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result: HR 0.78 (95% CI 0.67-0.92,  $P = 0.002$ ). A 6-month landmark analysis was used to determine the association between thyroid dysfunction and overall survival in each malignancy subgroup (Supplementary Figure S1, available at <https://doi.org/10.1016/j.annonc.2021.05.357>). Patients with lung cancer demonstrated the strongest relationship between thyroiditis and overall survival (HR for death 0.56 [95% CI 0.40-0.79],  $P < 0.001$ ). The relationship was least in breast, melanoma, and genitourinary tumors.

In conclusion, after accounting for immortal time bias, we showed a 20% reduction in the aHR for death in patients who develop ICI-induced thyroiditis. The association between thyroiditis and overall survival varied by tumor type, but was strongest in patients with lung cancer, possibly related to the shared developmental origin of thyroid and lung epithelia. Our study demonstrates the large effect of immortal time bias. Future studies with large cohorts are needed to examine the association of other irAEs with survival and must utilize methods that account for immortal time bias.

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## DISCLOSURE

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**Weak immunogenicity after a single dose of SARS-CoV-2 mRNA vaccine in treated cancer patients**



Active cancer and ongoing antineoplastic treatments are major factors for severe coronavirus disease 2019 (COVID-19) and death; reasons why the severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) vaccination remains a priority in cancer patients (CPs).<sup>1</sup> However, immunocompromised patients were excluded from major studies on mRNA vaccines,<sup>2,3</sup> and could have a decreased response to vaccination, as recently demonstrated in solid organ transplant recipients.<sup>4</sup> Herein, we aimed to assess the proportion of antibody response 4 weeks after the first injection of the BNT162b2 (Pfizer-BioNTech) vaccine in CPs and health care workers (HCWs) as the control population.

All consecutive patients with cancer on active treatment or with treatment in the last 2 years and HCWs who underwent SARS-CoV-2 vaccination between 17 February 2021 and 18 March 2021 at the Pitié Salpêtrière Hospital, Paris, France, were selected for analysis. The titration of SARS-CoV-2 antibodies was proposed just before the second injection of BNT162b2 vaccine. Serum anti-nucleoprotein (N) immunoglobulin G (IgG) and anti-spike protein (S) IgG against the receptor binding domain (RBD) of the S1 domain were detected using the Abbott SARS-CoV-2 IgG chemiluminescent microparticle immunoassay (CMIA), according to the manufacturer's instructions. The presence of anti-N IgG was used as a surrogate marker of prior COVID-19.

Statistical analysis consisted of univariable analysis (Chi-square tests) and then multivariable analysis (binary logistic regression, including all variables with  $P$  value  $< 0.1$  in univariable analysis) to determine the factors associated with the lack of seroconversion in CPs. Median titers of anti-S IgG were compared between CPs and HCWs, using a Mood's test. This study was approved by the Commission Nationale de l'Informatique et des Libertés (MR004, registration number: 2221945).

SARS-CoV-2 antibodies were measured in 110 CPs and 25 HCWs (Table 1). In CPs who did not have COVID-19 before vaccination, the seroconversion rate was only 55%, while it reached 100% in HCWs. Titers of anti-S IgG were significantly higher in HCWs in comparison with seropositive CPs (680 versus 315 UA/ml,  $P = 0.04$ ). Sex, cancer locations and metastatic status were similar in seroconverters and non-seroconverter CPs (Supplementary Table S1, available at <https://doi.org/10.1016/j.annonc.2021.04.020>). After adjustment for potential confounders, two factors were strongly associated with no seroconversion: age  $>65$  years [odds ratio 3.58, 95% confidence interval (CI) 1.40-9.15,  $P = 0.008$ ] and treatment by chemotherapy (odds ratio 4.34, 95% CI 1.67-11.30,  $P = 0.003$ ).

No symptomatic COVID-19 occurred between the two injections of vaccine in CPs and HCWs.

In summary, almost half of CPs showed no anti-spike antibody response after the first injection of BNT162b2 vaccine, and this low seroconversion rate could be much worse in elderly patients and in patients under chemotherapy. In comparison, 100% of the HCWs had anti-spike seroconversion. Moreover, even in CPs with seroconversion, the level of antibody response could be lower than expected.

**Table 1. Characteristics of cancer patients and health care workers with SARS-CoV-2 serological outcome**

Cancer patients (N = 110)	
Sex, n (%)	
Women	66 (60)
Men	44 (40)
Age, years, median (IQR)	66 (54-74)
Cancer location, n (%) <sup>a</sup>	
Breast	37 (34)
Lung	15 (14)
Gynecological	15 (14)
Prostate	11 (10)
Digestive	8 (7.3)
Kidney	7 (6.4)
Bladder	5 (4.5)
Upper aero-digestive tract	6 (5.5)
Thyroid	5 (4.5)
Others	3 (2.7)
Cancer staging, n (%)	
Local	47 (43)
Metastatic	63 (57)
Cancer treatment, n (%) <sup>b</sup>	
Chemotherapy	38 (35)
Targeted therapy	26 (24)
Immunotherapy	17 (16)
Hormonotherapy	16 (15)
Radiotherapy	6 (5.5)
Clinical surveillance	18 (16)
Time between first vaccine injection and SARS-CoV-2 serology, days, median (IQR)	27 (26-28)
Positive anti-N IgG, n (%) <sup>c</sup>	15 (14)
Positive anti-S IgG, n (%) <sup>c</sup>	
In all patients	64 (58)
Among patients with positive anti-N IgG (N = 15)	12 (80)
Among patients with negative anti-N IgG (N = 95)	52 (55)
Titer of anti-S IgG, UA/mL, median (IQR)	
In all anti-S positive patients (N = 64)	359 (178-998)
Among patients with positive anti-N IgG (N = 12)	657 (366-14, 112)
Among patients with negative anti-N IgG (N = 52)	315 (140-748)
Health care workers (N = 25)	
Sex, n (%)	
Women	18 (72)
Men	7 (28)
Age, years, median (IQR)	55 (38-62)
Time between first vaccine injection and SARS-CoV-2 serology, days, median (IQR)	23 (21-27)
Positive anti-N IgG, n (%) <sup>c</sup>	0 (0)
Positive anti-S IgG, n (%) <sup>c</sup>	25 (100)
Titer of anti-S IgG, UA/mL, median (IQR)	680 (360-930)

IQR, interquartile range; N, nucleoprotein; S, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup> Two patients had synchronous cancers (prostate + lung and prostate + colon).

<sup>b</sup> Non-exclusive categories.

<sup>c</sup> Abbott SARS-CoV-2 IgG chemiluminescent microparticle immunoassay (CMIA), with detection threshold: 0.8 UA/ml for anti-N IgG, and detection threshold: 50 UA/ml for anti-S IgG.

In conclusion, our findings argue for not extending the 21-day period between the two SARS-CoV-2 vaccine injections in CPs, and for performing serological monitoring to assess antibody response in this particular population, which could lead to adapting this vaccine strategy. We would also recommend a vaccine strategy including family and friendship circles.

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## Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors



Patients in the active phase of treatment for cancer are a population at risk of coronavirus disease-19 (COVID-19) with poor prognosis.<sup>1</sup> While a majority of patients treated for cancer expressed their will to be vaccinated as early as December 2020 in a French survey,<sup>2</sup> no data were available in terms of vaccine efficacy and tolerance, because they were excluded from initial registration trials.

From the beginning of French vaccination campaign, we set up a BNT162b2 (Pfizer/BioNtech) vaccine monitoring observatory (VMO) for vaccinated patients under active treatment in the Department of Oncology of the Saint Jean Polyclinic, Nice, France (~9000 annual treatment sessions). All participants signed a written consent after receiving an information letter and the VMO was registered with the French authorities, according to ethical and legal policies. A control group of healthy volunteers (HVs), i.e. without known ongoing cancer, was also formed and vaccinated during the same period. Serological assays were realized at week (w) 0 during the first vaccination, during the booster (w3-w4) and 3-4 weeks after the booster (w6-w8). Immunogenicity was measured with Elecsys® Anti-SARS-CoV-2 immunoassay (Roche Diagnostics, Mélan, France) with detection of antibodies directed to total antibodies against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein receptor-binding domain (quantitative detection). Serum showing a result  $\geq 0.8$  UI/ml was declared positive.

We report the results of the first 122 assessable patients with solid tumors included since 18 January 2021 having carried out at least two serologies by 15 March 2021 out of 194 vaccinated patients during this period (64.4%). Three patients were excluded from the final analysis because they had pre-vaccine anti-SARS-CoV-2 immunity. The median age of the 122 patients was 69.5 years (44-90 years), with 64 men (52.5%) and 58 women (47.5%). We analyzed 31 HVs; 2 were excluded from the analysis because they had pre-vaccine immunity against SARS-CoV-2. Among the remaining 29 HVs with a median age of 53 years (range: 21-81 years), 13 carried out the intermediate assessment at w3-w4 and 24 carried out their final w6-w8 assessment.

Among the 122 patients, 105 (86.0%) were treated with chemotherapy (CT)  $\pm$  targeted therapy. One patient developed COVID-19 with a positive PCR at day 12 from vaccine dose 1. The outcome was quickly favorable and the patient had his booster dose at w3. During the first