SIU UPDATES

ASCO GU

ASCO GENITOURINARY CANCER SYMPOSIUM

Kidney Cancer

COORDINATOR: **Alessandro Volpe,**

TEAM: **Alessandro Antonelli, Marco Carini, Giacomo Cartenì, Francesco Ferraù**

Case 1
E.P., male, 59 y.o.

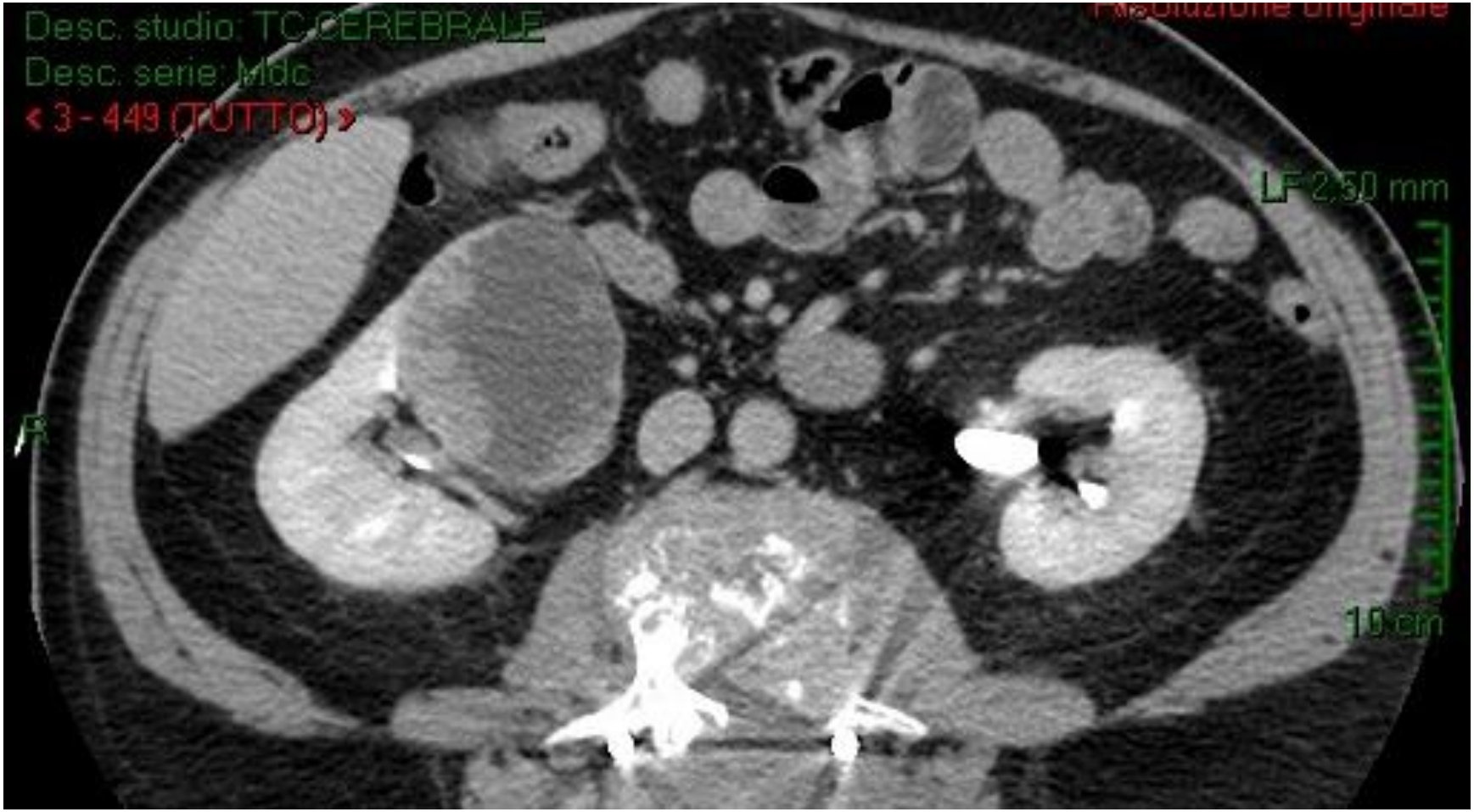
- Obesity (100 Kg)
- OSAS
- High blood pressure
- Colon diverticulosis

NOV
2014

- Acute lumbar pain with irradiation to the left lower limb and paresthesia
- MRI spine: L3 vertebral collapse without spinal cord injury

Lumbar arthrodesis was indicated

- Total body CT scan
  - Brain/neck/chest negative



- Bone scan
  - Significant uptake at the level of L3
  - Focal area at the distal third of the left femur (not confirmed at MRI)

Bone biopsy at the time of arthrodesis

Pathology:

clear cell neoplasm, likely of renal origin

Case 1
E.P., male, 59 y.o.

- Metastatic RCC (bone)
- ECOG 1 (lumbar pain irradiated to the hip and right lower limb in upright position, not at rest)
- sCr 0.77 mg/dL
- Hb 11.9 g/dL, WBC and PLTs normal
- Albumin, calcium, ALP, LDH normal
- MSKCC / IMDC score 2 (intermediate risk)

CYTOREDUCTIVE NEPHRECTOMY

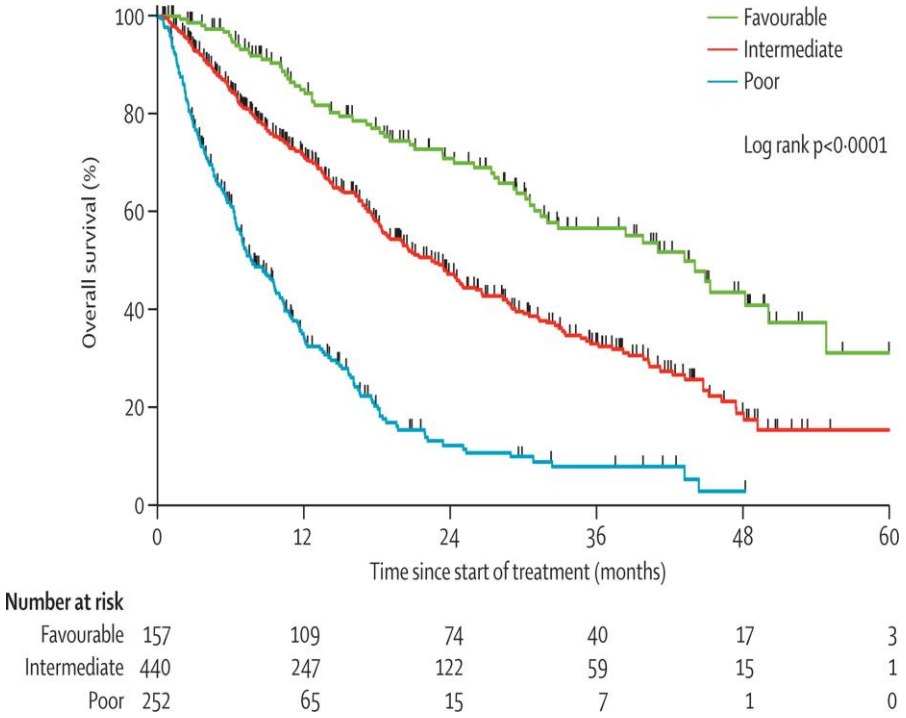
- Tumour resection is curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligo-metastatic resectable disease.

- For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary.

SELECTION IS KEY
PATIENT FEATURES

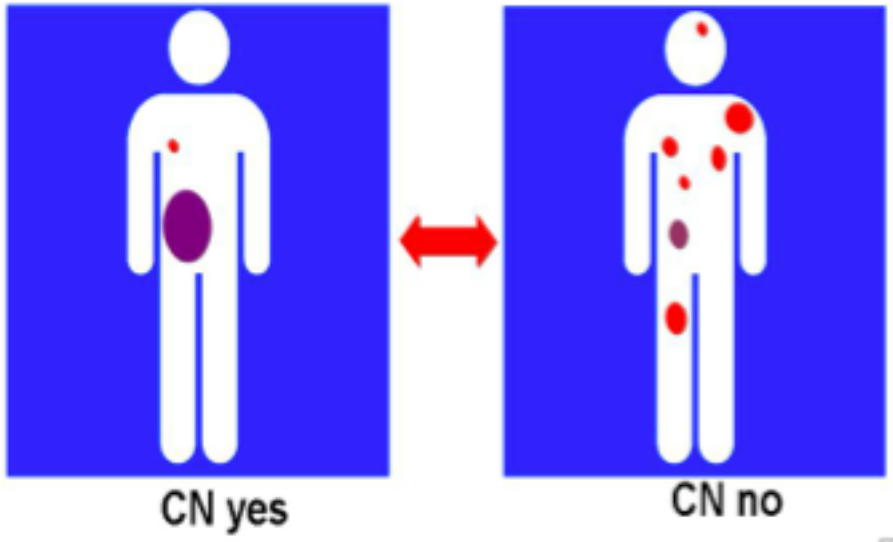
Individual factors

- Karnofsky performance < 80 %
- anemia
- thrombocytosis
- neutrophilia
- hypercalcemia
- time from diagnosis to treatment < 1 year

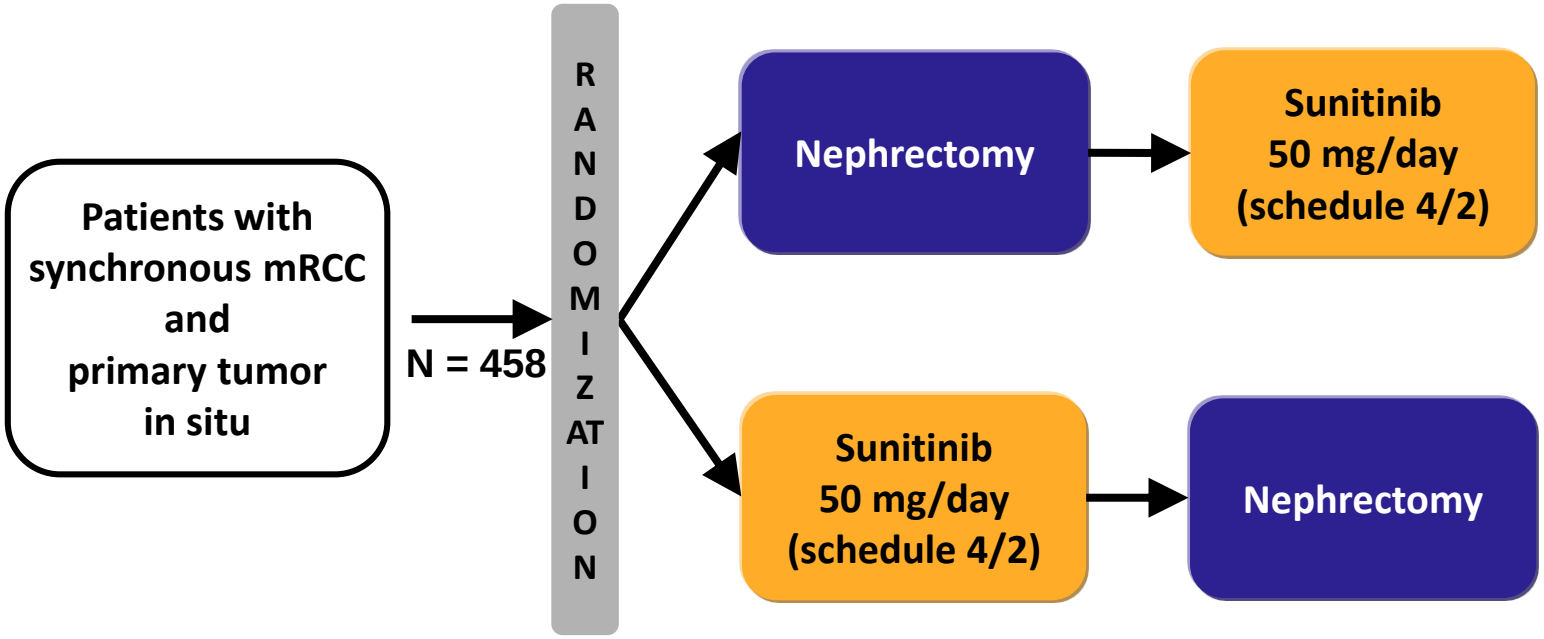


Heng et al., External validation and comparison of the IMDC prognostic model with other models The Lancet Oncology 14 (2)141-8, 2013

SELECTION IS KEY
TUMOR FEATURES



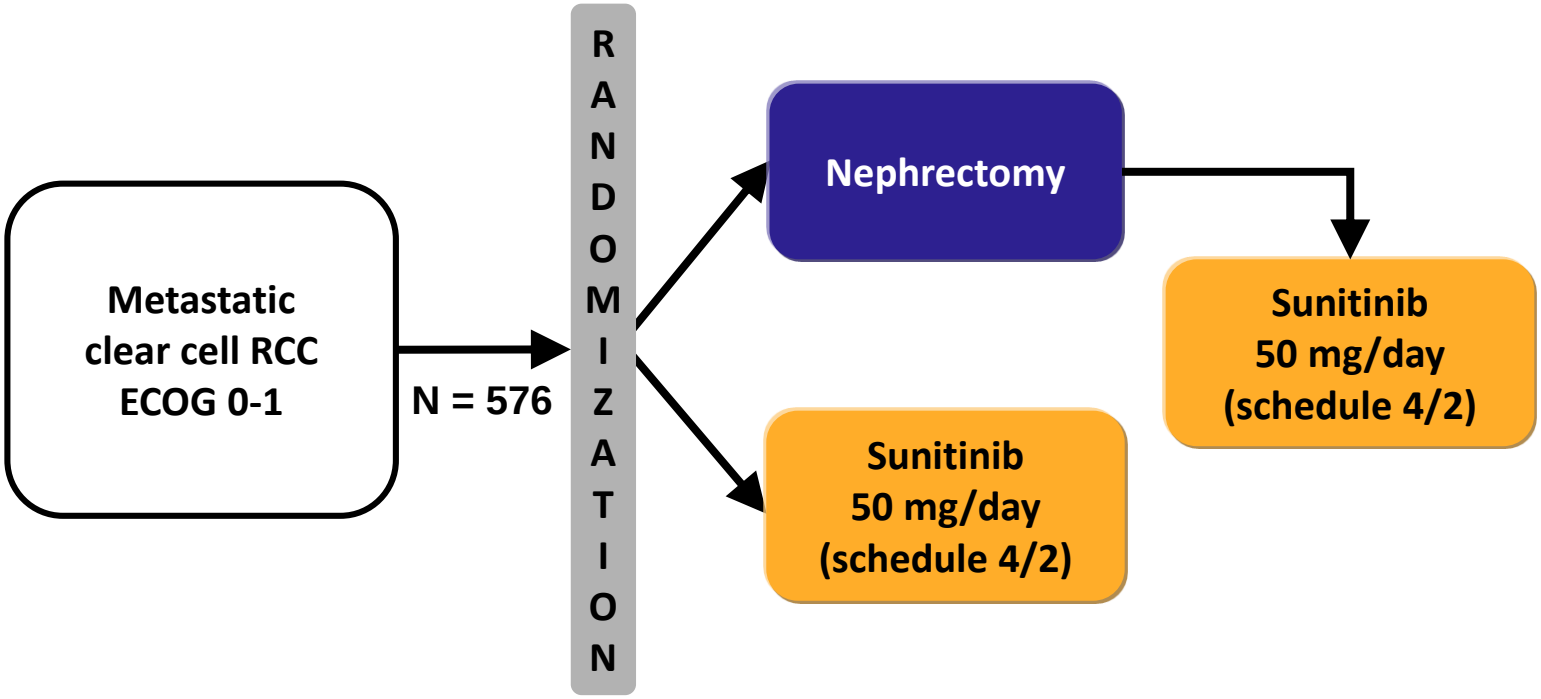
SURTIME, a EORTC-GU 30073 Phase III Study Investigating the Sequence of Nephrectomy and Sunitinib



- Primary end point: PFS
- Secondary end points: OS, association with prognostic gene and protein expression profiles

Bex et al

CARMENA Phase III Study of Sunitinib Only vs. Nephrectomy Followed by Sunitinib



- **Primary objective**: Is sunitinib alone non-inferior to nephrectomy plus sunitinib in terms of OS?
- Note: NO stratification in MSKCC or IMDC risk

Radiation therapy on L2-L4 (8 Gy)

Laparoscopic right radical nephrectomy +
Paracaval/interaortocaval LND

Pathology

Clear cell RCC - Grade III-IV – diffuse necrosis

pT2 N0

LYMPH NODE DISSECTION

Platinum Priority – Kidney Cancer

Editorial by Urs E. Studer and Frédéric D. Birkhäuser on pp. 35–37 of this issue

Radical Nephrectomy with and without Lymph-Node Dissection: Final Results of European Organization for Research and Treatment of Cancer (EORTC) Randomized Phase 3 Trial 30881

Jan H.M. Blom[a,], Hein van Poppel[b], Jean M. Maréchal[c], Didier Jacqmin[d], Fritz H. Schröder[e], Linda de Prijck[f], Richard Sylvester[f], for the EORTC Genitourinary Tract Cancer Group*

OUTCOMES

383 RN+LND

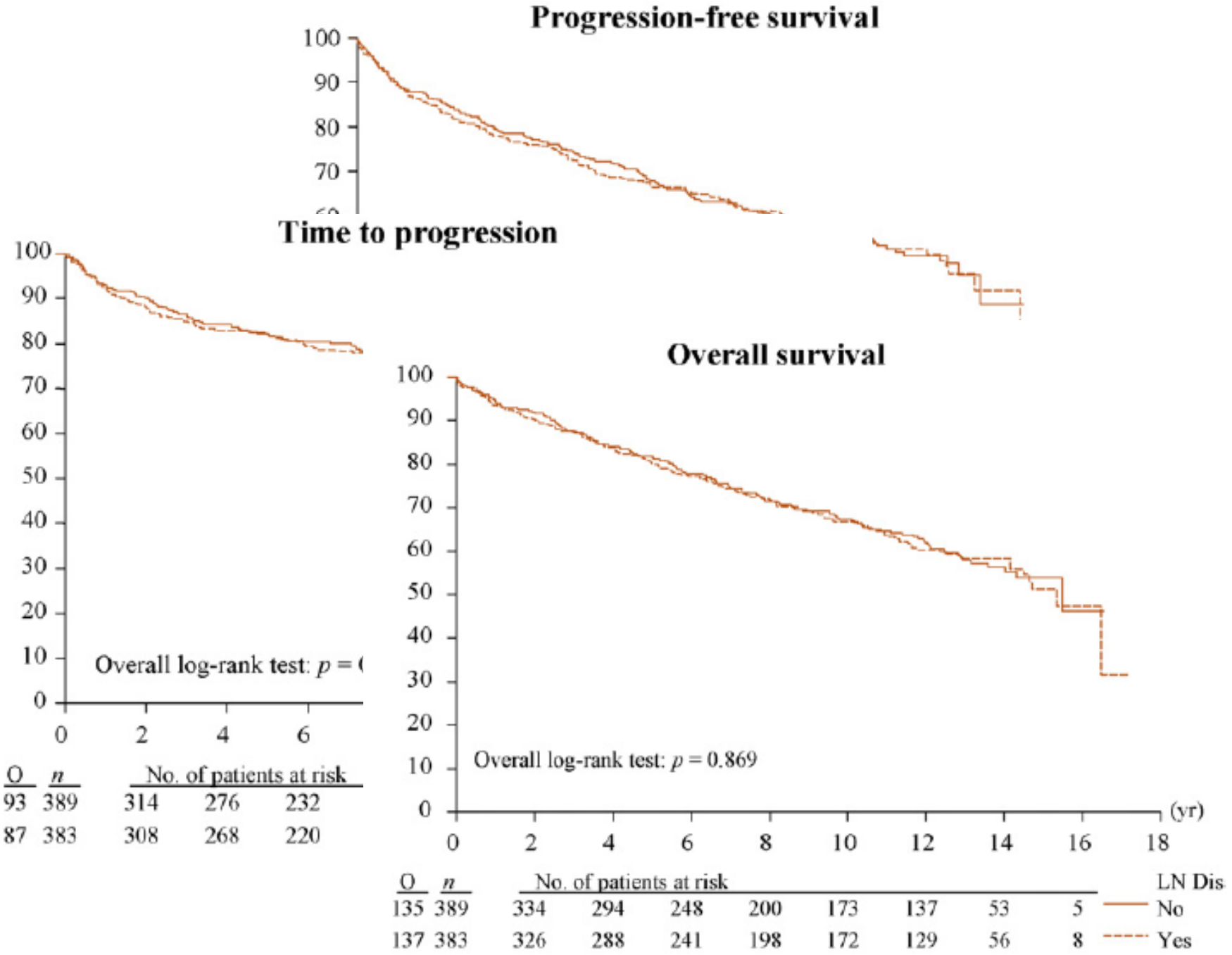
vs.

389 RN alone

Time-to-progression

Overall survival

Progression-free survival


Progression-free survival
100
90
80
70
Time to progression
100
90
80
70
60
50
40
30
20
10
0
Overall log-rank test: p = (
0
2
4
6
O n No. of patients at risk
93 389 314 276 232
87 383 308 268 220
Overall survival
100
90
80
70
60
50
40
30
20
10
0
Overall log-rank test: p = 0.869
(yr)
0
2
4
6
8
10
12
14
16
18
O n No. of patients at risk
135 389 334 294 248 200 173 137 53 5
137 383 326 288 241 198 172 129 56 8
LN Dis
No
Yes

Low-risk population

All cN0 patients

	Without lymph-node dissection		With complete lymph-node dissection	
	n	%	*n*	%
Site of the tumor				
Right side	195	53	198	54
Left side	172	47	169	46
Tumor category				
T1	23	6	34	9
T2	242	66	221	60
T3	101	28	112	31
Tumor diameter, cm				
Median	6		5.5	
Maximum	20		19	

Radical Nephrectomy with and without Lymph-Node Dissection: Final Results of European Organization for Research and Treatment of Cancer (EORTC) Randomized Phase 3 Trial 30881

Jan H.M. Blom [a,], Hein van Poppel [b], Jean M. Maréchal [c], Didier Jacqmin [d], Fritz H. Schröder [e], Linda de Prijck [f], Richard Sylvester [f], for the EORTC Genitourinary Tract Cancer Group*

	Without lymph-node dissection		With complete lymph-node dissection	
	n	%	*n*	%
pT category				
T0	5	1	4	1
T1	19	5	21	6
T2	230	65	221	63
T3	96	27	101	29
T4	2	1	3	1
TX	2	1	3	1
pN-category				
N0	–	–	332	96
N1	–	–	5	1
N2	–	–	6	2
N3	–	–	3	1

pN+ = 4%

Radical Nephrectomy With or Without Lymph Node Dissection for Nonmetastatic Renal Cell Carcinoma: A Propensity Score-based Analysis

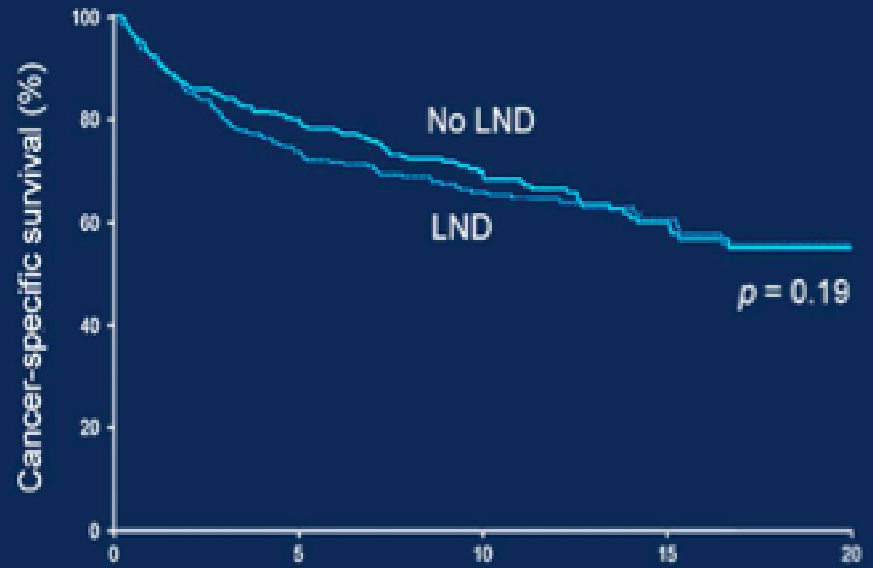
Boris Gershman [a], R. Houston Thompson [b], Daniel M. Moreira [c], Stephen A. Boorjian [b], Matthew K. Tollefson [b], Christine M. Lohse [d], Brian A. Costello [e], John C. Cheville [f], Bradley C. Leibovich [b,]*

MAYO CLINIC

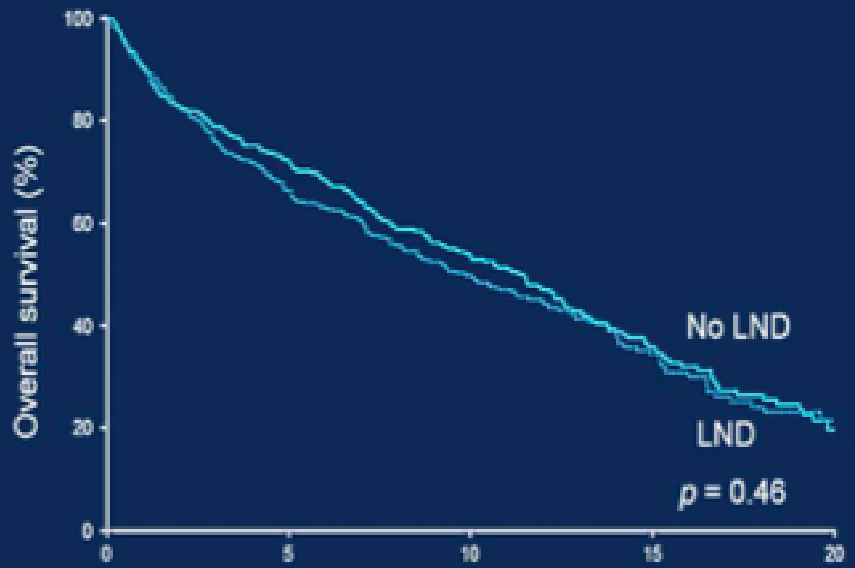
- Retrospective cohort study
- Single institution
- 1,797 cM0 RCC pts
- 1990-2010
- 34% underwent LND

Gershman et al. Eur Urol 2017

No survival effect after matching 1:1



N at Risk					
NO LND	355	235	137	54	11
LND	351	221	117	46	12

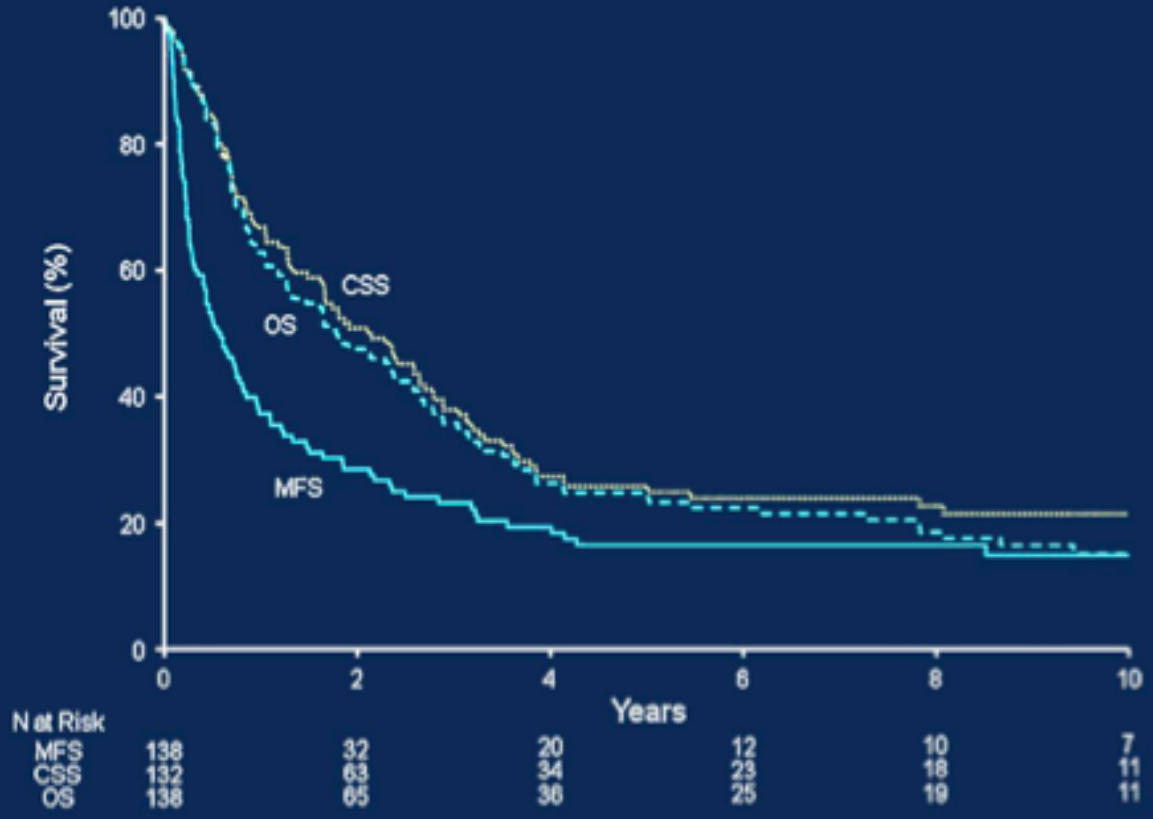


N at Risk					
NO LND	370	249	146	57	11
LND	370	229	122	52	12

Gershman et al. Eur Urol 2017

Key role of LND in terms of prognosis

Gershman et al. Eur Urol 2017



Median MFS: <9 months

Median survival: 2 yrs

Can we predict LNI ?

Lymph Node Dissection at the Time of Radical Nephrectomy for High-Risk Clear Cell Renal Cell Carcinoma: Indications and Recommendations for Surgical Templates

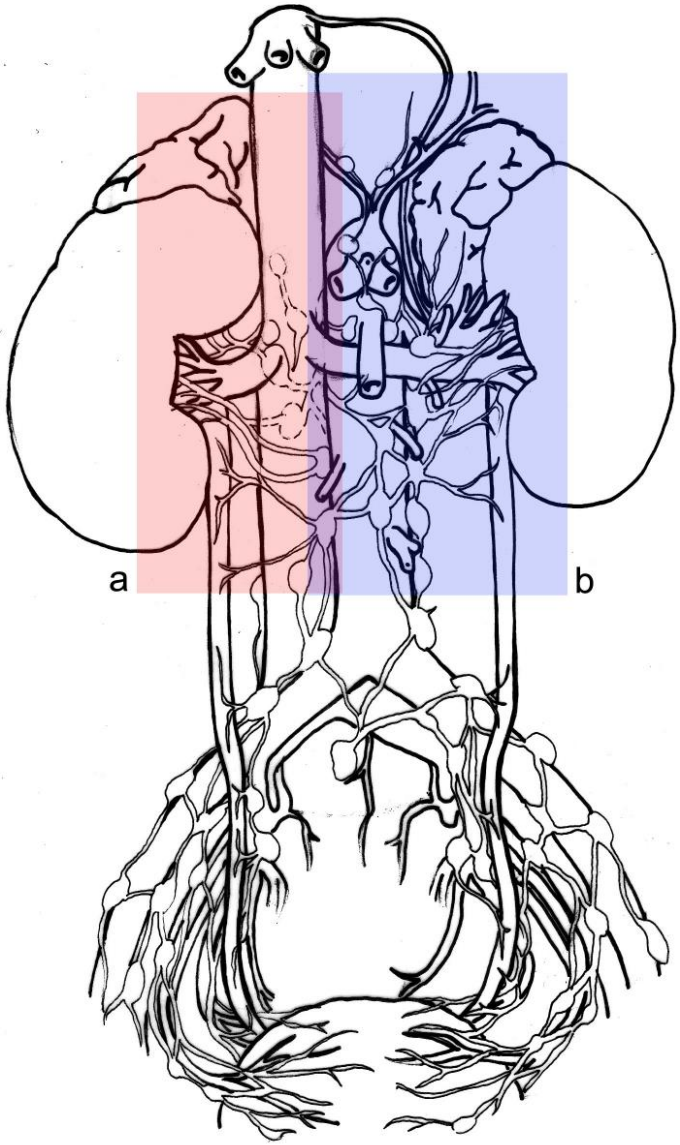
Paul L. Crispen [a], Rodney H. Breau [a], Cristine Allmer [b], Christine M. Lohse [b], John C. Cheville [c], Bradley C. Leibovich [a], Michael L. Blute [a,]*

- Non standardized LND in 415 cN0 patients
- 5 risk factors:
    1. Tumor size > 10 cm
    2. Fuhrman 3-4
    3. Sarcomatoid component
    4. pT3-pT4
    5. Histologic tumor necrosis

169 high-risk patients

LNI 38%

LND in RCC. Which template?



Predilection of RCC for early haematogenic dissemination ≈57% TanyN0M1

Directly to the thoracic duct ≈30%

Many possible different lymphatic routes in normal retroperitoneal anatomy

Collateral lymphatic drainage and invasion of tissue with different lymphatic drainage (e.g. perinephric fat)

Isolated metastases in the ipsilateral iliac and supraclavicular nodes ≈10%

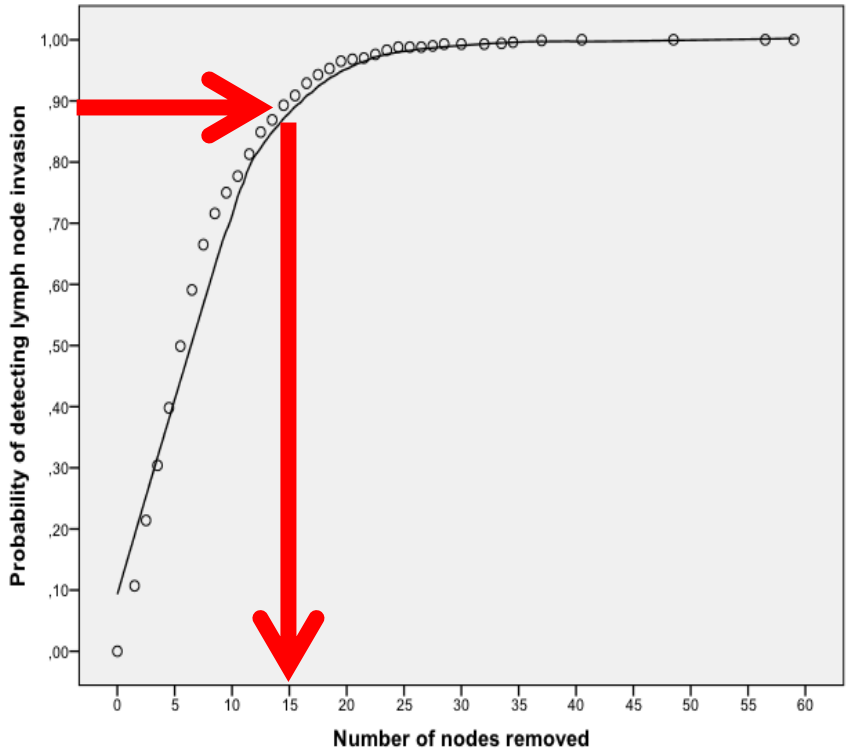
Staging lymphadenectomy in renal cell carcinoma must be extended: a sensitivity curve analysis

Umberto Capitanio, Nazareno Suardi, Rayan Matloob, Firas Abdollah, Fabio Castiglione, Alberto Briganti, Cristina Carenzi, Marco Roscigno, Francesco Montorsi and Roberto Bertini

Department of Urology, University Vita-Salute, San Raffaele Hospital, Milan, Italy

n = 850; $T_{any}N0\text{-}1M_{any}$ RCC + LND (1987-2011)

90%



15 nodes

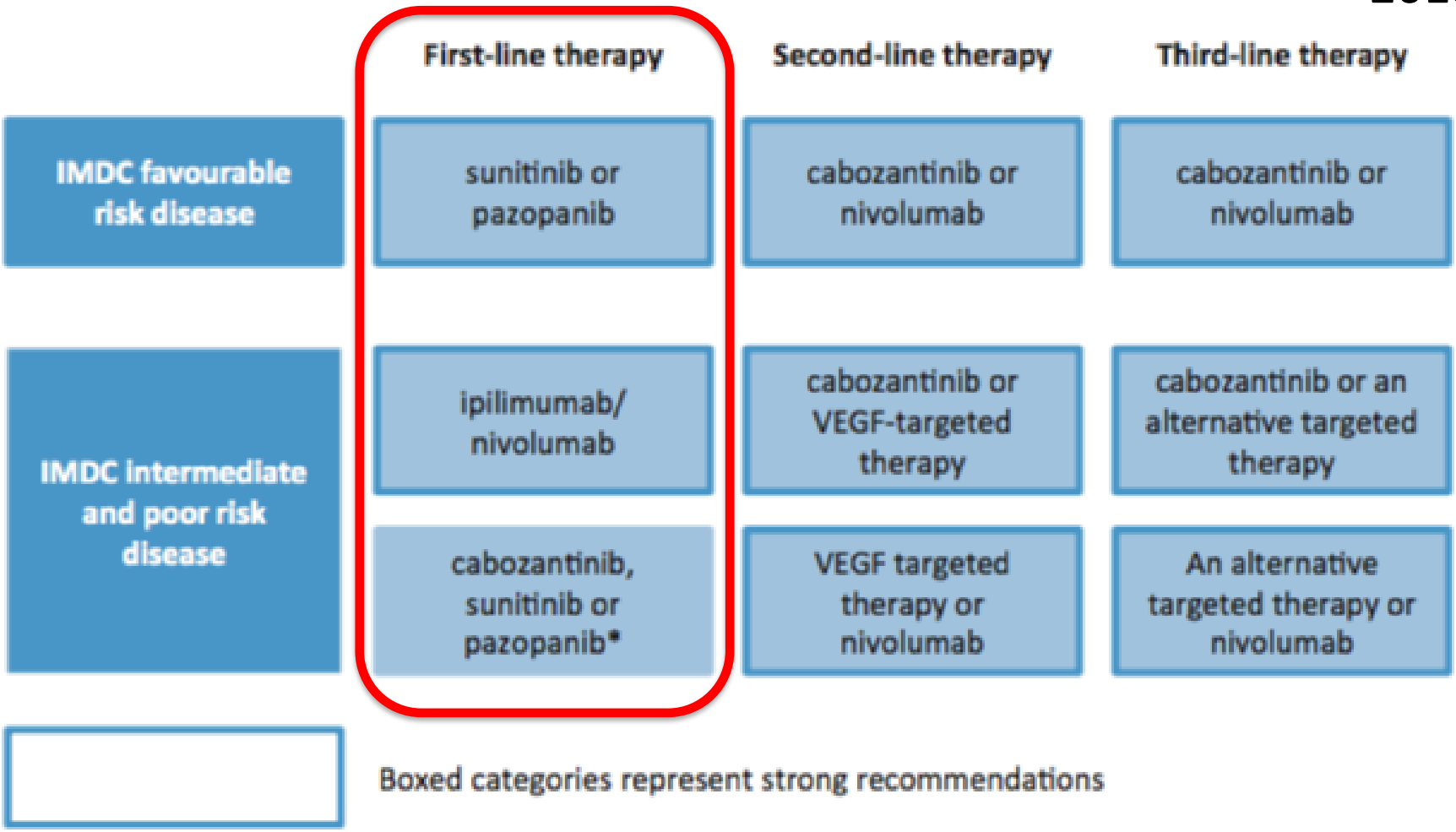
© 2012 BJU International | 111, 412–418 | doi:10.1111/j.1464-410X.2012.11313.x

FIRST LINE SYSTEMIC THERAPY

EAU Guidelines on

Renal Cell Carcinoma

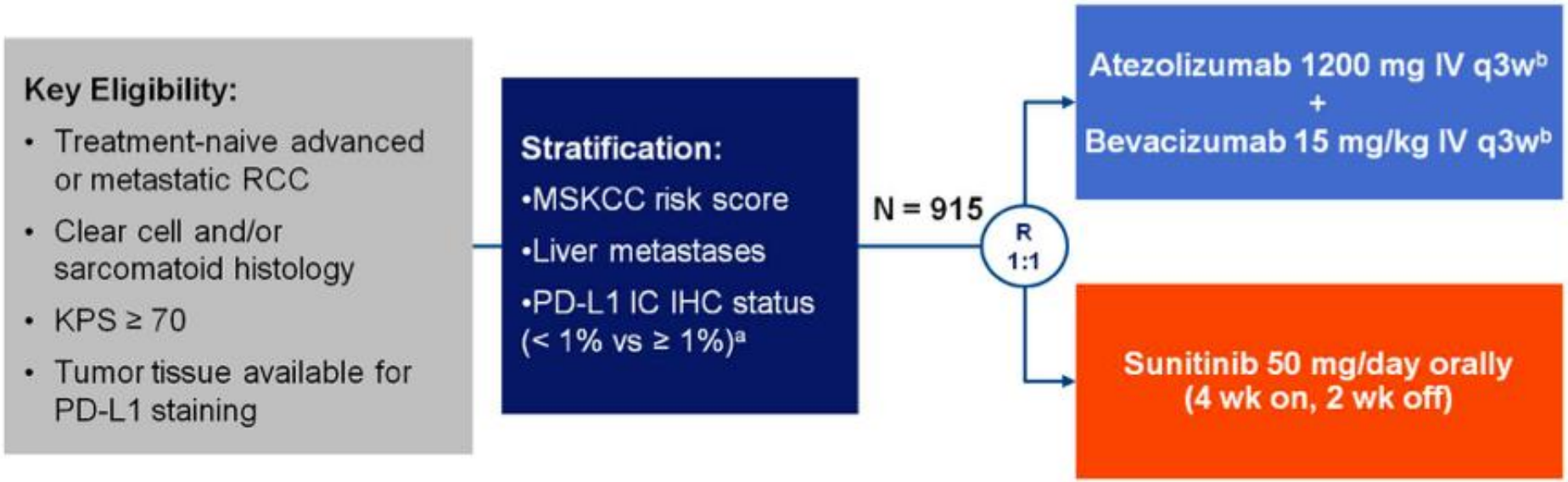
2018



The combination of nivolumab and ipilimumab in treatment-naïve patients with clear-cell metastatic RCC of IMDC intermediate- and poor-risk leads to superior survival compared to sunitinib.	1b
The combination of nivolumab and ipilimumab in the ITT population of treatment-naïve unselected patients with clear-cell metastatic RCC leads to superior survival compared to sunitinib.	2b
Due to the exploratory nature of PD-L1 tumour expression, the small sample size, the lack of OS data and the premature results in this subpopulation, definitive conclusions cannot be drawn.	2b
Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity and 1.5% treatment-related deaths.	1b

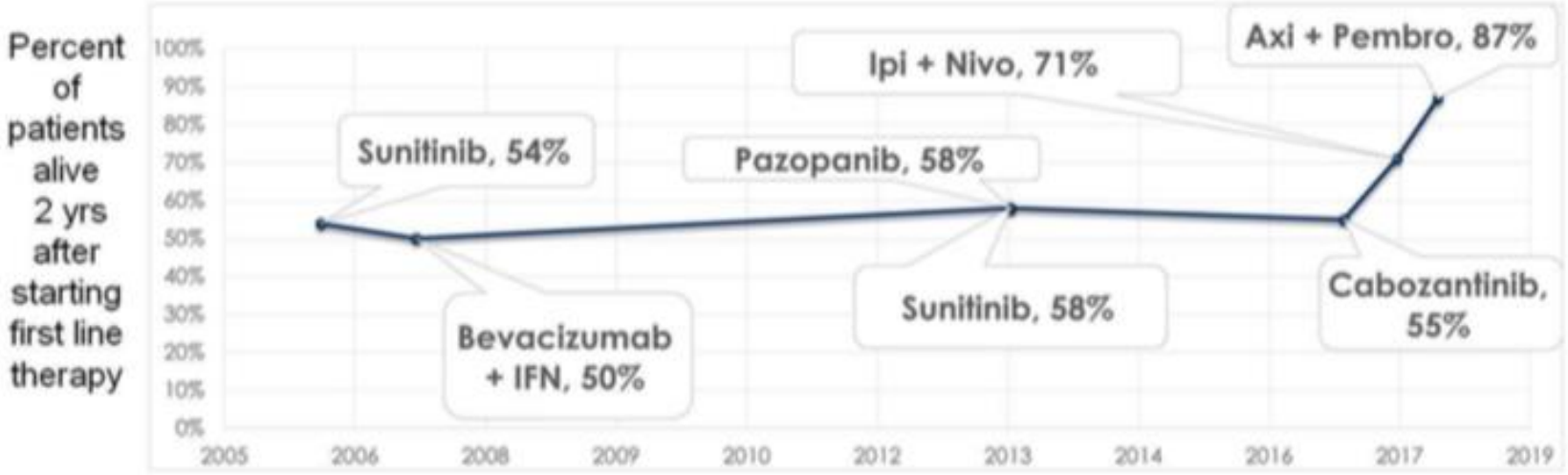
Recommendation	Strength rating
Use ipilimumab plus nivolumab in treatment-naïve patients with clear-cell metastatic RCC of IMDC intermediate and poor risk.	Strong
Offer nivolumab after one or two lines of VEGF-targeted therapy in metastatic RCC.	Strong
Do not offer monotherapy with interferon-α or high-dose bolus interleukin-2 as first-line therapy in metastatic RCC.	Weak
Do not use bevacizumab plus IFN-α in treatment-naïve clear-cell favourable- and intermediate-risk RCC patients.	Weak
Do not use PD-L1 tumour expression as a predictive biomarker.	Weak
Administer nivolumab plus ipilimumab in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	Weak
Do not rechallenge patients who stop nivolumab plus ipilimumab because of toxicity with the same drugs in the future without expert guidance and support from a multidisciplinary team.	Strong

Study Design



- **Primary Endpoints**
  - PFS by investigator-assessment in PD-L1+ patients, defined as ≥ 1% expression on tumor-infiltrating immune cells (IC) as determined by immunohistochemistry (IHC)[a]
  - OS in ITT

Progress in metastatic RCC



PubMed PMID:
23598172
26482279
23598172
20549832
29550566
29562145
29439857

...nell'era delle COMBO IO+IO o IO+Tki...

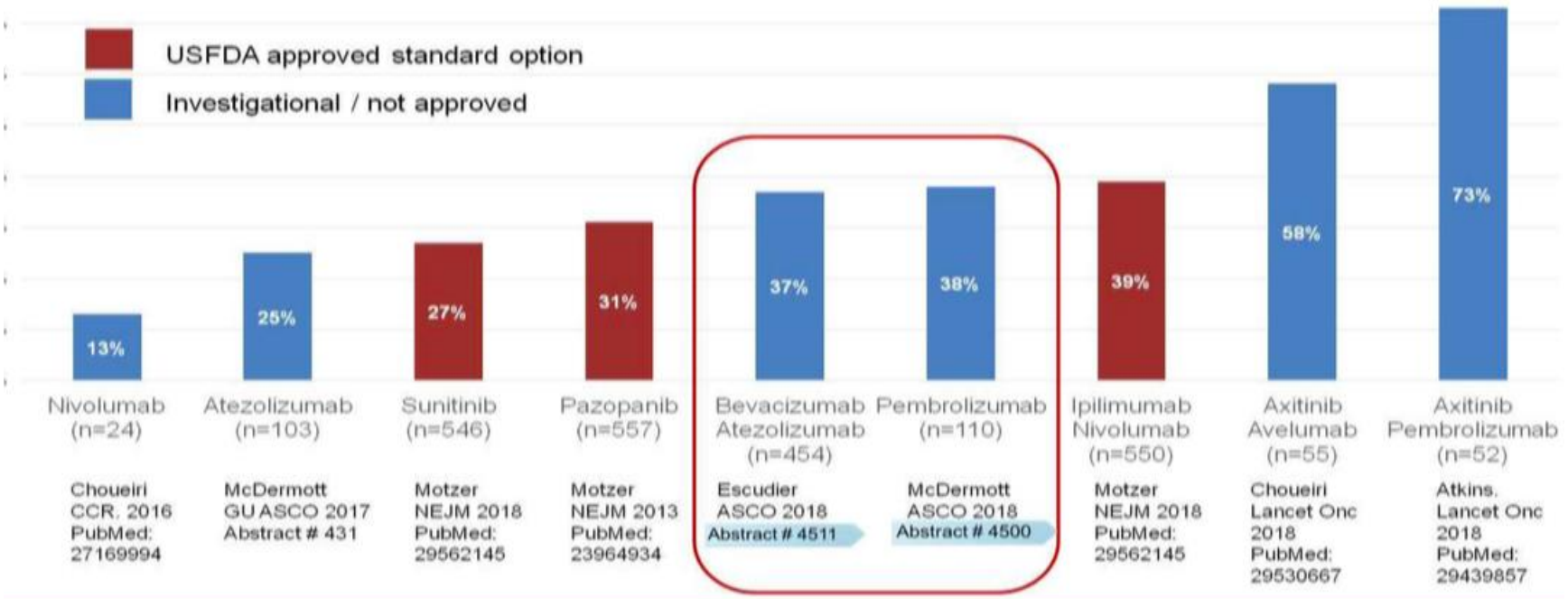
RCC landscape today: Combinations: IO/IO and IO/VEGF

	I-O + TKI (phase 1/2)			I-O + I-O (phase 3) *CheckMate-214*	I-O + VEGF mAb (phase 3) *IMmotion151*	*TKI (comparator)*
TRIAL	Pembrolizumab + Axitinib[1]	Pembrolizumab + Levantinib[2]	Avelumab + Axitinib[3]	Nivolumab + Ipilimumab Vs. Sunitinib[4,5]	Atezolizumab + Bevacizumab Vs. Sunitinib[6]	*Sunitinib[6]*
N	52	30	55	425 *Int/Poor risk subgroup*	454	*461*
Prior allowed therapy	No	Yes	No	No	No	*No*
ORR	73%	63%	58%	42%	37%	*33%*

[1]NCT02133742, Atkins et al. Lancet Oncol 2018; [2]NCT02501096, Lee et al. ESMO 2017; [3]NCT02493751, Choueiri et al. Lancet Oncol 2018; [4,5]NCT02231749, Motzer et al. SITC 2017 and NEJM 2018; [6]NCT01984242 Motzer et al. ASCO GU 2018

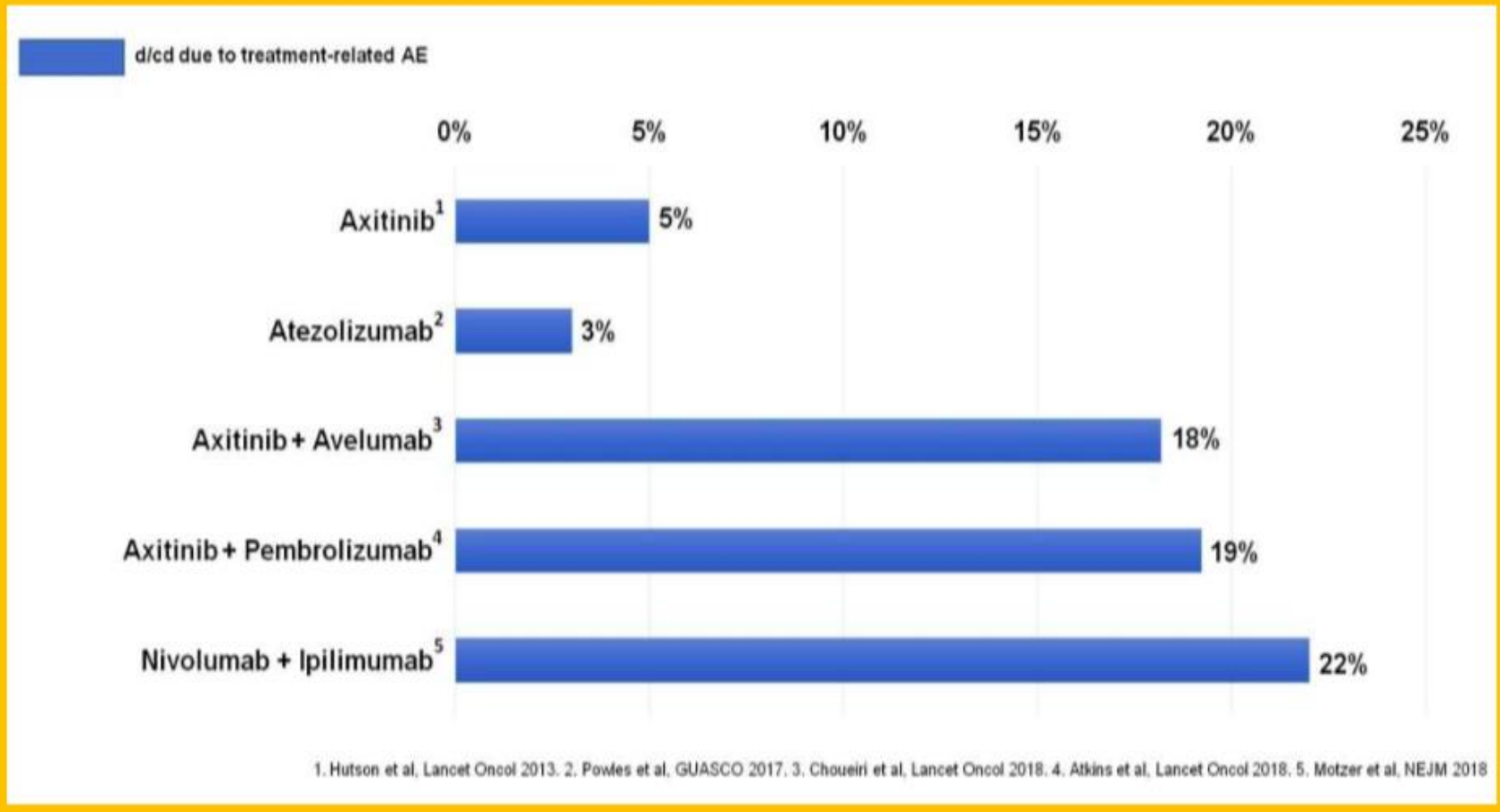
Courtesy: AK Lalani, Z. Bakouny, TK Choueiri

Response Rates in Front Line metastatic ccRCC (all risk groups)



Presented By Elizabeth Plimack at 2018 ASCO Annual Meeting

...ma Tki o IO in monoterapia hanno meno tossicità delle COMBO



1. Hutson et al, Lancet Oncol 2013. 2. Powles et al, GUASCO 2017. 3. Choueiri et al, Lancet Oncol 2018. 4. Atkins et al, Lancet Oncol 2018. 5. Motzer et al, NEJM 2018

Data with single agents first-line PD-1/PD-L1 inhibitors in ccRCC

	Phase	N	IMDC poor	ORR	CR	ORR (PD-L1 +)	mPFS	Trt disc due to AEs
Nivolumab[1]	Ib (CA209-009)	24	NA	13%	8%	NA	6m	NA
Atezolizumab[2]	II (IMmotion150)	103	8%	25%	11%	28%	6.1m	3%
Pembrolizumab[3]	II (KEYNOTE-427)	110	15.5%	38%	2.7%	50%	8.7m	10.9%

ITT: Intention to Treat
NA: Not Available

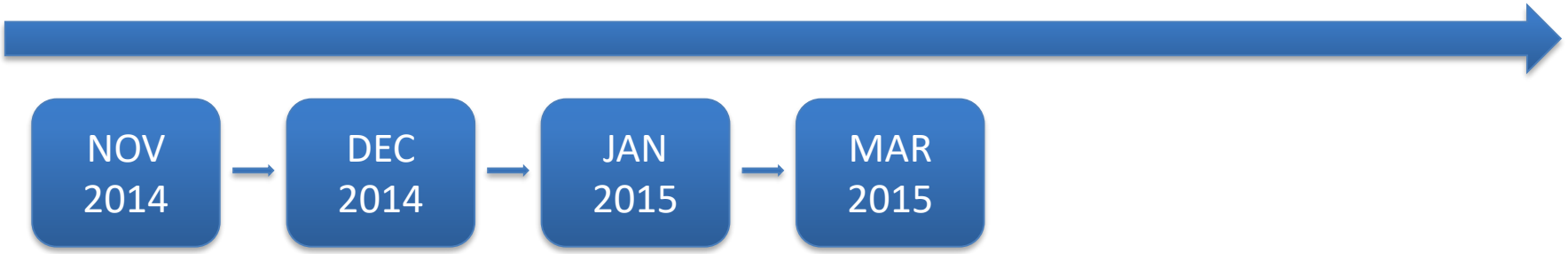
1. Choueiri TK et al, Clin Cancer Res 2017. 2. Atkins MB et al, ASCO 2017 and McDermott et al, GUASCO 2017.. 3. McDermott DF et al, ASCO 2018.

Decisions Regarding Front line Therapy

- Patient Factors:
  - Age
  - Organ Function
  - Immune Status
  - Comorbid Conditions
  - IMDC Risk
  - Neutrophil-Lymphocyte Ratio
  - Urgency of Response

- Disease Factors:
  - Histology
  - Presentation: Synchronous/Metachronous
  - Symptomatic or Not
  - Sites of Metastases
  - IMDC risk
  - PDL-1 status
  - Tumor genomic mutations

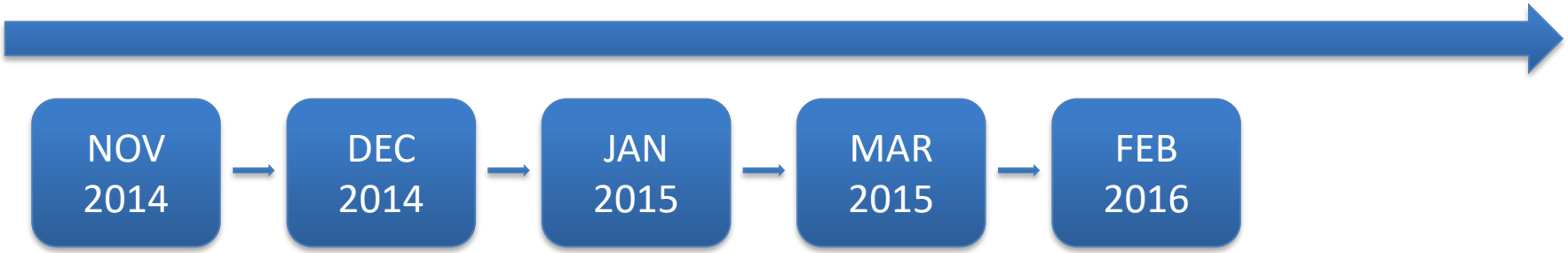
L'importanza del Team multidisciplinare



Starts

Sunitinib 50 mg

4 weeks on / 2 weeks off



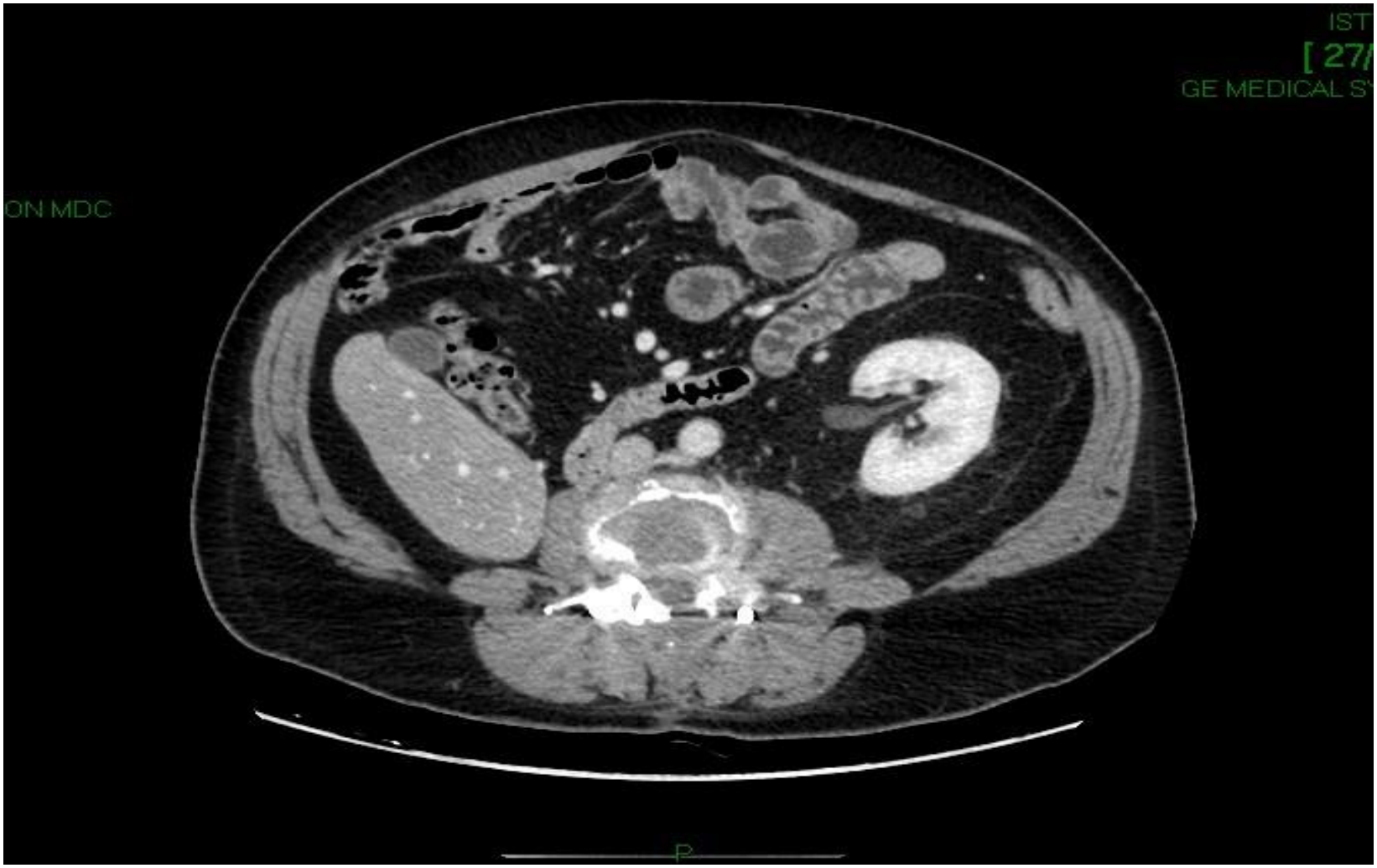
Stable disease

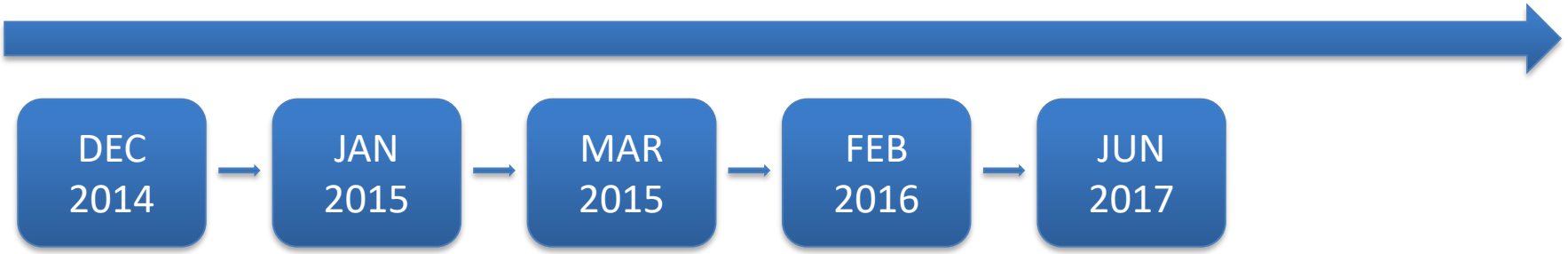
Sunitinib 50 mg weeks 4/6

4 weeks on / 2 weeks off

Toxicity: nausea, vomiting and diarrhea G2

NOV 2014 → DIC 2014 → GEN 2015 → MAR 2015 → FEB 2016





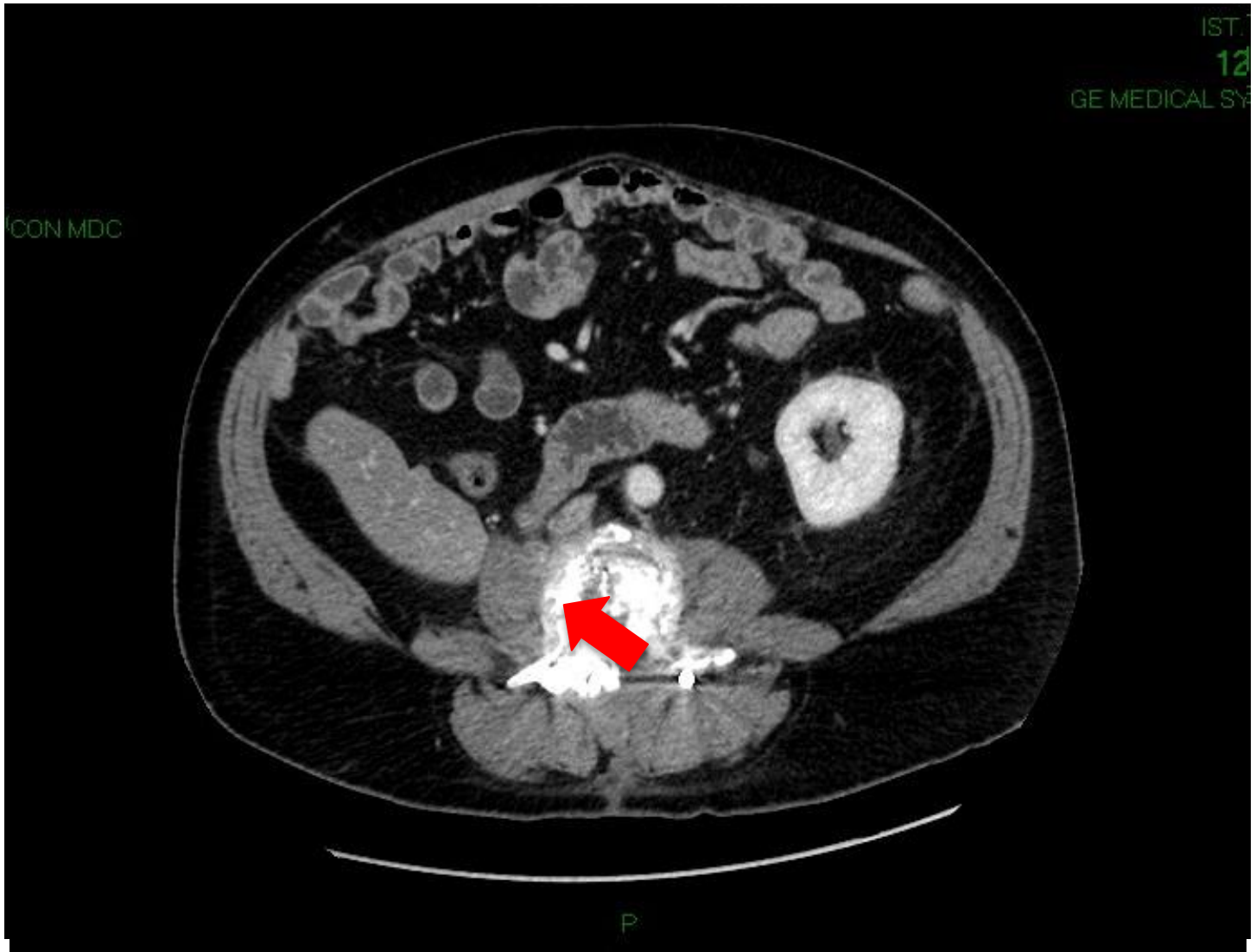
Continue Sunitinib

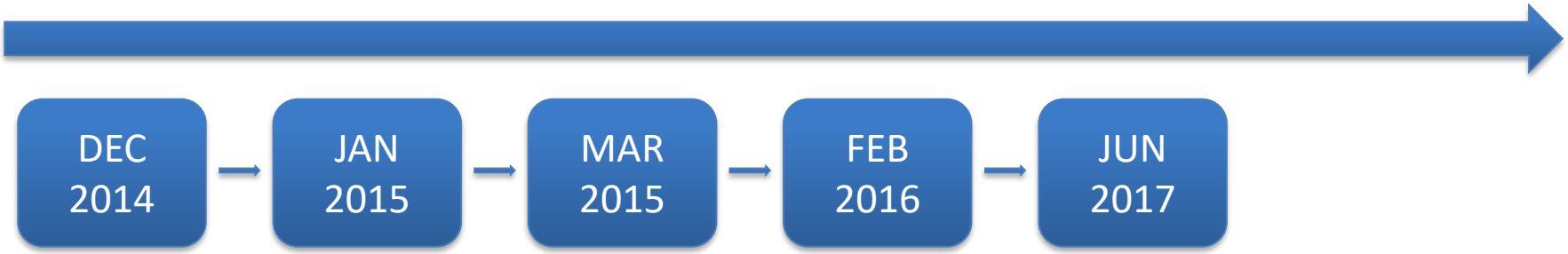
Sunitinib 50 mg orally

4 weeks on / 2 weeks off

Toxicity: diarrhea G2, hand-foot syndrome G2-3

DEC 2014 → JAN 2015 → MAR 2015 → FEB 2016 → JUN 2017

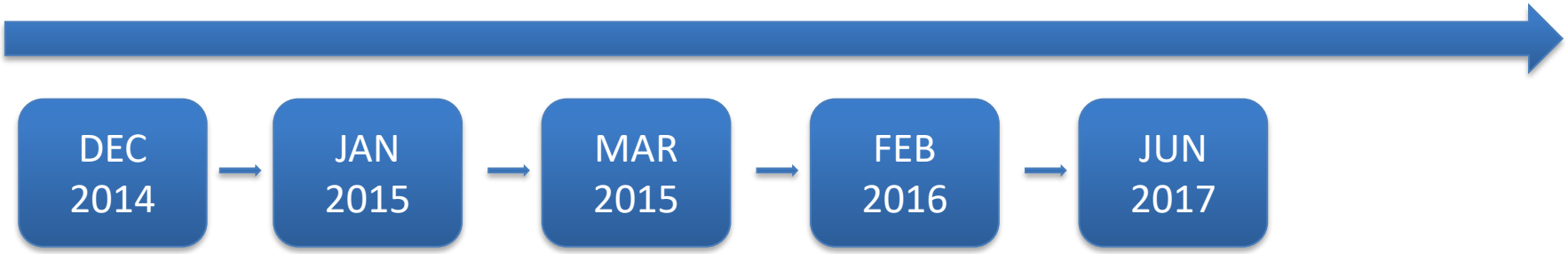




- Worsening lumbar pain
- Total body CT scan
  - Chest and abdominal PD
    - 4 pulmonary lesions – max 16 mm
    - Mediastinal and retroperitoneal lymphadenopathy
  - Bone PD
    - Infiltration of left psoas muscle at the level of L3

Case 1
E.P., male, 61 y.o.

- Metastatic RCC (bone, lung, mediastinum)
- ECOG 0
- sCr 1.1 mg/dL
- Hb 12.1 g/dL, WBC and PLTs normal
- Albumin, calcium, ALP, LDH normal



Radiation therapy on L2-L4 (20 Gy/5 fractions)

Switch to second line systemic therapy

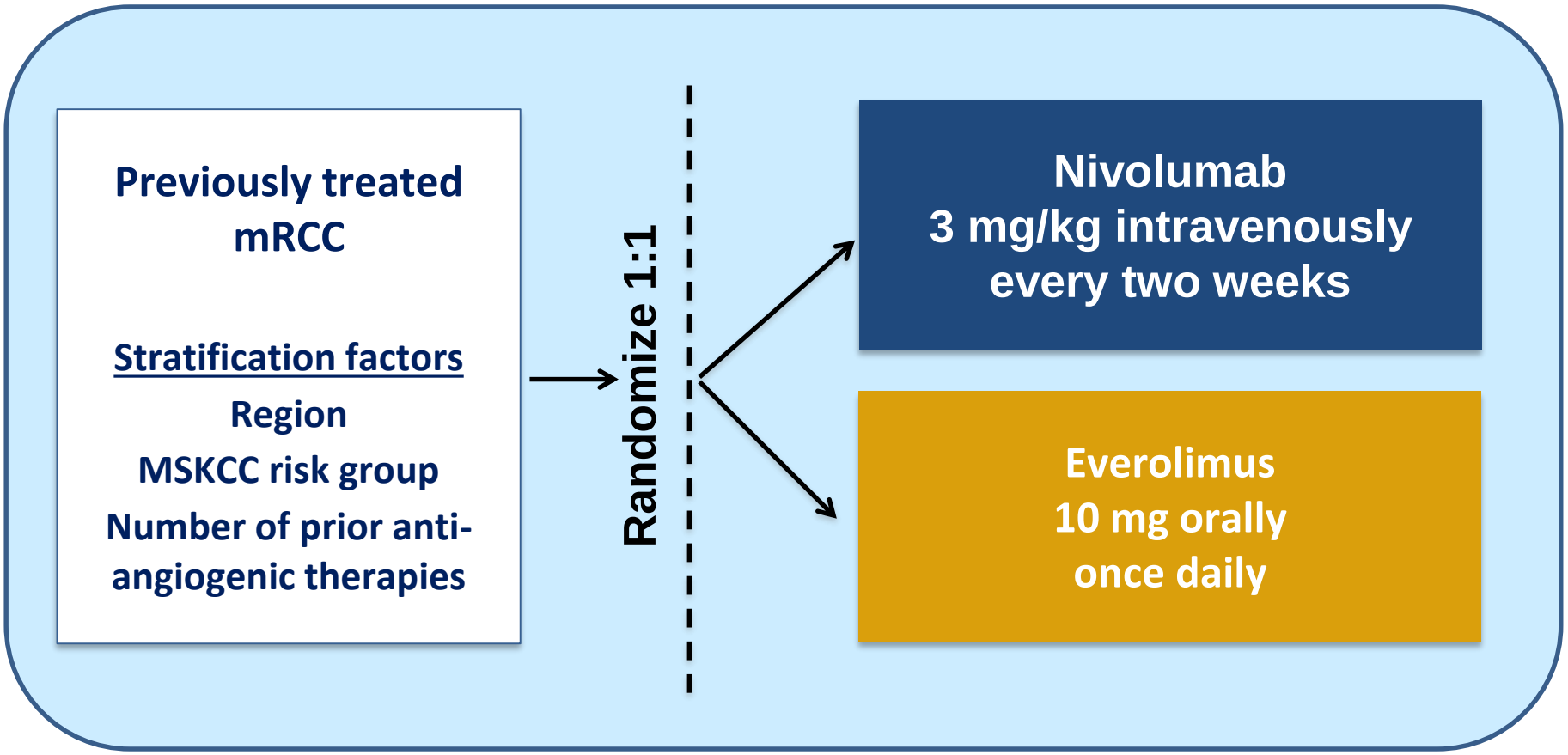
SECOND LINE SYSTEMIC THERAPY

ORIGINAL ARTICLE

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Checkmate 025-Study design



- Patients were treated until progression or intolerable toxicity occurred
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

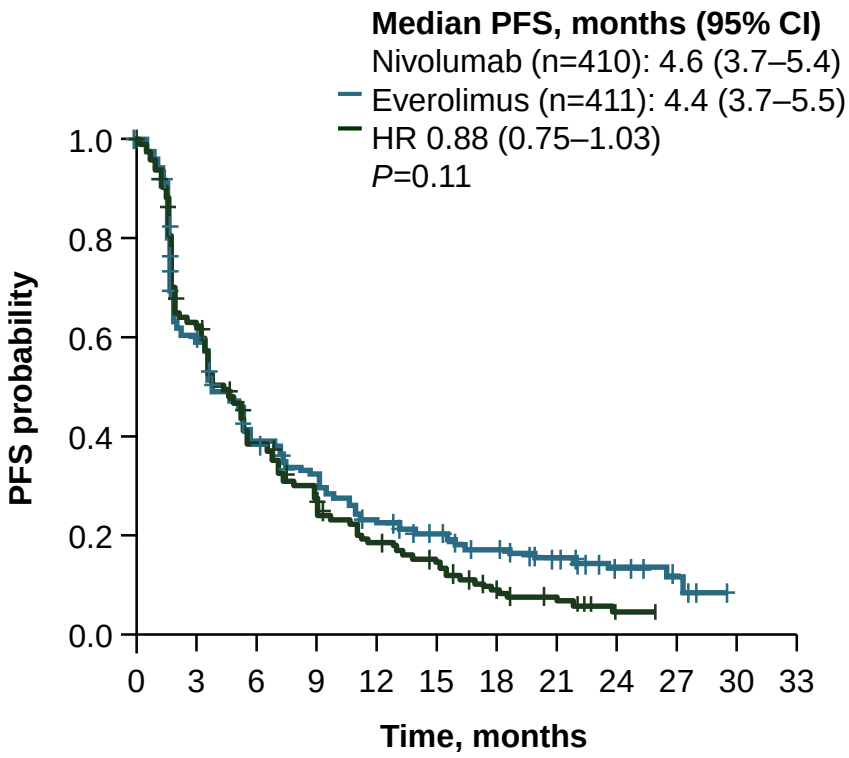
Presented By P. Sharma at the European Cancer Congress, Vienna, 26 September 2015

MSKCC, Memorial Sloan-Kettering Cancer Center.

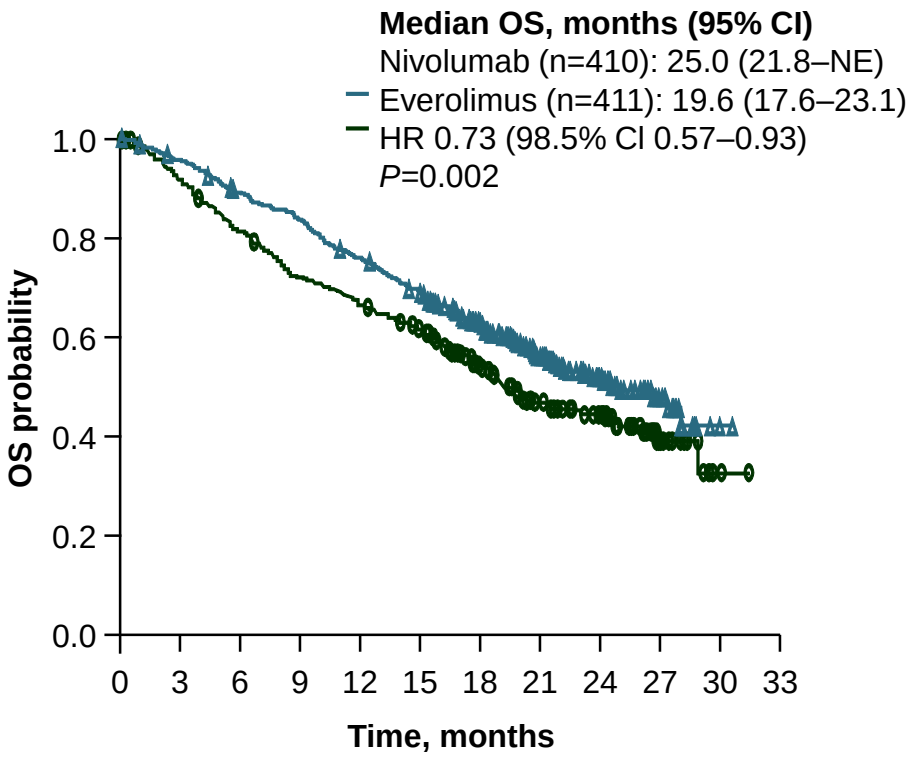
Motzer et al. NEJM 2015

CheckMate-025: Nivolumab versus everolimus in second-line advanced RCC

Progression-free survival



Overall survival



CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Motzer RJ et al. *N Engl J Med*. 2015;373:1803–1813.

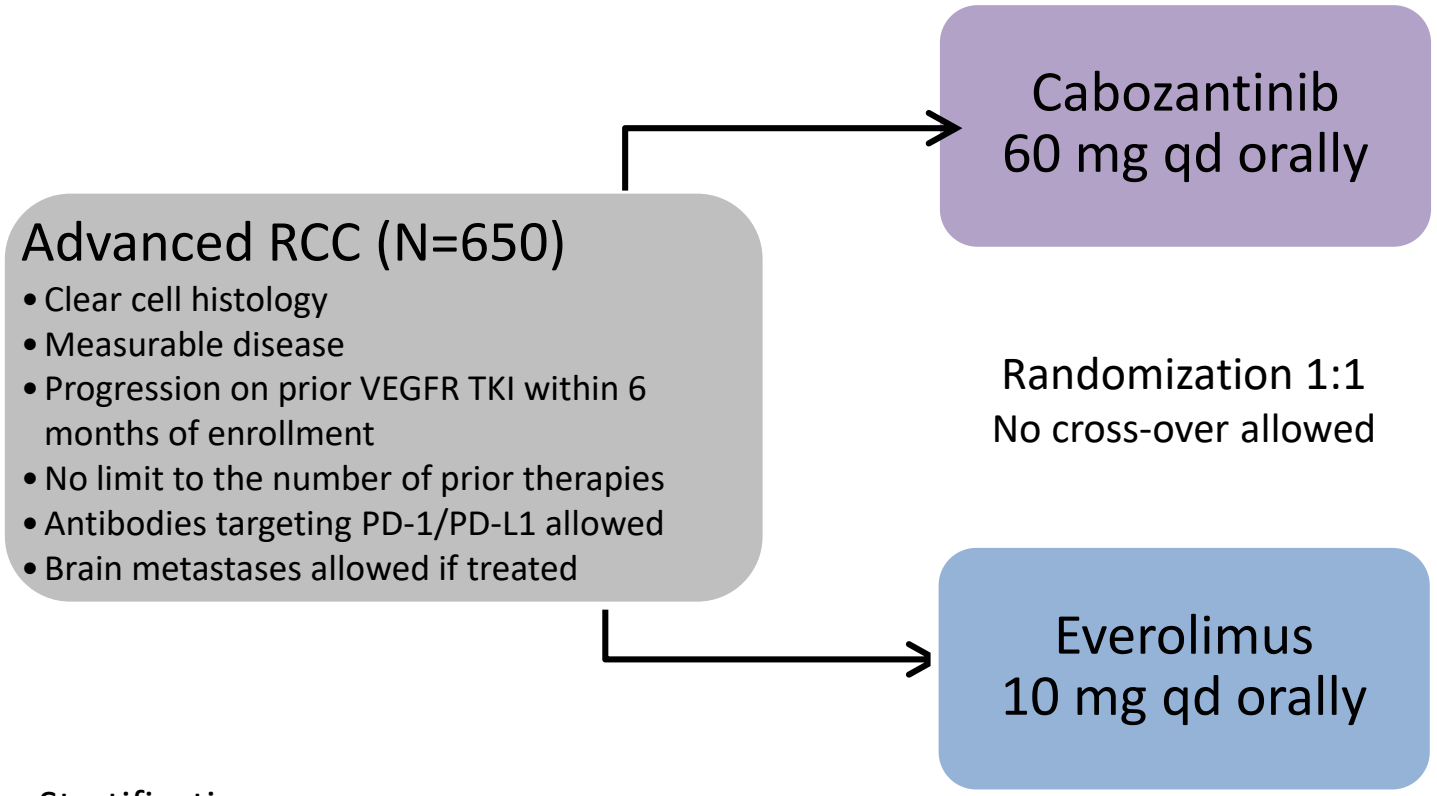
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*

METEOR Study Design



Tumor assessment by RECIST 1.1 every 8 weeks

Treatment until loss of clinical benefit or intolerable toxicity

<u>Stratification:</u>

- MSKCC[1] risk groups: favorable, intermediate, poor
- Number prior VEGFR-TKIs: 1, 2 or more

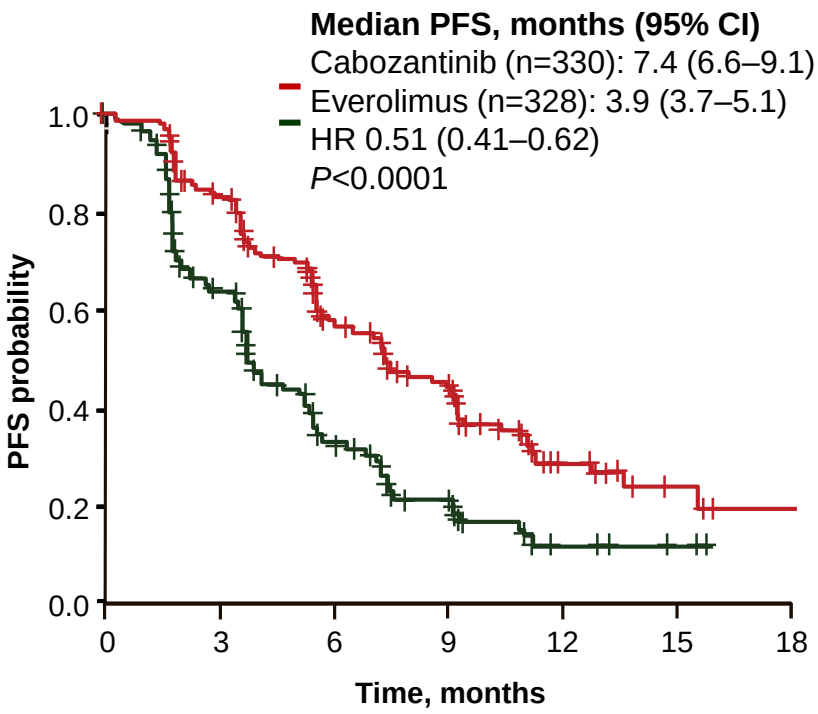
[1] Motzer R. et al., J Clin Oncol, 2004

Presented by TK Choueiri at the European Cancer Congress, Vienna, 26 September 2015

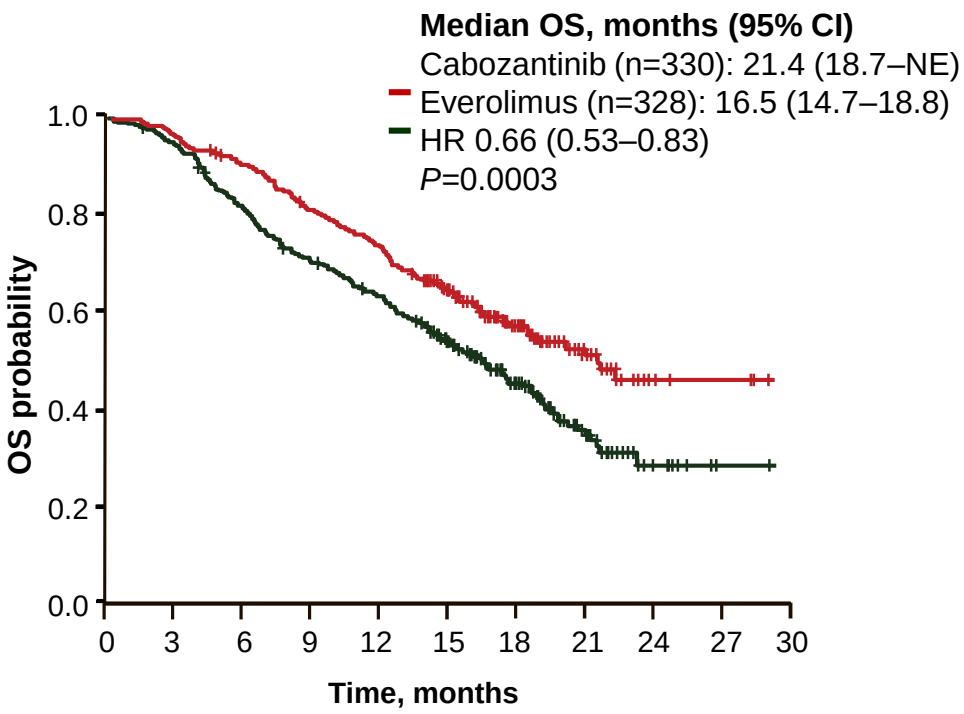
Choueiri et al. NEJM 2015

METEOR Study Design

Progression-free survival



Overall survival



Choueiri TK et al. *Lancet Oncol*. 2016;17:917–927.

EAU Guidelines on

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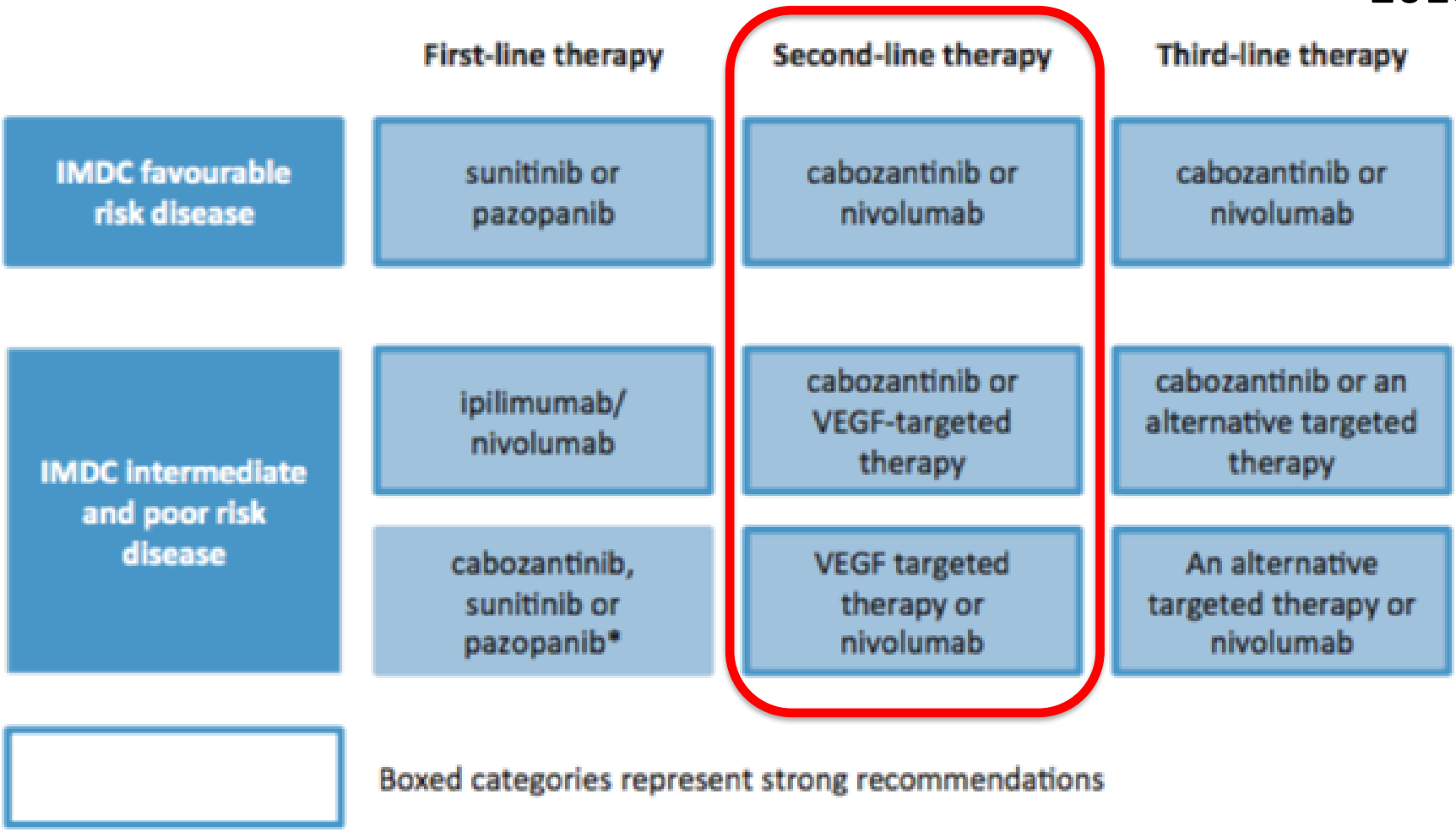
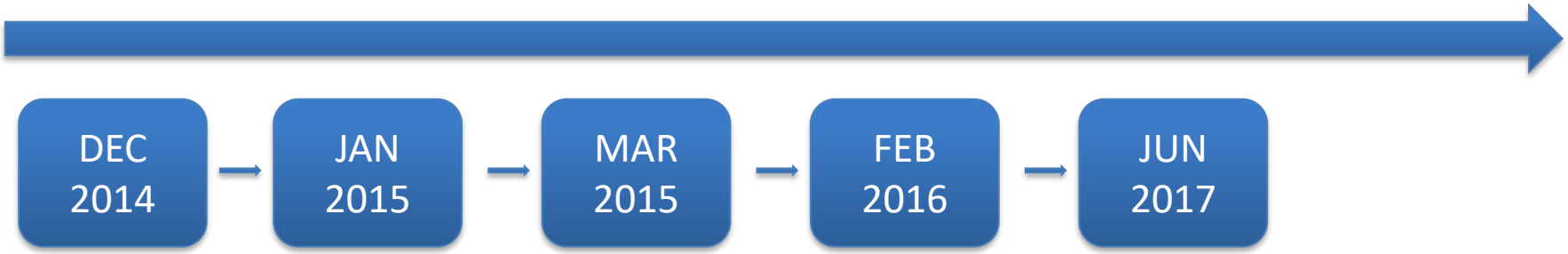
2018

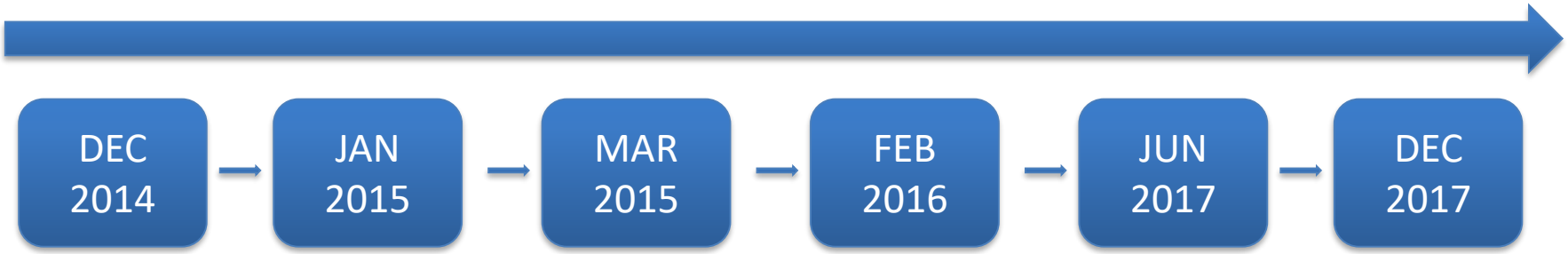




Starts

Nivolumab 3 mg/kg iv

every 2 wks

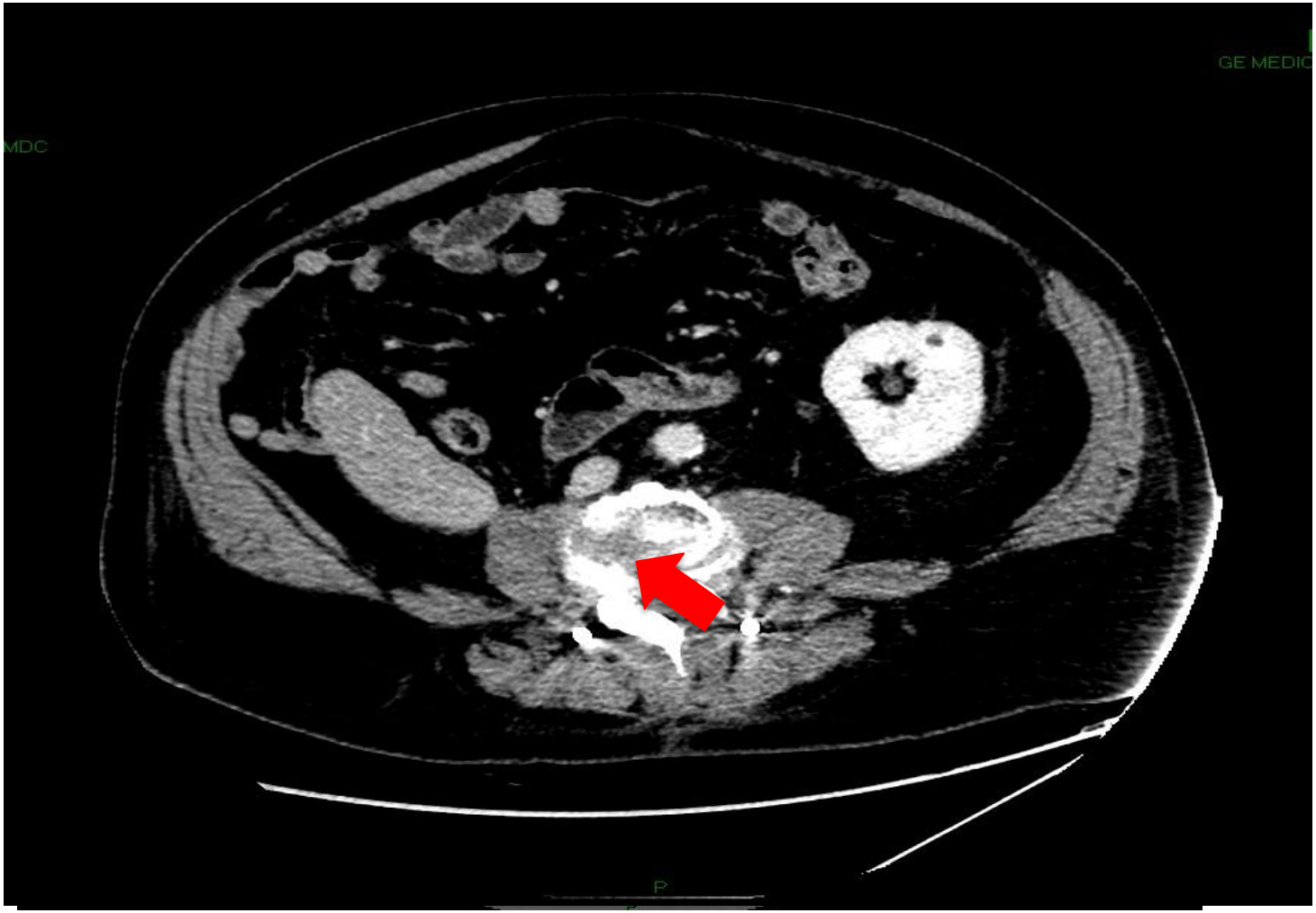


Nivolumab 3 mg/kg iv

every 2 wks

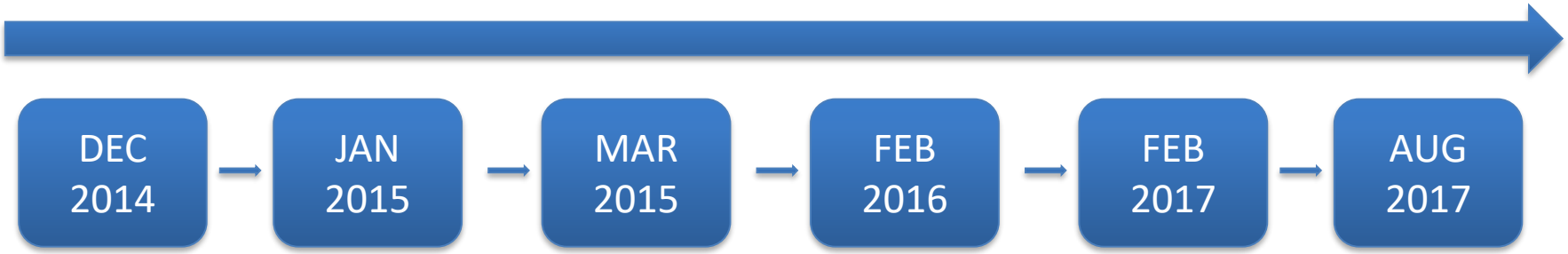
DVT of right superficial femural vein -> LMWE

DEC 2014 → JAN 2015 → MAR 2015 → FEB 2016 → JUN 2017 → DEC 2017



Case 1
E.P., male, 62 y.o.

- Metastatic RCC (bone, lung, mediastinum)
- PD (lung and mediastinum) SD (bone)
- ECOG 0-1 (intermittent hip and lumbar pain)
- sCr 1.15 mg/dL
- Hb 12.5 g/dL, WBC and PLTs normal
- Albumin, calcium, ALP, LDH normal



Switch to third line systemic therapy

THIRD LINE SYSTEMIC THERAPY

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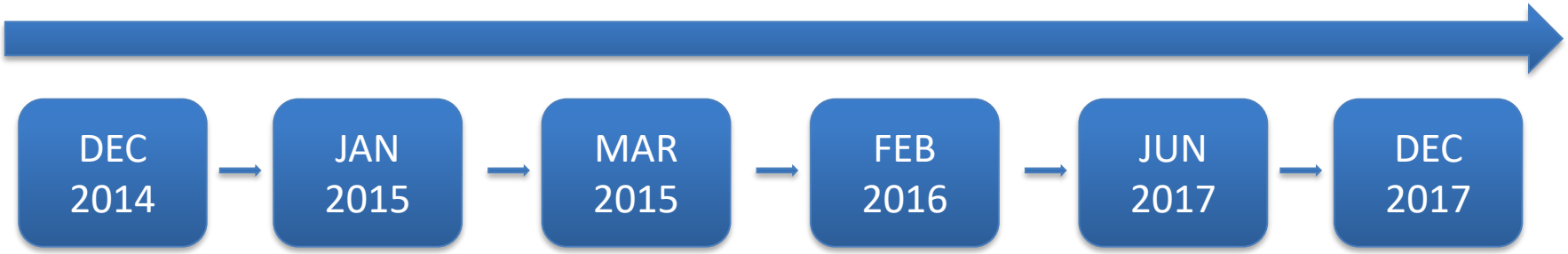
2018

	First-line therapy	Second-line therapy	Third-line therapy
IMDC favourable risk disease	sunitinib or pazopanib	cabozantinib or nivolumab	cabozantinib or nivolumab
IMDC intermediate and poor risk disease	ipilimumab/ nivolumab	cabozantinib or VEGF-targeted therapy	cabozantinib or an alternative targeted therapy
	cabozantinib, sunitinib or pazopanib*	VEGF targeted therapy or nivolumab	An alternative targeted therapy or nivolumab

Boxed categories represent strong recommendations



Starts

Cabozantinib 60 mg/die per os

Stable disease at CT scan in April 2018

SYSTEMIC ADJUVANT TREATMENT

ADJUVANT TRIALS OF TARGETED AGENTS IN RCC

Study	Type of Drug	Duration	Primary Endpoint	Patient Population	Status (www.CT.gov)
ASSURE	VEGF (Sunitinib, sorafenib)	1 year	DFS	High & Int Risk N=1923	Negative
S-TRAC	VEGF (Sunitinib)	1 year	DFS	High Risk N=720[a]	Positive for DFS, not for OS
ATLAS	VEGF (Axitinib)	1 year 3 years	DFS	High Risk N=700	Trial ongoing Projected Readout Date: June 2017
SORCE	VEGF (Sorafenib)	3 years	DFS	High & Int Risk N=1656	Awaiting results Projected Readout Date: Completed accrual
PROTECT	VEGF (Pazopanib)	1 year	DFS	High & Int Risk N=1500	Negative
EVEREST	mTOR (Everolimus)	1 year	RFS	High & Int Risk N=1218	Awaiting results Projected Readout Date: Completed accrual

PATIENT SELECTION

- The currently used prognostic tools do not capture well the biology of the tumor and do not adequately discriminate recurrence risk

- Grade, necrosis and performance status are subject to substantial interobserver variability

- The addition of prognostic molecular and genetic biomarkers may improve the identification of the very high risk population

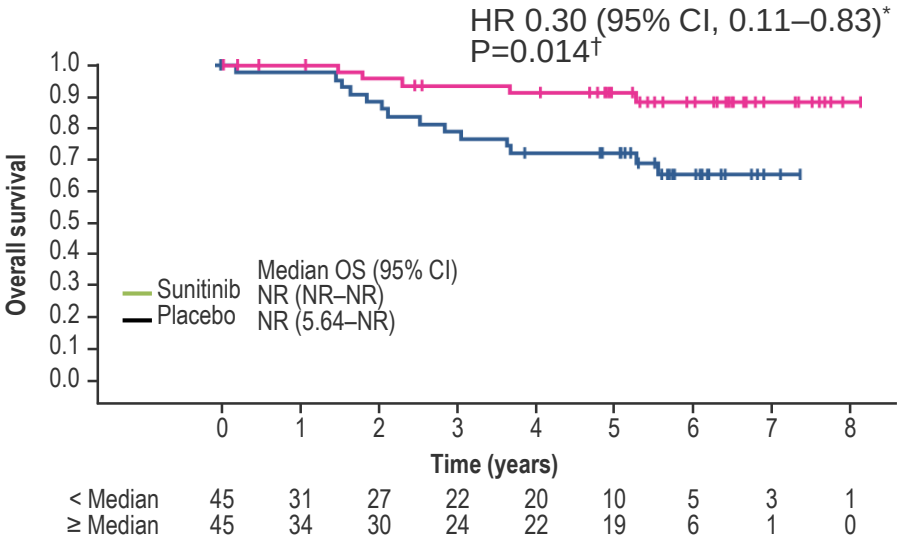
S-TRAC: BIOMARKER ANALYSIS BY IHC

CD8+ T-cells in tumour tissue may be a predictive biomarker

Tissue from 191 of the 615 patients (31.1%) analysed

- n=101/90 (sunitinib/placebo)
- PD-L1, CD4, CD8 and CD68 analysed
- No DFS difference between PD-L1-positive and negative subgroups in both arms
  - Prognostic value should be further explored[1]
- No statistically significant association between tumour-infiltrating CD4 or CD68 levels and DFS or OS, in either group
- **Increased density of CD8+ T-cells in tumour tissue was associated with longer DFS/OS in sunitinib-, but not placebo-treated patients, suggesting a predictive role**

Comparison of ≥ median density of positive cells, sunitinib vs placebo



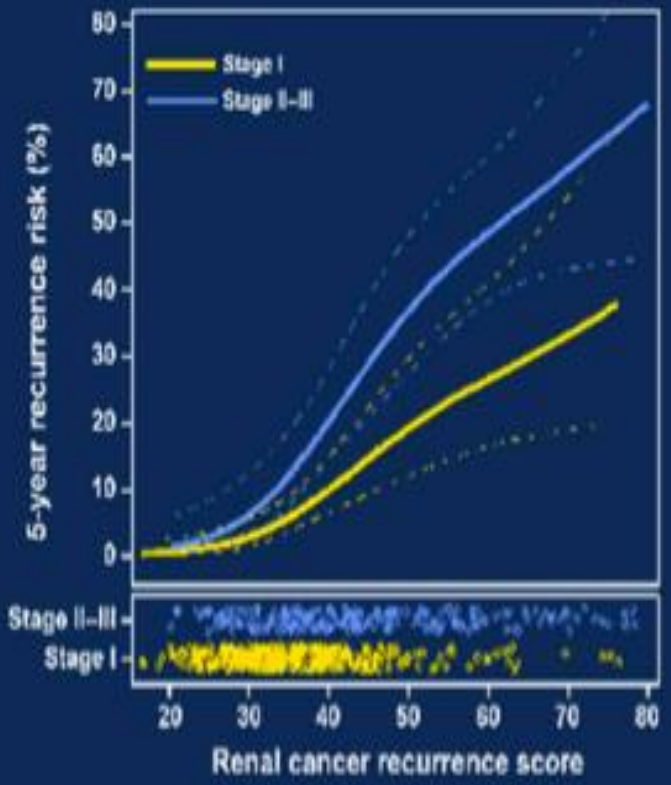
*Sunitinib vs placebo. †Unstratified log rank test.

DFS, disease-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio; NR, not reached.

1. George D et al. Poster 1771 presented at AACR Annual Meeting, Washington DC, USA April 1-5 2017.

The 16-Gene RS Assay

Risk profiles of continuous RS vs 5-year recurrence risk by stage in the validation cohort[1]



Genes Associated with Better Outcome

Vascular
APOLD1
EDNRB
NOS3
PPAP2B

Immune Response
CEACAM1
CX3CL1
CCL5

Genes Associated with Worse Outcome

Cell Growth/Division
EIF4EBP1
TUBB2A
LMNB1

Inflammation
IL6

Reference Genes
AAMP *GPX1*
ARF1 *RPLP1*
ATP5E

Recurrence Score = - 0.45 x vascular group score – 0.31 x immune response score + 0.27 x cell growth / division score + 0.04 x inflammation / scaled to 0–100

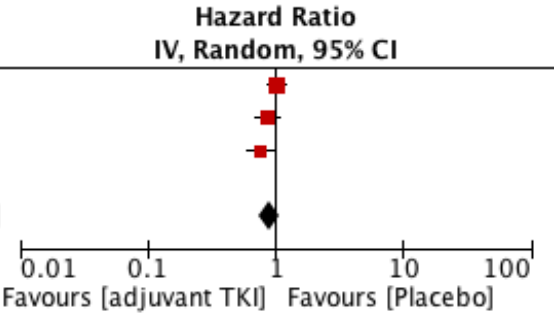
1. Rini BI, et al. Lancet Oncol 2015;16:676-85.

Inter-trial metaanalysis for ASSURE, PROTECT and S-TRAC

Study or Subgroup	log[Hazard Ratio]	SE	adjuvant TKI Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
ASSURE	0.0198	0.0824	647	647	40.5%	1.02 [0.87, 1.20]
PROTECT	-0.1485	0.1069	571	564	32.4%	0.86 [0.70, 1.06]
S-TRAC	-0.2731	0.1264	309	306	27.1%	0.76 [0.59, 0.97]
Total (95% CI)			**1527**	**1517**	**100.0%**	**0.89 [0.75, 1.06]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.17$, df = 2 (P = 0.12); $I^2 = 52\%$

Test for overall effect: Z = 1.32 (P = 0.19)



Marconi et al., personal communication

⇩

ASSESSMENT OF EVIDENCE ON ADJUVANT SUNITINIB

GRADE

Domaines	Items
Quality of evidence weak	- Conflicting DFS - No OS benefit yet
Harms-benefits ratio weak	- Significant reduction in QoL items
Values and preferences weak	- Inconsistent and premature
Costs weak	- High in view of the above

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available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

Updated European Association of Urology Guidelines Regarding Adjuvant Therapy for Renal Cell Carcinoma

Axel Bex[a,*], *Laurence Albiges*[b], *Börje Ljungberg*[c], *Karim Bensalah*[d], *Saeed Dabestani*[e], *Rachel H. Giles*[f,g], *Fabian Hofmann*[h], *Milan Hora*[i], *Markus A. Kuczyk*[j], *Thomas B. Lam*[k,l], *Lorenzo Marconi*[m], *Axel S. Merseburger*[n], *Michael Staehler*[o], *Alessandro Volpe*[p], *Thomas Powles*[q]

Summary of evidence	LE
Adjuvant cytokines do not improve survival after nephrectomy.	1b
Adjuvant sunitinib improved disease-free survival in one of the two available studies, but not overall survival, after nephrectomy, in selected high-risk patients.	1b

Recommendation	Strength rating
Do not offer adjuvant therapy with sorafenib or pazopanib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell cancer.	Weak

CONCLUSIONS

- Currently published trial on adjuvant treatment with TKIs after nephrectomy for RCC differ significantly in terms of population size and characteristics
- The evidence of efficacy of TKIs is discordant (significant DFS benefit only in S-TRAC, no OS benefit)
- The profile of adverse event of TKIs is consistent with the metastatic setting, but leads to a significant proportion of dose reductions and treatment discontinuations in the adjuvant setting

CONCLUSIONS

- Adjuvant treatment with TKIs is not recommended by the guidelines but sunitinib is an option in selected cases
- Accurate selection based on clinical features and biological/genetic tumor characteristics is crucial to identify the ideal candidates
- The results of the ongoing trials of targeted and immunotherapy agents in the adjuvant setting are awaited