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Neoadjuvant anti-PD-1-based immunotherapy: evolving a new standard of care

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ABSTRACT

Neoadjuvant (presurgical) anti-programmed cell death protein-1 (PD-1)-based immunotherapy as a new approach to cancer treatment has been developing on an accelerated trajectory since the seminal clinical trial results from studies in lung cancer and melanoma were published in 2018. Groundbreaking regulatory approvals in triple-negative breast cancer, non-small cell lung cancer and melanoma will certainly be followed by additional approvals in other disease indications, as clinical and basic research are burgeoning globally in hundreds of clinical trials across dozens of cancer types. As this field is evolving, it is addressing gaps in our understanding of biological mechanisms underlying PD-1 pathway blockade and their synergy with other antineoplastic drugs, probing mechanisms of response and resistance to neoadjuvant immunotherapy, optimizing efficacious clinical strategies, and analyzing commonalities and differences across cancer types. Knowledge gained thus far provides a firm foundation from which to launch the next phase of translational research in this expanding arena of biomedical investigation.

INTRODUCTION

The most effective cancer immunotherapies in wide use today include drugs blocking the programmed cell death protein-1 (PD-1):programmed death-ligand 1 (PD-L1) immune checkpoint pathway or treatment combinations built on an anti-PD-(L)1 backbone. With US Food and Drug Administration (FDA) approvals in over 20 different cancer types, anti-PD-(L)1 has become a foundational "common denominator" for treating patients with advanced unresectable cancers. Its favorable safety profile, coupled with refined guidelines and algorithms for early adverse event recognition and effective medical management, encouraged investigators to apply anti-PD-(L)1 therapy in earlier stages of cancer with the goal of preventing progression to late-stage disease. This prevention concept was borne out in phase 3 trials of adjuvant (postsurgical) anti-PD-(L)1, demonstrating a significant decrease in relapse rates and warranting FDA approvals in select cancer types. However, emerging scientific evidence suggested that it might be ideal to apply immune checkpoint blockade (ICB) in the neoadjuvant, or presurgical setting, while the tumor is still in place.[1] Hypothetically, this would promote the reactivation of antigen-experienced PD-1+ T cells already infiltrating the tumor, as well as the priming of antigen-naïve T cells in tumor-draining lymph nodes (TDLN), allowing tumor-specific T cells to enter the blood, traffic to and destroy micrometastases that would otherwise become a nidus for postoperative relapse. This notion differs from the conventional paradigm for neoadjuvant chemoradiotherapy, viewed simply as a means to reduce tumor size thereby facilitating surgical resection of large invasive primary cancers. The concept of neoadjuvant ICB as promoting systemic antitumor immunity is supported by results emerging from scientific investigations linked to clinical trials, showing increased frequencies of circulating tumor-specific T cells following neoadjuvant ICB.[2 3] Proof for the superiority of neoadjuvant over adjuvant ICB came recently from two randomized trials in patients with resectable stage III/IV melanoma, demonstrating prolonged event-free survival (EFS, time to relapse or death) with neoadjuvant/adjuvant versus adjuvant-only ICB.[4 5] Meanwhile, seminal FDA approvals for neoadjuvant ICB/chemotherapy combinations in triple-negative breast cancer (TNBC) in 2021[6] and non-small cell lung cancer (NSCLC) in 2022[2] have been followed by five additional regulatory approvals: three from the FDA in NSCLC in 2023–2024, an Australian approval in melanoma in 2023, and a Netherlands approval in melanoma in 2024. A deluge of clinical trials has been launched across multiple other disease indications. Intense translational research efforts focused on neoadjuvant ICB have yielded valuable lessons and highlighted important issues for the future development and refinement of this treatment approach.

CLINICAL TRIAL DESIGN AND ENDPOINTS

Neoadjuvant ICB trials are designed to treat patients with cancers that are deemed surgically "resectable for cure" but at high risk for postoperative relapse based on clinicopathologic characteristics. It is important to remember that (1) a proportion of these patients will be cured by surgery alone, and (2) ICB is not without risk (eg, cancer progression during the neoadjuvant period, or drug-related adverse events delaying surgery). Therefore, risk:benefit considerations are paramount in the design of neoadjuvant ICB trials, especially for platform trials designed to rapidly evaluate novel therapeutics. Such considerations may vary among cancer types.

Neoadjuvant ICB automatically offers a new potential biomarker to predict long-term clinical outcomes, namely, the extent of pathologic response in the surgical specimen. The first published trial of neoadjuvant anti-PD-1, in NSCLC,[2] reported that histologic evidence of tumor regression far outpaced the radiographic "gold standard" of Response Evaluation Criteria in Solid Tumors (RECIST) assessment. This paradigm has been confirmed in numerous subsequent trials across a variety of cancer types, inviting speculation about whether substantial pathologic response may underlie radiographically-defined durable disease stabilization or partial regression in patients with advanced unresectable cancers receiving ICB. Currently pathologic response, providing an early marker of neoadjuvant treatment effect, is not accepted as a stand-alone primary endpoint for FDA approval of neoadjuvant ICB regimens. EFS has been required as a primary or co-primary endpoint. However, this may change as data accumulate to support the predictive value of pathologic response. Whether the level of pathologic response (complete pathologic response, or various degrees of incomplete response[7]) can be used reliably to guide postsurgical treatment decisions is a very important open question. In the NADINA (Neoadjuvant Ipilimumab plus Nivolumab versis Standard Adjuvant Nivolumab in Macroscopic Stage III Melanoma) trial, patients with residual viable tumor ≤10% in the resection specimen ("major pathologic response") were assigned to postsurgical observation, while those with >10% residual tumor received standard-of-care adjuvant therapies.[5] These choices were based on data from smaller, earlier melanoma trials. However, in the absence of randomized postsurgical treatment arms, it is unknown if optimal outcomes were achieved using the 10% threshold defined in the NADINA trial.

Although most of the regulatory approvals to date have been for combined neoadjuvant/adjuvant ICB regimens—the sole exception being the 2022 FDA approval for neoadjuvant-only nivolumab plus chemotherapy in NSCLC—trials supporting registration were not designed to dissect the contributions of the neoadjuvant and adjuvant phases in achieving their endpoints. In fact, it is possible that some patients were over-treated. The absence of validated biomarkers to guide postsurgical treatment decision-making has been particularly notable in this regard; complete pathologic response and clearance of circulating tumor DNA (ctDNA) during the neoadjuvant treatment phase[2] have emerged as two potential biomarkers that deserve further prospective testing as potential factors to guide de-escalation strategies. The FDA has expressed concerns regarding potential overtreatment, and has strongly encouraged three-arm and four-arm clinical trial designs to elucidate the contributions of the neoadjuvant and adjuvant treatment phases in meeting prespecified endpoints.[8] This is likely to reshape the design of future perioperative ICB trials. Of interest, although cross-trial results should be interpreted cautiously, a recent retrospective analysis comparing individual patient-level data from two phase 3 trials in NSCLC—neoadjuvant chemoimmunotherapy with no adjuvant treatment phase (CheckMate 816,[2]) versus neoadjuvant chemoimmunotherapy followed by adjuvant nivolumab (CheckMate 77T,[9])—demonstrated improved EFS with the perioperative regimen.[10]

COMMONALITIES VERSUS UNIQUE FEATURES ACROSS CANCER TYPES

Some features of neoadjuvant ICB are shared across tumor types, for instance, the ability to prime systemic antitumor immunity while the tumor is still in place, pathologic response as a forerunner of radiographic response, and the common histologic characteristics of pathologic response—proliferative fibrosis, immune cell infiltrates, neovascularization, and tertiary lymphoid structures.[1] Thus, some lessons learned from clinical trials of neoadjuvant ICB in one cancer type have been applicable to others.[11] However, there are also unique features of neoadjuvant ICB that have emerged, according to cancer type and subtype. Differential ICB response kinetics, as well as traditional treatment standards for particular cancers, have spawned neoadjuvant treatment intervals ranging from 4 weeks (Merkel cell carcinoma) to 6 months (TNBC), and treatment regimens of anti-PD-1 monotherapy (eg, cutaneous squamous cell carcinoma, Merkel cell carcinoma) versus combination chemotherapy regimens (eg, NSCLC, TNBC). Although it was assumed that ICB might be more effective in the neoadjuvant setting addressing earlier-stage cancers than in advanced unresectable disease, this has not generally been the case. In most cancers, neoadjuvant ICB effects seem to parallel advanced disease efficacy. However, in others, results in the neoadjuvant setting have been disappointing. For instance, ICB is effective and in standard use in the adjuvant and advanced unresectable disease settings in renal cell carcinoma (RCC), but so far ICB has not proved effective in the neoadjuvant setting. Such disparities may reflect differential tumor burden, metabolic volume, or anatomic location. In the RCC example, ICB is used to treat large necrotic primary tumors in the neoadjuvant setting, compared with micrometastatic disease in the adjuvant setting, or distant multiorgan macroscopic metastases in advanced unresectable

disease. Even within a given cancer type, the effects of neoadjuvant ICB can vary across tumor subtypes. Breast cancer is a prime example, in which TNBC is particularly susceptible to neoadjuvant ICB compared with other subtypes. Thus, neoadjuvant ICB is not a "one size fits all" treatment approach across all cancers. Instead, it needs to be tailored to the biological behavior and current treatment standards characteristic of different cancer types and subtypes.

DISCOVERY OPPORTUNITIES AFFORDED BY NEOADJUVANT ICB

Because surgical resection following neoadjuvant therapy generally provides much more tissue than biopsies, allowing unprecedented access to large quantities of viable tissue, this therapeutically valuable platform offers unique opportunities to study treatment effects on the tumor microenvironment (TME). The transformative single-cell coupled RNA sequencing (RNAseq)/T–cell receptor sequencing (TCRseq) technology is being actively applied to dissecting immune components of the TME, comparing pathologic responders versus non-responders to define associated molecules, signaling pathways and cellular activation states.[12] These studies are already revealing new therapeutic targets for blockade or stimulation, to be tested clinically in conjunction with anti-PD-(L)1. More recently, analysis of cell–cell interactions and proximity relationships critical to cellular communication in the TME is becoming accessible via new spatial proteomics and transcriptomics platforms applied to neoadjuvant ICB resection specimens.

Beyond allowing analysis of the primary tumor, standard surgical resections for many cancers commonly involve the removal of TDLN for clinical staging. The association between pathologic response to neoadjuvant ICB and improved relapse-free survival in patients supports conclusions from murine studies that this treatment approach can prime systemic antitumor immunity. Priming of T cell immune responses occurs in lymph nodes draining sites of antigen expression, so access to TDLN is a gold mine to study this process in the context of human cancer immunotherapy. This immense scientific opportunity, heretofore unavailable in human studies, must not be overlooked in the ongoing clinical trials of neoadjuvant ICB.

CONCLUSIONS

Neoadjuvant ICB has emerged as a major advance in cancer treatment both at the clinical level and for its scientific discovery potential. While intense clinical research activity in this area will undoubtedly lead to additional regulatory approvals, it will be critical to explore improved neoadjuvant treatment combinations and define biomarkers to determine who should receive follow-up adjuvant therapy. In this regard, both refined pathologic analysis of surgical resection specimens and high-sensitivity ctDNA assays will be key drivers of therapeutic optimization for individual patients. Indeed, initial results from neoadjuvant ICB combinations in NSCLC and esophageal cancer emphasize the value of ctDNA in predicting tumor relapse.[2 13] From the scientific perspective, the application of high-dimensional profiling technologies to the on-therapy tissue samples available at resection and annotated for pathological response represents the single best clinical opportunity to define the processes necessary to promote successful antitumor immunity.

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