CellPress

Cancer Cell

Letter

Immune responses following third COVID-19 vaccination are reduced in patients with hematological malignancies compared to patients with solid cancer

Annika Fendler,[1,30] Scott T.C. Shepherd,[1,2,30] Lewis Au,[1,2,30] Katalin A. Wilkinson,[3,4,30] Mary Wu,[5,30] Andreas M. Schmitt,[2] Zayd Tippu,[1,2] Sheima Farag,[2] Aljosja Rogiers,[2] Ruth Harvey,[6] Eleanor Carlyle,[2] Kim Edmonds,[2] Lyra Del Rosario,[2] Karla Lingard,[2] Mary Mangwende,[2] Lucy Holt,[2] Hamid Ahmod,[2] Justine Korteweg,[2] Tara Foley,[2] Taja Barber,[1] Andrea Emslie-Henry,[1] Niamh Caulfield-Lynch,[1] Fiona Byrne,[1] Benjamin Shum,[1,2] Camille L. Gerard,[1] Daqi Deng,[1] Svend Kjaer,[7] Ok-Ryul Song,[5] Christophe Queval,[5] Caitlin Kavanagh,[5] Emma C. Wall,[3,9] Edward J. Carr,[10] Sina Namjou,[11] Simon Caidan,[11] Mike Gavrielides,[12] James I. MacRae,[13] Gavin Kelly,[14] Kema Peat,[2] Denise Kelly,[2] Aida Murra,[2] Kayleigh Kelly,[2] Molly O'Flaherty,[2] Robyn L. Shea,[15,16] Gail Gardner,[16] Darren Murray,[16] Sanjay Popat,[17] Nadia Yousaf,[17,18] Shaman Jhanji,[19] Nicholas Van As,[20] Kate Young,[2] Andrew J.S. Furness,[2] Lisa Pickering,[2] Rupert Beale,[9,29] Charles Swanton,[21,22] Crick COVID19 consortium, Sonia Gandhi,[23,24] Steve Gamblin,[8] David L.V. Bauer,[25] George Kassiotis,[26] Michael Howell,[5] Emma Nicholson,[27] Susanna Walker,[18] Robert J. Wilkinson,[3,4,28] James Larkin,[2] Samra Turajlic,[1,2,*] and CAPTURE consortium

[1]Cancer Dynamics Laboratory, The Francis Crick Institute, London, NW1 1AT, UK
[2]Skin and Renal Units, The Royal Marsden NHS Foundation Trust, London, SW3 6JJ, UK
[3]Tuberculosis Laboratory, The Francis Crick Institute, London, NW1 1AT, UK
[4]Wellcome Center for Infectious Disease Research in Africa, University of Cape Town, Observatory 7925, Republic of South Africa
[5]High Throughput Screening Laboratory, The Francis Crick Institute, London, NW1 1AT, UK
[6]Worldwide Influenza Centre, The Francis Crick Institute, London, NW1 1AT, UK
[7]Structural Biology STP, The Francis Crick Institute, London NW1 1AT, UK
[8]Structural Biology of Disease Processes Laboratory, The Francis Crick Institute, London, NW1 1AT, UK
[9]University College London Hospitals NHS Foundation Trust Biomedical Research Centre, London, WC1E 6BT, UK
[10]Cell Biology of Infection Laboratory, The Francis Crick Institute, London, NW1 1AT, UK
[11]Safety, Health & Sustainability, The Francis Crick Institute, London, NW1 1AT, UK
[12]Scientific Computing Scientific Technology Platform, The Francis Crick Institute, London, NW1 1AT, UK
[13]Metabolomics Scientific Technology Platform, The Francis Crick Institute, London, NW1 1AT, UK
[14]Department of Bioinformatics and Biostatistics, The Francis Crick Institute, London, UK
[15]Department of Pathology, The Royal Marsden NHS Foundation Trust, London, NW1 1AT, UK
[16]Translational Cancer Biochemistry Laboratory, The Institute of Cancer Research, London, SW7 3RP, UK
[17]Lung Unit, The Royal Marsden NHS Foundation Trust, London, SW3 6JJ, UK
[18]Acute Oncology Service, The Royal Marsden NHS Foundation Trust, London, SW3 6JJ, UK
[19]Anaesthetics, Perioperative Medicine, and Pain Department, The Royal Marsden NHS Foundation Trust, London, SW3 6JJ, UK
[20]Clincal Oncology Unit, The Royal Marsden NHS Foundation Trust, London, NW1 1AT, UK
[21]Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London, NW1 1AT, UK
[22]University College London Cancer Institute, London WC1E 6DD, UK
[23]Neurodegeneration Biology Laboratory, The Francis Crick Institute, London, NW1 1AT, UK
[24]UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, UK
[25]RNA Virus Replication Laboratory, The Francis Crick Institute, London, NW1 1AT, UK
[26]Retroviral Immunology Laboratory, The Francis Crick Institute, London, NW1 1AT, UK
[27]Haemato-oncology Unit, The Royal Marsden NHS Foundation Trust, London, SW3 6JJ, UK
[28]Department of Infectious Disease, Imperial College London, London, W12 0NN, UK
[29]Division of Medicine, University College London, London NW1 2PG, UK
[30]These authors contributed equally
*Correspondence: samra.turajlic@crick.ac.uk
https://doi.org/10.1016/j.ccell.2021.12.013

Patients with cancer are at higher risk of severe COVID-19 (Grivas et al., 2021; Kuderer et al., 2020), and they are currently prioritized globally for a third COVID-19 vaccine dose. Humoral and cellular immune responses are detected after two primary COVID-19 vaccine doses in most patients with cancer (Ehmsen et al., 2021; Fendler et al., 2021; Oosting et al., 2021), although neutralizing responses against variants of concern (VOCs) are reduced. Neutralizing responses are frequently impaired in patients with hematological malignancies, especially those receiving B cell-depleting therapies (Ehmsen et al., 2021; Fendler et al., 2021; Thakkar et al., 2021). Because neutralizing antibody (NAb) responses are directly associated with vaccine efficacy (Gilbert et al., 2021; Khoury et al., 2021), these patients without a neutralizing response are at higher risk of breakthrough infections (Hippisley-Cox et al., 2021). Here, we report follow-up results from CAPTURE (NCT03226886), a longitudinal, prospective cohort study of vaccine response in patients with cancer, relative to the duration of response after two doses of either the BNT162b2 (Pfizer) or ChAdOx1 (AstraZeneca) vaccine; and following third vaccination with BNT162b2. We present data on NAb and T cell responses against whole live virus, including wild-type SARS-CoV-2 (WT), Beta, and Delta VOCs. We

specifically evaluated responses to Beta and Delta given their known immune-evasive capacity.

We assessed the durability of NAb responses in 353 patients (77% [n = 271] with solid cancer and 23% [n = 82] with hematological malignancies; Table S1) following two doses of COVID-19 vaccine (72% [n = 255] ChAdOx1 and 28% [n = 98] BNT162b2). NAbs against WT were undetectable after 14–28 days and up to 110 days (range 84–153) following the second dose in 4% (n = 12) of patients with solid cancer and 30% (n = 25) of patients with hematological malignancies. In those who initially had detectable post-second-dose NAb against WT (n = 316, 71% against Beta, and 62% against Delta), we observed a time-dependent decline in NAb titers (NAbT) during follow-up (median of 111 days, range 37–252 days after the second vaccine dose; Figure S1A). After an initial response to two vaccine doses, in patients with solid cancer (n = 259), 1% (n = 3) had undetectable NAbs against WT, 16% (n = 43) against Beta, and 18% (n = 47) against Delta; in patients with hematological malignancies (n = 57), 7% (n = 4) had undetectable NAbT against WT, 9% (n = 5) against Beta, and 16% (n = 9) against Delta. The proportions of those with waning NAb did not differ significantly among patients with solid cancer or hematological malignancies apart from WT (Chi^2 test: WT, p value = 0.02; Beta, p value = 0.16; Delta, p value = 0.67).

We previously reported that T cell responses, measured 14–28 days after the second dose, are comparable between patients with solid cancer and hematological malignancies and can also be detected in those without NAb responses (Fendler et al., 2021). During follow-up (median of 93 days [range: 63–171 days] after the second dose), we evaluated T cell responses in 55 patients. Patients without a detectable T cell response following the second dose remained negative. In those with an initial response (n = 43 with solid cancer and n = 12 with hematological malignancy; Figure S1B), it was maintained in 49% (n = 21) of patients with solid cancer and 42% (n = 5) with hematological malignancies (Wilcoxon signed rank test, p = 0.56).

During the course of routine clinical care, eight CAPTURE participants (n = 7 with solid cancer and n = 1 with hematological malignancies) were diagnosed with SARS-COV-2 following two vaccine doses between July and October 2021 (median time between second vaccine dose and infection: 118 days [range: 59–173]), and these were likely to have been caused by the Delta variant that was dominant in the UK at that time. The symptoms were either mild (n = 7 patients; WHO severity score 2–3; fever [n = 5], coryza [n = 4], anosmia [n = 4], and cough [n = 3]) or absent (n = 1 patient), no patient requiring hospital care, and all recovered. We evaluated immune responses prior to infection following two vaccine doses; although all patients had detectable NAbT against WT SARS-CoV-2, only one had detectable NAbT against Delta. Following infection, all patients mounted detectable neutralizing responses to Delta (Figure S1C). T cell responses were evaluable in five patients prior to infection and in seven patients following infection. Although only 1/5 patients had detectable T cell responses to WT prior to infection, 5/7 had a detectable T cell responses following infection, including 2/4 patients who had undetectable T cell responses before infection (Figure S1D).

We next evaluated 199 cancer patients (n = 115 [58%] with solid cancer) who received a third vaccine dose per UK guidelines. Patients who tested positive via RT-PCR for SARS-CoV-2 between their second and third doses were excluded from this analysis. All patients received a third dose of BNT162b2 following two doses of either BNT162b2 (33%) or ChAdOx1 (67%) (Table S1). The median time between second and third vaccine dose was 176 days (range 65–274 days), and immune responses were measured at a median of 23 days after the third dose (range: 11–47 days). Prior to the third dose, 88% (n = 176) had detectable NAb against WT, but given the dominance of Delta, we considered all patients with undetectable NAb against Delta to be "non-responders" to two doses (51% [n = 102]; 43% [n = 50] of patients with solid cancer and 62% [n = 52] of patients with hematological malignancy; Table S1).

Considering non-responders to Delta after two vaccine doses, in solid cancer patients (n = 50), following the third dose, 94% (n = 47) had detectable NAb against Delta and 88% (n = 44) against Beta (Figure S1E); in patients with hematological malignancy (n = 52), following the third dose, 54% (n = 28) had detectable NAb against Delta and 54% (n = 28) against Beta. The proportion of those with detectable NAb after third dose was significantly higher in patients with solid cancer (Chi^2 test: Beta, p value = 0.0002; Delta, p value < 0.0001). Finally, following the third dose, we observed an increase in median NAbT against all variants in initial responders (patients with detectable NAbs against Delta after two vaccine doses).

Our data indicate that a third vaccine dose can generate NAb in patients who are non-responders following two doses, and it further boosts NAbT against VOCs in responders. However, the proportion of patients with hematological malignancies who have undetectable NAbT against Delta following the third vaccine dose remains significant (46%).

Multivariable binary regression analysis showed that the presence of hematological malignancy was significantly associated with undetectable NAb against Beta or Delta after the third dose (variables included: cancer type, age, primary vaccine type, and sex). Considering patients with hematological malignancies in a further multivariable analysis (see Table S1 for included variables), primary vaccination with BNT162b2 (n = 17) versus ChAdOx1 (n = 35) was significantly associated with lack of neutralizing responses against Beta and Delta (BNT162b2: Delta, 29% [n = 5]; Beta, 35% [n = 6]. ChAdOx1: Delta, 66% [n = 23]; Beta, 63% [n = 22]), and these results suggest a benefit of the heterologous vaccination approach. Following the third vaccine dose, in patients who had received anti-CD20 in the 12 months prior to the first vaccine dose, 1/6 had detectable NAbT against Delta and 2/6 against Beta. In the group of patients who commenced anti-CD20 therapy between the second and third dose, 3/4 patients had detectable NAbT against Delta and Beta following the third dose.

Following stimulation with WT, Beta, and Delta spike-specific peptide pools, T cell responses were measured using IFN-γ ELISPOT (Fendler et al., 2021) in a subset of 48 patients (69% [n = 33] with solid cancer) who are representative of the cohort that received a third dose. Prior to third dose, 33% (n = 11) of patients with solid cancer and 40% (n = 6) of patients with hematological malignancies had

detectable T cell responses. Following the third vaccine dose, this rose to 73% (n = 24) and 73% (n = 11), respectively. The number of Spot Forming Units (SFU)/10^6 was significantly increased after the third dose relative to post-second dose (Figure S1F).

Our data show that a third dose of COVID-19 vaccine boosts NAb responses in patients with cancer, including those that had undetectable NAbT following two vaccine doses or for whom NAbT waned. We found that NAbT were higher in patients who received two doses of ChAdOx1 and a third dose of BNT162b2 compared to three doses of BNT162b2. Further, we show that T cell responses are amplified following the third vaccine dose, and this likely offers additional protection—especially in individuals with low or absent neutralizing responses. Encouragingly, the proportion of patients with solid cancer who had detectable responses after third vaccination is high and comparable to individuals without cancer. In contrast, a significant number of patients with hematological malignancies still had undetectable neutralizing responses following a third vaccine dose, especially against VOCs, and remain at risk of breakthrough infection. These findings are particularly pertinent given reports of reduced vaccine efficacy and NAb activity against the emerging Omicron VOC compared to Delta (Cele et al., 2021).

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.12.013.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

Cele, S., Jackson, L., Khan, K., Khoury, D.S., Moyo-Gwete, T., Tegally, H., Scheepers, C., Amoako, D., Karim, F., Bernstein, M., et al. (2021). SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. medRxiv. https://doi.org/10.1101/2021.12.08.21267417.

Ehmsen, S., Asmussen, A., Jeppesen, S.S., Nilsson, A.C., Østerlev, S., Vestergaard, H., Justesen, U.S., Johansen, I.S., Frederiksen, H., and Ditzel, H.J. (2021). Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. Cancer Cell *39*, 1034–1036.

Fendler, A., Shepherd, S.T.C., Au, L., Wilkinson, K.A., Wu, M., Byrne, F., Cerrone, M., Schmitt, A.M., Joharatnam-Hogan, N., Shum, B., et al. (2021). Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: the CAPTURE study (Nature Cancer).

Gilbert, P.B., Montefiori, D.C., McDermott, A.B., Fong, Y., Benkeser, D., Deng, W., Zhou, H., Houchens, C.R., Martins, K., Jayashankar, L., et al.; Immune Assays Team§; Moderna, Inc. Team§; Coronavirus Vaccine Prevention Network (CoVPN)/Coronavirus Efficacy (COVE) Team§; United States Government (USG)/CoVPN Biostatistics Team§ (2021). Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. Science *374*, eab3435. https://doi.org/10.1126/science.abm3425.

Grivas, P., Khaki, A.R., Wise-Draper, T.M., French, B., Hennessy, C., Hsu, C.Y., Shyr, Y., Li, X., Choueiri, T.K., Painter, C.A., et al. (2021). Association of clinical factors and recent anticancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium. Ann. Oncol. *32*, 787–800.

Hippisley-Cox, J., Coupland, C.A., Mehta, N., Keogh, R.H., Diaz-Ordaz, K., Khunti, K., Lyons, R.A., Kee, F., Sheikh, A., Rahman, S., et al. (2021). Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study. BMJ *374*, n2244.

Khoury, D.S., Cromer, D., Reynaldi, A., Schlub, T.E., Wheatley, A.K., Juno, J.A., Subbarao, K., Kent, S.J., Triccas, J.A., and Davenport, M.P. (2021). Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat. Med. *27*, 1205–1211.

Kuderer, N.M., Choueiri, T.K., Shah, D.P., Shyr, Y., Rubinstein, S.M., Rivera, D.R., Shete, S., Hsu, C.Y., Desai, A., de Lima Lopes, G., Jr., et al.; COVID-19 and Cancer Consortium (2020). Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet *395*, 1907–1918.

Oosting, S.F., van der Veldt, A.A.M., GeurtsvanKessel, C.H., Fehrmann, R.S.N., van Binnendijk, R.S., Dingemans, A.C., Smit, E.F., Hiltermann, T.J.N., den Hartog, G., Jalving, M., et al. (2021). mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. Lancet Oncol. *22*, 1681–1691.

Thakkar, A., Gonzalez-Lugo, J.D., Goradia, N., Gali, R., Shapiro, L.C., Pradhan, K., Rahman, S., Kim, S.Y., Ko, B., Sica, R.A., et al. (2021). Seroconversion rates following COVID-19 vaccination among patients with cancer. Cancer Cell *39*, 1081–1090.e2.

Cancer Cell, Volume *40*

Supplemental information

Immune responses following third COVID-19 vaccination are reduced in patients with hematological malignancies compared to patients with solid cancer

Annika Fendler, Scott T.C. Shepherd, Lewis Au, Katalin A. Wilkinson, Mary Wu, Andreas M. Schmitt, Zayd Tippu, Sheima Farag, Aljosja Rogiers, Ruth Harvey, Eleanor Carlyle, Kim Edmonds, Lyra Del Rosario, Karla Lingard, Mary Mangwende, Lucy Holt, Hamid Ahmod, Justine Korteweg, Tara Foley, Taja Barber, Andrea Emslie-Henry, Niamh Caulfield-Lynch, Fiona Byrne, Benjamin Shum, Camille L. Gerard, Daqi Deng, Svend Kjaer, Ok-Ryul Song, Christophe Queval, Caitlin Kavanagh, Emma C. Wall, Edward J. Carr, Sina Namjou, Simon Caidan, Mike Gavrielides, James I. MacRae, Gavin Kelly, Kema Peat, Denise Kelly, Aida Murra, Kayleigh Kelly, Molly O'Flaherty, Robyn L. Shea, Gail Gardner, Darren Murray, Sanjay Popat, Nadia Yousaf, Shaman Jhanji, Nicholas Van As, Kate Young, Andrew J.S. Furness, Lisa Pickering, Rupert Beale, Charles Swanton, Crick COVID19 consortium, Sonia Gandhi, Steve Gamblin, David L.V. Bauer, George Kassiotis, Michael Howell, Emma Nicholson, Susanna Walker, Robert J. Wilkinson, James Larkin, Samra Turajlic, and CAPTURE consortium

Supplementary Material

Table S1: Baseline characteristics of post-second vaccine follow-up and booster vaccination cohorts.

	Post second vaccine dose follow-up cohort, n= 353			Third vaccine cohort, n= 199			
	Cohort, All n= 353	NAb to WT n= 316	No NAb WT n= 37	Cohort, All n=199	NAb to Delta n= 97	No NAb Delta, n= 102	p-value
*Age, years (median, range)	59 (18-87)	59 (18-87)	64 (46–78)	60 (19-84)	59 (19-83)	60 (26 – 81)	0.874
Male	197 (56)	180 (57)	17 (46)	113 (57)	53 (55)	60 (59)	0.659
Ethnicity, white	312 (88)	278 (88)	34 (92)	179 (90)	89 (92)	90 (88)	0.172
***Primary COVID-19 vaccine, n (%)**							
ChAdOx1	255 (72)	233 (74)	22 (59)	134 (67)	61 (63)	73 (72)	0.248
BNT162b2	98 (28)	83 (26)	15 (41)	65 (33)	36 (37)	29 (28)	
Third COVID-19 vaccine, n(%)							
ChAdOx1	-	-	-	0	0	0	
BNT162b2	-	-	-	199 (100)	97 (100)	102 (100)	NA
Time to 3rd vaccination, days median (range)	-	-	-	176 (65-274)	175 (97 – 274)	176 (102 – 258)	0.146
***Cancer type**							
Solid	271 (77)	259 (82)	12 (32)	115 (58)	65 (67)	50 (49)	**0.015**
Hematologic	82 (23)	57 (18)	25 (68)	84 (42)	32 (33)	52 (51)	
Solid cancers	**n =271**	**n = 259**	**n = 12**	**n = 115**	**n = 65**	**n = 50**	
Stage I-II	29 (11)	27 (10)	2 (17)	17 (15)	9 (14)	8 (16)	
Stage III	48 (18)	46 (18)	2 (17)	26 (22)	14 (22)	12 (24)	0.877
Stage IV	194 (72)	186 (72)	8 (67)	72 (63)	42 (65)	30 (60)	
Rx at 1st vaccination							
Chemotherapy, <28 days	53 (20)	30 (12)	3 (25)	26 (23)	15 (23)	11 (22)	1
Targeted therapy, <28 days	87 (32)	73 (28)	3 (25)	39 (34)	21 (32)	18 (36)	0.829
Anti-PD(L)1 ± anti-CTLA4, <183 days	75 (28)	54 (21)	4 (33)	28 (24)	16 (25)	12 (24)	1
No recent SACT	82 (30)	48 (19)	4 (33)	36 (31)	28 (43)	13 (26)	0.958
Rx at 3rd vaccine dose	-	-	-				
Chemotherapy, <28 days	-	-	-	21(18)	12 (18)	9 (18)	1
Targeted therapy, <28 days	-	-	-	41 (36)	21 (32)	20 (40)	0.510
Anti-PD(L)1 ± anti-CTLA4, <183 days	-	-	-	26 (23)	11 (17)	13 (26)	0.591

No recent SACT	-	-	-	45 (39)	28 (43)	13 (26)	0.089
***Hematologic malignancies**	**n = 82**	**n = 57**	**n = 25**	**n = 84**	**n = 32**	**n = 52**	
Diagnosis							
Lymphoma	26 (32)	16 (28)	10 (40)	25 (30)	6 (19)	19 (37)	
Myeloma	29 (35)	27 (47)	2 (8)	29 (35)	11 (34)	18 (35)	
CLL	10 (12)	3 (5)	7 (28)	17 (20)	7 (22)	10 (19)	0.1052
Acute Leukaemia	14 (17)	10 (18)	4 (16)	10 (12)	5 (16)	5 (10)	
Myelodysplastic syndrome	3 (4)	1 (2)	2 (8)	3 (4)	3 (9)	0 (0)	
Rx at first vaccination							
Chemotherapy	5 (6)	3 (5)	2 (8)	7 (8)	2 (6)	5 (10)	0.892
Targeted therapy, <28 days	40 (49)	26 (46)	14 (56)	26 (31)	8 (25)	18 (35)	0.795
Anti-CD20 mAb, <12 mths	8 (10)	0 (0)	8 (32)	7 (8)	0 (0)	7 (13)	0.078
BTKi therapy, <28 days	5 (6)	3 (5)	2 (8)	5 (6)	1 (3)	4 (8)	0.701
No recent SACT	38 (46)	30 (53)	8 (32)	50 (60)	22 (69)	28 (54)	0.261
HSCT, ever	39 (48)	33 (58)	6 (24)	35 (42)	18 (56)	17 (33)	0.057
*Autograft, ever	19 (23)	16 (28)	3 (12)	22 (26)	9 (28)	13 (25)	0.751
Allograft, ever	19 (23)	16 (28)	3 (12)	13 (15)	9 (28)	4 (8)	**0.027**
HSCT, <6 months	3 (4)	2 (4)	1 (4)	7 (8)	4 (13)	2 (4)	0.136
*CAR-T, <6 months	2 (2)	0 (0)	2 (8)	3 (4)	0 (0)	3 (6)	0.436
Rx at 3rd vaccine dose							
*Chemotherapy, <28 days	-	-	-	13 (15)	5 (16)	8 (15)	1
*Targeted therapy, <28 days	-	-	-	31 (37)	11 (34)	20 (38)	1
*Anti-CD20 mAb, <12 mths	-	-	-	10 (13)	0 (0)	10 (19)	**0.022**
*BTKi therapy, <28 days	-	-	-	5 (6)	1 (3)	4 (8)	0.701
*No recent SACT	-	-	-	42 (50)	18 (56)	22 (42)	0.308

Post-second vaccine follow-up cohort: All patients with cancer received 2 doses of COVID-19 vaccination (n=353) and were followed up longitudinally, split by presence or absence of NAb to WT SARS-CoV-2 at 14-28 days post vaccination. **Third vaccination cohort**: patients that received a third COVID-19 vaccination (n=199), with the cohort split by presence or absence of detectable NAb to Delta variant of concern *prior* to third vaccination.

Values are numbers and percentages n(%) unless otherwise stated. Comparison of baseline characteristics was performed using either chi-squared test for categorical variables or Mann-Whitney U test for continuous variables. Variables utilised in multivariate analysis are denoted with *.

BTK-I, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T cell; CLL, chronic lymphocytic leukaemia; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HSCT, hematopoietic stem cell transplant; mAB, monoclonal antibody; NR, non-responders; PD-1, programmed death ligand-1; Rx, treatment; SACT, systemic anti-cancer therapy; WT, wildtype.

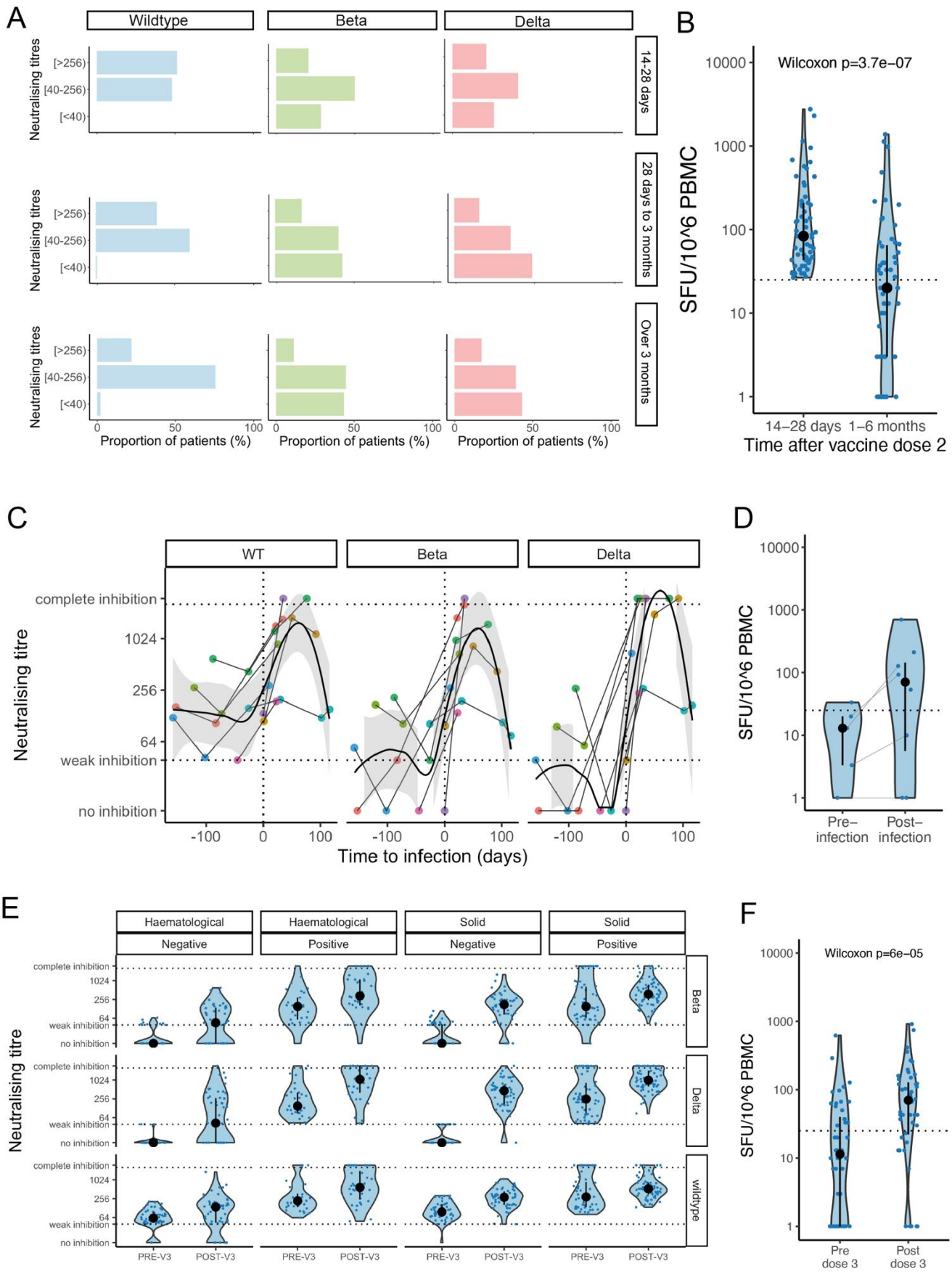
A
Wildtype
Beta
Delta
Neutralising titres
[>256)
[40-256)
[<40)
14-28 days
28 days to 3 months
Over 3 months
0
50
100
Proportion of patients (%)
B
Wilcoxon p=3.7e−07
SFU/10^6 PBMC
10000
1000
100
10
1
14–28 days
1–6 months
Time after vaccine dose 2
C
WT
Beta
Delta
Neutralising titre
complete inhibition
1024
256
64
weak inhibition
no inhibition
-100
0
100
Time to infection (days)
D
SFU/10^6 PBMC
Pre–infection
Post–infection
E
Haematological
Negative
Haematological
Positive
Solid
Negative
Solid
Positive
Beta
Delta
wildtype
PRE-V3
POST-V3
F
Wilcoxon p=6e−05
SFU/10^6 PBMC
Pre dose 3
Post dose 3

Figure S1: Immune responses of patients with cancer after two and three doses of COVID-19 vaccine A) NAbT against WT, Beta, and Delta were measured 14-28 days after first dose and at least 37 days after second vaccine dose. NAbT were grouped into high (IC_{50} titres >256), medium (IC50 titres >40 and ≤ 256) and undetectable (IC50 titres <40). Data are shown as proportion of patients within the indicated timespan. B) Duration of T cell responses in patients with initial positive response after two doses. Responses were measured 14-28 days after second dose or at least one months after second dose and are defined as IFN-y spot-forming units (SFU) per 10^6 PBMC. Dotted line denotes the limit of positivity. Significance was tested by 2-sided Wilcoxon signed rank test. Violin plots denote density of data, Pointrange denotes the median and the 25^{th} and 75^{th} percentile. Patients are indicated as individuals datapoints. C) NAbT against WT, Beta, and Delta in patients with breakthrough infections. Time of infection is denoted with a vertical line; upper and lower limit of detection is denoted with horizontal lines. Values from individual patients are indicated by different colours and are connected. Regression line and 95% CI was fitted using LOESS regression. D) T cell responses in patients with breakthrough infection. Responses are defined as IFN-y spot-forming units (SFU) per 10^6 PBMC. Dotted line denotes the limit of positivity. Violin plots denote density of data, Pointrange denotes the median and the 25^{th} and 75^{th} percentile. Patients are indicated as individuals datapoints when values for both timepoints were available. E) NAbT against Wt, Beta, and Delta after three vaccine doses (POST-V3) in patients with undetectable (Negative) or detectable (Positive) NAbT against Delta after two vaccine doses (PRE-V3). Haematological: patients with haematological malignancies; Solid: patients with solid cancer. Horizontal lines denote upper and lower limit of detection. Violin plots denote density of data, Pointrange denotes the median and the 25^{th} and 75^{th} percentile. Patients are indicated as individuals datapoints F) T cell responses in patients before and after third vaccine dose. Responses are defined as IFN-y spot-forming units (SFU) per 10^6 PBMC. Dotted line denotes the limit of positivity. Significance was tested by 2-sided Wilcoxon signed rank test. Violin plots denote density of data, Pointrange denotes the median and the 25^{th} and 75^{th} percentile. Patients are indicated as individuals datapoints.

Methods

Study design

CAPTURE (NCT03226886) is a prospective, longitudinal cohort study that commenced recruitment in May 2020, and continues to enrol patients at the Royal Marsden NHS Foundation Trust. The study design has been previously published (Au et al., 2020). In brief, adult patients with current or history of invasive cancer are eligible for enrolment. Inclusion criteria are intentionally broad, and patients were recruited irrespective of cancer type, stage, or treatment. Patients recruited to the CAPTURE study who have received at least one dose of COVID-19 vaccine will be included in an analysis to explore vaccine immunogenicity in cancer patients. Patients were included in the analysis regardless of prior SARS-CoV-2 infection status. The primary outcome for this analysis was be the seroconversion rate in cancer patients at 14-28 days following the second dose of vaccine. At establishment of the study protocol, there was no prior published data of seroconversion in cancer patients in this setting and thus sample size was exploratory. The most precise estimate of seroconversion in cancer patients would therefore be achieved through recruitment of as many patients as possible in the time period.

CAPTURE was approved as a substudy of TRACERx Renal (NCT03226886). TRACERx Renal was initially approved by the NRES Committee London, Fulham, on January 17, 2012. The TRACERx Renal sub-study CAPTURE was submitted as part of Substantial Amendment 9 and approved by the Health Research Authority on April 30, 2020 and the NRES Committee London - Fulham on May 1, 2020. CAPTURE was being conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements. All patients provided written, informed consent to participate.

Study schedule and follow-up

Clinical data and sample collection for participating cancer patients was performed at baseline (pre-first dose vaccine or within 14 days of first dose vaccine), at timepoints follow-up 1 (FU1; 2-4 weeks post-first dose vaccine); FU2 (within 14 days prior to second vaccine); FU3 (2-4 weeks post-second dose vaccine).

Patient data and sample Sources

Demographic, epidemiological and clinical data (e.g. cancer type, cancer stage, treatment history) were collected from the internal electronic patient record and pseudonymised data was entered into in a cloud-based electronic database (Ninox Software, Berlin, Germany). Regarding systemic-anticancer therapy (SACT), we deemed chemotherapy, targeted therapy (small molecule inhibitors or monoclonal antibodies) or endocrine therapy to be current if given within 28 days of vaccination. CPI given within six months was considered significant given the prolonged receptor occupancy with these agents(Fessas et al., 2017). Concomitant medications were recorded for corticosteroids (considered significant if >10mg prednisolone equivalent given for at least 7 days); GCSF when given within 48 hours of vaccination or five days if pegylated preparation; other immunosuppressive drugs taken within 48 hours of vaccination.

Patients were grouped by cancer diagnosis (solid vs hematological malignancy) for downstream analysis. Where two independent diagnoses of cancer were identified in the same patient, the case was reviewed by two clinicians (STCS & AMS) and the highest stage and/or cancer receiving active

treatment was used for classification. Patients with haematological malignancies were grouped by conventional subtypes.

Detailed sampling schedule and methodology has been previously described(Au et al., 2020). Study biospecimens included per-protocol blood samples, oropharyngeal swabs and cryostored serum from routine clinical investigations. Collected data and study samples were de-identified and stored with only the study-specific study identification number.

Definition of breakthrough SARS-CoV-2 infection

Most patients underwent RT-PCR screening as part of routine clinical care. We considered patients to have had a breakthrough SARS-CoV-2 infection if they had SARS-CoV-2 positive RT-PCR at least 7 days following the second COVID-19 vaccine dose.

WHO classification of severity of COVID-19

We classified severity of COVID-19 according to the WHO clinical progression scale(Reynolds et al., 2020). Uninfected: uninfected, no viral RNA detected – 0; Asymptomatic: viral RNA and/or S1-reactive IgG detected – 1; mild (ambulatory): symptomatic, independent – 2; symptomatic, assistance needed - 3; moderate (hospitalised): no oxygen therapy (if hospitalised for isolation only, record status as for ambulatory patient) – 4; oxygen by mask or nasal prongs - 5; severe (hospitalised): oxygen by non-invasive ventilation or high flow – 6; intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ – 7; mechanical ventilation, $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors – 8; mechanical ventilation, $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or extracorporeal membrane oxygenation - 9; Dead - 10.

Handling of whole blood samples

All blood samples and isolated products were handled in a CL2 laboratory inside a biosafety cabinet using appropriate personal protective equipment and safety measures, which were in accordance with a risk assessment and standard operating procedure approved by the safety, health and sustainability committee of the Francis Crick Institute. For indicated experiments, serum or plasma samples were heat-inactivated at 56ºC for 30 minutes prior to use after which they were used in a CL1 laboratory.

Plasma and PBMC isolation

Whole blood was collected in EDTA tubes (VWR) and stored at 4ºC until processing. All samples were processed within 24 hours. Time of blood draw, processing, and freezing was recorded for each sample. Prior to processing, tubes were brought to room temperature (RT). PBMC and plasma were isolated by density-gradient centrifugation using pre-filled centrifugation tubes (pluriSelect). Up to 30 ml of undiluted blood was added on top of the sponge and centrifuged for 30 minutes at 1000g at RT. Plasma was carefully removed then centrifuged for 10 minutes at 4000g to remove debris, aliquoted and stored at -80ºC. The cell layer was then collected and washed twice in PBS by centrifugation for 10 minutes at 300g at RT. PBMC were resuspended in Recovery cell culture freezing medium (Fisher Scientific) containing 10% DMSO, placed overnight in CoolCell freezing containers (Corning) at -80ºC and then stored at -80ºC.

Serum isolation

Whole blood was collected in serum coagulation tubes (Vacuette CAT tubes, Greiner) for serum isolation and stored at 4ºC until processing. All samples were processed within 24 hrs. Time of blood draw, processing, and freezing was recorded for each sample. Tubes were centrifuged for 10 minutes at 2000g at 4ºC. Serum was separated from the clotted portion, aliquoted and stored at -80ºC.

Virus variants & culture

The SARS-CoV-2 reference isolate (referred to as WT) was hCoV19/England/02/2020, obtained from the Respiratory Virus Unit, Public Health England, UK, (GISAID EpiCov accession EPI_ISL_407073). The B.1.1 strain ("D614G") was isolated from a swab from an infected healthcare worker at UCLH, obtained through the SAFER study,2 and carries only the D614G mutation in its spike. The B.1.1.7 isolate ("B.1.1.7") was the hCoV19/England/204690005/2020, which carries the D614G, Δ69-70, Δ144, N501Y, A570D, P681H, T716I, S982A and D1118H mutations,3 obtained from Public Health England (PHE), UK, through Prof. Wendy Barclay, Imperial College London, London, UK through the Genotype-to-Phenotype National Virology Consortium (G2P-UK). The B.1.351 virus isolate was the 501Y.V2.HV001, which carries the D614G, L18F, D80A, D215G, Δ242-244, K417N, E484K, N501Y, A701V mutations, and was kindly provided by Prof. Alex Sigal and Prof. Tulio de Oliveira; 4 sequencing of viral isolates received identified the Q677H and R682W mutations at the furin cleavage site in approximately 50% of the genomes, which was maintained upon passage in cell culture. The B.1.617.2 isolate was MS066352H (GISAID accession number EPI_ISL_1731019), which carries the T19R, K77R, G142D, Δ156-157/R158G, A222V, L452R, T478K, D614G, P681R, D950N, and was kindly provided by Prof. Wendy Barclay, Imperial College London, London, UK through the Genotype-to-Phenotype National Virology Consortium (G2P-UK). All viral isolates were propagated in Vero V1 cells. Briefly, 50% confluent monolayers of Vero E6 cells were infected with the given SARS CoV-2 strains at an MOI of approx. 0.001. Cells were washed once with DMEM (Sigma; D6429), then 5 ml virus inoculum made up in DMEM was added to each T175 flask and incubated at room temperature for 30 minutes. DMEM + 1% FCS (Biosera; FB-1001/500) was added to each flask. Cells were incubated at 37° C, 5% CO^2 for 4 days until extensive cytopathogenic effect was observed. Supernatant was harvested and clarified by centrifugation at 2000 rpm for 10 minutes in a benchtop centrifuge. Supernatant was aliquoted and frozen at -80°C.

Virus PCR and sequencing

All virus stocks generated for use in neutralisation assays were sequence-validated prior to use. To confirm the identity of cultured VoC samples, 8ul of viral RNA was prepared for sequencing by the ARTIC method (https://www.protocols.io/view/ncov-2019-sequencingprotocol-v3-locost-bh42j8ye) and sequenced on the ONT GridION platform to >30k reads / sample. The data was demultiplexed and processed using the viralrecon pipeline (https://github.com/nf-core/viralrecon).

High-throughput live virus microneutralisation assay

High-throughput live virus microneutralisation assays were performed as described previously(Faulkner et al., 2021). Briefly, Vero E6 cells (Institut Pasteur) or Vero E6 cells expressing ACE2 and TMPRSS2 (VAT-1) (Centre for Virus Research)(Rihn et al., 2021) at 90-100% confluency in 384-well format were first titrated with varying MOI of each SARS-CoV-2 variant and varying concentrations of a control monoclonal nanobody in order to normalise for possible replicative differences between variants and select conditions equivalent to wild-type virus. Following this calibration, cells were infected in the presence of serial dilutions of patient serum samples. After

infection (24 hrs Vero E6 Pasteur, 16hrs VAT-1), cells were fixed with 4% final Formaldehyde, permeabilised with 0.2% TritonX-100, 3% BSA in PBS (v/v), and stained for SARS-CoV-2 N protein using Alexa488-labelled-CR3009 antibody produced in-house and cellular DNA using DAPI(Brink et al., 2005). Whole-well imaging at 5x was carried out using an Opera Phenix (Perkin Elmer) and fluorescent areas and intensity calculated using the Phenix-associated software Harmony 9 (Perkin Elmer). Inhibition was estimated from the measured area of infected cells/total area occupied by all cells. The inhibitory profile of each serum sample was estimated by fitting a 4-parameter dose response curve executed in SciPy. Neutralising antibody titres are reported as the fold-dilution of serum required to inhibit 50% of viral replication (IC_{50}), and are further annotated if they lie above the quantitative (complete inhibition) range, below the quantitative range but still within the qualitative range (i.e. partial inhibition is observed but a dose- response curve cannot be fit because it does not sufficiently span the IC_{50}), or if they show no inhibition at all. IC_{50} values above the quantitative limit of detection of the assay (>2560) were recoded as 3000; IC_{50} values below the quantitative limit of the assay (< 40) but within the qualitative range were recoded as 39 and data below the qualitative range (i.e. no response observed) were recoded as 10.

ELISpot assay

IFN-γ Precoated ELISpot (Mabtech, UK) plates were blocked with complete medium (RPMI, 5% human AB serum) before 300,000 PBMC were seeded per well and stimulated for 18 h. Synthetic SARS-CoV-2 PepTivator peptides (Miltenyi Biotec, Surrey, UK), consisting of 15-mer sequences with 11 amino acid overlap were used at a final concentration of 1 µg/ml/peptide, as follows: (1) PepTivator SARS-CoV-2 Prot_S1 (amino acids 1-692); (2) PepTivator SARS-CoV-2 Prot_S (covering the sequences 304-338, 421-475, 492-519, 683-707, 741-770, 785-802 and 885-1273) and PepTivator SARS-CoV-2 Prot_S+ (amino acids 689-895) combined into a single pool broadly representing S2; (3) PepTivator SARS-CoV-2 Prot_M (covering the complete membrane glycoprotein); (4) PepTivator SARS-CoV-2 Prot_N (covering the complete nucleocapsid phosphoprotein), (5) PepTivator SARS-CoV-2 Prot_S B.1.1.7 Mutation Pool (34 peptides covering the mutated regions in spike of the Alpha VOC); (6) The PepTivator SARS-CoV-2 Prot_S B.1.617.2 Mutation Pool covers selectively the mutated regions (32 peptides covering the mutated regions in spike of the Delta).

Plates were developed with human biotinylated IFN-γ detection antibody (7-B6-1-ALP, 1:200), followed by incubation BCIP/NBT Phosphatase Substrate (SeraCare). Spot forming units (Mabtech) were quantified with ImmunoSpot. To quantify positive peptide-specific responses, spots of the unstimulated wells were subtracted from the peptide-stimulated wells, and the results expressed as SFU per million. Samples where positive controls were <10 SFU/10^6 spots per well were excluded, as were samples with negative control >50 SFU/10^6. The cut-off threshold for a positive result was the mean of the negative control well plus 2 times the standard deviation (24 SFU/10^6)(Adriana et al., 2021). The magnitude of the response (i.e. SFU/10^6) could not be compared between WT and VOC due to the reduced number of peptides in the VOC pools.

Quantification and statistical analysis

Data and statistical analysis were done in R v3.6.1 in R studio v1.2.1335. Gaussian distribution was tested by Kolmogorov-Smirnov test. Wilcoxon signed rank test, Chi2, Fisher's exact test were performed for statistical significance. A p-value <0.05 was considered significant. All tests were performed two-sided. Statistical details for each experiment are provided in the figure legends. The ggplot2 package in R was used for data visualization and illustrative figures were created with

BioRender.com. Data are usually plotted as single data points and violin or box plots on a logarithmic scale. PointRange in violin plots denotes median and upper and lower quartiles. Multivariable binary logistic regression analysis was performed using the glm function with the stats package in R.

Supplemental References

Adriana, T., Donal, T.S., Ane, O., Daniel, O., Connor*, Matthew, P., Emily, A., Frances, A., Mohammad, A., Kirk, A.*, et al.* (2021). Research Square.

Au, L., Boos, L.A., Swerdlow, A., Byrne, F., Shepherd, S.T.C., Fendler, A., and Turajlic, S. (2020). Cancer, COVID-19, and Antiviral Immunity: The CAPTURE Study. Cell *183*, 4-10.

Brink, E.N.v.d., Meulen, J.t., Cox, F., Jongeneelen, M.A.C., Thijsse, A., Throsby, M., Marissen, W.E., Rood, P.M.L., Bakker, A.B.H., Gelderblom, H.R.*, et al.* (2005). Molecular and Biological Characterization of Human Monoclonal Antibodies Binding to the Spike and Nucleocapsid Proteins of Severe Acute Respiratory Syndrome Coronavirus. Journal of Virology *79*, 1635-1644.

Faulkner, N., Ng, K.W., Wu, M.Y., Harvey, R., Margaritis, M., Paraskevopoulou, S., Houlihan, C., Hussain, S., Greco, M., Bolland, W.*, et al.* (2021). Reduced antibody cross-reactivity following infection with B.1.1.7 than with parental SARS-CoV-2 strains. eLife *10*, e69317.

Fessas, P., Lee, H., Ikemizu, S., and Janowitz, T. (2017). A molecular and preclinical comparison of the PD-1-targeted T-cell checkpoint inhibitors nivolumab and pembrolizumab. Semin Oncol *44*, 136-140.

Reynolds, C.J., Swadling, L., Gibbons, J.M., Pade, C., Jensen, M.P., Diniz, M.O., Schmidt, N.M., Butler, D., Amin, O.E., Bailey, S.N.L.*, et al.* (2020). Healthcare workers with mild / asymptomatic SARS-CoV-2 infection show T cell responses and neutralising antibodies after the first wave. medRxiv, 2020.2010.2013.20211763.

Rihn, S.J., Merits, A., Bakshi, S., Turnbull, M.L., Wickenhagen, A., Alexander, A.J.T., Baillie, C., Brennan, B., Brown, F., Brunker, K.*, et al.* (2021). A plasmid DNA-launched SARS-CoV-2 reverse genetics system and coronavirus toolkit for COVID-19 research. PLoS Biol *19*, e3001091.

Acknowledgements

We thank the clinical leads and subunit teams for recruiting patients to the study, including F. Gronthoud, C. Messiou, D. Cunningham, I. Chau, N. Starling, N. Turner, L. Welsh, R. L. Jones, J. Droney, S. Banerjee, K. C. Tatham, K. Harrington, S. Bhide, A. Okines, A. Reid, S. Kumar. We thank the CAPTURE trial team, including E. Carlyle, K. Edmonds and L. Del Rosario, as well as H. Ahmod, L. Holt, M. O'Flaherty, D. Kelly, R. Dhaliwal, N. Ash, M. Mumin, L. Dowdie, K. Kelly, F. Williams, T. Foley, C. Lewis, M. Ndlovu, S. Ali, K. Lingard, S. Sarker, M. Mangwende, N. Hunter, J. Korteweg, A. Murra, N Shaikh , K. Peat, Mandisa Ndlovu, Kate Cullinan, Fiona Dexter and Nikhil Rudra. We thank the administrative team that delivered the RMH vaccine program, including E. Mossman and J. Codet-Boise. We thank the following for their assistance with trial conduct and. data collection, Laurie Boos, Nalinie Joharatnam-Hogan, Wanyuan Cui, Javier Pascual, Simon Rodney, Justin Mencel, Olivia Curtis, Clemency Stephenson, Anna Robinson, Bhavna Oza, Sheima Farag, Isla Leslie, We thank clinical research network nurses for their input with consent and specimen collection including H. Evans, N. Evans, S. Cooper, S. Jain, S. White, L. Roland, L. Hobbs and J. Dobbyn. We acknowledge the tremendous support from clinical and research teams at participating units at the Royal Marsden Hospital, including E. Black, A. Dela Rosa, C. Pearce, J. Bazin, L. Conneely, C. Burrows, T. Brown, J. Tai, E. Lidington, H. Hogan, A. Upadhyay, D. Capdeferro, I. Potyka, A. Drescher, F. Baksh, M. Balcorta, C. Da Costa Mendes, J. Amorim, V. Orejudos and L. Davison. We also thank volunteer staff at the Francis Crick Institute, the Crick COVID-19 Consortium and A. Lilley for help with neutralizing assays. Due to the pace at which the field is evolving, we acknowledge researchers of COVID-19, particularly those furthering our understanding of the COVID-19 vaccine-induced immune response, and we apologize for work that was not cited. We thank S. Mao for his editorial input. This research was funded in part by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust (RMCC32), Cancer Research UK (CRUK) (grant reference number C50947/A18176). This work was supported by the Francis Crick Institute, which receives its core funding from CRUK (FC001988, FC001218, FC001099, FC001002, FC001078, FC001169, FC001030, FC011104), the UK Medical Research Council (FC001988, FC001218, FC001099, FC001002, FC001078, FC001169, FC001030, FC011104) and the Wellcome Trust (FC001988, FC001218, FC001099, FC001002, FC001078, FC001169, FC001030, FC011104). For the purpose of open access, the authors have applied a CC BY public copyright licence to any author accepted manuscript version arising from this submission. TRACERx Renal is partly funded by the NIHR Biomedical Research Centre at the Royal Marsden Hospital and the ICR (A109). The CAPTURE study is sponsored by the Royal Marsden NHS Foundation Trust and funded from a grant from the Royal Marsden Cancer Charity. A. Rogiers is supported by an ESMO clinical research fellowship. R.J.W. and K.A.W. receive support from Rosetrees (M926). A.F. has received funding from the European Union's Horizon 2020 research and innovation program under Marie Skłodowska-Curie grant agreement no. 892360. S.T.C.S. is supported and funded by a CRUK Clinician PhD Fellowship award. L.A. is funded by the Royal Marsden Cancer Charity. F.B. is funded by Rosetrees Charity (grant reference M829). S.T. is funded by CRUK (grant reference number C50947/A18176), the NIHR Biomedical Research Centre at the Royal Marsden Hospital and the Institute of Cancer Research (grant reference number A109), the Kidney and Melanoma Cancer Fund of the Royal Marsden Cancer Charity, the Rosetrees Trust (grant reference number A2204), Ventana Medical Systems (grant reference numbers 10467 and 10530), the National Institutes of Health (US) and the Melanoma Research Alliance. A.M.S. received an educational grant from Janssen-Cilag. C. Swanton is funded by CRUK

(TRACERx, PEACE and CRUK Cancer Immunotherapy Catalyst Network), the CRUK Lung Cancer Centre of Excellence (C11496/A30025), the Rosetrees Trust, Butterfield and Stoneygate Trusts, the Novo Nordisk Foundation (ID16584), a Royal Society Professorship Enhancement award (RP/EA/180007), the NIHR Biomedical Research Centre at University College London Hospitals, the CRUK University College London Centre, the Experimental Cancer Medicine Centre and the Breast Cancer Research Foundation (BCRF 20-157). This work was supported by a Stand Up To Cancer-LUNGevity-American Lung Association Lung Cancer Interception Dream Team Translational research grant (grant number SU2C-AACR-DT23-17 to S.M. Dubinett and A.E. Spira). Stand Up To Cancer is a division of the Entertainment Industry Foundation. Research grants are administered by the American Association for Cancer Research, the scientific partner of SU2C. C. Swanton received an ERC Advanced Grant (PROTEUS) from the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement no. 835297). C. Swanton is a Royal Society Napier Research Professor (RP150154). R.J.W. has received funding from the Francis Crick Institute, which receives it's core funding by Wellcome (FC0010218), UKRI (FC0010218) and CRUK (FC0010218) and research funding from Wellcome (203135 and 222754), Rosetrees (M926) and the South African MRC.

Declaration of interests

The authors declare no competing interests.

Consortia Member Lists

The CAPTURE consortium

The members of the CAPTURE consortium include Lewis Au, Susana Banerjee, Katie Bentley, Shree Bhide, Laura Amanda Boos, Fiona Byrne, The Crick COVID-19 Consortium, Ian Chau, David Cunningham, Joanne Droney, Annika Fendler, Andrew Furness, Camille Gerard, Firza Gronthud, Kevin Harrington, Shaman Jhanji, Robin Jones, George Kassiotis, Sacheen Kumar, James Larkin, Ethna McFerran, Christina Messiou, Emma Nicholson, Alicia Okines, Clare Peckitt, Lisa Pickering, Alison Reid, Jennifer Rusby, Andreas Schmitt, Scott Shepherd, Ben Shum, Naureen Starling, Anthony Swerdlow, Kate Tatham, Samra Turajlic, Nicholas Turner, Liam Welsh, Katalin Wilkinson, Robert J. Wilkinson, Matthew Wheater, Kate Young, and Nadia Yousaf.

The Crick COVID-19 Consortium

Titilayo Abiola, Jim Aitken, Zoe Allen, Rachel Ambler, Karen Ambrose, Emma Ashton, Alida Avola, Samutheswari Balakrishnan, Caitlin Barns-Jenkins, Genevieve Barr, Sam Barrell, Souradeep Basu, Rodrigo Batalha, Rupert Beale, Clare Beesley, Teresa Bertran, Natalie Bevan, Nisha Bhardwaj, Shahnaz Bibi, Ganka Bineva-Todd, Dhruva Biswas, Michael J Blackman, Dominique Bonnet, Carles Bosch, Faye Bowker, Malgorzata Broncel, Claire Brooks, Michael D Buck, Andrew Buckton, Timothy Budd, Alana Burrell, Louise Busby, Claudio Bussi, Simon Butterworth, Matthew Byott, Fiona Byrne, Richard Byrne, Simon Caidan, Veronique Calleja, Enrica Calvani, Joanna Campbell, Johnathan Canton, Ana Cardoso, Nick Carter, Luiz Carvalho, Raffaella Carzaniga, Antonio Casal, Natalie Chandler, Qu Chen, Peter Cherepanov, Laura Churchward, Graham Clark, Bobbi Clayton, Clementina Cobolli Gigli, Zena Collins, Nicola Cook, Cristina Cotobal Martin, Sally Cottrell, Margaret Crawford, Stefania Crotta, Laura Cubitt, Tom Cullup, Annalisa D'Avola, Heledd Davies, Patrick Davis, Dara Davison, Joost De Folter, Vicky Dearing, Solene Debaisieux, Monica Diaz-Romero, Alison Dibbs, Jessica Diring, Paul C Driscoll, Christopher Earl, Amelia Edwards, Chris Ekin, Dimitrios Evangelopoulos, Todd Fallesen, Rupert Faraway, Antony Fearns, Aaron Ferron, Efthymios Fidanis, Patricia Figuiredo-Nunes, Katja Finsterbusch, Dan Fitz, James Fleming, Helen Flynn, Ashley Fowler, Daniel Frampton , Bruno Frederico, Alessandra Gaiba, Anthony Gait, Steve Gamblin, Sonia Gandhi, Julian Gannon, Edmund Garr, Kathleen Gärtner, Acely Garza-Garcia, Liam Gaul, Helen M Golding, Jacki Goldman, Robert Goldstone, Belen Gomez Dominguez, Hui Gong, Ilaria Gori, Paul R Grant, Maria Greco, Mariana Grobler, Anabel Guedan, Silvana Guioli, Maximiliano G Gutierrez, Fiona Hackett, Chris Hadjigeorgiou, Ross Hall, Steinar Halldorsson, Suzanne Harris, Sugera Hashim, Emine Hatipoglu, Lyn Healy, Judith Heaney, Susanne Herbst, Graeme Hewitt, Theresa Higgins, Prisca Hill, Steve Hindmarsh, Rajnika Hirani, Han Ngoc Ho, Maxine Holder, Joshua Hope, Elizabeth Horton, Beth Hoskins, Catherine F Houlihan, Michael Howell, Louise Howitt, Jacqueline Hoyle, Mint R Htun, Michael Hubank, Hector Huerga Encabo, Deborah Hughes, Jane Hughes, Almaz Huseynova, Ming-Shih Hwang, Fairouz Ibrahim, Rachael Instrell, Deborah Jackson, Mariam Jamal-Hanjani, Lucy Jenkins, Ming Jiang, Mark Johnson, Leigh Jones, Neil Justin, Nnennaya Kanu, George Kassiotis, Gavin Kelly, Geoff Kelly, Louise Kiely, Anastacio King Spert Teixeira, Fiona Kinnis, Stuart Kirk, Svend Kjaer, Ellen Knuepfer, Nikita Komarov, Paul Kotzampaltiris, Konstantinos Kousis, Tammy Krylova, Ania Kucharska, Robyn Labrum, Catherine Lambe, Michelle Lappin, Stacey-Ann Lee, Andrew Levett, Lisa Levett, Marcel Levi,

Nick Lewis, Hon-Wing Liu, Shuangyan Liu, Sam Loughlin, Wei-Ting Lu, Robert Ludwig, James I MacRae, Akshay Madoo, Sarah Manni, Julie A Marczak, Manuella Marques, Mimmi Martensson, Thomas Martinez, Bishara Marzook, John Matthews, Joachim M Matz, Samuel McCall, Laura E McCoy, Fiona McKay, Edel C McNamara, Sofanit Mebrate, Hilina Mehari, Manuela Melchionda, Carlos M Minutti, Gita Mistry, Miriam Molina-Arcas, Beatriz Montaner, Kylie Montgomery, Catherine Moore, David Moore, Anastasia Moraiti, Raveena Morar, Lucia Moreira-Teixeira, Joyita Mukherjee, Cristina Naceur-Lombardelli, Eleni Nastouli, Aileen Nelson, Jerome Nicod, Luke Nightingale, Stephanie Nofal, Paul Nurse, Savita Nutan, Anne O'Garra, Jean D O'Leary, Olga O'Neill, Nicola O'Reilly, Caroline Oedekoven, Jessica Olsen, Paula Ordonez Suarez, Neil Osborne, Amar Pabari, Aleksandra Pajak, Venizelos Papayannopoulos, Stavroula M Paraskevopoulou, Namita Patel, Yogen Patel, Oana Paun, Nigel Peat, Laura Peces-Barba Castano, Ana Perez Caballero, Jimena Perez-Lloret, Magali S Perrault, Abigail Perrin, Roy Poh, Enzo Z Poirier, James M Polke, Marc Pollitt, Lucia Prieto-Godino, Alize Proust, Clinda Puvirajasinghe, Val Pye, Christophe Queval, Vijaya Ramachandran, Abhinay Ramaprasad, Peter Ratcliffe, Minoo Razi, Laura Reed, Caetano Reis e Sousa, Kayleigh Richardson, Sophie Ridewood, Karine Rizzoti, Fiona Roberts, Rowenna Roberts, Angela Rodgers, Pablo Romero Clavijo, Annachiara Rosa, Alice Rossi, Chloe Roustan, Andrew Rowan, Erik Sahai, Aaron Sait, Katarzyna Sala, Emilie Sanchez, Theo Sanderson, Pierre Santucci, Fatima Sardar, Adam Sateriale, Jill A Saunders, Chelsea Sawyer, Anja Schlott, Edina Schweighoffer, Sandra SeguraBayona, Rajvee Shah Punatar, Maryam Shahmanesh, Joe Shaw, Gee Yen Shin, Mariana Silva Dos Santos, Margaux Silvestre, Matthew Singer, Marie Sjothun, Daniel M Snell, Ok-Ryul Song, Christelle Soudy, Moira J Spyer, Louisa Steel, Amy Strange, Adrienne E Sullivan, Charles Swanton, Michele SY Tan, Zoe H Tautz-Davis, Raquel Taveira-Marques, Effie Taylor, Gunes Taylor, Harriet B Taylor, Alison Taylor-Beadling, Fernanda Teixeira Subtil, Berta Terré Torras, Goran Tomic, Patrick Toolan-Kerr, Francesca Torelli, Tea Toteva, Moritz Treeck, Hadija Trojer, Ming-Han C Tsai, James MA Turner, Melanie Turner, Jernej Ule, Rachel Ulferts, Sharon P Vanloo, Selvaraju Veeriah, Raju Veeriah, Mani Venkatesan, Subramanian Venkatesan, Ferdinando Verdirame, Karen Vousden, Andreas Wack, Claire Walder, Jane Walker, Philip A Walker, Yiran Wang, Sophia Ward, Catharina Wenman, Luke Wiliams, Matthew J Williams, Cherry Wong, Wai Keong Wong, Chi Wong, Joshua Wright, Mary Wu, Lauren Wynne, Zheng Xiang, Melvyn Yap, Julian A Zagalak, Davide Zecchin, Rachel Zillwood