Immunotherapy for Resected Pulmonary Metastases

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BACKGROUND ON IMMUNE SYSTEM AND IMMUNOTHERAPY/IMMUNITY IN THE LUNG

The high rate of recurrence after metastasectomy of most malignancies demonstrates that controlling micrometastatic disease remains a challenge. Although there has been considerable interest in applying chemotherapy and targeted therapies to prevent recurrence, immunotherapy has appeal, as by its very nature the immune system has both innate and adaptive elements that could provide long-term control of tumors, prevention of new tumors, and, potentially, elimination of the more aggressive clones, all possible with limited cycles of therapy. Furthermore, it is clear from most animal models of immunotherapy that immune effectors are most effective against the smallest volumes of disease, such that adjuvant therapy may have the greatest potential to demonstrate efficacy of immunotherapy.

Immunotherapy takes advantage of or interacts with the processes that lead to activation of immune responses naturally.1 Tumor-specific immune responses depend on the uptake of tumor proteins, peptides, and genetic material (antigens) released during cell death by professional antigen-presenting cells (dendritic cells), which process and present the tumor antigens to T cells along with costimulatory molecules, which leads to T-cell activation and indirectly B-cell activation.

It is well established that T cells and antibodies that recognize tumors (T cells through T-cell receptor [TCR] recognition of their cognate peptide presented within major histocompatibility complex [MHC] class I or II molecules on the tumor surface and antibodies by binding to 3-dimensional structures recognized by their complementarity determining regions) are present in the tumor-bearing host and can have antitumor activity. T-cell activation can also be countered by upregulated expression of inhibitory molecules (eg, CTLA4).2 Activated T cells traffic to and infiltrate the tumor. Those that are not suppressed by regulatory T cells and

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myeloid-derived suppressor cells and their cytokines have the opportunity to bind to tumor cells expressing their cognate antigen and set off a cascade of events culminating in tumor cell death; however, some T cells that express the activation marker programmed death-1 (PD-1)\(^3\) are suppressed by tumor-expressed PD ligand-1 (PD-L1). T-cell destruction of tumor releases antigens that can begin the cycle again if they are taken up by dendritic cells. Therefore, immunotherapies may be applied at all key steps in the immunity cycle, the initial phase of antigen delivery to dendritic cells (vaccines), T-cell activation (cytokines), trafficking of T cells to tumor (chemokines), and then T-cell attack on tumor cells recognized by the TCR (tumor-infiltrating lymphocytes [TILs] and chimeric antigen-receptor T cells [CAR-Ts]), and preservation of T-cell functionality (anti-PD-1 and anti-PD-L1 antibodies). Because metastasectomy provides fresh tumor tissue, it is particularly suited to strategies that use tumor-derived components as part of the immunotherapy strategy. For example, TILs may be retrieved from disaggregated tissue and cultured in vitro before re-administration as adoptive immunotherapy. Although TILs may be functionally suppressed in the tumor milieu, when cultured ex vivo in interleukin 2 (IL-2), their functionality as demonstrated by expression of TCR zeta and epsilon chains, p56, FAS, and FAS-ligand is increased. Other tumor constituents, including the malignant cells themselves and peptide, protein, and mRNA derivatives, may be used as components in cancer vaccines. Although the lungs have a different immune milieu by virtue of the exposure to a panoply of air-borne allergens compared with the bowel or liver that are exposed to orally administered antigens or the skin that is exposed to contact immunogens and the different microbiome, there are limited data on whether considerations for immunotherapy for resected pulmonary metastases should be different than that of immunotherapy for resected liver metastases, for example. Therefore, this review attempts to focus on issues relevant for pulmonary metastasectomy but also discusses immunotherapy for other sights of metastases where relevant. What may differ is the immune response, in particular the T-cell infiltration into tumor, for different malignancies. For example, Rosenberg’s group at the National Cancer Institute observed that fewer CD3+ T cells were found to infiltrate gastrointestinal (GI) cancer compared with melanoma metastases (to liver and lungs) and very few TILs from GI cancer metastases were tumor reactive.\(^4\) Therefore, the author discusses immunotherapy considerations for different tumors separately.

**MELANOMA**

It is well established that the immune system responds to melanoma and it is in melanoma that many of the established tumor antigens were first identified and new discoveries on targeting tumor antigens are being made.\(^5\) Higher total and CD8+ T-cell frequency in melanoma metastases is associated with improved overall survival (OS),\(^6\) and numerous immunologic approaches have demonstrated antitumor activity for unresectable metastatic disease.\(^7\) Immunotherapy with interferon-α (IFN-α) and its pegylated form\(^8\) have long been a standard adjuvant therapy based on the recurrence-free survival (RFS) and OS benefit in resected stage III melanoma. IFNs have direct antitumor activity and are involved in activation of T and B cells, macrophages, and natural killer (NK) cells. More recently, the anti-CTLA4 antibody ipilimumab improved recurrence-free survival compared with placebo in resected stage III melanoma.\(^9\) Tested in a randomized study following resection of stage IIIB/IIIC/IV or mucosal melanoma, recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) showed an improvement in disease-free survival (DFS) and a trend toward improved OS in the sub-group of patients with stage IV disease compared with placebo.\(^10\) These data support the hypothesis that immunotherapy could have a role in resected metastatic melanoma, including pulmonary metastasectomies.

Although none were focused on pulmonary metastases, several studies have evaluated patients who have undergone lymphadenectomy or metastasectomy to determine whether various immunotherapies might reduce recurrence. Single-arm studies of vaccines following metastasectomies, in aggregate, have demonstrated long-term survival, although the number with lung metastasectomies is small.\(^11\) Unfortunately, a phase III randomized protocol comparing polyvalent-cultured melanoma cell vaccine (Canvaxin) combined with BCG versus BCG alone for patients with resected stage III/IV melanoma was closed early for futility due to failure to improve DFS and OS and a decrease in survival for vaccinated patients.\(^12\) A single-arm study of patients with stage III/IV melanoma (the majority with macroscopic lymph node metastases but some with resected stage IV disease) who had no evidence of disease after surgery tested dendritic cells (DC) electroporated with mRNA encoding a fusion protein between MAGE-A1, -A3, -C2; tyrosinase; MelanA/MART-1; or gp100 and an HLA class II-targeting sequence along with IFN-α-2b.\(^13\) The median OS had not been reached; the 2-year and 4-year survival rates...
were 93% and 70%, respectively. Although the lack of a control group does not allow direct assessment of the impact of the vaccine, comparison with similar patients treated with IFN alone suggested a favorable survival benefit. Further, the investigators commented that some recurrences were single lesions that could be resected leading again to no evidence of disease. Whether immunotherapy is associated with more indolent recurrences or whether patients who can undergo metastasectomy have tumor biology more likely to lead to limited recurrences is unclear.

As noted earlier, because metastasectomy provides access to tumor tissue from which TILs may be extracted and activated, it is well suited to applications using TILs. Although TIL therapy has been predominantly reported in the setting of advanced metastatic disease, there is some reported experience following metastasectomy to prevent recurrence. The potentially greater efficacy of TILs in patients after metastasectomy compared with active metastatic disease was suggested by a preliminary study of adoptive TIL in combination with IL-2 in patients with advanced melanoma, colorectal carcinoma, and renal cell carcinoma, which was followed by enrollment of patients with no evidence of disease following metastasectomy.14 Although there was no objective response observed in the advanced patients and all progressed after a median of 1.5 months, among the adjuvant postmetastasectomy patients, more than half (13 of 22) remained disease free after a median of 23+ months. Follow-up data from these patients demonstrated that 64.7% (11 of 17) of the initially disease-free group were still free of disease after a median of 37+ months (range, 5+ - 69+).15 In a follow-up single-arm study of TIL administered with infusions of IL-2 to patients with stage III/IV melanoma who underwent resection of synchronous metastases,16 a total of 8 of 22 (36.3%) evaluable patients were disease free at a median follow-up of 5 years. Again, it is difficult to determine whether these results exceed those of other modalities but does provide additional feasibility and long-term safety data that could support randomized studies in the future.

Based on activity for systemically administered, high-dose IL-2 against metastatic melanoma and the widespread experience with inhalation therapies, both inhaled low-dose17 and high-dose18 IL-2 have been studied. Although not a postmetastasectomy study, the high-dose IL-2 experience16 is instructive of several issues regarding effects of the therapy. Patients with pulmonary-predominant metastatic melanoma received dacarbazine (DTIC) and inhalation IL-2 therapy (36 million IU per day, 6 days per week, monthly). Demonstrating the local rather than regional activity of this strategy was the observation that there were no responses to treatment outside of the lung; but for lung metastases, there were 18.5% durable complete response (CR) (5 of 27), 29.6% (8 of 27) partial response (PR), and 18.5% (5 of 27) stable disease (SD), rates higher than expected from DTIC alone. Most of the SD and PR progressed (off therapy) by 6 months, suggesting the need for continued therapy. Mild fever and cough were the predominant toxicities, dramatically lower than intravenous high-dose IL-2 regimens. There were no correlative studies evaluating the intrapulmonary immune response, so the mechanism of activity is speculative. The lower-dose study17 enrolled previously treated patients with lung-metastatic melanoma and patients who had undergone pulmonary metastasectomy, receiving IL-2 as prophylaxis against recurrence. All received daily inhalations of 3 x 3 million IU recombinant IL-2 on an ongoing basis. Patients with extrapulmonary metastases also received DTIC intravenously. Clinical benefit included PR (27%) or SD (33%) but no CR in those with metastatic disease. Those with clinical benefit tended to develop few new pulmonary metastases subsequently. None of the postmetastasectomy patients showed recurrence of lung metastases during the treatment period (median 24.5 months). The investigators noted their lack of CR compared with the high-dose experience, which did report CR. They think this is related to the fact that most patients in the low-dose study had extrapulmonary metastases compared with half in the high-dose study.

Another concern with this approach is that in pulmonary metastasectomy patients, the most common site of subsequent recurrence is an extrapulmonary visceral organ (44% in one study19), suggesting systemic therapy could still be needed along with inhalation therapy. GM-CSF that stimulates dendritic cells leading to enhanced immune responses has also been studied for inhalation therapy in patients with advanced melanoma, demonstrating safety and activation systemic immune responses in a minority of patients; but clinical efficacy data are limited.20

As anti–PD-1 and anti–PD-L1 have demonstrated significant activity in metastatic melanoma,21 there is of course interest in their efficacy in the adjuvant setting. Gibney22 treated HLA-A*0201–positive patients with the anti–PD-1 antibody nivolumab (1 mg/kg, 3 mg/kg, or 10 mg/kg intravenously) with a multi-peptide vaccine (gp100, MART-1, and NY-ESO-1 with Montanide ISA 51 VG) every 2 weeks for 12 doses followed by nivolumab maintenance every 12 weeks for 8
doses. Of the 31 patients with metastases, 7 had lung metastasis resected. Overall, 10 of 33 patients relapsed; the median relapse-free survival (RFS) was 47.1 months. Given the tolerability and efficacy of PD-1/PD-L1 targeting therapy, it is likely that it will be tested as an adjuvant more commonly in the future.

Although most of the studies using immunotherapy and surgery report immunotherapy as a postoperative adjuvant, it is also possible to administer immunotherapy and then resect residual disease. Reasons for residual disease could include tumor antigenic heterogeneity with some masses not expressing antigens recognizable by T cells or downregulation of MHC molecules by tumors or failure of T cells to infiltrate these tumors. Removing these resistant sites would allow elimination of the disease. Yang and colleagues reported that among patients with melanoma with partial responses to high-dose IL-2, surgical salvage results in approximately 20% of patients seeming to be cured and 36% surviving for at least 5 years after salvage surgery.

In summary, because pulmonary metastasectomy of melanoma is associated with longer survival but a significant risk of extrapulmonary visceral relapse, adjuvant systemic therapies (or local plus systemic therapies) will likely be necessary. The availability of the tumor provides an opportunity for TIL therapy, and the demonstrated efficacy of systemic immunotherapies in melanoma in general provides additional tools for combination to enhance the survival rate.

**RENAL CELL CARCINOMA**

Renal cell carcinoma (RCC) is frequently lymphocyte infiltrated, suggesting it is a target for immune effectors; however, immune dysfunction arises from both defective dendritic cell differentiation and anergy-associated genes in T cells. An important observation in RCC is that removing the primary tumor before immunotherapy enhances the survival benefit from the immunotherapy. The explanation for this observation is still debated, but it is assumed that the primary tumor harbors cytokines (IL-4, IL-10, transforming growth factor-β [TGF-β], vascular endothelial growth factor) or cell types (T regulatory cells [Treg], myeloid derived suppressor cell [MDSC]) that cause dendritic cell or T-cell dysfunction. Lauerova reported that reduced CD80+ and CD19+/80+ cells (presumably antigen-presenting cells expressing costimulatory molecules) before nephrectomy was associated with a greater risk of relapse after IL-2/IFN immunotherapy; however, Wald found that early after nephrectomy, there was little change in the peripheral blood immune parameters except for a decrease in the CD8+ T cells expressing the inhibitory molecule B- and T-lymphocyte attenuator (BTLA). There are no data regarding changes in the immune milieu of the metastatic sites following nephrectomy. Further, it is not known how the resection of the metastases may alter immune responses to micrometastatic disease. Nonetheless, the data regarding improved outcome of immunotherapy after nephrectomy support the hypothesis that removing metastases could alter immune function and enhance the efficacy of postmetastasectomy immunotherapy.

The role of adjuvant immunotherapy for RCC, localized or metastatic, remains unclear. In a study of adjuvant DC vaccination combined with cytokine-induced killer cell therapy after RCC resection, there was a prolonged PFS and reduced mortality compared with patients receiving IFN. In a randomized study of autologous tumor lysate-pulsed DCs and cytokine-induced killer cells compared with IFN-α or no postoperative adjuvant therapy for resected localized or locally advanced RCC, OS was significantly greater in the DC/cytokine-induced killer group and IFN-α group than in the control group; but there was no difference between the DC/cytokine-induced killer group and IFN-α group. Unfortunately, studies of adjuvant autologous tumor cells or cytokines after resection of primary tumors have not demonstrated survival benefits. Similarly, a nonrandomized trial comparing patients who received immunotherapy after metastasectomy of RCC also concluded that there was no difference in survival for those who received postoperative immunotherapy.

Newer agents under development, such as anti-CTLA4 antibodies and PD-1/PD-L1 antibodies, have demonstrated preliminary evidence of activity in metastatic RCC. For example, response rates ranged from 43% to 48% with nivolumab/ipilimumab and 52% with nivolumab/sunitinib. Whether there is enough of a T-cell infiltrate in micrometastatic disease to benefit from blockade of T-cell inhibitory pathways is unclear, but these high response rates support use as adjuvant therapy. Achieving a T-cell infiltrate may require use of cancer vaccines. Vaccines based on peptides and viral vectors and dendritic cell vaccines that have been tested or are in late-phase studies in RCC include IMA901, TG-4010, MVA-5T4, and the personalized DC-based therapy AGS-003. Preliminary data with AGS-003 indicate improved PFS and OS when compared with historic controls of patients with unfavorable-risk metastatic renal cell carcinoma (mRCC). Again, these have not
been tested after metastasectomy but would be theoretically applicable because autologous tissue would be available from this procedure.

As with melanoma, inhaled IL-2 has been administered for pulmonary metastases of IL-2 (although not as adjuvant therapy). Interestingly, there was a suggestion that the inhaled IL-2 could be associated with a greater chance of long-term survival than systemic IL-2.

**SARCOMA**

Sarcoma was one of the first areas where observations on immunotherapy of cancer were made. The lymphocytic response to sarcomas has been studied to a limited degree and seems to be more complicated to characterize than in other malignancies. CD3+, CD4+, and CD8+ T-cell infiltration did not correlate with outcomes; but intratumoral CD20+ B-cell density was a good prognosis factor in patients with wide resection margins. However, in another study from this group, a high density of CD20+ lymphocytes in the peritumoral capsule was a negative prognostic indicator, and there was no effect on prognosis of the peritumoral capsule was a negative prognostic factor in patients with wide resection margins. Interestingly, subsequent analysis of the group with metastases (including lung metastases) did not show a significant DFS and OS, but the investigators concluded that there was a trend for improved survival for patients receiving L-MTP-PE. In a nonrandomized study of patients with high-risk, recurrent, and/or metastatic osteosarcoma, L-MTP-PE with and without chemotherapy was associated with survival comparable with prior studies with this agent and 2-year OS of 45.9%; but the nonrandomized nature of the study precluded more definitive conclusions.

Multiple small studies have reported on cancer vaccines for patients with sarcomas; a randomized phase II trial of a vaccine intended to activate antibody responses against the gangliosides GD2, GD3, and GM2 is being studied in patients who have undergone metastasectomy (NCT01141491); but the results are unavailable. A recent study of autologous tumor vaccines modified to secrete GM-CSF in patients with advanced alveolar soft-part sarcoma and clear cell sarcoma (chosen because they have some biological similarities to melanoma) demonstrated immunogenicity but no tumor regression. However, tumor biopsies showed PD-1–positive CD8+ T cells located in association with PD-L1-expressing sarcoma cells. This finding suggests the potential role of PD-1/PD-L1 targeting therapies.

Because established tumor antigens have been identified as expressed by sarcomas, adoptive cell transfer with TILS, T cells modified to express tumor antigen–specific TCRs, or CAR-Ts (T cells modified to express chimeric antigen receptor for a tumor antigen, often in conjunction with
additional components of T-cell signaling) have been studied. A recent report suggested the possible utility of this approach. The investigators generated IGF1R and ROR1 CAR-Ts based on observation of IGF1R and ROR1 expression in most Ewing sarcoma, osteosarcoma, alveolar or embryonal rhabdomyosarcoma, and fibrosarcoma cell lines. Adoptive transfer of the IGF1R and ROR1 CAR-Ts derived from a patient with sarcoma significantly reduced tumor growth in osteosarcoma xenograft models. In a phase I/II clinical trial of 19 patients with recurrent/refractory HER2-positive tumors (16 osteosarcomas, one Ewing sarcoma, one primitive neuroectodermal tumor, and one desmoplastic small round cell tumor) received HER2–CAR-Ts. The T-cell infusions were well tolerated without dose-limiting toxicity, and 4 of 17 evaluable patients had stable disease for 12 weeks to 14 months. The median OS was 10.3 months (range, 5.1–29.1 months). A patient with osteosarcoma who had lung/pleural metastases resected after T-cell infusions was noted to have experienced 90% or greater necrosis of the tumor. The HER2–CAR-Ts persisted for at least 6 weeks in most receiving the highest doses; importantly, HER2–CAR-Ts could traffic to tumors as they were detected at tumor sites of 2 of 2 patients examined; however, there are limited data as to whether CAR-Ts can traffic to micrometastatic disease. Therefore, it is unclear whether CAR-Ts will eventually be used as adjuvant therapy after metastasectomy of sarcoma.

COLON CANCER

T-cell infiltration into colorectal cancers is associated with improved survival in those with resected disease (although the association is less clear for metastases). Further, the induction of an immune response by cancer vaccines has been associated with a clinical benefit. Prior studies of vaccination following liver metastasectomy of colon cancer have suggested clinical benefits in subgroup analyses. A study comparing 2 dendritic cell vaccine strategies following resection of metastases enrolled 26 patients with liver (n = 24) and lung (n = 2) metastases. Among the 24 who were disease free at the time of vaccination, the RFS was 58% at 1 year, 42% at 2 years, and 38% at 5 years. After more than 5 years of follow-up, 8 are alive and disease free, 4 are alive with recurrent disease, and 12 have died of colorectal cancer. RFS was higher for the 11 patients who developed a tumor-specific immune response following vaccination. Because there was no significant difference in RFS between the patients who had evidence of an immune response against a control antigen and those with no immune response and patients with no evidence of response, this was thought to be the result of an induction against tumor antigen rather than a better outcome merely because of better immune biology. The author's group reported adjuvant treatment of patients with colorectal cancer with a DC vaccine after metastasis resection. In this study, 9 of 13 patients treated with a carciinoembryonic antigen (CEA) mRNA-loaded DC vaccine relapsed at a median of 122 days, and few antipeptide responses were detected. More recently, the author performed a phase II randomized clinical trial comparing autologous DC modified with poxvectors encoding CEA and MUC1 and costimulatory molecules (CD54, CD58, CD80) versus the poxvectors alone in 76 patients who had undergone resection of hepatic or pulmonary metastases. Approximately 25% in each arm had lung metastases. The RFS was similar for both arms and a contemporary control group, but the OS was longer for the combined group of vaccinated patients compared with the control group. The author did not separate the results by the presence of lung or liver metastases. Survival was longer for patients who developed an immune response to the vaccine-encoded CEA.

The author has also studied premetastasectomy Flt3 ligand (FLT3L) administration. FLT3L is a cytokine that stimulates bone marrow progenitors, increases DC in the peripheral blood and tumor, and heightens T-cell responses and NK function, resulting in antitumor activity. Of the 12 patients enrolled, 7 patients had liver metastases and 5 had lung metastases. As expected, the percentage of CD11c+(+)CD14(−) DCs in peripheral blood mononuclear cells PBMCs increased. Although there were no objective responses, there was an increase in the number of DCs observed at the peripheral tumors of patients who received FLT3L compared with those of patients who had not. One patient with multiple pulmonary metastases who underwent resection, then received FLT3L followed by another resection, had an increase (nearly two-fold) in the number of fascin-positive DCs in the second specimen. Another patient who received FLT3L followed by a pulmonary metastasis resection and then another cycle of FLT3L followed by a second resection had a three-fold increase in the number of fascin-positive DC in the periphery of the tumor from the second specimen. Further, delayed-type hypersensitivity responses to recall antigens (candida, mumps, and tetanus) showed marginally significant increases in reactivity after FLT3L administration. These data suggested that
pretreatment cytokines could induce an immune response directed at the tumor with the hope that this response may persist after surgery. With a median follow-up of 300 days, 6 of the 8 patients who underwent resections had recurrences at a median period of 256 days; but long-term survival data are not available.

In summary, there may be a benefit for adjuvant therapy after metastasectomy of colorectal cancer but larger, randomized studies will be required. Further, subgroups with particularly high responses to immunotherapy may be the preferred group. For example, colorectal cancers with mismatch repair (MMR) defects (microsatellite instability high) are highly T-cell infiltrated. Le and colleagues recently reported that patients with MMR-deficient colon cancer experienced response rates and disease control rates of 40% and 90% following pembrolizumab administration. These exciting results open the possibility of using adjuvant immunotherapy in this small, but important, subgroup.

**OTHER MALIGNANCIES**

Pulmonary metastasectomy is occasional performed for other malignancies, which have been studied as targets for immunotherapy. For example, lung cancers presenting with metachronous metastases to the lung may be candidates for a resection. Immunotherapy of lung cancer has been an area of significant interest, but studies of adjuvant vaccination have not been successful. For example, in the highly anticipated MAGRIT trial, a randomized trial of recombinant MAGE-3 plus AS15 adjuvant versus placebo for completely resected (R0), MAGE-A3-positive non–small cell lung cancer (stages IB, II, and IIIA) following standard therapy, there was no improvement in DFS with the vaccine. The recent reports of efficacy for the anti–PD-1 targeting therapy for non–small cell lung cancer opens the possibility for ultimately using these drugs as adjuvant therapies.

Breast cancer has also been the focus of numerous immunotherapy studies. In phase I/II clinical trials in which patients with breast cancer were vaccinated with E75 (nelipepimut-S) HER2 peptide and GM-CSF in the adjuvant setting, the 5-year DFS was 89.7% in the vaccinated patients versus 80.2% in the control group. Although this was not statistically significant, among patients who were optimally doses, there was a statistically significant reduction in recurrence. These data support possible immunotherapy studies following resection of lung metastases of breast cancer.

Bladder cancer, at least the localized form, has been treated with immunologic therapies, such as BCG installation; but such therapy is unlikely to be applicable for resected metastases. However, the recent demonstration of benefit for anti–PD-L1 therapy in advanced urothelial cancers also raises the question of whether it could be used as an adjuvant in the future.

**SUMMARY**

Adjuvant immunotherapy has been of substantial interest because of the hope of preventing recurrences after surgical resection of primary or metastatic disease without the toxic chemotherapies that are currently used. Although lung metastases could present a biologically different immune milieu, adjuvant immunotherapy studies have, in general, not focused on pulmonary metastasectomies; therefore, immunotherapies that are in development for disease at any site of the body are likely reasonable candidates to test in patients who have undergone pulmonary metastasectomies. The availability of tumor tissue has fueled enthusiasm for vaccines based on tumor cells or their constituents and for T-cell therapeutics based on the TILs extracted from tumor tissue. The high rates of clinical activity in some malignancies following anti–PD-1 or anti–PD-L1 therapy has now suggested these biologics may be tested as adjuvant therapies following surgical resections. More efficacious therapies may of course increase the number who may undergo metastasectomies, and debulking metastasectomies may become of greater interest if it is known that adjuvant therapies may be able to control the growth of small-volume residual disease.

**REFERENCES**


Immunotherapy for Resected Pulmonary Metastases


