| Characteristic          | N (%) |
|------------------------|-------|
| Overall                | 59 (100) |
| Age (years)            |       |
| <70                    | 39 (66) |
| ≥70                    | 20 (34) |
| Sex                    |       |
| Male                   | 33 (56) |
| Female                 | 26 (44) |
| Mutation status        |       |
| BRAF                   | 18 (31) |
| NRAS                   | 8 (14)  |
| CKIT                   | 1 (2)   |
| None                   | 32 (54) |
| Stage at diagnosis     |       |
| I                      | 10 (17) |
| II                     | 11 (19) |
| III                    | 22 (37) |
| IV                     | 12 (20) |
| Not available          | 4 (7)   |
| Treatment              |       |
| Pembrolizumab          | 23 (39) |
| Nivolumab              | 11 (19) |
| Ipilimumab plus nivolumab | 25 (42) |
| Best overall response  |       |
| Complete response      | 10 (17) |
| Partial response       | 16 (27) |
| Stable disease         | 17 (29) |
| Progressive disease    | 16 (27) |
| Durable clinical benefit |     |
| Yes                    | 36 (61) |
| No                     | 23 (39) |

Supplementary Table 1. Patient characteristics.
| Variable                          | Coefficient  |
|----------------------------------|--------------|
| CCNO                             | 0.0181943    |
| ID4                              | -0.030076    |
| IER3                             | -0.006943    |
| MSH2 in s100/HMB45               | 0.0547323    |
| MGMT                             | 0.0386636    |
| NRDE2                            | -0.06098     |
| TNFAIP6                          | -0.009739    |
| IL2RB                            | 0.0320801    |

**Supplementary Table 2. Variables and corresponding coefficients that comprise the YMMM.**
| #  | Target                      | CAB |
|----|-----------------------------|-----|
| 1  | Beta-Catenin                | 963 |
| 2  | PMS2                        | 934 |
| 3  | CD8                         | 1022|
| 4  | B7-H3                       | 959 |
| 5  | CD4                         | 941 |
| 6  | Phospho-p70S6K              | 336 |
| 7  | Mouse IgG1                  | 891 |
| 8  | CD68                        | 1023|
| 9  | Phospho-RPS6                | 767 |
| 10 | Rabbit IgG                  | 836 |
| 11 | MLH1                        | 937 |
| 12 | CD34                        | 1041|
| 13 | MSH2                        | 919 |
| 14 | S6                          | 837 |
| 15 | GZMB                        | 1068|
| 16 | Ki-67                       | 314 |
| 17 | Beta-2-microglobulin        | 964 |
| 18 | Histone H3                  | 387 |
| 19 | Akt                         | 962 |
| 20 | CD3                         | 1019|
| 21 | MSH6                        | 920 |
| 22 | VISTA                       | 940 |
| 23 | PD1                         | 1024|
| 24 | Phospho-STAT3               | 458 |
| 25 | STAT3                       | 957 |
| 26 | CD56                        | 1020|
| 27 | PD-L1                       | 1039|
| 28 | CD45                        | 1018|
| 29 | Tim3                        | 1038|
| 30 | HLA-DR                      | 1052|
| 31 | CD20                        | 706 |
| 32 | Pan-Cytokeratin             | 886 |
| 33 | CD45RO                      | 77  |
| 34 | Bcl-2                       | 960 |
| 35 | B7-H4                       | 1053|
| 36 | Ik-Ba                       | 907 |
| 37 | BIM                         | 894 |
| 38 | IDO1                        | 1033|
| 39 | CD11c                       | 1036|
| 40 | Mouse IgG2a                 | 1258|
| 41 | BCL6                        | 880 |
| 42 | c-Myc                       | 878 |
| 43 | Phospho-STAT5               | 882 |
| 44 | CD163                       | 1031|

**Supplementary Table 3. DSP antibody panel.** CAB is custom antibody ID, which uniquely identifies this reagent.
Supplementary Figure 1. Identification of the optimal number of predictors for final model inclusion.

a-d. Sensitivity (a), specificity (b), positive predictive value (c) and negative predictive value (d) and 95% confidence intervals based on the number of predictors included in the model; all curves peak when 8 predictors are included in the model.
Supplementary Figure 2. Representative image of DSP compartment selection. a-b, Tumor compartment (green) is defined by s100/HMB45 positivity, while stromal compartment (purple) is defined by s100/HMB45 negativity. c-d, Stroma is further divided to macrophage compartment that is CD68-positive (cyan) and leukocyte compartment that is CD45+ (magenta).