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Brief Communication

Neoadjuvant vs perioperative chemo-immunotherapy according to pathological response in resectable non-small cell lung cancer: a reconstructed individual patient data meta-analysis

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Abstract

Neoadjuvant chemo-immunotherapy transformed early stage non-small cell lung cancer (NSCLC) treatment. However, the prognostic value of different pathological responses and the impact of adjuvant immunotherapy within a chemotherapy-immunotherapy perioperative strategy remains unclear. We estimated time-to-event outcomes by graphical reconstruction of event-free survival curves by pathological response (major pathological response, no major pathological response) reported in early stage NSCLC neoadjuvant or perioperative chemotherapy-immunotherapy trials. The major pathological response 1%-10% subgroup, previously unreported, was retrieved by removing patients achieving pathological response from the major pathological response group. Survival analysis by pathological response and comparison between neoadjuvant or perioperative strategies within subgroups were assessed. A statistically significant event-free survival difference according to pathological response was found, showing a prognostic gradient shifting from pathological response (good), major pathological response 1%-10% (intermediate), and no major pathological response (poor). There was no difference between neoadjuvant or perioperative strategies within subgroups; however, a trend for event-free survival benefit with perioperative and neoadjuvant chemotherapy-immunotherapy was observed in major pathological response 1%-10% and no major pathological response patients, respectively. In conclusion, a pathological response–based algorithm could better tailor early stage NSCLC treatment.

To date, head-to-head comparison between neoadjuvant and perioperative chemotherapy-immunotherapy in resectable non-small cell lung cancer (NSCLC) is lacking. The US Food and Drug Administration has recently raised concerns regarding the capability of current randomized clinical trials (RCTs) to assess the contribution of each individual phase (neoadjuvant and adjuvant) to the overall treatment effect.[1]

This concern may be particularly relevant for patients who achieve pathological complete response, defined as 0% of residual viable tumor in primary tumor and lymph nodes, and major pathological responses, defined as no more than 10% residual viable tumor surgery specimen after neoadjuvant induction phase. Indeed, these patients already experience long-term survival benefit,[2] and therefore, receiving additional postoperative treatment could expose them to an uncertain risk of overtreatment. Additional complexity arises from the heterogeneity within the major pathological response category, which encompasses pathological response and major pathological response 1%-10%, defined as 1%-10% residual viable tumor, whose relative weight on major pathological response Kaplan–Meier curves remains unclear. Finally, the contribution of pathological response, major pathological response 1%-10%, and no major pathological

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response (residual viable tumor >10%) subgroups to the overall event-free survival from neoadjuvant or perioperative chemotherapy-immunotherapy is yet to be determined.

We conducted an individual patient data (IPD) meta-analysis with reconstruction of Kaplan–Meier curves and extraction of major pathological response 1%-10% time-to-event data from patients achieving pathological response among the major pathological response group to assess the prognostic value of the different pathological response categories and to compare neoadjuvant and perioperative strategies according to pathological assessment.

Phase II and III RCTs comparing neoadjuvant or perioperative chemotherapy-immunotherapy with neoadjuvant chemotherapy alone in patients with resectable NSCLC and reporting event-free survival Kaplan–Meier curves by pathological response (pathological response and/or major pathological response) were selected. Estimated time-to-event outcomes from reported Kaplan–Meier plots were retrieved with a graphical reconstructive algorithm by methods described by Guyot et al.[3]

IPD were collected for pathological response, major pathological response, and no major pathological response patients from 1 neoadjuvant (CheckMate-816)[4] and 4 perioperative (CheckMate-77T, KEYNOTE-671, NADIM-II, NeoTORCH)[5-8] chemotherapy-immunotherapy RCTs. Quality of the Kaplan–Meier reconstruction was evaluated by visual comparison of curve shapes, hazard ratios (HRs), and patients at risk between plots and data from original papers and the corresponding reconstruction (Table S1A).

Bipartite-matching algorithm[9] was used to derive unreported data of patients achieving major pathological response 1%-10% (1%-10% residual viable tumor) by subtracting the pathological response (0% residual viable tumor) IPD from the major pathological response (≤10% residual viable tumor) IPD group. Empirical cumulative distribution and Bland–Altman plot of follow-up times were used to assess the discrepancies between matched pairs[9] (Table S1B). Data extraction was conducted with KMsubtraction and IPDfromKM R-packages (version 4.0.5). Event-free survival Kaplan–Meier curves for pathological response subgroups (pathological response, major pathological response 1%-10%, no major pathological response) overall and by treatment strategy (perioperative and neoadjuvant) were reconstructed. Survival analyses were performed by Cox proportional hazard model and log-rank test using MedCalc software (version 23.0.2).

A pooled analysis was conducted to evaluate the interaction between pathological response subgroups and treatment strategies. Statistical heterogeneity among subgroups was assessed using the Cochrane Q test, with a statistically significant threshold set at an alpha of 0.1. Inconsistency among subgroups was quantified by the I^2 statistic with an I^2 greater than 70% judged as statistically significant heterogeneity. Statistical significance was set at a P value of no more than .05.

Event-free survival with neoadjuvant or perioperative chemotherapy-immunotherapy showed a prognostic gradient according to pathological response (Figure 1, A), from pathological response (good prognosis) to major pathological response 1%-10% (intermediate prognosis) and no major pathological response (poor prognosis). In particular, the differences between the pathological response group and major pathological response 1%-10% (HR = 0.37, 95% confidence interval [CI] = 0.21 to 0.66; $P < .001$) or no major pathological response (HR = 0.12, 95% CI = 0.07 to 0.19; $P < .001$) were statistically significant. Similarly, major pathological response 1%-10% was associated with a statistically significant improvement in event-free survival compared with no major pathological response (HR = 0.58, 95% CI = 0.48 to 0.70; $P < .001$).

No statistically significant difference in event-free survival between perioperative and neoadjuvant chemotherapy-immunotherapy was observed in the pathological response (HR = 0.70, 95% CI = 0.26 to 1.88; $P = .48$) (Figure 1, B), major pathological response 1%-10% (HR = 0.63, 95% CI = 0.26 to 1.41; $P = .26$) (Figure 1, C), and no major pathological response (HR = 1.14, 95% CI = 0.79 to 1.65; $P = .47$) subgroups (Figure 1, D). Nevertheless, Kaplan–Meier curves showed a separation favoring perioperative and neoadjuvant chemotherapy-immunotherapy in the major pathological response 1%-10% and no major pathological response subgroups, respectively. No statistically significant subgroup interaction between pathological response categories and treatment strategy was observed by aggregate data analysis ($P = .33$) (Figure 2, A). A treatment algorithm according to pathological response category is proposed in Figure 2, B.

We previously reported no statistically significant survival differences between neoadjuvant and perioperative chemotherapy-immunotherapy by indirect comparison of aggregate data.[10] In the present manuscript we further explored this topic, implementing IPD reconstruction and performing separate analyses according to pathological response.

The prognostic gradient among pathological response, major pathological response 1%-10%, and no major pathological response together with the different shape of event-free survival Kaplan–Meier curves with neoadjuvant and perioperative chemotherapy-immunotherapy within these pathological categories suggest that a personalized approach according to a pathological response–based algorithm could be worthwhile.

In the pathological response group, the already substantial event-free survival benefit with chemotherapy-immunotherapy and the overlapping Kaplan–Meier curves between neoadjuvant and perioperative chemotherapy-immunotherapy suggest that the contribution of adjuvant immunotherapy to the overall treatment effect could be minimal. In line with these results, a recent exploratory analysis of CheckMate-816 and CheckMate-77T showed no event-free survival difference between neoadjuvant and perioperative chemotherapy-immunotherapy in patients achieving a pathological response.[11] Therefore, in pathological response patients, a de-escalation to a neoadjuvant-only chemotherapy-immunotherapy strategy would preserve the efficacy of the neoadjuvant phase while minimizing the risk of additional toxicities related to a postoperative active treatment. Toxicity of adjuvant immunotherapy could be a relevant issue, considering that 8% of patients treated with perioperative chemotherapy-immunotherapy had severe (grade 3-4) treatment-related adverse events in the postoperative phase[12] and that up to 35% of patients treated with immunotherapy across different cancer types may experience long-lasting immune-related toxicities[13] including pneumonitis.[14]

In the major pathological response 1%-10% group, the intermediate prognosis and the separation of the Kaplan–Meier curves in favor of perioperative chemotherapy-immunotherapy strategy suggests a beneficial role for continuing immunotherapy after surgery in those patients. A similar strategy was reported for some RCTs with perioperative chemotherapy in resectable NSCLC, where only patients with a major radiological tumor shrinkage were offered to receive additional chemotherapy after surgery.[15] In addition, CheckMate-816 and CheckMate-77T exploratory analyses recently reported an event-free survival benefit in favor of a perioperative strategy in no pathological response patients.[11] However, the no pathological response

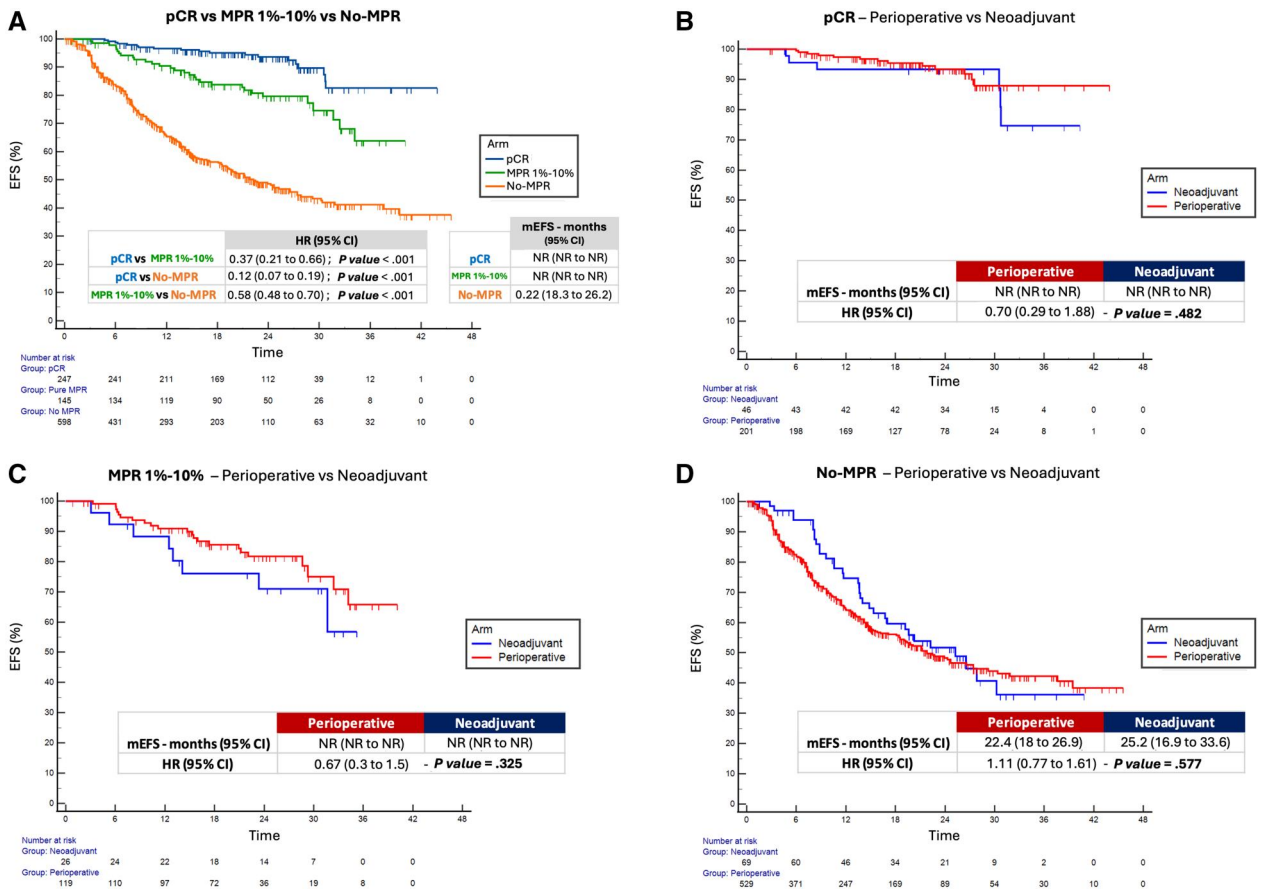


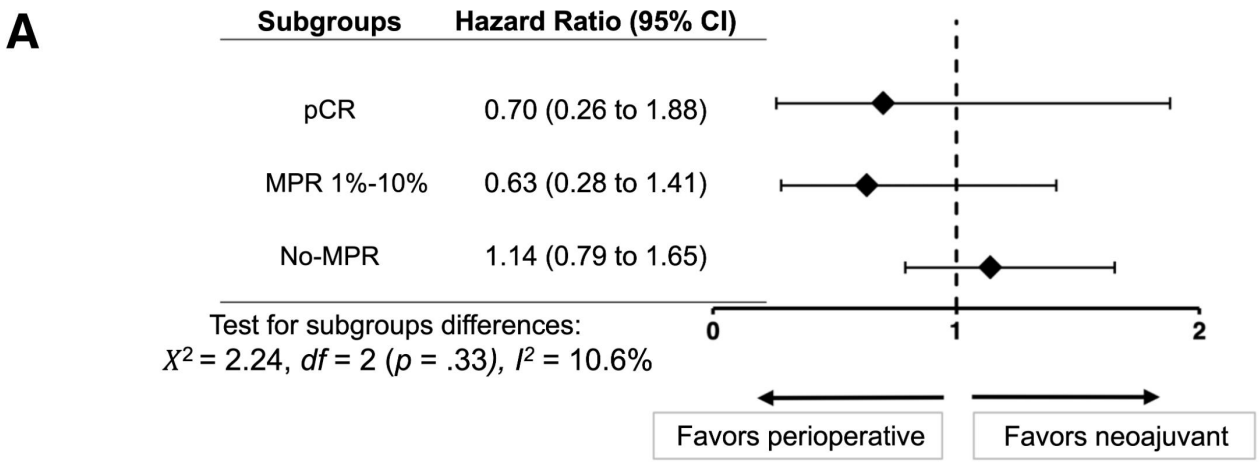
Figure 1. Kaplan–Meier curves comparing event-free survival by pathological response **(A)**, perioperative vs neoadjuvant strategies by pathological response **(B)**, major pathological response 1%-10% **(C)**, and no major pathological response **(D)** status. All Kaplan–Meier curves were reconstructed with individual patient data from CheckMate-77T, CheckMate-816, KEYNOTE-671, and NeoTORCH. pCR subgroups from Figure 1A and 1B also contain NADIM-II IPD. Abbreviations: CI = confidence interval; mEFS = median event-free survival (in brackets 95% confidence interval for median EFS); MPR = major pathological response; NR = not reached; pCR = pathological response.

category is highly heterogeneous and includes patients with a wide range of residual viable tumor. The present analysis suggests that the benefit in no pathological response could derive mainly from the better event-free survival with maintenance immunotherapy in patients with major pathological response 1%-10%. These findings in early stage NSCLC could potentially mirror previous results coming from the metastatic setting in case the best treatment response is partial response. In this regard, the CheckMate-153 trial showed that continuous administration of nivolumab in patients obtaining an initial response during the first year of treatment was associated with better survival outcome.[1]

Lastly, in the no major pathological response group, the poor prognosis and the separation of Kaplan–Meier curves in favor of neoadjuvant chemotherapy-immunotherapy suggest that the utility of postoperative administration of immunotherapy monotherapy remains unclear. Of note, in the no major pathological response group, event-free survival statistically varies according to the different residual viable tumor values with neoadjuvant[4] and perioperative chemotherapy-immunotherapy. A recent post hoc analysis for event-free survival based on residual viable tumor values in the KEYNOTE-671 trial showed no benefit for perioperative chemotherapy-immunotherapy in patients achieving residual viable tumor of more than 60%.[16] These findings are in line with our results and provide evidence in favor of novel escalating adjuvant regimens in the no major pathological response category, particularly in the poor prognostic subgroup of patients with elevated residual viable tumors.

In addition, the no major pathological response group contains patients both undergoing surgery and achieving more than 10% residual viable tumor pathological response and patients lost to surgery because of early tumor progression or other reasons (ie, drug-related adverse events). Taking up parallelism with the metastatic setting, no major pathological response would mirror the case of patients whose best treatment response is not optimal, like stable disease or progressive disease. In CheckMate-153, the continuation over 1 year of immunotherapy monotherapy in patients with stable disease as best response showed no difference in progression-free survival compared with patients stopping immunotherapy at 1 year.[17] Similarly, the continuation of immunotherapy monotherapy beyond progressive disease in metastatic NSCLC is indicated only in the very rare case of pseudoprogression.[18] Indeed, in other patterns of progression, immunotherapy administration even beyond progressive disease is generally recommended in combination with other systemic[19] or local[20] treatments.

The present analysis is hypothesis generating and has some limitations to be addressed. Endpoints, such as major pathological response 1%-10%, were not predefined in the original published RCTs and could suffer inadequate sample size and uncertainties about patients' covariates. Moreover, the heterogeneity in reported outcomes from the included RCTs could affect



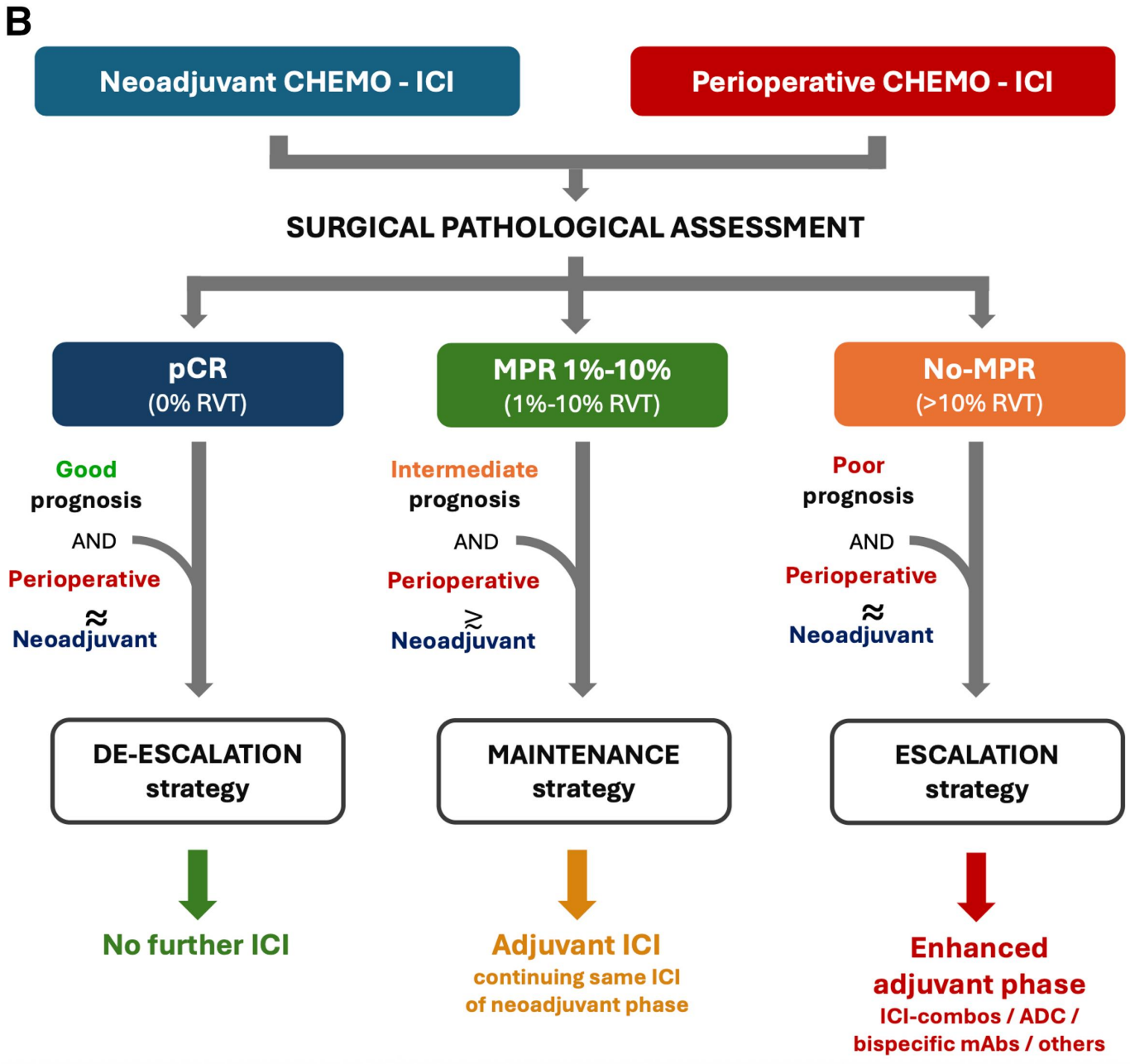


Figure 2. Subgroup analysis for event-free survival of neoadjuvant vs perioperative chemotherapy-immunotherapy by pathological response, major pathological response 1%-10%, and no major pathological response status **(A)**. Proposed algorithm based on response to neoadjuvant chemotherapy-immunotherapy **(B)**. Abbreviations: chemo-ICI = chemotherapy-immunotherapy; ADC = Antibody-Drug Conjugate; CI = confidence interval; mAbs = monoclonal antibodies; MPR = major pathological response; pCR = pathological response; RVT = residual viable tumor.

the generalizability of the results of the present analysis. In particular, pathological assessment was performed differently in CheckMate-77T and CheckMate-816, which used immune-related criteria,[21] compared with other RCTs, which adopted International Association for the Study of Lung Cancer criteria.[22] In this regard, a relatively lower interpathologist variability in scoring pathological response by immune-related compared with International Association for the Study of Lung Cancer response criteria was reported.[21]

Another potential source of heterogeneity derives from the lymph nodes pathological assessment after neoadjuvant chemotherapy-immunotherapy. Indeed, with neoadjuvant chemotherapy the prognostic value of major pathological response can vary whether residual viable tumor assessment includes lymph nodes (ypN+ vs ypN-).[23] Unfortunately, this information cannot be retrieved from existing RCTs with perioperative chemotherapy-immunotherapy. Checkmate 816 was the only study that reported major pathological response according to lymph node involvement, showing that pathological response is the major determinant for event-free survival benefit, regardless of lymph node status. Finally, although all RCTs performed blinded pathological assessments, the lack of a standardized method for examining surgical samples and the variability in grossing procedures for primary tumor beds more than 3 cm may further jeopardize the definition and prognostic significance of pathological response categories.

Despite these limitations, the present study provides a granular perspective about personalization of perioperative chemotherapy-immunotherapy in resectable NSCLC. The proposed pathological response–based algorithm could be helpful in better tailoring neoadjuvant or perioperative strategies, reducing potential toxicities and treatment burden in a curative setting. Recently, minimal residual disease assessed by circulating tumor DNA monitoring has been described as a promising tool able to integrate pathological response status and to guide adjuvant treatment plan.[24]

A pathological response–based algorithm, together with minimal residual disease monitoring, should be included in the adaptive design of next-generation clinical trials in the early stage setting, paving the way toward novel de-escalation or escalation adjuvant treatment approaches.

Author contributions

Antonio Nuccio (Conceptualization, Data curation, Formal analysis, Methodology, Writing—original draft, Writing—review & editing), Fabio Salomone (Conceptualization, Data curation, Formal analysis, Methodology, Writing—original draft), Alberto Servetto (Writing—review & editing), Biagio Ricciuti (Visualization, Writing—review & editing), Daniele Marinelli (Visualization, Writing—review & editing), Alessandra Bulotta (Writing—review & editing), Giulia Veronesi (Writing—review & editing), Marina Chiara Garassino (Writing—review & editing), Valter Torri (Data curation, Writing—original draft), Benjamin Besse (Writing—review & editing), Giuseppe Viscardi (Supervision, Visualization, Writing—review & editing), and Roberto Ferrara (Supervision, Visualization, Writing—review & editing).

Supplementary material

Supplementary material is available at *JNCI: Journal of the National Cancer Institute* online.

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Conflicts of interest

All authors declare no conflicts of interest with the present manuscript.

Data availability

All data generated from analysis of the selected studies will be shared with any researcher upon request to the corresponding author.

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