Use and Toxicity of Checkpoint Inhibitors for Solid Tumor Treatment in a Veteran Population

Sara E. Gordon, PharmD, BCOP; William E. Bryan III, PharmD, BCPS; and Julia M. Hammond, PharmD, BCOP

Background: New immunotherapy agents have provided additional options for the treatment of a variety of malignancies, including the programmed death 1 (PD-1) protein inhibitors nivolumab and pembrolizumab. Initial dosing was based on patient weight, but subsequent studies supported fixed dosing, thereby prompting a change in US Food and Drug Administration-approved dosing. Depending on patient weight, one dosing strategy may be more cost-effective than another; thereby, a combination of dosing strategies may be beneficial for institutions. While these agents have been shown to be efficacious, they have been associated with immune-related adverse events (IrAEs). The purpose of this study was to determine the dosing strategy used and identify actual and potential cost savings, as well as to determine the incidence of hypothyroidism with PD-1 inhibitors in patients of the US Department of Veterans Affairs (VA).

Methods: This was a retrospective chart review of VA patients who received a PD-1 inhibitor for the treatment of a solid tumor between January 2015 and July 2017. Data were collected from the VA Corporate Data Warehouse through the VA Informatics and Computing Infrastructure. The dosing strategy for a PD-1 inhibitor was categorized into weight-based vs fixed-dosing where possible and used to identify actual and potential cost-savings opportunities. Thyroid laboratory values and levothyroxine prescriptions were evaluated to determine the overall incidence of the prespecified IrAEs. Descriptive statistics were used for primary and secondary outcomes.

Results: Nivolumab was the primary PD-1 inhibitor used for solid tumor treatment. Both nivolumab and pembrolizumab were primarily dosed based on patient weight. Nivolumab orders resulted in $8,514,300 estimated actual cost savings with $5,591,250 estimated missed cost savings identified. Of the patients who received nivolumab, 3249 patients were evaluated for thyroid dysfunction; 514 (15.8%) developed primary hypothyroidism based on laboratory values and levothyroxine prescription data.

Conclusions: Utilization of a combination of both weight-based and fixed-dosing strategies for nivolumab has the potential for cost savings, thereby benefiting the health care institution. The incidence of IrAEs identified among patients who received PD-1 inhibitor within the VA health care system was similar to the incidences reported in published literature. This further supports recommendations for close IrAE monitoring and treatment.

Sara Gordon is a Clinical Pharmacy Specialist, Hematology/Oncology in the Pharmacy Service at Veterans Affairs Northeast Ohio Healthcare System in Cleveland. **William Bryan** is a Clinical Pharmacy Specialist, Geriatrics, and **Julia Hammond** is a Clinical Pharmacy Specialist, Hematology/Oncology, both at Durham Veterans Affairs Health Care System in North Carolina.
Correspondence: Sara Gordon (sara.gordon@va.gov)

Fed Pract. 2021;8 (suppl 3). Published online August 16. doi:10.12788/fp.0164

Due to the high cost of newer chemotherapy agents, institutions search for strategies to minimize drug cost and drug waste. Programmed death-1 (PD-1) inhibitors, nivolumab and pembrolizumab, are commonly used in the treatment of solid tumors; however, the agents cost thousands of dollars per dose. Nivolumab and pembrolizumab were initially approved using weight-based dosing, but package labeling for both agents now includes fixed dosing.[1,2] A combination of these 2 dosing strategies could be used by institutions depending on individual patient's weight to maximize cost savings, minimize drug waste, and maintain safety and efficacy of PD-1 inhibitors. Irrespective of dosing strategy, the development of immune-related adverse events (IrAEs) has been demonstrated with PD-1 inhibitors as a result of the mechanism of action.

PD-1 expression suppresses T cell activity to prevent the development of autoimmunity; however, this is also a mechanism in which tumor cells can evade the host immune system.[3-5] Binding of PD-1 and programmed death-ligand 1 (PD-L1) suppresses T cell activity, whereas the inhibition of PD-1 and PD-L1 results in T cell activation.[4,5] Increased T cell activity elicits the anticancer effect, but also contributes to the development of IrAEs.[4,5] Hypothyroidism is one of the most common IrAEs, with a reported incidence of 9% with nivolumab therapy and 8.5% with pembrolizumab.[1,2]

Data from the US Department of Veterans Affairs (VA) medical centers is stored in the centralized Corporate Data Warehouse (CDW). VA researchers can obtain approval to use CDW data, which allows for large scale retrospective review of veterans who have received care at VA medical centers (VAMCs). This study aimed to describe the PD-1 inhibitor dosing used within VAMCs and identify actual and potential cost savings. Due to the frequency of immune-mediated hypothyroidism and objective data that can be obtained from CDW reports, the study estimated the incidence of immune-mediated hypothyroidism within the veteran population as a safety outcome.

BACKGROUND

The US Food and Drug Administration (FDA) initially approved dosing for IV nivolumab at 3 mg/kg of patient body weight every 2 weeks and for IV pembrolizumab 2 mg/kg of

patient body weight every 3 weeks.[1,2] Subsequent pharmacokinetic studies found that these agents have similar exposure and efficacy with fixed doses of nivolumab 240 mg IV every 2 weeks and pembrolizumab 200 mg IV every 3 weeks; in 2016, FDA labeling shifted from weight-based dosing to fixed dosing for most solid tumor indications.[6-9] Depending on patient weight, a combination of weight-based and fixed dosing could be used by institutions to maximize cost-savings opportunities, minimize drug waste, and maintain clinical efficacy with PD-1 inhibitors. For example, a patient initiating nivolumab who weighs 80 kg would receive 240 mg for both weight-based (3 mg/kg x 80 kg = 240 mg) and fixed dosing; therefore, no cost-savings opportunities would be available. However, for a patient who weighs ≤ 73.3 kg, it would be more cost-effective to use weight-based dosing vs the fixed dose. Since nivolumab is available in 40-mg, 100-mg, and 240-mg vials with similar unit prices, a combination of vial sizes could be used to minimize drug waste. Alternatively, for a patient who weighs ≥ 86.7 kg, it would be more cost-effective to administer the fixed, 240 mg dose when compared with the weight-based dose. Pembrolizumab is available only in a 100-mg vial; therefore, weight-based dosing may result in drug waste.

IrAEs can be seen with PD-1 inhibitors due to increased T cell activity, which is independent of dosing strategy and can affect any organ system. However, immune-mediated hypothyroidism has been commonly seen with PD-1 inhibitors. For patients with immune-mediated hypothyroidism, levothyroxine can be considered for asymptomatic patients with thyroid-stimulating hormone (TSH) > 10 uIU/mL with normal thyroxine (T4), or patients with clinical primary hypothyroidism (TSH > 10 uIU/mL with low free T4 and clinical symptoms). Additionally, since hypothyroidism usually follows immunotherapy induced thyrotoxicosis, thyroid function tests should be monitored and levothyroxine initiated if TSH is > 10 uIU/mL for these patients.[10,11]

Hypothyroidism also can be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events. Hypothyroidism is considered grade 1 when hypothyroidism is demonstrated through clinical or diagnostic observations only and the patient is asymptomatic and no intervention needed. Grade 2 occurs when the patient is symptomatic and limits instrumental activities of daily living (ADLs), prompting thyroid replacement therapy. In grade 3, patients experience severe symptoms that restrict self-care ADLs, and hospitalization is indicated. Grade 4 has life-threatening consequences, and urgent intervention is indicated. Grade 5 results in the death of the patient.[12]

TABLE 1 Programmed Death-1 Inhibitor Dosing Strategies

Dosing Strategies	Nivolumab, No. (%) (n = 23,478)	Pembrolizumab, No. (%) (n = 5309)
Weight-based	11,794 (50)	2599 (49)
Fixed	6546 (28)	1940 (37)
Converging	5138 (22)	770 (14)

Electronic health records (EHRs) of veterans who receive care at a VAMC are stored in CDW and available through the VA Informatics and Computing Infrastructure (VINCI), which provides access to data while ensuring veterans' privacy and data security. This feature of the VA EHR allows for analysis of data across the VA health care system, and larger data sets can be used for retrospective chart reviews.

Using reports from CDW, the primary objective of this study was to describe the dosing strategy used for PD-1 inhibitors, and the primary safety outcome was to determine the incidence of immune-mediated hypothyroidism. The secondary objective was to estimate potential cost-savings opportunities using a combination of PD-1 inhibitor dosing strategies.

METHODS

This was a retrospective study including data stored in CDW. The study was approved by the Durham VA Health Care System Institutional Review Board and VINCI/Data Access request tracker. Data were limited to nivolumab and pembrolizumab because they received earlier FDA approval, had multiple solid tumor indications, and 2 FDA-approved dosing strategies. The incidence of IrAEs was limited to hypothyroidism, which could be objectively verified with laboratory monitoring of thyroid function tests, including TSH, free or total T4, and triiodothyronine (T3), all of which were available in CDW data. Additionally, most patients with hypothyroidism initiate treatment with levothyroxine. Prescription refill history could also be retrieved using CDW reports.

TABLE 2 Estimated Actual and Potential Cost Savings for Nivolumab Orders

Nivolumab Order Periods	No.	Actual Cost Savings, $	Potential Cost Savings, $
January 1, 2015 to July 1, 2017	23478	8,514,300	5,591,250
September 1, 2016 to July 1, 2017	8013	5,198,570	2,907,180

TABLE 3 Levothyroxine Prescriptions During PD-1 Inhibitor Therapy (n = 3249)

Levothyroxine Prescription Initiations	Patients, No. (%)
Prior therapy	274 (8.4)
Continuation of previous dose	152 (4.6)
Dose increase	91 (2.8)
During therapy	187 (5.7)

Abbreviation: PD-1, programmed death-1.

Hypothyroidism was defined as T4 below lower limit of normal (LLN), TSH above upper limit of normal (ULN), or any increase in levothyroxine dosage. Patients were excluded if they received PD-1 inhibitor for an indication other than solid tumor treatment, such as hematologic malignancy, or if dosing did not follow weight-based or fixed-dosing strategies, such as nivolumab 1 mg/kg when used in combination with ipilimumab, or pembrolizumab 10 mg/kg. The primary endpoint was the percentage of orders for each dosing strategy, and the primary safety outcome was the incidence of immune-mediated hypothyroidism. Secondary endpoints included estimated cost savings and cost-savings opportunities through nivolumab dose rounding and incidence of levothyroxine initiation or dose change. Descriptive statistics were used for the primary and secondary endpoints.

A report in CDW identified patients who received a dose of nivolumab or pembrolizumab between January 1, 2015 and July 1, 2017 at any VAMC. The CDW report obtained weight at time of PD-1 inhibitor therapy initiation, dose of PD-1 inhibitor given, administration date of PD-1 inhibitor, and VA site. Depending on PD-1 inhibitor administered, weight in kg was multiplied by 3 mg/kg or 2 mg/kg to obtain patient's anticipated weight-based nivolumab and pembrolizumab dose, respectively. The calculated weight-based dose, fixed dose, and administered dose were compared to infer dosing strategy used at the time of ordering. If the patient's weight-based dose was within 10% of the fixed dose, the order was categorized as converging because the doses were too similar to determine which dosing strategy was intended.

After determination of dosing strategy, the nivolumab orders were evaluated for actual vs missed cost savings. The cost-savings evaluation included only nivolumab orders because nivolumab is available in a 40-mg, 100-mg, and 240-mg vials and, therefore, has more potential for dose-rounding opportunities with minimal drug waste compared with pembrolizumab, which is available only in a 100-mg vial. Actual cost savings included patients who weighed ≤ 73.3 kg and received nivolumab dose based on 3 mg/kg or patients who weighed ≥ 86.7 kg and received nivolumab 240 mg (fixed dose). Missed cost savings comprised patients who weighed ≤ 73.3 kg who received 240 mg nivolumab or patients who weighed ≥ 86.7 kg and received a nivolumab dose > 240 mg. The cost difference between the dose given and theoretical cost-effective dose was calculated to determine actual and potential cost savings. Converging orders were not included in the cost-savings analysis as the intended nivolumab dose could not be determined. An additional cost analysis of nivolumab orders prescribed between September 1, 2016 and July 1, 2017 was also performed because nivolumab fixed dosing was FDA-approved for most solid tumor indications in September 2016.

To determine the incidence of immune-mediated hypothyroidism for patients who received a dose of a PD-1 inhibitor at a VAMC, a CDW report with thyroid function laboratory values (TSH, T4, or T3), including reference range values based on specific VA site, and levothyroxine prescriptions issued during PD-1 inhibitor therapy was obtained. A patient was considered to have experienced immune-mediated hypothyroidism if the patient's laboratory values demonstrated T4 below the LLN, TSH above the ULN, or if the medication fill history demonstrated levothyroxine initiation or a levothyroxine dose increase.

RESULTS

The CDW report identified 32,769 total PD-1 inhibitor orders. There were 3982 orders that did not meet inclusion criteria or inadequate data were obtained with CDW report and were excluded (Figure). The remaining 28,787 PD-1 inhibitor orders were evaluated for actual or missed cost savings. The distribution of dosing strategies can be found in Table 1.

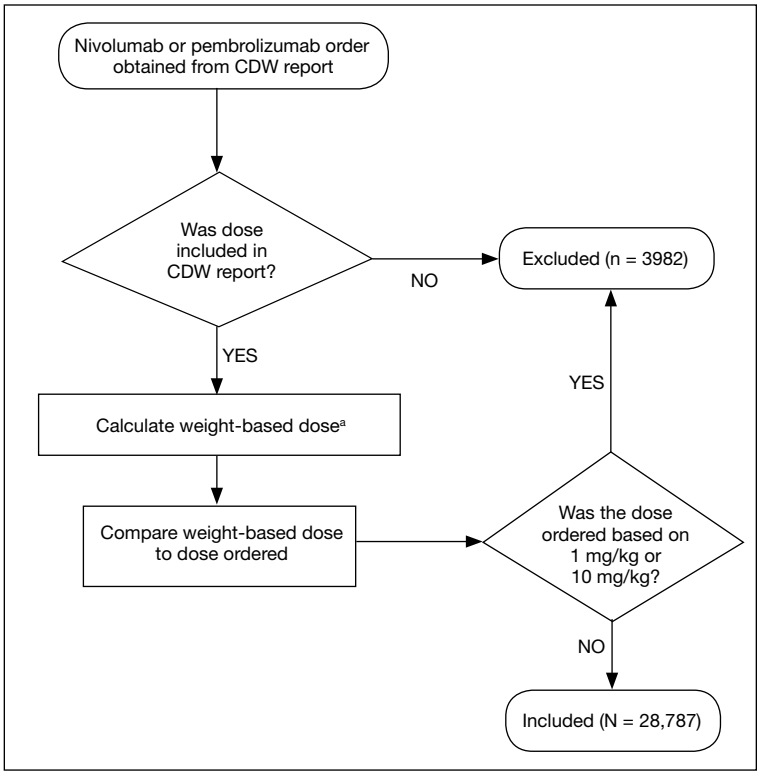
Nivolumab accounted for 81.5% of all PD-1 inhibitor orders. Using the most cost-effective nivolumab dosing, the actual cost savings was estimated to be $8,514,300 with potential additional $5,591,250 of missed cost-savings opportunities. There were 8013 nivolumab orders written between September 1, 2016 and July 1, 2017. Cost-effective dosing was used in 4687 of these orders, which accounted for a cost savings of $5,198,570. The remaining 3326 orders had a missed cost-savings opportunity, which accounted for an additional $2,907,180 potential cost savings (Table 2).

PD-1 inhibitors were used for the treatment of 3249 unique patients. Based on abnormal thyroid function tests and levothyroxine initiation or dose increase, it is estimated that 514 (15.8%) patients experienced hypothyroidism during PD-1 inhibitor therapy. However, prior to PD-1 inhibitor therapy, 274 patients were receiving levothyroxine, suggesting baseline thyroid dysfunction. Of these patients, 152 (55.5%) patients maintained the same levothyroxine dose during PD-1 inhibitor therapy, but 91 (33.2%) required a levothyroxine dose increase. There were 187 patients who initiated levothyroxine during PD-1 inhibitor therapy (Table 3).

DISCUSSION

Changes in FDA-approved dosing for PD-1 inhibitors allowed a combination of dosing strategies. Depending on patient weight, a weight-based or fixed-dosing strategy can be used to reduce drug cost while maintaining equivalent efficacy. This study evaluated use of dose rounding for PD-1 inhibitors within the VA health care system to identify actual and potential cost savings. To our knowledge, this is the first study to demonstrate cost savings through use of a combination of PD-1 inhibitor dosing strategies. Using CDW, researchers were able to review PD-1 dosing from all VAMCs and include a larger number of orders in a single retrospective study.

FIGURE Patient Inclusion and Exclusion



Abbreviation: CDW, Corporate Data Warehouse.
[a]Weight-based dose = weight (kg) × 3 mg/kg (nivolumab) or 2 mg/kg pembraolizumab

Nivolumab was the primary agent used within VAMCs. Depending on the indication, pembrolizumab requires PD-1 expression testing prior to its use in several solid tumor indications. Consequently, additional testing and patient eligibility is needed prior to use. Both PD-1 inhibitors were primarily dosed based on patient weight since this was the first FDA-approved dosing strategy. Nivolumab had more orders categorized as converging, which may be due to the therapeutic weight-based dose of 3 mg/kg for nivolumab vs 2 mg/kg for pembrolizumab. The calculated weight-based dose of nivolumab for an 80-kg patient is 240 mg, which also is the fixed dose. A 80-kg patient on pembrolizumab at 2 mg/kg would receive a 160-mg dose, whereas the fixed dose of pembrolizumab is 200 mg. Pembrolizumab is available only in a 100-mg vial, which limits opportunities for dose rounding without drug waste and could explain the higher amount of pembrolizumab orders in the fixed-dose category.

In this review of PD-1 inhibitor orders over approximately a 2.5-year study period, we

identified $8,514,300 estimated cost savings with $5,591,250 estimated missed cost savings. When looking at orders administered after FDA approval for nivolumab-fixed dosing in September 2016, there was substantial cost savings of $5,198,570 with the potential for an additional $2,907,180 missed cost savings. Due to lower drug acquisition costs within the VA health care system, there may be higher cost-savings opportunities within other health care systems.

Through review of abnormal thyroid laboratory values and levothyroxine initiation or dose changes, this study estimated the incidence of hypothyroidism in patients receiving PD-1 inhibitor therapy at the VA. The incidence of primary hypothyroidism identified in this study was slightly higher at 15.8% compared with the 8.5 to 9.0% incidence reported from clinical trials.[1,2] There are several reasons why the incidence of hypothyroidism appeared higher in this study. Abnormal laboratory values were not assessed for the degree of deviation from the reference range; any TSH above the ULN, T4 below the LLN, or levothyroxine dose increase was included as thyroid dysfunction in this review. There is also the potential for endogenous age-related thyroid fluctuation, and the development of hypothyroidism may not have been related to PD-1 inhibitor therapy. Within this patient population, 8.4% were receiving levothyroxine prior to PD-1 inhibitor initiation indicating baseline thyroid dysfunction, and it is unclear whether levothyroxine dose increases were due to PD-1 inhibitor or endogenous fluctuation.

Limitations

There are several limitations to acknowledge. The dosing strategy and apparent dose rounding was determined by investigator inference and may not accurately represent the intended dosing strategy. This study did not address efficacy of PD-1 inhibitor and dosing strategy; however, clinical trials have demonstrated equivalent efficacy to generate the change in FDA-approved dosing. Additionally, FDA approval for nivolumab fixed dosing was indication specific. Starting in September 2016, many solid tumor indications had fixed dosing approved, but this approval was not necessarily all encompassing.

While the use of CDW allowed for a greater number of PD-1 inhibitor orders to be included in retrospective review, there also were limitations of the CDW report. The patient weight was limited to weight at time of therapy initiation. Due to the potential for weight changes, nivolumab dosing may have seemed inappropriate to investigators, and thereby excluded. Based on data available from CDW reports, hypothyroidism could not be graded according to NCI Common Terminology Criteria for Adverse Events, and the incidence of clinically significant hypothyroidism could not be determined.

CONCLUSIONS

With increasing drug acquisition costs, particularly among antineoplastic agents, health care systems frequently seek out cost-savings opportunities. Using a combination of weight-based and fixed-dosing strategies for PD-1 inhibitors can be a mechanism to achieve cost-savings. Through the identification of the dosing strategy used for PD-1 inhibitors, we were able to identify and report instances for potential cost-savings opportunities among veterans treated within VA health care system. Use of CDW allows for data from all VAMCs to be evaluated in a single retrospective chart review, which allows for the inclusion of a larger sample size. This study identified a substantial cost savings for nivolumab through a combination of weight-based and fixed-dosing strategies. Due to the novel mechanism of action, ongoing real-world evaluation of adverse events and IrAEs is warranted.

Dosing strategies with nivolumab and pembrolizumab continue to evolve. In March 2018, nivolumab 480 mg IV every 4 weeks was FDA approved and in April 2020, pembrolizumab 400 mg IV every 6 weeks was FDA approved.[13,14] While the drug costs will remain the same, extended interval dosing strategies have cost avoidance such as fewer clinic appointments, resulting in decreased staffing costs and decreased patient travel. Additional studies will be needed to evaluate the cost and safety of the recently approved dosing strategies.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of *Federal Practitioner,* Frontline Medical Communications Inc., the US Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review the complete

prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

References

1. OPDIVO (nivolumab) injection, for intravenous infusion. Package Insert. Princeton, NJ: Bristol-Myers Squibb Company; 2014.
2. Keytruda (pembrolizumab) injection, for intravenous infusion. Package Insert. Whitehouse Station, NJ: Merck & Co, Inc; 2016.
3. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012;12(4):252-264. doi:10.1038/nrc3239
4. Yao H, Wang H, Li C, Fang J-Y, Xu J. Cancer cell-intrinsic PD-1 and implications in combinatorial immunotherapy. *Front Immunol.* 2018;9:1774. doi:10.3389/fimmu.2018.01774
5. Wang Y, Wang H, Yao H, Li C, Fang J-Y, Xu J. Regulation of PD-L1: emerging routes for targeting tumor immune evasion. *Front Pharmacol.* 2018;9:536. doi:10.3389/fphar.2018.00536
6. Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. *Clin Cancer Res*. 2015;21(19):4286-4293. doi:10.1158/1078-0432.CCR-14-2607
7. Zhao X, Suryawanshi S, Hruska M, et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. *Ann Oncol.* 2017;28(8):2002-2008. doi:10.1093/annonc/mdx235
8. Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. *J Immunother Cancer.* 2017;5:43. doi:10.1186/s40425-017-0242-5
9. US Food and Drug Administration. Modification of the dosage regimen for nivolumab. Updated September 15, 2016. Accessed July 8, 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/modification-dosage-regimen-nivolumab
10. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2018;36(17):1714-1768. doi:10.1200/JCO.2017.77.6385
11. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Management of immunotherapy-related toxicities. version 3.2021. Updated May 14, 2021. Accessed July 8, 2021. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
12. National Institutes of Health, National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 5.0. Updated November 17, 2017. Accessed July 8, 2021. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
13. Zhao X, Ivaturi V, Gopalakrishnan M, Shen J, et al. A model-based exposure-response (E-R) assessment of a nivolumab (NIVO) 4-weekly dosing schedule across multiple tumor types. Abstract presented at: American Association of Cancer Research Annual Meeting 2017; April 1-5, 2017; Washington, DC. doi:10.1158/1538-7445.AM2017-CT101
14. US Food and Drug Administration approves new dosing regimen for pembrolizumab. Updated April 29, 2020. Accessed July 8, 2021. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-new-dosing-regimen-pembrolizumab