Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

SARS-CoV-2 infections in melanoma patients treated with PD-1 inhibitors: A survey of the German ADOREG melanoma registry

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Dear editors,

Currently, a second dramatic upsurge of SARS-CoV-2 infection rates is observed across Europe, and there is an urgent need to clarify the imminent risk for our melanoma patients under immune checkpoint inhibition (ICI). To this aim, we reviewed the clinical course of disease for all patients included in the registry of the German working group of dermato-oncology (ADOreg, www.hautkrebsregister.de) database with confirmed SARS-CoV-2 infection.

ICI treatment for melanoma might influence the clinical course of a SARS-CoV-2 infection in different ways:

First, cancer patients in general have a compromised immune response and are at a higher risk for severe infections, as reported by Bitterman (2018) [1] for influenza infections. According to several reports from Wuhan (China), the risk for intensive care or mechanical ventilation was higher for cancer patients with COVID-19 than the general population and even more marked when cancer treatment had been received within 14 days of disease onset [2,3].

Second, ICI therapy by itself does not seem to expose cancer patients to an elevated risk of severe infections. In the context of influenza infections, Bersanelli et al.

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Table 1
Patient characteristics.

Sex	Age	Stage (AJCC 2017[a])	Checkpoint inhibitor	Indication[b]	Comorbidities	Symptoms	Days of hospitalisation (ICU[c])	Outcome
m	30	IIIB	Nivolumab	Adjuvant	None	Flu-like, dysgeusia	0	Fully recovered
m	72	IV	Nivolumab +ipilimumab	Palliative	None	Fever, flu-like, dysgeusia	0	Fully recovered
m	62	IV	Nivolumab +ipilimumab	Palliative	Cardiovascular, gastrointestinal	None	0	Asymptomatic
m	71	IV	Nivolumab +ipilimumab	Palliative	Cardiovascular, respiratory	None	0	Asymptomatic
w	65	IIIC	Pembrolizumab	Adjuvant	None	Cough	0	Fully recovered
w	83	IV	Nivolumab +ipilimumab	Adjuvant	Cardiovascular, hypothyroidism, thromboembolism	Cough, fever, dyspnoea, diarrhoea, circulatory symptoms	50(31)	Recovered with sequelae
w	65	IV	Pembrolizumab	Palliative	Cardiovascular	Cough, flu-like symptoms, dysgeusia, headache	0	Fully recovered
m	50	IV	Pembrolizumab	Palliative	None	Cough, fever, dyspnoea, diarrhoea, circulatory symptoms	0	Fully recovered
w	76	IV	Nivolumab	Adjuvant	Cardiovascular, previous cancer, hypothyroidism	Flu-like symptoms, dysgeusia, cough, headache	0	Fully recovered
m	26	IV	Pembrolizumab	Palliative	None	Dysgeusia	0	Fully recovered
w	63	IV	Nivolumab	Palliative	Hypothyroidism	Fever, diarrhoea	10	Fully recovered
w	87	IV	Nivolumab +ipilimumab	Palliative	Rheumatoid arthritis	None	0	Asymptomatic
m	88	IV	Pembrolizumab	Palliative	Hypothyroidism, haematologic, renal insufficiency, cardiovascular, thromboembolism	None	0	Asymptomatic

[a] American Joint Committee on Cancer.
[b] Palliative: in unresectable stage III or IV disease.
[c] ICU, intensive care unit; m, men; w, women.

(2020) [4] even suggested beneficial effects to the immune response, making an argument that these patients might not be at a specific risk and even be protected from severe infections. Flow cytometry studies showed that among others, PD-1 was increased in T-cells patients with COVID-19 who rapidly deteriorated [5], suggesting a potential positive effect of a PD-1 blockade.

Third, in several cases COVID-19 was associated with a cytokine release syndrome because of a massive secretion of pro-inflammatory cytokines, and severe, acute systemic symptoms involving the IL-6 signalling pathway [6]. Similar cytokine release syndromes have been observed under checkpoint inhibition [7]. This might explain a tendency for more severe symptoms, a high rate of hospitalisations [8] and a worse outcome as reported by Robilotti *et al.* [9]. However, it remains unclear if patients on checkpoint-inhibitor treatment are truly more susceptible for a cytokine release syndrome because of COVID-19. Patients with lung cancer were highly represented in all analysed patient groups, and age distribution and comorbidities in these patients differ markedly from melanoma patients.

Among 652 melanoma patients on active ICI in the registry, 13 patients from 10 skin cancer centres were identified between March and July 2020. Median age was 65 (26–88) years. The last treatment cycle was between 0 and 51 days (median: 17) before a positive COVID-19 PCR-test result. Notably, in five cases the infection was presumably transmitted by medical or paramedical staff. Detailed patient data, treatment details, symptoms and outcome are summarised in Table 1.

Four patients had no symptoms associated with COVID-19, and seven had a mild to moderate clinical course. Most frequently flu-like symptoms, cough and dysgeusia were reported. Two patients were hospitalised due to severe symptoms. The first was a 63-year old with a history of hypothyroidism who was hospitalised for 10 days with diarrhoea and fever. The latter, an 83-year old with multiple comorbidities receiving ipilimumab and nivolumab in a good general status (Eastern Cooperative Oncology Group [ECOG] 0) developed fever, dyspnoea, circulatory symptoms and diarrhoea and received treatment in an intensive care unit due to acute respiratory distress syndrome (ARDS) for 31 days and

with mechanical ventilation for 44 days. Fifty days after onset of symptoms, she was discharged without need of oxygenation, but currently remains in a reduced general condition (ECOG 3).

Among seven patients with mild or moderate symptoms (age: 26–71), one without relevant comorbidities had received ipilimumab and nivolumab and six anti-PD1-monotherapy. Of these six, four had no comorbidities, one suffered from arterial hypertension and one had a history of severe cardiovascular disease with myocardial infarction and a history of breast cancer.

Of four asymptomatic patients three had received combination ICI (age 62, 71, 87) and one anti-PD1-monotherapy (age 88). Each except one of them had risk factors for severe COVID-19 due to comorbidities (Table 1).

In summary, we identified few COVID-19 cases among our patients with metastatic melanoma treated with ICI, and the observed course of the disease was mainly asymptomatic or mild without need for intensive care or mechanical ventilation. No exacerbation of immune-related adverse events was observed. One patient developed severe respiratory symptoms with ARDS, and a cytokine release syndrome cannot be excluded in retrospect. Contrarily, three other patients who had also received ipilimumab and nivolumab with equally severe risk factors did not develop severe symptoms of COVID-19, underlining how COVID-19 intensity may vary markedly among individuals and factors other than age and comorbidities yet have to be identified.

In the group of patients treated with PD-1 monotherapy only few patients were asymptomatic. Nevertheless, none had a very severe course of the disease, despite other risk factors such as age and comorbidities. Notably, we observed that patients <75 years and without relevant comorbidities frequently reported symptoms. This might either be explained by a less pronounced immune reaction in the comorbid and elderly or simply by a tendency to associate symptoms to pre-existing conditions rather than COVID-19.

It is noteworthy that at least five patients were infected in medical or paramedical institutions. We therefore strongly advise to reconsider contacts to medical or paramedical staff in regions with a high rate of COVID-19 infections, particularly for patients with comorbidities, who are more susceptible to severe courses of the disease. Repeated COVID-19 testing of patients and medical staff involved must be encouraged.

National and European guidelines for management of cancer during the COVID-19 pandemic offer medical and ethical guidance to reduce infection risks without jeopardising effective and potentially life-saving treatments [10]. However, these recommendations need to be adapted to the local infection rate and the pressure on the healthcare system. The presented data support the authors' current strategy to avoid postponing, interrupting or pausing ICI treatment in melanoma patients due to the COVID-19 pandemic because, the beneficial effects on long-term survival of approximately 50% of patients outweigh the potential risk of a severe COVID-19 infection.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Katharina C Kähler reports being a consultant to Roche, BMS, MSD, Pierre Fabre and receiving travel grants and speaker fees from Roche, BMS, MSD, Amgen, Pierre Fabre and Philogen.

Ralf Gutzmer reports receiving honoraria from Roche, BMS, MSD, Novartis, Amgen, Merck Serono, Almirall Hermal, SUN, Sanofi, Pierre Fabre and being a consultant or advisor for BMS, Roche, Novartis, Almirall Hermal, MSD, Amgen, SUN, Sanofi, Pierre Fabre, merck serono, Bayer, Pfizer. RG reports receiving research funding from Novartis, Pfizer, Johnson & Johnson, Amgen, Merck Serono, Sun Pharma, Sanofi and travel accommodations and expenses from Roche, BMS, Sun Pharma, Merck Serono and Pierre Fabre.

Julia Welzel reports receiving honoraria from MSD.

Lisa Zimmer: LZ reports receiving honoraria from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Pierre Fabre; research funding from Novartis; advisory board roles for Bristol-Myers Squibb, Novartis, Pierre Fabre, Sun Pharma, Sanofi, and Merck Sharp & Dohme; and travel support from Bristol-Myers Squibb, Pierre Fabre, Sanofi, Amgen, Novartis, and Sun Pharma.

Max Schlaak reports receiving honoraria and participation in advisory boards of Bristol-Myers Squibb, Novartis, MSD, Roche, Pierre Fabre, Kyowa Kirin, and Sanofi-Genzyme. MS received travel accommodation and expenses by Novartis, Pierre Fabre, and Sun Pharma.

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Rose KC Moritz reports receiving honoraria from BMS, Pfizer, Merck Serono, Kyowa Kirin and participation in advisory boards by Takeda, Novartis, MSD, BMS, Roche, and Merck Serono. RKCM reports receiving travel accommodations and expenses by BMS, Novartis, Kyowa Kirin, and Ricordati.

All other authors declare no conflict of interest.

References

[1] Bitterman R, et al. Influenza vaccines in immunosuppressed adults with cancer. Cochrane Database Syst Rev 2018;2018.

[2] Liang W, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335–7.
[3] Zhang L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020. https://doi.org/10.1016/j.annonc.2020.03.296.
[4] Bersanelli M, et al. Immunological insights in influenza infection an vaccination during Immune checkpoint blockade in cancer patients. Immunotherapy 2020;12(2):105–10.
[5] Chiappelli F. CoVID-19 immunopathology & immunotherapy. Bioinformation 2020;16:219–22.
[6] Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020. https://doi.org/10.1016/j.ijantimicag.2020.105954.
[7] Slota A, Khan R, Rahman A, Warner EA. Cytokine release syndrome as a rare complication of nivolumab: a case report. Blood 2019;134. 5630–5630.
[8] Rogiers A, et al. Clinical characteristics and outcomes of Coronavirus 2019 disease (COVID-19) in cancer patients treated with immune checkpoint inhibitors (ICI). In: American Assosiation for Cancer Research (AACR) conference proceedings; 2020.
[9] Robilotti EV, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med 2020:1–6. https://doi.org/10.1038/s41591-020-0979-0.
[10] Cancer Patient Management During the COVID-19 Pandemic | ESMO. Available at: https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic. (Accessed: 21st May 2020).