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Original Research

Acute vascular events as a possibly related adverse event of immunotherapy: a single-institute retrospective study☆

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Lung adenocarcinoma;
Immune-related adverse events;
Immune checkpoint inhibitors

Abstract ***Aim:*** Immune-related toxicities of immune checkpoint inhibitors (CPIs) require prompt diagnosis and treatment. Atherosclerosis has an inflammatory component; we speculated this inflammation could be enhanced by CPIs. We aimed to evaluate the risk of acute vascular events (AVEs) on CPIs.
Methods: Patients treated by CPIs in Sheba Medical Center (Israel) between January 2015 and May 2018 were retrospectively identified from electronic medical records. AVEs were identified and verified by chart review. Age, sex, diabetes, hypertension, smoking, dyslipidemia, previous AVE, renal failure, cancer type and specific treatments were evaluated as potential risk factors. AVE rate on CPIs was compared with that on chemotherapy or on combined chemo-immunotherapy in patients with lung adenocarcinoma. Survival of patients with AVEs was compared with that of patients without AVEs.
Results: CPI was administered to 1215 patients. AVEs within six months after CPI initiation occurred in 2.6% (95% confidence interval [CI]: 1.8–3.6) of patients, more common than in later time periods. In lung adenocarcinoma, event rate was 5.2% (95% CI: 2.8–9.2). Lung adenocarcinoma, prior AVE, hypertension and dyslipidemia were correlated with AVEs.

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AVE rate in patients with non-small cell lung cancer adenocarcinoma was similar whether on chemotherapy or on CPI. Survival of patients with AVEs was worse than that of those without AVEs.

Conclusion: The similarly increased rates of AVEs for patients on CPI, on chemotherapy or on both suggest that although CPI may not augment the risk of AVE over that of chemotherapy, it carries a similar and significant risk of such adverse event. Caution should be exercised for patients with risk factors for AVEs.

1. Introduction

The most promising anti-cancer treatment currently is immunotherapy – mostly anti–programmed cell death-1 (PD-1), anti–PD-ligand-1 (PD-L1) antibodies and anti–cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies [1], jointly referred to as immune checkpoint inhibitors (CPIs). Long-term survival has been reported for some patients with advanced melanoma treated with CPIs [2], non-small cell lung cancer (NSCLC) patients [3] and other malignancies. Numerous clinical studies are currently evaluating immunotherapy drugs in various indications and settings, including adjuvant, neo-adjuvant and in combination with chemotherapy and with other anti-cancer agents.

In light of the widespread and growing usage of immunotherapy, awareness of rare toxicities must be augmented. Toxicity from CPIs consists of any conceivable type of auto-immune phenomena [4] (i.e. immune-related adverse events [irAEs]). Reported rates of grade III–IV toxicities are approximately 10% in most studies of anti–PD-1/PD-L1 and as high as 30–40% in studies of high-dose anti–CTLA-4 [5]. Toxicities of anti–PD-1/PD-L1 seem unrelated to dose, unlike anti–CTLA-4 toxicities. Guidelines for the management of irAEs have been suggested [6,7]. Timing of toxicity varies and may be delayed [8], sometimes seen even many months after stopping treatment.

Acute vascular events (AVEs) are generally not considered irAEs. However, considering the role of inflammation in acute ischaemic cardiovascular events and following sporadic reports [9], we speculated that such events can be triggered by CPIs. Plaque rupture is known to involve an inflammatory process [10]. Modulating this inflammation, PD-1 is expressed on vessel wall–residing T cells, and PD-L1 is expressed on endothelial cells [11], dendritic cells and macrophages within this microenvironment [12]. Mice deficient of PD-1 demonstrate enhanced T-cell infiltration and activation within atherosclerotic plaques and accelerated atherosclerosis [13,14]. Blocking PD-1 by an inhibitory antibody had a similar augmenting effect on the inflammatory infiltrate in atherosclerotic lesions [14]. Inhibition of interleukin-1β, a major inflammatory mediator, is being evaluated as a treatment for atherosclerosis [15]. A recent clinical trial tested canakinumab (anti–interleukin-1β antibody) in patients with previous myocardial infarction (MI) and a high C-reactive protein (CRP) level, demonstrating a reduction in acute cardiovascular events [16]. This trial complements a large body of correlative studies, connecting levels of inflammatory mediators such as CRP with acute ischaemic events [17,18]. Considering these data, an acute enhancement of inflammatory processes could conceivably bring about plaque rupture, thrombotic or thromboembolic events and their clinical sequela.

To further study the potential role of CPIs as a cause of AVEs, we aimed to evaluate AVEs occurring after the initiation of CPI treatment. For this goal, we retrospectively analysed the electronic medical record (EMR) database of a single oncology institute.

2. Materials and methods

2.1. Collection of data

Computerised search of Sheba Medical Center (SMC) EMR was performed for patients who received CPIs (any of pembrolizumab, nivolumab, atezolizumab, ipilimumab). Study period was from 1st January 2015 (before which only rare CPI use was identified in our search) to 31st May 2018. The EMR software used was Chameleon software, implemented in the SMC Institute of Oncology in 2011 and in other wards in the SMC mainly during 2011–2013. It should be noted that the majority of ipilimumab treatments were recorded on an older EMR that was not accessible during the current search. Of the identified patients, we searched for cases with a diagnosis of AVEs within 12 months after initiation of CPIs. Search terms were as follows: cerebrovascular accident, transient ischaemic attack, MI, non-ST-elevation MI, ST-elevation MI, acute coronary syndrome, embolic event, pulmonary emboli and deep vein thrombosis (DVT). AVE cases occurring during the first six months after initiation of CPIs were manually reviewed. To increase the specificity of our results, we excluded cases of DVT, besides cases of coincident multi-sites DVT events.

A similar search was conducted in the SMC EMR for patients with a diagnosis of NSCLC, with adenocarcinoma subtype that received platinum-based doublet chemotherapy (search items: cisplatin, carboplatin, bevacizumab) and had an AVE within six months from initiation of chemotherapy. Identified cases were manually reviewed.

Diabetes, hypertension, dyslipidaemia and renal failure were identified in the recorded diagnoses. Hyperlipidaemia, obesity or hypercholesterolaemia were coded as dyslipidaemia. Prior acute vascular events (AVEs) at any time before starting CPIs were identified on the SMC EMR using the same search terms as for ACE on CPI. Lactate dehydrogenase (LDH) blood levels were identified on the SMC EMR and considered as baseline if recorded as close as available to and up to three months before CPI initiation. Performance status was not included as a parameter collected in our study because on previous analyses conducted on this set of patients or parts of this set of patients, we found a large proportion of missing data in this field.

To evaluate the use of anti-platelet, thrombin and Xa inhibitors and anti-coagulants among the patients with AVEs, the medical charts of these patients were searched for all relevant drugs that are approved in Israel. Endocrinopathies were identified by search for abnormal laboratory values of free T4, thyroid-stimulating hormone, adrenocortical stimulatory hormone and cortisol. Abnormalities in these values that evolved after CPI initiation were assumed to be irAEs.

Survival of the cohort patients was calculated from initiation of CPIs until death, or censored at the last follow-up. Tumour response to therapy was evaluated based on investigators' assessment.

The study was conducted, analysed and reported according to REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines, the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) and RECORD-pharmacoepidemiological research (RECORD-PE) guidelines [19].

2.2. Statistical analysis

Crude incidence of AVEs was calculated for each month from the CPI initiation until 12 months later. The number at risk each month after CPI initiation was the number of patients alive and on follow-up (averaged between the start and end of each month). Fisher exact test was used to compare the AVE rate during different time periods. Two-sided 95% confidence interval (CI) was calculated for the event rate of AVEs in different patient groups by adjusted Wald method, using 'Epitools' website [20,21]. Fisher exact test was calculated for potential AVE risk factors. All considered factors were nominal, besides age which was converted to categorial for hazard ratio assessment. Cox regression was calculated, based on forward stepwise selection model (likelihood ratio), including all assessed potential risk factors for AVEs on CPIs. Survival was evaluated using the Kaplan-Meier method, and groups compared by log-rank test; hazard ratio was calculated by Cox regression analysis. Statistical analysis was performed using IBM SPSS statistics, version 25.

2.3. Ethics

Ethics approval for retrospective evaluation of patients' charts and waiver from informed consent were granted from the local ethics review board.

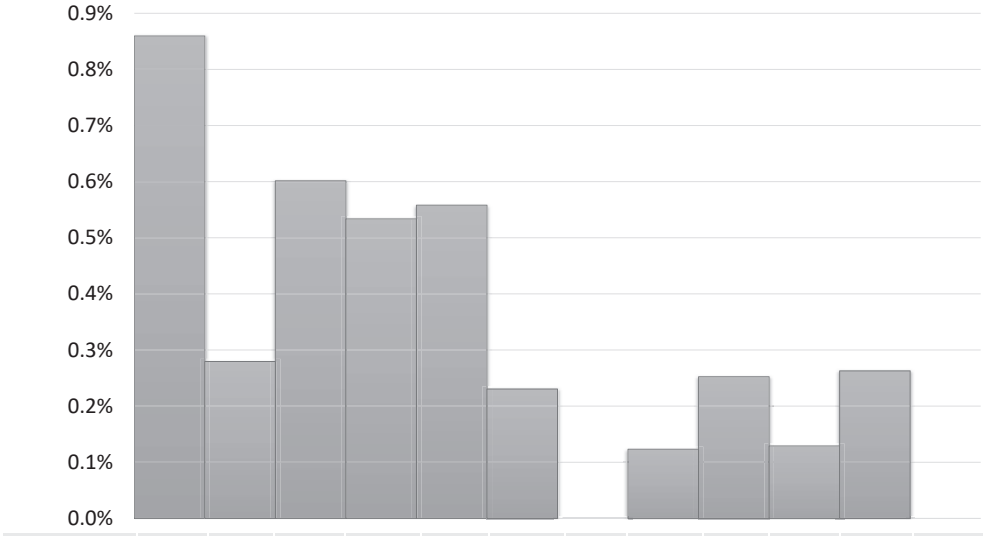
3. Results

A total of 1215 patients were identified as having started CPI treatment (excluding concomitant CPI-chemotherapy) in SMC during the study period. AVE event rate for each month after starting CPIs until a year after the first treatment is depicted in Fig. 1. AVE cases occurring after CPIs but also after chemotherapy were not counted here if the chemotherapy was given after CPIs. A higher incidence during the first few months after CPI initiation is suggested from the data. Comparing the AVE rate during the first 6 months (31 events, 1215 patients at risk) with the rate during 7–12 months after CPI initiation (6 events, 822 patients at risk) revealed a significant difference (odds ratio: 3.49, 95% CI: 1.45–8.41; Fisher exact test p-value: 0.002). As a sensitivity test, this analysis was repeated with DVT counted also as AVEs (Supplementary Fig. 1); similar conclusions were reached, with higher rate of events seen during the first six months after CPI initiation (59 events) than during 7–12 months after treatment initiation (11 events; odds ratio: 3.64, 95% CI: 1.90–6.98, p value < 0.001).

Further analyses focused on the first six months after CPI initiation. Table 1 presents the clinical characteristics of all the 1215 CPI-treated patients and of the 31 patients with AVEs during this time window. The event rate for each subgroup of patients is presented with the corresponding 95% CI.

Regarding combined CPI-chemotherapy, none of the 16 cases identified to receive concomitant CPI-chemotherapy had an AVE. In addition, 45 patients started chemotherapy within a month after the end of immunotherapy. Since the half-life of most antibodies is around one month, we considered those cases as sequential CPI-chemo. None of those patients had an AVE. Chemotherapy given more than a month after CPI was not considered as concomitant or sequential treatment for this analysis.

Odds ratio (Fisher exact test) was calculated for the association of apparent or possible risk factors and the rate of AVE within six months of CPI treatment (univariate analysis, Table 2). Tumour types evaluated as



Month	1	2	3	4	5	6	7	8	9	10	11	12
N of AVE	10	3	6	5	5	2	0	1	2	1	2	0
Number at Risk	1215	1112	1034	961	913	879	856	822	802	783	768	754

Fig. 1. Rate of AVEs in each month after starting CPIs, until one year later. The number of events and patients at risk is shown for each month. Single-site DVT cases were excluded from this analysis, as well as concomitant or sequential chemotherapy-treated patients. AVE: acute vascular event; CPI: checkpoint inhibitor; DVT: deep vein thrombosis.

variables in the odds ratio analysis included only melanoma and lung adenocarcinoma because of the small number of cases seen with other malignancies. Treatments were grouped by mechanism of action (i.e., anti−PD-1, anti−PD-L1, anti−CTLA-4).

Multivariate Cox regression model was built, including all factors of interest (Table 3). Based on the Fisher exact odds ratio results, tumour type for the Cox regression model was evaluated as lung adenocarcinoma versus all other types. The factors significantly associated with AVEs on CPI treatment are highlighted in Table 3.

Precise stage data were not available in our data set for most patients, thus not analysed for correlation with AVE occurrence. We assume almost all the patients on this study were patients with stage 4 cancer as this is the current label for most CPIs. The exception to this would be usage of adjuvant nivolumab in stage III melanoma, which entered clinical practice at the end of 2017 [22]; thus, it would be relevant only for a small subset of the study data set. (Efficacy of adjuvant ipilimumab was reported in 2015 [23], but very few ipilimumab treatments were recorded in our cohort.) As a surrogate for stage of disease, we examined LDH serum levels before initiation of immunotherapy, in a subgroup of patients with melanoma where these data could be retrieved (N = 213), and found no correlation with AVE occurrence (Cox regression analysis, p value: 0.999).

To further investigate a potential contributory role of CPI as a trigger for AVEs, we wanted to compare it with chemotherapy. We focused on NSCLC adenocarcinoma; 159 patients with NSCLC adenocarcinoma treated with platinum-based doublets who never received CPI were identified in our database. These were compared with 92 patients with lung adenocarcinoma who have received CPI treatment and never received chemotherapy and with another group of 125 patients with lung adenocarcinoma who have been exposed to both CPI and chemotherapy (at any sequence and interval; Table 4). The frequency of AVEs as evaluated in this analysis was not significantly different among the different groups (formal statistical comparison not done because of small groups; see overlapping 95% CIs). Generally similar AVE frequencies were seen also when this analysis was repeated with DVT included as an AVE (chemotherapy only: 11.9%, 95% CI: 7.7−18.0. CPI only: 12.0%, 95% CI: 6.6−20.3. CPI and chemotherapy: 11.2%, 95% CI: 6.7−18.0).

Clinical characteristics and relevant risk factors for AVEs on CPIs for each of the 31 patients who had an AVE on CPI only are presented in Supplementary Table 1. Of these patients, 90% had two or more risk factors (out of smoking history, diabetes mellitus, HTN, hyperlipidaemia, male sex, past history of AVE and renal failure) and 55% had three or more risk factors. Of these 31 patients, 19 (61.3%) were on anti-platelet, thrombin and Xa inhibitors or anti-coagulants at the time of the AVE [specifically aspirin (13), clopidrogel (3), low-molecular-weight heparin (2) and apixaban (1)]. Interestingly, pulmonary emboli were the most common type of AVEs in patients with lung cancer compared with other malignancies (not statistically significant).

We examined the possibility that occurrence of irAEs is correlated with AVEs. We focused on immune-related

Table 1
Characteristics of CPI-treated patients, with or without an AVE within 6 months of starting CPI treatment.

Parameters:	Total N (%)	Patients with AVEs N (%)	Event rate, % (95% CI)
	1215 (100)	31 (100)	2.6 (1.8–3.6)
Age < 65 years	579 (47.7)	13 (41.9)	2.2 (1.3–3.8)
Age ≥ 65 years	636 (52.3)	18 (58.1)	2.8 (1.7–4.3)
Male	717 (59.0)	24 (77.4)	3.3 (2.3–5.0)
Female	498 (41.0)	7 (22.6)	1.4 (0.6–2.9)
Type of cancer			
Melanoma	492 (40.5)	11 (35.5)	2.2 (1.2–4.0)
NSCLC – non-adenocarcinoma	139 (11.4)	2 (6.5)	1.4 (0.1–5.4)
NSCLC – adenocarcinoma	210 (17.3)[a]	11 (35.5)	5.2 (2.8–9.2)
Breast cancer	13 (1.1)	–	–
GI – gastric	16 (1.3)	–	–
GI – pancreas	13 (1.1)	1 (3.2)	7.7 (0–35.4)
GI – other	64 (5.3)	1 (3.2)	1.6 (0.0–9.1)
Genitourinary malignancy	127 (10.5)[a]	4 (12.9)	3.1 (1.0–8.1)
Gynaecologic malignancy	60 (4.9)	1 (3.2)	1.7 (0.0–9.7)
Head and neck cancer	33 (2.7)	–	–
Other solid tumours	23 (1.9)	–	–
Haematologic malignancies	19 (1.6)	–	–
CNS malignancies	6 (0.5)	–	–
Immunotherapy treatment			
Nivolumab	418 (34.4)	12 (38.7)	2.9 (1.6–5.0)
Pembrolizumab	576 (47.4)	14 (45.2)	2.4 (1.4–4.1)
Atezolizumab	48 (4.0)	–	–
Ipilimumab	19 (1.6)	1 (3.2)	5.3 (0.0–26.5)
Durvalumab	14 (1.2)	–	–
CPI plus CPI[b]	140 (11.5)	4 (12.9)	2.9 (0.9–7.4)
Risk factors			
Smoking	470 (38.7)	16 (51.6)	3.4 (2.1–5.5)
Past history of AVE	112 (9.2)	8 (25.8)	7.1 (3.5–13.6)
HTN	420 (34.6)	18 (58.1)	4.3 (2.7–6.7)
Diabetes	205 (16.9)	8 (25.8)	3.9 (1.9–7.6)
Dyslipidemia	354 (29.1)	9 (29.0)	2.5 (1.3–4.8)
Renal failure	155 (12.8)	5 (16.1)	3.2 (1.2–7.5)

Age groups are split by the median age of all patients.
AVE: acute vascular event; CI: confidence interval; GI: gastrointestinal; NSCLC: non-small cell lung cancer; CNS: central nervous system; CPI: immune checkpoint inhibitor; HTN: hypertension.
[a] One patient with both genitourinary cancer and adenocarcinoma NSCLC and an AVE is coded as genitourinary only, aiming to simplify the analysis of patients with NSCLC.
[b] Clinical trials with anti–CTLA-4/placebo, administered with anti–PD-(L)1.

endocrinopathies, events which were relatively common, and fully captured for the entire cohort. No correlation was found between immune-related endocrinopathies (any grade) and AVEs. Specifically, among 31 patients with AVEs, five patients had endocrinopathies, all thyroiditis grade I. Among the patients with no AVEs (n = 1184), 182 had endocrinopathies (thyroiditis only, 166; adrenal insufficiency only, 10; hypophysitis only, 3; thyroiditis & adrenal insufficiency, 2; thyroiditis & hypophysitis, 1), all assessed to be immune-related (Fisher exact test, non-significant).

We aimed to evaluate a possible correlation between AVEs and response to therapy. Among the 31 patients with an AVE treated with CPIs, eight died within a month and additional two patients died before disease could be evaluated, leaving 21 patients evaluable for response. Of these 21, only four were evaluated as responding (19% response rate). Another four patients were evaluated as stable disease, with a disease control rate of 38.1% (8 of 21 patients). No complete responses were seen. We then compared response to therapy in patients with AVEs, in CPI-treated vs. chemo-treated (patients characteristics in Table 4, including only patients with lung adenocarcinoma). Out of six CPI-treated patients with AVEs, only two were evaluable for response, both of whom had progressive disease as best response (0% response rate and 0% disease control rate). Out of the seven chemo-treated patients with AVEs, three were evaluable for response. No responses were seen, and one patient had stable disease as best response (0% response rate, 33% disease control rate). We could not identify any trend of a high response rate to CPI, nor to chemotherapy, in patients with AVEs.

Overall survival analysis was performed, comparing the outcome of 31 patients who developed an AVE on CPI only with the 1184 patients who did not

Table 2
Odd ratio (Fisher exact test) analysis of potential risk factors for AVEs.

Risk factors	Fisher exact P value	Odds ratio (95% CI)
Age[a]	0.587	1.27 (0.62–2.60)
Sex[b]	**0.041**	**2.43 (1.04–5.68)**
Tumour type:		
NSCLC – adenocarcinoma	**0.013**	**2.72 (1.28–5.77)**
Melanoma	0.711	1.24 (0.59–2.62)
Treatment type:		
Anti–PD-1 (nivolumab, pembrolizumab)	0.657	1.43 (0.54–3.77)
Anti–PD-L1 (atezolizumab, durvalumab)	0.396	0.95 (0.94–0.96)
Anti–CTLA-4 (ipilimumab)	0.390	2.16 (0.28–16.71)
CPI plus CPI[c]	0.774	1.15 (0.40–3.34)
CPI-chemo-sequential	1.000	1.20 (0.16–8.97)
Atherosclerosis risk factors:		
Smoking history	0.139	1.71 (0.84–3.50)
Past history of AVE	**0.005**	**3.61 (1.58–8.28)**
HTN	**0.007**	**2.70 (1.31–5.55)**
Diabetes	0.220	1.74 (0.77–3.95)
Dyslipidemia	0.836	1.22 (0.52–2.86)
Renal disease	0.582	1.33 (0.50–3.50)

Tumour types included were compared in each case to all other malignancies. Treatment types were compared in each case to all other treatment types. Risk factors with a p value < 0.05 are in bold.
CI: confidence interval; HTN: hypertension; AVE: acute vascular event.
[a] Above median (65 years) vs. below median.
[b] Males vs. Females.
[c] Clinical trials with anti–CTLA-4/placebo, administered with anti–PD-(L)1.

Table 3
Cox regression analysis of potential risk factor for AVEs.

Risk factors	*P* value (Cox regression)	Hazard ratio (95% CI)
NSCLC – adenocarcinoma[a]	**0.005**	**2.93 (1.38–6.22)**
Past history of AVE	**0.008**	**3.08 (1.34–7.08)**
HTN	**0.003**	**3.19 (1.50–6.78)**
Dyslipidemia	**0.039**	**2.93 (1.38–6.22)**
Treatment[b]	NS	
Age[c]	NS	
Sex	NS	
Smoking history	NS	
Diabetes	NS	
Renal disease	NS	

CI: confidence interval; HTN: hypertension; AVE: acute vascular event; NS: non-significant.
Data relating to risk factors with a *P* value of less than 0.05 are in bold.
[a] NSCLC adenocarcinoma was compared with all other malignancies.
[b] All treatments as categorised in Table 2.
[c] Age considered as a continuous variable.

(considering only AVE during the first 6 months after CPI initiation; Fig. 2). Patients with no AVE had a significantly longer overall survival (median of 14 months, 95% CI: 10.8–17.2, vs. 3 months, 95% CI: 1.9–4.1, Cox regression analysis univariate hazard ratio: 3.01, 95% CI: 2.07–4.39, p-value <0.0001). As mentioned previously, in eight cases (25.8% of the AVE cases), death occurred within a month of the AVE, thus probably related to this event.

4. Discussion

We have analysed a well-annotated retrospective database for the frequency of AVEs occurring after initiation of CPI treatment. We believe this report to be a unique and thorough assessment of the potential risk of AVEs that are possibly related to CPIs. The identified thrombotic/embolic events are distinct from the recognised cardiovascular immune-related events such as vasculitis, myocarditis and pericarditis. A cause-effect conclusion cannot be drawn, but the timing of the events, occurring mostly close after initiation of CPIs, suggests the immunotherapy treatment to be a possible risk factor of AVEs. Among patients with lung cancer, we found the risk of AVEs after CPIs to be in a similar range to the risk of AVEs after chemotherapy treatment, which is a recognised risk factor for AVEs [24]. The seemingly similar rates of AVE for patients on CPI, on

Table 4
Clinical characteristics of patients with NSCLC adenocarcinoma on chemotherapy only or on CPI only or patients who have been exposed to both (at any sequence or time interval) and AVE event rate during the first six months after initiation of treatment.

Parameters	Chemotherapy only			CPI only			CPI and chemotherapy		
	N (%)		Event rate, % (95% CI)	N (%)		Event rate, % (95% CI)	N (%)		Event rate, % (95% CI)
	Without AVE	With AVE		Without AVE	With AVE		Without AVE	With AVE	
N	152 (100)	7 (100)	**4.4 (2.0–9.0)**	86 (100)	6 (100)	**6.5 (3.6–17.3)**	118 (100)	7 (100)	**5.6 (2.5–11.3)**
Age									
<65 years	64 (42.1)	4 (57.1)	**5.9 (1.9–14.6)**	34 (39.5)	NA	**NA**	57 (48.3)	6 (85.7)	**8.2 (3.5–17.1)**
≥65 years	88 (57.9)	3 (42.9)	**3.3 (0.7–9.7)**	52 (60.5)	6	**10.3 (4.5–21.1)**	61 (51.7)	1 (14.3)	**1.6 (0.0–9.4)**
Sex									
Male	92 (60.5)	4 (57.1)	**4.2 (1.3–10.6)**	56 (65.1)	4 (66.7)	**6.7 (2.3–17.5)**	75 (63.6)	3 (42.9)	**3.8 (0.9–11.2)**
Female	60 (39.5)	3 (42.9)	**4.8 (1.1–13.6)**	30 (34.9)	2 (33.3)	**6.7 (0.7–21.2)**	43 (36.4)	4 (57.1)	**8.5 (2.8–20.5)**
Chemotherapy treatments									
Carboplatin	113 (74.3)	3 (42.9)	**2.6 (0.6–7.7)**	NA			99 (83.9)	6 (85.7)	**5.7 (2.4–12.2)**
Cisplatin	38 (25.0)	4 (57.1)	**9.5 (3.2–22.6)**	13 (11.0)	1 (14.3)	**7.1 (0.0–33.5)**			
Bev [a]	1 (0.7)	–	NA	6 (5.1)	–	NA			
Immunotherapy treatments									
Anti–PD-1	NA			82 (95.3)	5 (83.3)	**5.7 (2.2–13.1)**	95 (80.5)	6 (85.7)	**5.9 (2.5–12.6)**
Anti–PD-L1	1 (1.2)	–	**NA**	15 (12.7)	–	**NA**			
Anti–CTLA-4	–	–	**NA**	–	–	**NA**			
CPI plus CPI [b]	3 (3.5)	1 (16.7)	**25.0 (3.4–71.1)**	–	–	**NA**			
CPI-Chemo				8 (6.8)	1 (14.3)	**11.1 (0.0–45.7)**			

For CPI and chemotherapy combined group, the period where AVEs were evaluated started at the first CPI treatment. Percentages of patients with or without an AVE relate to the total of each column. One patient with two malignancies who had an AVE on CPIs was excluded from this analysis.
Chemo: chemotherapy; AVE: acute vascular event; CPI: immune checkpoint inhibitor; CI: confidence interval; NA: not applicable.
[a] Bevacizumab plus carboplatin.
[b] Clinical trials with anti–CTLA-4/placebo administered with anti–PD-(L)1.

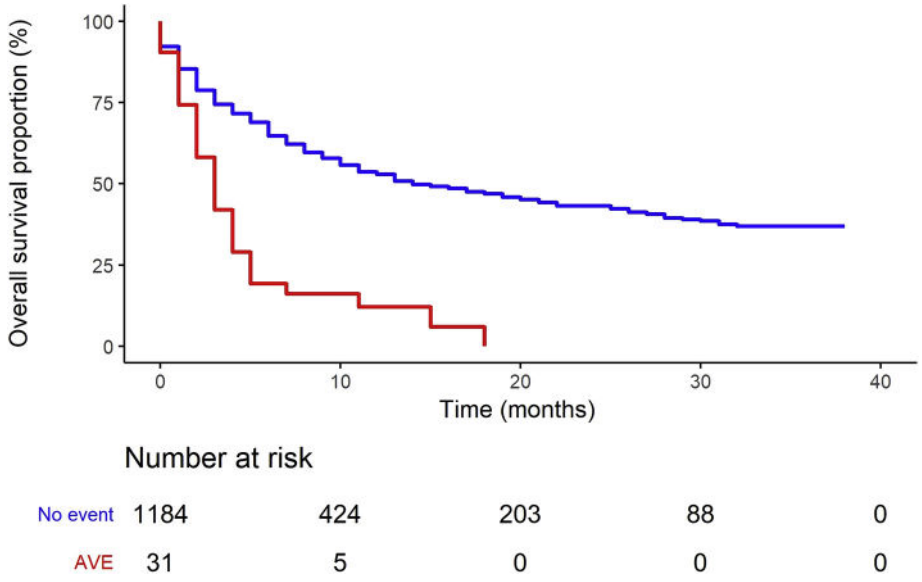


Fig. 2. Survival of patients with cancer who received CPI treatment with (red line) or without an AVE (blue line) within six month of treatment initiation. AVE: acute vascular event; CPI: checkpoint inhibitor.

chemotherapy or on both suggest that although CPIs may not augment the risk of AVEs over that of chemotherapy, they carry a similar and significant risk of such adverse events. Notably, patients on CPIs who had an AVE had a significantly worse outcome than patients without this complication.

A few previous reports hint also at AVEs as potentially triggered by CPIs [9]. A recently reported analysis of cardiovascular AEs in CPI trials identified 0.58% and 0.3% event rates of ischaemia and sudden cardiac death, respectively, within the first 6 months after starting CPIs [25]. The risk of those events relative to chemotherapy-treated patients was 1.35 (95% CI: 0.76–2.4) for ischaemia and 0.7 (95% CI: 0.38–1.27) for sudden cardiac death. The reported event rate seems strikingly smaller than the 2.6% event rate we report. Potential reasons for the difference may be different characteristics of the patients included in our data set or under-reporting of such events. A related topic, under-reporting of venous thromboembolism (VTE) has been found; in one example, an event rate of 0.7% VTE increased to 10.2% after chart review of trial participants [26]. Our detailed analyses provide data that might be missed in retrospective analyses of AE reports from clinical trials.

The patients who presented with an AVE after CPI initiation were prone to such complications; many of these patients had prior AVEs and/or recognised risk factors for atherosclerosis. We hypothesise that CPI may allow augmentation of an inflammatory process within an already inflamed atherosclerotic plaque, as the AVE pathogenesis. Accordingly, we would not expect AVEs after CPI treatment in patients without an ongoing atherosclerotic disease. Our results suggest caution in starting CPI for patients with cancer with high risk for the presence of arterial atherosclerosis and careful monitoring, especially during the first few months of treatment. Various immune checkpoint molecules can potentially both attenuate and enhance atherosclerosis [27]. Deeper insight into the precise mechanisms at play may allow in the future modulation of atherosclerosis by inhibition or activation of specific immune checkpoints [28,29].

We have identified a 5.2% event rate in patients with lung adenocarcinoma, a diagnosis found to be an independent risk factor in multivariate analysis. Lung cancer, and mostly adenocarcinoma, is a recognised risk factor for VTE [30]. VTE is correlated with arterial ischaemic events [31], but in general, arterial ischaemic events were not clearly linked to lung cancer [32,33]. A large data set study did not find a correlation of a specific cancer diagnosis and ischaemic stroke diagnosis [34]. Among admitted patients with cancer and neutropenia, or who underwent blood or platelet transfusion, lung ancer was correlated with arterial thrombotic events [35,36]. Awareness of the higher risk for this complication in patients with lung adenocarcinoma is required.

The limitations of this study include its retrospective nature, it being based on a single-institute EMR and the unknown extent of missing data. AVE might have occurred in a different institute; however, diagnoses such as MI or cerebro-vascular accident (CVA) are likely to be recorded in EMRs even if not occurred at the recording centre [37]. In addition, since 2011, a national electronic health record–sharing system is in the process of implementation across all Israeli medical institutes with a high rate of participation. Detailed manual chart review was performed only for patients

with an identified or suspected AVE (based on diagnoses documented in the EMR). As mentioned, ipilimumab-treated patients were mostly missed because of its documentation on an older EMR that was not accessible to us. Patients who received CPIs or other types of immunotherapies as part of the clinical trial may have been missed if the name of the protocol did not include the recognised name of the drugs we searched for. Another limitation is the relatively small number of patients on CPIs or on chemotherapy for lung adenocarcinoma included in the comparison of AVEs. Despite those limitations, we have identified a large cohort of patients with cancer treated by immunotherapy, with a high probability captured most cases of AVE on this treatment and characterised them.

5. Conclusions

We have identified a higher event rate of AVEs within the first six months after initiation of CPI than at later time periods. AVE rate was 5.2% in this period in patients with lung adenocarcinoma, similar to AVE rate of patients on chemotherapy alone. The outcome of patients with such events was significantly worse than that of the other patients on the cohort. Prior ischaemic events, HTN, hyperlipidaemia and a diagnosis of lung adenocarcinoma were strongly associated with ischaemic events on CPI. Awareness of AVEs occurring on immunotherapy as often as on chemotherapy should be increased.

Conflict of interest statement

In the interest of full transparency: J.B. reports receiving honoraria from AstraZeneca, MSD, Boehringer Ingelheim, Roche, BMS, Takeda, Abbvie and VBL. G.M. reports receiving honoraria and serving the role of a member of the speaker's bureau of BMS, MSD, Roche and Novartis and advisory boards of Novartis and MSD. R.P. reports receiving honoraria from BMS. R.L-.A. reports receiving honoraria from Roche, MSD, BMS, Janssen, Astellas and Pfizer. T.G. reports receiving grant supports from AstraZeneca and MSD and consultation fees from Abbvie. E.D. reports receiving honoraria from Roche, Boehringer Ingelheim, AstraZeneca, Pfizer, MSD, BMS, Novartis and Takeda. D.U. reports receiving honoraria from BI, Roche, BMS, MSD, Teva, AstraZeneca and Takeda. All the aforementioned conflicts are unrelated to the submitted work. All other authors declare no potential conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.06.021.

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