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Immune Checkpoint Inhibitors and Risk of Type 1 Diabetes

Xuan Chen,[1] Alison H. Affinati,[2] Yungchun Lee,[1] Adina F. Turcu,[2] Norah Lynn Henry,[3] Elena Schiopu,[3] Angel Qin,[3] Megan Othus,[4] Dan Clauw,[5] Nithya Ramnath,[3,6] and Lili Zhao[1]

OBJECTIVE

Type 1 diabetes mellitus (T1DM) is a rare, irreversible immune-related adverse event reported in patients receiving treatment with immune checkpoint inhibitors (ICI). However, clinical risk factors for ICI-induced T1DM (ICI-T1DM) and its impact on survival in patients remain unknown.

RESEARCH DESIGN AND METHODS

We used Optum's Clinformatics Data Mart database for assessment of the incidence and characteristics of T1DM in a large de-identified cohort of patients treated with ICI between 2017 and 2020. We applied Fine-Gray and cause-specific hazard models to study associations between patient/treatment characteristics and ICI-T1DM and applied the Cox model with ICI-T1DM as a time-varying covariate to assess the impact of ICI-T1DM on survival.

RESULTS

ICI-T1DM was observed in 261 of 30,337 (0.86%) patients. Dual use of antibodies to cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) was associated with increasing risk of ICI-T1DM (hazard ratio [HR] 1.62; 95% CI 1.15–2.26) vs. anti–PD-L1 or anti–PD-1 alone. Younger age (HR 1.19 for every 5-year decrease; 95% CI 1.13–1.25) and preexisting non-T1DM diabetes (HR 4.48; 95% CI 3.45–5.83) were also associated with higher risk of ICI-T1DM. Conversely, prior use of immunosuppressive medications (HR 0.57; 95% CI 0.34–0.95) was associated with lower incidence of ICI-T1DM, but part of its protective effect may be due to the increased mortality rate. Development of ICI-T1DM does not seem to significantly impact patient survival.

CONCLUSIONS

The risk of ICI-T1DM is associated with the type of ICI therapy, patient age, and preexisting non-T1DM diabetes. These data may help guide risk assessment and screening practices for patients during ICI therapy.

Immune checkpoint inhibitors (ICI), including anti–cytotoxic T lymphocyte antigen 4 (CTLA-4), anti–programmed cell death 1 (PD-1), and anti–programmed cell death ligand 1 (PD-L1) antibodies, have revolutionized cancer treatment. Treatment with ICI therapy has improved survival in multiple malignancies, including previously treatment refractory cancers such as melanoma and lung cancer. ICI release the brakes on the immune system, allowing immune cells to detect and destroy tumor cells. With reactivation of T cells, however, ICI are associated with many immune-related adverse events, including autoimmune-like disorders. Autoimmune endocrinopathies

[1]Department of Biostatistics, University of Michigan, Ann Arbor, MI
[2]Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI
[3]Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[4]Biostatistics and Biomathematics Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Ann Arbor, MI
[5]Department of Anesthesiology, University of Michigan, Ann Arbor, MI
[6]Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI

Corresponding author: Lili Zhao, zhaolili@umich.edu

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associated with ICI have been reported in up to 4–30% of patients, with thyroid disorders being the most common (1–4). ICI-induced type 1 diabetes mellitus (ICI-T1DM) is a rare, but potentially life-threatening complication that occurs in 0.6–1.4% of patients receiving ICI (5–7).

ICI-T1DM is characterized by rapid β-cell destruction, which can occur as early as 5 days after ICI initiation and up to several months after ICI discontinuation (8–11). Of patients diagnosed with ICI-T1DM, 40–76% present with diabetic ketoacidosis (DKA), often requiring intensive care unit treatment (5,8,9,11–14), and almost all will require lifelong insulin therapy (8,9,12). To date, the focus of most studies with identification of risk factors for developing ICI-T1DM has been on clinical and laboratory data, such as HLA haplotype and autoantibody presence, which are typically not available to the clinician at the time of ICI initiation (10,12,15); in other studies investigators have relied on pooled data from ICI randomized controlled trials, which exclude patients at potentially higher risk of adverse events (16). To address these gaps, we used a national insurance claims database for assessment of incidence of ICI-T1DM, clinically available characteristics of patients with ICI-T1DM, and impact on survival of ICI-T1DM in a large cohort of patients treated with ICI.

RESEARCH DESIGN AND METHODS

Database and Data Extraction

We studied a de-identified cohort of Optum's Clinformatics Data Mart, which captures a privately insured population from a diverse group of health plans in the U.S. We included patients who were treated with pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, ce miplimab, or ipilimumab between 2017 and 2020 and who had at least 12 mon ths of medical records available prior to the start of ICI. We identified patients with T1DM based on ICD-10 diagnosis codes under the category of E10. We first removed patients who had at least one ICD-10 code of T1DM prior to the start of ICI and then identified patients who had ICI-T1DM based on two outpatient ICD-10 codes of T1DM at least 30 days apart or one inpatient ICD-10 code of T1DM occurring after ICI therapy (17). The onset date of T1DM was defined as the earliest date of all ICD-10 codes of T1DM. Patients who did not die were censored at the date of last follow-up. Patient characteristics recorded included age; sex; race; smoking status (former and current smoker vs. nonsmoker); ICI type (anti–CTLA-4, anti–PD-L1/anti–PD-1, or anti–CTLA-4 + anti–PD-1/anti–PD-L1); prior use of immunosuppressant medications, including traditional and biologic disease-modifying antirheumatic drug and glucocorticoids (Supplementary Table 1) within 3 months prior to the start of ICI; and Elixhauser Comorbidity Index (CMI) score (18), calculated with use of diagnosis codes in the 12-month history before ICI treatment. Specifically, we defined a combination of anti–CTLA-4 and anti–PD1/PD-L1 if both treatments were administered before ICI-T1DM for patients with ICI-T1DM, or before the last follow up for patients without ICI-T1DM, regardless of the proximity or order in which they were prescribed. We defined immunosuppressive drugs as traditional and biologic disease-modifying antirheumatic drug or glucocorticoids at supraphysiological doses (see Supplementary Table 2) for at least 30 days (19). Historically, the immunosuppressive effects of steroids are dose dependent, but it is not entirely clear whether glucocorticoids at lower doses have some immunosuppressive effects. Therefore, for differentiation of this group from the group not taking immunosuppressants, patients taking glucocorticoids at lower doses, or for shorter periods of time, were grouped as a separate category ("low-dose glucocorticoids").

Statistical Analysis

Clinical characteristics were reported by ICI-TIDM status with categorical variables expressed as frequency and continuous variables expressed as median (range). Fine-Gray (FG) (20) and cause-specific hazard (CS) models were used to assess effects of patient/treatment characteristics on the risk of ICI-T1DM. The FG model estimates the effect of covariates on the subdistribution hazard function. Hence, significant effects of the covariates in this model can be interpreted as influencing the cumulative incidence function. The CS model estimates the effect of covariates on the hazard rate of ICI-T1DM in subjects who are still alive. The FG and CS models are based on different model assumptions and provide different interpretations. The two analyses complement each other. We implemented the CS model using the conventional Cox proportional hazards model by treating death as censoring and the FG model using cmprsk package in R. Time-varying Cox model (ICI-T1DM as a time-varying covariate and other patient characteristics as time-fixed covariates) was used to evaluate the impact of ICI-T1DM on patient survival (21). Missing data were assumed to be random and were excluded or considered as a separate category in the analyses. Statistical significance is determined with P value <0.05.

RESULTS

Incidence and Presentation of ICI-T1DM

Based on the entry criteria, we identified 30,337 patients treated with ICI between 2017 and 2020, with a median follow-up time of 308 days. ICI-T1DM was observed in 261 patients (0.86%). The median time from ICI initiation to T1DM diagnosis was 10 weeks (range 1–95). Of the 261 patients, 78 (29.9%) presented with DKA, 76 (97.4%) of whom were hospitalized. Among the 97 patients with no prior history of diabetes, and who were thus unlikely to be checking blood glucose levels on a regular basis prior to ICI-T1DM diagnosis, 47 (48.4%) presented with DKA. Additionally, eight (3.1%) patients presented with pancreatitis, all of whom were hospitalized.

Factors Associated With ICI-T1DM

On univariate analysis based on the FG model (Table 1), Black race (hazard ratio [HR] 1.53; 95% CI 1.07–2.19) and preexisting diagnosis of other types of diabetes, including type 2 diabetes mellitus (T2DM) and ketosis-prone diabetes (HR 5.28; 95% CI 3.91–7.12), were associated with a higher incidence of ICI-T1DM. Combination therapy (anti–CTLA-4 + anti–PD-1/PD-L1) increased the risk of ICI-T1DM compared with anti–PD-1/PD-L1 monotherapy (HR 1.93; 95% CI 1.40–2.66). Younger age (HR 1.12 for every 5-year decrease; 95% CI 1.08–1.18) was also associated with higher risk of ICI-T1DM. Conversely, a higher comorbidity index ($\geq$5 vs $<$5: HR 0.48; 95% CI 0.28–0.83) was associated with lower risk of ICI-TIDM, and prior use of immunosuppressive drugs (HR 0.61; 95% CI 0.27–1.00) was marginally associated with lower risk

Table 1—Univariate FG model for effects of patient/treatment characteristics on incidence of ICI-T1DM

	T1DM		FG model	
	Yes (n = 261)	No (n = 30,076)	HR (95% CI)	P
Age, years, median (range)	70 (19–89)	72 (4–90)	0.89 (0.85, 0.93)*	<0.0001
≤60	52	4,317	Reference	
>60	209	25,759	0.65 (0.48, 0.88)	0.006
Tumor type				
Melanoma	39	4,042	Reference	
Lung	124	15,711	0.81 (0.56, 1.16)	0.25
Both	14	1,398	1.04 (0.57, 1.92)	0.89
Other	84	8,808	1.00 (0.69, 1.47)	0.99
NA	117	0		
ICI types				
Anti–PD-1/PD-L1	215	27,133	Reference	
Anti–CTLA-4	1	83	1.50 (0.21, 10.69)	0.69
Anti–PD-1/PD-L1 + anti–CTLA-4	45	2,880	1.93 (1.40, 2.66)	0.0001
Sex				
Male	151	16,846	Reference	
Female	110	13,225	0.93 (0.73, 1.19)	0.55
NA	0	5		
Race				
White	162	19,970	Reference	
Black	37	2,968	1.53 (1.07, 2.19)	0.019
Asian	8	708	1.41 (0.69, 2.86)	0.35
Hispanic	20	2,005	1.25 (0.78, 1.98)	0.35
NA	34	4,425		
Weighted CMI				
<5	14	795	Reference	
≥5	233	28,552	0.48 (0.28, 0.83)	0.008
NA	34	4,425		
Diabetes before ICI				
No	97	21,339	Reference	
Yes	150	8,008	5.28 (3.91, 7,12)	<0.0001
NA	14	729		
Smoking				
No	64	8,483	Reference	
Yes	197	21,593	1.19 (0.90, 1.58)	0.23
Immunosuppressant†				
No	214	22,517	Reference	
Low-dose glucocorticoids	30	4,584	0.70 (0.48, 1.03)	0.072
Immunosuppressive drugs	17	2,975	0.61 (0.37, 1.00)	0.051

*Denotes the HR for every 5-year increase in age. †Use of immunosuppressant medications within 3 months prior to the start of ICI. NA represents missing data.

of ICI-TIDM. Conclusions in the CS model were the same (data not shown).

In multivariable analysis with the FG model, younger age (HR 1.19 for every 5-year increase; 95% CI 1.13–1.25), prior diagnosis of other forms of diabetes (HR 4.48; 95% CI 3.45–5.83), and use of combination ICI therapy (comparing anti–CTLA-4 + anti–PD-1/PD-L1 with anti–PD-1/PD-L1) (HR 1.71; 95% CI 1.23–2.39) remained associated with higher risk of ICI-T1DM (Table 2). Prior use of immunosuppressive drugs was associated with lower risk (HR 0.57; 95% CI 0.34–0.95) of ICI-T1DM, while use of low-dose glucocorticoids seems to be associated with a reduced risk of ICI-T1DM, but it did not reach statistical significance (HR 0.72; 95% CI 0.49–1.06).

Age, prior diagnosis of other forms of diabetes, and use of combination ICI therapy remained significant in the CS model, indicating that these factors influenced both the incidence and CS of ICI-T1DM. However, the effect of prior use of immunosuppressive drugs on risk of ICI-T1DM became nonsignificant (HR 0.67; 95% CI 0.40–1.11). As we found that prior use of immunosuppressive drugs was associated with a higher mortality rate (HR 1.67; 95% CI 1.59–1.76 [based on CS model]), different results from the FG and CS models suggest that part of the protective effect of the prior use of immunosuppressive drugs on diagnosis of ICI-T1DM is due to the increased mortality rate, preventing ICI-T1DM from being observed.

ICI-T1DM and Survival

Of the 30,337 patients, 15,359 (50.63%) died during 2017–2020, and of these, 143 died after diagnosis of ICI-T1DM. Occurrence of T1DM following ICI had

Table 2—Multivariable FG and CS models for effects of patient/treatment characteristics on incidence of ICI-T1DM

	FG model		CS model	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (unit = 5 years)	0.84 (0.80, 0.89)	<0.0001	0.85 (0.80, 0.90)*	<0.0001
ICI types				
Anti–PD-1/PD-L1	Reference		Reference	
Anti–CTLA-4	1.46 (0.21, 10.33)	0.70	1.40 (0.20, 10.07)	0.74
Anti–PD-1/PD-L1 + anti–CTLA-4	1.71 (1.23, 2.39)	0.0016	1.61 (1.15, 2.26)	0.0055
Sex				
Male	Reference		Reference	
Female	1.05 (0.81, 1.35)	0.74	1.02 (0.79, 1.32)	0.88
Race/ethnicity				
White	Reference		Reference	
Black	1.25 (0.87, 1.81)	0.23	1.25 (0.86, 1.81)	0.24
Asian	1.10 (0.51, 2.35)	0.81	1.09 (0.51, 2.33)	0.83
Hispanic	1.03 (0.64, 1.67)	0.89	1.04 (0.64, 1.68)	0.87
Weighted CMI				
<5	Reference		Reference	
≥5	0.61 (0.35, 1.05)	0.072	0.69 (0.40, 1.18)	0.17
Diabetes before ICI				
No	Reference		Reference	
Yes	4.48 (3.45, 5.83)	<0.0001	4.66 (3.58, 6.06)	<0.0001
Smoking				
No	Reference		Reference	
Yes	1.27 (0.94, 1.72)	0.12	1.29 (0.96, 1.74)	0.091
Immunosuppressant†				
No	Reference		Reference	
Low-dose glucocorticoids	0.72 (0.49, 1.06)	0.091	0.75 (0.51, 1.10)	0.15
Immunosuppressive drugs	0.57 (0.34, 0.95)	0.031	0.67 (0.40, 1.11)	0.12

†Use of immunosuppressant medication within 3 months prior to the start of ICI.

no significant impact on overall survival in univariate (Fig. 1) or multivariable analysis after adjustment for age, sex, race, cancer type, ICI type, CMI, smoking status, and prior use of immunosuppressants (Table 3).

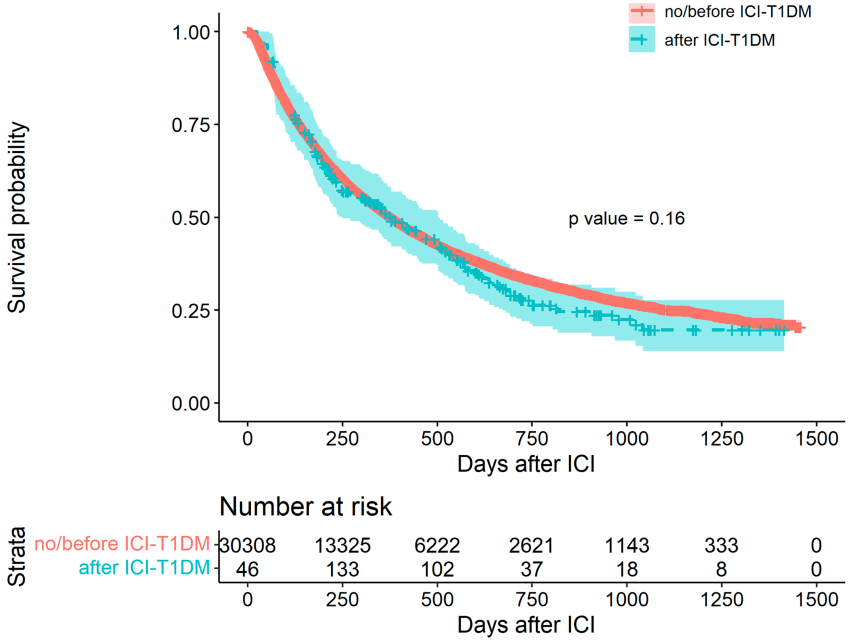

Figure 1—Kaplan-Meier curves for overall survival (ICI-TIDM is a time-varying covariate).

Older age (HR 1.07; 95% CI 1.06–1.08), male sex (HR 1.12; 95% CI 1.08–1.16), higher CMI (>5 vs. ≤5, HR 1.53; 95% CI 1.36–1.73), smoking (HR 1.13; 95% CI 1.08–1.18), lung cancer (HR 1.70; 95% CI 1.59–1.81), prior use of immunosuppressive drugs (HR 1.63; 95% CI 1.55–1.72), use of low-dose glucocorticoids (HR 1.21; 95% CI 1.15–1.27), and presence of other types of diabetes prior to ICI therapy (HR 1.12; 95% CI 1.08–1.16) were associated with shorter survival.

CONCLUSIONS

To our knowledge, this is the largest study of ICI-induced T1DM and the first using U.S.-based insurance claims data to evaluate potential risk factors that would be available at the time of ICI treatment initiation. Insurance claims data present a cost-effective way to study rare adverse events such as ICI-T1DM, providing tremendous analytical flexibility that is not possible even with large epidemiologic cohorts. We found that the risk of ICI-T1DM is low (0.86%), and >30% patients

Table 3—Multivariable time-varying Cox regression for effect of ICI-T1DM on overall survival

	HR (95% CI)	*P*
T1DM	1.14 (0.95, 1.37)	0.16
Age (unit = 5 years)	1.07 (1.06, 1.08)	<0.0001
ICI types		
Anti–PD-1/PD-L1	Reference	
Anti–CTLA-4	0.73 (0.49, 1.08)	0.11
Anti–PD-1/PD-L1 + anti–CTLA-4	0.89 (0.84, 0.95)	0.0003
Tumor type		
Melanoma	Reference	
Lung	1.70 (1.59, 1.81)	<0.0001
Both	1.70 (1.55, 1.87)	<0.0001
Other	1.81 (1.70, 1.93)	<0.0001
Sex		
Male	Reference	
Female	0.89 (0.86, 0.92)	<0.0001
Race		
White	Reference	
Black	0.99 (0.94, 1.07)	0.64
Asian	0.98 (0.88, 1.09)	0.69
Hispanic	0.94 (0.88, 1.01)	0.07
Weighted CMI		
<5	Reference	
≥5	1.53 (1.36, 1.73)	<0.0001
Diabetes before ICI		
No	Reference	
Yes	1.12 (1.08, 1.16)	<0.0001
Smoking		
No	Reference	
Yes	1.13 (1.08, 1.18)	<0.0001
Immunosuppressant†		
No	Reference	
Low-dose glucocorticoids	1.21 (1.15, 1.27)	<0.0001
Immunosuppressive drugs	1.63 (1.55, 1.72)	<0.0001

†Use of immunosuppressant medication within 3 months prior to the start of ICI.

with ICI-T1DM present with serious acute complications, such as DKA or pancreatitis, and both complications often require hospitalization.

Our study found that dual ICI therapy increased the risk of developing T1DM-ICI, which is consistent with prior case reports of patients who developed fulminant diabetes after receiving both anti–CTLA-4 and anti–PD-1/anti–PD-L1 treatment (8,9,22). While anti–PD-1 therapy has previously been linked to ICI-T1DM, less is known about dual ICI use. PD-1 promotes islet-specific tolerance, while PD-1 inactivation has been linked to autoreactive T-cell activation in mouse models of autoimmune diabetes (23,24). CTLA-4 has not been linked with β-cell tolerance or T1DM specifically but, rather, affects T-cell activation through a pathway different from that of PD-1 (25,26). As anti–PD-1 and anti–CTLA-4 therapies target different components of the T-cell response, dual use of both types of therapy may lead to a two-hit model in which CTLA-4 inhibition increases T-cell activation and PD-1 inhibition leads to β-cell–specific targeting.

The average age of patients who developed ICI-T1DM in our analysis was 68 years, consistent with prior studies. As others have noted, age at diagnosis of ICI-T1DM is significantly higher than what is typically seen in T1DM, likely reflecting the patient population that receives ICI (8,10–12). Because our data set includes a large population with a wide range of ages (4–90 years), we were able to identify younger age as a risk factor for developing ICI-T1DM, which has not previously been shown. While it is unclear why younger age increases risk for ICI-T1DM, this finding may be an important part of risk assessment in initiating ICI.

The results of our analysis demonstrate that patients with a history of T2DM and other types of diabetes prior to ICI initiation had an increased risk of developing ICI-T1DM, as previously suggested in several case reports (9). While the underlying cause of T2DM is insulin resistance, patients with long-standing T2DM have decreased β-cell mass and β-cell failure (27–29). Similarly, most diagnoses coded within E13 ("other specified diabetes mellitus") are due to non-immune-mediated insulin deficiency. Thus, even a small amount of ICI-mediated β-cell destruction may result in profound insulin deficiency, DKA, and de novo insulin requirement in patients with underlying T2DM or other forms of diabetes. Others have hypothesized that some patients with a history of T2DM who subsequently develop ICI-T1DM may have latent autoimmune diabetes of adults with anti-GAD antibodies, predisposing them ICI-T1DM (30). While worsening of T2DM and other types of diabetes could conceivably be miscoded as T1DM, our entry criterion of two T1DM codes 30 days apart makes this less likely.

In contrast to early reports identifying White race to be associated with the highest risk of ICI-T1DM (11,31), we found that ICI-T1DM was more likely to occur in the case of Black race in our univariate analysis. However, after controlling for confounders, such as age, sex, and prior history of T2DM, this association was no longer significant. T2DM is more common in African Americans in the U.S. (32), and we also observed an increased risk of ICI-T1DM in patients with a history of T2DM. Therefore, the high prevalence of T2DM for Black race is the likely explanation for the significant finding in the unadjusted univariate analysis.

Another finding in our study is that prior immunosuppressive therapy decreased the risk of developing ICI-T1DM. With further analysis we found that part of the reason for this protective effect might be the increased mortality rate. To our knowledge, this is the first effort to explore the role of prior immunosuppression in this patient population. Our observation that the increased risk of prior immunosuppressive therapy on the mortality rate may be due to either the

effects of immunosuppressive therapies themselves, or the underlying disease that immunosuppressive therapies are treating, such as rheumatologic, pulmonary, gastrointestinal or endocrine disorders. However, identifying a specific autoimmune disease based on ICD-10 codes is challenging; therefore, additional studies will be needed to determine the mechanism through which a history of prior immunosuppressive therapy leads to increased mortality rate.

Study limitations include dependence on ICD-10 codes and lack of information on severity of adverse events and tumor stage. Due to these limitations, studying the effect of ICI-T1DM on patient survival is challenging, as survival is related to the severity of ICI-TIDM and cancer stage. Identifying a specific autoimmune disease based on ICD-10 codes is challenging; therefore, it is hard to tell whether the significant association between prior use of immunosuppressants and poor survival is due to the effect of medication or due to the underlying autoimmune disease that is not captured in our data.

Despite these limitations, our data provide important insights into ICI-T1DM. While the incidence of ICI-T1DM is low, the occurrence of DKA and pancreatitis can be life-threatening. Early identification through monitoring symptoms and glucose levels is important. Health care providers must be aware of this new form of T1DM in patients treated with ICI, and patient education on early hyperglycemia symptoms, such as hunger, thirst, and frequent urination, should be provided in high-risk populations prior to ICI initiation. HLA genotypes and other patient characteristics possibly serving as predictive biomarkers are the subject of ongoing studies.

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