Utilization of systemic therapy in cancer patients near the end-of-life in the pre- vs. post-checkpoint inhibitor eras

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Abstract

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Introduction: Use of systemic therapy for advanced cancer patients near the end-of-life (EOL) is a low-value medical practice. However, immune checkpoint inhibitor (ICI) use at the EOL may be on the rise due to a favorable toxicity profile. We hypothesize that systemic therapy use in the last 30 days of life (DOL) increased since ICI approval in 2014.

Methods: We investigated the change in prevalence of systemic therapy use in the last 30 DOL before and after the first anti-PD-1 ICI was approved in September 2014. We used cases from Fred Hutchinson Cancer Research Center's population-based Cancer Surveillance System linked to commercial and Medicare insurance claims. Patients who died between 2011-2018, with AJCC stage 3, 4 or unknown solid tumors and six months of continuous insurance coverage were included. Secondary analyses measured cost of care during the last 30 DOL.

Results: A total of 8,871 patients (median age 73) were included in the analysis with 34% in the pre-ICI period (2011-2014) and 66% in the post-ICI period (2014-2018). Prevalence of systemic therapy in the last 30 DOL was lower in the post-ICI period vs pre-ICI period (12.4% vs 14.4%; difference -2.0% [95% CI -3.5 to -0.5]). The annual prevalence of systemic therapy in the last 30 DOL also declined, though ICI use comprised a rising proportion of systemic therapy. Relative to those receiving non-ICI systemic therapy, patients treated with ICI in last 30 DOL had higher overall costs and drug costs.

Discussion: Systemic therapy use in the last 30 DOL was lower in the period after ICI approval. However, ICI use rose during the study period and had higher costs than those receiving non-ICI systemic therapy in last 30 DOL. Systemic therapy use at the EOL warrants close monitoring, especially as ICI availability may enable treatment in older, frailer patients approaching the EOL.

Introduction

Use of systemic chemotherapy in patients with advanced cancer and poor prognosis approaching the end of life (EOL) has been associated with significant toxicity and worse quality of life compared to supportive care.[1,2] Therefore, this practice has been discouraged by the American Society of Clinical Oncology and is a metric of low-value care by Choosing Wisely©.[3] The extent to which real world clinical oncology practices adhere to these recommendations, particularly since the emergence of immune checkpoint inhibitors (ICIs), is poorly understood.

Multiple agents targeting cell surface markers involved in immune checkpoints like cytotoxic T-lymphocyte-associated-protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) and its ligand, program cell death ligand 1 (PD-L1) have been approved by the US Food and Drug Administration (FDA) for the treatment of melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC) and others. These agents have been shown to be safe and produce modest but durable responses. While the first agent (ipilimumab targeting CTLA-4) was approved in 2011, the ICI "revolution" came about with approval of anti-PD(L)1 agents with the first FDA approval for melanoma on September 4, 2014.[4]

The promising aspects of these drugs, however, may also contribute to their overuse. For example, the favorable toxicity profile of ICIs relative to conventional chemotherapy may encourage use in patients with advanced disease, comorbidities, and poor performance status who would previously not have been considered treatment candidates. Further, the potential for durable response contributes to patients' and providers' overestimation of the benefit of ICIs relative to actual benefit observed in clinical trials.[5,6] Given the high cost and known immune related toxicities associated with ICIs, overuse of these drugs in the community may lead to unnecessary medical and financial burdens for patients and the health care system.

We therefore conducted a study to better understand use of systemic therapy near EOL since ICI approval. The primary analysis compared prevalence of systemic therapy in the last 30 days of life (DOL) in the period immediately before and after the date of the first anti-PD1 drug approval in 2014. We also investigated the populations treated with ICIs and the cost to patients and the healthcare system associated with ICI therapy.

Methods

Study design, data source and population

The primary objective of the study was to compare prevalence of systemic therapy use in the last 30 DOL before and after ICI drug approval. Accordingly, we conducted a cross-sectional study using the Hutchinson Institute for Cancer Outcomes Research (HICOR) database[7] that links a population-based cancer registry to health insurance claims for multiple regional and national insurers (Medicare, Premera Blue Cross, Regence BlueShield and Uniform Medical Plan). This database draws cancer diagnosis information from the Fred Hutchinson Cancer Research Center's Cancer Surveillance System (CSS), which collects information on cancer staging, initial treatment and survival for all persons diagnosed with cancer, excluding non-melanoma skin cancer, who are residents of 13 counties of western Washington state when diagnosed.[8] Among the 234,143 cases in CSS between 2011 and 2018, 85% have a linked file in the HICOR database.

We included adult cancer cases in the HICOR database with American Joint Committee on Cancer (AJCC) stage 3, 4 or unknown staged solid tumor who died between 2011 and 2018 and had 6 months of continuous insurance enrollment prior to death. We excluded patients with multiple tumors and those with incomplete treatment information (e.g., diagnosis at death precluding treatment, lack of outpatient pharmacy plan enrollment).

Determination of systemic therapy, ICI use and costs

Systemic therapy, ICI use and costs were assessed using insurance claims. Systemic therapy was identified as any claim of an anti-cancer therapy (including oral medications and IV infusions). ICI use was identified based on HCPCs and NDC codes listed in **Table 1**. We also identified infusion billing codes without an associated medication and calculated prevalence in the pre- and post-ICI periods as a potential surrogate for off-label or compassionate care use not captured by insurance claims.

Statistical Analysis

Baseline information included demographic characteristics (age, sex, race), AJCC staging, Charlson Comorbidity Index, and insurance type. The Charlson Comorbidity Index[9] was first developed as a weighted index to predict risk of death within 1 year of hospitalization for patients with specific comorbid conditions; we identified the individual Charlson comorbidities using claims in the period prior to death and then categorized patients into three groups based on number of non-cancer comorbidities (0, 1 and ≥2). Charlson Comorbidity Index for patients without a full year of insurance coverage preceding cancer diagnosis was considered missing. Insurance type was classified as commercial, Medicare or multiple (both commercial and Medicare). Descriptive statistics were used to summarize the baseline information in the two exposure groups (pre- and post-ICI).

For our primary analysis, we defined our exposure based on the era during which patients died (pre- or post-ICI approval). The ICI "revolution" is attributed to the anti-PD(L)1 agents and the first approval was pembrolizumab for melanoma on September 4, 2014. Thus, we categorized cases as pre-ICI approval if the date of death occurred between January 1, 2011 and September 4, 2014 and post-ICI if the date of death occurred between September 5, 2014 and December 31,

2018. We estimated the prevalence of systemic therapy use in the last 30 DOL in the pre- and post-ICI groups, regardless of whether or not patients had a diagnosis for which there was an FDA-approved ICI indication. We then calculated the difference and corresponding confidence interval (CI) between the two time periods and also fit a multivariable model using Poisson regression to estimate the prevalence ratio (PR) of systemic therapy use in the last 30 DOL adjusted for covariates.[10] Covariates considered for the multivariable model included demographic characteristics (age, sex, race), Charlson Comorbidity Index, and insurance type. Each covariate was included individually in the regression model and retained in the final model if the covariate resulted in 10% or greater change in the adjusted PR. We also estimated the annual prevalence of systemic therapy and ICI use in the last 30 DOL and calculated the proportion of last 30 DOL systemic therapy that was an ICI.

We conducted a sensitivity analysis estimating prevalence of systemic therapy use before and after 2014 for *all* cancer types with an early ICI indication and in each specific cancer subgroup. We thought that this analysis may better capture practice allowing for some time for uptake after drug approval. We defined early ICI indication as a cancer type with an FDA-approved ICI indication before 2017. Five cancer types met this definition: melanoma, NSCLC, RCC, urothelial carcinoma and head and neck squamous cell carcinoma (HNSCC). We identified each of the five cancer subgroups using ICD-O-3 site and histology codes from CSS. For the analyses by specific cancer type, the baseline and exposure periods were adjusted based on the time of FDA approval for the specific cancer.

In addition to above, we also compared baseline characteristics, prevalence of use of other intensive interventions (emergency department visits and hospital admissions) and calculated the medical costs in the last 30 DOL between patients who were treated with ICI vs non-ICI systemic

therapy in the last 30 DOL. For medical costs, we used diagnosis and procedure codes to identify all medical services used in the last 30 DOL and calculated overall costs (direct medical costs) by summing all paid claims for all medical services. We also calculated all drug related and specifically ICI related costs.

Results

Patient population

A total of 8,871 cancer patients met eligibility criteria and were included in the study; 3,045 (34%) died between January 1, 2011 and September 4, 2014 (pre-ICI approval) and 5,826 (66%) died between September 5, 2014 and December 31, 2018 (post-ICI approval). Figure 1 shows a CONSORT[11] diagram for the population included. The pre-ICI group had a higher proportion of missing (29%) for the Charlson Comorbidity Score (**Table 2**). Otherwise, the pre- and post-ICI groups had similar demographic characteristics, comorbidity scores, stage, and insurance.

Prevalence of systemic therapy near EOL

The prevalence of systemic therapy use in the last 30 DOL in the overall study population was 14.4% before ICI approval and 12.4% after ICI approval for a difference of -2.0% (95% CI -3.5 to -0.5) and a PR of 0.86 (95% CI 0.77-0.96; **Table 3**). Among the cases with an early FDA-approved ICI indication, the difference between the two time periods (-1.4% [95% CI -4.4 to 1.7]) and the PR (0.92 [95% CI 0.77-1.11]) was smaller and not significantly different. Among the five diagnoses with an early indication, there was more prevalent use of systemic therapy in the post-ICI period for patients with melanoma, RCC and HNSCC but less prevalent use with NSCLC and urothelial carcinoma (**Table 4**). However, none of the tumor-specific differences had confidence intervals that excluded the null value.

We also calculated the annual prevalence of systemic therapy and ICI use in the last 30 DOL. While the annual prevalence of systemic therapy trended down from 16.1% in 2011 to 10.4% in 2018, ICI use rose from 0% to 2.4% over the same time period (**Figure 2**). Notably, ICI use made up 23% of all systemic therapy use in the last 30 DOL in 2018 compared to 1% in 2014.

Characteristics of patients receiving ICI

Patient characteristics for patients receiving ICI and non-ICI systemic therapy in the last 30 DOL are shown in **Table 5**. A substantially higher proportion of patients receiving ICI in the last 30 DOL had a diagnosis with an early (pre-2017) ICI approval (74% vs 31%). Otherwise, the population receiving ICI in the last 30 DOL had similar characteristics to the population receiving non-ICI therapy in the last 30 DOL.

Cost of ICI

Estimates of cost in the last 30 DOL and use of other intensive interventions (emergency department visits and hospital admissions) for patients receiving ICI and non-ICI systemic therapy in the last 30 DOL are shown in **Table 6**. This was most notable with higher drug costs ($8,100 vs $2,100) with 88% of drug costs attributable to ICI. Patients receiving ICI also had higher prevalence of ≥1 emergency department visits and ≥2 inpatient admissions.

Discussion

ICIs are a promising treatment option for patients with a broad range of cancers and have revolutionized cancer care. However, there is still potential for overuse, especially near the EOL, as some have advocated.[12] In our study, we investigated changes in the prevalence of systemic therapy in the last 30 DOL before and after the first anti-PD-1 ICI was approved among patients

with solid tumors diagnosed between 2011 and 2018. Contrary to our hypothesis of higher systemic therapy use in the last 30 DOL, we note a lower prevalence of systemic therapy use after ICI approval in 2014.

Some studies investigating ICI use near the EOL have estimated similar use as noted in our study[13], while others have observed higher use[14–16]. For example, a recent study by Riaz et al. using the Flatiron Health Database noted higher ICI use near EOL.[15] In this study, patients with melanoma or NSCLC had an increase in systemic therapy use after ICI approval, whereas those with microsatellite stable colon cancer (a cancer type without ICI indication) did not experience a similar rise. Most of the change in systemic therapy noted was due to ICIs. In addition, an earlier study with the Flatiron Health Database also noted high use of ICIs in patients with urothelial carcinoma near the EOL.[16] Notably, in our study when we limited our population to those with an early ICI indication (including melanoma, NSCLC and urothelial carcinoma) we still do not find an increase in prevalence of systemic therapy use. One possible explanation for the discrepancy is the different patient populations included. In Riaz et al. 28.8% of patients with NSCLC and 32.3% of patients with melanoma were >75 years of age and 53.4% and 44.2% had no comorbidities, whereas the median age in our population was 74 and 73 for the pre- and post-ICI periods and only 27% and 33% had no comorbidities, suggesting our population was older with more comorbidities. Looking at specific characteristics of those treated with ICI near the EOL in our study, we noted a slightly higher proportion with more comorbidity than noted in those receiving non-ICI systemic therapy near EOL. This is consistent with ICI being less toxic and more tolerable than systemic chemotherapy but would not explain the high ICI use in the Riaz et al. study.

Our findings are consistent with previous trends reported from linked SEER-Medicare data. A prior study from Fang et al. reported a steady decline in systemic therapy use the last 14 days

and 30 DOL from 2007 to 2013.[17] The prevalence of systemic therapy in the last 30 DOL in this study was ~15%. In our study, in the pre-ICI period from 2011-2014, we note a similar 14.4% prevalence of systemic therapy and the steady trend to lower use continues even after ICI approvals. Fang et al. concluded from their study that the decline in systemic therapy use near the EOL likely suggested recognition by oncologists that this was a low-value practice, suggesting success of efforts by CMS, the National Quality Forum and ASCO Choosing Wisely to draw attention to this issue.[3,18,19] Our findings showing a continued decline despite widespread ICI approvals continue to support this assertion.

While overall, the decline in systemic therapy use remains promising, it is notable that ICI therapy made up an increasing proportion of systemic therapy use in our study. By 2018, ICIs made up 25% of systemic therapy in the last 30 DOL. This is consistent with the rise in ICI indications during this time. Between 2015 and 2018, the proportion of cancer patients eligible for ICIs increased from 26.9% to 44.6%.[20] Recent tumor agnostic approvals for pembrolizumab for metastatic, microsatellite instability-high or mismatch repair deficient tumors and for tumors with tumor mutational burden high (≥10 mutations/megabase) likely further increase the population eligible for ICI therapy.[21,22] However, while more cancer indications have received approval, there has also been a trend to move ICI therapy to earlier lines of treatment, including perioperatively for earlier stage tumors and in earlier lines for metastatic cancers. This shift to earlier treatments may also reduce the use of ICI near EOL as patients may already be treated with these agents earlier in their disease course. Ultimately, the true impact of ICIs on treatment near the EOL will require further follow-up.

One additional finding in our study was the higher cost of care with ICI therapy. Over two-thirds of the annualized cost for medical services for cancer patients have been estimated to be spent in the last year of life, making the EOL phase of cancer care the most costly.[23] Further, the cost

of cancer care also puts patients with cancer at greater risk for bankruptcy and has been associated with patients turning to crowd funding to cover financial obligations.[24,25] In our study, in addition to higher total medical costs, those receiving ICI therapy had higher drug costs and out-of-pockets costs than those receiving other systemic therapy in the last 30 DOL. Patients receiving ICI were also more likely to have ED presentations and higher numbers of inpatient hospitalizations than those that received other systemic therapy in the last 30 DOL. These findings suggest that use of ICI may also be more costly and lead to a more intense EOL experience for patients.

Our study has several limitations. The small sample size of our study introduces the potential that we did not have sufficient power to detect a statistical difference between time periods. It is also possible that we are not capturing all ICI use near EOL if patients received ICIs on clinical trials or under compassionate use protocols not billed to insurance. We think it is unlikely that many patients near EOL would be on clinical trials, and when we used alternate insurance billing codes to identify compassionate use cases there were no meaningful changes to our results. For these reasons we think misclassification of ICI use is unlikely. We also did not have certain clinical data available (e.g. ECOG performance status, laboratory results, or molecular pathologic markers [like PD-L1 staining]), limiting our characterization of factors associated with ICI use. Similarly, while we measured systemic therapy use near the EOL, we are unable to assess the appropriateness of that therapy or the predictability of death, so it is possible that in some cases, therapy was appropriate and death was unexpected.[26] Despite these limitations, the strengths of our study include a population-based contemporary analysis of changes in systemic therapy near EOL and the inclusion of cost data to estimate the financial burden of ICI use near EOL.

In summary, we show in our study that overall systemic therapy use in the last 30 DOL for solid tumor patients declined after the first anti-PD-1 ICI approval in 2014. However, ICI use near the EOL is slowly increasing and was more costly than other systemic therapy near EOL. Future studies with a larger population are needed to validate our findings. In addition, further work to characterize patient populations with high use of ICI near EOL can help identify interventions to curb low value utilization practices.

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Figure 1. Study CONSORT diagram for assessing use of Immune Checkpoint Inhibitors in the last 30 DOL

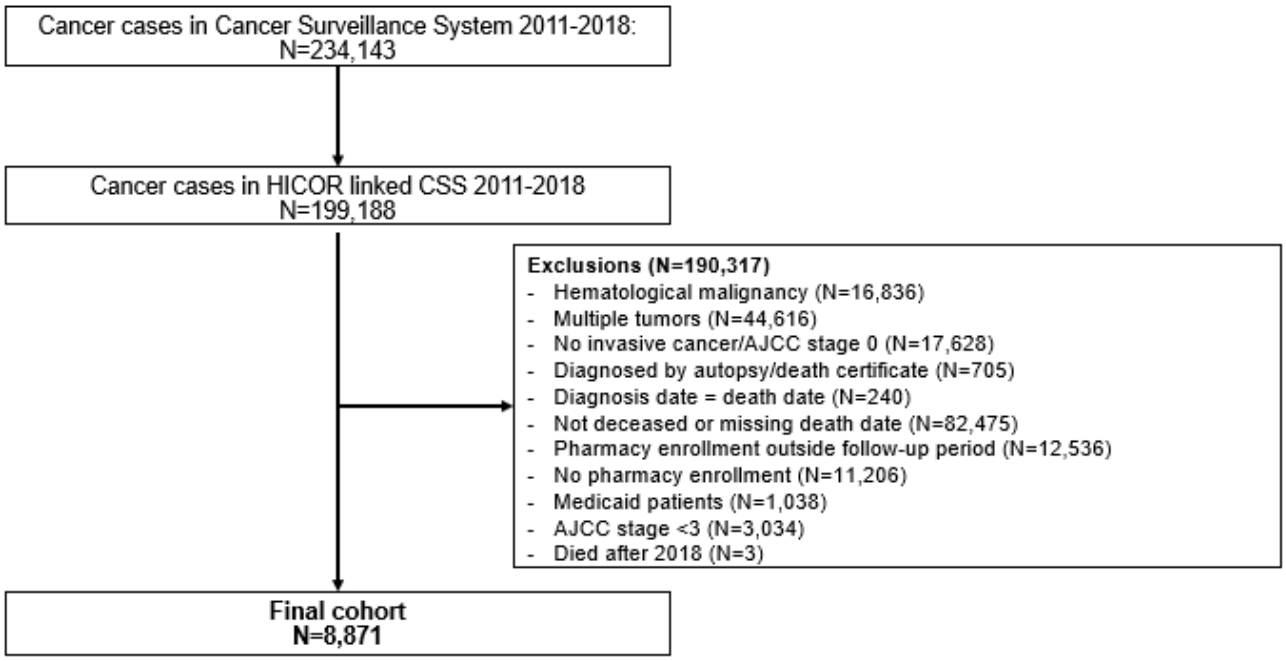

Figure 2. Annual prevalence of systemic therapy and immune checkpoint inhibitor use among cancer patients in Western Washington in last 30 days of life between 2007 and 2018, Cancer Surveillance System and Linked Pharmacy Claims.

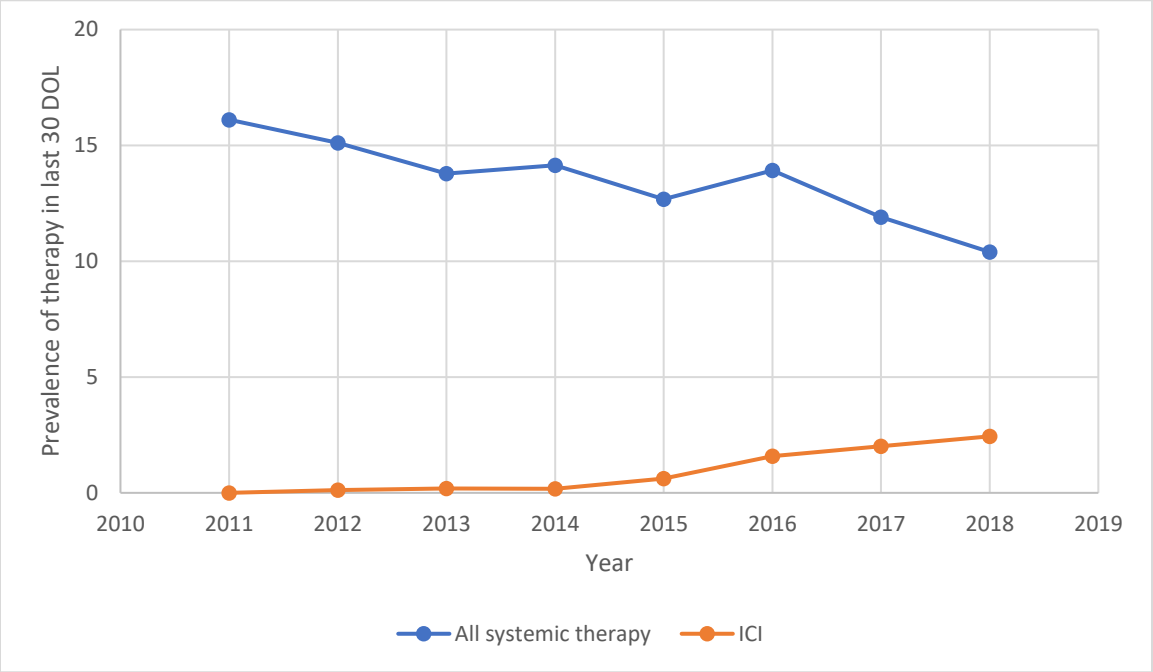

Table 1. Billing codes used to identify immune checkpoint inhibitors in the HICOR database.

Type	Code	Drug
HCPCS	C9284	Ipilimumab
HCPCS	J9228	Ipilimumab
HCPCS	C9453	Nivolumab
HCPCS	J9299	Nivolumab
HCPCS	J9228	Nivolumab
HCPCS	C9483	Atezolizumab
HCPCS	J9022	Atezolizumab
HCPCS	C9492	Durvalumab
HCPCS	C9027	Pembrolizumab
HCPCS	J9271	Pembrolizumab
HCPCS	J9023	Avelumab
HCPCS	C9491	Avelumab
HCPCS	J9022	Atezolizumab
HCPCS	C9483	Atezolizumab
NDC	50242091786	Atezolizumab
NDC	50242091701	Atezolizumab
NDC	310450012	Durvalumab
NDC	310461150	Durvalumab
NDC	3232711	Ipilimumab
NDC	3232822	Ipilimumab
NDC	3232822	Nivolumab
NDC	2121711	Nivolumab
NDC	3377211	Nivolumab
NDC	3373413	Nivolumab
NDC	3377412	Nivolumab
NDC	6302602	Pembrolizumab
NDC	6302902	Pembrolizumab
NDC	50242091786	Atezolizumab
NDC	50242091701	Atezolizumab
NDC	64370030861	Avelumab

Table 2. Demographic, health and tumor characteristics of deceased cancer cases diagnosed with AJCC stage 3, 4 or unknown solid tumors, by date of death (pre- or post-ICI approval), Cancer Surveillance System and Linked Pharmacy Claims, 2011-2018

Characteristic	Death pre-ICI approval N=3,045	Death post-ICI approval N=5,826
Age, median (IQR)	74 (66-82)	73 (66-81)
Sex, N (%)		
Male	1,479 (49)	2,903 (50)
Female	1,564 (51)	2,922 (50)
Race, N (%)		
White	2,707 (89)	5,227 (90)
Black	91 (3)	124 (2)
Asian/Pacific Islander	216 (7)	382 (7)
American Indian/Alaskan Native	28 (1)	74 (1)
Hispanic ethnicity, N (%)	82 (3)	125 (2)
Charlson Comorbidity Score, N (%)		
0	829 (27)	1,895 (33)
1	499 (16)	1,108 (19)
2+	830 (27)	1,825 (31)
Missing	887 (29)	998 (17)
AJCC Stage, N (%)		
Stage 3	594 (20)	1,275 (22)
Stage 4	1,582 (52)	2,913 (50)
Unknown	869 (29)	1,638 (28)
Insurer, N (%)		
Commercial	610 (20)	969 (17)
Medicare	1,994 (66)	4,101 (70)
Multiple	441 (15)	756 (13)
Death year, N (%)		
2011	360 (12)	0
2012	867 (28)	0
2013	1,074 (35)	0
2014	744 (24)	366 (6)
2015	0	1,285 (22)
2016	0	1,386 (24)
2017	0	1,395 (24)
2018	0	1,394 (24)

Table 3. Prevalence of systemic therapy use in the last 30 days of life by date of death (pre- or post-ICI approval) for deceased cancer cases diagnosed with AJCC stage 3, 4 or unknown solid tumors, Cancer Surveillance System and Linked Pharmacy Claims, 2011-2018

Measure	All cancers (N=8,871)		Cancers with FDA approved ICI before 2017 (N=2,478)	
	N	% (95% CI)	N	% (95% CI)
Pre-ICI death prevalence	438	14.4 (13.2-15.7)	155	17.1 (14.8-19.7)
Post-ICI death prevalence	723	12.4 (11.6-13.3)	247	15.7 (14.0-17.6)
Prevalence difference (95% CI)		-2.0 (-3.5 to -0.5)		-1.4 (-4.4 to 1.7)
Prevalence ratio (PR)[a]		0.86 (0.77-0.96)		0.92 (0.77-1.11)

[a]Pre-ICI time period was reference

Table 4. Prevalence ratio of systemic therapy use in the last 30 days of life before and after FDA approval for the five tumor groups with FDA approval before 2017, Cancer Surveillance System and Linked Pharmacy Claims, 2011-2018

Cancer types	N	Prevalence Ratio (95% CI)[a]
Melanoma[b]	145	1.26 (0.57-2.79)
NSCLC[c]	1,706	0.89 (0.73-1.10)
RCC[d]	169	1.69 (0.51-5.64)
Urothelial carcinoma[e]	201	0.87 (0.37-2.06)
HNSCC[f]	257	1.51 (0.64-3.58)

[a]Pre-ICI time period was reference
[b]Approval date 9/4/2014
[c]Approval date 3/4/15
[d]Approval date 11/23/15
[e]Approval date 5/18/16
[f]Approval date 8/5/16

Table 5. Patient characteristics for those treated with non-ICI systemic therapy and ICI in the last 30 DOL, Cancer Surveillance System and Linked Pharmacy Claims, 2011-2018

	Non-ICI systemic therapy N=1,064	ICI N=97
Age, median (IQR)	69 (62-75)	69 (63-75)
Sex, N (%)		
Male	550 (52)	57 (59)
Female	514 (48)	40 (41)
Charlson comorbidity score, N (%)		
0	389 (37)	34 (35)
1	160 (15)	24 (25)
2+	245 (23)	27 (28)
Missing	270 (25)	12 (12)
AJCC Stage, N (%)		
Stage 3	219 (21)	35 (36)
Stage 4	640 (60)	53 (55)
Unknown	205 (19)	9 (9)
ICI indication before 2017, N (%)		
No	734 (69)	25 (26)
Yes	330 (31)	72 (74)
Medicare insurance, N (%)	609 (57)	65 (67)

Table 6. Estimate of total medical cost, drug costs, and use of other intensive interventions in last 30 DOL for patients who received systemic therapy in last 30 DOL, Cancer Surveillance System and Linked Pharmacy Claims, 2011-2018

	Non-ICI systemic therapy N=1,064	**ICI N=97**
Total Paid*	23.9 (15.2-39.9)	28.4 (16.5-42.8)
Drug cost*	2.1 (0.5-7.5)	8.1 (5.3-12.1)
ICI cost*		7.4 (5.1-10.5)
ED Visits (%)		
0	75	67
1	22	33
≥2	4	0
Inpatient admissions (%)		
0	9	9
1	67	59
≥2	24	32

*All cost values presented as $1000s