CHECKPOINT INHIBITOR USE AND THE OCCURRENCE OF INSULIN-DEPENDENT OR DRUG-INDUCED DIABETES: WHAT CAN WE LEARN FROM REAL WORLD DATA?

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OBJECTIVES

The aims of this analysis were as follows:

- **Aim One.** Understand the lines of treatment (LOT) within the checkpoint inhibitor (CPI) class of drugs
- **Aim Two.** Assess the risk of insulin-dependent or drug-induced diabetes (IDDID) among patients treated with a CPI
- **Aim Three.** Examine comorbidities prior to the diagnosis of IDDID.

METHODS

U.S. patients were identified through the TNX platform, a federated network of electronic medical records, and were required to have stage 3 or 4 lung, melanoma, or bladder cancer (Figure 1).

A LOT was initiated on the date the first CPI was recorded in the patients' record and each LOT lasted a minimum of 30-days. Other CPI treatments that occurred within the 30-day period were combined into a single LOT. A second LOT was initiated if a new CPI was recorded in the patients' record after the 30-day period.

To assess the risk of IDDID, patients treated with a CPI were matched 1-to-1 with patients treated with a targeted therapy (TT) other than a CPI, using a greedy-nearest-neighbor algorithm (Table 1). The risk of new-onset IDDID was measured 1-year following the date of the index treatment. IDDID was defined by ICD codes E09, E10, or a RxNorm code for insulin.

Comorbidities in the 3-months prior to the first diagnosis of IDDID were examined among CPI-treated patients.

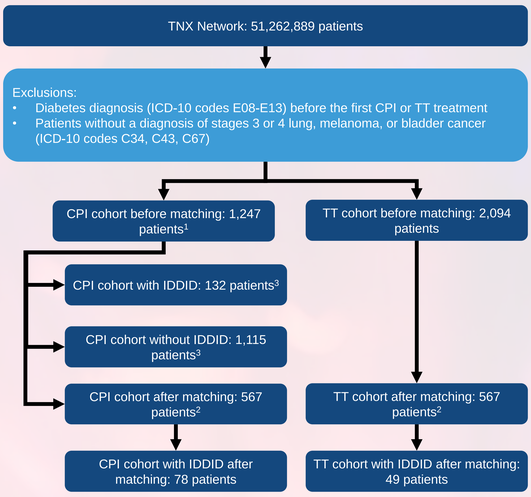

Figure 1. Patient flow diagram
[1]Cohort used to examine LOTs (Aim One). [2]Cohorts used to measure the occurrence of IDDID (Aim Two). [3]Cohorts used to compare differences between CPI patients with and without IDDID (Aim Three)

RESULTS FOR AIM ONE

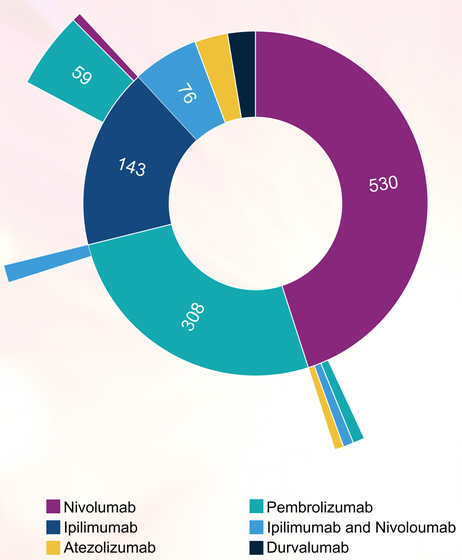

Figure 2. Sunburst diagram of first- and second-line CPIs
Sixteen patients treated with a combination of CPIs or a third line CPI were not displayed in the sunburst diagram because the prevalence of these treatments was less than 1% of the treated cohort.

RESULTS FOR AIM TWO

	Before Matching		After Matching	
	CPI	TT	CPI	TT
Total number of patients	1,247	2,094	567	567
Mean age (SD)	63.5 (11.3)	61.8 (12.3)	63.5 (11.1)	63.3 (11.6)
Female	47%	53%	48%	50%
White	87%	79%	86%	87%
Black or African American	9%	9%	9%	9%
Asian	1%	5%	2%	2%
Hispanic or Latino	1%	4%	1%	2%
Diseases of the circulatory system	61%	49%	61%	63%
Metabolic disorders	43%	33%	43%	43%
Hypertensive diseases	36%	32%	37%	38%
Malaise and fatigue	26%	16%	24%	24%
Disorders of lipoprotein metabolism and other lipidemias	23%	20%	23%	24%
Disorders of thyroid gland	16%	10%	15%	16%
Other hypothyroidism	12%	7%	11%	11%
Disorders of other endocrine glands	11%	8%	10%	11%
Osteoarthritis	9%	7%	9%	10%
Noninfective enteritis and colitis	7%	5%	7%	7%
Other and unspecified noninfective gastroenteritis and colitis	6%	5%	6%	6%
Disorders of gallbladder, biliary tract and pancreas	7%	5%	6%	6%
Elevated blood glucose level	5%	4%	5%	5%
Overweight, obesity and other hyperalimentation	5%	3%	4%	4%
Other inflammatory liver diseases	2%	1%	2%	2%
CNS medications	94%	78%	94%	95%
Dermatological medications	95%	71%	94%	94%
Ophthalmic agents	94%	74%	93%	94%
Gastrointestinal medications	90%	74%	90%	91%
Respiratory tract medications	90%	68%	90%	92%
Nasal and throat medications	90%	66%	89%	90%
Therapeutic nutrients	88%	63%	87%	89%
Surgery procedures	80%	60%	79%	81%
Pathology and laboratory procedures	12%	5%	10%	11%
Radiation Therapy	5%	7%	5%	6%

Table 1. Patient characteristics before and after matching
All standardized mean differences were less than 10% after matching.

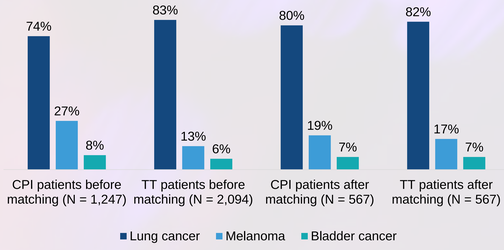

Figure 3. Cancer diagnoses by treatment group
All standardized mean differences were less than 10% after matching. Percentages do not sum to 100% because a subset of patients were diagnosed with more than one type of cancer.

After controlling for confounding, patients treated with a CPI were 1.6 (95% CI) times as likely to develop IDDID than TT-treated patients.

RESULTS FOR AIM THREE

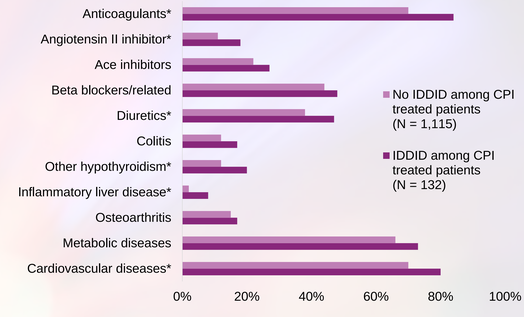

Figure 4. Comorbidities prior to diagnosis of IDDID among CPI-treated patients
*p<0.05 based on Chi-square statistic

CONCLUSIONS

Patients with advanced stage lung, melanoma, and/or bladder cancer who were treated with a CPI were at increased risk of IDDID in the year following treatment. Although IDDID is not a common adverse event, CPI-treated patients who go on to be diagnosed with IDDID represent a patient population with a significant disease burden. CPI-treated patients were more likely to have a history of cardiovascular disease, liver disease, or hypothyroidism and more likely to have a history of being treated with cardiovascular medications. The inclusions of insulin medication in the definition of IDDID likely overestimates the occurrence of the outcome as some patients may be treated with insulin potentiation therapy (IPT) after a diagnosis of advanced cancer. However, IPT is not likely to differ between patients treated with a CPI vs other TT.