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SOCIETÀ ITALIANA DI OSTEONCOLOGIA
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Proposed Project:

Role of receptor activator of nuclear factor kappa-B ligand (RANKL) and Bone Turnover Markers as potential biomarkers of response to immune checkpoint inhibitors (ICIs) in metastatic renal cell carcinoma patients: a multicenter prospective study

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Open access

Original research



Extensive plasma proteomic profiling revealed receptor activator of nuclear factor kappa-B ligand (RANKL) as emerging biomarker of nivolumab clinical benefit in patients with metastatic renal cell carcinoma

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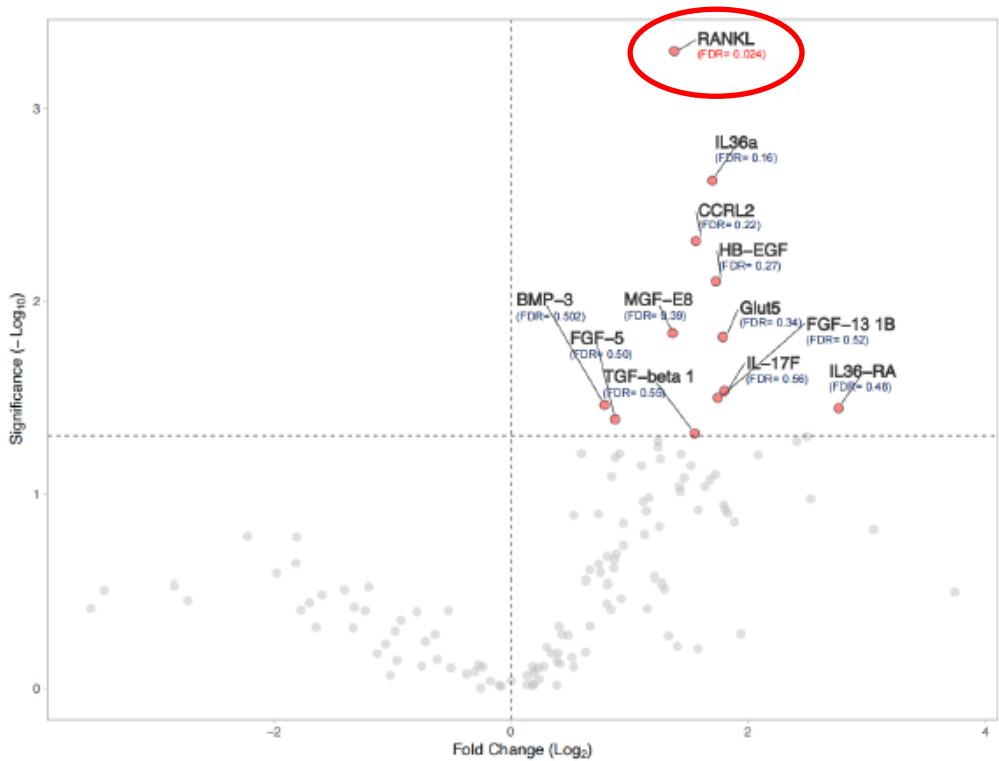
31 patients with mRCC treated with nivolumab were enrolled at Fondazione Policlinico Universitario Campus Bio-Medico

the study was designed to provide an adequate discovery set (16 patients) and validation cohort (15 patients)

Table 1 Clinicopathological variables of study population

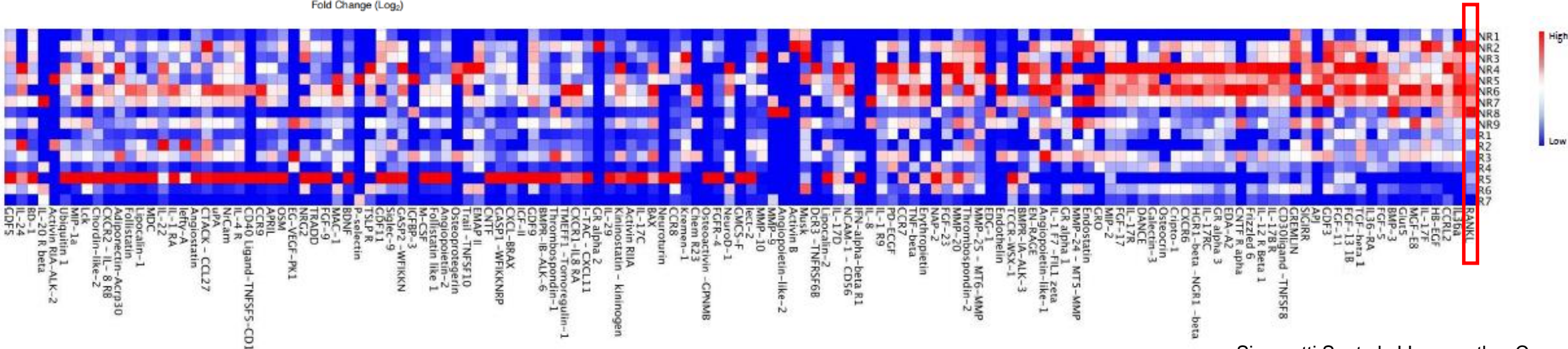
	Discovery set (N=16)	Validation set (N=15)
Sex		
Female	5 (31%)	4 (27%)
Male	11 (69%)	11 (73%)
Age		
≥66	9 (56%)	7 (47%)
<66	7 (44%)	8 (53%)
Therapy line		
Second	13 (81%)	12 (75%)
Third	3 (19%)	3 (25%)
First-line TKI		
Sunitinib	11 (69%)	8 (53%)
Pazopanib	5 (31%)	7 (47%)
IMDC score		
Good risk	5 (31%)	5 (33%)
Intermediate risk	11 (69%)	10 (67%)
IMDC, International Metastatic RCC Database Consortium; TKI, tyrosine kinase inhibitor .		

RATIONALE (1): RANKL as potential biomarker of ICIs response in mRCC patients

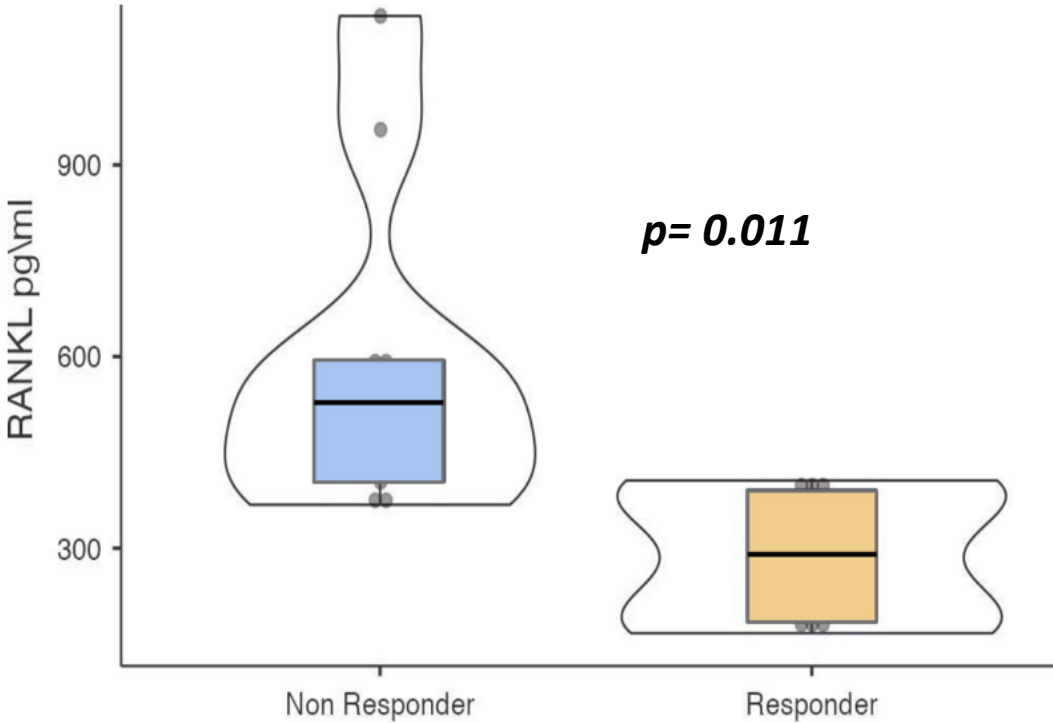


An extensive proteome soluble profile including 507 molecules in plasma of 16 mRCC patients treated with nivolumab (discovery set) was performed

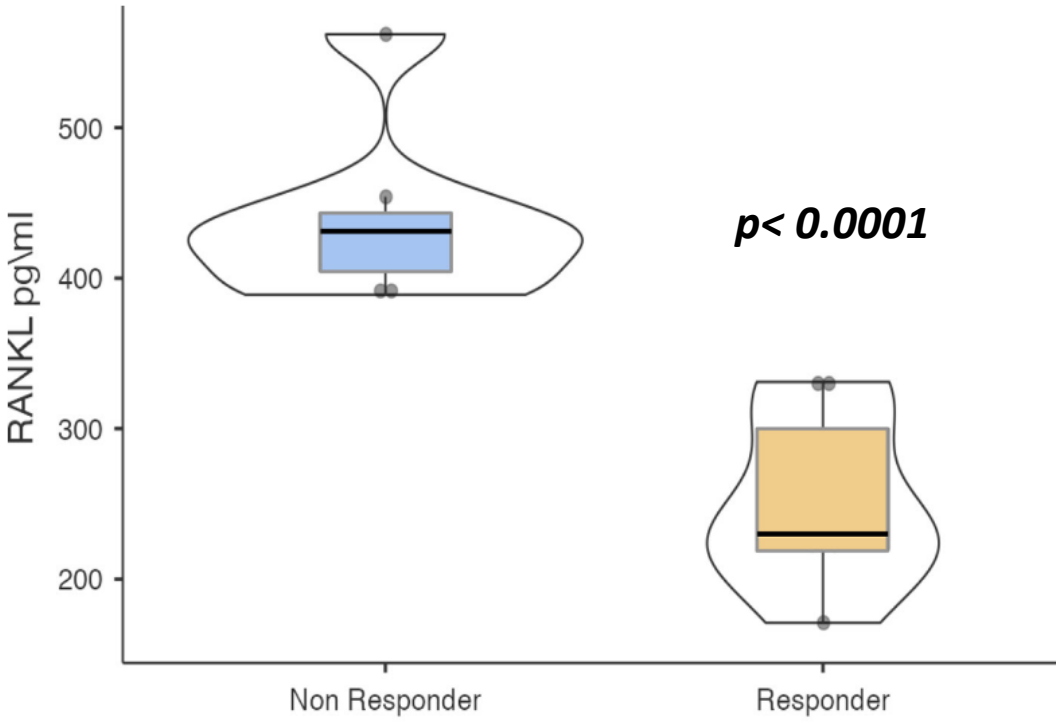
After FDR correction, RANKL was found to be the only significant overexpressed factor (FDR: 0.023)



RATIONALE (1): RANKL as potential biomarker of ICIs response in mRCC patients

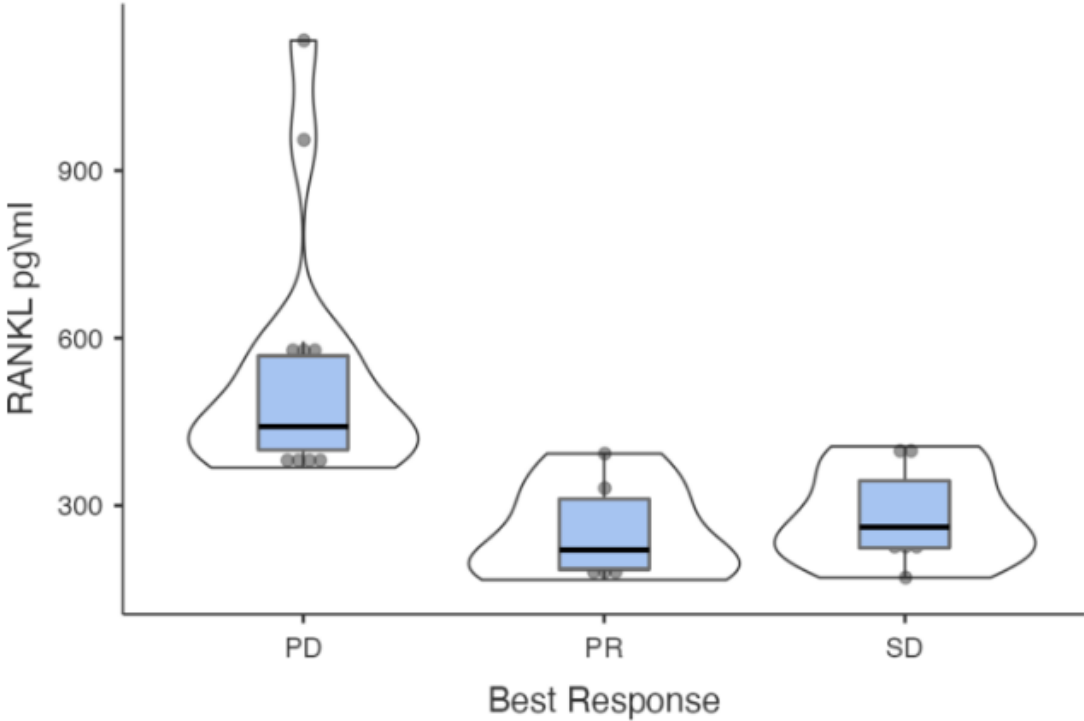


ELISA assay confirmed that RANKL levels were higher in Non Responder group (DISCOVERY SET)



An overexpression of RANKL in plasma of Non Responder patients was confirmed in the VALIDATION SET

RATIONALE (1): RANKL as potential biomarker of ICI's response in mRCC patients

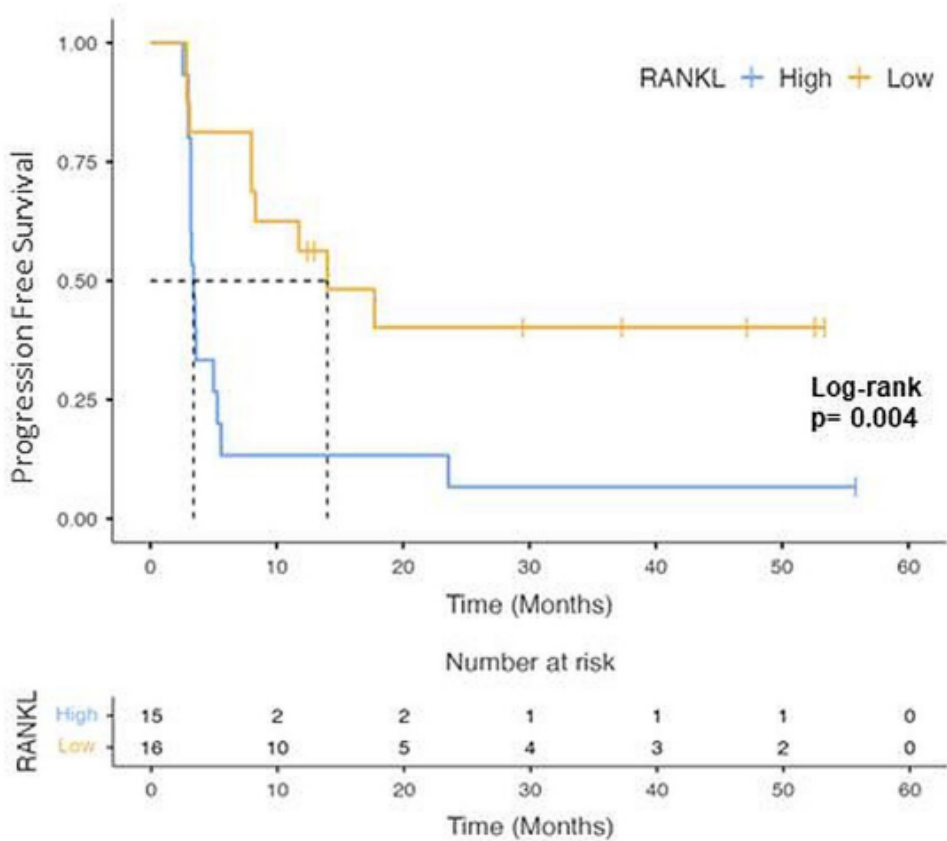


	Best Response	N	Mean	SD	SE
RANKL pg/ml	PD	16	532	215.6	53.9
	PR	7	253	86.7	32.8
	SD	8	283	85.3	30.2

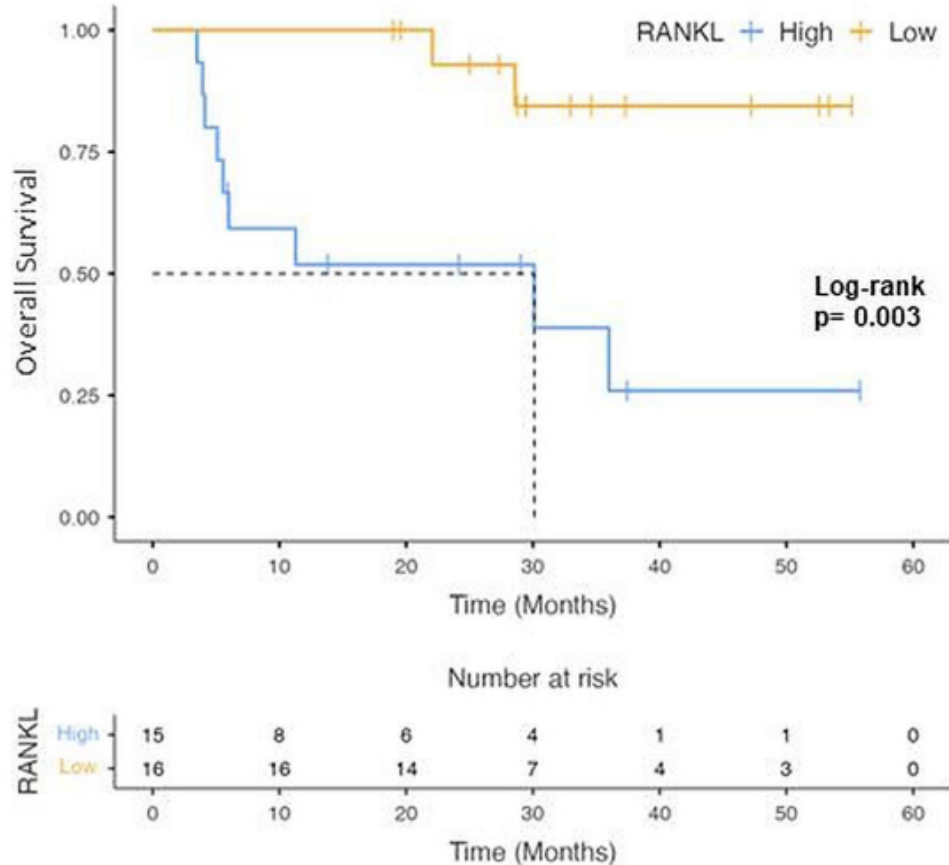
		PD	PR	SD
PD	Mean difference	—	279	248.3
	p-value	—	0.003	0.006
PR	Mean difference		—	- 30.4
	p-value		—	0.935
SD	Mean difference			—
	p-value			—

Higher RANKL levels were found in patients who progressed from nivolumab treatment compared with those had a partial response (PR) or stable disease (SD)
No significant differences were observed in Responder group (PR vs SD patients)

RATIONALE (1): RANKL as potential biomarker of ICIs response in mRCC patients



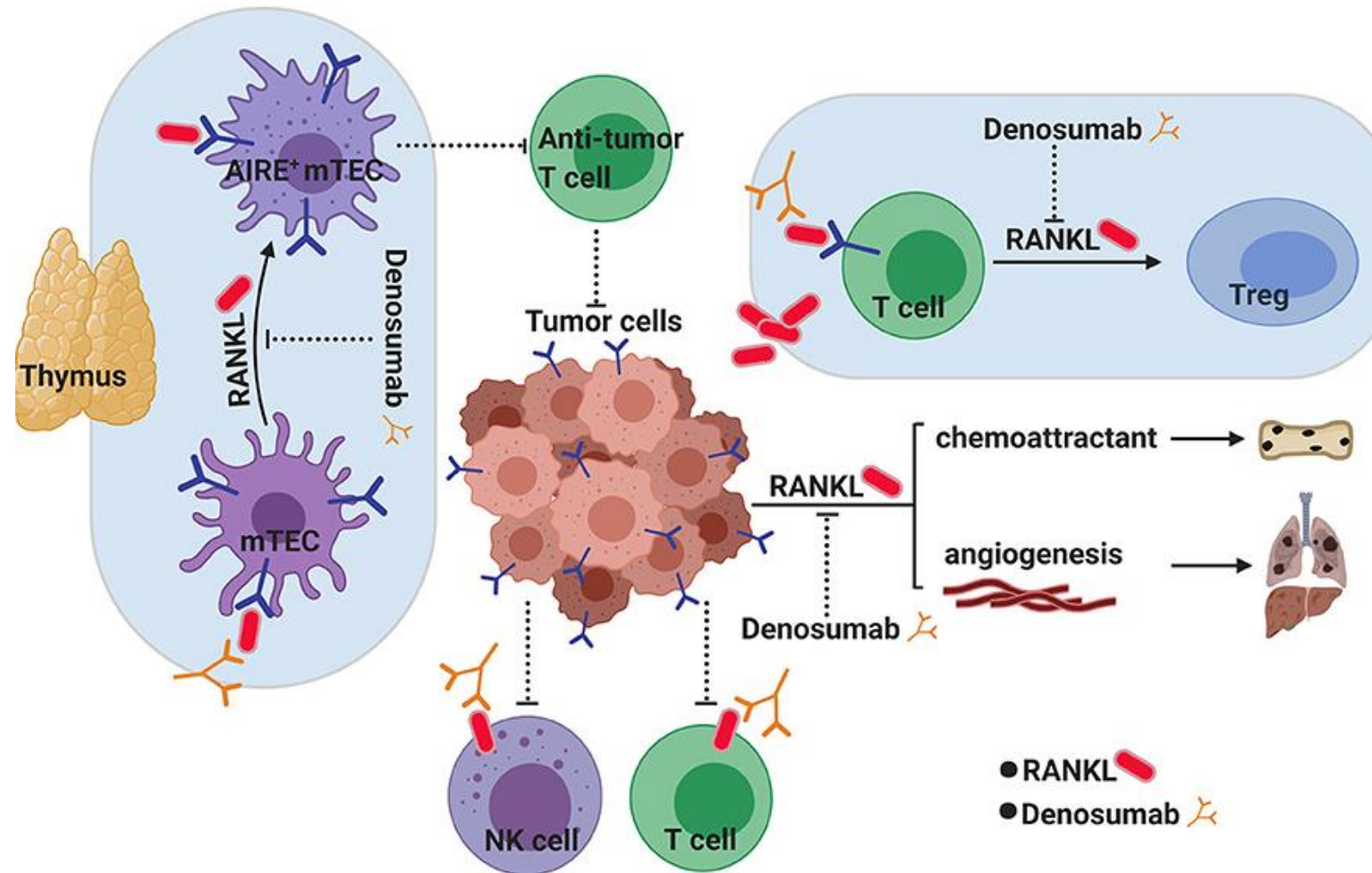
	N	Events	Median	95% ConfidenceInterval	
				Lower	Upper
High RANKL	15	14	3.42	3.20	5.60
Low RANKL	16	9	14.00	7.99	NaN



	N	Events	Median	95% ConfidenceInterval	
				Lower	Upper
High RANKL	15	9	30.1	5.56	NaN
Low RANKL	16	2	NaN	NaN	NaN

RANKL low-expressing patients had significant improvements in both PFS and OS

RANKL/RANK is involved not only in bone homeostasis, but also in several physiological immune processes

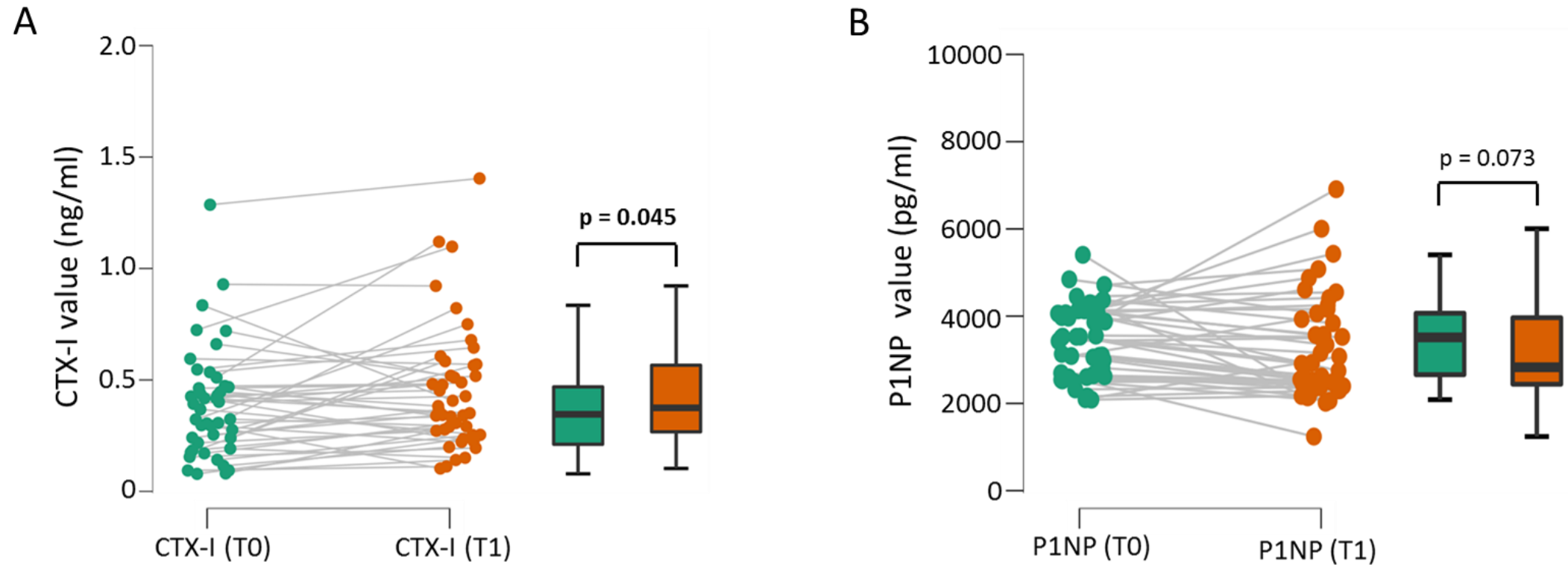


Rationale (2): Bone Turnover Markers as potential biomarkers of ICIs response in mRCC patients

	Overall (N=44)
Sex	
<i>Female</i>	19 (43%)
<i>Male</i>	25 (57%)
Age	
≥ 70	22 (50%)
< 70	22 (50%)
ECOG	
0	29 (66%)
1	15 (34%)
Tumor type	
<i>NSCLC</i>	36 (82%)
<i>RCC</i>	8 (18%)
Treatment	
<i>Nivolumab</i>	23 (52%)
<i>Pembrolizumab</i>	16 (36%)
<i>Atezolizumab</i>	5 (12%)
Treatment Line	
<i>First line</i>	17 (39%)
<i>Second or Third</i>	27 (61%)
Primary Tumor	
<i>Non resected</i>	19 (43%)
<i>Resected</i>	25 (57%)
No. metastatic sites	
1	15 (34%)
2	17 (39%)
>2	12 (27%)

A series of 44 patients treated with anti-PD1 therapy as monotherapy was prospectively enrolled including 36 patients affected by advanced NSCLC and 8 patients suffering from metastatic RCC

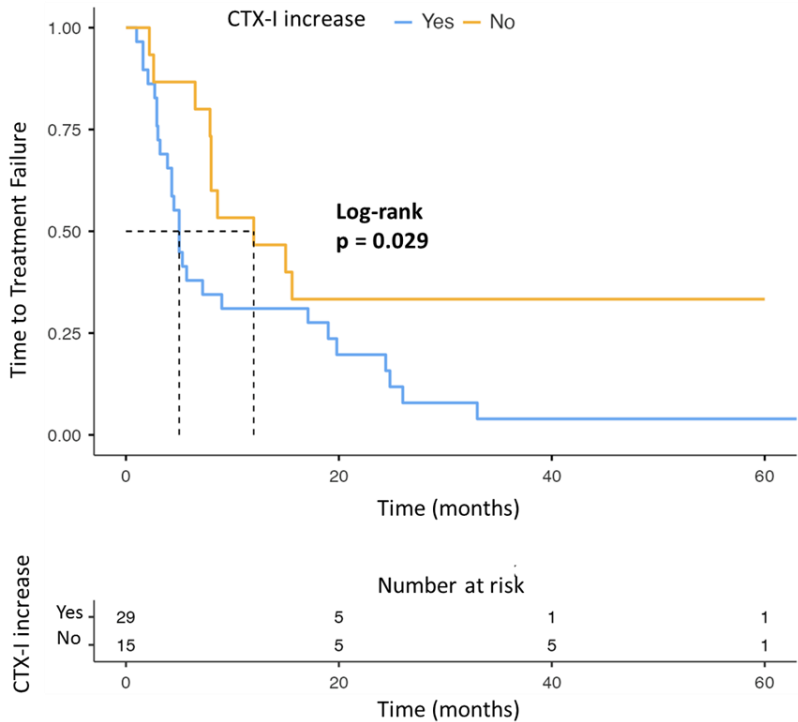
Rationale (2): Bone Turnover Markers as potential biomarkers of ICIs response in mRCC patients



A significant increase of CTX-I with a concomitant decreasing trend towards the reduction of PINP was observed after 3 months of treatment

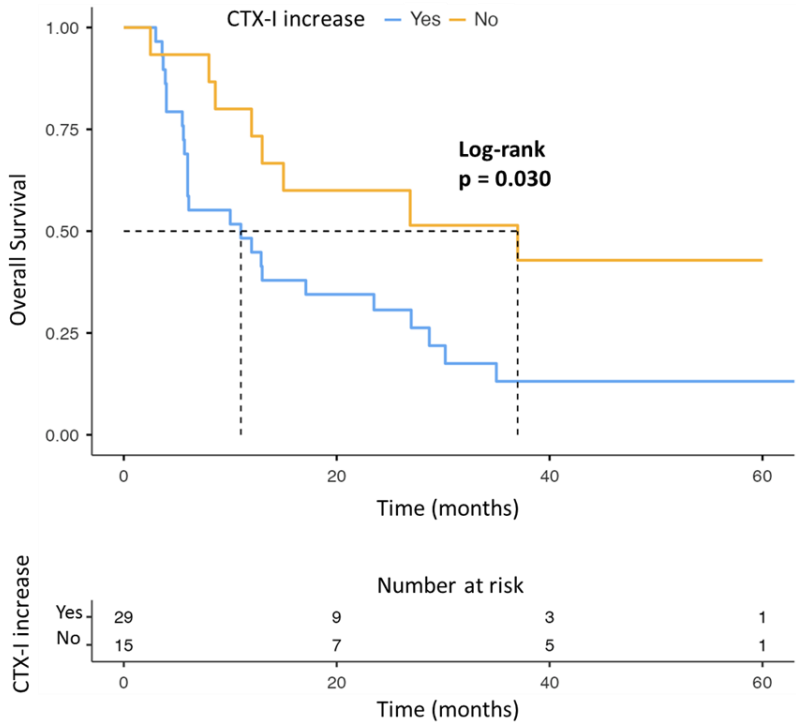
Rationale (2): Bone Turnover Markers as potential biomarkers of ICIs response in mRCC patients

A



95% Confidence Interval					
	Records	Events	Median	Lower	Upper
Yes	29	27	5.0	4.3	17.1
No	15	10	12.0	8.0	NaN

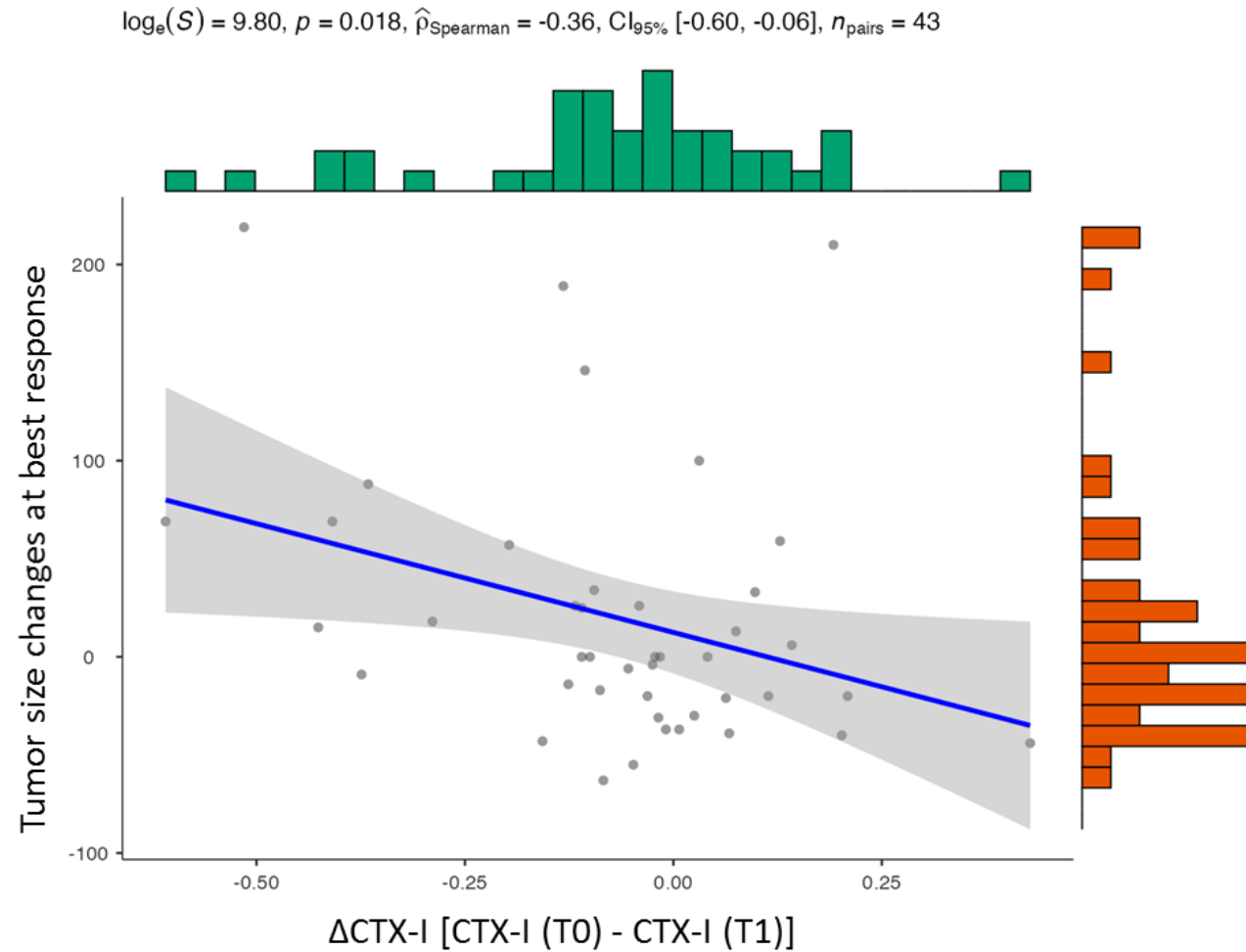
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95% Confidence Interval					
	Records	Events	Median	Lower	Upper
Yes	29	24	11.0	6.0	27.1
No	15	8	37.0	13.0	NaN

CTX-I increase was associated with poor prognosis in terms of treatment response and survival

Rationale (2): Bone Turnover Markers as potential biomarkers of ICIs response in mRCC patients



CTX-I increase was significantly associated with an increased tumor size during ICIs

OBJECTIVES OF THE STUDY

To evaluate **RANKL** and **Bone Turnover Markers** changes in a prospective larger cohort of mRCC patients treated with ICI and/or ICI plus Tyrosine Kinase Inhibitors (TKIs) to confirm and assess their relationship with clinical outcomes

Specific objectives:

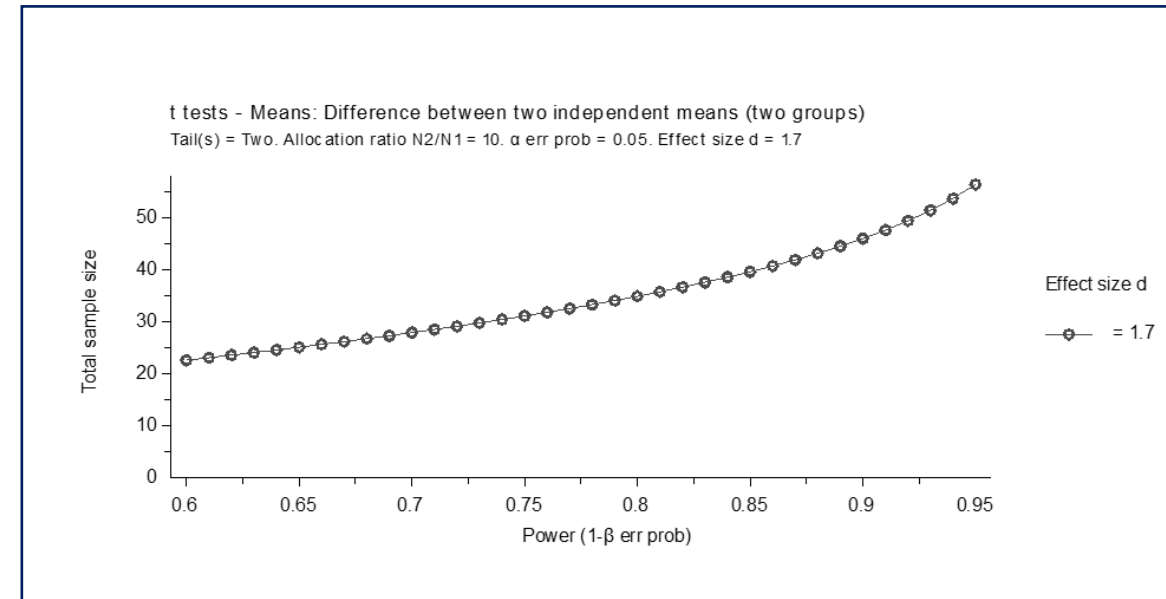
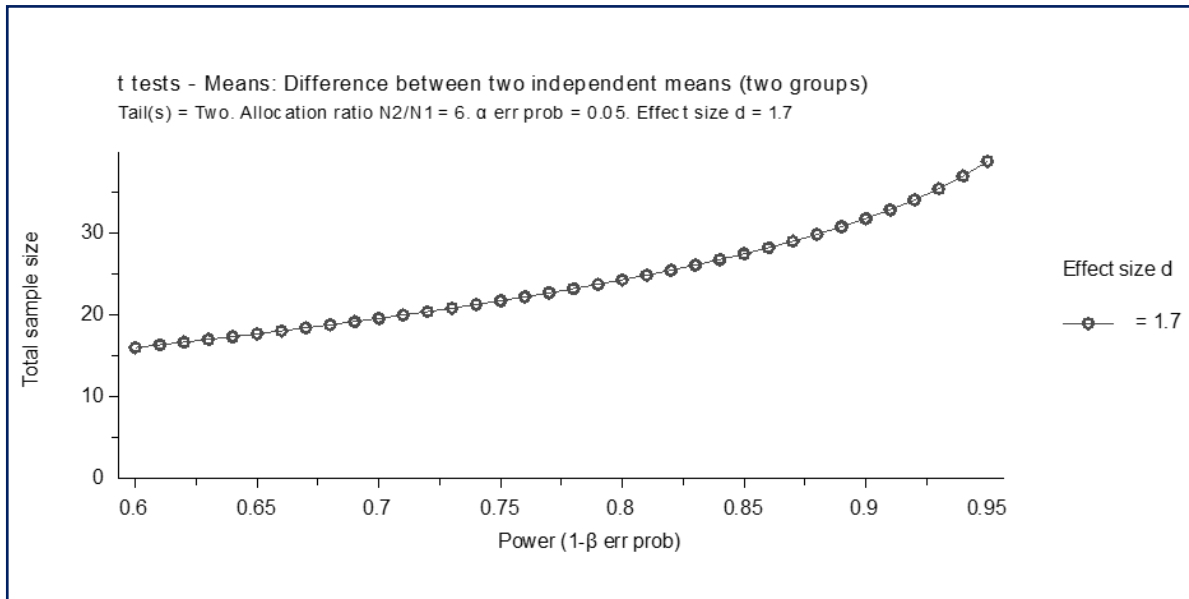
- To evaluate the prognostic/predictive role of basal plasmatic levels of **RANKL** and **Bone Turnover Markers** and the percentage of primary refractory mRCC patients treated with first line ICI or ICI-Tki combinations
- To evaluate the prognostic/predictive role of basal plasmatic levels of **RANKL** and the efficacy outcomes (ORR, TTTF, OS) in the same population
- To evaluate the prognostic/predictive role of basal plasmatic levels of **CTX**, **P1NP** and the efficacy outcomes (ORR, TTTF, OS) in the same population
- To evaluate the relationship between the variations (basal and after 2/3 months) of **RANKL**, **CTX**, **P1NP** and the efficacy outcome (ORR, TTF, OS) in the same population



SAMPLE SIZE ESTIMATION

Our previous data showed a mean value of RANKL in non-responder group of 532 pg/ml with a standard deviation of 216 compared to 260 pg/ml with a standard deviation of 86 corresponding to an Effect size d of 1.7

Considering a one tail t-test statistics with an alpha error probability of 0.05, a power of 0.90 and an allocation ratio of 6 in ICIs group and 10 in ICIs-TKI group we will enroll **32 patients in ICIs group** and **48 patients in ICIs-TKI group**



Methods

- mRCC patients treated with ICI as monotherapy or in combination with TKIs will be prospectively enrolled
- The inclusion criteria will be ≥ 18 years old patients, with a performance status of 0-1, no signs of active autoimmune disease, without presence of bone metastases and/or previous osteoporotic fractures.
- Plasma samples will be collected at the day of the first cycle of treatment before the infusion and after 2/3 months of treatment.
- RANKL and Bone Turnover Markers assessment will be performed by ELISA test

