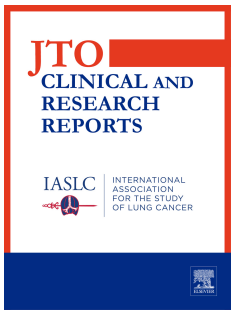

Effectiveness and safety of atezolizumab monotherapy in previously treated Japanese patients with unresectable advanced or recurrent non-small cell lung cancer: A multicenter, prospective, observational study (J-TAIL)

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PII: S2666-3643(23)00023-1

DOI: https://doi.org/10.1016/j.jtocrr.2023.100484

Reference: JTOCRR 100484

To appear in: *JTO Clinical and Research Reports*

Received Date: 3 October 2022

Revised Date: 19 January 2023

Accepted Date: 16 February 2023

Please cite this article as: Miura S, Nishio M, Akamatsu H, Goto Y, Hayashi H, Gemma A, Yoshino I, Misumi T, Hata A, Hataji O, Fujita K, Seike M, Yanagitani N, Nishino K, Hara S, Saito R, Mori M, Tsuda T, Iwasawa S, Nakagawa S, Mitsudomi T, Effectiveness and safety of atezolizumab monotherapy in previously treated Japanese patients with unresectable advanced or recurrent non-small cell lung cancer: A multicenter, prospective, observational study (J-TAIL), *JTO Clinical and Research Reports* (2023), doi: https://doi.org/10.1016/j.jtocrr.2023.100484.

Effectiveness and safety of atezolizumab monotherapy in previously treated Japanese patients with unresectable advanced or recurrent non-small cell lung cancer: A multicenter, prospective, observational study (J-TAIL)

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Disclosure of Funding

This study was funded by Chugai Pharmaceutical Co., Ltd., Tokyo, Japan.

Conflict of Interest Statement

Satoru Miura reports honoraria from Chugai Pharma, Taiho Pharma, Eli Lilly, Boehringer-Ingelheim, Ono Pharma, AstraZeneca, MSD, and Bristol-Myers Squibb. **Makoto Nishio** reports payment/honoraria from Ono Pharmaceutical, Bristol-Myers Squibb, Pfizer, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, Boehringer-Ingelheim, MSD, Novartis, Sankyo Healthcare, Taiho Pharmaceutical, Merck Serono, and Astellas. **Hiroaki**

Akamatsu reports research funding from Amgen, Chugai Pharmaceutical Co. Ltd., and MSD K.K.; honoraria from AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Nippon Kayaku Co. Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., Pfizer Inc., and Taiho Pharmaceutical Co. Ltd.; and an advisory board membership for Amgen Inc., and Janssen Pharmaceutical K.K. **Yasushi Goto** reports grants or contracts to the clinical trial group from AstraZeneca K.K, and Pfizer; grants or contracts to own institution from Abbvie, Eli Lilly, Pfizer, Bristol Myers Squibb, Ono, Novartis, Kyorin, Daiichi Sankyo, Novartis, and Prefered Network; payment/honoraria from Eli Lilly, Chugai, Taiho, Boehringer Ingelheim, Ono, Bristol Myers Squibb, Pfizer, MSD, Novartis, Merck, and Thermo Fisher; participation on a data safety monitoring board or advisory board for AstraZeneca, Chugai, Boehringer Ingelheim, Eli Lilly, Taiho, Pfizer, Novartis, Guardant Health Inc., Illumina, Daiichi Sankyo, Ono Pharmaceutical, Bristol Myers Squibb, and MSD; and a leadership or fiduciary role in other board, society, committee or advocacy group for Cancer Net Japan, and JAMT. **Hidetoshi Hayashi** reports grants or contracts from AstraZeneca K.K., Astellas Pharma Inc., MSD K.K., Ono Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Pfizer Japan Inc., Bristol Myers Squibb Company, Eli Lilly Japan K.K., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Merck Serono Co., Ltd./ Merck Biopharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., SymBio Pharmaceuticals Limited, AbbVie Inc., inVentiv Health Japan, ICON Japan K.K., GRITSONE ONCOLOGY Inc., PAREXEL International Corp., Kissei Pharmaceutical Co., Ltd., EPS Corporation, Syneos Health, Pfizer R&D Japan G.K., A2 Healthcare Corp., Quintiles Inc./IQVIA Services Japan K.K., EP-CRSU Co., Ltd., Linical Co., Ltd., Eisai Co., Ltd., CMIC Shift Zero K.K., Kyowa Hakko Kirin Co., Ltd., Bayer Yakuhin Ltd., EPS International Co., Ltd., and Otsuka Pharmaceutical Co., Ltd.; and payment/honoraria from Amgen K.K, AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Bristol-Myers Squibb Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Guardant Healthcare, Kyorin

Pharmaceutical Co., Ltd., Merck Biopharma Co., Ltd., MSD K.K., Novartis Pharmaceuticals K.K., Ono Pharmaceutical Co., Ltd., Shanghai Haihe Biopharm, Taiho Pharmaceutical Co., Ltd., Pfizer, and Takeda Pharmaceutical Co., Ltd. **Akihiko Gemma** reports lecture fees from Chugai Pharmaceutical Co., Ltd. **Ichiro Yoshino** reports lecture fees/advisory fees from Chugai Pharmaceutical, Intuitive Surgical, AstraZeneca, Johnson and Johnson and Covidien Japan, grants/lecture fees from TAIHO Pharmaceutical and Dai-ichi Sankyo Chemical Pharma, and lecture fees from Japan Blood Products Organization, Astellas, Bristol-Meyers Squibb, Shionogi Pharmaceutical, Eli Lilly, CSL Behring, MSD, Ono pharmaceutical and Care Net, advisory fee from Medicaroid, and grants from Pfizer. **Toshihiro Misumi** reports grants or contracts to own institution from Chugai Pharmaceutical Co., Ltd. **Akito Hata** reports grants or contracts from MSD, Eli Lilly, Boehringer Ingelheim, and AstraZeneca; and payment/honoraria from Eli Lilly, Chugai, Pfizer, AstraZeneca, and Boehringer Ingelheim. **Osamu Hataji** reports grants or contracts from AstraZeneca, Novartis Pharma, MSD, Daiichi Sankyo Company Limited, Bayer Yakuhin, AbbVie, Eli Lilly, Janssen Pharmaceutical K.K, and Ono Pharmaceutical; and payment/honoraria from AstraZeneca, Chugai Pharmaceutical, Takeda Pharmaceutical, MSD, Merck KGaA, Daiichi Sankyo Company Limited, Eli Lilly, AbbVie, Boehringer Ingelheim, Nippon Kayaku, and Taiho Pharmaceutical. **Masahiro Seike** reports research funding from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical, MSD K.K., Nippon Boehringer Ingelheim, and Eli Lilly; and honoraria for lectures from Chugai Pharmaceutical Co., Ltd., AstraZeneca, MSD K.K., Taiho Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Kyowa Hakko Kirin, Daiichi-Sankyo Company, Novartis, and Nippon Kayaku. **Noriko Yanagitani** reports payment/honoraria from Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Bristol Myers Squibb, Pfizer Inc., Eli Lilly and Company, AstraZeneca plc, Takeda Pharmaceutical Company Limited, and Bayer Yakuhin Ltd.; and payment for expert testimony from Chugai Pharmaceutical Co., Ltd. **Kazumi Nishino** reports grants or contracts to own institution from, ONO PHARMACEUTICAL CO., LTD., TAIHO

PHARMACEUTICAL CO., LTD., MSD, AbbVie, DAIICHI SANKYO COMPANY LIMITED, Amgen, Eisai Co., Ltd., Eli Lilly Japan, Nippon Boehringer Ingelheim, Pfizer, Takeda Pharmaceutical Company Limited, Merck, Janssen Pharmaceutical K.K., and AstraZeneca; and honoraria for lectures from Eli Lilly Japan, Nippon Boehringer Ingelheim, Novartis, Pfizer, Takeda Pharmaceutical Company Limited, Merck, Janssen Pharmaceutical K.K., Bristol Myers Squibb, Nippon Kayaku, and AstraZeneca. **Masahide Mori** reports research funding from Chugai, Ono, MSD, and Delta-fly; and lecture fees from AstraZeneca, Boehringer Ingelheim, MSD, Eli Lilly, Novartis, Chugai, Taiho, Kyowa-Kirin, Ono Pharmaceutical, Otsuka, Nihon-kayaku, Pfizer, Daiichi Sankyo, Takeda, and Shionogi. **Takeshi Tsuda** reports honoraria from Chugai Pharmaceutical Co., Ltd. **Shunichiro Iwasawa** reports honoraria for lectures from Chugai Pharmaceutical Co., Ltd., Bristol-Myers Squibb Company, Ono Pharmaceutical Co., Ltd., and AstraZeneca K.K; and is an employee of Chugai Pharmaceutical Co., Ltd. **Shintaro Nakagawa** is an employee of Chugai Pharmaceutical Co., Ltd. **Tetsuya Mitsudomi** reports grants or contracts from Ono Pharmaceutical, Chugai Pharmaceutical, AstraZeneca, and MSD; consulting fees from Ono Pharmaceutical, BMS, MSD, Chugai, and AstraZeneca; and payment/honoraria from Ono Pharmaceutical, BMS, MSD, Chugai, and AstraZeneca. **Kohei Fujita**, **Satoshi Hara**, and **Ryota Saito** declare no potential conflicts of interest.

Running title: Atezolizumab in NSCLC patients

Word count, abstract: 250 (limit: 250)

Word count, text: 3986 (limit: 4000) (Introduction to conclusion)

Number of tables/figures: 3/3 (limit: 6)

Supplementary materials: 3 tables and 4 figures

Abstract

Introduction: The efficacy and safety of atezolizumab in previously treated patients with non-small cell lung cancer (NSCLC) have been established in the registrational phase III OAK trial. In this study, we evaluated the effectiveness and safety of atezolizumab monotherapy in a large real-world cohort to confirm the reproducibility of the results of the registrational trial.

Methods: This was a multicenter, prospective, single-arm observational study. Consecutive patients with previously treated NSCLC scheduled to receive atezolizumab monotherapy were enrolled. The primary endpoint was the 18-month overall survival (OS) rate. The incidence of adverse events (AEs) and immune-related AEs (irAEs) was evaluated.

Results: Overall, 1002 patients were included in the safety analysis set and 1000 in the full analysis set (FAS). Median follow-up was 11.5 months. Of the FAS, 62% were ineligible for the OAK trial (OAK-unlike subpopulation). The 18-month OS rate was 41.1%, with a median OS of 13.0 months (95% confidence interval [CI], 12.2–15.1). The 18-month OS rate was 49.4% and 36.1% in OAK-like and OAK-unlike subpopulations, respectively; that in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 was 14.3%. The incidence of AEs overall, in the OAK-like, and OAK-unlike subpopulations was 43.9%, 46.2%, and 42.5%; that of irAEs was 19.0%, 20.1%, and 18.3%, respectively.

Conclusions: The findings suggest atezolizumab may be effective and safe for previously treated patients with NSCLC in real-world settings; however, atezolizumab administration should be considered carefully regarding the benefit–risk balance for the OAK-unlike subpopulation, especially in patients with ECOG PS ≥2.

Keywords: non-small cell lung cancer, immune checkpoint inhibitors, atezolizumab, observational study

INTRODUCTION

Until the advent of immunotherapy, the 5-year survival rate of patients with advanced non-small cell lung cancer (NSCLC) treated with chemotherapy was less than 5%.[1] When cancer spreads from the lung to distant parts of the body, it is advanced and uncurable and is known as metastatic NSCLC. Effective treatments for metastatic NSCLC are limited, especially for patients without targetable oncogene driver mutations. Immune checkpoint inhibitors (ICIs) demonstrate clinically meaningful survival benefits, durable responses, and favorable safety profiles versus chemotherapy and are treatment options for patients with advanced NSCLC.[2-6] Therefore, the treatment landscape for patients with advanced NSCLC is gradually improving.

Atezolizumab is a recombinant humanized monoclonal antibody of the IgG1 subclass against human programmed death ligand-1 (PD-L1) that targets PD-L1 expressed in tumor or immune cells. The OAK trial was the first randomized, open-label, global phase 3 study to evaluate the efficacy and safety of PD-L1-targeted therapy with atezolizumab versus docetaxel (standard of care) in previously treated patients with NSCLC.[5] The results showed a statistically and clinically significant improvement in overall survival (OS) with atezolizumab versus docetaxel in this patient population, regardless of PD-L1 expression or histology, with a favorable safety profile compared with docetaxel.

Because of strict eligibility criteria, patients enrolled in clinical trials do not typically have the same characteristics as those encountered in real-world settings. The OAK trial, similar to other clinical trials, did not enroll patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 2–4, patients with untreated central nervous system (CNS) metastasis, those with autoimmune disease and those who had three or more previous treatment regimens.[5] Furthermore, detailed data regarding immune-related adverse events (irAEs) have not been reported. Therefore, we considered it important to determine whether the results of clinical trials can be reproduced in terms of effectiveness and frequency of toxicity, including problematic irAEs, among patients in a real-world setting.

A global phase III/IV study, TAIL (NCT03285763), confirmed the benefit–risk profile of atezolizumab monotherapy in a clinically diverse population of patients with previously treated NSCLC.[7] In this study, patients ineligible for registrational trials accounted for approximately 66%, confirming the landmark survival rate at 12 months.

Based on the above, this current study aimed to evaluate the reproducibility of the effectiveness and safety of atezolizumab monotherapy in a large sample of real-world Japanese patients with unresectable advanced or recurrent NSCLC, considering the eligibility criteria of the OAK trial.

MATERIALS AND METHODS

Study design and treatment

The present study was a multicenter, non-interventional, non-blinded, single-arm, prospective observational study. Consecutive patients scheduled to receive atezolizumab monotherapy were enrolled from August 15, 2018, through October 16, 2019, at 197 institutions in Japan.

Each patient received atezolizumab monotherapy according to the latest package insert.[8] Decisions on dose interruptions or withdrawals of atezolizumab were made at the physician's discretion in accordance with the atezolizumab package insert and the Guidelines for the Promotion of Optimal Use.[9]

The present study was conducted in accordance with the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects, and the International Council for Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent for study participation. This study was registered at UMIN-CTR under the identifier number UMIN000033133 and at ClinicalTrials.gov under the identifier number NCT03645330.

Patients

Details of eligibility and exclusion criteria are shown in **Supplementary Table 1**. Patients who were scheduled to receive atezolizumab monotherapy and met the following enrollment criteria were included: aged ≥20 years at the time of informed consent, diagnosed with unresectable advanced or recurrent NSCLC, and previously treated with systemic therapy. Patients were excluded if they were considered unsuitable for enrollment by the investigator.

Effectiveness endpoints

The primary endpoint was the OS rate at 18 months. Secondary endpoints were median OS; OS rate at 12 and 24 months; median progression-free survival (PFS); PFS rates at 6, 12, 18, and 24 months; time-to-treatment failure (TTF); TTF rates at 6, 12, 18, and 24 months; objective response rate (ORR); duration of response (DOR); and disease control rate (DCR). The investigators assessed progression and response according to Response Evaluation Criteria in Solid Tumors v1.1, without confirmatory measurement.[10]

Safety endpoints

The frequency of adverse events (AEs) and immune-related AEs (irAEs) were tabulated according to grade and severity assessed by the investigators based on National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.[11]

Subgroup analysis

The effectiveness and safety analyses were conducted in patient subgroups according to baseline characteristics, including CNS metastasis at the time of registration, age ≥75 years, ECOG PS ≥2, previous treatment with ICIs, history of autoimmune disease, and targetable driver oncogene status (*EGFR* mutation status, *ALK* rearrangement status, *ROS1* rearrangement status, and *BRAF* V600E mutation status).

Considering the differences between patients enrolled in clinical trials and those from real-world settings, the effectiveness endpoints were evaluated in OAK-like and OAK-unlike subpopulations. Patients who met the following criteria were classified as the OAK-unlike subpopulation: those with ECOG PS 2–4, previous treatment with ICIs, CNS metastases at baseline, creatine clearance <30 mL/min, liver impairment, history of autoimmune disease, with three or more previous treatment regimens, and had not received previous platinum combination therapy. Patients with missing data on these criteria were classified as the OAK-unlike population. Other than the OAK-unlike subpopulation, all patients were classified as the OAK-like subpopulation. In addition, a subgroup analysis by PD-L1 expression (tumor proportion score [TPS] <1%, 1–49%, ≥50%), using PD-L1 22C3 immunohistochemistry assay, was performed in OAK-like and OAK-unlike subpopulations.

Patient-reported outcomes (PROs)

PROs were evaluated using the Japanese version of the European Quality of Life Five Dimension Five Level (EQ-5D-5L) questionnaire.[12,13] This questionnaire measures five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Higher scores represent better quality of life. A worsening symptom was defined as a score reduction of 0.05 or 0.1 from baseline.

Statistical methods

There was no formal statistical hypothesis linked to the sample size calculation. The planned sample size was 1000 patients, which was considered sufficient to estimate a 95% confidence interval (CI) within a range of 20% for the 18-month OS rate of the subpopulation of clinical interest.

The safety analysis set was used to assess safety, and the full analysis set (FAS) was used as the primary analysis population to evaluate effectiveness. PROs were evaluated in the

PRO analysis population. The safety analysis set included patients who received at least one dose of the study drug after enrollment. The FAS included all enrolled patients, excluding ineligible patients and those with no post-dose effectiveness evaluation. The PRO analysis population included the FAS population who completed a baseline PRO survey and had at least one PRO survey assessment after baseline.

Descriptive statistics were used to summarize the baseline characteristics of patients, using median (interquartile range or range) for continuous variables and n (%) for categorical variables. The Kaplan–Meier method was used to estimate the OS rates at 12, 18, and 24 months and PFS and TTF rates at 6, 12, 18, and 24 months, and 95% CIs were calculated using the Greenwood formula. For secondary effectiveness endpoints (median OS, PFS, TTF, and DOR), a Kaplan–Meier curve was constructed to calculate the median time-to-event onset, and 95% CIs were calculated using the Brookmeyer–Crowley method. The hazard ratio (HR) was estimated with a stratified Cox regression analysis to compare the OAK-like and -unlike subpopulations. The proportion of patients with complete response (CR) or partial response (PR) was calculated for ORR. For DCR, the proportion of patients with CR, PR, or stable disease (SD) maintaining for more than 24 weeks was calculated; a normal approximation was used to calculate the 95% CIs. No imputation method was employed for missing data. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients

A total of 1039 patients were enrolled between August 2018 and October 2019 at 169 sites in Japan. Among them, 1002 were included in the safety analysis set, and 1000 were included in the FAS (**Figure 1**). The median follow-up was 11.5 months (interquartile range, 4.3–20.3) in the FAS.

Patient baseline demographic and clinical characteristics are shown in **Table 1**. In the FAS, 289 (28.9%) patients were ≥75 years old, 120 (12.0%) patients had an ECOG PS ≥2, 20 (2.0%) patients had a history of autoimmune disease, 191 (19.1%) patients had CNS metastases, 355 (35.5%) patients had received atezolizumab as ≥4th-line treatment, and 219 (21.9%) patients had previous treatment with ICIs. *EGFR*, *ALK*, *ROS1*, and *BRAF* targetable driver gene alterations were present in 146 (14.6%), five (0.5%), three (0.3%), and one (0.1%) patient(s), respectively. Of the PD-L1 assays, the most frequent were PD-L1 22C3 immunohistochemistry assay (80.1%, n = 801), and patients with TPS <1% (44.4%, n = 356) were the most common. Details of PD-L1 assays are shown in **Supplementary Table 2**. The OAK-like subpopulation comprised 37.9% of the FAS (n = 379). Patient baseline demographic and clinical characteristics in the OAK-like and -unlike subpopulations are shown in **Supplementary Table 3**.

Effectiveness in the FAS population

Effectiveness endpoints in the FAS are summarized in **Table 2**. The OS rate at 18 months (primary effectiveness endpoint) was 41.1% (95% CI, 38.0–44.3) in the FAS. Regarding secondary effectiveness endpoints, the median OS was 13.0 months (95% CI, 12.2–15.1) (**Figure 2A**), the median PFS was 2.1 months (95% CI, 2.1–2.3) (**Supplementary Figure 1A**), and the median TTF was 2.1 months (95% CI, 2.0–2.1) (**Supplementary Figure 1B**).

Among 979 patients with measurable lesions, the best overall response was CR in nine (0.9%) patients, PR in 77 (7.9%) patients, SD in 311 (31.8%) patients, and progressive disease in 470 (48.0%) patients (**Table 2**). The ORR was 8.8% (95% CI, 7.0–10.6), and DCR was 14.8% (95% CI, 12.6–17.0). The median DOR was 15.6 months (95% CI, 12.3–not evaluable [NE]) (**Supplementary Figure 1C**).

Effectiveness in subgroups

Patient baseline demographic and clinical characteristics according to subgroups are shown in **Supplementary Table 3.** Effectiveness endpoints in the selected subgroups are summarized in **Table 2.** Results for subgroup analysis by targetable driver oncogene status are shown in **Supplementary Table 4**. Kaplan–Meier curves for OS and PFS in the subgroups according to targetable driver oncogene status are shown in **Supplementary Figures 2A** and **2B**. The OS and PFS tended to be slightly poorer in mutation-positive patients than in negative patients. The OAK-like and OAK-unlike subpopulations achieved an 18-month survival rate of 49.4% (95% CI, 44.1–54.7) and 36.1% (95% CI, 32.1–40.0), respectively. The median OS was 17.7 months (95% CI, 15.8–20.5) in the OAK-like subpopulation versus 11.1 months (95% CI, 9.2–12.6) in the OAK-unlike subpopulation (HR: 0.64; 95% CI, 0.54–0.75; p<0.0001). The median PFS was 2.6 months (95% CI, 2.2–3.0) in the OAK-like subpopulation versus 2.1 months (95% CI, 2.0–2.1) in the OAK-unlike subpopulation (HR: 0.81; 95% CI, 0.71–0.93; p=0.0022). Kaplan–Meier curves for OS and PFS in the OAK-like and OAK-unlike subpopulations are shown in **Figure 2B** and **Supplementary Figure 3A**.

Kaplan–Meier curves for OS by PD-L1 expression status in the OAK-like and -unlike subpopulations are shown in **Figures 2C** and **2D.** In patients with TPS ≥50%, the OS rate at 18 months was 68.7% and 31.1% in the OAK-like and -unlike subpopulations, respectively. In the OAK-like subpopulation, the median OS was not reached (95% CI, 13.5–NE) for TPS ≥50%, 15.8 months (95% CI, 12.8–19.1) for TPS 1–49%, and 16.5 months (95% CI, 14.2–22.0) for TPS <1%; in the OAK-unlike subpopulation, 8.5 months (95% CI, 5.3–11.6) for TPS ≥50%, 9.6 months (95% CI, 7.2–12.4) for TPS 1–49%, and 12.4 months (95% CI, 8.5–17.0) for TPS <1%. The median PFS in the OAK-like subpopulation by PD-L1 expression status in the OAK-like subpopulation was 5.2 months (95% CI, 2.1–17.1) for TPS ≥50%, 2.6 months (95% CI, 2.1–3.3) for TPS 1–49%, and 2.3 months (95% CI, 2.0–3.0) for TPS <1% (**Supplementary Figure 3B**); and 2.0 months (95% CI, 1.6–2.7) for TPS ≥50%, 2.0 months (95% CI, 1.6–2.1) for TPS 1–49%, and 2.1 months (95% CI, 1.9–2.3) for TPS <1% (**Supplementary Figure 3C**).

Kaplan–Meier curves for OS and 18-month OS rates in the OAK-unlike population with the selected subgroups are shown in **Figure 3** and **Table 2.** Kaplan–Meier curves for PFS in the OAK-unlike population with the selected subgroups are shown in **Supplementary Figure 4**. Patients previously treated with ICIs had a relatively favorable median OS in this OAK-unlike subpopulation. Patients in the subgroups of CNS metastases, ECOG PS ≥2, and a history of autoimmune disease had a generally poor prognosis (**Figure 3 and Table 2**). The best overall response, ORR, and DCR in the selected subgroups are shown in **Table 2**. While the tumor response was equivalent among patients aged over 75 years (ORR, 11.3%; 95% CI, 7.6%–15.0%) and the overall population, tumor responses in other subgroups were limited.

Safety

The incidence of AEs was 43.9% (440/1002), and that of irAEs was 19.0% (190/1002) in the safety analysis set (**Supplementary Table 5** and **Table 3**). The incidence of treatment-related AEs was 26.4% (265/1002); grade 3 or 4 treatment-related AEs, 8.7% (87/1002); serious AEs, 20.6% (206/1002); and treatment-related deaths, 1.4% (14/1002) (**Supplementary Table 5**). The incidence of treatment-related irAEs was 18.2% (182/1002); grade 3–4 treatment-related irAEs, 7.0% (70/1002); and irAEs leading to withdrawal from treatment, 5.8% (58/1002) (**Table 3**).

Safety in subgroups

The incidence of AEs and irAEs in subgroups according to baseline characteristics are shown in **Supplementary Table 5** and **Table 3**. The incidence of AEs, irAEs, and irAEs leading to treatment discontinuation in patients with a history of autoimmune disease tended to be higher, at 60.0%, 35.0%, and 15.0%, respectively. The incidence of AEs and irAEs in the other subgroups was consistent.

PROs

Kaplan–Meier curves for time to worsening symptoms with a 0.05 and 0.1 reduction from baseline in EQ-5D-5L are shown in **Supplementary Figures 5A** and **5B**.

DISCUSSION

In the present study, we evaluated the real-world effectiveness and safety of atezolizumab monotherapy in a very large number of patients with unresectable advanced or recurrent NSCLC. The present study enrolled over 1000 patients to evaluate diverse characteristics in the real-world setting with a relatively long follow-up, including those not eligible for the registrational trial and provided clinically meaningful data, including effectiveness and safety in older patients with poor prognosis as often encountered in real-world settings. Atezolizumab monotherapy yielded expected survival rates without new safety signals in patients with previously treated NSCLC, which were comparable with that of the registrational trial.

The primary endpoint of this study was the OS rate at 18 months in recurrent NSCLC patients treated with atezolizumab in a real-world setting. We set this primary endpoint to assess longer-term landmark survival data concerning the median survival time of 13.8 months reported in the registrational phase III OAK trial.[5] In the present study, atezolizumab monotherapy showed comparable effectiveness with the OAK trial despite including patients excluded from the OAK trial (OAK-unlike subpopulation). The OS rate at 18 months was 41.1% in the FAS of the present study (median OS, 13.0 months [95% CI, 12.2–15.1]) with a median follow-up of 11.5 months. These data were comparable with the atezolizumab arm of the OAK trial (18-month OS rate, 40%; median OS, 13.8 months [95% CI, 11.8–15.7]) with a median follow-up of 21.0 months.[5] In this study, the median follow-up was immature for assessing the OS rate at 18 months. Further updates are needed to increase the robustness of the results.

In clinical practice, physicians often encounter patients whose characteristics do not match the eligibility criteria of registrational trials such as the OAK trial. Therefore, it is essential

385 to understand the features of the OAK-unlike subpopulation. Atezolizumab monotherapy
386 showed the benefit–risk profile in a clinically diverse population of patients with previously
387 treated NSCLC, according to a recent report from the global phase III/IV TAIL study.[7] Subgroup
388 data for the OAK-like population in the TAIL trial were comparable to the OAK trial (median OS
389 13.8 months [95% CI, 11.8–15.7]), despite being conducted in a real-world setting. In contrast,
390 the results of the OAK-unlike population were not shown. In this study, the OAK-unlike
391 subpopulation accounted for approximately 60% of the overall study population, which was
392 higher than that in the TAIL study (34%). While the clinical background of the OAK-unlike
393 population is concerning, this study demonstrates effectiveness and safety in such a population.
394 Notably, patients with a history of ICI treatment and those with ECOG PS ≥2 accounted for
395 21.9% and 12.0% of the present study, respectively. The median OS of 11.1 months in the
396 OAK-unlike subpopulation was shorter compared with 17.7 months in the OAK-like
397 subpopulation (HR: 0.64). Additionally, patients aged ≥75 years accounted for 28.9% of the
398 study population. Although there is still debate on how aging affects the efficacy of ICIs,
399 previous studies, including the TAIL study, demonstrated that ICIs appear to be effective in
400 patients aged ≥ 75 years.[7,14,15] As in previous reports, ICIs were shown to be effective regardless
401 of age in the relatively large number of real-world patients in this study, supporting the notion
402 that ICI therapy may be an important treatment option for older patients. For clinical practice, the
403 present data should be interpreted with caution considering the registration study results and
404 strongly suggest the importance of a real-world-based study.
405 PD-L1 expression status using the 22C3 antibody is an important biomarker for selecting
406 the most suitable treatment regimen in our clinical practice. Regarding the analyses of PD-L1
407 expression in the OAK-like subpopulation, better trends in both OS and PFS were observed in
408 the subgroup with TPS ≥50% compared with subgroups with TPS 1–49% or <1% in the present
409 study (Figure 2C). This analysis strongly suggests that PD-L1 expression evaluation using the
410 22C3 antibody might be feasible and valuable as a predictive biomarker of the effectiveness of

atezolizumab therapy for real-world patients who match the eligibility for the registration trials. Additionally, the efficacy of atezolizumab on PD-L1 negative patients shown in the OAK study was reproduced in this real-world population analysis. Conversely, in the OAK-unlike subpopulation, OS and PFS were similar irrespective of PD-L1 expression level. The OAK-unlike subpopulation was heterogeneous and included patients with various background factors, such as patients who had received steroid therapy for CNS metastasis, previously treated with ICIs, or those with complex comorbidities. These individual factors were very diverse, and it was not easy to discern or analyze these factors in each case. This is one of the limitations of this real-world study; nevertheless, these results highlight the vague use of ICIs that relies on PD-L1 expression among high-risk patients who do not qualify for enrollment in registration trials.

In the present study, the incidence of AEs and treatment-related AEs was 43.9% and 26.4%, respectively. The incidence of these AEs was less than half that in the atezolizumab arm of the OAK trial (94% and 64%, respectively).[5] AEs of less severity are generally not as well recorded in the real world as in clinical trials, which could explain the lower incidence of these AEs in our study compared with the OAK trial. The toxicity profiles of irAEs associated with atezolizumab were reported in the TAIL study, and the incidence of irAEs in the overall population was 9.6%.[7] In the present study, the incidence of irAEs was 19.0%. There is a difference in the definition of irAEs between the TAIL study (AEs of special interest requiring corticosteroid treatment within 30 days of onset) and the present study (AEs judged to be irAEs by the investigator); the difference in the incidence may be because of this variation in definition. However, the percentages of serious irAEs, irAEs leading to treatment discontinuation, and treatment-related death were 8.7%, 5.8%, and 1.2%, respectively. Despite the relatively high frequency of irAEs, the lower incidence of irAEs leading to treatment discontinuation and treatment-related death in our study suggests that atezolizumab treatment was well managed under actual clinical conditions with adequate caution for serious irAEs.

In the subgroup analysis, age did not affect the effectiveness of atezolizumab. Older age has been considered a negative predictor in ICI therapy because of aging-related immunosenescence. Several reports, including the TAIL study, recently indicated that older age was not associated with survival outcomes and severe toxicities.[16] The results of this study support the idea that age should not be a deciding factor for prescribing ICIs. Similarly, a history of ICI therapy was not a negative predictor for survival outcomes. However, this population's response rate and median PFS were 5.2% and 2.1 months, respectively (Table 2). The use of atezolizumab beyond progression may provide favorable disease control in the post-hoc analysis of the OAK trial.[17] Atezolizumab may be a suitable treatment option in this setting, but physicians should consider the benefit–risk balance carefully, including the economic burden. The present study showed that the incidence of irAEs tended to be higher among patients with autoimmune disease than in other patient subgroups. This trend was similar to that shown in previous reports.[7,18] In terms of effectiveness, although the median OS in patients with an autoimmune disease in the present study was short at 8.6 months, their OS rate at 18 months (35.0%) was comparable to that of the OAK trial at 18 months (40.0%). These findings suggest that careful attention should be given to the onset of irAEs; however, treatment should not be delayed due to autoimmune disease complications alone. Long-term survivors were generally recognized even among patients with several characteristics that led to the ineligibility for the OAK trial, such as CNS metastasis and a history of autoimmune disease. For the OAK-unlike population, atezolizumab may be a reasonable therapy option with careful consideration of the benefit–risk balance; however, effectiveness outcomes were unfavorable for patients with ECOG PS ≥2, consistent with previous studies. This strongly suggests that poor PS was a negative predictive and prognostic factor of immunotherapy with PD-1/PD-L1 inhibitors.[19,20] Although no safety concerns were observed in this study regarding the poor PS population, the benefits were limited. Thus, ICI therapy for this population should be considered with great caution.

The present study has some limitations. First, this study has an observational design. Owing to the study's observational nature, there was no control group. Moreover, the progression measurement was prone to error, and the frequency of radiographic examinations was uneven across participating sites for PFS evaluation. Second, the median observation period of this study was 11.5 months, which was not sufficient to evaluate the "long-tail effect". Although the adequate observation period to evaluate the so-called "long-tail effect" has not been established, it is considered that an observation period of over 5 years has been required empirically. Future observation and updates of survival and longer-term safety data are needed. Third, this study was conducted only in Japan and results are based only on the Japanese population. However, while studies on the effect of ICI monotherapy for NSCLC with driver mutations including *EGFR* mutation are limited, this study analyzed a large number of patients (n = 146) and found a slightly inferior trend in positivity, as in previous reports. The OS and PFS tended to be slightly poorer in mutation-positive patients than in negative patients, in line with a previous report.[21] Prospective studies, including the ongoing chemotherapy + ICI study, will demonstrate the use of ICIs in NSCLC with driver mutations.

In conclusion, the results of the J-TAIL study showed comparable effectiveness of atezolizumab to the registrational phase III OAK trial. In addition, no new safety signals were identified. An acceptable benefit–risk profile was observed among patients who would have been ineligible for the OAK trial. However, the administration of atezolizumab should be considered carefully regarding its effectiveness for patients with ECOG PS ≥2, along with its safety in those with a history of autoimmune disease. In clinical practice, PD-L1 expression level may not predict effectiveness in patients who are ineligible for clinical trials.

Acknowledgments

We would like to thank the patients, their families, the investigators, and the clinical study sites for participating in this study. We would also like to express our gratitude to the late Dr. Koichi Nakatani and the late Dr. Toru Kumagai for their contributions to this study. We would also like to thank Michelle Belanger, MD, of Edanz (www.edanz.com), for providing medical writing support, funded by Chugai Pharmaceutical Co., Ltd., and the staff members of Mebix, Inc. for their assistance with the study management, data collection, storage, statistical analysis, and medical writing support funded by Chugai Pharmaceutical Co., Ltd.

Role of the Funding Source

This study was funded by Chugai Pharmaceutical Co., Ltd., which jointly conducted this study with the Japanese Lung Cancer Association and collaborated with the academic authors on the study design, data collection, analysis, and interpretation. The authors prepared all manuscript drafts with editorial assistance funded by Chugai Pharmaceutical Co., Ltd. All authors approved the submission.

Data availability

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://www.clinicalstudydatarequest.com/Default.aspx). For further details on the data sharing policy of Chugai Pharmaceutical Co., Ltd. and how to request access to related clinical study documents, see here (www.chugai-pharm.co.jp/english/profile/rd/ctds_request.html).

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564 **Figure legends**

565

566 **Figure 1.** Patient disposition

567 Abbreviation: PRO, patient-reported outcomes.

568 **Figure 2.** Kaplan–Meier curves for OS

569 A. FAS

570 B. OAK-like and OAK-unlike subpopulations

571 C. OAK-like subpopulation according to PD-L1 expression

572 D. OAK-unlike subpopulation according to PD-L1 expression

573 Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NR,

574 not reached; NE, not estimable; OS, overall survival; PD-L1, programmed death ligand-1; TPS,

575 tumor proportion score

576 **Figure 3.** Kaplan–Meier curve for OS in the subgroups.

577 Abbreviations: CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern

578 Cooperative Oncology Group performance status; ICIs, immune checkpoint inhibitors; mo,

579 months; OS, overall survival

580

581 **Tables**

582 **Table 1.** Patient background demographic and clinical characteristics (full analysis set)

Characteristics	Full analysis set N = 1000
Sex	
Male	718 (71.8)
Female	282 (28.2)
Age, years	
Median age (range)	71 (34–93)
≥75	289 (28.9)
Histology	
Squamous	216 (21.6)
Non-squamous	737 (73.7)
Other	47 (4.7)
ECOG PS	
0	335 (33.5)
1	545 (54.5)
2	107 (10.7)
3	13 (1.3)
4	0 (0)
Smoking history	756 (75.6)
Medical history	
Autoimmune disease	20 (2.0)
Other than autoimmune disease	537 (53.7)
Complications	

Autoimmune disease	68 (6.8)
Other than autoimmune disease	708 (70.8)
Primary tumor surgery	286 (28.6)
Metastases	
CNS	191 (19.1)
Bone	263 (26.3)
Adrenal	91 (9.1)
Liver	126 (12.6)
Kidney	13 (1.3)
Other*	806 (80.6)
Stage	
IIIA	42 (4.2)
IIIB	60 (6.0)
IIIC	14 (1.4)
IVA	284 (28.4)
IVB	311 (31.1)
Post-surgery recurrence	211 (21.1)
Post chemoradiation therapy recurrence	78 (7.8)
Treatment line of atezolizumab	
2	425 (42.5)
3	220 (22.0)
≥4	355 (35.5)
Prior drug therapy	
Immune checkpoint inhibitors	219 (21.9)
Chemotherapy	988 (98.8)

Angiogenesis inhibitor	388 (38.8)
EGFR inhibitor	156 (15.6)
ALK inhibitor	7 (0.7)
Other	7 (0.7)
Prior radiation therapy	288 (28.8)
Targetable driver oncogene status	
Negative†	128 (12.8)
Positive†	155 (15.5)
Unknown†	593 (59.3)
EGFR mutation status	
Positive	146 (14.6)
ALK rearrangement status	
Positive	5 (0.5)
ROS1 rearrangement status	
Positive	3 (0.3)
BRAF V600E mutation status	
Positive	1 (0.1)
PD-L1	
22C3	
n	801
TPS ≥50%	138 (17.2)
TPS 1–49%	307 (38.3)
TPS <1%	356 (44.4)
Additional predefined key subgroups	
OAK-like population	379 (37.9)

OAK-unlike population	621 (62.1)
Renal impairment‡	25 (2.5)
Liver impairment‡	51 (5.1)

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ICIs, immune checkpoint inhibitors; PD-L1, programmed death ligand-1; TPS, tumor proportion score.

*Other includes patients with pleural effusion.

†Negative, all targetable driver oncogene statuses (*EGFR* mutation status, *ALK* rearrangement status, *ROS1* rearrangement status, and *BRAF* V600E mutation status) were negative; positive, one or more were positive; unknown, none of the positives, any were unknown or not tested.

‡Based on baseline laboratory values, any missing values were treated as impairment.

Table 2. Effectiveness in all patients and selected subgroups

		Overall	OAK-like population	OAK-unlike population	CNS metastases	ECOG PS ≥2	Previous treatment with ICIs	Autoimmune disease	Age ≥75 years
N		**1000**	**379**	**621**	**191**	**120**	**219**	**20**	**289**
OS events		622	205	417	142	100	156	14	184
Median OS, months (95% CI)		13.0 (12.2–15.1)	17.7 (15.8–20.5)	11.1 (9.2–12.6)	7.7 (6.0–10.7)	2.8 (2.3–3.8)	10.3 (8,1–12.2)	8.6 (5.6–19.9)	12.7 (9.6–14.6)
18-month OS, % (95% CI)		41.1 (38.0–44.3)	49.4 (44.1–54.7)	36.1 (32.1–40.0)	27.4 (20.8–34.0)	14.3 (7.6–21.0)	29.9 (23.6–36.3)	35.0 (14.1–55.9)	36.0 (30.1–41.9)
Median PFS, months (95% CI)		2.1 (2.1–2.3)	2.6 (2.2–3.0)	2.1 (2.0–2.1)	1.6 (1.4–1.9)	1.2 (1.0–1.5)	2.1 (1.8–2.2)	2.6 (2.1–5.6)	2.2 (2.1–2.6)
BOR	n (%)	979	377	602	181	114	213	20	283
	CR	9 (0.9)	3 (0.8)	6 (1.0)	-	-	2 (0.9)	-	5 (1.8)
	PR	77 (7.9)	38 (10.1)	39 (6.5)	9 (5.0)	4 (3.5)	9 (4.2)	1 (5.0)	27 (9.5)
	SD	311 (31.8)	131 (34.7)	180 (29.9)	40 (22.1)	22 (19.3)	68 (31.9)	7 (35.0)	87 (30.7)

	PD	470 (48.0)	172 (45.6)	298 (49.5)	104 (57.5)	51 (44.7)	104 (48.8)	9 (45.0)	129 (45.6)
	NE	112 (11.4)	33 (8.8)	79 (13.1)	28 (15.5)	37 (32.5)	30 (14.1)	3 (15.0)	35 (12.4)
ORR	n (%)	86 (8.8)	41 (10.9)	45 (7.5)	9 (5.0)	4 (3.5)	11 (5.2)	1 (5.0)	32 (11.3)
	95% CI	(7.0–10.6)	(7.7–14.0)	(5.4–9.6)	(1.8–8.1)	(0.1–6.9)	(2.2–8.1)	(0.0–14.6)	(7.6–15.0)
DCR	n (%)	145 (14.8)	70 (18.6)	75 (12.5)	15 (8.3)	7 (6.1)	20 (9.4)	2 (10.0)	45 (15.9)
	95% CI	(12.6–17.0)	(14.6–22.5)	(9.8–15.1)	(4.3–12.3)	(1.7–10.5)	(5.5–13.3)	(0.0–23.1)	(11.6–20.2)
Maintaining SD 24 weeks, n (%)		59 (6.0)	29 (7.7)	30 (5.0)	6 (3.3)	3 (2.6)	9 (4.2)	1 (5.0)	13 (4.6)

Abbreviations: BOR, best overall response; CI, confidence interval; CNS, central nervous system; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; ICIs, immune checkpoint inhibitors; NE, not evaluable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 3. Summary of irAEs in the overall study population and patient subgroups (Safety analysis set)

	Overall	OAK-like population	OAK-unlike population	CNS metastases	ECOG PS ≥2	Previous treatment with ICIs	Autoimmune disease	Age ≥75 years
N	1002	379	623	191	120	219	20	290
All irAEs	190 (19.0)	76 (20.1)	114 (18.3)	31 (16.2)	15 (12.5)	34 (15.5)	7 (35.0)	58 (20.0)
Treatment-related irAEs	182 (18.2)	72 (19.0)	110 (17.7)	30 (15.7)	15 (12.5)	32 (14.6)	7 (35.0)	57 (19.7)
Grade 3 or 4 irAEs	74 (7.4)	28 (7.4)	46 (7.4)	15 (7.9)	6 (5.0)	14 (6.4)	3 (15.0)	21 (7.2)
Grade 3 or 4 treatment-related irAEs	70 (7.0)	26 (6.9)	44 (7.1)	14 (7.3)	6 (5.0)	12 (5.5)	3 (15.0)	20 (6.9)
All deaths	12 (1.2)	4 (1.1)	8 (1.3)	2 (1.0)	2 (1.7)	3 (1.4)	0 (0)	3 (1.0)
Treatment-related deaths	12 (1.2)	4 (1.1)	8 (1.3)	2 (1.0)	2 (1.7)	3 (1.4)	0 (0)	3 (1.0)
Serious irAEs	87 (8.7)	34 (9.0)	53 (8.5)	18 (9.4)	9 (7.5)	17 (7.8)	1 (5.0)	26 (9.0)
irAEs leading to withdrawal from treatment	58 (5.8)	21 (5.5)	37 (5.9)	7 (3.7)	5 (4.2)	13 (5.9)	3 (15.0)	13 (4.5)
irAEs leading to dose interruption	71 (7.1)	26 (6.9)	45 (7.2)	15 (7.9)	4 (3.3)	11 (5.0)	3 (15.0)	24 (8.3)

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events.

Supplementary Materials

Supplementary Figure 1. Kaplan–Meier curves for PFS (A), TTF (B), and DOR (C) in the FAS
(Miura et al. Supplemental Figure 1)

Supplementary Figure 2. Kaplan–Meier curves for OS (A) and PFS (B) in the subgroups according to targetable driver oncogene status
(Miura et al. Supplemental Figure 2)

Supplementary Figure 3. Kaplan–Meier curves for PFS in OAK-like and OAK-unlike subpopulations (A), OAK-like subpopulation according to PD-L1 expression (B), and OAK-unlike subpopulation according to PD-L1 expression (C)
(Miura et al. Supplemental Figure 3)

Supplementary Figure 4. Kaplan–Meier curve for PFS in the subgroups
(Miura et al. Supplemental Figure 4)

Supplementary Figure 5. Kaplan–Meier curves for time to worsening symptoms with (A) a 0.05 and (B) a 0.1 reduction from baseline using the Japanese version of the EQ-5D-5L questionnaire
(Miura et al. Supplemental Figure 5)

Supplementary Table 1. Eligibility criteria for J-TAIL
(Miura et al. Supplemental Table 1)

Supplementary Table 2. Details of PD-L1 assays
(Miura et al. Supplemental Table 2)

Supplementary Table 3. Patient background demographic and clinical characteristics according to subgroups

(Miura et al. Supplemental Table 3)

Supplementary Table 4. Effectiveness in subgroups according to targetable driver oncogene status

(Miura et al. Supplemental Table 4)

Supplementary Table 5. Summary of AEs in the overall study population and patient subgroups (Safety analysis set)

(Miura et al. Supplemental Table 5)

Figure 1

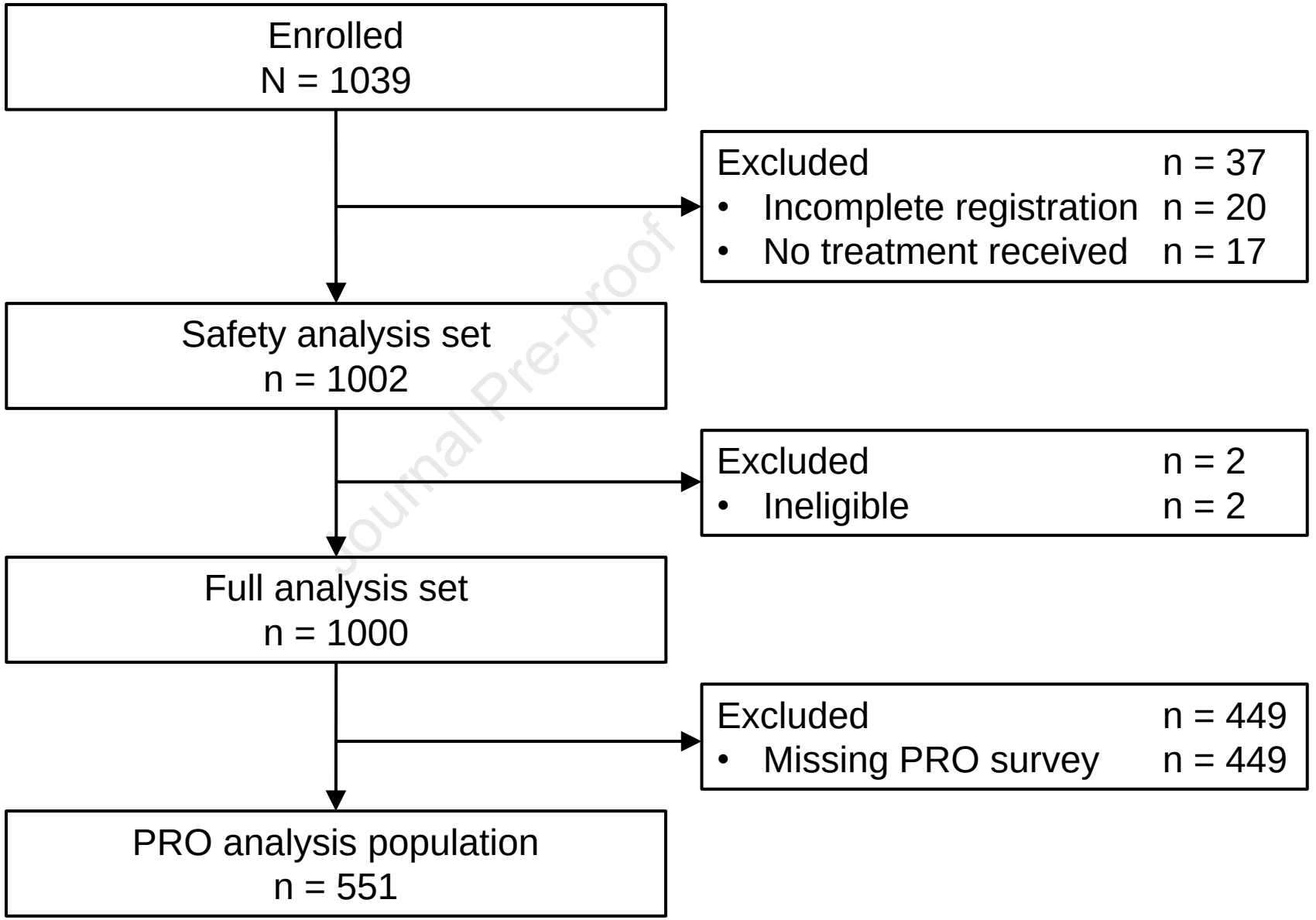


Figure 2A

	N	OS rate			Median OS months (95% CI)
		12-month	18-month	24-month	
FAS	1000	53.5%	41.1%	30.1%	13.0 (12.2–15.1)

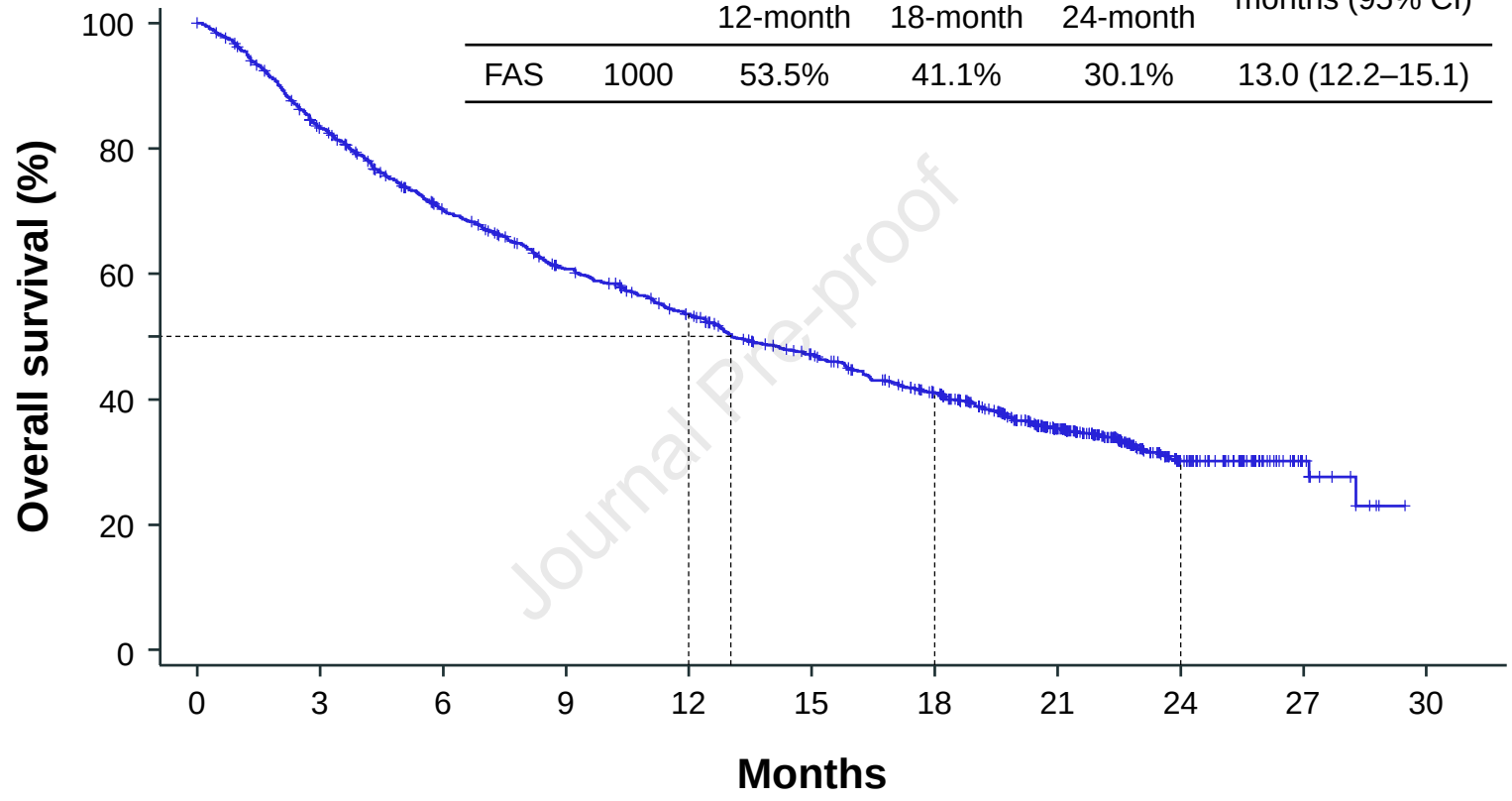
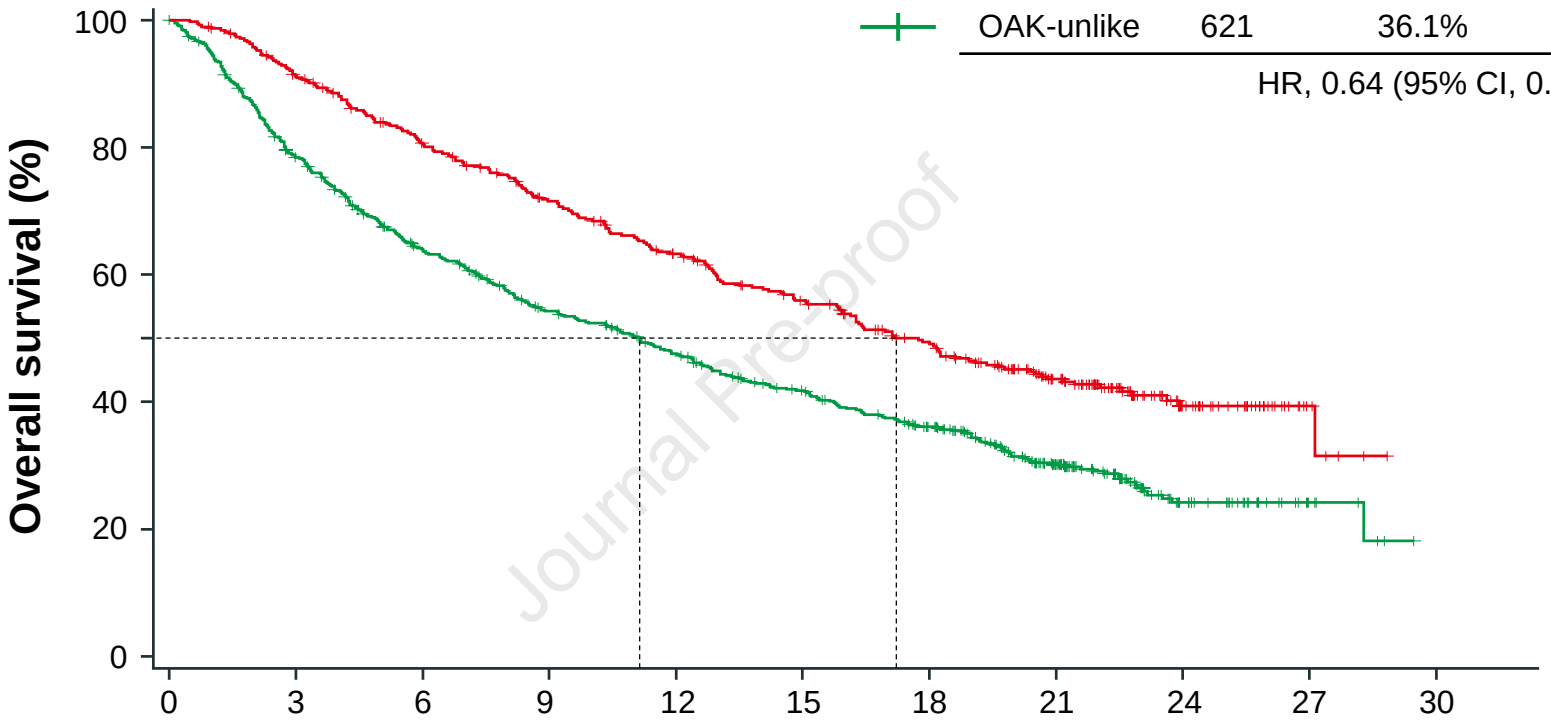


Figure 2B

	N	18-month OS rate	Median OS months (95% CI)
OAK-like	379	49.4%	17.7 (15.8–20.5)
OAK-unlike	621	36.1%	11.1 (9.2–12.6)

HR, 0.64 (95% CI, 0.54–0.75); p<0.0001

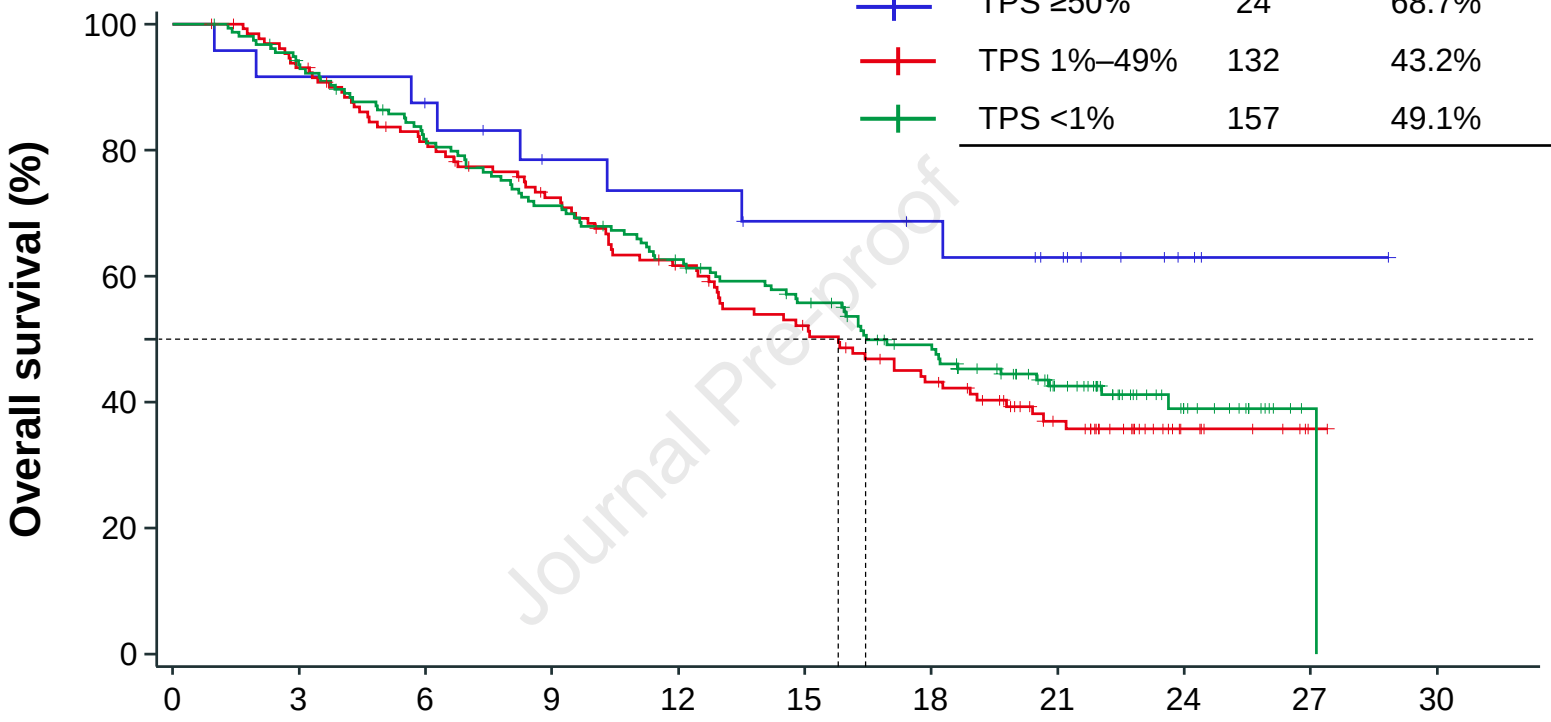


No. at risk

OAK-like	379	341	294	254	219	186	154	106	38	6	0
OAK-unlike	621	478	379	313	268	223	179	105	34	7	0

Figure 2C

	N	18-month OS rate	Median OS months (95% CI)
TPS ≥50%	24	68.7%	NR (13.5–NE)
TPS 1%–49%	132	43.2%	15.8 (12.8–19.1)
TPS <1%	157	49.1%	16.5 (14.2–22.0)

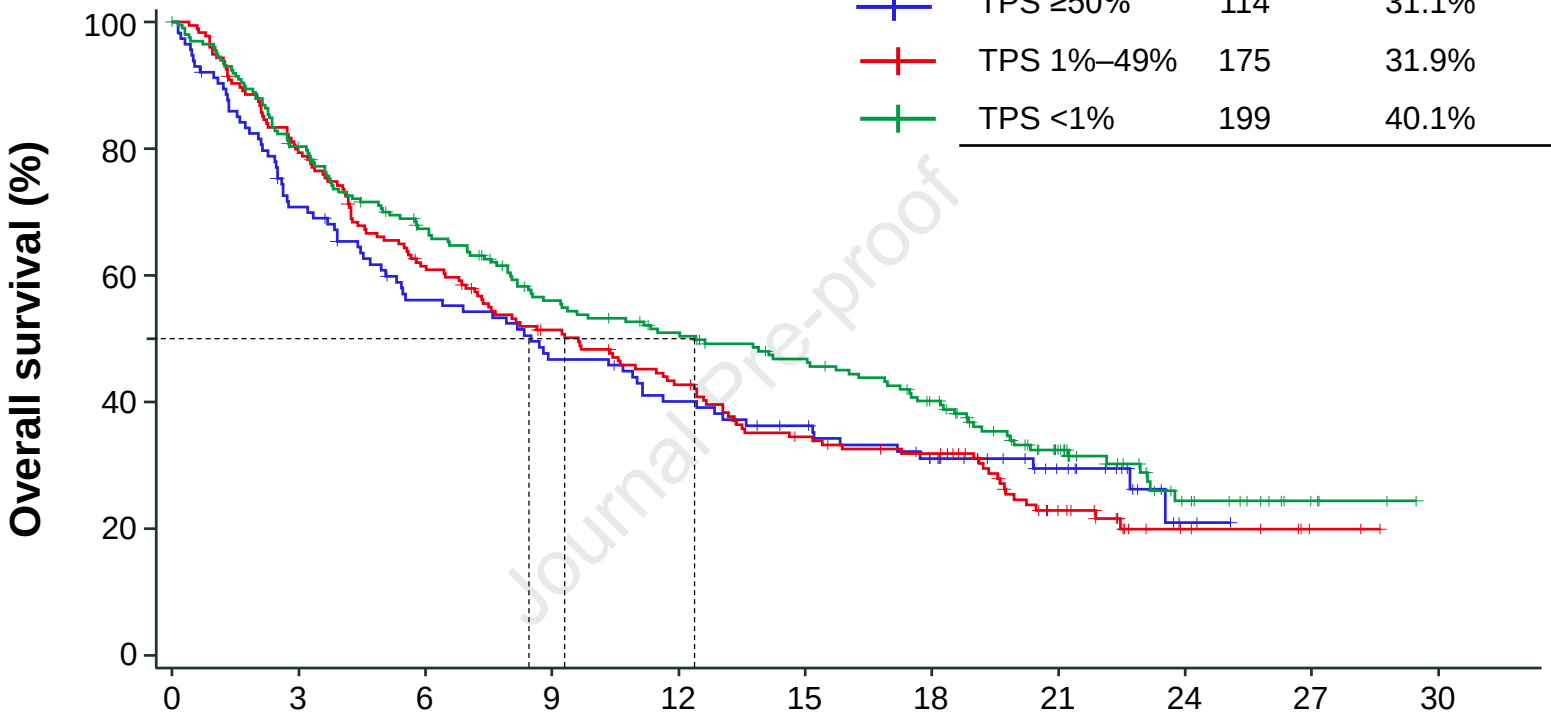


No. at risk

TPS ≥50%	24	22	20	16	15	13	12	9	3	1	0
TPS 1%–49%	132	121	103	88	72	59	47	30	9	1	0
TPS <1%	157	144	124	108	93	80	64	40	15	1	0

Figure 2D

	N	18-month OS rate	Median OS months (95% CI)
TPS ≥50%	114	31.1%	8.5 (5.3–11.6)
TPS 1%–49%	175	31.9%	9.6 (7.2–12.4)
TPS <1%	199	40.1%	12.4 (8.5–17.0)

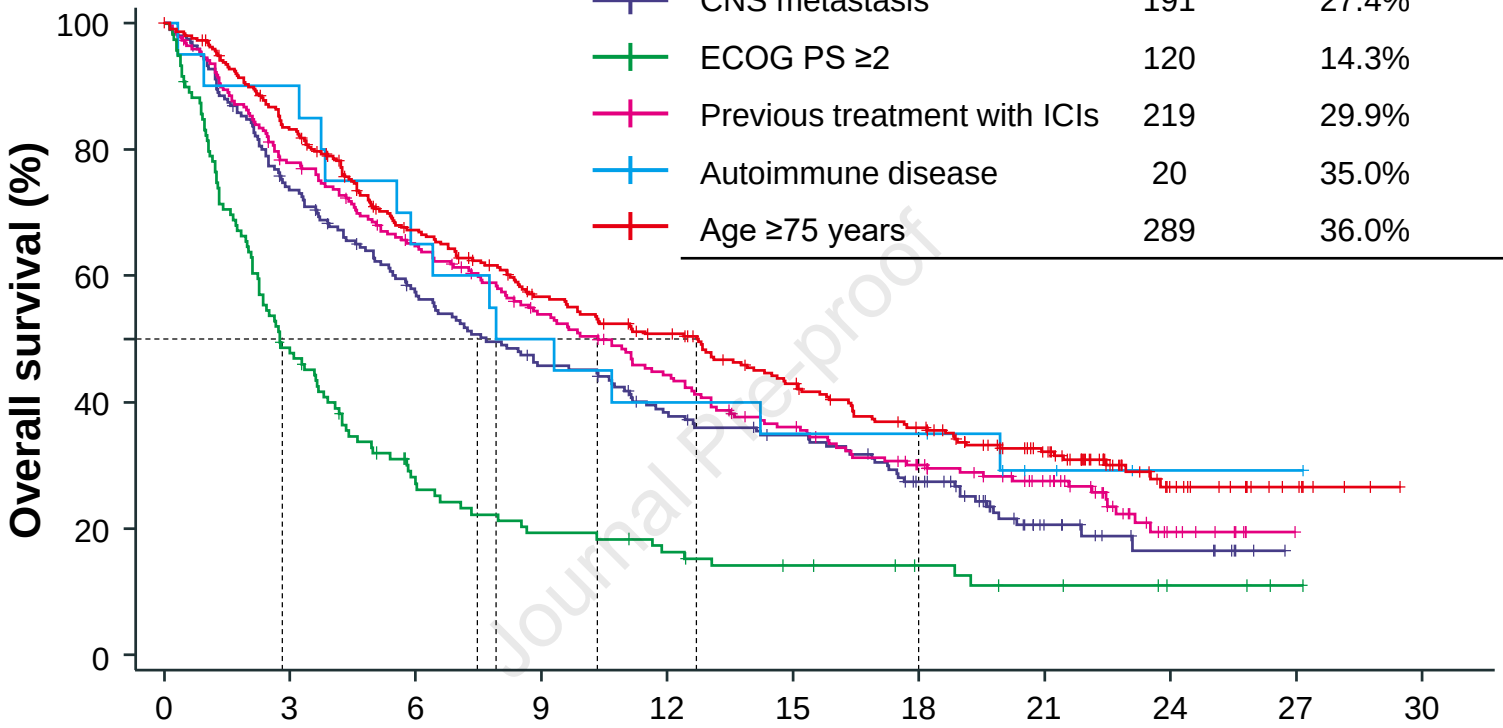


No. at risk

TPS ≥50%	114	79	60	50	42	36	27	16	2	0	0
TPS 1%–49%	175	138	105	84	69	53	47	21	7	2	0
TPS <1%	199	157	127	101	89	78	63	36	14	4	0

Figure 3

	N	18-month OS rate	Median OS months (95% CI)
CNS metastasis	191	27.4%	7.7 (6.0–10.7)
ECOG PS ≥2	120	14.3%	2.8 (2.3–3.8)
Previous treatment with ICIs	219	29.9%	10.3 (8.1–12.2)
Autoimmune disease	20	35.0%	8.6 (5.6–19.9)
Age ≥75 years	289	36.0%	12.7 (9.6–14.6)



No. at risk											
CNS metastasis	191	138	104	82	66	57	41	15	7	0	0
ECOG PS ≥2	120	56	28	20	16	12	9	6	3	1	0
Previous treatment with ICIs	219	167	135	108	87	68	51	36	10	0	0
Autoimmune disease	20	18	13	10	8	7	7	3	1	1	0
Age ≥75 years	289	236	181	146	127	102	81	56	19	7	0

CRediT Authorship Contribution Statement

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Makoto Nishio: Conceptualization, Resources, Supervision, Investigation, Writing–review and editing.

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