Kidney Cancer Research Summit KCRS21

University of Iowa Holden Comprehensive Cancer Center
University of Iowa Health Care

Potential Role of Seleno-L-Methionine (SLM) in the Stabilization of Tumor Vasculature and Enhanced Efficacy of Axitinib in Previously Treated Patients with Advanced Clear Cell Renal Cell Carcinoma (ccRCC)

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Disclosure

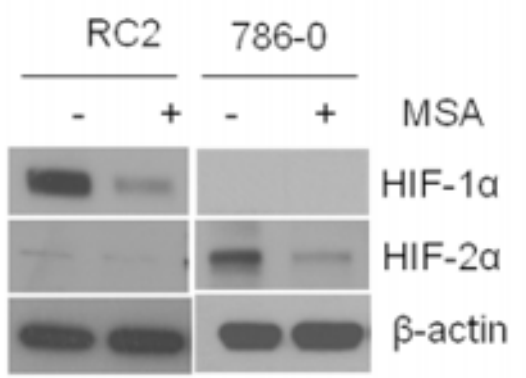
- Advisory Board: Amgen, Roche Diagnostics, Novartis, Janssen, Eisai, Exelixis, Castle Bioscience, Clovis Oncology, Seattle Genetics, EMD Serono, AstraZeneca, Pfizer, BMS.

- DSMC: Janssen, TTC

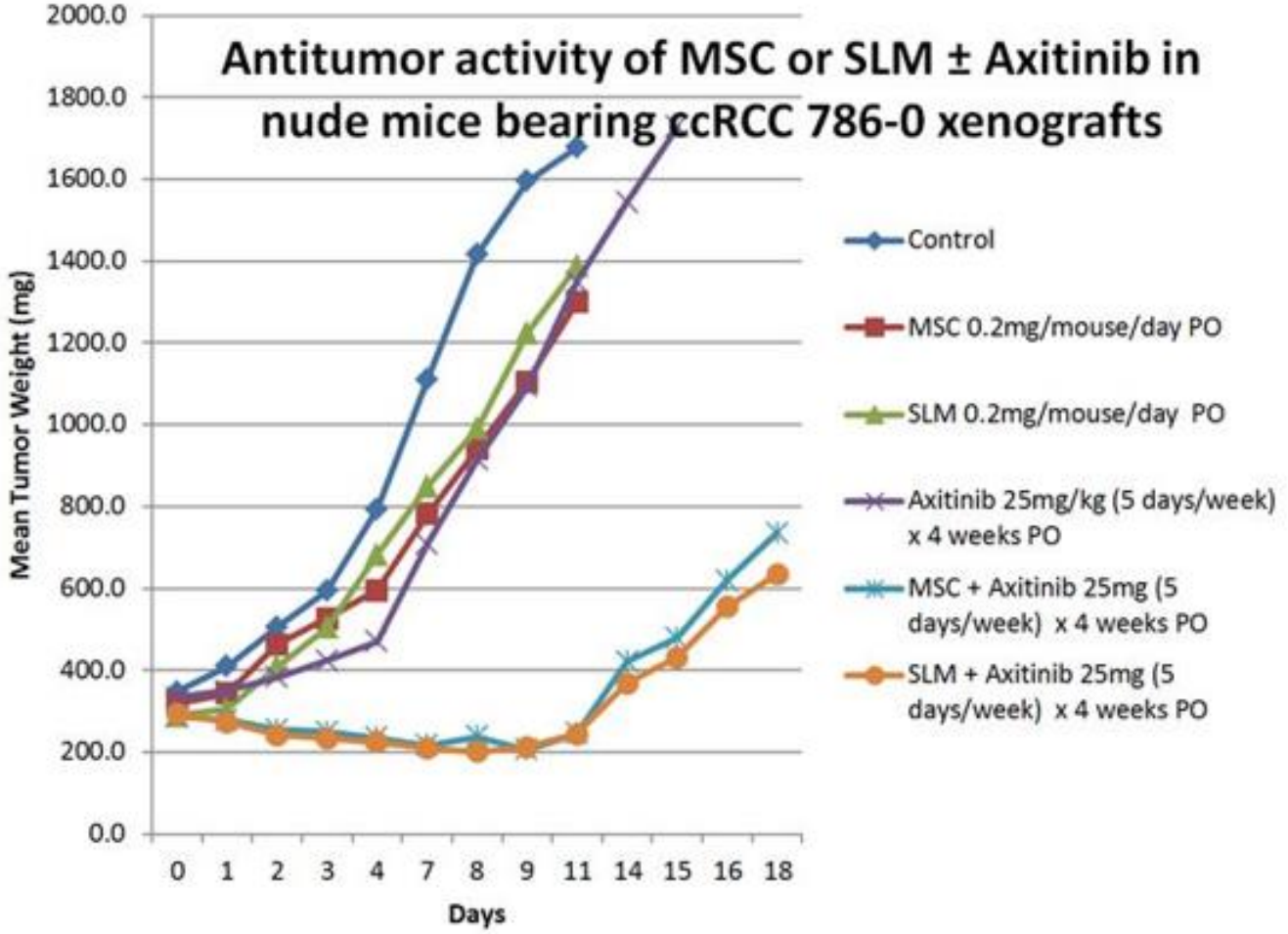
- Institutional Research Support for IITs: **Pfizer**, Exelixis, Eisai.

Preclinical Rationale

a.

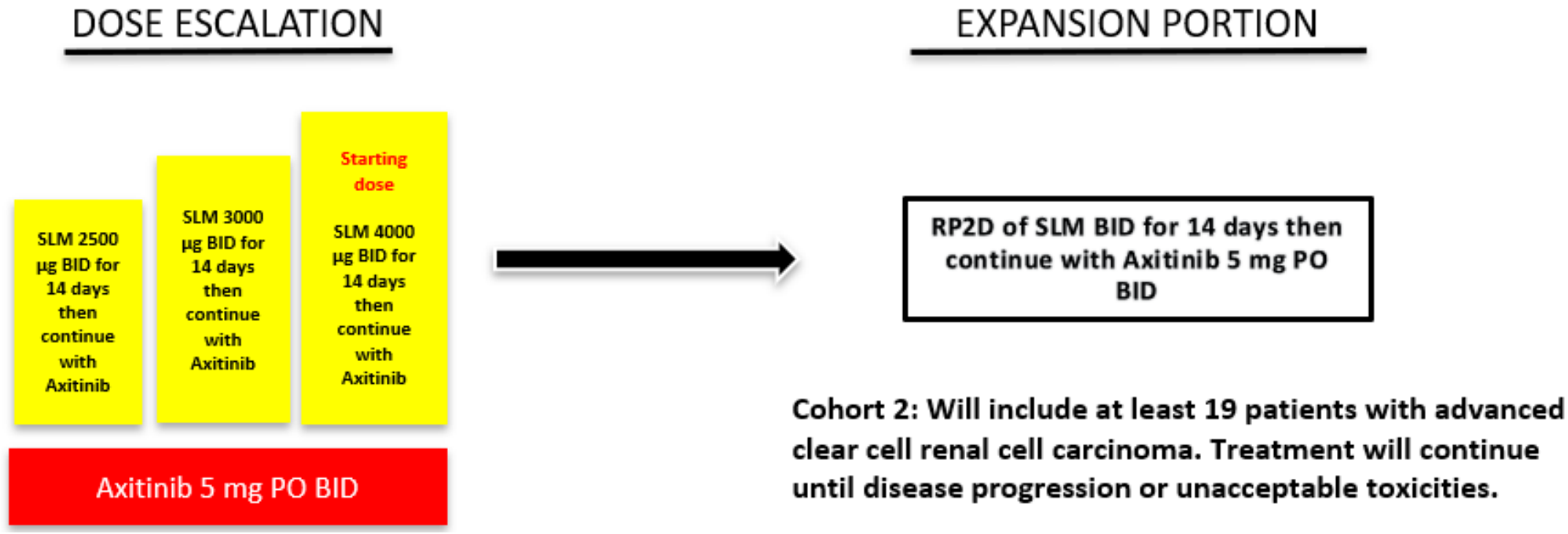


b.



a. Chintala et al. 2012
b. Durrani et al, 2015

Trial Design (NCT02535533)



Adult patients with histologically-proven ccRCC and imaging confirmation of advanced disease are included.

DECT at baseline, day 14 and 3 months.

Primary EP: Safety. Secondary EP: ORR, mPFS, OS.

Baseline Characteristics

Patient Characteristics	ITT Population (N=35)
Age, median (range), years	62 (39-77)
Sex, n (%)	
Female	5 (14)
Male	30 (86)
IMDC* Risk Group, n (%)	
Favorable	7 (20)
Intermediate	22 (63)
Poor	6 (17)
Sarcomatoid Features	6 (17)

*IMDC - International Metastatic Renal Cell Carcinoma Database Consortium

Treatment Characteristics	ITT Population (N=35)
Prior systemic therapies, median (range), n	2 (1-4)
Prior systemic therapies, n (%)	
1	18 (51)
2	9 (26)
≥3	8 (23)
Prior anticancer therapies, n (%)**	
Ipilimumab/Nivolumab	14 (40)
Sunitinib	9 (26)
Nivolumab alone	6 (17)
Pazopanib	6 (17)
Cabozantinib	6 (17)
Durvalumab/Guadecitabine	5 (14)
Interleukin-2	3 (9)
Everolimus	3 (9)
Axitinib/TRC-105	2 (6)
Sunitinib/AGS-003	2 (6)
Axitinib/X4P	1 (3)

**Prior therapies received by >1 patient or including axitinib

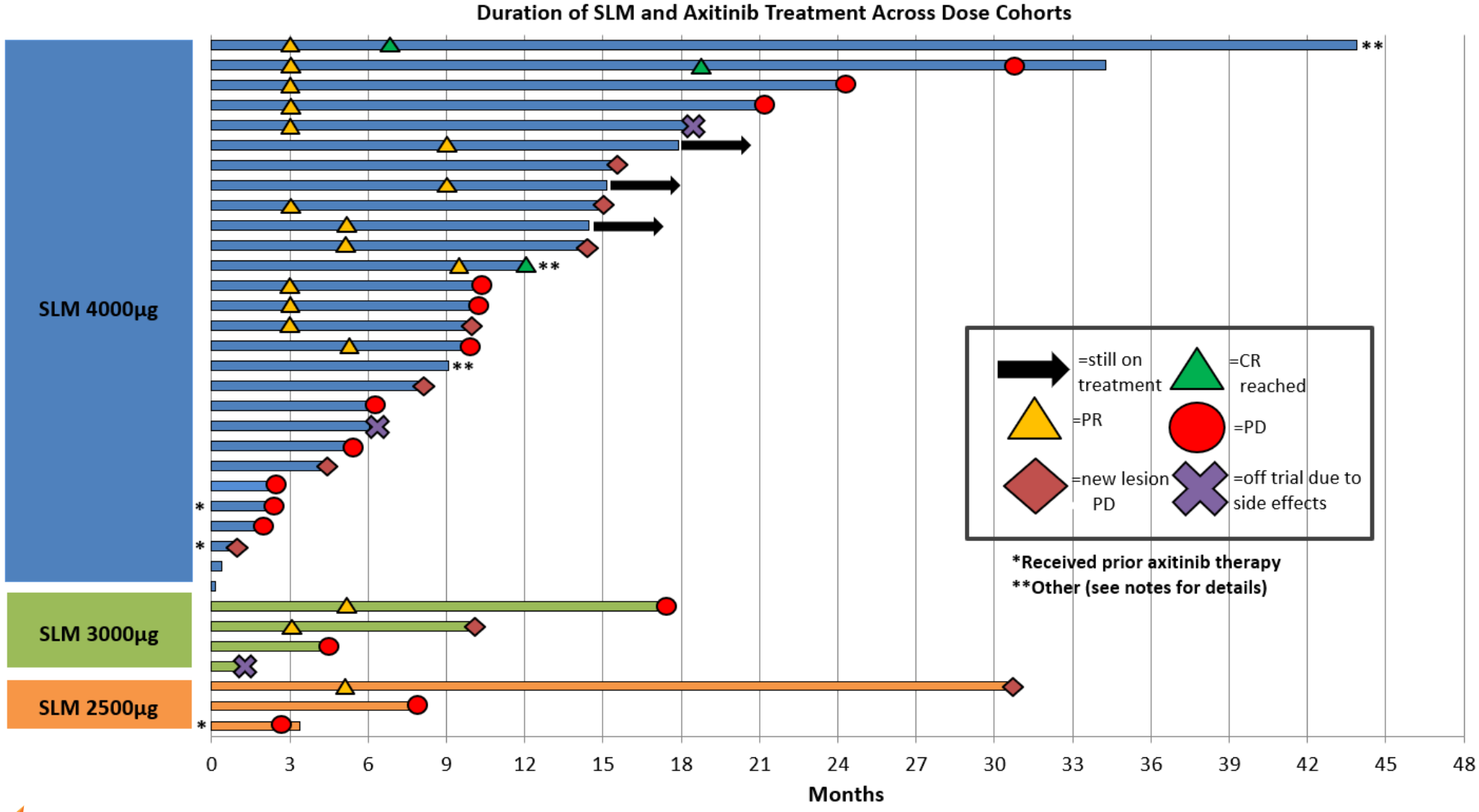
Clinical Reponses

Efficacy Parameter N (%)	ITT Population N=35
ORR (CR+PR)	18 (51)
CR	3 (9)
PR	15 (43)
SD (Lasting longer than 6 months)	7 (20)
Disease Control Rate (CR+PR+SD)	25 (71)
PD	10 (29)

Clinical Reponses

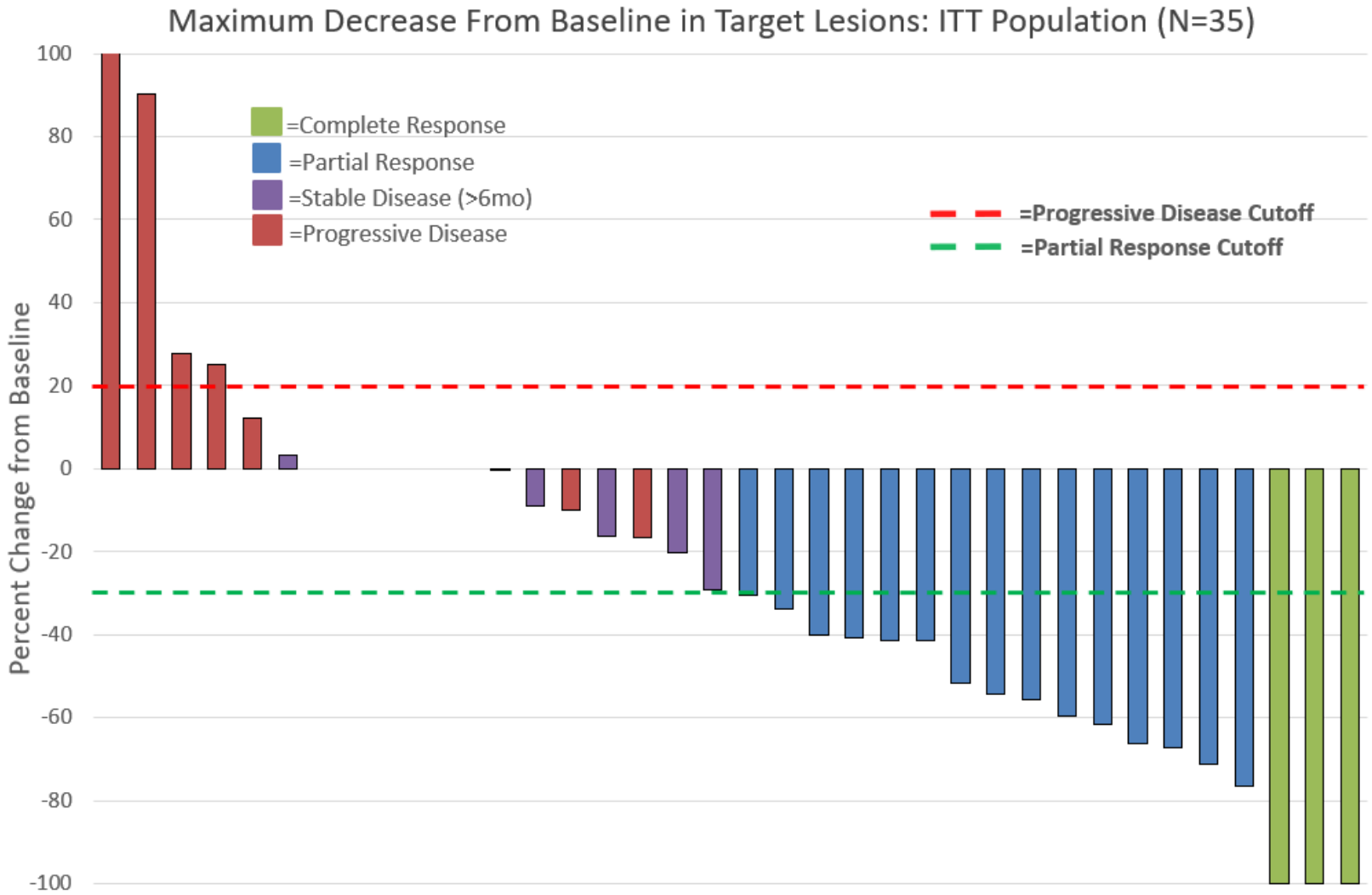
Efficacy Parameter N (%)	ITT Population N=35	Evaluable 4000µg SLM Dose Cohort N=25
ORR (CR+PR)	18 (51)	15 (60)
CR	3 (9)	3 (12)
PR	15 (43)	12 (48)
SD (Lasting longer than 6 months)	7 (20)	5 (19)
Disease Control Rate (CR+PR+SD)	25 (71)	20 (80)
PD	10 (29)	5 (20)

Response Duration



Best Response

24 of 35 patients (69%) experiences tumor shrinkage



Cohort	mPFS	mOS
ITT Population (N=35)	**9.93 months** 95% CI: (7.8-17.1)	**17.9 months** 95% CI: (12.8-NR)
4000µg SLM Eval. Population (N=25)	**14.8 months** 95% CI: (9.5-23.7)	**21.7 months** 95% CI: (15.3-NR)

ITT

PFS and OS at 12 months of treatment were 42% and 74%, respectively.

Evaluable 4,000µg SLM

PFS and OS at 12 months of treatment were 50% and 71%, respectively.

NR: Not reached.

All-Cause >20% Adverse Events*

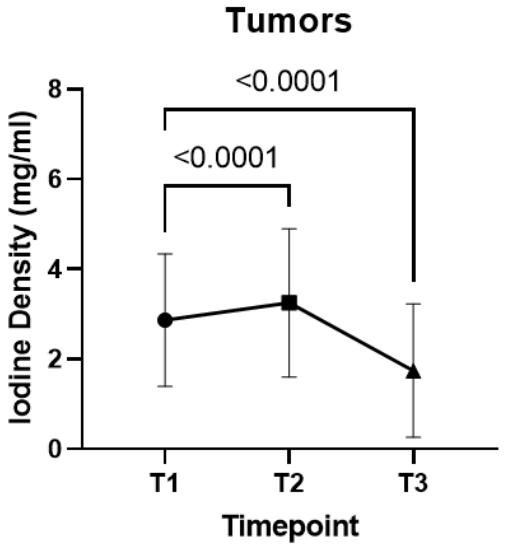
-Grade 4 toxicities include: AKI (N=2), Cholecystitis, Creatinine Increased, Hypercalcemia, Hypokalemia, Hypotension, Respiratory Failure, and Sepsis (each N=1)

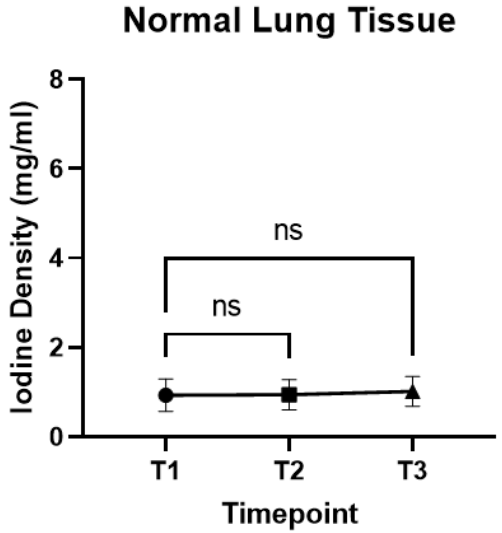
All Grade 4 AEs were deemed unrelated or unlikely related to either study drug

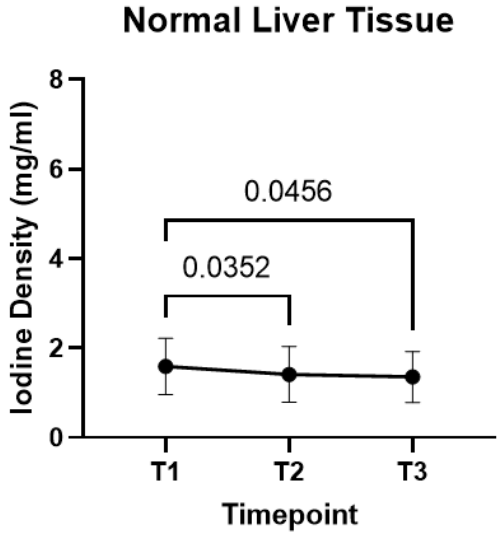
AEs (N=35)	All Grades	Grade 1/2	Grade 3
Fatigue	29 (83%)	22 (63%)	7 (20%)
Diarrhea	25 (71%)	22 (63%)	3 (9%)
Anorexia	20 (57%)	16 (46%)	4 (11%)
Weight Loss	20 (57%)	11 (31%)	9 (26%)
Nausea	18 (51%)	17 (49%)	1 (3%)
Hypertension	17 (49%)	5 (14%)	12 (34%)
Hoarseness	16 (46%)	16 (46%)	0
Cough	13 (37%)	12 (34%)	1 (3%)
Hyponatremia	11 (31%)	8 (23%)	3 (9%)
Proteinuria	11 (31%)	7 (20%)	4 (11%)
Vomiting	11 (31%)	11 (31%)	0
Abdominal Pain	10 (29%)	8 (23%)	2 (6%)
Generalized Muscle Weakness	9 (26%)	7 (20%)	2 (6%)
Dehydration	9 (26%)	5 (14%)	4 (11%)
Anemia	9 (26%)	4 (11%)	5 (14%)
Hyperkalemia	8 (23%)	6 (17%)	2 (6%)
Mucositis Oral	8 (23%)	7 (20%)	1 (3%)
Palmar-Plantar Erythrodysesthesia Syndrome	8 (23%)	7 (20%)	1 (3%)

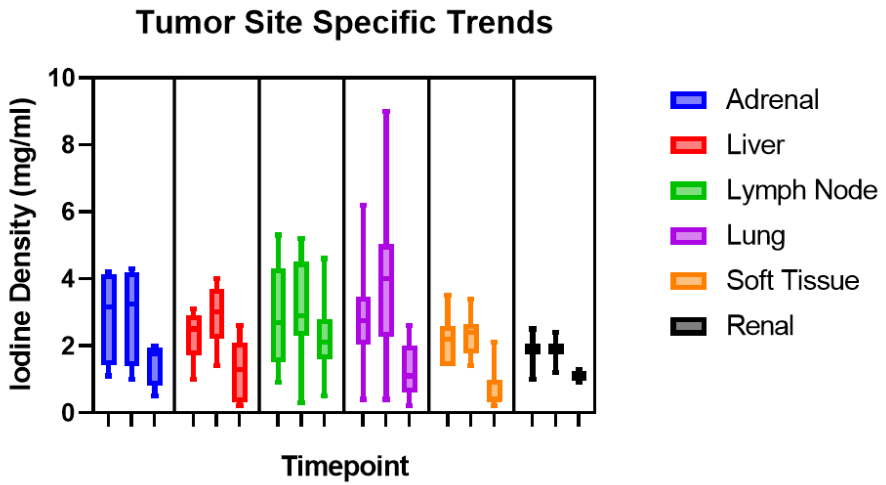
*Other AEs present in >20% of participants include the following: Dyspnea (48%), Constipation (33%), Creatinine Increased (30%), Dysgeusia, Headache (each 27%), Back Pain, Fever, Pain in Extremity (each 24%), Alanine Aminotransferase Increase, Alkaline Phosphatase Increased, Rash maculo-papular, and Sore Throat (each 21%)

Dual-Energy CT (DECT) Data

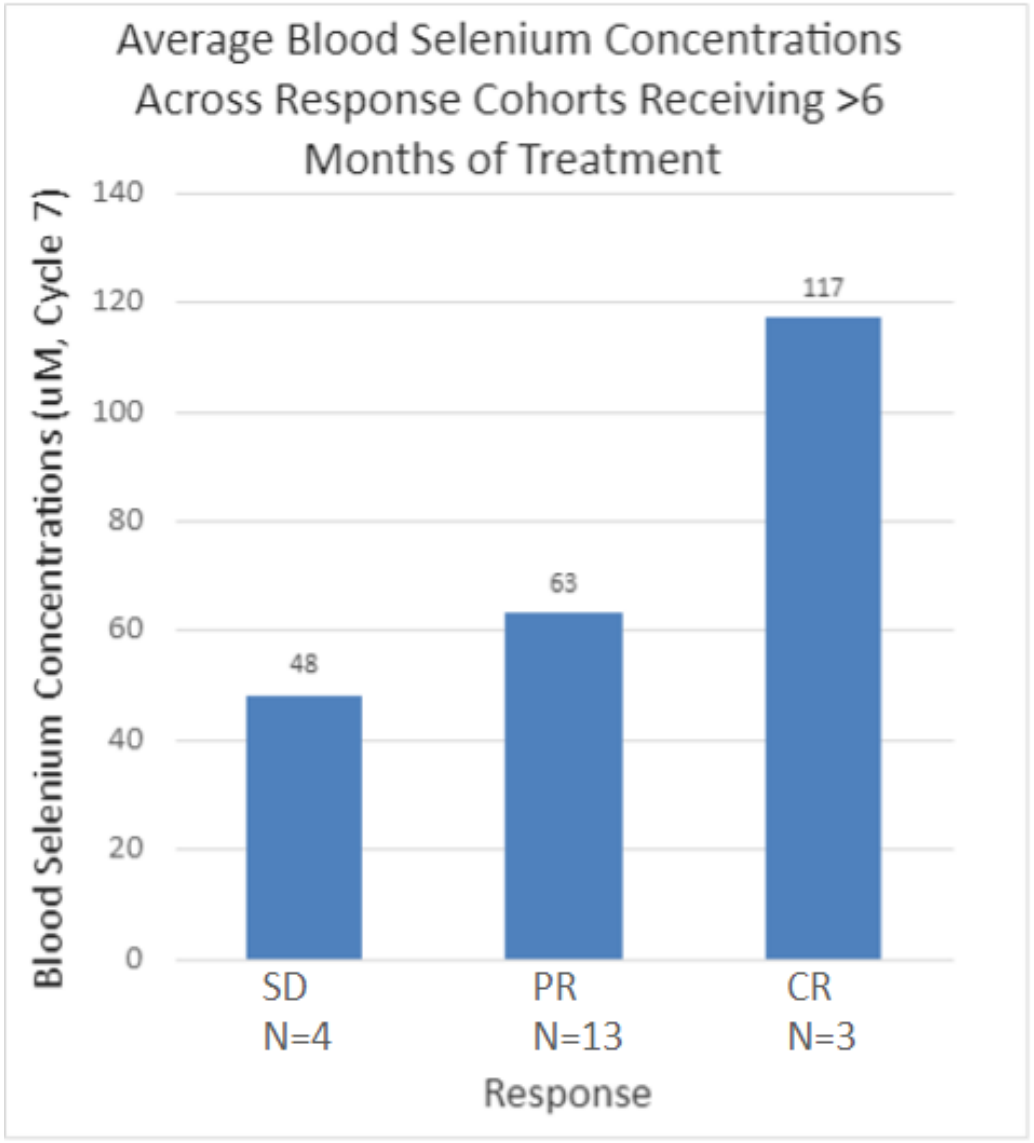


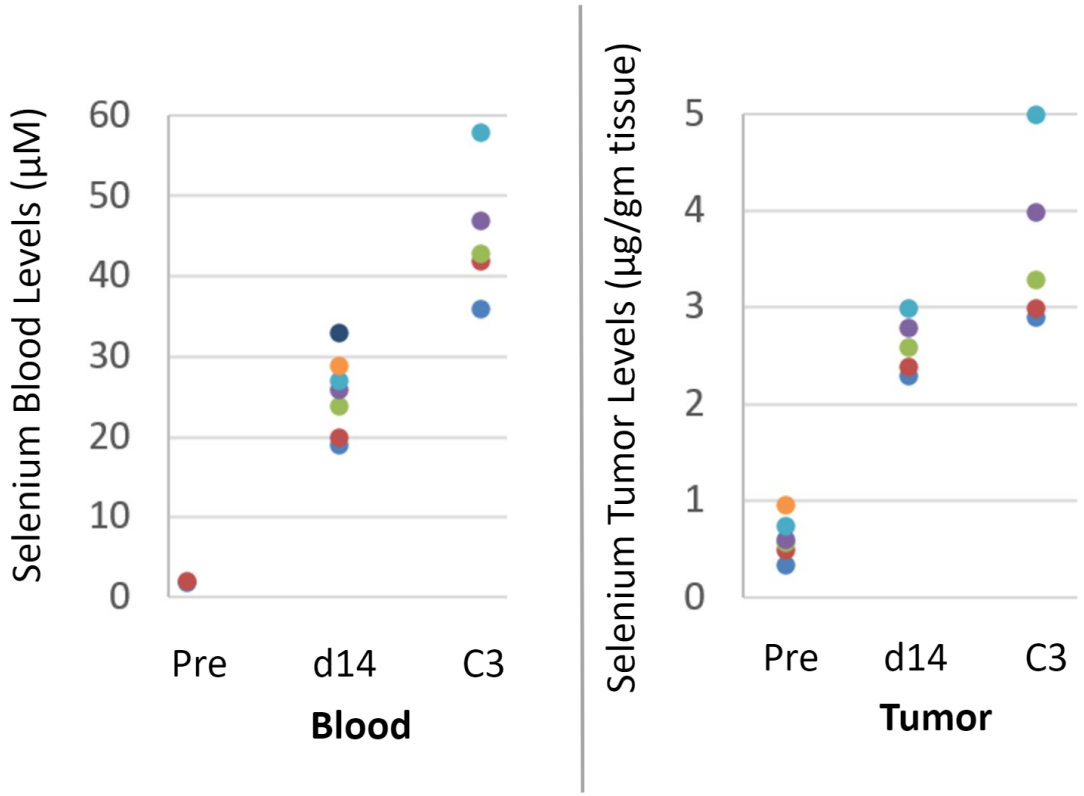






Selenium blood concentrations are associated with increased tumor selenium concentrations





Conclusion

- Combination of high dose SLM and axi is safe with no death
- The observed ORR 60%, mPFS and OS of 14.8m and 21.7m respectively in the 25 relapsed patients treated with the 4000 mcg SLM/axi are very encouraging and should be confirmed in larger clinical trial.
- Response to SLM/axi combination is SLM dose and sequence dependent
- Increase in iodine density in tumor but not normal tissue is consistent with the hypothesis that SLM normalizes tumor vasculature and could result in increased drug delivery to tumor tissues.
- Upfront SLM/ axi/ pembro combination trial is underway.

Acknowledgements and Thank You

- Patients and Families
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