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Reframing adjuvant immunotherapy in melanoma: all of it starts with priming

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SUMMARY

Checkpoint inhibitors best perform in neoadjuvant settings for a number of solid malignancies including cutaneous melanoma as compared with adjuvant schemes. A key difference between both treatment settings is the availability of tumor antigens to continuously prime antitumor T lymphocytes. Mounting evidence indicates that priming is a function chiefly performed by a subset of dendritic cells that cross-present tumor antigens rather than by malignant cells themselves. Acting in favor of these mechanisms to foster tumor-antigen priming is proposed to enhance the efficacy of adjuvant schemes.

Despite the success of immunotherapy in the adjuvant treatment of melanoma, recent failures of phase III trials combining checkpoint inhibitors in this postsurgical setting raise critical questions.[1–3] In contrast to metastatic or neoadjuvant therapy, where the tumor-immune system interaction is evident, adjuvant therapy targets micrometastatic minimal residual disease (MRD), a context where immune priming may be limited.[4] We hypothesize that effective adjuvant immunotherapy would require agents that actually enhance quantitatively or qualitatively priming, such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors or messenger RNA (mRNA) vaccines.[5 6] Trials like CheckMate 915[1], KeyVibe-010[2], and RELATIVITY-098[3] failed to improve outcomes like relapse-free survival (RFS) versus monotherapy, suggesting that dual checkpoint inhibition is useless in MRD. By contrast, early data on mRNA vaccines formulated in lipid nanoparticles combined with anti-programmed cell death protein-1 (PD-1) show potential to enhance priming and broaden immune responses against tumor antigens.[7]

Future trial design must consider MRD biology, incorporate biomarkers, and prioritize mechanistic rationale over empirical combination. The key question here is what is the most different immunological feature between adjuvant and neoadjuvant immunotherapy approaches that would explain the superiority of the neoadjuvant schemes. The most likely answer is that opportunity for significant antitumor antigen priming is much higher when the primary tumor and tumor-draining lymph nodes are still present in the patient (figure 1). This simple interpretation predicts that for immunomodulatory agents relying on endogenous tumor-antigen priming, neoadjuvant treatments will be more efficacious to treat micrometastases.

Adjuvant therapy in melanoma is now well established. Anti-PD-1 agents such as nivolumab and pembrolizumab have significantly improved RFS,[8] and BRAF/MEK inhibitors have demonstrated comparable efficacy in BRAF-mutant patients.[9] Notably, the COMBI-AD trial showed enhanced benefit in patients with an interferon-gamma gene expression signature in the surgical specimen, suggesting an immunomodulatory role of targeted therapy.[10] Preclinical and translational studies support the idea that BRAF/MEK inhibitors can induce T-cell infiltration and restore an inflamed tumor microenvironment, perhaps as a result of immunogenic cell death.[11 12] In fact, BRAF/MEK inhibitors may act through mechanisms shared with immunotherapy.

However, the biology of adjuvant therapy differs fundamentally from that of metastatic disease or neoadjuvant approaches. In MRD, there may be little or no tumor burden to sustain antigenic stimulation.[4] Thus, the blockade of the PD-1/programmed death-ligand 1 (PD-L1) axis, which requires ongoing tumor-immune interaction, may be insufficient alone. This may explain why combinations effective in metastatic settings, such as nivolumab plus ipilimumab[1] or nivolumab plus relatlimab,[3] have failed to outperform monotherapy in trials such as CheckMate 915 and RELATIVITY-098.

These disappointing results suggest that in MRD, the mere addition of a second checkpoint inhibitor may not suffice to initiate effective priming if the initial T-cell activation driven by antigen lacks adequate stimulation.

To advance adjuvant immunotherapy, future trial designs must consider the unique biology of MRD. Combinations should be

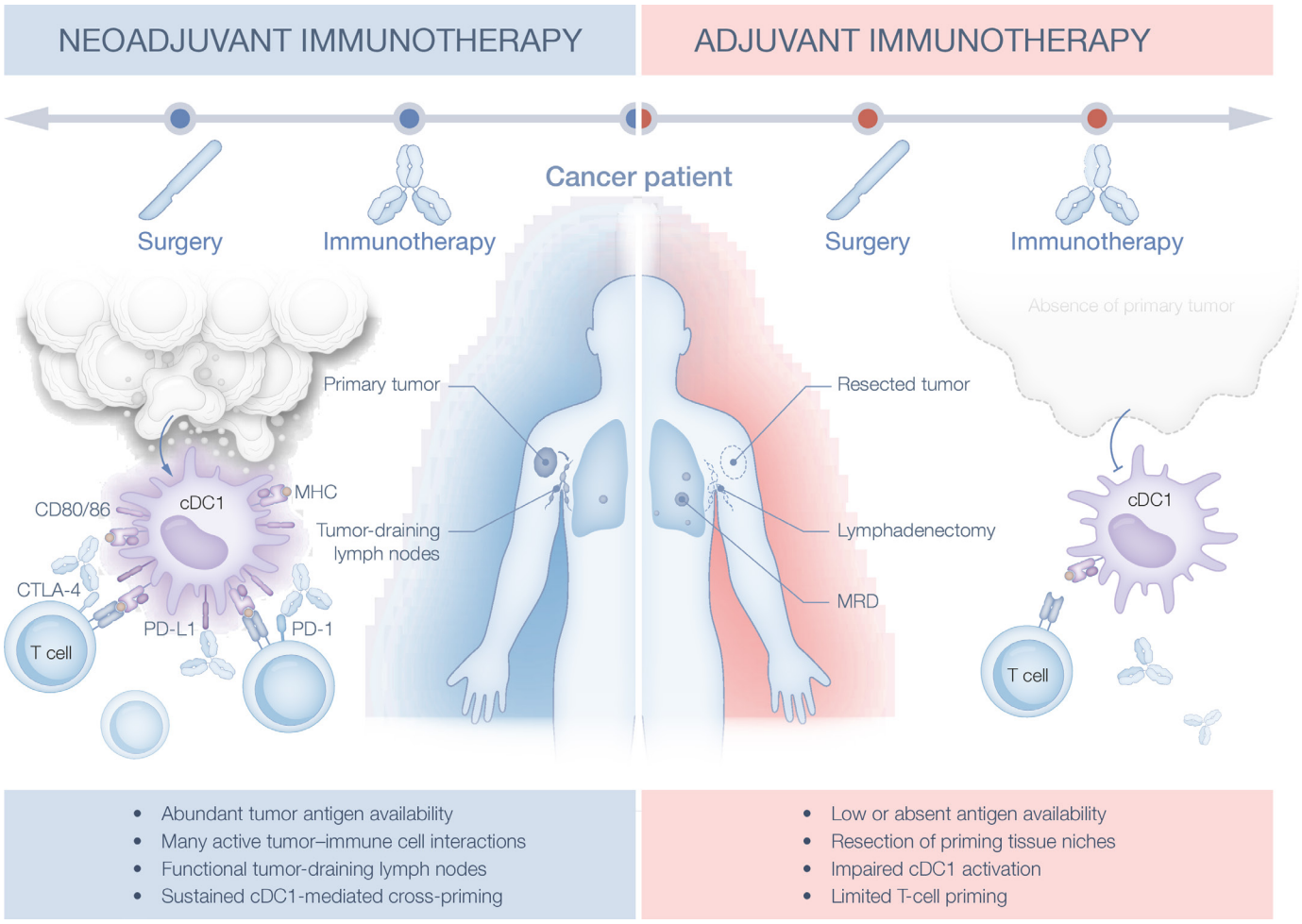

Figure 1 Key mechanistic differences regarding tumor-antigen priming comparing neoadjuvant versus adjuvant immunotherapy schemes. In neoadjuvant therapy (left), the malignant cells provide a rich source of tumor antigens that can be cross-presented by cDC1 cells, resulting in abundant cytotoxic T lymphocytes that can tackle micrometastasis and prevent local relapse. Tumor-draining lymph nodes could be also relevant sites for priming. Checkpoint inhibitors mainly act by means of potentiating costimulation mediated by CD80 and CD86 (signal 2) but can do very little in the absence of antigen-specific priming (signal 1). On the contrary, in adjuvant checkpoint-inhibitor immunotherapy started following surgical resection, lack of malignant cells results in weaker or non-existent cross-priming (right). Possibly, lymphadenectomy worsens the situation as a result of removing a crucial interface of the tumor and the immune system. cDC1, conventional type 1 dendritic cells; MHC, major histocompatibility complex; MRD, minimal residual disease; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

mechanistically rational, not simply borrowed from metastatic protocols. Biomarker-driven selection, immune monitoring, and adaptive designs will be crucial in optimizing benefit while avoiding overtreatment.[12]

IMMUNE PRIMING AND MINIMAL RESIDUAL DISEASE: THE MISSING LINK

In the adjuvant setting, the fundamental challenge lies in the nature of MRD. Unlike metastatic or bulky neoadjuvant disease, where tumor antigens continuously interact with immune cells, MRD is characterized by low antigenic load and sparse tumor-immune system engagement.[13] This undermines the central mechanism of PD-1/PD-L1 inhibitors, which rely on reinvigorating exhausted T cells in an active immune-tumor interface.[12 14]

For immunotherapy to be effective in MRD, T-cell priming becomes essential: naive T cells must be activated de novo and a fresh antitumor immune response must be generated.[5] CTLA-4 blockade has been known to facilitate this process, allowing for more active CD28 costimulation in immune synapses,[5 15] but recent studies in established disease suggest that PD-1 inhibitors may also foster priming activity to some extent.[16] These include the appearance of new responding T-cell clonotypes, broader T-cell receptor repertoire diversity, increased interaction with dendritic cells, and stimulation of T follicular helper cells.[16 17]

The weakness of these mechanisms could explain the limited efficacy of dual checkpoint blockade in MRD, where adding a second checkpoint inhibitor may not enhance priming but rather amplify a response that has

not yet been effectively initiated or is weak.[1–3] Strategies that boost priming, such as personalized mRNA vaccines or agents targeting dendritic cell activation, could offer a more rational combination with anti-PD-1 agents in this setting.[6–8 18] Indeed, this immunological void impairs the licensing of conventional type 1 dendritic cells (cDC1), the gatekeepers of cytotoxic T-cell activation.[19 20] Recent studies further highlight the centrality of cDC1-driven Antigen Presenting Cell (APC) niches. Kissick and colleagues demonstrated that these niches sustain T-Cell Factor 1 ($TCF1^{+}$) stem-like $CD8^{+}$ T cells, which are essential for effective PD-1 blockade.[21] Notably, similar biology was observed with Tyrosine-Kinase Inhibitors (TKIs) such as cabozantinib, even in the neoadjuvant setting,[22] suggesting that interventions capable of preserving or expanding APC niches may enhance responses to immunotherapy. Without the danger signals derived from ongoing tumor cell death or inflammation, effective immune priming does not occur.[19]

Immune priming is orchestrated by cDC1 through cross-presentation of tumor antigens and co-stimulatory signaling via CD40/CD40L, IL-12, CD137 (4-1BB)[23 24] and IL-15.[19 20] Recent evidence shows that anti-PD-1 therapy contributes to facilitate T-cell priming, not only reinvigoration.[16 17] Studies have demonstrated that anti-PD-1 agents can enhance priming efficacy, particularly in early disease settings.[18–20 25] Similarly, BRAF/MEK inhibitors modulate the tumor microenvironment and improve antigen presentation, favoring cDC1 function.[9–11 26] As recently reviewed,[27] these priming-related mechanisms underpin the efficacy of several immunotherapeutic approaches (see online supplemental table 1). Adjuvant agents that work do so because they prime.[27]

Results in mouse experiments are highly conclusive. The moment the cDC1 dendritic cell population is depleted, checkpoint inhibitors cease to exert any therapeutic effects.[28] Of note, in transgenic melanoma mouse models, the density of cDC1 in the tumor dictates response to immunotherapy.[29] Across tumors and clinical trials, we find strong associations of cDC1 infiltration and response to immunotherapy including adjuvant settings (A Lopez-Janerio *et al* submitted). Cross-presentation of antigens, a sort of secondhand antigen presentation from dead or dying cells, is key for the induction and the sustenance of cytotoxic T-cell responses against viruses and cancer. This function is mainly, if not almost exclusively, mediated by cDC1. Such professional antigen-presenting cells operate at the tumor and tumor-draining lymph nodes to cross-present tumor antigens, also providing the array of costimulatory ligands and cytokines to activate and expand antigen-cognate CD8 T cells.[30] These notions are reminiscent of the two-signal model of T-cell activation in which signal 1 is mediated by antigen sensing and signal 2 by costimulatory receptors.[27] The missing point in the use of current immunotherapies in adjuvant settings is an insufficient level of signal 1.

An important question is the potential deleterious effect of lymphadenectomies that might remove key tumor-antigen presenting sites. Micrometastatic lymph nodes could be important for the success of adjuvant immunotherapy. It could be even advisable to perform lymphadenectomy at a later surgical time once the patient is already on immunotherapy.[31]

NEOADJUVANT VERSUS ADJUVANT: THE ROLE OF THE TUMOR MICROENVIRONMENT

The clinical difference between neoadjuvant and adjuvant immunotherapy highlights the importance of an active tumor microenvironment in enabling effective immune priming. Neoadjuvant trials such as SWOG S1801[32] and NADINA[33] have demonstrated superior event-free survival compared with adjuvant approaches, likely due to the presence of tumor antigen, tumor antigen cross-presentation and robust tumor-immune interaction at the time of therapy initiation. This reinforces the idea that priming during immunomodulatory treatments is a critical prerequisite for effective checkpoint inhibition.[27]

The lack of additional benefit observed in trials combining anti-PD-1 with anti-CTLA-4 or anti-Lymphocyte-Activation Gene 3 (LAG3) agents, such as CheckMate 915, KeyVibe-010, and RELATIVITY-098, underscores a biological ceiling effect for adjuvant therapies. These combinations do not enhance immune priming beyond what is achieved with anti-PD-1 monotherapy in the absence of macroscopic tumor. This plateau effect reveals a central truth: immune reinvigoration cannot replace the foundational need for proper ongoing T-cell priming against tumor antigens.[1–4]

Conversely, recent advances in mRNA vaccine technologies, such as the personalized neoantigen vaccines V940 (KEYNOTE-942) and cevumeran, demonstrate that effective priming in the adjuvant setting is feasible and clinically impactful. These vaccines elicit neoantigen-specific $CD8^{+}$ T cells, generate durable memory, and show higher efficacy post-resection than in late-stage disease.[6 7] The success of these strategies emphasizes the importance of initiating the immune response de novo. However, vaccines may need refinements such as, for instance, imprinting proper migration cues to primed T cells, dealing with tumor spatial heterogeneity or increasing potency with adjuvants to generate more meaningful T-cell expansions, for instance, exploiting cDC1-mediated cross-priming.

CONCLUSION

Future adjuvant strategies must prioritize immune priming. Approaches under investigation include systemic FMS-related tyrosine kinase 3 ligand (FLT3L) to expand cDC1s,[34 35] intratumoral Toll-Like Receptor (TLR) and STING agonists,[23 36] and mRNA platforms that deliver antigen to $XCR1^{+}$ or $CLEC9A^{+}$ dendritic cells in a targeted fashion.[24] Combinations may still have a role, but the optimal sequence needs to be determined. In line with this concept, several intratumoral approaches further

support the importance of immune priming, including recent evidence that intratumoral TLR9 agonists are associated with more frequent major pathologic responses and improved RFS in resected melanoma.[37 38] Priming first, checkpoint modulation second. A fundamental shift is required. The failure of dual checkpoint blockade in the adjuvant setting is not due to lack of synergy; it is due to lack of immune activation upstream requiring tumor antigen sensing. These mechanisms were conceptualized in the cancer immunity cycle as steps 1 and 2.[39] Adjuvant immunotherapy must evolve from passive maintenance to active immunization. It all starts with priming.

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