

Figure 1A

SNPs genotyped in AVITA and associated with bevacizumab outcome

	SNP_ID	Rare diagnostic allele	SEQUENCE
SEQ ID NO:1	rs9554316	T	ATAGACACAAATTCTAAGAAATCGTAAAGACATCATTCGATTTTTTTTCT[T/T/G]GAACTCAATG GAATTCTCAGCCCCCAGCCCTTGGTCATGGTCTCCAGCAA
SEQ ID NO:2	rs9582036	C	TGCTGCGATTACAGGCACGAGCCACTGTGCCCAGCAACAATAGCCTTCTT[C/A]CAAAAATGT ATACTAAAGTATTTAGGAGTAAAGTGCTATTATGCCTTAAGC
SEQ ID NO:3	rs9513070	G	TTGCTTTTATACTATAATGCAAGCTTGCCCCAACTTGTGGCCCCACGGGCT[G/A]CATGAATCC CAGGATGGCTTTGAGTGCAGCCCAACAACTCGTAACT
SEQ ID NO:4	rs9554320	A	TTTCCGGGGCTGTGAGCAAGGTTCCCTGTGTGTAGCTGATCATTTCTCCCCC[A/C]GCACTGCA AAGCCGCTGTTACAAACTGGCCTCCCACTCAAGGCACAC

Figure 1B

SNPs belonging to the rs9554316 and rs9582036 haplotype block (within the locus) but not genotyped within AVITA

	SNP_ID	Rare diagnostic allele	SEQUENCE
SEQ ID NO:5	rs17619037	G	AGTGCAAAACATCCACAAGCCCCAGGAAAAAAGTGTCCAAGACAGGCA[A/G]GCAAGTG CAATTTGCACAGTGGAGAAAGCCTCACATGGACACCCGAAAAG
SEQ ID NO:6	rs9579177	G	ACATTACTGGCGTTGGTGTGTTGGAAGGATCTGAAGAAGGGTCTATCGG[G/A]GTGCACT AGGTACCTTAACCTCACGACTTACATCAAAACATGGAGGTGGCA
SEQ ID NO:7	rs9579176	G	CCCCTTAGCCCCCTCAACCCACATCACAGGGCTTTAGAGAGAAGAGCTGG[G/A]AGACCTCT TGTTTGCCAGGCTATACTGTTAGCTTCTCCCATTTGTATTG
SEQ ID NO:8	rs9554319	C	CTTCTTCCAAAATGTATACTAAAGTATTTAGGAGTAAAGTGCTATTATGC[C/T]TTAAGCCTC CTTTTAAATGGTTTGGCAAAAAGAAAAATCCGTAAACAAACA
SEQ ID NO:9	rs7996030	A	CTCCAGAGGGACCTACTCTGTCCGTTGTGAAATCAGAGAATGCCAGAC[A/G]TAGGAGA GACTGGAGGCATCATCTCGTCTGAGTGCCCAATGGCACAGGAG
SEQ ID NO:10	rs9513075	G	GAGGACACCAACGACAGTGACAAGAACAGGTCCTCCCTTCCCTAC[G/A]CTCAGGC AGAGCTCCCAAGCCCTGCTGTGGGCTGAGTCTCCTGTCCAC
SEQ ID NO:11	rs7993418	G	TCCTCAAAGGTTTGTATTCTTCCAGGCTCATGAACCTTGAAGCATTTTAC[G/A]TATCTAATGA AGAAACAGAAAGAATTATCAAGACAGGAAAGGCATCCAG
SEQ ID NO:12	rs9513071	G	TTACTTGTGCTGGGAGATGGCGTTGCTGGGAAAAAACCTGAGAAACCC[T/G]AGTTTCAT ATCCTCCCTCTGACACCTTCTTAGAGGTATGCCTTTAGGGGGCG

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Figure 1C

SNPs 5' up or downstream of the haplotype block (outside the locus) and in LD ($D'/\text{LOD} > 80$) with rs9554316 or rs9582036 but not typed in AVITA

	SNP_ID	Rare diagnostic allele	SEQUENCE
SEQ ID NO:13	rs11620238	G	AGGAAGTGCATGATCTTTCTGACCTGGCCTCCAAGCCATGCAGTGTCCC[T/G]TCTTTC ACATTGCATTGATCACAAAGTGAGTCTTAAGCTAGCTCTGATTCT
SEQ ID NO:14	rs17618631	G	CTTCAAGTCAATTTGCCCTGAATGAATGATTTTATTCTTATGTTATGAAACC[C/G]ATAATAC TTTTTAAAGGATTTTCAGATTCTTGAAAGACAAAATGCCTCTTGC
SEQ ID NO:15	rs12429309	C	GCAGTGTATGAGGGTTCCAATTTCTCCATATCCTCGCCACACTGACTTCA[T/C]CTAGCT ATCCTCATGGCGTAAAGTGGTATCTTATGGTAATTTCTTTCCC
SEQ ID NO:16	rs7982251	C	GTGGCTGTCTGCAGGGACATGCTCTGCATTGAGAGAACACTGGGGAGA[C/T]GACAC GTTTCTCTTTTGTGAAACATGCTCCCGTAGTGATTACTAAATGA
SEQ ID NO:17	rs9508016	A	AGGAGGACATGGGAGGTGATCCACAAAAGTGAATAAATAACACTATGTCT[A/G]AAAAAC AAGCAGGGAAGAGAGCCAGTACGAGCCAGCGGGGAGATGCTAGG
SEQ ID NO:18	rs7982957	A	AGAACAAGTGGGAGACGACACGTTTCTCTTTTGTGAAACATGCTCCCGT[A/T]GTGATT ACTAAATGACATTCTCCAGAGCATGCAACACCGGCAGAGCTA
SEQ ID NO:19	rs3794400	T	AGAAGGACAGAAATACGTTTGTGAGGAGGGAGAGGCAAAAGCCAGCCTCCC[T/C]GCCT CTTAACCAAGACCCCTTGCGAGTAGAGCGGCTTCTGGTTACTGTACACA

Linkage disequilibrium was defined here as having a $D'/\text{LOD} > 80$

Figure 1D

SNPs linked with r^2 equal or larger than 0.12 to rs9554316 (SEQ ID NO. 1), rs9582036 (SEQ ID NO. 2), rs9513070 (SEQ ID NO. 3) or rs9554320 (SEQ ID NO. 4)

	SNP_ID	Rare diagnostic allele	SEQUENCE
SEQ ID NO: 40	rs45455097	C	TGTGTTTTTTAAATTTTTTAAACCAATTTCTTAATACATTTCATTTT[C]ATTATTAATATTT ATACTTCTAAGTATTTTCTTAAGGAAAGTACTTC
SEQ ID NO: 41	rs1886233	A	TACTGGGAGAAAAATTATGAGCATCAACTGGGTAAACTATAATACAAAC[A/G]AACGTTAAG CGTGAAAGGGATAGAAACATAGGGCAGTGTTTGTAAAAAT
SEQ ID NO: 42	rs9554309	C	TAAATAATTTTCATAGAAAGTTCACTAGTAGTACGTAATCTTGTAAAGAGTAT[C/T]GTATGCAAGC TCTCTGATGCCACCCACTGTAGTTCAAATTGAGATTT
SEQ ID NO: 43	rs11619230	T	TGTATGCCACCCACTGTTAGTTCAAATTGAGATTTTGTGTTTGTTC[C/T]TTAAGAACATA CCAAGAAATACCAAGTGAATTGTTGGATATGAATTCCT
SEQ ID NO: 44	rs9554311	C	AAATTGAGATTTTGTGTTTGTGTTTCTTAAGAACATACCAAGAAAAATA[C/T]CAGTGAATTG TTGGATATGAATTCCTGTTAGTTGATTTAAATCCTTCT
SEQ ID NO: 45	rs4771233	T	GAGCCAGAGTTTGTAGACAGGCTGGCAACATAGTGAGACCTTGTCTC[T/C]ACAAAAAG TAAATCAGCCAGGCATGTTGTCAGCACCTGTAGCCCCAGC
SEQ ID NO: 46	rs6491274	C	GGAGCACCTTACATGGCTCCATGTGGCTTAGGTTCTCCAAGTATGGC[T/C]GCTGGGTC CCTGGCGGAACTGTTGAAGAGTGAGTGACCAAGACTCAGG
SEQ ID NO: 47	rs7982639	G	TTCAAAAGTCAGGAAAAAGAGGTAAACCCAGCAAAAGACAGCAGGTAGCCT[A/G]TGAGATGG GAAGAAAGAAATCATGTCCTGGAAACCAACTGAAGTTGTT
SEQ ID NO: 48	rs12877718	C	ATAAGTGTGTTCTTTAAAGCACTTTAAATAGTTGCTGGCACATATTGGG[T/C]ACTCAAATGA TAGCAATGATAGCAATTACTAGCTATCACTGCTTCCCAA
SEQ ID NO: 49	rs10507382	C	TGGAAAAAGAAAGGATAATATAGGTATGTTTCAAAACAAATATATTTTAG[T/C]CTGAGATTAA GCCCTTCCACCTTTTAAATGGGTTTTCTCTATGAAAAAG
SEQ ID NO: 50	rs57354941	T	AACATTAGTAGCATCTGGTTGGATTTTGGTTTTTTTTTCCCCCTCCCT[C/T]AAGTGTTCTT AGCTCGCAGAAAGAAAGTGGCCATCCCTGTGTTGGAT
SEQ ID NO: 51	rs17086497	A	AGTTCCAGAGCCATGAGAACATTTCTAACTGACGTGACATGATTCTCCT[C/A]AAGCATTCCT CAAGTCATTTGCCGTGAATGAATGATTTTATCTTATGTTA
SEQ ID NO: 52	rs3794395	T	TGGCATGGCTACACGGCTAAATATTATTAATGGCATAATCGAGTGCTAG[C/T]GCCAGGCTT GTATTTTGTGTGTGTGATTACAGATTGGGAGAAATTGG
SEQ ID NO: 53	rs9554317	T	CCATCTCGGCCTCCAGAGTGCTGGGATTACAGGCGTGAGCCACTGTGCC[C/T]GGCCGCAA GCAGTATTTTCTGACTGCTGAGCTTCTTCCCATATCTCCC
SEQ ID NO: 54	rs9513073	G	TATGTAAAGACTTGAAGGTTTGAGAAAGTCCAAAGCAGTTTTTGGTCCAA[A/G]GCTGATGTG ACTTTGTACCTCTGAGTTATTTGCGACCACAGCCTGGGTAT

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SNPs linked with r^2 equal or larger than 0.12 to rs9554316 (SEQ ID NO. 1), rs9582036 (SEQ ID NO. 2), rs9513070 (SEQ ID NO. 3) or rs9554320 (SEQ ID NO. 4)

	SNP_ID	Rare diagnostic allele	SEQUENCE
SEQ ID NO: 55	rs9513074	T	ATGCTTAAATAGTGGCACTTATAAGCACCAATAACTATTTAATCAGTA[C/T]TATTCAATAC TGTATAATAAACTAATTCAGGCCAGGCATGGAGGCT
SEQ ID NO: 56	rs9508015	T	TAGTGGCACTTATAAGCACCAATAACTATTTAATCAGTACTATTCAATA[C/T]TGTATTATAATAA AACTAATTCAGGCCAGGCATGGAGGCTACGCCTGTA
SEQ ID NO: 57	rs2011950	G	CTGCAATCTCGCTTCATAGGCTCAAGTGATTCTCATGCCTCAGCCTCCC[A/G]AGTAGCTGC CACCAGGCCGGCTAACTTTTGTATTTTAGTAGAGACGGG
SEQ ID NO: 58	rs9513110	G	AACAGATCTTTGTTTAGAAAGAGAAAGACAATCCGAAACAACCAAGG[T/G]GGACTCTAG ACCCCATGGAGGAGTGATCAGAGCTCATGAGAGTACCAG
SEQ ID NO: 59	rs9513112	A	TAGCTCTATAGTAGGCAGAAATATCCTTAAAGTTCAATTAAGTTCTCAG[G/A]TCTTATTTAA AGAAATGTACCCCAATGCTAGCAATGATTACAACCTTGCA
SEQ ID NO: 60	rs9513113	T	CGTTACACGTTTTGTGCTAAGTTATTCATTTCCATGGCGAGAAATGT[C/T]GATGAAAAAC AACACTAGCTTGAGGCTGATGCATTAATCTTTCATACATA
SEQ ID NO: 61	rs9551471	G	ACAATCCCTTTTCTCCACCTAGAAATCATGCAATAGAAATACCAGTCTAC[A/G]CTCTTCAAAA CAAAACCCCGAGACATCAAAAGACAGTATCTATGCATATC
SEQ ID NO: 62	rs2296285	A	CCAGTTGAAAAAGGGGAAAAAATCAAAATACCTTCCCCCAACAGATTA[T/A]AAAAGGAAAT ACCAACAGCCACAAAGAGCTCGAAACCTTTTCTATCGCC
SEQ ID NO: 63	rs9513116	A	CTCTAAAGCCAATACCAATTTAGCACTGGGTCCACTGAAATTTCTATCC[G/A]AAGATATCA GAACTTCAGTGATTGTGTCCCTCCAAACACTATGCAAAAC
SEQ ID NO: 64	rs9551473	G	ACATATAAAAGAAATATATACAATGCCCAAGTGGGATTTTTCAGGAA[T/G]GCAAGATTG GTTTAACATCCAAAAACCAATGTAATTACTATATCATGTCA
SEQ ID NO: 65	rs7330109	T	TAAATGGCAGAAAGAGATTGACAAAAATCCAAGCTCCTTTTCGTGATG[A/T]AAACACTCA GGAAATGGGAATTGCACTGAATTTCTCAACCTAATAAAT
SEQ ID NO: 66	rs9508037	G	AGAAATTAAAGAAAGATCTACTAAGTGGGAAACATCTCATGTTCTGGATT[A/G]GAAGACTTA ATATTGTTAAGATGTTAATGTCCCCCAAATTGATCTACAGA
SEQ ID NO: 67	rs1924981	T	ATACATGAAAGAACCTCAAAAATATTATGCTGAGTGAAGAAATTAGTCA[C/T]JAAAAGACTA CAAATTATGTAATCTATTATATAAAATATCCATGAGACAA
SEQ ID NO: 68	rs34140996	G	ATAAGGGGTGATAGCTAAAGGCTATGGAGTTTATTTGAGACAATGACAT[A/G]TTCCTAAAT TGACCGTGATGATGATTGTCATATATCTGTCAATATGCT
SEQ ID NO: 69	rs7985584	A	TGTCAATATGCTACAAACCACTGAATCATCATTTTAAATGGGTGTGGTAT[G/A]TAAATTATAT CTCAATAAAACCTATTGTAATTAATAAACAGAGTTTAGTC
SEQ ID NO: 70	rs7992940	G	AATAAGAAAGTGCCTCTTTCTAAAAAGAGCTCTTTCCTACTACCTGCCT[T/G]TCTCAGAA GAAAGACATTGCTTTTGTGTTTGTGTTTGTGTTT

SNPs linked with r^2 equal or larger than 0.12 to rs9554316 (SEQ ID NO. 1), rs9582036 (SEQ ID NO. 2), rs9513070 (SEQ ID NO. 3) or rs9554320 (SEQ ID NO.4)

SEQ ID NO: 71	SNP_ID	Rare diagnostic allele	SEQUENCE
SEQ ID NO: 71	rs718273	T	CCTTGAAGCTATTACTGACCAATCAGAATACTACTAAGGATCTCTCT[C/T]GCCTCCTTCC TCCCTCATCCCTCAGTCTCTCTTCTCCTTCTCCCTCTTC

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Figure 2

		2nd-PCR PRIMER SEQ	
SEQ ID NO:2	SNP ID	ACGTTGGATGACTGTGCCCCAGCAACAATAG	SEQ ID NO:20
SEQ ID NO:1	rs9582036	ACGTTGGATGATCGTAAAGACATCATTCG	SEQ ID NO:25
SEQ ID NO:4	rs9554316	ACGTTGGATGTTGGAGGCCAGTTTGTAAAC	SEQ ID NO:30
SEQ ID NO:3	rs9554320	ACGTTGGATGGCAAGCTTGCCCAACTGTG	SEQ ID NO:35
SEQ ID NO:3	rs9513070		

		1st-PCR PRIMER SEQ	
SEQ ID NO:2	SNP ID	ACGTTGGATGGCATAATAGCACTTTACTCC	SEQ ID NO:21
SEQ ID NO:1	rs9582036	ACGTTGGATGTGCTGGAGACCATGACCAAG	SEQ ID NO:26
SEQ ID NO:4	rs9554316	ACGTTGGATGAGCAAGGTTCTGTGTAG	SEQ ID NO:31
SEQ ID NO:3	rs9554320	ACGTTGGATGGTTTGTGTGGGCTGCACTC	SEQ ID NO:36
SEQ ID NO:3	rs9513070		

		AL	MT	UEP MASS	UEP SEQ	
SEQ ID NO:2	SNP ID	91	46,9	5442,6	AGCAACAATAGCCTTCTT	SEQ ID NO:22
SEQ ID NO:1	rs9582036	100	48,2	7282,8	AAGACATCATTCGATTTTCTTCT	SEQ ID NO:27
SEQ ID NO:4	rs9554316	93	98,4	5515,6	ACAGCGGCTTGCAGTGC	SEQ ID NO:32
SEQ ID NO:3	rs9554320	93	97	5203,4	CGTGTGGCCCCACGGGCT	SEQ ID NO:37
SEQ ID NO:3	rs9513070					

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Figure 2 (continued)

	SNP ID	EXT1_CALL	EXT1_MASS	EXT1_SEQ	
SEQ ID NO:2	rs9582036	C	5689,8	AGCAACAATAGCCTTCTTC	SEQ ID NO:23
SEQ ID NO:1	rs9554316	G	7570	AAGACATCATTCGATTTTCTG	SEQ ID NO:28
SEQ ID NO:4	rs9554320	C	5802,8	ACAGCGGCTTTCAGTGCG	SEQ ID NO:33
SEQ ID NO:3	rs9513070	A	5474,6	CGTGTGGCCACGGGCTA	SEQ ID NO:38

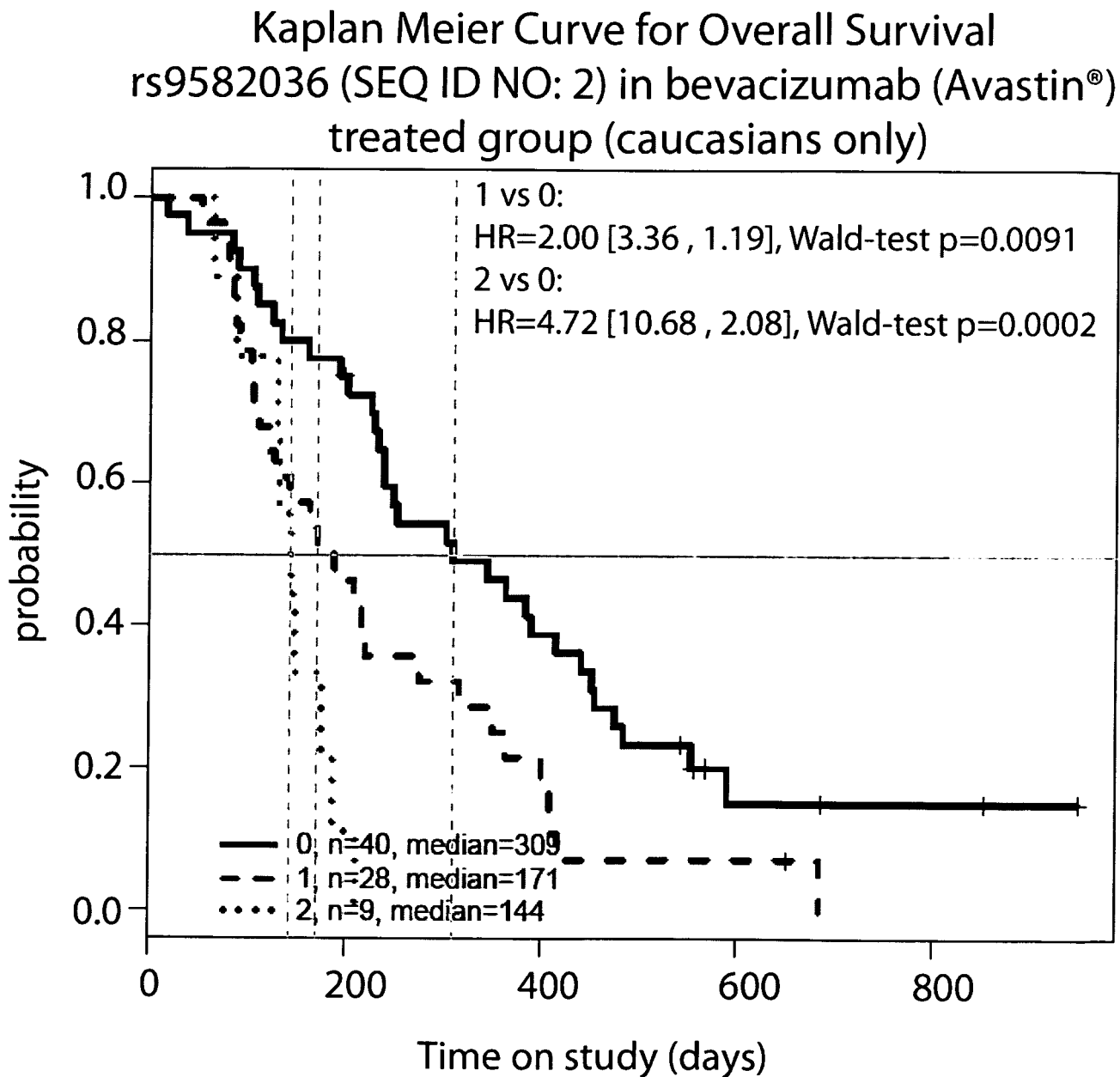
	SNP ID	EXT2_CALL	EXT2_MASS	EXT2_SEQ	
SEQ ID NO:2	rs9582036	A	5713,8	AGCAACAATAGCCTTCTTA	SEQ ID NO:24
SEQ ID NO:1	rs9554316	T	7609,9	AAGACATCATTCGATTTTCTT	SEQ ID NO:29
SEQ ID NO:4	rs9554320	A	5842,7	ACAGCGGCTTTCAGTGCT	SEQ ID NO:34
SEQ ID NO:3	rs9513070	G	5490,6	CGTGTGGCCACGGGCTG	SEQ ID NO:39

Abbreviations:

SEQ Sequence
 AL AMPLICON LENGTH
 MT Melting Temperature
 UEP Unextended primer mass
 EXT1 Extended product 1
 EXT2 Extended product 2

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Figure 3



In the legend 0, 1 and 2 refer to genotypes:

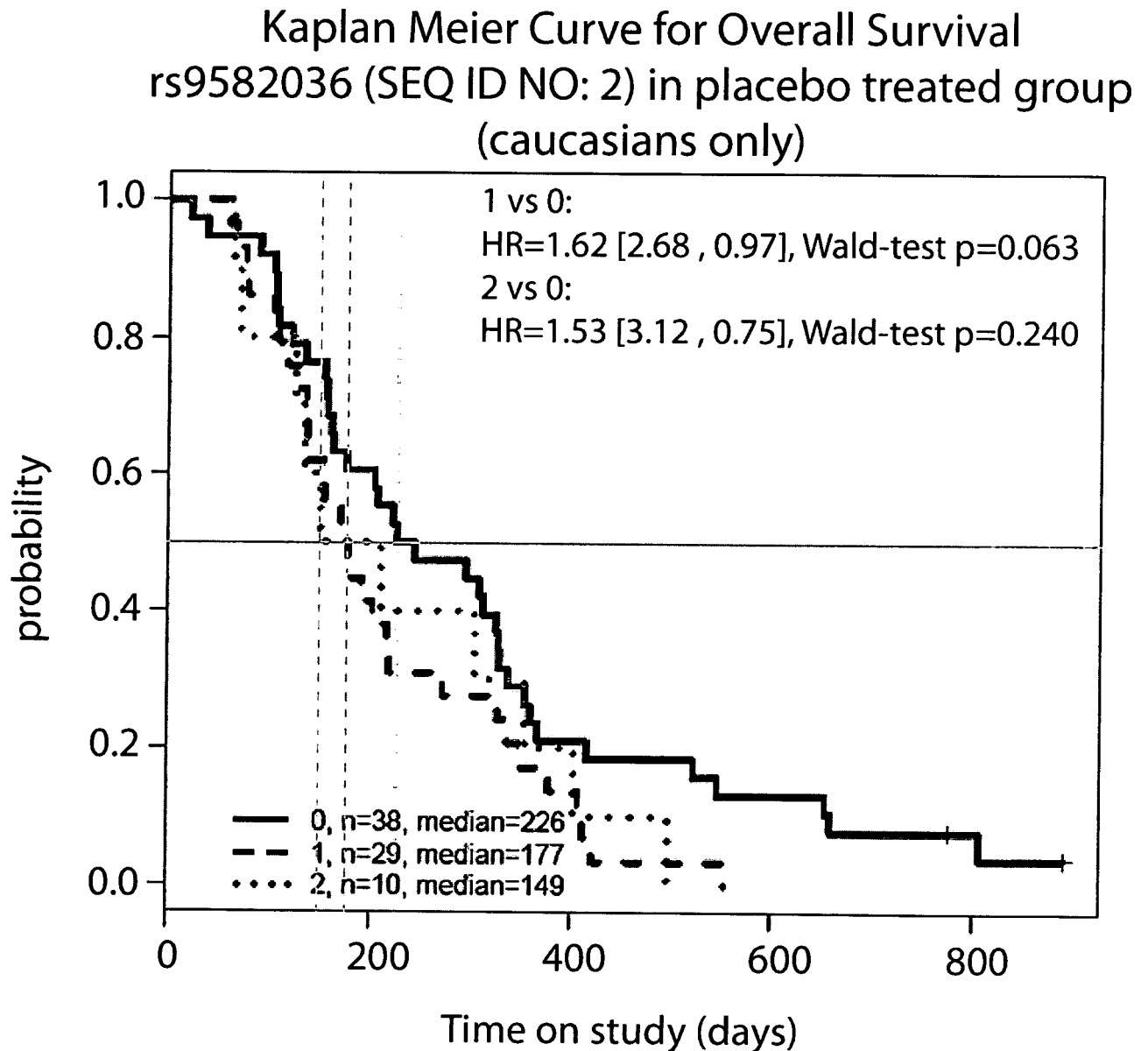
0: AA (n=40, median=309)

1: AC (n=28, median=171)

2: CC (n=9, median=144)

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Figure 4

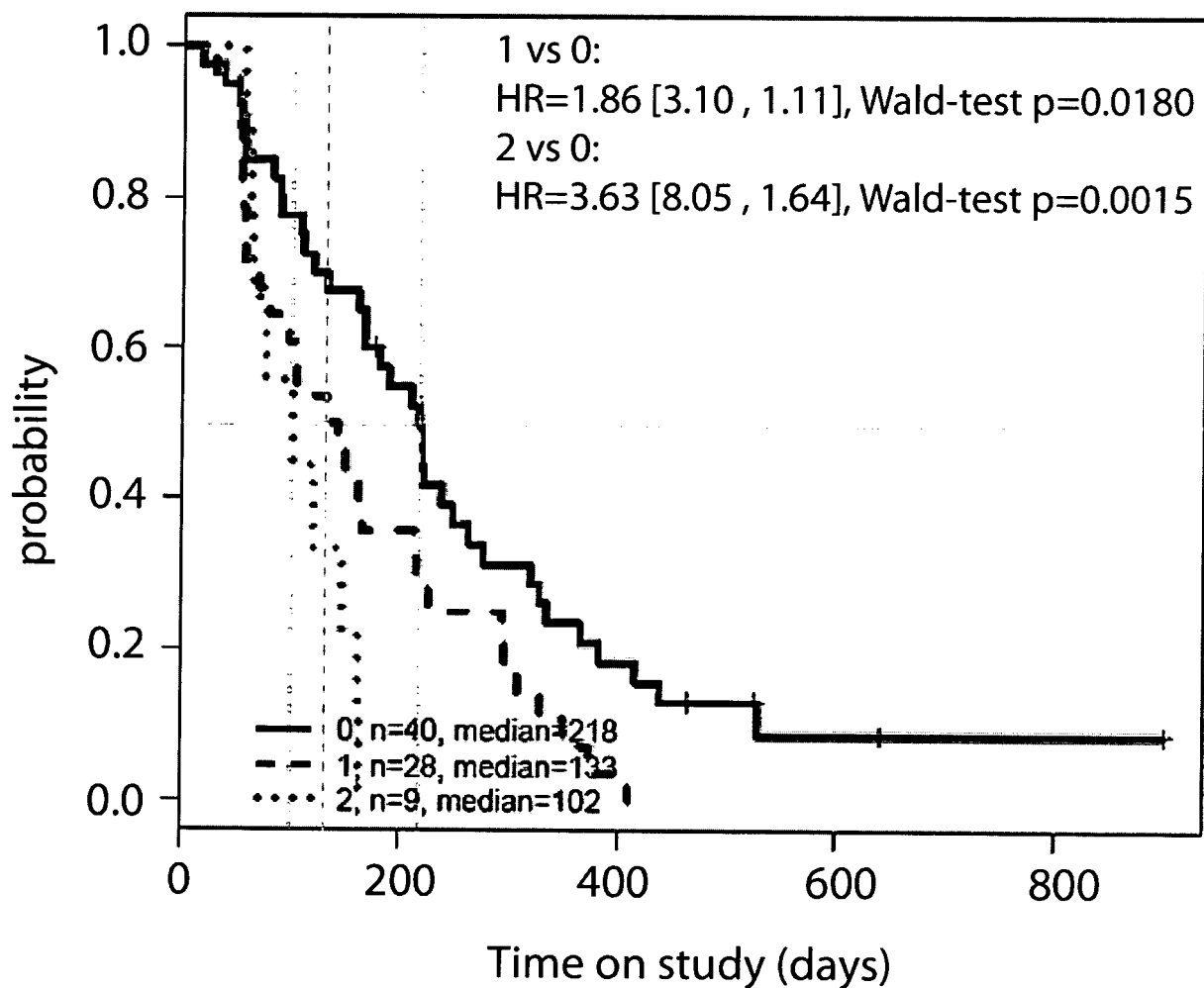


In the legend 0, 1 and 2 refer to genotypes:
0: AA (n=38, median=226)
1: AC (n=29, median=177)
2: CC (n=10, median=149)

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Figure 5

Kaplan Meier Curve for Progression Free Survival
rs9582036 (SEQ ID NO: 2) in bevacizumab (Avastin®)
treated group (caucasians only)



In the legend 0, 1 and 2 refer to genotypes:

0: AA (n=40, median=218)

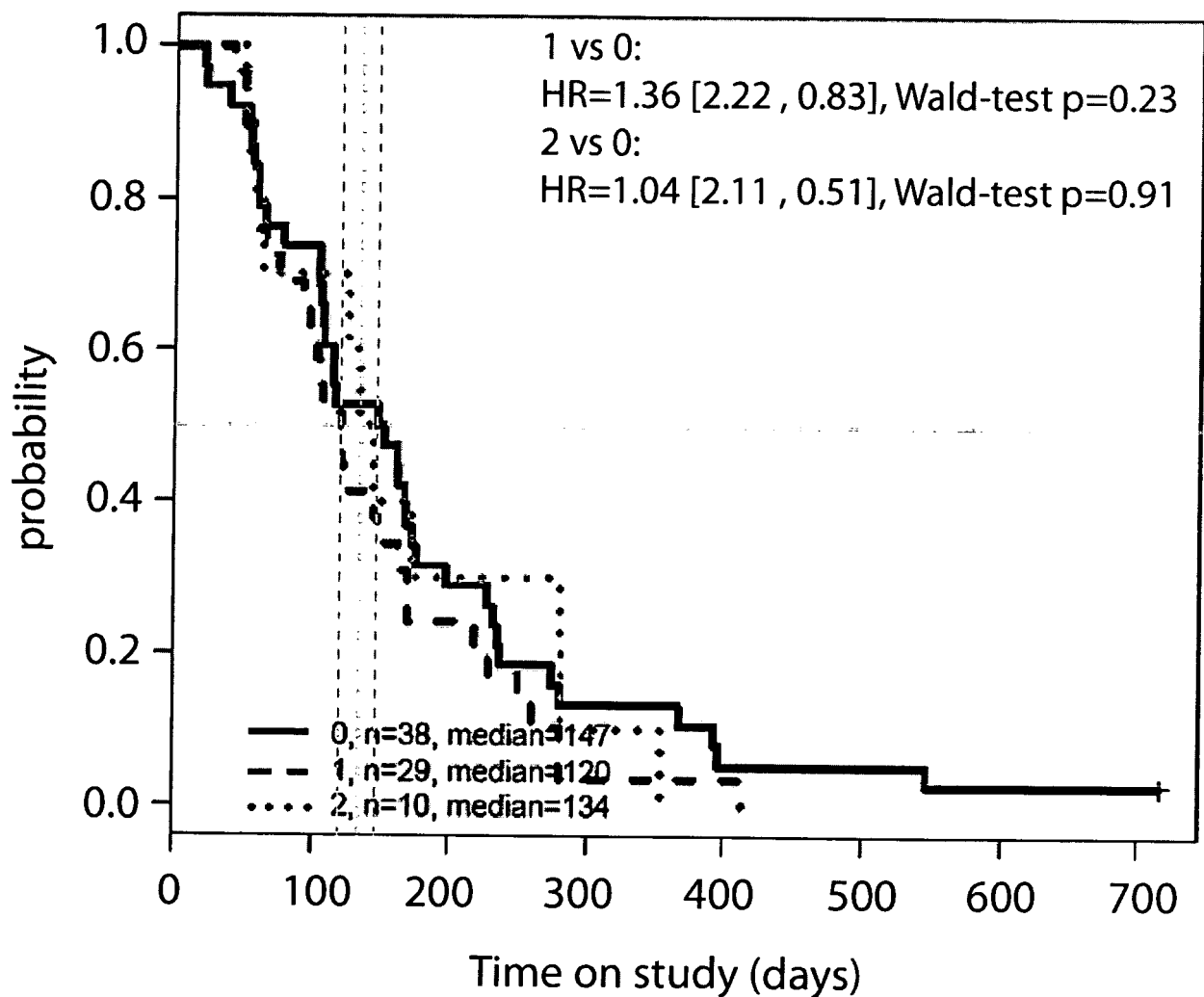
1: AC (n=28, median=133)

2: CC (n=9, median=102)

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Figure 6

Kaplan Meier Curve for Progression Free Survival
rs9582036 (SEQ ID NO: 2) in placebo treated group
(caucasians only)



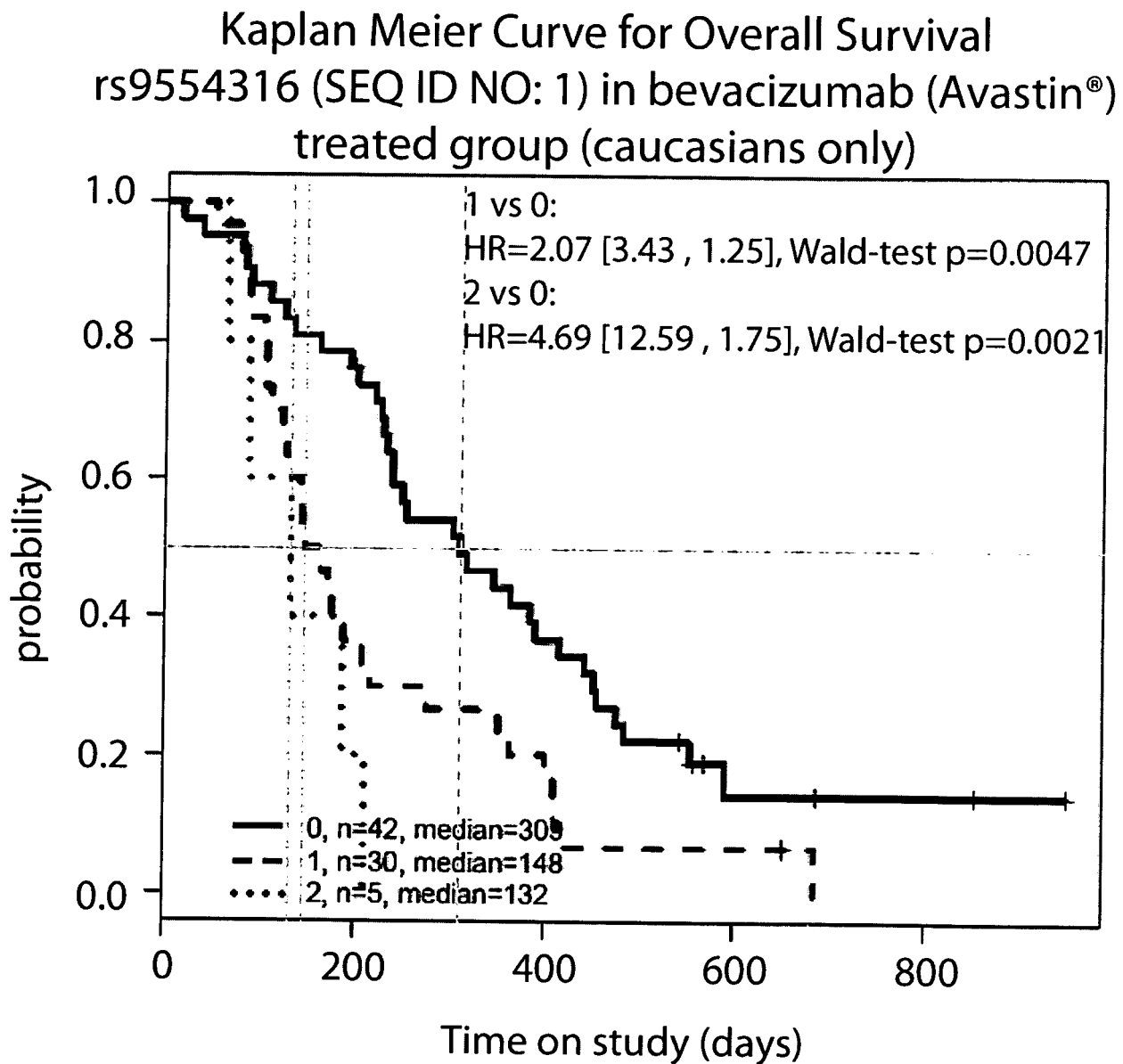
In the legend 0, 1 and 2 refer to genotypes:

0: AA (n=38, median=147)

1: AC (n=29, median=120)

2: CC (n=10, median=134)

Figure 7



In the legend 0, 1 and 2 refer to genotypes:

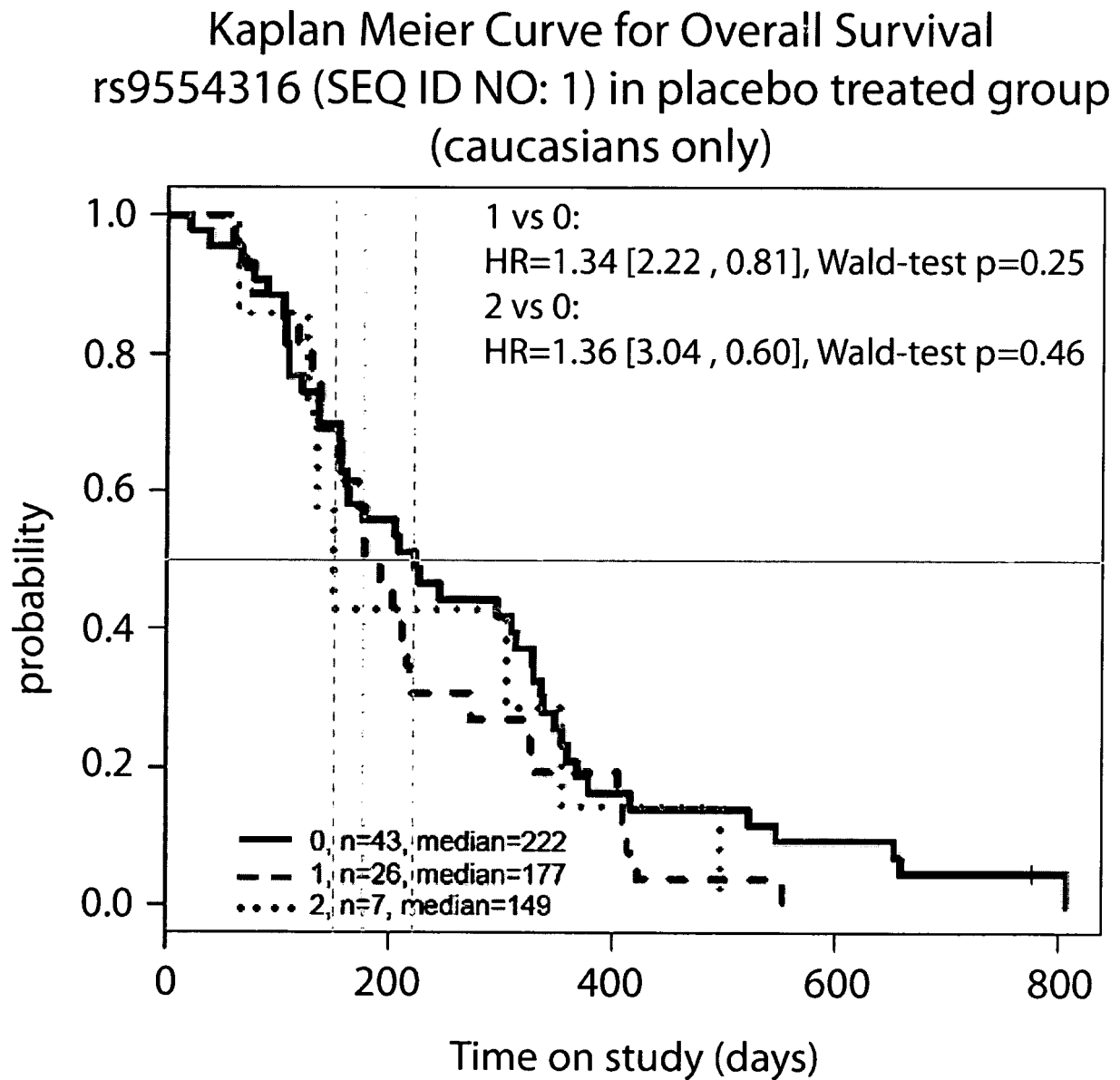
0: GG (n=42, median=309)

1: TG (n=30, median=148)

2: TT (n=5, median=132)

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Figure 8



In the legend 0, 1 and 2 refer to genotypes:

0: GG (n=43, median=222)

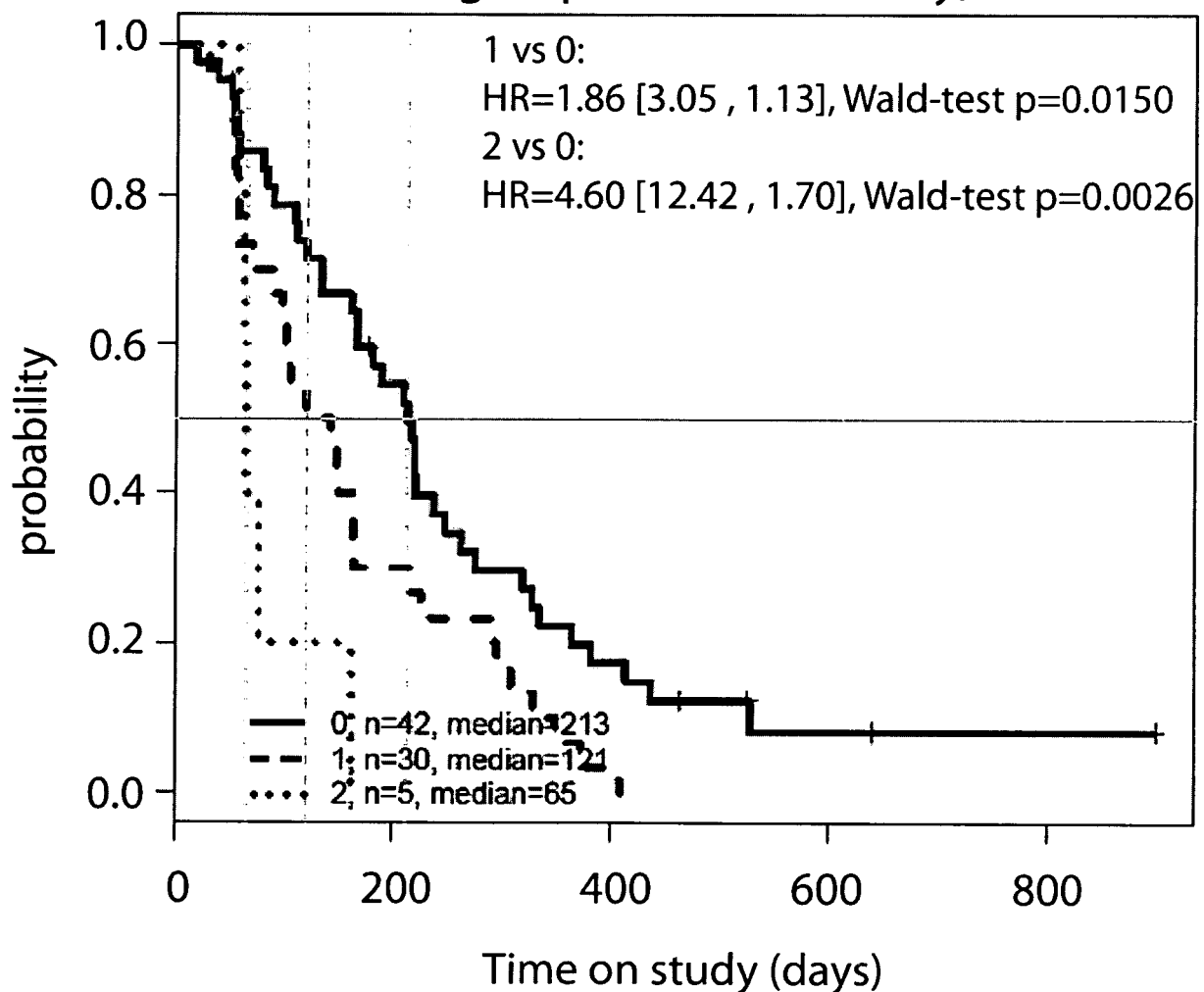
1: TG (n=26, median=177)

2: TT (n=7, median=149)

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Figure 9

Kaplan Meier Curve for Progression Free Survival
rs9554316 (SEQ ID NO: 1) in bevacizumab (Avastin®)
treated group (caucasians only)



In the legend 0, 1 and 2 refer to genotypes:

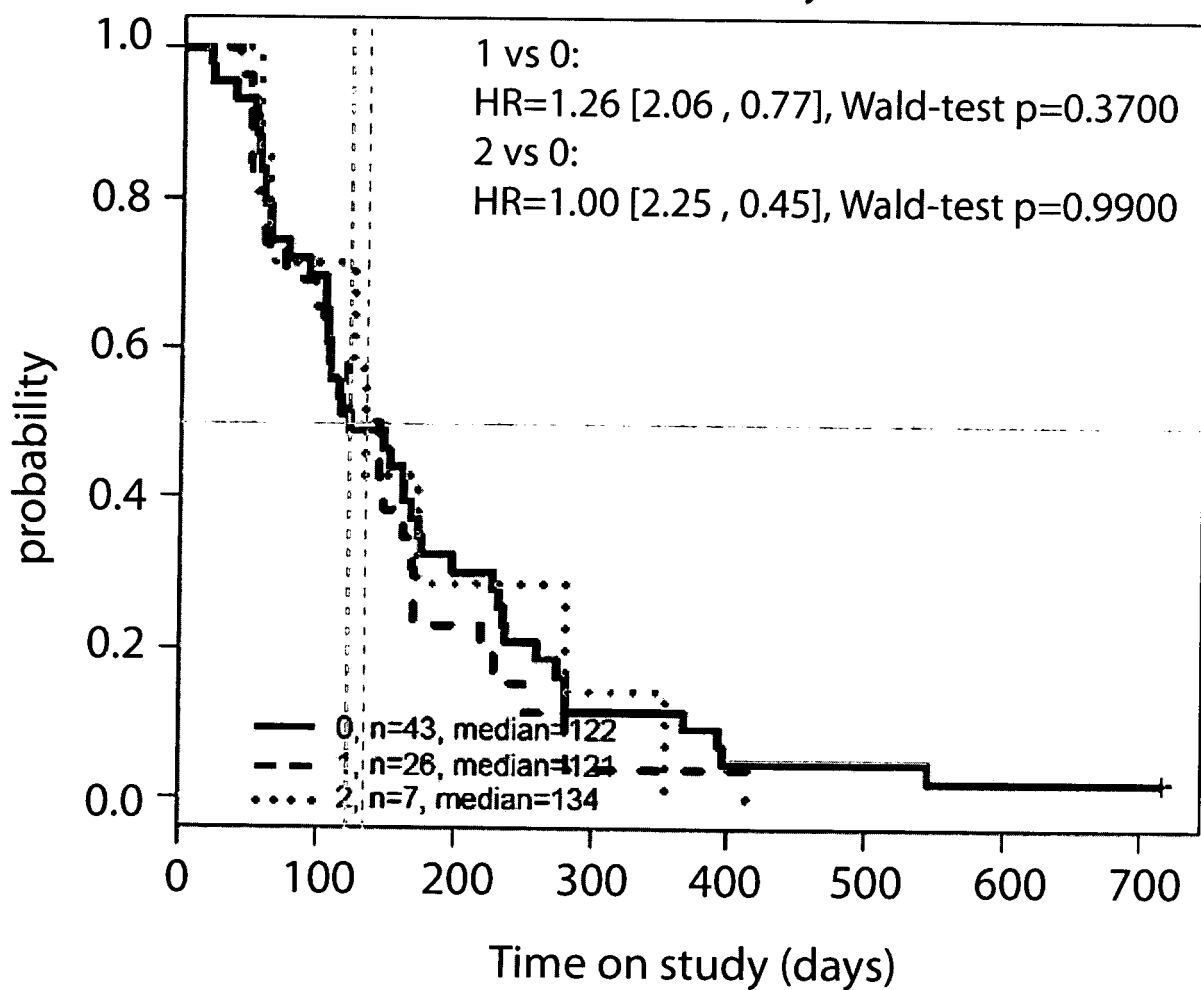
0: GG (n=42, median=213)

1: TG (n=30, median=121)

2: TT (n=5, median=65)

Figure 10

Kaplan Meier Curve for Progression Free Survival
rs9554316 (SEQ ID NO: 1) in placebo treated group
(caucasians only)



In the legend 0, 1 and 2 refer to genotypes:

0: GG (n=43, median=122)

1: TG (n=26, median=121)

2: TT (n=7, median=134)

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Figure 11

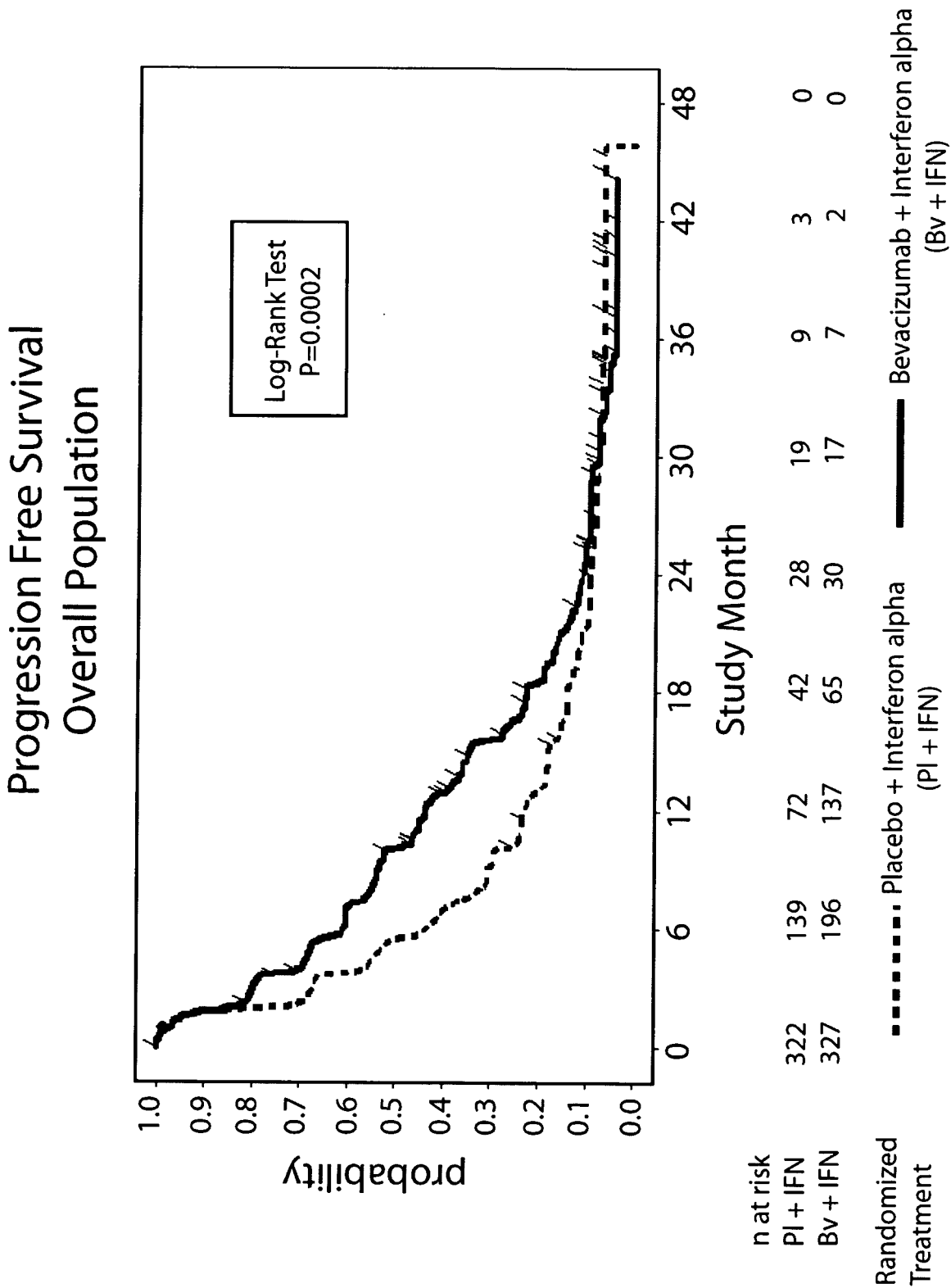
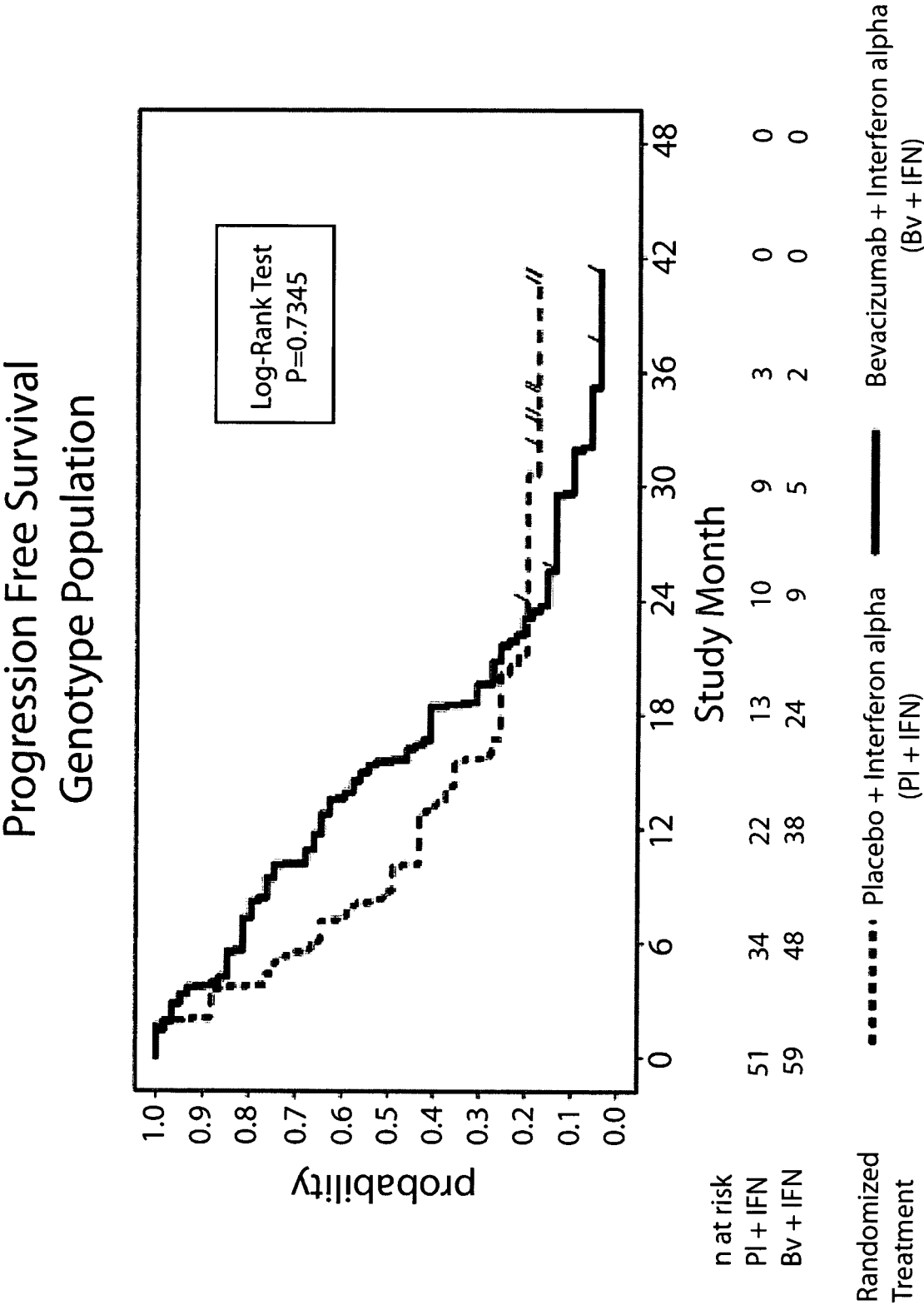
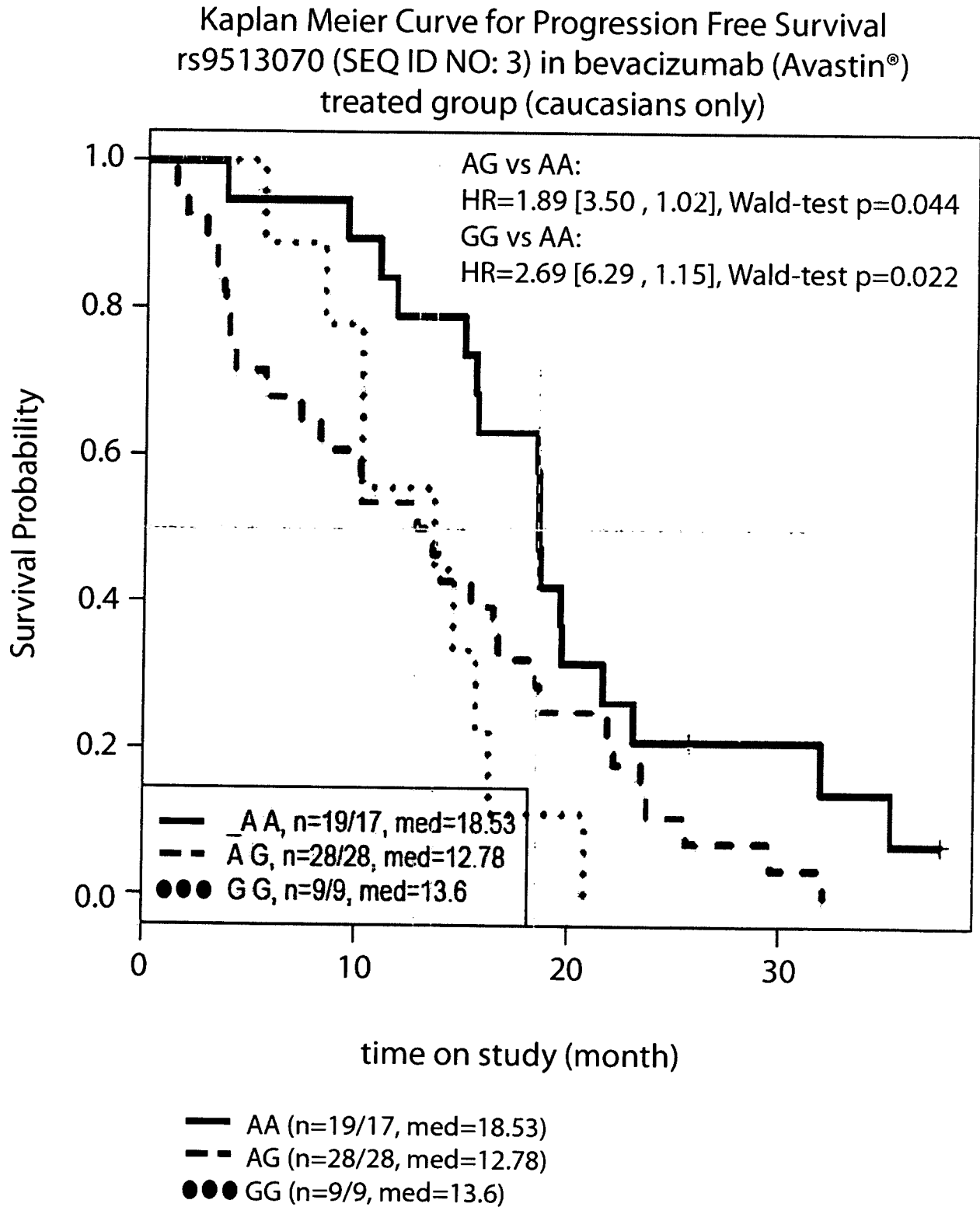


Figure 12



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Figure 13



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Figure 14

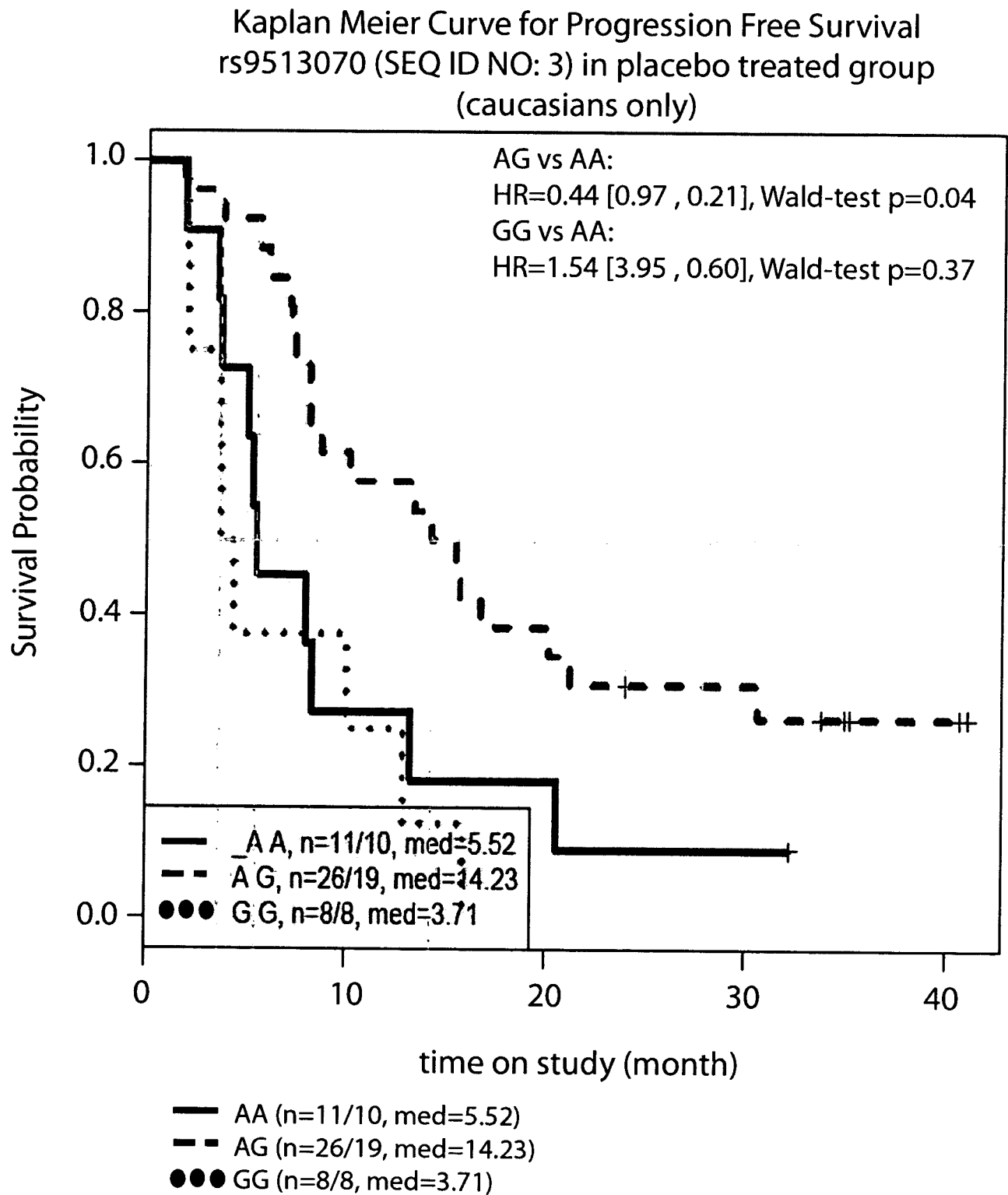
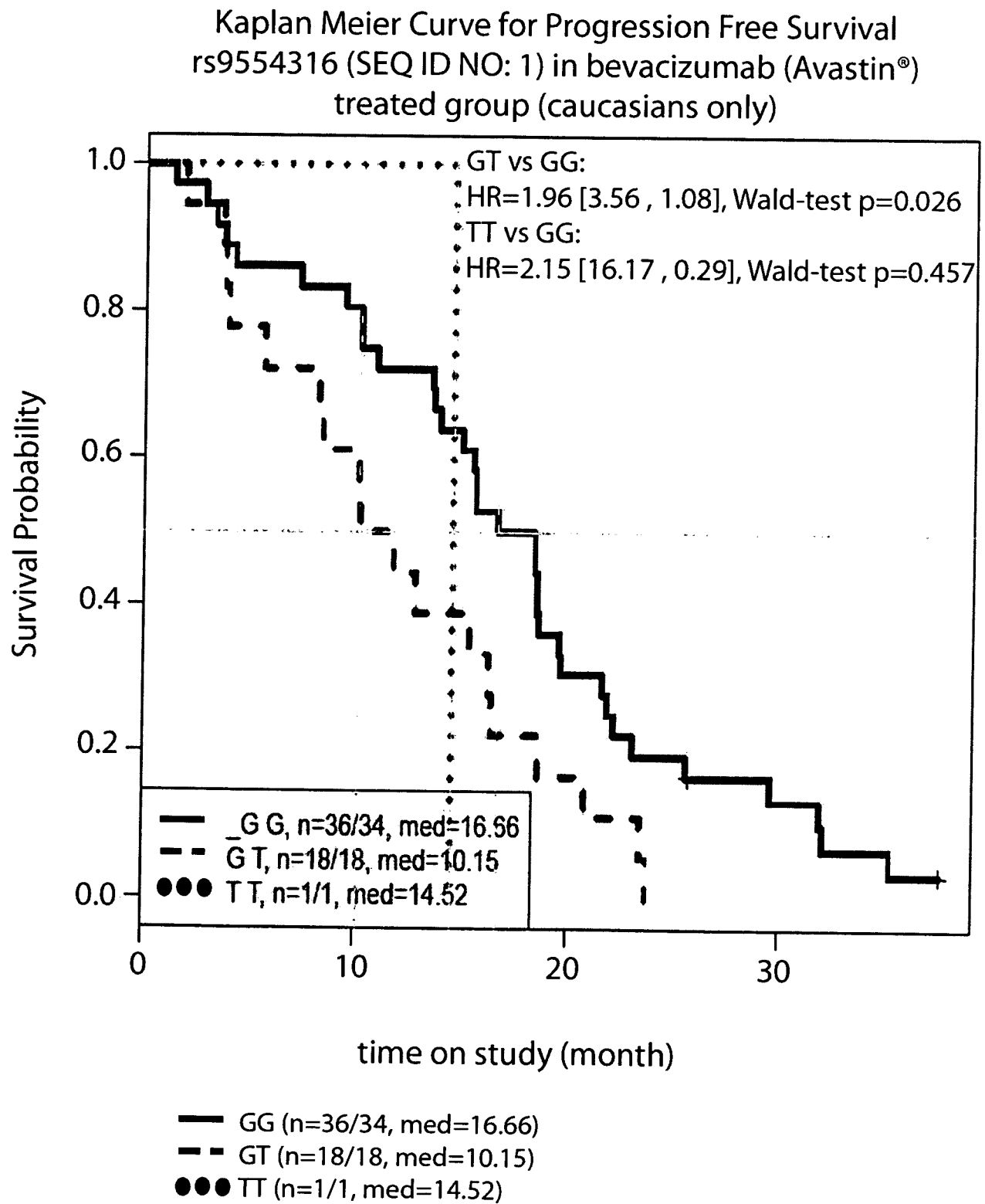


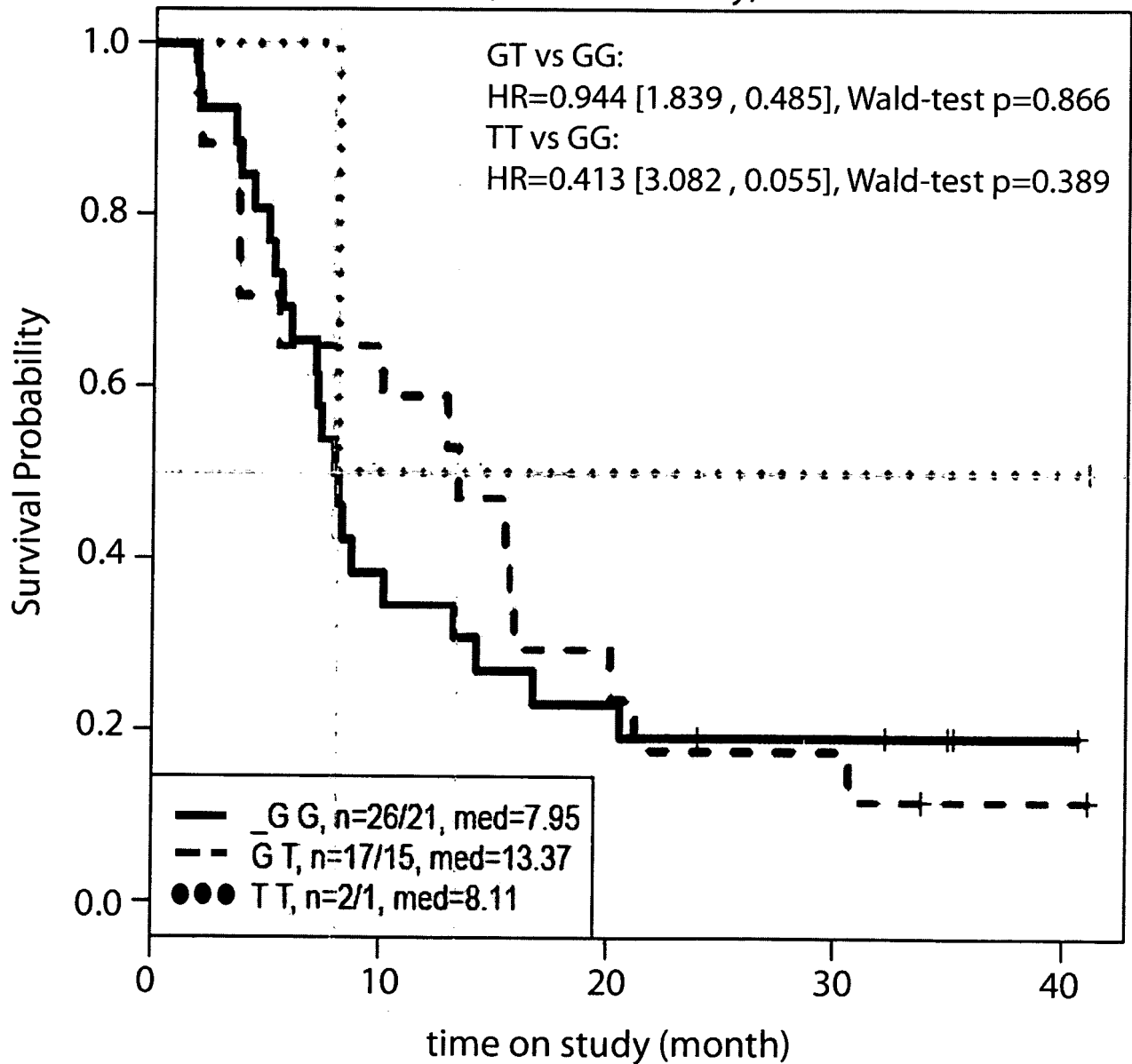
Figure 15



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Figure 16

Kaplan Meier Curve for Progression Free Survival
rs9554316 (SEQ ID NO: 1) in placebo treated group
(caucasians only)



— GG (n=26/21, med=7.95)
- - GT (n=17/15, med=13.37)
●●● TT (n=2/1, med=8.11)