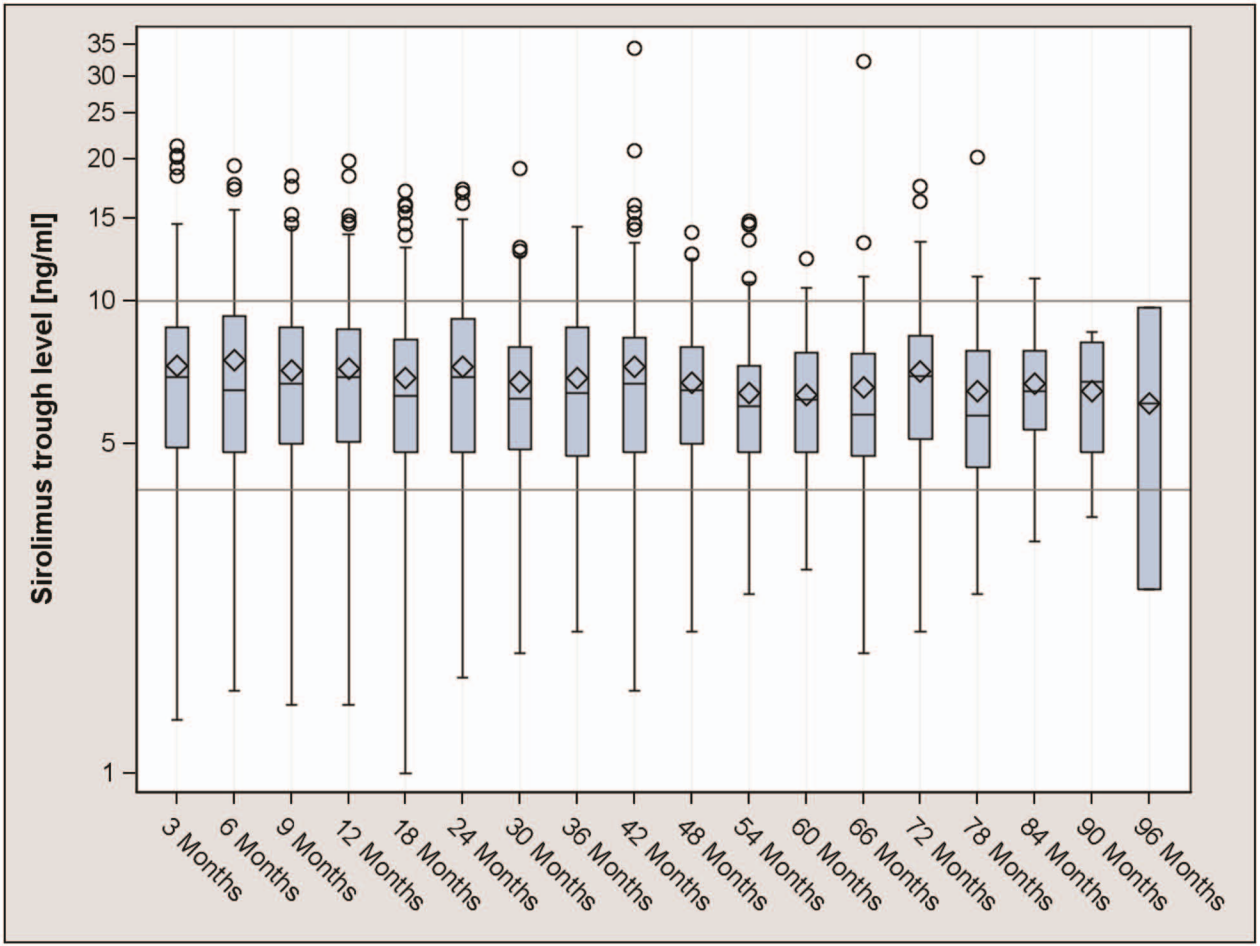
***Appendix Figure 1.*** Sirolimus trough levels during the study



## *Supplementary Digital Content*

***Supplementary Table 1.*** Surgical procedures used

| | Group A | Group B | Total |
|---|---|---|---|
| Transplant technique | | | |
| Piggy back | 141 (55.1%) | 143 (56.7%) | 284 (55.9%) |
| Caval cross-clamping | 107 (41.8%) | 99 (39.3%) | 206 (40.6%) |
| Porto-systemic shunt | 50 (19.5%) | 47 (18.7%) | 97 (19.1%) |
| Reperfusion simultaneously | 82 (32.0%) | 79 (31.3%) | 161 (31.7%) |
| Packing | 4 (1.6%) | 11 (4.4%) | 15 (3.0%) |
| **N** | **256** | **252** | **508** |
| Transfusion Cell Saver | | | |
| Yes | 45 (17.6%) | 58 (23.0%) | 103 (20.3%) |
| No | 199 (77.7%) | 183 (72.6%) | 382 (75.2%) |
| **N*** | **244** | **241** | **485** |

Note: Denominator for percentages is column N

*Not reported for all liver transplant procedures

***Supplementary Table 2.*** Summary of recipient pre-transplant co-morbidity status (ITT population)

| | **Group A (N=256)** | **Group B (N=252)** | **Total (N=508)** |
|---|---|---|---|
| Cardio-vascular disease | 82 (32.0%) | 101 (40.1%) | 183 (36.0%) |
| Heart infarction | 9 (3.5%) | 6 (2.4%) | 15 (3.0%) |
| Cardiac Insufficiency | | | |
| NYHA I | 8 (3.1%) | 9 (3.6%) | 17 (3.3%) |
| NYHA II | 1 (0.4%) | 2 (0.8%) | 3 (0.6%) |
| NYHA III | 2 (0.8%) | - | 2 (0.4%) |
| Hypertension | 81 (31.6%) | 96 (38.1%) | 177 (34.8%) |
| Obstructive pulmonary disease | | | |
| COPD | 18 (7.0%) | 19 (7.5%) | 37 (7.3%) |
| Asthma | 8 (3.1%) | 7 (2.8%) | 15 (3.0%) |
| Restrictive pulmonary disease | | | |
| Fibrosis | 3 (1.2%) | - | 3 (0.6%) |
| Edema | 7 (2.7%) | 4 (1.6%) | 11 (2.2%) |
| Renal insufficiency | | | |
| HRS | 16 (6.3%) | 15 (6.0%) | 31 (6.1%) |
| Chronic renal insufficiency | 23 (9.0%) | 19 (7.5%) | 42 (8.3%) |
| Metabolic disease | | | |
| Diabetes mellitus | 80 (31.3%) | 81 (32.1%) | 161 (31.7%) |
| Hyperlipidaemia | 14 (5.5%) | 20 (7.9%) | 34 (6.7%) |
| Hyperuricemia | 17 (6.6%) | 8 (3.2 %) | 25 (4.9%) |
| Other risk factors | | | |
| Nicotin abuse | 116 (45.3%) | 126 (50.0%) | 242 (47.6%) |
| Alcohol abuse | 125 (48.8%) | 127 (50.4%) | 252 (49.6%) |
| Other drug abuse | 28 (10.9%) | 22 (8.7%) | 50 (9.8%) |
| Thrombosis | 21 (8.2%) | 16 (6.3%) | 37 (7.3%) |

More than one disease/factor could be reported per patient

NYHA: New York Heart Association functional classification,COPD: chronic obstructive pulmonary disease, HRS: hepatorenal syndrome

***Supplementary Table 3.*** Summary of underlying liver disease in transplant recipients (ITT population)

| | **Group A (N=256)** | **Group B (N=252)** | **Total (N=508)** |
|---|---|---|---|
| Cirrhosis | 245 (95.7%) | 243 (96.4%) | 488 (96.1%) |
| Cause of cirrhosis | | | |
| Viral infection: HBV | 32 (12.5%) | 28 (11.1%) | 60 (11.8%) |
| Viral infection: HCV | 93 (36.3%) | 93 (36.9%) | 186 (36.6%) |
| Alcoholic | 77 (30.1%) | 81 (32.1%) | 158 (31.1%) |
| PSC | - | 1 (0.4%) | 1 (0.2%) |
| PBC | 4 (1.6%) | 1 (0.4%) | 5 (1.0%) |
| Autoimmune disease | 2 (0.8%) | 1 (0.4%) | 3 (0.6%) |
| Hemochromatosis | - | 3 (1.2%) | 3 (0.6%) |
| Other metabolic disease | 2 (0.8%) | 1 (0.4%) | 3 (0.6%) |
| Other | 35 (13.7%) | 34 (13.5%) | 69 (13.6%) |
| Esophagious varicosis | | | |
| Grade I | 72 (28.1%) | 66 (26.2%) | 138 (27.2%) |
| Grade II | 59 (23.0%) | 60 (23.8%) | 119 (23.4%) |
| Grade III | 24 (9.4%) | 8 (3.2%) | 32 (6.3%) |
| History of variceal bleeding | 51 (19.9%) | 44 (17.5%) | 95 (18.7%) |
| Splenomegaly | 141 (55.1%) | 142 (56.3%) | 283 (55.7%) |
| Pretreatment of underlying disease | | | |
| Lamivudine | 26 (10.2%) | 22 (8.7%) | 48 (9.4%) |
| Interferon | 62 (24.2%) | 59 (23.4%) | 121 (23.8%) |
| Adevovir | 15 (5.9%) | 8 (3.2%) | 23 (4.5%) |
| Tenovovir | 3 (1.2%) | 1 (0.4%) | 4 (0.8%) |
| Ribavirin | 51 (19.9%) | 50 (19.8%) | 101 (19.9%) |
| HBIg | 5 (2.0%) | 1 (0.4%) | 6 (1.2%) |
| Other virostatic drugs | 8 (3.1%) | 6 (2.4%) | 14 (2.8%) |
| Steroids | 4 (1.6%) | 1 (0.4%) | 5 (1.0%) |
| Desferroxamine | 1 (0.4%) | 1 (0.4%) | 2 (0.4%) |
| TIPS | 11 (4.3%) | 8 (3.2%) | 19 (3.7%) |
| Other | 19 (7.4%) | 21 (8.3%) | 40 (7.9%) |

Note: more than one treatment could be reported per patient

HBV: hepatitis B virus, HCV: hepatitis C virus, PSC: primary sclerosing cholangitis, PBC: primary biliary cirrhosis, HBIg: hepatitis B immune globulin, TIPS: transjugular intrahepatic portosystemic shunt

***Supplementary Table 4.*** HCC number and size distribution in explanted liver pathology report (ITT population)

| | Group A | Group B | Total |
|---|---|---|---|
| **Milan Criteria at randomisation** | | | |
| within Milan Criteria | 162 (63.3%) | 164 (65.1%) | 326 (64.2%) |
| outside Milan Criteria | 94 (36.7%) | 88 (34.9%) | 182 (35.8%) |
| N | 256 | 252 | 508 |
| **Number of Lesions** | | | |
| 1 | 98 (43.2%) | 99 (44.2%) | 197 (43.7%) |
| 2 | 41 (18.1%) | 52 (23.2%) | 93 (20.6%) |
| 3 | 32 (14.1%) | 29 (12.9%) | 61 (13.5%) |
| 4-5 | 28 (12.3%) | 21 (9.4%) | 49 (10.9%) |
| >5 | 28 (12.3%) | 23 (10.3%) | 51 (11.3%) |
| N* | 227 | 224 | 451 |
| **Maximum Tumor Size** | | | |
| <3 cm | 116 (51.1%) | 90 (40.2%) | 206 (45.7%) |
| 3-5 cm | 87 (38.3%) | 111 (49.6%) | 198 (43.9%) |
| 5.5-7.5 cm | 13 (5.7%) | 16 (7.1%) | 29 (6.4%) |
| >7.5 cm | 11 (4.9%) | 7 (3.1%) | 18 (4.0%) |
| N* | 227 | 224 | 451 |
| **TNM Classification – G** | | | |
| 1 | 47 (18.4%) | 53 (21.0%) | 100 (19.7%) |
| 2 | 122 (47.7%) | 113 (44.8%) | 235 (46.3%) |
| 3 | 36 (14.1%) | 34 (13.5%) | 70 (13.8%) |
| N** | 205 | 200 | 405 |

*Complete data is not available for all patients due to cases lacking viable tumor evidence in the explanted liver. Lack of viable tumor is expected in some cases because of pre-LTx tumor reduction therapy. According to the trial protocol, final Milan Criteria assessment was based on the post-LTx pathology report, even in cases where there was tumor treatment reduction resulting in a shift from the high to low risk category, pre and post-LTx, respectively.

** The number of patients where TNM Classification grading was performed according to this scheme.

***Supplementary Table 5.*** Treatment of lesions prior to liver transplantation (ITT population)

| | **Group A (N=256)** | **Group B (N=252)** | **Total (N=508)** |
|---|---|---|---|
| No treatment | 74 (28.9%) | 69 (27.4%) | 143 (28.1%) |
| Resection | 26 (10.2%) | 24 (9.5%) | 50 (9.8%) |
| TACE | 110 (43.0%) | 123 (48.8%) | 233 (45.9%) |
| RFA | 64 (25.0%) | 55 (21.8%) | 119 (23.4%) |
| PEI | 14 (5.5%) | 21 (8.3%) | 35 (6.9%) |
| Chemotherapy | 6 (2.3%) | 2 (0.8%) | 8 (1.6%) |
| Other | 11 (4.3%) | 14 (5.6%) | 25 (4.9%) |

More than one treatment could be reported per patient

TACE: transarterial chemoembolization, RFA: radiofrequency ablation, PEI: percuataneous ethanol injection

***Supplementary Table 6***. Calcineurin-inhibitor exposure at 1, 3 and 5 years

| | Group A | Group B |
|---|---|---|
| **Year 1** | | |
| Cyclosporine dose [mg/kg BW/d] | | |
| N | 52 | 26 |
| Mean | 2.55 | 1.83 |
| SD | 0.98 | 0.81 |
| Tacrolimus dose [mg/kg BW/d] | | |
| N | 166 | 113 |
| Mean | 0.05 | 0.04 |
| SD | 0.03 | 0.04 |
| **Year 3** | | |
| Cyclosporine dose [mg/kg BW/d] | | |
| N | 44 | 19 |
| Mean | 1.87 | 1.42 |
| SD | 0.89 | 0.60 |
| Tacrolimus dose [mg/kg BW/d] | | |
| N | 121 | 79 |
| Mean | 0.04 | 0.03 |
| SD | 0.03 | 0.03 |
| **Year 5** | | |
| Cyclosporine dose [mg/kg BW/d] | | |
| N | 35 | 18 |
| Mean | 1.83 | 1.24 |
| SD | 2.26 | 0.64 |
| Tacrolimus dose [mg/kg BW/d] | | |
| N | 107 | 67 |
| Mean | 0.04 | 0.03 |
| SD | 0.03 | 0.03 |

N= number of patients with available data

***Supplementary Table 7***. Location of HCC recurrence

| | **Group A** | **Group B** |
|---|---|---|
| Number of patients → | **N=49** | **N=38** |
| Number of recurrence sites → | **N=56** | **N=42** |
| **Location** | | |
| Intra-abdominal | 14***** (25.0%)****** | 12 (28.6%) |
| Intrahepatic | 15 (26.8%) | 14 (33.3%) |
| Thoracic | 18 (32.1%) | 9 (21.4%) |
| Bone | 9 (16.1%) | 7 (16.7%) |

*****Number of patients with an HCC recurrence located at this site at the time of HCC recurrence; more than one HCC location could be reported per patient.

******Distribution of HCC recurrence location as a percentage of the total number of recurrence sites.

***Supplementary Table 8***. Causes of death (ITT-population)

| | Age ≤ 60 years | | Age > 60 years | | Total | |
|---|---|---|---|---|---|---|
| | **Group A** | **Group B** | **Group A** | **Group B** | **Group A** | **Group B** |
| Cardiovascular | | | | | | |
| Cardiac failure | 2 | 0 | 1 | 2 | 3 | 2 |
| ICB | 0 | 2 | 3 | 0 | 3 | 2 |
| Stroke | 1 | 0 | | | 1 | 0 |
| Pulmonary embolism | | | 1 | 1 | 1 | 1 |
| Aortal aneurysm | | | 0 | 1 | 0 | 1 |
| Myocardial infarction | 0 | 1 | 0 | 1 | 0 | 2 |
| Infectious | | | | | | |
| Septic MOF | 5 | 0 | 3 | 4 | 8 | 4 |
| Pneumonitis | | | 0 | 1 | 0 | 1 |
| Biliary sepsis | | | 2 | 3 | 2 | 3 |
| SBP | | | 0 | 2 | 0 | 2 |
| Pneumonia | 2 | 2 | 1 | 3 | 3 | 5 |
| Lung failure | 2 | 0 | | | 2 | 0 |
| Colon perforation | 1 | 0 | 1 | 0 | 2 | 0 |
| Fournier Gangrain | 1 | 0 | | | 1 | 0 |
| Tumor-associated | | | | | | |
| HCC-progress | 19 | 9 | 14 | 15 | 33 | 24 |
| Lung Ca | 3 | 0 | 3 | 0 | 6 | 0 |
| Urothel Ca | | | 1 | 0 | 1 | 0 |
| Adeno Ca | 1 | 0 | 0 | 1 | 1 | 1 |
| Kaposi sarcoma | | | 1 | 0 | 1 | 0 |
| Pancreatic Ca | | | 0 | 1 | 0 | 1 |
| Pharynx Ca | | | 1 | 0 | 1 | 0 |
| Esophagus Ca | | | 1 | 0 | 1 | 0 |
| PTLD | 0 | 1 | | | 0 | 1 |
| Thymus Ca | | | 1 | 0 | 1 | 0 |
| Other | | | | | | |
| Unknown | 0 | 1 | 1 | 2 | 1 | 3 |
| Suicide | | | 0 | 2 | 0 | 2 |
| Graft failure | 4 | 3 | 5 | 5 | 9 | 8 |
| NASH | | | 0 | 1 | 0 | 1 |
| **Sum** | **41** | **19** | **40** | **45** | **81** | **64** |

ICB: intracranial bleeding, MOF: multi-organ failure, SBP: spontaneous bacterial peritonitis, HCC: hepatocellular carcinoma, Ca: carcinoma, PTLD: posttransplant lymphoproliferative disease, NASH: non-alcoholic steatohepatitis

***Supplementary Table 9.*** Summary of baseline characteristics recipient - co-morbidity status for ≤60 years age subgroup (patient history)

| | **Group A ≤ 60 years (N=155)** | **Group B ≤ 60 years (N=145)** | **Total ≤ 60 years (N=300)** |
|---|---|---|---|
| Cardio-vascular disease | 42 (27.1%) | 45 (31.0%) | 87 (29.0%) |
| Heart infarction | 1 (0.6%) | 2 (1.4%) | 3 (1.0%) |
| Cardiac Insufficiency | | | |
| NYHA I | 4 (2.6%) | 3 (2.1%) | 7 (2.3%) |
| NYHA II | 1 (0.6%) | - | 1 (0.3%) |
| NYHA III | 1 (0.6%) | - | 1 (0.3%) |
| Hypertension | 41 (26.5%) | 45 (31.0%) | 86 (28.7%) |
| Obstructive pulmonary disease | | | |
| COPD | 9 (5.8%) | 6 (4.1%) | 15 (5.0%) |
| Asthma | 5 (3.2%) | 2 (1.4%) | 7 (2.3%) |
| Restrictive pulmonary disease | | | |
| Fibrosis | - | - | - |
| Edema | 4 (2.6%) | 3 (2.1%) | 7 (2.3%) |
| Renal insufficiency | | | |
| HRS | 8 (5.2%) | 10 (6.9%) | 18 (6.0%) |
| Chronic renal insufficiency | 13 (8.4%) | 11 (7.6%) | 24 (8.0%) |
| Metabolic disease | | | |
| Diabetes mellitus | 46 (29.7%) | 43 (29.7%) | 89 (29.7%) |
| Hyperlipidemia | 10 (6.5%) | 9 (6.2%) | 19 (6.3%) |
| Hyperuricemia | 10 (6.5%) | 5 (3.4%) | 15 (5.0%) |
| Other risk factors | | | |
| Nicotine abuse | 85 (54.8%) | 80 (55.2%) | 165 (55.0%) |
| Alcohol abuse | 82 (52.9%) | 75 (51.7%) | 157 (52.3%) |
| Other drug abuse | 26 (16.8%) | 22 (15.2%) | 48 (16.0%) |
| Thrombosis | 12 (7.7%) | 13 (9.0%) | 25 (8.3%) |

More than one disease/factor could be reported per patient

NYHA: New York Heart Association functional classification, COPD: chronic obstructive pulmonary disease, HRS: hepatorenal syndrome

***Supplementary Table 10.*** Overview of adverse effects in all randomized patients (number of patients with events)

| | **Group A (N=264)** | **Group B (N=261)** | **Total (N=525)** |
|---|---|---|---|
| All events | 257 (97.3%) | 255 (97.7%) | 512 (97.5%) |
| Serious events | 218 (82.6%) | 225 (86.2%) | 443 (84.4%) |
| Events leading to death | 82 (31.1%) | 64 (24.5%) | 146 (27.8%) |
| Related events***** | 161 (61.0%) | 225 (86.2%) | 386 (73.5%) |
| Serious related events | 58 (22.0%) | 106 (40.6%) | 164 (31.2%) |
| Related events leading to death | 8 (3.0%) | 7 (2.7%) | 15 (2.9%) |

*****Related events refer to a possible, probable or certain relationship to a study medication in the treatment arm, as assessed by the local investigator.

All numbers shown represent the number of patients with the indicated event.