1-1-2020

Immunotherapy For Advanced Cancer Patients With Autoimmune Disease

Huaqi Li
huaqili23@gmail.com

Immunotherapy for advanced cancer patients with autoimmune disease

Name: Huaqi Li

Year Completed: 2020
Year Degree Awarded: 2020
Degree Awarded: Master of Public Health
Department: School of Public Health

Advisor/Committee Chair: Dr. Shiyi Wang
Committee Members: Dr. Scott Huntington

ABSTRACT

Purpose

Immunotherapy (IT) has been shown to improve cancer survival but there is limited evidence regarding use in patients with advanced cancer and pre-existing autoimmune disease (AI). We sought to address these knowledge gaps and determine IT utilization patterns and overall survival (OS) for these patients.

Patients and Methods

This retrospective cohort study used data from Flatiron Health's nationwide oncology database. Patients diagnosed with advanced cancer where there was ≥ 1 FDA approved IT were included. Baseline demographics were analyzed using $\chi 2$ and t-tests. Patterns of IT use were assessed using logistic regression. OS was estimated using Kaplan-Meier and Cox proportional hazards models.

Results

Of the 70,964 patients included, 1,801 had AI. Controlling for demographic and clinical variables, AI was not associated with IT use in general (Odds Ratio [OR]=0.90, 95% CI 0.79-1.03), but was associated with lower odds of receiving first-line IT (OR=0.72, 95% CI 0.61-0.84). IT usage differed by cancer type. Overall, on multivariate analysis, patients with AI had better survival than those without AI. This remained true for overall IT (Hazard Ratio [HR]=0.86, 95% CI 0.81-0.91) and for first-line IT (HR=0.79, 95% CI 0.71-0.88). Interaction between IT and AI was significant, with IT having stronger association in patients with AI compared to those without (HR=0.57, 95% CI 0.50-0.64 vs HR=0.66, 95% CI 0.64-0.68). Among patients treated with IT, interaction between first-line IT and AI was not significant. Among patients with AI, receiving first-line IT had no survival benefit (HR=0.95, 95% CI 0.77-1.17).

Conclusion

Receipt of IT had greater survival benefit for patients with AI compared to those without AI; first-line IT did not result in further survival benefit. Patients with advanced cancer and pre-existing AI should receive IT, potentially as second or third-line treatment.

TABLE OF CONTENTS

List of Tables

List of Figures

INTRODUCTION

Background

Cancer immunotherapy involves treatment that better allows the immune system to detect and target tumor cells. Immunotherapy has been shown to improve survival in many promising reports regarding treatment regimens such as immune checkpoint inhibitors and CAR T-cell therapies (1-5), but even though the use of cancer immunotherapy has been rapidly increasing, there is still limited evidence regarding use in patients with pre-existing autoimmune disease. The side effects of immunotherapy include excessive inflammatory responses due to errors in self-recognition by the immune system (6) which is especially relevant for patients with autoimmune diseases because the immune systems of these patients are already prone to erroneously targeting healthy self-tissue as foreign tissue. Thus, even though 10-30% of patients have both cancer and an autoimmune disease (7), immunotherapy is often not recommended for patients with pre-existing autoimmune disease.

A series of case reports (8-13) has suggested that patients with both cancer and autoimmune disease may respond just as well as patients without autoimmune disease. These patients may potentially receive immunotherapy as second or third-line treatment instead of first-line treatment. However, because this patient demographic has been excluded from previous clinical trials involving cancer immunotherapy due to concerns of exacerbating pre-existing autoimmune diseases (14), the benefits of immunotherapy are unclear and it is uncertain whether or not patients with autoimmune disease have poorer prognosis. The first clinical trial in this patient population was recently initiated (15) in a cohort of 260 patients with advanced cancer and autoimmune disease that will receive the immune checkpoint inhibitor nivolumab.

Given these knowledge gaps, we sought to determine the utilization patterns and survival outcomes of patients with both cancer and autoimmune diseases treated with immunotherapy. Demonstrating that patients with existing autoimmune disease receive immunotherapy during routine-care and have clinical

outcomes similar to those without pre-existing autoimmune conditions could increase the use of immunotherapy in this at-risk population.

Objectives

Our primary objective was to measure immunotherapy use patterns between patients with and without pre-existing autoimmune disease. We hypothesized that patients with autoimmune disease and advanced cancer would be less likely to receive immunotherapy compared to advanced cancer patients with no autoimmune disease.

Our secondary objectives were to assess overall survival (OS) outcomes among patients with and without pre-existing autoimmune disease who had received immunotherapy. We hypothesized that survival would be similar between those with and without pre-existing autoimmune conditions, after controlling for line of treatment when immunotherapy was initiated.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort study that used patient-level data from Flatiron Health's nationwide electronic health record (EHR) oncology database.

Data Sources

Flatiron Health's EHR oncology database provides longitudinal, deidentified health record data abstracted from structured and unstructured information sources (16). At the time of data collection, the database included more than 265 cancer clinics across the United States, representing more than 2 million patients (17). Due to the nature of secondary analysis of de-identified data, this study received designation as non-human subjects research from the Yale University Institutional Review Board.

Cohort Selection

Patients diagnosed with advanced cancers in which there was at least 1 FDA approved immunotherapy from January 1, 2011 to June 30, 2019 (date of data cut-off) were included in this analysis. A total of 7 cancer types were included: melanoma, non-small cell lung cancer (NSCLC), gastric cancer, urothelial carcinoma, head and neck cancer, metastatic colorectal cancer, and metastatic renal cell carcinoma. This data set excluded patients with a gap >90 days between diagnosis and first visit or medication order. Only the primary cancer was included for patients with more than 1 diagnosis of advanced cancer. Patients were excluded if they did not receive any form of systemic therapy (i.e. immunotherapy and chemotherapy) or if they had missing data for gender (Figure 1).

Outcome Measures

Baseline demographic and clinical characteristics of patients were documented. The most recent Eastern Cooperative Oncology Group (ECOG) performance status and insurance type following diagnosis of advanced diseases were identified. International Classification of Diseases, Ninth and Tenth Revision (ICD-9, ICD-10) codes were used for classification of autoimmune disease (Appendix 1). Details of medications administered after diagnosis of advanced disease were documented and data on first-line of treatment after diagnosis of advanced disease were extracted. Median OS was defined as date of advanced cancer diagnosis to last day in their month of death. Patients who had not died by the end of the study were censored at the data cut-off date of June 30, 2019.

Statistical Analyses

All statistical analyses were performed using SAS University Edition (SAS Institute Inc, Cary, NC). Baseline demographics were analyzed using $\chi 2$ tests and t-tests for categorical and continuous variables, respectively. Patterns of immunotherapy use in general and as first-line therapy after diagnosis of advanced disease were assessed using logistic regression and the Wald $\chi 2$ test. Kaplan-Meier methods were used to estimate the median OS from diagnosis of advanced cancer. Patients with length of follow-

up shorter than 30 days were excluded from the survival analyses. Cox proportional hazards models were used to estimate differences in OS between those with and without autoimmune disease. The log-rank test was used to assess differences in survival and the Wald $\chi 2$ test was used to assess differences in hazards.

RESULTS

Patient Characteristics

A total of 70,964 patients who were diagnosed with advanced cancer and treated with systemic therapy (i.e. immunotherapy and/or chemotherapy) between January 1, 2011, and June 30, 2019 were identified and included in this study. Of these patients, 1,801 had a pre-existing diagnosis of autoimmune disease and 69,163 did not have such a diagnosis. Compared to those with no autoimmune disease, patients with autoimmune disease were older (67 vs 66 years, p=0.031) and more likely to be female (50.51% vs 38.8%, p<0.001), be White (78.40% VS 70.93%, p<0.001), be on Medicare (20.38% vs 14.20%, p<0.001), have received care at an academic center (24.54% vs 6.99%, p<0.001), have Melanoma or NSCLC (10.61% vs 6.30% and 54.75% vs 47.78%, p<0.001), and have an ECOG value of 2 or ≥3 (11.38% vs 10.30% and 2.83% vs 2.40%, p=0.008) (Table 1).

Patients with autoimmune disease were more likely to have received immunotherapy in general (41.98% vs 36.58%, p<0.001) and as first-line treatment (25.10% vs 22.11%, p=0.003) (Table 1).

Immunotherapy Usage Patterns

After controlling for age, year of advanced diagnosis, cancer type, gender, race, practice type, insurance status, ECOG value, and smoking status, autoimmune disease was not associated with use of immunotherapy in general (Odds Ratio [OR]=0.90, 95% CI 0.79-1.03), but was associated with being less likely to receive immunotherapy as first-line treatment (OR=0.72, 95% CI 0.61-0.84) (Table 2). The interaction effect between practice type and autoimmune disease was not significant with regards to

receipt of immunotherapy in general (p=0.786) and receipt of immunotherapy as first-line treatment (p=0.238).

We also conducted stratified analyses based on cancer type. Use of immunotherapy in general and as first-line was most common in metastatic RCC and melanoma for patients with and without autoimmune disease (Figure 2). In metastatic CRC and gastric cancer, few patients received first-line immunotherapy, but a substantial proportion of patients with autoimmune disease received immunotherapy in general compared to those without autoimmune disease (Figure 2).

Overall Survival

Overall, patients with autoimmune disease had better median survival than patients without autoimmune disease (749 vs 605 days). Of the patients who did not have autoimmune disease, those who did not receive immunotherapy had a median survival of 512 days and those who did receive immunotherapy had a median survival of 822 days (Figure 3). Of the patients who did have autoimmune disease, those who did not receive immunotherapy had a median survival of 531 days and those who did receive immunotherapy had a median survival of 1152 days (Figure 3). Using the Cox proportional hazards model to control for age, year of advanced diagnosis, cancer type, gender, race, practice type, insurance status, ECOG value, and smoking status, having autoimmune disease remained associated with better survival outcome (Hazard Ratio [HR]=0.86, 95% CI 0.81-0.91) (Table 3). The interaction between immunotherapy and autoimmune disease was significant (p=0.018) (Table 3).

Among patients treated with immunotherapy, those who did not have autoimmune disease and did not receive first-line immunotherapy had a median survival of 764 days and those who did receive first-line immunotherapy had a median survival of 941 days (Figure 4). Among patients treated with immunotherapy, those who did have autoimmune disease and did not receive first-line immunotherapy had a median survival of 993 days and those who did receive first-line immunotherapy had a median survival of 1603 days (Figure 4). Using the Cox proportional hazards model to control for age, year of

advanced diagnosis, cancer type, gender, race, practice type, insurance status, ECOG value, and smoking status, having autoimmune disease remained associated with better survival outcome (HR=0.79, 95% CI 0.71-0.88) (Table 4). The interaction between first-line immunotherapy and autoimmune disease was not significant (p=0.469) (Table 4).

DISCUSSION

Conclusions

Upon univariate analysis, patients with autoimmune disease were more likely to receive immunotherapy in general and as first-line treatment compared to patients without autoimmune disease. However, after controlling for demographic and clinical variables, we observed that autoimmune disease was not associated with immunotherapy use in general and was associated with a lower likelihood of receiving immunotherapy as first-line treatment.

We also observed differences in immunotherapy usage by cancer types. The high proportion of patients receiving both immunotherapy in general and as first-line treatment in melanoma and metastatic RCC is likely because these types of cancer have had a more established history of immunotherapy and such treatments are part of the current standard of care (18,19). On the other hand, immunotherapy is still a relatively new treatment modality in cancers such as metastatic CRC and gastric cancer (20,21), which is likely why fewer patients in these groups were observed to receive immunotherapy as a first-line treatment.

Overall, patients with autoimmune disease had better survival than those without autoimmune disease. This remained true in patients who received overall immunotherapy and in patients who received first-line immunotherapy. This was unexpected and the interpretation of these findings should be careful. There are mixed conclusions within the limited literature on survival in patients with advanced cancer and autoimmune disease. In a study on autoimmune diseases and mortality risk in sepsis (22), the

authors found that those with autoimmune disease had lower 30-day mortality risk unrelated to mechanisms associated with chronic use of immunomodulation medications. Specifically, these were autoimmune diseases associated with the overexpression of pro-inflammatory cytokines IL-12 and INF-γ. The authors posit that the immunosuppressive state induced by sepsis may have a critical role in mortality (22) and thus survival may have been improved by the increased expression of IL-12 and INF-γ brought about by autoimmune disease. This is relevant in cancer populations since tumors are also actively immunosuppressive, both inside and outside the tumor microenvironment (23). Additionally, a study on survival in patients with autoimmune disease and lung cancer (24) showed that having autoimmune disease did not influence prognosis. The authors argue that this may be due to the inherently poor prognosis of lung cancer (24) since in a previous study, they found that despite increased risk of death in patients with autoimmune disease in cancers with intermediary prognosis, mortality in patients with autoimmune disease did not increase for stomach cancer which has poor prognosis (25).

The interaction between immunotherapy and autoimmune disease was significant, with receipt of immunotherapy having a larger magnitude of effect in patients with autoimmune disease compared to those without autoimmune disease (HR=0.57, 95% CI 0.50-0.64 vs HR=0.66, 95% CI 0.64-0.68). Among patients treated with immunotherapy, the interaction between first-line immunotherapy and autoimmune disease was not significant. The survival curves crossed for patients with autoimmune disease who received versus did not receive first-line immunotherapy. Among patients with autoimmune disease, receiving first-line immunotherapy did not result in significant survival benefit (HR=0.95, 95% CI 0.77-1.17).

Limitations

This was a retrospective study and thus relied on pre-existing data. However, we are confident in the quality and comprehensiveness of the data provided by Flatiron Health. In our analyses, we included all

patients who had ever been diagnosed with an autoimmune disease and did not specify when autoimmune disease was diagnosed i.e. whether it was before or after the initiation of systemic therapy. This could introduce bias because autoimmune disease is generally a contraindication for immunotherapy, so oncologists may be more likely to indicate a diagnosis of autoimmune disease when they are considering immunotherapy. It is also unclear whether our data includes patients who were treated in other facilities for early stage disease and then subsequently received treatment for advanced disease at Flatiron Health-affiliated clinics. Overall, some of the cancer types included in this study had low absolute numbers of patients who had autoimmune disease and received immunotherapy.

Recommendations

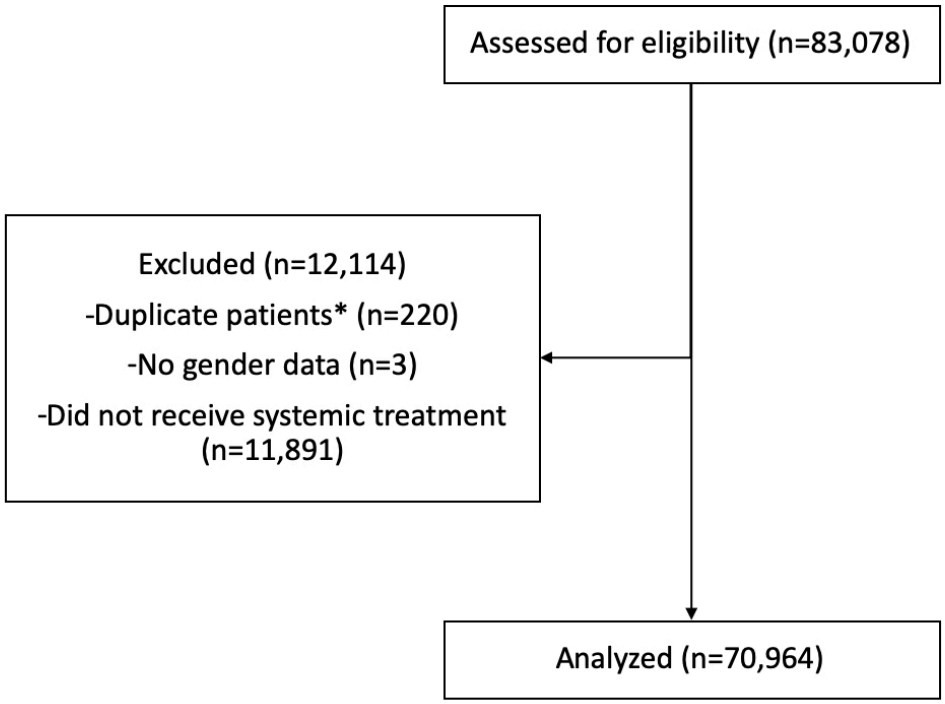
Our findings show that receipt of immunotherapy had greater survival benefit for patients with autoimmune disease compared to those without autoimmune disease and that receipt of first-line immunotherapy did not result in further survival benefit among patients with autoimmune disease. This is clinically meaningful as it suggests that patients with advanced cancer and autoimmune disease should receive immunotherapy and that whether or not this is given as a first-line treatment is unimportant to survival. Taking into consideration the potential side effects of immunotherapy in this patient population, clinical practices should give thought to adopting immunotherapy regimens later on in the treatment pathway. The intersection between autoimmune disease and cancer is understudied and more research in this area is needed to better understand the nuances observed in this study. We await the results of the recently initiated phase Ib nivolumab trial in this patient population to confirm our present findings.

FIGURES AND TABLES

Table 1: Baseline Patient Characteristics			
	Autoimmune Disease (n = 1,801)	No Autoimmune Disease (n = 69,163)	p-value
Age (Mean)	67	66	0.031[1]
Advanced Cancer Diagnosis Year			
2011	95 (5.27%)	3,674 (5.31%)	0.055[2]
2012	120 (6.68%)	4,895 (7.08%)	
2013	198 (11.05%)	7,794 (11.27%)	
2014	255 (14.14%)	8,968 (12.97%)	
2015	293 (16.22%)	10,116 (14.63%)	
2016	267 (14.81%)	10,564 (15.27%)	
2017	289 (16.11%)	10,674 (15.43%)	
2018	234 (13.02%)	9,629 (13.92%)	
2019	50 (2.69%)	2,849 (4.12%)	
Gender			<0.001[2]
Female	915 (50.81%)	26,853 (38.8%)	
Male	886 (49.19%)	42,310 (61.17%)	
Race			<0.001[2]
White	1,412 (78.40%)	49,059 (70.93%)	
Black	118 (6.55%)	5,419 (7.84%)	
Asian	26 (1.44%)	1,444 (2.09%)	
Other	127 (7.05%)	7,183 (10.39%)	
Unknown	118 (6.55%)	6,058 (8.76%)	
Insurance Type			<0.001[2]
Commercial Health Plan	749 (41.59%)	30,092 (43.51%)	
Medicaid	66 (3.66%)	3,025 (4.37%)	
Medicare	367 (20.38%)	9,824 (14.20%)	
Other	127 (7.05%)	6,911 (9.99%)	
Unknown	492 (27.32%)	19,311 (27.92%)	
Practice Type			<0.001[2]
Academic	442 (24.54%)	4,836 (6.99%)	
Community	1,359 (75.46%)	64,327 (93.01%)	
Smoking status			0.181[2]
History of smoking	1,087 (60.36%)	41,393 (59.85%)	
No history of smoking	233 (12.94%)	8,194 (11.85%)	
Unknown	481 (26.71%)	19,576 (28.30%)	
Cancer Type			<0.001[2]
Bladder Cancer	104 (5.77%)	4,957 (7.17%)	
Colorectal Cancer	280 (15.55%)	14,653 (21.19%)	
Gastric Cancer	101 (5.61%)	5,716 (8.26%)	
Head and Neck Cancer	73 (4.05%)	4,148 (6.00%)	
Melanoma	191 (10.61%)	4,359 (6.30%)	
Non-Small Cell Lung Cancer	986 (54.75%)	33,048 (47.78%)	
Renal Cell Carcinoma	66 (3.66%)	2,282 (3.30%)	
ECOG Value			0.008[2]
0	468 (25.99%)	20,483 (29.62%)	

1	582 (32.32%)	22,242 (32.16%)	
2	205 (11.38%)	7,124 (10.30%)	
≥3	51 (2.83%)	1,658 (2.40%)	
Unknown	495 (27.48%)	17,656 (25.53%)	
Immunotherapy			
Yes	756 (41.98%)	25,300 (36.58%)	<0.001[2]
No	1,045 (58.02%)	43,863 (63.42%)	
Immunotherapy as First-line			0.003[2]
Yes	452 (25.10%)	15,294 (22.11%)	
No	1,349 (74.90%)	53,869 (77.89%)	
[1]T-test, [2]Chi-squared test			

Figure 1: Patient Flow Diagram

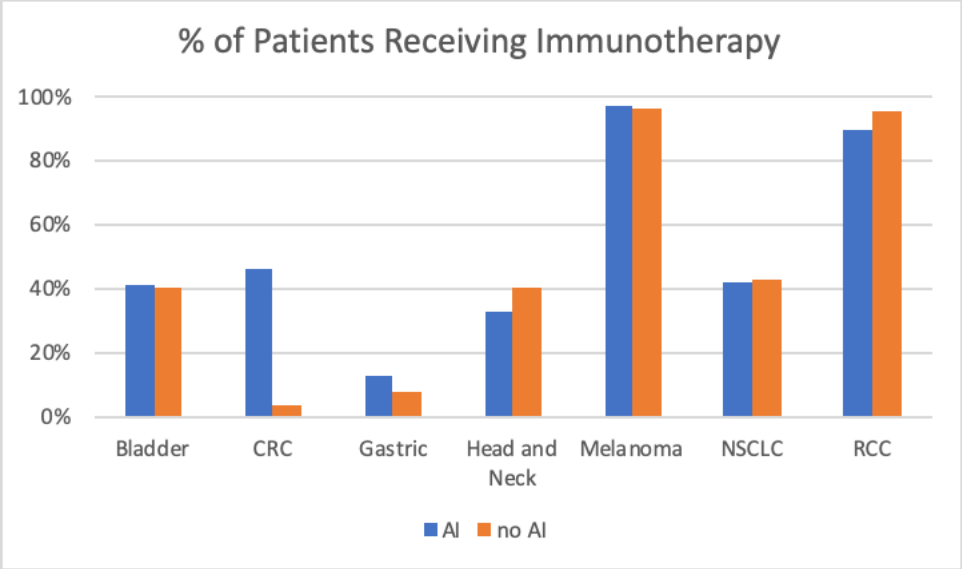


*There were 218 patients who had 2 unique diagnoses of advanced cancer and 1 patient with 3 diagnoses. We extracted data related to the patient's earliest diagnosis of advanced cancer.

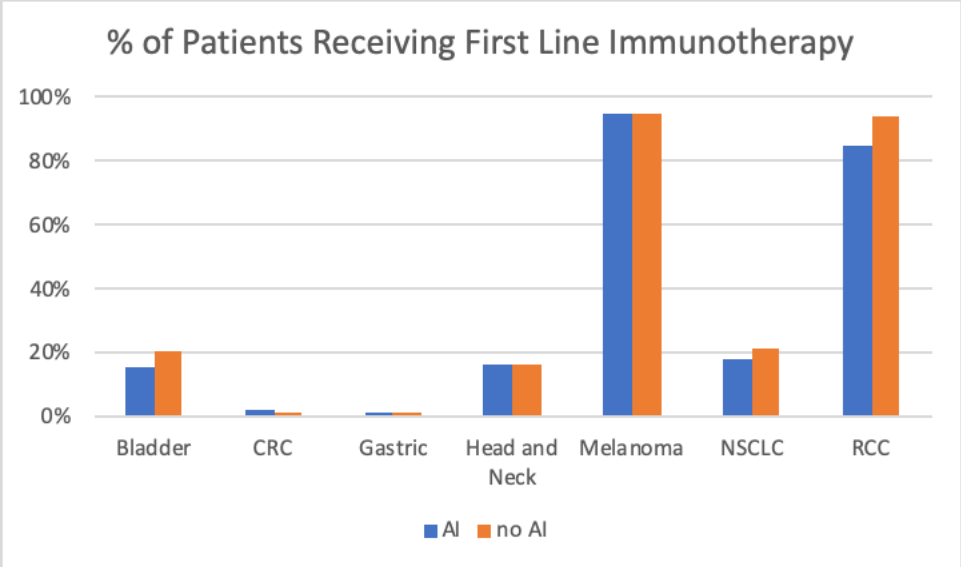
Table 2: Logistic regression of covariates associated with immunotherapy use						
	Overall Immunotherapy			First-line Immunotherapy		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (Continuous)	1.00	1.00-1.00	<0.001	1.01	1.01-1.01	<0.001
Autoimmune Disease						
No	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
Yes	0.90	0.79-1.03	0.112	0.72	0.61-0.84	<0.001
Advanced Cancer Diagnosis						
2011	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
2012	1.45	1.22-1.72	<0.001	1.26	0.99-1.61	0.062
2013	2.67	2.28-3.13	<0.001	1.86	1.48-2.33	<0.001
2014	5.12	4.39-5.96	<0.001	2.89	2.32-3.59	<0.001
2015	12.41	10.69-14.40	<0.001	5.44	4.41-6.70	<0.001
2016	18.52	15.95-21.49	<0.001	10.74	8.75-13.19	<0.001
2017	30.80	26.52-35.77	<0.001	28.91	23.60-35.42	<0.001
2018	41.34	35.53-48.10	<0.001	49.98	40.77-61.27	<0.001
2019	27.78	23.44-32.93	<0.001	65.63	52.74-81.68	<0.001
Gender						
Male	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
Female	1.08	1.04-1.13	<0.001	1.09	1.03-1.14	0.003
Race						
White	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
Black	0.91	0.84-0.98	0.014	0.86	0.78-0.95	0.003
Asian	1.06	0.91-1.22	0.460	1.04	0.86-1.25	0.715
Other	1.01	0.95-1.09	0.711	0.95	0.87-1.03	0.197
Unknown	0.73	0.67-0.78	<0.001	0.85	0.78-0.93	<0.001
Insurance Type						
Commercial Health Plan	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
Medicaid	0.78	0.70-0.87	<0.001	0.80	0.70-0.92	0.001
Medicare	1.05	0.98-1.11	0.173	1.02	0.94-1.10	0.643
Other	1.22	1.13-1.31	<0.001	1.07	0.99-1.17	0.108
Unknown	0.90	0.86-0.95	<0.001	1.01	0.95-1.08	0.718
Practice Type						
Community	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
Academic	1.51	1.40-1.64	<0.001	1.66	1.51-1.82	<0.001
Smoking status						
No history of smoking	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
History of smoking	0.84	0.78-0.89	<0.001	0.84	0.77-0.90	<0.001
Unknown	0.42	0.30-0.57	<0.001	0.69	0.44-1.06	0.092
Cancer Type						
Bladder Cancer	0.78	0.73-0.84	<0.001	0.82	0.75-0.89	<0.001
Colorectal Cancer	0.06	0.04-0.08	<0.001	0.04	0.02-0.06	<0.001
Gastric Cancer	0.07	0.07-0.08	<0.001	0.04	0.03-0.04	<0.001
Head and Neck Cancer	0.73	0.68-0.79	<0.001	0.68	0.62-0.75	<0.001
Melanoma	150.03	104.56-215.27	<0.001	270.75	170.98-428.75	<0.001

Non-Small Cell Lung Cancer	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
Renal Cell Carcinoma	36.43	29.62-44.81	<0.001	119.50	99.31-143.81	<0.001
ECOG Value						
0	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
1	0.91	0.87-0.96	<0.001	1.04	0.97-1.10	0.282
2	0.74	0.69-0.80	<0.001	1.09	1.00-1.19	0.043
≥3	0.59	0.51-0.67	<0.001	1.26	1.08-1.47	0.003
Unknown	0.52	0.49-0.55	<0.001	0.81	0.75-0.87	<0.001

Figure 2: Immunotherapy Usage by Cancer Type

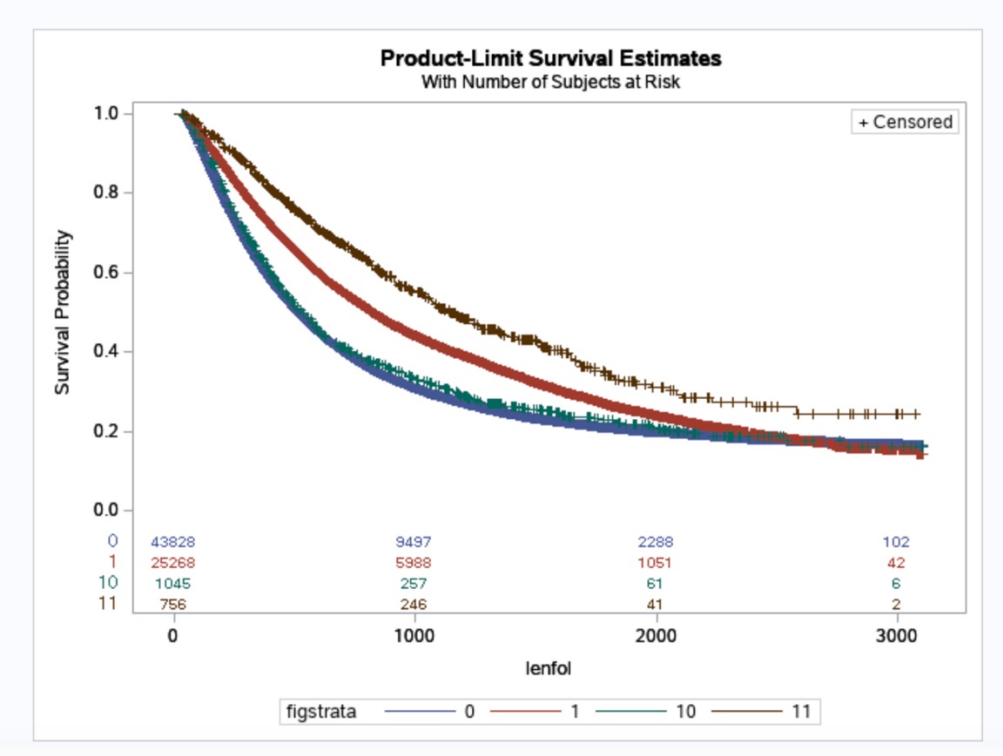


a) Percentage of patients receiving immunotherapy in general



b) Percentage of patients receiving immunotherapy first-line

Figure 3: Overall Survival in Patients Receiving Immunotherapy



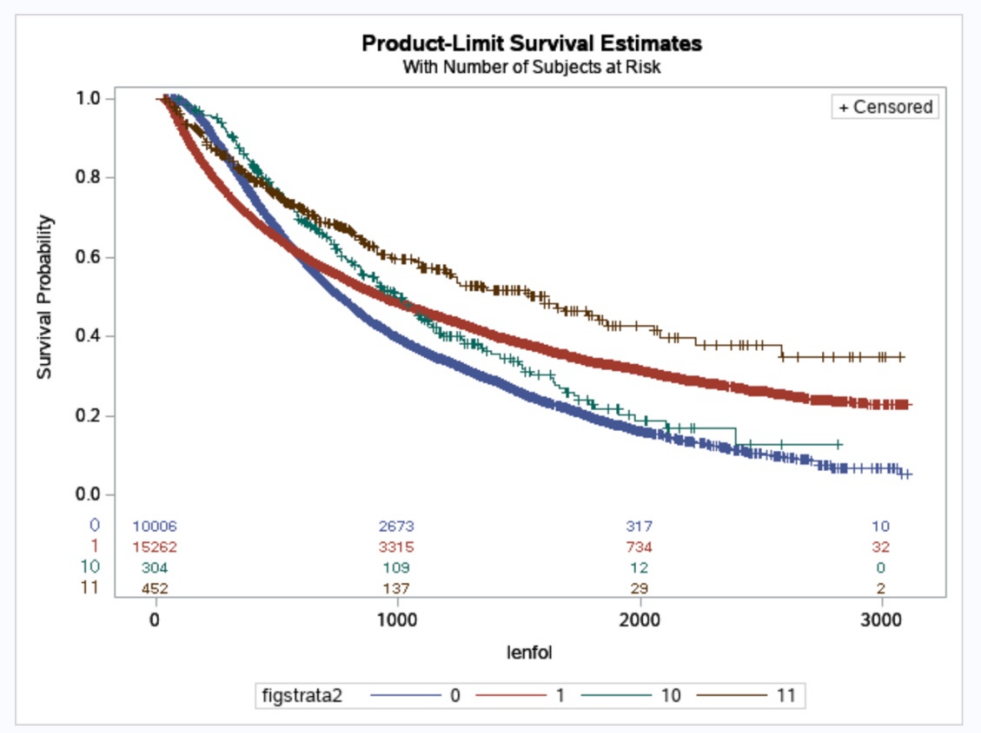
*0 is no AI and no IT, 1 is no AI yes IT, 10 is yes AI no IT, 11 is yes AI yes IT

Table 3: Cox-regression of covariates associated with overall mortality in all patients

	Model 1			Model 2			Model 3		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Autoimmune Disease									
No	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference	-	-	Reference
Yes	0.86	0.81-0.91	<0.001	0.86	0.81-0.91	<0.001	-	-	0.007
Immunotherapy									
No	-	-	-	1.00	1.00-1.00	Reference	-	-	Reference
Yes	-	-	-	0.66	0.64-0.68	<0.001	-	-	<0.001
Interaction Term									0.018
IT Yes vs No*AI No	-	-	-	-	-	-	0.66	0.64-0.68	
IT Yes vs No*AI Yes	-	-	-	-	-	-	0.57	0.50-0.64	

All 3 models include the following covariates: age (continuous), year of advanced diagnosis, cancer type, gender, race, practice type, insurance status, ECOG value, smoking status.

Figure 4: Overall Survival in Patients Receiving Immunotherapy First-line



*Among patients treated with IT: 0 is no AI and no IT first-line, 1 is no AI yes IT first-line, 10 is yes AI no IT first-line, 11 is yes AI yes IT first-line

Table 4: Cox-regression of covariates associated with overall mortality in patients treated with immunotherapy

	Model 1			Model 2		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Autoimmune Disease						
No	1.00	1.00-1.00	Reference	1.00	1.00-1.00	Reference
Yes	0.79	0.71-0.88	<0.001	0.79	0.71-0.88	<0.001
Immunotherapy as First-line						
No	-	-	-	1.00	1.00-1.00	Reference
Yes	-	-	-	1.02	0.98-1.06	0.282
Both models include the following covariates: age (continuous), year of advanced diagnosis, cancer type, gender, race, practice type, insurance status, ECOG value, smoking status.						

REFERENCES

1. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science (New York, NY). 2013;342(6165):1432-3.
2. Lipson EJ, Forde PM, Hammers HJ, Emens LA, Taube JM, Topalian SL. Antagonists of PD-1 and PD-L1 in Cancer Treatment. Seminars in oncology. 2015;42(4):587-600.
3. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2015;33(17):1889-94.
4. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The Lancet Oncology. 2016;17(11):1497-508.
5. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. The New England journal of medicine. 2012;366(26):2443-54.
6. Emens LA, Ascierto PA, Darcy PK, Demaria S, Eggermont AMM, Redmond WL, et al. Cancer immunotherapy: Opportunities and challenges in the rapidly evolving clinical landscape. European Journal of Cancer. 2017;81:116-29.
7. Immunotherapy in People with Cancer and Autoimmune Diseases [Internet]. National Cancer Institute. 2019 [cited 25 November 2019]. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2019/immunotherapy-cancer-autoimmune-diseases-clinical-trial
8. Kähler KC, Eigentler TK, Gesierich A, Heinzerling L, Loquai C, Meier F, et al. Ipilimumab in metastatic melanoma patients with pre-existing autoimmune disorders. Cancer Immunology, Immunotherapy. 2018;67(5):825-34.
9. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, et al. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders. JAMA Oncology. 2016;2(2):234-40.
10. Cortellini A, Buti S, Santini D, Perrone F, Giusti R, Tiseo M, et al. Clinical Outcomes of Patients with Advanced Cancer and Pre-Existing Autoimmune Diseases Treated with Anti-Programmed Death-1 Immunotherapy: A Real-World Transverse Study. The Oncologist. 2019;24(6):e327-e37.
11. Danlos F-X, Voisin A-L, Dyevre V, Michot J-M, Routier E, Taillade L, et al. Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. European Journal of Cancer. 2018;91:21-9.
12. Leonardi GC, Gainor JF, Altan M, Kravets S, Dahlberg SE, Gedmintas L, et al. Safety of Programmed Death–1 Pathway Inhibitors Among Patients With Non–Small-Cell Lung Cancer and Preexisting Autoimmune Disorders. Journal of Clinical Oncology. 2018;36(19):1905-12.
13. Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong ANM, Park JJ, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Annals of Oncology. 2016;28(2):368-76.

14. Pantuck M, McDermott D, Drakaki A. To treat or not to treat: Patient exclusion in immune oncology clinical trials due to preexisting autoimmune disease. Cancer. 2019;125(20):3506-13.
15. Nivolumab in Treating Patients With Autoimmune Disorders or Advanced, Metastatic, or Unresectable Cancer - Full Text View - ClinicalTrials.gov [Internet]. Clinicaltrials.gov. 2019 [cited 26 November 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT03816345
16. Abernethy AP, Gippetti J, Parulkar R, Revol C. Use of Electronic Health Record Data for Quality Reporting. Journal of Oncology Practice. 2017;13(8):530-4.
17. Griffith SD, Miksad RA, Calkins G, You P, Lipitz NG, Bourla AB, et al. Characterizing the Feasibility and Performance of Real-World Tumor Progression End Points and Their Association With Overall Survival in a Large Advanced Non-Small-Cell Lung Cancer Data Set. JCO Clin Cancer Inform. 2019;3:1-13.
18. Nixon NA, Blais N, Ernst S, Kollmannsberger C, Bebb G, Butler M, et al. Current landscape of immunotherapy in the treatment of solid tumours, with future opportunities and challenges. Curr Oncol. 2018;25(5):e373-e84.
19. Rini BI, Battle D, Figlin RA, George DJ, Hammers H, Hutson T, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma (RCC). Journal for ImmunoTherapy of Cancer. 2019;7(1):354.
20. Kalyan A, Kircher S, Shah H, Mulcahy M, Benson A. Updates on immunotherapy for colorectal cancer. J Gastrointest Oncol. 2018;9(1):160-9.
21. Brar G, Shah MA. The role of pembrolizumab in the treatment of PD-L1 expressing gastric and gastroesophageal junction adenocarcinoma. Therap Adv Gastroenterol. 2019;12:1756284819869767-.
22. Sheth M, Benedum CM, Celi LA, Mark RG, Markuzon N. The association between autoimmune disease and 30-day mortality among sepsis ICU patients: a cohort study. Critical Care. 2019;23(1):93.
23. Chambers WH, Rabinowich H, Herberman RB. Mechanisms of Immunosuppression. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003. Available from: https://www.ncbi.nlm.nih.gov/books/NBK12565/
24. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Effect of autoimmune diseases on risk and survival in histology-specific lung cancer. European Respiratory Journal. 2012;40(6):1489-95.
25. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Effect of autoimmune diseases on mortality and survival in subsequent digestive tract cancers. Annals of Oncology. 2012;23(8):2179-84.

APPENDICES

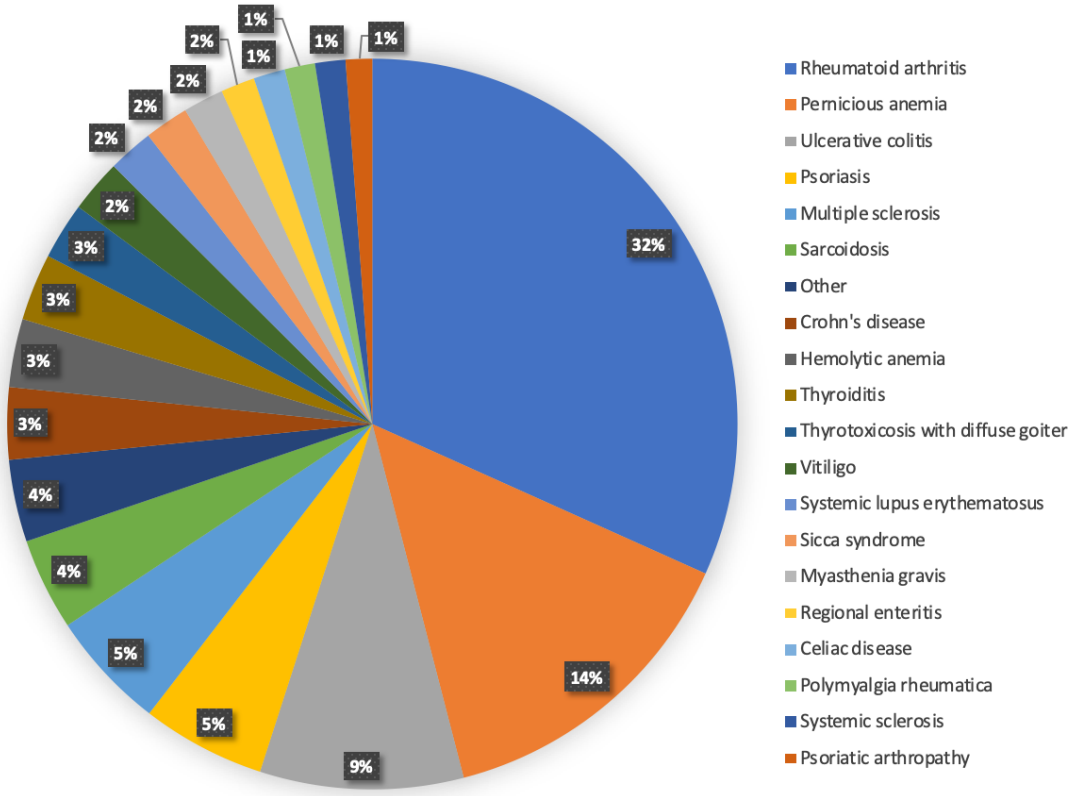
Appendix 1: ICD-9 and ICD-10 Codes for Autoimmune Disease

ICD Code	Code System	Disease
M06.1	ICD-10-CM	Adult-onset Still's disease
720	ICD-9-CM	Ankylosing spondylitis
M45.9	ICD-10-CM	Ankylosing spondylitis of unspecified sites in spine
283	ICD-9-CM	Autoimmune hemolytic anemias
E06.3	ICD-10-CM	Autoimmune thyroiditis
136.1	ICD-9-CM	Behcet's syndrome
K90.0	ICD-10-CM	Celiac disease
579	ICD-9-CM	Celiac disease
582.1	ICD-9-CM	Chronic glomerulonephritis with lesion of membranous
582	ICD-9-CM	Chronic glomerulonephritis with lesion of proliferative glomerulonephritis
582.9	ICD-9-CM	Chronic glomerulonephritis with unspecified pathological lesion in kidney
245.2	ICD-9-CM	Chronic lymphocytic thyroiditis
N03.2	ICD-10-CM	Chronic nephritic syndrome with diffuse membranous glomerulonephritis
N03.9	ICD-10-CM	Chronic nephritic syndrome with unspecified morphologic changes
M34.1	ICD-10-CM	CR(E)ST syndrome
K50.10	ICD-10-CM	Crohn's disease of large intestine without complications
K50.00	ICD-10-CM	Crohn's disease of small intestine without complications
K50.90	ICD-10-CM	Crohn's disease, unspecified, without complications
710.3	ICD-9-CM	Dermatomyositis
M33.90	ICD-10-CM	Dermatopolymyositis, unspecified, organ involvement unspecified
D59.0	ICD-10-CM	Drug-induced autoimmune hemolytic anemia
714.1	ICD-9-CM	Felty's syndrome
L40.1	ICD-10-CM	Generalized pustular psoriasis
446.5	ICD-9-CM	Giant cell arteritis
N08	ICD-10-CM	Glomerular disorders in diseases classified elsewhere
M31.0	ICD-10-CM	Hypersensitivity angiitis
K51.40	ICD-10-CM	Inflammatory polyps of colon without complications
K51.50	ICD-10-CM	Left sided colitis without complications
556.5	ICD-9-CM	Left-sided ulcerative (chronic) colitis
G35	ICD-10-CM	Multiple sclerosis
340	ICD-9-CM	Multiple sclerosis
G70.01	ICD-10-CM	Myasthenia gravis with (acute) exacerbation
G70.00	ICD-10-CM	Myasthenia gravis without (acute) exacerbation

358	ICD-9-CM	Myasthenia gravis without (acute) exacerbation
696.5	ICD-9-CM	Other and unspecified pityriasis
D59.1	ICD-10-CM	Other autoimmune hemolytic anemias
M31.6	ICD-10-CM	Other giant cell arteritis
L40.8	ICD-10-CM	Other psoriasis
696.1	ICD-9-CM	Other psoriasis
696.8	ICD-9-CM	Other psoriasis and similar disorders
L40.59	ICD-10-CM	Other psoriatic arthropathy
714.2	ICD-9-CM	Other rheumatoid arthritis with visceral or systemic involvement
L44.8	ICD-10-CM	Other specified papulosquamous disorders
556.8	ICD-9-CM	Other ulcerative colitis
K51.80	ICD-10-CM	Other ulcerative colitis without complications
696.2	ICD-9-CM	Parapsoriasis
M08.40	ICD-10-CM	Pauciarticular juvenile rheumatoid arthritis, unspecified site
281	ICD-9-CM	Pernicious anemia
L41.0	ICD-10-CM	Pityriasis lichenoides et varioliformis acuta
696.3	ICD-9-CM	Pityriasis rosea
L44.0	ICD-10-CM	Pityriasis rubra pilaris
725	ICD-9-CM	Polymyalgia rheumatica
710.4	ICD-9-CM	Polymyositis
M34.0	ICD-10-CM	Progressive systemic sclerosis
556.4	ICD-9-CM	Pseudopolyposis of colon
696	ICD-9-CM	Psoriatic arthropathy
555.1	ICD-9-CM	Regional enteritis of large intestine
555	ICD-9-CM	Regional enteritis of small intestine
555.9	ICD-9-CM	Regional enteritis of unspecified site
714	ICD-9-CM	Rheumatoid arthritis
M05.60	ICD-10-CM	Rheumatoid arthritis of unspecified site with involvement of other organs and systems
M06.9	ICD-10-CM	Rheumatoid arthritis, unspecified
M05.10	ICD-10-CM	Rheumatoid lung disease with rheumatoid arthritis of unspecified site
135	ICD-9-CM	Sarcoidosis
D86.9	ICD-10-CM	Sarcoidosis, unspecified
V82.1	ICD-9-CM	Screening for rheumatoid arthritis
710.2	ICD-9-CM	Sicca syndrome
M35.01	ICD-10-CM	Sicca syndrome with keratoconjunctivitis
M35.00	ICD-10-CM	Sicca syndrome, unspecified
710	ICD-9-CM	Systemic lupus erythematosus

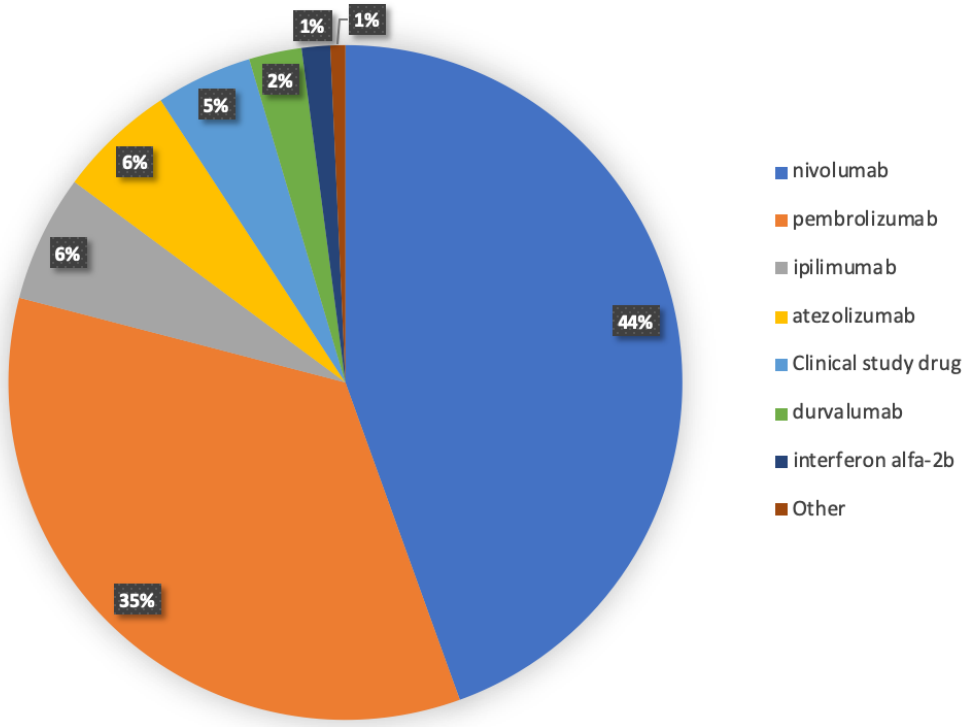
M32.10	ICD-10-CM	Systemic lupus erythematosus, organ or system involvement unspecified
710.1	ICD-9-CM	Systemic sclerosis
M34.9	ICD-10-CM	Systemic sclerosis, unspecified
E05.00	ICD-10-CM	Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm
242	ICD-9-CM	Toxic diffuse goiter without mention of thyrotoxic crisis or storm
556	ICD-9-CM	Ulcerative (chronic) enterocolitis
556.1	ICD-9-CM	Ulcerative (chronic) ileocolitis
K51.00	ICD-10-CM	Ulcerative (chronic) pancolitis without complications
556.2	ICD-9-CM	Ulcerative (chronic) proctitis
K51.20	ICD-10-CM	Ulcerative (chronic) proctitis without complications
K51.30	ICD-10-CM	Ulcerative (chronic) rectosigmoiditis without complications
556.9	ICD-9-CM	Ulcerative colitis, unspecified
K51.90	ICD-10-CM	Ulcerative colitis, unspecified, without complication
556.6	ICD-9-CM	Universal ulcerative (chronic) colitis
D51.0	ICD-10-CM	Vitamin B12 deficiency anemia due to intrinsic factor
L80	ICD-10-CM	Vitiligo
709.01	ICD-9-CM	Vitiligo

Appendix 2: Types of Autoimmune Disease



*Cells with less than 1% of patients were consolidated into the “Other” category which includes: Dermatopolymyositis, Giant cell arteritis, Ankylosing spondylitis, Inflammatory polyps of colon, Pseudopolyposis of colon, Polymyositis, Chronic nephritic syndrome, Hypersensitivity angiitis, Adult-onset Still's disease, Other and unspecified pityriasis, Pityriasis lichenoides et varioliformis acuta, Pityriasis rubra pilaris

Appendix 3: Types of Immunotherapy First Received by Patients



*Cells with less than 1% of patients were consolidated into the “Other” category which includes: aldesleukin, peginterferon alfa-2b, talimogene laherparepvec, bcg vaccine, avelumab, sipuleucel-t, cemiplimab, interferon alfa-2a