Optimising Therapy In Seminoma: Design of the OTIS clinical trial

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Background

Testicular seminoma represents the largest group presenting with GCTs and is one of the most common cancers in younger men. Dysgerminoma typically affects young women.

Tumours are radio- and chemo-sensitive and, overall, have an excellent prognosis. Extensive surveillance imaging and cisplatin- and bleomycin-containing regimens may not always be warranted. Such approaches are costly for the NHS, a burden for these young patients, and are associated with long-term toxicity risks.

Study aims

The OTIS trial, currently in development, aims to identify optimal treatment and management strategies for seminoma and dysgerminoma that maintain excellent outcomes whilst reducing/avoiding use of more intensive approaches.

The following questions will be addressed:

1. In stage I, can miRNA aid surveillance, reducing radiation exposure and attendances for imaging and allowing earlier detection of relapse? (**A1**, **A2**)
2. Is robotic RPLND with a single cycle of adjuvant carboplatin (AUC7) an effective treatment for stage IIA/B disease? (**B1**, **B2**)
3. When required (for stage IIA/B disease), can advanced radiotherapy delivery allow a shortened course of radiotherapy to be utilised? (**C**)
4. Can adjuvant carboplatin dose escalation reduce recurrences in stage I and II disease? (**A3**, **A4**, **C1**, **C2**)
5. In good prognosis metastatic disease, can carboplatin AUC10, with treatment de-escalation based on PET-CT, replace standard cisplatin-based regimens? (**D1**, **D2**)

Trial design

OTIS will be a comprehensive and inclusive platform, providing an efficient approach to address multiple questions within a single protocol (see figure).

Patients:

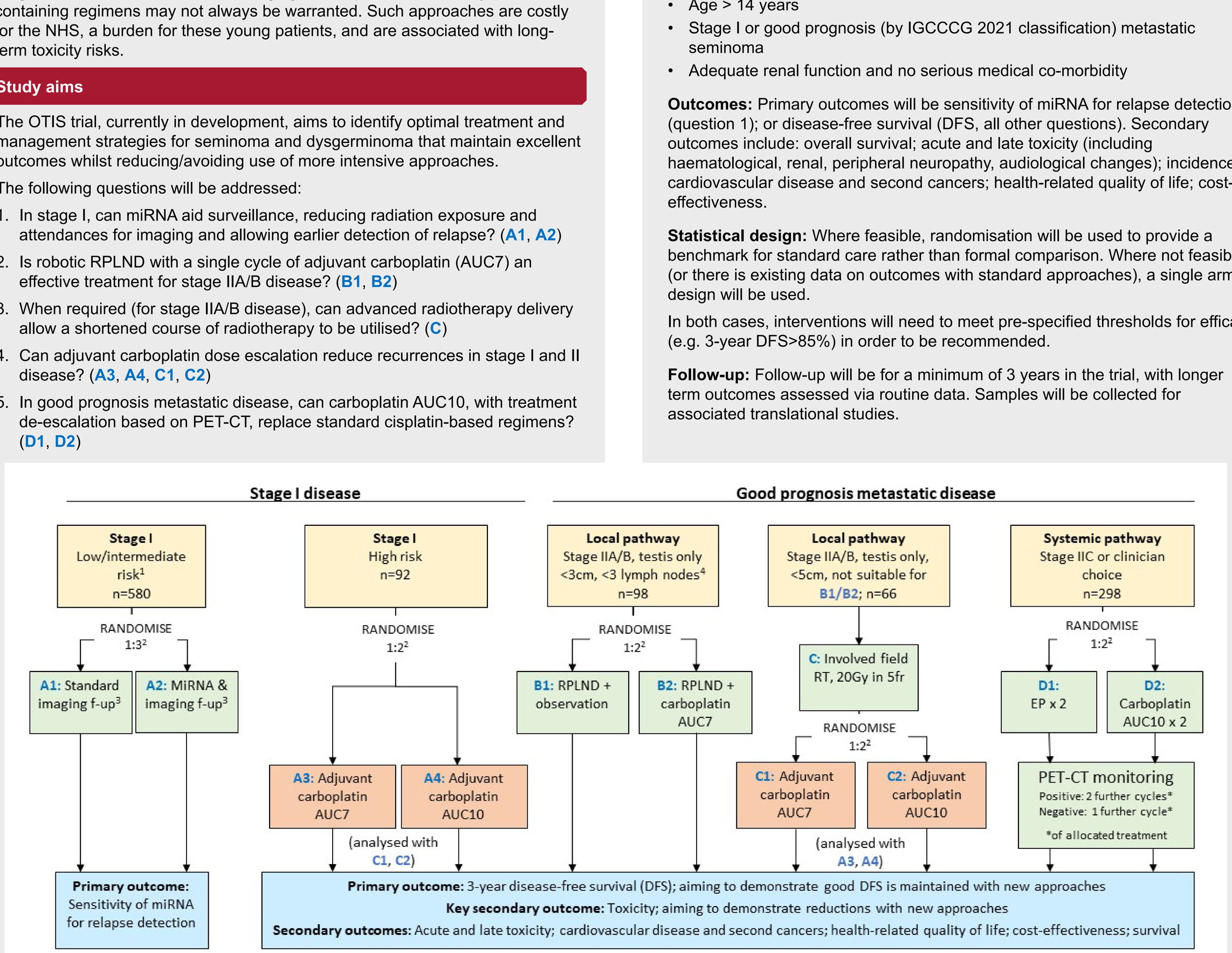
- Seminoma or dysgerminoma of any extra cranial site
- Age > 14 years
- Stage I or good prognosis (by IGCCCG 2021 classification) metastatic seminoma
- Adequate renal function and no serious medical co-morbidity

Outcomes: Primary outcomes will be sensitivity of miRNA for relapse detection (question 1); or disease-free survival (DFS, all other questions). Secondary outcomes include: overall survival; acute and late toxicity (including haematological, renal, peripheral neuropathy, audiological changes); incidence of cardiovascular disease and second cancers; health-related quality of life; cost-effectiveness.

Statistical design: Where feasible, randomisation will be used to provide a benchmark for standard care rather than formal comparison. Where not feasible (or there is existing data on outcomes with standard approaches), a single arm design will be used.

In both cases, interventions will need to meet pre-specified thresholds for efficacy (e.g. 3-year DFS>85%) in order to be recommended.

Follow-up: Follow-up will be for a minimum of 3 years in the trial, with longer term outcomes assessed via routine data. Samples will be collected for associated translational studies.



Developing the trial

The trial is being developed in discussion with the NCRI GCT subgroup and with input from MaGIC (Malignant Germ Cell International Consortium), specifically the dysgerminoma subgroup.

Patient focus groups are planned to establish the questions that are most important to patients and the acceptability of the proposed approaches.

The design will also be informed by a recent survey of 21 UK investigators.

A funding application will be submitted to Cancer Research UK in June 2023.

1. Or clinician-selected high risk patients planned for surveillance
2. Randomisation favours experimental arm; control arm used for benchmarking only
3. Imaging positive patients (either arm) managed as per groups B-D; miRNA positive, imaging negative patients will undergo RPLND as per B
4. MDT decision suitable for RPLND

Summary

OTIS is planned to be a UK-wide trial which will address key questions in seminoma and dysgerminoma management through an efficient, platform protocol.

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