Research Protocol

Tumour Lysis Syndrome Associated with Lenvatinib: an Investigator-Initiated, Retrospective Observational Post-Authorisation Safety Study

Clinical Pharmacology Unit

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RESEARCH PROTOCOL

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1. Background:

The Clinical Pharmacology Unit of ULS São João (ULSSJ) is developing an institutional Active Pharmacovigilance Program based on investigator-initiated Post-Authorization Safety Studies (PASS) that use real-world evidence (RWE) extracted from hospital electronic health records.

The purpose of this program is to proactively identify, quantify and characterize safety concerns highlighted by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) and to contribute local data to the European evidence base. Each PASS is designed as a pragmatic, non-interventional study that follows standardized methods for data extraction, signal verification, and adverse-reaction reporting to the National Pharmacovigilance System. Protocols approved within this framework will also be uploaded to the EMA RWD Studies Catalogue (https://catalogues.ema.europa.eu/catalogue-rwd-studies) to ensure transparency and facilitate regulatory alignment.

The present study constitutes the first proof-of-concept of this initiative and focuses on lenvatinib, a multikinase inhibitor of VEGFR1-3, FGFR1-4, PDGFR-α, RET and KIT, marketed in the European Union as Lenvima[1] and Kisplyx[2] (Eisai GmbH). Lenvatinib is authorised in the European Union for differentiated thyroid carcinoma refractory to radioactive iodine, for hepatocellular carcinoma, for advanced renal cell carcinoma either in combination with everolimus (following prior VEGF-targeted therapy) or with pembrolizumab (first-line setting), and for advanced or recurrent endometrial carcinoma in combination with pembrolizumab[1,2].

Although generally well tolerated, lenvatinib has been associated with metabolic and renal disturbances, and isolated post-marketing reports have described tumor lysis syndrome (TLS) shortly after treatment initiation, particularly in patients with high tumor burden or rapidly proliferating tumors[1-7].

TLS is a potentially life-threatening oncologic emergency caused by the rapid destruction of malignant cells, leading to the release of intracellular contents into the bloodstream8. The resulting metabolic disturbances include hyperuricaemia, hyperphosphataemia, hyperkalaemia, and secondary hypocalcaemia, which can precipitate acute kidney injury, arrhythmia, seizures, or death8. TLS is most frequently associated with highly proliferative haematologic malignancies but has also been reported with solid tumors exposed to targeted therapies [4].

In 2024, a global pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) identified lenvatinib among the anticancer agents with the strongest disproportionality

signals for TLS, reinforcing the biological plausibility of this association[4]. In September 2024, the PRAC detected a new safety signal for TLS associated with lenvatinib-containing products (EPITT 20108) and requested a cumulative case review from the marketing-authorisation holder[5]. Following assessment, in January 2025 the committee concluded that a causal association between lenvatinib and TLS is plausible, recommending an update of the Lenvima and Kisplyx product information to include TLS as a rare adverse reaction and to introduce a specific warning advising biochemical monitoring and prophylactic measures in high-risk patients[6,7].

Given this evolving regulatory context and the absence of real-world data quantifying TLS risk with lenvatinib, we designed an investigator-initiated, retrospective observational study to estimate the incidence proportion of TLS among patients treated with lenvatinib at ULSSJ, to characterize affected cases, and to strengthen the pharmacovigilance evidence supporting the updated EMA risk-management measures.

2. Objectives:

2.1 Primary objective

To estimate the incidence proportion of TLS, including both laboratory TLS and clinical TLS, defined according to Cairo–Bishop criteria, among patients treated with lenvatinib at ULSSJ during the study period.

2.2 Secondary objectives

2.2.1 To describe the clinical characteristics of patients who developed TLS while receiving lenvatinib, including oncologic indication, tumor burden, baseline renal function, laboratory parameters, and outcomes (recovery, sequelae, or death).
2.2.2 To compare the occurrence of TLS across relevant clinical subgroups, such as treatment indication, baseline renal function, and combination with pembrolizumab.
2.2.3 To classify the severity and assess the causality of TLS events using established pharmacovigilance criteria (CTCAE v5.0 and WHO-UMC).
2.2.4 To report all confirmed TLS events with a causal relationship deemed at least “possible” to the National Pharmacovigilance System (INFARMED, I.P.).
2.2.5 To establish the methodological framework for future investigator-initiated PASS using real-world data within the ULSSJ Active Pharmacovigilance Program**.**

3. Methods

3.1 Study design and setting

This is a retrospective, single-centre, observational study using routinely collected data from the electronic health record (EHR) systems of ULSSJ.

3.2 Study period and cohort identification

All adult patients who received at least one dispensation of lenvatinib between 28 May 2015 and 30 November 2025 will be identified through the Hospital Pharmacy Department's Management System (Sistema de Gestão Integrado do Circuito do Medicamento, SGICM) and cross-checked with the institutional prescribing and oncology consultation records to ensure completeness.

3.3 Eligibility criteria

Inclusion criteria

- Age ≥ 18 years;
- Treatment with lenvatinib for any oncologic indication during the study period;
- Availability of laboratory data before and during treatment allowing assessment of tumour lysis syndrome (TLS).

Exclusion criteria

- Concomitant participation in an interventional clinical trial with lenvatinib;
- Insufficient laboratory data to evaluate TLS.

3.4 Exposure and index date

The index date (Day 0) will correspond to the first administration or dispensation of lenvatinib recorded in the EHR or pharmacy system. All subsequent treatment periods, dose adjustments, and interruptions will be captured descriptively.

3.5 Baseline laboratory assessment

Baseline laboratory values will be defined as the measurements obtained within 30 days before Day 0. When multiple results are available, the value closest to Day 0 will be used. The baseline panel should include, whenever possible: uric acid, potassium, phosphate, total and/or corrected calcium, creatinine (for eGFR estimation), LDH, and urea.

3.6 Outcome definition (tumour lysis syndrome)

TLS will be defined according to Cairo–Bishop criteria[8]:

3.6.1 Laboratory TLS (LTLS): presence of at least two of the following abnormalities (either absolute threshold or ≥25% change from baseline):

- Uric acid ≥ 8 mg/dL or ↑ ≥25%;
- Potassium ≥ 6.0 mmol/L or ↑ ≥25%;
- Phosphate ≥ 4.5 mg/dL (1.45 mmol/L) or ↑ ≥25%;
- Corrected calcium ≤ 7.0 mg/dL (1.75 mmol/L) or ↓ ≥25%.

3.6.2 Clinical TLS (CTLS): LTLS accompanied by at least one compatible clinical complication: acute kidney injury (creatinine ≥1.5× baseline or KDIGO stage ≥1), cardiac arrhythmia or sudden death, or seizure.

Each patient will contribute only one event (the first occurrence meeting TLS criteria). LTLS and CTLS will also be described separately.

3.7 Observation period

Patients will be followed from Day 0 until permanent discontinuation of lenvatinib or last recorded contact during the study period. All TLS events occurring while the patient is receiving lenvatinib are eligible for analysis.

3.8 Evaluable cohort and coverage

The evaluable cohort will include patients with both:

- a baseline laboratory panel (Section 3.5); and
- at least one follow-up panel during treatment including the core parameters for TLS adjudication (uric acid, potassium, phosphate, and total or corrected calcium).

All treated patients lacking adequate laboratory information will be recorded as treated but non-evaluable to quantify data coverage.

3.9 Data elements

The following variables will be extracted from EHR and pharmacy systems:

- Demographics: age, sex.
- Oncologic data: diagnosis, stage/metastatic status, simple indicators of tumour burden (largest lesion diameter, number of metastatic sites, LDH at baseline).
- Treatment data: start and stop dates of lenvatinib, dose, adjustments, combination with pembrolizumab, use of TLS prophylaxis (e.g. allopurinol, rasburicase), and hydration.
- Laboratory data: full series relevant to TLS as defined above.

- Clinical events and outcomes: interventions for TLS, hospitalisation, dose interruption or discontinuation, recovery, sequelae, and death.

3.10 Case evaluation and validation

Potential TLS events identified by laboratory screening will be independently reviewed by two clinicians according to Cairo–Bishop criteria. Discrepancies will be resolved by consensus. For each confirmed case, a brief narrative will summarize chronology, laboratory evolution, relevant comorbidities, and therapeutic interventions. Causality will be assessed using the WHO-UMC algorithm, and severity will be graded according to CTCAE v5.0 definitions.

3.11 Statistical analysis

The main outcome measure will be the incidence proportion of TLS among patients treated with lenvatinib, defined as: Number of patients with ≥1 TLS event while on treatment / Number of evaluable exposed patients. Exact 95% binomial (Clopper–Pearson) confidence intervals will be calculated.

Secondary analyses will present the incidence proportion separately for LTLS and CTLS and use all exposed patients as denominator to describe laboratory coverage. Exploratory subgroup comparisons (by indication, renal function, LDH, and combination therapy) will be presented descriptively with risk ratios and 95% confidence intervals and evaluated using Fisher's exact test. All analyses will be performed using R (v4.3+).

3.12 Missing data

No imputation will be applied. The number of patients excluded from the evaluable cohort and the reasons (e.g., missing uric acid or calcium results) will be summarized to describe the completeness of laboratory monitoring.

3.13 Data management and quality assurance

A predefined data dictionary and case-report form will be used. The pseudonymised working database will be stored on secure institutional files with restricted access.

3.14 Study Tasks and Schedule:

Project initiation	December, 2025
Data collection	January-April, 2026
Statistical analysis	May, 2026
Writing and reporting	June-July, 2026

4. Ethical Considerations:

4.1 Study nature and risk assessment

This is a retrospective, non-interventional study using information already collected as part of routine clinical care. No additional diagnostic or therapeutic procedures will be performed for research purposes. The study therefore entails minimal risk to participants and will not interfere with clinical management.

4.2 Informed-consent waiver

Because all data will be obtained from existing institutional databases and electronic health records, obtaining individual informed consent from all past patients would be impracticable. A waiver of informed consent is therefore requested from the Ethics Committee of ULSSJ, justified by:

1. the impossibility of contacting all eligible patients;
2. the public-health relevance of pharmacovigilance studies;
3. the use of pseudonymised data only; and
4. The absence of any foreseeable risk or impact on patient care.

4.3 Data protection and confidentiality

All procedures will comply with the General Data Protection Regulation (GDPR, Regulation EU 2016/679) and the Portuguese Data-Protection Law (Law No. 58/2019). Each participant will be assigned a unique study code, and the correspondence table linking this code to direct identifiers will be stored in a separate encrypted file accessible only to the investigators. The analytical dataset will contain no direct identifiers (no names, national IDs, Hospital Record Number, or full dates of birth). Dates will be shifted or presented as month/year whenever feasible. The pseudonymised database will be stored on secure institutional servers within ULSSJ, protected by individual investigator credentials, and regular backups. No data will be transferred outside the EU or used for commercial purposes.

4.4 Data retention and destruction

All research data will be retained for two years after publication or completion of the project, whichever occurs later. After this period, datasets will be permanently deleted, and the linkage file will be destroyed.

4.5 Oversight and approvals

The protocol will be submitted for review and approval to the Ethics Committee of ULSSJ and to the Data-Protection Officer (Encarregado de Proteção de Dados) prior to data extraction. The study will also be listed in the EMA RWD Studies Catalogue as an investigator-initiated PASS within the Active Pharmacovigilance Program of the Clinical Pharmacology Unit.

4.6 Communication of findings

All confirmed adverse-reaction cases identified during the study will be reported to the National Pharmacovigilance System (INFARMED, I.P.) in accordance with national procedures. Aggregated study results will be disseminated through peer-reviewed publication and institutional reports, with limitation of individual identification.

4.7 Funding

This study is conducted without external financial support. It is an investigator-initiated project developed within the framework of the Active Pharmacovigilance Program of the Clinical Pharmacology Unit at ULSSJ. All activities, including data extraction, analysis, and reporting, will be carried out using institutional resources and existing infrastructure. No funding, materials, or services have been received from any pharmaceutical company.

4.8 Conflicts of Interest

All investigators declare no financial or personal relationships that could influence the conduct or reporting of this study. The investigators have no affiliations or consultancy roles with the marketing-authorisation holder of lenvatinib or its commercial partners. Any potential conflicts identified during the study period will be promptly disclosed to the Ethics Committee of ULSSJ and, if relevant, in the final publication and in the EMA RWD Studies Catalogue entry.

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