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Commentary

Eradicating micrometastases with immune checkpoint blockade: Strike while the iron is hot

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Immune checkpoint blockade (ICB) is transforming treatment for many cancers. While ICB alone initially demonstrated efficacy in patients with metastatic melanoma, it has expanded to other types and to earlier-stage cancers. We describe ICB history, mechanisms underlying variation in response, and how ICB is being integrated into adjuvant and neoadjuvant treatment approaches.

For most patients with localized, non-metastatic cancer, surgery that removes the primary tumor together with a part of or the entire cancerous organ and surrounding lymph nodes is a critical intervention to cure the disease. Unfortunately, despite complete resection by an expert surgeon, the risk of cancer recurrence resulting from the expansion of micrometastatic disease is substantial. To eradicate micrometastases—microscopic clusters of cancer cells seeded in circulation and distant organs—before detectable metastatic disease develops, systemic therapy is administered either after surgery (adjuvant treatment) or before (neoadjuvant). Adjuvant nivolumab (anti-PD-1) recently demonstrated a survival benefit for high-risk, resected bladder and esophageal or gastresophageal cancers, which join melanoma among the cancers for which adjuvant ICB has proven effective, a landmark step forward in cancer treatment (Table 1). Yet ICB does not work in most cases, and therefore continued research is needed to move the field forward.

ICB mechanism

Blockade of co-inhibitory pathways in T cells leads to antitumor immunity through distinct mechanisms. CTLA-4 blockade enhances co-stimulation, lowers the T cell receptor's (TCR) threshold for activation, likely limits the suppressive influence of regulatory T cells (Tregs), and expands T effector cells. PD-1 blockade also lowers the requirement for TCR signaling, reinvigorates antigen-experienced but exhausted $CD8^+$ T cells, and reprograms the tumor microenvironment to favor inflammatory rather than suppressive myeloid cells.

As suggested by these mechanisms, ICB works best in tumors that have been recognized by the immune system and already have T cells that can be "unleashed." Indeed, response to ICB is associated with signs of T cell activation, including T cell infiltration into tumors and PD-L1 expression. These events occur when the immune system has become aware of the cancer, which is statistically more likely to happen when a tumor has multiple mutations, as resulting novel antigens may be presented in the context of the major histocompatibility complex (MHC) to an antigen-presenting cell. Accordingly, the initial success of immunotherapy was observed in tumors with multiple mutations induced by chemical carcinogens or ultraviolet radiation, such as melanoma and lung and bladder cancer, and tumors that have multiple mutations due to genomic alterations such as microsatellite instability (MSI). Furthermore, correlative studies in mismatch repair-deficient tumors demonstrated that ICB expands peripheral $CD8^+$ T cells that are specific to tumor mutations, supporting tumor antigens as a potential target for the immune system. However, tumors with low mutational burden, such as renal cell cancer, can also respond well to ICB. The immune properties of tumors vary widely and are graded from "hot" (e.g., MSI-high [MSI-H] tumors), bearing many neoantigens and infiltrated by large numbers of T cells, to "cold" (e.g., pancreatic cancer), which are poorly antigenic and have little immune infiltration; the majority of cancers fall somewhere between these extremes.

Using adjuvant ICB to reduce recurrence and eliminate micrometastatic disease

As primary resection is a critical part of the path to cure, the initial extension of ICB from treatment of unresectable metastatic disease was treatment after surgery (adjuvant therapy), which treats remaining micrometastatic disease. Such an approach could prove to be at least as effective as administering these agents after the cancer relapses, if not more so, as the burden of tumor to be eradicated is significantly lower. Indeed, the efficacy and safety profile of adjuvant anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) in resectable melanoma are similar to those in unresectable stage IV disease. Relapse-free survival (RFS) benefit with adjuvant ipilimumab is ~10% (Eggermont et al., 2019); adjuvant nivolumab also improves RFS and is better tolerated than ipilimumab (Weber et al., 2017).

Further supporting the efficacy of ICB in micrometastatic disease are recent data

Table 1. Summary of published neoadjuvant and adjuvant studies across solid tumor

Cancer type	Reference	Outcome	Treatment setting	Comparators	N	Response rate or median survival (months) with ICB	Response rate or median survival (months)	p value
Bladder	Powles et al., *Nature Medicine*, 2019	positive	neoadjuvant	atezolizumab	88	pCR 31% (21%–41%)	–	–
	Necchi et al., *Journal of Clinical Oncology*, 2019	positive	neoadjuvant	pembrolizumab	114	pCR 37% (28%–46%)	–	–
	Bajorin et al., *New England Journal of Medicine*, 2021	positive	adjuvant	nivolumab versus placebo	709	DFS 21.0 (17.1–33.4)	10.9 (8.3–13.9)	0.0006
	Bellmunt et al., 2021	negative	adjuvant	atezolizumab versus observation	809	DFS 19.4 (15.9–24.8)	16.6 (11.2–24.8)	0.24
Breast	Schmid et al., 2020	positive	neoadjuvant	pembrolizumab + chemotherapy versus placebo + chemotherapy	1,174	pCR 64.8% (59.9%– 69.5%)	51.2% (44.1%– 58.3%)	<0.001
	Mittendorf et al., *The Lancet*, 2020	positive	neoadjuvant	atezolizumab + chemo versus placebo + chemo	333	pCR 58% (50%–65%)	41% (34%–49%)	0.0044
Colon	Chalabi et al., 2020	positive	neoadjuvant	nivolumab + ipilimumab	35	pCR 100% (86%–100%) dMMR; 27% (8%–55%) pMMR	–	–
Esophagus	Kelly et al., 2021	positive	adjuvant	nivolumab versus placebo	796	DFS 22.4 (16.6–34.0)	11.0 (8.3–14.3)	< 0.001
Lung	Forde et al., 2018	positive	neoadjuvant	nivolumab	20	pCR 45% (23%–68%)	–	–
	Kwiatkowski et al., *Journal of Clinical Oncology*, 2019		neoadjuvant	atezolizumab	101	MPR 8% (11%–28%)	–	–
	Cascone et al., *Journal of Clinical Oncology*, 2019		neoadjuvant	nivolumab + ipilimumab versus nivolumab	34	MPR 43%	20%	NR
	P. Forde et al., 2021, AACR, abstract	positive	neoadjuvant	nivolumab + platinum-doublet chemotherapy versus chemo	358	pCR 24.0%	2.2%	< 0.001
Melanoma	Weber et al., 2017	positive	adjuvant	nivolumab versus ipilimumab	906	Nivolumab 12-month RFS 70.5% (66.1%–74.5%)	Ipilimumab 60.8% (56.0%– 65.2%)	< 0.001
	Amaria et al., 2018		neoadjuvant	nivolumab + ipilimumab versus nivolumab	23	Combination pCR 45% (17%–77%)	Nivolumab 25%	0.40
	Blank et al., 2018		both	neoadjuvant versus adjuvant nivolumab + ipilimumab	20	Neoadjuvant pCR 33%	Not reported	
	Eggermont et al., 2019	positive	adjuvant	ipilimumab versus placebo	951	7-year RFS rate 39.2% (34.5%–43.9%)	30.9% (26.7%–35.2%)	< 0.001

ICB, immune checkpoint blockade; pCR, pathologic complete response; DFS, disease-free survival; dMMR, mismatch repair-deficient; pMMR, mismatch repair-proficient; MPR, major pathologic response defined as £10% viable tumor; RFS, recurrence-free survival.

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demonstrating the benefit of adjuvant nivolumab in resected esophageal and bladder cancers, in which responses to ICB had been limited to the metastatic setting in combination with chemotherapy. In esophageal cancer, adjuvant nivolumab doubled median disease-free survival (DFS) compared with placebo (22.4 versus 11.0 months; hazard ratio 0.69) (Kelly et al., 2021). In bladder cancer, adjuvant nivolumab led to a similar improvement in DFS (median DFS 21.0 versus 10.9 months) (D. Bajorin et al., 2021, *New England Journal of Medicine*). Notably, the surgery for both cancers involves complete removal of the diseased organ and thus entails prolonged recovery, meaning only select patients with adequate functional status were able to participate in these trials. Both studies enrolled patients at high risk of progression due to persistent residual disease in the surgical specimen despite receiving neoadjuvant chemotherapy before surgery. While the demonstration of improved DFS has already changed practice, longer follow-up is needed to determine whether treatment with anti-PD-1 therapy in the adjuvant setting instead of at the time of disease recurrence will help patients live longer and remain cancer-free.

As we wait for long-term follow-up from these practice-changing trials, we should carefully consider next steps. Adjuvant therapy studies take years to complete and require large numbers of patients to demonstrate efficacy, as they rely on long-term endpoints such as extension of disease-free or overall survival. These studies need to be large because the relative benefit is small, and many patients will not benefit from the treatment at all. The final analysis is susceptible to study design factors such as biomarker selection, timing of therapy after surgery, whether the study is placebo-controlled, and the patient dropout rate. For example, a large phase 3 adjuvant study failed to demonstrate survival benefit of atezolizumab (anti-PD-L1) over observation (Bellmunt et al., 2021) in a similar patient population to that studied in the bladder cancer trial of adjuvant nivolumab versus placebo cited above (D. Bajorin et al., 2021, *New England Journal of Medicine*). It remains unclear whether these differing outcomes are a result of trial design or difference in antibody and ligand inhibition (nivolumab inhibits PD-1, which binds both PD-L1 and PD-L2, while atezolizumab inhibits only PD-L1).

A logical way to move forward with adjuvant therapy is with the knowledge of clearance of minimal residual disease (MRD) via measurement of circulating tumor DNA (ctDNA) in plasma. This endpoint is assessable during treatment and addresses some of the challenges of adjuvant trials with survival endpoints by focusing on the highest-risk population and avoids exposing patients cured with surgery alone to the potential toxicities of ICB. Several ongoing studies are examining the role of intensified adjuvant therapy for patients with MRD following curative-intent therapy, using regimens with high response rates in the metastatic setting such as trastuzumab (anti-HER2) plus pembrolizumab (anti-PD-1) for *ERBB2*-amplified tumors (NCT04510285) (Janjigian et al., 2020) and pembrolizumab monotherapy for MSI-H tumors (NCT03832569). Similarly, the role of ctDNA monitoring to assess early response to therapy is the subject of several ongoing trials across solid tumors (NCT04576858, NCT03653052, NCT02838836, NCT04354064).

Choosing an ICB strategy: evidence from clinical trials and future directions

While adjuvant therapy appears promising in locally advanced tumors, in many cases neoadjuvant chemotherapy and radiation are needed to improve the chances of successful cancer removal and negative surgical margins. Furthermore, if surgery is associated with prolonged recovery and leaves the patient nutritionally and functionally compromised, it can be challenging to administer additional treatment, particularly if it is associated with high rates of adverse events. For example, only ~50% of esophageal and gastric cancer patients are able to complete all planned adjuvant chemotherapy, in part due to prior toxicity and postoperative complications. In addition, neoadjuvant therapy offers the opportunity to assess changes in the tumor and microenvironment, best defined as pathological response and tumor regression, after only a few doses.

Neoadjuvant therapy may expand tumor-infiltrating T cells, further priming an antitumor response and imparting immunological memory before T cells are removed with the diseased organ during surgery (Figure 1). Studies in two breast cancer preclinical models illustrated the significantly greater therapeutic power of neoadjuvant compared with adjuvant immunotherapies in the context of primary tumor resection, which was not observed with neoadjuvant chemotherapy (Liu et al., 2016). Further clinical evidence for a neoadjuvant immunologic benefit comes from the OpACIN-neo melanoma trial, where greater expansion of existing and new T cell clones was observed in the neoadjuvant than in the adjuvant group, suggesting that neoadjuvant treatment enhances T cell diversity (Rozeman et al., 2019).

Several trials have demonstrated considerable pathologic responses and enhanced immune activation with the neoadjuvant approach in multiple tumor types, although these trials have not directly compared it to adjuvant treatment. In non-small cell lung cancer and bladder cancer, neoadjuvant ICB led to impressive and deep pathological responses, particularly in patients with pre-existing immunity, defined as an antitumor T cell population (Forde et al., 2018). Complete or major (10% viable tumor cells) pathologic responses were seen in 19%–45% of resected lung cancers after two doses of neoadjuvant atezolizumab (D. Kwiatkowski et al., 2019, J. Clin. Oncol., abstract) or nivolumab (Forde et al., 2018). Similar to what has been demonstrated in stage IV disease, tumor mutational burden was predictive of the pathological response to PD-1 blockade, consistent with more diverse neoantigens leading to greater efficacy. Correlative studies of peripheral blood showed that nivolumab treatment induced expansion of mutation-associated, neoantigen-specific T cell clones (Forde et al., 2018). Lastly, in triple-negative breast cancer, neoadjuvant pembrolizumab with chemotherapy revealed improvements in pCR rates of 14% versus chemotherapy alone (Schmid et al., 2020).

A potential advantage of neoadjuvant therapy is the opportunity to examine whether pathological response correlates with longer-term outcomes. Early pathologic assessment is an excellent predictor of outcome with ICB in melanoma. In patients with a major pathologic response, disease recurrence was exceedingly rare

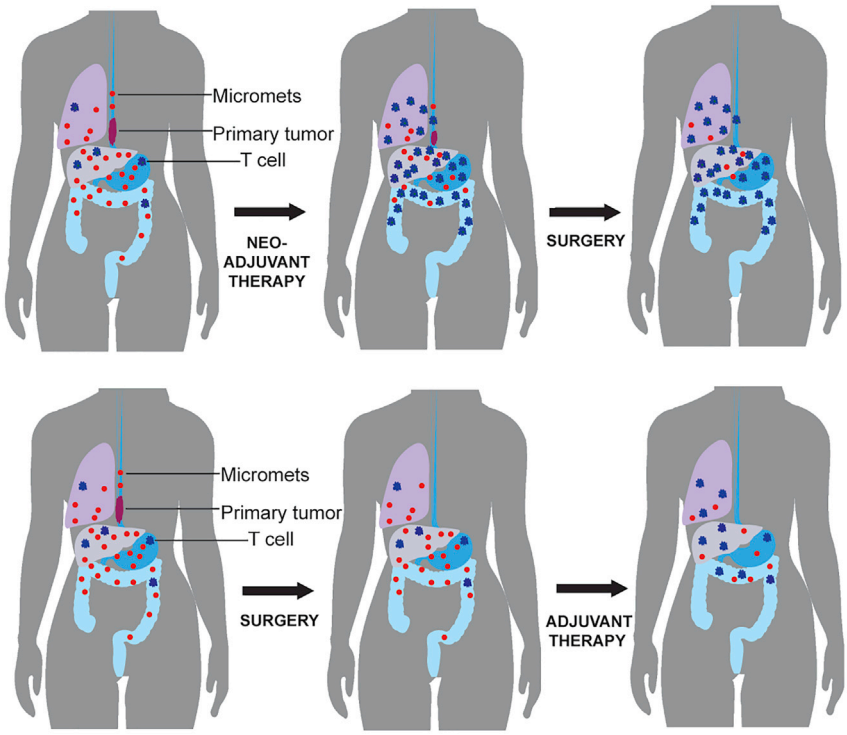

Figure 1. T cell response and expansion in patients with locally advanced resectable esophageal cancer who received neoadjuvant or adjuvant ICB

Schematic of T cell response and expansion in patients with locally advanced resectable esophageal cancer who received neoadjuvant (before surgery, top) or adjuvant (after surgery, bottom) immune checkpoint blockade (ICB). Neoadjuvant therapy may also include dual ICB and ICB in combination with chemotherapy and radiotherapy. The hypothesis is that while both approaches help expand and potentiate antitumor immune response and treat micrometastases (micromets), neoadjuvant ICB given while the tumor is still in place has the potential advantage over adjuvant therapy of enhancing a broader immune response to more abundant and diverse neoantigens that may lead to generation of more tumor-specific T cell clones to enter circulation and attack micrometastastases. These tumor-specific T cells presumably would continue to suppress metastatic disease, enabling the patient to live cancer-free. Primary tumor, burgundy; micromets, red; T cells, blue.

(4%), whereas even with pCR from targeted therapy, the 2-year RFS was only 79% (Menzies et al., 2021). Therefore, in select tumors with complete response after neoadjuvant therapy, a watchful waiting approach to surgery may allow organ preservation and is currently being studied in the PRADO trial (NCT02977052). Thus, care may be individualized based on early assessment of tumor response using on-treatment biopsies, or perhaps in the future, using functional imaging with immunologically relevant positron emission tomography tracers currently in development.

Organ preservation is particularly critical in rectal cancer, where cancer surgery involves losing normal organ function and living with an ostomy. Dual ICB or combination chemotherapy with immunotherapy may increase the chance of pCR. In a recent trial, all 20 (100%) patients with mismatch-repair-deficient tumors, which are generally MSI-H, had a pathological response to neoadjuvant nivolumab + ipilimumab, suggesting that this feature could be used to select likely responsive patients and possibly avoid surgery (Chalabi et al., 2020). Recently, in lung cancer the combination of nivolumab with chemotherapy showed a dramatic improvement in pCR over chemotherapy alone (24% versus 2.2%; odds ratio 13.94; $p < 0.0001$). While neoadjuvant chemotherapy has historically been less commonly used than adjuvant chemotherapy for this patient population, the treatment paradigm may shift, as the treatment was well tolerated and the addition of nivolumab did not decrease the likelihood of resection (P. Forde et al., 2021, AACR, abstract). Though other studies have observed lower rates of surgery with single-agent neoadjuvant ICB in melanoma, in combination with chemotherapy this is less of a risk for other solid tumors.

Conclusion

In summary, the success of ICB is already leading to greatly improved treatment options for cancers with traditionally low rates of survival. There are several advantages to the use of these therapies in the neoadjuvant setting, particularly because of the greater abundance and variety of tumor antigens prior to surgical removal of the tumor. Several trials have demonstrated the benefit of ICB while the tumor is still in place and therefore "hot." Definitive trials are underway, and this may emerge as a preferred approach across multiple tumor types, as it also enables organ preservation.

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