

IN THE SPOTLIGHT

Making the Most of Cancer Surgery with Neoadjuvant Immunotherapy

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Summary: Surgery remains our strongest treatment pillar against early stages of cancer. In a number of instances, the curative potential of surgery can be enhanced by treatments given before (neoadjuvant) or after (adjuvant) surgical procedures. Immunomodulation has emerged as a powerful tool to fight metastatic disease across cancer histologies and goes now to be tested at earlier surgically amenable stages. The work by Liu and colleagues in this issue provides solid preclinical evidence in support of neoadjuvant immunotherapy over adjuvant approaches. *Cancer Discov*; 6(12); 1312-4. ©2016 AACR.

See related article by Liu and colleagues, p. 1382 (7).

Cancer surgery is the treatment of choice for localized disease with the objective of achieving a surgical margin-free complete resection of the tumors. Procedures also usually involve lymphadenectomy seeking to remove metastatic and micrometastatic lymph nodes in the areas draining tumor tissue. Patients are frequently declared to have no evidence of disease based on postsurgical imaging techniques and pathology examination of the excised specimens, but a significant number of cases relapse at different intervals either locally or distantly with regard to the removed primary malignant lesion.

Starting with breast cancer (1) and followed by other diseases, evidence has been found that the adjuvant instigation of oncology anticancer therapies such as chemotherapy, radiotherapy, or targeted therapies following surgical healing statistically decreases and delays relapses, presumably dealing with minimal residual disease. In other studies, pharmacologic and radiotherapeutic treatments are delivered before the surgical procedure with the aim of cytoreduction, with a number of instances in which there is obvious long-term survival benefit that has turned neoadjuvant courses of treatment state-of-the-art.

In recent years, immunotherapy has been witnessing rapid progress that has resulted in more than nine FDA and European Medicines Agency approvals for immunotherapy agents targeting the PD-1/PD-L1 and CTLA-4 axes with immunomodulatory antibodies also known as checkpoint inhibitors (2). Success over standard of care as a second line of treatment against metastatic disease has

resulted in trials testing the efficacy to prevent or delay relapse following surgery in cases with high probability of relapse in melanoma (3), non-small cell lung cancer (NSCLC; for instance, NCT02595944 and NCT02504372), and other indications. These studies will tell in time if adjuvant immunotherapy with these agents is worthy of changing medical practice.

Neoadjuvant schemes are also under scrutiny in relatively small series of patients. These studies offer the possibility to make observations on the excised tissue to draw important mechanistic conclusions for the development of these extraordinary novel agents. Over 60 studies exploring checkpoint inhibitors (anti-PD-1/PD-L1 and anti-CTLA-4) as neoadjuvant strategies are now ongoing in several tumor types, including melanoma, NSCLC, bladder cancer, renal cell carcinoma, ovarian cancer, prostate cancer, gastroesophageal cancer, colorectal cancer, mesothelioma, pancreatic cancer, triple-negative breast cancer, and glioblastoma (Clinicaltrials.gov). Some of the main objectives of many of these studies are response rate and pathologic response rate following neoadjuvant therapy. Pathologic response rate is considered a major endpoint to estimate treatment efficacy in chemotherapy neoadjuvant studies in many tumor types. Yet, it remains to be seen whether response rate will truly capture the potential benefit on long-term survival of immune-checkpoint inhibitors administered preoperatively.

The field of immunostimulatory mAbs is not restricted to those tampering with inhibitory receptors (checkpoint inhibitors) such as CTLA-4, PD-1/PD-L1, LAG3, TIM3, TIGIT, and others. There is also a family of mAbs that agonistically act on TNFR family members that costimulate T and natural killer cells (4). These include antibodies against 41BB (CD137), OX40 (CD134), and anti-GITR (CD357) that are undergoing clinical trials (4). It is actually remarkable that immunostimulatory mAbs are often highly synergistic when used in combinations that are under clinical scrutiny and have resulted in the approval of a nivolumab plus ipilimumab regimen for the treatment of metastatic melanoma (5). In this regard, combinations of PD-1 blockade with agonist anti-CD137 mAbs offer outstanding efficacy in preclinical models, either transplantable or spontaneous (6).

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