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ABSTRACT

Immunotherapy is a breakthrough innovation in cancer care but is also among the most expensive treatments, with costs exceeding $150,000 per patient. We study the introduction of immune checkpoint inhibitors (ICIs), the most widely used class of immunotherapy drugs. In 2022, ICIs accounted for 44% of the $17.5 billion Medicare Part B cancer drug spending. We focus on metastatic melanoma, the first approved indication for ICIs. While overall cancer mortality rates declined since the 1990s, melanoma mortality rates increased through the early 2010s. Following the first ICI approvals in 2011 and 2014, melanoma mortality declined sharply. Using traditional Medicare claims, we estimate the impact of the introduction of ICIs on healthcare utilization, costs, and 1-year survival for patients with metastatic melanoma, relative to metastatic colorectal cancer (CRC), where ICIs were not approved until 2017. Variation in approval timing allows us to isolate the effect of ICIs from broader cancer care trends. We find that ICIs reduced 1-year mortality by 6.2%. Since about 1 in 5 metastatic melanoma patients received ICIs, this implies a 27.5% reduction among treated patients. The introduction of ICIs also reduced chemotherapy and radiation use, but increased Medicare spending by 59.3% or about 260% among ICI-treated patients. Accounting for life expectancy gains beyond one year, the benefits of ICIs for melanoma patients appear comparable, or potentially even greater, than the substantial added Medicare costs. Nonetheless, ICI use remains relatively low given large survival benefits and few alternative treatments, suggesting that costs and other barriers limit patient access.

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1 Introduction

Healthcare expenditures in the United States now make up almost 18 percent of GDP, with pharmaceutical spending accounting for an increasing share of overall costs (CMS, 2024a). The health economics literature has debated whether technological innovations deliver commensurate value for their costs, particularly as patent-protected medical technologies command monopoly prices upon market entry (Chandra & Skinner, 2012; Cutler & McClellan, 2001). The challenge is especially acute for breakthrough innovations, where clinical trial efficacy may not translate into population-level effectiveness due to patient selection, heterogeneity in provider expertise, and healthcare system constraints (Lakdawalla, 2018). Consequently, the productivity of pharmaceutical innovation has become a critical concern, given its implications for overall health care spending and, ultimately, patient outcomes. This issue is particularly salient in cancer care, where breakthrough treatments offer potentially transformative benefits, but often at a very high cost (Howard et al., 2015; IQVIA, 2023).

Innovation in cancer screening and treatment decreased mortality from invasive cancer by 17% between 1980 and 2010 (NCI, 2020; SEER, 2022). However, this progress was not uniform across cancer types. The mortality rate for metastatic melanoma actually increased by 15% over that same period (NCI, 2020; SEER, 2022). Melanoma is the deadliest type of skin cancer, with an estimated one-year mortality rate of 49% for patients with metastatic disease (Tas, 2012). Melanoma has been largely non-responsive to traditional cancer treatments such as chemotherapy, leaving patients with few treatment options (Davis et al., 2019; Schmitt & Larkin, 2023).

A breakthrough came in 2011 with the FDA approval of the first immune checkpoint inhibitor (ICI), Yervoy (ipilimumab), an immunotherapy cancer drug that harnesses the body's immune system to recognize and attack cancer cells. In 2014, two additional ICIs were approved, Keytruda (pembrolizumab) and Opdivo (nivolumab), which became the most widely adopted ICIs. Although these ICIs were eventually

approved to treat more than 27 types of cancer, they were first approved to treat metastatic melanoma.[1] As shown in Figure 1, from 2011 to 2022, the mortality rate for melanoma decreased sharply by 26%, marking the first sustained decline in mortality for this type of cancer in decades. This compares to a 16% decline during the same period for all other cancer types, which follows a continuation of a pre-existing decreasing mortality trend.

While ICIs are widely recognized as a revolutionary innovation in oncology care (Davis et al., 2019; Fellner, 2012; Hamid et al., 2017; Lamba et al., 2022; Robert et al., 2011), they are also expensive. The cost of a full course of treatment with an ICI can exceed $150,000.[2] In 2022, ICIs accounted for 44% of the $17.5 billion in spending on cancer drugs in Part B of traditional Medicare, with Keytruda, Opdivo, and Yervoy ranked 1st, 2nd, and 11th with respect to total Medicare FFS spending for cancer treatments by the end of our study period (CMS, 2024b; SEER, 2023). Moreover, as shown in Figure 2, total Medicare spending on cancer drugs has increased by 122% since their introduction, and 80% of this growth can be attributed to ICIs. Despite the rapid diffusion of ICIs, there is surprisingly little evidence on the "real-world" (as opposed to clinical trial) impact of this treatment on health outcomes and utilization for patients with cancer or its effects on health care spending.

In this paper, we investigate the impact of the introduction and diffusion of ICIs, focusing on patients with metastatic melanoma. This is the ideal setting to examine the impact of this transformative healthcare technology for multiple reasons. First, melanoma was the first cancer indication that ICIs were approved to treat, creating clear pre- and post-time periods. Second, FDA labeling indicates that all patients diagnosed with metastatic melanoma are eligible to be treated with ICIs without any additional biomarker testing requirements, meaning that we can readily define the group that is eligible for treatment in claims

[1] Metastatic melanoma was likely the first approved indication for ICIs precisely because of limited first-line treatment options, with clinical trial participation standard of care prior to their introduction, and because changes in outcomes could be relatively quickly determined given median survival of about 6 months (Hodi et al., 2010).

[2] Treatment cost is estimated for an average weight U.S. male adult in kilograms and the highest recommended milligram dose for the longest time between treatments, as reported in the seminal clinical trials, at the average sales price in 2020 from the Centers for Medicare and Medicaid, and ranges from $157,679 to $176,750 (Hamid et al., 2017; Robert et al., 2011, 2015).

data. Lastly, prior existing treatments for melanoma had limited efficacy; thus, there was not a compelling outside option to ICIs, again making it reasonably clear which patients were candidates for treatment.

A persistent challenge in studying the impact of new health technologies is that patients who access treatments differ systematically from those who do not. We address this by estimating a difference-in-differences specification that compares patients with metastatic melanoma to patients with metastatic colorectal cancer (CRC) before and after ICIs were introduced. We select patients with CRC as our comparison group because ICI approval for CRC occurred years after melanoma, and then only for patients with microsatellite instability high (MSI-H) CRC, as determined through biomarker diagnostic testing, affecting only about 15% of patients.[3] As a result, we observed almost no use of ICIs for CRC during our study period. The variation in approval timing across cancer types allows us to isolate the effect of ICIs from other changes in cancer treatment.

Our data comes from administrative fee-for-service claims for a 20% random sample of traditional Medicare patients between 2008 and 2018.[4] Medicare beneficiaries are 4.3 times more likely to be diagnosed with melanoma than the rest of the adult population in the U.S., which makes this a particularly important group to assess the use and impact of ICIs (SEER, 2022). We use standard claims-based algorithms to define patients with metastatic melanoma and metastatic colorectal cancer (Barzilai et al., 2004; CCW, 2023).

Our research design provides estimates of the intent-to-treat impact of ICIs. The study treatment period is defined by the three ICIs that were approved in 2011 (Yervoy) and 2014 (Keytruda and Opdivo),

[3] We observe limited ICI use in patients with CRC toward the end of the sample period, 5% in 2018 compared to 33.7% for patients with melanoma. This is a conservative approach, which may result in downward bias of our estimates.

[4] We focus on traditional fee-for-service Medicare beneficiaries because comparable treatment cost data is not available for beneficiaries with Medicare Advantage.

which we refer to as the first ICI and the second ICIs going forward.[5,6] For melanoma, use of ICIs increased from 5.4% in the first year of introduction to 33.7% among patients diagnosed in 2018; use of ICIs in CRC was much lower at essentially zero through 2016 and then just 3.8% in 2017 and 5.0% in 2018. The lower take-up among CRC patients reflects the later date of ICI approval for CRC and relatively narrow eligibility criteria once ICIs were approved for CRC in 2017. To address the comparability of patients with melanoma and CRC, we estimate event studies and show consistency in pre-trends between our treatment and comparison groups. We also conduct multiple robustness checks, including entropy weighting to ensure CRC and melanoma patients are balanced on observable characteristics, estimating an alternative specification that compares outcomes for melanoma patients with high versus low propensity for ICIs use, and, finally, comparing outcomes for melanoma patients diagnosed before versus after ICI introduction.

Across all these approaches, we find robust evidence that ICIs transformed melanoma care. Average treatment costs to Medicare increased by $8,321 per patient after the first ICI was introduced and an additional $10,840 after the second ICIs were introduced, a total of $19,161 for melanoma patients relative to CRC. The increase was driven by spending in the outpatient setting (where ICIs are administered) with limited offsets from decreased inpatient spending. We also find evidence of substitution away from existing standards of care, with chemotherapy and radiation decreasing by 39.1% and 7.2%, respectively, from pre-ICI use. We find a small, but not statistically significant increase, in 1-year mortality from the approval of the first ICI, but a 3.6pp reduction in 1-year mortality after the approval of the second relative to the first ICIs. When scaled by the first-stage estimate of ICI use, this represents a 27.5% improvement in survival among ICI users. Despite clear evidence of substantial health benefits, adoption was uneven across patient groups, with older and dual Medicare-Medicaid eligible patients showing the lowest usage rates. This finding raises concerns about equitable access for many of the most vulnerable patients to

[5] Yervoy (ipilimumab) is an ICI that targets the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) ICI protein and was approved in March 2011 for use in melanoma and July 2018 for MSI-H CRC; we refer to this ICI as the first ICI going forward.

[6] Keytruda (pembrolizumab) and Opdivo (nivolumab) are ICIs that target the programmed cell death protein 1 (PD-1) protein and were approved in September and December 2014 for melanoma, respectively, and in May and July 2017 for CRC, respectively. We refer to pembrolizumab and nivolumab collectively as second ICIs.

innovative treatments and highlights potential barriers to the diffusion of new high-cost medical technologies.

Our study contributes to several strands of literature. First, it adds to the health economics literature on the productivity of medical innovations. Prior research has shown that even low-cost, evidence-based innovations have variation in productivity due to disparities in adoption and access; yet, these technologies tend to have the largest impact on improving health (Baicker & Chandra, 2004; Chandra & Staiger, 2007; Skinner, 2011; Skinner & Staiger, 2007, 2015). Conversely, high-cost treatment innovations may increase costs without corresponding benefits, and productivity is often related to physician expertise, spillovers in care, and heterogeneous patient treatment effects (Carroll et al., 2023; Chandra et al., 2023; Chandra & Skinner, 2012; Chandra & Staiger, 2020; Cutler et al., 2010; Duggan, 2005; Horn et al., 2022; Hsia et al., 2024; O'Connor et al., 2018). We build on this literature by focusing on a high-cost cancer technology that has diffused particularly rapidly. Given the limited evidence regarding the productivity of this new technology, we produce new evidence to assess its impact.

This study also adds to our understanding of how novel cancer technologies are used in clinical practice and impact patients outside of highly controlled research studies. Innovation in cancer care has accelerated since the advent of immunotherapy, but our understanding of how new cancer technologies diffuse and impact outcomes in the real world remains limited. The results demonstrated in clinical trials may not clearly translate into clinical practice because of the very controlled nature of clinical trials, the distinct features of the United States (US) healthcare system, and individual decision-making. Specifically, differences in provider practice styles, patient adherence to treatment protocols, and the characteristics of patients treated outside of trials can generate differences in outcomes in real-world vs. clinical trial settings (Klonoff, 2020). Furthermore, patients may not be fully aware of or face the full cost of care, nor understand the risks and benefits of treatment due to information asymmetries. This leads some patients who are marginal or inappropriate for treatment to use therapies that may not be efficacious for them (Booth & Detsky, 2019; Fundytus et al., 2021; Tayapongsak Duggan et al., 2017). Relatedly, individuals may be willing to take greater risks and pay more for a mortality reduction toward the end of life, and doctors

typically have wide discretion to provide treatments even when empirical evidence to support use is thin (Fischer et al., 2018; Lakdawalla et al., 2012; NCI, 2022). On the other hand, there are multiple barriers to cancer treatment, including patient cost, insurance coverage differences, and provider propensity to take up new innovations, which can make diffusion uneven even when indicated (Dusetzina et al., 2014; Kaisaeng et al., 2014; Streeter et al., 2011).

Lastly, our paper contributes to the literature on the value of cancer innovations. Much of the existing work on the value of new cancer drugs uses estimates from clinical trials and does not account for differences between trial efficacy and the effectiveness of treatments in real-world settings, which, as discussed above, can diverge because of patient adherence and the characteristics of those treated in real-world settings relative to those enrolled in clinical trials. Consequently, prior evidence on whether the benefits of new cancer treatments are aligned with costs may not be fully informative (Chen et al., 2019; Del Paggio et al., 2017; Dusetzina, 2016; Fellner, 2012; Howard et al., 2015; Lakdawalla, 2018; Ridley & Lee, 2020; Tayapongsak Duggan et al., 2017; Vokinger et al., 2020). The findings from this study can inform policymakers about the opportunities and challenges of translating novel medical treatments into improved patient outcomes, which is particularly important given the increasing speed and cost of innovation in cancer care.

The remainder of this paper is organized as follows. Section 2 provides background on melanoma and ICIs and reviews the relevant literature. Section 3 details our research design and empirical strategy. Section 4 details our data sources and presents summary statistics. Section 5 presents our results. Section 6 discusses the implications of our findings and concludes.

2 Background

2.1 Melanoma Skin Cancer

Melanoma is a malignancy of melanocytes, the cells that produce the pigment melanin. Risk factors include ultraviolet light exposure, fair skin, family history, and atypical moles. When diagnosed at an early stage, melanoma can be cured with surgical resection, with five-year survival rates exceeding 95%. Once

the disease has metastasized to distant sites (most often lungs, brain, liver, and/or bones), prognosis was historically poor, with five-year survival rates below 10% prior to the advent of modern therapies (Garbe et al., 2011; Sabbatino et al., 2022). Melanoma causes the majority of skin cancer deaths (Davis et al., 2019), which totaled 9,154 nationally in 2010, just before the release of the first ICI in 2011.

Traditional treatments for melanoma include chemotherapy and radiation therapy. However, both have limited efficacy for melanoma. For example, dacarbazine, a standard chemotherapy agent, had a median overall survival of five to 11 months and a 1-year survival rate of 27% (Davis et al., 2019). This therapeutic landscape remained largely unchanged for decades until the development of more targeted therapies, starting with ICIs.

2.2 Immune Checkpoint Inhibitors (ICIs)

ICIs, immunotherapy drugs, represent a revolutionary approach to cancer treatment. Immune checkpoints are proteins found in the immune system that help regulate immune response (AACR, 2024). Under normal physiological conditions, immune checkpoints prevent excessive immune responses that could damage healthy tissues. Cancer cells can exploit these checkpoints to evade immune detection, thereby allowing uninhibited cancer growth. ICIs block tumor cells from sending these signals and mobilize the immune system to detect and attack cancer cells. By 2018, 43.6% of cancer patients were eligible to be treated with a checkpoint inhibitor (Haslam & Prasad, 2019). These drugs have curative benefits for some patients and an estimated overall response rate (i.e., tumors shrank or disappeared after treatment) of 12.5% from clinical-trial data (a 7.6 percentage point improvement over existing genome-targeted therapy) (Haslam & Prasad, 2019). The benefits of checkpoint inhibitors, however, come with the potential for serious side effects that can mimic autoimmune disorders.

Yervoy (ipilimumab), targeting Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), was the first ICI approved by the FDA on March 25, 2011 to treat melanoma. Compared with standard chemotherapy, in clinical trials, Yervoy demonstrated a 5% increase in response and an 11% increase in 1-year survival (Robert et al., 2011). Subsequently, Keytruda (pembrolizumab) and Opdivo (nivolumab),

targeting programmed death receptor-1 (PD-1) protein, were FDA-approved to treat melanoma on September 4, 2014, and December 22, 2014, respectively. The PD-1s pathway ICIs are considered an advance over Yervoy. According to clinical trial data, they improve the response rate by 25% on average and increase 1-year survival by 10-31% over standard chemotherapy (Hamid et al., 2017; Robert et al., 2015). See Appendix Table A1 for clinical trial results and treatment costs.

These therapies, while groundbreaking, come with substantial monetary costs. The estimated Medicare treatment cost for Yervoy alone typically exceeds $157,000 per course of therapy, while PD-1 inhibitors cost approximately $170,000.[7] Keytruda and Opdivo were among the top 10 selling drugs globally in 2023, with combined annual worldwide sales of $34 billion (Verdin, 2024). ICIs are also associated with unique immune-related adverse events that require specialized management, potentially adding to the overall monetary and non-monetary costs of care. Following our study period, additional ICIs were approved; however, Keytruda and Opdivo remain the most widely used ICIs for their protein targets.

3 Research Design

3.1 Empirical Framework

We aim to estimate the impact of ICI take-up on the utilization of other health care treatments, Medicare spending, and mortality among Medicare beneficiaries diagnosed with melanoma. This relationship can be expressed as follows:

$$Y_{it} = \beta_0 + \beta_1 \cdot ICI_i + \Gamma X_{it} + \tau_t + \epsilon_{it} \quad (1)$$

where Y_{it} is the outcome for patient i diagnosed in year t, ICI_i is an indicator that patient i used an ICI; X_{it} is a vector of patient characteristics (race, gender, 5-year age groups, mean Charlson Index in the 12 months before melanoma diagnosis, the number of months between melanoma diagnosis and metastatic determination, dual Medicare-Medicaid status at diagnosis, and diagnosis with an autoimmune disease[8]);

[7] Treatment cost is based on average weight in kg of a U.S. adult and the highest recommended dose for the longest time between treatments at average sales price in 2020 per the Centers for Medicare and Medicaid.

[8] Pre-existing autoimmune diagnoses have been considered a contraindication for ICI use; however, not specifically excluded on FDA labeling. These patients require additional monitoring as ICI use can exacerbate autoimmune conditions (Johnson et al., 2017).

τ_t is year of diagnosis fixed effects, and ϵ_{it} is the error term. However, there are two key challenges to identification: (1) there may be systematic differences between patients diagnosed before and after ICI approval; (2) ICI use is endogenous, as patients receiving ICIs may differ systematically from non-recipients in potentially unobserved ways that are correlated with our outcomes of interest. To address these challenges, we use a difference-in-differences specification.

3.2 Identification Strategy

We compare patients diagnosed with metastatic melanoma cancer to patients diagnosed with metastatic colorectal cancer (CRC) (henceforth, we refer to these as simply melanoma and CRC) before and after the FDA approval of ICIs. Our approach leverages the fact that the timing of FDA approval for ICIs varied by cancer type. ICIs were not approved for use in CRC until May 2017, and even then, only for the small subset of CRC patients with MSI-H tumors (approximately 15% of CRC patients). Our strategy of using a disease with differential treatment access as a control follows the approach of Finkelstein (2004), who compared vaccine development for diseases affected by regulatory changes to those unaffected, leveraging their common technological basis to control for underlying trends in outcomes.

Melanoma is an ideal treatment group because: (1) it was the first FDA-approved indication for ICIs, which means that patients did not have access to ICIs before FDA approval (even off-label), ensuring a clean pre- and post- period; (2) per FDA labeling, patients diagnosed with metastatic melanoma are universally eligible to use ICIs and do not require the specific biomarkers that other cancer types require, which allows us to readily identify eligible patients in claims data; (3) the outside option for melanoma treatment, chemotherapy, has limited effectiveness and high toxicity making it likely that most eligible patients would opt for ICIs if offered the option. Our comparison group of CRC offers several distinct advantages: (1) it is a common cancer that affects both sexes; (2) FDA approval for CRC was delayed and uptake is minimal relative to melanoma; (3) it shares many characteristics with melanoma such as similar

average patient age, high mortality, and comparable cancer care costs pre-ICIs.[9] We further verify that the outcomes we study trend similarly for melanoma and CRC prior to the introduction of ICIs. Other cancer types are less suitable for the comparison group because either the FDA approved use of ICIs for them shortly after melanoma, their incidence rates are too low to provide adequate power, or they only impact one sex. We estimate a difference-in-differences model of the following form:

$$Y_{it} = \beta_0 + \beta_1 \cdot \text{MELANOMA}_i + \beta_2 \cdot \left(MELANOMA_i \times POST_t^{First}\right) + \beta_3 \cdot \left(MELANOMA_i \times POST_t^{Second}\right) + \Gamma X_i + \tau_t + \epsilon_{it} \quad (2)$$

where the variable definitions are consistent with equation 1, and $MELANOMA_i$ equals 1 if patient i was diagnosed with melanoma and equals 0 if diagnosed with CRC. We measure outcomes, Y_{it}, within 12 months of diagnosis. We examine the take-up of ICIs, utilization of substitute cancer treatments, healthcare spending, and mortality. We define two post-periods related to the approval of ICIs for melanoma: $POST_t^{First}$ equals 1 following the introduction of the first ICI (Yervoy) in Q2 2011, and $POST_t^{Second}$ equals 1 following the introduction of the second ICIs (Keytruda and Opdivo) in Q3 2014.[10] Including the second post-period allows us to estimate the differential impact of the introduction of the second ICIs compared to the first ICI, which has different immune targets and increased efficacy.[11] The coefficients of interest are β_2 and β_3, which represent the differential changes in outcomes for patients with melanoma relative to patients with CRC following the introduction of each class of ICIs.[12] We can divide these estimates by an estimate of the change in ICI take-up following the introduction of ICIs to recover our estimate of the impact of ICI use on patient outcomes for those patients who use ICIs, i.e., the average treatment effect on

[9] As a check of robustness, we use entropy balancing, which reweights patients with CRC to be closer in observable characteristics to patients with melanoma. These results are similar to our main estimates.

[10] All three drugs are ICIs but have different targets: the first FDA-approved ICI targets the CLTA-4 protein; the second ICI-s approved target the PD-1 protein.

[11] Note that the Yervoy is now often used with one of the PD-1 ICI's (Opdivo), but the other PD-1 (Keytruda) is always used on its own.

[12] β_2 provides an estimate of the effect of Yervoy's introduction relative to the baseline period and β_3 provides an estimate of the differential effect of Keytruda/Opdivo's introduction relative to Yervoy's introduction. $\beta_2 + \beta_3$ provides an estimate of the full effect of all three ICIs post Q3 2014 relative to the baseline period.

the treated. Our key identifying assumption is that outcomes would have evolved similarly for melanoma and CRC patients in the absence of the new ICI treatments.

For sample patients diagnosed in the last year of our study period (2018), 33.7% of patients with melanoma used ICIs compared to only 5.0% of patients with CRC, reflecting the significant eligibility difference between these groups. Across our entire sample period, take-up of ICIs was 12.5% for melanoma compared to 1.0% for CRC. As noted, a small share of CRC patients became eligible for ICIs late in our study period, and there is a small amount of off-label use prior to FDA approval, which may attenuate our treatment estimates. This is a conservative approach that may bias our estimates downward.

Our identification strategy relies on the assumption that there were no concurrent changes to the treatment trajectory of melanoma and CRC outside of the introduction of ICIs. To test the validity of our parallel trends assumption, we estimate an event study with data beginning in 2008 that allows for time-varying treatment effects:

$$Y_{it} = \alpha_0 + \sum_{k \neq 2010} \beta_k (MELANOMA_i \times Yr_{kt}) + \gamma MELANOMA_i + \sum_{k \neq 2010} \delta_k Yr_{kt} + \Gamma X_{it} + \epsilon_{it} \quad (3)$$

where Yr_{kt} is a vector of indicator variables for the year of diagnosis. The reference period is 2010, the year before the first ICI was available.

3.3 Alternative Specifications

We estimate multiple alternative specifications to address potential concerns about the comparability of melanoma and CRC patients and the partial treatment of CRC patients. First, we use entropy balancing to reweight our observations to obtain balance in characteristics between patients with melanoma and CRC (Hainmueller, 2012). Second, we test the robustness of our results to ending our study period in May 2017, when CRC became an FDA-approved indication for ICI treatment, to allow for the most uncontaminated comparison group. Third, we estimate an alternative specification only using patients with melanoma, which compares patients who have a high (at or above median) propensity versus low propensity of receiving ICIs. This approach leverages the fact that certain patient groups were significantly more likely to receive ICIs following their introduction (e.g., because of age and other characteristics),

allowing us to estimate the differential impact of ICI exposure across groups. We assume that in the absence of ICIs, mortality and other outcomes for these groups would have continued to trend similarly. In this approach, we estimate a probit regression to predict each patient's probability of using ICIs with full controls. We then estimate a difference-in-differences model comparing high and low propensity groups before and after ICIs became available. Finally, we also estimate a similar specification for all melanoma patients without a comparison group, comparing outcomes for patients diagnosed with melanoma before versus after ICI introduction. The results from all of these exercises align with our primary specification findings.

4 Data and Descriptive Statistics

4.1 Study Sample

Our study sample includes patients diagnosed with either melanoma or CRC between 2008 and 2018. We use administrative claims data for a 20% random sample of beneficiaries enrolled in traditional, fee-for-service (FFS) Medicare to identify metastatic cancer diagnoses, track patterns of health care utilization, and measure outcomes. Sixty-two percent of patients with melanoma and seventy percent of patients with colorectal cancer in the U.S. are over the age of 65 and eligible for Medicare (SEER, 2022). Our dataset included claims from the Medicare Inpatient, Outpatient, Physician Office (Carrier), and Hospice files. We exclude Part D retail pharmacy claims in our analysis because ICIs are physician-administered and only covered under Part B, and there is no available oral substitute treatment under Part D that would serve as a plausible alternative to ICIs. Also, not all beneficiaries with melanoma are enrolled in Part D.

Using information from the Medicare Beneficiary Summary Files (MBSF), we restrict our sample to beneficiaries who were continuously enrolled in Medicare Part A and Part B and were not currently receiving Medicare benefits due to either disability or end-stage renal disease (ESRD), which may necessitate additional treatment considerations compared with beneficiaries who are eligible for Medicare based on age alone. Following previous research, melanoma diagnosis was identified using at least one

claim with diagnosis codes ICD-9 172.0–172.9 or ICD-10 C43* (Barzilai et al., 2004). An initial colorectal cancer diagnosis was defined using the MBSF Chronic Conditions Warehouse (CCW) indicator for colorectal cancer status by the end of the calendar year. This algorithm requires at least one inpatient or skilled nursing claim or two outpatient claims that are at least one day apart with a colorectal cancer diagnosis over a two-year reference period. We followed the CCW algorithm to determine metastatic disease status, which uses secondary cancer diagnosis codes (ICD-9 196.0-199.9 and ICD-10 C77*-C79*) (CCW, 2023). Patient characteristics and death date (if deceased) are from the MBSF.

Patients in our sample were between 66 and 89 years old at diagnosis and did not have any metastatic cancer diagnosis in the Medicare claims data in the 12 months before the current cancer diagnosis. Per the FDA labeling, all patients in our sample diagnosed with metastatic melanoma after the FDA approvals described above were eligible to use ICIs based on characteristics we can observe in our data, and use is not dependent on any biomarker testing requirements or recommendations. Conversely, ICIs are only indicated for patients with MSI-H CRC as identified using a biomarker test, which is estimated to be 15% of patients (Gatalica et al., 2016). Further, ICIs did not have FDA-approval extended to CRC until May 2017 for Keytruda and Opdivo and July 2018 for Yervoy. We included patients up to 89 years old at diagnosis because of demonstrated clinical safety and efficacy for older individuals in our study population (Cybulska-Stopa et al., 2019). We observed each patient for 12 months after their diagnosis, unless deceased. Our final sample included 17,215 and 34,248 beneficiaries with newly diagnosed metastatic melanoma and CRC, respectively, from 2008 to 2019 (12 months after the last cohort of patients was diagnosed). For reference, the total number of patients considered in the key clinical trials before FDA approval for the ICIs was just 1,280 (Hamid et al., 2017; Robert et al., 2011, 2015).

4.2 Data on Pharmaceutical Cancer Treatments

Information on cancer medications used under Medicare Part B, including ICIs and chemotherapy, came from the Cancer Medicines (CANMed) database provided by the Surveillance, Epidemiology, and

End Results Program (SEER) (SEER, 2023). The CANMed database includes major and minor drug classes, HCPCS codes, brand names, generic names, FDA approval dates, and CMS effective dates.

4.3 Study Outcomes

We examine several key outcomes. For treatment utilization, we assess the use of ICIs, plus chemotherapy and radiation, which were standard treatments before ICIs were available. For costs, we measure the total cost to Medicare in the year after diagnosis, with separate assessments of inpatient, outpatient (inclusive of Medicare Part B drug claims), and hospice care costs. All cost estimates reflect Medicare payments and exclude patient out-of-pocket or supplementary insurance (e.g., Medigap or Medicaid) expenses such as deductibles, coinsurance, and copayments, typically much smaller than Medicare payments. This approach avoids potential measurement issues since out-of-pocket costs covered by supplemental insurance are not observable in our data. Patients without supplemental insurance (Medicaid or Medigap) are responsible for 20% of all Part B costs (without an out-of-pocket maximum), which include ICIs. All dollar amounts are inflation-adjusted to 2020 US dollars. For patient outcomes, we measure the 1-year mortality rate from the initial diagnosis, a commonly used metric for cancer patients (Delgado & Guddati, 2021).

4.4 Descriptive Statistics

Table 1 provides descriptive statistics for sample patients segmented into three periods based on the timing of diagnoses: pre-ICIs (2008 to 2010), the period when the first ICI was available (2011 to 2014), and the period when the second ICIs were available (2015 to 2018). Columns 1-3 are for melanoma, and columns 4-6 are for CRC. The patient sample is majority male and non-Hispanic white for both cancer types; however, melanoma is more common among both male and non-Hispanic white patients than CRC.[13] The average patient age is similar for melanoma and CRC (77.5 versus 76.6). Age trends down slightly over time as the number of new Medicare beneficiaries expands due primarily to the entry into Medicare of the younger members of the "baby boom" generation. Approximately 20% of patients are diagnosed

[13] Melanoma is more common among men and fair-skinned individuals of European descent (Arnold et al., 2022).

with an autoimmune disorder, which is a potential contraindication for ICI use. The share of dual Medicare-Medicaid beneficiaries is higher for patients with CRC than melanoma, 0.15 versus 0.07 in the pre-ICI period, reflecting the disproportionate burden of CRC in lower-income populations (Berry et al., 2009; Carethers & Doubeni, 2020).

In alignment with FDA labeling and approval timing, ICI use is significantly higher for melanoma patients, increasing from 9% during the first ICI period to 25% during the second ICI period, while reaching just 3% among patients with CRC during the second ICI period.[14] Utilization of other cancer treatments, such as chemotherapy and radiation, declines significantly for melanoma over the study period, while staying roughly the same for CRC. Consistent with the increase in ICI uptake, the total cost of cancer care nearly doubles for patients with melanoma while remaining relatively constant for CRC patients over the study period. Importantly, the 1-year mortality rate for melanoma decreases from 49% at baseline to 44% after the second set of ICIs became available; the CRC mortality rate is unchanged at 38% (see Appendix Figure A1 for the graphical trend in mortality rates.)

5 Results

We begin by documenting large differences in ICI take-up between melanoma and CRC patients. We then estimate the causal impacts of these differences in ICI treatment on cancer care utilization, spending, and mortality.

5.1 Use of Immune Checkpoint Inhibitors

Figure 3 shows the raw trends in ICI use for patients with melanoma and CRC. We observe a consistent increase in ICI use from the introduction of the first ICI in 2011. For melanoma patients, utilization increases from 5.4% in 2011 to 13.7% in 2014, the year before the second ICIs were introduced. By 2018, take-up increases to nearly 34%. For patients diagnosed with CRC, take-up was 1.2% in 2015 and

[14] Note that once ICIs were approved for melanoma, they could be used off-label in CRC before the CRC was added as an indication.

grows to only 5% for those diagnosed at the end of the period.[15] The differential in ICI take-up between melanoma and CRC patients is shown in the event study in Figure 5. The gap grows over time as ICI treatment is increasingly adopted by melanoma patients.[16]

To quantify the magnitude of these differences, Table 2 column (1) provides the results from estimating the difference-in-differences specification (equation 2) for the utilization of ICIs. We find that the introduction of the first ICI led to an 8.8% take-up rate for ICIs, and the introduction of the second ICIs resulted in an additional 13.7 percentage point increase in take-up compared with patients diagnosed with CRC. Overall, take-up of ICIs for melanoma increased to 22.5% (8.8 + 13.7), relative to CRC, after all three ICIs were introduced. Estimates without covariates are quite similar (see Appendix Table A2), suggesting that selection into ICI use is unlikely to bias our results.

5.2 Treatment Cost

Given the differential take-up of ICIs between melanoma and CRC patients, we next examine the effects of ICI treatment on healthcare costs. We begin in Figure 5 with the event study estimates. Patients with melanoma have lower baseline treatment costs compared to patients with CRC ($32,325 versus $48,618). However, we find that spending was trending similarly for the two groups just before the introduction of the first ICI, satisfying the parallel trends assumption. Starting in the first year after ICIs were introduced, we observe a large and persistent increase in total spending (see Panel A) which follows the increasing trend in ICI diffusion. This is driven in all periods by outpatient spending (see Panel D), the primary setting for ICI use. We find no significant changes for either inpatient or hospice costs in any period (see Panel C and E).

Table 2, columns 2 through 6, summarizes the estimates of the impact of the introduction of ICIs on average Medicare cancer treatment costs. We find an increase in overall annual treatment cost of $8,321

[15] Following the approval of Yervoy in 2011, we observe a steady increase in ICI utilization. The introduction of the second ICIs dramatically accelerated this trend. See Appendix Figure A2.

[16] There is a very small amount of Yervoy use by patients diagnosed with melanoma in 2010 (the excluded reference year) because the drug became available within 12 months of their diagnosis. Thus, the coefficients in the pre-period are not precisely zero. In a robustness test, we exclude patients who are diagnosed within 6 months of the introduction of Yervoy which does not change our results.

due to the introduction of the first ICI and an additional increase of $10,840 from the second set of ICIs, a total increase of $19,161. This represents a 59.3% increase over pre-ICI melanoma annual spending of $32,325. Importantly, we find no significant change in overall treatment cost when spending on ICIs is excluded, column (3). Across the two post-introduction periods, the increase in total spending is driven by a combined $21,648 ($9,238+$12,410) increase in outpatient costs, the setting where ICIs are infused. This represents a 151% increase over pre-ICI outpatient spending of just $14,302. We find a small and statistically insignificant decrease in inpatient and hospice costs due to the second set of ICIs, columns (4) and (6). Among ICI users, when scaled by the take-up rate, we find an increase in total treatment costs of $85,160 across the two ICI periods, a 263.4% increase over pre-ICI spending.

5.3 Treatment Utilization

In Figure 6, we examine whether there is substitution between ICIs and existing standards of care: chemotherapy and radiation. Panel A demonstrates the dynamic effects of ICI introduction on chemotherapy use, showing a significant decrease in use that grows over time. However, there is a small (albeit statistically insignificant) pre-trend that could be reflective of clinicians recognizing the small or negligible benefits of chemotherapy in this population. Although chemotherapy use may have been trending down prior to 2011, we see an acceleration in the trend after the introduction of ICIs, suggesting substitution towards ICIs. The event study estimates for radiation, shown in Panel B, are statistically insignificant before and after ICI introduction. However, there is a small decrease in radiation use after the second ICIs were introduced in 2014.

Table 2 summarizes the estimates of the impact of ICI availability on chemotherapy (column 7) and radiation (column 8). We find a substantial drop in chemotherapy use among melanoma patients relative to CRC patients of 5.2pp after the introduction of the first ICI and an additional 5.8pp drop after the second set of ICIs were introduced. Relative to baseline usage, this represents a reduction of 39.1% overall, likely reflective of substitution toward ICIs given increased efficacy over chemotherapy. We find

no impact on radiation use among melanoma patients from the first ICI but a statistically significant 3.3pp (7.2%) decrease in radiation use after the second set of ICIs became available.

5.4 1-Year Mortality

Figure 7 shows event study estimates illustrating the dynamics of mortality after the introduction of ICIs. There is a slight decrease in the 1-year mortality rate between 2011 and 2013, but it is not until after 2014 when the second ICIs are introduced that the decrease is statistically significant and sustained. We find no evidence of differential pre-trends in the mortality rate for melanoma relative to CRC patients. The patterns clearly demonstrate that mortality did not significantly improve until after the introduction of the second set of ICIs in 2014.

We quantify the magnitude of these mortality effects in Table 2 (column 9). The move toward incorporating ICIs in treatment and away from standard chemotherapy decreases the 1-year mortality rate among melanoma patients by 3pp (0.006 – 0.036) after introducing the second ICIs. This represents a 6.2% decline in the 1-year mortality rate relative to baseline mortality of 48.5%. The impact of the first ICI introduction on mortality is not statistically significant. Scaling these estimates by the increase in the share of ICI users of 22.5pp, we find that the introduction of ICIs improved mortality among users by 27.5% a dramatic change in 1-year survival for patients with melanoma who use ICIs. This finding is in alignment with (and slightly larger than) the initial clinical trials for the second ICIs, which found a 30.8% and 10%[17] improvement in 1-year mortality over traditional chemotherapy for Opdivo and Keytruda, respectively (Appendix Table A1).[18] Our estimates could also partially reflect the interaction of effects between the first and second ICIs, which, in the case of Opdivo, is often used in combination with Yervoy in the treatment of melanoma, rather than the effect of the second ICIs alone.

[17] One-year survival was not explicitly reported in the pivotal KEYNOTE-002 study of Keytruda. The estimate provided here was extrapolated from the survival analysis and 2-year survival rates, unadjusted for crossover, for comparison across ICI clinical studies (Hamid et al., 2017). Follow-up studies of Keytruda find survival benefits comparable with Opdivo. For example, in a 10-year study of Keytruda vs. Yervoy, melanoma patients experienced a 29% reduction in overall survival from Keytruda (Long et al., 2024).

[18] Based on the distribution of ICI use in our sample, the estimated weighted average survival benefit over standard of care treatment is 17.8%.

In summary, we find that the introduction of ICIs resulted in significant increases in treatment costs, movement away from existing standards of care, and a decrease in 1-year mortality after the introduction of the second ICIs. As discussed in section 5.5 below, the direction, magnitude, and significance of these estimates are consistent across alternative specifications. Estimates without covariates are also similar, which suggests that selection into ICI treatment is unlikely to drive the estimated impacts (see Appendix Table A2).

5.5 Robustness

Our results are robust to multiple alternative specifications and sample restrictions. Table 3 presents our findings for the baseline specification (panel A) and several alternative specifications that address the comparability of melanoma and CRC patients as described in Section 3.3. Panel B uses entropy balancing to ensure that CRC and melanoma patients are similar based on observable characteristics. We also test the robustness of our results by using a sample of only melanoma patients and comparing outcomes for those with a higher or lower propensity of receiving ICIs (Panel C) and using no comparison group (Panel D).

Our estimates for use of ICIs, treatment costs, treatment utilization, and 1-year mortality are similar across all specifications. For ICI use, we find increases in the use of the first ICI between 8.6 and 9.0 percentage points across all specifications. For the second set of ICIs, we estimate an additional increase in use of between 13.0 and 13.7 percentage points, with one exception – a lower (4 percentage point) but still statistically significant increase in the high-versus-low propensity specification. In all specifications, we find a small and statistically insignificant change in mortality from the first ICI introduction. Importantly, we also find a sizeable (3.6 to 4.4 pp) and statistically significant decrease in the 1-year mortality rate after the introduction of the second set of ICIs. This translates into a decrease in 1-year mortality of 25.8% to 35.7% among users due to the introductions of ICIs.[19]

In Table 4, we further test the sensitivity of our estimates to spillovers in access to ICIs by excluding time periods and patients that could be partially treated. As in Table 3, we repeat the baseline

[19] Excludes the outlier specification of high-versus-low propensity which had an estimated 79.9% decrease in the 1-year mortality rate among high-propensity users.

results in Panel A. Panel B excludes patients who were diagnosed within six months of the first ICI approval, who will have partial exposure to the availability of ICI treatment.[20] Panel C excludes patients who were diagnosed after ICIs were approved for use in CRC, thus we end our study period in May 2017. The estimates using both sample restrictions are quite similar to the baseline estimates with two expected differences in magnitudes. Specifically, using the shorter post-period to exclude the period when ICIs became available for CRC, we unsurprisingly find a smaller (9.8 vs. 13.7 percentage point) increase in ICI uptake and spending ($8927 vs. $10840) after the approval of the second set of ICIs. We find a similar, but slightly larger mortality effect (-0.038 vs. -0.036), reflecting that our baseline estimates are biased downwards due to the small amount of ICI use among patients with CRC.

5.6 Heterogeneity

We also examine how the take-up of ICIs and outcomes vary by patient characteristics. Figure 8 illustrates raw ICI use rates among patient groups, limited to patients with melanoma who were diagnosed after the first ICI became available. While use is relatively similar between men and women and between white and non-white patients, there are notable disparities based on age and dual-eligible status. Older patients and those with dual Medicare-Medicaid enrollment show substantially lower rates of ICI adoption. Specifically, use is 18.0% among non-duals and 12.4% among duals, and use is 13.8% among those aged 78 and up versus 20.7% for those aged 66 through 77.

In Table 5, we show our main difference-in-differences estimates for utilization, costs, and mortality by sex (panel A), age (B), comorbidities (C), race (D), and dual status (E), controlling for all other patient characteristics. We estimate slightly higher ICI use for younger patients with fewer chronic conditions. We find that patients who are non-white have lower first ICI utilization but higher second ICI use compared to patients who are white. We also find lower use of the first ICI among dual Medicare-Medicaid patients, suggesting they are slower to adopt the innovation. Provider estimates of the likely effectiveness of ICIs across patient characteristics may partly drive these differences in utilization

[20] We use 6-months because this is typically when initial treatment plans are set. Patients diagnosed more than 6 months before Yervoy's introduction are much less likely to have access to ICI treatment.

(Cybulska-Stopa et al., 2019; Johnson et al., 2017; Rauwerdink et al., 2020; Yip et al., 2024). Differences in patient access may also explain these differences.

Changes in average Medicare expenditures are consistent across patient groups, apart from patients who are non-white or who are dually enrolled, who have no statistically significant change in cost after the first ICI introduction. The lack of cost increase reflects their significantly lower utilization of the new treatments. Those groups also showed no change in chemotherapy use after the first ICI introduction, where we found a consistent decrease for other groups. Lastly, we estimate a decrease in mortality for all groups from the second ICIs' introduction; however, these estimates are not significant for women, patients who are non-white, and dually enrolled patients. For non-white and dually enrolled patients, the magnitude of our estimates are similar; hence, the lack of significance is likely at least partly attributable to the much smaller sample sizes (and thus lower statistical precision) for these estimates. For women, this finding could reflect a differential impact of ICIs by gender. Some studies have suggested that without chemotherapy, ICIs are more effective in men (Wang et al., 2019). Given that we find a 10.2% decrease in chemotherapy use after ICIs are introduced among women, this could reflect that clinical premise. However, as clinicians' understanding evolves as ICIs are integrated into treatment, research on sex differences in ICI efficacy is ongoing.

6 Discussion and Conclusion

Immune checkpoint inhibitors (ICIs) are a revolutionary treatment for cancer. In this paper, we estimate how the first three ICIs[21] to be FDA-approved affected Medicare expenditures, health care utilization, and mortality for FFS Medicare beneficiaries with metastatic melanoma. Prior to the introduction of ICIs, metastatic melanoma patients had few effective treatment options and mortality rates that, in contrast to most other types of cancer, had been increasing for decades. We find that these therapies transformed the treatment landscape, leading to decreased use of traditional chemotherapy and significant

[21] Yervoy (ipilimumab, targeting the CLTA-4 protein), Opdivo (nivolumab, targeting the PD-1 protein), and Keytruda (pembrolizumab, targeting the PD-1 protein).

improvements in survival outcomes after the second wave of ICIs (Keytruda and Opdivo) became available. The magnitude of mortality reductions we observe, approximately 27.5% among patients who use ICIs, is consistent with the efficacy demonstrated in clinical trials despite use in patients that are often excluded from clinical trials (Liu et al., 2021), e.g., older patients with more comorbidities (Appendix Table A1). Importantly, our findings demonstrate that the clinical benefits observed in randomized trials can translate into real-world settings, particularly for serious illnesses with few treatment options. Second, they highlight the value of continued innovation, as the second generation of ICIs delivered greater mortality benefits not realized from the first generation.

Although the benefits of these treatments are substantial, the costs are also very high, constituting more than 44% of Part B spending on cancer drugs in traditional Medicare. A back-of-the-envelope calculation, based on our estimated mortality reduction of 27.5%, suggests a 1-year survival benefit valued at $13,200 to $19,800 per treated patient, when applying standard valuations of $100,000 to $150,000 per life-year gained.[22] In comparison, we estimate a $85,160 incremental increase in Medicare spending per patient receiving ICIs. Without observing long-term survival gains beyond one year, we cannot directly estimate whether the costs of ICIs exceed the health benefits using our data. However, ICIs would need to deliver 0.57 to 0.85 additional life-years per treated patient (more than 4 to 6 times the survival gain estimated in the first year) for the benefits to align with costs.[23] Evidence from long-term clinical trials suggests that the benefits could indeed be this large. For example, in a 10-year study of melanoma patients, those treated with Opdivo who survived to the first year experienced an additional median survival gain of 4 years compared to those treated with Yervoy (Wolchok et al., 2025).[24] Applying this estimate to our analysis would imply lifetime survival benefits valued at $52,800 to $79,200, which are more

[22] The baseline 1-year mortality rate is 0.48. $13,200 = 0.48 * 0.275 * $100,000. $19,800 = 0.48 * 0.275 * $150,000.
[23] We estimate an increase in 0.132 life-years per patient treated with ICIs (0.132 = 0.48 * 0.275) in the first year. Aligning the survival benefit with costs would require that ICIs deliver an increase in life-years of 0.57 (85,160/$150,000) to 0.85 (85,160/$100,000).
[24] Using the data presented in Figure 1 of Wolchok et al. (2025), we estimate that the additional median survival conditional on survival to one year is about 72 months for Opdivo versus 24 months for Yervoy, an additional 4 years.

comparable to costs.[25] Survival benefits could be even larger, as this study compared Opdivo with Yervoy and not chemotherapy, which was the predominant treatment prior to ICIs when median survival was only 6 months (Hodi et al., 2010). Moreover, our analysis does not account for combination therapies, such as Opdivo and Yervoy, where the estimated benefits are even larger (Wolchok et al., 2025). It is important to note that our estimates do not incorporate costs outside of Medicare (e.g., Medigap or patient out-of-pocket costs), nor do they account for changes in quality of life. Nevertheless, the evidence suggests that for melanoma patients, ICIs represent a significant breakthrough such that the benefits of this innovation likely exceed its substantial costs to Medicare.

This may explain why similar prices are observed for ICIs in other high-income countries. Interestingly, in 2018, prices for the three ICIs studied here were only 1.2 to 1.5 times higher in the U.S. than in "peer" nations (roughly the G7 and a subset of countries in Germany's reference pricing basket), while prices for many other drugs in the U.S. have much higher ratios (HHS, 2018). Specifically, the median price ratio for the other treatments considered in this study was 2.2. That prices are comparable for the three ICIs studied here in other industrialized nations suggests they these countries may recognize the substantial clinical benefits of ICIs.

Despite significant survival benefits, our results demonstrate that once available, the adoption of ICIs was relatively slow, with use increasing from 5.4% in the first year they were available to 33.7% by 2018. Moreover, adoption varied significantly across patient groups, with lower rates among older patients, those with more comorbidities, and individuals dually eligible for Medicare and Medicaid. These disparities raise concerns about differential access to innovative treatments. The costs to patients and health insurers are considerable. Traditional Medicare beneficiaries without supplemental insurance may be required to pay up to 20% as coinsurance, which likely limits ICI use. Geographic barriers may also limit access to

[25] The gain in median survival conditional on survival to one year for Opdivo is 4 years (Wolchok et al., 2025). Applying this to our estimate of 1-year mortality, we estimate 0.528 additional life-years attributable to ICIs in the long-run: 0.528 = 0.48 * 0.275 * 4 valued at $52,800 to $79,200 based on $100,000 or $150,000 values of a life-year.

specialized cancer centers with experience administering ICIs, which can be complex and require additional patient monitoring. Targeted interventions to address these barriers could help ensure that the benefits of innovative therapies are also enjoyed by low-income Medicare recipients dually eligible for Medicaid and other groups.

Our study provides timely insights into the real-world impact of a transformative healthcare technology on older adult Medicare patients in the U.S. Immune checkpoint inhibitors are an important advancement in the treatment of melanoma and other cancer types. While they come with considerable costs to patients and the healthcare system, they provide substantial survival benefits for patients who can access them. Uneven diffusion among certain disadvantaged groups is concerning. As new technology diffuses, special care should be taken by policymakers and clinicians to help disadvantaged groups gain access and overcome barriers to care, particularly for high-cost innovations.

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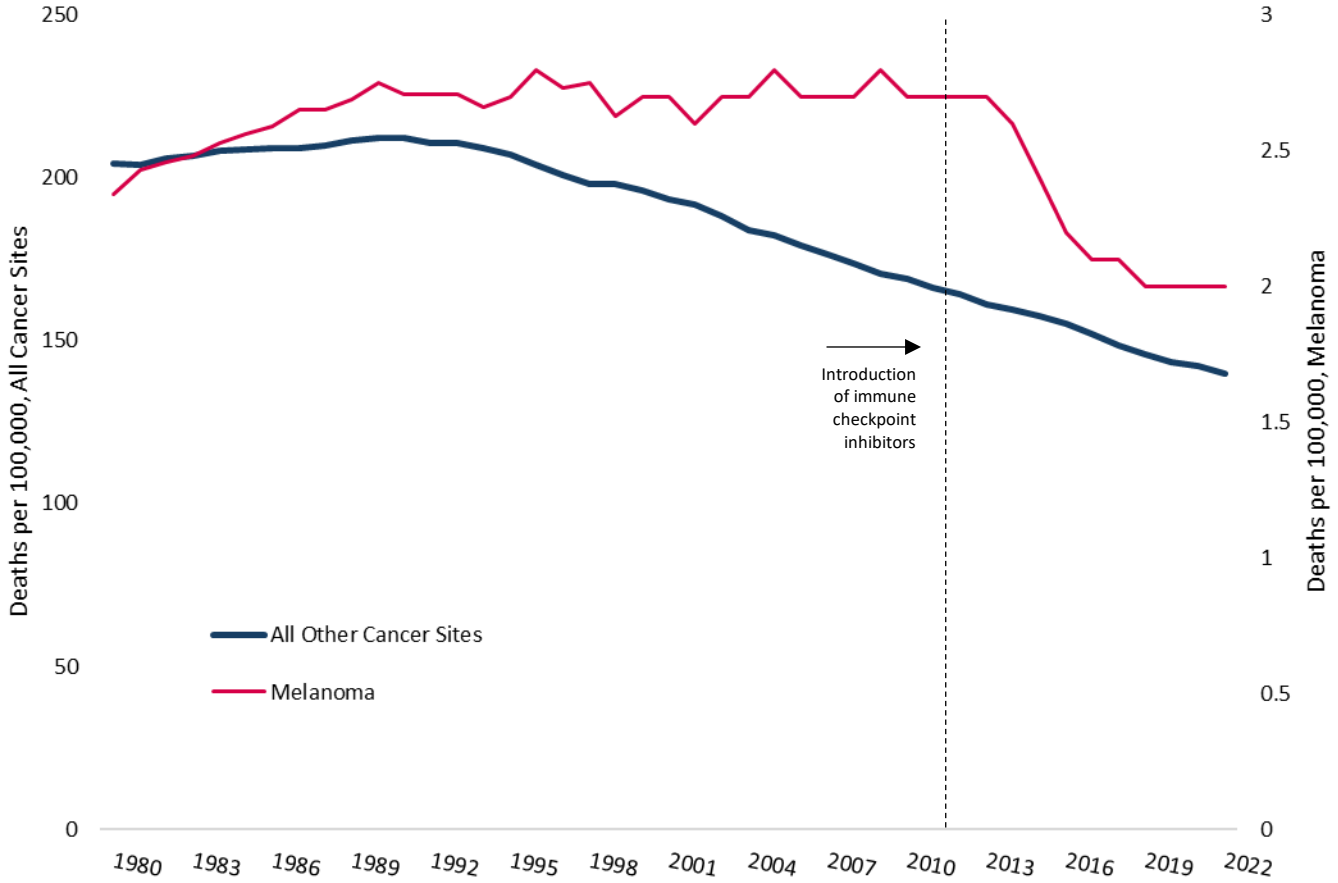
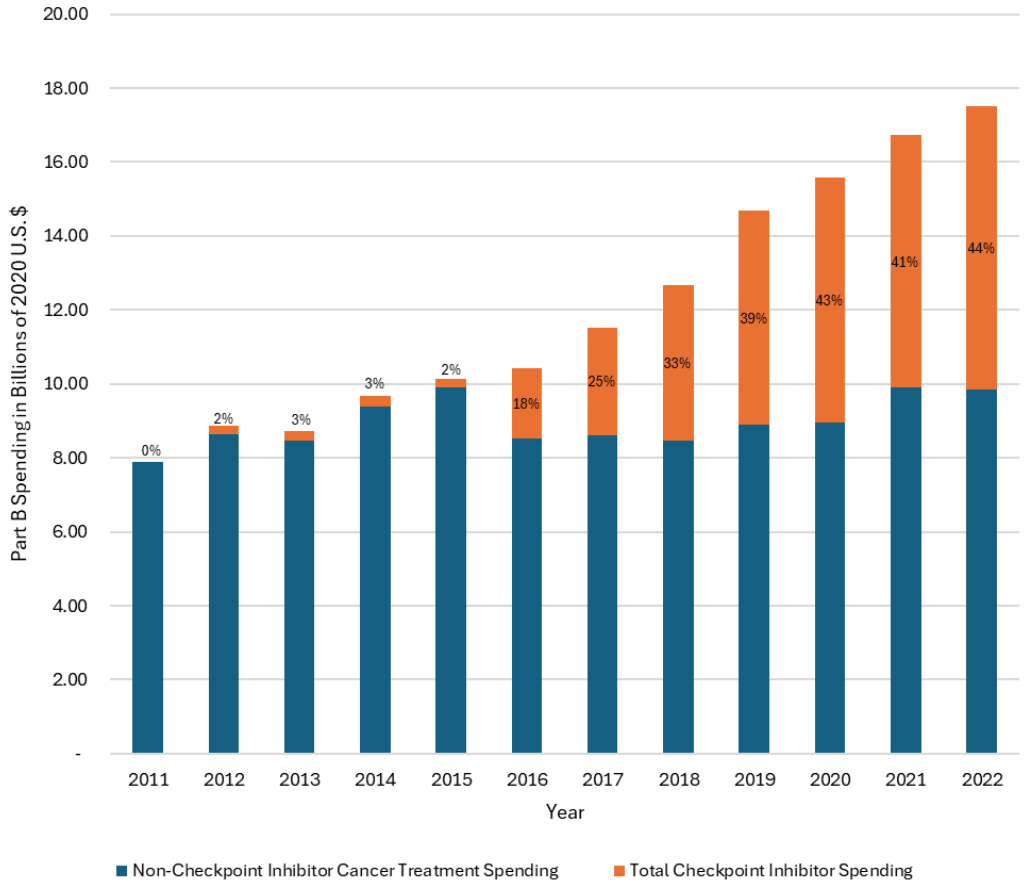
Figures

Figure 1: Cancer Mortality, 1980 to 2022



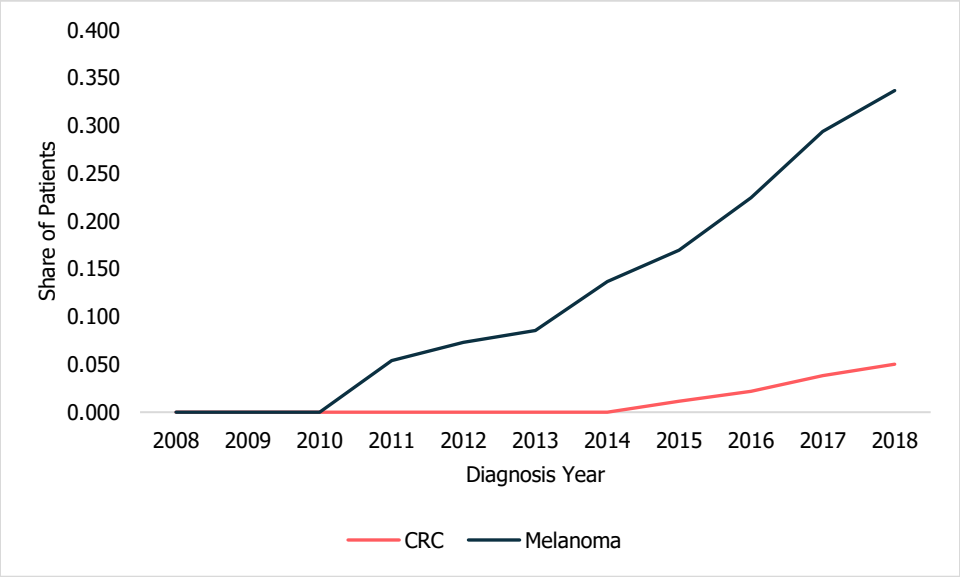
Notes: This figure illustrates cancer mortality over time. The curve for all cancer sites references the primary vertical axis on the left, and the curve for metastatic melanoma references the secondary axis on the right. Mortality rates are per 100,000 individuals. Source: NCI, 2020; SEER, 2022.

Figure 2: Spending on Cancer Drugs in FFS Medicare Part B



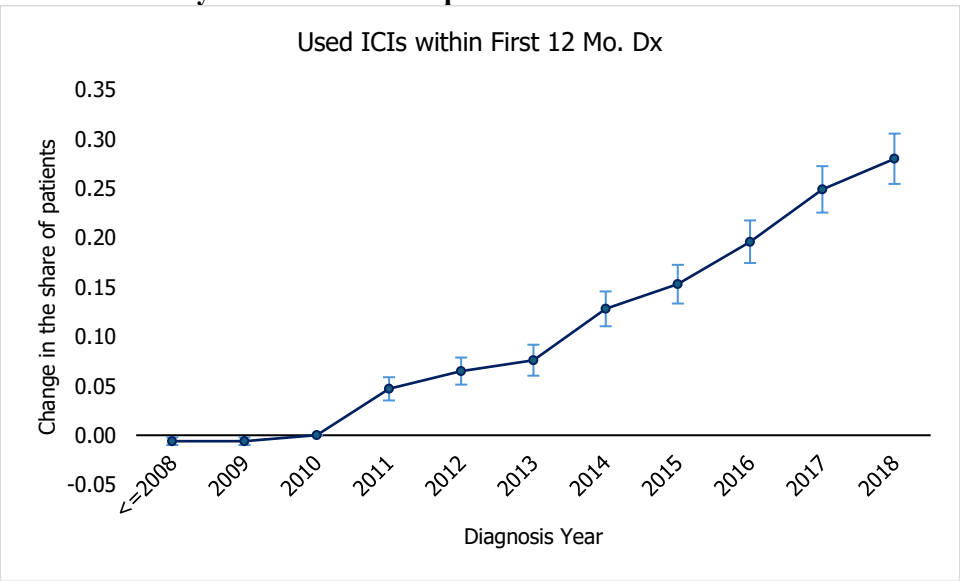
Notes: This figure illustrates spending on cancer drugs in fee-for-service Medicare Part B as classified by the SEER Cancer Medicines database. The orange bars represent spending on FDA-approved immune checkpoint inhibitors (ICIs) across all cancer indications. In 2022, eight ICIs were approved, but 83% of spending in that year was related to the three ICIs included in this study. Source: CMS, 2024.

Figure 3: Immune Checkpoint Inhibitor Use by Diagnosis



Notes: Mean share of patients using at least one ICI between patients diagnosed with metastatic melanoma and those diagnosed with metastatic colorectal cancer (CRC) by diagnosis year.

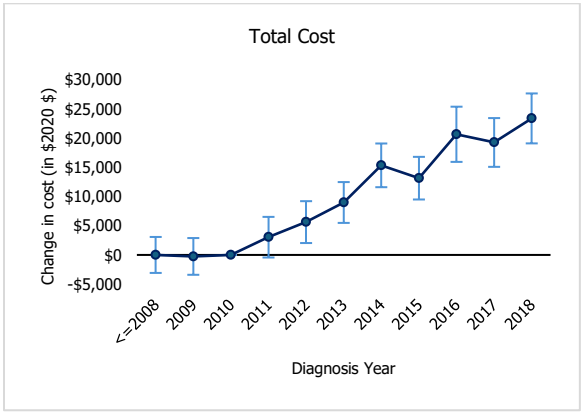
Figure 4: Event Study of Immune Checkpoint Inhibitor Use within the First 12 Months



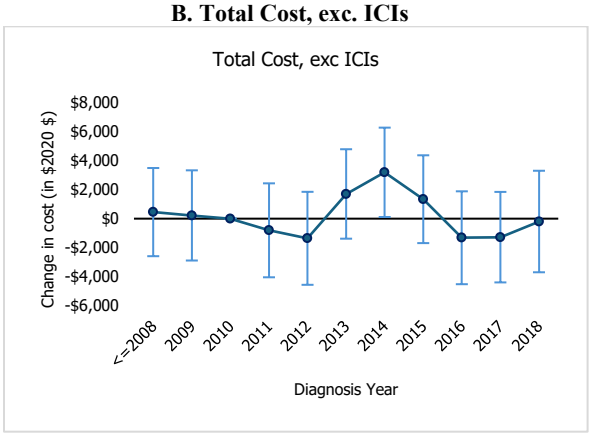
Notes: Event study estimate of the impact of ICIs. Ipilimumab (the first CLTA-4 ICI) was introduced in 2011. The reference period is the year prior, 2010. Error bars represent a 95% confidence interval.

Figure 5: Event Study of Treatment Cost

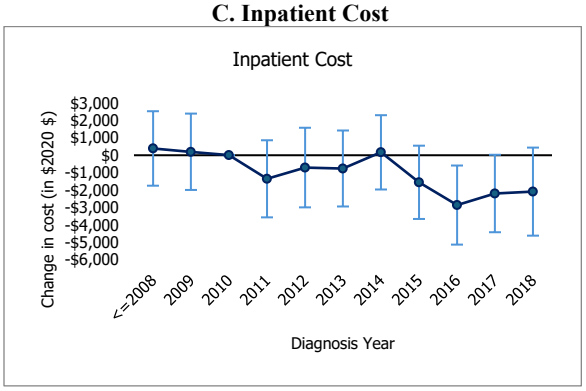
A. Total Treatment Cost



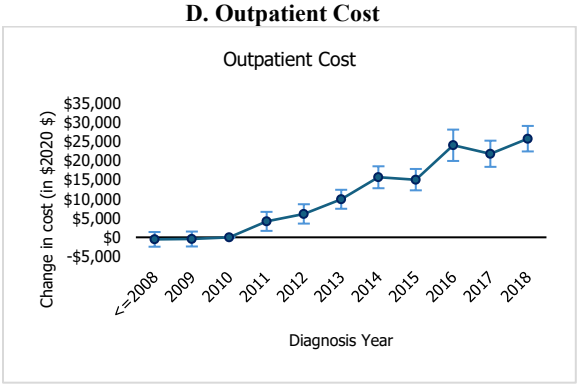
B. Total Cost, exc. ICIs



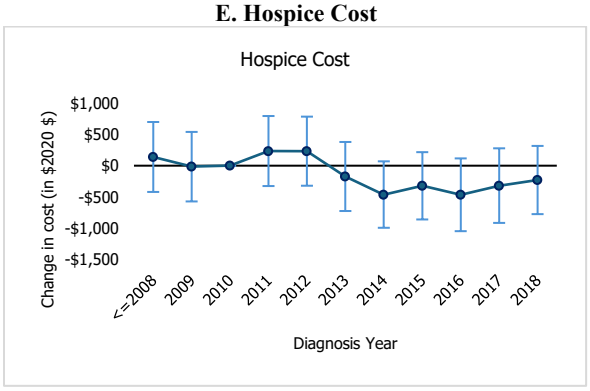
C. Inpatient Cost



D. Outpatient Cost

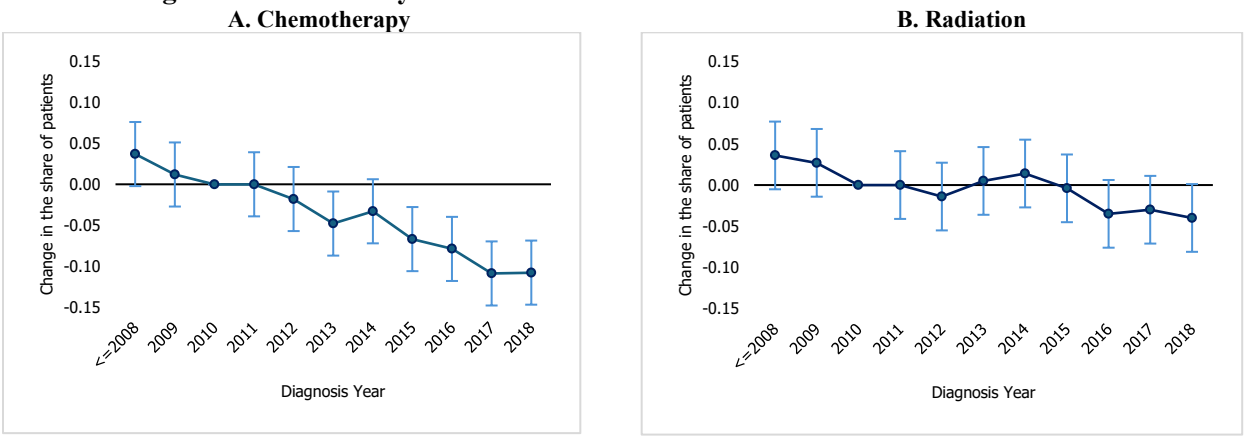


E. Hospice Cost



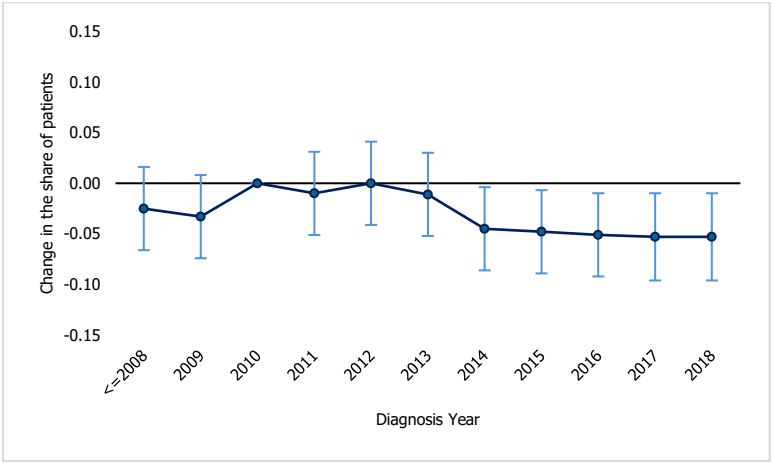
Notes: See Figure 4.

Figure 6: Event Study of Treatment Utilization Use within the First 12 Months



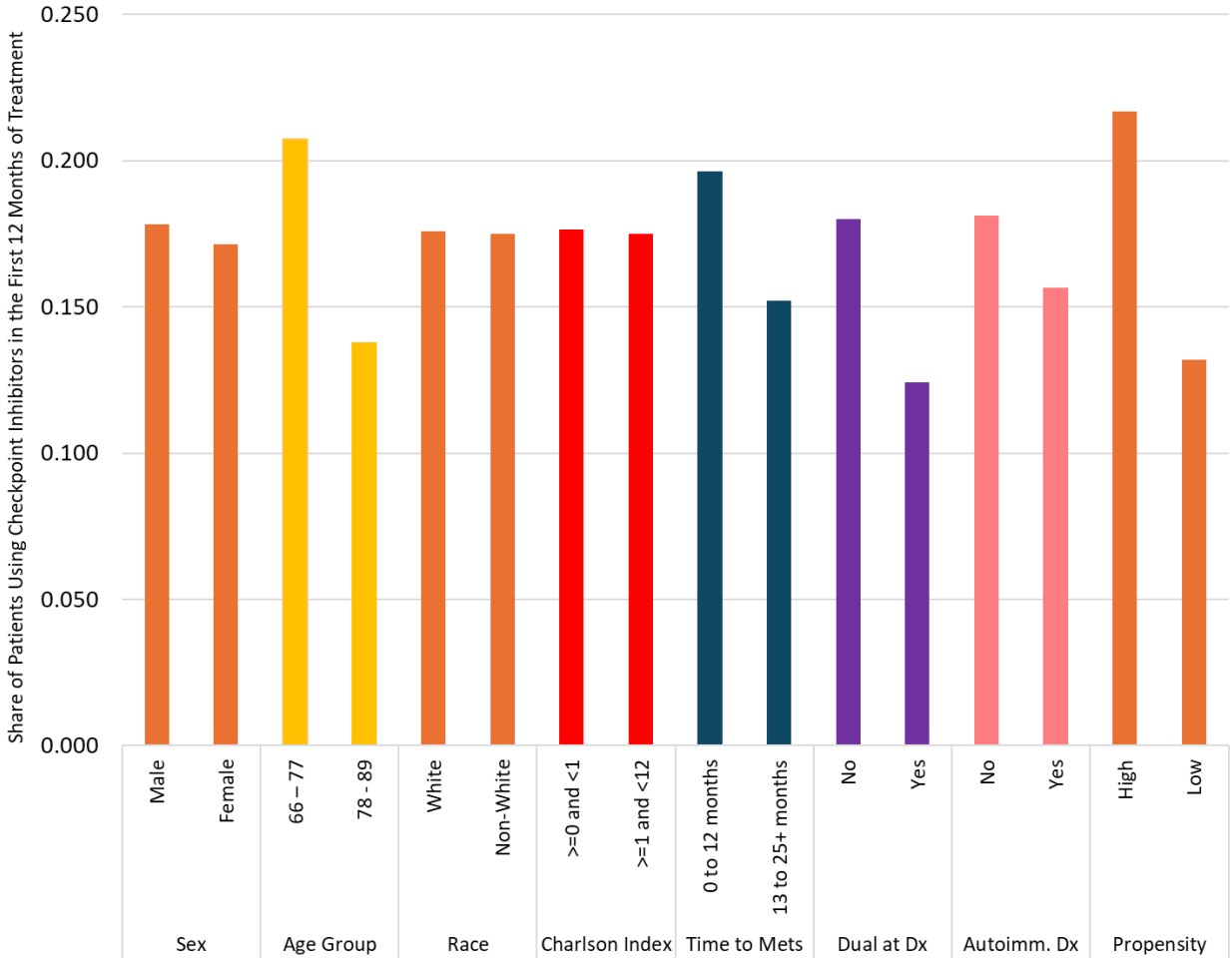
Notes: See Figure 4.

Figure 7: Event Study of 1-Year Mortality



Notes: See Figure 4.

Figure 8: Use of Immune Checkpoint Inhibitors by Patient Characteristics



Notes: This figure illustrates the share of each group of patients with metastatic melanoma that used immune checkpoint inhibitors (ICIs) within the 12 months after diagnosis, limited to patients diagnosed after ICIs became available in the second quarter of 2011.

Tables

Table 1: Summary Statistics

	Melanoma			Colorectal Cancer		
	2008 to 2010 [Pre-ICI] (1)	2011 to 2014 [First ICI] (2)	2015 to 2018 [Second ICIs] (3)	2008 to 2010 [Pre-ICI] (4)	2011 to 2014 [First ICI] (5)	2015 to 2018 [Second ICIs] (6)
Patinet Characteristics						
Male	0.65	0.66	0.66	0.52	0.52	0.53
Age at Dx	77.54	76.96	76.62	76.61	76.18	75.75
White	0.97	0.96	0.95	0.82	0.82	0.80
Non-White	0.03	0.04	0.05	0.18	0.18	0.20
Charlson Index	0.85	0.85	0.92	0.89	0.94	1.12
Autoimmune Dx	0.18	0.21	0.22	0.17	0.21	0.22
Dual	0.07	0.07	0.07	0.15	0.16	0.16
Utilization and Outcomes						
Used Chemo	0.28	0.25	0.20	0.47	0.48	0.50
Used Radiation	0.46	0.44	0.38	0.29	0.29	0.27
Used Checkpoint Inhibitors	0.00	0.09	0.25	0.00	#	0.03
Inpatient Stay	0.64	0.60	0.53	0.79	0.76	0.74
Hospice	0.33	0.34	0.32	0.25	0.26	0.28
Died within 1 Year	0.49	0.49	0.44	0.38	0.38	0.38
Died within 1 Year (used ICIs)	---	0.41	0.29	---	#	0.00
Treatment Costs						
Total Health Care Cost (in 2020 $)	$45,285.61	$52,091.19	$62,895.51	$61,815.31	$60,156.13	$58,244.48
Total Cancer Costs (in 2020 $)	$32,325.20	$38,866.76	$49,480.29	$48,617.97	$47,087.44	$46,794.45
N	4666	6256	6293	11182	12289	10777

Notes: At the patient-level, separated between patients diagnosed with metastatic melanoma and those diagnosed with metastatic colorectal cancer. The notation # indicates that fewer than 11 patients are indicated and the value is suppressed.

Table 2: Impact of Immune Checkpoint Inhibitor Use on Metastatic Melanoma Cost, Treatment Utilization, and Mortality

		Cost of Cancer Care (in 2020 $)					Treatments & Outcomes		
	ICI Use	Total Cost	Total Cost, Exc. ICIs	Inpatient	Outpatient	Hospice	Used Chemo	Used Radiation	Died within 1 Year
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Melanoma	0.01 ***	-14620.00 ***	-15120.00 ***	-6317.00 ***	-8385.00 ***	80.98	-0.19 ***	0.15 ***	0.09 ***
	(0.00)	(631.74)	(620.08)	(428.49)	(404.60)	(112.78)	(0.01)	(0.01)	(0.01)
Melanoma X Post First ICI	0.09 ***	8321.00 ***	20.47	-834.00	9238.00 ***	-82.41	-0.05 ***	-0.01	0.01
	(0.00)	(926.93)	(814.13)	(563.38)	(672.09)	(147.28)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.14 ***	10840.00 ***	-693.10	-1285.00 *	12410.00 ***	-285.60 *	-0.06 ***	-0.03 ***	-0.04 ***
	(0.01)	(1160.17)	(808.89)	(570.00)	(981.84)	(144.71)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$32,325	$32,052	$15,579	$14,302	$2,445	0.28	0.46	0.48
N	51,463	51,463	51,463	51,463	51,463	51,463	51,463	51,463	51,463

Notes: This table shows the results of estimating equation 2 on ICI use, patient treatment costs, other care utilization, and 1-year mortality. The first ICI is Yervoy (post-April 2011), and the second ICIs are Keytruda and Opdivo (post-October 2015). All costs are inflation-adjusted to US 2020 dollars. * p<0.05, ** p<0.01, *** p<0.001.

Table 3: Robustness – Alternative Specifications

	ICI Use	Total Cost of Cancer Care (in 2020 $)	Treatments & Outcomes		
			Used Chemo	Used Radiation	Died within 1 Year
	(1)	(2)	(3)	(4)	(5)
A. Baseline (N = 51436)					
Melanoma X Post First ICI	0.09 ***	8321.00 ***	-0.05 ***	-0.01	0.01
	(0.00)	(926.93)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.14 ***	10840.00 ***	-0.06 ***	-0.03 ***	-0.04 ***
	(0.01)	(1160.17)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$32,325	0.28	0.46	0.48
B. Entropy Balancing (N = 51436)					
Melanoma X Post First ICI	0.09 ***	7827.00 ***	-0.06 ***	-0.01	0.01
	(0.00)	(966.49)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.13 ***	10660.00 ***	-0.05 ***	-0.04 **	-0.04 **
	(0.01)	(1189.54)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$32,325	0.28	0.46	0.48
C. High vs. Low Propensity					
High Propensity X Post First ICI	0.06 ***	5822.00 ***	-0.08 ***	0.00	0.02
	(0.01)	(1537.21)	(0.02)	(0.02)	(0.02)
High Propensity X Post Second ICIs	0.04 ***	2390.00	-0.02	-0.03	-0.04 *
	(0.01)	(1988.97)	(0.01)	(0.02)	(0.02)
Pre-ICI Mean	---	$32,325	0.28	0.46	0.48
D. Without Control Group (N = 17215)					
Melanoma X Post First ICI	0.09 ***	5835.00 ***	-0.04 ***	-0.03 **	0.01
	(0.00)	(790.89)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.17 ***	10900.00 ***	-0.04 ***	-0.06 ***	-0.04 ***
	(0.01)	(1049.29)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$32,325	0.28	0.46	0.48

Notes: Panel A is the baseline specification with an indicator for melanoma, patient-level controls and diagnosis year fixed effects; Panel B uses entropy balancing to equalize the distribution of observable characteristics of the patients between melanoma and colorectal cancer samples. Panel C is an alternative specification that estimates a differences-in-differences specification only among patients diagnosed with metastatic melanoma. High propensity patients are those that are equal to or above the median propensity to use immune checkpoint inhibitors (ICIs); 21.7% of high propensity patients use ICIs compared to 13.2% of low-propensity patients among those diagnosed after ICIs are available. Panel D excludes CRC as the control group. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table 4: Robustness – Sample Restrictions

	ICI Use	Total Cost of Cancer Care (in 2020 $)	Treatments & Outcomes		
			Used Chemo	Used Radiation	Died within 1 Year
	(1)	(2)	(3)	(4)	(5)
A. Baseline (N = 51436)					
Melanoma X Post First ICI	0.09 ***	8321.00 ***	-0.05 ***	-0.01	0.01
	(0.00)	(926.93)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.14 ***	10840.00 ***	-0.06 ***	-0.03 ***	-0.04 ***
	(0.01)	(1160.17)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$32,325	0.28	0.46	0.48
B. Excluding Patients Diagnosed within 6 Mo. of the First ICI Approval (n = 49134)					
Melanoma X Post First ICI	0.09 ***	8962.00 ***	-0.05 ***	-0.02	0.00
	(0.00)	(976.47)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.14 ***	10750.00 ***	-0.06 ***	-0.03 ***	-0.03 **
	(0.01)	(1164.47)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$32,000	0.28	0.46	0.49
C. Excluding Post May 2017 when ICIs Received CRC Indication Approval (N = 44166)					
Melanoma X Post First ICI	0.09 ***	8271.00 ***	-0.05 ***	-0.01	0.01
	(0.00)	(927.15)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.10 ***	8927.00 ***	-0.05 ***	-0.03 *	-0.04 **
	(0.01)	(1441.18)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$32,325	0.28	0.46	0.48

Notes: Panel A is the baseline specification with patient-level controls and diagnosis year fixed effects; Panel B excludes patients diagnosed within six months of the first ICI becoming available; Panel C excludes all patients diagnosed with melanoma or CRC after May 2017 when CRC was added as an approved indication for ICIs. For a table that includes coefficients on metastatic melanoma representing baseline differences, see Appendix Table A5. * p<0.05, ** p<0.01, *** p<0.001.

Table 5: Heterogeneity

A. Sex

	ICI Use	Total Cost of Cancer Care (in 2020 $)	Treatments & Outcomes		
			Used Chemo	Used Radiation	Died within 1 Year
	(1)	(2)	(3)	(4)	(5)
Male (N = 29278)					
Melanoma X Post First ICI	0.09 ***	8810.00 ***	-0.07 ***	-0.02	0.00
	(0.01)	(1219.02)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.14 ***	12350.00 ***	-0.04 ***	-0.03 *	-0.05 ***
	(0.01)	(1524.80)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$33,090	0.30	0.48	0.50
Female (N = 22185)					
Melanoma X Post First ICI	0.09 ***	7847.00 ***	-0.01	0.01	0.02
	(0.01)	(1434.23)	(0.02)	(0.02)	(0.02)
Melanoma X Post Second ICIs	0.13 ***	8165.00 ***	-0.08 ***	-0.03 *	-0.01
	(0.01)	(1755.28)	(0.02)	(0.02)	(0.02)
Pre-ICI Mean	---	$30,894	0.24	0.42	0.45

B: Age

	ICI Use	Total Cost of Cancer Care (in 2020 $)	Treatments & Outcomes		
			Used Chemo	Used Radiation	Died within 1 Year
	(1)	(2)	(3)	(4)	(5)
Younger (N = 29184)					
Melanoma X Post First ICI	0.11 ***	12000.00 ***	-0.06 ***	-0.01	0.00
	(0.01)	(1406.06)	(0.01)	(0.02)	(0.02)
Melanoma X Post Second ICIs	0.15 ***	12360.00 ***	-0.07 ***	-0.04 **	-0.04 *
	(0.01)	(1728.01)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$35,687	0.33	0.49	0.42
Older (n = 22279)					
Melanoma X Post First ICI	0.06 ***	4521.00 ***	-0.04 *	-0.01	0.01
	(0.01)	(1170.47)	(0.01)	(0.02)	(0.02)
Melanoma X Post Second ICIs	0.11 ***	8796.00 ***	-0.04 **	-0.03	-0.04 *
	(0.01)	(1469.69)	(0.01)	(0.02)	(0.02)
Pre-ICI Mean	---	$29,032	0.23	0.43	0.55

C. Comorbidities

	ICI Use	Total Cost of Cancer Care (in 2020 $)	Treatments & Outcomes		
			Used Chemo	Used Radiation	Died within 1 Year
	(1)	(2)	(3)	(4)	(5)
Charlson Fewer (N = 21995)					
Melanoma X Post First ICI	0.09 ***	8249.00 ***	-0.06 ***	-0.03	0.02
	(0.01)	(1142.37)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.14 ***	11640.00 ***	-0.06 ***	-0.04 **	-0.03 *
	(0.01)	(1479.53)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$31,320	0.26	0.45	0.46
Charlson Greater (N = 19468)					
Melanoma X Post First ICI	0.08 ***	8584.00 ***	-0.03	0.01	-0.02
	(0.01)	(1578.29)	(0.02)	(0.02)	(0.02)
Melanoma X Post Second ICIs	0.14 ***	9213.00 ***	-0.07 ***	-0.03	-0.05 **
	(0.01)	(1868.15)	(0.02)	(0.02)	(0.02)
Pre-ICI Mean	---	$34,275	0.33	0.47	0.54

D. Race

	ICI Use	Total Cost of Cancer Care (in 2020 $)	Treatments & Outcomes		
			Used Chemo	Used Radiation	Died within 1 Year
	(1)	(2)	(3)	(4)	(5)
Non-White (N = 7022)					
Melanoma X Post First ICI	0.07 ***	-906.40	0.02	-0.06	0.05
	(0.02)	(5487.26)	(0.05)	(0.05)	(0.05)
Melanoma X Post Second ICIs	0.16 ***	18930.00 **	-0.13 **	-0.01	-0.05
	(0.03)	(5900.00)	(0.04)	(0.05)	(0.05)
Pre-ICI Mean	---	$43,080	0.21	0.48	0.49
White (N = 44414)					
Melanoma X Post First ICI	0.09 ***	8372.00 ***	-0.06 ***	-0.01	0.01
	(0.00)	(953.73)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.13 ***	10310.00 ***	-0.05 ***	-0.04 ***	-0.04 ***
	(0.01)	(1189.54)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$31,985	0.28	0.46	0.48

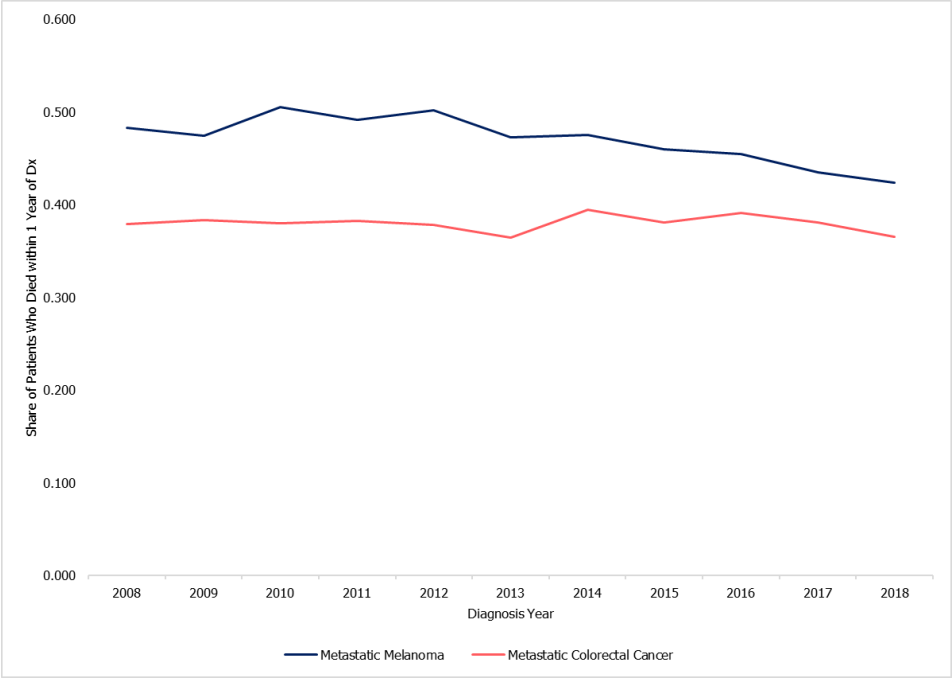
E. Dual Status

	ICI Use	Total Cost of Cancer Care (in 2020 $)	Treatments & Outcomes		
			Used Chemo	Used Radiation	Died within 1 Year
	(1)	(2)	(3)	(4)	(5)
Dual (N = 6517)					
Melanoma X Post First ICI	0.04 ***	964.30	0.00	-0.02	0.01
	(0.01)	(3028.04)	(0.03)	(0.04)	(0.04)
Melanoma X Post Second ICIs	0.14 ***	10110.00 *	-0.08 **	-0.04	-0.05
	(0.02)	(3978.69)	(0.03)	(0.04)	(0.04)
Pre-ICI Mean	---	$31,814	0.18	0.42	0.58
Non-Dual (N = 44946)					
Melanoma X Post First ICI	0.09 ***	9143.00 ***	-0.06 ***	-0.01	0.00
	(0.00)	(977.24)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.14 ***	10780.00 ***	-0.06 ***	-0.03 **	-0.03 **
	(0.01)	(1215.73)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$32,365	0.29	0.46	0.48

Notes: This table provides estimates of equation 2 segmented by different patient characteristics: sex (panel A), age (over versus under 77 years old, panel B), Charlson Index score (more or less than 1, panel C), race (white versus non-white, panel D), and dual status (panel E). The first ICI is Yervoy (post-April 2011), and the second ICIs are Keytruda and Opdivo (post-October 2015). All costs are inflation-adjusted to US 2020 dollars. For a table that includes coefficients on metastatic melanoma representing baseline differences, see Appendix Table A6. * p<0.05, ** p<0.01, *** p<0.001.

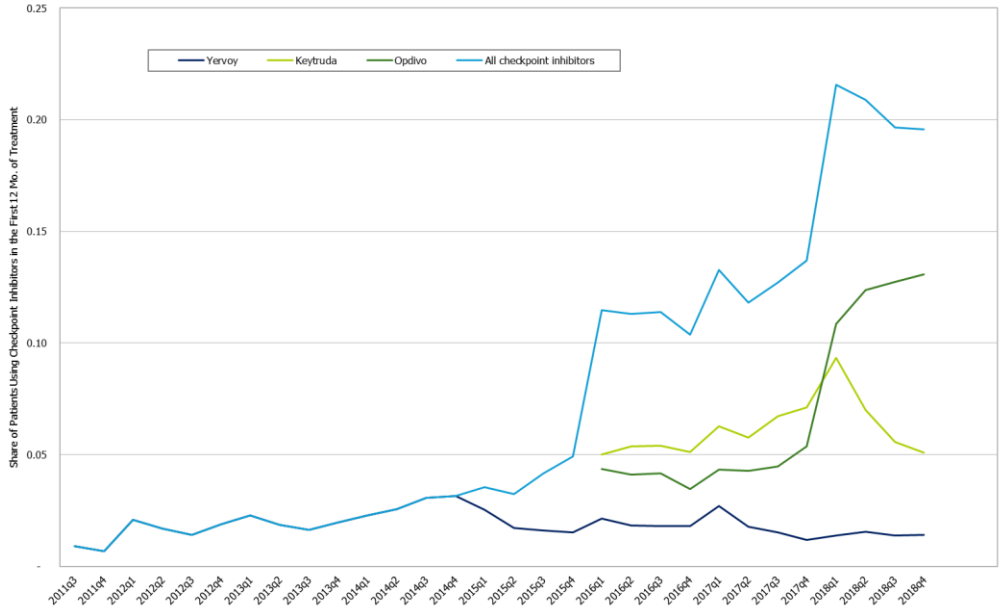
Appendix

Figure A1: 1-Year Mortality Rate by Year of Diagnosis, 2008 - 2018



Notes: Share of patients who died within 1-year of diagnosis with metastatic disease.

Figure A2: Share of Patients with Metastatic Melanoma Using Immune Checkpoint Inhibitors by Quarter



Notes: Share of patients using of immune checkpoint inhibitors by quarter among all patients within 12 months of metastatic melanoma diagnosis in the quarter.

Table A1: Clinical Trial Results and Treatment Costs for Immune Checkpoint Inhibitors

	Baseline Chemotherapy[a]	Yervoy (Ipilimumab)[1,b]	Opdivo (Nivolumab)[2]	Keytruda (Pembrolizumab)[3]
Response Rate	4% - 13%	+4.9%	+26.1%	+24.0%
1-Year Survival	36% - 44%	+11.0%	+30.8%	+10.0%[c]
Grade 3/4 Side Effects	17% - 27%	+0.3%	-5.9%	-9.5%
Est. Cost per Treatment Dose[d]	$45	$39,424	$13,708	$20,338
Est. Total Cost	$775	$157,697	$164,500	$176,750
Treatment Duration	1 Year	3 months	1+ Years	1+ Years

Notes: (a) In the pembrolizumab study, patients in control arm had disease progression after treatment with ipilimumab. If disease progressed on chemotherapy, patients in the control arm were allowed to move to treatment with pembrolizumab.
(b) The treatment arm in the study of ipilimumab was ipilimumab+chemotherapy.
(c) One-year survival was not explicitly reported in the reported study of Keytruda. The estimate provided here was extrapolated from the survival analysis and 2-year survival rates, unadjusted for crossover, for comparison across ICI clinical studies (Hamid et al., 2017).
(d) Treatment cost is based on average weight in kg of a U.S. adult and the highest recommended dose for the longest time between treatments. Chemotherapy treatment cost is based on generic dacarbazine.
1 Robert et al. (2011)
2 Robert et al. (2015)
3 Hamid et al. (2017)

Table A2: Estimates of the Impact of Immune Checkpoint Inhibitors without Controls

		Cost of Cancer Care (in 2020 $)					Treatments & Outcomes		
	ICI Use	Total Cost	Total Cost, Exc. ICIs	Inpatient	Outpatient	Hospice	Used Chemo	Used Radiation	Died within 1 Year
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Melanoma	0.00 ***	-16250.00 ***	-16640.00 ***	-7772.00 ***	-8633.00 ***	154.80	-0.19 ***	0.16 ***	0.10 ***
	(0.00)	(622.01)	(613.68)	(421.90)	(400.63)	(111.98)	(0.01)	(0.01)	(0.01)
Melanoma X Post First ICI	0.09 ***	8400.00 ***	66.00	-939.80	9443.00 ***	-102.90	-0.05 ***	-0.01	0.00
	(0.00)	(933.44)	(818.35)	(562.94)	(683.59)	(148.16)	(0.01)	(0.01)	(0.01)
Melanoma X Post Second ICIs	0.14 ***	11040.00 ***	-509.40	-1231.00 *	12580.00 ***	-307.70 *	-0.06 ***	-0.04 ***	-0.04 ***
	(0.01)	(1171.32)	(808.89)	(569.74)	(996.44)	(145.98)	(0.01)	(0.01)	(0.01)
Pre-ICI Mean	---	$32,325	$32,052	$15,579	$14,302	$2,445	0.28	0.46	0.48
N	51,463	51,463	51,463	51,463	51,463	51,463	51,463	51,463	51,463

Notes: This table shows the results of estimating equation 2 on ICI use, patient treatment costs, other care utilization, and 1-year mortality but without patient-level control variables. The first ICI is Yervoy (post-April 2011), and the second ICIs are Keytruda and Opdivo (post-October 2015). All costs are inflation-adjusted to US 2020 dollars. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.