FAKULTNÍ NEMOCNICE OLOMOUC

Lékařská fakulta Univerzity Palackého v Olomouci

Kardiovaskulární toxicita u urologických malignit

MUDr. Hana Študentová, Ph.D.

Obsah

- Toxicita onkologické terapie
- Pozdní následky onkologické terapie

Kardiovaskulární toxicita onkologické terapie

- Arteriální hypertenze
- Srdeční selhání
- Ischemické komplikace
- Prodloužení QT intervalu
- Arytmie

Rizikové faktory kardiovaskulární toxicity

Individuální rizikové faktory

- Kouření
- Arteriální hypertenze
- Diabetes mellitus
- Dyslipidémie
- Obezita
- Věk (› 60 let)
- KV anamnéza

S léčbou související rizikové faktory

- Antracykliny
- Radioterapie
- Monoklonální protilátky
- TKI

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii155–vii166, 2012
doi:10.1093/annonc/mds293

Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines†

G. Curigliano[1], D. Cardinale[2], T. Suter[3], G. Plataniotis[4], E. de Azambuja[5], M. T. Sandri[6], C. Criscitiello[1], A. Goldhirsch[1], C. Cipolla[2] & F. Roila[7], on behalf of the ESMO Guidelines Working Group*

Srdeční selhání

Lék		Četnost
antracykliny	kardiomyopatie	3-26 % (≤ 550 mg/m2) Akutní 1 % 1 rok po skončení terapie
alkylační látky (CFM)	dysfunkce LK perikardiální výpotek myoperikarditida	7 –28 % Dávkově závislé (≥ 1,5 g/m2/den)
Inhibitory polymerizace mikrotubulů	Městnavé srdeční selhání	0,7 % -1,6 % Závisí na dalších lécích
Monoklonální protilátky a cílená léčby	Srdeční selhání	3-34 %
Inhibitory tyrosinkináz (HER2 – EGFR)		1,4 % symptomatické srdeční selhání ≥10 % asymptomatický pokles LVEF

Curigliano et al. AnnalsOncol 2012; 23 (7)

Srdeční ischemie

Lék		Četnost
Antimetabolity (5-FU)	Srdeční ischemie Koronární trombóza Arteritida, Vasospasmus	1 –68 % (během 2-5 dní od zahájení terapie)
Inhibitory polymerizace mikrotubulů (paclitaxel)	Myokardiální ischemie	5 %
Aromatázové inhibitory	IM Srdeční selhání	0,5 %
Cílená léčba (TKI – sunitinib)	Mírný vzestup troponinu	18 %

Curiglianoet al. AnnalsOncol2012; 23 (7)

review

Annals of Oncology 22: 257–267, 2011
doi:10.1093/annonc/mdq609
Published online 18 October 2010

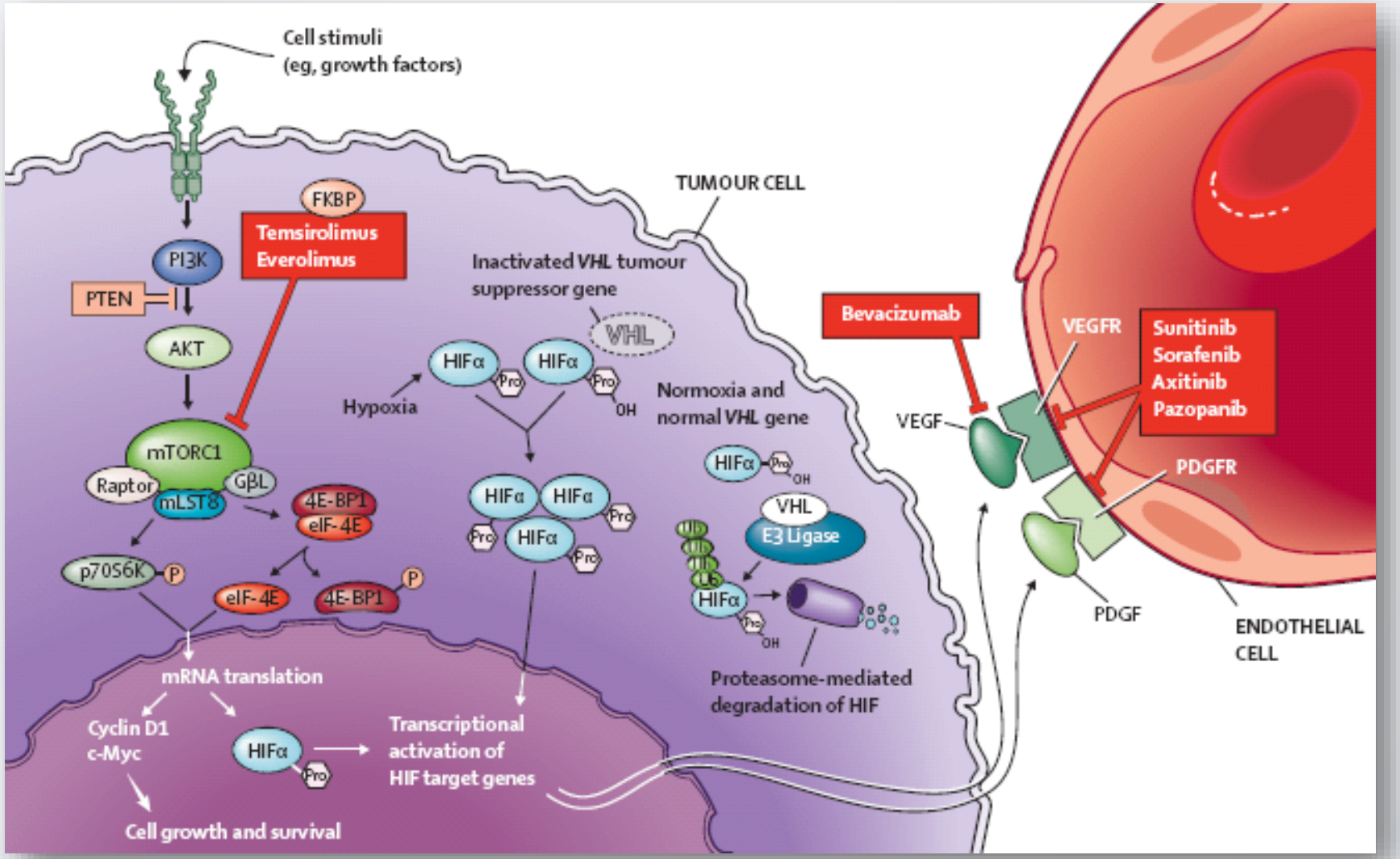
Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper

M. Aapro[1], C. Bernard-Marty[2], E. G. C. Brain[3*], G. Batist[4], F. Erdkamp[5], K. Krzemieniecki[6], R. Leonard[7], A. Lluch[8], S. Monfardini[9], M. Ryberg[10], P. Soubeyran[11] & U. Wedding[12]

[1]Institut Multidisciplinaire d'Oncologie, Clinique de Genolier, Genolier, Switzerland; [2]Department of Medical Oncology, Institut Claudius Regaud, Toulouse; [3]Department of Medical Oncology, Institut Curie/Hôpital René Huguenin, Saint-Cloud, France; [4]Department of Oncology, McGill University, Montreal, Canada; [5]Department of Internal Medicine, Maasland Hospital, Sittard, The Netherlands; [6]Department of Oncology, Jagiellonian University, Krakow, Poland; [7]Department of Cancer Services and Clinical Haematology, Charing Cross Hospital, London, UK; [8]Department of Haematology and Medical Oncology, University Hospital of Valencia, Valencia, Spain; [9]Department of Medical Oncology, Istituto Oncologico Veneto, Padova, Italy; [10]Department of Medical Oncology, Herlev Hospital, Herlev, Denmark; [11]Department of Medical Oncology, Institut Bergonié, Bordeaux, France; [12]Klinik für Innere Medizin II, University Clinic Jena, Jena, Germany

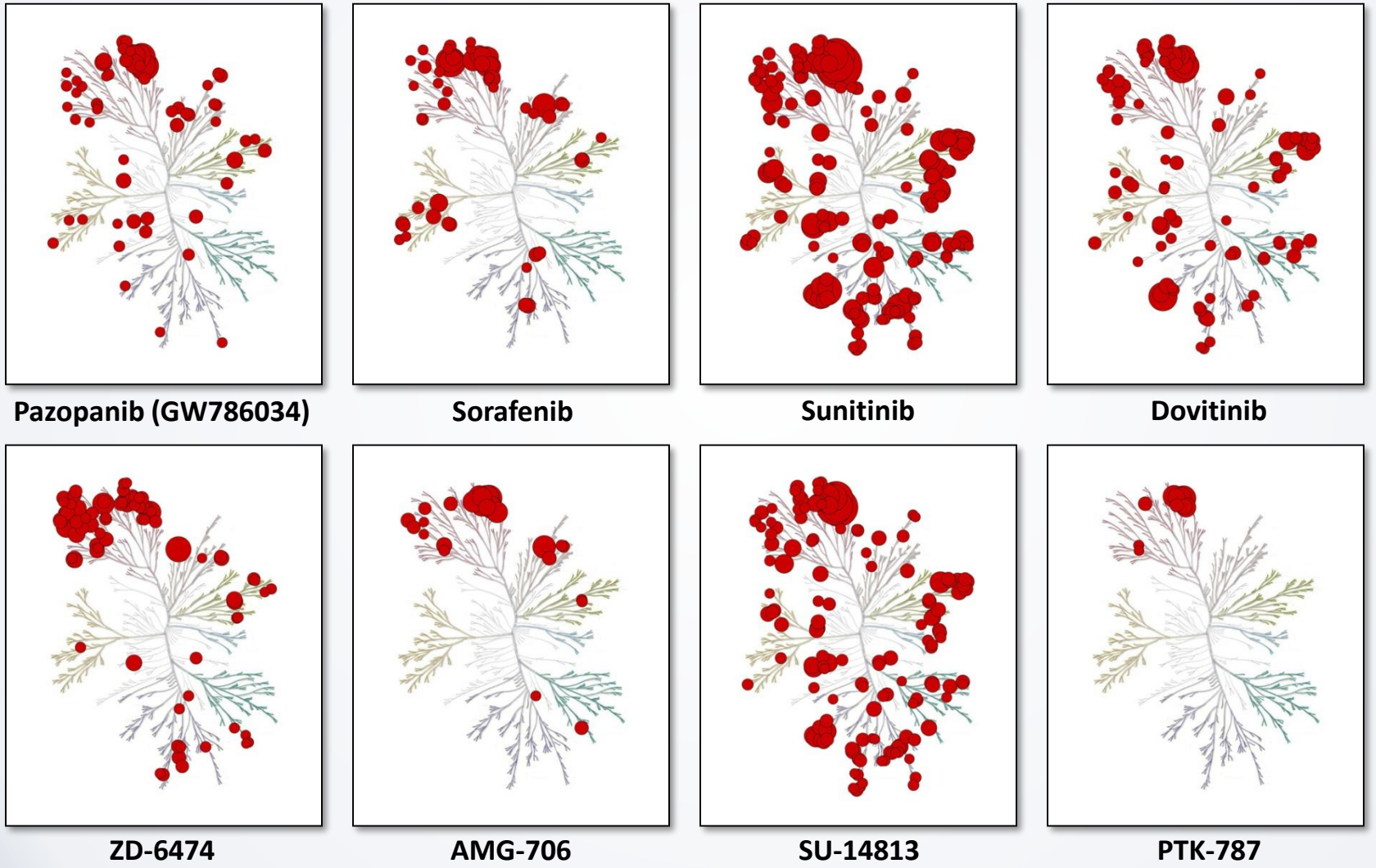
Toxicita cílené terapie

Mechanismy účinku cílené terapie



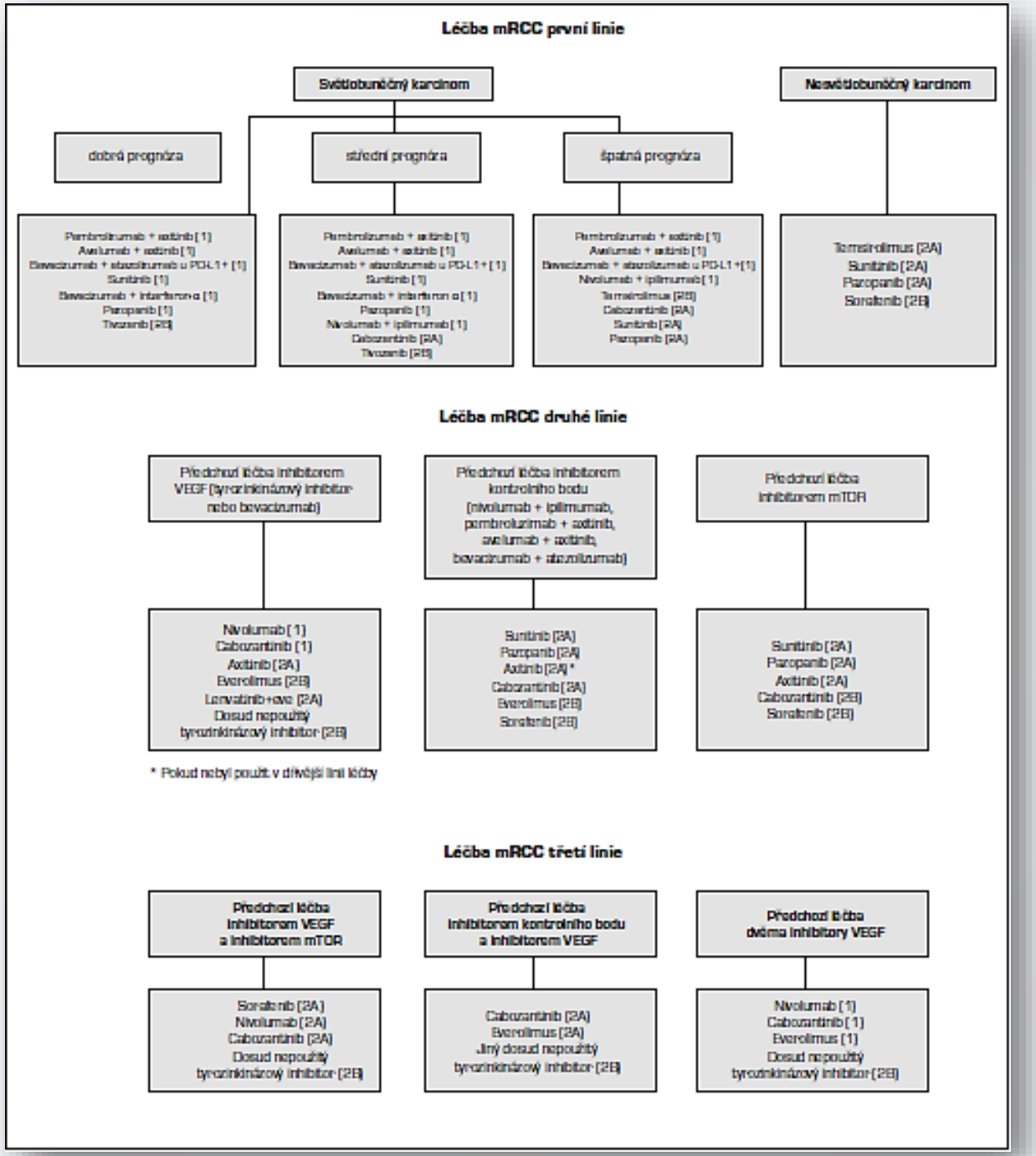
Rini. J Clin Oncol 2009; 27:3225-3234

VEGFR-TKI - interakční mapa kináz



Karaman, et al. *Nat Biotech.* 2008;26:127-132.

VEGFR = receptor pro vaskulární endoteliální růstový faktor



Modrá kniha 2020

Tyrosinkinázové inhibitory a kardiovaskulární toxicita

› Toxicology. 2019 Oct 1;426:152281. doi: 10.1016/j.tox.2019.152281. Epub 2019 Aug 22.

Mitochondrial oxidative stress plays a critical role in the cardiotoxicity of sunitinib: Running title: Sunitinib and oxidative stress in hearts

Jamal Bouitbir [1], Abdallah Alshaikhali [2], Miljenko V Panajatovic [2], Vanessa F Abegg [2], Franziska Paech [2], Stephan Krähenbühl [3]

Journal of the American College of Cardiology
Volume 66, Issue 10, 8 September 2015, Pages 1160-1178

The Present and Future
State-of-the-Art Review

Vascular and Metabolic Implications of Novel Targeted Cancer Therapies: Focus on Kinase Inhibitors

Weijuan Li MD, MS *, Kevin Croce MD, PhD †, David P. Steensma MD ‡, David F. McDermott MD §, Ori Ben-Yehuda MD ‖ ✉, Javid Moslehi MD ¶ ✉

Review › Curr Drug Metab. 2009 Jun;10(5):470-81. doi: 10.2174/138920009788897975.

Tyrosine kinase inhibitors – a review on pharmacology, metabolism and side effects

Jörg Thomas Hartmann [1], Michael Haap, Hans-Georg Kopp, Hans-Peter Lipp

Adv Ther (2020) 37:730–744
https://doi.org/10.1007/s12325-019-01167-2

Check for updates

ORIGINAL RESEARCH

Efficacy and Safety of Approved First-Line Tyrosine Kinase Inhibitor Treatments in Metastatic Renal Cell Carcinoma: A Network Meta-Analysis

Kirsi M. Manz · Klaus Fenchel · Andreas Eilers · Jonathan Morgan · Kirsten Wittling · Wolfram C. M. Dempke

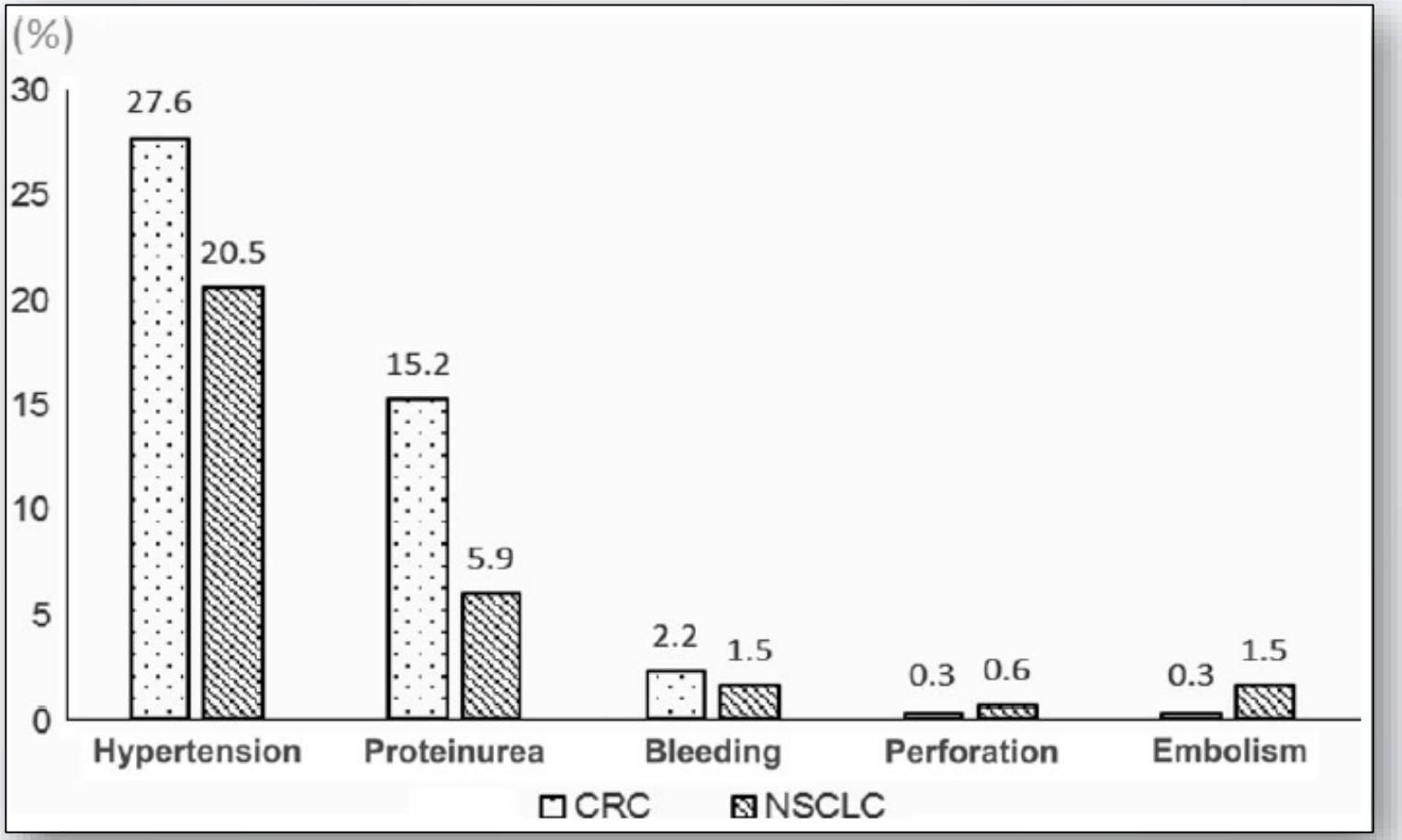
Hypertenze indukovaná onkologickou léčbou – VEGFi

Table 1. Incidence of hypertension with VEGF and multi-kinase inhibitors [37–53, 54•, 55]

VEGF or multi-kinase inhibitor	Therapeutic target(s)	FDA-labeled Indication(s)	Incidence of all-grade hypertension	Incidence of grade 3 and 4 hypertension
Bevacizumab	VEGF ligand	Cervical cancer, colorectal cancer, glioblastoma multiforme, non-small-cell lung cancer, ovarian cancer, renal cell cancer	22–24 %	8 %
Sunitinib	PDGFR, VEGFR, KIT, FLT3, CSR, RET	Gastrointestinal stromal tumors, pancreatic neuroendocrine tumor, renal cell cancer	15–34 %	7 %
Sorafenib	VEGF-R, PDGFR, KIT, FLT-3, RET	Hepatocellular cancer, renal cell cancer, thyroid cancer	17–29 %	4–11 %
Axitinib	VEGFR	Renal cell cancer	40 %	11–13 %
Pazopanib	VEGFR, PDGFR, FGFR, KIT, Itk, Lck, c-FMS	Renal cell cancer, soft-tissue sarcoma	36–46 %	4–7 %
Cediranib	VEGFR	None currently (being studied in recurrent ovarian carcinoma)	67 %	43 %

Brinda BJ et al. Curr Treat Opt Cardio Med 2016; 18:33

Nežádoucí účinky při léčbě bevacizumabem

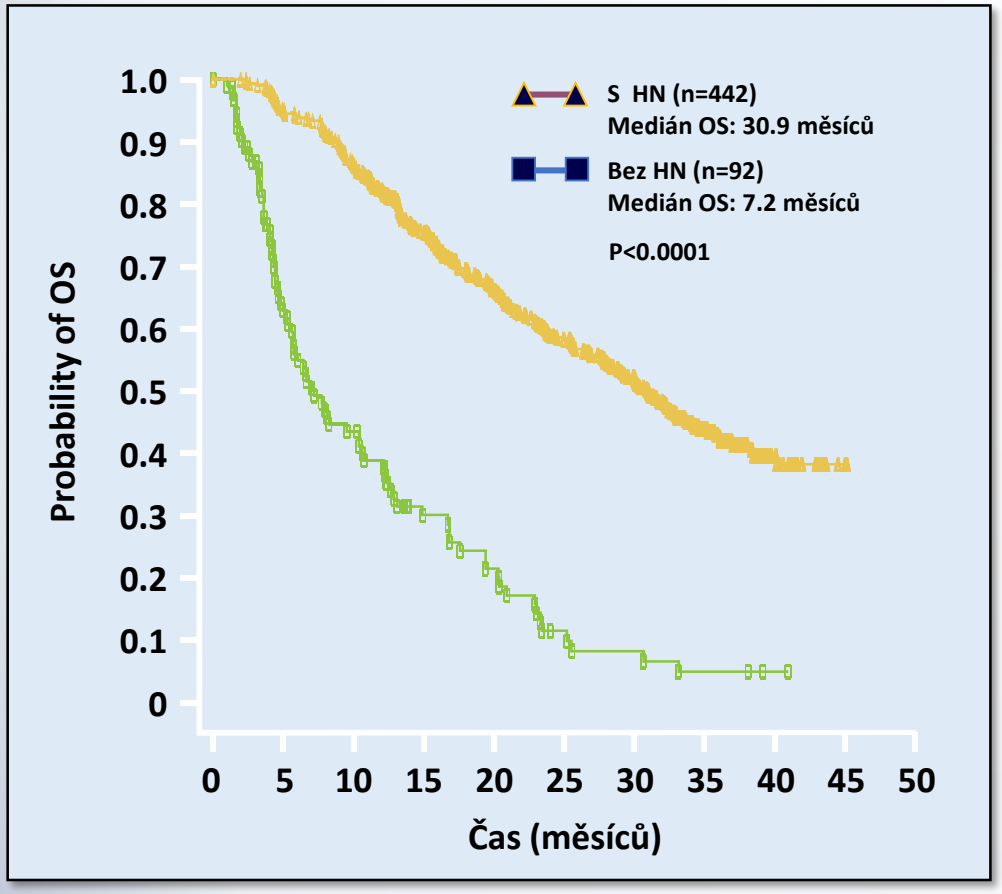


Frekvence nežádoucích účinků (%)

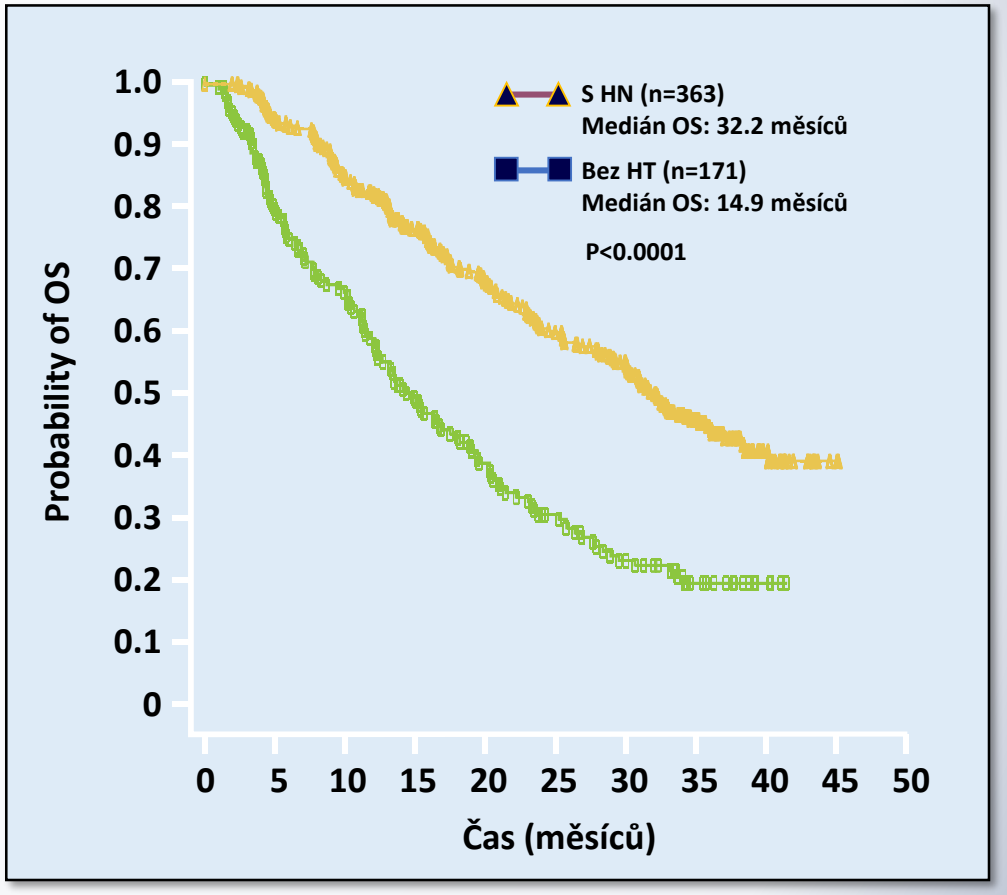
Nakaya A et al. Cancer Med 2016; doi: 10.1002/cam4.701

Median OS podle TK

Maximální STK ≥140 mmHg

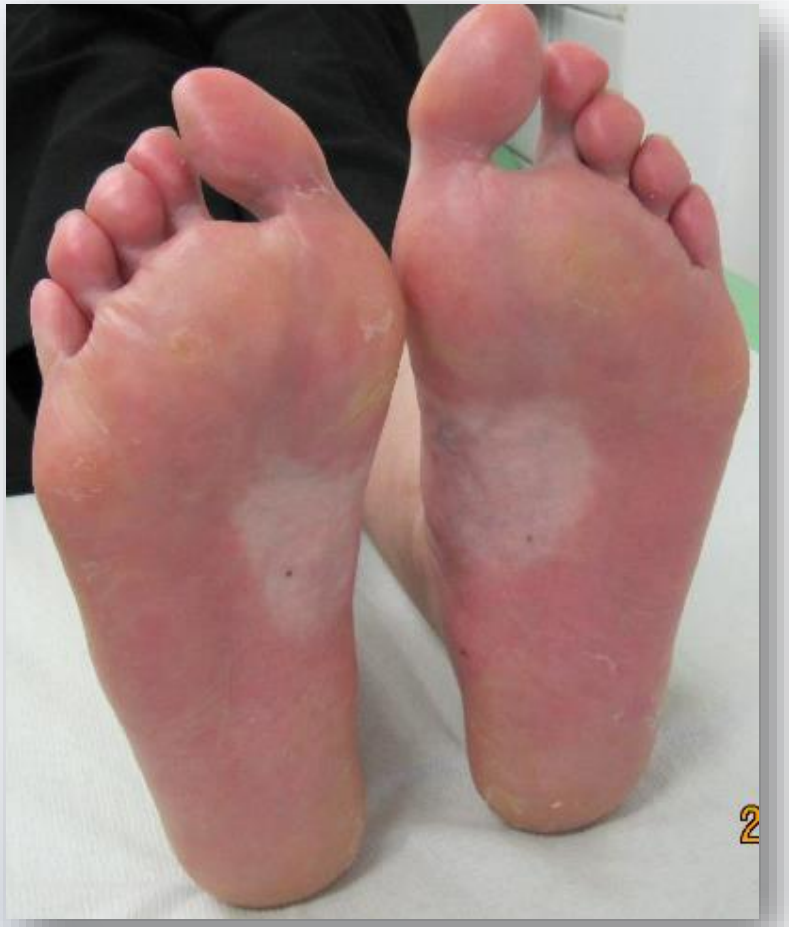


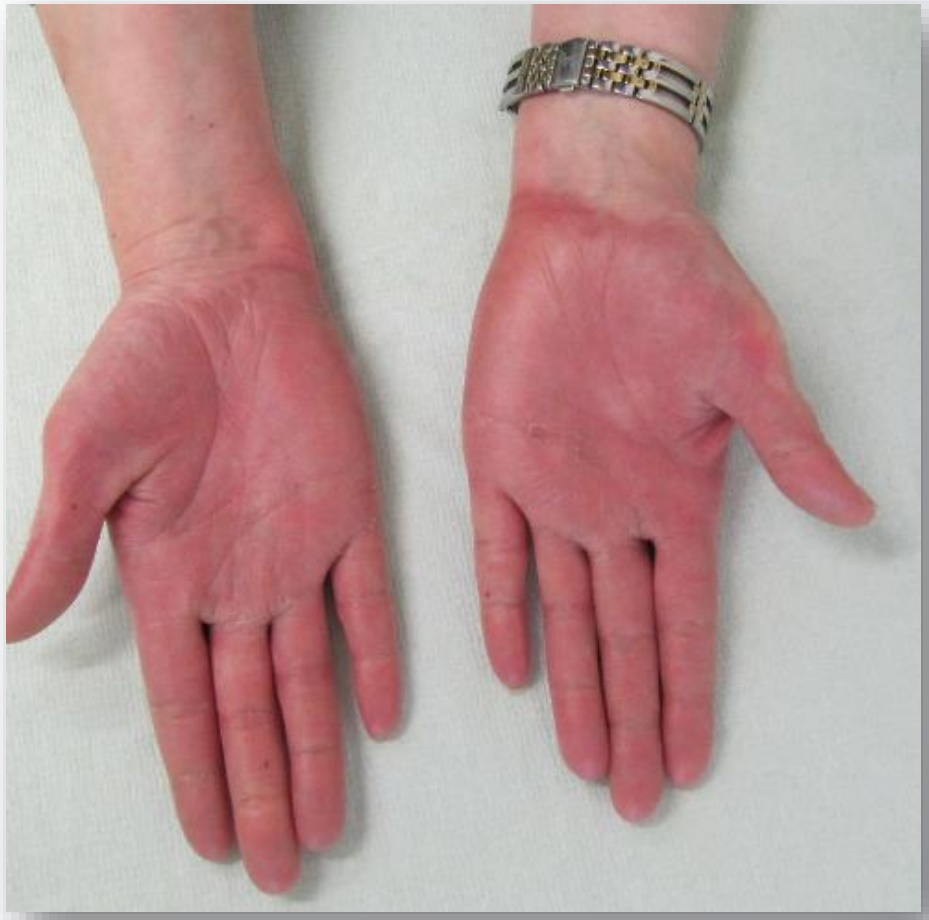
Maximální DTK ≥90 mmHg



Rini BI, et al. *J Natl Cancer Inst* 2011;103:763–73

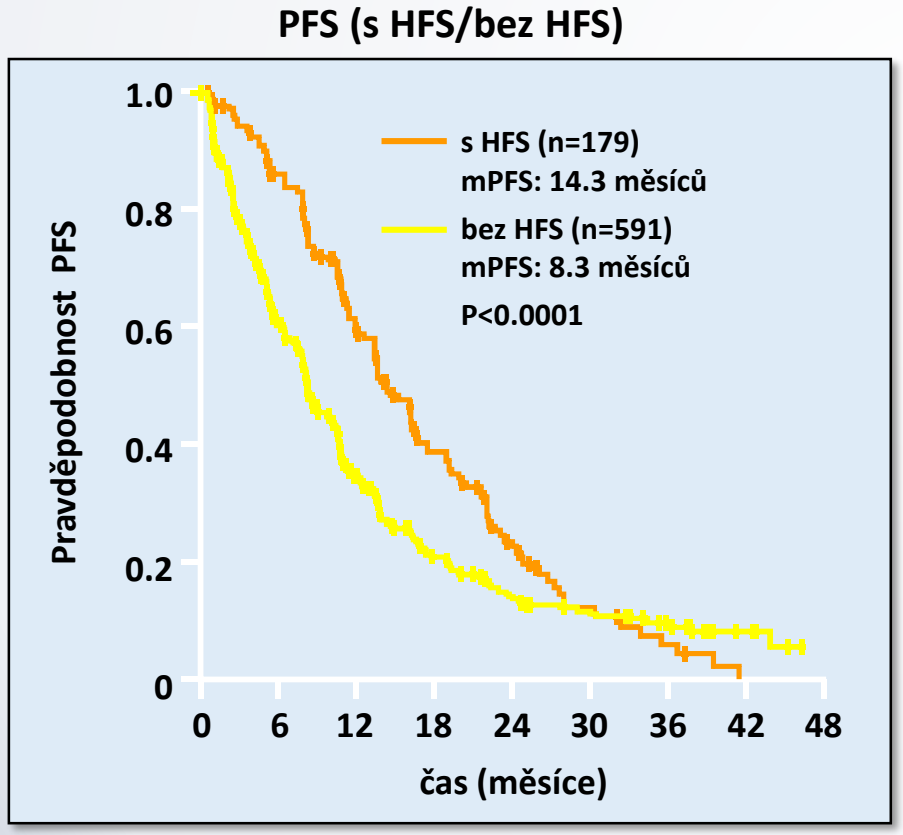
Hand–Foot syndrom

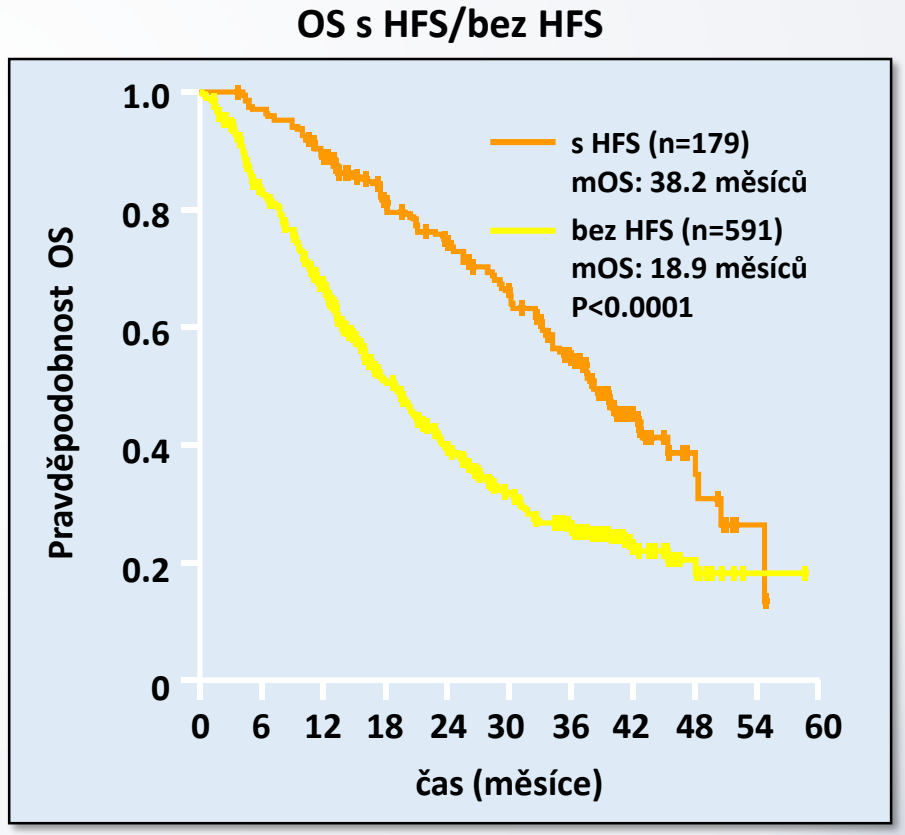




HFS souvisí se zlepšením PFS a OS

- Pacienti s HFS v kterékoliv fázi léčby měli signifikantně lepší klinický výsledek než pacienti bez HFS s ohledem na všechny sledované cíle
- ORR: 66.5% vs. 31.8% (P<0.0001)

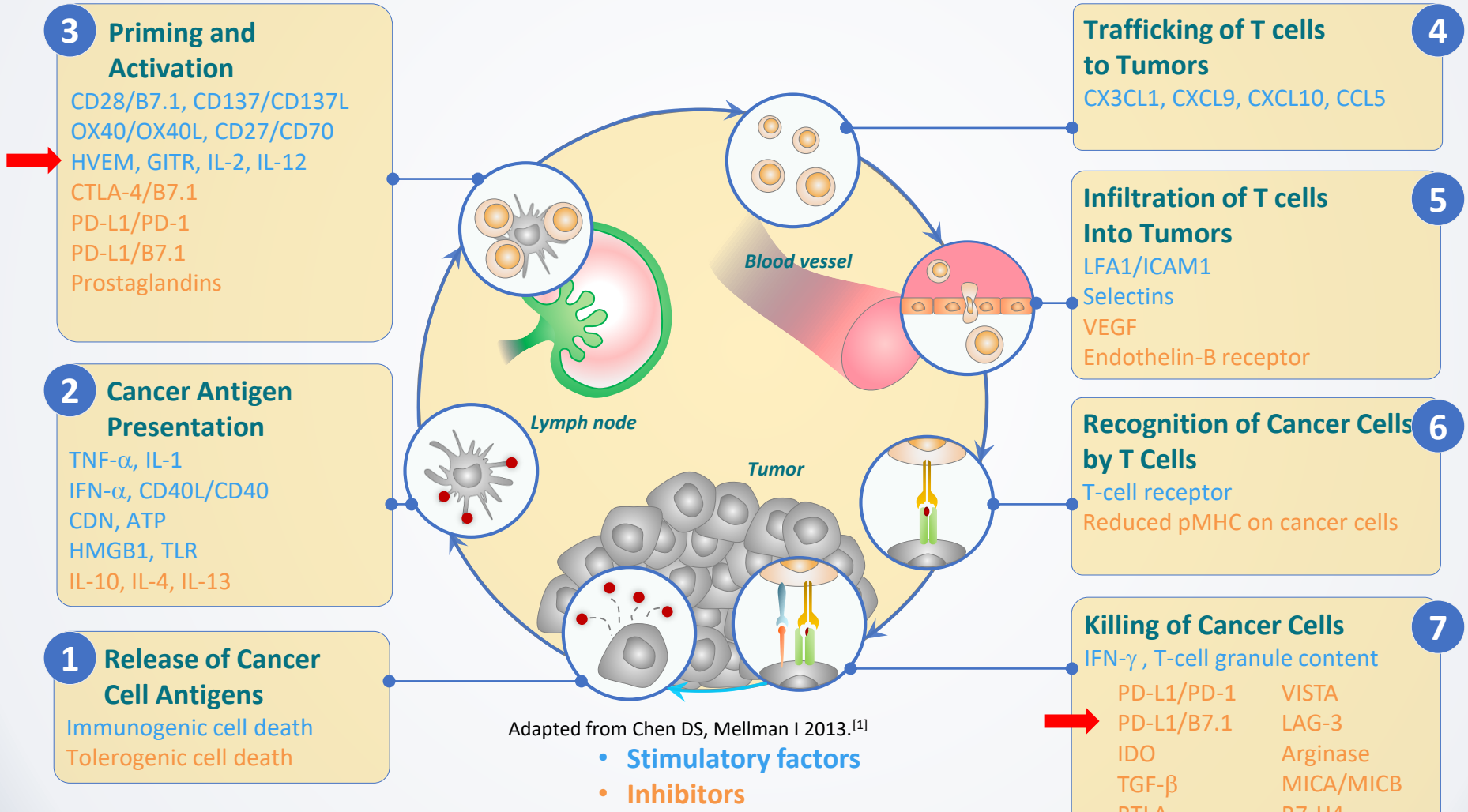




Michaelson MD, et al. ASCO Genitourinary Cancers Symposium 2011 Abstract 320

Toxicita imunoterapie

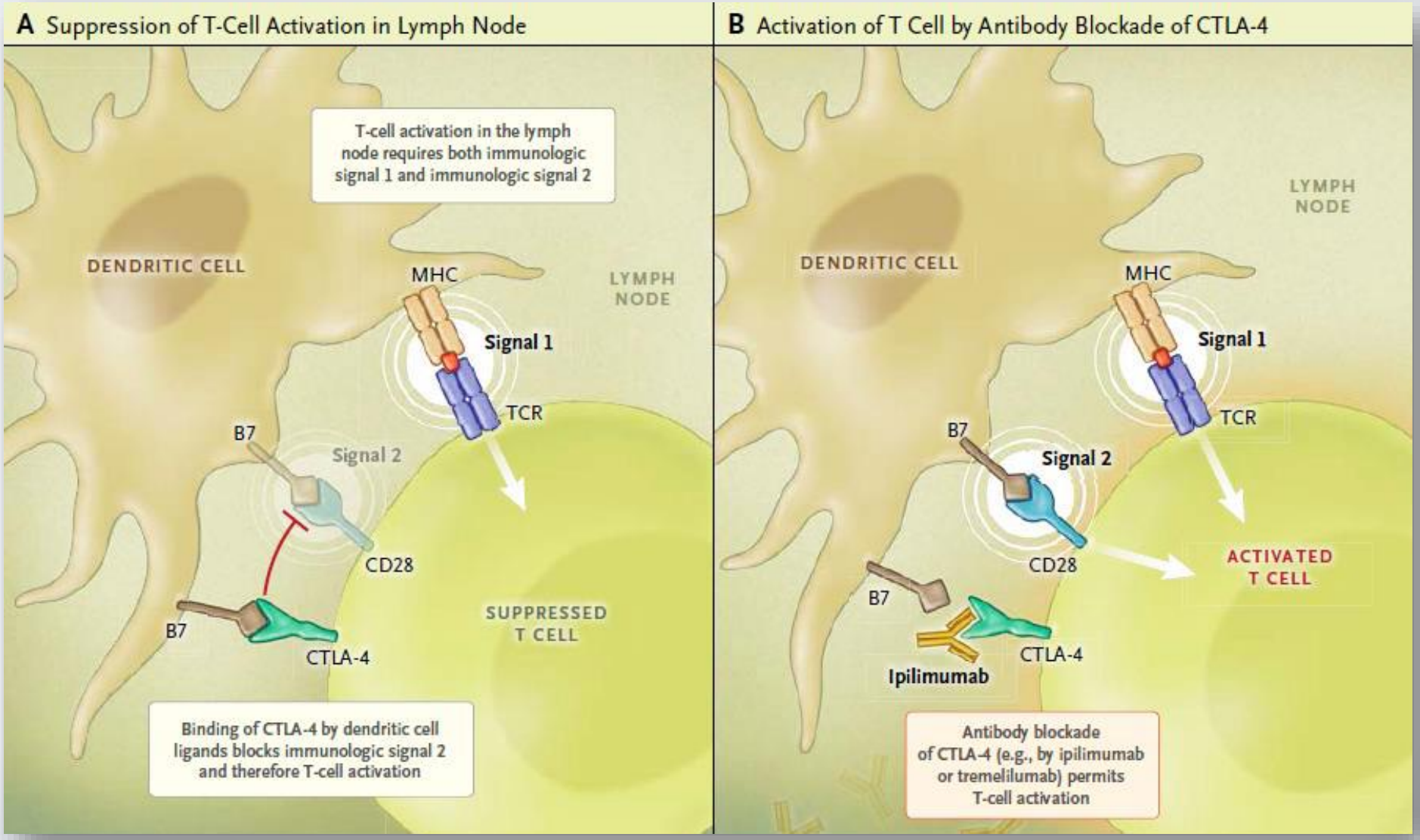
Ovlivnění různých kroků v protinádorovém imunitním cyklu: řada studií probíhá, ale na výsledky musíme ještě počkat



CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death-1; PD-L1, PD ligand-1

Chen DS, Mellman I. *Immunity.* 2013;39(1):1-10

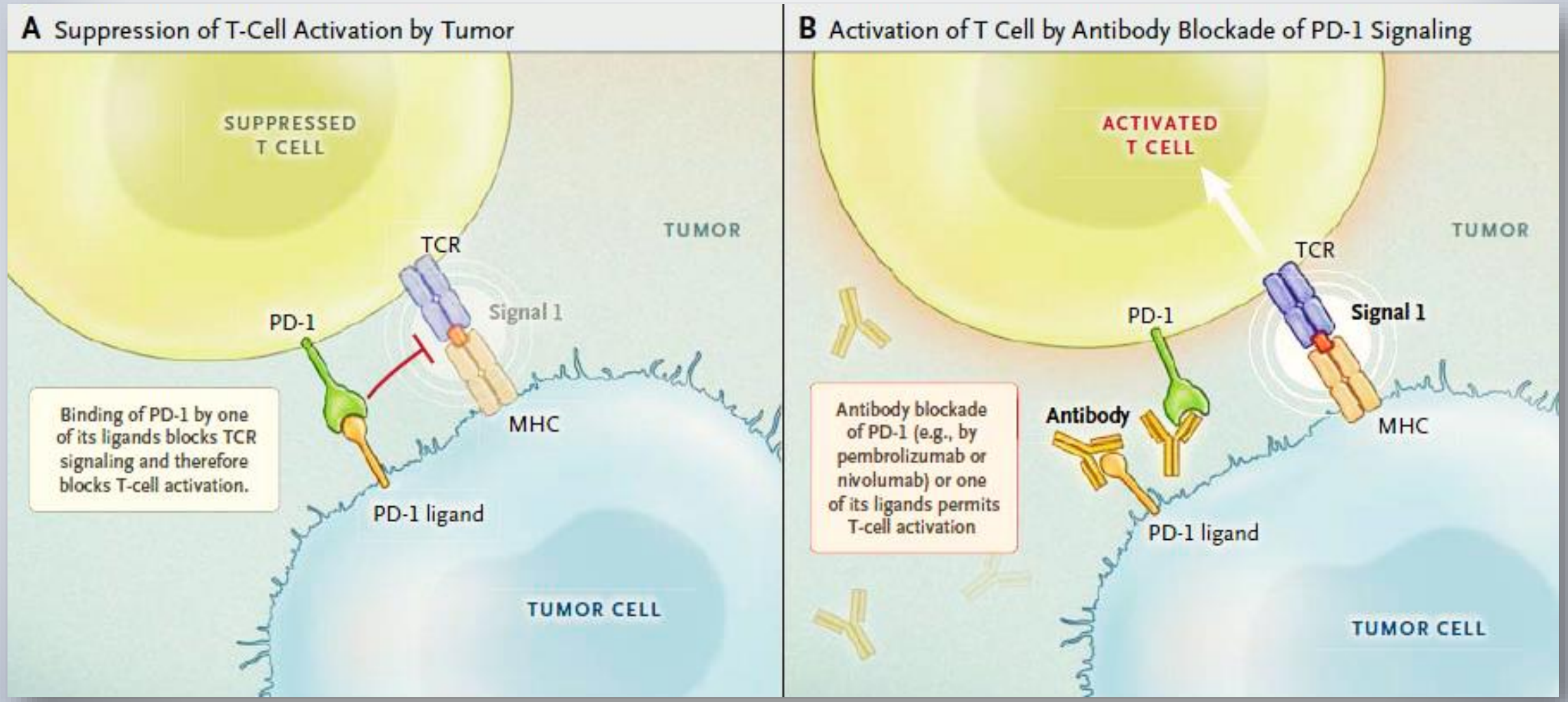
Cíle současné imunoterapie



monoklonální protilátky zaměřené na regulační mechanismy imunitní odpovědi

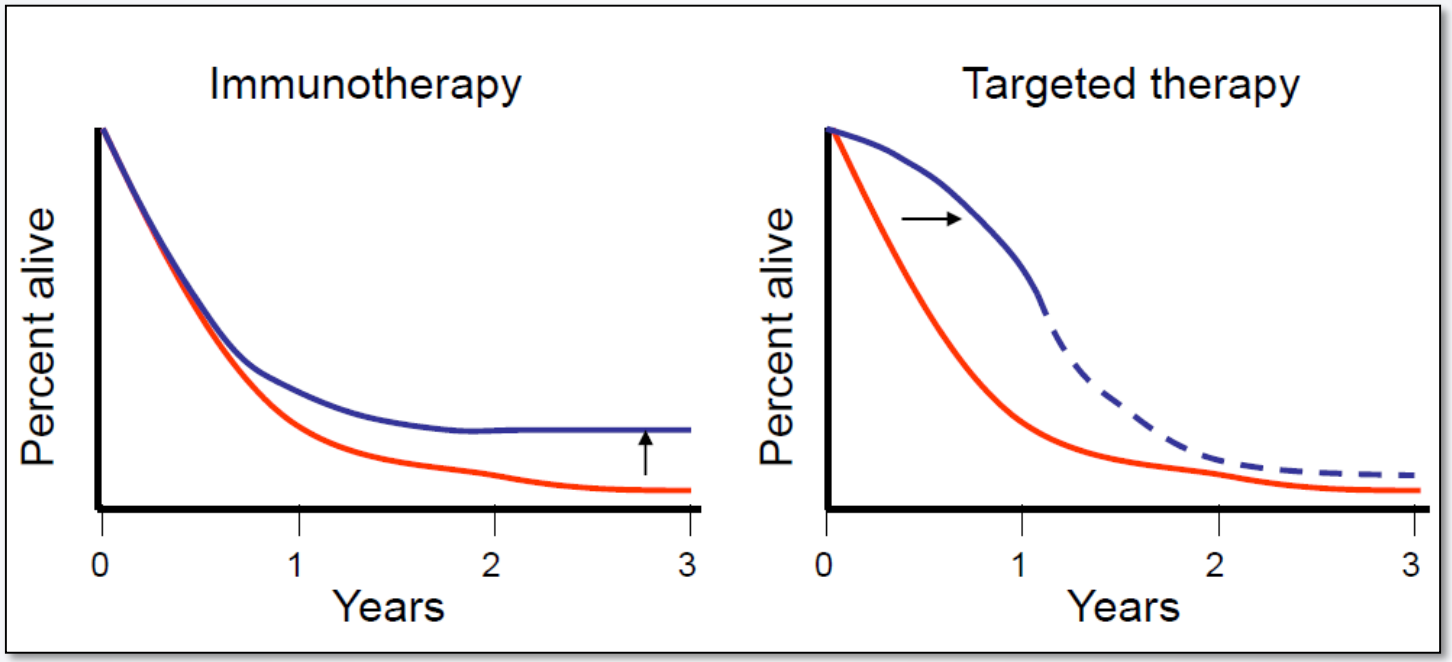
Ribas et al. *Clin Cancer Res.* 2012;18(2):336-41

Cíle současné imunoterapie



Ribas A. N Engl J Med 2015, 393, 1490-2.

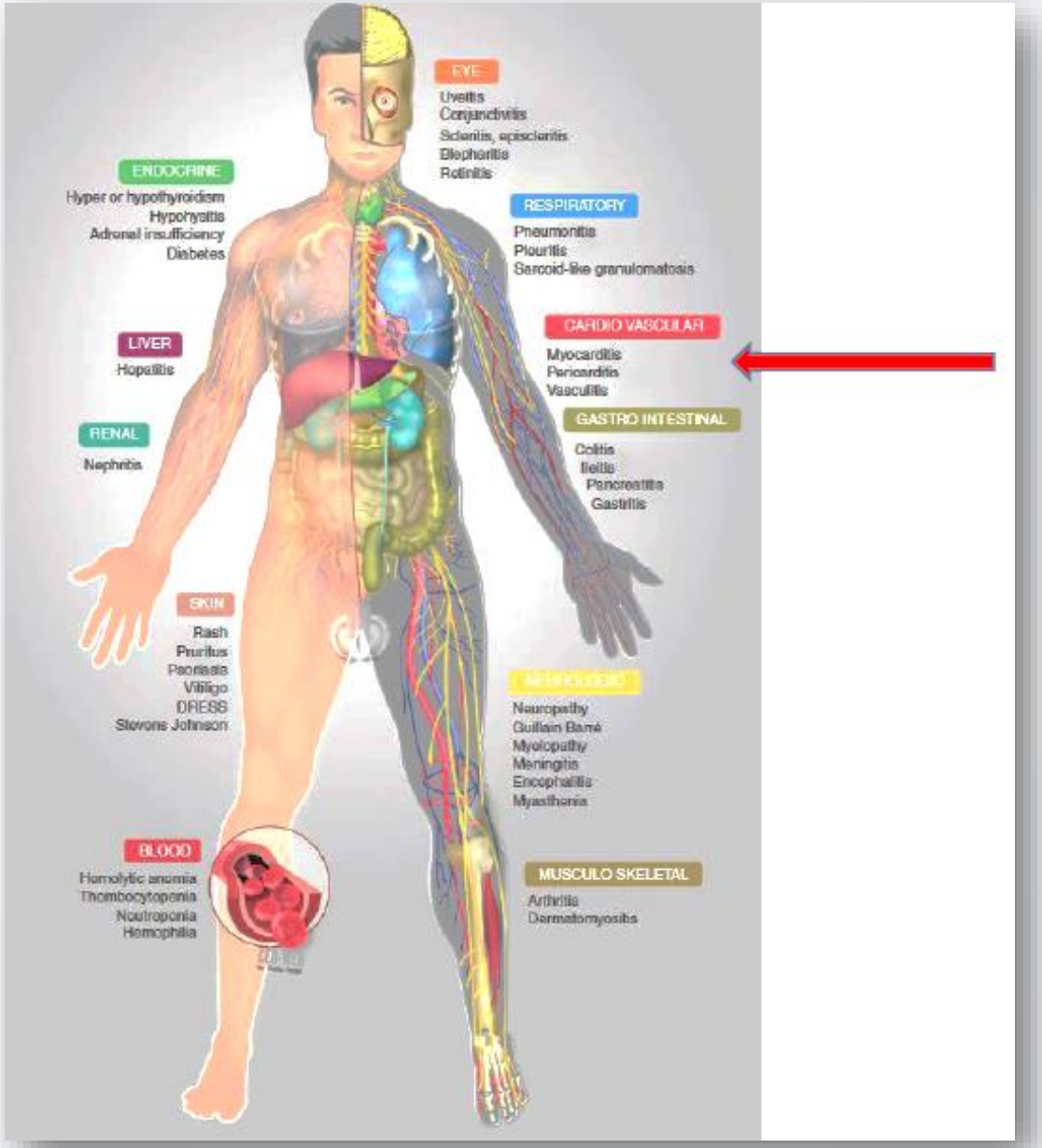
Imunoterapie vs cílená terapie



- **Imunoterapie:** nižší míra odpovědí, ale ty jsou obvykle dlouhotrvající, což vede k fázi plató na konci křivky přežívání...
- **Cílená terapie:** rychlá, ale většinou krátkodobá, odpověď u většiny pacientů, na konci OS křivky je efekt na přežití nejasný...

Ribas et al. *Clin Cancer Res.* 2012;18(2):336-41

Imunoterapie a možné nežádoucí účinky



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

Nežádoucí účinky imunoterapie

- Kardiovaskulární NÚ ‹ 1 % (vyšší v kombinaci)
- Toxicita:
    - Myokarditida
    - Perikarditida
    - Arytmie
    - Kardiomyopatie
    - Zhoršená funkce LK
- Konzultace kardiologa vhodná
- Účinné jsou kortikosteroidy a imunosupresiva

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
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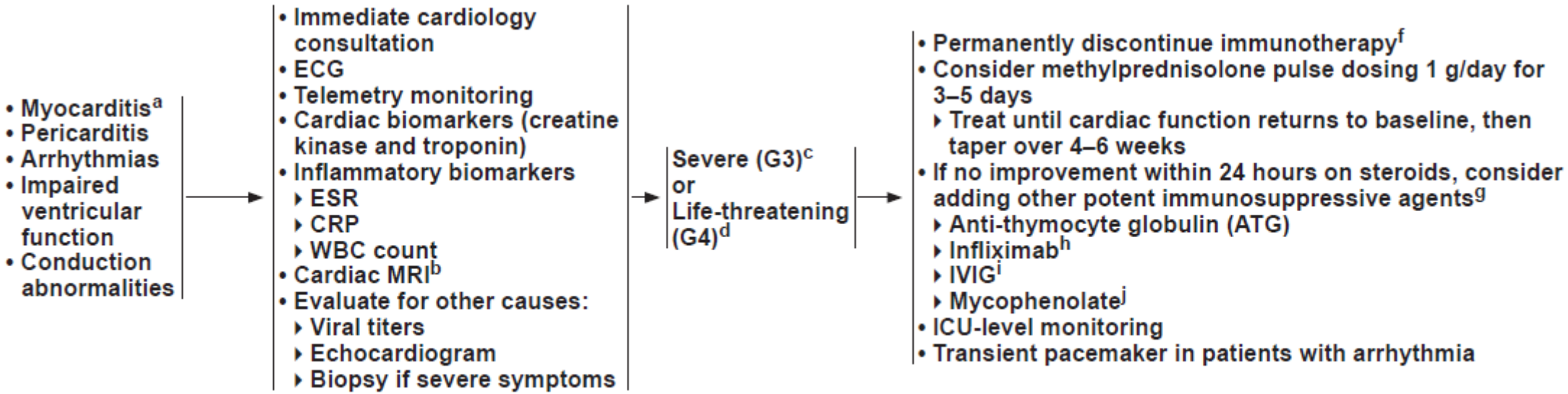
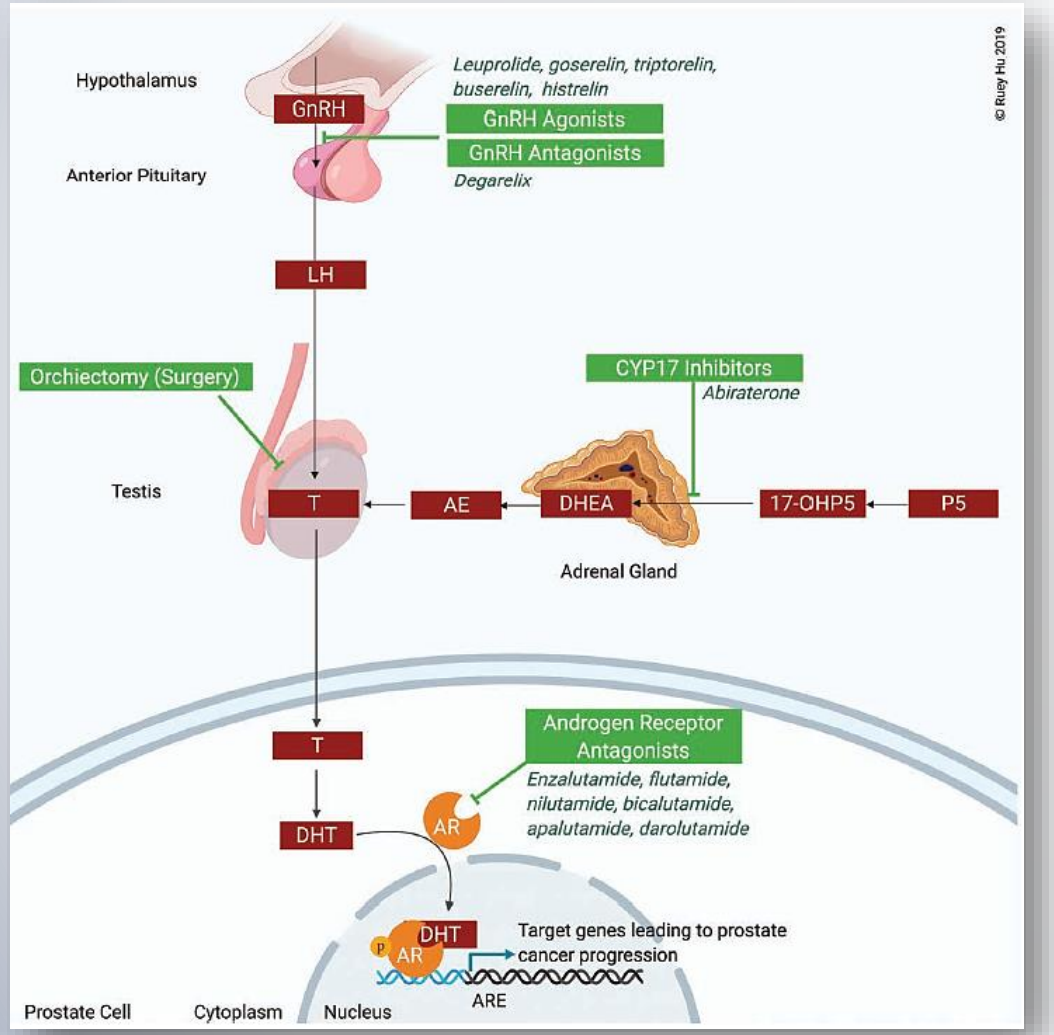
Discussion



Androgendeprivační terapie a kardiovaskulární komplikace



Cardiovascular Mortality in Patients With Metastatic Prostate Cancer Exposed to Androgen Deprivation Therapy: A Population-Based Study

Giorgio Gandaglia,[1,2] Maxine Sun,[1] Ioana Popa,[1] Jonas Schiffmann,[1] Vincent Trudeau,[1] Shahrokh F. Shariat,[3] Quoc-Dien Trinh,[4] Markus Graefen,[5] Hugues Widmer,[6] Fred Saad,[6] Alberto Briganti,[2] Francesco Montorsi,[2] Pierre I. Karakiewicz[1,6]

Prostate Cancer and Prostatic Diseases
https://doi.org/10.1038/s41391-020-00275-3

ARTICLE

Clinical Research

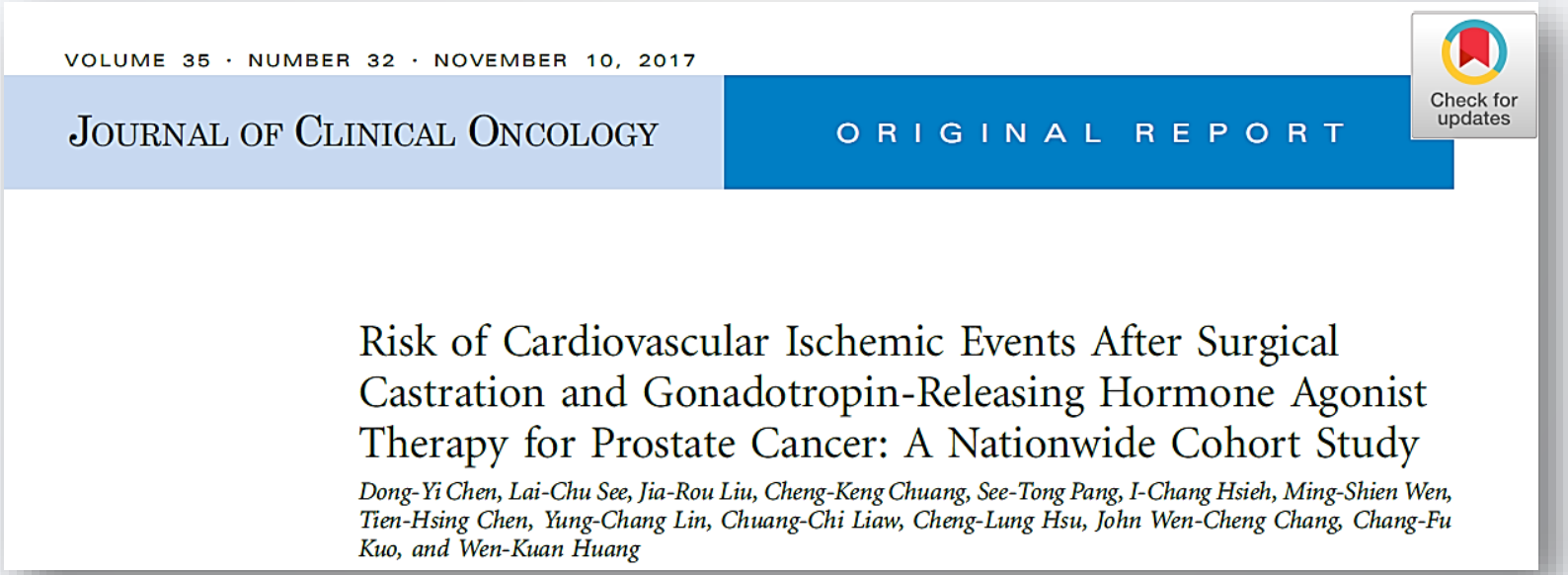
Abiraterone and enzalutamide had different adverse effects on the cardiovascular system: a systematic review with pairwise and network meta-analyses

Hsiang Ying Lee[1,2,3] · Hsiao-Ling Chen[4] · Jeremy Yuen-Chun Teoh[5] · Tun-Chieh Chen[6] · Shao-Yuan Hao[4] · Hsin-Yi Tsai[4] · Wei-Hsuan Huang[4] · Yung-Shun Juan[1,3] · Hao-Min Cheng[7,8,9] · Hsiu-Mei Chang[4]

Hu JR et al. *Arterioscler Thromb Vasc Biol.* 2020;40:e55–e64.

KV ischemické příhody po chirurgické kastraci vs LHRH terapie

- LHRH nezvyšuje riziko KV mortality ve srovnání s chirurgickou kastrací
- Orchiektomie souvisí s vyšším počtem KV ischemických příhod u starších nemocných a u pacientů s KV anamnézou v prvních 1,5 letech ADT


VOLUME 35 · NUMBER 32 · NOVEMBER 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Check for updates

Risk of Cardiovascular Ischemic Events After Surgical Castration and Gonadotropin-Releasing Hormone Agonist Therapy for Prostate Cancer: A Nationwide Cohort Study

Dong-Yi Chen, Lai-Chu See, Jia-Rou Liu, Cheng-Keng Chuang, See-Tong Pang, I-Chang Hsieh, Ming-Shien Wen, Tien-Hsing Chen, Yung-Chang Lin, Chuang-Chi Liaw, Cheng-Lung Hsu, John Wen-Cheng Chang, Chang-Fu Kuo, and Wen-Kuan Huang

ARTA v léčbě karcinomu prostaty

Prostate Cancer and Prostatic Diseases
https://doi.org/10.1038/s41391-020-00275-3

ARTICLE

Clinical Research

Abiraterone and enzalutamide had different adverse effects on the cardiovascular system: a systematic review with pairwise and network meta-analyses

Hsiang Ying Lee[1,2,3] · Hsiao-Ling Chen[4] · Jeremy Yuen-Chun Teoh[5] · Tun-Chieh Chen[6] · Shao-Yuan Hao[4] · Hsin-Yi Tsai[4] · Wei-Hsuan Huang[4] · Yung-Shun Juan[1,3] · Hao-Min Cheng[7,8,9] · Hsiu-Mei Chang[4]

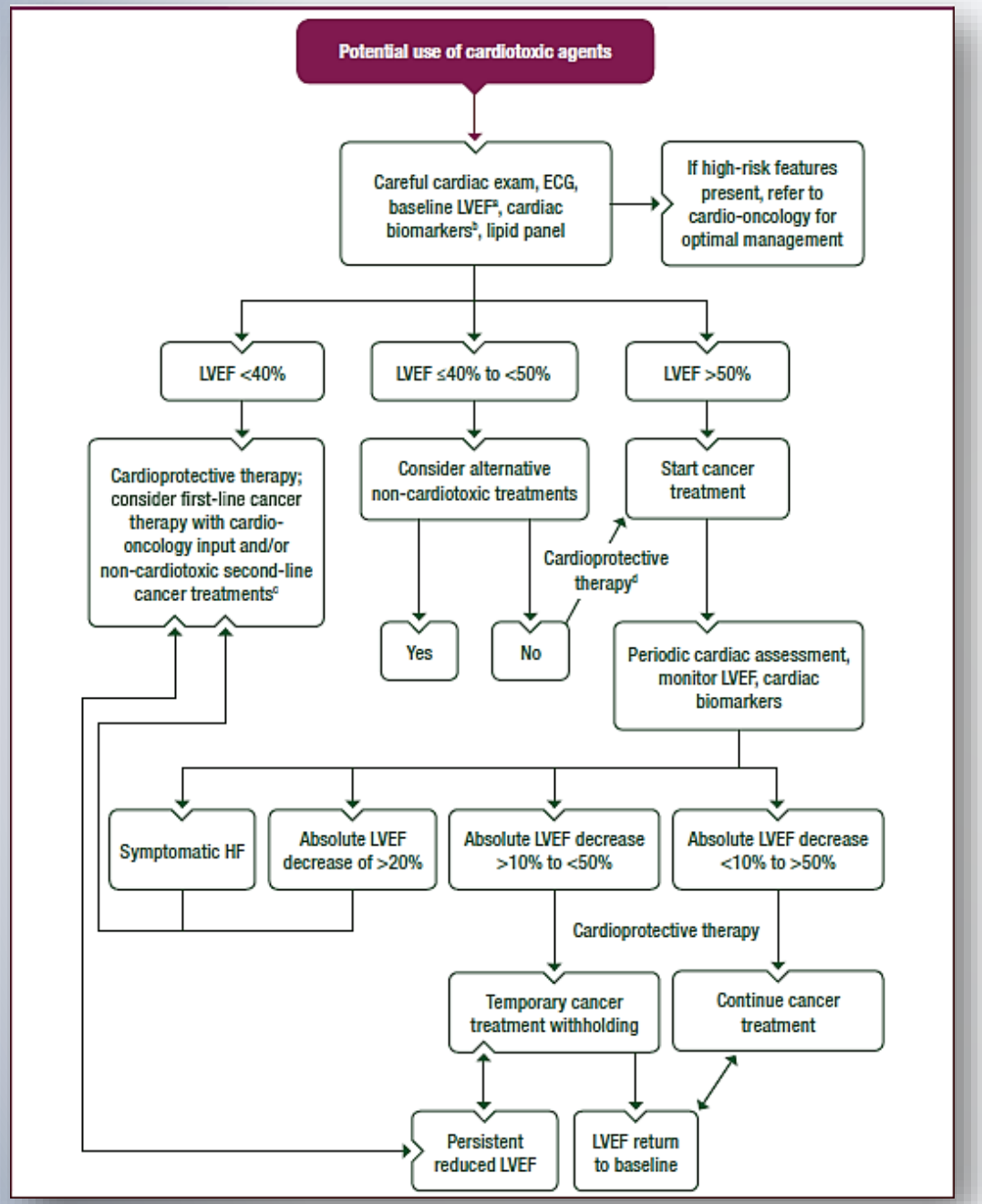
European Heart Journal (2016) 37, 2768–2801
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

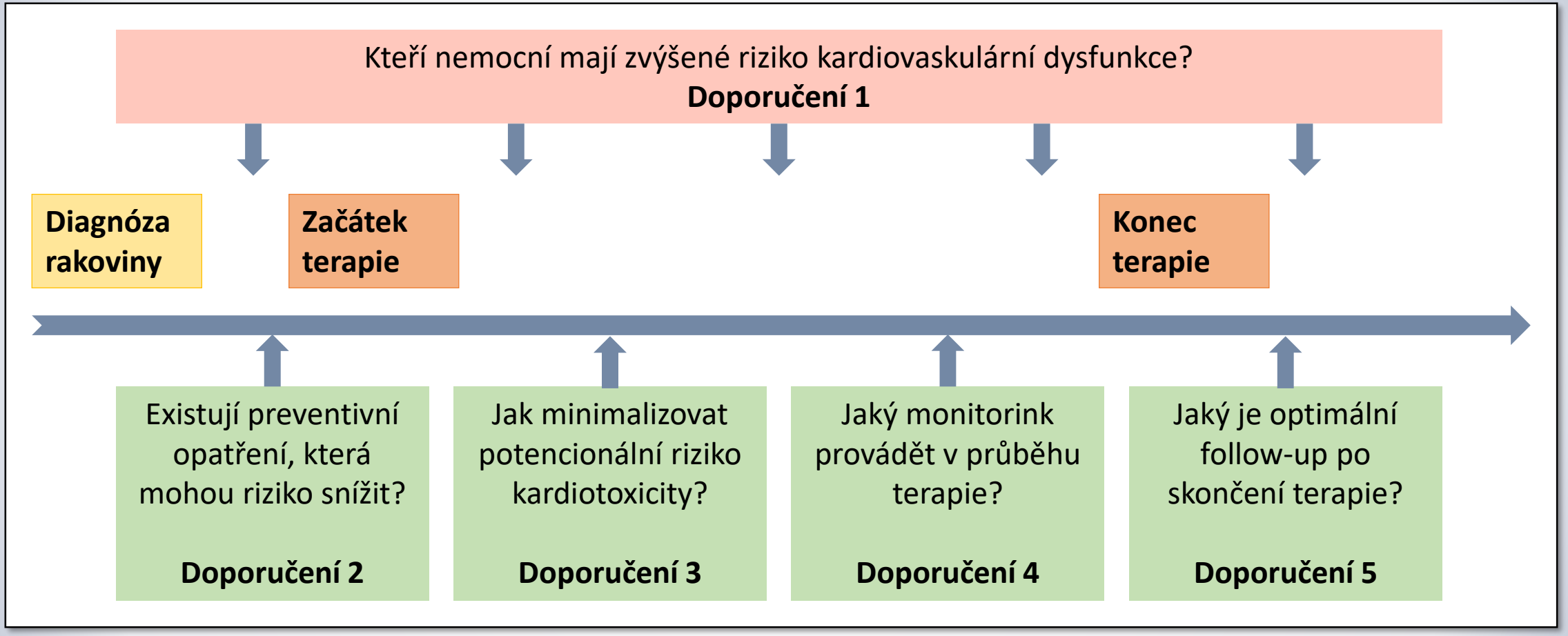
Authors/Task Force Members: Jose Luis Zamorano* (Chairperson) (Spain), Patrizio Lancellotti* (Co-Chairperson) (Belgium), Daniel Rodriguez Muñoz (Spain), Victor Aboyans (France), Riccardo Asteggiano (Italy), Maurizio Galderisi (Italy), Gilbert Habib (France), Daniel J. Lenihan[1] (USA), Gregory Y. H. Lip (UK), Alexander R. Lyon (UK), Teresa Lopez Fernandez (Spain), Dania Mohty (France), Massimo F. Piepoli (Italy), Juan Tamargo (Spain), Adam Torbicki (Poland), and Thomas M. Suter (Switzerland)



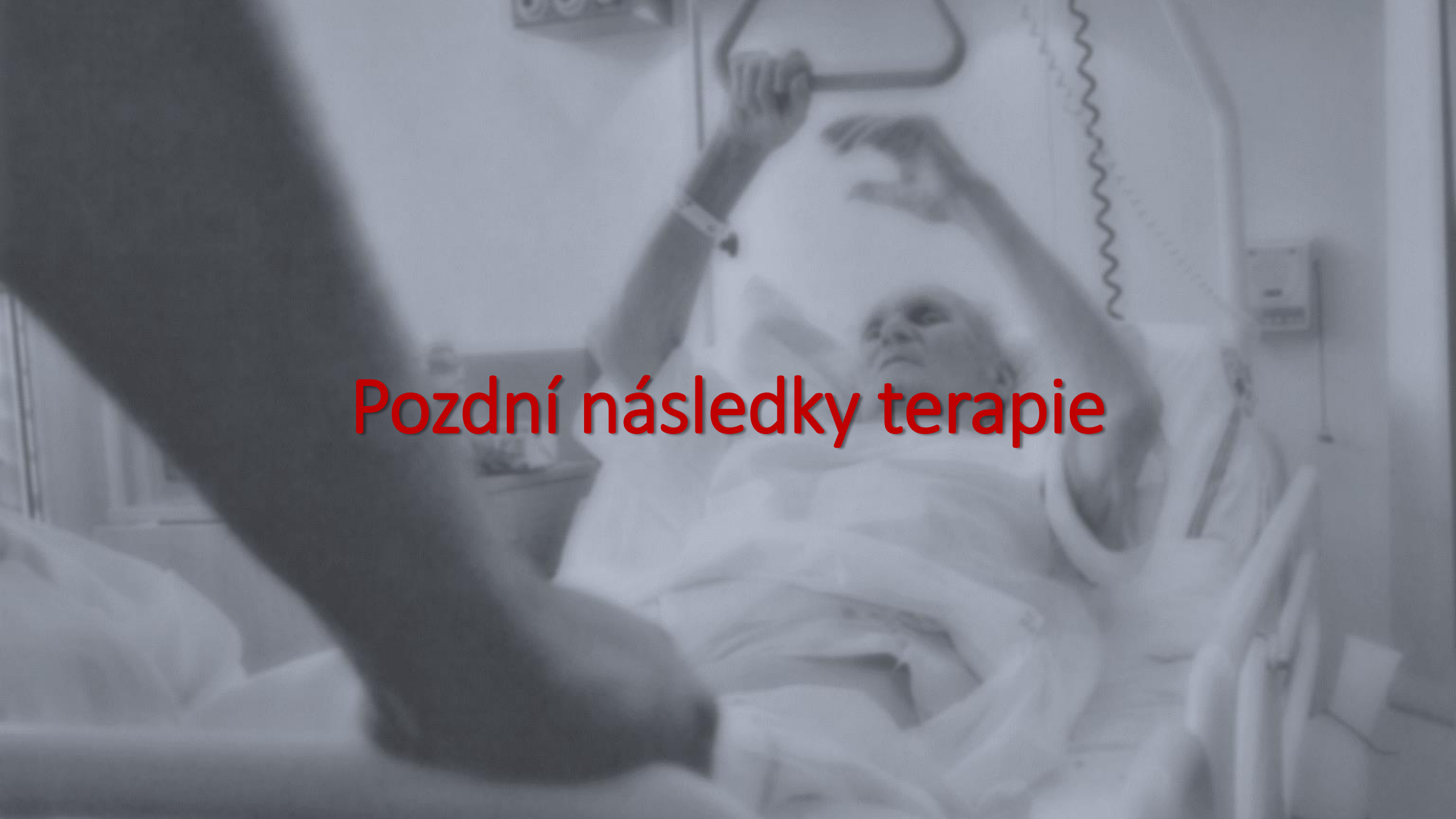
Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations

G. Curigliano[1,2†], D. Lenihan[3†], M. Fradley[4], S. Ganatra[5], A. Barac[6], A. Blaes[7], J. Herrmann[8], C. Porter[9], A. R. Lyon[10], P. Lancellotti[11], A. Patel[12], J. DeCara[13], J. Mitchell[14], E. Harrison[15], J. Moslehi[16], R. Witteles[17], M. G. Calabro[18], R. Orecchia[1], E. de Azambuja[19], J. L. Zamorano[20], R. Krone[21], Z. Iakobishvili[22], J. Carver[23], S. Armenian[24], B. Ky[25], D. Cardinale[26], C. M. Cipolla[27], S. Dent[28] & K. Jordan[29], on behalf of the ESMO Guidelines Committee*

ESMO recommendations 2020

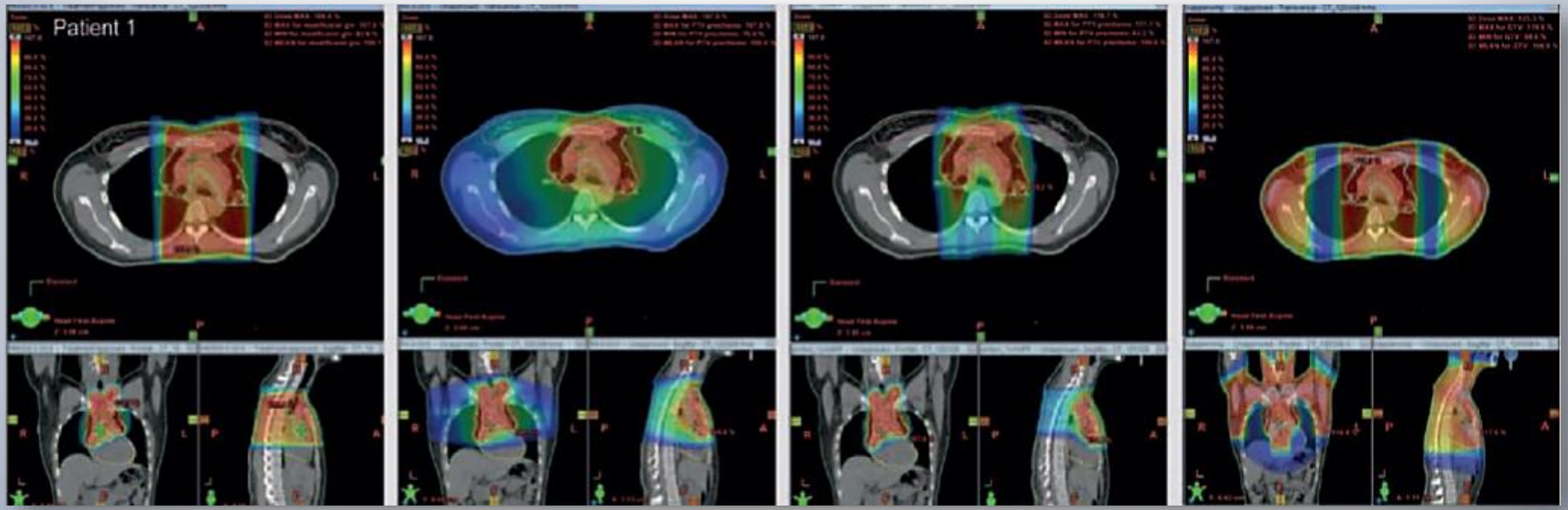


SH. Armenian et al. *JCO* **2017**, 35, 893-911.



Pozdní následky terapie

Moderní techniky
vs rozšířené ozařovací pole v minulosti



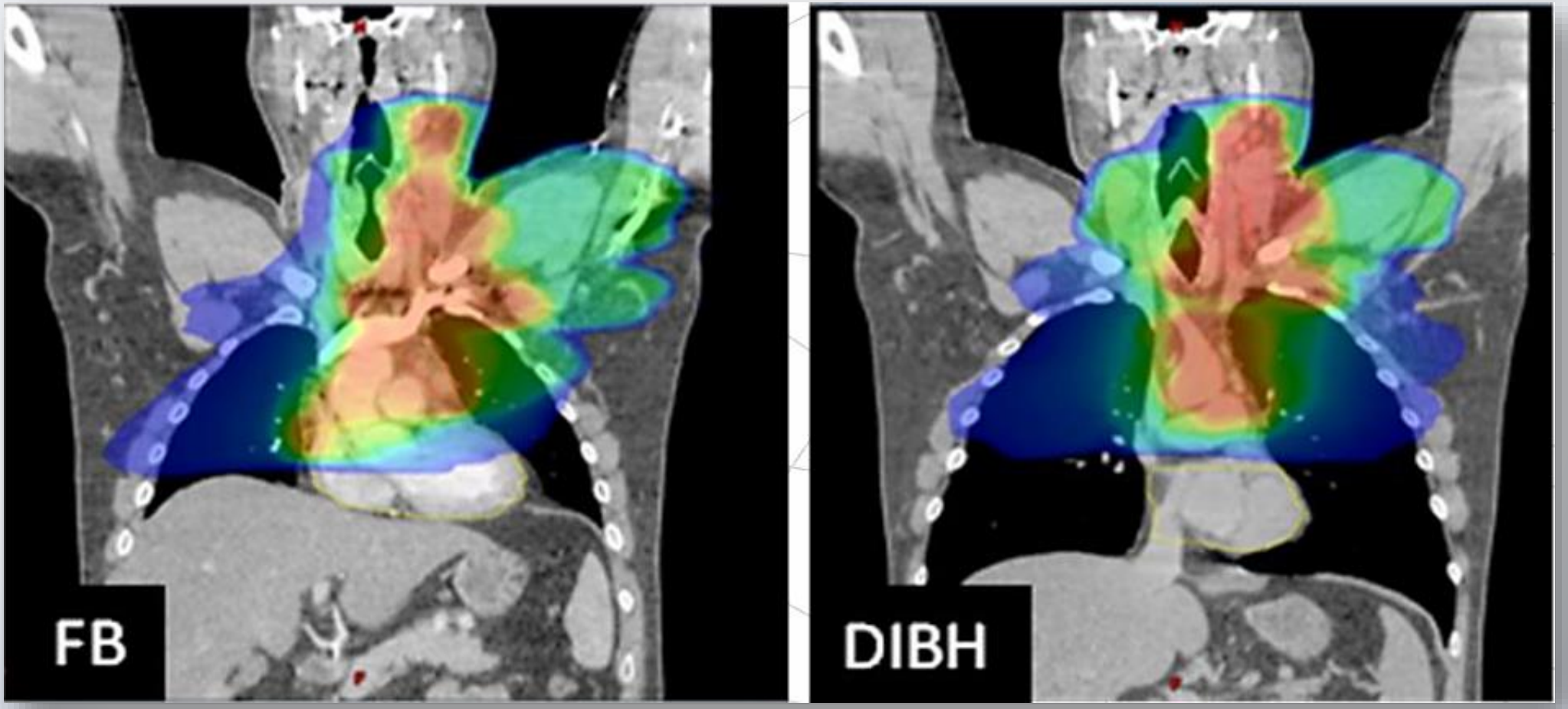
MaraldoM et al. Ann Oncol2013; 24: 2113-8

Celoživotní nárůst rizika u pacientů s Hodgkinovým lymfomem léčených radioterapií

	3D CRT		VMAT		PT		MF	
	Median	Range	Median	Range	Median	Range	Median	Range
Risk estimates (%)								
Cardiac mortality (CMort)	1.0	(0.2–2.7)	1.1	(0.3–2.1)	0.9	(0.1–1.9)	2.9	(2.2–3.4)
Cardiac morbidity (CMorb)	1.3	(0.5–7.1)	1.3	(0.6–4.0)	1.1	(0.5–3.3)	8.6	(4.6–14.3)
Myocardial infarction (MI)	5.5	(0.7–30.1)	5.9	(1.1–23.8)	4.7	(0.4–20.4)	19.8	(6.9–37.7)
Valvular disease (VD)	0	(0–0.2)	0	(0)	0	(0)	0.4	(0–3.7)
Radiation-induced lung cancer (LC)	4.4	(2.4–9.7)	6.0	(3.1–11.4)	3.3	(1.4–9.7)	10.5	(6.3–15.1)
Radiation-induced breast cancer (BC)	3.7	(0.2–11.8)	8.0	(0.6–13.4)	1.4	(0–8.1)	23.0	(7.5–34.5)
Life years lost (LYL)								
Total LYL	0.9	(0.2–1.6)	1.1	(0.2–2.3)	0.7	(0.1–1.6)	2.1	(0.6–3.6)

MaraldoM et al. Ann Oncol2013; 24: 2113-8

Dechem řízená radioterapie



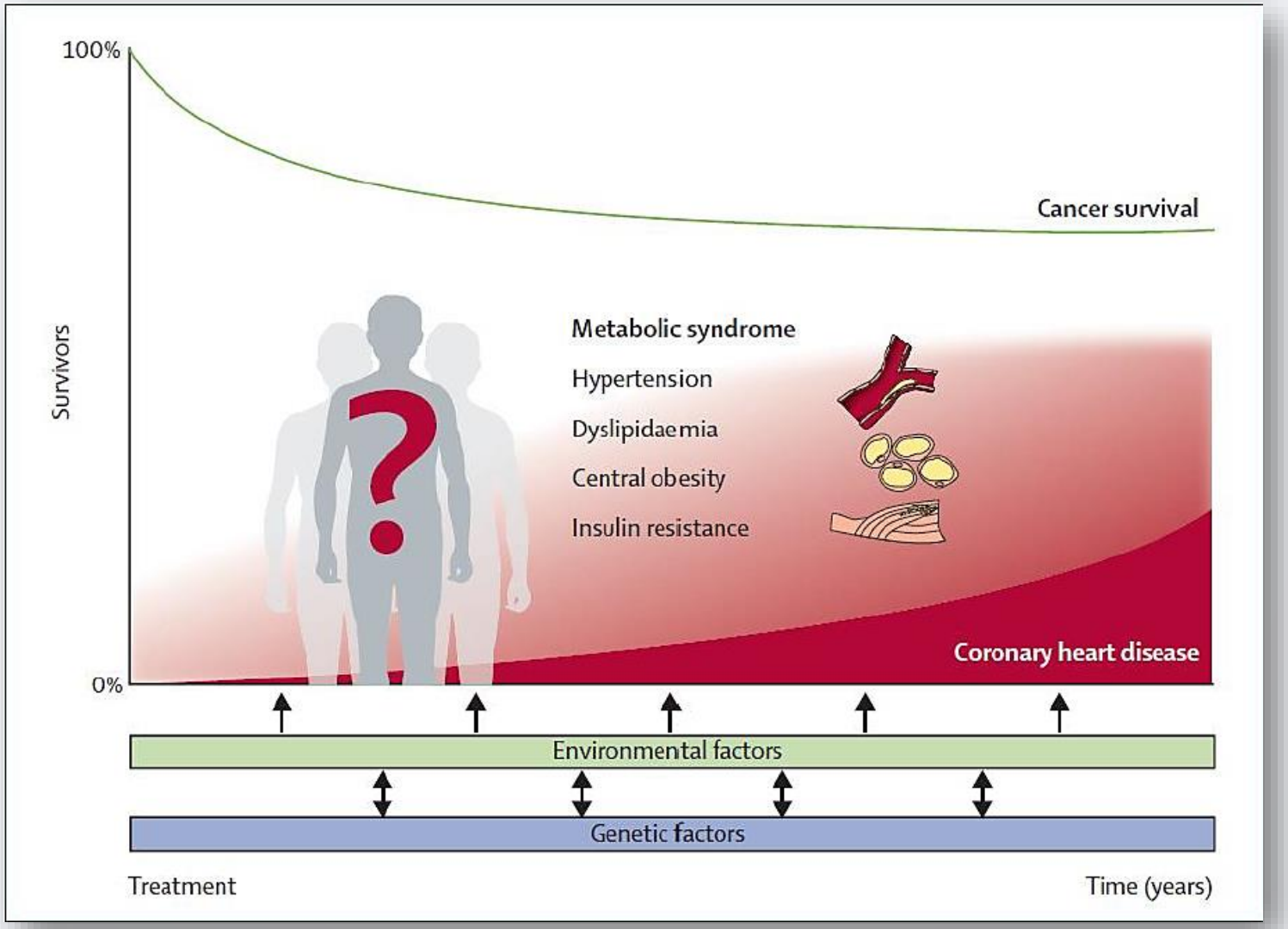
Petersen PM et al. Acta Oncol2015; 54: 60-6

Dávkové charakteristiky při volném dýchání a při hlubokém nádechu

Target							
PTV volume (cm^3)	1198	(132, 1877)	945	(131, 1949)	62	(−361, 634)	0.07
CTV volume (cm^3)	213	(21, 511)	198	(14, 561)	3	(−126, 209)	0.60
PTV $V_{95\%}$ (%)	94	(61, 98)	93	(78–97)	1	(−18, 7.4)	0.12
Lung							
Lung volume (cm^3)	2924	(1908, 5228)	4936	(3391, 8776)	−2300	(−5272, −1093)	<0.01
Mean lung dose (Gy)	8.5	(0.95, 18.9)	7.2	(1.0, 12.5)	2.0	(−0.08, 6.4)	<0.01
Lung V_{20Gy} (%)	14	(0, 46)	11	(0, 32)	5.3	(−1, 17)	<0.01
Heart							
Mean heart dose (Gy)	6.0	(0.12, 23)	3.9	(0.10, 17)	1.4	(0, 8.6)	<0.01
Heart V_{20Gy} (%)	15	(0.00, 76)	4.1	(0.00, 66)	6.3	(−2.7, 32)	<0.01
Heart V_{30Gy} (%)	2.0	(0.00, 35)	0.00	(0.00, 27)	0.8	(−7, 16)	0.01
Mean aortic valves dose (Gy)	26	(0.23, 31)	16	(0.20, 31)	1.9	(−1.8, 14)	<0.01
Mean mitral valve dose (Gy)	7.1	(0.12, 30)	1.9	(0.10, 29)	0.58	(−1.3, 16)	<0.01
Mean tricuspid valves dose (Gy)	2.6	(0.11, 30)	1.7	(0.10, 30)	0.43	(−4.6, 20)	0.01
Mean pulmonic valves dose (Gy)	26	(0.26, 32)	15	(0.23, 32)	1.4	(−1.9, 21)	<0.01
Mean LAD dose (Gy)	8.9	(0.10, 29)	5.0	(0.09, 27)	0.80	(−1.8, 14)	<0.01
Mean LMA dose (Gy)	25	(0.25, 32)	18	(0.20, 32)	3.0	(−11, 21)	<0.01
Mean LC dose (Gy)	11	(0.18, 31)	7.7	(0.15, 31)	0.40	(−4.0, 25)	0.02
Mean RCA dose (Gy)	27	(0.16, 31)	17	(0.01, 32)	0.29	(−17, 24)	0.06
Breast							
Mean dose right breast (Gy)	5.0	(0.11, 15)	6.4	(0.074, 13)	0.00	(−4.8, 2.2)	0.47
Mean dose left breast (Gy)	3.7	(0.11, 15)	3.2	(0.090, 13)	0.01	(−3.6, 6.8)	0.22

Petersen PM et al. Acta Oncol2015; 54: 60-6

Dopad chemoterapie na KV systém



De HaasEC. Lancet Oncol 2010; 11: 193-203

Příčiny KV komplikací u nemocných léčených systémovou terapií

ONCOLOGY LETTERS 11: 939-944, 2016

Risk factors of atherosclerosis during systemic therapy targeting vascular endothelial growth factor

HANA ŠTUDENTOVÁ[1], JARMILA INDRÁKOVÁ[2], PAVLA PETROVÁ[3], MILAN KAMÍNEK[4], HANA KALÁBOVÁ[1], VLASTISLAV ŠRÁMEK[1], TOMÁŠ ADAM[3] and BOHUSLAV MELICHAR[1,5]

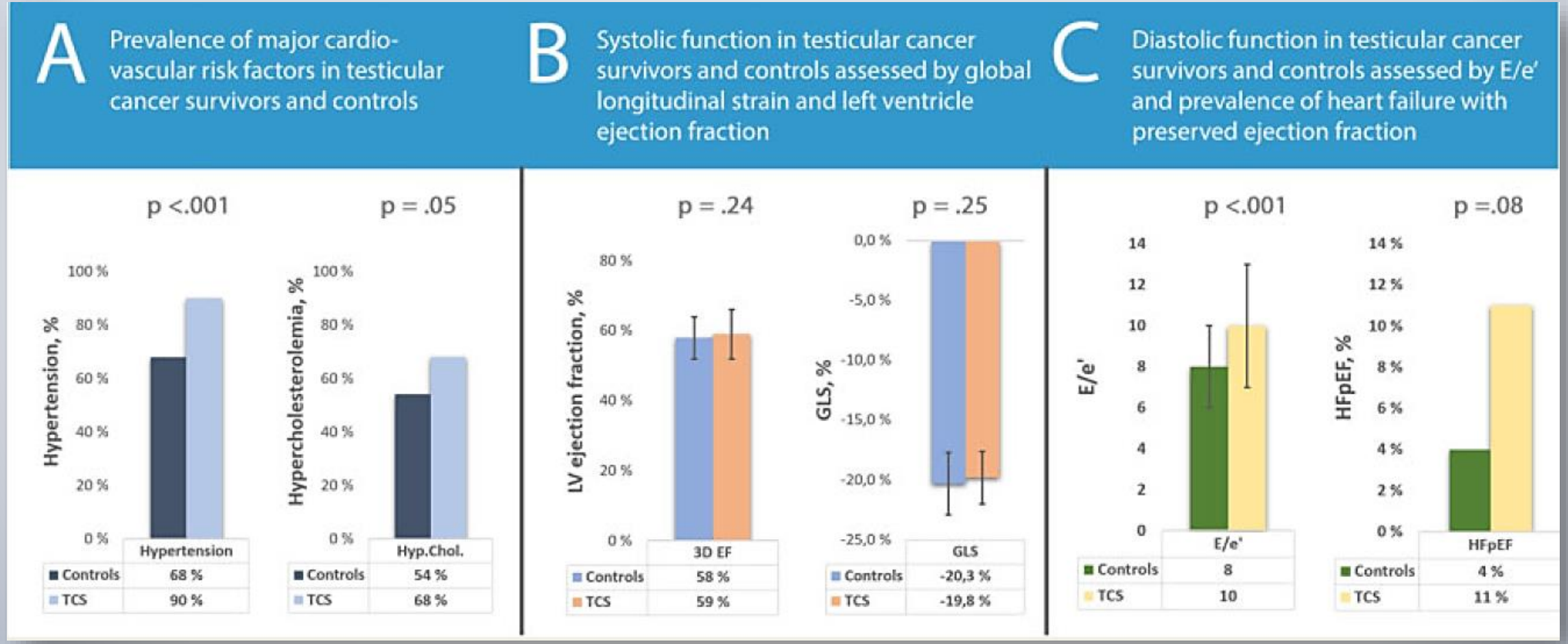
Departments of [1]Oncology, [2]Medicine, [3]Clinical Biochemistry and [4]Nuclear Medicine;
[5]Institute of Molecular and Translational Medicine, Palacký University Medical School and Teaching Hospital, Olomouc 775 20, Czech Republic

Příčiny KV komplikací u nemocných léčených systémovou terapií

- Změny v tloušťce IMT
- Arteriální hypertenze
- Změny na SPECT?

Študentová et al, 2016

Vliv chemoterapie na kardiovaskulární aparát – 30leté sledování po léčbě testikulárních nádorů



Bjerring et al. 2020

Pozdní komplikace léčby testikulárních nádorů

- Sekundární malignity (leukémie, solidní nádory)

- Kardiovaskulární toxicita (1,4-7,1x)
  - AP, IM, náhlé úmrtí
  - Kardiovaskulární morbidita (4,5 a 2,8x)

Fung C, Fossa SD, Milano MT, . Cardiovascular disease mortality after chemotherapy or surgery for testicular nonseminoma: a population-based study. J Clin Oncol 2017; 35: 1211-1222.
Haugnes HS, Wethal T, Aass N, . Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. *J Clin Oncol* 2010;28:4649–4657.
Huddart RA, Norman A, Shahidi M, . Cardiovascular disease as a long-term complication of treatment for testicular cancer. *J Clin Oncol* 2003;21:1513–1523. Meinardi MT, Gietema JA, van der Graaf WT, . Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. *J Clin Oncol* 2000;18

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Saro H. Armenian, Christina Lacchetti, Ana Barac, Joseph Carver, Louis S. Constine, Neelima Denduluri, Susan Dent, Pamela S. Douglas, Jean-Bernard Durand, Michael Ewer, Carol Fabian, Melissa Hudson, Mariell Jessup, Lee W. Jones, Bonnie Ky, Erica L. Mayer, Javid Moslehi, Kevin Oeffinger, Katharine Ray, Kathryn Ruddy, and Daniel Lenihan

DISKUSE