RESEARCH TOPIC PRIME10
Vascular Insights into Sarcoma Treatment with Eribulin (VISTE) study

Thematic field of the project
Biomaterials and biomedical engineering for infection research

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Main facility
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Other facility
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Main field of interest
Oncology

Abstract
Background and rationale Soft tissue sarcomas (STS) are rare, heterogeneous malignancies with poor outcomes in advanced and treatment-resistant settings. Chemotherapy resistance is partly driven by tumor microenvironment alterations, particularly abnormal vascular architecture, which leads to hypoxia, heterogeneous drug distribution, and reduced therapeutic efficacy. Eribulin (ERI), a microtubule-targeting agent, has demonstrated clinical activity in sarcoma, including liposarcoma and leiomyosarcoma. Beyond its cytotoxic effects, preclinical evidence suggests that ERI induces vascular remodeling, improving tumor perfusion and reducing hypoxia. This remodeling may enhance intratumoral drug delivery and potentiate the efficacy of co-administered chemotherapeutic agents such as docetaxel. Preliminary data from ERI-resistant leiomyosarcoma xenografts indicate that ERI enhances docetaxel efficacy by modifying drug distribution, likely through vascular effects rather than direct pharmacological interaction. However, the vascular and molecular mechanisms underlying ERI-induced remodeling in human sarcoma remain incompletely understood. The VISTE study aims to elucidate how ERI modulates tumor vasculature and how these changes influence drug distribution and therapeutic response, integrating spatial pathology, multi-omics profiling, metabolomics, and computational modeling using archived samples from the MALIBU clinical study.

Study population Archived sarcoma tumor samples collected during the MALIBU clinical trial (ONC-OSS-07-2018)

Study Objectives Primary objective:
To characterize vascular morphology and spatial tissue features associated with eribulin treatment in archived human sarcoma samples from the MALIBU study through: 1. spatial image analysis of vascular and hypoxia-related features; 2. identification of spatial molecular signatures associated with distinct vascular phenotypes. Secondary objectives: 1. To assess spatial metabolomic patterns associated with vascular remodeling in archived human sarcoma samples. 2. To integrate histologic, molecular, metabolomic, and clinical data using computational models. 3. To identify candidate spatial biomarkers associated with response to eribulin.

Study Endpoints/Outcomes Primary endpoint: Quantitative vascular and spatial pathology parameters, including vessel morphology, vessel density, perivascular features, and hypoxia-related markers. Secondary endpoints: 1. Spatial transcriptomic, proteomic, and/or metabolomic profiles associated with specific vascular regions or phenotypes. 2. Computational model outputs integrating spatial pathology and molecular data in human samples. 3. Candidate tissue biomarkers associated with clinical response patterns in the MALIBU cohort.

Study design Retrospective translational study based on the secondary use of archived tumor samples and pseudonymized clinical data from the MALIBU clinical trial. No active patient recruitment is planned.

Eligibility Criteria Inclusion Criteria Archived tumor samples meeting all of the following: - Histologically confirmed diagnosis of sarcoma. -Samples collected during the MALIBU clinical study. - Availability of pre- and/or post-treatment specimens suitable for spatial analyses. - Availability of associated pseudonymized clinical data relevant to treatment and response. Exclusion Criteria - Insufficient tissue material. -Inadequate tissue quality for spatial, molecular, or imaging analyses.

Study Procedures * Retrieval and quality assessment of archived tumor samples. * Spatial image analysis of vascular architecture and hypoxia markers. * Spatial transcriptomic and proteomic profiling. * Imaging Mass Spectrometry to evaluate metabolomic changes. * Computational modeling of spatial drug distribution using Gaussian Process regression. * Bayesian hierarchical modeling to integrate spatial and molecular datasets. * Validation of preclinical findings in human samples.

Sample size and statistical consideration The sample size is determined by the availability of eligible archived MALIBU tumor specimens. Statistical analyses will employ Bayesian hierarchical modeling using Stan (a probabilistic programming language) R and Python. Key methodological components include: * Hamiltonian Monte Carlo (No U-Turn Sampler). * Prior and posterior predictive simulations. * Convergence diagnostics (effective sample size,

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Gelman–Rubin R̂). * 89% highest posterior density intervals (HPDI) for compatibility intervals. * Multilevel (varying effects) models to account for data clustering. * Non-centered parameterization if needed to reduce divergent transitions. Spatial drug distribution will be modeled using Gaussian Process regression with radial basis function kernels, estimating signal variance and spatial correlation length scale. Posterior hyperparameter estimates will be compared against ground truth in synthetic datasets before application to real imaging data.

Study timetable As a retrospective study based on archived samples, no recruitment phase is required. The anticipated workflow includes: 1. Sample retrieval and quality assessment. 2. Spatial and multi-omics analyses. 3. Computational modeling and integration. 4. Validation and interpretation of findings. 5. Dissemination of results and preparation for prospective translational studies. The study is designed to be completed within the proposed funding timeframe, leveraging existing biological materials and established analytical platforms.

Main technical approaches
Digital pathology, computational pathology, spatial transcriptomics

Scientific references

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4. Grimaudo MS. Assessment of the Mechanisms of Action of Eribulin in Patients with Advanced Liposarcoma Through the Evaluation of Radiological, Functional, and Tissue Responses: A Prospective Monocentric Study (Malibu Study). Cancers (Basel). 2025 Mar 13;17(6):976

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Type of contract

PhD scholarship of € 21.000 gross per year awarded by Humanitas University. This sum is exempt from IRPEF income tax according to the provisions of art. 4 of Law no. 476 of 13th

August 1984 and is subject to social security contributions according to the provisions of art. 2, section 26 and subsequent sections, of Law no. 335 of 8th August 1995 and subsequent modifications.

Borsa di dottorato pari a € 21.000 annui lordi erogata da Humanitas University. Importo non soggetto a tassazione IRPEF a norma dell'art. 4 della L. 13 agosto 1984 n. 476 e soggetto, in materia previdenziale, alle norme di cui all'art. 2, commi 26 e segg., della L. 8 agosto 1995, n. 335 e successive modificazioni.

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