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RESEARCH

Immune response to anti-SARS-CoV-2 prime-vaccination in patients with cancer: a systematic review and meta-analysis

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Abstract

Purpose This systematic review and meta-analysis aimed to evaluate the immune response to anti-SARS-CoV-2 prime-vaccination in patients with cancer.

Methods We performed a systematic literature search using PubMed, Embase, and Cochrane Library until 28/09/2021, and conference proceedings from ASCO and ESMO 2021 annual meetings. We screened for observational or interventional studies including subjects ≥ 16 years old with cancer diagnosis who were vaccinated against SARS-CoV-2. Prime-vaccination was defined as one dose of Ad26.COV2-S vaccine or two doses of BNT162b2, mRNA-1273, ChAdOx1-S or inactivated SARS-CoV-2 vaccine. The outcomes were humoral and adaptive immune responses (proportion of subjects with positive titers of antibody anti-SARS-CoV-2 spike protein and anti-SARS-CoV-2 cellular responses, respectively).

Results We included 89 records reporting data from 30,183 subjects. The overall seropositive rate within the first month after complete anti-SARS-CoV-2 prime-vaccination was 80% [95% confidence interval (CI), 72–86%], 60% (95%CI, 53–67%) in patients with hematological malignancies (HM) versus 94% (95%CI, 88–97%) in patients with solid malignancies (SM). The diagnosis of HM was significantly associated with a lower seropositive rate on multivariate meta-regression (odds ratio 0.35, 95% CI 0.18–0.69, HM versus both, $p = 0.002$). The overall humoral response was 49% (95% CI, 42–56%) after incomplete prime-vaccination and 79% (95% CI, 70–86%) at 2 months after complete prime-vaccination. These responses were also lower in patients with HM at these time points. The overall cellular response rate at any time after vaccination was 61% (95% CI, 44–76%).

Conclusion This meta-analysis provides compelling evidence of humoral and adaptive immune responses against SARS-CoV-2 in patients with cancer, which last for at least 2 months following complete prime-vaccination.

Keywords Neoplasms · SARS-CoV-2 · COVID-19 · Vaccines

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Introduction

The COVID-19 pandemic has been the cause of millions of deaths worldwide (World Health Organization 2022a). Patients with cancer are at increased risk of complications and death from SARS-CoV-2 infection (Saini et al. 2020). Therefore, vaccination is critical to prevent severe COVID-19 in this vulnerable population. Several vaccines based on different platforms have been approved (World Health Organization 2022). This systematic review and meta-analysis aims to evaluate the immune response to anti-SARS-CoV-2 prime-vaccination in patients with cancer.

Methods

We performed a systematic literature search using PubMed, Embase, and Cochrane Library until 28/09/2021, and conference proceedings from ASCO and ESMO 2021 annual meetings. The search string included "cancer" AND "anti-SARS-CoV-2 vaccination". We included observational or interventional studies, including subjects ≥ 16 years old with cancer diagnosis and vaccinated against SARS-CoV-2, and reporting data of at least one of this meta-analysis' endpoints. Studies were excluded if ≥ 10% of the participants had other causes of immunosuppression, baseline anti-SARS-CoV-2 antibodies, or history of previous SARS-CoV-2 infection. For records of the same study with superimposable populations for the same study endpoint, we excluded the record with the smaller population size. The primary objective was to evaluate the humoral immune response against SARS-CoV-2 within the first month (≤ 4 weeks) after complete anti-SARS-CoV-2 prime-vaccination in patients with cancer. Prime-vaccination was defined as one dose of Ad26.COV2-S vaccine or two doses of BNT162b2, mRNA-1273, ChAdOx1-S or inactivated SARS-CoV-2 vaccine. Secondary objectives included humoral immune responses against SARS-CoV-2: after incomplete prime-vaccination, at two (> 4 weeks to 3 months), four (> 3–5 months), six (> 5–7 months), and any time after prime-vaccination. As exploratory objective we assessed the adaptive immune response against SARS-CoV-2 at any time after vaccination.

We calculated the combined overall immune responses rate per each time point by considering a meta-analysis of immune response rates. A random-effects estimation model was used to estimate combined proportions with 95% confidence intervals (CI) due to large heterogeneity between studies, as evaluated by the Higgins I^2 index. The combined proportion was estimated overall, and stratified by cancer type. Meta-regression was performed for the primary endpoint, using a random intercept logistic regression model with the following variables: age, sex, cancer type, disease status, and cancer treatment. The packages meta and metafor were used for all analyses in R version 4.1.2.

Results

A total of 89 records were included in this systematic review, reporting data from 30,183 subjects (Fig. 1). Forty-seven studies included only patients with hematological malignancies (HM) ($n = 9141$), while 24 studies measured the immune response only in patients with solid malignancies (SM) ($n = 7229$). The other 18 studies evaluated patients from both cancer type subgroups ($n = 13{,}813$). The main characteristics of the included studies are summarized in Table S1.

The overall seropositive rate within the first month after anti-SARS-CoV-2 prime-vaccination was 80% (95% CI, 72–86%) (30 studies, $n = 4113$ patients). There was a large heterogeneity between the included studies ($I^2 = 95\%$), with response rates ranging from 42 to 99%. Stratification by cancer type revealed 60% (95% CI, 53–67%) seropositive rate within the first month in patients with HM (13 studies, $n = 1486$ patients) and 94% (95% CI, 88–97%) in patients with SM (9 studies, $n = 1804$ patients) (Fig. 2B). Eight studies ($n = 823$ patients) including both subgroups of patients with HM and with SM, reported an overall seropositive rate of 81% (95% CI, 72–88%) within the first month after prime-vaccination. Only one study assessed the efficacy of inactivated SARS-CoV-2 vaccine in patients with SM, showing a lower seropositive rate of 64% (95% CI, 49–77%) (Karacin et al. 2021). In a meta-regression including all studies reporting this endpoint (30 studies), only the diagnosis of HM was significantly associated with lower seropositive rate: odds ratio (OR) 0.35 (95% CI, 0.18–0.69) of HM versus both (p value = 0.002), OR 3.02 (95% CI, 1.34–6.80) of SM versus both (p value = 0.007).

The humoral response rates after incomplete prime-vaccination were 49% (95% CI, 42–56%) for the overall population (38 studies, $n = 4154$ patients) and 51% (95% CI, 39–63%) for the studies including both subgroups of patients (8 studies, $n = 1241$ patients), while 42% (95% CI, 34–51%) and 60% (95% CI, 46–72%) for studies including only patients with HM (20 studies, $n = 1350$ patients) and SM (10 studies, $n = 1563$ patients), respectively (Fig. 2A). At 2 months after prime-vaccination, the overall seropositive rate was 79% (95% CI, 70–86%) (11 studies, $n = 1885$ patients), 71% (95% CI, 60–81%) in patients with HM (7 studies, $n = 992$ patients) as compared to 92% (95% CI, 87–95%) among patients with SM (2 studies, $n = 183$

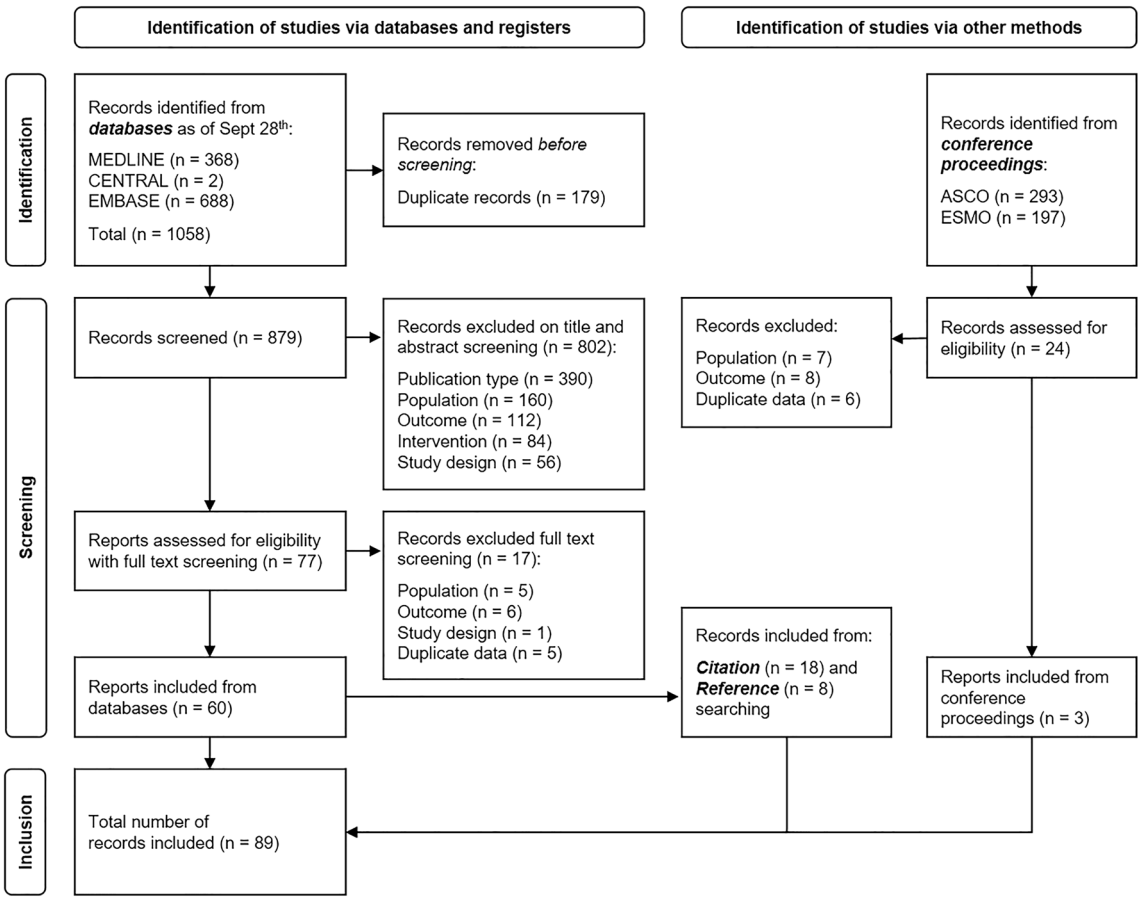


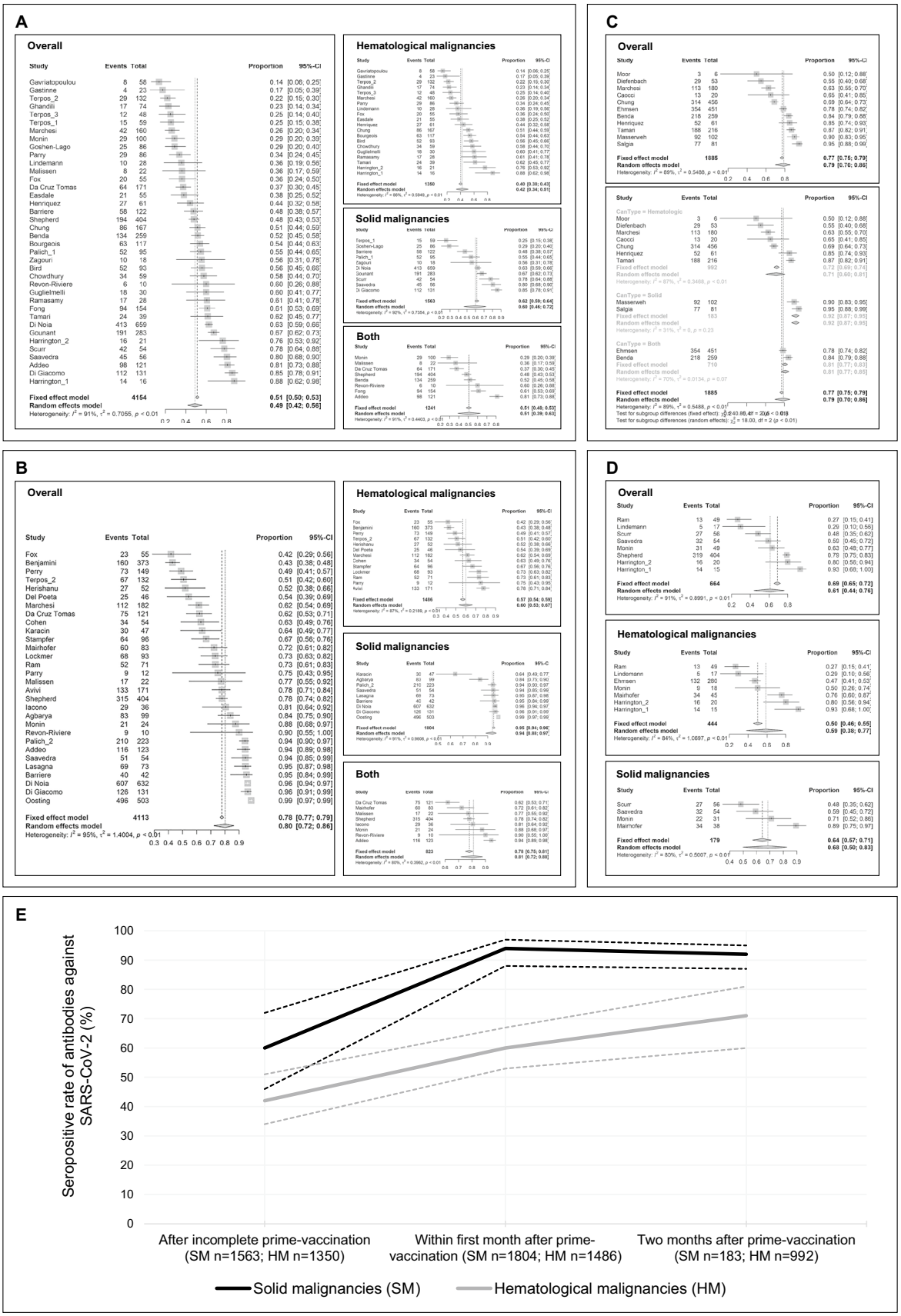
Fig. 1 PRISMA flowchart of the retrieved records

patients) (Fig. 2C). Only two studies ($n = 710$ patients) including both subgroups of patients reported 81% (95% CI, 77–85%) seropositive rate at two months after vaccination. In Fig. 2E, we describe the estimated seropositive rates at each time point by cancer type. Two studies including only patients with SM reported a seropositive rate of 87% (Eliakim-Raz et al. 2021) and 79% (Waldhorn et al. 2021) at four ($n = 95$ patients) and six months ($n = 154$ patients), respectively. The overall humoral response against SARS-CoV-2 at any time after prime-vaccination was 78% (95% CI, 73–82%) (64 studies, $n = 10{,}511$ patients).

The overall cellular response rate at any time after vaccination was 61% (95% CI, 44–76%) (8 studies, $n = 664$ patients), 59% (95% CI, 38–77) in patients with HM (7 studies, $n = 444$ patients), and 68% (95% CI, 50–83) in those with SM (4 studies, $n = 179$ patients) (Fig. 2D).

Discussion

To our knowledge, this is the largest systematic review and meta-analysis assessing immunogenicity of anti-SARS-CoV-2 vaccination in patients with cancer. With a high number of studies included, we reduced the impact of significant heterogeneity between published studies, permitting improved discrimination of the seropositive rate at specific time points after prime-vaccination. We also add more robust data on cellular immune responses. Our study estimates that only half of the patients with cancer seroconvert after incomplete prime-vaccination, whereas eight out of ten fully vaccinated patients are seropositive in the first month following prime-vaccination. These findings are in line with previous reports of smaller systematic reviews (Corti et al. 2021; Tran et al. 2021; Becerril-Gaitan et al. 2022); however, our meta-regression provides stronger evidence that patients with HM have a weaker humoral responses after SARS-CoV-2 prime-vaccination, potentially due to malignancy-associated lymphoid imbalances. This may principally reflect B-cell malignancies, such as B-cell non-Hodgkin Lymphoma and Chronic Lymphocyte Leukemia,


A
Overall
Hematological malignancies
Solid malignancies
Both
B
Overall
Hematological malignancies
Solid malignancies
Both
C
Overall
D
Overall
Hematological malignancies
Solid malignancies
E
Seropositive rate of antibodies against SARS-CoV-2 (%)
After incomplete prime-vaccination (SM n=1563; HM n=1350)
Within first month after prime-vaccination (SM n=1804; HM n=1486)
Two months after prime-vaccination (SM n=183; HM n=992)
Solid malignancies (SM)
Hematological malignancies (HM)

◂**Fig. 2** Forest plots of overall proportion of patients with cancer and positive titers of antibody against anti-SARS-CoV-2 spike protein after: **A** incomplete anti-SARS-CoV-2 prime-vaccination, by cancer type: overall ($N=38$ studies), hematological malignancies ($N=20$ studies), solid malignancies ($N=10$ studies), both ($N=8$ studies); **B** within the first month (≤ 4 weeks) after prime-vaccination, by cancer type: overall ($N=30$ studies), hematological malignancies ($N=13$ studies), solid malignancies ($N=9$ studies), both ($N=8$ studies); **C** at 2 months after anti-SARS-CoV-2 prime-vaccination, by cancer type: overall ($N=11$ studies), hematological malignancies ($N=7$ studies), solid malignancies ($N=2$ studies), and both ($N=2$ studies). **D** Forest plots of overall proportion of patients with cancer and positive adaptive immune response against SARS-CoV-2 spike protein at any time after anti-SARS-CoV-2 vaccination, by cancer type: overall ($N=8$ studies), hematological malignancies ($N=7$ studies), and solid malignancies ($N=4$ studies). **E** Graphical representation of the seropositive rates after incomplete prime-vaccination, within 1 month (≤ 4 weeks) after complete prime-vaccination, and at 2 months (>4 weeks to 3 months) after complete prime-vaccination, by cancer type: solid malignancies (dark) and hematological malignancies (light). Solid lines represent estimations and dashed lines represent 95% confidence intervals; *n* values stand for total number of patients

HM subgroups that seem to develop lower seropositive rates (Terpos et al. 2021). Moreover, the use of B-cell-depleting therapies is also described to negatively impact the humoral immune response to anti-SARS-CoV-2 vaccination, as demonstrated by the study with the largest subgroup of patients with HM actively treated with anti-CD20 included in our meta-analysis, in which only 7% of the patients were seropositive after prime-vaccination (Perry et al. 2021). On the other way, in this meta-analysis, we demonstrate that cellular immune responses were detected in approximately two-thirds of patients with HM, similar to patients with SM. For both cancer types, the seropositive rate remains stable at 2 months after prime-vaccination. Interestingly, for HM, the humoral response rate seems higher at two months following prime-vaccination, suggesting that these patients may have a delayed seroconversion. These data may argue in favor of a delayed booster for both tumor types beyond the two months following prime-vaccination. Long-term humoral and cellular immune responses after prime-vaccination and subsequent booster doses of anti-SARS-CoV-2 vaccination are currently being investigated (NCT05075538), and should contribute, together with data from this meta-analysis, in guiding future decisions on the optimal vaccination boost periodicity for patients with cancer.

Conclusion

This meta-analysis provides compelling evidence of humoral and adaptive immune responses against SARS-CoV-2 in patients with cancer, supporting the efficacy of this intervention in this vulnerable population. The humoral responses last for at least two months after prime-vaccination, even in patients with HM who show lower initial humoral response within the first month, despite similar adaptive immune responses.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-022-04185-w.

Author contributions DMB: conceptualization, methodology, investigation, data curation, writing—original draft preparation, and project administration; GNM: conceptualization, methodology, investigation, data curation, writing—review and editing, and project administration; ATV: investigation, data curation, and writing—review and editing; VD: investigation, data curation, and writing—review and editing; LA: methodology, formal analysis, data curation, and writing—review and editing; MB: writing—review and editing; KP: writing—review and editing; AL: writing—review and editing; KWG: writing—review and editing; CS: writing—review and editing; AA: writing—review and editing; MP: writing—review and editing; EdA: conceptualization, writing—review and editing, and supervision.

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Data availability The data underlying this article are available upon reasonable request to the corresponding author.

Declarations

Conflict of interest DMB: Honoraria and advisory board fees from Daiichi Sankyo, Janssen, Pfizer, Merck Sharp and Dohme, Angelini, AstraZeneca, and Novartis, meeting/travel grants from LEO Farmacêuticos, Merck Sharp and Dohme, Ipsen, Janssen, Roche, Laboratórios Vitória, and Novartis, and institutional research grant from F. Hoffmann-La Roche Ltd (all outside the submitted work); GNM: Support to attend medical conferences: Roche and Bayer (all outside the submitted work); ATV: Honoraria and advisory board fees from Roche, Pfizer, Novartis, Astellas, meeting/travel grants from Roche, Pfizer, Novartis (all outside the submitted work); MB: Meeting/travel grants from Roche/GNE, Sanofi and Takeda; speaker fees from Roche/GNE and Jansen (all outside the submitted work); KP: KP's institution received speaker fees, honoraria for advisory/consultancy roles and/or research funding from AstraZeneca, Eli Lilly, Gilead Sciences, Medscape, MSD, Mundi Pharma, Novartis, Pfizer, Pierre Fabre, Hoffmann/La Roche, Sanofi, Teva, Vifor Pharma. KP received travel support from AstraZeneca, Novartis, Pfizer, PharmaMar, Hoffmann/La Roche. K.P. received speaker fees and honoraria for advisory/consultancy roles from AstraZeneca, Gilead Sciences, Novartis, Roche, Seatlle Genetics (all outside the submitted work); KWG: Speaker fees, honoraria for advisory/consultancy roles and/or research funding from BMS, Pfizer, Philips and iTeos Therapeutics (all outside the submitted work); AA: Roche, Lilly, Amgen, EISAI, BMS, Pfizer, Novartis, MSD, Genomic Health, Ipsen, AstraZeneca, Bayer, Leo Pharma, Merck, Daiichi, Seattle Genetics, Pierre Fabre (all outside the submitted work); MP: Board Member (Scientific Board) from Oncolytics, consultant (honoraria) from AstraZeneca, Camel-IDS/Precirix, Gilead, Immunomedics, Lilly, Menarini, MSD, Novartis, Odonate, Pfizer, Roche-Genentech, Seattle Genetics, Immutep, Seagen, NBE Therapeutics, and Frame Therapeutics, and institutional research grants from AstraZeneca, Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, and Synthon (all outside the submitted work); EdA: Honoraria and/or advisory board from Roche/GNE, Novartis, Seattle Genetics, Zodiac, Libbs and Pierre Fabre. Travel grants from Roche/GNE and GSK/Novartis. Research grant to my institution from Roche/GNE,

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