Sequence Alignment of Variable Light-Chain Domain

```
                    |-------FR1-------|          CDR1          |-----
                    10        20        30        40
2H7                 QIVLSQSPAILSASPGEKVTMTC [ RASSSVS- YMH] WYQQKP
                    * ****    **      * **  *
hu2H7. v16          DIQMTQSPSSLSASVGDRVTITC [ RASSSVS- YMH] WYQQKP
                                          * * * **
hum κI              DI QMTQSPSSLSASVGDRVTI TC [ RASQSISNYLA] WYQQKP

                    FR2-----|    CDR2    |-----------FR3-----------
                            50        60        70        80
2H7                 GSSPKPWIY [ APSNLAS] GVPARFSGSGSGTSYSLTISRVEA
                     **   *                *         ***     *****
hu2H7. v16          GKAPKPLIY [ APSNLAS] GVPSRFSGSGSGTDFTLTISSLQP
                       *       * * *
hum κI              GKAPKLLI Y [ AASSLES] GVPSRFSGSGSGTDFTLTISSLQP

                    ----------|    CDR3    |--FR4--|
                              90        100
2H7                 EDAATYYC [ QQWSFNPPT] FGAGTKLELKR
                      *                   *   * *
hu2H7. v16          EDFATYYC [ QQWSFNPPT] FGQGTKVEIKR
                             ***** *
hum κI              EDFATYYC [ QQYNSLPWT] FGQGTKVEIKR
```

FIG. 1A

Sequence Alignment of Variable Heavy-Chain Domain

```
                  |-------FR1-------|          CDR1          |---
                    10        20          30          40
2H7               QAYLQQSGAELVRPGASVKMSCKAS [ GYTFTSYNMH] WVKQT
                  *** **  **  *  * **** *                  * *
hu2H7. v16        EVQLVESGGGLVQPGGSLRLSCAAS [ GYTFTSYNMH] WVRQA
                                            *  *  * *
hum I I I         EVQLVESGGGLVQPGGSLRLSCAAS [ GFTFSSYAMS] WVRQA

                  --FR2--|       CDR2          |---- FR3 ----
                        50 a      60          70          80
2H7               PRQGLEWIG [ AIYPGNGDTSYNQKFKG] KATLTVDKSSSTAYM
                  **   *                      ** **    ** * *
hu2H7. v16        PGKGLEWVG [ AIYPGNGDTSYNQKFKG] RFTISVDKSKNTLYL
                        *  * ***** * * *****       * *
hum I I I         PGKGLEWA [ VISGDGGSTYYADSVKG] RFTISRDNSKNTLTL

                  ----------------|      CDR3      |-- FR4 --|
                   abc     90         100abcde          110
2H7               QLSSLTSEDSAVYFCAR [ VVYYSNSYWYFDV] WGTGTTVTVSS
                  **  **  *   *                      *  *
hu2H7. v16        QMNSLRAEDTAVYYCAR [ VVYYSNSYWYFDV] WGQGTLVTVSS
                                    ******* *** *
hum I I I         QMNSLRAEDTAVYYCAR [ GRVGYSLY---DY] WGQGTLVTVSS
```

FIG. 1B

Humanized 2H7.v16 Light Chain

DIQMTQSPSSLSASVGDRVTITCRASSSVSYMHWYQQKPGKAPKPLIYAPSNLASGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQWSFNPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:13)

FIG. 2

Humanized 2H7.v16 Heavy Chain

EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYNMHWVRQAPGKGLEWVGAIYPGNGDTSYNQK
FKGRFTISVDKSKNTLYLQMNSLRAEDTAVYYCARVVYYSNSYWYFDVWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:14)

FIG. 3

Humanized 2H7.v31 Heavy Chain

EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYNMHWVRQAPGKGLEWVGAIYPGNGDTSYNQK
FKGRFTISVDKSKNTLYLQMNSLRAEDTAVYYCARVVYYSNSYWYFDVWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNATYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIAATISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:15)

FIG. 4

Light Chain Alignment

```
                1                                 32
hu2H7.v16       DIQMTQSPSSLSASVGDRVTITCRASSSVSYMHWYQQKPGKAPKPLIYAP
                ********************************* ********************
hu2H7.v511      DIQMTQSPSSLSASVGDRVTITCRASSSVSYLHWYQQKPGKAPKPLIYAP

                52
hu2H7.v16       SNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSFNPPTFGQG
                ************************************************ **********
hu2H7.v511      SNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWAFNPPTFGQG

                102
hu2H7.v16       TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
                ************************************************************
hu2H7.v511      TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD

                152
hu2H7.v16       NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL
                ************************************************************
hu2H7.v511      NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL

                202       214
hu2H7.v16       SSPVTKSFNRGEC
                *************
hu2H7.v511      SSPVTKSFNRGEC
```

FIG. 5

Heavy Chain Alignment

```
                  1
hu2H7.v16     EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYNMHW
              ************************************
hu2H7.v511    EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYNMHW

                 37              52a                                82abc
hu2H7.v16     VRQAPGKGLEWVGAIYPGNGDTSYNQKFKGRFTISVDKSKNTLYLQMNSL
              ********************* ********************************
hu2H7.v511    VRQAPGKGLEWVGAIYPGNGATSYNQKFKGRFTISVDKSKNTLYLQMNSL

                 83              100abcde          113
hu2H7.v16     RAEDTAVYYCARVVYYSNSYWYFDVWGQGTLVTVSS
              ******************  ******************
hu2H7.v511    RAEDTAVYYCARVVYYSYRYWYFDVWGQGTLVTVSS

                 118
hu2H7.v16     ASTKGPSVFPLAPS
              **************
hu2H7.v511    ASTKGPSVFPLAPS

                 132
hu2H7.v16     SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
              ***************************************************
hu2H7.v511    SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS

                 182
hu2H7.v16     LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA
              ***************************************************
hu2H7.v511    LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA

                 232
hu2H7.v16     PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
              ***************************************************
hu2H7.v511    PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG

                 282
hu2H7.v16     VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
              ****************** ****************************** ******
hu2H7.v511    VEVHNAKTKPREEQYNATYRVVSVLTVLHQDWLNGKEYKCKVSNAALPAP

                 332
hu2H7.v16     IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
              *  ***************************************************
hu2H7.v511    IAATISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW

                 382
hu2H7.v16     ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
              ***************************************************
hu2H7.v511    ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA

                 432             447
hu2H7.v16     LHNHYTQKSLSLSPGK
              ****************
hu2H7.v511    LHNHYTQKSLSLSPGK
```

FIG. 6

Overview of the Study Design and Dosing Regimen

Screening	Random-ization	Treatment Period						Treatment-free Period		
		96-Week Study Treatment Period (4 Treatment Cycles[1])						Follow-up Period	B-cell Monitoring Period	Observation Period
28 Days	Group	1st Cycle		2nd Cycle[2,7]		3rd Cycle[3,7]	4th Cycle[7]	24 Weeks	Variable	24 Weeks
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 1			
	A (1000 mg dose regimen)	Ocrelizumab 1000 mg i.v.	Ocrelizumab 1000 mg i.v.	Ocrelizumab 1000 mg i.v.	Placebo i.v.	Ocrelizumab 1000 mg i.v.[5]	Ocrelizumab 1000 mg i.v.[5]			
	B (600 mg dose regimen)	Ocrelizumab 300 mg i.v.	Ocrelizumab 300 mg i.v.	Ocrelizumab 600 mg i.v.	Placebo i.v.	Ocrelizumab 600 mg i.v.[6]	Ocrelizumab 600 mg i.v.[6]			
	C (Placebo)	Placebo i.v.	Placebo i.v.	Ocrelizumab 300 mg i.v.	Ocrelizumab 300 mg i.v.	Ocrelizumab 600 mg i.v.[6]	Ocrelizumab 600 mg i.v.[6]			
	D[4] (Avonex)	Avonex 30 µg i.m. Every Week		Ocrelizumab 300 mg i.v.	Ocrelizumab 300 mg i.v.	Ocrelizumab 600 mg i.v.[6]	Ocrelizumab 600 mg i.v.[6]			

1. Each treatment cycle has a duration of 24 weeks.
2. All groups will receive a dual infusion, *i.e.* two i.v. infusions separated by 14 days. To maintain the blind in groups A, B and C until database closure for the primary analysis, the dual infusion will be either ocrelizumab followed by placebo (Groups A and B) or ocrelizumab followed by ocrelizumab (Group C).
3. As of the third treatment cycle, single ocrelizumab infusion should be administered in all groups. However, patients who miss their 2nd treatment cycle dosing, will receive the dosing of the 2nd treatment cycle (two infusions separated by 14 days) during the 3rd treatment cycle.
4. Patients from Group D (Avonex) are offered to be dosed with ocrelizumab on a voluntary basis.
5. Patients will be treated with the 1000 mg dose until a preferred dose is chosen on the basis of the primary analysis, at which time investigators and ethics committees will be informed of the preferred dose. After the preferred dose has been chosen patients will receive the preferred dose (600 mg or 1000 mg) for their next treatment cycle(s).
6. Patients will be treated with the 600 mg dose until a preferred dose is chosen on the basis of the primary analysis, at which time investigators and ethics committees will be informed of the preferred dose. After the preferred dose has been chosen patients will receive the preferred dose (600 mg or 1000 mg) for their next treatment cycle(s).
7. Prior to the 2nd, 3rd and 4th dosing cycles, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.

FIG. 7

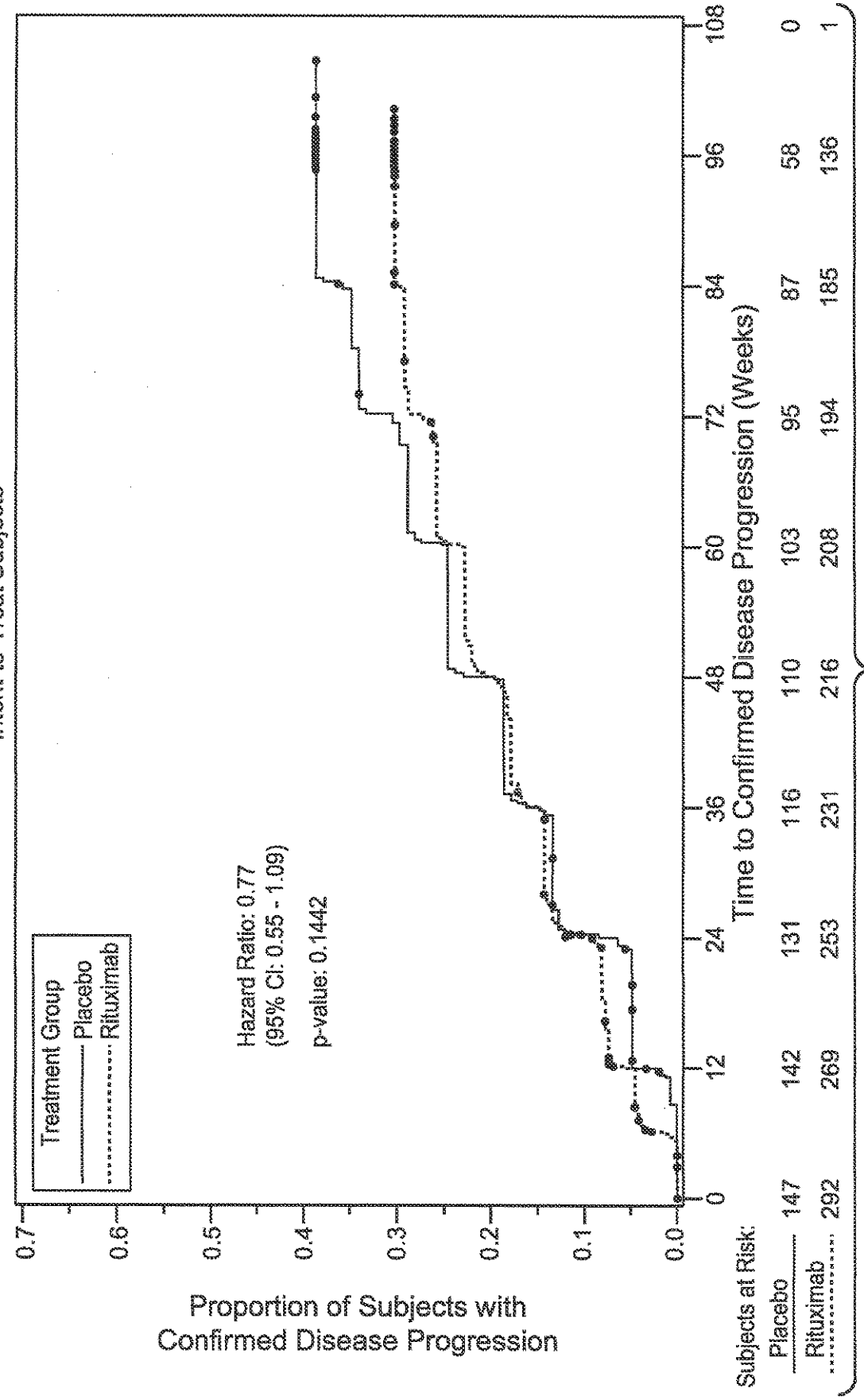

Time to Confirmed Disease Progression During Treatment Period
Intent-to-Treat Subjects
Treatment Group
Placebo
Rituximab
Hazard Ratio: 0.77
(95% CI: 0.55 - 1.09)
p-value: 0.1442
Proportion of Subjects with Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
12
24
36
48
60
72
84
96
108
Time to Confirmed Disease Progression (Weeks)
Subjects at Risk:
Placebo 147 142 131 116 110 103 95 87 58 0
Rituximab 292 269 253 231 216 208 194 185 136 1

FIG. 8

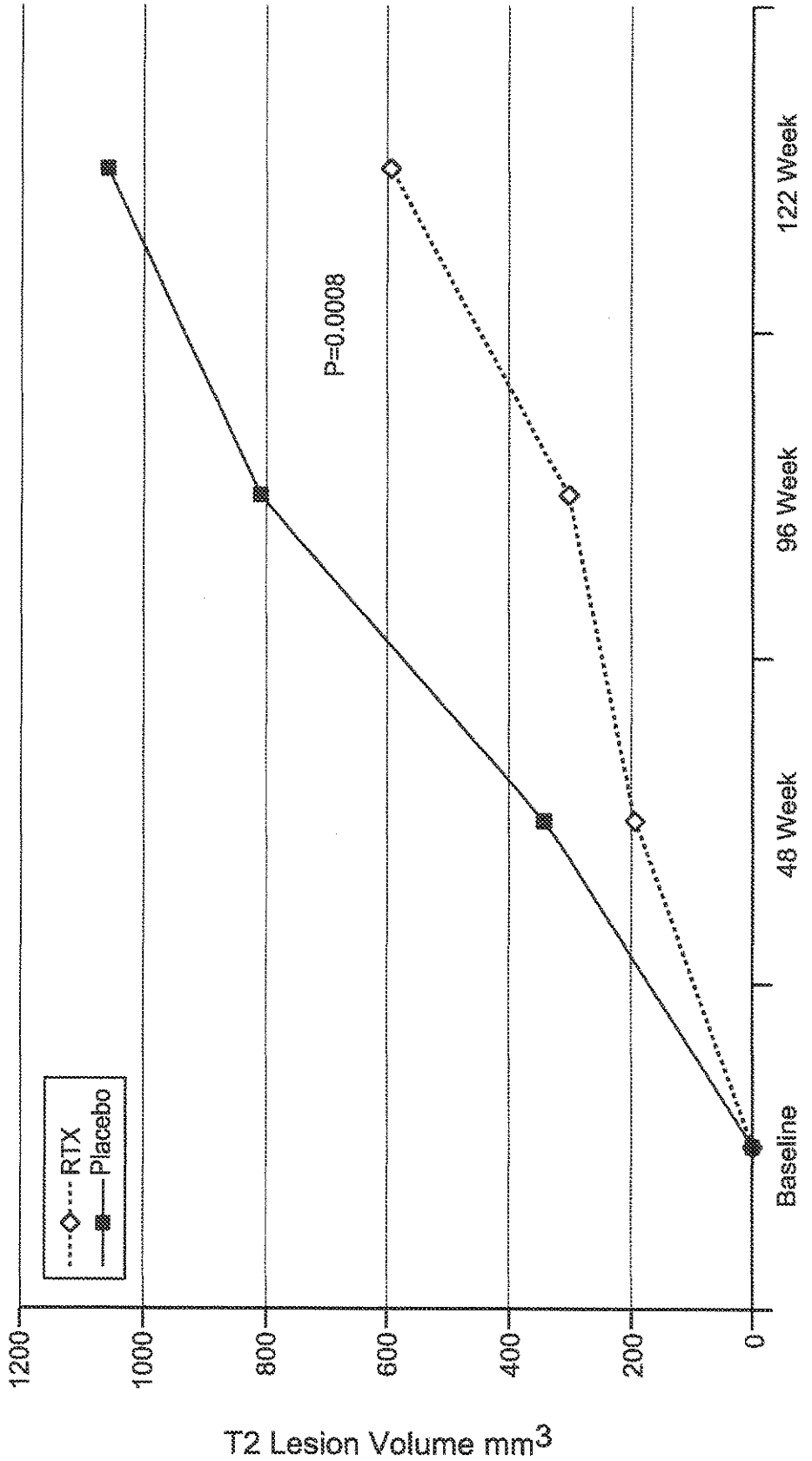
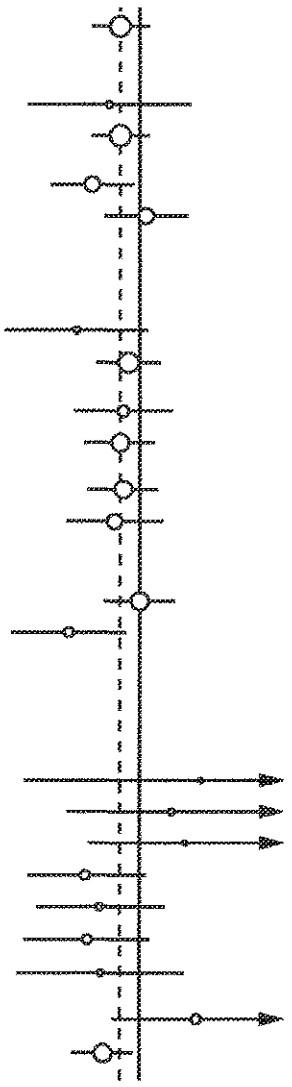

RTX
Placebo
P=0.0008
1200
1000
800
600
400
200
0
Baseline
48 Week
96 Week
122 Week
T2 Lesion Volume mm3

FIG. 9

FIG. 10

Baseline Characteristics	Total n	Proportion of Subjects with CDP: Placebo n	Placebo Week 48	Placebo Week 96	Rituximab n	Rituximab Week 48	Rituximab Week 96	Hazard Ratio	(95% CI)	Hazard Ratio
All Subjects	439	147	19.3%	38.5%	292	19.8%	30.2%	0.79	(0.56, 1.12)	
Age (years)										
< 40	60	20	22.0%	38.7%	40	18.8%	27.3%	0.69	(0.26, 1.81)	
>= 40	379	127	18.9%	38.5%	252	19.9%	30.7%	0.81	(0.56, 1.17)	
< 51	215	70	24.4%	44.9%	145	18.3%	27.5%	0.57	(0.35, 0.93)	
>= 51	224	77	14.8%	32.9%	147	21.2%	32.8%	1.08	(0.66, 1.77)	
Duration since MS onset										
<= 3 years	66	25	28.0%	48.0%	41	21.0%	23.8%	0.47	(0.20, 1.12)	
> 3 years	373	122	17.4%	36.4%	251	19.6%	31.2%	0.88	(0.60, 1.29)	
<= 5 years	128	50	20.5%	39.3%	78	21.6%	31.8%	0.83	(0.45, 1.52)	
> 5 years	311	97	18.6%	38.1%	214	19.1%	29.7%	0.79	(0.52, 1.20)	
<= 10 years	287	94	19.4%	39.3%	193	23.9%	30.7%	0.82	(0.54, 1.26)	
> 10 years	152	53	19.2%	37.1%	99	11.7%	29.2%	0.75	(0.42, 1.35)	
Baseline gd lesion										
0	330	110	16.1%	33.8%	220	22.0%	31.0%	0.98	(0.65, 1.47)	
>= 1	107	37	29.0%	52.8%	70	13.5%	27.4%	0.43	(0.22, 0.83)	
MSSS										
1 -< 2					2	0.0%	50.0%			
2 -< 3	11	3	0.0%	0.0%	8	12.5%	37.5%			
3 -< 4	29	8	12.5%	12.5%	21	15.3%	25.9%	2.11	(0.25, 18.05)	
4 -< 5	50	22	9.1%	18.2%	28	19.6%	24.3%	1.47	(0.41, 5.21)	
5 -< 6	37	15	30.0%	30.0%	22	34.5%	49.6%	1.74	(0.54, 5.54)	
6 -< 7	87	29	26.4%	53.5%	58	21.1%	29.8%	0.52	(0.26, 1.06)	
7 -< 8	73	22	18.7%	52.2%	51	16.1%	34.5%	0.61	(0.29, 1.30)	
8 -< 9	94	28	30.0%	46.1%	66	22.3%	25.7%	0.54	(0.25, 1.14)	
9 -< 10	56	20	5.3%	38.7%	36	15.1%	24.5%	0.62	(0.23, 1.72)	
<= 5.0	92	33	9.1%	15.2%	59	16.3%	28.0%	2.01	(0.73, 5.53)	
> 5.0	347	114	22.5%	45.9%	233	20.6%	30.8%	0.65	(0.45, 0.94)	



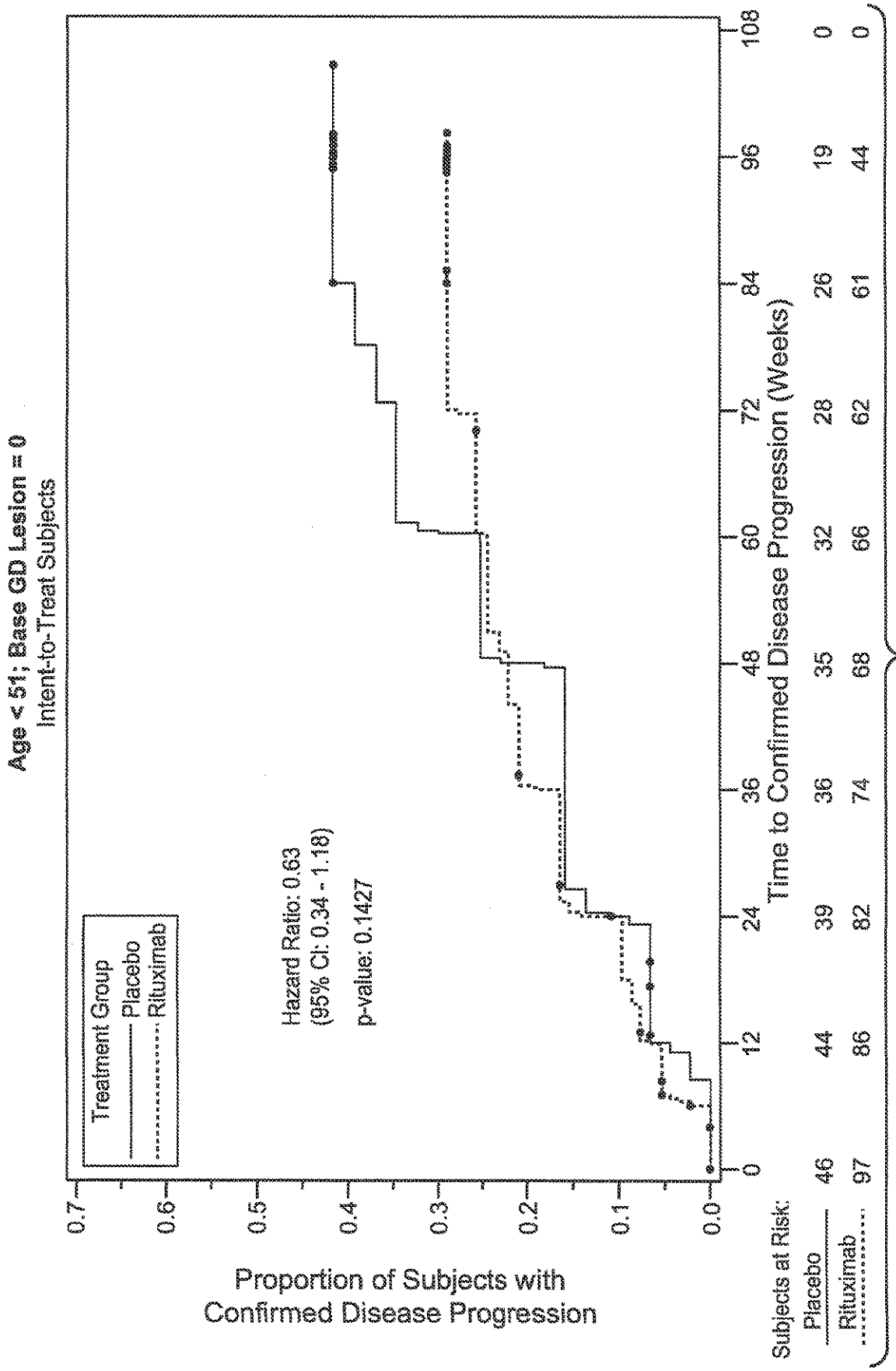

Age < 51; Base GD Lesion = 0
Intent-to-Treat Subjects
Treatment Group
Placebo
Rituximab
Hazard Ratio: 0.63
(95% CI: 0.34 - 1.18)
p-value: 0.1427
Proportion of Subjects with Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
12
24
36
48
60
72
84
96
108
Time to Confirmed Disease Progression (Weeks)
Subjects at Risk:
Placebo 46 44 39 36 35 32 28 26 19 0
Rituximab 97 86 82 74 68 66 62 61 44 0

FIG. 11A

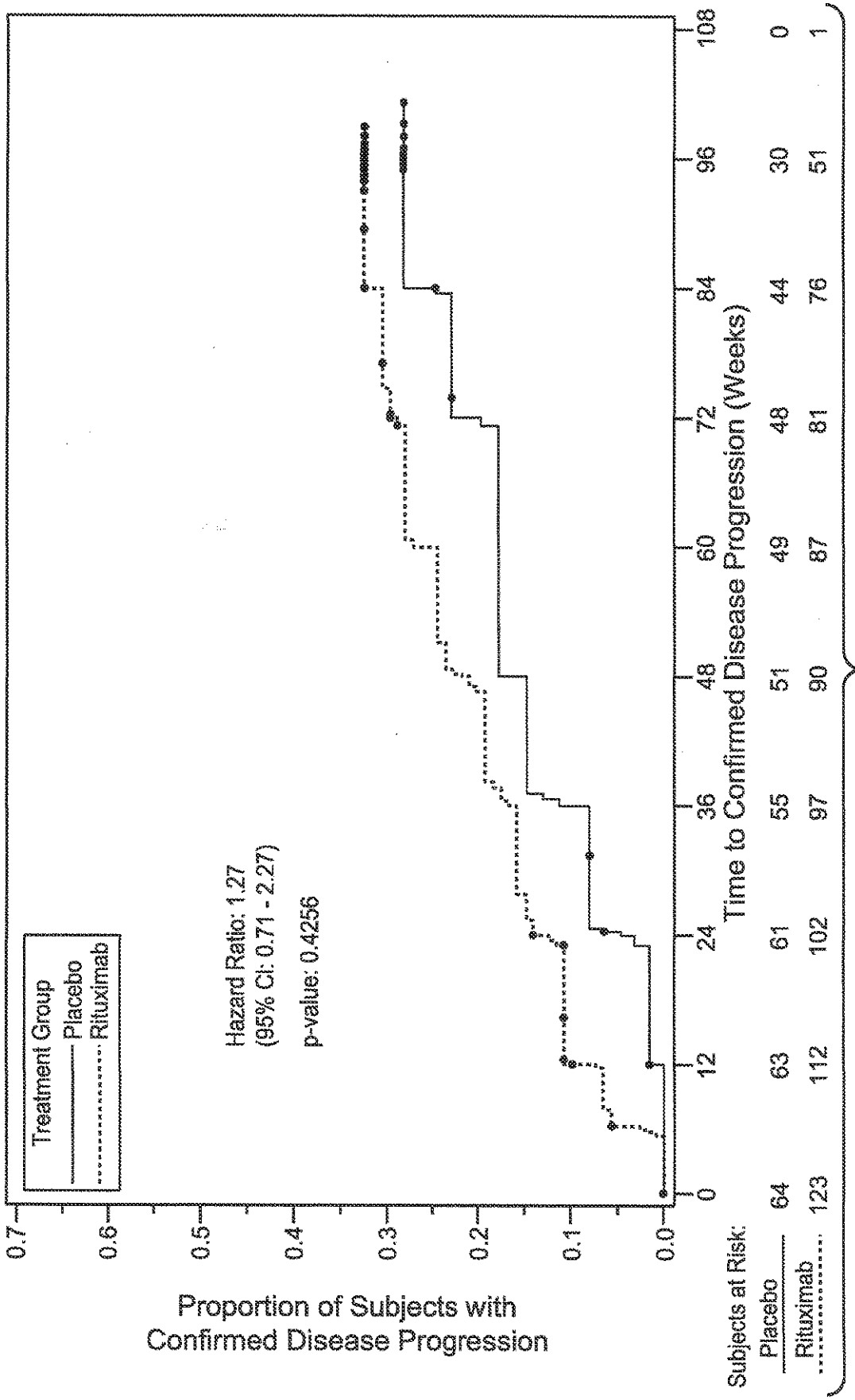

Age ≥ 51; Base GD Lesion = 0
Intent-to-Treat Subjects
Treatment Group
Placebo
Rituximab
Hazard Ratio: 1.27
(95% CI: 0.71 - 2.27)
p-value: 0.4256
Proportion of Subjects with Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
12
24
36
48
60
72
84
96
108
Time to Confirmed Disease Progression (Weeks)
Subjects at Risk:
Placebo 64 63 61 55 51 49 48 44 30 0
Rituximab 123 112 102 97 90 87 81 76 51 1

FIG. 11B

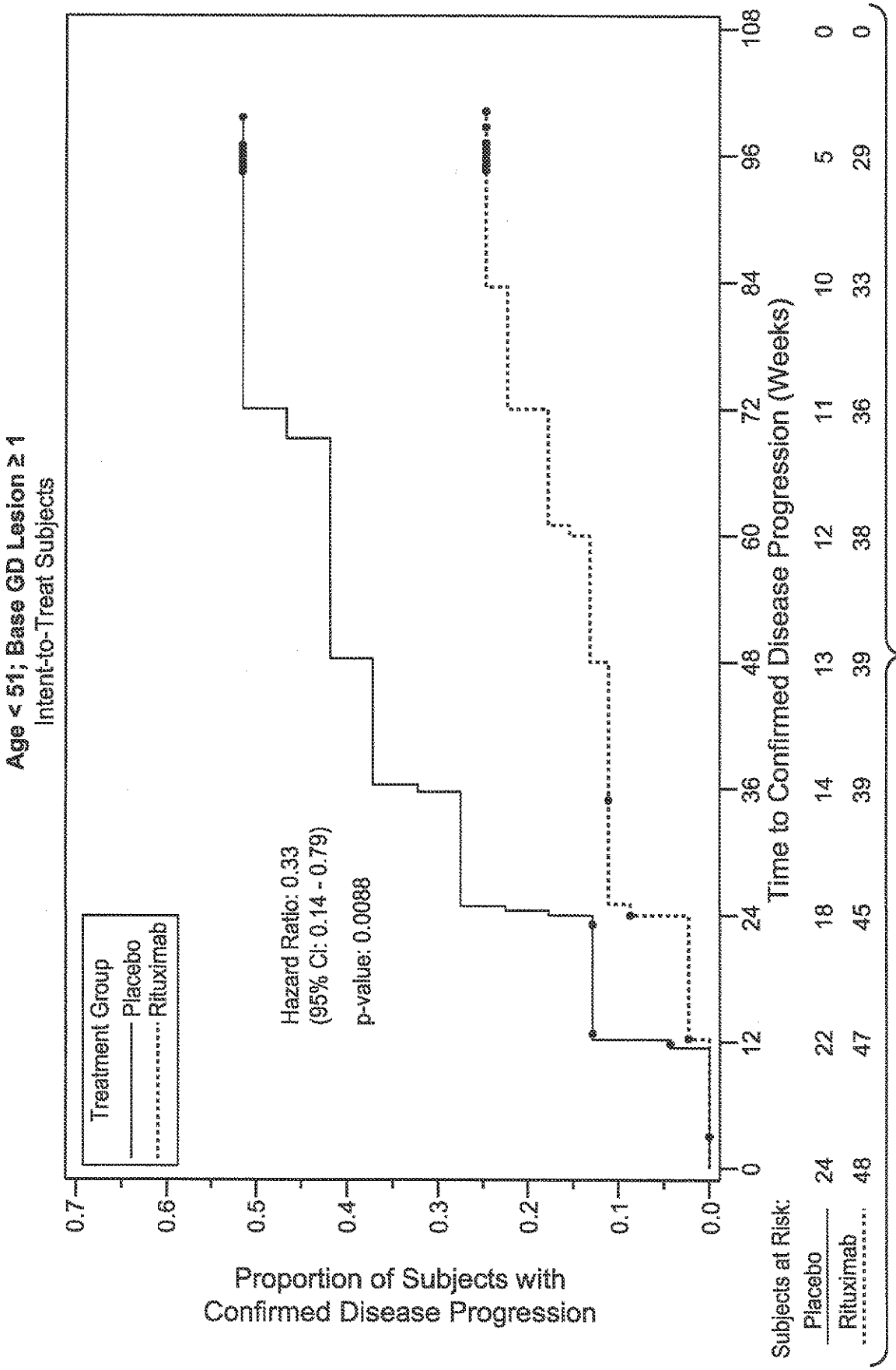

Age < 51; Base GD Lesion ≥ 1
Intent-to-Treat Subjects
Treatment Group
Placebo
Rituximab
Hazard Ratio: 0.33
(95% CI: 0.14 - 0.79)
p-value: 0.0088
Proportion of Subjects with Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
12
24
36
48
60
72
84
96
108
Time to Confirmed Disease Progression (Weeks)
Subjects at Risk:
Placebo 24 22 18 14 13 12 11 10 5 0
Rituximab 48 47 45 39 39 38 36 33 29 0

FIG. 11C

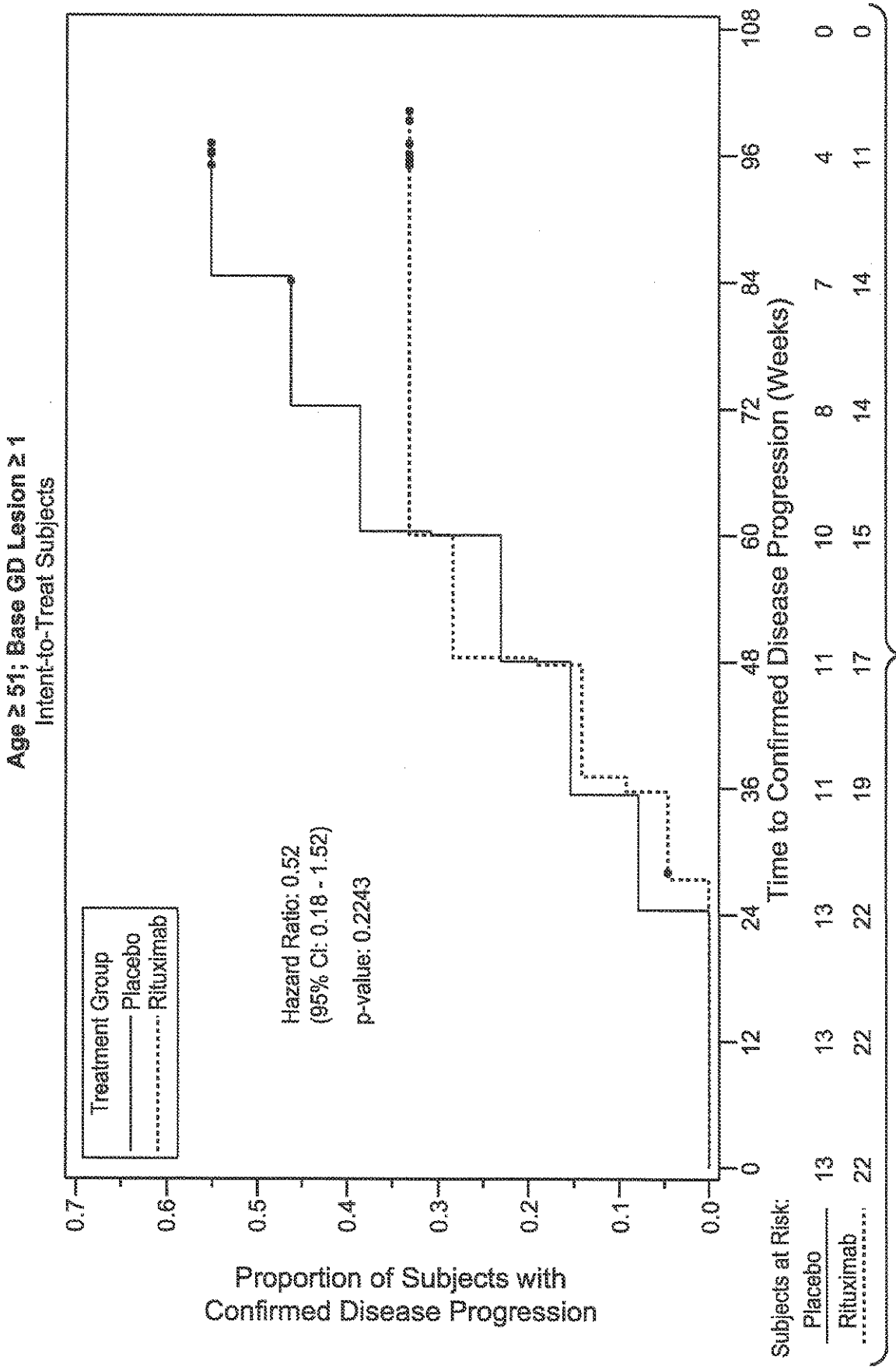

Age ≥ 51; Base GD Lesion ≥ 1
Intent-to-Treat Subjects
Treatment Group
Placebo
Rituximab
Hazard Ratio: 0.52
(95% CI: 0.18 - 1.52)
p-value: 0.2243
Proportion of Subjects with Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Time to Confirmed Disease Progression (Weeks)
0
12
24
36
48
60
72
84
96
108
Subjects at Risk:
Placebo 13 13 13 11 11 10 8 7 4 0
Rituximab 22 22 22 19 17 15 14 14 11 0

FIG. 11D

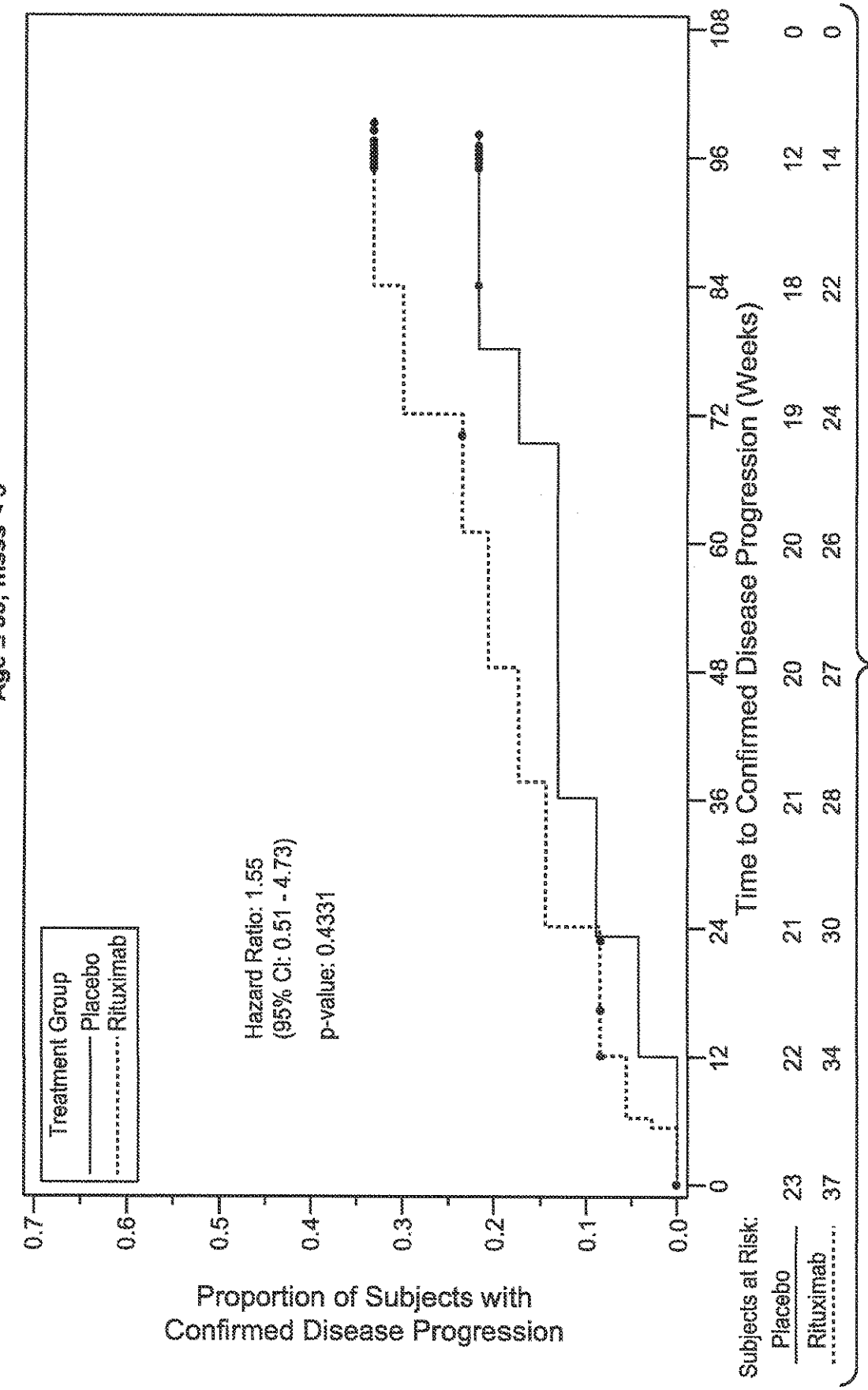

Age ≤ 55; msss < 5
Treatment Group
Placebo
Rituximab
Hazard Ratio: 1.55
(95% CI: 0.51 - 4.73)
p-value: 0.4331
Proportion of Subjects with Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Time to Confirmed Disease Progression (Weeks)
0
12
24
36
48
60
72
84
96
108
Subjects at Risk:
Placebo 23 22 21 21 20 20 19 18 12 0
Rituximab 37 34 30 28 27 26 24 22 14 0

FIG. 12A

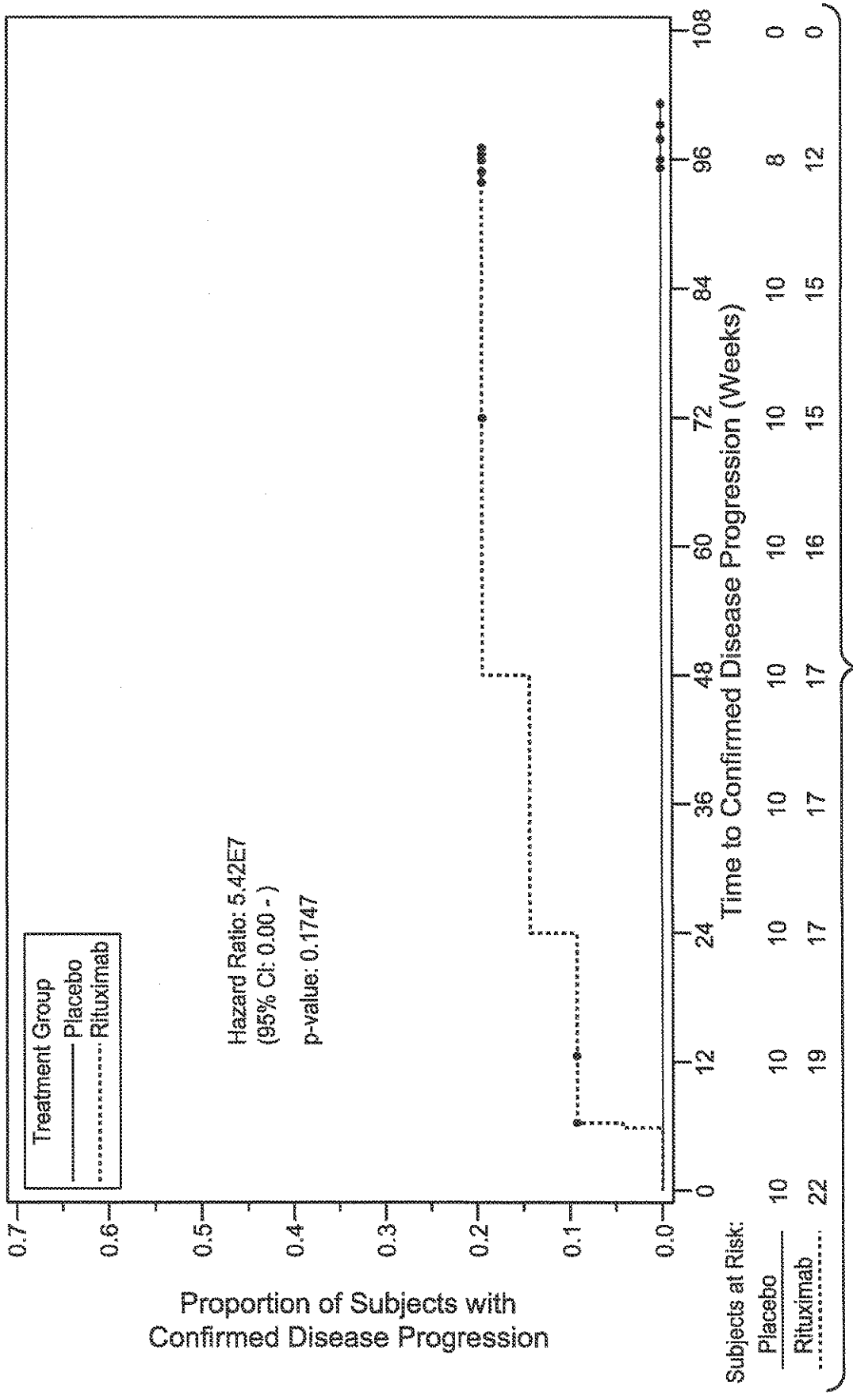

Age > 55; msss < 5
Treatment Group
Placebo
Rituximab
Hazard Ratio: 5.42E7
(95% CI: 0.00 -)
p-value: 0.1747
Proportion of Subjects with Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
12
24
36
48
60
72
84
96
108
Time to Confirmed Disease Progression (Weeks)
Subjects at Risk:
Placebo 10 10 10 10 10 10 10 10 8 0
Rituximab 22 19 17 17 17 16 15 15 12 0

FIG. 12B

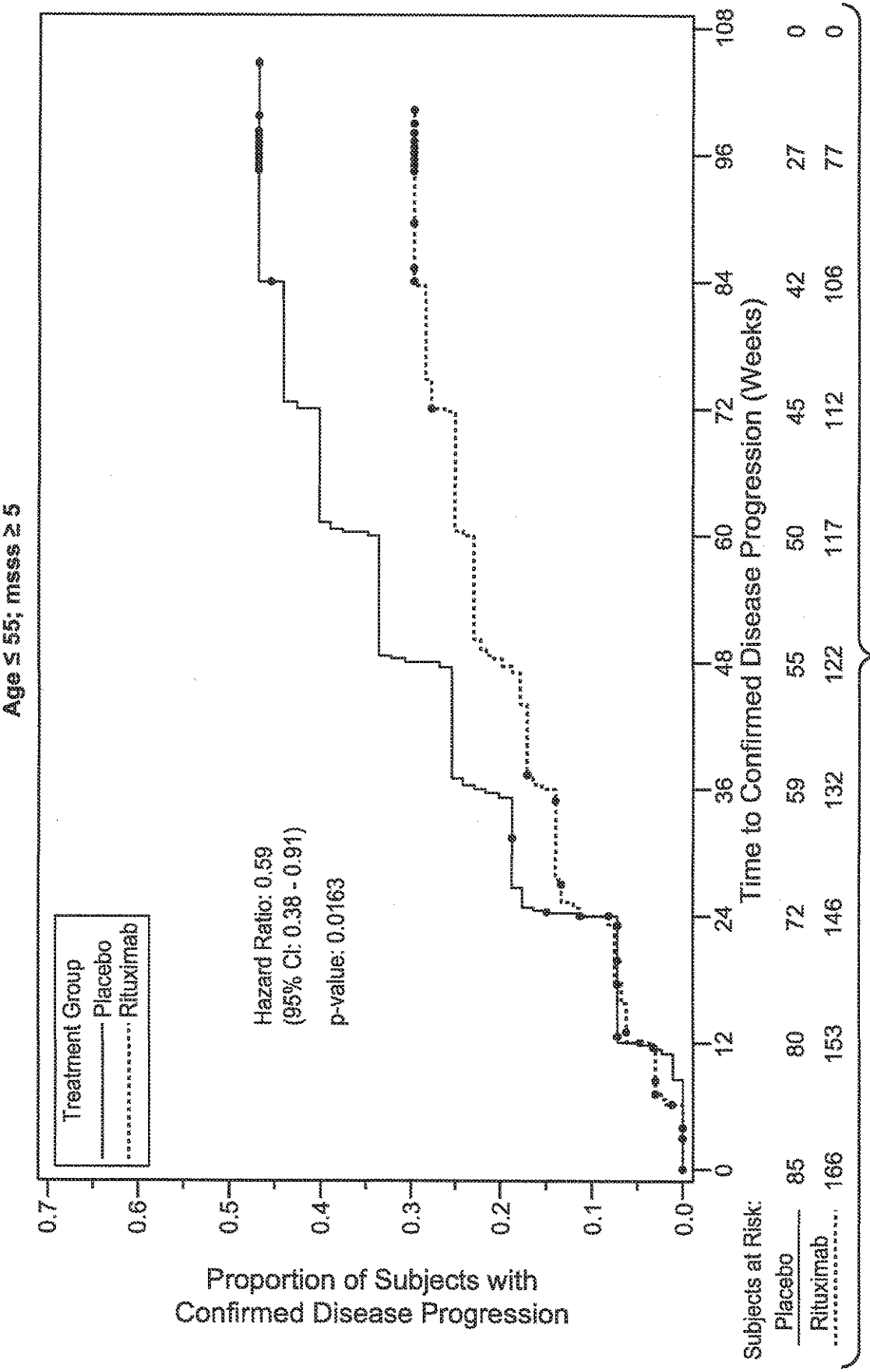

Age ≤ 55; msss ≥ 5
Treatment Group
Placebo
Rituximab
Hazard Ratio: 0.59
(95% CI: 0.38 - 0.91)
p-value: 0.0163
Proportion of Subjects with Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
12
24
36
48
60
72
84
96
108
Time to Confirmed Disease Progression (Weeks)
Subjects at Risk:
Placebo 85 80 72 59 55 50 45 42 27 0
Rituximab 166 153 146 132 122 117 112 106 77 0

FIG. 12C

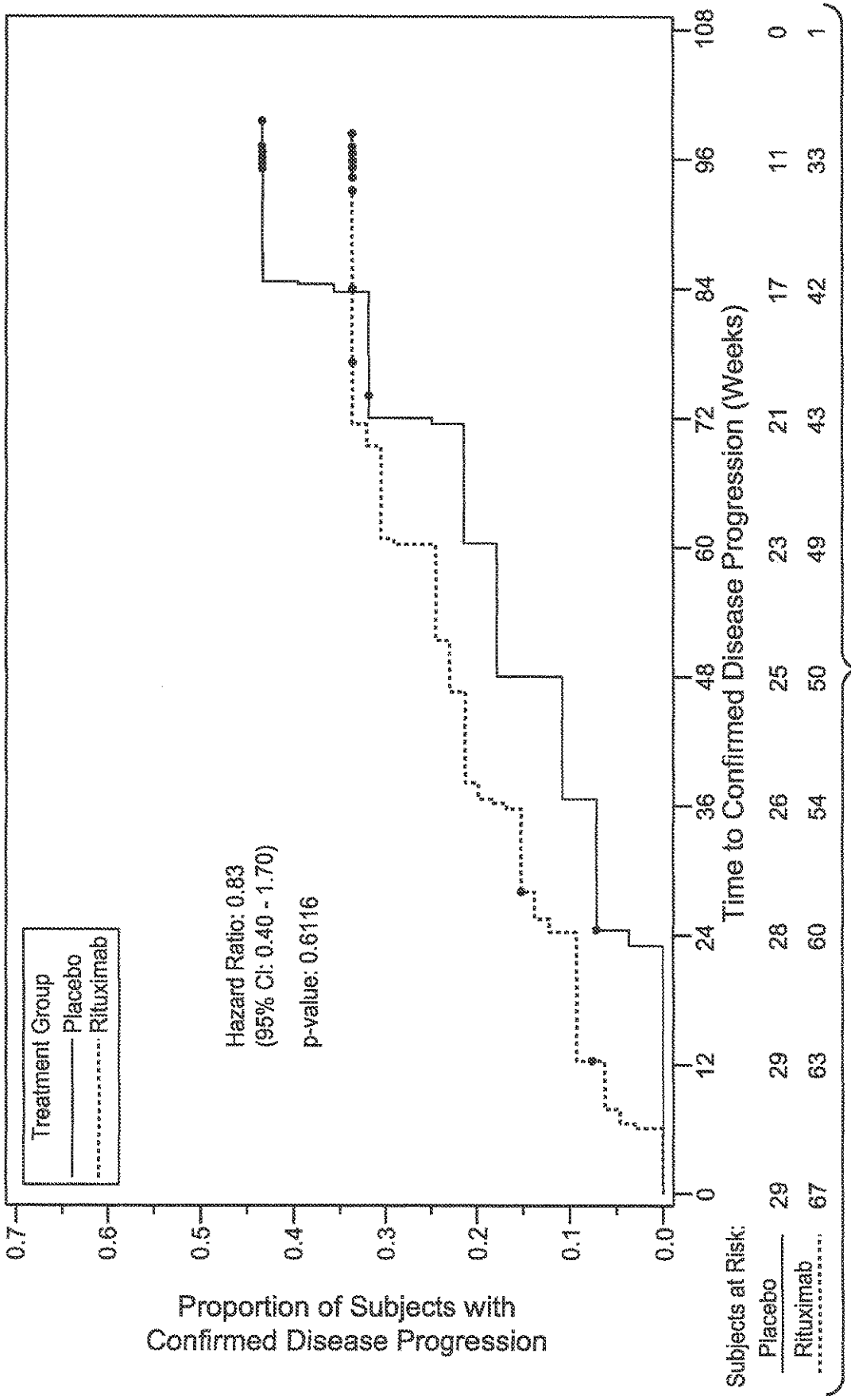

Age > 55; msss ≥ 5
Treatment Group
Placebo
Rituximab
Hazard Ratio: 0.83
(95% CI: 0.40 - 1.70)
p-value: 0.6116
Proportion of Subjects with Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Time to Confirmed Disease Progression (Weeks)
0
12
24
36
48
60
72
84
96
108
Subjects at Risk:
Placebo 29 29 28 26 25 23 21 17 11 0
Rituximab 67 63 60 54 50 49 43 42 33 1

FIG. 12D

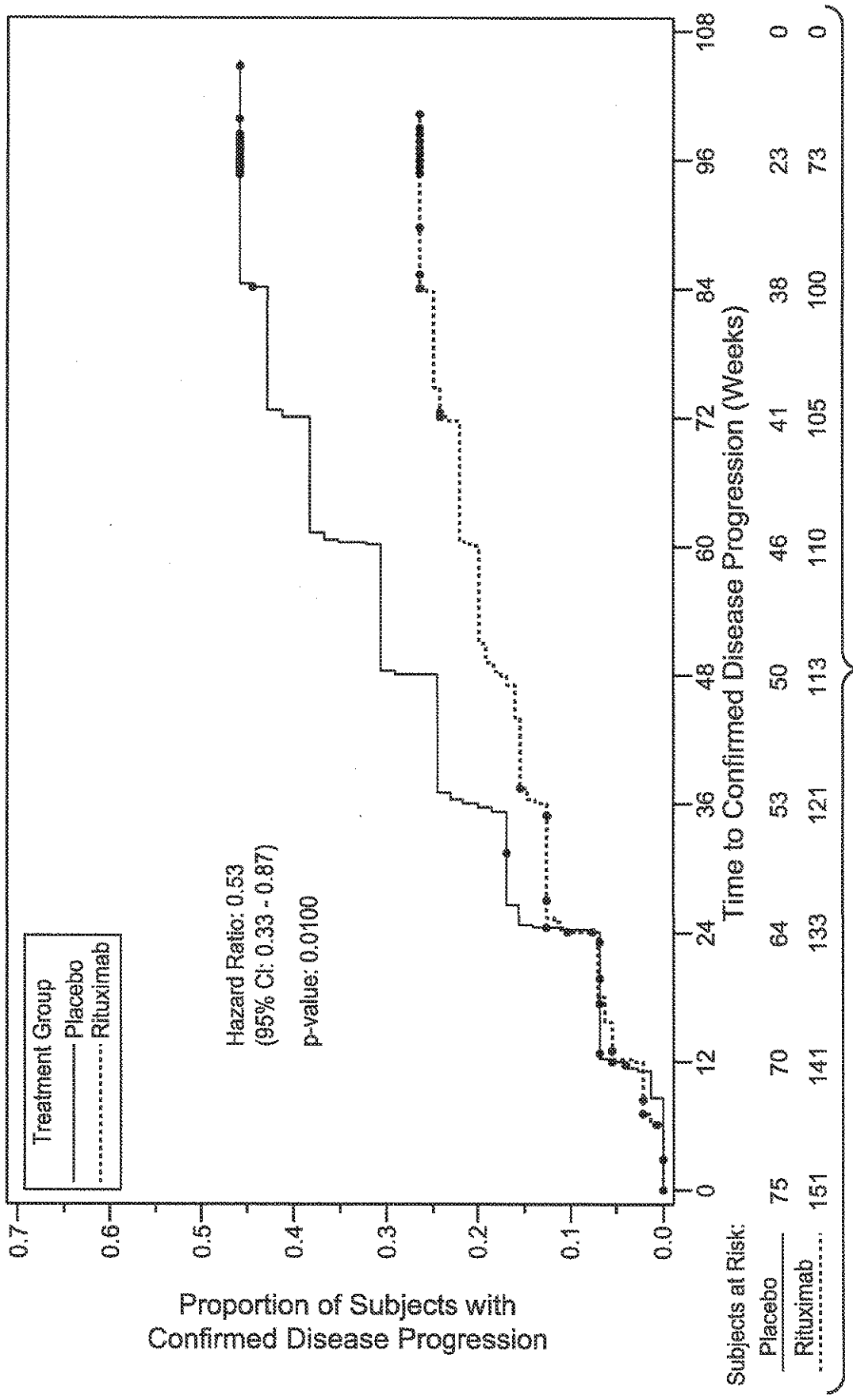

Treatment Group
Placebo
Rituximab
Hazard Ratio: 0.53
(95% CI: 0.33 - 0.87)
p-value: 0.0100
Proportion of Subjects with
Confirmed Disease Progression
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
12
24
36
48
60
72
84
96
108
Time to Confirmed Disease Progression (Weeks)
Subjects at Risk:
Placebo 75 70 64 53 50 46 41 38 23 0
Rituximab 151 141 133 121 113 110 105 100 73 0

FIG. 13