STUDY PROTOCOL

Metabolic Reprogramming, Immune Modulation, and Palliative Outcomes Associated With ET-SPACE Whole-Body Infrared Hyperthermia in Patients With Advanced Solid Tumors: An Ambispective Observational Cohort Study

Ambispective observational cohort study

Protocol Identifier: HEAIS-009

ClinicalTrials.gov Identifier: NCT Pending assignment

Sponsor: Zhejiang Hospital

Study Site: Sandun Campus, Zhejiang Hospital, Hangzhou, Zhejiang, China

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Document Control

Official title	Metabolic Reprogramming, Immune Modulation, and Palliative Outcomes Associated With ET-SPACE Whole-Body Infrared Hyperthermia in Patients With Advanced Solid Tumors: An Ambispective Observational Cohort Study
Brief title	ET-SPACE Whole-Body Infrared Hyperthermia in Patients With Advanced Solid Tumors
Protocol identifier	HEAIS-009
ClinicalTrials.gov identifier	NCT Pending assignment
Sponsor	Zhejiang Hospital
Study site	Sandun Campus, Zhejiang Hospital, Hangzhou, Zhejiang, China
Study design	Single-center, ambispective, non-interventional observational cohort
Study period	January 1, 2022 to December 31, 2028, with outcome follow-up extending beyond the final inclusion date
Version and date	Version 1.0; August 25, 2026

Version History

Version	Date	Description
1.0	August 25, 2026	Initial registry-ready protocol integrating the retrospective and prospective study components.

Protocol Synopsis

Rationale	To characterize patient-centered, immunologic, nutritional, metabolic, tumor-related, and safety outcomes observed after ET-SPACE whole-body infrared hyperthermia in a broad real-world population with advanced solid tumors.
Primary objective	To estimate the mean within-participant change in the EORTC QLQ-C30 global health status score from baseline to Week 4 after the first hyperthermia session.
Secondary objectives	To describe short-term and sustained changes in symptom burden, cancer pain, functional status, nutritional status, systemic inflammation, lymphocyte subsets, analgesic use, safety, treatment feasibility, tumor response, progression-free survival, and overall survival.
Population	Consecutive adults with unresectable locally advanced, recurrent, or metastatic solid tumors who initiated at least one ET-SPACE whole-body infrared hyperthermia session during the study period.

Sampling	Non-probability consecutive sampling of all eligible participants within a fixed calendar window.
Exposure	Initiation of ET-SPACE whole-body infrared hyperthermia during routine care. The study does not assign hyperthermia, systemic therapy, radiotherapy, surgery, or supportive care.
Index date	Date of the first eligible ET-SPACE whole-body infrared hyperthermia session.
Core assessments	Baseline within 7 days before the index session; acute assessment 24 to 72 hours after the index session; Week 4 plus or minus 7 days; Week 12 plus or minus 14 days; survival follow-up for up to 12 months.
Primary outcome	Mean change in EORTC QLQ-C30 global health status score from baseline to Week 4.
Sample size	All eligible participants will be included. The prospective patient-reported outcome component will aim for at least 85 participants with paired baseline and Week 4 EORTC QLQ-C30 data.
Primary analysis	Linear mixed-effects model with time as a fixed effect and participant as a random intercept; adjusted and sensitivity analyses will address cohort component, concurrent treatment, confounding, missing data, and informative attrition.
Ethics	Prospective enrollment and research-specific assessments will begin only after approval of the current protocol or an applicable amendment. Retrospective data use will follow the waiver or consent determination of the Ethics Review Committee of Zhejiang Hospital.

Abbreviations

Abbreviation	Definition
AE	Adverse event
BMI	Body mass index
CI	Confidence interval
CR	Complete response
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire
ESAS-r	Edmonton Symptom Assessment System-Revised
MAR	Missing at random

Abbreviation	Definition
MNAR	Missing not at random
NLR	Neutrophil-to-lymphocyte ratio
ORR	Objective response rate
OS	Overall survival
PG-SGA	Patient-Generated Subjective Global Assessment
PFS	Progression-free survival
PLR	Platelet-to-lymphocyte ratio
PNI	Prognostic Nutritional Index
PROM	Patient-reported outcome measure
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SII	Systemic Immune-Inflammation Index
WBH	Whole-body hyperthermia

Background and Rationale

Advanced solid tumors are frequently accompanied by symptom burden, cancer pain, functional decline, malnutrition, systemic inflammation, treatment intolerance, and impaired quality of life. These domains are clinically meaningful even when tumor-directed options are limited, and they may change over a shorter interval than radiographic or survival outcomes.

Whole-body hyperthermia exposes the body to controlled thermal stress. Its physiologic and biological effects vary substantially by temperature, duration, device, hydration, anesthesia, comorbidity, and concurrent anticancer treatment. Prior clinical and translational reports suggest that whole-body hyperthermia can alter peripheral immune-cell trafficking, cytokine concentrations, perfusion, stress responses, and treatment tolerability, but the direction and duration of these changes are heterogeneous and temperature dependent (1-5). A recent Zhejiang Hospital study demonstrated the feasibility of water-filtered infrared A whole-body hyperthermia combined with immune checkpoint inhibition in advanced gastrointestinal tumors, while emphasizing the need for larger and broader real-world evaluations (1).

ET-SPACE whole-body infrared hyperthermia is used in routine care at Zhejiang Hospital for selected patients with advanced malignancies. Clinical indications, session number, temperature, duration, and concomitant therapies are individualized by the treating team. This creates an opportunity to construct an inclusive longitudinal cohort that integrates routinely collected clinical data with prospective patient-reported and laboratory assessments.

The study is observational. It is designed to estimate within-participant changes and associations after treatment exposure, not to establish causal efficacy. Tumor response and survival will be interpreted in the context of concomitant anticancer therapy, disease trajectory, treatment selection, and other measured and unmeasured confounding. The phrase metabolic reprogramming in the official title refers to exploratory changes in prespecified systemic metabolic biomarkers; it will not be interpreted as evidence of tumor-cell metabolic reprogramming unless dedicated metabolomic analyses are performed.

Study Objectives and Hypotheses

Primary Objective

To estimate the mean change from baseline to Week 4 in the EORTC QLQ-C30 global health status score among participants with paired assessments.

Secondary Objectives

- To estimate the durability of quality-of-life changes through Week 12.
- To characterize changes in cancer pain, multidimensional symptom burden, ECOG performance status, analgesic requirements, and unplanned health-care use.
- To characterize changes in nutritional status using PNI, PG-SGA category, body weight, BMI, serum albumin, and prealbumin when available.
- To characterize acute and short-term changes in systemic immune-inflammatory measures, including SII, NLR, PLR, lymphocyte counts, lymphocyte subsets, and selected cytokines when available.
- To characterize acute and short-term changes in prespecified metabolism-related laboratory measures, including serum lactate, fasting glucose, triglycerides, and lactate dehydrogenase when systematically collected.
- To describe WBH delivery, treatment completion, physiologic tolerance, and WBH-related adverse events.
- To describe ORR, DCR, PFS, and OS without attributing these outcomes to WBH independently of concomitant treatment.

- To identify baseline and treatment-related factors associated with favorable patient-centered outcomes and safe achievement of planned thermal exposure.

Prespecified Hypotheses

- The mean EORTC QLQ-C30 global health status score at Week 4 will differ from baseline.
- Changes in patient-reported outcomes will be accompanied by measurable changes in nutritional and immune-inflammatory indices in at least a subset of participants.
- Observed responses will vary according to tumor type, baseline performance status, nutritional risk, concomitant therapy, achieved thermal exposure, and number of completed sessions.

Study Design

This is a single-center, ambispective, non-interventional cohort study. The retrospective component will identify eligible participants from electronic health records and hyperthermia treatment logs for treatment initiated from January 1, 2022 until prospective activation. The prospective component will consecutively enroll eligible participants after ethics approval and follow them under the same core definitions through December 31, 2028.

The exposure of interest is initiation of at least one ET-SPACE whole-body infrared hyperthermia session. No treatment is assigned by the protocol. Decisions regarding hyperthermia, anticancer therapy, palliative procedures, analgesia, nutritional support, hydration, and other supportive care remain the responsibility of the treating clinicians.

Study Setting

The study will be conducted at Sandun Campus, Zhejiang Hospital, Hangzhou, Zhejiang, China. Data may originate from oncology clinics, inpatient wards, the hyperthermia unit, laboratory and imaging systems, pharmacy and treatment administration systems, nursing records, and follow-up contacts conducted under approved procedures.

Study Timeline

Milestone	Timing
Retrospective observation window begins	January 1, 2022
Protocol version 1.0	August 25, 2026
Prospective activation	After approval of the current protocol or applicable amendment
Final inclusion date	December 31, 2028
Primary outcome completion	Approximately 4 weeks after the final participant initiates WBH
Study completion	Approximately 12 months after the final participant initiates WBH

Study Population

The study will seek a broad real-world population. Participants will not be excluded on the basis of sex, primary tumor type, metastatic site, treatment line, previous or concomitant anticancer therapy, ECOG performance status, comorbidity burden, or number of hyperthermia sessions. Missing individual outcomes will not by itself make a participant ineligible.

Inclusion Criteria

- Age 18 years or older at the first eligible WBH session.
- Histologically, cytologically, or clinically and radiologically confirmed advanced solid malignancy, including unresectable locally advanced, recurrent, or metastatic disease.
- Initiation of at least one ET-SPACE whole-body infrared hyperthermia session at Zhejiang Hospital between January 1, 2022 and December 31, 2028. Sessions that were interrupted or not completed remain eligible for safety analyses.
- Records sufficient to confirm the solid-tumor diagnosis and initiation of ET-SPACE WBH.
- For the prospective component, written informed consent from the participant or legally authorized representative. For the retrospective component, consent or waiver according to the ethics determination.

Exclusion Criteria

- No confirmed malignant solid tumor, including treatment only for a benign condition or an isolated hematologic malignancy.
- ET-SPACE WBH was planned but never initiated, or only local or regional hyperthermia was administered.
- Available records are insufficient to confirm participant identity, diagnosis, or WBH initiation.

- Duplicate records; duplicate episodes will be consolidated under one coded participant identifier rather than analyzed as separate participants.
- For the prospective component, refusal or withdrawal of consent, unless continued use of previously collected data is explicitly permitted by the consent form and ethics committee.

Recruitment and Sampling

Non-probability consecutive sampling will be used. Retrospective participants will be identified through structured searches of hyperthermia treatment records and electronic medical records. Prospective participants will be screened consecutively when WBH is planned as part of routine care. A screening log will document the number assessed, eligible, enrolled, excluded, and reasons for exclusion without public disclosure of identifying information.

Exposure and Routine Clinical Care

ET-SPACE Whole-Body Infrared Hyperthermia

ET-SPACE WBH uses infrared energy to raise body temperature in a controlled clinical environment. In routine practice, the commonly intended mild hyperthermia range is approximately 38.5 to 39.0 degrees C with an intended maintenance period of approximately 60 minutes, but the actual target, ramp-up duration, maintenance duration, cooling period, hydration, monitoring, interruption criteria, and total number of sessions are individualized. These parameters are observed and recorded; they are not mandated by this protocol.

- Session date and treatment sequence number.
- Device identification and treatment location.
- Baseline temperature, target temperature, maximum achieved core temperature, time to target, maintenance time, and total session duration.
- Temperature measurement method and frequency.
- Pre-session, intra-session, and post-session blood pressure, heart rate, respiratory rate, oxygen saturation, symptoms, hydration, and clinically indicated laboratory monitoring.
- Treatment interruption, early termination, failure to achieve target temperature, and documented reason.
- Concomitant medication, analgesia, antipyretics, fluid administration, and other supportive measures.

Concomitant Treatments

All systemic anticancer therapy, immunotherapy, targeted therapy, endocrine therapy, radiotherapy, surgery, interventional procedures, bone-modifying therapy, transfusion, antimicrobial therapy, nutritional support, palliative care, and analgesic therapy received during the observation window will be recorded when available. Timing will be expressed relative to the index WBH session to support confounding control and interpretation.

Assessment Schedule

Assessment	Baseline	24-72 h	Week 4	Week 12	Up to 12 mo
Eligibility and consent	X				
Demographics, cancer history, comorbidity	X		Update	Update	Update
WBH exposure and vital signs	X/session	X	Each session	Each session	As applicable
Blood count and routine chemistry	X	X if available	X	X	As clinically indicated
Immune subsets and cytokines	X if available	X if available	X if available	Optional	
EORTC QLQ-C30	X		X	X	Optional
Pain NRS and ESAS-r	X		X	X	As clinically indicated
ECOG performance status	X		X	X	Each follow-up
PG-SGA, weight, BMI	X		X	X	As clinically indicated
Analgesic use and OMEDD	X		X	X	Update
Adverse events	Baseline review	X	Continuous	Continuous	Through 30 days after last WBH
Tumor assessment	Most recent		If performed	Target window	Routine imaging
Progression and survival					Continuous

Assessment windows are anchored to the first eligible WBH session. Retrospective data will be mapped to the closest prespecified window using rules defined in the Statistical Analysis Plan. h, hours; mo, months; NRS, Numeric Rating Scale; OMEDD, oral morphine equivalent daily dose.

Data Sources and Variables

Core Clinical Domains

- Demographics: age, sex, residence, height, weight, BMI, tobacco and alcohol history when available.

- Cancer characteristics: primary site, histology, molecular subtype, diagnosis date, stage, recurrent or metastatic sites, measurable disease, tumor burden proxies, previous lines of treatment, and treatment intent.
- Clinical status: ECOG performance status, vital signs, comorbidities, recent infection, corticosteroid use, hospitalization, organ dysfunction, and frailty or geriatric measures when available.
- Treatment: current and prior systemic therapy, radiotherapy, surgery, local procedures, supportive therapy, nutritional intervention, analgesic therapy, and temporal relation to WBH.
- Laboratory data: complete blood count, liver and renal function, electrolytes, glucose, lipid profile, albumin, prealbumin, CRP, lactate dehydrogenase, serum lactate, and other clinically obtained tests.
- Immune data: absolute lymphocyte count, CD3-positive, CD4-positive, and CD8-positive T cells, CD4 to CD8 ratio, B cells, natural killer cells, immunoglobulins, and selected cytokines when available.
- Patient-centered outcomes: EORTC QLQ-C30, ESAS-r, pain NRS, ECOG performance status, PG-SGA, weight change, sleep, distress, and tumor-specific validated modules when prospectively administered.
- Tumor and survival outcomes: RECIST 1.1 response, progression date, death date, last known alive date, and cause of death when reliably available.
- Safety and feasibility: session completion, target temperature achievement, treatment interruption, acute symptoms, AE grade and attribution, SAE, and unplanned care.

Data Provenance

Each data element will retain a source label, collection date and time when available, and status as routine-care retrospective data, routine-care prospective data, or research-specific prospective assessment. Derived variables will be generated from source values according to locked algorithms in the Statistical Analysis Plan.

Outcome Measures

Type	Outcome	Metric	Participant-level time frame
Primary	EORTC QLQ-C30 global health status	Mean change; 0-100, higher is better	Baseline to Week 4
Secondary	EORTC QLQ-C30 global health status	Mean change	Baseline to Week 12
Secondary	Cancer pain intensity	Mean change on 0-10 NRS; higher is worse	Baseline to Week 4
Secondary	ESAS-r total symptom burden	Mean change; 0-90, higher is worse	Baseline to Week 4
Secondary	ECOG performance status	Improved, stable, or deteriorated by grade	Baseline to Week 4
Secondary	PNI	Mean change; albumin plus 5 times lymphocyte count	Baseline to Week 4
Secondary	SII	Mean change; platelets times neutrophils divided by lymphocytes	Baseline, 24-72 h, Week 4
Secondary	CD4 to CD8 T-cell ratio	Mean change when available	Baseline, 24-72 h, Week 4
Secondary	PG-SGA nutritional category	Category A, B, or C transition	Baseline to Week 12
Secondary	Daily OMEDD	Mean change in mg/day	Baseline to Week 4
Secondary	WBH-related adverse events	Participants and sessions with any AE and Grade 3 or higher AE	First WBH through 30 days after final WBH
Secondary	Objective response rate	Complete or partial response by RECIST 1.1	Through Week 12 assessment
Secondary	Disease control rate	Complete response, partial response, or stable disease	Through Week 12 assessment
Secondary	Progression-free survival	Time to progression or death	Up to 12 months
Secondary	Overall survival	Time to death from any cause	Up to 12 months

Exploratory Outcomes

- Mean changes in absolute lymphocyte count, NLR, PLR, lymphocyte-to-monocyte ratio, CRP, albumin, prealbumin, body weight, and BMI.
- Mean changes in peripheral natural killer cell proportion and selected circulating cytokines, including interleukin-6, tumor necrosis factor-alpha, interleukin-10, and interferon-gamma, when systematically measured.
- Mean changes in serum lactate, fasting plasma glucose, triglycerides, and lactate dehydrogenase. Each analyte will be analyzed and reported separately.
- Tumor-specific patient-reported outcome modules, with each validated instrument scored and reported separately.
- Session-level target temperature achievement, total thermal exposure, treatment completion, and factors associated with interruption or acute intolerance.
- Associations between cumulative WBH exposure and outcomes using methods that address time-dependent exposure and immortal-time bias.

Outcome Definitions

EORTC QLQ-C30 scores will be calculated according to the official scoring manual. All scales are transformed to 0 to 100; higher functioning and global health scores indicate better status, whereas higher symptom scores indicate greater symptom burden (6-8).

Pain will be recorded on an 11-point NRS from 0, no pain, to 10, worst imaginable pain. ESAS-r includes nine symptoms each rated 0 to 10; the prespecified total ranges from 0 to 90, with higher scores indicating greater symptom burden (9). ECOG performance status ranges from 0 to 5, with higher grades indicating poorer status (10).

PNI will be calculated as serum albumin in g/L plus 5 multiplied by absolute lymphocyte count in 10^9/L. SII will be calculated as platelet count multiplied by neutrophil count and divided by lymphocyte count, with all counts drawn from the same specimen. NLR and PLR will use absolute counts from the same blood draw.

RECIST 1.1 will define complete response, partial response, stable disease, and progressive disease (11). ORR is the proportion with complete or partial response; DCR is the proportion with complete response, partial response, or stable disease. PFS begins on the index date and ends at first documented progression or death. OS begins on the index date and ends at death from any cause.

Sample Size and Precision

The overall cohort will include every eligible participant in the fixed study window, with no fixed maximum. For the primary PROM analysis, a 10-point mean difference in EORTC QLQ-C30 global health status is used as a clinically interpretable planning target. Assuming a standard deviation of the within-participant change of 25 points, a two-sided alpha of 0.05, and 90 percent power, approximately 66 evaluable paired participants are required. Allowing for approximately 20 percent incomplete paired assessment, the prospective component will aim for at least 85 participants with evaluable baseline and Week 4 data. This calculation is a planning benchmark rather than a cap on enrollment.

The effective sample size will vary by outcome because retrospective and routine-care data are not uniformly measured. Every analysis will report the number eligible, the number with available data at each time point, and the number included in the model. Small tumor-specific subgroups will be described without unstable multivariable modeling.

Statistical Analysis Overview

- Descriptive statistics will characterize the cohort overall and by retrospective or prospective component, tumor group, concomitant therapy, and WBH exposure.
- The primary analysis will estimate change in EORTC QLQ-C30 global health status using a linear mixed-effects model with time as a fixed effect and participant as a random intercept. The baseline to Week 4 contrast will be reported with a 95 percent confidence interval and two-sided P value.
- Adjusted analyses will consider prespecified confounders, including age, sex, tumor group, disease status, baseline ECOG performance status, baseline outcome value, comorbidity, concurrent anticancer therapy, corticosteroid exposure, nutritional support, and cohort component, subject to events and sample-size constraints.
- Repeated continuous biomarkers will be analyzed using mixed-effects models or generalized estimating equations. Skewed biomarkers may be log transformed, with geometric mean ratios or back-transformed contrasts reported.
- Binary outcomes will be summarized using proportions and 95 percent confidence intervals. Ordinal outcomes will be summarized by category and analyzed using ordinal or multinomial models when appropriate.
- PFS and OS will be described using Kaplan-Meier methods. Cox models will be exploratory. Cumulative WBH exposure will not be treated as a fixed baseline variable; time-dependent or landmark methods will be used to reduce immortal-time bias.
- Missingness will be described by variable, time point, and cohort component. Mixed models under MAR will be the primary approach for repeated outcomes. Multiple imputation and MNAR sensitivity analyses will be used where justified.
- The primary outcome will use a two-sided alpha of 0.05. Secondary outcomes will be interpreted with effect estimates and confidence intervals; false discovery rate control will be applied within prespecified biomarker domains.

The standalone Statistical Analysis Plan provides detailed estimands, derivation rules, analysis populations, model specifications, diagnostics, missing-data procedures, subgroup analyses, sensitivity analyses, and reporting conventions.

Bias and Confounding Control

- Selection bias: use consecutive sampling, retain interrupted treatments in the safety cohort, document screening and missingness, and avoid exclusion based solely on absence of a specific outcome.
- Confounding by indication and concurrent treatment: measure clinical indication, disease burden, treatment line, baseline prognosis, and concomitant therapies; present adjusted analyses as associations rather than causal effects.
- Information bias: preserve source and timing metadata, use standardized windows and algorithms, and conduct blinded secondary data checks where feasible.
- Regression to the mean and natural disease fluctuation: report baseline trajectories when earlier measurements are available and interpret uncontrolled pre-post changes cautiously.
- Retrospective-prospective heterogeneity: include cohort component in adjusted models and perform prospective-only and retrospective-only sensitivity analyses.
- Immortal-time bias: model cumulative session exposure as time varying or use prespecified landmark analyses.
- Survivor and attrition bias: describe reasons for missing follow-up, use all available repeated measures, and conduct informative-missingness sensitivity analyses.

Safety Monitoring

Because the study does not assign treatment, clinical monitoring follows routine WBH practice and institutional emergency procedures. The research team will abstract adverse events and serious events temporally associated with WBH. Attribution will be categorized as unrelated, unlikely, possible, probable, or definite. Severity will be graded using CTCAE version 5.0 to maintain consistency across the 2022 to 2028 observation period (12). If the institution formally adopts another version, the protocol and analysis plan will document mapping and version-specific reporting.

- Pre-session clinical suitability and vital-sign review according to routine care.
- Core temperature and vital-sign monitoring during treatment.
- Documentation of hypotension, tachycardia, hypoxemia, electrolyte disturbance, glucose disturbance, persistent fever, dizziness, syncope, seizure, skin or soft-tissue injury, mucosal irritation, and any other clinically relevant event.
- Immediate interruption or termination of treatment when clinically indicated by the treating team.
- Review of unexpected serious WBH-related events by the principal investigator and ethics committee according to institutional requirements.

A formal independent data monitoring committee is not planned because this is a non-interventional observational study. This does not replace routine clinical safety oversight or required ethics reporting.

Data Management and Quality Assurance

- Each participant will be assigned a unique coded study identifier. The linkage key will be stored separately with restricted access.
- Electronic case-report forms will use predefined formats, range checks, required fields for core variables, and date logic checks.
- Data extraction algorithms, manual abstraction instructions, and variable definitions will be version controlled.
- A sample of critical variables will undergo source-data verification, including eligibility, index date, WBH exposure, primary outcome, progression, death, and serious adverse events.
- Duplicate participants and repeated episodes will be reconciled before database lock.
- All derivations will be reproducible from retained source variables. Statistical code and analysis outputs will be version controlled.
- Research data will be stored on approved institutional systems and retained according to institutional policy and applicable law.

Database Lock

Before final analysis, the team will resolve eligibility queries, confirm primary-outcome windows, freeze derivation code, document unresolved missingness, and approve a database-lock memorandum. Analyses not prespecified before lock will be labeled exploratory or post hoc.

Ethical and Regulatory Considerations

The study will be conducted in accordance with the Declaration of Helsinki, applicable Chinese laws and regulations, institutional policies, and the approved protocol. The existing ethics document reviewed during study planning has an approval period ending May 22, 2026 and addresses a related but not identical clinical study. It will not be represented as current approval for this protocol. Prospective enrollment and research-specific assessments under HEAIS-009 require a current approval, continuation approval, protocol amendment, or new approval that explicitly covers this ambispective cohort.

Consent

For the retrospective component, the ethics committee will determine whether informed consent may be waived because the research uses existing records and poses minimal additional risk. For the prospective component, written informed consent will be obtained before research-specific assessments. A legally authorized representative may provide consent when permitted. Refusal will not affect clinical care.

Confidentiality

No participant names, medical record numbers, direct contact details, facial images, signatures, or other direct identifiers will appear in public registry documents, publications, or shared analysis datasets. Only aggregate or deidentified results will be disseminated.

Dissemination and Data Sharing

Results will be submitted to ClinicalTrials.gov when applicable and reported in peer-reviewed publications and scientific meetings. Reporting will follow STROBE and, for routinely collected health data, relevant RECORD recommendations (13-15). Results will be reported regardless of whether observed changes are favorable, unfavorable, or null.

Deidentified participant-level data, the data dictionary, and analysis code may be made available to qualified researchers after publication upon reasonable request, subject to ethics approval, institutional review, a data-use agreement, and protection of participant confidentiality. Data that could permit reidentification will not be shared.

Protocol Deviations and Amendments

Protocol deviations affecting eligibility, informed consent, primary-outcome timing, safety reporting, or data integrity will be documented. Substantive changes to objectives, outcomes, eligibility, follow-up, or analysis will be approved before implementation when required, updated in the registry, and added to the version history. Changes made after database lock will be clearly labeled and justified.

References

1. Liu P, Wu J, Chen L, et al. Water-filtered infrared A radiation hyperthermia combined with immunotherapy for advanced gastrointestinal tumours. Cancer Med. 2024;13(14):e70024. doi:10.1002/cam4.70024.
2. Brancato L, Gorbaslieva I, Rudenko O, et al. The MATTERS Trial: safety and tolerability of whole-body hyperthermia at 41.50 degrees C in combination with chemotherapy in metastatic cancer patients. Cancer Res Commun. 2026;6(2):273-283. doi:10.1158/2767-9764.CRC-25-0660.
3. Dieing A, Ahlers O, Kerner T, et al. Whole body hyperthermia induces apoptosis in subpopulations of blood lymphocytes. Immunobiology. 2003;207(4):265-273. doi:10.1078/0171-2985-00236.
4. Ahlers O, Hildebrandt B, Dieing A, et al. Stress induced changes in lymphocyte subpopulations and associated cytokines during whole body hyperthermia of 41.8-42.2 degrees C. Eur J Appl Physiol. 2005;95(4):298-306. doi:10.1007/s00421-005-0009-4.
5. Atanackovic D, Pollok K, Faltz C, et al. Patients with solid tumors treated with high-temperature whole body hyperthermia show a redistribution of naive/memory T-cell subtypes. Am J Physiol Regul Integr Comp Physiol. 2006;290(3):R585-R594. doi:10.1152/ajpregu.00014.2005.
6. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-376.
7. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 Scoring Manual. 3rd ed. European Organisation for Research and Treatment of Cancer; 2001.
8. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139-144.

9. Watanabe SM, Nekolaichuk CL, Beaumont C. The Edmonton Symptom Assessment System, a proposed tool for distress screening in cancer patients: development and refinement. Psychooncology. 2012;21(9):977-985.
10. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.
11. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline, version 1.1. Eur J Cancer. 2009;45(2):228-247.

12. National Cancer Institute. Common Terminology Criteria for Adverse Events, Version 5.0. Published November 27, 2017.
13. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-1457.
14. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data statement. PLoS Med. 2015;12(10):e1001885.
15. Langan SM, Schmidt SAJ, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology. BMJ. 2018;363:k3532.
16. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med. 2011;30(4):377-399.
17. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research. BMJ. 2009;338:b2393.
18. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B. 1995;57(1):289-300.

Appendix: Minimum Core Dataset

- **Eligibility and provenance:** coded identifier; eligibility status; source system; retrospective or prospective component; consent or waiver status; index date.
- **Cancer status:** primary site; histology; stage; metastatic sites; diagnosis date; measurable disease; line of therapy; treatment intent.
- **Baseline prognosis:** age; sex; ECOG status; BMI; comorbidities; recent infection; corticosteroid use; albumin; CRP; complete blood count.
- **WBH exposure:** session date; target and achieved temperature; duration; vital signs; interruption; reason; supportive measures; adverse events.
- **Patient-centered outcomes:** EORTC QLQ-C30; ESAS-r; pain NRS; ECOG status; PG-SGA; weight; OMEDD.
- **Outcome follow-up:** Week 4 and Week 12 assessment dates; imaging response; progression; death; last contact; unplanned hospitalization.