MEDICAID EVIDENCE REVIEW AND COST INITIATIVE BRIEF

Pembrolizumab (Keytruda) for Cancer

OVERVIEW

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program estimates that 2 million people in the US were diagnosed with cancer in 2024, and that more than 600,000 people in the US died of cancer that same year.[1] While the median age at diagnosis is 67, 43% of those diagnosed with cancer are age 64 or younger.[2] As Medicaid covers a population primarily aged 64 or younger, coverage of cancer treatment is critical to Medicaid's population. The American Cancer Society estimates that 16.9% of those diagnosed with cancer in the US in 2019 had coverage from Medicaid.[3]

In 2014, the US Food and Drug Administration (FDA) gave pembrolizumab (branded as Keytruda) accelerated approval for the treatment of melanoma, a type of skin cancer.[4] Following this first approval, the drug's manufacturer has secured a combination of accelerated and traditional approvals from the FDA for over 40 cancer indications ranging from non–small cell lung cancer to breast cancer and colon cancer.

Pembrolizumab belongs to a class of cancer drugs known as immune checkpoint inhibitors (ICIs).[5,6]

MERCI Aims

The Medicaid Evidence and Review of Cost Initiative (MERCI) describes policy considerations for drugs approved by the US Food and Drug Administration (FDA) through the accelerated approval pathway. This brief provides information on:

- The estimated prevalence of target diagnoses (the accelerated approval drug's indication[s]) among Medicaid members;
- The clinical trial population used to support FDA approval, and how similar it is to Medicaid members overall; and
- Projected drug costs for state Medicaid programs, including a breakdown of state and federal funds using the Federal Medical Assistance Percentage (FMAP).

MERCI analyses include national and state-level data where available to inform budget and policy decisions by state and federal policymakers.

Since its first approval, the use of pembrolizumab among Medicaid members has increased steadily. In 2022, pembrolizumab ranked number 17 for highest overall total Medicaid spending for a drug at $706,795,740.[7] The drug, however, does have serious side effects that should be weighed against its potential to improve overall survival, which varies depending on the type of cancer being treated and its sensitivity to pembrolizumab's specific action as an ICI.

Which Types of Cancer Are the Most Common in the US?

Of the 2 million people in the US who are diagnosed with cancer each year, cancers of the breasts, lungs, colon, and rectum are amongst the most common and deadly cancers; collectively, cancers affecting these organs account for 36% of all new cases of cancer as well as 36% of all deaths caused by cancer of any type.[1]

What Is Pembrolizumab?

Pembrolizumab is a multi-indication biologic therapy for cancer and is the most widely used cancer drug for solid tumors.[8] In contrast to chemotherapy drugs, which directly target and kill cancer cells,[6,9] ICIs encourage the body's T cells (a type of immune cell) to kill cancer cells.[10] Pembrolizumab works by inhibiting a T cell checkpoint protein called programmed cell death protein 1 (PD-1).[5,6,11]

CANCER and PEMBROLIZUMAB

OVERVIEW

PREVALENCE

IN THE US

The National Cancer Institute estimates that 2 million people in the US are diagnosed with cancer each year

IN MEDICAID

24,692 beneficiaries had a claim for pembrolizumab between 2019 and 2021

PEMBROLIZUMAB FACTS

DRUG PRICE PER PATIENT

Approximately $200,000 per year

CURRENT NUMBER OF FDA-APPROVED INDICATIONS

40 unique cancer indications

FIRST FDA ACCELERATED APPROVAL DATE

September 2014: Unresectable or metastatic melanoma

FIRST FDA TRADITIONAL APPROVAL DATE

December 2015: Unresectable or metastatic melanoma

MEDICAID COST ESTIMATES

PROJECTED ANNUAL COST TO MEDICAID

$941.1 million, with $672.2 million coming from federal funds and $268.9 million from state funds; however, expenditures are expected to increase significantly if the manufacturer pursues its stated intent to increase the number of FDA-approved indications from 40 to 80 by 2028

Sources. Information sourced from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, IPD Analytics, FDA websites, and a Merck press release, unless otherwise referenced. Estimates of costs to Medicaid are based on our analysis presented in the sections about potential Medicaid spending on pembrolizumab.
Abbreviations. FDA: US Food and Drug Administration.

What Do Patients Experience When Their Cancer Is Treated With Pembrolizumab?

Patients treated with pembrolizumab typically receive an intravenous infusion in their arm every 3 weeks or every 6 weeks.[12,13] People who have a port (i.e., a surgically implanted venous access device commonly used for chemotherapy or frequent blood draws), may receive pembrolizumab via their port; however, a port is not required.[13]

Serious side effects from pembrolizumab are common.[11,12,14] Depending on the type of cancer, at least 20% of patients on pembrolizumab may experience liver toxicity or acute kidney injury.[12,14] Because it activates the body's own T cells, treatment with pembrolizumab can lead to the immune system attacking healthy cells and tissues throughout the body (i.e., autoimmunity).[6,12,15] These immune responses can lead to potentially fatal inflammation in any organ system.[6,10,12,14] Patients on ICIs may require emergency department visits,[16,17] emergency inpatient hospitalizations,[17,18] and intensive care unit admissions due to these immune reactions.[19,20]

The length of treatment with pembrolizumab depends on individual patient factors, including the type of cancer, how advanced the cancer is, whether the cancer improves or progresses after treatment with pembrolizumab, the type and severity of adverse reactions to pembrolizumab, and whether permanent discontinuation is required to mitigate potentially fatal adverse reactions to pembrolizumab.[6,12,21]

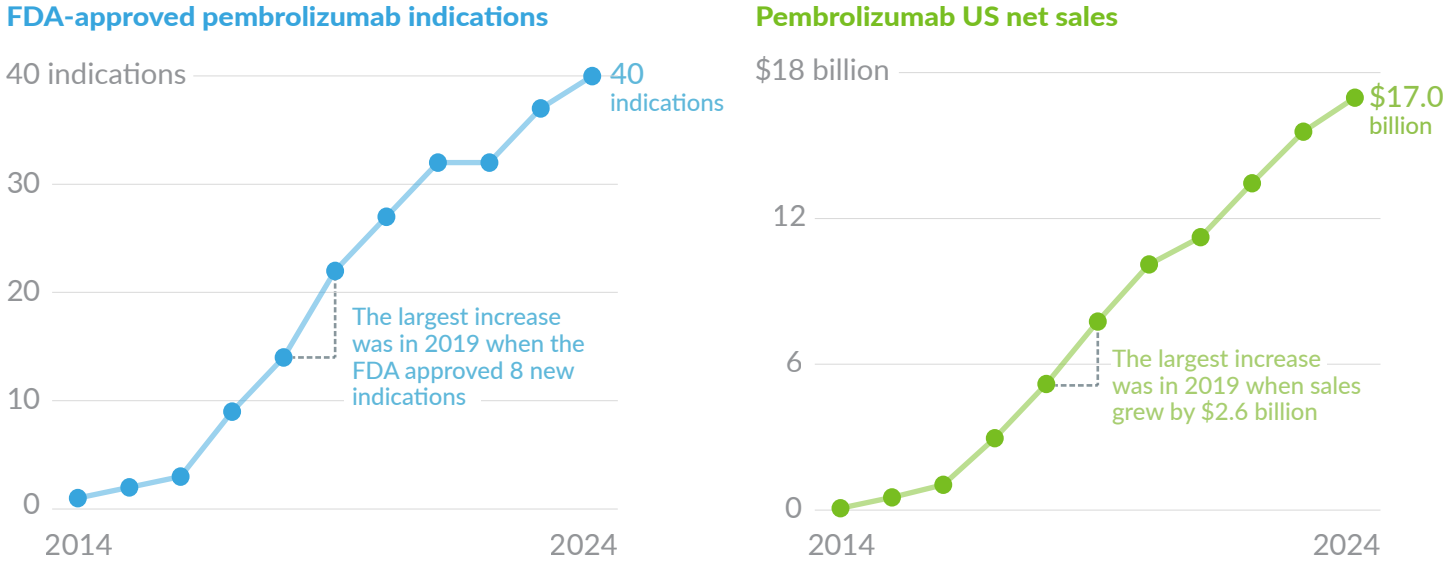
What Are the Costs of Treating Cancer With Pembrolizumab?

In the US, pembrolizumab (Keytruda) costs approximately US$200K per patient per year.[22] Since 2023, pembrolizumab has been the number 1 top-selling prescription drug globally.[23] In 2023 and 2024, net sales of pembrolizumab in the US were US$15.6 billion and US$17.0 billion, respectively.[24]

Exhibit 1 shows that pembrolizumab's US net sales have increased proportionally with the cumulative number of FDA-approved pembrolizumab indications over the last 10 years. As the number of FDA-approved indications have

EXHIBIT 1

Number of FDA-approved pembrolizumab indications and pembrolizumab US net sales (inflation-adjusted to 2024 US dollars) from 2014 to 2024



Sources. IPD Analytics and FDA approval letters.
Abbreviations. FDA: US Food and Drug Administration.

increased, annual US sales have increased by billions.

Pembrolizumab is forecast to remain the number 1 top-selling prescription drug until 2028.[23] By expanding the pembrolizumab pipeline, the manufacturer aims to receive more than 80 FDA-approved indications by 2028.[25] The manufacturer also aims to continue to get pembrolizumab into earlier lines of therapy and to create new treatments that combine pembrolizumab with other ICIs.[26]

PEMBROLIZUMAB Keytruda®

DRUG SUMMARY (1 of 2)

BASIC INFORMATION

DRUG CLASS
Immune checkpoint inhibitor (ICI)

MANUFACTURER
Merck Sharp & Dohme LLC

PRICE PER PATIENT
$196,591 per year

FDA APPROVAL

PATHWAY
40 unique cancer indications:
- 2 indications currently approved via accelerated approval
- 15 indications initially approved via accelerated approval then converted to traditional approval
- 23 indications initially approved via traditional approval

PRESCRIBING LABEL
https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s172lbl.pdf

APPROVED INDICATION(S)

For 40 unique indications that include the following cancers[a]:
- Biliary tract cancer
- Cervical cancer
- Classical Hodgkin lymphoma
- Colorectal cancer
- Cutaneous squamous cell carcinoma
- Endometrial carcinoma
- Esophageal cancer
- Gastric cancer
- Head and neck squamous cell cancer
- Hepatocellular carcinoma
- Malignant pleural mesothelioma
- Melanoma
- Merkel cell carcinoma
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors
- Non–small cell lung cancer (NSCLC)
- Primary mediastinal large B-cell lymphoma (PMBCL)
- Renal cell carcinoma
- Triple-negative breast cancer (TNBC)
- Tumor mutational burden-high (TMB-H) cancer
- Urothelial cancer

DOSING

ROUTE Intravenous (IV)

FORMULATIONS 100 mg/4 mL (25 mg/mL) solution in a single-dose vial

Sources. IPD Analytics and the FDA.
Notes. [a]See prescribing label for detailed indications.
Abbreviations. FDA: US Food and Drug Administration.

PEMBROLIZUMAB Keytruda®

DRUG SUMMARY (2 of 2)

SAFETY

BOXED WARNINGS None

PRECAUTIONS

Immune-mediated adverse reactions: may be severe or fatal, can occur in any organ system or tissue. Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. Withhold or permanently discontinue based on severity and type of reaction.

Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue Keytruda based on the severity of reaction.

Complications of allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective method of contraception.

ADVERSE REACTIONS

Most common (reported in ≥ 20% of patients): weight loss, fatigue/weakness, insomnia, fever, bleeding episodes (hemorrhagic events), anemia, low neutrophil counts, low platelet counts, liver toxicity, nausea, vomiting, decreased appetite, sore mouth/mucosal inflammation, diarrhea, constipation, musculoskeletal disorders, musculoskeletal pain, abdominal pain, shortness of breath, high blood pressure, headache, peripheral neuropathy, hair loss, hand-foot syndrome, rash, itching, cough, abnormal voice (dysphonia), high protein in the urine, urinary tract infection, acute kidney injury, and hypothyroidism.

Sources. IPD Analytics and the FDA.
Abbreviations. FDA: US Food and Drug Administration; HSCT: hematopoietic stem cell transplantations; PD-1: programmed cell death protein 1; PDL-1: programmed cell death ligand 1.

DRUG INFORMATION

Pembrolizumab was initially granted FDA accelerated approval as a treatment for melanoma, a type of skin cancer, in 2014.[4,27] The accelerated approval for melanoma was based on 2 intermediate clinical endpoints: tumor response rate and durability of response.[27]

As a provision of accelerated approval for the first indication of melanoma, the FDA required the manufacturer to complete a confirmatory trial verifying the clinical benefit of pembrolizumab in participants with melanoma; specifically, the trial needed to establish "the superiority of pembrolizumab over standard therapy."[4] In 2015, the manufacturer submitted the confirmatory trial results, and the FDA converted the first melanoma indication to traditional approval.[28]

From 2015 through 2024, the FDA approved pembrolizumab for over 40 additional unique cancer indications.[29-67] Seventeen of these indications were initially approved through the accelerated approval pathway[29-45]; of these, 13 have since been converted to traditional approval,[28,51,56,58,68-75] 2 remain approved via the accelerated pathway,[12] and 2 were withdrawn.[76,77] The withdrawals included the indication of small cell lung cancer and 1 of the 3 indications for gastric adenocarcinoma or gastroesophageal junction adenocarcinoma.[76,77] From 2017 through 2024, 24 of the indications were approved directly through the traditional

approval pathway.[46-67] Exhibit 2 illustrates the FDA approval status of pembrolizumab indications over time.

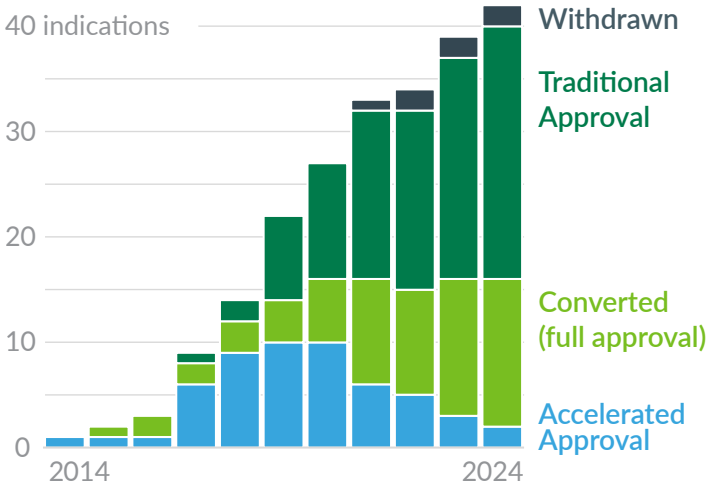
FINDINGS

What Evidence Was Used by the FDA to Approve the First Pembrolizumab Indication?

Exhibit 3 is a summary of the clinical trial[11,78] used to support the first pembrolizumab indication (treatment of unresectable or metastatic melanoma) approved through the accelerated approval pathway.

EXHIBIT 2

FDA approval status of pembrolizumab indications from 2014 to 2024



Abbreviations. FDA: US Food and Drug Administration

EXHIBIT 3

Summary characteristics of the study used to support accelerated FDA approval of pembrolizumab

	KEYNOTE-001
Official title	Study of pembrolizumab (MK-3475) in participants with progressive locally advanced or metastatic carcinoma, melanoma, or non-small cell lung carcinoma (KEYNOTE-001)
ClinicalTrials.gov ID	NCT01295827
Study design	Open-label (unblinded) trial
Clinical trial phase	Phase 1
Study population description	1,260 adults with various solid tumor cancers, including cohort of 173 adults with advanced or unresectable melanoma whose disease had progressed after at least 2 ipilimumab doses
Patient status requirement	Study eligibility required resolution of all ipilimumab-related adverse events to Eastern Cooperative Oncology Group (ECOG) grade 0 to 1 was required
Intervention	Randomized (1:1) to pembrolizumab 2 mg/kg every 3 weeks or pembrolizumab 10 mg/kg every 3 weeks
Control	No comparator group
Study duration	Participants with melanoma were administered pembrolizumab every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed with repeat imaging. The median duration of exposure to pembrolizumab was 6.2 months.
Primary outcome used for accelerated approval	Tumor response rate and durability of response. (Note: At the time of Biologics License Application in February 2014, only "response rate" was specified.)
Study funding	Merck Sharp & Dohme LLC

Sources. This information is sourced from the trial publications and historical ClinicalTrials.gov trial registry records and may differ from the prescribing label.

EXHIBIT 4

Summary characteristics of the studies used to support traditional FDA approval of pembrolizumab for unresectable or metastatic melanoma

	KEYNOTE-002	KEYNOTE-006
Official title	Study of pembrolizumab (MK-3475) versus chemotherapy in participants with advanced melanoma (KEYNOTE-002)	Study to evaluate the safety and efficacy of two different dosing schedules of pembrolizumab (MK-3475) compared to ipilimumab in participants with advanced melanoma (KEYNOTE-006)
ClinicalTrials.gov ID	NCT01704287	NCT01866319
Study design	Randomized, open-label	Randomized, open-label
Clinical trial phase	Phase 2	Phase 3
Study population description	540 adults with unresectable stage III or stage IV melanoma whose cancer had progressed after ipilimumab	834 adults with unresectable stage III or metastatic melanoma
Performance status requirement	Eastern Cooperative Oncology Group (ECOG) grade 0 to 1 was required	Eastern Cooperative Oncology Group (ECOG) grade 0 to 1 was required
Study arms	3 study arms	3 study arms
Intervention	Pembrolizumab 2 mg/kg every 3 weeks, or pembrolizumab 10 mg/kg every 3 weeks	Pembrolizumab 10 mg/kg every 2 weeks, or pembrolizumab 10 mg/kg every 3 weeks, for up to approximately 24 months
Comparator	Investigator-choice chemotherapy: carboplatin, paclitaxel, dacarbazine, or temozolomide	Ipilimumab 3 mg/kg every 3 weeks for a total of 4 doses (up to approximately 3 months)
Primary endpoint(s) used for traditional approval	Progression-free survival and overall survival were co-primary endpoints	Progression-free survival and overall survival were co-primary endpoints
Trial funding	Merck Sharp & Dohme LLC	Merck Sharp & Dohme LLC

Sources. This information is sourced from the trial publications and ClinicalTrials.gov trial registry records and may differ from the prescribing label.

Why Did the FDA Grant Accelerated Approval of the First Pembrolizumab Indication?

The FDA considered results from the phase 1, open-label KEYNOTE-001 trial,[11,78] in which a cohort of 173 adults with advanced or unresectable melanoma were exposed to pembrolizumab for a median of 6.2 months.[27] The indication was approved based on tumor response rate and durability of response; an improvement in survival or disease-related symptoms had not been established.[27]

What Evidence Was Used to Convert the First Pembrolizumab Indication to Traditional Approval?

As part of the accelerated approval in 2014, the FDA required completion of a postmarketing trial with the following instructions: "Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of

pembrolizumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab."[4]

Exhibit 4 is a summary of the 2 clinical trials used to support the conversion of pembrolizumab to full approval for the treatment of unresectable or metastatic melanoma.[79-81]

Why Did the FDA Grant Traditional Approval of the First Pembrolizumab Indication?

The manufacturer submitted the results of 2 post-marketing trials to the FDA in 2015.[28,79] In the open-label KEYNOTE-002 study, 540 participants with melanoma (which had progressed after ipilimumab) were randomized to pembrolizumab or chemotherapy.[80,81] In the open-label KEYNOTE-006 study, 834 participants with melanoma (who had never received treatment with ipilimumab) were randomized to pembrolizumab or ipilimumab.[82,83] Ipilimumab is an FDA-approved ICI that targets cytotoxic T-lymphocyte associated protein 4 (CTLA-4), a different checkpoint protein than the one inhibited by pembrolizumab.[84]

The FDA review of the KEYNOTE-002 and KEYNOTE-006 studies was summarized in a peer-reviewed article authored by employees of the FDA Center for Drug Evaluation and Research (CDER).[79] Results of the KEYNOTE-002 study suggested that 6-month progression-free survival was improved in participants assigned to pembrolizumab compared with participants assigned to investigator-choice chemotherapy; 6-month progression-free survival was 34% in participants assigned to pembrolizumab 2 mg/kg, 38% in participants assigned to pembrolizumab 10 mg/kg, and 16% in participants randomized to chemotherapy.[79,80]

Results of the KEYNOTE-006 study suggested that 6-month progression-free survival and 12-month survival rates were improved in participants assigned to pembrolizumab compared with participants assigned to ipilimumab.[79,82] Estimated 6-month progression-free survival was 47% in

DATA METHODS SUMMARY

Researchers at the Center for Evidence-based Policy (Center) used Transformed Medicaid Statistical Information System (T-MSIS) analytic files from the Centers for Medicare & Medicaid Services (CMS) to identify Medicaid members who had at least 1 claim for pembrolizumab.

We identified Medicaid members aged 0 to 64 years with at least 1 pharmacy claim with a procedure code or National Drug Code (NDC) for pembrolizumab in the years 2019, 2020, and 2021. As our focus was Medicaid expenditures, we excluded members with evidence of dual enrollment (members with both Medicaid and Medicare), as dually eligible members also have pharmacy benefits under Medicare Part D. Using these criteria, data from Alabama and Utah were excluded as these states do not report dual-enrollment status. Other state-based analysis exclusions were determined based on recommendations from the CMS Data Quality Atlas, which reports state-specific data availability and completeness; we generally did not report data elements (e.g., race or ethnicity) for states identified as "unusable" or "high concern" data quality according to Data Quality Atlas.[86] Due to unusable data quality for procedure codes in institutional outpatient claims submitted in Illinois and New York, we excluded those 2 states from the analysis.

Our cost model estimated annual cost for the drug based on drug uptake and treatment patterns observed in the data, as well as average drug acquisition costs and statutorily required rebates. Refer to Appendix A for additional detail on how we conducted this study.

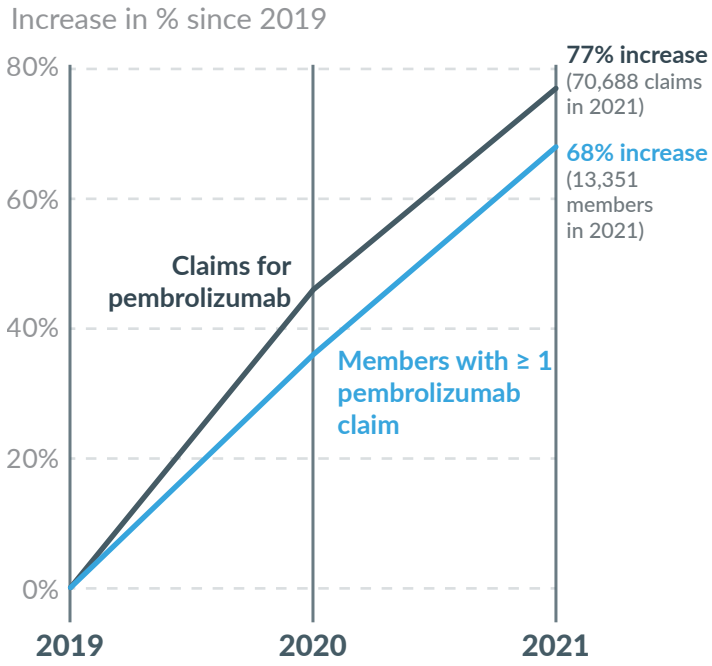
participants assigned to pembrolizumab 10 mg/kg every 2 weeks, 46% in participants assigned to pembrolizumab 10 mg/kg every 3 weeks, and 27% in participants assigned to ipilimumab; estimated 12-month survival rates were 74%, 68%, and 58%, respectively.[79,82]

How Many Indications Has the FDA Approved for Pembrolizumab?

The FDA has approved 42 total indications for pembrolizumab, 18 of them through the accelerated approval pathway.[4,29-31,33-45] Sixteen of the 18 indications approved through the accelerated pathway were approved based on tumor response rate and durability of response.[4,29-42,44,45] One of the indications for non–small cell lung cancer was approved through the accelerated pathway based on progression-free survival and tumor response rate[32] and 1 triple-negative breast cancer indication was approved through the accelerated pathway based only on progression-free survival.[43]

EXHIBIT 5

Percentage increase of (non-dually eligible) Medicaid members aged 0 to 64 years with at least 1 pembrolizumab claim and percentage increase of pembrolizumab claims, 2019 to 2021



Twenty-four of the 42 indications were directly approved through the traditional approval pathway.[46-67] For the FDA to approve cancer drugs and biologics through the traditional approval pathway, manufacturers can demonstrate *either* direct evidence of clinical benefit *or* improvement in a surrogate endpoint known to predict clinical benefit.[85]

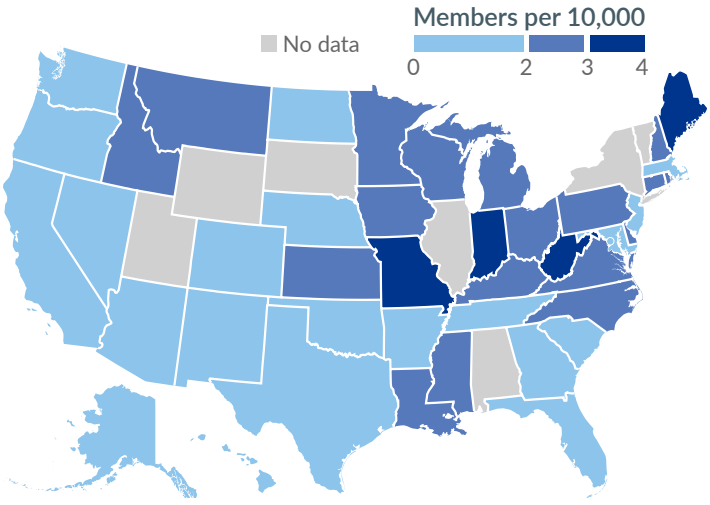
How Common Was Pembrolizumab Use Among Medicaid Members?

We identified 24,692 non–dually eligible Medicaid members aged 0 to 64 years with at least 1 claim for pembrolizumab from 2019 through 2021 (members in Alabama, Illinois, New York, and Utah were excluded due to limited data availability). These members had a total of 168,937 pharmacy or outpatient claims for pembrolizumab over 3 years.

Both the number of pembrolizumab claims and the number of Medicaid members with pembrolizumab claims increased over time (see Exhibit 5). The number of members with pembrolizumab claims varied among states, from 1 member per 10,000 members in New Mexico and Texas, to

EXHIBIT 6

Number of pembrolizumab claims per 10,000 members aged 0 to 64 years, by state, 2021



Note. Data not available for Alabama, Illinois, New York, and Utah, and suppressed (n < 11) for South Dakota, Vermont, and Wyoming.

3.6 members per 10,000 in Maine (see Exhibit 6, and Appendix B).

In 2021, pembrolizumab use was most common among Medicaid members with nonHispanic White, nonHispanic Black, and Hispanic races and ethnicities (61.2%, 19.3%, and 13.2%, respectively) and the majority of the members with claims were between the ages of 55 and 64 (60.4%; Exhibit 7).

Pembrolizumab-Indicated Cancers Among Medicaid Members With Pembrolizumab Claims

The prevalence of pembrolizumab-indicated cancers among members with pembrolizumab claims is reported in Exhibit 8. We identified the cancers for which pembrolizumab is indicated by hand-searching publicly-available prescribing

EXHIBIT 7

Characteristics of Medicaid members aged 0 to 64 with at least 1 pembrolizumab claim, 2021

	with at least 1 pembrolizumab claim[a]	%[c]	without pembrolizumab claim[a]	%[c]	without pembrolizumab-indicated cancer[a]	%[b]
Total members	*13,351*		*438,529*		*72,240,213*	
Age, in years						
0 to 44	2,057	15.4	121,319	27.7	61,255,204	84.8
45 to 54	3,225	24.2	108,071	24.6	5,458,232	7.6
55 to 64	8,069	60.4	209,139	47.7	4,827,789	6.7
Sex						
Female	6,844	51.8	290,910	66.7	38,807,492	54.2
Race and ethnicity						
American Indian/Alaska Native, non-Hispanic	117	1.2	4,159	1.3	829,461	1.6
Asian, non-Hispanic	371	3.8	14,953	4.6	2,218,356	4.2
Black, non-Hispanic	1,863	19.3	54,576	16.9	10,803,124	20.3
Hawaiian/Pacific Islander	42	< 1	1,488	< 1	269,060	< 1
Hispanic	1,280	13.2	66,245	20.5	16,502,256	31.0
White, non-Hispanic	5,913	61.2	178,766	55.4	21,867,014	41.1
Multiracial, non-Hispanic	41	< 1	1,387	< 1	536,048	1.0
Other race or ethnicity, non-Hispanic	41	< 1	1,173	< 1	190,741	< 1

Note. [a] Excludes dually eligible members and members in Alabama, Illinois, New York, and Utah. [b] Percentage of members with nonmissing data on demographic characteristics; 72.4% of members with at least 1 pembrolizumab claim and 73.7% of members without any pembrolizumab claims had nonmissing race or ethnicity data. For more detail see Appendix C.

EXHIBIT 8

Prevalence of pembrolizumab-indicated cancers in Medicaid members with pembrolizumab claims, 2021

Primary cancer type, with or without metastases	Medicaid members with at least 1 pembrolizumab claim: N	%
Total members[a]	*13,351*	-
Respiratory cancers	5,102	38.2
Multiple primary sites[b]	2,825	21.1
Breast cancer[c]	1,126	8.4
Cancers of the cervix	612	4.6
Cancers of the kidney	560	4.2
Colorectal cancers	437	3.3
Melanoma	426	3.9
Cancers of the endometrium	409	3.1
Secondary malignancies only[d]	388	2.9
Cancers of the bladder	246	1.8
Cancers of the esophagus	179	1.3

Note. [a] Excludes dually eligible members and members in Alabama, Illinois, New York, and Utah. [b]Includes members with multiple primary cancer types identified in outpatient, inpatient, or a combination of inpatient and outpatient claims; secondary malignancies (i.e., metastases at distance sites) were not calculated as a cancer type for this category. [c] Excludes ductal carcinoma in situ. [d] Includes members who only had claims for secondary malignancies (i.e., no primary cancer diagnosis codes were found).

label information and consulting with clinical experts. We then identified the *International Classification of Diseases, 10th Edition* (ICD-10) codes for each indication and aggregated them into clinically-meaningful categories using publicly available value sets from the Healthcare Cost and Utilization Project,[87] a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality, with input from clinical experts. Pembrolizumab-indicated cancers were identified in the year 2021 by the presence of either 1 inpatient or 2 outpatient claims over a 2-year lookback period. Categories are reported at the member-level and are mutually exclusive. Two identified indications were reliant upon tumor characteristics that were not specifically identifiable in administrative claims; those indications are not included here.

Of all Medicaid members with pembrolizumab claims in 2021, over 99% had claims for cancers for which pembrolizumab is indicated for treatment or those identified as reportable by the National Cancer Institute's SEER program. The SEER reportable cancers are those indicated as “in situ” or “invasive” in their respective ICD-10 codes[88] (see Appendix A). Of pembrolizumab-indicated cancers, respiratory (lung) cancers were the most common, followed by claims for individuals with multiple primary cancer types. Of the top 10 most common primary cancer sites identified, 3 were either specific to female reproductive anatomy or most commonly found in women (breast, cervix, and endometrium).

In members with multiple cancers, the most common combinations identified were multiple gastrointestinal cancers (esophagus, stomach), respiratory cancers paired with breast cancer, and multiple female reproductive cancers (cervix, endometrium). Of the 20 most common combinations, 13 were respiratory cancers paired with another primary cancer site. A full breakdown of identified cancers and multiple-cancer combinations can be found in the Appendix A.

Members with pembrolizumab claims had high hospital and emergency department use (Exhibit 9). Specifically, 53.5% of Medicaid members with pembrolizumab claims experienced at least 1 hospitalization in 2021, while 30.2% experienced 2 or more hospitalizations. The average length of stay was more than 11 days. In addition, over 70% of members with pembrolizumab claims experienced at least 1 emergency department visit.

EXHIBIT 9

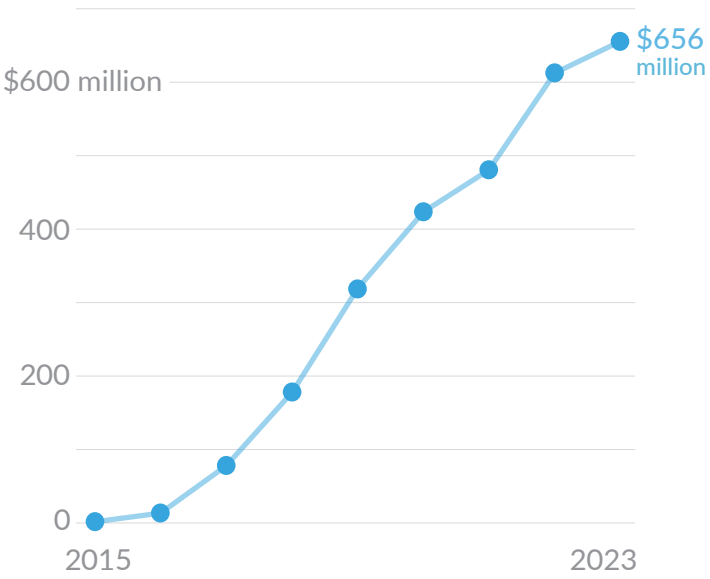
Health service use by Medicaid members with pembrolizumab claims, 2021

	members with at least 1 pembrolizumab claim
Total members[a]	*13,351*
Hospitalizations	
% with ≥ 1 hospitalization	53.5
% with ≥ 2 hospitalizations	30.2
Total hospitalizations, per 1,000 members	1,197
Total inpatient days, per 1,000 members	13,864
Average length of stay per hospitalization, days	11.6
% with ≥ 1 hospitalization lasting ≥ 5 days	34.5
Emergency visits	
% with ≥ 1 ED visit	70.1
% with ≥ 5 ED visits	15.8
Total ED visits, per 1,000 members	2,317

Note. [a] Excludes dually eligible members and members in Alabama, Illinois, New York, and Utah.
Abbreviation. ED: emergency department.

EXHIBIT 10

Total amount reimbursed by Medicaid for pembrolizumab, 2015 to 2023



Note: Amount reflects total means of finance for Medicaid (state and federal share) with the statutorily required rebates applied.
Source: Medicaid State Drug Utilization Data, 2015 to 2023.[89]

What Was the Impact of Pembrolizumab on State Medicaid Spending from 2015 to 2023?

Exhibit 10 shows the estimated upward trend in the amount reimbursed for pembrolizumab by Medicaid based on publicly available Medicaid State Drug Utilization Data from 2015 to 2023, adjusted for inflation.[89] These are the pre-rebate amounts reimbursed by Medicaid to pharmacies each year. They include dispensing fees but do not include any amount paid by parties other than Medicaid, such as other federal coverage (e.g., Medicare payments for dually eligible members), copays, or private insurance. Exhibit 10 also shows the estimated amounts net of rebates by applying the statutorily required rebate rate of 23.1% to the Medicaid-reimbursed amounts.[90]

What Is the Potential Impact of Pembrolizumab on State Medicaid Spending?

Due to provisions in the Omnibus Budget Reconciliation Act of 1990, which established the Medicaid Drug Rebate Program, state Medicaid programs must cover FDA-approved drugs if the manufacturer signs a rebate agreement with US Department of Health and Human Services.[90] Therefore, FDA approval, including accelerated approval, is a key factor in establishing the requirement for Medicaid coverage. We estimate the near-term future total annual cost of pembrolizumab for cancer treatment in Medicaid to be $941.1 million (95% confidence bounds, $589.5 million and $1.51 billion). This corresponds to a per-member per-month (PMPM) cost of $1.00 (95% confidence bounds, $0.84 and $1.37) for all Medicaid members. This estimate is based on the current price of pembrolizumab, and the assumption that the uptake rate of pembrolizumab will increase by 17.6% from the 2021 level. Our estimate of the increase in uptake is based on the trends in pembrolizumab uptake since its inception and does not directly take possible FDA approvals for additional indications into consideration. Our cost estimate represents the lower bound for future costs if the upward trend in treatment uptake, the number of FDA-approved indications, or its price continues. Refer to the Methods Appendix (Appendix A) for additional detail on model inputs and assumptions, and Appendix D for forecasted costs by state.

Based on the 2021 enrollment composition of the members with pembrolizumab claims in CHIP (Children's Health Insurance Program) and Medicaid expansion, and the weighted national average of corresponding federal match rates, we estimate that $672.2 million of the total costs would come from federal funds and the remaining $268.9 million would be paid by the states.

CONSIDERATIONS

ICIs like pembrolizumab offer individuals with cancer, their caregivers, and their clinicians an important tool to treat cancer. By encouraging the body's own T cells to fight cancer, ICIs provide a treatment option beyond chemotherapy and surgery.[10] The drug, however, is extraordinarily expensive to Medicaid and has side effects that pose real risks to patients and create additional health care costs for Medicaid. Moreover, the manufacturer's market access and patent strategies have a direct and definitive impact on Medicaid coverage policy and the prospects for biosimilars to offer price competition to reduce costs.

The cost of covering pembrolizumab for Medicaid members is substantial. Between 2015 and 2023, the Medicaid program spent $2.14 billion on pembrolizumab and in 2022, it ranked number 17 for highest total spending by Medicaid on any drug.

Liver toxicity and acute kidney injury are among the notable side effects of pembrolizumab, and immune-related adverse events are a well-documented side effect of ICIs, pembrolizumab included.[16-18] Recent studies have shown that a quarter to a third of patients taking ICIs should anticipate having an emergency department visit for an immune-related adverse event with a subset of those requiring hospitalization.[16-18] For pembrolizumab, state and federal policymakers should evaluate patient health outcomes, changes in health care service use, and the cost of immune-related adverse events to assess how care planning and negotiation with the manufacturer can ameliorate these impacts on patients and on Medicaid spending.

The future costs of pembrolizumab and potential for biosimilar competition are also critical considerations for state and federal policymakers. We estimate that Medicaid should plan for an annual future expenditure of $941.1 million, with the caveat that this future expenditure will increase

significantly if the manufacturer pursues its stated intent to increase the number of FDA-approved indications from 40 to 80 by 2028.[25] The intent to double the number of FDA-approved indications for pembrolizumab is notable, because it effectively sets Medicaid drug reimbursement policy as Medicaid is required to cover all drug and indication combinations approved by the FDA.[90]

The key patents covering pembrolizumab's anti-PD-1 antibody and drug formulation expire in 2028.[91] Normally, these expirations would allow biosimilars to enter the market, enabling price competition that might reduce costs to Medicaid and other payers. However, between 2002 and 2019, the manufacturer secured 129 patents related to pembrolizumab's product, method of treatment, method of production, and method of diagnosis and formulation.[92] This extensive set of patents, including a possible forthcoming patent for a subcutaneous formulation,[93] may result in dampening market entry and competition from biosimilars. Policymakers should monitor this patent activity to ensure biosimilar competition can come to market. Medicaid program officials should also employ utilization management tools to prefer therapeutically equivalent drugs with lower net costs to Medicaid.

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APPENDIX A
METHODS

See attachment for a full description of the methods used to prepare this brief.

EXHIBIT A1
Prevalence of pembrolizumab-indicated cancers in Medicaid members with pembrolizumab claims, 2021

EXHIBIT A2
Most common site combinations among Medicaid members with pembrolizumab claims and multiple primary cancer sites, 2021

EXHIBIT A3
Cost modeling inputs

APPENDIX B
PEMBROLIZUMAB CLAIMS, 2021

See attachment for this table.

APPENDIX C
DEMOGRAPHIC INFORMATION

See attachment for table describing the availability of demographic information of Medicaid members included in our study.

APPENDIX D
PEMBROLIZUMAB COSTS

See attachment for a table of forecasted annual cost by state.

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