# Immune checkpoint inhibition associated cardiovascular adverse events in cancer patients

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Primary objective: To assess the effect of ICI on progression of coronary non-calcified plaque volume and ICI-related cardiovascular events by measuring differences in plaque burden using repeated CCTA.Secondary objectives:- To evaluate the relation...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Coronary artery disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON51839

**Source**
ToetsingOnline

**Brief title**
ITHACA

### Condition

- Coronary artery disorders
- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Embolism and thrombosis

**Synonym**
cardiovascular disease (CVD); heart and vascular disease

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum

**Source(s) of monetary or material Support:** Schenking vanuit een stichting

## Intervention

**Keyword:** arterial thromboembolism, atherosclerosis, immune checkpoint inhibitors, venous thromboembolism

## Outcome measures

### Primary outcome

Primary parameter: absolute total coronary plaque volume progression

### Secondary outcome

Secundary parameters:

- CCTA (coronair): plaque progression and plaque characteristics

(vulnerability)

- CTA carotid): plaque progression and plaque characteristics (vulnerability)

- Clinical outcomes: cardiovacular disease events (i.e. myocardial infarction,

stroke), venous thromboembolism, immune related adverse events, death of any

cause

# Study description

### Background summary

Immune checkpoint inhibitors (ICI) have revolutionized cancer treatment and are available for different types of cancer. However, several studies reported the increased risk of arterial thromboembolism such as mycardial infarction and stroke. In these studies, patients on ICI treatment have a 4-5 fold increased risk of an ischemic event compared to cancer patients on other therapies. Pre-clinical date suggest that accelerated atherosclerosis with infiltration of immune cells is an important factor, although the mechanism is still unknown.

### Study objective

Primary objective: To assess the effect of ICI on progression of coronary

non-calcified plaque volume and ICI-related cardiovascular events by measuring differences in plaque burden using repeated CCTA.
Secondary objectives:
- To evaluate the relation between the duration and intensity of ICI therapy and progression of coronary and carotid non-calcified plaque volume;
- To evaluate clinical predictors and plasma and fecal biomarkers for progression of non-calcified plaque volume during ICI treatment;
- To evaluate the association between ICI therapy and arterial and venous thromboembolic events.

## Study design

This is a single-center, observational, prospective, parallel-group study of patients with different solid tumor types. Patients over 50 years with a solid tumor will be enrolled prior to start of therapy. At baseline, prior to start treatment, CCTA and CTA carotid are performed to determine the baseline coronary an carotid artery plaque burden, if present. After 12 months of treatment, CT scans are repeated to assess the difference in progression of plaque burden. At baseline and at days 90 (±7), and 365 (±21), blood will be drawn for circulating immune cells, cytokines, cardiovascular risk profile (i.g. lipid profile), markers of endothelial cell activation, and coagulation. Clinical data will be collected at every visit and include medication use, physical examination and vital signs. Feces will be collected for shotgun microbiota analysis at baseline and 12 months post-ICI. Clinical outcome on the incidence of ATE, VTE, immune-related adverse events, tumor response and death of any cause will be collected every visit (at baseline, day 90 and 12 months at end of treatment and annualy for 5 years after start of treatment. To study the potential causal effects of ICI therapy, we will compare cancer patients eligible for ICI therapy vs patients on other treatment regimes.

## Study burden and risks

Blood withdrawal for clinical laboratory assessment will include 150 mL (3 time points). Venapunction and intravenous cannulation will result in minor discomfort, with a small chance of hematoma occurrence. The CTA will approximately have a duration of 10 minutes. Radiation exposure will be 9.6 mSv in two years, slightly elevated compared to background radiation in the Netherlands (~2.9 mSv/year). If possible, we will combine CTA imaging with regular clinical care follow-up scans. Another potential risk is the use of iodinated contrast, which can induce contrast nephropathy. However, this risk is very low with low-dose, low-osmolality contrast media, and probably still overestimated in current practice. Risk factors for developing contrast nephropathy mainly include pre-existent renal insufficiency, which is one of our exclusion criteria. In addition to the low occurrence of contrast nephropathy, when occurring in patients without pre-existent renal insufficiency, this is mostly a reversible temporary decline in eGFR.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

- Adult male or female, age >=50 years
- Prior to start therapy
- Confirmed diagnosis of cancer:
- Treatment-naive advanced esophageal, gastric, or gastro-esophageal cancer planned for first-line nivolumab or chemotherapy only or follow-up only after resection
- Treatment-naive advanced colorectal cancer planned for first-line pembrolizumab or other systemic therapies
- Recurrent or metastatic head/neck squamous cell carcinoma with disease progression during platinum-based chemotherapy who are planned for pembrolizumab or other systemic therapies
- Non-small-cell lung carcinoma planned for pembrolizumab or durvalumab or

other systemic therapies
- Advanced renal cell carcinoma planned for first-line ipilimumab/nivolumab or other systemic therapies
- Inresectible or advanced melanoma planned for ipilimumab/ nivolumab

### Exclusion criteria

• ICI therapy in previous 12 months;
• Suspected or confirmed viral, fungal, or bacterial infectious disease;
• Use of immunosuppressive therapy prior to ICI start;
• Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2;
• Known allergy to iodinated contrast agents;
• Atrial fibrillation

## Study design

### Design

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|---|---|
| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Basic science |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 17-03-2023 |
| Enrollment: | 214 |
| Type: | Actual |

## Ethics review

Approved WMO

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| Date: | 25-01-2023 |

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| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| CCMO | NL82446.018.22 |