ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

www.immunoscienceacademy.be

Workshop A1

Cardio – Oncology

Convention room 3, Floor 1

Guy Jerusalem
CHU Liège

Marie Moonen
CHU Liège

Mercury number: ONCBE1908737-03
Date of preparation: December 2019

Disclaimer

- The case studies within are the speaker’s own, BMS has not had any medical input into these

Learning objectives

- Acute cardiac toxicity: challenges in diagnosis and treatment
- Continuation of immunotherapy after cardiovascular side effects: indications and patient monitoring
- Immunotherapy in patients with history of cardiovascular disease: initial work-up and monitoring of patients

irAEs, immune-related adverse events.

Case study 1

Patient case no.1: Mister H, 77 years old

- Patient history:
  - Ophthalmic transient ischemic attack 30 years ago? (Aspirin 160 mg/day)
  - Abdominal aortic aneurysm (surgery in 2015)
  - Smoking (stopped 10 years ago)
  - Normal LVEF

Patient case no.1: Mister H, 77 years old

2016

Bladder cancer; liver metastases. CDDP/GEM vs clinical trial (anti-PDL1)

4 weeks after starting immunotherapy (D1, cycle 2):

- Symptoms: dyspnoea (progressive increase with major impact on daily activities since 4 days), dry cough, fatigue and myalgia
- Signs: polypnea, SpO2 88%

POINT OF CARE				
pH (POC)		7.44		7.35 - 7.45
pCo2 (POC)		37.0	mm Hg	35.0 - 43.0
Standard bicarbonates (POC)	+	24.7	mmol/L	19 - 24
Excès de base (POC)		0.9	mmol/L	-3.0 - 3.0
pO2 (POC)	-	57	mm Hg	65 - 100
Oxyhémoglobine (POC)		88	%	80 - 100
Sodium POC		138	mmol/L	135 - 145
Potassium (POC)		4.4	mmol/L	3.1 - 4.9
Chlorures (POC)		104	mmol/L	98 - 108
Calcium ionisé (POC)		1.15	mmol/L	1.14 - 1.30
Glucose (POC-GAZ)	+	139	mg/dL	60 - 100
Hémoglobine (POC)		15.3	g/dL	13.2 - 16.9
Lactate (POC)		203	mg/L	60 - 220
carboxyhémoglobine (POC)		0.9	%	0.0 - 5.0
Méthémoglobine (POC)		0.4	%	0.0 - 3.0
Echantillon POC		sang artériel		

CDDP, cisplatin; GEM, gemcitabine; PD-L1, programmed death ligand-1; SpO2, oxygen saturation.

What is your diagnosis?

1. Pneumonitis?
2. Pulmonary embolism?
3. Immune checkpoints inhibitors associated myocarditis?
4. Immune checkpoints inhibitors associated myositis?

Nom :		Né le :		FC :	96 /min	RR :	627 ms
Prénom :		Sexe :		Axe P :	-21 °	P :	90 ms
IDP :		Taille :	-- cm	Axe QRS :	65 °	PQ :	190 ms
Visite :		Poids :	-- kg	Axe T :	248 °	QRS :	146 ms
Date :	08.03.2017	PA :	-- / -- mmHg			QT :	380 ms
Heure :	16:00:59	Origine :	Non défini			QTc :	481 ms

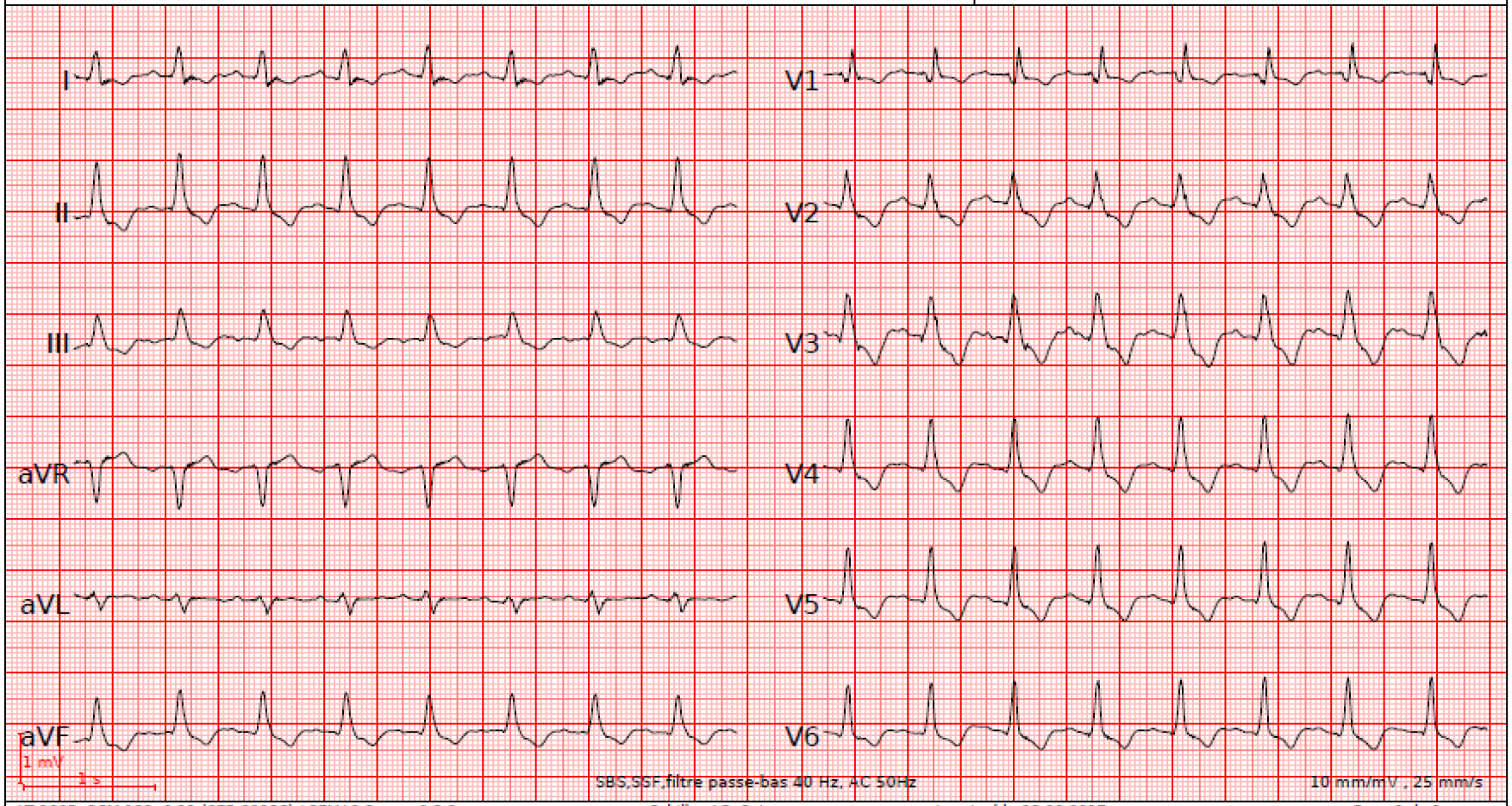
ID demande :
Remarques :
Traitement :

Émetteur de la

Validé par : --

RYTHME SINUSAL
BLOC DE BRANCHE DROIT
HYPERTROPHIE VENTRICULAIRE DROITE AVEC ANOMALIE ST/T
QRS(T) MODIFIE:
ANOMALIE EN ANTEROSEPT. NE PEUT ETRE EXCLU(E)

6.01 RAPPORT NON CONFIRMÉ



Patient case no.1: Mister H, 77 years old

CK: 1990 IU/L (normal level <168 IU/L)

CKMB: 132.6 µg/L (normal level <6.2 µg)

CKMB/CK: 6.7 µg/100 IU (normal level: 0–5 µg/100 IU)

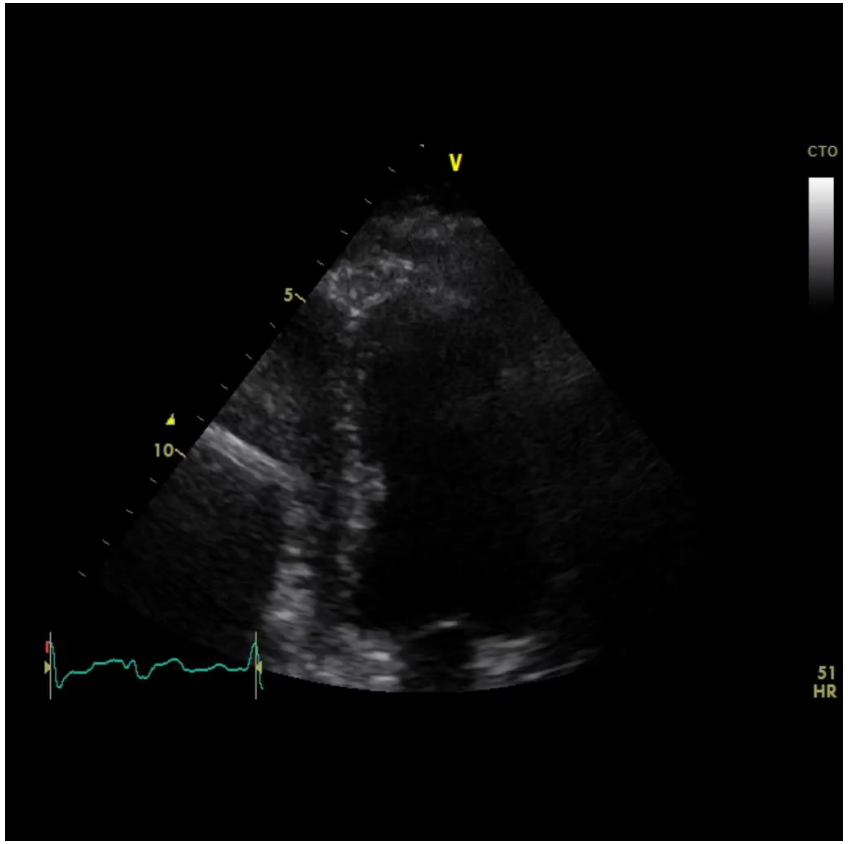
High sensitive troponin T: 2293 ng/L (normal level <14 ng/L)

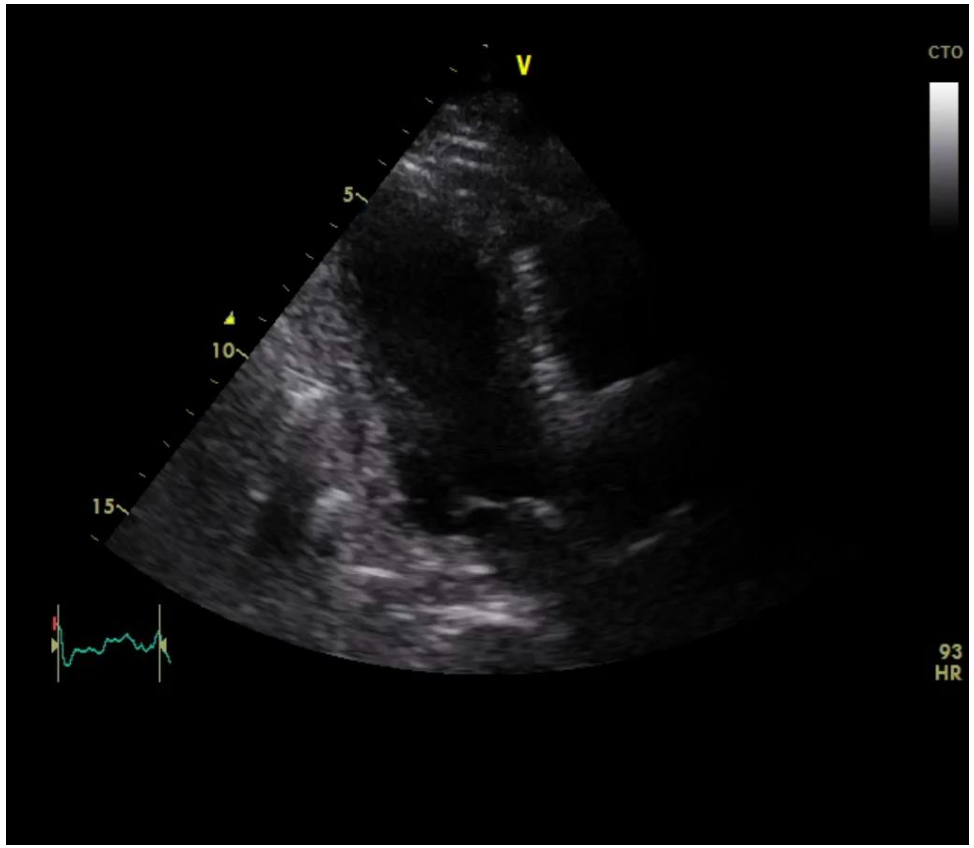
NTproBNP: 904 ng/L (normal level <156 ng/L)

Normal renal function

CK, creatine kinase; CKMB, creatine kinase myocardial band; NTproBNP, N-terminal pro-brain natriuretic peptide.

Transthoracic echocardiography





Routine monitoring of cardiac function?

1. ECG and BNP/troponin according to symptoms?
2. ECG and BNP/troponin q4 weeks during first 3 months?
3. ECG and BNP/troponin at baseline and after 3 months?
4. ECG and troponin baseline and weekly for the first 4–6 weeks?

Role of coronarography? Start of immunosuppression?

1. Immunosuppression according to the result of coronarography?
2. Start of immunosuppressive therapy is always a priority?
3. Fibrinolysis is the preferred upfront treatment?

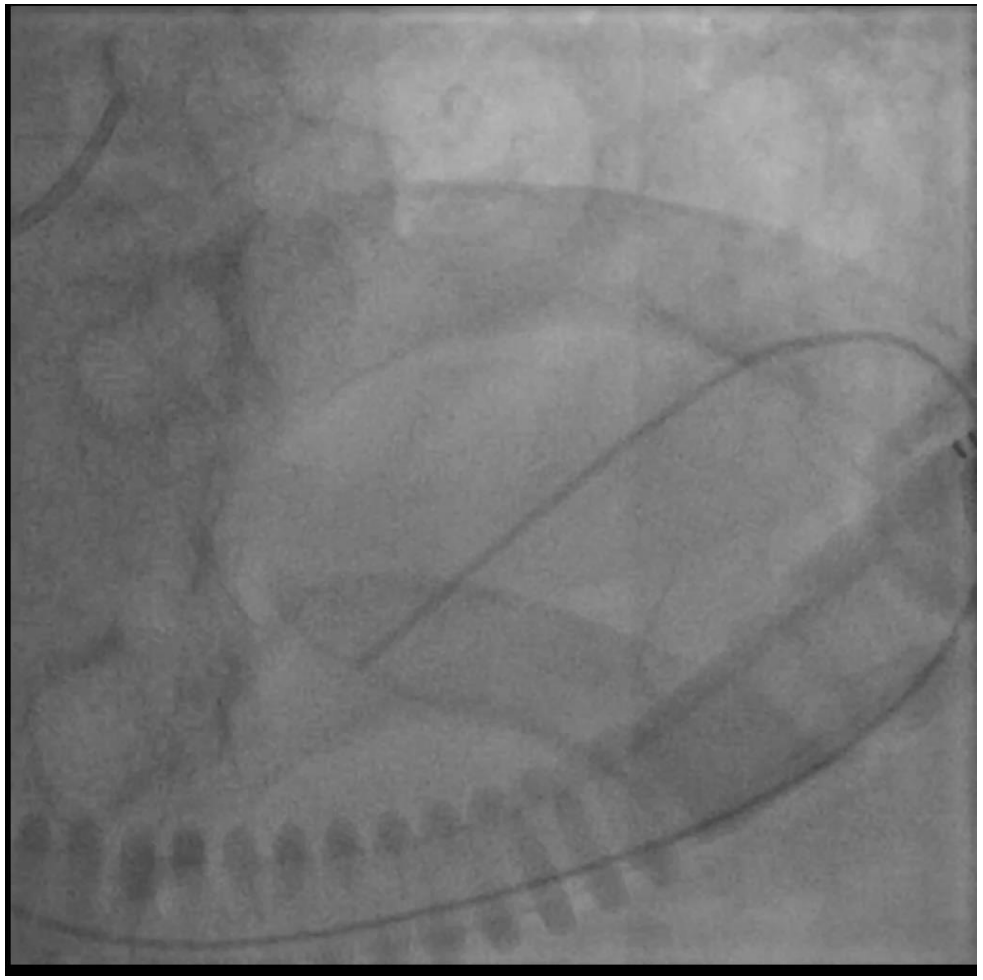
Suspected myocarditis – where should patients be treated?

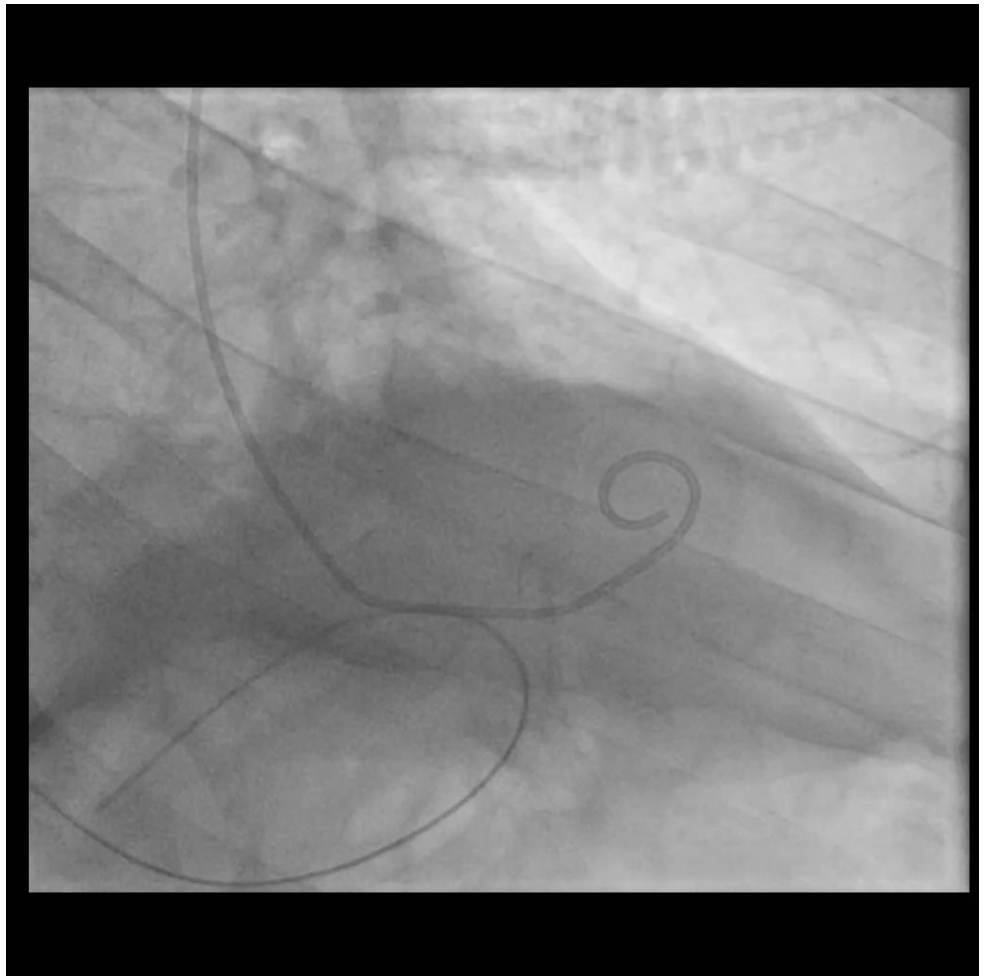
1. Oncology department as they are more familiar with other immune-related complications?
2. Oncology department as long as diagnosis is not confirmed?
3. Intensive care unit (risk of rapid progression)?

Indications for myocardial biopsy?

1. All patients with suspected myocarditis are candidates?
2. Only patients not responding to first-line therapy with steroids?
3. Only patients with a negative coronarography?

Coronary angiography





Cardiac enzymatic monitoring

	D2	D3	D4	D5	D6	D7
CK (IU/L)	1990	1499	1130	1365	1370	1450
CKMB (µg/L)	132.6	120	77.6	180	182	193
HS Troponin T (ng/l)	2293	1829		2817		3113

Coronary angiography

Repeated coronary angiography + EMB

CK, creatine kinase; CKMB, creatine kinase myocardial band; EMB, endomyocardial biopsy; HS, high-sensitive.

Cardiac enzymatic monitoring

	D2	D3	D4	D5	D6	D7	D8	D9	D10
CK (IU/L)	1990	1499	1130	1365	1370	1450	898	331	220
CKMB (µg/L)	132.6	120	77.6	180	182	193	121	24	29
HS Tropopin T (ng/L)	2293	1829		2817		3113		1856	1208

Intravenous corticosteroids
(methylprednisolone 1 mg/kg/12 H)

CK, creatine kinase; CKMB, creatine kinase myocardial band; EMB, endomyocardial biopsy; HS, high-sensitive.

Patient case no.1: Mister H, 77 years old

EMB:

- Patchy T-cell and macrophages infiltrates within the myocardium
- CD3, CD8
- CD68, CD163
- >14 leucocytes

CK, creatine kinase; CKMB, creatine kinase myocardial band; NTproBNP, N-terminal pro-brain natriuretic peptide.

Patient case no.1: Mister H, 77 years old

Failure of weaning from mechanical ventilation

D10: confirmation of a complete bilateral diaphramatic paralysis

- Tracheotomy
- Permanent invasive ventilation

D14: complete heart block

- Temporary percutaneous pacemaker
- Infliximab 5 mg/kg

Evolution towards refractory respiratory failure, therapeutic de-escalation

CK, creatine kinase; CKMB, creatine kinase myocardial band; NTproBNP, N-terminal pro-brain natriuretic peptide.

Case 1: immune checkpoints inhibitors associated myocarditis

Background

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

Douglas B. Johnson, M.D., Justin M. Balko, Pharm.D., Ph.D., Margaret L. Compton, M.D., Spyridon Chalkias, M.D., Joshua Gorham, B.A., Yaomin Xu, Ph.D., Mellissa Hicks, Ph.D., Igor Puzanov, M.D., Matthew R. Alexander, M.D., Ph.D., Tyler L. Bloomer, M.D., Jason R. Becker, M.D., David A. Slosky, M.D., Elizabeth J. Phillips, M.D., Mark A. Pilkinton, M.D., Ph.D., Laura Craig-Owens, M.D., Nina Kola, M.D., Gregory Plautz, M.D., Daniel S. Reshef, M.D., M.P.H., Ph.D., Jonathan S. Deutsch, M.D., Raquel P. Deering, Ph.D., Benjamin A. Olenchock, M.D., Ph.D., Andrew H. Lichtman, M.D., Dan M. Roden, M.D., Christine E. Seidman, M.D., Igor J. Koralnik, M.D., Jonathan G. Seidman, Ph.D., Robert D. Hoffman, M.D., Ph.D., Janis M. Taube, M.D., Luis A. Diaz, Jr., M.D., Robert A. Anders, M.D., Jeffrey A. Sosman, M.D., and Javid J. Moslehi, M.D.

N ENGL J MED 375;18 NEJM.ORG NOVEMBER 3, 2016

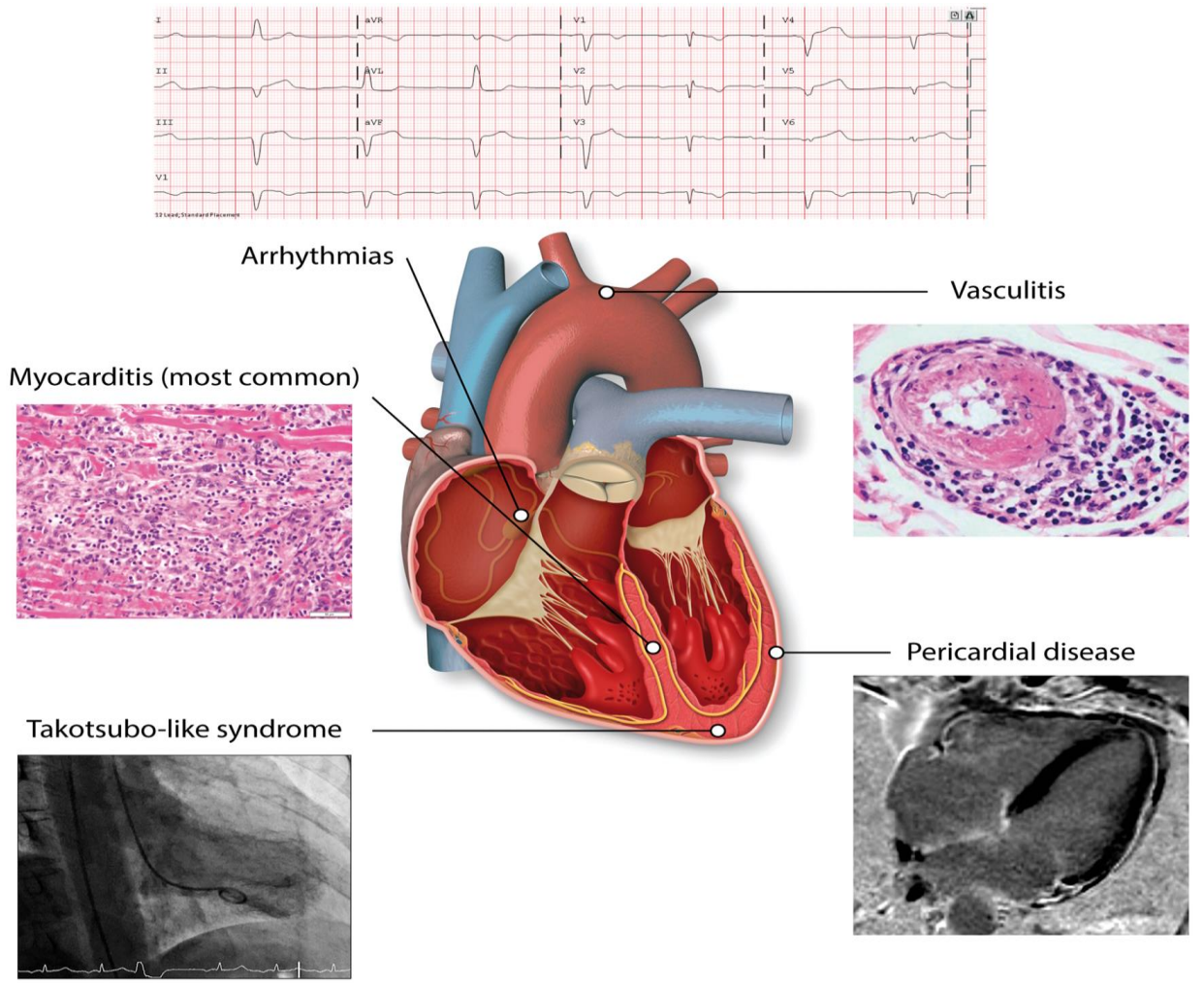
Epidemiology

- Cardiac AEs have been reported in 0.27-1.14% of patients on immune checkpoint inhibitors[1,2]
- Prevalence of myocarditis after immune checkpoint inhibitors has steadily increased over the years, which suggests that the burden of this complication is growing[3]
    - Increased immune checkpoint inhibitors prescription/indications
    - Greater awareness

AE, adverse event.

1. Johnson D, et al. *N Engl J Med* 2016;375:1749–55; 2. Mahmood SS, et al. *JACC* 2018;71:1755-64; 3. Salem JE, et al. *Lancel Oncol* 2018;19:1579–89.

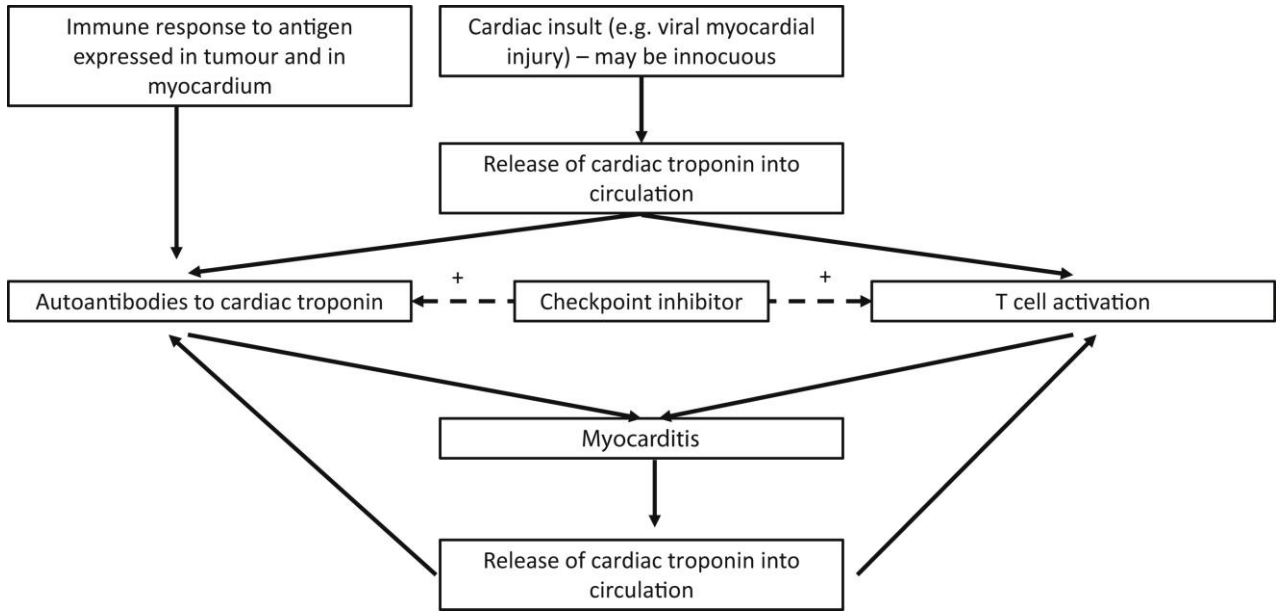
Cardiovascular toxicities associated with immune checkpoint inhibitors



Hu J, et al. *Cardiovasc Res* 2019;115:854–68.

Mechanism of immune checkpoint inhibitor cardiotoxicity

- Mechanism of immune checkpoint inhibitor-induced myocarditis is still unclear
- However, it has been hypothesised that myocarditis could be triggered by the release of cardiac antigens (i.e. troponin) into the circulation[1]
  - Antigen release may be the consequence of any deleterious process i.e. viral myocardial injury
  - While the interaction of PD-L1 and PD-1 prevents autoimmunity, the presence of an immune checkpoint inhibitor enables an autoimmune response against cardiac proteins, such as troponin
  - The autoimmune response leads to myocarditis



1. Mir H, et al. *Can J Cardiol* 2018;34:1059–68.

NCCN: principles of routine monitoring

- Baseline assessment[1]
  - Individualised assessment in cardiology consultation as indicated
    - *Note that the Toxic Management Working Group of the Society for Immunotherapy of Cancer recommends troponin assessement at baseline and a basal ECG, as prerequisite for analysing any change during therapy*[2]
  - Patients information on the warning signs and symptoms of irAEs: fatigue, chest pain, dyspnoea, palpitation, syncopa, peripheral oedema, hypotension
- Monitoring frequency[1]
  - Consider periodic testing for those with abnormal baseline or symptoms
  - Closer monitoring for patients with combination immunotherapy regimens
- Evaluation for abnormal findings/symptoms[1]
  - Individualised follow-up in consultation with cardiology as indicated

irAEs : immune-related adverse events

1. NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. Version 2.2019 — April 8, 2019; 2. Puzanov I, et al. *J Immunother Cancer* 2017;5:95.

Principles of routine monitoring: troponin

- Specific components of the contractile apparatus of cardiomyocytes
- Released in the bloodstream when cardiomyocytes are damages
  - Leading etiology: acute coronary syndrome
  - Confounding situations: skeletal muscle disorder, chronic kidney disease
- ASCO suggests consideration of baseline troponin determination, especially in patients who are receiving combination immune therapy, very helpful in case of subsequent unclear symptoms or equivocal diagnostic examinations[1]
- No indication is provided about serial troponin measurements because of the lack of supporting evidence,[1,2] and the sensitivity of such a screening is even lower in case of ICI monotherapy

1. Brahmer J, et al. *J Clin Oncol* 2018;36:1714–1768. 2. Puzanov I, et al. J Immunother Cancer 2017;5:95.

Development of myocarditis in patients treated with immune checkpoint inhibitors: risk factors & prognosis

- **Risk factor - combination immune checkpoint inhibition**
  - A study that interrogated a pharmacovigilance database of 20,594 patients reported that myocarditis is more frequent (4.74-fold risk) and severe with the combination of ipilimumab and nivolumab compared with nivolumab monotherapy, however, remains rare (<1%) with both regimens[1]

- **Poor prognosis**
  - A retrospective observational pharmacovigilance study conducted to identify and characterise cardiovascular irAEs that are significantly associated with ICIs has reported that of the 122 myocarditis cases, 50% resulted in death[2]

irAEs, immune-related adverse events.

1. Johnson D, et al. *N Engl J Med* 2016;375:1749–55; 2. Salem J, et al. Lancet Oncol 2018;19:1579–89.

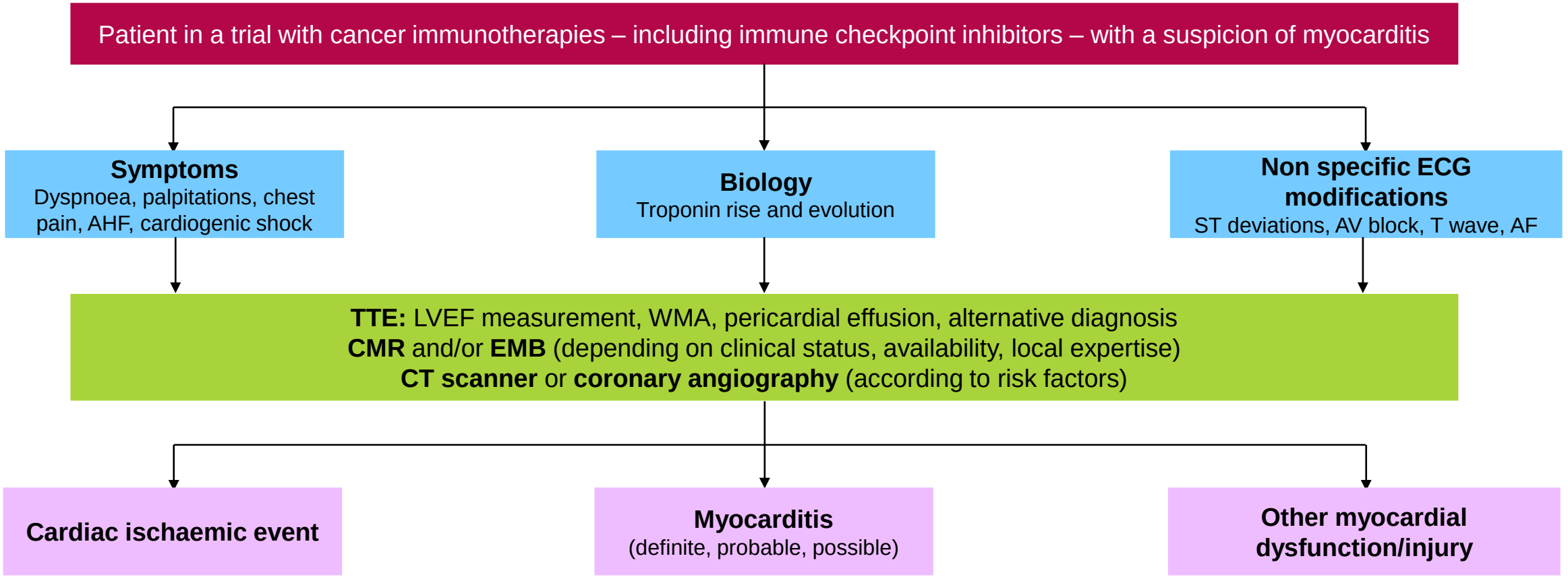
Clinical presentation of myocarditis & challenges in diagnosis

- **Early onset**
  - Severe myocarditis can occur as early as after the first ICI dose with a median time of 30 days (inter-quartile range : 18-60) after initial exposure to ICIs[1]
- In immune checkpoint inhibitor-associated myocarditis troponin T is elevated[2]
  - A retrospective and prospective multicentre registry study has reported that there was a 4-fold increased risk of MACE with troponin T of ≥1.5 ng/ml (hazard ratio: 4.0; 95% confidence interval: 1.5 to 10.9; p = 0.003)
- Key challenge: ~50% patients have no evidence of reduced ejection fraction, thus LVEF should not be relied on as an indicator of severity in immune checkpoint inhibitor-associated myocarditis[2]
- No age predisposition, male predominance
- Increased rate of co-occurring myasthenia gravis (10%) and myositis (25%)

LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events.

1. Salem J, et al. Lancet Oncol 2018;19:1579–89. 2. Mahmood S, et al. J Am Coll Cardiol. 2018;71:1755–64.

A proposed approach to **diagnosis** of myocarditis in the setting of immune checkpoint inhibitor use



Adapted from Bonaca et al. AF, atrial fibrillation; AHF, acute heart failure; AV, atrioventricular; CMR, cardiac magnetic resonance imaging; CT, computed tomography; EMB, endomyocardialbiopsy; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiography; WMA, wall motion abnormality.

Bonaca M, et al. *Circulation* 2019;140:80–91.

Myocarditis in the setting of cancer therapeutics: proposed definition

Pathology	Imaging	ECG	Syndrome	Biomarkers

For all other diagnosis/explanations (e.g. ACS) must be excluded

Definite Myocarditis:
- Pathology
  OR
- Diagnostic CMR + syndrome + (biomarker or ECG)
  OR
- ECHO WMA + syndrome + biomarker + ECG + negative angiography

Probable Myocarditis:
- Diagnostic CMR (no syndrome, ECG, biomarker)
  OR
- Suggestive CMR with either syndrome, ECG, or biomarker
  OR
- ECHO WMA and syndrome (with either biomarker or ECG)
  OR
- Syndrome with PET scan evidence and no alternative diagnosis

Possible Myocarditis:
- Suggestive CMR with no syndrome, ECG or biomarker
  OR
- ECHO WMA with syndrome or ECG only
  OR
- Elevated biomarker with syndrome or ECG and no alternative diagnosis

- The **clinical syndrome** associated with myocarditis is broad and can encompass a spectrum of symptoms including palpitations, chest pain, acute or chronic heart failure, as well as findings including pericarditis and pericardial effusion
- In addition, myocarditis may present in an indolent fashion with mild degrees of ventricular dysfunction

Adapted from Bonaca M, et al. ACS, acute coronary syndrome; CMR, cardiac magnetic resonance imaging; ECG, electrocardiographic; ECHO, echocardiography; PET, positron emission tomography; WMA, wall motion abnormality.

Bonaca M, et al. *Circulation* 2019;140:80–91.

NCCN: management of immune-related toxicities —cardiovascular

Management

General cardiac irAEs

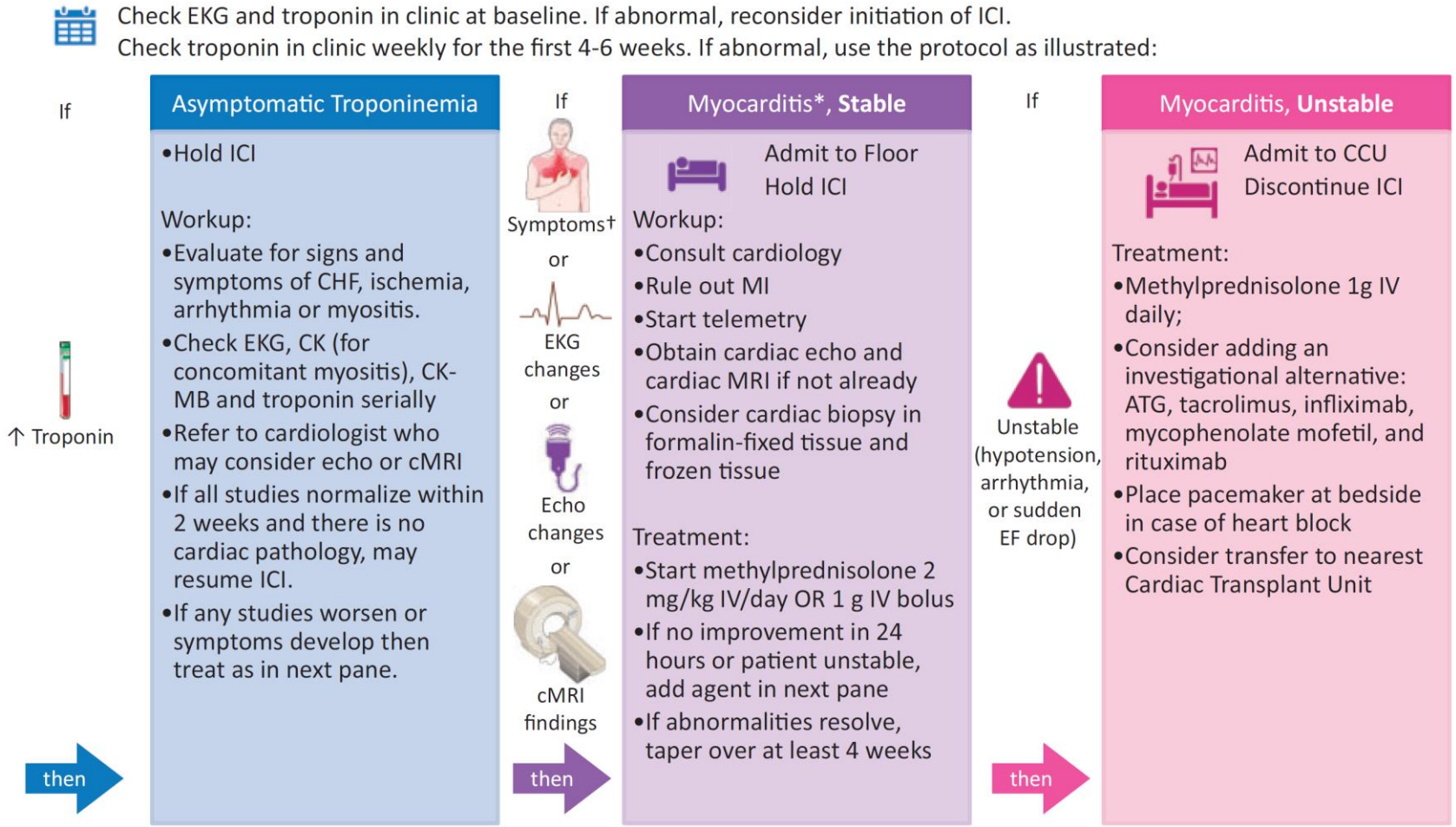
- Immediate cardiology consultation and inpatient care
- Assessment (telemetry monitoring, ECG, and cardiac MRI)
- Laboratory tests (cardiac biomarkers [creatine kinase and troponin] and inflammatory biomarkers [ESR, CRP, WBC count])
- Seek to rule out other potential causes via viral titers, echocardiogram, or biopsy in the case of severe symptoms

Severe (G3)* or life-threatening (G4)† cardiac irAEs

- Permanently discontinue immunotherapy
- Methylprednisolone pulse dosing (1 g/day for 3–5 days) until cardiac function returns to baseline, then dose taper over 4 to 6 weeks
- For G4, if no improvement is noted within 24 hours, consider adding infliximab or anti-thymocyte globulin

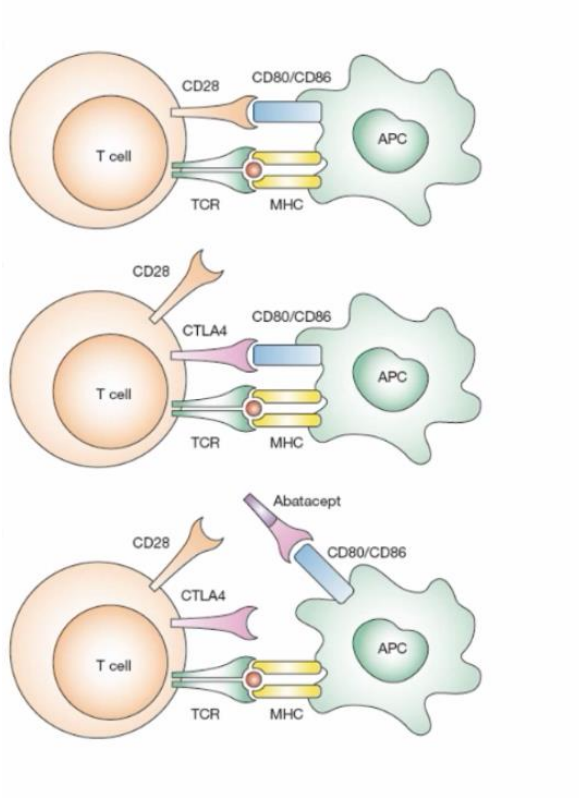
*arrhythmia may be accompanied by significant echocardiogram findings without hypotension, and cardiac biomarkers above the ULN; †arrhythmia, hemodynamic instability, and cardiac biomarkers more than 3 times the ULN.
ULN, upper limit of normal.

ESC: management of immune checkpoint inhibitor-associated myocarditis



Hu J, et al. *Cardiovasc Res* 2019;115:854–68.

CTLA-4 inhibitor: antidote for life-threatening refractory immune checkpoint inhibitor-associated myocarditis



NEJM case report, published in June 2019:

- 66-year-old woman with metastatic lung cancer
- Chest pain, troponin T increase, diagnostic cMRI and non-sustained VT after receiving 3 doses of nivolumab
- Failure of high-dose intravenous methylprednisolone and plasmapheresis
- Resolution after 500 mg abatacept every two weeks, for a total of 5 doses
- No tumor progression at the cross-sectional images obtained 1 month after the first abatacept dose

Salem J, et al. *NEJM* 2019;380:24.

Case study 2

Patient case no.2: Miss C. 51 years old

- Patient history:
  - Triple negative breast cancer in 2007
  - Adjuvant chemotherapy FEC 100 x 6 (epirubicine 600 mg/m² cumulative dose) + left chest wall irradiation
  - Metastatic NSCLC in 2018, anti PD1 therapy
  - Normal baseline ECG
  - Normal LVEF (cardiological assessment not carried out in a cardio-oncology service)
  - No baseline cardiac biomarkers

ECG, echocardiography; FEC 100, epirubicin 100 mg/m^2, 5-fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2; NSCLC, non-small cell lung cancer; PD1, programmed cell death 1.

Patient case no.2: Miss C. 51 years old

C11: « Incidental » dosing of myocardial necrosis enzymes

CK 164 IU/L (normal level <168 IU/L)

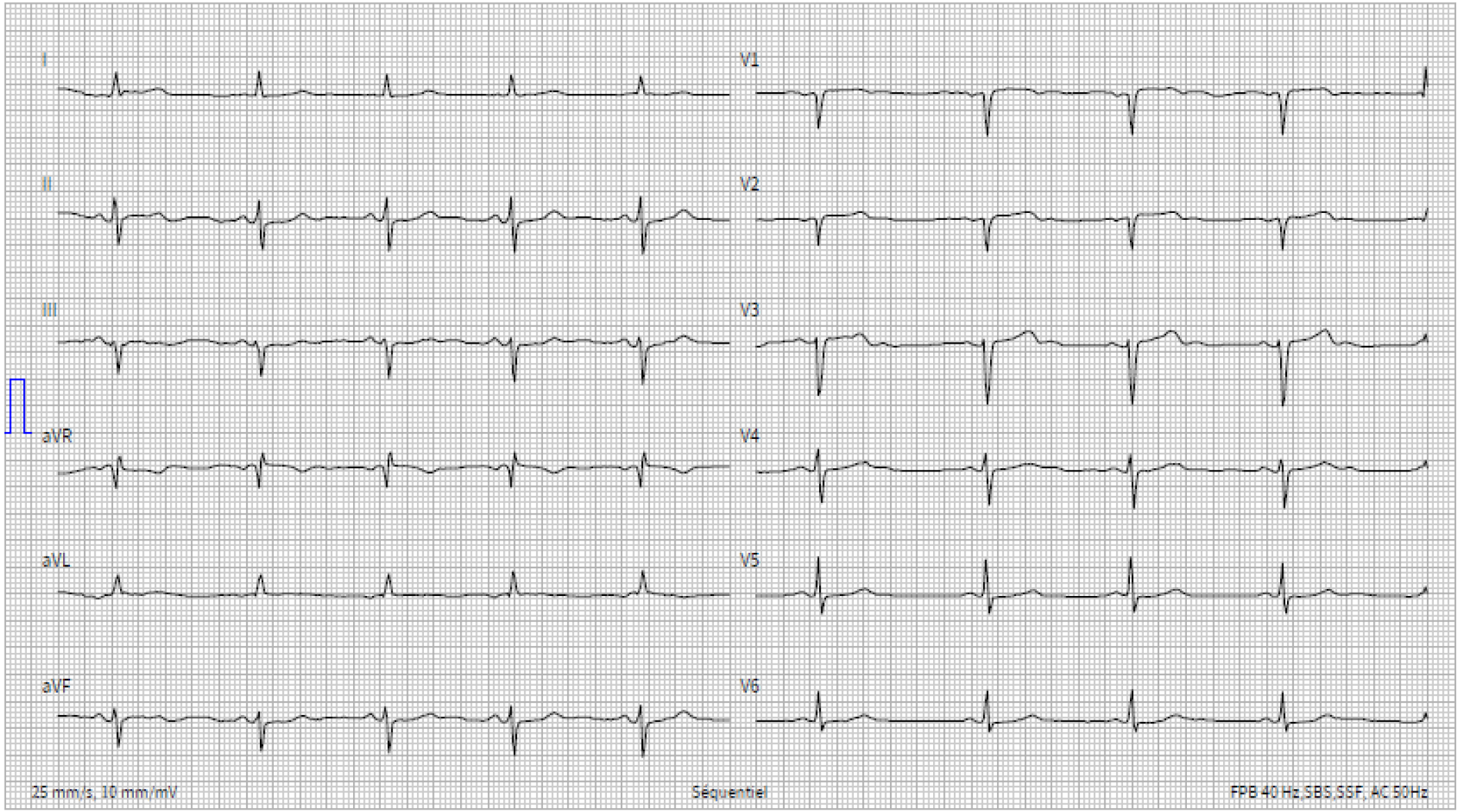
CKMB 3 µg/L (normal level <3.1 µg)

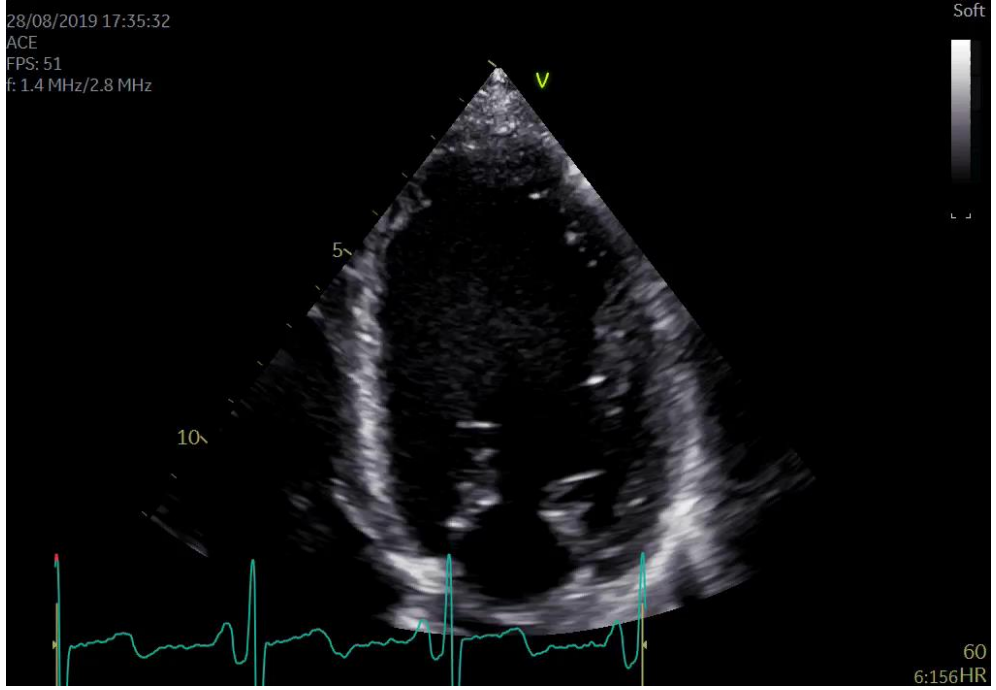
High sensitive troponin I 162 ng/L (normal level <15.6 ng/L)

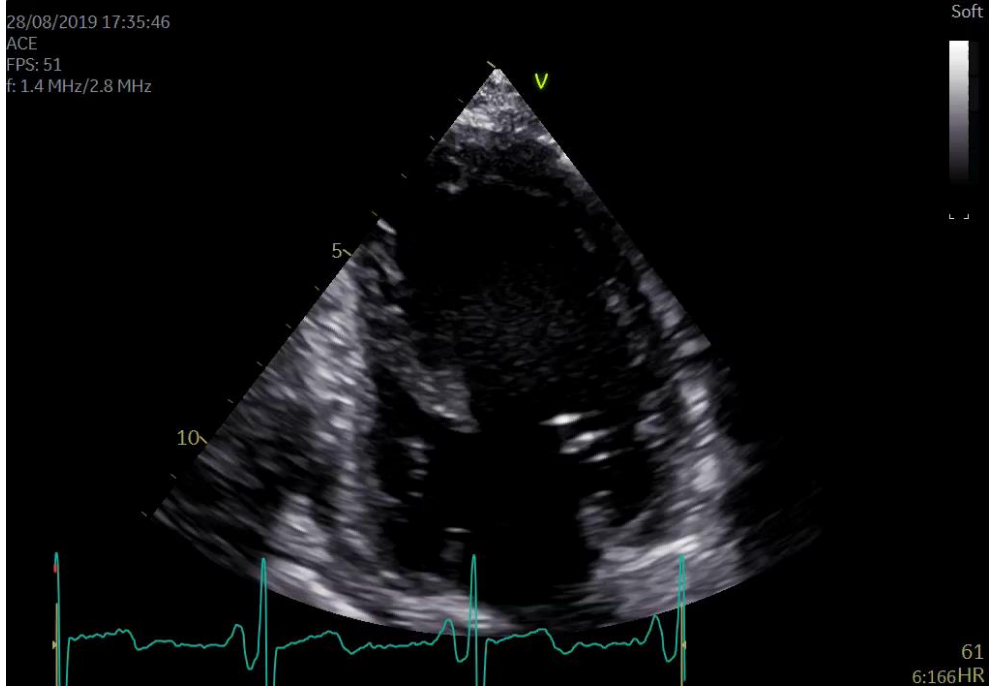
NTproBNP 342 ng/L

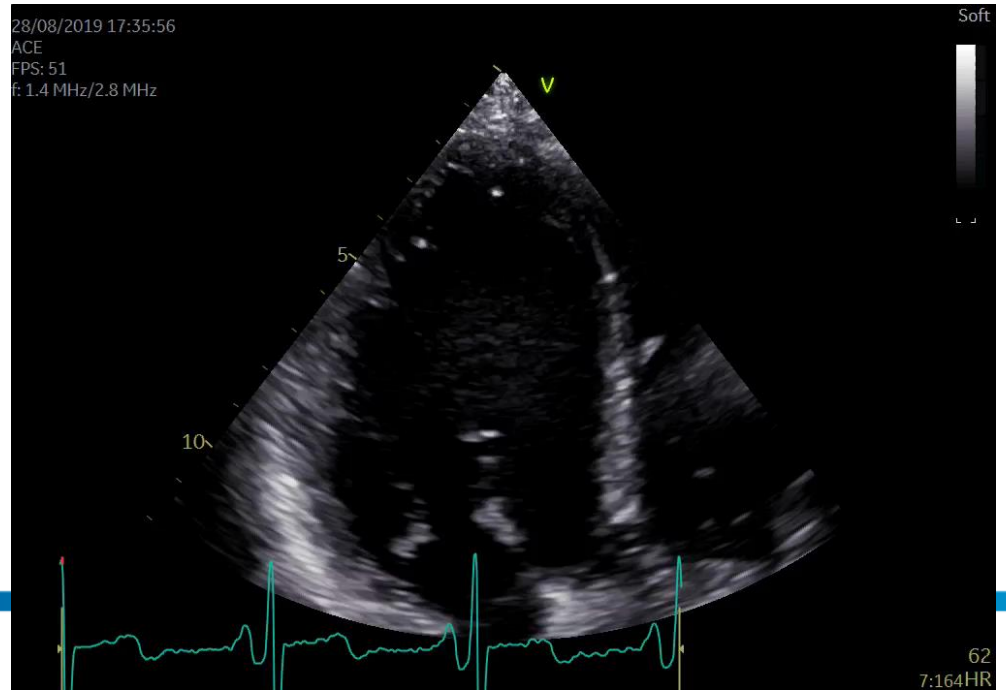
ER emergency room; HS, PD-L1, programmed cell death ligand-1; TTE, transthoracic echocardiogram.

FC	**56 bpm**	RR	1061 ms
		P	108 ms
		PR	148 ms
Axe P	71 °	QRS	80 ms
Axe QRS	-31 °	QT	442 ms
Axe T	64 °	QTcB	429 ms

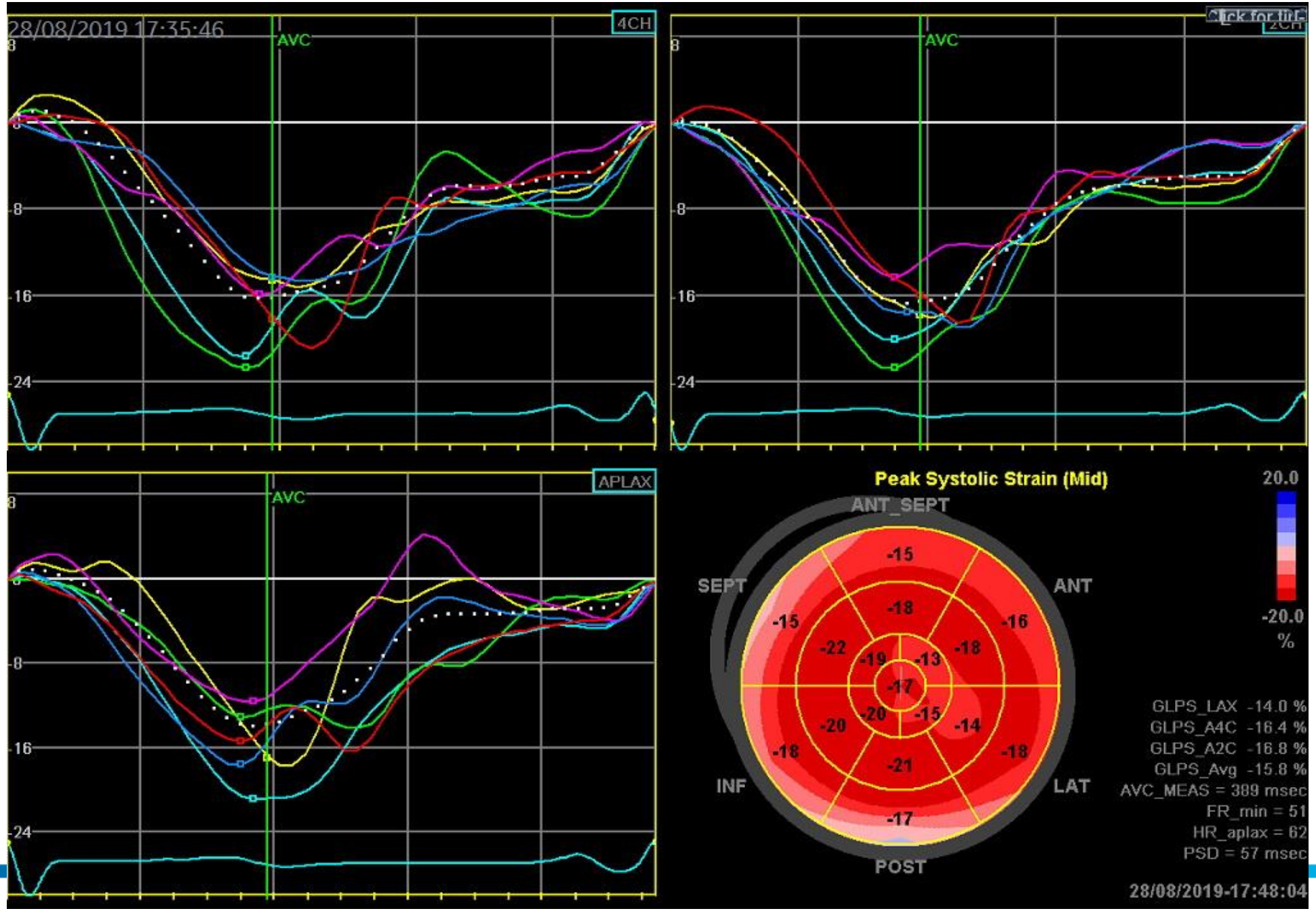








3DE LVEF = 53%
LVEDV = 155 ml
LVESV = 72 ml
SV = 83 ml
CO = 5.2 L/min


28/08/2019 17:35:46
4CH
AVC
2CH
AVC
APLAX
AVC
Peak Systolic Strain (Mid)
ANT_SEPT
SEPT
ANT
INF
LAT
POST
-15
-18
-16
-15
-22
-18
-19
-13
-17
-20
-15
-14
-20
-18
-18
-21
-17
20.0
-20.0
%
GLPS_LAX -14.0 %
GLPS_A4C -16.4 %
GLPS_A2C -16.8 %
GLPS_Avg -15.8 %
AVC_MEAS = 389 msec
FR_min = 51
HR_aplax = 62
PSD = 57 msec
28/08/2019-17:48:04

cMRI


fl3d_51seg_ir_SAX
Img10:17:03
SE42
ARS
I
R
P
S
L
A
PLI
TR848
TE1.65 EC1
14.45 HFS
4mm mm
GR\IR
SK\SP\MP\OSP
with contrast
salleIRM2 ST 1.5T
Lat 250
fl3d_51seg_ir_4ch
Img10:15:37
SE40
SPR
R
I
P
L
S
A
IAL
TR829.6
TE1.63 EC1
-15.84 HFS
5mm mm
GR\IR
SK\SP\MP\OSP
with contrast
salleIRM2 ST 1.5T
Lat 240
SL
A
L
I
P
R
S
IR
TR845.6
TE1.63 EC1
-1.614 HFS
5mm mm
fl3d_51seg_ir_2ch
Img10:16:25
SE41
GR\IR
SK\SP\MP\OSP
with contrast
salleIRM2 ST 1.5T
Lat 240

Can checkpoint inhibitor based therapy be considered in patients with history of significant cardiovascular disease?

1. Yes
2. No

Are biomarkers useful in the follow-up of patients at high risk for treatment related cardiotoxicity?

1. Yes
2. No

Is cardiac MRI standard of care in patients with high risk/suspicion for treatment related cardiotoxicity?

1. Yes
2. No

Patient case no.2: Miss C. 51 years old

Cardio-oncological proposed strategy:

- Clinical follow-up
- Serial cardiac biomarkers, ECG and TTE
- Cardioprotective treatment (enalapril 5 mg, bisoprolol 5 mg)
- Eviction from sports
- Without ICI interruption

Arguments: patient is asymptomatic and stable, « late onset », repeated cardiac evaluation after 2 weeks showed stable situation

Patient’s agreement of the proposed strategy

ER emergency room; HS, PD-L1, programmed cell death ligand-1; TTE, transthoracic echocardiogram.

Patient case no.2: Miss C. 51 years old

- Undoubtedly serum cardiac troponin I increase as an indicator of ongoing myocyte damage, but of unknown aetiology in this case. Prognosis value?
- Currently:
  - Patient remain strictly asymptomatic
  - TTE remains stable until now (6 months follow-up)

ER emergency room; HS, PD-L1, programmed cell death ligand-1; TTE, transthoracic echocardiogram.

Cardiac enzymatic monitoring

	04/06/2019	05/06/2019	11/06/2019	17/06/2019	01/07/2019	05/08/2019	13/08/2019	27/08/2019	03/09/2019	04/09/2019	18/09/2019	24/09/2019	29/10/2019
CK (IU/L)	164	125	109	143	68	171	73	132	103	65	216	217	140
CKMB (µg/L)	3	2.4	2	3.2	0.7	1.1		1	0.9	0.6	1.6	1.2	1.2
HS troponin I (ng/L)	162	173.1	112.3	80.3	63.2	49	49.4	44.4	56.1	46.5	50.8	53	37
NTpro BNP (ng/L)	342		266	379		480							472

Case 2: non-inflammatory cardiovascular toxicity?

Background

Patient case no.2: Miss C. 51 years old

Case reports :

- Takotsubo-like syndrome[1-4]
- Asymptomatic non-inflammatory left ventricular dysfunction[5]
- Myocardial infarction[6]
- Coronary vasospasm[7]
- ICPi-related myocarditis with isolated abnormal troponin[8]
  - Not consistent with myocarditis definition, which require 2 or more criteria (significant change in troponin, ECG or imaging) for the clinical diagnosis if the patient is asymptomatic

1. Geisler BP, et al. J Immunother Cancer 1015;3:4. 2. Anderson RD, et al. Int J Cardiol 2016;222:760-61. 3. Heinzerling L, et al. J Immunother Cancer 2016;4:50. 4. Ederhy S, et al. JACC Cardiovasc Imaging 2018;11:1187-1190. 5. Roth ME, et al. Am J Ther 2016;23:e1925-e1928. 6. Weinstock C, et al. Clin Cancer Res 2017;23:4534-4539. 7. Nykl R, et al. Arch Med Sci Atheroscler Dis 2017;2:100-102. 8. Norwood TG, et al. J Immunother Cancer 2017;5:91.

Case study 3

Patient case no.3: Miss J, 70 years old

- Patient history:
  - Breast cancer 15 years ago (6 cycles FEC 100 = epirubicin 600 mg/m²)
  - Metastatic Merkel cell carcinoma — candidate for anti-PDL1
  - Severe cardiac past medical history
    - Non-ischaemic dilated cardiomyopathy diagnosed in 07/2017 and attributed to previous anthracyclines and radiation therapy
    - LVEF: 30%
    - LBBB

FEC 100, epirubicin 100 mg/m^2, 5-fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction.

Can immunotherapy be started?

1. Yes
2. No

Patient case no.3: Miss J, 70 years old

Dec 2018 — Avelumab (anti-PD-L1) initiated

Feb 2019 — Admission to the ER for acute heart failure

➔ the patient is quickly addressed to our cardio-oncology service

Initial cardiac work-up

- Negative high sensitive troponin (initially and during all follow-up)
- TTE
- Hospitalisation for cardiac monitoring

Favourable clinical evolution with supportive therapy

TTE after recompensation: strickly identical to baseline

ER emergency room; HS, PD-L1, programmed cell death ligand-1; TTE, transthoracic echocardiogram.

How often should specialised cardio-onco follow-up be done?

1. Every month
2. Every 2 months
3. Every 4 months
4. Every 6 months

Patient case no.3: Miss J, 70 years old

No cardiac adverse event with 11 months follow-up without durvalumab interruption and under close cardio-oncological follow-up and cardiac pharmacological treatment titration

Excellent oncological response

ER emergency room; HS, PD-L1, programmed cell death ligand-1; TTE, transthoracic echocardiogram.

Key take-home messages

- Immune checkpoints inhibitors associated myocarditis is **rare** but **severe** (poor prognosis)[1]
  - Prescribers of ICIs should be aware of the recently identified risk factors and pattern of clinical presentation of ICIs associated myocarditis, in order not to delay diagnosis and management
  - ECG and troponin monitoring at baseline and weekly for the first 4–6 weeks may/should be recommended after ICIs initiation, particularly in case of combination[2,3]
- Cancers and cardiovascular diseases share the same risk factors
  - Cancer and cardiovascular disease frequently coexist in a same patient[4–6]
  - Thorough baseline cardiac evaluation before initiation of ICIs is of extreme importance for good decision making during treatment monitoring and so that ICIs are not wrongly interrupted[2,3]
- The level of alarm must be high in the suspicion of myocarditis, and direct referral to an emergency department is appropriate

ECG, echocardiography; ICI, immune-checkpoint inhibitors.

1. Johnson D, et al. *N Engl J Med* 2016;375:1749–55; 2. NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. Version 2.2019 — April 8, 2019; 3. Hu J, et al. *Cardiovasc Res* 2019;115:854–68; 4. Khorana AA, et al. *Cancer.* 2013;119:648–55; 5. Lip GY, et al. *Lancet Oncol* 2002;3:27–34; 6. De Cicco M, et al. *Crit Rev Oncol Hematol*. 2004;50:187–96.

Disclaimer

While Bristol-Myers Squibb uses reasonable efforts to include accurate and up-to-date information in this material, Bristol-Myers Squibb makes no warranties or representations as to its accuracy. Bristol-Myers Squibb assumes no liability or responsibility for any errors or omissions in the content of the material. Neither Bristol-Myers Squibb nor any other party involved in creating, producing or delivering the material is liable for any direct, incidental, consequential, indirect or punitive damages arising out of your access to, or use of, the material.

You should assume that everything you see or read on this presentation is copyrighted, unless otherwise noted, and may not be used without mentioning the source. Bristol-Myers Squibb neither warrants nor represents that your use of materials displayed on the Site will not infringe rights of third parties not owned by or affiliated with Bristol-Myers Squibb.

Nothing on these presentations should be construed as the giving of advice or the making of a recommendation and it should not be relied on as the basis for any decision or action. BMS, nor other parties involved, accepts no liability for the accuracy or completeness or use of, nor any liability to update, the information contained on this Presentation. These materials are provided "AS IS" WITHOUT WARRANTY OF ANY KIND, EITHER EXPRESSED OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT.