

**Supplementary Table S1.** Comparisons between clinical variables and achievement of partial or complete response with interleukin-1 targeting agents.

| Clinical and laboratory features             |                        | CR (n=25)        | PR (n=10)         | p-value |
|----------------------------------------------|------------------------|------------------|-------------------|---------|
| Thoracic pain, n (%)                         | No                     | 22 (88.0)        | 8 (80.0)          | 0.610   |
|                                              | Yes                    | 3 (12.0)         | 2 (20.0)          |         |
| Urticarial skin rash, n (%)                  | No                     | 2 (8.0)          | 1 (10.0)          | 1.00    |
|                                              | Yes                    | 23 (92.0)        | 9 (90.0)          |         |
| Other types of skin rash, n (%)              | No                     | 20 (80.0)        | 6 (60.0)          | 0.477   |
|                                              | Erysipelas-like, n (%) | 23 (92.0)        | 8 (80.0)          |         |
|                                              | No                     | 1 (4.0)          | 1 (10.0)          | 0.295   |
|                                              | Yes                    | 1 (4.0)          | 1 (10.0)          |         |
| Erythematous, n (%)                          | No                     | 22 (88.0)        | 7 (70.0)          | 0.295   |
|                                              | Yes                    | 2 (8.0)          | 2 (20.0)          |         |
|                                              | NK                     | 1 (4.0)          | 1 (10.0)          | 1.000   |
|                                              | No                     | 23 (92.0)        | 9 (90.0)          |         |
| Maculopapular, n (%)                         | Yes                    | 1 (4.0)          | 0 (0.0)           | 1.000   |
|                                              | NK                     | 1 (4.0)          | 1 (10.0)          |         |
| Pustular lesions, n (%)                      | No                     | 24 (96.0)        | 9 (90.0)          | NA      |
|                                              | NK                     | 1 (4.0)          | 1 (10.0)          |         |
| Angioedema, n (%)                            | No                     | 10 (40.0)        | 3 (30.0)          | 0.538   |
|                                              | Yes                    | 2 (8.0)          | 2 (20.0)          |         |
|                                              | NK                     | 13 (52.0)        | 5 (50.0)          | 0.372   |
|                                              | No                     | 17 (68.0)        | 7 (70.0)          |         |
| Lymphadenopathy, n (%)                       | Yes                    | 3 (12.0)         | 3 (30.0)          | 1.000   |
|                                              | NK                     | 5 (20.0)         | 0 (0.0)           |         |
| Splenomegaly, n (%)                          | No                     | 11 (44.0)        | 4 (40.0)          | 1.000   |
|                                              | Yes                    | 2 (8.0)          | 1 (10.0)          |         |
|                                              | NK                     | 12 (48.0)        | 5 (50.0)          | 0.515   |
|                                              | No                     | 11 (44.0)        | 4 (40.0)          |         |
| Hepatomegaly, n (%)                          | Yes                    | 1 (4.0)          | 1 (10.0)          | 0.190   |
|                                              | NK                     | 13 (52.0)        | 5 (50.0)          |         |
| Pericarditis, n (%)                          | No                     | 24 (96.0)        | 8 (80.0)          | 0.496   |
|                                              | Yes                    | 1 (4.0)          | 2 (20.0)          |         |
| Pleuritis, n (%)                             | No                     | 24 (96.0)        | 9 (90.0)          | 0.766   |
|                                              | Yes                    | 1 (4.0)          | 1 (10.0)          |         |
| Abdominal pain, n (%)                        | No                     | 22 (88.0)        | 8 (80.0)          | 1.000   |
|                                              | Yes                    | 1 (4.0)          | 1 (10.0)          |         |
| Myalgia, n (%)                               | No                     | 8 (32.0)         | 3 (30.0)          | 1.000   |
|                                              | Yes                    | 17 (68.0)        | 7 (70.0)          |         |
| Arthralgia, n (%)                            | No                     | 3 (12.0)         | 1 (10.0)          | 1.000   |
|                                              | Yes                    | 22 (88.0)        | 9 (90.0)          |         |
| Arthritis, n (%)                             | No                     | 22 (88.0)        | 9 (90.0)          | 1.000   |
|                                              | Yes                    | 3 (12.0)         | 1 (10.0)          |         |
| Bone pain, n (%)                             | No                     | 5 (20.0)         | 0 (0.0)           | 0.245   |
|                                              | Yes                    | 7 (28.0)         | 5 (50.0)          |         |
|                                              | NK                     | 13 (52.0)        | 5 (50.0)          | NA      |
|                                              | No                     | 7 (28.0)         | 2 (20.0)          |         |
| Keratopathy, n (%)                           | NK                     | 18 (72.0)        | 8 (80.0)          | 0.496   |
|                                              | No                     | 24 (96.0)        | 9 (90.0)          |         |
| Conjunctivitis, n (%)                        | Yes                    | 1 (4.0)          | 1 (10.0)          | 1.000   |
|                                              | No                     | 21 (84.0)        | 9 (90.0)          |         |
| Aseptic osteomyelitis, n (%)                 | Yes                    | 4 (16.0)         | 1 (10.0)          | 1.000   |
|                                              | No                     | 6 (24.0)         | 2 (20.0)          |         |
| Peripheral nervous system involvement, n (%) | yes                    | 1 (4.0)          | 0 (0.0)           | 1.000   |
|                                              | NK                     | 18 (72.0)        | 8 (80.0)          |         |
| csDMARD concomitant, n (%)                   | No                     | 20 (80.0)        | 8 (80.0)          | 1.000   |
|                                              | Yes                    | 5 (20.0)         | 2 (20.0)          |         |
| Colchicine concomitant, n (%)                | No                     | 22 (88.0)        | 9 (90.0)          | 1.000   |
|                                              | Yes                    | 3 (12.0)         | 1 (10.0)          |         |
| Methotrexate concomitant, n (%)              | No                     | 23 (92.0)        | 9 (90.0)          | 1.000   |
|                                              | Yes                    | 2 (8.0)          | 1 (10.0)          |         |
| Disease duration, mean (SD)                  | -                      | 71.59 (73.45)    | 79.11 (60.28)     | 0.788   |
| ESR, mm/1h (mean (SD))                       | -                      | 27.28 (15.20)    | 30.10 (27.89)     | 0.751   |
| Max ESR, mm/1h (mean (SD))                   | -                      | 45.00 (31.35)    | 38.33 (31.95)     | 0.655   |
| CRP, mg/dl (mean (SD))                       | -                      | 8.12 (25.60)     | 14.64 (28.80)     | 0.594   |
| Max CRP, mg/dl (mean (SD))                   | -                      | 15.74 (35.70)    | 19.12 (34.83)     | 0.838   |
| IgG M-protein, mg/dl (mean (SD))             | -                      | 616.37 (559.91)  | 2101.88 (2265.39) | 0.069   |
| Max IgG M-protein, mg/dl (mean (SD))         | -                      | 789.56 (600.42)  | 6750.00 (8838.83) | 0.032   |
| IgM M-protein, mg/dl (mean (SD))             | -                      | 924.15 (565.51)  | 459.00 (647.71)   | 0.328   |
| Max IgM M-protein, mg/dl (mean (SD))         | -                      | 1173.11 (646.36) | 459.00 (647.71)   | 0.191   |

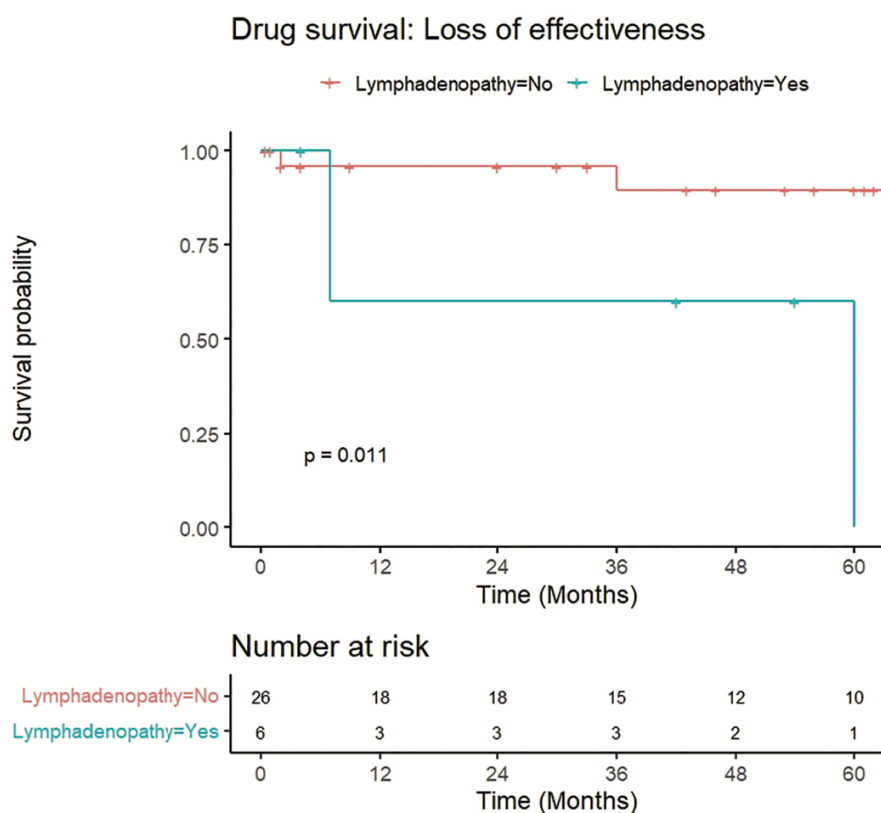
Note: 35 treatment courses were analysed.

csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; CR: complete response; CRP: C-reactive Protein; ESR: erythrocyte sedimentation rate; IgG, immunoglobulin G; IgM: immunoglobulin M; M-protein: myeloma protein; NA: not applicable; NK: not known; PR: partial response; SD: standard deviation.

**Supplementary Table S2.** Univariate Cox regression analyses to assess potential variables associated with drug survival for any treatment discontinuation events.

| Item                        | N° patients | HR   | 95% CI      | p-value |
|-----------------------------|-------------|------|-------------|---------|
| Thoracic pain               | 37          | 1.67 | 0.35, 8.06  | 0.52    |
| Urticarial skin rash        | 37          | 0.35 | 0.07, 1.67  | 0.19    |
| Erysipelas-like             | 35          | 2.22 | 0.28, 17.9  | 0.45    |
| Erythematous                | 35          | 1.58 | 0.32, 7.76  | 0.57    |
| Angioedema                  | 18          | 2.24 | 0.31, 16.2  | 0.42    |
| Lymphadenopathy             | 32          | 3.31 | 0.76, 14.4  | 0.11    |
| Splenomegaly                | 20          | 2.72 | 0.45, 16.3  | 0.27    |
| Hepatomegaly                | 18          | 2.82 | 0.29, 27.4  | 0.37    |
| Pericarditis                | 37          | 1.95 | 0.24, 15.9  | 0.53    |
| Pleuritis                   | 37          | 2.33 | 0.29, 18.7  | 0.43    |
| Myalgia                     | 18          | 1.21 | 0.25, 5.90  | 0.81    |
| Arthritis                   | 37          | 0.94 | 0.12, 7.54  | 0.95    |
| Conjunctivitis              | 37          | 2.87 | 0.34, 23.9  | 0.33    |
| Aseptic osteomyelitis       | 37          | 1.06 | 0.13, 8.59  | 0.95    |
| Concomitant cs DMARDs       | 37          | 3.74 | 0.95, 14.6  | 0.058   |
| Concomitant colchicine      | 37          | 3.93 | 0.96, 16.0  | 0.057   |
| Concomitant methotrexate    | 37          | 3.67 | 0.71, 19.0  | 0.12    |
| Disease duration, mean (SD) | 37          | 1.00 | 0.98, 1.01  | 0.50    |
| ESR mm/1h, mean (SD)        | 25          | 0.99 | 0.89, 1.09  | 0.79    |
| Max ESR, mm/1h (mean (SD))  | 25          | 0.96 | 0.89, 1.05  | 0.38    |
| CRP mg/dl, (mean (SD))      | 28          | 1.02 | 1.00, 1.05  | 0.075   |
| Max CRP, mg/dl (mean (SD))  | 28          | 1.01 | 0.99, 1.04  | 0.25    |
| IgG (mean (SD)), mg/dl      | 11          | 0.45 | 0.00, 2,183 | 0.85    |
| Max IgG, mg/dl (mean (SD))  | 11          | 0.69 | 0.20, 2.34  | 0.55    |

CRP: C-reactive Protein; CI: confidence interval; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HR: hazard ratio; IgG: immunoglobulin G; SD: standard deviation.

**Supplementary Fig. S1.** Lymphadenopathy as potential predictor of loss of effectiveness. Kaplan-Meier survival curves showing anakinra and canakinumab combined survival owing to loss of effectiveness as discontinuation event in patients with or without lymphadenopathy.