Clinical outcomes of NSCLC patients experiencing early immune-related adverse events to PD-1/PD-L1 checkpoint inhibitors leading to treatment discontinuation

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Introduction

In recent years, immunotherapy has dramatically changed the treatment landscape of lung cancer. Immune Checkpoints Inhibitors (ICIs) have significantly improved clinical outcomes of Non Small Cell Lung Cancer (NSCLC) patients without targetable driver mutations. PD-1/PD-L1 (programmed death-1/programmed death-ligand 1) checkpoint inhibitors, such as Pembrolizumab, Nivolumab and Atezolizumab, are currently used either as single or in combination with chemotherapy in first and/or subsequent lines of treatment for metastatic disease [1-3].

These treatments may be associated with peculiar inflammatory side effects, namely immune-related adverse events (irAEs). IrAEs spectrum is wide and somehow resembles autoimmune disorders. They can potentially involve every system-organ of the body, but the most frequently affected sites are the skin, the endocrine system and the and gastrointestinal tract. Even though less frequently, also lungs, liver, kidneys, musculoskeletal and nervous systems can be affected [4-6].

Overall, the reported incidence of any grade irAEs is up to 30%-40% with single-agent PD-1/PD-L1 inhibitors [7]. They are often mild to moderate and successfully managed with symptomatic therapy and corticosteroids. However, serious irAEs leading to treatment withdrawal are reported for approximately 5-10% of patients [7-8].

Although the exact pathophysiology behind irAEs remains partially unclear, it may be related to exuberant activation of the immune system and the consequent loss of immunologic homeostasis and tolerogenic mechanisms [9]. For this reason, irAEs are confirmed to be a surrogate predictive factor for increased antitumor immune response and clinical benefit with immunotherapy [10-14].

However, serious IrAEs leading to treatment discontinuation (LTD) can occur at any time, even after a single administration of ICIs. It is still unclear whether low exposure to immunotherapy in patients experiencing severe toxicity can maintain efficacy over time and finally improve prognosis. Our study aimed at evaluating ICIs efficacy and survival outcomes in advanced NSCLC patients who permanently discontinued immunotherapy after 1 or 2 administrations due to serious irAEs.

Materials and Methods

Study design

We conducted a real-world, multicenter, retrospective observational study aimed at evaluating clinical outcomes of stage IV NSCLC patients receiving single agent PD-1/PD-L1 checkpoint

inhibitors, who experienced early LTD irAEs. To properly evaluate our results, we used as a control group a cohort of NSCLC patients gathered from a large multicenter, observational study of advanced cancer patients receiving PD-1/PD-L1 checkpoint inhibitors in clinical practice aimed at investigating several clinical predictors of efficacy [15-22].

The LTD cohort included consecutive patients with confirmed diagnosis of stage IV NSCLC receiving single-agent PD-1/PD-L1 checkpoint inhibitors as 1st or subsequent line at the medical oncology departments of 13 Italian institutions (see Supplementary Table 1), between November 2015 and June 2019. The control cohort was gathered from a multicenter cross-malignancy cohort, finally including consecutive stage IV NSCLC patients receiving single-agent PD-1/PD-L1 checkpoint inhibitors as 1st or subsequent line at the medical oncology departments of 13 Italian institutions (see supplementary Table 1), between June 2014 and March 2020. Overall, 6 centers included patients in both the cohort. The measured clinical outcomes were objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). Patients were assessed with radiological imaging in clinical practice, with a frequency ranging from 8 to 12 weeks, radiologists' evaluation was based on RECIST criteria (v 1.1) [23]. ORR was defined as the percentage of patients experiencing an objective response (complete or partial response) as the best response to immunotherapy. Patients for whom a formal radiological assessment had not been performed at the data cut-off were not included in the ORR analysis. PFS was defined as the time from treatment initiation to disease progression or death, whichever occurred first. OS was defined as the time from treatment initiation to death. For PFS and OS, patients without events were considered censored at the time of the last follow-up. Data cut-off period was May 2020 for the control cohort.

We first compared some key baseline patients' characteristics, in order to evaluate whether some baseline features were more likely related to early LTD irAEs occurrence. The pre-planned covariates were: age (< 70 vs ≥ 70 years old) [24], sex (male vs female), Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) (0 vs 1 vs ≥ 2), burden of disease (number of metastatic sites ≤ 2 vs > 2), treatment line (first vs non-first). PD-L1 tumor expression was not used as a covariate, because it was not available for all the patients, however, we assumed that most of patients receiving first-line single agent PD-1 inhibitors had a PD-L1 expression $\geq 50\%$.

Considering the unbalanced sample sizes, after having explored clinical outcomes across the two whole populations, a random case-control matching was performed to ORR, PFS and OS between the two groups. All the cases (from the LTD cohort) were randomly paired to controls (from the control cohort) on the basis of sex (male, female), ECOG-PS (0, 1, 2), burden of disease (number of metastatic sites ≤ 2, > 2) and treatment line (first, non-first).

Immune-related adverse events

IrAEs were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE; version 4.0). Early LTD irAEs were defined as any irAEs which caused a permanent treatment interruption within the first two cycles.

IrAEs were categorized on the basis of the organ/system involved as follows: cutaneous irAEs, endocrine irAEs (including thyroid disorders), gastro-intestinal (GI) irAEs, hepatic irAEs, pulmonary irAEs, rheumatologic irAEs, neuro-muscular irAEs, and others irAEs (including asthenia) [25].

Statistical Analysis

Baseline patient characteristics were reported with descriptive statistics. $\chi 2$ test was used to compare baseline characteristics between the two cohorts. The Kaplan-Meier method was used to estimate median PFS and OS Median period of follow-up was calculated according to the reverse Kaplan-Meier method. After the random case-control matching, clinical outcomes of the two cohorts were compared with univariate analyses. Logistic regression was used for the univariate analysis of ORR and to compute the odds ratios (OR) for disease response with 95% confidence intervals (CI). Cox proportional hazards regression was used to estimate the hazard ratios (HR) for disease progression and death with 95% CIs. Considering the sample size of the control cohort a caliper width < 1.0 for the standard deviation was used for the random case-control matching [26]. All statistical analyses were performed using the MedCalc Statistical Software version 19.4.0 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020)

Results

Patients characteristics

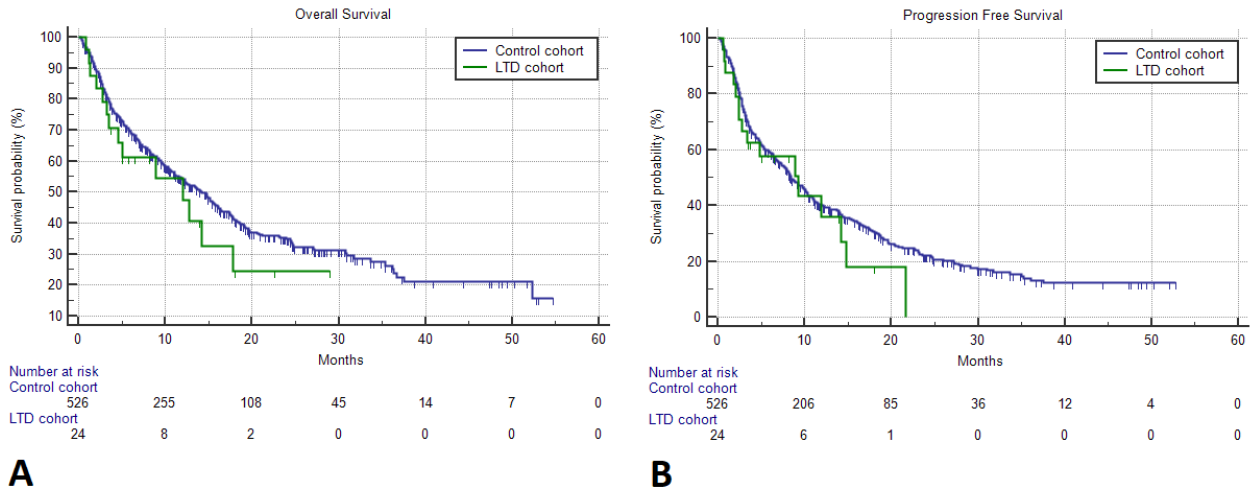
Twenty-four consecutive stage IV NSCLC patients were included in the LTD cohort, while the control cohort consisted of 526 NSCLC patients. Table 1 summarized baseline patients' characteristics of both cohorts. No significant differences were found regarding age ($p = 0.8842$), gender ($p = 0.2037$), burden of disease ($p = 0.4573$) and type of checkpoint inhibitor ($p = 0.2169$). No patients with ECOG-PS ≥ 2 were included in the LTD cohort, while among the control cohort were 13.7% ($p = 0.0180$). A significantly higher proportion of patients receiving first-line immunotherapy was included in the LTD cohort compared to the control cohort (62.5% vs 32.5%, $p = 0.0024$).

	LTD COHORT	CONTROL COHORT	
N° (%)	**24**	**526**	**χ2 test**
AGE, (YEARS)			
MEDIAN	70.0	69.5	
RANGE	49 – 86	34 – 91	P = 0.8842
ELDERLY (≥ 70)	12 (50.0)	255 (48.5)	
SEX			
MALE	13 (54.2)	351 (66.7)	P = 0.2037
FEMALE	11 (45.8)	175 (33.3)	
ECOG PS			
0	8 (33.3)	243 (46.2)	P = 0.0180
1	16 (66.7)	211 (40.1)	
2	-	72 (13.7)	
NO. OF METASTATIC SITES			
≤ 2	14 (58.3)	266 (50.6)	P = 0.4573
> 2	10 (41.7)	260 (49.4)	
TYPE OF ANTI-PD-1/PD-L1 AGENT			
PEMBROLIZUMAB	15 (62.5)	217 (41.2)	P = 0.2169
NIVOLUMAB	8 (33.3)	281 (53.4)	
ATEZOLIZUMAB	1 (4.2)	23 (4.4)	
OTHERS	-	5 (1.0)	
TREATMENT LINE OF IMMUNOTHERAPY			
FIRST	15 (62.5)	171 (32.5)	P = 0.0024
NON-FIRST	9 (37.5)	355 (67.5)	

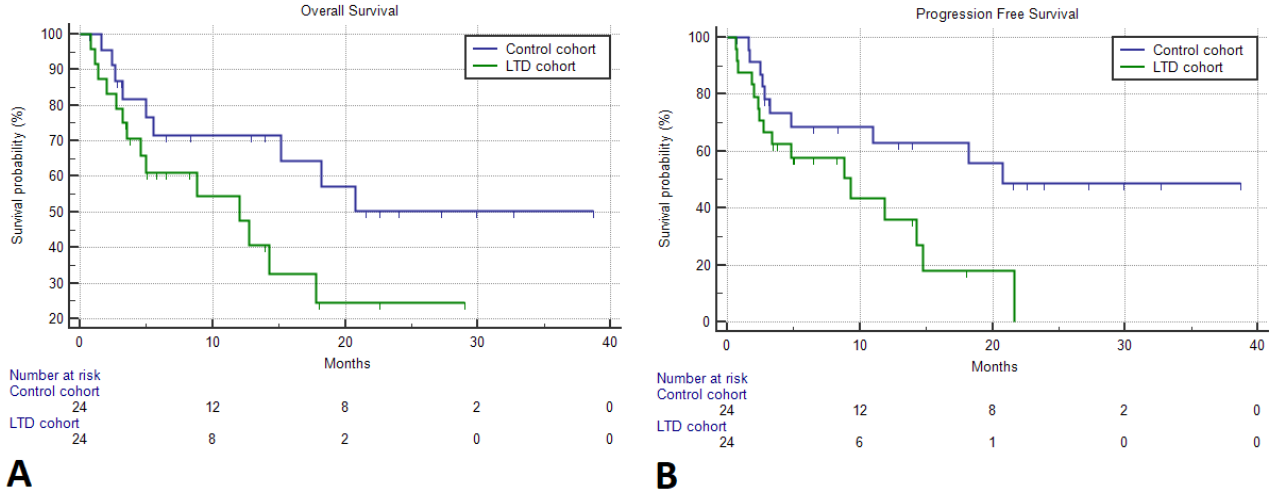
Table 1. Patients characteristics in LTD and Control cohort

Clinical outcomes

At the data cut-off, a formal radiological assessment had not been performed in 4 and 37 patients in the LTD and control cohorts, respectively. In the LTD cohort, the ORR was 40% (95%CI: 17.2-78.8), while in the control cohort the ORR was 32.7% (95%CI: 27.8-38.2). The median follow-up period was 18.1 months (95%CI: 5.7-29.0) and 22.6 months (95%CI: 19.9-54.7) for the LTD and control cohorts, respectively. The median PFS among the LTD and control cohorts was 9.3 months (95%CI: 2.4-21.6; 16 progression events), and 8.4 months (95%CI: 7.3-10.0; 380 progression events), respectively (Figure 1B), while the median OS in the LTD and control cohorts was 12.0 months (95%CI: 3.5-17.8; 10 censored patients), and 14.2 months (95%CI: 11.8-16.0; 218 censored patients), respectively (Figure 1 A).



After the random matching, 24 patients from the control cohort were perfectly paired with patients from the LTD cohort. Among the matched patients from the control cohort ORR was 30.4% (95%CI: 12.2 – 62.7), median PFS was 20.7 months (95%CI: 3.2 – 20.7; 10 progression events) and median OS was not reached (15 censored patients) (Figure 2). The LTD cohort showed a non-significantly higher probability of experience a disease response (OR = 1.52 [95%CI: 0.43 – 5-37], p = 0.5125). Conversely, LTD patients had a significantly higher risk of disease progression (HR = 2.52 [95%: 1.10 – 5.78], p = 0.0288) and a not significantly higher risk of death (HR = 2.14 [95%CI: 0.91 – 5.05], p = 0.0820).



Immune-related adverse events

Thirteen patients discontinued the ICI treatment after only one administration, while 11 patients after two administrations. In the LTD cohort, pneumonitis was the most common severe IrAE (12/24 patients) and five patients experienced multiple-site irAEs. However, no IrAE-related deaths were reported across the LTD cohort. Table 2 shows the ICI agents, IrAEs type, grading and management in the LTD cohort. 224 patients experienced irAEs of any grade in the control cohort (42.6%), while 66 (12.5%) experienced G3/G4 irAEs.

	Age	*Sex*	*Treatment*	*IrAE Type*	*Grading*	*Management*	*Other IrAEs*
1	86	F	Nivolumab	Thyroiditis	3	Hormone replacement	None
2	70	M	Nivolumab	Skin toxicity	3	HD corticosteroids	None
3	64	F	Pembrolizumab	Myocarditis	3	HD corticosteroids	Thyroiditis
4	76	F	Pembrolizumab	Pneumonitis	4	HD corticosteroids	None
5	65	M	Nivolumab	Pneumonitis	4	HD corticosteroids	None
6	73	M	Nivolumab	Colitis	3	HD corticosteroids	None
7	63	F	Nivolumab	Pancitopeny	4	HD corticosteroids	None

8	65	M	Nivolumab	Pneumonitis	4	HD corticosteroids	None
9	68	M	Pembrolizumab	Pneumonitis	4	HD corticosteroids	None
10	72	F	Pembrolizumab	Colitis	3	HD corticosteroids	Thyroiditis
11	67	F	Pembrolizumab	Pneumonitis	3	HD corticosteroids	None
12	73	M	Pembrolizumab	Pneumonitis	3	Immunosuppressors	Colitis
13	60	F	Nivolumab	Pneumonitis	3	Immunosuppressors	None
14	75	M	Pembrolizumab	Hepatitis	3	HD corticosteroids	None
15	43	F	Pembrolizumab	Pneumonitis	4	HD corticosteroids	None
16	75	M	Pembrolizumab	Pneumonitis	4	HD corticosteroids	None
17	49	M	Pembrolizumab	Pneumonitis	3	HD corticosteroids	None
18	82	M	Atezolizumab	Thrombocytopenia	4	Immunoglobulins	None
19	78	F	Pembrolizumab	Pneumonitis	3	HD corticosteroids	None
20	74	F	Pembrolizumab	Skin toxicity	4	HD corticosteroids	None
21	74	M	Pembrolizumab	Nephritis	3	HD corticosteroids	Penumonitis
22	69	M	Pembrolizumab	Asthenia	4	HD corticosteroids	Myositis
23	62	M	Pembrolizumab	Colitis	3	HD corticosteroids	None
24	63	F	Nivolumab	Pneumonitis	3	HD corticosteroids	None

Table 2. Immune-related adverse events in LTD cohort

Discussion

Several studies have already confirmed the association between irAEs occurrence and improved outcomes to ICIs in patients with NSCLC [27-31]. Toxicity appears to represent a surrogate marker of efficacy. The true nature and precise mechanisms underlying this relationship are not yet well-known. Berner et al. revealed that the correlation between skin toxicity and response to ICI in NSCLC patients could be mediated by T-cell activation against shared antigens between the tumor and the skin [32]. Other mechanisms, including activation of pre-existing antibodies and increasing of inflammatory cytokines, have been hypothesized but require further research [9, 33].

Being time-dependent events, also the timing of occurrence needs to be taken into account. In a prospective study involving 43 metastatic NSCLC patients receiving nivolumab, patients who experienced early irAE (onset at ≤ 2 and ≤ 6 weeks) achieved higher ORR and disease control rate [34]. Similar findings were also reported in another prospective cohort of NSCLC patients treated with nivolumab [35]. However, it is now well known that irAEs with single-agent PD-1/PD-L1 checkpoint inhibitors are usually mild and mostly appear in the time window between the 2nd and

the 6th months since treatment initiation [8,36]. Early irAEs leading to treatment discontinuation still represent an under-investigated clinical entity, and their management remains an area of unmet medical need.

In our study, the comparison of baseline patients' characteristics between the LTD and the control cohorts, revealed that there was a significantly higher proportion of patients treated in the first line setting ($p = 0.0024$) and with a better PS ($p = 0.0180$) within the LTD group. These results suggest that fitter patients, receiving immunotherapy in an earlier setting, are more prone to develop early LTD irAEs. From this perspective, our findings might reflect a condition of higher immune-susceptibility of treatment-naive patients with a good PS, and the incidence of irAEs in LTD patients might represent the upside-down of that hypersensitivity. Nevertheless, early LTD irAEs might be associated with an opposite effect, because of their intrinsic severity and the low exposure to treatment. Even though early irAEs could mirror a prompt anti-tumor immune-activation, on the other hand their severity and the permanent treatment discontinuation could also limit immunotherapy long-term benefit. Of note, the case-control matched analysis showed that LTD patients experienced a numerically higher ORR (the putative immune-activation), but a significantly worse PFS and a trend towards a shorter OS, compared to the control cohort. Even though no irAE-related death was reported, it can be assumed that the clinical deterioration associated with serious irAEs might have affected the global outcome.

If, from one side, the early and prompt activation of the immune system in our series of patients could also mirror an improved immune response against the tumor, on the other, the early start of immunosuppressive treatment could also limit the long-term benefit on survival. In this regard, a meta-analysis showed that only low-grade irAEs were associated with improved survival [11]. Moreover, it should be evaluated in larger series if specific types of early irAEs could better predict treatment efficacy, as it has been shown for endocrine and dermatological toxicities and immune checkpoint inhibitors use in general [11].

In our study, the main LTD irAE was pneumonitis. Its timely diagnosis in a clinical setting, or even better, its risk prediction, would optimize patients' management, avoiding serious events or treatments' delays/withdrawals. Serum biomarkers including circulating cytokines and multi-omic features have been associated with pneumonitis and other irAEs, but none of them have been validated for common use and further studies are still needed to establish better prediction strategies [37-42].

No patient in the LTD cohort received ICI re-treatment because it was considered unsafe. This issue represents a mined and little explored area in literature. Although results are discordant, some reports encourage the reuse of anti-PD-1 antibodies when there are no other therapeutic options, even in

patients who have previously experienced irAEs [43-47]. However, there are no data available on patients who had discontinued treatment after 1 or 2 administrations due to early and serious irAE. Moreover, up to half of the patients who discontinued PD-1/PD-L1 inhibitors due to severe irAEs, develop recurrent and/or new irAEs after treatment re-introduction [48,49]. Consequently, it is extremely difficult to strike the right balance between risks and benefits from a re-challenge approach. The safety and efficacy of treatment re-challenge after previous severe irAEs in NSCLC remain open questions requiring further evidence.

It also remains unclear why some patients maintain a long-lasting response after treatment discontinuation due to irAEs, despite limited exposure to immunotherapy [50]. The issue of optimal duration of ICIs is a matter of debate in several oncological fields. Whether eliciting an immune response would be enough to maintain a persistent activation of the antitumoral activity is not so clear. In fact, even after reaching a complete response to ICIs, it is not yet established the period of treatment continuation to achieve the maximum survival benefit [51]. Single administrations of ICI may enhance CD8 + T cell memory formation, function and maintenance of the immune response. Therefore, serious and early IrAEs could express an excessive stimulation of the immune system, such as providing a long memory of the activity of lymphocytes against tumor antigens. However, this mechanism is more plausible for anti-CTL4 antibodies which have a priming effect on lymphocyte activity and less for anti-PD-1 agents which act on the T-cell effector function [52].

The retrospective design, the relatively limited sample size of the LTD cohort and the lack of a centralized review are among the main limitations of the study. Our study produced important evidence on early irAEs leading to treatment discontinuation in NSCLC, even though we were not able to provide a clear estimation of their prevalence.

Conclusions

Early irAEs leading to treatment discontinuation still represent an under-investigated clinical entity, and their management remains an area of unmet medical need. We produced important evidence for their clinical implication and identified a significant association with first-line ICI treatment and good PS. Even though early irAEs occurrence might underly an immune anti-tumor activation, we found no survival benefit in the LTD cohort compared to the control cohort, possibly due to the very short exposure to ICI therapy. Our findings reinforce the need for further studies on risk prediction and management of serious and early irAEs in NSCLC patients.

Ethics approval and consent to participate

All patients alive at the time of data collection provided informed consent for the present retrospective analysis. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was approved by the respective local ethical committees on human experimentation of each institution, after previous approval by the coordinating center.

IRB reference for the control cohort: University of L'Aquila, Internal Review Board protocol number 32865, approved on July 24th, 2018.

IRB reference for the LTD cohort: Campus Bio-medico University of Rome, protocol number 37/19 OSS approved on July 24th 2019

Authors' contributions

Acknowledgments:

Funding:

Availability of data and materials:

Consent for publication

Conflicts of Interest:

Dr Alessio Cortellini received speaker fees and grant consultancies from Roche, MSD, BMS, AstraZeneca, Novartis, Astellas.

Dr Marco Russano received honoraria for consultancy and scientific talks from Roche, BMS, MSD, Boehringer Ingelheim, AstraZeneca.

Daniele Santini received speaker fees and grant consultancies from Janssen, Astellas, BMS, MSD, Pfizer, Boeringher Ingelheim, Roche, Eisai, Incyte, Novartis

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Supplementary Table

LTD Cohort	
Institution	**Department**
St. Salvatore Hospital, University of L'Aquila, L'Aquila	Medical Oncology Department
SS Annunziata Hospital, Chieti	Medical Oncology Department
St. Andrea Hospital, Rome	Medical Oncology Department
Campus Bio-Medico University, Rome	Medical Oncology Department
Policlinico Umberto I, Rome	Medical Oncology Department
Spedali Civili Hospital, Brescia	Medical Oncology Department
Humanitas Gavazzeni Hospital, Bergamo	Medical Oncology Department
University Hospital of Parma, Parma	Medical Oncology Department
University of Cagliari, Cagliari	Medical Oncology Department
Pisa University Hospital, Pisa	Medical Oncology Department
ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese	Medical Oncology Department
Mauriziano Hospital, Torino	Medical Oncology Department
St Bortolo Hospital, Vicenza	Medical Oncology Department

Control Cohort	
Institution	**Department**
St. Salvatore Hospital, University of L'Aquila, L'Aquila	Medical Oncology Department
SS Annunziata Hospital, Chieti	Medical Oncology Department
IRCCS Ospedale Sacro Cuore Don Calabria, Negrar	Medical Oncology Department
A.O. Papardo & Department of Human Pathology, University of Messina	Medical Oncology Department
S Maria Goretti Hospital, Latina	Medical Oncology Department
St. Andrea Hospital, Rome	Medical Oncology Department
Campus Bio-Medico University, Rome	Medical Oncology Department
Policlinico Umberto I, Rome	Medical Oncology Department
"UOC Oncologia Padova Sud - AULSS6 Euganea , Padova	Medical Oncology Department
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan	Medical Oncology Department
Hospital of Fermo, Fermo	Medical Oncology Department
ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese	Medical Oncology Department
Azienda Ospedaliera S. Maria, Terni	Medical Oncology Department