Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Data Sources and Record Selection

We identified all instances of pembrolizumab administration in the VA between April 1, 2020 and August 24, 2021 using the VA Corporate Data Warehouse (CDW), an engine of patient-level VA electronic health record data (**eFigure 1**). We extracted pembrolizumab start and discontinuation dates, age, sex, ICD-9 and ICD-10 codes, and non-cancer Charlson comorbidity index (CCI) components.[1] Due to the classification of this study as non-research (by virtue of proceeding under a Memorandum of Understanding between the VA Center for Clinical Management and Research [Ann Arbor, MI] and the VA National Oncology Program [Durham, NC]), evaluation of individual electronic health records and physician notes was not pursued and certain elements were not extracted, specifically patient weight trajectory and albumin (two surrogates for performance and nutritional status/drug clearance) and date of death.

We sought to compare the efficacy of standard- and extended-interval pembrolizumab administered as a single-agent for two major reasons. First, administering pembrolizumab in combination with cytotoxic chemotherapy marginally constrains prescriber choice of pembrolizumab administration frequency because chemotherapy often requires administration at least every 3 or 4 weeks. Second, and related, comparing standard-interval against extended-interval pembrolizumab without excluding chemotherapy would enrich the standard-interval subpopulation for low or absent expression of programmed cell death ligand 1 (PD-L1) – a subpopulation with lower likelihood of long-term survival and therefore biasing *against* standard-interval. We therefore excluded records for which chemotherapies or targeted therapies *approved by the FDA for use in combination with pembrolizumab* were administered contemporaneously. Co-administration of the following drugs led to record exclusion: Carboplatin, cisplatin, etoposide, paclitaxel, nab-paclitaxel, pemetrexed, fluorouracil, axitinib, lenvatinib, and gemcitabine.

Rarely, pembrolizumab is administered at a weight-based dose (2 mg/kg) rather than conventional flat dosing (200 mg or 400 mg). Common reasons for weight-based dosing have been discussed previously.[2] We excluded records for which pembrolizumab dosing was neither 200 mg nor 400 mg to better assess the two FDA-approved flat-dosing options, extended- and standard-interval.

Due to the circumstances caused by the onset of the COVID-19 pandemic, the analysis of extended-interval pembrolizumab deviated from traditional norms. One weakness of extended-interval's FDA approval process was the use of a historical control in the KEYNOTE-555 cohort B trial. For the purposes of real-world comparative effectiveness, then, it was important to ensure that the two subpopulations were contemporaneous and that there had not been major changes to standard of care that could have been introduced during the study window. We therefore evaluated only those records for which incident single-agent pembrolizumab administration was begun after FDA approval of extended-interval dosing by excluding records that had received any pembrolizumab in the 100 days preceding April 1, 2020. To achieve sufficiently long follow-up, we excluded records for which incident pembrolizumab dose was after September 6, 2020. The remaining patients comprised the *First Dose Cohort – All Diseases* (**eFigure 1A**).

Another weakness of extended-interval's FDA approval process was the short follow-up period in the unplanned KEYNOTE-555 cohort B analysis: Subjects eligible for response assessment alone, rather than, for example, progression-free survival (PFS), were included in the analysis. Consequently, the unplanned analysis included n=44 out of an intended n=100 cohort size.[3] To provide longer-term follow-up more in line with conventional FDA standards, we excluded records in which the incident pembrolizumab was administered after September 6, 2020. That is, we sought longer-term data due to our chosen primary outcome measure for real-world comparative effectiveness analysis, time-to-treatment discontinuation (TTD), which estimates the lower bound of PFS.[4]

The remaining patients comprised the *All Diseases* cohort for comparative effectiveness analysis (**eFigure 2A**). Unlike a prospective, randomized, controlled trial, where an *a priori* decision to pool multiple tumor types may not be justifiable, there are a number of features of the current study and the informational milieu in which it occurs that make pooling into an *All Diseases* cohort justifiable and appropriate. First, the primary sites of disease are balanced between

the extended- and standard-interval subpopulations. Extended- and standard-interval are essentially pharmacokinetically and pharmacodynamically equivalent *across indications*. There are no meaningful within-dose pharmacokinetic differences in pembrolizumab *across indications*. Both extended- and standard-interval provide sufficient pembrolizumab to saturate target *across indications*. Finally, pembrolizumab's dose-response relationship is the same *across indications* (see full analysis in Canadian Agency for Drugs and Technology in Health, *CADTH Technology Review: Optimal Use 360 Report no. 25*, 2019; https://www.cadth.ca/sites/default/files/ou-tr/ho0008-dosing-timing-immuno-oncology-drugs.pdf).[5] More detailed analyses of each tumor types may be feasible in the future as the number of patients receiving extended-interval pembrolizumab increase.

Given the heterogeneity of treatment indication in the pembrolizumab recipient population – as well as the high likelihood that a randomized, controlled trial comprised of disparate diseases would be insufficient to achieve accelerated or full regulatory approval by FDA – we sought to compare the TTD of patients with non-small cell lung cancer (NSCLC), pembrolizumab's most common indication in VA. To isolate NSCLC patients, we excluded records that, in the 6 months prior to April 1, 2020, carried the diagnostic code(s) of cancer(s) other than NSCLC for which pembrolizumab is FDA-approved (**eTable 1**). We excluded small cell lung cancer by having excluded records with platinum and etoposide co-administration (chemotherapy exclusions as above). We also presume a degree of exclusion of *second-line* pembrolizumab due to the availability of second- and later-line small cell lung cancer treatments in VA (e.g., lurbinectedin, temozolomide, topotecan, etc.), and anecdotally high rates of utilization for the FDA-approved chemoimmunotherapy (anti-PD-L1) combinations in first-line small cell lung cancer treatment (e.g., platinum, etoposide, and either durvalumab or atezolizumab). The remaining patients – those whose *only* oncologic diagnostic code was lung cancer – comprised the *NSCLC* Cohort (**eFigure 2B**). Graphical representations of cohort derivation were generated using a publicly available web-based application.[6]

Primary Outcome Measures

In describing extended-interval's adoption, we evaluated the number and proportion of pembrolizumab prescriptions that employed the extended-interval in a variety of clinical scenarios. First, we sought to describe extended-interval in terms of "market share", specifically what proportion of 1) *all* pembrolizumab prescriptions during a given time interval and 2) all *incident* pembrolizumab prescriptions during a given time interval was comprised of extended-interval prescriptions. Second, we sought to understand how different dose intervals were employed over time in the VA, specifically by evaluating 1) whether, after a certain amount of time, prescribers transition from standard- to extended-interval and 2) whether prescribers who *start* pembrolizumab using extended-interval dosing ever transition to standard-interval (out of concern for efficacy, convenience, etc.). Descriptive statistics were generated in Stata version 16.0 (StataCorp; College Station, TX).

To evaluate the real-world comparative effectiveness of extended- and standard-interval, we employ time-to-treatment discontinuation (TTD), a real-world outcome measure readily available from drug prescription records, defined as the time from incident prescription to the end date of the final or most recent prescription. In the case of pembrolizumab, the end date of the final prescription was t+21 days for standard-interval and t+42 days for extended-interval. In NSCLC, and particularly in NSCLC treated with immune checkpoint inhibitor in the context of a clinical trial, TTD is strongly correlated with both PFS and overall survival.[4] Reference 4 provides additional information in Table 3 (row 5, columns 9-11): For immune checkpoint inhibitors in NSCLC, TTD is strongly correlated with PFS (r = 0.85), and the TTD-OS correlation (r=0.72) appears *stronger* than that of PFS-OS (r=0.63). TTD, in theory, captures drug discontinuations due to progression of disease, death, or intolerable adverse events, therefore estimating the lower bound of progression-free survival,[4] and insofar as prescribers initiate a therapy believing it to be efficacious and in the best interests of the patient, TTD is a pragmatic endpoint with a great degree of clinical relevance to the individual prescriber.

We perform our real-world comparative effectiveness analysis in a manner akin to intention-to-treat, by grouping patients according to the dosing interval associated with their first pembrolizumab dose. In real-world practice, for a patient to transition from standard- to extended-interval dosing in a shared decision-making context, he/she must have survived long enough and tolerated pembrolizumab well enough to merit broaching the transition topic. Therefore, excluding the subpopulation of patients who transition from standard- to extended-interval altogether would bias *against* the standard-interval group by removing patients who experience rapid progression, hyper-progression, or immune-related adverse events shortly after starting standard-interval dosing and, as a result, have short TTDs. Kaplan-Meier statistic and curves and Cox proportional hazards regression models of TTD for both *All Diseases* and *NSCLC* were generated in Stata version 16.0 (StataCorp; College Station, TX).

Secondary Outcome Measures

Assessing for Immune-Related Adverse Events (irAE)

It is important to assess whether extended-interval pembrolizumab confers an obviously higher rate of immune-related adverse events (irAE). Given data limitations with non-research operations activity and the inability to directly assess for irAE in our cohort, we chose to assess *new* prescriptions of the medications that would be used to treat irAE, focusing on levothyroxine for immune-mediated thyroiditis and prednisone for the multitude of other irAEs that require corticosteroid treatment (e.g., pneumonitis, dermatitis, myositis). First, we excluded patients in the cohort who had received prescriptions for either levothyroxine or prednisone in the 90 days prior to their first dose of pembrolizumab. 90 days was chosen to sufficiently *exclude* those patients who chronically require these medications while *not excluding* those patients who may have received corticosteroid at some point as a pre-medication. After applying these criteria, we interrogated the VA Corporate Data Warehouse (CDW) for incident medication prescriptions in our cohort using the following code in Stata:

Levothyroxine

```
select distinct b.NationalDrugSID,b.NationalFormularyName,c.DosageForm
into #drugsid
from cdwwork.dim.DrugNameWithoutDose as a
join cdwwork.dim.NationalDrug as b on a.DrugNameWithoutDoseSID=b.DrugNameWithoutDoseSID
join cdwwork.dim.DosageForm as c on c.DosageFormSID=b.DosageFormSID
where DrugNameWithoutDose='levothyroxine';
```

Prednisone

```
select distinct b.NationalDrugSID,b.NationalFormularyName,c.DosageForm
into #drugsid
from cdwwork.dim.DrugNameWithoutDose as a
join cdwwork.dim.NationalDrug as b on a.DrugNameWithoutDoseSID=b.DrugNameWithoutDoseSID
join cdwwork.dim.DosageForm as c on c.DosageFormSID=b.DosageFormSID
where DrugNameWithoutDose='prednisone';
```

Assessing Frequency of Monitoring

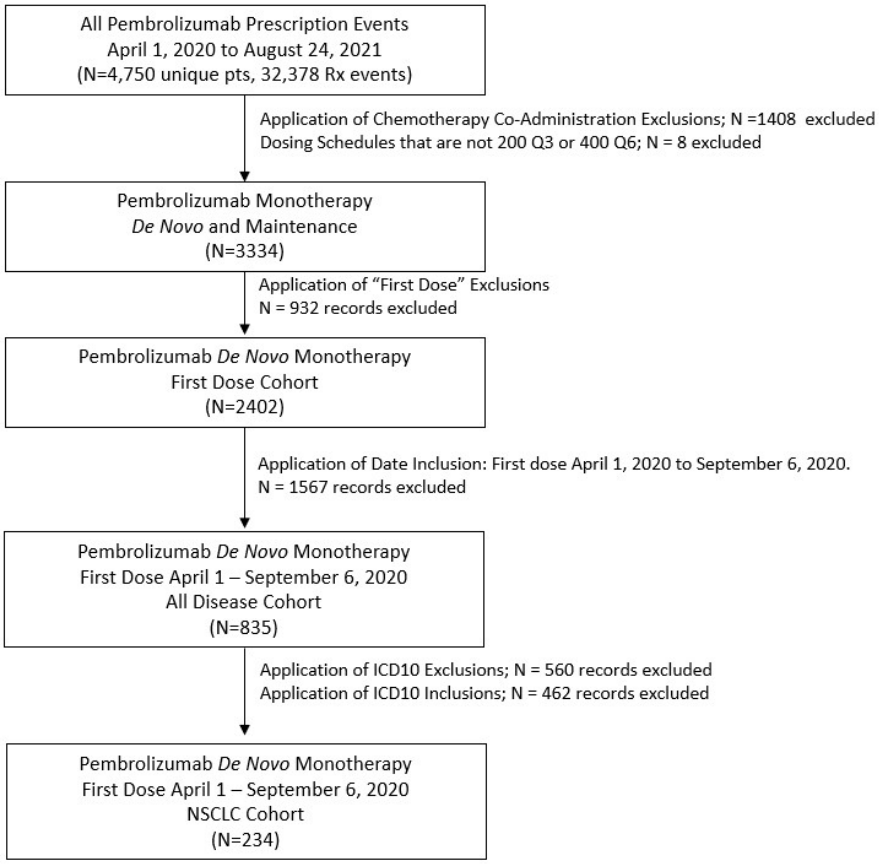
It is important to assess whether patients receiving standard-interval pembrolizumab are *more likely* to receive response assessment imaging than patients receiving extended-interval pembrolizumab. For each patient in our cohorts, we therefore assessed the number of computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) studies ordered for each patient *after* the date of pembrolizumab initiation. We used the following Current Procedural Terminology codes to do this:

CT: 70460, 70470, 70490, 70491, 70492, 71250, 71260, 71270, 74150, 74160, 74170, 74176, 74177, 74178

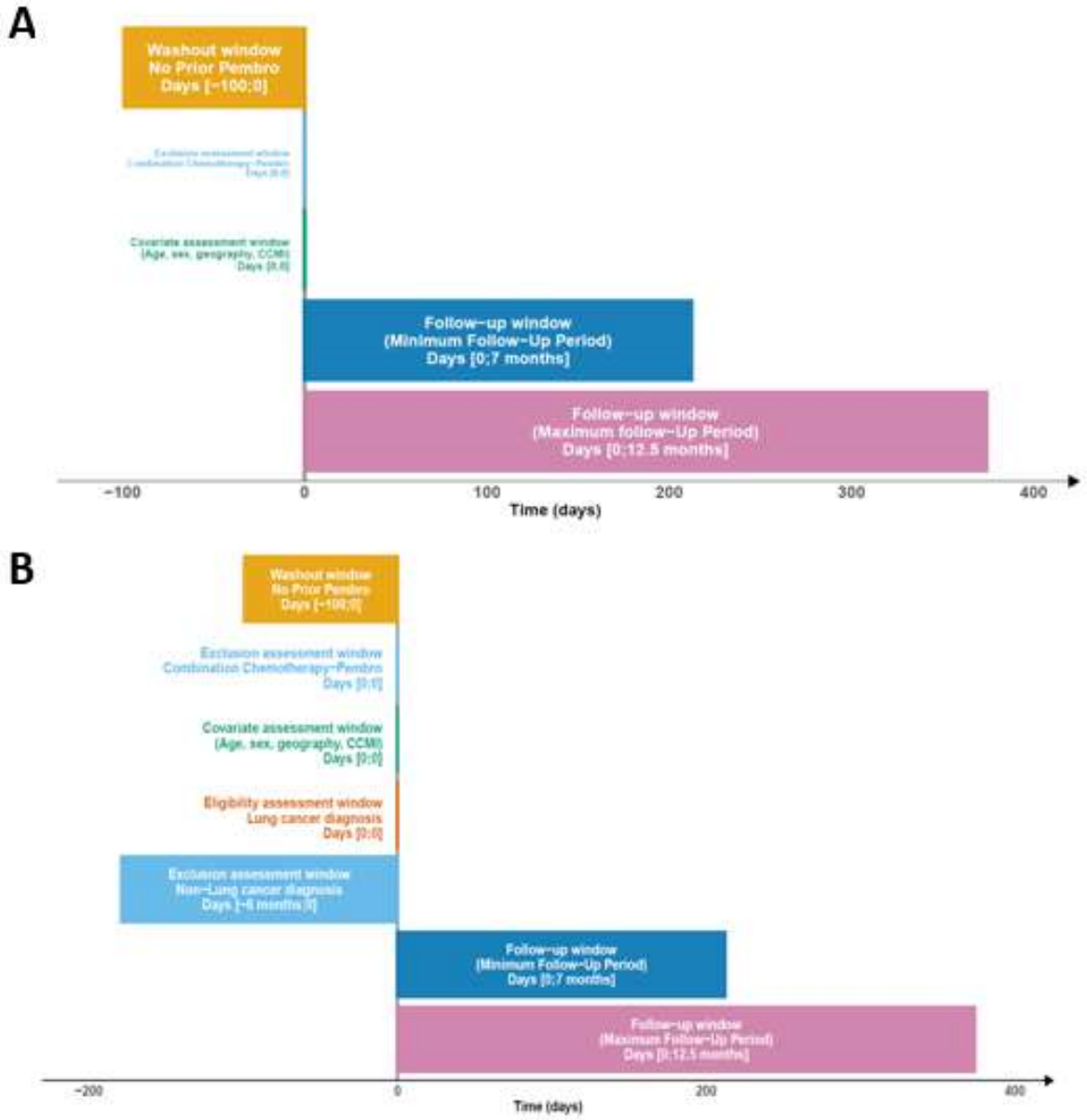
MRI: 70551, 70552, 70553

PET: 78814, 78815, 78816

eFigure 1. Flow of records through study.



eFigure 2. Derivation of the cohorts used in comparative effectiveness analysis. (A) All diseases cohort and (B) NSCLC cohort. Note that prior pembrolizumab led to exclusion from both cohorts. Note that in NSCLC (B), records were excluded if any of the exclusionary diagnostic codes in **eTable 1** were found. Figures were generated using publicly available software.[6]



eTable 1. Inclusionary and exclusionary ICD-9 and -10 codes for the NSCLC cohort.

Inclusions	
ICD10 code	**Diagnosis**
C34.xx	Lung cancer
C39.xx	Lung cancer
ICD9 code	**Diagnosis**
162.2	Lung cancer
162.3	Lung cancer
162.4	Lung cancer
162.5	Lung cancer
162.8	Lung cancer
162.9	Lung cancer
Exclusions	
ICD10 code	**Diagnosis**
C00.xx	Head and neck cancer
C01.xx	Head and neck cancer
C02.xx	Head and neck cancer
C03.xx	Head and neck cancer
C04.xx	Head and neck cancer
C05.xx	Head and neck cancer
C06.xx	Head and neck cancer
C07.xx	Head and neck cancer
C08.xx	Head and neck cancer
C09.xx	Head and neck cancer
C10.xx	Head and neck cancer
C11.xx	Head and neck cancer
C12.xx	Head and neck cancer
C13.xx	Head and neck cancer
C14.xx	Head and neck cancer
C15.xx	Gastroesophageal cancer
C16.xx	Gastroesophageal cancer
C18.xx	Colorectal cancer
C19.xx	Colorectal cancer
C20.xx	Colorectal cancer
C21.xx	Colorectal cancer
C22.xx	Hepatocellular carcinoma
C23.xx	Gallbladder cancer
C24.xx	Biliary tract unspecified
C30.xx	Nasal cavity cancer
C31.xx	Accessory sinus cancer
C32.xx	Laryngeal cancer
C37.xx	Thymic carcinoma/thymoma
C38.xx	Heart/mediastinum/pleura neoplasm
C43.xx	Melanoma
C44.xx	Other cutaneous skin cancer
C50.xx	Breast cancer
C53.xx	Cervical cancer
C54.xx	Endometrial carcinoma
C55.xx	Unspecified uterine cancer (possible miscoded endometrial)

C57.xx	Unspecified female organ cancer
C64.xx	Kidney cancer
C65.xx	Kidney cancer
C66.xx	Ureteral cancer (possibly urothelial)
C67.xx	Bladder cancer
C68.xx	Unspecified urinary organ cancer
C81.xx	Hodgkin lymphoma
C83.xx	Non-follicular (large B-cell) lymphoma
C85.xx	Unspecified types of non-Hodgkin lymphoma
C88.xx	Malignant immunoproliferative disease and other B-cell lymphomas
C4A.9	Merkel cell carcinoma

eTable 2. Time-to-treatment discontinuation of standard- and extended-interval pembrolizumab in the All Diseases cohort.

	Standard-Interval (N=534)	Standard-Interval → Extended-Interval (N=142)	Pooled Standard-Interval (N=676)	Extended-Interval (N=53)	Cohort (N=835)
Median Time-to-Treatment Discontinuation (days)	50	315	127.5	168	133
Total time on drug (days)	49	83	N/A	N/A	N/A
Time on originally prescribed dose (days)					

eTable 3. Time-to-treatment discontinuation of standard- and extended-interval pembrolizumab in the All Diseases Cohort, by primary site of disease.

	Median TTD (D), Standard-Interval	Median TTD (D), Extended-Interval
Primary Site		
Bladder	149	174.5
Kidney	148	216
Head and neck	129.5	104
Melanoma	165	293
Gastroesophageal	91	105.5
Colorectal	154	216
Hepatocellular	148	84
Ureteral	136	154

eTable 4. Incident prescriptions for levothyroxine and prednisone in the All Diseases Cohort.

	Standard-Interval	Extended-Interval	Cohort
Patients with New Levothyroxine Prescription (n, %)	84 (12.4%)	22 (13.8%)	106 (12.7%)
Patients with New Prednisone Prescription (n, %)	142 (21.0%)	32 (20.1%)	174 (20.8%)

eTable 5. Frequency of response assessment imaging ordering in the All Diseases Cohort. Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

	Standard-Interval	Extended-Interval	Cohort
# CT per Patient (mean +/- stdev)	2.02 (2.04)	1.82 (2.02)	1.99 (2.04)
# MRI per Patient (mean +/- stdev)	0.34 (0.83)	0.48 (0.96)	0.37 (0.86)
# PET per Patient (mean +/- stdev)	0.79 (1.36)	0.96 (1.30)	0.83 (1.35)

eTable 6. Time-to-treatment discontinuation of standard- and extended-interval pembrolizumab in the NSCLC cohort.

	Standard-Interval (N=151)	Standard-Interval → Extended-Interval (N=30)	Pooled Standard-Interval (N=181)	Extended-Interval (N=53)	Cohort (N=234)
Median Time-to-Treatment Discontinuation (days)	71	332	112	170	126
Total time on drug (days)	N/A	63	N/A	N/A	N/A
Time on originally prescribed dose (days)					

eTable 7. Incident prescriptions for levothyroxine and prednisone in the NSCLC Cohort.

	Standard-Interval	Extended-Interval	Cohort
Patients with New Levothyroxine Prescription (n, %)	12 (6.6%)	5 (9.4%)	17 (7.3%)
Patients with New Prednisone Prescription (n, %)	37 (20.4%)	13 (24.5%)	50 (21.4%)

eTable 8. Frequency of response assessment imaging ordering in the NSCLC Cohort. Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

	Standard-Interval	Extended-Interval	Cohort
# CT per Patient (mean +/- stdev)	1.91 (1.91)	1.74 (1.73)	1.87 (1.87)
# MRI per Patient (mean +/- stdev)	0.36 (0.73)	0.72 (1.25)	0.44 (0.88)
# PET per Patient (mean +/- stdev)	0.71 (1.23)	0.91 (1.29)	0.75 (1.24)

eReferences

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