Research Article

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Gastrointestinal complications in patients treated with ipilimumab and nivolumab combination therapy or monotherapy

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Aim & methods: A retrospective study using the IBM Explorys Universe Database assessed the risk of gastrointestinal events (enterocolitis or diarrhea) among melanoma and lung cancer patients treated with ipilimumab and nivolumab combination or monotherapy. **Results & conclusion:** There were 904 melanoma patients (607 ipilimumab, 140 nivolumab and 157 combo) and 1641 lung cancer patients (68 ipilimumab, 1542 nivolumab and 31 combo). Approximately, 37% of lung patients and 46% of melanoma patients experienced at least one adverse event. After adjusting for covariates, patients receiving combination therapy were more likely to have a gastrointestinal event compared with ipilimumab monotherapy patients (melanoma hazard ratio: 1.54; 95% CI: 1.06–2.25; lung hazard ratio: 2.93; 95% CI: 1.09–7.89).

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Keywords: colitis • gastrointestinal • immune-related adverse events • ipilimumab • lung cancer • melanoma • nivolumab

Recent advances in cancer therapy have focused on enhancing the immune response through inhibition of immune checkpoint proteins including cell surface receptors CTLA-4 and PD-1 [1]. Although many questions remain, it is believed that CTLA-4 and PD-1 play complementary roles in suppressing autoreactive T-cells at different stages of the immune response [2–4]. Enhancing the immune response by blocking these pathways with monoclonal antibodies is proving to be a novel and effective way to treat a variety of aggressive and otherwise refractory malignancies, such as metastatic melanoma and advanced lung cancer [5].

Metastatic melanoma is an aggressive disease with a 5-year relative survival rate of 20% based on Surveillance, Epidemiology and End Results data from 2007 to 2013 [6]. This survival rate has been improving over time, in part due to the introduction of immune checkpoint inhibitors, such as ipilimumab for CTLA-4 and nivolumab for PD-1 [6–9]. In addition to working independently, early evidence has shown that inhibition of CLTA-4 and PD-1 has synergistic effects, and early results from Phase II and Phase III trials of nivolumab plus ipilimumab in patients with advanced melanoma have shown increased progression-free survival and higher overall survival (OS) rates in patients treated with the combination compared with ipilimumab alone [10,11].

Since 2014, nivolumab has been approved for the treatment of a number of malignancies – including non-small-cell lung cancer, colorectal cancer and hepatocellular cancer – which have proven intractable to the classic modalities of cancer therapy: surgery, radiation and chemotherapy [12–14]. New approaches to lung cancer treatment are of particular interest, as it remains the leading cause of cancer-related deaths due its high incidence (estimated 234,030 new cases in 2018) and poor prognosis (5-year survival of 5%) [6]. Nivolumab has been shown to improve median OS compared with docetaxel with fewer treatment-related Grade 3 or 4 adverse events (AEs) in both squamous and nonsquamous non-small-cell lung cancer, and there are efforts to improve survival further with the addition of ipilimumab [14–16].

However, these immunotherapies are not without risks; specifically, by dysregulating the process which normally prevents autoimmune reactions, use of these agents can result in immune-related adverse events (IRAEs) including diarrhea, colitis, hepatitis and hypophysitis [17,18]. One study, which used aggregated safety data of clinical trials

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in melanoma, reported IRAE frequencies of 62.0, 73.2 and 87.9% for nivolumab, ipilimumab and combination therapy, respectively [19]. Severe grade 3 and 4 AEs, which are most likely to lead to discontinuation, were most common for the combination therapy and predominately impacted the gastrointestinal (GI) and hepatic systems [19,20]. Current first-line treatment for IRAEs involves delay or discontinuation of the immunotherapy and administration of corticosteroids [21,22]. For those who can restart treatment, the use of immunosuppressants does not appear to reduce OS; however, many patients, particularly those with GI complications, do not restart therapy [23]. Gastrointestinal complications have been found to be one of the most common reasons for discontinuation of checkpoint inhibitor therapies [18]

With the combined targeting of PD-1 and CTLA-4 growing in usage [24–26], it is critical to obtain a better understanding of the frequency and severity of IRAEs. Current data on the frequency IRAEs are limited to clinical trials, single-site reports and the US FDA Adverse Event Reporting System [19,20,23]. This retrospective cohort study uses electronic medical records (EMRs) to examine the real-world rate of AEs including IRAEs and other GI AEs in patients with advanced melanoma or lung cancer treated with nivolumab, ipilimumab or combination therapy.

Methods

Data source

This study utilized patient-level deidentified US EMR data from the IBM Explorys Universe Dataset (Explorys; IBM, NY, USA) for the period from 1 September 2010 to 8 May 2017. Explorys contains data for approximately 55 million patients (~15% of the US population) derived from integrated data networks across 23 large health systems, comprising approximately 360 hospitals and 330,000 providers. The data provide a full longitudinal view of a patient's medical history across the care continuum, including diagnoses, procedures and medications.

Study design & patient selection

This retrospective longitudinal observational cohort study used a large real-world EMR database to evaluate the rate of GI events among melanoma and lung cancer patients treated with ipilimumab, nivolumab or ipilimumab/nivolumab combination (combo) therapy. Patients were included if they had at least one prescription for ipilimumab or nivolumab between 1 March 2011 and 8 May 2017. The date of the earliest prescription was defined as the index date, and patients were required to be at least 18 years of age on the index date. Any patients with a diagnosis of metastatic melanoma or lung cancer prior to or within 60 days after of the index date were included in the study. Each cancer cohort (melanoma or lung) was then separated into three treatment subcohorts (ipilimumab, nivolumab or combo) based on the index checkpoint inhibitor therapy. The analysis period for each patient was from 6 months preindex until the end of data availability due to patient death, end of EMR enrollment or end of the study period (Figure 1).

Baseline characteristics

Patient demographics were measured on the index date and included age, gender, race, smoking status, BMI and index year. Racial categories were Caucasian, African–American, Hispanic, other and unknown.

Primary cancer diagnosis was captured during the 6-month preindex period and the first 60 days postindex. The National Cancer Institute (NCI) modification of the Deyo Charlson Comorbidity Index (DCCI) was calculated for the 6-month preindex period [27,28]. Comorbidities of interest were captured during the preindex period and included cerebrovascular disease, cardiac dysrhythmia, chronic obstructive pulmonary disorder, congestive heart failure, Crohn's disease, dementia, depression, hemiplegia or paraplegia, HIV infection, hypertension, hypotension, ischemic heart disease, liver disease, myocardial infarction, peptic ulcer, peripheral vascular disease, renal disease, rheumatologic disease, Type 2 diabetes mellitus and ulcerative colitis.

Outcomes

The index treatment regime began on the index date and comprised all agents prescribed within 28 days of the index date. The duration of therapy was calculated from the index date to the earliest of the following: addition of a new agent after 28 days; a gap of 60 days or more following the last administration of either nivolumab or ipilimumab; death recorded in Explorys or end of study period (8 May 2017). In addition to duration of therapy, the number, type and name of all systemic agents in the index treatment regime were recorded. Systemic agents captured in addition to ipilimumab and nivolumab included targeted therapies (cobimetinib, dabrafenib, trametinib and vemurafenib), immunotherapies (granulocyte-macrophage colony-stimulating factor, IL-2, IL α-

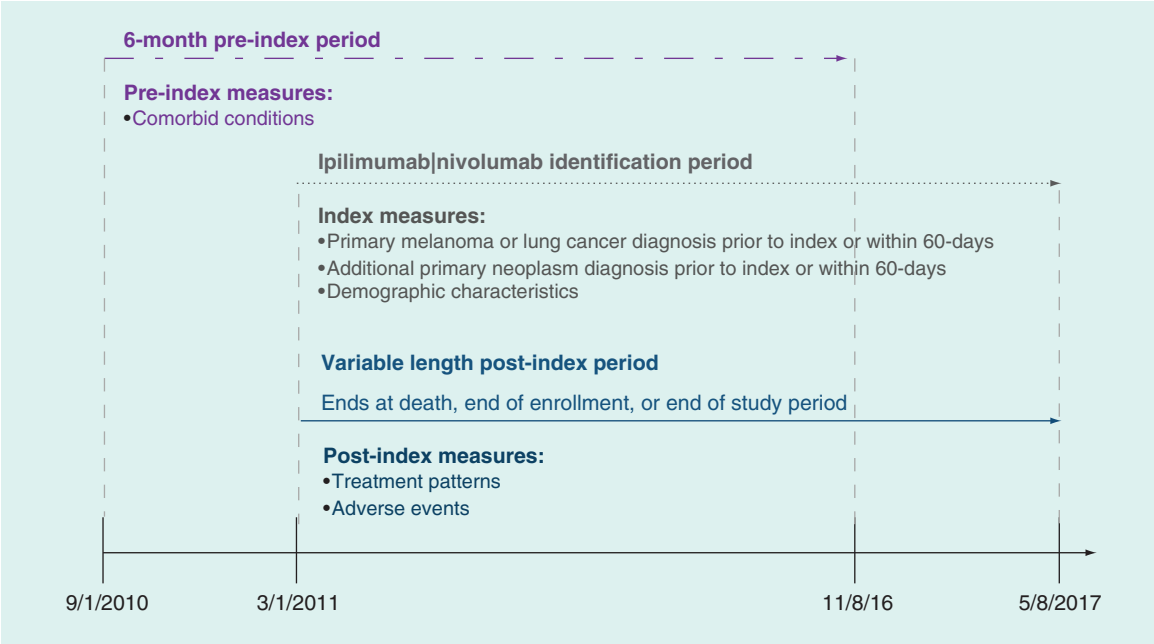


Figure 1. Study period.

2b and pembrolizumab), chemotherapeutic agents (carboplatin, carmustine, cisplatin, dacarbazine, docetaxel, paclitaxel, temozolomide and vinblastine) and immunosuppressants (corticosteroids and adalimumab).

The incidence of GI AEs was calculated for the duration of the index treatment regime. Only new events (i.e., events not present in the 6-month preindex period) were included in the analysis. These events included abdominal cramping/pain, anorexia, constipation, diarrhea, dyspepsia, enterocolitis, gingivitis, mucositis, nausea/vomiting and pancreatitis

Statistical analysis

The count and percentage of patients in each treatment cohort were calculated for categorical variables. The mean and standard deviation was calculated for continuous variables. Association between index treatment regimen (ipilimumab, nivolumab or combo) and the risk of incident GI complications (enterocolitis or diarrhea) was assessed using Cox proportional hazard models to control for baseline demographic and clinical characteristics. Separate models were built for the lung cancer and melanoma cohorts. The vector of covariates included in both models included age, sex, BMI, NCI DCCI, preindex neutropenia or leukopenia, preindex GI symptoms of nausea, vomiting, abdominal cramping/pain and constipation. Hazard ratios were computed for each variable and Kaplan–Meier curves were prepared for each treatment subcohort. The α level for all statistical analysis was set *a priori* at 0.05. Data management and statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc, NC, USA).

Results

Patient identification & demographic characteristics

During the identification period, 2545 metastatic melanoma and lung cancer patients were treated with nivolumab or ipilimumab, and, of these, 53.7% had a diagnosis of metastatic lung cancer and 29.6% had a diagnosis of metastatic melanoma. Baseline demographic characteristics by treatment subcohort within each diagnosis cohort are reported in Table 1. Patients in the lung cancer cohort had a mean age of 67.3 ± 10.3 years: 55% were male, 82% were Caucasian, 16% were current smokers and the average BMI was 22.8 ± 9.7. There was no substantial difference between treatment subcohorts. Patients in the melanoma cohort had a mean age of 63.5 ± 13.8 years: 65% were male, 93% were Caucasian, 9% were current smokers and the average BMI was 22.8 ± 12.7. Patients on nivolumab tended to be older (62.4 ± 13.5 years ipilimumab vs 70.8 ± 13.1 years nivolumab vs 61.0 ± 13.8 combo), but otherwise, the three treatment subcohorts were similar.

Table 1. Baseline demographic and clinical characteristics.

	Lung cancer			Melanoma		
	Ipilimumab	Nivolumab	Combo	Ipilimumab	Nivolumab	Combo
	n = 68	n = 1542	n = 31	n = 607	n = 14	n = 157
Age, mean ± SD	64.8 ± 12.7	67.5 ± 10.2	64.2 ± 11.0	62.4 ± 13.5	70.8 ± 13.1	60.0 ± 13.8
Male, n (%)	42 (61.8)	844 (54.7)	18 (58.1)	381 (62.8)	98 (70.0)	111 (70.7)
Race/ethnicity, n (%)						
– Caucasian	61 (89.7)	1262 (81.8)	27 (87.1)	561 (92.4)	127 (90.7)	152 (96.8)
– African–American	3 (4.4)	153 (9.9)	0 (0.0)	6 (1.0)	3 (2.1)	0 (0.0)
– Hispanic	0 (0)	4 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
– Other	0 (0)	47 (3.0)	0 (0.0)	8 (1.3)	1 (0.7)	1 (0.6)
– Unknown	4 (5.9)	76 (4.9)	4 (12.9)	31 (5.1)	9 (6.4)	4 (2.5)
Current smoker, n (%)	7 (10.3)	259 (16.8)	3 (9.7)	52 (8.6)	14 (10.0)	15 (9.6)
BMI, mean ± SD	23.6 ± 11.6	22.7 ± 9.6	24.4 ± 9.6	22.3 ± 13.4	22.3 ± 11.2	25.2 ± 11.1
NCI modified DCCI‡, mean ± SD	0.7 ± 1.1	0.8 ± 1.0	0.4 ± 0.6	0.4 ± 0.8	0.6 ± 1.0	0.4 ± 0.7
General comorbidities†‡, n (%)						
– Cerebrovascular disease	7 (10.3)	123 (8.0)	2 (6.5)	56 (9.2)	15 (10.7)	12 (7.6)
– Cardiac dysrhythmia	11 (16.2)	152 (9.9)	5 (16.1)	62 (10.2)	19 (13.6)	7 (4.5)
– Chronic obstructive pulmonary disorder	17 (25.0)	649 (42.1)	6 (19.4)	75 (12.4)	25 (17.9)	22 (14.0)
– Congestive heart failure	6 (8.8)	118 (7.7)	0 (0.0)	27 (4.4)	13 (9.3)	3 (1.9)
– Crohn's disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
– Dementia	0 (0.0)	8 (0.5)	0 (0.0)	5 (0.8)	5 (3.6)	1 (0.6)
– Depression	6 (8.8)	204 (13.2)	3 (9.7)	51 (8.4)	10 (7.1)	17 (10.8)
– Hypertension	38 (55.9)	685 (44.4)	15 (48.4)	233 (38.4)	78 (55.7)	59 (37.6)
– Hypotension	3 (4.4)	19 (1.2)	0 (0.0)	6 (1.0)	2 (1.4)	3 (1.9)
– Ischemic heart disease	10 (14.7)	262 (17.0)	5 (16.1)	64 (10.5)	26 (18.6)	18 (11.5)
– Liver disease	0 (0.0)	30 (1.9)	0 (0.0)	7 (1.2)	1 (0.7)	0 (0.0)
– Peripheral vascular disease	2 (2.9)	245 (15.9)	4 (12.9)	34 (5.6)	17 (12.1)	12 (7.6)
– Renal disease	4 (5.9)	138 (8.9)	1 (3.2)	23 (3.8)	17 (12.1)	5 (3.2)
– Rheumatologic disease	1 (1.5)	32 (2.1)	0 (0.0)	14 (2.3)	4 (2.9)	2 (1.3)
– Type 2 diabetes mellitus	10 (14.7)	231 (15.0)	3 (9.7)	86 (14.2)	24 (17.1)	13 (8.3)
– Ulcerative colitis	1 (1.5)	3 (0.2)	0 (0.0)	2 (0.3)	2 (1.4)	0 (0.0)

†The following general comorbidities were evaluated but occurred in less than 3% of any cohort: hemiplegia or paraplegia, HIV infection, myocardial infarction, peptic ulcer.
‡Measured during the 6-month preindex period.
BMI: Body mass index; DCCI: Deyo Charlson Comorbidity Index; NCI: National Cancer Institute; SD: Standard deviation.

Clinical characteristics

Clinical characteristics from the preindex period are reported in Table 1. Approximately 10–20% of patients had at least two primary cancer diagnosis in their EMR record. On average, the NCI DCCI was below 1.0 for both lung cancer patients (0.7 ± 1.1 ipilimumab vs 0.8 ± 1.0 nivolumab vs 0.4 ± 0.6 combo) and melanoma patients (0.4 ± 0.8 ipilimumab vs 0.6 ± 1.0 nivolumab vs 0.4 ± 0.7 combo). The top five comorbid conditions, in order of percentage of patients diagnosed, were hypertension (38−56%), chronic obstructive pulmonary disorder (12–42%), ischemic heart disease (11−19%), Type 2 diabetes mellitus (8−17%) and cardiac dysrhythmia (5−16%). Among lung cancer patients, the mean duration of time on therapy was 117.9 ± 216.8 days for the ipilimumab subcohort, 138.1 ± 145.1 days for the nivolumab subcohort and 112.4 ± 95.8 days for the combination drug subcohort; among melanoma patients, the mean duration of time on therapy was 107.2 ± 174.7 days for the ipilimumab subcohort, 120.8 ± 138.2 days for the nivolumab subcohort and 129.2 ± 126.5 days for the combination drug subcohort (data not shown).

Adverse events

New incident events of GI diagnoses were common during the index therapy regime (Table 2). At least 30% of patients in any subcohort had one or more AEs with similar treatment-related trends in both the lung cancer (63.2% ipilimumab vs 35.7% nivolumab vs 41.9% combo) and melanoma (49.3% ipilimumab vs 32.9% nivolumab vs

Table 2. Incident gastrointestinal events during the duration of the index treatment regimen.

Incidence of adverse events	Lung cancer			Melanoma		
	Ipilimumab	Nivolumab	Combo	Ipilimumab	Nivolumab	Combo
	n = 68	n = 1542	n = 31	n = 607	n = 140	n = 157
Abdominal cramping/pain, n (%)	11 (16.2)	146 (9.5)	5 (16.1)	100 (16.5)	15 (10.7)	21 (13.4)
Rate of abdominal cramping/pain†	134.6	148.9	291.5	133.3	175.8	208.3
Anorexia, n (%)	8 (11.8)	140 (9.1)	2 (6.5)	58 (9.6)	12 (8.6)	13 (8.3)
Rate of anorexia†	85.5	140.4	113.5	68.5	130.1	124.3
Constipation, n (%)	13 (19.1)	215 (13.9)	5 (16.1)	91 (15.0)	20 (14.3)	19 (12.1)
Rate of constipation†	141	226.7	312.1	111.6	228.8	189.1
Diarrhea, n (%)	15 (22.1)	104 (6.7)	5 (16.1)	122 (20.1)	16 (11.4)	33 (21)
Rate of diarrhea†	172.4	104.1	327.3	160.7	194.1	371.3
Dyspepsia, n (%)	4 (5.9)	26 (1.7)	2 (6.5)	19 (3.1)	4 (2.9)	5 (3.2)
Rate of dyspepsia†	41.2	24.4	120	21.5	43	46.5
Enterocolitis, n (%)	8 (11.8)	53 (3.4)	2 (6.5)	80 (13.2)	8 (5.7)	17 (10.8)
Rate of enterocolitis†	87.1	50.9	112.5	96.7	90.1	166.6
Nausea/vomiting, n (%)	24 (35.3)	189 (12.3)	8 (25.8)	138 (22.7)	20 (14.3)	37 (23.6)
Rate of nausea/vomiting†	300	202.9	608.1	187	236.8	415.3
Pancreatitis, n (%)	4 (5.9)	15 (1.0)	0 (0.0)	14 (2.3)	0 (0.0)	2 (1.3)
Rate of pancreatitis†	40.3	14.1	0	15.8	0	18

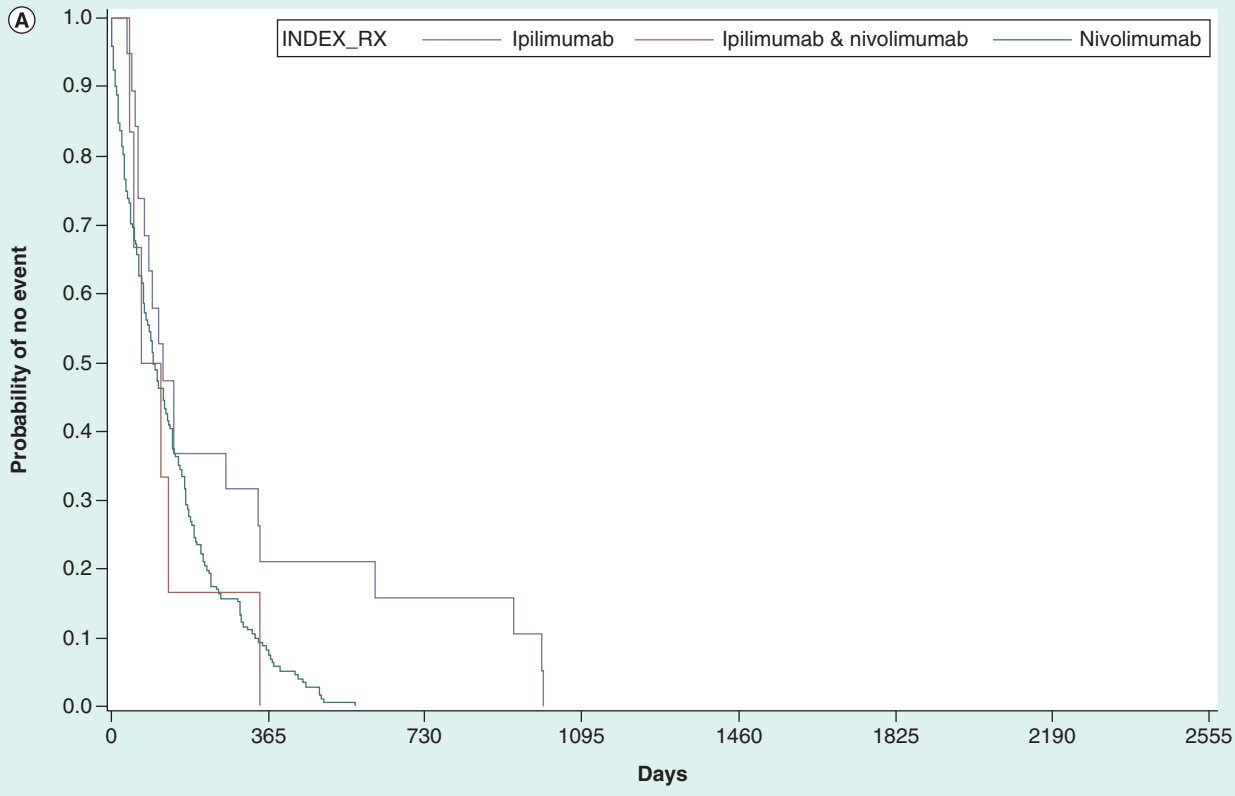
†per 1000 person years.
SD: Standard deviation.

44.6% combo) cohorts. The four most common incidence of AEs – by rate per 1000 person-years, for all subcohorts, regardless of diagnosis – were abdominal cramping/pain (lung cancer: 134.6 ipilimumab vs 148.9 nivolumab vs 291.5 combo; melanoma: 133.3 ipilimumab vs 175.8 nivolumab vs 208.3 combo), constipation (lung cancer: 141.0 ipilimumab vs 226.7 nivolumab vs 312.1 combo; melanoma: 111.6 ipilimumab vs 228.8 nivolumab vs 189.1 combo), diarrhea (lung cancer: 172.4 ipilimumab vs 104.1 nivolumab vs 327.3 combo; melanoma: 160.7 ipilimumab vs 194.1 nivolumab vs 371.3 combo) and nausea/vomiting (lung cancer: 300.0 ipilimumab vs 202.9 nivolumab vs 608.1 combo; melanoma: 187.0 ipilimumab vs 236.8 nivolumab vs 415.3 combo). The unadjusted rate of enterocolitis (per 1000 person-years) was lowest among patients on nivolumab and highest for those on combination therapy for both lung cancer (86.6 ipilimumab vs 50.9 nivolumab vs 112.5 combo) and melanoma (96.7 ipilimumab vs 90.1 nivolumab vs 166.6 combo). The time to first diarrhea or enterocolitis diagnosis during the treatment regimen is depicted in Figure 2. These AEs occurred significantly earlier for the combination treatment compared with the ipilimumab or nivolumab monotherapy (mean time to first diarrhea event lung cancer: ipilimumab 354 days, nivolumab 145 days, combo 138 days; melanoma diarrhea: ipilimumab 196 days, nivolumab 120 days, combo 119 days; lung cancer enterocolitis: ipilimumab 314 days, nivolumab 152 days, combo 106 days; melanoma enterocolitis: ipilimumab 169 days, nivolumab 156 days, combo 75 days).

Cox proportional hazard models were used to assess the hazard of incident enterocolitis or diarrhea among lung cancer and melanoma patients following the initiation of index drug. After adjusting for age, sex, BMI and comorbid conditions, compared with those receiving ipilimumab monotherapy, lung cancer patients receiving the combination therapy (hazard ratio [HR] = 2.93; 95% CI: 1.09−7.89; p = 0.03) or nivolumab monotherapy (HR = 2.13; 95% CI: 1.21−3.76; p = 0.009) had a statistically higher risk of a GI event (Figure 2A and 3). Among melanoma patients, the hazard of incident GI events was equivalent between patients on nivolumab and patients on ipilimumab (HR = 1.07; 95% CI: 0.68−1.70; p = 0.76) but significantly higher for patients on combination therapy compared with ipilimumab alone (HR = 1.54; 95% CI: 1.06−2.25; p = 0.02; Figures 2B and 3). None of the demographic or clinical covariates in either the lung cancer or melanoma models were statistically significant in the models.

Discussion

This retrospective study used EMR data to evaluate incident GI AEs among patients with melanoma and lung cancer taking ipilimumab or nivolumab monotherapy or combination therapy. Incident GI AEs were common,



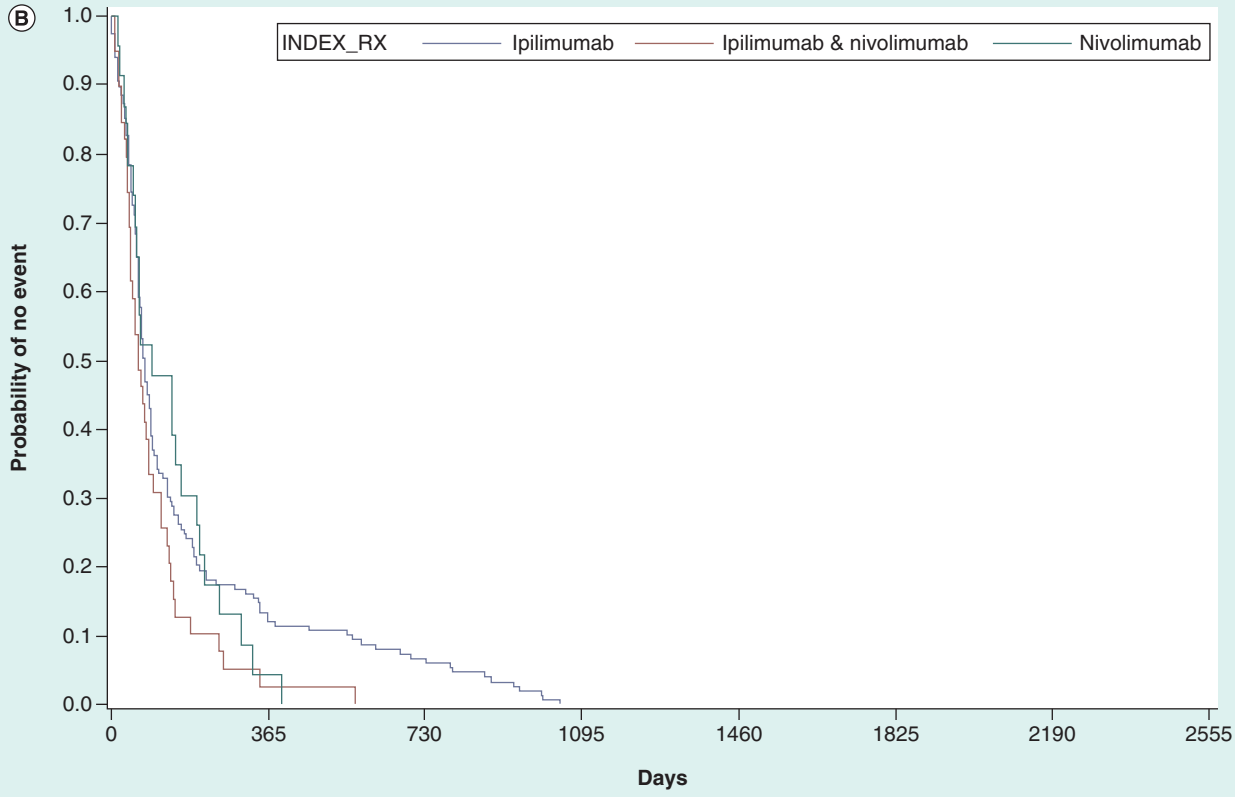


Figure 2. Adjusted hazard ratios of incident enterocolitis or diarrhea. (A) Lung cancer. **(B)** Melanoma. Ipilimumab monotherapy is the control subcohort. Models controlled for age, sex, BMI, National Cancer Institute modification of the Deyo Charlson Comorbidity Index, preindex neutropenia or leukopenia, nausea or vomiting, abdominal cramping/pain and constipation. None of the covariates were statistically significant in the model.

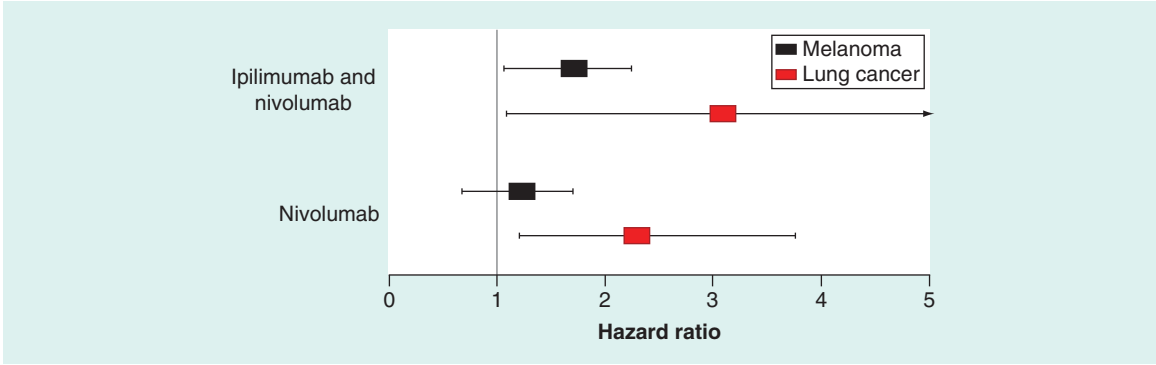


Figure 3. Time-to-incident enterocolitis or diarrhea during the duration of the index treatment regimen. Lung cancer patients (bottom, red) and melanoma patients (top, black).

and over 30% of patients in any subcohort had at least one event. The rate of AEs per 1000 patient-years ranged from 160.7 to 371.3 for diarrhea and from 50.9 to 166.6 for enterocolitis. The highest rates of enterocolitis were experienced by patients on the combination therapy (112.5 per 1000 lung cancer patient-years and 166.6 per 1000 melanoma person-years).

After adjusting for covariates, the hazard of incident enterocolitis or diarrhea was 1.5-times higher for melanoma patients on the combination of ipilimumab and nivolumab compared with ipilimumab monotherapy, and no statistical difference was observed when comparing the two monotherapies. In the lung cancer cohort, the hazard of incident enterocolitis or diarrhea was 2.9-times higher on the combination of ipilimumab and nivolumab, and 2.1-times higher on nivolumab monotherapy when compared with ipilimumab monotherapy. Patients in this real-world study were older than patients enrolled in previously reported clinical trials so it is possible that the age distribution of these real-world patients may have accounted for the relationship found between combination ipilimumab and nivolumab therapy and GI AEs [18]. However, this is not likely because the relationship between combination therapy and GI events remained after controlling for age, gender, comorbid conditions and other clinical variables in the multivariable models. In addition, none of these covariates were statistically significant in the models.

To our knowledge, this is the first study to compare the incidence rates of GI events between checkpoint inhibitors among melanoma and lung cancer patients using real-world data. Hassel *et al.* pooled AE data from four large advanced melanoma clinical trials on ipilimumab, nivolumab and/or combination therapy (Checkmate -037, -066, -067 and -069) [19]. They report the aggregated frequency of any GI events to be 42% for ipilimumab, 18% for nivolumab and 46% for combination therapy. The reported frequency of diarrhea was 34% for ipilimumab, 17% for nivolumab and 43% for combination therapy. The reported frequency of colitis was 12% for ipilimumab, 1% for nivolumab and 14% for combination therapy. These numbers are similar to the real-world data observed in this study. In general, patients in this study had slightly shorter durations of treatment compared with some of the clinical trials [29–32]. However, it is difficult to directly compare with clinical trial data because trials tend to have more stringent patient selection criteria (e.g., exclusion of patients who are less healthy or who have specific comorbid conditions) and protocol driven treatment regimens which likely impacts time on therapy.

A review of the published data for these trials found several differences in demographic and clinical characteristics between the real-world population in this study and the selected clinical trial populations [29–32] which may account for some of the differences seen. Patients in this real-world study were older than patients enrolled in previously reported clinical trials [18]. For example, although the mean age was similar, 58–65 years old, a greater proportion of the real-world population was 75 years or older (real-world = 21%; clinical trial = 13%). It is possible that the age distribution of these real-world patients may have accounted for the relationship found between combination ipilimumab and nivolumab therapy and GI AEs. However, this is not likely because the relationship between combination therapy and GI events remained after controlling for age, gender, comorbid conditions and other clinical variables in the multivariable models. In addition, none of these covariates were statistically significant in the models.

Limitations

Misclassification error is possible when relying on diagnosis coding from EMR, where the extent of missing or inaccurate codes is unknown. Patients' medical and prescription history was limited to EMR during the reporting months in this study. The identification of AEs is accomplished by identifying patients with ICD-9 and ICD-10 diagnoses recorded in the EMR data during the duration of the treatment episode. The EMR data does not indicate the grade, severity or duration of the AEs nor does it provide direct attribution of the AE to the specific medications used during the treatment episode. The EMR data, including diagnoses, prescriptions and procedures are only available when the patient is seen by a contributor to the EHR system, and any services conducted by providers external to contributing EMR systems were not captured. The Explorys Universe Database is a convenient sample of contributing data sources in the USA, and thus, findings may not be generalizable to other US or international patient populations. Multivariate analyses of outcomes provided further adjustment for potentially confounding covariates used in the matching process and an additional degree of robustness in cohort comparisons; however, the potential for unmeasured confounders is always present.

Conclusion

Incident GI AEs were common in patients treated with ipilimumab or nivolumab, and the rate of GI AEs increased when these drugs were used in combination. Our results suggest that there is an unmet clinical need for the treatment of GI AEs in patients on combination therapy to minimize treatment disruption and/or discontinuation.

Future perspective

Clinical trials have shown improved survival for advanced melanoma and lung cancer patients on combination ipilimumab and nivolumab therapy, and additional trials are ongoing in other cancer types. It seems likely that the use of ipilimumab and nivolumab combination therapy will continue to grow and, with the expanded use of these therapies, it is anticipated that treatment outcomes including survival will improve. However, improved outcomes are accompanied with an increased risk of GI-related AEs compared with older therapies. The GI AEs represent a major barrier to sustained adherence to these medications and they are one of the leading causes for treatment discontinuation [18]. Discontinuation and reduced adherence may negate the expected treatment benefits. Given that these newer therapies are costly to the healthcare system, improved adherence through mitigating GI AEs would be a key component to long-term cost-effectiveness. New treatments for these GI AEs are needed to reduce symptoms and to maximize the potential positive clinical impact of these immunotherapies. Future studies should examine the relationship of treatment adherence, AEs and the impact on outcomes such as OS.

Financial & competing interests disclosure

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Author contributions

All authors contributed to the conception of the study, analysis of the data, writing of the manuscript and approval of the final draft.

Ethical conduct of research

All study data were accessed with protocols compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations. As all database used in the study are fully deidentified and compliant with the Health Insurance Portability and Accountability Act, this study was exempted from Institutional Review Board approval.

Summary points

- This retrospective cohort study examined the hazard of incident gastrointestinal (GI) adverse events (enterocolitis or diarrhea) in melanoma and lung cancer patients treated with (ipilimumab alone, nivolumab alone or in combination).
- Data on patients with ≥1 record for ipilimumab or nivolumab between 1 March 2011 and 8 May 2017 and a diagnosis of melanoma (607 on ipilimumab, 140 on nivolumab and 157 on combo) or lung cancer (68 on ipilimumab, 1542 on nivolumab and 31 on combo) was extracted from a deidentified EMR dataset.
- Index treatment regime, time on therapy and rate of any GI events were assessed using descriptive statistics for each cancer type.
- In the lung cancer cohort, for patients on ipilimumab, nivolumab or combo therapy, the average time on therapy was 117.9 ± 216.8 days versus 138.1 ± 145.1 days versus 112.4 ± 95.8 days, the percentage of patients with at least one GI adverse event was 63.2 versus 35.7 versus 41.9%, and the rate of enterocolitis was 87.1 versus 50.9 versus 112.5 per 1000 patient-years.
- In the melanoma cohort, for patients on ipilimumab, nivolumab or combo therapy, the average time on therapy was 107.2 ± 174.7 days versus 120.8 ± 138.2 days versus 129.2 ± 126.5 days, the percentage of patients with at least one GI adverse event was 49.3 versus 32.9 versus 44.6%, and the rate of enterocolitis was 96.7 versus 90.1 versus 166.6 per 1000 patient-years.
- Cox proportional hazard models were used to estimate the hazard ratio (HR) of any incident enterocolitis or diarrhea by index drug group, adjusting for age, sex, BMI and comorbid conditions.
- In the hazard model for GI events, melanoma and lung patients on the combination therapy were at a significantly increased risk of enterocolitis or diarrhea while on therapy compared with those on ipilimumab monotherapy (melanoma HR: 1.54; 95% CI: 1.06–2.25; p = 0.02; lung HR: 2.93; 95% CI: 1.09–7.89; p = 0.03).
- There is an unmet clinical need for the management of GI events in patients treated with ipilimumab and nivolumab combo therapy.

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