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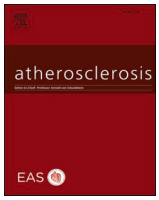

Arterial inflammation on [^{18}F]FDG PET/CT in melanoma patients treated with and without immune checkpoint inhibitors: *CHECK-FLAME I*

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ABSTRACT

Background and aims: Immune checkpoint inhibitors (ICIs) revolutionized cancer treatment. However, ICIs may increase the immune response to non-tumor cells, possibly resulting in increased arterial inflammation, raising the risk of atherosclerotic events. Nevertheless, malignancies may induce a pro-inflammatory state and the association between ICIs and arterial inflammation remains to be clarified. This study aims to assess differences in increase in arterial inflammation between patients with advanced melanoma treated with ICIs compared to a control group without ICIs.

Methods: Patients with advanced melanoma who underwent [^{18}F]FDG PET/CT scans at baseline, 6 months (T1) and 18 months (T2) were included in this retrospective observational study. Arterial inflammation was evaluated in eight segments by calculating the target-to-background ratio (TBR). The primary study outcome was the difference in increase in mean TBR_{max} between patients treated with and without ICIs.

Results: We included 132 patients of whom 72.7 % were treated with ICIs. After exclusion for the use of anti-inflammatory medication, patients treated with ICIs showed a significant increase in mean TBR_{max} between baseline and T1 from 1.29 ± 0.12 to 1.33 ± 0.13 ($p = 0.017$), while in the control group, no change in mean TBR_{max} (1.30 ± 0.12 to 1.28 ± 0.10, $p = 0.22$) was observed ($p = 0.027$). During longer follow-up, mean TBR_{max} remained stable in both groups. Arterial inflammation increased significantly after ICI therapy in patients without active inflammation ($p < 0.001$) and in patients without calcifications ($p = 0.013$).

Conclusions: A significant increase in arterial inflammation as measured on [^{18}F]FDG PET/CT was observed in patients with advanced melanoma treated with ICIs only in the first six months after initiation of therapy, whereas no changes were observed in the control group. Moreover, arterial inflammation was mainly increased in patients without pre-existing inflammatory activity and with non-calcified lesions.

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1. Introduction

Immune checkpoint inhibitor (ICI) therapy has revolutionized cancer treatment in the past decade [1]. Nowadays, more than 40 % of the patients with cancer are eligible for ICI treatment, with unprecedented response rates [2]. ICIs are monoclonal antibodies directed against co-inhibitory molecules, including cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed death-ligand 1 (PD-L1), programmed cell death 1 (PD-1) and/or lymphocyte activation gene-3 (LAG-3). By blocking these inhibitory proteins, ICIs promote T cell activation and elicit potent anti-tumor immune responses [3,4]. The increasing clinical application of ICIs increased our knowledge on their toxicity. In addition to common acute immune-related adverse events, ICI therapy may also affect more chronic inflammatory conditions, such as atherosclerosis, which is a chronic, low grade inflammatory disease of the large arteries and a major cause of cardiovascular disease (CVD) [3,5,6].

Prior studies have shown that ICI therapy is associated with a two-to-threefold increased risk of cardiovascular events, possibly due to inflammatory processes and development to unstable plaque [7–9]. Studies suggest that ICIs may induce T cell-mediated inflammatory processes by increasing T cell influx and, as a result of ICI-mediated T cell activation, T cells possibly trigger the initiation of atherosclerosis and development to unstable atherosclerotic plaques post ICI-therapy [3]. Therefore, treatment with ICIs could induce pro-atherogenic effects.

Arterial inflammation can be assessed on 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography with computed tomography (PET/CT) scans, which are routinely performed during cancer treatment, using the target-to-background ratio (TBR) [10,11]. Research with [^{18}F]FDG PET/CT scans in small cohorts of melanoma and (non-) Hodgkin lymphoma patients has suggested an increased uptake of [^{18}F]FDG in the large arteries post-ICI therapy [8,9].

However, studies comparing the increase of arterial inflammation on [^{18}F]FDG PET/CT scans of patients treated with ICIs to a control population have not been performed yet. As malignancies may also induce a pro-inflammatory state, the role of ICIs in this pathophysiological process has yet to be clarified. Therefore, the purpose of this study is to assess differences in increase of arterial inflammation in the large arteries on [^{18}F]FDG PET/CT scans in patients with advanced melanoma treated with ICI therapy compared to patients not treated with ICIs, but with surgical excision alone or in combination with targeted therapy or radiotherapy.

2. Patients and methods

2.1. Study population

Patients with resected or irresectable stage III/IV melanoma, who were referred to the outpatient medical oncology, dermatology or surgery department of the Leiden University Medical Center (LUMC) between 2016 and 2023 and underwent [^{18}F]FDG PET/CT scans at three predefined timepoints, were screened for eligibility. All patients in the exposure group were treated with ICIs as adjuvant therapy (resected stage III/IV) or as palliative treatment (irresectable stage IIIc/IV). Patients in the control group were treated with surgical excision alone, or in combination with targeted therapy or radiotherapy. These patients did not receive ICIs since adjuvant ICIs were not recognized as standard treatment prior to 2018. Patients were included in the study if [^{18}F]FDG PET/CT scans were available at baseline, defined as the most recent PET/CT scan before start of ICI therapy for the exposure group and <1 year after diagnosis of advanced melanoma for the control group, at T1, defined as a PET/CT scan 6 months after baseline scan and at T2, defined as a PET/CT scan 18 months after baseline scan. Patients were excluded if they had a history of coronary artery disease (CAD) and if the PET/CT scan did not meet the European Association of Nuclear Medicine (EANM) and EANM Research GmbH (EARL) criteria [12]. This study was approved by the local Medical Ethical Committee (METC LDD G21.202) and complies with the declaration of Helsinki.

2.2. Data collection

Data on demographics, laboratory results, [^{18}F]FDG PET/CT scans, medical history, medication and cardiovascular risk factors were collected through pharmacy records (HiX Version 6.3 Chipsoft, Amsterdam, The Netherlands). Data on cardiovascular events were gathered through the departmental Cardiology Information System (EPD-Vision®, Leiden, The Netherlands). Information regarding oncological characteristics (date of diagnosis, cancer therapy, metastases) was obtained from the internal oncology registry (OncDoc), which is connected to the Netherlands Cancer Registry. The cause of death was acquired from the civil municipal registry.

2.3. [^{18}F]FDG PET/CT acquisition

[^{18}F]FDG PET/CT scans were acquired on two EARL certified PET/CT scanners (Vereos and Gemini TF-64, Philips Healthcare, Best, the Netherlands) and reconstructed according to the EANM guidelines [13]. Patients fasted for at least 6 hours prior to intravenous administration of [^{18}F]FDG and were required to drink 1L of water in the 2 hours prior to the scan, according to the guidelines [14]. Acquisition of PET-images took place 60 min after [^{18}F]FDG administration according to the EANM guidelines. Prior to the PET acquisition, patients underwent a low-dose CT scan for attenuation correction purposes (Vereos: 120 kV, 35mA$_{eff}$, Gemini: 120 kV, 80mA$_{eff}$).

2.4. [^{18}F]FDG PET/CT image analysis

To assess arterial inflammation in the large arteries, eight arterial segments were analyzed: the left and right carotid artery, ascending aorta, aortic arch, thoracic descending aorta, abdominal aorta and left and right iliac artery. The researchers who analyzed the images were blinded for the cancer treatment strategy. In each arterial segment, a 1 cm^2 region of interest (ROI) was drawn covering the whole vessel diameter (carotid and iliac arteries) or vessel wall and part of the lumen (aortic segments) using dedicated post-processing software (Philips IntelliSpace Portal Version 12.1, Philips Healthcare, The Netherlands). The maximum standardized uptake value (SUV$_{max}$) per arterial segment was captured. To measure the blood pool activity, 1 cm^2 ROIs were drawn in the vena cava superior and vena cava inferior. ROIs in the blood pool covered solely the lumen and the blood pool activity (SUV$_{bloodpool}$), referring to the background SUV, was defined as the mean of the mean SUV (SUV$_{mean}$) of the vena cava superior and the SUV$_{mean}$ of the vena cava inferior. The TBR of each arterial segment was obtained by dividing the SUV$_{max}$ of each arterial segment by the SUV$_{bloodpool}$ [15]. The total TBR (TBR$_{total}$) per patient was the sum of the TBR values of all eight arterial segments. By dividing the TBR$_{total}$ by eight, the mean TBR$_{max}$ per patient was derived. The threshold TBR for increased inflammation in the arterial segments was defined as a TBR $\geq$ 1.6 according to the EANM position paper, as a TBR < 1.6 is associated with <5 % inflammation [15]. Myocardial uptake was not measured, as the fasting time required was <18 hours.

2.5. CT image analysis

The abovementioned eight arterial segments were also analyzed to assess calcifications on low-dose CT scans. In the presence of calcifications, the maximum Hounsfield Units (HU), were measured and scored

ordinally per arterial segment: 0 in the absence of calcifications (< 130 HU), 1 if mild calcification was present (130–399 HU) and 2 in the presence of severe calcification (≥ 400 HU) [8]. Non-calcified lesions were defined as segments without calcifications (< 130 HU) and calcified lesions were defined as segments with calcifications ≥ 130 HU.

2.6. Follow-up and study endpoint

The primary outcome measure was the difference in increase of mean TBR_{max} between two timepoints compared between the two groups. Secondary study outcomes were the difference in increase of mean TBR_{max} between pre-existing *vs.* no pre-existing inflammatory activity, pre-existing calcifications *vs.* no pre-existing calcifications and combination therapy *vs.* monotherapy. Moreover, patients were followed for the occurrence of major adverse cardiovascular events: acute coronary syndrome, elective percutaneous coronary intervention (PCI), cardiac surgery, myocarditis, AV-conduction disturbances, ischemic stroke, peripheral artery disease requiring revascularization, admission for heart failure and out-of-hospital cardiac arrest (OHCA).

2.7. Statistical analysis

Normally distributed continuous variables are expressed as mean ± standard deviation (SD). Non-normally distributed continuous variables are expressed as median and interquartile range [IQR]. The normality of distribution was assessed graphically. Categorical variables are presented as frequencies or percentages. To assess differences in the change of mean TBR_{max} between two timepoints between the groups, the independent samples *t*-test was conducted and the paired samples *t*-test was used to assess differences in change of mean TBR_{max} between two timepoints within a group. The chi-squared test was performed to assess differences in binary and categorical variables. Median follow-up time was estimated by the reverse Kaplan-Meier method. A two-sided *p*-value <0.05 was considered as statistically significant. All statistical analyses were performed in STATA version 17.0 (StataCorp 2021, Texas, United States).

3. Results

3.1. Study population

A total of 242 patients were screened for eligibility of whom 132 were included (Fig. 1). The study population consisted of 96 patients who were treated with ICIs (72.7 %) of whom 49.0 % (n = 47) were female. The median age at baseline PET/CT was 62.2 [50.8–71.9] years. Patients were treated with ICIs during 9 [4.0-13.0] cycles for a median of 0.85 [0.2–0.93] years. The control group of our study population consisted of 36 patients (27.3 %) with a median age of 60.1 [53.0–67.6] years of whom 55.6 % (n = 20) were female. Baseline characteristics of both groups are shown in Table 1. The majority of the patients with melanoma stage IV were treated with ICIs (91.3 %). Oncological characteristics of the study population are described in Table 2. In the ICI group, 26 patients (27.1 %) and 4 patients (4.2 %) were treated with a second and third ICI regimen, respectively. Combined treatment with PD-1/CTLA-4 inhibitors was administered in 29 patients (30.2 %).

The median follow-up time was 2.3 [1.8–3.3] years. During this period, three patients experienced a cardiovascular event: one patient in the exposure group underwent an elective PCI and two patients in the control group had an ischemic stroke and an OHCA. During follow-up, 15 patients (11.4 %) died of whom 12 (80.0 %) as a result of progression of the melanoma, one patient (6.7 %) had a cardiac cause of death after OHCA and two patients (13.3 %) had another cause of death.

3.2. Changes in arterial inflammation on PET/CT during treatment

Median time between baseline PET/CT and T1 was 5.9 [4.4–7.0] months and this was 1.6 [1.3–1.7] years between baseline and T2. In the ICI group (n = 96), mean TBR_{max} increased significantly between baseline and T2 from 1.29 ± 0.12 to 1.32 ± 0.14 ($p = 0.046$). No difference in the change of mean TBR_{max} between the two groups was observed. Between baseline PET/CT and T1 no significant changes in mean TBR_{max} were observed in the ICI group (1.29 ± 0.12 to 1.32 ± 0.12, $p = 0.07$) or in the control group (1.28 ± 0.12 to 1.27 ± 0.11, $p = 0.62$). Between T1 and T2, mean TBR_{max} remained constant in both groups ($p = 0.98$), see Fig. 2A.

Subsequently, all patients treated with medication with anti-inflammatory effects (statins: n = 26, corticosteroids: n = 5, both: n = 1) at baseline were excluded and a subanalysis was performed. This

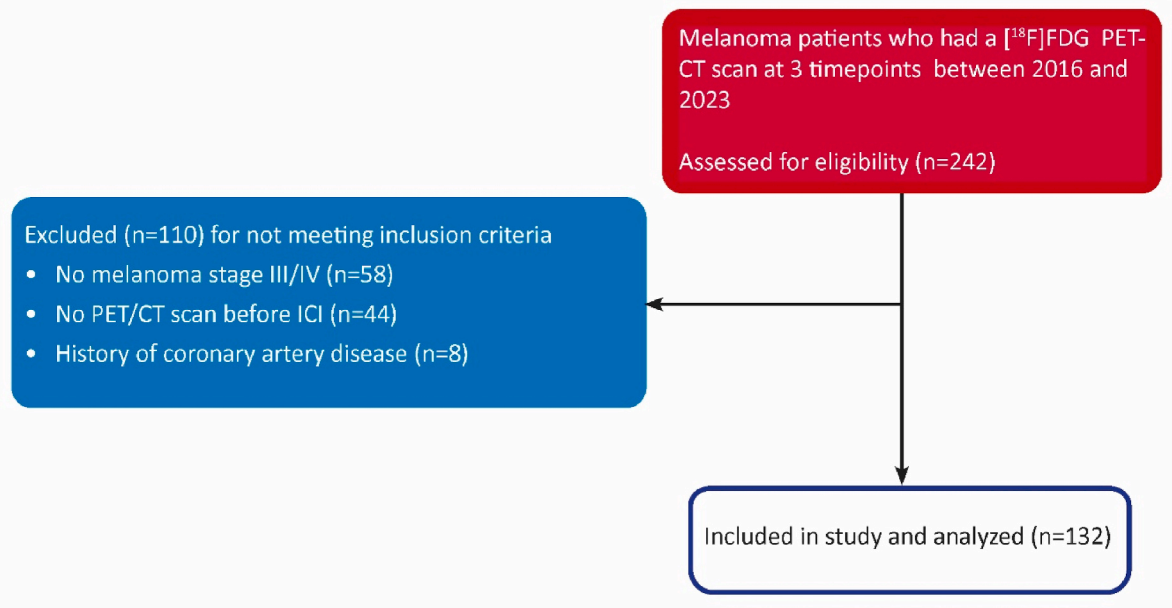

Fig. 1. STROBE diagram. Process of patient inclusion.

Table 1
Baseline characteristics.

	Total (n = 132)	No ICI (n = 36)	ICI (n = 96)	*p*-value
Female sex	67 (50.8 %)	20 (55.6 %)	47 (49.0 %)	0.50
Age at diagnosis advanced melanoma, yrs	61.1 [51.8–69.6]	60.1 [53.0–67.6]	62.2 [50.8–71.9]	0.27
BMI, kg/m^2	26.3 [23.7–29.9]	27.7 [24.1–31.0]	25.8 [23.5–29.2]	0.085
Cardiovascular risk factors				
Hypertension	28 (21.2 %)	9 (25.0 %)	19 (19.8 %)	0.51
Hypercholesterolemia[a]	11 (8.3 %)	2 (5.6 %)	9 (9.4 %)	0.48
Diabetes mellitus	11 (8.3 %)	1 (2.8 %)	10 (10.4 %)	0.16
Auto-immune disease	1 (0.8 %)	1 (2.8 %)	0 (0.0 %)	0.10
Smoking[b]	55 (42.0 %)	12 (33.3 %)	43 (45.3 %)	0.22
Cardiac medication	54 (40.9 %)	15 (41.7 %)	39 (40.6 %)	0.91
Beta blocker	17 (31.5 %)	5 (33.3 %)	12 (30.8 %)	0.86
Ascal	7 (13.0 %)	1 (6.7 %)	6 (15.4 %)	0.39
ACE inhibitor	15 (27.8 %)	4 (26.7 %)	11 (28.2 %)	0.91
Calcium channel blocker	15 (27.8 %)	3 (20.0 %)	12 (30.8 %)	0.43
ARB	12 (22.2 %)	4 (26.7 %)	8 (20.5 %)	0.63
Anticoagulants	6 (11.1 %)	1 (6.7 %)	5 (12.8 %)	0.52
Statins	27 (50.0 %)	7 (46.7 %)	20 (51.3 %)	0.76
Immunosuppressive drugs	6 (4.5 %)	1 (2.8 %)	5 (5.2 %)	0.55
Insulin	8 (6.1 %)	0 (0.0 %)	8 (8.3 %)	0.078
Laboratory values				
Hb, mmol/L	8.9 [8.2–9.4]	8.8 [8.2–9.3]	8.9 [8.2–9.4]	0.46
Leukocytes, x10^9/L	7.4 [6.0–9.2]	8.3 [7.3–10.4]	7.1 [5.9–8.8]	0.007
ESR, mm/hr	11.0 [2.0–22.0]	15.5 [10.0–32.5]	9.0 [2.0–19.0]	0.078
LDH, IU/L	184.0 [160.5–219.0]	195.5 [179.0–220.0]	182.5 [159.0–205.0]	0.046
Glucose, mmol/L	5.4 [4.9–6.0]	5.4 [5.1–5.9]	5.4 [4.9–6.0]	0.69
CRP, mg/L	2.3 [1.0–6.0]	3.2 [2.5–28.4]	2.0 [0.9–4.8]	0.002
Creatinine, μmol/L	76.0 [67.0–85.0]	76.0 [69.0–88.0]	76.0 [66.0–85.0]	0.61

BMI = body mass index; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; Hb = hemoglobin; LDH = lactate dehydrogenase.
[a] Hypercholesterolemia was defined as a total cholesterol ≥5 mmol/L or a history of hypercholesterolemia.
[b] Smoking was defined as prior smoking or active smoking.

Table 2
Oncological characteristics of the study population.

	Total (n = 132)	No ICI (n = 36)	ICI (n = 96)	*p*-value
Melanoma stage III	86 (65.2 %)	32 (88.9 %)	54 (56.3 %)	0.003
Melanoma stage IV	46 (34.8 %)	4 (11.1 %)	42 (43.8 %)	0.003
Treatment with ICI monotherapy	96 (72.7 %)	0 (0 %)	96 (100.0 %)	<0.001
Nivolumab	53 (40.2 %)	0 (0 %)	53 (55.2 %)	–
Pembrolizumab	35 (26.5 %)	0 (0 %)	35 (36.5 %)	–
Ipilimumab	8 (6.1 %)	0 (0 %)	8 (8.3 %)	–
Treated with combination therapy ipilimumab/nivolumab	29 (22.0 %)	–	29 (30.2 %)	–
Other treatments				
Surgical excision	105 (79.5 %)	36 (100.0 %)	69 (71.9 %)	<0.001
Targeted therapy	39 (29.5 %)	10 (27.8 %)	29 (30.2 %)	0.79
Radiotherapy	37 (28.0 %)	8 (22.2 %)	29 (30.2 %)	0.36
Radiotherapy dose, Gy	48.0 [32.0–54.0]	48.0 [48.0–48.0]	48.0 [30.0–55.0]	0.90
Chemotherapy	2 (1.5 %)	0 (0.0 %)	2 (2.1 %)	0.38
Total ICI cycles	9.0 [4.0–13.0]	–	9.0 [4.0–13.0]	–
Duration of ICI treatment, yrs	0.8 [0.2–0.9]	–	0.8 [0.2–0.9]	–

Table 2 shows an overview of the oncological characteristics of the study population. Also, all ICI treatments of the exposure population are shown. Some patients were treated consecutively with more than one ICI regimen, e.g. first in an adjuvant setting, followed by treatment for irresectable metastases. ICI = immune checkpoint inhibitor.

study population consisted of 100 patients of whom 72 (72.0 %) were treated with ICIs and 28 (28.0 %) were not treated with ICIs. In the ICI group (n = 72), mean TBR_{max} increased significantly between baseline and T1 from 1.29 ± 0.12 to 1.33 ± 0.13 (p = 0.017). In the control group, mean TBR_{max} did not show significant changes (1.30 ± 0.12 to 1.28 ± 0.10 (p = 0.22)). These findings are shown in Fig. 2B. We observed a significant difference between the groups in the change of mean TBR_{max} between baseline and T1 (p = 0.027). During longer follow-up, between T1 and T2, no significant difference was observed in the change of mean TBR_{max} between the groups (p = 0.54). The change in mean TBR_{max} for all patients in the subpopulation is presented in Fig. 3. Fig. 4 provides an example of a patient with strong TBR increase in the aortic arch between baseline and T1 and decrease in TBR between T1 and T2.

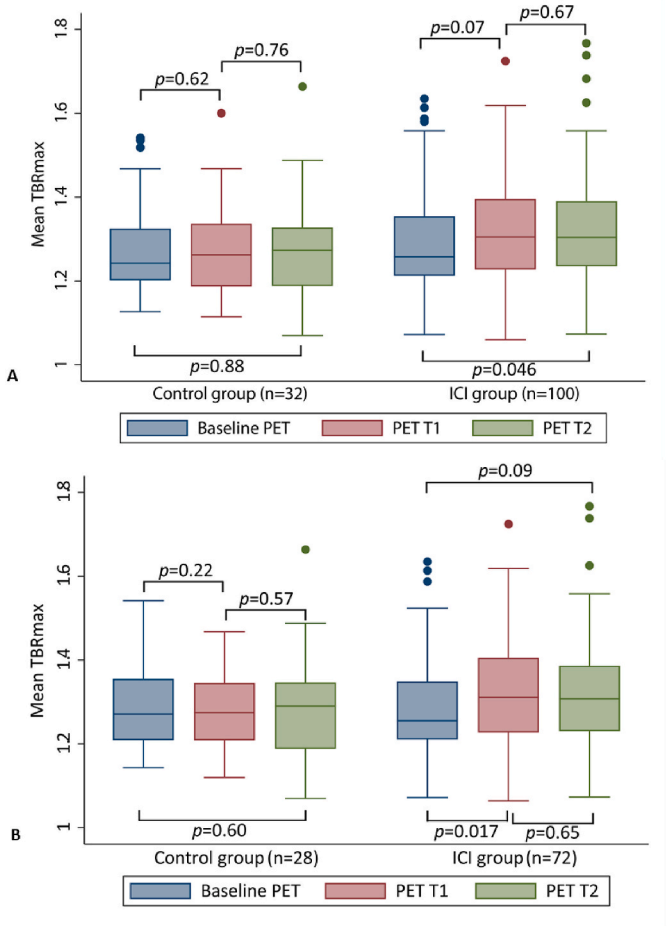

Fig. 2. Change in arterial inflammation within the groups. (A) Change in arterial inflammation within the two groups of the whole population (n = 132) between baseline, six months (T1) and 18 months (T2). Patients treated with ICIs show a significant increase in arterial inflammation between baseline and T2. (B) The same results for the subpopulation (n = 100) are shown. Patients treated with ICIs show a significant increase in mean TBR_{max} between baseline PET/CT and T1 ($p = 0.017$).

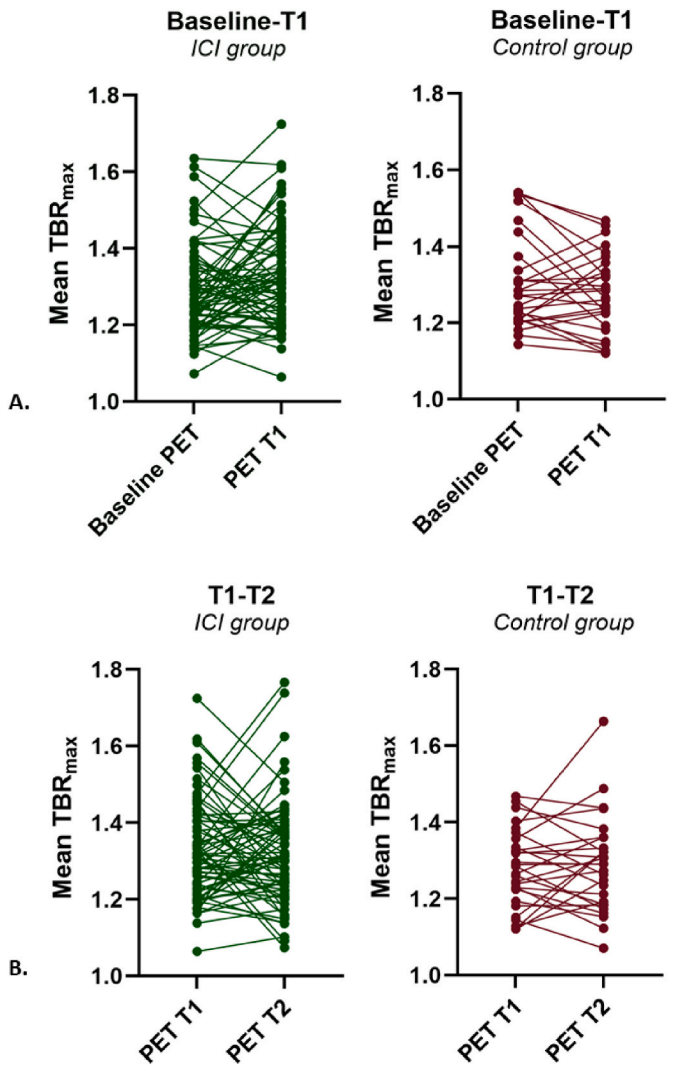

Fig. 3. Change in arterial inflammation between the groups. (A) Mean TBR_{max} at baseline and 6 months for the subpopulation (n = 100) of both groups. A significant difference in the change of mean TBR_{max} was observed between patients treated with ICIs and a control group ($p = 0.027$). (B) Mean TBR_{max} at 6 months and 18 months for both groups. No significant differences in the change of mean TBR_{max} are observed ($p = 0.54$).

3.3. Combination therapy

Twenty-nine patients (30.2 %) in the whole study population (n = 96) and 24 patients (33.3 %) in the subpopulation (n = 72) were treated with combination ICI therapy with PD-1 and CTLA-4 inhibitors. In both groups, no significant differences in the increase of arterial inflammation between baseline PET/CT scan and T1 were observed for patients treated with combined therapy compared to monotherapy. In the whole study population, mean TBR_{max} changed from 1.31 ± 0.11 to 1.35 ± 0.14 ($p = 0.18$) for combination therapy *vs.* 1.28 ± 0.12 to 1.30 ± 0.11 ($p = 0.22$) for monotherapy ($p = 0.58$). In the subpopulation the mean TBR_{max} changed from 1.32 ± 0.12 to 1.37 ± 0.13 ($p = 0.06$) and 1.28 ± 0.12 to 1.31 ± 0.12 ($p = 0.12$) respectively ($p = 0.50$).

3.4. Patients with pre-existing inflammatory activity

Increased inflammatory activity at baseline was defined as a TBR ≥ 1.6 in at least one arterial segment. In the whole study population (n = 132), 48 patients (50.0 %) in the ICI group and 15 patients (41.7 %) in the control group showed increased inflammatory activity at baseline ($p = 0.39$). No significant differences were found between the two groups for an increased TBR at baseline or T1. However at T2, 61 patients (63.5 %) in the ICI group showed increased inflammatory activity compared to 14 patients (38.9 %) in the control group ($p = 0.011$).

In patients without pre-existing inflammatory activity, a significant increase in mean TBR_{max} from 1.22 ± 0.06 to 1.27 ± 0.11 ($p < 0.001$) between baseline and T1 was observed compared to stable mean TBR_{max} (1.37 ± 0.12 to 1.35 ± 0.12, $p = 0.18$) in patients with pre-existing inflammatory activity ($p < 0.001$). These observations are presented in Fig. 5A. This effect was also observed in patients without pre-existing inflammatory activity in the subpopulation: 1.22 ± 0.06 to 1.28 ± 0.11 ($p = 0.001$) *vs.* 1.37 ± 0.12 to 1.35 ± 0.12 ($p = 0.42$) in patients with pre-existing inflammatory activity ($p = 0.005$).

Differences in the change of mean TBR_{max} were also assessed for the ICI and control groups separately. In patients treated with ICIs (Fig. 5B) without pre-existing inflammation (n = 48), mean TBR_{max} increased significantly between baseline and T1 (1.22 ± 0.07 to 1.28 ± 0.11, $p = 0.001$) and remained stable between T1 and T2 (1.28 ± 0.11 to 1.30 ± 0.13, $p = 0.56$). No changes in arterial inflammation were observed for patients with pre-existing inflammatory activity. In the control population (Fig. 5C), mean TBR_{max} remained stable between baseline and T1 (1.20 ± 0.05 to 1.23 ± 0.09, $p = 0.17$) and T1 and T2 (1.23 ± 0.09 to 1.26 ± 0.11, $p = 0.15$) in patients without inflammatory activity (n = 21). Patients with pre-existing inflammatory activity (n = 15), showed

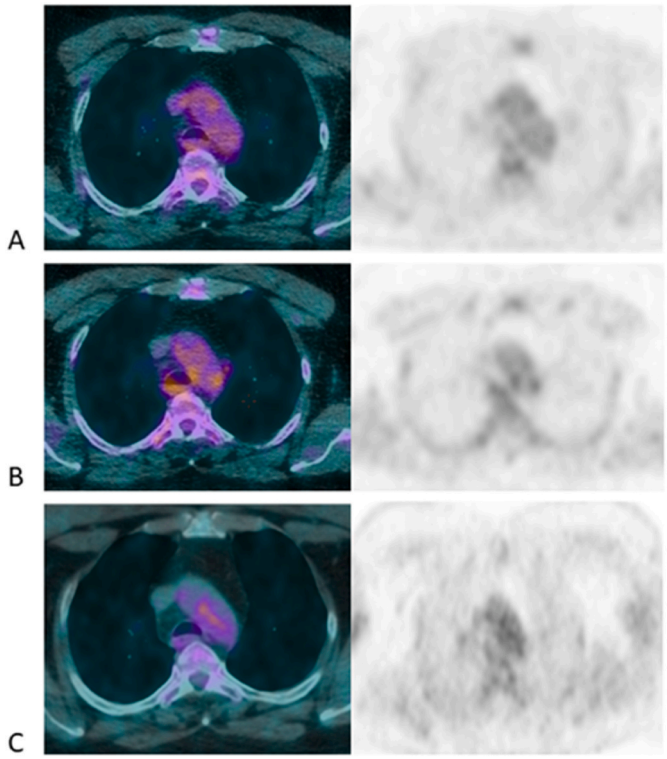

Fig. 4. Arterial inflammation in a patient treated with ICI. PET/CT scans at baseline, T1 and T2 of a patient with melanoma stage IV are shown. This patient was treated with 13 cycles of monotherapy nivolumab. (A) PET/CT scan at baseline, one month before start of ICI therapy. TBR in the aortic arch was 1.46. (B) PET/CT scan performed after three doses of nivolumab. TBR in the aortic arch was 2.06 (+41 %). The third PET-CT scan was performed 10 months after termination of ICI treatment. TBR in the aortic arch was 1.85 (−11 %). Left panels show [^{18}F]FDG uptake on fusion images of PET and CT and right panels show images of [^{18}F]FDG uptake on PET.

no increase in arterial inflammation between any of the timepoints. However, a significant decrease in mean TBR_{max} (1.39 ± 0.11 to 1.31 ± 0.13, $p = 0.014$) between baseline an T2 was observed. These results shows that arterial inflammation increases in the first six months after initiation of ICI therapy in patients treated with ICIs without inflammatory lesions, whereas no change was observed for patients with pre-existent inflammatory lesions.

3.5. Calcifications in relation to arterial inflammation

In arterial segments with calcifications, maximum HU were measured and classified according to three prior described categories. On baseline PET/CT, 77.1 % of the patients in the exposure group and 83.3 % of the patients in the control group showed calcifications of ≥130 HU ($p = 0.43$). Also, no significant differences in presence of (severe) calcifications between the groups were observed at the other timepoints. In the whole population (n = 132), a significant increase in mean TBR_{max} between baseline and T1 from 1.31 ± 0.13 to 1.37 ± 0.13 ($p = 0.013$) was observed in patients without calcifications at baseline, whereas mean TBR_{max} remained stable (1.28 ± 0.12 to 1.29 ± 0.11, $p = 0.78$) in patients with calcifications at baseline ($p = 0.037$), see Fig. 6A. In patients treated with ICIs (n = 96) without calcified lesions (n = 22), mean TBR_{max} increased significantly from 1.31 ± 0.13 to 1.37 ± 0.14 ($p = 0.027$) compared to a stable mean TBR_{max} of 1.29 ± 0.12 to 1.29 ± 0.11 ($p = 0.42$) between baseline and T1 in patients with calcifications (n = 74). Between T1 and T2 mean TBR_{max} remained stable in both groups (Fig. 6B). In the control population (n = 36), no changes in mean TBR_{max} were observed for patients without calcifications (n = 6)

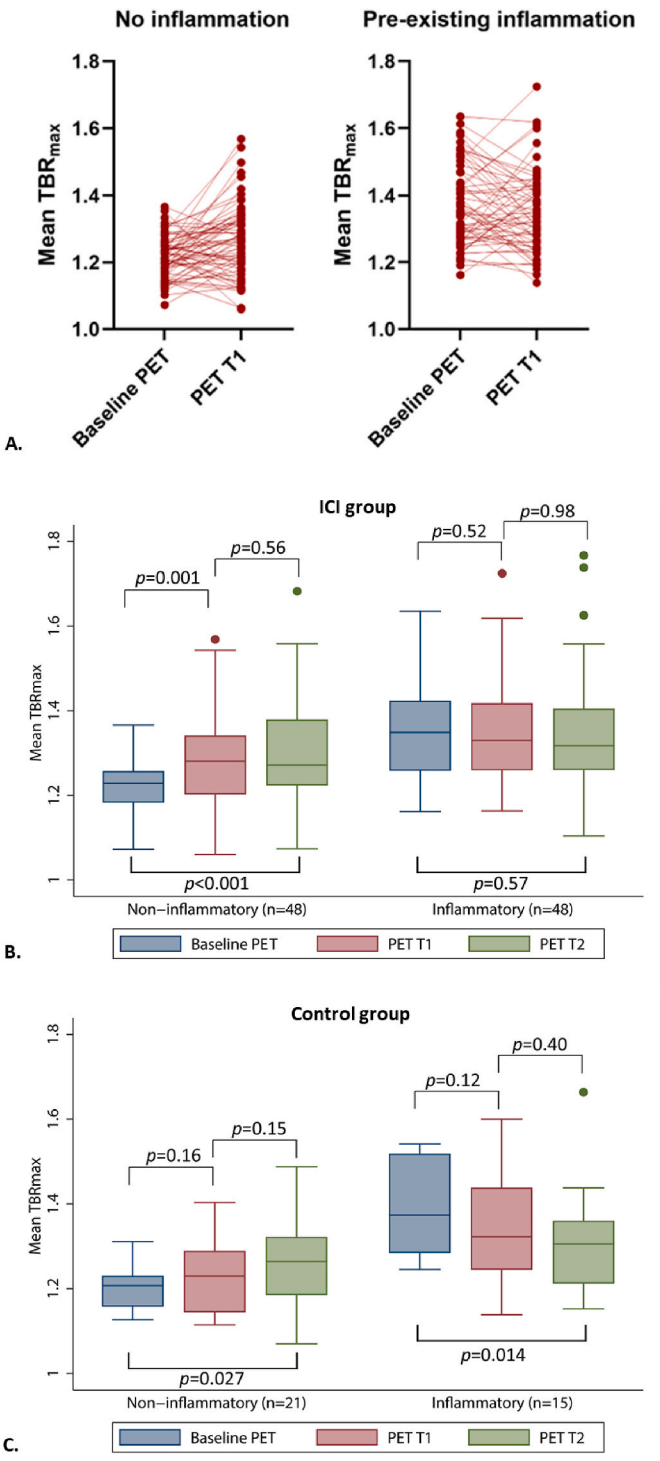

Fig. 5. Pre-existing *vs.* no pre-existing inflammatory activity. (A) Change in mean TBR_{max} between baseline and 6 months (T1) for the whole study population. Patients without pre-existing inflammatory activity show a significant increase in mean TBR_{max} compared to a stable mean TBR_{max} in patients with pre-existing inflammatory activity ($p < 0.001$). (B) Mean TBR_{max} at baseline, 6 months (T1) and 18 months (T2) for patients treated with ICIs without pre-existing inflammation *vs.* pre-existing inflammation. Between baseline and T1 and baseline T2, patients without pre-existing inflammation show a significant increase in mean TBR_{max}. (C) Control population. A significant decrease in mean TBR_{max} between baseline and T2 was observed.

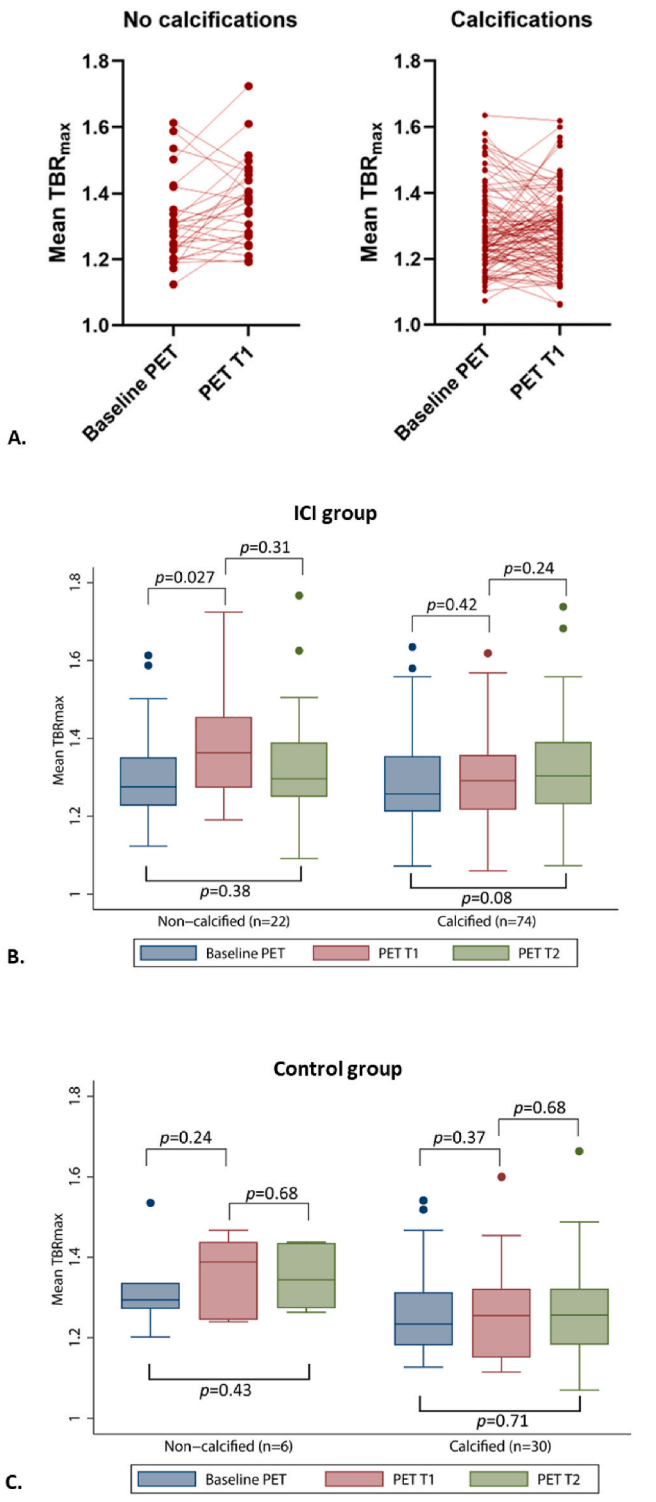

Fig. 6. Calcifications *vs.* no calcifications. (A) Change in mean TBR_{max} between baseline and 6 months (T1) for the whole study population. Patients without calcifications at baseline show a significant increase in mean TBR_{max}, whereas no change is observed for patients with calcifications (p = 0.037). (B) Mean TBR_{max} at baseline, 6 months (T1) and 18 months (T2) for patients treated with ICIs for non-calcified *vs.* pre-existing calcified lesions (HU ≥ 130) at baseline. Patients with non-calcified lesions show a significant increase in mean TBR_{max} between baseline and T1 (p = 0.027). (C) Similar findings for the control population where no significant differences in mean TBR_{max} between the timepoints were observed.

between baseline and T1 (1.32 ± 0.11 to 1.36 ± 0.10, $p = 0.24$) and for patients with calcifications (1.27 ± 0.13 to 1.25 ± 0.11, $p = 0.37$). In both groups, mean TBR_{max} remained stable between T1 and T2. These results are presented in Fig. 6C.

3.6. Stratification by plasma CRP levels

C-reactive protein (CRP) levels were significantly higher in the control group compared to patients treated with ICIs (3.2 [2.5–28.4] mg/L *vs.* 2.0 [0.9–4.8] mg/L, $p = 0.002$). Patients were stratified according to CRP levels with the median CRP of 2.3 mg/L as cut-off value. In patients with CRP levels ≥ 2.3 mg/L, mean TBR_{max} remained stable between baseline PET/CT and T1 (1.29 ± 0.13, $p = 0.68$) compared to a significant increase in mean TBR_{max} from 1.28 ± 0.11 to 1.32 ± 0.10 ($p = 0.019$) in patients with CRP levels < 2.3 mg/L ($p = 0.032$). Patients treated with ICIs (n = 96) who had CRP levels < 2.3 mg/L, also showed a significant increase in mean TBR_{max} (1.27 ± 0.11 to 1.32 ± 0.11, $p = 0.001$) compared to a stable mean TBR_{max} (1.32 ± 0.14 to 1.31 ± 0.14, $p = 0.82$) for CRP levels ≥ 2.3 mg/L ($p = 0.06$) between baseline and T1.

4. Discussion

This is the first study that observed a significant difference in the change of arterial inflammation during the first six months after initiation of ICI therapy between patients with advanced melanoma on [^{18}F]FDG PET/CT treated with ICIs compared to a control group without ICI treatment. First, in the entire study population no significant differences were found in changes of arterial inflammation. However, in a subpopulation of patients not using drugs that have anti-inflammatory effects (statins and corticosteroids) a significant difference in the change of arterial inflammation was observed. Interestingly, in the period thereafter, this difference between the two groups stabilized [16]. Moreover, patients without pre-existing arterial inflammation and without calcifications at baseline treated with ICIs showed a significant increase in arterial inflammation during short-term follow-up.

4.1. Systemic low-grade inflammation in atherogenesis and carcinogenesis

Cardiovascular disease and cancer share many risk factors, which can be responsible for an increase in systemic low-grade inflammation [6,17]. In a chronic pro-inflammatory state, adhesion molecules are expressed on endothelial cells, resulting in recruitment of leukocytes to the blood vessel wall [18–20]. Macrophages and neutrophils produce reactive oxygen and nitrogen species which can induce damage to the DNA, thereby initiating tumor growth [21]. Therefore, low-grade inflammation may be the underlying mechanism of both atherogenesis and carcinogenesis [19].

Low-grade inflammation is associated with cancer incidence [22,23], whereby higher levels of CRP correlate with an increased risk of predominantly lung cancer [17,22]. A previous study in patients with stable cardiovascular disease and CRP levels ≤ 10 mg showed that CRP levels in the fifth quintile were associated with an elevated risk of cancer and recurrence of cardiovascular events compared to CRP levels in the first quintile [17]. Studies observing inflammation on PET/CT scans have demonstrated that higher [^{18}F]FDG uptake in the large arteries predicts future cardiovascular events [11,24].

Although CRP levels were higher in our control group with median CRP levels of 3.5 [2.4–48.5] mg/L compared to 2.2 [0.95–5.3] mg/L in the ICI group, the control group showed no significant increase in arterial inflammation in the first six months, which may underestimate the effect of ICIs on the increase of arterial inflammation. Also, ICIs probably influence local innate immune cells, such as macrophages and natural killer cells that trigger cytokine release and low-grade inflammation in the arterial wall, affecting predominantly non-calcified lesions, in line with the results of our study, increasing the risk of plaque rupture [25].

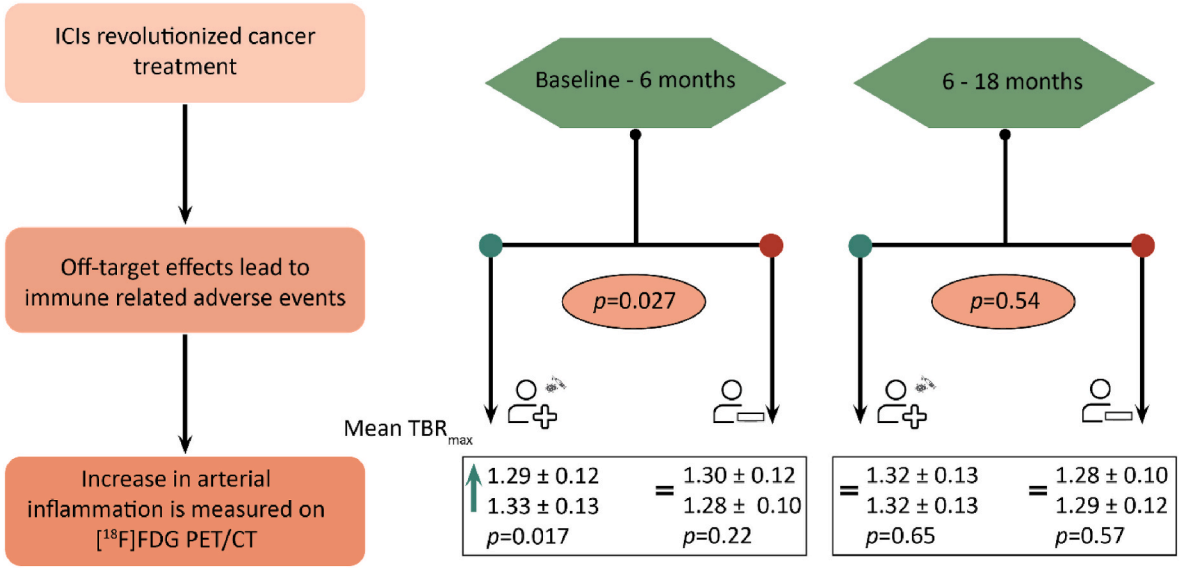

Fig. 7. Graphical abstract. The graphical abstract shows the change in mean TBR_{max} during short-term and long-term follow-up for advanced melanoma patients treated with ICIs and a control group of patients not treated with ICIs, after exclusion for anti-inflammatory medication. Patients treated with ICIs show a significant increase in mean TBR_{max} between baseline and 6 months and a significant difference in the change of mean TBR_{max} was observed during short-term follow-up for patients treated with ICIs compared to patients not treated with ICIs.

4.2. Association between immune checkpoint pathways and T cell-driven inflammatory response

Inhibition of PD-1 and CTLA-4 in hypercholesterolemic *Ldlr*$^{-/-}$ mice results in higher expression of adhesion molecules, reflecting activation of the endothelium, thereby enhancing recruitment of immune cells to the atherosclerotic plaque. Antibody-mediated inhibition of CTLA-4 induces T cell-driven inflammation and results showed that short term ICI treatment in mice induced a hyperinflammatory atherosclerotic plaque phenotype, promoting atherosclerotic lesion progression towards clinically unfavorable and unstable plaques [3,26,27].

Atherogenic T cell response and atherosclerosis are downregulated by the PD-1/PD-L1 pathway as it limits APC-dependent T cell activation [28]. In *Ldlr*$^{-/-}$ models lacking PD-1, an increase in apoptosis of endothelial cells and smooth muscle cells was observed, stimulating the atherosclerotic process [3].

Subclinical atherosclerosis is present in the majority of cancer patients and an autopsy study [29], which matched 11 patients treated with ICIs to patients not treated with ICIs, suggests that inhibition of PD (L)-1 alone or in combination with CTLA-4 leads to an increased CD3/CD68 T cell ratio by infiltration or (re)activation of T cells in the plaque or an increase of macrophage apoptosis driven by T cells. This increased ratio was related to plaque instability associated with CAD and a higher prevalence of $CD4^+$ and $CD8^+$ cells, which increases the risk of atherogenesis and less favorable plaques. It was also observed that human atherosclerotic plaques contain clusters of $CD4^+$ and $CD8^+$ cells that express high levels of the inhibitory marker PD-1, characterizing an exhausted T cell phenotype. This could possibly be driven by low-grade inflammation resulting from ICI therapy [3,6,29].

Limited data are available regarding the change in arterial inflammation after ICI treatment. A small study by Calabretta et al. in twelve lymphoma patients without or with limited cardiovascular risk factors, who were treated with PD-1 inhibitors, reported a significant increase in TBR in the large arteries in the first six months after start of ICI treatment [9]. Furthermore, this study showed a significant difference in TBR increase for segments with pre-existing arterial inflammation (defined as TBR $\geq$ 1.48) compared to segments without pre-existing inflammation, which is consistent with our results.

Another small study on twenty melanoma patients treated with ICIs also reported a significant increase in inflammatory activity in the large arteries [8]. This study also showed increased inflammatory activity in non-calcified and mildly calcified lesions (0–399 HU), compared to calcified lesions ($\geq$ 400 HU), which is in accordance with our short-term findings on TBR increase in calcified and non-calcified lesions. [^{18}F]FDG PET has been established as an useful imaging modality for visualizing atherosclerotic plaque inflammation and can visualize tissue glucose metabolism with high sensitivity [30]. In line, several studies have shown that [^{18}F]FDG uptake is attributed to infiltrating inflammatory cells and subendothelial proliferation of macrophages and smooth muscle cells within atherosclerotic lesions [31]. Moreover, a study by Iwatsuka et al. reported that arterial inflammation as evaluated by TBR on [^{18}F]FDG PET/CT is associated with future cardiovascular events [32].

4.3. Anti-inflammatory effects of statins

Although statins are predominantly prescribed as lipid-lowering drugs, they have been shown to possess pleiotropic effects that contribute to plaque stabilization and anti-inflammatory properties by interfering with different pathways, thereby reducing the release of proteins that are associated with the inflammatory processes involved in atherosclerosis [33–37]. Drobni et al. conducted a study on a subpopulation of 40 melanoma patients and observed that patients treated with ICIs showed an increase in total and non-calcified plaque volume and a higher plaque progression rate. The results demonstrated 50 % lower plaque progression rate in patients who were treated with statins or corticosteroids [7]. This suggests, in line with the findings in our study, that statins play a protective role in inflammatory and atherosclerotic processes.

Various randomized controlled trials have reported that the use of statins reduces the risk of major cardiovascular events significantly and leads to a decrease in serum levels of hs-CRP [37–40]. Tahara et al. compared treatment with simvastatin to dietary management in healthy patients who underwent a PET/CT scan for cancer screening purposes. At baseline, no differences in SUV uptake in the thoracic aorta and carotid arteries were observed between the two groups. However, three months after baseline, a significant reduction in SUV uptake was reported for patients treated with statins compared to the control

population [31].

4.4. ICI treatment and cardiovascular events

Prior studies reported that ICIs are associated with a two-to-four fold increased risk of cardiovascular events in the first six months after start of ICI therapy as well as in the period after initiation of ICI therapy compared to the period before [7,16,41–43]. Nevertheless, one of these studies also presented stabilization of cardiovascular events after six months compared to heathy controls [16]. In this study, the majority of the patients who experienced events already had cardiovascular risk factors or a history of acute vascular events, suggesting that ICI therapy may induce progression of existing atherosclerosis and that patients without atherosclerosis are at low risk for ischemic cardiovascular events post-ICI therapy.

As several studies describe an increased risk of cardiovascular events in the first six months after initiation of ICI therapy, it can be suggested that this increased risk can be attributed to changes in vasoreactivity and destabilization of plaque [44]. However, as atherosclerosis is a process that develops over a longer period of time, the long-term effects of ICIs are still unknown and longer follow-up studies are required [6,16].

4.5. Limitations

This study is subject to several limitations. First, it is a retrospective single-center study and has a relatively small sample size of 132 cases. However, to our knowledge, this is the first study assessing arterial inflammation after ICI therapy compared to a control group and uses information on available PET/CT scans without extra costs or radiation exposure for the patients that may enhance patient-tailored risk estimation. Furthermore, as CRP levels were significantly higher in the control group, the effect of ICIs on inflammation may be underestimated in our results. Also, the limited availability of data on cholesterol levels prevented the investigation of the association between elevated cholesterol levels and the presence of inflammation. Moreover, due to its retrospective nature, PET/CT images were acquired only 1 hour after administration of ^{18}F[FDG] and this was the only tracer available. Finally, due to low incidence of cardiovascular events, the present study was unable to assess the potential clinical relevance of our findings on the occurrence of cardiovascular events.

4.6. Conclusion

A significant increase in arterial inflammation as measured on [^{18}F] FDG PET/CT was observed in patients with advanced melanoma treated with ICIs only in the first six months after initiation of therapy. Moreover, arterial inflammation during ICI treatment was mainly increased in patients without pre-existing inflammatory activity and non-calcified lesions. Further studies are needed to relate the increased arterial inflammation to cardiovascular events and to investigate possible preventive measures e.g. with statin therapy (Fig. 7).

CRediT author contribution statement

E.A.S.P.: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **J.C.H.:** Conceptualization, Methodology, Writing – review & editing, Software, Formal analysis. **T.T.P.S:** Conceptualization, Writing – review & editing. **M.L.A:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision, Project administration, Methodology. **H.W.K.:** Methodology, Validation, Resources, Writing – review & editing, Supervision. **A.B.:** Methodology, Writing – review & editing. **F.H.P.V.:** Methodology, Writing – review & editing. **P.D.:** Methodology, Writing – review & editing. **J.L.S.:** Methodology, Writing – review & editing. **G.M.L:** Methodology, Writing – review & editing. **L.F.G.:** Methodology, Validation, Resources, Writing – review & editing, Supervision. **G.M.K.:** Software. **A.V.K.:** Formal analysis, Investigation. **J.W.J.:** Writing – review & editing, Supervision. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2024.118595.

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