

Table S1. List of randomized clinical trials that led to the approval of anticancer agents in RCC patients and the reported adverse events related to bone metabolism.

Clinical Trial	Trial Phase (Year of publication)	Histology - Line of treatment	Experimental Arm	Control Arm	Adverse Events							
					High Calcium	Low Calcium	Low Phosphate	Low Magnesium	High Magnesium	Fractures	BMD alterations	Osteoporosis
ARCC [1]	Phase III (2007)	ccRCC - FL	Temsirolimus - Temsirolimus + Interferon alfa	Interferon alfa	NR	NR	NR	NR	NR	NR	NR	NR
NCT00098657 [2]	Phase III (2007)	ccRCC - FL	Sunitinib	Interferon alfa	NR	NR	36% (AG)	NR	NR	NR	NR	NR
TARGET [3]	Phase III (2007)	ccRCC - SL	Sorafenib	Placebo	NR	NR	NR	NR	NR	NR	NR	NR
NCT00410124 [4]	Phase III (2008)	ccRCC - SL	Everolimus	Placebo	NR	17% (AG)	32% (AG)	NR	NR	NR	NR	NR
NCT00334282 [5]	Phase III (2010)	ccRCC - FL	Pazopanib	Placebo	NR	33% (AG)	34% (AG)	11% (AG)	NR	NR	NR	NR
AXIS [6]	Phase III (2011)	ccRCC - SL	Axitinib	Sorafenib	6% (AG)	39% (AG)	13% (AG)	NR	NR	NR	NR	NR
COMPARZ [7]	Phase III (2013)	ccRCC - FL	Pazopanib	Sunitinib	NR	NR	36% (AG)*	23% (AG)*	12% (AG)*	NR	NR	NR
NCT00920816 [8]	Phase III (2013)	ccRCC - FL	Axitinib	Sorafenib	NR	NR	NR	NR	NR	NR	NR	NR
CheckMate 025 [9]	Phase III (2015)	ccRCC - SL	Nivolumab	Everolimus	NR	NR	NR	NR	NR	NR	NR	NR
METEOR [10]	Phase III (2015)	ccRCC - SL	Cabozantinib	Everolimus	NR	NR	10% (AG)	16% (AG)	NR	NR	NR	NR
NCT01136733 [11]	Phase II (2015)	ccRCC - SL	Lenvatinib - Everolimus + Lenvatinib	Everolimus	NR	NR	NR	NR	NR	NR	NR	NR
ASPEN [12]	Phase II (2016)	nccRCC - FL	Sunitinib	Everolimus	NR	NR	NR	5% (G1-2)	NR	NR	NR	NR
CABOSUN [13]	Phase II (2016)	ccRCC - FL	Cabozantinib	Sunitinib	NR	NR	NR	NR	NR	NR	NR	NR
CheckMate 214 [14]	Phase III (2018)	ccRCC - FL	Ipilimumab + Nivolumab	Sunitinib	NR	NR	NR	NR	NR	NR	NR	NR

JAVELINE Renal 101 [15]	Phase III (2019)	ccRCC - FL	Axitinib + Avelumab	Sunitinib	NR	NR	NR	NR	NR	NR	NR	NR
KEYNOTE-426 [16]	Phase III (2019)	ccRCC - FL	Axitinib + Pembrolizumab	Sunitinib	NR	NR	NR	NR	NR	NR	NR	NR
TIVO-3 [17]	Phase III (2019)	ccRCC - SL	Tivozanib	Sorafenib	NR	NR	NR	NR	NR	NR	NR	NR
CheckMate 9ER [18]	Phase III (2021)	ccRCC - FL	Cabozantinib + Nivolumab	Sunitinib	NR	NR	14,4% (AG)	13,8% (AG)	NR	NR	NR	NR
CLEAR [19]	Phase III (2021)	ccRCC - FL	Lenvatinib + Pembrolizumab - Lenvatinib + Everolimus	Sunitinib	NR	1,4% (AG)**	NR	NR	NR	NR	NR	NR
SWOG 1500 [20]	Phase II (2021)	nccRCC - FL	Cabozantinib - Crizotinib - Savolitinib	Sunitinib	NR	10% (AG)	11% (AG)	9% (AG)	NR	NR	NR	NR

Adverse events reported in the Table refer to the “experimental arm”.

*Adverse events related to Sunitinib.

**Adverse events related to Lenvatinib_Pembrolizumab

Abbreviations: Any Grade (AG) - Clear Cell Renal Cell Carcinoma (ccRCC) – First Line (FL) – Not Clear Cell Renal Cell Carcinoma (nccRCC) - Not Reported (NR) – Renal Cell Carcinoma (RCC) - Subsequent Line (SL) – Von Hippel Lindau (VHL).

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