat population is unable to present an effective immune response,[4] which could mean patients are unable to benefit from anti-PD-L1/PD-1 therapy. Compared with 6.5% of the overall population, over half of the patients in the prior anti-PD-1 treatment subgroup had received ≥3 lines of NSCLC therapy,[1] suggesting that they may have CPI-resistant disease, which led to a poorer prognosis.

Although TAIL provides data on the use of atezolizumab in a diverse population, the subgroups did not include enough patients to allow for significant conclusions about atezolizumab treatment in these populations. The similarity between the final safety and efficacy results of the TAIL OAK-like population and OAK indicates that atezolizumab therapy is beneficial across PD-L1 subgroups.[1 3 9] In conclusion, these updated data confirm a positive risk-benefit ratio for atezolizumab in the previously treated NSCLC setting, support the findings of OAK, and may prove useful for informing treatment decisions in patients generally excluded from pivotal NSCLC trials in second-line and later therapy.

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Competing interests AA reports personal honoraria for lectures from BMS, Astra Zeneca, and MSD; advisory board participation for Roche, Astra Zeneca, BMS, Sanofi, and Eli Lilly. BR-V reports honoraria for educational events for Janssen, MSD, and Bristol-Myers Squibb; advisory board participation for MSD and Takeda. DR-A reports personal and/or other fees from BMS, MSD, Roche/Genentech, Novartis, Astra Zeneca, and Boehringer-Ingelheim. JA-A reports advisory board participation for Astra Zeneca, Roche, MSD, BMS, Takeda, and Pfizer; speaker bureau for Roche, MSD, BMS, Takeda, and Pfizer. HJMS reports payment for expert testimony from BMS for immune-oncology educational website advice; advisory board participation for MSD. EH reports employment by Roche and stockholding in Roche. MK reports employment by Genentech and stockholding in Roche. JT reports former employment by Roche and stockholding in Roche. YH reports employment by Roche and stockholding in Roche. HKV reports employment by Roche and stockholding in Roche. TN-D reports personal consulting fees from Takeda, Pfizer, Roche, Amgen, Astra Zeneca, Bayer, BMS, Boehringer-Ingelheim, Chugai, Janssen, Lilly, Merck, MSD, Novartis, and Otsuka; personal honoraria for lectures/presentations from Takeda, Pfizer, Roche, Amgen, Astra Zeneca, Bayer, BMS, Boehringer-Ingelheim, Chugai, Janssen, Lilly, Merck, MSD, Novartis, and Otsuka; support for attending meetings and/or travel from Astra Zeneca, BMS, Boehringer-Ingelheim, MSD, Roche, and Takeda; chair of the independent monitoring committee for Roche and BluePrint Medicines. SA, JY, and KS report no competing interests.

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