

SUPPLEMENTAL TABLE S1: overview of clinical results obtained for anti-VEGF agents

ANTI-ANGIOGENIC DRUG	INDICATION (TUMOR TYPE)	TUMOR STAGE / TREATMENT SETTING A	TREATMENT	PATIENTS (N)	IMPROVEMENT OF PFS (MONTHS) B	IMPROVEMENT OF OS (MONTHS) B	REFERENCE
Bevacizumab (BV) (Avastin®)	Breast Cancer	Metastatic / 2nd or 3rd line	Capecitabine ± BV (15 mg/kg) (3-weekly)	462	Not improved	Not improved	AVF2119 [133]
		Metastatic / 1st line	Paclitaxel ± BV (10 mg/kg) (2-weekly)	722	11.8 vs. 5.9 (p<0.0001)	Not improved	E2100 [134]
		Metastatic / 1st line	Docetaxel ± BV (7.5 mg/kg) or BV (15 mg/kg) (BV 3-weekly)	736	10.0 vs. 8.1 (p<0.001) (BV 15mg/kg) 10.0 vs 9.0 (p=0.45) (BV 7.5mg/kg)	Not reported (NR)	AVADO [135]
		Metastatic / 1st line	Capecitabine, Taxane or Anthracycline-based treatment ± BV (15 mg/kg) (-3weekly)	1237	Capecitabine cohort: 8.6 vs. 5.7 (p<0.001) Taxane/Anthracycline cohort: 9.2 vs. 8.0 (p=<0.001)	Not improved	RIBBON-1 [133]
		Metastatic / 2nd line	Chemotherapy* ± BV (15 mg/kg)(3-weekly)	684	7.2 vs. 5.1 (P=0.0072)	Not improved.	RIBBON-2 [133]
	Colorectal Cancer	Neoadjuvant	Epirubicin / Cyclophosphamide / Docetaxel ± BV (15mg/kg) (3-weekly)	1948	Rate of pathological complete response§: 14.9% vs. 18.4% (p=0.04)	NR	GeparQuinto [80]
		Metastatic / 1st line	IFL ± BV (5mg/kg) (2-weekly)	813	10.6 vs. 6.2 (p<0.001)	20.3 vs. 15.6 (p<0.001)	AVF2107 [136]
		Metastatic / 1st line	FOLFOX /XELOX ± BV (7.5mg/kg) (2-weekly with FOLFOX, 3-weekly with XELOX)	1401	9.4 vs. 8.0 (p=0.023)	21.3 v. 19.9 (p=0.077)	N016966 [133]
		Metastatic / 2nd line	FOLFOX ± BV (10 mg/kg) (2-weekly)	829	7.3 vs. 4.7 (p<0.0001)	12.9 vs. 10.8 (p=0.011)	E3200 [137]
		Metastatic / 1st line	Capecitabine and Capecitabine/Mitomycin ± BV (7.5 mg/kg)(3-weekly)	471	8.5 vs. 5.7 (p<0.001) (Capecitabine vs Capecitabine/BV) 8.4 vs. 5.7 (p<0.001) (Capecitabine vs. Capecitabine / Mitomycin /BV)	Not improved	MAX III [137]

	Metastatic / 1st line	FOLFIRI /BV (5mg/kg) (2-weekly) vs. modified bolus ILF/BV (7.5mg/kg)(3-weekly)	117	11.2 vs. 8.3 (p=0.28)	Not yet reached vs. 19.2 (p=0.007)	BICC-C [137]
	Metastatic / 1st line	BV (7.5mg/kg)(3-weekly) / Capecitabine/ Oxaliplatin ± Cetuximab	755	9.4 vs. 10.7 (p=0.01) (decreased upon addition of Cetuximab)	NR	CAIRO2 [82]
	Metastatic / 1st line	BV (dose chosen by investigator, 2-weekly) / Irinotecan- or Oxaliplatin ± Panitumumab	1053	10.0 vs. 11.7 (not significantly decreased upon addition of Panitumumab)	19.4 vs. 24.5 (significant) decreased upon addition of Panitumumab)	PACCE [133]
	Metastatic / 1st line	BV (5mg/kg, 2-weekly) + FOLFOX vs. BV (5mg/kg, 2-weekly) + FOLF + Cetuximab	247	Not improved	Not improved	[138]
	Metastatic / 2nd line after BV progression	Infusional or bolus fluorouracil with Irinotecan or Oxaliplatin ± BV (5mg/kg if 2-weekly, 7.5mg/kg if 3-weekly)	409	5.7 vs. 4.1 (p<0.0001)	11.2 vs. 9.8 (p=0.0062)	ML18147 [115]
	Adjuvant	FOLFOX ± BV (5mg/kg, 2-weekly)	2672	Not improved	NR	NSABPC-08 [113]
	Adjuvant	FOLFOX c BV (5mg/kg, 2-weekly) and XELOX ± BV (7.5mg/kg, 3-weekly),	3451	Not improved	Not improved	AVANT [133]
NSCLC	Locally advanced or metastatic (stage IIIB and IV) / 1st line	Carboplatin / Paclitaxel ± BV (15mg/kg, 3-weekly)	878	6.2 vs. 4.5 (p<0.001)	12.3 vs. 10.3 (p=0.003)	ECOG-E4599 [137]
	Locally advanced or metastatic (stage IIIB and IV) / 1st line	Cisplatin/ Gemcitabine ± BV (7.5 mg/kg or 15 mg/kg)	1043	Improved with BV: 7.5 mg/kg (p=0.0003) 15 mg/kg (p=0.0456)	Not improved	AVAIL [139]
	Recurrent /Refractory / 2nd line	Erlotinib ± BV (15mg/kg 3-weekly)	636	3.4 vs. 1.7 (significance not calculated for statistical reasons because primary endpoint OS not reached)	Not improved	BeTa[140]
Renal Cell Carcinoma	Metastatic / 1st line	Interferon α-2a ± BV (10mg/kg, 2-weekly)	649	10.2 vs. 5.4 (p<0.001)	Not improved	AVOREN [137]
	Metastatic / 1st line	Interferon alfa-2a ± BV (10 mg/kg	732	NR	Not improved	CALGB 90206 [141]
Glioblastoma	Recurrent / 2nd line or higher	BV (10 mg/kg, 2 weekly) ± Irinotecan	167 (Phase II)	5.6 vs. 4.2 (BV vs BV+Irinotecan)	9.2 vs. 8.7 (BV vs BV + Irinotecan)	[142]
	Recurrent / 2nd line or higher	BV (10 mg/kg, 2 weekly) monotherapy	48 (Phase II)	16 weeks (increased in comparison to a historic control group)	31 weeks (increased in comparison to a historic control group)	[137]
Ovarian Cancer	High risk stage I-IIA, stage III/IV (all grades,	Carboplatin/ Paclitaxel ± BV (7.5mg/kg, 3-weekly)	1528	24.1 vs. 22.4 (p=0.04)	Not improved	ICON7 [123]

		all histological types) / 1st line					
		Stage III/IV / 1st line	Carboplatin / Paclitaxel ± BV (15 mg/kg) (cycles 2 to 22)	1873	14.1 vs. 10.3 (p<0,001)	NR	GOG0218 [143]
		Recurrent / 2nd line	Gemcitabine / Carboplatin ± BV (15mg/kg, 3-weekly)	484	12.8 vs. 8.4 (p<0.001)	NR	OCEANS [144]
	Gastric Cancer	Unresectable locally advanced or metastatic / 1st line	Capecitabine or 5-FU and Cisplatin ± BV (7.5mg/kg, 3-weekly)	774	6.7 vs. 5.3 (p=0.037)	Not improved	AVAGAST [133]
	Pancreatic Cancer	Unresectable locally advanced or metastatic / 1st line	Gemcitabine ± BV (10mg/kg, 2-weekly)	535	Not improved	Not improved	CALG80303 [145]
		Metastatic / 1st line	Gemcitabine / Erlotinib ± BV (5mg/kg, 2-weekly)	301	4.6 vs. 3.6 (p=0.0002)	Not improved	AviTA [133]
	Prostate Cancer	Metastatic, castration resistant / 1st line	Docetaxel / Prednisolone ± BV (15mg/kg, 3-weekly)	1050	9.9 vs. 7.5 (p<0.001)	Not improved	CALBG90401 [133]
Aflibercept (Zaltrap®)	Colorectal Cancer	Metastatic / 2nd line	FOLFIRI ± Aflibercept (4mg/kg, 2-weekly)	1226	6.9 vs. 4.67 (p<0.001)	13.5 vs. 12.06 (p=0.0032)	VELOUR [86]
	Pancreatic Cancer	Metastatic / 1st line	Gemcitabine ± Aflibercept (4mg/kg, 2-weekly)	546	Not improved	Not improved	VANILLA [133] #
	NSCLC	Metastatic / 2nd line	Docetaxel ± Aflibercept (6mg/kg, 3-weekly)	913	5.2 vs. 4.1 (p=0.035)	Not improved	VITAL [146]
Sorafenib (Nexavar®)	Renal Cell Carcinoma	Unresectable locally advanced or metastatic / 2nd line	Sorafenib (400mg twice daily) vs. Placebo	903	5.5 vs. 2.8 (p<0.00001)	Not improved	TARGET [147]
	Hepatocellular Carcinoma	Unresectable locally advanced or metastatic / 1st line	Sorafenib (400mg twice daily) vs. Placebo	602	Not improved **	10.7 vs. 7.9 (p<0.001)	SHARP[148]
	Melanoma	Metastatic / 2nd line	Carboplatin / Paclitaxel ± Sorafenib (400mg twice daily)	270	Not improved	Not improved	PRISM [133]
	NSCLC	Unresectable locally advanced or metastatic / 1st line	Carboplatin / Paclitaxel ± Sorafenib (400mg twice daily)	926	Not improved	Not improved	ESCAPE [133]
Sunitinib (Sutent®)	Renal Cell Carcinoma	Metastatic / 1st line	Sunitinib (50mg daily, 4weeks on, 2 weeks off) vs. Interferon alfa-2a	755	11 vs. 5 (p<0.001)	26.4 vs. 21.8 (p=0.049)	NCT00083889[149]
	GIST	Unresectable locally advanced or metastatic / 2nd line (Imatinib resistant or refractory)	Sunitinib (50mg, 4weeks on, 2 weeks off) vs. Placebo	312	27.3 vs. 6.4 weeks (p=<0.0001)	NR	SUN1112[150]
	Pancreatic neuroendocrine tumors	Unresectable locally advanced or metastatic / 2nd line	Sunitinib (37.5mg daily) vs. Placebo	117	11.4 vs. 5.5 (p<0.001)	Improved***	NCT00428597 [151]

	Breast Cancer	Metastatic / 2nd line	Sunitinib (37.5mg daily) vs. Capecitabine	700	Not improved	Not improved	SUN1107 [133] #
		Metastatic / 1st line	Sunitinib (25 to 37.5mg, daily) + Paclitaxel vs. BV (10mg/kg, 2-weekly) + Paclitaxel	242	Not improved	NR	SUN1094 #
		Metastatic / 1st line	Docetaxel ± Sunitinib (37.5mg daily)	442	Not improved	Not improved	SUN1064 / NCT00393939 **** #
		Metastatic / 2nd line	Sunitinib (37.5mg daily) vs. Capecitabine	594	Not improved	Not improved	SUN1099 / NCT00373113 **** #
	Hepatocellular Carcinoma	Advanced /	Sunitinib monotherapy		NR	Not improved	SUN1170 **** #
	Colorectal Cancer	Metastatic / 1st line	FOLFIRI ± Sunitinib (37.5mg daily, 4 weeks on, 2 weeks off) +		Not improved	Not improved	SUN1122 / NCT00457691 **** #
	NSCLC	Metastatic/ 2nd or 3rd line	Erlotinib ± Sunitinib (37.5mg daily) + Erlotinib	960	3.6 vs. 2.0 (p=0.023)	Not improved	SUN1087
	Prostate Cancer	Metastatic, castration resistant / 2nd line	Prednisolone ± Sunitinib (37.5mg, daily)		24.1 vs. 17.9 weeks (p<0.001)	Not improved	SUN1120 NCT00676650 **** #
Pazopanib (Votrient®)	Renal Cell Carcinoma	Locally advanced / metastatic / 2nd line	Pazopanib (800mg daily) vs. Placebo	435	9.2 vs. 4.2 (p<0.0001)	Not improved	VEG105192 [152]
Vandetanib	NSCLC	Unresectable locally advanced or metastatic / 2nd line	Docetaxel. ± Vandetanib (100mg daily)	1391	4.0 vs. 3.2 (p<0.0001)	Not improved	ZODIAC [154]
		Unresectable locally advanced or metastatic / 2nd or 3rd line	Vandetanib (300mg daily) vs. Erlotinib	1240	Not improved	Not improved	ZEST [133]
		Unresectable locally advanced or metastatic / 2nd line	Pemetrexed ± Vandetanib (100mg daily)	534	Not improved	Not improved	ZEAL [133]
Vatalanib / PTK 787	Colorectal Cancer	Metastatic / 2nd line	FOLFOX ± Vatalanib (1250mg daily)	855	5.0 vs. 4.1 (p=0.026)	Not improved	CONFIRM2 [133]
		Metastatic / 1st line	FOLFOX ± Vatalanib (1250mg daily)	1168	Not improved	Not improved	CONFIRM1 [133]
Cediranib	Colorectal Cancer	Metastatic / 1st line	Modified FOLFOX + Cediranib (20 or 30mg daily) vs. modified FOLFOX + Bevacizumab (5mg/kg, 2-weekly)	1422	Not improved	Not improved	HORIZON III [156]
		Metastatic / 1st line	FOLFOX/CAPOX ± Cediranib (20 and 30mg daily)	860	Not improved	Not improved	HORIZON II

	Glioblastoma	Recurrent 2nd line	Cediranib (30mg) vs Cediranib 30mg daily + Lomustine vs. Lomustine	325	Not improved	Not improved	REGAL / NCT00777153 ****
Axitinib	Renal Cell Carcinoma	Metastatic / 2nd line	Axitinib (5 mg twice daily) vs. Sorafenib (400mg twice daily)	732	8.3 vs. 5.7 (p<0.0001)	Not improved	NCT00678392 [157]
	Pancreatic Cancer	Metastatic and advanced / 1st line	Gemcitabine ± Axitinib (5 to 10mg daily)	630	Not improved	Not improved	NCT00471146

- ^a anti-angiogenic treatment vs. non-anti-angiogenic treatment if not mentioned otherwise
- ^b referring to treatment setting: 1st line; 2nd line ; 3rd line
- BV: bevacizumab; NR: not reported
- * Different agents including Capecitabine, protein-bound Paclitaxel, Paclitaxel, Docetaxel, Gemcitabine, Vinorelbine.
- ** no difference in median time to symptomatic progression, statistical significant difference in median time to radiologic progression (5.5 vs. 2.8 month; p<0.001).
- *** The study was discontinued after independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo group.
- **** citation not available
- # Study discontinued by investigator.
- § pathological complete response: surrogate marker for long-term outcome.