A randomised controlled trial comparing hyperthermia plus mitomycin (HM) to a second course of bacillus Calmette-Guérin (BCG) or standard therapy in patients with recurrence of non-muscle invasive bladder cancer following induction or maintenance BCG therapy.

TRIAL SYNOPSIS

Acronym: HYMN

Title: A randomised controlled, phase III trial comparing hyperthermia plus mitomycin to a second course of bacillus Calmette-Guérin or standard therapy in patients with recurrence of non-muscle invasive bladder cancer following induction or maintenance bacillus Calmette-Guérin therapy.

Design: A phase III, open label, multi-centre, randomised controlled trial.

Objectives: To determine whether hyperthermia plus intravesical mitomycin (HM) is an effective second-line therapy for patients with recurrence of **non-muscle invasive bladder cancer** (NMIBC) following **bacillus Calmette-Guérin** (BCG) therapy. The trial will also address quality of life, cost-effectiveness and translational endpoints, in patients with NMIBC.

Patient Population: Patients with a prior history of NMIBC who have recurrence of NMIBC following induction or maintenance BCG therapy. Patients who are not fit for, or not willing to proceed to, cystectomy are suitable for this trial.

Sample size: The trial aims to recruit at least 242 patients over a 48 month accrual period, who will be followed-up for at least 24 months to generate the required number of events. With 81 events per arm, the trial will have 80% power to detect an increase in 24-month disease-free survival from 45% to 60% at the 5% two-sided significance level. In addition, an embedded subgroup analysis of CIS patients requires at least 27 patients per arm with complete follow-up to detect an increase in complete response rate at three-months from 40% to 80%, with 80% power at the 5% two-sided significance level.

Trial duration: The start date for recruitment is April 2010 and it is anticipated that recruitment will be completed in approximately 4 years.. All patients will be followed-up for at least 24 months.

Primary outcome measures:

- Disease-free survival time
- Complete response rate at 3 months, in the subgroup of trial patients with CIS.

Secondary outcome measures:

- Recurrence-free survival time
- Progression-free survival time
- Overall survival time
- Disease-specific survival time
- Safety and tolerability of HM
- Quality of life
- Cost effectiveness

Translational outcome measures:

HYMN will incorporate translational components: blood, urine and tissue will be collected for future studies.

Main (*but not exhaustive*) inclusion criteria

- Age ≥ 18
- Previous BCG induction or maintenance therapy for NMIBC.
- Recurrence of disease following induction or maintenance BCG defined as:
    - Grade 3 or grade 2 stage Ta/T1disease
    - CIS with grade 3, grade 2 or grade 1 stage Ta/T1 disease
    - CIS alone
- Have undergone a re-resection of all T1 disease to exclude muscle-invasive disease.
- Normal kidney and ureters (it is recommended that this is confirmed by CT scan).
- Normal haematological and biochemistry values.
- Negative pregnancy test for women of child-bearing potential.
- Available for long-term follow-up.

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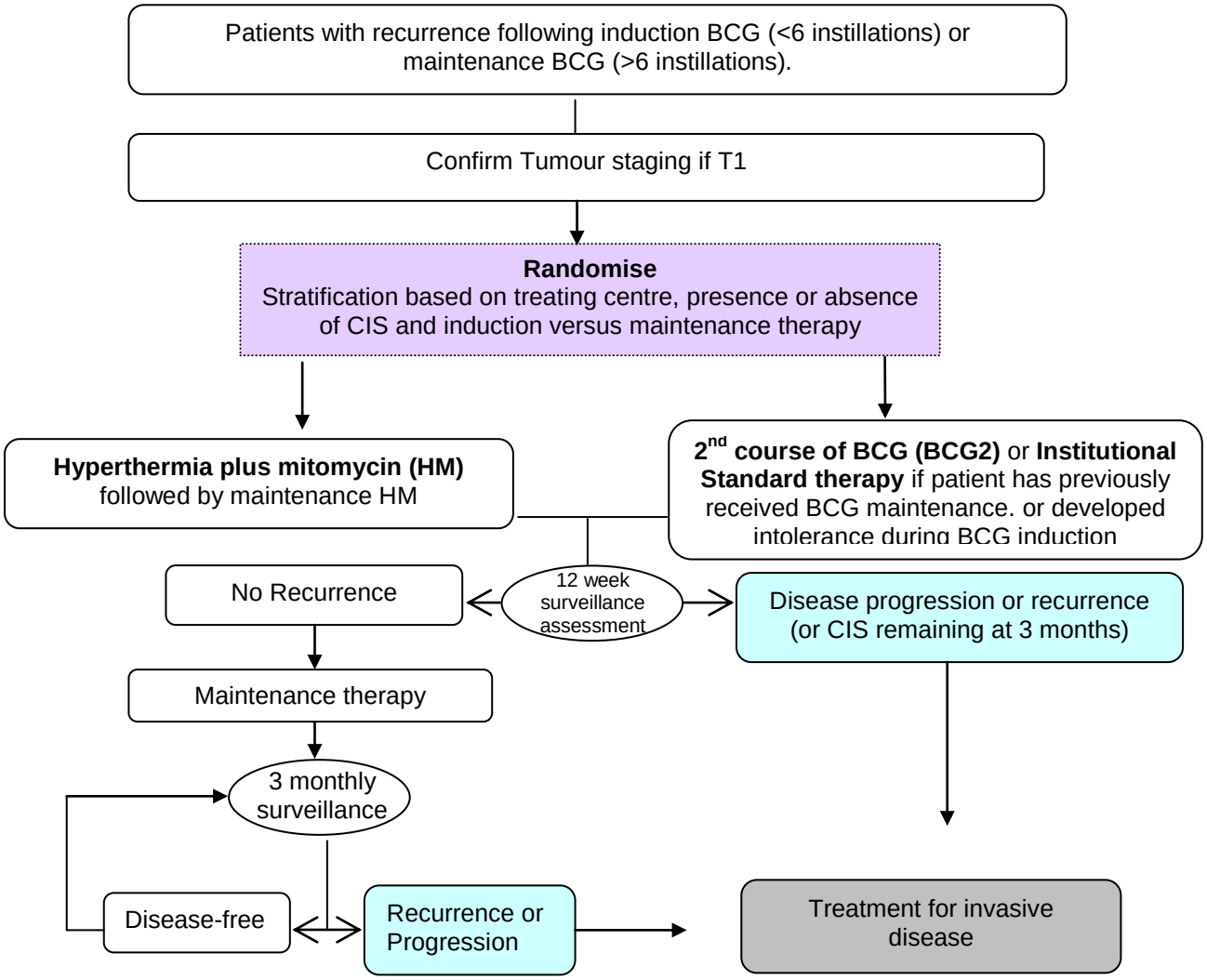
Main (*but not exhaustive*) exclusion criteria

- Recurrence of grade 1 Urothelial cell carcinoma (UCC) without CIS following BCG induction.
- Intravesical chemotherapy in previous 6 months other than single-instillation post-TUR.
- UCC involving the prostatic urethra or upper urinary tract.
- ≥ stage T2 UCC.
- Significant bleeding disorder.
- Pregnant or lactating women or women of childbearing potential unwilling/unable to use adequate non-hormonal contraception.
- Other malignancy within the past 5 years (except curatively-treated non-melanoma skin cancer, or carcinoma *in situ* of the cervix, or DCIS/LCIS of the breast) or stable prostate cancer (under active surveillance or hormone control) with a life expectancy of more than 5 years.
- Concurrent chemotherapy

Trial Schema



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