Cardio-oncologie

Hartproblemen tijdens oncologische behandelingen - immuuntherapie

Constantijn Franssen

Kennis / Ervaring / Zorg

Stichting tegen Kanker

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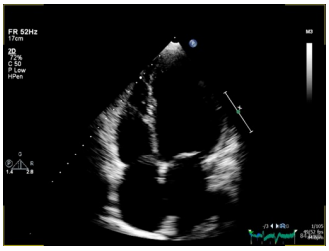
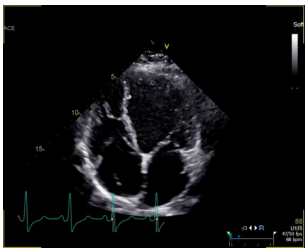
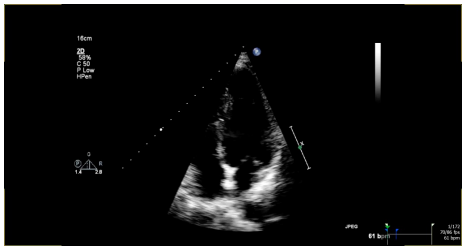
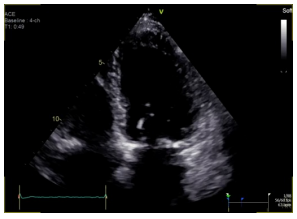
1

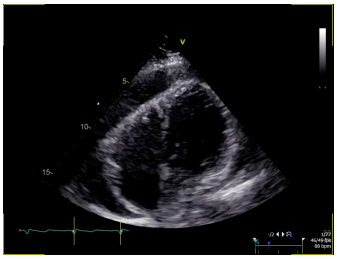
Wat heeft een cardioloog te maken met oncologie?

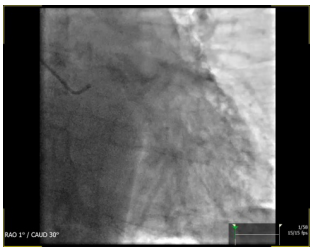












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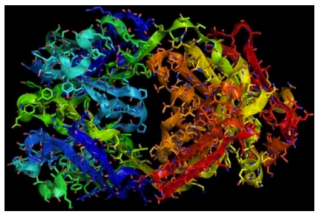
De ”klassiekers” – enkele voorbeelden

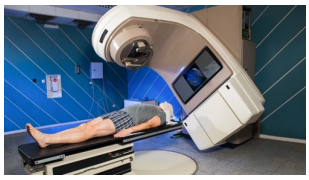
Anthracyclines
Doxorubicine, epirubicine, daunorubicine, idarubicine

Hartfalen



Anti-Her2 behandeling
Trastuzumab *Herceptine®*
Pertuzumab *Perjeta®*

Hartfalen



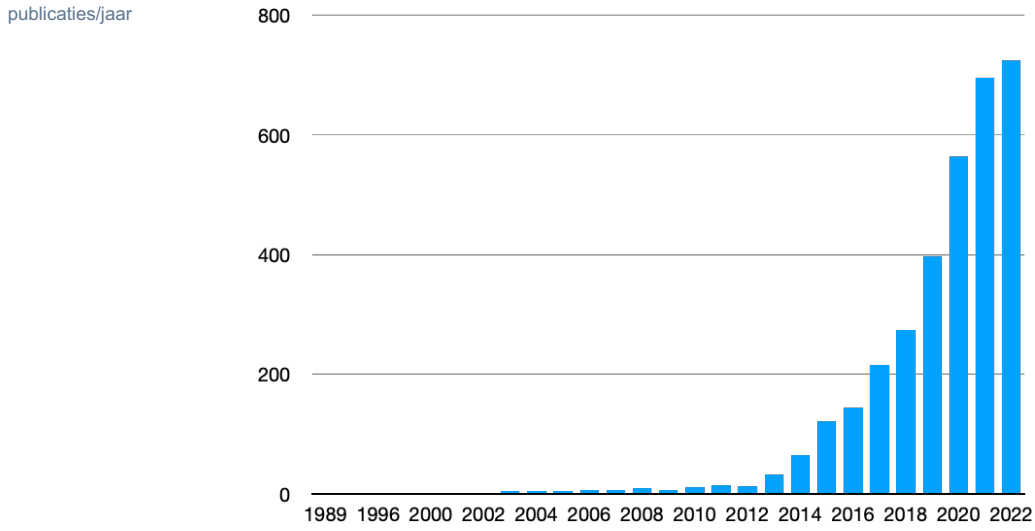
Radiotherapie
Mantle field radiotherapy - Hodgkin

Kleplijden, bloedvataantasting

De ”klassiekers” – enkele voorbeelden

- 5-FU: spasmen van bloedvaten rond het hart
- VEGF-i: hoge bloeddruk
- BTKinhibitoren: atriumfibrilleren
- Diverse producten: “QTc” verlenging (risico op ritmestoornissen)

Publicaties in wetenschappelijke tijdschriften



Discipline die te danken is aan betere oncologische prognose!

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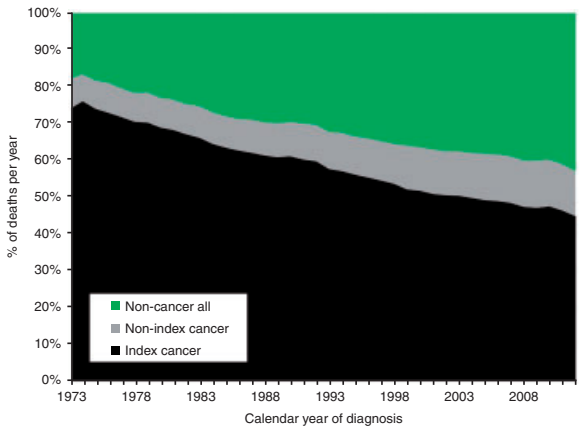
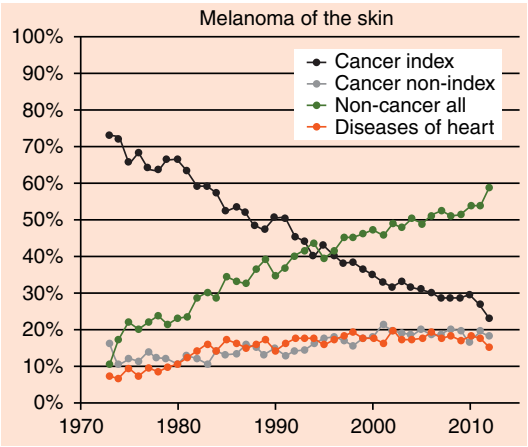
Overlijdens door / met kanker





Zaorsky, Annals of Oncology 2017

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ESC European Society of Cardiology

European Heart Journal (2022) 00, 1–133
https://doi.org/10.1093/eurheartj/ehac244

ESC GUIDELINES

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)

Anthracyclines

EGRF-i

Fluoropyrimidines

ICI

Bruton TKi

anti-HER2

Aplastic lymphoma kinase inhibitors

Multiple myeloma's

Hormoonbehandeling BK

CAR-T en TIL

BCR-ABL TKi

Overig

RAF en MEK-i

Stamcel-tx

VEGF inhibitors

CDK 4/6-i

Androgen deprivatie

Radiotherapie

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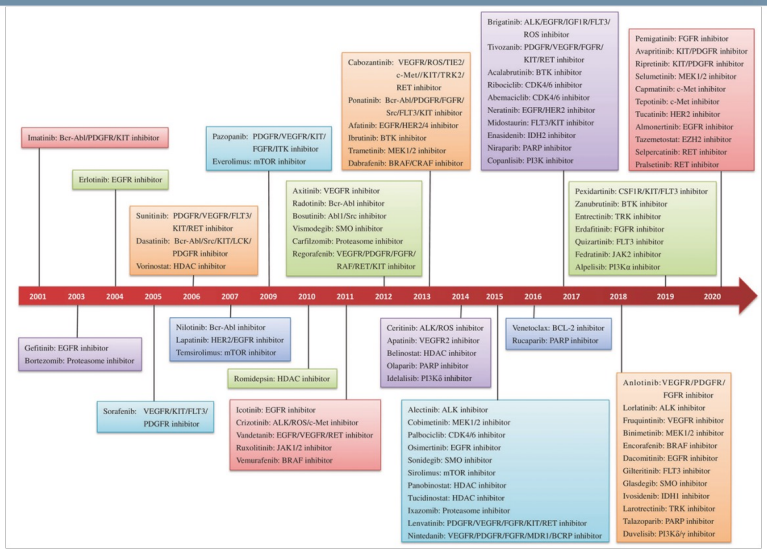
Cardiale veiligheid?



Zhong, Signal Transduction and Targeted Therapy 2021

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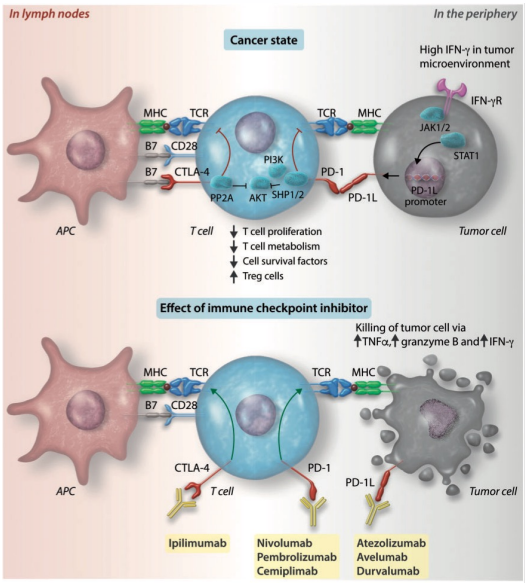
Cardio-oncologie: risico's inschatten

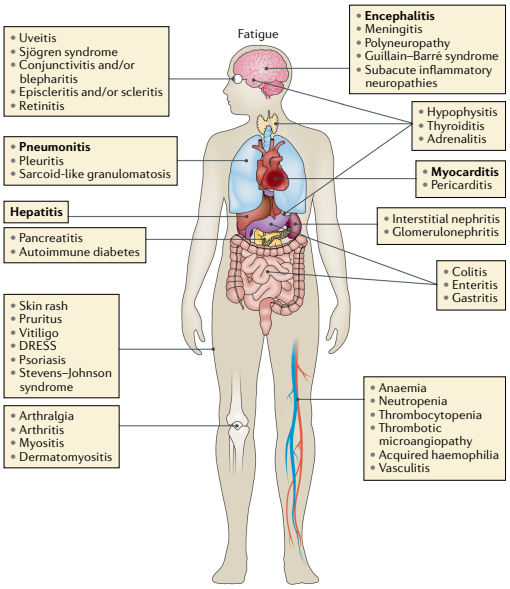
- Faciliteren
- Cardiovasculaire risicofactoren
  - Voorafbestaande hartziekten
  - Hoge bloeddruk
  - Diabetes mellitus
  - Obesitas
  - Hoog cholesterol
  - Roken
- Risicofactoren verbonden aan de behandeling
  - Kunnen het cardiovasculaire risicoprofiel beïnvloeden
  - Vroegere behandelingen
  - Dosis

Immuun Checkpointinhibitoren



Hu, Cardiovasc Res 2019

Geen rozen zonder doorns



Martins, Nature Rev Clin Oncol 2019

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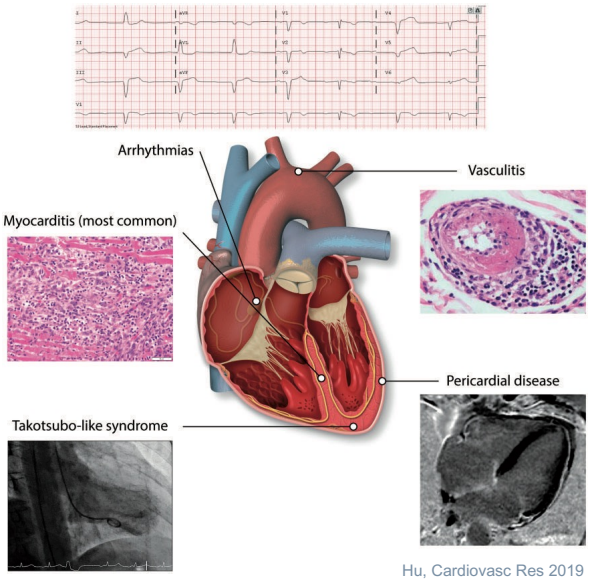
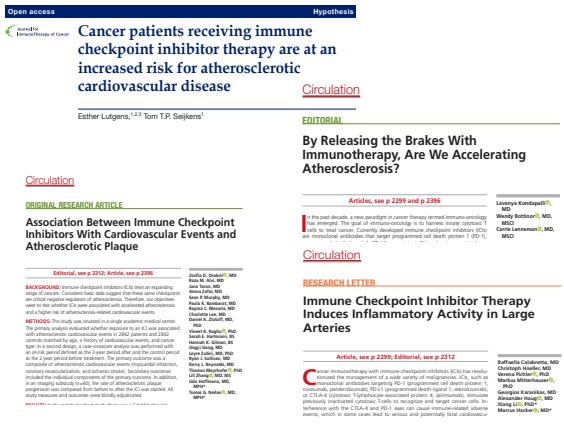
Geen rozen zonder doorns



Hu, Cardiovasc Res 2019



Open access Hypothesis

Cancer patients receiving immune checkpoint inhibitor therapy are at an increased risk for atherosclerotic cardiovascular disease

Esther Lutgens, Tom T.P. Seijkens

Circulation

ORIGINAL RESEARCH ARTICLE

Association Between Immune Checkpoint Inhibitors With Cardiovascular Events and Atherosclerotic Plaque

Circulation

EDITORIAL

By Releasing the Brakes With Immunotherapy, Are We Accelerating Atherosclerosis?

Circulation

RESEARCH LETTER

Immune Checkpoint Inhibitor Therapy Induces Inflammatory Activity in Large Arteries

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Myocarditis

- Variabele presentatie: ongemerkt tot fulminant
- Vaak tezamen met andere irAES, met name ontsteking van skeletspieren of myasthenia gravis
- Meestal eerste 3 maanden (+- 6 weken)
- Fulminant – 1% van alle ICI-behandelingen?
  - Hoog risico om te overlijden
  - Zeer aggressieve behandeling
- Ongemerkt:
  - Effecten op langere termijn?
- Screening: ”hartenzymes”, ECG
  - Bij afwijkingen – cardio-oncoloog
    - Monitoring, echo, biopt, MRI, behandeling

Single center (Florida) data uit elektronische patientendossiers

Table 1 Demographic and clinical characteristics of patients treated with immune checkpoint inhibitors

Characteristics	All (*n* = 424)	Newly diagnosed CVD (*n* = 62)	No CVD (*n* = 362)	P
Age (year)	62 ± 13.1	64.3 ± 10.2	62.1 ± 13.5	0.135
Sex				0.924
Women	155 (36.6%)	23 (37.1%)	132 (36.5%)	
Men	269 (63.4%)	39 (62.9%)	230 (63.5%)	
Race/Ethnicity				0.772
White (non-Hispanic)	363 (85.6%)	55 (88.7%)	308 (85.0%)	
Black (non-Hispanic)	32 (7.6%)	4 (6.5%)	28 (7.8%)	
Hispanic	16 (3.8%)	1 (1.6%)	15 (4.2%)	
Other	13 (3.1%)	2 (3.2%)	11 (3.1%)	
Primary cancer diagnosis				0.163
Lung cancer	126 (29.7%)	20 (32.3%)	106 (29.3%)	
Melanoma	72 (17.0%)	16 (25.8%)	56 (15.5%)	
Kidney cancer	54 (12.7%)	7 (11.3%)	47 (13.0%)	
Head and neck cancer	45 (10.6%)	6 (9.7%)	39 (10.8%)	
Urothelial carcinoma	34 (8.0%)	6 (9.7%)	28 (7.7%)	
Colorectal cancer	19 (4.5%)	4 (6.5%)	15 (4.1%)	
Gastrointestinal cancers (other)	8 (1.9)	1 (1.6%)	7 (1.9%)	
Hodgkin Lymphoma	7 (1.6%)	0	7 (1.9%)	
Other cancer	59 (13.9%)	2 (3.2%)	57 (15.8%)	
Cardiovascular risk factors				
Hypertension	210 (49.5%)	36 (58.1%)	174 (48.1%)	0.146
Ischemic heart disease	54 (12.7%)	9 (14.5%)	45 (12.4%)	0.649
Hyperlipidemia	128 (30.2%)	24 (38.7%)	104 (28.7%)	0.114
Diabetes	76 (17.9%)	14 (22.6%)	62 (17.1%)	0.301
Other cancer medications				
Doxorubicin	14 (3.3%)	3 (4.8%)	11 (3.0%)	0.464
Carboplatin	114 (26.9%)	18 (29.0%)	96 (26.5%)	0.68
Paclitaxel	88 (20.8%)	15 (24.2%)	73 (20.2%)	0.47
Cyclophosphamide	4 (0.9%)	1 (1.6%)	3 (0.8%)	0.555

Values were reported as mean ± standard deviation for continuous variables and frequency (%) for categorical variables

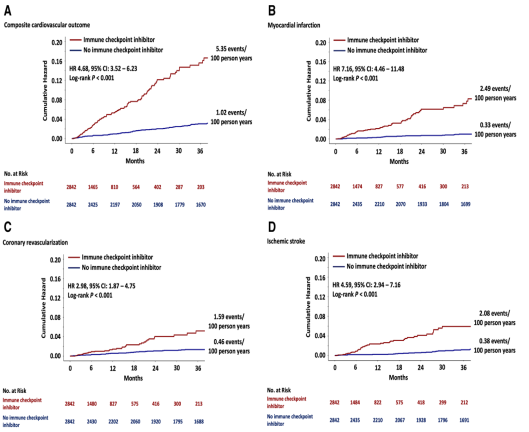
Table 2 Newly diagnosed cardiovascular disease after ICI initiation

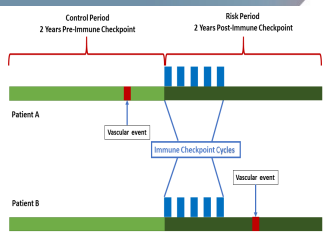
Immune Checkpoint Inhibitor	Cardiomyopathy, n (%)	Heart failure, n (%)	Arrhythmia, n (%)	Pericardial disease, n (%)	Heart block, n (%)	Myocarditis, n (%)	Any cardiotoxicity, n (%)	Median (IQR) time to cardiotoxicity, days
PD-1 inhibitors								
nivolumab (*n* = 217)	1 (0.46)	10 (4.61)	15 (6.91)	7 (3.23)	6 (2.76)	1 (0.46)	33 (15.21)	52 (37–203)
pembrolizumab (*n* = 123)	0	6 (4.88)	3 (2.44)	1 (0.81)	1 (0.81)	0	11 (8.94)	65 (30–175)
PD-L1 inhibitors								
atezolizumab (*n* = 17)	0	1 (5.88)	2 (11.76)	0	0	0	3 (17.65)	22 (2–172)
durvalumab (n = 4)	1 (25)	0	0	0	0	0	1 (25.00)	30
CTLA-4 inhibitor								
ipilimumab (*n* = 13)	0	4 (30.77)	1 (7.69)	0	1 (7.69)	0	6 (46.15)	709 (78–1469)
CTLA-4 + PD-1/PD-L1 inhibitor combination								
ipilimumab + nivolumab (*n* = 29)	2 (6.9)	1 (3.45)	4 (13.79)	0	1 (3.45)	0	7 (24.14)	95 (11–119)
ipilimumab + pembrolizumab (*n* = 7)	0	1 (14.29)	1 (14.29)	0	0	0	1 (14.29)	62
tremelimumab + durvalumab (n = 3)	0	0	0	0	0	0	0	
PD-1/PD-L1 dual sequential								
nivolumab - > pembrolizumab (n = 4)	0	0	0	0	0	0	0	
nivolumab - > atezolizumab (*n* = 3)	0	0	0	0	0	0	0	
pembrolizumab - > atezolizumab (n = 3)	0	0	0	0	0	0	0	
Three-drug sequential								
ipilimumab + nivolumab - > pembrolizumab (n = 1)	0	0	0	0	0	0	0	
Total (n = 424)	4 (0.94)	23 (5.42)	26 (6.13)	8 (1.89)	9 (2.12)	1 (0.24)	62 (14.62)	63 (30–175)

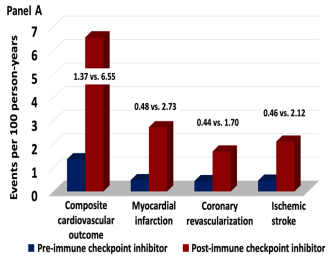
IQR inter-quartile range

Waheed, Cardio-Oncology 2021

“Retrospectief” onderzoek







Drobni, Circulation 2020

“Retrospectief” onderzoek

Wang et al. Cardio-Oncology (2022) 8:23
https://doi.org/10.1186/s40959-022-00149-8

Cardio-Oncology

RESEARCH Open Access

Immune checkpoint inhibitors and the risk of major atherosclerotic cardiovascular events in patients with high-risk or advanced melanoma: a retrospective cohort study

Charlie Wang[1,2*], Sophia Zoungas[2], Mabel Yan[1,2], Rory Wolfe[2], Andrew Haydon[3], Mark Shackleton[3], Mark Voskoboynik[3,4], Maggie Moore[3], Miles C. Andrews[3,4], Stephen J. Nicholls[5,6] and Victoria Mar[1,2]

Abstract

Background: Immune checkpoint inhibitors (ICI) are associated with immune-mediated adverse effects, potentially involving any organ. ICI has also been associated with an increased risk of cardiovascular disease in cancer populations.

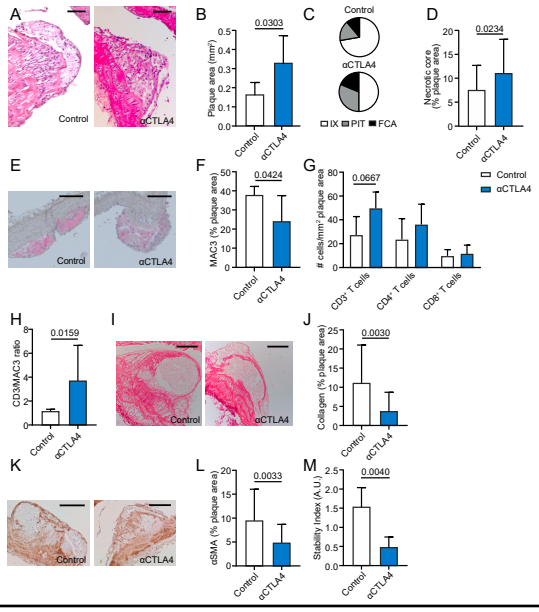
Objective: To characterize the incidence and risk of major atherosclerotic cardiovascular events associated with ICI use in a high-risk and advanced melanoma population.

Methods: We conducted a retrospective cohort study of patients with high-risk or advanced melanoma (AJCC stage II, III or IV) presenting to an academic tertiary hospital between 2015–2020. The main outcome was major atherosclerotic cardiovascular events (MACE) including acute myocardial infarction, ischemic stroke, acute limb ischemia and coronary revascularization.

Results: The study cohort consisted of 646 patients, including 289 who had been treated with ICI. The incidence of MACE was higher in the ICI treated group (3.6 vs. 0.9 events per 100-person years). After adjusting for age, sex, smoking history and prior BRAF and/or MEK inhibitor use, ICI treatment was associated with an increased risk of MACE (HR_{adj} 2.8, 95% CI 1.1–6.9, $p = 0.03$). Elevated risk was especially pronounced in patients with a past history of MACE (HR 14.4, 95% CI 1.9–112.3, $p = 0.01$).

Conclusion: Patients with high-risk or advanced melanoma are at an increased risk of atherosclerotic cardiovascular events following ICI treatment, particularly those with a history of cardiovascular disease.

Meer ontstekingscellen in plaques bij muizen met anti-CTLA4



Poels, Cells 2020

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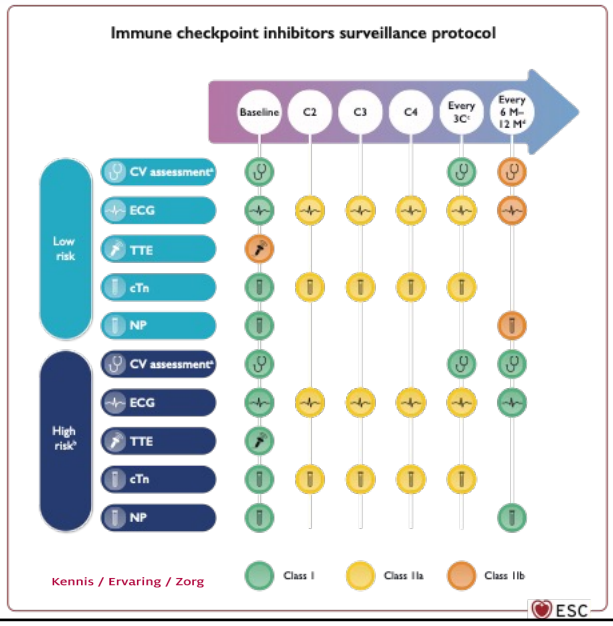
Reden tot ongerustheid? Richtlijnen.



- Systematische opvolging
- Bepaling “hartenzymes” voor elke toediening de eerste 3 maanden
- ECG voor elke toediening de eerste 3 maanden
- Bij mensen met risicofactoren vooraf een echo van het hart

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CAVACI : ism AZ Maria Middelares Gent

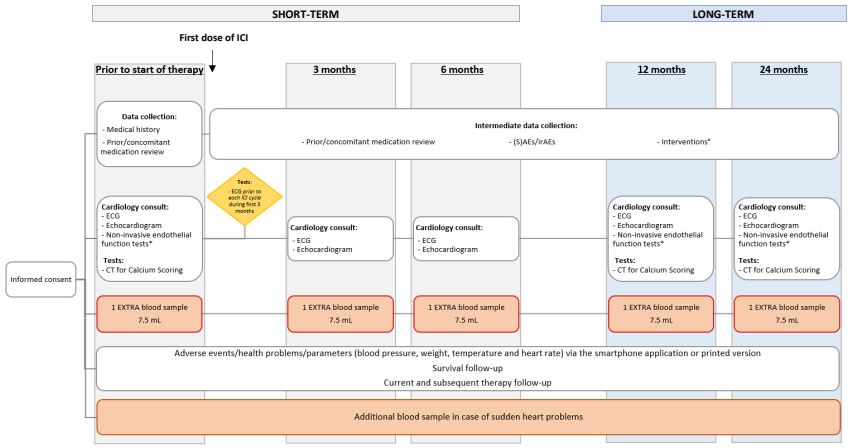

Figure 1 *Study flow. An overview of the (additional) tests/consultations and time points (Work Package 2)*
*Interventions may include the following: cardiac MRI, chest X-Ray, coronary angiography, myocardial perfusion scan, cardiac CT-scan
*These tests will only be performed in patients included by UZA (executed by a dedicated technician under supervision of a cardiologist)
CT = computed tomography; ECG = electrocardiogram; irAE = immune-related adverse event; MRI = magnetic resonance imaging; SAE = serious adverse event

Blood sample collections Short-term cardiovascular follow-up Long-term cardiovascular follow-up

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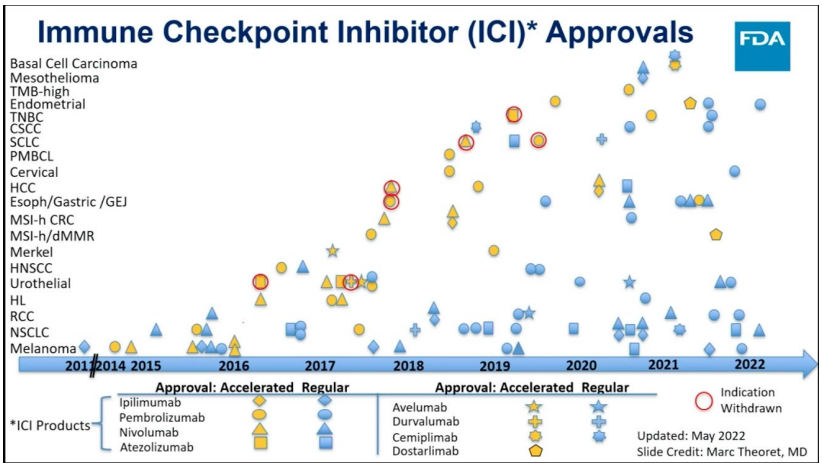
FDA goedgekeure ICI-indicaties



"It's going so fast that the science is beginning to fall behind"
James P. Allison

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Kernboodschappen

- Immuun checkpointinhibitoren zijn en blijven een beloftevolle behandeling
- Cardiovasculaire veiligheid begint nu onderzocht te worden
- Toekomst?
  - Betere opvolging
  - Vermoedelijk niet voor iedereen even veilig
  - Preventieve behandelingen?
- Voorlopig geen reden voor ongerustheid
  - Blijven goedverdragen behandeling met goede resultaten
  - Zeer toepasbare richtlijnen omtrent opvolging en risicobeperking
    - frequente aanpassingen door veel onderzoek

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