Drug Safety

Drug-Related Adverse Events Predict the Efficacy of Apatinib on Advanced Hepatocellular Carcinoma

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|                                | Before PSM | After PSM | P value | Before PSM | After PSM | P value |
|--------------------------------|------------|-----------|---------|------------|-----------|---------|
| **Sex**                        |            |           | 0.849   |            | 0.817    |         |
| Female                         | 18 (14.3%) | 10 (12.3%)| 12 (16.0%) | 10 (13.3%)|           |         |
| Male                           | 108 (85.7%)| 71 (87.7%)| 63 (84.0%) | 65 (86.7%)|           |         |
| **Age**                        |            |           | 0.610   |            | 0.867    |         |
| < 60 years                     | 72 (57.1%) | 50 (61.7%)| 47 (62.7%) | 45 (60.0%)|           |         |
| ≥60 years                      | 54 (42.9%) | 31 (38.3%)| 28 (37.3%) | 30 (40.0%)|           |         |
| **Initial dose**               |            |           | 0.011   |            | 1.000    |         |
| 500mg/d                        | 4 (3.17%)  | 11 (13.6%)| 4 (5.3%)  | 5 (6.7%)  |           |         |
| 250mg/d                        | 122 (96.8%)| 70 (86.4%)| 71 (94.7%)| 70 (93.3%)|           |         |
| **ECOGPS**                     |            |           | 1.000   |            | 0.870    |         |
| 1                              | 66 (52.4%) | 42 (51.9%)| 42 (56.0%) | 40 (53.3%)|           |         |
| 0                              | 60 (47.6%) | 39 (48.1%)| 33 (44.0%) | 35 (46.7%)|           |         |
| **AFP**                        |            |           | 0.886   |            | 0.743    |         |
| < 400μg/L                      | 69 (54.8%) | 46 (56.8%)| 39 (52.0%) | 42 (56.0%)|           |         |
| ≥400μg/L                       | 57 (45.2%) | 35 (43.2%)| 36 (48.0%) | 33 (44.0%)|           |         |
| **Child-Pugh**                 |            |           | 0.514   |            | 1.000    |         |
| A                              | 90 (71.4%) | 62 (76.5%)| 56 (74.7%) | 57 (76.0%)|           |         |
| B                              | 36 (28.6%) | 19 (23.5%)| 19 (25.3%) | 18 (24.0%)|           |         |
| **BCLC**                       |            |           | 1.000   |            | 1.000    |         |
| B                              | 25 (19.8%) | 16 (19.8%)| 15 (20.0%) | 15 (20.0%)|           |         |
| C                              | 101 (80.2%)| 65 (80.2%)| 60 (80.0%) | 60 (80.0%)|           |         |
| Hepatitis                      |            |           | 1.000   |            | 1.000    |         |
| Hepatitis B                    | 97 (77.0%) | 63 (77.8%)| 59 (78.7%) | 59 (78.7%)|           |         |
| Hepatitis C                    | 4 (3.17%)  | 2 (2.47%) | 3 (4.00%) | 2 (2.67%) |           |         |
| None                           | 23 (18.3%) | 15 (18.5%)| 13 (17.3%) | 13 (17.3%)|           |         |
| **TACE**                       |            |           | 0.013   |            | 0.824    |         |
| no                             | 41 (32.5%) | 13 (16.0%)| 11 (14.7%) | 13 (17.3%)|           |         |
| yes                            | 85 (67.5%) | 68 (84.0%)| 64 (85.3%) | 62 (82.7%)|           |         |
| **MVI**                        |            |           | 0.916   |            | 1.000    |         |
| no                             | 66 (52.4%) | 41 (50.6%)| 40 (53.3%) | 40 (53.3%)|           |         |
| yes                            | 60 (47.6%) | 40 (49.4%)| 35 (46.7%) | 35 (46.7%)|           |         |
| **EHS**                        |            |           | 0.847   |            | 1.000    |         |
| no                             | 59 (46.8%) | 36 (44.4%)| 33 (44.0%) | 33 (44.0%)|           |         |
| yes                            | 67 (53.2%) | 45 (55.6%)| 42 (56.0%) | 42 (56.0%)|           |         |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status score; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; MVI, macrovascular invasion; EHS, extrahepatic spread; HFS, Hand and foot syndrome.
|                  | Before PSM | After PSM | P value | Before PSM | After PSM | P value |
|------------------|------------|-----------|---------|------------|-----------|---------|
|                  | Non-Proteinuria (N=157) | Proteinuria (N=50) | P value | Non-Proteinuria (N=46) | Proteinuria (N=46) | P value |
| Sex              |            |           |         |            |           |         |
| Female           | 23 (14.6%) | 5 (10.0%) | 0.549   | 6 (13.0%)  | 5 (10.9%) | 1.000   |
| Male             | 134 (85.4%) | 45 (90.0%) |         | 40 (87.0%) | 41 (89.1%) |         |
| Age              |            |           | 0.317   |            |           | 1.000   |
| < 60 years       | 89 (56.7%) | 33 (66.0%) |         | 31 (67.4%) | 30 (65.2%) |         |
| ≥60 years        | 68 (43.3%) | 17 (34.0%) |         | 15 (32.6%) | 16 (34.8%) |         |
| Initial dose     |            |           | 0.011   |            |           | 1.000   |
| 500mg/d          | 7 (4.46%)  | 8 (16.0%) |         | 5 (10.9%)  | 4 (8.7%)  |         |
| 250mg/d          | 150 (95.5%) | 42 (84.0%) |         | 41 (89.1%) | 42 (91.3%) |         |
| ECOG PS          |            |           | 0.606   |            |           | 0.531   |
| 1                | 84 (53.5%) | 24 (48.0%) |         | 20 (43.5%) | 24 (52.2%) |         |
| 0                | 73 (46.5%) | 26 (52.0%) |         | 26 (56.5%) | 22 (47.8%) |         |
| AFP              |            |           | 0.928   |            |           | 0.677   |
| < 400μg/L        | 88 (56.1%) | 27 (54.0%) |         | 22 (47.8%) | 25 (54.3%) |         |
| ≥400μg/L         | 69 (43.9%) | 23 (46.0%) |         | 24 (52.2%) | 21 (45.7%) |         |
| Child-Pugh       |            |           | 0.937   |            |           | 0.821   |
| A                | 116 (73.9%) | 36 (72.0%) |         | 31 (67.4%) | 33 (71.7%) |         |
| B                | 41 (26.1%) | 14 (28.0%) |         | 15 (32.6%) | 13 (28.3%) |         |
| BCLC             |            |           | 0.869   |            |           | 1.000   |
| B                | 32 (20.4%) | 9 (18.0%) |         | 7 (15.2%)  | 8 (17.4%)  |         |
| C                | 125 (79.6%) | 41 (82.0%) |         | 39 (84.8%) | 38 (82.6%) |         |
| Hepatitis        |            |           | 1.000   |            |           | 0.793   |
| Hepatitis B      | 120 (76.4%) | 40 (80.0%) |         | 36 (78.3%) | 37 (80.4%) |         |
| Hepatitis C      | 5 (3.18%)  | 1 (2.00%)  |         | 0 (0.00%)  | 1 (2.17%)  |         |
| None             | 29 (18.5%) | 9 (18.0%)  |         | 10 (21.7%) | 8 (17.4%)  |         |
| TACE             |            |           | 0.590   |            |           | 1.000   |
| no               | 39 (24.8%) | 15 (30.0%) |         | 14 (30.4%) | 14 (30.4%) |         |
| yes              | 118 (75.2%) | 35 (70.0%) |         | 32 (69.6%) | 32 (69.6%) |         |
| MVI              |            |           | 1.000   |            |           | 0.835   |
| no               | 81 (51.6%) | 26 (52.0%) |         | 22 (47.8%) | 24 (52.2%) |         |
| yes              | 76 (48.4%) | 24 (48.0%) |         | 24 (52.2%) | 22 (47.8%) |         |
| EHS              |            |           | 0.405   |            |           | 0.835   |
| no               | 69 (43.9%) | 26 (52.0%) |         | 21 (45.7%) | 23 (50.0%) |         |
| yes              | 88 (56.1%) | 24 (48.0%) |         | 25 (54.3%) | 23 (50.0%) |         |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status score; BCLC, Barcelona Clinic Liver Cancer; AFP, alphafetoprotein; MVI, macrovascular invasion; EHS, extrahepatic spread.
Table S3 Baseline characteristics of patients before and after PSM (Non-diarrhea vs. Diarrhea)

|                        | Before PSM |                      | After PSM |                      | P value |
|------------------------|------------|----------------------|-----------|----------------------|---------|
|                        | Non-diarrhea (N=160) | Diarrhea (N=47) | P value | Non-diarrhea (N=43) | Diarrhea (N=43) | P value |
| **Sex**                |            |                      |           |                      |                      |         |
| Female                 | 24 (15.0%) | 4 (8.51%)            | 0.368     | 4 (9.30%)            | 4 (9.30%)          | 1.000   |
| Male                   | 136 (85.0%) | 43 (91.5%)           | 0.200     | 39 (90.7%)           | 39 (90.7%)         | 1.000   |
| **Age**                |            |                      |           |                      |                      |         |
| < 60 years             | 90 (56.2%) | 32 (68.1%)           | 0.048     | 29 (67.4%)           | 28 (65.1%)         | 1.000   |
| ≥60 years              | 70 (43.8%) | 15 (31.9%)           |           | 14 (32.6%)           | 15 (34.9%)         |         |
| **Initial dose**       |            |                      |           |                      |                      |         |
| 500mg/d                | 8 (5.00%)  | 7 (14.9%)            | 0.502     | 3 (6.98%)            | 3 (6.98%)          | 0.188   |
| 250mg/d                | 152 (95.0%) | 40 (85.1%)           |           | 40 (93.0%)           | 40 (93.0%)         |         |
| **ECOGPS**             |            |                      |           |                      |                      |         |
| 1                      | 86 (53.8%) | 22 (46.8%)           | 0.897     | 14 (32.6%)           | 21 (48.8%)         | 0.195   |
| 0                      | 74 (46.2%) | 25 (53.2%)           |           | 29 (67.4%)           | 22 (51.2%)         |         |
| **AFP**                |            |                      |           |                      |                      |         |
| < 400μg/L              | 88 (55.0%) | 27 (57.4%)           | 0.711     | 19 (44.2%)           | 26 (60.5%)         | 1.000   |
| ≥400μg/L               | 72 (45.0%) | 20 (42.6%)           |           | 24 (55.8%)           | 17 (39.5%)         |         |
| **Child-Pugh**         |            |                      |           |                      |                      |         |
| A                      | 116 (72.5%) | 36 (76.6%)          | 1.000     | 31 (72.1%)           | 32 (74.4%)         |         |
| B                      | 44 (27.5%) | 11 (23.4%)           |           | 12 (27.9%)           | 11 (25.6%)         |         |
| **BCLC**               |            |                      |           |                      |                      |         |
| B                      | 32 (20.0%) | 9 (19.1%)            | 1.000     | 9 (20.9%)            | 9 (20.9%)          |         |
| C                      | 128 (80.0%) | 38 (80.9%)          |           | 34 (79.1%)           | 34 (79.1%)         |         |
| **Hepatitis**          |            |                      |           |                      |                      |         |
| Hepatitis B            | 119 (74.4%) | 41 (87.2%)          | 0.364     | 34 (79.1%)           | 37 (86.0%)         | 0.463   |
| Hepatitis C            | 5 (3.12%)  | 1 (2.13%)            |           | 0 (0.00%)            | 1 (2.33%)          |         |
| None                   | 33 (20.6%) | 5 (10.6%)            |           | 8 (18.6%)            | 5 (11.6%)          |         |
| **TACE**               |            |                      |           |                      |                      |         |
| no                     | 45 (28.1%) | 9 (19.1%)            | 0.297     | 8 (18.6%)            | 9 (20.9%)          | 1.000   |
| yes                    | 115 (71.9%) | 38 (80.9%)          |           | 35 (81.4%)           | 34 (79.1%)         |         |
| **MVI**                |            |                      |           |                      |                      |         |
| no                     | 84 (52.5%) | 23 (48.9%)           | 0.792     | 22 (51.2%)           | 22 (51.2%)         | 1.000   |
| yes                    | 76 (47.5%) | 24 (51.1%)           |           | 21 (48.8%)           | 21 (48.8%)         |         |
| **EHS**                |            |                      |           |                      |                      |         |
| no                     | 72 (45.0%) | 23 (48.9%)           | 0.757     | 20 (46.5%)           | 22 (51.2%)         | 0.829   |
| yes                    | 88 (55.0%) | 24 (51.1%)           |           | 23 (53.5%)           | 21 (48.8%)         |         |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status score; BCLC, Barcelona Clinic Liver Cancer; AFP, alphafetoprotein; MVI, macrovascular invasion; EHS, extrahepatic spread.