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Letter

COVID-19 mRNA booster vaccines elicit strong protection against SARS-CoV-2 Omicron variant in patients with cancer

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The emerging SARS-CoV-2 Omicron (B.1.1.529) variant has caused considerable concern about the future of containing the ongoing COVID-19 pandemic (World Health Organization, 2021). First isolated in late November of 2021, the Omicron variant harbors a staggering 30–40 mutations in the viral spike (S) protein, including substantial changes to the S-receptor-binding domain, that have produced significant concern about the potentially high immune evasion of this variant (World Health Organization, 2021). Additionally, the rapid increase in COVID-19 cases attributed to the Omicron variant (Karim and Karim, 2021) has caused major public health concern about its increased transmissibility. We recently reported that the Omicron variant exhibits drastic resistance to neutralizing antibodies (nAbs) in healthy recipients of two-dose mRNA-1273 or BNT162b2 mRNA vaccines, as well as in COVID-19 patients (Zeng et al., 2021a). However, healthy individuals who received an additional third mRNA booster vaccine dose exhibit much stronger protection against the Omicron variant, comparable to their protection against other SARS-CoV-2 variants of concern (VOCs) (Zeng et al., 2021a). Our results indicate that not only does booster vaccination enhances nAb levels, but it also broadens the nAb response against these VOCs, including the Omicron variant.

However, it remains unclear how booster vaccination impacts immunity against the Omicron variant in immunocompromised groups, especially in patients with cancer who are on active therapy. A report from our group has recently shown that patients with cancer are a key group of immunocompromised individuals with reduced responsiveness to two-dose mRNA vaccination (Zeng et al., 2021b). This reduced vaccine responsiveness can be somewhat overcome by the administration of booster vaccine doses (Greenberger et al., 2021; Shapiro et al., 2021). However, the breadth of the nAb response in these boosted patients, in particular their immunity against the Omicron variant, remains unclear. This is a critical question to resolve in order to determine future vaccination strategies, especially the administration of additional booster doses, for immunocompromised groups.

To address this urgent need, we utilized our previously reported, highly sensitive, pseudotyped-lentivirus neutralization assay (Zeng et al., 2020) to examine the nAb response to Omicron compared to Delta and the ancestral D614G variants in patients with cancer (n = 50) following two mRNA vaccine doses (n = 23) and three doses including a third booster vaccine (n = 27). Samples were collected between 31 and 121 days (median 95 days) after the second mRNA vaccine dose for 15 lung cancer patients vaccinated with mRNA-1273 (n = 10) or BNT162b2 (n = 5) and 8 breast cancer patients vaccinated with mRNA-1273 (n = 2) or BNT162b2 (n = 6). For booster vaccine recipients, samples were collected between 2 and 112 days (median 47 days) after the third mRNA vaccine dose for patient with solid tumors, including 12 breast cancer patients vaccinated with mRNA-1273 (n = 4) or BNT162b2 (n = 8) and a mix of patients with 15 other types of solid tumor (such as melanoma, genitourinary, gastrointestinal, etc.) who were vaccinated with either mRNA-1273 (n = 5) or BNT162b2 (n = 10) (Table S1).

Neutralizing Ab titers (NT_{50}) were measured against the Omicron variant, along with the ancestral D614G SARS-CoV-2 and the Delta variant, the latter being responsible for the most recent wave of infections. We found that, for recipients of two mRNA vaccine doses, the Delta and Omicron variants exhibited a 4.2-fold ($p < 0.01$) and 21.3-fold ($p < 0.01$) reduction in NT_{50}, respectively, compared to D614G (Figure S1A). Notably, 0% (0/23), 13.0% (3/23), and 52.2% (12/23) of patients exhibited nAb titers below the limit of detection ($NT_{50} < 40$, as determined by the lowest dilution used in the neutralization assay) for the D614G, Delta, and Omicron variants (Figure S1A), respectively. These results clearly demonstrate the strong nAb resistance of the Omicron variant against two mRNA vaccine doses in patients with cancer. Additionally, mRNA-1273 patients exhibited statistically insignificant higher nAb titers compared to those vaccinated with BNT162b2 (Figure S1B).

We further examined the nAb titers against the Omicron, D614G, and Delta variants for patients with cancer who received a third dose of vaccine, i.e., a booster dose. Overall, booster recipients exhibited dramatically increased nAb titers (Figure S1C). Strikingly, we found that the Omicron variant only exhibited a 5.1-fold ($p < 0.0001$) reduction in nAb titers, compared to D614G (Figure S1C), and this indicates generation of a stronger and much broader neutralization against the Omicron variant after the booster vaccination. The nAb titer against the Delta variant in booster recipients dropped by 3.6-fold compared to D614G, which was comparable to the two-dose vaccination (Figure S1C). Of note, 0% (0/27), 0% (0/27), and 11.1% (3/27) patients exhibited nAb titers below the limit of detection ($NT_{50} < 80$; the lowest dilution used was 1:80 because of relatively high titer for boosters) for the D614G, Delta, and Omicron variants, respectively (Figure S1C). These results were in sharp contrast to the results for the two-dose vaccination regime, showing that a booster mRNA vaccine dose likely provides significantly enhanced broader protection against the Omicron variant for patients with cancer, which is similar to the observed protection against Omicron in healthy boosted individuals. We found that BNT162b2-boosted patients showed higher nAb titers than did mRNA-1273-boosted patients, although the difference was not statistically significant (Figure S1D).

We also examined the impact of anti-PD-1/PD-L1 treatments on nAb response in two-dose and booster-vaccinated patients with cancer. We observed statistically insignificant differences in NT_{50} titers in non-PD-1/PD-L1-treated patients compared to patients treated with immune checkpoint blockers regardless of whether they had received two-dose vaccines or three doses including the booster shots (Figure S1E).

Despite previous findings that nAb response to mRNA vaccination is age dependent (Collier et al., 2021), we did not observe a statistically significant correlation between age and NT_{50} values in these patients with cancer (Figure S1F); this was likely due to the skewing to older populations and the relatively small size of this cohort. Given increasing concerns about declining efficacy of SARS-CoV-2 vaccines, especially against VOCs (Keehner et al., 2021), we also examined the correlation between NT_{50} and time after the second vaccine dose for patients with cancer. We observed a negative correlation between time after second and booster doses of mRNA vaccine and NT_{50} values (Figures S1G); however, these correlations were not statistically significant, again likely because of the limited sample sizes in this cohort. Nevertheless, these results suggest possible waning immune protection of nAbs against SARS-CoV-2 and VOCs following mRNA vaccination, including vaccination with the booster.

In this work, we investigated the efficacy of mRNA-vaccine-induced nAb response in patients with solid tumors against the Omicron variant in parallel with the ancestral D614G and the Delta variants. Our results demonstrate that patients with cancer who received a booster dose of the mRNA vaccine displayed a significantly greater neutralizing capacity against the Omicron variant in comparison to those recipients of only the two-dose mRNA vaccine. This result aligns with findings in health care workers (HCWs) (Zeng et al., 2021a). Although the mechanism underlying the enhanced breadth of the nAb activity against Omicron, and likely other emerging variants, requires further investigation, our results provide reassurance that a booster after two-dose mRNA vaccination likely enhances protection in patients with solid tumors.

The recent emergence of VOCs for SARS-CoV-2 has made the impact of vaccine response in immunocompromised individuals, and particularly in patients with cancer, a topic of significant interest. Our study demonstrates that the diagnosis of a solid cancer *per se* does not appear to negatively impact the humoral immune response to booster-mediated protections against SARS-CoV-2 variants, including Omicron. Some of the limitations of this study include the small size of the cohort (n = 50 patients with cancer), the differences between the two-dose and booster cohorts regarding solid tumor subtypes, and also the timing of sample collection after vaccination. Additionally, the utilization of a single assay to evaluate nAb levels may not be fully representative of the status of infection protection in these patients with cancer. Finally, our study did not address the risk of breakthrough infections clinically. Therefore, patients with cancer should still remain cautious regarding immunity to the Omicron variant even after vaccination with an mRNA booster.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.12.014.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

Collier, D.A., Ferreira, I.A.T.M., Kotagiri, P., Datir, R.P., Lim, E.Y., Touizer, E., Meng, B., Abdullahi, A., Elmer, A., Kingston, N., et al.; CITIID-NIHR BioResource COVID-19 Collaboration (2021). Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature *596*, 417–422.

Greenberger, L.M., Saltzman, L.A., Senefeld, J.W., Johnson, P.W., DeGennaro, L.J., and Nichols, G.L. (2021). Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B cell-derived hematologic malignancies. Cancer Cell *39*, 1297–1299.

Karim, S.S.A., and Karim, Q.A. (2021). Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. Lancet *398*, 2126–2128.

Keehner, J., Horton, L.E., Binkin, N.J., Laurent, L.C., Pride, D., Longhurst, C.A., Abeles, S.R., and Torriani, F.J.; SEARCH Alliance (2021). Resurgence of SARS-CoV-2 infection in a highly vaccinated health system workforce. N. Engl. J. Med. *385*, 1330–1332.

Shapiro, L.C., Thakkar, A., Campbell, S.T., Forest, S.K., Pradhan, K., Gonzalez-Lugo, J.D., Quinn, R., Bhagat, T.D., Choudhary, G.S., McCort, M., et al. (2021). Efficacy of booster doses in augmenting waning immune responses to COVID-19 vaccine in patients with cancer. Cancer Cell *40*, S1535-6108(21)00606-1.

World Health Organization (2021). Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. Pulliam, J.R.C., Schalkwyk, C.V, Govender, N., Gottberg, A.V., Cohen, C., Groome, M. J., Dushoff, J., Mlisana, K, and Moultrie, H. (2021). Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa (MedRxiv).

Zeng, C., Evans, J.P., Pearson, R., Qu, P., Zheng, Y.-M., Robinson, R.T., Hall-Stoodley, L., Yount, J., Pannu, S., Mallampalli, R.K., et al. (2020). Neutralizing antibody against SARS-CoV-2 spike in COVID-19 patients, health care workers, and convalescent plasma donors. JCI Insight *5*, 143213.

Zeng, C., Evans, J.P., Qu, P., Faraone, J., Zheng, Y.-M., Carlin, C., Bednash, J.S., Zhou, T., Lozanski, G., Mallampalli, R., et al. (2021a). Neutralization and stability of SARS-CoV-2 Omicron variant. bioRxiv. https://doi.org/10.1101/2021.12.16.472934.

Zeng, C., Evans, J.P., Reisinger, S., Woyach, J., Liscynesky, C., Boghdadly, Z.E., Rubinstein, M.P., Chakravarthy, K., Saif, L., Oltz, E.M., et al. (2021b). Impaired neutralizing antibody response to COVID-19 mRNA vaccines in cancer patients. Cell Biosci. *11*, 197.

Cancer Cell, Volume *40*

Supplemental information

COVID-19 mRNA booster vaccines elicit strong protection against SARS-CoV-2 Omicron variant in patients with cancer

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Supplemental Methods

Patient Cohorts

Sera were obtained from patients with cancer under an approved IRB protocol (2021C0041). Samples were collected between 31 and 121 days post-second mRNA vaccine dose (n = 23) for 8 breast cancer patients (all female) vaccinated with mRNA-1273 (n = 2) or BNT162b2 (n = 6) and for 15 lung cancer patients (6 female and 9 male) vaccinated with mRNA-1273 (n = 10) or BNT162b2 (n = 5). These patients had a median age of 63 (IQR = 13).

For booster vaccine recipients (n = 27), samples were collected between 2 and 112 days post second mRNA vaccine dose for 12 breast cancer patients (all females) vaccinated with mRNA-1273 (n = 4) or BNT162b2 (n = 8); 5 genitourinary cancer, 5 gastrointestinal cancer, 3 melanoma, 1 sarcoma, and 1 thymic cancer patients vaccinated with mRNA-1273 (n = 5) or BNT162b2 (n = 10); these patients had a median age of 58 (IQR = 13).

Plasmids

For pseudotyped virus production we utilized our previously reported pNL4-3-inGluc lentivirus vector (Zeng et al., 2021a). This vector is based on ΔEnv HIV-1 and bears a *Gaussia* luciferase reporter gene in anti-sense orientation relative to the HIV-1 genome. The reporter gene then contains an intron oriented in the sense orientation relative to the HIV-1 genome to prevent *Gaussia* luciferase expression in the virus producer cells. Additionally, we utilized N- and C-terminally Flag-tagged SARS-CoV-2 S expression constructs that were generated and cloned into pcDNA3.1 using Kpn I and BamH I restriction enzyme cloning by GenScript Biotech (Piscataway, NJ). The constructs contained the following mutations, D614G: D614G; Delta (B.1.617.2): T19R, Δ156-158, L452R, T478K, D614G, P681R, D950N; and Omicron (B.1.1.529): A67V, Δ69-70,

T95I, G142D, Δ143-145, N211I, L212VPE, V213P, R214E, G339D, R346K, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F.

Cell Lines and Maintenance

HEK293T (ATCC CRL-11268, CVCL_1926) and HEK293T-ACE2 (BEI NR-52511) cells were maintained in DMEM (Gibco, 11965-092) supplemented with 10% FBS (Sigma, F1051) and 1% penicillin-streptomycin (HyClone, SV30010) and kept at 37°C and 5% CO_2.

Virus Production and Titering

Lentiviral pseudotypes were produced as previously reported (Zeng et al., 2020, Zeng et al., 2021a). HEK293T cells were transfected with pNL4-3-inGluc and various S constructs in a 2:1 ratio using polyethylenimine transfection. Virus was collected 24, 48, and 72 hrs after transfection, pooled, and stored at -80°C. To determine the relative infectivity of pseudotypes, virus was used to infect HEK293T-ACE2 cells and media from infected cells was assayed for *Gaussia* luciferase activity 48 and 72 hrs after infection, by combining 20 μL of cell culture media with 20 μL of *Gaussia* luciferase substrate (0.1 M Tris (MilliporeSigma, #T6066) pH 7.4, 0.3 M sodium ascorbate (Spectrum, S1349), 10 μM coelenterazine (GoldBio, CZ2.5)). Luminescence measurements were taken with a BioTek Cytation5 plate reader.

Pseudotyped Lentivirus Neutralization Assays

Pseudotyped lentivirus neutralization assays were performed as previously described(1, 2). Briefly, patient sera were 4-fold serially diluted and then incubated with pseudotyped virus at 37°C for 1 hr (final dilutions of 1:40, 1:160, 1:640, 1:2560, 1:10240, and no serum control). Following incubation, sera and virus was transferred to seeded HEK293T-ACE2 cells for infection. Media of infected cells was assayed for *Gaussia* luciferase activity 48 and 72 hrs after infection by combining 20 μL of cell culture media with 20 μL or *Gaussia* luciferase substrate. Luminescence was measured by a BioTek Cytation5 plate reader. 50% neutralization titers (NT_{50}) values were calculated from luminescence readout by least-squares-fit, non-linear regression performed in GraphPad Prism 5 (San Diego, CA).

Statistics

Comparisons between multiple groups were made using one-way ANOVA with Bonferroni's multiple testing correction. Comparisons between two groups were made using two-tailed t-test with Welch's correction.

Supplemental References

Zeng, C., Evans, J.P., Qu, P., Faraone, J., Zheng, Y.-M., Carlin, C., Bednash, J.S., Zhou, T., Lozanski, G., Mallampalli, R., Saif, L.J., Oltz, E.O., Mohler, P., Xu, K., Gumina, R.J., and Liu, S.-L. (2021). Neutralization and stability of SARS-CoV-2 Omicron variant. *BioRxiv*.

Zeng, C., Evans, J.P., Pearson, R., Qu, P., Zheng, Y.-M., Robinson, R.T., Hall-Stoodley, L., Yount, J., Pannu, S., Mallampalli, R.K., Linda, S., Oltz, E., Lozanski, G., and Liu, S.-L. (2020). Neutralizing antibody against SARS-CoV-2 spike in COVID-19 patients, health care workers, and convalescent plasma donors. *JCI insight* **5**.

Table S1. Demographic information of patients with cancer

		Total (n=50)		Two-Dose (n=23)		Booster (n=27)	
		n	(%)	n	(%)	n	(%)
Age Group (years)	30-44	4	8.0%	1	4.3%	3	11.1%
	45-59	20	40.0%	9	39.1%	11	40.7%
	60-74	23	46.0%	11	47.9%	12	44.5%
	75-85	3	6.0%	2	8.7%	1	3.7%
Sex	Male	16	32.0%	9	39.1%	7	25.9
	Female	34	68.0%	14	60.9%	20	74.1
Race	African American/Black	3	6.0%	2	8.7%	1	3.7%
	Asian Chinese	1	2.0%	0	0.0%	1	3.7%
	White	45	90.0%	21	91.3%	24	88.9%
	American Indian/Alaskan	1	2.0%	0	0.0%	1	3.7%
Vaccine	mRNA-1273	21	42.0%	12	52.2%	9	33.3%
	BNT162b2	29	58.0%	11	47.8%	18	66.7%
Solid Tumor Type	Lung	15	30.0%	15	65.2%	0	0.0%
	Breast	20	40.0%	8	34.8%	12	44.4%
	Gastrointestinal	5	10.0%	0	0.0%	5	18.5%
	Genitourinary	5	10.0%	0	0.0%	5	18.5%
	Melanoma	3	6.0%	0	0.0%	3	11.2%
	Thymic carcinoma	1	2.0%	0	0.0%	1	3.7%
	Sarcoma	1	2.0%	0	0.0%	1	3.7%
WBC (k/µL)	<4.5	13	26.0%	4	17.4%	9	33.3%
	4.5–11.0	32	64.0%	15	65.2%	17	63.0%
	>11.0	5	10.0%	4	17.4%	1	3.7%
Lymphocyte Count (k/µL)	<1.0	20	40.0%	12	52.2%	8	3.0%
	1.0–4.8	29	58.0%	10	43.5%	19	70.0%
	>4.8	1	2.0%	1	4.3%	0	0.0%
Immunotherapy	Anti-PD-1/PD-L1*	25	50.0%	13	56.5%	12	44.4%

*The anti-PD-1/PD-L1 drugs include Nivolumab, Pembrolizumab, Durvalumab, Atezolizumab, and Avelumab.

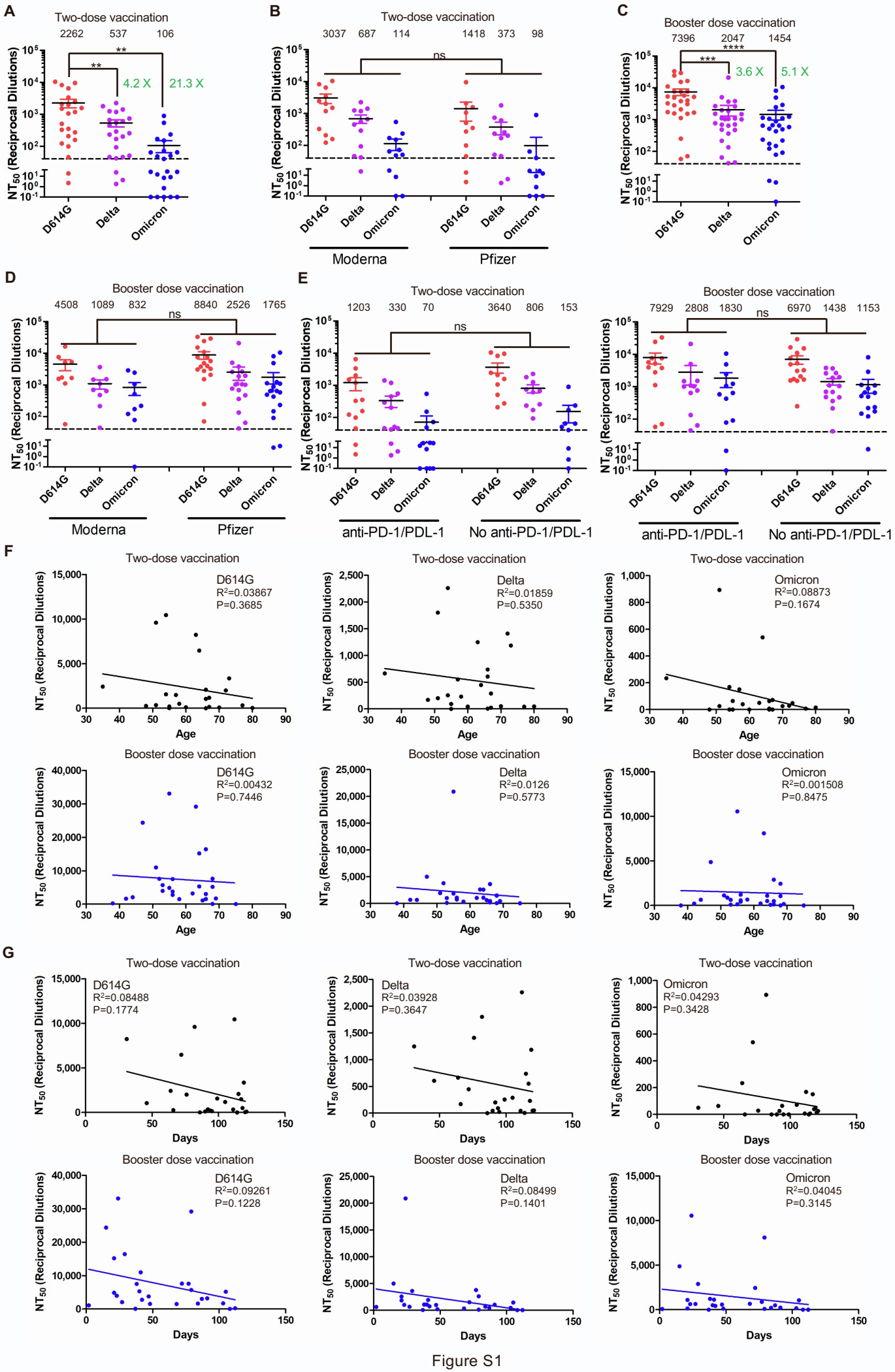
A
Two-dose vaccination
2262 537 106
**
**
4.2 X
21.3 X
B
Two-dose vaccination
3037 687 114 1418 373 98
ns
Moderna
Pfizer
C
Booster dose vaccination
7396 2047 1454
***
****
3.6 X
5.1 X
D
Booster dose vaccination
4508 1089 832 8840 2526 1765
ns
Moderna
Pfizer
E
Two-dose vaccination
1203 330 70 3640 806 153
ns
anti-PD-1/PDL-1
No anti-PD-1/PDL-1
Booster dose vaccination
7929 2808 1830 6970 1438 1153
ns
anti-PD-1/PDL-1
No anti-PD-1/PDL-1
NT50 (Reciprocal Dilutions)
D614G
Delta
Omicron
F
Two-dose vaccination
D614G
R²=0.03867
P=0.3685
Delta
R²=0.01859
P=0.5350
Omicron
R²=0.08873
P=0.1674
Booster dose vaccination
D614G
R²=0.00432
P=0.7446
Delta
R²=0.0126
P=0.5773
Omicron
R²=0.001508
P=0.8475
Age
G
Two-dose vaccination
D614G
R²=0.08488
P=0.1774
Delta
R²=0.03928
P=0.3647
Omicron
R²=0.04293
P=0.3428
Booster dose vaccination
D614G
R²=0.09261
P=0.1228
Delta
R²=0.08499
P=0.1401
Omicron
R²=0.04045
P=0.3145
Days

Figure S1

Figure S1. The Omicron variant exhibits strong immune-escape in two-dose-vaccinated patients with cancer which is overcome by booster vaccinations

Gaussia luciferase reporter gene-bearing lentiviral vector was pseudotyped with spike from SARS-CoV-2 variant of interest, and pseudotyped viruses were then incubated with serially-diluted patient serum before being used to infect HEK293T-ACE2 cells. Culture media were changed after overnight infection and were measured for the luciferase activity at 48 and 72 hrs post-infection. (**A** and **B**) Sera from 23 patients with solid cancer collected after second mRNA vaccine dose (12 mRNA-1273 and 11 BNT16b2) were used to neutralize pseudotyped virus bearing the spike of D614G, Delta and Omicron variants, and resulting 50% neutralization titers (NT_{50}) were calculated. (**C** and **D**) Sera from 27 patients with solid cancer collected after booster vaccination (9 mRNA-1273 and 18 BNT16b2) were used to neutralize pseudotyped viruses of D614G, Delta or Omicron variants, with NT_{50} calculated. (**E**) NT_{50} values against D614G, Delta and Omicron variants in cancer patients, with or without anti-PD-1/PDL-1 treatments: two-dose vaccination and booster dose vaccination. (**F**) Correlative analyses between NT_{50} values against variants and patient's age: two-dose vaccination and booster vaccination. (**G**) Correlative analyses between NT_{50} against variants and sera collection days: two-dose vaccination and booster vaccination. In all cases, mean NT_{50} values are displayed at the top of each plot; bars represent mean +/- standard error, and significance is determined by one-way ANOVA with Bonferroni's multiple testing correction. P-values are represented as ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; ns, not significant (defined as $P > 0.05$).