End of Clinical Trial Report

A randomised phase II screening trial with functional imaging and patient reported toxicity sub-studies comparing LApatiNib plus capecitabine versus Trastuzumab plus capecitabine after local therapy in patients with ERb B2 positive metastatic breast cancer developing braiN metastasis/es

1. Trial Summary

EudraCT	2010-022737-28
ISRCTN	ISRCTN58771616
Sponsor No.	CO10/9344
Sponsor	Leeds Teaching Hospitals NHS Trust
Chief Investigator	Professor David Dodwell, Consultant in Clinical Oncology, St James's University Hospital, Leeds LS9 7TF; david.dodwell@nhs.net; Tel: 0113 206 8938
Trial Contact	Jamie Oughton, Senior Trial Manager, Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, LS2 9JT; j.oughton@leeds.ac.uk; Tel: 0113 343 1494
CTA Approval	Licencing Authority: MHRA Date of CTA: 03/02/2011
Main REC Approval	Name: Leeds East Research Ethics Committee. Date: 21/12/2010. REC reference number: 10/H1306/81.
Final protocol version and date	Version 7.0 (13/02/2013)
Full Title	LANTERN: A randomised phase II screening trial with functional imaging and patient reported toxicity sub-studies comparing LApatiNib plus capecitabine versus Trastuzumab plus capecitabine after local therapy in patients with ERb B2 positive metastatic breast cancer developing braiN metastasis/es
Phase of study	II
Study period	2.7 years. Opened to recruitment: 22/09/2011. End of study date: 09/05/14.
Investigational Medicinal Product (IMP)	Lapatinib (oral) 1250mg once daily + capecitabine (oral) 2000mg/ m^2/day/ d1-14 Trastuzumab (IV) 6 mg/kg 3-weekly + capecitabine (oral) 2500 mg/m^2 / day/ d1-14
Treatment Groups	Patients are randomised on a 1:1 basis to receive three weekly cycles of either: • Lapatinib (oral) 1250mg once daily + capecitabine (oral) 2000mg/m^2/day or • Trastuzumab (iv) 6mg/kg once + capecitabine (oral) 2500mg/m^2/day
Target number of patients	130
Final number patients recruited	34 recruited 30 randomised

Professor David Dodwell

Chief Investigator	Signature	Date
		22-4-15

2. Study Investigators and Centres

Investigators:
Prof David Dodwell, Prof Stephen Johnston, Prof David Buckley, Prof Galina Velikova, Dr Luis Daverede, Mrs Victoria Hiley, Miss Alexandra Smith, Mrs Helen Marshall, Miss Alex Wright-Hughes, Mr Peter Heudtlass, Mr Jamie Oughton, Mrs Geraldine Murden, Miss Victoria Liversedge, Miss Cathryn Tyas, Dr Mohammed Rizwanullah, Dr Christopher Price, Dr Matthew Hatton, Dr Anne Armstrong, Dr Laura Kenny, Dr Clive Irwin, Dr Johnathan Joffe, Mr Varadarajan Kumar, Dr Hafiz Algurafi, Dr Helen Passant, Dr Daniel Rea, Dr Karen McAdam, Dr Jill Bishop.

Study Centres:
Beatson Oncology Centre, Bristol Haematology and Oncology Centre, Royal Marsden Hospital, Weston Park Hospital, Christie Hospital, Imperial College, University Hospital Coventry, Huddersfield Royal Infirmary, Royal Preston Hospital, Southend University Hospital, St James' University Hospital, Velindre Hospital, Queen Elizabeth Hospital (Birmingham), Peterborough City Hospital, Glan Clwyd Hospital, Ysbyty Gywnedd.

Good Clinical Practice Compliance
The trial was conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006.

3. Trial Design

LANTERN was a randomised, multi-centre, prospective, controlled, open label, parallel group phase II screening trial [1-2] of lapatinib in combination with capecitabine versus continued trastuzumab in combination with capecitabine for patients with advanced ErbB2-positive metastatic breast cancer with newly diagnosed or recent progression of Central Nervous System (CNS) metastases. Such patients had previously had local therapy (Whole Brain Radiotherapy / Stereotactic Radiosurgery) for brain metastases and previous or current treatment with trastuzumab.

The total planned recruitment for the LANTERN trial was 130 participants, randomised on an equal basis to receive lapatinib plus capecitabine or trastuzumab plus capecitabine. Participants were followed up on trial treatment for up to 24 weeks, with continued safety monitoring of serious adverse reactions / suspected unexpected serious adverse reactions beyond 24 weeks for participants who remained on treatment and until the end of trial (defined as the later of 30 days after the last 24 week clinical review visit or 30 days after the last lapatinib trial treatment was administered).

The phase II trial design was chosen rather than a phase III due to the limited evidence in this patient population relating to the size of the treatment effect, allowing for a preliminary and non-definitive randomised comparison to be made, and to determine if recruitment to a large phase III trial would be feasible. A randomised screening trial was considered appropriate as lapatinib in combination with capecitabine had already been licensed in the metastatic breast cancer setting.

Participants were initially randomised via stratified permuted blocks incorporating the following patient characteristics:

- Presence of symptoms (yes versus no) as defined as neurological symptoms and/or headaches,
- Type of local therapy performed (radiosurgery versus whole brain radiotherapy) as a surrogate for volume of brain metastases.

Following a substantial protocol amendment to version 7.0 in April 2013, the primary purpose of which was to widen the eligibility criteria with a view to improving recruitment, participants were randomised on a 1:1 basis via a computer-generated adaptive minimisation algorithm, incorporating a random element, to ensure the treatment arms were well balanced for the following characteristics:

- Type of prior local therapy performed (radiosurgery, whole brain radiotherapy, both),
- Prior trastuzumab treatment (Current i.e. within 3 months, Metastatic +/- adjuvant, Adjuvant only),
- Original diagnosis of CNS metastases (≤12 months, >12 months with progression within 12 months).

The planned 130 participants were to be recruited within a two year period starting in September 2011, however, recruitment to LANTERN closed after two years having randomised 30 participants.

4. Trial Objectives

Primary objective:
To investigate the effect of lapatinib plus capecitabine compared with trastuzumab plus capecitabine on time to progression of CNS metastases.

Secondary objectives:
To evaluate and compare the two treatment arms for the following:

- Progression-free survival (CNS or non-CNS)
- Overall survival (deaths from any cause)
- CNS overall response rate (Complete Response [CR] or Partial Response [PR])
- CNS clinical benefit response rate (confirmed CR or PR at any time or SD at the 24-week time-point)
- Total days of steroid use for palliation of CNS symptoms
- General and neurological quality of life (QoL)
- Delay/stabilisation of CNS symptoms
- Clinically assessed and patient reported symptoms/toxicities
- Assess the feasibility of recruitment into and patient follow-up in a phase III trial

Sub-studies:
LANTERN included three sub-studies with the following aims:

- Quality of Life and Patient-reported symptoms and side-effects assessment sub-study: assess the general and neurological quality of life (QoL) and the method and outcome of patient-reported toxicity.
- Functional imaging sub-study: investigate the relationship between blood brain barrier (BBB) permeability and response to treatment by quantifying indices of BBB integrity over time.
- Pharmacokinetic (PK) Sampling sub-study: examine the effect on lapatinib exposure when participants have been exposed to high dose steroids.

5. Population

The eligibility criteria changed during the trial following a protocol amendment in April 2013. The following are the main criteria for protocol version 7.0 (final protocol version), such that patients with the following characteristics were eligible for the study:

- ErbB2 positive metastatic breast cancer with newly diagnosed or progression of CNS metastasis/es within the last 12 months
- Evidence of metastatic brain disease (at least one measurable brain lesion that can be accurately measured in at least one dimension as >10mm by CT or MRI)
- Prior (in the adjuvant or metastatic setting) or current treatment with trastuzumab
- Completed local cranial therapy (Stereotactic Radio Surgery and/ or Whole Brain Radiotherapy) for current or prior CNS metastasis/es.
- Male or female aged ≥18 years old
- Given written informed consent prior to any trial specific procedures
- Expected survival ≥ 12 weeks
- Performance Status 0-2

6. Trial Treatment and Assessments

Patients randomised to the lapatinib plus capecitabine arm received daily 1250 mg of lapatinib from day 1 to 21 of every 21 day treatment cycle plus capecitabine (1000 mg/m^2 twice daily) from day 1 to day 14 of every treatment cycle. Patients randomised to the trastuzumab plus capecitabine arm received 3-weekly 6 mg/kg of Lapatinib on day 1 of every 21 day treatment cycle plus capecitabine (1250 mg/m^2 twice daily) from day 1 to day 14 of every treatment cycle. The planned duration of trial treatment was 24 weeks (8 cycles), however treatment cycles were repeated until disease progression or unacceptable toxicity in both arms, and safety monitoring continued for the duration of the trial for participants remaining on treatment.

Efficacy assessments including cranial MRI scans and patient-reported neurological quality of life (EORTC QLQ-C30 and BN20 questionnaires) were scheduled at baseline, 12 and 24 weeks. In addition, safety assessments of adverse reactions and events, including physical exam and laboratory assessments, were conducted every 3 weeks during treatment. Cardiac (LVEF) monitoring was required on all participants at baseline prior to initial dosing with study regimens, at 12 weeks post-randomisation and then at the local clinicians discretion.

Please see Appendix 1 for a study flow diagram of planned trial treatment and assessments.

7. Participant Flow and Trial Closure

Over the two years trial was open to recruitment, between September 2011 and October 2013, a total of 109 patients were screened for eligibility to the trial, of which 34 patients were registered and 30 randomised: 16 to receive lapatinib plus capecitabine, and 14 to receive trastuzumab plus capecitabine. The flow of patients through the trial is outlined in the CONSORT diagram of Appendix 2 and reasons for non-randomisation are listed in Section 9.1.

The trial closed to recruitment after the original two year recruitment period had been reached. Despite widening the eligibility with a protocol amendment and other efforts to improve recruitment the independent Trial Steering Committee (TSC) and Data Monitoring Committee both recommended that the trial should close due to the poor rate of recruitment, this was accepted by the Trial Management Group and the last participant was randomised 27/09/13.

All randomised participants received at least one cycle of the allocated treatment (n=30). During the trial follow up period of 24 weeks 19 (63.3%) participants stopped trial treatment: 11 (68.8%) participants randomised to lapatinib plus capecitabine and 8 (57.1%) participants randomised to trastuzumab plus capecitabine; of which two participants (one in each arm) then went on to cross over having received the non-allocated trial treatment off trial. Withdrawals were requested for two participants (4.7% of randomised), one in each arm, both from trial treatment and the trial follow up schedule, with the lapatinib participant further withdrawing from data collection at their standard visits, hence this participant was fully lost to follow up.

8. Statistical Methods

Due to the closure of recruitment to LANTERN after 30 participants had been randomised, the Statistical Analysis Plan outlined in the protocol and formal hypothesis testing were no longer appropriate. As such all analyses, unless otherwise stated below, were based upon summary and descriptive statistics only. A full statistical analysis plan was written and signed off prior to the final data download in May 2014. All statistical analyses were carried out in SAS version 9.2.

Analyses was conducted on the intention-to-treat (ITT) population, where participants were included according to the treatment arm they were randomised to regardless of whether they prematurely discontinued the treatment or did not comply with the regimen. The intention-to-treat (ITT) population therefore included all 30 randomised participants, and was the same as the Safety population as all participants received at least one does of study drug.

Survival curves for CNS progression-free survival (primary outcome), progression-free survival (CNS and non-CNS), and overall survival were calculated using the Kaplan Meier method and an unadjusted analysis was conducted using a two-sided log-rank test to assess the difference between the treatment arms.

General and neurological quality of life was summarised for each treatment arm at each time point using unadjusted mean scores and 95% CIs for each EORTC QLQ-C30 and EORTC QLQ-BN20 domain.

For the primary endpoint, time to progression of CNS metastases was defined as time from randomisation to the date of diagnosis of CNS disease progression as measured by either clinical or radiological evidence of disease progression, based upon:

- The date of progression confirmed by cranial MRI scans according to RECIST version 1.1.
- Local standard clinical practice where cranial MRI scans were not performed (i.e. clinical or other radiological evidence of disease progression).

Participants with missing follow-up data, or who were alive and CNS progression free at the time of analysis, were censored at the last date they were known to be alive and CNS progression-free (date of last disease assessment). Participants with disease progression confirmed during their 24 week follow up assessment (clinical or MRI) whose 24 week follow up assessment fell outside of the 2 week window were included as having disease progression on their follow up assessment date. Participants still receiving treatment following the final 24 week follow up assessment, for whom it was subsequently reported that they discontinued treatment due to CNS disease progression (after the 24 week follow up assessment) were censored at the last date they were known to be alive and CNS progression-free (date of 24 week disease assessment).

9. Results

9.1 Enrolment

Between September 2011 – October 2013, a total of 109 patients were screened for eligibility from 14 centres (17 were opened), of which 34 patients were registered and 30 randomised (Appendix 3): 16 to receive lapatinib plus capecitabine, and 14 to receive trastuzumab plus capecitabine. Reasons for non-registration were that the patient did not meet the eligibility criteria (n=57), the patient declined to participate (n=7), the patient was too ill to consent (n=1), lapatinib was given off trial (n=3), and other reasons for 7 patients.

Nine participants (30.0%) were randomised from Beatson Oncology Centre, 6 (20.0%) at Bristol Haematology & Oncology Centre, 4 (13.3%) at Royal Marsden Hospital (Sutton), 2 (6.7%) at Royal Marsden Hospital (London), 2 (6.7%) at Weston Park, Sheffield, 1 (3.3%) at Christie Hospital (Manchester), 1 (3.3%) at Huddersfield Royal Infirmary, 1 (3.3%) at Imperial College (Charing Cross), 1 (3.3%) at Royal Preston Hospital, 1 (3.3%) at Southend University Hospital and 1 (3.3%) at University Hospital Coventry.

9.2 Treatment

During the trial period of 24 weeks 19 (63.3%) participants stopped trial treatment: 11 (68.8%) lapatinib plus capecitabine participants and 8 (57.1%) trastuzumab plus capecitabine participants. At the time of data lock (May 2014) a total of 25 (83.3%) participants were known to have stopped trial treatment, this included all lapatinib participants and 9 (64.3%) trastuzumab participants. The most frequent reason for ending treatment was CNS disease progression: 47.4% within the trial period and 56% overall. In participants known to have stopped trial treatment, the median time to end of treatment was 20 weeks.

Following the end of trial treatment (within the 24 week trial period), 5 participants were reported to have gone on to receive off trial treatment, two of which lead to trial treatment crossovers for which: a lapatinib plus capecitabine participant subsequently received trastuzumab and capecitabine; and a trastuzumab and capecitabine participant subsequently received trastuzumab, lapatinib and capecitabine.

Trial treatment delays (up to 2 weeks), omissions and dose reductions (a maximum of 2

permitted for lapatinib and none for trastuzumab) were frequent in both trial arms. Of lapatinib plus capecitabine participants, 8 (50%) had at least one capecitabine treatment delay, 2 (12.5%) omitted capecitabine for a single cycle, 9 (56.3%) had at least one capecitabine dose reduction, 7 (43.8%) had at least one lapatinib treatment delay, and a single lapatinib dose reduction was reported for 3 (18.8%) participants. Of trastuzumab plus capecitabine participants, 10 (71.4%) had at least one capecitabine treatment delay, 3 (21.4%) omitted capecitabine for at least one cycle, 9 (64.3%) had at least one capecitabine dose reduction, and 10 (71.4%) had at least one trastuzumab treatment delay. The most frequently reported reason for treatment delays and dose reductions was non-haematological toxicity.

a. Effectiveness

Primary endpoint

CNS disease progression was reported in 14 (46.7%) participants during their 24 week trial follow up period: 8 lapatinib plus capecitabine participants (50%) and 6 (42.9%) trastuzumab plus capecitabine participants.

Accounting for participants censored before and after 24 weeks, the Kaplan Meier estimate of CNS progression-free survival at 24 weeks was 58.2% (95% CI: 32.5%, 83.9%) in the lapatinib plus capecitabine arm and 58.8% (95% CI: 30.4%, 87.2%) in the trastuzumab plus capecitabine arm. The number of randomised participants was insufficient to detect any meaningful differences in time to disease progression between participants in the intervention and control arm.

Secondary endpoints

For Progression-free survival, CNS or non-CNS disease progression or death was reported in 16 (53.3%) participants: 10 (62.5%) lapatinib plus capecitabine participants with a median time to progression of 18.1 months, and 6 (42.9%) trastuzumab plus capecitabine participants with a median time to progression of 21.1 months. Accounting for participants censored before and after 24 weeks, the Kaplan Meier estimator estimates progression-free survival at 24 weeks as 44.4% (95% CI: 18.1% - 70.8%) in the lapatinib plus capecitabine arm and 50.0% (95% CI: 20.9% - 79.1%) in the trastuzumab plus capecitabine arm.

Deaths were reported for 5 (16.7%) participants, all caused by disease progression: 3 (18.8%) lapatinib plus capecitabine participants with a median time to death of 19.0 months, and 2 (14.3%) trastuzumab plus capecitabine participants with a median time to death of 22.1 months.

A total of 14 (46.7%) participants were reported to have had a CNS overall response defined as a complete or partial response during the trial follow up period, that is: 4 (25%) lapatinib participants, and 10 (71.4%) trastuzumab participants. Furthermore, with the inclusion of participants with stable disease at 24 weeks, a total of 18 (60%) participants were reported to have had a CNS clinical benefit response, that is: 7 (43.8%) lapatinib participants, and 11 (78.6%) trastuzumab participants.

A total of 17 (56.7%) participants were reported to have used steroids for palliation of CNS symptoms during treatment: 10 (62.5%) lapatinib participants, and 7 (50%) trastuzumab participants.

Comparison of all functioning, global, and symptom scores of the Quality of life (QoL) questionnaires suggested a slightly worse quality of life at baseline in participants randomised to receive lapatinib. It was not possible to tell whether this pattern persisted in QoL assessments during follow up, due to high levels of non-completion (i.e. participant choice, admin error, death, withdrawal) with missing data for 26.7% of participants at 12 weeks and 63.3% at 24 weeks.

With the exception of baseline and cycle 5, the proportion of participants experiencing CNS symptoms was slightly higher in the trastuzumab arm; however this corresponded to a maximum difference of just 3 participants.

The most frequent clinician reported toxicities (≥ grade 1) were: fatigue and diarrhoea (both in 25 [83.3%] participants), nausea (23 [76.7 %%]), other (21 [30%]), hand-foot syndrome (19 [63.3%]), stomatitis - mouth (16 [53.3%]). No grade 4/5 toxicities were reported. Those for which more than 10% of patients experienced a maximum grade of grade 3 were: hand-foot syndrome (Lap: 3 [18.8%], Tras: 1 [7.1%]), diarrhoea (Lap: 5 [31.3%], Tras: 2 [14.3%]), nausea (Lap: 2 [12.5%], Tras: 1 [7.1%]), ALT/AST (Lap: 0 [0%], Tras: 3 [21.4%]), other (Lap: 2 [12.5%], Tras: 1 [7.1%]). The participant reported signs and symptoms questionnaire showed that, with the exception of skin rash, all symptoms were reported for at least 50% of participants, with fatigue the most frequent reported in all participants.

b. Toxicity and Serious Adverse Events

A total of 13 serious adverse events (SAEs) were reported in 12 (40%) participants with 10 events in 9 (56.3%) lapatinib plus capecitabine participants and 3 events in 3 (21.4%) trastuzumab plus capecitabine participants. Five (38.5%) SAEs were suspected to be related to trial medication (lapatinib and capecitabine for 2 and capecitabine for 3), 8 (61.5%) were not suspected to be related to trial medication, and no suspected unexpected serious adverse reactions were reported. All but one SAE, in a lapatinib plus capecitabine participant, resulted in the requirement for hospitalisation or prolonged hospitalisation, and the remaining SAE was reported to have been life-threatening. All participants recovered from each SAE with the exception of 2 lapatinib plus capecitabine participants for whom one participant recovered with sequelae and the other for whom their condition deteriorated.

There were no further SAEs reported between the final DSUR report cut-off (02/02/14) and the protocol-defined end of trial (09/05/14). The protocol-defined end of trial was defined as 30 days 30 days after the last lapatinib trial treatment was administered.

10. Conclusions

Due to the poor recruitment rate experienced, we conclude that a phase III trial in the UK is not feasible. Furthermore, as a result, the study did not have the statistical power to identify significant differences in treatment effect, safety or survival between the two treatment arms.

11. Publications

None at time of preparing the report but this is currently under active consideration. We will make every effort to publish the findings in a peer reviewed journal.

12. Presentations

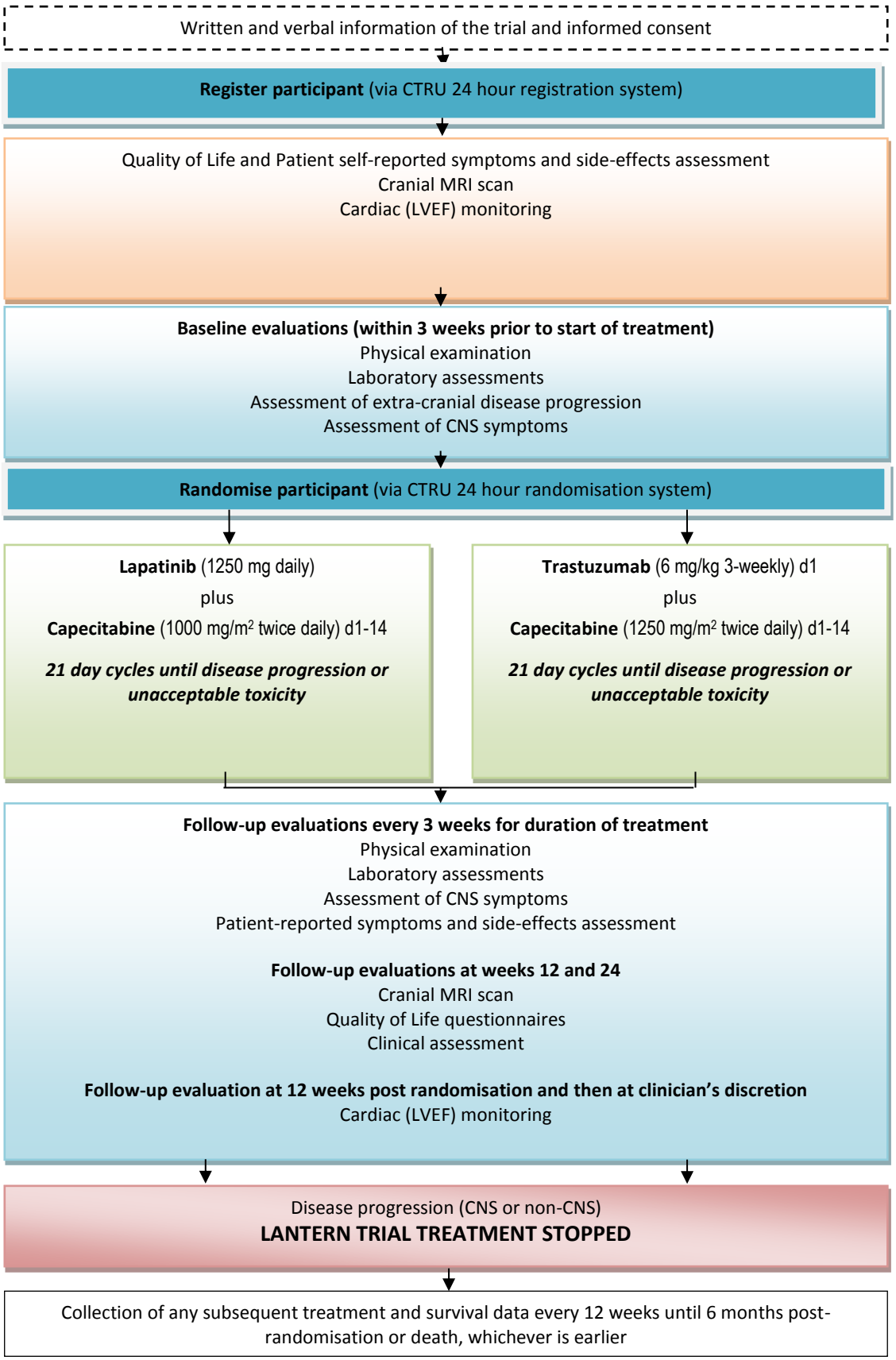
J Oughton, A Wright-Hughes, D Dodwell. “When the LANTERN goes out: Feasibility studies in a changing clinical environment” Poster presented at the annual Society for Clinical Trials Conference, Philadelphia, USA, May 2014

13. References

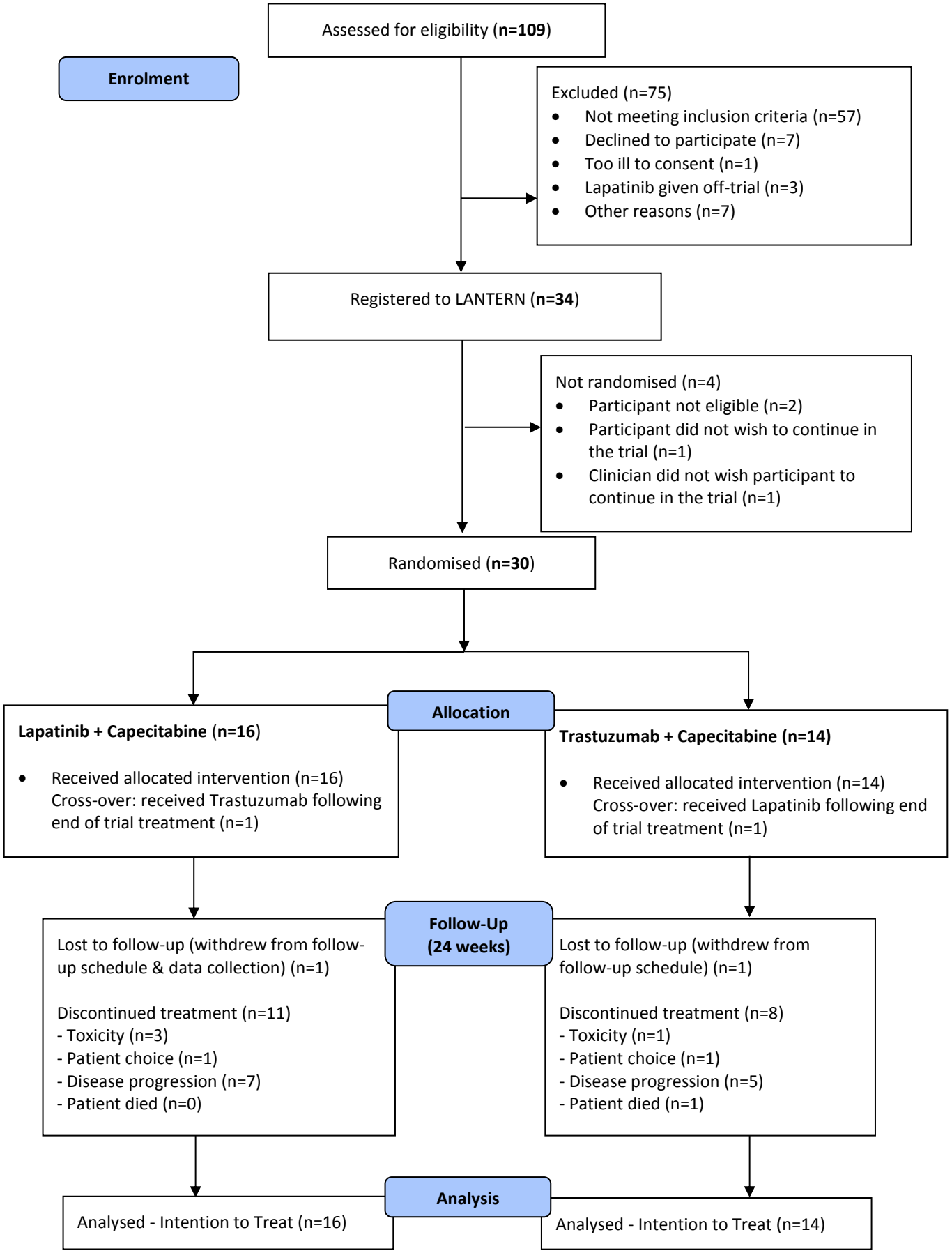
1. Ratain MJ, Sargent DJ. Optimising the design of phase II oncology trials: The importance of randomisation. European Journal of Cancer. 2009; 45:275-280.
2. Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design Issues of Randomized Phase II Trials and a Proposal for Phase II Screening Trials. Journal of Clinical Oncology. 2005; 23(28):7199-7206.

Appendices

Appendix 1. Planned Trial treatment/assessments Flow Diagram



Appendix 2. CONSORT Diagram



Appendix 3. Recruitment Chart