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Original Article

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Multicenter Real-World Study on Effectiveness and Early Discontinuation Predictors in Patients With Non-small Cell Lung Cancer Receiving Nivolumab

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Abstract

Background: Real-world (RW) evidence on nivolumab in pretreated patients with non-small cell lung cancer (NSCLC) by matching data from administrative health flows (AHFs) and clinical records (CRs) may close the gap between pivotal trials and clinical practice.

Methods: This multicenter RW study aims at investigating median time to treatment discontinuation (mTTD), overall survival (mOS) of nivolumab in pretreated patients with NSCLC both from AHF and CR; clinical-pathological features predictive of early treatment discontinuation (etd), budget impact (BI), and cost-effectiveness analysis were investigated; mOS in patients receiving nivolumab and docetaxel was assessed.

Results: Overall, 237 patients with NSCLC treated with nivolumab were identified from AHFs; mTTD and mOS were 4.2 and 9.8 months, respectively; 141 (59%) received at least 6 treatment cycles, 96 (41%) received < 6 (etd). Median overall survival in patients with and without etd were 3.3 and 19.6 months, respectively ($P < .0001$). Higher number, longer duration, and higher cost of hospitalizations were observed in etd cases. Clinical records were available for 162 patients treated with nivolumab (cohort 1) and 83 with docetaxel (cohort 2). Median time to treatment discontinuation was 4.8 and 2.6 months, respectively ($P < .0001$); risk of death was significantly higher in cohort 2 or cohort 1 with etd compared with cohort 1 without etd ($P < .0001$). Predictors of etd were body mass index <25, Eastern Cooperative Oncology Group performance status >1, neutrophile-to-lymphocyte ratio >2.91, and concomitant treatment with antibiotics and glucocorticoids. The incremental cost-effectiveness ratio of nivolumab was 3323.64 euros ($3757.37) in all patients and 2805.75 euros ($3171.47) for patients without etd. Finally, the BI gap (real-theoretical) was 857 188 euros ($969 050.18).

Conclusion: We defined predictors and prognostic-economic impact of nivolumab in etd patients.

Key words: real-world evidence; cost-effectiveness; immune-checkpoint inhibitors; NSCLC

Implications for Practice

Patients with non-small cell lung cancer should be carefully selected for treatment with immune checkpont inhibitors on the basis of specific clinical-pathological features to avoid harmful treatments (early drug discontinuation and short survival) leading to a worst cost-effectiveness ratio.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases.[1] For many years, docetaxel was the best option after failure of the platinum-based chemotherapy in advanced (1) patients with NSCLC. In this setting, immune-checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1), and its ligand (PD-L1) drastically changed the treatment scenario.[2] Nivolumab, a fully human antibody directed against PD-1, was the first ICI approved by regulatory agencies for the treatment of patients with advanced NSCLC.[3]

The CheckMate-017 and CheckMate-057 phase III trials investigated nivolumab in pretreated PD-L1 unselected squamous cell carcinoma (SqCC) and non-squamous (non-sq) patients with NSCLC, respectively. In each case, nivolumab demonstrated a significant survival benefit with an improved safety profile over the standard of care, docetaxel. In these pivotal trials, median overall survival (mOS) with nivolumab was 9.2 months versus 6.0 months with docetaxel in SqCC (hazard ratio [HR] 0.59; 95% CI, 0.44-0.79; $P < .001$) and 12.2 months versus 9.4 months in non-sq patients with NSCLC (HR 0.73; 96% CI, 0.59-0.89; $P = .002$).[4,5]

Despite the survival advantages registered with nivolumab, progressive disease (PD) ratios were higher than docetaxel both in SqCC (41% vs. 35%) and non-Sq NSCLC (44% vs. 29%). Moreover, the Kaplan-Meier OS curve for nivolumab in non-sq patients shows a temporal drop below that for docetaxel during the first 6 months. These data suggest considerable heterogeneity within the non-sq histology and the presence of a subpopulation that does not benefit from nivolumab treatment, or even might be harmed.

A post hoc retrospective exploratory analysis of CheckMate-057 data reported a higher risk of death with nivolumab in the first 3 months compared with docetaxel. In this work, poor prognostic features and aggressive disease (less than 3 months since last treatment, PD as the best response to prior treatment, and an Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 1) combined with low PD-L1 expression on tumor cells, were reported as significantly associated with the risk of early death.[6]

The use of the anti-PD-1 agents with[7,8] or without[9] chemotherapy has currently been translated into the first-line setting, thus limiting the ratio of ICI-naïve patients eligible for second-line nivolumab. Nevertheless, the choice of the best treatment in pretreated patients and the potential benefit of a rechallenge with ICIs are still open issues.

In this scenario, the identification of patients who could still benefit from docetaxel over nivolumab is an unmet medical need and a matter of debate.

Several real-world (RW) studies collecting data from populations treated in clinical practice have been conducted to describe the outcome and identify predictive and prognostic biomarkers on a wide unselected population.[10-17] In RW studies, the OS of patients treated with nivolumab seems to be shorter than in clinical trials, probably due to less strict exclusion criteria.[13,14] A poor PS, the presence of *EGFR* mutations, liver and/or bone metastases, and limited benefit from previous chemotherapy treatment were described as associated with the worst outcome.[10,11,15,17]

Real-world studies have become an essential tool of evidence-based medicine since they provide the scientific community with data on effectiveness, safety, treatment sequence, disease progression management, guideline adherence, and costs, which are difficult to assess in randomized clinical trials (RCTs). In particular, a detailed budget impact (BI) analysis on a specific health system is only feasible in an RW setting focused on a defined region.[18-20] The RW data can be collected from various sources of electronic healthcare records, such as administrative health flows (AHFs), disease registries, databases from networks, and drug registries.

Administrative health flows data refer to anonymous information tracked by regional or national government for an administrative purpose (ie, hospital discharge forms, outpatient specialist' services, high-cost drug monitoring). While not originally intended for research, AHFs can be used by different providers as a source of information.

Administrative health flows capture all individuals belonging to a given target population (population-based) and may be considered as useful tools to map all patients treated with a specific drug, to collect more complete and reliable data.[21,22] Administrative health flows data, however, are available only for specific drugs (such high-cost monitored drugs) and often lack of relevant clinical information useful to explore predictive and prognostic factors in a selected population.

Differently, CRs data are information registered in hospital's documents for a single non-anonymous patient during the routine clinical activity and include several information on patient and disease features, diagnostic assessments and therapeutic pathways, drugs prescription and interruption, doses reduction, and reasons for these.

Thus, these 2 data sources may complement each other to provide different stakeholders with useful clinical and economical information on a diagnostic-therapeutic pathway of patients with cancer.

The Veneto Oncology Network (Rete Oncologica Veneta, ROV) was established in 2013 by the Regional Government. The aim was to develop common diagnostic-therapeutic pathways and to share treatment recommendations among the oncology units of the regional health system covering almost 5 million people. The Aderenza ai PDTA come espressione di appropriatezza, sostenibilità e qualità di cura nel tumore della mamnmella e del polmone: rilevabilità, riproducibilità ed efficienza degli indicatori (ARGO) study is a multicenter project promoted by the Veneto Oncology Network aimed at assessing adherence to the diagnostic-therapeutic pathways as a measure of appropriateness, sustainability, and quality of health care in breast and lung cancer. ARGO-Lung is a sub-study of the main project focusing on the outcome and BI analysis of patients with NSCLC treated with nivolumab as opposed to docetaxel in clinical practice.

Patients and Methods

Study Objectives

ARGO-Lung is an RW observational retrospective multicenter study, promoted by the Veneto Oncology Network, aiming at investigating the effectiveness of nivolumab in previously treated patients with NSCLC referred to oncology units in the Veneto Region in 2017.

This study's primary objectives were to investigate the median time to treatment discontinuation (mTTD) of nivolumab in an RW population and the mOS in patients with and without early treatment discontinuation (etd).

Secondarily, we aimed to investigate: the clinical-pathological features predictive of etd; the BI of patients with

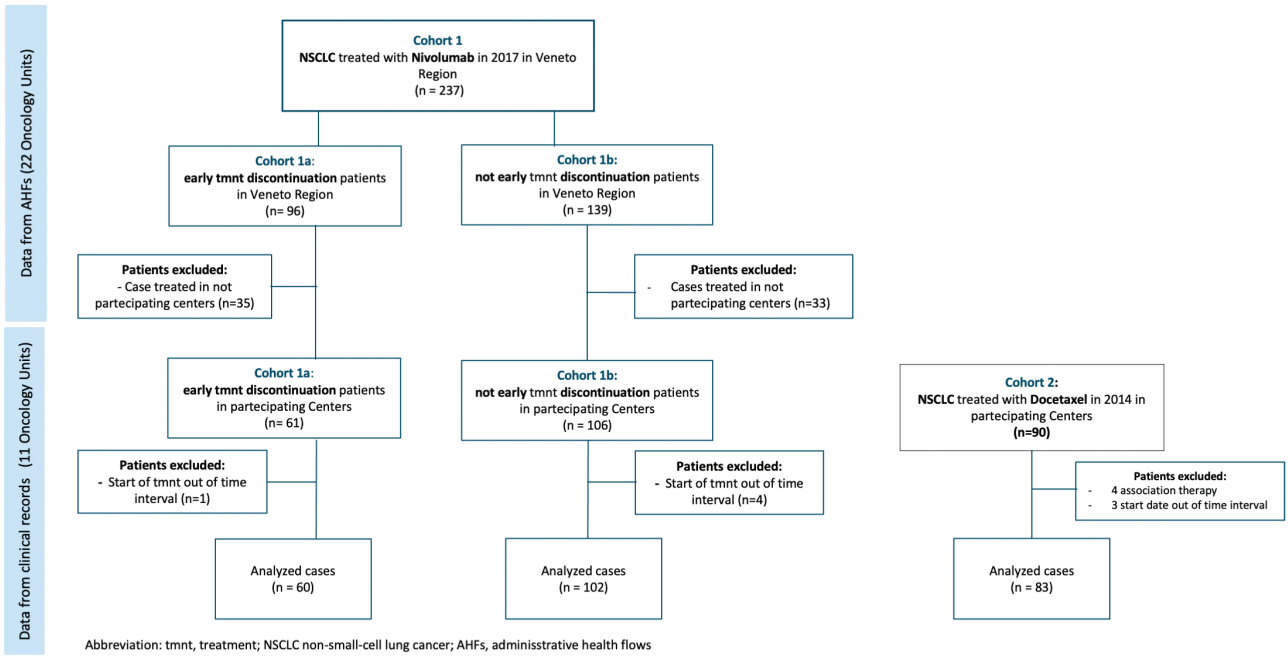

Figure 1. Study design. Administrative health flows were collected for 237 patients treated with nivolumab in 2017. Ninety-six patients experienced early treatment discontinuation (cohort 1a) and 139 continued treatment (cohort 1b), with the clinical-pathological data of 162 of these patients made available from clinical records. Moreover, the clinical records of 83 patients receiving docetaxel in the year 2014 were also collected for the case-control study (cohort 2).

and without etd, and the theoretical versus the real BI of patients treated with nivolumab.

Finally, we described the mOS and mTTD in 2 cohorts of patients who received nivolumab and docetaxel prior to the introduction of nivolumab in clinical practice, and the cost-effectiveness of the 2 treatments.

Study Design

As a first phase, data from AHFs were collected from different sources: drug prescriptions (DPs) issued by the National Health Service in the 2015-2020 period, both in hospital and in outpatient settings, and delivered by the Health Units and hospitals in the Veneto Region; hospital discharge records (HDR) between 2007 and 2017, including all hospitalizations (and their costs) in the region's public hospitals or with public reimbursement; and the regional health registry (RHR) updated at December 31, 2020.

Through AHFs, we are able to capture all patients receiving nivolumab in a selected time in the Veneto Region.

In all flows, a unique anonymized code is routinely assigned to each patient by the regional data warehouse administration, making it possible to link the records referring to the same patient while preventing her/his identification. AHF patient selection comprises 3 steps: (1) the selection of patients from DPs in conjunction with the first delivery of nivolumab in the year 2017; (2) matching selected patients with HDR; and (3) the selection of those with a diagnosis related to lung cancer, before or after the start of treatment; for patients without any HDR, the selection of those treated with another drug exclusively indicated for lung cancer (Pemetrexed, Vinorelbine, or Erlotinib), before or after treatment with Nivolumab. Drug prescriptions for Nivolumab were available until December 31, 2020, and the vital status was ascertained at the same date from RHR. First outcome analysis was performed on anonymous cases extracted from AHFs. Categorization of patients in 2 subpopulations (with and without etd), was performed to explore the difference in outcome (mOS) and in the number, duration, and cost of hospitalization in all patients receiving nivolumab in the Veneto region. As a second step, data from CRs of enrolled patients who received nivolumab between January 1, 2017, and December 31, 2017 (cohort 1) and docetaxel between January 1, 2014, and December 31, 2014 (cohort 2) at the participating centers were collected and analyzed to confirm data from AHFs by data from a real patient population. Clinical-pathological predictors of etd and survival were also identified. The study design is summarized in Fig. 1.

The clinical-pathological features collected were: gender, age, smoking status, body mass index (BMI), Charlson Comorbidity Index, ECOG PS, histologic tumor type, stage according to the 8th edition of the tumor, node, metastasis (TNM) Classification of Malignant Tumors, number, and localization of metastatic sites before investigating treatment and best response to previous treatments. The neutrophil-to-lymphocyte ratio (NLR) was registered. This ratio was calculated by dividing the absolute neutrophil count by the lymphocyte count on blood samples performed within 14 days prior to the start of treatment. The concomitant use of systemic corticosteroids and systemic antibiotics administered during treatment was also collected.

Radiological tumor assessment was performed through the chest and abdomen computerized tomography (CT) scan with iodine contrast or chest CT scan and abdominal ultrasound depending on the clinical practice of each oncological center. Treatment response was determined according to Response Evaluation Criteria in Solid Tumors (version 1.1).

The study was approved by the Veneto Oncology Network Ethical Committee (Internal Code IOV 2019/39/PU) and by each participating center's ethical committee; every patient

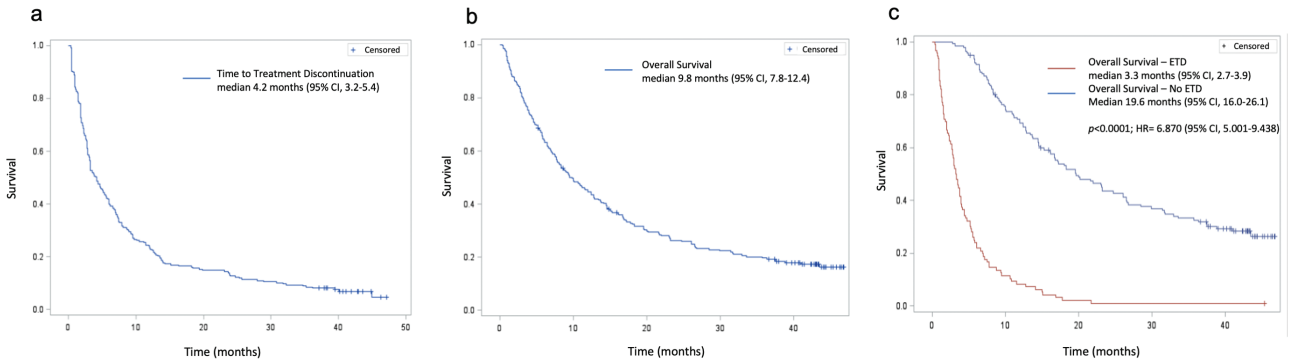

Figure 2. Time to treatment discontinuation (**A**) and overall survival (**B**) from the anonymous administrative health flows of patients receiving nivolumab in the year 2017; overall survival of patients receiving nivolumab with and without early treatment discontinuation (etd) (**C**).

who was still alive signed an informed consent form. The last follow-up was on December 31, 2020.

Time to treatment discontinuation was calculated as the difference between the last and first drug delivery, plus the interval between consecutive cycles (14 days in patients treated with nivolumab; 7 or 21 days in patients treated with weekly or 3-weekly docetaxel, respectively). In case the patient was dead or lost to follow-up between 2 cycles (14, 7, and 21 days respectively for nivolumab and weekly or 3-weekly docetaxel) the difference between the date of death or last follow-up and the last delivery, was added to the difference between the last and first drug delivery, to calculate TTD. For patients who were still alive at data cutoff, TTD is deemed to be censored if the last drug administration occurred less than 90 days before.

Early treatment discontinuation was defined as being < 6 nivolumab doses received, according to the median number of treatment cycles from pivotal trials.[4,5]

Overall survival was calculated as the difference between the date of death and the first drug administration. Patients who were still alive at the last follow-up date were censored.

BI Analysis

The analysis of the cost-effectiveness of the 2 study treatments (nivolumab and docetaxel) was performed using the incremental cost-effectiveness ratio (ICER), which represents the average incremental cost of the drugs associated with 1 additional unit of effectiveness. ICER is calculated as the ratio between the difference in costs and the difference in effectiveness, as follows:

$$\mathrm{ICER} = \frac{\mathrm{Costs}_{\mathrm{Nivo}} - \mathrm{Costs}_{\mathrm{Doce}}}{\mathrm{Effectiveness}_{\mathrm{Nivo}} - \mathrm{Effectiveness}_{\mathrm{Doce}}}$$

To evaluate the costs of drugs, ex-factory prices were considered, net of any reductions as provided for by law and negotiated discounts, but gross of 10% Value Added Tax. Alternatively, in the presence of specific contractual agreements (Managed Entry Agreements—MEA), costs are presented net of the discount deriving from the application of the MEA. Drug costs are calculated as the difference of each treatment cost calculated per month of treatment and multiplied for the mTTD, while effectiveness is represented by the difference of the 2 treatments' mOS in the real study population.

The BI analysis compares forecast costs (theoretical BI) based on data from pivotal trials with respect to the real impact on regional health expenditure (actual BI). Real costs are calculated by multiplying the monthly cost per patient by the number of treated patients and mTTD in the real study population. Theoretical costs are calculated by considering the median progression-free survival (PFS) as reported in pivotal studies.

Statistical Analysis

Statistical analysis was performed through SAS software, version 9.4. The Kaplan-Meier estimator was applied to evaluate mTTD and mOS. The log-rank test and the Cox proportional hazards model for univariate and multivariate analysis were applied to identify the impact of each clinical-pathological feature on the outcome.

The differences concerning number, duration, and costs of hospitalization were tested by the Wilcoxon rank-sum test.

Results

Treatment Outcome and Hospitalization of Patients Treated With Nivolumab From AHFs

Data from AHFs were collected from 237 patients who received nivolumab in 22 oncology units in the Veneto region during 2017. Median follow-up was 43 months (95% CI, 41-44), while median TTD was 4.2 months (95% CI, 3.20-5.40) (Fig. 2A). Early treatment discontinuation was observed in 96/237 patients (41%). Median OS in the overall population was 9.8 months (95% CI, 7.80-12.43) (Fig. 2B); mOS in patients with and without etd was 3.3 months (95% CI, 2.67-3.97) and 19.6 months (95% CI, 16.03-26.10), respectively ($P < .0001$; HR = 6.870; 95% CI, 5.001-9.438) (Fig. 2C).

Overall, the number, duration, and cost of hospitalization at different time points from the commencement of nivolumab were higher in patients with etd than in those without. Indeed, among patients with and without etd the number of hospitalizations was 60 (63%) versus 11 (8%) ($P < .0001$) at 3 months, 74 (77%) versus 22 (16%) ($P < .0001$) at 6, and 78 (81%) versus 59 (42%) ($P = .042$) at 12 months, respectively. The mean duration of hospitalization was 10.9, 14.3, and 16.1 days in patients with early discontinuation at 3, 6, and 12 months, compared with.08, 2.6, and 8 days respectively in patients without treatment discontinuation ($P < .0001$). Finally, the mean cost of hospitalization was Euro 3.745 (4.228 $) compared with Euro 351 (396 $) at 3 months ($P < .0001$), Euro 4.757 (5370 $) compared with Euro 905 (1022 $) at 6 months ($P < .0001$), and Euro 5.310 (5994 $) versus Euro 2.607 (2943 $) at 12 months ($P < .0001$), respectively, in patient subpopulations.

Table 1. Patients characteristics.

Variable	Cohort 1		Cohort 2		Total	
	N	%	N	%	N	%
Number of cases	162	66	83	34	245	100
Median survival (months)	12.00 (8.37-13.93)		6.17 (4.13-7.50)		8.07 (7.07-9.97)	
Gender						
Male	111	69	62	75	173	71
Female	51	31	21	25	72	29
Age, years, median (range)	67.3 (40-82)		67.0 (29-82)		67.2 (29-82)	
Histology						
Adenocarcinoma	102	63	55	66	157	64
Non-adenocarcinoma	60	37	28	34	88	36
Metastasis						
>2 metastatic sites	40	25	28	34	68	28
Liver metastasis	29	18	26	31	55	22
Brain metastasis	25	15	11	13	36	15
Smoking habits						
Smoker[a]	128	79	58	70	186	76
Nonsmoker	22	14	13	16	35	14
Missing	12	7	12	14	24	10
mCCI	5.09 (0-9)		6.04 (2-12)		5,41 (0-12)	
Median CCI (range)	6.00 (0-9)		6.00 (2-12)		6.00 (0-12)	
ECOG PS						
0-1	123	76	41	49	164	67
≥2	10	6	8	10	18	7
Missing	29	18	34	41	63	26
Subsequent treatment lines						
Yes	60	37	33	40	93	38
No	102	63	50	60	152	62

[a]Included both former and current smokers.
Abbreviations: CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status.

Treatment Outcome and Predictors in Patients Treated With Nivolumab and Docetaxel: Retrospective Data From CRs

Clinical-pathological data from 162 patients in cohort 1 and 83 patients in cohort 2 were collected from 11 participating oncology units. Patient characteristics were mainly overlapping between the 2 groups with the exception of the number (>2 metastatic sites, 25% versus 34%) and localization of metastatic sites (liver, 18% versus 31%), smoking status (smoker, 79% versus 70%), and PS ECOG (0-1, 76% versus 49%) (Table 1). As far as smoking status and PS ECOG variables are concerned, missing data are 7% versus 14% and 18% versus 41%, respectively in cohorts 1 and 2. Other differences could be related to different prescription time.

The median follow-up in the overall population was 43.4 months (95% CI, 42.53-44.53), 43.2 months in cohort 1 (95% CI, 40.2-44.37), and 73.6 months in cohort 2 (95% CI, 15.4-75.23).

The median TTD was 4.8 months (95% CI, 3.5-6.5) in cohort 1 and 2.6 months (95% CI, 2.1-2.93) in cohort 2 ($P < .0001$, HR 2.956; 95% CI, 2.176-4.016) (Fig. 3A).

Early treatment discontinuation in cohort 1 occurred in 60 patients (37%), while treatment was continued in 102 patients (63%). The main reasons for etds were disease progression or death in 43 patients (72%), toxicity in 8 patients (13%), physician's decision in 6 patients (10%), and patient refusal in 3 patients (5%).

Predictors of etd were a BMI lower than 25 ($P = .005$), an ECOG PS higher than 1 ($P = .013$), a NLR higher than 2.91 ($P = .009$), and concomitant treatment with antibiotics ($P = .0012$) and glucocorticoids ($P = .014$) (Table 2).

The mOS was 12 months (95% CI, 9.8-13.9) in cohort 1 and 6.2 months (95% CI, 4.1-7.5) in cohort 2 ($P < .0001$; HR 2.029, 95% CI, 1.527-2.696) (Fig. 3B). The risk of death was significantly higher in patients who received docetaxel (HR 3.431; 95% CI, 2.48-4.746) or nivolumab with etd (mOS 3.32 months; 95% CI, 2.3-4.4; HR 5.599; 95% CI, 3.907-8.025), compared to patients without early nivolumab discontinuation (median OS 19.53; 95% CI, 15.3-23.0; $P < .0001$) (Fig. 3C).

The negative prognostic impact of systemic treatment with docetaxel was confirmed ($P = .0002$) with the multivariate analysis. Other covariates which negatively impacted on OS were a poor ECOG PS ($P = .0042$), the presence of liver ($P = .039$), brain ($P = .0404$), adrenal ($P = .005$), and bone metastases ($P = .009$), disease progression to previous systemic treatment ($P = .016$), and no post-progression systemic treatment ($P = .0004$) (Table 3).

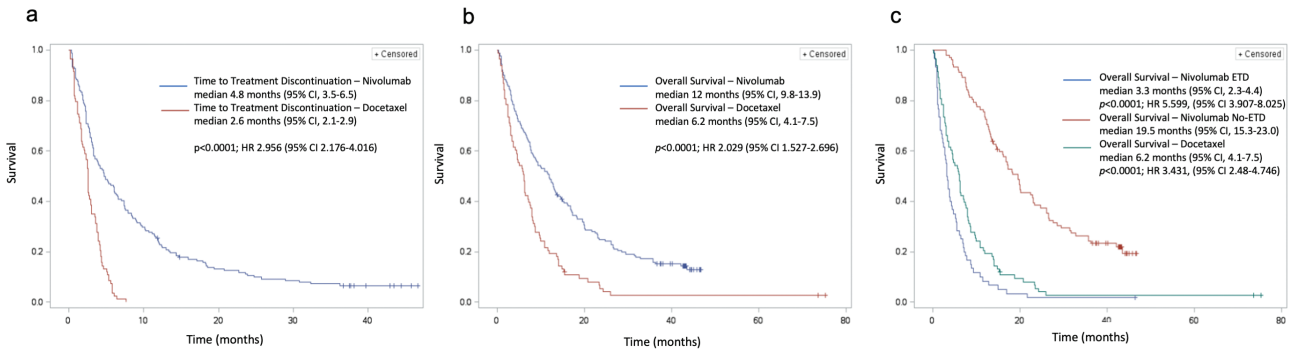

Figure 3. Time to treatment discontinuation (**A**) and overall survival (**B**) of patients receiving docetaxel versus nivolumab (**B**) with and without early treatment discontinuation (etd) (**C**) in the case-control study.

When stratified according to treatment groups, OS in patients receiving docetaxel was longer in males (P = .0096), nonsmokers (P = .0024) and patients who received further treatment lines (P < .0001); on the opposite way OS in patients treated with nivolumab was longer in people smoking cigarettes (P = .017), who had no disease progression to previous treatment lines (P = .0257) and without liver (P = .025), brain (P = .02), and adrenal metastases (.0008). Eastern Cooperative Oncology Group PS confirmed its prognostic role in both treatment groups (P = .03 in cohort 1; P = .05 in cohort 2) (data not shown).

BI and Cost-Effectiveness Analysis

The ICER/month of nivolumab was Euro 3323.64 ($3757.37) when all patients who received nivolumab were considered in the analysis. This decreased to Euro 2805.75 ($3171.47) when only those patients whose treatment was not discontinued early were considered (Supplementary Table 1). The ICER expressed by life years gained was Euro 39 883.68 ($44 934.15) in the intention to treat population, and Euros 36 474.75 ($41 093.55) when only patients without etd were considered.

The theoretical BI was calculated for the non-sq (N = 150) and sq (N =12) patients with NSCLC included in our study by considering the median PFS of 3.5 and 3.6 months in the randomized CheckMate-057 and -017 phase III trials, respectively. This stood at Euro 2.112.600 ($2399.597) in non-sq and Euro 173.831 ($196.516) in sq NSCLC, for an overall theoretical BI of Euro 2.286.431 ($2584.808). The actual BI calculated for the overall study population (N = 162), considering a median TTD of 4.83 months, was Euro 3.148.619 ($3559.511). Finally, the BI gap (actual-theoretical) was Euro 857.188 (969.050 $, Supplementary Table 2).

Discussion

The decision-making process in clinical practice is driven by available evidence on a selected treatment's effectiveness and safety data. Although they provide the highest level of evidence, RCTs are insufficient for this purpose due to the lack of external validity. Indeed, it has been estimated that only 2%-4% of patients with cancer are enrolled in RCTs, thus raising the issue of the representativeness of the population treated in clinical practice.[22-24]

In this scenario, RW studies on the outcome of ICI treatment by matching data from AHFs and CRs may close the gap between randomized clinical trials and real practice.[25]

In our study, data from AHFs made it possible to estimate the mTTD and mOS in the overall population receiving nivolumab in oncology units in the Veneto Region in 2017. Notably, survival outcomes from AHFs are comparable with those from medical records (MR), especially for patients with or without etd, so excluding selection bias and confirming the reliability and complementarity of these 2 data sources in outcome evaluation. The presence of a second group of patients treated with docetaxel before the advent of ICIs in clinical practice may be considered added value to the present work, since it tends to confirm the superiority of nivolumab compared to docetaxel in an RW population.

Survival results are in line with previous pivotal and RW studies, adding consistency to the effectiveness of nivolumab in pretreated patients. The pooled analysis of the CheckMate-017 and 057 trials showed an mOS of 11.1 months (95% CI, 9.2-13.1) with nivolumab, which seems comparable to our findings, despite differences in baseline clinical characteristics. Indeed, our RW population was composed of older patients with poorer PS and with a higher rate of brain metastasis compared to pivotal trials.[26] Furthermore, the majority of previous RW studies showed similar results[27-31] and a shorter OS was only reported in 2 RW populations of NSCLC treated with nivolumab (mOS 7.8 and 5.9 months). This is probably due to the high rate of patients with poor PS (23.6% and 46%, respectively versus 6% in our study).[11,12] Poor PS also appears to be consistently associated with worse OS in our work. Other negative prognostic factors were in line with previous RW studies[12,15,17,32-36] and, altogether, these data underline the careful case-by-case clinical evaluation in clinical practice prior to prescribing an ICI.

Only high-cost innovative drugs can currently be accurately tracked by AHFs, and clinical information in administrative datasets are limited and restricted to HDR.[22] A promising strategy to produce reliable evidence may be the matching of AHF data with data from MR.[37] In particular, AHFs data allowed us to observe a significantly higher rate of hospitalization and costs at different time points for patients with etd of nivolumab. This suggests that patients with etd need more intensive medical assistance because of poor clinical conditions or treatment-related safety issues.

This hypothesis is also supported by the characteristics of patients who experienced etd (low BMI, poor PS, high NLR, and concomitant use of antibiotics and glucocorticoids), which define a population requiring more supportive therapy. These findings are in line with literature data reporting the worst outcomes in these subgroups.[15,38-41]

Table 2. Predictors of early treatment discontinuation

Variable	Cohort 1a		Cohort 1b		Total, *N*	*P*
	N	%	*N*	%		
Number of cases	60	37	102	63	162	
Gender						.969
Male	41	68	70	69	111	
Female	19	32	32	31	51	
Age, years, median (range)	68.5 (40-81)		69.0 (41-82)			.1569
Age groups, years						.517
18-59	13	22	13	13	26	
60-64	10	16	16	16	26	
65-69	15	25	24	23	39	
70-74	9	15	23	23	32	
75	13	22	26	25	39	
BMI						**.0054**
≤25	24	40	40	39	64	
>25	17	28	49	48	66	
Missing	19	32	13	13	32	
Histology						.6805
Adenocarcinoma	39	65	63	62	102	
Non-adenocarcinoma	21	35	39	38	60	
Metastasis						
>2 metastatic sites						**.0504**
Yes	20	33	20	20	40	
No	40	67	82	80	122	
Liver metastasis						.1666
Yes	14	23	15	15	29	
No	46	77	87	85	133	
Brain metastasis						.092
Yes	13	22	12	12	25	
No	47	78	90	88	137	
Smoking habits						.4917
Smoker	47	78	81	79	128	
Nonsmoker	10	17	12	12	22	
Missing	3	5	9	9	12	
ECOG PS						**.0132**
0-1	41	68	82	80	123	
2	8	13	2	2	10	
Missing	11	18	18	18	29	
Neutrophil/lymphocyte ratio (median)	3,65 (0.26-20.86)		2,42(0.13-17.23)			**.0089**
≤2.91	17	28	57	56	74	**.0004**
>2.91	34	57	27	26	61	
Missing	9	15	18	18	27	
Concomitant treatment						
Antibiotics						**.0012**
Yes	30	50	46	45	76	
No	11	18	43	42	54	
Missing	19	32	13	13	32	
Glucocorticoids						**.0136**
Yes	24	40	50	49	74	
No	17	28	39	38	56	
Missing	19	32	13	13	32	

Cohort 1a = early treatment discontinuation (etd).
Cohort 1b = Not early treatment discontinuation (Not etd).
Values in bold are statistically significant.
Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status PS.

Table 3. Multivariate analysis: covariates impact on overall survival.

Variable	Reference category parameter		DF	Chi-square	Pr > Chi-square	Hazard ratio	95% hazard ratio confidence limits	
Cohort	1 Nivolumab	2 Docetaxel	1	14.195	**0.0002**	**1.888**	1.356	2.627
Gender	Male	Female	1	0.036	0.8505	1.033	0.737	1.448
Age	>75	18-59	1	1.247	0.2641	0.762	0.473	1.227
		60-64	1	0.008	0.9285	0.979	0.619	1.549
		65-69	1	2.102	0.1471	1.367	0.896	2.085
		70-74	1	2.261	0.1327	1.376	0.908	2.085
Smoking habits	Yes	Missing	1	1.367	0.2424	0.735	0.439	1.231
	Yes	No	1	0.059	0.8074	1.059	0.669	1.677
Histology	Adenocarcinoma	Non-adenocarcinoma	1	2.366	0.1240	1.291	0.932	1.787
CCI_GT_7	No	Yes	1	2.163	0.1413	1.494	0.875	2.55
ECOG PS 0-1	Yes	Missing	1	0.730	0.3929	1.159	0.826	1.626
	Yes	No	1	8.195	**0.0042**	**2.389**	1.316	4.338
Number of metastatic sites	≤2	>2	1	2.272	0.1318	0.677	0.408	1.124
Presence of lung metastasis	No	Yes	1	2.005	0.1568	1.263	0.914	1.745
Presence of liver metastasis	No	Yes	1	4.242	**0.0394**	**1.505**	1.02	2.221
Presence of brain metastasis	No	Yes	1	4.202	**0.0404**	**1.592**	1.021	2.482
Presence of pleural metastasis	No	Yes	1	3.529	0.0603	1.461	0.984	2.17
Presence of bone metastasis	No	Yes	1	6.823	**0.0090**	**1.640**	1.131	2.377
Presence of adrenal gland metastasis	No	Yes	1	7.759	**0.0053**	**1.780**	1.186	2.67
Presence of lymph node metastasis	No	Yes	1	3.567	0.0589	1.438	0.986	2.097
Presence of another metastasis	No	Yes	1	2.629	0.1049	1.536	0.914	2.581
Progression to previous treatment lines	Yes	No	1	5.827	**0.0158**	**0.653**	0.462	0.923
Further treatment	No	Yes	1	12.390	**0.0004**	**0.582**	0.431	0.787

Values in bold are statistically significant.
Abbreviations: CCI, Charlson Comorbidity Index; DF, degree of freedom; ECOG PS, Eastern Cooperative Oncology Group performance status PS.

An analysis of the causes of etd and the identification of its predictors through MR data, could avoid ineffective and potentially detrimental treatments and favor other systemic treatments and/or simultaneous care activation in this population. Worth noting is that patients with etd experienced a slightly lower OS than patients treated with docetaxel.

A proper selection of the population that could benefit from treatment also impacts cost-effectiveness. Indeed, a lower ICER was observed when only patients without etd were included in the analysis, and the ICER expressed as LGY in those patients may be considered as acceptable according to the threshold proposed by the Health Economics Italian Society.[42] Moreover, the BI gap (actual-theoretical, Euro 857.188; $969.050) reported in our study highlights that a cost estimation based on median PFS from pivotal trials does not reflect the real treatment duration and subsequent costs in clinical practice. Thus, this suggests that TTD from RW studies may be useful tools in the drug price negotiation process. This type of analysis is recommended to ensure the health system's sustainability.[43]

In the era of chemotherapy plus immunotherapy combination front-line therapy, single-agent immunotherapy in pretreated patients still has an important role in clinical practice and in the current treatment algorithms. First, not all patients are able to receive a triplet composed of platinum-based chemotherapy plus immunotherapy in the first-line setting, thus reserving anti-PD-1/PDL-1 as second-line treatment. Second, immunotherapy rechallenge is under investigation as a treatment option after initial discontinuation,[44-45] and will probably be the future cornerstone of combination regimens or control arms for clinical trials under development.

In conclusion, nivolumab confirmed its effectiveness in this RW population. However, an appropriate selection of patients who may benefit from a longer treatment duration and subsequently a better outcome (eg, good PS, smokers, low-tumor load) is mandatory to avoid ineffective treatment and improve the cost-effectiveness of innovative drugs in oncology. Clinical and economical information derived from the present work are assumed as important steps in the decision-making process of different stakeholders such as physicians, health manager, researchers, and industries which should work together to allow every patient to receive the appropriate treatment.

The integration of data from different sources, such as CRs and AHFs, may be considered as an innovative method to be applied soon to all innovative drugs in different settings, particularly to the current extensive use of ICIs in a first-line setting. Indeed, the latter is the object of a currently ongoing prospective evaluation by our regional network.

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Conflict of Interest

Valentina Guarneri: Eli Lilly, Novartis (Other—Speaker's Bureau), Eli Lilly, Novartis, Roche, MSD (SAB). The other authors indicated no financial relationships.

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Author Contributions

Conception/design: M.L., P.C., V.G., A.B. **Provision of study material/patients:** L.C., C.O., A.P., A.F., G.P., P.G., F.Z., A.B., D.B., M.M., G.A., P.M., L.B. **Collection and/or assembly of data:** G.C., G.S., V.M. **Data analysis and interpretation:** S.T., G.P., V.G., G.A., P.C. **Manuscript writing:** G.P., G.C., M.L., V.G. **Final approval of manuscript:** All authors

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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