Immune checkpoint inhibitors have demonstrable clinical activity in various advanced malignancies. Avelumab—a human anti-programmed death-ligand 1 (anti-PD-L1) monoclonal antibody that inhibits signaling through the programmed death 1 (PD-1) immune checkpoint—has shown clinical activity in patients with recurrent or metastatic non-small cell lung cancer (NSCLC) (1), refractory metastatic urothelial carcinoma (mUC) (2), refractory metastatic Merkel cell carcinoma (mMCC) (3,4), and other advanced cancers. Avelumab has been approved by the United States Food and Drug Administration for the treatment of patients with mMCC and locally advanced or mUC who have disease progression during or following platinum-containing chemotherapy (5). In addition, the European Medicines Agency Committee for Medicinal Products for Human Use has recommended its approval for the treatment of patients with mMCC.

Infusion-related reactions (IRRs) are a commonly reported side effect of treatment with monoclonal antibody therapies (e.g., trastuzumab, rituximab, cetuximab) and chemotherapy (e.g., taxanes) (6,7). In addition to avelumab, other checkpoint inhibitors are also associated with IRRs during treatment, and their incidence and management are included in the prescribing information for each of these medications (5,8-11). The majority of IRRs associated with avelumab are low grade (i.e., grade 1/2), do not result in treatment discontinuation, and have very straightforward management (1,3,12). Most reactions are mild, occur during drug administration or shortly thereafter, and have been rarely observed after the first 4 infusions of avelumab, with the majority occurring at initial infusion (12). Following grade 1 or 2 events, IRRs can be managed by slowing the infusion rate or interrupting and restarting at a temporarily slower rate—but not reducing the overall dose of avelumab—and by administering supportive medications, allowing oncologists to continue giving avelumab to patients who have advanced malignancies and limited treatment options. Using a premedication regimen of antihistamine and acetaminophen prior to the first 4 infusions is recommended in the avelumab prescribing information and is based on experience from clinical trials, in which most patients received diphenhydramine, an H1-antihistamine (5). Clinical practice experience suggests that other selective H1-receptor antagonists, such as fexofenadine or cetirizine, may also be effective and have a less sedating effect. In some cases, premedication with low-dose corticosteroids has also been used to effectively mitigate the incidence of IRRs (6). In our clinics, we have successfully employed such measures while treating patients with avelumab and with other checkpoint inhibitors. Experienced oncology physicians and nurses observing patients during avelumab infusions are well prepared to
promptly and efficiently recognize and manage IRRs.

Cross-study comparisons of IRRs should be interpreted with caution. In Gulley et al. (1), IRRs were identified using a composite definition that included IRR, drug hypersensitivity, and anaphylactic reaction—or related symptoms, including fever, chills, rigors, pyrexia, and flushing—that occurred within 1 day of infusion and resolved within 2 days of infusion. Other studies used in the comparison made by Tanvetyanon (13) articulate no clear definition of IRR (14) or apply one limited to 1 or 2 adverse-event terms, including hypersensitivity/infusion reaction (15), infusion reaction (16), or IRR (8). In addition, study design, dosing schedules, and patient characteristics vary considerably in the studies cited by Tanvetyanon, which included trials in NSCLC and mUC (1,8,11,15,16). The expanded, comprehensive definition of an IRR in the large, multicohort JAVELIN Solid Tumor study (NCT01772004) and other clinical trials of avelumab has been used consistently, and the data show that, regardless of tumor type, IRRs associated with avelumab treatment are mostly temporary, low grade, and rarely lead to permanent discontinuation (in up to 2.0% of patients) (5,12).

Avelumab is unique among approved PD-1 or PD-L1 immune checkpoint inhibitors in that it retains an intact Fc region and is capable of inducing antibody-dependent cell-mediated cytotoxicity (ADCC), as shown in in vitro studies of human cells (17-19). Although the overall contribution of ADCC to the clinical activity of avelumab is still being investigated, ongoing phase 1/2 combination studies will investigate its potential to improve the clinical activity of avelumab monotherapy in various tumor types.

Differences in disease (i.e., NSCLC vs. mUC), number of prior therapies, eligibility criteria, stratification, dosing schedule, and, most importantly, the definition of an IRR make drawing conclusions from interstudy comparisons a challenge. The compelling clinical activity of avelumab in these difficult-to-treat diseases far outweighs the modest inconvenience of low-grade, easy-to-manage IRRs. Oncologists and oncology nurses experienced with administering chemotherapy and targeted therapies to patients with cancer are well positioned to use avelumab and other approved immune checkpoint inhibitors safely and appropriately in the clinical setting.

Acknowledgements

Medical writing assistance was provided by ClinicalThinking, Inc, and funded by Merck KgaA, Darmstadt, Germany.

Footnote

Conflicts of Interest: J. L. G.’s institution has received research funding from EMD Serono, Bavarian Nordic, and Celgene, and reagents from Astellas Medivation. K. K. reports consultancy for Synta, AstraZeneca, Clovis Oncology, ARIAD, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech/Roche, Lilly, and G1 Therapeutics; reimbursement for travel and accommodations from AstraZeneca, Roche, Bristol-Myers Squibb, ARIAD, Genentech/Roche, and Merck KgaA, Darmstadt, Germany; author royalties for UpToDate; received honoraria from Roche, Bristol-Myers Squibb, and Merck KgaA, Darmstadt, Germany; K. K.’s institution received research funding from Millenium, Novartis, EMD Serono, Lilly, Genentech, AbbVie, Gilead Sciences, Celgene, Five Prime Therapeutics, and Transgene.

References