

| Surface Marker | Clone | Fluorochrome | Company | Cat-Nr. | Panel |
|---------------------|--------|-----------------|-----------|-------------|---------|
| CD3 | UCHT1 | FITC | BioLegend | 300440 | 1, 2, 4 |
| CD4 | RPAT4 | APC Fire 750 | BioLegend | 300560 | 1 |
| CD25 | M-A251 | BV785 | BioLegend | 356140 | 1 |
| CD127 | A019D5 | APC | BioLegend | 351316 | 1 |
| CXCR5 | J25204 | PE/Dazzle 594 | BioLegend | 356928 | 1 |
| CD45RA | H100 | BV605 | BioLegend | 304134 | 1,2 |
| CCR7 | G043H7 | PerCP/Cy5.5 | BioLegend | 353220 | 1,2 |
| CCR6 | 11A9 | PE | BD | 559562 | 1 |
| CXCR3 | G025H7 | BV650 | BioLegend | 353730 | 1 |
| CCR4 | L2A1H4 | BV421 | BioLegend | 359414 | 1 |
| CD8 | SK1 | APC Fire 750 | BioLegend | 344746 | 2 |
| CD161 | HP3G10 | PE | BioLegend | 339904 | 2 |
| V87.2 | 3C10 | BV785 | BioLegend | 351722 | 2 |
| TCR γ/δ | 11F2 | APC | Miltenyi | 130-113-500 | 2 |
| V82 | B6 | BV421 | BioLegend | 331428 | 2 |
| CD19 | H1B19 | FITC | BioLegend | 302206 | 3, 4 |
| IgD | 1A6-2 | PE/Dazzle 594 | BioLegend | 348240 | 3 |
| CD45 | H130 | Alexa Fluor 700 | BioLegend | 304024 | 3, 4 |
| CD27 | 323 | BV421 | BioLegend | 302824 | 3 |
| CD38 | HIT2 | APC | BioLegend | 303510 | 3 |
| CD34 | 563 | PE | BD | 550761 | 3 |
| CD11c | B-LY6 | APC | BD | 559877 | 4 |
| CD14 | HCD14 | PE/Dazzle 594 | BioLegend | 325634 | 4 |
| CD16 | 3G8 | APC Fire 750 | BioLegend | 302060 | 4 |
| CD56 | HCD56 | PerCP/Cy5.5 | BioLegend | 318322 | 4 |
| CD11b | ICRF44 | PE | BioLegend | 301306 | 4 |
| CD123 | 6H6 | BV605 | BioLegend | 306026 | 4 |
| HLA-DR | L243 | BV785 | BioLegend | 307642 | 4 |

Supplementary Table S1: List of antibodies used for in-depth immunophenotyping.

| Panel 1 - CD4 T cells | | | |
|-------------------------------------|--------------------------------------|---|---|
| Cell type | Gating strategy | | |
| CD4+ T cells | CD3 ⁺ CD4 ⁺ | CXCR5 ⁺ | |
| T follicular helper (Tfh) | | CXCR5 ⁻ CD25 ^{high} CD127 ^{low} | |
| T regulatory cells (Tregs) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁺ CCR6 ⁻ | |
| T helper 1 (Th1) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁺ CCR6 ⁺ | |
| T helper 1/T helper 17 (Th1/Th17) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁻ CCR6 ⁻ CCR4 ⁺ | |
| T helper 17 (Th17) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁻ CCR6 ⁻ CCR4 ⁻ | |
| T helper 2 (Th2) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁻ CCR6 ⁻ CCR4 ⁻ | |
| T CD4 terminal effector (T CD4 TE) | | CCR7 ⁻ CD45RA ^{low} | |
| T CD4 Naïve | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁻ CCR6 ⁻ CCR4 ⁻ CCR7 ⁺ CD45RA ^{high} | |
| Panel 2 - CD8, γ/δ and MAIT T cells | | | |
| Cell type | Gating strategy | | |
| CD8+ T cells | CD3 ⁺ | TCR γ/δ ⁻ | CD16 ^{high} NOT Vα7.2 ⁺ |
| γ/δ Vd2 ⁺ (T gd Vd2+) | | TCR γ/δ ⁺ | Vd2 ⁺ |
| γ/δ Vd2 ⁻ (T gd non-Vd2) | | | Vd2 ⁻ |
| MAIT | | TCR γ/δ ⁻ Vd2 ⁻ | Vα7.2 ⁺ CD161 ^{high} |
| T CD8 Naïve | | CD8 ⁺ TCR γ/δ ⁻ Vd2 ⁻ | CCR7 ⁺ CD45RA ⁺ |
| T CD8 central memory (CM) | | | CCR7 ⁺ CD45RA ⁻ |
| T CD8 effector memory (EM) | | | CCR7 ⁻ CD45RA ⁻ |
| T CD8 terminal effector (TE) | | | CCR7 ⁻ CD45RA ⁺ |
| PANEL 3 - B cells and Progenitors | | | |
| Cell type | Gating strategy | | |
| Progenitors | CD45 ⁺ | CD34 ⁺ CD45 ^{low} | |
| Total B cells (B cells) | | CD19 ⁺ CD34 ⁻ | CD27 ⁻ IgD ⁺ |
| Naïve B cells (B naïve) | | | CD27 ⁺ IgD ⁺ |
| Nonswitched memory B cells (B NSM) | | | |
| Exhausted B cells (B EX) | | | CD27 ⁻ IgD ⁻ |

| Switched memory B cells (B SM) | | | CD27 ⁺ IgD ⁻ CD38 ^{low} |
|--|--|-------------------------------------|--|
| Plasmablasts | | | CD27 ⁺ IgD ⁻ CD38 ^{high} |
| Panel 4 - Monocytes, DCs, NK cells, Low-density basophils | | | |
| Cell type | Gating strategy | | |
| NK cells | CD45 ⁺ CD3 ⁻ CD19 ⁻ | | CD16 ^{+/-} CD56 ^{+/low} CD14 ⁻ CD11c ⁻ |
| Classic monocytes (C) | | | CD14 ⁺ CD16 ⁻ |
| Intermediate monocytes (I) | | CD11c ⁺ | CD14 ⁺ CD16 ⁺ |
| Nonclassic monocytes (NC) | | | CD14 ^{low} CD16 ⁺ |
| Myeloid dendritic cells (mDCs) | | CD16 ⁻ CD56 ⁻ | HLA-DR ⁺ CD11c ⁺ CD123 ^{low} |
| Plasmacytoid dendritic cells (pDCs) | | | HLA-DR ⁺ CD11c ⁻ CD123 ⁺ |
| Low-density basophils (LD) | | | HLA-DR ⁻ CD123 ⁺ CD11b ⁺ |

Supplementary Table S2: Gating strategies for in-depth immuno-phenotyping of immune cell subsets.

| Characteristics | PA+BA+placebo (n=24) | 2FL+placebo (n=24) | 2FL+PA+BA (n=24) |
|----------------------------|-------------------------|-----------------------|---------------------|
| Female sex | 13 (54.2%) | 9 (37.5%) | 13 (54.2%) |
| Age, years | 62(±9) | 67 (±12) | 65 (±8) |
| Duration of disease, years | 7 (±7) | 6 (±6) | 4 (±4) |
| BMI | 26 (±4) | 26 (±3) | 25 (±3) |
| Subgroups | | | |
| akinetetic-rigid | 8 (33.3%) | 9 (37.5%) | 11 (45.8%) |
| equivalent | 14 (58.3%) | 12 (50%) | 12 (50%) |
| tremordominant | 2 (8.3 %) | 3 (12.5%) | 1 (4.17%) |
| Medication | | | |
| LEDD [mg] | 770 (±302) | 785 (±267) | 756 (±261) |
| 95% CI | 642.1-897.1 | 672.2-897.3 | 646-866.5 |
| Benserazide | 24 (100%) | 22 (91.7%) | 23 (95.8%) |
| Carbidopa | 4 (16.7%) | 5 (20.8%) | 2 (8.3%) |
| Piribedil | 2 (8.3%) | 0 | 2 (8.3%) |
| Rotigotine | 2 (8.3%) | 3 (12.5%) | 3 (12.5%) |
| Ropinirole | 2 (8.3%) | 1 (4.17%) | 2 (8.3%) |
| Pramipexole | 4 (16.7%) | 2 (8.3%) | 4 (16.7%) |
| Rasagiline | 13 (54.2%) | 8 (33.3%) | 14 (58.3%) |
| Selegiline | 3 (12.5%) | 9 (37.5%) | 3 (12.5%) |
| Safinamide | 2 (8.3%) | 1 (4.2%) | 2 (8.3%) |
| COMT-inhibitor | 6 (25%) | 8 (33.3%) | 9 (37.5%) |
| Amantadine | 2 (8.3 %) | 2 (8.3 %) | 1 (4.2%) |
| Apomorphine | 0 | 0 | 0 |
| Anticholinergics | 0 | 1 (4.2%) | 0 |
| Clozapine | 1 (4.2%) | 0 | 2 (8.3%) |
| Quetiapine | 1 (4.2%) | 3 (12.5%) | 1 (4.2%) |
| PD Clinical Scores | | | |
| MDS-UPDRS I | 10 (±10) | 17 (±12) | 17 (±13) |
| 95% CI | 12.6-21 | 12.1-22.5 | 11.2-22.1 |
| MDS-UPDRS II | 9 (±6) | 9 (±8) | 10 (±9) |

| | | | |
|--------------------|-----------------|-----------------|-----------------|
| 95% CI | 6.8-12.1 | 6.3-12.7 | 6-13.4 |
| MDS-UPDRS III | 29 (± 17) | 33 (± 16) | 30 (± 16) |
| 95% CI | 22.1-36.3 | 26.3-40 | 23-36.8 |
| MDS-UPDRS IV | 3 (± 3) | 5 (± 5) | 3 (± 3) |
| 95% CI | 1.8-4.2 | 2.5-6.3 | 1.4-4.1 |
| Hoehn & Yahr scale | 2 (± 1) | 2 (± 1) | 2 (± 1) |
| 95% CI | 1.9-2.5 | 1.9-2.4 | 1.9-2.7 |
| PANDA | 25 (± 4) | 33 (± 16) | 30 (± 16) |
| 95% CI | 23.7-26.7 | 18.9-24.8 | 20.8-26.1 |
| Olfactory score | 8 (± 3) | 7 (± 3) | 7 (± 3) |
| 95% CI | 6.8-9 | 5.9-8.1 | 5.6-8.1 |

Supplementary Table 3. Demographic data and characteristics of patients prior to therapeutic intervention. Main demographics and clinical and treatment characteristics of participants at study entry. Data are presented as the mean \pm SD or n (%).