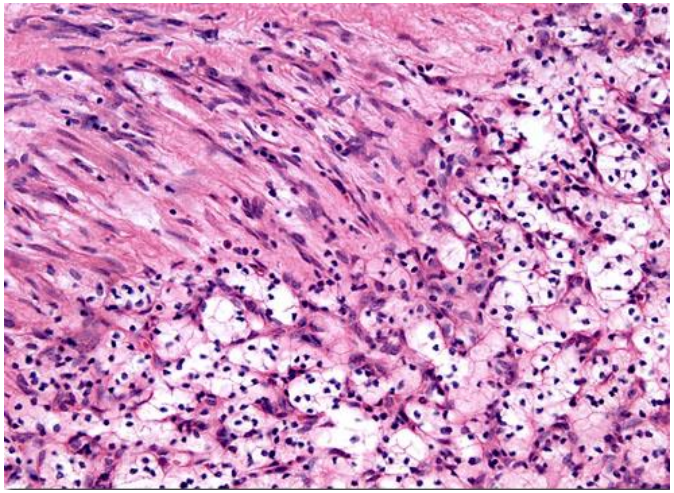
Cezary Szczylik
Klinika Onkologii
Wojskowy Instytut Medyczny. Warszawa

Rak nerkowokomórkowy w Polsce.

Epidemiologia : Rak nerkowokomórkowy RNK

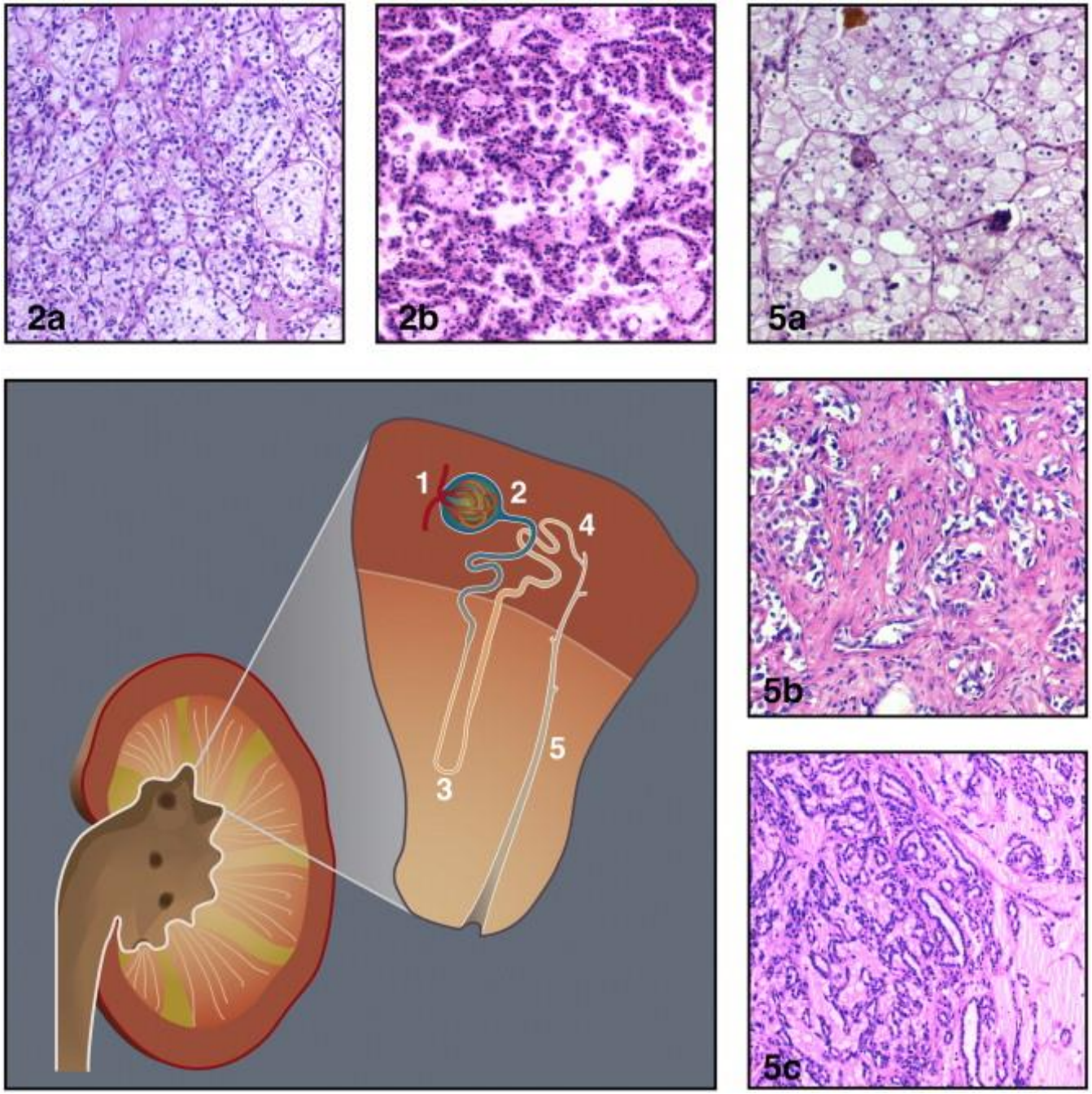


- RNK* stanowi **3%** nowotworów u dorosłych i **90–95%** guzów nerki
- częstość : 3/10 000

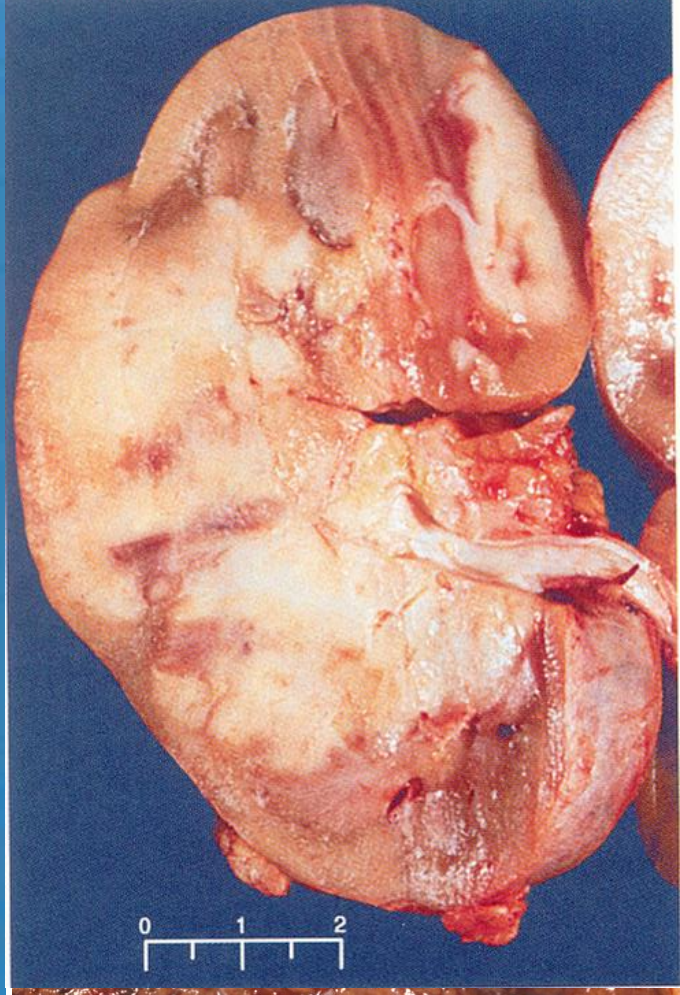
(w Polsce 5200 /rok/38 000 000 mieszk)

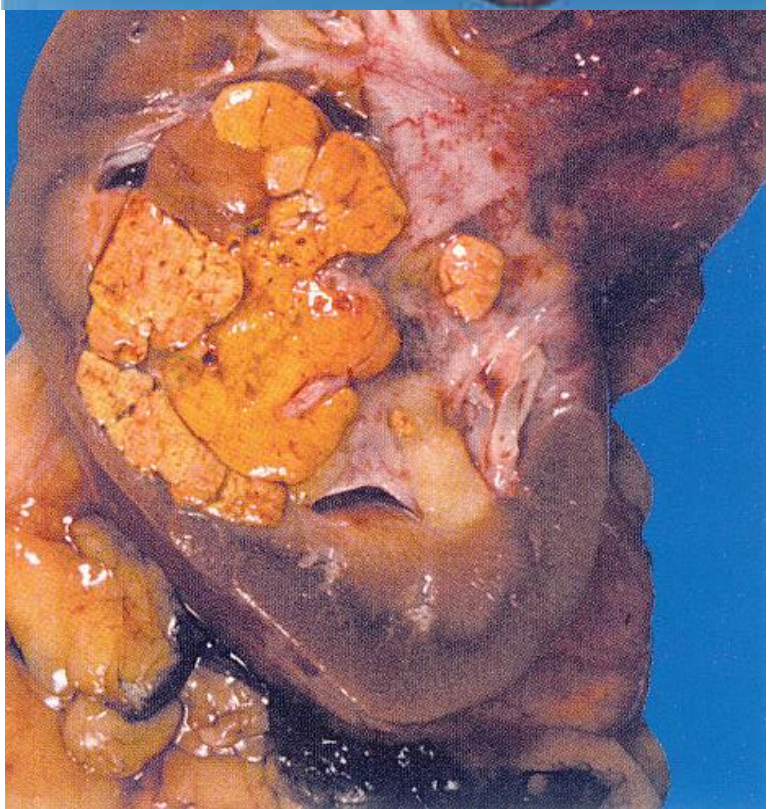
- M/F ratio : 1.6/1
- Średni wiek~ **60 rż**

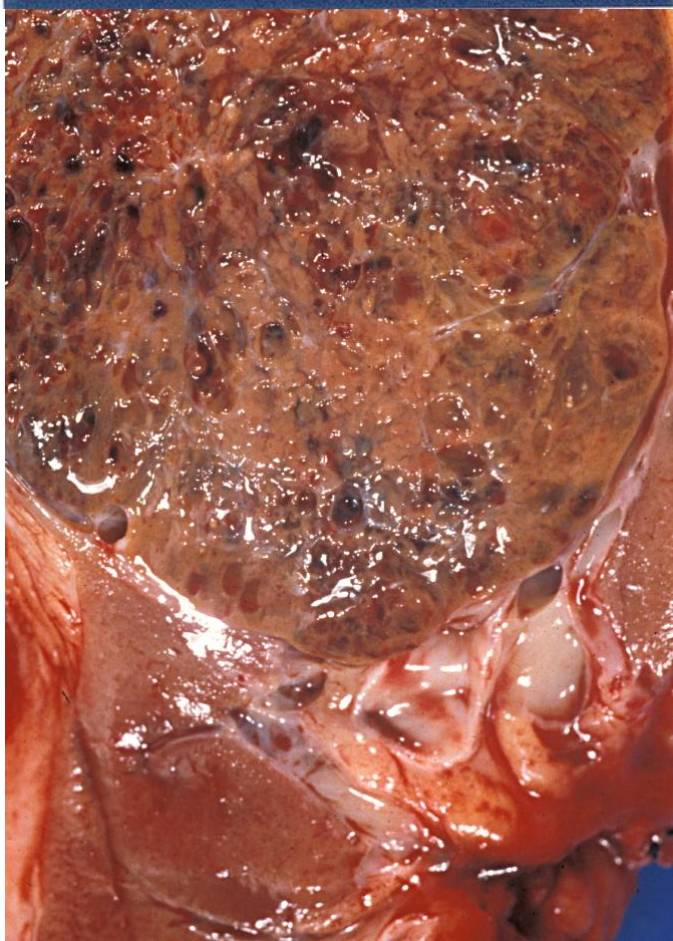
* Rak nerkowokomórkowy



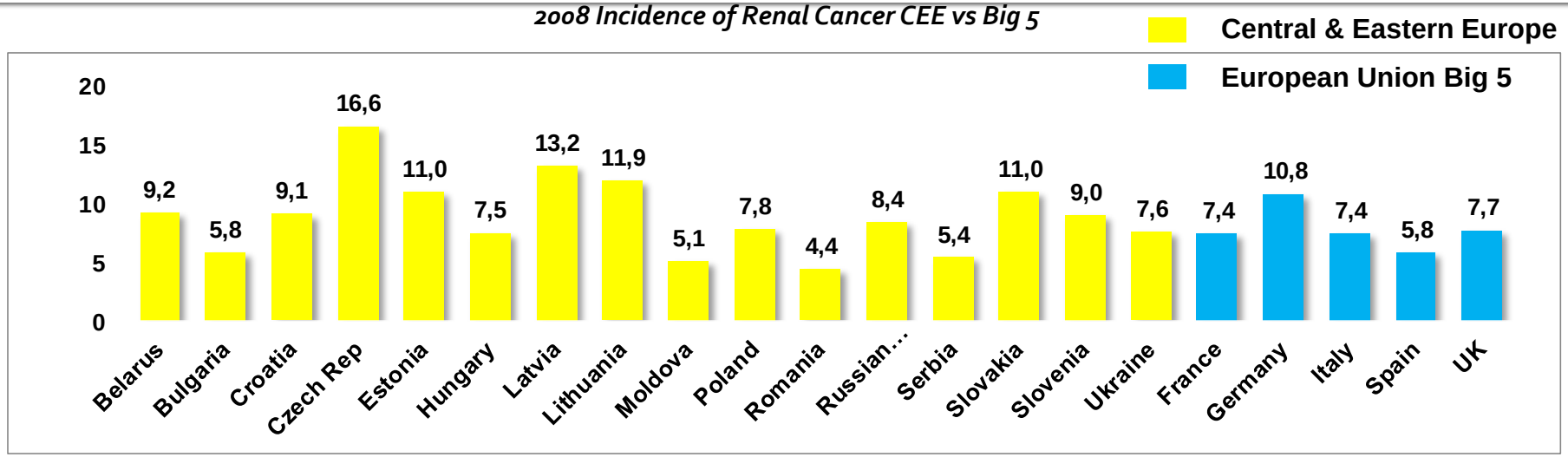
Baldewijns MM, van Vlodrop IJH, Schouten LJ, Soetekouw PM, de Bruïne AP, van Engeland M:
Genetics and epigenetics of renal cell cancer. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer* 2008; 1785 (2); 133–155

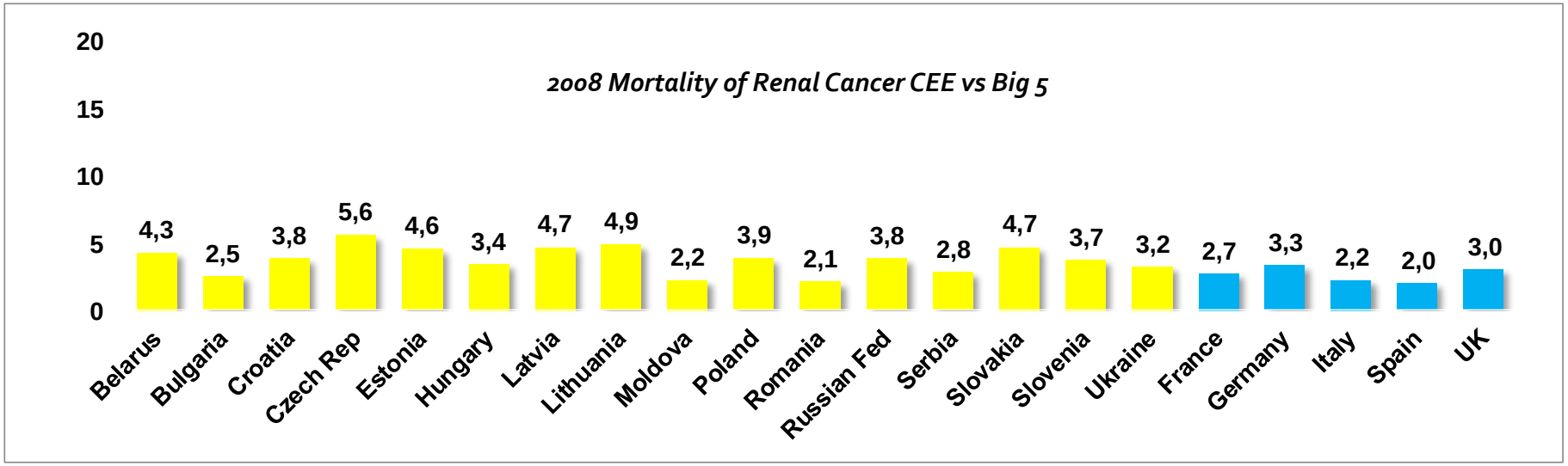

0
1
2





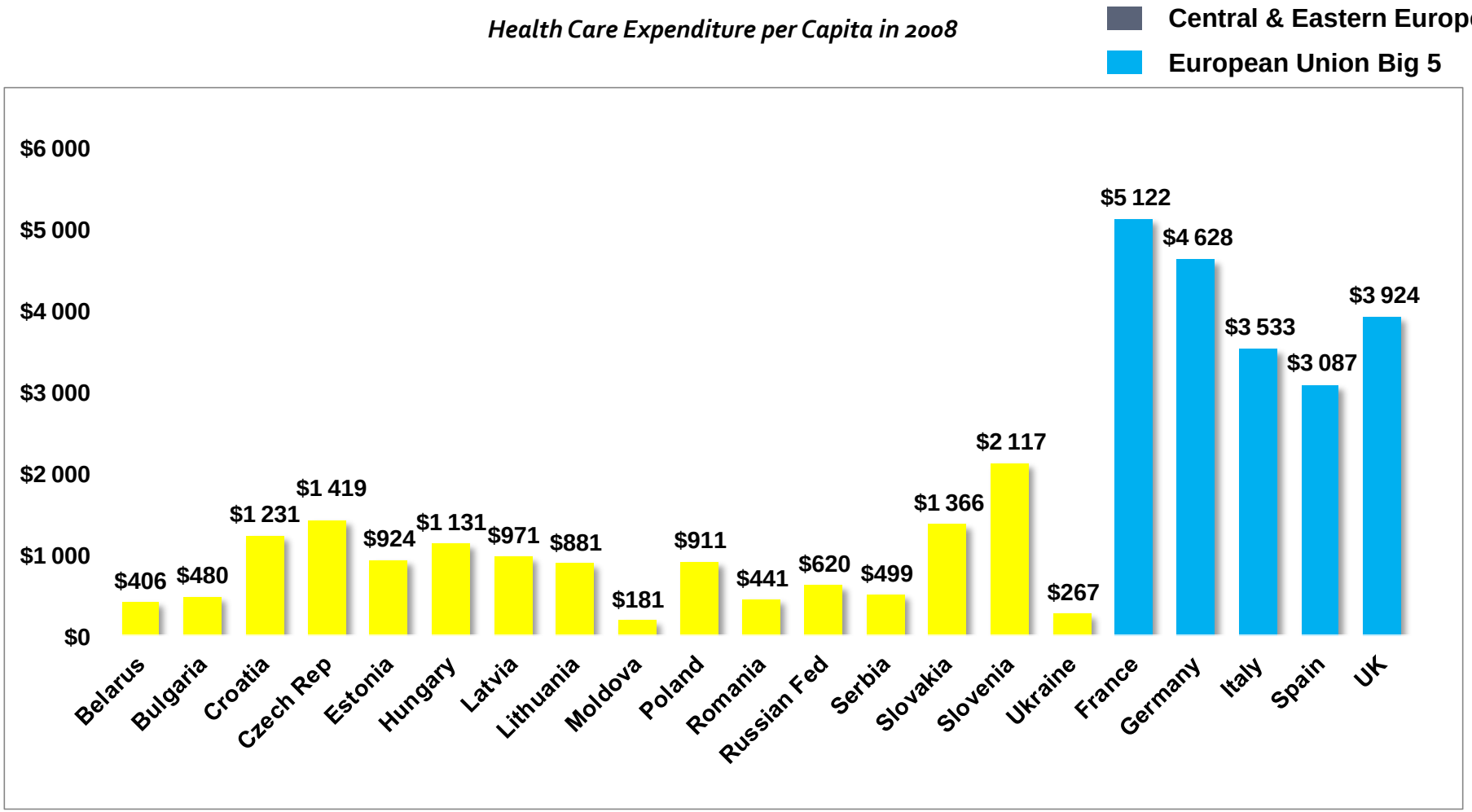
In CEE countries, incidence and mortality rates of RCC are among the highest in the world





Vrdoljak E *et al*.. *Expert Opin Pharmacother* 2012;13:159–174

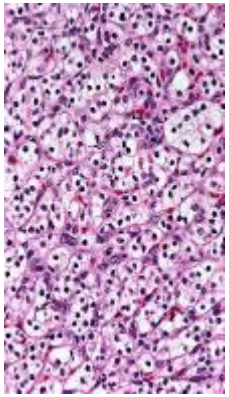
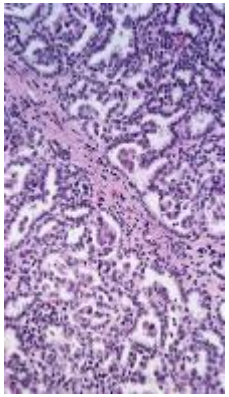
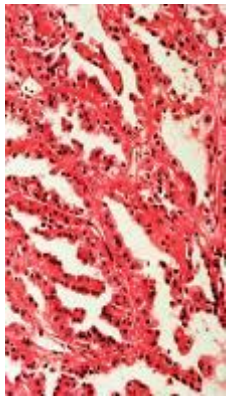
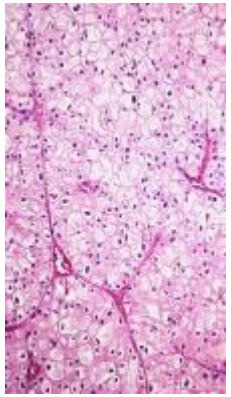
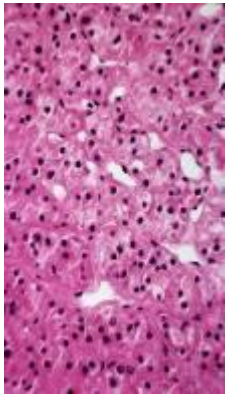
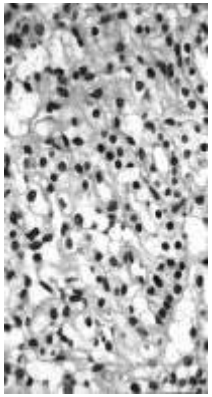
Total health care expenditure in CEE countries is far lower than Western Europe



Vrdoljak E *et al*.. *Expert Opin Pharmacother* 2012;13:159–174

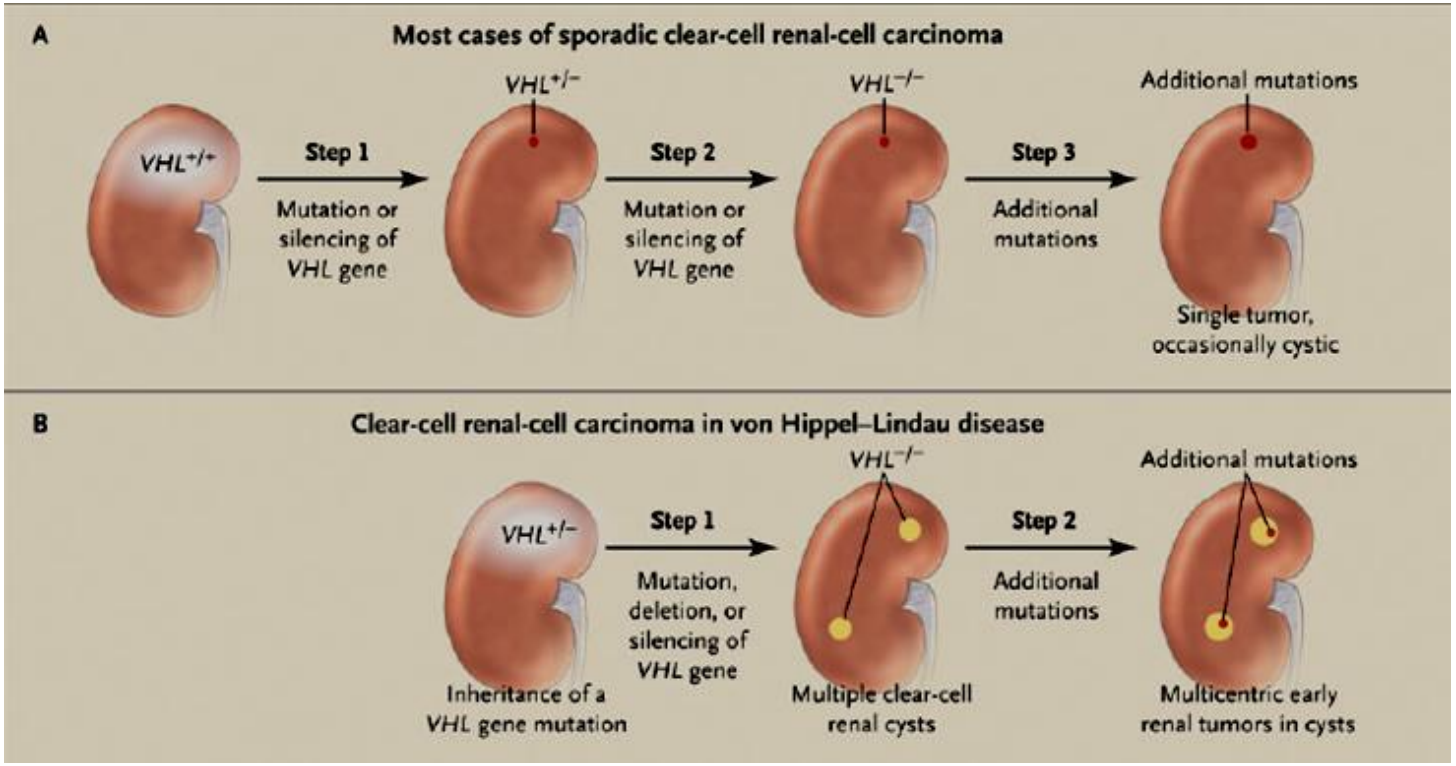
RNK: histologia i patogeneza molekularna

- RNK to heterogenna grupa nowotworów
  - Większość przypadków stanowi rak jasnokomórkowy

	Jasnokomórkowy	Nie-jasnokomórkowy			
Guz - typ histologiczny						
		Papillarny typ I,II		Chromopho	Oncocytic	
Częstość	75–85	12–14		4–6	2–4	1
Mutacja genetyczna	*VHL*	*c-MET*	*FH*			

BHD = Birt–Hogg–Dubé; FH = fumarate hydratase; VHL = von Hippel–Lindau

Genetyka VHL

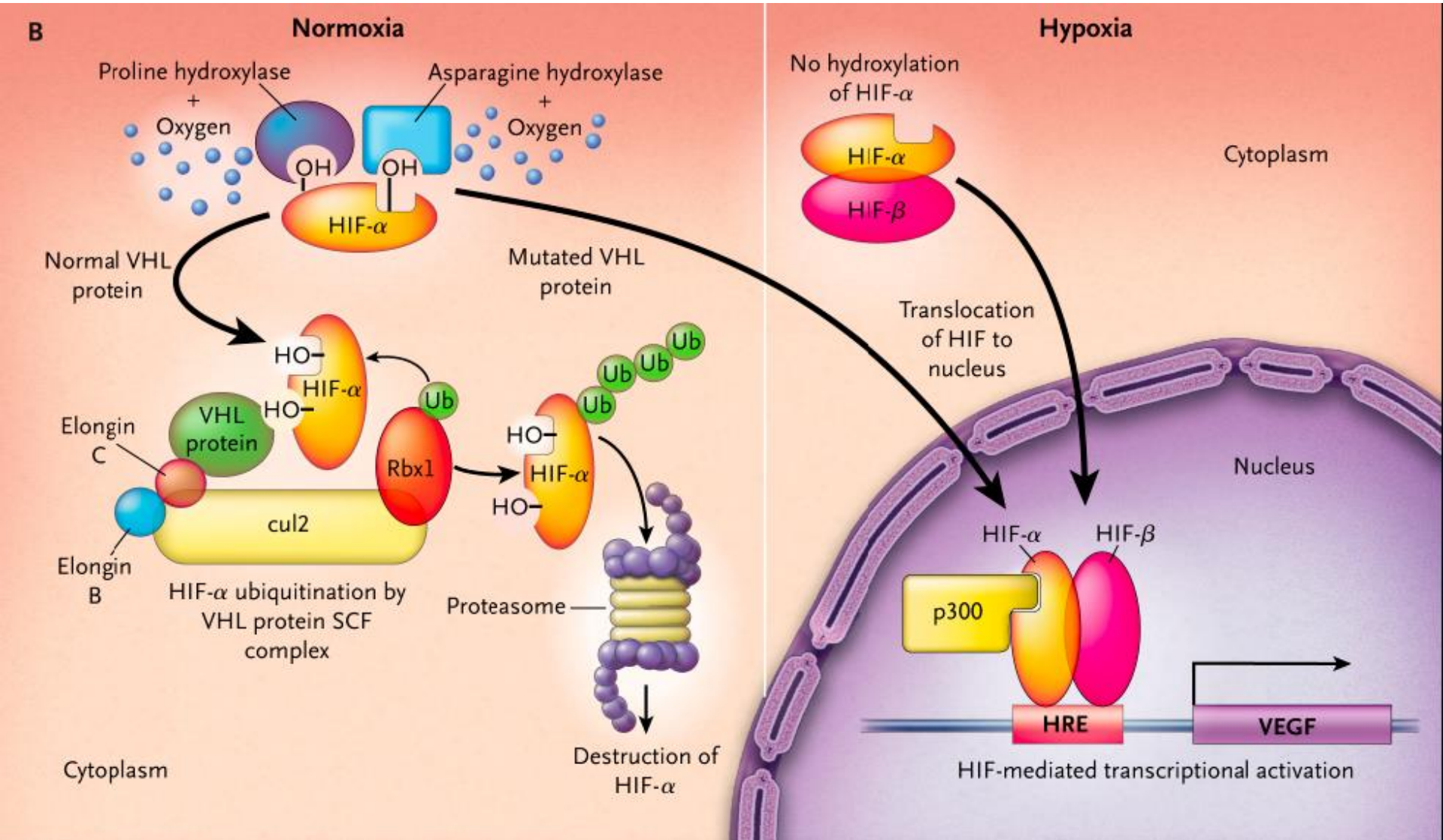


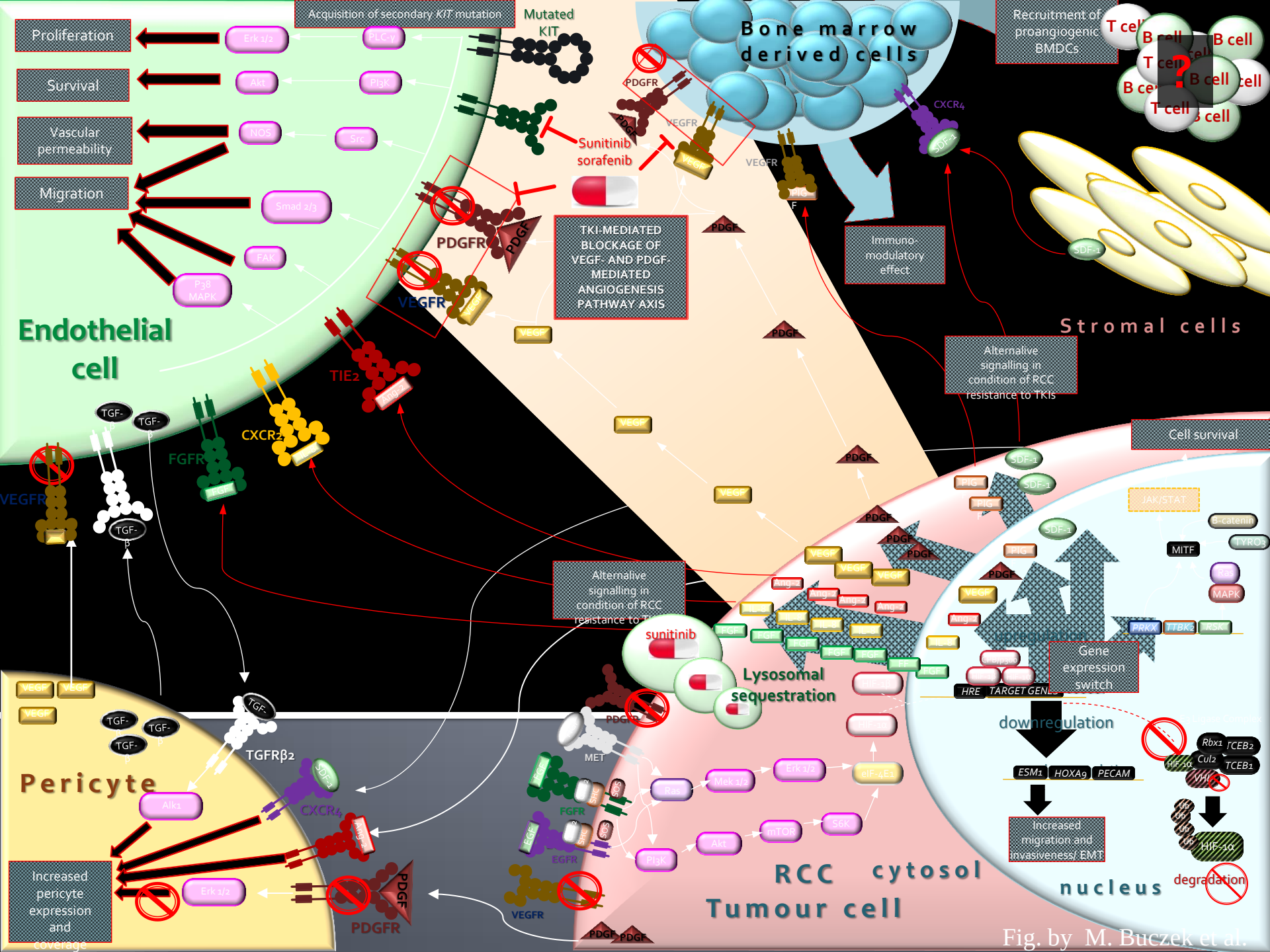
Cohen NEJM 2005

- sporadyczny RNK ccRCC: Teoria 2 uderzeń
  - 84-98% delecja jednego allelu (LOH)
  - mutacje w 34-57% innych alleli
  - Metylacja w 5-19%
    - ➔ więcej 80% CCC: mutacje genu VHL

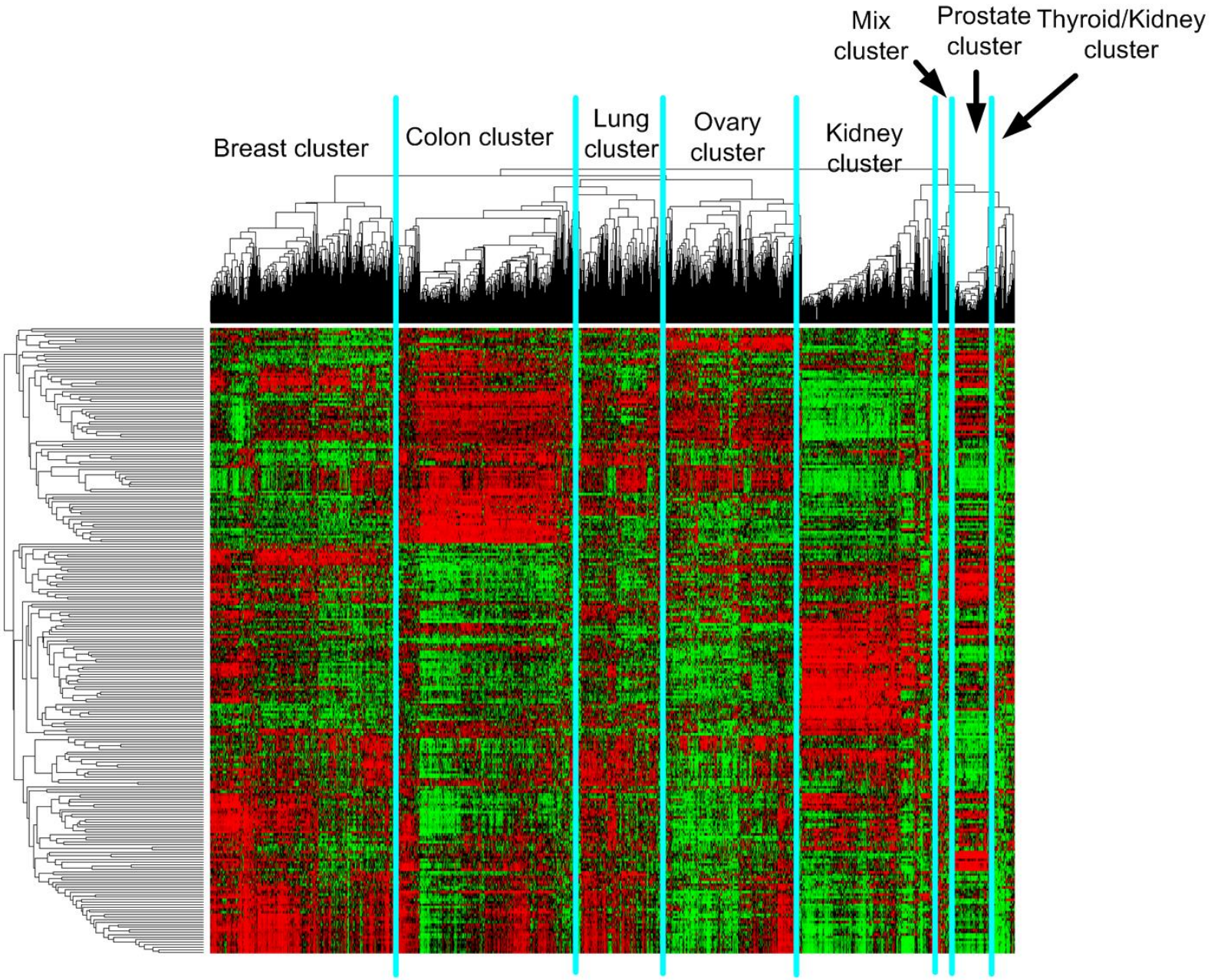
Rini JCO 2005

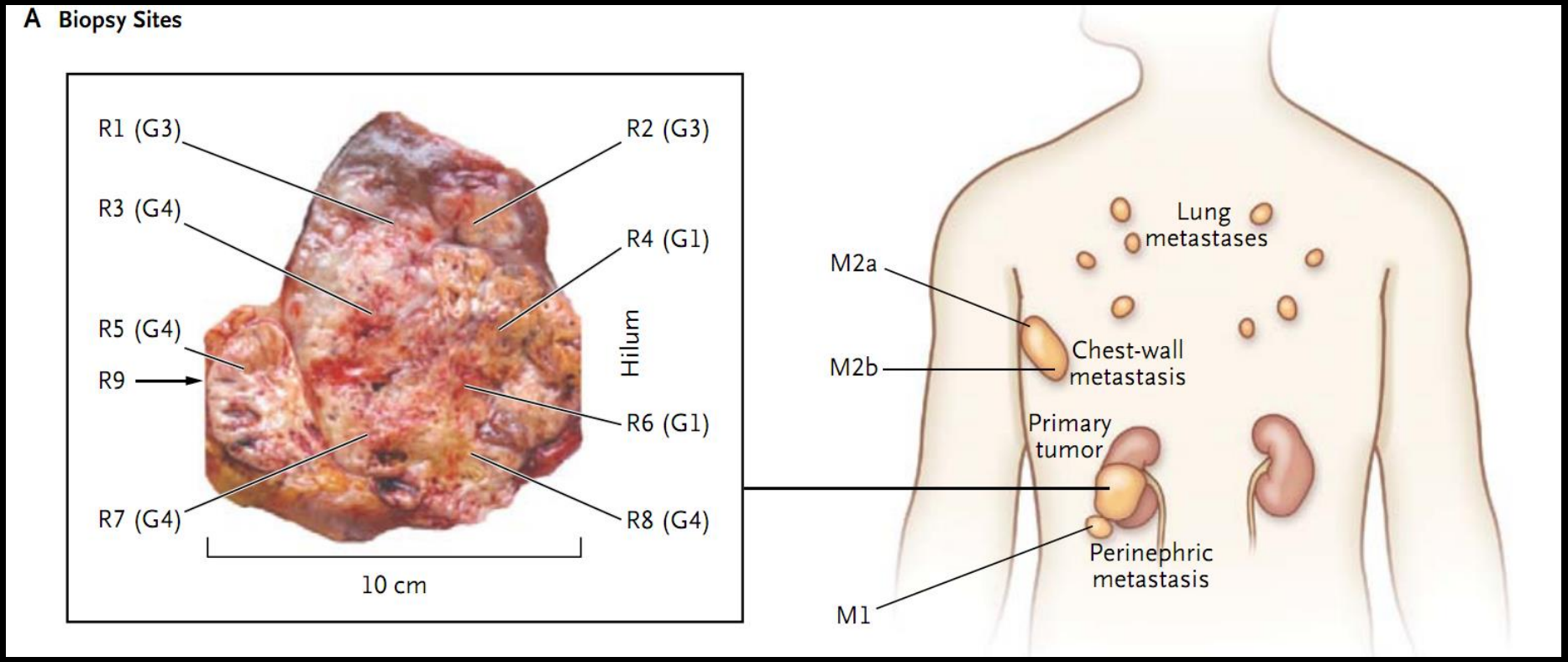
Patologia molekularna raka jasnokomórkowego nerki



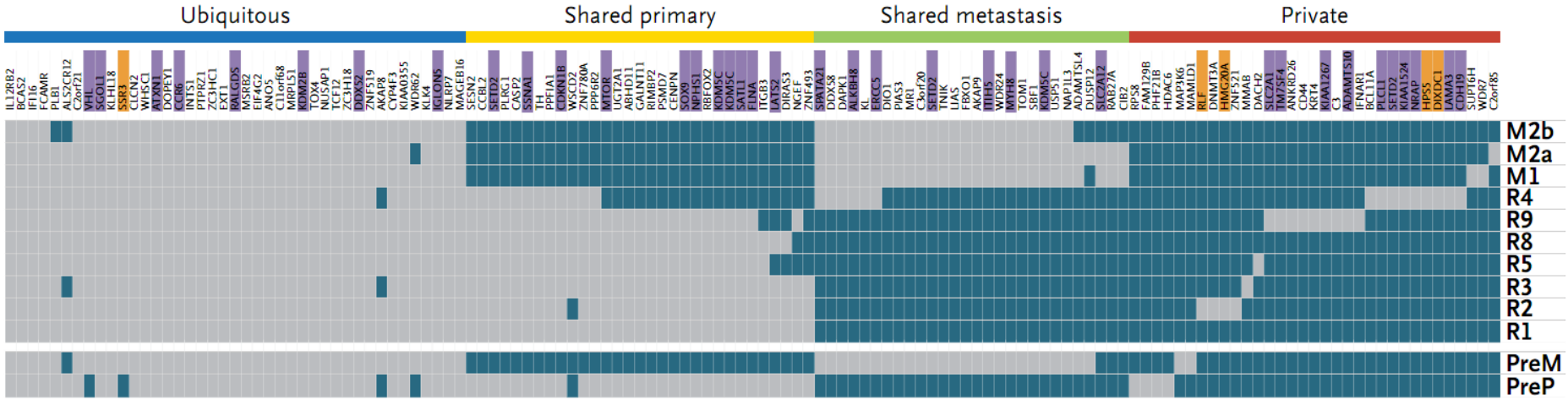

Acquisition of secondary KIT mutation
Mutated KIT
Bone marrow derived cells
Recruitment of proangiogenic BMDCs
Proliferation
Survival
Vascular permeability
Migration
Erk 1/2
PLC-γ
Akt
PI3K
NOS
Src
Smad 2/3
FAK
P38 MAPK
Sunitinib
sorafenib
PDGFR
VEGFR
TKI-MEDIATED BLOCKAGE OF VEGF- AND PDGF-MEDIATED ANGIOGENESIS PATHWAY AXIS
Immuno-modulatory effect
CXCR4
SDF-1
Stromal cells
Endothelial cell
TIE2
CXCR2
FGFR
TGF-β
Alternalive signalling in condition of RCC resistance to TKIs
Cell survival
JAK/STAT
B-catenin
TYRO3
MITF
MAPK
PRKX
TTBK2
RSK
Gene expression switch
HRE
TARGET GENES
downregulation
ESM1
HOXA9
PECAM
Increased migration and invasiveness/ EMT
nucleus
Rbx1
TCEB2
Cul2
TCEB1
HIF-1α
degradation
sunitinib
Lysosomal sequestration
MET
Ras
Mek 1/2
Erk 1/2
eIF-4E1
mTOR
S6K
PI3K
Akt
RCC Tumour cell
cytosol
Pericyte
TGFRβ2
Alk1
Increased pericyte expression and coverage
Fig. by M. Buczek et al.

1566 pierwotnych guzów epitelialnych i 178 guzów przerzutowych

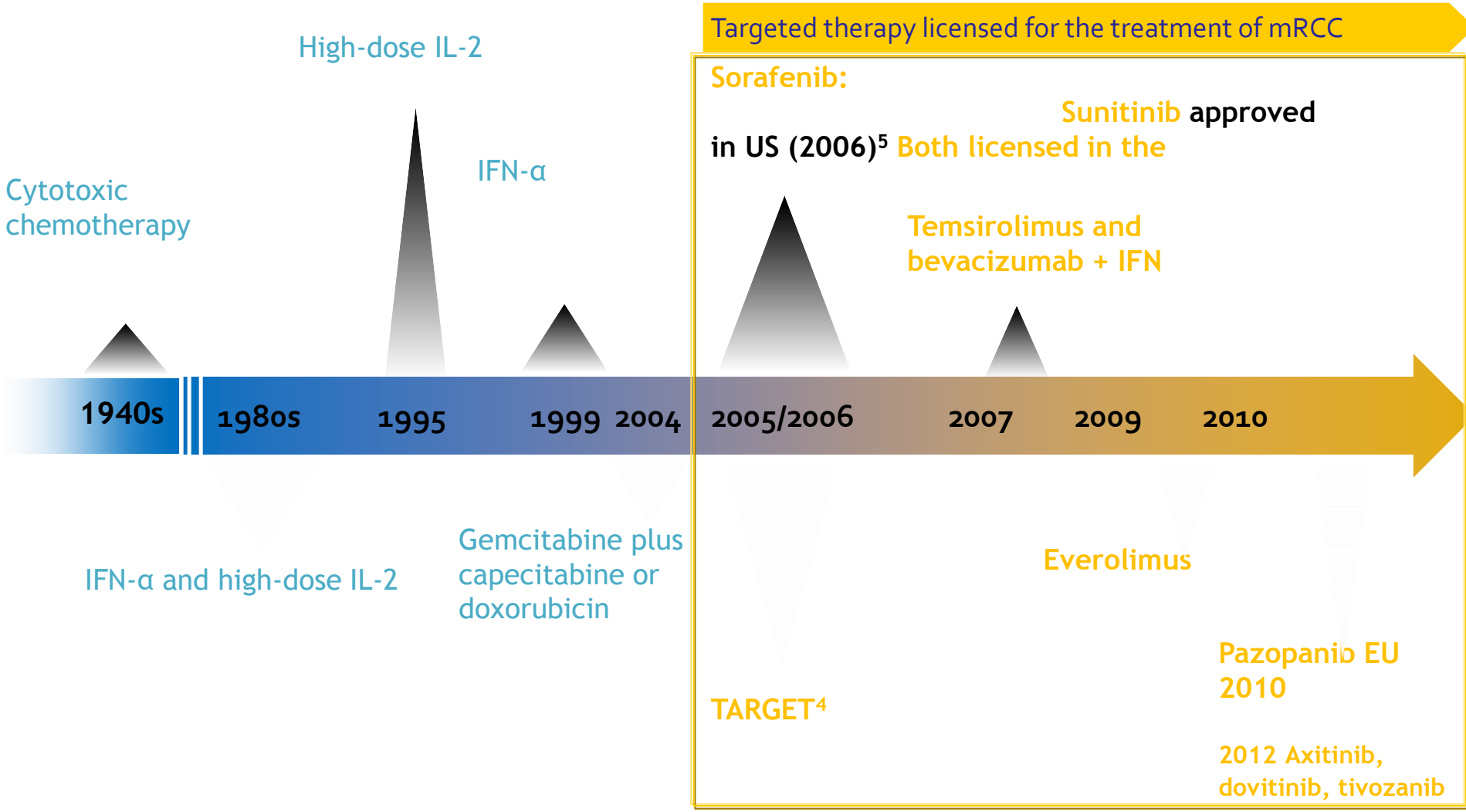



A Biopsy Sites
R1 (G3)
R2 (G3)
R3 (G4)
R4 (G1)
R5 (G4)
R9
Hilum
R6 (G1)
R7 (G4)
R8 (G4)
10 cm
Lung metastases
M2a
M2b
Chest-wall metastasis
Primary tumor
Perinephric metastasis
M1

B Regional Distribution of Mutations



Postęp w leczeniu RCC: terapie systemowe- terapie celowane



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2007 VOL. 356 NO. 2

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., Pharm.D., Piotr Tomczak, M.D., M. Dror Michaelson, M.D., Ph.D., Ronald M. Bukowski, M.D., Olivier Rixe, M.D., Ph.D., Stéphane Oudard, M.D., Ph.D., Sylvie Negrier, M.D., Ph.D., Cezary Szczylik, M.D., Ph.D., Sindy T. Kim, B.S., Isan Chen, M.D., Paul W. Bycott, Dr.P.H., Charles M. Baum, M.D., Ph.D., and Robert A. Figlin, M.D.*

Targeted therapies: more options for RCC treatment

		Phase III data		
Agent/ Class	Comparator	Line of treatment	Benefit in PFS/OS	Main exclusion criteria
Sorafenib[1] Oral TKI	Placebo	CK treated or CK unsuitable	Yes	Brain metastases, previous exposure to VEGF inhibitors
Sunitinib2 Oral TKI	IFN-α	First line	Yes	Brain metastases, previous systemic therapy, uncontrolled hypertension, cardiovascular events
Temsirolimus3 IV mTOR inhibitor	IFN-α	First line poor risk only	Yes	Previous systemic therapy
Bevacizumab + IFN-α4 IV anti-VEGF Ab	IFN-α	First line	Yes	Previous systemic therapy, brain metastases, uncontrolled hypertension, cardiovascular disease, recent major surgery, anti-coagulant medication
Everolimus5 Oral mTOR inhibitor	Placebo	≥ Second line	Yes	Brain metastases, previous exposure to mTOR inhibitors, uncontrolled medical conditions
Pazopanib6 Oral TKI	Placebo	First line or CK treated	Yes	Brain metastases, poorly controlled hypertension, cardiovascular or cerebrovascular events, prior exposure to targeted therapy

1. Escudier B, et al. N Engl J Med 2007;356:125–34. 2. Motzer RJ, et al. N Engl J Med 2007;356:115–24.
3. Hudes G, et al. N Engl J Med 2007;356:2271–81. 4. Escudier B, et al. Lancet. 2007;370:2103–11.
5. Motzer RJ, et al. Cancer 2010;116:4256–65. 6. Sternberg CN, et al. J Clin Oncol 2010;28:1061–8.

CK = cytokine

ESMO 2013 Renal cell carcinoma guidelines

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii49-iii56, 2014
doi:10.1093/annonc/mdu259

Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

B. Escudier[1], C. Porta[2], M. Schmidinger[3], F. Algaba[4], J. J. Patard[5], V. Khoo[6,7], T. Eisen[8] & A. Horwich[6] on behalf of the ESMO Guidelines Working Group*

[1]Institut Gustave Roussy, Villejuif, France; [2]IRCCS San Matteo University Hospital Foundation, Pavia, Italy; [3]Clinical Division of Oncology, Department of Medicine I and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [4]Department of Pathology, Fundació Puigvert, Universitat Autónoma de Barcelona, Barcelona, Spain; [5]CHU Bichât, Université Paris XI, Kremlin Bicêtre, France; [6]Institute of Cancer Research and Royal Marsden Hospital, London, UK; [7]Monash University, Melbourne, Australia; [8]Cambridge Biomedical Campus, Cambridge, UK

incidence and epidemiology

Renal cell carcinoma (RCC) accounts for 2%–3% of all adult malignancies, representing the seventh most common cancer in men and the ninth most common cancer in women [1].

Worldwide, there are ~209 000 new cases and 102 000 deaths per year. The incidence of all stages of RCC has increased over the past several years, contributing to a steadily increasing mortality rate per unit population. Active and passive cigarette smoking is an established risk factor for RCC as well as hypertension. However, anti-hypertensive medications such as diuretics are not independently associated with RCC development. RCC also appears to be more common in patients with obesity, end-stage renal failure, acquired renal cystic disease and tuberous sclerosis.

Approximately 2%–3% of RCC are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being Von Hippel Lindau disease.

In recent years, many new genes associated with RCC have been reported (such as PBRM1, SETD2, BAP1). Their roles in pathogenesis and as prognostic biomarkers are currently under investigation.

diagnosis and pathology/molecular biology

The proportion of small and incidental renal tumours has significantly increased owing to the widespread use of abdominal imaging e.g. ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). More than 50% of RCCs are currently detected incidentally. However, some patients with RCC still present with clinical symptoms, such as flank pain, gross haematuria and palpable abdominal mass (the classical triad); metastatic symptoms like bone pain or lung nodules; or paraneoplastic syndromes, such as hypercalcaemia, unexplained fever, erythrocytosis or wasting syndromes.

Physical examination alone directs further examinations especially when symptoms and signs mentioned above are present. Suspicion of RCC should prompt laboratory examinations of serum creatinine, haemoglobin, leukocyte and platelet counts, lactate dehydrogenase and serum-corrected calcium, in addition to other symptom derived tests [IV, B]. Inflammatory syndrome tests such as C-reactive protein (CRP) and erythrocyte sedimentation rate have been suggested. Some of these tests are prognosticators for survival and used for risk assessment (see later).

Most cases of RCC are strongly suspected by imaging. Diagnosis is usually suggested by ultrasonography and further investigated by CT scan, which allows for assessment of local invasiveness, lymph node involvement or other metastases. MRI may provide additional information in investigating local advancement and venous involvement by tumour thrombus. MRI may also be useful in situations where i.v. contrast cannot be used.

For accurate staging of RCC, abdominal and chest CT or MRI is mandatory [III, A]. Chest CT is the most sensitive approach for chest staging [III, A]. Unless indicated by clinical or laboratory signs or symptoms, the use of bone scan or CT (or MRI) of the brain is not recommended for routine clinical practice [III, A]. Positron emission tomography is not a standard investigation in the diagnosis and staging of RCC [I, B].

A renal tumour core biopsy provides histopathological confirmation of malignancy with high sensitivity and specificity. A diagnostic biopsy is especially required before treatment with ablative therapies [III, B]. It is also indicated in patients with metastatic disease before commencing systemic treatment [III, B]. The final histopathological diagnosis, classification, grading and evaluation of prognostic factors are based on the nephrectomy specimen when available.

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Working Group: September 2008, last update July 2014. This publication supersedes the previously published version—Ann Oncol 2012; 23 (Suppl. 7): vii65–vii71.

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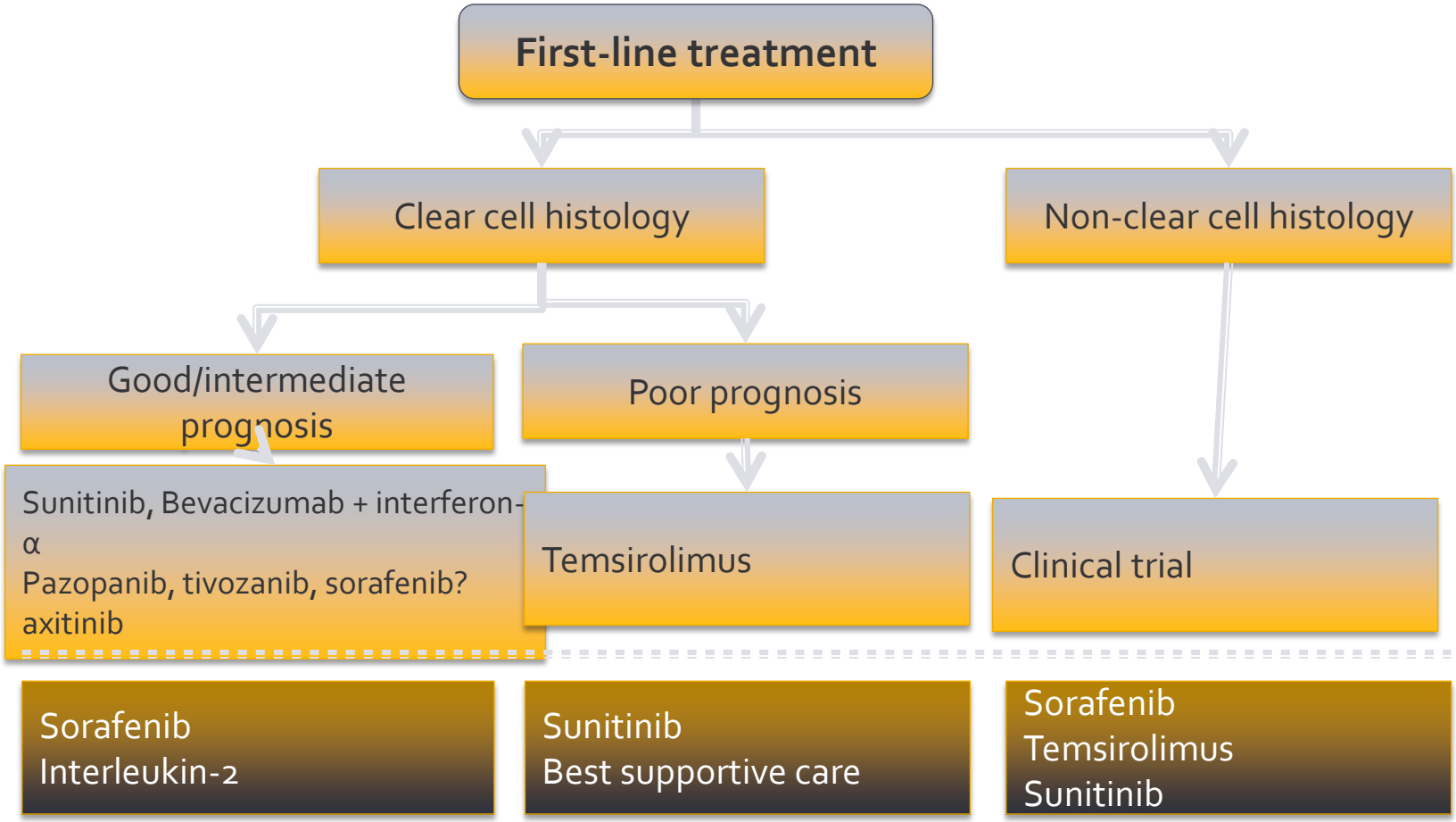
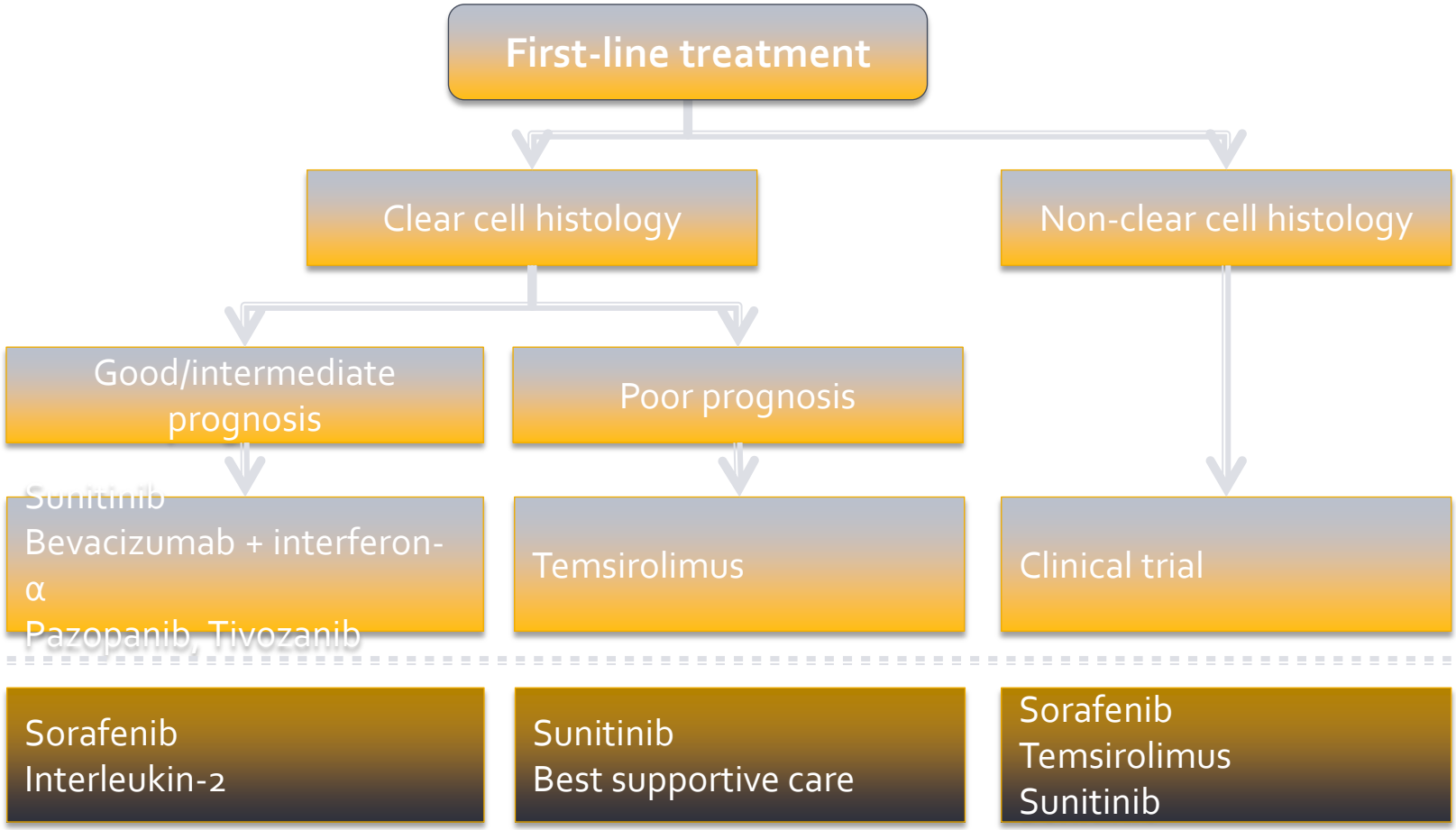
2013 ESMO guidelines: 1st-line treatment?



Escudier et al. Ann Oncol 2012;23(Suppl. 7):vii65-vii71

2012 ESMO guidelines: 1st-line treatment



Escudier et al. Ann Oncol 2012;23(Suppl. 7):vii65-vii71

What are II line scenarios for long-term response?

C -> A -> B -> D

A -> C -> B

B -> A -> C….

A -> B -> D

C -> D -> A -> B

D -> A -> C -> B

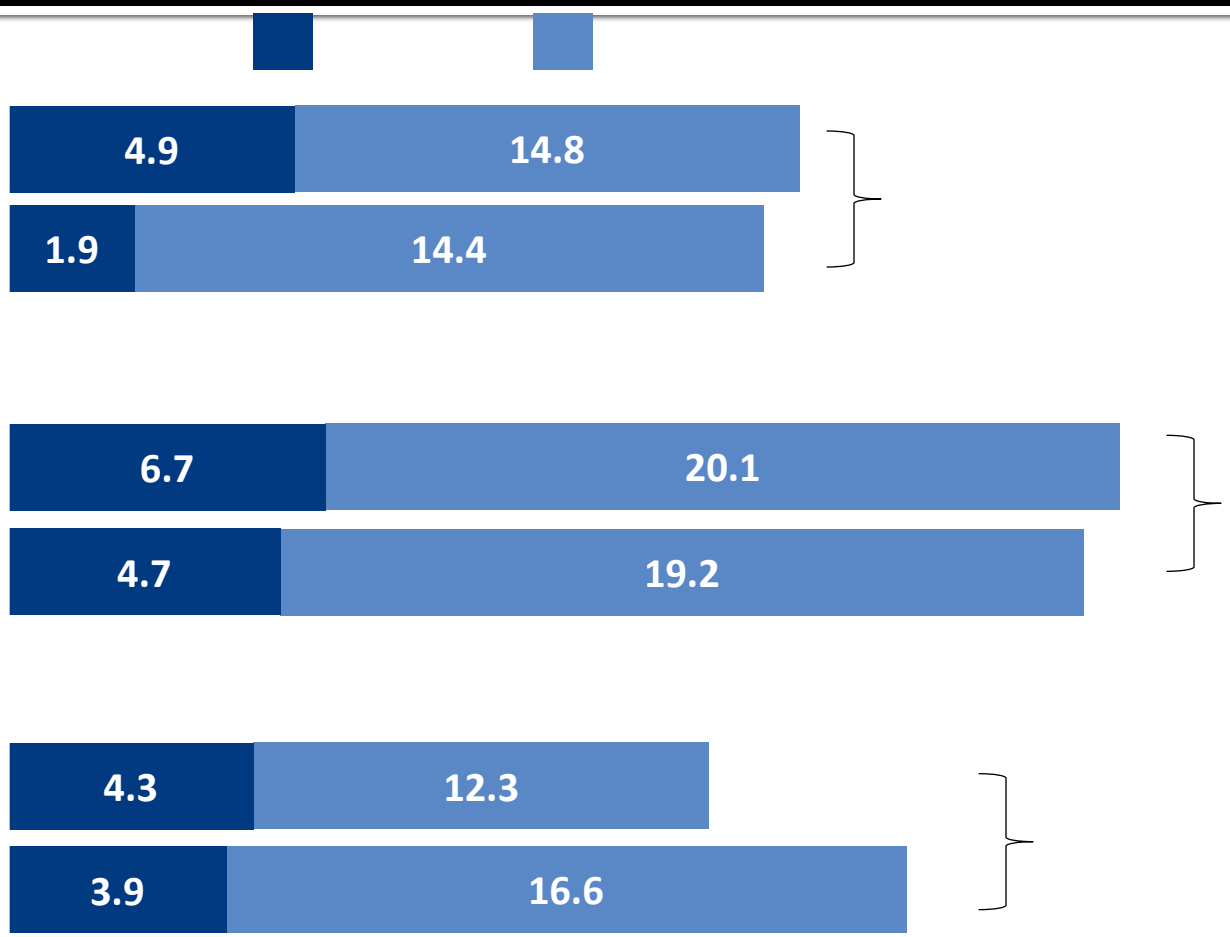
B -> A -> D…..

2014 NCCN guidelines for clear-cell mRCC: Second-line therapy

- Axitinib (1* following cytokine therapy and other TKIs)
- Sunitinib (1 following cytokine therapy, 2A† following other TKI)
- Sorafenib (1 following cytokine therapy, 2A following other TKI)
- Pazopanib (1 following cytokine therapy, 3 following other TKI)
- Everolimus (1 following TKI therapy)
- Temsirolimus (2A following cytokine therapy, 2B‡ following TKI)
- Bevacizumab (2A following cytokine therapy, 2B following TKI)
- IL-2 (2B)
- Best supportive care¶: See NCCN Palliative Care Guidelines
- Clinical trial

RCC = metastatic renal cell carcinoma;

Summarizing RCTs in 2nd line



1. Motzer RJ, et al. *Cancer* 2010;116:4256–65; 2. Rini BI, et al. *Lancet* 2011;378:1931–9; 3. Hutson TE, et al. *ESMO* 2012;abstract LBA22

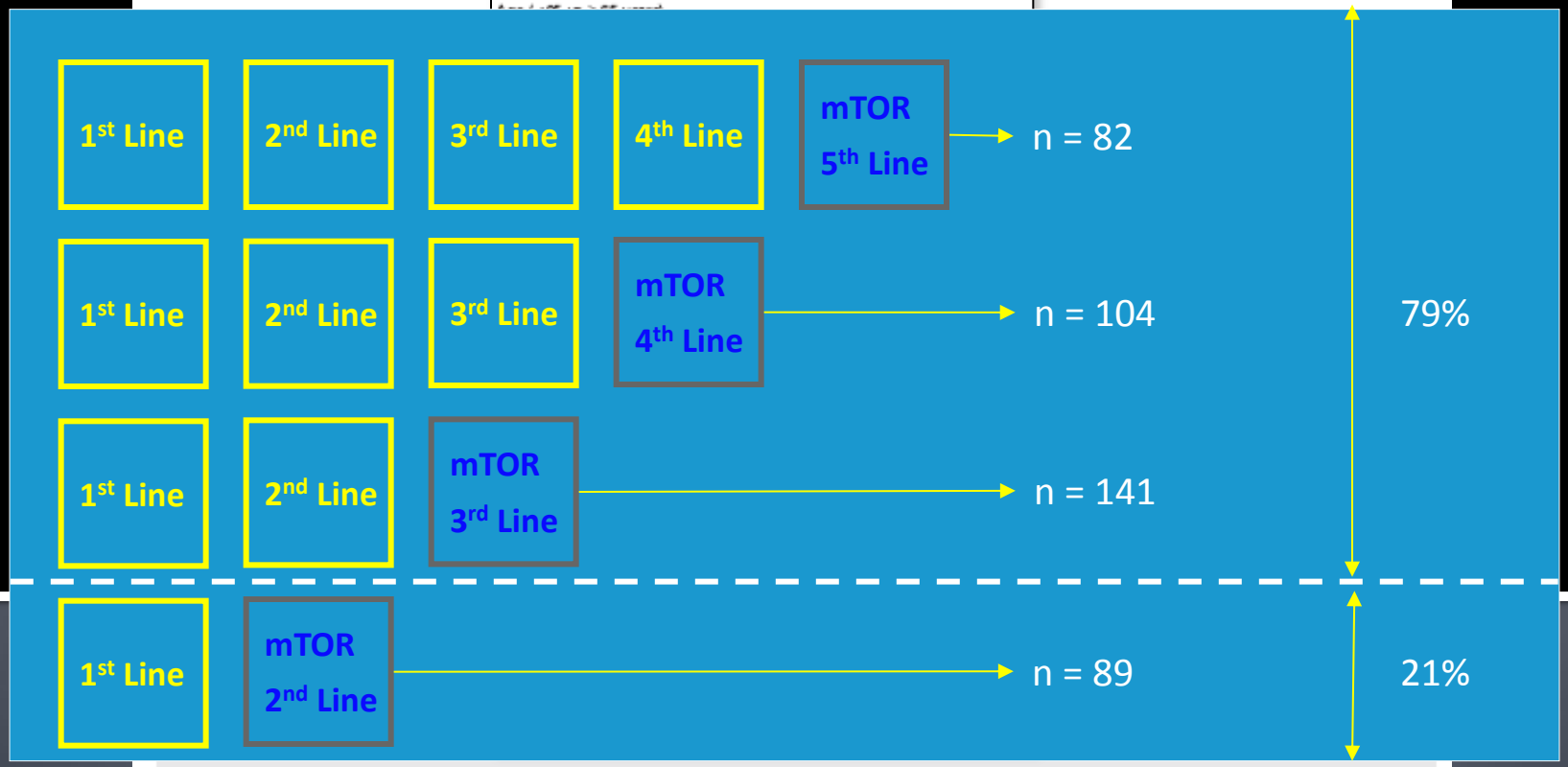
RECORD-1: which line of Tx?

Original Article

Phase 3 Trial … etastatic Renal Cell C…

Table 3. Results of Univariate Analysis for All Predefined Prognostic Factors

Factor	$P < .05$ on Univariate Analysis[a]	
	PFS	OS
KPS (<80 vs ≥80)[b]		x
Sex		



1. Motzer RJ, et al. *Lancet* 2008;372:449-56; 2. Motzer RJ, et al. *Cancer* 2010;116:4256-65; 3. Calvo E, et al. *Eur J Cancer* 2012;48:333-9.

Optymalna sekwencja leczenia – czy zawsze konieczna jest zmiana mech. działania?

TKI/VEGF inhibitor → **TKI/VEGF inhibitor** → **mTOR inhibitor** ✓

7 badań retrospektywnych

>400 pacjentów

wspierają leczenie sekwencyjne z TKI[1-7]

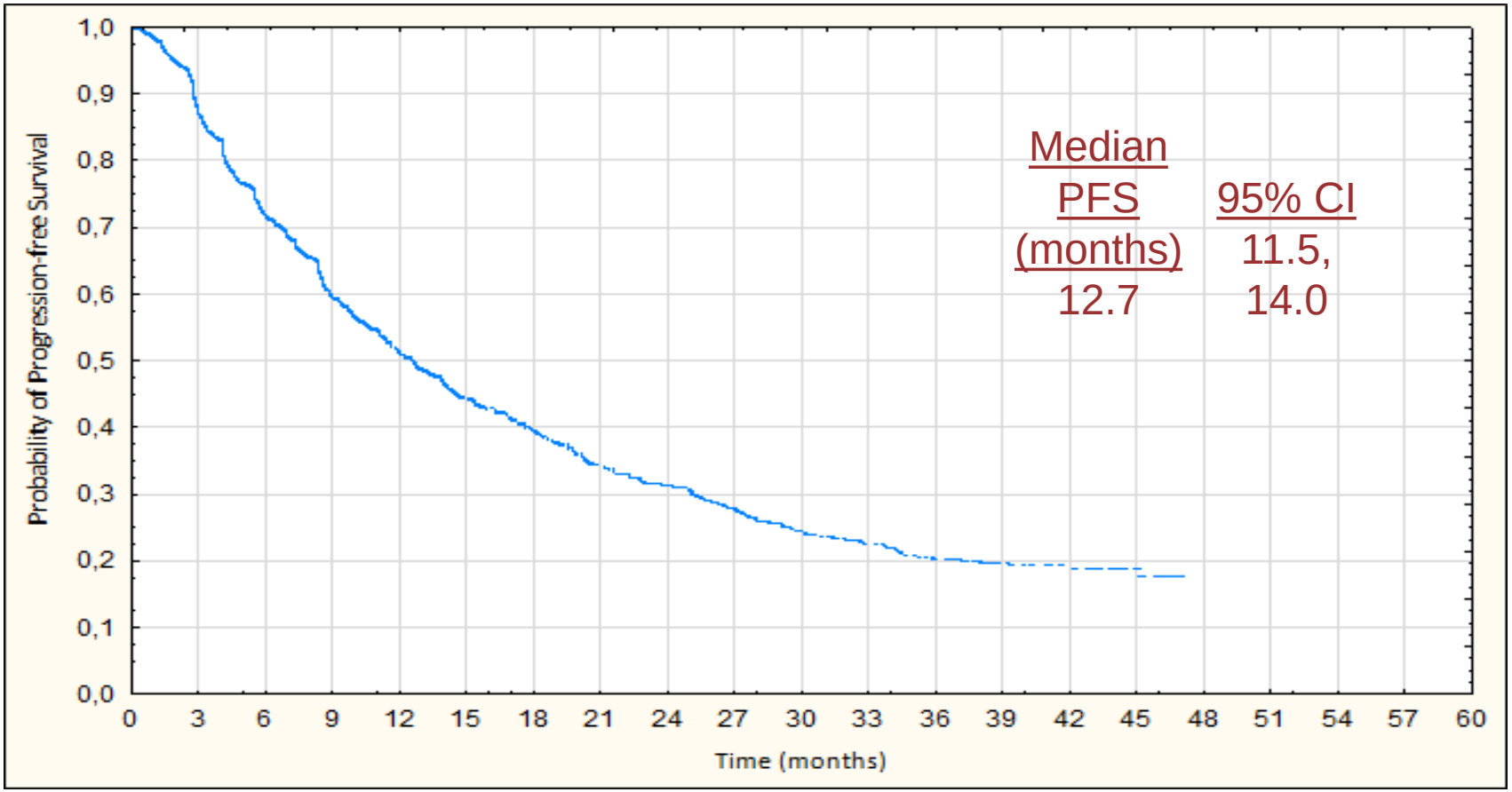
Skuteczność ewerolimusu jest porównywalna bez wgzlędu na liczbę stosowanych TKI[8]

TKI/VEGF inhibitor → **mTOR inhibitor** → **?**

Jak dotąd brak danych dot. skuteczności innych leków po inhibitorach mTOR

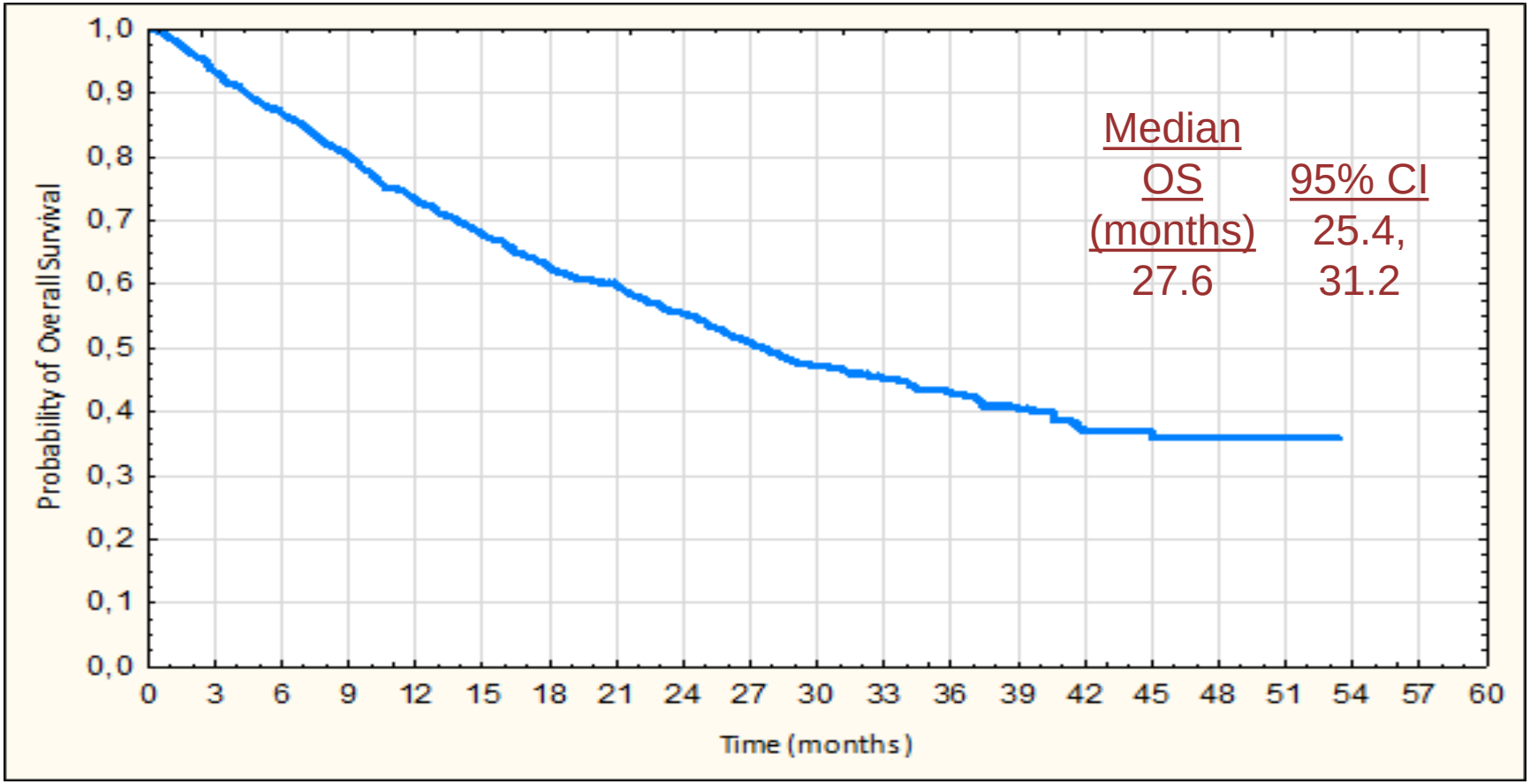
1. Tamaskar I, et al. J Urol 2008;179:81–6. 2. Richter S, et al. Onkologie 2008;31:234, abst V684
3. Choueiri TK, et al. ESMO 2008; abstr 593. 4. Eichelberg C, et al. Eur Urol 2007; 54:1373-78
5. Dudek AZ, et al. Cancer 2009; 115:61–7. 6. Sablin MP, et al. ASCO 2007, abstr 5038
7. Porta EAU 2009; abstr ? 8. Escudier B et al. presentation at ESMO 2008; abstr 720

PROGRESSION-FREE SURVIVAL
SUNITINIB



No. patients at risk

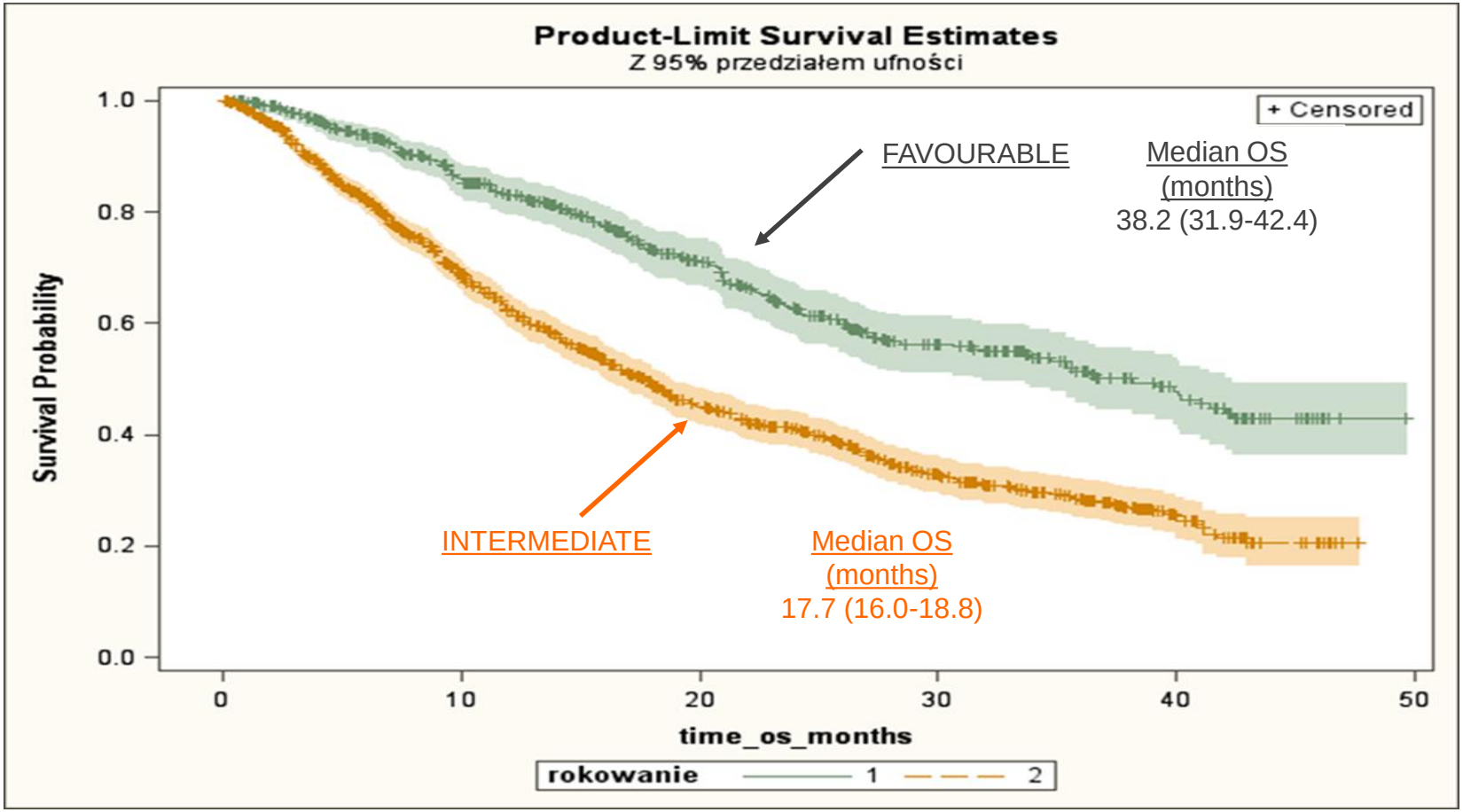
OVERALL SURVIVAL
SUNITINIB



No. patients at risk

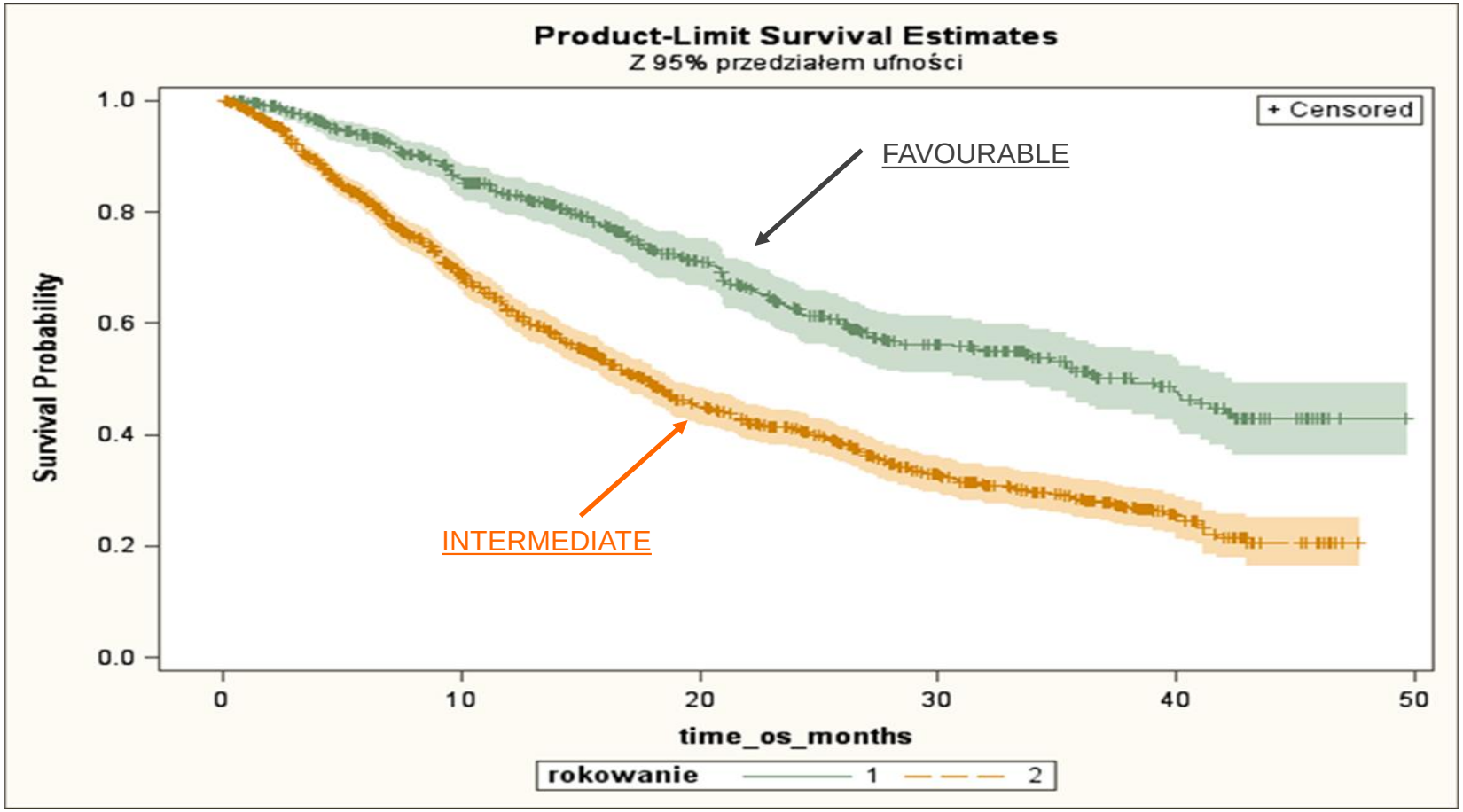
OVERALL SURVIVAL – SUNITINIB

(FAVOURABLE AND INTERMEDIATE MSKCC RISK GROUPS)

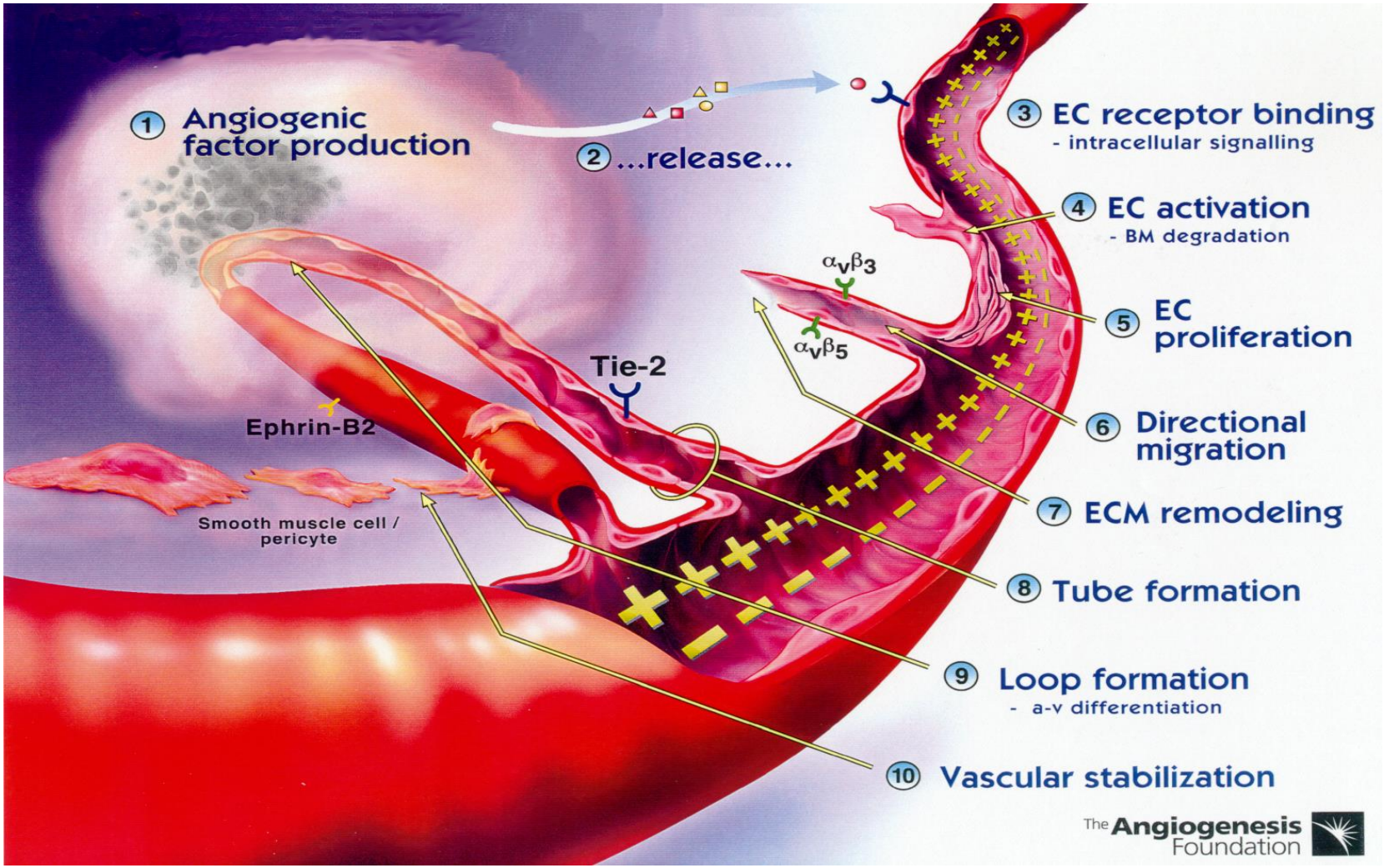


OVERALL SURVIVAL – SUNITINIB

(FAVOURABLE AND INTERMEDIATE MSKCC RISK GROUPS)



Przyszłość w leczeniu raka nerkowokomórkowego

- Lepsze zrozumienie biologii molekularnej dla losów przyszłych terapii
- Poszukiwanie komórek macierzystych RNK i analiza jej kontaktów z otaczającym środowiskiem
- Aktywne kontynuowanie badań nad
  - Nowymi lekami i ich kombinacjami
  - Leczeniem sekwencyjnym
  - Eskalacją dawki
  - Rolą chirurgii
  - Leczeniem neo-adjuwantowym i adjuwantowym
  - Szybsze wdrażania standardów międzynarodowych przez NFZ

Dlaczego rak nerki – to pole bitwy współczesnej onkologii – bo angiogeneza nie jest swoista tylko dla raka nerki