(PD39-02)

Results of Phase 1 Clinical Trial of High Doses of Seleno-L-Methionine (SLM) with Axitinib in metastatic Clear Cell RCC

Yousef Zakharia, Rohan Garje, James Brown, Kenneth Nepple, Ryan Reis, Andrew Bellizzi, Jaime Bonner, Deborah Parr, Janelle B. Born, Jessica C. Sieren, Jinha Park, Mohammad Milhem, Youcef Rustum.

University of Iowa

Holden Comprehensive Cancer Center

@zakhariayousef

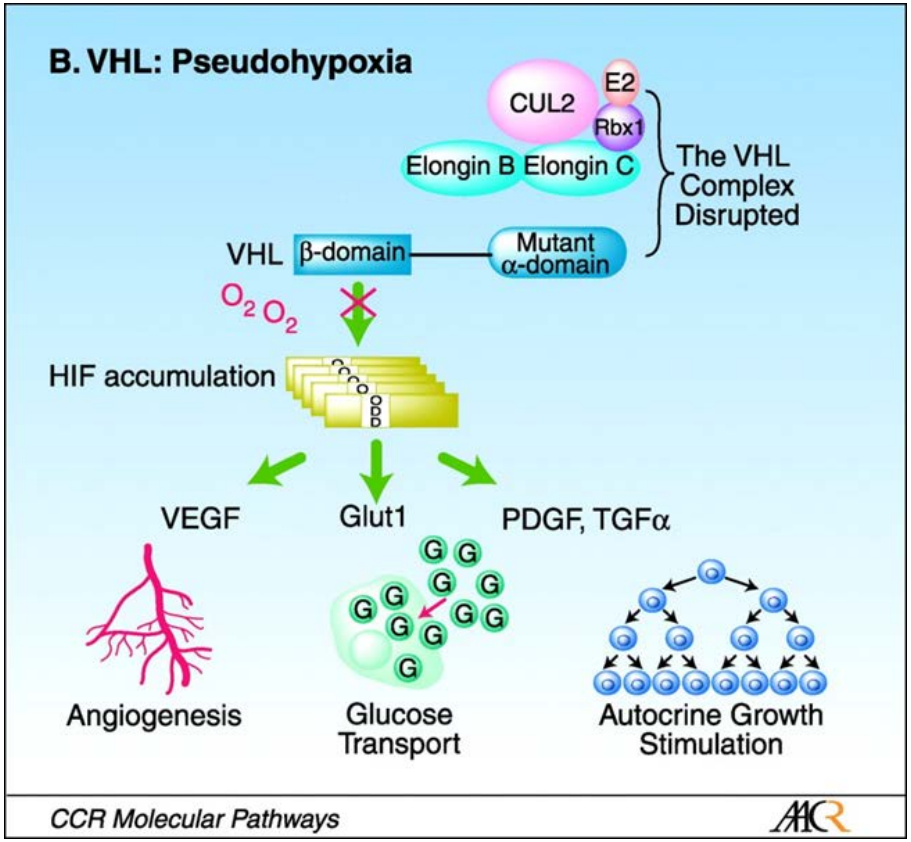
Presented By Yousef Zakharia at 2020 American Urology Association (AUA) Annual Meeting

Disclosures

- Advisory Board: Amgen, Roche Diagnostics, Novartis, Jansen, Eisai, Exelixis, Castle Bioscience, Array, Bayer, Pfizer, Clovis, EMD serono.

- Grant/research support from: Institution clinical trial support from NewLink Genetics, Pfizer, Exelixis, Eisai.

- DSMC: Jansen

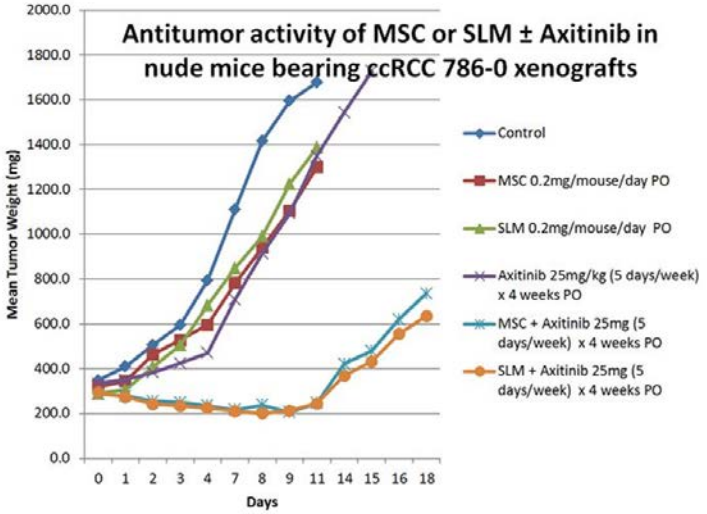


- VHL/ HIF/ VEGF pathway is a key axis in clear cell RCC
- Multiple VEGF/ VEGFR inhibitors are currently the standard of care in metastatic RCC
- Single agent axitinib is approved after failure of one prior systemic therapy with ORR 20% and PFS 6-8 months.

- Bratslavsky G *et al*. Clinical Cancer Research 2007
- Rini B *et al*. Lancet 2011

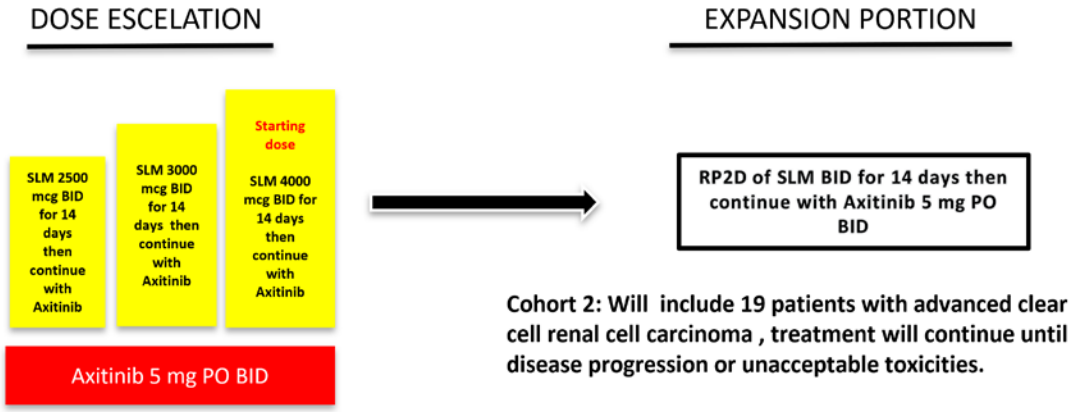
Seleno-L-methionine(SLM)

- Natural nonmetal element, orally bioavailable
- Pleiotropic actions: Antioxidant, down regulates the expression levels of HIFs, VEGF, and oncogenic miRNAs-210 /155
- Normalize tumor vasculature, resulting in increased drug delivery to tumor tissues
- Protects normal tissues against toxicity induced by chemotherapy



- Chintala, Rustum *et al*, BMC Cancer 2012, 12:293
- Zakharia, Rustum *et al*, Oncotarget 2018
- Durrani, *et al*, Trends in Cell & Molecular Biology 2015

Phase 1b/2 Advanced metastatic ccRCC: SLM- Axitinib
NCT02535533
IND number: 126767



Adult patients with histologically proven clear cell renal cell carcinoma.
After progression of at least 1 prior line of therapy in metastatic setting

Key endpoints: Safety, Objective response rate (ORR), PFS
28 days DLT period for dose escalation
19 subjects screened, 17 were eligible to start treatment, 15 were evaluable for efficacy.
Data cutoff: December 2019

Baseline Characteristics

Characteristics	All Patients (N=17)
Age, median (range), years	62 (51-77)
Sex, n (%)	
Female	3 (18)
Male	14 (82)
Prior systemic therapies, median (range), n	2 (1-4)
Prior systemic therapies, n (%)	
1	7 (41)
2	5 (29)
≥3	5 (29)
Prior anticancer therapies, n (%)	
VEGF/VEGFR	12 (71)
Immune Checkpoint Inhibitor	11 (65)
Investigational/Other	6 (35)
Axitinib (alone or in combination)	2 (12)
mTOR Inhibitor	2 (12)
Cytokine	2 (12)
IMDC* Risk Group, n (%)	
Favorable	3 (18)
Intermediate	10 (59)
Poor	4 (24)
*IMDC - International Metastatic Renal Cell Carcinoma Database Consortium	

Adverse Event Summary

AEs-Evaluable Patients (N=17)	N (%)
Any AE	17 (100)
Grade 3 AE	11 (65)
Any Treatment Related Adverse Event (TRAE)*	16 (94)
Grade 3 TRAE	8 (47)
Discontinuation due to TRAE	1 (6)**
Death from AE	0

*AE is considered TRAE if AE association between either SLM and/or Axitinib is "possible, probable, or definite"

**One patient self-removed from treatment due to AEs previously experienced with another TKI

All-Cause >20% Adverse Events*

AEs (N=17)	Grade 1/2	Grade 3	Grade 4**	All Grades
Fatigue	10 (59%)	4 (24%)	0	14 (82%)
Diarrhea	13 (76%)	0	0	13 (76%)
Nausea	10 (59%)	1 (6%)	0	11 (65%)
Anorexia	7 (41%)	3 (18%)	0	10 (59%)
Hypertension	2 (12%)	7 (41%)	0	9 (53%)
Cough	7 (41%)	1 (6%)	0	8 (47%)
Proteinuria	5 (29%)	2 (12%)	0	7 (41%)
Weight Loss	5 (29%)	2 (12%)	0	7 (41%)
Anemia	4 (24%)	2 (12%)	0	6 (35%)
Vomiting	6 (35%)	0	0	6 (35%)
Constipation	5 (29%)	0	0	5 (29%)
Hoarseness	5 (29%)	0	0	5 (29%)
Maculopapular Rash	4 (24%)	0	0	4 (24%)

*Other AEs present in >20% of participants include the following (%): Dyspnea (47), Alanine Aminotransferase Increase (35), Dehydration (35), Headache (35), Pain in Extremity (35), Alkaline Phosphatase Increase (29), Aspartate Aminotransferase Increase (29), Back Pain (29), Dysgeusia (29), Fever (29), Abdominal Pain (24), Chills (24), Dizziness (24), Hypercalcemia (24), Hyperkalemia (24), Hyponatremia (24), and Lymphocyte Count Decrease (24)

**A single Grade 4 toxicity of Cholecystitis was experienced by one patient, deemed unrelated to study drugs; No Grade 5 toxicities were documented in any patients

Best Objective Response by RECIST v1.1

Efficacy Parameter N (%)	Evaluable Patients N=15	IMDC Risk Favorable (0) N=2*	IMDC Risk Intermediate (1-2) N=9*	IMDC Risk Poor (3+) N=4
ORR (CR+PR)	8 (53)	2 (100)	4 (44)	2 (50)
CR	2 (13)	2 (100)	0	0
PR	6 (40)	0	4 (44)	2 (50)
SD (Lasting longer than 6 months)	3 (20)	0	2 (22)	1 (25)
Disease Control Rate (CR+PR+SD)	11 (73)	2 (100)	6 (67)	3 (75)
PD	4 (27)	0	3 (33)	1 (25)

* Two subjects came off study prior to first scan deemed unevaluable for efficacy

Best Objective Response by RECIST v1.1

Efficacy Parameter N (%)	Evaluable Patients N=15	IMDC Risk Favorable (0) N=2*	IMDC Risk Intermediate (1-2) N=9*	IMDC Risk Poor (3+) N=4
ORR (CR+PR)	8 (53)	2 (100)	4 (44)	2 (50)
CR	2 (13)	2 (100)	0	0
PR	6 (40)	0	4 (44)	2 (50)
SD (Lasting longer than 6 months)	3 (20)	0	2 (22)	1 (25)
Disease Control Rate (CR+PR+SD)	11 (73)	2 (100)	6 (67)	3 (75)
PD	4 (27)	0	3 (33)	1 (25)

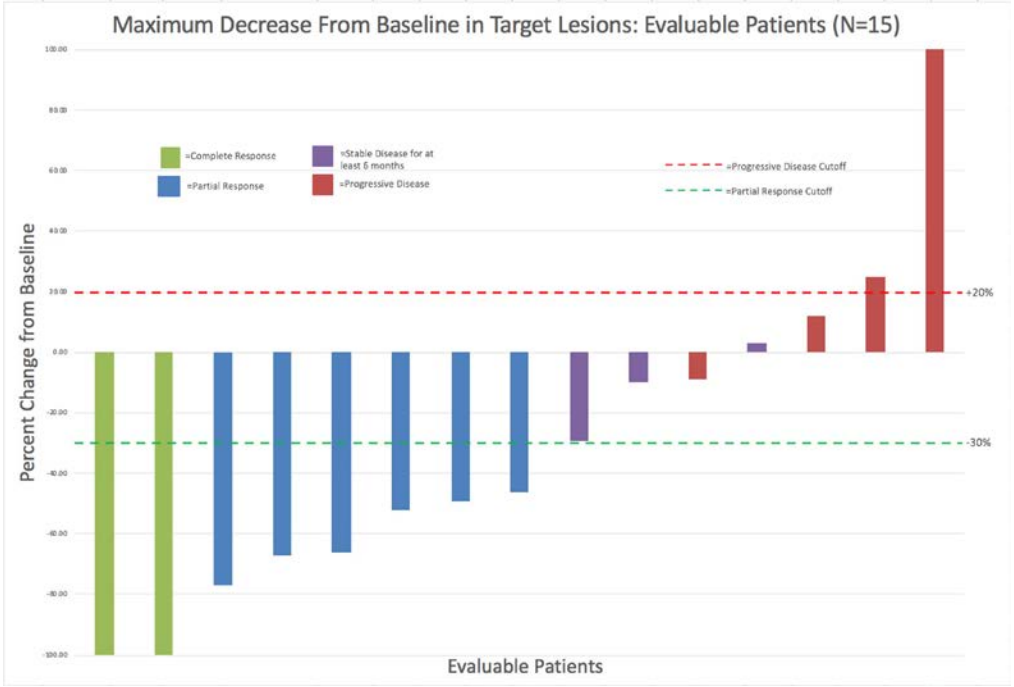
* Two subjects came off study prior to first scan deemed unevaluable for efficacy

Best Objective Response by RECIST v1.1

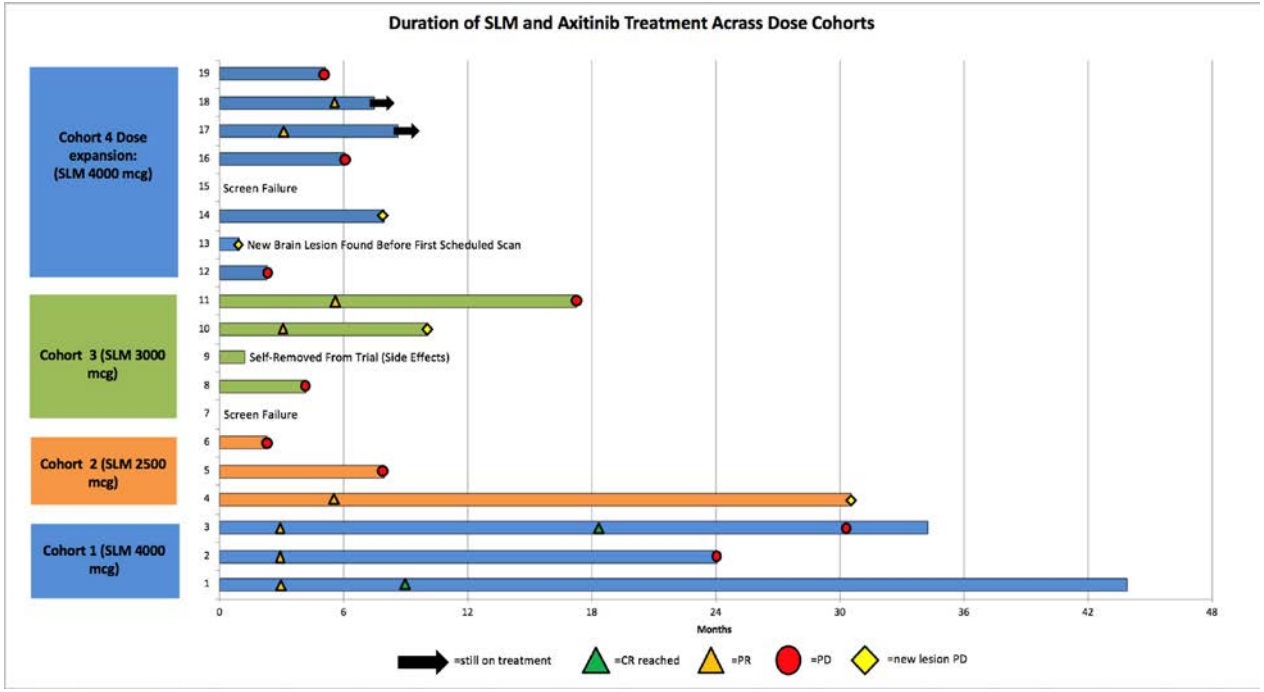
Efficacy Parameter N (%)	Evaluable Patients N=15	IMDC Risk Favorable (0) N=2*	IMDC Risk Intermediate (1-2) N=9*	IMDC Risk Poor (3+) N=4
ORR (CR+PR)	8 (53)	2 (100)	4 (44)	2 (50)
CR	2 (13)	2 (100)	0	0
PR	6 (40)	0	4 (44)	2 (50)
SD (Lasting longer than 6 months)	3 (20)	0	2 (22)	1 (25)
Disease Control Rate (CR+PR+SD)	11 (73)	2 (100)	6 (67)	3 (75)
PD	4 (27)	0	3 (33)	1 (25)

* Two subjects came off study prior to first scan deemed unevaluable for efficacy

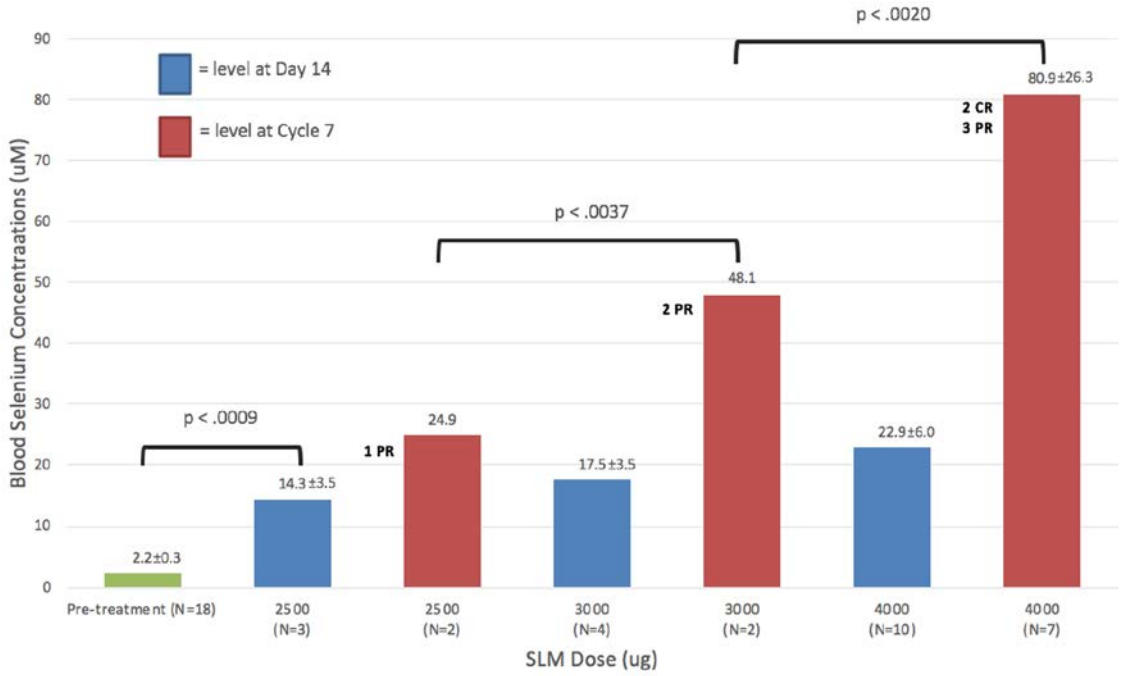
Target Tumor(s) Maximum Response

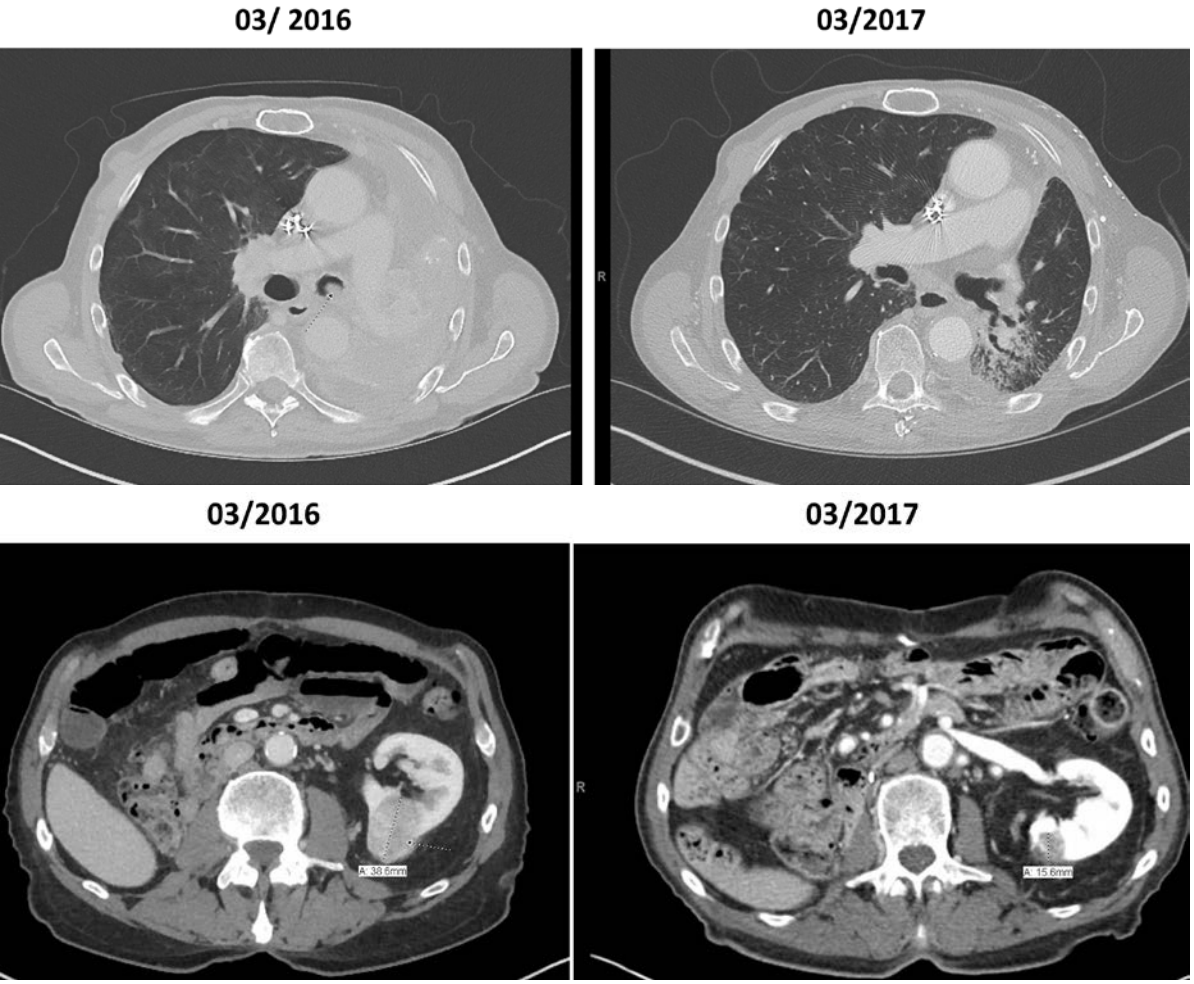


Duration of Response by Cohort



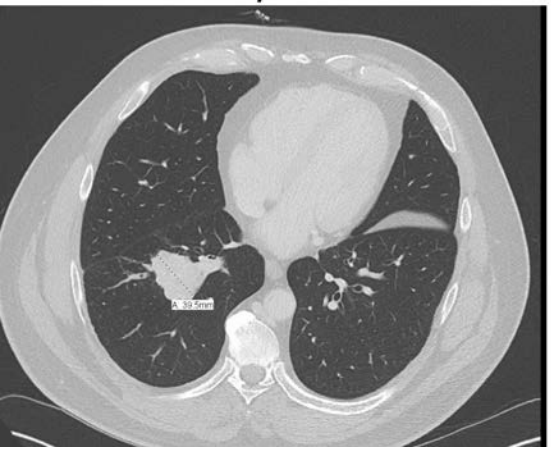
Blood Selenium Levels



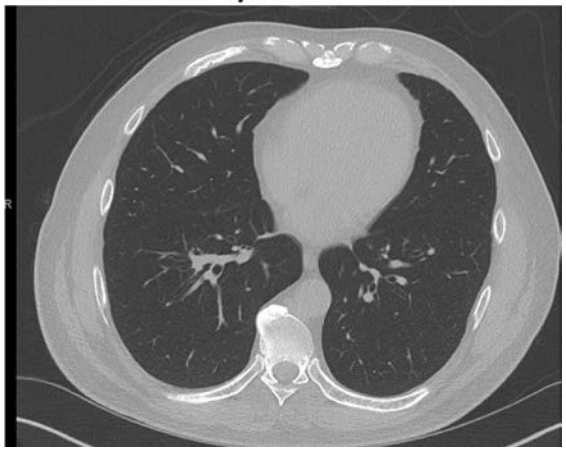


Patient with metastatic ccRCC treated by primary oncologist with sunitinib, nivolumab, everolimus, pazopanib presented with collapsed lung.
Started on SLM+ axitinib
Achieved PR for 2 years
Went skiing in Europe

04/2016

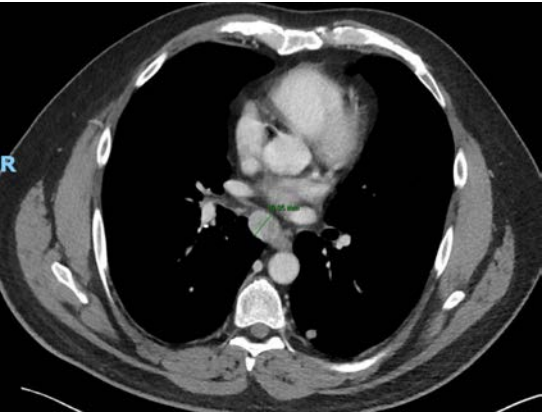


04/2017

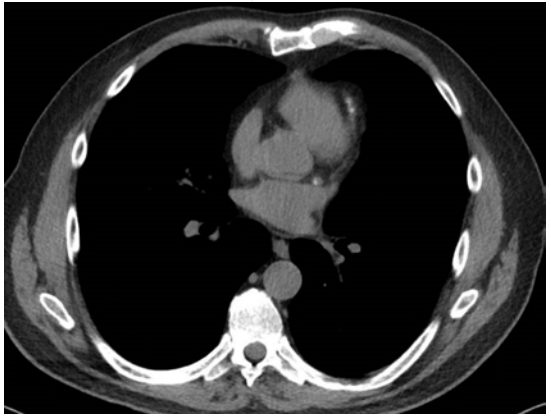


Metastatic RCC to lung and lymph nodes, progressed on clinical trial with ipilimumab and nivolumab
Achieved CR for 30 months

04/2016



04/2017



Conclusions

Blood selenium concentrations determined therapeutically synergistic with anticancer therapy in Xenografts were achieved clinically without dose limiting toxicity that can be attributed to SLM

No dose limiting toxicity encountered, no treatment related grade 4 or 5 toxicities
No side effects encountered due to SLM alone treatment for 14 days.

Promising efficacy observed, with ORR of 53% in the evaluable cohort of 15 subjects, .

Future Directions:

- Study is ongoing in expansion phase using SLM 4000 mcg
- Another cohort is being considered using BSA based SLM dose.
- Dual Energy CT (DECT) scan at day 0, 15 and 75 in expansion phase.
- Optional biopsies for biomarkers at baseline, day 14 and 74.

Acknowledge:

- Patients and Families

Clinical collaborators:

- Rohan Garje MD
- James Brown MD
- Ken Nepple MD
- Michael O'Donnell
- Paul Gelhaus
- Chad Tracy
- Ryan Reis
- Mohammed Milhem MD
- Jaime Bonner NP
- Deb Parr PA
- Jerri Ranson RN
- Janelle Born RN
- Amy Koski RN
- Andrew Bellizzi MD
- Laila Dahmoush MD

Lab collaborators:

- Youcef Rustum Ph.D
- Eric Devor Ph.D
- Stipp Lab
- Michael Henry Ph.D
- Garry Buettner, Ph.D
- Prabhat Goswami Ph.D
- Douglas Spitz, Ph.D
- Jeffrey Stolwijk

Radiology collaborators:

- Jessica Sieren, Ph.D
- Eric Hoffman, Ph.D
- Jinha Park. MD

Statistician

- Gideon Zamba Ph.D
- Sarah Bell, MS

- HCCC Regulatory Office

- HCCC/ Hem Onc Division PACT/ NCI P3086862
- Rock n Ride
- Pfizer
- Sabinsa