

**Table S1A. Time-to-Efficacy Signals Comparison for a moderately active control**

**regimen.** This analysis applied a complete response rate ~5% and partial response rate ~30%. We performed one hundredfold / thousandfold simulations of time to study positivity as a function of sample size for Kaplan-Meier estimation of Progression Free Survival and Overall Survival, and for Chauhan Weighted Trajectory Analysis (CWTA) for a range of hazard ratios. CWTA demonstrated consistently shorter time to study positivity; this effect was most profound in studies with a highly effective intervention (that is, a low hazard ratio).

HR	SS	Time-to-Efficacy (months; mean $\pm$ SD)			CWTA vs PFS		CWTA vs OS	
		CWTA	PFS	OS	% $\Delta$ t	P-value	% $\Delta$ t	P-value
0.5	30	25.0 $\pm$ 14	34.8 $\pm$ 12	44.2 $\pm$ 8	28%	<0.0001	43%	<0.0001
	60	20.7 $\pm$ 13	29.1 $\pm$ 12	40.3 $\pm$ 8	29%	<0.0001	49%	<0.0001
	90	16.4 $\pm$ 12	26.8 $\pm$ 11	37.2 $\pm$ 8	39%	<0.0001	56%	<0.0001
	120	13.6 $\pm$ 9	23.6 $\pm$ 11	33.6 $\pm$ 7	43%	<0.0001	60%	<0.0001
	150	12.4 $\pm$ 9	22.6 $\pm$ 10	33.1 $\pm$ 7	45%	<0.0001	62%	<0.0001
	180	10.2 $\pm$ 8	21.1 $\pm$ 8	32.0 $\pm$ 6	52%	<0.0001	68%	<0.0001
	210	9.7 $\pm$ 7	19.6 $\pm$ 8	29.0 $\pm$ 5	51%	<0.0001	67%	<0.0001
	240	8.5 $\pm$ 7	20.4 $\pm$ 8	30.7 $\pm$ 6	58%	<0.0001	72%	<0.0001
	270	7.9 $\pm$ 6	18.6 $\pm$ 8	28.7 $\pm$ 5	58%	<0.0001	73%	<0.0001
	300	7.0 $\pm$ 5	17.0 $\pm$ 6	27.7 $\pm$ 5	59%	<0.0001	75%	<0.0001
	350	6.2 $\pm$ 5	15.9 $\pm$ 7	27.3 $\pm$ 5	61%	<0.0001	77%	<0.0001
	400	5.4 $\pm$ 4	14.9 $\pm$ 6	25.9 $\pm$ 5	64%	<0.0001	79%	<0.0001
	500	4.8 $\pm$ 4	13.6 $\pm$ 6	25.0 $\pm$ 4	65%	<0.0001	81%	<0.0001
0.6	30	28.7 $\pm$ 16	37.1 $\pm$ 12	45.8 $\pm$ 8	23%	<0.005	37%	<0.0001
	60	26.4 $\pm$ 15	32.8 $\pm$ 13	42.8 $\pm$ 9	20%	<0.005	38%	<0.0001
	90	20.4 $\pm$ 14	30.2 $\pm$ 13	39.4 $\pm$ 9	32%	<0.0001	48%	<0.0001
	120	19.1 $\pm$ 12	28.7 $\pm$ 12	38.1 $\pm$ 9	33%	<0.0001	50%	<0.0001
	150	19.7 $\pm$ 13	28.9 $\pm$ 13	35.7 $\pm$ 8	32%	<0.0001	45%	<0.0001
	180	16.8 $\pm$ 13	25.8 $\pm$ 12	32.9 $\pm$ 8	35%	<0.0001	49%	<0.0001
	210	14.2 $\pm$ 10	22.6 $\pm$ 12	32.2 $\pm$ 8	37%	<0.0001	56%	<0.0001
	240	12.5 $\pm$ 9	21.6 $\pm$ 11	31.6 $\pm$ 7	42%	<0.0001	61%	<0.0001
	270	11.6 $\pm$ 8	21.4 $\pm$ 9	31.5 $\pm$ 7	46%	<0.0001	63%	<0.0001
	300	10.2 $\pm$ 9	20.7 $\pm$ 10	29.9 $\pm$ 6	51%	<0.0001	66%	<0.0001
	350	8.9 $\pm$ 6	19.1 $\pm$ 9	29.2 $\pm$ 7	53%	<0.0001	70%	<0.0001
	400	8.9 $\pm$ 6	17.3 $\pm$ 8	27.7 $\pm$ 6	49%	<0.0001	68%	<0.0001
	500	6.2 $\pm$ 5	16.8 $\pm$ 8	27.3 $\pm$ 5	63%	<0.0001	77%	<0.0001
0.7	30	30.9 $\pm$ 16	37.6 $\pm$ 12	43.1 $\pm$ 6	18%	<0.05	28%	<0.0001

	60	26.1 ± 17	31.7 ± 14	41.7 ± 8	18%	<0.05	37%	<0.0001
	90	23.2 ± 16	30.8 ± 15	39.6 ± 10	25%	<0.005	41%	<0.0001
	120	23.5 ± 16	31.8 ± 14	39.7 ± 10	26%	<0.0005	41%	<0.0001
	150	22.6 ± 16	28.4 ± 14	35.6 ± 9	20%	<0.05	36%	<0.0001
	180	20.1 ± 15	26.7 ± 14	37.6 ± 10	25%	<0.005	46%	<0.0001
	210	19.3 ± 13	28.9 ± 14	37.4 ± 10	33%	<0.0001	48%	<0.0001
	240	19.0 ± 14	24.9 ± 12	35.7 ± 9	24%	<0.005	47%	<0.0001
	270	19.0 ± 13	24.6 ± 12	33.9 ± 9	23%	<0.005	44%	<0.0001
	300	16.1 ± 12	25.8 ± 13	34.3 ± 9	38%	<0.0001	53%	<0.0001
	350	14.8 ± 12	23.4 ± 12	32.8 ± 9	37%	<0.0001	55%	<0.0001
	400	13.7 ± 12	23.8 ± 12	33.3 ± 7	42%	<0.0001	59%	<0.0001
	500	12.2 ± 10	22.2 ± 9	31.1 ± 7	45%	<0.0001	61%	<0.0001
0.8 (1000- fold)	30	27.4 ± 15	31.7 ± 12	43.6 ± 8	14%	0.19	37%	<0.0001
	60	26.0 ± 16	30.0 ± 13	41.5 ± 9	14%	0.18	37%	<0.0001
	90	24.3 ± 16	28.1 ± 13	40.1 ± 10	14%	0.19	39%	<0.0001
	120	25.7 ± 17	29.4 ± 15	39.3 ± 10	13%	0.22	35%	<0.0001
	150	24.1 ± 17	28.3 ± 15	38.2 ± 11	15%	0.13	37%	<0.0001
	180	24.5 ± 17	28.1 ± 15	37.8 ± 11	13%	0.18	35%	<0.0001
	210	24.6 ± 17	28.5 ± 15	38.1 ± 11	14%	0.14	36%	<0.0001
	240	23.3 ± 16	28.2 ± 15	37.1 ± 11	17%	0.05	37%	<0.0001
	270	22.9 ± 16	27.9 ± 15	36.7 ± 11	18%	<0.05	38%	<0.0001
	300	23.4 ± 16	27.2 ± 15	36.9 ± 11	14%	0.12	37%	<0.0001
	350	21.9 ± 15	26.6 ± 14	36.3 ± 11	18%	<0.05	40%	<0.0001
	400	21.7 ± 15	26.7 ± 15	34.9 ± 10	19%	<0.05	38%	<0.0001
	500	20.5 ± 14	26.1 ± 14	35.1 ± 10	22%	<0.05	42%	<0.0001

**Table S1B. Time-to-Efficacy Signals Comparison for highly active control regimen.**

This is a sensitivity analysis using a complete response rate ~10% and partial response rate ~50%. We performed one hundredfold / thousandfold simulations of time to study positivity as a function of sample size for Kaplan-Meier estimation of Progression Free Survival and Overall Survival, and for Chauhan Weighted Trajectory Analysis (CWTA) for a range of hazard ratios. CWTA demonstrated consistently shorter time to study positivity; this effect was most profound in studies with a highly effective intervention (that is, a low hazard ratio).

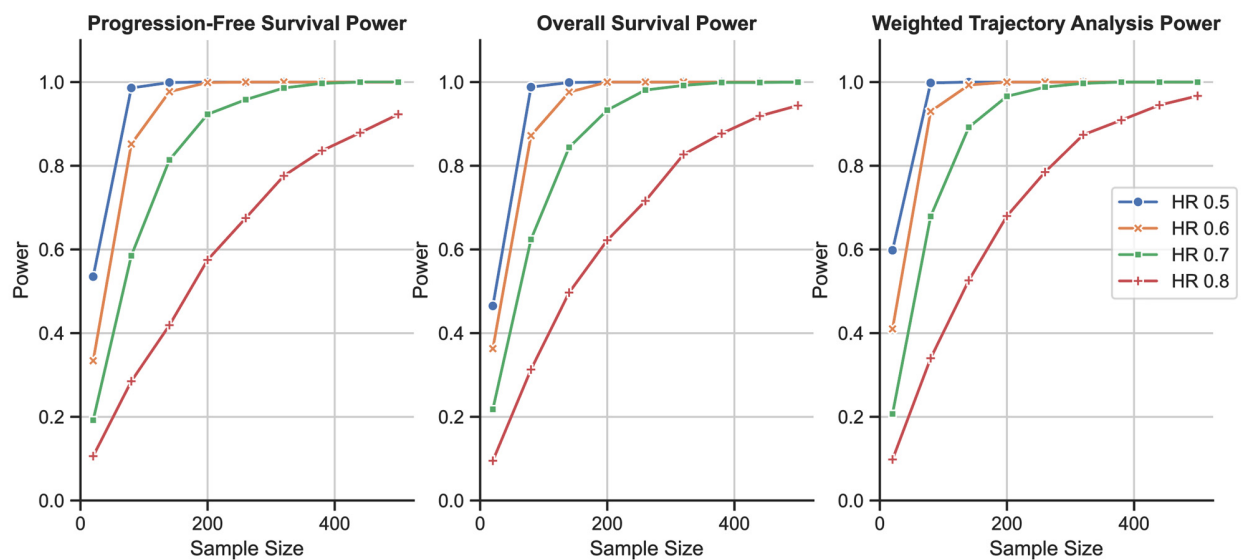
HR	SS	Time-to-Efficacy (months; mean $\pm$ SD)			CWTA vs PFS		CWTA vs OS	
		CWTA	PFS	OS	% $\Delta$ t	P-value	% $\Delta$ t	P-value
0.5	30	21.4 $\pm$ 16	34.1 $\pm$ 12	45.0 $\pm$ 7	37%	<0.0001	52%	<0.0001
	60	14.7 $\pm$ 12	28.5 $\pm$ 12	38.7 $\pm$ 8	49%	<0.0001	62%	<0.0001
	90	11.4 $\pm$ 8	24.2 $\pm$ 11	34.8 $\pm$ 7	53%	<0.0001	67%	<0.0001
	120	8.3 $\pm$ 8	20.8 $\pm$ 8	34.4 $\pm$ 8	60%	<0.0001	76%	<0.0001
	150	7.9 $\pm$ 7	18.9 $\pm$ 7	30.2 $\pm$ 6	58%	<0.0001	74%	<0.0001
	180	5.6 $\pm$ 4	18.1 $\pm$ 7	29.3 $\pm$ 5	69%	<0.0001	81%	<0.0001
	210	4.7 $\pm$ 4	16.3 $\pm$ 6	28.2 $\pm$ 5	71%	<0.0001	83%	<0.0001
	240	4.1 $\pm$ 3	15.2 $\pm$ 6	27.8 $\pm$ 5	73%	<0.0001	85%	<0.0001
	270	4.1 $\pm$ 3	14.7 $\pm$ 6	26.7 $\pm$ 5	72%	<0.0001	85%	<0.0001
	300	4.1 $\pm$ 4	14.8 $\pm$ 6	26.6 $\pm$ 5	72%	<0.0001	85%	<0.0001
	350	3.3 $\pm$ 3	13.5 $\pm$ 5	25.2 $\pm$ 5	76%	<0.0001	87%	<0.0001
	400	3.3 $\pm$ 2	12.3 $\pm$ 5	24.9 $\pm$ 5	73%	<0.0001	87%	<0.0001
	500	2.8 $\pm$ 2	11.9 $\pm$ 5	22.9 $\pm$ 4	76%	<0.0001	88%	<0.0001
0.6	30	24.4 $\pm$ 17	32.5 $\pm$ 12	45.5 $\pm$ 8	25%	<0.005	46%	<0.0001
	60	18.4 $\pm$ 15	28.8 $\pm$ 14	41.4 $\pm$ 9	36%	<0.0001	56%	<0.0001
	90	19.3 $\pm$ 14	26.4 $\pm$ 12	38.4 $\pm$ 8	27%	<0.0005	50%	<0.0001
	120	13.8 $\pm$ 11	25.7 $\pm$ 11	35.4 $\pm$ 8	46%	<0.0001	61%	<0.0001
	150	12.9 $\pm$ 10	24.2 $\pm$ 11	34.2 $\pm$ 8	47%	<0.0001	62%	<0.0001
	180	8.8 $\pm$ 7	19.5 $\pm$ 9	32.2 $\pm$ 7	55%	<0.0001	73%	<0.0001
	210	11.0 $\pm$ 8	19.6 $\pm$ 9	30.9 $\pm$ 7	44%	<0.0001	64%	<0.0001
	240	8.0 $\pm$ 7	18.0 $\pm$ 8	29.3 $\pm$ 7	55%	<0.0001	73%	<0.0001
	270	8.3 $\pm$ 7	19.1 $\pm$ 9	29.7 $\pm$ 7	57%	<0.0001	72%	<0.0001
	300	6.6 $\pm$ 6	16.9 $\pm$ 7	27.6 $\pm$ 6	61%	<0.0001	76%	<0.0001
	350	5.5 $\pm$ 5	16.0 $\pm$ 7	27.0 $\pm$ 6	66%	<0.0001	80%	<0.0001
	400	5.8 $\pm$ 5	15.1 $\pm$ 7	26.4 $\pm$ 6	61%	<0.0001	78%	<0.0001
	500	4.6 $\pm$ 3	13.9 $\pm$ 6	25.7 $\pm$ 5	67%	<0.0001	82%	<0.0001
0.7	30	24.6 $\pm$ 15	34.8 $\pm$ 12	44.3 $\pm$ 8	29%	<0.0005	44%	<0.0001

	60	22.3 ± 15	31.5 ± 15	41.5 ± 10	29%	<0.0005	46%	<0.0001
	90	20.4 ± 17	30.4 ± 16	41.0 ± 10	33%	<0.0001	50%	<0.0001
	120	18.9 ± 15	28.3 ± 13	38.7 ± 9	33%	<0.0001	51%	<0.0001
	150	19.6 ± 16	26.4 ± 13	38.2 ± 10	26%	<0.005	49%	<0.0001
	180	17.6 ± 14	28.7 ± 13	34.9 ± 10	39%	<0.0001	50%	<0.0001
	210	16.0 ± 13	26.3 ± 13	34.7 ± 9	39%	<0.0001	54%	<0.0001
	240	14.8 ± 12	22.8 ± 13	33.3 ± 9	35%	<0.0001	55%	<0.0001
	270	14.2 ± 11	22.2 ± 11	33.2 ± 9	36%	<0.0001	57%	<0.0001
	300	13.1 ± 9	22.2 ± 10	31.6 ± 9	41%	<0.0001	58%	<0.0001
	350	12.5 ± 10	21.0 ± 10	31.6 ± 8	41%	<0.0001	61%	<0.0001
	400	10.3 ± 10	19.1 ± 11	31.2 ± 9	46%	<0.0001	67%	<0.0001
	500	9.7 ± 7	17.3 ± 9	27.3 ± 7	44%	<0.0001	64%	<0.0001
0.8 (1000- fold)	30	23.1 ± 17	30.8 ± 13	43.3 ± 9	25%	<0.05	47%	<0.0001
	60	22.8 ± 17	28.7 ± 14	40.3 ± 10	21%	0.06	44%	<0.0001
	90	22.6 ± 17	28.6 ± 14	40.5 ± 10	21%	<0.05	44%	<0.0001
	120	21.4 ± 17	28.9 ± 15	38.8 ± 11	26%	<0.05	45%	<0.0001
	150	22.2 ± 16	27.8 ± 15	38.2 ± 11	20%	<0.05	42%	<0.0001
	180	22.5 ± 17	27.9 ± 14	37.9 ± 11	19%	<0.05	41%	<0.0001
	210	22.4 ± 17	27.1 ± 15	37.9 ± 11	17%	0.05	41%	<0.0001
	240	21.4 ± 16	26.4 ± 15	37.0 ± 11	19%	<0.05	42%	<0.0001
	270	21.8 ± 16	27.6 ± 15	36.8 ± 11	21%	<0.05	41%	<0.0001
	300	20.2 ± 15	26.8 ± 14	35.9 ± 11	25%	<0.005	44%	<0.0001
	350	19.2 ± 15	25.9 ± 14	35.3 ± 11	26%	<0.005	46%	<0.0001
	400	18.3 ± 14	25.2 ± 14	34.3 ± 11	27%	<0.005	47%	<0.0001
	500	16.2 ± 13	24.3 ± 13	32.9 ± 10	33%	<0.0001	51%	<0.0001

**Table S2. 80% Power Sample Size Interpolation for Kaplan-Meier estimation of Progression-Free Survival and Overall Survival, and Chauhan Weighted Trajectory Analysis (CWTA) across a range of hazard ratios, using a highly active control regimen.** This is a sensitivity analysis using a complete response rate ~10% and partial response rate ~50%. CWTA reduces the required sample size for 80% power by 9% to 22% versus KM PFS and 10% to 14% versus KM OS.

HR	Sample Size required for 80% Power			Sample Size Reduction using CWTA	
	CWTA	PFS	OS	vs PFS	vs OS
0.5	50	55	58	9%	14%
0.6	65	74	72	12%	10%
0.7	114	136	128	16%	11%
0.8	270	344	305	22%	11%

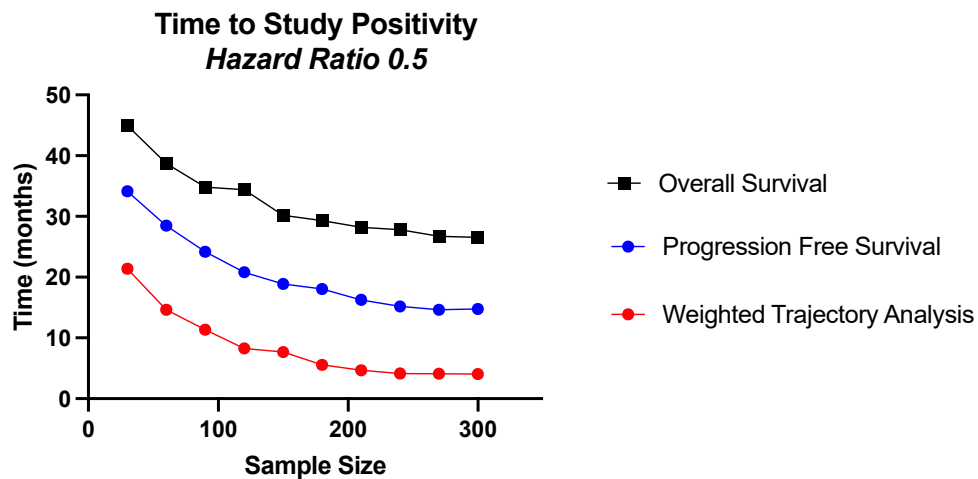
**Figure S1. Power as a function of sample size for Kaplan-Meier estimation of Progression-Free Survival and Overall Survival, and Chauhan Weighted Trajectory Analysis (CWTA) using a highly active control regimen.** This is a sensitivity analysis using a complete response rate ~10% and partial response rate ~50%. We performed thousandfold simulations of power as a function of sample size for Kaplan-Meier estimation of Progression-Free Survival and Overall Survival, and Chauhan Weighted Trajectory Analysis (CWTA) across a range of hazard ratios. CWTA demonstrated consistently higher power, reflecting a smaller sample size requirement during trial design. Assuming a trial designed to achieve a power of 0.8, WTA reduced sample size requirements by 9% to 22% when compared to KM PFS, and 11% to 13% when compared to KM OS; the sample size reductions were most marked for studies designed for interventions with higher hazard ratios (that is, less effective interventions).



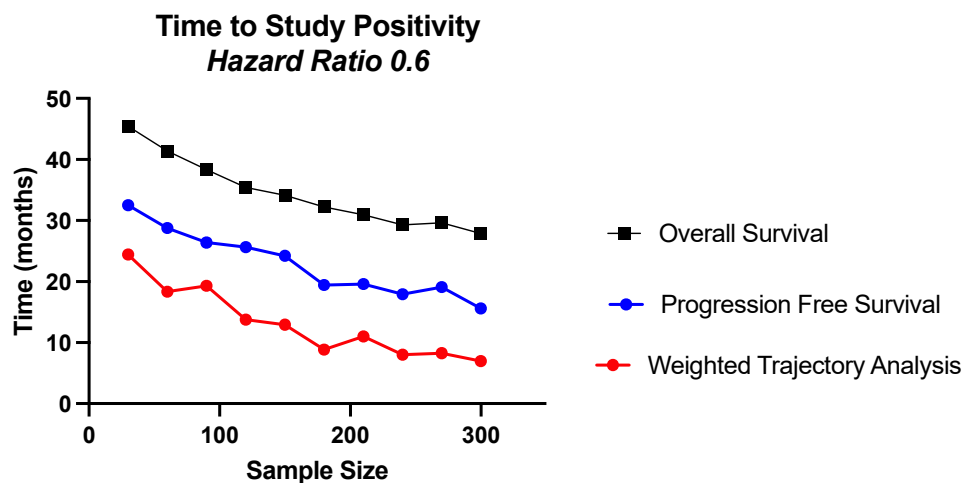
**Figure S2. Time-to-efficacy signals comparison using a highly active control regimen.** This is a sensitivity analysis using a complete response rate ~10% and partial response rate ~50%. One hundredfold / thousandfold simulations of time to study positivity as a function of sample size for Kaplan-Meier estimation of Progression Free Survival and

Overall Survival, and for Chauhan Weighted Trajectory Analysis (CWTA) for a range of hazard ratios. CWTA demonstrated consistently shorter time to study positivity; this effect was most profound in studies with a highly effective intervention (that is, a low hazard ratio).

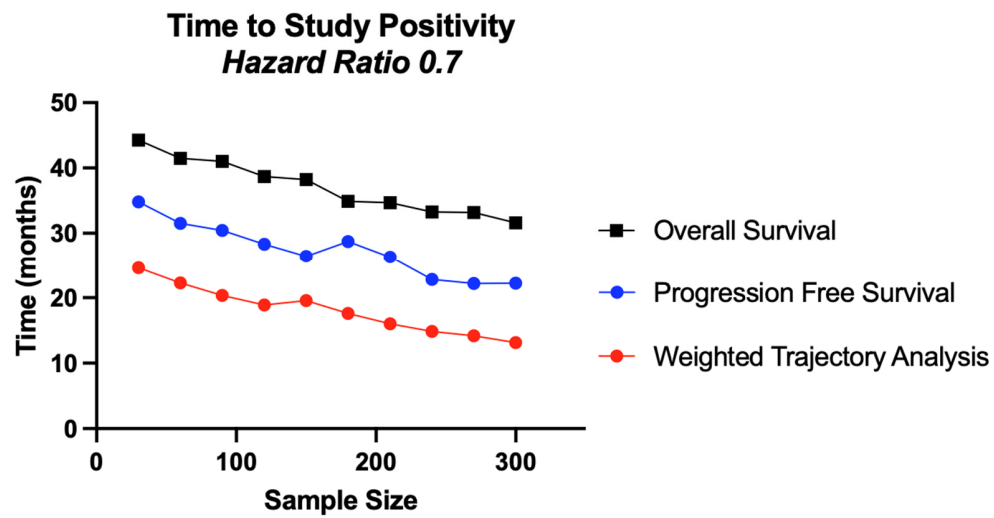
(a)



(b)



(c)



(d)

