

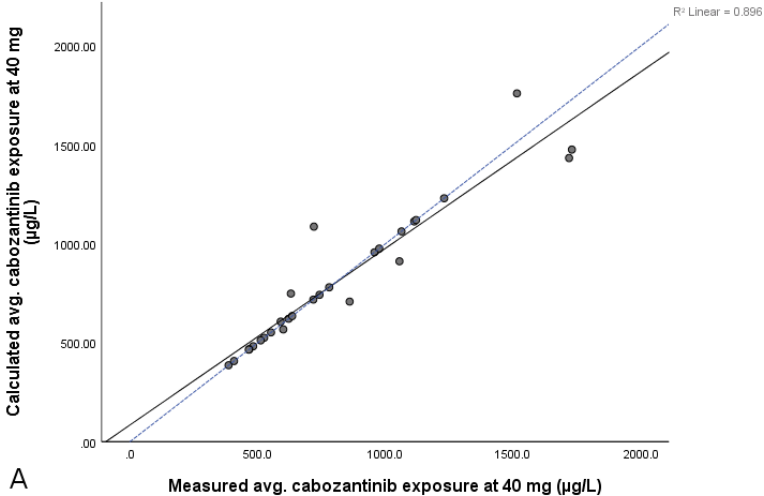
## Exposure-toxicity relationship of cabozantinib in patients with renal cell cancer and salivary gland cancer

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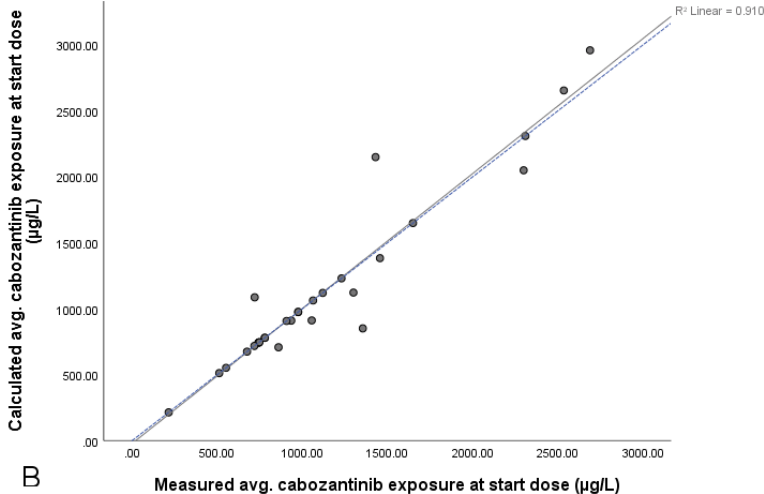
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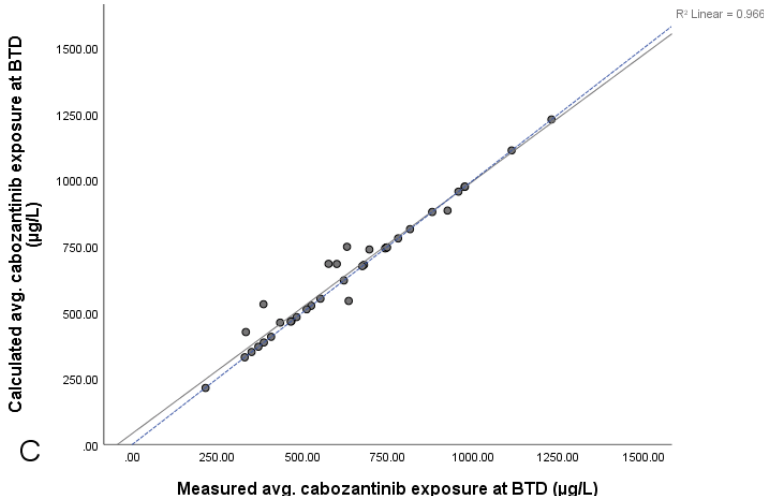
**Supplementary Figure 1** Correlation between measured and calculated average cabozantinib  $C_{min}$  levels for (A) the 40 mg dose level, (B) the dose level at start and (C) BTD level



A



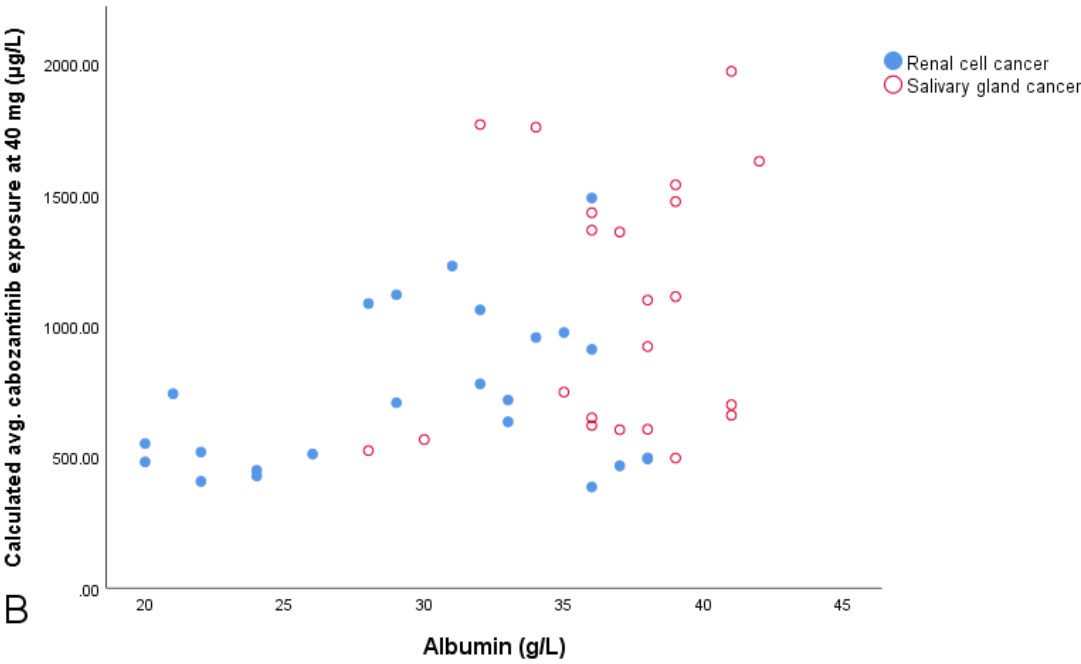
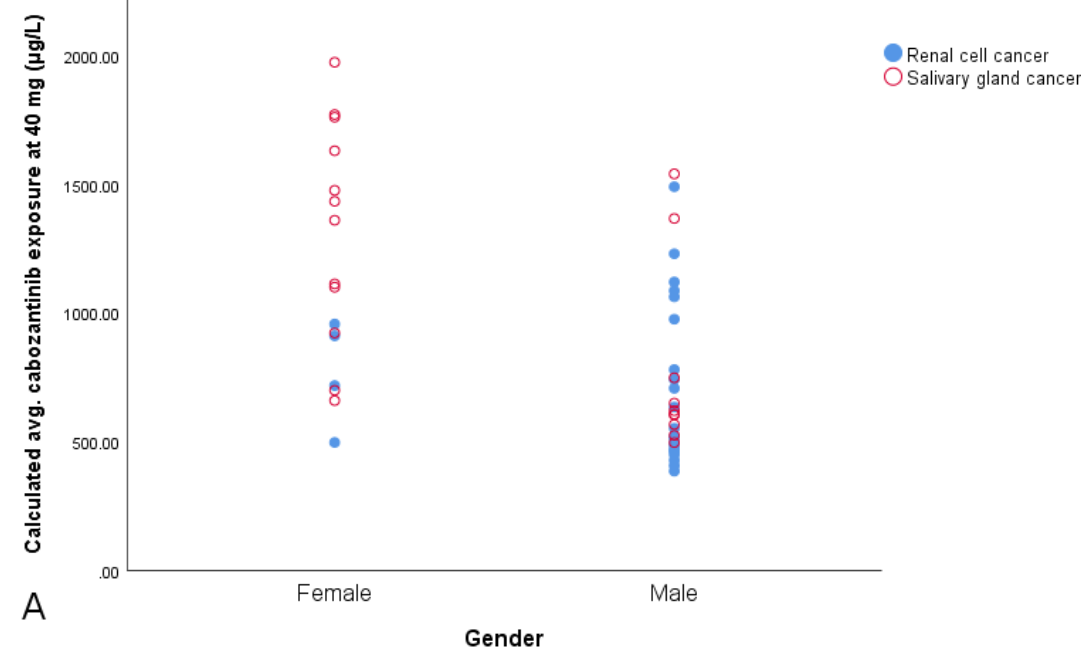
B



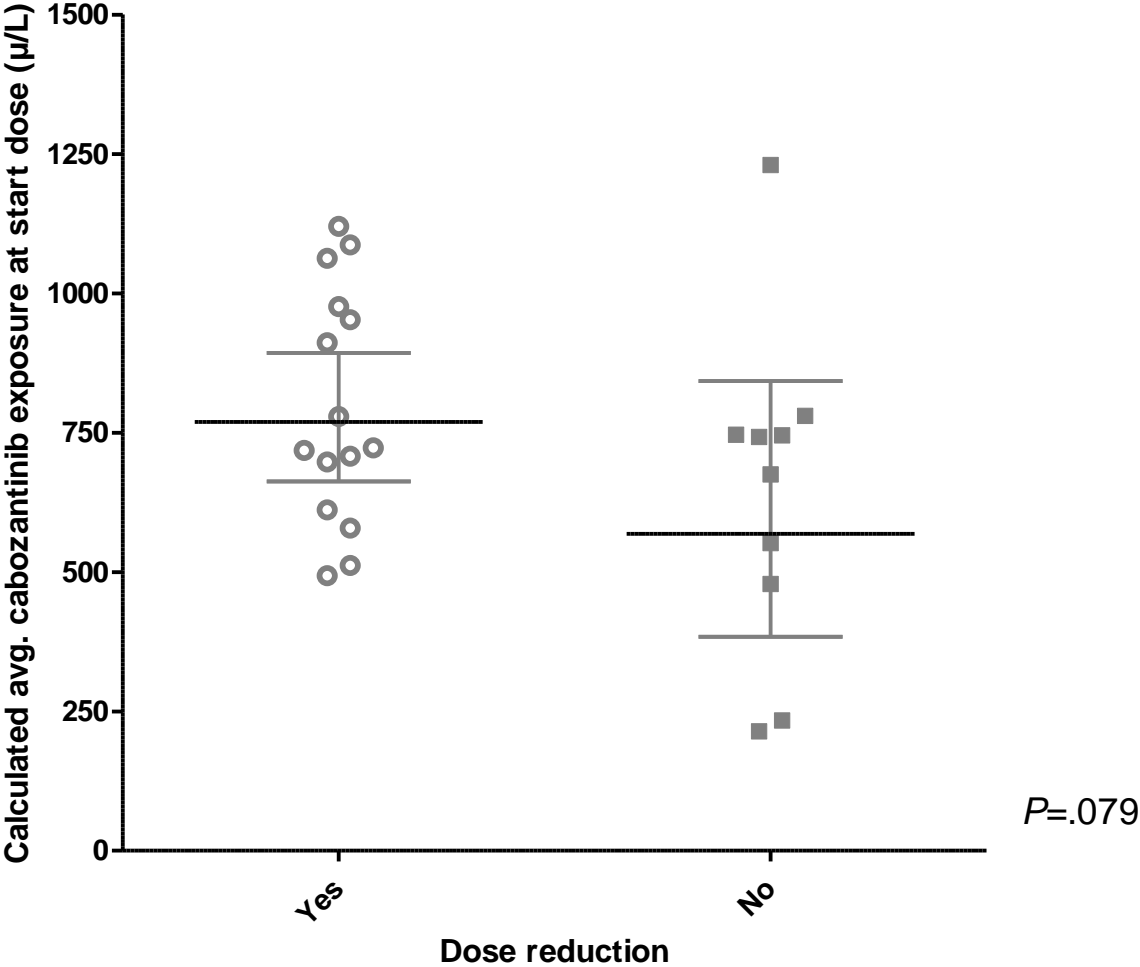
C

Blue dotted line represents reference line of  $y=x$ .

**Supplementary Figure 2** Scatter plot of gender (A) and baseline albumin levels (B) versus calculated cabozantinib  $C_{min}$  levels at 40 mg

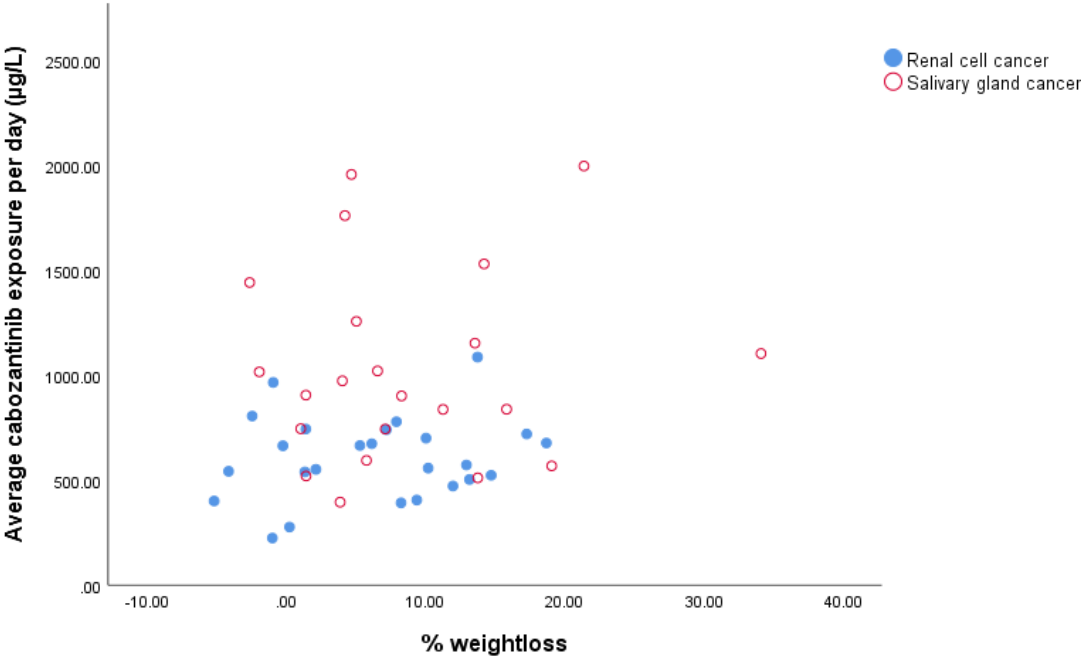


**Supplementary Figure 3** Scatter plot of the calculated individual cabozantinib  $C_{min}$  levels at the start dose for RCC patients who did and did not receive a dose reduction relative to the starting dose

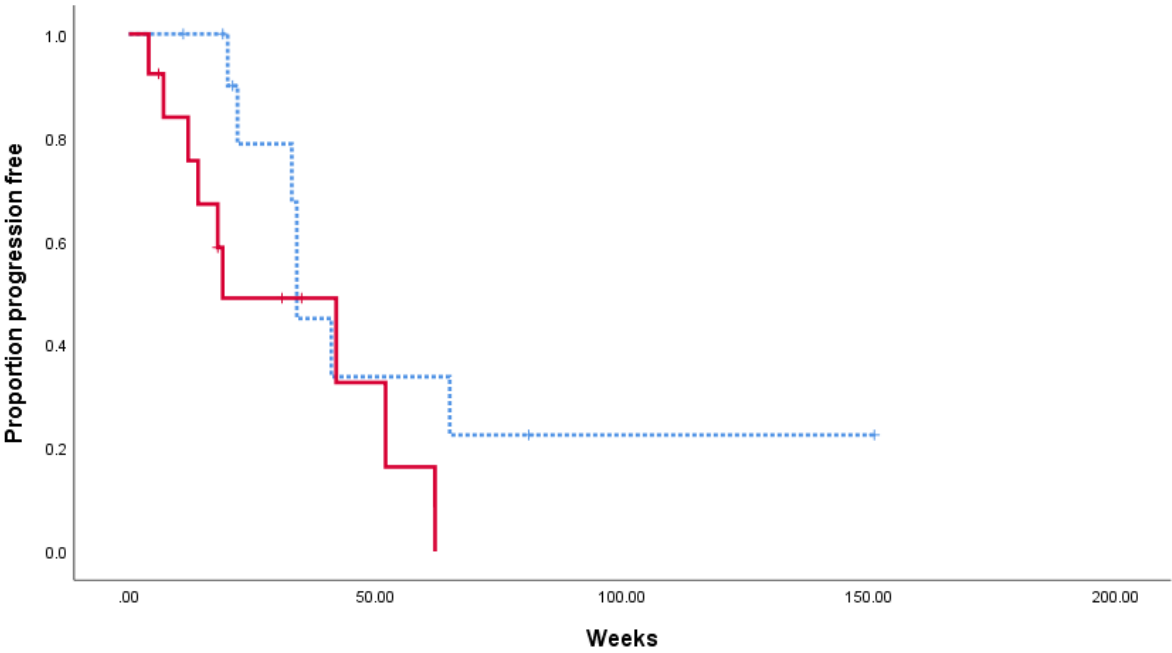


Data are presented with geometric mean and 95% CI.

**Supplementary Figure 4** Scatter plot of percentage weight loss from baseline versus average cabozantinib  $C_{min}$  exposure



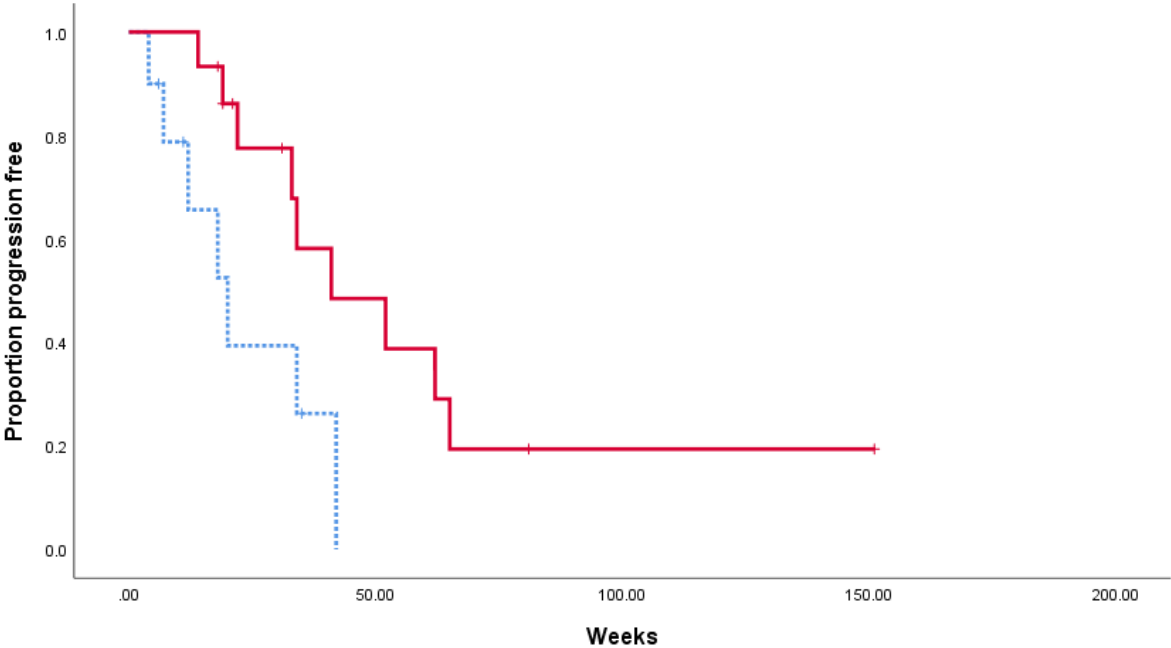
**Supplementary Figure 5** Kaplan-Meier curve of progression free survival for patients with advanced RCC with an exposure above and below the median average exposure of 573 µg/L



Median PFS was 19 weeks (95% CI: 0-45.7) in the group with an exposure equal or above 573 µg/L (solid red line) vs 34 weeks (95% CI 32.6-35.5) in the group with an exposure below 573 µg/L (dotted blue line) ( $P=.13$ )

No. at risk	0	25	50	75	100	125	150
≥ 573 µg/L	13	5	2	0	0	0	0
< 573 µg/L	12	7	3	2	1	1	1

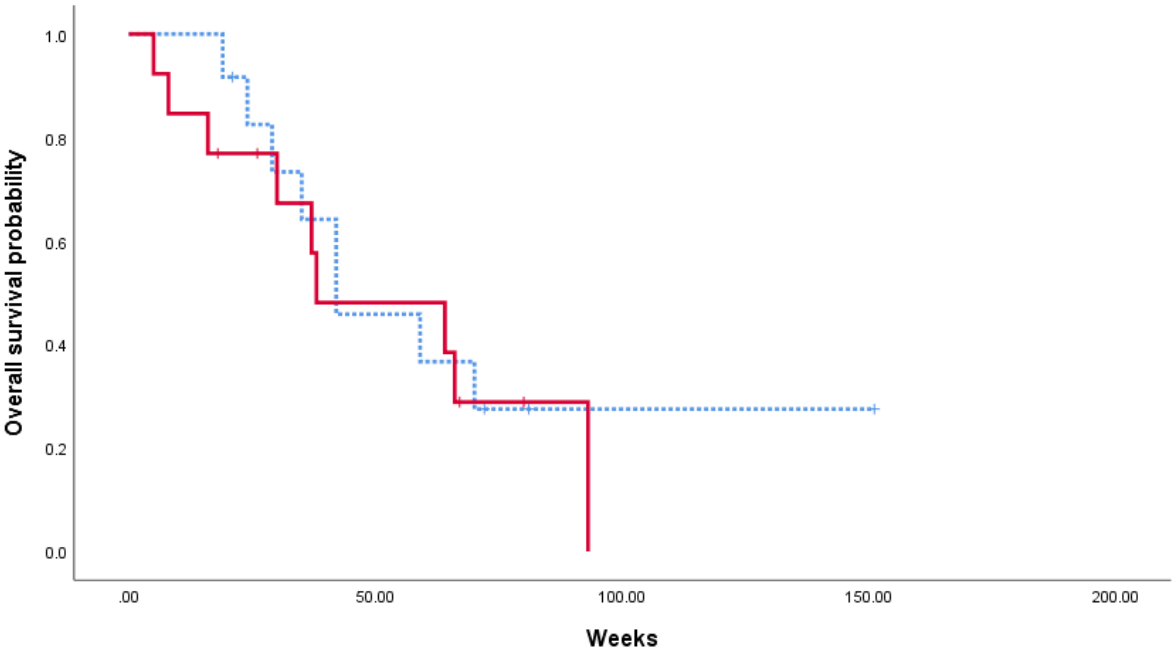
**Supplementary Figure 6** Kaplan-Meier curve of progression free survival for patients with advanced RCC with an without dose reductions relative to the starting dose level



Median PFS was 41.0 (95% CI: 13.5-68.5) weeks in the group with a dose reduction (solid red line) vs 20.0 (95% CI: 9.6-30.4) weeks in the group without dose reduction (dotted blue line) ( $P=.023$ )

No. at risk	0	25	50	75	100	125	150
With dose reduction	15	9	5	2	1	1	1
Without dose reduction	10	3	0	0	0	0	0

**Supplementary Figure 7** Kaplan-Meier curve of overall survival for patients with advanced RCC with an exposure above and below the median average exposure of 573 µg/L

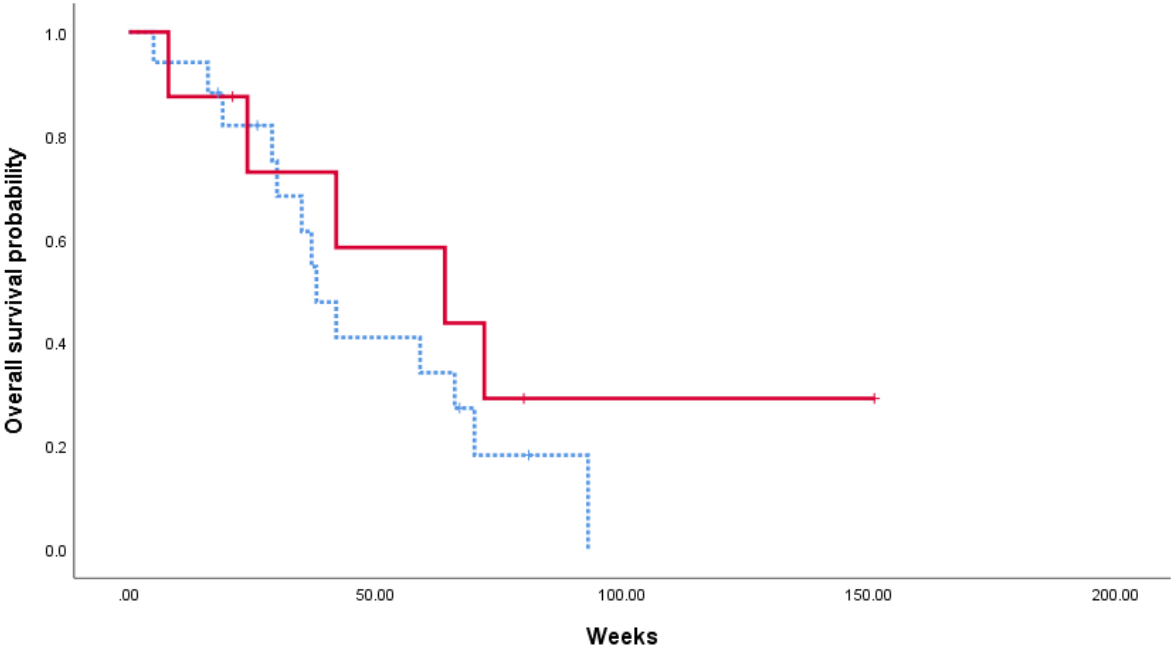


Median OS was 38 weeks (95% CI: 0-79) in the group with an exposure equal or above 573 µg/L (solid red line) vs 42 weeks (95% CI: 16-68) in the group with an exposure below 573 µg/L (dotted blue line). ( $P=.6$ )

No. at risk	0	25	50	75	100	125	150
≥ 573 µg/L	13	9	5	2	0	0	0
< 573 µg/L	12	9	5	2	1	1	1



**Supplementary Figure 8** Kaplan-Meier curve of overall survival for patients with advanced RCC with a 60 mg starting dose and those with a lower than 60 mg starting dose



Median OS was 64 weeks (95% CI: 8-120) in the group with a start dose of 60 mg (solid red line) vs 38 weeks (95%CI: 29-47) in the group with a lower starting dose (dotted blue line). (P=.3)

No. at risk	0	25	50	75	100	125	150
60 mg starting dose	8	5	4	2	1	1	1
< 60 mg starting dose	17	13	6	2	0	0	0