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Spotlight

When immunotherapy meets surgery in non-small cell lung cancer

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The results of the most recent Checkmate-816 trial in *The New England Journal of Medicine* using combination neoadjuvant immunotherapy with platinum-based chemotherapy in resectable non-small cell lung cancer demonstrate the effectiveness of neoadjuvant immunotherapy and provide further support that biology and personalized therapy represent the foundation of lung cancer treatment.

Despite efforts at primary prevention, advances in lung cancer screening, and earlier detection of disease, lung cancer remains the leading cause of cancer death worldwide, in large part due to its metastatic presentation in more than half of cases (Siegel et al., 2020) (Figure 1). While 5-year overall survival (OS) rates have improved and a cure is possible with surgery and in some cases radiation therapy, up to 80% of tumors recur. Multimodality therapy had traditionally been the standard treatment approach, consisting of surgery, chemotherapy, and radiation therapy, unless in a metastatic setting, where only chemotherapy is possible. The late Emil "Tom" Frei III and others taught us that the best approach against lung cancer was to move our most effective therapies to earlier settings (Figure 1). In the late 90s with the advent of new chemotherapy regimens, lung cancer treatment improved to the point where in the metastatic setting, the OS rates nearly doubled. However, there was still enormous room for improvement.

Harnessing an anti-tumor immune response has long been a fundamental strategy in cancer immunotherapy. Initial immunotherapeutic approaches focused on amplifying immune activation mechanisms in tumors that are typically activated to eliminate invaders such as viruses and bacteria. This strategy resulted in rare objective responses and in some cases significant toxicity. In the last decade, higher objective response rates have been observed by targeting the PD-L1/PD-1 immune checkpoint pathway (herein anti-PD therapy). This stems from distinct mechanisms of action that restore tumor-induced immunity deficiency selectively in a tumor microenvironment (TME) (Dong et al., 2002; Sanmamed and Chen, 2018). The therapeutic efficacy of these anti-PD1 therapies relies on endogenous tumor-antigen-specific T cells that are functionally held in check in the tumor microenvironment (TME) due to PD-L1 inhibitory signaling through PD-1. Anti-PD therapy results in the adaptive increase of functional T cells, which translates into tumor regression (Figure 1).

From the first study of nivolumab initiated in 2006, it was observed that 15% of patients who received nivolumab versus standard of care in the refractory setting achieved 5-year survival. This was also seen with pembrolizumab in the Keynote-010 study, which randomized against docetaxel and developed PD-L1 as a biomarker (Herbst et al., 2016). The potential for improved survival was further supported by Keynote-024, a study that assessed front-line immunotherapy versus chemotherapy in patients with PD-L1-high tumors (reviewed in Wang et al., 2021). In this study, it was confirmed that in selected patients, immunotherapy could improve 5-year survival rates to 35% versus 16% for chemotherapy alone (followed by crossover). This represents incredible progress in the field. However, there is clearly a need for further selection, as many patients do not benefit and continue to deal with issues of resistance to these agents, which will likely require more combination approaches in the future.

Cytotoxic adjuvant therapy improves survival in lung cancer, albeit modestly. In the adjuvant setting, cisplatin-based regimens show a 5.8% improvement in disease-free survival and a 5.4% improvement in 5-year OS based on several studies (Chaft et al., 2022). Neoadjuvant therapy has been used with similar limited success, and these approaches require well-coordinated multidisciplinary teams with tumor boards to review surgical operability and management. Many questions remain regarding the magnitude of the benefit associated with adjuvant and neoadjuvant therapy, and some who are treated do not benefit, while still having toxicity. It has been suggested that using neoadjuvant therapy has several advantages, including downstaging tumor burden to allow a smaller surgery with fewer complications along with the ability to assess therapeutic response on surgical resection of the tumor (known as pathologic response). Immunotherapy before surgery may also offer the advantage of enhanced T cell priming and increased expansion of antitumor T cells along with continued T cell activity against micro-metastases after resection (Janjigian et al., 2021).

There have been recent reports on successful strategies for lung cancer treatment by utilizing the most efficacious EGFR targeted therapies earlier in the disease course as adjuvant therapy to provide the most enhanced patient benefits (Wu et al., 2020). It is therefore logical that the new paradigm of the treatment strategy should now include neoadjuvant immunotherapy combinations with surgery or radiation, but more compelling data are needed. Several studies have demonstrated the success of immunotherapy in the adjuvant setting, including

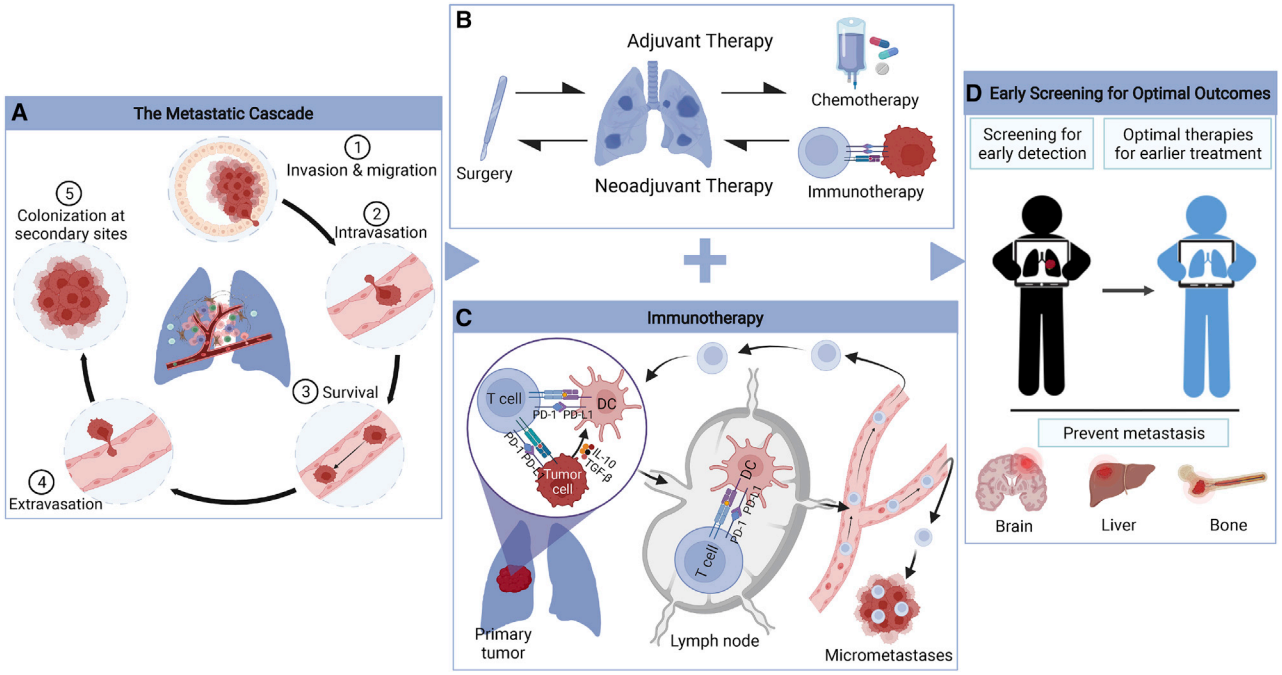

Figure 1. Lung cancer treatment strategy

The five major metastatic cascade steps (A) begin with (1) migration and invasion, (2) intravasation, (3) tumor cells' survival and circulation through the bloodstream, (4) extravasation, and (5) colonization at secondary sites and escape immune surveillance. Personalized adjuvant therapy and neoadjuvant therapy (B), with the addition of immunotherapy (C), are transforming of lung cancer treatment. The key to improve lung cancer treatment will be to bring the best therapies earlier in the disease course to avoid metastasis and for the most enhanced patient benefit (D). DC, dendritic cell.

Impower-010 (Felip et al., 2021) and the recently presented PEARLS/KEYNOTE-091. However, only certain subgroups of patients benefitted in the Impower study. Until now, immunotherapy in the neoadjuvant setting had not been established, though many clinical trials are underway.

In a recent study published in *The New England Journal of Medicine*, Forde et al. report the results of the Checkmate-816 trial, the first stage 3 randomized neoadjuvant immunotherapy-based combination study in resectable non-small cell lung cancer (NSCLC) (Forde et al., 2022). They demonstrate that neoadjuvant nivolumab plus platinum-based chemotherapy resulted in 11-month-longer event-free survival (31.6 versus 20.8 months) and a higher pathological complete response (pCR) than chemotherapy alone. This is a practice-changing trial that resulted in the recent FDA approval of neoadjuvant nivolumab plus chemotherapy in resectable NSCLC.

In this study, patients with stage IB to IIIA NSCLC received three cycles of neoadjuvant nivolumab with platinum-based chemotherapy or chemotherapy alone before definitive resection (Forde et al., 2022). The primary endpoints were event-free survival and pCR. In addition to the improved event-free survival, the hazard ratio for disease progression, disease recurrence, and death was 0.63, representing a 37% improvement. Remarkably, a pCR was detected in 24% of the patients in the nivolumab with chemotherapy group as compared to 2.2% with chemotherapy alone. Benefits were observed across all analyzed subgroups. Minimally invasive surgery was more common, and pneumonectomy less common, with nivolumab plus chemotherapy than with chemotherapy alone, with minimal delays in surgery observed and minimal difference in the treatment-related adverse events. These results confirm that neoadjuvant immunotherapy in combination with chemotherapy is significantly more efficacious than chemotherapy alone for resectable NSCLC.

Longer follow-up of this study is required to determine whether the improvement in pCR or event-free survival will translate to an overall survival benefit, the most important endpoint. Questions also remain regarding the role of post-operative therapy, either chemotherapy or radiation, and the need for further anti-PD therapy. Additional studies of sensitivity and resistance will be critical (taking the resected specimens back to the laboratory to develop biomarkers) to better select patients to receive neoadjuvant therapy. It is also likely that liquid biopsies measuring circulating tumor DNA (ctDNA) will be used to assess minimal residual disease and hence the need for further therapy. Nevertheless, the results of this trial represent a positive and hopeful starting point.

These data without question amplify that biology and personalized therapy are the foundation of lung cancer treatment. We are only at the tip of the iceberg, as these therapies are still not yet truly being personalized; in other words, patients are being treated with chemotherapy and nivolumab regardless of their PD-L1 expression or other tumor biomarker status. These studies, however, are amassing large amounts of biospecimens for research, which will allow us to elucidate predictive markers of sensitivity and resistance to help inform future combination therapeutic approaches. Additionally, we need to avoid or minimize toxicities by using these agents only when truly effective. More work is needed to understand mechanisms of resistance and sensitivity and to classify patients by the resistant treatment type (Sanmamed and Chen,

2018; Vesely et al., 2022). Clearly, the future is bright, and as the late Dr. Isaiah Fidler used to proclaim, biology truly is the foundation of therapy (Figure 1).

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