Supplementary Material

Comparative Efficacy of Brolucizumab in the Treatment of Neovascular Age-Related Macular Degeneration: A Systematic Literature Review and Network Meta-Analysis

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Search strings

Table S 1. Search strategy using EMBASE via www.embase.com

PICOS component	#	Search terms	# of Hits
Disease: nAMD	#1	'macular degeneration'/exp OR 'macular degeneration':ti,ab	43,234
	#2	'retinal degeneration'/exp OR 'retinal degeneration':ti,ab	66,544
	#3	'choroidal neovascular*'	10,143
	#4	‘macula lutea’/exp	12,372
	#5	‘retinal drusen’/exp	3,572
	#6	(neovascular OR exudative) AND degener*	10,088
	#7	(macul* OR retina* OR choroid* OR wet) AND degener*	73,419
	#8	(macul* OR retina* OR choroid*) AND neovasc*	30,006
	#9	maculopath* OR drusen*	15,107
	#10	macul* AND (lutea* OR syndrome)	24,407
	#11	macul* AND dystroph*	5,063
	#12	(macul* OR 'geography') AND atroph*	8,821
	#13	choroid* AND polyp*	2,463
	#14	amd OR armd OR namd	25,279
	#15	retina* AND angiomat* AND prolif*	540
	#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	137,777
	#17	‘acid mine drainage’	2,305
	#18	#16 NOT #17	136,815
Interventions and Comparators	#19	'brolucizumab'/exp OR brolucizumab:ti,ab,tn OR esba1008 OR dlx1008	190
	#20	'ranibizumab'/exp OR ranibizumab:ti,ab,tn OR lucentris:ti,ab,tn OR rg3645:ti,ab,tn	10,731
	#21	‘bevacizumab’/exp OR bevacizumab:ti,ab,tn OR avastin:ti,ab,tn OR 'rhumbab-vegf':ti,ab,tn	63,547
	#22	‘aflibercept’/exp OR aflibercept:ti,ab,tn OR eylae:ti,ab,tn OR 'bay865321':ti,ab,tn OR pegaptanib:ti,ab,tn OR macugen:ti,ab,tn	8,211
	#23	trapeye*:ti,ab,tn OR 'trap eye*':ti,ab,tn	97
	#24	'photochemotherapy'/exp OR photochemotherapy:ti,ab OR 'photodynamic therapy'/exp OR 'photodynamic therapy':ti,ab	48,978
	#25	‘macul* surger*’	282
	#26	verteporfin:ti,ab,tn OR visudyne:ti,ab,tn	2,598
	#27	#19 OR #20 OR #21 OR #22 OR #23 OR #24 or #25 or #26	119,582
Study type	#28	'clinical trial'/exp	1,610,710
	#29	'randomized controlled trial'/exp	661,306

	#30	'randomization'/exp	91,042
	#31	'single blind procedure'/exp	42,856
	#32	'double blind procedure'/exp	184,824
	#33	'crossover procedure'/exp	67,005
	#34	'multicenter study'/exp	287,798
	#35	'comparative study'/exp	1,507,390
	#36	'placebo'/exp	374,131
	#37	'randomi*ed controlled trial*':ti,ab,kw	265,300
	#38	rct:ti,ab,kw	44,635
	#39	'random* allocat*':ti,ab,kw	41,770
	#40	'allocated randomly':ti,ab,kw	2,677
	#41	(allocated NEXT/2 random):ti,ab,kw	881
	#42	'single blind*':ti,ab,kw	27,027
	#43	'double blind*':ti,ab,kw	222,153
	#44	((treble OR triple) NEXT/1 blind*):ti,ab,kw	1,385
	#45	‘placebo*’:ti,ab,kw	327,404
	#46	‘prospective study’/exp	688,170
	#47	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46	3,814,977
	#48	'case study'/exp	78,232
	#49	'case report':ti,ab	464,231
	#50	'abstract report'/exp OR 'letter'/exp	1,201,385
	#51	'conference proceeding':it	0
	#52	'conference abstract':it	4,103,001
	#53	'editorial':it	686,637
	#54	'letter':it	1,162,760
	#55	'note':it	843,361
	#56	#48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55	7,303,783
	#57	#47 NOT #56	3,014,281
Disease, Treatments, Study Type	#58	#18 AND #27 AND #57	3,224
Remove Animal Studies	#59	'animal'/exp	29,069,630
	#60	'human'/exp	23,451,941
	#61	#59 NOT #60	5,617,689
	#62	#58 NOT #61	3,199
Limit to English and Date	#63	#62 AND [english]/lim AND [10-9-2018]/sd NOT [13-6-2019]/sd	265

Date of search: 03/06/2021

Table S 2. Search strategy using MEDLINE and MEDLINE-IN-PROCESS via www.pubmed.com

PICOS Component		Search Terms	# of Hits
Disease: nAMD	#1	“macular degeneration”[TIAB] OR “macular degeneration”[MH]	34,344
	#2	“retinal degeneration”[TIAB] OR “retinal degeneration”[MH]	47,274
	#3	"Choroidal Neovascular*"[MH] OR "Macula lutea"[MH] OR "Retinal drusen"[MH]	20,164
	#4	(neovascular[TIAB] OR exudative[TIAB]) AND degener*[TIAB]	7,047
	#5	(macul*[TIAB] OR retina*[TIAB] OR choroid*[TIAB] OR wet[TIAB]) AND (degener*[TIAB])	39,213
	#6	(macul*[TIAB] OR retina*[TIAB] OR choroid*[TIAB]) AND (neovasc*[TIAB])	17,616
	#7	maculopath*[TIAB] OR drusen*[TIAB]	7,893
	#8	macul*[TIAB] AND (lutea*[TIAB] OR syndrome[TIAB])	4,452
	#9	macul*[TIAB] AND dystroph*[TIAB]	2,937
	#10	((macul*[TIAB] OR geographic*[TIAB]) AND atroph*[TIAB])	5,155
	#11	choroid*[TIAB] AND polyp*[TIAB]	1,631
	#12	AMD[TIAB] OR ARMD[TIAB] OR nAMD[TIAB]	15,389
	#13	retina*[TIAB] AND angiomat*[TIAB] AND prolif*[TIAB]	380
	#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	92,703
	#15	acid mine drainage	1,687
	#16	#14 NOT #15	91,855
Interventions and Comparators	#17	Brolucizumab[TIAB] OR Brolucizumab[MH] OR esba1008[TIAB] OR dlx1008[TIAB]	94
	#18	Ranibizumab[TIAB] OR ranibizumab[MH] OR lucentis[TIAB] OR lucentis[MH] OR RG3645[TIAB]	5,310
	#19	bevacizumab[TIAB] OR bevacizumab[MH] OR Avastin[TIAB] OR Avastin[MH] OR "rhuMAb-VEGF"[TIAB]	19,603
	#20	Aflibercept[TIAB] OR aflibercept[MH] OR Eylea[TIAB] OR "BAY86-5321"[TIAB] OR pegaptanib[TIAB] OR pegaptanib[MH] OR macugen[TIAB] OR macugen[MH]	2,765
	#21	"Trap Eye*"[TIAB] OR Trap-Eye*[TIAB]	52

	#22	photochemotherapy[TIAB] OR photochemotherapy[MH] OR "photodynamic therapy"[TIAB] OR "photodynamic therap"[MH]	30,040
	#23	macul*[TIAB] AND surger*[TIAB]	8,066
	#24	verteporfin[TIAB] OR visudyne[TIAB]	1,607
	#25	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	61,418
Study Type (modified SIGN Filters)	#26	Randomized Controlled Trials as Topic[MH]	147,879
	#27	randomized controlled trial[MH]	147,879
	#28	random allocation[MH]	105,411
	#29	single blind method[MH]	30,280
	#30	double blind method[MH]	164,733
	#31	Clinical trial[MH]	358,078
	#32	“clinical trial, phase I”[PT]	21,685
	#33	“clinical trial, phase II”[PT]	34,932
	#34	“clinical trial, phase III”[PT]	18,468
	#35	“clinical trial, phase IV”[PT]	2,107
	#36	“controlled clinical trial”[PT]	623,044
	#37	“randomized controlled trial”[PT]	533,728
	#38	“multicenter study”[PT]	295,484
	#39	“clinical trial”[PT]	895,068
	#40	Clinical trials as topic[MeSH Terms]	358,078
	#41	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	1,433,093
	#42	“clinical trial*”[TW]	1,066,906
	#43	“single blind*”[TW] OR “double blind*”[TW] OR “treble blind*”[TW] OR “triple blind*”[TW]	246,494
	#44	Placebos[MeSH]	38,241
	#45	Placebo*[TW]	239,887
	#46	“allocated random*”[TW]	0
	#47	#42 OR #43 OR #44 OR #45 OR #46	1,232,802
	#48	#41 OR #47	1,725,992
	#49	“case report”[TW]	338,208
	#50	Letter/	1,207,889
	#51	Historical article/	402,932
	#52	#49 OR #50 OR #51	1,930,182
	#53	#48 NOT #52	1,680,722
Disease, Treatments, Study Type	#54	#16 AND #25 AND #53	2,534
Remove Animal Studies	#55	animal/	7,056,387
	#56	human/	20,118,108
	#57	#55 NOT #56	4,593,432
	#58	#54 NOT #57	2,520

Limit to English	#59	English[Language]	27,871,083
	#60	#58 AND #59	2,316
Date Restriction	#61	#60 AND ("2020/05"[Date - Publication] : "2021/06"[Date - Publication])	149

Date of search: 03/06/2021

Networks for all endpoints of the network meta-analysis

Figure S 1. Network for mean change in BCVA at 2 years

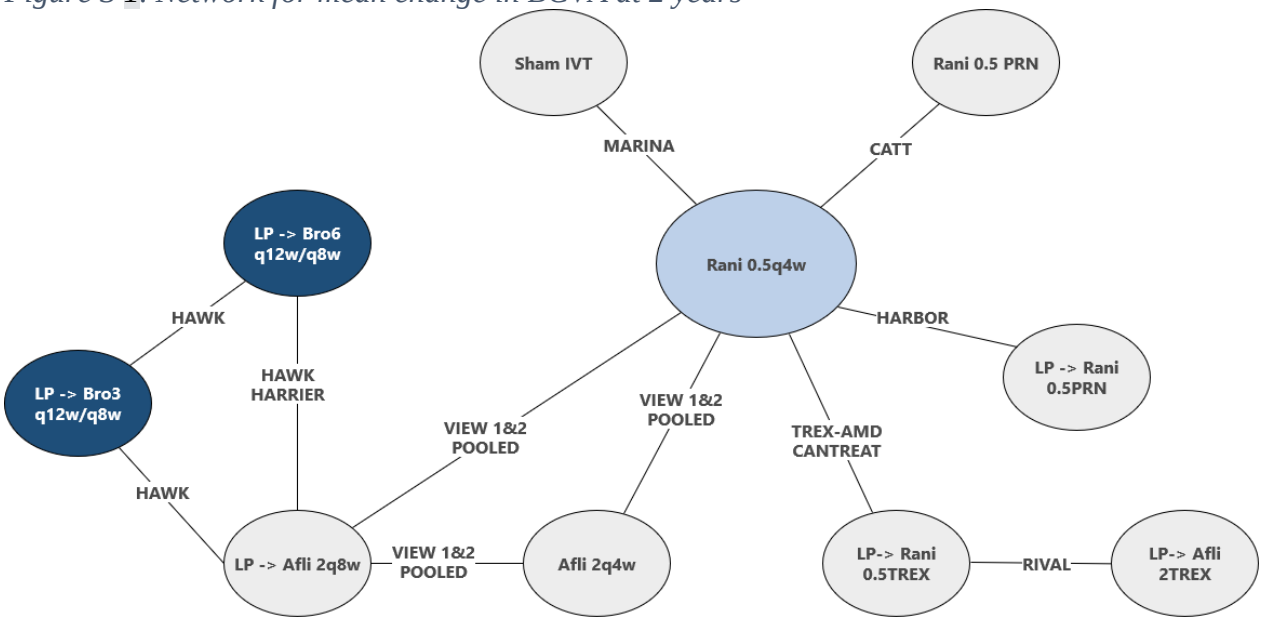


Figure S 2. Network for mean change in retinal thickness at 1 year

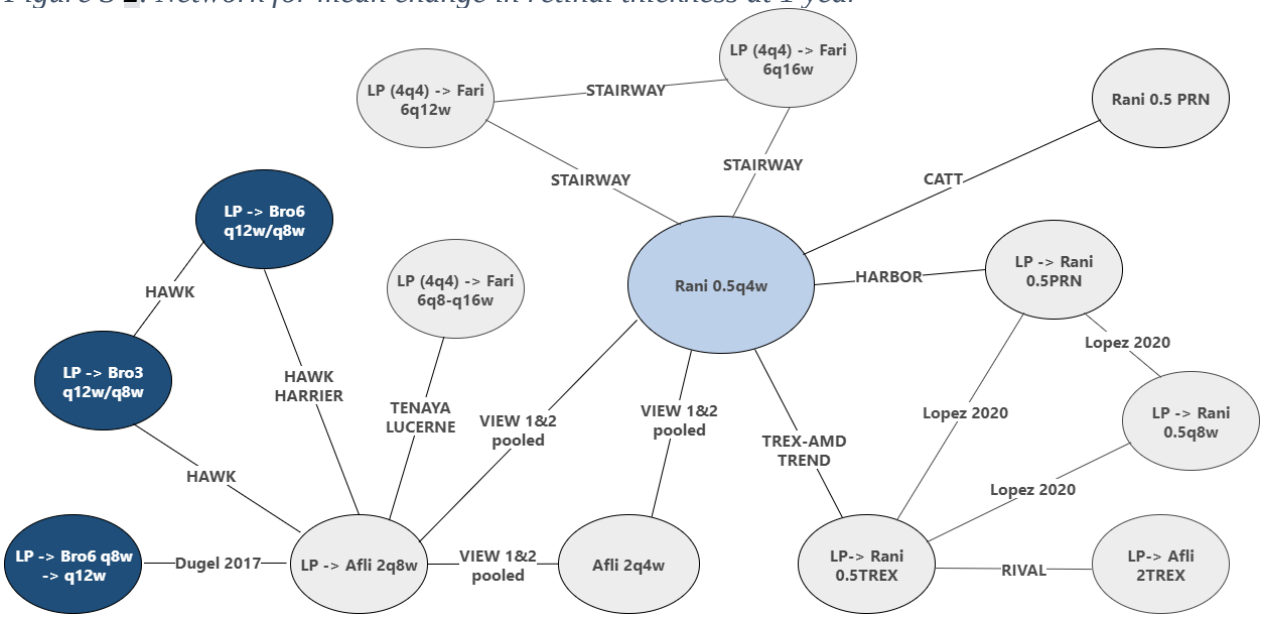


Figure S 3. Network for mean change in retinal thickness at 2 years

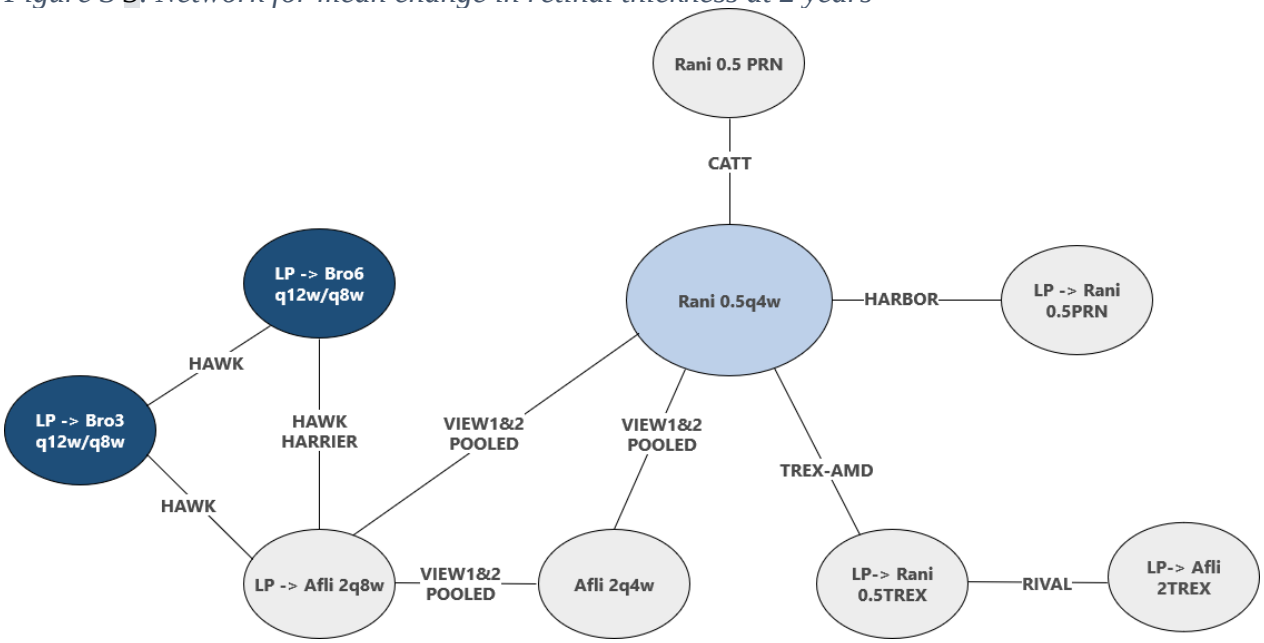


Figure S 4. Network for patients losing at least 15 letters at 1 year

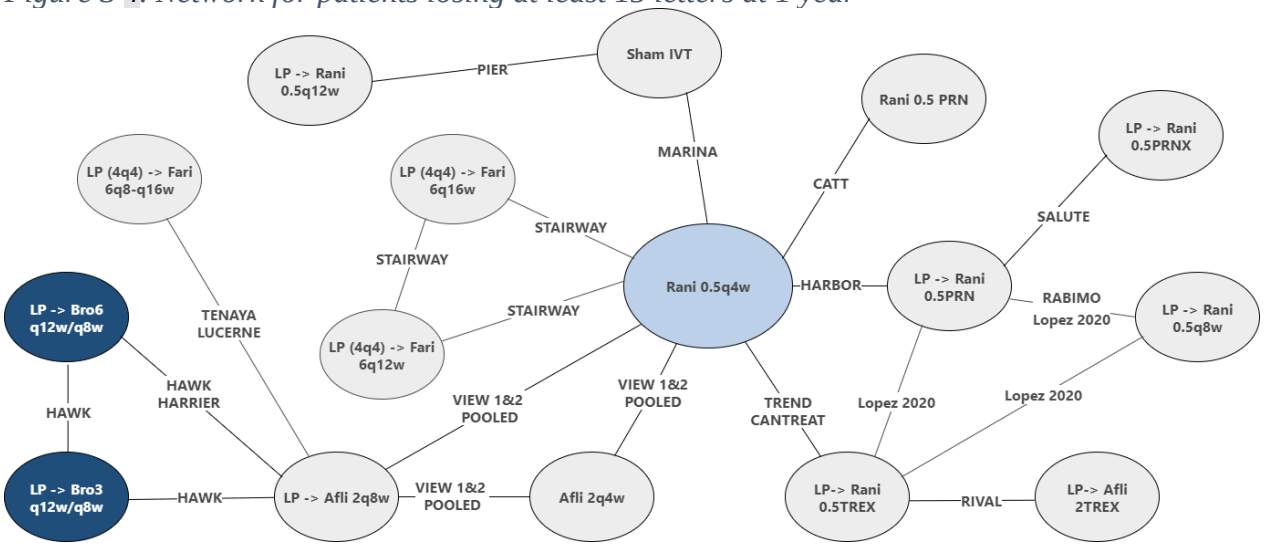


Figure S 5. Network for patients losing at least 15 letters at 2 years

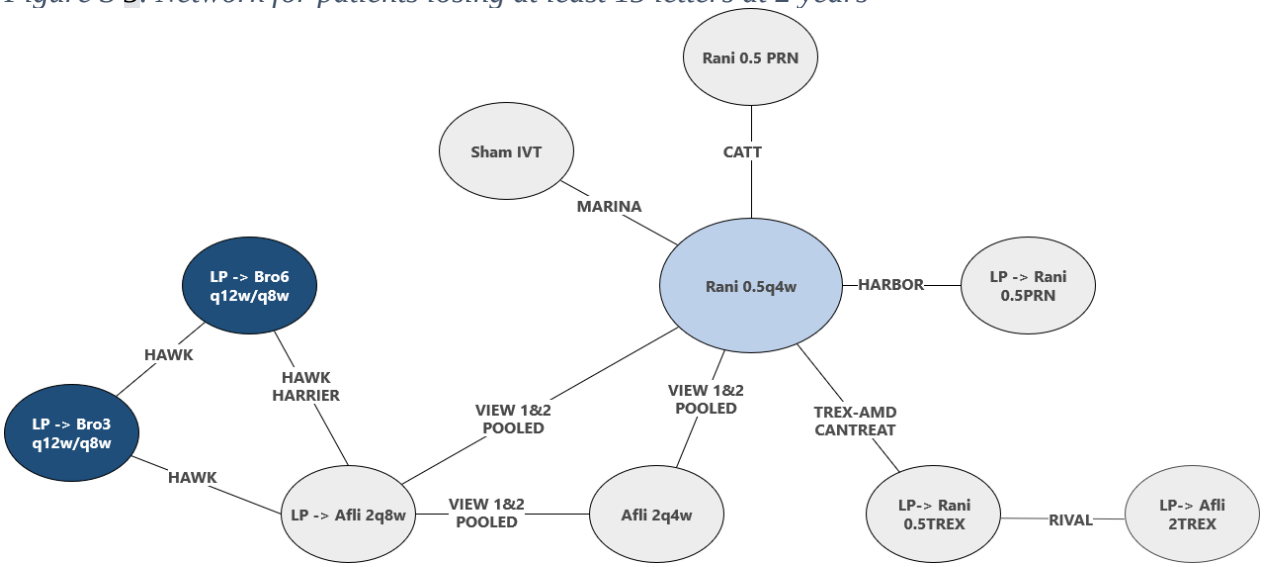


Figure S 6. Network for patients gaining at least 15 letters at 1 year

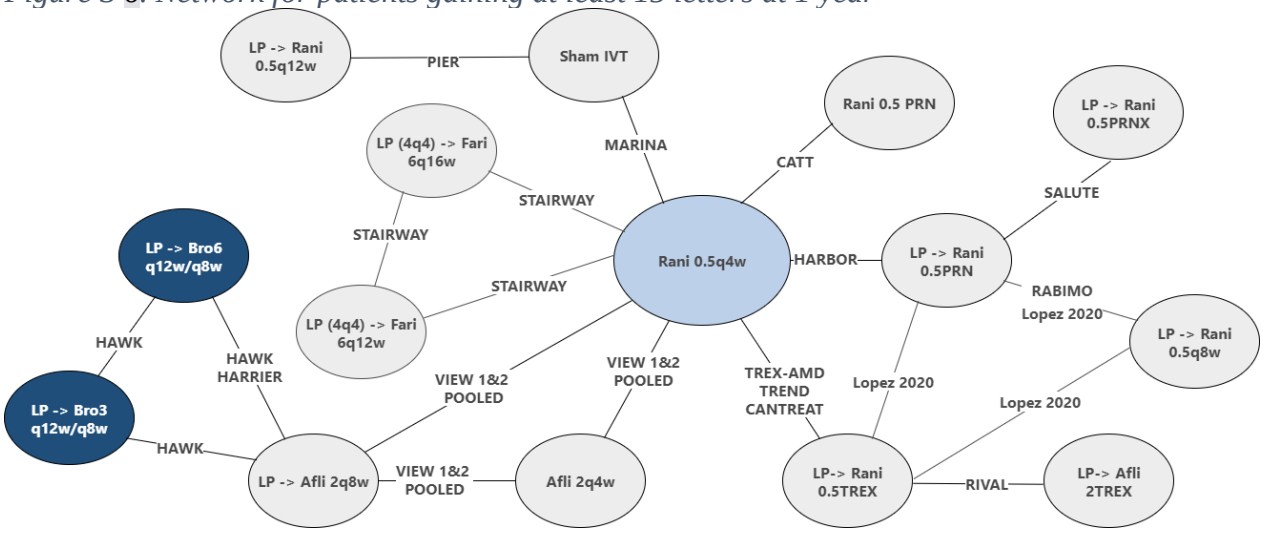


Figure S 7. Network for patients gaining at least 15 letters at 2 years

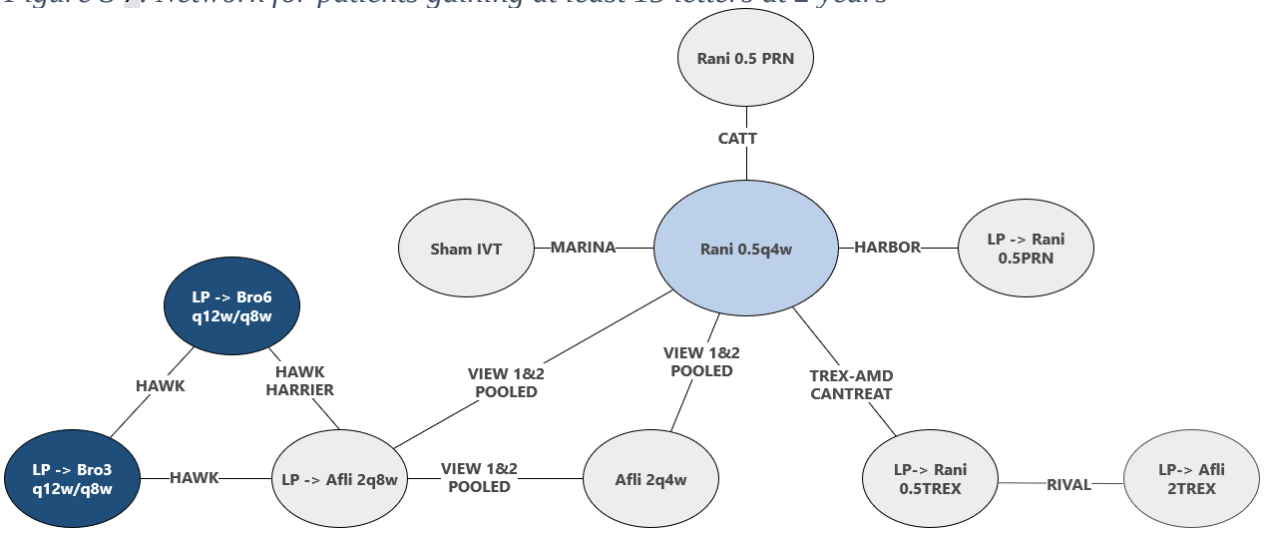


Figure S 8. Network for discontinuation at 1 year

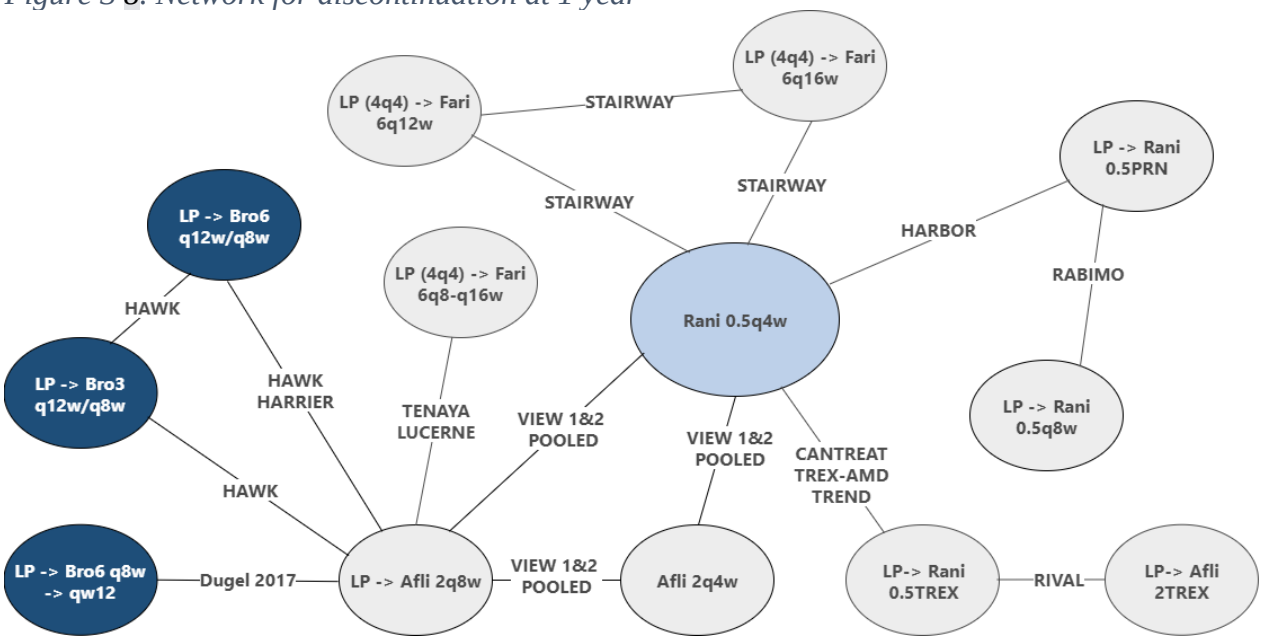
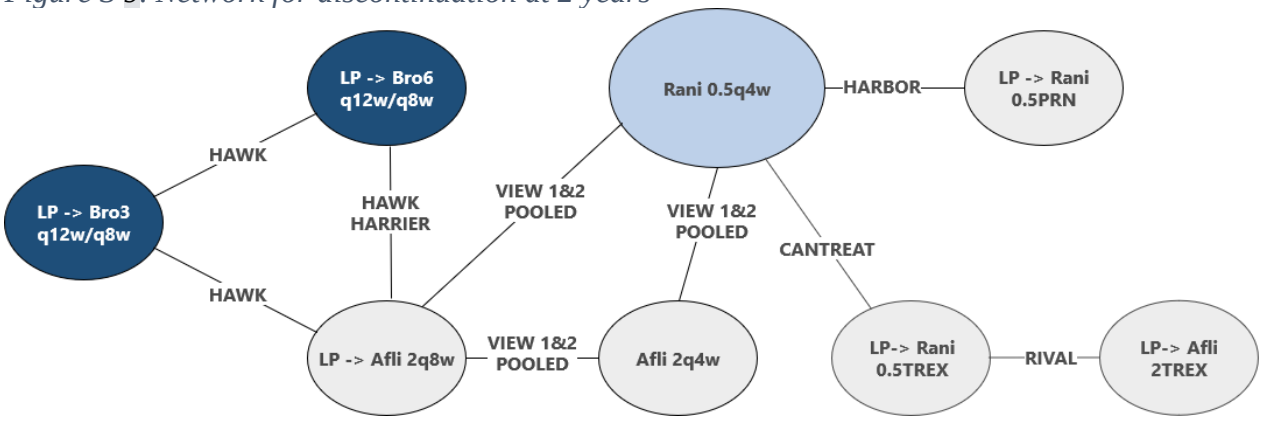


Figure S 9. Network for discontinuation at 2 years



Inconsistency assessment results

Table S 3. Results from the inconsistency assessment for all endpoints of the network meta-analyses

Loop / Endpoint	Difference (SE) - Direct vs. indirect comparison	Z-score	P-value
Loop with LP -> Afli 2q8, LP -> Bro 6q12/q8, and LP -> Bro 3q12/q8			
Change in BCVA			
1 year	0.23 (1.19)	0.19	0.846
2 years	0.59 (1.34)	0.44	0.662
1->2 years	0.38 (1.62)	0.30	0.763
Change in retinal thickness			
1 year	10.18 (11.79)	0.86	0.388
2 years	8.59 (12.41)	0.69	0.489
Patients gaining ≥ 15 letters			
1 year	0.21 (0.26)	0.81	0.420
2 years	0.22 (0.25)	0.86	0.387
Patients losing ≥ 15 letters			
1 year	0.18 (0.26)	0.35	0.727
2 years	0.08 (0.43)	0.18	0.855
Discontinuation			
1 year	-0.11 (0.40)	-0.28	0.781
2 years	0.01 (0.30)	0.02	0.982
Loop with Rani 0.5q4, LP -> Rani 0.5TREX, and LP -> Rani 0.5PRN (1 year)			
Change in BCVA	-2.77 (2.54)	-1.09	0.276
Change in retinal thickness	-13.05 (25.46)	-0.51	0.608
Patients gaining ≥ 15 letters	-0.73 (0.39)	-1.89	0.059
Patients losing ≥ 15 letters	0.03 (0.84)	0.03	0.973

Heterogeneity assessment results

Table S 4. Summary of direct comparison results for mean change in BCVA at 1 year

Comparison	Trials	Mean diff [95% CI]		I-square	P-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP -> Rani 0.5TREX vs. Rani 0.5q4	TREND TREX-AMD CAN-TREAT	0.26 [-1.08; 1.61]	0.32 [-3.20; 3.84]	78.83%	0.009+
Rani 0.5q4 vs LP-> Afli 2q8	VIEW 1 VIEW 2	0.36 [-1.28; 2.00]	0.36 [-1.28; 2.00]	0.00%	0.858
Rani 0.5q4 vs. Afli 2q4	VIEW 1 VIEW 2	-0.26 [-1.81; 1.29]	-0.47 [-4.98; 4.04]	88.03%	0.004+
LP -> Afli 2q8 vs. Afli 2q4	VIEW 1 VIEW 2	-0.70 [-2.26; 0.87]	-0.83 [-5.04; 3.38]	86.14%	0.007+
LP -> Afli 2q8 vs. LP -> Bro 6q12/q8	HARRIER HAWK	0.43 [-0.85; 1.71]	0.43 [-0.85; 1.71]	0.00%	0.762
LP -> Afli 2q8 vs. LP (4q4) -> Fari 6q8-q16	TENAYA LUCERNE	-0.2 [-1.54;1.14]	-0.2 [-1.54;1.14]	0.00%	0.884

Table S 5. Summary of direct comparisons results for mean change in BCVA at 2 years

Comparison	**Included trials**	**Mean diff (95% CI)**		**I-square**	**P-value Cochran test**
		Fixed-effects model	**Random-effects model**		
LP -> Bro 6q12/q8 vs. LP -> Afli 2q8	HARRIER HAWK	0.01 [-1.46;1.49]	0.01 [-1.46;1.49]	0.00%	0.467
LP -> Rani 0.5TREX vs. Rani 0.5q4	TREX-AMD CAN-TREAT	0.42 [-1.67;2.50]	-0.11 [-3.66;3.43]	28.43%	0.237

Table S 6. Summary of direct comparison results for mean change in retinal thickness at 1 year

Comparison	Trials	Mean diff [95% CI]		I-square	P-value Cochran test
		Fixed-effects model	Random-effects model		
LP -> Rani 0.5TREX vs. Rani 0.5q4	TREND TREX-AMD	11.04 [-13.08;35.16]	29.34 [-36.46;95.15]	65.4%	0.089
Rani 0.5q4 vs LP-> Afli 2q8	VIEW 1 VIEW 2	11.26 [-1.67; 24.18]	11.26 [-1.67; 24.18]	0.0%	0.940
Rani 0.5q4 vs. Afli 2q4	VIEW 1 VIEW 2	7.41 [-5.22; 20.04]	8.21 [-9.95; 26.38]	50.6%	0.155
LP -> Afli 2q8 vs. Afli 2q4	VIEW 1 VIEW 2	-3.66 [-16.16; 8.85]	-2.83 [-22; 16.34]	56.7%	0.129
LP -> Bro 6q12/q8 vs. LP -> Afli 2q8	HARRIER HAWK	-39.28 [-52.55;-26.02]	-39.41 [-59.79;-19.03]	57.6%	0.125
LP -> Afli 2q8 vs. LP -> Fari 6q8-q16	TENAYA LUCERNE	12.21 [5.68;18.75]	12.21 [5.68;18.75]	0.00%	0.799

Table S 7. Summary of direct comparison results for mean change in retinal thickness at 2 years

Comparison	Included trials	Mean diff (95% CI)		I-square	P-value Cochran test
		Fixed-effects model	Random-effects model		
LP -> Bro 6q12/q8 vs. LP -> Afli 2q8	HARRIER HAWK	-34.69 [-48.64; -20.74]	-34.60 [-50.77; -18.44]	25.4%	0.247

Table S 8. Summary of direct comparison results for odds of losing at least 15 letters at 1 year

Comparison	Trials	OR [95% CI]		I-square	P-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP -> Afli 2q8 vs. Rani 0.5q4	VIEW 1 VIEW 2	0.83 [0.50; 1.38]	0.83 [0.50; 1.38]	0.0%	0.826
Afli 2q4 vs. Rani 0.5q4	VIEW 1 VIEW 2	0.91 [0.55; 1.50]	0.91 [0.55; 1.50]	0.0%	0.530
LP -> Afli 2q8 vs. Afli 2q4	VIEW 1 VIEW 2	1.10 [0.66; 1.84]	1.10 [0.66; 1.84]	0.0%	0.698
LP -> Bro 6q12/q8 vs. LP -> Afli 2q8	HARRIER HAWK	0.97 [0.61; 1.55]	0.97 [0.61; 1.55]	0.00%	0.390
LP -> Rani 0.5q8 vs. LP -> Rani 0.5PRN	RABIMO Lopez 2020	1.57 [0.45;5.54]	1.57 [0.44;5.54]	0.00%	0.786
LP -> Rani 0.5TREX vs. Rani 0.5q4	TREND CAN-TREAT	1.12 [0.63;1.98]	1.06 [0.39;2.85]	64.04%	0.095
LP -> Afli 2q8 vs. LP -> Fari 6q8-q16	TENAYA LUCERNE	0.93 [0.57;1.55]	0.93 [0.53;1.62]	16.21%	0.275

Table S 9. Summary of direct comparison results for odds of losing at least 15 letters at 2 years

Comparison	**Included trials**	**OR (95% CI)**		**I-square**	**P-value Cochran test**
		Fixed-effects model	**Random-effects model**		
LP -> Bro 6q12/q8 vs. LP -> Afli 2q8	HARRIER HAWK	1.00 [0.68; 1.47]	1.00 [0.68; 1.47]	0.0%	0.686
LP -> Rani 0.5TREX vs. Rani 0.5q4	TREX-AMD CAN-TREAT	1.34 [0.67;2.68]	1.34 [0.54;3.34]	7.7%	0.298

Table S 10. Summary of direct comparison results for odds of gaining at least 15 letters at 1 year

Comparison	Trials	OR [95% CI]		I-square	P-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP -> Rani 0.5TREX vs Rani 0.5q4	TREND TREX-AMD CAN-TREAT	1.18 [0.90; 1.54]	1.18 [0.9;1.54]	0.0%	0.489
LP -> Afli 2q8 vs. Rani 0.5q4	VIEW 1 VIEW 2	0.93 [0.73; 1.19]	0.93 [0.73; 1.19]	0.0%	0.676
Afli 2q4 vs. Rani 0.5q4	VIEW 1 VIEW 2	1.05 [0.82; 1.33]	1.04 [0.64; 1.71]	76.3%	0.040
LP -> Afli 2q8 vs. Afli 2q4	VIEW 1 VIEW 2	1.12 [0.88;1.43]	1.12 [0.75; 1.65]	62.3%	0.103
LP -> Bro 6q12/q8 vs. LP -> Afli 2q8	HARRIER HAWK	1.19 [0.95; 1.49]	1.19 [0.79; 1.80]	69.7%	0.069
LP -> Rani 0.5q8 vs. LP -> Rani 0.5PRN	RABIMO Lopez 2020	0.68 [0.39;1.18]	0.68 [0.39;1.18]	0.00%	0.924

Table S 11. Summary of direct comparison results for odds of gaining at least 15 letters at 2 years

Comparison	**Included trials**	**OR (95% CI)**		**I-square**	**P-value Cochran test**
		Fixed-effects model	**Random-effects model**		
LP -> Bro 6q12/q8 vs. LP -> Afli 2q8	HARRIER HAWK	1.11 [0.89; 1.39]	1.12 [0.73; 1.71]	72.4%	0.057
LP -> Rani 0.5TREX vs. Rani 0.5q4	TREX-AMD CAN-TREAT	1.19 [0.81;1.75]	1.19 [0.81;1.75]	0.0%	0.561

Table S 12. Summary of direct comparison results for discontinuation at 1 year

Comparison	Trials	OR [95% CI]		I-square	P-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP -> Rani 0.5TREX vs. Rani 0.5q4	TREND TREX-AMD CAN-TREAT	0.79 [0.54;1.14]	0.84 [0.39;1.81]	64.48%	0.060
LP -> Afli 2q8 vs. Rani 0.5q4	VIEW 1 VIEW 2	1.04 [0.72; 1.51]	1.04 [0.72; 1.51]	0.00%	0.668
Afli 2q4 vs. Rani 0.5q4	VIEW 1 VIEW 2	0.86 [0.58; 1.27]	0.82 [0.44; 1.54]	59.14%	0.118
Afli 2q4 vs. LP -> Afli 2q8	VIEW 1 VIEW 2	0.83 [0.56; 1.23]	0.78 [0.35; 1.72]	74.53%	0.048+
LP -> Bro 6q12/q8 vs. LP -> Afli 2q8	HARRIER HAWK	0.87 [0.61; 1.25]	0.87 [0.61; 1.25]	0.00%	0.447
LP -> Afli 2q8 vs. LP -> Fari 6q8-q16	TENAYA LUCERNE	0.83 [0.53;1.31]	0.83 [0.37;1.86]	67.53%	0.079

Table S 13. Summary of direct comparison results for discontinuation at 2 years

Comparison	Included trials	OR (95% CI)		I-square	P-value Cochran test
		Fixed-effects model	Random-effects model		
LP -> Bro 6q12/q8 vs. LP -> Afli 2q8	HARRIER HAWK	0.81 [0.61; 1.07]	0.81 [0.61; 1.07]	0.0%	0.954

Adverse events results – pooled treatment effects

Table S 14. Pooled proportion of patients with serious adverse events by treatment molecule at 1 and 2 years

Molecule	Number of Trials	Average proportion of patients with serious adverse event	Standard Error	Cochran Q Statistic	P-value of Cochran Q
Cataract - 1 year					
Aflibercept	6	0.0030	0.0001	2.0600	0.8408
Brolucizumab	2	0.0030	0.0001	0.0000	1.0000
Ranibizumab	6	0.0038	0.0015	85.8176	0.0000
Faricimab	0		Not reported		
Sham	0		Not reported		
Cataract - 2 years					
Aflibercept	4	0.0059	0.0006	16.9328	0.0020
Brolucizumab	2	0.0030	0.0001	0.0000	1.0000
Ranibizumab	1	0.0045	0.0025	72.4200	0.0000
Faricimab	0		Not reported		
Sham	0		Not reported		
Endophthalmitis – 1 year					
Aflibercept	6	0.0031	0.0023	58.4628	0.0000
Brolucizumab	2	0.0045	0.0015	73.1813	0.0000
Ranibizumab	15	0.0050	0.0012	255.7260	0.0000
Faricimab	0		Not reported		
Sham	1	0.0000	0.0000	.	.
Endophthalmitis – 2 years					
Aflibercept	5	0.0054	0.0015	237.6613	0.0000
Brolucizumab	2	0.0055	0.0025	125.5503	0.0000
Ranibizumab	7	0.0094	0.0020	86.5610	0.0000
Faricimab	0		Not reported		
Sham	1	0.0000	0.0000	.	.
Intraocular inflammation – 1 year					
Aflibercept	0		Not reported		
Brolucizumab	0		Not reported		
Ranibizumab	5	0.0000	0.0000	0.0000	1.0000
Faricimab	0		Not reported		
Sham	1	0.0000	0.0000	0.0000	.
Intraocular inflammation – 2 years					
Aflibercept	2	0.0000	0.0000	0.0000	0.0000
Brolucizumab	2	0.0095	0.0015	18.1886	0.0000
Ranibizumab	2	0.0000	0.0000	0.0000	0.0000
Faricimab	0		Not reported		
Sham	0		Not reported		
Retinal detachment – 1 year					

Aflibercept	6	0.0030	0.0002	2.0201	0.8464
Brolucizumab	2	0.0030	0.0002	0.7402	0.3896
Ranibizumab	9	0.0030	0.0001	2.4175	0.9655
Faricimab	0		Not reported		
Sham	1	0.0000	0.0000	.	.
Retinal detachment – 2 years					
Aflibercept	5	0.0038	0.0006	155.0532	0.0000
Brolucizumab	2	0.0030	0.0001	0.0000	1.0000
Ranibizumab	5	0.0049	0.0003	4.0286	0.4022
Faricimab	0		Not reported		
Sham	1	0.0040	0.0003	.	.
Retinal pigment epithelial tear – 1 year					
Aflibercept	6	0.0030	0.0001	2.0893	0.8367
Brolucizumab	2	0.0040	0.0010	43.5997	0.0000
Ranibizumab	6	0.0110	0.0048	35.9310	0.0000
Faricimab	0		Not reported		
Sham	0		Not reported		
Retinal pigment epithelial tear – 2 years					
Aflibercept	4	0.0024	0.0015	19.1822	0.0003
Brolucizumab	2	0.0040	0.0010	43.5997	0.0000
Ranibizumab	1	0.0020	0.0001	0.0000	.
Faricimab	0		Not reported		
Sham	0		Not reported		
Retinal tear – 1 year					
Aflibercept	2	0.0000	0.0000	0.0000	1.0000
Brolucizumab	0		Not reported		
Ranibizumab	7	0.0030	0.0001	1.6657	0.9477
Faricimab	0		Not reported		
Sham	0		Not reported		
Retinal tear – 2 years					
Aflibercept	1	0.0030	0.0002	0.0000	.
Brolucizumab	1	0.0050	0.0003	0.0000	.
Ranibizumab	3	0.0040	0.0003	1.4049	0.4954
Faricimab	0		Not reported		
Sham	1	0.0000	0.0000	0.0000	.
Stroke – 1 year					
Aflibercept	8	0.0045	0.0006	295.5113	0.0000
Brolucizumab	2	0.0063	0.0048	23.4139	0.0000
Ranibizumab	13	0.0058	0.0009	288.3556	0.0000
Faricimab	2	0.0042	0.0022	4.4246	0.0354
Sham	1	0.0079	0.0112	0.0000	.
Stroke – 2 years					
Aflibercept	4	0.0094	0.0009	64.7270	0.0000
Brolucizumab	2	0.0063	0.0048	23.4139	0.0000

Ranibizumab	4	0.0104	0.0018	257.7988	0.0000
Faricimab	0	Not reported			
Sham	1	0.0080	0.0005	0.0000	.

Inclusion of unlicensed bevacizumab

Table S 15. Details of trials assessing unlicensed bevacizumab

Trial #	Author, year	Trial name	Time of assessment (months)	Previous anti-VEGF therapy	Intervention	Comparator
1	Martin 2011 / Martin 2012	CATT	12 / 24	Treatment-naive	Rani 0.5q4 Rani 0.5PRN	Bev 1.25q4 Bev 1.25 PRN
2	Berg 2015/2016	LUCAS	12 / 24	Treatment-naive	Bev 1.25TREX	LP -> Rani 0.5TREX
3	Kodjikian 2013	GEFAL	12	Treatment-naive	LP -> Bev 1.25PRN	LP -> Rani 0.5PRN
4	Krebs 2013	MANTA	12	Treatment-naive	LP -> Bev 1.25PRN	LP -> Rani 0.5PRN
5	Li 2012	NATTB	11	Treatment-naive	Bev 1.25q6	LP (q6) -> Bev 1.25q12
6	Lushchyk 2013	NR	12	Treatment-naive	Bev 1.25q4	Bev 1.25q6 Bev 1.25q8
7	Menon 2013	BEMOC	12	Treatment-naive	LP (q6) -> Bev 1.25PRN	Bev 1.25PRN
8	Nunes 2019	NR	12	Treatment-naive	LP -> Bev 1.25PRN LP (q2) -> Bev 1.25PRN	LP -> Rani 0.5PRN
9	Schauwvlieghe 2016	BRAMD	12	Previously treated	Bev 1.25q4	Rani 0.5q4
10	Scholler 2014	NR	12	Treatment-naive	LP -> Rani 0.5PRN	LP -> Bev 1.25PRN

Figure S 10. Network for mean change in BCVA at 1 year with unlicensed bevacizumab

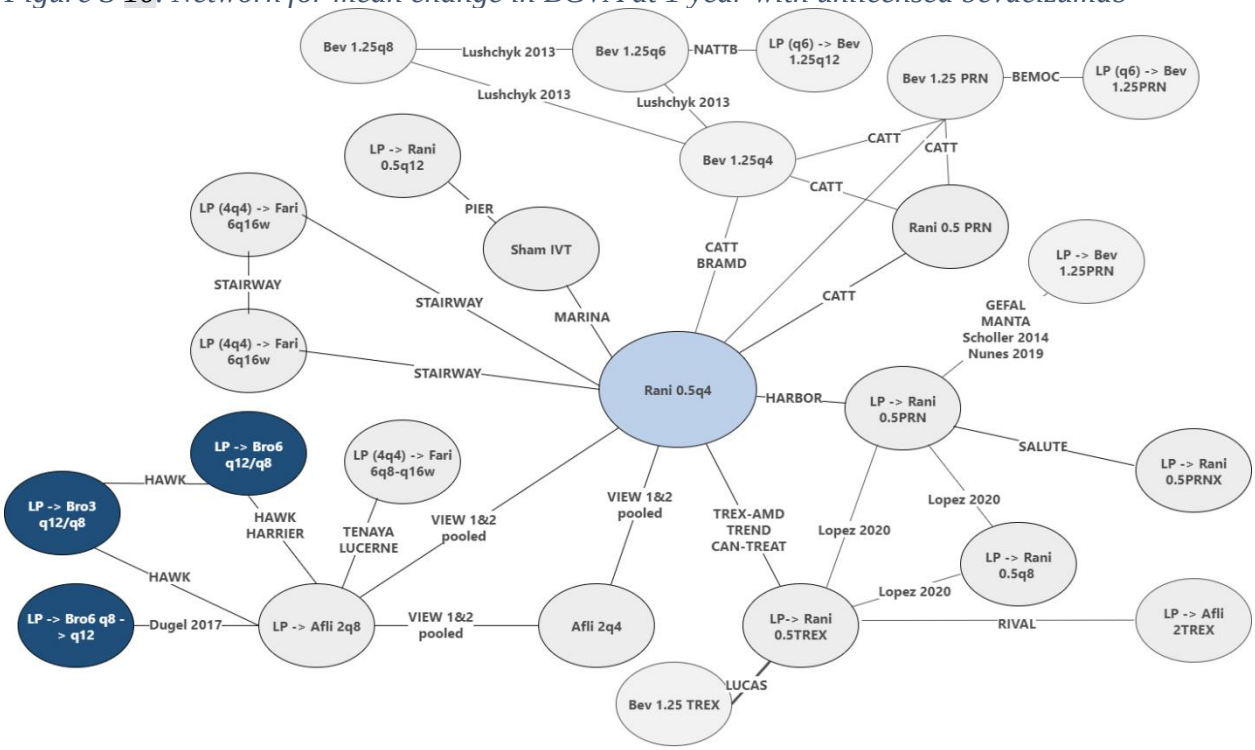


Figure S 11. Network for mean change in BCVA at 2 years with unlicensed bevacizumab

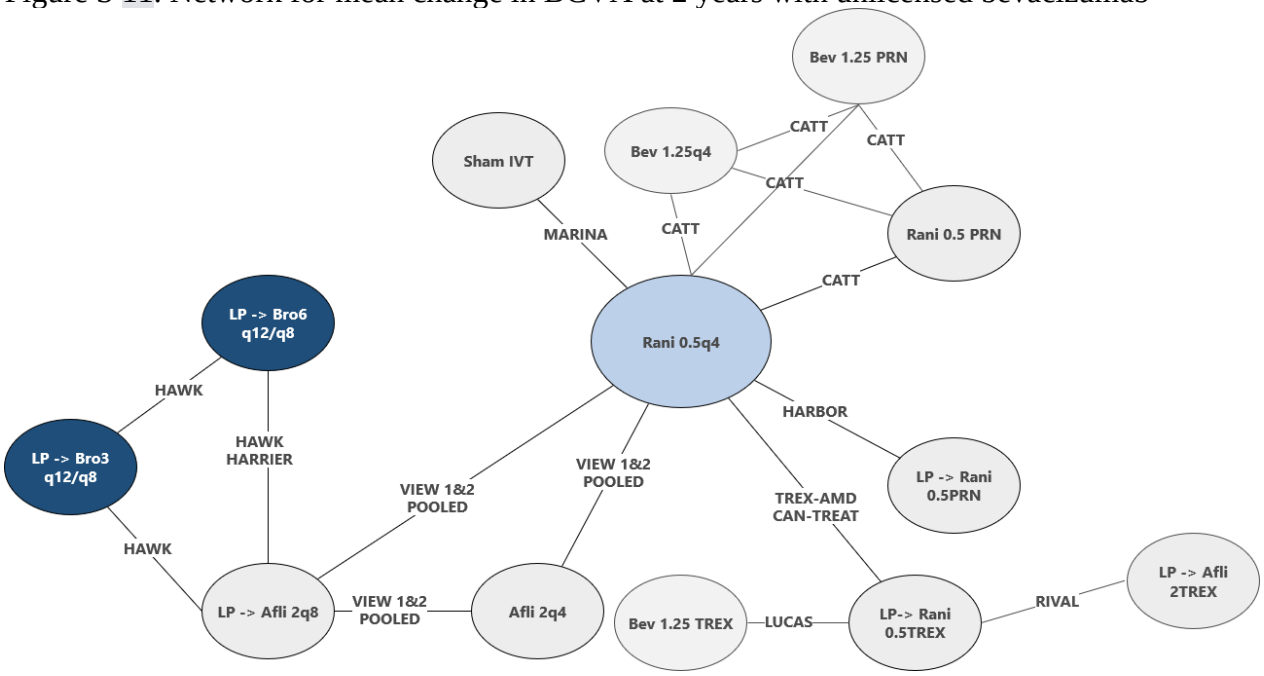


Figure S 12. Network for mean change in retinal thickness at 1 year with unlicensed bevacizumab

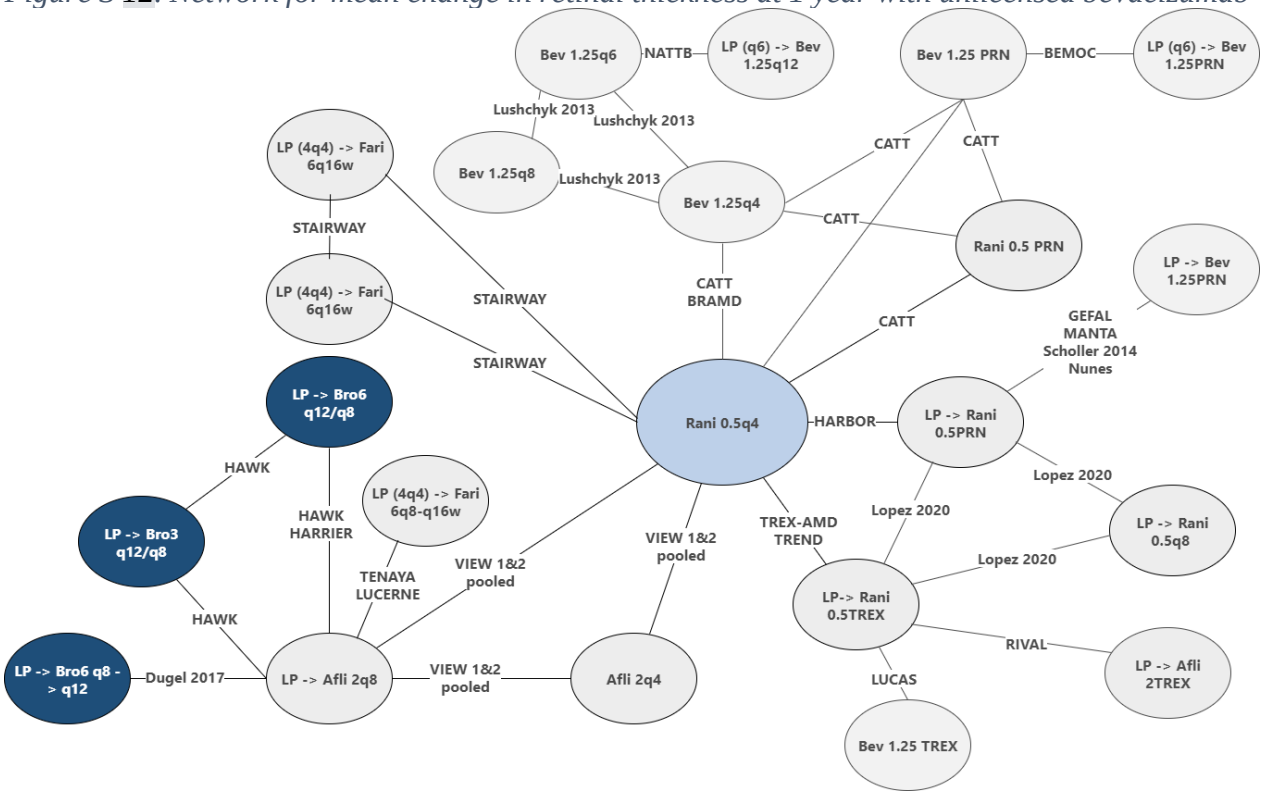


Figure S 13. Network for mean change in retinal thickness at 2 years with unlicensed bevacizumab

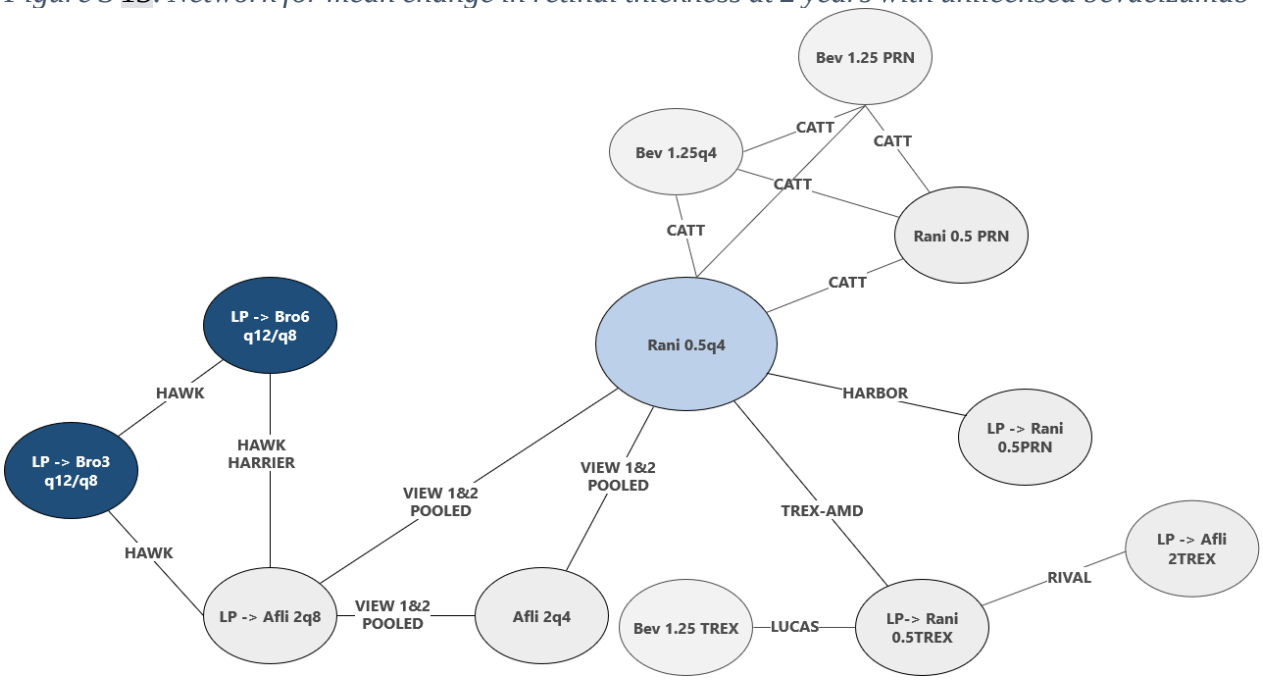


Figure S 14. Network for patients losing at least 15 letters at 1 year with unlicensed bevacizumab

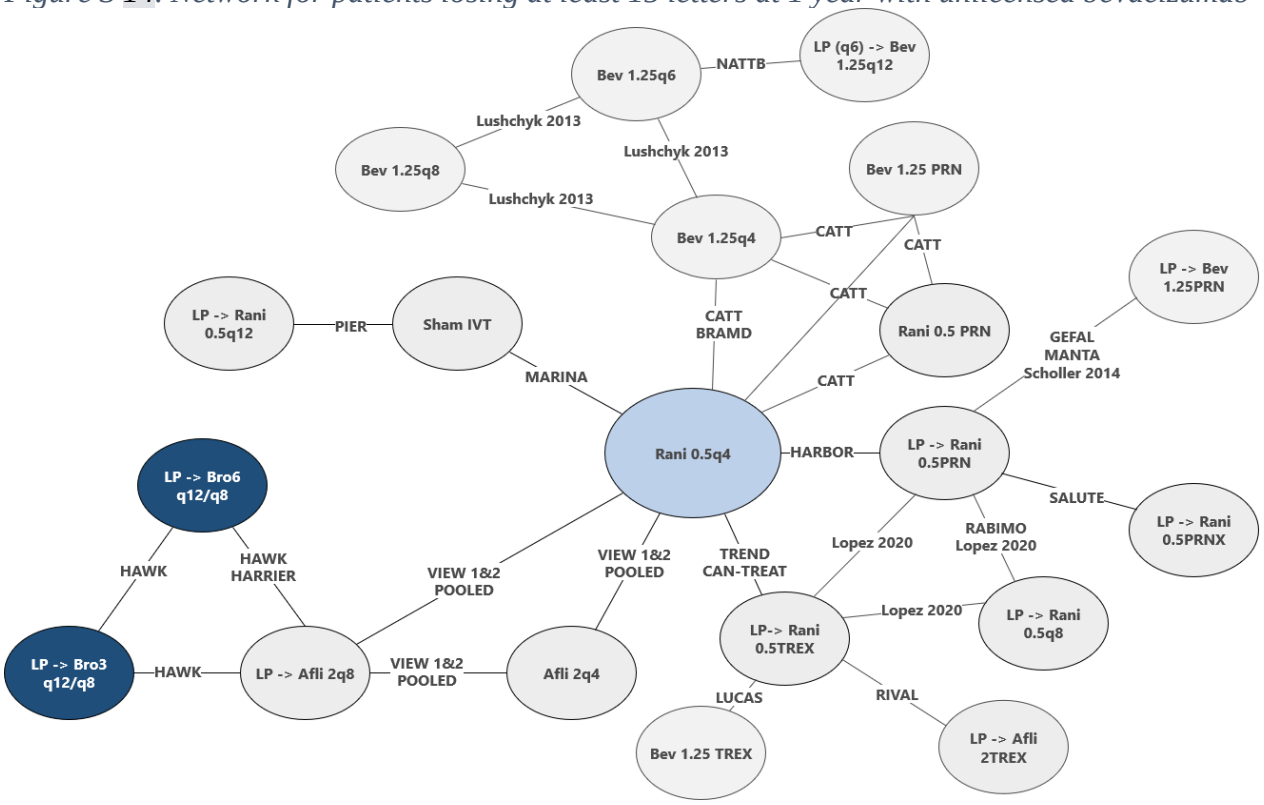


Figure S 15. Network for patients losing at least 15 letters at 2 years with unlicensed bevacizumab

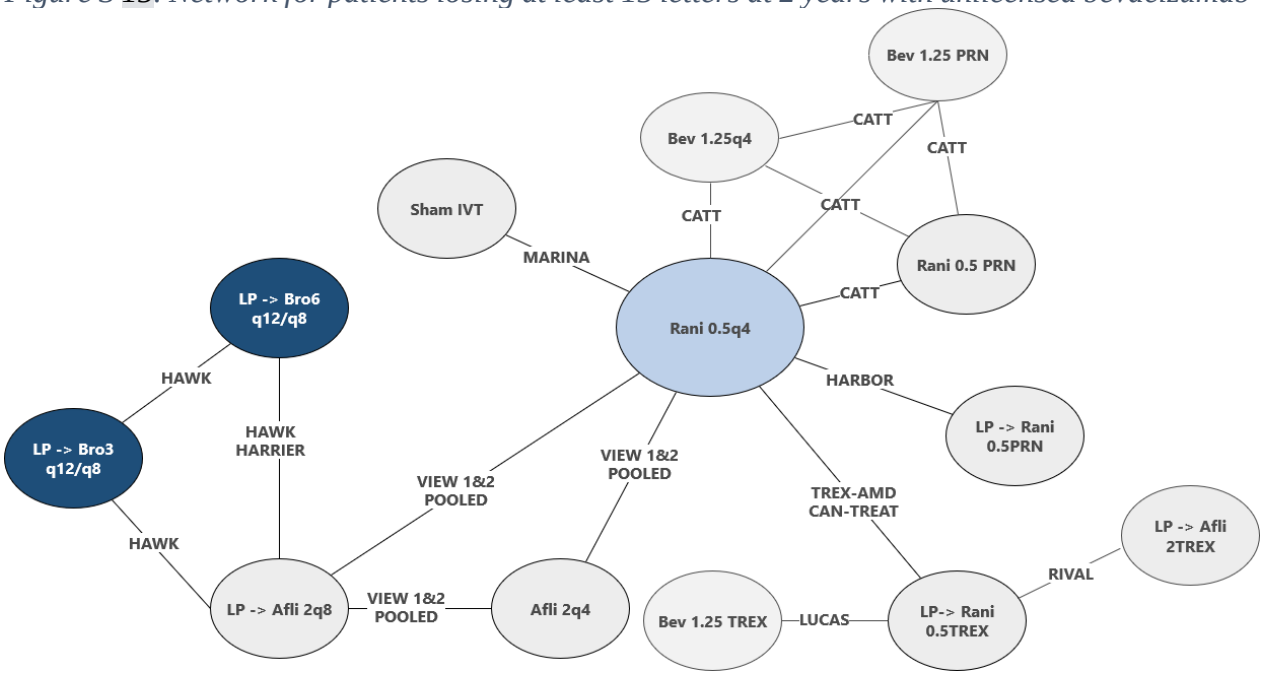


Figure S 16. Network for patients gaining at least 15 letters at 1 year with unlicensed bevacizumab

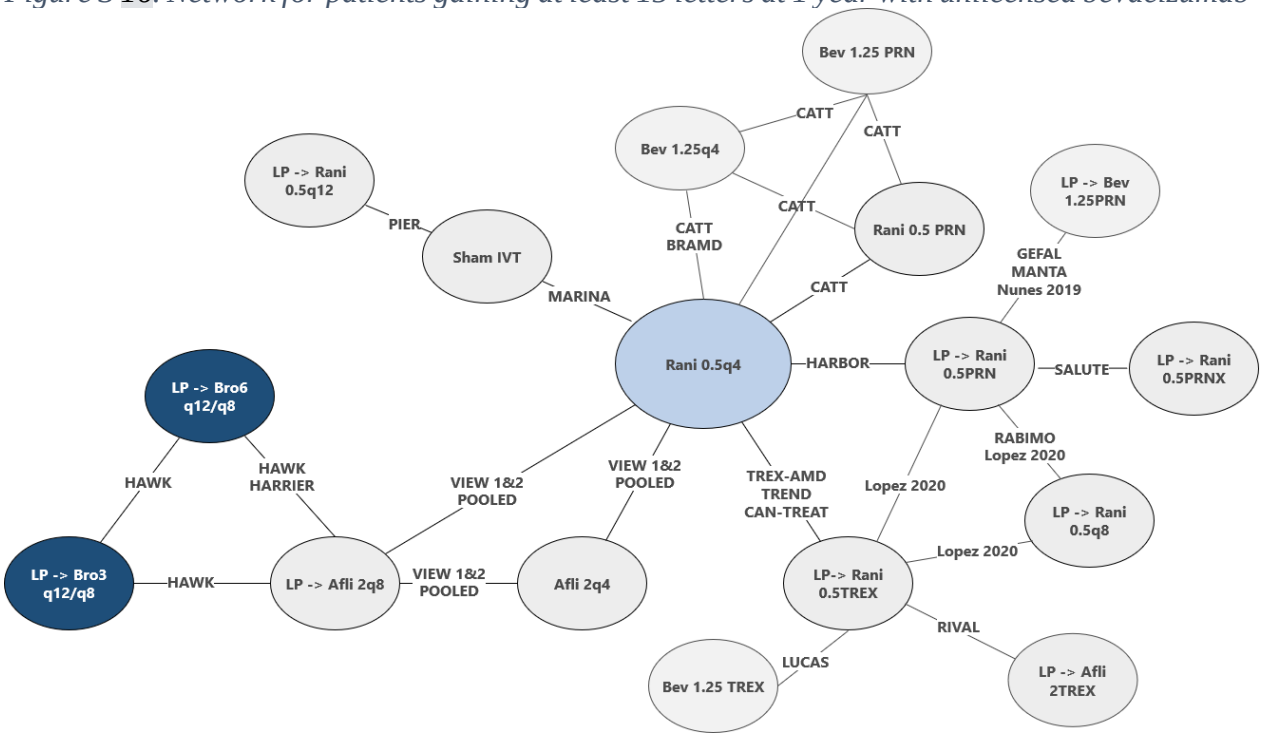


Figure S 17. Network for patients gaining at least 15 letters at 2 years with unlicensed bevacizumab

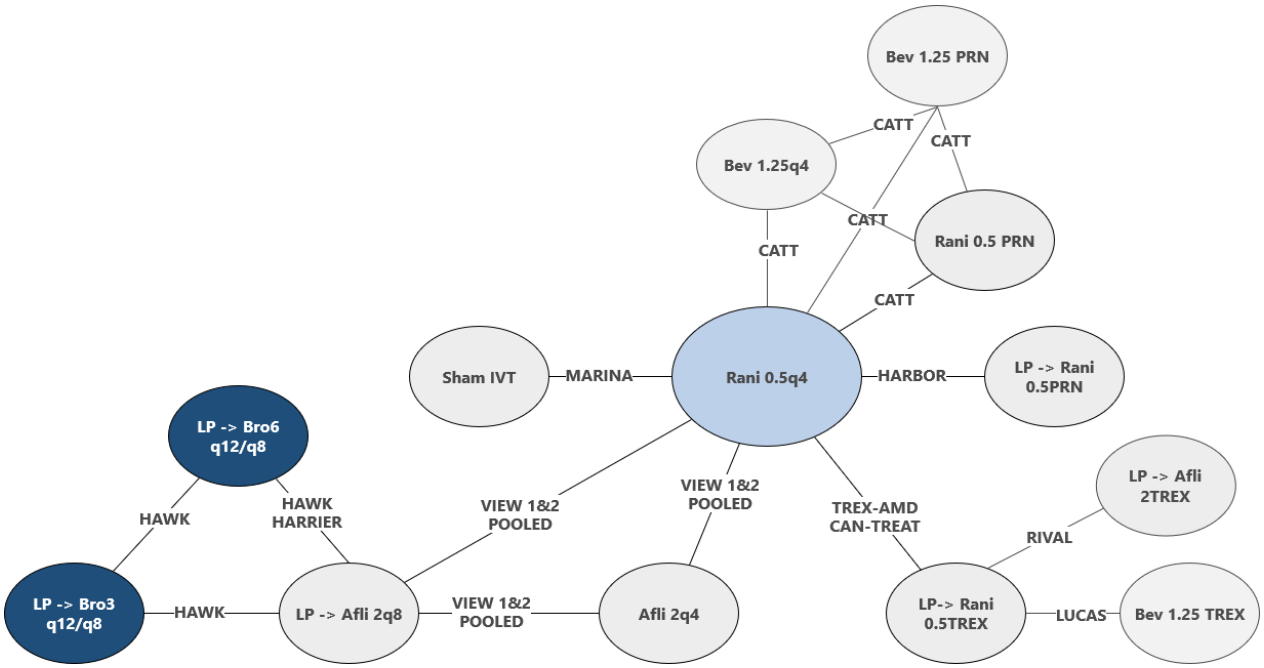


Figure S 18. Network for discontinuation at 1 year with unlicensed bevacizumab

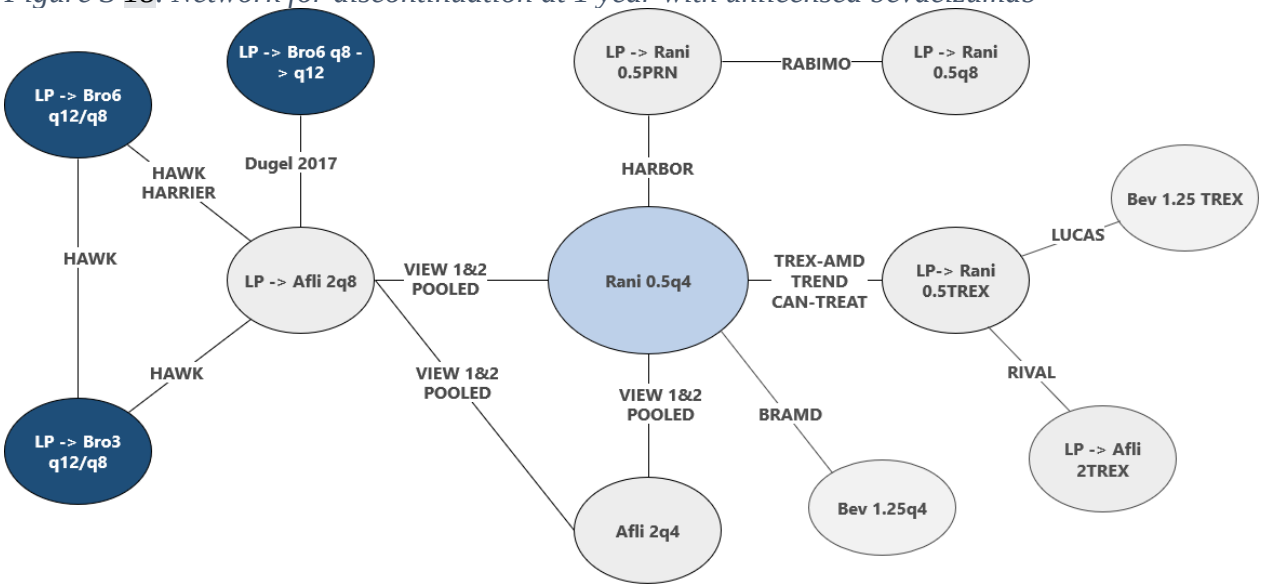


Figure S 19. Network for discontinuation at 2 years with unlicensed bevacizumab

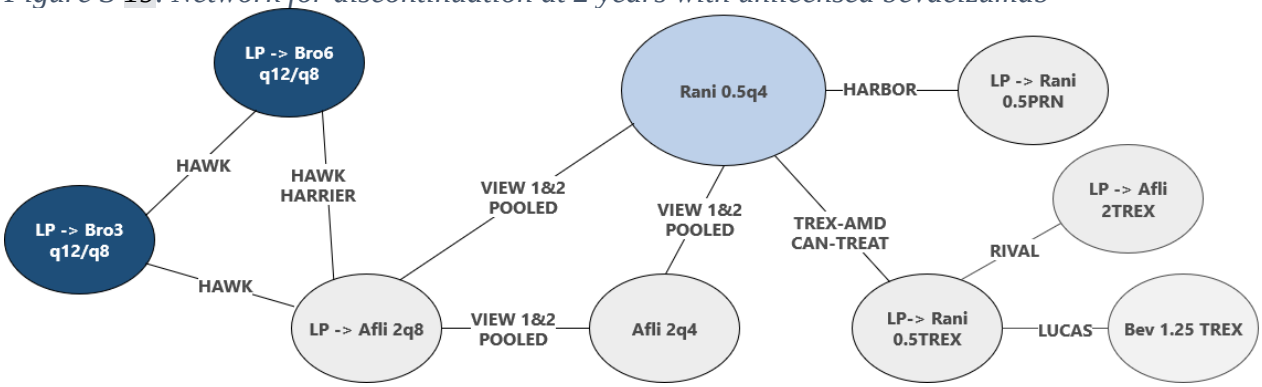


Table S 16. Summary of additional direct comparison results for mean change in BCVA at 1 year

Comparison	Trials	Mean diff [95% CI]		I-square	P-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP -> Bev 1.25PRN vs. LP -> Rani 0.5PRN	GEFAL MANTA Scholler 2014 Nunes 2019	1.34 [-1.22, 3.9]	1.35 [-1.97, 4.67]	29.4%	0.236
Bev 1.25q4 vs. Rani 0.5q4	BRAMD CATT	-0.85 [-2.71, 1.02]	-0.85 [-2.71, 1.02]	0%	0.674

Table S 17. Summary of additional direct comparison results for mean change in retinal thickness at 1 year

Comparison	Trials	Mean diff [95% CI]		I-square	P-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP -> Bev 1.25PRN vs. LP -> Rani 0.5PRN	GEFAL MANTA Scholler 2014 Nunes 2019	14.4 [-2.91, 31.71]	15.76 [-4.23, 35.75]	14.38%	0.320
Bev 1.25q4 vs. Rani 0.5q4	BRAMD CATT	17.99 [-2.01, 37.99]	18.48 [-5.94, 42.9]	32.37%	0.224

Table S 18. Summary of additional direct comparison results for patients losing at least 15 letters at 1 year

Comparison	Trials	Mean diff [95% CI]		I-square	P-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP -> Bev 1.25PRN vs. LP -> Rani 0.5PRN	GEFAL MANTA Scholler 2014	0.88 [0.51, 1.51]	0.88 [0.51, 1.51]	0.00%	0.994
Bev 1.25q4 vs. Rani 0.5q4	BRAMD CATT	1.53 [0.89, 2.63]	1.58 [0.7, 3.57]	53.45%	0.143

Table S 19. Summary of additional direct comparison results for patients gaining at least 15 letters at 1 year

Comparison	Trials	Mean diff [95% CI]		I-square	P-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP -> Bev 1.25PRN vs. LP -> Rani 0.5PRN	GEFAL MANTA Nunes 2019	0.96 [0.68, 1.37]	0.96 [0.66, 1.40]	6.59%	0.343
Bev 1.25q4 vs. Rani 0.5q4	BRAMD CATT	1.00 [0.75, 1.35]	1.04 [0.69, 1.55]	40.17%	0.196

Table S 20. Cumulative surface under the cumulative ranking curves (SUCRA), comparison of LP -> Bro 6q12/q8 versus of each comparator and probabilities for LP -> Bro 6q12/q8 to perform better than each comparator for all outcomes at 1 and 2 years with unlicensed bevacizumab

Treatment	SUCRA	Comparison* of LP -> Bro 6q12/q8 vs each comparator [95% CrI]	Probability for LP -> Bro 6q12/q8 to perform better than each comparator	SUCRA	Comparison* of LP -> Bro 6q12/q8 vs each comparator [95% CrI]	Probability for LP -> Bro 6q12/q8 to perform better than each comparator
Mean change in BCVA		**1 year**			**2 years**	
Rani 0.5q4	64%	-0.76 [-2.74,1.26]	23%	69%	-0.27 [-2.45, 1.9]	40%
Rani 0.5PRN	33%	1.08 [-1.84,3.99]	77%	32%	1.85 [-2.06, 5.71]	83%
Bev 1.25q4	48%	0.08 [-2.68,2.80]	52%	50%	0.72 [-3.59, 5.08]	63%
Bev 1.25PRN	22%	1.98 [-1.12,5.05]	90%	14%	3.54 [-0.55, 7.63]	95%
LP -> Afli 2q8	58%	-0.44 [-1.74,0.85]	25%	61%	0.02 [-1.45, 1.50]	51%
LP -> Bro 6q8 -> q12	43%	0.75 [-5.63,7.10]	59%	-	-	-
LP -> Rani 0.5PRN	38%	0.63 [-2.16,3.43]	67%	43%	0.92 [-2.35, 4.22]	71%
LP -> Bro 6q12/q8	49%	-	-	61%	-	-
LP -> Bro 3q12/q8	42%	0.38 [-1.41,2.18]	66%	61%	0.01 [-2.00, 2.04]	50%
Sham IVT	0%	16.84 [13.33,20.35]	100%	0%	21.23 [17.45, 25.05]	100%
LP -> Rani 0.5q12	44%	0.75 [-6.78,8.27]	58%	-	-	-
LP -> Rani 0.5TREX	65%	-0.83 [-3.23,1.55]	25%	77%	-0.74 [-3.80, 2.27]	31%
Afli 2q4	74%	-1.34 [-3.33,0.64]	9%	60%	0.02 [-2.15, 2.2]	51%
LP -> Rani 0.5q8	55%	-0.36 [-4.40,3.68]	43%	-	-	-
LP -> Rani 0.5PRNX	79%	-3.83 [-12.59,4.87]	20%	-	-	-
LP -> Afli 2TREX	28%	1.57 [-1.81,4.97]	82%	39%	1.27 [-2.86, 5.35]	73%
Bev 1.25q6	46%	0.43 [-5.24,6.04]	56%	-	-	-
LP -> Bev 1.25TREX	57%	-0.57 [-6.08,4.94]	42%	-	-	-
LP -> Bev 1.25PRN	61%	-0.71 [-4.49,3.09]	36%	-	-	-
LP (q26) -> Bev 1.25q12	27%	2.95 [-5.14,10.9]	76%	-	-	-
LP (q26) -> Bev 1.25PRN	32%	1.87 [-4.32,7.99]	72%	-	-	-

Bev 1.25q8	88%	-3.97 [-9.40,1.35]	7%	-	-	-
LP (4q4) -> Fari 6q8-q16	62%	-0.65 [-2.50,1.23]	25%	-	-	-
LP (4q4) -> Fari 6q12	61%	-1.24 [-8.66,6.28]	37%	-	-	-
LP (4q4) -> Fari 6q16	73%	-2.53 [-9.68,4.61]	24%	-	-	-
Bev 1.25 TREX	-	-	-	82%	-1.54 [-6.05, 2.93]	25%
Mean change in retinal thickness		**1 year**			**2 years**	
Rani 0.5q4	58%	-50.23 [-70.26,-29.77]	100%	65%	-49.41 [-71.45, -27.99]	100%
LP -> Afli 2q8	71%	-39.61 [-52.84,-26.39]	100%	44%	-35.04 [-48.98, -21.14]	100%
LP -> Rani 0.5PRN	42%	-61.92 [-90.77,-32.83]	100%	75%	-58.25 [-90.78, -25.37]	100%
Afli 2q4	70%	-40.29 [-60.64,-19.77]	100%	50%	-39.53 [-61.25, -17.98]	100%
Rani 0.5PRN	35%	-67.89 [-101.95,-33.89]	100%	82%	-67.75 [-109.63, -26.06]	100%
LP -> Bro 6q8 -> q12	80%	-22.84 [-77.22,31.52]	80%	-	-	-
LP -> Bro 6q12/q8	98%	-	-	15%	-	-
LP -> Bro 3q12/q8	93%	-10.37 [-28.06,7.37]	87%	15%	0.39 [-17.96, 18.85]	48%
LP -> Rani 0.5TREX	52%	-54.77 [-84.06,-25.62]	100%	36%	-19.89 [-87.84, 48.04]	72%
LP -> Rani 0.5q8	31%	-71.54 [-109.18,-33.89]	100%	-	-	-
LP -> Afli 2TREX	79%	-28.95 [-72.07,14.56]	90%	12%	11.26 [-64.61, 87.31]	39%
Bev 1.25q4	39%	-64.38 [-92.70,-36.24]	100%	67%	-54.02 [-102.49, -5.77]	99%
Bev 1.25PRN	20%	-82.78 [-116.69,-49.02]	100%	93%	-80.57 [-122.98, -38.70]	100%
Bev 1.25TREX	42%	-61.97 [-97.59,-26.54]	100%	46%	-28.27 [-100.15, 42.35]	78%
LP -> Bev 1.25PRN	27%	-74.31 [-108.21,-40.97]	100%	-	-	-
Bev 1.25q6	24%	-81.4 [-125.45,-36.87]	100%	-	-	-
LP (q26) -> Bev 1.25q12	3%	-132.56 [-196.36,-69.46]	100%	-	-	-
Bev 1.25q8	28%	-76.72 [-121.91,-31.44]	100%	-	-	-

LP (q26) -> Bev 1.25PRN	5%	-124.25 [-182.71,-65.51]	100%	-	-	-
LP (4q4) -> Fari 6q8-q16	83%	-27.57 [-42.38,-12.8]	100%	-	-	-
LP (4q4) -> Fari 6q12	70%	-39.47 [-77.91,-1.09]	98%	-	-	-
LP (4q4) -> Fari 6q16	50%	-55.32 [-92.47,-18.24]	100%	-	-	-
Patients losing at least 15 letters		**1 year**			**2 years**	
Rani 0.5q4	67%	0.80 [0.39,1.65]	73%	63%	0.89 [0.50, 1.56]	65%
LP -> Rani 0.5PRN	25%	0.31 [0.10,0.91]	98%	29%	0.54 [0.23, 1.28]	92%
LP -> Afli 2q8	77%	0.97 [0.61,1.54]	55%	73%	1.00 [0.68, 1.48]	50%
LP -> Rani 0.5q12	63%	0.74 [0.19,3.21]	66%	-	-	-
LP -> Rani 0.5q8	37%	0.41 [0.11,1.56]	90%	-	-	-
Afli 2q4	77%	0.97 [0.47,2.01]	53%	69%	0.97 [0.54, 1.71]	55%
LP -> Rani 0.5TREX	60%	0.71 [0.29,1.74]	77%	39%	0.65 [0.26, 1.61]	82%
Rani 0.5PRN	69%	0.83 [0.29,2.36]	64%	57%	0.82 [0.28, 2.2]	66%
LP -> Bro 6q12/q8	78%	-	-	72%	-	-
LP -> Bro 3q12/q8	78%	1.01 [0.56,1.84]	49%	61%	0.89 [0.54, 1.47]	68%
Sham IVT	3%	0.07 [0.03,0.19]	100%	0%	0.11 [0.05, 0.23]	100%
LP -> Rani 0.5PRNX	31%	0.30 [0.04,2.00]	89%	-	-	-
LP -> Afli 2TREX	40%	0.42 [0.08,2.12]	85%	48%	0.70 [0.16, 3.17]	68%
Bev 1.25TREX	66%	0.81 [0.20,3.29]	62%	63%	0.91 [0.28, 3.01]	56%
LP -> Bev 1.25PRN	32%	0.36 [0.10,1.20]	95%	-	-	-
Bev 1.25q6	29%	0.28 [0.04,1.59]	92%	-	-	-
LP (q26) -> Bev 1.25q12	19%	0.16 [0.01,1.62]	94%	-	-	-
Bev 1.25q4	44%	0.52 [0.21,1.27]	93%	53%	0.77 [0.25, 2.33]	68%
Bev 1.25PRN	35%	0.42 [0.16,1.11]	96%	22%	0.48 [0.17, 1.24]	93%
LP (4q4) -> Fari 6q8-q16	72%	0.9 [0.45,1.82]	61%	-	-	-
LP (4q4) -> Fari 6q16	49%	0.48 [0,32.07]	63%	-	-	-

Patients gaining at least 15 letters		**1 year**			**2 years**	
Rani 0.5q4	60%	1.12 [0.81,1.57]	75%	49%	1.22 [0.88, 1.69]	88%
LP -> Rani 0.5PRN	56%	1.16 [0.73,1.84]	74%	42%	1.3 [0.80, 2.10]	85%
LP -> Afli 2q8	51%	1.2 [0.95,1.50]	94%	62%	1.11 [0.89, 1.39]	83%
LP -> Rani 0.5q12	5%	7.72 [1.94,30.76]	100%	-	-	-
LP -> Rani 0.5q8	37%	1.41 [0.74,2.69]	85%	-	-	-
Afli 2q4	67%	1.07 [0.77,1.49]	65%	45%	1.24 [0.90, 1.73]	90%
LP -> Rani 0.5TREX	69%	1.05 [0.69,1.59]	59%	73%	1.02 [0.61, 1.70]	53%
Rani 0.5PRN	22%	1.65 [1.02,2.68]	98%	40%	1.34 [0.77, 2.34]	85%
LP -> Bro 6q12/q8	74%	-	-	77%	-	-
LP -> Bro 3q12/q8	37%	1.37 [1.01,1.86]	98%	80%	0.96 [0.72, 1.29]	40%
Sham IVT	1%	11.11 [5.53,23.86]	100%	0%	16.09 [7.55, 37.64]	100%
LP -> Rani 0.5PRNX	85%	0.66 [0.21,2.01]	23%	-	-	-
LP -> Afli 2TREX	57%	1.15 [0.55,2.4]	64%	34%	1.49 [0.66, 3.43]	83%
Bev 1.25TREX	60%	1.11 [0.6,2.09]	63%	73%	0.98 [0.49, 1.97]	48%
LP -> Bev 1.25PRN	51%	1.21 [0.67,2.16]	74%	-	-	-
Bev 1.25q4	61%	1.12 [0.72,1.74]	69%	47%	1.28 [0.69, 2.37]	78%
LP (4q4) -> Fari 6q12	47%	1.35 [0.33,5.54]	66%	-	-	-
Bev 1.25PRN	35%	1.4 [0.87,2.29]	92%	27%	1.51 [0.86, 2.64]	92%
LP (4q4) -> Fari 6q16	74%	0.8 [0.21,2.92]	37%	-	-	-
Discontinuation		**1 year**			**2 years**	
Rani 0.5q4	48%	1.00 [0.59,1.71]	49%	33%	0.94 [0.61, 1.41]	38%
LP -> Afli 2q8	36%	0.87 [0.61,1.25]	77%	12%	0.81 [0.61, 1.06]	7%
LP -> Rani 0.5PRN	69%	1.35 [0.57,3.26]	25%	71%	1.24 [0.66, 2.32]	75%
LP -> Rani 0.5q8	93%	4.6 [0.63,46.15]	7%	-	-	-
Afli 2q4	63%	1.17 [0.67,2.02]	29%	42%	0.98 [0.64, 1.48]	45%
LP -> Rani 0.5TREX	69%	1.28 [0.67,2.44]	23%	76%	1.28 [0.71, 2.28]	79%

LP -> Bro 6q8 -> q12	58%	1.2 [0.23,7.14]	41%	-	-	-
LP -> Bro 6q12/q8	49%	-	-	46%	-	-
LP -> Bro 3q12/q8	69%	1.29 [0.81,2.10]	14%	59%	1.09 [0.76, 1.57]	68%
LP -> Afli 2TREX	52%	1.06 [0.38,2.91]	46%	41%	0.97 [0.42, 2.24]	47%
Bev 1.25TREX	65%	1.27 [0.5,3.2.00]	30%	70%	1.27 [0.60, 2.67]	73%
Bev 1.25q4	32%	0.79 [0.37,1.69]	72%	-	-	-
LP (4q4) -> Fari 6q8-q16	26%	0.73 [0.41,1.30]	86%	-	-	-
LP (4q4) -> Fari 6q12	8%	0.10 [0.00,1.77]	93%	-	-	-
LP (4q4) -> Fari 6q16	13%	0.14 [0.00,2.35]	90%	-	-	-

*Comparison corresponds to odds ratio for patients losing at least 15 letters, patients gaining at least 15 letters and discontinuation and corresponds to mean differences for mean change in BCVA and mean change in retinal thickness