ABSTRACT

Title of Dissertation:	NOVEL IMMUNOTHERAPY AGENTS IN ONCOLOGY: GENERALIZABILITY OF TRIAL RESULTS AND DRIVERS OF CLINICAL UTILIZATION
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Cancer is the second most common cause of death in the United States after heart disease. Novel immunotherapy agents such as nivolumab and pembrolizumab have become an essential, albeit extremely expensive, component of oncology care since their first approvals in melanoma in 2014 and lung cancer in 2015. However, little is known about differences between immunotherapy clinical trial participants and the real-world patient population, or about the drivers of provider utilization of these agents.

The first objective of this dissertation used the SEER-Medicare linked database with claims data from 2014-2016 to conduct two aims analyzing potential disparities between Medicare beneficiaries on active treatment for melanoma and lung cancer and Medicare clinical trial participants. Aim one compared the

characteristics of Medicare patients on active cancer treatment to Medicare patients on active cancer treatment clinical trials. Aim two compared Medicare patients receiving the novel immunotherapy agents nivolumab or pembrolizumab to Medicare patients participating in trials of these two immunotherapy agents. Because of the demographic differences in the melanoma and lung cancer patient populations, these aims were analyzed separately in melanoma and lung cancer. As hypothesized, patients in clinical trials were significantly younger and had fewer comorbid conditions than patients undergoing active cancer treatment not in clinical trials. Underrepresentation of non-White and female patients in clinical trials was hypothesized, but these results were less consistent.

The second objective used Medicare Open Payments data from 2016 and Medicare provider utilization data from 2017 to analyze 1) if industry payments promoting nivolumab or pembrolizumab were positively associated with whether a provider was a high utilizer of the agent, and 2) among these high utilizers, if industry payments were positively associated with greater utilization amounts. The hypothesized results, that industry payments were associated with greater likelihood of high utilization and more utilization among high utilizers, were seen in some of the analyses but not consistently throughout the study. Through unique analyses of recent datasets, this dissertation advances our understanding of potential disparities in clinical trial representativeness and the generally positive relationship between promotional payments and provider utilization of immunotherapy agents in the Medicare cancer patient population.

NOVEL IMMUNOTHERAPY AGENTS IN ONCOLOGY: GENERALIZABILITY OF TRIAL RESULTS AND DRIVERS OF CLINICAL UTILIZATION

by

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List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ALK	Anaplastic Lymphoma Kinase
ASCO	American Society of Clinical Oncology
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FDASIA	FDA Safety and Innovation Act
FLT3	FMS-Like Tyrosine Kinase 3
GAM	Generalized Additive Model
HCC	Hierarchical Condition Category
HCPCS	Healthcare Common Procedural Coding System
HER2	Human Epidermal Growth Factor Receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hormone Receptor
ICD	International Classification of Diseases
IMS	Information Management Services, Inc.
IRB	Institutional Review Board

JAMA	Journal of the American Medical Association
MEK	MAPK/ERK Kinase
MET	Mesenchymal-Epithelial Transition
MRI	Magnetic Resonance Imaging
NAS	Network Attached Storage
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NPI	National Provider Identifier
NSCLC	Non-Small Cell Lung Cancer
NSS	Networked Storage Service
OR	Odds Ratio
PD-1	Programmed Cell Death Receptor 1
PD-L1	Programmed Death-Ligand 1
PET	Positron Emission Tomography
PUF	Public Use File
Ref	Reference
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
US	United States
VEGF	Vascular Endothelial Growth Factor

Chapter 1: Introduction and Theoretical Framework

Introduction

Cancer is an important disease area for public health research in the United States. Cancer is the second most common cause of death, after heart disease, and more than 5,200 new cancer diagnoses are expected daily, for a total of nearly 1.9 million new cases in 2021.[1] Advances in cancer treatment have the potential to significantly improve outcomes for many people. A recent analysis found that more than 10,000 lung cancer deaths were averted between 2014 and 2016 due to improved treatments, including immunotherapies.[2]

Novel immunotherapy agents have become an essential, albeit extremely expensive, component of oncology care in recent years. In the United States, the first Food and Drug Administration (FDA) approvals of PD-1 checkpoint inhibitors pembrolizumab and nivolumab came in 2014 in melanoma and in 2015 in non-small cell lung cancer. These checkpoint inhibitors differ from most antineoplastic therapies in two key ways: instead of targeting the tumor cells, they directly target the immune system, and instead of trying to boost immune system activity, they block checkpoints where tumor cells can act to slow down or stop the immune system.[3]

The initial pembrolizumab and nivolumab approvals were based on promising early findings in small, individual trials, which were confirmed in later trials. However, little is known about differences between immunotherapy clinical trial participants and the real-world immunotherapy patient population or the drivers of real-world immunotherapy utilization. This information is essential to prioritizing

additional research evaluating the efficacy of immunotherapy agents in realistic patient populations, as well as assessing whether current utilization is appropriate. Evidence regarding utilization of these agents is also limited because the related claims are so recent. In the United States, Medicare-eligible patients represent the majority of cancer patients,[4] and Medicare claims data and related physician utilization data for these years are just now becoming available. The studies included in this dissertation take advantage of these newly released Medicare datasets to produce related papers providing an innovative, essential, and timely analysis of novel immunotherapy agents from a health services research perspective.

Theoretical Frameworks

Sketris Framework for Factors Affecting Prescribing

When considering the drivers of physician utilization of novel immunotherapy agents, this analysis builds on the framework described by Sketris et al. in a 2007 report prepared for the Health Council of Canada.[5] The Sketris framework was intended to guide evaluation of interventions to optimize prescribing. However, it is also useful as a framework for understanding individual prescribing decisions in drug utilization research.[6]

In this framework, factors are broadly broken down into four main categories: prescriber factors, patient factors, drug factors, and other environmental factors.[5] **Prescriber factors** include both individual prescriber characteristics and the characteristics of the organization the provider practices within. **Patient factors** similarly include both individual patient characteristics and the support systems surrounding the patient. **Drug factors** include the scientific evidence in support of

the drug, as well as other characteristics of the drug such as its available dosage forms and the pharmacodynamics and pharmacokinetics.

The other potential environmental factors are broad and diverse. As described by Sketris et al., they can include the **professional societies** that put out practice guidelines; **regulatory bodies** that determine drug approvals and physician licensing; private sectors such as the **drug industry**, **insurers**, and **employers**; **governments** that set policies and determine health care financing; **media** and other information sources; other **health service delivery organizations** such as hospitals; the **volunteer health sector** that includes advocates and research funders; **academia** in its research and education roles; and **society**'s values and preferences.

Diffusion of Innovation Theory and Drug Utilization Research

This work ties the Sketris framework to elements from the diffusion of innovation theory. The theoretical framework for diffusion of innovation theory was formalized in Dr. Everett Rogers' 1962 book, *Diffusion of Innovations*, which has since been revised and updated in multiple editions.[7] The theory includes four main elements: 1) an **idea**, or innovation; 2) the **channels** through which the idea is communicated; 3) the **time** period over which diffusion of the idea takes place; and 4) the individuals within the **social system** that the idea is spreading in. Not all ideas are equal: several characteristics of the innovation contribute to its diffusion. These include the **perceived relative advantage** of the new innovation compared to the status quo; the **compatibility** of the innovation with the values and needs of the individuals who may adopt it; the perceived **complexity** of the innovation to understand and use; the degree to which the innovation can be tried out without

committing to it fully (i.e., its **trialability)**; and the **observability** of the effects of the innovation in friends and colleagues.[7] Innovations that have greater perceived relative advantage, high compatibility, low complexity, greater trialability and greater observability will spread more rapidly than innovations that do not.

Diffusion of innovation theory has a long and complicated history in public health dissemination and implementation research and practice.[8] One of the seminal works in early diffusion of innovation research by Coleman and colleagues explored diffusion of a new drug among physicians.[9,10] This early social network analysis found that more closely interconnected physicians were more likely to begin using the new drug sooner. However, a reanalysis of the original dataset by Van den Bulte and Lilien found that the "social contagion" effect on uptake of the new drug could instead be explained by marketing effects; that is, the contagion effect was no longer significant when drug advertising was controlled for.[11]

As these examples show, diffusion of innovation theory can be difficult to apply appropriately. However, within the context of drug utilization, each of the innovation characteristics identified by Rogers could clearly contribute to diffusion of a new agent by providers.[7] Agents with a significant relative advantage in terms of overall survival, disease response, or side effects would likely be adopted rapidly. When the relative advantage is less clear, issues such as compatibility of providing the agent within the existing medical system and the complexity of providing the agent will likely play a bigger role. Observability is likely important when dealing with a new class of agents with less certain side effect management. By observing their colleagues using these agents and by treating patients who may have already

received these agents from others, providers can become more comfortable with their ability to successfully utilize the agents and become more familiar with the relative advantages of the agents. Finally, trialability is likely more relevant to the adoption of medical devices that may require a significant investment but could still be a factor in drug utilization – particularly with drugs that may have "free samples" available that could be shared with patients considering their utilization. However, relative trialability seems less relevant in the context of oncology since the standard across diseases typically involves starting with a therapy but being willing to change depending on response and adverse events.

Diffusion of Innovation Research in Oncology

Researchers have utilized diffusion of innovation theory to analyze the uptake of agents by oncologists. Unger et al. used data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) cancer registry program linkage with Medicare claims data from 1995 to 2008 to explore the uptake of docetaxel among prostate cancer patients by demographic and socioeconomic characteristics after docetaxel was found to improve survival in castration-resistant prostate cancer and received FDA approval in 2004.[12] This analysis found that adoption of docetaxel was significantly slower for patients who were older, black, or lower income. Interestingly, eighty percent of the adoption of docetaxel took place before the 2004 approval. Instead, adoption coincided with the adoption of docetaxel in other disease areas where approvals came in the 1990s.

A study of gemcitabine adoption in pancreatic cancer, which also used SEER-Medicare data, found that the odds of receiving gemcitabine dropped with each older

age group and that patients with higher socioeconomic status were significantly more likely to receive gemcitabine.[13] However, a more recent analysis of another chemotherapeutic agent, bevacizumab, in a random sample of 20% of Medicare beneficiaries receiving chemotherapy for cancer, found minimal differences in adoption by patient demographic characteristics.[14]

A non-drug analysis in oncology by Pollack et al. examined the adoption of unproven imaging modalities, magnetic resonance imaging (MRI) and positron emission tomography (PET), in breast cancer.[15] This study used SEER-Medicare data to focus on the social contagion of the non-evidence-based MRI/PET imaging. The researchers found that peer use of MRI and PET imaging was significantly associated with provider utilization of these imaging modalities. However, this study and others focused on social contagion in medicine do not describe whether marketing effects were controlled for, perhaps because of the lack of data previously available to assess marketing.[16-19]

Application of Frameworks to FDA Expedited Review

The expedited regulatory review pathways described earlier are of interest when considering drivers of physician utilization of agents for at least two key reasons. First, being granted an expedited review through one or more of these pathways may be used as an indicator of the potential value of an agent. The breakthrough designation granted for pembrolizumab in advanced melanoma in 2013 was one of the first times the designation had been used. Although the FDA does not report these designations, Merck issued a press release publicizing the decision.[20] It was then widely reported in trade publications.[21-23] (In reviewing these documents, it

is important to note that at the time of breakthrough designation, the generic name for pembrolizumab was lambrolizumab; its name was changed before its initial approval.) Bristol-Myers Squibb similarly issued a press release describing the regulatory milestones achieved for nivolumab, including its breakthrough designation in melanoma, which came after receipt of breakthrough designation in lung cancer.[24] The release received coverage in the oncology press.[25]

As these examples show, FDA decisions to grant expedited review pathways give companies an opportunity to promote their product before an approval decision has been made. Information about an FDA decision to grant expedited review of an agent contributes to physician decisions about drug utilization through at least three of the influencing organizations described in the Sketris framework. These include **regulatory bodies** in the form of the FDA decision, the **drug industry** in the form of their marketing of the decision, and the **media** in the form of their coverage of the decision.

A second reason expedited review pathways are of interest focuses more on the accelerated approval pathway. As discussed earlier, this pathway is the only form of expedited review that actually alters the requirements for an initial approval of an agent, and it is often granted in conjunction with other expedited review mechanisms. Because accelerated approval allows an initial approval decision to be made based on surrogate endpoints, rather than on endpoints that are directly clinically meaningful, there is less certainty of clinical benefit for agents that have received only accelerated approval and have not yet converted to full approval.[26] This most clearly ties into the **drug factors** in the Sketris framework, in that there is less scientific evidence

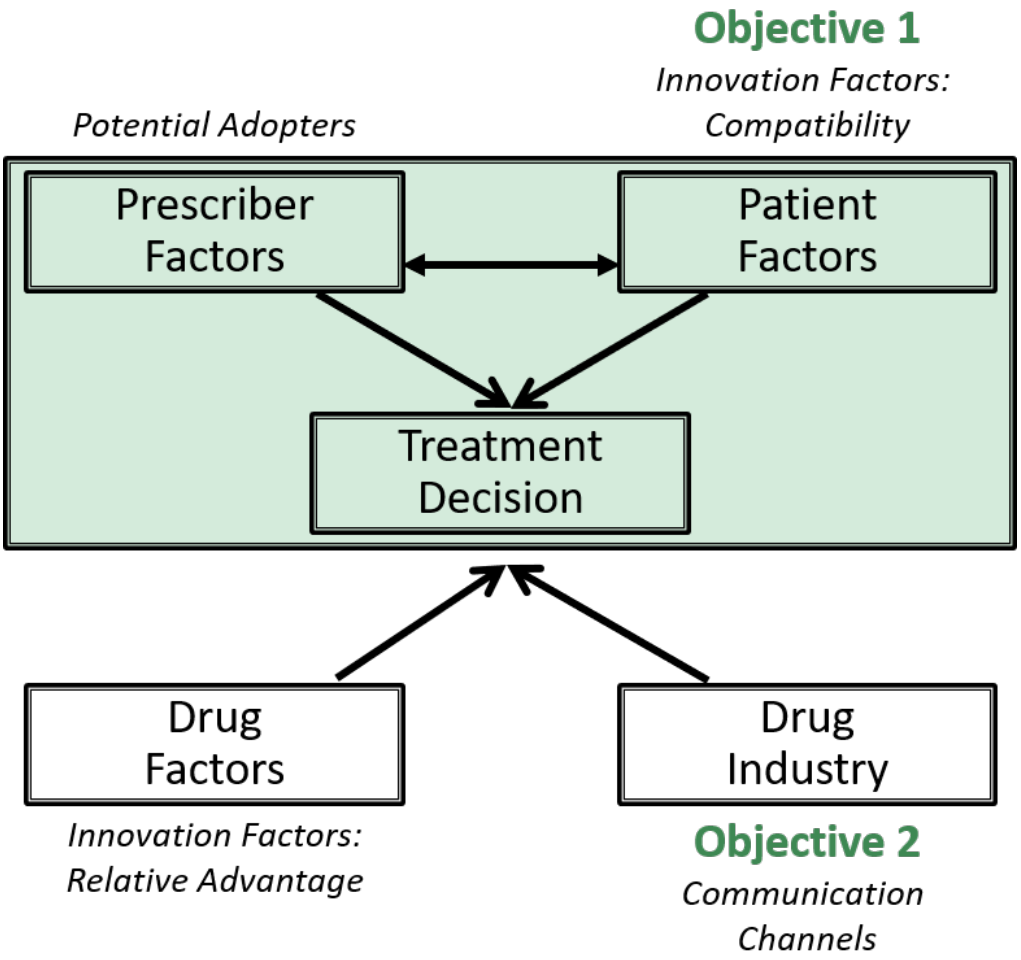
supporting utilization of the agent than would be expected if the agent had full approval. However, the accelerated approval is still an approval granted by a **regulatory body** making the agent more generally accessible through standard **insurer** reimbursement policies.

Adapted Framework

This dissertation has adapted the Sketris framework to emphasize the factors most applicable to this study of uptake of immunotherapy agents in the United States Medicare population and to tie the key factors in the framework to the relevant characteristics from diffusion of innovation theory. This adapted framework, shown in **Figure 1**, guided the analysis but is not comprehensively tested as part of this dissertation. The framework includes both **prescriber** and **patient factors** from Sketris et al. The patient factors element is linked to the innovation characteristic of **compatibility** from diffusion of innovation theory. This is linked to the research representativeness in clinical trials, because compatibility is more uncertain if the patient was not represented in the research population. **Drug factors** are linked to the innovation characteristic of **relative advantage**, in the form of perceived efficacy and side effects of the agents.

The adapted framework does not include professional societies. National practice guidelines may not be updated as rapidly as agents are approved. More importantly, for the purposes of study agent uptake within a single country – the United States – and within a single group of providers – oncologists – practice guidelines are arguably less likely to be useful in analyzing individual-level utilization decisions since they are occurring at the same time for all providers within

Figure 1. Framework of Factors Contributing to Drug Utilization Decision, Adapted from Sketris et al. and Rogers



the country. In the United States, the National Comprehensive Cancer Network (NCCN) offers widely accepted practice guidelines that are regularly reviewed and updated by a panel of experts. Requests for changes are publicly documented, including the source of the request, discussion by the panel, and ultimate panel vote.[27] Similarly, the adapted framework does not include regulatory bodies, since the FDA decisions apply across the United States, or government, since most health care legislation affecting the Medicare population is at the national level. Media, society,

and volunteer health sector factors are also not included because their effects are expected to largely be national.

From the private sector, the adapted framework includes the **drug industry**, which is the focus of Chapter 4 of this dissertation. In the United States, drug industry marketing to physicians is a key potential driver of utilization. Thus, this element is tied to the **communication channels** component of diffusion of innovation theory. Insurers and employers are not included because the population of interest for this analysis is Medicare patients. Other health service delivery organizations could potentially be of interest but are not included because preliminary analysis indicates pembrolizumab and nivolumab are overwhelmingly given in provider office settings.

Chapter 2: Background and Literature Review

This literature review begins by describing the emergence of immunotherapy agents in oncology and the significance of their utilization in the current health care system. Next, it describes the origins of the modern clinical research system in the United States. This lays the groundwork for understanding key regulatory and ethical concerns in the approvals and utilization of novel immunotherapy agents. Finally, key historical events and research around disparities in clinical research participation are described.

Immunotherapy in Oncology

The Nobel Prize for Medicine was awarded on October 1, 2018 to two researchers who identified key immunotherapy targets.[28] The prize was jointly awarded to James Allison from MD Anderson Cancer Center and Tashuku Honju from Kyoto University for their individual work identifying two immunotherapy targets that have led to approved agents in oncology. As the prize highlights, immunotherapies in oncology have been in development for decades: the work being recognized was largely done in the 1990s. However, it set the stage for key clinical advances that are still now being recognized. The American Society of Clinical Oncology (ASCO) named immunotherapy the cancer "Advance of the Year" in both their 2016 and 2017 Annual Reports on Progress Against Cancer.[29,30] In 2016, ASCO president Julie Vose introduced the report by saying, "No recent advance has been more transformative than the rise of immunotherapy."[29] For 2018, ASCO highlighted a particularly type of immunotherapy – adoptive cell immunotherapy – as the advance of the year.[31]

Regulatory Approvals of Immunotherapy Agents in Melanoma

The first FDA approval of the modern class of immunotherapy checkpoint inhibitors was ipilimumab (brand name Yervoy) in March 2011 in advanced melanoma.[32] A single clinical trial was submitted to the FDA in support of the new drug application. The trial was called MDX010-20. The study was a three-arm trial, with patients randomized (3:1:1) to ipilimumab plus an experimental vaccine, ipilimumab plus a vaccine placebo, or a placebo plus an experimental vaccine. Patients were enrolled between 2004 and 2008; the study was completed in 2009. Because this trial was designed as a three-arm study intended to show the benefit of the combination, the analytic plan focused on the combination. The ipilimumab-vaccine combination arm had a significantly greater overall survival than the vaccine alone arm. The ipilimumab alone arm also had higher overall survival, leading the FDA to approve ipilimumab alone.

However, ipilimumab was quickly surpassed by newer immunotherapy checkpoint inhibitors targeting the programmed cell death receptor 1 (PD-1) or the programmed death-ligand 1 (PD-L1). These checkpoint inhibitors, including pembrolizumab (brand name Keytruda) and nivolumab (brand name Opdivo), demonstrated greater activity and lower toxicity than ipilimumab in the first publications of results from phase three studies.[33,34] In a three-arm trial of nivolumab in advanced melanoma, 945 patients were randomized (1:1:1) to nivolumab, nivolumab and ipilimumab, or ipilimumab.[34] Nivolumab alone had significantly longer progression-free survival in melanoma at 6.9 months than ipilimumab alone at 2.9 months. Treatment-related adverse events led to discontinuation of treatment in

just 7.7% of patients receiving nivolumab alone compared to 14.8% of patients receiving just ipilimumab. Similarly, in a three-arm trial of pembrolizumab in advanced melanoma, 834 patients were randomized (1:1:1) to pembrolizumab every two weeks, pembrolizumab every three weeks, or ipilimumab every three weeks.[33] Patients in both of the pembrolizumab arms had similarly higher rates of progression-free-survival at six months and overall survival at 12 months than patients in the ipilimumab arm, as well as lower rates of high-grade treatment-related adverse events.

The first approvals for pembrolizumab and nivolumab both came in 2014 in melanoma.[35,36] Merck's pembrolizumab was granted approval under the FDA's accelerated approval pathway on September 4, 2014.[37] The approved indication was for patients with metastatic or unresectable melanoma whose melanoma progressed after receiving ipilimumab and, if the melanoma had a mutation in the BRAF V600 gene, a BRAF inhibiting agent. The pembrolizumab application was granted breakthrough therapy designation.[36] The pembrolizumab accelerated approval was based on a cohort of 173 patients enrolled within a large expansion study. These patients had a response rate of 24%, exceeding the pre-specified criteria of 10%. Toxicities were evaluated in a larger pool of melanoma patients who had received pembrolizumab. The most significant adverse events were autoimmune disorders, including pneumonitis and colitis. The FDA found that, although the response rate was objectively small, it was still significantly better than the standard treatment in melanoma at the time. This served as the basis for the accelerated approval decision.

Bristol-Myers Squibb's nivolumab was similarly approved under the accelerated approval pathway on December 22, 2014 for the same melanoma indication.[37] Nivolumab had also been granted a breakthrough therapy designation.[38] The nivolumab accelerated approval was based on an interim analysis of a subset of trial patients from a single arm of a study. In the interim analysis, 120 patients receiving nivolumab had an overall response rate of 31.7%, exceeding the pre-specified minimum response rate of less than 15%, which was approximately the expected response rate for standard of care treatment. The trial in which these patients were enrolled was actually a randomized (2:1) trial comparing nivolumab to chemotherapy, but at the time of the FDA review, the only comparative data examined was safety data. Key adverse events noted were autoimmune toxicities. Overall, the FDA's risk-benefit assessment recommended accelerated approval given the increased efficacy compared to standard treatment and the tolerable toxicities reported.

Regulatory Approvals of Immunotherapy Agents in Lung Cancer

Pembrolizumab and nivolumab each also gained approvals in non-small cell lung cancer (NSCLC) in 2015.[39,40] Nivolumab was granted regular approval on March 4, 2015 for an indication in "metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy." The nivolumab application was originally submitted seeking accelerated approval based on a randomized phase three trial of 272 patients with a surrogate endpoint of overall response rate.[41] However, approval was not granted until there was an interim analysis of a clinical endpoint, overall survival, which supported the regular approval.

Pembrolizumab was granted accelerated approval on October 2, 2015 for an indication in "patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy."[40] This accelerated approval was based on a study with a surrogate endpoint of overall response rate.

Utilization of Expedited Regulatory Review Programs

In these and later reviews and approvals, novel immunotherapy agents utilized a range of expedited review programs available through the FDA to facilitate review of promising agents. These expedited review programs include the accelerated approval pathway, fast track designation, priority review designation, and most recently, breakthrough therapy designation.[42] According to the FDA's guidance on the expedited review programs, agents must be intended to treat a "serious condition" to qualify for any of these four programs.[43] The FDA defines a serious condition as a condition, disease, or illness that has significant, persistent morbidity or is life-threatening. Other requirements vary across the four programs, including whether the agent meets an unmet medical need, the type of preliminary data available, and the type of research proposed for the initial FDA approval.

Of the four programs, accelerated approval and breakthrough therapy designation have arguably been the most significant in oncology. Priority review moves up the FDA review deadline from 10 months to six months for agents addressing serious conditions that could significantly improve safety or efficacy.[43] Most oncology agents are intended to treat serious conditions and are in development only in the hopes that they would improve on current safety or efficacy, so this

mechanism should be broadly used. Fast track designation focuses on improving communication between the FDA and industry for agents addressing serious conditions with the potential to fill an unmet medical need. However, there are not associated deadlines; all features of the fast track designation are included in the breakthrough therapy designation.

Accelerated approval is the only expedited review program that is an alternative approval pathway rather than an effort to speed the overall review process.[43] For accelerated approval, unlike regular approval, an application can rely on so-called surrogate or intermediate research endpoints that are likely to predict the actual clinical benefit. As part of the accelerated approval, a company is required to carry out confirmatory trials to verify the clinical benefit assumed based on surrogate or intermediate endpoints. If that benefit is not seen, approval can be withdrawn.

The accelerated approval pathway was first codified in 1992 and the FDA recently published a review of the first 25 years of utilization of accelerated approval in oncology and malignant hematology.[44] As of May 31, 2017, 64 agents had received accelerated approval in 93 indications in oncology and malignant hematology. The most frequently used intermediate or surrogate endpoints were response rates, with a small number of indications relying on endpoints such as progression-free survival. Importantly, 72% of the accelerated approvals relied on single-arm trials rather than the gold standard of a randomized controlled trial. It is this utilization of earlier-phase trials that has made it possible for accelerated approval to lead to expedited approvals of new agents.

Breakthrough therapy designation was a designation developed by the FDA when implementing the FDA Safety and Innovation Act of 2012 (FDASIA) as a supplement to the existing programs.[42] Thus, we do not have as much evidence of how breakthrough therapy designation has been used in oncology. Through 2017, the FDA approved 46 agents across disease areas that had been granted breakthrough therapy designation; of these, 25 were in cancer.[45] All 46 agents had been given priority review designation, 24 had been given fast track designation, and 18 received accelerated approval. Based on an analysis in the Journal of the American Medical Association (JAMA), most if not all of the 25 cancer approvals were based on a single pivotal efficacy trial. Of the 25 cancer approvals, 10 relied on one or more trials with randomization and a comparator group, while 15 relied only on single arm trials.

Uptake of Immunotherapy Agents in Clinical Practice

Since the initial FDA approvals, there has been significant uptake of nivolumab and pembrolizumab throughout the United States. This was most strikingly demonstrated by a retrospective analysis of patients with melanoma, lung cancer, and renal cancer whose medical data was abstracted by the Flatiron Health Network.[46] The Flatiron electronic health record database includes data from 233 oncology practices with a generally demographically representative patient population for the three cancers studied. This analysis included 3,089 patients eligible for an anti-PD-1 immunotherapy agents. Although the cohorts of patients immediately eligible were small, the analysis found that within 4 months of FDA approval in each disease area, more than 60% of eligible patients in each disease area

had received immunotherapy treatment. These real-world patients were significantly more likely to be older than the patients in the key clinical trials.

Rise of Randomized Controlled Trials in Clinical Research

Although medical research has taken place across generations, clinical research as we know it began only in the 1960s and 1970s. The early Food, Drug, and Insecticide Administration had limited scope, and its regulation of drugs was primarily focused on regulating blatantly false marketing claims made on elixir labels. Its scope was expanded after a tragic accident in 1937, when an elixir manufacturer sold sulfa antibiotics dissolved in poisonous antifreeze. Because there was no requirement that drugs be tested for safety or efficacy, more than 100 people died before FDA employees seized the remaining elixir.[47] The resulting Federal Food, Drug, and Cosmetic Act (FD&C Act), passed in 1938, required that drugs be proven safe, but there were still no requirements for proof of efficacy.[48]

It took another tragedy to prompt the next major change. The sedative thalidomide was already approved in Europe for morning sickness, so the application to the FDA was expected to go through quickly when it was received in 1960.[49] However, medical reviewer Frances Kelsey had questions about some of the safety data, prompting an escalating back-and-forth between the drug manufacturer and the FDA. Before that was resolved, reports from around the world of the devastating teratogenic effects of thalidomide made it clear that the drug was not safe. The Kefauver-Harris amendments to the FD&C Act included specific provisions to reduce the chances of a disastrous drug like thalidomide being approved in the U.S. and were unanimously passed in 1962.[50]

While public attention was focused on the treatment of thalidomide, the Kefauver-Harris amendments also materially increased the scope of the FDA by requiring "substantial evidence" of both safety and effectiveness for new drug applications, where "the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."[51] This legislative language has generally been interpreted by the FDA to mean that, with some exceptions, at least two "adequate and well-controlled" studies are required to convincingly prove effectiveness and provide sufficient information for its review of the risk-benefit balance for a given drug's safety and efficacy.[52] Before this time, medical research was being conducted in a much less regulated and systematic way. Thus, the 1962 FD&C Act amendments marked the beginning of our current age of clinical research, with a focus on well-documented randomized trials.

Disparities in Clinical Research Participation

Within the context of a well-controlled clinical research system, disparities in clinical research participation can translate to disparities in medical advances. This section briefly describes pivotal ethical failures in clinical research. Then, it explores how those failures contribute to ongoing research disparities. The section concludes by emphasizing the importance of representation in clinical research and describing our current understanding of disparities in research participation.

Ethics and Ethical Failures in Clinical Research

The Kefauver-Harris amendments also required for the first time that research participants in the U.S. be asked for informed consent.[51] Research sponsors were required to ensure that all investigators would "inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives." The issue of informed consent for research had been highlighted following recognition of the atrocities performed in the name of science during World War II; first, in the 1948 Nuremberg Code, and then again in the World Medical Association's Declaration of Helsinki in 1964.[53]

The infamous Tuskegee Syphilis Study failed to meet any standard of informed consent. In this study, conducted between 1932 and 1972, hundreds of black men with syphilis were told they were being treated but were actually blocked from receiving treatment.[54] The study continued denying men treatment despite penicillin being widely accepted as the preferred treatment of syphilis in 1945. The Tuskegee Syphilis Study, and others like it, have contributed to a significant legacy of distrust of medicine and particularly medical research among Black communities.[55,56]

This distrust was visible in the burst of research in human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) that took place relatively soon after the emergence of a more systematic clinical research system. One article by Thomas and Quinn noted the impact of Tuskegee on HIV and AIDS education programs in Black communities, tracking rumors, which were picked up by

the news media, that AIDS was an intentional genocide being inflicted on the Black population.[57] This paper was also one of the first documenting the lasting effects of Tuskegee in public health, and urged greater recognition and discussion of the distrust arising from Tuskegee – particularly so that it would not impede future research participation. Unfortunately, disparities in clinical research participation, and particularly in cancer clinical trials, have been documented as an ongoing issue.[58,59]

Importance of Representation in Clinical Research

Representation in clinical trials is important for several reasons. First, if representative participants are not included in clinical trials, the safety and efficacy results may not be generalizable to the wider population.[60] For reasons not fully understood, certain drugs work better or have more severe side effects in some patient sub-populations than in others. This is widely recognized in cardiovascular disease, where a focus on studying white men obscured understanding of heart disease in women for decades.[61,62] Cardiovascular research also provides evidence of the importance of racial diversity in clinical trials: some agents have different risk-benefit profiles for Black and White populations.[63]

Second, clinical trial results that are most applicable to White populations may further compound existing health disparities.[64] Thus, research has the potential to widen the disparities gap without careful attention to representativeness in clinical trial participation. And third, all aspects of research should be conducted in accordance with the principles of the Belmont Report, which calls for equity and social justice in clinical trials participation.[65]

Although ethical failures and patient distrust play a significant role, other factors also contribute to lack of representation in clinical trials.[66] One often-highlighted factor in cancer trials has been eligibility criteria.[67] Other elements include provider bias and false perceptions and access to care.[68] A systematic review grouped barriers in three categories: lack of awareness of trials due to factors such as low health literacy and limited culturally competent educational resources; lack of opportunity to participate due to factors such as eligibility criteria, provider attitudes, or costs; and lack of acceptance of the offer to participate due to factors such as distrust or fear.[69] However, an analysis found that people of color are not less willing to participate in trials when offered the opportunity.[70]

Clinical Research Disparities and the Covid-19 Pandemic

Concerns about clinical research disparities came to a head during the Covid-19 pandemic. Clinicians and researchers quickly identified disparities in Covid-19 incidence and outcomes in the United States, particularly in African American, Black, and Latinx populations.[71] Without time to analyze whether these disparities were primarily driven by social determinants of health or if genetic or biologic factors may have contributed, it was especially important to ensure that patients enrolled in Covid-19 prevention and treatment trials represented the populations most affected by the disease, but initial trials still underrepresented non-White populations.[72] This led to an increased emphasis on engaging diverse communities for Covid-19 research, including the creation of the Community Engagement Alliance (CEAL) Against COVID-19 Disparities by the National Institutes of Health.[73]

Relatively low enrollment of non-White participants on the Moderna Covid-19 vaccine trial led the company to slow trial enrollment and refocus efforts on engaging people of color.[74] Pfizer added an additional 14,000 participants to its original vaccine trial cohort of 30,000 in an effort to increase participant diversity and open enrollment to adolescents and individuals with comorbid infections such as HIV.[75] Concerns about adequate representation in these trials may have added to mistrust of the Covid-19 vaccine among people of color. This mistrust, along with significant disadvantages in health care access, has contributed to disparities in the early distribution of these vaccines, further exacerbating health disparities.[76]

Covid-19 also disproportionately affects older adults.[77] Greater age is associated with greater risk of severe disease, hospitalization, and death.[78] Unfortunately, enrollment of older adults in Covid-19 vaccine trials was variable. Just 12% of participants in the main trial of the one-shot AstraZeneca vaccine were over age 55, and these participants had less follow-up data. The European Medicines Agency (EMA) which is the equivalent of the FDA in the European Union, approved the AstraZeneca vaccine for all ages.[79] However, the lack of trial data in older adults led many European countries, including France, Norway, and Germany, to recommend the use of the AstraZeneca vaccine only in people under 65, while Italy and Spain recommended use only in those under 55 until more efficacy data in older adults were available.[80]

Disparities in Cancer Clinical Research Participation

Most analyses of the demographics of cancer clinical trial participants have focused on race, ethnicity, and age. In an early analysis conducted by Tejeda et al.,

there were significant disparities in enrollment in NCI's group clinical trials by age, with only 1.5% of patients age 50 or older enrolling on trials, compared to 4% of patients ages 20 to 49.[81] Several studies have since confirmed the challenge of enrolling older patients.[58,82,83] An analysis of nearly 60,000 patients enrolled on NCI group trials from 1997 to 2000 found that only 32% of participants were aged 65 or older, compared to 61% of the incident population.[84] Enrollment appears to become a greater challenge with greater age. An FDA analysis of cancer patients enrolled on trials for new drug approvals between 1995 and 2002 found that just 20% of the enrolled patients were 70 years or older, and 9% were 75 years or older, while these groups represented 46% and 31% of the United States cancer patient population.[85] These and similar findings led ASCO to issue a statement in 2015 that called for improving the evidence base for treating older cancer patients, in large part by increasing accrual among this population.[86]

The early Tejeda study differed from studies in the 2000s in its finding that participation rates for African-Americans, Hispanics, and Whites were generally proportionate to their cancer incidence.[81] In contrast, Murthy et al. found a lower enrollment fraction for Hispanic and African American patients than for White patients in NCI group prostate, lung, colorectal, and breast cancer trials between 2000 and 2002.[58] Similar disparities for Black patients were found in analyses of trial participation in California and Maryland.[83,87] However, some more recent analyses have found less evidence of racial and ethnic disparities in NCI trials.[88]

There are a number of possible explanations for the persistence of disparities in cancer clinical trial participation. One analysis of 4,509 clinical trial screening and

accrual records at 29 sites that were funded by the NCI through the National Cancer Institute's Community Cancer Centers Program (NCCCP) did not find differences in rates of clinical trial enrollment or refusal by race or ethnicity who were eligible for and offered a trial.[89] However, there were differences in comorbid conditions that may be associated with trial eligibility: greater odds of comorbid conditions were associated with being non-Hispanic Black, being male, and older age.

Analyses of clinical trial participation rates and disparities typically focus on NCI trials because industry participation rates are rarely publicly accessible. However, the Drug Trial Snapshots initiative launched by the FDA in 2015 is making more information available about subgroups of trial participants for newly approved drugs.[90] These are largely industry trials, allowing for a greater understanding of participation in this subset of trials. One important limitation to the Drug Trial Snapshots is that snapshots are provided only for newly approved molecular entities. Approvals of supplemental indications for agents that have already been approved in at least one setting are not summarized, which means no snapshots are available for nivolumab or pembrolizumab supplemental indications. However, the snapshots provide an interesting overview.

The FDA published a five-year summary report of the Drug Trials Snapshots program in November 2020.[91] This report summarized the snapshots provided from 2015 to 2019, including new drugs for both oncology indications and non-oncology indications. The report spanned 231 snapshots that provided data on 292,766 clinical trial participants, of whom only 35% were enrolled in the United States. Within oncology, the geographic breakdown over the five-year period was less than 30%.

The total racial distribution of clinical trial participants was also reported for participants enrolled in the United States as opposed to the rest of the world. While 7% of all participants were Black or African American, just 2% of participants enrolled outside of the United States were Black or African American, compared to 16% of participants enrolled in the United States. This information was not reported by therapeutic area, so the breakdown for oncology is not known.

The eight novel approvals for lung cancer and melanoma indications from 2017 through 2020 are shown in **Table 1** below. It is clear from the information available for these approvals that trial demographics varied across the drugs to some degree. However, African American patients generally participated at a lower rate than we might expect from the population demographics, with participation rates of 1% or lower in all but one of the eight approvals. Participation by Asian patients was higher than might be expected for many of the approvals, reaching as high as 77% for Vizimpro. All but two of the drugs were approved based on trials with the majority of participants coming outside of the United States.

Table 1. Patient Demographics for FDA Novel Oncology Drug Approvals in Lung Cancer and Melanoma, 2017-2020

Year	Brand Name	Indication	From United States	Women	White	Asian	Black & African American	Hispanic	Age 65 & Older
2017	Alunbrig	ALK-positive metastatic non-small cell lung cancer (NSCLC)	NR	57%	67%	31%	1%	6%	23%
2018	Braftovi	Unresectable/metastatic melanoma with BRAF V600E or V600K mutation	9%	41%	91%	3%	0%	9%	29%
2018	Lorbrena	ALK-positive metastatic NSCLC	34%	58%	49%	37%	1%	NR	18%
2018	Vizimpro	EGFR-positive metastatic NSCLC	0%	60%	23%	77%	<1%	0%	40%
2019	Rozlytrek	ROS1-positive metastatic NSCLC and solid tumors with NTRK gene fusion	51%	55%	66%	23%	5%	3%	25%
2020	Gavreto	RET fusion-positive metastatic NSCLC	26%	52%	50%	41%	0%	4%	37%
2020	Tabrecta	MET exon 14 skipping mutation-positive metastatic NSCLC	10%	41%	74%	24%	1%	7%	57%
2020	Zepzelca	Metastatic small cell lung cancer	10%	40%	75%	1%	1%	NR	35%

Table adapted from the 2017-2020 Drug Trials Snapshots Summary Reports[92-95]

Chapter 3: Representativeness of Cancer Clinical Trial Participants

Background

Melanoma and lung cancer received the first FDA approvals in immunotherapy, but the patient populations are very different. In the 2020 release of data by the United States Cancer Statistics Working Group for 5-year limited duration prevalence estimates, 99.1% of the approximately 331,000 melanoma patients estimated to be alive in 2017 after a diagnosis of melanoma between 2012 and 2016 were White, and only 0.4% were Black.[4] In lung cancer, the approximately 385,000 patients alive in 2017 after diagnoses in the previous five years were 85.9% White and 10.2% Black. The prevalent melanoma patient population was estimated to included more male patients than female patients (57.2% male vs. 42.8% female), while the lung cancer patient population was the reverse (46.7% male vs. 53.3% female). Finally, an estimated 38.9% of the prevalent melanoma patient population was age 70 or older, compared to 53.3% of the lung cancer patient population. These numbers are estimates based on a broad patient population, and are valuable when considering the general characteristics of patients in a disease area.

Although nivolumab and pembrolizumab have not had FDA Snapshots, some demographic data are available within the publicly posted FDA review documents for the initial approvals. For pembrolizumab's initial melanoma approval, patients enrolled in the key efficacy study were more likely to be male (61%), under age 65 (64%), enrolled in the United States (76%), and White (97%).[96] For nivolumab's

initial melanoma approval, the 120 patients receiving nivolumab in the key efficacy study were similarly more likely to be male (65%), under age 65 (68%), and White (98%), with 43% of these patients enrolled from the United States.[97] When compared to the 2017 prevalence estimates, participants in these pivotal melanoma trials appear somewhat more likely to be male and younger than the broader United States melanoma patient population, but the participation by White patients was similar to the estimated prevalent patient population.

Reviews for the pembrolizumab lung cancer supplemental approval were not publicly posted. However, for nivolumab, reviews for the initial lung cancer approval were posted. In the randomized phase three trial for this approval, enrolled patients were more likely to be male (76.5%) and White (92.6%); the mean and median age was 63.[41] Unlike in melanoma, the key lung cancer trials significantly overrepresented male patients and White patients than might be expected given the prevalence estimates, while also underrepresenting older patients.

Initial evaluations of potential disparities in efficacy of immunotherapy agents across demographic characteristics have been limited. An early meta-analysis of the comparative effectiveness of immunotherapy agents in younger and older patients in clinical trials found consistent survival benefits in both groups but did not include patients over the age of 70.[98] A retrospective analysis of adverse events and outcomes of patients treated with immunotherapy agents at two academic medical centers found similar safety and efficacy across age groups; this analysis consisted of 254 patients, with 18.5% aged 75 or older.[99]

An analysis of the characteristics of real-world metastatic lung cancer patients receiving immunotherapy in the clinic found that the median age was 69, with more than 27% of real-world patients aged 75 or over.[100] This was a much older population than was represented in the clinical trials. Although this analysis also considered other elements of demographic representativeness, the data source was not nationally representative, so it was difficult to draw conclusions about potential differences between the race and ethnicity of the real-world and clinical trial populations.

The initial approvals of the immunotherapy agents were in limited indications, with additional disease areas being added as clinical trials proved positive over time. As an example of this iterative process, key changes in the nivolumab approved indications are shown in **Table 2**, using the approved label language available in the labels posted on the Drugs@FDA website.[101] This table provides a brief explanation for 17 key indication changes that were made to the nivolumab label between the initial approval in December 2014 and the end of 2020, including the addition of new disease areas and changes to the scope of the initial approvals in melanoma and lung cancer.

Some indication changes were omitted from this table. These were primarily changes that involved adding approval for nivolumab to be used as a single agent or in combination with ipilimumab. Ipilimumab is an earlier-generation immunotherapy agent that is also manufactured by Bristol-Myers Squibb, the company that holds nivolumab.

Table 2. Key Nivolumab Label Indication Changes and Additions, 2014-2020.

Date	Key Indication Language Added or Changed	Explanation
12/22/2014	Initial approval: "patients with unresectable or metastatic **melanoma** and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor"	Approved in metastatic / unresectable melanoma as a 2nd or 3rd line therapy after use of ipilimumab and, if applicable, a BRAF inhibitor
9/30/2015	"Unresectable or metastatic **melanoma** in combination with ipilimumab in patients with BRAF V600 wild-type Melanoma"	Added approval as a 1st line combination therapy in metastatic / unresectable melanoma patients who do not have a BRAF V600 mutation
9/30/2015 and 10/09/2015	"Metastatic **non-small cell lung cancer** in patients with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO"	The initial 9/30/2015 label adding approval for metastatic lung cancer patients to the nivolumab label was revised 10/9/2015. The initial label said the agent was indicated in metastatic non-small cell lung cancer as a 2nd line agent after progression with platinum-based chemotherapy. The revision added that nivolumab should be a 3rd line agent after approved therapies for any EGFR or ALK mutations, if applicable.
11/23/2015	"Advanced **renal cell carcinoma** in patients who have received prior antiangiogenic therapy"	Added approval in advanced kidney cancer patients as a 2nd line therapy
5/17/2016	"Classical **Hodgkin lymphoma** that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin."	Added approval in Hodgkin lymphoma after stem cell transplant and post-transplant treatment
11/10/2016	"Recurrent or metastatic squamous cell carcinoma of the **head and neck** with disease progression on or after a platinum-based therapy"	Added approval in metastatic / recurrent head and neck cancer as a 2nd line therapy after platinum-based chemotherapy
2/2/2017	"Locally advanced or metastatic **urothelial** carcinoma who: - have disease progression during or following platinum-containing chemotherapy - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy"	Added approval in locally advanced or metastatic bladder cancer as a 2nd line therapy after platinum-based chemotherapy

7/31/2017	"adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic **colorectal** cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan."	Added approval in colorectal cancer with certain mutations (MSI-H or dMMR) as a 2nd line therapy; the standard 1st line therapies combine fluoropyrimidine, oxaliplatin, and irinotecan
9/22/2017	"patients with **hepatocellular** carcinoma who have been previously treated with sorafenib"	Added approval in liver cancer as a 2nd line therapy after sorafenib
12/20/2017	"patients with **melanoma** with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting"	Added approval in resectable melanoma as a 1st line therapy
4/16/2018	"patients with intermediate or poor risk, previously untreated advanced **renal** cell carcinoma, in combination with ipilimumab"	Added approval in higher risk advanced renal cell patients as a 1st line combination therapy
8/1/2018	"patients with metastatic **small cell lung cancer** with progression after platinum-based chemotherapy and at least one other line of therapy"	Added approval in small cell lung cancer as a 3rd line therapy after platinum-based chemotherapy and another therapy
5/15/2020	"adult patients with metastatic **non-small cell lung cancer** expressing PD-L1(≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab"	Added approval in PD-L1 positive metastatic non-small cell lung cancer patients as a 1st line combination therapy, as long as patient does not have other actionable mutations (EGFR or ALK)
5/26/2020	"adult patients with metastatic or recurrent **non-small cell lung cancer** with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy"	Added approval in metastatic non-small cell lung cancer patients regardless of PD-L1 positive status as a 1st line combination therapy, where the combination must include ipilimumab and platinum-based chemotherapy, and the patient does not have other actionable mutations
6/10/2020	"patients with unresectable advanced, recurrent or metastatic **esophageal** squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy"	Added approval in unresectable advanced / recurrent / metastatic esophageal cancer as a 2nd line therapy
10/2/2020	"adult patients with unresectable malignant pleural **mesothelioma**, as first-line treatment in combination with ipilimumab"	Added approval in unresectable mesothelioma as a 1st line combination therapy
12/29/2020		Bristol Myers Squibb voluntarily withdrew the indication for small

		cell lung cancer after confirmatory studies intended to allow the accelerated approval to be converted to regular approval did not meet the required endpoints.

As **Table 2** shows, nivolumab was only approved in melanoma, non-small cell lung cancer, and kidney cancer through 2015, but added approvals in five other disease areas in 2016 and 2017. Many of these were accelerated approvals, where the company had post-marketing requirements to confirm clinical benefit before full approval of the indication could be granted. Indications were expanded in several disease areas in 2018, including adding approval as a first line therapy instead of just a second line therapy in certain renal cell carcinoma patients and adding approvals for small cell lung cancer instead of just the more common non-small cell lung cancer.

Accelerated approval of nivolumab in small cell lung cancer was granted in 2018, representing the first approval in small cell lung cancer in nearly two decades.[102] However, the confirmatory studies of nivolumab in small cell lung cancer did not meet their specified endpoints. Bristol Myers Squibb (rebranded in 2020 to remove the hyphen from the company name) voluntarily withdrew the indication for nivolumab in small cell lung cancer in December 2020 during a broader industry-wide review of accelerated approvals granted by the FDA. Merck had received a similar accelerated approval for pembrolizumab in small cell lung cancer in 2019 and announced that it was voluntarily withdrawing the indication in March 2021.[103]

The specific language used for the approvals shown in **Table 2** depends on the treatment options available in a given disease area. In most disease areas, nivolumab has been approved for advanced or metastatic patients as a second- or third-line treatment option, after one or two other approved therapies have not worked. This

means that, for the majority of patients in these disease areas who do not have advanced or metastatic cancer, nivolumab is not an FDA-approved treatment. These patients may, however, still be able to receive nivolumab for their cancer treatment as an off-label treatment.

One study of off-label utilization of cancer chemotherapy agents analyzed a billing dataset used by 122 oncology practices across 35 states between 2004 and 2009 that included regularly-updated entries for cancer diagnosis, stage, and line of treatment.[104] In this analysis, 30% of chemotherapy utilization was outside of the FDA-approved indications. When this off-label use was further broken down, 14% was in a setting supported by cancer treatment clinical guidelines, while 10% was in a cancer type that had an FDA-approval for some stage or line of therapy but was not supported by clinical guidelines.

Off-label use may not be inappropriate care; there may be evidence of benefit from a treatment, particularly in a rare cancer, that a company does not believe is sufficient to support an application to the FDA to change the approved indication.[105] However, off-label use may also indicate an extension of the expected risks and benefits from the approved cancer setting to an as-yet-unapproved setting in which the risk-benefit balance may be different. One example of this is the oncology agent bevacizumab, which was proven effective in metastatic colorectal cancer and, immediately after approval in the metastatic setting, began to be used by some oncologists in earlier-stage colorectal cancer patients.[106] Bevacizumab later failed to show efficacy in clinical trials in earlier-stage settings.[105]

Because of this type of off-label use, without regularly updated information about the cancer stage and treatment history, it is difficult to identify whether patients receiving a recently-approved agent are receiving it on-label or off-label. As a result, following the 2014 approvals for nivolumab and pembrolizumab in metastatic or unresectable melanoma and then the added approvals shortly thereafter in 2015 in metastatic lung cancer, a variety of cancer patients may have been treated with these agents. This includes patients for whom the agents were FDA-approved because they had the required advanced disease and prior treatments, as well as patients who might have been receiving the agents off-label. The off-label use could include patients with advanced disease who had not already progressed on prior treatments, and instead may have been using the agents in an unapproved first-line setting. Off-label use could also include patients with earlier-stage disease.

This is not to say that the off-label use is expected to be overly extensive in these immunotherapy agents; oncologists are still making the decision they believe is best for the patient based on available information and in addition to the regulatory approvals are constrained by what off-label situations insurance payers may be willing to cover.[105] However, it does complicate our understanding of what patients may have been receiving treatments as a standard therapy outside of a clinical trial at a given time. At the same time, there were also clinical trials being conducted to evaluate the risk-benefit profile of the agents in these earlier stage, earlier line patient populations. For instance, an NCI-funded phase 3 trial of pembrolizumab in resected stage III-IV melanoma opened to enrollment in October 2015.[107]

Specific Aims

This study analyzed the demographic characteristics, including race, ethnicity, sex, age, and number of comorbidities, between directly comparable groups of lung cancer and melanoma clinical trial participants and non-participants using SEER-Medicare claims data. The study evaluated two aims. Aim one compared the demographics of Medicare patients within the disease area who are also clinical trial participants (comparison group) with the characteristics of Medicare patients within the disease area who are receiving cancer treatment but not participating in a clinical trial (control group). Aim two compared the Medicare clinical trial participants in immunotherapy trials (comparison group) with Medicare patients being prescribed novel immunotherapy agents outside of a trial (control group). Due to the demographic differences in the patient populations and the expectation that disparities in representation may differ by disease group, lung cancer and melanoma patients were analyzed separately for each of the two aims.

Hypotheses

For both aims one and two, clinical trial participants were hypothesized to include a significantly greater proportion of White non-Hispanic patients and male patients than the broader patient population. Clinical trial participants were hypothesized to have a lower mean age and to have fewer comorbid conditions than the broader patient population.

Methods

Data Sources

This study primarily relied on Medicare claims data from the NCI's Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.[108] All analyses complied with the Centers for Medicare and Medicaid Services (CMS) cell size suppression policy. This policy stipulates that any counts with a value of one to 10 cannot be reported directly or be derivable from the reported results. This includes counts of patients or services. The primary SEER-Medicare dataset was supplemented with information from ClinicalTrials.gov, the clinical trials registry managed by the National Library of Medicine.[109]

This study was submitted to the University of Maryland Institutional Review Board (IRB). Because the study used existing data with no identifiable private information, it was deemed not human subjects research and thus exempt from IRB review. However, the SEER-Medicare data do contain geographic county information and service dates, and as such are considered a "limited data set" under the Health Insurance Portability and Accountability Act (HIPAA). To comply with the data use requirements for the SEER-Medicare data, the data were housed within the University of Maryland's enterprise storage and backup environment, the Networked Storage Service (NSS), which is a Network Attached Storage (NAS) service utilizing Dell/EMC Isilon storage arrays. The NSS is housed in secure data centers. The secure data were configured to allow access only by approved individuals who had signed the SEER-Medicare data use agreement.

The SEER Program is conducted by the NCI and collects information about cancer diagnoses occurring in geographic areas that cover approximately 35% of the United States population.[110] As the only comprehensive, population-based cancer registry in the United States, SEER data contribute significantly to cancer statistics that are produced in the U.S., as well as academic research conducted in cancer.[111-113] The SEER registry was linked to Medicare data for the first time in 1991, and the SEER-Medicare linked database continues to be updated regularly.[108] This study uses data from the SEER-Medicare database that were released in 2018.

Obtaining SEER-Medicare data requires submission of a detailed proposal. Upon proposal approval, the SEER-Medicare contractor extracts the requested files necessary for completion of the approved project. All data requests are driven by the selection of a pool of patients based on year of diagnosis, which is the point at which patients enter the SEER registry. Because this study did not restrict the population based on year of diagnosis, a broad set of diagnosis years was requested. Claims from 2012 to 2016 were requested for this study. To include claims data for patients most likely to be treated for advanced lung cancer or advanced melanoma during this time period, data for patients diagnosed from 2002 to 2015 were requested, starting with diagnoses up to ten years before the claims data. As a result, the data also included claims for many people no longer in active treatment.

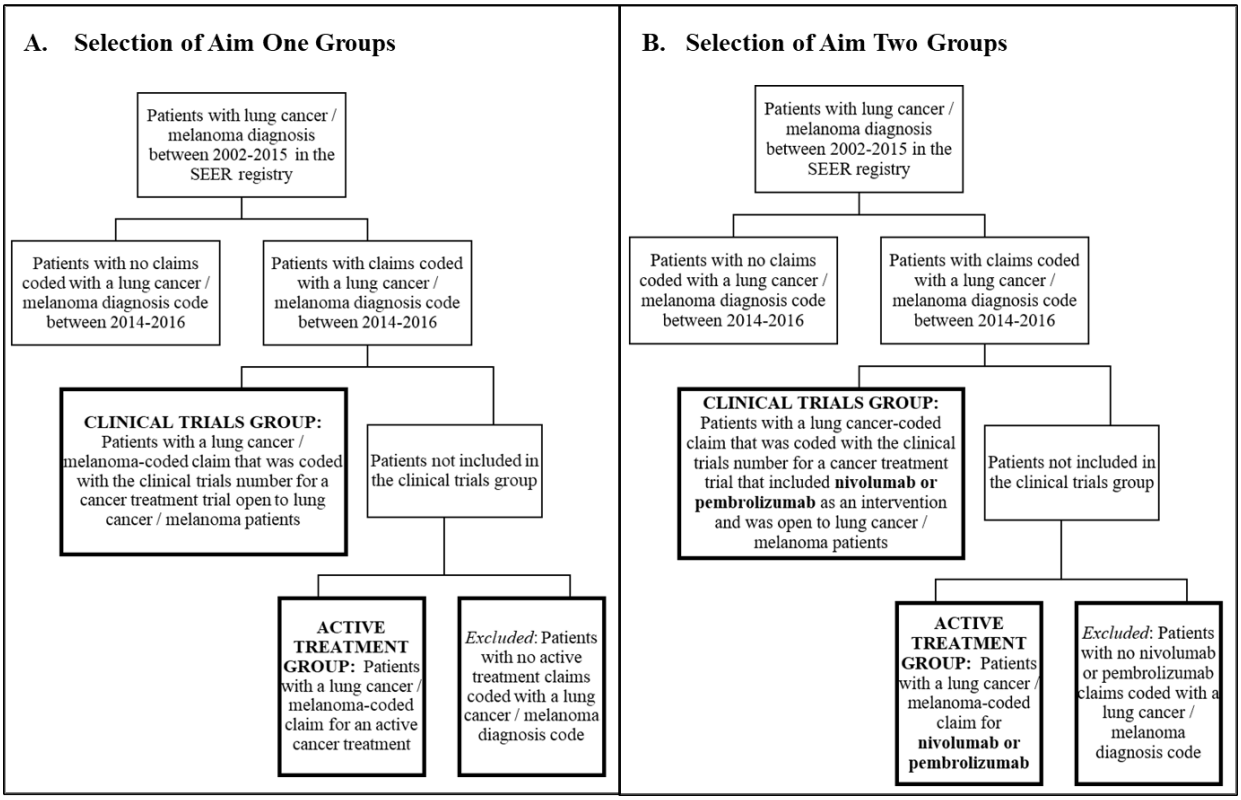
Several steps were taken to identify the population and data of interest in the claims data. The general approach is shown in **Figure 2** and described in more detail in the following pages. Briefly, patients were first limited to those with a claim coded with the disease code of interest, either lung cancer or melanoma, that occurred between 2014

and 2016. This limited set was used to select the clinical trials group, which consisted of patients with a disease-coded claim that was also coded with the clinical trial number for either an active cancer treatment trial in the disease area (aim one) or a trial using nivolumab or pembrolizumab as an intervention (aim two). From the remaining patients, the active treatment group was selected based on the presence of either a disease-coded claim for an active cancer treatment (aim one) or for nivolumab or pembrolizumab (aim two).

As **Figure 2** shows, first, in each disease area, claims were filtered on each of the possible diagnosis code fields so that the dataset only included claims with a diagnosis code under the International Classification of Diseases (ICD) classifications for the relevant disease. Given the claim years included in the analysis, both ICD-9 and ICD-10 codes were used. For lung cancer, the included diagnosis codes were 162.x for ICD-9 and C34.x for ICD-10. For melanoma, the included diagnosis codes were 172.x for ICD-9 and C43.x for ICD-10.

This dataset, filtered by diagnosis code, was used to identify potential clinical trial participants to serve as the control groups in aims one and two of this study. This broader diagnosis code dataset was used instead of the dataset limited to claims for active treatment because patients receiving active therapy on a cancer clinical trial may not be billed for the active therapy received on that trial. For this clinical trials subset, patients were identified based on the diagnosis code, code modifiers, and the clinical trial number code associated with their claims in accordance with the CMS requirements for reporting of claims related to clinical trial participation.[114]

Figure 2. Flow Charts Showing the Selection of the Comparison Groups for Objective One Aim One (Figure A) and Aim Two (Figure B)



For outpatient clinical trial claims, CMS requires that providers use ID-9 diagnosis code V70.7 or ICD-10 diagnosis code Z00.6 as the primary or secondary code. CMS requires utilization of the Healthcare Common Procedure Coding System (HCPCS) when billing claims to Medicare. As of January 2008, CMS has required that providers use the HCPCS modifier code Q0 for any claims that contain an investigational item or service and HCPCS modifier code Q1 for any claims for routine care provided as part of a covered clinical trial. Finally, providers could opt to include the 8-digit clinical trial number registered in ClinicalTrials.gov beginning in April 2008, and that became a requirement starting in January 2014.

This study sought to use claims data starting in 2012 by filtering on a combination of diagnosis code, HCPCS modifier code, and clinical trial number to

identify clinical trial participants. If any of the four HCPCS code modifiers associated with a claim was coded as "Q1" or "Q0", if a diagnosis code of V70.7 or Z00.6 was entered as the first or second diagnosis code, or if a clinical trial number was coded for the claim, the patient was identified as a potential clinical trial participant. An initial evaluation identified a high proportion of claims from 2012 and 2013, before reporting the clinical trial number was required, in which patients were identified as potential clinical trial participants based on the diagnosis code and/or HCPCS code modifier but no clinical trials number was used. This initial evaluation also found that the reported clinical trials numbers included non-cancer treatment trials. Because this study sought to compare patients receiving active cancer treatment to similar patients receiving active cancer treatment through a clinical trial, the final analysis was limited to claims data for 2014-2016 for which a clinical trials number was reported.

For all reported clinical trials numbers, the clinical trial records from ClinicalTrials.gov were individually reviewed and coded based on the trial details. Trials were included for the purposes of this analysis if they were registered in ClinicalTrials.gov as interventional trials. For the lung cancer analysis, the eligible population for the trial had to include lung cancer patients. For the melanoma analysis, the eligible population had to include melanoma patients. The eligible population was determined based on the eligible conditions listed in ClinicalTrials.gov. Trials with broad eligible conditions, such as "cancer," "advanced solid tumors," or "neoplasms" were assumed to be open to lung cancer or melanoma patients. Trials such as supportive care studies were excluded because their primary

objective was not evaluating an anti-cancer treatment. Ultimately, patients were included in the clinical trials group for the aim one analysis only if they had at least one claim coded with the clinical trial number for an active cancer treatment trial in that disease area.

This subset of clinical trials participants was then filtered further to identify the patients to include in the clinical trials group for aim two. Patients were included in the aim two clinical trials group if they had at least one claim coded with the clinical trial number for an active cancer treatment trial in the given disease area for which nivolumab or pembrolizumab was listed as an intervention. The intervention terms used to identify the relevant trials included the drug generic names, nivolumab and pembrolizumab, as well as the other names used throughout agent development. For nivolumab, these were BMS-936558 and ONO-4538. For pembrolizumab, these were lambrolizumab and MK-3475.

The broader claims dataset, filtered solely by diagnosis code, was also used to select the active treatment group for aim one of this study. Among the claims coded with a lung cancer or melanoma diagnosis code, claims were further filtered to include only selected HCPCS codes corresponding with active cancer treatment. Several codes were used to filter both disease areas: “Radiation Oncology Treatment” codes ranging from 77261-77799; “Chemotherapy Administration and Other Highly Complex Drug or Highly Complex Biologic Agent Administration” codes ranging from 96401-96549; and the CMS J9000-J9999 codes for chemotherapy drugs. In lung cancer, “Excision / Resection Procedures on the Lungs and Pleura” codes ranging from 32310-32405 and the “Stereotactic Radiation Therapy Procedures on

the Lungs and Pleura" code 32701 were added to the more general cancer treatment codes. In melanoma, "Excision-Malignant Lesions Procedures on the Skin" codes ranging from 11600-11646 were added to the more general cancer treatment codes.

The aim one control group included patients in the disease area who were not included in the aim one clinical trials group and who had disease-coded claims for any of the active cancer treatment HCPCS codes identified above for that disease area. This dataset was further filtered for the aim two active treatment group. The aim two active treatment group included patients who were not in the nivolumab/pembrolizumab clinical trials group and had a claim in the disease area for either the nivolumab HCPCS code, J9299, or the pembrolizumab HCPCS code, J9271.

Throughout this study, dates were assessed as of the first claim date for an applicable claim. For aim one, for patients in the active treatment code group, this was the earliest date associated with a claim for an active cancer treatment that was coded with the cancer diagnosis code. For patients in the clinical trials group for aim one, this was the earliest date associated with a claim coded with an included clinical trials number that was also coded with the cancer diagnosis code. For aim two, this was the earliest date associated with either a claim for nivolumab or pembrolizumab or associated with a clinical trial containing one of those agents. The dataset also included date of birth information, which was used to calculate patient ages. The SEER-Medicare data contains only month and year of birth, so the day of the month was set as 1 for all patients.

Measures

The analyses were run separately for the two disease areas, lung cancer and melanoma. There were two aims analyzed in each disease area. For the first aim, the dependent variable was the binary variable indicating whether a patient had claims data indicating that they were a clinical trial participant or not. The second aim was restricted to patients who either had claims indicating that they received the immunotherapy agents as standard of care or in a clinical trial, and the dependent variable was whether they were a clinical trial participant or not.

In both aims, the independent variables were patient demographic information. Race, ethnicity, and sex were binary independent variables. The SEER data for race, ethnicity and sex were used. In lung cancer, patients were included if their demographic information indicated that their race was White, Black, or Asian/Pacific Islander. Due to the small number of patients identified as American Indian/Alaska Native, these patients were excluded from the analysis. In lung cancer, race and ethnicity were coded as White non-Hispanic, Black non-Hispanic, Asian/Pacific Islander non-Hispanic, or Hispanic. In melanoma, due to the small number of non-White patients, race and ethnicity were further grouped. For aim one in melanoma, race and ethnicity were grouped as White non-Hispanic, non-White non-Hispanic, or Hispanic. For aim two in melanoma, race and ethnicity were grouped as White non-Hispanic or non-White and/or Hispanic. In both disease areas, sex was coded as male or female.

Age and patient comorbidity were continuous independent variables. Age was calculated as the difference between the first claim date for a patient and their

date of birth. Patient comorbidity was a continuous variable calculated as a count of how many relevant comorbid condition flags were present for the patient during the year of the first applicable claim. Up to 14 key chronic conditions tracked by the CMS Chronic Conditions Warehouse were counted: Alzheimer's, acute myocardial infarction, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, diabetes, hip or pelvic fracture, ischemic heart disease, depression, rheumatoid arthritis, stroke or transient ischemic attack, and acquired hypothyroidism.

Analysis

Relationships between the dependent variable and the independent variables were assessed through chi-square tests of independence for binary variables and t-tests for continuous variables. Due to the number of statistical tests being performed, the Holm-Bonferroni method was used to correct for multiple comparisons.[115,116] In lung cancer, six variables were compared: race (Black non-Hispanic), race (Asian/Pacific Islander non-Hispanic), sex, ethnicity, age, and comorbidity. The Holm-Bonferroni corrected p-value used to assess the significance of the first hypothesis in lung cancer was $\alpha / n = (0.05)/6 = 0.0083$. In melanoma, five variables were compared: race (White non-Hispanic), sex, ethnicity, age, and comorbidity. The Holm-Bonferroni corrected p-value used to assess the significance of the first hypothesis in in melanoma was $\alpha / n = (0.05)/5 = 0.01$. For each successive hypothesis h, the p-value used was $\alpha / (n - h + 1)$

To supplement the individual comparisons, a regression model was used. The number of patients coded as being in a clinical trial was expected to be very small

compared to the number of patients being treated overall, with many factors outside of the available independent variables contributing to whether a patient was a clinical trial participant or not. As a result, the regression model has important limitations and was not the primary analysis; instead, it helped to assess the robustness of the findings from the individual tests. Because the dependent variables were binary, a logistic regression model was used with coefficients interpreted in terms of odds ratios. In lung cancer, the model was:

$$binaryClinicalTrialParticipantLung = \beta0 + \beta1*BlackNH + \beta2*AsianPINH + + \beta3*Hispanic + \beta4*sex + \beta5*age + \beta6*comorbidity + \varepsilon$$

In melanoma, the model was:

$$binaryClinicalTrialParticipantMelanoma = \beta0 + \beta1*WhiteNH + \beta2*Hispanic + \beta3*sex + \beta4*age + \beta5*comorbidity + \varepsilon$$

Data were cleaned and processed using SAS software, version 9.4 for Windows.[117] SEER-Medicare data files were read in using the SEER-Medicare SAS Input Statements.[118] Statistical analyses were performed using R statistical software version 3.5.1.[119]

Results in Lung Cancer

The claims data for patients with a lung cancer diagnosis in the SEER registry between 2002 and 2015 included 161,803 patients who had a claim coded under a lung cancer diagnosis in the claims entered between 2012 and 2016. The dataset included a total of 4,292 patients with a lung cancer claim that was coded in a way that indicated clinical trial participation. Across the included claims years there were significant changes in the quality of clinical trials reporting, as is shown in **Table 3**.

Among lung cancer patients whose first clinical trials-coded claim was in 2012, 95.8% of patients had no valid clinical trials number associated with any clinical trials-coded claim. This dropped to 81.2% for patients whose first clinical trials claim was in 2013. Between 2014 and 2016, no more than 17.4% of patients with a clinical trials-coded claim had no valid clinical trials number associated with a claim. Based on this trend in the quality of clinical trials number reporting, all lung cancer analyses were limited to claims from 2014 through 2016.

Table 3. Lung Cancer Clinical Trials Patients by First Year of Clinical Trials-Coded Claim and Coding of Clinical Trials Numbers

First Year With Clinical Trials Claim for Patient	**No Valid Clinical Trials Number was Entered for Patient**		**Valid Clinical Trials Number was Entered for Patient on At Least One Claim**		**Total**
	n	*%*	*n*	*%*	#
2012	1,306	95.7%	58	4.3%	1,364
2013	641	81.2%	148	18.8%	789
2014	134	17.4%	637	82.6%	771
2015	72	9.6%	679	90.4%	751
2016	96	15.6%	521	84.4%	617
Grand Total	**2,249**	**52.4%**	**2,043**	**47.6%**	**4,292**

There were 107,560 patients with a lung cancer diagnosis between 2002 and 2015 in the SEER registry and at least one claim coded under a lung cancer diagnosis between 2014 and 2016. The dataset included 1,641 clinical trial participant patients with at least one clinical trial number for an active cancer treatment trial open to lung cancer patients. Of these patients, 17 were removed due to incomplete or unusable demographic data, leaving 1,624 patients in the aim one clinical trials group.

Among all 107,560 patients with lung cancer claims between 2014 and 2016, 35,457 had at least one claim for an active treatment code. However, this included

889 patients who were also in the clinical trials group. The clinical trials patients were removed from the active treatment group, leaving 34,568 patients with claims data indicating they were undergoing active cancer treatment. A total of 491 patients were removed due to incomplete or unusable demographic data, leaving 34,077 patients in the aim one active treatment group.

Of the 1,624 lung cancer patients in the aim one clinical trials group, 1,152 were in a trial that did not include nivolumab or pembrolizumab as an intervention. The aim two clinical trials group included the remaining 472 who had a valid clinical trial number for a trial that included nivolumab or pembrolizumab. Among the active cancer treatment patients not in this nivolumab/pembrolizumab clinical trials group, there were 1,728 patients who had a claim for the agent nivolumab or pembrolizumab associated with a lung cancer diagnostic code. Of these, 25 patients were removed due to incomplete or unusable demographic data. The aim two control group included the remaining 1,703 patients with immunotherapy agent claims who were not in a clinical trial for these agents. The demographic characteristics of the 35,701 total patients included in the **aim one** clinical trials and active treatment groups and the 2,175 total patients included in the **aim two** clinical trials and active treatment groups are shown in **Table 4**.

Table 4. Demographic Characteristics of Lung Cancer Patients In Analysis

	Aim One Lung Cancer Patient Characteristics (n=35,701)	**Aim Two Lung Cancer Patient Characteristics** (n=2,175)
	n (%)	*n (%)*
Sex		
Male	17,640 (49.4%)	1,095 (50.3%
Female	18,061 (50.6%)	1,080 (49.7%)
Race and Ethnicity		

	Aim One Lung Cancer Patient Characteristics (n=35,701)	**Aim Two Lung Cancer Patient Characteristics** (n=2,175)
Asian/Pacific Islander Non-Hispanic		
Yes	1,997 (5.6%)	172 (7.9%)
No	33,704 (94.4%)	2,003 (92.1%)
Black Non-Hispanic		
Yes	3,166 (8.9%)	128 (5.9%)
No	32,535 (91.1%)	2,047 (94.1%)
White Non-Hispanic		
Yes	28,967 (81.1%)	1,759 (80.9%)
No	6,734 (18.9%)	416 (19.1%)
Hispanic		
Yes	1,571 (4.4%)	116 (5.3%)
No	34,130 (95.6%)	2,059 (94.7%)
	Average (sd)	*Average (sd)*
Age at first claim date	73.5 (8.2)	73.2 (7.8)
Comorbidity Count	4.5 (2.5)	4.3 (2.5)

For aim one, **Table 5** shows the demographic characteristics and independent tests for significant differences between the 1,624 lung cancer clinical trial participants and 34,077 non-clinical trial participants for aim one. In this broad population of Medicare beneficiaries with lung cancer, clinical trial participants were significantly more likely than non-clinical trial participants to be female (53.6% vs. 50.4%, $p=0.0149$) or Asian/Pacific Islander non-Hispanic (13.0% vs. 5.2%, $p<0.0001$). Clinical trial participants were significantly less likely to be Black non-Hispanic (5.2% vs. 9.0%, $p<0.0001$) or White non-Hispanic (76.5% vs. 81.4%, $p<0.0001$). Clinical trial participants were significantly younger (average age = 70.7 vs. 73.7, $p<0.0001$) and had significantly fewer comorbidities (3.0 vs. 4.6, $p<0.0001$). There was not a significant difference by ethnicity (5.2% vs. 4.4%, $p=0.1064$).

Table 5. Demographic Characteristics of Lung Cancer Patients Who Are and Are Not Clinical Trial Participants

	Aim One Clinical Trial Participants (n=1,624)	**Aim One Non-Clinical Trial Patients** (n=34,077)	**Aim One Chi-Squared or T-Test P-Value**
	n (%)	*n (%)*	
Sex			
Male	754 (46.4%)	16,886 (49.6%)	0.0149*
Female	870 (53.6%)	17,191 (50.4%)	
Race and Ethnicity			
Asian/Pacific Islander Non-Hispanic			
Yes	211 (13.0%)	1,786 (5.2%)	<0.0001*
No	1,413 (87.0%)	32,291 (94.8%)	
Black Non-Hispanic			
Yes	85 (5.2%)	3,081 (9.0%)	<0.0001*
No	1,539 (94.8%)	30,996 (91.0%)	
White Non-Hispanic			
Yes	1,243 (76.5%)	27,724 (81.4%)	<0.0001*
No	381 (23.5%)	6,353 (18.6%)	
Hispanic			
Yes	85 (5.2%)	1,486 (4.4%)	0.1064
No	1,539 (94.8%)	32,591 (95.6%)	
	Average (sd)	*Average (sd)*	
Age at first claim date	70.7 (7.8)	73.7 (8.2)	<0.0001*
Comorbidity Count	3.0 (2.3)	4.6 (2.5)	<0.0001*

*Results were statistically significant per the Holm-Bonferroni corrected p-value.

For aim two, **Table 6** shows the differences in demographic characteristics of lung cancer nivolumab or pembrolizumab clinical trial participants and non-clinical trial patients who received nivolumab or pembrolizumab. In this narrower population of Medicare beneficiaries with lung cancer who either participated in a trial of nivolumab or pembrolizumab or received at least one of these agents as part of standard of care, clinical trial participants were significantly younger (average age = 70.9 vs. 73.8, $p<0.001$) and had significantly fewer comorbidities (3.1 vs. 4.6,

p<0.0001). In these data, there was not a statistically significant difference between the two groups by sex (49.8% female versus 49.6%, p=0.9894). There were no significant differences by race or ethnicity (Asian/Pacific Islander non-Hispanic: 7.4% vs. 8.0%, p=0.7249; Black non-Hispanic: 4.2% vs. 6.3%, p=0.1077; White non-Hispanic: 83.3% vs. 80.2%, p=0.1541; Hispanic: 5.1% vs. 5.4%, p=0.8761).

Table 6. Demographic Characteristics of Lung Cancer Patients Who Are Immunotherapy Clinical Trial Participants or Received Immunotherapy Outside of a Clinical Trial

	Aim Two Clinical Trial Participants (n=472)	**Aim Two Non-Clinical Trial Patients** (n=1,703)	**Aim Two Chi-Squared or T-Test P-Value**
	n (%)	*n (%)*	
Sex			
Male	237 (50.2%)	858 (50.4%)	0.9894
Female	235 (49.8%)	845 (49.6%)	
Race and Ethnicity			
Asian/Pacific Islander Non-Hispanic			
Yes	35 (7.4%)	137 (8.0%)	0.7249
No	437 (92.6%)	1,566 (92.0%)	
Black Non-Hispanic			
Yes	20 (4.2%)	108 (6.3%)	0.1077
No	452 (95.8%)	1,595 (93.7%)	
White Non-Hispanic			
Yes	393 (83.3%)	1,366 (80.2%)	0.1541
No	79 (16.7%)	337 (19.8%)	
Hispanic			
Yes	24 (5.1%)	92 (5.4%)	0.8761
No	448 (94.9%)	1,611 (94.6%)	
	Average (sd)	*Average (sd)*	
Age at first claim date	70.9 (7.9)	73.8 (7.6)	<0.0001*
Comorbidity Count	3.1 (2.3)	4.6 (2.5)	<0.0001*

*Results were statistically significant per the Holm-Bonferroni corrected p-value.

Table 7 provides the odds ratios and 95% confidence intervals for the aim one logistic regression assessing the association between lung cancer patient demographics and clinical trial participation. Lung cancer patients had increased odds of participating in a clinical trial if they were female (OR=1.152, p=0.006, 95% CI 1.041-1.275) compared to if they were male. For the combined variable of race and ethnicity, compared to a White non-Hispanic reference group, patients had increased odds of participating in a clinical trial if they were Asian/Pacific Islander (OR=2.135, p<0.001, 95% CI 1.822-2.501). Compared to the White non-Hispanic reference, patients had decreased odds of participating in a clinical trial if they were Black (OR=0.566, p<0.001, 95% CI 0.452-0.710). Patients had decreased odds of participating in a clinical trial with greater age (OR=0.974, p<0.001, 95% CI 0.967-0.980) and with greater number of chronic conditions (OR=0.784, p<0.001, 95% CI 0.766-0.803). Ethnicity was not significant (Hispanic OR=1.172, p=0.174, 95% CI 0.932-1.474).

Table 7. Logistic Regression Results for Likelihood of Lung Cancer Patients to Be Clinical Trial Participants

Patient Characteristic	**Aim One Odds Ratio**	**Aim One 95% Confidence Interval**	**Aim One P-Value**
Sex			
Male (Ref)	1		
Female	1.152**	(1.041, 1.275)	0.006
Race and Ethnicity			
White Non-Hispanic (Ref)	1		
Asian/Pacific Islander Non-Hispanic	2.135***	(1.822, 2.501)	<0.001
Black Non-Hispanic	0.566***	(0.452, 0.710)	<0.001
Hispanic	1.172	(0.932, 1.474)	0.174
Age at first claim date	0.974***	(0.967, 0.980)	<0.001
Comorbidity Count	0.784***	(0.766, 0.803)	<0.001

Observations	35,701		
Akaike Information Criterion	12,387		
Note: *p<0.05; **p<0.01; ***p<0.001			

Table 8 provides the odds ratios and 95% confidence intervals for the aim two logistic regression assessing the association between lung cancer patient demographics and clinical trial participation. Lung cancer patients had decreased odds of participating in a trial that included nivolumab or pembrolizumab with greater age (OR=0.974, p<0.001, 95% CI 0.960-0.989) and with greater number of comorbid conditions (OR=0.783, p<0.001, 95% CI 0.745-0.823). Compared to the White non-Hispanic reference, patients had decreased odds of participating in a clinical trial if they were Black (OR=0.548, p<0.05, 95% CI 0.329-0.913). There was no significant association by sex (female OR=0.943, p=0.587, 95% CI 0.762-1.166) or for patients who were Hispanic (OR=0.793, p=0.346, 95% CI 0.489-1.284) or Asian/Pacific Islander (OR=0.693, p=0.077, 95% CI 0.462-1.041).

Table 8. Logistic Regression Results for Likelihood of Lung Cancer Patients Receiving Immunotherapy to Be Immunotherapy Clinical Trial Participants

Patient Characteristic	**Aim Two Odds Ratio**	**Aim Two 95% Confidence Interval**	**Aim Two P-Value**
Sex			
Male (Ref)	1		
Female	0.943	(0.762, 1.166)	0.587
Race and Ethnicity			
White Non-Hispanic (Ref)	1		
Asian/Pacific Islander Non-Hispanic	0.693	(0.462, 1.041)	0.077
Black Non-Hispanic	0.548*	(0.329, 0.913)	0.021
Hispanic	0.793	(0.489, 1.284)	0.346
Age at first claim date	0.974***	(0.960, 0.989)	<0.001

Patient Characteristic	Aim Two Odds Ratio	Aim Two 95% Confidence Interval	Aim Two P-Value
Comorbidity Count	0.783***	(0.745, 0.823)	<0.001
Observations	2,175		
Akaike Information Criterion	2,127		
Note: *p<0.05; **p<0.01; ***p<0.001			

Results in Melanoma

The claims data for patients with a melanoma diagnosis in the SEER registry between 2002 and 2015 included 76,619 patients who had a claim coded under a melanoma diagnosis between 2012 and 2016. The dataset included a total of 1,010 patients with a melanoma claim that was coded in a way that indicated clinical trial participation. As **Table 9** shows, the quality of reporting for the clinical trials number improved dramatically between 2012 and 2016. Among patients whose initial clinical trials-coded claim was in 2012, only 17.2% of patients had at least one claim coded with a valid clinical trials number. This increased to 48.5% for patients with an initial clinical trials code in 2013, and then 85.3% in 2014. Based on this trend, these analyses were limited to claims from 2014 through 2016.

Table 9. Melanoma Cancer Clinical Trials Patients by First Year of Clinical Trials-Coded Claim and Coding of Clinical Trials Numbers

First Year With Clinical Trials Claim for Patient	No Valid Clinical Trials Number was Entered for Patient		Valid Clinical Trials Number was Entered for Patient on At Least One Claim		Total
	n	*%*	*n*	*%*	#
2012	173	82.8%	36	17.2%	209
2013	86	51.5%	81	48.5%	167
2014	30	14.7%	174	85.3%	204
2015	13	6.2%	196	93.8%	209

First Year With Clinical Trials Claim for Patient	No Valid Clinical Trials Number was Entered for Patient		Valid Clinical Trials Number was Entered for Patient on At Least One Claim		Total
	n	%	*n*	%	#
2016	23	10.4%	198	89.6%	221
Grand Total	325	32.2%	685	67.8%	1,010

There were 52,312 patients with at least one claim coded under a melanoma diagnosis between 2014 and 2016. This included 553 patients with at least one claim coded with a clinical trial number for an active cancer treatment trial open to melanoma patients. A total of 6 patients were removed due to incomplete or unusable demographic data, leaving 547 patients in the clinical trials group for aim one.

When the data for the 52,312 patients with any melanoma claim were further filtered by cancer treatment HCPCS codes, the data included 22,657 patients. This included 218 patients removed because they were in the clinical trials group, leaving 22,439 potential active cancer treatment patients. A total of 1,662 patients were removed due to incomplete or unusable demographic data, leaving 20,777 patients in the active treatment group for aim one.

Of the 547 melanoma clinical trial participants from aim one, 263 were in a trial that did not include nivolumab or pembrolizumab. The aim two clinical trials group included the remaining 284 who had a valid clinical trial number for a trial that included nivolumab or pembrolizumab. Among the melanoma patients in the dataset who did not have a claim coded for a nivolumab or pembrolizumab clinical trial, there were 471 patients who had a claim for the agent nivolumab or pembrolizumab associated with a melanoma diagnostic code. Of these, 8 patients were removed due to incomplete demographic data. The aim two active treatment group included the

remaining 463 patients with immunotherapy agent claims who were not in a clinical trial for these agents. The demographic characteristics of the 21,324 total patients included in the aim one clinical trials and active treatment groups and the 747 total patients included in the clinical trials and active treatment groups are shown in **Table 10**.

In an attempt to maximize the ability to analyze different associations for different demographic groups while complying with the CMS cell suppression policy, different groupings for race and ethnicity are used for aims one and two in melanoma. The larger aim one analysis includes groups for White non-Hispanic patients, non-White non-Hispanic patients, and Hispanic patients. The more narrow aim two analysis compares White non-Hispanic patients to patients who are non-White and/or Hispanic. The latter group includes just 42 of the 747 patients in the aim two melanoma analysis, and when further divided into groups of clinical trial participants and non-participants, this is the smallest allowable subset.

Table 10. Demographic Characteristics of Melanoma Patients In Analysis

	Aim One Melanoma Patient Characteristics (n=21,324)	**Aim Two Melanoma Patient Characteristics** (n=747)
	n (%)	*n (%)*
Sex		
Male	14,022 (65.8%)	533 (71.4%)
Female	7,302 (34.2%)	214 (28.6%)
Aim One Race and Ethnicity		
White Non-Hispanic		
Yes	20,828 (97.7%)	-
No	496 (2.3%)	-
Non-White Non-Hispanic		
Yes	159 (0.7%)	-
No	21,165 (99.3%)	-
Hispanic		

	Aim One Melanoma Patient Characteristics (n=21,324)	**Aim Two Melanoma Patient Characteristics** (n=747)
Yes	337 (1.6%)	-
No	20,987 (98.4%)	-
Aim Two Race and Ethnicity		
White Non-Hispanic	-	705 (94.4%)
Non-White and/or Hispanic	-	42 (5.6%)
	Average (sd)	*Average (sd)*
Age at first claim date	75.9 (8.6)	73.5 (9.9)
Comorbidity Count	3.2 (2.4)	3.5 (2.5)

Table 11 shows the differences in demographic characteristics of melanoma clinical trial participants and non-clinical trial participants for aim one. In this broad population of Medicare beneficiaries with melanoma, clinical trial participants were significantly more likely than non-clinical trial participants to be male (72.6% vs. 65.6%, p=0.0008) and non-White and non-Hispanic (2.4% vs. 0.7%, p<0.0001), and significantly less likely to be White non-Hispanic (95.6% vs. 97.7%, p=0.0020). Clinical trial participants were significantly younger (average age = 71.3 vs. 76.0, p<0.0001) and had significantly fewer comorbidities (2.3 vs. 3.2, p<0.0001). Hispanic ethnicity was not significant (2.0% vs. 1.6%, p=0.5193).

Table 11. Demographic Characteristics of Melanoma Patients Who Are and Are Not Clinical Trial Participants

	Aim One Clinical Trial Participants (n=547)	**Aim One Non-Clinical Trial Patients** (n=20,777)	**Aim One Chi-Squared or T-Test P-Value**
	n (%)	*n (%)*	
Sex			
Male	397 (72.6%)	13,625 (65.6%)	0.0008*
Female	150 (27.4%)	7,152 (34.4%)	

	Aim One Clinical Trial Participants (n=547)	**Aim One Non-Clinical Trial Patients** (n=20,777)	**Aim One Chi-Squared or T-Test P-Value**
Race and Ethnicity			
White Non-Hispanic			
Yes	523 (95.6%)	20,305 (97.7%)	0.0020*
No	24 (4.4%)	472 (2.3%)	
Non-White Non-Hispanic			
Yes	13 (2.4%)	146 (0.7%)	<0.0001*
No	534 (97.6%)	20,631 (99.3%)	
Hispanic			
Yes	11 (2.0%)	326 (1.6%)	0.5193
No	536 (98.0%)	20,451 (98.4%)	
	Average (sd)	*Average (sd)*	
Age at first claim date	71.3 (8.5)	76.0 (8.6)	<0.0001*
Comorbidity Count	2.4 (2.2)	3.2 (2.4)	<0.0001*

*Results were statistically significant per the Holm-Bonferroni corrected p-value.

Table 12 shows the differences in demographic characteristics of melanoma nivolumab or pembrolizumab clinical trial participants and non-clinical trial patients who received nivolumab or pembrolizumab. In this narrower population of Medicare beneficiaries with melanoma who either participated in a trial of nivolumab or pembrolizumab or received at least one of these agents as part of standard of care, clinical trial participants were significantly younger (average age = 71.0 vs. 75.1, $p<0.0001$) and had significantly fewer comorbidities (2.4 vs. 4.2, $p<0.0001$). In these data, there was not a statistically significant difference between the two groups by sex (male: 73.2% vs. 70.2%, $p=0.4178$) or by the combined variable for race and ethnicity (White non-Hispanic: 95.1% vs. 94.0%, $p=0.6310$).

Table 12. Demographic Characteristics of Melanoma Patients Who Are Immunotherapy Clinical Trial Participants or Received Immunotherapy Outside of a Clinical Trial

	Aim Two Clinical Trial Participants (n=284)	**Aim Two Non-Clinical Trial Patients** (n=463)	**Aim Two Chi-Squared or T-Test P-Value**
	n (%)	*n (%)*	
Sex			
Male	208 (73.2%)	325 (70.2%)	0.4178
Female	76 (26.8%)	138 (29.8%)	
Race & Ethnicity			
White Non-Hispanic	270 (95.1%)	435 (94.0%)	0.6310
Non-White and/or Hispanic	14 (4.9%)	28 (6.0%)	
	Average (sd)	*Average (sd)*	
Age at first claim date	71.0 (8.9)	75.1 (10.2)	<0.0001*
Comorbidity Count	2.4 (2.1)	4.2 (2.5)	<0.0001*

*Results were statistically significant per the Holm-Bonferroni corrected p-value.

For aim one, **Table 13** provides the odds ratios and 95% confidence intervals for the logistic regression assessing the association between melanoma patient demographics and clinical trial participation. Melanoma patients who were female had decreased odds of participating in a clinical trial compared to patients who were male (OR=0.673, p<0.001, 95% CI 0.555-0.815). Patients had increased odds of participating in a clinical trial if they were not White and non-Hispanic (OR=3.353, p<0.001, 95% CI 1.872-6.004). Patients had decreased odds of participating in a clinical trial with greater age (OR=0.949, p<0.001, 95% CI 0.940-0.958) and with greater number of chronic conditions (OR=0.922, p<0.001, 95% CI 0.883-0.961). There was no significant association for patients who were Hispanic (OR=1.258, p=0.465, 95% CI 0.679-2.332).

Table 13. Logistic Regression Results for Likelihood of Melanoma Patients to Be Clinical Trial Participants

Patient Characteristic	**Aim One Odds Ratio**	**Aim One 95% Confidence Interval**	**Aim One P-Value**
Sex			
Male (Ref)	1		
Female	0.673***	(0.555, 0.815)	<0.001
Race			
White non-Hispanic (Ref.)	1		
Non-White non-Hispanic	3.353***	(1.872, 6.004)	<0.001
Hispanic	1.258	0.679, 2.332)	0.465
Age at first claim date	0.949***	(0.940, 0.958)	<0.001
Comorbidity Count	0.922***	(0.883, 0.961)	<0.001
Observations	21,324		
Akaike Information Criterion	4,905		
Note: *p<0.05; **p<0.01; ***p<0.001			

Table 14 provides the odds ratios and 95% confidence intervals for the aim two logistic regression assessing the association between melanoma patient demographics and clinical trial participation. Melanoma patients had decreased odds of participating in a trial that included nivolumab or pembrolizumab with greater number of comorbid conditions (OR=0.724, p<0.001, 95% CI 0.669-0.785). There was no significant association by age (OR=0.989, p=0.242, 95% CI 0.972-1.007), sex (female OR=0.865, p=0.426, 95% CI 0.605-1.236), or race and ethnicity (non-White and/or Hispanic OR=1.059, p=0.876, 95% CI 0.513-2.187).

Table 14. Logistic Regression Results for Likelihood of Melanoma Patients Receiving Immunotherapy to Be Immunotherapy Clinical Trial Participants

Patient Characteristic	**Aim Two Odds Ratio**	**Aim Two 95% Confidence Interval**	**Aim Two P-Value**
Sex			
Male (Ref)	1		
Female	0.865	(0.605, 1.236)	0.426
Race			
White non-Hispanic (Ref.)	1		
Non White and/or Hispanic	1.059	(0.513, 2.187)	0.876
Age at first claim date	0.989	(0.972, 1.007)	0.242
Comorbidity Count	0.724***	(0.669, 0.785)	<0.001
Observations	747		
Akaike Information Criterion	898		
Note: *p<0.05; **p<0.01; ***p<0.001			

Discussion

Potential disparities in clinical research participation are an important concern in public health and medical research, but our understanding of these disparities has been hampered by a lack of good comparison groups. The demographics of the patient population that is eligible for a clinical trial might be very different than the demographics of the overall population, or even of the incident disease population. This study sought to contribute to the field by comparing the demographics of clinical trial participants with equivalent comparison groups. A total of four comparisons were conducted. Two comparisons were each conducted in both lung cancer and melanoma patient populations: the broad group of patients in active treatment were compared to patients on active cancer treatment trials (aim one), and a more narrow

group of patients receiving nivolumab or pembrolizumab as an active treatment were compared to patients receiving those agents on trials (aim two).

As hypothesized, clinical trial patients were younger and had fewer comorbidities in each of the four analyses. These disparities were statistically significant in all of the individual comparison chi-square tests and in all but one of the regressions. The difference in average age ranged from two to three years in lung cancer to four to five years in melanoma. Representation of older adults in cancer clinical trials has been a persistent concern. The biology of some cancers may change with age and thus the treatment outcomes may differ in older patients; older, more frail patients may not be as able to tolerate rigorous cancer treatments with significant side effects; and without evidence from older populations, clinicians may provide different treatment to even non-frail older adults.[120] This analysis shows that, even within the older Medicare population, older adults are less likely to participate in cancer trials. This issue may be linked with the similar finding on comorbidities. Assessments of multiple comorbidities vary, but consistently find increasing comorbid conditions with greater age.[121,122] Comorbid conditions may limit the availability of trials for a patient depending on the trial eligibility criteria. Recent efforts in the cancer community have led to consensus modernized eligibility criteria which may make trials accessible to a broader population, but in some cases, strict eligibility criteria are necessary to ensure patient safety.[67,123]

The results were less consistent for sex, race, and ethnicity. The hypothesized results for race were not seen for the aim one analyses: White non-Hispanic patients were significantly less likely to be clinical trial participants. In the aim two analyses,

a slightly greater proportion of White non-Hispanic patients were in the clinical trials group than in the active treatment group, but these results were not significant. As expected based on the results for White non-Hispanic patients, in each of the aim one analyses, at least one other group had greater clinical trial representation. In the lung cancer aim one analysis, Asian/Pacific Islander patients were significantly more likely to be clinical trial participants, and in melanoma, non-White non-Hispanic patients were. In the larger aim one lung cancer analysis, Black patients were significantly less likely to be clinical trial participants. Again unlike what was hypothesized, clinical trial participants were significantly more likely to be female than male in the aim one lung cancer analysis, but were more likely to be male than female in the aim one melanoma analysis. The comparisons by sex were not significant for the aim two analyses.

Limitations

This analysis has important limitations. It is based on an analysis of Medicare claims data that relies on the accuracy of the claim coding. As this analysis found, fields such as clinical trials number are not always accurately coded. For instance, for the aim one analysis in lung cancer, 15.6% of patients identified as potential clinical trial participants based on the diagnosis code or HCPCS modifier in their 2016 claims data did not have any claims coded with a valid clinical trials number, even though entry of this number was required by CMS starting in 2014. As a result, some clinical trial participants were likely not included in the clinical trials group and may have instead been in the active treatment group.

Despite the broad disease areas including claims across three years, in three of the four analyses included in this study, the clinical trials group had fewer than 600 patients. Demographic subgroups were, of course, even smaller. These small numbers mean that some demographic differences between the clinical trials group and the active treatment group may not have been statistically significant but cannot prove the absence of a disparity.

Similarly, due to the CMS restriction on releasing information about patient counts less than 11, it was not possible to produce more granular analyses by race or ethnicity, particularly in melanoma. Although these counts may have been too small to include in statistical analyses such as chi square tests, the descriptive information would have been helpful to share with the community. Semi-arbitrary groupings of race and ethnicity may disguise important differences. This can be seen in the aim one lung cancer analysis. Asian/Pacific Islander patients had greater rates of clinical trial participation, while Black patients had lower rates. When these groups were initially combined for this analysis, it appeared that non-White patients had overall greater representation in clinical trials; however, this was entirely due to the higher rates in the Asian/Pacific Islander population.

Because this analysis was designed to evaluate the associations between demographic characteristics and clinical trial participation, it does not support conclusions about any potential causal relationships. Additionally, there are important limitations on the generalizability of the study findings. Because the analysis was limited to patients covered by Medicare, the results may not be applicable to younger populations that do not have guaranteed insurance coverage.

Finally, due to the limitations of the data available in Medicare claims, this analysis was not able to compare disease characteristics between the trial group and the active treatment group. Despite the efforts made to ensure equivalent groups, there may still have been differences in the cancer staging between these two populations.

Conclusions

This study lays the groundwork for future research using the SEER-Medicare database to better understand potential disparities in clinical trial participation. The focus of this analysis was lung cancer and melanoma patient populations because these disease groups were the first to see FDA approvals for the novel immunotherapy agents nivolumab and pembrolizumab. Expanding this analysis to other, more common cancer types with greater representation in the SEER registry may produce even more robust findings and allow more granular analyses by race and ethnicity. Additionally, the new SEER-Medicare 2020 linkage will provide more claims years after the CMS requirement to report clinical trial number was instituted in 2014. These additional years of data may make it possible to conduct analyses of demographic subgroups in more disease areas.

Even in rarer disease areas in which the clinical trials comparison group would be too small to allow meaningful analyses, there is great value in providing demographic information about cancer patient groups in active treatment. As this study has discussed, it is difficult to meaningfully evaluate whether enrollment to a clinical trial was sufficiently representative because we do not have good comparison groups. Any demographic information to better inform this comparison is likely to be better than what we currently have. More importantly, this information can allow

researchers to better prospectively identify the patient population they should be trying to enroll. Potential disparities in clinical trial participation can be addressed only if researchers can calculate their planned enrollment by demographic group based on the true disease population, track their progress as the study accrues, and take corrective actions to improve outreach and accessibility of the trial as necessary.

Chapter 4: Industry Payments and Provider Utilization of Immunotherapy Agents

Background

A recent JAMA Special Communication on the topic of medical marketing provided a comprehensive overview of the different forms this marketing can take and the changing investments made by the pharmaceutical industry over two decades.[124] It is important to note that medical marketing is not seen as universally negative. One study in the 1970s highlighted concerns about dissemination of new information such as important clinical trial results, suggesting that journals and continuing medical education requirements may not be enough.[125] More recent research has continued to find insufficient dissemination of knowledge about medical innovation, although specialists were more likely than general practitioners to be aware of key advances.[126] Pharmaceutical industry promotion has been seen as an effective way to increase awareness of agents, but also a potential contributor to overuse.[127,128]

Pharmaceutical payments to physicians in the form of food, gifts, or other compensation are a key component of medical marketing in the United States, totaling nearly one billion dollars in 2016.[124] Until recently, most research investigating the relationship between pharmaceutical payments and provider utilization was based on aggregate data.[129] Limited physician-level data were available to allow for more detailed analyses. One recently-published study by Datta et al. (2017) is an exception, using data from 1997 to 1999 for nearly 150,000 physicians to analyze the effects of promotions for a specific Herpes agent,

famciclovir, on its utilization and the utilization of other agents in the same class.[130] Unfortunately, this analysis has several limitations: it required compiling market research data from various sources with potentially questionable comparability, and it included promotional efforts only for famciclovir, not the other available agents. Perhaps most importantly, it considered a relatively small portion of potential promotional efforts and did not assign them a monetary value. Instead, the independent variables representing industry promotion were number of visits by sales representatives and number of free drug samples received. The authors found that, in this case, there was a significant relationship between promotions and utilization, but the relationship was smaller than what was predicted by aggregate studies. They argue that this suggests selection bias likely drives most of the observed relationship.

Endogeneity is a concern in this literature, but researchers have largely left the potential targeting of physicians by pharmaceutical companies as a key limitation to their work. Efforts to control for endogeneity have not been taken up by the field. For instance, a 2014 analysis combined data from two ProPublica datasets: an opt-in database of industry payments to physicians and a database of physician-level Medicare Part D reimbursements.[131] To attempt to control for industry selection, the authors used geographic distance from the physician office to the industry firm headquarters as an instrumental variable. They found that there was still a significant relationship between industry payments and physician prescribing. However, it is unclear whether this instrument was valid and it has not been used by others. This analysis was focused on payments data from 2009 to 2011. The geographic instrumental variable assumed a relationship between distance from headquarters and

likelihood of sales representatives to travel for medical detailing, but international pharmaceutical companies such as AstraZeneca, Merck, and Pfizer are likely to have sales teams based out of multiple regions. Other geographical factors may also contribute to marketing decisions; an analysis by Alpert et al. described recently unsealed marketing documents from Purdue Pharma that showed how the company did not invest as much OxyContin marketing in states with greater opioid regulations.[132]

In 2010, the U.S. Congress responded to longstanding concerns regarding the effect of pharmaceutical industry promotions on physician practice[133-135] by passing the Physician Payments Sunshine Act as part of the Patient Protection and Affordable Care Act.[136] The Sunshine Act mandated that as of August 2013, CMS collect and report information on payments from industry manufacturers to physicians.[137] These data have been made publicly available through the CMS Open Payment program.[138]

The initial publication of the 2013 Open Payments program data in September 2014[139] came shortly after CMS made Medicare provider utilization data publicly available for the first time in April 2014.[140] Researchers have begun to analyze relationships between pharmaceutical industry payments in the Open Payments datasets and pharmaceutical use information in the Medicare Provider Utilization and Payment Data datasets, finding that industry payments across physician specialties and regions are associated with greater Medicare Part D prescribing costs.[141-144]

Despite the new availability of high-quality data, research has still been limited. One key barrier to researchers is that linking provider information between the two datasets is hampered by the fact that the Open Payments dataset is statutorily

prohibited from publishing the National Provider Identifier (NPI)[145] which serves as the primary provider identifier in the utilization datasets. As a result, physician records must instead be matched on characteristics such as name and address. One of the first high-profile analyses of the Open Payments data, conducted by Tringale et al. and published in *JAMA* in 2017, focused simply on describing the characteristics of physicians reported to have received industry payments without connecting utilization data.[146]

Analyses thus far have also remained focused on better examining either the overall association between payments and utilization or the association seen in a specific sub-field. One field that has seen relatively high levels of research interest is opioid prescribing. Hadland and colleagues have published a series of increasingly specific analyses in this area, starting with a 2017 publication in the American Journal of Public Health, examining just the Open Payments data, which found that more than 8% of U.S. physicians received an opioid-related payment.[147] They went on to combine the Open Payments and Part D utilization datasets, finding that physicians receiving opioid-related payments were more likely to prescribe opioids and that higher payments were associated with greater utilization.[148] The authors note as an important limitation that reverse causality is possible and that their results establish association, not causation. Finally, an analysis just published in 2019 linked Open Payments data to county-level opioid overdose mortality data and found that mortality significantly increased with higher promotional payments.[149]

Other researchers have confirmed the findings by Hadland and colleagues on opioid-related payments. Zezza et al. combined the Open Payments and Part D data

from 2013 to 2015 and analyzed separate cohorts of physicians.[150] They created a matched comparison group, based on state, specialty, and baseline opioid reimbursement levels, that did not receive any opioid payments, and conducted a difference-in-difference regression analysis. Like Hadland et al., they found that payments were associated with greater utilization. More recently, Nguyen et al. used two models to analyze Open Payments and Part D data from 2014 to 2016.[151] First, they used a regression model where the independent variable was a binary indication of whether the physician had received any opioid-related payments; then, they performed a similar regression solely among physicians who had received payments to assess the effect of payment amount on utilization. The authors found that any receipt of payment was associated with greater utilization and higher payments were associated with higher utilization.

A 2020 systematic review by Mitchell et al. extracted the results of 36 studies with 101 total analyses between pharmaceutical payments and utilization.[152] At least one positive association was found in every study, and 89 of the 101 analyses found a positive association between payment and greater prescribing. The authors further note that no studies found an inverse association. Five of the included studies were in oncology, including two led by the lead author of the systematic review.

A review of trends in payments to medical oncologists practicing from 2014 to 2019, over the first five full years of Open Payments reporting, found that the number of oncologists receiving a payment declined by 15.1% from 2014 to 2019, and the payment amounts for those receiving less than $10,000 also declined.[153] However, payment amounts increased among those receiving greater amounts. This

review suggests that pharmaceutical industry promotional practices for oncology are changing, perhaps due to the new reporting requirements.

Generally in oncology, researchers have found a more mixed relationship between industry payments and oncology utilization of Part D agents. Bandari and colleagues used 2014 Open Payments and Part D utilization data to examine the separate associations between payments and utilization of two agents indicated for metastatic castration-resistant prostate cancer.[154] They found that there were many more payment recipients than there were prescribers, although more than half of prescribers received a payment. Ultimately, they did not see an association between payments and utilization for either agent.

Similarly, a 2018 publication by Mitchell et al. used 2013 and 2014 Open Payments and Part D utilization data to examine the associations between payments related to two sets of targeted oncology agents and their utilization.[155] Each set included three brand-name agents approved for the treatment of the same targeted disease setting, one in metastatic renal cell cancer and one in chronic myeloid leukemia. The authors found that receiving payments related to one of the six drugs was significantly associated with greater utilization for three of the drugs; for one of the drugs, imatinib, payments were associated with less utilization. Imatinib was nearing patent expiration, and the authors hypothesized that the company may have been discussing imatinib but also more heavily promoting another drug in their portfolio that would remain under patent. It is unclear why this was not reported as a finding of an inverse association in Mitchell et al.'s recent systematic review.[152]

One key gap in the research to date is that the analyses have primarily focused on utilization in the Part D Prescriber dataset, excluding the provider-administered prescription drug utilization that is covered by Medicare Part B and captured in the Physician and Other Supplier dataset. Medicare Part B utilization of cancer drugs made up 42.1% of Medicare spending for Part B drugs in 2014 and totaled 7.8 billion dollars,[156] representing more than five percent of the $143 billion in total Medicare prescription drug spending.[157] Increasing costs of cancer drugs are an area of significant concern, but Medicare's ability to control spending on cancer drugs is limited, particularly for drugs covered by Part B.[158] A demonstration project proposed in 2016, the Medicare Part B Drug Payment Model, would have sought to assess the impact of changes in reimbursement strategies on Part B drug utilization,[159] and would potentially have a significant impact on oncologists.[160] However, the project was opposed by oncology professional organizations,[161] and it was officially withdrawn in 2017.[162] More information is needed to assess potential drivers of Medicare Part B drug spending among oncologists, which could include industry payments.

One analysis of industry payments and Part B utilization, which examined industry payments to ophthalmologists related to anti-vascular endothelial growth factor (VEGF) injections and the related Part B prescribing, found a significant association between numbers of industry payments received and use of industry-marketed anti-VEGF injections.[163] Additionally, researchers have not focused on payments and utilization associated with the release of new agents. No literature was

found analyzing relationships between payments data and utilization of immunotherapy agents.

Specific Aims

This study used Medicare utilization and Open Payments data to complete two aims evaluating the potential association between receipt of industry promotional payments and utilization of nivolumab and pembrolizumab. Because the data for the two agents could not be meaningfully merged, separate analyses were conducted for nivolumab and pembrolizumab. Aim one analyzed the association between receipt of any industry payment and whether providers are high utilizers of novel immunotherapy agents, first in a selected pool of providers likely to treat melanoma and lung cancer patients, and then among all oncology providers. Aim two evaluated the association between amount of industry payment received and amount of immunotherapy agent utilization among high utilizers of the agent.

Hypotheses

For aim one, in both the pool of lung and/or melanoma oncologists and in the larger group of all oncologists, the presence of any industry payment was hypothesized to correlate with increased likelihood of using the promoted agent in 11 or more beneficiaries. For aim two, the amount and number of industry payments were hypothesized to correlate with utilization of the promoted agent in a larger percentage of the provider's beneficiaries.

Methods

Data Sources: Utilization Data

Data from the Medicare Provider Utilization and Payment: Physician and Other Supplier Public Use File (PUF) for calendar years 2015 through 2018 and CMS Open Payments dataset for calendar years 2015 through 2017 was used to conduct this analysis.[164,165] Information from the Medicare Provider Utilization and Payment: Part D Prescriber PUF informed data selection.[166] Each of these datasets is publicly available and prepared by CMS. Because the data used are publicly available, this study was deemed not human subjects research by the University of Maryland IRB and thus exempt from IRB review.

Both the PUF and Open Payments data sets include information about provider specialty. To limit the analysis to oncologists, data were extracted for physicians with an oncology specialty, including medical oncology, gynecologic oncology, surgical oncology, radiation oncology, or hematology and oncology. Additional summary information for providers was used from the Medicare Physician and Other Supplier Aggregate Dataset for the particular utilization year. This dataset includes variables describing overall characteristics of the beneficiaries seen by the provider.

The Physician and Other Supplier PUF dataset contains aggregated information on Medicare claims and payments by provider and medical procedure. Providers are identified by National Provider Identifier (NPI) as well as name and address. Procedures are classified by HCPCS code and include utilization of Part B drugs (e.g., drugs administered by a provider rather than dispensed by prescription).

The Part B dataset covers non-institutional Part B claims for Medicare fee-for-service beneficiaries. The Part D Prescriber PUF dataset contains aggregated information on Medicare prescription drug claims by prescriber and agent.[164] The Part D dataset covers prescription drugs prescribed and paid for under the Medicare Part D Prescription Drug Program.[166] Approximately two-thirds of Medicare beneficiaries are enrolled in the Part D program. In accordance with the CMS cell size suppression policy, aggregated claims records in all public datasets are omitted if they are based on counts of fewer than 11 Medicare beneficiaries.[167]

Aim one was conducted in two separate populations. First, to assess whether any pharmaceutical payment was associated with high utilization of the agent, which was defined as utilization in 11 or more beneficiaries, the provider population was restricted to a subset of providers of interest representing the pool of providers who might be expected to utilize nivolumab and/or pembrolizumab in their treatment of melanoma and lung cancer patients. The aim one analyses were also conducted in the broader population of all identified oncologists who had any CMS utilization records for the year.

For the narrower pool analysis, the physician population from the PUF dataset was restricted to oncologists who had utilization records for 13 selected agents between 2015 and 2018 that were FDA approved only for melanoma or lung cancer during the given year. Approved indications for each year were found by reviewing the approved drug labels for 2015 to 2018 as posted in the Drugs@FDA database.[101] Although providers may have used these agents off-label in other disease areas, this

filter served as a best approximation to limit the initial analysis to a pool of providers likely treating melanoma and/or lung cancer.

The identified agents and their FDA-approved indications are shown in **Table 15**. For the analysis, provider utilization of these 13 agents and inclusion in the analysis pool was determined by presence of a record for the provider's utilization of the agent in the Part D prescriber or Part B Physicians and Other Supplier PUFs. Three of the 13 agents were approved for additional oncology indications in 2018: dabrafenib and trametinib were approved in thyroid cancer, while ipilimumab was approved in renal cell cancer. Utilization of these three agents was only based on records from 2015 to 2017, when the agents were approved only in melanoma. In the tables, the 2018 provider and beneficiary numbers for these three agents are shaded and italicized to indicate that they were not included.

Table 15. Agents Approved for Melanoma and Lung Cancer with No Other FDA Oncology Approvals Through 2017/2018.

Agent	Indication(s)
Afatinib	Lung – EGFR inhibitor
Alectinib	Lung – ALK inhibitor
Ceritinib	Lung – ALK inhibitor
Cobimetinib	Melanoma – MEK inhibitor
Crizotinib	Lung – ALK inhibitor
Gefitinib	Lung – EGFR inhibitor
Osimertinib	Lung – EGFR inhibitor
Pemetrexed	Lung and mesothelioma – metabolic inhibitor
Vemurafenib	Melanoma – BRAF inhibitor
Vinorelbine	Lung – vinca alkaloid
Dabrafenib	Melanoma – BRAF inhibitor (2018: added lung and thyroid)
Ipilimumab	Melanoma – CTLA-4 inhibitor (2018: added renal)
Trametinib	Melanoma – MEK inhibitor (2018: added thyroid)

In addition to identifying the pool of providers for the aim one analysis, the Part B Physician and Other Supplier PUF dataset was also the source of provider-level records for utilization of the immunotherapy agents. Records were filtered by the HCPCS codes, J9299 for nivolumab and J9271 for pembrolizumab, for services between 2016 and 2018. Because the 2018 provider-level records were more robust, this analysis focused on whether payments made in 2017 were associated with 2018 utilization.

Data Sources: Payments Data

The Open Payments dataset includes records of payments made by drug and device companies to physicians and teaching hospitals. Companies report payments or in-kind payments to physicians such as speaking and consulting fees, research, educational materials, food and drink, and travel. If a payment was related to a specific drug, that drug is identified. As many as five drugs can be associated with an individual payment. Each payment is classified as either research or non-research. Payments are reported annually by CMS for each calendar year. This analysis solely includes non-research payments to physicians with a specialty type of oncology when the payment was associated with one of the approved IO agents: pembrolizumab (Keytruda) or nivolumab (Opdivo).

Data Sources: Matching Utilization and Payments Data

The NPI is used by CMS to collect and aggregate payment data, but regulations prohibit NPIs from being included in the Open Payments data released to the public. As a result, providers are identified only by name, address, and a unique Open Payments identifier. To create a link between the Physician and Other Supplier

PUF NPI and the Open Payments identifier, a series of steps were followed. This process used all available years for the Physician and Other Supplier PUF to create a dataset of physicians identified for any year with a specialty in oncology. The available Open Payments data includes a single Physician Profile Supplement file with information about physicians across all years who received at least one published payment. This supplement file has taxonomy fields to capture up to five specialties for each physician. The supplement file was filtered to create a dataset including all physicians with an oncology specialty code listed in any of the taxonomy fields. Both datasets were cleaned to reduce inconsistencies in punctuation and abbreviations.

The unique identifier in each dataset was used to generate records of individual physicians and identify cases of identical first and last names. For physicians with names that had a single match between the two datasets, the NPIs were mapped to Open Payments identifiers based on this match. In cases of duplicate names, where names were not enough to generate an accurate match, names and addresses were examined individually and matched. Finally, unmatched names were manually compared based on a combination of name and address information to identify matches where data discrepancies meant that the information in the two datasets was not identical. In a preliminary study linking these datasets for an analysis of granulocyte colony stimulating factor utilization by oncologists, fewer than five percent of individuals who prescribed these agents in the PUF dataset did not match to the Open Payments dataset.

Measures

The analyses were run separately for the two immunotherapy agents, nivolumab and pembrolizumab. Two models were used for each agent, corresponding to the two aims. For the first model, for aim one, the dependent variable was the binary variable indicating whether a given provider was a high utilizer of the immunotherapy agent in 2018. The second model, for aim two, was restricted to high utilizers and the dependent variable was a continuous variable for percentage of the provider's total beneficiaries who were administered the immunotherapy agent in 2018.

In the first model, the primary independent variable was a binary variable indicating whether the provider received any pharmaceutical industry payments associated with the immunotherapy agent of interest in 2017. The model was first run just in the pool of oncologists identified as likely providers for melanoma and/or lung cancer patients. Then, when the model was run in the broader population of all oncologists with CMS records for that year, an additional independent variable was added for whether the oncologist was identified in the pool or not.

For the second model, the primary independent variable was the amount of pharmaceutical industry payments for the immunotherapy agent of interest in 2017. For payments that were associated with more than one agent, the payment amount was adjusted by dividing the total amount by the number of associated agents. Although the number of payments was also available as a potential independent variable, the number of payments was highly collinear with the amount of the payments. The amount of payments was chosen as the primary independent variable

because it was expected to better capture the relationship between the payments and agent utilization. The number of payments was expected to potentially be more of a proxy for the number of communications or contacts between the pharmaceutical company and the provider.

Additional independent variables controlled for in the models included characteristics of the Medicare beneficiaries served by each provider. These beneficiary characteristics are made available with the PUF data and include average beneficiary age, average beneficiary Hierarchical Condition Category (HCC) risk score, and total number of unique Medicare beneficiaries given services by a provider, which is an indicator of practice volume. HCC scores are used by Medicare to estimate the risk of higher than expected costs for a given patient for health plan payment purposes and allow basic comparisons of the health of two patient populations.[168] All preceding independent variables were continuous variables. The sole binary variable was provider gender.

Analysis

All statistical analyses were performed using R statistical software version 4.0.3.[169] Independent associations between the dependent variables and the independent variables were assessed through chi-square tests of independence for binary variables and t-tests for continuous variables. Multivariate regressions were the primary focus of the analysis. After each regression model was run, potential outliers were identified using Bonferroni outlier tests to identify observations for which the studentized residual was statistically different than those of other observations. This was done using the outlier.test function in the car package in R

developed by John Fox.[170] The identified observations were examined individually to evaluate if there were extreme values for any of the variables, and, if warranted, the outliers were removed.

For aim one, in the analyses of the pool of providers and the broader group of all oncologists, the dependent variable for the model was the binary variable for whether the provider was a high utilizer of the agent and the primary independent variable was the receipt of any associated payment. The independent relationship between these two variables was assessed using chi-squared tests of independence. A logistic regression model was used as the primary analysis approach to assess the relationship when controlling for appropriate covariates. Covariates were interpreted in terms of odds ratios. In the regression model for the broad analysis, an additional covariate was added based on whether the provider was identified for inclusion in the pool analysis based on utilization of other lung cancer and/or melanoma therapies. This logistic regression model was used:

$$binaryHighUtilizerAgent = \beta 0 + \beta 1 * binaryAnyIOPayment +$$
$$\beta 2 * providerGender + [\beta 3 * pool +] \beta 4 * numUniqueBenes +$$
$$\beta 5 * beneAverageAge + \beta 6 * beneAverageHCC + \varepsilon$$

For aim two, in the analysis of high utilizers of the immunotherapy agent, the dependent variable was a continuous variable for the percentage of beneficiaries with utilization of the immunotherapy agent and the primary independent variable was the adjusted amount of the associated payment. The relationship between these two continuous variables was not always linear. For linear relationships, a Pearson

correlation test was run to assess the independent relationship. For non-linear relationships, a generalized additive model using just the two variables was run.

Similarly, due to the non-linear relationships uniformly seen for adjusted amount of payment and the total number of unique beneficiaries, a generalized additive model (GAM) was used for the aim two regression.[171,172] The model was run in R using the mgcv package designed by Simon Wood, which is based on using penalized regression splines to balance minimizing the mean squared error while penalizing models that are overfitted and thus become overly wiggly.[173,174] For this model, the binary covariates for provider gender and whether the provider was identified as part of the aim one pool were added without smooth terms. The continuous covariates – adjusted amount of payment, number of unique beneficiaries, beneficiary average age, and beneficiary average HCC score – were added to the initial model with smooth terms. If the model results indicated that the relationship for a continuous variable was linear, the smooth term was removed for that variable and the model re-run. The initial model was:

$$pctIOBeneficiaries = \beta 0 + \beta 1 * providerGender + \beta 2 * pool + f1(adjAmtIOPayments) + f2(numUniqueBenes) + f3(beneAverageAge) + f4(beneAverageHCC) + \varepsilon$$

Results for Data Filtering and Matching

Utilization Data

Table 16 gives an overview of the number of providers in the Part B and Part D PUF dataset by year. Between 2015 and 2018, there were a total of 1,811,023 distinct providers with services reported in either the Part B dataset, the Part D

dataset, or both. In addition to the overall number of providers, the table shows the number of providers who reported an oncology specialty in that given year. When all of the oncology providers from 2015 to 2018 were combined, there were 21,603 unique oncology providers.

Table 16. Number of Providers in Part B and Part D Utilization Datasets by Year.

	2015	2016	2017	2018	All Years
Total Number of Providers					
Part B	1,019,442	1,053,958	1,088,687	1,121,462	1,299,609
Part D	1,102,253	1,131,550	1,162,898	1,204,935	1,394,595
Total Distinct in Either Part B or D	1,442,065	1,482,851	1,525,686	1,579,507	1,811,023
Number of Providers with Oncology Specialty in That Year					
Part B	17,196	17,609	18,090	18,278	20,628
Part D	17,318	17,682	18,066	18,158	20,938
Total Distinct in Either Part B or D	18,054	18,473	18,963	19,128	**21,603**

Table 17 shows the number of provider-level records available in each year in the Part B and Part D datasets. There is a unique provider-level record for each service type that the provider performed for 11 or more Medicare beneficiaries in a given year. The table includes the number of service records overall and for the identified list of 21,603 oncologists.

Table 17. Number of Services in Part B and Part D Utilization Datasets by Year.

	2015	2016	2017	2018
Total Number of Provider-Level Service Descriptions				
Part B	9,497,892	9,714,897	9,847,444	9,961,866
Part D	24,524,894	24,964,300	25,209,130	25,311,600
Total Number of Provider-Level Service Descriptions for Oncologists				
Part B	319,970	327,268	325,221	321,770
Part D	253,653	259,210	260,492	259,385

The Part B PUF records were filtered to identify the provider-level records for utilization of the immunotherapy agents. **Table 18** shows the number of provider-level records for utilization of each of these agents by year, as well as the national numbers for the actual number of providers utilizing each agent. As this shows, the Part B provider-level PUF for 2018 included records for 17.3% of the 4,482 providers who utilized nivolumab and 14.7% of the 4,370 providers who utilized pembrolizumab. The remaining 82.7% of nivolumab utilizers and 85.4% of pembrolizumab utilizers did not have provider-level service records for the agent, likely because the records were suppressed because they included counts of 10 or fewer patients.

Table 18. Number of Providers with Nivolumab or Pembrolizumab Services in the Provider-Level PUF and Nationally, By Year.

	Number of Part B Providers With Provider-Level Records in PUF			**Number of Part B Providers According to National Numbers**		
Agent (HCPCS code)	**2016**	**2017**	**2018**	**2016**	**2017**	**2018**
Nivolumab (J9299)	546	649	777	4,385	4,528	4,482
Pembrolizumab (J9271)	27	181	641	2,139	3,821	4,370

Service records for the 21,603 unique oncologists in the PUF data were analyzed to determine usage of the 13 agents that were identified in **Table 15**. This usage determined the subset of providers who were considered likely to treat lung cancer and/or melanoma patients, and thus would make up the pool of providers for the aim one analysis of agent utilization. There were 356 unique providers with high utilization of these agents who were identified for inclusion in the pool from the Part

B records and 2,028 unique providers identified for inclusion in the pool from the Part D records. There was an overlap of 222 providers included in both the Part B and Part D records, so the final pool of providers for the first aim one analysis included up to 2,250 unique oncologists. Of these 2,250 potential pool oncologists, 2,146 had Part B utilization records and demographic information for 2018. Thus, the aim one pool analysis included 2,146 providers. **Table 19** provides key characteristics for the 2,146 providers in the aim one pool and the 19,159 providers in the aim one broad analysis.

Table 19. Characteristics of Providers in Pool and Broad Analysis Groups for Utilization and Payments Analysis

	Pool Analysis Provider Characteristics (n=2,146)	**Broad Analysis Provider Characteristics** (n=19,159)
	n (%)	*n (%)*
Provider Gender		
Male	1,624 (75.7%)	12,912 (67.4%)
Female	522 (24.3%)	6,247 (32.6%)
Nivolumab – Presence of Payment and High Utilization		
Received a Nivolumab-Associated Payment in 2017	1,034 (48.2%)	4,635 (24.2%)
High Utilizer of Nivolumab in 2018	362 (16.9%)	777 (4.1%)
Pembrolizumab – Presence of Payment and High Utilization		
Received a Pembrolizumab-Associated Payment in 2017	1,045 (48.7%)	4,498 (23.5%)
High Utilizer of Pembrolizumab in 2018	321 (15.0%)	641 (3.3%)
Receipt of Associated Payment(s) Across Both Agents		

	Pool Analysis Provider Characteristics (n=2,146)	**Broad Analysis Provider Characteristics** (n=19,159)
Received Both a Nivolumab-Associated and a Pembrolizumab-Associated Payment in 2017	821 (38.3%)	3,227 (16.8%)
Did Not Receive Either a Nivolumab-Associated Payment or a Pembrolizumab-Associated Payment in 2017	888 (41.4%)	13,253 (69.2%)
High Utilization Across Both Agents		
High Utilizer of Both Nivolumab and Pembrolizumab in 2018	231 (10.8%)	403 (2.1%)
Not a High Utilizer of Either Nivolumab or Pembrolizumab in 2018	1,694 (78.9%)	18,144 (94.7%)
Averages	*Average (sd)*	*Average (sd)*
Total Number of Unique Beneficiaries	511.4 (404.4)	301.4 (337.8)
Beneficiary Average Age	73.2 (2.2)	72.3 (2.8)
Beneficiary Average HCC	2.2 (0.4)	2.0 (0.5)
Nivolumab-Associated Payments		
If nivolumab-associated payment was received, adjusted **amount** of payment	$2,242.5 (12,234.6)	$1,207.7 (8,977.6)
If payment was received, **number** of payments	7.7 (8.7)	6.0 (7.2)
High Utilization of Nivolumab		
If provider was a high utilizer of nivolumab, **number** of beneficiaries in which nivolumab was utilized	18.2 (6.9)	16.8 (5.9)
If provider was a high utilizer of nivolumab, **percentage** of beneficiaries in which nivolumab was utilized	1.99% (1.06)	2.11% (1.32)
Pembrolizumab-Associated Payments		
If pembrolizumab-associated payment was received, adjusted **amount** of payment	$1,118.4 (6,337.3)	$629.2 (4,951.2)
If payment was received, **number** of payments	6.1 (6.3)	4.9 (5.7)

	Pool Analysis Provider Characteristics (n=2,146)	**Broad Analysis Provider Characteristics** (n=19,159)
High Utilization of Pembrolizumab		
If provider was a high utilizer of pembrolizumab, **number** of beneficiaries in which pembrolizumab was utilized	16.7 (5.5)	15.6 (4.7)
If provider was a high utilizer of pembrolizumab, **proportion** of beneficiaries in which pembrolizumab was utilized	1.98% (1.34)	2.23% (1.54)

Payments Data

The 2017 Open Payments dataset included a total of 632,201 providers with 11,239,733 payments. When the dataset was limited to oncologists, there were 18,307 providers with 527,579 payments totaling over $128 million. These oncologists had an average of 28.8 (sd=28.8) payments for an average of $7,013 (sd=31,167). In this group, 3,499 (19%) had just one payment, and 7,616 (41.6%) had fewer than five payments.

Food and beverage made up the overwhelming majority of the number of payments (n=435,477, 82.5%) but represented just 8.3% of the total payment amounts ($10,589,060). The greatest payment amounts were in the categories of compensation for services other than consulting, which made up 39.0% of the total paid (n=17,141, $50,118,179), and in consulting fees, which were 31.8% (n=13,338, $40,853,734). The 100 oncologists with the greatest summed payment amounts, representing just 0.5% of the providers, received 24% of the total payment amount.

Matched Provider Utilization and Payments Data

There were 21,603 unique providers in the PUF data with an oncologist specialty in at least one of the years considered. In the Open Payments Physician Profile Supplement file, which includes information about all providers who ever received a payment, there were 27,407 unique providers with an oncologist specialty. A total of 18,335 providers were matched between the two datasets, for a match rate of 84.9% of the PUF providers. The remaining 3,268 (15.1%) of PUF providers were assumed to have no match because they did not receive any payments. The 9,072 Open Payments providers with no match were assumed to have not provided services through Medicare between 2015 and 2018 and thus not be included in the PUF.

Results for Nivolumab

Nivolumab Aim One Pool Analyses

Of the 2,146 providers in the aim one pool, one significant outlier was identified during nivolumab regression modeling. This provider had 3,584 total unique beneficiaries, compared to the next highest value of 3,259. This outlier was removed, leaving 2,145 providers in the pool. For these providers, 362 (16.9%) were high utilizers of nivolumab, while 1,783 (83.1%) had no record of nivolumab utilization. **Table 20** provides the characteristics of the providers in the pool, grouped by whether the provider was a high utilizer or not. The table includes whether each characteristic was significantly independently associated with whether a provider is a high utilizer. High utilizers of nivolumab were more likely than providers who were not high utilizers to have received a nivolumab-associated payment in the preceding year (63.5% vs. 45.1%, $p<0.0001$), be male (82.9% vs.

74.3%, p=0.0006), and have more unique beneficiaries (average 1,051 vs. 400, p<0.0001). Differences between the groups by beneficiary average age (73.8 vs. 73.1, p<0.0001) and average HCC score (2.10 vs. 2.18, p<0.0001) were also statistically significant.

Table 20. Demographic Characteristics of Identified Pool of Providers Who Were and Were Not High Utilizers of Nivolumab, 2018

	High Utilizer of Nivolumab (n=361)	**Not a High Utilizer of Nivolumab** (n=1,783)	**Chi-Squared or T-Test P-Value**
	n (%)	*n (%)*	
Received a Nivolumab-Associated Payment in 2017			
Yes	230 (63.5%)	803 (45.0%)	<0.0001***
No	132 (36.5%)	980 (55.0%)	
Provider Gender			
Male	300 (82.9%)	1,324 (74.3%)	0.0006***
Female	62 (17.1%)	459 (25.7%)	
	Average (sd)	*Average (sd)*	
Total Number of Unique Beneficiaries	1,050.6 (461.6)	400.2 (277.4)	<0.0001***
Beneficiary Average Age	73.8 (1.3)	73.1 (2.3)	<0.0001***
Beneficiary Average HCC	2.10 (0.23)	2.18 (0.39)	<0.0001***
*Note: *p<0.05; **p<0.01; ***p<0.001*			

Table 21 provides the odds ratios and 95% confidence intervals for the logistic regression assessing the association between high utilization of nivolumab and other provider characteristics within the identified provider pool. In the regression model, the only significant association with high utilization of nivolumab was the provider's total number of unique beneficiaries. Additional unique beneficiaries served were associated with significantly increased odds of the high

nivolumab utilization (OR=1.005, p<0.001, 95% CI 1.004-1.005). There were no significant associations by receipt of nivolumab-associated payment (OR 1.142, p=0.396, 95% CI 0.841-1.551), provider gender (female OR 0.840, p=0.382, 95% CI 0.569-1.241), beneficiary average age (OR 0.945, p=0.212, 95% CI 0.864-1.033), or beneficiary average HCC (OR 1.504, p=0.114, 95% CI 0.907-2.494).

Table 21. Logistic Regression Results for Likelihood of Providers To Be High Utilizers of Nivolumab, 2018

Characteristic	Odds Ratio	95% Confidence Interval	P-Value
Received a Nivolumab-Associated Payment in 2017			
No (Ref.)	1		
Yes	1.142	(0.841, 1.551)	0.396
Provider Gender			
Male (Ref.)	1		
Female	0.840	(0.569, 1.241)	0.382
Total Number of Unique Beneficiaries	1.005***	(1.004, 1.005)	<0.001
Beneficiary Average Age	0.945	(0.864, 1.033)	0.212
Beneficiary Average HCC	1.504	(0.907, 2.494)	0.114
Observations	2,145		
Akaike Information Criterion	1,197		
Note: *p<0.05; **p<0.01; ***p<0.001			

Nivolumab Aim One Broad Analyses

The broad analysis included 19,159 providers with an oncology specialty during the identified years and demographic data and records for the 2018 utilization

PUF. There were five significant outliers removed with greater than 5,000 total unique beneficiaries, leaving 19,154 records included in the analysis. Of these, 776 (4.1%) were high utilizers of nivolumab. **Table 22** shows the characteristics of this broad group of providers by whether or not there were high utilizers of nivolumab in 2018, as well as the results of the independent test of significance between the characteristic and high utilization of nivolumab. The independent tests were significant for each included characteristic. High utilizers were significantly more likely to have received a nivolumab-associated payment in 2017 (54.3% vs. 22.9%, $p<0.001$), to be male (80.2% vs. 66.8%, $p<0.001$), to have been identified for inclusion in the aim one pool based on prescribing other lung cancer and/or melanoma therapies (46.6% vs. 9.7%, $p<0.001$), to have beneficiaries with a greater average age (73.6 years vs. 72.3 years, $p<0.001$), to have beneficiaries with a greater average HCC (2.111 vs. 2.043, $p<0.001$), and to have more total unique beneficiaries (average of 934.1 vs. 272.3, $p<0.001$).

Table 22. Demographic Characteristics of Broad Group of Providers Who Were and Were Not High Utilizers of Nivolumab, 2018

	High Utilizer of Nivolumab (n=776)	**Not a High Utilizer of Nivolumab** (n=18,378)	**Chi-Squared or T-Test P-Value**
	n (%)	*n (%)*	
Received a Nivolumab-Associated Payment in 2017			
Yes	421 (54.3%)	4,213 (22.9%)	<0.001***
No	355 (45.7%)	14,165 (77.1%)	
Provider Gender			
Male	622 (80.2%)	12,285 (66.8%)	<0.001***
Female	154 (19.8%)	6,093 (33.2%)	
In Aim One Pool			

	High Utilizer of Nivolumab (n=776)	**Not a High Utilizer of Nivolumab** (n=18,378)	**Chi-Squared or T-Test P-Value**
Yes	362 (46.6%)	1,784 (9.7%)	<0.001***
No	414 (53.4%)	16,594 (90.3%)	
	Average (sd)	*Average (sd)*	
Total Number of Unique Beneficiaries	934.1 (425.6)	272.3 (251.1)	<0.001***
Beneficiary Average Age	73.6 (1.5)	72.3 (2.8)	<0.001***
Beneficiary Average HCC	2.111 (0.242)	2.043 (0.558)	<0.001***
*Note: *p<0.05; **p<0.01; ***p<0.001*			

Table 23 provides the odds ratios and 95% confidence intervals for the logistic regression assessing the association between high nivolumab utilization and other provider characteristics in this broader group of oncologists. In this group, each of the covariates was significant. Receipt of a nivolumab-associated payment in 2017 was associated with greater likelihood of high utilization of nivolumab (OR 1.58, p<0.001, 95% CI 1.32-1.89), as was being in the aim one pool (OR 3.25, p<0.001, 95% CI 2.72-3.90), while female provider gender was associated with lower likelihood (OR 0.77, p=0.015, 95% CI 0.62-0.95). Additional unique beneficiaries (OR 1.004, p<0.001, 95% CI 1.003-1.004), higher average beneficiary age (OR 1.05, p=0.028, 95% CI 1.01-1.10), and higher average beneficiary HCC (OR 1.67, p<0.001, 95% CI 1.37-2.03) were all significantly associated with greater likelihood of high utilization in this model.

Table 23. Logistic Regression Results for Likelihood of Broad Group of Providers to Be High Utilizers of Nivolumab, 2018

Characteristic	Odds Ratio	95% Confidence Interval	P-Value
Received a Nivolumab-Associated Payment in 2017			
No (Ref.)	1		
Yes	1.58***	(1.32, 1.89)	<0.001
Provider Gender			
Male (Ref.)	1		
Female	0.77*	(0.62, 0.95)	0.015
In Aim One Pool			
No (Ref.)	1		
Yes	3.25***	(2.72, 3.90)	<0.001
Total Number of Unique Beneficiaries	1.004***	(1.003, 1.004)	<0.001
Beneficiary Average Age	1.05*	(1.01, 1.10)	0.028
Beneficiary Average HCC	1.67***	(1.37, 2.03)	<0.001
Observations	19,154		
Akaike Information Criterion	4,277		
Note: *p<0.05; **p<0.01; ***p<0.001			

Nivolumab Aim Two Analyses

The aim two analysis was limited to high utilizers of nivolumab and the dependent variable was the percentage of the provider's total beneficiaries who had utilized nivolumab. Among the 777 providers who were high utilizers of nivolumab in 2018, six providers who utilized nivolumab in more than 7.3% of their beneficiaries and one provider with 5,170 unique beneficiaries were removed as outliers, leaving 770 providers for the aim two analysis. These 770 providers had

utilized nivolumab in an average of 2.03% of their total beneficiaries (sd 0.95). The percentage utilization ranged from 0.39% to 7.14%, with 408 (53.0%) having utilization in between 1% and 2% of their beneficiaries. A total of 416 (54.0%) of the 770 had received a nivolumab-associated payment. The average adjusted payment amount for those who received a payment was $2,474.82. However, this distribution was right-skewed: 33.9% of those who received a payment had an adjusted payment amount of less than $50, and 52.9% had an amount less than $100. In an independent test of association, among the high utilizers of nivolumab included for this analysis, providers who had received any nivolumab-associated payment in 2017 had a significantly higher percentage utilization of nivolumab (2.14% vs. 1.95%, p=0.006).

The GAM to evaluate the association between total adjusted nivolumab-associated payment received and percentage utilization of nivolumab found a significant relationship ($p<0.001$). This can be seen in **Figure 3**. There was an increase in utilization seen for payments up to $15,000 to $25,000. Above that, the utilization percentage was similar with greater payment amounts.

Figure 3. Smoothed Fit With 95% Confidence Bounds for the Percent of Nivolumab Utilization in 2018 and Total Adjusted Nivolumab-Associated Payment in 2017.

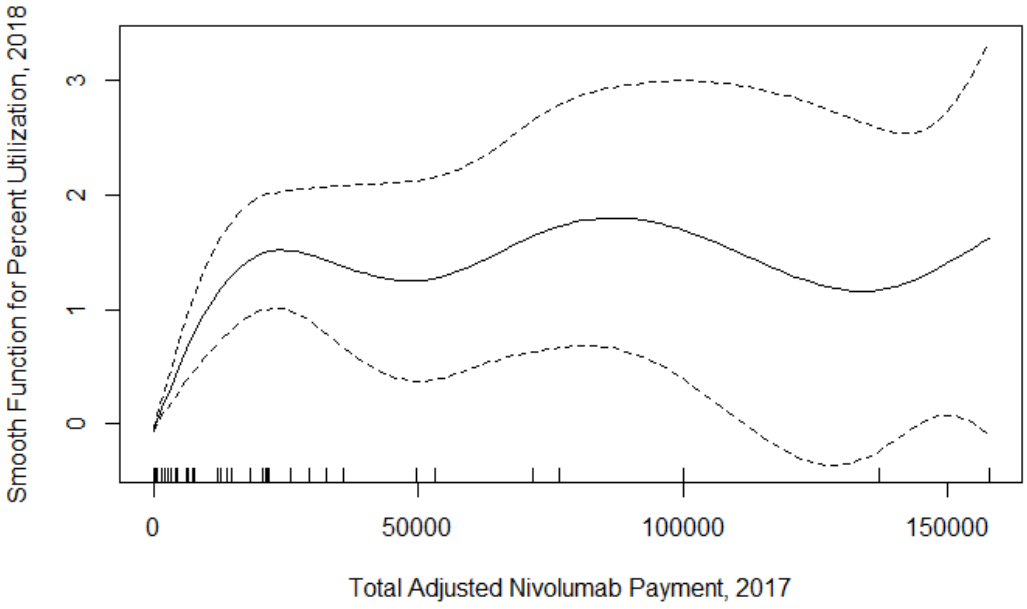


Table 24 shows the results of the aim two regression, which also used a GAM. The binary variables for whether the provider was in the aim one pool and the provider gender were included in the model as parametric terms. The continuous variables for beneficiary average age and beneficiary average HCC score had linear relationships when they were run with smooth terms in the initial model, so for the final model these variables were also included as parametric terms. The total adjusted nivolumab-associated payment and total unique beneficiaries were included with smooth functions.

Adjusted nivolumab-associated payment amount, number of unique beneficiaries, average beneficiary age, and average beneficiary HCC were all significantly associated with utilization of nivolumab in a higher percentage of beneficiaries, while provider gender was not significant (p=0.45). Controlling for the

other covariates, a one year increase in average beneficiary age was associated with a decrease in nivolumab utilization of 0.05% (p=0.002), while a 0.1 unit increase in average beneficiary HCC was associated with an increase in nivolumab utilization of 0.033% (p<0.001). Controlling for the other covariates, providers in the aim one pool had 0.17% greater nivolumab utilization than providers not in the pool (p<0.001). The total regression model accounted for 62.5% of the variance in utilization of nivolumab in this provider group.

Table 24. GAM Regression Results for Percentage of Beneficiaries Utilizing Nivolumab, 2018

Parametric Terms	**Parametric Coefficient**	**Standard Error**	**p-Value**
Beneficiary Average Age	-0.05**	0.02	0.002
Beneficiary Average HCC	0.33***	0.10	<0.001
Provider Gender			
Male	Ref.		
Female	-0.04	0.05	0.45
In Aim One Pool			
No	Ref.		
Yes	0.17***	0.05	<0.001
Non-Parametric Terms	**Effective Degrees of Freedom**		**p-Value**
Adjusted Nivolumab-Associated Payment in 2017	3.9***		<0.001
Number of Unique Beneficiaries	9.0***		<0.001
Note: *p<0.05; **p<0.01; ***p<0.001			
Adjusted R-squared: 0.62			
Deviance explained: 62.5%			
Observations: 770			

The functional forms for the non-linear relationships between percent utilization and two covariates, total adjusted payment and total unique beneficiaries, are shown in **Figure 4** and **Figure 5**. Among the majority of providers with smaller payment amounts less than approximately $25,000, there was an increase in percent utilization with greater payment amounts. Greater payments were not associated with continuing increases in percent utilization for higher payment amounts (edf=3.9, $p<0.001$). The percent utilization declined significantly with increasing total unique beneficiaries up to approximately 600 and then remained fairly constant (edf=9.0, $p<0.001$).

Figure 4. Smoothed Fit with 95% Confidence Bounds Modelling the Total Adjusted Nivolumab Payment, 2017, and Percent of Nivolumab Utilization, 2018

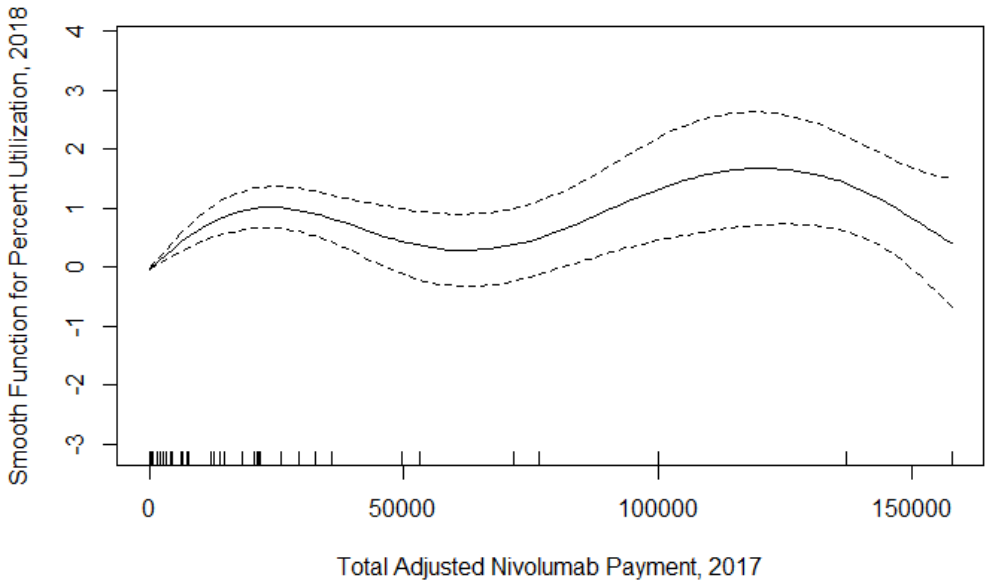
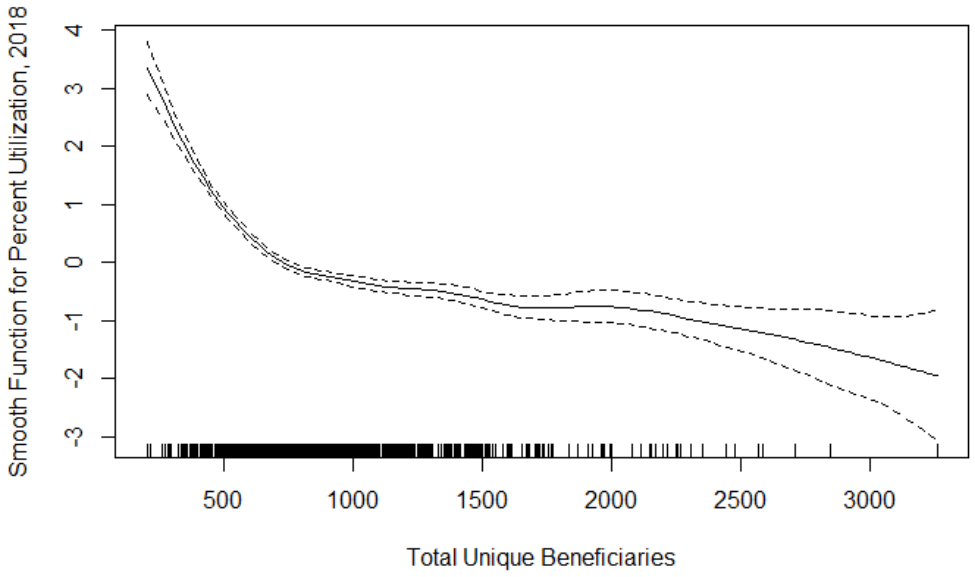


Figure 5. Smoothed Fit with 95% Confidence Bounds Modelling the Total Unique Beneficiaries and Percent of Nivolumab Utilization, 2018



Results for Pembrolizumab

Pembrolizumab Aim One Pool Analyses

For the analysis of pembrolizumab in the selected provider pool, one outlier with 3,584 total unique beneficiaries was removed from the 2,146 providers in the aim one pool. The next highest number of beneficiaries among these providers was 3,259. This left 2,145 providers whose pembrolizumab usage was analyzed for aim one. Within this pool, 321 (15.0%) were high utilizers of pembrolizumab, compared to 1,824 (85.0%) who were not high utilizers.

The demographic information for this group is shown in **Table 25**. In this selected provider pool, providers who were high utilizers of pembrolizumab were significantly more likely to have received a pembrolizumab-associated payment in 2017 (60.4% vs. 46.6%, $p<0.0001$) and be male (82.6% vs. 74.5%, $p=0.0024$).

Greater likelihood of being a high utilizer was significantly associated with more unique beneficiaries (average 1,023.4 vs. 419.6, p<0.0001), as well greater beneficiary average age (73.8 vs. 73.1, p<0.0001), and lower beneficiary average HCC (2.11 vs. 2.18, p<0.0001).

Table 25. Demographic Characteristics of Providers in Pool Who Were and Were Not High Utilizers of Pembrolizumab, 2018

	High Utilizer of Pembrolizumab (n=321)	**Not a High Utilizer of Pembrolizumab** (n=1,824)	**Chi-Squared or T-Test P-Value**
	n (%)	*n (%)*	
Received a Pembrolizumab-Associated Payment in 2017			
Yes	194 (60.4%)	850 (46.6%)	<0.0001*
No	127 (39.6%)	974 (53.4%)	
Provider Gender			
Male	265 (82.6%)	1359 (74.5%)	0.0024*
Female	56 (17.4%)	465 (25.5%)	
	Average (sd)	*Average (sd)*	
Total Number of Unique Beneficiaries	1,023.4 (465.7)	419.6 (307.6)	<0.0001*
Beneficiary Average Age	73.8 (1.5)	73.1 (2.3)	<0.0001*
Beneficiary Average HCC	2.11 (0.22)	2.18 (0.39)	<0.0001*
*Results were statistically significant.			

Table 26 shows the odds ratios and 95% confidence intervals for the logistic regression in this pool of providers. A greater number of unique beneficiaries was significantly associated with being a high utilizer of pembrolizumab in this population (OR=1.004, p<0.001, 95% CI 1.003-1.004). Greater beneficiary average HCC also had a positive significant association with high utilization (OR=1.72,

p=0.027, 95% CI 1.06-2.77). The other associations, including receipt of a pembrolizumab-associated payment (OR 0.95, p=0.74, 95% CI 0.71-1.28), female provider gender (OR 0.86, p=0.42, 95% CI 0.59-1.25), and greater beneficiary average age (OR 1.03, p=0.56, 95% CI 0.94-1.12) were not significant.

Table 26. Logistic Regression Results for Likelihood of Providers in Pool to Be a High Utilizer of Pembrolizumab, 2018

Characteristic	Odds Ratio	95% Confidence Interval	P-Value
Received a Pembrolizumab-Associated Payment in 2017			
No (Ref.)	1		
Yes	0.95	(0.71, 1.28)	0.74
Provider Gender			
Male (Ref.)	1		
Female	0.86	(0.59, 1.25)	0.42
Total Number of Unique Beneficiaries	1.004***	(1.003, 1.004)	<0.001
Beneficiary Average Age	1.03	(0.94, 1.12)	0.56
Beneficiary Average HCC	1.72*	(1.06, 2.77)	0.027
Observations	2,145		
Akaike Information Criterion	1,271.29		
Note: *p<0.05; **p<0.01; ***p<0.001			

Pembrolizumab Aim One Broad Analyses

Of the 19,159 oncologists with records available for the broad analysis, three were identified as outliers with more than 5,000 unique beneficiaries. An additional two providers had 20,837 beneficiaries and 5,710 unique beneficiaries. These five

providers were removed, leaving 19,154 providers for the analysis. In this broad provider group, 639 (3.3%) were high utilizers of pembrolizumab, while 18,515 (96.7%) were not.

Table 27 provides the demographic information for the broad analysis group for aim one. Providers who were high utilizers of pembrolizumab in 2018 were significantly more likely to have received a pembrolizumab-associated payment in 2017 (51.8% vs. 22.5%, p<0.001), be male (78.6% vs. 67.0%, p<0.001), be in the aim one pool of providers (50.2% vs. 9.9%, p<0.001), and have more unique beneficiaries on average (901.8 vs. 278.3, p<0.001). Greater beneficiary average age (73.5 vs. 72.3, p<0.001) and greater beneficiary average HCC (2.14 vs. 2.04, p<0.001) were also significantly associated with being a high utilizer.

Table 27. Demographic Characteristics of Broad Group of Providers Who Were and Were Not High Utilizers of Pembrolizumab, 2018

Characteristic	**High Utilizer of Pembrolizumab** (n=639)	**Not a High Utilizer of Pembrolizumab** (n=18,515)	**Chi-Squared or T-Test P-Value**
	n (%)	*n (%)*	
Received a Pembrolizumab-Associated Payment in 2017			
Yes	331 (51.8%)	4,164 (22.5%)	<0.001***
No	308 (48.2%)	14,351 (77.5%)	
Provider Gender			
Male	502 (78.6%)	12,405 (67.0%)	<0.001***
Female	137 (21.4%)	6,110 (33.0%)	
In Aim One Pool			
Yes	321 (50.2%)	1,825 (9.9%)	<0.001***
No	318 (49.8%)	16,690 (90.1%)	
	Average (sd)	*Average (sd)*	

Characteristic	High Utilizer of Pembrolizumab (n=639)	Not a High Utilizer of Pembrolizumab (n=18,515)	Chi-Squared or T-Test P-Value
Total Number of Unique Beneficiaries	901.8 (455.9)	278.3 (260.1)	<0.001***
Beneficiary Average Age	73.5 (1.6)	72.3 (2.8)	<0.001***
Beneficiary Average HCC	2.14 (0.25)	2.04 (0.56)	<0.001***
*Note: *p<0.05; **p<0.01; ***p<0.001*			

The results for the logistic regression in this broad group are shown in **Table 28**. In this broad provider population, each of the covariates except provider gender was significant. Greater likelihood of being a high utilizer of pembrolizumab was associated with receipt of pembrolizumab-associated payment in 2017 (OR 1.46, p<0.001, 95% CI 1.21-1.76), being in the aim one pool (OR 4.17, p<0.001, 95% CI 3.46-5.06), and greater number of unique beneficiaries (OR 1.003, p<0.001, 95% CI 1.003-1.003). Similarly, greater beneficiary average age (OR 1.06, p=0.013, 95% CI 1.01-1.11) and greater beneficiary average HCC (OR 1.90, p<0.001, 95% CI 1.56-2.31) were also associated with greater likelihood of being a high utilizer.

Table 28. Logistic Regression Results for Likelihood of Broad Group of Providers to be High Utilizers of Pembrolizumab, 2018

Characteristic	Odds Ratio	95% Confidence Interval	P-Value
Received a Pembrolizumab-Associated Payment in 2017			
No (Ref.)	1		
Yes	1.46***	(1.21,1.76)	<0.001
Provider Gender			
Male (Ref.)	1		
Female	0.88	(0.71, 1.10)	0.258

Characteristic	Odds Ratio	95% Confidence Interval	P-Value
In Aim One Pool			
No (Ref.)	1		
Yes	4.17***	(3.46, 5.06)	<0.001
Total Number of Unique Beneficiaries	1.003***	(1.003, 1.003)	<0.001
Beneficiary Average Age	1.06**	(1.01, 1.11)	0.013
Beneficiary Average HCC	1.90***	(1.56, 2.31)	<0.001
Observations	19,154		
Akaike Information Criterion	3,954		
Note: *p<0.05; **p<0.01; ***p<0.001			

Pembrolizumab Aim Two Analyses

Of the 641 high utilizers of pembrolizumab, five were identified as outliers in the initial regression model. This included four providers with a utilization rate higher than 9% and one provider with 20,837 unique beneficiaries. This left 636 high utilization providers included in this analysis. In this group, 331 (52.0%) had received a pembrolizumab-associated payment in 2017, and 305 (48.0%) had not. The average adjusted payment amount among those who received a payment was $1,064, with 150 (45.3%) receiving adjusted payments less than $50 and 212 (64.0%) receiving adjusted payments less than $100. On average, providers in this group utilized pembrolizumab in 2.18% (sd 1.36) of their beneficiaries. The percentage utilization ranged from 0.34% to 8.37%, with 307 (48.3%) having utilization in between one and two percent of their beneficiaries.

Providers who had received a pembrolizumab-associated payment had a significantly lower mean percentage of utilization among their beneficiaries than providers who had not received a payment (1.89%, sd 1.1 vs. 2.50%, sd 1.6, $p<0.001$). There was a linear relationship between the amount of pembrolizumab-associated payment and percentage utilization of pembrolizumab, so a Pearson correlation test was run. The variables were significantly correlated, with a correlation coefficient of 0.19 ($p<0.001$).

Table 29 shows the results of the regression for aim two, which used a GAM due to the non-linear relationship seen for total unique beneficiaries. The binary variables for provider gender and whether the provider was in the aim one pool were included as parametric terms. The adjusted pembrolizumab-associated payment amount and the beneficiary average HCC had linear relationships in the initial GAM so they were included as parametric terms in the final model. Total number of unique beneficiaries and beneficiary average age were included with smooth functions.

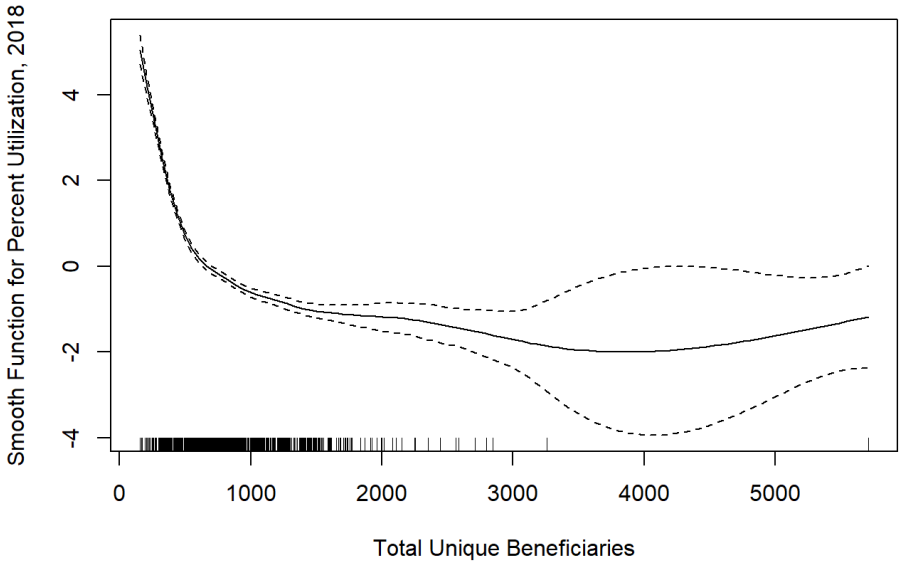
Three of the covariates were not significant in this model: adjusted pembrolizumab-associated payment ($p=0.092$), provider gender ($p=0.304$), and beneficiary average age ($p=0.337$). Controlling for the other covariates, a 0.1 unit increase in average beneficiary HCC was associated with an increase in pembrolizumab utilization of 0.04%, which was significant ($p<0.001$), but extremely small. Providers in the aim one pool had 0.179% greater pembrolizumab utilization than providers not in the pool ($p<0.001$). The functional form for the significant non-linear relationship between percent utilization and total unique beneficiaries is shown in **Figure 6**. As this figure shows, there was a strong decrease in percent utilization

with increasing number of total beneficiaries up to approximately 1,000 total beneficiaries, and the relationship then remained fairly constant (edf=10.35, p<0.001). The total regression model accounted for 81.5% of the variance in utilization of pembrolizumab in this provider group.

Table 29. GAM Regression Results for Percentage of Beneficiaries Using Pembrolizumab, 2018

Parametric Terms	**Parametric Coefficient**	**Standard Error**	**p-Value**
Adjusted Pembrolizumab-Associated Payment in 2017	-0.000008	0.000005	0.092
Beneficiary Average HCC	0.441***	0.108	<0.001
Provider Gender			
Male	Ref.		
Female	0.061	0.060	0.304
Pool			
No	Ref.		
Yes	0.179***	0.050	<0.001
Non-Parametric Terms	**Effective Degrees of Freedom**		**p-Value**
Number of Unique Beneficiaries	10.35***		<0.001
Beneficiary Average Age	2.10		0.337
Note: *p<0.05; **p<0.01; ***p<0.001			
Adjusted R-squared: 0.81			
Deviance explained: 81.5%			
Observations: 636			

Figure 6. Smoothed Fit with 95% Confidence Bounds Modelling the Percent of Pembrolizumab Utilization and Total Unique Beneficiaries, 2018



Discussion

This study sought to examine the effect of one aspect of industry promotion of novel immunotherapy agents by analyzing the potential association between promotional payments made by pharmaceutical companies to providers and provider utilization of the promoted agents. The hypothesized results, that any receipt of any industry payment in promotion of an immunotherapy agent was associated with greater likelihood of being a high utilizer of the agent and that greater payment amounts were associated with greater utilization, were not consistently borne out. When evaluated as an independent association, there was a consistently significant relationship between receipt of payment and high utilization, and between amount of payment and amount of utilization. However, particularly in the analysis of the pool of oncologists selected based on their utilization records indicating treatment of lung cancer and melanoma patients, receipt of payment was not significantly associated

with high utilization when controlling for the other covariates in some of the regression models. In the pembrolizumab analysis, the amount of associated payment received was not significantly associated with the percent utilization of pembrolizumab.

This study focused on the potential association between payments and utilization among high utilizers of the immunotherapy agents, which was a decision driven in part by the available data. The CMS public use files do not include provider-level data for services with a patient count of 10 or fewer. However, using this as a cut-off point for high utilization of the agent seems reasonable when comparing the proportion of services carried out by the high utilizers and the non-high utilizers based on the national data. At a national level, the CMS data shows that there were 4,482 providers who utilized nivolumab through 27,939 unique beneficiary interactions and 4,370 who utilized pembrolizumab through 25,072 unique interactions with Medicare beneficiaries in 2018. The 777 high utilizing providers of nivolumab made up 17% of the total providers, but provided 47% of the unique beneficiary interactions. Similarly, the 641 high utilizing providers of pembrolizumab were 15% of the total providers and provided 40% of the unique beneficiary interactions. The providers included in this analysis represent a significant proportion of the utilization of these agents.

Despite these caveats when linking the Open Payments and CMS PUF datasets, the data are still likely to be of use in agents with broader applicability. For instance, in earlier work, these files produced meaningful results in an analysis of supportive care drugs used across disease areas in oncology. Active oncology agents

used in broader patient populations could also be analyzable. Future researchers can assess whether these data may be appropriate for their research question by comparing the number of providers for a given drug or service in the national summary to the number of provider-level records for that drug or service.

Limitations

This analysis had important limitations. Most significantly, as discussed above, the results are primarily applicable to high utilizers of agents rather than providers who may utilize a wider variety of agents across their patient population without having high utilization of the particular agents. The regression models may not have included key variables that were not available within these datasets. Finally, these retrospective analyses of observational data can only identify associations that may be worth future study to explore potential causal relationships.

Conclusions

This study contributes to the growing body of research supporting a positive association between pharmaceutical industry promotional payments and high provider utilization of the promoted novel immunotherapy agents. While the findings in this study were not consistently significant across all of the included analyses, the study is in line with others in the area that found either positive or mixed positive and null results.[152] The significance of this study is in extending previous research to analyze recently approved agents with a novel mechanism of action. Additionally, the application of the generalized additive model to the non-linear relationships identified between payment amounts and utilization in this study is a promising methodology for future study in additional agents and disease areas.

Chapter 5: Conclusion

Summary of the Results

Novel immunotherapy agents, including nivolumab and pembrolizumab, have been the focus of extensive clinical research in oncology, but real-world research has been limited due to lack of available data. Relatively little has been known about differences between immunotherapy clinical trial participants and the broader patient population receiving these agents as standard of care, or about the drivers of provider utilization of immunotherapy agents. Medicare-eligible individuals represent a significant proportion of cancer patients and, as such, are an important population in which to study these agents.

This dissertation sought to fill these research gaps through several innovative analyses. The first objective used SEER-Medicare claims data between 2014 and 2016 to compare the demographics of Medicare clinical trial participants with the demographics of Medicare patients receiving standard cancer care. Aim one of this objective was a broad comparison evaluating differences between Medicare patients with claims data for any active cancer treatment and Medicare patients with claims for active cancer treatment clinical trials. Aim two was a narrower comparison looking at Medicare patients with claims for nivolumab or pembrolizumab received as standard cancer care and Medicare patients with claims for nivolumab or pembrolizumab clinical trials. These two aims were evaluated separately in lung cancer and melanoma patient populations. As hypothesized, these analyses consistently found that patients in clinical trials were significantly younger and had fewer comorbid conditions than the broader patient population. Findings were less

consistent for disparities by race, ethnicity, and sex. In the lung cancer broader aim one analysis, Black patients were significantly less likely to be clinical trial participants, while Asian/Pacific Islanders were significantly more likely to be in a clinical trial. For the melanoma aim one analysis, non-White non-Hispanic patients were more likely to be clinical trial participants, but due to small numbers, it was not possible to analyze this group with more granular groupings. Female patients were more likely to be in a clinical trial in the lung cancer aim one analysis, while male patients were more likely to be clinical trial participants in the melanoma aim one analysis.

The second objective of this dissertation analyzed, for both nivolumab and pembrolizumab, the association between industry payments to promote nivolumab or pembrolizumab and high provider utilization of the agent using data from the Medicare Provider Utilization and Payment: Physician and Other Supplier Public Use File and the Medicare Open Payments datasets. Aim one evaluated this potential association in two groups: first, a selected pool of oncologists identified as likely to treat lung cancer and melanoma patients based on their use of other agents, and second, the broad pool of oncologists in the utilization dataset. Aim two was restricted to providers with high utilization for nivolumab or pembrolizumab, and evaluated the association between the amount of the industry payment and the amount of utilization. The hypothesized results – that industry payments would be associated with greater likelihood of utilization and that more industry payments would be associated with greater utilization amounts – were consistently seen in independent

tests of association, but were not significant when controlling for the covariates in some of the regression models.

Limitations

Both objectives in this dissertation were retrospective analyses of existing datasets, and could only assess potential associations, not causation. The datasets did not include measurements of all of the variables likely to affect the dependent variables of interest. Additionally, both objectives used data focused on Medicare beneficiaries and the results may not be generalizable to non-Medicare populations. For objective one, the analyses depend on the accuracy and completeness of the Medicare claims coding. For objective two, the results are primarily applicable to providers with high agent utilization.

Conclusions and Directions for Future Research

The studies described in this dissertation represent a significant contribution to our understanding of clinical trial representativeness, real-world utilization of immunotherapy agents, and potential relationships between industry payments and provider utilization of these agents. In the first objective, this dissertation showed that non-White patients were not uniformly underrepresented in cancer clinical trials, despite what some previous literature had suggested. Additional research is needed to identify disease areas in which particular populations are truly underrepresented so that additional efforts and resources to improve enrollment diversity can be focused where they are most needed. Particular attention may need to be paid to enrollment of older populations, who were consistently underrepresented in trials according to these analyses.

In this second objective, this dissertation contributed to the growing body of research into the association between industry promotions and provider utilization. The results aligned with other research, which has found generally positive and occasionally null relationships between payments and utilization, but extended our understanding of the role of pharmaceutical promotion of novel immunotherapy agents. As these agents are approved in broader disease settings and additional years of payment and utilization data are available, the generalized additive model used here may be built upon by future researchers to examine time series relationships among a broader group of providers.

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