

SUPPLEMENTAL MATERIALS

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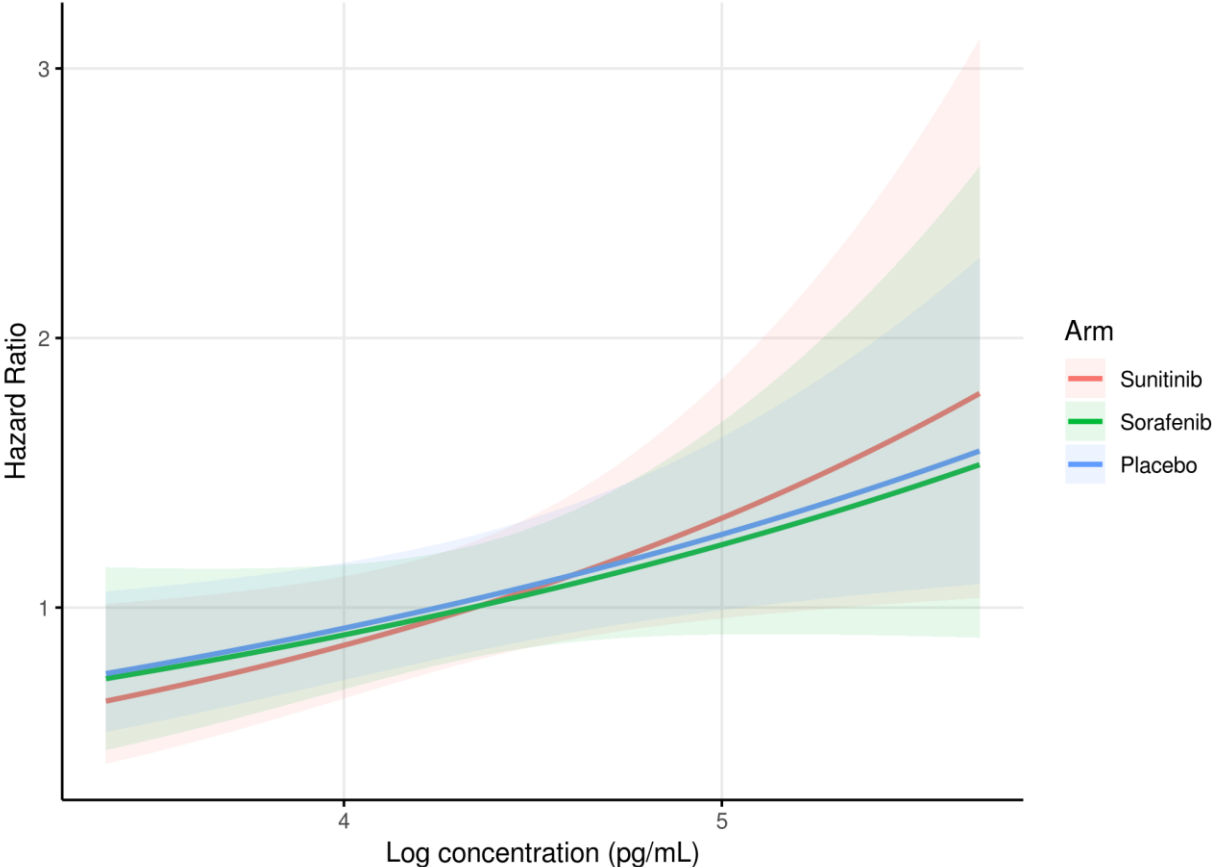
Supplemental Table 5: Evaluation for interaction effects between treatment arm and the association between baseline CXCL10 and DFS

Supplemental Table 1: MSD assays used for cytokine measurement

Cytokine(s)	MSD Catalog Number
IL8, CXCL9, CXCL10, CXCL11	N75CA (custom multiplex)
VEGF, sFlt1, PlGF, bFGF	N75CA (custom multiplex)
sVEGFR-2	K151BOC
Ang2	N45ZA
IFN γ	K151AEC
HGF	K15029C

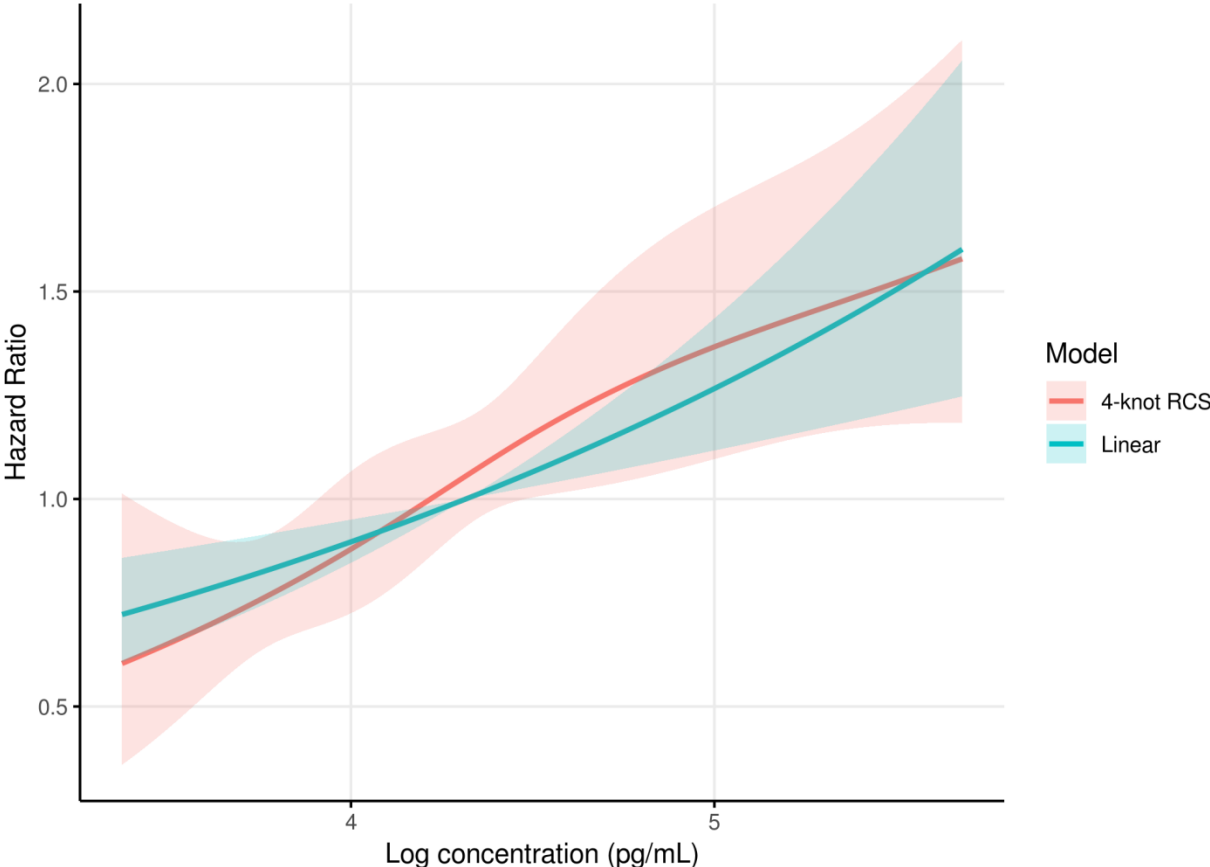
Supplemental Figure 1: Hazard ratio for CXCL10 and DFS by treatment arm

Plot of predicted hazard ratio from a Cox model including interaction between CXCL10 and treatment arm. There was no significant difference seen in the CXCL10 effect on DFS between treatment arms.



Supplemental Figure 2: Assessment of log-linearity for relationship between IP-10 and recurrence risk

Predicted HR over the range of IP-10 values for both the linear model and a model using a restricted cubic spline with 4 knots.



Supplemental Table 2: Median changes in cytokines at weeks 4 and 6

Raw median and range values for changes in each cytokine at weeks 4 and 6 are presented.

Molecule	Arm	Post-tx time point	Median fold change	Range
Ang2	Sunitinib	Week 4	0.79	(0.21, 4.95)
		Week 6	1.03	(0.35, 2.85)
	Sorafenib	Week 4	1.16	(0.00, 5.06)
		Week 6	1.10	(0.18, 2.96)
	Placebo	Week 4	1.06	(0.37, 3.41)
		Week 6	1.01	(0.27, 4.03)
bFGF	Sunitinib	Week 4	0.96	(0.14, 12.79)
		Week 6	1.29	(0.25, 8.65)
	Sorafenib	Week 4	0.92	(0.08, 21.92)
		Week 6	0.98	(0.24, 9.43)
	Placebo	Week 4	1.07	(0.10, 6.68)
		Week 6	0.81	(0.31, 4.64)
HGF	Sunitinib	Week 4	1.01	(0.22, 2.32)
		Week 6	1.00	(0.42, 10.08)
	Sorafenib	Week 4	0.91	(0.25, 2.73)
		Week 6	0.96	(0.15, 2.84)
	Placebo	Week 4	1.05	(0.26, 3.50)
		Week 6	1.00	(0.48, 3.56)
IFN-g	Sunitinib	Week 4	1.35	(0.00, 42.05)
		Week 6	1.09	(0.04, 62.09)
	Sorafenib	Week 4	1.05	(0.01, 122.72)
		Week 6	1.06	(0.05, 18.04)
	Placebo	Week 4	1.04	(0.02, 435.42)

		Week 6	0.96	(0.01, 20.34)
IL-8	Sunitinib	Week 4	2.00	(0.00, 335.22)
		Week 6	0.56	(0.00, 298.38)
	Sorafenib	Week 4	1.46	(0.00, 165.27)
		Week 6	1.00	(0.00, 38.47)
	Placebo	Week 4	1.28	(0.00, 452.42)
		Week 6	0.91	(0.01, 577.22)
CXCL10	Sunitinib	Week 4	2.19	(0.80, 40.31)
		Week 6	1.17	(0.45, 4.42)
	Sorafenib	Week 4	1.62	(0.25, 24.92)
		Week 6	1.14	(0.32, 56.34)
	Placebo	Week 4	1.10	(0.48, 46.71)
		Week 6	1.02	(0.09, 8.13)
CXCL11	Sunitinib	Week 4	1.18	(0.44, 7.55)
		Week 6	1.07	(0.32, 3.14)
	Sorafenib	Week 4	1.19	(0.29, 13.20)
		Week 6	1.11	(0.14, 4.24)
	Placebo	Week 4	1.01	(0.16, 5.68)
		Week 6	1.00	(0.41, 4.92)
sVEGFR-2	Sunitinib	Week 4	0.64	(0.29, 1.12)
		Week 6	0.77	(0.27, 1.67)
	Sorafenib	Week 4	0.74	(0.13, 1.35)
		Week 6	0.80	(0.38, 1.33)
	Placebo	Week 4	0.95	(0.71, 1.41)
		Week 6	1.08	(0.49, 1.67)
MIG	Sunitinib	Week 4	2.02	(0.71, 33.46)

		Week 6	1.00	(0.35, 6.22)
	Sorafenib	Week 4	1.24	(0.28, 39.86)
		Week 6	1.08	(0.41, 26.94)
	Placebo	Week 4	0.98	(0.12, 2.33)
		Week 6	0.90	(0.40, 4.99)
PIGF	Sunitinib	Week 4	3.64	(0.15, 32.49)
		Week 6	1.08	(0.34, 10.12)
	Sorafenib	Week 4	1.86	(0.49, 9.34)
		Week 6	1.53	(0.61, 7.23)
	Placebo	Week 4	0.93	(0.19, 2.68)
		Week 6	0.98	(0.21, 1.93)
sFlt-1	Sunitinib	Week 4	0.84	(0.33, 2.19)
		Week 6	0.93	(0.24, 3.31)
	Sorafenib	Week 4	0.90	(0.27, 3.58)
		Week 6	0.77	(0.13, 3.92)
	Placebo	Week 4	1.07	(0.33, 6.62)
		Week 6	0.95	(0.27, 2.64)
VEGF	Sunitinib	Week 4	1.69	(0.47, 8.68)
		Week 6	1.03	(0.27, 3.43)
	Sorafenib	Week 4	1.20	(0.30, 11.03)
		Week 6	1.27	(0.31, 6.98)
	Placebo	Week 4	0.99	(0.21, 3.54)
		Week 6	0.93	(0.26, 1.79)

Supplemental Table 3: Relationship between on-treatment cytokine levels and DFS

Results are shown after adjusting for baseline levels in the mixed effects model. P-values are adjusted using the Bonferroni correction.

	HR	95% CI	Adjusted p-value
Ang2	1.21	(0.97, 1.50)	1
bFGF	1.13	(0.94, 1.36)	1
HGF	1.47	(1.13, 1.93)	0.056
IFN γ	0.96	(0.83, 1.10)	1
IL8	1	(0.93, 1.08)	1
CXCL10	1.05	(0.89, 1.23)	1
CXCL11	1.11	(0.89, 1.38)	1
sVEGFR-2	0.88	(0.60, 1.29)	1
CXCL9	1.04	(0.89, 1.21)	1
PlGF	1.13	(0.92, 1.38)	1
sFlt1	1.12	(0.80, 1.56)	1
VEGF	1.24	(0.99, 1.56)	0.73

Supplemental Table 4: Subset analysis for cytokine changes among patients who did not recur

Changes at week 4 and week 6 are presented for each cytokine and treatment arm among the subset of patients who did not have disease recurrence. A repeated measures model was used to estimate baseline and followup values for each cytokine, and to test for differences between baseline and post-treatment time points.

Molecule	Arm	Post-tx time point	Log change from baseline (pg/mL)	95% CI (Lower)	95% CI (Upper)	Bonferroni adjusted p
Ang2	Sunitinib	Week 4	-0.1021	0.1193	-0.3234	1
Ang2	Sorafenib	Week 4	0.00137	0.1959	-0.1932	1
Ang2	Placebo	Week 4	0.00226	0.1905	-0.186	1
			-			
Ang2	Sunitinib	Week 6	0.05743	0.03713	-0.152	1
Ang2	Sorafenib	Week 6	0.06227	0.1496	-0.0251	1
			-			
Ang2	Placebo	Week 6	-0.1324	0.03754	-0.2273	0.46
bFGF	Sunitinib	Week 4	-0.1206	0.07924	-0.3205	1
bFGF	Sorafenib	Week 4	0.00312	0.1756	-0.1694	1
bFGF	Placebo	Week 4	-0.059	0.1109	-0.2289	1
bFGF	Sunitinib	Week 6	0.4021	0.5654	0.2388	<0.001
bFGF	Sorafenib	Week 6	0.2744	0.4275	0.1212	0.035
bFGF	Placebo	Week 6	-0.1113	0.05182	-0.2745	1.000
CXCL10	Sunitinib	Week 4	1.0961	1.2863	0.9058	<0.001
CXCL10	Sorafenib	Week 4	0.6165	0.776	0.4571	<0.001
CXCL10	Placebo	Week 4	0.3001	0.4719	0.1283	0.048
CXCL10	Sunitinib	Week 6	0.2627	0.3652	0.1602	<0.001
CXCL10	Sorafenib	Week 6	0.1808	0.2801	0.08152	0.028
CXCL10	Placebo	Week 6	0.115	0.2188	0.01114	1.000
			-			
HGF	Sunitinib	Week 4	0.0329	0.1178	0.05196	1.000
			-			
HGF	Sorafenib	Week 4	0.05159	0.01991	-0.1231	1.000
			-			
HGF	Placebo	Week 4	0.00333	0.07335	0.08002	1.000
			-			
HGF	Sunitinib	Week 6	0.05532	0.1257	0.01504	1.000
			-			
HGF	Sorafenib	Week 6	0.08723	0.01913	-0.1553	0.878
HGF	Placebo	Week 6	0.0023	0.07351	-0.0689	1.000
			-			
IFNg	Sunitinib	Week 4	0.02463	0.4547	-0.5039	1.000

IFNg	Sorafenib	Week 4	0.114	0.5086	-0.2806	1.000
			-			
IFNg	Placebo	Week 4	0.00623	0.4033	-0.4158	1.000
IFNg	Sunitinib	Week 6	0.3268	0.6088	0.04488	1.000
IFNg	Sorafenib	Week 6	-0.1638	0.1245	-0.4521	1.000
			-			
IFNg	Placebo	Week 6	0.03261	0.2612	-0.3264	1.000
IL8	Sunitinib	Week 4	0.3463	0.8265	-0.134	1.000
			-			
IL8	Sorafenib	Week 4	0.3518	0.7695	0.06603	1.000
IL8	Placebo	Week 4	1.0729	1.5069	0.639	<0.001
IL8	Sunitinib	Week 6	-0.1045	0.2944	-0.5034	1.000
IL8	Sorafenib	Week 6	-0.8608	-0.4657	-1.2558	0.002
IL8	Placebo	Week 6	-0.1363	0.2672	-0.5399	1.000
ITAC	Sunitinib	Week 4	0.2965	0.4265	0.1664	0.001
ITAC	Sorafenib	Week 4	0.2098	0.3189	0.1007	0.013
			-			
ITAC	Placebo	Week 4	0.03401	0.08322	-0.1512	1.000
ITAC	Sunitinib	Week 6	0.1568	0.2509	0.06273	0.083
			-			
ITAC	Sorafenib	Week 6	0.05396	0.1447	0.03679	1.000
			-			
ITAC	Placebo	Week 6	0.08153	0.1765	0.01345	1.000
KDR	Sunitinib	Week 4	-0.4932	-0.4418	-0.5446	<0.001
KDR	Sorafenib	Week 4	-0.2877	-0.2438	-0.3315	0.000
			-			
KDR	Placebo	Week 4	0.02166	0.02171	0.06502	1.000
KDR	Sunitinib	Week 6	-0.2478	-0.1954	-0.3002	<0.001
KDR	Sorafenib	Week 6	-0.2451	-0.1964	-0.2937	<0.001
			-			
KDR	Placebo	Week 6	0.04411	0.00831	0.09654	1.000
MIG	Sunitinib	Week 4	1.045	1.22	0.8699	<0.001
MIG	Sorafenib	Week 4	0.4507	0.5979	0.3036	<0.001
			-			
MIG	Placebo	Week 4	0.02218	0.1362	-0.1806	1.000
			-			
MIG	Sunitinib	Week 6	0.04591	0.1453	0.05345	1.000
			-			
MIG	Sorafenib	Week 6	0.08672	0.1829	0.00943	1.000
			-			
MIG	Placebo	Week 6	0.0551	0.1557	0.04547	1.000
PIGF	Sunitinib	Week 4	1.3394	1.4653	1.2135	<0.001
PIGF	Sorafenib	Week 4	0.5816	0.691	0.4723	<0.001
PIGF	Placebo	Week 4	-0.1058	0.0001	-0.2117	1.000
PIGF	Sunitinib	Week 6	0.2142	0.315	0.1133	0.003

PIGF	Sorafenib	Week 6	0.5055	0.6003	0.4107	<0.001
PIGF	Placebo	Week 6	-0.1596	-0.0579	-0.2614	0.158
SFlt1	Sunitinib	Week 4	-0.2415	-0.1625	-0.3206	0.000
			-			
SFlt1	Sorafenib	Week 4	0.04771	0.02108	-0.1165	1.000
SFlt1	Placebo	Week 4	0.02356	0.08986	0.04273	1.000
			-			
SFlt1	Sunitinib	Week 6	0.03404	0.0293	0.09737	1.000
SFlt1	Sorafenib	Week 6	-0.146	0.08593	-0.206	<0.001
			-			
SFlt1	Placebo	Week 6	0.04758	0.01631	-0.1115	1.000
VEGF	Sunitinib	Week 4	0.6297	0.757	0.5023	<0.001
VEGF	Sorafenib	Week 4	0.2543	0.3655	0.1431	0.001
VEGF	Placebo	Week 4	-0.1596	0.05232	-0.2669	0.263
VEGF	Sunitinib	Week 6	0.03211	0.1452	0.08098	1.000
VEGF	Sorafenib	Week 6	0.2921	0.3974	0.1868	<0.001
			-			
VEGF	Placebo	Week 6	0.01503	0.09872	-0.1288	1.000

Supplemental Table 5: Evaluation for interaction effects between treatment arm and the association between baseline CXCL10 and DFS

We assessed for interaction terms between baseline CXCL10 and treatment arm. There were no statistically significant interactions in this setting.

	HR	95% CI	p-value
Baseline log CXCL10	1.37	(1.07, 1.77)	0.013
Sunitinib	0.58	(0.07, 4.53)	0.60
Sorafenib	0.98	(0.12, 7.92)	0.98
CXCL10 : Sunitinib	1.13	(0.71, 1.78)	0.61
CXCL10 : Sorafenib	1.00	(0.63, 1.59)	0.99