The 6th Indonesian
Symposium on Heart Failure and
Cardiometabolic Disease

Current Approaches in Cancer Treatment: Opportunities and the associated CV Risks

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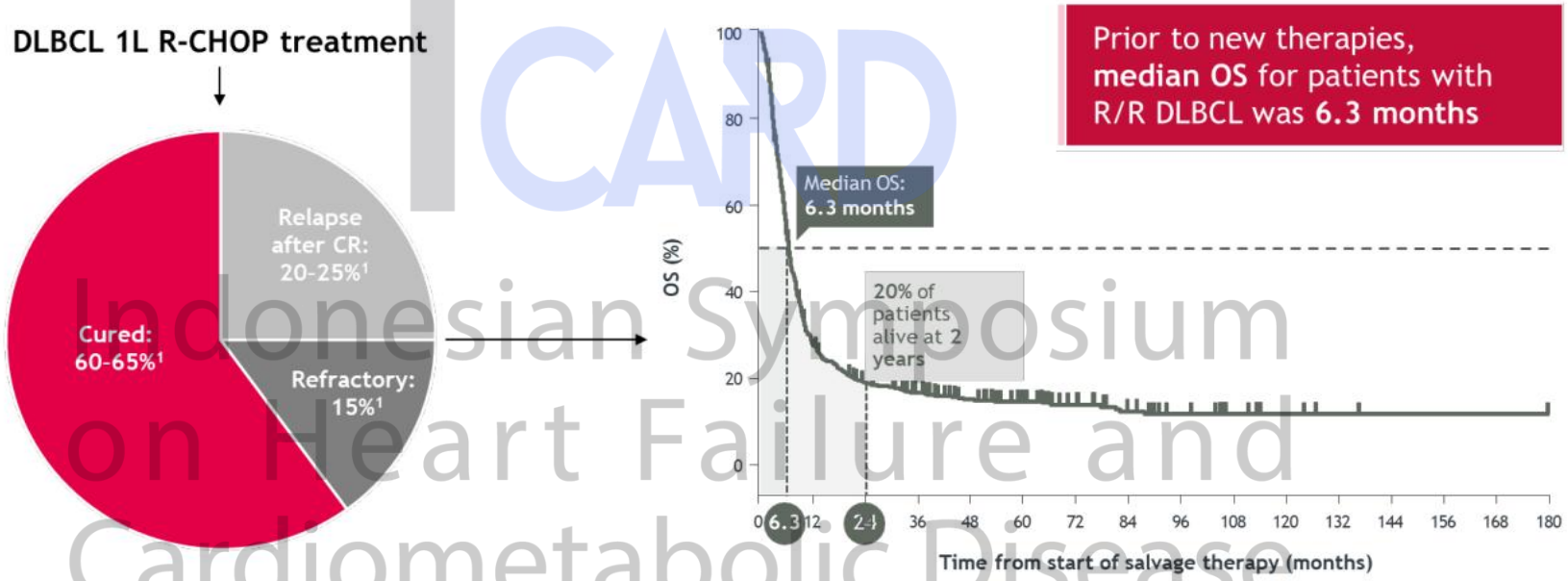
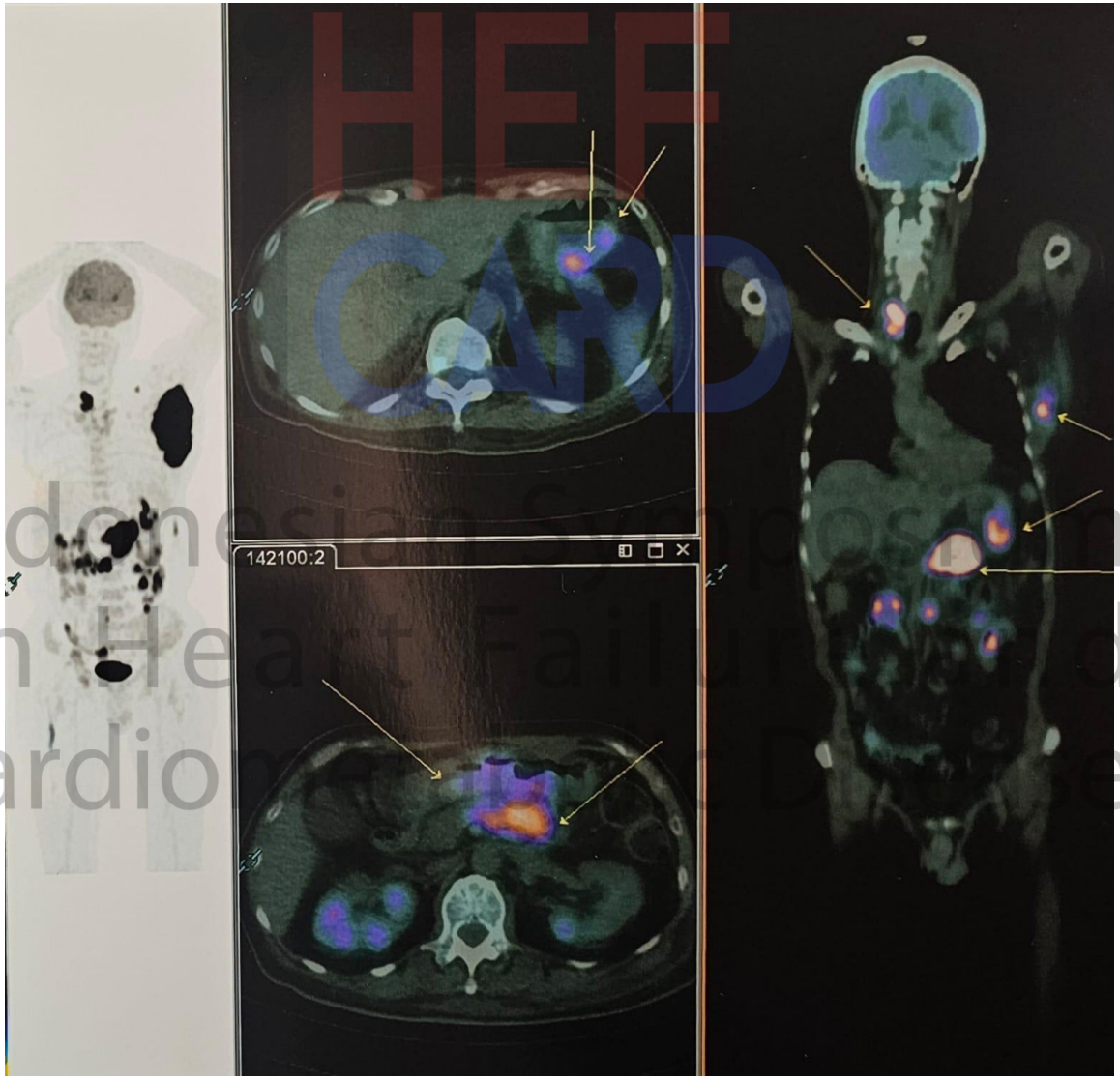
Diffuse Large B Cell Lymphoma (DLBCL) is potentially cured after 1st line chemoimmunotherapy



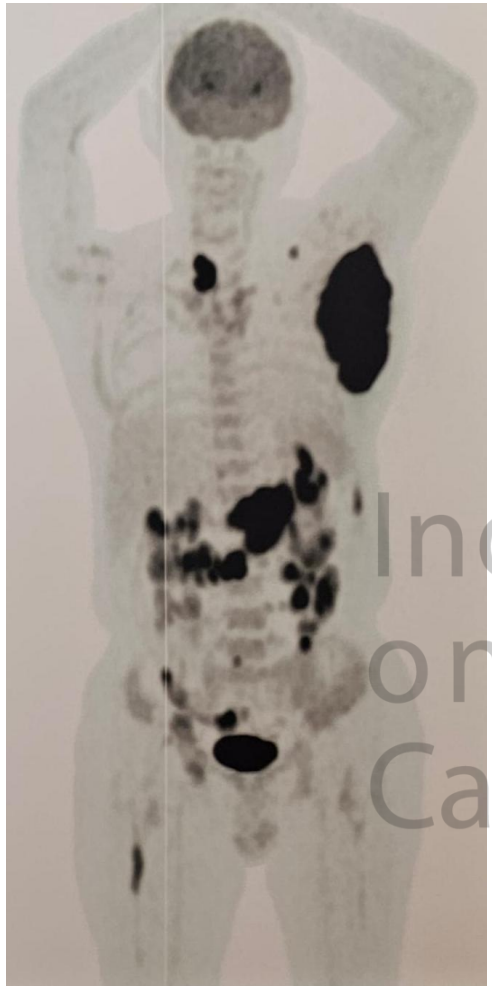
1L, first line; 2L, second line; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone

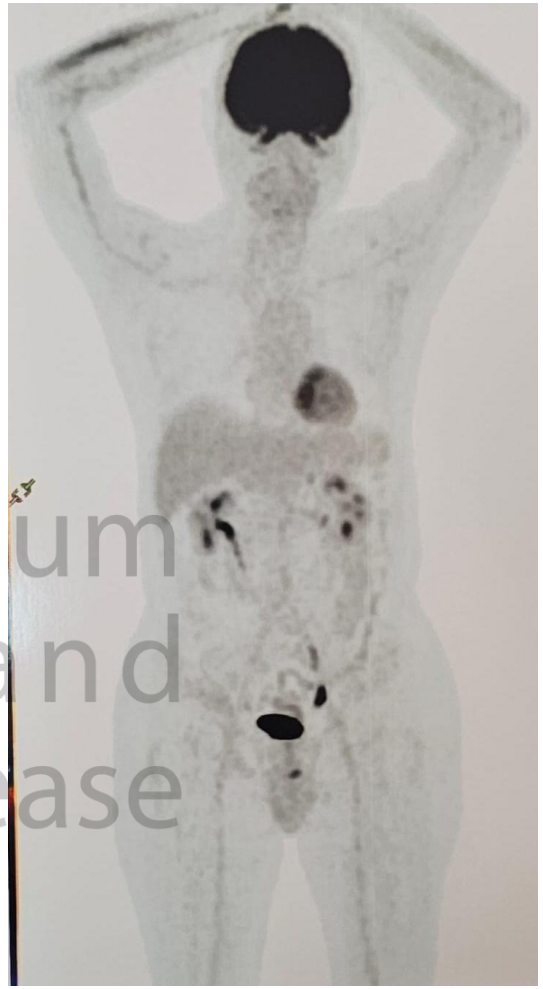
Crump M, et al. Blood 2017;130:1800-1808 Copyright ©2020 by American Society of Hematology

Case 1: A-66-year-old male with DLBCL GCB of Gastric infiltration to pancreas, stage 4, IPI score: 4

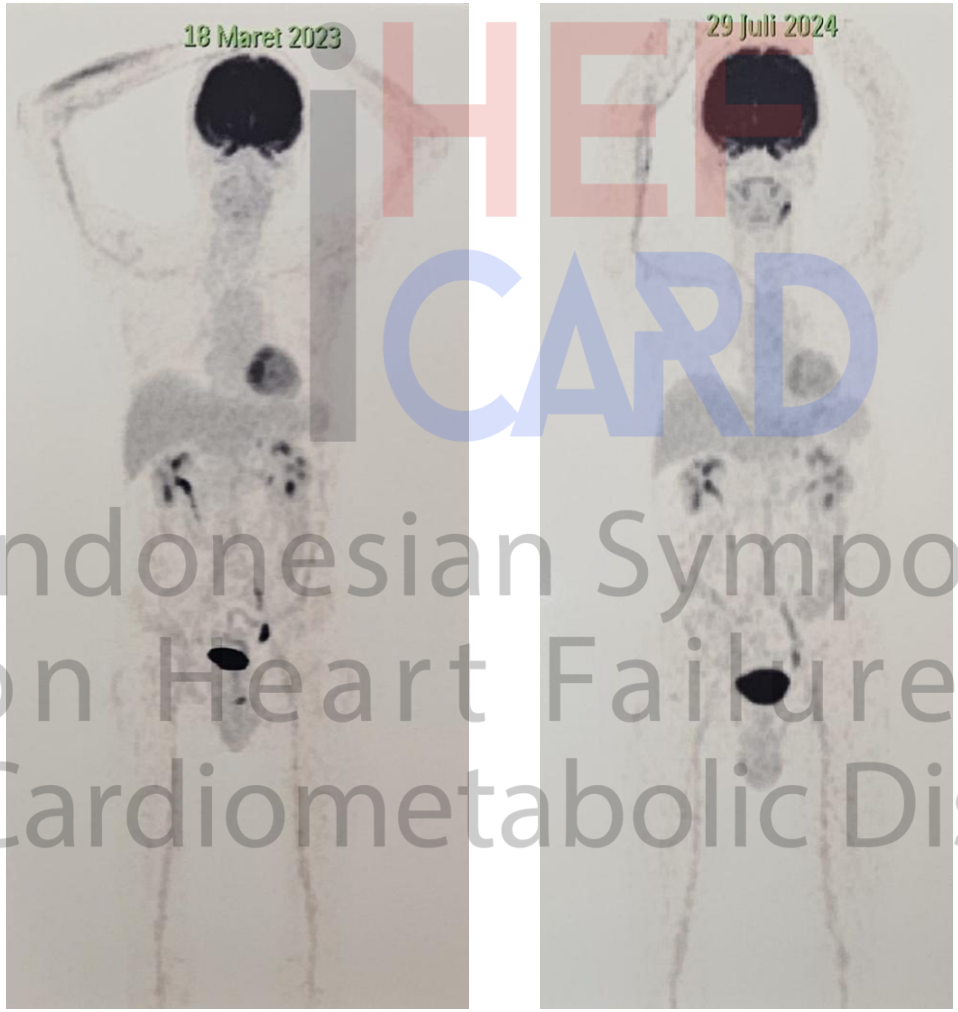


We administered chemoimmunotherapy RCHOP every 3 weeks x 6 cycles + 2R.





Still CR at 2 year



Doxorubicin-induced cardiomyopathy

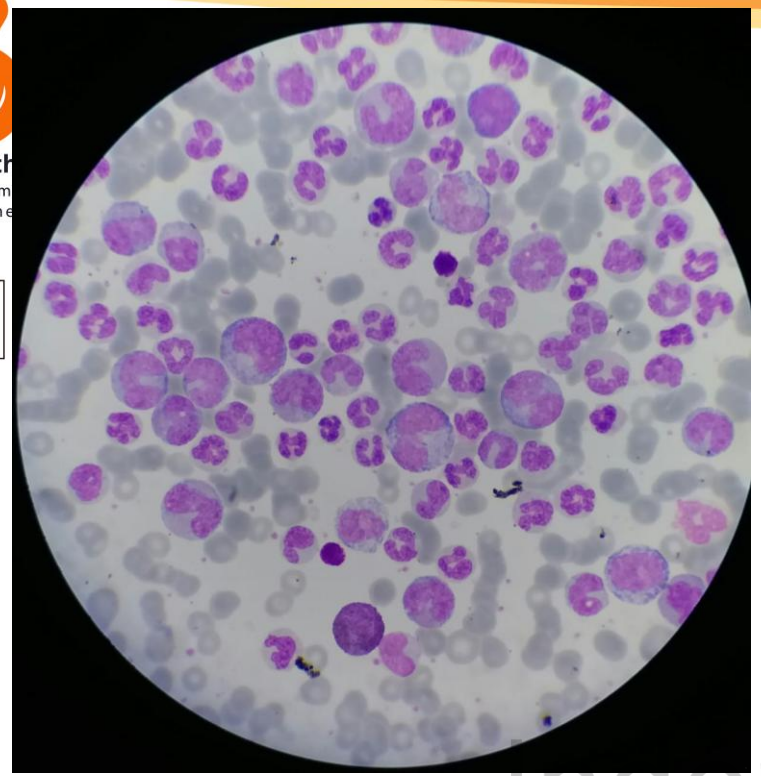
- It is a serious, often irreversible, dose-dependent form of heart failure caused by the chemotherapy agent doxorubicin.
- Characterized by oxidative stress, cardiomyocyte death (apoptosis), and mitochondrial damage.
- It typically presents with a significant decline in left ventricular ejection fraction, leading to chronic, dilated cardiomyopathy.
- The risk increases sharply with cumulative doses, typically >450 mg/m2-550 mg/m2.

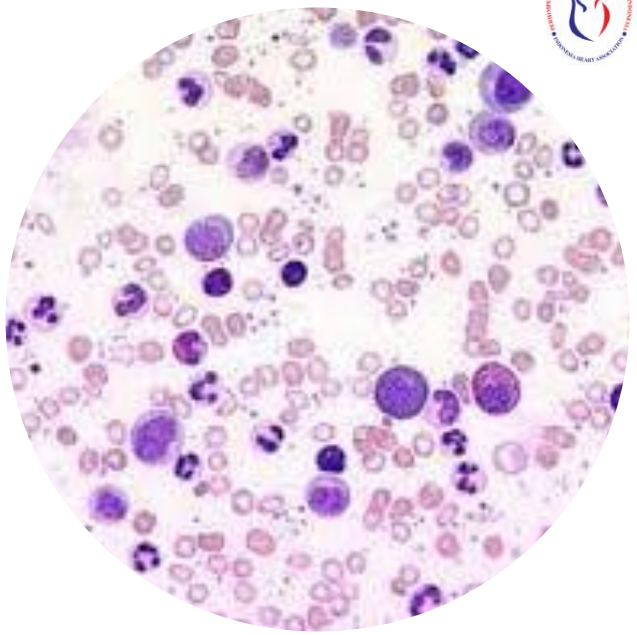
Prevention & Treatment

Monitoring: Baseline and *periodic* echocardiograms (measuring ejection fraction and global longitudinal strain) to monitor left ventricular dysfunction.

Management: Standard heart failure therapies (e.g., ACE inhibitors, beta-blockers) are generally used, but established cardiomyopathy has a poor prognosis.

Note: The management of cancer patients requires close coordination between oncologists and cardiologists.



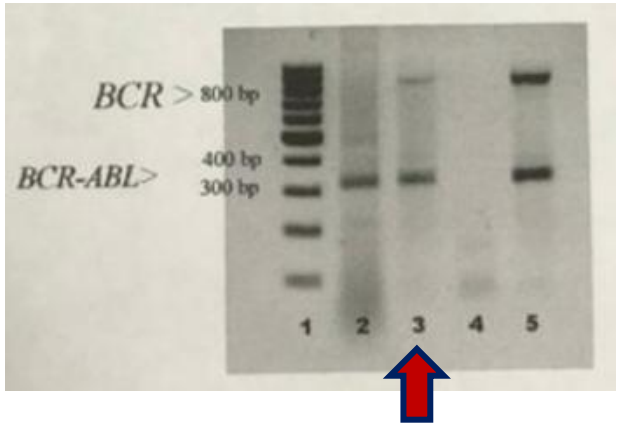


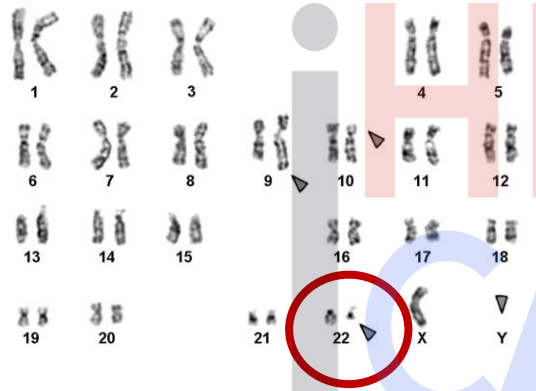
Leukemia Granulositik Kronik (LGK)

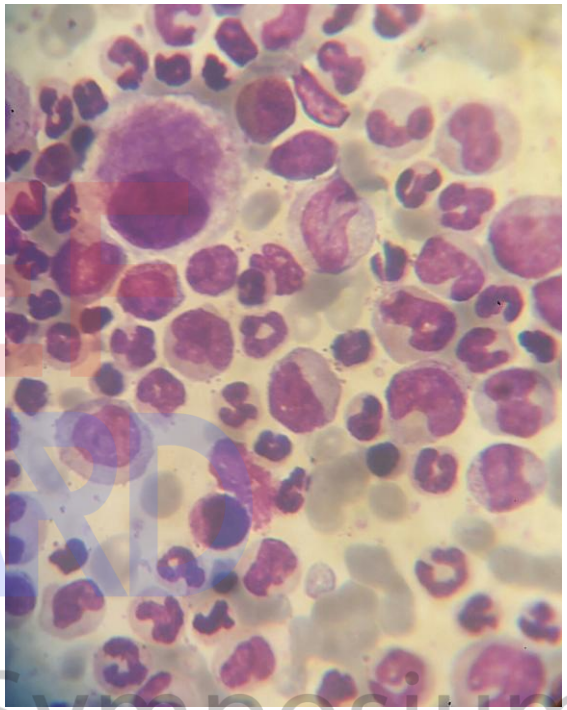
1-2 kasus baru per 100.000 penduduk per tahun; pria>wanita; bisa menyerang semua usia, tersering rentang usia 45-55 tahun.

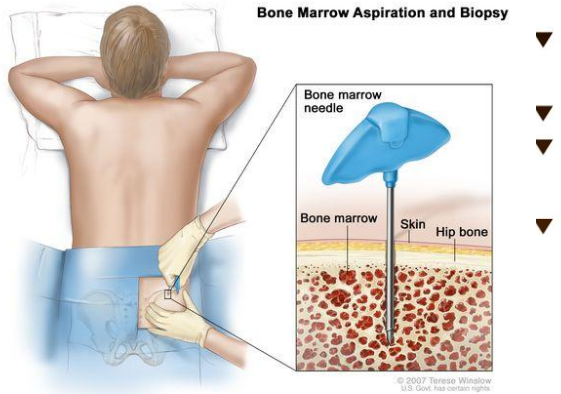
Klinis:
- asimtomatik;
- simtomatik → splenomegaly;

Lab: anemia ringan; leukositosis >100.000 few blast, progranulosit, mielosit, metamielosit, batang, segmen...; trombositosis/ N.









How to establish the diagnosis: Bone marrow aspiration: morphology, cytogenetic, and RT-PCR BCR-ABL


TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?


NOVARTIS
NDC 0078-0373-66
Gleevec™
(imatinib mesylate)
Capsules
100 mg
120 Capsules

Case 2...

- A 51-year-old male visited policlinic Hematology-Medical Oncology due to referral from regional hospital due to severe leukocytosis. Physical examination: there was no splenomegaly.

- CBC: Hb 12.4 g/dL (N: 13-17 g/dL), WBC 133.500/uL (N: 5000-10.000/uL), Plt 577.000/uL (N:150.000-400.000/uL) basophil 0% eosinophil 1% neutrophil band 23% neutrophil segment 55% lymphocyte 10% monocyte 2% blast 2% myelocytes 4% metamyelocytes 3%.

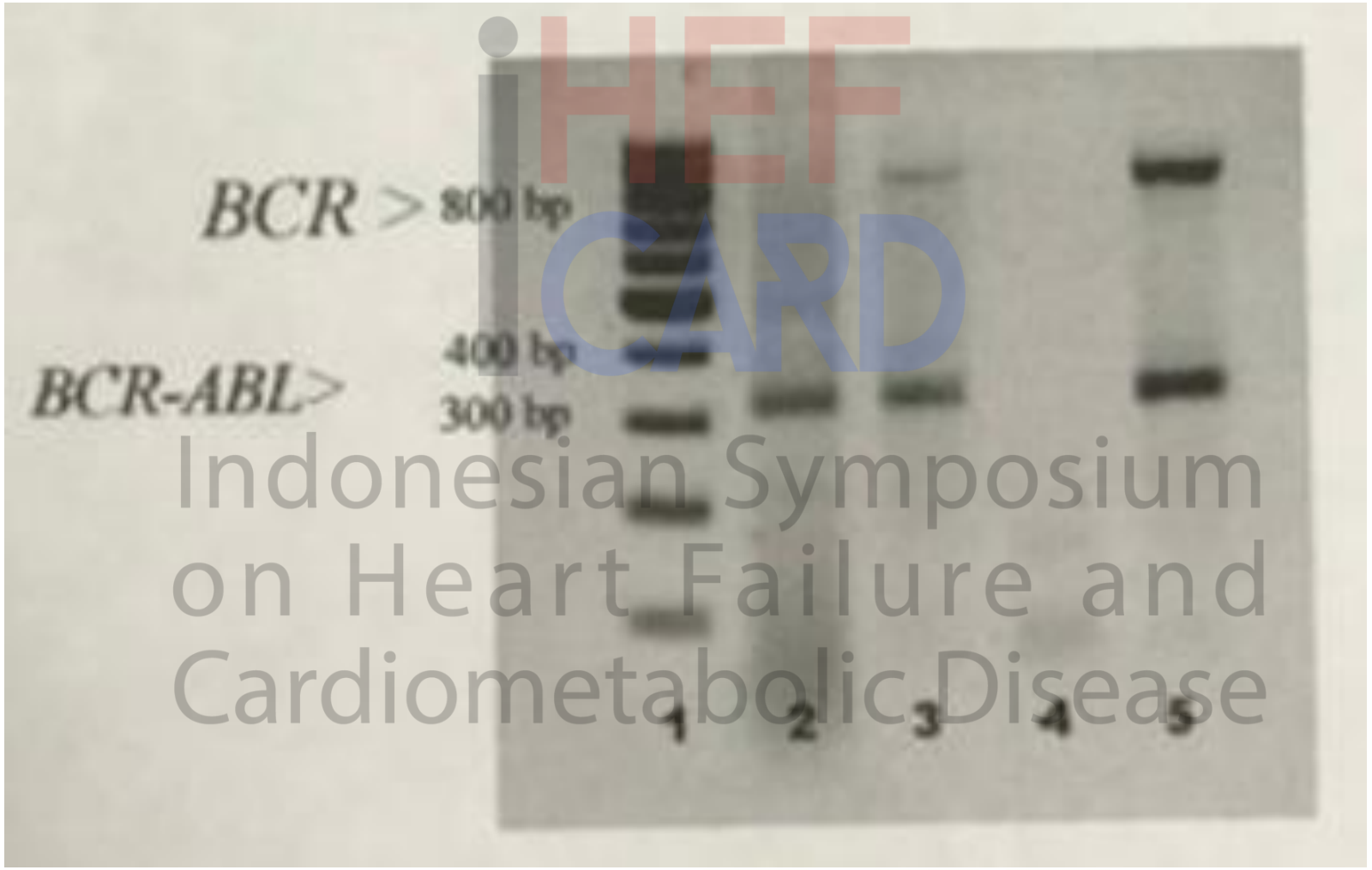
- Wd: Chronic phase CML and performed bone marrow aspiration and RT-PCR BCR ABL from peripheral blood.

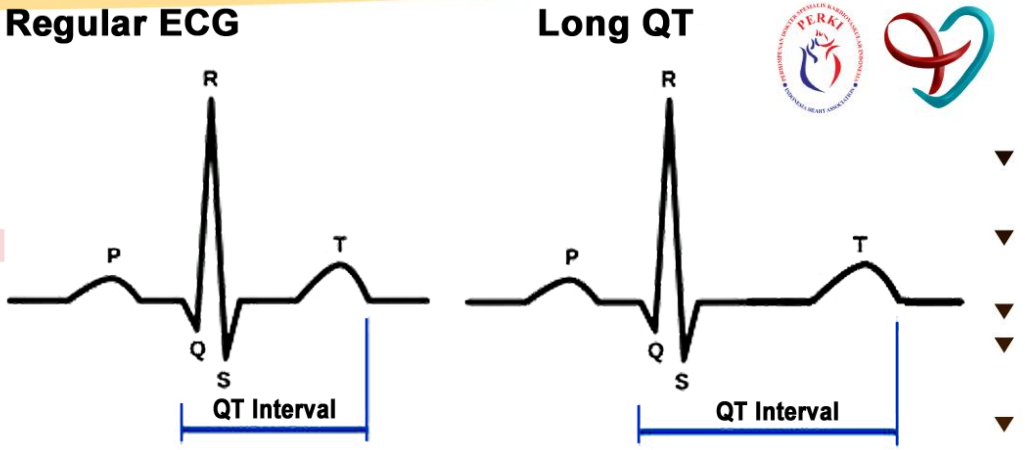
- After 1 week apart the result of morphology of bone marrow showed: hypercellular, blast 1%, Myeloid : Erythroid (M:E) ratio = 15:1, suppression of erythropoiesis, hyperplasia of granulopoiesis, and increased number of megakaryocytes. The RT-PCR BCR-ABL transcript was detected with international scale ratio was 69%.

- We established the diagnosis of Chronic Phase CML BCR-ABL (+)

Bone marrow cytomorphology: hypercellular, blast 1%, Myeloid : Erythroid (M:E) ratio = 15:1, suppression of erythropoiesis, hyperplasia of granulopoiesis, and increased number of megakaryocytes.

The RT-PCR BCR-ABL transcript was detected



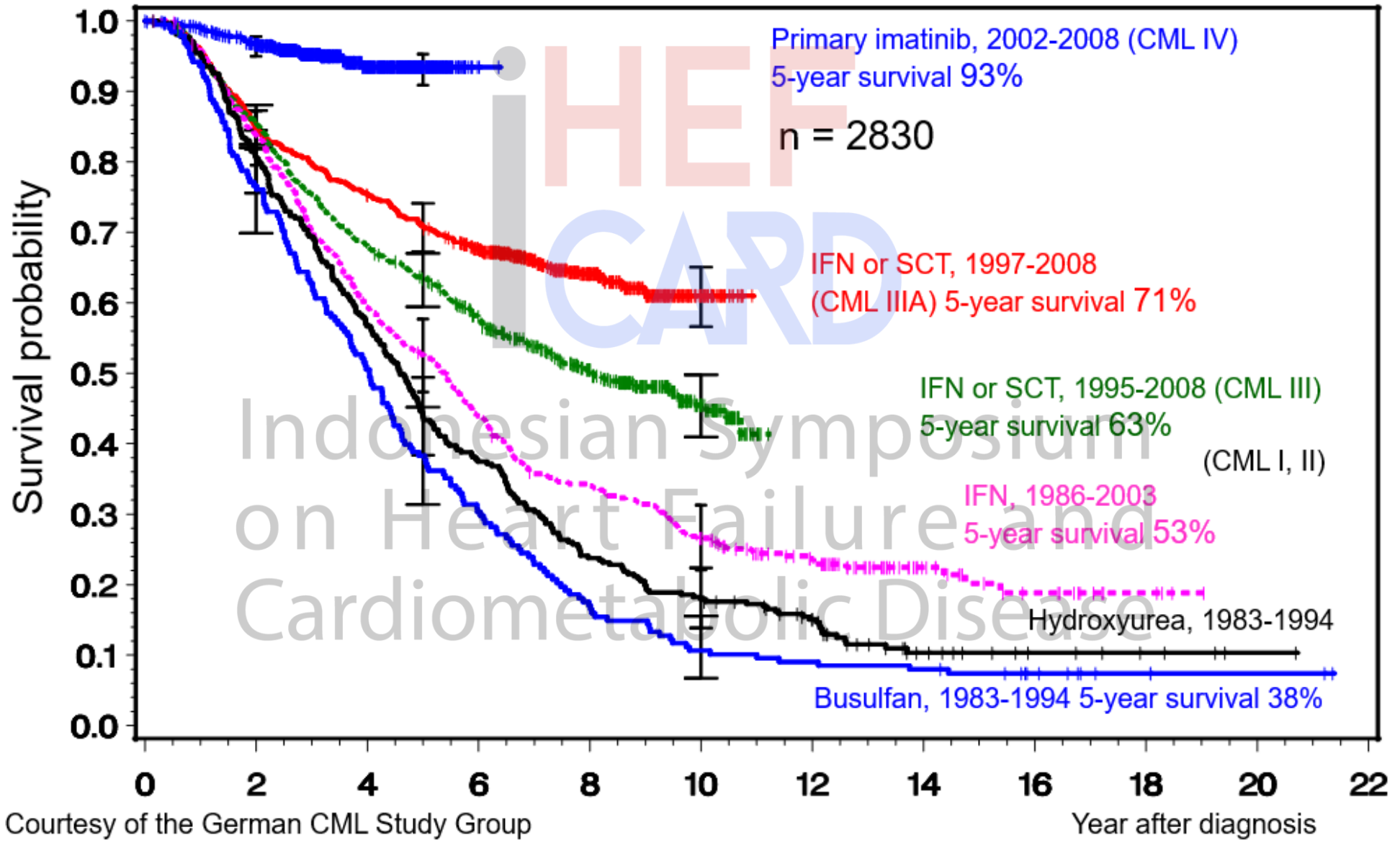


The Sokal score was 0.9 points (intermediate) and the EUTOS long-term survival (ELTS) score was 1.0821 (low-risk group).

- **After the result of BCR-ABL, we started to administer Imatinib 400 mg once daily,**
- **After 3 months patient achieved complete hematologic response**
- **And at 6 , 12, and 24 months the patient achieved molecular response with international scale ratio 0.05%, 0.032% and no transcript detected.**
- **We plan to check qBCR-ABL every 6 months.**
- **The patient can tolerate the side effects of Imatinib and can continue the treatment.**

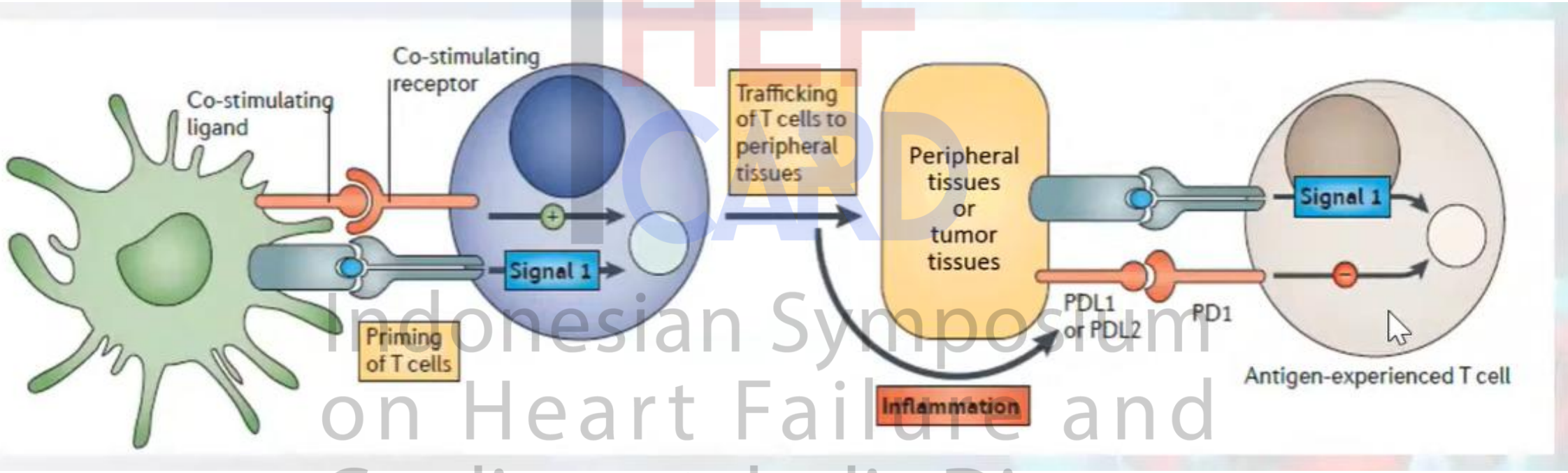
Lab	Week 0	Week 2	Month 1	Month 3	Month 6	Month 12	Month 24
Hb	12.4	11.4	12.1	14.4	15.4	14.8	15.1
WBC	133.500	33.400	4500	4700	3800	3700	4500
Platelet	577.000	439.000	320.000	235.000	280.000	357.000	282.000
qBCR-ABL					0.05%	0.032%	Not detected

Survival 1983-2008



Courtesy of the German CML Study Group

Immunotherapy



T Cell tolerance

"Driving" an Immune Response

TCR: antigen-MHC

Signal 1

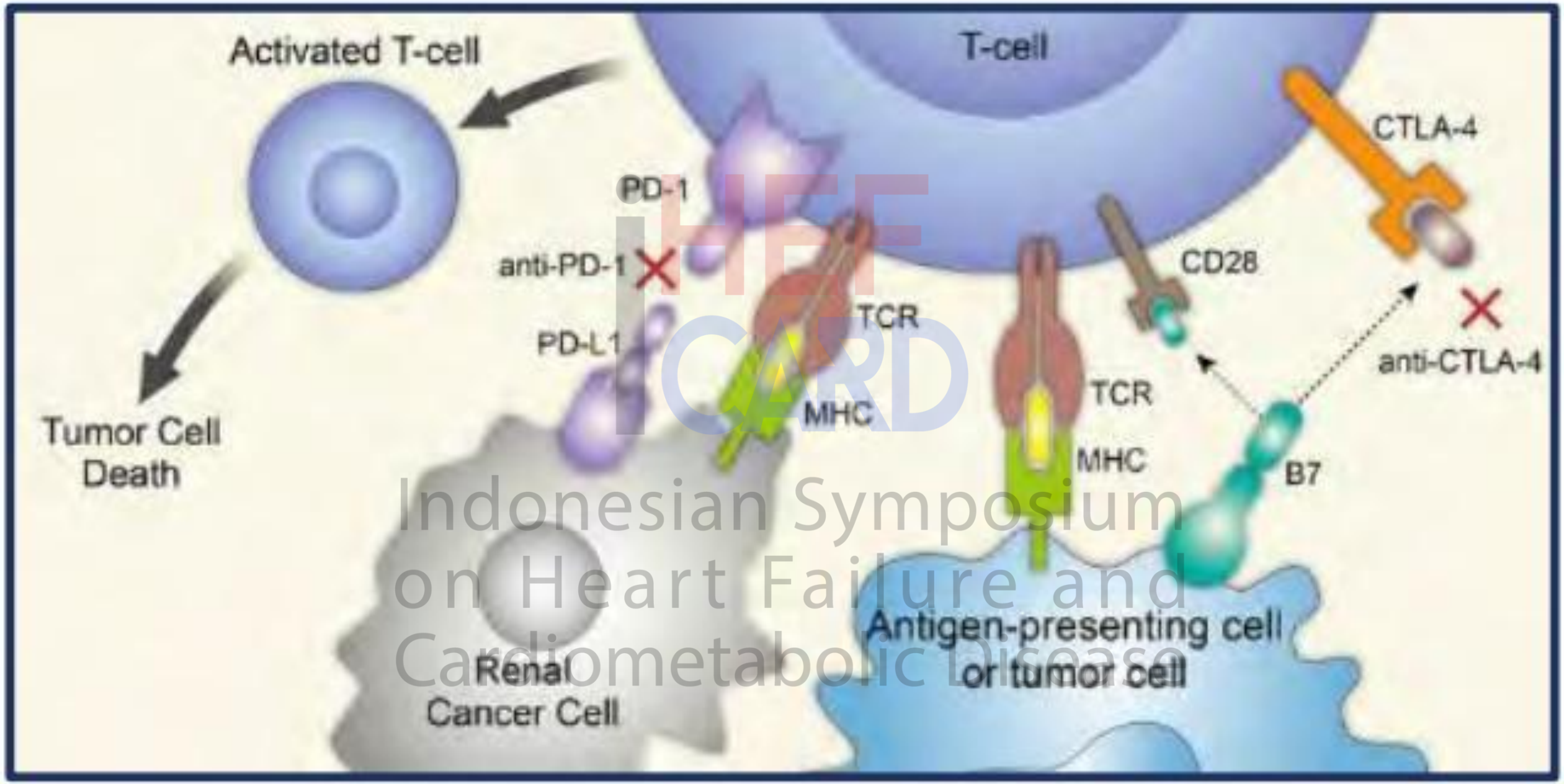
CD28: B7

Signal 2

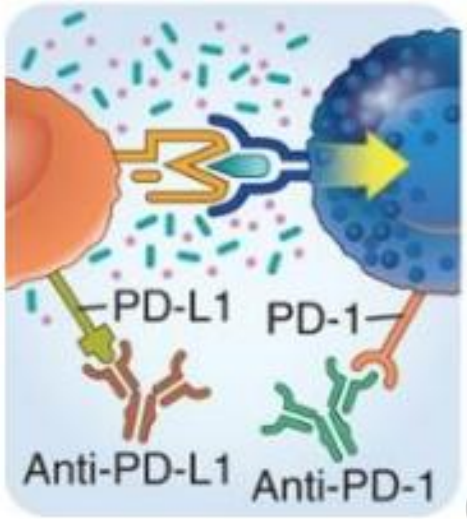
CTLA4: B7
PD-1: PD-L1

Blockade of Signal 2

Immune Check Point

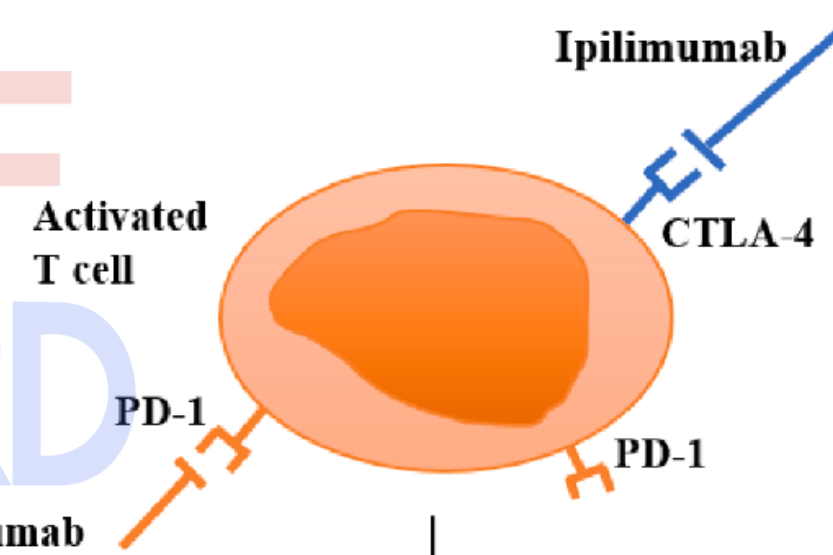


Yao Cancer Manag Res 2018;



Activated CTL

Dead tumor cell



Cardiomyocyte damage

Approved indications for anti-PD-1/PD-L1 therapies

Table 1 Immune checkpoint inhibitors and their US FDA/EMA/China NMPA approved indications

Immune checkpoint inhibitor	Targets	US FDA/EMA approved indications	China NMPA approved indications
Pembrolizumab	PD-1	Melanoma, non-small cell lung cancer, head and neck cancer, Hodgkin's lymphoma, urothelial carcinoma, MSI-H/dMMR* colorectal cancer, MSI-H/dMMR cancers, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, small cell l ung cancer, esophageal carcinoma, endometrial cancer	Melanoma, non-small cell lung cancer
Nivolumab	PD-1	Melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, urothelial carcinoma, MSI-H/dMMR colorectal cancer, hepatocellular carcinoma, small cell lung cancer	Non-small cell lung cancer
Atezolizumab	PD-L1	Urothelial cancer, non-small cell lung cancer, breast cancer, small cell lung cancer	Non-small cell lung cancer
Durvalumab	PD-L1	Urothelial carcinoma, non-small cell lung cancer	
Avelumab	PD-L1	Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma	
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma	
Ipilimumab	CTLA4	Melanoma, metastatic, renal cell carcinoma, MSI-H/dMMR colorectal cancer	
Toripalimab	PD-1		Melanoma
Sintilimab	PD-1		Hodgkin's lymphoma
Camrelizumab	PD-1		Hodgkin's lymphoma
Tislelizumab	PD-1		Hodgkin's lymphoma

*Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR)

Pan et al. Journal of Hematology & Oncology, 2020

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irAEs can affect any organs at anytime

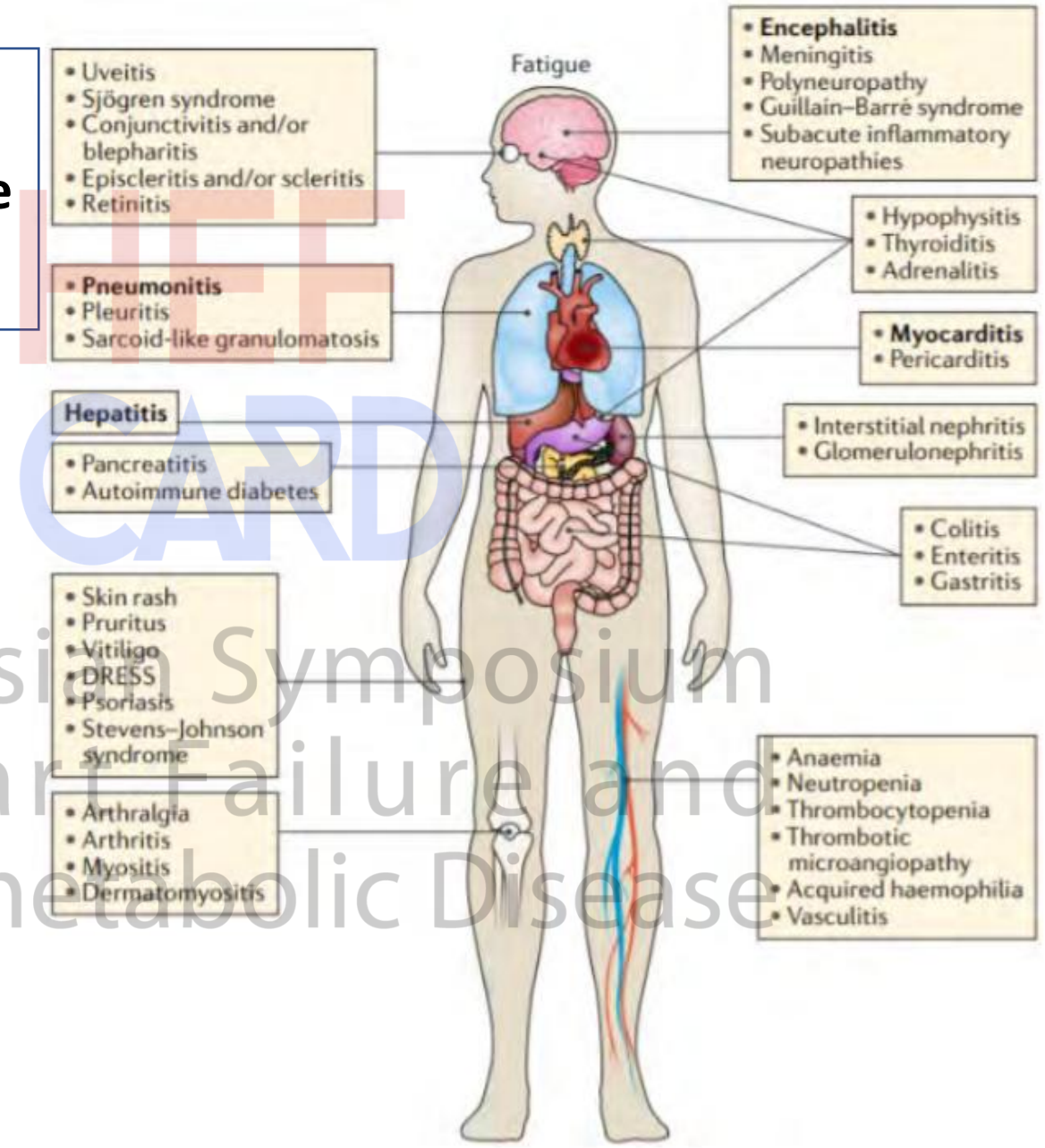
- The frequency and severity of irAEs is mainly dependent on the IC used, regimen but also on the specific characteristics of individual patients
- The toxicity mimics classical autoimmune diseases AID but remains different entities on biological and clinical levels
- ICI-related colitis ≠ IBD, ICI-related GBS ≠ GBS, ICI-related hepatitis ≠ AIH

Treatment of irAE

- **the treatment is built by analogy on that of AID**
- **None randomized clinical trials for irAEs treatment**
- **Treatment of ICI-related pneumonitis beyond corticosteroid is based on colitis experience**

- Pleomorphic presentations continues to accumulate

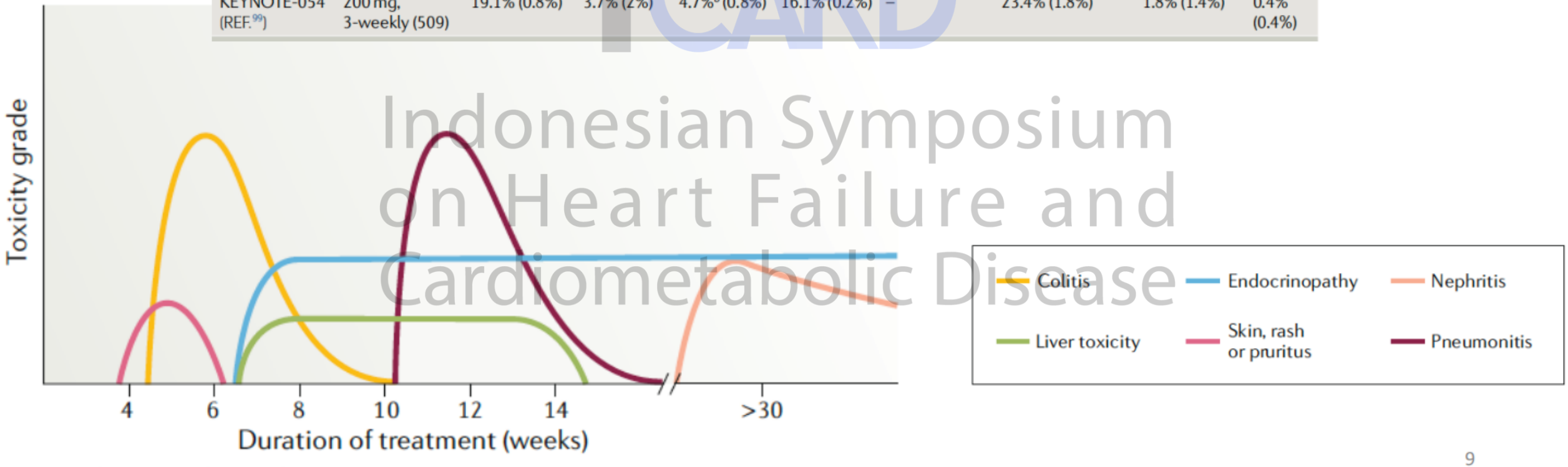
A broad spectrum of immune-related adverse events irAEs



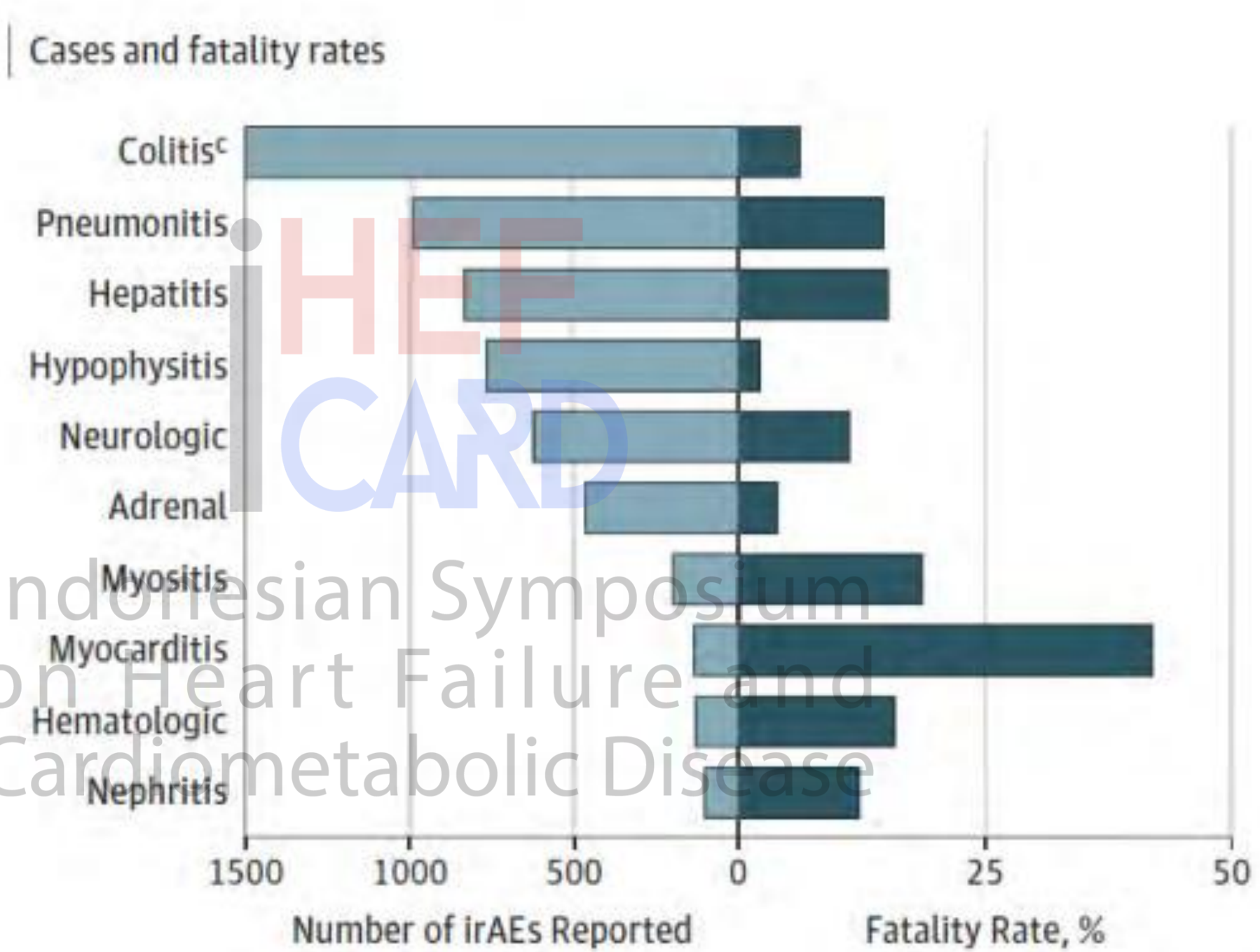
Martins et al., & Obeid M, Nature Reviews Clinical Oncology, 16, 2019

irAE kinetics of anti-PD-1

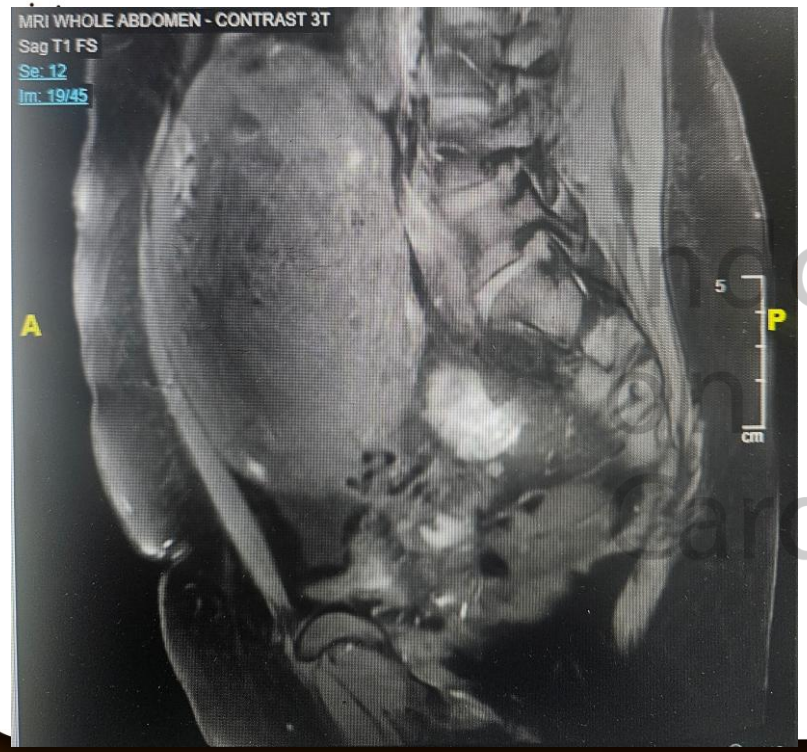
Study details		Any-grade adverse events (grade ≥3 adverse events)							
Study	**Dose (n)**	**Diarrhoea**	**Colitis**	**Pulmonary**	**Rash**	**Neurological**	**Endocrinopathy**	**Hepatic**	**Renal**
Nivolumab									
CheckMate 066 (REF.[21])	3 mg/kg, 2-weekly (206)	16% (1%)	1% (0.5%)	1.5% (0%)	15% (0.5%)	–	7.3% (1%)	3.4% (1.5%)	1.9% (0.5%)
CheckMate 057 (REF.[167])	3 mg/kg, 2-weekly (287)	8% (1%)	1% (0.3%)	4.9% (1.4%)	9% (3.5%)	0.3% (0.3%)[a]	10.5% (0%)	10.8% (1.4%)	2% (0%)
Pembrolizumab									
KEYNOTE-010 (REF.[146])	2 mg/kg, 3-weekly (339)	7% (1%)	1% (1%)	5% (2%)	9% (0.3%)	–	15% (1%)	0.3% (0.3%)	–
KEYNOTE-010 (REF.[146])	10 mg/kg, 3-weekly (343)	6% (0%)	1% (0.3%)	4% (2%)	13% (0.3%)	–	16.5% (2%)	1% (0%)	–
KEYNOTE-054 (REF.[99])	200 mg, 3-weekly (509)	19.1% (0.8%)	3.7% (2%)	4.7%[b] (0.8%)	16.1% (0.2%)	–	23.4% (1.8%)	1.8% (1.4%)	0.4% (0.4%)

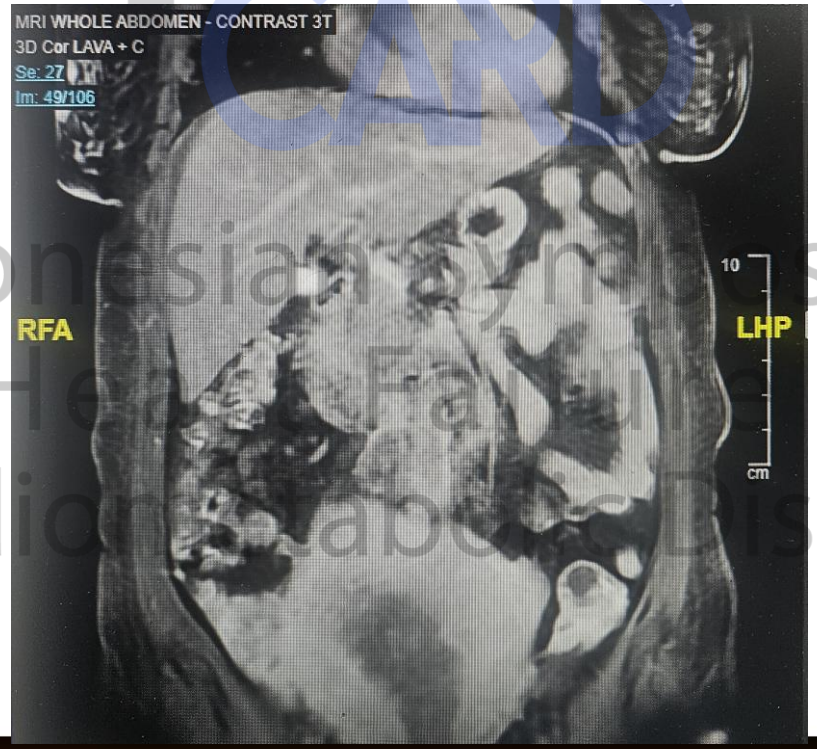


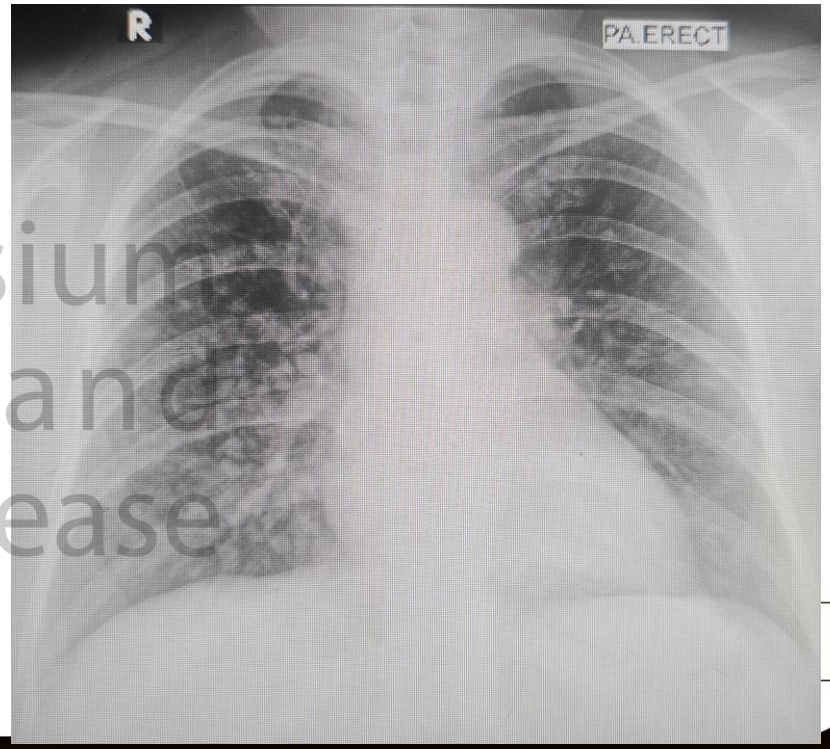
Martins et al., Nat Rev Clin Oncol 2019



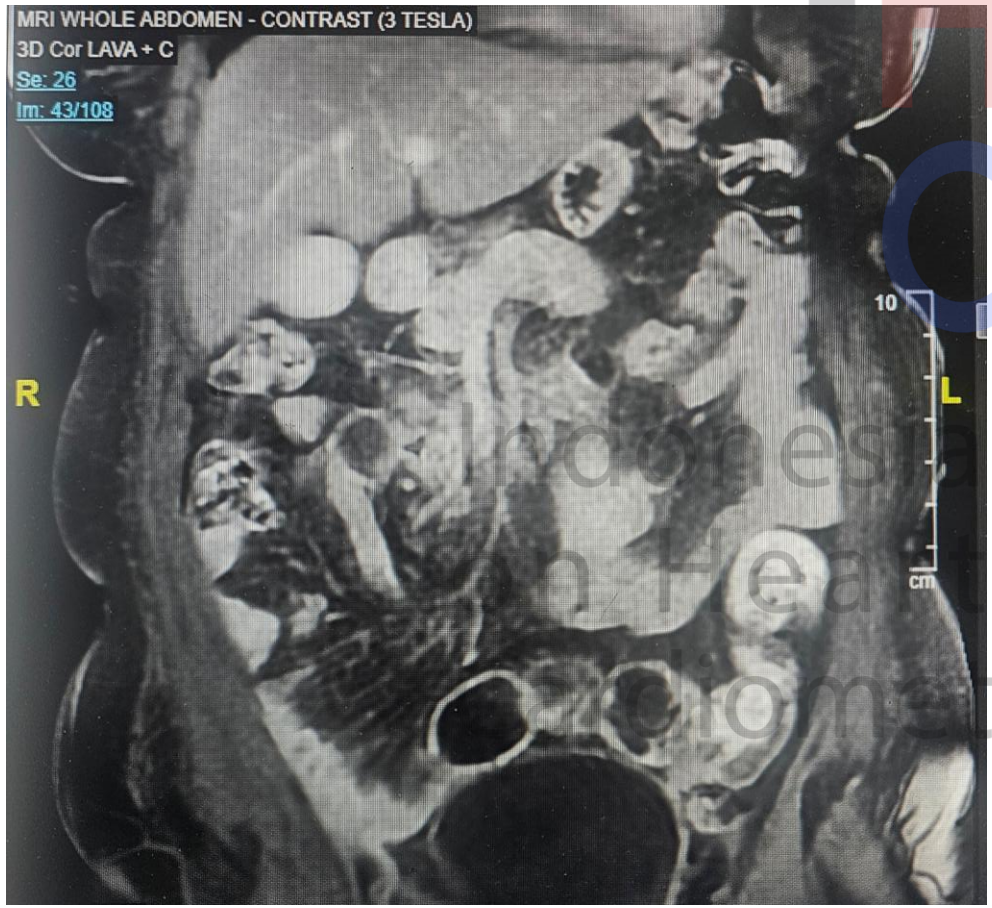
Case 3: A-56-year-old female: Adenoca endometrium
We administered Carboplatin Paclitaxel Pembrolizumab every 3 weeks x 6 cycles

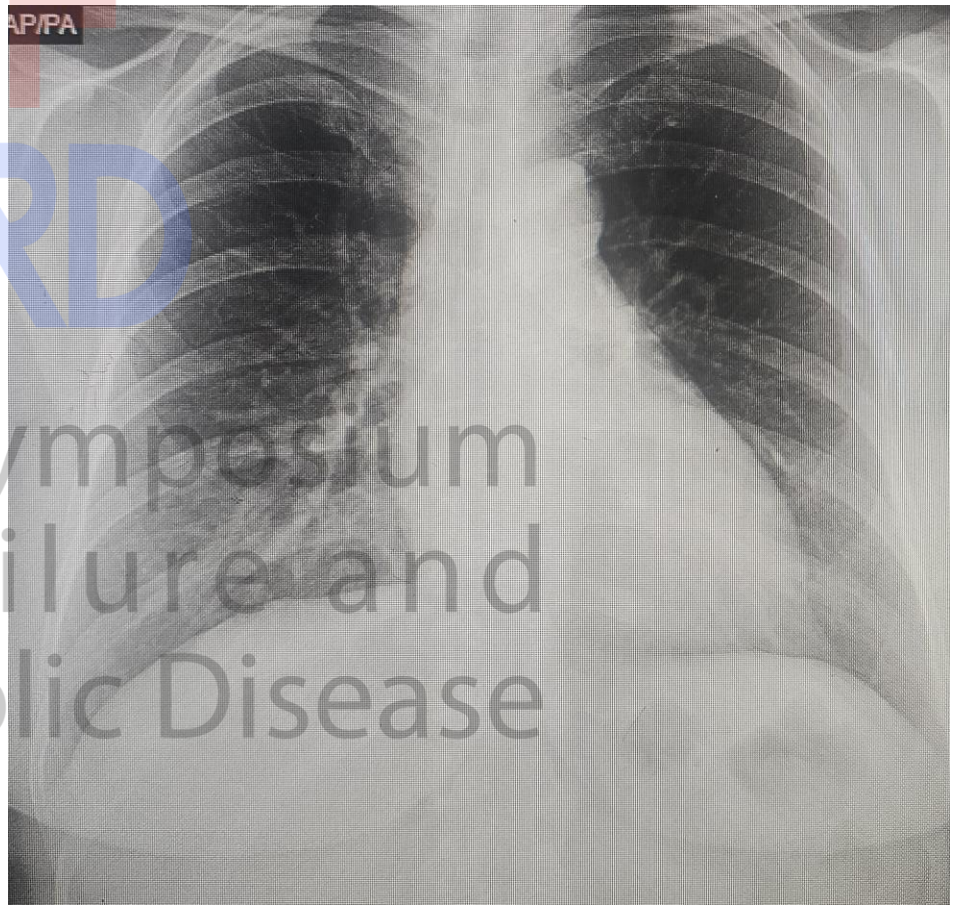






Complete Remission
We continued Pembrolizumab every 3 weeks up to 35 cycles

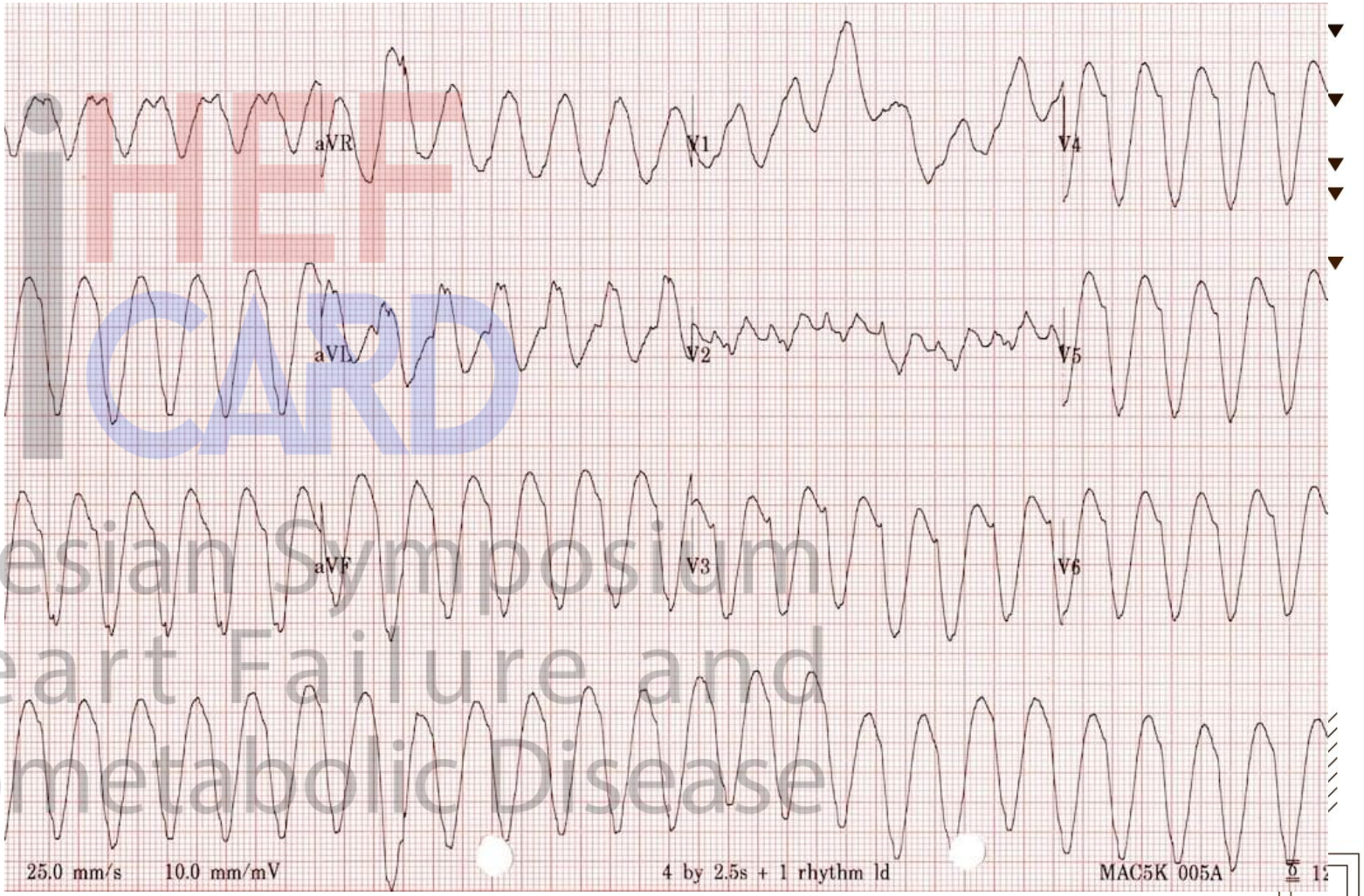




Case 4: Resectable early-stage NSCLC

- A-62 yo male, ex-smoker 30 pack years, quit 10 y ago, retired police officer.
- Comorbidities: renal calculi, GERD, Hep C on treatment.
- R lower lobectomy, incidental CT-scan RLL mass 7 cm, PA: Adenoca TTF-1 (+), no nodal involvement, PDL-1 (+), EGFR mutant (-).
- IMpower010: Adj Chemo + Adj Immunotherapy Atezolizumab 1200 mg q21days x 16 cycles as part of a clinical trial.

Case 4 continued:
irAE hyperthyroidism with TSHs↓ and FT4↑
ICCU, reverted with sotolol IV than oral atenolol, Carbimazol, Oral prednisone 1 mg/kgbb and PCP prophylaxis.
Withhold Atezolizumab..



Case 5: metastatic SCC lung cancer

- Cisplatin
- Gemcitabine
- **Pembrolizumab**

After **5** cycles of pembrolizumab administration, he developed severe weakness and shortness of breath

Side effects

ECG: new onset of left bundle branch block

Laboratory: ↑ troponin I, ↑ NTproBNP

ECHO: global hypokinesis of right and left ventricles, ejection fraction 37%

Discontinuation of antitumour therapy

Coronary angiography no any obstructive disease

Cardic MRI was recommended

Lake Louise Criteria for myocarditis were detected

Prednisolone and **infliximab** treatment was started

runs of non-sustained ventricular tachycardia

Bisoprolol 5 mg/day was initiated

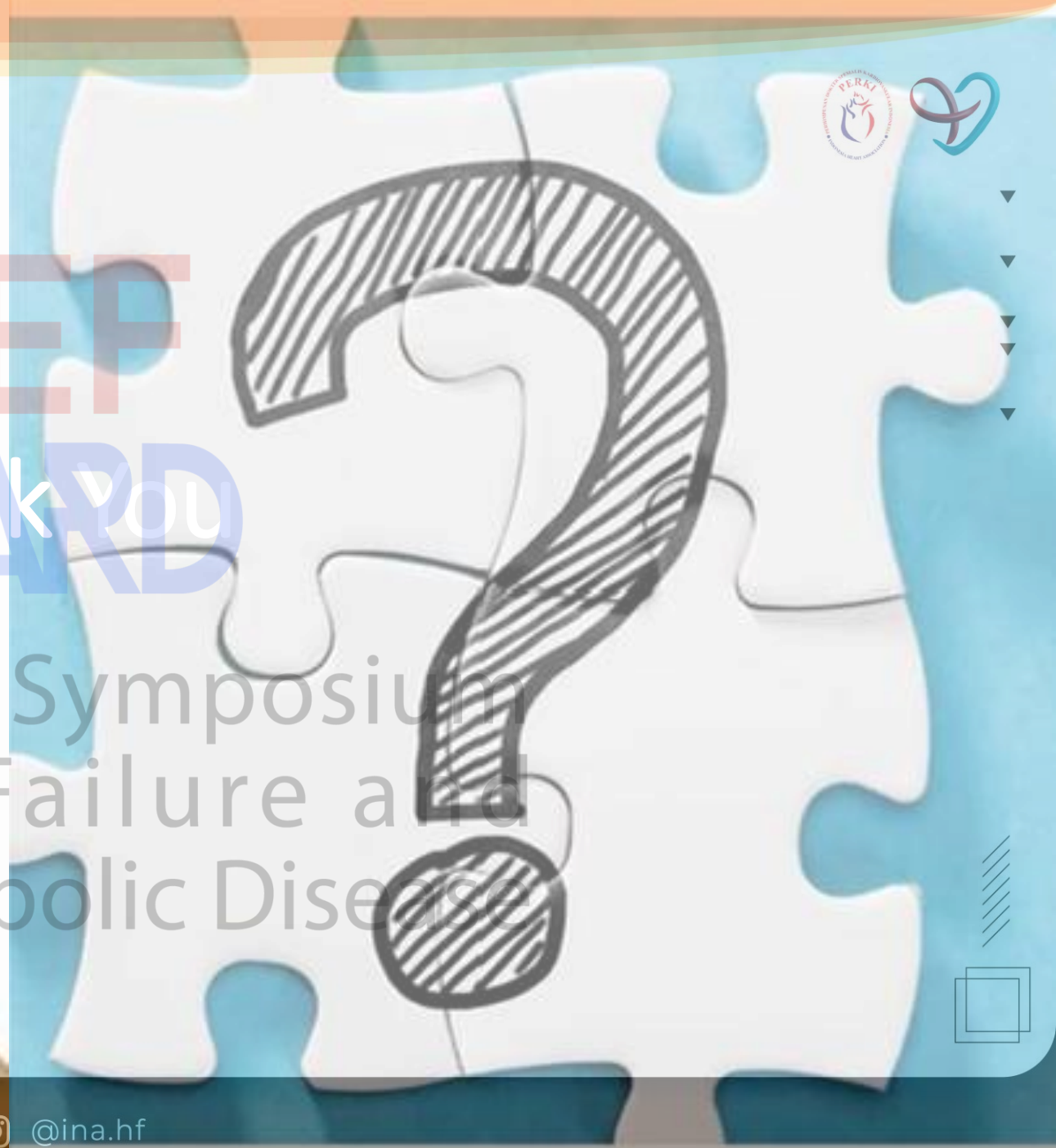
Heart failure symptoms resolved. Follow-up with cardiology and oncology was continued.

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) targeting HER2, and while it is effective, it carries risks of cardiac side effects, particularly relating to reduced heart function.

Case 6: mBC HER2 low

Important take-home messages,,,

- We have already recognized side effects of chemotherapy, prolonged QT of TKIs, irAEs of Immunotherapy, and ADC which can affect any organ and occur anytime.
- Baseline check up + treatment monitoring,,,
- Treatment: supportive, steroid, and immunosuppressive agents.
- Withhold treatment.



Thank You

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