

**Table S1.** Comparison of patients' characteristics treated or not with lenalidomide before treatment with KRd in real life.

|                                      | Previous Exposure to Lenalidomide<br>(n = 53)<br>Group A | No Previous Exposure to Lenalidomide<br>(n = 77)<br>Group B | p-Value       |
|--------------------------------------|--|---|---------------|
| <b>Median age, years (range)</b>     | 65 (45–86)   | 64 (33–78)  | 0.92          |
| <b>Males, n (%)</b>                  | 30 (57%)   | 43 (56%)  | 0.98          |
| <b>Paraproteins (isotype), n (%)</b> |  |   |               |
| Immunoglobulin G                     | 33 (62%)   | 45 (59%)  | 0.92          |
| Immunoglobulin A                     | 11 (21%)   | 13 (17%)  | 0.88          |
| Immunoglobulin M                     | 1 (2%)   | 1 (1%)  | 0.96          |
| Light chain only                     | 8 (15%)  | 16 (21%)  | 0.75          |
| Not secretory                        | 0 (0%)   | 2 (2%)  | 0.65          |
| <b>FISH</b>                          |  |   |               |
| failed- or not evaluable             | 28 (53%)   | 38 (49%)  | 0.78          |
| Standard risk                        | 15 (28%)   | 30 (39%)  | <b>0.02</b>   |
| High-risk                            | 10 (19%)   | 9 (12%)   | <b>0.02</b>   |
| <b>ISS stage</b>                     |  |   |               |
| I                                    | 36 (68%)   | 45 (58%)  | <b>0.02</b>   |
| II                                   | 9 (17%)  | 16 (21%)  | <b>0.02</b>   |
| III                                  | 8 (15%)  | 16 (21%)  | <b>0.02</b>   |
| <b>Previous treatments</b>           |  |   |               |
| Single autologous SCT                | 15 (28%)   | 25 (32%)  | 0.87          |
| Double autologous SCT                | 17 (32%)   | 23 (30%)  | 0.92          |
| Median of prior treatments           | 2 (1–10)   | 1 (1–7)   | <b>0.0001</b> |

**Table S2.** Comparison of patients' characteristics treated or not with pomalidomide before treatment with KRd in real life.

|                                      | Previous Exposure to Pomalidomide<br>(n = 16) | No Previous Exposure to Pomalidomide<br>(n = 114) | p-Value     |
|--------------------------------------|---|---|-------------|
| <b>Median age, years (range)</b>     | 68 (52–77)                                    | 64 (33–86)  | <b>0.03</b> |
| <b>Males, n (%)</b>                  | 9 (56%)                                       | 64 (56%)  | 0.89        |
| <b>Paraproteins (isotype), n (%)</b> |   |   |             |
| Immunoglobulin G                     | 6 (38%)                                       | 69 (61%)  | <b>0.03</b> |
| Immunoglobulin A                     | 3 (19%)                                       | 23 (20%)  | 0.89        |
| Light chain only                     | 7 (43%)                                       | 22 (19%)  | <b>0.02</b> |
| <b>FISH</b>                          |   |   |             |
| failed-not evaluable                 | 13 (81%)                                      | 85 (75%)  | 0.89        |
| del13q                               | 0 (0%)  | 1 (0.9%)  | 0.91        |
| t4,14 or t 11,14                     | 1 (6%)  | 9 (8.1%)  | 0.88        |
| del17p                               | 2 (12%)                                       | 3 (26%)   | 0.72        |
| No alterations identified            | 0 (0%)  | 16 (14%)  | 0.03        |
| <b>ISS stage</b>                     |   |   |             |
| I                                    | 9 (56%)                                       | 72 (63%)  | 0.23        |
| II                                   | 4 (25%)                                       | 21 (18%)  | 0.22        |

|                            |          |          |               |
|----------------------------|----------|----------|---------------|
| III                        | 3 (19%)  | 21 (18%) | 0.89          |
| Previous treatment         |          |          |               |
| Single autologous SCT      | 6 (38%)  | 34 (30%) | <b>0.06</b>   |
| Double autologous SCT      | 2 (13%)  | 38 (33%) | <b>0.04</b>   |
| Median of prior treatments | 4 (1-10) | 2 (1-7)  | <b>0.0001</b> |

**Table S3** Univariate and multivariate analysis of PFS and OS in 21 patients who completed at least 18 cycles of KRd.

|                              |             | n  | Univariate Analysis |                   | Multivariate Analysis |              | Univariate Analysis |                   | Multivariate Analysis |         |
|------------------------------|-------------|----|---------------------|-------------------|-----------------------|--------------|---------------------|-------------------|-----------------------|---------|
|                              |             |    | PFS @ 24 moNths     | p-value           | HR (95% CI)           | p-Value      | OS @ 24 Months      | p-Value           | HR (95% CI)           | p-Value |
| Age                          | <=65        | 7  | 94.1                | 0.3               |                       |              | 93.7                | 0.19              |                       |         |
|                              | >65         | 14 | 57.6                |                   |                       |              | 77.9                |                   |                       |         |
| Gender                       | male        | 11 | 90.5                | 0.08              |                       |              | 90.5                | 0.45              |                       |         |
|                              | female      | 10 | 57.8                |                   |                       |              | 77.8                |                   |                       |         |
| ISS                          | I-II        | 14 | 8.5                 | 0.33              |                       |              | 91.3                | 0.15              |                       |         |
|                              | III         | 7  | 71.4                |                   |                       |              | 71.4                |                   |                       |         |
| Prior lines                  | 1, 2        | 14 | 84.1                | 0.052             |                       |              | 95.5                | <b>0.004</b>      |                       |         |
|                              | more than 2 | 7  | 57.1                |                   |                       |              | 57.1                |                   |                       |         |
| Previous lenalidomide        | no          | 4  | 98.0                | 0.09              |                       |              | 98.0                | 0.21              |                       |         |
|                              | yes         | 17 | 69.4                |                   |                       |              | 81.7                |                   |                       |         |
| Previous pomalidomide        | no          | 20 | 78                  | 0.62              |                       |              | 86.2                | 0.70              |                       |         |
|                              | yes         | 1  | 100                 |                   |                       |              | 100                 |                   |                       |         |
| Previous BMT                 | no          | 6  | 44.4                | <b>0.01</b>       |                       |              | 77.8                | 0.33              |                       |         |
|                              | yes         | 15 | 90.7                |                   |                       |              | 90.4                |                   |                       |         |
| Zoledronic acid exposure     | no          | 5  | 75.0                | 0.48              |                       |              | 87.5                | 0.98              |                       |         |
|                              | yes         | 16 | 81.0                |                   |                       |              | 86.1                |                   |                       |         |
| Relapse                      | biochemical | 6  | 83.3                | 0.96              |                       |              | 83.3                | 0.64              |                       |         |
|                              | clinical    | 15 | 78.0                |                   |                       |              | 87.7                |                   |                       |         |
| ClCr                         | <30 ml/min  | 6  | 33.3                | <b>&lt;0.0001</b> | 22 (2.5-202.3)        | <b>0.006</b> | 33.3                | <b>&lt;0.0001</b> | na                    |         |
|                              | >30ml/min   | 15 | 90.4                |                   |                       |              | 98.2                |                   |                       |         |
| K Cumulative dose (2 cycles) | <310mg/m q  | 7  | 78.6                | 0.65              |                       |              | 85.4                | 0.83              |                       |         |
|                              | >310mg/m q  | 14 | 88.9                |                   |                       |              | 87.5                |                   |                       |         |
| Best response                | <VGPR       | 8  | 76.2                | 0.92              |                       |              | 85.7                | 0.94              |                       |         |
|                              | CR+VGPR     | 13 | 80.0                |                   |                       |              | 86.7                |                   |                       |         |