

How to Deal with RCC Oligometastases

Chad Tang

Associate Professor-Genitourinary Radiation Oncology

MD Anderson Cancer Center

Location lorem ipsum

bmuc.be/bmuc2024



**12th Belgian Multidisciplinary
Meeting on Urological Cancers**

Conflicts of interest

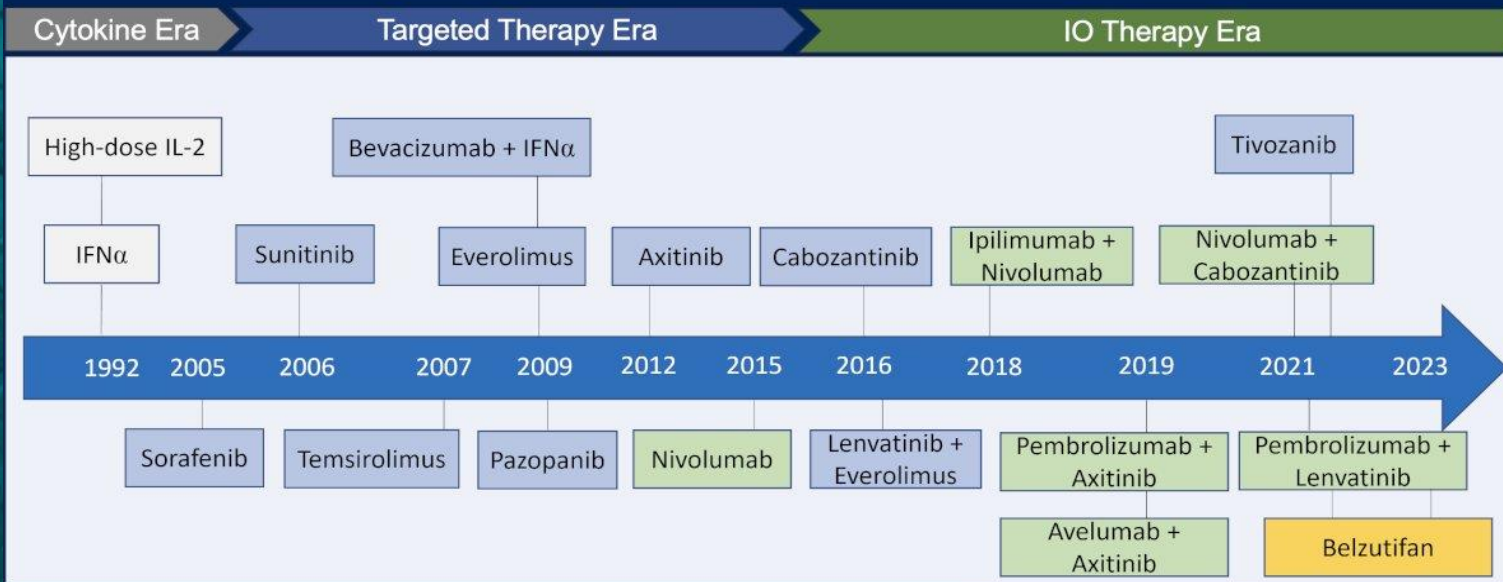
- I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	Merck, Myriad Genetics
Receipt of honoraria or consultation fees:	Lantheus, Telix, Boston Scientific, Molli Surgical, Vision RT, Elekta, Bayer
Participation in a company sponsored speaker's bureau:	NA
Stock shareholder:	NA
Spouse/partner:	NA
Other support (please specify):	Editor of MD Anderson Handbook of Radiation Oncology, published by Wolter Kluwer (1 st and 2 nd Editions)



Treatment Paradigm in mRCC

3



Future/Completed trials:
COSMIC and
PDGREE: Nivo+Ipi+Cabo

LITESPARK-012:
Lenvatinib+pembro+belzutifan

ADENOCARCINOMA OF THE KIDNEY WITH METASTASIS TO THE LUNG

CURED BY NEPHRECTOMY AND LOBECTOMY¹

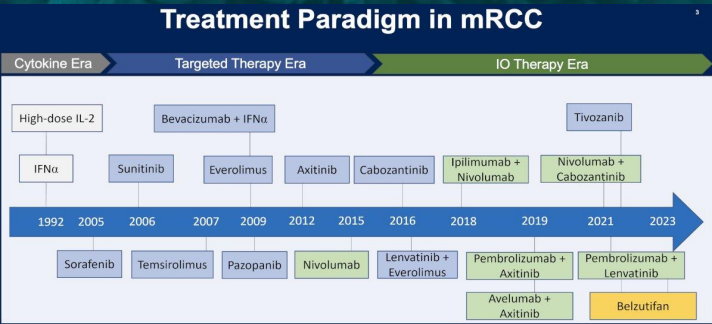
J. DELLINGER BARNEY AND EDWARD J. CHURCHILL

From the Surgical Services of the Massachusetts General Hospital

Adenocarcinoma of the kidney (hypernephroma) is a neoplasm that on occasion may be treated by removal of the primary growth and an apparently single metastasis. The following case history relates the course of a patient in whom x-ray evidence of a metastatic nodule in the lung was the first sign of disease. A nephrectomy was performed 5 months later, and 15 months following the nephrectomy the pulmonary metastasis was excised by sub-total lobectomy. The patient is surviving 5 years later in good health, without evidence of disease.

¹Read at the annual meeting of the American Association of Genito-Urinary Surgeons, Absecon, New Jersey, May 2, 1938.

1938



ADENOCARCINOMA OF THE KIDNEY WITH METASTASIS TO THE LUNG

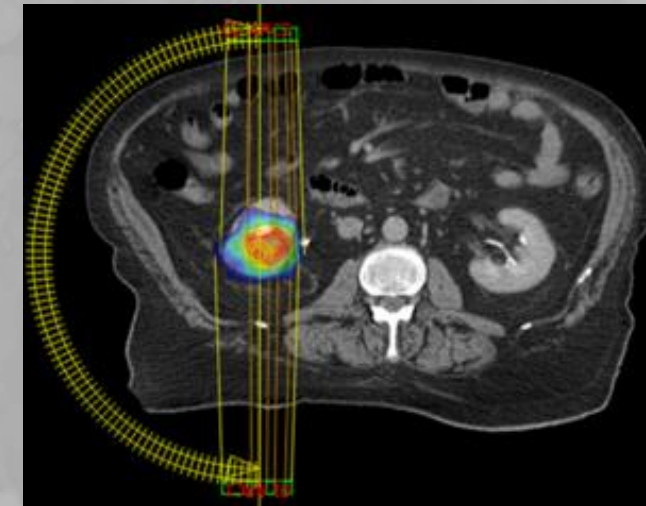
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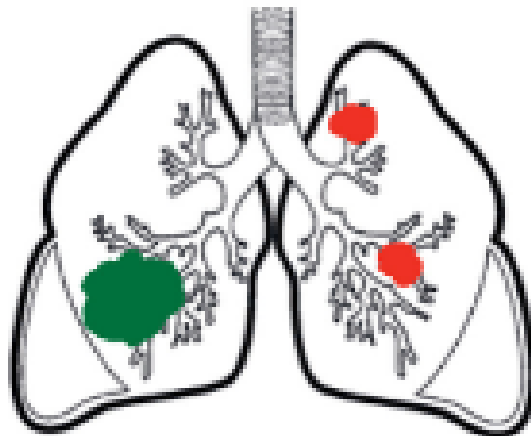


MRI Based Motion Gating





MDT to Defer Systemic Therapy



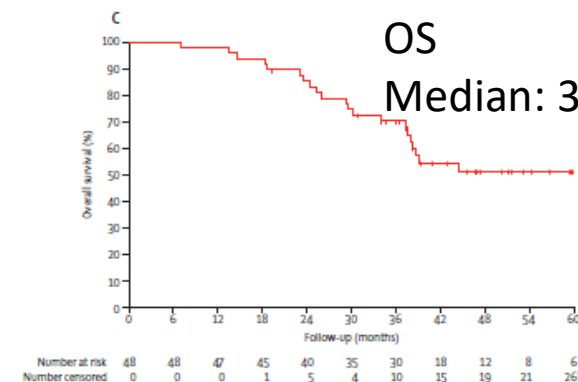
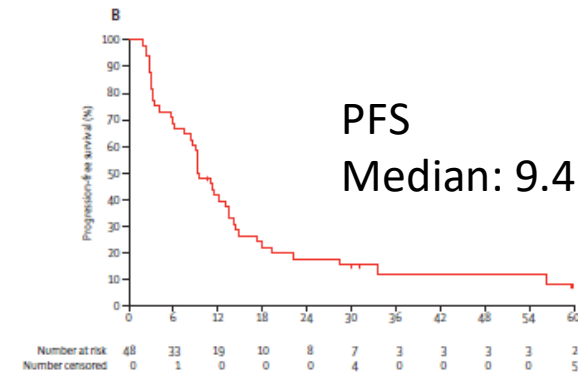
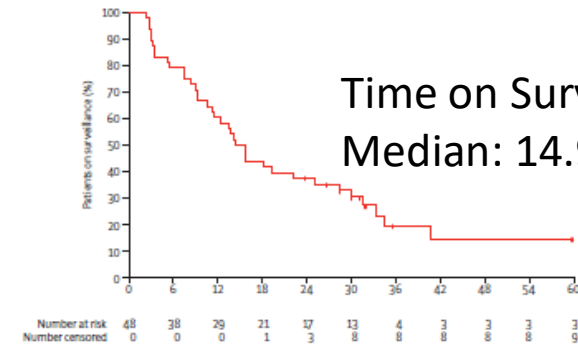
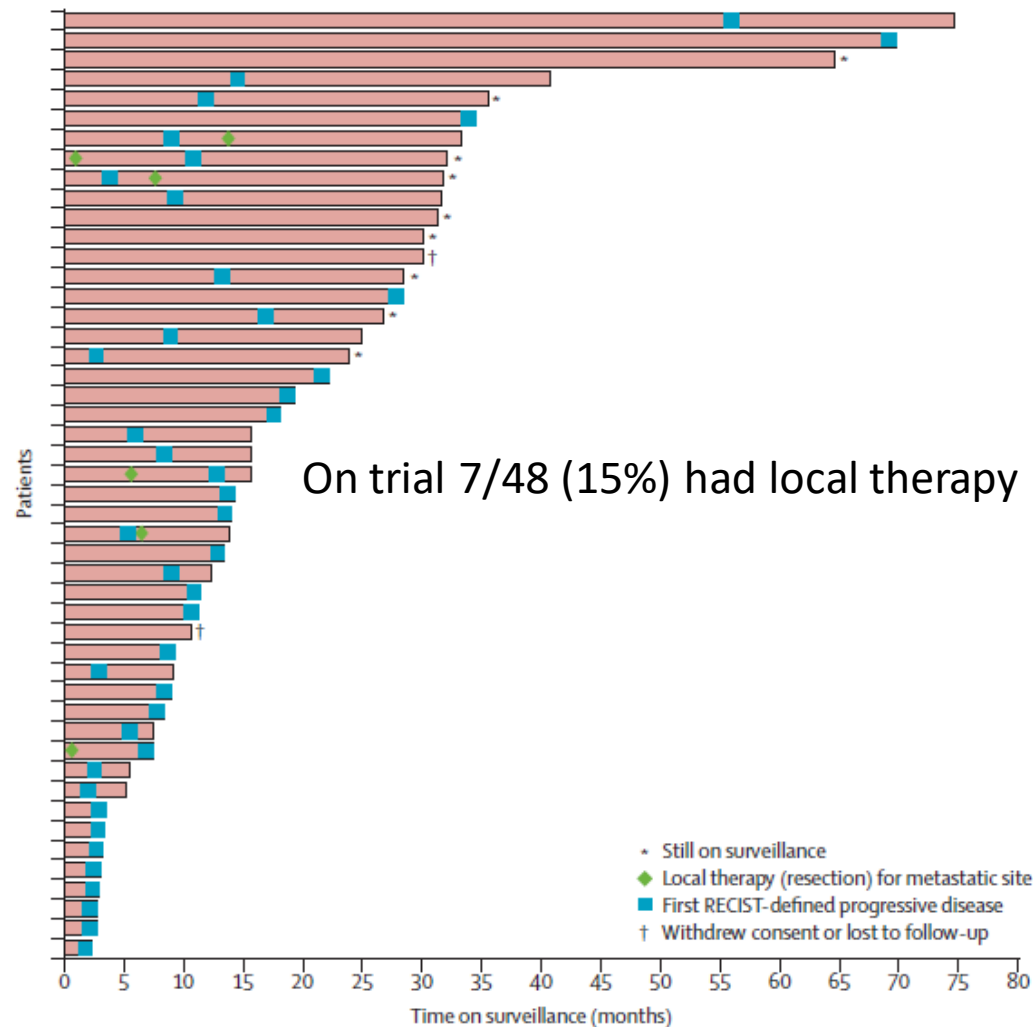
A patient with only a limited number of metastatic sites of disease ($\leq 3-5$)

Surveillance for Low Volume

- Phase II trial of 48 systemic therapy naïve RCC patients enrolled between 2008 to 2013
- Median FU 38 months
- Primary outcome was time on surveillance (e.g. time until systemic therapy start)

Patients (n=48)	
Age (years)	67 (62-75)
Sex	
Male	36 (75%)
Female	12 (25%)
Karnofsky performance status	
100	30 (63%)
90	15 (31%)
80	3 (6%)
Histology*	
Clear cell	46 (96%)
Chromophobe	2 (4%)
Sarcomatoid dedifferentiation†	6 (13%)
Time from diagnosis to metastatic disease (months)	5.1 (0.7-25.7)
Prior nephrectomy	47 (98%)
IMDC risk factors ¹²	
0 (favourable)	11 (23%)
1-2 (intermediate)	36 (75%)
3 or more (poor)	1 (2%)
MSKCC risk factors‡	
0 (favourable)	11 (24%)
1-2 (intermediate)	35 (76%)
Site of metastatic disease§	
Lung	34 (71%)
Lymph nodes	12 (25%)
Bone	10 (21%)
Kidney	9 (19%)
Adrenal	6 (13%)
Liver	2 (4%)
Number of organ sites with metastases	
1	25 (52%)
2	15 (31%)
3	6 (13%)
4	2 (4%)
Tumour burden at baseline (sum in cm of RECIST tumour measurements)¶	3.2 (1.5-6.7)

Low Volume Surveillance



UROLOGY - RADIATION ONCOLOGY - MEDICAL ONCOLOGY

```
graph LR; A["Oligometastatic RCC  
-clear cell histology  
-up to 5 mets  
-no prior systemic therapy or  
>1 month off prior systemic therapy"] --> B["Stereotactic radiation +/- surgical local  
therapy to all sites of disease"]; B --> C((Progression)); B -- "3 mo: Research  
Re-biopsy" --> D["Start Systemic therapy"]; C -- "Polymet progression in >3 sites of  
disease treatable with definitive RT" --> D; A -- "Standard of care imaging  
+ standard of care biopsy" --> B; B -- "Correlative blood draw" --> E[ ]; C -- "Standard of care imaging" --> F[ ]; C -- "Correlative blood draw" --> G[ ]; C -- "Correlative blood draw" --> H[ ];
```

The flowchart illustrates the clinical trial protocol for Oligometastatic RCC. It begins with a teal box on the left containing the criteria for Oligometastatic RCC: clear cell histology, up to 5 metastases, and no prior systemic therapy or more than 1 month off prior systemic therapy. An arrow points from this box to a central white box with a red border, labeled "Stereotactic radiation +/- surgical local therapy to all sites of disease". Above this central box, an arrow points down from the text "Standard of care imaging + standard of care biopsy". Below the central box, an arrow points up from the text "Correlative blood draw". An arrow points from the central box to a teal circle on the right labeled "Progression". Above this arrow, an arrow points down from the text "3 mo: Research Re-biopsy". Below the arrow, three arrows point up from the text "Standard of care imaging" and "Correlative blood draw" (repeated twice). An arrow points from the "Progression" circle to a teal box at the top right labeled "Start Systemic therapy". Above this arrow, an arrow points down from the text "Polymet progression in >3 sites of disease treatable with definitive RT".



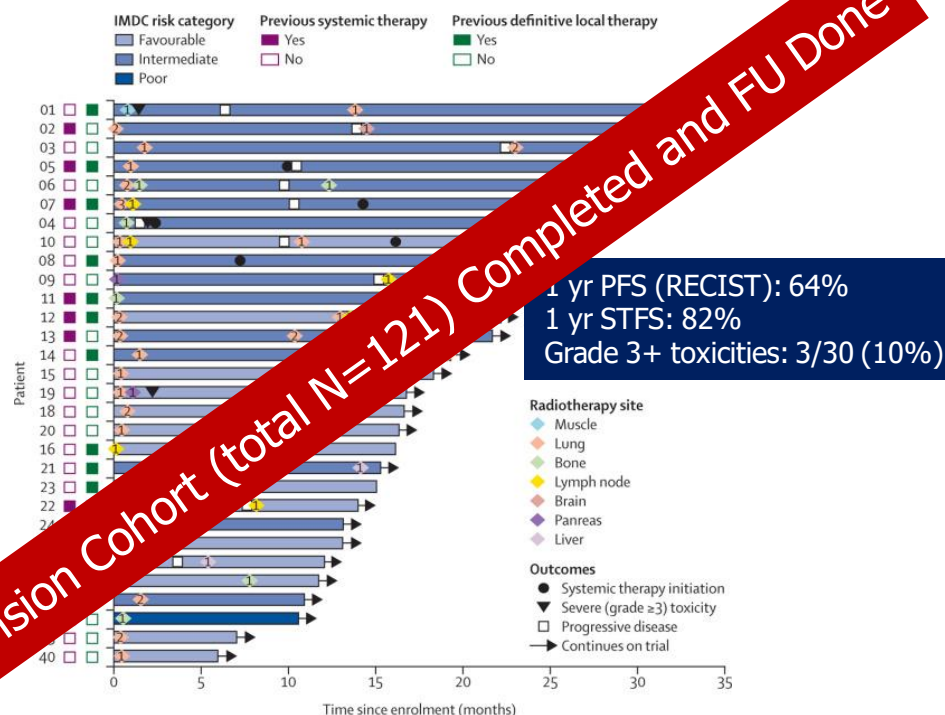
Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm, single-centre, feasibility, phase 2 trial

Chad Tang*, Pavlos Msaouel*, Kieko Hara, Haesun Choi, Venus Le, Amishi Y Shah, Jennifer Wang, Eric Jonasch, Seungtaek Choi, Quynh-nhu Nguyen, Prajnan Das, Surendra Prajapati, Zhiqian Yu, Khaja Khan, Steven Powell, Ravi Murthy, Kanishka Sircar, Nizar M Tannir

Lancet Oncol 2021; 22: 1732-39
Published Online
October 27, 2021

Summary

Background The role of radiotherapy in metastatic renal cell carcinoma is controversial. We prospectively tested the feasibility and efficacy of radiotherapy to defer systemic therapy for patients with oligometastatic renal cell carcinoma.

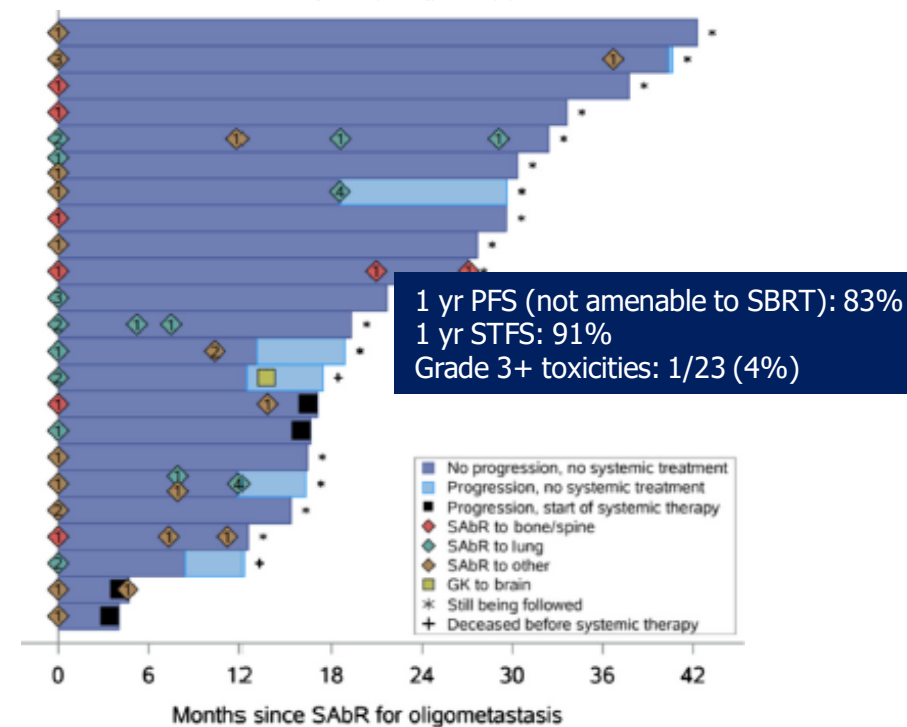


European Association of Urology

Stereotactic Ablative Radiation for Systemic Therapy-naïve Oligometastatic Kidney Cancer

Raquibul Hannan^{a,b,*}, Michael Christensen^a, Alana Christie^b, Aurelie Garant^{a,b}, Ivan Pedrosa^{b,d}, Liliana Robles^a, Samantha Mannala^a, Chiachien Wang^a, Hans Hammers^{b,c}, Waddah Ararat^{b,c}, Kevin Courtney^{b,c}, Isaac A. Bowman^{b,c}, David Sher^a, Chul Ahn^b, Suzanne Cole^{b,c}, Hak Choy^a, Robert Timmerman^{a,b,*}, James Brugarolas^{b,c,*}

^a Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX, USA; ^b Kidney Cancer Program, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, USA; ^c Department of Internal Medicine, Hematology-Oncology Division, University of Texas Southwestern Medical Center, Dallas, TX, USA; ^d Department of Radiology, University of Texas Southwestern, Dallas, TX, USA



Patient Characteristics

- 121 patients enrolled between July 2018 to May 2023
- Median follow up 36.3 Months

Patient Characteristics (N=121)		
Age, median IQR		66 (61–72)
Time from Nephrectomy to Registration, mo, median IQR		71 (37–117)
Prior Nephrectomy		
	Yes	118 (98%)
	No	3 (2%)
IMDC Score		
	0	63 (52%)
	1	45 (37%)
	2-3	13 (11%)
Prior Therapies		
	Systemic	36 (30%)
	Surgery	39 (32%)
	Radiation	19 (16%)
	Interventional Radiology Ablation	10 (8%)
Number of Initial Metastatic Lesions		
	1	71 (59%)
	2	38 (31%)
	3-5	12 (10%)

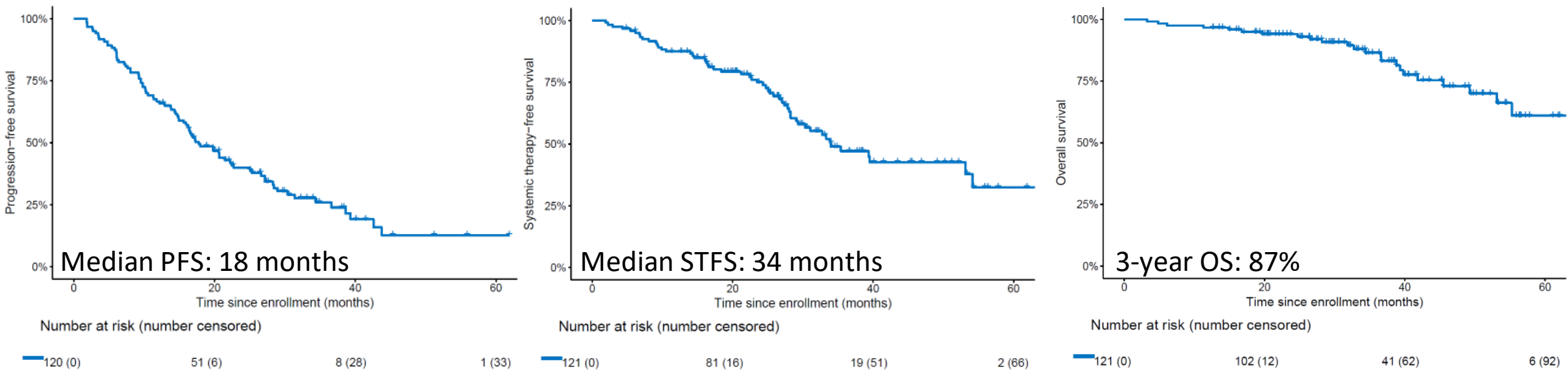
Treatment Characteristics

Treatment Characteristics		1 st Round MDT (n=121)
Tumor volume (cc), median IQR		5·7 (3·1-19·2)
Organ Involvement		
	Lung	76
	Lymph Node	16
	Pancreas	14
	Bone	11
	Brain	2
	Other	12
Number of Sites Treated		
	1	71 (58%)
	2	38 (31%)
	3	8 (7%)
	4	3 (2%)
	5	2 (2%)
Other Local Therapy		
	Surgery	3
	IR ablation	0



121 patient update (36.3 Median FU month)

Powered to test whether median STFS with this treatment approach exceeded 24 months (upper bounds of Rini et al. STFS).



Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial

Brian I Rini, Tanya B Dorff, Paul Elson, Cristina Suarez Rodriguez, Dale Shepard, Laura Wood, Jordi Humbert, Linda Pyle, Yu-Ning Wong, James H Finke, Patricia A Rayman, James M G Larkin, Jorge A Garcia, Elizabeth R Plimack



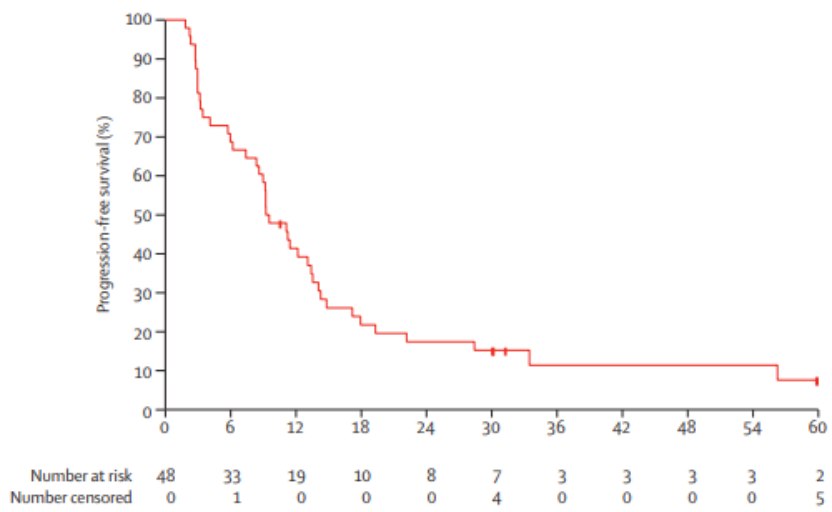
12th Belgian Multidisciplinary Meeting on Urological Cancers

Summary

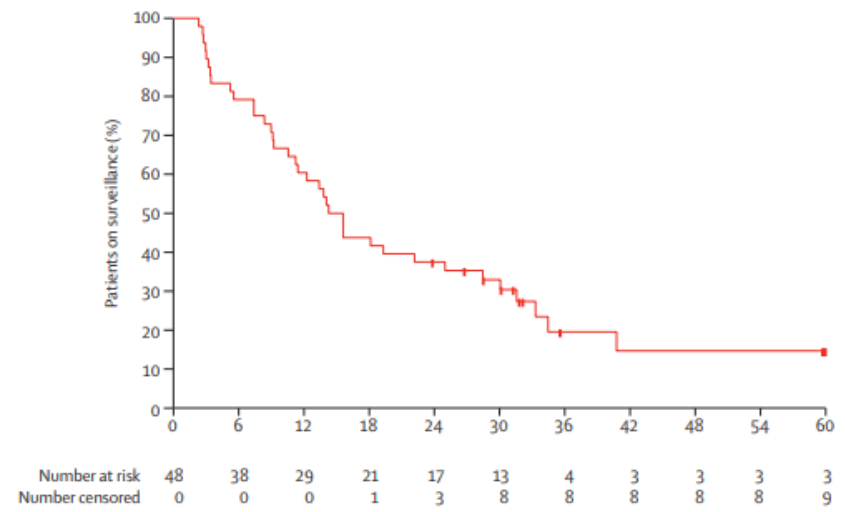
Background A subset of patients with metastatic renal-cell carcinoma show indolent growth of metastases. Because of the toxicity and non-curative nature of systemic therapy, some of these patients could benefit from initial active surveillance. We aimed to characterise the time to initiation of systemic therapy in patients with metastatic renal-cell carcinoma under active surveillance.

Lancet Oncol 2016; 17: 1317-24
Published Online
August 3, 2016
[http://dx.doi.org/10.1016/S1470-2045\(16\)30196-6](http://dx.doi.org/10.1016/S1470-2045(16)30196-6)

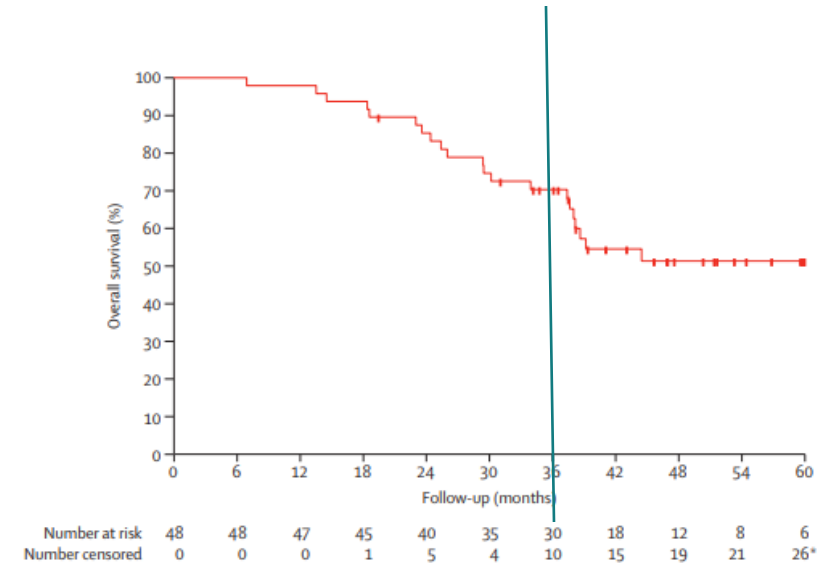
Median FU: 38.1 months



Median PFS: 9.4 months



Median STFS: 14.9 months

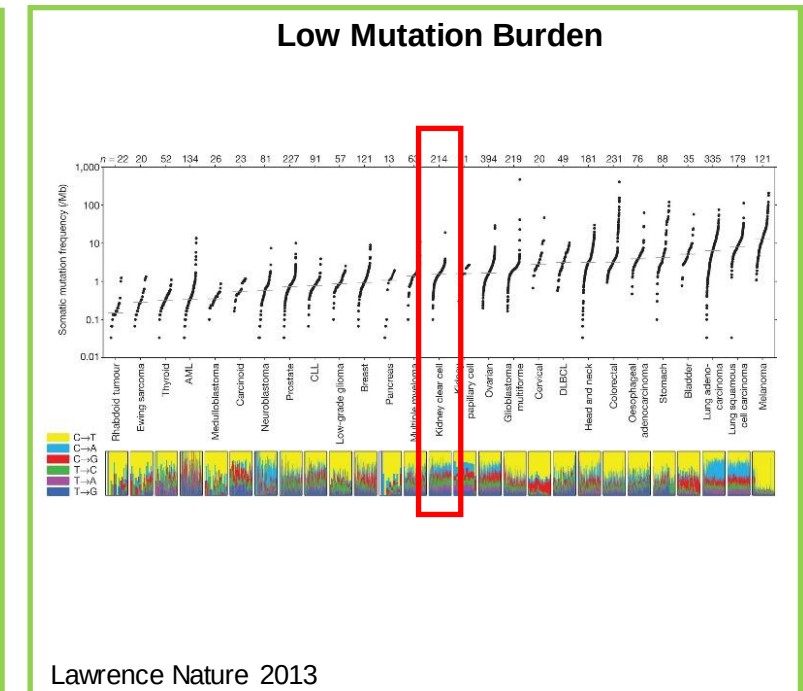
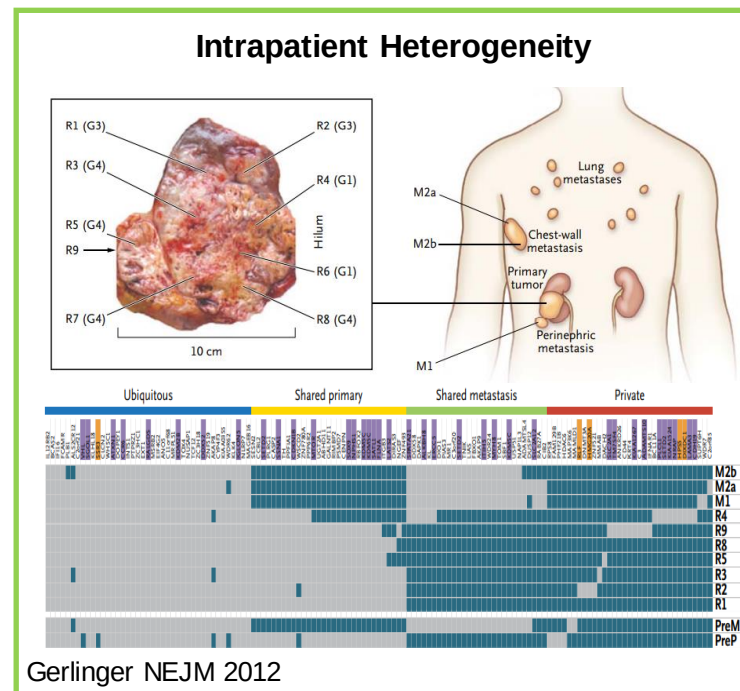
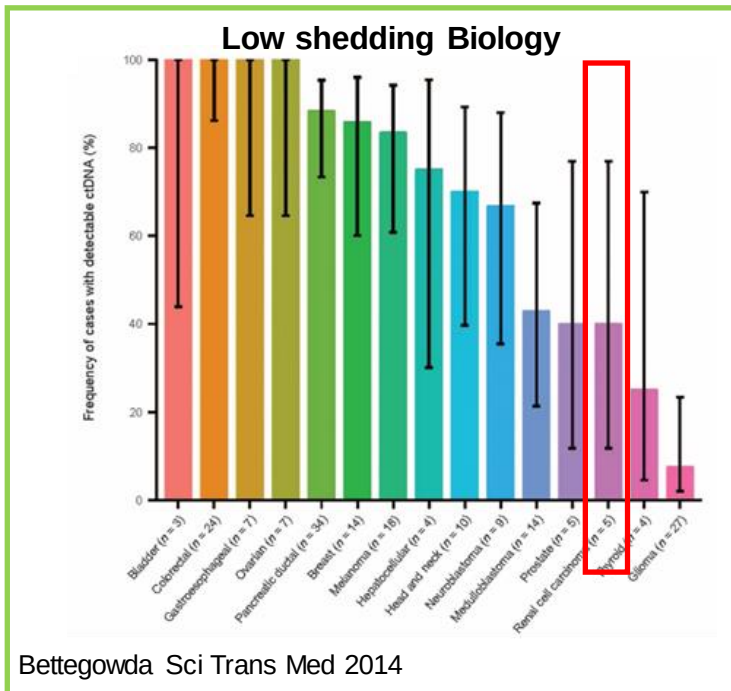


3-year OS: ~70%



Prognostic Markers for Oligometastatic RCC

- One of the greatest barriers to MDT without systemic therapy are prognostic markers
- ctDNA offers an accessible and quantitative solution. However, challenges exist for ctDNA in RCC, which are compounded by indolent low volume disease.



NEW GAME
CHOOSE SKILL LEVEL:
I'M TOO YOUNG TO DIE.
HEY, NOT TOO ROUGH.
HURT ME PLENTY.
ULTRA-VIOLENCE.
 NIGHTMARE!

45

AMMO

0%

HEALTH

2 3 9
5 6 7

ARMS



0%

ARMOR

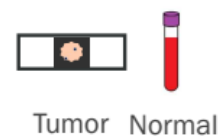
BULL
SHEL
ROCK
CELL

45
0
0
0

200
50
50
300

Myriad Genetics 2nd Generation ctDNA Assay

Tumor-Normal WGS $\geq 30X$



Somatic Pipeline

- SNVs, indels, CNAs via custom ensemble-based pipeline

1000s
Somatic
candidate sites

Personalized Assay Design

Up to 1000
Sites

Prioritization Rules

- High-Confidence variant
- Low intrinsic error rate
- Detectability in plasma

Add-On custom targets

- Clinical hotspots
- Therapeutic targets
- Other custom content

Plasma Monitoring

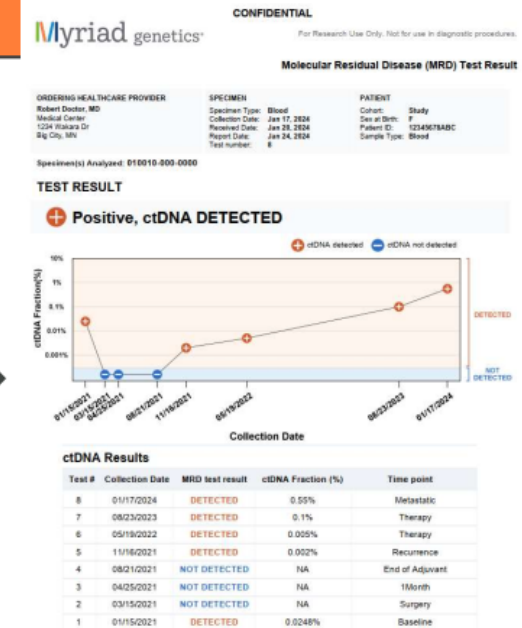
$T_1 - T_2 \dots T_N$



Personalized Hybrid-Capture Panel

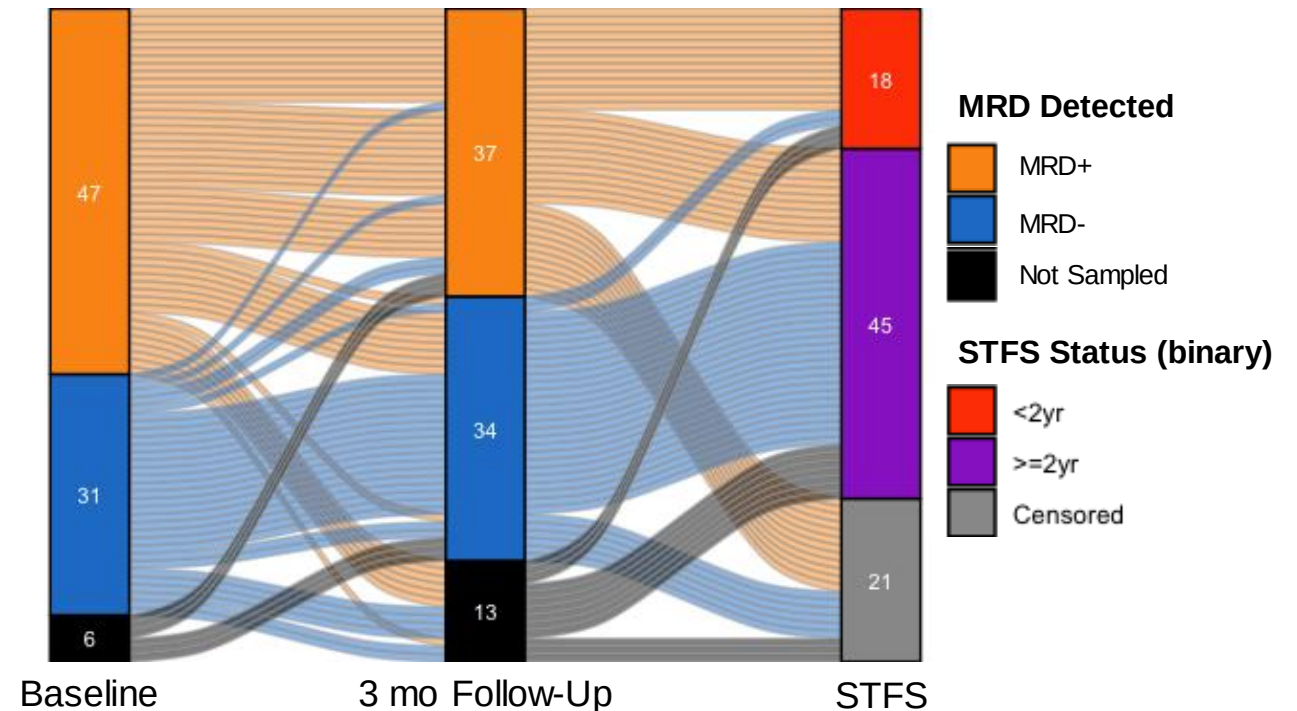
Plasma Pipeline

- Ultra-deep NGS w/ UMI error correction
- Accounts for CNA to estimate tumor fraction

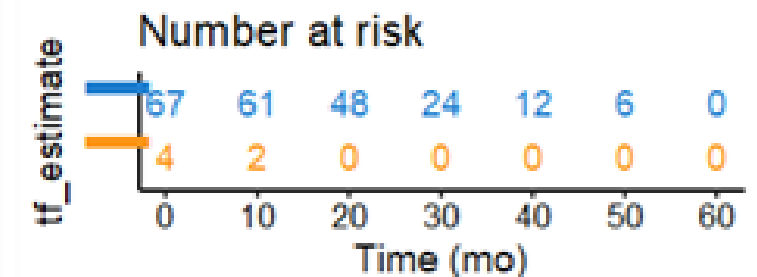
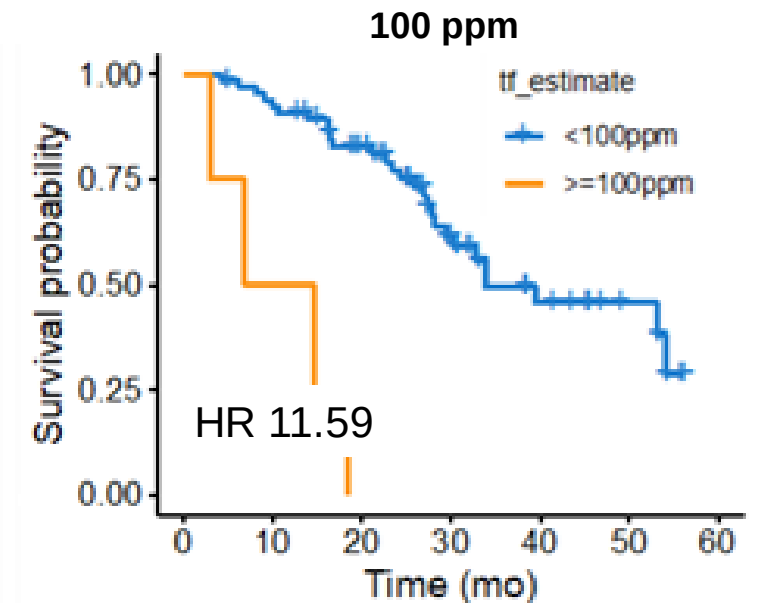
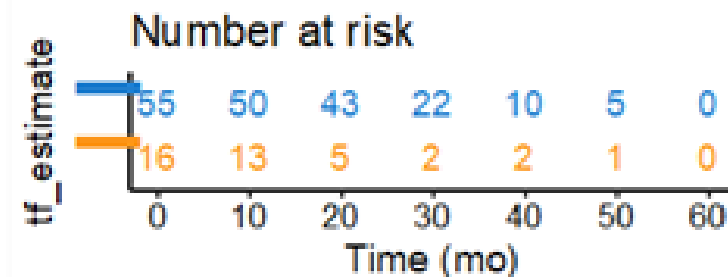
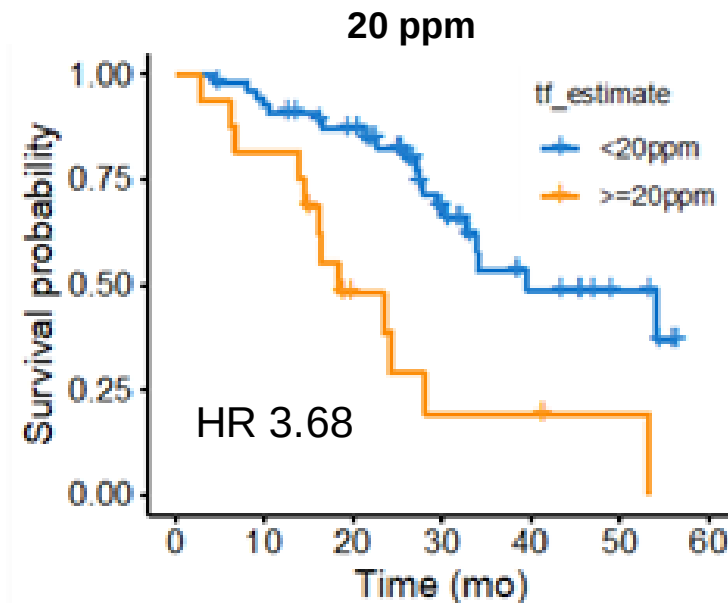
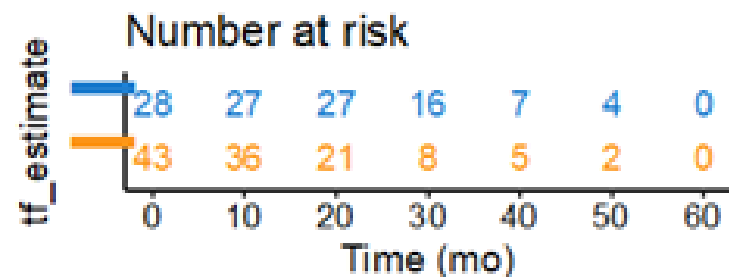
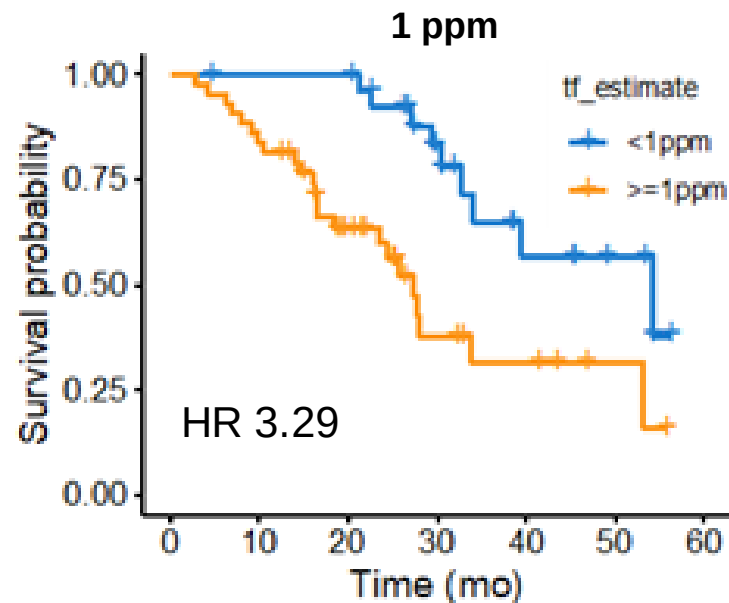


ctDNA MRD and STFS

- Baseline 47 of 78 (60%) patients were MRD+
- At 3 months FU, 25% of patients baseline MRD+ converted to MRD negative
- Median tumor fraction among MRD+ patients was 22.5 ppm at baseline and was 18.5 ppm at 3 months FU



ctDNA tumor fraction and STFS



% MRD+ at ppm threshold: 60%

Median STFS at ppm
threshold: 25.8 mo

23%

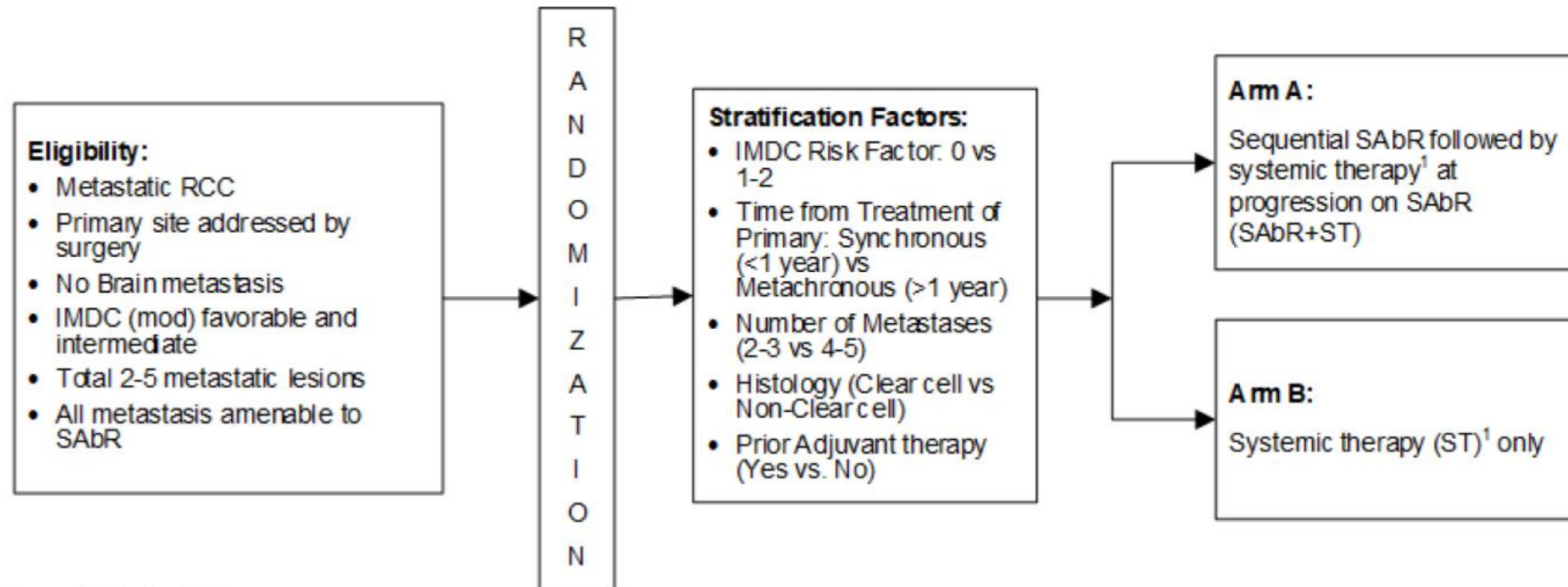
16.4 mo

6%

6.8 mo

EA8211/SOAR

Randomized Phase III Non-inferiority Trial of SAbR vs Systemic Therapy for Oligometastatic RCC



Accrual Goal = 472

Cycle Length = assessments will be done every 3 months

1. Systemic therapy will consist of standard FDA approved first line systemic therapy for renal cell carcinoma, as per NCCN guidelines and with the options outlined in Section 5.1.2. The selection of the systemic therapy regimen used is at the discretion of the treating physician and in agreement with the patient. Once the regimen has been declared and started, patients may not switch to another regimen option.

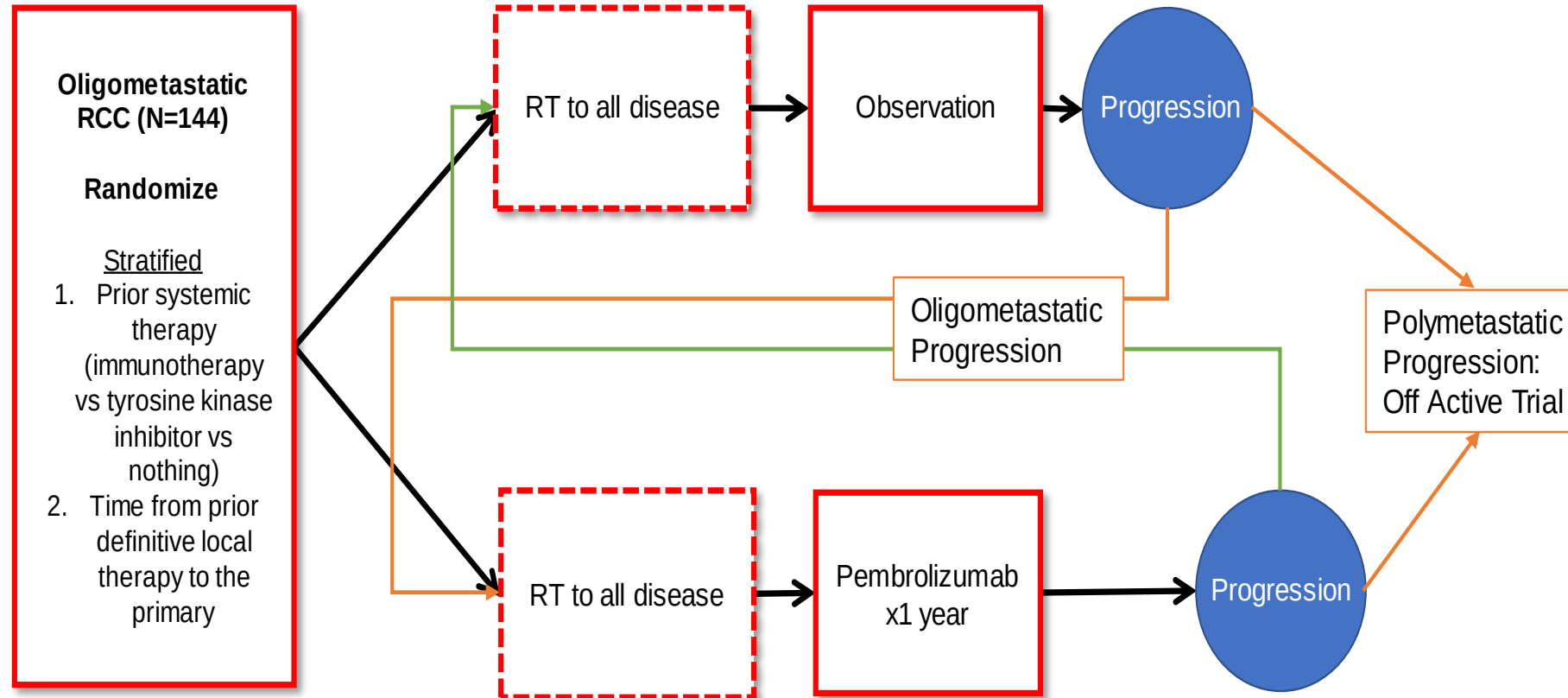


Raquib Hannan, MD PhD
Principal Investigator
UT Southwestern



Suzanne Cole, MD
CO-Principal Investigator
UT Southwestern

ASTROs Trial



Activated: November 2023
Anticipated close: Early 2027
Primary endpoint: PFS

Chad Tang, MD
Principal Investigator

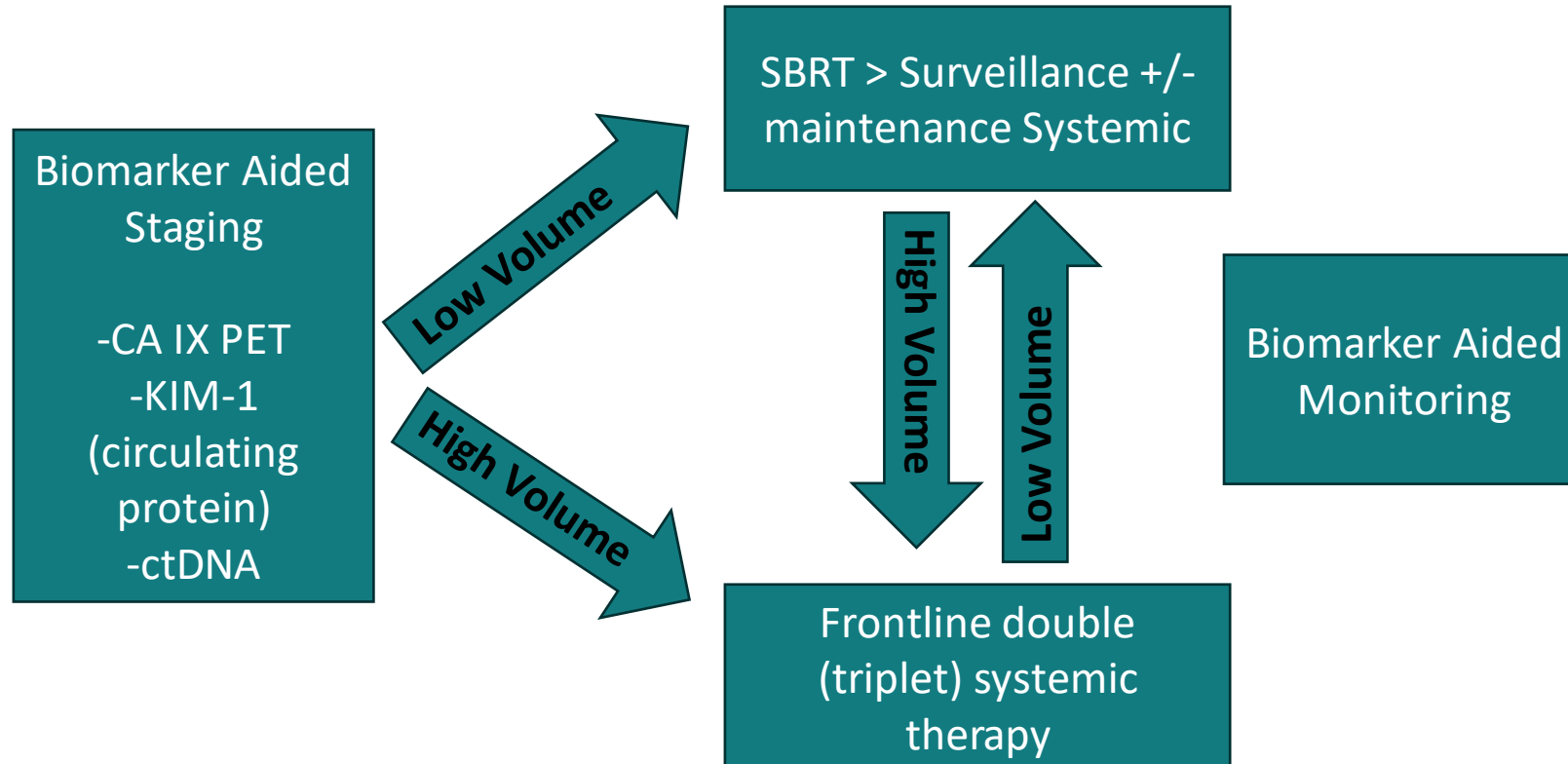


Pavlos Msaouel, MD PhD
Co-PI

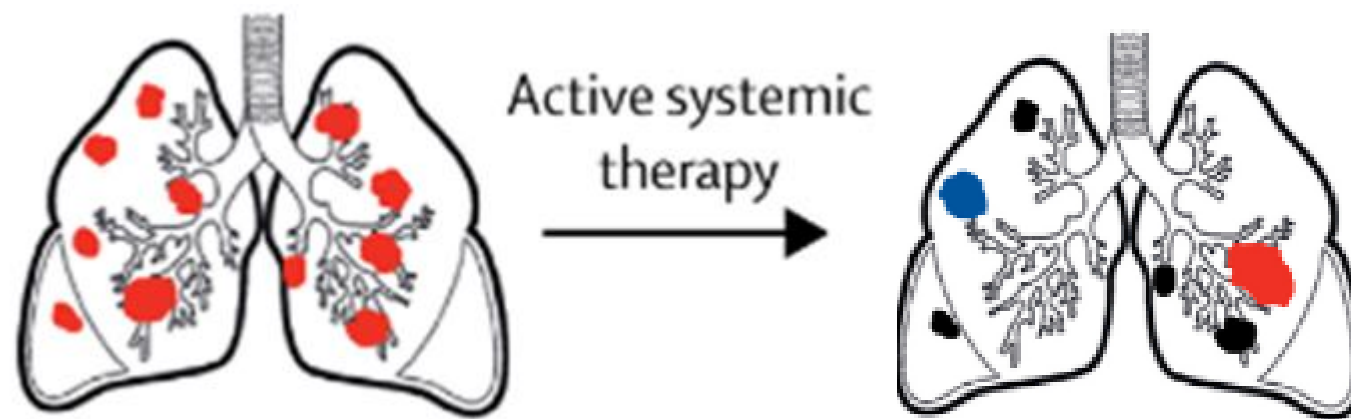


Nizar Tannir, MD
Co-PI

Metastatic Kidney Cancer – Dynamic Escalation/De-escalation



MDT to EXTEND Systemic Therapy



Patient with unlimited number of metastatic lesions initially, but through active systemic therapy all are controlled except for a limited number of growing ones (oligoprogressive lesions).

Prospective Studies



	Cheung et al. European Urology 2021	Hannan et al. European Urology Oncology 2022
Number of oligoprogressive sites	1-5	1-3
Histology	Required clear cell component	Mixed (90% clear cell)
Systemic Therapy	TKI monotherapy only	Mixed
Patient Number	38 (anticipated 62)	20

Prospective Studies Results

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



Platinum Priority – Kidney Cancer

Editorial by Shankar Siva, Piet Ost, Nicholas Zaorsky and Michael Staehler on pp. 701–702 of this issue

Stereotactic Radiotherapy for Oligoprogression in Metastatic Renal Cell Cancer Patients Receiving Tyrosine Kinase Inhibitor Therapy: A Phase 2 Prospective Multicenter Study

Patrick Cheung^a, Samir Patel^b, Scott A. North^c, Arjun Sahgal^a, William Chu^a, Hany Soliman^a, Belal Ahmad^d, Eric Winquist^e, Tamim Niazi^f, Francois Patenaude^g, Gerald Lim^h, Daniel Yick Chin Hengⁱ, Arbind Dubey^j, Piotr Czaykowski^k, Rebecca K.S. Wong^l, Anand Swaminath^m, Scott C. Morganⁿ, Rupi Mangat^o, Sareh Keshavarzi^p, Georg A. Bjarnason^{q,*}

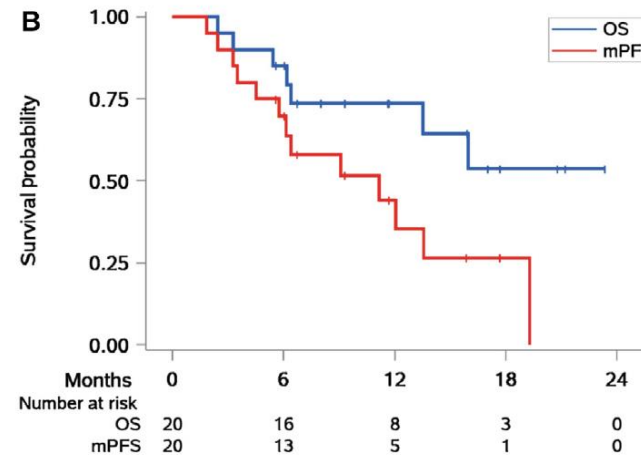
available at www.sciencedirect.com
journal homepage: eunocology.europeanurology.com



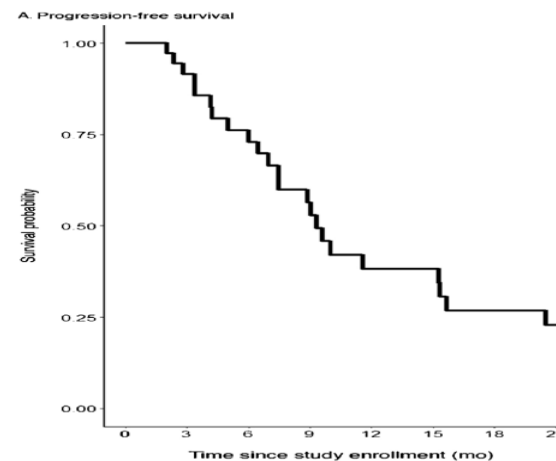
EUO Priority Article – Kidney Cancer

Phase II Trial of Stereotactic Ablative Radiation for Oligoprogressive Metastatic Kidney Cancer

Raquibul Hannan^{a,b,*}, Michael Christensen^a, Hans Hammers^{b,c}, Alana Christie^b, Brendan Paulman^a, Dandan Lin^a, Aurelie Garant^{a,b}, Waddah Arafat^{b,c}, Kevin Courtney^{b,c}, Isaac Bowman^{b,c}, Suzanne Cole^{b,c}, David Sher^a, Chul Ahn^c, Hak Choy^a, Robert Timmerman^{a,b,*}, James Brugarolas^{b,c,*}



Median PFS: 9.3 mo
New systemic therapy: 12.6 mo
Grade 3+ toxicities: 0%

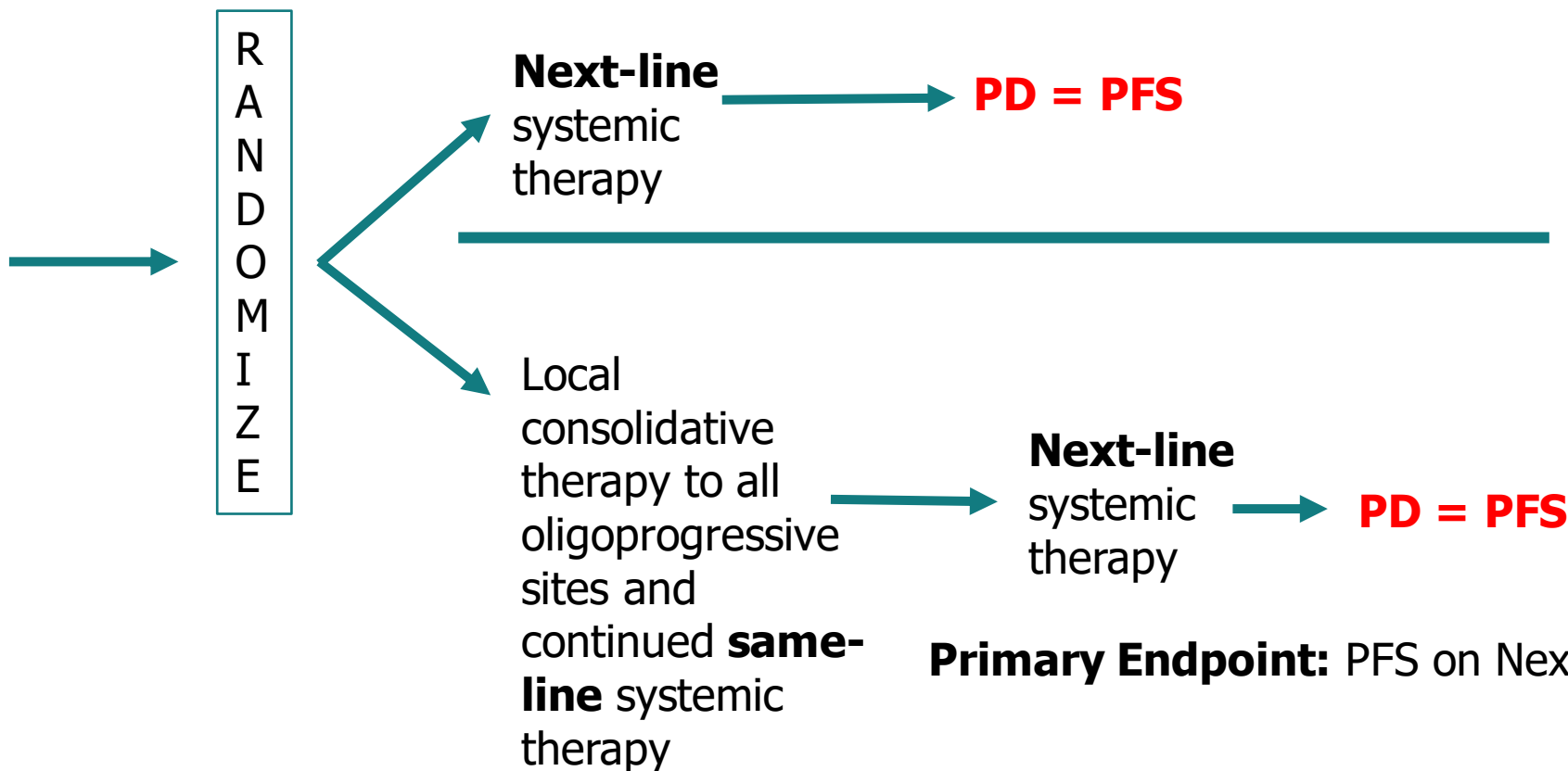


New systemic therapy/Death: 11.1 mo
Grade 3+ Toxicities: 1/20 (5%)

EXTEND-OP

Individual Histology Baskets

1. Prostate
2. **Renal**
3. Bladder
4. Colorectal
5. Breast
6. Esophageal
/gastric
7. Pancreatic



Ethan Ludmir, MD
Principal Investigator
UT MD Anderson



Chad Tang, MD
Co-Principal Investigator
UT MD Anderson

Finally, a Cautionary Note

Off-Protocol Radiation Therapy in Phase 3 Metastatic Solid Tumor Trials

Alexander D. Sherry, MD,* Timothy A. Lin, MD, MBA,[†] Zachary R. McCaw, PhD,^{‡,§} Esther J. Beck, BA,*
Ramez Kouzy, MD,* Joseph Abi Jaoude, MD,^{||} Adina H. Passy, MPH,* Avital M. Miller, BA,*
Gabrielle S. Kupferman, BA,* Clifton David Fuller, MD, PhD,* Charles R. Thomas, Jr, MD,[¶]
Eugene J. Koay, MD, PhD,[#] Chad Tang, MD,^{**††‡‡} Pavlos Msaouel, MD, PhD,^{††§§} and Ethan B. Ludmir, MD^{#,|||}

Methods and Materials: Two-arm, superiority-design, phase 3 randomized trials testing systemic therapy were screened from ClinicalTrials.gov. Protocol availability was required to assess the trial approach to off-protocol radiation therapy if not described in the manuscript. Adjusted odds ratios with 95% CI were calculated by logistic regression.

Results: A total of 112 trials enrolling 80,134 patients were included, with publication dates between 2010 and 2019. Of these, off-protocol radiation therapy was allowed, not discussed, or prohibited during study systemic therapy in 52% (N = 58), 25% (N = 28), and 23% (N = 26) of trials, respectively. However, only 2% (2 of 112) of trials reported off-protocol radiation therapy utilization rates, although no data were reported on the use of ablative off-protocol radiation therapy. No trials evaluated or adjusted for the potential influence of off-protocol radiation therapy on study endpoints. Among the subset of open-label studies, trials permissive toward off-protocol radiation therapy were more likely to meet their primary endpoint (adjusted odds ratio, 4.50; 95% CI, 1.23-20.23; P = .04).

Conclusions: Although most trials allowed off-protocol radiation therapy during the receipt of the study systemic therapy, the influence of off-protocol radiation therapy, especially ablative radiation therapy, on study outcomes is underevaluated among phase 3 systemic therapy trials. © 2024 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

In Conclusion

- RCC exhibits a spectrum of clinical behavior. A substantial proportion of patients exhibit indolent low volume disease that may benefit from treatment de-escalation with MDT.
- Prognostic markers are being developed for oligometastatic RCC. ctDNA utilizing a 2nd generation assay exhibits promise.
- Future randomized trials are needed to compare MDT versus systemic therapy, the addition of maintenance pembro to MDT, and evaluate prognostic markers.
- For oligoprogressive disease treatment of progressing lesions prolongs time on current line systemic therapy; however no randomized trials have been reported



Thank you
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