CLINICAL PROTOCOL INT 80/09 SYNOPSIS
Version 2.0 April 1st, 2011

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.

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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 (Ministry 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/](http://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](http://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

**SCREENING PHASE**

- HCC exceeding Milan Criteria
- Prediction of survival > 50% at 5 yrs (Metroticket calculator)
- Child Pugh A-B7

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

**DOWNSTAGING PHASE**

Duration: < 18 months
Visits: every 3 months ± 21 days
Downstaging procedures left to Center’s choice

**BRIDGING PHASE**

Duration: 3 months
Visits: every month ± 10 days
Administration of Sorafenib at a target dose of 400 mg bd

**STUDY PHASE**

Duration: months
Visits:
- at 3°, 6° and 8° month ± 21 days after randomization
- every 4 month ± 21 days thereafter
Continue with Sorafenib until progression or transplantation
Treatments for progression left to Center’s choice
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 ≤ 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 electronically 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 transplantation 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.

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

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).

![AFP monitoring diagram](image)

**Figure 2a.** Assessment of response according to AFP levels during downstaging period, in patients without 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 landmark 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)


<table>
<thead>
<tr>
<th>Types</th>
<th>Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I: Tumor thrombi involving segmental branches of portal vein or above</td>
<td>Type Ia: Tumor thrombi involving segmental branches of portal vein or above&lt;br&gt;Type Ib: Tumor thrombi involving segmental branches of portal vein extending to sectoral branch</td>
</tr>
<tr>
<td>Type II: Tumor thrombi involving right/left portal vein</td>
<td>Type IIa: Tumor thrombi involving right/left portal vein&lt;br&gt;Type IIb: Tumor thrombi involving both left and right portal veins</td>
</tr>
<tr>
<td>Type III: Tumor thrombi involving the main portal vein trunk</td>
<td>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&lt;br&gt;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</td>
</tr>
<tr>
<td>Type IV: Tumor thrombi involving the superior mesenteric vein</td>
<td></td>
</tr>
</tbody>
</table>

**ECOG Performance Status**

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>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</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
NYHA functional classification

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

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

<table>
<thead>
<tr>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coordination Center IRB approval</td>
<td>IRB approval participating Centers</td>
<td>Implementation of eCRF</td>
<td>Evaluation of recruitment status</td>
<td>Ad-interim analysis for Phase IIb</td>
<td></td>
</tr>
<tr>
<td>Discussion and revision of the protocol with participating Centers</td>
<td>KICK-OFF MEETING</td>
<td>Investigators meeting</td>
<td>Investigators meeting</td>
<td>Investigators meeting</td>
<td></td>
</tr>
<tr>
<td>Contract with external CRO for study monitoring and management</td>
<td>Implementation of Independent Radiology Committee (IRC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of recruitment</td>
<td>End of recruitment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ESTIMATED ENROLLEMENT RATE

| Italy | 80 pts/yr | 100 pts/yr | 70 pts/yr |
REFERENCES