

The CONVERGENCE trial protocol: A phase II/III trial for conversion surgery for gastric cancer with peritoneal metastases

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Study protocol

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Abstract

Background: The benefit of surgical resection in addition to systemic therapy in patients with gastric/gastroesophageal cancer and peritoneal metastases (GCPM) is controversial. This CONVERGENCE trial aims to study the potential benefits of conversion surgery in patients with peritoneal metastases.

Methods: This is a prospective, pragmatically designed, multicentre, randomized, investigator-initiated phase II/III trial. Patients with synchronous GCPM who have undergone either systemic therapy (including 1L chemotherapy +/- targeted therapy +/- immunotherapy) +/- peritoneal directed chemotherapy with response would be randomized in 1:1 ratio to Arm 1 (Conversion surgery followed by systemic +/- peritoneal directed chemotherapy or Arm 2 (continual systemic +/- peritoneal directed chemotherapy). In the initial Phase II trial, 136 patients will be recruited and randomized. The primary endpoint is overall survival; main secondary endpoints include progression-free survival, R0 resection and complete cytoreduction rates, surgical morbidity/mortality and quality of life outcomes. If pre-defined thresholds of improved overall survival are met, the trial will expand to adequately power a phase III randomized controlled trial (n=300).

Discussion: If survival benefit in conversion gastrectomy is demonstrated, this could potentially be a new standard of care for patients with peritoneal metastases from gastric or gastroesophageal junction cancer. Conversely, negative findings may lead to the avoidance of unnecessary surgical procedures and morbidity in these patients.

Trial registration number(ClinicalTrials.gov ID): NCT07241715

BACKGROUND

Patients with gastric/gastroesophageal junction cancer and peritoneal metastases (GCPM) have debilitating symptoms and a dismal prognosis of approximately 10 months survival with conventional palliative chemotherapy, among which bowel obstruction stands out as one of the most severe and potentially life-threatening complications. [1-5] Currently, systemic treatment +/- immunotherapy +/- targeted therapy is the standard of care in the management of metastatic gastric cancer. [6-9] In addition, several novel treatment approaches have been described with promising early results for patients with GCPM, such as combining systemic treatment with emerging peritoneal-directed approaches such as bi-directional chemotherapy (systemic and intraperitoneal (IP) chemotherapy and cytoreductive surgery with Hyperthermic Intra-peritoneal Chemotherapy (CRS-HIPEC).

Within the framework of bidirectional chemotherapy, several routes of IP chemotherapy delivery have been previously reported. These include delivery of normothermic drugs via an indwelling catheter, laparoscopic approach for administration of HIPEC and pressurized intraperitoneal aerosol chemotherapy (PIPAC) with promising results. [7-12] While multiple clinical trials have demonstrated the benefit of therapies like immune checkpoint inhibition or zolbetuximab in suitable patients, majority of

GCPM patients are PD-L1 CPS <1, HER2-negative and CLDN18 negative, representing a significant population with limited treatment options beyond conventional systemic chemotherapy and underscore the urgent need for better therapeutic strategies. [13-18] Currently, the optimal treatment strategy for patients with good response and improvement or resolution of the PM is uncertain. In patients with complete or near-complete resolution of PM, the concept of “conversion” surgery comprising radical gastrectomy with D2 lymphadenectomy after bidirectional therapy has been described by Arigami, Chia and Ishigami et al, with reported median overall survival (OS) of 24.2 – 34.6 months. [8, 10, 11] However, it remains unclear if the observed improvement in OS is attributable to the treatment intervention of conversion surgery or the selection of patients with favourable disease biology who had exhibited good response to treatment. [12] In addition, the extent of optimal surgical resection remains contentious, with the CYTO-CHIP cohort reporting sequelae of HIPEC with or without CRS that included 90-day mortality rate of 8.4%, major morbidity rate of 54.3% and surgical complication rate of 37.7%. Hence, there is an urgent need to investigate the possible benefit and harm of conversion surgery in GCPM patients with good response to preoperative treatment in the setting of a randomized study.

METHODS/DESIGN

Protocol overview

CONVERGENCE is a prospective, pragmatic-designed, multicentre, randomized, investigator-initiated phase II/III trial. Patients with synchronous GCPM (primary tumour still in-situ) who have undergone either systemic therapy (including 1L chemotherapy +/- targeted therapy +/- immunotherapy) +/- peritoneal directed chemotherapy with good response to initial treatment would be randomized in 1:1 ratio to Arm 1 (Conversion surgery followed by systemic therapy (including 1L chemotherapy +/- targeted therapy +/- immunotherapy) +/- peritoneal directed chemotherapy) or Arm 2 (continual systemic therapy (including 1L chemotherapy +/- targeted therapy +/- immunotherapy) +/- peritoneal directed chemotherapy).

The randomized phase II/III design is proposed to compare a control arm against the intervention arm. To date, published data reporting the natural history and expected OS in GCPM patients with good response to systemic, bidirectional and/or combination therapy is limited, retrospective and not randomized, thereby not allowing for reliable conclusions. The phase II/III design allows for a smaller initial sample size to assess for early evidence of difference in intervention before expanding recruitment to an adequately powered phase III trial. [19]

Objectives

This study aims to determine the role of conversion surgery in GCPM patients with good response to preoperative systemic therapy (including 1L chemotherapy +/- targeted therapy +/- immunotherapy) +/-

peritoneal directed chemotherapy. Response will be determined radiologically (RECIST and iRECIST) and clinically through staging laparoscopy.

Primary endpoint

The primary endpoint in both phase II and phase III components will be OS, defined as the time interval from randomization to death from any cause. Patients who remained alive at the time of analysis or who are lost to follow-up will be censored at the date last seen and intention-to-treat analysis will be performed. Adjustment for relevant variables will be performed by regression modelling as specified in the *Statistical Analysis* portion below.

Secondary endpoint

Secondary endpoints of this phase II/III trial are

- a) Progression-free survival (PFS) defined as time interval from randomization to either radiological/clinical recurrence (Arm 1) or progression (Arm 2) or death from any cause, whichever is earlier. Patients who remained alive and without recurrence / progression / death at the time of analysis or who are lost to follow-up will be censored at the date last seen. Adjustment for relevant variables will be performed by regression modelling as specified in the *Statistical Analysis* portion below.
- b) Surgical outcomes after conversion surgery in Arm 1 including R0 resection rate (negative microscopic margins), rate of CC (completeness of cytoreduction) score: 0 and surgical morbidity and mortality as defined by Clavien-Dindo classification [20]
- c) Quality of life (QoL) outcomes as determined by QLQ-C30, OG-25, EQ5D-5L questionnaires.

Inclusion criteria

General criteria

- GCPM detected on surgical exploration and demonstrated by histology or cytology
- Primary GC not resected
- Age ≥ 21 years (or ≥ 18 years as allowed by individual institution review boards)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1

- Basic laboratory tests demonstrating adequate bone marrow function (neutrophil count $\geq 1500\text{mm}^3$, haemoglobin $\geq 8\text{g/dL}$, platelet count $\geq 100,000/\text{mm}^3$), adequate liver function (bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within upper limits of normal), adequate renal function (serum creatinine within the upper limit of normal)
- Expected survival > 3 months
- Able to tolerate enteral nutrition and adequate mental capacity to give informed consent
- Completed ≥ 4 months of first-line standard-of-care systemic therapy, such as the example provided here but not limited to (doublet regimen platinum/fluoropyrimidine OR taxane/fluoropyrimidine OR triplet regimen platinum/fluoropyrimidine/taxane) [21] Additional treatment including anti-HER2 therapy, immunotherapy/immune checkpoint inhibition, novel targeted therapies (anti-CLDN18.2, anti-FGFR2B), bi-directional therapy (IP catheter-based chemotherapy, PIPAC, laparoscopic HIPEC) and other experimental therapeutics in addition to standard-of-care treatment is permissible in selected centres where available or as part of an ongoing clinical trial.
- Repeat diagnostic laparoscopy after first-line treatment prior to randomization demonstrating feasible resection of both primary tumour and peritoneal metastases.
- Partial or complete radiological response of the primary tumour after 4 months of chemotherapy or stable disease of the primary tumour after 6 months of chemotherapy ^a
- Complete, partial or at least stable disease of PM after at least 4 months of chemotherapy ^b

Eligibility criteria for resection & extent of proposed resection

- Staging scans (cross-sectional imaging) demonstrating no extra-peritoneal metastases (includes liver, lung, adrenal, bone and non-regional lymph nodes)
- Cross-sectional imaging demonstrating no local progression of PM
- PCI score < 7 [12]
 - o PCI <7 at randomisation; PCI progression but within this limit would be considered as eligible for recruitment ^c
- Cytology positive alone (no gross PM) permissible for enrolment
- Feasible R0 resection (reasonable chance of negative margins on histology)
- Feasible D1, D1+ or D2 lymphadenectomy
- Limited extended resection and/or cytoreduction beyond radical gastrectomy

- o No extensive or systematic peritonectomy [22]
- o No more than 2 bowel resections (other than gastrectomy), preserving adequate small bowel length (>200cm) to minimize the risk of short gut syndrome [23]
- o No resection involving pancreaticoduodenectomy or biliary or vascular reconstruction. However, performing distal pancreatectomy and/or splenectomy are permissible.
- o No thoracotomy
- o Oophorectomy for Krukenberg tumours is permissible

Exclusion criteria

- Any extra-peritoneal metastasis at diagnosis or during systemic treatment.
- History of malignancy other than gastric cancer diagnosed in the last 5 years except for basal cell carcinoma of skin or preinvasive cancer of cervix
- Recent radiotherapy within 180 days
- Patients in the reproductive age who declined to use an adequate means of contraception
- Significant disease or conditions which, in the investigator's opinion, would exclude patient from the study
- Uncontrolled concurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia
- Psychiatric illness/social situations that would limit compliance with study requirements
- Pregnant and lactating females
- Prior surgical treatment for GC involving resection
- Clinical or radiological progression during 1st line systemic treatment
- o Patients with radiological progression of primary tumour and/or PM (determined by RECIST criteria) to be excluded as disease is likely not responding well to 1st line treatment.
- o Patients with clinical progression of PM as defined by increasing ascites requiring intervention (ascitic tap/drain, hospital admission etc) or causing significant symptoms to the patient (tense distended abdomen, early satiety, shortness of breath etc).

§ Ascites volume as a reflection of disease control is difficult to assess and quantify pre-operatively. Ascites may not only be a reflection of disease progression, but also secondary to IP treatment. [24]

- Any patient deemed unresectable or requiring extensive resection beyond procedure approved in the study protocol
- o PCI ≥ 7 on re-laparoscopy, ideally verified by histological assessment.
- o Extensive bowel / mesentery involvement requiring > 2 separate / non-contiguous small or large bowel resections in addition to the gastrectomy
- o Involvement of the head of pancreas or bile duct
- o PM or nodal disease in the hepatoduodenal ligament requiring pancreaticoduodenectomy or biliary or vascular reconstruction. Stripping of the peritoneum or lymphadenectomy with feasible R0 resection is permissible.
- o Involvement of major vascular structures
- o Involvement of oesophagus precluding a reasonable chance of R0 resection by trans-hiatal approach
- o Para-aortic or retroperitoneal nodes requiring beyond D2 resection

^a Radiological response of the primary tumour is considered to be an important surrogate of disease biology. In the event that there is no radiological response at 4 months, additional systemic treatment is recommended to ensure stable disease for a longer duration of at least 6 months to be deemed eligible.

^b Standard imaging modalities may not have adequate sensitivity to accurately evaluate disease response in PM. As such, radiological stable disease would be adequate for inclusion.

^c Inter-operator variability may affect PCI scoring. If PCI increases without radiological progression and remains <7, the patient may still be considered for trial inclusion, provided resectability criteria are otherwise met.

Withdrawal Criteria

- Patient decides to withdraw from the study, or
- The investigator concludes that it is in the patient's best interest to discontinue study treatment.

Trial proceedings

This study was conducted in accordance with the Declaration of Helsinki and ICH–Good Clinical Practice guidelines. Ethics approval was obtained from the National Healthcare Group Domain Specific Review

Board (DSRB), Singapore (Ref: 2024/ 00052), with site-specific approvals at all participating centres. Written informed consent was obtained from all participants prior to enrolment.

This international investigator-initiated trial does not have a single central funding source. Each participating centre is supported by its respective institutional or national research funding mechanisms. In France, the study is supported by the Programme Hospitalier de Recherche Clinique en Cancérologie (PHRCK 2024), which provides funding for 70 patients over 60 months. No other participating sites received external funding specifically for this trial at the time of submission. There are no conflicts of interest within this study.

Patients who have received optimal first-line medical treatment for at least 4 months (Figure 1) as stipulated in the inclusion criteria will be considered for recruitment into this study. A complete history and physical examination will be performed by the clinical team prior to recruitment into the study. Routine laboratory investigation will also be done as part of the standard of care to ensure that patients are eligible for the study as stipulated by the inclusion criteria. Patients will repeat cross-sectional imaging comprising Computed Tomography of the thorax, abdomen and pelvis (CT TAP) and diagnostic laparoscopy within 1 month of recruitment into the trial to assess the radiological status, PCI score and resectability of the GCPM. Videos of the diagnostic laparoscopy will be recorded for verification.

Randomization

The study will adopt a 1:1 randomization between Arm 1 (Intervention) / Arm 2 (Control). Block randomization would be performed, stratified by geographic regions (Figure 2). There will be no cross-over design in this trial. The allocation sequence will be generated and maintained by the trial biostatistician in collaboration with the Singapore Clinical Research Institute (SCRI) and implemented via a secure web-based randomization platform. Allocation will be concealed until the point of assignment; investigators will access the system only after confirming patient eligibility and obtaining informed consent. Site investigators will enrol participants, and the centralized platform will assign treatment arms based on the pre-generated concealed sequence, ensuring allocation concealment and minimizing selection bias.

Treatment Arms

Arm 1 (Intervention arm)

Conversion surgery will be scheduled within 1 month of randomization after careful clinical assessment of the patient, taking into account recovery from preoperative therapy and nutritional status. Conversion surgery will include radical gastrectomy with D2 lymphadenectomy and complete resection of PM (CC-0). In patients receiving prior bi-directional treatment via IP catheter, the port may be kept in-situ for post-operative bidirectional therapy. [9] Intraoperative HIPEC will be permissible in this trial. Videos of the peritoneal cavity (including resection bed, areas of debulking and reconstruction) will be recorded after

the completion of conversion surgery to confirm surgical quality. The videos will need to be uploaded to the designated platform. A clinic visit with the surgeon will be scheduled within 21 days after surgery to monitor for potential surgical complications. Investigator will perform clinical examinations to ensure the patient has recovered from surgery and is able to tolerate the postoperative medical therapy (including systemic therapy +/- peritoneal directed chemotherapy) according to the practice of the institution; necessary dose reduction or modification of regimen to limit toxicity and for tolerability will be permissible. Postoperative systemic therapy +/- peritoneal directed chemotherapy will be continued after surgery. Upon resumption of the therapy, surveillance CT TAP will be performed every 90 days (± 60 days) for the first year (± 60 days). Subsequently, radiological assessment will be performed every 180 days (± 60 days) or upon the patient's progression, whichever comes earlier. In the presence of clinical or radiological progression, the patient will be transitioned to 2nd line treatment in keeping with local multidisciplinary practice. Quality of life (QoL) assessments will be performed as part of this protocol.

Arm 2 (Control arm)

Patients randomized to Arm 2 will continue medical therapy (including 1L chemotherapy +/- targeted therapy +/- immunotherapy) +/- peritoneal directed chemotherapy according to the practice of the institution and undergo CT TAP every 90 days (± 60 days) for the first year (± 60 days). Subsequently, radiological assessment will be performed every 180 days (± 60 days) or upon the patient's progression, whichever comes earlier. In the presence of clinical or radiological progression, the patient will be transitioned to 2nd line treatment in keeping with local multidisciplinary practice. QoL assessments will be performed as part of this protocol.

Measurement of response

Patients will be followed up for 36 months after randomization. Clinical progression will be determined by imaging and/or assessment during clinical evaluation and laparoscopy/laparotomy. In patients with increasing ascites, determination of progression will be based on the judgement of the clinician in line with criteria discussed under "Exclusion criteria" above. The limitations and challenges of radiological assessment of PM are well known and acknowledged. [24] Radiological evidence of disease progression will be defined based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and iRECIST for patients receiving immunotherapy. [25, 26] In addition, new-onset nodules, ascites or distant (non-peritoneal) metastases will be considered as radiologic criteria of progression.

Statistical analysis

Sample size

This study will utilize a seamless phase II/III trial design. In the initial stage of the trial, the phase II component aims to identify potential benefit from conversion surgery and assumes a conservative

Hazard Ratio (HR) of 0.55 with reference to existing published literature, assuming the probability of survival at 18 months to be 68% in Arm 1 and 50% in Arm 2. [8, 10, 27, 28] Parameters for the initial phase assume a one-sided $\alpha = 0.15$ and $\beta = 0.20$ as per Rubinstein et al. [22] Based on a power of 80% using log rank test assuming a 1:1 allocation ratio, this requires at least 44 events and a total sample size of 106 patients (53 per arm). [29] Assuming a dropout rate of 10% after randomization and 10 % who are lost to follow-up, a total of 136 patients will be recruited and randomized in phase II.

The results of the phase II trial will be analysed when at least 106 of 136 patients randomized (assuming an overall attrition of 20% dropout) have completed 18 months follow-up or 44 deaths have been observed, whichever is earlier. The Data Safety and Monitoring Board (DSMB) will review the results at this point to evaluate the phase II hypothesis based on a one-sided α of 0.15 and ensure that the complication rate is not unacceptably high in the intervention arm, in order to justify proceeding to Phase III. As the analysis at the end of Phase II is also the only interim analysis for the Phase III component, a more stringent criterion such as the Haybittle-Peto rule ($p < 0.001$) will be applied for potential early stopping, to ensure rigorous decision-making. If the trial continues, the final analysis of the trial will be conducted at the design α of 0.05.

For the Phase III study, assuming a HR of 0.55 and probability of survival at 18 months to be 68% in Arm 1 and 50% in Arm 2, (two-sided $\alpha = 0.05$, $\beta = 0.20$), a sample size of 240 patients would be required; after accounting for a dropout rate of 10% after randomization and 10% lost to follow-up. The total sample size for the Phase III trial is thus 300.

Data analysis

Patients will be analysed in the groups to which they were assigned (intention-to-treat). Per-protocol analysis will also be performed to account for dropouts and non-compliance to treatment protocol.

Primary endpoint

OS will be evaluated using Kaplan-Meier methods with observed differences compared using log-rank test. Additional survival analysis will be performed using stratified Cox-regression, and adjusting for variables that may influence survival, such as disease characteristics (histological subtype, cytology status), treatment therapy and its duration.

Secondary endpoint

PFS will be evaluated similarly to OS as defined above. Clinical scoring for completeness of cytoreduction (gross residual disease after resection) and resection margins will also be collated. Data on surgical outcomes including the rate of surgical morbidity will be collated and summarized both in terms of the composite event as well as individually; major complications will be defined as Clavien-

Dindo 3b (complication requiring re-operation under general anaesthesia) and beyond. Categorical or binary outcomes will be compared between treatment arms using Fisher's exact or Chi-square test and quantified in terms of relative risks and its associated 95% CI. QoL outcomes will be collated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, OG-25 & EQ5D-5L at baseline before randomization and 1, 6, 12, 18, 24, 30, 36 months after randomization. The QoL domain scores will be compared using linear mixed effect model to consider the correlation between the repeated outcome measures. Further adjustment for the respective baseline covariates as well as treatment therapy and its duration, will be considered in these models. The effect estimate will be interpreted in terms of absolute difference in mean, and its 95% CI. Where the continuous secondary outcomes are not normally distributed, natural log transformation will be implemented to normalise the data, and the effect estimate will be interpreted in terms of the ratio of geometric mean and its 95% CI.

Quality assurance & safety

All patients will be discussed at a multidisciplinary tumour board and be vetted by the central committee of the trial prior to recruitment. Each participating centre is required to perform a minimum of 10 gastrectomy cases per year in the past 5 years. All conversion gastrectomy should be performed by specialist upper GI consultant surgeons during this trial.

The progress of individual patients including surveillance scans will be collated and monitored. Equivocal imaging findings for progression should be discussed with an independent radiologist / oncologist / surgeon. Prior to randomization, photo or video evidence of the diagnostic laparoscopy demonstrating the primary tumour, falciform, 4 quadrants and root of the mesentery should be captured and documented. During conversion surgery, photographic or videographic evidence of the resection bed and D2 lymphadenectomy should be documented and archived. Toxicity will be carefully monitored for patients undergoing conversion surgery, including those receiving intraoperative chemotherapy. Clinical examinations, as described earlier in the trial schedule, will be conducted after surgery to ensure the patient has recovered from surgery and is able to tolerate the postoperative systemic therapy +/- peritoneal directed chemotherapy; necessary dose reduction or modification of regimen to limit toxicity and for tolerability will be permissible. Data on adverse events (AEs) after systemic treatment, changes due to toxicity and changes to subsequent lines of chemotherapy will be collated at routine clinical visits. AEs will be graded according to CTCAE (v5).

Discussion

The role for conversion surgery in GCPM remains undefined, particularly in patients who achieve good disease response or control with systemic therapy. While conversion surgery has been reported to potentially offer durable response and disease control, it has not been confirmed in the setting of a phase III prospective randomized trial. [8, 10, 30, 31] The potential benefit of resecting the primary tumour and limited debulking was first seen in the AIO-FLOT 3 trial, an exploratory phase II study that

reported a median OS of 22.9 months (95% CI 16.5 months – upper level not achieved) in patients who received systemic treatment followed by resection compared to systemic treatment alone. [32] However, the potential benefits of conversion surgery for gastric cancer, need to be weighed against significant risk of morbidity following gastrectomy with/without CRS which may reach a 90-day mortality rate of 8% and major complication rate of 54%. [12] The recently presented IKF-575/RENAISSANCE phase III trial compared the surgery arm versus FLOT arm in patients with limited metastatic gastric and/or gastroesophageal junction cancer. Their results showed increased mortality in the surgery arm compared to the chemotherapy arm, while patients with minimal response to chemotherapy or patients with peritoneal disease had decreased OS. The trial included patients with multiple different sites of metastases and is not powered to evaluate the survival specifically in GCPM patients. [33-34] On the contrary, our study, only focused on GCPM, allows the use of intraperitoneal chemotherapy as we believe the tumour biology of PM behaves differently from solid organs metastases. Furthermore, our patients undergo a longer duration of chemotherapy (minimal of 4 months), which may allow for greater regression of the disease prior to surgery. We also adopted a more stringent criteria with regards to the extent of peritoneal disease as only patients with a PCI <7 are candidates for the trial, and technically we had limited the extent of resection (to avoid extensive peritonectomy, vascular resection and biliary resection) to mitigate the risk of harm caused by intervention. IKF-575/RENAISSANCE phase III trial had a more expansive criteria for their patients amenable to resection and showed early mortality in their surgical arm. [33-34] Our study included only experienced centres with surgeons specialized in this field with a minimum of 10 gastrectomies per year over the past 5 years to standardize surgical treatments offered to patients. The surgeons are also required to have video and image documentation of the abdomen post resection for standardization as a quality control measure. Lastly our phase II/III design enables us with the flexibility to achieve both aims of a phase II and III study in one single trial.

Of note, there are other distinctives in our proposed study. Firstly, this trial aims to recruit patients with favourable disease biology who demonstrate radiological response or prolonged disease control following systemic chemotherapy, within the limits of radiological assessment. The criticism of published data suggests that only patients with good disease response are considered for conversion surgery and/or CRS, making it unclear whether the improved OS is a function of good disease biology (and response) or the surgery itself. When compared to patients who did not undergo conversion surgery (poor responders or frail patients), patients who were surgical candidates would undoubtedly perform better. Hence, this trial evaluates conversion surgery against maintenance chemotherapy in good responders to 1st line treatment. Secondly, in contrast to other randomized trials investigating GC with various metastatic sites, this is one of the first proposed trials dedicated to investigating GCPM with good response after the GASTRIPEC-I-Trial which did not select patients with PCI < 7. [33] We believe that the behaviour and biology of PM is different compared to extra-peritoneal metastases and that this proposed study is unique compared to the recently presented IKF-575/RENAISSANCE trial. [27] In addition, given the emerging evidence for immunotherapy and recent trials demonstrating the benefit of novel therapeutic agents targeting Claudin 18.2, fibroblast growth factor receptor 2 – isoform 2B and

multi-kinase inhibitors, the design of this trial allows for patients receiving these contemporary drugs to be included in our trial. [15, 34-38]

The CONVERGENCE trial will face several challenges. The specific nature of the target population may make recruitment challenging. There are currently multiple competing modalities of therapy and centres that do not offer conversion surgery may not refer patients to trial centres. In addition, in patients with good response to systemic chemotherapy, surgeons/investigators may have difficulty potentially randomizing patients to the control arm. However, in light of the equipoise that exists not only for the treating physician but the referring physician as well, recruitment and randomization to either arm may be justified given the risk of morbidity following aggressive surgical procedures that requires high-quality evidence to justify its risk to patients. [39] Nevertheless, this may result in a high drop-out rate in patients who are randomized to continue systemic chemotherapy, may slow recruitment or decline participation and may cause an over-estimation of effect size by introduction selection bias, given that only high-risk patients (borderline poor performance status, borderline resectable) may agree to remain in the control group. To address these concerns, we adopt a pragmatic approach in trial design and inclusion criteria to allow various modalities of preoperative treatment. In addition, we selected only large academic medical centres with special interest and expertise on treating GCPM to participate in this study. Educational materials will be prepared for patients to explain that there is true equipoise when considering conversion surgery for GCPM. Finally, we have projected for a significant drop-out rate of 10% after randomization and 10% lost to follow-up in our sample size estimation.

To conclude, this multicentre international study will provide high-quality evidence to support or refute the role of conversion surgery in GCPM after good response to contemporary medical therapy. If the CONVERGENCE trial substantiates the benefit of conversion surgery, this treatment may become the standard of care for these GCPM patients. If the CONVERGENCE trial disproves the benefits of conversion surgery, the morbidity and sequelae of surgery may potentially be spared as centres move away from non-beneficial treatment.

Declarations

This study was conducted in accordance with the Declaration of Helsinki and ICH–Good Clinical Practice guidelines. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (DSRB), Singapore (Ref: 2024/ 00052), with site-specific approvals at all participating centres. Written informed consent was obtained from all participants prior to enrolment.

This international investigator-initiated trial does not have a single central funding source. Each participating centre is supported by its respective institutional or national research funding mechanisms. In France, the study is supported by the Programme Hospitalier de Recherche Clinique en Cancérologie (PHRCK 2024), which provides funding for 70 patients over 60 months. No other participating sites received external funding specifically for this trial at the time of submission. There are no conflicts of interest within this study.

Data sharing is not applicable to this article as no datasets were generated or analysed as the study has not concluded.

Contributions

Conceptualisation & trial design: Professor Jimmy So Bok Yan, Dr Yong Wei Peng, Associate Professor Tai Bee Choo, Dr Daryl Chia, Professor Magnus Nilsson, and Professor Olivier Glehen, with input from all international site Principal Investigators.

Methodology: Professor Jimmy So Bok Yan, Dr Yong Wei Peng, Associate Professor Tai Bee Choo, Dr Daryl Chia, Professor Magnus Nilsson, Professor Olivier Glehen, and international site Principal Investigators.

Statistical design: Associate Professor Tai Bee Choo (sample size determination and statistical analysis plan), with input from the study leadership team.

Investigation/clinical leadership: Professor Jimmy So Bok Yan (overall Principal Investigator oversight), Dr Daryl Chia (Co-Principal Investigator), Dr Yong Wei Peng (oncology and systemic/peritoneal-directed therapy oversight), and Associate Professor Asim Shabbir (departmental/institutional support and recruitment).

Site implementation & recruitment: International site Principal Investigators (site start-up and local regulatory coordination, participant recruitment, protocol compliance, and site oversight).

Project administration & data management: Ms Chan Xin Yi (study coordination, project management, and data management), in collaboration with the study leadership team and participating sites.

Data curation & quality assurance: Study leadership team with participating sites; Professor Jimmy So Bok Yan oversaw surgical quality assurance across centres.

Formal analysis & interpretation: Associate Professor Tai Bee Choo led the analyses; results were interpreted by Professor Jimmy So Bok Yan, Dr Daryl Chia, Dr Yong Wei Peng, Professor Magnus Nilsson, and site Principal Investigators.

Writing—original draft / writing—review & editing: Dr Tan Yu Chuan wrote and revised the manuscript with the supervision of the study leadership team drafted and review by international collaborators. Dr Tan Yu Chuan provided administrative and manuscript submission support, supported by Dr Daryl Chia and Professor Jimmy So Bok Yan.

Supervision: Professor Jimmy So Bok Yan provided overall trial governance and supervision, supported by Dr Daryl Chia, Dr Yong Wei Peng, and participating site Principal Investigators.

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Figures

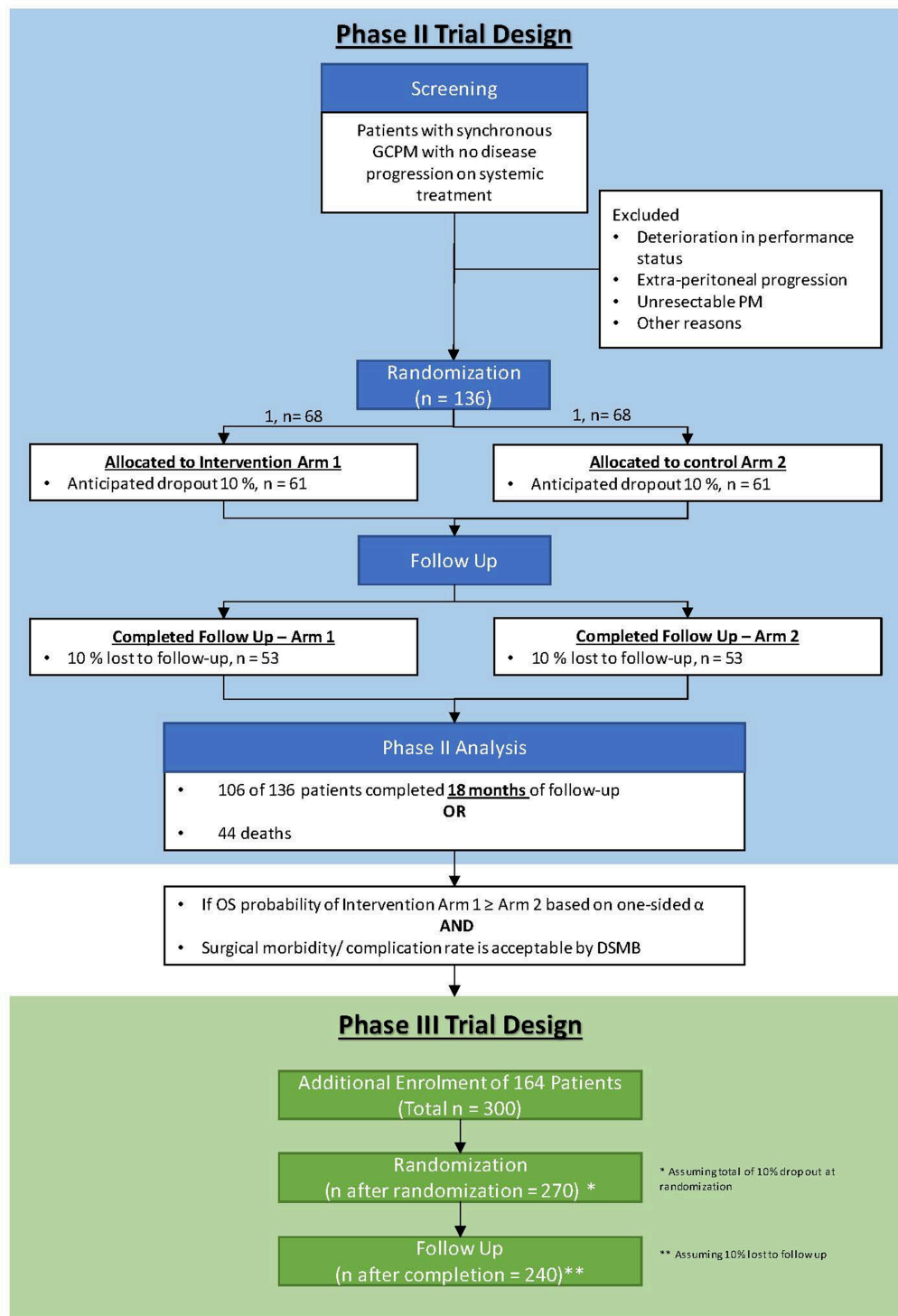


Figure 1

Overall study design

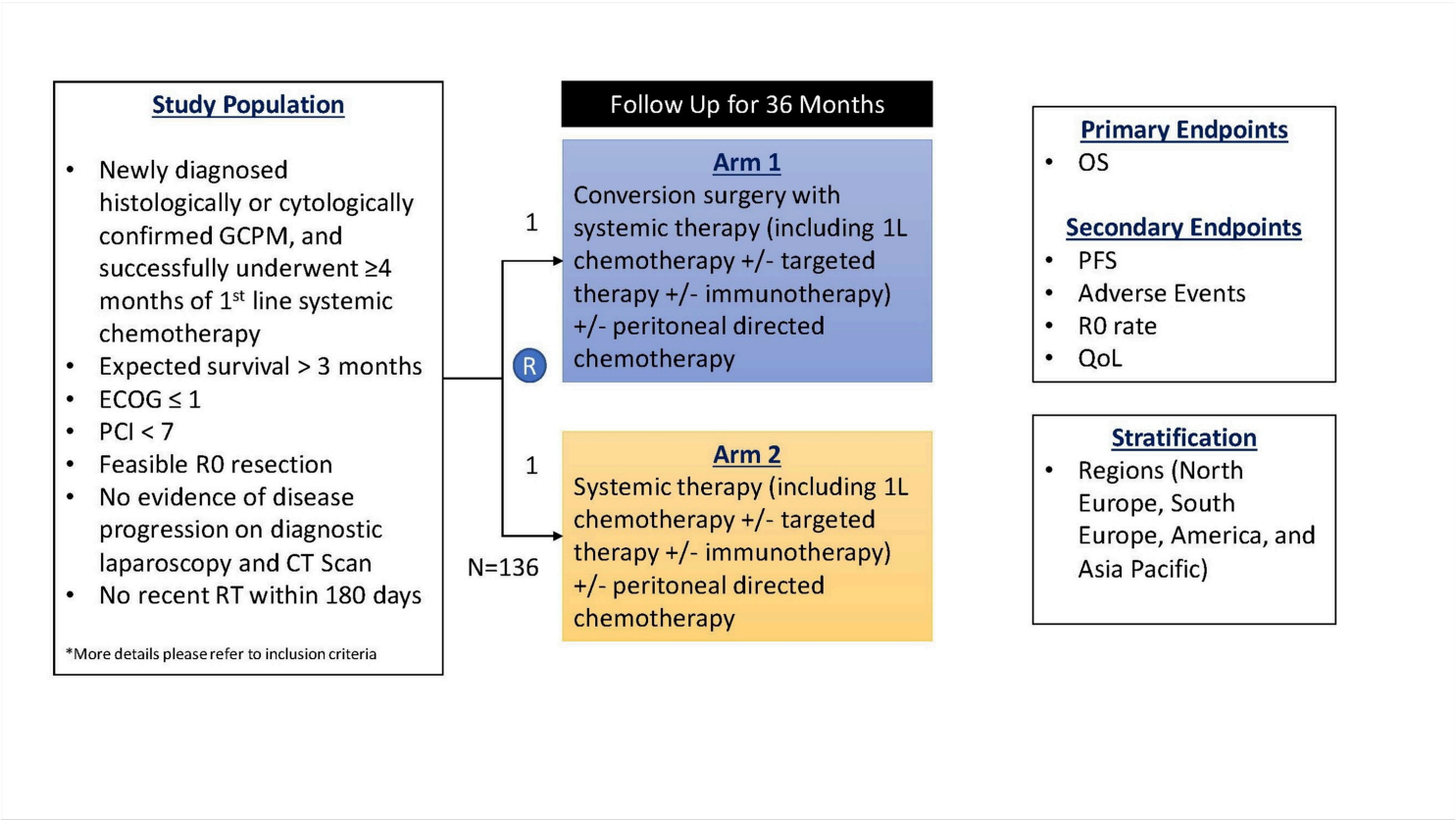


Figure 2

Phase 2 Protocol Overview