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MESO-FAP: Protocol for a Phase 1a/1b Study of [177Lu]Lu-FAP-2286 Radioligand Therapy Combined with Nivolumab and Ipilimumab in Advanced Malignant Pleural Mesothelioma

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Abstract

Background

Malignant pleural mesothelioma (MPM) remains an aggressive malignancy associated with poor prognosis despite advances in systemic therapy. Dual immune checkpoint blockade with nivolumab and ipilimumab has improved survival outcomes and is established as a first-line treatment option for unresectable disease; however, durable responses occur in only a subset of patients, and treatment resistance remains common. Increasing evidence implicates the tumour microenvironment, particularly cancer-associated fibroblasts (CAFs) and stromal-mediated immune exclusion, as important contributors to therapeutic resistance. Fibroblast activation protein (FAP), highly expressed on activated CAFs within mesothelioma stroma, represents a promising theranostic target. FAP-directed radioligand therapy using [^{177}Lu]Lu-FAP-2286 has demonstrated favourable tumour targeting and encouraging preclinical anti-tumour activity and may enhance anti-tumour immunity through modulation of the tumour microenvironment.

Results

MESO-FAP is an investigator-initiated multicentre phase 1a/1b study evaluating [^{177}Lu]Lu-FAP-2286 in combination with nivolumab and ipilimumab in patients with unresectable or advanced malignant pleural mesothelioma. The study comprises a dose-escalation phase using a conventional 3 + 3 design followed by a dose-expansion cohort. Eligible participants must demonstrate FAP-positive disease on screening [^{68}Ga]Ga-FAP-2286 PET/CT. Primary endpoints include safety, dose-limiting toxicities, determination of the maximum tolerated dose, and establishment of the recommended phase 2 dose. Secondary and exploratory endpoints include treatment response, survival outcomes, radiation dosimetry, molecular imaging biomarkers, and integrated translational analyses incorporating tissue and blood-based biomarkers.

Conclusions

MESO-FAP is the first prospective study investigating FAP-targeted radioligand therapy combined with dual immune checkpoint blockade in mesothelioma. The study incorporates a theranostic framework integrating molecular imaging, dosimetry, and translational biomarker analyses to establish the safety profile and recommended Phase 2 dose of stromal-directed radio-immunotherapy in MPM while generating mechanistic insights to guide future biomarker-driven clinical development.

Trial registration

Australian New Zealand Clinical Trials Registry (ANZCTR),

ACTRN12626000505303.

Registered 23 April 2026,

https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=391496&isReview=true

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive malignancy arising from the pleural mesothelium and remains associated with poor clinical outcomes despite advances in systemic therapy. [1–3] Dual immune checkpoint blockade with nivolumab and ipilimumab has improved overall survival and is now an established first-line treatment option for unresectable disease. [4, 5] Nevertheless, objective response rates remain modest and most patients ultimately experience disease progression.[6, 7] Emerging evidence suggests that both primary and acquired resistance to immunotherapy are influenced by the complex tumour microenvironment characteristic of mesothelioma, which is enriched with cancer-associated fibroblasts (CAFs), extracellular matrix deposition, immunosuppressive macrophages, and relative exclusion of effector T cells.[8, 9]

Fibroblast activation protein (FAP) is a membrane-bound serine protease highly expressed on activated CAFs and stromal elements within a broad range of epithelial malignancies, including mesothelioma. [10–12] FAP-positive CAFs contribute to extracellular matrix remodelling, tumour invasion, angiogenesis, and suppression of anti-tumour immune responses. [11, 13–15] Because expression in normal adult tissues is limited, FAP has emerged as an attractive target for both molecular imaging and targeted radionuclide therapy. [10, 11] FAP-targeted PET imaging demonstrates high tumour-to-background contrast and has shown promise for non-invasive assessment of tumour biology, patient selection, and treatment monitoring.[16–19]

[^{177}Lu]Lu-FAP-2286 is a peptide-based FAP-targeted radioligand designed to selectively deliver beta radiation to FAP-expressing stromal compartments.[20–22] Preclinical studies have demonstrated favourable tumour uptake, prolonged tumour retention, and significant anti-tumour activity with limited normal tissue exposure.[23] In addition to direct radiation-induced cytotoxicity, FAP-targeted radioligand therapy may alter the tumour microenvironment through stromal remodelling, enhanced antigen presentation, and activation of interferon-associated immune pathways.[24, 25] Experimental studies have demonstrated increased CD8 + T-cell infiltration and enhanced responsiveness to immune checkpoint inhibition following FAP-directed radionuclide therapy.[26–28]

Clinical evaluation of [^{177}Lu]Lu-FAP-2286 is ongoing in advanced solid tumours. [20, 29–31] Early clinical experience has demonstrated an acceptable safety profile and preliminary evidence of anti-tumour activity, with disease control observed in approximately one-third of heavily pre-treated patients. Haematological toxicities have represented the most common treatment-related adverse events, while clinically significant organ toxicity has been uncommon at lower administered activity levels.[20, 29]

MESO-FAP was developed on the hypothesis that stromal-directed radioligand therapy may enhance responsiveness to immune checkpoint blockade by modifying the tumour microenvironment and reducing stromal-mediated immune resistance. The study is a multicentre Phase 1a/1b investigator-

initiated trial evaluating the safety, feasibility, and preliminary biological and clinical activity of [^{177}Lu]Lu-FAP-2286 in combination with nivolumab and ipilimumab in patients with unresectable or advanced MPM.

METHODS

Study design

MESO-FAP is a prospective, multicentre, open-label, investigator-initiated Phase 1a/1b dose-escalation and expansion study enrolling approximately 20–30 patients to evaluate [^{177}Lu]Lu-FAP-2286 in combination with nivolumab and ipilimumab in patients with unresectable or advanced malignant pleural mesothelioma.

The study comprises two sequential components: a Phase 1a dose-escalation component using a conventional 3 + 3 design to determine dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D), followed by a Phase 1b expansion cohort treated at the RP2D to further evaluate preliminary anti-tumour activity and translational endpoints. Figure 1.

The study is being conducted at Fiona Stanley Hospital and Sir Charles Gairdner Hospital, Western Australia, under the coordination of the Nuclear Medicine Clinical Trials Unit at Fiona Stanley Hospital.

Proposed participant flow through screening, enrolment, treatment allocation, dose escalation, expansion cohort participation, and analysis populations.

Study objectives

Study objectives are summarised in Table 1. The primary objectives are to determine the safety profile, MTD and RP2D of [^{177}Lu]Lu-FAP-2286 in combination with nivolumab and ipilimumab. Secondary and exploratory objectives will evaluate preliminary efficacy, imaging biomarkers, dosimetry, and other translational correlates.

Table 1
Study objectives and endpoints for MESO-FAP

Objective category	Objective	Endpoint(s)
Primary	Determine the safety and tolerability of [^{177}Lu]Lu-FAP-2286 in combination with nivolumab and ipilimumab and establish the MTD/RP2D	Incidence and severity of treatment-emergent adverse events (AEs); dose-limiting toxicities (DLTs); maximum tolerated dose (MTD); recommended Phase 2 dose (RP2D)
Secondary	Evaluate preliminary anti-tumour activity	Objective response rate (ORR) according to mRECIST; disease control rate (DCR); duration of response; progression-free survival (PFS); overall survival (OS)
Secondary	Assess imaging biomarkers using [^{68}Ga]Ga-FAP-2286 PET/CT	Baseline tumour uptake, SUVmax, SUVpeak, tumour-to-background ratios, whole-body FAP-positive tumour volume, total lesion FAP uptake, uptake heterogeneity, longitudinal changes following treatment, and associations with clinical outcomes.
Secondary	Characterise biodistribution, blood clearance and radiation dosimetry	Organ absorbed dose (Gy/GBq); tumour absorbed dose; cumulative radiation exposure, blood clearance parameters, and biodistribution characteristics.
Secondary	Assess quality of life	Changes in EORTC QLQ-C30 and QLQ-LC13 scores
Exploratory	Evaluate tumour microenvironment modulation	Tumour-cell and stromal FAP expression, cancer-associated fibroblast abundance, CD8 + and CD4 + T-cell infiltration, macrophage phenotype, PD-L1 expression, and inflammatory signatures
Exploratory	Evaluate circulating biomarkers	Circulating cytokines, immune phenotyping, and ctDNA dynamics
Exploratory	Explore radiomic and molecular correlates	Associations between PET radiomic features, molecular markers and treatment response

Participant Eligibility

Eligible participants are adults aged 18 years or older with histologically confirmed unresectable or advanced malignant pleural mesothelioma meeting protocol-defined eligibility criteria summarised in Table 2. Participants must have measurable disease according to modified RECIST criteria, ECOG performance status 0–1, and adequate haematological, renal, and hepatic function.

Screening [^{68}Ga]Ga-FAP-2286 PET/CT must demonstrate FAP-positive disease. At least one measurable tumour lesion must show visually appreciable tracer uptake above blood-pool background, consistent

with significant tumour FAP expression, as determined by central nuclear medicine physician review. Because MESO-FAP is a Phase 1 study, a qualitative imaging criterion is used rather than a predefined SUV threshold. Patients with absent or minimal tumour uptake not exceeding background blood-pool activity are considered ineligible for enrolment.

Major exclusion criteria include previous FAP-targeted radioligand therapy, prior severe immune-related toxicity associated with checkpoint inhibitor therapy, active uncontrolled infection, significant uncontrolled comorbidity, and active autoimmune disease requiring systemic treatment. Patients with vitiligo, type 1 diabetes mellitus, Graves' disease, residual hypothyroidism requiring hormone replacement only, or psoriasis not requiring systemic treatment within the preceding two years remain eligible.

Key laboratory eligibility criteria include haemoglobin ≥ 90 g/L, absolute neutrophil count ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, serum creatinine ≤ 1.5 × upper limit of normal (ULN) or creatinine clearance ≥ 40 mL/min, alanine aminotransferase and aspartate aminotransferase ≤ 3 × ULN (or ≤ 5 × ULN in the presence of hepatic involvement), and total bilirubin ≤ 1.5 × ULN.

Study Treatment

Participants will receive [^{177}Lu]Lu-FAP-2286 in combination with nivolumab and ipilimumab. [^{177}Lu]Lu-FAP-2286 will be administered approximately 3–5 days before immunotherapy treatment cycles. Nivolumab will be administered at a fixed dose of 360 mg intravenously on Days 1 and 22 of each 42-day cycle, while ipilimumab will be administered at 1 mg/kg intravenously on Day 1 of each cycle.

[^{177}Lu]Lu-FAP-2286 Production, Administration, and Dosimetry

[^{177}Lu]Lu-FAP-2286 is a peptide-based fibroblast activation protein (FAP)-targeted radioligand comprising the FAP-2286 peptide linked via a DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) chelator to lutetium-177. Lutetium-177 is a β-emitting radionuclide with a physical half-life of approximately 6.65 days and emits medium-energy beta particles with a tissue penetration range of approximately 1–2 mm together with low-energy γ emissions suitable for post-therapy imaging.

[^{177}Lu]Lu-FAP-2286 will be manufactured and supplied under Good Manufacturing Practice (GMP) conditions by Novartis or its designated radiopharmacy partner as a sterile radiolabelled preparation for intravenous administration, calibrated to planned administration date and time, and within the validated expiry period. Radiopharmaceutical preparation and quality assurance procedures will be performed according to manufacturer specifications and institutional radiopharmacy standards.

[^{177}Lu]Lu-FAP-2286 will be administered by intravenous infusion over approximately 5–10 minutes in an ambulatory treatment setting. Following radioligand administration, participants will receive intravenous hydration with normal saline (minimum 500 mL) to facilitate radiopharmaceutical clearance in accordance with institutional procedures.

The dose-escalation component will evaluate three planned [^{177}Lu]Lu-FAP-2286 activity levels of 1.85 GBq, 3.7 GBq, and 5.5 GBq. These activity levels were selected based on available clinical safety, biodistribution, and dosimetry data from ongoing studies of [^{177}Lu]Lu-FAP-2286 and provide a stepwise escalation across a clinically relevant therapeutic range.

Dose escalation will proceed using a conventional 3+3 design. Participants will receive [177Lu]Lu-FAP-2286 at their assigned activity level once every 6 weeks for up to four treatment cycles, provided there is no disease progression, unacceptable toxicity, or other protocol-defined safety concern. Dose-limiting toxicities will be assessed during the first treatment cycle according to protocol-defined criteria. The maximum tolerated dose will be defined as the highest administered activity level at which no more than one of six evaluable participants experiences a dose-limiting toxicity during the DLT assessment period. Following determination of the RP2D, an expansion cohort of approximately 6–12 additional participants will be enrolled.

Baseline [^{68}Ga]Ga-FAP-2286 PET/CT Imaging

All participants will undergo screening [^{68}Ga]Ga-FAP-2286 PET/CT prior to enrolment. Imaging will be performed according to institutional radiopharmacy and imaging procedures. PET/CT images will be reviewed locally by experienced nuclear medicine physicians for assessment of tumour FAP expression and disease distribution. All screening PET studies will subsequently undergo central review to confirm eligibility for [^{177}Lu]Lu-FAP-2286 treatment. Eligibility requires at least one measurable tumour lesion demonstrating visually appreciable uptake above blood-pool background, consistent with FAP-positive disease.

Quantitative PET parameters, including SUVmax, SUVpeak, tumour-to-background ratios (including tumour-to-blood pool and tumour-to-liver ratios), whole-body FAP-positive tumour volume, total lesion FAP uptake, and measures of uptake heterogeneity, will be recorded as exploratory imaging biomarkers. Repeat [^{68}Ga]Ga-FAP-2286 PET/CT imaging after approximately two treatment cycles will be performed to evaluate longitudinal changes in tumour uptake and imaging biomarkers associated with treatment response and resistance. Exploratory analyses will investigate associations between baseline and longitudinal PET-derived biomarkers, radiation dosimetry, and clinical outcomes.

Radiation Dosimetry

Radiation dosimetry analyses will characterise biodistribution and estimate absorbed radiation dose to tumour lesions and normal tissues. During Cycle 1, the first three participants will undergo intensive dosimetry imaging using planar scintigraphy and SPECT/CT at approximately 4 hours, 24 hours, and 5 days following treatment administration. Subsequent participants and later treatment cycles will undergo abbreviated dosimetry consisting primarily of 24-hour SPECT/CT imaging.

Serial blood samples will be collected at predefined post-treatment timepoints, nominally approximately 4, 24, and 48 hours following [177Lu]Lu-FAP-2286 administration, to assess blood radioactivity clearance

and support biodistribution and dosimetry analyses

Dosimetric analyses will be performed using the MIM software platform to estimate absorbed radiation doses to tumour lesions, bone marrow, kidneys, liver, and whole-body compartments. Absorbed dose estimates will be expressed as radiation dose per administered activity (Gy/GBq), and cumulative radiation exposure across treatment cycles will be evaluated. Exploratory analyses will investigate associations between absorbed tumour dose, imaging biomarkers, and clinical outcomes.

Imaging and Translational Assessments

Conventional anatomical imaging for disease response assessment will be performed at protocol-defined intervals and evaluated according to modified RECIST criteria for mesothelioma.

The MESO-FAP study incorporates an integrated translational research programme to investigate mechanisms of treatment response and resistance. Archival tumour tissue obtained during routine diagnostic procedures will be collected where available.

Participants may additionally consent to optional image-guided tumour biopsies at predefined translational research timepoints, including during treatment after approximately 1–2 treatment cycles and, where clinically appropriate, at disease progression. Tissue analyses will evaluate tumour-cell and stromal FAP expression, cancer-associated fibroblast abundance, CD8+ and CD4+ T-cell infiltration, macrophage phenotype, PD-L1 expression, and inflammatory immune signatures.

Peripheral blood samples will be collected for immune profiling, circulating cytokine analyses, circulating tumour DNA assessment, and exploratory biomarker studies. Integrated analyses will evaluate relationships between imaging biomarkers, tissue biomarkers, radiation dosimetry, and clinical outcomes.

Outcomes

Outcome measures correspond to the predefined study objectives and are summarised in Table 1. The primary endpoints are safety and tolerability, including treatment-related adverse events, dose-limiting toxicities (DLTs), determination of the maximum tolerated dose (MTD), and establishment of the recommended Phase 2 dose (RP2D) of [^{177}Lu]Lu-FAP-2286 in combination with nivolumab and ipilimumab.

Secondary endpoints include objective response rate, disease control rate, progression-free survival, overall survival, quality-of-life outcomes, and radiation dosimetry measures. Exploratory endpoints include quantitative molecular imaging biomarkers, translational tissue and blood-based biomarkers, and integrated analyses investigating associations between imaging characteristics, radiation dosimetry, biological correlates, and clinical outcomes. Figure 2.

Statistical considerations

As this is an early-phase, first-in-disease combination study, formal hypothesis-driven power calculations were not performed. The primary purpose of the study is to establish safety, identify dose-limiting toxicities (DLTs), determine the maximum tolerated dose (MTD), and establish the recommended Phase 2 dose (RP2D) of [^{177}Lu]Lu-FAP-2286 when administered in combination with nivolumab and ipilimumab.

The dose-escalation component uses a conventional 3+3 design. Depending on the number of dose-escalation cohorts explored and occurrence of DLTs, enrolment is anticipated to include approximately 20–30 participants across both study phases.

Safety analyses will include all participants receiving at least one administration of study treatment. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and summarised descriptively according to frequency and severity.

Tumour response will be assessed using modified RECIST criteria for mesothelioma. Objective response rate and disease control rate will be summarised descriptively. Progression-free survival and overall survival will be estimated using Kaplan–Meier methodology with corresponding confidence intervals where appropriate.

Exploratory analyses will investigate relationships between imaging biomarkers, radiation dosimetry, tissue and circulating biomarkers, and clinical outcomes. Given the limited sample size, these analyses will be considered hypothesis-generating and interpreted descriptively.

Ethics and dissemination

The MESO-FAP study was approved by the WA Health Central Human Research Ethics Committee (approval number: EC00481) and is sponsored by South Metropolitan Health Service (SMHS). The study has been prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12626000505303).

The study will be conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines, and applicable national and institutional regulatory requirements. Written informed consent will be obtained from all participants prior to enrolment and completion of study-specific procedures.

Study findings will be disseminated through peer-reviewed publications, scientific conference presentations, and academic reporting. Authorship will be determined in accordance with the recommendations of the International Committee of Medical Journal Editors (ICMJE).

RESULTS

The MESO-FAP study has received ethics approval from the WA Health Central Human Research Ethics Committee (EC00481) and has been prospectively registered with the Australian New Zealand Clinical

Trials Registry (ACTRN12626000505303). Site initiation and study activation procedures are underway, with participant recruitment planned to commence following completion of site activation activities. No participant outcome data are available at the time of manuscript submission.

DISCUSSION

Malignant pleural mesothelioma remains a disease with substantial unmet clinical need despite recent advances in immunotherapy. Although dual immune checkpoint blockade with nivolumab and ipilimumab has improved survival outcomes and established a new first-line treatment standard, objective responses remain limited and most patients ultimately experience disease progression. In the CheckMate 743 trial, nivolumab plus ipilimumab achieved an objective response rate of approximately 40%, with a median progression-free survival of 6.8 months and a median overall survival of 18.1 months; however, long-term follow-up demonstrated that a substantial proportion of patients still developed progressive disease.[4, 5] Increasing evidence suggests that resistance is influenced not only by tumour-intrinsic factors but also by the complex tumour microenvironment characteristic of mesothelioma.[32, 33] This microenvironment is enriched with cancer-associated fibroblasts (CAFs), extracellular matrix deposition, immunosuppressive myeloid populations, and relative exclusion of effector T cells, all of which may contribute to immune evasion and resistance to checkpoint inhibition.

MESO-FAP evaluates a stromal-directed therapeutic strategy designed to target this biological vulnerability. Rather than focusing solely on tumour cells, the study targets FAP-expressing stromal compartments within the tumour microenvironment. FAP is highly expressed on activated CAFs and has been implicated in extracellular matrix remodelling, immune exclusion, angiogenesis, and maintenance of tumour-supportive stromal architecture. [10, 11] By selectively delivering beta radiation to FAP-expressing stromal elements, [^{177}Lu]Lu-FAP-2286 may disrupt these pro-tumoural pathways while simultaneously enhancing susceptibility to immune checkpoint blockade. Figure 3. Preclinical studies have demonstrated that FAP-targeted radioligand therapy may promote immune activation, increase tumour infiltration by CD8-positive T cells, and augment the activity of PD-1/PD-L1-directed immunotherapy, providing a strong biological rationale for combination treatment.

The theranostic framework incorporated within MESO-FAP represents an additional strength of the study design. Baseline [^{68}Ga]Ga-FAP-2286 PET/CT is used not only for molecular patient selection but also for quantitative assessment of tumour FAP expression and disease distribution. Eligibility requires demonstration of FAP-positive disease, defined as visually appreciable tumour uptake above blood-pool background in at least one measurable lesion following central review. This approach ensures evidence of target expression while avoiding potentially arbitrary quantitative PET thresholds in an early-phase clinical study. Longitudinal molecular imaging may additionally provide insights into treatment-induced changes in tumour biology and identify imaging biomarkers associated with therapeutic response, resistance, and radiation dosimetry.

A major objective of MESO-FAP is to generate translational data that may inform future development of stromal-directed radio-immunotherapy. The study incorporates integrated tissue, blood-based, and imaging biomarker analyses to investigate mechanisms of response and resistance. Optional serial tumour biopsies and peripheral blood sampling will enable assessment of tumour-cell and stromal FAP expression, cancer-associated fibroblast abundance, immune-cell infiltration, macrophage phenotype, PD-L1 expression, circulating cytokines, and circulating tumour DNA dynamics. Correlation of these findings with molecular imaging and dosimetry data may improve understanding of treatment mechanisms and support development of future biomarker-driven patient-selection strategies.

The study may also contribute important dosimetric data regarding [^{177}Lu]Lu-FAP-2286 in mesothelioma. Although clinical experience with FAP-targeted radioligand therapy is expanding, data regarding absorbed tumour dose, normal-organ exposure, and optimal activity levels remain limited. The integrated dosimetry programme incorporated within MESO-FAP may help define relationships between administered activity, tumour targeting, absorbed dose, toxicity, and clinical outcome, thereby informing future optimisation of treatment protocols.

Several limitations should be acknowledged. As a Phase 1 study, MESO-FAP is primarily designed to establish safety, determine the maximum tolerated dose, and identify the recommended Phase 2 dose of [^{177}Lu]Lu-FAP-2286 in combination with nivolumab and ipilimumab. The relatively small sample size and single-arm design limit interpretation of efficacy outcomes and exploratory biomarker associations. Furthermore, although translational analyses may generate important biological insights, these findings will be hypothesis-generating and require validation in subsequent studies. Nevertheless, MESO-FAP represents the first prospective investigation of FAP-targeted radioligand therapy combined with dual immune checkpoint blockade in mesothelioma and will establish the safety profile, feasibility, and preliminary biological activity of stromal-directed radio-immunotherapy while generating critical imaging, dosimetric, and translational data to support future clinical development.

CONCLUSIONS

MESO-FAP is the first prospective clinical trial to investigate fibroblast activation protein-targeted radioligand therapy with [^{177}Lu]Lu-FAP-2286 in combination with nivolumab and ipilimumab in malignant pleural mesothelioma. Through integration of molecular imaging, radiation dosimetry, and translational biomarker analyses, the study aims to establish the safety and feasibility of this novel stromal-directed radio-immunotherapy strategy and to generate mechanistic insights that may inform future therapeutic development in mesothelioma and other stromal-rich malignancies.

Proposed biological mechanism of action of [^{177}Lu]Lu-FAP-2286 combined with nivolumab and ipilimumab, including cancer-associated fibroblasts, stromal remodelling, radiation-induced immune activation, and checkpoint blockade synergy.

Declarations

Ethics approval and consent to participate

The MESO-FAP study was approved by the WA Health Central Human Research Ethics Committee (approval number EC00481). The study will be conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines, and applicable national and institutional regulatory requirements. Written informed consent will be obtained from all participants prior to enrolment and completion of study-specific procedures.

Consent for publication

Not applicable.

Availability of data and materials

No datasets were generated or analysed during the current study. Data generated during the MESO-FAP study will be available from the corresponding author on reasonable request following study completion and in accordance with institutional, ethical, and regulatory requirements.

Competing interests

The MESO-FAP study is an investigator-initiated study sponsored by South Metropolitan Health Service (SMHS). Advanced Accelerator Applications International S.A. (ADACAP), a Novartis company, provides [177Lu]Lu-FAP-2286 and HKG-301 cold kits for radiopharmaceutical preparation for use in the MESO-FAP study under an investigator-initiated trial agreement. Novartis had no role in the preparation of this manuscript or in the decision to submit for publication. The remaining authors declare that they have no competing interests.

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Authors' contributions

ZA conceived and designed the study and drafted the manuscript. WSL, WLC, AC, ACa, AR, and RF contributed to study conception and design and critically revised the manuscript for important intellectual content. All authors reviewed, edited, and approved the final manuscript.

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Figures

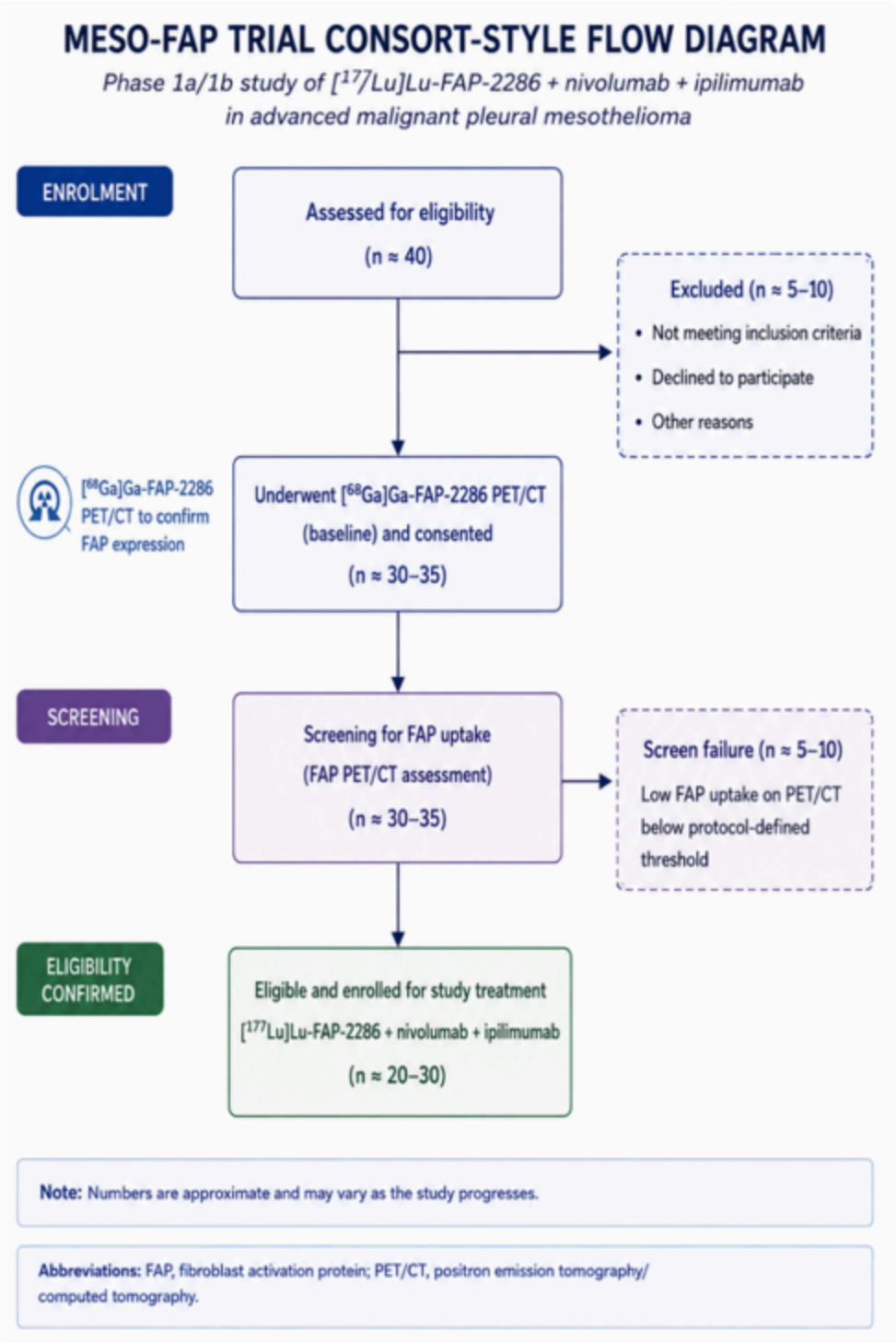


Figure 1

CONSORT-style trial flow diagram

Proposed participant flow through screening, enrolment, treatment allocation, dose escalation, expansion cohort participation, and analysis populations.

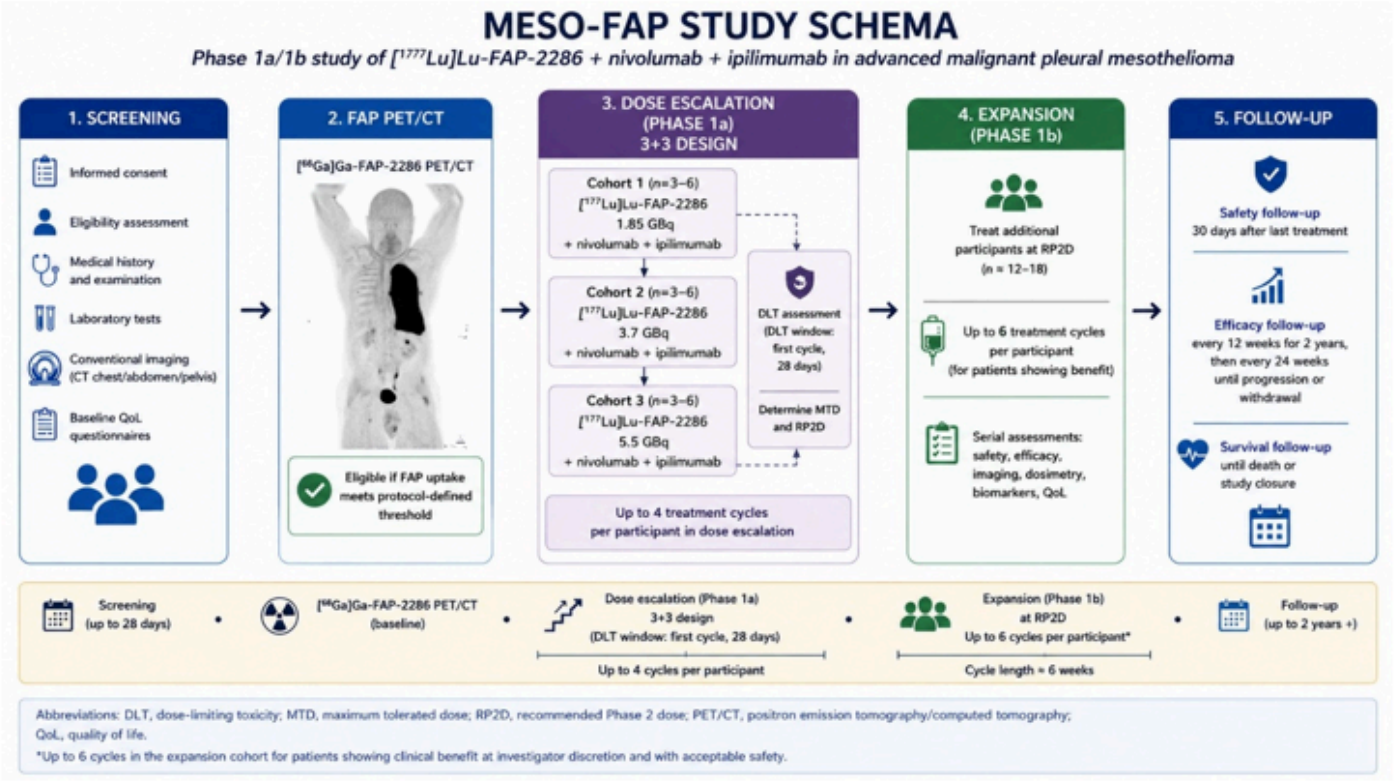


Figure 2

MESO-FAP study schema

Overview of the MESO-FAP Phase 1a/1b study design illustrating timing of [^{68}Ga]Ga-FAP-2286 PET/CT, [^{177}Lu]Lu-FAP-2286 administration, immunotherapy, dosimetry imaging, translational sampling, and follow-up assessments.

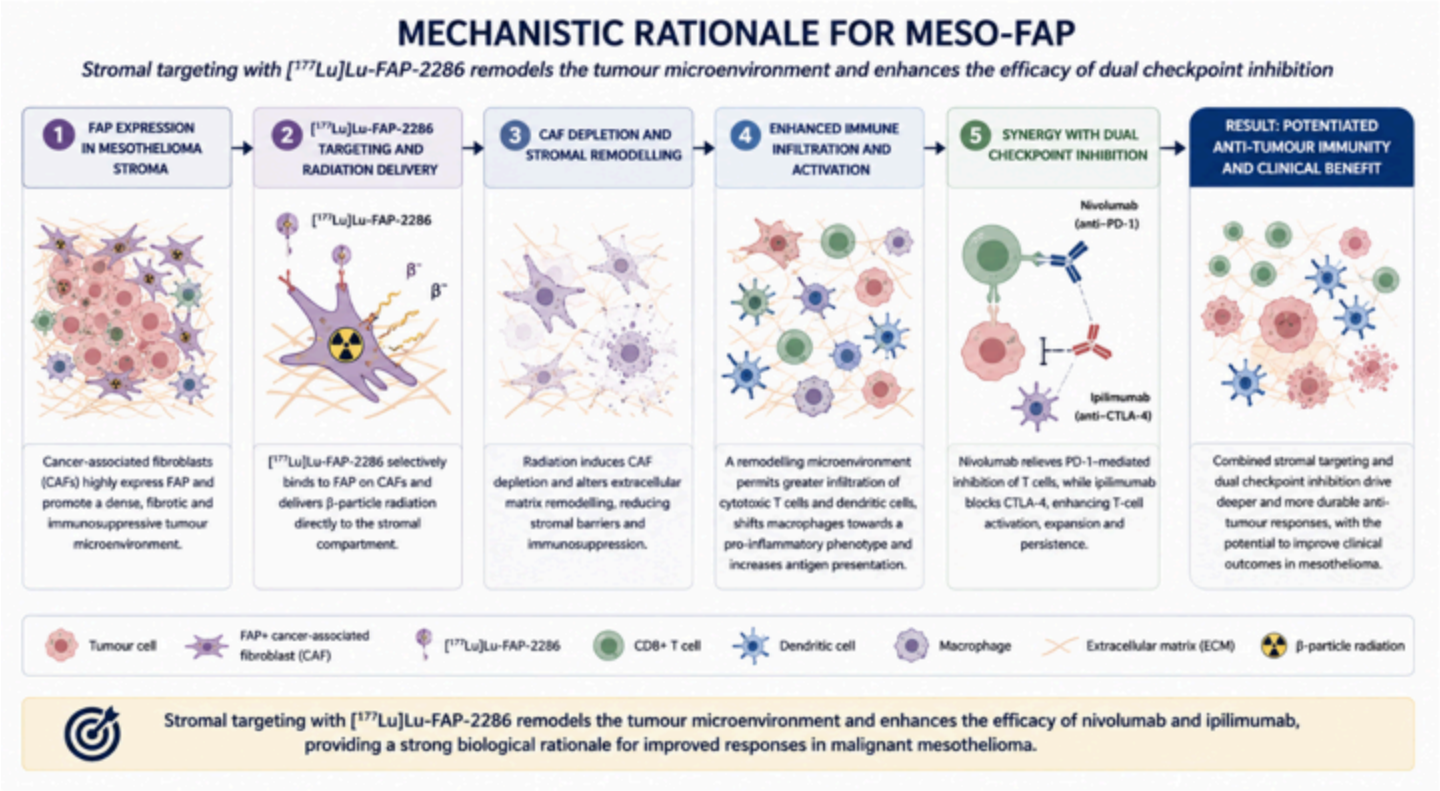


Figure 3

Mechanistic rationale for stromal-directed radio-immunotherapy in MESO-FAP

Proposed biological mechanism of action of [^{177}Lu]Lu-FAP-2286 combined with nivolumab and ipilimumab, including cancer-associated fibroblasts, stromal remodelling, radiation-induced immune activation, and checkpoint blockade synergy.