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SaLudo: a randomized phase IIb/III study of lurbinectedin plus doxorubicin as first-line treatment in leiomyosarcoma

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ABSTRACT

Previous phase I/II trials indicate promising activity of lurbinectedin plus doxorubicin (DOX) in leiomyosarcoma (LMS). We describe here the rationale and design of SaLuDo, an open label, randomized, multicenter, seamless phase IIb/III study to evaluate the antitumor activity and safety of lurbinectedin plus DOX *versus* DOX alone in the first-line setting of metastatic LMS. The phase IIb stage will evaluate two schedules of the combination for the phase III stage given every 3 weeks (q3wk): DOX 50 mg/m^2 plus lurbinectedin 2.2 mg/m^2, and DOX 25 mg/m^2 plus lurbinectedin 3.2 mg/m^2. The control arm will be DOX 75 mg/m^2 q3wk. The primary endpoint is progression-free survival by independent review; overall survival is the key secondary endpoint. Clinical trial registration: www.clinicaltrials.gov identifier is NCT06088290.

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Leiomyosarcoma; lurbinectedin; doxorubicin; progression-free survival; overall survival; phase IIb/III; seamless adaptive design

1. Leiomyosarcoma: background of the disease

Leiomyosarcoma (LMS), a malignancy of smooth muscle differentiation [1], is one of the most common subtypes of soft tissue sarcomas (STS), comprising up to 25% of all sarcomas and nearly 80% of all uterine sarcomas [2]. Surgical resection, with or without radiation, is the cornerstone treatment for patients with localized LMS regardless of the site of origin. Unfortunately, LMS recurs frequently as locally advanced or metastatic disease. Metastatic disease is generally considered incurable, with median progression-free survival (PFS) of 5–7 months and median overall survival (OS) of 18–24 months [3–6].

Doxorubicin (DOX) monotherapy has been the standard treatment for first-line therapy of metastatic sarcoma despite numerous attempts over the last decades to demonstrate superiority of new agents or combinations [3–9]. Most of these trials included a wide variety of sarcoma histologies while LMS-04 [9] was the only specific trial for LMS (uterine in 45%). LMS-04 compared DOX *vs*. the combination of DOX and trabectedin followed by maintenance with trabectedin alone in patients with metastatic or locally advanced LMS treated in the first line. Recently published results with an extended median follow-up of 55 months have shown longer median PFS with DOX/trabectedin (12 months *vs*. 6 months for DOX alone; hazard ratio [HR] = 0.37; 95%CI, 0.26–0.53), and longer median OS (33 months *vs*. 24 months for DOX alone; HR = 0.65; 95%CI, 0.44–0.95) [10].

2. Lurbinectedin

Lurbinectedin is a synthetic chemical entity structurally related to trabectedin that inhibits oncogenic transcription and is active in tumors addicted to transcription [11–13]. Lurbinectedin 3.2 mg/m^2 administered on Day 1 every three weeks (q3wk) was approved for the treatment of adults with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy first in the US [14] and later in several countries worldwide.

3. The SaLuDo study

Here, we describe the rationale and design for the SaLuDo study (NCT06088290), an open-label, randomized, seamless adaptive phase IIb/III study to evaluate the antitumor activity and safety of the combination of lurbinectedin and DOX *versus* single-agent

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Article highlights

- Leiomyosarcoma (LMS) is an aggressive, rare cancer with limited treatment options.
- Doxorubicin (DOX) alone or in combination is given as first line though outcomes in metastatic disease are poor.
- Trabectedin, a synthetic chemical entity structurally related to lurbinectedin, has demonstrated encouraging efficacy results in a recent phase III trial (LMS-04), both in PFS and OS.
- Lurbinectedin is a novel anticancer marine derivative agent which inhibits active transcription of protein-coding genes.
- Early phase I/II clinical trials indicated promising antitumor activity of lurbinectedin combined with DOX in pretreated LMS, with a favorable safety profile.
- SaLuDo is an open-label, randomized, seamless phase IIb/III trial to evaluate the antitumor activity and safety of the combination of lurbinectedin and DOX versus single-agent DOX in patients with metastatic LMS in the first-line setting.
- The study has two stages. In the phase IIb stage, two schedules of lurbinectedin plus DOX combination will be evaluated in two experimental arms with a control arm consisting of DOX alone. The phase III stage will continue evaluating the experimental arm selected in the phase IIb stage as well as the control DOX arm.
- The study started enrollment in September 2023 and the analysis of the primary endpoint (progression-free survival by Independent Review Committee) is anticipated 14 months after the last patient is randomized.
- The results of this pivotal trial will help to define the role of lurbinectedin plus DOX combination in the first-line therapy of patients with metastatic LMS.

DOX in patients with metastatic LMS in the first-line setting. The study is funded by Pharma Mar SA, Madrid, Spain.

3.1. Background & rationale

A phase I study evaluated initially lurbinectedin in combination with DOX in patients with pretreated selected advanced solid tumors [15,16]. Lurbinectedin, a trabectedin analog with improved hepatic toxicity, showed promising results in early trials for STS. Based on these results, including a radiological complete response in a phase I study, further clinical investigations were launched to evaluate the efficacy of lurbinectedin as monotherapy or in combination with DOX for sarcoma treatment.

A signal-seeking phase II study evaluated lurbinectedin as a single agent or in combination with DOX or gemcitabine in metastatic and/or unresectable sarcomas [17]. Twenty patients received intermediate doses of lurbinectedin (2 mg/m^2) and DOX (50 mg/m^2) q3wk followed by lurbinectedin monotherapy at the approved dose for SCLC (3.2 mg/m^2) in a cohort that included different STS histologies, although LMS was the predominant (12/20 patients). Overall response rate (ORR) was 35% and disease control rate at 24 weeks was 40%. Three of 12 patients with LMS had objective responses and one patient had disease control for over 15 months. This schedule was well tolerated, with manageable cytopenias (only one case of febrile neutropenia was reported), and toxicities were as anticipated for the cytotoxic agents in the study (one case of grade 3 fatigue and one of grade 3 nausea). Thus, these pilot study data supported further investigation of the lurbinectedin/DOX combination in sarcomas.

In a *post hoc* analysis of the phase III ATLANTIS study, where SCLC patients were treated with lurbinectedin 2 mg/m^2 plus DOX 40 mg/m^2, complete maximum anthracycline dosing (10 cycles) was achieved by 50 patients, who transitioned to maintenance lurbinectedin at 3.2 mg/m^2 [18]. In these 50 patients who switched to lurbinectedin monotherapy, tumor response was maintained or even improved. Similarly, eight of 20 STS patients treated in the prior phase II study completed DOX treatment and received lurbinectedin monotherapy maintenance [17]. Two of these eight patients improved their response according to RECIST from stable disease to partial response. Therefore, these analyses suggested that it might be beneficial to maximize lurbinectedin dosing when given in combination with DOX.

A phase Ib/II trial is currently being conducted in patients with advanced/metastatic STS and no prior anthracycline/lurbinectedin/trabectedin to evaluate a full dose of lurbinectedin combined with DOX at a lower dose q3wk. The phase Ib was completed and the recommended dose was lurbinectedin 3.2 mg/m^2 plus DOX 25 mg/m^2 with mandatory growth colony-stimulating factor (G-CSF) primary prophylaxis [19]. Response rate was 60% in 10 advanced STS patients, with three partial responses observed in 5 LMS patients. Preliminary median PFS in phase Ib was 16.5 months. The most common treatment-emergent adverse events were grade 2 fatigue and nausea, and grade 2 cytopenias with no febrile neutropenia events. Dose-limiting toxicities (grade 2/3 transaminase increases and grade 3 neutropenia) were reversible, and all patients continued the study. This trial entered the phase II stage and is currently ongoing.

The encouraging results observed in these trials for lurbinectedin combined with DOX provided a rationale for further exploring this combination in the SaLuDo phase IIb/III trial as first-line therapy for metastatic LMS.

3.2. SaLudo study design

SaLuDo is a multicenter, open-label, randomized phase IIb/III trial with an adaptive design. The primary objective is to evaluate whether the combination of lurbinectedin plus DOX given as first-line treatment for metastatic LMS prolongs the progression-free survival (PFS) by Independent Review Committee (IRC) when compared to DOX alone. This trial has a seamless study design based on the multiple arms-multiple stages adaptive design theory [20,21]. The study is split into two stages. The phase IIb stage will evaluate two schedules of lurbinectedin plus DOX combination in two experimental arms and a control arm (DOX alone). This first stage will include a prospectively planned interim analysis to drop one of the two experimental schedules. Subsequently, the phase III stage will recruit more patients in the selected experimental arm as well as in the control arm. Crossover is not allowed.

3.3. Key eligibility criteria

Key inclusion criteria include age ≥18 years; histologically confirmed diagnosis of metastatic LMS not candidate for curative resection; radiologically measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1; no

previous systemic therapy for metastatic disease and no previous anthracyclines (prior chemotherapy without anthracycline as adjuvant/neoadjuvant therapy is allowed); Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1; adequate hematological, renal, metabolic and hepatic function, and a washout of at least 3 weeks since last prior anticancer systemic treatment, at least 3 weeks since last prior major surgery (one week since last prior minor surgery) and at least 2 weeks since completion of prior radiotherapy. Key exclusion criteria include prior treatment with anthracyclines, lurbinectedin or trabectedin; known low grade LMS (i.e., grade 1); need of rapid tumor shrinkage (e.g., when a tumor is close to a critical structure); prior irradiation if only one target lesion is available, unless progression of the lesion has been confirmed; known myopathy, and relevant diseases or clinical situations that may increase the risk of toxicity for the patient.

3.4. Treatment per stage of the study

In the phase IIb stage, patients will be randomized 1:1:1 to receive one of three treatment regimens: DOX 50 mg/m^2 plus lurbinectedin 2.2 mg/m^2 (Experimental Arm A), doxorubicin 25 mg/m^2 plus lurbinectedin 3.2 mg/m^2 (Experimental Arm B), or DOX 75 mg/m^2 alone (Control) (Figure 1). All treatments will be administered intravenously on Day 1 q3wk, with DOX discontinued at a cumulative dose of 450 mg/m^2. Patients in the experimental arms may continue lurbinectedin monotherapy (3.2 mg/m^2 alone i.v. on Day 1 q3wk) if beneficial. G-CSF prophylaxis will be mandatory for experimental arms and optional for the control arm, while standard antiemetics and optional dexrazoxane as a cardioprotective agent will be administered to all patients according to the investigator´s criteria. In the subsequent phase III stage, patients will be randomized 1:1 to either the selected lurbinectedin-DOX regimen from phase IIb or DOX 75 mg/m^2 alone (Figure 2).

3.5. Rationale for the doses evaluated

The two lurbinectedin plus DOX schedules evaluated during the phase IIb stage have previously shown promising antitumor activity in patients with metastatic LMS [17,19]. The lurbinectedin dose of 2.2 mg/m^2 used in the Experimental arm A is close to the 2.0 mg/m^2 dose used in a previous phase II study [17], and is similar to the 4.0 mg flat dose (FD) defined as RD in an early phase I study, as 4.0 mg FD corrected by the median patient BSA observed in that study (1.8 m^2) results in a BSA-based dose of 2.2 mg/m^2 [15]. In these two previous trials, the DOX dose was 50 mg/m^2. The dose used in Experimental Arm B is the RD found for lurbinectedin plus DOX combination in the previous phase Ib/II trial [19].

Even though the dose of DOX used in the experimental arms is lower than the usual dose of 60–75 mg/m^2, the efficacy results observed in the previously mentioned trials (ORR = 35–60%) [17,19] are consistent with prior reports of anthracycline chemotherapy combinations: 47% (DOX, ifosfamide, dacarbazine) [22], 32% (DOX/ifosfamide/dacarbazine) [23], 34% (DOX/ifosfamide) [24], or 36% (trabectedin/DOX) [9]. Moreover, the tolerability of the DOX/lurbinectedin combination was much more favorable than that observed in the above-mentioned combinations. Unlike these trials, in SaLuDo phase IIb/III trial, the histologic subtype will be restricted to LMS (a sarcoma subtype known to be sensitive to trabectedin, compound of the same drug class), and patients will not be allowed to have received prior systemic therapy for advanced disease, two factors that are expected to further support the benefit of this combination. The use of a low dose of another agent with full/almost full dose of lurbinectedin is also supported by a recent presentation [25] describing the use of trabectedin in combination with irinotecan given at low dose in patients with Ewing sarcoma. Even though irinotecan was used at a much lower dose (25 mg D1-D4 q3wk), antitumor activity was considerable (ORR = 28%) in a heavily pretreated population and with a favorable safety profile.

The dose of DOX in the control arm (75 mg/m^2) is a standard first-line treatment and has been used as control arm in all phase III trials of first-line therapy of metastatic sarcoma in the last decades [3–6].

3.6. Assessments per study period

The study consists of three periods including screening, treatment, and follow-up in both the phase IIb (Figure 1) and in the phase III stage (Figure 2). After informed consent, eligibility assessments are performed during the screening period, including medical history and clinical examination, laboratory tests, electrocardiogram, measurement of left ventricular ejection fraction (LVEF) by echocardiogram or multiple-gated acquisition scan, pregnancy test (for women of childbearing age), clinical and radiological tumor assessment, patient-reported outcomes using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, and adverse event reporting with grading per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5.

Central randomization will be implemented in all patients that fulfill the inclusion/exclusion criteria. Stratification will be performed according to site of primary tumor (uterine *vs*. soft tissue), sites of metastatic disease (lung as unique site *vs*. other), and time from diagnosis to study entry (≤12 months *vs*. > 12 months). Treatment (cycle 1 day 1) must start within 72 hours after randomization. The treatment period extends from randomization to disease progression, investigator's decision, start of any new antitumor therapy, unacceptable toxicity or withdrawal of consent. During the treatment period, evaluations include: clinical examination, ECOG PS and vital signs on day 1 of cycle 2 and subsequent cycles; laboratory tests on days 1, 8 and 15 of cycle 1 and 2 and day 1 of subsequent cycles; measurement of LVEF once a minimum cumulative DOX dose of 300 mg/m^2 and 375 mg/m^2 is reached, and once the maximum cumulative DOX dose of 450 mg/m^2 is reached; ECG if clinically indicated; pregnancy test each cycle (for woman of childbearing age); pharmacokinetic sampling in Cycle 1; pharmacogenomics for patients who provide specific written informed consent (archived tumor tissue at screening and from patients that undergo surgery while on study, and blood samples in Cycles 1 and 2 and at end of treatment); clinical and radiological tumor assessment and patient-

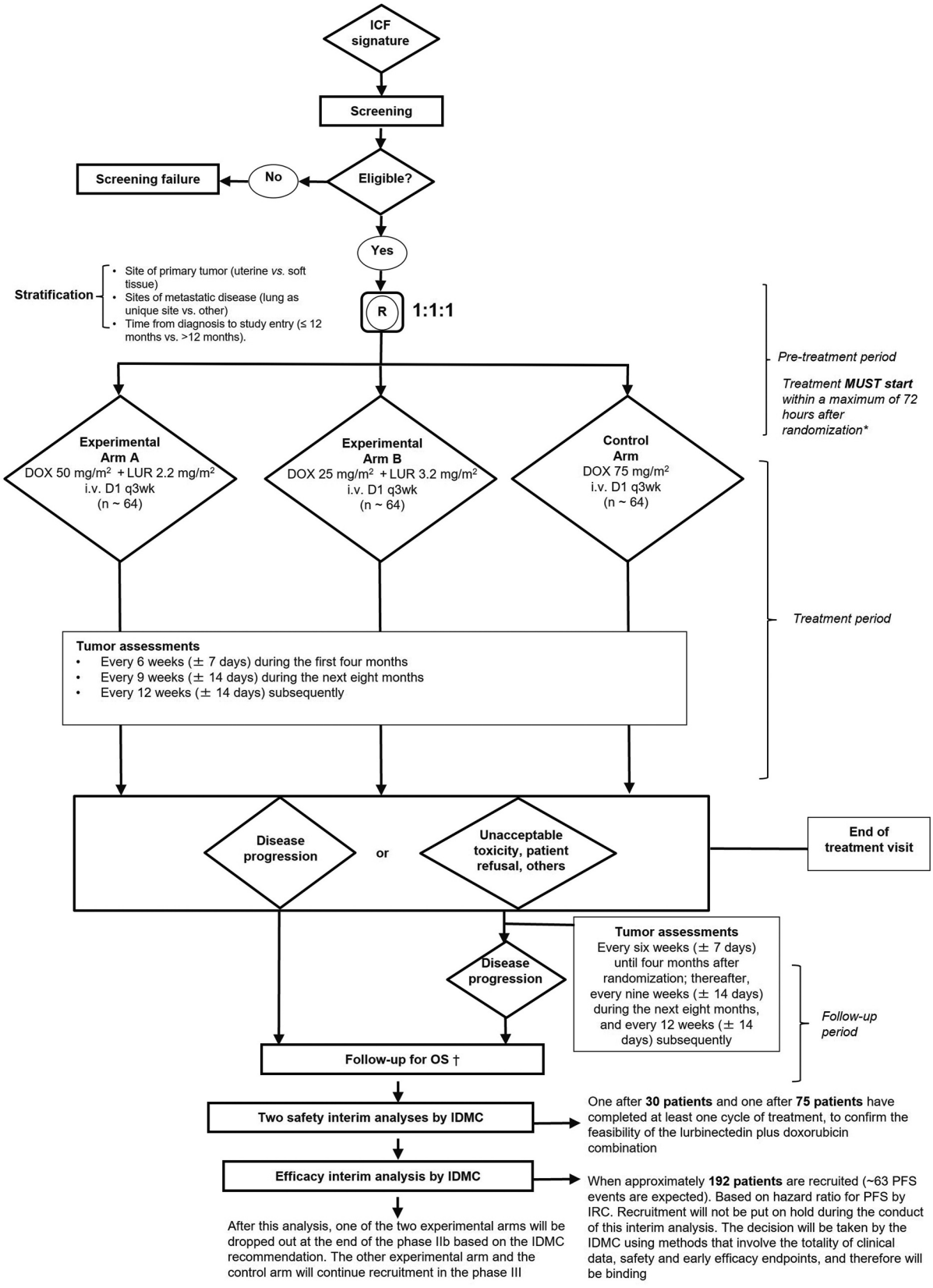

Figure 1. Study design of the phase IIb stage (SaLudo trial).

*Applicable assessments outside accepted windows must be repeated and treatment criteria must be fulfilled before treatment start.

†Patients will be followed every three months (± two weeks) until death of any cause or date of study termination, whichever occurs first. Once the whole recruitment is completed, the survival follow-up procedure will change: all ongoing patients (i.e., patient still alive and not lost to follow-up) will be followed every three months for the first year, and every six months thereafter until death or study completion.

D, day; DOX, doxorubicin; ICF, informed consent form; IRC, Independent Review Committee; i.v., intravenous; LUR, lurbinectedin; OS, overall survival; PFS, progression-free survival; q3wk, every three weeks; R, randomization; RD, recommended dose.

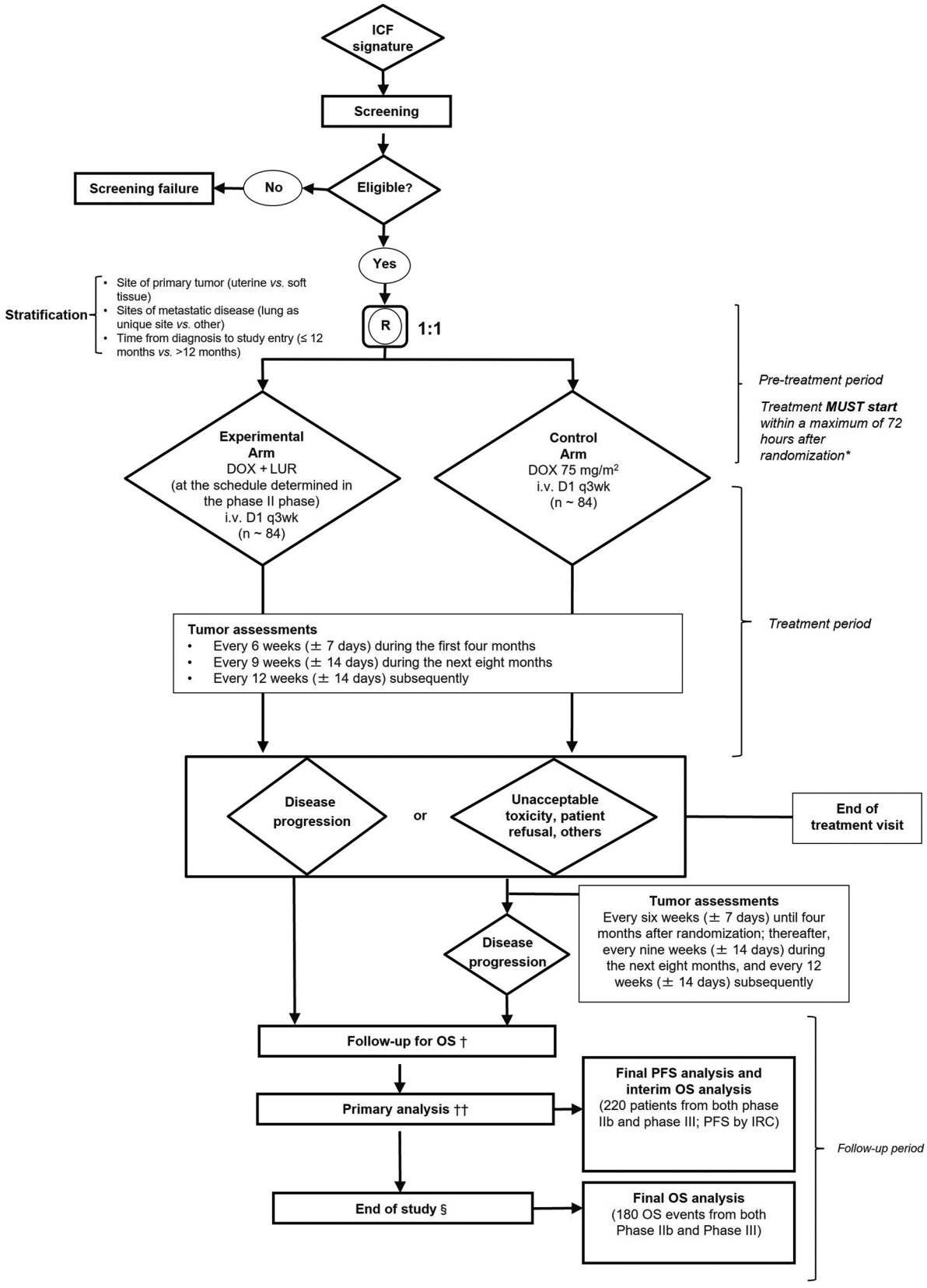

Figure 2. Study design of the phase III stage (SaLudo trial).

*Applicable assessment outside accepted windows must be repeated and treatment criteria must be fulfilled before treatment starts.

†Patients will be followed every three months (± two weeks) until death of any cause or date of study termination, whichever occurs first. Once the whole recruitment is completed, the survival follow-up procedure will change: all ongoing patients (i.e., patient still alive and not lost to follow-up) will be followed every three months for the first year, and every six months thereafter until death or study completion.

††Approximately 14 months after the last patient is randomized.

§Approximately 25 months after the final PFS analysis.

D, day; DOX, doxorubicin; ICF, informed consent form; IRC, Independent Review Committee; i.v., intravenous; LUR, lurbinectedin; OS, overall survival; PFS, progression-free survival; q3wk, every three weeks; R, randomization; RD, recommended dose.

reported outcomes; concomitant therapies and adverse events as per NCI-CTCAE v.5.

Patients who discontinue treatment without progressive disease will be followed every six weeks until four months after randomization; thereafter, every nine weeks during the next eight months, and every 12 weeks subsequently until progressive disease (PD) or start of a new antitumor therapy, death or date of study termination (clinical cutoff), whichever occurs first. After PD is documented or a new antitumor therapy is started, patients will be followed for survival every 3 months until death of any cause or date of study termination, whichever occurs first. Once recruitment is completed, the survival follow-up procedure will change: all ongoing patients will be followed every three months for the first year, and every six months thereafter until death or study completion.

Surgery, stereotactic body radiation therapy (SBRT), or ablative procedures for residual disease are possible after six cycles (in case of non-progressive disease – associated with lack of any tumor increase according to RECIST v.1.1) for both experimental arms and the control arm. After surgery/SBRT or ablative procedures for residual disease, patients in any of the experimental arms may resume treatment (lurbinectedin plus DOX or single agent lurbinectedin) according to the Investigator´s decision within 10 weeks since the last study treatment administration. In the control arm, patients will continue on follow-up, as the maximum cumulative DOX dose has already been achieved.

3.7. Primary and secondary endpoints

The primary endpoint is PFS by IRC defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death. OS is the key secondary endpoint. Other secondary endpoints include PFS by investigator; ORR, duration of response and clinical benefit rate (objective response plus stable disease ≥6 months) both by IRC and investigator; PFS on next line therapy (PFS2); safety; patient-reported outcomes; pharmacokinetics and pharmacogenomics.

3.8. Efficacy evaluations

Tumor assessments will be conducted using RECIST v.1.1 through computed tomography (CT) scans or magnetic resonance imaging (MRI). The frequency of these evaluations will be every six weeks for the first four months post-randomization, every nine weeks for the subsequent eight months, and every 12 weeks thereafter. These assessments will continue until disease progression, initiation of new antitumor therapy, death, or study termination, whichever occurs first. An IRC will evaluate all imaging studies to ensure objective and consistent interpretation of results.

3.9. Safety evaluations

Patients will be evaluable for safety if they have received any partial or complete treatment infusion. All adverse events will be graded according to the NCI-CTCAE v.5. Treatment delays, dose reductions, and reasons for treatment discontinuation will be monitored throughout the study.

An Independent Data Monitoring Committee (IDMC) is overseeing the conduct of the study. Two interim safety analyses will be performed by the IDMC in the phase IIb stage to confirm the feasibility of the lurbinectedin plus DOX combination in the two experimental arms: one after 30 patients and one after 75 patients have completed in total at least one cycle of treatment (Figure 1). Efficacy parameters will not be analyzed in these interim safety evaluations and, therefore, type I error correction will not be applied.

3.10. Planned sample size

SaLuDo is a global phase IIb/III trial being conducted in more than 70 sites in the USA and Europe. Trial enrollment started in September 2023. The prospective assumption is a 40.0% decrease in the risk of progression or death to be achieved with the experimental arm (hazard ratio [HR] = 0.6). PFS for the control arm is expected to be around six months based on data from study LMS-04 (PFS by IRC of 6.2 months in the control arm, DOX alone) [9]. Lurbinectedin is a novel compound closely related to trabectedin. According to the Answers from the Committee for Medicinal Products for Human Use (CHMP) Scientific Advisory Group for Oncology for Revision of the anticancer guideline "*when designing studies aiming to show a difference in PFS in the metastatic setting, if the prognosis is in the order of 2–3 years OS or less, an improvement in median PFS in the order 3–4 months or larger is considered adequate*." With a reasonable timeframe and an affordable required number of events, a risk reduction of 40% is forecasted for the alternative hypothesis to have enough power to reject the null hypothesis.

The study is planned to enroll 360 patients overall. One of the two experimental arms will be dropped at the end of the phase IIb based on an efficacy interim analysis performed when ~ 63 PFS events have occurred; the IDMC recommendation will be binding. This is anticipated after approximately 192 patients have been recruited to the three treatment arms. Selection rules to choose the investigational arm at the efficacy interim analysis by the IDMC will be based on both safety and efficacy. If both experimental arms pass the futility rules, a risk-benefit measure will be calculated using a generalized pairwise comparison between experimental arms.

Recruitment will not be put on hold during the conduct of this interim analysis and no claim for superiority in efficacy between any of the experimental arms against the control arm will be performed (Figure 1). After this interim analysis, approximately 168 additional patients will be enrolled in the second stage (phase III) and randomized to the selected experimental arm and the control arm at an equal 1:1 allocation ratio to complete the target number of 360 patients.

3.11. Statistical analyses

The final PFS analysis will be performed when a total number of 220 PFS events are observed in the selected experimental arm and the control arm combined. This includes the PFS

events collected from patients in the first stage (phase IIb) in the selected experimental arm and control arm (expected to be 105), and the PFS events observed from patients enrolled in the second stage (phase III) (expected to be 115). At that time, an interim analysis for the key secondary endpoint OS will also be conducted. The final OS analysis will be performed when a total number of 180 OS events are observed in the selected arm and the control arm combined from both phase IIb and phase II stages.

The analysis of the primary endpoint (PFS by IRC) will be performed by means of the stratified log-rank test selecting the randomization values of the stratification factors on the intention-to-treat (ITT) population, defined as all randomized patients analyzed in the group where they were allocated. The type-1 error control in face of data-dependent experimental schedule dose selection is achieved by utilizing the closed testing principle together with the inverse normal combination approach as proposed by Carreras *et al*. (2015) [20]. The Hochberg method is selected to determine p-values for the intersection hypothesis. The following hierarchical predefined order is established if the primary endpoint is significant: OS will be analyzed in the multiple testing strategy as key secondary endpoint in a fixed sequence procedure aimed to not inflate type-1 error. No alpha allocation of other endpoints is foreseen. For the key secondary endpoint, OS, the type-1 error control is achieved following the same approach selected for primary endpoint analysis, utilizing the closed testing principle together with the inverse normal combination approach. In addition, the weighted Bonferroni testing procedure will be used to calculate the significance levels and boundaries at the interim and final OS analyses to preserve the type-1 error level control.

Sensitivity analyses for PFS will be performed (e.g., changing censoring rules) to confirm the estimand consistency. Forest plots will be plotted for PFS and OS summarizing main results, stratification and factors/covariates used in multivariable analyses.

3.12. Ethical considerations

The protocol has been approved by each participating institutional ethics review board and the study design has been discussed with Health Agencies. The study will be performed in accordance with the ethical principles of the Declaration of Helsinki and conducted in adherence to the study protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations in which the study is being conducted. Informed written consent will be obtained from all patients before any study-related procedures are conducted.

4. Conclusion

The SaLuDo trial aims to evaluate the efficacy of lurbinectedin combined with doxorubicin as a first-line treatment for metastatic LMS. This investigation is based on promising results from earlier phase I/II studies. The primary objective is to determine if this combination therapy improves PFS compared to the current standard-of-care chemotherapy. If successful, the SaLuDo trial could potentially establish a new first-line treatment option for metastatic LMS patients, addressing an important unmet need in this challenging cancer type.

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The design of the SaLuDo study has been previously presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting: Cote GM, Chawla SP, Demetri G *et al*. Randomized controlled, open-label, phase IIb/III study of lurbinectedin in combination with doxorubicin versus doxorubicin alone as first-line treatment in patients with metastatic leiomyosarcoma. Journal of Clinical Oncology 42(16_suppl), TPS11590-TPS11590 (2024).

Author contributions statement

All authors have made substantial contributions to the writing of this manuscript. Specifically: GM Cote, A Le Cesne, G Boggio, C Fernandez, C Kahatt and V Alfaro contributed to the conception and design of the study protocol. A Nieto was involved in the statistical analysis design and sample size calculation. GM Cote, SP Chawla, G Demetri, B Kasper, RL Jones, J Martin Broto, J Wooley, MC Weiss, S Tafuto, G Badalamenti, I Carrasco, P Peinado, JY Blay, G Boggio, C Fernandez, C Kahatt, and A Le Cesne made substantial contributions to the organization of this study. GM Cote, A Le Cesne, G Boggio, C Fernandez, C Kahatt and V Alfaro wrote the first draft of the manuscript. All authors were involved in revising the manuscript. All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure statement

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No writing assistance was utilized in the production of this manuscript.

Ethical declaration

The protocol has been approved by each participating institutional ethics review board and the study design has been discussed with Health Agencies. The study will be performed in accordance with the ethical principles of the Declaration of Helsinki and conducted in adherence to the study protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations in which the study is being conducted. Informed written consent will be obtained from all patients at each study site before any study-related procedures are conducted.

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Data sharing statement

This is only the description of a Clinical Trial Protocol and therefore is no data to share at this time. Posting of clinical trial summary results will be placed in the European Clinical Trials Database (https://www.clinicaltrialsregister.eu) and ClinicalTrials.gov (https://clinicaltrials.gov) upon completion of this study.

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