Economic Burden of Early Treatment Failure with PD-1 Inhibitor Immunotherapy in Metastatic Non-Small Cell Lung Cancer

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Abstract

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Metastatic non-small cell lung cancer (mNSCLC) remains a major clinical and economic burden, and early treatment failure (ETF) after first-line PD-1 inhibitor therapy may identify patients with poor downstream cost outcomes. This retrospective cohort study used Merative MarketScan Commercial Claims and Medicare Supplemental data from 2019-2023 to evaluate ETF among adults with mNSCLC initiating first-line pembrolizumab, nivolumab, or cemiplimab. A 90-day landmark design was used, and ETF was defined as early discontinuation of the indexed PD-1 inhibitor, initiation of a new systemic anticancer therapy not included in the original regimen, or both. Survival-adjusted cumulative costs were estimated using overlap-weighted Kaplan-Meier sample average methods, and survival, per-patient-per-month (PPPM) cost, and utilization outcomes were analyzed using overlap-weighted, covariate-adjusted models.

Among 1,873 patients in the analytic cohort, 720 were classified as ETF and 1,153 as No ETF. ETF was associated with worse overall survival after the landmark (HR, 2.17; 95% CI, 1.81 to 2.60). At 365 days, survival-adjusted cumulative costs were higher in patients with No ETF than ETF ($278,151 vs $177,502; difference, -$100,649; 95% CI, -$120,309 to -$81,361). Total PPPM cost was also lower in ETF than No ETF ($20,484 vs $25,734; difference, -$5,250; 95% CI, -$8,335 to -$3,133). ETF was associated with higher inpatient admissions and inpatient days. Overall, ETF was associated with worse survival and greater inpatient burden, whereas patients without ETF accumulated higher healthcare costs over follow-up.

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1. Introduction

Metastatic non-small cell lung cancer (mNSCLC) remains a major source of morbidity, mortality, and healthcare spending in the United States.[1,2] PD-1 inhibitors, including pembrolizumab, nivolumab, and cemiplimab, are immune checkpoint inhibitors that have become important first-line treatment options for eligible patients with mNSCLC, either as monotherapy or in combination with chemotherapy and/or other systemic agents.[3-8] Despite these advances, outcomes in real-world practice remain heterogeneous. Prior observational studies have shown that first-line NSCLC treatment patterns have shifted with adoption of immunotherapy, but treatment duration, survival, healthcare utilization, and costs vary across regimens and patient populations.[9-13]

This variability highlights the importance of identifying patients who experience poor outcomes soon after treatment initiation. Early treatment failure (ETF) may identify a clinically important subgroup with particularly poor prognosis.[14] In practice, early discontinuation of therapy or early initiation of a new systemic regimen may reflect rapid progression, treatment intolerance, lack of response, or a combination of these factors.[9,10,14] As a result, ETF may serve as a useful claims-based marker of an early adverse treatment trajectory and may also be associated with differences in downstream healthcare utilization and costs.[11-14]

Prior real-world studies in advanced or metastatic NSCLC have examined treatment persistence, discontinuation, switching, survival, and overall healthcare costs associated with immunotherapy and other systemic anticancer therapies.[9-14] However, much of the literature has focused on treatment patterns, clinical outcomes, or economic outcomes separately, and fewer studies have examined early treatment failure as a claims-based marker of an adverse early treatment trajectory. In addition, standard cumulative cost comparisons may be difficult to interpret when survival differs between groups, because patients who survive longer have more opportunity to accumulate healthcare costs.[15,16] Therefore, methods that account for differential survival are important when estimating the economic burden associated with ETF.[15,16]

This study evaluated the clinical and economic burden associated with ETF among adults with mNSCLC initiating first-line PD-1 inhibitor therapy. Using a 90-day landmark design, the study compared patients

with ETF and those without ETF with respect to overall survival, survival-adjusted cumulative healthcare costs, total PPPM costs, and healthcare utilization during follow-up. The primary objective was to estimate the difference in survival-adjusted cumulative healthcare costs between patients experiencing ETF and those who did not after the 90-day landmark.

2. Methods

2.1. Study Design and Data Source

We conducted a retrospective cohort study to assess healthcare costs and healthcare resource utilization in mNSCLC patients with ETF and no ETF in the United States between 2019 and 2023. This study used administrative claims data from the Merative™ MarketScan® Commercial Claims and Encounters Database and Medicare Supplemental Database. These databases include longitudinal enrollment, inpatient, outpatient, pharmacy, and paid claims information for commercially insured and Medicare Supplemental beneficiaries in the United States. Available data spanned January 1, 2019 through December 31, 2023. All-cause mortality was identified using the MarketScan mortality file.

2.2. Study Timeline

Eligible patients were identified based on first observed PD-1 inhibitor initiation between July 1, 2019 and October 2, 2023. The baseline period was defined as 180 days before the index date. The index date was the date of the first observed PD-1 inhibitor claim. The exposure assessment period extended from the index date through 90 days post-index. The landmark date was defined as 90 days after the index date. Follow-up began at the landmark date and continued until death, disenrollment, or December 31, 2023, whichever occurred first (Figure 1). A landmark design was used to ensure that ETF status was fully defined before follow-up outcomes were measured and to reduce the potential for immortal time bias.[17,18]

2.3. Patient Selection

The study population included adults aged 18 years or older with claims-based evidence of mNSCLC who initiated a first observed PD-1 inhibitor regimen, with no evidence of systemic anticancer therapy during the 180-day baseline period. PD-1 inhibitors of interest were pembrolizumab, nivolumab, and cemiplimab.

Evidence of NSCLC on or before the index date was defined as at least 1 inpatient claim with a diagnosis code for lung cancer or at least 2 outpatient claims with a diagnosis for lung cancer separated by at least 7 days. Metastatic disease was defined as at least 1 claim with a diagnosis code for secondary malignant neoplasm on or before the index date. Claims-based first observed PD-1 initiation was defined as at least 1 medical or pharmacy claim for pembrolizumab, nivolumab, or cemiplimab, with the first such claim establishing the index date (Supplemental Table 1).

Patients were required to have continuous medical and pharmacy enrollment during the 180-day baseline period and through the 90-day landmark. Patients were excluded if they had evidence of other primary malignancies during baseline, prior systemic anticancer therapy during baseline, or any gap in baseline enrollment. Patients who died on or before the 90-day landmark were excluded from comparative outcome analyses.

2.4. Early Treatment Failure Definition

ETF was defined during the 90-day exposure assessment period from day 0 through day 90 after the index date. Patients were classified as experiencing ETF if they met either of two criteria during the exposure assessment period: early discontinuation of the indexed PD-1 inhibitor or initiation of a new systemic anticancer therapy not included in the original treatment regimen. This claims-based ETF definition was informed by prior real-world NSCLC literature using early immunotherapy discontinuation as a marker of poor prognosis and economic burden, while adapting the operational definition to claims-based dosing intervals and treatment-switching patterns.[14]

The indexed PD-1 inhibitor was classified as pembrolizumab, nivolumab, or cemiplimab. Expected dosing intervals were defined as 14 days for nivolumab and 21 days for pembrolizumab and cemiplimab, based on labeled dosing schedules commonly used for these agents.[19-21]

PD-1 administrations were identified using medical claims corresponding to the index agent, and multiple claims on the same calendar date were treated as a single administration. For each administration, the expected next administration date was calculated as the administration date plus the expected dosing interval. A fixed 45-day grace period was selected to accommodate delayed administration, temporary treatment holds, scheduling variability, and longer real-world dosing intervals while preserving the ability to classify early discontinuation within the 90-day exposure assessment window. When added to the expected dosing interval, this allowed approximately 59 days for nivolumab and 66 days for pembrolizumab or cemiplimab before discontinuation classification. Discontinuation was defined as the absence of a subsequent indexed PD-1 administration on or before the discontinuation threshold, defined as the expected next administration date plus 45 days.

When the discontinuation threshold extended beyond the 90-day landmark, a limited look-ahead was used only to identify whether a subsequent indexed PD-1 administration occurred within the prespecified 45-day grace period. This look-ahead was used to avoid misclassifying patients as having discontinued therapy when a delayed dose occurred shortly after the landmark. Post-landmark claims were not used to define new systemic therapy initiation during the exposure window or to measure follow-up outcomes before the landmark.

Initiation of new systemic anticancer therapy was defined as the first observed claim for a systemic anticancer agent that was not part of the original treatment regimen and occurred after day 28 post-index and on or before day 90. The original treatment regimen was defined as all systemic anticancer therapy administered from 28 days before through 28 days after the index date. Under this definition, new systemic therapy could represent either a switch to a different systemic agent or the addition of a new systemic agent to ongoing PD-1 therapy. Patients meeting either ETF criterion during the exposure assessment period were classified as ETF. Patients who did not meet either criterion and remained alive and continuously enrolled through the landmark were classified as No ETF (Figure 2). Because ETF was defined over a 90-day assessment window, comparative analyses were restricted

to patients who survived and remained enrolled through the landmark date. Therefore, the analytic cohort represents 90-day survivors rather than the full population of PD-1 inhibitor initiators.

2.5. Outcomes

The primary outcome was survival-adjusted cumulative total healthcare cost during follow-up, estimated using the Kaplan-Meier sample average (KMSA) method. Cumulative costs were reported at 180 and 365 days after the landmark, with exploratory extension to 730 days. Total healthcare costs included all medical and pharmacy claims and were inflation-adjusted to 2025 U.S. dollars using the Medical Care Consumer Price Index.[22]

Secondary economic outcomes included total healthcare cost per patient per month (PPPM), calculated as total follow-up cost divided by follow-up time in months. Follow-up months were calculated as follow-up days divided by average days per month (30.4375 days). Secondary healthcare utilization outcomes included cumulative counts of inpatient admissions, inpatient days, emergency department visits, outpatient visits, and prescriptions during follow-up. Any hospitalization was defined as a binary indicator for one or more inpatient admissions during follow-up. All outcomes were measured during follow-up after the 90-day landmark.

2.6. Covariates

Baseline covariates were measured during the 180-day baseline period before the index date. Covariates included age, sex, geographic region, year of PD-1 initiation, indexed PD-1 inhibitor, treatment regimen type, modified noncancer Charlson Comorbidity Index, baseline healthcare utilization, and baseline healthcare costs (Table 1). Charlson Comorbidity Index was calculated using baseline diagnosis codes.[23,24] Treatment regimen type was defined using therapy received from 28 days before through 28 days after the index date and categorized as PD-1 monotherapy, PD-1 plus chemotherapy, PD-1 plus immunotherapy or biologic therapy, or PD-1 plus combination chemotherapy and immunotherapy or biologic therapy. Baseline cost variables were inflation-adjusted to 2025 U.S. dollars.

2.7. Statistical Analysis

Propensity score overlap weighting was used to improve baseline comparability between ETF and No ETF. Propensity scores were estimated using logistic regression with ETF status as the dependent variable and the following baseline covariates as predictors: age, sex, geographic region, index year, indexed PD-1 inhibitor, treatment regimen type, modified noncancer Charlson Comorbidity Index, baseline outpatient visits, baseline ED visits, baseline inpatient admissions, baseline prescriptions, baseline total healthcare costs, baseline medical costs, and baseline pharmacy costs. Overlap weights were calculated as 1 – e(X) for patients with ETF and e(X) for patients with No ETF, where e(X) was the estimated propensity score.[25,26] Covariate balance before and after weighting was assessed using standardized mean differences, with values below 0.10 considered acceptable.[27] Effective sample size and propensity score distributions were also examined.

For regression-based outcomes, the primary analytic approach combined overlap weighting with direct covariate adjustment. Overall survival was evaluated using an overlap-weighted, covariate-adjusted Cox proportional hazards model. Total PPPM cost was analyzed using an overlap-weighted, covariate-adjusted generalized linear model with Gamma distribution and log link. Count utilization outcomes were analyzed as rates using overlap-weighted, covariate-adjusted negative binomial regression models with follow-up months included as an offset. Any hospitalization was analyzed separately using an overlap-weighted, covariate-adjusted logistic regression model because it was a binary indicator of one or more inpatient admissions during follow-up. For regression-based outcomes, adjusted group-specific estimates and between-group differences were derived using recycled predictions where applicable.

Survival-adjusted cumulative costs were estimated using overlap-weighted KMSA methods. Follow-up was partitioned into fixed 30-day intervals beginning at the landmark date. Costs were assigned to the interval in which they were observed, and no proration of partial intervals was performed. Survival probabilities were estimated using overlap-weighted Kaplan-Meier estimators. Cumulative costs were calculated as the sum across intervals of the survival probability at the start of each interval multiplied by the weighted mean cost among patients alive and under observation during that interval.[15,16]

For cumulative cost, PPPM cost, and utilization outcomes, uncertainty was estimated using nonparametric bootstrap resampling with 1,000 replications. Confidence intervals were based on the 2.5th and 97.5th percentiles of the bootstrap distribution. A fixed seed of 12345 was used for reproducibility.

2.8. Sensitivity and Exploratory Analyses

Sensitivity analyses included unweighted analyses, overlap-weighted analyses without additional covariate adjustment, and directly adjusted models without overlap weighting. Exploratory analyses extended KMSA estimates to 730 days, examined weighted mean 30-day interval cost trends, and summarized PPPM cost components, including medical, pharmacy, payer, and out-of-pocket costs.

3. Results

3.1. Baseline Characteristics

A total of 28,234 PD-1 inhibitor initiators were identified during the study period. After applying inclusion and exclusion criteria, 1,944 otherwise eligible patients remained before the landmark death exclusion. Of these, 71 patients (3.7%) died on or before the 90-day landmark and were excluded from comparative outcome analyses. The final analytic cohort included 1,873 patients at the 90-day landmark, with 720 patients classified as ETF and 1,153 patients classified as No ETF (Figure 3).

Before weighting, baseline differences were observed between groups, including indexed PD-1 inhibitor agent and selected baseline utilization and cost measures. After overlap weighting, all included baseline covariates achieved acceptable balance, with weighted standardized mean differences below 0.10. Effective sample sizes after weighting were approximately 1,085 for No ETF and 676 for ETF (Table 1).

3.2. Survival Outcomes

In weighted descriptive analyses, patients with ETF had shorter follow-up than patients without ETF, with weighted mean follow-up of 233 days versus 371 days, respectively. Weighted death risk was also higher in ETF than No ETF: 0.349 versus 0.240, respectively (Table 2).

In the overlap-weighted, covariate-adjusted Cox model, ETF was associated with worse overall survival compared with No ETF (HR: 2.17, 95% CI: 1.81, 2.60). Sensitivity analyses were directionally consistent, with HRs of 2.02 (95% CI: 1.69, 2.41) in the unweighted model, 2.19 (95% CI: 1.84, 2.61) in the overlap-weighted model, and 2.20 (95% CI: 1.82, 2.64) in the directly adjusted model.

3.3. Survival-Adjusted Cumulative Costs

Survival-adjusted cumulative total healthcare costs were higher in No ETF than ETF at all evaluated time points (Table 3; Figure 5). At 180 days after the landmark, cumulative costs were $155,476 in No ETF and $98,609 in ETF, yielding a between-group difference of -$56,867 (95% CI: -$67,185, -$46,457). At 365 days, cumulative costs were $278,151 in No ETF and $177,502 in ETF, yielding a between-group difference of -$100,649 (95% CI: -$120,309, -$81,361).

In the exploratory 730-day analysis, cumulative costs were $424,272 in No ETF and $268,619 in ETF, yielding a between-group difference of -$155,654 (95% CI: -$191,038, -$118,269) (Supplemental Figure 1). Unweighted cumulative cost estimates were directionally similar, with between-group differences of -$51,873, -$90,640, and -$135,952 at 180, 365, and 730 days, respectively.

3.4. PPPM Costs

Total PPPM cost was also lower in ETF than in No ETF in the primary overlap-weighted, covariate-adjusted model (Table 3). Estimated total PPPM cost was $25,734 in No ETF and $20,484 in ETF, corresponding to a between-group difference of -$5,250 (95% CI: -$8,335 to -$3,133). Sensitivity analyses were directionally similar, with incremental differences of -$1,925 in the unweighted analysis, -$2,182 in the overlap-weighted analysis, and -$4,744 in the directly adjusted analysis.

3.5. Healthcare Utilization Outcomes

ETF was associated with higher inpatient utilization during follow-up (Table 4). In the primary overlap-weighted, covariate-adjusted model, inpatient admissions were higher in ETF than No ETF, with an estimated 1.22 versus 0.853 admissions, respectively (RR, 1.42; 95% CI: 1.15, 1.77). Inpatient days were also higher in ETF than No ETF, with an estimated 11.4 versus 6.10 days, respectively (RR, 1.86; 95% CI: 1.35, 2.56).

Other utilization outcomes were not statistically different between groups. ED visits were 5.58 in ETF and 4.78 in No ETF (RR, 1.17; 95% CI: 0.827, 1.64), while outpatient visits were 47.3 and 48.2, respectively (RR, 0.982; 95% CI: 0.904, 1.07). Follow-up prescriptions were 37.2 in ETF and 38.9 in No ETF (RR, 0.955; 95% CI: 0.870, 1.05). The probability of any hospitalization, defined as one or more inpatient admissions during follow-up, was 0.423 in ETF and 0.455 in No ETF (OR, 0.873; 95% CI: 0.659, 1.16).

3.6. Exploratory Cost Analyses

Exploratory interval-level analyses showed higher weighted mean 30-day interval costs in No ETF across much of follow-up, including much of the first year after landmark (Supplemental Figure 2). PPPM component summaries showed higher medical and payer PPPM in No ETF, higher pharmacy PPPM in ETF, and similar out-of-pocket PPPM between groups (Supplemental Table 2).

4. Discussion

In this retrospective claims-based cohort study of adults with metastatic non-small cell lung cancer initiating first-line PD-1 inhibitor therapy, ETF was associated with substantially worse survival after the 90-day landmark. ETF was also associated with greater inpatient burden, including higher rates of inpatient admissions and inpatient days. In contrast, patients with No ETF accumulated higher survival-adjusted cumulative healthcare costs over follow-up, with differences observed at 180 and 365 days and persisting in the exploratory 730-day analysis.

These findings support the clinical relevance of ETF as a marker of an adverse early treatment trajectory. Patients who discontinue or change therapy soon after initiation may represent a poorer-prognosis subgroup, potentially reflecting rapid progression, treatment intolerance, lack of response, financial toxicity, access barriers, or other clinical and nonclinical factors not directly observable in claims data. This interpretation is consistent with prior real-world NSCLC evidence showing that early immunotherapy discontinuation is associated with worse outcomes and greater hospitalization-related burden.[14]

A central finding of this study is that worse clinical outcomes in the ETF group did not correspond to higher cumulative total cost over follow-up. Instead, survival-adjusted cumulative costs were higher in the

No ETF group. This pattern is plausible in the setting of differential survival, as patients without ETF survived longer and therefore had more time to remain under observation and continue accruing treatment and healthcare costs. Patients without ETF may also have been healthier or more able to continue receiving active treatment, which could have contributed to higher ongoing medical cost accumulation. Although the KMSA approach accounts for censoring and differential survival, higher survival in the No ETF group still reflects a larger proportion of patients remaining alive and at risk for cost accumulation over time.[15,16] Exploratory interval-level analyses further suggested that the No ETF group had higher mean 30-day interval costs across much of follow-up, particularly earlier in follow-up. Together, these findings suggest that the cumulative cost difference may reflect longer survival, greater ability to continue active treatment, and higher ongoing medical cost accumulation among patients in the No ETF group.

The PPPM results provide a complementary time-standardized perspective. In the primary overlap-weighted, covariate-adjusted model, total PPPM cost was lower in ETF than in No ETF. Exploratory component summaries suggested that this pattern was driven primarily by higher medical and payer spending in the No ETF group, whereas pharmacy PPPM was higher in the ETF group and out-of-pocket PPPM was similar between groups. One possible explanation is that infused oncology therapies and administration services can be captured in medical claims, so continued treatment among patients without ETF may have contributed to higher medical cost accumulation. These findings indicate that the economic burden of ETF is not captured by a single cost measure and that cumulative and time-standardized costs may lead to different interpretations when survival differs between groups.

The utilization findings were also informative. ETF was associated with higher inpatient admissions and inpatient days, despite smaller differences in ED visits, outpatient visits, and any hospitalization. Although ETF was not associated with a higher probability of having any hospitalization, ETF was associated with more inpatient admissions and more inpatient days. This suggests that inpatient burden in the ETF group may have reflected more frequent or longer hospital stays rather than a higher proportion of patients being hospitalized. Follow-up prescriptions were lower in ETF, although this difference was not statistically significant in the primary model.

Prior real-world NSCLC studies have described treatment patterns, treatment duration, discontinuation, survival, and costs associated with immunotherapies.[9-13] The current study builds on this literature by evaluating ETF as a claims-based exposure within a landmark design and by evaluating both cumulative and time-standardized costs. This approach helps contextualize economic burden when survival differs substantially between comparison groups.[15,16]

Methodologically, this study used overlap weighting to improve baseline comparability and covariate-adjusted regression models for survival, PPPM cost, and healthcare utilization outcomes. Across sensitivity analyses, the association between ETF and worse survival was stable, and the direction of the PPPM and utilization findings was also consistent. These patterns support the robustness of the main findings, although the magnitude of some cost estimates was more sensitive to analytic approach than the survival estimates.

This study has several strengths. It used a large longitudinal claims database, a clearly defined landmark design to reduce the potential for immortal time bias, and a prespecified claims-based ETF definition. The analysis incorporated overlap weighting to improve baseline comparability and used KMSA methods to account for differential survival in cumulative cost estimation. Exploratory interval-level and component-specific cost summaries also provided additional context for interpreting the economic findings.

Several limitations should be acknowledged. First, ETF was defined using claims-based treatment patterns and may not perfectly correspond to clinical progression or physician-assessed treatment failure. Discontinuation or treatment change may also reflect financial toxicity, access barriers, patient preference, toxicity management, or planned treatment holds. This may result in exposure misclassification if ETF captures nonclinical barriers rather than treatment failure alone. Second, claims data do not reliably capture detailed information on tumor characteristics, disease severity, performance status, biomarker status, rurality, transportation barriers, caregiver availability, ease of access to oncology care, or reasons for treatment discontinuation or switching. These unmeasured factors may influence both ETF and downstream survival, cost, and utilization outcomes, so residual confounding remains possible despite overlap weighting and covariate adjustment. Third, because treatment history was observable only during MarketScan enrollment, patients may have received cancer diagnosis or treatment before enrollment or

outside captured claims. Therefore, first-line PD-1 initiation should be interpreted as claims-based first observed PD-1 initiation rather than confirmed lifetime first-line therapy. Fourth, the study population was limited to commercially insured and Medicare Supplemental beneficiaries, which may limit generalizability to other populations.

The 90-day landmark design also has important implications for interpretation because patients were required to survive and remain enrolled through the landmark date. In the final stage of cohort construction, 71 of 1,944 otherwise eligible patients (3.7%) died on or before the landmark, leaving 1,873 patients for the comparative analyses. Thus, the death-based landmark exclusion was relatively small in this claims-defined cohort, but results should still be interpreted as applying to 90-day survivors rather than all patients initiating PD-1 inhibitor therapy. As a result, the comparative analyses may not capture the full burden associated with very early clinical decline or death after treatment initiation. Patients who died before the landmark were excluded because ETF status could not be fully classified under the treatment-pattern-based exposure definition used in this study. Future work could evaluate alternative composite definitions of ETF that incorporate early mortality within the assessment window.

Finally, later follow-up estimates are more affected by censoring and smaller numbers at risk, so the exploratory 730-day and later interval-level findings should be interpreted cautiously. The exploratory component-specific cost findings were descriptive and were not based on separate covariate-adjusted component-level outcome models. Therefore, these summaries should be interpreted as exploratory evidence about which cost categories may have contributed to the total PPPM difference rather than as definitive estimates of component-specific cost differences. Future work could evaluate component-specific costs using formal adjusted component-level models.

5. Conclusion

In conclusion, ETF after first-line PD-1 inhibitor therapy was associated with substantially worse survival and greater inpatient burden among patients with metastatic NSCLC. However, patients without ETF accumulated higher survival-adjusted cumulative healthcare costs over follow-up, which may reflect longer survival and higher ongoing medical cost accumulation. These findings highlight the importance of

evaluating both cumulative and time-standardized cost outcomes when comparing economic burden across groups with meaningful survival differences.

6. Tables

6.1. Table 1. Baseline Characteristics

Table 1. Baseline Characteristics by Early Treatment Failure Status
Panel A. Unweighted Cohort

Characteristic	No ETF (n=1,153)	ETF (n=720)	SMD
Demographics			
Age, mean (SD)	65.8 (10.2)	64.7 (10.9)	0.104
Female sex, n (%)	616 (53.4)	384 (53.3)	0.002
Geographic region, n (%)			0.100
Northeast	156 (13.5)	93 (12.9)	
North Central	470 (40.8)	266 (36.9)	
South	429 (37.2)	296 (41.1)	
West	97 (8.4)	63 (8.8)	
Unknown	1 (0.1)	2 (0.3)	
Clinical Characteristics			
Index PD-1 agent, n (%)			0.253
Cemiplimab	12 (1.0)	7 (1.0)	
Nivolumab	121 (10.5)	140 (19.4)	
Pembrolizumab	1,020 (88.5)	573 (79.6)	
Regimen type, n (%)			0.095
PD-1 plus chemotherapy	722 (62.6)	469 (65.1)	
PD-1 plus chemotherapy and immunotherapy/biologic	27 (2.3)	9 (1.2)	
PD-1 plus immunotherapy/biologic	52 (4.5)	35 (4.9)	
PD-1 monotherapy	352 (30.5)	207 (28.7)	
Modified noncancer CCI, mean (SD)	2.3 (3.3)	2.5 (3.4)	0.054
Healthcare Utilization			
Baseline outpatient visits, mean (SD)	23.5 (11.8)	24.2 (12.8)	0.058
Baseline ED visits, mean (SD)	2.8 (7.8)	3.1 (8.4)	0.039
Baseline inpatient admissions, mean (SD)	0.6 (0.8)	0.7 (0.9)	0.081
Baseline inpatient days, mean (SD)	2.9 (5.3)	3.4 (6.5)	0.085
Baseline prescriptions, mean (SD)	20.0 (13.8)	21.6 (14.9)	0.111
Cost characteristics			
Baseline total cost, mean (SD)	54,105.27 (53,749.79)	57,915.37 (59,558.78)	0.067
Baseline medical cost, mean (SD)	48,064.33 (49,376.27)	51,582.34 (56,907.94)	0.066
Baseline pharmacy cost, mean (SD)	6,040.94 (19,064.31)	6,333.02 (18,739.14)	0.015

Table 1. **Baseline Characteristics by Early Treatment Failure Status**
Panel B. **Weighted Cohort**

Characteristic	No ETF (weighted)	ETF (weighted)	SMD
Effective sample size	1,086	676	
Demographics			
Age, mean (SD)	65.3 (10.2)	65.3 (10.9)	<0.001
Female sex, n (%)	223.0 (53.5)	223.0 (53.5)	<0.001
Geographic region, n (%)			<0.001
Northeast	53.9 (12.9)	53.9 (12.9)	
North Central	161.7 (38.8)	161.7 (38.8)	
South	163.3 (39.2)	163.3 (39.2)	
West	37.0 (8.9)	37.0 (8.9)	
Unknown	0.7 (0.2)	0.7 (0.2)	
Index year, n (%)			0.075
2019	47.8 (11.5)	54.7 (13.1)	
2020	98.5 (23.6)	94.0 (22.6)	
2021	97.7 (23.5)	93.3 (22.4)	
2022	102.9 (24.7)	97.6 (23.4)	
2023	69.7 (16.7)	77.0 (18.5)	
Clinical Characteristics			
Index PD-1 agent, n (%)			<0.001
Cemiplimab	4.5 (1.1)	4.5 (1.1)	
Nivolumab	55.1 (13.2)	55.1 (13.2)	
Pembrolizumab	356.9 (85.7)	356.9 (85.7)	
Regimen type, n (%)			<0.001
PD-1 plus chemotherapy	265.6 (63.8)	265.6 (63.8)	
PD-1 plus chemotherapy and immunotherapy/biologic	6.4 (1.5)	6.4 (1.5)	
PD-1 plus immunotherapy/biologic	20.8 (5.0)	20.8 (5.0)	
PD-1 monotherapy	123.8 (29.7)	123.8 (29.7)	
Modified noncancer CCI, mean (SD)	2.47 (3.34)	2.47 (3.37)	<0.001
Baseline outpatient visits, mean (SD)	24.1 (12.3)	24.1 (12.4)	<0.001
Baseline ED visits, mean (SD)	2.9 (7.5)	2.9 (7.6)	<0.001
Healthcare Utilization			
Baseline inpatient admissions, mean (SD)	0.64 (0.81)	0.64 (0.84)	<0.001
Baseline inpatient days, mean (SD)	3.2 (5.7)	3.2 (6.1)	<0.001
Baseline prescriptions, mean (SD)	21.0 (14.7)	21.0 (14.4)	<0.001
Cost Characteristics			
Baseline total cost, mean (SD)	56,988.46 (56,817.38)	56,988.46 (59,780.00)	<0.001
Baseline medical cost, mean (SD)	50,700.60 (52,164.63)	50,700.60 (57,214.69)	<0.001
Baseline pharmacy cost, mean (SD)	6,287.86 (19,470.11)	6,287.86 (18,687.23)	<0.001

Abbreviations: CCI, Charlson Comorbidity Index; ED, emergency department; No ETF, no early treatment failure; ETF, early treatment failure; PD-1, programmed cell death protein 1; SMD, standardized mean difference.
Notes: Weighted estimates are overlap-weighted and therefore may not sum to integer counts.

6.2. Table 2. Survival Results

Table 2. Survival Results
Panel A. Weighted Descriptive Survival Summary

Outcome	No ETF	ETF
Weighted follow-up days	371	233
Weighted death risk	0.240	0.349

Panel B. Weighted Survival Model

Outcome	Effect Estimate	95% CI
Overall survival (ETF vs No ETF)	HR 2.17	1.81 to 2.60

Abbreviations: No ETF, no early treatment failure; ETF, early treatment failure.
Note. Hazard ratio is shown for ETF relative to No ETF. Weighted follow-up and weighted death risk are descriptive weighted estimates.

6.3. Table 3. Survival-Adjusted Cost Results

Table 3. Survival-Adjusted Cost Results

Outcome	No ETF	ETF	Effect Estimate	95% CI
KMSA cumulative cost at 180 days	$155,476	$98,609	-$56,867	-67,185 to -46,457
KMSA cumulative cost at 365 days	$278,151	$177,502	-$100,649	-120,309 to -81,361
KMSA cumulative cost at 730 days	$424,272	$268,619	-$155,654	-191,038 to -118,269
Total PPPM cost	$25,734	$20,484	-$5,250	-8,335 to -3,133

Abbreviations: KMSA, Kaplan-Meier sample average; PPPM, per patient per month; No ETF, no early treatment failure; ETF, early treatment failure.
Note. Costs are all-cause healthcare costs presented in 2025 U.S. dollars. KMSA estimates are survival-adjusted cumulative costs estimated using the Kaplan-Meier sample average method. Between-group differences are calculated as ETF minus No ETF. The 730-day estimate was exploratory.

6.4. Table 4. Healthcare Utilization

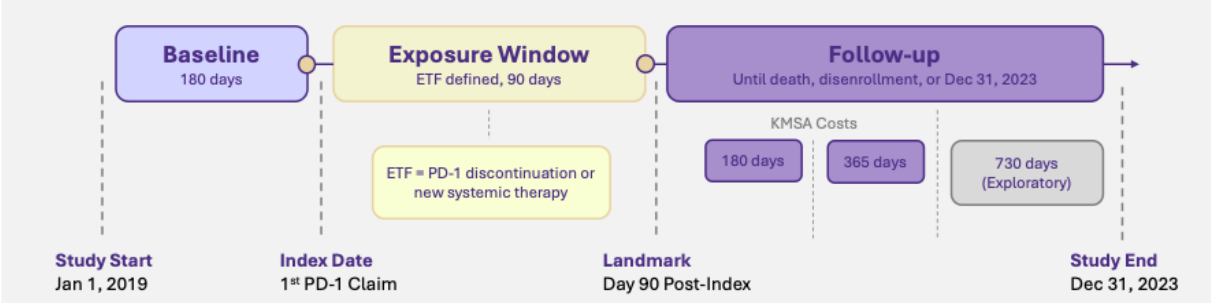
Table 4. **Healthcare Utilization**

Outcome	No ETF	ETF	Absolute Difference	Relative Effect	95% CI
Inpatient admissions	0.853	1.22	0.367	RR 1.42	1.15 to 1.77
Inpatient days	6.10	11.4	5.30	RR 1.86	1.35 to 2.56
ED visits	4.78	5.58	0.80	RR 1.17	0.827 to 1.64
Outpatient visits	48.2	47.3	-0.90	RR 0.982	0.904 to 1.07
Follow-up prescriptions	38.9	37.2	-1.70	RR 0.955	0.870 to 1.05
Any hospitalization	0.455	0.423	-0.032	OR 0.873	0.659 to 1.16

Abbreviations: No ETF, no early treatment failure; ETF, early treatment failure; ED, emergency department; RR, rate ratio; OR, odds ratio.
Note. Count outcomes were modeled using negative binomial regression with follow-up months as an offset and are summarized using adjusted mean counts, absolute differences, and rate ratios. Any hospitalization was defined as one or more inpatient admissions during follow-up and was modeled as a binary outcome using logistic regression and reported with an odds ratio. Absolute differences are calculated as ETF minus No ETF.

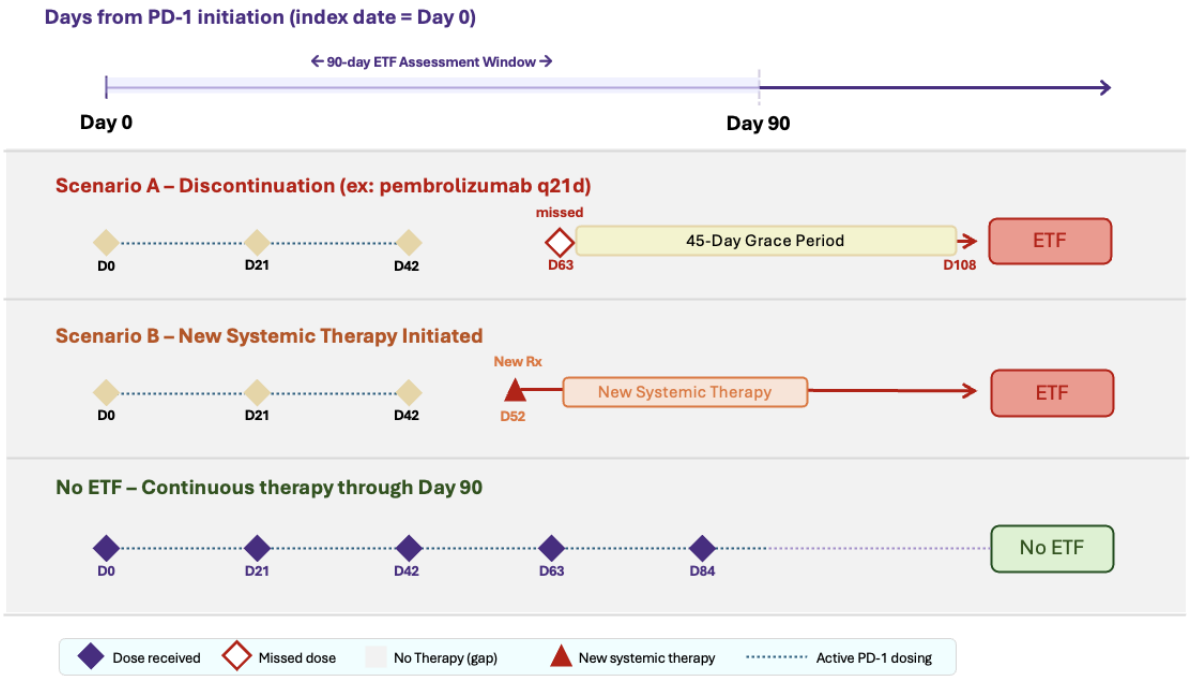
7. Figures

7.1. Figure 1. Study Timeline



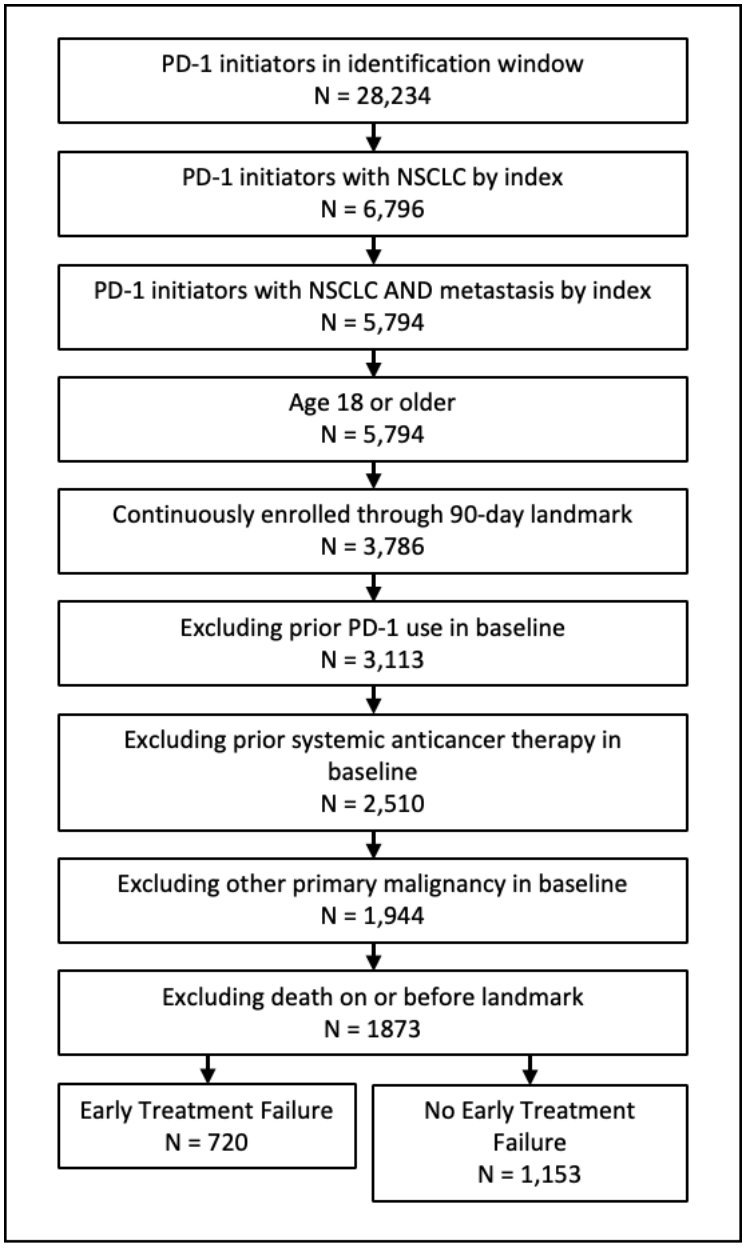
Note. Study design timeline showing the 180-day baseline period, 90-day exposure assessment window used to classify ETF, landmark date at day 90 post-index, and follow-up through death, disenrollment, or December 31, 2023. Survival-adjusted cumulative costs were evaluated at 180, 365, and exploratory 730 days after landmark.

7.2. Figure 2. ETF Definition



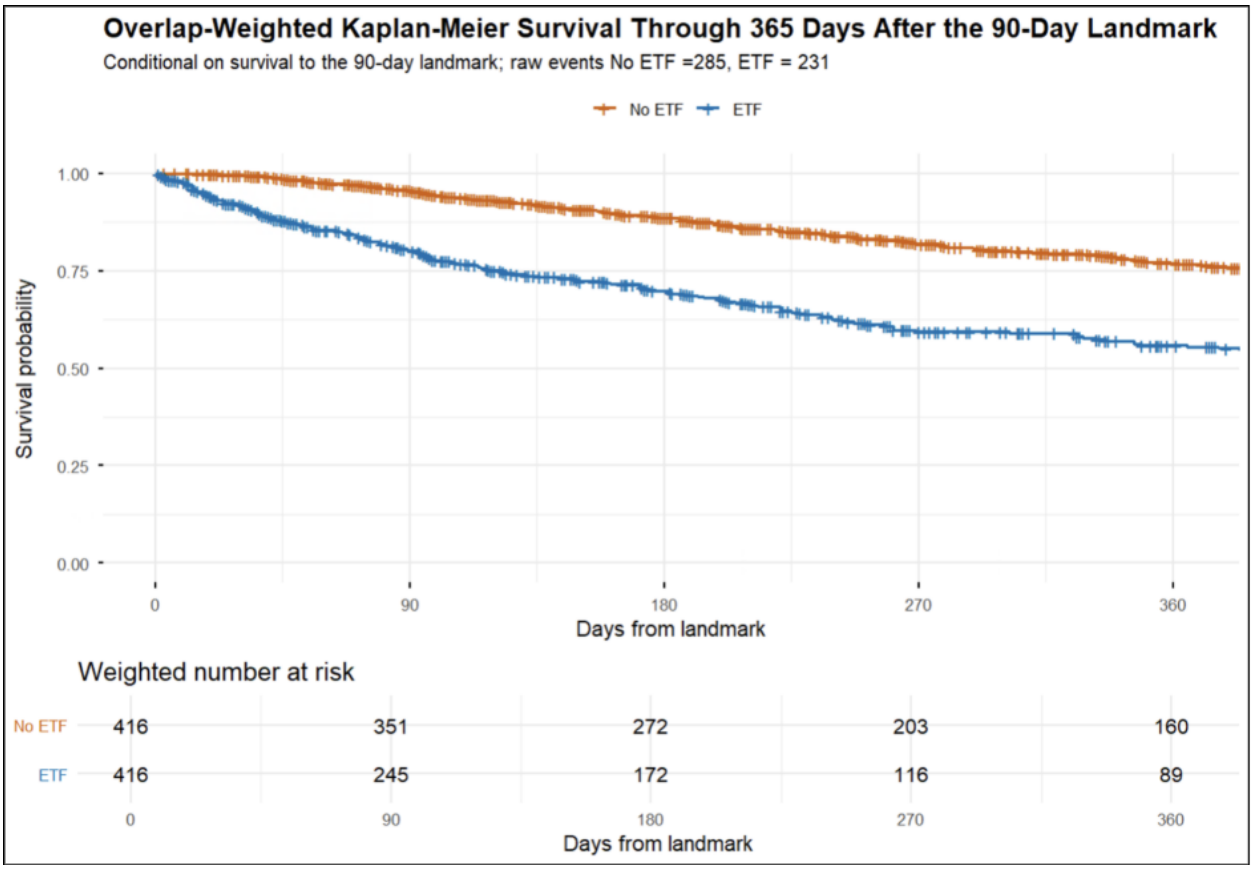
Note. ETF was classified during the 90-day post-index assessment window based on early discontinuation of the indexed PD-1 inhibitor, initiation of a new systemic anticancer therapy not included in the original regimen, or both. Patients remaining on therapy through day 90 without meeting either criterion were classified as No ETF.

7.3. Figure 3. Study Cohort Flow Diagram



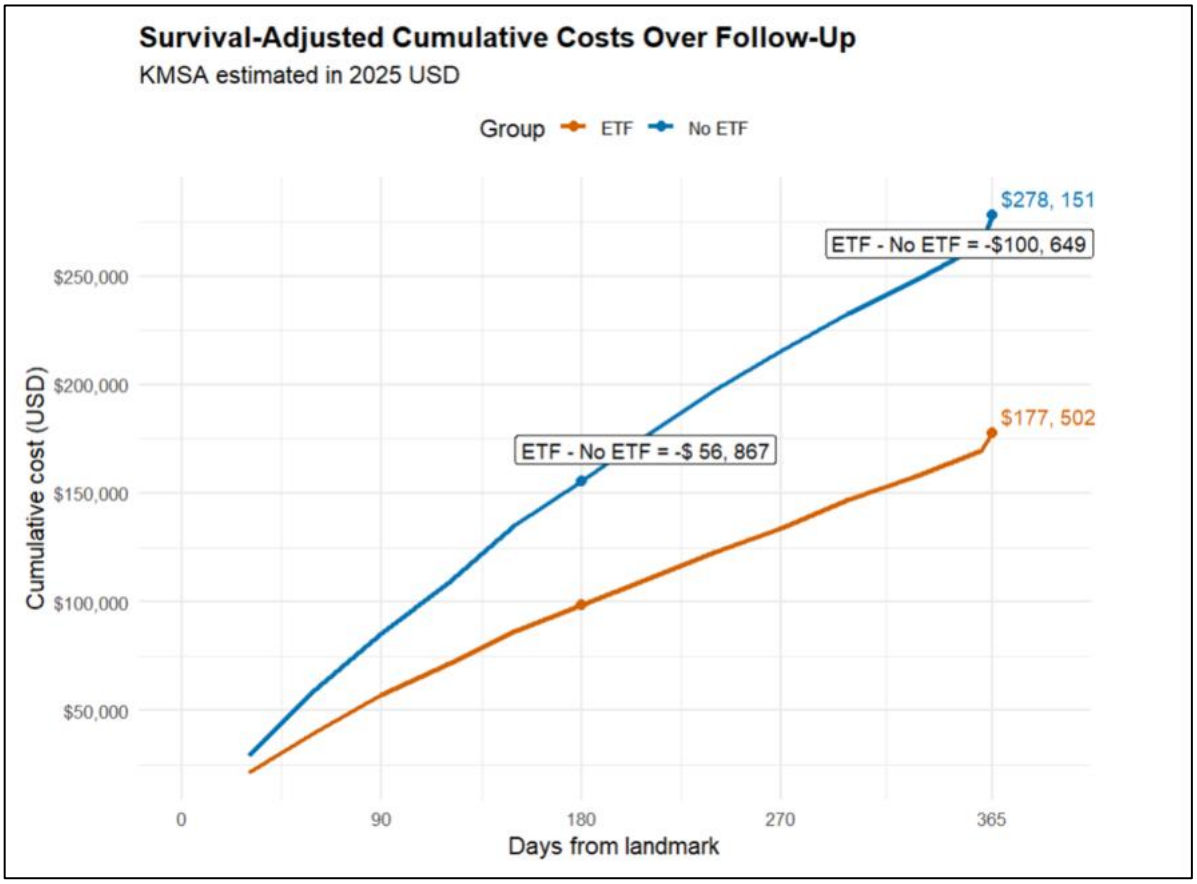
Note. Study cohort flow diagram showing sequential application of inclusion and exclusion criteria to the final analytic cohort. Among otherwise eligible patients before the landmark death exclusion, 71 of 1,944 patients (3.7%) died on or before the landmark and were excluded from comparative analyses.

7.4. Figure 4. Overlap-weighted Kaplan-Meier Curves



Abbreviations: ETF, early treatment failure; No ETF, no early treatment failure.
Note. Overlap-weighted Kaplan-Meier curves comparing overall survival between patients with ETF and no ETF after first-line PD-1-based therapy. ETF was associated with worse overall survival than no ETF (weighted Cox hazard ratio 2.17, 95% CI 1.81 to 2.60). Risk table values represent overlap-weighted pseudo-counts, and event counts are raw counts.

7.5. Figure 5. Survival-Adjusted Cumulative Healthcare Costs Over Follow-Up



Abbreviations: ETF, early treatment failure; No ETF, no early treatment failure.
Note. Survival-adjusted cumulative healthcare costs estimated using Kaplan-Meier sample average (KMSA) methods, reported in 2025 USD. Patients without ETF accumulated higher costs over follow-up than patients with ETF, with estimated cumulative cost differences of -$56,867 at 180 days and -$100,649 at 365 days (ETF minus No ETF).

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9. Supplemental Materials

9.1. Supplemental Table 1. Claims-based Code Lists and Operational Definitions Used for Cohort Identification and Treatment Classification

Supplemental Table 1.
Panel A. PD-1 inhibitors and systemic anticancer therapy HCPCS codes

Drug Class	Generic name	Brand name	HCPCS code	Use in study
PD-1 inhibitor	Pembrolizumab	Keytruda	J9271	Indexed PD-1 Agent
PD-1 inhibitor	Nivolumab	Opdivo	J9299	Indexed PD-1 Agent
PD-1 inhibitor	Cemiplimab-rwlc	Libtayo	J9119	Indexed PD-1 Agent
Platinum chemotherapy	Carboplatin	Paraplatin	J9045	Systemic therapy
Platinum chemotherapy	Cisplatin	Platinol	J9060	Systemic therapy
Platinum chemotherapy	Cisplatin	Platinol	J9062	Systemic therapy
Antimetabolite	Pemetrexed	Alimta	J9305	Systemic therapy
Antimetabolite	Gemcitabine	Gemzar	J9201	Systemic therapy
Taxane	Paclitaxel	Taxol	J9267	Systemic therapy
Taxane	Albumin-bound paclitaxel	Abraxane	J9264	Systemic therapy
CTLA-4 inhibitor	Ipilimumab	Yervoy	J9228	Systemic therapy
VEGF inhibitor	Bevacizumab	Avastin	J9035	Systemic therapy
VEGF inhibitor	Bevacizumab-awwb	Mvasi	Q5107	Systemic therapy
VEGF inhibitor	Bevacizumab-bvzr	Zirabev	Q5118	Systemic therapy
Taxane	Docetaxel	Taxotere	J9171	Systemic therapy
VEGF inhibitor	Ramucirumab	Cyramza	J9308	Systemic therapy
Vinca alkaloid	Vinorelbine	Navelbine	J9390	Systemic therapy
Topoisomerase inhibitor	Etoposide	—	J9181	Systemic therapy

Panel B. NSCLC and metastatic disease diagnosis codes

Condition	Coding system	Code(s)	Definition/Use
Primary NSCLC/ NSCLC site	ICD-10-CM	C340, C341, C342, C343, C348, C349	Used to identify lung cancer on or before index
Metastatic disease	ICD-10-CM	C77, C78, C79	Used to identify secondary malignant neoplasm on or before index

Note: Lung cancer was identified using at least 1 inpatient claim or at least 2 outpatient claims separated by at least 7 days. Metastatic disease required at least 1 claim with a secondary malignant neoplasm code on or before the index date.

Panel C. Other primary malignancy exclusion codes

Exclusion category	Coding system	Code Range	Use
Other primary malignancy	ICD-10-CM	C00-C96, excluding C34 and C77-C79	Used during the 180-day baseline period

Panel D. ETF treatment-classification parameters

Parameter	Value	Notes
Exposure assessment window	90 days post-index	Used to classify ETF
Pembrolizumab expected dosing	21 days	Agent-specific discontinuation
Nivolumab expected dosing	14 days	Agent-specific discontinuation
Cemiplimab expected dosing	21 days	Agent-specific discontinuation
Grace period	45 days	Added to expected next administration date
Original regimen window	28 days before through 28 days after index	Used to define original regimen
New systemic therapy	Any systemic anticancer therapy not included in the original regimen and first observed after day 28 post-index	Counted toward ETF classification
ETF definition	Early discontinuation of indexed PD-1 therapy, initiation of new systemic therapy, or both within 90 days	Primary exposure definition

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ETF, early treatment failure; HCPCS, Healthcare Common Procedure Coding System; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; VEGF, vascular endothelial growth factor.

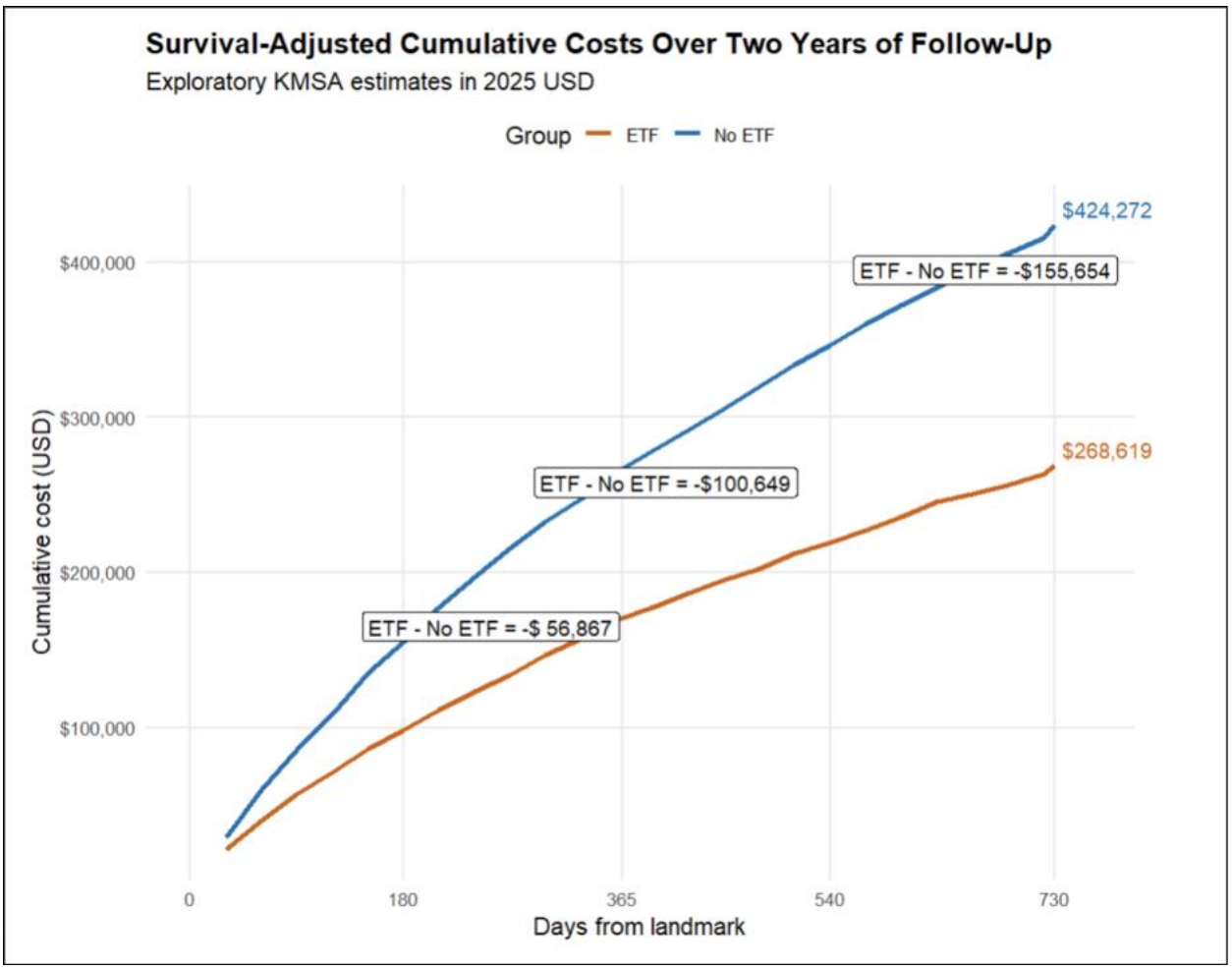
9.2. Supplemental Table 2. Exploratory PPPM Component Summaries by ETF Status

Supplemental Table 2.

Cost Component	ETF	No ETF	**Difference** (ETF – No ETF)
Total PPPM	$23,413	$25,595	-$2,182
Medical PPPM	$21,643	$24,707	-$3,064
Pharmacy PPPM	$1,770	$888	$882
Payer PPPM	$22,444	$23,868	-$1,424
Out-of-pocket PPPM	$264	$251	$13

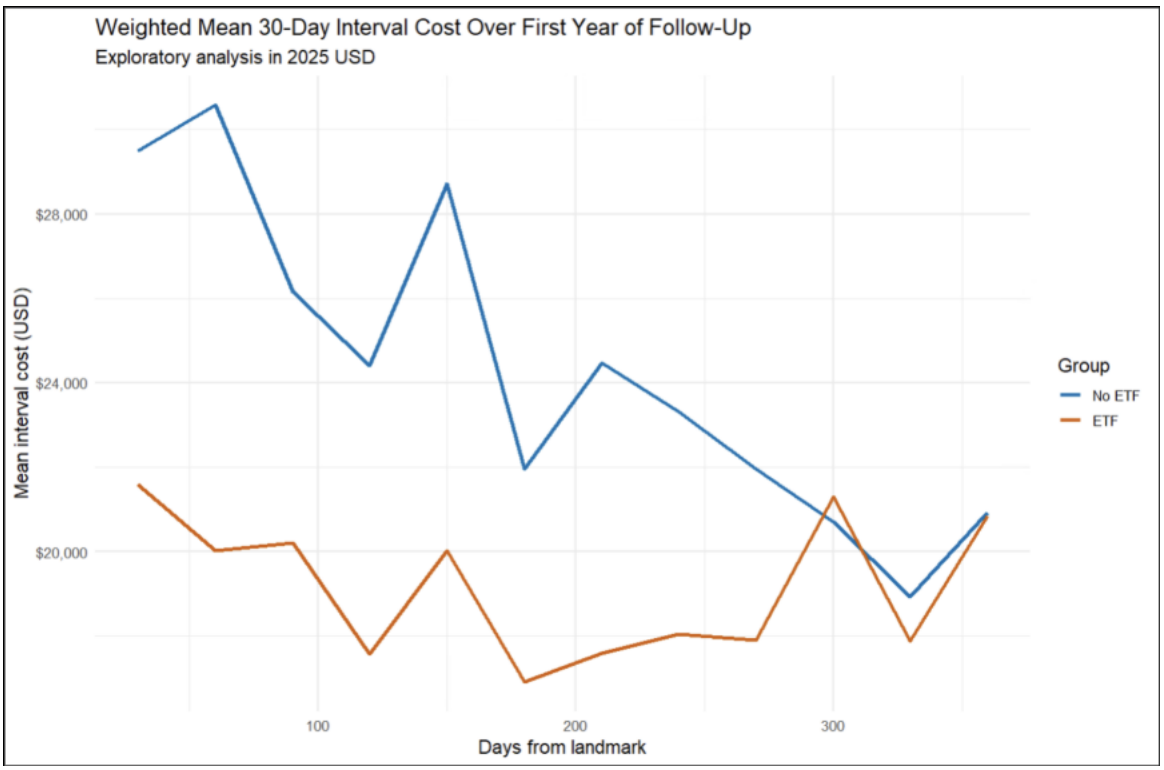
Abbreviations: PPPM, per patient per month; ETF, early treatment failure; No ETF, no early treatment failure.
Note. Values are descriptive exploratory summaries.

9.3. Supplemental Figure 1. Exploratory 730-Day Survival-Adjusted Cumulative Cost



Abbreviations: ETF, early treatment failure; No ETF, no early treatment failure.
Note. Overlap-weighted Kaplan-Meier sample average estimates of cumulative total healthcare cost through 730 days after the 90-day landmark.

9.4. Supplemental Figure 2. Weighted Mean 30-Day interval Cost Over Follow-up



Abbreviations: ETF, early treatment failure; No ETF, no early treatment failure.
Note. Exploratory weighted mean total healthcare cost within each 30-day interval after the landmark date.