Immune checkpoint inhibitors at any treatment line in advanced NSCLC: Real-world overall survival in a large Italian cohort

Anita Andreano [a], Walter Bergamaschi [b], Antonio Giampiero Russo [a,*]

[a] *Epidemiology Unit, Agency for Health Protection (ATS) of Milan, C.so Italia 52, 20122 Milano, Italy*
[b] *Directorate General, Agency for Health Protection (ATS) of Milan, C.so Italia 52, 20122 Milano, Italy*

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ABSTRACT

Objectives: To estimate the average treatment effect of immune checkpoint inhibitors in any line of treatment in a 2016–2018 population-based cohort of patients with advanced non-small-cell lung cancer (NSCLC).
Materials and methods: The cohort, and information on the tumor, were derived from the cancer registry of the Agency for Health Protection of Milan, Italy. Inclusion criteria were adult age, microscopically confirmed NSCLC, stage IIIB or IV at diagnosis, and having received at least one line of treatment. Treatment with all licensed anti PD-1/PD-L1 inhibitors was derived from inpatients and outpatients' pharmaceutical databases of the ATS and vital status at 31 December 2019 from the health registry office of the Lombardy region. We investigated, with a causal approach, the relationship between survival and anti PD-1/PD-L1 treatment at any line constructing a directed acyclic graph and fitting a Marginal Structural Cox Model (MSCM).
Results: Of 1673 subjects, 324 received anti PD-1/PD-L1 at any treatment line. Overall, one-year survival was 61.1% (95 %CI, 55.6–66.2%) in the group treated with anti PD-1/PD-L1 at any line and 31.1% (95 %CI, 28.6–33.5%) among not treated. One-year hazard ratio (HR) of death for not treated vs. treated was 2.15 (95 % CI, 1.91–2.41), decreasing to 1.23 (95 %CI, 1.03–1.46) at two years and reaching one in the third year.
Conclusion: In un unselected population-based cohort with advanced lung cancer, treatment with anti PD-1/PD-L1 at any line lowered the hazard of death up to two-years from date of diagnosis, confirming the efficacy of immunotherapy outside clinical trials.

1. Introduction

In Europe, lung cancer is the second most frequent oncological disease in males and the third in females, with 315,054 and 162,480 incident cases expected in 2020 [1]. The incidence, reflecting changes in smoking habit, has been constantly decreasing among men in the last three to four decades in most European countries and increasing among women in the same time interval, with only a few countries reaching a plateau in the last 10–5 years [2,3]. Lung cancer still ranks first among the causes of cancer death in men. Considering all Europe, in women it is a close second after breast cancer. However, in some countries such as the United Kingdom and Northern Europe it has become the first oncologic cause of death also in women [4,5]. The 5-year survival estimates in Europe in the period 2000–2007 were around 13%, ranging from 11% to 15% across regions. These low figures are primarily due to frequent advanced stage presentation, with about half of lung cancers still diagnosed as metastatic [6].

In recent years, new treatments have emerged and have demonstrated their efficacy in advanced and metastatic stages in several randomized clinical trials. On the one hand, treatments have been developed targeting oncogenic driver mutations, such as EGFR, ALK or RAS [7–10]. On the other hand, there has been a development of immune checkpoint inhibitors, in particular of the monoclonal antibodies anti PD-1 (receptor programmed cell death 1) and PD-L1 (programmed death ligand 1) [11]. The licensed drugs in Europe include atezolizumab, durvalumab, nivolumab, and pembrolizumab, with slightly different approved indications [12]. In the study period (2016–2018), the main use of immune checkpoint inhibitors was as second or third-line after failure of platinum-based chemotherapy and targeted therapy against oncogenic driver mutations, if present [13–15]. The European Medicines Agency (EMA) approved Nivolumab and Atezolizumab for this indication, and regardless of PD-L1 status, in 2015 and 2017. Pembrolizumab was approved for the same indication in 2016, if PD-L1 tumor proportion score (TPS) is equal or higher than 1% [12,16,17]. In

advanced-stage non-small-cell lung cancer (NSCLC), decision for first-line treatment depends on the presence of driver mutations for which targeted therapy is already available. However, they are cumulatively present only in about 25% of Caucasian patients with adenocarcinomas and 5% of squamous cell carcinomas [18,19]. In the remaining patients, treatment options are, depending mainly on stage and performance status (PS), concurrent radio-chemotherapy, platinum-based chemotherapy and immune checkpoint inhibitors [20]. Pembrolizumab, was approved in 2016 for first-line therapy alone if PD-L1 TPS is equal or greater than 50%, and in 2018 in combination with chemotherapy in NSCLC regardless of PD-L1 expression [21,22]. Atezolizumab was also approved for combined first-line treatment in 2019 [23]. A more recent indication, for which durvalumab was approved in 2018, is consolidation after platinum-based chemotherapy for tumors expressing PD-L1with a TPS $\geq$ 1% [24].

The longer overall survival for patients treated with immune checkpoint inhibitors compared to platinum-based chemotherapy, demonstrated in randomized trials as first or second-line treatment, needs however to be confirmed in real-world studies. At present, a number of studies from large multicentric hospital cohorts or derived from electronic clinical records have been published, confirming the effectiveness of immunotherapy for advanced lung cancer [25–34]. However, some of them are limited to patients treated in tertiary settings [25,30,31], almost all (Aarnink et al. [25] being the exception) explicitly selected the population on a performance status (PS) equal or lower than 2, and all cited studies investigated short-term survival. None of them, with the exception of Ruiz-Patiño et al. [27] contrasting with a historical cohort, compared results for patients treated with immunotherapy to similar subjects not treated with it. The aim of this study was to estimate, adopting a causal inference perspective with a counterfactual approach, the average treatment effect (ATE) of immune checkpoint inhibitors in any line of treatment in a 2016–2018 population-based cohort of patients with advanced NSCLC, with no selection on PS. The survival advantage was explored up to 3 years and a time-varying effect was estimated.

2. Material and methods

2.1. Study design and population

A retrospective cohort study was conducted on patients diagnosed with lung cancer (ICD-O-3[35], C33-C34) between 2016 and 2018 in the territory of the Agency for Health Protection (ATS) of Milan, Italy, and registered in its population cancer registry, member of the International Association of Cancer Registries (IACR) [36]. Inclusion criteria were adult age (over 18-year-old), microscopically confirmed malignant tumor with NSCLC histology, TNM 8th edition stage IIIB or IV at diagnosis, and having received at least one line of treatment [37]. No exclusions were made on the basis of PS [38]. Approval was obtained from the local ethics committee of Milan-Area 2.

2.2. Data sources and measures

Information on the tumor were derived from the ATS of Milan cancer registry, and included date of diagnosis (according to international cancer registration rules, the first available date among those of pathological examination or clinical diagnosis [39]), age, sex, TNM 8th edition pathological or, if missing, clinical stage at diagnosis [37], histologic type (adenocarcinomas, squamous cell carcinomas, other specified histology, and nonspecific morphologic ICD-O-3 code; code grouping is reported in Appendix Table A.1), presence of oncogenic driver mutations for which treatment is available (any EGFR, ALK, ROS-1 mutation vs. none), PD-L1 expression level (TPS dichotomized as $\geq$1% vs. <1%), smoking status and PS. Marital status, education level and the information used to define treatment with PD-L1, to calculate Charlson's comorbidity index [40] and, partially, PS came from electronic sources

of health data, including hospital discharge, prescription, outpatient diagnostic and therapeutic procedures databases of the Lombardy Regional Health System, available at the ATS level for assisted residents. For subjects with a missing value in the registry, PS was predicted as good (0–2) or poor (3–5) on the basis of a logistic regression model (including age, gender, stage, Charlson's index, chronic obstructive pulmonary disease (COPD), number of hospitalizations, outpatient visits and emergency access in the previous year, durable medical equipment and number of prescribed drugs) which was developed (AUC = 0.76) on 2444 and validated (AUC = 0.73) on 2444 different subjects with registered lung cancer and a PS value obtained from clinical records (incidence years: 2010 to 2018), in analogy with Salloum et al. [41] (details in Andreano et al. [42]). The socioeconomic deprivation index quintile was calculated, at the census section level, from data provided by the National Institute of Statistics (ISTAT) and normalized to the average of the ATS. It was then assigned to each patient based on the address of residence in the year of cancer diagnosis [43].

Deterministic record linkage on a unique key was used to match all information at patient level within the information system of the ATS, which houses the cancer registry and the administrative data, and was anonymized prior to analysis.

2.3. Treatment and outcome definitions

To define treatment with anti PD-1/PD-L1, inpatients and outpatients' pharmaceutical databases of the ATS were searched for the following ATC codes: L01XC17 (nivolumab), L01XC18 (pembrolizumab), L01XC28 (durvalumab), and L01XC32 (atezolizumab). With an intention to treat approach, even a single prescription was considered sufficient to consider the patient as treated with an anti PD-1/PD-L1. We derived the patient vital status from the health registry office of the Lombardy region [44]. Patients moving outside the Lombardy region were lost to follow-up and censored at the last available contact. Administrative censoring was set at 31 December 2019, avoiding interference from the COVID-19 epidemic. We investigated the relationship between survival and anti PD-1/PD-L1 treatment at any line, with a causal approach and in a counterfactual framework, in the population of microscopically confirmed, advanced stage, lung cancer patients that started at least one treatment line. We hypothesized a causal relationship model with a directed acyclic graph using Dagitty [45,46] (DAG, Appendix Figure B.1). After selecting a minimal sufficient adjustment set of variables, we created a pseudo-population by the use of (stabilized) inverse probability of treatment and censoring weights to mitigate the differences between patients treated and not treated with anti PD-1/PD-L1. The Marginal Structural Cox Model (MSCM) [47,48] enabled, in the pseudopopulation, the comparison of the hazard functions of patients treated with anti PD-1/PD-L1 at any line and of those having never being treated with anti PD-1/PD-L1.

2.4. Statistical analysis

Differences in distributions of the covariates between patients treated with anti PD-1/PD-L1 and those not were assessed using the χ^2 test for categorical and Mantel-Haenszel test for ordinal variables, and Wilcoxon Rank Sum test for age. Not declared or unknown categories were excluded from the test. Anti PD-1/PD-L1 at any line analysis was performed both from time of diagnosis, as defined, and from time of treatment (anti PD-1/PD-L1 administration if treated and first oncologic treatment if not). The Kaplan-Meier method was used to estimate unadjusted overall survival in the two treatment groups. Median follow-up time was estimated overall and for the two treatment groups, using the Kaplan-Meier estimate of potential follow-up (reverse Kaplan-Meier) [49]. The proportional hazards (PH) assumption appeared to be violated both examining the log minus log probability of survival plot and performing the test based on martingale residuals proposed by Lin [50](p < 0.0001). Consequently, we introduced a time-varying

Fig. 1. Selection of the cohort.
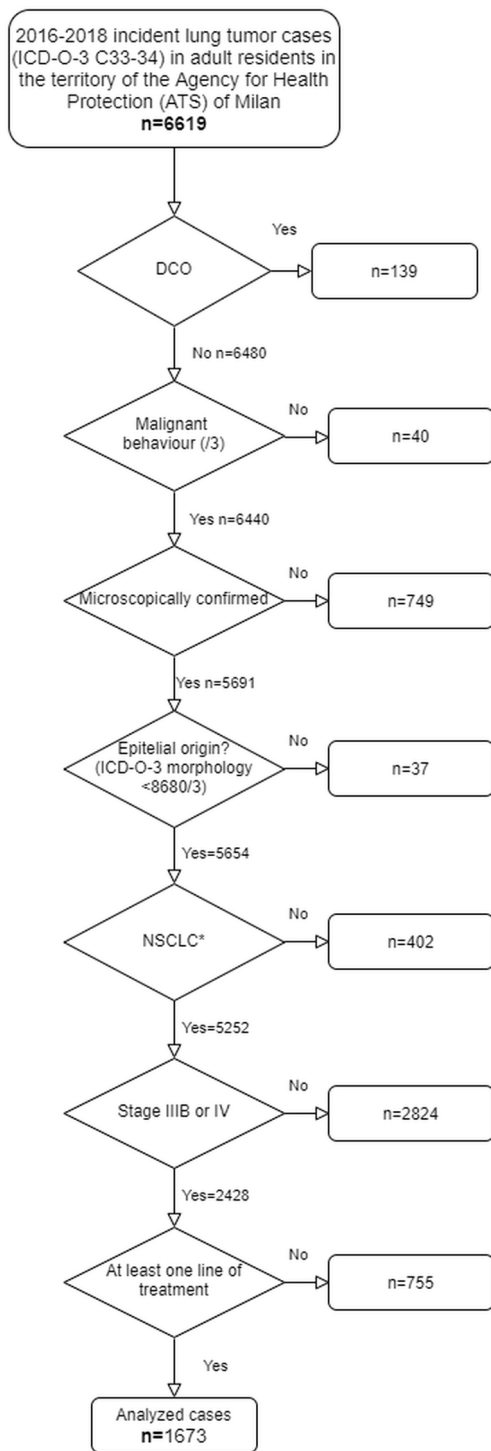
* ICD-O-3 morphology code not in 8041 8042 8043 8044 8045
DCO Death Certificate Only
ICD-O-3 International Classification of Diseases for Oncology

coefficient for treatment using the time^2 function, on the basis of non-parametric unadjusted hazards estimation and scaled Schoenfeld residuals.

Treatment weights were estimated through a multivariable logistic regression model on anti PD-1/PD-L1 treatment. Censoring weights were estimated through a multivariable logistic regression model on estimating the probability of being censored [51]. The DAG and the

Table 1

Characteristics of the 1673 adult subjects residing in the territory of the Agency for Health protection of Milan with microscopically confirmed NSCLC, incident in the period 2016–2018.

	Total		Treatment with PD-L1				
			Not treated with PD-L1 N = 1349		Treated with PD-L1 N = 324		p-value*
	N	%	N	%	N	%	
Gender							0.69
Female	578	35	463	34	115	35	
Male	1095	65	886	66	209	65	
Age classes							< 0.0001
≤ 50 years	75	4	60	4	15	5	
51–65	493	29	376	28	117	36	
66–80	944	56	764	57	180	56	
>80 years	161	10	149	11	12	4	
Education level							0.0008
Middle school or lower	1104	66	924	68	180	56	
High school	363	22	274	20	89	27	
College or higher	140	8	109	8	31	10	
Not delcleared	66	4	42	3	24	7	
Marital status							0.20
Not married	160	10	126	9	34	10	
Married	1159	69	939	70	220	68	
Divorced/Widower	313	19	255	19	58	18	
Not delcleared	41	2	29	2	12	4	
Deprivation index (census section)							0.39
I – less deprived	318	19	257	19	61	19	
II	301	18	234	17	67	21	
III	350	21	283	21	67	21	
IV	303	18	247	18	56	17	
V – most deprived	401	24	328	24	73	23	
Smoking status							0.38
Current smoker	287	17	227	17	60	19	
Ex-smoker	175	10	132	10	43	13	
Never smoker	127	8	93	7	34	10	
Unknown	1084	65	897	66	187	58	
Charlson's index							0.28
0	558	33	446	33	112	35	
1	550	33	439	33	111	34	
2	305	18	248	18	57	18	
3	145	9	120	9	25	8	
≥ 4	115	7	96	7	19	6	
Performance status (ECOG)							<0.0001
0–2	1397	84	1100	82	297	92	
3–5	276	16	249	18	27	8	
Histology							0.048
Adenocarcinoma	1068	64	871	65	197	61	
SCC	233	14	173	13	60	19	
Other, specified	88	5	75	6	13	4	
Nonspecific	284	17	230	17	54	17	
PD-L1 expression							<0.0001
Not tested**	1243	74	1076	80	167	52	
<1	184	11	144	11	40	12	
≥ 1	246	15	129	10	117	36	
Driver mutations (EGFR/ALK/ROS1)							<0.0001
Present	54	3	49	4	5	2	
Absent	653	39	491	36	162	50	
Not tested	966	58	809	60	157	48	
Stage							0.0014
IIIB	78	5	52	4	26	8	
IV	1595	95	1297	96	298	92	

* χ^2 test for categorical, Mantel-Haenszel test for ordinal and Wilcoxon Rank Sum test for age. Not declared or unknown categories excluded from test.

** For PD-L1 expression level, the tests performed outside the NHS could not be traced.

minimal sets of potential confounders included as covariates in each analysis are presented in Appendix Figure B.1 and Appendix Table A2. The functional form of the relationship between age and treatment probability was explored, and the linear function was selected on AIC basis over restricted cubic splines with 3 to 5 knots. Stabilized treatment weights (SW_T) were computed as $P[T=1]/P[T=1|\mathbf{L}]$ for treated and $P[T=0]/1-P[T=1|\mathbf{L}]$ for not treated subjects where T equals treatment and $\mathbf{L}$ is the vector of covariates. Stabilized censoring weights (SW_C) were calculated as $P[C=0/T]/P[C=0|T, \mathbf{L}]$, where C is the censoring indicator [52]. Treatment and censoring weights were then multiplied to obtain SW. The distribution of SW_C, SW_T, SW and trimmed weights (upper and lower 1%, SW_{TR}) is presented in Appendix Table A.3. In order to evaluate the balance induced by SW_T, the confounders between patients treated and not with ant PD-1/PD-L1 were compared by standardized differences of the mean/proportion [53] (Appendix Figure B.2). We then fitted the MSCMs, in which the contribution of patient i was weighted by SW or SW_{TR} [54–56]. Results of these models are presented as HRs of death for not treated vs. treated with anti PD-1/PD-L1, with their robust Wald 95% confidence intervals (CI). The time-varying HR is also presented graphically up to 36 months, when only 21 patients were left at risk in the anti PD-1/PD-L1 group. The analysis was repeated using time from PD-1/PD-L1 treatment. Sensitivity analyses were performed excluding first-line treated patients, analyzing each year of diagnosis separately and including only subjects with known performance status. All tests were two-sided and significance level was set at α = 0.05. Analyses were performed using SAS software (v9.4, SAS Institute Inc., Cary, NC, USA) and R (v4.0.3, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Description of the cohort

In the period 2016–2018 there were 6619 cases of lung tumor (ICD-O-3 topographic codes C33-34) in adults residing in the ATS of Milan.

After excluding DCO (Death Certificate only), nonmalignant, not microscopically confirmed, not epithelial and small cell lung cancer cases, the cohort included 5252 subjects (Fig. 1). After excluding TNM stages other than IIIB or IV at diagnosis (n = 2824) and never treated subjects (n = 755), the remaining 1673 cases were included in the present study. The characteristic of the entire cohort in terms of patients' demographics and health status, and tumor features are reported in Table 1. Overall, 19% (n = 324) of patients had been treated with anti PD-1/PD-L1 as any treatment line. Of those, 63 (19%) received immunotherapy as a first line treatment. Of the 324 treated patients, 3% of patients were treated with anti PD-1/PD-L1 in 2016, 34% in 2017, 42% in 2018 and 20% in 2019. The administered molecule was nivolumab in 47% (n = 153), pembrolizumab in 41% (n = 134), atezolizumab in 11% (n = 36) patients, and durvalumab in 1 (0.3%) case.

Patients treated with anti PD-1/PD-L1 were younger (median age 68

Table 2

Results from the anti PD-1/PD-L1 at any line of treatment analysis in advanced lung cancer patients (treated subjects n = 324, not treated n = 1,349) from time of diagnosis.

	Time (months)	HR	95% CI*	
Unadjusted confounded association				
PH Cox model		1.82	1.58	2.09
non-PH Cox model**	0	2.46	2.08	2.91
	12	1.92	1.66	2.22
	24	0.91	0.73	1.15
Average Treatment Effect from Marginal Structural Cox models				
PH Cox model, stabilized weights		1.99	1.58	2.50
PH Cox model, stabilized weights, second or further lines only***		2.03	1.66	2.50
Non-PH Cox model**, stabilized weights	0	2.58	2.26	2.95
	12	2.15	1.91	2.41
	24	1.23	1.03	1.46

*For Marginal Structural Cox models, Wald robust 95% confidence intervals are presented **quadratic function of time ***excluding n = 63 patients that received immunotherapy as first-line treatment.
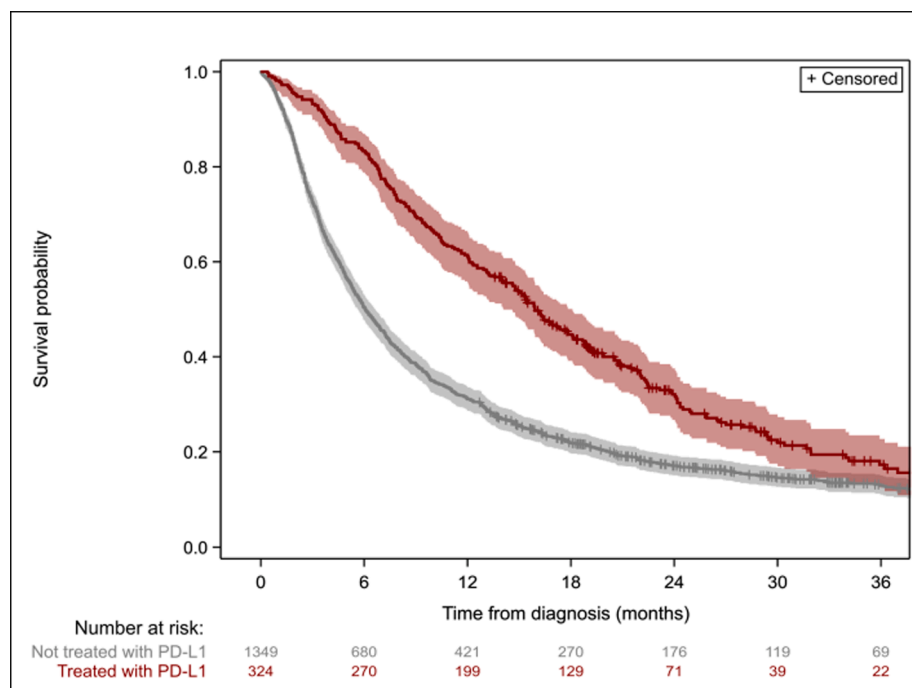PH: model assuming proportional hazards.

Fig. 2. Overall survival from diagnosis in patients with advanced lung cancer treated and not treated with anti PD-1/PD-L1 at any line.
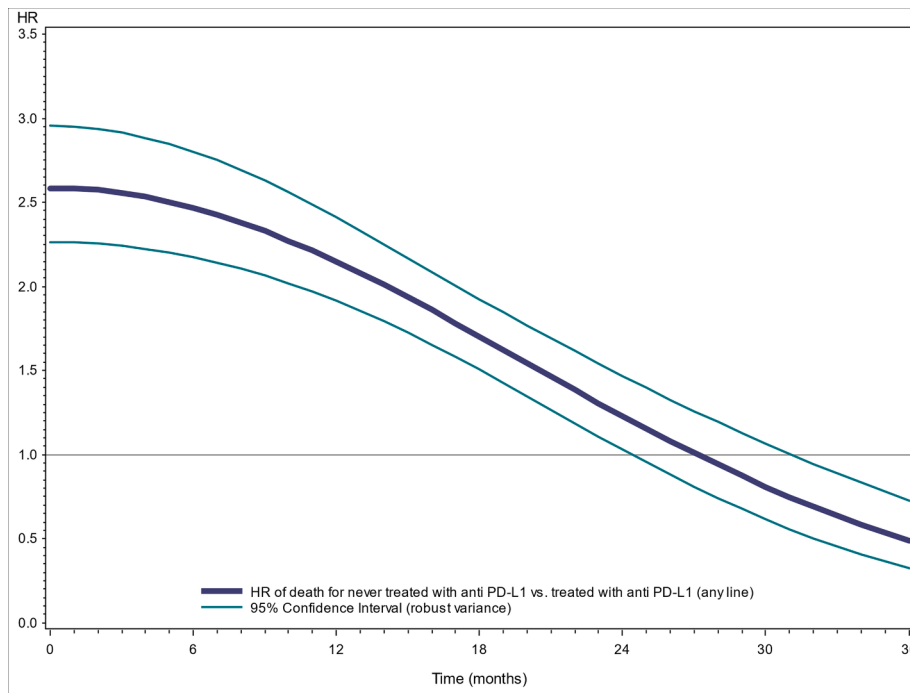
Fig. 3. Hazard ratio (HR) of death, over time from diagnosis, for subjects with advanced lung cancer not-treated vs. treated at any line with anti PD-1/PD-L1.

Table A1
Grouping of morphologic ICD-O-3 codes into histologic categories used in the analysis.

Histologic groups	Histology	Morphology ICD-O-3 codes
Adenocarcinoma	Adenocarcinoma	8140 8141 8143 8147 8200 8250 8251 8252 8253 8254 8255 8260 8310 8480 8481 8490 8551
		8550 8570 8571 8572 8573 8574 8575 8256 8257
	Carcinoid	8020 8050 8051 8010 8011 8240 8246 8249
	Large cell carcinomas	8012 8013 8014 8021 8023 8082 8030
Squamous cell carcinoma		8052 8070 8071 8072 8073 8074 8575 8076 8078 8084 8083 8123
Other, specified		8560 8033 8022 8032 8031 8980 8972 8430 8200 8562 8002 8015 8075 8123 8201 8211 8280 8503 8552 8256 8046
Nonspecific		8001 8003 8004

Table A2
Adjustment sets used to estimate inverse probability weights of treatment and censoring in the anti PD-1/PD-L1 at any line analysis.

Logistic model to estimate the probability of:	Included variables
Treatment	Gender, age, education, quintiles of deprivation index, CCI, PS, CCI*PS, histology, PD-L1 expression level, presence of oncogenic driver mutations, stage
Censoring	Anti PD-1/PD-L1 at any line, gender, age, education, quintiles of deprivation index, CCI, PS, CCI*PS, stage

CCI = Charlson comorbidity index, PS = performance status.

vs. 71 years), had a higher education level (56% middle school or lower vs. 68% in not treated), and a better performance status (92% with good PS vs. 82% among not treated). At univariate analysis, no differences between treatment groups were found for sex, marital status, deprivation index of the census section, smoking status (albeit available for 35%

Table A3
Distributions of treatment and censoring weights used in the anti PD-1/PD-L1 at any line analysis.

Stabilized Weights inverse probability of:	Mean	s.d.	Median	I q	III q	Min	Max
treatment	1.00	0.38	0.93	0.88	1.02	0.22	5.33
censoring	1.39	0.85	1.24	0.79	1.69	0.20	5.59
treatment and censoring	1.39	1.27	1.18	0.76	1.64	0.07	29.81
trimmed (1%) treatment and censoring	1.35	0.86	1.18	0.76	1.64	0.19	4.56

of patients only), Charlson's index and histological type.

After weighting, the standardized differences of the mean/proportion in confounders between subjects treated and not treated with anti PD-1/PD-L1 were all equal or lower than 0.1 (Appendix Figure B.2).

3.2. Effect of treatment with anti PD-1/PD-L1 at any-line

Median potential follow-up time was 33.1 months (95 %CI, 30.9–33.8 months), 30.8 months (95 %CI, 29.0–35.4 months) for treated and 33.3 months (95 %CI, 31.0–34.0) for not treated subjects. No patient emigrated outside the region during follow-up. Overall, 1 and 3-year survival were 36.9% (95 %CI, 34.6–39.2%) and 13.8% (95 %CI, 11.9–15.7%). One–year survival was 61.1% (95 %CI, 55.6–66.2%) in the treated group and 31.1% (95 %CI, 28.6–33.5%) in not treated. At 3-year, it was 16.5% (95 %CI, 11.7–21.9%) in the treated and 12.7% (95 %CI, 10.8–14.8%) in the not treated group (Fig. 2).

For the analysis from time of diagnosis, the unadjusted risk of death was about 80% higher for patients not treated compared to those treated with anti PD-1/PD-L1 at any line (HR, 1.82; 95% CI, 1.58–2.09, Table 2). The average treatment effect estimated from the Marginal Structural Cox model was similar using trimmed and not trimmed weights. With the latter model, the risk of death was two-fold higher for patients not treated compared to those treated with anti PD–1/PD–L1 at any line

Table A4
Sensitivity analyses for the anti PD-1/PD-L1 effectiveness in advanced lung cancer patients from time of diagnosis. Results from Average Treatment Effect from Marginal Structural Proportional hazard Cox models, using stabilized weights.

Sensitivity analyses	Incidence period	Line of treatment	N of patients	N of treated patients	HR	95% CI***	
Main analysis (for comparison)	2016–2018	any	1673	324	1.99	1.58	2.50
Excluding first-line treated patients	2016–2018	Second or further	1610	261	2.03	1.66	2.50
By year of diagnosis**	2016	Second or further*	553	78	1.96	1.53	2.51
	2017	any	611	108	1.69	1.33	2.15
	2018	any	508	137	1.97	1.56	2.49
Including patients with known Performance status only**	2016–2018	any	380	92	1.77	1.35	2.33

*the only first-line treated patient in 2016 was excluded. **interaction between Charlson comorbidity index and Performance status removed from models estimating the weights due to quasi-complete separation. ***Wald robust 95% confidence intervals

(HR, 1.99; 95% CI,1.58–2.50). Sensitivity analysis including only second or further lines of treatment showed a similar effect (HR, 2.03; 95 % 1.66–2.50), as well as analyses by year and excluding patients with model predicted PS (Appendix Table A.4). The model allowing the HR to vary over time, showed a decreasing protective effect of treatment with a HR starting from 2.58 and attaining 1.01 at 27 months (Fig. 3).

For the analysis from time of first anti PD-1/PD-L1, 1-year overall survival was 35.2% (95 %CI, 29.9–40.6) for treated and 26.1% (95 %CI, 23.8–28.5) for not treated subjects, and the unadjusted HR of death for not treated was 1.19 (95% CI, 1.05–1.35). Results from the proportional hazards MSCM showed a HR of 1.22; (95% CI, 0.98–1.53). The MSCM allowing the HR to vary over time, fitted due to violation of the PH assumption, showed an estimate of 1.42 (95 %CI, 1.26–1.60) at time 0, decreasing to 1.16 (95 %CI, 1.04–1.30) at 12 months and reaching 1.00 (95 %CI, 0.88–1.13) at 16 months.

4. Discussion

In this population-based cohort of patients with advanced lung cancer, treatment with anti PD-1/PD-L1 at any line resulted in a higher overall survival from date of diagnosis. The estimated marginal causal hazard of death for never treated patients was about 2.5 times higher compared to treated subjects for the first 6 months and then decreased reaching one between 24 and 30 months.

A study based on a retrospective cohort of 296 Hispanic patients from reference centers in four countries and analyzing immunotherapy at any line found a median overall survival 6 months longer for patients treated with anti PD-1/PD-L1 vs. a historical matched cohort of platinum-based chemotherapy treated patients (17.1 months vs. 11.3 months), measuring survival from date of immunotherapy administration [27]. A retrospective cohort study, based on electronic clinical records of 5,257 patients with advanced stage at presentation or recurring NSCLC treated with anti PD-1/PD–L1 at any line between the end of 2014 and the first half of 2017, found a median overall survival of 9.3 months for any-line treatment with anti PD-1/PD-L1 [29]. For comparison, in our cohort the same figure from date of first PD-1/PD-L1 treatment was 7 months (95 %CI, 5–9 months). However, the study of Khozin et al. included a larger proportion of stage III patients. Another study performing a retrospective analysis of electronic medical record data of 9656 subjects with metastatic NSCLC in the period 2013–2017, found that global overall survival from diagnosis was 11.7 months (7.4 months with 95 %CI 6.9–7.9 in our study). Median OS was 17.5 months with first-line immunotherapy vs. 15 months with other therapies [57]. We were not able to study PD-1/PD-L1 at first line, as this treatment modality actually started in mid-2017 and the number of patients receiving anti PD-1/PD-L1 at first line was too small (n = 63) to obtain a solid estimate from the MSCM model.

Our analysis, allowing the HR to vary over time, shows that the very large proportion of the survival benefit is seen in the first 1–2 years (one and two-year HR of 2.15 and 1.23 respectively), while in the third year the HR reaches one (Fig. 3). This may be partially related to the commonly practiced stop of immunotherapy after 2-years, in line with some clinical guidelines [58]. However, the reduction of the effect over

time is visible also during the second year. Conclusions cannot be drawn for first-line treatment, due to the small number of subjects preventing a separate analysis.

Differently from some of the real-world hospital cohort studies, we did not exclude patients based on PS, as there are evidences that even in patients with a PS higher than 2 benefits on survival may be obtained. Also, our study includes data from patients treated in all the hospitals of the ATS, not only the referral or academic hospitals.

This is an observational study, consequently prone to confounding by the biology of the cancer and patient characteristics. To account properly for that, we took a causal inference approach, hypothesizing a network of causal relationships visualized by the DAG. A minimum set of confounders was identified and accounted for in the analysis. However, residual potential confounding for variables not included in the DAG may still be present. Also, PS was not directly available from clinical records for about two-thirds of patients and was estimated with a predictive model using data available in administrative datasets, analogous to the one developed by Salloum et al. [41]. Likewise, education and comorbidities were derived from administrative datasets. For PD-L1 expression level, the tests performed outside the Regional Health Service and not included in the examined clinical records could not be traced. This reflects in 52% (n = 167) of patients treated with immunotherapy without having a PD-1 or PD-L1 status tested, a percentage that is probably falsely overestimated.

5. Conclusions

In un unselected population-based cohort with advanced lung cancer, treatment with anti PD-1/PD-L1 at any line lowered the hazard of death up to two-years from date of diagnosis, confirming the efficacy of immunotherapy outside clinical trials.

Data sharing statement

The dataset from this study is held securely at the ATS of Milan, Epidemiology Unit. Data sharing agreements prohibit the ATS of Milan from making the dataset publicly available. The full dataset creation plan and underlying analytic code are available from the authors upon request.

CRediT authorship contribution statement

Anita Andreano: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing - review & editing. **Walter Bergamaschi:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing - review & editing. **Antonio Giampiero Russo:** Conceptualization, Methodology, Supervision,

Project administration, Funding acquisition, Writing - review & editing.

Appendix A

See Tables A1–A4.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2021.06.019.

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