Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial

Elsevier Editorial System(tm) for The Lancet Oncology

Manuscript Draft

Manuscript Number: THELANCETONCOLOGY-D-19-01452

Title: Expanding Criteria for Liver Transplantation in Hepatocellular Carcinoma after Tumor Downstaging: a Prospective Randomized Trial

Article Type: Article (Clinical Trials)

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Manuscript Region of Origin: ITALY

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Methods. This multi-center trial aimed at comparing successfully downstaged HCC followed by transplantation vs. non-transplant therapies. Eligible patients had good liver function (Child-Pugh A-B7), HCC beyond Milan, 5-year estimated post-transplant survival ≥50%, no macrovascular or extrahepatic spread. Only partial-complete responses according to modified-RECIST were randomized 1:1 after 3 months observation period, during which sorafenib was allowed. Co-endpoints were survival and time-to-tumor event. We used Kaplan-Meier method, log-rank test, Cox regression for intention-to-treat analysis. Survival benefit was the difference between groups mean survival time. Organ allocation policy changed over time and limited patients' accrual to 4 years. After 4 additional years conditional power calculation estimated the probability that the final results would be statistically significant in the remaining study, given the data observed. ClinicalTrials.gov NCT01387503.
Findings. 74 patients were enrolled between March 2011 to March 2015: 29 dropped-out pre-randomization. Downstaging median duration was 6 months (1-17). Success-rate was 73%. Progression during observation was 17%. 45

patients were randomized: 23 transplanted vs. 22 controls. Median follow-up was 71 months (IQR 60-85). 5-year overall survival was 77.5% (95%CI 61.9-97.1%) in transplants vs. 31.2% (95%CI: 16.6-58.5%) in controls (Cox hazard ratio [HR] 0.22, 95%CI: 0.08-0.61; p=0.004). 5-year tumor event-free survival was 76.8 (95%CI: 60.8-96.9%) vs. 18.3% (95%CI: 7.1-47.0%) in controls (HR: 0.14, 95%CI: 0.05-0.38; p<0001). 5-year survival-benefit favored transplantation by 14.5 months (95%CI: 3.6-25.3; p=0.009). The trial retained a conditional power of 98.6%.
Interpretation. After effective and sustained downstaging of eligible HCCs beyond Milan criteria, liver transplantation is superior to non-transplant therapies. Post-downstaging tumor response should contribute to HCC transplant criteria expansion.
Funding. Italian Ministry of Health

Expanding Criteria for Liver Transplantation in Hepatocellular Carcinoma after Tumor Downstaging: a Prospective Randomized Trial

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SUMMARY

Background. Liver transplantation cures hepatocellular carcinoma (HCC) if within conventional selection criteria. Expanded criteria are elusive. Loco-regional treatments pursue tumor downstaging from outside Milan criteria to within criteria. No trial investigated HCC-downstaging strategy to expand transplant eligibility.

Methods. This multi-center trial aimed at comparing successfully downstaged HCC followed by transplantation vs. non-transplant therapies. Eligible patients had good liver function (Child-Pugh A-B7), HCC beyond Milan, 5-year estimated post-transplant survival ≥50%, no macrovascular or extrahepatic spread. Only partial-complete responses according to modified-RECIST were randomized 1:1 after 3 months observation period, during which sorafenib was allowed. Co-endpoints were survival and time-to-tumor event. We used Kaplan-Meier method, log-rank test, Cox regression for intention-to-treat analysis. Survival benefit was the difference between groups mean survival time. Organ allocation policy changed over time and limited patients' accrual to 4 years. After 4 additional years conditional power calculation estimated the probability that the final results would be statistically significant in the remaining study, given the data observed. ClinicalTrials.gov NCT01387503.

Findings. 74 patients were enrolled between March 2011 to March 2015: 29 dropped-out pre-randomization. Downstaging median duration was 6 months (1-17). Success-rate was 73%. Progression during observation was 17%. 45 patients were randomized: 23 transplanted vs. 22 controls. Median follow-up was 71 months (IQR 60-85). 5-year overall survival was 77·5% (95%CI 61·9-97·1%) in transplants vs. 31·2% (95%CI: 16·6-58·5%) in controls (Cox hazard ratio [HR] 0·22, 95%CI: 0·08-0·61; p=0·004). 5-year tumor event-free survival was 76·8 (95%CI: 60·8-96·9%) vs. 18·3% (95%CI: 7·1-47·0%) in controls (HR: 0·14, 95%CI: 0·05-0·38; p<0·0001). 5-year survival-benefit favored transplantation by 14·5 months (95%CI: 3·6-25·3; p=0·009). The trial retained a conditional power of 98·6%.

Interpretation. After effective and sustained downstaging of eligible HCCs beyond Milan criteria, liver transplantation is superior to non-transplant therapies. Post-downstaging tumor response should contribute to HCC transplant criteria expansion.

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RESEARCH IN CONTEXT

Evidence before this study.

We searched PubMed for clinical studies published in English between Jan 1, 2000, and July 31, 2019, with the terms “hepatocellular carcinoma” AND “transplantation” AND “selection criteria” AND “tumor downstaging” AND “neoadjuvant therapy” AND “drop-out” AND “survival” OR “recurrence-free survival”. We identified 25 relevant publications. The large majority of these studies are retrospective and often consider bridging together with downstaging treatments. Only 7 studies report dropout rates, while most studies fail to assess outcomes on an intention-to-treat basis. With the exception of two studies targeting tumor response with no pre-determined tumor burden to be reached, the endpoint of all studies using loco-regional neoadjuvant treatments (mainly trans-arterial chemoembolization and ablation) was the conversion of hepatocellular carcinoma (HCC) presenting beyond Milan criteria to within the criteria. That is because “downstaging” within Milan allows liver transplantation listing, although with priorities in organ assignment upon which no consensus exists. Systematic reviews and main guidelines recognize a moderate evidence of effectiveness for HCC downstaging and recommend it in subgroups of patients. Large heterogeneity does exist on downstaging schedules and eligibility criteria. In all studies, outcome measures (i.e. tumor response, transplant-list drop-out and post-transplant recurrence-rate) are related to tumor burden at transplantation.

Two prospective cohort series from the University of California in S. Francisco (UCSF) and the University of Bologna incorporated pre-determined eligibility criteria for HCC downstaging, and added to conversion to within Milan criteria also the endpoint of serum alpha-fetoprotein (AFP) below 400 ng/mL and 1000 ng/mL, respectively, as a surrogate of tumor biology. The standardized UCSF protocol is able to achieve a response rate to downstaging of 65·3%, a drop-out-rate from transplant of 34·7%, a 5-year post-transplant survival and HCC recurrence-free survival of 78% and 91%, respectively.

As frequently observed in liver transplantation, particularly for cancer patients, several limitations in graft allocation policies have so far prevented prospective randomized studies on pre-transplant HCC downstaging.

Added value of this study.

In the present study we confirm a high success-rate of tumor downstaging in patients with HCC beyond Milan criteria bearing no signs of extrahepatic or macrovascular tumor spread. Through the first prospective, randomized, multicenter trial in this context we add the evidence that in these patients the option of liver transplantation achieves optimal post-transplant outcomes (survival and tumor event-free survival) that are superior to any other non-transplant therapy. The benefit in survival at 5-years after liver transplantation in successfully downstaged HCC was about 15 months with respect to controls. Pathology analysis of downstaged HCC conducted in livers obtained at the time of transplant, showed the tendency to tumor re-growth even in case of radiologic complete response. That did not apparently affect survival, as the time-to-transplantation was reasonably contained. Conversely, control patients not receiving liver transplantation after successful tumor downstaging showed long-term outcomes that are comparable to those obtained by loco-regional therapies in patients with intermediate-stage HCC.

Implications of all the available evidence.

Absence of randomized prospective trials has impeded until now a conclusive approach to neoadjuvant, pre-transplant HCC downstaging, specifically when competitive allocation of donated organs to patients with or without liver cancer are considered. This study should contribute to include downstaging and post-downstaging tumor response when proposing HCC transplant criteria expansion. In addition, it may influence priority assignment to HCC patients showing partial or complete tumor response to loco-regional therapies. Utility and benefit of liver transplantation in curing HCC with respect to non-transplant therapies could be increased by more effective downstaging protocols, including pharmacologic therapeutics combined with conventional loco-regional treatments.

INTRODUCTION

Background

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death. The incidence of HCC is increasing in many countries and is currently the main event leading to death in patients with cirrhosis.[1] Multiple treatment modalities are available for patients with HCC[2] and among them liver transplantation (LT) offers the best long-term outcomes when adequate patient selection is provided. Size of the tumor, number of tumor nodules and alpha-fetoprotein (AFP) level are the main drivers for patients' selection. Starting from the Milan criteria (single tumor less than 5 cm, or up to 3 tumors less than 3 cm), patients' eligibility to liver transplantation has evolved and the concept of "expanded criteria" has been proposed in many variants, although without consensus, as prospective studies on expanded limits determined a-priori are lacking.

One of the most attractive strategy in this context is the use of loco-regional treatments to bring patients whose tumor burden is outside pre-established limits to within Milan criteria (MC). In prospective uncontrolled series, tumor downstaging showed to be beneficial, with post-transplant outcome not significantly different from historic patients whose tumors met MC at presentation.[3–6] At present, no trial have investigated tumor downstaging as a tool to expand the conventional criteria for liver transplantation in HCC and to optimize the limited resource of donated organs for both cancer and non-cancer indications.

In addition, following the implementation of treatments against hepatitis C (HCV) with direct antiviral agents (DAA) a universal drop in the number of transplants for HCV-related cirrhosis has occurred,[7,8] with potential relative increase in graft availability for other indications. In this context, less restriction for HCC transplant candidates may be justified for those tumors undergoing successful downstaging, with the aim to reduce at once the risk of pre-transplant progression and post-transplant recurrence.[9]

Objectives

To assess whether liver transplantation provides a survival benefit to cirrhotic patients with HCC beyond Milan criteria who had a demonstrated and sustained tumor response after neoadjuvant loco-regional treatments, we conducted a randomized controlled trial, to test

prospectively the difference in outcomes after liver transplantation vs. continuation of conventional anti-cancer therapies.

METHODS

Trial design

The study, defined as “Expansion of Conventional Criteria for Liver Transplantation in Hepatocellular Carcinoma Through Downstaging (XXL Trial)”, was an investigator driven, open label, multi-center trial with balanced randomization (1:1), comparing successful downstaging of HCC followed by liver transplantation (interventional group) versus successful downstaging followed by non-transplant, best available tumor treatment (control group).

The study, approved by the Institutional Review Board of each participating site and conducted in accordance with the Good Clinical Practices and Declaration of Helsinki, was conducted on patients presenting with an HCC beyond Milan criteria at 9 Italian tertiary care and transplant Centers, with availability of all type of therapies for HCC. All patients provided written informed consent to the protocol and to each administered treatment. The study was registered at ClinicalTrials.gov NCT01387503.

Participants

Trial flow-chart and the summary of patients grouping is presented in Figure 1.

Main tumor-related eligibility criteria were: biopsy proven or presence of radiology hallmarks of HCC according to AASLD[5] or EASL guidelines[10] with a 5-year estimated post-transplant survival of at least 50% at first presentation, according to the Metroticket calculator (www.hcc-olt-metroticket.org)[11]. Only patients with liver function meeting Child-Pugh class A-B7, Eastern Cooperative Oncology Group (ECOG) performance status 0-1 and age >18 years-old were included. Patients with recurrent HCC were allowed to be enrolled if the first occurring and cured HCC was meeting Milan criteria. General contraindications to transplantation and HIV infection were considered exclusion criteria.

Main tumor-related exclusion criteria were: presence of extrahepatic spread at any digital-based imaging (CT-scan or MRI), presence of hepatic hilum lymph nodes with short axis >2 cm and portal vein tumor thrombosis/invasion.

For patients with AFP ≥ 400 ng/mL at the time of enrolment, tumor assessment after downstaging had to include in case of response a parallel percentage decrease of the AFP level. Similarly, in patients with AFP below 400 ng/mL at the time of recruitment, an increase in AFP above 400 ng/ml after downstaging procedures was considered as tumor progression independently of radiological assessment.

Interventions

Tumor downstaging was allowed through an unrestricted use of the approved therapies against HCC, single or multiple, alone or in combinations, including surgical resection, radio-frequency or microwave ablation (RFA), trans-arterial chemoembolization (TACE) and Yttrium-90 selective internal radiotherapy (SIRT). Choice of therapy and schedule of treatment cycles were Center-based, according to local expertise. Each treatment cycle identified a series of single or combined sessions of loco-regional treatments[12] that were considered concluded after multidisciplinary discussion in case of: (i) complete radiological tumor response, (ii) best achievable response, (iii) technical infeasibility to proceed. Response to treatments was evaluated at 30 days intervals by means of CT-scan or MRI, laboratory tests and AFP determination. Treatments could be repeated or combined up to maximum 18 months and were aimed at reaching either complete or best tumor response. Whenever downstaging was considered completed after multidisciplinary board discussion, final response was determined by means of CT-scan or MRI according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. In case of stable disease (SD) or tumor progression (PD) patients were excluded from the study and treated according to Center's policy (i.e.: *downstaging failures* in Fig. 1).

In case of partial response (i.e. reduction of vital, tumor contrast-enhanced areas of at least 50% or decrease in the sum of diameters of viable target lesions of at least 30%) or complete response (CR), patients entered a non-intervention period of at least 3 months, at the end of which sustained response had to be confirmed at CT-scan or MRI. During the non-intervention phase, a non-mandatory treatment of the downstaged HCCs was allowed with sorafenib 400-800 mg daily according to patients' tolerance. Sorafenib withdrawal for toxicity or patients' refusal was not considered an exclusion criteria.

Conversely, patients experiencing tumor progression during the observation phase were excluded from the study and treated as necessary (i.e.: *pre-random drop-outs*). Only patients with a sustained response after the 3 months non-intervention phase were randomized in a 1:1 ratio for LT listing (*treatment group*) or treated with the best alternative strategy at the time of progression (*control group*).

Patients enlisted for liver transplant did not receive specific prioritization with respect to non-cancer candidates. During the study period, donation after brain-death (DBD donors) were used according to Centers policy. Liver transplantation was conducted using conventional or split (adult-pediatric) techniques. Immunosuppression strategy was Center-specific as for various combinations of calcineurin inhibitors (CNI), mycophenolate mofetil (MMF) and steroids. Steroid-free immunosuppression regimen was recommended from the second post-transplant month onward, although not mandatory; mTOR inihibitors were allowed in case of suboptimal renal function.

Patients allocated to non-transplant strategy (controls) continued follow-up until progression; in such instance, loco-regional/surgical/systemic therapies were applied for tumor control, according to multidisciplinary decision.

Blood tests, AFP, and abdominal/thoracic CT-scan or MRI were performed every 3 months in both groups to assess tumor-related events, that were progression (in controls) or recurrence (in the transplant group). Adverse events (AE) were recorded and graded according to the National Cancer Institute Common Toxicity Criteria (CTCAE) version 4.0.

Outcomes

The primary aim of the study was to assess the efficacy of liver transplantation after successful tumor downstaging. That was investigated by using as primary endpoint the overall survival (OS). OS time was calculated as the interval between the randomization date and that of death from any cause, and was censored at the date of last follow-up for patients remaining alive.

Co-endpoint was time to tumoral event (TTE), calculated as the interval between the randomization date and the date of tumor recurrence (for patients with no evidence of residual disease, either because of liver transplantation or complete response after downstaging procedures) or the date of tumor progression otherwise, with censoring at the date of death or last contact for event-free patients.

Sample size

The study was designed to detect a 25% survival increase in the experimental group, from an anticipated 20% at 5 years in the control group (based on published literature and pilot data). Such a difference corresponds to a hazard ratio of 0·50. It was estimated that 87 deaths, requiring the accrual of 130 patients per group over 3 years and a minimum follow up of six months, would yield 90% power to detect the target difference at a 2·5% significance level (1 sided log-rank test). There was no provision for a formal interim analysis.

Randomization

Patients were randomized in a 1:1 ratio to transplant (treatment group) and non-transplant strategy (control group). A block randomization, stratified by center and compliance to sorafenib treatment was applied, separating compliance to sorafenib treatment during the bridging phase into two groups, whether ≤50% or >50% of the standard dosage (800 mg/day) had been administered. In order to guarantee an appropriate balancing between the two groups in each stratum, permuted blocks of size 2 were applied.
The randomization list was generated by OPIS s.r.l. (Desio, MB, Italy) through a SAS® program. The random allocation was centrally managed by means of a validated Interactive Web Response System (IWRS) linked to the eCRF. According to the study protocol, the investigator sent to Coordinating Center an automatic request for randomization through the eCRF. Only in case of approval the IWRS allowed the patient randomization and assigned a randomization number and the treatment group allocation.

Statistical methods

Conventional descriptive statistics were used to describe continuous and categorical variables. Comparisons between treatment groups were performed by means of Chi-square test for categorical variables, and Kruskal-Wallis or Mann-Whitney tests, where appropriate, for continuous variables. Time to tumor event and survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. The treatment hazard ratio and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression.

The survival benefit was the difference between mean survival time in the treatment and control groups by resorting the method based on “pseudo values” calculation and Generalized Estimating Equation (GEE) modeling.[13] An additional analysis exploring the possible modifying effect of response status after downstaging on the benefit of transplantation was performed by fitting GEE multivariable model including treatment arm, response and their interaction as covariates; a significant interaction would indicate a trend in favor of a different post-transplant gain in survival according to response status after downstaging.

Statistical methodology allowing interpretation of data from trials terminated early was applied calculating the conditional power (CP) with the Proschan’s method,[14] and its applications.[15] Conditional power is the probability that the final study results will be statistically significant, given the data observed thus far and specific assumptions about the pattern of the data to be observed in the remainder of the study, by assuming the original design effect.

Statistical analyses were performed according to intent-to-treat population, i.e. including all patients as randomized, and were performed using SAS (SAS Institute Inc., SAS OnlineDoc® 9.4, Cary, NC: SAS Institute Inc.) and R (R version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

This is an investigator-initiated trial designed and coordinated by the Fondazione IRCCS Istituto Nazionale Tumori (INT) of Milan and the University of Milan. The study was endorsed by the Italian Association for the Study of the Liver (AISF), the North Italian Transplant (NITp) and the Italian National Transplant Center (CNT). Funding were obtained with grant of the Ministry of Health (Finalized Research Program in Oncology, RF-INT-2006-394471). No industry support was requested. Study design, data collection, data analysis, data interpretation and writing of the report is on the entire responsibility of the investigators.

RESULTS

From March 1, 2011, to March 31, 2015, 74 patients from 9 participating Centers met the entry criteria and were enrolled in the study protocol. Their baseline characteristics are summarized in Table 1.

Pre-randomization phases: tumor downstaging, observation period and evaluation of sustained response

Tumor downstaging achieved partial or complete response eligible to the subsequent no-treatment (observation) phase in 54 patients (73% success rate). During the subsequent observation phase preceding randomization 30 out of 54 patients received sorafenib throughout, while 24 (44%) had the drug withdrawn due to intolerance or worsened liver function. During the observation period, tumor progression occurred in 9 additional patients (17%) who were excluded from the study. Eventually, 45 patients out of 74 (61%) were eligible to randomization, after achieving a sustained tumor response of at least 3 months.

Overall, the failure rate of the pre-randomization downstaging protocol was 39%. Reasons of failure in the 29 pre-randomization drop-outs are summarized in Figure 1. Overall, tumor progression was the reason for downstaging failure in 22 out of 29 patients (76%) while 7 developed other conditions. Two patients died during downstaging for myocardial infarction (on day 54 after chemoembolization) and liver decompensation (on day 96 after radiofrequency ablation) respectively. None of these two grade-5 events was found directly related to downstaging, while grade 3/4 toxicity attributable to downstaging procedures occurred in 10 patients (13%) who were managed with medical treatments allowing for completion of the scheduled treatment. The complete list of complications observed during downstaging is on supplementary material (Table 1s).

Median duration of HCC downstaging was 6 months (range: 1-17), according to various treatment schedules summarized in Table 2. The observation period lasted for 3 months in all successfully downstaged patients. Overall sustained objective tumor response in the 45 randomized patients was complete or partial in 26 (58%) and 19 (42%) patients, respectively.

When tumor burden was measured as the sum of number of tumor nodules + size of the largest nodule (in cm),[11] the observed responses at the main protocol checkpoints are

summarized in Figure 2. After sustained downstaging (45 patients available) tumor burden decreased from a median of 7·3 (range: 5·5-10·4) at baseline to 0 (range: 0-6·8) ($p<0·0001$) at randomization. A trend toward tumor re-growth was registered then at the time of transplantation (i.e. on explant pathology of the 23 available patients), when tumor burden returned to a median of 4·8 (range: 0-9·6) ($p= 0·158$).

The grade of tumor response was related to the duration of downstaging, as tumor burden underwent a median reduction of 71% in patients who received loco-regional treatments up to 6 months vs. 100% in those who received downstaging treatments for more than 6 months ($p=0·03$, supplementary Figure 1s). However, the duration of tumor downstaging did not correlate with overall survival (supplementary Figure 2s).

Out of the 22 patients excluded from the study due to demonstrated progressive disease, 13 (59%) showed HCC progression during the downstaging phase and 9 (41%) during the observation phase when loco-regional therapies had been considered completed. Overall, 20 (91%) intra- and 2 (9%) extra-hepatic progressions were detected. When comparing 4 HCC progressions in 30 sorafenib-tolerant patients vs. 5 out of 24 in sorafenib-intolerant/withdrawals, tumor progression after downstaging did not appear to be significantly related to the use of sorafenib during the observation period ($p=0·46$).

Post-randomization phases: patient outcomes

As shown in Table 2, baseline characteristics of the 45 patients randomized to receive liver transplant (23 patients: transplant-group) vs. non-transplant treatment (22 patients: no-transplant controls) were similar. The most common cause of liver cirrhosis in both groups was hepatitis-C (62%) and 89% of the patients were Child-Pugh A at the time of randomization. With respect to transplant criteria at the time of randomization, 9% of transplant-group vs. 0% of controls had HCC beyond Milan Criteria, whilst all cases met UCSF, Up-to-7, French model and HALT-HCC low-risk score requirements, as shown in Table 2. Even if HCC stage was similar in both groups, residual tumor burden was higher in the transplant group ($p=0·03$).

At data cutoff on July 31, 2019 median follow-up for the randomized population was 71 months (IQR 60-85). Median time from randomization to transplant was 3 months (IQR 2-5). Two out of the 23 patients randomized to transplant eventually refused the operation: they both progressed at 5 and 12 months and died at 17 and 20 months, respectively, after

being treated with chemoembolization. They were censored in the intervention group according to the intention-to-treat principle.

Median donor age was 69 years (range: 18-84); whole liver grafts were used in 19 LT (90%) while two patients (10%) were transplanted using split livers. Median D-MELD (the product of donor age and preoperative recipient MELD score) was 594 (range: 162-1764) and macrosteatosis ≥10% was present in 8 out of 22 donated livers.

As direct antiviral agents (DAA) against HCV were introduced in 2014, only 2 patients in the transplant group (9%) and 2 patients in the control group (9%) received antiviral treatment (p=0·96). No irreversible deterioration of hepatic function was observed in either group due to recurrent HCV; only one other patient survived re-transplantation at 22 months because of late graft malfunction due to biliary complications and recurrent viral hepatitis.

Death occurred in 5 transplant patients and 16 controls. Tumor progression was the main cause of death in both groups: cancer-related deaths were 60% vs. 87·5% in the transplant and non-transplant groups, respectively (p= 0·17). In the transplant group, 2 patients died within 30 days for non-cancer-related events (at 10 and 20 days for myocardial infarction and multiorgan failure, respectively), while the other 3 deaths were caused by HCC recurrence (or progression, in a patient who refused liver transplantation). Out of 16 deaths in the control group, 14 were caused by tumor progression and 2 to liver failure unrelated to cancer progression.

Five out of 23 patients in the liver transplant group had HCC recurrence, while 18 out of 22 controls had HCC progression. Out of the 4 controls whose disease did not recur following downstaging treatment, 2 died from other causes at 11 and 24 months while 2 achieved a prolonged complete response after successful tumor ablation and liver resection.

Figure 3 shows the Kaplan-Meier curves of overall survival (panel A) and time-to-tumor events (TTE) (panel B) according to treatment arm. Five-year overall survival was 77·5% (95%CI: 61·9-97·1%) vs. 31·2% (95%CI: 16·6-58·5%) in transplant vs. non-transplant group, respectively (Figure 3A: HR: 0·22, 95%CI: 0·08-0·61, p=0·004). Median survival was not reached in transplant patients, while it was 30·5 months in the non-transplant group. Liver transplantation demonstrated a protective effect against the risk of HCC recurrence (Figure 3B: HR: 0·14, 95%CI: 0·05-0·38, p<0·0001), since transplant patients had a significant improvement of TTE compared to controls (median not reached vs. 13 months, respectively) and a 5-year tumor event-free survival of 76·8% (95%CI: 60·8-96·9%) vs. 18·3% (95%CI: 7·1-47%).

Survival benefit

Overall survival benefit of liver transplantation at 60 months was 14.5 months (95%CI 3·6-25·3; p=0·009) with some differences according to tumor response. As noted in Table 3 (multivariable model), a trend in favor of a higher post-LT gain in survival was observed in HCC with partial response after downstaging (26·5 months; 95%CI: 13·6-39·3) with respect to complete response (9·9 months; 95%CI: -5·5-25·3). Such consistent difference of nearly 17 months in survival benefit according to response status was not statistically significant at the 5% level (p value for interaction treatment by response=0·105). Median wait-time to transplantation was 3 months and did not differ among complete vs. partial response groups (range: 1-6 and 1-10, respectively; p=0·28).

Conditional Power

The original design (see Statistical methods above) established that an overall number of 87 deaths would have allowed a HR=0.5 with a 90% power. After patients' accrual was started, a national program for expansion of donor pool including donation after cardiac death and revision of transplant priorities for HCC[16] was implemented. These major changes, not considered in the study design, forced the trial monitoring committee to recommend to close the study at 45 randomized patients and to test the results after four additional years of follow-up, adding conditional power analysis to the scrutinized data. According to the study design input and assuming that the consistent transplant effect (HR=0·22) actually observed in the cohort of 45 enrolled patients (having generated 21 deaths) is attenuated up to the planned HR=0·50 in the hypothetical future cohort of additional 215 patients (that would have generated 65 deaths to reach the planned number of 86 deaths), the estimation of the conditional power of the trial is 98·6%.

DISCUSSION

This is the first prospective, randomized, controlled trial exploring the benefit of liver transplantation in patients who achieved successful and sustained downstaging of HCCs exceeding Milan criteria. The study demonstrates significantly longer patient survival and less tumoral events in patients receiving liver transplantation with respect to conventional non-transplant therapies. In fact, median overall survival and tumoral event-free survival were not reached in transplanted patients vs. 30·5 and 13 months, respectively, in controls. Groups comparison (Figure 3) assigned a significant overall survival advantage to liver transplant patients over no-transplant treatments (log-rank test p=0·002, with Cox model HR=4·50 in patients not-receiving transplant with respect to transplant ones) and also in time-to-tumor events (p<0·0001; HR= 7·19). At the 5-year interval, liver transplantation in successfully downstaged HCCs achieved a remarkable gain in mean survival of about 15 months with respect to non-transplant therapies (p=0·009).

These results provide additional evidence to previous observations showing comparable post-transplant outcomes in HCC beyond Milan criteria undergoing downstaging with respect to HCC within Milan criteria at inception.[3,4,17–22] In addition (Table 1), the study demonstrates that neoadjuvant loco-regional therapies aimed at reduction of intra-hepatic tumor load may be proposed to any patient beyond Milan criteria with an expected post-transplant survival of at least 50% at metroticket calculator.[11]

Randomized control trials testing transplant intervention are very difficult to conduct and this study is not an exception. Due to concurrent national changes in graft allocation policy and HCC priorities, not predictable in the study design,[16] the trial suffered from limitations in patients recruitment forcing the study to be concluded ahead of time. To overcome such insurmountable limit in recruitment while retaining information derived from an unprecedented trial on HCC beyond Milan criteria, the Study Monitoring Committee recommended to close the trial at 45 patients and to prolong follow-up. The conditional power analysis showed that, although an attenuation of the current effect of liver transplant intervention was observed (from the HR=0·22 currently estimated on 45 patients to the design-fixed HR=0·50 for additional hypothetical 215 patients), there are 98·6% chances that the statistical significance in favor of liver transplant intervention would persist.

This was in fact a multi-phase study (Figure 1) intended to optimize the use of cadaveric grafts in patients with HCC beyond conventional criteria while remaining in the interest of liver transplantation.

To secure homogeneity of the various downstaging protocols (Table 2), two requirements were determined at the beginning and end of the process. First, no pre-defined upper limit for implementing downstaging was set, with the single exception of tumor macroscopic vascular invasion. Notably, the upper limit for downstaging eligibility was determined on prediction of outcome (i.e. at least 50% survival at 5-year by means of Metroticket calculator[11]), and not on pre-determined cutoff in size and number of tumor nodules at presentation.[22] Secondly, when the process was concluded – namely, after assessment of a successful downstaging – an observation period of 3 months before enlisting allowed the selection of favorable tumor biology[23] (i.e.: 17% of the successfully downstaged patients dropped-out during the observation phase). Such precaution avoided early post-transplant recurrences, as observed in patients beyond criteria receiving living donation[24] or being transplanted in short-waiting time regions.[25]

Similar to the University of San Francisco experience,[9] our downstaging-aimed therapies achieved a response rate of 73%, with 41% complete responses, which confirms the efficacy of neoadjuvant protocols despite different schedules. Less than one fifth of the control patients (4 patients: 17%) did not show recurrence after complete downstaging and spared transplantation. Two of them died from other causes within 2 years, possibly preventing the occurrence of a late recurrence, while the other 2 were successfully downstaged with ablation and liver resection, confirming that trans-arterial chemoembolization rarely achieve cure in HCC, despite achievement of radiological complete response.

Patient outcomes registered in the control group (31·2% and 18·3% survival and event-free survival at 5-years, respectively) were similar to those expected following modern loco-regional treatments for intermediate stage HCC (BCLC-B). This speaks in favor of optimal downstaging treatments for a series presenting with a median of 4 nodules of 42 mm in size (Table 1).

The potential of complete tumor downstaging to eradicate HCC and spare transplantation in a subset of patients, emphasizes the role of response to neoadjuvant treatment as a key determinant of HCC management[3,26]. Utility and benefit of liver transplantation with respect

to non-transplant therapies in curing HCC could be increased by more effective downstaging protocols combining efficacious pharmacologic therapeutics with conventional loco-regional treatments.

Interestingly, patients with partial tumor responses who underwent transplant (Table 3) nearly tripled their post-transplant survival gain (26·5 months) with respect to patients showing complete responses (9·9 months). This supports the current tendency to assign priority to HCC patients in the transplant wait-list based on tumor re-assessment after neoadjuvant therapies rather that at presentation,[26–28] also considering the time-related tendency of HCC to progress even after complete radiologic response (Figure 2). Based on the presented results, the proposal to prioritize partially responding HCC still meeting transplant criteria despite optimal treatment delivery, receives a support that is worth discussion within organ allocation Agencies.

Predictability of tumor downstaging success in patients with HCC beyond Milan was beyond the scope of the study. This would require specific protocols, particularly in case of HCV-related liver disease, which affected more than 60% of our cirrhotic patients. Although the future of liver transplantation for HCC will predictably be HCV-free,[7,8] the aim of tumor downstaging in patients with well-compensated liver function will persist, regardless of the etiology of cirrhosis. Notably, NASH/NAFLD-related cirrhotics present more frequently with HCCs beyond Milan criteria,[29] therefore with tumors more likely to be downstaged with respect to those virus-related.

The downstaged HCC population is, by definition, a fraction of the total amount of HCCs with potential indication to transplantation, with a demonstrated correlation between tumor response to neoadjuvant therapies and HCC biological behavior.[30] Even though pathology features, size and number of nodules in downstaged HCCs may be similar to patients who are T2 at presentation (i.e. within Milan criteria), this study shows that downstaged HCCs tend to exhibit an accelerated time-dependent risk of progression (Figure 2). More detailed studies are needed to assess pathology/radiology correlation in downstaged HCC, as well as genetic and microenviromental conditions identifying responding patients with different probabilities of cancer progression. If the granularity of treatment response to downstaging will be captured in a more standardized manner, downstaging strategies may become the best tool for expanding HCC criteria according to the transplant benefit principle.[26]

Although pre-surgical treatment per-se may not necessarily change the outcome of liver transplant for HCCs beyond Milan criteria, the large majority of the current cancer indications is represented by downstaged tumors. In such perspective, the results of this trial confirms that liver transplantation after effective and sustained downstaging of HCCs beyond Milan criteria is superior to any other currently available non-transplant therapy.
Even though limitations in the analyzed sample size and heterogeneities of the applied downstaging protocols may limit the strength of this conclusion, the practice of neoadjuvant therapies in liver transplantation for HCC may become, as in other cancers, a standard that favors patient selection, waiting list management and post-operative survival.

Contributors

VM was the chief investigator of the trial. DC, MB, MDDB, RM and CS were involved in conception, study design and data analysis. All authors have contributed to a greater or lesser extent to the recruitment of patients, data collection and results interpretation. VM, CS and RM were responsible for data analysis and interpretation. VM, SB, MB and CS were responsible for the preparation and writing of the manuscript. All authors contributed to the manuscript and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank all the participating groups, their coordinating teams, principal investigators, staff, nurses clinical research teams, and the patients who participated in the trial, especially when allocated to groups different from their expectations.
The XXL trial was possible thanks to a concerted effort of the hepato-oncology Italian community, the support of National and Regional procurement and allocation Agencies. In particular Alessandro Nanni Costa, Giuseppe Piccolo, Tullia De Feo, Massimo Cardillo and several members of AISF, SITO, NITp and CNT are gratefully acknowledged. Also, we thank the members of the Ethical Committees examining the study protocol for thorough discussion and productive advices.

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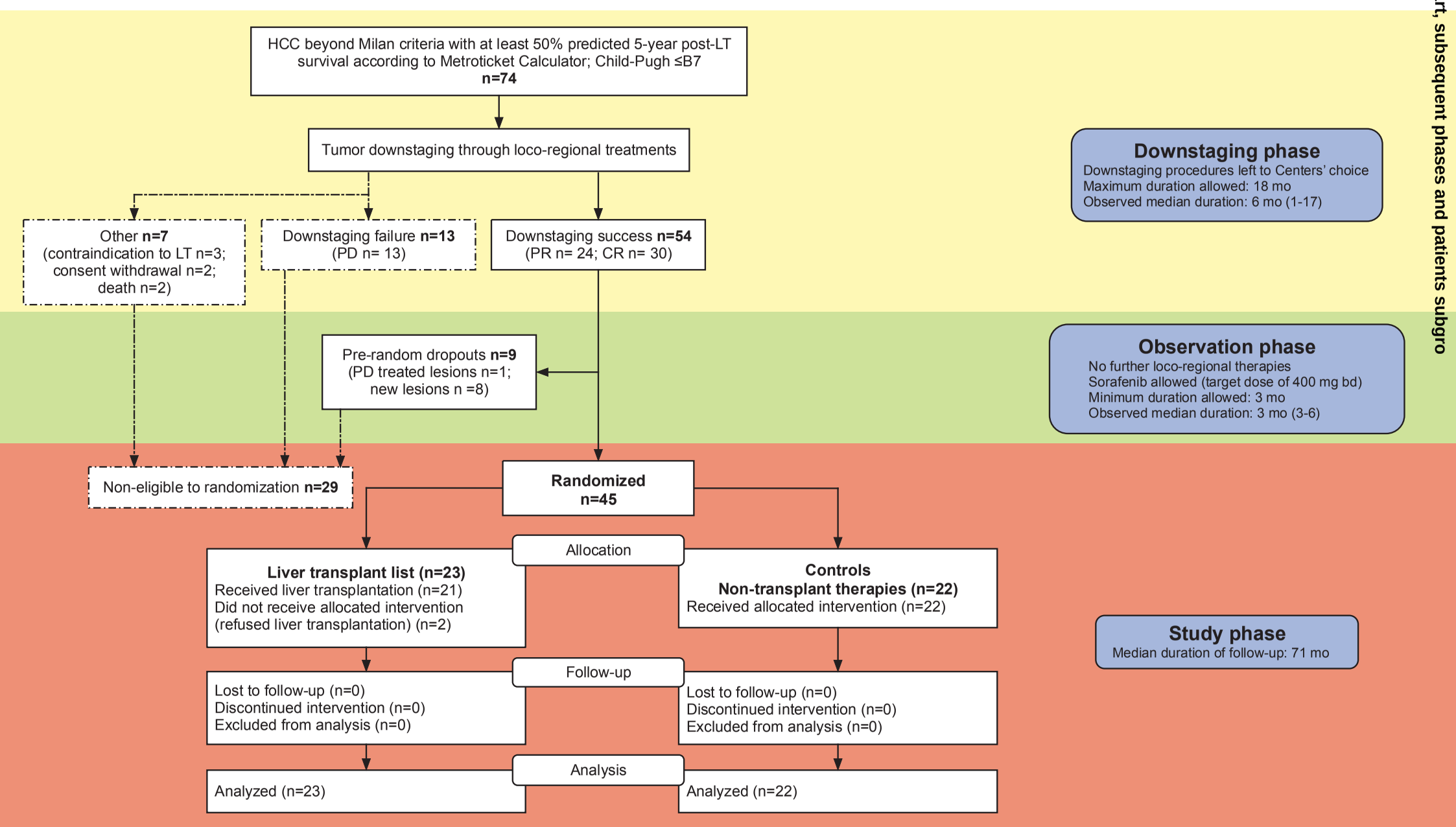
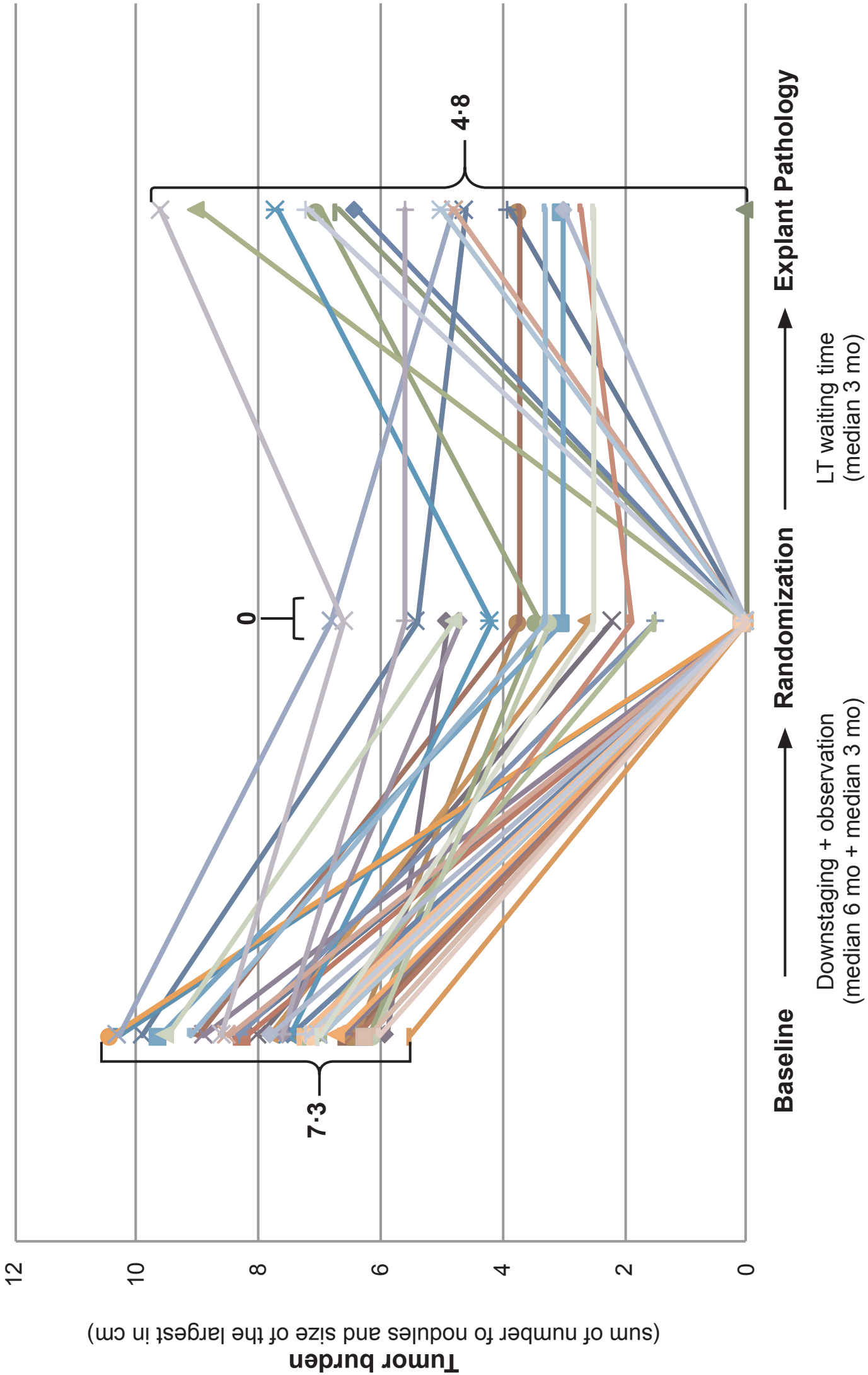


Figure 1. Study flowchart, subsequent phases and patients subgro

Figure 2. Tumor burden (single patient value and median) at prot



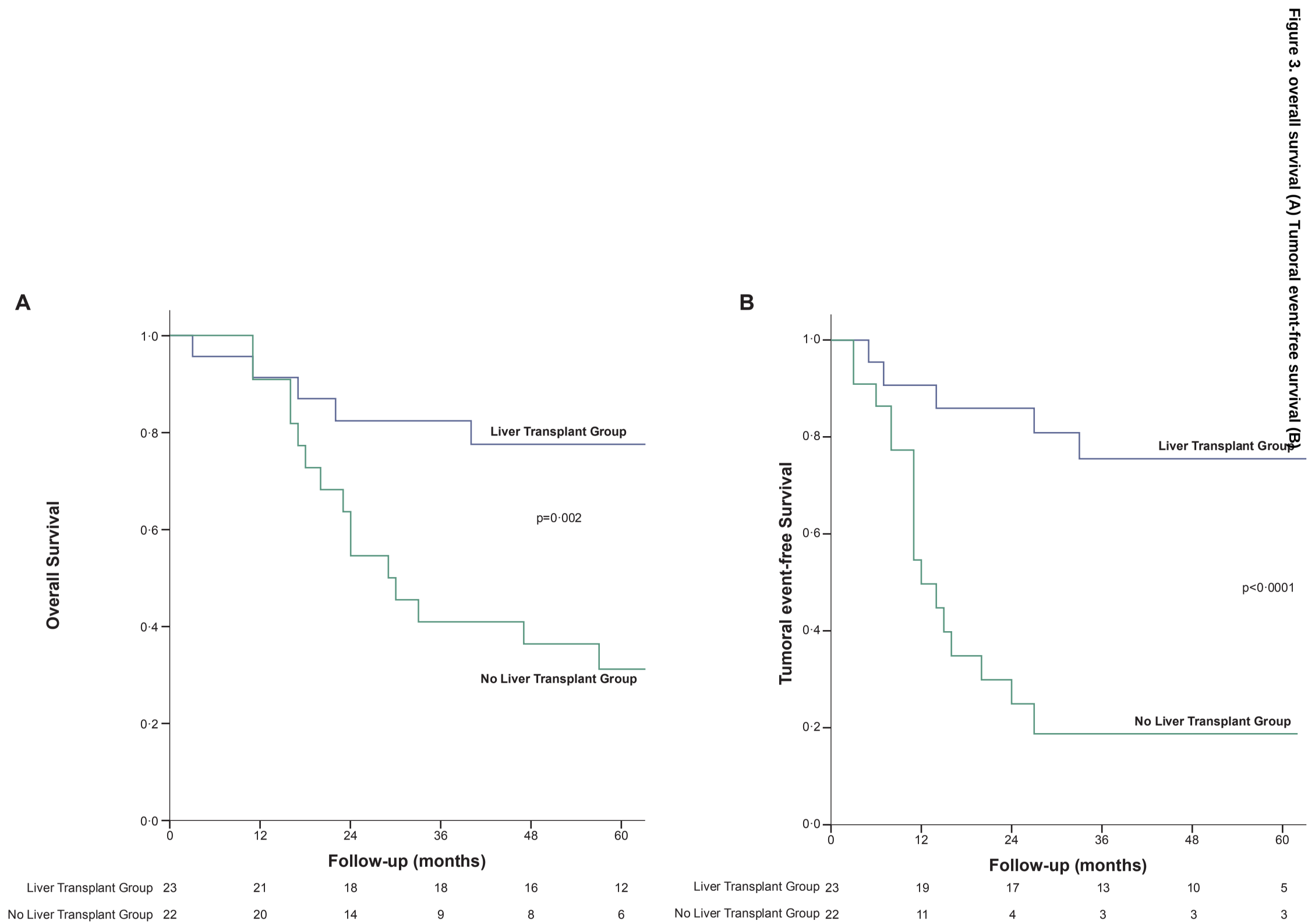


Figure 3. overall survival (A) Tumoral event-free survival (B)

Table 1. Baseline characteristics of the recruited population of 74 patients with HCC beyond Milan Criteria meeting the study inclusion criteria for downstaging.

Characteristics	Recruited population (n=74)
Age (years)	56 (46-68)
Sex	
Male	69 (93%)
Female	5 (7%)
BMI	26 (19-33)
Etiology of liver disease	
HCV	49 (66%)
HBV	12 (16%)
Alcohol/Metabolic	11 (15%)
Other	2 (3%)
MELD score	8 (6-17)
Child-Pugh class	
A	65 (88%)
B	9 (12%)
Tumor presentation	
First diagnosis	64 (86%)
Recurrent HCC	10 (14%)
Number of nodules	3·5 (1-9)
Largest tumor diameter (mm)	41·5 (12-80)
Sum of the diameters of viable tumor (mm)	75·5 (13-155)
Tumor burden*	7·3 (5·2-13)
AFP (ng/ml)	13 (1-4539)
BCLC stage	
A	11(15%)
B	63 (85%)
C	0
Milan criteria	
IN	0 (0%)
OUT	74 (100%)
Up-to-7 criteria	
IN	33 (45%)
OUT	41 (55%)
UCSF criteria	
IN	33 (45%)
OUT	41 (55%)
French model	
Low risk (≤2 points)	36 (49%)
High risk (>2points)	38 (51%)
HALT-HCC score	
<17	0 (0%)
≥17	0 (0%)

Data are expressed as the median (range) or absolute number (%) as appropriate.

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, Model for End Stage Liver Disease; AFP, alphafetoprotein; BCLC, Barcelona Clinic Liver Cancer; UCSF, University of California San Francisco; HALT-HCC, Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma

*Tumor burden is calculated as the sum of the number of nodules and the size in cm of the largest nodule

Table 2. Detailed description of 45 patients with HCC beyond Milan Criteria in which successful and sustained HCC downstaging was achieved

	At Baseline				At Randomization			
	Study population (n=45)	**LT (n=23)**	**no LT (n=22)**	**p**	**Study population (n=45)**	**LT (n=23)**	**no LT (n=22)**	**p**
Age	56 (46-66)	55 (47-65)	59 (46-66)	0·38				
BMI	26 (20-33)	26·7(23-33)	25·5 (20-30)	0·08				
Etiology of liver disease				0·2				
HCV	28 (62%)	11 (48%)	17 (77%)					
HBV	7 (16%)	5 (22%)	2 (9%)					
Alcohol/Metabolic	8 (18%)	6 (26%)	2 (9%)					
Other	2 (4%)	1 (4%)	1 (5%)					
Disease presentation				0·07				
First diagnosis	39 (87%)	22 (96%)	17 (77%)					
Recurrent HCC	6 (13%)	1 (4%)	5 (23%)					
Downstaging procedures								
TACE only	22 (49%)	12 (52%)	10 (45%)	0·65				
RFA only	4 (9%)	2 (9%)	2 (9%)	0·96				
TARE only	1 (2%)	1 (4%)	0	0·32				
Surgery only	3 (7%)	2 (9%)	1 (5%)	0·97				
Combination	15 (33%)	6 (26%)	9 (41%)	0·43				
TACE (at least one)	35 (78%)	17 (74%)	18 (82%)	0·52				
RFA (at least one)	17 (38%)	8 (35%)	9 (41%)	0·67				
TARE (at least one)	2 (5%)	1 (4%)	1 (5%)	0·98				
Surgical resection (at least one)	7 (16%)	4 (17%)	3 (14%)	0·95				
Number of treatment sessions				0·21				
1	18 (40%)	10 (43%)	8 (36%)					
2	13 (29%)	8 (35%)	5 (23%)					
3	7 (16%)	4 (17%)	3 (14%)					
>3	7 (16%)	1 (4%)	6 (27%)					
MELD score	8 (6-14)	8 (6-13)	7 (6-14)	0·37	8 (6-18)	9 (6-18)	6 (0-257)	0·82
Child-Pugh class				0·6				0·37
A	40 (89%)	21 (91%)	19 (86%)		39 (87%)	19 (83%)	20 (91%)	
B	5 (11%)	2 (9%)	3 (14%)		4 (9%)	2 (9%)	2 (9%)	
C	0 (0%)	0 (0%)	0 (0%)		2 (4%)	2 (9%)	0 (0%)	
Number of nodules	3 (1-6)	3 (1-5)	3·5 (1-6)	0·9	0 (0-3)	1 (0-3)	0 (0-3)	0·07
Largest tumor diameter (mm)	46 (13-80)	50 (20-80)	40 (13-62)	0·08	0 (0-46)	10 (0-46)	0 (0-27)	**0·02**
Sum of the diameters of viable tumor (mm)	77 (13-155)	79 (62-116)	71 (13-155)	0·27	0 (0-63)	12 (0-63)	0 (0-41)	**0·03**
Tumor burden*	7·3 (5·5-10·4)	7·5 (6·2-10·3)	7 (5·5-10·4)	0·07	0 (0-6·8)	2·2 (0-6·8)	0 (0-4·9)	**0·03**
AFP (ng/ml)	10 (1-4539)	12 (2-1750)	8·5 (1-4539)	0·58	6 (0-257)	6 (0-257)	7 (2-114)	0·67
Tumor response after downstaging (at radiology)								
CR					26 (58%)	10 (57%)	13 (59%)	
PR					19 (42%)	13 (43%)	9 (41%)	
Milan Criteria								
IN	0 (0%)	0 (0%)	0 (0%)		43 (96%)	21 (91%)	22 (100%)	
OUT	45 (100%)	23 (100%)	22 (100%)		2 (4%)	2 (9%)	0 (0%)	
Up-to-7 criteria				0·1				
IN	19 (42%)	7 (30%)	12 (55%)		45 (100%)	23 (100%)	22 (100%)	
OUT	26 (58%)	16 (70%)	10 (45%)		0 (0%)	0 (0%)	0 (0%)	
UCSF criteria				0·64				
IN	25 (55%)	12 (52%)	13 (59%)		45 (100%)	23 (100%)	22 (100%)	
OUT	20 (45%)	11 (48%)	9 (41%)		0 (0%)	0 (0%)	0 (0%)	
French model				0·66				
Low risk (≤2 points)	21 (47%)	10 (43%)	11 (50%)		45 (100%)	23 (100%)	22 (100%)	
High risk (>2points)	24(53%)	13(57%)	11 (50%)		0 (0%)	0 (0%)	0 (0%)	
HALT-HCC score								
<17	45(100%)	23 (100%)	22 (100%)		45 (100%)	23 (100%)	22 (100%)	
≥ 17	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	

Data are expressed as the median (range) or absolute number (%), as appropriate. Abbreviations: MELD, Model for End Stage Liver Disease; AFP, alphafetoprotein; BCLC, Barcelona Clinic LIver Cancer; UCSF, University of California San Francisco; HALT-HCC, Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma

*Tumor burden is calculated as the sum of the number of nodules and the size in cm of the largest nodule.

Table 3. Survival benefit of liver transplantation at 5 years in patients with HCC beyond Milan criteria with successful and sustained downstaging.

	Univariable model		**Multivariable model with interaction treatment by response**	
	D-MST (95% CI) (months)	p value	D-MST (95% CI) (months)	p value
At 5 years				
LT vs. no LT	14·5 (3·6-25·3)	**0·009**		0·105
CR	--	**--**	9·9 (-5·5 - 25·3)	
PR	--	**--**	26·5 (13·6 – 39·3)	

D-MST: difference in mean survival time expressed in months; LT: liver transplantation; no LT: non-transplantation therapies; CR, complete response; PR, partial response;

Supplementary table and figures

Click here to download Necessary Additional Data: Supplementary Tables and figures.pdf

CLINICAL PROTOCOL INT 80/09 SYNOPSIS – Version 2.0

TRIAL TITLE

Controlled Expansion of Conventional Criteria for Liver Transplantation in Hepatocellular Carcinoma Through Downstaging Procedures: a Randomized Trial

ABBREVIATION

XXL-Trial

TYPE OF PROTOCOL

Phase IIb-III, open-label randomized, multicenter, prospective study

TRIAL SITES, COORDINATION AND PRINCIPAL INVESTIGATORS

This is a national and international, multi-center collaborative study conducted in referring Liver Transplant Centers to be approved by each Institution IRB and/or Ethical Committee.

Principal Investigator: Vincenzo Mazzaferro (INT-Milan)
Co-Principal Investigators: Mario Scalamogna (NITp-Milan) and Medical and Surgical Directors of each participating Center
Study Coordinators: Sherrie Bhoori, Tullia De Feo, Carlo Sposito
Independent centralized Radiology review Committee (IRC): Riccardo Lencioni (coordinator)
Center Investigators: to be determined
Data storage and management: Tiziana Camerini, Maria Flores and OPIS (On Pharmaceutical Industry Service) S.r.l., Milano, Italy
Statisticians: Luigi Mariani, Rosalba Miceli
Scientific Secretariat: Daniela Guarneri, Barbara Formisano
Sponsor: This is an investigator-initiated trial (IIT) designed and conducted by the Clinical Investigators of the Fondazione Istituto Nazionale Tumori (National Cancer Institute of Milan). The study has been endorsed by the following Societies: AISF (Associazione Italiana Studio Fegato), NITp (Nord Italia Transplant project), Centro Nazionale Trapianti, Ministero della Salute and Regione Basilicata.
Funding has been obtained by grant application to public and non-profit Institutions (Ministery of Health and Basilicata Region). No industry support has been requested to support the study.

STUDY OBJECTIVES

The study is aimed at extending the chance of liver transplantation to those patients with hepatocellular carcinoma (HCC) exceeding conventional Milan criteria who achieved a sustained tumor response after downstaging procedures.
The general design consists of a phase IIb -III randomized prospective trial comparing downstaging + transplantation strategy *(experimental group)* vs. downstaging + non-transplantation conventional best care strategy *(control group).*
Downstaging schedule (series of consecutive treatments) is unrestricted as part of each Center's policy as well as patient referral, which will be maintained within the chosen transplant Center.

This trial is designed in two phases:
- Phase IIb: (exploratory phase) aimed at determining the benefit of transplantation in delaying tumor recurrence. This will be determined through TTTE (time to tumor event) that is TTR (time-to-recurrence) or TTP (time-to-progression) according to group assignment.
- Phase III: (confirmatory phase) aimed at determining whether the above benefit translates into prolonged overall survival.

Primary end point is different according to the considered phase of the study:

- **phase IIb**: TTE (time to tumoral event): which will be TTR (time-to-recurrence) for the study group (Group 1) and TTP (time-to-progression, Group 2) for the control group. More specifically TTE will be calculated as the interval between the randomization date and the date of tumour recurrence for tumor-free patients (either because of liver transplantation or complete response after downstaging procedures) or the date of tumour progression otherwise, with censoring at the date of last contact for event-free patients.
- **phase III**: Overall patient Survival (OS).

Secondary end points are:

- Transplant vs. non transplant cost-benefit analysis
- Efficacy analysis on downstaging therapies and on prevention of drop-outs from the transplant waiting list
- Radiology/pathology correlation on efficacy of downstaging treatments in achieving tumor response, as a basis for possible validation of modified RECIST criteria.

- Assessment of whether the Metroticket prognostication model is suitable for prediction in this study population based on the original tumour characteristics (size, number, vascular invasion), and whether model performance may be improved by the inclusion of additional biological variables (grading, microsatellites, gene signature of mVI).

STUDY POPULATION

Patients with a confirmed radiological diagnosis of HCC in cirrhosis (Child-Pugh A-B7), exceeding Milan Criteria, no extra-hepatic spread (EHS) and with at least >50% 5-yr estimation of survival after liver transplantation, according to the Metroticket Calculator (*www.hcc-olt-metroticket.org/*).

Inclusion Criteria

Patients between 18 and 65 years of age, regardless of race or sex, may be enrolled if they meet the following eligibility criteria at entry:

- Presence of cirrhosis (clinical or histological) of any etiology:
    - Child-Pugh class A-B7
    - ECOG Performance Status 0-1
    - Confirmed diagnosis of HCC according to AASLD non invasive criteria
- HCC exceeding Milan Criteria with a 5-yr estimated survival >50% after transplantation according to the Metroticket Calculator: vascular invasion unknown, except for G3 tumors (if biopsied) or presence of PVT type 1 which should be considered as vascular invasion present in the metroticket prognostication algorithm (*www.hcc-olt-metroticket.org/*).
- Previous diagnosis and treatments:
    - First diagnosis of previously untreated HCC in cirrhosis of any etiology maximum 6 months prior to first downstaging treatment.
    - Patients who initiated treatments for an HCC complying with the aforementioned limitations although at < 18 months before enrolment either at the recruiting Center or elsewhere.

        Note 1. patients who have already achieved complete response (CR) as a consequence of a downstaging strategy performed before enrolment, although within the timeframe assigned for enrolment, will NOT be eligible for the study: see "Exclusion Criteria".

        Note 2. patients who initiated treatments before enrolment are eligible for the study even if presenting with a progression of disease, providing that the initial presentation of HCC complies with the inclusion criteria (HCC exceeding Milan Criteria with a 5-yr estimated survival >50% after transplantation according to the Metroticket Calculator).
- Recurrent HCC after curative treatments (namely surgical resection and radiofrequency ablation): patients that present with a new occurrence of HCC, providing the radiological demonstration of a

complete tumor response after the previous curative treatment. Recurrent HCCs after locoregional treatments other than radiofrequency ablation and surgical resection are not considered eligible for the present study.

- *Late recurrent HCC*, namely patients with at least two years time-span from the end of previous curative treatments, providing the demonstration that the recurrent intrahepatic tumor exceeds Milan Criteria with a 5-yr estimated survival >50% after transplantation according to the Metroticket Calculator (*www.hcc-olt-metroticket.org/*)
- *Early recurrent HCC*, namely with less than two years time-span from the end of previous curative treatments, in the particular case of:
  - HCC within Milan at the time of first treatment, while exceeding Milan at the cumulative tumor staging (i.e. the HCC stage resulting from the sum of first occurring + recurrent HCC)
  - Survival prediction above 50% at 5 yrs, loading in the Metroticket calculator tumor characteristics of the cumulative tumor staging (*www.hcc-olt-metroticket.org/*).
  - Patients with early/late recurrence eligible for the study according to previous points should comply with the time frame reported at paragraph on Timing and scheduled treatment with respect to checkpoints

- Signed informed consent for the present clinical study. Centralized biopsy studies (gene signature for mVI and other determinations are optional) should be presented as different studies with dedicated informed consent for investigational markers or biopsy-derived prognostic factors
- Women of child bearing potential with a negative serum pregnancy test performed before enrolment
- Absence of general contraindications to Sorafenib treatment

Exclusion Criteria

- Presence of extra-hepatic spread (EHS) defined as:
  - Organ involvement other than the liver
  - Hepatic hilum lymphnodes with short axis > 2 cm
- Presence of macrovascular invasion defined as:
  - PVT with invasion of main trunk, or left/right branches (type 2-4 according to Shi et al. 2010), except for PVT type 1. Segmental branch PVT can be considered for downstaging protocol in those patients with a prediction of survival above 50% at 5 yrs according to Metroticket calculator and considering segmental PVT as a surrogate of mVI- present in

the calculator data entry. (*www.hcc-olt-metroticket.org/*). In addition AFP level has to be ≤ 400 ng/mL

- Invasion of vena cava or main trunks of hepatic veins

- Patients who have already achieved a PR or CR after downstaging completed before enrolment, although within the timeframe assigned for enrolment will NOT be eligible for the study.
- Sorafenib treatment if started and maintained for > 2 months before enrolment
- Previous or concurrent cancer that is distinct in primary site or histology from HCC, except cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors (Ta, Tis, T1).
- Other cancers curatively treated < 5 years from study entry
- Active intra-venous or alcohol abusers (patients may be eligible if abstention > 6 months is demonstrated)
- HIV infection
- HBV-DNA > 20.000 UI/mL
- Active clinically serious infections, except for HCV and HBV infections
- History of cardiac disease:
    - Congestive heart failure > New York Heart Association (NYHA) Class II
    - Active coronary artery disease (CAD) (myocardial infarction more than 6 months prior to study entry is allowed)
    - Cardiac arrhythmias (> Grade 2 NCI-CTCAE Version 4.0) which are poorly controlled with anti-arrhythmic therapy or requiring pace-maker
    - Uncontrolled hypertension
- Severe pulmonary hypertension, with PAM ≥ 45mmHg, not treatable with medical therapy
- Hepatopulmonary diasease with SO2<50%
- Psychiatric disorders, if not adequately supported by medical treatment and family
- Severe neurological disease (Alzheimer disease etc.)
- History of severe allergy or intolerance to contrast agents, narcotics, sedatives or atropine that cannot be managed medically
- Pregnant or breast-feeding subjects
- Patients with a life expectancy of less than 3 months due to HCC or less than 6 months due to any other disease

INVESTIGATIONAL PLAN AND STUDY FLOWCHART

Study flowchart is depicted in Figure 1 and is analyzed in detail as follows:

- **Inclusion of patients (Checkpoint-1)**

  - Assess medical history of patient

  - Physical examination

  - Evaluate performance status, liver status and complete pretransplant blood work-out (including hepatitis viral markers)

  - Check indications/contraindications to liver transplantation

  - Undergo abdominal and chest CT / MRI scan in order to confirm tumor location within the liver and exclude extra-hepatic disease; patient stratification

  - Assessment of 5-yr estimation of survival with the Metroticket Calculator, freely available at the following address *www.hcc-olt-metroticket.org/*

  - Signature of informed consent

  - Biopsy of the largest lesion and non-tumoral liver (optional)

- **Downstaging procedures**

Downstaging procedures should be performed according to Center's policies. Length and intensity of downstaging is center specific and not centrally pre-determined but should be inferior to 18 months.

- **Assessment of downstaging efficacy (Checkpoint -2)**

When end of treatment has been established, mRECIST criteria according to viable tumor diameter is assessed:

  - If PR or CR is assessed patients should discontinue loco-regional downstaging treatment and pass to the bridging period (sorafenib treatment for at least 3 months)

  - If SD or PD is assessed patients will not be admitted to the study and treated according to Center's policy. Such patients will be followed up until death.

- **Bridging period (timeframe between Checkpoint-2 and Checkpoint-3)**

Patients that achieved PR or CR after downstaging will receive systemic therapy with sorafenib for three months.

- **Assessment of sustained response (Checkpoint-3)**

After three months radiological response will be assessed:

- if SD is confirmed patients will be suitable for randomization

- if PD is assessed patients will not be admitted to the study and will be treated according to Center's policy. Such patients will be followed up until death.

- **Randomization**

Administration of sorafenib for the three-months bridging phase after successful downstaging is aimed at sustain the response (PR, CR) achieved with downstaging. Only patients with a sustained response will be randomized in a 1:1 ratio, using computer generated list stratified by Center and by compliance to sorafenib treatment.

In fact, randomization will be stratified according to compliance to sorafenib treatment during the bridging phase in two groups whether ≤50% or > 50% of the standard dosage (800 mg/day) has been administered. Stratification is aimed at balancing pharmacological intervention (sorafenib) in the neoadjuvant pre-transplant setting.

1) The **experimental treatment group** will be enlisted for transplantation with no differences in initial prioritization criteria with respect to other transplant indications (see paragraph on: "Timing and Scheduled Treatment" for the protocol requirement of performing transplantation within 8 months from randomization - failure in complying with the time from randomization to transplant will be considered as major protocol violation and the patients will drop out from the study).

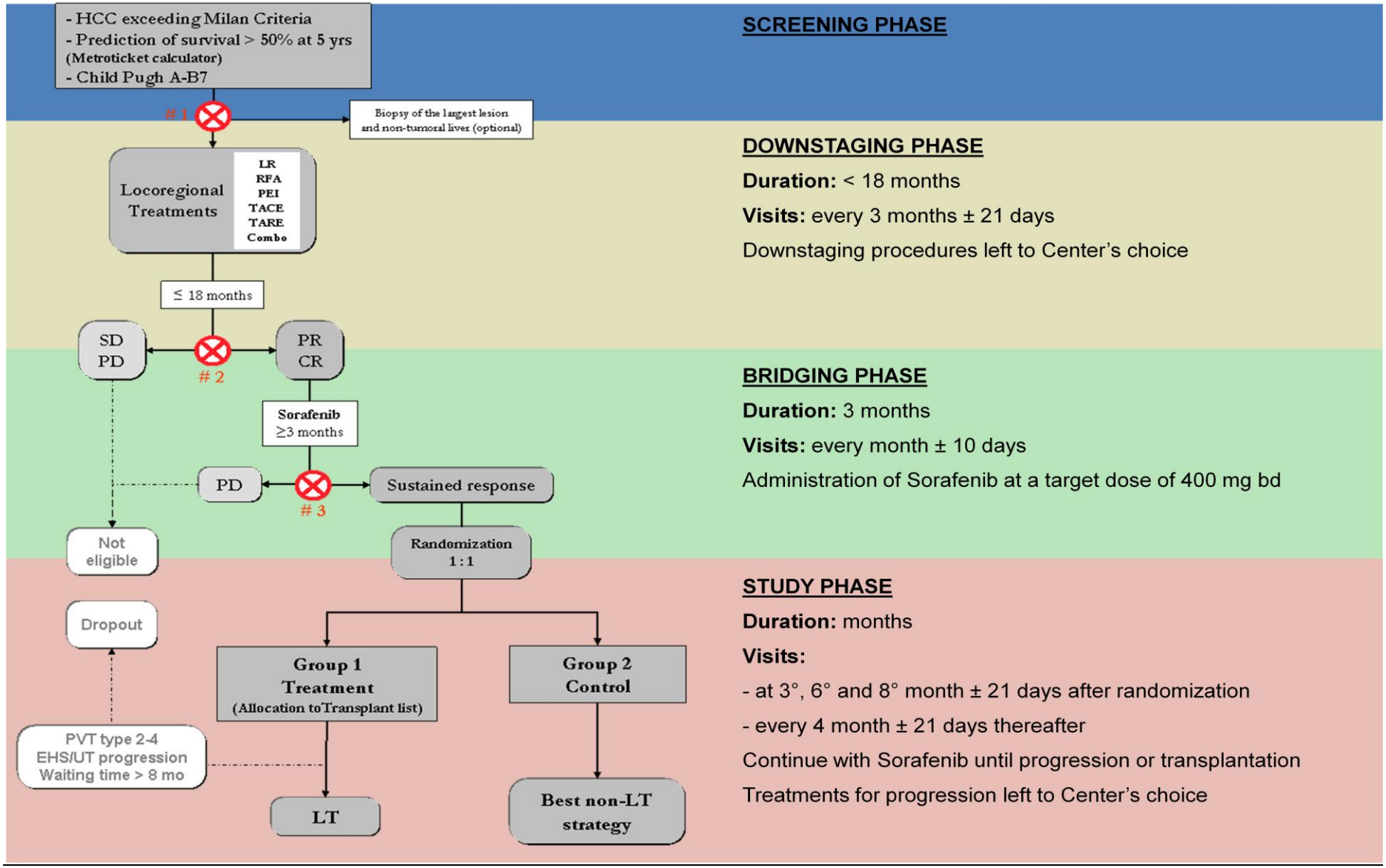
- Patients will continue with sorafenib treatment, if tolerated, until transplantation.

- Intrahepatic progression while on waiting list will be treated according to Center's policy (see paragraph on "Management of group 1").

- Assessment of extrahepatic tumor spread, PVT (type II-IV) or untransplantable progression (UT progression) will be responsible for patient drop out.

2) The **control group** (best non-transplant strategy) will continue with sorafenib until progression. Then they may be treated with locoregional/surgical therapies according to best practice and Centers' policy, excluding transplantation.

Figure 1: Study Flowchart



TIMING AND SCHEDULED TREATMENT WITH RESPECT TO CHECKPOINTS

In naïve patients (non previously treated for HCC exceeding Milan Criteria) the timing from first diagnosis of HCC to first downstaging treatment (Checkpoint-1) should be of maximum 6 months. The maximum allowed interval from first treatment to end of downstaging and efficacy assessment (Checkpoint-2) should be of maximum 18 months.

Patients without major contraindication to transplantation and who have already initiated treatments for an HCC exceeding Milan Criteria prior to enrolment or elsewhere, may be eligible for downstaging efficacy evaluation (Checkpoint-2) providing that the patient remains eligible to a further treatment in the recruiting Center. In fact, patients considered as having completed downstaging elsewhere are not eligible for the trial, unless at least one downstaging treatment is performed in the recruiting Center. The rationale for this is two-fold: a) from the ethical standpoint to obtain patients'consent ahead of any downstaging strategy (intention-to-treat); b) from the oncological standpoint to avoid improper treatments and biased tumor assessments demonstrated to occur in Centers lacking transplant facilities.

If downstaging efficacy evaluation confirms tumor response, sorafenib may be started at standard dosage (800 mg/day) if the time interval from the first treatment done and Checkpoint 2 is $\leq$ 18 months.

From Checkpoint-2 onwards (namely after downstaging efficacy assessment), all patients should adhere to the following time frame:

- From efficacy assessment of downstaging to evaluation of sustained response (Checkpoint-3) the time interval should be of 3 months (i.e. 90±10 days)
- Randomization request should be sent after radiological evaluation of sustained response has been completed. Randomization group will be elettronically assigned within 72 hours, after central revision. Patients allocated to Group 1 (liver transplant) should be enlisted within 28 days from randomization.

Prioritization policy for patients allocated to transplant

For Group 1 (liver transplant) patients eligible for liver replacement should be transplanted within 8 months from randomization. This interval doubles the median Italian waiting time for HCC patients as registered during the last 2 years. Different mechanisms of prioritization within each Center are allowed in order to comply with this requirement (for instance, assigning MELD-HCC extrapoints). Whenever patients will be still on the waiting list after 6 months from randomization, prioritization is strongly suggested in order to avoid drop-out.

MANAGEMENT AFTER GROUP ALLOCATION (RANDOMIZATION)

Group 1 – Management during liver transplantion waiting list

All patients allocated to Group 1 will be treated with sorafenib while on waiting list until LT (unless impeded by toxicity or other reasons to be described in the electronic Case Report Form: eCRF).

- Sorafenib may be withdrawn in case of toxicity grade 3 and not replaced by other molecular targeted therapies.
- Patients for whom sorafenib is withdrawn are not eligible to any other active trials involving novel molecular therapies: they should not receive any other systemic treatment while on the waiting list.

Given this, two possible conditions may occur after allocation to Group 1 (LT):

- Condition 1: stable tumoral disease (SD) while on waiting list.

  Patients belonging to this group, should continue sorafenib till the date of transplantation and should not be treated with loco-regional treatments

- Condition 2: progression of tumoral disease (PD) while on waiting list.

  All patients presenting with tumoral progression on waiting list (i.e. following allocation to transplant list) have to withdraw sorafenib. Patients for whom sorafenib is withdrawn are not eligible to any other active trials involving novel molecular therapies: they should not receive any other systemic treatment while on the waiting list.

  In patients belonging to condition 2, tumor progression may present as:

  2.1. Intra-hepatic progression:

  a) occurrence of a new nodule/nodules in different segments with respect to previously downstaged lesions
  b) progression of nodules previously treated within the downstaging protocol

  - Patients with *treatable* progression will remain on waiting list and may be re-treated with loco-regional therapies, according to best practice and Center policy.
  - Patients with *untransplantable* progression (defined so according to Center policy) will drop-out from transplant list and they will be censored for tumoral event while remaining in the study group for survival calculation (see paragraph on "Statistics-Method of analysis").

2.2. Extra-hepatic progression (EHS):

- EHS is defined as appearance of tumor niches in organs other than liver and/or lymph-node involvement and/or macrovascular invasion (MVI); including PVT defined as invasion of main trunk, or left/right branches (type II-IV according to Shi 2010).
- EHS has to be proven by radiological or histological confirmation. In particular, histological confirmation is compulsory in case of lymphnode hilar involvement ≤ 2 cm (in short axis), while hilar lymphnodes > 2 cm (in short axis) at CT/RMN scan may be considered as metastatic by radiological confirmation.

Patients who may *present with EHS* (as described above) will drop-out from transplant list: they may be re-treated according to best practice and Center policy or may be treated with other molecular targeted therapies different from sorafenib as long as not in an active trial on HCC.

Group 1 –Management following liver transplantation

Immunosuppression

Immunosuppression strategy will not be centralized and will rather follow Center specific protocols. For the purpose of the present study investigators should only provide every 4 months (±21 days) information on the ongoing immunosuppression regimen as for various combinations of calcineurin inhibitors (CNI), mTOR inhibitors, mycophenolate(MMF), steroids etc.. As for alternative options, if m-TOR inhibitors are included in the immunosuppression regimen (whether or not associated to CNI), reason for their use should be specified and will be asked in the eCRF. Steroid-free immunosuppression regimen from the second post-transplant month onward are suggested, although not mandatory.

Graft recurring hepatitis and other reasons for graft failure or death

1) Pre- and post-transplant antiviral strategy (for both HBV and HCV infections) will not be centralized and will rather follow Center specific protocols.

For the purpose of the present study investigators will be asked to provide every 4 months information on main antiviral drug administered after transplantation (i.e.: IFN or no treatment for HCV infection, Entecavir for HBV etc.).

2) Any cause of graft loss, re-transplantation or patient death will be censored together with timing of its occurrence.

Tumor recurrence

Patients who may present with post-transplant recurrence will be treated according to Centers' judgement. Pattern and timing of first recurrence will be registered as well as treatments offered for recurrence. Patients will be followed-up until death.

Group 2 - Non transplant strategy (Controls)

- All patients allocated to Group 2 will be treated with sorafenib till progression, unless impeded by toxicity or other reasons to be described in the eCRF. Sorafenib dose adjustment or interruption are allowed according to investigator judgement, patients' tolerance and guidelines on drug administration.
- Tumor progression, will be censored whether intra- or extra-hepatic. In case of tumor progression patients may be re-treated with locoregional/surgical therapies according to best practice and Centers' policy and also with other molecular targeted therapies different from sorafenib (i.e.: mTOR inhibitors) as long as not in an active trial on second-line systemic therapies for HCC.
- Any treatment against HCC progression and/or the evolution of the underlying liver disease (i.e. Child Pugh stage deterioration) will be registered and patients will be followed-up until death.

MANAGEMENT OF FOLLOW-UP AFTER RANDOMIZATION AND SAE REPORT

Local investigators in each Center will be requested to complete follow-up forms every 4 months after randomization.

For the purpose of this trial only events that require hospital stay for at least 3 days will be considered as Serious Adverse Events (SAE). Each SAE complying with such definition has to be registered in the eCRF and specified whether related to treatment, cirrhosis, tumor or other reasons. SAE should be graded according to NCI CTC 4.0.

Although radiological and biochemical assessment of SAE will be Center specific, in order to limit SAE reports only to those focused on hard endpoints (see above for SAE definition). Investigators are requested to adhere to the following minimal requirements for follow-up assessment:

- at least 2 chest-abdomen dynamic imaging techniques (CT scan/MRI) per year
- at least 2 abdominal ultrasound (with/without contrast) per year
- at least 4 assessments of serum Alphafetoprotein (AFP) per year
- at least 3 specific investigator summary per year containing information on immunosuppression, viral status and related treatment, liver function (Child deterioration) and graft status (see previous paragraph on “Groups management following randomization”.

ASSESSMENT OF RESPONSE

Response evaluation criteria

Assessment of response at Checkpoints-2 and -3 will be done according to modified RECIST criteria (mRECIST, endorsed by EASL and AASLD guidelines). In case of impossibility to adhere to mRECIST criteria (i.e. because of hypovascular or infiltrative tumors), it will be allowed to assess response with other criteria such as RECIST or EASL. Any investigator change in response evaluation criteria with respect to mRECIST has to be justified and will be asked in a specific data-file of the eCRF form. Changes in assessment criteria will undergo central revision before being used for pre-randomization final evaluation.

Summary of assessment of response is reported in Table 1.

	EASL	**RECIST**	**mRECIST**
BEST RESPONSE	***Estimation of reduction in viable tumor volume (necrosis= non enhanced area at CT)***	***Change in the sum of diameter of target lesions***	***Change in the sum of diameter of viable (enhancement in the arterial phase) target lesions***
CR	Disappearance of all enhanced tumor areas	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	Decrease >50% of enhanced areas	30% decrease in the sum of diameters of target lesions	30% decrease in the sum of diameters of viable target lesions
SD	Neither CR nor PR nor PD	Neither CR nor PR nor PD	Neither CR nor PR nor PD
PD	an increase >25% in the size of ≥ 1 measurable lesion(s)	20% increase in the sum of the longest diameter of target lesions	20% increase in the sum of the diameter of viable of target lesion

Table 1. Assessment of response according to EASL, RECIST and modified RECIST criteria (mRECIST)

Differently from the published guidelines on modified RECIST criteria, for the purposes of this trial the appearance of new lesions during the downstaging period will not qualify the patient for "Tumor Progression" at the time of "End of downstaging evaluation" if: the new tumor lesions are less than three and are completely inactive (according to mRECIST criteria) at the time of "End of downstaging evaluation" as the result of previous loco-regional treatment.

AFP monitoring

In order to capture tumor response (or progression) in patients expressing AFP > 400 ng/mL at the time of enrolment, this tumoral marker will be contemplated in the assessment of response.

That is, PR/CR at radiology in patients with AFP above 400 ng/mL at the time of recruitment has to be confirmed by a parallel decrease of at least 30% in both tumor reduction and AFP level. Similarly, in patients with AFP below 400 ng/mL at the time of recruitment, such a cut-off in AFP level should not be exceeded for rating a CR/PR at radiology assessment after downstaging.

In any case the prosecution to the bridging period will be allowed only for patients expressing an AFP level < 1000 ng/mL at the end of downstaging (Figure 2a and 2b).

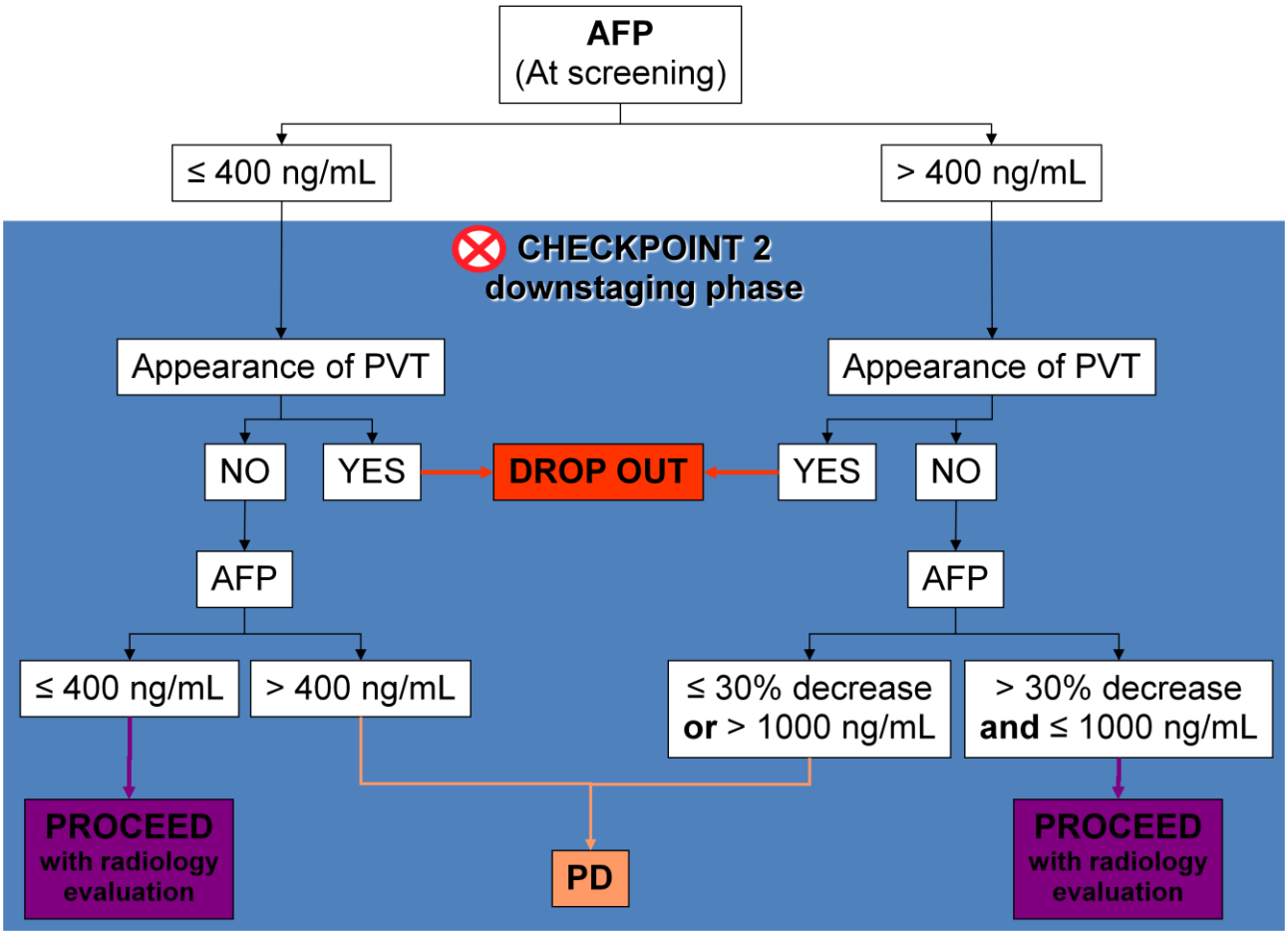


Figure 2a. Assessment of response according to AFP levels during downstaging period, in patients without PVT at enrolment.

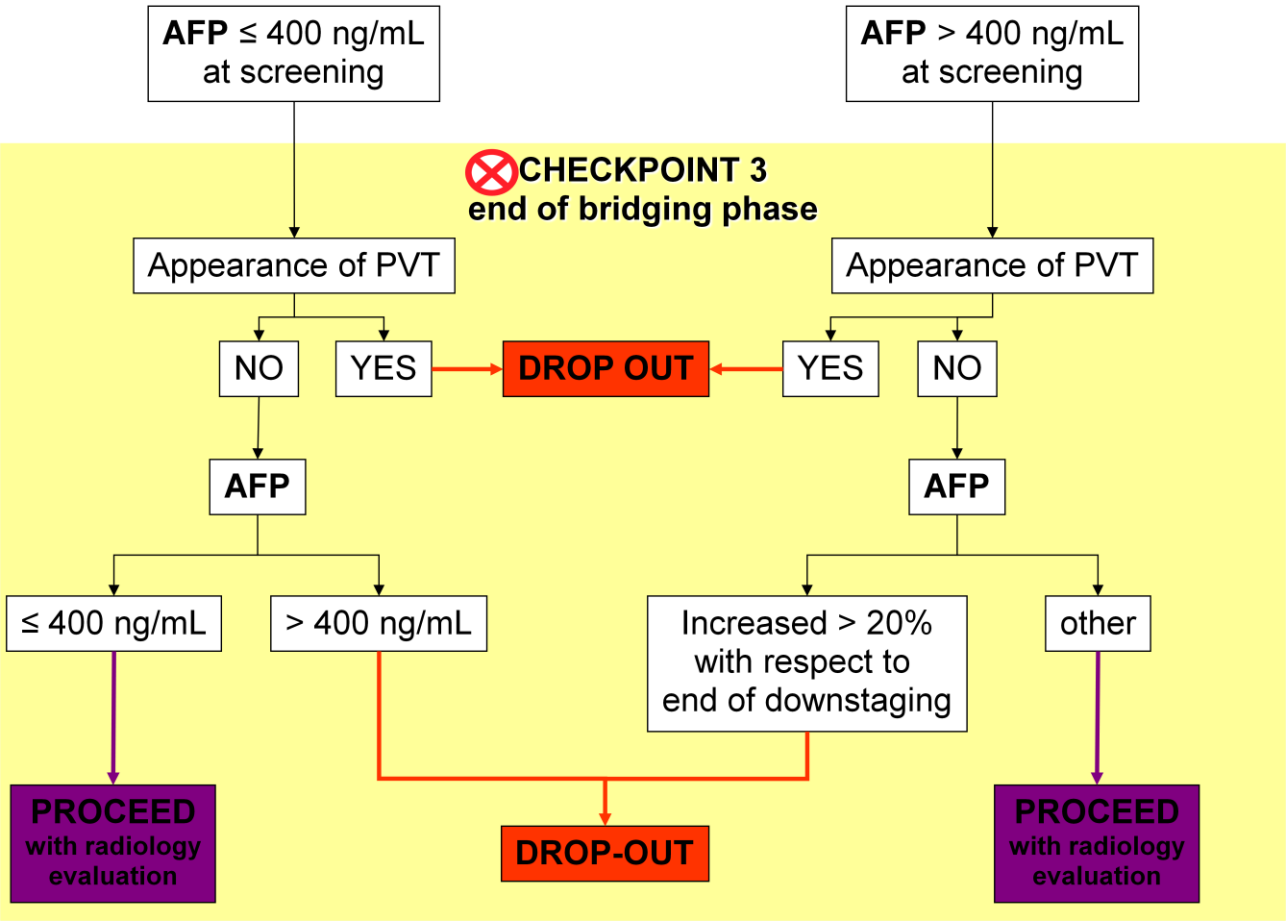


Figure 2b. Assessment of response according to AFP levels during bridging period, in patients with no PVT at enrolment.

Segmental and subsegmental PVT

Differently from trunk/branched PVT (types II-IV according to Shi 2010), segmental PVT (type I) may be included in the downstaging phase of the study if associated with measurable HCC lesions and AFP < 400 ng/mL.

However, type I PVT (uncertain whether of neoplastic aetiology or bland thrombosis) are eligible to randomization only if both following conditions are satisfied:

a) Complete response on target lesions at radiological assessment (i.e. at Check-Point 2 and 3)

b) AFP remaining < 400 ng/mL

The appearance of a tumoral type I PVT during whichever phase of the study, in patients without PVT at enrolment, will cause patient drop-out from the study (Figure 3a and 3b).

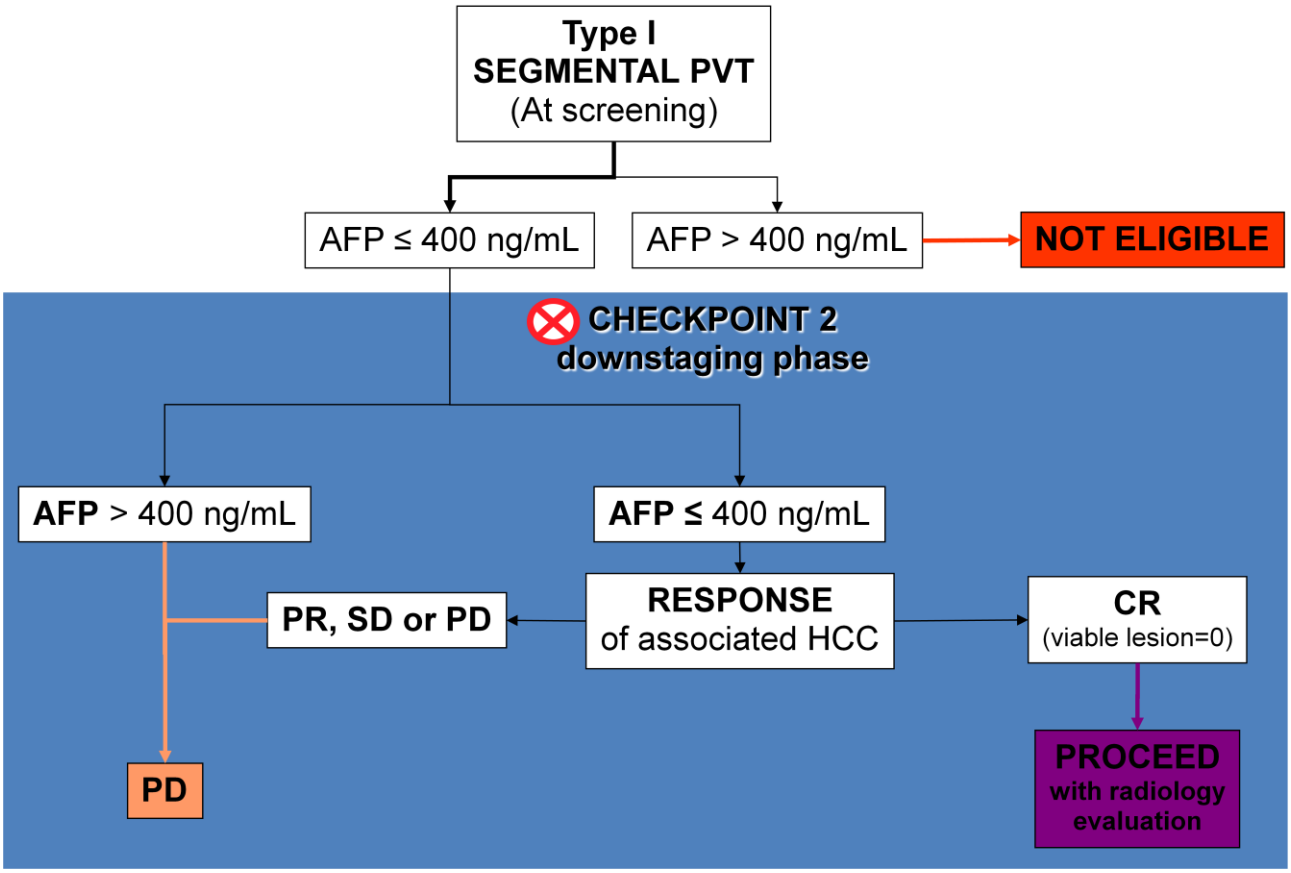


Figure 3a. Assessment of response according to AFP levels during downstaging period, in patients with PVT type I at enrolment.

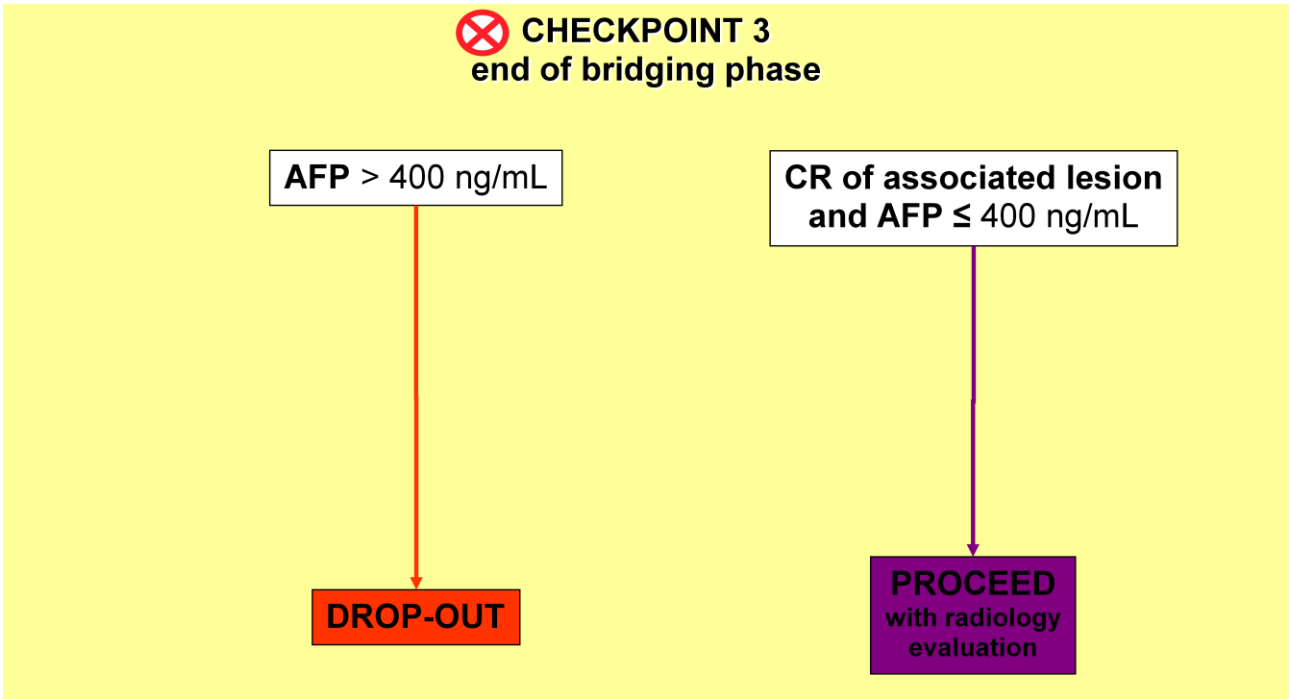


Figure 3b. Assessment of response according to AFP levels during bridging period, in patients with PVT type I at enrolment.

REASONS FOR STUDY ENDING

Patients qualify for study ending in case of:

a) Tumor progression or stable disease at the end of downstaging phase
b) Tumor progression at the end of bridging phase
c) Untransplantable progression occurring while on waiting list for patients allocated to Group 1
d) Occurrence of liver transplant contraindications, other than tumoral events, at whatever phase of the study (refer to exclusion criteria of the present trial).
e) SAE that according to the investigators' judgement prevents the patient to proceed in the study during the first two phases.
f) Protocol violation, particularly those transgressing the timeframes assigned to each phase.
g) Consent withdrawal
h) Patients lost to follow-up at any phase.
i) Death (whether tumor related or not)

Patient qualified for study ending will be traced into the eCRF system according to the EOS (End Of Study) form.

In patients for whom EOS form has been filled up for reasons other than consent withdrawal, lost to follow-up or death, survival should be registered every 4 months until death.

INFORMED CONSENT

A single, exhaustive, informed consent has been prepared in Italian as Addendum to the present protocol. Consent form will be administered to all patients at the time of enrolment, as it illustrates the general purposes and the different phases of the study. It is of utmost importance that such consent includes the information regarding the 50% probability, after randomization, to be enlisted for liver replacement, providing a successful downstaging of a tumor beyond conventional criteria and therefore not eligible to liver transplantation under current national/international guidelines.
A signed informed consent to the present study should not be considered as a substitute of the Center specific transplant consent which will be administered at enlisting.

As previously described (see "Inclusion Criteria") patients may be enrolled in the study depending whether treatment will be performed in the recruiting Center or has been initiated elsewhere.
Patients will be informed on the aim and technique of the locoregional treatments performed with the purpose of tumor downstaging. They also will be informed on the possibility of proceeding in the study only if assessment of response at the end of downstaging will demonstrate a partial (PR) or a complete response (CR) (see previous paragraph on "Assessment of Response").
A signed informed consent to the present study should not be considered as a substitute of the Center specific consent for all downstaging procedures.

INDEPENDENT CENTRALIZED RADIOLOGY REVIEW

Assessment of response at Checkpoint -1, -2 and -3 and during follow-up after randomization, will be carried out by the participating Centers performing the downstaging procedures, according to the described criteria (see "Investigation Plan", "Assessment of response" and "Management after Group Allocation" paragraphs).
At each pre- and post-randomization interval, radiological scans will have to be forwarded to an independent centralized radiology review committee (IRC) which will take care of the final confirmation of radiological assessment. Should IRC not confirm the original Center's report at any time during the study, patient may be re-discussed and considered for either protocol violation or for trial reconsideration. In such instances decision will have to be taken within 14 days.

SAMPLE SIZE AND STATISTICS

Study design

The study is designed as a IIb/III trial. Design and endpoints were chosen following the recommendations by the Panel of Experts in HCC-Design Clinical Trials.

The first step (phase IIb, exploratory) is aimed at showing a liver transplantation benefit in delaying tumor recurrence. The second step (phase III, confirmatory) is to demonstrate clinical benefits on overall survival.

Populations and Subgroups

- Intent To Treat population (ITT, following an intent-to-treat principle): all randomized patients analyzed according to their assigned arm.
- Restricted ITT population (RITT): patients from the ITT population, after the exclusion of those for whom the requirements for transplantation are lost while on the waiting list (within a landmark window, as later explained).

Study end-points

1) Primary end-points

- Phase IIb: Time to Tumoral Event (TTE). Time will be calculated as the interval between the randomization date and, respectively, the date of tumour recurrence for tumor-free patients (either because of liver transplantation or complete response after downstaging procedures) or the date of tumour progression otherwise, with censoring at the date of last contact for event-free patients.

  Progression is defined according to mRECIST or EASL definition (namely both a 20% increase in the sum of the diameter of viable of target lesion or appearance of new lesions - see Table 1 and above definitions).

- Phase III: Overall survival (OS). Time will be calculated as the interval between the randomization date and the date of death for any cause, with censoring at the date of last contact for patients alive.

2) Secondary end-points

- Transplant vs. non transplant cost-benefit analysis
- Efficacy analysis on downstaging therapies and on prevention of drop-outs from the transplant waiting list
- Radiology/pathology correlation on efficacy of downstaging treatments in achieving tumor response, as a basis for possible validation of modified RECIST criteria.
- Assessment of whether the Metroticket prognostication model is suitable for prediction in this study population based on the original tumour characteristics (size, number, vascular invasion), and whether model performance may be improved by the inclusion of additional biological variables (grading, microsatellites, gene signature of mVI).

Statistical analyses for primary end-points

1) Phase IIb

The Kaplan-Meier method will be used to estimate the TTE curves in the two treatment arms; comparison between the curves will be performed using the log-rank test.

Both the failure to perform liver transplantation in Group 1 patients and the occurrence of tumoral events before transplantation imply a dilution effect in the assessment of experimental treatment efficacy. To avoid such a bias, which is detrimental in phase IIb studies, it is planned to perform TTE analysis only in RITT population and by resorting to a "land-mark" approach.

This approach will be applied by disregarding tumoral events occurring in Group 1 patients still in the waiting list and, for symmetry reasons, the events occurring in Group 2 patients before the "land-mark time". This is defined as the median waiting time for liver transplantation (around 4 months, according to past experience), which will be estimated for Group 1 patients at the time of analysis.

2) Decision rule for phase IIb-phase III transition.

A one-sided log-rank test p<50% (in favour of Group 1) at the end of phase IIb will imply patient accrual continuation, so as to achieve the overall sample size required by phase III. Such a criterion may be regarded as a stopping rule based on futility.

3) Phase III.

The Kaplan-Meier method will be used to estimate the OS curves in the two treatment arms; comparison between the curves will be performed using a one-sided log-rank test at the 2.5% significance level.

In a phase IIb-III study the experimental treatment is repeatedly tested. Furthermore, the phase III analysis incorporates data from patients already considered in phase IIb analysis, which introduces dependence between the two phases. The use of a 2.5% significance level represents a conservative choice aimed at preserving the overall type I error.

Overall survival analysis will be performed both on ITT (main analysis) and RITT populations. TTE analysis will be repeated upon completion of phase III in two different ways: i) in the RITT population, following the previously described land-mark approach; ii) in the ITT population, using a Cox model including a time-dependent covariate for liver transplantation, and adjustment for known HCC prognostic covariates.

Determination of sample size

Given the uncertainty on many aspects with potential impact on sample size in the setting of transplanted patients, both study phases will be driven by the number of end point events, which only depend on the targeted hazard ratio (HR).

1) Phase IIb

The phase IIb TTE analysis will require the observation of 52 tumoral events overall. It has been estimated that such a number will require accrual of 65 patients per group over 1 ½ - 2 year and minimum follow-up of six months.

Such a calculation was performed incorporating the above described futility stopping rule (50% significance level), around 10% patient loss in the RITT population compared to ITT population, a median baseline TTE of 12 months, and a 90% power to detect a 30% relative hazard reduction (HR=0.70).

2) Phase III

The phase III OS analysis will require the observation of 87 deaths overall. It has been estimated that such a number will require accrual of 130 patients per group over 3 years and minimum follow-up of six months. Such a calculation was performed incorporating a 20% baseline survival at 5 years, and a 90% power to detect a 25% survival increase in the experimental group (HR=0.50).

Study duration

A number of regional, national and international Centers will participate to the trial, aimed at accomplishing patient recruitment within 2 years (if regional+national+international recruitment will occur) or 3 years (in case of regional+national participation) or 4 years (if only regional recruitment will be carried out).

COLLATERAL STUDIES

If a sufficient number of optional parameters are obtained (i.e. pre-downstaging biopsy assessment, biomarkers for mVI of other prognostic factors, pathology/radiology response correlation) exploratory correlative analysis will be performed.

As an exploratory analyses, patient's biomarkers status at baseline may be correlated with treatment effect in TTTE, OS and other outcome measures. In addition association between changes in biomarkers versus TTTE, OS and other outcome measures will also be performed. These exploratory evaluations will provide a mechanists understanding of the disease and will provide an assessment of potential predictive markers for downstaging of HCC in combination or not with transplantation.

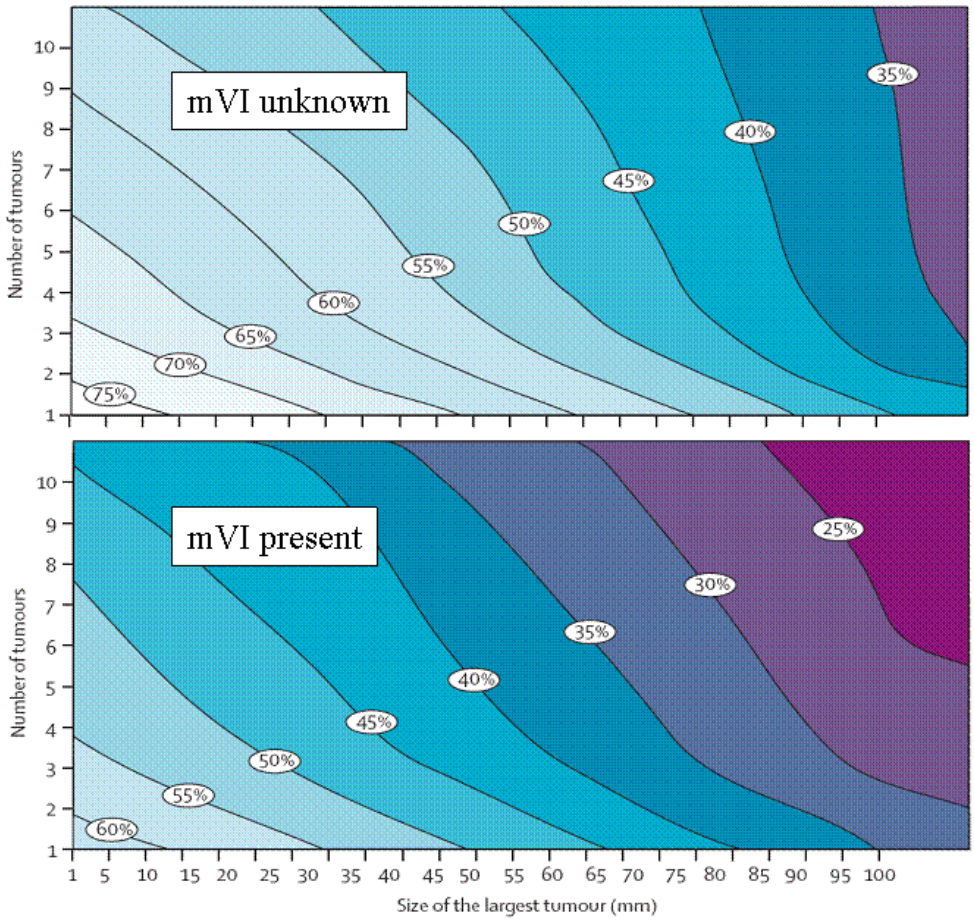
This data will be reported separately.

PUBLICATION POLICY

The Principal Investigator declares that the Investigators rights of data release and publication are guaranteed in the context of the present clinical study, and that there are no Promoter's related constraints on the release and publication of results, as for Italian Ministerial Decree 12 may 2006.

APPENDIX

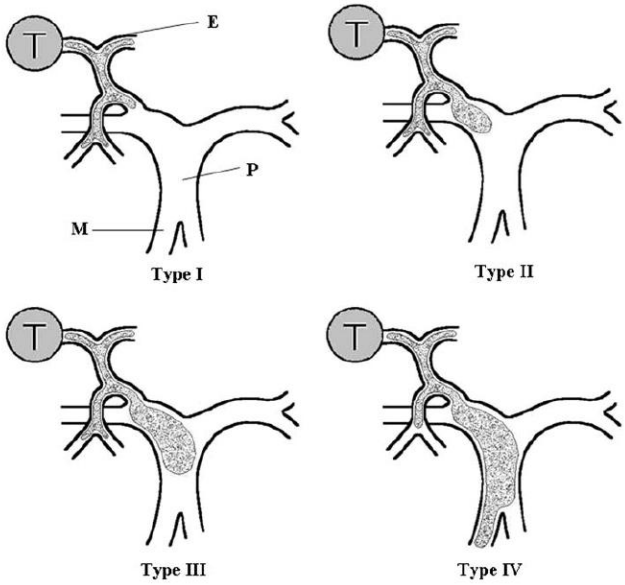
Metroticket forecast chart for post-transplant survival (Lancet Oncol 2009)



Contour plot of the 5-year overall-survival probability according to size of the largest tumour, number of tumours, and presence or absence of microvascular invasion

- Survival estimates according to size and number, not considering microvascular invasion (median SE 4·2% [interquartile range 3·6–5·2]).
- Survival estimates according to or presence of microvascular invasion (median 3·7% [3·1–4·7]).

Classification of PVT (Ann Surg Oncol 2010)



Patterns of tumor thrombus types system. T: tumor, E: tumor embolus, P: main portal vein, M superior mesenteric vein.

Types	Subtypes
Type I_0: Tumor thrombi formation found under microscopy	
Type I: Tumor thrombi involving segmental branches of portal vein or above	Type Ia: Tumor thrombi involving segmental branches of portal vein or above
	Type Ib: Tumor thrombi involving segmental branches of portal vein extending to sectoral branch
Type II: Tumor thrombi involving right/left portal vein	Type IIa: Tumor thrombi involving right/left portal vein
	Type IIb: Tumor thrombi involving both left and right portal veins
Type III: Tumor thrombi involving the main portal vein trunk	Type IIIa: Tumor thrombi involving the main portal vein trunk for no more than 2 cm below the confluence of the left and right portal veins
	Type IIIb: Tumor thrombi involving the main portal vein trunk for more than 2 cm below the confluence of the left and right portal veins
Type IV: Tumor thrombi involving the superior mesenteric vein	

ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

NYHA functional classification

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

EQ 5D questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

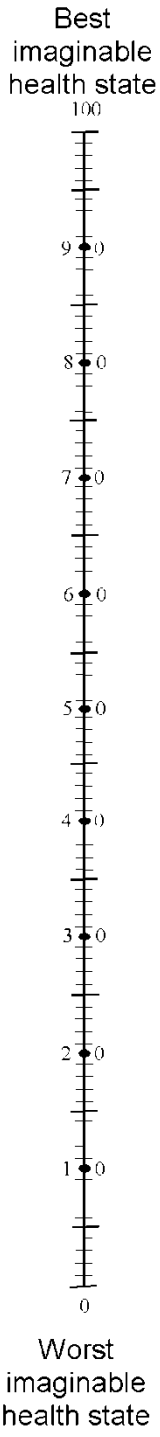
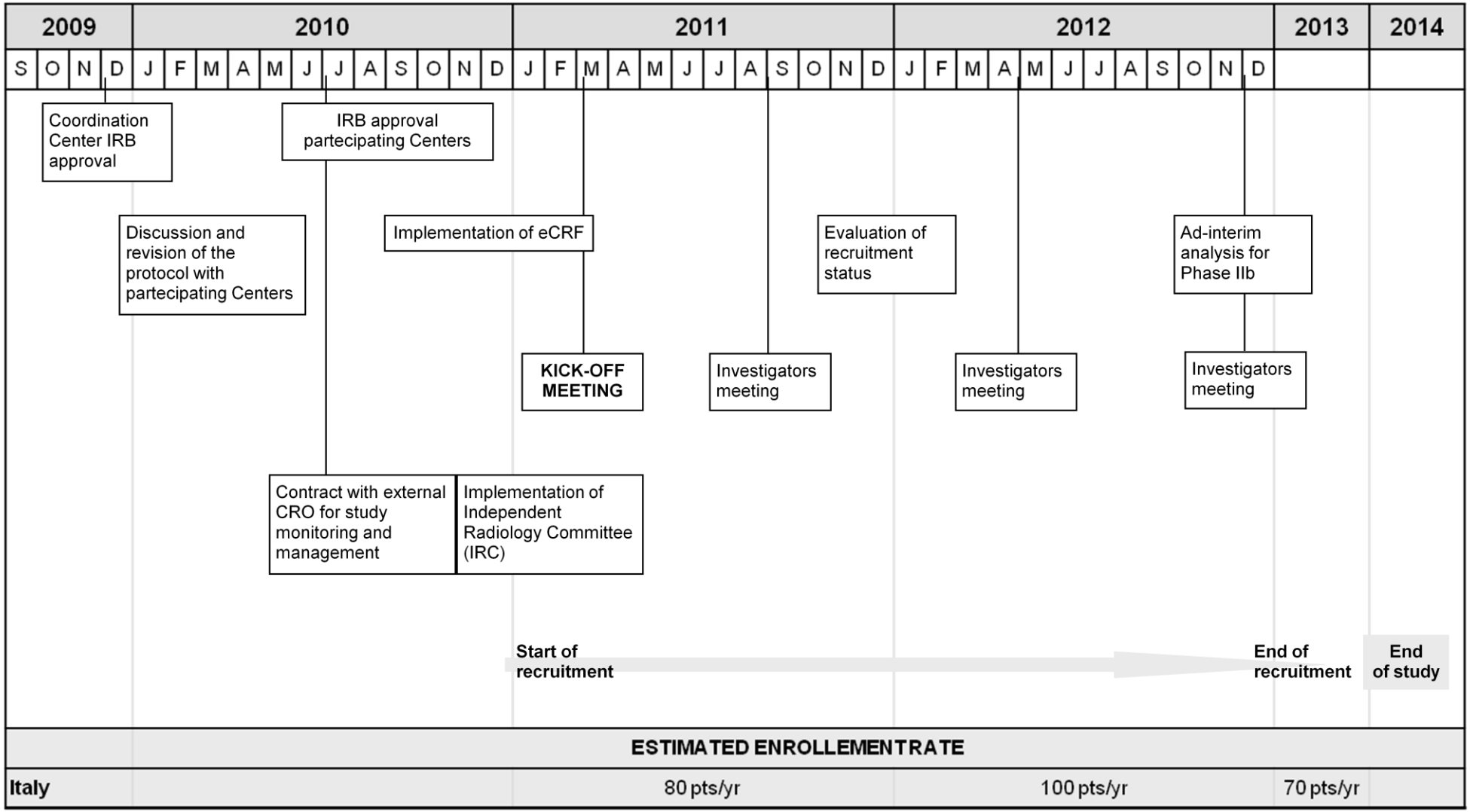


Figure 1. Gantt chart of strategic work plan for XXL Trial



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