Reply to K. Takada et al.

To the Editor:

We thank Takada et al.[1] for their insightful comments on our recent article that describes the tolerability of coronavirus disease 2019 (COVID-19) vaccines, BNT162b2 and mRNA-1273, in patients with thymic epithelial tumors (TETs).[2]

Takada et al. raise an important point on the potential impact of concomitant medications on the tolerability of vaccination and highlight a recent article by Nelli et al.[3] which found that patients receiving granulocyte colony-stimulating factor (G-CSF) had a statistically significant increase in the risk of fever after vaccination with the BNT162b2 vaccine (OR = 3.37, $p = 0.022$). Recognizing the impact of concomitant medications, especially those that can suppress potential vaccine-related adverse events (AEs), we had reported use of immunosuppressants, including corticosteroids, nonsteroidal anti-inflammatory drugs, and acetaminophen in our article.[2] To address the observation of an increase in the risk of systemic AEs after vaccination with BNT162b2 in patients receiving concomitant G-CSF which was reported after publication of our article, we have evaluated the effect of concurrent anticancer therapy and G-CSF on the tolerability of the BNT162b2 and mRNA-1273 vaccines in our patient cohort. Information on anticancer therapy at the time of administration of the first dose of these vaccines was available for 52 patients. A total of 26 patients (50%) were receiving anticancer therapy (chemotherapy, n = 12; immunotherapy, n = 9; other anticancer therapy, n = 5). No substantial differences in the tolerability of the BNT162b2 or mRNA-1273 vaccine were observed between individuals receiving anticancer therapy and those who were not on active anticancer treatment (Table 1). Furthermore, information on concurrent G-CSF use was available for 50 patients, and only two patients (4%) were receiving G-CSF at the time of vaccination (BNT162b2, n = 1; mRNA-1273, n = 1). Neither patient developed fever or other systemic AEs after either dose of the vaccine, except for moderate, self-limited fatigue after the second dose of the BNT162b2 vaccine, which could also have been related to concurrent chemotherapy. Although comparisons are limited by the relatively small number of participants reporting AEs in each group, our results reveal no substantial effect of concurrent anticancer therapy or G-CSF use on the tolerability of the BNT162b2 and mRNA-1273 vaccines in patients with TETs.

Takada et al. also note the frequency of axillary lymphadenopathy on computed tomography scans after vaccination with the BNT162b2 and mRNA-1273 vaccines in patients with thoracic malignancies reported by Nishino et al.[4] recently (7.4% and 21%, respectively). This is an important clinical consideration not only because painful lymphadenopathy can adversely affect the tolerability of vaccination but also because the emergence of lymphadenopathy can be misinterpreted as progression of the underlying cancer. As pointed out by Takada et al., we reported "axillary swelling" in 1 of 29 patients with TETs (3.45%) after the second dose of the mRNA-1273 vaccine compared with 1956 participants (14.03%) in the Moderna vaccine trial.[2] We did not report the frequency of axillary lymphadenopathy after vaccination with BNT162b2 for the following reasons: first, Pfizer-BioNTech did not consider lymphadenopathy a solicited AE in clinical trials of BNT162b2; second, although BNT162b2-related lymphadenopathy is reported as an unsolicited AE in 64 individuals (0.3%) who participated in clinical trials of the vaccine, it is unclear if these cases refer to axillary lymphadenopathy alone or lymph node enlargement at other anatomical sites.[5] Thus, it was difficult to make a direct comparison of the frequency of axillary lymphadenopathy after BNT162b2 vaccination in patients with TETs versus participants in clinical trials of the vaccine. Nevertheless, 2 of the 25 patients (8.0%) with TETs who received the BNT162b2 vaccine experienced "axillary swelling" after their first dose, as did 1 of the 23 patients (4.3%) with TETs who received a second dose of the BNT162b2 vaccine before data cutoff. These results are consistent with the observations of Nishino et al.[4] and attest to the favorable safety profile of these vaccines in patients with TETs.

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Table 1. Effect of Anticancer Treatment on the Tolerability of the BNT162b2 and mRNA-1273 Vaccines in Patients With Thymic Epithelial Tumors

Both Vaccines Combined

	AEs After Vaccination, n (%)			AEs After Vaccination, n (%)		
Symptoms	On Concurrent Anticancer Treatment	No Concurrent Anticancer Treatment	*p* Value	On Concurrent Chemotherapy	No Concurrent Chemotherapy	*p* Value
Local pain	20 (76.9)	20 (76.9)	1.00	8 (66.7)	32 (80)	0.44
Local redness	1 (3.9)	1 (3.9)	1.00	1 (8.3)	1 (2.5)	0.41
Local swelling	2 (7.7)	3 (11.5)	1.00	1 (8.3)	4 (10)	1.00
Axillary LAD	1 (3.9)	1 (3.9)	1.00	1 (8.3)	1 (2.5)	0.41
Fatigue	7 (26.9)	5 (19.2)	0.74	2 (16.7)	10 (25)	0.71
Headache	7 (26.9)	3 (11.5)	0.29	3 (25)	7 (17.5)	0.68
Myalgia	3 (11.5)	1 (3.9)	0.61	1 (8.3)	3 (7.5)	1.00
Arthralgia	2 (7.7)	2 (7.7)	1.00	1 (8.3)	3 (7.5)	1.00
Chills	2 (7.7)	2 (7.7)	1.00	1 (8.3)	3 (7.5)	1.00
Fever	1 (3.9)	0 (0)	1.00	0 (0)	1 (2.5)	1.00
Nausea	1 (3.9)	0 (0)	1.00	0 (0)	1 (2.5)	1.00
Vomiting	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Diarrhea	3 (11.5)	0 (0)	0.24	2 (16.7)	1 (2.5)	0.13

BNT-162b2

	AEs After Vaccination, n (%)			AEs After Vaccination, n (%)		
Symptoms	On Concurrent Anticancer Treatment	No Concurrent Anticancer Treatment	*p* Value	On Concurrent Chemotherapy	No Concurrent Chemotherapy	*p* Value
Local pain	6 (60)	9 (64.3)	1.00	3 (50)	12 (66.7)	0.63
Local redness	0 (0)	1 (7.14)	1.00	0 (0)	1 (5.6)	1.00
Local swelling	0 (0)	2 (14.3)	0.49	0 (0)	2 (11.1)	1.00
Axillary LAD	1 (10)	1 (7.1)	1.00	1 (16.7)	1 (5.6)	0.45
Fatigue	3 (30)	4 (28.6)	1.00	1 (16.7)	6 (33.3)	0.63
Headache	3 (30)	1 (7.1)	0.27	1 (16.7)	3 (16.7)	1.00
Myalgia	1 (10)	0 (0)	0.42	0 (0)	1 (5.6)	1.00
Arthralgia	1 (10)	1 (7.1)	1.00	0 (0)	2 (11.1)	1.00
Chills	1 (10)	1 (7.1)	1.00	0 (0)	2 (11.1)	1.00
Fever	1 (10)	0 (0)	0.42	0 (0)	1 (5.6)	1.00
Nausea	1 (10)	0 (0)	0.42	0 (0)	1 (5.6)	1.00
Vomiting	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Diarrhea	0 (0)	0 (0)	—	0 (0)	0 (0)	—

(continued)

Table 1. Continued

mRNA-1273

Symptoms	AEs After Vaccination, n (%)			AEs After Vaccination, n (%)		
	On Concurrent Anticancer Treatment	No Concurrent Anticancer Treatment	*p* Value	On Concurrent Chemotherapy	No Concurrent Chemotherapy	*p* Value
Local pain	14 (87.5)	11 (91.7)	1.00	5 (83.3)	20 (90.9)	0.53
Local redness	1 (6.3)	0 (0)	1.00	1 (16.7)	0 (0)	0.21
Local swelling	2 (12.5)	1 (8.3)	1.00	1 (16.7)	2 (9.1)	0.53
Axillary LAD	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Fatigue	4 (25)	1 (8.3)	0.36	1 (16.7)	4 (18.2)	1.00
Headache	4 (25)	2 (16.7)	0.67	2 (33.3)	4 (18.2)	0.58
Myalgia	2 (12.5)	1 (8.3)	1.00	1 (16.7)	2 (9.1)	0.53
Arthralgia	1 (6.3)	1 (8.3)	1.00	1 (16.7)	1 (4.6)	0.39
Chills	1 (6.3)	1 (8.3)	1.00	2 (16.7)	1 (4.6)	0.39
Fever	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Nausea	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Vomiting	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Diarrhea	3 (18.8)	0 (0)	0.24	3 (33.3)	1 (4.6)	0.11

Note: AE data are presented for the first dose of vaccination for the combined study population and for individuals receiving each vaccine. Concurrent anticancer treatment, including chemotherapy, does not seem to have a substantial impact on the tolerability of the BNT162b2 and mRNA-1273 vaccines. Anticancer treatment includes chemotherapy (n = 12), immunotherapy (immune checkpoint inhibitors, n = 7; immunocytokine, n = 1; antibody-drug conjugate, n = 1), and targeted therapy (small molecule inhibitors, n = 4; somatostatin analogue, n = 1).
AE, adverse event; LAD, lymphadenopathy.

Rapidly emerging data from studies in individuals with different medical conditions, including cancer, are likely to further clarify the impact of clinical variables on the safety and clinical activity of COVID-19 vaccines. On the basis of currently available data, we continue to encourage consideration of vaccination against COVID-19 in patients with TETs because potential benefits outweigh the risk of vaccine-related AEs.

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Eva Szabo: Visualization, Writing—review and editing.

Seth M. Steinberg: Methodology, Formal analysis, Software, Resources, Writing—review and editing.

Arun Rajan: Conceptualization, Methodology, Visualization, Project administration, Resources, Supervision, Writing—original draft, Writing—review and editing.

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