**Supplementary Material**

**Supplemental Table 1: Treatment characteristics according to lenvatinib dose at baseline**

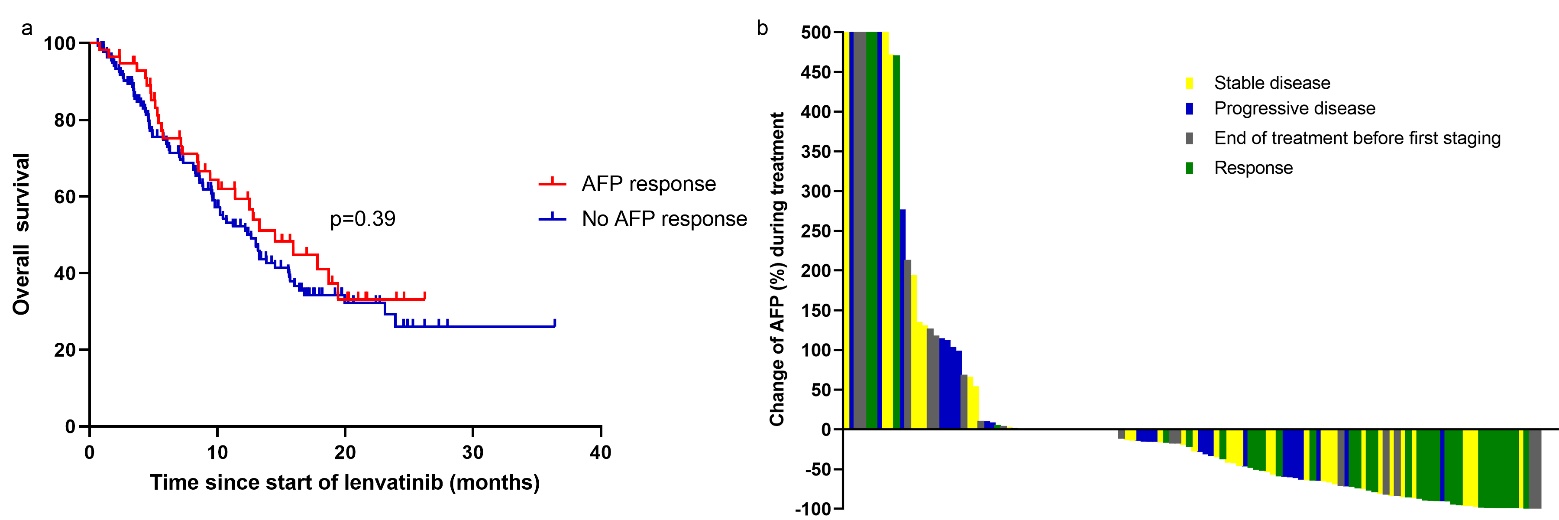
|  |  |  |  |
| --- | --- | --- | --- |
|  | Overall  (n=205) | Standard dose (n=89) | Reduced dose (n=114) |
| Median overall survival (months) | 12.8 | 13.8 | 10.4 |
| 95% confidence interval of median overall survival (months) | 10.9-14.7 | 11.1-16.5 | 7.8-13.1 |
| Median progression free survival (months) | 6.4 | 6.7 | 5.9 |
| 95% confidence interval of progression free survival (months) | 5.1- 7.7 | 4.8-8.6 | 4.5-7.3 |
| Disease control | 117 (57.1) | 48 (53.9) | 68 (59.6) |
| Overall response | 48 (23.4) | 23 (25.8) | 25 (21.9) |

**Supplemental Table 2: Subsequent treatment after lenvatinib**

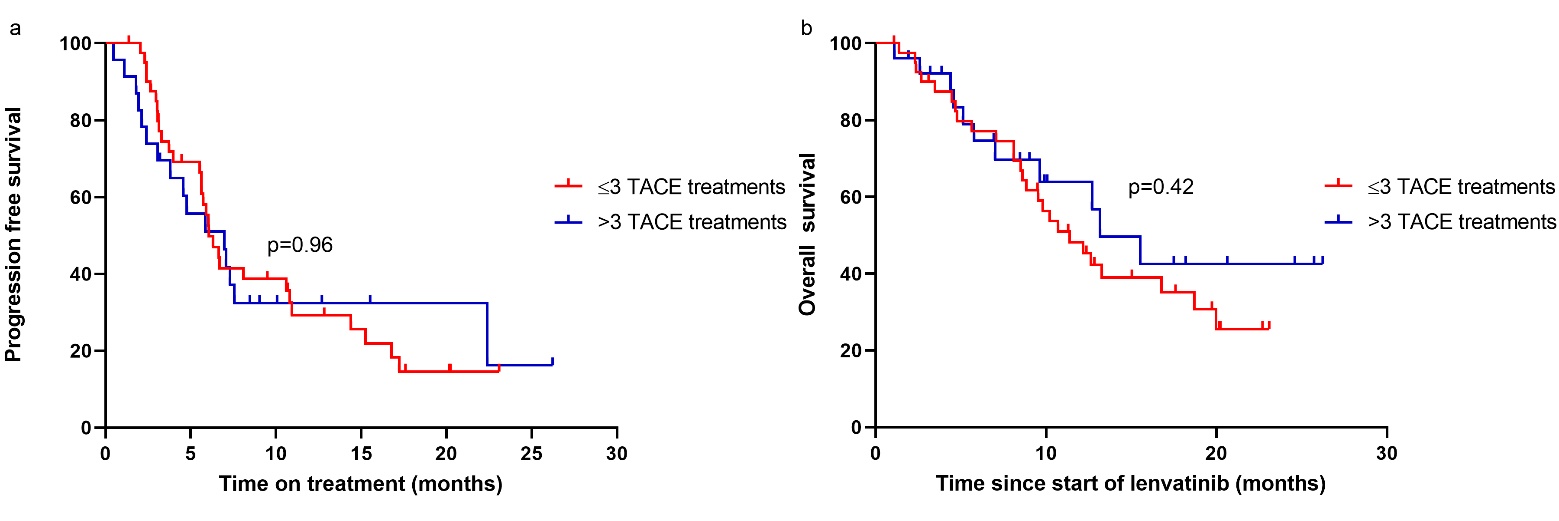
|  |  |
| --- | --- |
| Subsequent treatment (n=97) |  |
| Systemic second-line (n=88) |  |
| Sorafenib | 56 (63.3) |
| Ramucirumab | 9 (10.2) |
| Pembrolizumab | 4 (4.5) |
| Nivolumab | 2 (2.3) |
| Atezolizumab plus Bevacizumab | 3 (3.4) |
| Regorafenib | 2 (2.3) |
| Cabozantinib | 11 (12.5) |
| Ipilimumab plus Nivolumab | 2 (2.3) |
| Other | 1 (1.1) |
| Subsequent Immunotherapy independent from treatment line | 11 (12.5) |
| Anti cancer procedures (n=9) |  |
| Transplantation | 1 (1.1) |
| TACE | 0 |
| SIRT | 3 (3.4) |
| Radiation | 3 (3.4) |
| Ablation | 2 (2.3) |
| Resection | 0 |

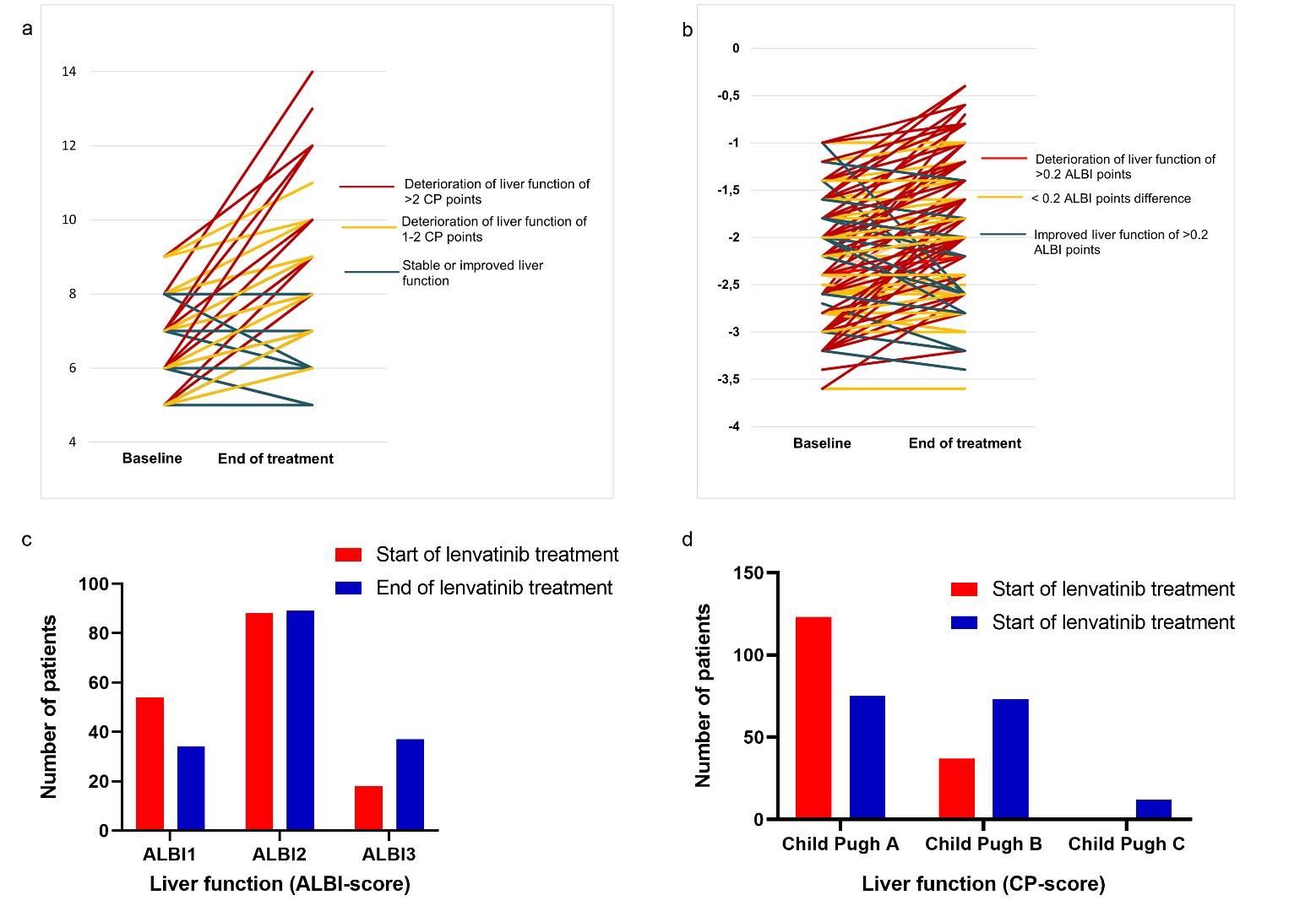
**Supplemental Table 3: Frequency of adverse events**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Frequency of adverse events | Overall  (n=205) | Standard  Dose  (n=89) | Reduced dose  (n=114) | Unknown dose  (n=2) |
| Adverse events | 160 (78.1) | 66 (74.2) | 94 (82.5) | 0 |
| Diarrhea | 38 (18.5) | 16 (18.0) | 22 (19.3) | 0 |
| Fatigue | 72 (35.1) | 29 (32.6) | 43 (37.7) | 0 |
| Hypertension | 18 (8.8) | 8 (9.0) | 9 (7.9) | 1 (50) |
| Weight loss | 32 (15.6) | 13 (14.6) | 19 (16.7) | 0 |
| Appetite loss | 42 (20.5) | 9 (10.1) | 31 (27.2) | 2 (100) |
| Skin reaction | 15 (7.3) | 7 (7.9) | 8 (7.0) | 0 |
| No Adverse Events reported or documented | 45 (21.9) | 23 (25.8) | 20 (17.5) | 2 (100) |
| Severe adverse events (≥grade 3) | 97 (47.3) | 37 (41.6) | 58 (50.9) | 2 (100) |
|  |  |  |  |  |
| Treatment interruption due to AEs | 63 (30.7) | 24 (27.0) | 38 (33.3) | 1 (50) |
| Dose reduction due to AEs | 73 (35.6) | 30 (33.7) | 42 (36.8) | 1 (50) |
| End of treatment due to significantly liver dysfunction | 30 (14.6) | 12 (13.5) | 18 (15.8) | 0 |
| Progress or onset of ascites | 34 (19.6) | 15 (16.9) | 19 (16.7) | 0 |
| Ascitic decompensation under treatment | 6 (2.9) | 1 (1.1) | 5 (4.4) | 0 |
| Newly diagnosed hepatic encephalopathy under treatment | 18 (8.8) | 9 (10.1) | 9 (7.9) | 0 |
| Severe hepatic encephalopathy  (Grade III or IV) under treatment | 8 (3.9) | 5 (5.6) | 3 (2.6) | 0 |
| Treatment discontinuation due to AEs (other than liver dysfunction) | 45 (21.9) | 19 (21.3) | 26 (22.8) | 0 |

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**Supplemental Fig. 1.** Kaplan-Meier analysis of progression free survival (Supplemental Fig 1a) and overall survival (Supplemental Fig 1b) divided by the number of TACE treatments before start of lenvatinib

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**Supplemental Fig. 2.** Kaplan-Meier analysis of overall survival according to AFP response (Supplemental Fig 2a), and correlation between AFP response and radiological response (Supplemental Fig 2b)

**Supplemental Fig 3.** Comparison of liver function at baseline and end of treatment measured by Child Pugh score (Supplemental Fig 3a, 3d) and ALBI Score (Supplemental Fig 3b, 3c)