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Review

Third dose of anti-SARS-CoV-2 vaccine for patients with cancer: Should humoral responses be monitored? A position article

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Abstract Taking into account higher risk of severe coronavirus disease 2019 or death among patients with cancer, as well as impaired immunogenicity after anti-SARS-CoV-2 vaccines, in addition to waning immunity, booster dosing appears mandatory in this patient population. This review sought to provide reasonable evidence so as to assist oncologists in their daily practice, helping them decide when an anti-SARS-Cov2 antibody (Ab) dosage should be scheduled after a full two-dose vaccination and, if necessary, propose an early third dose (D3). Such D3 could apply to non-responder patients with anti-Spike (S) Abs titres <40 binding Ab unit (BAU)/mL. For lowresponder patients with anti-S Ab titres between 40 BAU/mL

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and 100/260 BAU/mL (suggested area of uncertainty), an early D3 may similarly be proposed. Nevertheless, this D3 could be administered in a less urgent manner, taking into account associated comorbidities and regional epidemic incidence rates. This latter strategy may comprise a monthly dosage of anti-S titres so as to better assess the kinetics of waning immunity. For responder patients with anti-S titres above 260 BAU/mL, we suggest to follow the recommendations outlined for the general population. Given this context, patients with anti-S titres above 1000 BAU/mL should be given the possibility to undergo anti-S titre control after three months, designed to assess rapid humoral waning immunity. We strongly recommend that patients with cancer be included into observational serological monitoring studies or clinical trials that are dedicated to severe immunocompromised patients without any humoral seroconversion after D3.

1. Introduction

Several countries around the world are in the process of setting up their anti-SARS-CoV-2 vaccination booster campaign, predominantly designed for people attaining the six-month time interval after the second vaccine shot. This strategy is supported by several studies focused on the durability of vaccine-induced antibody (Ab) levels and clinical studies conducted in the general population, as well [1–5]. Nevertheless, to date, there are no recommendations allowing for a personalised prescription dedicated to immunocompromised people, including patients with cancer displaying lower anti-SARS-CoV-2 vaccine immune responses [6–10]. Another issue is still unresolved, and it concerns the exact timing of the earlier waning immunity observed at postvaccination in immunocompromised patients, such as patients with cancer undergoing immunosuppressive therapy. Besides, the proposal for an international standard of SARS-Cov2 immunoglobulins [11] implies establishing a reliable equivalence among different commercially available kits, which is not yet possible [12]. Thus, defining an Ab threshold that is associated with ineffective immunity is still tricky. In addition to this, immunity cannot be exclusively summarised by the humoral response [13]. Therefore, further clinical studies are required to precisely define the optimal vaccination schedule in such specific patient populations. Before providing recommendations concerning the third dose (D3) and serum Ab titre thresholds for daily oncology practice, a thorough review of the existing scientific evidence is mandatory.

We have summarised herein the available data concerning the efficacy of anti-SARS-CoV-2 vaccines administered to patients with cancer with either solid tumours or haematological malignancies (HMs) in preventing severe infection, hospitalisation and death. This has been carried out specifically in relation with patients' postvaccine humoral responses. Such review sought to provide reasonable evidence to help oncologists in their daily practice, enabling them to decide the following:

- when an anti-SARS-Cov2 Ab dosage should be scheduled after a full two-dose vaccination;
- why D3 vaccine injections should be carried out.

2. Seroconversion rates after two doses in patients with cancer

Patients with cancer are at greater risk of developing severe coronavirus disease 2019 (COVID-19), especially at advanced stages of lung cancer or HMs [14–17]. Particularly patients with lymphoid malignancies (LMs) are at an increased risk of hospitalisations, death or long shedding, after receiving anti-CD20 Abs, given that their humoral response is greatly impacted by such treatments [18–20]. For this reason, by the end of 2020, national and international oncology societies advocated emergency vaccination of patients with cancer [21,22] and call for action to evaluate vaccine efficacy and tolerance, as well as serological responses [23].

From the end of April 2021 onwards, vaccine efficacy studies conducted among patients with cancer were published [6,7], these patients having been excluded from registration trials without any initial efficacy data. Around the same time, the first comparative data focused on humoral and cellular vaccine responses in patients with solid cancer, and HMs were published [8], and many publications have recently been reviewed [24–26].

The main data concerning humoral vaccine responses in patients with solid cancer or HMs can be summarised as follows:

- low seroconversion rate after the first vaccine dose (D1) [6–10].
- Conversely, an overall high seroconversion rate in solid oncology patients after the second dose (D2), with more than 80–90% of them having developed anti-Spike (S) Abs [6–10,27–29].
- Lower median anti-S Ab levels compared with the healthy control (HC) group, consisting of highly heterogeneous responses with patients classified from low-responders to high-responders, the latter displaying a similar humoral response than the HC group [6–10,27–29];

- A much lower seroconversion rate in patients with HMs [30–32], especially those exhibiting chronic lymphoid leukaemia (CLL), even when left untreated [31], as well as patients with multiple myeloma and those with additional deleterious prognostic factors, including age [31].
- The poorest vaccine response rate was recorded in patients undergoing anti-CD20 therapy or having stopped it for less than 12 months, with virtually no humoral response at all after a full two-dose vaccination [32,33].

Added to chemotherapy negative impact, some factors were found to be significantly associated with a lack of immunisation [34,35]: age, long-term corticosteroid treatment and lymphocyte count $<1 \times 10^9$/L.

Based on selected serological studies, comparative median anti-S Ab titres, converted in binding Ab unit (BAU)/mL, among the different populations of interest with cancer, have been schematised in Fig. 1, as adapted from the series of Barriere et al. [7] using *Roche Elecsys* or Palich et al. [27], Addeo et al. [29] and Gounant et al. [35] using Abbott immunoglobulin G (IgG) II. This illustration clearly depicts the substantial differences in postvaccination median anti-S titres measured in patients with cancer, varying from 230 (*Roche Elecsys*) to 671 (*Abbott IgG II*) BAU/mL, being four to 10 times lower than those observed in HCs. Nevertheless, these anti-S Ab titres were at least 14 times higher than the values documented in patients with HMs, whereas patients treated using anti-CD20 Abs exhibited a complete lack of seroconversion, with median anti-S titres at 0 BAU/mL after D2.

Concerning clinical vaccine efficacy in patients with cancer, Heudel et al. [36] reported convincing data involving 1503 vaccinated cancer patients. These authors reported a statistically significant difference in mortality between patients who received two vaccine doses in comparison with those who received only one dose. This latter observation clearly suggests that delaying the D2 from four to 12 weeks after D1 injections, as proposed in early 2021 in some countries owing to vaccine shortage, could be deleterious to patients with cancer, thereby increasing the risk of SARS-CoV-2 breakthrough infection between D1 and D2 injection timing.

3. Third dose data in immunocompromised patients

With this background in mind, we were able to observe that some patients were probably not sufficiently protected based on a traditional two-dose vaccination schedule. As of April 2021, the French authorities rendered it thus possible to administer a D3 to immunocompromised patients, thereby targeting at first transplanted patients and those suffering from HM [37]. By the end June of 2021, the first global publication focussing on D3 was published, primarily involving transplanted patients [38]. This was quickly followed by other series confirming the beneficial contribution of D3 in these immunocompromised patients [39,40]. In a randomised trial [41], either D3 or placebo was randomly administered to transplanted patients, using mRNA-1273 vaccine (Moderna) at month 2 after D2 injection. At month 4, overall 55% of patients having received D3 exhibited anti-S glycoprotein-specific IgG receptor-binding domain (RBD) Ab levels of at least 100 arbitrary unit (AU)/mL (*Roche Elecsys*) versus 18% in the placebo group ($P < 0.001$). Nevertheless, on account

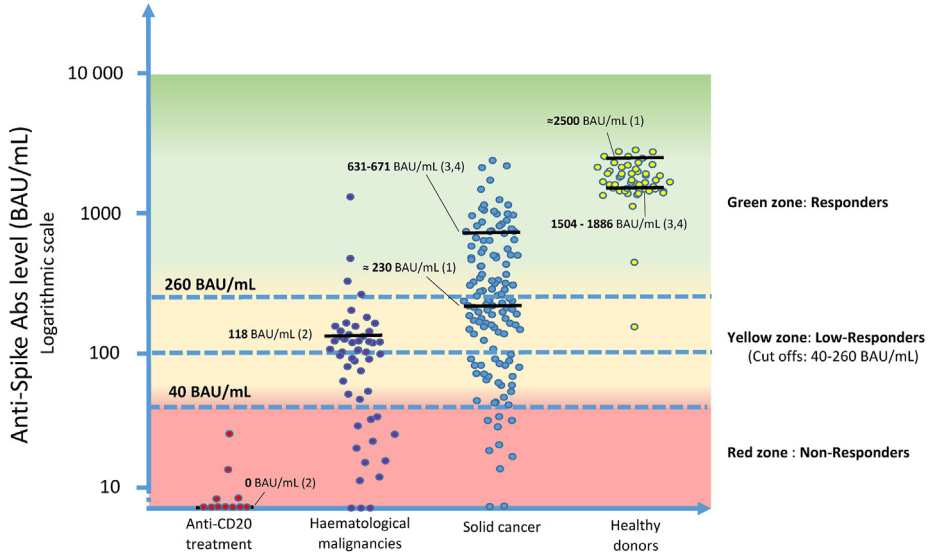

Fig. 1. **Schematic comparative humoral responses in oncology at week 6–8 after BNT162b2 anti-SARS-CoV-2 full vaccination. Range of responses as per anti-S Ab titre converted into binding antibody unit (BAU)/mL (**Schematic representation without reporting individual data). Adapted from Barrière et al. (1 => ref 7); Addeo et al. (2 => ref 29); Palich et al. (3 => ref 27); Gounant et al. (4 => ref 35). AU, arbitrary unit; Abs, antibodies; D3, third vaccine dose; BAU/mL = AU/mL ELECSYS ROCHE **x 0.972** (≈1), BAU/mL = AU/mL ABBOTT **x 0.142,** Plain black lines indicate median values.

of the small patient number and the short follow-up, no conclusion with respect to the associated clinical protection could be drawn. In this trial, only one single patient from the placebo group actually developed COVID-19, exhibiting a preinfection anti-RBD Ab level of 75 AU/mL.

In the oncology field, three studies with currently available data evaluated the impact of early D3 vaccine injection in poor humoral responders' patients with LM [42], with thoracic cancer [35] and in allogenic transplanted patients in remission of an HM [43]. Nevertheless, these studies used different serological assays rendering data comparison rather difficult, unless using the conversion factors proposed by the World Health Organisation (WHO) (National Institute for Biological Standards and Control (NIBSC) code 20/136). These factors enable conversion of AU used by each manufacturer into BAUs [44]. In this context, a factor x 0.972 (≈ 1) for Roche Elecsys) SARS-CoV-2 anti-S Abs (*Roche Elecsys*), x 0.142 for Abbott SARS-CoV-2 IgG II Quant-test (*Abbott IgG II*) or x 2.6 for DiaSorin Liaison SARS-CoV-2 TrimericS IgG (DiaSorin TriS IgG) must be applied to convert the assay results for obtaining comparative data [12].

In the first study, Re et al. [42], while using the *Roche Elecsys* assay, demonstrated that patients with LM with positive anti-S Ab titres after D2 similarly exhibited increased neutralising antibodies (NAbs), with a >80% correlation between NAb levels and anti-S Ab titres above >400 BAU/mL. In patients with multiple myeloma, the median anti-S Ab titre before D3 was 100 BAU/mL, rising to 2700 BAU/mL ($p < 0.0001$) thereafter, which is comparable to anti-S Ab serum levels from vaccinated healthy donors 6–8 weeks after D2 [7], using the same technique. However, some patients with CLL or non-Hodgkin lymphoma, as well as those undergoing anti-CD20 therapy, displayed no seroconversion after either D2 or D3, whereas a significant stimulation of T-cell response was observed in a subset of patients. Around 20% of patients were considered 'double negative,' thereby exhibiting neither B nor T-cell responses. Indeed, these patients were considered to be vaccine failures.

In the Bichat Hospital study (Paris, France) [35], overall 306 patients with thoracic cancer received two vaccine shots at 28-day intervals. In this same study, a deleterious impact on immunisation was recorded, which was revealed to be dependent on age, recent chemotherapy and chronic corticosteroids. Overall, 30 patients exhibited low anti-S IgG titres <300 AU/mL (<42 BAU/mL; *Abbott IgG II*) after D2 vaccination, this threshold corresponding to 12.5th percentile of anti-S Abs titre distribution after D1 vaccination, which was strongly correlated with the positive NAb pseudoneutralisation assay. These 30 patients were proposed a D3 injection. Of 26/30 patients with available results, a dramatic rise in anti-S IgG levels, exceeding 300 AU/mL, occurred in 23 (88%), which suggested correct protection against infection. Concerning the whole initial cohort, only eight SARS-CoV-2 benign infections were observed, with none of them occurring in the 30 patients who received a D3 booster.

In 42 allogenic transplanted patients, three BNT162b2 mRNA vaccine doses were similarly shown to result in a significant rise of anti-SARS-CoV-2 Abs, with IgG (S-RBD) (*Abbott IgG II*) levels increasing from 737 AU/mL (105 BAU/mL) to 11 099 AU/mL (1576 BAU/mL) ($p < 0{\cdot}001$) [43]. In the latter study, two factors were associated with the rise of Abs to the protective Ab threshold. These factors included a B-cell count exceeding 0·25 g/L in the peripheral blood at D3 and an IgG (S-RBD) concentration exceeding 1000 AU/mL after D2, namely, patients with more than 140 BAU/mL after conversion. In this study, 52% of patients displayed anti-S Ab levels below 4160 AU/mL (590 BAU/mL); the latter levels are considered a surrogate measure of vaccine protection, corresponding to a 0·95 probability of obtaining *in-vitro* evidenced NAbs, which were, however, not correlated to a clinical infection.

4. Correlation data between humoral response and clinical outcome

Vaccine research is primarily aimed to identify a vaccine-induced humoral response that predicts protection from infection or disease [45]. Immunisation after viral infection and vaccine efficacy has previously been related to NAb rates [46], thereby reducing clinical events [47] or, in specific conditions, helping consider revaccination (i.e. booster dose, challenge dose or revaccination with a complete series) [48].

Currently, evidence is accumulating establishing a definite link between the level of SARS-CoV-2 humoral immunity and COVID-19 clinical protection, without any threshold level being clearly relevant for clinical practice [49–52]. Although delayed anti-SARS-CoV-2 NAb production was associated with increased rates of COVID-19 death [53], poor anti-S responders after vaccination in the oncology setting were clearly likely to keep the poorest prognosis [23].

Immunisation against SARS-Cov-2 appears durable in the case of remaining NAbs after 12 months from infection [54,55]. Half-life of anti-S (RBD) IgG levels from 393 convalescent COVID-19 health-care workers (HCWs) was found to be 725 days (24 months) [55], with an incidence of SARS-CoV-2 infections of 0.4 per 100 person-years compared with 12.22 in COVID-19-negative HCWs. This observation is highly suggestive of a durable protection against reinfection after a first COVID-19 infection. Indeed, PCR-proven reinfections were rare in the young and international population of Qatar [56]. Natural infection most likely elicits strong protection against reinfection, displaying an efficacy of approximately 95% for at least seven months. Whether

such long protection induced by natural infection could be similar to that acquired after vaccination is highly questionable. A non-negligible reinfection rate among populations vaccinated for more than 6 months was already observed [4,5]. These reinfections were associated with higher infectious power and viral burden, with immune host defences being overwhelmed in the presence of low anti-S Ab levels, as recorded with B.1.617.2 Delta variant of concern (VOC) [57]. In a large population study involving patients reverse transcriptase polymerase chain reaction (RT-PCR)-tested for SARS-CoV-2 after two doses of mRNA BNT162b2 vaccine, there was a significantly increased infection risk observed in individuals who received their last vaccine dose more than 146 days prior, particularly among patients aged older than 60 years [4]. In this cohort, patients with solid tumour were identified as one of the subgroups exhibiting higher risk for such postvaccine waning immunity (odds ratio = 0.642 [0.494–0.834]).

The best immunity stimuli against SARS-CoV-2 are most likely the association of a previous COVID-19 infection followed at least two months after natural infection by a single mRNA vaccine dose, when anti-S Ab levels in such patients are compared with those measured after two mRNA vaccines in injections in SARS-CoV-2-naive participants in the general population [58–60] or patients with cancer [61]. In addition, although the protective Ab levels appear to be higher in the days after vaccination versus after a COVID-19 infection, the decrease is likely more rapid in the vaccinated group, with Ab titres decreased by up to 40% at each subsequent month, whereas in convalescents, these Ab titres were shown to decrease by less than 5% per month [62]. Six months after BNT162b2 vaccination, 16.1% participants displayed Ab levels below the seropositivity threshold of <50 AU/mL (*Abbott IgG II*), whereas only 10.8% of convalescent patients were below the <50 AU/mL threshold nine months after SARS-CoV-2 infection.

These recent data suggest the need for a D3 booster dose among defined populations. However, to date, no randomised trial data are available, enabling physicians to choose between a strategy based on a potential serological threshold or a vaccination schedule designed for all, without prior biological examination. This strategy has currently been selected by various states that since summer 2021, have started revaccination in the population considered at risk, recently reporting clinical benefits in terms of reinfection rates [1].

5. Do we have reliable data concerning anti-S levels and clinical protection?

Several published studies reported correlations between anti-S Abs and NAb levels and SARS-CoV-2 (re)infection incidences in either patient with cancer or the general population.

- A randomised efficacy trial investigating ChAdOx1 nCoV-19 (AZD1222) vaccine, conducted in the United Kingdom, showed the total anti-S IgG levels to be associated with 80% vaccine efficacy against symptomatic COVID-19 caused by the B.1.1.7 Alpha variant (Abs levels around 260 BAU/mL, 95% confidence interval:108–806) [63]. However, no correlation with clinical efficacy was found for asymptomatic infection. Based on this study, this level was therefore proposed by French Health Authorities in August 2021 to enable prescription of anti-SARS-CoV-2 monoclonal Abassociation casirivimab-imdevimab in pre- or post-COVID-19 exposure setting for immunocompromised patients, stating *de facto* anti-S Ab dosing was required for such patients.
- In a live-virus neutralisation assay, Gallais et al. [55] reported that in 393 convalescent COVID-19 HCWs from Strasbourg University Hospital that after one year B.1.1.7 Alpha variants, yet to a lesser extent B.1.351 Beta variants, were sensitive to anti-S Abs at 1.4 log BAU/mL (26 BAU/mL) (*Abbott IgG II*), whereas IgG >2.0 log BAU/mL (>100 BAU/mL) strongly neutralised all variants. These latter anti-S IgG titres were reached by all vaccinated HCWs participating in the study, regardless of prevaccination IgG levels and vaccine types. In this study, the reinfection rate was 0.40 per 100 person-years versus 12.22 in a non-vaccinated cohort. Therefore, there was a relative reduction in the SARS-CoV-2 reinfection incidence of 96.7%, which, however, was observed before the B.1.617.2 Delta variant wave.
- In a cohort of 8758 French HCWs, 9.65% of HCWs on average without any NAbs became infected after a median 275-day follow-up, as did 2.2% of those with low NAb titres yet none of those with high NAb titres [64]. Based on a correlation rate with NAbs of approximatively 0.8, individuals with anti-S titres below 141 BAU/mL (*Wantai Biological Pharmacy Enterprise Co., Ltd, China*) displayed about 10% risk of becoming infected within a year versus a 1.3% risk for HCWs with titres between 141 and 1700 BAU/mL and no infection risk for those exhibiting titres above 1700 BAU/mL.
- In the Maccabi Healthcare Services Israeli study [65], 5141 vaccinated participants underwent anti-S IgG dosages (Abbott IgG II) at both four weeks and six months after D2 vaccination. The rate of participants with a PCR-positive SARS-CoV-2 infection significantly differed depending on anti-S IgG titre levels, ranging from 1.2 to 1.3% for those with anti-S titres below 299 AU/ml (<42 BAU/mL), yet being only 0.2% for those with anti-S titres above 300 AU/ml (>42 BAU/mL), (p = 0.004). These data suggest that anti-S IgG titres are a good correlate for symptomatic infection risk.

Taken together, there seems to be a link between humoral immunity levels, whether postvaccination or postinfectious and clinical protection. As a result, there is, therefore, a group at high risk of reinfection, namely, those with low anti-S levels <40 BAU/mL and another group at low risk of infection and thus severe COVID-19, with anti-S levels above 100–260 BAU/mL. Of note, 140 BAU/mL corresponds to 1000 AU/mL with *Abbott IgG II*, this threshold representing the first quartile of

the anti-S Ab distribution after the first vaccine shot in patients with thoracic cancer [35]. In contrast, patients with HL exhibited a median 118 BAU/mL after two vaccine shots in Addeo A. et al. [29] series, resulting in 100 BAU/mL representing the lower limit of this quite consistent window.

Nevertheless, it seems important to us to clarify certain technical limitations before proposing a clear course of action designed to guide medical oncologists in their vaccination management of patients with cancer.

6. Lack of technique harmonisation

The lack of technique and assay harmonisation, which often impedes cross-comparison of studies, renders it difficult to establish a clear definition of serum anti-S titre cutoff. Such a cutoff threshold could serve to provide strong guidance in terms of vaccination booster timing. Otherwise, while waiting, only a vaccination schedule for all that is not based on individual serological rates should be recommended.

As mentioned previously, the international standard for anti-SARS-CoV-2 immunoglobulins (NIBSC code 20/136), which was proposed by the WHO, was designed to uniformise dosage results, by defining common units, meaning the BAU per millilitre (BAU/mL) [44]. Ab titres were determined after SARS COV-2 infection, and four groups were described: high responders with median anti-S IgG titres of 832 BAU/mL, mid responders with median anti-S IgG titres of 241 BAU/mL, as well as low S IgG/high nucleocapsid (N) antigen responders with 86 median anti-S IgG titres of BAU/mL and low responders with median anti-S IgG titres of 53 BAU/mL. As already stated, all manufacturers are supposed to give concertiser factor for their assay that allows to uniformise results [11]. In August 2020, the United States Food and Drug Administration (FDA) authorised the emergency use of COVID-19 convalescent plasma for treating hospitalised patients affected by COVID-19. Later, in March 2021, the FDA provided a table of tests acceptable for use in the manufacture defining a high titre COVID-19 convalescent plasma. For *Roche Elecsys*, the required level of anti-S Abs was $\geq$132 AU/mL ($\approx$ BAU/mL), for *Abbott IgG II* on Architect or Alinity, this level was $\geq$840 AU/mL (120 BAU/mL), whereas for *DiaSorin TriS IgG*, it was $\geq$52 AU/mL (135 BAU/mL) [66].

Most anti-S techniques measure anti-S IgGs, whereas some others, such as *Roche Elecsys*, measure total anti-S Abs, including IgG, IgA and IgM. In addition, the assay targets differ in recognising either the entire spike protein, S1 and S2 subunits cleaved from the spike, or the RBD of the spike protein from the spike S1 subunit. In all assays, the manufacturer is thought to provide detection range, clinical specificity and sensitivity.

Despite WHO's proposal, clinical follow-up studies investigating immune responses over time after either infection or vaccination often use various commercial tests for IgG assays and this with or without conversion to BAU/mL [67–71]. Such studies are not always able to establish reliable cutoffs, which could be applied to clarify which SARS-Cov-2 Ab levels would support revaccination of former infected or vaccinated people, owing to waning immunity. A surprising issue is that even though the sensitivity and specificity of various tests are excellent [72], the conversion of units from AU/ml to BAU/mL is not at all linear, as reported by others [12,73–75]. Kim et al. [75]nicely illustrated that a factor 4.5 should be applied to convert Roche Elecsys anti-S Ab titres to *Abbott IgG II*. Perkman et al. [76] reported comparative anti-S Ab titres from 50 participants that underwent homologous AZD1222 vaccination using Roche Elecsys and *Abbott IgG II*, based on a surrogate neutralisation assay. The comparability of quantitative SARS-CoV-2 Ab tests was highly dependent on the timing of blood collection after vaccination. Although three weeks after D1, anti-S Ab titres (converted in BAU/mL) provided by *Abbott IgG II* were three times higher than those measured using Roche Elecsys, 11 weeks after D1 injection, the values obtained when using *Roche Elecsys* were twice as high as those attained by Abbott IgG II, and three weeks after D2, these *Roche Elecsys* values were even five to six times higher than those of *Abbott IgG II*. According to the authors, standardisation of blood collection timing is required for the comparability of different quantitative SARS-COV-2 Ab assays.

However, for low anti-S Abs titres (poor-responders), the impact of the difference appears less crucial. Therefore, defining a low anti-S Ab level remains relevant. Even when using conversion factors, head-to-head comparison remains hazardous. Comparison data with clinically relevant cutoffs depending on the assays used are currently urgently required.

7. Authors' recommendations for anti-S monitoring in patients with cancer

7.1. Recommendation number #1: publish results in BAU/mL

Because most Western countries are likely to proceed to a booster dose vaccine for their whole population older than 60 or 65 years old, the current issue is to provide clear guidance for younger people, especially if they suffer from cancer. To be able to compare future data across different studies, assays and countries, our first recommendation is to publish the results pertaining to anti-S Ab serology using the WHO BAU/mL units. Indeed, although the techniques may not be completely comparable, this will at least avoid potential sources of

confusion when analysing comparative data. Moreover, comparative studies using different immunological assays must be performed, with results compared at different time points. Ideally, international units should then be proposed [11].

7.2. Recommendation number #2: monitor vaccine response at week 3-4 after D2

Despite remaining uncertainties, in our view, the currently available data are sufficient to propose serological monitoring in patients at risk of lower seroconversion rates, including patients with cancer. Moreover, our data similarly support serology reimbursement by health authorities with dosing proposed 3–4 weeks after D2 and during follow-up, as necessary. Indeed, as already mentioned, the delay in the appearance of NAbs is now a well-established risk factor for COVID-related death [53]. In addition, a low level of postvaccination Abs has been formally identified as a risk factor of death [36]. Moreover, in the general population, waning immunity has been established to occur from the fifth month postvaccination, with initial higher anti-S IgG titres.

Anti-S Ab dosage at 3–4 weeks after D2 would seek to assess the responders and identify three different groups (Fig. 1), depending on their anti-S IgG levels.

We have summarised our approach in Fig. 2.

7.2.1. Situation #1: anti-S Abs titre < 40 BAU/mL

We recommend proposing an early D3 to **no-responder** patients with cancer (**red zone**: anti-S Ab titre < **40 BAU/mL** (<280–300 AU/mL for the *Abbott IgG II* assay) (Figs. 1–2). For these patients, along with the encouragement of relatives to get vaccinated and the drastic maintenance of social protection measures, as well (class 2 filtering face piece masks), repeated immune stimulation with a fourth vaccine dose (D4), with either multimodal immune stimulation using heterologous prime-boost vaccination (mRNA vaccine then adenoviral-based vaccines) or a maximised immune stimulation double-dose approach, should be considered [17]. These strategies, however, still need to be evaluated in randomised clinical trials. Preexposition or post-exposition COVID 19 prophylactic approaches or treatment in the early disease phase (<5 days), using a monoclonal Ab association like casirivimab-imdevimab or long-acting Ab combination AZD7442, can be prescribed.

7.2.2. Situation #2: anti-S Ab titre between 40 BAU/mL and 100/260 BAU/mL

The second category defines as **low-responder** patients with cancer (**yellow zone**: anti-S Ab titre between **40 and 100–260 BAU/mL**, suggested area of uncertainty, i.e. values between 280-300 and 700–1800 UA with the *Abbott IgG II* assay [Figs. 1–2]). These patients may also be proposed a D3. Yet, this third injection could be carried out in a less urgent manner, while taking into account associated comorbidities and regional epidemic incidence rates, followed by a monthly dosage of anti-S Ab titres so as to assess the kinetics of waning immunity, if possible. These patients, likely to be less at risk than those of the first group, could markedly benefit from an early D3. Once again, while such a strategy seems to be worth it, more data are still needed to best identify potential predictive rates of increased responses to a booster. Like the no-responder group, administration of monoclonal Abs should be considered (see above).

7.2.3. Situation #3: anti-S Ab titre > 260 BAU/mL

The last category can be defined as **responders** (**green zone**: anti-S Abs titre > **260 BAU/mL** [> 1800 AU/mL for *Abbott IgG II*] Figs. 1–2). This group may wait a few months before receiving D3, after the recommendations are established for the general population. Taking into account the slope of waning immunity with time in patients with comorbidities, including patients with cancer [4], we suggest considering anti-S Ab dosage at three months, particularly in intermediate-responders,

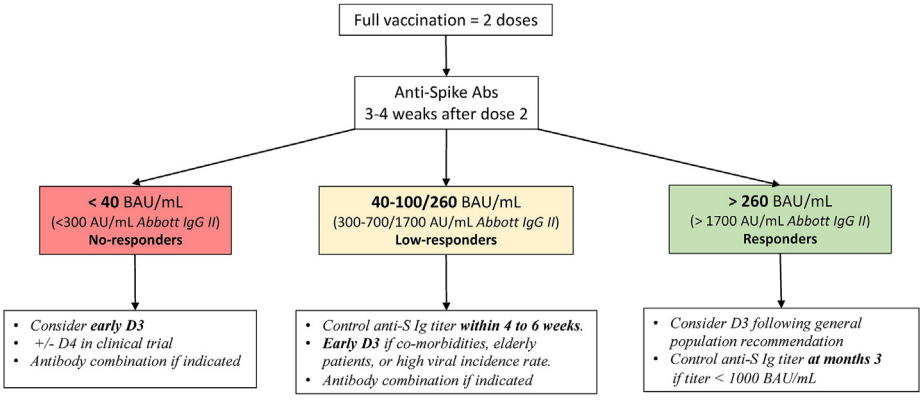

Fig. 2. Authors' recommendations for anti-S Ab monitoring in patients with cancer and for timing of D3 booster dose. D3, third vaccine dose.

meaning those with anti-S Ab titres between 100 BAU/mL and ~1000 BAU/mL. Given this context, D3 vaccine should be administered as soon as anti-S Ab levels decrease, becoming close to or below 100–260 BAU/mL, as seen in situation #2.

As advantage of such policy, this would enable us to spare vaccine doses and keep them for developing countries or higher-risk patients, including solid organ transplant patients, octogenarians and so on. In addition, delaying D3 would have the additional advantage of further expending the protection period of these patients by moving forward the limit of humoral protection. After six months from vaccination, depending on the recommendations in force as per the patient's age, a D3 may be offered without serological control unless the patient is part of a serological monitoring observatory.

7.3. Recommendation number # 3: after D3, anti-S IgG level assessment at 3–4 weeks

After administering D3, regardless of the indication and threshold selected for such decision, we suggest to measure anti-S Ab levels at 3–4 weeks after D3, to ascertain the rise of protecting serum Ab above 260 BAU/ml. If it is the case, a new measurement could be performed at 5–6 months. Yet, we do not know what will be the slope of the anti-S Ab decrease, which may indeed be slower than the one after the two initial shots. Whether ulterior injections would be needed is still unknown, owing to uncertainties about the viral circulation level at that time across the five continents. Other uncertainties pertain to the VOCs that will be predominantly circulating during the first 2022 semester and the eventual future vaccine mRNA formulations that will later be at our disposal. Clearly, there are currently no scientific data in relation to an eventual fourth vaccine dose injection (D4) after eventual immunity waning after D3. However, one exception deserves to be mentioned here. Indeed, such repeated vaccine injections have already been administered to some severely immune-compromised patients, to those with solid organ transplantation or to patients with HMs treated using anti-CD20 therapeutic monoclonal Abs. Nevertheless, such repeated vaccine dose injection has not been proven efficient to date.

7.4. Recommendation number #4: patients to be included in observational serological monitoring studies or dedicated clinical trials

We strongly recommend the continuation of observational studies, with the pooling of their data, to obtain solid epidemiological data. A prospective study [77] is currently in progress, which should enable us to establish with certainty a link between the Ab level and clinical protection over time, with a specific focus on patients with cancer.

We are aware that our recommendations based on anti-S Abs titres could be extensively debated, until prospective large-sized study data are being made available, enabling us to validate our proposals. Moreover, even if waning specific T immunity has similarly been reported, specifically depending on age and being directed against VOC [78], it is clear that humoral immunity does not summarise the whole anti-SARS-CoV-2 immunity field [13,79]. The same is true for the oncology domain [80]. The presence of memory T- and B-cells has been clearly shown in germinal centres [81], which could support higher protection towards SARS-CoV-2 in vaccines, even in the event of low serum anti-S IgG titres. The contrast between high-breakthrough infection levels in large populations vaccinated during the December 2020–January 2021 period and the relatively low level of severe or deadly COVID-19 overwhelming hospitals, notably in Israel or Singapore, would suggest the existence of such memory immunity, thereby protecting people against severe COVID-19, even in the event of serum anti-S IgG decreases. However, we are still lacking routine, fast and cost-effective techniques to monitor specific T-response or specific memory immune cell responses, which would allow us to ascertain such hypothesis. Therefore, pragmatically, we feel that serum anti-S IgG monitoring could offer a relatively low-cost monitoring strategy, whereas it is still an imperfect readout for assessing anti-SARS-CoV-2 immunity in high-risk cancer patients. We urgently call for reimbursement of such tests for patients with cancer, along with a prospective evaluation of our proposed strategy. Given the risk of vaccine failure in some patients with cancer, we strongly encourage vaccination campaigns with a full-dose schedule for households, with a six-month booster after country policies, close contacts and the general population.

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Conflict of interest statement

J. Barrière reports fees from BMS and Mylan Medical, all outside the submitted work. C. Audigier-Valette reports personal fees from AstraZeneca,

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