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Transmission of the SARS-CoV-2 virus and its corresponding disease (COVID-19) has been shown to impose a higher burden on cancer patients than on the general population. Approved vaccines for use include new technology mRNA vaccines such as BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna), and nonreplcating viral vector vaccines such as Ad26.COV2.S (Johnson & Johnson) and AZD1222 (AstraZeneca). Impaired or delayed humoral and diminished T-cell responses are evident in patients with cancer, especially in patients with haematological cancers or those under active chemotherapy. Herein we review the current data on vaccine immunogenicity in cancer patients, including recommendations for current practice and future research.

COVID-19 vaccines in patients with cancer

Transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has led to the ongoing global coronavirus disease 2019 (COVID-19) pandemic. Patients with cancer are at higher risk of significant COVID-19-associated morbidity and mortality than the general population [1,2]. Prolonged viral shedding, delayed seroconversion (see Glossary), and an exhausted T-cell phenotype have been demonstrated in SARS-CoV-2-infected cancer patients [3]. Patients with lung cancer and haematological malignancies are at highest risk, as are recipients of stem-cell transplants and adoptive cellular therapies [4–7]. Effective measures taken to protect patients with cancer from contracting COVID-19 have included prioritisation of vaccination against SARS-CoV-2 and public health measures. Approved vaccines for use include new technology mRNA vaccines such as BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna), and nonreplcating viral vector vaccines such as Janssen’s Ad26.COV2.S (Johnson & Johnson) and AZD1222 (AstraZeneca) (Figure 1, Key figure) [8–11]. The exclusion of patients with cancer and other immunocompromised groups from registration in COVID-19 vaccine trials has meant that vaccine efficacy in this patient population has had to be elucidated from small prospective observational studies focused on immunological or antibody responses [12–14], as opposed to data on protection against breakthrough or symptomatic coronavirus infections, coronavirus hospitalisation, or death. Herein we review the available evidence evaluating the safety and the antibody and cellular responses in cancer patients to COVID-19 vaccinations, and the longevity of those responses.

Impaired serological responses in patients with cancer following COVID-19 vaccination

Assessment of vaccine-induced immune responses in patients with cancer has largely focused on evaluating the presence of antibodies binding the SARS-CoV-2 spike protein to establish rates of seroconversion and mean antibody titres (Table 1, Figure 2). First data reporting on the immunogenicity of the BNT162b2 mRNA vaccine in patients with cancer confirmed that only 38% of patients with solid tumours and <20% of patients with haematological malignancies developed SARS-CoV-2 S-specific IgG following the primary vaccine inoculum, contrasting with 79% seroconversion in healthy controls (Table 1). Rates of seroconversion are lower in patients with haematological malignancies and higher in patients on immunotherapy and endocrine/targeted therapies. In studies that have measured IgG and IgA antibody titres, neutralising antibodies are less frequently detected than IgG and IgA (Table 2). Differences in seroconversion rates are evident in patients with different primary malignancies (Table 3) and those with different antecedent treatments (Table 4). Rates of seroconversion are higher in patients with solid tumours than in patients with haematological malignancies [12–14]. Rates of seroconversion are lower in patients on immunotherapy and endocrine/targeted therapies than in patients on chemotherapy alone (Table 4). In studies that have measured T-cell responses, some seronegative patients can generate robust T-cell responses, showing disparate responses to vaccines in patients with cancer, and potentiating roles for T-cell responses as a possible correlate of protection.

Third booster doses have shown benefit in a few patients, but seronegative patients who are also negative for T-cell responses remain unprotected.
with 94% in the control cohort of predominantly healthcare workers without cancer [12]. The poor immune efficacy of the priming dose of COVID-19 vaccines in patients with solid cancer has been shown to be rescued by a subsequent second dose of the vaccine administered with seropositivity reported as ranging between 75% and 95% across the studies [15–30]. Patients on active
| Cancer type                     | Control (n = 26) | Country        | Median age (years) (IQR/range) | Vaccine      | Seroconversion (cancer) | Seroconversion (control) | Refs |
|-------------------------------|-----------------|----------------|-------------------------------|--------------|-------------------------|--------------------------|------|
| Haematological MM (n = 171)   | Control (n = 64) | Israel         | Patient: 70 (38–94)          | BNT162b2     | 1st dose: NA             | 1st dose: NA              | [104]|
| Solid cancer (n = 122)        | Control (n = 29) | France         | Patient: 69.5 (44–90) Control: 53 (21–81) | BNT162b2     | 1st dose: 47.5% 2nd dose: 95.2% | 1st dose: 100% 2nd dose: 100% | [16]|
| Solid cancer (n = 136)        | NA              | Austria        | Patient: 65.1 (12.2)         | BNT162b2     | 1st dose (solid cancer): 60% 2nd dose (solid cancer): 43.4% 2nd dose (haematological): 71.4% | NA | [106]|
| CLL (n = 373)                 | NA              | Israel         | Patient: 70 (40–89)          | BNT162b2     | 2nd dose: 43%             | NA                       | [106]|
| Multiple myeloma (n = 93)     | Control (n = 177) | UK             | Patient: 67 (47–84)          | BNT162b2     | 1st dose: 56% (70% when measuring total antibody) 2nd dose: NA | 1st dose: 99% 2nd dose: NA | [100]|
| Solid cancer (n = 169)        | NA              | France         | Patient: 66 (27–89)          | BNT162b2     | 1st dose: 15% 2nd dose: 66% 3rd dose: 75% (27/36) suboptimal responders only | NA | [81]|
| Solid cancer (n = 257)        | Control         | Italy          | Patient: 65 (28–86) Control: NA | BNT162b2     | 1st dose: NA 2nd dose: 75.88% | 1st dose: NA 2nd dose: 100% | [19]|
| Haematological (n = 241)      | NA              | Spain          | Patient: 63 (53–71)          | mRNA-1273    | 1st dose: NA 2nd dose: 76.3% | NA | [90]|
| Myeloid cancer (n = 59)       | Control (n = 232) | UK             | Patient: 62 (52–73) Control: 62 (60–76) | BNT162b2     | 1st dose: 58% | BNT162b2 1st dose: 98% AZD1222 1st dose: 92 | [107]|
| Solid cancer                  | NA              | Belgium        | Patient: 62.0 (26.0–86.0)    | BNT162b2     | Targeted/hormonal 2nd dose: 97% 3rd dose: 100% Chemotherapy 2nd dose: 75% 3rd dose: 83% Chemoimmunotherapy 2nd dose: 100% 3rd dose: 100% | NA | [90]|
| Solid cancer (n = 816)        | Control (n = 274) | Italy          | Patient: 62 (21–97) Control: 47 (21–69) | BNT162b2     | 1st dose: 14.2% 2nd dose: 86% | 1st dose: 33.6% 2nd dose: 99.2% | [24]|
Table 1. (continued)

| Cancer type | Control | Country      | Median age (years) (IQR/range) | Vaccine | Seroconversion (cancer) | Seroconversion (control) | Refs |
|-------------|---------|--------------|-------------------------------|---------|-------------------------|--------------------------|------|
| Solid cancer \(n = 201\) Haematological \(n = 323\) | NA      | Denmark      | Patient: 70 (63–75)           | BNT162b2 mRNA-1273 | Solid cancer 1st dose: 77% 2nd dose: 93% Haematological 1st dose: 2nd dose: 66% | NA | [21] |
| Haematological MM \(n = 77\) | Control \(n = 24\) | Germany | Patient: 67 (60–72) Control: 66 (50.25–77.50) | BNT162b2 | 1st dose: NA 2nd dose: 53% | 1st dose: 2nd dose: 100% | [69] |
| Solid cancer \(n = 271\) Haematological \(n = 82\) | NA      | UK           | Patient: 58 (18–87)           | BNT162b2 AZD1222 | Solid cancer 2nd dose: 96% Blood cancer 2nd dose: 73% | NA | [66] |
| Solid cancer \(n = 115\) Haematological \(n = 84\) | NA      | UK           | Patient: 63 (55–70)           | BNT162b2 AZD1222 | Omicron Solid cancer 2nd dose: 37% Solid cancer 3rd dose: 90% Blood cancer 2nd dose: 19% Blood cancer 3rd dose: 56% Delta Solid cancer 2nd dose: 56% Solid cancer 3rd dose: 97% Blood cancer 2nd dose: 58% Blood cancer 3rd dose: 71% WT Solid cancer 2nd dose: 97% Solid cancer 3rd dose: 99% Blood cancer 2nd dose: 89% Blood cancer 3rd dose: 86% | NA | [66] |
| Solid cancer \(n = 447\) Haematological \(n = 138\) | NA      | UK           | Patient: 60 (52–68)           | BNT162b2 AZD1222 | Solid cancer 1st dose: 44% 2nd dose: 85% Haematological 1st dose: 27% 2nd dose: 59% | NA | [13] |
| Solid cancer \(n = 171\) Haematological \(n = 195\) | Control \(n = 1245\) | USA          | Patient: 65 (56–63) Control: 38 (32–49) | BNT162b2 mRNA-1273 | Solid cancer 1st dose: NA 2nd dose: 96.9% Haematological 1st dose: NA 2nd dose: 81.9% | NA | [29] |
| Solid cancer \(n = 94\) Haematological \(n = 56\) | NA      | Italy        | Patient: 68 (31–85)           | BNT162b2 | 1st dose: 61% 2nd dose: 85.7% | NA | [108] |
| Haematological \(n = 58\) WM, CLL, NHL | Control \(n = 213\) | Greece | Patient: 75 (40–88) Control: 75 (61–95) | BNT162b2 AZD1222 | 1st dose: 14% 1st dose: NA 2nd dose: 100% | 1st dose: 54% | [86] |
| B-cell lymphoma \(n = 86\) | Control \(n = 201\) | USA          | Patient (BCL): 72 (47–91) | BNT162b2 mRNA-1273 AZd26.COV2.S | 1st dose: 2nd dose: 41.9% 1st dose: 2nd dose: 100% | 1st dose: 2nd dose: 100% | [109] |
| Solid cancer \(n = 232\) | Control \(n = 261\) | Israel       | Patient: 66 (SD = 12.09) | BNT162b2 | 1st dose: 29% 2nd dose: 86% 1st dose: 84% 2nd dose: NA | 1st dose: 2nd dose: NA | [30] |
| Thoracic cancer \(n = 306\) | Control \(n = 18\) | France       | Patient: 67 (58–74)           | BNT162b2 mRNA-1273 AZD1222 | 1st dose: NA 2nd dose: 93.7% 1st dose: NA 2nd dose: 100% | 1st dose: 2nd dose: NA | [29] |
| Haematological \(n = 1445\) | NA      | USA          | Patient: 66 (16–110)          | BNT162b2 mRNA-1273 | 1st dose: NA 2nd dose: 75% | NA | [34] |
| Haematological MPN \(n = 21\) | NA      | UK           | Patient: 55 (36–72)           | BNT162b2 | 1st dose: 85.7% 2nd dose: NA | NA | [66] |

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| Table 1. (continued) |
|----------------------|
| Cancer type          | Control | Country | Median age (years) (IQR/range) | Vaccine | Seroconversion (cancer) | Seroconversion (control) | Refs |
|----------------------|---------|---------|-------------------------------|---------|------------------------|--------------------------|------|
| Haematological       | NA      | UK      | Patient: 45.6                  | BNT162b2| 1st dose: 87.5%        | 2nd dose: NA              | [65] |
| CML (n = 16)         |         |         |                               |         |                        |                          |      |
| Haematological       | Control (n = 52) | Israel | Patient: 71 (63–76) Control: 68 (64–74) | BNT162b2| 1st dose: NA           | 2nd dose: 39.5%           | [82] |
| CLL (n = 167)        |         |         |                               |         |                        |                          |      |
| Haematological (n = 315) | Control (n = 108) | Israel | Patient: 71 (61–78) Control: 69 (58–74) | BNT162b2| 1st dose: NA           | 2nd dose: 75%             | [32] |
| (n = 503)            |         |         |                               |         |                        |                          |      |
| Cohort B (n = 132)   |         |         |                               |         |                        |                          |      |
| Cohort C (n = 229)   |         |         |                               |         |                        |                          |      |
| Cohort D (n = 143)   |         |         |                               |         |                        |                          |      |
| Control (n = 58)     |         | Austria | Patient: 64 (19–87) Vienna cohort 63 (28–85) Meran cohort 70 (24–90) Control: 39 (22–59) | BNT162b2| Vienna 1st dose: 73%   | (all vaccine, n = 15) 2nd dose: 91.8% 3rd dose: 100% | [11] |
| Solid cancer (n = 295) | Control (n = 58) | Italy        | Patient: 64 (19–87) Vienna Patient: 69 (24–96) Meran | BNT162b2| Vienna 1st dose: 73%   | (all vaccine, n = 15) 2nd dose: 91.8% 3rd dose: 100% | [40] |
| Haematological (n = 213) |         |         |                               |         |                        |                          |      |
| (n = 39)             |         | Austria | Patient (BNT162b2): 69 (20–83) | BNT162b2| Solid cancer 1st dose: NA | 2nd dose: 100%           | [22] |
| (n = 48)             |         |         |                               |         |                        |                          |      |
| Cancer type (n) | Control (n) | Country | Median age (years) (IQR/range) | Vaccine | Seroconversion (cancer) | Seroconversion (control) | Refs |
|----------------|-------------|---------|--------------------------------|---------|-------------------------|--------------------------|------|
| Solid cancer (n = 110) | Control (n = 25) | France | Patient: 66 (54–74) Control: 55 (38–62) | BNT162b2 | 1st dose: 65% 2nd dose: NA | 1st dose: 100% 2nd dose: NA | [102] |
| Solid cancer (n = 223) | Control (n = 49) | France | Patient: 67 (60–75) Control: 53 (46–60) | BNT162b2 | 1st dose: NA 2nd dose: 94% | 1st dose: NA 2nd dose: 100% | [27] |
| CLL (n = 299) | Control (n = 93) | UK | Patient: 69 (63–74) | BNT162b2 | 1st dose: 34% 2nd dose: 75% | 1st dose: 94% 2nd dose: 100% | [113] |
| Solid cancer (n = 159) | Control (n = 40) | Belgium | Patient: 62 (25–88) Control: 48 (23–64) | BNT162b2 | Solid cancer 1st dose NA 2nd dose: 95% (targeted/hormonal) 2nd dose: 80% (immunotherapy) 2nd dose: 55% (chemotherapy) Haematological 1st dose: NA 2nd dose: 29% | 1st dose: NA 2nd dose: 100% | 29 |

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| Cancer type                        | Control                  | Country | Median age (years) (IQR/range) | Vaccine | Seroconversion (cancer) | Seroconversion (control) | Refs |
|-----------------------------------|--------------------------|---------|-------------------------------|---------|------------------------|--------------------------|------|
| Haematological MM (n = 42)        | Control (n = 37)         | Italy   | Patients (MM): 73 (47–78)     | BNT162b2| MM                     | 1st dose: 21.4% 2nd dose: 78.6% | [36] |
|                                   |                          |         | Patients (MPM): 70 (28–80)    |         |                        | MPM 1st dose: 52% 2nd dose: 68% |      |
| Myelofibrosis (n = 10)            | NA                       | Italy   | Patient: 72 (52–82)           | BNT162b2| Myelofibrosis          | 1st dose: 10% 2nd dose: 60% | [114]|
| Essential thrombocythaemia (ET)   | NA                       | Italy   | Patient: 59 (50–64)           | BNT162b2| ET and PV              | 1st dose: 68.8% 2nd dose: 93.8% |      |
| Polycythaemia vera (PV) (n = 15)  | NA                       | Austria | Patient: 72 (60–78)           | BNT162b2| Booster: AD26.COV2.S   | Nine patients with serological response (31%) | NA   |
| Haematological (n = 102)          | NA                       | France  | Patient: 75.5 (33–93)         | BNT162b2| mRNA-1273              | 3rd dose: 58% (25/43) |      |
| CLL (n = 13)                      | Control (n = 10)         | France  | Patient: 77 (37–92)           | BNT162b2|                       |                           |      |
| B cell non-Hodgkin lymphoma (n = 14) |                     |         |                               |         |                        |                           |      |
| Multiple myeloma (n = 16)         |                          |         |                               |         |                        |                           |      |
| Haematological HSCT (n = 42)      | NA                       | France  | Patient: 59 (50–64)           | BNT162b2|                       | 3rd dose: 48% | NA   |
| Haematological (n = 20)           | NA                       | Austria | Patient: 72 (60–78)           | BNT162b2| mRNA-1273              | 1st dose: 32.4% 2nd dose: 84.1% | [26] |
| Serological non-responders to two doses of BNT162b2 | NA | Austria | Patient: 72 (60–78) | BNT162b2 | mRNA-1273 | 1st dose: 32.4% 2nd dose: 84.1% | [26] |
| Haematological (n = 44)           | NA                       | Italy   | Patient: 71 (37–89)           | BNT162b2|                       | 1st dose: NA 2nd dose: 52% | NA   |
| CLL (n = 37)                      | NA                       | Israel  | Patient: 67 (43–88)           | BNT162b2|                       | 36/37 patients | NA   |
| Solid cancer (n = 129)            | Control (n = 609)        | Israel  | Patient: 63.7 Control: 41.3   | BNT162b2|                       | 1st dose: 67% 2nd dose: 80% | [23] |
| Solid cancer (n = 52)             | Control (n = 50)         | USA     | Patient: 63.7 Control: 41.3   | BNT162b2|                       | 1st dose: 67% 2nd dose: 80% | [23] |
| Haematological MM (n = 103)       | Control (n = 31)         | USA     | Patient: 68 (35–68)           | BNT162b2|                       | 1st dose: 21% 2nd dose: 67% | [45] |
|                                   |                          |         | Control: 61 (26–89)           |         |                        | 1st dose: NA 2nd dose: 100% |      |
| Solid cancer (n = 134)            | Control (n = 26)         | USA     | Patient: 67 (27–90)           | BNT162b2| mRNA-1273              | 1st dose: NA 2nd dose: 94% |      |
| Haematological (n = 66)           |                          |         | Control: 64 (37–82)           |         |                        | Solid cancer 1st dose: NA 2nd dose: 98% |      |
|                                   |                          |         |                                |         |                        | Haematological 1st dose: NA 2nd dose: 85% |      |
|                                   |                          |         |                                |         |                        | 1st dose: NA 2nd dose: 100% |      |
| Multiple myeloma (n = 260)        | Control (n = 67)         | USA     | Patient: 68 (38–93)           | BNT162b2| mRNA-1273              | 1st dose: NA 2nd dose: 84.2% |      |
|                                   |                          |         | Control: >50                  |         |                        | 1st dose: NA 2nd dose: 100% | [37] |
| Solid cancer (n = 50)             | NA                       | USA     | Patient: 30–85                 | BNT162b2| mRNA-1273              | 2nd dose: WT 100% Omicron 47.8% Delta 87% 3rd dose: WT 100% Omicron 88.9% Delta 100% | NA   |
| Solid cancer (n = 50)             | NA                       | USA     | Patient: 30–85                 | BNT162b2| mRNA-1273              | 2nd dose: WT 100% Omicron 47.8% Delta 87% 3rd dose: WT 100% Omicron 88.9% Delta 100% | NA   |
cytotoxic chemotherapy and immune-cell-depleting agents (anti-CD20, anti-CD38) show the poorest seroconversion, unlike those on endocrine therapy and immune checkpoint inhibitors where reduced antibody responses are less common [31]. Therefore, given the adequate antibody protection provided by two vaccine doses in patients with solid cancer, a third vaccine dose is strongly encouraged particularly for individuals with haematological malignancies, in whom two doses do not provide sufficient immune protection.
Reporting vaccine immunogenicity in single-cancer cohorts enables further stratification of high versus low serological responders. This is especially important in haematological neoplasms where response variability is common, as seen in one study where seropositivity was lowest in chronic lymphocytic leukaemia (CLL), non-Hodgkin’s lymphoma (NHL), and multiple myeloma (MM), and highest in chronic myeloid leukaemia (CML), myeloproliferative neoplasms (MPN), and myelodysplastic syndromes (MDS) [32]. CLL is characterised by mononuclear proliferation of dysfunctional B cells and associated disruption of T-cell function, further disrupted by Bruton’s tyrosine kinase inhibitors (BTKis) such as ibrutinib [33]. Thus, in CLL, impaired immune responses to vaccines can be influenced by disease- and treatment-related factors. In one study, 72% of seronegative CLL patients were on treatment for 2 years prior highlighting treatment as a potential confounder of antibody responses, and the remaining 28% of patients could attribute their poor responses to their fundamental B- and T-cell dysfunction [34]. Moreover, in another study, 79.2% of patients in clinical remission after effective treatment at the time of vaccination were serological responders, suggesting that defective humoral immunity can be rescued upon vaccination with disease control [35]. MM is a neoplasm of plasma cells with major immune dysfunction, and after complete vaccination seroconversion was shown to be 76.6% [36]. However, the responses were not considered robust, as antibody titres in the responders were conspicuously low, and another study showed that 15.8% of patients do not develop any detectable antibody titres [37]. The dysfunctional plasma cells in these patients secrete cytokines such transforming growth factor β (TGFβ), IL-10, and IL-6 which impair B- and T-cell functions such as B-cell differentiation and antibody response and T-cell cytotoxicity that can ultimately culminate in a reduced vaccine-induced response [38]. By contrast, and reassuringly, a study on MDS patients showed all patients (n = 15) who received BNT162b2, and 76.5% (16/21) of those who received AZD1222, were serological responders [39]. The lower rates of seroconversion observed in haematological patients, particularly those with CLL, NHL, and MM, highlight their increased vulnerability and the requirement for further studies to evaluate the most effective vaccination schedule in combination with ongoing treatment regimens.

Quantification of spike-binding antibody titres (anti-S) in numerous studies also shows reduced median IgG titres in patients with solid cancer compared to healthy volunteers [16,18,19,27]. In one study with the BNT162b2 vaccine, median IgG titres against the S1 and S2 subunits of the SARS-CoV-2 spike protein were significantly reduced at 118 (interquartile range, IQR 16.9–401) AU/ml in solid cancer patients compared with 380.5 (IQR 234–401) AU/ml in controls [19]. Comparisons of antibody titres in patients with haematological versus solid malignancies who received mRNA vaccines showed that haematological patients’ median anti-S titres were lower at 832 (IQR 24–2500) versus 2500 (IQR 514–2500) U/ml [23]. Patients with haematological cancer on B-cell-targeting therapies who received mRNA or AZD1222 vaccines were shown to have a significant reduction in median anti-S titres compared with those on other treatment modalities and patients with solid cancer, at 1.6, 191.6, and 246.4 AU/ml, respectively [40]. Another study in which mRNA and viral vector Ad26.COV.S vaccines were administered showed median anti-S titre values of 7858 AU/ml in solid and 2528 AU/ml in haematological patients; however, the reduction in antibody titres in comparison with control cohorts was significant only in the haematological patients [15].

Most of these studies focused on antibody responses against the spike protein, and often used different assays for quantification of anti-S titres; however, a standardised approach would allow for more accurate comparisons to be made. Nevertheless, determining the levels of antibodies directed specifically against the receptor-binding domain (RBD) on the spike protein – which engages the angiotensin-converting enzyme (ACE2) receptor, allowing viral entry into host cells – may be more clinically relevant as an indicator of protection against COVID-19 disease as such
antibodies have shown higher neutralisation capacity [41,42]. One study analysing anti-S2 and anti-RBD antibodies showed a decrease in these antibodies in patients with solid tumours, with an 11-fold decrease against the RBD alone in comparison with healthy controls [20]. Interestingly, geometric mean titres (GMT) of RBD-IgG in haematological patients (17.61 IU/ml) and patients with solid cancers on chemotherapy (234.05 IU/ml) were significantly lower than in healthy controls (2955.04 IU/ml), whilst patients with solid cancer on hormonal or targeted therapies had comparable levels (1844.93 IU/ml) [17]. The effect of treatment on the generation of antibody titres was also emphasised in a study where patients with lymphoma not on anti-CD20 therapies for >6 months had titres comparable with those in healthy controls [14]. These studies highlight the variability of humoral responses with different treatment modalities within cancer subgroups. One suggestion is to stratify patients into optimised vaccination pathways to ensure that maximum protection is generated within each subgroup, warranting the most effective utilisation of resources.

The use of vaccine adjuvants is an important part of improving the quality and magnitude of adaptive immune responses following vaccination. The abovementioned nucleoside-modified mRNA vaccines, encapsulated with lipid nanoparticles (LNP), are thought to utilise these LNPs to protect the mRNA from degradation and facilitate delivery into the cytoplasm of host cells for subsequent expression and presentation to the immune system. For example, Alameh et al. recently described an ionisable LNP formulation that elicits robust Tfh cell responses and durable protective antibody titres when combined with a variety of vaccine antigens, suggesting additional mechanisms by which currently approved vaccines may be improved for specific patient populations (such as those with cancers) [43].

Viral vector vaccines such as AZD1222 and Ad26.COV.S have been shown to have reduced antibody titres in comparison with the BNT162b2 and mRNA-1273 mRNA vaccines [14,44]. Specific comparisons of the two mRNA vaccines have shown the superiority of the mRNA-1273 vaccine, including in a cohort with multiple myeloma patients [15,25,34,45]. Although the vaccines encode almost identical products, the mRNA-1273 primary two-dose vaccine series consists of two 100 µg/0.5 ml dose (i.e., total 200 µg) as compared with 60 µg in BNT162b2 two-dose primary series (30 µg/0.3 ml per dose). It is possible the higher dosing within the primary vaccination series could offer greater protection to patients with cancer, although this warrants further investigation as Phase 3 trials in healthy individuals showed similar vaccine efficacies [45]. The overall reduced levels of antibody titres in vaccinated patients with cancer indicate incomplete protection in this vulnerable population, with increased risks of earlier seroconversion in patients who are serological responders after two doses [37].

**Good concordance of SARS-CoV-2-binding antibody responses with functional neutralisation antibodies**

Serological detection of spike-binding antibodies in patients with cancer has been widely reported as a major immunological endpoint, but this may not necessarily correlate with functional virus-neutralising activity, especially against variants of concern (VOCs). The presence of both binding and neutralising antibodies (nAbs) has been shown to be strongly predictive of protection against symptomatic SARS-CoV-2 infection; however, a clinically relevant threshold correlating with protection has yet to be established [46,47]. The SOAP-02 study showed that after one dose of the BNT162b2 vaccine, all serological responders except for one haematological patient could neutralise the wild-type (WT) SARS-CoV-2 strain, and anti-S titres correlated strongly in patients with solid tumours and the controls [12]. However, in a study with MM patients, one dose only generated nAbs in 4/48 patients compared to 21/104 controls to a titre clinically relevant for viral inhibition [48].
After two doses, all serological responders were shown to be able to neutralise the WT and Alpha and Delta VOCs, except for one CLL patient on a BTKi with a trend for greater neutralisation of the WT strains compared with the VOCs. Increased anti-S titres after the second dose correlated well with neutralisation in healthy controls, but were variable in patients with solid cancer [49]. Concordance of SARS-CoV-2-binding titres and neutralisation of the WT strain was seen in patients with solid cancers who received the mRNA-1273 vaccine as part of the VOICE study, and in lymphoma patients receiving BTN162b2 and AZD1222 through the UK PROSECO study [50,51]. Live neutralisation of SARS-CoV-2 WA1 isolates after the second dose of BTN162b2 showed that neutralising titres (NTs) were detected in 80% of patients with cancer, although at reduced levels in comparison with the controls: median 90% plaque reduction neutralization tests (PRNT90) titre of 60 versus 540 [20]. Interestingly, another study showed that 69% of patients who received a single dose of the Ad26.COV.2.S vaccine had undetectable neutralisation titres, and superior responses were seen with the mRNA-1273 vaccine followed by the BNT162b2 [44].

Regardless of the vaccine given, reduced responses to Alpha, Beta, Gamma, and Delta VOCs relative to the WT strain were seen in a cohort of patients with cancer [13]. The capacity to neutralise multiple variants, which is denoted as neutralisation breadth, was linked to a stronger neutralisation response against the WT [52]. The CAPTURE study investigated functional live-virus neutralisation against VOCs following BTN162b2 and AZD1222 vaccination in patients with cancer; after the first dose, 49% had titres against the WT, with low responses to Alpha (15%), Beta (9%) and Delta (9%). After two doses, 83%, 61%, 53%, and 54% of all patients and 100%, 96%, 86%, and 85% of the healthy cohort had detectable nAbs against the WT, Alpha, Beta, and Delta variants respectively [13]. Mutations in Beta are associated with increased transmissibility, and antibody escape with the Delta variant also possessing immune evasion mutations [53]. The proportion of patients vaccinated with BTN162b2 that developed nAbs against the VOCs was increased along with the significantly higher median nAb titres in comparison with the AZD1222 cohort. Additionally, although titres of anti-S1 binding antibodies could predict neutralisation against the WT strain, discordance was observed with VOCs [13]. Overall, mRNA-based vaccines have shown greater neutralisation ability than adenoviral vaccines against both WT and VOC. Therefore, mRNA vaccines should be prioritised for use in cancer patients wherever possible. Although responses to VOCs are improved after the second dose, booster doses will ensure greater protection against emerging variants and should therefore be recommended for cancer patients where available.

Patients with haematological malignancies displayed heterogeneous responses in comparison with solid cancers, and had decreased neutralisation activity to both the WT and VOCs. Consistent with reduced seroconversion rates in patients with CLL, nAbs were also reduced in this cohort (WT 20%, Alpha 0%, Beta 10%, Delta 20%) [13]. The most recent VOC, Omicron (B.1.1.529) – first isolated in November 2021 – possesses more than 60 mutations, more than half of which are located in the spike protein, and of these 15 are within the RBD, raising concerns regarding potentially high immune evasion [54]. In a study of 50 patients with solid cancer, nAb titres (50% NT) after two mRNA vaccine doses displayed a 4.2- and 21.3-fold reduction against the Delta and Omicron VOCs, respectively, relative to the ancestral strain; 52.2% of the patients had no detectable titres against Omicron, highlighting yet another aspect of vulnerability in this patient cohort [55]. Despite good correlations of the anti-spike IgG levels with the ancestral SARS-CoV-2 strain neutralisation activity, if the discordance with VOCs is not factored in any analysis/modelling, serological testing may misrepresent the likelihood of breakthrough infection and associated symptomology.
COVID-19 vaccination elicits T-cell responses at modestly lower levels than controls in patients with cancer, irrespective of serological status

T cells are an important component in generating adaptive immune responses against COVID-19, and may correlate better with long-lasting immune memory and protection from severe disease than humoral responses (Figure 2) [56]. Recent reports have highlighted discordance of the humoral response with T-cell responses in patients with cancer in contrast to healthy controls, where responses are better coordinated. This is demonstrated by studies where seronegative individuals display robust T-cell responses following stimulation with SARS-CoV-2-derived peptides [12,13,21,57,58]. In particular, 74% of seronegative haematological patients were shown to have T-cell responses as evidenced by the generation of Th1-related cytokines upon spike peptide stimulation 14 days after a second dose of mRNA-based vaccine [59]. A similar study yielded more modest observations, with only 24% of solid and 26% of haematological seronegative responders generating T-cell responses, although evaluated 36 days after the second dose using different assays [21].

In the general cohorts, T-cell responses are elicited after two doses of COVID-19 vaccines in both solid cancer and haematological patients, with several studies showing comparable responses between the two groups and similarities in proportions of responders to healthy control cohorts [13,20–22,49,60]. However, diminished magnitudes of T-cell responses in patients with cancer relative to controls can be observed with quantification of interferon-γ (IFN-γ) enzyme-linked immunospot (ELISPOT) assays or flow-cytometry detected cytokine-producing T cells [13,20]. T-cell responses to Alpha and Delta peptide pools were seen in addition to responses to WT S1/S2 peptides, confirming previous observations that vaccine-induced T cells can target a diverse repertoire of epitopes [13,61]. Overall, whilst poor humoral responses in patients with cancer does not necessarily correlate with the presence of a T-cell response, the observed magnitudes of these T-cell responses are lower in these patients compared with healthy individuals. This should be considered when evaluating the level of protection generated through COVID-19 vaccination.

Coordinated efforts of both CD4 and CD8 T cells are needed for viral clearance. CD4 T cells mediate the Th1 immune response, providing cognate help to CD8 T cells and B cells allowing for a cytotoxic response to be generated by CD8 T cells and virus-specific antibody production by B cells [62,63]. Fascinatingly, a report on MM patients showed seropositive individuals had comparable CD4-T-cell responses to healthy controls and similar distributions of mono- and polyfunctional T cells which are known to be elevated upon viral infection [57,64]. Of note, 34% of seronegative individuals had CD4 responses with mainly IL-2-only monofunctional cells [57]. Similarly, median IL-2 levels were shown to be increased in patients with lymphoid malignancies compared to healthy controls after spike stimulation, but had lower levels of IFN-γ and tumour necrosis factor α (TNF-α), suggesting a reduced magnitude of protection by T-cell responses in these individuals as substantiated by their monofunctional phenotype [57,59]. Despite this, polyfunctional T cells were found in 65% of CML patients [65], and MPN patients had 80% and 60% of patients with polyfunctional CD4 and CD8 T cells, respectively [66]. The proportion of SARS-CoV-2-specific CD8 T cells in MM patients was shown to be comparable to that in healthy controls [57]. The protective role of CD8 T cells in improving survival in SARS-CoV-2-infected haematological patients has recently been shown, suggesting that the presence of SARS-CoV-2-specific T cells after vaccination could be a strong correlate of protection [67].

Although the data regarding T-cell responses are promising, caution needs to be taken when inferring the levels of protection present, particularly against VOCs which have not been widely scrutinised in this patient population. The majority of the studies have focused on stimulating
T cells with WT S1/S2 peptides which have shown cross-reactivity with the original SARS-CoV virus and are supported by the observation that 22% of infection-naïve patients at baseline (prevaccination) displayed T-cell responses to WT S-derived peptide pools \[13,68\]. Other studies have evaluated RBD-specific T-cell responses and saw that in haematological patients RBD responsiveness was lower but robust responses to control peptides remained (CEF/CEFT) \[12,49\]. In line with this, RBD responsiveness in MM was shown to be 34.2% compared to 71.4% in healthy controls \[69\]. This possibly implies that T-cell responses could be a result of cross-reactivity in seronegative individuals to pre-existing memory T cells generated against other coronaviruses. Moreover, the strong response to control peptides indicates that the absence of vaccine-induced T-cell responses is not related to disease-specific immunosuppression but rather to a failure to generate a durable immune response to novel antigens. This is possibly the outcome of uncoordinated vaccine responses of the humoral and cellular arms of immunity in patients with cancer.

As seen with antibody responses, the mRNA-1273 vaccine yielded better T-cell responses than BNT162b2, but by contrast the viral vector AZD1222 has shown improved responses compared to BNT162b2, implying that heterologous booster regimens may confer more complete immune protection, as reported in a recent trial \[22,51,70\]. Adenoviral vaccines and mRNA-based vaccines vary with how they trigger the innate immune response, as the pathogen-associated molecular patterns (PAMPs) present in the vaccines are sensed by different Toll-like receptors (TLRs). Innate sensors for adenoviral vaccines include membrane-located TLR2, TLR4, and the major DNA sensor TLR9, whilst mRNA vaccines stimulate endosomal RNA sensors such as TLR3, TLR7, and TLR8 \[71\]. Heterologous vaccine regimens will be able to trigger different receptor pathways for downstream signalling, resulting in the secretion of type I IFNs, proinflammatory cytokines, and chemokines that can aid alongside an adaptive response, and thus the varied mode of immune activation could provide better protection overall in patients with cancer \[72\].

**Durability of B-cell immune memory after COVID-19 vaccination**

Very few studies have evaluated the presence of SARS-CoV-2-reactive B cells after vaccination in patients with cancer \[20,57\]. In patients with MM, investigators tested the hypothesis that the lack of antibody response seen in this patient cohort was a direct effect of an incapability to generate spike-reactive B cells. Using flow cytometry, they found that spike-reactive B cells were seen in all healthy controls and all but one of the seropositive MM groups. In contrast, only 6/15 seronegative individuals (40%) possessed these spike-reactive B cells \[57\].

Another study showed that vaccination was able to increase RBD-specific B cells in patients with solid tumours, but this increase was significant only in healthy controls \[20\]. More specifically, isotype-switched pre-plasmablast CD21-, RBD-, and S1-specific B cells were increased in patients but at median levels tenfold lower than those in controls. Although patients without detectable nAbs had a paucity of spike-reactive B cells, those with modest but detectable nAbs generated spike-reactive B cells.

These data can prove to be useful to further characterise the reduced humoral responses seen particularly in patients with haematological malignancies, so that informed decisions regarding the management of nonresponders can be made. It has also been shown that B cells can persist and increase after vaccination even if anti-spike antibodies are seen to decline, and thus quantification of memory B cells can help to fully depict long-term immunological protection against SARS-CoV-2 infection along with antibody and T-cell responses \[73,74\].
Waning humoral immunity in patients with cancer and its rescue by additional vaccine doses

COVID-19 vaccination regimens in patients with cancer have been shown to be effective with a well-tolerated safety profile, but over time vaccine efficacy decreases for all vaccines due to waning humoral immunity and the emergence of novel VOCs. Longitudinal studies showed similar seronegative rates for patients with solid tumours on active cancer treatment of 21% and 16% compared with controls, and patterns of decline are similar in haematological patients, implying a similar decline in antibody titres [75,76]. Administration of booster doses has been rolled out to rescue immunogenicity in immunocompromised cohorts and to combat waning humoral immunity in the general population. Increased antibody titres in patients with cancer have been seen in numerous studies, including with RBD-binding titres, and as a result nAbs have also shown threefold increases compared with prebooster doses [20,40,44,77–81]. Additionally, booster doses have allowed seroconversion of previously seronegative patients, with one study showing that 56% of individuals were able to rescue humoral responses [20,44,58,82–84]. Heterologous boosting regimens and boosting with mRNA-1273 was shown to increase anti-spike titres and where AZD1222 and BNT162b2 vaccines were used, increases in nAbs were also observed [58,85].

Subsets of participants who had low neutralising titres after two vaccine doses were subject to a third booster dose which enhanced the neutralisation of numerous VOCs, including Alpha, Beta, Gamma, and Delta [52]. Neutralising titres were also increased against Omicron in 199 evaluated patients with cancer, further favouring the administration of a third dose in this patient cohort. In patients with solid cancer, nAbs were detected in 37%, 56%, and 97% after two doses which increased to 90%, 97%, and 99% after the third dose against Omicron, Delta, and WT strains respectively [86]. In haematological patients, the benefits of boosting were also evident as 45% of patients who had undetectable titres against Omicron after the second dose developed a response with the booster [55,86].

A small proportion of serological and cellular nonresponder patients remain despite repeated vaccination doses in cancer patients

Although benefits of boosting are seen with elevated humoral responses in patients with cancer, evidence of improving the magnitude of T-cell responses has not been elucidated as responses were comparable to baseline (i.e., after the second dose) [20,78]. Only one study with a small cohort showed increases in the proportion of T-cell responders and in the magnitude of response in prior responders after the booster, albeit responses were still markedly reduced in haematological patients [85]. Factors contributing to seronegative responses even after booster doses included a diagnosis of haematological malignancy and treatment with anti-CD20 therapy [44,51,58,78,84]. Five patients with no humoral or cellular responses to three doses of vaccines were all haematological patients, specifically three with CLL and two with NHL. These patients may need further boosting as a study in Israel has shown that a fourth dose administered 4 months after the third dose in an elderly population was effective in reducing the risk of COVID-19-related outcomes in the short term [87].

Anticancer therapies associated with reduced immunogenicity after COVID-19 vaccines

Although impaired immune responses to vaccines in patients with cancer can be attributed to advanced disease and underlying disease-related immunosuppression, in many cases treatment-induced factors are also at play, particularly regarding the timing of treatment and concomitant vaccine administration [45]. In haematological malignancies, B-cell-targeted therapies such as anti-CD20 monoclonal antibody (mAb) (e.g., rituximab, and BTKis such as ibrutinib)
have been associated with reduced humoral responses and were strong predictors of impaired seroconversion [13,15,17,22,25,35,59,84,88–92]. Anti-CD20 mAbs work through several mechanisms to induce tumour killing and cause depletion of CD20-positive B cells. These include, for example, complement activation and subsequent complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and nonclassical apoptosis induced by crosslinking of CD20 molecules [93]. Anti-CD20 treatment has also been shown to cause a marked reduction in numbers of T cells, for example through the off-target depletion of CD20-positive T cells which account for up to 5% of the CD3+ population [94]. Nonetheless, anti-CD20 therapy was not shown to significantly affect T-cell functionality, and patients maintained the ability to mount an effective T-cell response [60,92,95].

BTKs such as ibrutinib work by blocking signalling activity essential for B-cell growth and survival. For example, treatment results in the inhibition of nuclear factor κB (NF-κB) and nuclear factor of activated T cells (NFAT), which are key transcription factors involved in regulating the expression of downstream genes controlling characteristics such as proliferation, survival, and chemokine production [96]. Ibrutinib can also block interleukin-2-inducible T-cell kinase (ITK), and this off-target effect can lead to the loss of Th2 cells through the reduction of cytokines that promote Th2 differentiation [97]. Th1 cells are less compromised due to their expression of resting lymphocyte kinase (Rlk) which can compensate for ITK inhibition resulting in Th1 skewing [98]. mRNA-based vaccines have been shown to elicit a favourable Th1-driven response which may account for the maintenance of the T-cell response seen in patients targeted with these therapies [63,99].

In MM patients on anti-CD38 treatment, reduced seroconversion rates and CD4-T-cell responses were observed [36,37,57,100]. These treatments inhibit long-term B-cell-mediated immunity through the reduction of antibody-producing plasma cells, which may explain reduced seroconversion in response to SARS-CoV-2 vaccination. Similarly to anti-CD20 therapies, anti-CD38 treatment can also cause off-target T-cell depletion. CD38 is a characteristic marker for T-cell activation, and therefore treatments such as daratumumab could be responsible for a depletion in the activated vaccine-induced spike-reactive T cells, possibly contributing to the observed reduction in the CD4 T-cell response.

In patients with solid cancer, recommendations around the timing of active cytotoxic chemotherapy and COVID-19 vaccinations were not established to facilitate faster vaccination of immunocompromised cohorts. Chemotherapy inhibits cell growth and proliferation, and therefore has broad immunosuppressive effects, potentially diminishing spike-reactive T and B cells. As a result, chemotherapy has been shown to be a negative predictor of lower humoral responses [5,9,12,13,15,18–23,25,32,37,45,46,76,78,]. Use of immunosuppressive treatment with steroids has been shown to be associated with patients who failed to mount both a serological and a cellular response [49]. Meanwhile, immunotherapy and the use of immune checkpoint inhibitors (ICIs) have shown improved seroconversion rates in patients compared with those on other modalities [15,17,21,50]. Immunotherapies can enhance the immune response by reinvigorating exhausted T cells, and therefore may potentiate cell-mediated vaccine responses. Despite the amplified immune response with ICIs, patients rarely display symptoms of immune-related adverse events (irAEs) or cytokine release syndrome (CRS), thus highlighting a favourable safety profile in this cohort [103]. Patients on endocrine or targeted therapies are unlikely to have treatment-driven reduced vaccine-induced immune responses [15–17,23]. Recommendations for improving responses would be to avoid administration of COVID-19 vaccinations on the same day as immunosuppressive therapies such as chemotherapy, and providing third doses as the chances of seroconverting even on active cancer therapy were increased in this setting [51,58,77]. This, however, remains an issue for the patients on anti-CD20 therapy where no
nAbs against the Omicron VOC were seen following the third dose [86]. In these patients, a strategy to vaccinate their immediate circles needs to be promoted, and perhaps the use of prophylactic neutralising anti-spike antibodies should be investigated [59].

Concluding remarks
Long-term follow-up studies in patients with cancer who have received COVID-19 vaccines have shown an excellent safety profile in this cohort, with immunogenicity elicited in most of the population. Patients with solid cancers demonstrate responses at levels almost comparable with those in the general population, with the exception of those few patients on chemotherapy. However, impaired humoral responses in patients with haematological malignancies are evident in the studies to date and show discordant correlations with T-cell responses, particularly in patients on anti-CD20 therapies and high-dose steroids. Although subsequent boosting doses may rescue some immune dysfunction in vaccine responses, these patients may additionally benefit from alternative measures (see Clinician’s corner). Further research into optimal timing and possible heterologous booster regimens are to be explored to improve vaccine efficacy in patients with cancer (see Outstanding questions). In this review we summarise immunogenicity data from mainly viral vector and mRNA-based vaccines, but increased global efforts in reporting on protein-based or inactivated virus vaccines in this special cohort are needed to provide recommendations where these vaccines are predominant. There is a great deal of heterogeneity in the studies reporting responses to vaccines, which complicates comparisons being made of similar patient groups, thus more standardisation of reporting is needed. We also encourage longitudinal follow-up studies of these patients to define standardised correlates of protection offered by serological testing alongside reporting of memory T- and B-cell responses to better inform public health measures.

Declaration of interests
No interests are declared.

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Outstanding questions
Do heterologous vaccine boosting regimens generate improved vaccine-induced immune responses in patients with cancer?

How can serological testing of anti-S antibodies and the presence of anti-S-specific memory T and B cells correlate to protection in vivo against SARS-CoV-2 infection or COVID-19 disease?

What is the durability of protection offered by the COVID-19 vaccines in patients with cancer, and how can anticancer treatments influence this?

Is vaccine-induced protection sustained against emerging VOCs, and would novel vaccines be needed against later strains for better protection?

What are the best alternative options for patients who do not display any immune responses to the current COVID-19 vaccines?
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