31 GIORNATE CARDIOLOGICHE TORINESI

TURIN
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24th-26th
2019

CARDIONCOLOGY TODAY

Hematology and Cardiotoxicity

Pregno Patrizia
S.C. Ematologia
Città della Salute e della Scienza di Torino

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

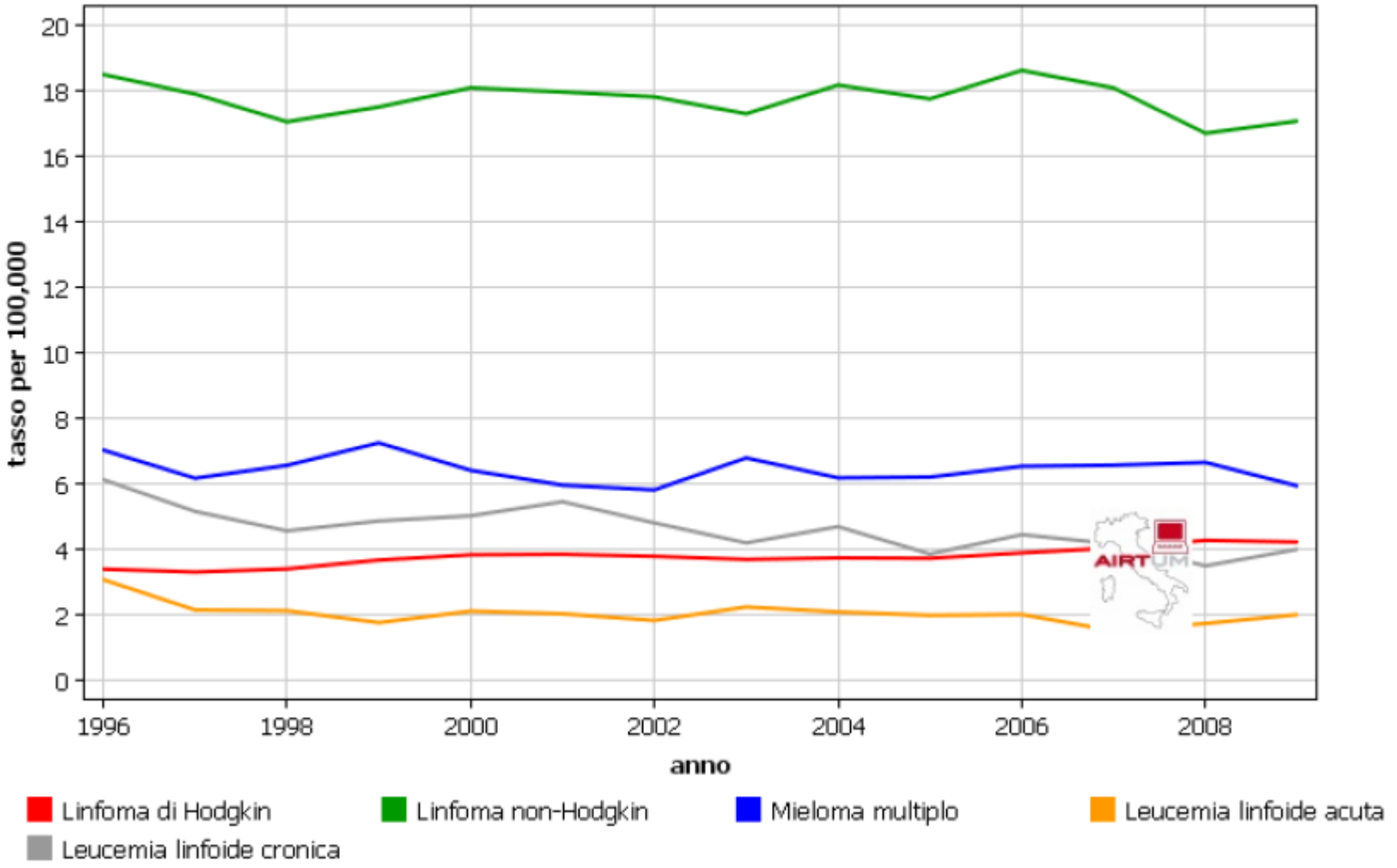
Introduction

- Onco-hematologic therapies developed in recent years have significantly improved patient survival.

- This resulted in a chronicization of some types of neoplasms.

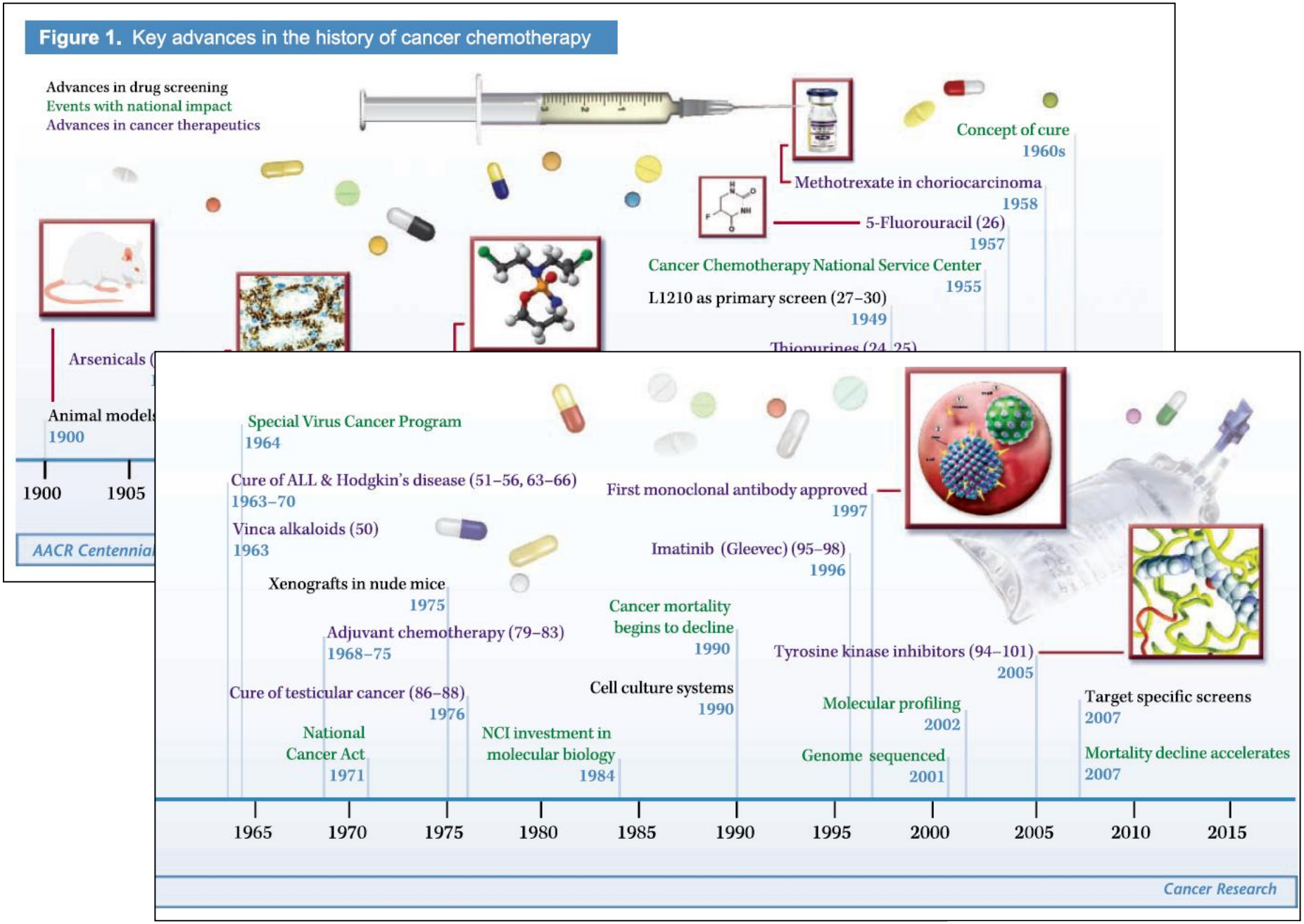
- The correct evaluation and treatment of cardiovascular comorbidities and / or cardiac complications during cancer therapies is therefore very important.

AIRTUM (Pool 9 Registri)
Incidenza: TSE (Europea), Maschi età (0-85+)



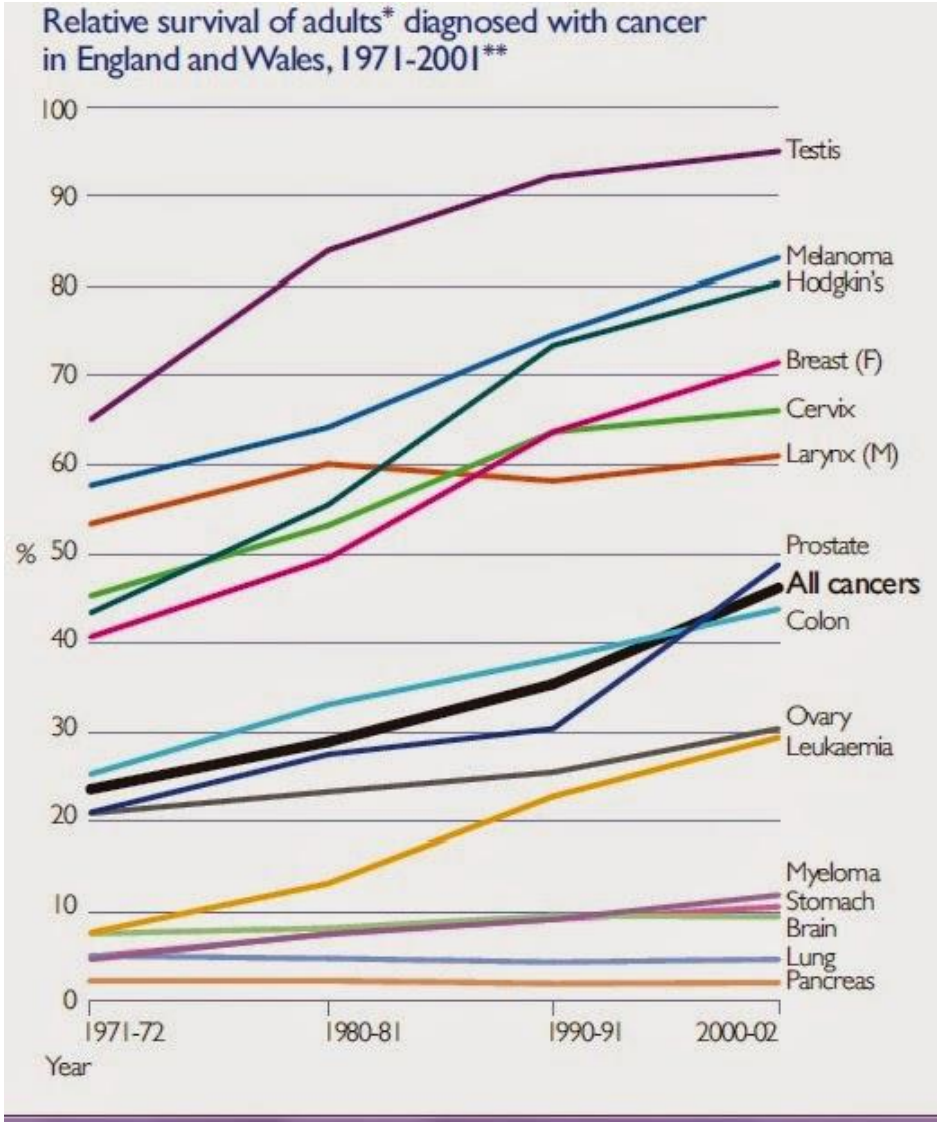
AIRTUM, Associazione Italiana dei Registri Tumori (11.12.2015)

Figure 1. Key advances in the history of cancer chemotherapy



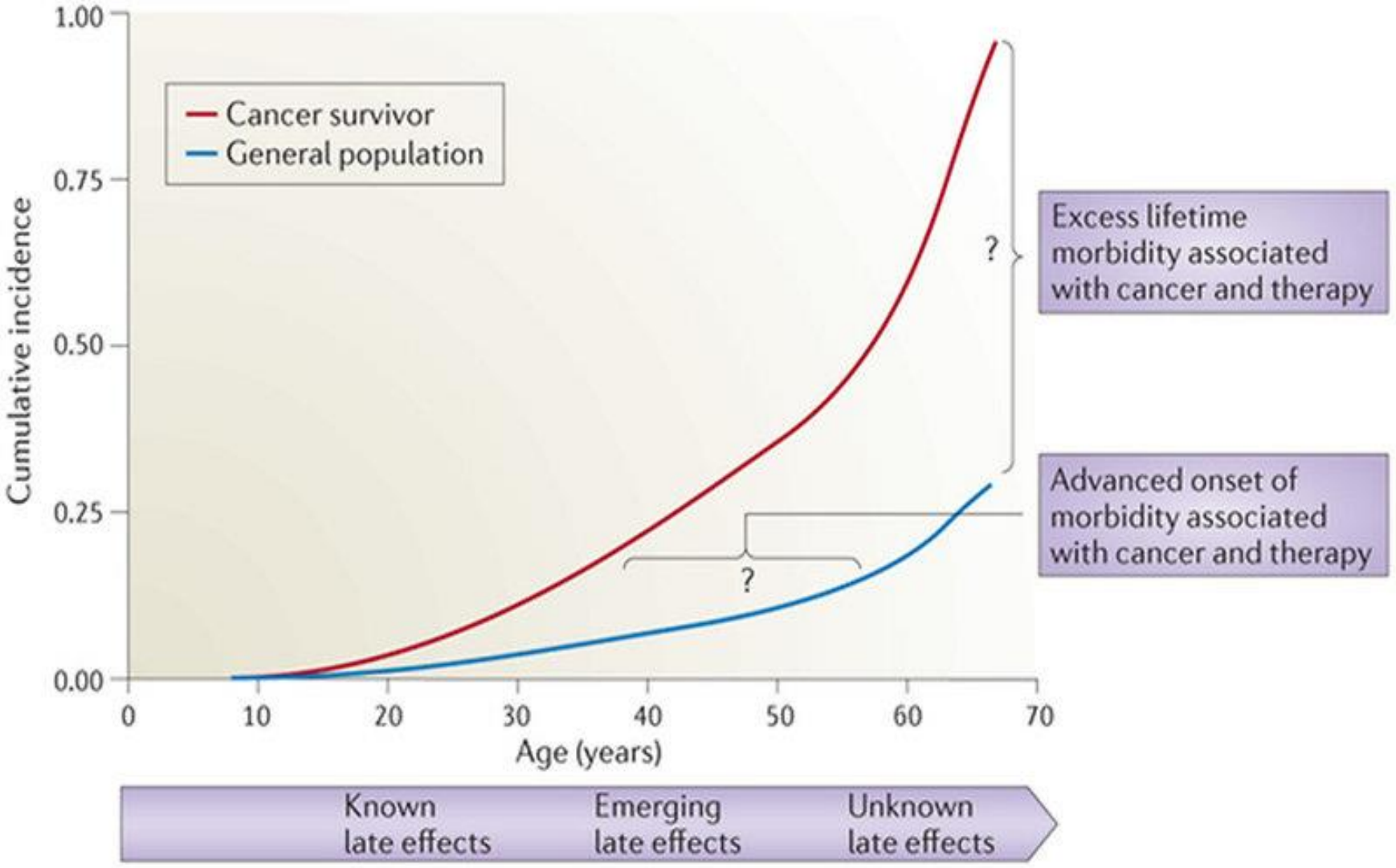
DeVita V T , and Chu E Cancer Res 2008;68:8643-8653

Survival of Cancer Patients in Europe, 1999–2007: The EUROCARE-5 Study

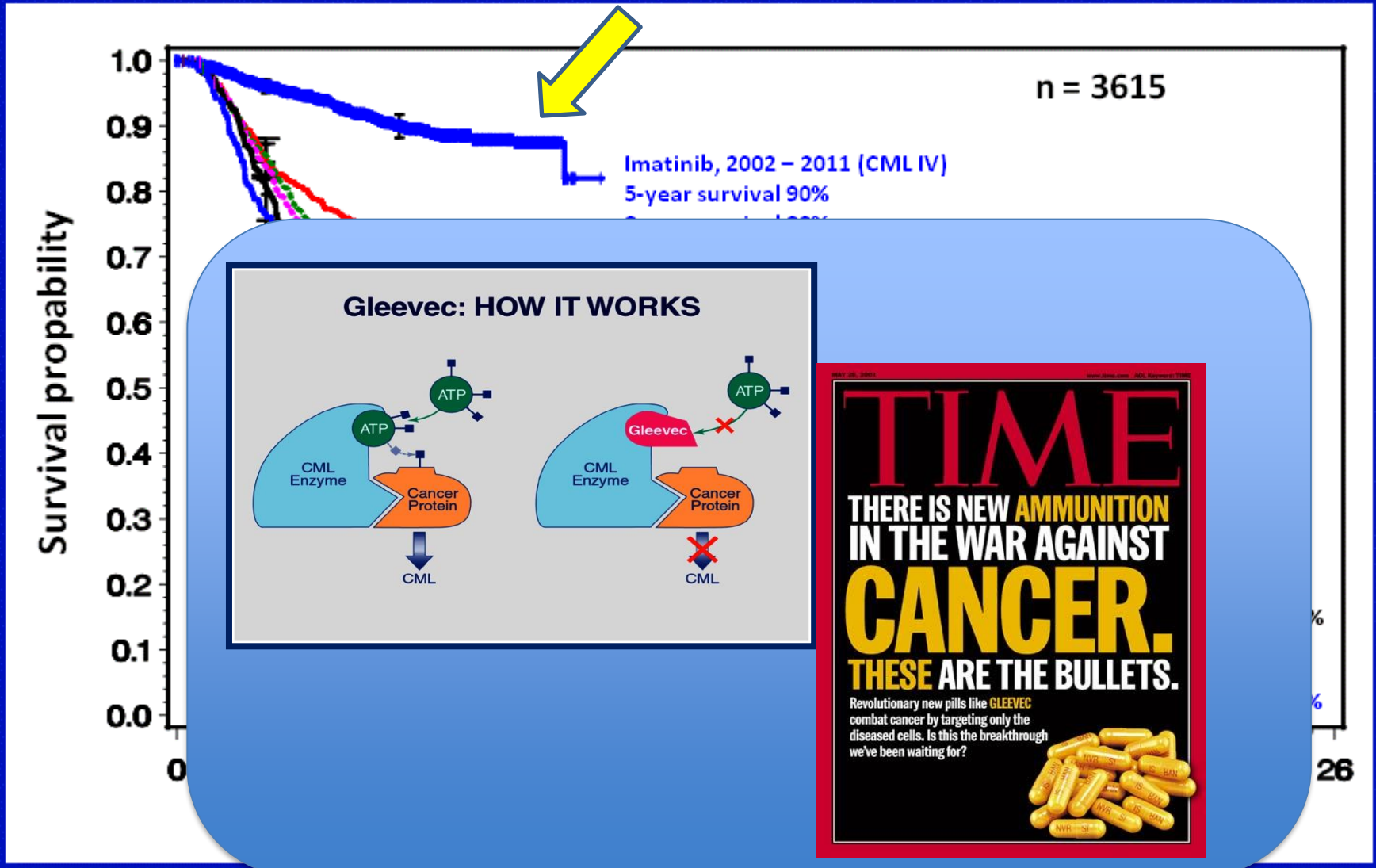


Eur. J. Cancer, 51, 15, 2015: P. Minicozzi, R. Otter, M. Primic-Žakelj and S. Francisci

Effects of long-term therapy in long-term cancer survivors



Improvement of survival of CML by therapy 1983 – 2011



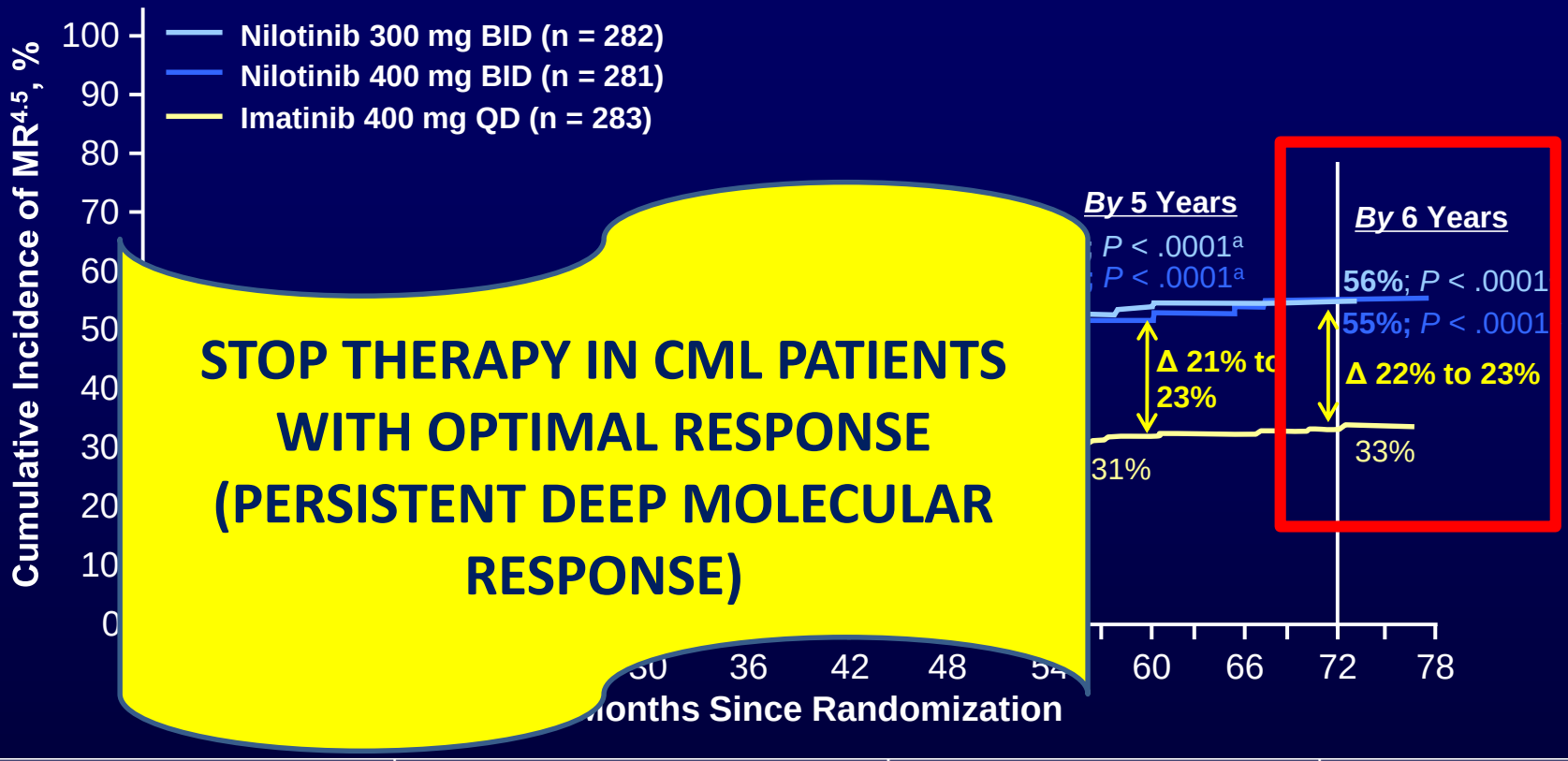
First line Tki therapy for CP-CML: Long-term FU data from phase III studies

Trial	Study Arms	N° pts	Median FU	CCyR %	MMR%	Disease progression n (%)	PFS %	OS %
IRIS[1]	Imatinib 400	553	11 ys	83	-	38 (37)	92	83
	α-IFN+LD ARA-C	553		-	-	71 (13)	-	79
DASISION[2]	Dasatinib 100	259	5 ys	-	76 P=.002	12 (5)	85	91
	Imatinib 400	260		-	64	19 (7)	86	90
ENESTnd[3]	Nilotinib 600	282	5 ys	-	77 P vs IMA <.0001	10 (4)	92	94
	Nilotinib 800	281		-	77 P vs IMA <.0001	8 (2)	96	96
	Imatinib 400	283		-	60	21 (7)	91	92
BFORE[4]	Bosutinib 400	268	12 ms	77 P=.0075	47 P=.02	4 (2)	-	-
	Imatinib 400	268		66	37	6 (3)	-	-

1. Hochhaus A et al, N Engl J Med, 2017 2. Cortes JE et al J Clin Oncol 2016
3. Hochhaus A et al, Leukemia 2016 4. Cortes JE et al, J Clin Oncol 2018

NCCN Guidelines 1/19, August 2018

Figure 3. Cumulative Incidence of MR$^{4.5}$ and Time to First MR$^{4.5}$



Treatment Arm	Kaplan-Meier Estimated Median Time to First MR$^{4.5}$, months	Hazard Ratio vs Imatinib (95% Confidence Interval)	*P* value[a]
Nilotinib 300 mg BID	45.5	2.0387 (1.5807-2.6295)	< .0001
Nilotinib 400 mg BID	49.8	1.7770 (1.3780-2.2915)	< .0001
Imatinib 400 mg QD	61.1	–	–

[a] *P* values are nominal, were provided for descriptive purposes only, and were not adjusted for multiple comparisons.

Hughes TP, et al. *Haematologica*. 2015;100:[abstract P228].

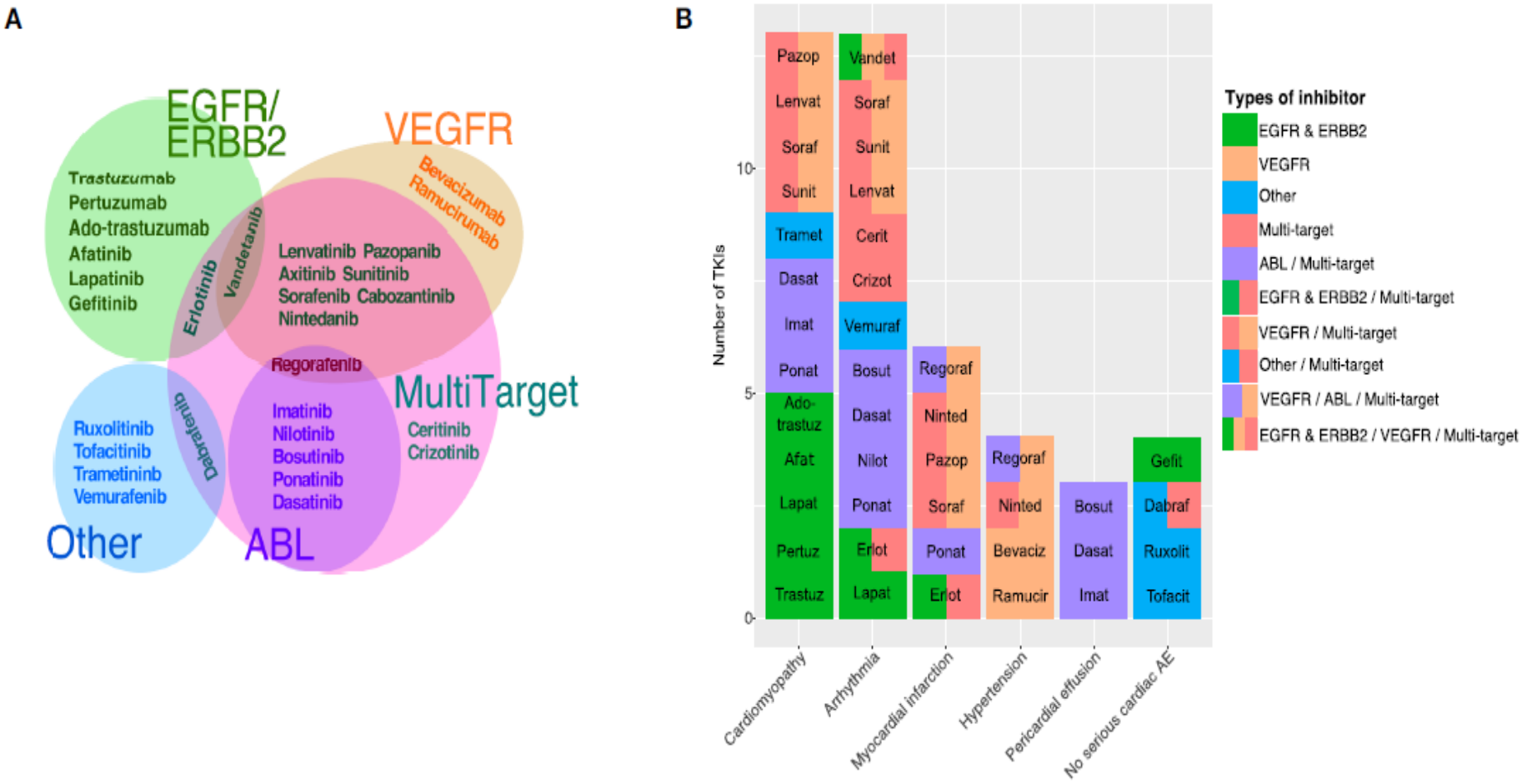


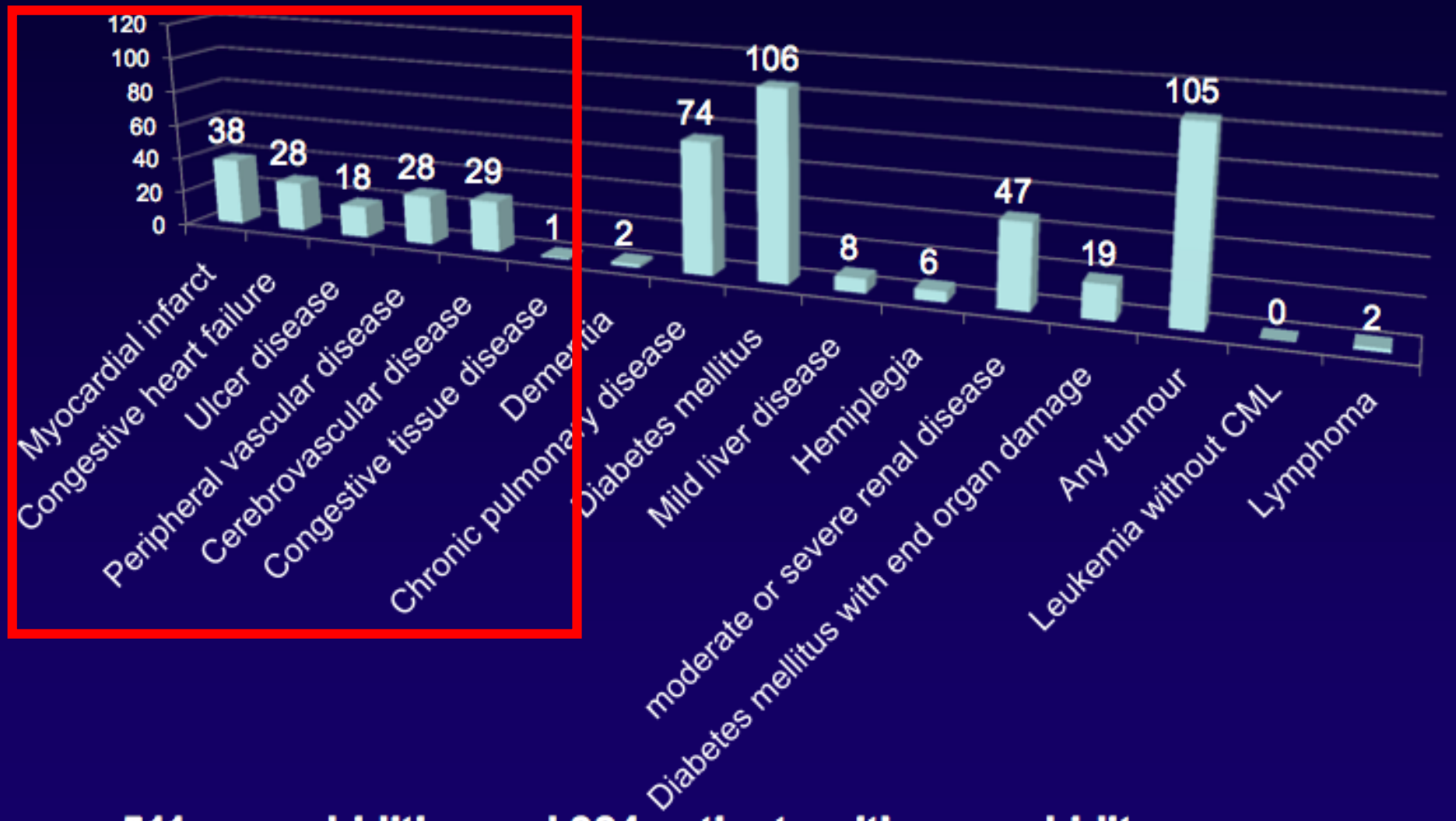
FIGURE 1 | TKI targets and associated adverse events. **(A)** Euler diagram of tyrosine kinase inhibitors grouped based on the primary intended target(s). The three major primary targets are EGFR/ERBB2 (8 TKIs), VEGFR (11 TKIs), and ABL (6 TKIs). The category "Other" comprises five relatively newer TKIs with primary targets in different categories, such as vemurafenib (B-Raf). Out of 30 approved TKIs, 18 were identified as having intended targets in more than one category. **(B)** Black box warnings associated with tyrosine kinase inhibitors are indicated, with closely-related toxicities grouped to ease visualization. *Cardiomyopathy* category includes: "cardiac dysfunction," "congestive heart failure," "left ventricular dysfunction," and "cardiomyopathy." *Arrhythmia* includes: "prolonged QT interval," "cardiac bradyarrhythmia," and "cardiac arrhythmia." *Pericardial effusion* includes both "pericardial/pleural effusion," and "cardiac tamponade." Four approved drugs have no cardiac-associated boxed warning (i.e., no serious cardiac adverse events listed in the drug's package insert).

Shim J.V. et al, 2017

frontiers in Physiology

Which patient?

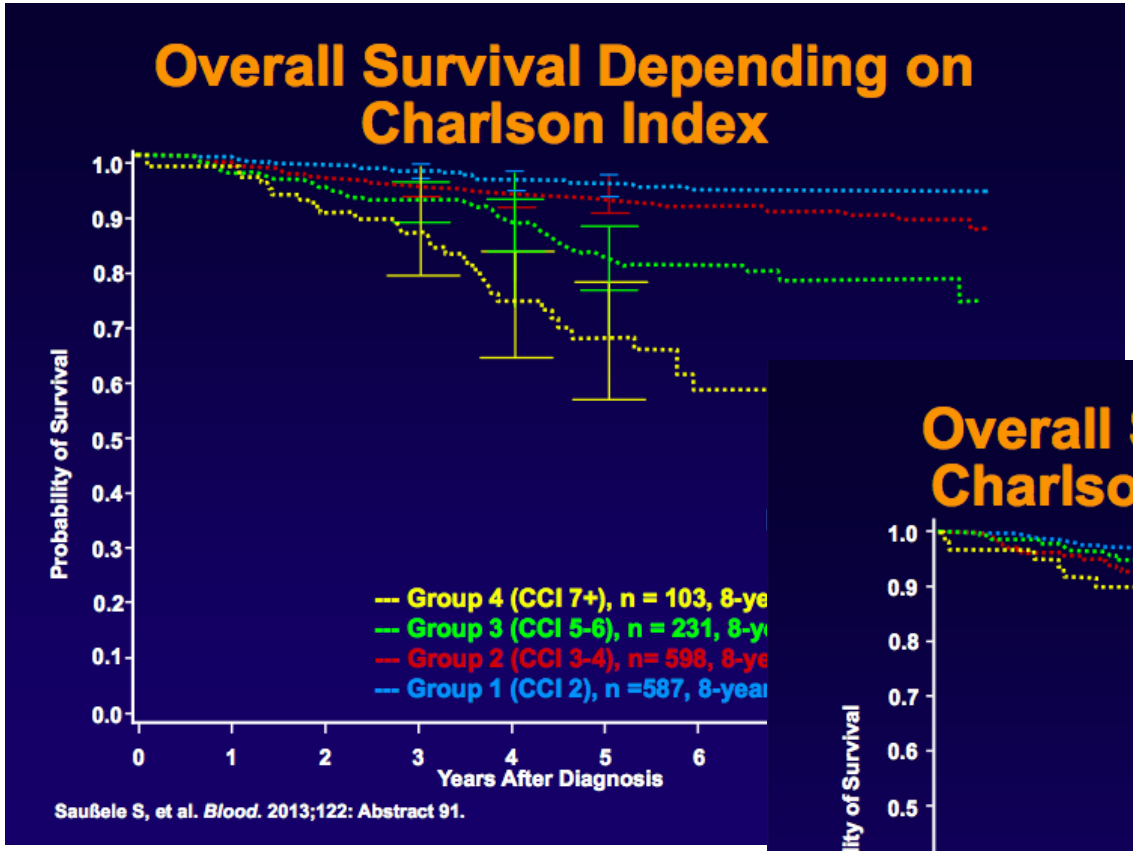
Documented Comorbidities (n = 511)

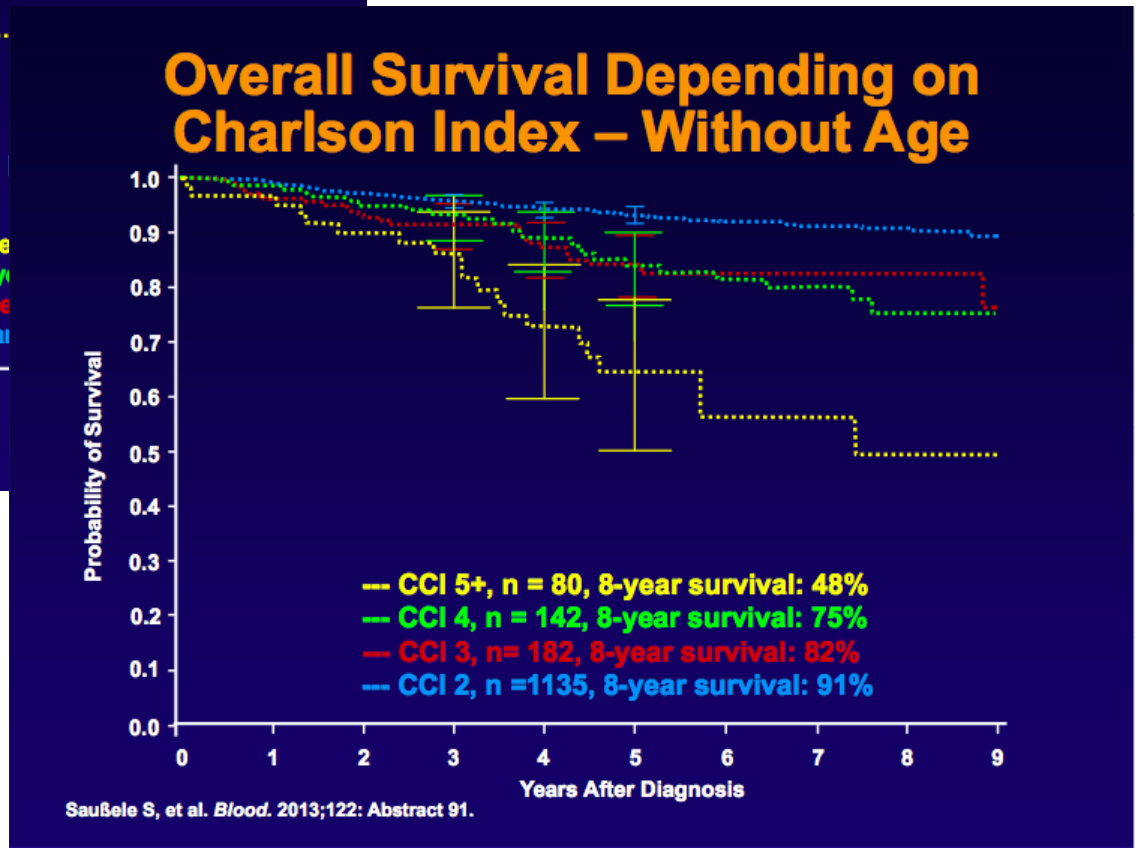


- **511 comorbidities and 384 patients with comorbidity**

Saußele S, et al. *Blood.* 2013;122: Abstract 91.

Outcome is influenced by comorbidities





Saußele S. et al, Blood 2013

Cardiovascular toxicity in CML pts treated with IIGEN-TKIs and identification of risk factors

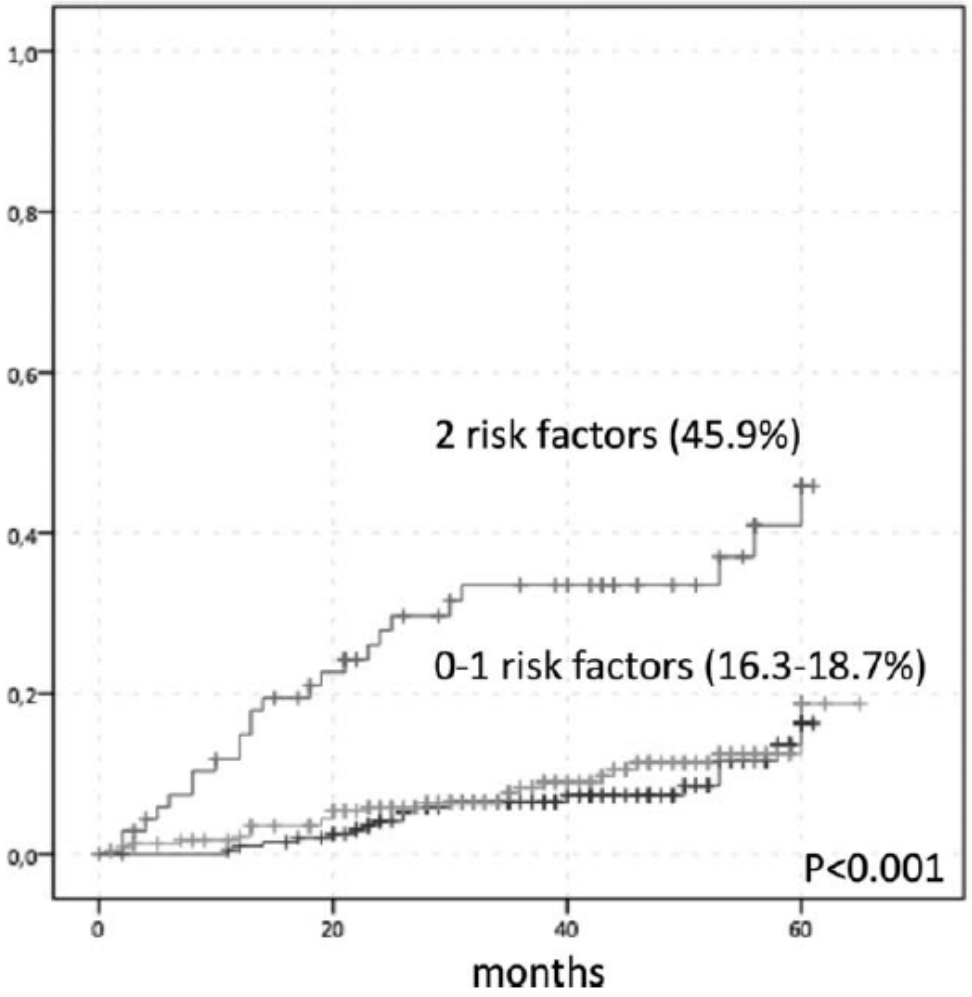


FIGURE 1 Cardio-vascular adverse event incidence in 436 patients with standard risk (0 or 1 risk factor considering a positive anamnesis for CV disease and treatment with 2^{ndG}TKIs administered as second-line or beyond) and 70 patients with high-risk CML- cardiovascular score (both risk factors were present). 2ndGTKI, second-generation tyrosine kinase inhibitor; CML, chronic myeloid leukemia [Color figure can be viewed at wileyonlinelibrary.com]

Caocci G. et al; A.J. Hematol , 2018

Heart - Tyrosine-Kinase Proteins

PDGF-R

- Regulation of interstitial fluid pressure
- Stressed cardiomyocyte repair by hemodinamic overload

→ *EDEMA*

SRC

- Vascular permeability
- Pleural space homeostasis

→ *PLEURAL EFFUSION*

ABL-ARG

- Response to DNA damage
- Protection to oxidative stress

→ *CARDIOMYOCYTE TOXICITY*

VEGF-R

- Angiogenesis,
- Cardiac homeostasis

→ *HYPERTENSION*
HEART FAILURE
THROMBOSIS
ARTERIAL OCCLUSION

TYPES OF CARDIOVASCULAR DAMAGE CAUSED BY TKI

Types of cardiovascular morbidity	Causative factor	Risk of CT- related damage
CHF and LV dysfunction	**Trastuzumab**	**relatively unfrequent**
	Bevacizumab	**rare**
→	**Imatinib**	**rare**
	Sorafenib	**rare**
	Sunitinib	**rare**
Cardiac Ischemia	**Bevacizumab**	**rare**
	Sorafenib	**rare**
→	**Nilotinib**	**relatively unfrequent**
→	**Ponatinib**	**relatively unfrequent**
Hypotension	Alemtuzumab	frequent
	Rituximab	relatively unfrequent
	Cetuximab	**rare**
Hypertension	**Bevacizumab**	**frequent**
	Sorafenib	**frequent**
	Sunitinib	**frequent**
→	**Ponatinib**	**frequent**
	Alemtuzumab	relatively unfrequent
	Rituximab	relatively unfrequent

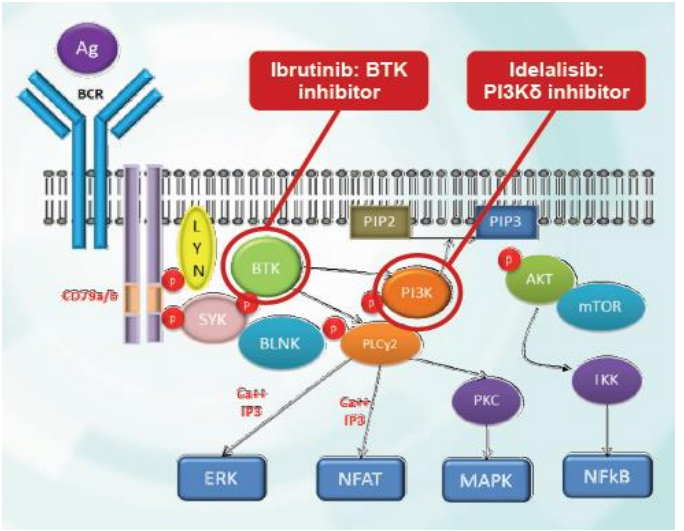
E. Senkus et al: Cancer Treat. Reviews. Vol. 37, Issue 4, 2011

TYPES OF CARDIOVASCULAR DAMAGE CAUSED BY TKI

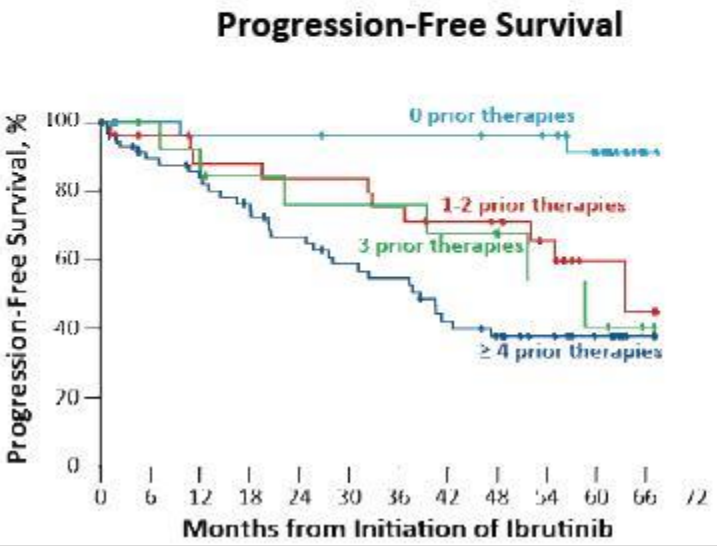
Types of cardiovascular morbidity	Causative factor	Risk of CT- related damage
Arrhythmias and conduction Disorder	Rituximab	rare
Edema	Imatinib	very frequent
QT prolongation or Torsades de Pointes	Sorafenib	relatively unfrequent
	Sunitinib	relatively unfrequent
Thrombo-embolic complications	Bevacizumab	relatively unfrequent
Pericarditis and Pericardial Effusion	Imatinib	relatively unfrequent
	Dasatinib	relatively unfrequent
Pulmonary Hypertnesion	Dasatinib	rare

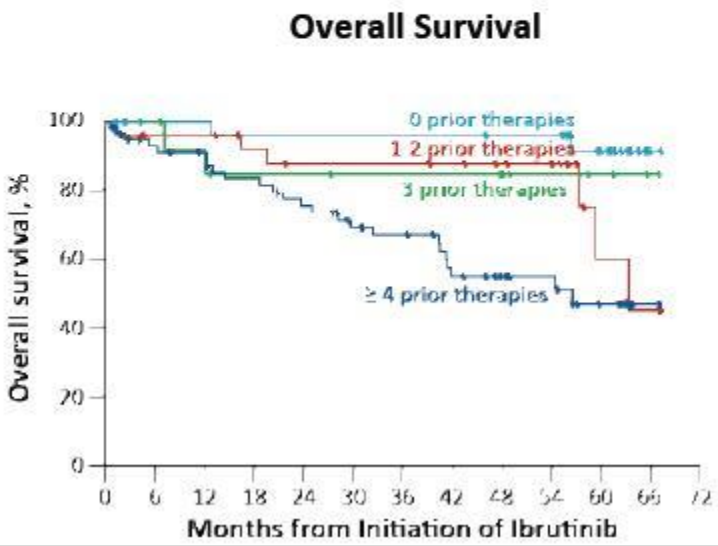
E. Senkus et al: Cancer Treat. Reviews. Vol. 37, Issue 4, 2011

The BTKi IBRUTINIB is the standard of care in untreated del17p or p53 mutated B-LLC or relapsed/refractory B-LLC and MCL and in Waldenstrom Macroglobulinemia.



Ibrutinib Survival by Number of Lines of Prior Therapies





Ibrutinib–Related Atrial Fibrillation (IRAF)

✓ **Reported IRAF incidence of 3.5-7.7%, significantly higher than alternative therapies (0.5-2.4%) or general population**

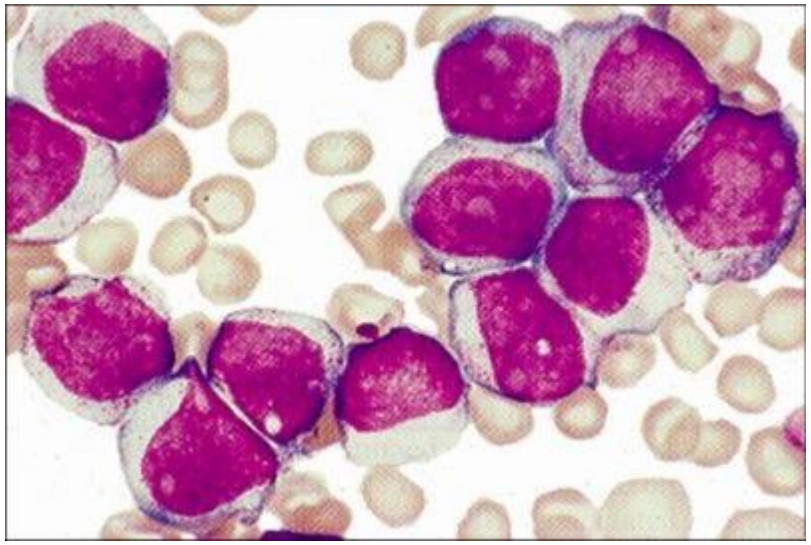
✓ **Median time of onset 3.8 months with >80% of AF events occurring in the first 6 months.**

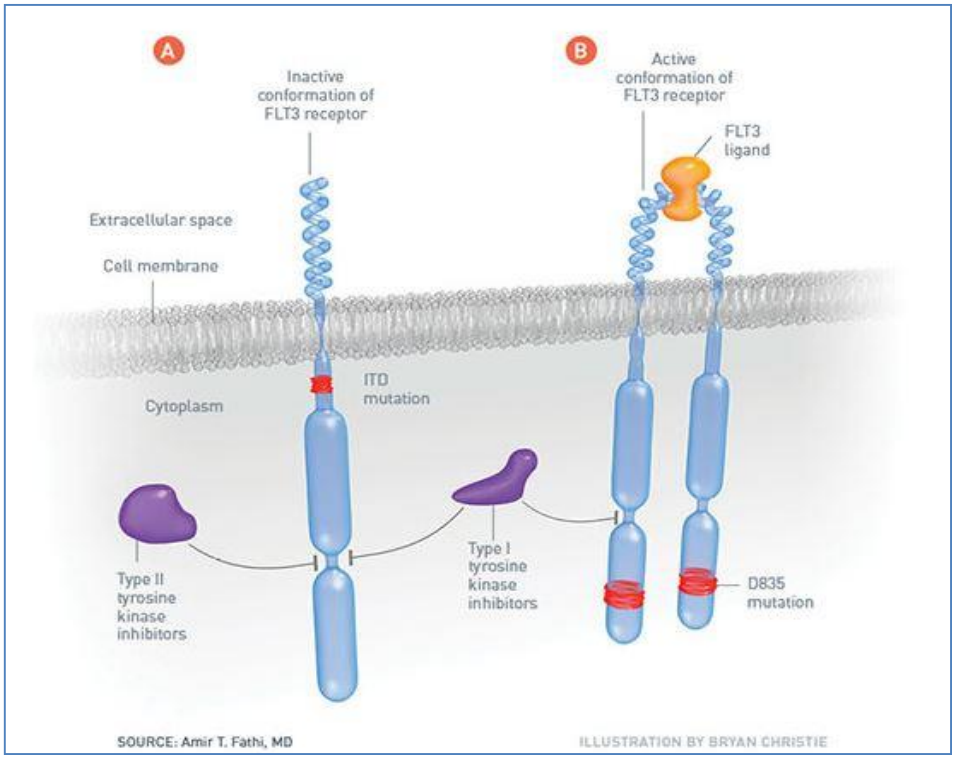
UNCLEAR MECHANISM OF ACTION

- **Both BTK and TEC transcripts were expressed in human heart tissue and were is a higher expression in atrial tissue in AF condition than synus rhytm**
- **BTK and TEC regulate the PI3k-AKT pathway, thas is a critical regulator of cardiac protection under stress condition**
- **Ibrutinib significantly reduced PI3k-AKT activity in cardiac cells**
- **Inhibition of BTK and TEC kinases, that leads to decreased PI3k-AKT signalling, is one potential explanation of IRAF**

McMullen JR, et al; Blood, 2014
Thompson PA, et al; BJH, 2016

FLT3 Mutation in AML





- **The mutation FLT3-ID is observed in 30% of the cases of AML and it is associated with poor prognosis do to higher rate of relapse**

- **FLT3-ITD mutation lead to activation of FLT3 TK and is a potential therapeutic target.**

Pemmaraju N et al, Cancer 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner

N ENGL J MED 377;5 NEJM.ORG AUGUST 3, 2017

Induzione, consolidamento e mantenimento	Intervallo QTc >470 ms e ≤500 ms	Diminuire Rydapt a 50 mg una volta al giorno per il resto del ciclo. Riprendere Rydapt alla dose iniziale nel ciclo successivo a condizione che l'intervallo QTc migliori fino a ≤470 ms all'inizio di quel ciclo. Altrimenti continuare Rydapt 50 mg una volta al giorno.
	Intervallo QTc >500 ms	Sospendere o interrompere temporaneamente Rydapt per il resto del ciclo. Se il QTc migliora a ≤470 ms appena prima del ciclo successivo, riprendere Rydapt alla dose iniziale. Se l'intervallo QTc non è migliorato in tempo per iniziare il ciclo successivo non somministrare Rydapt durante tale ciclo. Rydapt può essere sospeso per il numero di cicli necessario fino a miglioramento del QTc.

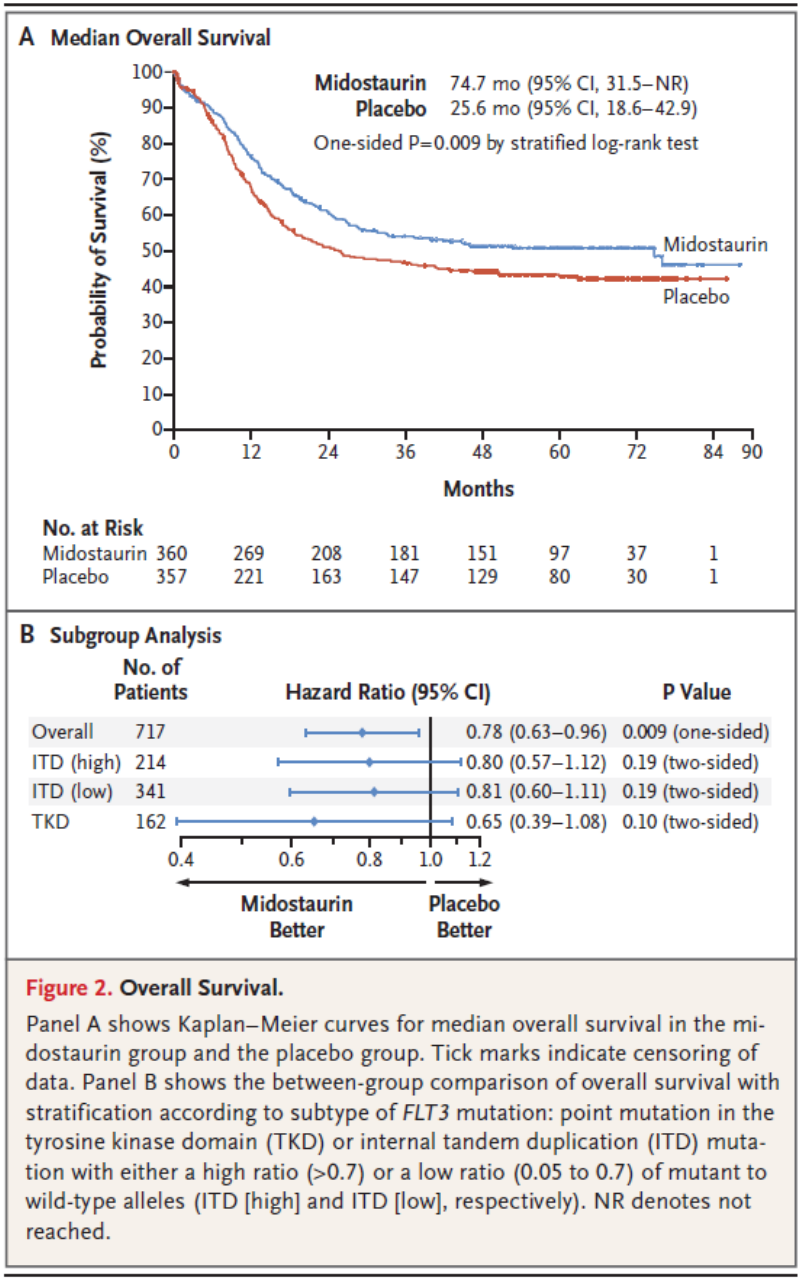
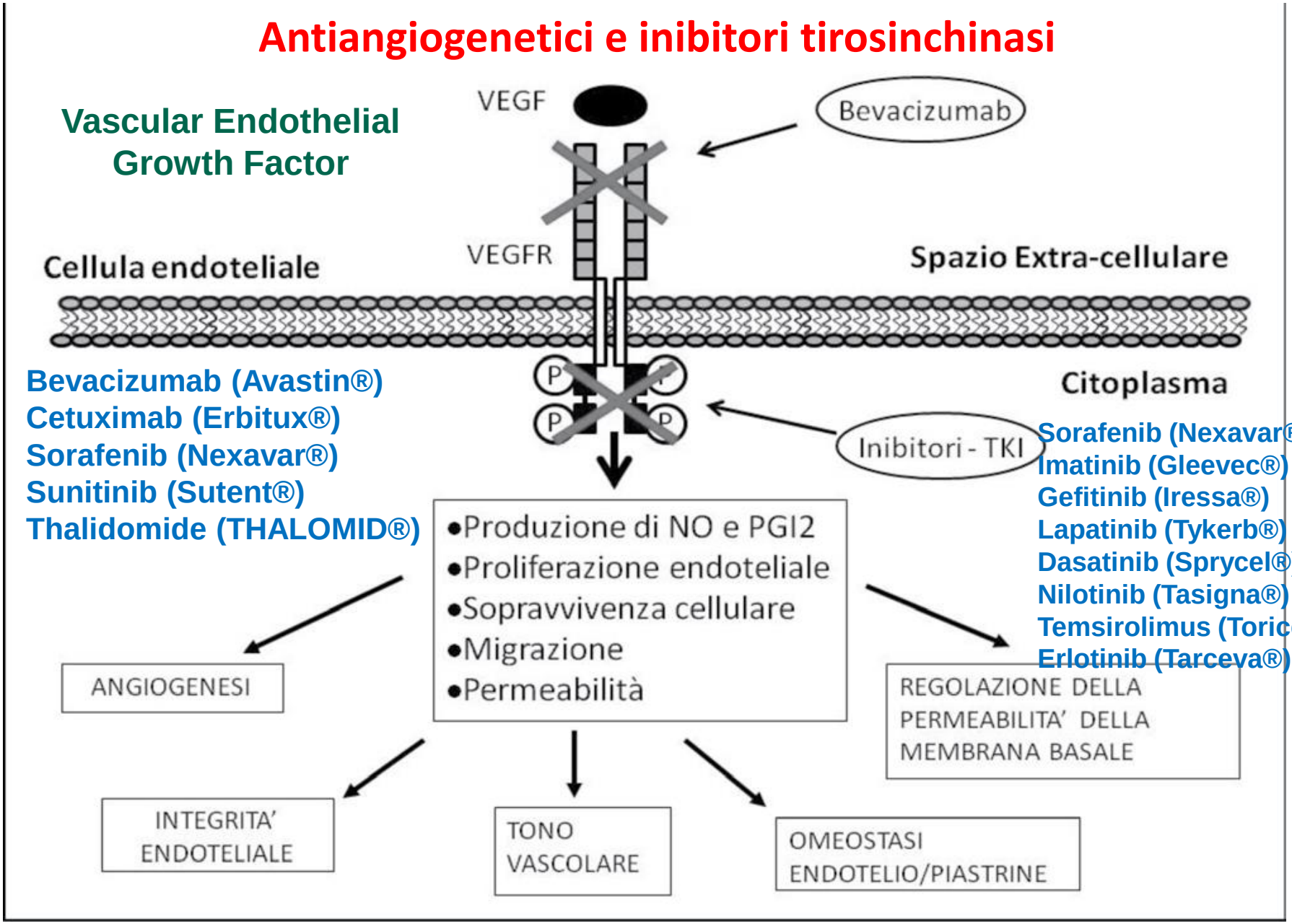


Figure 2. Overall Survival.

Panel A shows Kaplan–Meier curves for median overall survival in the midostaurin group and the placebo group. Tick marks indicate censoring of data. Panel B shows the between-group comparison of overall survival with stratification according to subtype of *FLT3* mutation: point mutation in the tyrosine kinase domain (TKD) or internal tandem duplication (ITD) mutation with either a high ratio (>0.7) or a low ratio (0.05 to 0.7) of mutant to wild-type alleles (ITD [high] and ITD [low], respectively). NR denotes not reached.

Antiangiogenetici e inibitori tirosinchinasi



Grazie a M Mistrangelo

Cardiotoxicity with VEGF Inhibitor therapy

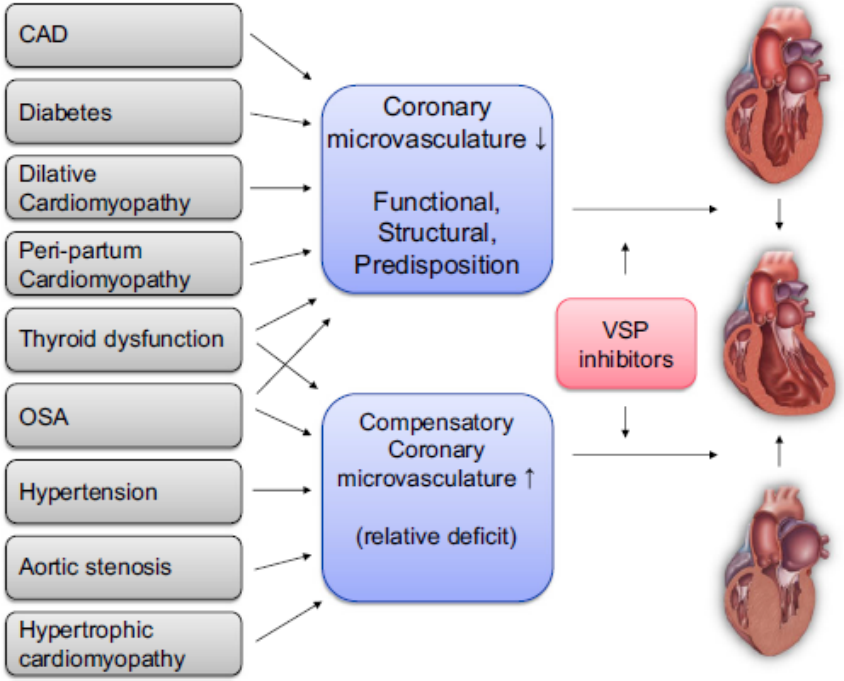


Fig. 4 Conceptual outline of the vascular nature of VSP inhibitor cardiotoxicity. Outline of the concept of absolute or relative and structural or functional coronary microvascular deficit and cardiomyopathy with VSP inhibitor therapy

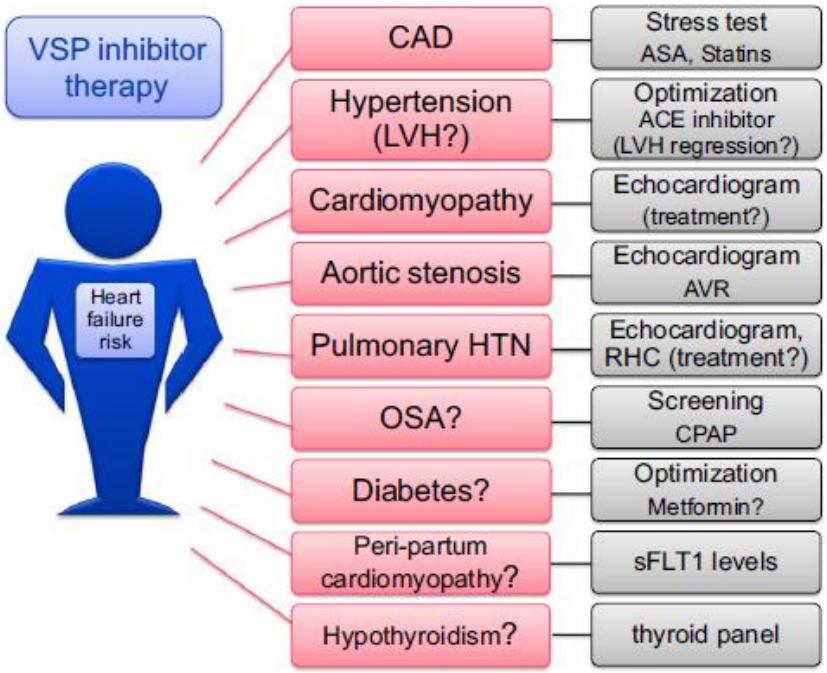


Fig. 5 Comorbidities contributing to the vascular nature of VSP inhibitor cardiotoxicity. Illustration of the comorbidities to consider and to screen for in patients who are considered for VSP therapy matching the pathophysiological concept introduced in Fig. 4

Touyz R.M. NPJPrec Oncol 2018

Cardiovascular Side Effects of Proteasome Inhibitors

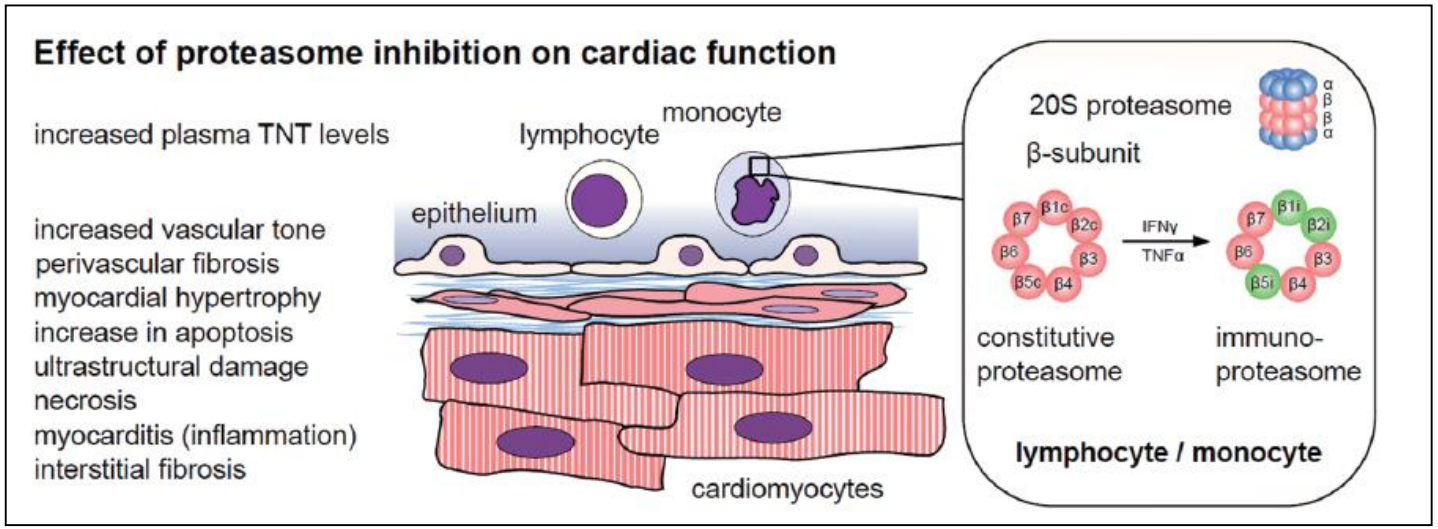
Table 1 Selected published clinical trials on EMA and FDA approved proteasome inhibitors in multiple myeloma

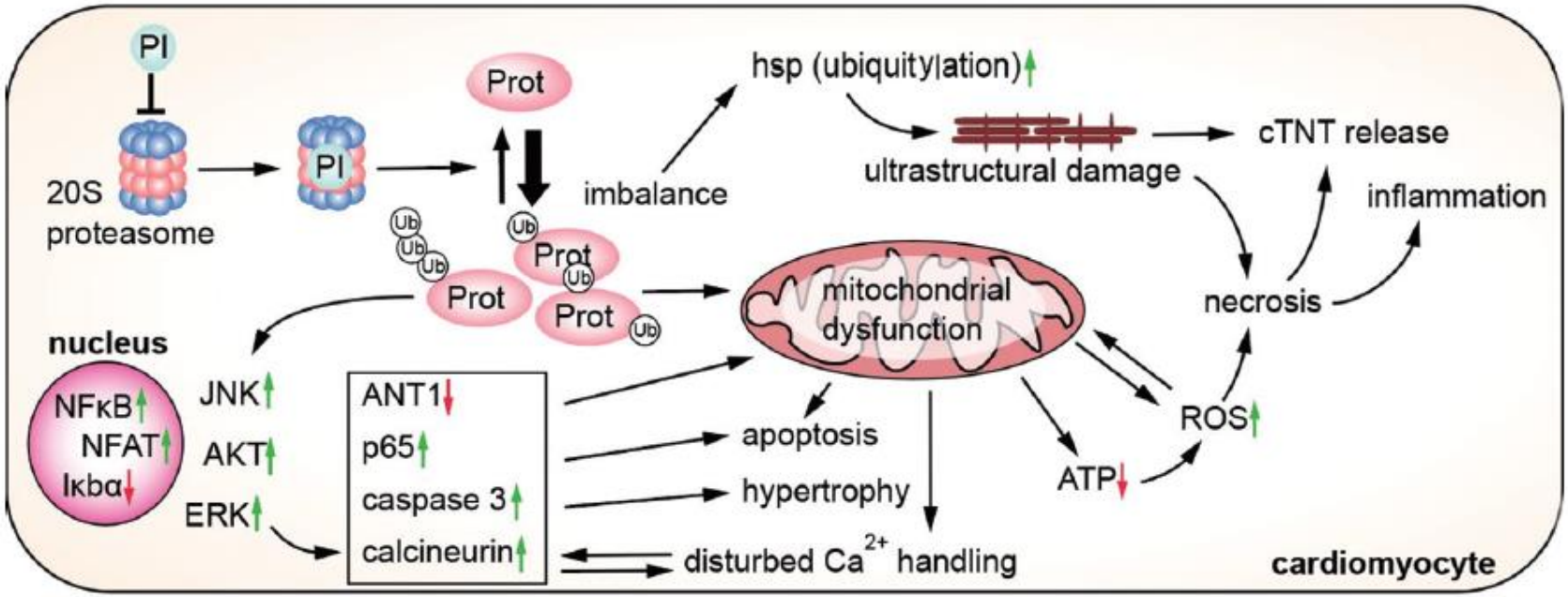
Proteasome inhibitor	Acronym	Phase	No. subjects	Clinical setting	Treatment	ORR	Cardiovascular adverse events	Ref.
Bortezomib	Summit	II	196	Relapsed MM	BTZ	35%	Not reported/ measured	(5)
Bortezomib	APEX	III	669	Relapsed MM	BTZ *vs.* Dexa	38% *vs.* 18%	Cardiac events 15% *vs.* 13%; heart failure 2% in both groups	(6)
Bortezomib	MMVAR/IFM 2005-04	III	269	Relapsed MM after AT	BTZ + TH + Dexa *vs.* TH + Dexa	56% *vs.* 35%	Cardiac grade 3 and 4 adverse events: 1.5% *vs.* 0.7%	(10)
Bortezomib	HOVON-65/ GMMG-HD4	III	827	Newly diagnosed MM	BTZ + Doxo + Dexa *vs.* Vinc + Doxo + Dexa	36% *vs.* 24%	Not reported/ measured	(11)
Bortezomib	–	II	64	Relapsed/ refractory MM	BTZ + LEN + Dexa	64%	Atrial fibrillation 3%; Hypotension 2%; venous thromboembolism 3%	(12)
Carfilzomib	–	II	50	Relapsed/ refractory MM	CFZ	26%	Congestive heart failure 6%; no notable changes on ECG	(13)
Carfilzomib	ASPIRE	III	792	Relapsed MM	CFZ + Len + Dexa *vs.* Len + Dexa	87% *vs.* 67%	Hypertension 14.3% *vs.* 6.9%; cardiac failure 6.4% *vs.* 4.1%; ischemic heart disease 5.9% *vs.* 4.6%	(8)
Carfilzomib/ Bortezomib	ENDEAVOR	III	929	Relapsed/ refractory MM	CFZ + Dexa *vs.* BTZ + Dexa	54% *vs.* 29%	Hypertension 24.8% *vs.* 8.7%; cardiac failure 8.2% *vs.* 2.8%; ischemic heart disease 2.6% *vs.* 1.9%; LVEF only measured in sub-study of 151 patients	(9)
Carfilzomib	FOCUS	III	315	Relapsed/ refractory MM	CFZ *vs.* corticosteroids	19% *vs.* 11%	Hypertension 15% *vs.* 6%; cardiac failure 5% *vs.* 1%	(14)
Ixazomib	TOURMALINE-MM1	III	722	Relapsed/ refractory MM	IXZ + Len + Dexa *vs.* Len + Dexa	78% *vs.* 72%	Hypertension 6% *vs.* 5%; hypotension 6% *vs.* 6%; venous thromboembolism 8% *vs.* 11%; heart failure 4% *vs.* 4%; arrhythmia 16% *vs.* 15%; myocardial infarction 1% *vs.* 2%	(15)

MM, multiple myeloma; BTZ, bortezomib; Dexa, dexamethasone; TH, thalidomide; Vinc, vincristine; Doxo, doxorubicin; Len, lenalidomide; CFZ, carfilzomib; IXZ, ixazomib; ORR, overall response rate; EMA, European Medicines Agency; FDA, Food and Drug Administration.

Heckmann M.B. et al, J. Thorac. Dis, 2018

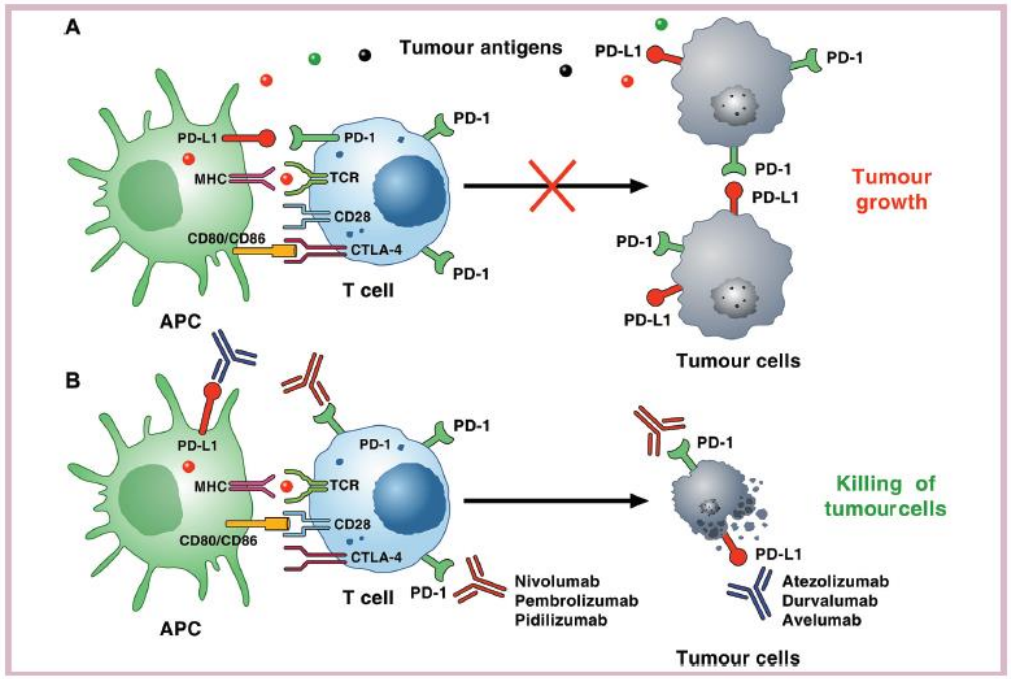
Cardiovascular Side Effects of Proteasome Inhibitors



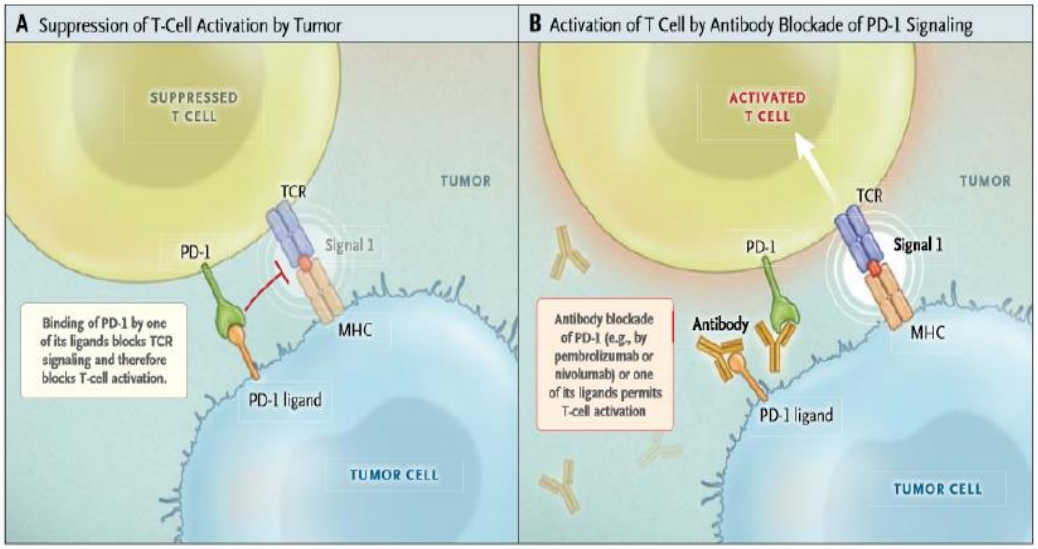


Heckmann M.B. et al, J. Thorac. Dis, 2018

Immune Checkpoint Inhibitors for cancer therapy: cHL



- PD-1 ligands are overexpressed in inflammatory environment and attenuate the immune response via PD-1 on immune effector cells
- PD-L1 expressed on malignant cells and/or in the tumor microenviroment suppressed tumor infiltrating lymphocyte activity

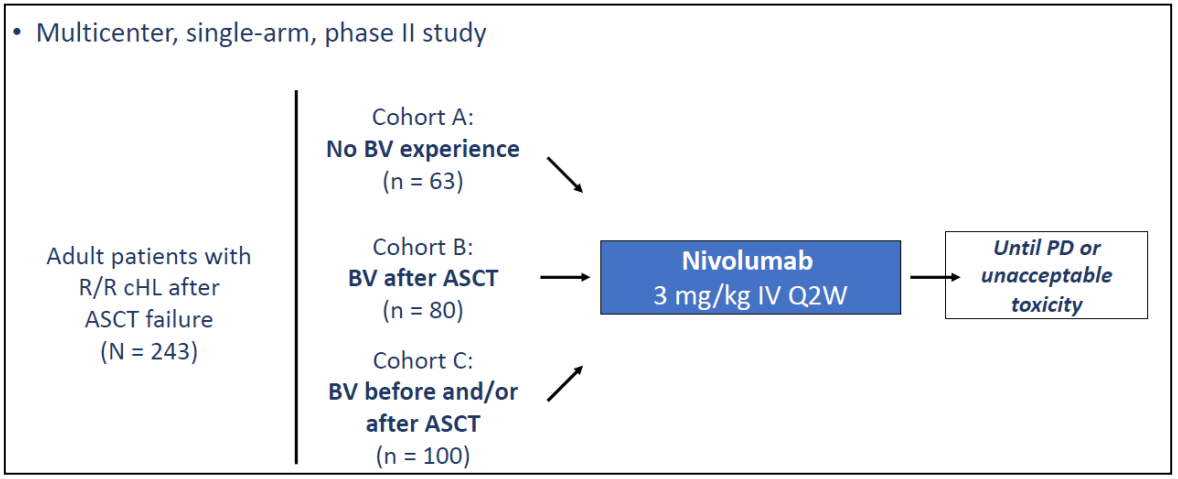


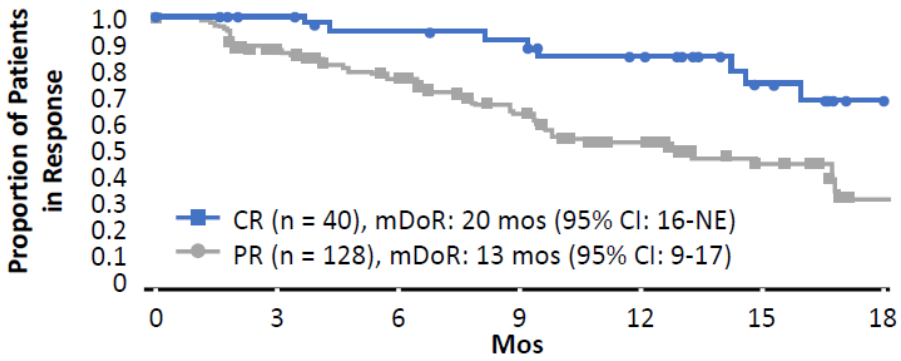
Classical HL may be vulnerable to PD-1 blockade:

- PD-1 ligand are overexpressed in Red Stemberg cells of c HL
- Amplification of 9p24 upregulate the genes for PD-1 ligands and activates JAK-STAT which further induces PD-1 ligand
- EBV infection increase PD-1 ligand in EBV+ cHL

CheckMate 205: NIVOLUMAB for relapsed/refractory cHL after ASCT

Armand et al J.Clin .Oncol. 2018



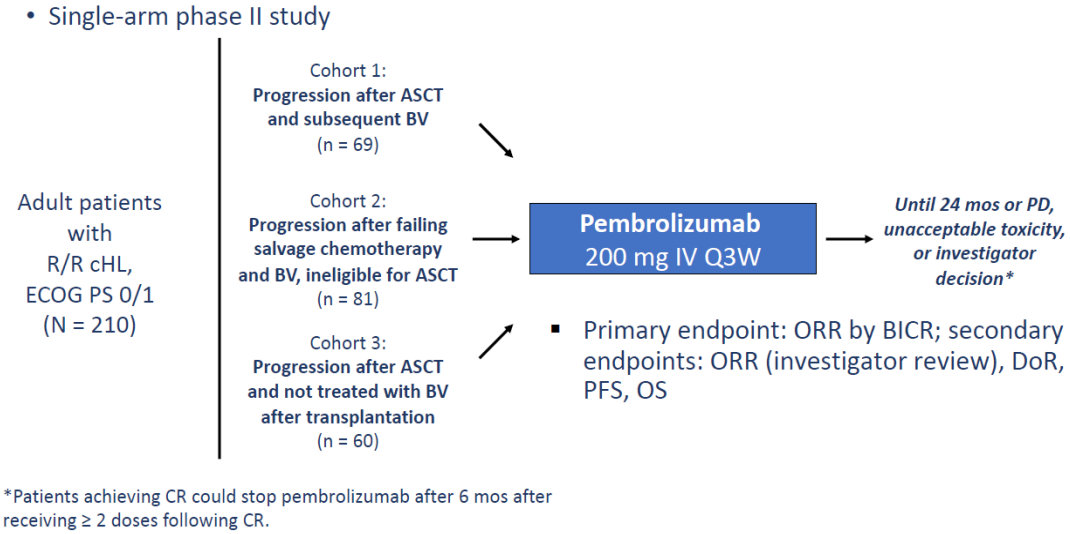


- ORR (investigator): 72% (CR: 33%)
- Post hoc analyses: similar responses regardless of treatment sequence

Median DoR, Mos (95% CI)	Cohort A BV Naive (n = 63)	Cohort B BV After ASCT (n = 80)	Cohort C BV Before and/or After ASCT (n = 100)	Overall (N = 243)
In all responders	20 (13-20)	16 (8-20)	15 (9-17)	17 (13-20)
In CR patients	20 (NE-NE)	20 (4-NE)	15 (8-NE)	20 (16-NE)
In PR patients	17 (9-NE)	11 (7-18)	13 (9-17)	13 (9-17)

KEYNOTE-087: PEMBROLIZUMAB for relapsed/refractory cHL

Chen et al J.Clin .Oncol. 2017

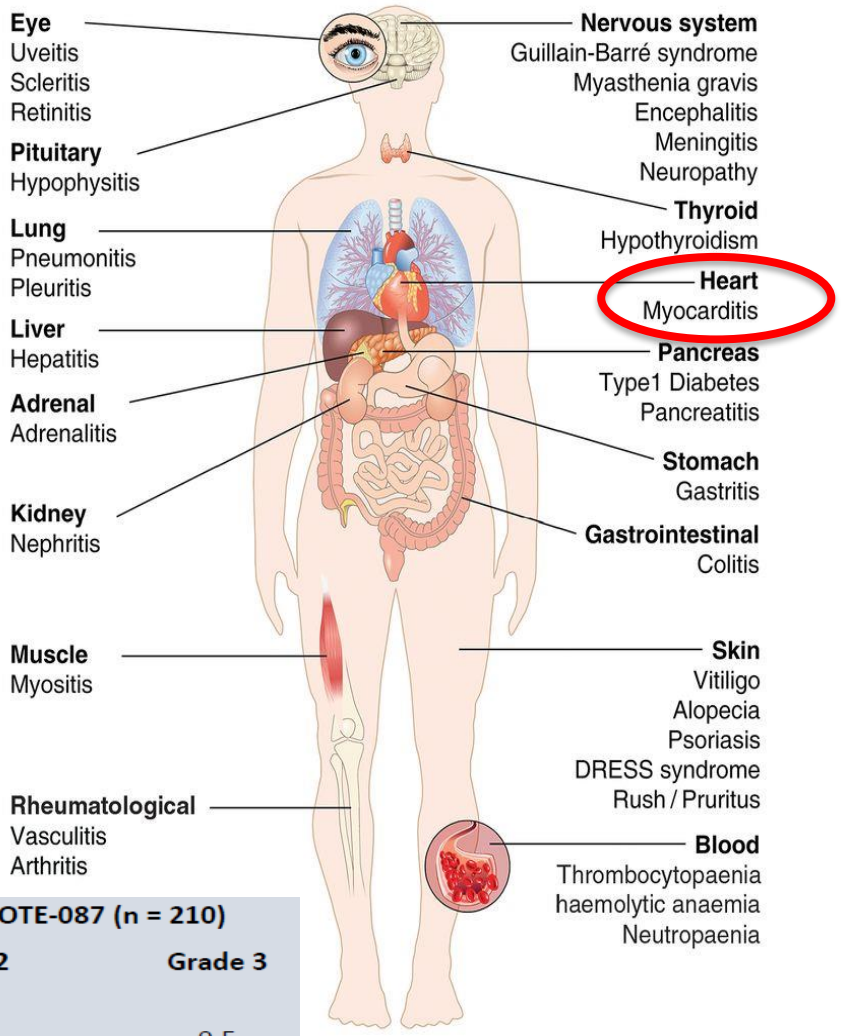


Response	Cohort 1 After ASCT/BV (n = 69)		Cohort 2 ASCT Ineligible/BV Failure (n = 81)		Cohort 3 No BV After ASCT (n = 60)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
ORR	51 (73.9)	61.9-83.7	52 (64.2)	52.8-74.6	42 (70.0)	56.8-81.2
▪ CR	15 (21.7)	12.7-33.3	20 (24.7)	15.8-35.5	12 (20.0)	10.8-32.3
▪ PR	36 (52.2)	39.8-64.4	32 (39.5)	28.8-51.0	30 (50.0)	36.8-63.2
SD	11 (15.9)	8.2-26.7	10 (12.3)	6.1-21.5	10 (16.7)	8.3-28.5
PD	5 (7.2)	2.4-16.1	17 (21.0)	12.7-31.5	8 (13.3)	5.9-24.6
Unable to determine	2 (2.9)	0.4-10.1	2 (2.5)	0.3-8.6	0	--

Current Approved Indications for PD-1 Inhibitors in Relapsed/Refractory HL

AGENT	INDICATIONS
NIVOLUMAB Dosing: 240 mg/2 w or 480 mg/4w	▪ Adult pts with relapsed/refractory disease after ASCT and brentuximab vedotin ▪ Adult pts with relapsed/refractory disease after ≥ 3 lines of sistemic therapy including ASCT
PEMBROLIZUMAB Dosing: 200 mg/3w(adult pts) or 2mg/Kg /3 w (pediatric pts)	▪ Adult or pediadric pts with refractory disease or who have relapsed after ≥ lines of therapy

Immune-related adverse effects (IRAEs) associated with checkpoints inhibitors in patients with cancer.



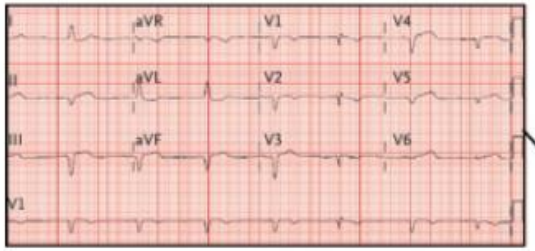
Adverse Event, %	CheckMate 205 (n = 80)		KEYNOTE-087 (n = 210)	
	Grade 1/2	Grade 3	Grade 1/2	Grade 3
Fatigue	25	0	8.6	0.5
Hypothyroidism	NR	NR	11.9	0.5
Pyrexia	14	0	10.0	0.5
Rash	15	1	7.6	0
Diarrhea	10	0	6.2	1.0
Nausea	13	0	5.7	0
Pruritus	10	0	3.8	0

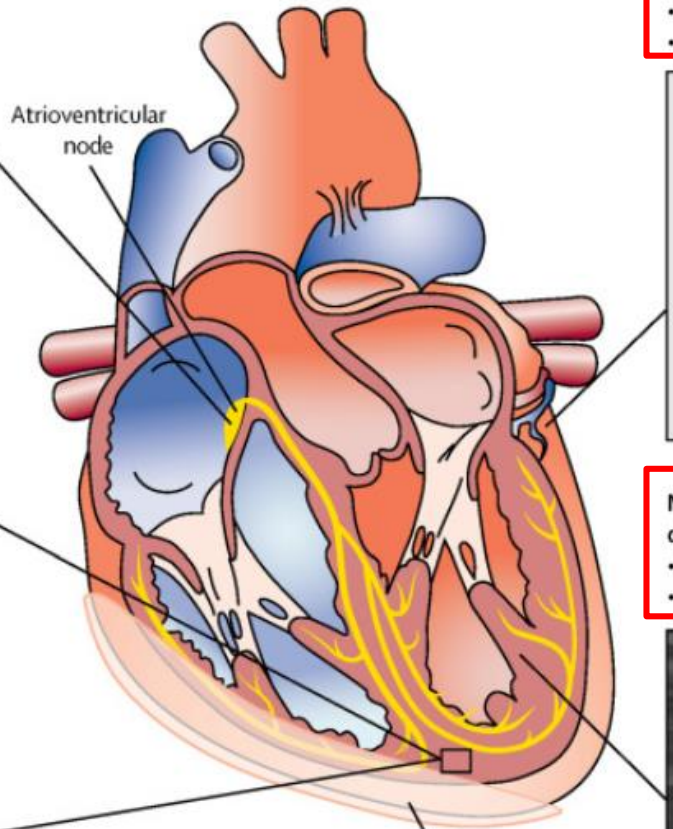
Younes et al. Lancet Oncol. 2016
Chen D-Y et al J. Clin. Ooncol. 2017

Cardiotoxicity for immune checkpoint inhibitors

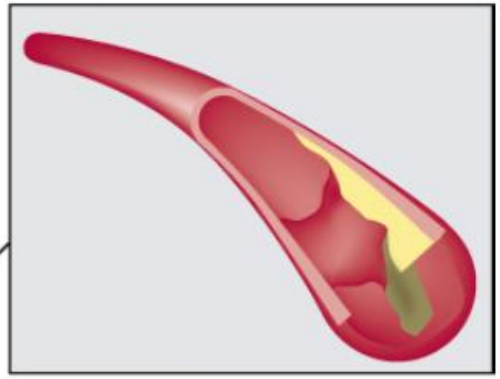
Incidence rare

Conduction disease
- Atrioventricular block

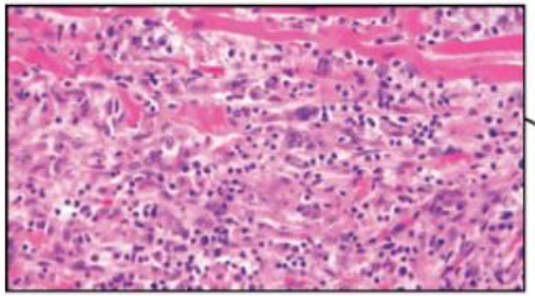


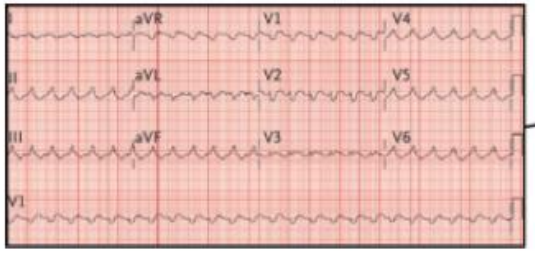


Coronary artery disease
- Atheriosclerotic plaque rupture
- Acute myocardial infarction
- Coronary vasculitis

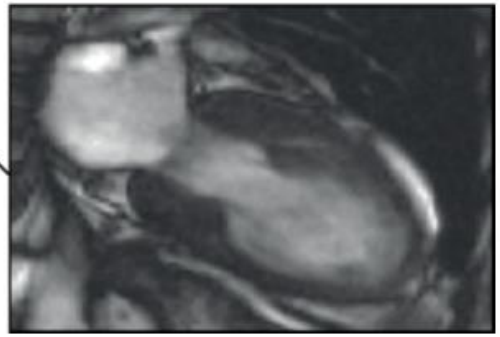


Myocarditis
- Heart failure
- Ventricular arrhythmias





Non-inflammatory left ventricular dysfunction
- Heart failure
- Takotsubo syndrome



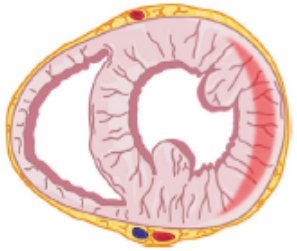
Pericarditis
- Effusion
- Tamponade

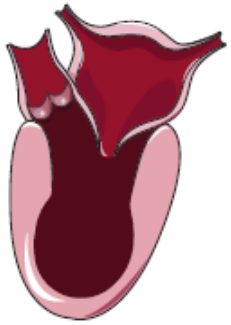
Incidence 0.1-1%
Fatal rate 27-46%
Early phase: 14-34 days after start therapy

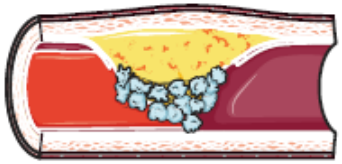
Incidence 7-13% of all respective studies
Fatal rate 21%

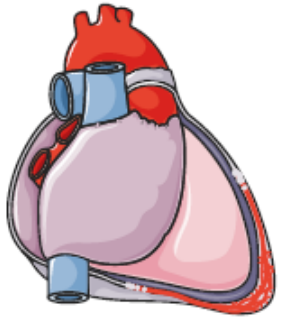
Takotsubo s.: Incidence rare in retrospective studies

Cardiotoxicity from immune checkpoint inhibitors





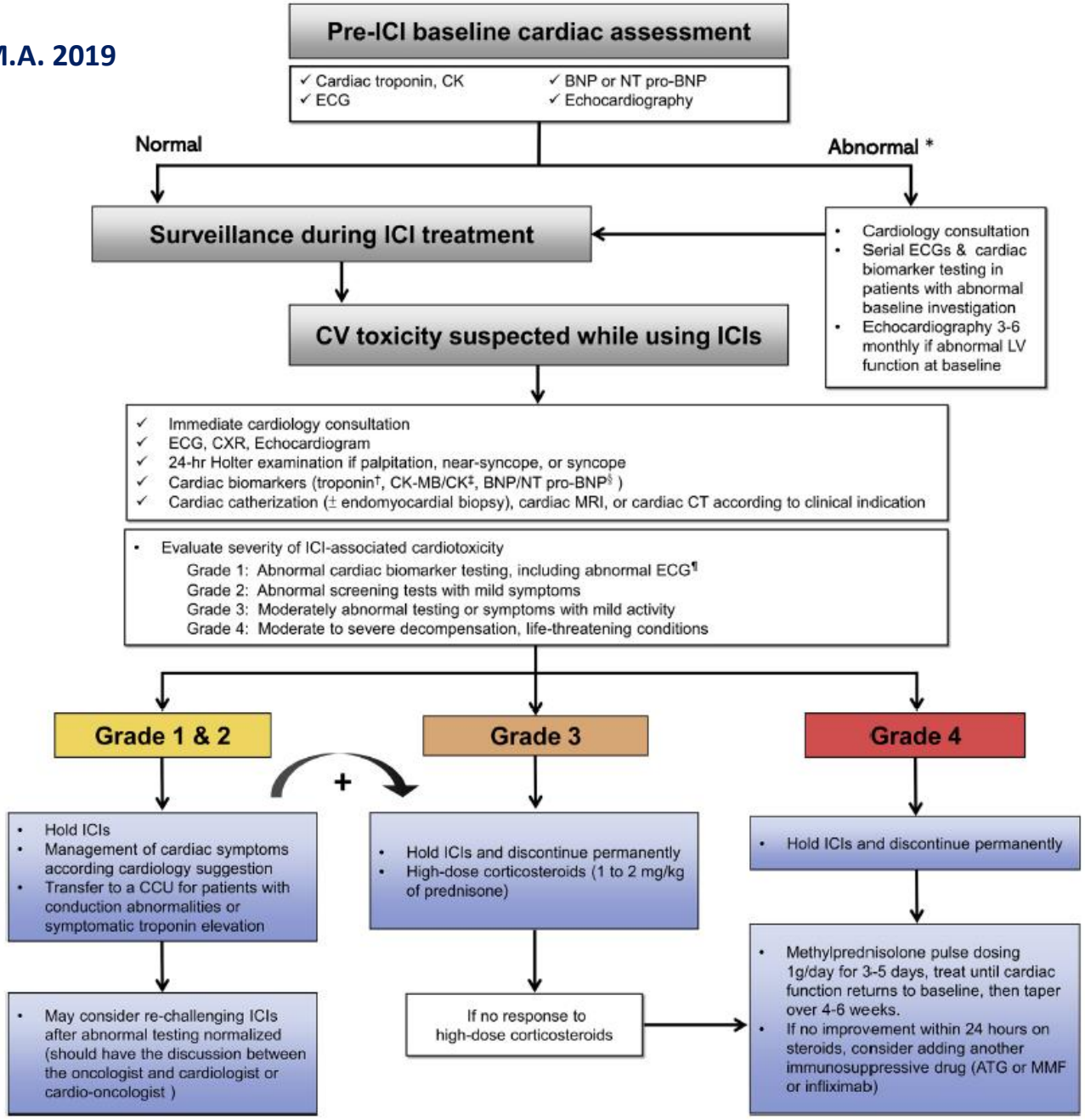




	Myocarditis	Takotsubo syndrome	ACS	Pericardial disease
Diagnosis	• ECG • Echocardiography including strain analysis • Troponin, NT-proBNP • Chest X-ray • CMR	• Echocardiography • Troponin, NT-proBNP • CMR • Exclusion of ACS according to ESC and AHA guidelines	• ECG • Troponin • Diagnostic algorithm according to ESC and AHA guidelines	• Echocardiography • CMR • Evaluation of myocarditis • Cardiac fluid pathology • Monitor pericardial effusion
Treatment	• Stop ICI therapy permanently • Prednisone adapted to severity (up to 1 g daily) • No response: consider mycophenolate mofetil, infliximab, antithymocyte globulin	• Stop ICI therapy initially • Prednisone 1 g daily • Avoid QT-prolonging drugs	• Treatment according to ESC and AHA guidelines • Stop ICI therapy initially • Consider ICI therapy rechallenge >30 days in stable patient • Consider prednisone in case of coronary vasculitis	• Pericardiocentesis when indicated • Stop ICI therapy initially • 500-1000 mg prednisone daily • Consider colchicin, NSAIDs • Consider ICI therapy rechallenge after recovery

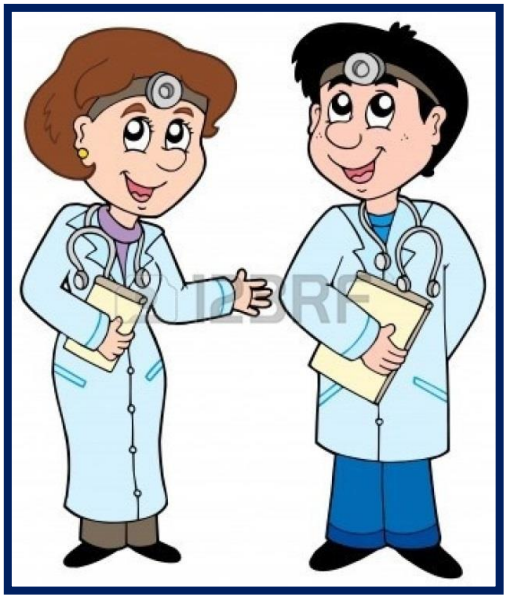
Cardiotoxicity for immune checkpoint inhibitors

Chen D-Y et al J.of F.M.A. 2019



The management of cardiotoxicity in onco-hematology

rete oncologica
PIEMONTE | VALLE D'AOSTA
si prende cura di te



- ✓ Cardiovascular assessment study group
- ✓ Long-term patient monitoring study group: toxicity of anticancer therapies

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

THANK YOU

ppregno@cittadellasalute.to.it