Title: 111-A single arm, phase 3 trial evaluating one cycle of BEP as adjuvant chemotherapy in high-risk, stage 1 non-seminomatous or combined germ cell tumours of the testis (NSGCTT).

Authors:

M. Cullen[+*1], MD, R. Huddart[*2, 3], PhD, J. Joffe[4], FRCP, D. Gardiner[5], BSc (Hons), L. Maynard[5], MSc, P. Hutton[1], PDGip, D. Mazhar[6], PhD, J. Shamash[7], FRCP, M. Wheater[8], FRCP, J. White[9], FRCP (Glasgow), A. Goubar[5], PhD, N. Porta[5], PhD, S. Witts[5], BSc (Hons) R. Lewis[5], BSc, E. Hall[5] PhD, on behalf of the 111 Trial Management Group

+Chief Investigator

*MC, RH joint first authors

Affiliations:

1. University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
2. The Institute Of Cancer Research, London, UK
3. The Royal Marsden NHS Foundation Trust, London, UK
4. The Leeds Teaching Hospitals NHS Trust, Leeds, UK
5. Clinical Trials and Statistics Unit at The Institute of Cancer Research, London, UK
6. Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
7. Barts Health NHS Trust, London, UK
8. University Hospital Southampton NHS Foundation Trust, Southampton, UK
9. Beatson West of Scotland Cancer Centre, NHS Greater Glasgow and Clyde, Glasgow, UK

Corresponding author:

Prof Robert Huddart

The Institute of Cancer Research, London, SM2 5NG

Email: robert.huddart@icr.ac.uk

Telephone: 020 8661 3425

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Abstract

Background:

Standard adjuvant treatment in the UK for high-risk stage one non-seminoma germ cell tumours of the testis (NSGCTT) is two cycles of bleomycin, etoposide (360mg/m^2) and cisplatin ($BE_{360}P$) chemotherapy.

Objective:

To test whether one cycle of $BE_{500}P$ achieves similar recurrence rates to standard treatment.

Design, setting and participants:

246 patients with vascular invasion positive, stage one NSGCTT or combined seminoma+NSGCTT were centrally registered in a single arm prospective study.

Intervention:

One cycle of bleomycin 30000IU d1,8,15, etoposide 165mg/m^2 d1-3 and cisplatin 50mg/m^2 d1-2, plus antibacterial and GCSF prophylaxis.

Outcome measurements and statistical analysis:

The primary endpoint was two-year malignant recurrence (MR), aiming to exclude a rate of ≥5%. Participants had regular imaging and tumour marker (TM) assessment for five years.

Results and limitations:

Median follow-up was 49 months (IQR 37-60). Ten patients with rising TM at baseline were excluded. Four patients had MR at 6, 7, 13, and 27 months; all received second line chemotherapy and surgery; three remained recurrence free at five years. Two-year MR rate was 1.3% (95% CI: 0.3-3.7%). Three patients developed non-malignant recurrences with localized teratoma differentiated, rendered disease-free post surgery. Grade 3-4 febrile neutropenia occurred in 6.8% of participants.

Conclusions:

$BE_{500}P$ is safe and the two-year MR rate is consistent with that seen following two $BE_{360}P$ cycles. 111 is the largest prospective trial investigating adjuvant $BE_{500}P$ x1 in high-risk stage one NSGCTT. The adoption of $BE_{500}P$ x1 as standard would reduce overall exposure to chemotherapy in this young population.

Patient summary:

Removing the testicle fails to cure many patients with high-risk primary testicular cancer since undetectable cancers are often present elsewhere. A standard additional treatment within Europe is two cycles of chemotherapy to eradicate these. This trial shows one cycle has few adverse effects and comparable outcomes to those seen with two cycles.

Introduction

Testicular cancer is the most common cancer in young men in Western populations and most patients present in stage one. Many with non-seminomas and combined germ cell tumours (NSCGCT) have vascular invasion (VI+) by malignant cells and are at high-risk (~50%) of harbouring undetected metastases,[1,2] confirmed consistently in many studies of surveillance.[3]

Standard post-orchidectomy management options in Europe for this patient population are adjuvant chemotherapy with two cycles of bleomycin, etoposide, cisplatin ($BE_{360}Px2$) or surveillance with $BE_{500}Px3$ on recurrence.[4] Adjuvant $BE_{360}Px2$ results in malignant recurrence rates of <5%. Both management options yield cure rates approaching 100%.[5,6] Proponents of surveillance cite 50% of patients receiving unnecessary AC,[7] whilst AC proponents highlight poor adherence to surveillance and recurrence with advanced disease sometimes requiring retroperitoneal lymph node dissection (RPLND).[8] Clearly it is important to expose patients to the minimum treatment necessary. Frequency of immediate and late chemotherapy toxicity is closely related to total doses received; if AC $BE_{500}Px1$ were as effective as $BE_{360}Px2$, it would substantially reduce the total chemotherapy burden since approximately half of surveillance cases recur, requiring $BE_{500}Px3$.

Over recent years evidence has accumulated supporting the efficacy of $BE_{500}Px1$,[9 10-13] nevertheless uptake of single cycle AC remains patchy.

The 111 study was designed as a practice changing study to confirm the efficacy signals of these smaller studies. It tested $BE_{500}Px1$ within a prospective, multicentre single arm trial in a patient population with an expected risk of recurrence of ~50%. Based on the experience of testicular cancer key opinion leaders and trial collaborators and existing data, the figure considered acceptable for relapse after

BE_{500}Px1 was <5%. The aim was to demonstrate whether AC with BE_{500}Px1 confers a 2-year malignant recurrence rate <5% in high-risk stage one testicular NSCGCT, with acceptable short-term toxicity in line with, and no worse than, the established toxicity profile for patients receiving BE_{360}Px2.

Methods

Study design and participants

BEP111 is a single group, non-randomised phase-3, open-label, multicentre trial of novel design employing sequential application of defined stopping rules based on robust historical BE_{360}Px2 malignant recurrence rate data, monitored by an Independent Data Monitoring Committee (IDMC). The trial, conducted in accordance with principles of good clinical practice, was approved by the Medicines and Healthcare Products Regulatory Authority and London (South East) Research Ethics Committee (09/H1102/86) and co-sponsored by University Hospitals Birmingham NHS Trust and The Institute of Cancer Research (ICR). The study is registered (ISRCTN37875250). All participants provided written informed consent. The Clinical Trials and Statistics Unit at the ICR (ICR-CTSU) coordinated the study and carried out central data management, statistical data monitoring and all analyses. The trial was overseen by an independent Trial Steering Committee (TSC).

Newly diagnosed testicular cancer patients with NSCGCTT with VI+ stage one disease, able to start chemotherapy ideally within six weeks of orchidectomy (but no later than eight weeks unless agreed by the Chief Investigator with a repeat CT scan to confirm stage 1), were eligible (Table 1 reports the full eligibility criteria). Baseline assessments included CT of the chest, abdomen and pelvis and TM (AFP, LDH and HCG) to confirm stage 1 disease. Patients were centrally registered with ICR-CTSU prior to commencing treatment.

Procedures

Participants received $BE_{500}Px1$ over three weeks (bleomycin 30,000IU d1, 8, 15, cisplatin 50mg/m^2 d1-2, etoposide 165mg/m^2 d1-3). Prophylaxis with an oral fluoroquinolone antibacterial[14] and subcutaneous granulocyte colony stimulating factor (GCSF) was mandated to reduce neutropenic sepsis.[15]

Patients had full clinical assessment including adverse events (AEs), graded using the National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI CTCAE v3), no later than 4 weeks following $BE_{500}Px1$, then 2-monthly until 6 months, 3-monthly until 24 months, 4-monthly during the third year and 6-monthly during the fourth and fifth years post-treatment. Computerised tomographic (CT) scans of chest, abdomen and pelvis were required at 6, 12, 24 and 60 months, with chest x-ray at all other visits. Physical examination and TM measurements were required at each visit to assess signs of recurrence or development of second primary.

Outcomes

For purposes of analysis, recurrences were defined in two categories:

Malignant recurrence (MR) defined as a recurrence indicated by rising TM (AFP and/or HCG) from two consecutive results taken ≥1 week apart showing >50% increase above the upper limit of normal and/or a histologically malignant recurrence (e.g. undifferentiated, yolk sac or choriocarcinoma) and/or at multiple sites.

Benign recurrence (BR) defined as a single site recurrence with no TM elevation, consisting of fully resected, differentiated teratoma (TD) with no histological evidence of viable malignancy. These do not imply failure of AC since TD is unresponsive to chemotherapy and is analogous to 'growing teratoma' syndrome after chemotherapy for metastatic disease.

All recurrences were prospectively reviewed and classified by the Chief Investigator and the IDMC.

The primary endpoint was the rate of MR at 2 years, secondary efficacy outcome measures included BR rate, overall recurrence rate, development of contralateral second primary testicular germ cell malignancy, relapse free survival (defined as the time from registration until first confirmed relapse or death from any cause) and overall survival. Additional secondary endpoints were immediate and delayed toxicity. Treatment emergent acute toxicity was any AE not present prior to the initiation of trial treatment, or already present but worsening following exposure to the trial treatment. Delayed toxicity was reported in the time intervals 2-12 months, 18-24 months and >24 months. Emergent delayed toxicity in the 2-12 months is any AE that was not present or worsened from baseline or end of cycle.

Statistical analysis

The trial was powered to exclude a 2-year MR rate ≥5% in high-risk stage one NSCGCTT. Based on exact binomial probabilities, with 80% power and one-sided 5% alpha, the minimum sample size required was 236 patients. In practice this means that if ≥230 patients remained MR-free, the true MR rate is highly likely to be <5%. After each recurrence event, sequential early stopping rules for futility were applied based on the probability that the final relapse rate ≥5% (conditional on the data and follow-up available at that time), monitored by the IDMC. Adequate beta spending functions were chosen via simulation to ensure that despite multiple analyses the final alpha and power are 5% and 80%. A formal interim analysis was conducted when 157 patients had been followed up for ≥2 years.

Analyses of outcomes included all eligible registered patients. For safety endpoints, analyses were according to treatment received. The MR rate at 2 years and its 95%

confidence interval (95% CI) were estimated using exact binomial probabilities. Patients without complete data at 2 years of follow-up were assumed to have no malignant recurrence at 2 years. To account for such censoring, the 2-year MR rate was also estimated using Kaplan-Meier methods. Patients with BR were censored at the time of the event. Both methods had to yield upper limits of 95% CI <5% to exclude an MR rate ≥5%. Sensitivity analyses of the primary endpoint on the per protocol population were performed.

Similar analysis methods were used for other efficacy endpoints. In the absence of discrepancy between exact binomial and Kaplan-Meier methods, the latter are reported. The frequency and nature of toxicities are summarised by worst CTCAE grade, for each of the reporting periods (end of cycle, delayed 2-12, 18-24, >24 months). Analyses were based on a database snapshot taken 04/12/2017 and were performed using STATA version 13.1.[16]

Results

Between 18/02/2010 and 31/07/2014, 246 patients were registered from 33 UK NHS hospitals (Figure 1) all of which were peer-reviewed accredited testis tumour treatment centres. The median follow-up at the time of reporting is 49 months (interquartile range 37-60). Ten patients were replaced after they were found ineligible post-registration due to rising TM. In 114/246 cases (46%) there was histopathological evidence of seminoma in addition to unequivocal VI+ NSGCTT (Table 2). Of the 236 patients included in the analysis, 228 (97%) were followed up to at least 2 years.

Median time between orchidectomy and start of treatment was 6 weeks (IQR 5-7) and all 236 patients started $BE_{500}P$. Treatment was received as planned in 221/236 (94%) of eligible patients. Eight patients (3.4%) received a per protocol bleomycin dose

195 reduction due to neutropenia. There was good adherence to neutropenic sepsis
196 prophylaxis, with 219/236 (93%) receiving this per protocol. The remaining 17
197 patients received some prophylaxis, either GCSF or antibacterial.
198 There were four MR at 6, 7, 13 and 27 months post-trial registration all of which were
199 confirmed as malignant NSGCT through histological examination and/or rising TM
200 (Table 3). The 2-year MR rate is 1.3% estimated using exact binomial probabilities
201 (95% CI 0.3-3.7%) and Kaplan-Meier methods (0.4%, 4.0%). With both methods, a
202 2-year MR rate ≥5% can be excluded. The 4-year MR rate is 1.8% (95% CI 0.7-
203 4.6%). All four malignant recurrences required surgical intervention and second line
204 chemotherapy. Three patients achieved complete remission, remaining well 5 years
205 after treatment. The patient with MR at 6 months had very extensive, unresectable
206 retroperitoneal NSGCT that failed to respond to chemotherapy and died 2 months
207 later. This was the only case of MR with an International Germ Cell Cancer
208 Collaborative Group (IGCCCG) metastatic prognostic classification of 'intermediate',
209 all others fell within the 'good' prognosis category.[17]
210 There were three BR consisting exclusively of histologically confirmed TD with no
211 evidence of viable cancer at 7, 10 and 13 months post-trial registration (Table 3). All
212 three had RPLND and remained well 55, 26 and 24 months following BR.
213 The MR+BR rate at 2 years is 2.6% (95% CI 1.2-5.7%), and at 4 years is 3.1% (95%
214 CI 1.5-6.3%) (Figure 2).
215 Sensitivity analysis in the per protocol population (consisting of 208 eligible patients,
216 compliant with treatment and with complete 2-year follow-up) provided a 2-year MR
217 rate of 1.5% (95% CI 0.5-4.4%), while the MR+BR rate at 2 years was 2.4% (95% CI
218 1.0-5.7%).

No cases of contralateral second primary testicular germ cell malignancy were reported. The 2-year relapse free survival was 97% (95% CI 94-99%). There were two unrelated deaths in patients free from recurrent testicular cancer: one due to small cell lung cancer at 18 months post-trial registration, and one from self-administered drug overdose at 45 months. The 2-year overall survival is 99% (95% CI: 97-100%). Acute emergent toxicity within 4 weeks following $BE_{500}P$ was assessed on 233/236 cases with paired baseline and end of cycle assessments. Ninety-five (41%) patients had at least one severe (grade 3-4) toxicity, including: neutropenia, 75 (32%); leukopenia, 40 (17%); febrile neutropenia, 16 (6.8%); thrombocytopenia, 8 (3.4%); non-neutropenic sepsis, 7 (3.0%); and emesis, 6 (2.6%). Fewer than 3% of patients reported grade 3-4 late emergent toxicities (Table 4). Data on fertility indices will be published separately.

Discussion

The 111 trial has demonstrated the efficacy of adjuvant $BE_{500}Px1$ for high-risk (VI+), stage one NSCGCTT. The two and four year MR rates of just 1.3% and 1.8% respectively are almost identical to the results reported following $BE_{360}Px2$.[5,10,18,19]. As seen in other studies of AC in this patient group,[20] an additional three patients developed localized BR due, we believe, to growing teratoma resulting from successful treatment of malignant disease. The pragmatic decision to rely on a non-randomised trial design was made in light of the rarity of the patient group under study, and the low expected event rate in the study population. A non-inferiority trial to demonstrate that one cycle was no worse than 3% less effective than two (80% power, 1-sided alpha=5%) would have required 1110 participants, an impossible target within a reasonable timeframe.

The 111 trial design was developed in collaboration with investigators, to identify an acceptable MR rate with $BE_{500}Px1$ which would lead to adoption of the regimen, thus fulfilling phase 3 criteria. This design was cited as a model option in a recent review of novel research methods aiming to change clinical practice for patients with rare cancers.[21]

The MR rates observed in 111 are consistent with three small, single centre studies including 112 patients.[11-13] They also reflect those reported in a population-based study by the Swedish and Norwegian Testicular Cancer Project that included both low and high-risk patients treated with $BE_{500}Px1$ or $BE_{500}Px2$. In their latest update[22], among 258 VI+ patients who chose $BE_{500}Px1$ there were eight malignant recurrences (3.2%; 95% CI 1.6–6.4%) during a median follow-up of 7.9 years. A randomised German trial of $BE_{500}Px1$ versus RPLND reported only two recurrences among 191 patients randomised to $BE_{500}Px1$ (only one of which was malignant), but just 42% of randomised cases were classified as high-risk and the outcome of this subgroup was not reported separately.[9] The authors concluded that their data 'should encourage investigators to test the promising approach of one course $BE_{500}P$.'

Febrile neutropenia (FN) remains a serious risk of full dose etoposide chemotherapy with occasional fatalities hence the use of dual infection prophylaxis in this adjuvant context. This appears to have been effective since the rate of severe FN was 6.8% (with no deaths) compared to 20% following cycle one in 111 control testicular cancer patients having BEP and allocated to placebo in a randomised trial of prophylactic levofloxacin.[15]

Late toxicity is a clear concern with adjuvant $BE_{500}P$. A small number (<3%) developed grade 3-4 late toxicity. There is ample evidence in testicular cancer of a direct relationship between cycle number (i.e. cumulative dose) and delayed toxicity

in terms of infertility, metabolic syndrome, neuropathy, lung, and renal function.[23-27] However, any toxicity developing after $BE_{500}Px1$ has to be balanced by the greater risk of toxicity with the higher doses which would be given to the 50% of patients expected to relapse if surveillance is used. Post-treatment fertility indices will be reported separately, but on the basis of published data following $BE_{360}Px2$ it is unlikely that serious impairment of spermatogenesis will be demonstrated following one cycle.[23]

The German and Scandinavian studies cited provided important foundations and rationale for the present trial.[9,10] Since their publication there has been controversy surrounding the options of AC versus surveillance in stage one NSGCTT. In their 2013 paper, Nichols *et al.* clearly favour surveillance.[7] However, important differences between testicular cancer types and risk categories are obfuscated in this review. For instance, the authors mention recent trends towards less intensive surveillance with fewer CT scans and hence less radiation exposure. But two studies cited in support excluded high-risk stage one NSGCTT.[28,29] They also omit to consider the risk of requiring elective surgery (commonly RPLND) following chemotherapy for recurrence on surveillance. De Wit noted that in the biggest recent study of surveillance 26% of relapsing patients required post chemotherapy surgery.[6,8] In the 111 trial 3% of patients (7/236) required surgery for malignant or benign recurrence. The much higher level of surgery required in surveillance patients relates to more advanced disease stages at the time of chemotherapy exposure. This drawback is exacerbated by poor compliance with surveillance schedules as reported in several studies, particularly those relating to surveillance in the community setting.[30] Treatment of MR, though usually successful, involves more intensive chemotherapy and major surgery as well as being extremely disruptive to the lives of

young men and their families. RPLND has been used in this scenario as an alternative but a German study showed that recurrences were frequent in unselected stage pN0 NSGCT patients than after adjuvant BEP chemotherapy (8% v 1%), and in VI+ patients recurrence rates are 28%[31] unless adjuvant chemotherapy is used in pN+ cases.

111 is the first prospective trial of $BE_{500}Px1$ with sufficient high-risk stage one NSGCTT or combined seminoma plus NSGCTT patients to exclude a MR rate at 2 years ≥5%. Despite the unavoidable limitation of being a single arm study, 111 achieved its aim, a malignant failure rate of just 1.3%, with very low levels of serious short-term and delayed toxicity. This trial confirms that $BE_{500}Px1$ should replace $BE_{360}Px2$ as the standard adjuvant therapy offered to all patients with VI+ stage one NSCGCTT.

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Recruiting consultants according to centre (number of patients recruited in bold): Queen Elizabeth Hospital, Birmingham, **23**, Prof. M Cullen, Dr E Porfiri; Royal Marsden Hospital, Sutton, **23**, Prof. R Huddart; Beatson West of Scotland Cancer Centre, Glasgow, **21**, Dr J White, Dr A Waterston; St James's University Hospital, Leeds, **21**, Dr J Joffe, Dr D Stark; Bristol Haematology and Oncology Centre, **16**, Dr J Braybrook; St Bartholomew's Hospital, London, **14**, Dr J Shamash; Southampton General Hospital, **13**, Dr M Wheater, Dr P Simmonds, Dr G Mead; Addenbrooke's Hospital, Cambridge, **9**, Dr D Mazhar; Castle Hill Hospital, Hull, **9**, Dr M Butt; Royal Liverpool & Broadgreen University Hospital, **9**, Prof. P Clark; Weston Park Hospital, Sheffield, **9**, Dr L Evans, Prof. R Coleman; Leicester Royal Infirmary, **8**, Dr G Faust, Dr C Esler; Nottingham University Hospital, **8**, Dr I Hennig; Royal Sussex County

Hospital, Brighton, **7**, Dr D Bloomfield; Clatterbridge Cancer Centre, Wirral, **6**, Prof. P Clark, Dr J Carser; Royal Devon & Exeter Hospital, Exeter, **6**, Dr A Hong; University College Hospital, London, **6**, Dr S Harland; Western General Hospital, Edinburgh, **5**, Dr A Law, Dr D McLaren; Aberdeen Royal Infirmary, **4**, Dr G MacDonald; Guy's Hospital, London, **4**, Dr S Rudman, Dr S Chowdhury; Maidstone Hospital, **4**, Dr S Beesley, Dr H Taylor; Royal Derby Hospital, **3**, Dr P Chakraborti; Royal Surrey County Hospital, Guildford, **3**, Dr J Money-Kyrle; Lincoln County Hospital, **2**, Dr T Sreenivasan; Norfolk & Norwich University Hosptial, **2**, Dr G Kapur, Dr S Alexander; Pilgrim Hospital, Boston, **2**, Dr Addeo; Royal Berkshire Hospital, Reading, **2**, Dr P Rogers; Ysbyty Gwynedd Hospital, Bangor, **2**, Dr N Stuart; Cheltenham General Hospital, **1**, Dr R Owen; Churchill Hospital, Oxford, **1**, Dr A Protheroe; Ipswich Hospital, **1**, Dr R Venkitaraman; University Hospitals of Coventry & Warwickshire NHS Trust, **1**, Dr A Stockdale; Velindre Cancer Centre, Cardiff, **1**, Dr S Kumar.

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All remaining authors have declared no conflicts of interest.

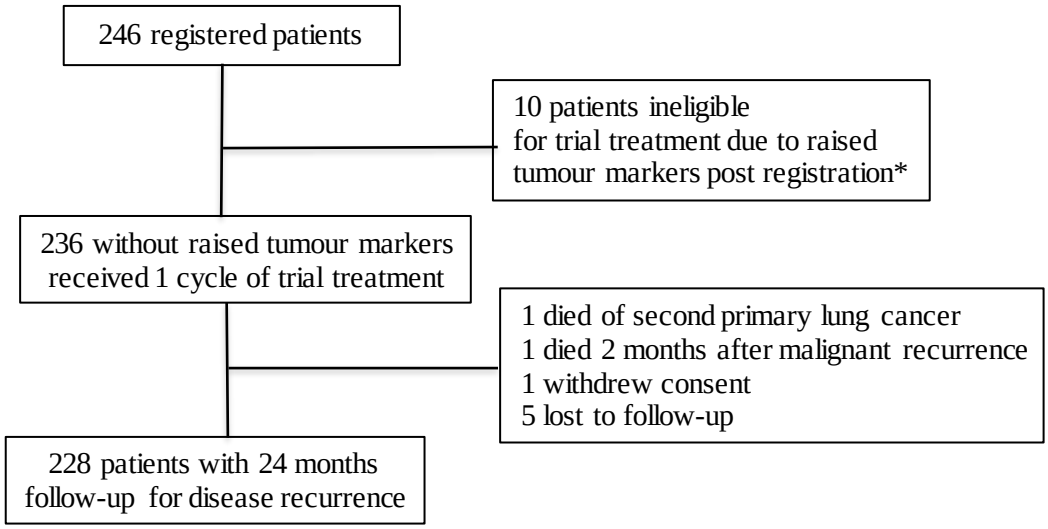
Table 1 Eligibility criteria for entry into 111 trial

Inclusion criteria	Exclusion criteria
Newly diagnosed, histologically proven Pure NSGCT* or Combined seminoma plus NSGCT of testis	Previous chemotherapy
Vascular invasion of primary tumour into testicular veins or lymphatics	Previous malignant disease
Stage 1B (T2N0M0), evidence of no metastases on CT scanning or tumour marker (AFP, HCG) estimations. †	Liver function impairment (bilirubin >1.25 x upper limit of normal range for reporting laboratory
Age ≥16 years	Pre-existing neuropathy
Fit to receive chemotherapy	Pulmonary fibrosis
Creatinine clearance >50 ml/min	Serious illness or medical conditions incompatible with safe protocol treatment
WBC >1.5 x 10^9/l and platelets >100 x 10^9/l	
Able to start BEP chemotherapy within 6 weeks of orchidectomy	
Written informed consent	

*Non-seminomatous germ cell tumour

†Where markers raised pre-orchidectomy, optimum marker decline approaching normal levels required post-operatively, prior to commencing trial therapy

Figure 1 CONSORT diagram



*Ineligibility confirmed by central review. Patients followed-up but data are not included within the primary intention to treat analysis in accordance with the statistical analysis plan.

Table 2 Patient characteristics on entry to 111 trial

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		N	**%**
Age (*n=246*) median 31 IQR (25,39)	≤24	*57*	23
	25-29	*65*	26
	30-39	*70*	29
	40-49	*38*	15
	50+	*16*	6.5
WHO performance status (*n=239*)	0	*230*	96
	1	*9*	3.8
Tumour diameter (cm) (*n=239*)	<2	*47*	20
	2-5	*121*	51
	>5	*71*	30
Histopathology type (*n=246*)	Pure NSGCTT	*132*	54
	Combined seminoma/NSGCTT	*114*	46
Pathological tumour stage (*n=246*)	pT2 (blood vessel and or lymphatic invasion, VI+)	*237*	96
	pT3 (VI+ and tumour extending to the spermatic cord)	*9*	3.7

Table 3 Details of all recurrences in the analysed population (N=236)

	Age at baseline (years)	Histology type (orchidectomy)	Tumour size (orchidectomy)	Time of recurrence from registration (months)	Site of recurrence	IGCCCG prognostic category	Surgical management	Chemotherapy regimen and cycle number	Outcome (months last follow-up)
Malignant									
1	55	NSGCTT	>5 cm	5.8	RPLN+ raised AFP	Intermediate (LDH 1.5 - 10xULN)	Attempted RPLND. Extensive unresectable tumours	IPE x2	Died at 9 months with resistant malignant NSGCT
2	24	NSGCTT	>5 cm	6.7	Lung	Good	Video assisted wedge resection	TIP x4	CR (60.9)
3	42	Mixed seminoma/ NSGCTT	2-5 cm	12.5	RPLN +raised AFP	Good	RPLND	BEP x3	CR (60.4)
4	31	Mixed seminoma/ NSGCTT	2-5 cm	27.1	Right inguinal region + raised HCG	Good	Excision of spermatic cord and external iliac lymph node	TIP x3	CR (62.6)
Benign									
1	22	NSGCTT	2-5 cm	6.8	RPLN	Good	RPLND	None	CR (61.9)
2	22	Mixed seminoma/ NSGCTT	2-5 cm	10.2	RPLN	Good	RPLND	None	CR (36.2)
3	29	NSGCTT	<2 cm	13.1	RPLN	Good	RPLND	None	CR (37.3)

Abbreviations: RPLN retroperitoneal lymph node, RPLND retroperitoneal lymph node dissection, IPE ifosfamide cisplatin etoposide, NSGCT non-seminoma germ cell tumour, CR complete remission, TIP paclitaxel ifosfamide cisplatin, BEP bleomycin etoposide cisplatin, LDH lactate dehydrogenase, ULN upper limit of normal.

Figure 2 Recurrence rate estimated by Kaplan-Meier methods

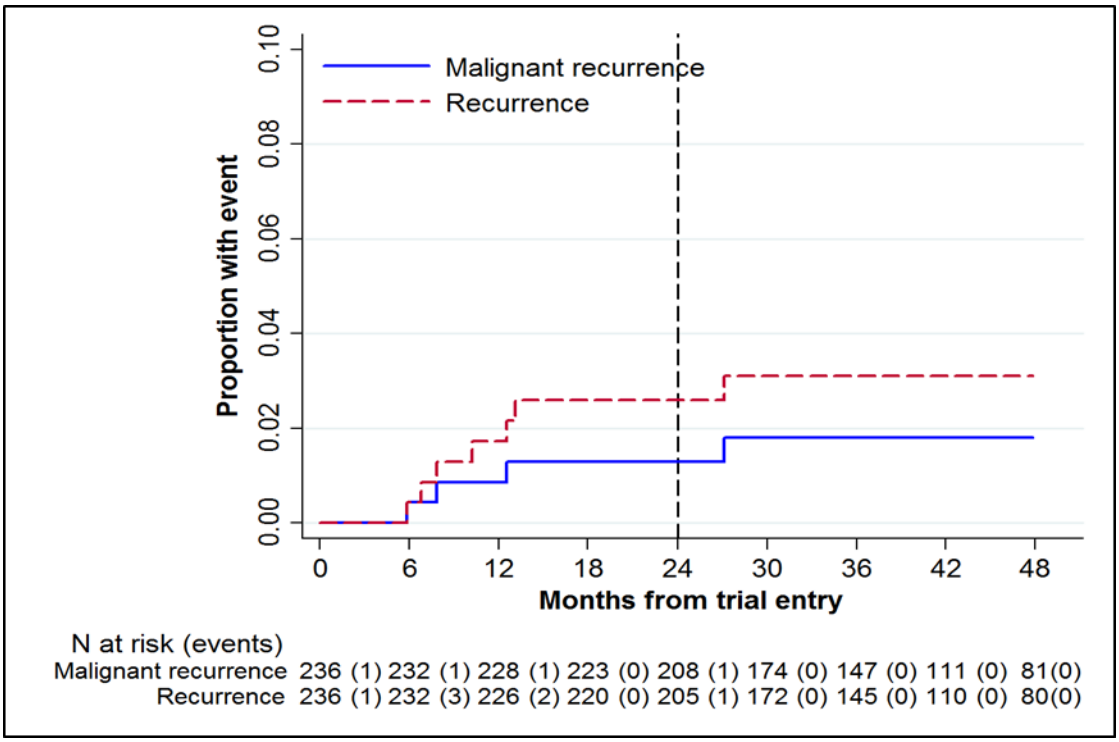

Table 4 Delayed toxicity - worst CTCAE grade adverse event per patient

	2-12 months (*N=233*)*				**18-24 months (*N=215*)**				**>24 months (*N=184*)**			
	Grade 1+		**Grade 3+**		**Grade 1+**		**Grade 3+**		**Grade 1+**		**Grade 3+**	
	N	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Any toxicity	*137*	59	*6*	2.6	*107*	50	*2*	0.9	*79*	43	*3*	1.6
Specific toxicities of interest:												
Dyspnoea	*15*	6.4	*0*	0.0	*10*	4.7	*0*	0	*8*	4.3	*0*	0
Ear and labyrinth disorders†	*17*	7.3	*2*	0.9	*17*	7.9	*1*	0.5	*7*	3.8	*1*	0.5
Psychiatric disorders¥	*9*	3.9	*1*	0.4	*3*	1.4	*0*	0	*4*	2.2	*0*	0
Fatigue	*4*	1.7	*0*	0	*0*	0	*0*	0	*1*	0.5	*0*	0
Insomnia	*2*	0.9	*0*	0	*2*	0.9	*0*	0	*1*	0.5	*0*	0

*For the 2-12 months reporting period, emergent toxicities are presented (not present at or worsening from baseline/end of cycle). For the other reporting time periods, toxicities as reported.
†Ototoxicity, deafness and tinnitus
¥ Includes depression, anxiety, depressed mood and mood altered

Details of grade 3-4 toxicities:
2-12 months: *G3 (anaemia, 2 ototoxicity, weight increased, depression), G4 (thrombocytopenia, osteonecrosis),*
18-24 months: *G3 (osteonecrosis, ototoxicity, tinnitus)*
>24 months: *G3 (Diabetes, lethargy), G4 (Deafness)*

References

1. Freedman LS, Parkinson MC, Jones WG, et al. Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchidectomy alone. Lancet 1987;2:294-8.
2. Read G, Stenning SP, Cullen MH, et al. Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. J Clin Oncol 1992;10:1762-8.
3. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Albers P, Habbema JD. Predictors of occult metastasis in clinical stage I nonseminoma: a systematic review. J Clin Oncol 2003;21:4092-9.
4. Beyer J, Albers P, Altena R, et al. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. Ann Oncol 2013;24:878-88.
5. Cullen MH, Stenning SP, Parkinson MC, et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. J Clin Oncol 1996;14:1106-13.
6. Daugaard G, Gundgaard MG, Mortensen MS, et al. Surveillance for stage I nonseminoma testicular cancer: outcomes and long-term follow-up in a population-based cohort. J Clin Oncol 2014;32:3817-23.
7. Nichols CR, Roth B, Albers P, et al. Active surveillance is the preferred approach to clinical stage I testicular cancer. J Clin Oncol 2013;31:3490-3.
8. de Wit R. Optimal management of clinical stage I nonseminoma: new data for patients to consider. J Clin Oncol 2014;32:3792-3.
9. Albers P, Siener R, Krege S, et al. Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I Nonseminomatous testicular germ cell tumors: AUO trial AH 01/94 by the German Testicular Cancer Study Group. J Clin Oncol 2008;26:2966-72.
10. Tandstad T, Dahl O, Cohn-Cedermark G, et al. Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. J Clin Oncol 2009;27:2122-8.
11. Vidal AD, Thalmann GN, Karamitopoulou-Diamantis E, Fey MF, Studer UE. Long-term outcome of patients with clinical stage I high-risk nonseminomatous germ-cell tumors 15 years after one adjuvant cycle of bleomycin, etoposide, and cisplatin chemotherapy. Ann Oncol 2015;26:374-7.
12. Gilbert DC, Norman AR, Nicholl J, Dearnaley DP, Horwich A, Huddart RA. Treating stage I nonseminomatous germ cell tumours with a single cycle of chemotherapy. BJU Int 2006;98:67-9.
13. Oliver RT, Ong J, Shamash J, et al. Long-term follow-up of Anglian Germ Cell Cancer Group surveillance versus patients with Stage 1 nonseminoma treated with adjuvant chemotherapy. Urology 2004;63:556-61.
14. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005;353:988-98.
15. Cullen MH, Billingham LJ, Gaunt CH, Steven NM. Rational selection of patients for antibacterial prophylaxis after chemotherapy. J Clin Oncol 2007;25:4821-8.
16. StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP 2013.

17. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 1997;15:594-603.
18. Pont J, Albrecht W, Postner G, Sellner F, Angel K, Holtl W. Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. J Clin Oncol 1996;14:441-8.
19. Bohlen D, Borner M, Sonntag RW, Fey MF, Studer UE. Long-term results following adjuvant chemotherapy in patients with clinical stage I testicular nonseminomatous malignant germ cell tumors with high risk factors. J Urol 1999;161:1148-52.
20. Huddart RA, Reid AM. Adjuvant Therapy for Stage IB Germ Cell Tumors: One versus Two Cycles of BEP. Adv Urol 2018;2018:8781698.
21. Billingham L, Malottki K, Steven N. Research methods to change clinical practice for patients with rare cancers. Lancet Oncol 2016;17:e70-e80.
22. Tandstad T, Stahl O, Hakansson U, et al. One course of adjuvant BEP in clinical stage I nonseminoma mature and expanded results from the SWENOTECA group. Ann Oncol 2014;25:2167-72.
23. Brydoy M, Fossa SD, Klepp O, et al. Paternity and testicular function among testicular cancer survivors treated with two to four cycles of cisplatin-based chemotherapy. Eur Urol 2010;58:134-40.
24. Haugnes HS, Aass N, Fossa SD, et al. Components of the metabolic syndrome in long-term survivors of testicular cancer. Ann Oncol 2007;18:241-8.
25. Haugnes HS, Aass N, Fossa SD, et al. Pulmonary function in long-term survivors of testicular cancer. J Clin Oncol 2009;27:2779-86.
26. Suer E, Mermerkaya M, Gulpinar O, et al. Does the number of cycles of cisplatin based chemotherapy have any effect on renal function in patients with testicular germ cell tumor? J Urol 2013;190:2081-5.
27. Glendenning JL, Barbachano Y, Norman AR, Dearnaley DP, Horwich A, Huddart RA. Long-term neurologic and peripheral vascular toxicity after chemotherapy treatment of testicular cancer. Cancer 2010;116:2322-31.
28. Rustin GJ, Mead GM, Stenning SP, et al. Randomized trial of two or five computed tomography scans in the surveillance of patients with stage I nonseminomatous germ cell tumors of the testis: Medical Research Council Trial TE08, ISRCTN56475197--the National Cancer Research Institute Testis Cancer Clinical Studies Group. J Clin Oncol 2007;25:1310-5.
29. Cathomas R, Helbling D, Stenner F, et al. Interdisciplinary evidence-based recommendations for the follow-up of testicular cancer patients: a joint effort. Swiss Med Wkly 2010;140:356-69.
30. Yu HY, Madison RA, Setodji CM, Saigal CS. Quality of surveillance for stage I testis cancer in the community. J Clin Oncol 2009;27:4327-32.
31. Nicolai N, Miceli R, Necchi A, et al. Retroperitoneal lymph node dissection with no adjuvant chemotherapy in clinical stage I nonseminomatous germ cell tumours: long-term outcome and analysis of risk factors of recurrence. Eur Urol 2010;58:912-8.