

Supplemental Tables

Table S1. Analysis data sets. uMRD = undetectable MRD.

| Analysis | Tables and Figures | MRD data included | IR | FCR |
|--|---------------------------------------|---|---------|---------|
| Baseline characteristics: (1) patients with MRD data vs. those without MRD data, and (2) patients achieving uMRD vs. not | Tables: S2a, S2b, 1a, 1b, 2a, 2b | All available | 290 pts | 122 pts |
| MRD levels at each timepoint and their associations with PFS | Figures: All (including supplemental) | Before progression and within window ¹ | 287 pts | 119 pts |
| Risk of progression over time | Tables: 3a, 3b | Before progression | 290 pts | 122 pts |

1. The 3-month timepoint included measurements between 2 to 4 months after randomization, whereas the three later timepoints at 12, 24 and 36 months allowed a window of +/- 2 months around the original target timepoint.

Table S2a. Baseline patient characteristics by MRD data availability for the IR arm.

| Variable | Category | MRD data available | No MRD data | Total | P-value |
|--------------------------------|--------------------|---------------------|--------------------|---------------------|---------|
| Total | | 291 | 63 | 354 | – |
| Age | Mean (SD) | 56.3 (7.3) | 58.6 (7.9) | 56.7 (7.5) | 0.004 |
| | Median (Q1,Q3) | 57.0 (52.0,62.0) | 61.0 (56.0,64.0) | 58.0 (52.0,62.0) | |
| | [Min, Max] | [31.0,70.0] | [35.0,70.0] | [31.0,70.0] | |
| | Freq. of Missing | 0 | 0 | 0 | |
| Age, category | <60 | 183 (62.9) | 26 (41.3) | 209 (59.0) | 0.002 |
| | >=60 | 108 (37.1) | 37 (58.7) | 145 (41.0) | |
| | Unknown/Missing | 0 | 0 | 0 | |
| Gender | Female | 96 (33.0) | 22 (34.9) | 118 (33.3) | 0.770 |
| | Male | 195 (67.0) | 41 (65.1) | 236 (66.7) | |
| | Unknown/Missing | 0 | 0 | 0 | |
| RAI Stage | Low, 0 | 11 (3.8) | 0 (0.0) | 11 (3.1) | 0.062 |
| | Intermediate, I-II | 159 (54.6) | 28 (44.4) | 187 (52.8) | |
| | High, III-IV | 121 (41.6) | 35 (55.6) | 156 (44.1) | |
| | Unknown/Missing | 0 | 0 | 0 | |
| ECOG Performance Status | 0 | 181 (62.2) | 45 (71.4) | 226 (63.8) | 0.017 |
| | 1 | 105 (36.1) | 14 (22.2) | 119 (33.6) | |
| | 2 | 5 (1.7) | 4 (6.3) | 9 (2.5) | |
| | Unknown/Missing | 0 | 0 | 0 | |
| Hemoglobin, g/dL | Mean (SD) | 12.2 (2.2) | 11.8 (2.3) | 12.2 (2.2) | 0.158 |
| | Median (Q1,Q3) | 12.4 (10.7,14.0) | 12.0 (10.0,13.3) | 12.3 (10.6,13.9) | |
| | [Min, Max] | [4.4,17.5] | [6.7,16.4] | [4.4,17.5] | |
| | Freq. of Missing | 2 | 4 | 6 | |
| Platelets, 10 ³ /uL | Mean (SD) | 161.7 (71.8) | 142.6 (67.6) | 158.3 (71.3) | 0.039 |
| | Median (Q1,Q3) | 152.0 (110.0,201.0) | 130.0 (91.5,179.0) | 150.0 (107.0,200.8) | |
| | [Min, Max] | [9.6,508.0] | [16.0,305.0] | [9.6,508.0] | |
| | Freq. of Missing | 0 | 0 | 0 | |
| WBC, 10 ³ /uL | Mean (SD) | 107.0 (116.5) | 119.9 (116.9) | 109.3 (116.5) | 0.393 |
| | Median (Q1,Q3) | 63.9 (20.2,156.4) | 80.8 (19.6,160.1) | 73.6 (20.1,157.3) | |
| | [Min, Max] | [1.6,617.5] | [3.2,529.6] | [1.6,617.5] | |
| | Freq. of Missing | 0 | 0 | 0 | |
| Beta-2 Microglobulin, | Mean (SD) | 3.9 (2.0) | 4.3 (2.3) | 4.0 (2.1) | 0.234 |

| | | | | | |
|---|--|--|--|---|-------|
| mg/L | Median (Q1,Q3) [Min, Max] Freq. of Missing | 3.6 (2.5,4.6) [1.3,14.4] 2 | 3.8 (2.9,5.0) [1.8,12.7] 3 | 3.6 (2.6,4.6) [1.3,14.4] 5 | |
| Creatinine Clearance ¹ (ml/min) | Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing | 100.4 (31.8) 96.3 (78.4,118.1) [41.0,220.1] 1 | 97.2 (31.5) 93.3 (74.4,113.2) [49.2,190.9] 3 | 99.9 (31.7) 96.3 (77.2,116.8) [41.0,220.1] 4 | 0.381 |
| Coombs Test ² | Negative Positive Unknown/Missing | 266 (94.0) 17 (6.0) 8 | 50 (86.2) 8 (13.8) 5 | 316 (92.7) 25 (7.3) 13 | 0.051 |
| Splenomegaly | No Yes Unknown/Missing | 181 (62.2) 110 (37.8) 0 | 31 (49.2) 32 (50.8) 0 | 212 (59.9) 142 (40.1) 0 | 0.066 |
| Lymphadenopathy | No Yes Unknown/Missing | 84 (28.9) 207 (71.1) 0 | 19 (30.2) 44 (69.8) 0 | 103 (29.1) 251 (70.9) 0 | 0.879 |
| Del(11q22.3) | Abnormal Normal Unknown/Missing | 68 (23.4) 222 (76.6) 1 | 10 (16.1) 52 (83.9) 1 | 78 (22.2) 274 (77.8) 2 | 0.241 |
| Dohner Classification ³ | del(17p) del(11q22) trisomy 12 normal del(13q) other Unknown/Missing | 0 (0.0) 68 (23.4) 62 (21.3) 54 (18.6) 94 (32.3) 13 (4.5) 0 | 2 (3.2) 10 (15.9) 8 (12.7) 15 (23.8) 27 (42.9) 1 (1.6) 0 | 2 (0.6) 78 (22.0) 70 (19.8) 69 (19.5) 121 (34.2) 14 (4.0) 0 | 0.024 |
| IGHV | Mutated Unmutated Unknown/Missing | 62 (24.0) 196 (76.0) 33 | 8 (36.4) 14 (63.6) 41 | 70 (25.0) 210 (75.0) 74 | 0.206 |

1. Determined based on the CKD-EPI formula.
2. Direct anti-globulin test.
3. Based on Döhner et al 2000.

Table S2b. Baseline patient characteristics by MRD data availability for the FCR arm.

| Variable | Category | MRD data available | No MRD data | Total | P-value |
|------------------|---|--|--|--|---------|
| Total | | 122 | 53 | 175 | – |
| Age | Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing | 56.4 (7.1) 57.0 (52.0,61.8) [28.0,69.0] 0 | 57.5 (7.5) 59.0 (54.0,61.0) [29.0,70.0] 0 | 56.7 (7.2) 57.0 (53.0,61.5) [28.0,70.0] 0 | 0.292 |
| Age, category | <60 >=60 Unknown/Missing | 75 (61.5) 47 (38.5) 0 | 30 (56.6) 23 (43.4) 0 | 105 (60.0) 70 (40.0) 0 | 0.615 |
| Gender | Female Male Unknown/Missing | 40 (32.8) 82 (67.2) 0 | 15 (28.3) 38 (71.7) 0 | 55 (31.4) 120 (68.6) 0 | 0.599 |
| RAI Stage | Low, 0 Intermediate, I-II High, III-IV Unknown/Missing | 9 (7.4) 66 (54.1) 47 (38.5) 0 | 0 (0.0) 28 (52.8) 25 (47.2) 0 | 9 (5.1) 94 (53.7) 72 (41.1) 0 | 0.090 |
| ECOG Performance | 0 | 70 (57.4) | 39 (73.6) | 109 (62.3) | 0.080 |

| Status | 1 2 Unknown/Missing | 50 (41.0) 2 (1.6) 0 | 13 (24.5) 1 (1.9) 0 | 63 (36.0) 3 (1.7) 0 | |
|---|--|--|---|--|-------|
| Hemoglobin, g/dL | Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing | 12.2 (2.0) 12.5 (11.2,13.8) [5.5,17.6] 2 | 11.7 (2.3) 12.2 (10.3,13.2) [6.3,16.5] 1 | 12.1 (2.1) 12.4 (11.0,13.6) [5.5,17.6] 3 | 0.136 |
| Platelets, 10 ³ /uL | Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing | 159.9 (81.0) 144.5 (103.5,191.5) [13.0,485.0] 0 | 151.3 (73.0) 134.0 (100.0,194.0) [18.0,446.0] 0 | 157.3 (78.5) 143.0 (102.0,193.5) [13.0,485.0] 0 | 0.712 |
| WBC, 10 ³ /uL | Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing | 104.7 (104.1) 72.4 (26.4,160.8) [3.1,638.9] 0 | 118.6 (125.7) 77.3 (27.2,185.6) [2.3,672.0] 0 | 108.9 (110.9) 72.7 (26.5,167.3) [2.3,672.0] 0 | 0.847 |
| Beta-2 Microglobulin, mg/L | Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing | 4.0 (1.9) 3.4 (2.7,4.8) [1.3,12.2] 0 | 3.9 (1.8) 3.5 (2.7,4.6) [1.0,10.9] 0 | 4.0 (1.9) 3.4 (2.7,4.8) [1.0,12.2] 0 | 0.837 |
| Creatinine Clearance ¹ (ml/min) | Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing | 107.5 (43.4) 96.8 (80.3,125.2) [47.7,331.4] 0 | 98.1 (28.7) 94.1 (76.2,119.2) [46.0,159.6] 17 | 105.4 (40.7) 96.8 (77.8,123.0) [46.0,331.4] 17 | 0.498 |
| Coombs Test ² | Negative Positive Unknown/Missing | 113 (94.2) 7 (5.8) 2 | 44 (88.0) 6 (12.0) 3 | 157 (92.4) 13 (7.6) 5 | 0.206 |
| Splenomegaly | No Yes Unknown/Missing | 70 (57.4) 52 (42.6) 0 | 29 (54.7) 24 (45.3) 0 | 99 (56.6) 76 (43.4) 0 | 0.743 |
| Lymphadenopathy | No Yes Unknown/Missing | 40 (32.8) 82 (67.2) 0 | 16 (30.2) 37 (69.8) 0 | 56 (32.0) 119 (68.0) 0 | 0.860 |
| Del(11q22.3) | Abnormal Normal Unknown/Missing | 26 (21.3) 96 (78.7) 0 | 13 (24.5) 40 (75.5) 0 | 39 (22.3) 136 (77.7) 0 | 0.694 |
| Dohner Classification ³ | del(17p) del(11q22) trisomy 12 normal del(13q) other Unknown/Missing | 0 (0.0) 26 (21.3) 24 (19.7) 22 (18.0) 40 (32.8) 10 (8.2) 0 | 0 (0.0) 13 (24.5) 3 (5.7) 15 (28.3) 18 (34.0) 4 (7.5) 0 | 0 (0.0) 39 (22.3) 27 (15.4) 37 (21.1) 58 (33.1) 14 (8.0) 0 | 0.129 |
| IGHV | Mutated Unmutated Unknown/Missing | 43 (41.3) 61 (58.7) 18 | 1 (9.1) 10 (90.9) 42 | 44 (38.3) 71 (61.7) 60 | 0.049 |

1. Determined based on the CKD-EPI formula.
2. Direct anti-globulin test.
3. Based on Döhner et al 2000.

Supplemental Figures

Figure S1. Ratio of MRD levels for the same patient between two time points. MRD level of 10^{-5} is used for samples with undetectable MRD to avoid division by 0. Ratio of 1 indicates no change; ratios above 1 indicates increase in MRD level from timepoint 1 to timepoint 2; ratios below 1 indicates decrease in MRD level from timepoint 1 to timepoint 2.

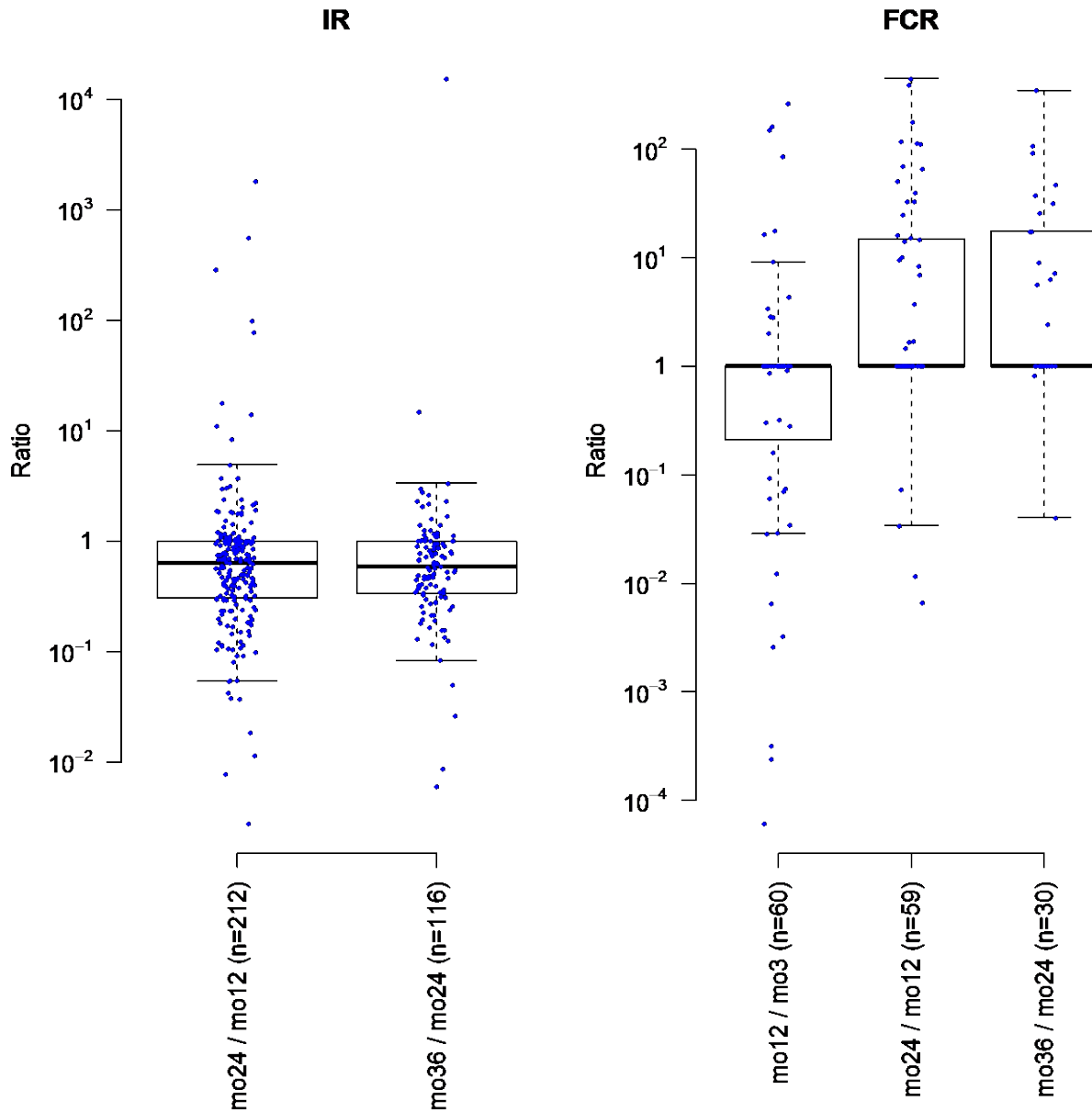


Figure S2. Progression-free survival by MRD levels (uMRD, low MRD and high MRD) at defined timepoints for patients randomized to the FCR arm. (a) MRD level at 3 months. (b) MRD level at 12 months. (c) MRD level at 24 months. (d) MRD levels at 36 months.

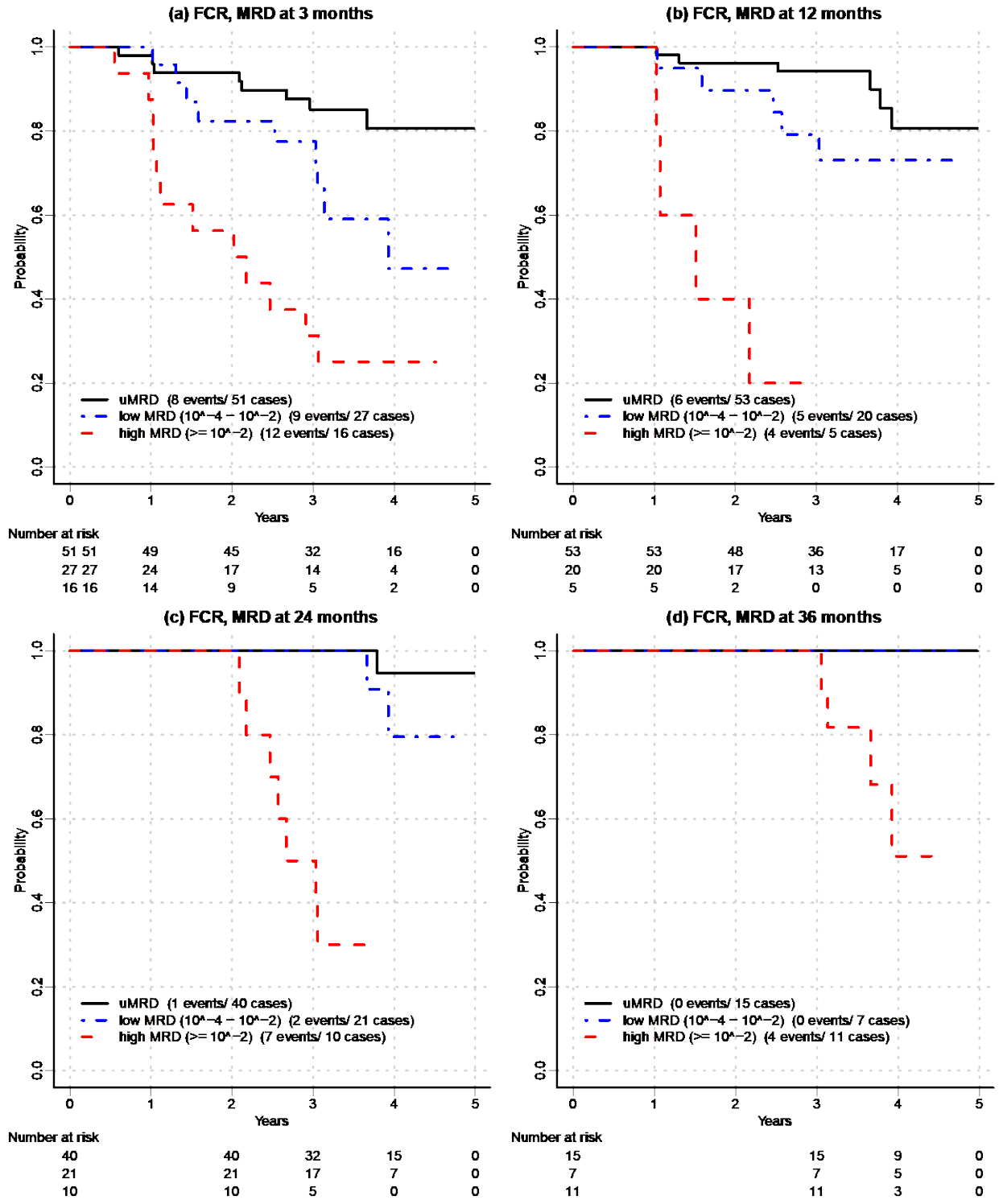
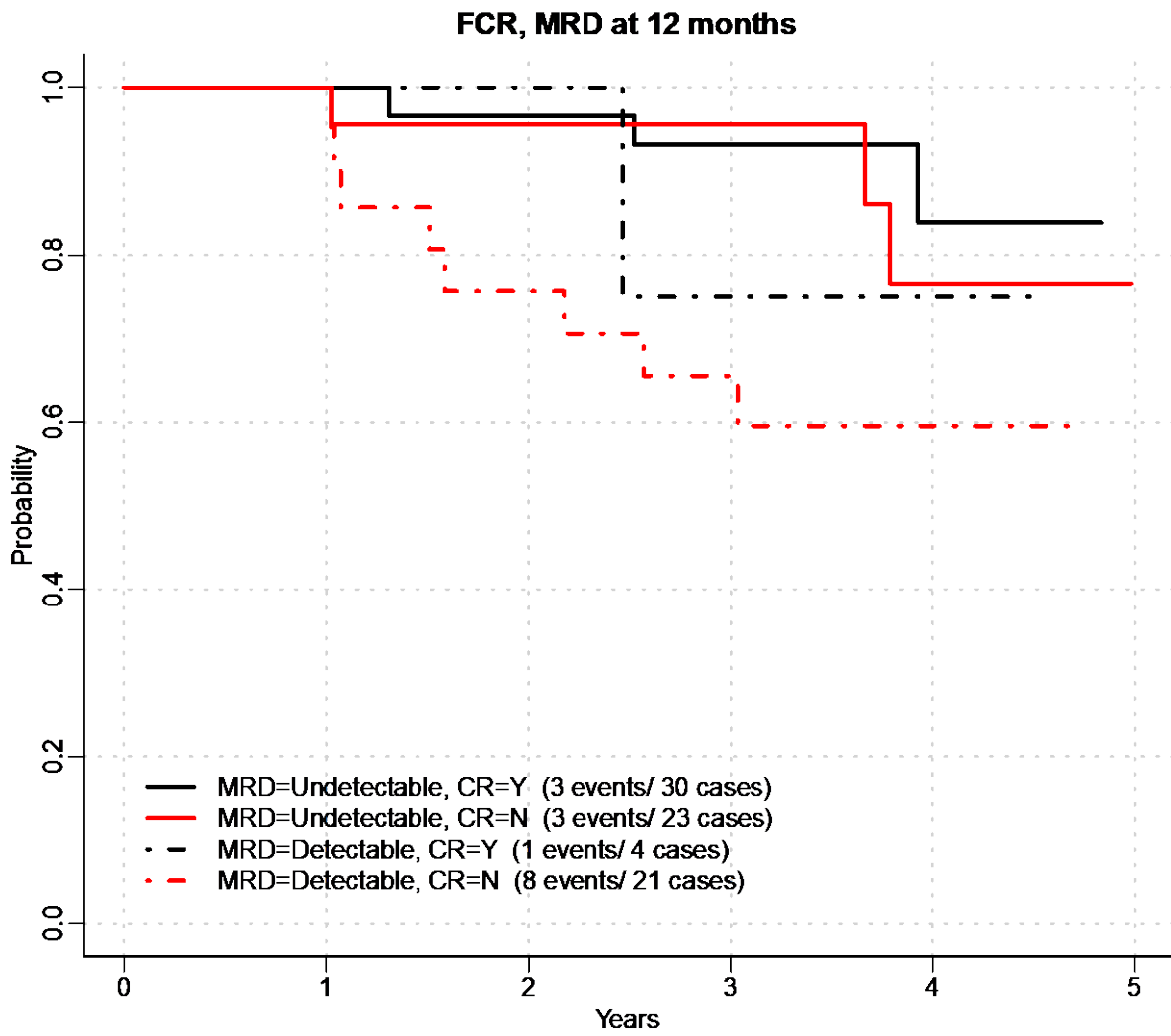


Figure S3. Progression-free survival by CR and MRD status at 12 months for the FCR arm.



| Number at risk | | | | | | |
|----------------|----|----|----|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | |
| 30 | 30 | 28 | 20 | 9 | 0 | MRD=Undetectable, CR=Y (3 events/ 30 cases) |
| 23 | 23 | 20 | 16 | 8 | 0 | MRD=Undetectable, CR=N (3 events/ 23 cases) |
| 4 | 4 | 4 | 2 | 1 | 0 | MRD=Detectable, CR=Y (1 events/ 4 cases) |
| 21 | 21 | 15 | 11 | 4 | 0 | MRD=Detectable, CR=N (8 events/ 21 cases) |

Figure S4. Progression-free survival by baseline IGHV mutation and MRD status at (a) 3 months, (b) 12 months, (c) 24 months and (d) 36 months for the FCR arm.

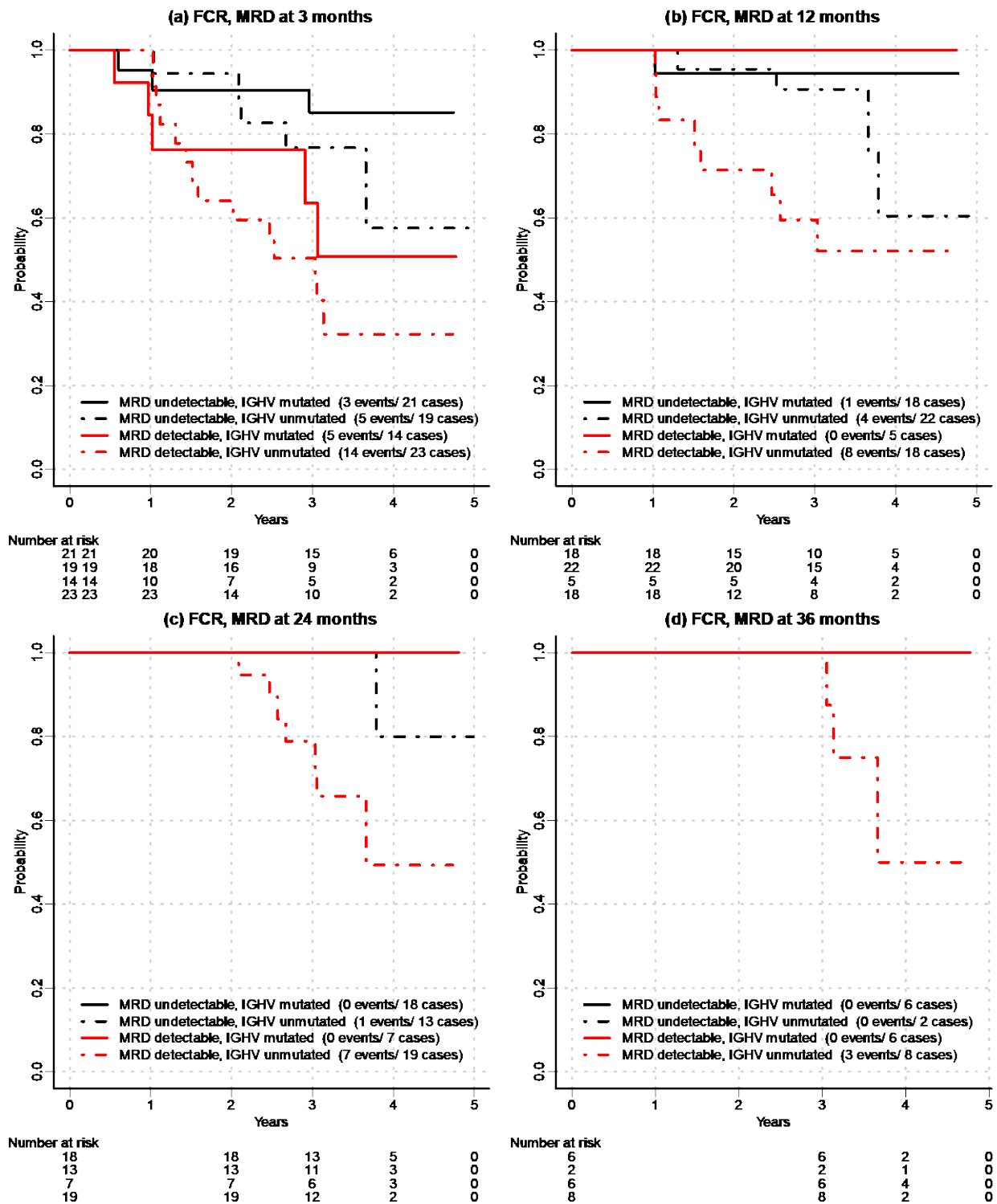


Figure S5. Progression-free survival by MRD levels (uMRD, low MRD and high MRD) at defined timepoints for patients randomized to the IR arm. (a) MRD level at 12 months. (b) MRD level at 24 months. (c) MRD level at 36 months.

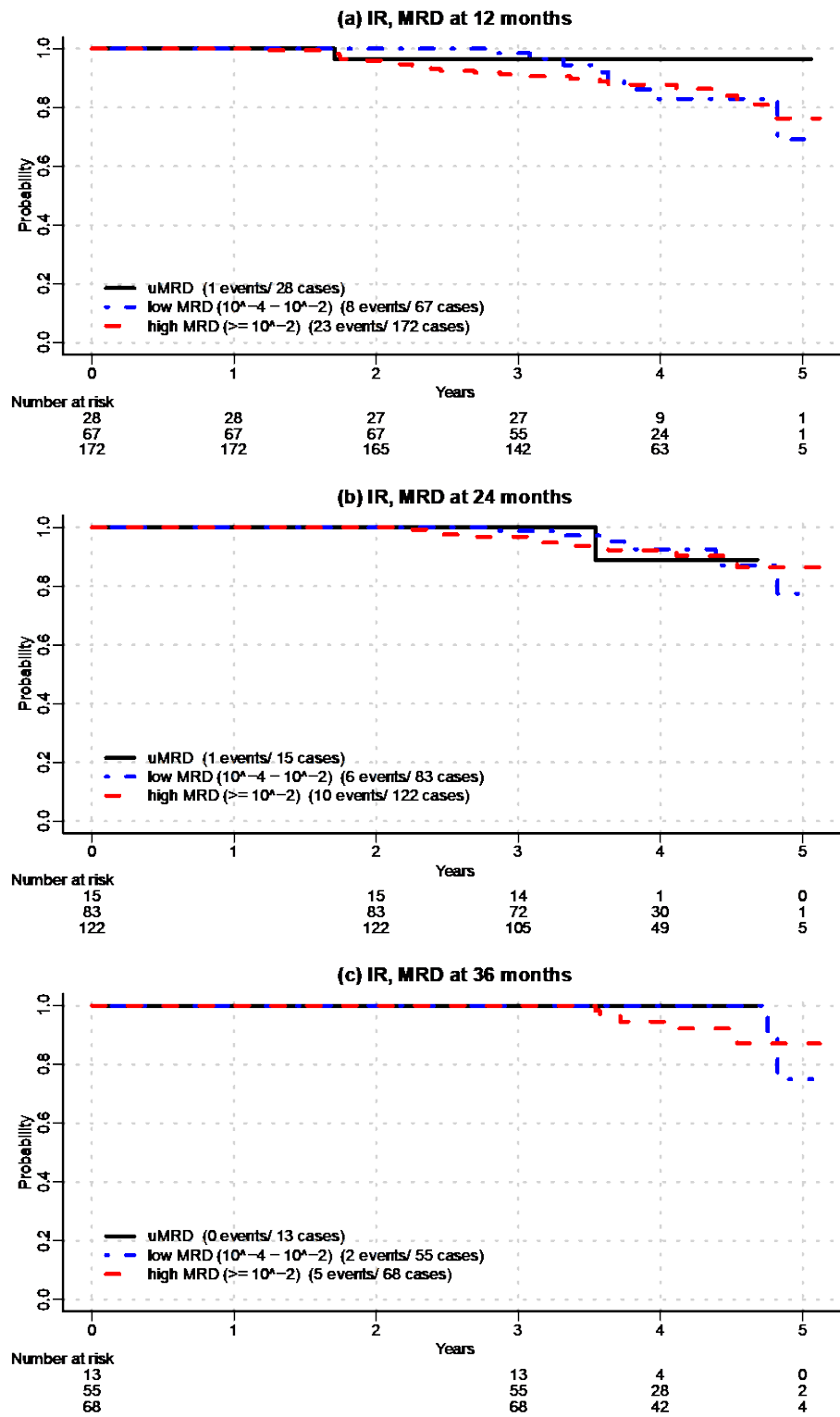
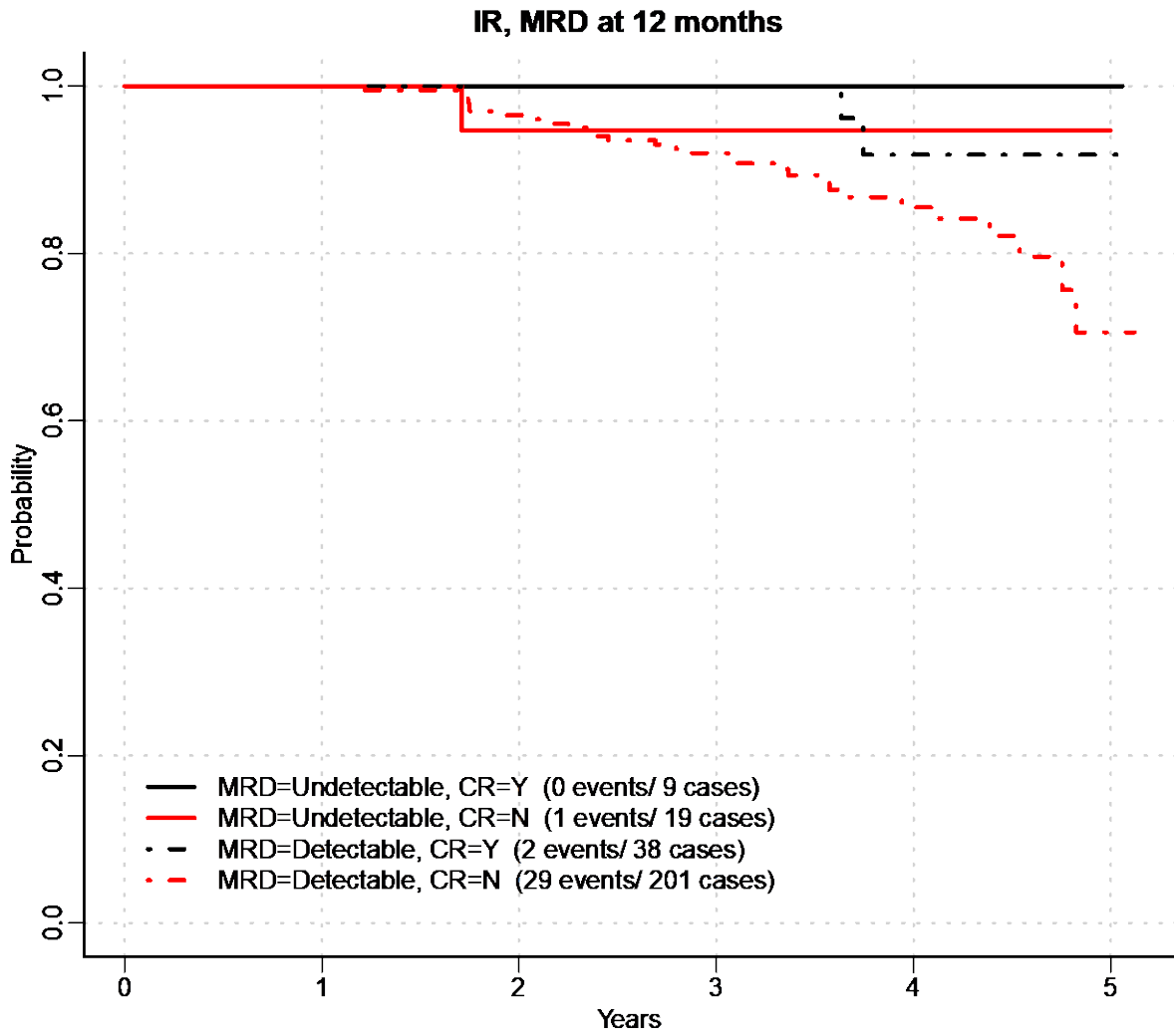


Figure S6. Progression-free survival by CR and MRD status at 12 months for the IR arm.



| Number at risk | | | | | | | |
|----------------|-----|-----|-----|----|---|--|--|
| 0 | 1 | 2 | 3 | 4 | 5 | | |
| 9 | 9 | 9 | 9 | 4 | 1 | | |
| 19 | 19 | 18 | 18 | 5 | 0 | | |
| 38 | 38 | 38 | 35 | 20 | 2 | | |
| 201 | 201 | 194 | 162 | 67 | 4 | | |

Figure S7. Progression-free survival by baseline IGHV mutation status and MRD levels at (a) 12 months, (b) 24 months and (c) 36 months for the IR arm.

