A major transformation is underway in solid cancer oncology, which can be best characterized as a shift from treating to curing. Immunotherapy, in particular, the broad approach of inhibiting the negative feedback occurring with time in every antitumor immune response through immune checkpoint inhibition (1), carries major promise for cancer cure. With the approval of the U.S. Food and Drug Administration in March 2011 of the first immune checkpoint inhibitor (ICI), ipilimumab (Yervoy), an anti-CTLA-4 antibody, long-term stability or even cure became a realistic goal in a disease that resisted progress the longest—malignant melanoma. Other ICIs, including anti-PD1 antibodies (nivolumab and MK-3475) and anti-PD-L1 antibodies (BMS-936559, RG7446, and MEDI4736) promise to extend the realm of cure from a proportion of patients with melanoma to most patients with this cancer and to patients with other stage IV solid cancers (eg, patients with renal cell cancer, the squamous cell variety of non–small-cell lung cancer, prostate cancer, and colon cancer).

Ipilimumab, the first ICI to be approved, achieves improvement in survival and long-term stability in 25%–30% of patients with melanoma (2). This percentage can be significantly increased by combining ipilimumab therapy with concomitant radiation (3). In patients treated with ipilimumab, radiation of some cancer lesions may unleash an immune response, which kills most or all unirradiated cancer foci as well. In the presence of an immune checkpoint blockade, this response becomes robust enough to lead to long-term cancer control or cure. This so-called abscopal effect (4) is most likely a
consequence of radiation causing immunogenic cell death (ICD) of cancer cells, which triggers an anticancer immune response that is sustained while ICIs are given.

In ICD, a danger signal is released from the dying cell that induces inflammation, which eventually triggers an immune response directed at specific antigens of the dying cell. Although death by apoptosis does not trigger inflammation and immune responses, death by necrosis is often immunogenic. The danger signal consists of externalized calreticulin, heat shock protein 90, and secreted adenosine triphosphate, which attract phagocytes (5). Phagocytes internalize and process antigens of dead cells, while presenting tumor antigens to T lymphocytes, initiating a specific effector immune response against the cancer. Multiple tumor-specific antigens are known and well characterized, but, most importantly, the cancer genome atlas project, in which full genomes of thousands of cancers have been sequenced clearly, shows that cancers driven by carcinogens carry thousands of passenger mutations (6), some of which must code for neoantigens.

Different physical manipulations used to ablate tumors by interventional radiologists are associated with cancer cell death through necrosis. Various procedures differ in their potential to induce an inflammatory response and occasionally an antitumor response through ICD. Understanding ICD already guides the preparation of tumor vaccines (eg, for prostate cancer therapy) (7). In vivo studies that would indicate which type of ablation is optimally inducing immunogenic death to trigger an immune reaction are needed. In the era of immune checkpoint blockade, information about immune consequences of different ablative procedures has become very interesting because metastatic cancers, which so far have not benefited from ICIs, could potentially benefit from combining selected ablation procedures with different ICIs or combinations thereof.

In their article in this issue, Erinjeri et al (8) raise interesting questions. Because the trend of interleukin (IL)-6 elevation in the plasma within the first 48 hours after ablation parallels the trend of ICI sensitivity (ie, melanoma most sensitive, kidney cancer less sensitive, and lung cancer the least sensitive), it is possible that IL-6 plasma levels could act as surrogates for ICD. Erinjeri et al (8) also show that the plasma concentration of any of the measured cytokines (ie, IL-1α, IL-2, IL-6, IL-10, and tumor necrosis factor-α) were normalized within 1–5 weeks, indicating that ICIs should be given within 48 hours of an ablative procedure for the patient to benefit with regard to triggering a powerful anticancer immune response.

The combination of immunogenic death-inducing procedures with ICIs needs optimization to achieve cure in every patient. If surrogate markers of immunogenic death, such as cytokine concentrations measured in the study by Erinjeri et al (8), could be used, the path to cure of many solid tumors would be shortened.

REFERENCES