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LETTER

Serum TARC dynamics during anti-PD1-based first-line Hodgkin lymphoma treatment: An analysis from the GHSG NIVAHL trial

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Immune checkpoint inhibition (ICI) with anti-programmed death protein 1 (PD-1) antibodies is highly active as monotherapy in patients with relapsed classic Hodgkin lymphoma (cHL).[1,2] Recent studies combining nivolumab (N) with chemotherapy in first-line cHL treatment have demonstrated impressive outcomes in both early- and advanced-stage disease.[3,4] These studies did, however, not incorporate early response adaptations to guide treatment, but exposed all patients to full intensity chemo- and/or radiotherapy. This raises the question whether a one-size-fits-all approach is appropriate to reach the goal of minimizing treatment toxicity while maximizing efficacy in cHL. It can be envisioned that patients with an early and deep response to ICI-based first-line therapy are candidates for treatment de-escalation strategies, reducing exposure to chemo- and radiotherapy and resulting morbidity and mortality.[5]

To this end, recent studies incorporating other highly effective treatment regimens such as BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) have demonstrated that response-adapted treatment enables de-escalation in patients with a negative interim 18F-FDG positron emission tomography (PET).[4] However, the use of FDG-PET for response assessment to guide treatment has important limitations: Nonspecific uptake of 18F-FDG may result in a high number of false positives, particularly for patients with small tumor lesions classified as Deauville score (DS) 4.[4,6] The uncertainty due to false positivity seems even more important in the context of ICI, due to systemic inflammatory effects. Indeed, immune flare observed in 12%–23% of patients in the pivotal studies on nivolumab and pembrolizumab in cHL[7,8] led to the introduction of ICI-specific response criteria.[9]

Thymus and Activation Regulating Chemokine (TARC, or CCL17) has emerged as a biomarker for cHL disease activity. TARC is produced in large quantities by the malignant Hodgkin and Reed–Sternberg (HRS) cells and can aid in diagnosis using immunohistochemistry.[10] In about 90% of patients, TARC is elevated in serum, with levels up to 400 times higher than those in healthy controls, and correlates with quantified FDG-PET results, particularly total metabolic tumor volume (TMTV).[11] Notably, serum TARC (sTARC) levels can be elevated years before clinical diagnosis.[12] In patients treated with ABVD, eBEACOPP, or salvage chemotherapies, sTARC dynamics correspond with response, and early sTARC reduction correlates with favorable outcome despite PET positivity.[11,13–15] Next to PET response, sTARC might hence be incorporated in future interim response-adapted strategies to tailor treatment intensity to individual need. However, to our knowledge, no data exist on the applicability of sTARC and its kinetics in first-line anti-PD1-based treatment.

In the prospective German Hodgkin Study Group (GHSG) randomized Phase II NIVAHL trial, patients with early-stage unfavorable HL were randomly assigned between concomitant N-AVD (nivolumab, doxorubicin, vinblastine, dacarbazine) or sequential N

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and (N-)AVD, each followed by 30 Gy involved-site radiotherapy (IS-RT). Outcomes in both treatment arms were excellent, also supported by quantified FDG-PET response using TMTV.[4,16] The aim of the current study was to evaluate sTARC dynamics during concomitant and sequential N-AVD treatment in NIVAHL and compare sTARC response with FDG-PET-based response assessment.

Patients in the randomized Phase II GHSG NIVAHL trial (NCT03004833) were evaluated for early treatment response by PET2 after either two cycles of concomitant N-AVD (Arm A) or four cycles of N monotherapy (Arm B) and after completion of systemic therapy as previously described.[4] The current study includes all 78 patients out of 109 with informed consent, available serum samples at baseline and ≥1 additional timepoint, collected after 1 week of treatment, at PET2, after end of systemic treatment (EOT), and/or post-consolidative 30 Gy IS-RT (Table S1). Patients were excluded from sTARC response assessment if baseline sTARC was below the previously established[15] and predefined cutoff of 1000 pg/mL (7/78). sTARC levels were measured using a standardized ELISA (R&D Systems, USA, Human CCL17/TARC Quantikine ELISA Kit) being blinded to treatment arm and response. Findings of sTARC were correlated with FDG-PET results using the DS and TMTV, as was previously described[16] and to clinical outcomes. Differences in median sTARC levels across all timepoints were tested with Kruskal–Wallis, and a chi-square test was used to evaluate the association between categorical variables, with $P < 0.05$ considered statistically significant. All data were analyzed by GraphPad Prism 9.0 software. This study was conducted in accordance with the principles of the Declaration of Helsinki.

At baseline, elevated sTARC levels were observed in 71/78 patients (91%). The median sTARC level in these was 17,255 pg/mL (range: 1489–339,073 pg/mL). Compared to patients with sTARC elevation, patients without elevation were more often EBV+ (57% vs. 13%; $P = 0.013$). Baseline sTARC levels correlated with baseline TMTV in line with previous studies (Figure S1).[11,15] sTARC levels sharply decreased already 1 week after start of treatment in both treatment arms (Figure 1, $P = 0.001$). By the time of PET-2, only 8 of 65 (12%) patients with available samples at the time of PET-2 remained with elevated sTARC levels. At the EOT and after the end of treatment (i.e., after 30 Gy IS-RT), only 1 out of 56 patients (2%) and none out of 57 patients (0%) had sTARC above the threshold, respectively. Median sTARC levels at all timepoints during and after treatment were significantly lower compared to baseline sTARC values. Once normalized, sTARC levels did not increase above the threshold in any of the patients. In both treatment arms, sTARC normalization after 1 week or at first restaging was highly correlated with end-of-treatment PET negativity ($P < 0.001$).

During concomitant N-AVD treatment in Arm A, 8/34 patients (24%) remained FDG-PET positive with DS4 at interim-restaging after 2× N-AVD. sTARC was available in six of these patients; all of these patients had sTARC levels below the threshold. At EOT and after 30 Gy IS-RT, eight and four patients remained PET positive, respectively. Remarkably, all patients with available samples (seven and four) had sTARC normalization at these timepoints. None of these patients ultimately progressed or relapsed during a median of 41 months of follow-up, potentially indicating false-positive interim and EOT PET results in these patients using the DS4 cutoff (Figure 2A,B). The favorable early response pattern was further supported by a sharp decrease in mean TMTV of 97% at PET2 in 25 patients with available PET scans suitable for TMTV quantification.

In Arm B, after four infusions of N monotherapy, 13/37 patients (35%) remained PET positive with a DS of 4. Six out of 35 patients with available samples (17%) had sTARC levels above

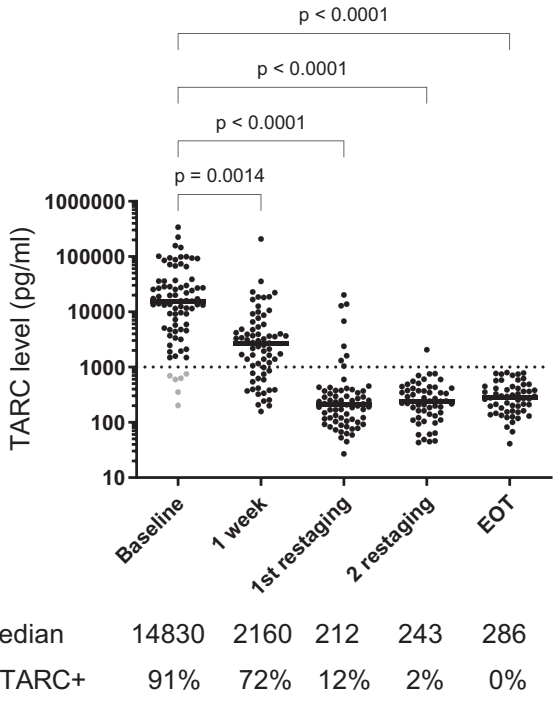

FIGURE 1 **Serum Thymus and Activation Regulating Chemokine (sTARC) dynamics during anti-PD1-based first-line treatment in the NIVAHL trial.** The percentage of patients who had positive sTARC levels (>1000 pg/mL) as well as the median sTARC values (pg/mL) are indicated below the graph. Patients with sTARC values < 1000 pg/mL at baseline (9%) are excluded from remaining timepoints. Compared to baseline sTARC values, all other timepoints were significantly lower. Abbreviation: EOT, end of systemic treatment.

the threshold, with a partial response in five patients and stable disease in one by PET. Quantified PET results indicated a decrease in mean TMTV of 87% in sTARC-positive patients versus 99% in sTARC-negative patients at PET2, further supporting the deep response achieved after N monotherapy, reflected by both TARC and TMTV. Notably, the few patients with a sTARC normalization after 1 week of N monotherapy all had a negative PET at first restaging. After completion of systemic treatment with 2× N-AVD and 2× AVD, three patients still had a positive PET scan. Normalization of sTARC levels was observed in the single patient with an available sample. In the other two patients, sTARC level had already decreased to normal at first restaging in one patient and was normalized after radiotherapy in the other patient. All patients achieved a complete remission, reflected by both negativity of sTARC and PET after radiotherapy (Figure 2C,D).

One of the key observations from this first-ever study on sTARC dynamics during ICI-based first-line HL treatment is the rapid normalization of sTARC levels, regardless of whether nivolumab was administered concomitantly or sequentially with standard AVD chemotherapy. However, a slight difference in pattern between both treatment groups was observed, with earlier sTARC and PET normalization in the concomitant treatment arm. Summarizing results at first interim restaging in both study arms, sTARC was below 1000 pg/mL in 12/18 patients (67%) who still had a positive PET2 and available sample. Our results hence suggest that combining sTARC with PET imaging can help identify a relevant proportion of PET2-positive patients with a favorable prognosis early after the start of ICI-based first-line treatment. Next, all four patients with positive PET by DS at EOT had normal sTARC levels and did not show PD or relapse,[17] further indicating

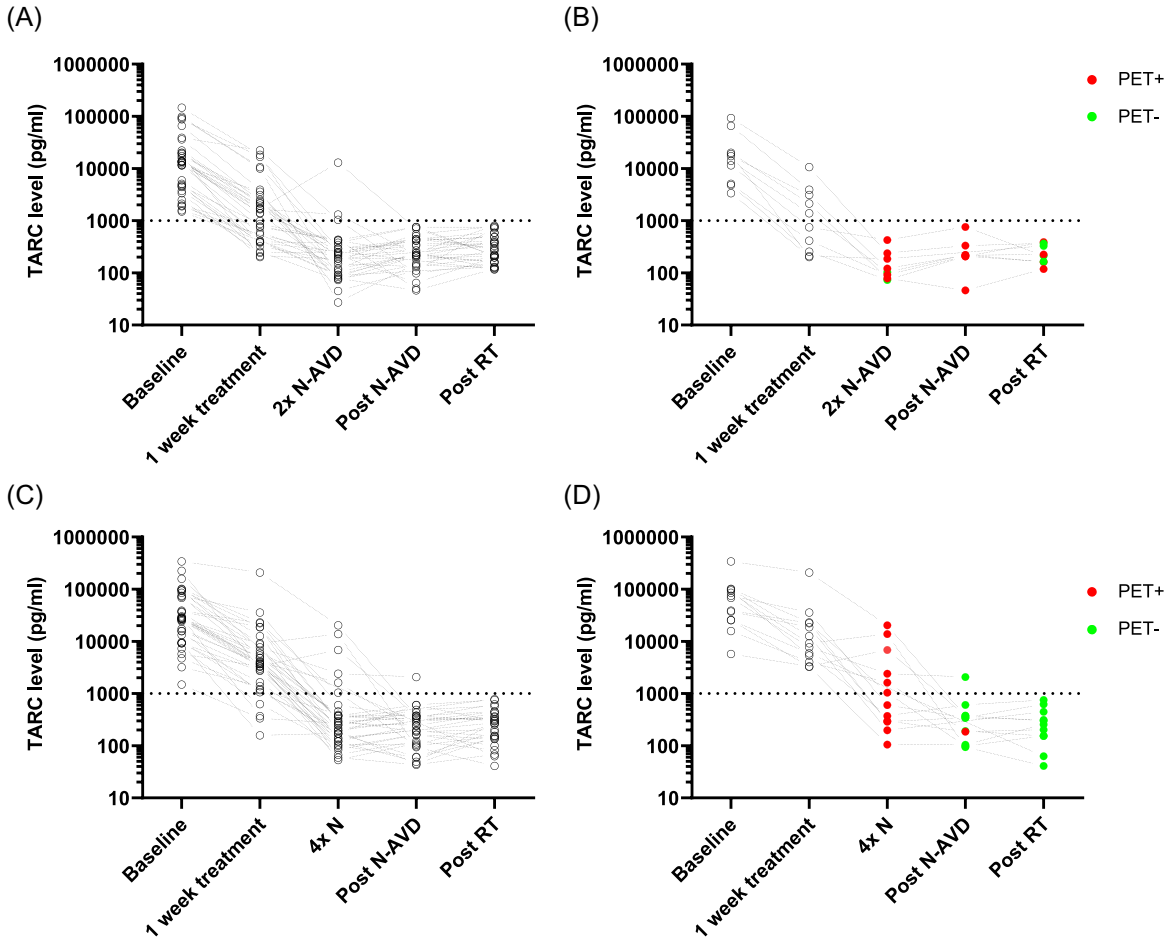

FIGURE 2 **Serum Thymus and Activation Regulating Chemokine (sTARC) dynamics and positron emission tomography (PET)-based response in NIVAHL. (A)** All patients who received concomitant N-AVD (nivolumab, doxorubicin, vinblastine, dacarbazine) treatment. **(B)** Patients receiving concomitant N-AVD treatment with a positive PET scan based on Deauville score at a timepoint during or after treatment and the respective sTARC values. **(C)** All patients who received sequential nivolumab and (N-)AVD treatment. **(D)** Patients receiving sequential nivolumab and (N-)AVD with a positive PET scan based on Deauville score at a timepoint during or after treatment and the respective sTARC values. Abbreviation: RT, radiotherapy.

the applicability of sTARC to reduce the number of false-positive PET scans, better tailor individual treatment exposure, and guide consolidative RT.

In light of the favorable response demonstrated by early sTARC negativity and sharp decrease in TMTV, our results imply that a relevant proportion of patients might be suitable for sTARC and PET response-based de-escalation strategies of anti-PD1-based first-line treatment. In early-stage cHL, these strategies might include the omission or reduction of chemotherapy and/or omission of radiotherapy, as is currently explored guided by MTV in the ongoing GHSG INDIE trial.[18] In advanced-stage cHL, an intuitive strategy would be to reduce the number of N-AVD cycles in patients with early deep remission indicated by sTARC in light of quantified PET response at an interim restaging timepoint.[19] Conversely—and as observed in some NIVAHL patients initially receiving nivolumab monotherapy—sTARC persistence during anti-PD1-based first-line treatment could indicate the need for more intensive treatment. Since the NIVAHL study was not designed in a response-adapted manner, no definitive conclusions can be drawn to support this approach. However, our findings do support the design and prospective evaluation of response-adapted anti-PD1-based treatment strategies in cHL using both sTARC and FDG-PET for response assessment. A potential limitation on the use of sTARC in response assessment is that a minority of patients (~10%) are TARC negative at baseline. Here, FDG-PET or assessment of measurable residual disease through circulating tumor DNA should be considered.[20]

In conclusion, we observed high applicability of sTARC as a biomarker for treatment response during anti-PD1-based first-line treatment in cHL. Incorporating sTARC in response assessment in cHL has the potential to identify false-positive FDG-PET results. It might serve as an easily accessible, fast, and relatively cheap tool to explore individualized de-escalation strategies to further reduce treatment exposure and related morbidity in cHL patients.

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AUTHOR CONTRIBUTIONS

Wouter J. Plattel: Conceptualization; investigation; funding acquisition; writing—original draft; methodology; formal analysis; project administration; data curation; supervision; resources; visualization.

Sophie Teesink: Investigation; writing—original draft; methodology; formal analysis; data curation; visualization. **Lydia Visser**: Investigation; writing—review and editing. **Conrad-Amadeus Voltin**: Investigation; writing—review and editing; formal analysis; data curation. **Helen Kaul**: Investigation; writing—review and editing; methodology; formal analysis; data curation. **Hans A. Schlößer**: Investigation; writing—review and editing; resources. **Bart-Jan Kroesen**: Investigation; writing—review and editing. **Carsten Kobe**: Investigation; writing—review and editing; supervision. **Bastian von Tresckow**: Investigation; writing—review and editing; supervision. **Peter Borchmann**: Supervision; writing—review and editing; investigation. **Arjan Diepstra**: Investigation; conceptualization; funding acquisition; writing—original draft; methodology; formal analysis; supervision; data curation; resources; project administration. **Paul J. Bröckelmann**: Conceptualization; investigation; writing—original draft; funding acquisition; methodology; project administration; data curation; supervision; resources.

CONFLICT OF INTEREST STATEMENT

W.J.P. has received honoraria or travel support from Jansen-Cilag (institution) and Takeda (institution). B.v.T. is an advisor or consultant for Allogene, Amgen, BMS/Celgene, Cerus, Gilead Kite, Incyte, IQVIA, Janssen-Cilag, Lilly, Merck Sharp & Dohme (MSD), Miltenyi, Novartis, Noscendo, Pentixapharm, Pfizer, Pierre Fabre, Qualworld, Regeneron, Roche, SOBI, and Takeda; has received honoraria from AbbVie, AstraZeneca, BMS/Celgene, Gilead Kite, Incyte, Janssen-Cilag, Lilly, MSD, Novartis, Roche, Serb and Takeda; reports research funding from Esteve (insitution), MSD (insitution), Novartis (insitution), and Takeda (insitution); reports travel support from AbbVie, AstraZeneca, Gilead Kite, Janssen-Cilag, Lilly, MSD, Pierre Fabre, Roche, Takeda, and Novartis; and is member of steering committees for Regeneron (insitution) and Takeda. P.J.B. is an advisor or consultant for Hexal, MSD, Need Inc., Stemline, and Takeda; holds stock options in Need Inc.; has received honoraria from AstraZeneca, BeiGene, Bristol-Myers Squibb/Celgene (BMS), Eli Lilly, MSD, Need Inc., Stemline, and Takeda; and reports research funding from BeiGene (institution), BMS (institution), MSD (institution), and Takeda (institution). The other authors declare no potential COI.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol*. 2016;17(9):1283-1294. doi:10.1016/S1470-2045(16)30167-X
2. Domingo-Domènech E, Ramchandren R, Rueda A, et al. S821 nivolumab plus doxorubicin, vinblastine and dacarbazine for newly diagnosed advanced-stage classical Hodgkin lymphoma: 2-year extended follow-up from cohort D of the phase 2 CheckMate 205 study. *HemaSphere*. 2019;3(S1):363. doi:10.1097/01.hs9.0000561564.12955.95
3. Borchmann P, Ferdinandus J, Schneider G, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. *Lancet*. 2024;404(10450):341-352. doi:10.1016/S0140-6736(24)01315-1
4. Spaepen K, Stroobants S, Dupont P, et al. [^{18}F]FDG PET monitoring of tumour response to chemotherapy: does [^{18}F]FDG uptake correlate with the viable tumour cell fraction? *Eur J Nucl Med Mol Imaging*. 2003;30(5):682-688. doi:10.1007/s00259-003-1120-6
5. Bröckelmann PJ. Hodgkin lymphoma: great progress with room for improvement. *Nat Rev Clin Oncol*. 2025;22:379-381.
6. Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet*. 2017;390(10114):2790-2802. doi:10.1016/S0140-6736(17)32134-7
7. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311-319. doi:10.1056/NEJMoa1411087
8. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. *J Clin Oncol*. 2016;34(31):3733-3739. doi:10.1200/JCO.2016.67.3467
9. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. *Blood*. 2016;128(21):2489-2496. doi:10.1182/blood-2016-05-718528
10. Kilsdonk M, Veldman C, Rosati S, Plattel W, Diepstra A. The value of thymus and activation related chemokine immunohistochemistry in classic Hodgkin lymphoma diagnostics. *Histopathology*. 2023;82(3):495-503. doi:10.1111/his.14836
11. Driessen J, Kersten MJ, Visser L, et al. Prognostic value of TARC and quantitative PET parameters in relapsed or refractory Hodgkin lymphoma patients treated with brentuximab vedotin and DHAP. *Leukemia*. 2022;36(12):2853-2862. doi:10.1038/s41375-022-01717-8
12. Diepstra A, Nolte IM, van den Berg A, Magpantay LI, Martínez-Maza O, Levin LI. Elevated serum TARC levels precede classic Hodgkin lymphoma diagnosis by several years. *Blood*. 2023;142(22):1928-1931. doi:10.1182/blood.2023020959
13. Guidetti A, Mazzocchi A, Miceli R, et al. Early reduction of serum TARC levels may predict for success of ABVD as frontline treatment in patients with Hodgkin Lymphoma. *Leuk Res*. 2017;62:91-97. doi:10.1016/j.leukres.2017.09.018
14. Plattel WJ, Visser L, Diepstra A, et al. Interim thymus and activation regulated chemokine *versus* interim ^{18}F-fluorodeoxyglucose positron-emission tomography in classical Hodgkin lymphoma response evaluation. *Br J Haematol*. 2020;190(1):40-44. doi:10.1111/bjh.16514
15. Plattel WJ, van den Berg A, Visser L, et al. Plasma thymus and activation-regulated chemokine as an early response marker in classical Hodgkin's lymphoma. *Haematologica*. 2012;97(3):410-415. doi:10.3324/haematol.2011.053199

16. Voltin CA, Mettler J, van Heek L, et al. Early response to first-line anti–PD-1 treatment in Hodgkin lymphoma: a PET-based analysis from the prospective, randomized phase II NIVAHL trial. *Clin Cancer Res*. 2021;27(2):402-407. doi:10.1158/1078-0432.CCR-20-3303
17. Bröckelmann PJ, Bühnen I, Meissner J, et al. Nivolumab and doxorubicin, vinblastine, and dacarbazine in early-stage unfavorable Hodgkin lymphoma: final analysis of the randomized German Hodgkin Study Group Phase II NIVAHL trial. *J Clin Oncol*. 2023;41(6):1193-1199. doi:10.1200/JCO.22.02355
18. Bröckelmann PJ, Kaul H, Fuchs M, et al. Individualized immunotherapy in early-stage unfavorable Hodgkin Lymphoma—the investigator-initiated phase II GSHG Indie Trial (trial in progress) [abstract]. *HemaSphere*. 2024;8(S2):054.
19. Ferdinandus J, Kaul H, Schneider G, et al. Metabolic tumor volume after two cycles of chemotherapy in patients treated for advanced-stage Hodgkin lymphoma: analysis of the German Hodgkin Study Group Phase III HD18 and HD21 trials. *Blood*. 2024;144(suppl 1):566.
20. Heger JM, Mammadova L, Mattlener J, et al. Circulating tumor DNA sequencing for biologic classification and individualized risk stratification in patients with Hodgkin lymphoma. *J Clin Oncol*. 2024;42(35):4218-4230. doi:10.1200/JCO.23.01867