Association of physical activity with survival and severe immune-related adverse events in patients undergoing immune checkpoint inhibition.

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Layman summary

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For patients diagnosed with advanced-stage cancer, immunotherapies, known as immune checkpoint inhibitors (ICIs), have improved outcomes for many patients. These new treatments target the immune system to maximise its function and attack cancer cells. However, there is a major downside to these drugs: they can cause severe adverse events due to the heightened immune response and are known as immune-related adverse events (irAEs). The novelty of these drugs highlights that further research is needed to find specific characteristics and lifestyle behaviours of patients that could affect overall survival (OS) and the occurrence of immune-related adverse events.

Given the well-established connection between exercise and improved immune-system function, it is hypothesized that physical activity (PA) could enhance the effectiveness of immunotherapy. In this study, we investigated the association between PA and OS and the development of irAEs of patients undergoing ICI therapy.

To conduct this research, participants reported their average weekly PA levels through a questionnaire, at the onset of treatment, and relevant clinical data was collected. The main research questions were studied using various statistical analyses including survival analysis and logistic regression, for OS and correlations with irAEs, respectively.

Our results show that patients who report higher levels of PA have improved OS, and lower occurrence of irAEs, however future research is needed to investigate whether sedentary patients could benefit from increased PA after diagnosis.

Abstract

Introduction

Immune checkpoint inhibitors (ICIs) can induce very durable responses in metastatic cancer. However, they frequently cause severe immune-related adverse events (irAEs). While physical activity (PA) has been associated with diminished side effects and better prognoses in chemotherapy-treated patients, these associations are currently unknown for ICI-treated patients. We aimed to study the association between PA, overall survival (OS), and irAE occurrence in patients undergoing ICI.

Methods

Patients receiving ICI were enrolled in the UMCU UNICIT cohort. All participants who completed the PA-SQUASH questionnaire at start of treatment were included. PA was quantified by calculating Metabolic Equivalent Task (MET) hours per week and moderate to vigorous sport and leisure time activity. Association of PA with OS was assessed using Cox proportional hazard regression. Association of PA with occurrence of a severe irAE (grade 3 or higher) within one year was evaluated using logistic regression including patients with at least one year follow-up. All analyses were performed using PA categorically, linearly, and flexibly with the use of restricted cubic splines and adjusted for sex, age, tumour type, treatment intent and ICI type.

Results

In total, 251 patients were included, with a median follow-up of 20 months. Compared to low levels of total PA, moderate and high levels of total MET-hours were associated with prolonged survival (adjusted HR: 0.56 (95%CI 0.31-1.02) and 0.47 (95%CI 0.26-0.86), respectively).

Compared to patients with low PA levels, patients with moderate or high levels of total PA had lower adjusted odds of developing severe irAEs within one year (adjusted odds ratios: 0.35 (95%CI 0.12-0.90) and 0.19 (95%CI 0.06-0.56), respectively). Similar trends were observed for both outcomes, when analysing moderate to vigorous PA.

Conclusion

Higher physical activity levels at start of ICI treatment are associated with prolonged survival and lower risk of severe irAEs. Future research is needed to investigate whether inactive patients benefit from increasing PA levels after diagnosis.

INTRODUCTION

Over the past decade, immunotherapy has revolutionised the cancer treatment landscape. Specifically, the emergence of immune checkpoint inhibitors (ICI) has significantly improved patient prognosis and extended survival for many individuals previously considered untreatable [1–3].

ICI therapy involves monoclonal antibodies that target immune checkpoints, the proteins on cell surfaces that regulate and limit immune response. By disrupting these interactions, ICI treatment can magnify the immune system's anti-tumour response [4]. Despite the clinical benefits, ICI can cause immune related adverse events (irAEs). These adverse events can affect almost every organ or system, ranging from mild to severe with some cases proving fatal [3,5,6] .The incidence and onset of irAEs can vary between patients and the type of ICIs administered, with a median onset being approximately 4 months from the start of treatment[7]. Only 5-7% of patients experience irAEs more than one year after ICI initiation.

Research is being conducted on patient characteristics and lifestyle habits that could impact survival and irAEs occurrence in patients treated with ICI. Genetics, microbiome, sleep and physical activity are all examples of variables intrinsically related to the immune system that could therefore affect ICI efficacy and safety [8–11]. Additionally, several studies have linked higher levels of PA with improved overall survival, as well as diminished side effects for patients treated with chemotherapy [12–14].

This plethora of evidence supports the hypothesis that routine PA could have a synergistic effect with ICI therapy and could potentially enhance treatment efficacy [15]. With this study, we aimed to investigate the association between PA at start of treatment on OS and irAEs in patients undergoing ICI therapy.

METHODOLOGY

Study sample

Patients from the UNICIT biobank within the Universitiy Medical Center Utrecht, the Netherlands were included in this observational study [16]. Adult patients undergoing ICI treatment, with anti-PD-1 monotherapy, combined anti-CTLA-4 plus anti-PD-1 (cICI) and anti-PD-(L)1 combined with chemotherapy (ICI + chemotherapy) were prospectively enrolled between October 2019 and October 2022 and followed up until January 31st 2023. Biological material was collected, and health-related questionnaires were filled in at baseline. Patients were followed up periodically and their clinical data and vital statuses recorded.

The UNICIT biobank study was not considered subject to the Dutch Medical Research with Human Subjects Law by the medical research ethics committee and was approved by the institutional biobank review committee (Tcbio 18-123). All participants provided written informed consent.

Assessment of physical activity

Physical activity was assessed at treatment initiation using the validated Dutch short questionnaire to assess health enhancing physical activity (SQUASH) [17]. The aim of the SQUASH is to estimate the intensity and amount of PA during an average week. The questions are categorised into the following topics: commuting activities, activities at work and school, household tasks and sports, and leisure time activity.

The self-reported values were transformed into a Metabolic Equivalent of Task score for each activity and domain, which was based on the Ainsworth Compendium of Physical Activities categorisation. The levels of intensity were ranked as light (<3.0 METs), moderate (3.0–5.9 METs), or vigorous (≥6.0 METs)[18].

Total MET hours per week (MET-hours) were obtained by multiplying time spent on the activity with its corresponding MET value. Moderate to vigorous sports and leisure time (MVPA-SL) was quantified as time spent on activities with ≥3.0 MET within sports and leisure time domains [13].

Outcome assessment

Overall survival (OS) was defined as time from therapy initiation until death, and patients were censored at last follow-up date if they were still alive. Vital status details, including cause of death and date were retrieved from medical records. Data was recorded in the UNICIT database and updated periodically, including last follow up.

Clinically relevant immune related adverse events were defined by the treating physician according to the Common Terminology Criteria for Adverse Events (CTCAE) as grade 3 or above [24]. Only severe

immune related adverse events within the first year were considered for analyses, and to prevent misclassification patients who started ICI at least one year before the data cut off were included (February 1st, 2023)[19]. The outcomes used in the analyses correspond to the last follow up update of the cohort, that took place in February 2023.

Statistical analysis

To investigate the potential association between physical activity (PA) and overall survival (OS), we performed categorical and continuous analyses of PA. We defined PA categories based on tertiles, ensuring each category had a comparable number of patients when determining the cut-off points. The categories were established for both MET-hours and moderate to vigorous physical activity (MVPA-SL), with the lowest tertile of each measure serving as a reference. We used the Kaplan Meier method to generate survival curves and employed multivariable Cox regression models to quantify hazard ratios (HRs) with 95% confidence intervals (CI) to assess the relationship between OS and PA. We visually evaluated the proportional hazards assumption using Schoenfeld residuals and found no violations.

We checked for linear associations using PA as a continuous determinant and accounted for potential non-linear effects of PA on OS by using a Cox model with restricted cubic splines and three knots of flexibility for both MET-hours and MVPA-SL. This resulted in HR plots that represented the estimated change in HR alongside a 95% CI.

To explore the correlation between PA and incidence of immune-related adverse events (irAEs), we used logistic regression models on patients with at least one year of follow-up, accounting for enrolment time differences. We used the same approach as with OS, first using PA in categorical form (tertiles) and then utilizing restricted cubic splines to model PA continuously with three knots. We obtained odds ratios (ORs) and portrayed graphs of the estimates.

All models, including restricted cubic splines, were adjusted for age, sex, treatment intent (palliative or adjuvant), ICI therapy type (combination therapy, PD-L1 inhibitor, and ICI + chemo or targeted therapy), and type of primary tumour. We conducted sensitivity analyses by restricting the models to the subgroup of patients with melanoma and adding lactate dehydrogenase (LDH) levels, an established risk factor for OS and irAEs in melanoma patients, as an added covariate. Analyses were also performed on patients with performance status 0-1 in the ECOG scale.

Additionally, to account for death as a competing risk, we used a Fine and Gray sub-distribution hazard model [20] to further characterize the relationship between the occurrence of irAEs and PA, with death as a competing risk.

To further confirm the results obtained on the association with irAE, we performed the analyses on patients treated only with combination ICI therapy.

We conducted all data management and statistical analyses using R version 4.2.2.All statistical tests were two-sided with an alpha level of 0.05.

RESULTS

Patient population

A cohort of 251 patients were included in this study, with a median follow-up duration of 20 months. The majority of patients were male (66.5%), with a mean age of 64 years, and received palliative treatment (59.8%). The patients' weekly moderate-to-vigorous physical activity (MVPA-SL) in MET-hours ranged from 0 to 38.5, with a median of 4 MET-hours/week. Baseline and treatment characteristics of the patients were stratified by tertiles of weekly MET-hours and for the total study population (**Table 1**). When comparing the tertiles, the distribution of characteristics was consistent except for treatment intent. Most patients received anti-PD(L)-1 therapy.

Physical activity and overall survival

A total of 70 deaths occurred during follow-up time among the 251 patients. The survival curves stratified by tertiles, of both, MET-hours and MVPA-SL (hours week) showed that the median survival time was only reached by the low tertile of the MVPA-SL determinant (**Figure 1a**, **Figure 1c**, respectively)

Hazard ratios obtained from the Cox regression models, showed that moderate and high levels of MET-hours are associated with improved overall survival, as compared with the lowest tertile (adjusted HR: 0.56 (95%CI 0.31-1.02) and 0.47 (95%CI 0.26-0.86), respectively). To further evaluate the exact nature of the relationship between PA and survival, we used restricted cubic spline models to assess the presence of a possible nonlinear association (**Figure 1b**). Compared to zero MET-hours per week, there was a steep decline until approximately 100 MET-hours per week, after which there was a plateau of the estimate which can be assumed to be due to the low number of patients reporting extremely high values of PA.

Similar trends were observed for the MVPA-SL determinant, for which higher levels of moderate-to-vigorous PA were associated with prolonged survival (adjusted HR: 0.69 (95% CI 0.40-1.20) and 0.57 (0.30-1.09), respectively). Restricted cubic spline graphs were also obtained for MVPA-SL, indicating a similar nonlinear association with OS.

These results were supported by sensitivity analyses restricted to melanoma patients, with the addition of LDH in the model, and this yielded comparable estimates. When restricting to patients with ECOG performance status 0 or 1, comparable trends were shown, although no longer significant (**Supplementary Table 1 and 2; Supplementary Figure 1 and 2**).

Physical activity and immune related adverse events

A total of 209 patients had at least one year of follow up and were included. One patient that developed irAE after 16 months and was therefore classified as 'without irAE' in the analyses. A total of thirty-eight patients developed a severe irAEs within the first year.

An adjusted logistic regression model was used to analyse the data and showed that patients reporting moderate or high levels of MET-hours/week had lower odds of developing severe irAEs (OR 0.35 (95%CI 0.12-0.90) and 0.19 (95%CI 0.06-0.56), respectively). This result was supported by the restricted cubic spline models, which showed that an increase in MET-hours per week was associated with a decreased risk of severe irAEs (**Figure 2a**). Similarly, moderate, and high levels of MVPA-SL were associated with lower odds of developing irAEs compared to low levels (0.41 (0.15-1.03) and 0.11 (95%CI 0.03-0.36), respectively).

The results were further supported by visual representations of the cubic splines (**Figure 2b**), which showed a clear decrease in the odds of irAEs for both higher MET-hours/week and moderate to vigorous MET-hours, with the lowest odds ratio values corresponding to the interval of 100 to 150 MET-hours/week. However, past the plateau of 100 MET-hours and 10 MVPA-SL MET-hours, the curves and 95%CI intervals widened, indicating reduced reliability as sample size for extreme values of PA is lower.

When restricting to patients treated with combination ICI therapy, similar associations were observed between higher PA and lower odds of irAE occurrence (**Supplementary Table 3**; **Supplementary Figure 3**).

A Fine and Gray subdistribution hazard model was used to further characterize the correlation between PA and irAEs. Results indicated that higher PA levels decreased the incidence of irAEs, in both instances, for total MET-hours and MVPA (**Supplementary Table 4**; **Supplementary Figure 4**).

DISCUSSION

In this observational study, our aim was to investigate the relationship between physical activity, overall survival, and immune related adverse events at start of ICI treatment in patients undergoing ICI therapy. Our results indicated that moderate to high levels of PA at the start of ICI treatment can be associated with improved OS compared to those reporting low levels of PA. Additionally, patients in high PA categories had lower odds of developing severe ICI toxicity compared to those reporting low PA levels.

The underlying mechanisms of the immunomodulatory effects of PA are complex, but current research suggests that physical activity has the ability to improve immunosenescence and promote anti-tumour responses by creating a more "normalised" microenvironment [20,9,12]. While previous studies have demonstrated the benefits effects of physical activity and the importance of a healthy and active lifestyle in chemotherapy treated patients [12–14,21], the association with immunotherapy is still unclear. Recently a study by Liu et al concluded that regular PA improved therapeutic endpoint of PD(L)-1 based therapy [10]. Though, sample size was one of their main limitations, our findings are in line with their conclusions, showcasing the potential benefits of PA in our population.

It is important to acknowledge that our study has some limitations, mainly related to the assessment and quantification of PA. Self-reported measures are vulnerable to being overreported [22]. This study took place during the COVID-19 pandemic, during which the everyday lives and routines of many were disrupted, signifying that the reported PA levels may not accurately reflect all participants' average week.

Nevertheless, the use of a validated PA questionnaire such as SQUASH and statistical tools such as restricted cubic splines helped to provide reliable insights into the effect of PA on overall survival and irAE incidence in our population. Furthermore, the single measurement of PA at treatment initiation increases the risk of reverse causation, which we addressed by adjusting for prognostic factors in our statistical analysis.

The association between post-diagnosis physical activity and improved overall survival suggests that healthcare providers should encourage patients to engage in physical activity as part of their cancer treatment plan. Additionally, the association between physical activity and lower incidence of immune-related adverse events suggests that physical activity may have a protective effect on the immune system, potentially increasing ICI efficacy.

Our study provides valuable insights into the association between PA and OS in patients undergoing ICI therapy. The use of a prospective cohort and with good reporting of outcomes and clinical information, as well as using robust statistical techniques, including the use the use of both linear and nonlinear models enabled us to shape this relationship as well as the direction of future research.

These results highlight the importance of promoting a physically active lifestyle in patients with cancer, and further research is warranted to explore the association with extreme levels of physical activity and OS and irAEs.

CONCLUSIONS

Higher physical activity levels at start of ICI treatment are associated with prolonged survival and reduce occurrence of severe irAEs. Future research is needed to investigate whether patients with low PA levels benefit from increasing PA levels after diagnosis.

REFERENCES

Ethics statement

The UNICIT biobank study was not considered subject to the Dutch Medical Research with Human Subjects Law by the medical research ethics committee and was approved by the institutional biobank review committee (TCbio 18-123). All participants provided written informed consent.

Informed Consent Statement:

Written informed consent was obtained from all subjects involved in the current analysis.

Funding

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Table 1. Patient characteristics by tertiles of MET-hours per week

Characteristics	**Low PA (n = 84)** [0,51]	**Moderate PA (n = 83)** [51,101]	**High PA (n = 84)** [101,371]	**Total (n = 251)** [0, 371]
MET-hours/week, [Q1, Q3	30.0 [16.9-39.9]	75.7 [62.3-86.4]	128.9 [112.7-165.6]	75.7 [40.0-112.7]
MVPA-SL-(hours/week, median [Q1, Q3]	0.875 [0, 2.44]	5.00 [1.50, 8.00]	8.88 [4.38, 15.0]	4.00 [0.875, 8.50]
Sex				
Male	54 (64.3%)	60 (72.3%)	53 (63.1%)	167 (66.5%)
Female	30 (35.7%)	23 (27.7%)	31 (36.9%)	84 (33.5%)
Age (years)				
Median [Q1, Q3]	67.0 [59.0, 73.0]	65.0 [54.0, 73.0]	61.5 [54.8, 69.3]	64.0 [55.0, 73.0]
Treatment intent				
Adjuvant	22 (26.2%)	37 (44.6%)	42 (50.0%)	101 (40.2%)
Palliative	62 (73.8%)	46 (55.4%)	42 (50.0%)	150 (59.8%)
Therapy				
anti-PD-(L)1	52 (61.9%)	60 (72.3%)	53 (63.1%)	165 (65.7%)
clCl	21 (25.0%)	18 (21.7%)	22 (26.2%)	61 (24.3%)
ICI + chemotherapy	11 (13.1%)	5 (6.0%)	9 (10.7%)	25 (10.0%)
Primary tumour				
Melanoma	40 (47.6%)	54 (65.1%)	59 (70.2%)	153 (61.0%)
NSCLC	18 (21.4%)	8 (9.6%)	12 (14.3%)	38 (15.1%)
RCC	10 (11.9%)	9 (10.8%)	9 (10.7%)	28 (11.2%)
Other	16 (19.0%)	12 (14.5%)	4 (4.8%)	32 (12.7%)
Cancer stage				
III	25 (29.7%)	38 (48.8%)	41 (48.8%)	104 (41.4%)
IV	58 (60.8)	43 (51.8%)	43 (51.2%)	144 (57.4%)
Other	1 (1.2%)	2 (2.4%)	0 (0%)	3 (1.2%)
LDH				

<1x ULN	62 (74.7%)	73 (90.1%)	70 (85.4%)	70 (85.4%)
1-2xULN	19 (22.9%)	8 (9.9%)	10 (12.2%)	10 (12.2%)
>2x ULN	2 (2.4%)	0 (0%)	2 (2.4%)	2 (2.4%)
Missing	1 (1.2%)	2 (2.4%)	2 (2.4%)	2 (2.4%)
ECOG performance status				
0	31 (36.9%)	39 (47.0%)	56 (66.7%)	126 (50.2%)
1	38 (45.2%)	41 (49.4%)	22 (26.2%)	101 (40.2%)
2	12 (14.3%)	1 (1.2%)	3 (3.6%)	16 (6.4%)
3	2 (2.4%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
unknown	1 (1.2%)	2 (2.4%)	3 (3.6%)	6 (2.4%)

Low PA, moderate PA, and high PA refer to tertiles of weekly MET-hours. Abbreviations: PA: physical activity; MET: metabolic equivalent task; MVPA-SL: moderate-to-vigorous-intensity physical activity during sports and leisure time; Q1: first quartile, Q3: third quartile; N: number of patients; anti-PD-(L)1: anti-programmed cell death (ligand) 1 monotherapy; cICI: combined immune checkpoint inhibition; NSCLC: non-small cell lung carcinoma; RCC: renal cell carcinoma

Figure 1: Association between physical activity at immune checkpoint inhibitor initiation and overall survival. Kaplan Meier curves (**a,c**) and restricted cubic spline models (**b,d**) of survival of patients with cancer treated with immune checkpoint inhibitors stratified by physical activity levels. **a,b** Metabolic Equivalent Task (MET) hours per week. **c,d** Time spent on moderate-to-vigorous-intensity activities during sports and leisure time (MVPA-SL). Restricted cubic spline models (**b,d**) represent hazard ratio (HR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, tumour type, treatment intent and type of therapy.

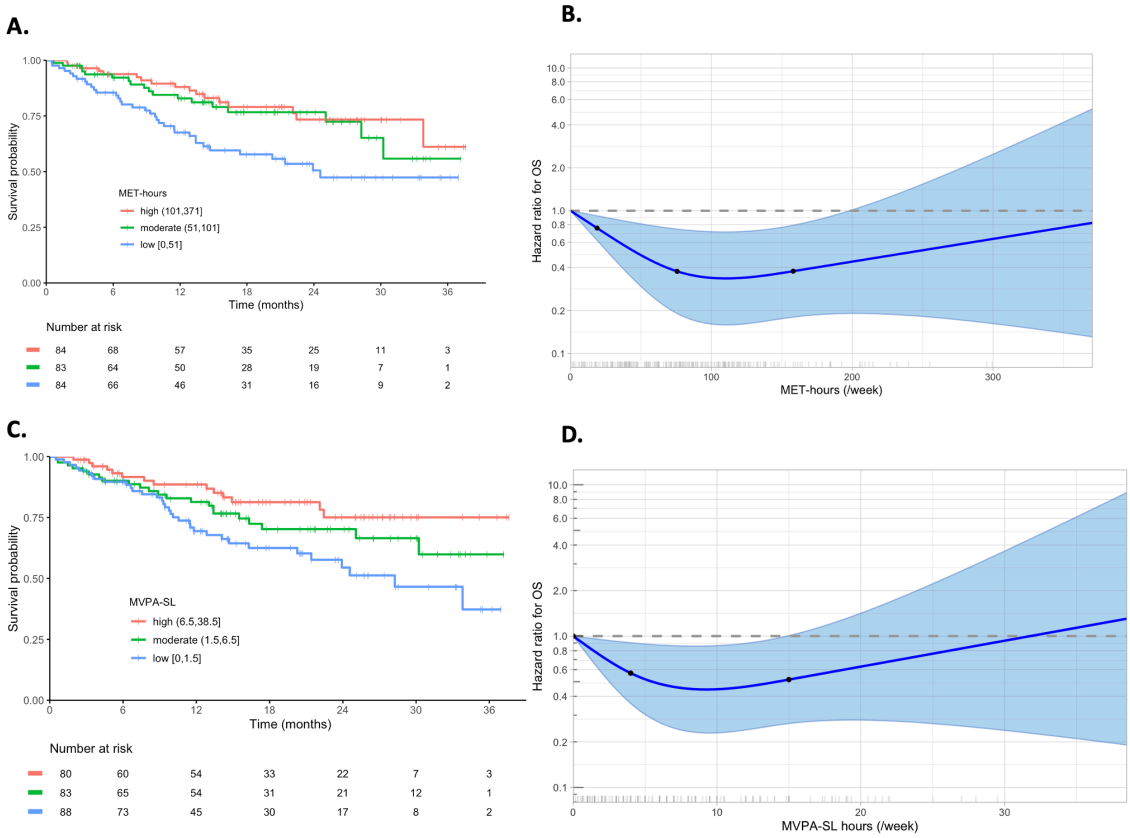
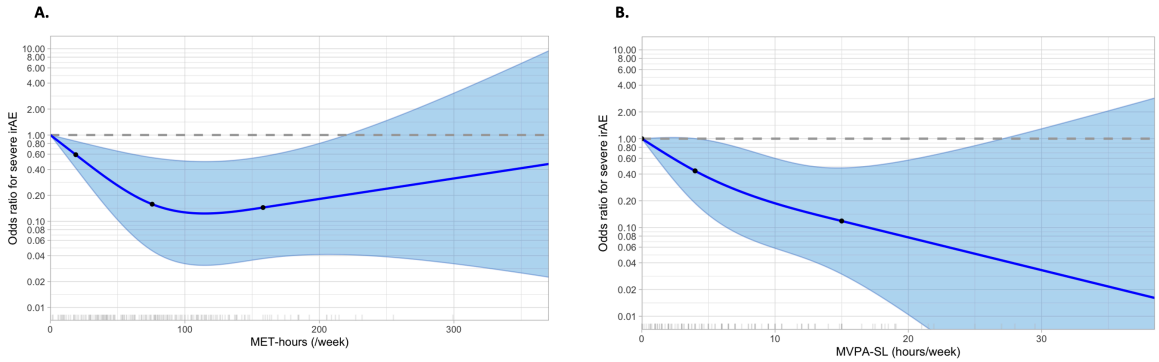


Figure 2: Association between physical activity at immune checkpoint inhibitor initiation and severe immune-related adverse events (irAE) within one year in patients with cancer. a Metabolic Equivalent Task (MET) hours per week. **b** Time spent on moderate-to-vigorous-intensity physical activity during sports and leisure time (MVPA-SL). These curves represent odds ratio (OR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, tumour type, treatment intent and type of therapy.



SUPPLEMENTARY MATERIAL

Supplementary Table 1: Association of physical activity at immune checkpoint inhibitor initiation with overall survival in patients with melanoma.

Total physical activity (MET hours/week)	**HR_{adj} (95%CI) of death**
Low [0 to 51]	ref
Intermediate (51 to 101]	0.82 (0.32-2.11)
High (101 to 371]	0.69 (0.26-1.81)
Moderate to vigorous leisure time and sports (hours/week)	**HR_{adj} (95%CI) of death**
Low [0 to 1.5]	ref
Intermediate (1.5 to 6.5]	0.44 (0.16-1.19)
High (6.5 to 38.5]	0.59 (0.21-1.63)

Abbreviations: HR: hazard ratio; CI: confidence interval; MET: Metabolic Equivalent Task. These analyses are adjusted for sex, age, setting (palliative, adjuvant), type of therapy, and LDH levels.

Supplementary Table 2: Association of physical activity at immune checkpoint inhibitor initiation with overall survival in patients with ECOG performance status 0 or 1.

Total physical activity (MET hours/week)	**HR_{adj} (95%CI) of death**
Low [0 to 51]	ref
Intermediate (51 to 101]	0.73 (0.39 -1.38)
High (101 to 371]	0.56 (0.29- 1.07)
Moderate to vigorous leisure time and sports (hours/week)	**HR_{adj} (95%CI) of death**
Low [0 to 1.5]	ref
Intermediate (1.5 to 6.5]	0.68 (0.37- 1.24)
High (6.5 to 38.5]	0.65 (0.32 - 1.33)

Abbreviations: HR: hazard ratio; CI: confidence interval; MET: Metabolic Equivalent Task. These analyses are adjusted for sex, age, tumor type, setting (palliative, adjuvant), and type of therapy.

Supplementary Table 3: Association of physical activity at initiation of ipiliumumab+nivolumab with severe immune-related adverse events (irAEs) within one year.

Total physical activity (MET hours/week)	**OR_{adj} (95%CI) of severe irAE**
Low [0 to 51]	ref
Intermediate (51 to 101]	0.46 (0.10-1.89)
High (101 to 371]	0.54 (0.13-2.14)
Moderate to vigorous leisure time and sports (hours/week)	**OR_{adj} (95%CI) of severe irAE**
Low [0 to 1.5]	ref
Intermediate (1.5 to 6.5]	0.58 (0.14-2.26)
High (6.5 to 38.5]	0.31 (0.06-1.41)

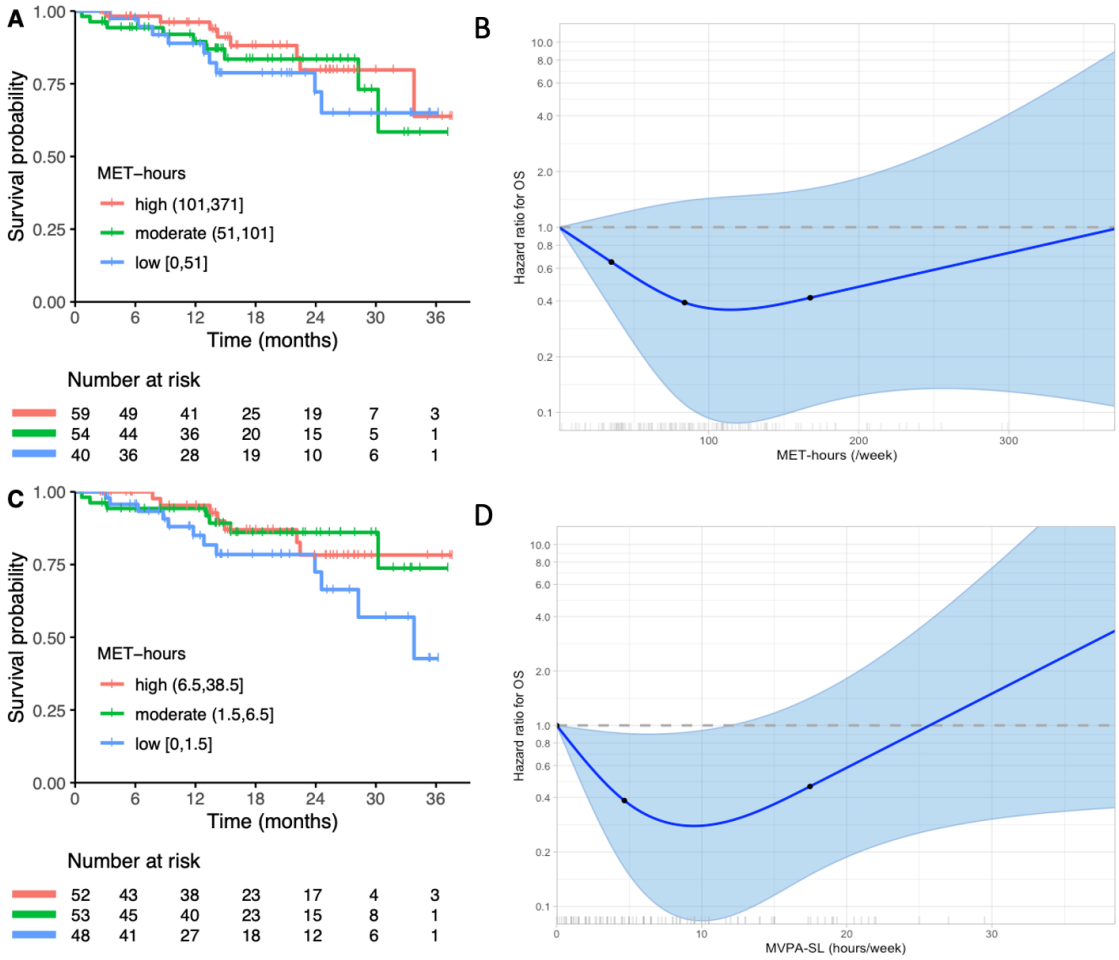
Abbreviations: OR: odds ratio; CI: confidence interval; MET: Metabolic Equivalent Task. These analyses are adjusted for sex and age.

Supplementary Table 4: Fine and Gray subdistribution hazard model of the association of physical activity at immune checkpoint inhibitor initiation with severe immune-related adverse events (irAE) in patients with cancer, accounting for death as competing risk.

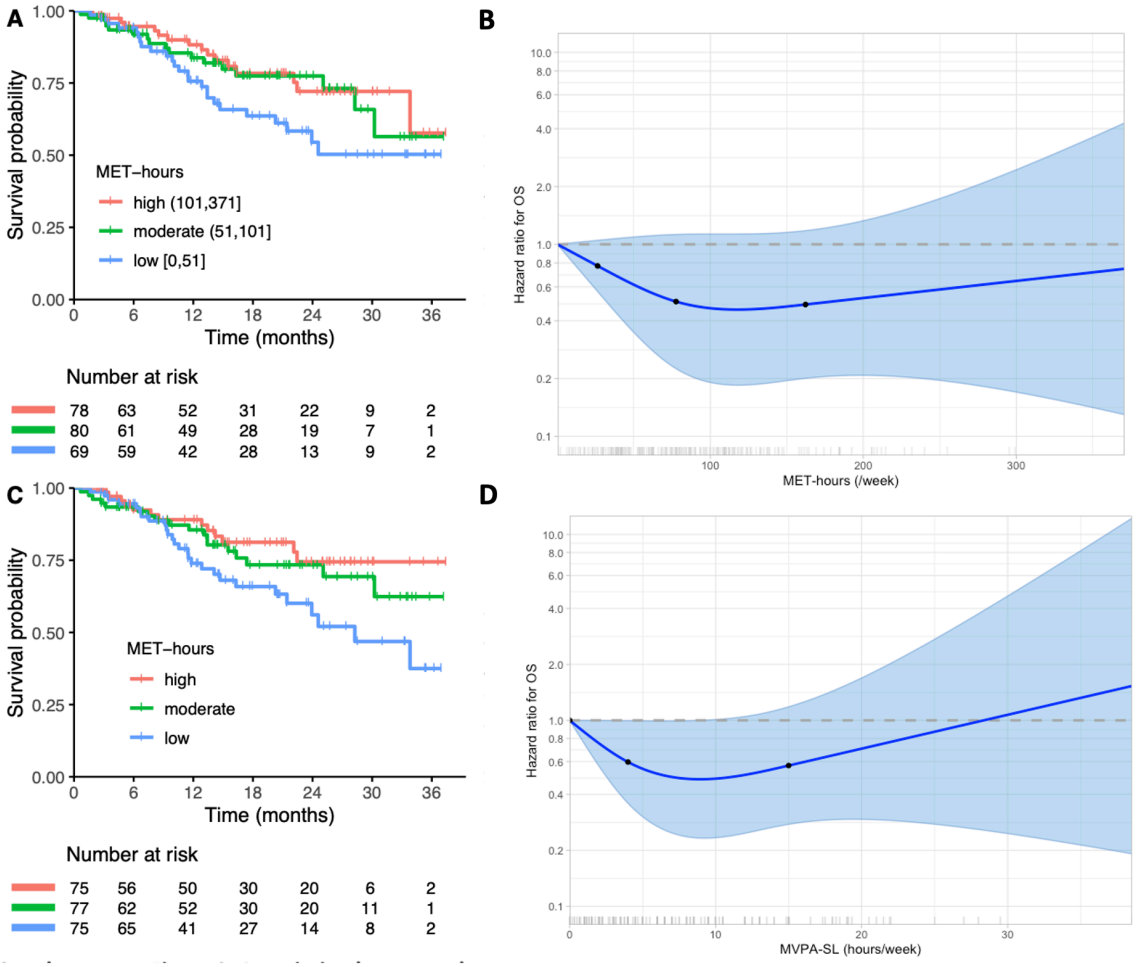
Total physical activity (MET-hours/week)	**HR (95%CI) of severe irAE**
Low [0 to 51]	ref
Intermediate (51 to 101]	0.46 (0.21-1.03)
High (101 to 371]	0.43 (0.21-0.90)
Moderate to vigorous leisure time and sports (hours/week)	**HR (95%CI) of severe irAE**
Low [0 to 1.5]	ref
Intermediate (1.5 to 6.5]	0.59 (0.28-1.23)
High (6.5 to 38.5]	0.37 (0.16-0.86)

HR, subdistribution hazard ratio; CI confidence interval; MET, Metabolic equivalent task. These analyses are djusted for: sex, age, tumor type, setting (palliative, adjuvant), and type of therapy.

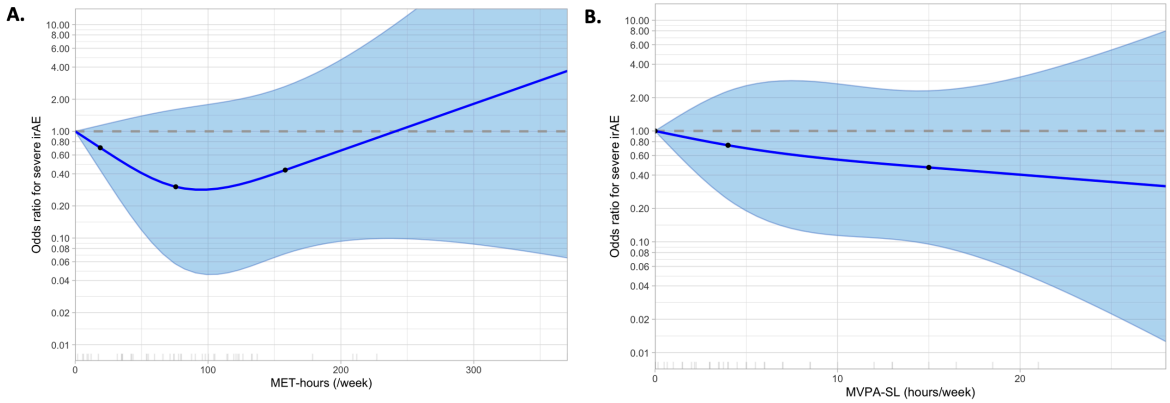
Supplementary Figure 1: Association between physical activity at immune checkpoint inhibitor initiation and overall survival in patients with melanoma. Kaplan Meier curves (**a,c**) and restricted cubic spline models (**b,d**) of survival of patients with melanoma treated with immune checkpoint inhibitors stratified by physical activity levels. **a,b** Metabolic Equivalent Task (MET) hours per week. **c,d** Time spent on moderate-to-vigorous-intensity activities during sports and leisure time (MVPA-SL). Restricted cubic spline models (**b,d**) represent hazard ratio (HR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, treatment intent, type of therapy, and lactate dehydrogenase (LDH).



Supplementary Figure 2: Association between physical activity at immune checkpoint inhibitor initiation and overall survival in patients with cancer with ECOG performance status 0 or 1. Kaplan Meier curves (**a,c**) and restricted cubic spline models (**b,d**) of survival of patients with melanoma treated with immune checkpoint inhibitors stratified by physical activity levels. **a,b** Metabolic Equivalent Task (MET) hours per week. **c,d** Time spent on moderate-to-vigorous-intensity activities during sports and leisure time (MVPA-SL). Restricted cubic spline models (**b,d**) represent hazard ratio (HR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, treatment intent, type of therapy, and lactate dehydrogenase (LDH).



Supplementary Figure 3: Association between physical activity at immune checkpoint inhibitor initiation and severe immune-related adverse events (irAE) in patients with cancer. a Metabolic Equivalent Task (MET) hours per week. **b** Time spent on moderate-to-vigorous-intensity physical activity during sports and leisure time (MVPA-SL). These curves represent odds ratio (OR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, tumour type, treatment intent and type of therapy.



Supplementary Figure 4: Cumulative incidence functions of death and severe immune-related adverse events (SirAE) according to physical activity at immune checkpoint inhibitor initiation. a Metabolic Equivalent Time (MET) hours per week; **b** time spent on moderate-to-vigorous-intensity physical activity during sports and leisure time (MVPA-SL).