stead may be guided by molecular mechanisms related to the histologic features or oncogenic signaling pathways of the tumor or factors induced within the tumor microenvironment. Understanding the tumor selectivity of PD-1 or PD-L1 antagonistic antibodies provides a great opportunity for selection of patients on the basis of tumor markers. Key to this understanding is the study of the expression of the PD-1 ligands PD-L1 and PD-L2 in the tumor microenvironment. Preliminary evidence suggests that the expression of PD-L1 may indeed select for patients with an improved response to PD-1 axis inhibitors.

The next frontier in the treatment of cancer requires meeting the goal of inducing a high frequency of long-lasting tumor response on the basis of selectable markers in order to personalize therapies. Inhibition of PD-1 may meet these expectations in selected cancers. The immune system remembers what it targets, so once the system is correctly activated, it may mediate a durable tumor response, as demonstrated previously in clinical trials of high-dose interleukin-2 and anti–CTLA-4 antibodies. The durability of the tumor response to anti–PD-1 and anti–PD-L1 antibodies in a great majority of patients who had objective tumor regressions in the studies by Topalian et al. and Brahmer et al. predicts that these antibodies unleash a memory immune response to cancer. The use of PD-1 blockade — with its reduced rate of toxic effects and potential ability to further select patients who have an increased likelihood of tumor response — may well have a major effect on cancer treatment.

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Native-Valve Infective Endocarditis — When Does It Require Surgery?

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Guidelines, not backed by evidence from randomized trials, strongly recommend urgent surgery for patients with infective endocarditis and congestive heart failure due to valvular regurgitation.[1,2] Management algorithms for infective endocarditis have been developed, and a recent study showed that surgery is still required in 50% of patients who receive antibiotics.[3] Experience shows that surgery in patients with active infective endocarditis is associated with low mortality.[4]

Debate continues, however, about the timing of surgery to prevent embolic events when there are large or mobile vegetations or vegetations in particular locations and when patients have severe valve dysfunction but do not have heart failure. Postponing surgery on the presumption that operating on a patient with active infection is too risky and technically demanding exposes the patient to the risk of further destruction of cardiac tissue as well as to the potential development of heart failure, atrioventricular block,

and embolic events, and it increases the possibility that the patient may subsequently be ineligible for surgery because of complications of the disease or its treatment. In this issue of the *Journal*, Kang and colleagues[5] address the timing dilemma in precisely this group of patients — those with large vegetations and valve dysfunction but without urgent indications for surgery — in a report on a randomized, controlled trial.

In this study, 76 patients with left-sided, native-valve infective endocarditis (defined according to the modified Duke criteria), vegetations with a diameter greater than 10 mm, and severe valve dysfunction were randomly assigned to surgery within 48 hours after enrollment (early surgery) or to antibiotic therapy (conventional treatment). The primary end point was a composite of embolic events or death within 6 weeks after randomization; secondary end points, at 6 months of follow-up, were embolic events, recurrent endocarditis, repeat hospitalization due to the development of congestive heart failure, or death from any cause. Early surgery prevented any additional embolic events without increased mortality, whereas 8 patients in the conventional-treatment group had additional embolic events, including stroke in 5 patients that left residual deficits. Even more striking was the observation that 30 of 39 patients in the conventional-treatment group (77%) underwent surgery for infective endocarditis, including 27 (69%) during the initial hospitalization. Eleven patients were discharged without having undergone surgery; 6 of these patients (55%) had symptoms caused by the regurgitant valves: 2 underwent subsequent surgery with good outcomes and 4 declined surgery or were no longer surgical candidates. Among the 5 patients (45%) who did not have symptoms, 3 remained asymptomatic, 1 died suddenly within 1 month after completing the course of antibiotics, and 1 had recurrent infective endocarditis and required urgent surgery.

This study had several limitations. It was essentially a single-center study with a relatively small number of patients, and enrollment occurred over a 4.5-year period. The interval from randomization to surgery is reported but not the interval from the diagnosis of infective endocarditis to surgery or from the onset of symptoms to surgery. Although the echocardiographic and surgical findings are convincing, no data are provided on pathological confirmation of valve infection. Finally, viridans streptococci were the predominant pathogens in this study, and findings may not be generalizable to other organisms.

The work of Kang and colleagues provides data to help define the gray zone in which randomized studies to establish indications for surgery are reasonable. In this context, the implication of this study for early surgery is profound and raises the bar for the treatment of patients who do not have urgent indications but do have valve dysfunction and vegetations. This study underscores the points that infective endocarditis is a dangerous condition and that the benefits of timely surgical intervention in patients with large vegetations and severe valvular dysfunction, even if they do not have congestive heart failure, outweigh the additional risk of surgery in patients with active infection. In this study, only nine patients did not undergo surgery: one died in the hospital 5 days after randomization, four patients with symptoms declined surgery, one asymptomatic patient died suddenly, and three remained asymptomatic but still had severe valve dysfunction (one with severe aortic-valve regurgitation and two with severe mitral-valve regurgitation) and are likely to require surgery in the future. Severe valve dysfunction without infective endocarditis is a class II indication in the case of aortic valve disease and a class I or II indication in the case of mitral valve disease, depending on left ventricular dimensions and function, rhythm, and the prospect of repair according to present guidelines.[6] In the study by Kang and colleagues, no cases of recurrent infective endocarditis were observed in the patients who underwent surgery. Surgical success during active infective endocarditis requires adequate débridement and organism sensitivity to prescribed antibiotics. Because it is difficult to identify patients who might benefit from early surgery, we would argue that early referral to medical centers with the necessary cardiac surgical experience and resources is warranted for all patients with left-sided, native-valve infective endocarditis who have important valve dysfunction, large vegetations, or invasive disease beyond the cusps or leaflets — not just for those patients with urgent indications. The study by Kang and colleagues provides the stim-

ulus for designing randomized trials that will further refine the indications for and timing of surgery.

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