Supplementary Table S1. Summary of the multivariable Cox regression models based on dataset GSE4581 [Zhan et al, Blood 2006] for the effect of DSG2 expression on overall survival

| Cox Model          | Model Covariates                  | Hazard Ratio | 95% Confidence Interval | p value |
|--------------------|-----------------------------------|--------------|-------------------------|---------|
| Model 1 (all patients) | • DSG2 expression level          | 2.69         | 1.73 – 4.18             | < 0.001 |
| Model 2 (all patients)  | • DSG2 expression level          | 3.03         | 1.75 – 5.25             | < 0.001 |
|                     | • Genetic subgroup                |              |                         |         |
| Model 3 (non-MS cohort) | • DSG2 expression level          | 3.68         | 2.18 – 6.22             | < 0.001 |
|                     | • MS cohort                       |              |                         |         |
| Model 4 (all patients)   | • DSG2 expression level          | 4.30         | 2.47 – 7.48             | < 0.001 |
|                     | • MS cohort                       |              |                         |         |
|                     | • Therapy                         |              |                         |         |
**Supplementary Table S2.** The effect DSG2 expression on patient overall survival in each genetic subgroup using dataset GSE4581 and univariable Cox regression modelling

| Genetic Grouping | Prognostic Significance | DSG2 (high/low) | Hazard Ratio | 95% Confidence Interval | p value | Adjusted Confidence Interval (99%) | Adjusted p value |
|------------------|-------------------------|-----------------|--------------|-------------------------|---------|-----------------------------------|-----------------|
| CD-1 (n=28)      | Low-risk                | 5 / 23          | 6.60         | 0.91 – 47.56            | 0.06    | 0.49 – 88.46                      | 0.37            |
| CD-2 (n=59)      | Low-risk                | 12 / 48         | 0.62         | 0.07 – 5.18             | 0.66    | 0.04 – 10.07                      | 4.00            |
| HY (n=116)       | Low-risk                | 12 / 104        | 3.21         | 1.04 – 9.92             | 0.04    | 0.73 – 14.14                      | 0.26            |
| LB (n=58)        | Low-risk                | 4 / 54          | 9.08         | 1.65 – 50.13            | 0.01    | 0.96 – 85.75                      | 0.07            |
| MF (n=37)        | High-risk               | 9 / 28          | 8.76         | 1.70 – 45.20            | 0.01    | 1.01 – 75.70                      | 0.06            |
| MS (n=68)        | Indeterminate           | 66 / 2          | Indeterminate| Indeterminate            | Indeterminate| Indeterminate                     |                 |
| PR (n=47)        | High-risk               | 17 / 30         | 2.00         | 0.79 – 5.11             | 0.15    | 0.59 – 6.85                       | 0.87            |
Supplementary Table S3. Multivariable Cox regression model of the coMMpass study data for progression-free survival by DSG2 expression level and frontline therapy

| Therapy  | Median PFS (months) | Multivariable Cox Regression (DSG2-high vs DSG2-low) |
|----------|---------------------|------------------------------------------------------|
|          | DSG2-low | DSG2-high |                                                     |
| Bortezomib | 22       | 15        | HR 1.49, CI 1.10 – 2.03, P = 0.01                     |
| Carfilzomib | NR       | 26        | HR 2.41, CI 0.64 – 9.10, P = 0.19                     |
| Lenalidomide | 21       | 22        | HR 1.20, CI 0.67 – 2.13, P = 0.55                     |

Supplementary Table S4. Multivariable Cox regression model of the coMMpass study data for overall survival by DSG2 expression level and frontline therapy

| Therapy  | Median OS (months) | Multivariable Cox Regression (DSG2-high vs DSG2-low) |
|----------|-------------------|------------------------------------------------------|
|          | DSG2-low | DSG2-high |                                                     |
| Bortezomib | 58       | 36        | HR 1.86, CI 1.27 – 2.71, P < 0.01                    |
| Carfilzomib | NR       | NR        | HR 1.17, CI 0.20 – 7.04, P = 0.86                    |
| Lenalidomide | 60       | 61        | HR 1.00, CI 0.41 – 2.38, P = 0.99                    |
**Supplementary Table S5.** Correlation of DSG2 expression on patient MM PC against routinely measured blood parameters.

| Biomarker                                      | Linear Regression (p value) | Pearson Correlation (r value, p value) |
|------------------------------------------------|-----------------------------|----------------------------------------|
| Paraprotein                                    | 0.151                       | - 0.091, 0.543                         |
| κ light chain                                  | 0.549                       | - 0.090, 0.549                         |
| λ light chain                                  | 0.488                       | 0.104, 0.488                           |
| κ:λ ratio                                      | 0.655                       | -0.067, 0.655                          |
| Haemoglobin                                    | 0.131                       | - 0.224, 0.131                         |
| White cell count                               | 0.518                       | 0.097, 0.518                           |
| Platelet count                                 | 0.700                       | 0.058, 0.700                           |
| β₂-microglobulin                               | 0.425                       | -0.027, 0.860                          |
| Urea                                           | 0.738                       | 0.051, 0.738                           |
| Creatinine                                     | 0.558                       | 0.088, 0.558                           |
| Calcium                                        | 0.929                       | -0.013, 0.929                          |
| Albumin                                        | 0.143                       | -0.217, 0.143                          |
| Lactate dehydrogenase                          | 0.168                       | -0.135, 0.365                          |
| Plasma cell percentage (marrow aspirate)       | 0.154                       | -0.055, 0.716                          |
| Plasma cell percentage (CD138⁺ IHC of trephine)| 0.442                       | -0.145, 0.331                          |