

CHECKPOINT INHIBITOR PNEUMONITIS IN LUNG CANCER

Supplemental Data:

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Supplemental Table S1: Query codes

Codes include those from the International Classification of Diseases Tenth Revision (ICD-10), Current Procedural Terminology (CPT), RxNorm, Healthcare Common Procedure Coding System (HCPCS), and TriNetX-specific codes.

Cancer Types		
Lung cancer	ICD-10	C34 Malignant neoplasm of bronchus and lung
Renal cell carcinoma	ICD-10	C64 Malignant neoplasm of kidney, except renal pelvis
Melanoma	ICD-10	C43 Malignant melanoma of skin
Gastrointestinal cancers	ICD-10	C15 Malignant neoplasm of esophagus C16 Malignant neoplasm of stomach C18 Malignant neoplasm of colon C19 Malignant neoplasm of rectosigmoid junction C20 Malignant neoplasm of rectum C21 Malignant neoplasm of anus and anal canal C22 Malignant neoplasm of liver and intrahepatic bile ducts
Metastatic disease	ICD-10	C77 Secondary and unspecified malignant neoplasm of lymph nodes
		C78 Secondary malignant neoplasm of respiratory and digestive organs
		C79 Secondary malignant neoplasm of other and unspecified sites
		C7B Secondary neuroendocrine tumors
Immune Checkpoint Inhibitors		
Ipilimumab	RxNorm	1094833 ipilimumab
Pembrolizumab	RxNorm	1547545 pembrolizumab
Nivolumab	RxNorm	1597876 nivolumab
Durvalumab	RxNorm	1919503 durvalumab
Atezolizumab	RxNorm	1792776 atezolizumab
Cemiplimab	RxNorm	2058826 cemiplimab
Avelumab	RxNorm	1875534 avelumab
Lung Cancer Chemotherapy/Targeted Therapy		
Carboplatin	RxNorm	40048 carboplatin
Cisplatin	RxNorm	2555 cisplatin
Gemcitabine	RxNorm	12574 gemcitabine
Pemetrexed	RxNorm	68446 pemetrexed
Paclitaxel	RxNorm	56949 paclitaxel
Docetaxel	RxNorm	72962 docetaxel
Etoposide	RxNorm	4179 etoposide
Irinotecan	RxNorm	51499 irinotecan
Vinorelbine	RxNorm	39541 vinorelbine
Afatinib	RxNorm	1430438 afatinib
Erlotinib	RxNorm	337525 erlotinib
Dacomitinib	RxNorm	2058849 dacomitinib
Gefitinib	RxNorm	328134 gefitinib
Osimertinib	RxNorm	1721560 osimertinib
Mobocertinib	RxNorm	2570736 mobocertinib

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Sotorasib	RxNorm	2550714 sotorasib
Alectinib	RxNorm	1727455 alectinib
Brigatinib	RxNorm	1921217 brigatinib
Ceritinib	RxNorm	1535457 ceritinib
Crizotinib	RxNorm	1148495 crizotinib
Lorlatinib	RxNorm	2103164 lorlatinib
Entrectinib	RxNorm	2197862 entrectinib
Dabrafenib	RxNorm	1424911 dabrafenib
Vemurafenib	RxNorm	1147220 vemurafenib
Larotrectinib	RxNorm	2105628 larotrectinib
Capmatinib	RxNorm	2362165 capmatinib
Teponitib	RxNorm	2477103 tepotinib
Selpercatinib	RxNorm	2370147 selpercatinib
Pralsetinib	RxNorm	2394936 pralsetinib
Cabozantinib	RxNorm	1363268 cabozantinib
Renal Cell Carcinoma Chemotherapy/Targeted Therapy		
Everolimus	RxNorm	141704 everolimus
Axitinib	RxNorm	1242999 axitinib
Cabozantinib	RxNorm	1363268 cabozantinib
Tivozanib	RxNorm	2534233 tivozanib
Lenvatinib	RxNorm	1603296 lenvatinib
Sorafenib	RxNorm	495881 sorafenib
Pazopanib	RxNorm	714438 pazopanib
Sunitinib	RxNorm	357977 sunitinib
Temsirolimus	RxNorm	657797 temsirolimus
Gastrointestinal Cancer Chemotherapy/Targeted Therapy		
Irinotecan	RxNorm	51499 irinotecan
Capecitabine	RxNorm	19400 capecitabine
Fluorouracil	RxNorm	4492 fluorouracil
Oxaliplatin	RxNorm	32592 oxaliplatin
Leucovorin	RxNorm	6313 leucovorin
Paclitaxel	RxNorm	56946 paclitaxel
Docetaxel	RxNorm	72962 docetaxel
Doxorubicin	RxNorm	3639 doxorubicin
Mitomycin	RxNorm	632 mitomycin
Trifluridine	RxNorm	10803 trifluridine
Tipiracil	RxNorm	1670304 tipiracil
Ramucirumab	RxNorm	1535922 ramucirumab
Cetuximab	RxNorm	318341 cetuximab
Aflibercept	RxNorm	1232150 aflibercept
Cabozantinib	RxNorm	1363268 cabozantinib
Panitumumab	RxNorm	263034 panitumumab
Regorafenib	RxNorm	1312397 regorafenib
Infigratinib	RxNorm	2550729 infigratinib
Sorafenib	RxNorm	495881 sorafenib
Pemigatinib	RxNorm	2359268 pemigatinib
Melanoma Chemotherapy/Targeted Therapy		
Dacarbazine	RxNorm	3098 dacarbazine
Temozolomide	RxNorm	37776 temozolomide

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Carboplatin	RxNorm	40048 carboplatin
Cisplatin	RxNorm	2555 cisplatin
Paclitaxel	RxNorm	56946 paclitaxel
Docetaxel	RxNorm	72962 docetaxel
Lomustine	RxNorm	6466 lomustine
Vinblastine	RxNorm	11198 vinblastine
Vemurafenib	RxNorm	1147220 vemurafenib
Dabrafenib	RxNorm	1424911 dabrafenib
Encorafenib	RxNorm	2049106 encorafenib
Trametinib	RxNorm	1425099 trametinib
Binimetinib	RxNorm	2049122 binimetinib
Pneumonitis/pneumonia Codes		
Drug-Induced Respiratory Conditions	ICD-10	J70.2 Acute drug-induced interstitial lung disorders
		J70.3 Chronic drug-induced interstitial lung disorders
		J70.4 Drug-induced interstitial lung disorders, unspecified
		J70.8 Respiratory conditions due to other specified external agents
		J70.9 Respiratory conditions due to unspecified external agent
Interstitial Lung Disease	ICD-10	J84.11 Idiopathic interstitial pneumonia
		J84.89 Other specified interstitial pulmonary diseases
		J84.9 Interstitial pulmonary disease, unspecified
Pneumonia	ICD-10	J18.9 Pneumonia, not otherwise specified
Co-existing conditions		
Smoking	ICD-10	Z87.891 Personal history of nicotine dependence
Prior encounter for antineoplastic radiation therapy	ICD-10	Z51.0 Encounter for antineoplastic radiation therapy
History of acute radiation pneumonitis	ICD-10	J70.0 Acute pulmonary manifestations due to radiation
History of chronic obstructive pulmonary disease	ICD-10	J44 other chronic obstructive pulmonary disease
History of asthma	ICD-10	J45 asthma
History of pleural disease	ICD-10	J90-J94 Other diseases of the pleura
Medications		
Prednisone	RxNorm	8640 prednisone
Methylprednisolone	RxNorm	6902 methylprednisolone
Antimicrobials	RxNorm	AM000 antimicrobials
3 rd generation cephalosporins	RxNorm	AM117 cephalosporin 3 rd generation
4 th generation cephalosporins	RxNorm	AM118 cephalosporin 4 th generation
Piperacillin	RxNorm	8339 piperacillin
Macrolides	RxNorm	AM100 erythromycins/macrolides
Infliximab	RxNorm	191831 infliximab
Cyclophosphamide	RxNorm	3002 cyclophosphamide

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Mycophenolate mofetil	RxNorm	265323 mycophenolate 68149 mycophenolate mofetil
Intravenous immune globulin	RxNorm	5666 immunoglobulin G
Procedures		
Bronchoscopy	CPT	1005899 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed
Healthcare Services		
Emergency department visit	TriNetX	Visit: Emergency
Hospitalization	TriNetX	Visit: Inpatient Encounter Visit: Inpatient Non-acute Visit: Short Stay
	CPT	1013659 Hospital Inpatient Services 1013729 Critical Care Services
Critical Care Services	CPT	31500 Intubation, endotracheal, emergency procedure 1013729 Critical Care Services 95420-6 Whether the patient was admitted to intensive care unit (ICU) for condition of interest

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Supplemental Table S2: Pneumonitis/pneumonia incidence in patients with lung cancer by code group

N = 13,113		1 month	3 months	6 months	9 months	12 months	Relative risk (95% CI) at 12 months	P-value
Composite Pneumonitis/Pneumonia (all codes)	Chemotherapy/targeted therapy	964 (7.4)	1,545 (11.8)	2,044 (15.6)	2,357 (18.0)	2,564 (19.6)	1.13 (1.08 – 1.18)	<0.0001
	ICI	969 (7.4)	1,593 (12.1)	2,234 (17.0)	2,614 (19.9)	2,890 (22.0)		
Drug-induced respiratory conditions (J70.2, 3, 4, 8, 9)	Chemotherapy/targeted therapy	10 (0.1)	19 (0.1)	30 (0.2)	38 (0.3)	43 (0.3)	4.00 (2.87 – 5.58)	<0.0001
	ICI	17 (0.1)	60 (0.5)	108 (0.8)	144 (1.1)	172 (1.3)		
Interstitial lung disease (J84.11, 89, 9)	Chemotherapy/targeted therapy	32 (0.2)	78 (0.6)	135 (1.0)	165 (1.3)	184 (1.4)	1.16 (0.96 – 1.41)	0.13
	ICI	36 (0.3)	81 (0.6)	140 (1.1)	182 (1.4)	214 (1.6)		
Pneumonia (J18.9)	Chemotherapy/targeted therapy	942 (7.2)	1,497 (11.4)	1,983 (15.1)	2,284 (17.4)	2,484 (18.9)	1.13 (1.07 – 1.18)	<0.0001
	ICI	947 (7.2)	1,546 (11.8)	2,167 (16.5)	2,535 (19.3)	2,801 (21.4)		

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Supplemental Table S3: Baseline characteristics of propensity score-matched cancer cohorts

Demographic data was obtained from coded TriNetX data. Type of ICI counts patients who received both a PD-1 or PD-L1 inhibitor at any point in both categories. Line of therapy data was not available for every patient. Tables are included for A) Renal cell carcinoma (RCC), B) Gastrointestinal (GI) cancers, and C) Melanoma

* Starred variables were used for propensity score matching.

A) Renal cell carcinoma

Characteristic	Matched	
	Chemotherapy/ targeted therapy- treated controls	ICI-treated cases
N	1,845	1,845
Demographics		
Age at Index* - Mean (SD)	65.6 (11.5)	65.5 (11.7)
Male sex* – no. (%)	1,284 (69.6)	1,285 (69.6)
Race* – no. (%)		
White	1,392 (75.4)	1,384 (75.0)
Black/African American	156 (8.5)	152 (8.2)
Asian	22 (1.2)	27 (1.5)
American Indian/Native American	≤10 (0.5)	≤10 (0.5)
Native Hawaiian/Pacific Islander	≤10 (0.5)	≤10 (0.5)
Unknown	270 (14.6)	273 (14.8)
Cancer		
Secondary Malignancy* – no. (%)		
Lymph nodes	298 (16.2)	322 (17.5)
Respiratory/digestive	783 (42.4)	774 (42.0)
Other	882 (47.8)	874 (47.4)
Neuroendocrine tumor	≤10 (0.5)	≤10 (0.5)
Type of therapy		
PD-1	–	1,845 (100.0)
PD-L1	–	≤10 (0.5)
Chemotherapy	66 (3.6)	137 (7.4)
Targeted therapy	1845 (100.0)	709 (38.4)
Line of Therapy* – no. (%)		
1 st line	1,349 (73.1)	1,400 (75.9)
2 nd line	203 (11.0)	154 (8.3)
3 rd and above	52 (2.8)	68 (3.7)
Co-existing conditions		
Personal history of nicotine dependence*	324 (17.6)	368 (19.9)
Prior encounter for antineoplastic radiation therapy*	71 (3.8)	85 (4.6)
History of acute radiation pneumonitis*	≤10 (0.5)	≤10 (0.5)
History of prior lung disease*		
Chronic obstructive pulmonary disease	118 (6.4)	124 (6.7)
Asthma	64 (3.5)	77 (4.2)
Pleural disease	209 (11.3)	194 (10.5)

B) Gastrointestinal cancers

Characteristic	Matched	
	Chemotherapy/ targeted therapy- treated controls	ICI-treated cases
N	4,813	4,813
Demographics		
Age at Index* - Mean (SD)	65.5 (11.5)	65.0 (12.5)
Male sex* – no. (%)	2,965 (61.6)	3,029 (62.9)

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Race* – no. (%)		
White	3,450 (71.7)	3,385 (70.3)
Black/African American	503 (10.5)	549 (11.4)
Asian	172 (3.6)	157 (3.3)
American Indian/Native American	30 (0.6)	25 (0.5)
Native Hawaiian/Pacific Islander	≤10 (0.2)	0 (0)
Unknown	655 (13.6)	697 (14.5)
Cancer		
Secondary Malignancy*– no. (%)		
Lymph nodes	1,024 (21.3)	1,047 (21.8)
Respiratory/digestive	2,135 (44.4)	2,078 (43.2)
Other	1,662 (34.5)	1,566 (32.5)
Neuroendocrine tumor	56 (1.2)	51 (1.1)
Type of therapy		
PD-1	–	4,813 (100.0)
PD-L1	–	14 (0.3)
Chemotherapy	4,328 (89.9)	2,499 (51.9)
Targeted therapy	531 (11.0)	680 (14.1)
Line of Therapy* – no. (%)		
1 st line	471 (9.8)	722 (15.0)
2 nd line	1,750 (36.4)	1,330 (27.6)
3 rd and above	567 (11.8)	748 (15.5)
Co-existing conditions		
Personal history of nicotine dependence*	1,158 (24.1)	1,141 (23.7)
Prior encounter for antineoplastic radiation therapy*	279 (5.8)	297 (6.2)
History of acute radiation pneumonitis*	≤10 (0.2)	≤10 (0.2)
History of prior lung disease*		
Chronic obstructive pulmonary disease	468 (9.7)	470 (9.8)
Asthma	209 (4.3)	227 (4.7)
Pleural disease	633 (13.2)	632 (13.1)

C) Melanoma

Characteristic	Matched	
	Chemotherapy/ targeted therapy- treated controls	ICI-treated cases
N	2,427	2,427
Demographics		
Age at Index* - Mean (SD)	61.9 (14.1)	61.8 (15.5)
Male sex* – no. (%)	1,405 (57.9)	1,413 (58.2)
Race* – no. (%)		
White	1,982 (81.7)	2,001 (82.4)
Black/African American	39 (1.6)	35 (1.4)
Asian	≤10 (0.4)	≤10 (0.4)
American Indian/Native American	≤10 (0.4)	≤10 (0.4)
Native Hawaiian/Pacific Islander	0 (0)	≤10 (0.4)
Unknown	396 (15.3)	379 (15.6)
Cancer		
Secondary Malignancy*– no. (%)		
Lymph nodes	791 (32.6)	757 (31.2)
Respiratory/digestive	671 (27.6)	716 (29.5)
Other	1,223 (50.4)	1,252 (51.6)
Neuroendocrine tumor	15 (0.6)	13 (0.5)
Type of therapy		
PD-1	–	2,412 (99.4)
PD-L1	–	15 (0.6)
Chemotherapy	1,104 (45.5)	200 (8.2)
Targeted therapy	1,323 (54.5)	124 (5.1)
Line of Therapy* – no. (%)		
1 st line	1,734 (71.4)	1,715 (70.7)
2 nd line	234 (9.6)	262 (10.8)
3 rd and above	119 (4.9)	108 (4.5)
Co-existing conditions		

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Personal history of nicotine dependence*	380 (15.7)	335 (13.8)
Prior encounter for antineoplastic radiation therapy*	113 (4.7)	123 (5.1)
History of acute radiation pneumonitis*	≤10 (0.4)	≤10 (0.4)
History of prior lung disease*		
Chronic obstructive pulmonary disease	124 (5.1)	121 (5.0)
Asthma	123 (5.1)	116 (4.8)
Pleural disease	217 (8.9)	225 (9.3)