**Supplementary Materials**

**Table S1.** Fragility subgroup analysis for the FIRST study. Adapted from [14, 15].

|  |  |  |  |
| --- | --- | --- | --- |
| **Median PFS**  **(months)** | **Fit patients**  **(*fit*)** | **Intermediately fit**  **(*intermediate patient*)** | **Frail patients**  **(*frail*)** |
| Median PFS  (months) for Rd | 43.7 | 31.1 | 20.3 |
| Median PFS  (months) for MPT | 23.9 | 22.6 | 20.2 |
| Hazard ratio | 0.56; 95% Cl (0.38-0.84) | 0.62; 95% Cl (0.46-0.85) | 0.79; 95% Cl (0.64-0.97) |

Abbreviations: CI – confidence intervals; MPT – melphalan-prednisone-thalidomide; PFS – progression-free survival; Rd - lenalidomide-dexamethasone.

**Table S2.** Fragility scale according to the International Myeloma Working Group.

|  |  |
| --- | --- |
| **Age (in years)** | **Result** |
| ≤75 | 0 |
| 75–80 | 1 |
| >80 | 2 |
| **Katz Daily Fitness Scale** |  |
| >4 | 0 |
| ≤4 | 1 |
| **Lawton’s Advanced Activities of Daily Living Scale** |  |
| >5 | 0 |
| ≤5 | 1 |
| **Charlson Comorbidity Scale** |  |
| ≤1 | 0 |
| ≥2 | 1 |
| **RESULTS** | |
| Fit/ Efficient | 0 |
| Intermediately fit | 1 |
| Fraily/ Fragile | ≥2 |

**Table S3.** International Myeloma Working Group scale for patients over 75.

|  |  |
| --- | --- |
| **Intermediately fit** | **Fraily** |
| Age 76-80 or ADL ≤ 4 or I-ADL ≤ 5 or CCI ≥ 2 | 1. Age > 80 regardless of ADL, I-ADL, CCl 2. 76–80 years old and both ADL ≤ 4, I-ADL ≤ 5, CCI ≥ 2. 3. Age ≤ 75 years old and at least 2 with ADL ≤4, I-ADL ≤5, CCI ≥2. |
| Recommended treatment: reduction of treatment intensity. | Absolute dose reduction. |
| Reduced three-drug or full/reduced two-drug regimens. | Two-drug-reduced regimens.  The most important – palliative and supportive treatment. |

Abbreviations: ADL – Katz Scale; CCI – Charlson Comorbidity Index; I-ADL – Lawton Scale.

**Table S4.** Comparison of fitness scales for the elderly with multiple myeloma.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Scale** | **Biological factors** | **Performance test** | **Comparison with IMWG** | **Origin of the study population** | **Prospective assessment** |
| IMWG (Palumbo) | -age  -CC\* | -Katz scale  -I-ADL scale | not applicable | from clinical trials | No |
| R-MCI | -age  -lung diseases  -kidney disease (eGFR) | -performance status according to Karnofsky  -assessment of functioning: subjective assessment or geriatric “Get up and go” test or I-ADL | Yes | -from clinical trials  -general population | No |
| Mayo Risk Score (MRS) | -age  -NT-proBNP | -ECOG performance status (WHO) | No | -from clinical trials  -general  population | No |
| \* CCI ( Charlson-comorbidity-index)  \* Revised Myeloma Comorbidity Index  Abbreviations: ECOG - Eastern Cooperative Oncology Group; eGFR – estimated glomerular filtration rate; I-ADL – Lawton Scale; IMWG – International Myeloma Working group; NT-proBNP - N-terminal pro-brain natriuretic peptide; WHO –World Health Organization. | | | | | |

**Table S5.** Response to first line treatment depending on whether drugs were modified or not.

|  |  |  |  |
| --- | --- | --- | --- |
| **Response for first Line Therapy** | Treatment with schema **without** modification drugs | Treatment with schema **with** modification drugs | p-val |
| Complete Response (CR) | 12 (8,4%) | 6 (11,1%) | 0,084 |
| Very good Partial Response and Partial Response (VGPR and PR) | 98 (68,5%) | 27 (50%) |
| Stable Disease (SD) | 21 (14,7%) | 15 (27,8%) |
| Progressive Disease (PD) | 12 (8,4%) | 6 (11,1%) |

**Table S6.** Use of regimens with or without drug modification.

|  |  |  |  |
| --- | --- | --- | --- |
| **Schema in first line therapy** | Modification | | p- val |
| Without modification drugs | With  modification |
| 3 –drug schema | 122 (85,3%) | 35 (64,8%) | **0,003** |
| 2 – drug schema | 21 (14,7%) | 19 (35,2%) |

**Table S7.** Use of regimens with or without drug modification according of fraily.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Fragility scale** (International Myeloma Working Group) | First line therapy | | | | | |
| Treatment with 3 drug regimen | | | Treatment with 2 drug regimen | | |
| Without modification drugs (%) | With  Modification drug | | Without modification drugs | With  Modification drug | |
| **Intermediately fit** | 27 (62,8%) | 7 (27,2%) | | 5 (55,6%) | 4 (44,4%) | |
| 34 (85%) | | | 9 (15%) | | |
| **Frailty** | 95 (77,2%) | 28 (22,8%) | | 16 (51,6%) | 15 (49,4%) | |
| 123 (79,8%) | | | 31 (20,8%) | | |
| **Total numer** | 122 (77,7%) | 35 (22,3%) | | 21 (52,5%) | 19 (47,5%) | |
| 157 (79,7%) | | | 40 (20,3%) | | |
| Frailty (only 80 years old & older) | 35 (70%) | | 15 (30%) | 6 (40%) | | 9 (60%) |
| 50 (76,9%) | | | 15 (23,1%) | | |

**Table S8.** The relationship between the number of comorbidities identified in each patient and the treatment protocol selected.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Number of comorbidities** | **Number of cases (%)** | **Number (%) of patients treated with a 2-drug vs. a 3-drug regimen** | | **Trend evaluation**  **p-value** | **Independence assessment**  **p-value** |
| **3-drug schema** | **2-drug schema** |
| None | 21 (11%) | 18 (85.7%) | 3 (14.3%) | 0.335 | 0.395 |
| 1 | 35 (18%) | 27 (77.1%) | 8 (22.9%) |
| 2 | 54 (27%) | 44 (81.5%) | 10 (18.5%) |
| 3 | 34 (17,1%) | 30 (88.2%) | 4 (11.8%) |
| 4 or more | 53 (26.9%) | 38 (71.7%) | 15 (28.3%) |

**Table S9.** Responses to bortezomib use in first-line treatment.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **I line** | | **Response to first-line treatment** | | | | |
| **Complete remission (CR)** | **Very good partial response (VGPR)** | **Partial response (PR)** | **Disease stabilization (SD)** | **Disease progression** |
| **bortezomib** | Not used | 11 (9.6%) | 6 (5.3%) | 71 (62.3%) | 18 (15.8%) | 8 (7%) |
| Used | 7 (8.4%) | 9 (10.8%) | 39 (47%) | 18 (21.7%) | 10 (12%) |

**Table S10.** The relationship between co-existing disease and the treatment protocol selected.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Number of cases/N important\***  **cases/total\*** | **Number of patients with a given treatment regimen (%)** | | **Independence assessment**  **p-value** |
| **3-drug** | **2-drug** |
| Total | 197/197 | **157 (100%)** | **40 (100%)** |
| Presence of cardiovascular disease (any) | 166/197 | 129 (82.2%)/157 | 37 (92.5%)/40 | 0.145 |
| Hypertension | 158/197 | 124 (79%)/157 | 34 (85%)/40 | 0.507 |
| Ischemic heart disease | 58/197 | 46 (29.3%)/157 | 12 (30%)/40 | 1 |
| Circulatory failure | 50/161 | 38 (30.9%)/123 | 12 (31.6%)/38 | 1 |
| Kidney disease | 48/133 | 33 (32.7%)/101 | 15 (46.9%)/32 | 0.204\* |
| Respiratory disease | 40/197 | 34 (21.7%)/157 | 6 (15%)/40 | 0.509 |
| Diabetes | 40/197 | 32 (20.4%)/157 | 8 (20%)/40 | 1 |
| Gastritis/GERD | 29/138 | 21 (19.8%)/106 | 8 (25%)/32 | 0.621 |
| Other cancer types | 28/145 | 22 (19.5%)/113 | 6 (18.8%)/32 | 1 |
| Liver dysfunction | 21/197 | 16 (10.2%)/157 | 5 (12.5%)/40 | 0.774 |
| Cerebral circulation disorders | 18/197 | 13 (12.3%)/106 | 5 (16.1%)/31 | 0.556 |

\* missing data have been omitted

*Second-Line Treatment*

Within 12 months of diagnosis, 84 (42.6%) individuals received second-line treatment, of which 28 (33.3%) were due to disease resistance to first-line of treatment, and 56 (66.7%) were due to progression after the previous response (response to treatment lasted more than 60 days) (Table 6 and 9).

During the second line of treatment, three-drug and two-drug regimens were used (Table 9). Two-component schemes were chosen more often in the second line and were used in 54 patients (64.3%), with the remaining 30 (35.7%) receiving three-component schemes. Among those who received a three-component first-line treatment, 44 (66.75) received a two-component second-line treatment, and 22 (33.3%) received another three-component treatment. Ten (55.6%) of the patients who received a first-line two-drug treatment also received two-drug second-line treatment, while the other eight patients (44.4%) received a three-drug treatment (Table 9).

The reimbursement possibilities in Poland probably dictated the frequency of choosing a two-component treatment in the second line of treatment. Therefore, it is difficult to determine the dependence of such a choice. However, it should be noted that a three-drug regimen was used more often in patients after a previous two-drug regimen (44.4% vs. 33.3% for patients previously treated with a three-drug regimen).

**Table S11.** The second-line treatment used**.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **First-line treatment** | **Number of patients (n)** | **Number of patients (%)** | **Second-line treatment** | **Number of patients (n)** | **Number of patients (%)** |
| **First line of treatment** | 3-component scheme | 66 | 78.6% | 3-component scheme | 22 | 33.3% |
| 2-component scheme | 44 | 66.7% |
| 2-component scheme | 18 | 21.4% | 3-component scheme | 8 | 44.4% |
| 2-component scheme | 10 | 55.6% |

**Table S12.** Analysis of deaths.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cause of death** | **Cases (% of patients, N=197)** | **The treatment respectively: in the first line and in the second line** | | **ECOG** | | **ADL (according to Katz)** | | | **Number of comorbidities** | |
| **3- drug schema** | **2- drug schema** | **0–2** | **3–4** | **Fully independent** | **Moderate impairment** | **Completely dependent** | **Below 4 comorbidities** | **4 or more comorbidities** |
| Deaths in the first line of treatment | Disease progression | 6 (3.0) | 5 | 1 | 2 | 4 | 2 | 2 | 2 | 4 | 2 |
| Infection | 5 (2.5) | 4 | 1 | 5 | 0 | 5 | 0 | 0 | 2 | 3 |
| Other reason | 3 (1.5) | 3 | 0 | 3 | 0 | 3 | 0 | 0 | 1 | 2 |
| Deaths in the second line of treatment | Disease progression | 9 (4.6) | 4 | 5 | 8 | 1 | 8 | no data | no data | 6 | 3 |
| Infection | 2 (1.0) | 2 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
| Other reason | 0 (0.0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total number of deaths | Disease progression | 15 (7.6) | 9 | 6 | 10 | 5 | 13 | 0 | 0 | 10 | 5 |
| Infection | 7 (3.6) | 6 | 1 | 6 | 1 | 6 | 0 | 1 | 3 | 4 |
| Other reason | 3 (1.5) | 3 | 0 | 3 | 0 | 3 | 0 | 0 | 1 | 2 |
|  | **Total number of deaths**  **(% of deaths)** | **25**  **(100)** | **18**  **(72.0)** | **7**  **(18.0)** | **19 (76.0)** | **6 (24.0)** | **19 (76.0)** | **2**  **(8.0)** | **3**  **(12.0)** | **14**  **(56.0)** | **11**  **(44.0)** |