The role of metastatectomy and additional therapy in kidney cancer

Leonard J. Appleman MD PhD
UPMC Hillman Cancer Center, Pittsburgh, PA

Case Presentation

- 62 year old man underwent CT scan after auto collision, and found to have 8 cm kidney tumor.
- Underwent nephrectomy

Case Presentation

- No evidence of disease following surgery
- Five years later:
- 2 cm RLL lung nodule on surveillance CT scan.
- Feeling well.

CASE PRESENTATION: What to do next?

LOCAL THERAPY?

SYSTEMIC THERAPY?

OBSERVATION?

METASTASECTOMY

DEFINITION: Surgery to remove cancer beyond the primary site

Can be performed at the time the primary is removed or Years later

RATIONALE:

- Alleviate or prevent local symptoms
- Control the cancer: Help the patient live longer with good quality of life
- Obtain tissue for molecular analysis

METASTASECTOMY

- **Control the cancer:** *Help the patient live longer with good quality of life*
- 1. Avoid systemic treatment and its potential toxicities
- or
- 2. Follow up with systemic treatment: Delay the development of resistant clones

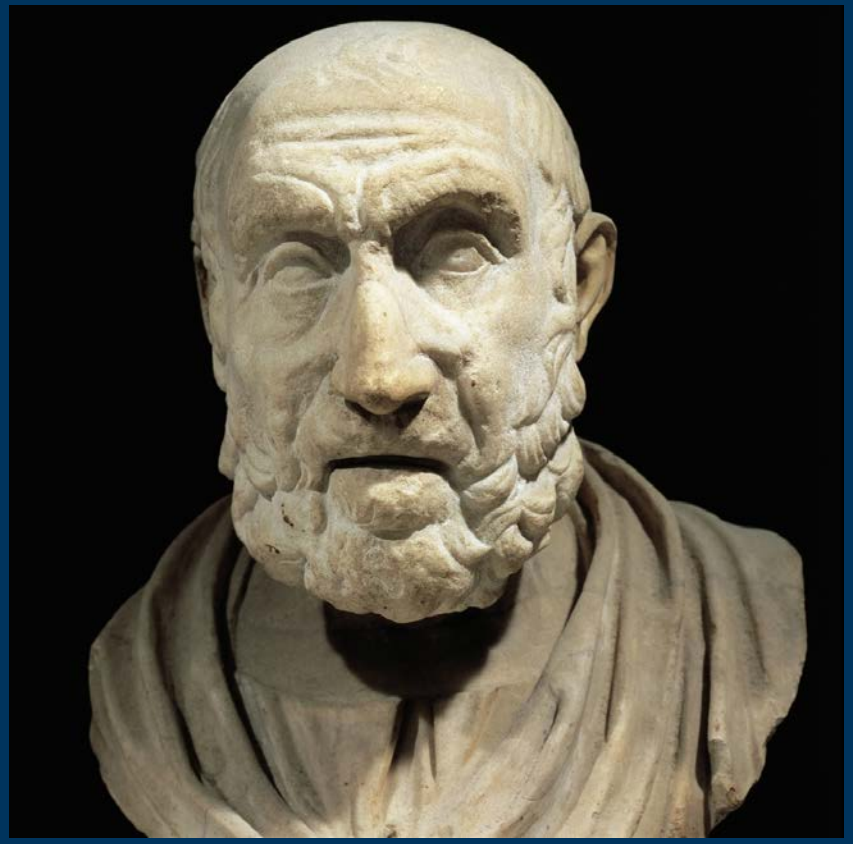
METASTASECTOMY

SHOULD WE DO IT?

Do the risks of the operation outweigh the benefit from removing the visible cancer ?

ANCIENT HISTORY OF SURGERY FOR CANCER

400 BC Hippocrates describes the stages of cancer and *advises against surgery for advanced disease*[1]



1. Principles of Surgical Oncology Dr. Khdair Al-Rawaq

Does Metastasectomy help patients?

How do we know?

Randomized Clinical Trial ???

Does Metastasectomy help?

How do we know?

~~Randomized Clinical Trial~~

PERSONAL EXPERIENCE
EXPERT OPINION

METASTASECTOMY

SHOULD WE DO IT?

WHO WILL BENEFIT?

All patients are not the same

How can we tell?

METASTASECTOMY-WHAT FACTORS PREDICT LONGER TIME UNTIL RECURRENCE?

NUMBER OF METASTATIC SITES

DISEASE-FREE INTERVAL

2019: No set “formula” or highly evidence-based approach. Treatment is individualized based on clinical features, MD experience and patient preference

Case Presentation Continued

- 62 year old man underwent nephrectomy for T3a ccRCC 5 years ago.
- CT now: 2 cm RLL lung nodule
- Nodule Resected
- No evidence of disease following surgery
- Medical oncologist recommends close follow up

- Thoracic Surgeon is **FURIOUS** that no systemic treatment is offered after the operation…

The Metastasectomy Dilemma

- Metastasectomy has been performed for mRCC for over 80 years.
  - *Synchronous*: at time of nephrectomy; *Metachronous*: later

- Risk of recurrent disease is **high**

- No systemic therapy has been shown to improve outcomes in patients NED after metastasectomy:

UNMET NEED

A randomized, open label, multicenter phase 2 study, to evaluate the efficacy of Sorafenib in patients with advanced Renal Cell Carcinoma (RCC) after a radical resection of the metastases: RESORT trial.

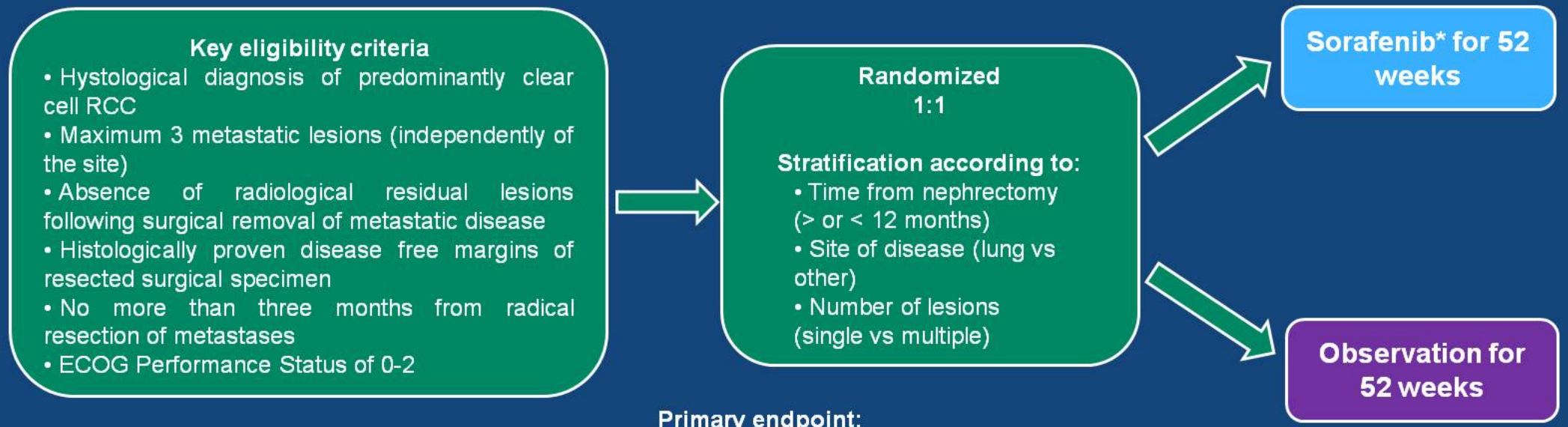
Giuseppe Procopio[1], Francesco Cognetti[2], Rosalba Miceli[1], Michele Milella[2], Alessandra Mosca[3], Vincenzo Chiuri[4], Alessandra Bearz[5], Franco Morelli[6], Cinzia Ortega[7], Francesco Atzori[8], Maddalena Donini[9], Raffaele Ratta[1], Antonella Martinetti[1], Rosanna Montone[1], Filippo de Braud[1], Vera Cappelletti[1], Elena Verzoni[1]

[1]Istituto Nazionale Tumori, Milan; [2]IRCCS Regina Elena National Cancer Institute, Rome; [3]AOU Maggiore della Carità, [4]Ospedale Vito Fazzi, Lecce; [5]CRO, Aviano; [6]Casa Sollievo della Sofferenza, S. Giovanni Rotondo; [7]Fondazione del Pi per l'Oncologia, IRCCS Candiolo (TO); [8]Azienda Ospedaliera Universitaria, Cagliari; [9]AO Istituti Ospitalieri, Cremona

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Giuseppe Procopio, MD

RESORT: Study Design



Primary endpoint:
RFS

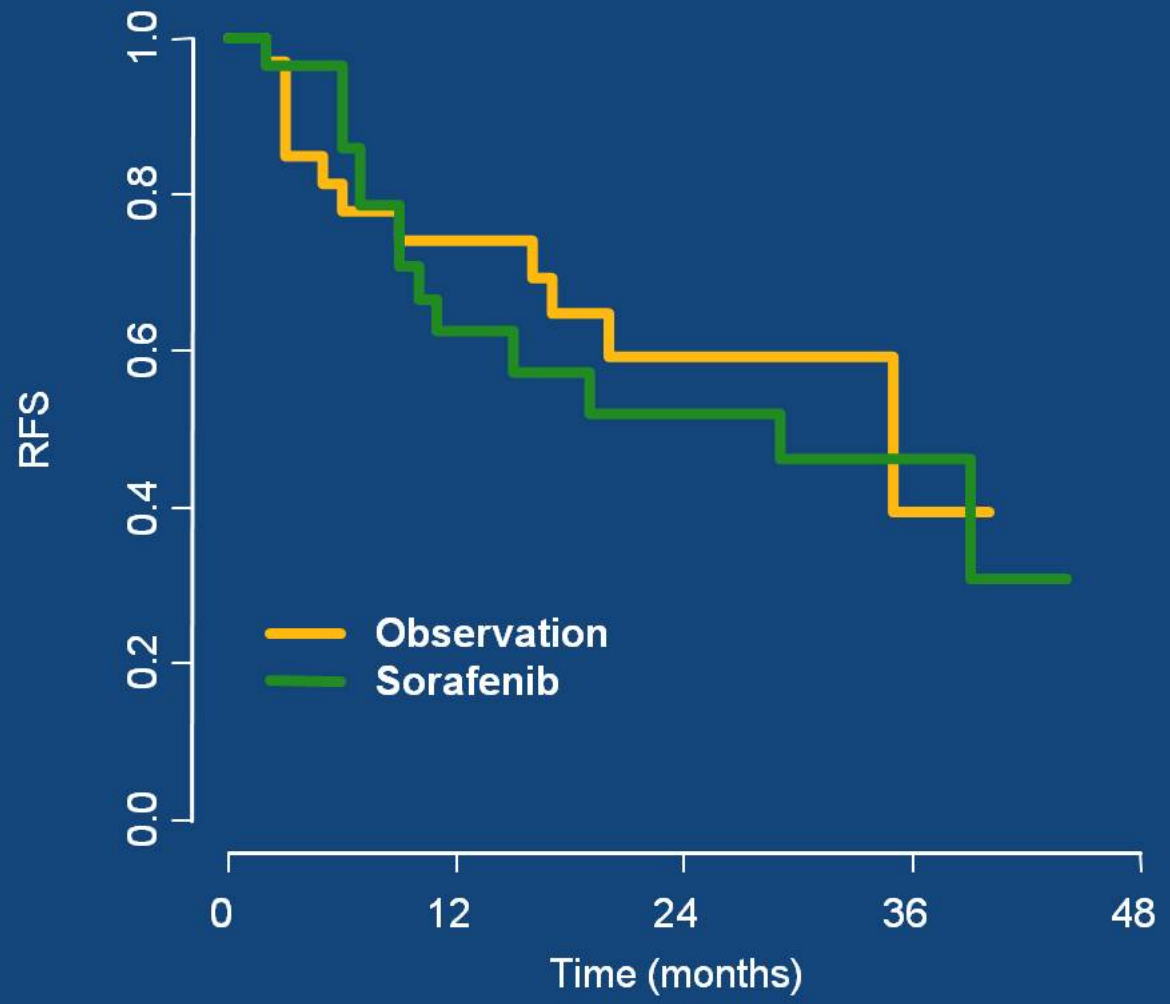
Secondary endpoints:
OS
Safety profile

Exploratory endpoints:
Translational analyses on blood and tumor samples

*Starting dose: Sorafenib 400 mg once a day for 3 weeks. After 21 days the dose should be increased to the standard dose (400 mg bid) if the patient has not experienced greater than Grade I skin toxicity or greater than Grade II of any other toxicity.

RFS, Recurrence Free Survival
OS, Overall Survival

mRFS in the two treatment arms



	n. of pts*	n. of events	median (months)
arm= OBS**	36	12	35.0
arm= SORAFENIB	32	14	29.0

	12 months RFS (%, 95% CI)	24 months RFS (%, 95% CI)
arm= OBS**	74 (59-91)	59 (42-82)
arm= SORAFENIB	62 (46-84)	52 (35-76)

* pts, patients
** OBS, observation

Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy: A trial of the ECOG-ACRIN cancer research group (E2810)

Leonard J. Appleman, Maneka Puligandla, Sumanta K. Pal, Wayne Harris, Neeraj Agarwal, Brian A. Costello, Christopher W. Ryan, Michael Pins, Jill Kolesar, Daniel A. Vaena, Rahul A. Parikh, Mehmood Hashmi, Janice P. Dutcher, Robert S. DiPaola, Naomi B. Haas, Michael A. Carducci;

UPMC Hillman Cancer Center, Pittsburgh, PA; Dana Farber Cancer Institute, Boston, MA; City of Hope Comprehensive Cancer Center, Duarte, CA; Emory University School of Medicine, Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Mayo Clinic, Rochester, MN; Oregon Health & Science University, Knight Cancer Institute, Portland, OR; University of Illinois College of Medicine, Chicago, IL; University of Wisconsin Carbone Cancer Center, Madison, WI; University of Iowa Hospitals and Clinics, Holden Comprehensive Cancer Center, Iowa City, IA; University of Kansas Cancer Center, Westwood, KS; University of Kansas, Kansas City, KS; Our Lady of Mercy Cancer Center, New York, NY; University of Kentucky, Lexington, KY; Penn Medicine Abramson Cancer Center, Philadelphia, PA; Sidney Kimmel Cancer Center At Johns Hopkins, Baltimore, MD

Pazopanib

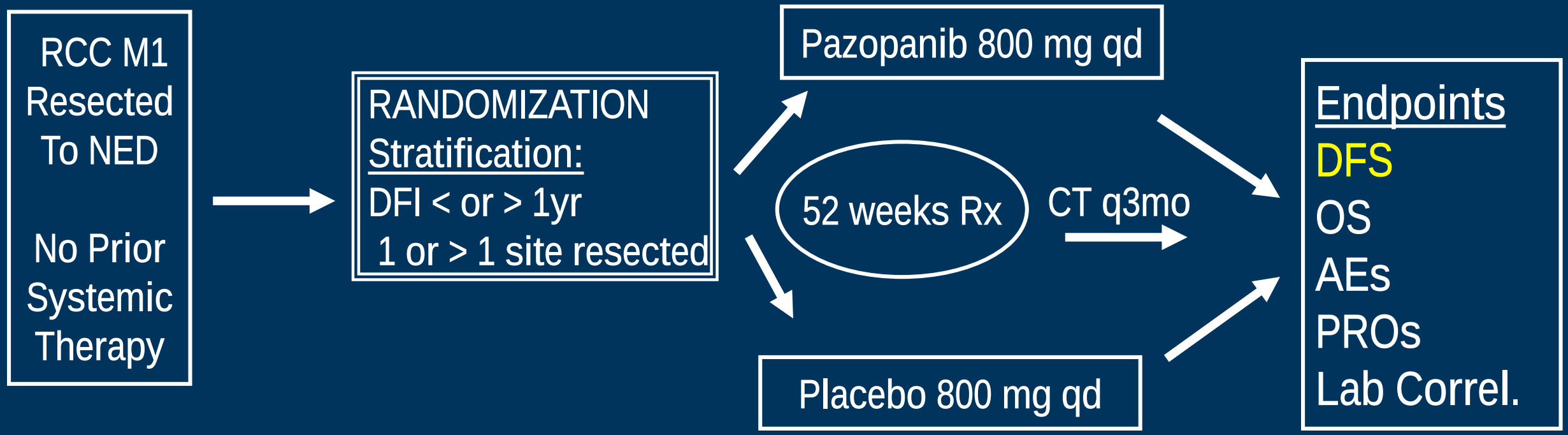
- **Pazopanib** has been a standard of care for first-line systemic therapy for metastatic RCC based upon improved progression-free survival (PFS) compared to placebo (**Sternberg** *et al.* 2010). PFS was non-inferior *vs.* sunitinib and favorable patient reported outcomes (Motzer *et al.* 2013).

- Utility of VEGF-targeted agents in the NED (adjuvant or post-metastasectomy) state was unknown at study conception

E2810 Hypothesis

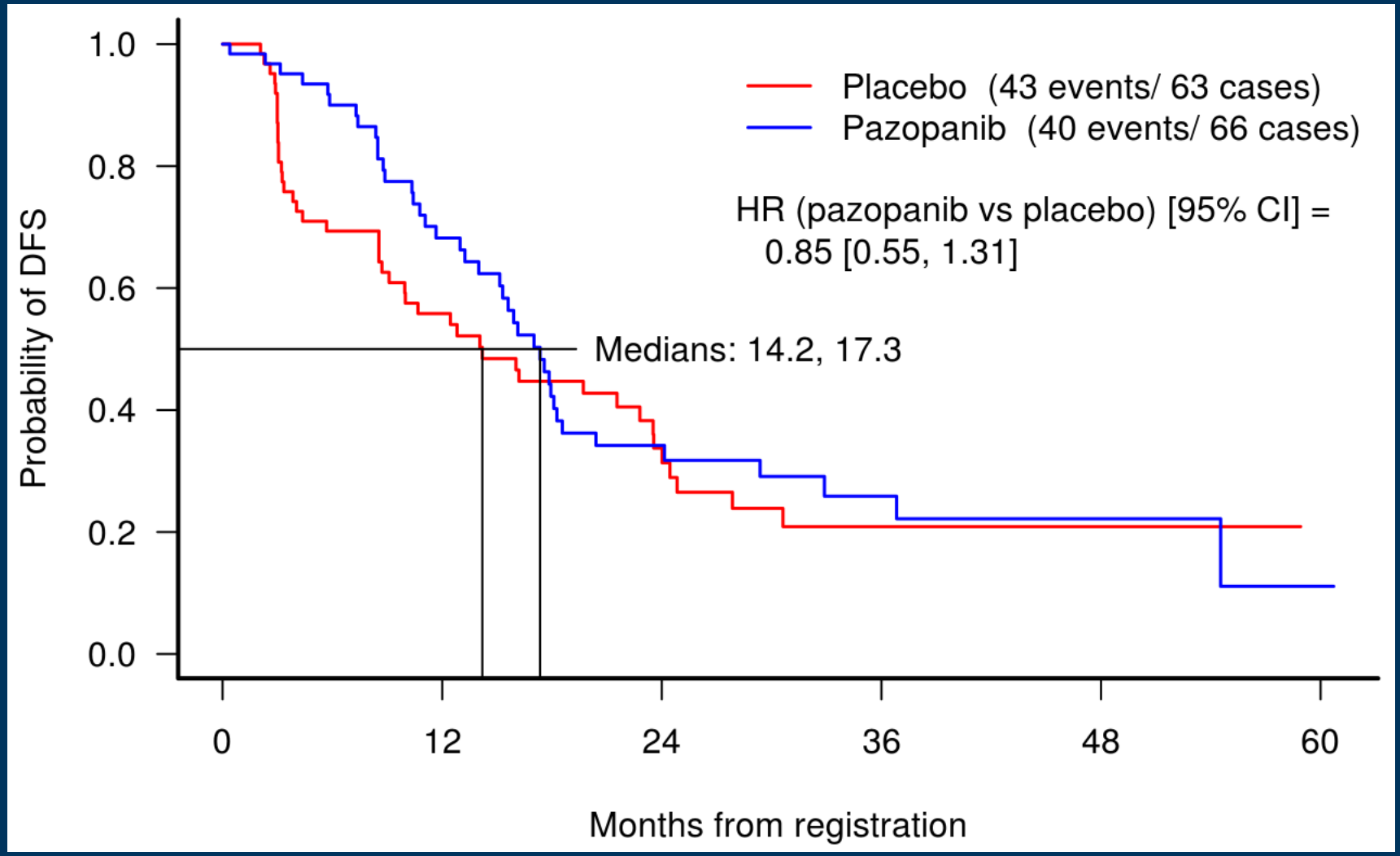
12 months of pazopanib treatment will increase disease-free survival in patients with metastatic RCC who have been rendered radiographically disease free by surgical metastasectomy

E2810 STUDY SCHEMA

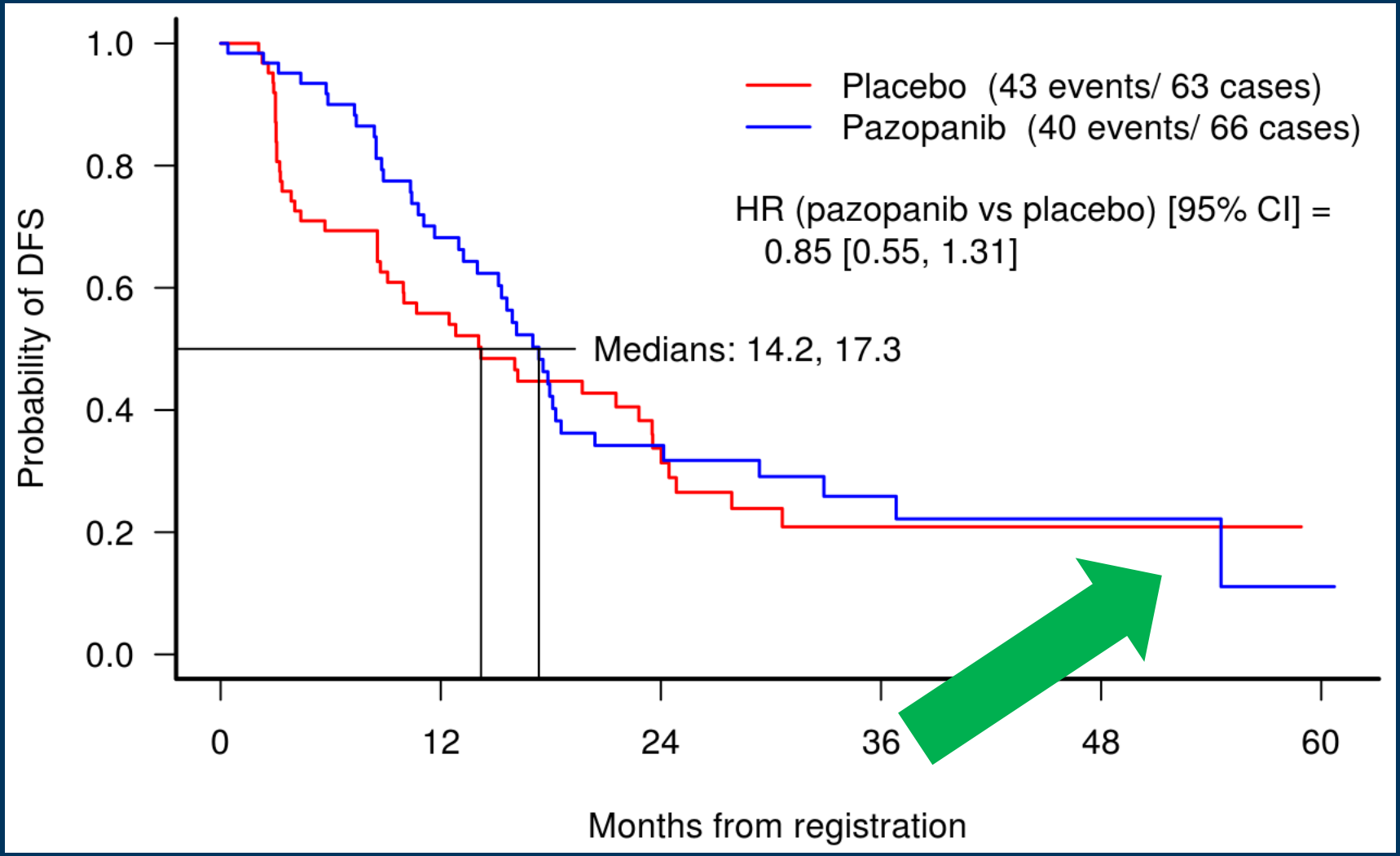


DFI: disease-free interval
DFS: disease-free survival
PRO: patient reported outcome

Pazopanib did not improve disease-free survival



Pazopanib did not improve disease-free survival



Median follow up-30 months
83/129 DFS events (64%)

36 month DFS:
Pazopanib 26%
Placebo 22%

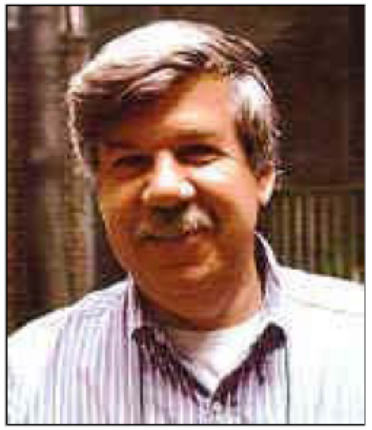
(estimated 25% at start of study)

OUTCOMES AFTER METASTASECTOMY
MEDIAN VS. “TAIL OF THE CURVE”

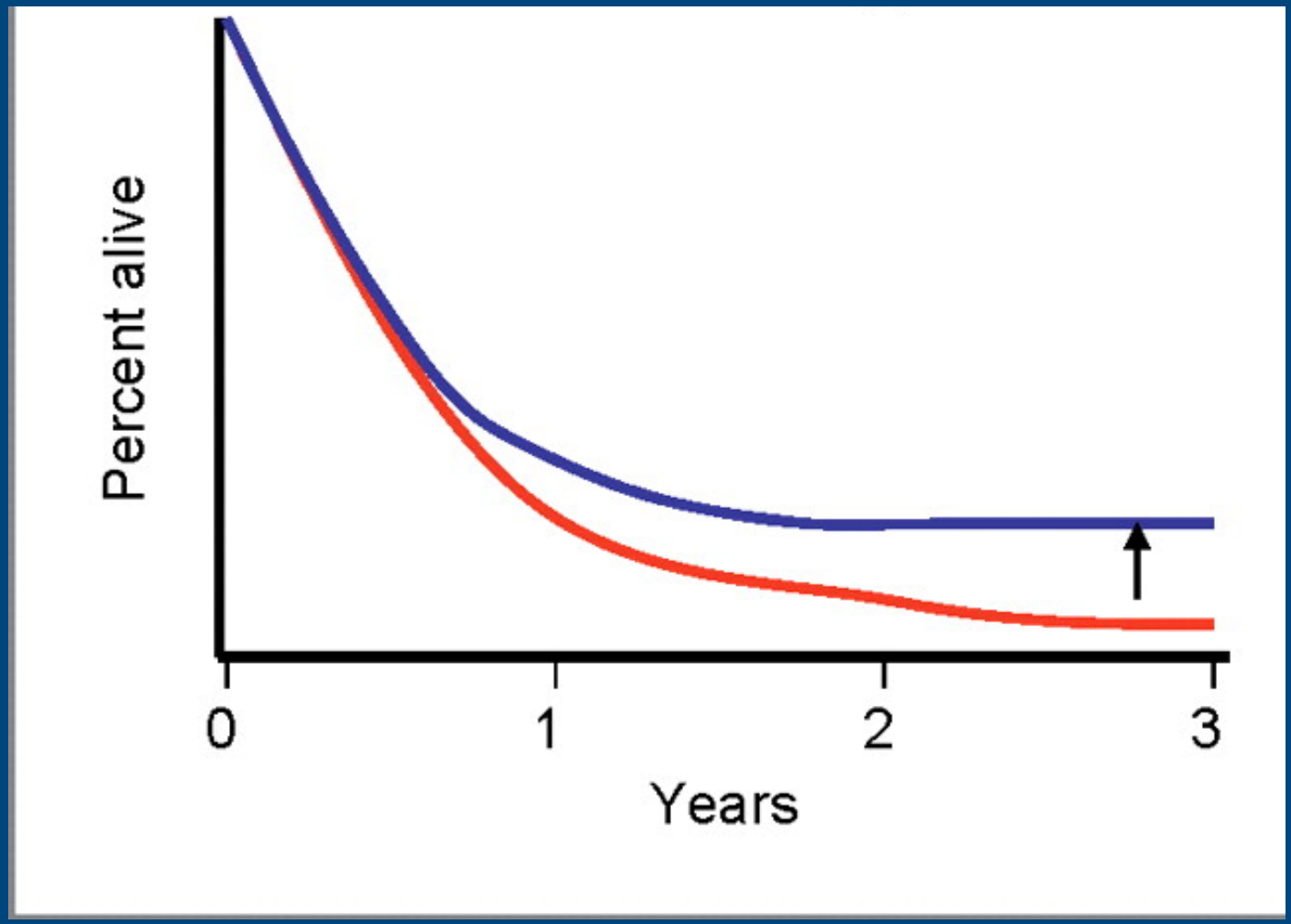
"This is a personal story of statistics..."

THE MEDIAN ISN'T THE MESSAGE

by Stephen Jay Gould

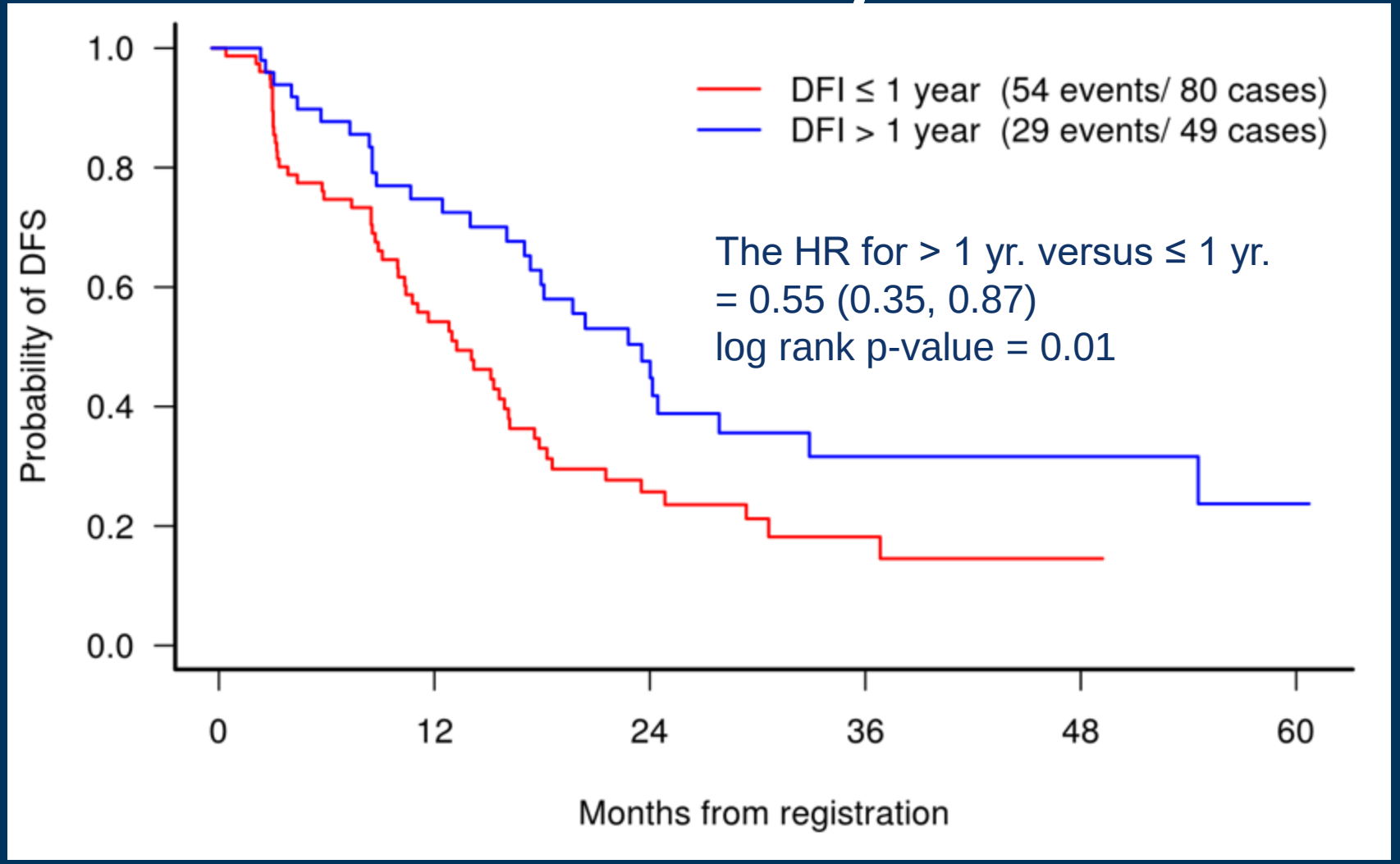


Born in 1941, Stephen Jay Gould was a geologist, zoologist, paleontologist and evolutionary biologist at Harvard. He was also one of the most noted, prolific and best-selling scientific writers of our day. He was diagnosed in 1982 with abdominal mesothelioma, a rare and very deadly form of cancer associated with exposure to asbestos. This is his story. It was first published in Discover magazine in June 1985 and was reprinted here at Phoenix5 with his kind permission. He beat the cancer for 20 years, finally passing on May 20, 2002, giving all of us a valuable lesson in beating the odds.

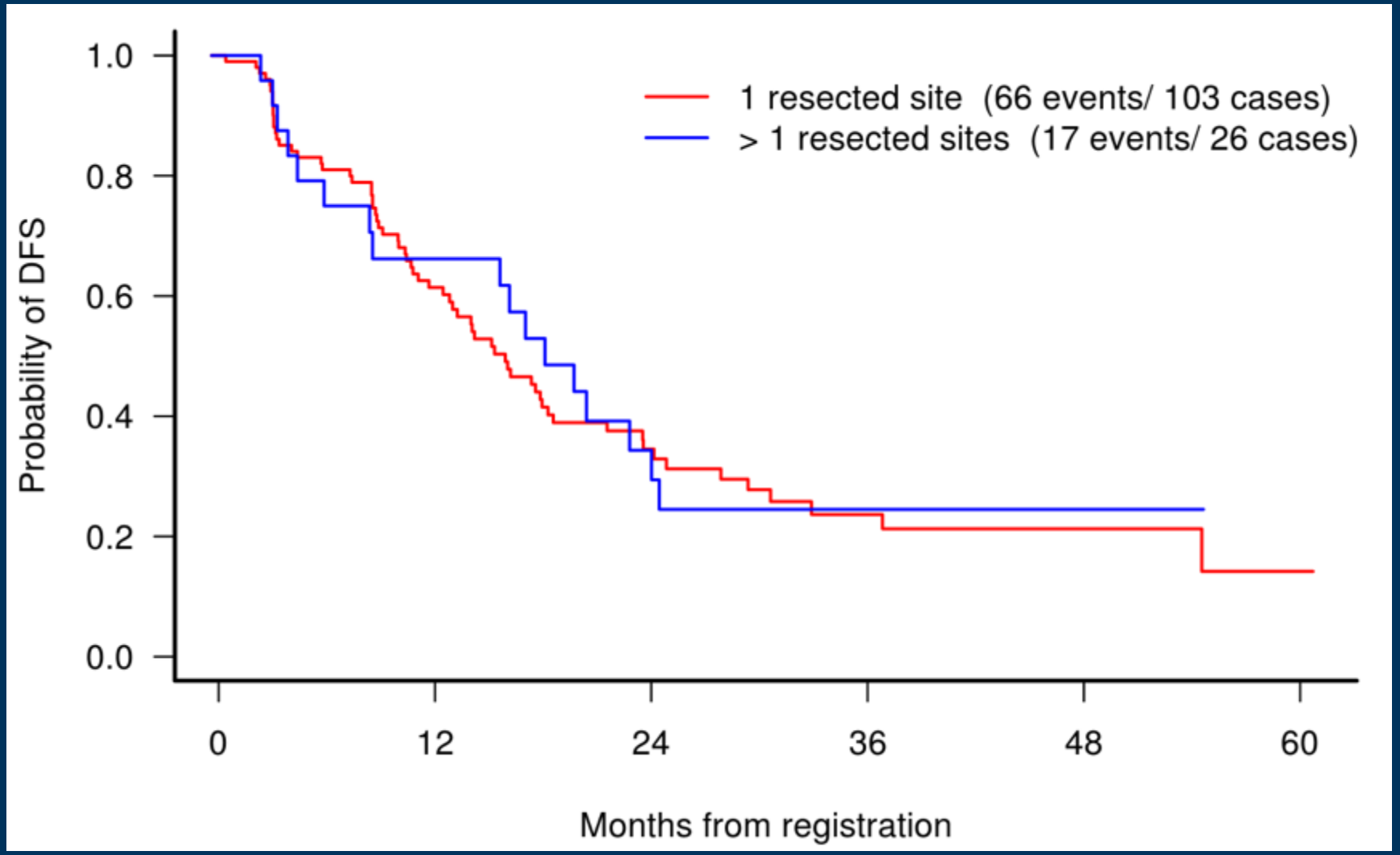


Ribas,Hersey, Middleton, Gogas, Flaherty, Sondak, Kirkwood 2012

Trend toward improved disease-free survival for disease-free interval > 1 year



DFS by Stratification Factor: Number of Resected Sites



CYTOREDUCTIVE NEPHRECTOMY

One third of patients with renal cell carcinoma present with metastatic disease

Hypothesis: removal of primary tumor will be beneficial
Because…

1. Alleviation of tumor-mediated immune suppression

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CYTOREDUCTIVE NEPHRECTOMY IN PATIENTS WITH METASTATIC RENAL CANCER: A COMBINED ANALYSIS

ROBERT C. FLANIGAN,* G. MICKISCH, RICHARD SYLVESTER, CATHY TANGEN,†
H. VAN POPPEL AND E. DAVID CRAWFORD

From the Southwest Oncology Group and European Organization for the Research and Treatment of Cancer Genitourinary Group, Loyola University Medical Center (RCF), Maywood, Illinois, Centrum Fuer Operative Urologie (GM), Bremen, Germany, European Organization for the Research and Treatment of Cancer Data Center (RS), Brussels and UZ Gasthuisberg (HVP), Leuven, Belgium, Southwest Oncology Group Statistical Center (CT), Seattle, Washington, and University of Colorado Medical Center (EDC), Denver, Colorado

Two Randomized studies: Newly diagnosed metastatic RCC with primary in place:

Interferon-α2b*

vs.

Cytoreductive nephrectomy followed by Interferon-α2b

SWOG (n=241) and EORTC (n=83); 1990s

*Median PFS 5-6 months. Response rate 6%.
Significant chronic and constitutional toxicity

Cytoreductive nephrectomy +IFN vs IFN Alone: Combined SWOG/EORTC OVERALL SURVIVAL

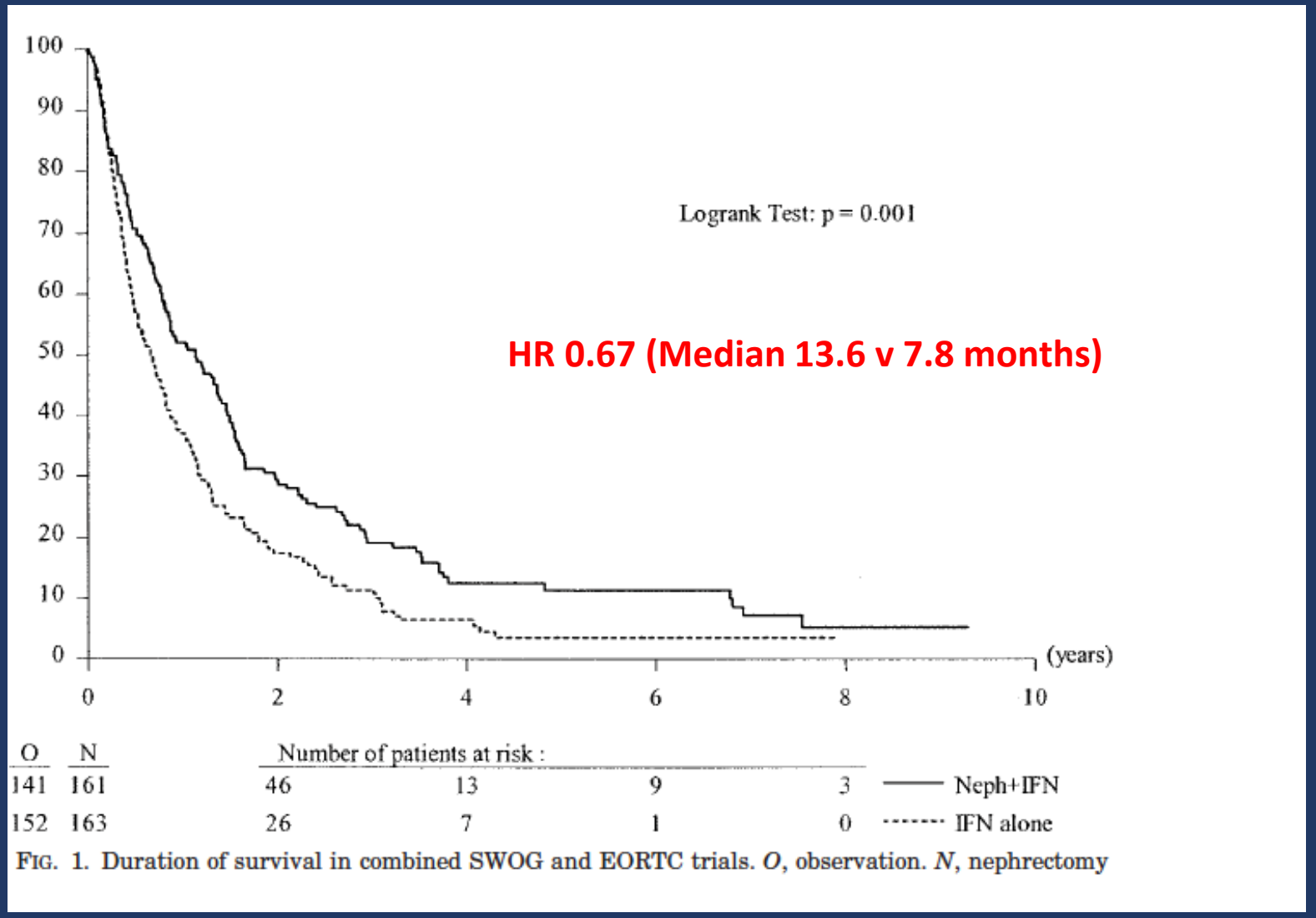


FIG. 1. Duration of survival in combined SWOG and EORTC trials. *O*, observation. *N*, nephrectomy

1990s-2006

Interferon-a2b

2006-2013

Targeted Rx

Sorafenib, sunitinib, temsirolimus, everolimus, pazopanib, axitinib, bevacizumab,cabozantinib

Is there a benefit to cytoreductive nephrectomy for patients treated with targeted therapy against VEFG and other pathways?

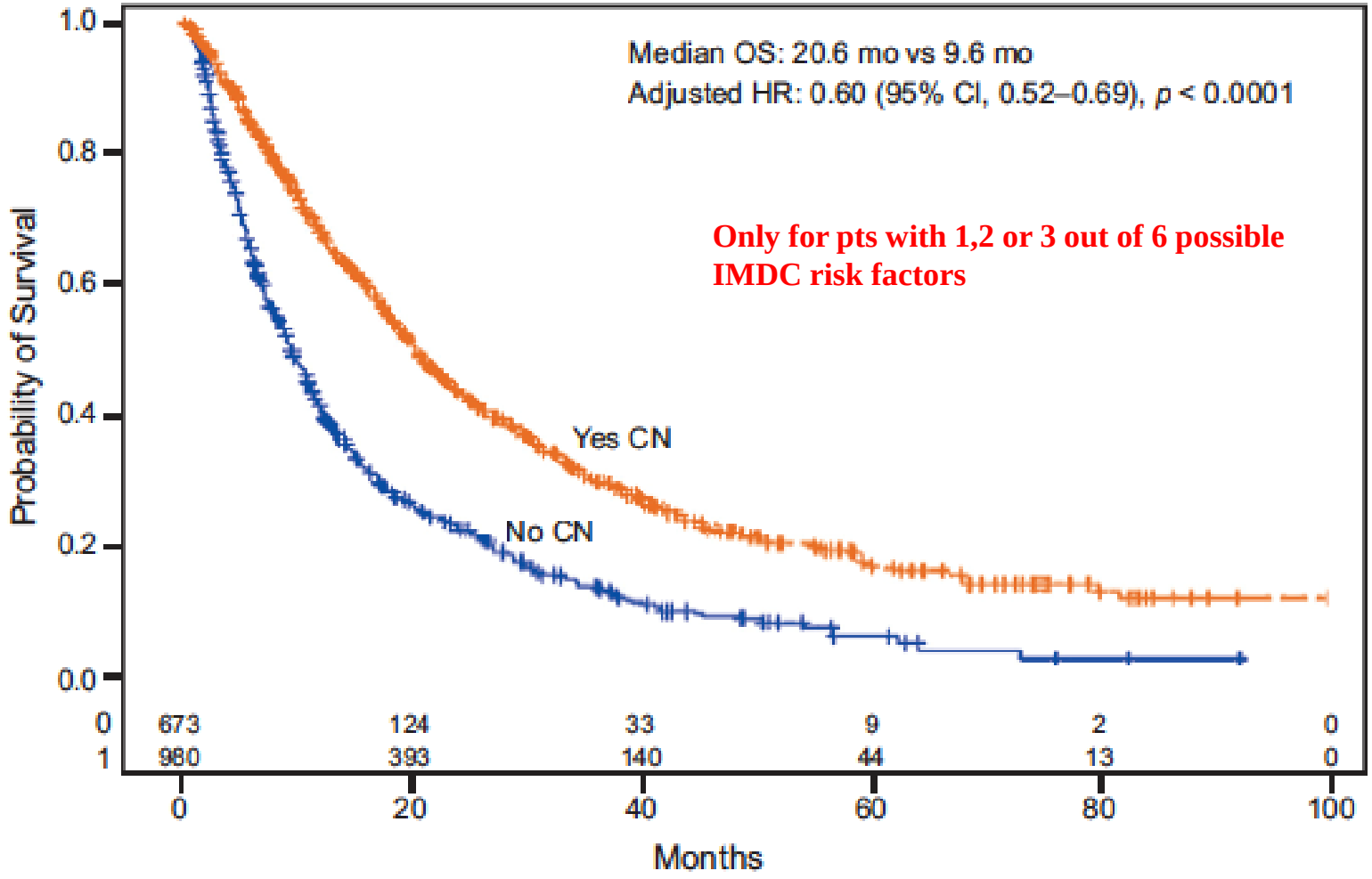
European Association of Urology

Platinum Priority – Kidney Cancer
Editorial by Stephen H. Culp on pp. 711–712 of this issue

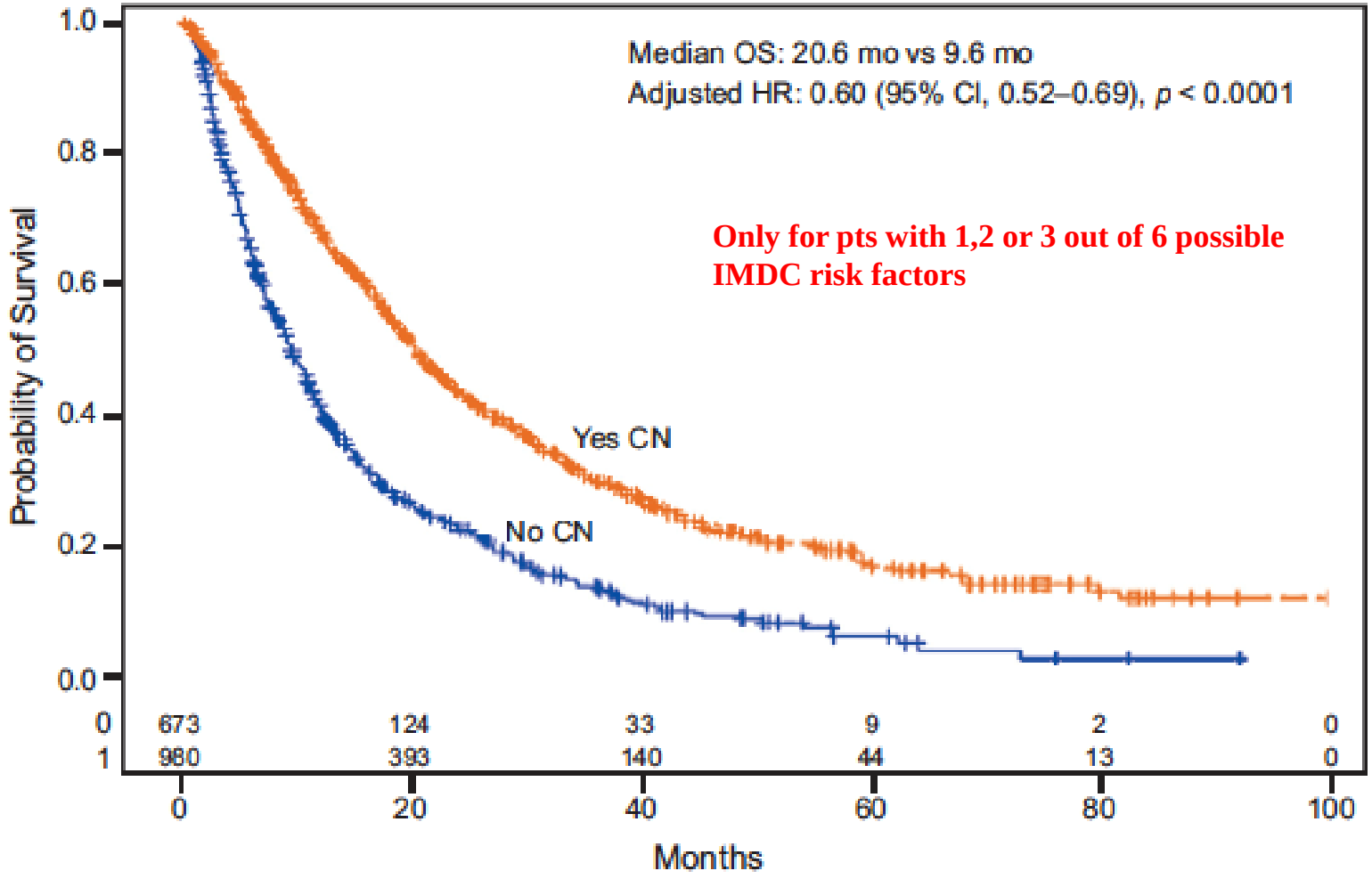
Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Daniel Y.C. Heng[a,,†], J. Connor Wells[a,†], Brian I. Rini[b], Benoit Beuselinck[c], Jae-Lyun Lee[d], Jennifer J. Knox[e], Georg A. Bjarnason[f], Sumanta Kumar Pal[g], Christian K. Kollmannsberger[h], Takeshi Yuasa[i], Sandy Srinivas[j], Frede Donskov[k], Aristotelis Bamias[l], Lori A. Wood[m], D. Scott Ernst[n], Neeraj Agarwal[o], Ulka N. Vaishampayan[p], Sun Young Rha[q], Jenny J. Kim[r], Toni K. Choueiri[s]*

Heng *et al.* Overall Survival



Heng *et al.* Overall Survival



RETROSPECTIVE

CARMENA : Cytoreductive nephrectomy followed by sunitinib versus sunitinib alone in metastatic renal cell carcinoma (mRCC) - Results of a phase III non-inferiority trial. (NCT00930033)

Arnaud Méjean, Alain Ravaud, Simon Thezenas, Sandra Colas, Jean-Baptiste Beauval, Karim Bensalah, Lionnel Geoffrois, Antoine Thiery-Vuillemin, Luc Cormier, Hervé Lang, Laurent Guy, Gwenaelle Gravis, Frederic Rolland, Claude Linassier, Eric Lechevallier, Christian Beisland, Michael Aitchison, Stephane Oudard, Jean-Jacques Patard, Christine Theodore, Christine Chevreau, Brigitte Laguerre, Jacques Hubert, Marine Gross-Goupil, Jean-Christophe Bernhard, Laurence Albiges, Marc-Olivier Timsit, Thierry Lebret, Bernard Escudier

On Behalf of Carmena investigators

Arnaud Méjean

@MejeanArnaud

Professeur d'Urologie, HEGP, Hopital Necker, APHP, Université Paris Descartes, Responsable Comité de Cancérologie de l'AFU Administrateur de l'AFU

PRESENTED BY: Arnaud Méjean

Presented By Arnaud Mejean at 2018 ASCO Annual Meeting

CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study

- Confirmed metastatic clear cell RCC / Biopsy
- ECOG-PS 0-1
- Amenable to nephrectomy
- Eligible for sunitinib
- Brain metastases absent/controlled by treatment
- No prior systemic therapy for RCC

R
1:1

Stratification
- MSKCC risk group
- Center location

Arm A

nephrectomy → 3-6 weeks → Sunitinib
50 mg QD 4 wks on / 2 wks off

Arm B

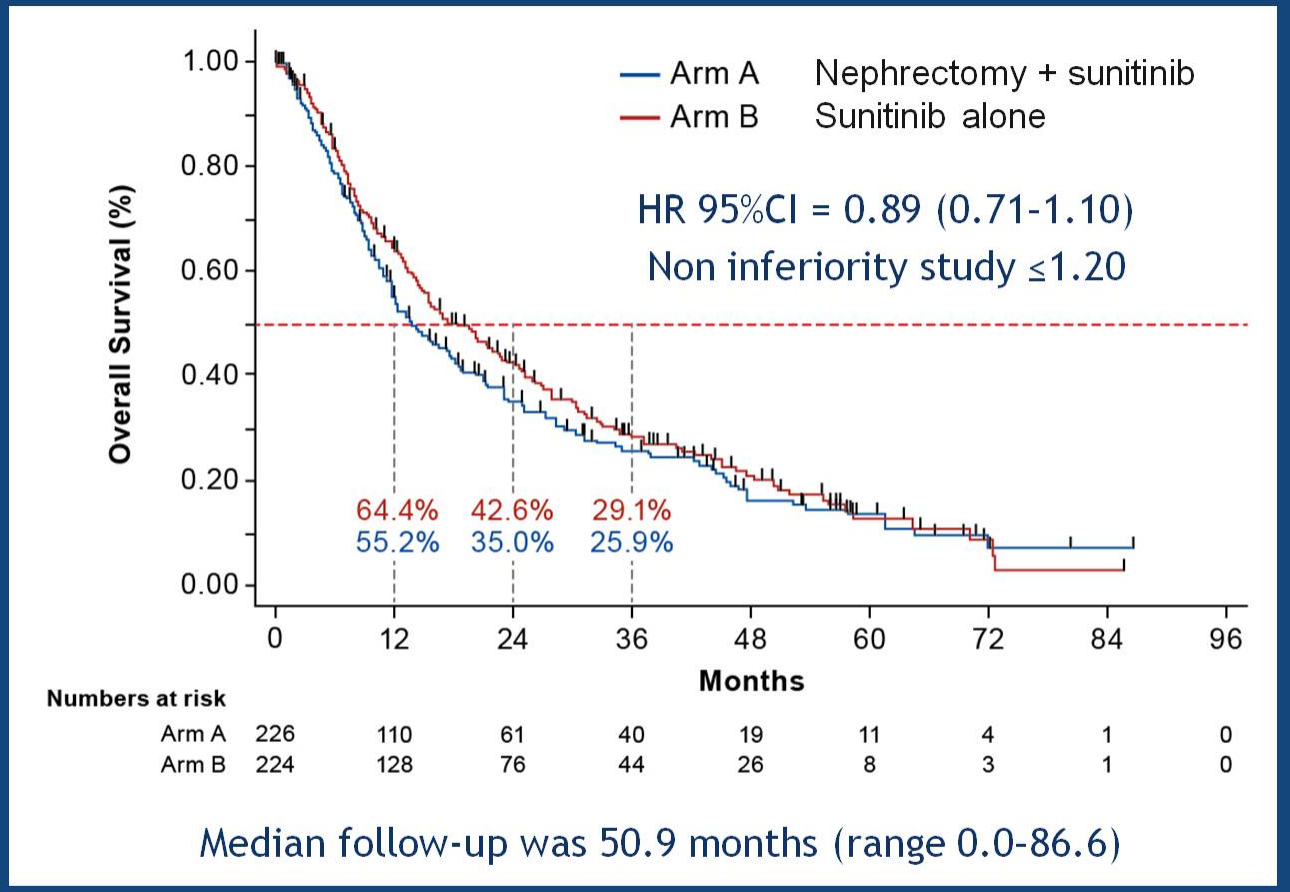
Sunitinib
50 mg QD 4 wks on / 2 wks off

Primary endpoint:
Overall survival

Secondary endpoints:
Progression-free survival, objective response rate, clinical benefit, safety

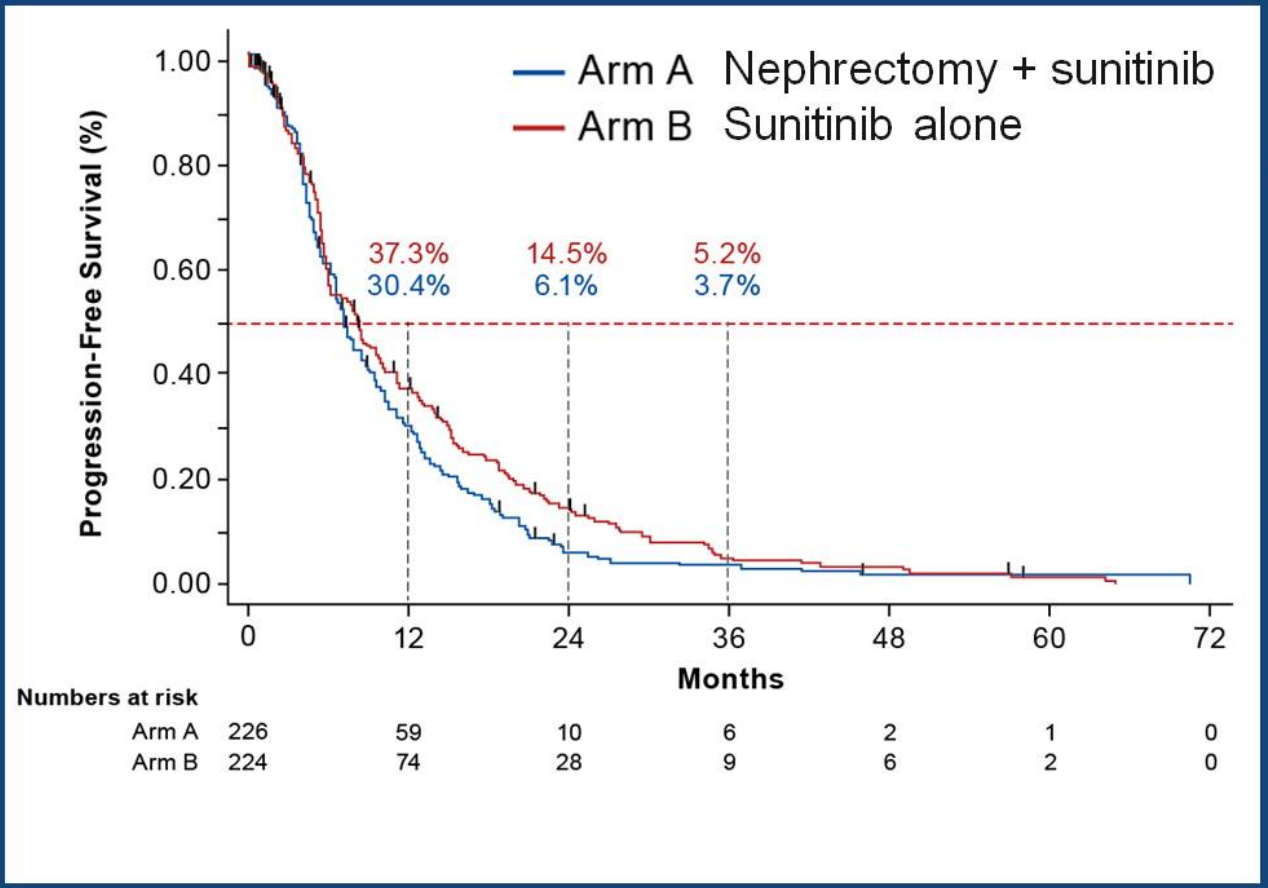
LPI, last patient included; MSKCC, Memorial Sloan Kettering Cancer Center; QD, once daily; R, randomization; RCC, renal cell carcinoma

Overall survival (ITT)



Median follow-up was 50.9 months (range 0.0-86.6)

Progression free survival (ITT)



	Median PFS, months (95% CI)	HR (95% CI)
Arm A: Nephrectomy + Sunitinib (n = 226)	7.2 (6.5-8.5)	0.82 (0.67-1.00)
Arm B: Sunitinib alone (n = 224)	8.3 (6.2-9.9)	

CN, cytoreductive nephrectomy; PFS, progression-free survival

CARMENA STUDY

- How should/will this change practice?

- Would be helpful to know about patients who were not considered for the study and went to surgery as standard of care because physician or patient preference (including outcomes).

- How to reconcile with IMDC data?

1990s-2006
Interferon-a2b

2006-2016
Targeted Rx
Sorafenib, sunitinib, temsirolimus, everolimus, pazopanib, axitinib, bevacizumab,cabozantinib

2019-
PD-1 antibodies, Combos

FUTURE DIRECTIONS

Metastasectomy and Immune checkpoint inhibitors

- Oligometastatic disease allowed in ongoing adjuvant randomized studies:

  - **PROSPER-RCC** (EA8143, NCT03055013) (metastasectomy allowed within 12 weeks of nephrectomy). (Nivolumab vs. observation; pre/post-op; L. Harshman, P.I.)
  - **KEYNOTE 564** (NCT03142334; Pazopanib vs. placebo (metastasectomy allowed within 1 year)
  - **IMmotion010** (NCT03024996; atezolizumab vs. placebo; metachronous or synchronous metastasectomy allowed)

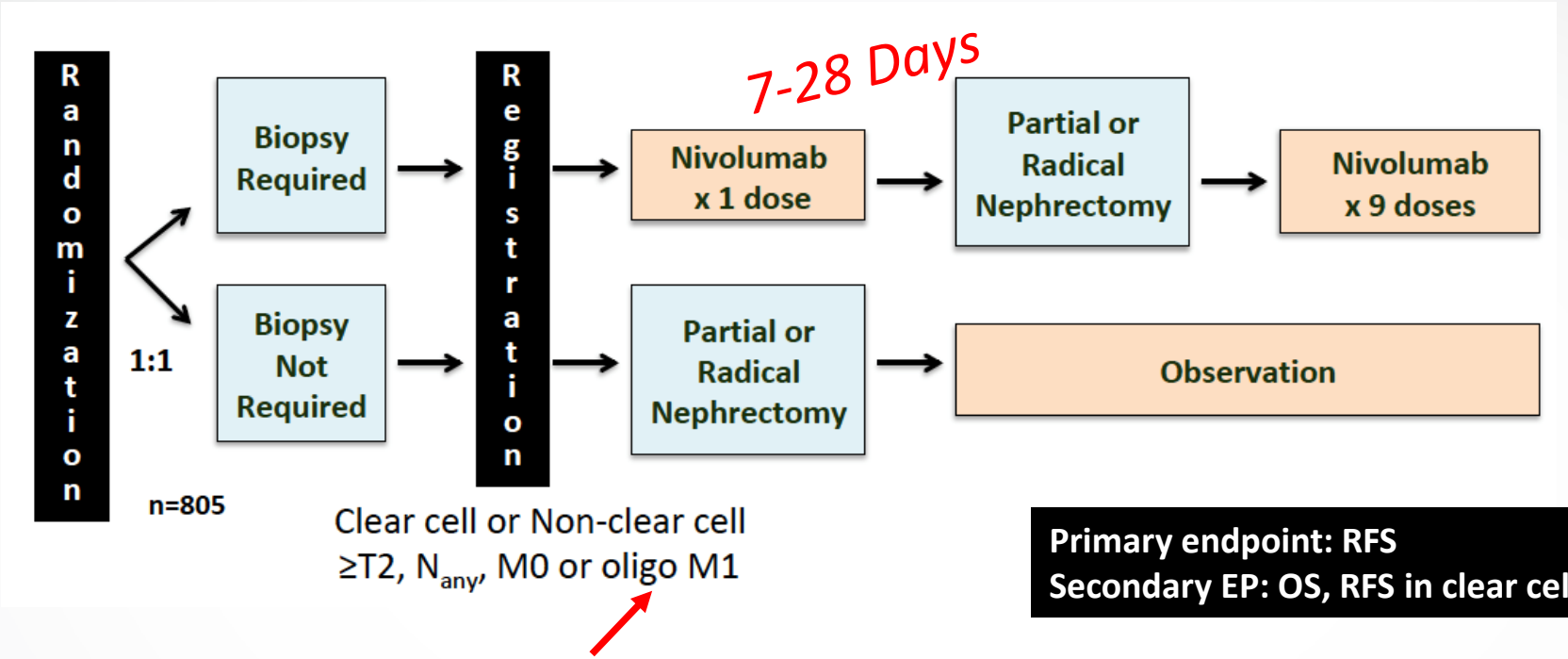
EA8143 Study Update

A Phase 3 RandOmized Study Comparing PERioperative Nivolumab vs. Observation in Patients with Localized Renal Cell Carcinoma Undergoing Nephrectomy (PROSPER RCC)

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Lauren Harshman, MD
EA8143 Study Chair
ECOG-ACRIN Fall Group Meeting
October 2018
Fort Lauderdale, FL

EA8143 PROSPER RCC: Adjuvant Therapy with a Twist



- Need the trifecta: presurgical priming with PD-1 blockade necessary for enhanced efficacy
- 1 adjuvant dose may not be sufficient→ further engage with adjuvant therapy
- No Placebo—patients really do care about this!

ADDITIONAL LOCAL TREATMENT OPTIONS

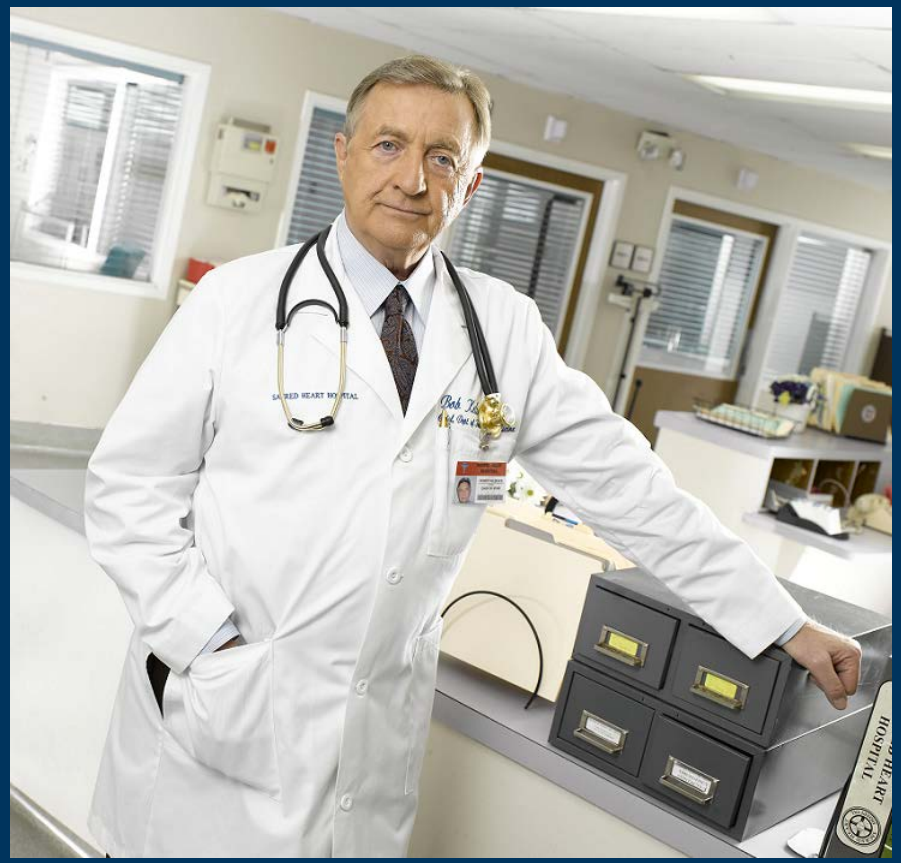
- Radiation Therapy (including stereotactic radiation)
  - Kidney cancer not particularly sensitive to radiation but new techniques can achieve higher doses without damage to normal tissues

- Thermal energy techniques
  - Cryotherapy (tumor ice ball)
  - Radiofrequency ablation (kill it with fire!)
  - Embolization/chemoembolization

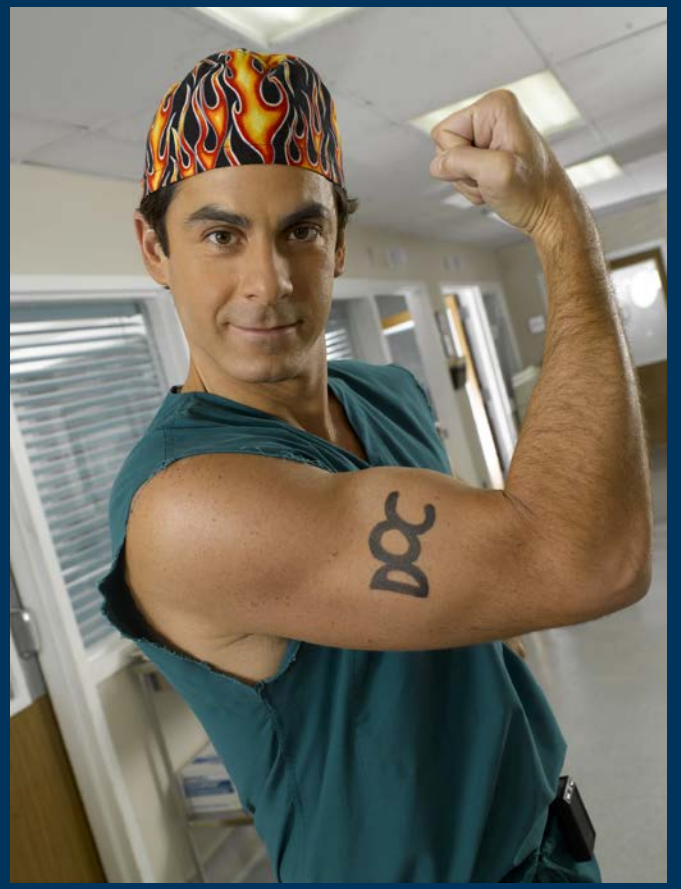
Future treatment paradigm?

- Pre-operative priming with immunotherapy (anti-PD-1)
- Surgery to remove metastasis
- Post-operative immunotherapy and close monitoring.

Medicine vs. Surgery



vs.



Medicine AND Surgery
(for some patients)

THANK YOU