Association of Diabetes Status With Survival After Immune Checkpoint Inhibitor Treatment for Advanced Lung Cancer: a Retrospective Study in Japan

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Abstract

Introduction: Although immune checkpoint inhibitors (ICIs) are promising in the treatment of advanced cancer, they may lead to immune-related adverse events (irAEs), which can affect endocrine organ systems. However, development of the irAEs was associated with improved cancer-specific survival, the risk for years have not been elucidated. We investigated the association of pre-ICI comorbidities—including diabetes—with years and overall survival (OS) and progression-free survival (PFS) in advanced lung cancer.

Research design and methods: Patients with lung cancer who were treated with ICIs at the period from September 1, 2015 through July 31, 2018 were retrospectively enrolled. All data were collected from the university patient NEPTUNE database. Hazard ratios were estimated by using Cox regression weighted for propensity scores. Odds ratios were calculated by logistic regression and adjusted for unbalanced variables. The Kaplan−Meier method was used to compare OS, and the generalized Wilcoxon test was used to compare median survival.

The results: Among the 88 patients identified, 22 (25.0%) had diabetes (DM) before ICI treatment and 57 (75.0%) did not (non-DM). Iris developed in 12.2% of patients with DM and in 9.1% of patients in non-DM (p=0.87). Diabetes status was not associated with auras risk in relation to baseline characteristics (age, sex, TNM staging, thyroid and renal function) or after propensity score matching analysis (age, TNM staging). During a mean follow-up of 30 months, OS and cancer-specific PFS were significantly higher in patients who developed iris (Kaplan−Meier estimates, p=0·04 and 0·03, respectively). In propensity score−matched analysis, diabetes was significantly associated with lower OS (multivariate hazard ratio, 0·36; 95% CI, 0·13−0·98). Irrespective of eras, PFS was lower among patients with DM than among non-DM (Kaplan−Meier estimate, p=0·04).

Conclusions: Pre-existing diabetes was associated with higher mortality in advanced lung cancer, regardless of irAEs development after treatment with ICIs.

Article Summary

⬜Immune checkpoint inhibitors (ICIs) treatment has feasible outcomes in advanced stage cancer treatment, however, they potentially consequences of immune-related adverse events (irAEs).

⬜The development of the irAEs which was linked with positive cancer specific survival outcomes, however risk factors were not fully investigated.

⬜Thus, we concentrate on the pre-ICIs comorbidities, including diabetes before the ICI treatment, which has had any impact to the irAEs rates, despite the short overall survival and progression-free survival in advanced lung cancer.

Introduction

The development of immune checkpoint inhibitors (ICIs) is an important milestone in cancer therapy. There are three types of ICI, and six products have been approved in Japan (ipilimumb, nibolumab, pembrolizumab, avelumab, atezolizmab, and durvalumab). Nivolumab and pembrolizmab—monoclonal antibodies that target the programmed cell death 1 (PD-1) protein on the surface of cells—have been approved for treatment of metastatic non−small cell lung cancer since 2015.

In a randomised controlled trial of cancer adjuvants for NSCLC patients, response duration and overall survival were longer for nivolumab than for docetaxel (1). The intermediate survival period was 12.2 months (95% CI, 9.7−15.0)

for nivolumab and 9.4 months (95% CI, 8.1–10.7) for docetaxel, and the response rate was higher for nivolumab than for docetaxel (19% vs 12%, p = 0.02). Nivolumab has been changed the guideline development and revision of the NSCLC and other solid cancer treatment (2–5). New classes of drugs (e.g. ICI) improved patient outcomes in advanced NSCLC, which might facilitate their further use in the near future (6) (7).

ICI can trigger autoimmune-related reactions in organ systems. Such reactions are referred to as immune-related adverse events (irAEs). Among the most common irAEs is endocrine dysfunction, including dysfunction of the thyroid, pituitary, adrenal grand, and pancreatic islets (8–10). Development of irAEs was found to be positively associated with survival (11) (12). Potential risk factors associated with irAEs, including age, sex, gene mutations, and smoking status, are currently being investigated worldwide (13)(14). However, antecedent factors related to irAEs and the precise mechanisms involved are unknown. Therefore, we investigated comorbidities associated with irAEs, which are important in subsequent improvement in overall survival (OS) and progression-free survival (PFS).

Lung cancer mortality rates are lower for patients with diabetes than for normoglycemic patients (15)(17). Diabetes might therefore have some effect on chemotherapeutic agents used to treat cancer. To our knowledge, no study has examined the association between diabetes status before ICI treatment and outcomes of treatment for advanced lung cancer. Our primary hypothesis was that reverse causality may have a role in the association between glucose tolerance, lack of association with diabetes, and irAEs, does interfere the effects of ICI, resulting in poor cancer-specific OS and PFS. To address these criticisms, we analyzed the association between diabetes status before ICI treatment and the rate of irAEs. Propensity score matching analysis was used to adjust for differences in baseline covariates, including age, TNM staging, and comorbidities for cancer neoadjuvant chemotherapy. In addition, conventional Cox regression analysis was used to analyze OS and cancer-specific PFS in relation to diabetes status before ICI treatment.

Methods

Patients And Public Involvement

This study was conducted in the Division of Diabetes, Metabolism, and Endocrinology, Department of Internal Medicine, at Toho University School of Medicine, Tokyo, Japan (M19129). The participants were patients with lung cancer or mediastinal tumors that were treated with nivolumab or pembrolizumab in the department of respiratory medicine during the period from January 2015 through August 2018. Patients treated with other ICIs were excluded. Among 88 patients, 27% (n = 24) had diabetes before ICI treatment and 73% (n = 64) did not. They were followed during February 2019, and development of irAEs (thyroid dysfunction, hypopituitarism, adrenal insufficiency, and insulin-deficient diabetes) was investigated and recorded.

Study Design

The first anti–PD-1 antibody treatment was approved in Japan in 2014, and all data for patients at our centre who received anti–PD-1 antibodies for lung cancer were collected from the NEPTUNE database. Using propensity score matching, we conducted 1:1 (diabetes/non-diabetes) matched case-control analysis (18) and a comprehensive comparison of cofounding factors affecting lung cancer outcomes for patients with and without diabetes. In addition, we used multiple logistic regression to calculate adjusted odds ratios to compare both OS and PFS in patients with and without diabetes who had advanced lung cancer. Because patients with diabetes before ICI treatment were more likely to have risk factors (including age, sex, year of diagnosis, comorbidity, cancer type, and

TNM staging) known to be associated with shorter OS (15–17), we attempted to reduce selection bias by propensity scoring. We used age, sex, and TNM staging in propensity matching. For the matched and unmatched groups, no factors significantly differed in relation to diabetes status. The study protocol and all procedures were in accordance with the ethical standards of the Ethics Committee of the Toho University Omori Medical Center Hospital and the 1964 Helsinki Declaration and its amendments and were approved by the relevant institutional review board (M19129). This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as JPRN-UMIN 000037931. For further details of propensity score matching, see Supplementary Appendix 1–3. All extra data can be request to the corresponding author.

Statistical analysis

Propensity score matching was used to select comparable groups of patients. The propensity matching score was estimated by multivariable logistic regression, and 1-to-1 matching (without replacement) by propensity score was performed by using the nearest neighbour method with a calliper width equal to 0.2 standard deviations. In the regression model, OS and PFS were the dependent variables. The independent variables were age, %PD-1, creatinine, blood glucose, thyroid function, c-peptide, %irAEs, serum cortisol, and number of treatments.

After the propensity score was estimated, patients with diabetes were matched in a 1:1 ratio to those without diabetes. For multiple comparisons of normally distributed variables between more than two groups, one-way analysis of variance was used with the post-hoc *t* test. For time-to-event variables, survival functions were estimated with the Kaplan–Meier method and compared with the log-rank test. Cox proportional hazards regression was used to obtain hazard ratios.

Role Of The Funding Source

There was no funder in this study. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 88 patients who were treated with ICIs during the study period, 4.5% (n = 1) of those with diabetes and 10.6% (n = 7) of those without diabetes developed irAEs. Propensity score matching was used to mitigate the effect of potential selection bias. In matched-pair samples, the mean distance in the estimated propensity score was 0.2. The two populations of 30 patients, i.e., those with and without diabetes, were well matched (Table 1). On completion of follow-up (median follow-up, 14.0 months), the frequency of irAEs did not significantly differ between groups (p = 0.71 for the unmatched cohort; p = 1.0 for the propensity-matched cohort).

OS and PFS were estimated in the two groups. Figure 1A shows Kaplan–Meier curves of OS, and Fig. 1B shows cancer-specific PFS, with and without irAEs. As was noted in a previous study (11)(12), outcomes were better in patients with irAEs than in those without irAEs (OS, p = 0.0237; PFS, p = 0.0396, respectively). Figure 2a shows the Kaplan–Meier curves for cancer-specific PFS, and Fig. 3 shows the Kaplan–Meier curves for OS for all patients. PFS was shorter for patients with diabetes (n = 24) than for those without diabetes (n = 64) (p = 0.0467). In addition, PFS was significantly shorter in patients with diabetes. PFS was affected only by lung cancer, which indicates that diabetes directly affects survival rate in lung cancer patients. Table 2 shows the multivariate Cox proportional hazards regression model for cancer-specific PFS and OS. In univariate and multivariate analyses, diabetes status

was not significantly associated with OS or PFS in the entire, unmatched cohort; however, after propensity score matching, OS was significantly shorter (p = 0.044) in patients with diabetes.

Table 1
Baseline Characteristics of the Patients

	Unmatched		P value	Propensity score matched		P value
	Pretreatment DM(n = 24)	non DM (n = 64)		Pretreatment DM (n = 15)	non DM (n = 15)	
Age (yr)	66.58 ± 9.86	66.17 ± 9.85	0.86	64.91 ± 10.32	65.7 ± 10.02	0.7
Gender (%)	Male:87.5% Female:12.5%	Male:79.7% Female:20.3%	0.22	Male:67% Female:33%	Male:73% Female:26%	0.10
Tumor type[1] (%)	Adeno:45.8% Squamous:37.5% Other[2]:8.3% Unknown:8.3%	Adeno:65.6% Squamous:21.9% Other:6.25% Unknown:6.25%	0.27	Adeno:46.7% Squamous:46.7% Other: 0% Unknown:6.7%	Adeno:66.7% Squemous:13.3% Other:6.7% Unknown:13.3%	0.13
TMN Staging (%)	Ⅰ:8.3% Ⅱ:12.5% Ⅲ:29.2% Ⅳ:50%	Ⅰ:9.38% Ⅱ:9.38% Ⅲ:25% Ⅳ:56.3%	0.16	Ⅰ:6.7% Ⅱ:13.3% Ⅲ:33.3% Ⅳ 46.7%	Ⅰ:6.7% Ⅱ:6.7% Ⅲ:13.3% Ⅳ:71.3%	0.084
%PD1	0.48 ± 0.20	0.35 ± 0.40	0.22	0.26 ± 0.38	0.32 ± 0.39	0.52
Serum creatine (mg/dl)	0.70 ± 0.18	0.77 ± 0.20	0.08	0.76 ± 0.19	0.77 ± 0.19	0.24
Plasma glucose (mg/dl)	159.8 ± 98.6	11.3 ± 20.8	0.03*	113.9 ± 22.0	113.27 ± 21.21	0.87
FT3 (pg/ml)	2.71 ± 0.55	2.84 ± 0.55	0.33	2.89 ± 0.57	2.87 ± 0.56	0.91
FT4 (ng/ml)	1.30 ± 0.19	1.29 ± 0.18	0.53	1.30 ± 0.17	1.29 ± 0.19	0.21
TSH (μIU/ml)	1.20 ± 1.40	2.18 ± 2.30	0.51	2.23 ± 2.28	2.25 ± 2.39	0.54

Values are mean ± SD. *P < 0.05 represents significant.

1) Tumor type consists of four types.

2) Other includes undifferentiated carcinoma, polymorphic carcinoma, and poorly differentiated carcinoma. The term "unknown" indicates dissatisfied tumor type.

3) %PD-1 is the rate of expression of PD-1 on lung cancer cells.

Abbreviations: % PD-1, programmed death-1; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; irAEs, immune-related Adverse Events; OS, overall survival; Tx number; treatment number.

	Unmatched		P value	Propensity score matched		P value
C-peptide (ng/ml)	2.68 ± 1.83	3.30 ± 2.90	0.23	3.04 ± 2.45	3.33 ± 3.0	0.63
cortisol (μg/dl)	8.53 ± 0.16	10.13 ± 6.05	0.28	9.70 ± 6.11	9.75 ± 6.19	0.81
irAEs (%)	Yes:29.2% No:70.8%	Yes:3.1% No:96.9%	0.39	Yes:26.7% No:73.3%	Yes:26.7% No:73.3%	0.18
OS (Mo)	12.30 ± 10.00	14.4 ± 9.73	0.38	14.14 ± 10.25	14.75 ± 10.31	0.744
Tx number	9.17 ± 11.90	11.34 ± 11.90	0.45	10.83 ± 11.78	11.41 ± 12.31	0.731

Values are mean ± SD. *P < 0.05 represents significant.

1) Tumor type consists of four types.

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Abbreviations: % PD-1, programmed death-1; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; irAEs, immune-related Adverse Events; OS, overall survival; Tx number; treatment number.

Table 2

Multivariate Cox proportional hazard regression model of cancer specific progression free survival and overall survival in subjects between unmatched and matched cohorts

	DM vs non-DM (unmatched, n = 88)				DM vs non-DM (Propensity score matched, n = 30)			
Models	Univariable Hazard Ratio(95%,CI)	P value	Multivariable Hazard Ratio (95%,CI)	P value	Univariable Hazard Ratio (95%,CI)	P value	Multivariable Hazard Ratio (95%,CI)	P value
Cancer specific progression free survival	0.45 (0.40–0.51)	0.491	0.95 (0.41–2.50)	0.499	0.89 (0.43–1.84)	0.762	0.54 (0.23–1.30)	0.173
Overall survival	1.24 (0.37–4.05)	0.721	0.99 (0.27–3.53)	0.988	0.85 (0.41–1.75)	0.668	0.36 (0.13–0.98)	**0.044**

Propensity score matched cohorts includes age, gender, TNM staging matching. For multiple comparisons of normally distributed variables between more than two groups, one-way analysis of variance (ANOVA) was used with post-hoc t tests. For time-to-event variables, the survival functions were estimated with the Kaplan-Meier method and compared by log-rank. Cox's proportional hazard regression was used to obtain hazard ratios (HRs).

Discussion

We hypothesized that presence of diabetes before ICI treatment would be associated with fewer irAEs in patients receiving treatment for advanced lung cancer. However, diabetes was not associated with the rate of irAEs, although it was associated with shorter PFS in this patient group. The structural and conformational dynamics of the immune-related cancer agents nivolumab and pembrolizumab are referred to as anti–PD-1 antibody (1). Tumor cells express programmed death-ligand 1 (PD-L1) on their surface, to avoid attack from the immune system. However, PD-L1 binds to PD-1, which is expressed on the surface of T cells, thereby suppressing the immune system. Anti–PD-1 antibody binds to PD-1, thus inhibiting interaction of cancer cells and immune cells (19). However, this immunotherapeutic approach is often associated with immune-mediated toxic events, known as irAEs. Interestingly, irAEs were found to be associated with improved OS and cancer-specific PFS in several advanced cancers (11)(12).

Diabetes And Immune Reactivity

Recognize immune systems by several T cell clones of its cognate antigen results in the initiation of an immune response (20). A recent study reported that diabetes is a chronic, low-grade inflammatory disease in which expression or activation of immune-related molecules is altered (21). T cells differentiate various types of immune cells by specific stimulation and the source of energetic nutrient transport. Under conditions of normoglycemia, naive T cells use lipids as their predominant energy substrate to differentiate regulatory T cells. However, under conditions of hyperglycaemia, glucose is mainly used as the energy substrate to differentiate to Th17 (22). Furthermore, PD-1 expression on tumor cell surfaces is diminished in diabetes, which blunts the response to activated T cells (23). Although hyperglycaemia, including diabetes, is known to alter immune T cell activity, the response to ICIs in the context of advanced cancer treatment is not well understood. Our findings showed no association between diabetes before ICI and irAE incidence, which was associated with subsequent OS and PFS. The results were similar in the PFS-matched cohort and overall, unmatched cohort.

Diabetes And Cancer-specific Outcomes

Ten percent of the world population will develop diabetes during their life (24), 55% of whom will receive a cancer diagnosis. Reverse causality may play a role in diabetes and cancer, and the link between the two diseases facilitates further development and vice versa. PFS was poor in the present patients with diabetes. Diabetes before ICI treatment was associated with worse PFS in lung cancer patients, and pre-treatment diabetes was associated with poor outcomes after chemotherapy for other cancers (25)(26).

Diabetes and cancer share several intrinsic risk factors (obesity, poor diet, and aging) (25), and our results indicate that diabetes was associated with worse OS and PFS, regardless of irAE development. Although the underlying biological mechanisms are unclear, several hypotheses have been suggested. First, hyperinsulinemia and hyperglycaemia associated with diabetes may increase tumor cell proliferation and metastasis (25). Adipose tissue inflammation may play a role, and insulin resistance might further enhance production of inflammatory cytokines, which could alter the immune system (25). Secondly, patients with diabetes are more likely to develop adverse effects during chemotherapy, which decreases the effectiveness of such treatments (25)(26). Although ICIs clearly improve outcomes in patients with advanced lung cancer, they are costly and associated with adverse events (irAEs). In our current health care environment, policy makers, providers, and patients need more evidence, to determine the value of therapeutic alternatives to ICI treatment. We must examine covariates that might affect ICI effectiveness. Inappropriate ICI treatment results in detrimental risks, both in social health costs and patient

selection bias. Our results shed light on the positive effects of ICIs on OS and PFS in patients without diabetes before ICI treatment.

Limitations

The present study has some limitations. It was retrospective and enrolled only a small number of Japanese patients at a single centre. This study does not described one's all life span, lifetime research may elicit different findings. Large-scale, multicentre, prospective studies are needed. We found that age, sex, TNM staging, %PD-1, creatinine, blood glucose level, thyroid function, c-peptide, serum cortisol, %irAEs, and number of ICI treatments were not potential predictors of irAEs. However, multicentre trials of many cancer types are clearly necessary.

Conclusions

Pre-treatment diabetes status was not associated with subsequent irAEs. However, irAE incidence after ICI treatment was associated with OS and PFS in patients with advanced lung cancer. The unforeseen risks of irAEs related to ICI treatment may be an important consideration in improving cancer outcomes. Further studies should attempt to identify predictors of irAEs, to aid in the selection of patients likely to benefit from ICI treatment. This result will feed back to the participants through publication of this manuscript.

Declarations

Contributors

HU coordinated the study, and KH, KN, MM, FY, GS, KI, and SH codesigned the study. KH, HU, and TH were responsible for screening and enrolling participants, arranging informed consent from participants, and providing patient care. KH, HU, and TH wrote the report. FY, GS, and KI contributed to data analysis, including the statistical analyses. SH designed and implemented the clinical variables. HU, KH, MM, FY, GS, KI, SH, and TH contributed to the interpretation of the results. All authors critically reviewed the manuscript. We also thank to KI for being a patient adviser.

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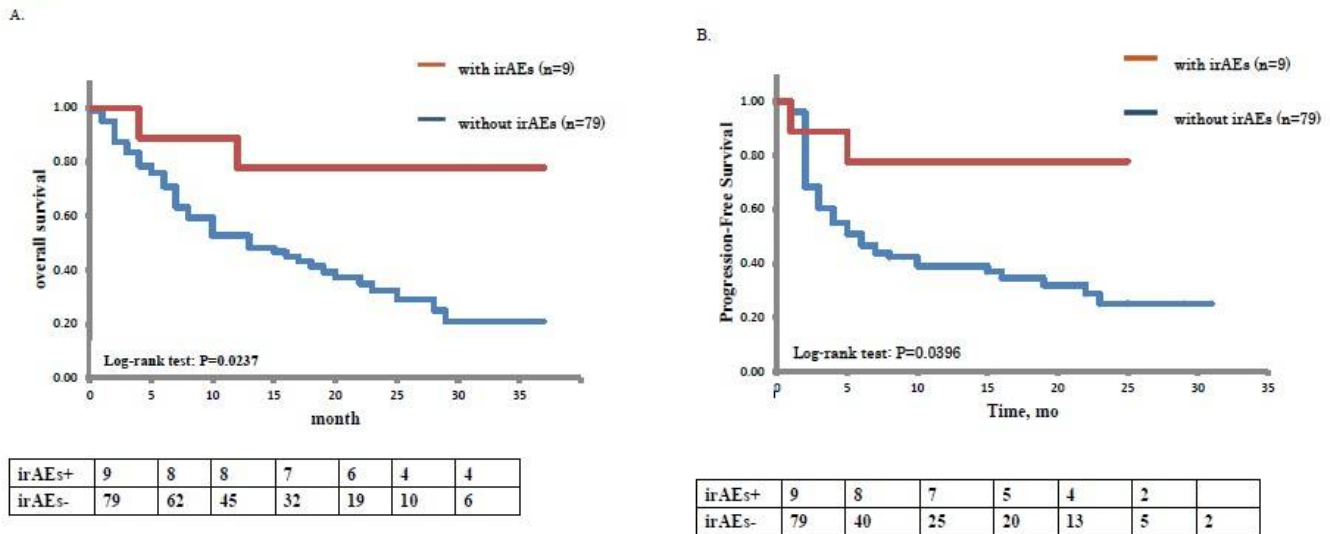
Figures

Figure 1
A.

| irAEs+ | 9 | 8 | 8 | 7 | 6 | 4 | 4 |
| irAEs- | 79 | 62 | 45 | 32 | 19 | 10 | 6 |

B.

| irAEs+ | 9 | 8 | 7 | 5 | 4 | 2 | |
| irAEs- | 79 | 40 | 25 | 20 | 13 | 5 | 2 |

Figure 1

Association between irAEs and clinical outcomes. Kaplan−Meier plots of (A) overall survival (OS) and (B) progression-free survival (PFS) in patients who developed irAEs (n=9), as compared with patients without irAEs (n=79) (red line, irAEs group; blue line, no-irAEs group). The log-rank test was used to compare survival curves. irAEs indicates immune-related adverse events. All p values those less than .05 were considered statistically significant.
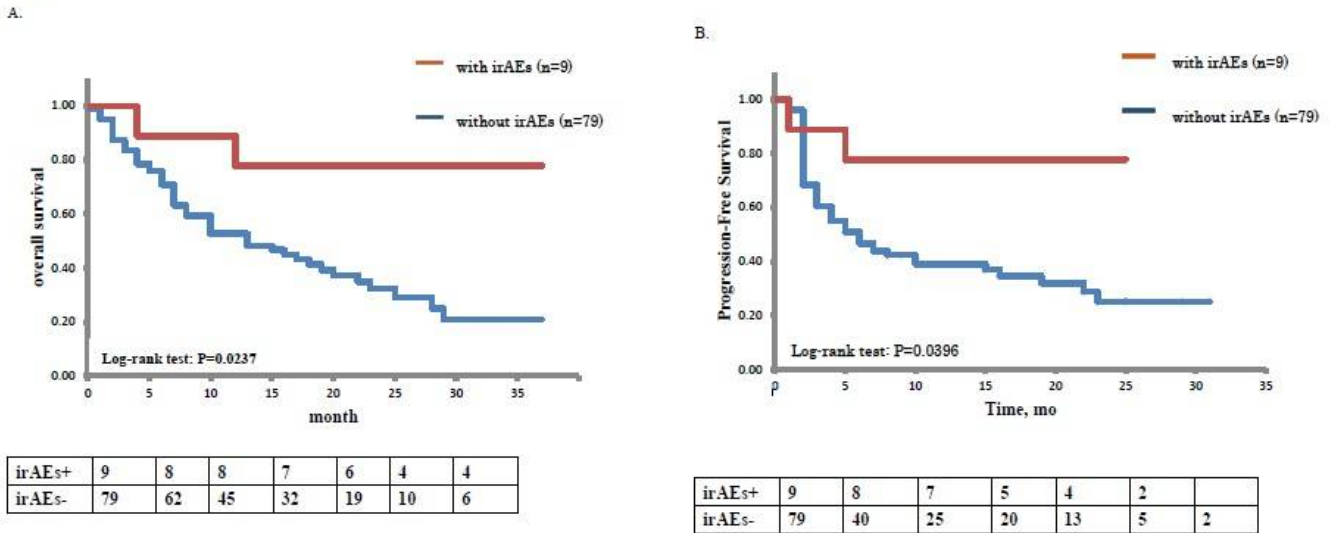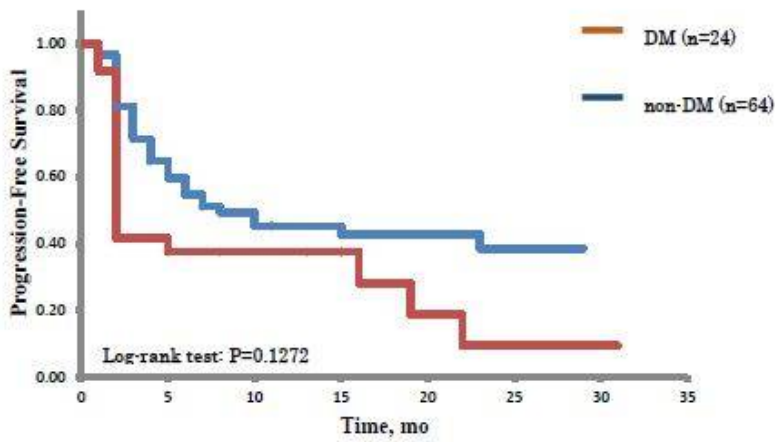
Figure 1

A.

B.

irAEs+	9	8	8	7	6	4	4
irAEs-	79	62	45	32	19	10	6

irAEs+	9	8	7	5	4	2	
irAEs-	79	40	25	20	13	5	2

Figure 1

Association between irAEs and clinical outcomes. Kaplan–Meier plots of (A) overall survival (OS) and (B) progression-free survival (PFS) in patients who developed irAEs (n=9), as compared with patients without irAEs (n=79) (red line, irAEs group; blue line, no-irAEs group). The log-rank test was used to compare survival curves. irAEs indicates immune-related adverse events. All p values those less than .05 were considered statistically significant.
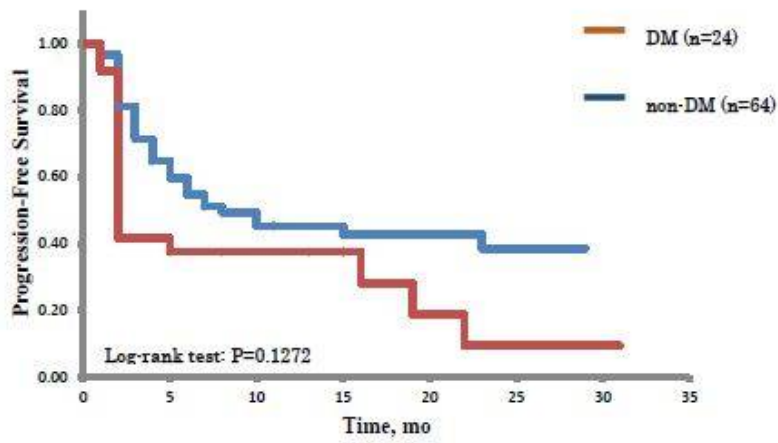
Figure 2

DM	24	17	12	9	6	5	3
non-DM	64	53	41	30	20	10	6

Figure 2

Kaplan–Meier curves of cancer-specific progression-free survival in the DM and non-DM groups (red line, DM group; blue line, non-DM group).
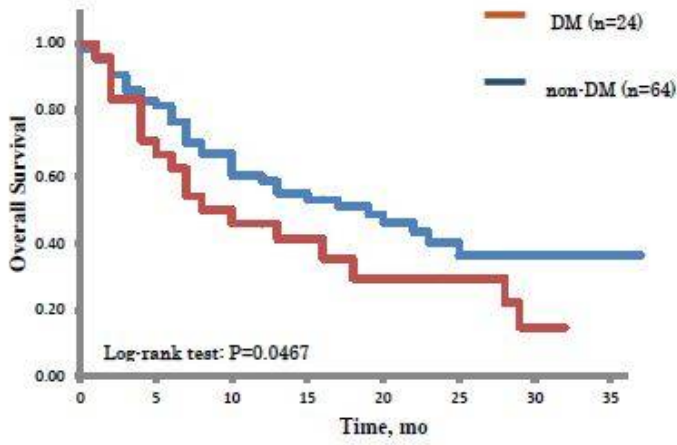
Figure 2

| DM | 24 | 17 | 12 | 9 | 6 | 5 | 3 |
| non-DM | 64 | 53 | 41 | 30 | 20 | 10 | 6 |

Figure 2

Kaplan–Meier curves of cancer-specific progression-free survival in the DM and non-DM groups (red line, DM group; blue line, non-DM group).
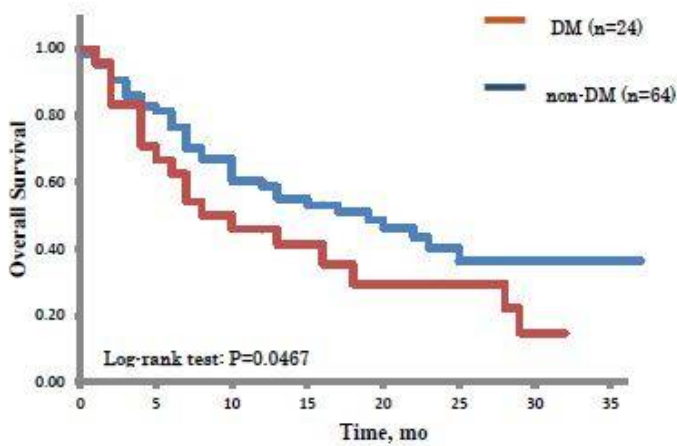
Figure 3

| DM | 24 | 10 | 6 | 3 | 2 | 2 | 1 |
| non-DM | 64 | 38 | 24 | 18 | 12 | 6 | |

Figure 3

Kaplan−Meier curves of overall survival in the DM and non-DM groups (red line, DM group; blue line, non-DM group).

Figure 3

Kaplan–Meier curves of overall survival in the DM and non-DM groups (red line, DM group; blue line, non-DM group).

Supplementary Files

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- STROBEchecklistv4combined.docx
- Supplementary13.pdf
- Supplementary13.pdf