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# Italian survey on managing immune checkpoint inhibitors in oncology during COVID-19 outbreak

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## Abstract

**Background:** During COVID-19 outbreak, oncological care has been reorganized. Patients with cancer have been reported to experience a more severe COVID-19 syndrome; moreover, there are concerns of a potential interference between immune checkpoint inhibitors (ICIs) and SARS-CoV-2 pathogenesis.

**Materials and methods:** Between 6 and 16 May 2020, a 22-item survey was sent to Italian physicians involved in administering ICIs. It aimed at exploring the perception about SARS-CoV-2-related risks in cancer patients receiving ICIs, and the attitudes towards their management.

**Results:** The 104 respondents had a median age of 35.5 years, 58.7% were females and 71.2% worked in Northern Italy. 47.1% of respondents argued a synergism between ICIs and SARS-CoV-2 pathogenesis leading to worse outcomes, but 97.1% would not deny an ICI only for the risk of infection. During COVID-19 outbreak, to reduce hospital visits, 55.8% and 30.8% opted for the highest labelled dose of each ICI and/or, among different ICIs for the same indication, for the one with the longer interval between cycles, respectively. 53.8% of respondents suggested testing for SARS-CoV-2 every cancer patient candidate to ICIs. 71.2% declared to manage patients with onset of dyspnoea and cough as infected by SARS-CoV-2 until otherwise proven; however, 96.2% did not reduce the use of steroids to manage immune-related toxicities. The administration of ICIs in specific situations for different cancer types has not been drastically conditioned.

**Conclusions:** These results highlight the uncertainties around the perception of a potential interference between ICIs and COVID-19, supporting the need of focused studies on this topic.

**KEYWORDS**
cancer, COVID-19, immune checkpoint inhibitors, immunotherapy, SARS-CoV-2

# 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) outbreak has led to the reorganization of national health systems in many specialties including medical oncology.[1,2] Infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for a wide range of clinical conditions.[3,4] Independent risk factors for infection and development of severe events are older age and pre-existing comorbidities.[5,6] Patients with cancer have been also reported to be at potential higher risk of complications and death, particularly if immunosuppressive drugs are administered close to the time of infection.[7,8]

The host immune system is crucial in determining the clinical course of COVID-19.[9] It is implicated into the clearance of the virus when effective, and in disease propagation when deficient.[10] The severity of COVID-19 is caused not only by direct viral damage, but also by an impaired immune host reaction, sometimes resulting in an extremely strong inflammatory response leading to airways damage and life-threatening acute respiratory distress syndrome.[9] A cytokine release syndrome (CRS) seems to be responsible for the most severe conditions.[10,11]

Immune checkpoint inhibitors (ICIs) constitute a crucial drug class for the treatment of many cancer types in different settings.[12] Negative checkpoint blockade removes the inhibition on T-cell activation, driving effective long-lasting antitumor response through central and peripheral immune mechanisms.[13,14] Whether and how ICIs can interfere with the physiopathology of SARS-CoV-2 infection is still matter of discussion. This interaction may worsen the hyperinflammation with CRS observed in severe cases of COVID-19, but the antagonism of checkpoint axis like PD-1/PD-L1 could also potentially participate in accelerating the resolution of viral infection.[15,16] Beyond this complexity, SARS-CoV-2 infection in patients with cancer poses also issues related to the differential diagnosis between cancer-related symptoms or immune-related adverse events (irAEs) and COVID-19 manifestations.[17] Despite immunotherapy cannot be considered immunosuppressive per se, a special consideration when referring to the risk of SARS-CoV-2 infection should be given to patients treated with long course of corticosteroids for irAEs after or during treatment with ICIs.[18] First reports assessing the impact of ICIs on clinical outcomes of cancer patients with SARS-CoV-2 infection produced contrasting results.[19-22]

Here, we present the results of a survey conducted among Italian physicians involved in the administration of ICIs in oncology to explore their perception about SARS-CoV-2-related risks in patients with cancer receiving these therapies, and the attitudes towards their management during COVID-19 outbreak.

# 2 | MATERIAL AND METHODS

An anonymous 22-item questionnaire was shared on 6 May 2020 on a social media platform created during COVID-19 pandemic with private access dedicated to Italian physicians involved in cancer care.

The link to fill the survey remained active until 16 May 2020. Respondents had to answer all the questions in order to send the survey.

Reporting of the study conforms to broad EQUATOR guideline.[23]

## 2.1 | Study objectives

The objectives of this survey were to examine the perception of Italian physicians involved in the administration of ICIs about SARS-CoV-2-related risks in patients with cancer receiving these therapies, and their attitudes towards the management of ICIs in oncology during COVID-19 outbreak.

We also investigated how COVID-19 outbreak has modified the approach of respondents in specific clinical settings.

## 2.2 | Characteristics of the survey

The survey (Appendix S1) was composed of four sections: (a) demographic, training and employment details of respondents (Q1-8); (b) perception of the risk related to SARS-CoV-2 infection in patients with cancer treated with ICIs (Q9-11); (c) attitudes towards the administration of ICIs and management of toxicities during COVID-19 outbreak (Q12-16); and (d) specific questions focused on attitudes towards the prescription of ICIs for the treatment of different cancer types during COVID-19 outbreak (Q17-22).

This survey was conceived by physicians who are involved in the administration of ICIs for treating patients with different types of cancer.

## 2.3 | Statistical analysis

Considering the descriptive nature of the study, a pre-planned sample size was not established. However, estimating a target population of around 1,300 physicians who could have access to the survey, we aimed to reach at least 100 responses to have a margin of error less than 10% with a 95% confidence level.

Characteristics of responding physicians were analysed using descriptive statistics, and results were reported as percentage of respondents to each answer on the total number of people filling the survey or dealing with a particular cancer disease.

**TABLE 1** Demographic, training and employment details of responding physicians (n = 104)

| Variable | Respondents, n (%) |
|---|---|
| Age, median (IQR) | 35.5 (30.3-44.0) |
| Gender | |
| Male | 43 (41.3) |
| Female | 61 (58.7) |
| Region of practice | |
| North of Italy | 74 (71.2) |
| Center of Italy | 13 (12.5) |
| South of Italy | 7 (6.7) |
| Islands | 10 (9.6) |
| Practice environment | |
| Public | 97 (93.3) |
| Private | 4 (3.8) |
| Both (public and private) | 2 (1.9) |
| Other | 1 (1) |
| Years of clinical practice, median (IQR) | 10 (5-20) |
| Type of cancer mainly managed | |
| Lung cancers | 24 (23.1) |
| Breast cancers | 21 (20.2) |
| Gastrointestinal cancers | 15 (14.4) |
| Skin cancers | 13 (12.2) |
| Gynaecological cancers | 4 (3.8) |
| Urogenital cancers | 20 (19.2) |
| Head and neck cancers | 4 (3.8) |
| Others | 3 (2.8) |
| Number of new cases of any type of cancer seen every year | |
| <100 | 4 (3.8) |
| 100-200 | 19 (18.3) |
| 201-300 | 20 (19.2) |
| >300 | 61 (58.7) |

Abbreviation: IQR, interquantile range.

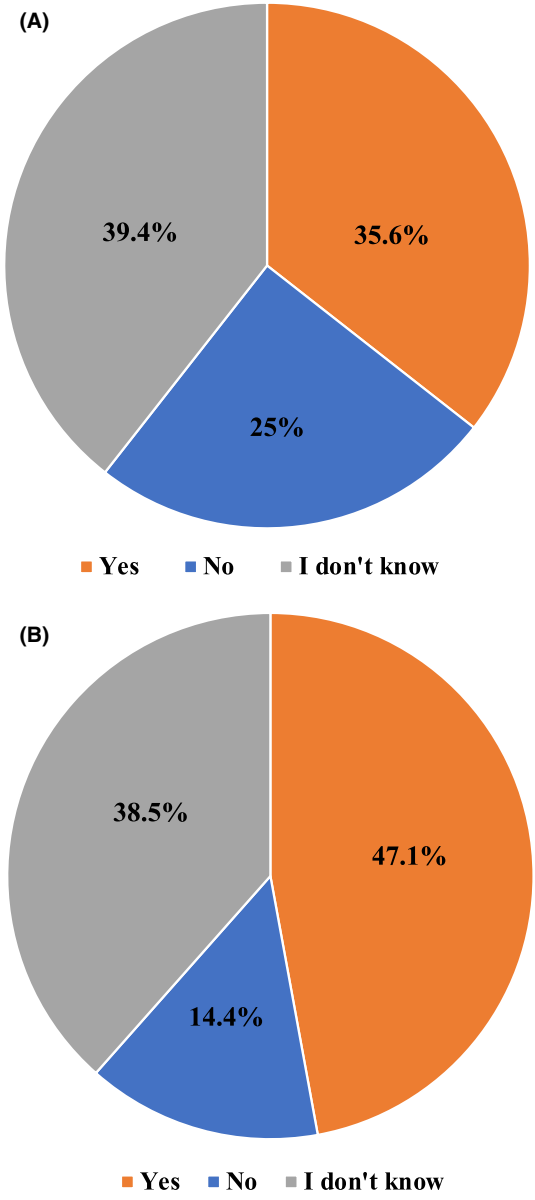


**FIGURE 1** A, Perception regarding a possible interference between the activity of immune checkpoint inhibitors and the pathogenesis of SARS-CoV-2 infection. B, Perception regarding the potential increased risk of severe events related to SARS-CoV-2 infection in cancer patients treated with immune checkpoint inhibitors

## 3 | RESULTS

Complete results are displayed in Appendix S2.

### 3.1 | Demographic, training and employment details of respondents

The survey reached around 1300 physicians involved in cancer care. A total of 104 physicians dealing with the administration of ICIs for treating patients with cancer answered the questionnaire. Table 1 reports their demographic, medical training and employment information. Median age was 35.5 years (interquartile range [IQR], 30.3-44.0 years). Most of respondents were female (n = 61, 58.7%), mainly working in public hospitals (n = 97, 93.3%) with a volume of new cancer cases managed per year greater than 300 (n = 61, 58.7%). The median duration of clinical practice, including fellowship, was 10 years (IQR, 5-20 years). The five most represented tumour types managed by the respondents were lung (n = 24, 23.1%), breast (n = 21, 20.2%), genitourinary (n = 20, 19.2%), gastrointestinal (n = 15, 14.4%) and skin (n = 13, 12.2%). Most respondents worked in Northern Italy (n = 74, 71.2%).

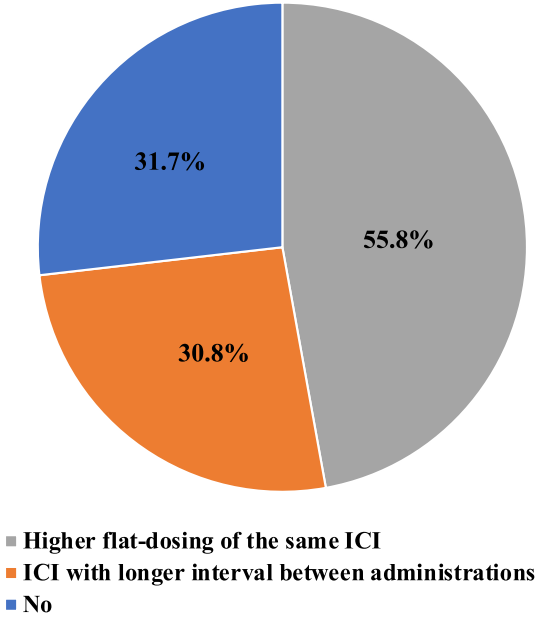


**FIGURE 2** Attitude towards the type of immune checkpoint inhibitor chosen and the treatment's schedule. (Abbreviation: ICI, immune checkpoint inhibitor)

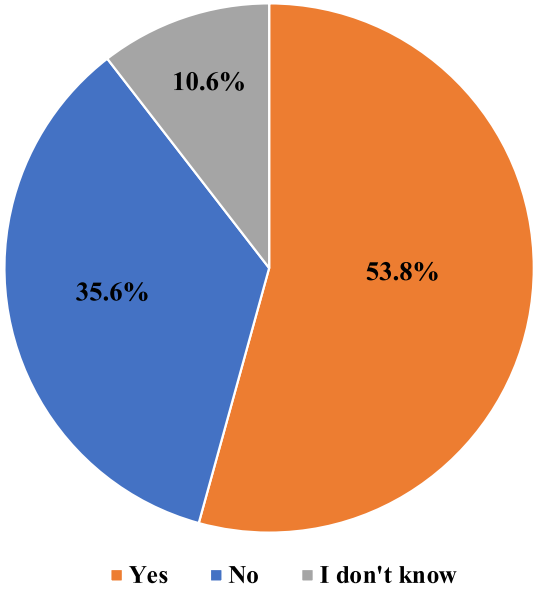


**FIGURE 3** Indication to test for SARS-CoV-2 every cancer patient candidate to receive an immune checkpoint inhibitor

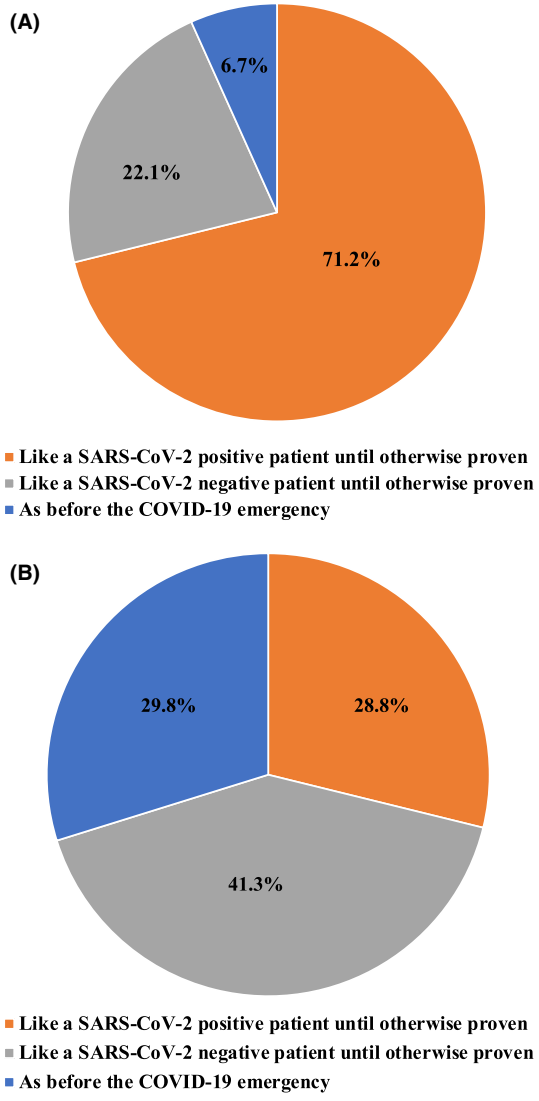


**FIGURE 4** A, Management of dyspnoea and cough in cancer patients treated with immune checkpoint inhibitors during COVID-19 outbreak. B, Management of colitis in cancer patients treated with immune checkpoint inhibitors during COVID-19 outbreak

## 3.2 | Perception of the risk related to SARS-CoV-2 infection in cancer patients treated with ICIs

A total of 39.4% (n = 41) of respondents did not feel confident to give an opinion on whether an interference between the activity of ICIs and the pathogenesis of SARS-CoV-2 infection exists; 35.6% (n = 37) believed that the activity of ICIs may interfere with the pathogenesis of SARS-CoV-2 infection, while 25% (n = 26) did not (Figure 1A).

The perception of respondents regarding the potential increased risk of severe events related to SARS-CoV-2 infection in cancer patients treated with ICIs is displayed in Figure 1B. A total of 47.1% (n = 49) of respondents agreed on these concerns, while 14.4% (n = 15) and 38.5% (n = 40) did not or did not know, respectively.

The vast majority of respondents (n = 101, 97.1%) would not deny an ICI to a patient with cancer during COVID-19 pandemic only based on the potential eventuality of infection by SARS-CoV-2.

### 3.3 | Attitudes towards the administration of ICIs and management of their toxicity during COVID-19 outbreak

Figure 2 depicts whether responding physicians have modified their attitudes in the choice of the ICI to administer and its schedule during COVID-19 outbreak (notably, more than one answer could be selected for this question). A total of 55.8% (n = 58) of respondents declared to have modified their clinical activity by preferring, when allowed and in indication, the higher flat-dosing regimen of an ICI (ie the regimen with the longer interval between administrations) in order to reduce the frequency of hospital visits. Similarly, 30.8% (n = 32) of respondents declared to prefer, between different ICIs indicated for the same clinical situation, the one with the longer interval between the administrations.

Regarding the adoption of measures to reduce the risk of infection for cancer patients treated with ICIs, 53.8% (n = 56) of respondents stated that the SARS-CoV-2 testing should be carried out at baseline in every cancer patient candidate to ICIs (Figure 3).

Two clinical situations were explored to assess the issues related to the differential diagnosis between irAEs and COVID-19 manifestations in cancer patients treated with ICIs: (a) how to manage a patient with onset of dyspnoea and cough (Figure 4A); (b) how to manage a patient whit onset of diarrhoea (Figure 4B).

A total of 71.2% (n = 74) of respondents declared to manage a patient in scenario A like a COVID-19-infected patient until otherwise proven (ie waiting for the result of SARS-CoV-2 test before doing other diagnostic or therapeutic procedures). On the contrary, 22.1% (n = 23) declared to manage this case like a patient without SARS-CoV-2 infection until otherwise proven (ie performing the swab test for SARS-CoV-2 but adopting prompt diagnostic and therapeutic measures without waiting its result).

Conversely, only 28.8% (n = 30) of respondents reported to manage a patient in scenario B as a SARS-CoV-2-infected patient until otherwise proven, while 41.3% (n = 43) and 29.8% (n = 31) declared to manage this case as a SARS-CoV-2 negative-patient until otherwise proven and as before the COVID-19 outbreak, respectively.

A total of 96.2% (n = 100) of respondents did not modify the attitude in administering corticosteroids to treat irAEs during COVID-19 outbreak.

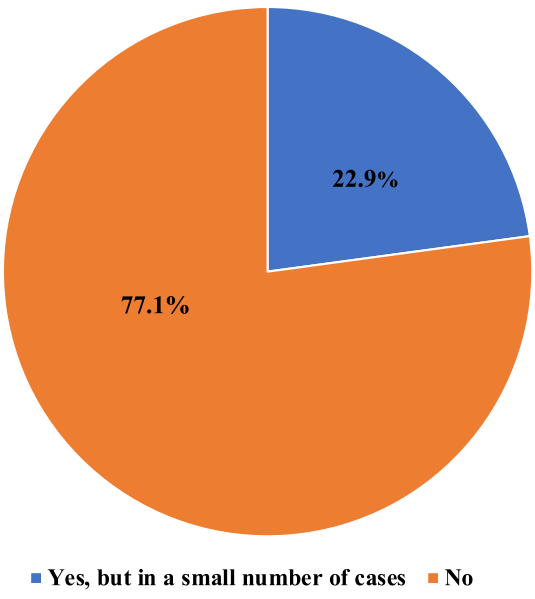


**FIGURE 5** Use of immune checkpoint inhibitors in the adjuvant setting for patients with stage III melanoma older than 75 years

### 3.4 | Specific questions focused on the attitudes towards prescription of ICIs for the treatment of different cancer types during COVID-19 outbreak

#### 3.4.1 | Lung cancer

Prescription of durvalumab as maintenance therapy after chemo-radiotherapy for unresectable locally advanced non–small-cell lung cancer (NSCLC) with PD-L1 expression ≥1% was assessed. Among the 53 respondents who declared to deal with lung cancer in their practice, 49 (92.5%) stated to have not reduced its use in this setting.

Prescription of pembrolizumab as a combination treatment with a platinum-based doublet with pemetrexed as first-line for metastatic non-squamous NSCLC with PD-L1 expression <50% (negative for EGFR and ALK) was then explored. A total of 47 (85.5%) respondents did not reduce its use in clinical practice.

#### 3.4.2 | Melanoma

The use of ICIs in the adjuvant setting for patients with stage III melanoma older than 75 years was investigated. Among the 35 respondents who declared to deal with melanoma in their practice, 8 (22.9%) declared to have renounced to the prescription of ICIs in a limited number of cases. On the contrary, 27 (77.1%) respondents did not modify the indication for ICIs in this setting (Figure 5).

#### 3.4.3 | Breast cancer

The use of atezolizumab as first-line treatment in combination with nab-paclitaxel for PD-L1-positive triple-negative advanced breast cancer was investigated (notably, this regimen is not reimbursed by the Italian Healthcare System, but

it is currently accessible through a compassionate use program). Among the 47 respondents who declared to deal with breast cancer in their practice, 43 (91.5%) did not reduce the use of this drug.

### 3.4.4 | Bladder cancer

The use of pembrolizumab as second-line treatment for patients with advanced bladder carcinoma progressing on platinum-based chemotherapy was explored. Among the 57 respondents who declared to deal with bladder cancer in their practice, 91.2% (n = 52) did not reduce its use in this setting.

### 3.4.5 | Kidney carcinoma

The choose of nivolumab as second-line therapy for patients with advanced kidney cancer progressing on a tyrosine kinase inhibitor was assessed. Among the 60 respondents who declared to deal with kidney cancer in their practice, 57 (95%) stated to have not reduced its use in this setting.

## 4 | DISCUSSION

Since the first reported cases of SARS-CoV-2 infections in cancer patients, some concerns have been raised on whether and how ICIs could interfere with the pathogenesis of the virus worsening the hyperinflammation with CRS, thus if receiving or having received an ICI should be considered as an independent negative prognostic factor for the outcome of SARS-CoV-2 infection.[17] Moreover, besides the overlapping between cancer-related signs/symptoms or side effects of oncological treatments (including irAEs) and COVID-19 manifestations, additional issues could emerge from the differential diagnosis between radiological findings of lung involvement from SARS-CoV-2 and pneumonitis induced by ICIs.[9,24]

To the best of our knowledge, this is the first study exploring the perception of physicians towards these unsolved issues, and whether the outbreak has modified the clinical practice in managing the treatment with ICIs in oncology.

The perception of Italian physicians involved in the administration of ICIs concerning a possible interference between the activity of ICIs and the pathogenesis of SARS-CoV-2 was diversified. Almost 40% of respondents was not confident to give an answer, while 35.6% reported that an interaction may exists. This uncertainty is likely due to the lack of univocal evidence on this regard.[19-22] Furthermore, 47.1% of respondents supported the hypothesis of a synergism between the mechanism of action of ICIs and the pathogenesis of SARS-CoV-2 infections, thus being worried about the potential higher risks of COVID-19-related complications in this patient population. Nevertheless, it is comforting that 97.1% of respondents would not deny ICIs as a treatment option at the time of COVID-19 outbreak only based on the possible risks of infection by SARS-CoV-2, considering that so far a clear evidence of a detrimental effect of their administration still lacks.

While it is essential to ensure the best care to patients with cancer during the current health emergency, also by giving access to ICIs that have demonstrated clinically relevant results in terms of efficacy, it is also advisable to find strategies to reduce the risk of SARS-CoV-2 infections. The European Society for Medical Oncology (ESMO) has created dedicated recommendations for the management of various aspects of oncological care, in order to mitigate the negative impact of COVID-19 outbreak on patients with cancer.[25]

Only 31.7% of respondents did not modify the choice of the ICI and the schedule of administration in order to reduce the number of hospital visits. Currently, the preference for the higher flat-dose of an ICI as single agent, whenever allowed, is supported by evidences of comparable safety and efficacy between different schedules.[26,27] Reducing the number of hospital visits while maintaining treatment effect is a reasonable safety measure that should be taken into account during COVID-19 outbreak. For patients beginning the treatment, the choice for an ICI rather than another with a different interval between the administrations, if in indication in the same setting, should be done on a case by case evaluation on the basis of available efficacy and safety data in that setting of disease.

Testing patients with cancer for SARS-CoV-2, with the aim to identify and isolate also asymptomatic carriers, is a strategy for the control of the contagion that has already been claimed.[28,29] This perception finds a confirmation in our survey, in which 53.8% of respondents supported this approach before starting treatment with ICIs.

The overlapping between clinical manifestations of irAEs and COVID-19, and the consequent management, is an additional concern. While immune related pneumonitis is not so frequent in patients with cancer treated with ICIs (1%-5% with anti-CTLA-4 or anti PD-1/PD-L1 as monotherapy, 5%-10% with combination strategies),[30,31] it enters in the differential diagnosis list at the time of COVID-19 outbreak for almost all respondents. On the contrary, diarrhoea is one of the most frequent irAE,[32] and despite its overall rate is 10.4% in patients with COVID-19 in a pooled analysis, only 28.8% of respondents reported to manage a patient with colitis as a SARS-CoV-2-infected patient until otherwise proven, potentially leading to a risk of contagion in the case of underlying infection by SARS-CoV-2.[33,34] Having dedicated facilities where cancer patients could be managed also in the case of suspected SARS-CoV-2 infection should be considered of

high priority in order to continue providing the needed care in the safest possible environment.[35]

The 96.2% of respondents did not modify the use of corticosteroids for the treatment of irAEs. Notably, its use has also been associated with a reduction in the risk of death in patients with COVID-19-related pneumonia.[36] Hence, whenever needed, corticosteroids for managing irAEs should not be denied.

The integration of ICIs in oncology has been associated with improved progression-free and overall survival in different cancer types and settings, including lung cancer,[37,38] melanoma,[39,40] triple-negative breast cancer,[41] urothelial cancer[42] and renal cell carcinoma.[43] The results of our survey do not demonstrate a significant change in the attitudes of Italian physicians towards the prescription of ICIs during COVID-19 outbreak. However, we observed that 22.9% of respondents dedicated to the treatment of melanoma declared to have reduced its use in the adjuvant setting for stage III elderly patients. These data, probably driven by the higher risk of COVID-19 severe events in the elderly population, deserve a reflection considering the significant benefit associated with ICIs in this setting.[39,40]

## 5 | LIMITATIONS

This study has some limitations, mainly derived by the relatively small number of respondents. Nevertheless, it gives a representative picture of the perception of physicians dealing with SARS-CoV-2-related issues towards the management of ICIs in oncology during COVID-19 outbreak, as the majority of respondents work in the most affected area of Italy (ie the North). Another limitation is that we have explored the attitudes of Italian physicians towards the use of ICIs in limited and specific clinical conditions. However, we believe that these were the situations in which the role of ICIs could be questioned in such a health emergency.

## 6 | CONCLUSIONS

With this study we have reported the perception and attitudes of Italian physicians towards the management of ICIs during COVID-19 outbreak. These results underline the uncertainties regarding the potential impact of SARS-CoV-2 infection in cancer patients treated with ICIs. Future studies are needed to support evidence-based behaviors of physicians dealing with immunotherapy in oncology, and to better define the immune mechanisms behind this possible interaction.

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### CONFLICTS OF INTEREST

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Tagliamento reported travel grants from Roche, Bristol-Myers Squibb, AstraZeneca, Takeda and Honoraria as medical writer from Novartis outside the submitted work. Dr Poggio declares travel, accommodations, expenses supported by Takeda, Ely Lilly, and received honoraria from Merck Sharp & Dohme, Ely Lilly, Novartis outside the submitted work. Dr Del Mastro declares personal fees from Roche, Pfeizer, Ipsen, Eli Lilly, Novartis, Takeda, Merck Sharp & Dohme, Genomic Health and Seattle Genetics, and non-financial support from Celgene, outside the submitted work. Dr Di Maio acted as consultant for Eisai, Takeda, Janssen, Astellas, Pfizer and AstraZeneca, outside the submitted work. Dr Lambertini acted as a consultant for Roche and Novartis, and received honoraria from Theramex, Roche, Lilly, Pfizer and Novartisoutside the submitted work. Dr Spagnolo, Dr Soldato, Dr Conte, Dr Ruelle, Dr Barisione and Dr De Maria declare no competing interests.

### AUTHOR CONTRIBUTIONS

Tagliamento, Spagnolo, Di Maio and Lambertini had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Tagliamento, Spagnolo, Di Maio and Lambertini contributed to c*oncept and design*; Tagliamento, Spagnolo, Poggio, Soldato, Conte, Ruelle, Barisione, De Maria, Del Mastro, Di Maio and Lambertini contributed to acquisition, analysis or interpretation of data and critical revision of the manuscript for important intellectual content and provided administrative, technical or material support; Tagliamento and Lambertini contributed to drafting of the manuscript; Tagliamento and Di Maio contributed to statistical analysis.

### ROLE OF THE SPONSORS

The funder had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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