Cardiotoxicity surveillance with myocardial work among cancer patients treated with immunotherapy

Supplementary Appendix

Table S1. Adherence to biomarker collection

Adherence to biomarker collection						
Month	0	1	2	5	8	11
0	80%	43%	67%	79%	60%	9%
**Note: Considering months 1 and 2, there was the addition of 1 participant (who did not collect), the adherence was 69,23%						

Table S2. Baseline echocardiographic characteristics

	CT	N-CT	p-value		CT	N-CT	p-value
Indexed AE (ml/m²)	23 (17-38)	25 (11-59)	0.469	**SLG (%)**	18.9 (13-24)	19 (13-23)	0.706
DDVE (mm)	44 (41-55)	46 (34-54)	0.987	**GCW (mmHg)**	2458 (1362-3273)	2766 (1729-3696)	0.164
Indexed Mass (g/m²)	78 (63-114)	83 (42-162)	0.376	**GWE (%)**	90 (75-99)	94 (88-99)	0.162
Posterior Wall (mm)	9 (7-11)	9 (7-13)	0.811	**GWI (mmHg)**	2142 (1187-2977)	2417 (1448-3299)	0.174
Septum (mm)	10 (8-12)	10 (8-15)	0.973	**GWW (mmHg)**	178 (25-701)	134 (20-327)	0.446
VD Base (mm)	33 (24-38)	31 (24-39)	0.410	**EF (%)**	62.5 (55-70)	67 (57-76)	0.014
A Wave	0.71 (0.59 – 1.27)	0.84 (0.30 – 1.24)	0.850	**PSAP (mmHg)**	31 (20-41)	23 (13-49)	0.198
E Wave	0.70 (0.47 – 0.88)	0.84 (0.52 – 1.45)	0.274	**DT (ms)**	204 (170-271)	221 (123-291)	0.769
e'	0.09 (0.05-0.11)	0.10 (0.06 - 0.90)	0.150	**S' (cm/s)**	14 (11-19)	12 (10-20)	0.321
E/A	0.82 (0.47-1.46)	1.02 (0.57-4.83)	0.449	**TAPSE (mm)**	22.5 (17-27)	22 (15-29)	0.884
E/e'	8.30 (4.41-11.77)	7.70 (5.04-20.38)	0.933				

Comparing baseline TTE characteristics between groups, CTRCD group had lower LVEF (67 vs. 63 %, p=0.014, respectively), accompanied by no statistically significant lower MW values, as well as a lower E/A, a TTE measure to assess the diastolic function of the heart, particularly of the left ventricle, (0.82 vs. 1.02, p=0.449).

Indexed AE - indexed area of the left atrium, adjusted for body surface area; **DDVE** - left ventricular end diastolic dimension; **Indexed Mass** - left ventricular mass indexed for body surface area ;**VD Base** - basal dimension of the right ventricle; **EF** - ejection fraction; **A Wave** - amplitude of the A wave (left atrial contraction and aids in assessing

diastolic function); **E Wave** - amplitude of the E wave (early diastolic filling of the left ventricle and is crucial for evaluating diastolic function); **e'**- the early diastolic tissue *doppler* velocity at the mitral annulus and provides information about the relaxation of the left ventricle; **DT** - deceleration time is the interval from the peak of the E wave (early diastolic filling wave) to the point where the E wave velocity decreases to zero. It is measured in milliseconds and reflects the rate at which the left ventricle fills with blood during early diastole. **S'** - the systolic tissue d*oppler* velocity and indicates the contraction of the heart muscle during systole and is used in assessing left ventricular systolic function. **E/A Ratio** - ratio of the peak velocities of the E wave to the A wave. It helps evaluate diastolic function and can indicate impaired or preserved relaxation. **TAPSE** - Tricuspid Annular Plane Systolic Excursion. It measures the movement of the tricuspid valve annulus during systole and is a simple marker of right ventricular function. **E/e'** - This ratio is the early diastolic filling pressure, calculated from the E wave and e' measurement. This ratio helps assess left atrial pressure and indicates diastolic dysfunction.

Table S3. Results of Multivariable Logistic Regression Analysis of CTRCD predictors

Predictor	**Sig.**	**OR**	**95% IC**
GWE_delta	0.754	1.058	0.743 – 1.507
GWW_delta	0.328	1.006	0.994 - 1.017
GLS_delta	0.007	0.491	0.293 – 0.822
Constant	0.005	0.127	-
Multivariate analysis - the logistic regression revealed that delta GLS was the strongest predictor of the outcome (OR 0.491; 95% CI, 0.293 – 0,822; P = 0.007). GLS - Global Longitudinal Strain; GWE - Global Work Efficiency; GWW - Global Wasted Work.			

Table S4. Cardiac dimensions and *doppler* findings on the second-month exam

	CT	**N-CT**	**p-value**		**CT**	**N-CT**	**p-value**
Indexed Mass (g/m²)	75 (50-101)	79.62 (42-162.97)	0.303	**LV systolic Volume (ml)**	23.5 (12-68)	18 (8-45)	0.114
DDVE (mm)	44 (35-57)	44 (34-56)	0.722	**LV Diastolic Volume (ml)**	58.5 (41-121)	56 (28-112)	0.629
Indexed Left Atrium (ml/m²)	24.46 (12.84-33.81)	27.09 (19.41-65.46)	0.281	**e'**	0.09 (0.05-0.11)	0.10 (0.05-0.14)	0.130
Posterior Wall (mm)	9 (7-12)	9 (7-14)	0.920	**E/A**	0.80 (0.38-1.35)	0.93 (0.54-1.73)	0.213
Septum (mm)	9 (8-12)	10 (7-15)	0.177	**E/e'**	8.44 (4.43-9.77)	7.62 (0-18.31)	0.875
Right Ventricle Base (mm)	32 (26-40)	29 (22-39)	0.175	**A Wave**	0.71 (0.54-1.20)	0.88 (0.56-1.33)	0.835
DT (ms)	207 (127-281)	238 (148-335)	0.220	**E Wave**	0.55 (0.36-1.05)	0.74 (0.43-1.11)	0.104
TAPSE (mm)	22 (17-28)	22 (18-28)	0.581	**S' (cm/s)**	13 (11-18)	13 (10-18)	0.521
PSAP (mmHg)	27 (16-34)	25 (14-43)	0.863				

Echocardiographic characteristics assessed in the second month. There were no significant changes in cardiac dimensions and Doppler findings.
VE - left ventricle; DDVE - diastolic diameter of the left ventricle; AE: left atrium; VD: right ventricle; DT - deceleration time; TAPSE- tricuspid annular plane systolic excursion; PSAP - pulmonary artery systolic pressure

Table S5. Baseline characteristics – patients with lung cancer

	Overall (n=39)	CTRCD (n=10)	No-CTRCD (n=29)	p-value
Age (Years)	71 (55-86)	70 (56-84)	71 (55-86)	0.584
Weight (kg)	69,43 (40-97)	69,1 (40-97)	69,75 (42-94)	0.416
BMI (kg/m^2)	26,8 (16-34)	26,8 (16-31)	26,1 (17-34)	0.721
Gender, n (%)				1.000
Female	10 (48)	3 (43)	7 (50)	
Male	11 (52)	4 (57)	7 (50)	
Stage, n (%)				0.521
III	3 (14)	0 (0)	3 (21)	
IV	18 (86)	7 (100)	11 (79)	
NYHA, n (%)				0.124
0	10 (47)	3 (43)	7 (50)	
1	7 (33)	1 (14)	6 (43)	
2	4 (19)	3 (43)	1 (7)	
Comorbidities, n (%)				
Smoking	15 (71)	5 (71)	11 (79)	1.000
Diabetes Mellitus	7 (33)	3 (43)	4 (28)	0.638
Hypertension	15 (71)	4 (57)	9 (64)	1.000
Coronary Artery Disease	0 (0)	0 (0)	0 (0)	
Heart Disease	1 (5)	0 (0)	1 (7)	
Medication, n (%)				
ACE Inhibitors/ARBs	18 (46)	5 (50)	13 (45)	1.000
Antiplatelets	3 (8)	1 (10)	2 (7)	1.000
Beta-blockers	9 (23)	0 (0)	9 (31)	0.402
Statins	11 (28)	4 (40)	7 (24)	0.424
Anticoagulants	2 (5)	0 (0)	2 (7)	1.000
Metformin	9 (23)	3 (30)	6 (21)	0.669
Calcium Score Classification, n (%)				0.574
0	4 (19)	2 (28)	2 (14)	
1-3	10 (47)	2 (28)	8 (57)	
4-12	7 (33)	3 (43)	4 (29)	
Radiation Therapy, n (%)				
Thorax	6 (28)	1 (20)	5(21)	0.613
Immunotherapy, n (%)				0.227
Atezolizumab	3 (14)	1 (14)	2 (14)	
Durvalumab	3 (14)	0 (0)	3 (21)	
Pembrolizumab	15 (71)	6 (86)	9 (64)	
Type of Treatment, n (%)				
Chemoimmunotherapy	18 (46)	5 (50)	13 (45)	1.000
Immunotherapy-Immunotherapy	2 (5)	0 (0)	2 (7)	
Anti-angiogenic.	3 (14)	1 (14)	2 (14)	1.000

Baseline characteristics of patients with lung cancer. Groups were similar, except for a higher number of patients with previous use of statins in the CTRCD group.

ACE - angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blockers; BMI – body mass index; CTRCD - cancer therapy-related cardiac dysfunction;; NYHA - New York Heart Association score

Table S6. Baseline echocardiographic characteristics – patients with lung cancer

	CT	N-CT	p-value		CT	N-CT	p-value
Indexed AE (ml/m²)	21 (17-38)	24(15-40)	0.551	**SLG (%)**	18,9 (17-24)	20 (17-23)	0.932
DDVE (mm)	43 (41-55)	44 (34-49)	0.851	**GCW (mmHg)**	2374 (1556-3273)	2706 (1729-3683)	0.452
Indexed Mass (g/m²)	75 (63-114)	83 (42-106)	0.654	**GWE (%)**	91 (75-99)	93 (88-97)	0.605
Posterior Wall (mm)	9 (7-11)	9 (7-11)	0.670	**GWI (mmHg)**	2095 (1356-2977)	2408 (1448-3299)	0.322
Septum (mm)	10 (8-12)	10 (8-14)	0.729	**GWW (mmHg)**	195 (25-701)	151 (67-327)	0.663
VD Base (mm)	32 (24-33)	31 (24-34)	0.938	**EF (%)**	64 (55-70)	67 (62-76)	0.043
A Wave	0,71 (0,59 – 1,27)	0,85 (0,49 – 1,24)	0.399	**PSAP (mmHg)**	32 (20-41)	23 (19-49)	0.642
E Wave	0,70 (0,47 – 0,88)	0,85 (0,52 – 1,18)	0.349	**DT (ms)**	204 (178-271)	220 (123-288)	0.779
e'	0,07 (0,05-0,11)	0,10 (0,08 -0.12)	0.640	**S' (cm/s)**	15 (11-19)	13 (10-20)	0.310
E/A	0,82 (0,47-1,46)	0,82 (0,47-1,49)	0.888	**TAPSE (mm)**	22. (17-27)	22 (17-27)	0.652
E/e'	9,86 (4,41-11,77)	8,12 (5,04-11,92)	0.640				

Baseline TTE characteristics of patients with lung cancer. The CTRCD group had a lower baseline LVEF (64 vs. 67 %, p=0.043), as well as a trend towards reduced MW and Doppler parameters

Indexed AE - indexed area of the left atrium, adjusted for body surface area; **DDVE** - left ventricular end diastolic dimension; **Indexed Mass** - left ventricular mass indexed for body surface area ;**VD Base** - basal dimension of the right ventricle; **EF** - ejection fraction; **A Wave** - amplitude of the A wave (left atrial contraction and aids in assessing diastolic function); **E Wave** - amplitude of the E wave (early diastolic filling of the left ventricle and is crucial for evaluating diastolic function); **e'**- the early diastolic tissue *doppler* velocity at the mitral annulus and provides information about the relaxation of the left ventricle; **DT** - deceleration time is the interval from the peak of the E wave (early diastolic filling wave) to the point where the E wave velocity decreases to zero. It is measured in milliseconds and reflects the rate at which the left ventricle fills with blood during early diastole; **S'** - the systolic tissue d*oppler* velocity and indicates the contraction of the heart muscle during systole and is used in assessing left ventricular systolic function. **E/A Ratio** - ratio of the peak velocities of the E wave to the A wave. It helps evaluate diastolic function and can indicate impaired or preserved relaxation. **TAPSE** - Tricuspid Annular Plane Systolic Excursion. It measures the movement of the tricuspid valve annulus during systole and is a simple marker of right ventricular function. **E/e'** - This ratio is the early diastolic filling pressure, calculated from the E wave and e' measurement. This ratio helps assess left atrial pressure and indicates diastolic dysfunction.

Table S7. Media and DP of parameters. the moment of most marked TTE difference and with the highest incidence of CTRCD was at the second-month evaluation, followed by a reduction in the TTE difference between groups.

	Baseline			2nd month			5th month			8th month			11th month		
	CTRCD (10)	NCTRCD (29)	p-value	CTRCD (10)	NCTRCD (29)	p-value	CTRCD (5)	N-CTRCD (19)	p-value	CTRCD (6)	N-CTRCD (14)	p-value	CTRCD (5)	N-CTRCD (6)	p-value
FE	62,5±4,6	67±4,6	0,012	59,5±9,5	67±5,8	0,012	63,5±5	70±5,4	0,134	54±12	68±6,9	0,112	58,5±6,4	71,5±7,7	0,038
GLS	18,9±3,2	19,3±2,7	0,791	16±3,4	21±2,5	0,001	17±2,6	19,5±2,4	0,211	17,5±3,3	20,5±2,4	0,157	17,5±0.9	19±3	0,277
GWI	2142±616	2417±508	0,164	1833±474	2393±541	0,02	1992±344	2335±446	0,077	1571±599	2253±674	0,135	1820±256	2261±681	0,261
GCW	2458±613	2766±575	0,138	2299±494	2694±559	0,027	2475±566	2685±412	0,744	1881±710	2445±648	0,255	2091±293	2644±710	0,240
GWW	178±203	134±84	0,309	286±268	116±110	0,063	308±363	180±76	0,154	222±182	126±92	0,296	124±131	163±206	0,781
GWE	90,5±7,3	94±2,7	0,149	83±8,5	95±3,7	0,025	86±7,5	92,5±3	0,103	89±5,2	93±4,4	0,199	93±3,7	94,5±6	0,894