# GU-CA-COVID: a clinical audit among Italian genitourinary oncologists during the first COVID-19 outbreak

**Melissa Bersanelli, Sebastiano Buti, Mimma Rizzo, Alessio Cortellini, Carlo Cattrini, Francesco Massari, Cristina Masini, Maria Giuseppa Vitale, Giuseppe Fornarini, Orazio Caffo, Francesco Atzori, Alice Gatti, Serena Macrini, Claudia Mucciarini, Luca Galli, Franco Morelli, Marco Stellato, Martina Fanelli, Francesca Corti, Paolo Andrea Zucali, Ilaria Toscani, Alberto Dalla Volta, Angela Gernone, Cinzia Baldessari, Leonardo La Torre, Diego Zara, Alessandra Gennari, Sergio Bracarda, Giuseppe Procopio and Camillo Porta**

***Abstract***

**Background:** Considering the growing genitourinary (GU) cancer population undergoing systemic treatment with immune checkpoint inhibitors (ICIs) in the context of the COVID-19 pandemic, we planned a clinical audit in 24 Italian institutions treating GU malignancies.

**Objective:** The primary objective was investigating the clinical impact of COVID-19 in GU cancer patients undergoing ICI-based therapy during the first outbreak of SARS-CoV-2 contagion in Italy.

**Design, setting, and participants:** The included centers were 24 Oncology Departments. Two online forms were completed by the responsible Oncology Consultants, respectively, for metastatic renal cell carcinoma (mRCC) and metastatic urothelial carcinoma (mUC) patients receiving at least one administration of ICIs between 31 January 2020 and 30 June 2020.

**Results and limitation:** In total, 287 mRCC patients and 130 mUC patients were included. The COVID-19 incidence was, respectively, 3.5%, with mortality 1%, in mRCC patients and 7.7%, with mortality 3.1%, in mUC patients. In both groups, 40% of patients developing COVID-19 permanently discontinued anticancer treatment. The pre-test SARS-CoV-2 probability in the subgroup of patients who underwent nasal/pharyngeal swab ranged from 14% in mRCC to 26% in mUC. The main limitation of the work was its nature of audit: data were not recorded at the single-patient level.

**Conclusion:** GU cancer patients undergoing active treatment with ICIs have meaningful risk factors for developing severe events from COVID-19 and permanent discontinuation of therapy after the infection. Treatment delays due to organizational issues during the pandemic were unlikely to affect the treatment outcome in this population.

***Keywords:*** bladder cancer, cancer patients, COVID-19, genitourinary cancers, renal cancer: urothelial cancer, SARS-CoV-2

Received: 22 March 2021; revised manuscript accepted: 30 September 2021.

*Ther Adv Urol*

2021, Vol. 13: 1–6

DOI: 10.1177/17562872211054302



Correspondence to:
**Melissa Bersanelli**
Medical Oncology Unit, University Hospital of Parma, Via Gramsci 14, 43126 Parma, Italy

Medicine and Surgery Department, University of Parma, Parma, Italy.
**bersamel@libero.it**

**Sebastiano Buti**
Medical Oncology Unit, University Hospital of Parma, Parma, Italy

**Mimma Rizzo**
Division of Translational Oncology, IRCCS Istituti Clinici Scientifici Maugeri, Pavia, Italy

**Alessio Cortellini**
Department of Biotechnology and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

Department of Surgery and Cancer, Imperial College London, London, UK

**Carlo Cattrini**
**Alice Gatti**
Division of Oncology, Maggiore della Carità Hospital, Novara, Italy

**Francesco Massari**
Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

**Cristina Masini**
Oncology Unit, Clinical Cancer Centre, AUSL-IRCCS di Reggio Emilia, Emilia, Italy

**Maria Giuseppa Vitale**
**Martina Fanelli**
**Cinzia Baldessari**
Department of Oncology and Haematology, University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria of Modena, Modena, Italy

**Giuseppe Fornarini**
Department of Medical Oncology, IRCCS Azienda Ospedaliera Universitaria San Martino-IST Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy

## Introduction

At the end of June 2020, COVID-19 had affected more than 10 million people worldwide, being responsible for more than 500,000 deaths.[1] Italy was the first European Country to detect SARS-CoV-2 infections in February 2020, with subsequent exponential growth in the infection rate. From March to June 2020 in Italy, there was a

**Orazio Caffo**
Medical Oncology Department, Santa Chiara Hospital, Trento, Italy

**Francesco Atzori**
Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy

**Serena Macrini**
**Sergio Bracarda**
Medical and Translational Oncology, Department of Oncology. Azienda Ospedaliera Santa Maria Terni, Italy

**Claudia Mucciarini** Medical Oncology Unit, Ramazzini Hospital, Carpi, Italy

**Luca Galli**
Medical Oncology Unit, Department of Translational Research and New Technologies in Medicine, University of Pisa, Pisa, Italy

**Franco Morelli**
Medical Oncology Department, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

**Marco Stellato**
Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy

**Francesca Corti**
**Giuseppe Procopio**
Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

**Paolo Andrea Zucali**
Department of Biomedical Sciences, Humanitas University, Milan, Italy

Department of Oncology, IRCCS Humanitas Research Hospital, Milan, Italy

**Ilaria Toscani**
Oncology & Hematology Department, Oncology Unit, Piacenza General Hospital, Piacenza, Italy

**Alberto Dalla Volta**
Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Medical Oncology, University of Brescia, ASST Spedali Civili, Brescia, Italy

**Angela Gernone**
Division of Oncology, AOU Consorziale Policlinico di Bari, Bari, Italy

**Leonardo La Torre** Medical Oncology Department, Santa Maria della Scaletta Hospital, Imola, Italy

**Diego Zara**
Department of Medicine (DAME), University of Udine, Udine, Italy

Department of Oncology, ASUFC University Hospital of Udine, Udine, Italy

strict lockdown due to the epidemic peak of COVID-19. At the end of June 2020, over a population of 60,317,000 inhabitants, the confirmed cases of COVID-19 in Italy were 238,499, of whom 34,634 were dead, 20,972 were patients with active illness (18,510 were outpatient, 2314 were inpatients in COVID-19 wards, and 148 were in intensive care units), and 182,893 were healed.[2] The lethality of 14.5% for COVID-19 in our Country at the end of June was calculated considering the overall denominator of asymptomatic and symptomatic infections, mainly detected by reverse transcription polymerase chain reaction (RT-PCR) swab screening, carried out in leopard spots in the national population. According to the previously cited data, the national incidence of SARS-CoV-2 infection in Italy was about 0.39%.

From the beginning of the pandemic, cancer emerged as a vulnerability factor for severe COVID-19 infection, patients with advanced cancer undergoing active treatment (especially chemotherapy) being particularly exposed.[3,4] Nevertheless, while the immunosuppressive effect of chemotherapy is established, the debate is still open about the immunological status (and the infectious risk) of patients treated with immune checkpoint inhibitors (ICIs).[5] If, on one hand, ICIs can restore cellular immunocompetence, possibly triggering anti-viral responses, on the other hand, their theoretical contribution to severe COVID-19 pathogenesis cannot be ruled out.[6]

In the last few years, the cancer treatment scenario has been completely revolutionized by anti-PD-1, anti-PD-L1, and anti-CTLA-4 ICIs, currently representing the standard of care for several metastatic solid tumors.[7] In particular, anti-PD-1 therapies have been approved in the treatment of advanced or metastatic genitourinary (GU) malignancies, such as metastatic renal cell carcinoma (mRCC) and metastatic urothelial carcinoma (mUC).[8]

Considering the growing GU cancer population undergoing systemic treatment with ICIs in the context of the COVID-19 pandemic, we planned a clinical audit in 24 Italian institutions involved in the clinical management of patients with GU malignancies. The primary objective of the audit, completed by the respective responsible Oncology Consultants of each institution, was investigating the clinical impact of COVID-19 in their GU cancer patients undergoing ICI-based therapy during the first outbreak of SARS-CoV-2 contagion in Italy (conventionally initiating when the emergency was officially declared in our Country, at the end of January 2020, with a peak in April 2020, and a progressive decrease until June 2020).

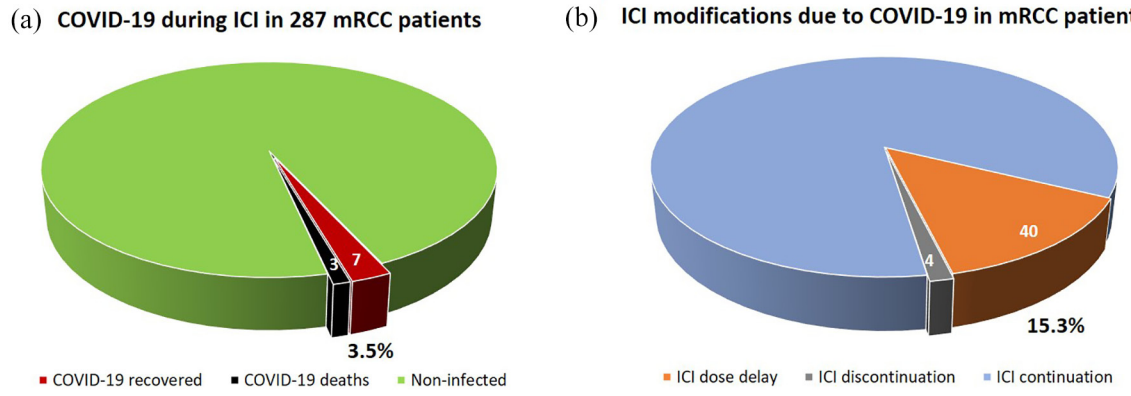
## Methods

A multicenter clinical audit was conducted in Italy in June 2020, after the end of the first COVID-19 outbreak peak. The study was performed in accordance with national legislation, and as such, approval by Ethics Committee or Institutional Review Board was not applicable due to the nature of the study (clinical audit among physicians). Patient consent was not required as no identifiable data were collected. Data were not recorded at the single-patient level and were only obtained in an aggregated form.

The included centers were 24 Oncology Departments of Italian hospitals treating GU malignancies. Two online forms were completed, by the responsible Oncology Consultants, respectively, for mRCC and mUC patients. All patients receiving at least one administration of anti-PD-1, anti-PD-L1, or anti-CTLA-4 therapy, alone or in combinations, between 31 January 2020 and 30 June 2020, were eligible. All treatment lines in the advanced/metastatic setting only were considered. COVID-19 was defined with laboratory confirmation of SARS-CoV-2 infection at RT-PCR oropharyngeal swab. The outcomes of interest (co-primary endpoints) were the incidence of COVID-19, the severity in terms of symptoms and hospitalization, the overall COVID-19 mortality, the laboratory test coverage, and the pre-test probability of SARS-CoV-2 positivity for the patients included (herein defined as the number of patients with a positive swab on the overall number of patients receiving at least a swab). The oncological outcomes of interest (secondary endpoints) regarded ICI-treatment compliance in terms of permanent discontinuation or treatment delay due to COVID-19 emergency (both considering cases of infection or organizational issues), disease progression due to delay/discontinuation, and recovery after SARS-CoV-2 infection with ICI treatment resumption.

## Results

Overall, 24 Italian institutions participated in the audit. Medical oncologists responsible for the treatment choices in GU patients and their




**Alessandra Gennari**
Department of Translational Medicine, University of Piemonte Orientale, Vercelli, Italy; Division of Oncology, Maggiore della Carità Hospital, Novara, Italy

**Camillo Porta**
Division of Oncology, AOU Consorziale Policlinico di Bari, Bari, Italy

Chair of Oncology, Department of Biomedical Sciences and Human Oncology, University of Bari 'A. Moro', Bari, Italy

**Figure 1.** (a) COVID-19 cases and deaths in metastatic renal cancer (mRCC) patients treated with immune checkpoint inhibitors (ICIs). (b) ICI treatment delays and discontinuations in mRCC patients during the first COVID-19 outbreak in Italy.

collaborating senior oncology fellows contributed to the replies: only a single survey was completed in each center. Respectively, 23 centers completed the survey for both renal and urothelial cancer patients, and the 24th center completed the survey for renal cancer patients only.

### *Renal cancer patient population*

Within the 24 Italian institutions included in the mRCC audit, 287 patients diagnosed with mRCC were undergoing immunotherapy with ICI during the first COVID-19 outbreak (i.e. between January and June 2020). Of them, 259 were receiving ICIs only (alone or in combination), 15 were treated with ICI plus anti-vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI), and 13 with ICI plus other experimental agents; 42 patients also received radiotherapy during the time frame of interest. More than 45% were elderly (134 patients ⩾ 70 years).

In this population of mRCC patients undergoing ICI-based active treatment, the detected incidence of COVID-19 was 3.5% (10 patients; COVID-19 cases were reported in five centers). All these 10 cases were confirmed by RT-PCR swab positive for SARS-CoV-2; 5 of them (50%) required hospitalization due to the infection, and 3 (30%) died from severe COVID-19 (Figure 1(a)). Seven patients diagnosed with COVID-19 obtained complete recovery from the infection (five patients were utterly asymptomatic), and their ICI treatment was resumed. The overall COVID-19 mortality in this population was 1%. The laboratory test coverage was relatively low (25%) since 72 patients only received at least one RT-PCR swab during the observation period. The pre-test probability of SARS-CoV-2 infection was 13.9%.

Regarding the anticancer treatment compliance, four patients permanently discontinued ICI due to COVID-19 occurrence (40% of patients developing COVID-19). On the contrary, despite not developing the infection, 40 patients (13.9% of all mRCC patients) had a treatment delay due to COVID-19 emergency, but none of these patients had a disease progression after this temporary discontinuation (Figure 1(b)).

### *Urothelial cancer patient population*

In the 23 Italian institutions included in the mUC audit, 130 patients diagnosed with mUC were undergoing immunotherapy with ICI at the first COVID-19 outbreak. Of them, 116 were receiving ICIs only (alone or in combination), 6 were treated with ICI plus chemotherapy, and 8 with ICI plus other compounds within clinical trials; 30 patients also received radiotherapy. More than 45% were elderly (60 patients ⩾ 70 years).

In this mUC population undergoing ICI-based active treatment, the detected incidence of COVID-19 was 7.7% (10 patients; COVID-19 cases were reported in four centers). All these 10 cases were confirmed by RT-PCR swab positive for SARS-CoV-2; 5 of them (50%) required hospitalization due to the infection, and 4 (40%) died from severe COVID-19 (Figure 2(a)). Six patients diagnosed with COVID-19 obtained complete recovery from the infection (four patients were utterly asymptomatic), and their ICI anticancer treatment was resumed.

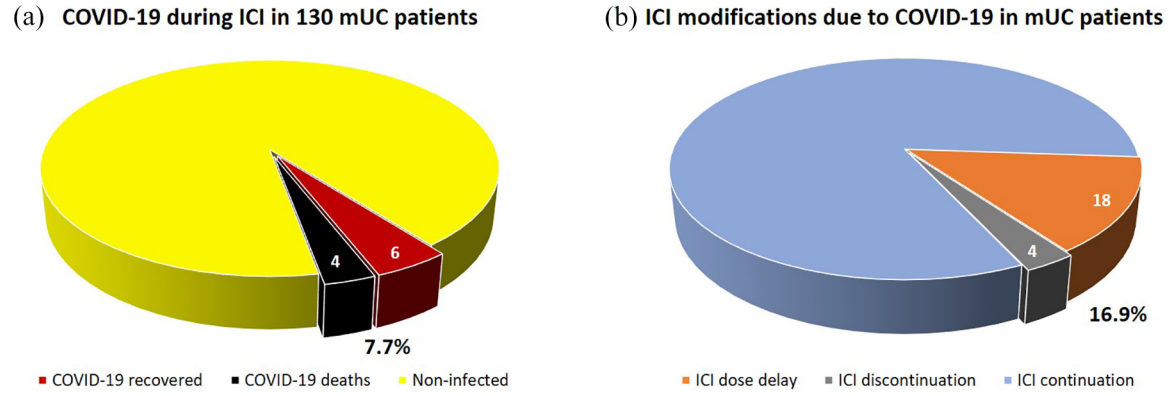



**Figure 2.** (a) COVID-19 cases and deaths in metastatic urothelial cancer (mUC) patients treated with immune checkpoint inhibitors (ICIs). (b) ICI treatment delays and discontinuations in mUC patients during the first COVID-19 outbreak in Italy.

The overall COVID-19 mortality in this population was 3.1%. The laboratory test coverage was relatively low (29.2%) since 38 patients only received at least one RT-PCR swab during the observation period. The pre-test probability of SARS-CoV-2 infection was 26.3%.

Regarding the anticancer treatment compliance, 4 patients permanently discontinued ICI due to COVID-19 (40% of mUC patients developing the infection); 18 patients (13.8%) had a treatment delay (17) or permanent discontinuation (1) due to the emergency during the outbreak, only one of them having a disease progression after discontinuation (Figure 2(b)).

## Discussion

Could immunotherapy with ICIs contribute to the risk of severe progression of SARS-CoV-2 infection? Literature data are still controversial.

Among several retrospective studies published, Robilotti *et al.*[3] reported that treatment with ICIs (but not with chemotherapy or major surgery) was a predictor for hospitalization and severe COVID-19. In other reports, receiving treatment with chemotherapy alone was associated with an increased risk of death in patients with cancer developing COVID-19 (hazard ratio (HR) 2.54, 1.09–6.11).[4]

In the recently published COVID-19 analysis of the prospective INVIDIa-2 study, all the symptomatic COVID-19 events were recorded in 955 cancer patients receiving immunotherapy during the first COVID-19 outbreak in Italy. The incidence of 0.9%, the hospitalization rate of 100%, and the disease's lethality of 77.8% from confirmed COVID-19 reported in this population were meaningful.[9] Nevertheless, the subjects included in this study were all symptomatic, and most of them were lung cancer patients, possibly increasing their risk of severe respiratory complications when developing SARS-CoV-2 infection.[9,10]

A GU case series was published by Szabados *et al.*, exploring the incidence of COVID-19 among 74 GU cancer patients on ICI treatment. In this report, four patients had symptomatic COVID-19, confirmed with an oropharyngeal swab. All these cases had mild symptoms and complete recovery of the illness. The authors concluded that the higher risk of COVID-19 death associated with systemic therapy in cancer might not apply to patients on ICIs.[11] On the contrary, such data could be interpreted as a potentially low lethality of COVID-19 in GU malignancies.[10]

Contrariwise, the findings provided by the present clinical audit seem to suggest a particular susceptibility to SARS-CoV-2 infection and severity, even more pronounced in mUC patients (incidence 7.7% and mortality 3.1%) than in mRCC patients (incidence 3.5% and mortality 1%). The contribution of chemotherapy in combination with ICI (or likely previously received) in the case of mUC may have had some relevance, but our data were not recorded at the single-patient level, and we could not verify which treatment was ongoing for patients developing COVID-19. Other possible reasons to explain this finding include the fact that mUC patients often have several comorbidities and are often

smokers, both well known as risk factors for a severe outcome from COVID-19,[12] not to take into account the fact that they are usually quite susceptible to bacterial superinfections when hospitalized, considering their frequent use of urinary catheters and derivations. Beyond the disease's overall mortality and incidence, to be contextualized in our Country's epidemiological reality and in the included regions, the case fatality of COVID-19 (30% and 40% in mRCC and mUC patients) was significantly high in our population of GU cancer patients. These findings suggest that GU cancer patients undergoing active treatment with ICIs can have further risk factors for developing severe events in the case of SARS-CoV-2 infection.

The outcomes of interest of the present clinical audit also regarded treatment compliance. During a time frame in which most health care resources were dedicated to managing the COVID-19 emergency, the continuation of anticancer treatments has sometimes been challenging or even impossible, leading to frequent delays and some discontinuations. Furthermore, in the case of COVID-19 infection during ICI treatment, the presence of interstitial pneumonia has been usually perceived as a contraindication to ICI continuation.[6] Patients undergoing systemic treatment for mRCC or mUC, in the case of COVID-19 occurrence during ICI, should temporarily discontinue cancer therapy until complete clinical recovery, and in the case of interstitial pneumonitis at the computed tomography (CT) scan, even in asymptomatic patients, ICI-based therapies should be cautiously discontinued until radiological resolution. Fortunately, our findings suggested that treatment delays or discontinuations due to COVID-19 were rarely responsible for cancer progression.

The main limitation of the present work was its nature of audit: data were not recorded at the single-patient level, with wide margins of uncertainty and approximation when compared with a prospective data collection, given the risk of detection bias. On the contrary, this represents one of the most extensive series of GU cancer patients undergoing immunotherapy, reporting their COVID-19 incidence, outcome, and anticancer treatment management during the pandemic.

Considering the findings emerged, we can speculate that an extensive screening may be offered to these patients before ICI initiation and periodically during treatment. A rapid antigenic swab could be employed in asymptomatic subjects, aiming to detect the infection early and improve their clinical management. This measure would be helpful especially considering the high pre-test probability and the possible severe evolution of COVID-19 in this population, especially in the case of late diagnosis.

## Author contributions

All the authors made a substantial contribution to the concept or design of the work or acquisition, analysis, or interpretation of data; drafted the article or revised it critically for important intellectual content; and approved the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

## Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors declare that there is no conflict of interest for the present article, except those reported herein: Melissa Bersanelli received honoraria as a speaker at scientific events by Bristol-Myers Squibb (BMS), Novartis, AstraZeneca, Pierre Fabre, and Pfizer, and as a consultant for advisory role by Novartis, BMS, IPSEN, and Pfizer; she also received fees for copyright transfer by Sciclone Pharmaceuticals and research funding by Roche S.p.A., Seqirus UK, Pfizer, Novartis, BMS, AstraZeneca, and Sanofi Genzyme. Sebastiano Buti received honoraria as a speaker at scientific events and advisory role by BMS, Pfizer, Merck Sharp & Dohme (MSD), Ipsen, Roche, Eli-Lilly, AstraZeneca, and Novartis; he also received research funding from Novartis. Alessio Cortellini received consulting/advisory board fees from AstraZeneca, MSD, Roche, and BMS; and speakers' fee from Novartis, Astellas, MSD, and AstraZeneca. Orazio Caffo received honoraria as a speaker by Astellas, Bayer, AstraZeneca, Janssen, Pfizer, and Sanofi, and a consultant for advisory role by Astellas, Janssen, and MSD. Paolo Andrea Zucali reports outside the submitted work personal fees for advisory role, speaker engagements, and travel and accommodation expenses from MSD, Astellas, Janssen, Sanofi, Ipsen, Pfizer, Novartis, BMS, Amgen, AstraZeneca, Roche, and Bayer. Camillo Porta received honoraria as a Consultant or Speaker for Angelini, AstraZeneca, BMS, Eisai, EUSA,

General Electric, Ipsen, Janssen, Merck, MSD, Novartis, and Pfizer; acted as an Expert Testimony for EUSA and Pfizer; and was a Protocol Steering Committee Member of BMS, Eisai, and EUSA Pharma. Finally, he did receive travel support from Roche. All other authors have no conflict of interest to declare.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

## ORCID iDs

Melissa Bersanelli https://orcid.org/0000-0002-6527-6281

Marco Stellato https://orcid.org/0000-0002-0993-7540

Sergio Bracarda https://orcid.org/0000-0002-0703-2959

Giuseppe Procopio https://orcid.org/0000-0002-2498-402X

## References

1. World Health Organization. Coronavirus disease (COVID-19) weekly epidemiological update and weekly operational update, 2020, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
2. Covid-19, i casi in Italia: 21 giugno ore 18, https://www.salute.gov.it/portale/nuovocoronavirus/dettaglioNotizieNuovoCoronavirus.jsp?lingua=italiano&menu=notizie&p=dalministero&id=4922
3. Robilotti EV, Babady NE, Mead PA, *et al.* Determinants of COVID-19 disease severity in patients with cancer. *Nat Med* 2020; 26: 1218–1223.
4. Garassino MC, Whisenant JG, Huang LC, *et al.* COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol* 2020; 21: 914–922.
5. Lee LYw, Cazier JB, Angelis V, *et al.* COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet* 2020; 395: 1919–1926.
6. Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. *Immunotherapy* 2020; 12: 269–273.
7. Ribas A and Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science* 2018; 359: 1350–1355.
8. Gandhy SU, Madan RA and Aragon-Ching JB. The immunotherapy revolution in genitourinary malignancies. *Immunotherapy* 2020; 12: 819–831.
9. Bersanelli M, Giannarelli D, De Giorgi U, *et al.* Symptomatic COVID-19 in advanced-cancer patients treated with immune-checkpoint inhibitors: prospective analysis from a multicentre observational trial by FICOG. *Ther Adv Med Oncol* 2020; 12: 1758835920968463.
10. Yu J, Ouyang W, Chua MLK, *et al.* SARS-CoV-2 transmission in patients with cancer at a Tertiary Care Hospital in Wuhan, China. *JAMA Oncol* 2020; 6: 1108–1110.
11. Szabados B, Abu-Ghanem Y, Grant M, *et al.* Clinical characteristics and outcome for four SARS-CoV-2-infected cancer patients treated with immune checkpoint inhibitors. *Eur Urol* 2020; 78: 276–280.
12. Zheng Z, Peng F, Xu B, *et al.* Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect* 2020; 81: e16–e25.