**Table S1. Comparison of the comorbidities between the advanced and non-advanced groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristics | Total | Advanced | Non-advanced | *P*-value\* |
| Patient number | 138 | 37 | 101 |  |
| Diabetes mellitus | 39 (28.3) | 13 (35.1) | 26 (25.7) | 0.278 |
| Hypertension | 37 (26.8) | 10 (27.0) | 27 (26.7) | 0.972 |
| Hyperlipidemia | 29 (21.0) | 7 (18.9) | 22 (21.8) | 0.715 |
| Gastroesophageal reflux disease | 15 (1.09) | 1 (2.7) | 14 (13.9) | 0.070 |
| Ischemic heart disease | 15 (10.9) | 5 (13.5) | 10 (9.9) | 0.546 |
| Non-tuberculosis mycobacterium | 9 (6.5) | 3 (8.1) | 6 (5.9) | 0.701 |
| Chronic liver disease | 7 (5.1) | 3 (8.1) | 4 (4.0) | 0.385 |
| Arrhythmia | 4 (2.9) | 1 (2.7) | 3 (3.0) | 1.000 |

Data are presented as number (%), unless indicated otherwise.

\*Pearson’s Chi-squared test or Fisher’s exact.

**Table S2 Comparison of the baseline characteristics between patients included and excluded in the efficacy analysis.**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Patients included | Patients excluded | *P*-value† |
| Patient number | 81 | 57 |  |
| Advanced group | 17 (21.0) | 20 (35.1) | 0.066 |
| Age, years | 67.3 ± 6.8 | 69.0 ± 8.1 | 0.194 |
| Male | 65 (80.2) | 48 (84.2) | 0.552 |
| Body mass index, kg/m2 | 24.3 ± 3.0 | 23.2 ± 3.3 | 0.057 |
| Smoking |  |  | 0.183 |
| Never | 2 (2.5) | 3 (5.3) |  |
| Former | 51 (63.0) | 42 (73.7) |  |
| Current | 28 (34.6) | 12 (21.1) |  |
| Amount, pack years | 22.2 ± 21.0 | 24.1 ± 23.2 | 0.587 |
| Surgical lung biopsy | 38 (46.9) | 18 (31.6) | 0.071 |
| Previous treatment\* |  |  |  |
| Corticosteroid | 118 (22.2) | 9 (15.8) | 0.348 |
| Immunosuppressant | 7 (8.6) | 1 (1.8) | 0.140 |
| N-acetylcysteine | 33 (40.7) | 15 (26.3) | 0.080 |
| None | 33 (40.7) | 38 (66.7) | 0.003 |
| Home oxygen therapy | 17 (21.0) | 12 (21.1) | 0.993 |
| Pulmonary hypertension¶, | 9 (11.1) | 6 (10.5) | 0.913 |
| Pulmonary function test |  |  |  |
| FVC, % predicted | 61.2 ± 13.7 | 56.8 ± 16.0 | 0.089 |
| DLco, % predicted | 44.9 ± 12.0 | 45.8 ± 17.4 | 0.742 |
| TLC, % predicted | 60.9 ± 10.8 | 59.7 ± 11.0 | 0.535 |
| 6MWT |  |  |  |
| Distance, m | 396.0 ± 96.4 | 377.4 ± 125.1 | 0.333 |
| Lowest SaO2, % | 87.1 ± 4.6 | 89.1 ± 5.4 | 0.230 |

Data are presented as mean ± standard deviation or number (%), unless indicated otherwise.

FVC, forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; TLC, total lung capacity; 6MWT, 6-minute walk test; SaO2, saturation of oxygen.

\*Treatment received within the last 3 months prior to commencement of pirfenidone.

¶Pulmonary hypertension was defined as estimated systolic pulmonary artery pressure over 40 mmHg measured by echocardiography.

†Pearson’s Chi-squared test or Fisher’s exact test (categorical variables), Student t test or Mann-Whitney U test (continuous variables).

**Table S3. Odds ratios for the development of adverse events adjusted by treatment duration in the advanced group compared with the non-advanced idiopathic pulmonary fibrosis group**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | OR\* | 95% CI | *P*-value† |
| Adverse events | 0.667 | 0.240-1.855 | 0.437 |
| Anorexia | 0.524 | 0.239-1.147 | 0.106 |
| Nausea/vomiting | 0.860 | 0.380-1.946 | 0.718 |
| Dyspepsia/abdominal pain | 1.514 | 0.591-3.877 | 0.387 |
| Diarrhea | 1.103 | 0.304-4.002 | 0.882 |
| Hepatotoxicity | 2.891 | 0.688-12.141 | 0.147 |
| Constipation | 8.898 | 1.365-57.988 | 0.022 |
| Photosensitivity | 0.687 | 0.250-1.892 | 0.468 |
| Pruritus | 0.330 | 0.069-1.598 | 0.167 |
| Rash | 1.145 | 0.277-4.739 | 0.851 |
| General weakness | 0.719 | 0.218-2.366 | 0.587 |
| Insomnia | 0.545 | 0.111-2.673 | 0.454 |
| Dizziness | 1.331 | 0.313-5.664 | 0.699 |

OR, odds ratio; CI, confidence interval.

\* Compared with the non-advanced group.

†logistic regression analysis

**Table S4. Comparison of time to occurrence of adverse events between the advanced and non-advanced idiopathic pulmonary fibrosis groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristics | Total | Advanced | Non-advanced | *P*-value\* |
| Time to occurrence, weeks | 5.6 (4.4-6.7) | 4.6 (3.6-5.6) | 6.0 (4.4-7.6) | 0.139 |
| Anorexia | 6.1 (5.0-7.3\_ | 5.0 (2.9-7.1) | 7.0 (5.3-8.7) | 0.131 |
| Nausea/vomiting | 6.0 (5.3-6.7) | 6.0 (3.6-8.4) | 6.0 (4.6-7.4) | 0.316 |
| Dyspepsia/abdominal pain | 14.0 (5.6-22.4) | 12.7 (0.0-25.6) | 14.4 (4.4-24.4) | 0.459 |
| Diarrhea | 4.4 (3.7-5.1) | 1.3 (0.0-2.8) | 8.0 (0.0-21.9) | 0.001 |
| Hepatotoxicity | 16.6 (0.0-42.9) | 26.0 (1.1-50.9) | 7.0 (3.9-10.1)) | 0.083 |
| Constipation | 9.3 (4.8-13.7) | 9.3 (0.0-19.4) | 9.0 (1.3-32.7) | 0.441 |
| Pruritus | 17.0 (5.1-28.9) | 9.3 (8.1-13.1)) | 18.3 (15.2-19.4) | 0.329 |
| Photosensitivity | 19.3 (11.8-26.9) | 4.3 (0.0-23.5) | 19.3 (11.4-27.1) | 0.108 |
| Rash | 28.3 (0.0-74.6) | 37.3 (0.0-77.1)) | 5.6 (0.0-25.0) | 0.631 |
| General weakness | 11.3 (6.6-16.0) | 4.0 (0.0-14.2) | 11.3 (4.7-17.9) | 0.648 |
| Insomnia | 8.0 (3.2-12.9) | 7.6 (0.0-17.7) | 8.0 (3.6-12.4) | 0.577 |
| Dizziness | 30.1 (0.0-72.9) | 4.6 (0.5-8.7) | 36.7 (34.0-39.5) | 0.046 |

Data are presented as median (95% confidence interval), unless otherwise indicated.

\*log-rank test