Received: 3 June 2022 | Revised: 6 February 2023 | Accepted: 17 February 2023

DOI: 10.1002/cncr.34918

ORIGINAL ARTICLE

Association between diabetes mellitus and reduced efficacy of pembrolizumab in non–small cell lung cancer

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Abstract

Background: Diabetes mellitus (DM) is a highly prevalent chronic metabolic disorder. Although DM has been associated with immune dysfunction, the effect of DM on the efficacy of immunotherapy is unknown. This study aimed to evaluate the impact of DM on the efficacy of pembrolizumab in metastatic non–small cell lung cancer (NSCLC).

Methods: The authors reviewed the medical records of consecutive metastatic NSCLC patients treated with first-line pembrolizumab either alone or in combination with chemotherapy at a single tertiary center. For validation, a computerized data from Maccabi Healthcare Services, a 2.5–million-member state health service was used.

Results: Of the 203 eligible patients, 51 (25%) had DM. Patients with DM had a significantly shorter median progression-free survival (PFS) (5.9 vs. 7.1 months, p = .004) and overall survival (OS) (12 vs. 21 months, p = .006). The shorter OS in diabetic patients was more pronounced when pembrolizumab was given alone (12 vs. 27 months, p = .03) than when combined with chemotherapy (14.3 vs. 19.4 months, p = .06). Multivariate analysis confirmed DM as an independent risk factor for shorter PFS (hazard ratio [HR], 1.67; 95% confidence interval [CI], 1.11–2.50, p = .01) and OS (HR, 1.73; 95% CI, 1.09–2.76, p = .02). In a validation cohort of 452 metastatic NSCLC patients, the time on pembrolizumab treatment was shorter in diabetic patients (p = .025), with only 19.6% of patients remaining on treatment at 12 months compared to 31.7% of the nondiabetic patients.

Conclusions: This study suggests immunotherapy is less beneficial in diabetic NSCLC patients. More work is needed to verify our findings and explore similar effects in other cancer entities.

KEYWORDS
diabetes mellitus, immunotherapy, NSCLC, PD-1, pembrolizumab

INTRODUCTION

Immune checkpoint inhibitors (ICI) are used as the standard first-line treatment in patients with metastatic non–small cell lung cancer (NSCLC) that do not harbor targetable mutations. Nevertheless, many patients either do not respond or gain only a short-term benefit, with a median progression-free survival (PFS) that does not exceed a year.[1–3] Biomarkers are essential to tailor the treatment to each patient and prolong survival. Although tumor-related factors, including the expression of programmed death-ligand 1 (PD-L1) and tumor mutational burden (TMB) correlate to some extent with a response to ICI, factors related to host immunity are not well characterized.[4]

Type 2 diabetes mellitus is characterized by an increased blood glucose level due to insulin resistance followed by insufficient insulin production from pancreatic β cells.[5] Its incidence increases with age, reaching more than 20% above age 65.[6] Patients with diabetes mellitus (DM) often present with immune dysregulation. For example, a common feature of DM is an increased basal level of certain cytokines, including C-reactive protein and interleukin (IL)-6, suggestive of low-grade inflammation.[7,8] However, cytokine production in response to strong pathogenic immune stimuli such as lipopolysaccharides is diminished.[9–11] Moreover, immune cells from patients with DM have a reduced ability to migrate to inflamed tissue, produce reactive oxygen species, or perform phagocytosis.[10,12,13] Not surprisingly, diabetic patients exhibit increased susceptibility to infection including, skin, urinary tract, and pneumonia.[14–16]

DM has been identified as an independent factor associated with a higher incidence and a reduced survival in several malignancies, including colorectal, breast, endometrial, gallbladder, and hepatocellular.[17, 18] Although DM is not considered a risk factor for NSCLC, similar to the general population, over 20% of NSCLC patients are also expected to have DM. Moreover, a recent meta-analysis has indicated that DM negatively affects the survival of patients with NSCLC.[19] Antitumor immunity is emerging as one of a few mechanisms underlining this association. Studies in mice showed that high glucose levels lead to an increased tumor growth rate in immune-competent but not in immune-deficient animals. Mechanistically, preclinical studies suggest that hyperglycemia promotes immune evasion by increasing both CD8 T-cell dysfunction and the presence of protumorigenic macrophages.[20–22] A few studies suggest that diabetic patients exhibit altered expression patterns of immune checkpoints.[23,24] Taken together, the above studies raise the possibility that DM may reduce the efficacy of ICI. Indeed, a recent study suggested that DM impends the prognosis of NSCLC patients receiving a wide range of single-agent ICI given at advanced lines of treatment.[25] However, the effect of DM on the efficacy of current standard first-line treatment with either pembrolizumab alone or pembrolizumab combined with chemotherapy is unknown.[26]

In this study, we analyzed the association between DM and the outcome of metastatic NSCLC patients treated with first-line pembrolizumab, either alone or with chemotherapy. Our data indicate a clear correlation between DM and both shorter PFS and overall survival (OS).

MATERIALS AND METHODS

Setting and patients

The study was conducted at Tel Aviv Sourasky Medical Center, a tertiary cancer center in Israel. Consecutive patients receiving pembrolizumab were identified and electronic files of patients with metastatic NSCLC who had received pembrolizumab as a first-line treatment were reviewed. Excluded were patients who were lost to follow-up or had tumors harboring actionable mutations. Because a response to ICI requires several weeks to initiate,[27] we also excluded patients who had received only one cycle of treatment. The study was approved by the local ethics committee of the Tel Aviv Sourasky Medical Center institutional review board (0618-19 TLV).

Data review

The hospital's electronic medical records were reviewed, and clinical data including age, gender, pretreatment comorbidities, body mass index (BMI), smoking history, and Eastern Cooperative Oncology Group (ECOG) performance status were collected. We did not have access to pretreatment values of hemoglobin A_{1c} (HbA_{1c}). Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) below 45. Tumor histology was divided into three categorical groups: adenocarcinoma, squamous carcinoma, and NSCLC not otherwise specified (NOS) which included poorly differentiated carcinoma and large cell carcinoma. Tumors were defined as PD-L1 high if more than 50% of the tumor cells were stained positive by immunohistochemistry using the 22C3 pharmDx test (Dako). Best overall response and PFS were evaluated based on radiological reports of patients' computed tomography (CT) or positron emission tomography (PET)-CT as documented in the electronic medical records. PFS was calculated from the first day of pembrolizumab treatment to the date of progression or death. OS was calculated from the first day of pembrolizumab treatment to death. Data on patients who were still alive at the time of data analysis were censored at the date of their last hospital visit.

Statistical analysis

We applied descriptive statistics reflecting the mean and confidence interval (CI) for continuous variables and frequency for categorical variables. Continuous variables were compared using

the Mann-Whitney test and categorical variables using the χ^2 test. PFS and OS were estimated by the Kaplan–Meier method. The log-rank test was used to examine whether there was a significant difference between diabetic and nondiabetic patients. Cox proportional hazards regression model was performed to investigate the influence of diabetes on PFS and OS adjusted for demographic (age, gender, BMI, and smoking), and clinical (cancer treatment, histology, ECOG, hypertension status, presence of ischemic heart disease [IHD], and CKD) characteristics of the patients. For statistical analyses we used Prism, SPSS, and SAS software.

Validation cohort

Newly diagnosed metastatic NSCLC patients (at least 18 years of age at diagnosis and had at least 1 year of continuous health care enrollment in Maccabi Healthcare Services [MHS]) with negative or unknown EGFR driver mutations, who initiated first-line pembrolizumab treatment (monotherapy or in combination with chemotherapy) were identified from the national cancer registry and MHS database from January 2017 to December 2020. Diabetes mellitus was identified at baseline from the MHS registry.[28] Time on treatment (ToT) was defined as the length of time between first and last administration date. Patients were considered discontinued if they had a record of next line of therapy, or death, or whose last activity date was ≥120 days from the last administration date. Outcomes were assessed at minimum 6 months follow-up (cutoff: June 30, 2021) and were assessed using Kaplan–Meier analysis. All analyses were conducted using IBM SPSS Statistics for Windows (version 22.0. Armonk, NY: IBM Corp and R version 3.5.1). The study was approved by the local ethics review board of MHS in Israel.

RESULTS

Demographic and clinical characteristics of NSCLC patients with DM

Of 234 metastatic NSCLC patients receiving first-line pembrolizumab at our medical center from January 2017 to July 2021, 203 were found eligible and were included in the analysis. Of those, 128 were male (63%), 152 had adenocarcinoma (75%), 105 (52%) received monotherapy pembrolizumab, and 51 had DM (25%).

Of these 51 diabetic patients, the majority (42 patients, 82%) were treated with oral hypoglycemic agents, most commonly metformin (32 patients, 63%), and seven patients were treated with insulin (14%). As shown in Table 1, the patients with DM were significantly older, on average, than the nondiabetic patients (mean age, 73 vs. 67 years, respectively, $p < .001$), had significantly higher BMI (26.7 vs. 23.6, respectively, $p < .001$), and more commonly had hypertension (61% vs. 43%, $p = .032$), and CKD (18% vs. 7%, $p = .032$). The two groups did not differ in the prevalence of IHD, past or current use of cigarettes, or ECOG performance status.

To further characterize our cohort, we collected information about the tumors. We found that the distribution of tumor histology varied significantly ($p = .042$). Compared to nondiabetic patients, those with DM presented with higher rates of squamous cell carcinoma (24% vs. 16%) and NSCLC NOS (14% vs. 5%), whereas nondiabetic patients had a higher rate of adenocarcinoma (79% vs. 63%). The rates of tumors that had PD-L1 above 50% did not vary significantly between the two groups.

Clinical outcome of NSCLC in patients with DM

The median follow-up at the time of data analysis was 26.9 months. As shown in Figure 1A, the median PFS was shorter in diabetic patients; reaching to 5.9 months compared to 7.1 months in nondiabetic patients ($p = .004$). Median OS was also shorter in diabetic patients reaching to 12 months compared to 21 months in nondiabetic patients (Figure 1B; $p = .006$). There was a nonsignificant trend towered a lower response rate ($p = .3$) in diabetic patients (24 of 51; 47%) compared to nondiabetic patients (84 of 152; 55%). To further investigate how DM influenced the treatment outcome in our patients, we analyzed the PFS and the OS in patients treated only with single agent pembrolizumab separately from patients treated with both pembrolizumab and chemotherapy. A reduced PFS in diabetic compared to nondiabetic patients was more noticeable when pembrolizumab was administered alone (Figure 1C) (6.5 vs. 8.5 months; $p = .009$), than when given together with chemotherapy (Figure 1E) (5.9 vs. 6.7 months, $p = .14$). Similarly, the observed reduction in median OS in diabetic compared to nondiabetic patients was more significant in the pembrolizumab treated (Figure 1D) (12 vs. 27 months; $p = .03$) than in the pembrolizumab and chemotherapy treated group (Figure 1F) (14.3 vs. 19.4 months, $p = .06$).

Multivariate analysis

A multivariate analysis was conducted using Cox proportional hazard regression mode to exclude the possibility that the shorter median PFS and OS in the diabetic compared to nondiabetic patients resulted from confounding variables. We found that histology ($p = .004$), cancer treatment ($p = .04$), ECOG performance status ($p = .003$), and DM ($p = .014$) have a significant effect on PFS. We found that the presence of DM significantly reduced the PFS of patients with a hazard ratio (HR) of 1.67 (95% CI, 1.11-2.5). That is, among diabetic subjects, the risk of disease

TABLE 1 Patients' characteristics.

	DM+ (n = 51)	DM− (n = 152)	p
Female gender, No. (%)	15 (29)	60 (39)	.198
Mean age, years (95% CI)	73 (70–76)	67 (65–69)	<.001
Age >70 years, No. (%)	31 (61)	57 (38)	.004
ECOG PS 2-4	9 (18)	26 (17)	.929
Comorbidities, No. (%)			
Hypertension	31 (61)	66 (43)	.032
Ischemic heart disease	12 (24)	28 (18)	.427
GFR <45	9 (18)	11 (7)	0.031
Current/past smoker	45 (88)	124 (82)	.270
BMI average (95% CI)	26.7 (25.5–27.9)	23.6 (23–24.2)	<.001
BMI categories, No. (%)			<.001
Cachexia (BMI <19)	1 (2)	15 (10)	
Normal weight	17 (33)	91 (60)	
Overweight (BMI 25–30)	23 (45)	34 (22)	
Morbid obese (BMI >30)	9 (18)	11 (7)	
Histology			.042
ADC	32 (63)	120 (79)	
SCC	12 (24)	24 (16)	
NSCLC NOS	7 (14)	8 (5)	
PD-L1 >50%	24 (47)	89 (59)	.153
1st-line therapy, No. (%)			.902
P	26 (51)	79 (52)	
P+C	25 (49)	73 (48)	
2nd-line therapy, No. (%)			
Any 2nd-line therapy	14 (27)	49 (32)	.523
2nd-line of a platin chemotherapy	6 (12)	19 (13)	.890
DM treatment, No. (%)			
Oral anti-diabetic treatment	42 (82)		
Insulin use	7 (14)		
Metformin use	32 (63)		
No treatment	7 (14)		

Abbreviations: ADC, adenocarcinoma; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; NSCLC NOS, non–small cell lung cancer not otherwise specified; P, pembrolizumab; P+C, pembrolizumab and chemotherapy; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma.

progression was 67% higher than in nondiabetic subjects. The influence of all other explanatory variables: age (p = .18), gender (p = .65), BMI (p = .55), smoking history (0.3), CKD (p = .80), IHD (p = .83) and hypertension (HTN) (p = .59) on PFS was not significant (Table 2).

Similarly, we found that OS was significantly influenced by histology (p < .001), IHD (p = .046), ECOG performance status (p < .001) and DM (p = .02). We found that the presence of DM significantly reduced the OS of patients with a HR of 1.73 (95% CI, 1.09–2.76). That is, among diabetic subjects, the risk of death was 73% higher than in nondiabetic subjects. The influence of all other explanatory variables: age (p = .39), gender (p = .21), BMI (p = .42), smoking history (0.43), cancer treatment (p = .23), CKD (p = .61), and HTN (p = .87) on OS was not significant (Table 3).

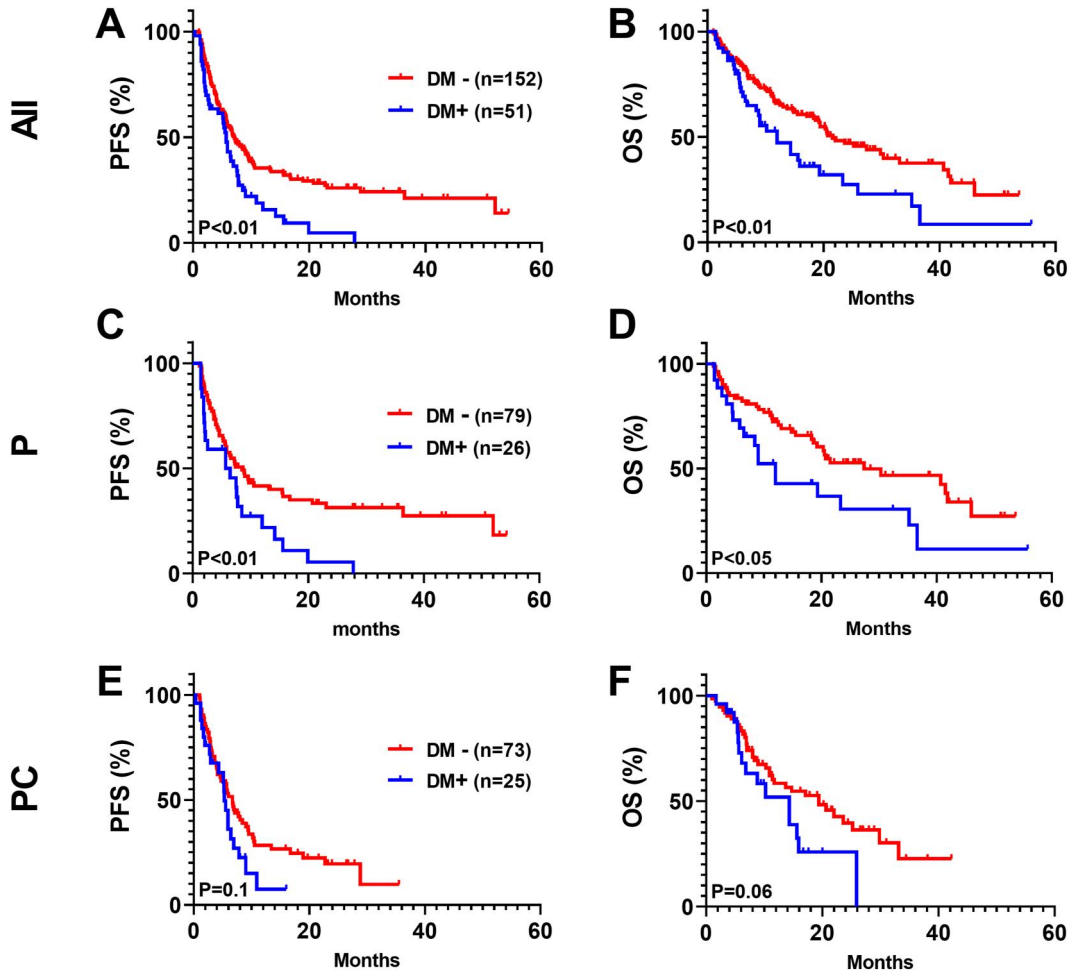

FIGURE 1 Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) of non–small cell lung cancer (NSCLC) patients receiving pembrolizumab (P) with and without diabetes mellitus (DM). (A and B) PFS and OS of all patients in our cohort. (C and D) PFS and OS of patients treated with P alone, or (E and F) pembrolizumab and chemotherapy (PC). The number of patients for each treatment condition is noted in the graphs.

Validation cohort

To verify our observations, we analyzed the ToT in a cohort of metastatic NSCLC patients registered to MHS, the second largest health care service in Israel, with over 2.5-million members. Of 452 eligible patients receiving first-line pembrolizumab, 124 had DM (27%). As shown in Figure 2, the ToT was shorter in diabetic compared to nondiabetic patients ($p = .025$). Diabetic patients were less likely to stay on treatment at 6 (38.5% vs. 45.4%) and 12 months (19.6% vs. 31.7%).

DISCUSSION

We report here that DM is associated with reduced efficacy in metastatic NSCLC patients treated with first-line pembrolizumab in both a single-center retrospective study and a validation cohort from a nationally distributed health care service. Unlike other modes of treatments, including chemotherapy and targeted therapy, immunotherapy modifies the host and only indirectly influences cancer cells. Our data suggest the possibility that the presence of DM may hinder the host's ability to mount an effective antitumor immunity.

Pre-existing DM was found in 25% (51 of 203) of the patients in our cohort. Of these, only 14% (7 of 51) were treated with insulin suggesting that the vast majority of patients had type 2 DM. A similar prevalence of DM (27%, 124 of 452) was noted in the validation cohort. The prevalence of both DM and cancer increases with age. The mean age in our cohort was 67 years. The high prevalence of DM among our patients is in line with published statistics of this age group.[29,30] As NSCLC patients with DM constitute a significant subgroup, there is an urgent need to validate our findings and explore whether outcomes in these patients can be improved by better glycemic control.

The KEYNOTE-024 trial evaluated the treatment of pembrolizumab monotherapy in metastatic NSCLC patients with PD-L1 >50%. The median OS of pembrolizumab treated patients in that trial was 26.3 months.[3] In our study, the median OS in the pembrolizumab treated patients was 27 months in nondiabetic, and 12

TABLE 2 Multivariate analysis of PFS in NSCLC patients receiving pembrolizumab alone or with chemotherapy.

	HR (95% CI)	p
Age group, years		
>70 vs. ≤70	1.34 (0.87–2.05)	.18
Gender		
Female vs. male	0.91 (0.6–1.38)	.65
BMI group		.55
Normal vs. low	0.7 (0.37–1.33)	.28
Overweight vs. low	0.88 (0.43–1.78)	.72
Obesity vs. low	0.98 (0.39–2.44)	.96
Smoking		
Former + current vs. nonsmoker	0.75 (0.43–1.3)	.3
IHD		
Present vs. absent	0.95 (0.57–1.58)	.83
CKD		
eGFR <45 vs. eGFR ≥45	1.1 (0.53–2.29)	.8
HTN		
Present vs. absent	0.88 (0.57–1.38)	.59
DM		
Present vs absent	1.67 (1.11–2.5)	.014
Histology		.004
SCC vs. ADC	1.9 (1.24–3)	.004
ADC vs. NSCLC NOS	1.8 (0.72–4.55)	.210
SCC vs. NSCLC NOS	3.5 (1.33–9.17)	.011
ECOG		
2–4 vs. 0–1	1.9 (1.23–2.87)	.003
Cancer treatment		
PC vs. P	1.5 (1.01–2.12)	.045

Abbreviations: ADC, adenocarcinoma; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; HTN, hypertension; HR, hazard ratio; IHD, ischemic heart disease; NSCLC NOS, non–small cell lung cancer not otherwise specified; P, pembrolizumab; PC, pembrolizumab and chemotherapy; PFS, progression-free survival; SCC, squamous cell carcinoma.

TABLE 3 Multivariate analysis of OS in NSCLC patients receiving pembrolizumab alone or with chemotherapy.

	HR (95% CI)	p
Age group, years		
>70 vs. ≤70	1.25 (0.75–2.08)	.39
Gender		
Female vs. male	0.73 (0.44–1.2)	.21
BMI group		.42
Normal vs. low	0.57 (0.28–1.17)	.12
Overweight vs. low	0.54 (0.24–1.23)	.14
Obesity vs. low	0.7 (0.25–1.93)	.49
Smoking		
Former + current vs. nonsmoker	0.76 (0.39–1.5)	.43
IHD		
Present vs. absent	1.6 (1.01–2.7)	.046
CKD		
eGFR <45 vs. eGFR ≥45	1.24 (0.54–2.81)	.61
HTN		
Present vs. absent	0.96 (0.56–1.65)	.87
DM		
Present vs. absent	1.73 (1.09–2.76)	.020
Histology		<.001
SCC vs. ADC	2.7 (1.65–4.42)	<.001
ADC vs. NSCLC NOS	1.26 (0.45–3.54)	.667
SCC vs. NSCLC NOS	3.4 (1.16–10)	.026
ECOG		
2–4 vs. 0–1	2.3 (1.44–3.6)	<.001
Cancer treatment		
PC vs. P	1.33 (0.83–2.12)	.23

Abbreviations: ADC, adenocarcinoma; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; HTN, hypertension; HR, hazard ratio; IHD, ischemic heart disease; NSCLC NOS, non–small cell lung cancer not otherwise specified; P, pembrolizumab; PC, pembrolizumab and chemotherapy; OS, overall survival; SCC, squamous cell carcinoma.

months in diabetic patients. KEYNOTE-407 and KEYNOTE-189 evaluated the efficacy of pembrolizumab and chemotherapy treatment in squamous and nonsquamous NSCLC patients, respectively. The median OS in KEYNOTE-407 was 17.1 months,[1] and the median OS in KEYNOTE-189 was 22 months.[2] In our study, the median OS in patients treated with pembrolizumab and chemotherapy was 19.4 months in non–diabetic patients and 14.3 months in diabetic patients. These comparisons suggest that the outcome for non–diabetic patients in our cohort was similar to that achieved in the abovementioned clinical trials. None of those trials had included a subgroup analysis of patients with DM. Clinical trials are subject to a selection bias for younger patients and those with fewer comorbidities.[31,32] Because diabetic patients are on average older, have higher BMI and more comorbidities, it is possible that they are not well represented in clinical trials.

Our findings align with substantial evidence indicating that diabetes causes immune dysfunction.[9,11,13,21] Patients with DM are

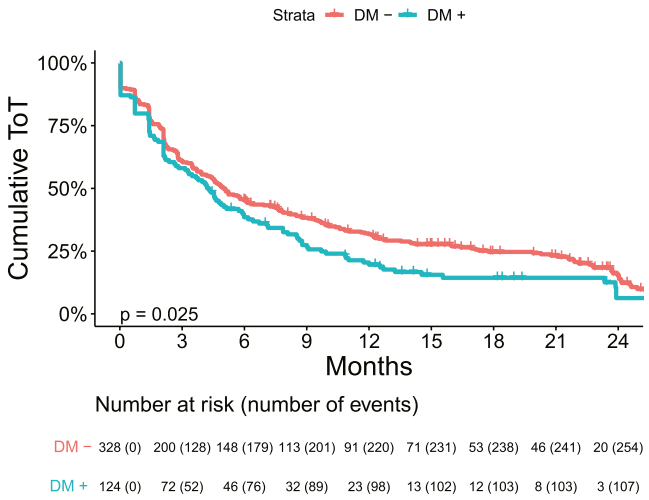

FIGURE 2 Kaplan–Meier curves of time on pembrolizumab treatment (ToT) in patients with non–small cell lung cancer (NSCLC) registered to Maccabi Healthcare Services with and without diabetes mellitus (DM).

reportedly more prone to hospitalization and death due to bacterial and viral pathogens.[33,34] Moreover, several studies show that tight glycemic control reduces the severity of infectious diseases in diabetic patients.[15,16]

Diabetes was associated with an increased cancer incidence and a reduced survival of cancer patients even before the era of immunotherapy.[35–37] Two of the mechanisms proposed to underlie this association are hyperinsulinemia and hyperglycemia. Work done in murine cancer models showed that it is hyperglycemia and not hyperinsulinemia that enhances tumor growth. Importantly, the accelerated growth was immune-mediated.[21,22]

Metformin, a widespread medication for type 2 DM, was previously suggested as a beneficial modulator of antitumor immunity.[38] Although most diabetic patients in our cohort received metformin, diabetic patients had a worse outcome. More work will be needed to clarify whether metformin modulates ICI efficacy in diabetic patients.

In our cohort, an increased proportion of patients with DM had squamous cell carcinoma compared to patients without DM. It was suggested that lung squamous cell carcinoma is more dependent on glucose metabolism compared to other subtypes.[39,40]

Diabetes and poor glycemic control have previously been associated with compromised efficacy of chemotherapy.[41,42] Our findings indicate a stronger association between DM and a poor outcome in patients treated with pembrolizumab alone than in those treated with pembrolizumab and chemotherapy. It seems, therefore, that chemotherapy may offset some of the deleterious effects of the DM.

Our findings align with a recently published study showing a compromised outcome of metastatic NSCLC patients with DM receiving immunotherapy.[25] However, the study cohort does not represent the current standard of care because it consisted mostly of patients receiving second, or third-line immunotherapy without concomitant use of chemotherapy.

This study has several unique strengths, including a homogeneous patient population, long follow-up, and access to electronic medical records of a large health care service to validate our findings. However, full demographic and clinical characteristics were available only for the exploratory cohort. A major limitation was that we lacked access to blood test results outside the hospital, including fasting glucose or HbA_{1c}. Thus, we could not determine whether better glycemic control might have modified the association found. The study is also limited by its retrospective nature. The type of diabetes in our cohort was not well documented. More work will be needed to clarify if the type of diabetes influences patient's response to pembrolizumab.

Altogether, this study shows a correlation between diabetes and poor outcome in metastatic NSCLC patients receiving pembrolizumab. This is especially alarming considering that one in four patients in our cohort had DM. More work is needed to verify our findings and search for ways to overcome this effect.

AUTHOR CONTRIBUTIONS

Yasmin Leshem: Conceptualization, data acquisition, and writing–original draft. **Yardenna Dolev:** Data acquisition. **Nava Siegelmann-Danieli:** Validation cohort data and statistical analysis. **Sarah Sharman Moser:** Validation cohort data and statistical analysis. **Lior Apter:** Validation cohort data and statistical analysis. **Gabriel Chodick:** Validation cohort data and statistical analysis. **Alla Nikolaevski-Berlin:** Statistical analysis. **Ido Wolf:** Supervision and writing–original draft. All authors provided comments and adjustments for the final manuscript version and approved the final manuscript submission.

CONFLICT OF INTEREST STATEMENT

Sivan Shamai reports independent contractor and/or other fees from Merck Sharp and Dohme. Ido Wolf reports consulting fees from Bristol-Myers Squibb, F. Hozmann-La Roche, Merck, Merck Sharp and Dohme, and Novartis. The other authors declare no conflicts of interest.

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REFERENCES

1. Paz-Ares L, Vicente D, Tafreshi A, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. *J Thorac Oncol*. 2020;15(10):1657-1669. doi:10.1016/j.jtho.2020.06.015
2. Rodríguez-Abreu D, Powell SF, Hochmair MJ, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. *Ann Oncol*. 2021;32(7):881-895. doi:10.1016/j.annonc.2021.04.008
3. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥50. *J Clin Oncol*. 2021;39(21):2339-2349. doi:10.1200/jco.21.00174

4. Maleki Vareki S, Garrigós C, Duran I. Biomarkers of response to PD-1/PD-L1 inhibition. *Crit Rev Oncol Hematol*. 2017;116:116-124. doi:10.1016/j.critrevonc.2017.06.001
5. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. *Nat Rev Dis Prim*. 2015;1:15019. doi:10.1038/nrdp.2015.19
6. Wang L, Li X, Wang Z, Bancks MP, et al. Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999-2018. *JAMA*. 2021;326(8):704. doi:10.1001/jama.2021.9883
7. Mirza S, Hossain M, Mathews C, et al. Type 2-diabetes is associated with elevated levels of TNF-alpha, IL-6 and adiponectin and low levels of leptin in a population of Mexican Americans: a cross-sectional study. *Cytokine*. 2012;57(1):136-142. doi:10.1016/j.cyto.2011.09.029
8. Devaraj S, Dasu MR, Jialal I. Diabetes is a proinflammatory state: a translational perspective. *Expert Rev Endocrinol Metab*. 2010;5(1):19-28. doi:10.1586/eem.09.44
9. Geerlings SE, Brouwer EC, Van Kessel KC, Gaastra W, Stolk RP, Hoepelman AI. Cytokine secretion is impaired in women with diabetes mellitus. *Eur J Clin Invest*. 2000;30(11):995-1001. doi:10.1046/j.1365-2362.2000.00745.x
10. Joshi MB, Ahamed R, Hegde M, Nair AS, Ramachandra L, Satyamoorthy K. Glucose induces metabolic reprogramming in neutrophils during type 2 diabetes to form constitutive extracellular traps and decreased responsiveness to lipopolysaccharides. *Biochim Biophys Acta Mol Basis Dis*. 2020;1866(12):165940. doi:10.1016/j.bbadis.2020.165940
11. Khondkaryan L, Margaryan S, Poghosyan D, Manukyan G. Impaired inflammatory response to LPS in type 2 diabetes mellitus. *Int J Inflam*. 2018;2018:2157434. doi:10.1155/2018/2157434
12. Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. *Am J Med Sci*. 2016;351(2):201-211. doi:10.1016/j.amjms.2015.11.011
13. Gilardini Montani MS, Granato M, Cuomo L, et al. High glucose and hyperglycemic sera from type 2 diabetic patients impair DC differentiation by inducing ROS and activating Wnt/β-catenin and p38 MAPK. *Biochim Biophys Acta*. 2016;1862(4):805-813. doi:10.1016/j.bbadis.2016.01.001
14. Erener S. Diabetes, infection risk and COVID-19. *Mol Metab*. 2020;39:101044. doi:10.1016/j.molmet.2020.101044
15. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. *Diabetes Care*. 2018;41(10):2127-2135. doi:10.2337/dc18-0287
16. Mor A, Dekkers OM, Nielsen JS, Beck-Nielsen H, Sørensen HT, Thomsen RW. Impact of glycemic control on risk of infections in patients with type 2 diabetes: a population-based cohort study. *Am J Epidemiol*. 2017;186(2):227-236. doi:10.1093/aje/kwx049
17. Wang M, Yang Y, Liao Z. Diabetes and cancer: epidemiological and biological links. *World J Diabetes*. 2020;11(6):227-238. doi:10.4239/wjd.v11.i6.227
18. Pearson-Stuttard J, Papadimitriou N, Markozannes G, et al. Type 2 diabetes and cancer: an umbrella review of observational and mendelian randomization studies. *Cancer Epidemiol Biomarkers Prev*. 2021;30(6):1218-1228. doi:10.1158/1055-9965.epi-20-1245
19. Bi G, Yao G, Bian Y, et al. The effect of diabetes mellitus on prognosis of patients with non-small-cell lung cancer: a systematic review and meta-analysis. *Ann Thorac Cardiovasc Surg*. 2020;26(1):1-12. doi:10.5761/atcs.ra.19-00170
20. Nojima I, Eikawa S, Tomonobu N, et al. Dysfunction of CD8 + PD-1 + T cells in type 2 diabetes caused by the impairment of metabolism-immune axis. *Sci Rep*. 2020;10(1):14928. doi:10.1038/s41598-020-71946-3
21. Rodrigues Mantuano N, Stanczak MA, de Oliveira IA, et al. Hyperglycemia enhances cancer immune evasion by inducing alternative macrophage polarization through increased O-glcanacylation. *Cancer Immunol Res*. 2020;8(10):1262-1272. doi:10.1158/2326-6066.cir-19-0904
22. Kavazović I, Krapić M, Beumer-Chuwonpad A, et al. Hyperglycemia and not hyperinsulinemia mediates diabetes-induced memory Cd8 T cell dysfunction. *Diabetes*. 2022;71(4):db210209. doi:10.2337/db21-0209
23. Heckl SM, Mau F, Senftleben A, et al. Programmed death-ligand 1 (PD-L1) expression is induced by insulin in pancreatic ductal adenocarcinoma cells pointing to its role in immune checkpoint control. *Med Sci*. 2021;9(3):48. doi:10.3390/medsci9030048
24. Mallardo D, Cortellini A, Capone M, et al. Concomitant type 2 diabetes mellitus (T2DM) in metastatic melanoma patients could be related to lower level of LAG-3: a transcriptomic analysis of a retrospective cohort. *Ann Oncol*. 2022;33(4):445-447. doi:10.1016/j.annonc.2022.01.007
25. Jacobi O, Landman Y, Reinhorn D, et al. The relationship of diabetes mellitus to efficacy of immune checkpoint inhibitors in patients with advanced non-small cell lung cancer. *Oncology*. 2021;99(9):555-561. doi:10.1159/000516671
26. Gubens MA, Davies M. NCCN guidelines updates: new immunotherapy strategies for improving outcomes in non-small cell lung cancer. *J Natl Compr Canc Netw*. 2019;17(5.5):574-578.
27. Goldberg SB, Narayan A, Kole AJ, et al. Early assessment of lung cancer immunotherapy response via circulating tumor DNA. *Clin Cancer Res*. 2018;24(8):1872-1880. doi:10.1158/1078-0432.ccr-17-1341
28. Chodick G, Heymann AD, Shalev V, Kookia E. The epidemiology of diabetes in a large Israeli HMO. *Eur J Epidemiol*. 2003;18(12):1143-1146. doi:10.1023/b:ejep.0000006635.36802.c8
29. Karpati T, Cohen-Stavi CJ, Leibowitz M, Hoshen M, Feldman BS, Balicer RD. Towards a subsiding diabetes epidemic: trends from a large population-based study in Israel. *Popul Health Metr*. 2014;12(1):32. doi:10.1186/s12963-014-0032-y
30. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119. doi:10.1016/j.diabres.2021.109119
31. Unger JM, Hershman DL, Fleury ME, Vaidya R. Association of patient comorbid conditions with cancer clinical trial participation. *JAMA Oncol*. 2019;5(3):326-333. doi:10.1001/jamaoncol.2018.5953
32. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol*. 2004;22(22):4626-4631. doi:10.1200/jco.2004.02.175
33. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - a systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr*. 2020;14(4):395-403. doi:10.1016/j.dsx.2020.04.018
34. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. *Diabetes Care*. 2018;41(3):513-521. doi:10.2337/dc17-2131
35. Xu CX, Zhu HH, Zhu YM. Diabetes and cancer: associations, mechanisms, and implications for medical practice. *World J Diabetes*. 2014;5(3):372-380. doi:10.4239/wjd.v5.i3.372
36. Villarreal-Garza C, Shaw-Dulin R, Lara-Medina F, et al. Impact of diabetes and hyperglycemia on survival in advanced breast cancer patients. *Exp Diabetes Res*. 2012;2012:732027. doi:10.1155/2012/732027
37. Luo J, Hendryx M, Qi L, Ho GY, Margolis KL. Pre-existing diabetes and lung cancer prognosis. *Br J Cancer*. 2016;115(1):76-79. doi:10.1038/bjc.2016.141
38. Skuli SJ, Alomari S, Gaitsch H, Bakayoko A, Skuli N, Tyler BM. Metformin and cancer, an ambiguanidous relationship. *Pharmaceuticals*. 2022;15(5):626. doi:10.3390/ph15050626

39. Goodwin J, Neugent ML, Lee SY, et al. The distinct metabolic phenotype of lung squamous cell carcinoma defines selective vulnerability to glycolytic inhibition. *Nat Commun*. 2017;8(1):15503. doi:10.1038/ncomms15503
40. Melkonian SC, Daniel CR, Ye Y, Pierzynski JA, Roth JA, Wu X. Glycemic index, glycemic load, and lung cancer risk in non-Hispanic Whites. *Cancer Epidemiol Biomarkers Prev*. 2016;25(3):532-539. doi:10.1158/1055-9965.epi-15-0765
41. Li J, Ning NY, Rao QX, Chen R, Wang LJ, Lin ZQ. Pretreatment glycemic control status is an independent prognostic factor for cervical cancer patients receiving neoadjuvant chemotherapy for locally advanced disease. *BMC Cancer*. 2017;17(1):517. doi:10.1186/s12885-017-3510-3
42. Zeng X, Xu C, Cheng J, et al. Poor glycemic control might compromise the efficacy of chemotherapy in non–small cell lung cancer patients with diabetes mellitus. *Cancer Med*. 2020;9(3):902-911. doi:10.1002/cam4.2750

How to cite this article: Leshem Y, Dolev Y, Siegelmann-Danieli N, et al. Association between diabetes mellitus and reduced efficacy of pembrolizumab in non–small cell lung cancer. *Cancer*. 2023;129(18):2789-2797. doi:10.1002/cncr.34918