

## SUPPLEMENTARY METHODS

### Classification of therapy and eligibility criteria based on treatment

Line of therapy (LoT) was derived from a complex set of data, incorporating structured data elements from therapies ordered and administered and abstracted data elements from transplant and oral therapies (start date and stop date).

In brief, a LoT was generally the first eligible drug episode plus other eligible drugs given within 28 days. The start of the first LoT (LoT1) was the date of the first drug episode observed as structured data in the network; that is, an eligible therapy initiated within the window of 14 days before the diagnosis date or after the diagnosis date, but after the start of structured activity (earliest structured visit or therapy). The name of the “regimen” for that LoT is the combination of therapies in that line, (within 28 days) unless otherwise noted.

A regimen such as induction of bortezomib, lenalidomide, and dexamethasone (VRd) may form one block of a LoT; if a patient also received a transplant, that would form an additional block of a LoT (starting on the date on which the transplanted cells are infused). If a patient then subsequently received a maintenance regimen (exceeding 60 days of continuous therapy, and following transplant by less than 6 months), that was also considered a block within the same LoT. Maintenance regimens following an induction combination (without transplant) were a separate block within the LoT. Transplant and maintenance regimens following these rules did not advance the LoT.

### Eligibility criteria

Following evaluation of the treatment in the Flatiron Health database, the study team considered the following eligibility criteria to be applicable when conducting studies to understand treatment patterns or treatment of patients with multiple myeloma (MM):

- Exclude patients with no treatment received or documented
- Exclude “Line 0” patients: “Line 0” is a flag created by Flatiron Health to indicate patients for whom early treatment data may be missing from the database. These patients have some evidence (through unstructured data) of MM treatment occurring >30 days before the start of structured activity in the Flatiron Health network. In these patients, Line 0 extends from the start of MM treatment to the start of structured activity, but does not contain complete information on specific therapies. Therefore, assumptions about what LoT is labeled as LoT1 may be misclassified if these patients are included
- Exclude patients with a record of “Clinical Study Drug” in the LoT of interest (patients would not be excluded from a first-line cohort if they had a clinical study drug in LoT3, but for analyses of second-line or third-line cohorts, patients receiving clinical study drug in the line of interest are excluded)
- Exclude patients with combination regimens indicated for the active treatment of cancers other than MM in LoT1 e.g., cisplatin plus etoposide; (or any other LoT where a study is indexed on that LoT); however, common maintenance therapies for other cancers could be co-administered with MM therapies, and there is not a strong enough rationale to exclude patients who were co-administered maintenance therapies for other cancers. These co-administered therapies included anastrozole, leuprolide, hydroxyurea, letrozole,

methotrexate, tamoxifen, bicalutamide, abiraterone, fulvestrant, exemestane, and capecitabine. Where these occurred in a LoT, they were either:

- Removed from the LoT label, or
- Ignored where they were stand-alone therapies in a LoT, or
- Suppressed from advancing the LoT.
- Exclude patients who were not receiving recognized or indicated MM induction regimens in first-line according to National Comprehensive Cancer Network (NCCN) guidelines, and/or non-indicated first-line combinations e.g., a pomalidomide-containing regimen in first-line or monotherapy in first-line
  - A total of 47 combinations of MM therapies were considered

Certain additional modifications were made:

- In first-line, we observed a proportion of patients for whom an immunomodulating drug or proteasome inhibitor or steroid was observed administered as monotherapy and then a combination regimen was initiated >28 days after the start of the monotherapy, which according to the LoT rules would be a second-line. For example, bortezomib being initiated as 1–2 cycles of monotherapy (>28 days) before cyclophosphamide plus dexamethasone or lenalidomide plus dexamethasone are added to complete the induction regimen (CVd or VRd, respectively). Where this gap was less than 60 days, we merged and considered this a first-line combination
- Modified classification of maintenance post-transplant: maintenance therapies as recognized by the NCCN are lenalidomide, bortezomib, and ixazomib as monotherapy, and combination bortezomib plus lenalidomide. There were ~280 patients where these regimens appeared in a stand-alone LoT directly following a transplant (from a previous LoT) but were not classified as maintenance in Flatiron rules. Based on minimal evidence of progression in the response data (<10 cases) at the end of the transplant block and preceding the LoT containing the maintenance regimen, these regimens were reclassified as maintenance and rolled into the prior LoT, containing maintenance as a treatment block within the LoT

## SUPPLEMENTARY RESULTS

**Table S1 Cytogenetics (FISH and karyotype) classification.**

| Cytogenetic classification, n (%)                                 | First-line<br>(n=4614) | Second-line<br>(n=2642) | Third-line<br>(n=1422) |
|-------------------------------------------------------------------|------------------------|-------------------------|------------------------|
| All patients with t(11;14), regardless of other high-risk factors | 645 (14.0)             | 372 (14.1)              | 201 (14.1)             |
| <b>t(11;14) without high-risk factors</b>                         | <b>446 (9.7)</b>       | <b>247 (9.3)</b>        | <b>127 (8.9)</b>       |
| t(11;14) with any high-risk factor                                | 199 (4.3)              | 125 (4.7)               | 74 (5.2)               |
| t(11;14) with del(17p)                                            | 76 (1.6)               | 46 (1.7)                | 29 (2.0)               |
| <b>High-risk*</b>                                                 | <b>1624 (35.2)</b>     | <b>923 (34.9)</b>       | <b>517 (36.4)</b>      |
| High-risk with t(4;14), t(14;16), or del(17p)                     | 755 (16.4)             | 447 (16.9)              | 261 (18.4)             |
| <b>Standard-risk</b>                                              | <b>2544 (55.1)</b>     | <b>1472 (55.7)</b>      | <b>778 (54.7)</b>      |

The three subgroups considered in the current analysis are highlighted in bold.

\*Includes all patients with high-risk factors (including chromosome 1 abnormalities), and those with co-occurrence of t(11;14).

*del* deletion, *t* translocation.

**Table S2 Baseline demographics and characteristics by risk status.**

|                                         | First-line (n=6137) |                      |                |                | Second-line (n=3160) |                      |                |                | Third-line (n=1654) |                      |                |                |
|-----------------------------------------|---------------------|----------------------|----------------|----------------|----------------------|----------------------|----------------|----------------|---------------------|----------------------|----------------|----------------|
|                                         | HR<br>(n=1624)      | t(11;14)+<br>(n=446) | SR<br>(n=2544) | UR<br>(n=1523) | HR<br>(n=923)        | t(11;14)+<br>(n=247) | SR<br>(n=1472) | UR<br>(n=518)  | HR<br>(n=517)       | t(11;14)+<br>(n=127) | SR<br>(n=778)  | UR<br>(n=232)  |
| Sex, n (%)                              |                     |                      |                |                |                      |                      |                |                |                     |                      |                |                |
| Male                                    | 837 (52)            | 270 (61)             | 1452 (57)      | 826 (54)       | 473 (51)             | 151 (61)             | 846 (58)       | 252 (49)       | 271 (52)            | 73 (58)              | 436 (56)       | 105 (45)       |
| Race, n (%)                             |                     |                      |                |                |                      |                      |                |                |                     |                      |                |                |
| White                                   | 990 (61)            | 279 (63)             | 1,595 (63)     | 940 (62)       | 598 (65)             | 160 (65)             | 922 (63)       | 338 (65)       | 337 (65)            | 79 (62)              | 499 (64)       | 154 (66)       |
| African American                        | 240 (15)            | 70 (16)              | 434 (17)       | 238 (16)       | 128 (14)             | 36 (15)              | 272 (19)       | 82 (16)        | 82 (16)             | 18 (14)              | 138 (18)       | 38 (16)        |
| Asian                                   | 37 (2)              | 5 (1)                | 49 (2)         | 19 (1)         | 23 (3)               | 1 (<1)               | 30 (2)         | 6 (1)          | 10 (2)              | 1 (1)                | 16 (2)         | 0              |
| Other                                   | 207 (13)            | 53 (12)              | 317 (12)       | 204 (13)       | 113 (12)             | 30 (12)              | 179 (12)       | 64 (12)        | 60 (12)             | 20 (16)              | 88 (11)        | 30 (13)        |
| Missing                                 | 150 (9)             | 39 (9)               | 149 (6)        | 122 (8)        | 61 (7)               | 20 (8)               | 69 (5)         | 28 (5)         | 28 (5)              | 9 (7)                | 37 (5)         | 10 (4)         |
| Median age at diagnosis, years [Q1, Q3] | 69<br>[62, 76]      | 69<br>[61, 76]       | 69<br>[60, 76] | 70<br>[62, 77] | 68<br>[60, 75]       | 68<br>[61, 77]       | 67<br>[59, 75] | 70<br>[62, 77] | 67<br>[59, 74]      | 66<br>[60, 74]       | 66<br>[58, 74] | 70<br>[63, 76] |
| Practice type, n (%)                    |                     |                      |                |                |                      |                      |                |                |                     |                      |                |                |
| Academic                                | 158 (10)            | 46 (10)              | 234 (9)        | 242 (16)       | 112 (12)             | 30 (12)              | 162 (11)       | 91 (18)        | 69 (13)             | 17 (13)              | 95 (12)        | 42 (18)        |
| Community                               | 1466 (90)           | 400 (90)             | 2310 (91)      | 1281 (84)      | 811 (88)             | 217 (88)             | 1310 (89)      | 427 (82)       | 448 (87)            | 110 (87)             | 683 (88)       | 190 (82)       |
| Median follow-up time, months [Q1, Q3]  | 19<br>[8, 36]       | 22<br>[10, 45]       | 26<br>[11, 49] | 21<br>[8, 43]  | 16<br>[6, 31]        | 17<br>[7, 38]        | 20<br>[8, 41]  | 17<br>[6, 35]  | 13<br>[5, 24]       | 16<br>[6, 32]        | 17<br>[7, 35]  | 12<br>[4, 28]  |
| ECOG PS, n (%)                          |                     |                      |                |                |                      |                      |                |                |                     |                      |                |                |
| 0                                       | 380 (23)            | 108 (24)             | 500 (20)       | 234 (15)       | 195 (21)             | 56 (23)              | 336 (23)       | 105 (20)       | 112 (22)            | 35 (28)              | 186 (24)       | 46 (20)        |
| 1                                       | 346 (21)            | 96 (22)              | 542 (21)       | 264 (17)       | 278 (30)             | 81 (33)              | 469 (32)       | 146 (28)       | 182 (35)            | 45 (35)              | 269 (35)       | 82 (35)        |
| 2                                       | 135 (8)             | 23 (5)               | 192 (8)        | 135 (9)        | 117 (13)             | 26 (11)              | 157 (11)       | 69 (13)        | 67 (13)             | 16 (13)              | 104 (13)       | 39 (17)        |
| 3                                       | 41 (3)              | 14 (3)               | 57 (2)         | 56 (4)         | 35 (4)               | 5 (2)                | 37 (3)         | 18 (4)         | 19 (4)              | 4 (3)                | 16 (2)         | 12 (5)         |
| Missing                                 | 722 (45)            | 205 (46)             | 1253 (49)      | 834 (55)       | 298 (32)             | 79 (32)              | 473 (32)       | 180 (35)       | 137 (27)            | 27 (21)              | 203 (26)       | 53 (23)        |
| ISS stage at diagnosis, n (%)           |                     |                      |                |                |                      |                      |                |                |                     |                      |                |                |
| Stage I                                 | 273 (17)            | 107 (24)             | 521 (21)       | 251 (17)       | 140 (15)             | 55 (22)              | 301 (20)       | 82 (16)        | 82 (16)             | 25 (20)              | 160 (21)       | 35 (15)        |
| Stage II                                | 355 (22)            | 103 (23)             | 501 (20)       | 249 (16)       | 203 (22)             | 68 (28)              | 274 (19)       | 93 (18)        | 119 (23)            | 36 (28)              | 144 (19)       | 43 (19)        |
| Stage III                               | 396 (24)            | 84 (19)              | 507 (20)       | 267 (18)       | 246 (27)             | 47 (19)              | 295 (20)       | 98 (19)        | 139 (27)            | 23 (18)              | 167 (22)       | 39 (17)        |
| Unknown                                 | 600 (37)            | 152 (34)             | 1,015 (40)     | 756 (50)       | 334 (36)             | 77 (31)              | 602 (41)       | 245 (47)       | 177 (34)            | 43 (34)              | 307 (40)       | 115 (50)       |

|                                                                       | First-line (n=6137) |                      |                |                | Second-line (n=3160) |                      |                |               | Third-line (n=1654) |                      |                |               |
|-----------------------------------------------------------------------|---------------------|----------------------|----------------|----------------|----------------------|----------------------|----------------|---------------|---------------------|----------------------|----------------|---------------|
|                                                                       | HR<br>(n=1624)      | t(11;14)+<br>(n=446) | SR<br>(n=2544) | UR<br>(n=1523) | HR<br>(n=923)        | t(11;14)+<br>(n=247) | SR<br>(n=1472) | UR<br>(n=518) | HR<br>(n=517)       | t(11;14)+<br>(n=127) | SR<br>(n=778)  | UR<br>(n=232) |
| Prior malignancy, n (%)                                               |                     |                      |                |                |                      |                      |                |               |                     |                      |                |               |
| Yes                                                                   | 151 (9)             | 38 (9)               | 236 (9)        | 169 (11)       | 84 (9)               | 22 (9)               | 151 (10)       | 53 (10)       | 41 (8)              | 11 (9)               | 83 (11)        | 24 (10)       |
| No                                                                    | 1473 (91)           | 408 (92)             | 2308 (91)      | 1354 (89)      | 839 (91)             | 225 (91)             | 1321 (90)      | 465 (90)      | 476 (92)            | 116 (91)             | 695 (89)       | 208 (90)      |
| Received maintenance therapy, n (%)                                   |                     |                      |                |                |                      |                      |                |               |                     |                      |                |               |
| No                                                                    | 1249 (77)           | 339 (76)             | 1979 (78)      | 1287 (85)      | 821 (89)             | 228 (92)             | 1311 (89)      | 476 (92)      | 490 (95)            | 117 (92)             | 735 (95)       | 227 (98)      |
| Yes                                                                   | 211 (13)            | 71 (16)              | 356 (14)       | 139 (9)        | 42 (5)               | 7 (3)                | 86 (6)         | 20 (4)        | 7 (1)               | 0                    | 13 (2)         | 1 (<1)        |
| Missing                                                               | 164 (10)            | 36 (8)               | 209 (8)        | 97 (6)         | 60 (7)               | 12 (5)               | 75 (5)         | 22 (4)        | 20 (4)              | 10 (8)               | 30 (4)         | 4 (2)         |
| Cytogenetic test type, n (%)                                          |                     |                      |                |                |                      |                      |                |               |                     |                      |                |               |
| FISH & karyotype                                                      | 1280 (79)           | 350 (79)             | 1665 (65)      | 0              | 766 (83)             | 206 (83)             | 1026 (70)      | 0             | 452 (87)            | 112 (88)             | 571 (73)       | 0             |
| FISH only                                                             | 344 (21)            | 96 (22)              | 353 (14)       | 36 (2)         | 157 (17)             | 41 (17)              | 161 (11)       | 16 (3)        | 65 (13)             | 15 (12)              | 71 (9)         | 10 (4)        |
| Karyotype only                                                        | 0                   | 0                    | 526 (21)       | 0              | 0                    | 0                    | 285 (19)       | 0             | 0                   | 0                    | 136 (18)       | 0             |
| Missing                                                               | 0                   | 0                    | 0              | 1487 (98)      | 0                    | 0                    | 0              | 502 (97)      | 0                   | 0                    | 0              | 222 (96)      |
| FISH cytogenetic abnormality, n (%)                                   |                     |                      |                |                |                      |                      |                |               |                     |                      |                |               |
| No abnormalities                                                      | 0                   | 0                    | 1442 (57)      | 36 (2)         | 0                    | 0                    | 862 (59)       | 16 (3)        | 0                   | 0                    | 443 (57)       | 10 (4)        |
| Present                                                               | 1624 (100)          | 446 (100)            | 1102 (43)      | 0              | 923 (100)            | 247 (100)            | 610 (41)       | 0             | 517 (100)           | 127 (100)            | 335 (43)       | 0             |
| Missing                                                               | 0                   | 0                    | 0              | 1487 (98)      | 0                    | 0                    | 0              | 502 (97)      | 0                   | 0                    | 0              | 222 (96)      |
| Median karyotype cytogenetic abnormality, no. of chromosomes [Q1, Q3] | 46<br>[45, 53]      | 46<br>[45, 56]       | 51<br>[46, 54] | 51<br>[47, 55] | 47<br>[45, 53]       | 46<br>[45, 46]       | 52<br>[46, 54] | NA            | 47<br>[45, 53]      | 46<br>[45, 46]       | 52<br>[46, 55] | NA            |

ECOG PS Eastern Cooperative Oncology Group performance status, FISH fluorescence in situ hybridization, HR high-risk; ISS International Staging System, Q quartile, SR standard-risk, t translocation, UR undocumented risk.

**Table S3 Treatment classes per line of treatment.**

| <b>Treatment class</b>             | <b>First-line<br/>(n=6137)</b> | <b>Second-line<br/>(n=3160)</b> | <b>Third-line<br/>(n=1654)</b> |
|------------------------------------|--------------------------------|---------------------------------|--------------------------------|
| PI + steroid + IMiD                | 2779 (45.3)                    | 835 (26.4)                      | 340 (20.6)                     |
| Steroid + IMiD                     | 1102 (18.0)                    | 559 (17.7)                      | 264 (16.0)                     |
| PI + steroid                       | 1010 (16.5)                    | 416 (13.2)                      | 222 (13.4)                     |
| PI + chemotherapy + steroid        | 878 (14.3)                     | 251 (7.9)                       | 98 (5.9)                       |
| Steroid + chemotherapy             | 141 (2.3)                      | 83 (2.6)                        | 40 (2.4)                       |
| PI + steroid + IMiD + chemotherapy | 115 (1.9)                      | 64 (2.0)                        | 24 (1.5)                       |
| Steroid + chemotherapy + IMiD      | 47 (0.8)                       | 34 (1.1)                        | 20 (1.2)                       |
| IMiD + PI                          | 27 (0.4)                       | 70 (2.2)                        | 32 (1.9)                       |
| PI + mAb + IMiD + steroid          | 14 (0.2)                       | 30 (1.0)                        | 25 (1.5)                       |
| Steroid + IMiD + mAb               | 11 (0.2)                       | 178 (5.6)                       | 170 (10.3)                     |
| PI + steroid + mAb                 | 10 (0.2)                       | 84 (2.7)                        | 53 (3.2)                       |
| IMiD monotherapy                   | –                              | 183 (5.8)                       | 92 (5.6)                       |
| PI monotherapy                     | –                              | 133 (4.2)                       | 66 (4.0)                       |
| Steroid monotherapy                | –                              | 100 (3.2)                       | 44 (2.7)                       |
| Other*                             | –                              | 63 (2.0)                        | 53 (3.2)                       |
| Steroid + mAb                      | –                              | 42 (1.3)                        | 71 (4.3)                       |
| Chemotherapy alone                 | –                              | 13 (0.4)                        | 9 (0.5)                        |
| mAb monotherapy                    | –                              | 11 (0.4)                        | 20 (1.2)                       |
| mAb + IMiD                         | –                              | 8 (0.3)                         | 10 (0.6)                       |

\*Other includes MM-indicated therapies in combination with other systemic anticancer therapies.

Treatment classes used in at least 5 patients are displayed.

**Chemotherapy:** Cyclophosphamide, doxorubicin, melphalan; vincristine or bendamustine.

**IMiD:** Lenalidomide, pomalidomide or thalidomide.

**mAb:** Daratumumab, elotuzumab or isatuximab.

**PI:** Bortezomib, carfilzomib, or ixazomib.

**Steroid:** Dexamethasone, prednisone methylprednisolone, prednisolone.

*IMiD* immunomodulating drug, *mAb* monoclonal antibody, *MM* multiple myeloma, *PI* proteasome inhibitor.

**Table S4 Median OS for patients with t(11;14) with or without high-risk factors.**

|                                     | <b>N</b> | <b>Events</b> | <b>Median,<br/>months</b> | <b>95% CI, months</b> |
|-------------------------------------|----------|---------------|---------------------------|-----------------------|
| t(11;14) all-comers                 | 645      | 196           | 68.6                      | 60.5–91.9             |
| t(11;14) with no high-risk factors  | 446      | 127           | 74.0                      | 66.1–NE               |
| t(11;14) with any high-risk factors | 199      | 69            | 41.9                      | 37.5–NE               |
| t(11;14) with del(17p)              | 76       | 35            | 33.1                      | 12.9–NE               |
| t(11;14) with remaining high risk*  | 142      | 41            | NE                        | 40.1–NE               |

\*Patients with high-risk factors other than or in addition to del(17p).

*CI* confidence interval, *del* deletion, *NE* not estimable, *OS* overall survival, *t* translocation.

**Table S5 Maintenance therapy, transplant, and cytogenetics classification (FISH and karyotyping) for the VRd sensitivity analysis cohort.**

|                                                                                             | <b>First-line<br/>(n=2636)</b> |
|---------------------------------------------------------------------------------------------|--------------------------------|
| <b>Received maintenance* therapy, n (%)</b>                                                 |                                |
| No                                                                                          | 1889 (71.7)                    |
| Yes                                                                                         | 500 (19.0)                     |
| Missing                                                                                     | 247 (9.4)                      |
| <b>Received transplant in first-line or second-line, n (%)</b>                              |                                |
| No                                                                                          | 1889 (71.7)                    |
| Yes                                                                                         | 747 (28.3)                     |
| <b>Cytogenetics test, n (%)</b>                                                             |                                |
| Results unknown/not documented                                                              | 540 (2.0.5)                    |
| Yes                                                                                         | 2082 (79.0)                    |
| No                                                                                          | 14 (0.5)                       |
| <b>Cytogenetic classification, n (% of patients with cytogenetic test results [n=2082])</b> |                                |
| All patients with t(11;14), regardless of other high-risk factors                           | 312 (15.0)                     |
| <b>t(11;14) without high-risk factors</b>                                                   | <b>206 (9.9)</b>               |
| t(11;14) with any high-risk factor                                                          | 106 (5.1)                      |
| t(11;14) with del(17p)                                                                      | 42 (2.0)                       |
| <b>High-risk<sup>†</sup></b>                                                                | <b>804 (38.6)</b>              |
| High-risk with t(4;14), t(14;16), or del(17p)                                               | 372 (17.9)                     |
| <b>Standard-risk</b>                                                                        | <b>1,072 (51.5)</b>            |

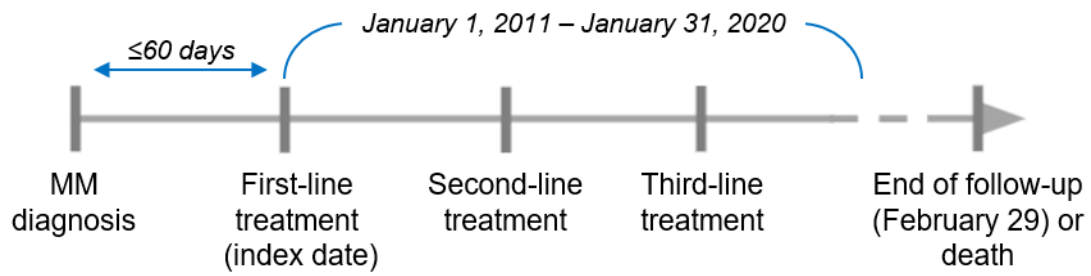
The three subgroups considered in the current analysis are highlighted in bold.

\*Maintenance defined only in patients who had transplants.

<sup>†</sup>Includes all patients with high-risk factors (including chromosome 1 abnormalities) and those with co-occurrence of t(11;14).

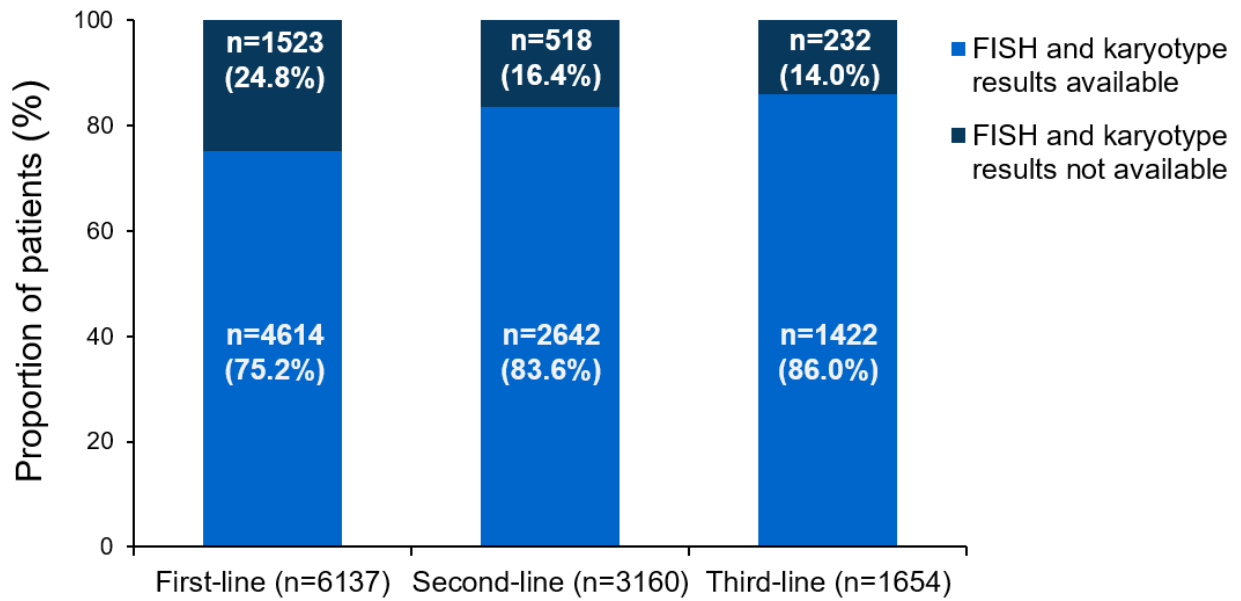
*FISH* fluorescence in situ hybridization, *t* translocation, *VRd* bortezomib, lenalidomide, and dexamethasone.

**Fig. S1 Study duration and treatment lines.**



MM multiple myeloma.

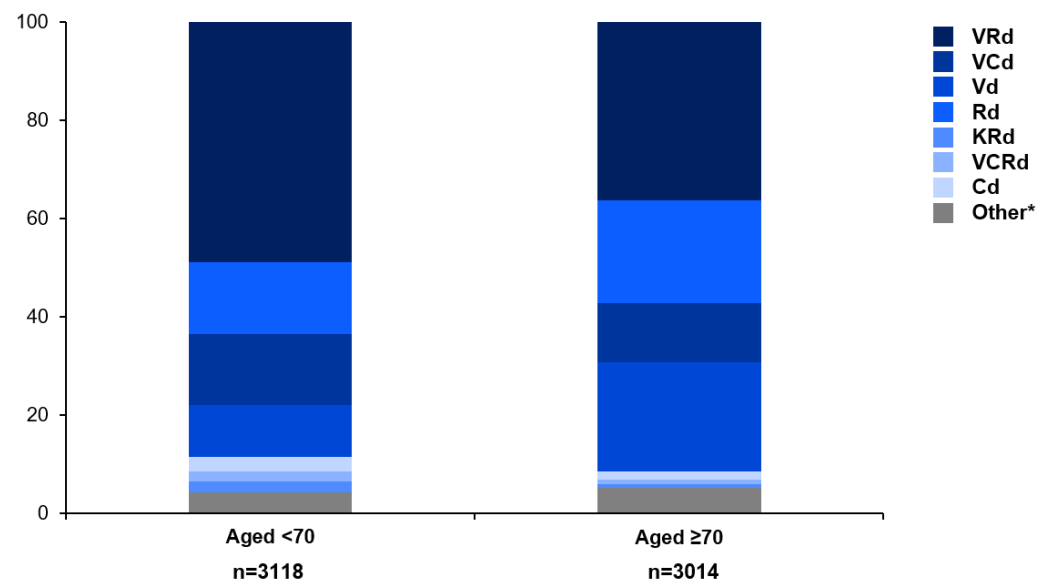
**Fig. S2 Availability of FISH and karyotype results before line of treatment initiation.**



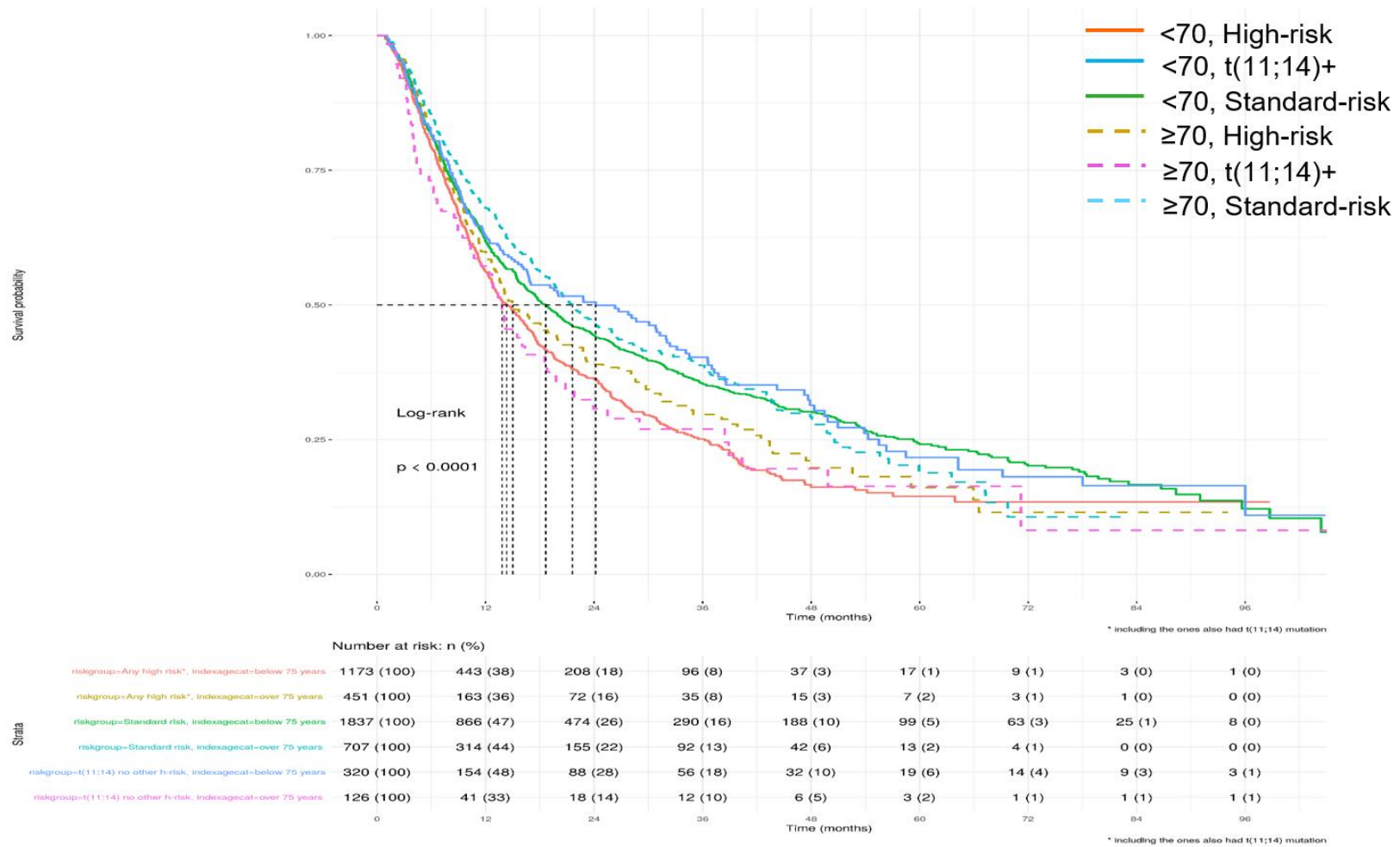
*FISH* fluorescence in situ hybridization.

**Fig. S3 Sensitivity analysis. Treatment patterns (A) and Kaplan–Meier curves for TTNT (B), and OS (C) for patients aged <70 vs ≥70 years.**

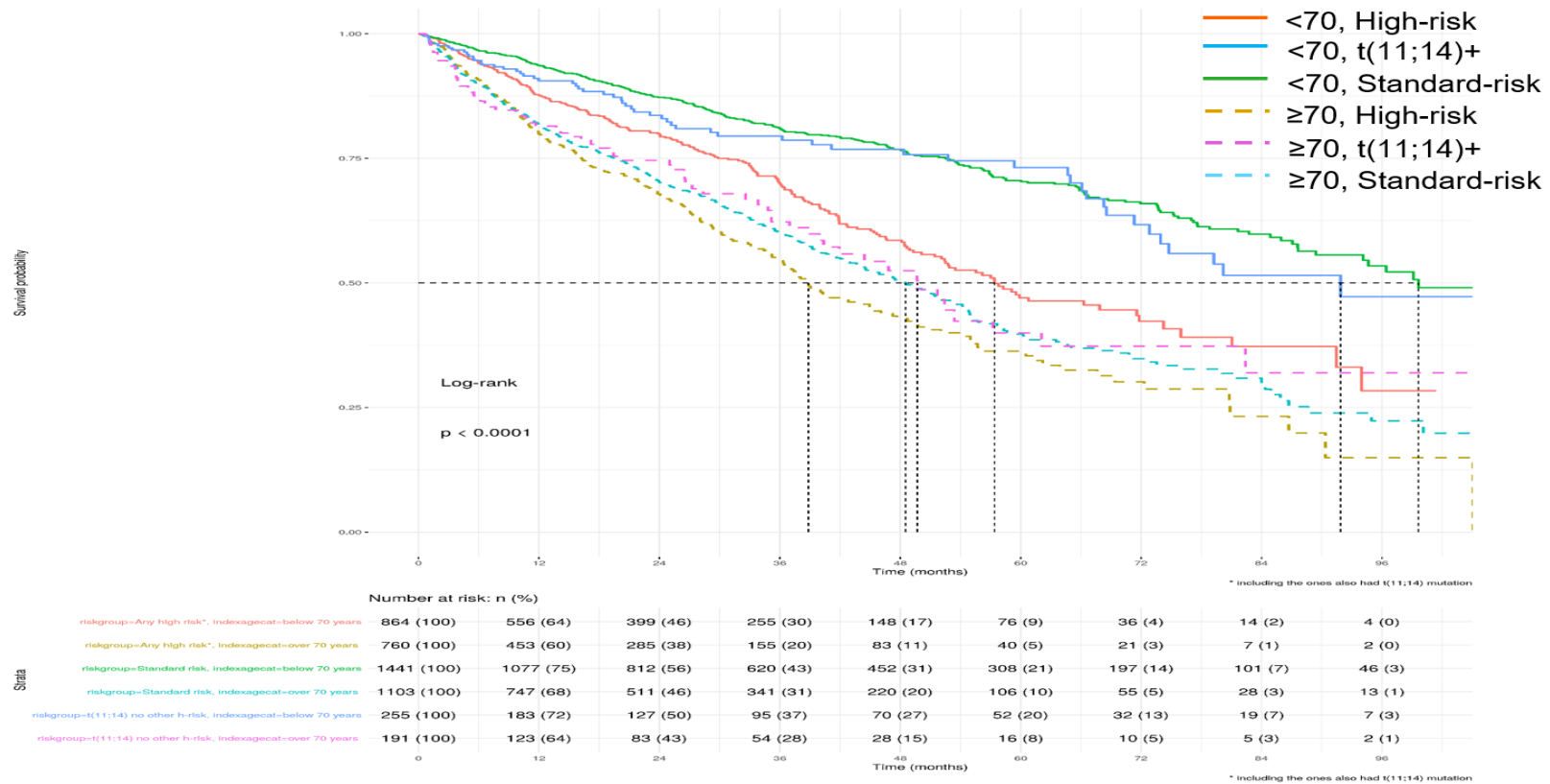
**A**



B



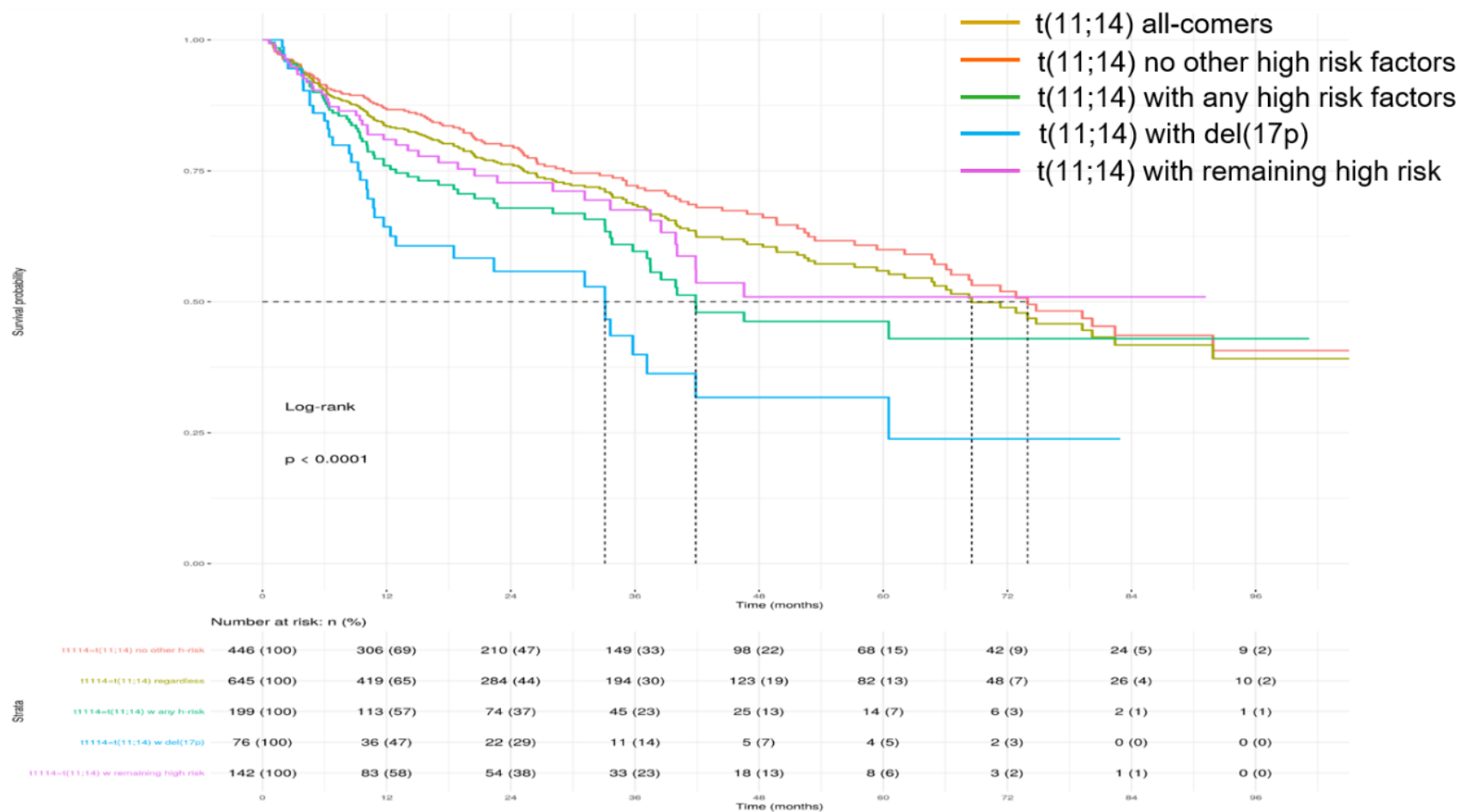
C



\*Represents all other therapies, where <1% of patients receive a particular treatment regimen.

C cyclophosphamide, d dexamethasone, del deletion, K carfilzomib, OS overall survival, R lenalidomide, t translocation, TTNT time to next treatment, V bortezomib.

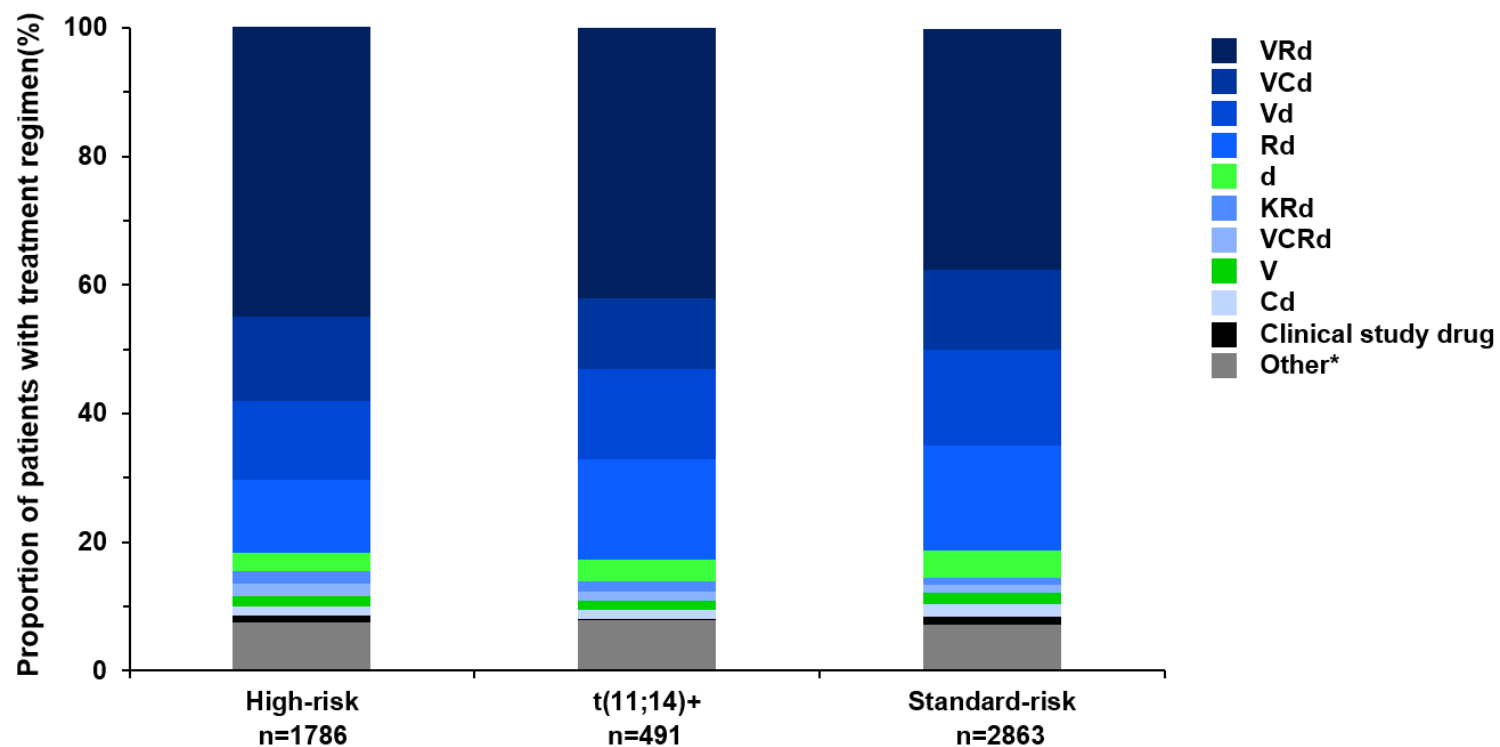
Fig. S4 Sensitivity analysis. OS for patients with t(11;14) with or without high risk factors.



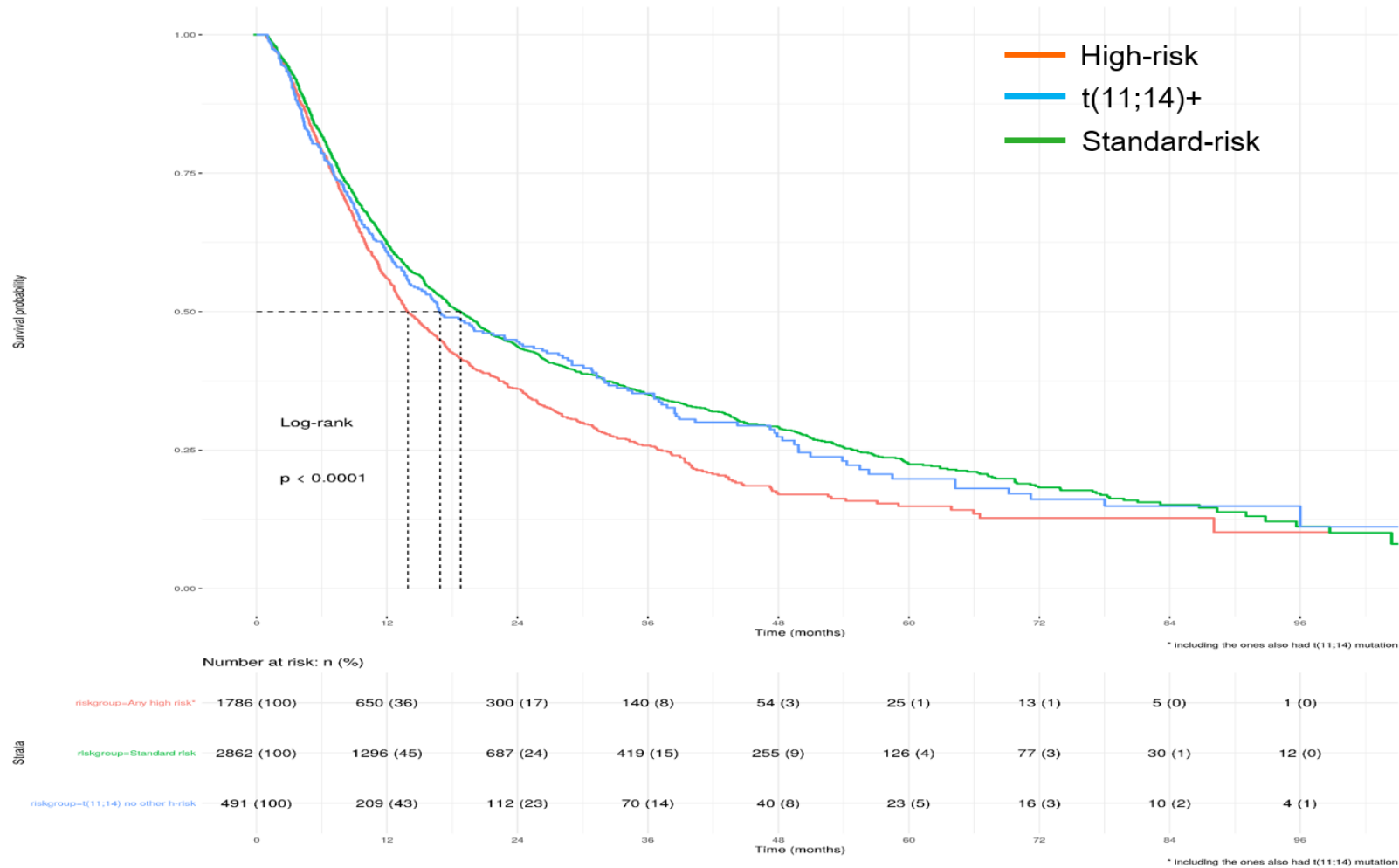
OS overall survival.

Fig. S5 Sensitivity analysis. Treatment patterns for the expanded first-line cohort (A) and Kaplan–Meier curves by risk-subgroup for TTNT (B) and OS (C).

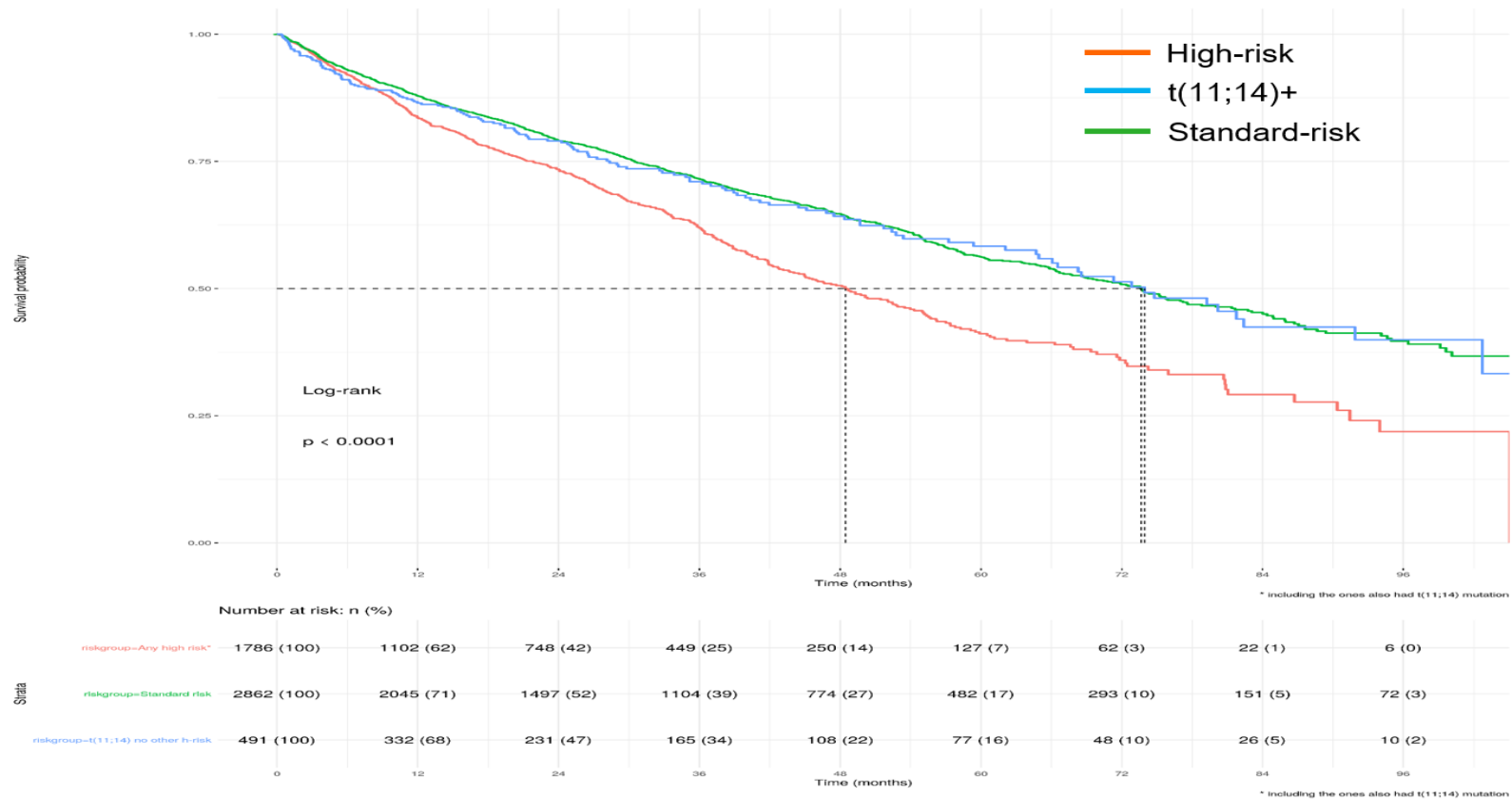
A



B



C



\*Represents all other therapies, where <1% of patients receive a particular treatment regimen.

C cyclophosphamide, d dexamethasone, K carfilzomib, OS overall survival, R lenalidomide, TTNT time to next treatment, V bortezomib.