denosomab as “promising.”

We suggest that it would be inappropriate to include denosomab in any future guidelines as a component of adjuvant therapy for women with breast cancer based on current information.

In summary, the SUCCESS-A trial that compared duration of adjuvant zoledronate in women with early breast cancer at high risk of recurrence did not show statistically significant differences in DFS, bone recurrence-free survival, and OS, and if zoledronate is included as a component of adjuvant therapy, a shorter duration of treatment is sufficient. While limitations such as inclusion of premenopausal women not receiving ovarian suppression and low event rates may have influenced the observed outcomes in SUCCESS-A, it is unlikely that a substantial difference would have been observed in the absence of these limitations. In light of this, and the modest outcomes of bisphosphonates compared with no bone-targeted therapy in historical trials, an important question needs to be answered: in a contemporary breast cancer setting in which DFS events are infrequent, what, if any, is the benefit from adjuvant bisphosphonates? It is time to reevaluate the guidelines.

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with solid tumors compared with 81.7% with hematologic cancers.3

In this issue of JAMA Oncology, 2 groups investigate the immune response to SARS-CoV-2, by proxy of antibody assays, in patients with solid malignant neoplasms who were undergoing active cancer therapy. In the first article, Massarweh et al4 report a 90% seropositivity rate in 102 patients with solid cancers in Israel tested at least 12 days after receipt of the second BNT162b2 mRNA vaccine dose, compared with 100% seropositivity in noncancer controls. The median immunoglobulin G (IgG) titer was lower in patients with cancer than noncancer controls (1931 vs 7160 AU/mL). While 10 patients with cancer did not experience seroconversion, most patients, including those on chemotherapy, mounted a detectable antibody response to vaccination.4

The second study, by Yazaki et al,5 reports findings from a population-based seroprevalence study of 500 patients with cancer and 1190 health care workers (HCWs) in Japan from August to October 2020, with the analytic population focusing on those with no known history of SARS-CoV-2 infection. Although seroprevalence was low and did not differ between patients with cancer and HCWs (1.0% vs 0.67%), IgG levels against nucleocapsid and spike proteins were significantly lower among patients with cancer.5

Both studies used a chemiluminescence immunoassay with prespecified thresholds to define seropositivity. Despite the excellent test performance characteristics of both assays used, including sensitivity and specificity greater than 98%, it is important to note that seropositivity is a key but imperfect correlate for protection against SARS-CoV-2 infection, and the association between antibody binding titers and antibody effector function is poorly understood.6 In addition, antibody titers do not fully account for protection against SARS-CoV-2, as other forms of immunity, such as SARS-CoV-2-specific memory T cells, may be protective even in seronegative patients.6,7 Although both studies provide quantitative IgG titers as well as binary seropositivity status, interpretability of these continuous measures is challenging. For instance, is a statistically significant difference in IgG titer between patients with cancer and controls truly a clinically significant one, particularly given the wide range of median titer values? This is of particular concern in the Japanese study, where low seroprevalence in both the cancer and control populations was attributable to low levels of background community spread—potentially as a result of a successful nationwide public health response. In a setting where most patients were likely never exposed to SARS-CoV-2, quantitative differences in SARS-CoV-2 IgG titers become even more difficult to interpret. In addition, the duration of protective immunity, especially in patients who go on to receive immunomodulatory anticancer therapy, remains a crucial unanswered question that will require further longitudinal study. Thus, even with highly reliable antibody assays, seropositivity remains an imperfect proxy for clinically protective immunity against SARS-CoV-2.

The influence of cancer treatment type and timing on the immune response to SARS-CoV-2 remains a topic of clinical interest and controversy. Large studies and meta-analyses have reported mixed results on the association between active cancer-directed therapy, including cytotoxic chemotherapy, and poor COVID-19 outcomes, including death.6,9 In the Japanese seroprevalence study,7 IgG levels against nucleocapsid (but not spike) protein were lower in patients who received chemotherapy within 1 month compared with those who did not receive chemotherapy, although this association was not significant on multivariable regression. Immune checkpoint inhibitor therapy, on the other hand, was associated with higher adjusted nucleocapsid IgG and spike IgG levels compared with no immune checkpoint inhibitor therapy. However, these titers were measured in a largely unexposed population and may reflect factors other than COVID-19-specific immune response. In the Israeli vaccination study,4 the only treatment regimen associated with significantly lower IgG levels on multivariable analysis was chemotherapy with immunotherapy; however, only 14 patients received this combination therapy, and no association was seen with either chemotherapy or immunotherapy alone. Given that chemotherapy combined with immunotherapy is only used in select cancer types (eg, lung cancer, triple-negative breast cancer), it is possible that other cancer-specific factors drove the observation in this small subset. Until more definitive data emerge, decisions around delivery or interruption of anticancer therapy should be based on individual risk-benefit assessment incorporating factors including cancer prognosis and patient comorbidities.

The authors of both studies should be commended for conducting large, well-designed cohort studies that incorporate a valid control group (family/caregivers4 or HCWs5) and use multivariable regression to control for baseline differences between groups—both critical components to improving the validity and interpretation of observational studies.10 These results add to our multicountry perspective on this global pandemic, which will be particularly critical in light of differing vaccine availability, schedule, and practices across different countries, especially low- and middle-income countries. With at least 30 vaccines anticipated to be available worldwide by the end of 2021, it will be crucial to determine which vaccines are most effective among patients with cancer.

Overall, both of these studies4,5 reinforce the importance of optimizing delivery of a full course of vaccination for patients with cancer, who are at high risk for morbidity and mortality from COVID-19. An interim analysis of a prospective observational study of the BNT162b2 mRNA vaccine in patients with cancer11 showed poor efficacy (as measured by seroconversion, viral neutralization, and T-cell responses) after a single dose but substantially improved immunogenicity in those who received a vaccine boost at day 21. These data suggest that timely delivery of the second vaccine dose is crucial among patients with cancer, particularly those who are actively receiving systemic therapy.

If some patients with cancer mount a less robust immune response to vaccination, should additional booster doses of the same vaccine be considered to improve immunogenicity? Although to our knowledge there is as of yet no evidence for the safety or efficacy of such an approach, it is not without precedent in oncology practice. For example, current guidelines recommend revaccinating hematopoietic
cell transplant recipients to reestablish immunity to vaccine-preventable diseases, such as pneumococcus, meningococcus, tetanus, and varicella. Booster doses of vaccine have also been proposed in the general population as a strategy to counteract emerging SARS-CoV-2 variants. Finally, in patients who mount an inadequate immune response to SARS-CoV-2 exposure or vaccination, convalescent plasma or monoclonal antibody therapy may provide an additional layer of protective immunity. These strategies, however, remain speculative at this time and highlight the need for well-designed prospective studies, which remain the cornerstone of clinical research even in the era of rapidly accumulating observational data during the COVID-19 pandemic. In particular, because cross-sectional and cohort studies, such as those by Massarweh et al and Yazaki et al, are not able to inform critical questions such as optimal timing of revaccination, longitudinal data collection will be key.

Several prospective studies (eg, NCT04715438, NCT04865133) are investigating the immune response to COVID-19 vaccination in patients with cancer and will yield valuable information about the safety and efficacy of vaccination as well as the duration of protective immunity in this population. Meanwhile, it is vitally important to continue transmission mitigation measures, within both community and health care settings, to help protect vulnerable patients with cancer from SARS-CoV-2 exposure, infection, and life-threatening outcomes.

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