The 111 Study: A Single-arm, Phase 3 Trial Evaluating One Cycle of Bleomycin, Etoposide, and Cisplatin as Adjuvant Chemotherapy in High-risk, Stage 1 Nonseminomatous or Combined Germ Cell Tumours of the Testis

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Abstract

Background: Standard management in the UK for high-risk stage 1 nonseminoma germ cell tumours of the testis (NSGCTT) is two cycles of adjuvant bleomycin, etoposide (360 mg/m²), and cisplatin (BE360P) chemotherapy, or surveillance.

Objective: To test whether one cycle of BE500P achieves similar recurrence rates to two cycles of BE360P.

Design, setting, and participants: A total of 246 patients with vascular invasion–positive stage 1 NSGCTT or combined seminoma + NSGCTT were centrally registered in a single-arm prospective study.

Intervention: One cycle comprising bleomycin 30000 IU on days 1, 8, and 15, etoposide 165 mg/m² on days 1–3, and cisplatin 50 mg/m² on days 1–2, plus antibacterial and granulocyte colony stimulating factor prophylaxis.

Outcome measurements and statistical analysis: The primary endpoint was 2-yr malignant recurrence (MR); the aim was to exclude a rate of ≥5%. Participants had regular imaging and tumour marker (TM) assessment for 5 yr.

Results and limitations: The median follow-up was 49 mo (interquartile range 37–60). Ten patients with rising TMs at baseline were excluded. Four patients had MR at 6, 7,13, and 27 mo; all received second-line chemotherapy and surgery and three remained recurrence-free at 5 yr. The 2-yr MR rate was 1.3% (95% confidence interval 0.3–3.7%). Three patients developed nonmalignant recurrences with localised teratoma differentiated, rendered disease-free after surgery. Grade 3–4 febrile neutropenia occurred in 6.8% of participants.

Conclusions: BE500P is safe and the 2-yr MR rate is consistent with that seen following two BE360P cycles. The 111 study is the largest prospective trial investigating one cycle of adjuvant BE500P in high-risk stage 1 NSGCTT. Adoption of one cycle of BE500P as standard would reduce overall exposure to chemotherapy in this young population.

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1. Introduction

Testicular cancer is the most common cancer among young men in Western populations and most patients present with stage 1 disease. Many nonseminomas and combined germ cell tumours of the testis (NSCGCTT) 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-orchiectomy management options in Europe for this patient population are adjuvant chemotherapy (AC) with two cycles of bleomycin, etoposide, cisplatin (BE360Px2) or surveillance with BE500Px3 on recurrence [4]. Adjuvant BE500Px2 results in malignant recurrence rates of <5%. Both management options yield cure rates approaching 100% [5,6]. According to proponents of surveillance, 50% of patients receive unnecessary AC [7], while AC proponents highlight poor adherence to surveillance and recurrence with advanced disease sometimes requiring retroperitoneal lymph node dissection (RPLND) [8]. It is clearly important to expose patients to the minimum treatment necessary. The frequency of immediate and late chemotherapy toxicity is closely related to total doses received; if AC BE500Px1 were as effective as BE360Px2, the former would substantially reduce the total chemotherapy burden since approximately half of surveillance cases recur, requiring BE500Px3.

Over recent years evidence has accumulated supporting the efficacy of BE500Px1 [9–13]; nevertheless, uptake of single-cycle AC remains patchy.

The 111 study was designed as a practice-changing trial to confirm the efficacy signals from these smaller studies. It tested BE500Px1 in a prospective, multicentre, single-arm trial in a patient population with an expected risk of recurrence of 50%. On the basis of the experience of key opinion leaders and trial collaborators in testicular cancer and existing data, the figure considered acceptable for the minimum risk necessary. The frequency of immediate and late chemotherapy toxicity is closely related to total doses received; if AC BE500Px1 were as effective as BE360Px2, the former would substantially reduce the total chemotherapy burden since approximately half of surveillance cases recur, requiring BE500Px3.

Table 1 – Eligibility criteria for entry into the 111 trial.

| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| Newly diagnosed, histologically proven pure NSGCT or combined seminoma + NSGCT of the 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 or tumour marker (AFP, HCG) estimations | Liver function impairment (bilirubin >1.25 × upper limit of normal for reporting laboratory) |
| Age ≥16 yr | Pre-existing neuropathy |
| Fit to receive chemotherapy | Pulmonary fibrosis |
| Creatinine clearance >50 ml/min | Serious illness or medical conditions incompatible with safe protocol treatment |
| WBCs >1.5 × 10^9/l and platelets >100 × 10^9/l | |
| Able to start BEP chemotherapy within 6 wk of orchidectomy | |
| Written informed consent | |

NSGCT = nonseminomatous germ cell tumour; AFP = α-fetoprotein; HCG = human chorionic gonadotropin; WBCs = white blood cells; BEP = bleomycin, etoposide, and cisplatin.

* In cases in which markers were raised before orchidectomy, an optimum marker decline approaching normal levels was required postoperatively before commencing trial treatment.
granulocyte colony stimulating factor (GCSF) was mandated to reduce neutropenic sepsis [15].

Patients had a full clinical assessment including grading of adverse events (AEs) using the National Cancer Institute’s Common Toxicity Criteria for Adverse Events (CTCAE v3) no later than 4 wk following BE500Px1, then every 2 mo until 6 mo, every 3 mo until 24 mo, every 4 mo during the third year, and every 6 mo during the fourth and fifth years after treatment. Computed tomography (CT) scans of the chest, abdomen, and pelvis were required at 6, 12, 24, and 60 mo, with a chest X-ray at all other visits. A physical examination and TM measurements were required at each visit to assess signs of recurrence or development of a second primary tumour.

2.3. Outcomes

For analysis purposes, recurrences were defined using two categories. MR was defined as a recurrence indicated by rising TM (AFP and/or HCG) from two consecutive results taken ≥1 wk apart showing a >50% increase above the upper limit of normal and/or a histologically MR (eg, undifferentiated, yolk sac, or choriocarcinoma) and/or recurrence at multiple sites. Benign recurrence (BR) was defined as a single-site recurrence with no TM elevation, consisting of fully resected, differentiated teratoma (TD) with no histological evidence of viable malignancy. This does 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 MR rate at 2 yr. Secondary efficacy outcome measures included the 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 before initiation of the trial treatment or already present but worsening following exposure to the trial treatment. Delayed toxicity was reported for the time intervals 2–12 mo, 18–24 mo, and >24 mo. Emergent delayed toxicity within 2–12 mo was any AE that was not present or worsened from baseline or end of cycle.

2.4. Statistical analysis

The trial was powered to exclude a 2-year MR rate ≥5% in high-risk stage 1 NSGCTT. Based on exact binomial probabilities with 80% power and a one-sided α of 5%, 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 of the final relapse rate being ≥5% (conditional on the data and follow-up available at that time), as monitored by the IDMC. Adequate β spending functions were chosen via simulation to ensure that despite multiple analyses the final α and power are 5% and 80%, respectively. A formal interim analysis was conducted when 157 patients had been followed up for ≥2 yr.

Analyses of outcomes included all eligible registered patients. For safety endpoints, analyses were according to treatment received. The MR rate at 2 yr and its 95% confidence interval (CI) were estimated using exact binomial probabilities. Patients without complete data at 2 yr of follow-up were assumed to have no MR at 2 yr. To account for such censoring, the 2-yr MR rate was also estimated using the Kaplan-Meier method. Patients with BR were censored at the time of the event. Both methods had to yield upper 95% CI limits of <5% to exclude an MR rate ≥5%. Sensitivity analyses of the primary endpoint were performed for the per protocol population.

Similar analysis methods were used for other efficacy endpoints. In the absence of a discrepancy between the exact binomial and Kaplan-Meier methods, the latter are reported. The frequency and nature of toxicities are summarised using the worst CTCAE grade for each of the reporting periods (end of cycle, delayed 2–12, 18–24, and >24 mo). Analyses were based on a database snapshot taken December 4, 2017 and were performed using Stata v13.1 [16].

3. Results

Between February 18, 2010 and March 31, 2014, 246 patients were registered from 33 UK NHS hospitals (Fig. 1), all of which were peer-reviewed accredited testis tumour treatment centres. The median follow-up at the time of reporting is 49 mo (interquartile range [IQR] 37–60). Ten patients were replaced after they were identified as ineligible following registration because of rising TMs. 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 yr.

The median time between orchidectomy and the start of treatment was 6 wk (IQR 5–7) and all 236 patients started BE500P. Treatment was received as planned by 221/236 (94%) of eligible patients. Eight patients (3.4%) received a per-protocol bleomycin dose reduction because of neutropenia. There was good adherence to neutropenic sepsis prophylaxis, with 219/236 (93%) receiving this per protocol. The remaining 17 patients received some prophylaxis (either GCSF or antibacterial).

There were four MR cases at 6, 7, 13, and 27 mo after trial registration, all of which were confirmed as malignant NSGCT via histological examination and/or rising TMs (Table 3). The 2-yr MR rate is 1.3% estimated using exact binomial probabilities (95% CI 0.3–3.7%) and Kaplan-Meier methods (95% CI 0.4–4.0%). With both methods, a 2-yr MR rate ≥5% can be excluded. The 4-yr MR rate is 1.8% (95% CI 0.7–4.6%). All four MR cases required surgical intervention.
and second-line chemotherapy. Three patients achieved complete remission, remaining well 5 yr after treatment. The patient with MR at 6 mo had very extensive, unresectable retroperitoneal NSGCT that failed to respond to chemotherapy, and the patient died 2 mo later. This was the only case of MR with an International Germ Cell Cancer Collaborative Group metastatic prognostic classification of intermediate; all others fell in the good prognosis category [17].

There were three BR cases consisting exclusively of histologically confirmed TD with no evidence of viable cancer at 7, 10, and 13 mo after trial registration (Table 3). All three underwent RPLND and remained well at 55, 26, and 24 mo following BR.

The MR + BR rate is 2.6% (95% CI 1.2–5.7%) at 2 yr and 3.1% (95% CI 1.5–6.3%) at 4 yr (Fig. 2).

Sensitivity analysis for the per protocol population (consisting of 208 eligible patients, compliant with treatment and with complete 2-yr follow-up) provided a 2-yr MR rate of 1.5% (95% CI 0.5–4.4%), while the MR + BR rate at 2 yr was 2.4% (95% CI 1.0–5.7%).

No cases of contralateral second primary testicular germ cell malignancy were reported. The 2-yr 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 mo after trial registration, and one from a self-administered drug overdose at 45 mo. The 2-yr overall survival is 99% (95% CI 97–100%).

Acute emergent toxicity within 4 wk following BE500P was assessed for 233/236 cases with paired baseline and end-of-cycle assessments. Ninety-five patients (41%) had at least one severe toxicity, including: neutropenia, 75 (32%); leukopenia, 40 (17%); febrile neutropenia (FN), 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.

4. Discussion

The 111 trial has demonstrated the efficacy of adjuvant BE500P/x1 for high-risk (VI+) stage 1 NSCGCTT. The 2- and 4-yr MR rates of just 1.3% and 1.8%, respectively, are almost...
Table 3 – Details of all recurrences in the population analysed (n = 236).

| Age at BL (yr) | Histology type | Site of recurrence | IGCCCG prognostic category | Surgery management | Chemotherapy regimen and cycles | Outcome (last FU, mo) |
|---------------|----------------|--------------------|-----------------------------|--------------------|----------------------------------|----------------------|
| 15            | Pure NSGCTT    | >5                 | Intermediate                | Attempted RPLND, Extensive resection | Ife × 2             | Died at 9 mo with resistant malignant NSGCT |
| 24            | Pure NSGCTT    | >5                 | Intermediate                | RPLN + raised AP   | TIP × 4                         | CR (60.5)            |
| 42            | Combined       | 2–5               | Good                        | RPLN               | BEP × 3                         | CR (60.4)            |
| 31            | Combined       | 2–5               | Good                        | RPLN               | TIP × 3                         | CR (62.6)            |
| 42            | Combined       | >2                | Good                        | RPLN               | None                            | CR (61.9)            |
| 22            | Pure NSGCTT    |>2                 | Good                        | None               | None                            | CR (36.2)            |
| 29            | Pure NSGCTT    |2                 | Good                        | None               | RPLND                           | CR (37.1)            |

Note: BL = baseline; TRR = time of recurrence from registration; TS = tumour size at orchidectomy; IGCCCG = International Germ Cell Cancer Collaborative Group; RPLN = retroperitoneal lymph node; RPLND = RPLN dissection; IPE = ifosfamide, cisplatin, and etoposide; NSGCTT = nonseminoma germ cell tumour; FU = follow-up; CR = complete remission; TIP = paclitaxel, ifosfamide, and cisplatin; BEP = bleomycin, etoposide, and cisplatin; LDH = lactate dehydrogenase; ULN = upper limit of normal.

identical to the results reported following BE360Px2 [5,10,18,19]. As seen in other studies of AC in this patient group [20], an additional three patients developed localised BR due, we believe, to growing teratoma resulting from successful treatment of malignant disease. The pragmatic decision to rely on a nonrandomised 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 noninferiority trial to demonstrate that one cycle was no worse than 3% less effective than two cycles (80% power, one-sided α of 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 BE500Px1 that would lead to adoption of the regimen, and thus fulfilled 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 the 111 trial are consistent with three small, single-centre studies involving 112 patients [11–13]. They also reflect findings in a population-based study by the Swedish and Norwegian Testicular Cancer Project that included patients with low or high risk treated with BE500Px1 or BE500Px2. In their latest update [22], among 258 VI+ patients who chose BE500Px1 there were eight cases of MR (3.2%; 95% CI 1.6–6.4%) during median follow-up of 7.9 yr. A randomised German trial of BE500Px1 versus RPLND reported only two recurrences among 191 patients randomised to BE500Px1 (only one of which was malignant), but just 42% of randomised cases were classified as high risk and the outcome for this subgroup was not reported separately [9]. The authors concluded that their data “should encourage investigators to test the promising approach of one course BE500P”.

FN remains a serious risk with full-dose etoposide chemotherapy, with occasional fatalities, which is why we used 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 1 among 111 control testicular cancer patients receiving BEP and allocated to placebo in a randomised trial of prophylactic levofloxacin [15].

Late toxicity is a clear concern with adjuvant BE500P. A small number of patients (<3%) developed grade 3–4 late toxicity. There is ample evidence in testicular cancer of a direct relationship between cycle number (ie, cumulative dose) and delayed toxicity in terms of infertility, metabolic syndrome, neuropathy, and lung and renal function [23–27]. However, any toxicity developing after BE500Px1 has to be balanced against the greater risk of toxicity with the higher doses that would be given to the 50% of patients expected to relapse on a surveillance programme. Post-treatment fertility indices will be reported separately, but on the basis of published data following BE360Px2 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 a rationale for the present trial.
Since their publication there has been controversy surrounding the options of AC versus surveillance in stage 1 NSGCTT. In their 2013 paper, Nichols et al [7] clearly favour surveillance. 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. However, two studies cited in support excluded high-risk stage 1 NSGCTT [28,29]. The authors also failed to consider the risk of requiring elective surgery (commonly RPLND) following chemotherapy for recurrence on surveillance. de Wit [8] noted that in the largest recent study of surveillance, 26% of relapsing patients required post-chemotherapy surgery [6]. In the 111 trial, 3% of patients (7/236) required surgery for MR or BR. The much higher level of surgery required among 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 in those relating to surveillance in the community setting [30]. Treatment of MR, although usually successful, involves more intensive chemotherapy and major surgery and is 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 more frequent among unselected stage pN0 NSGCT patients than after adjuvant BEP chemotherapy (8% vs 1%), and in VI patients the recurrence rate is 28% [31] unless adjuvant chemotherapy is used in pN+ cases.

5. Conclusions

The 111 study is the first prospective trial of BE500Px1 with sufficient high-risk stage 1 NSGCTT or combined seminoma + NSGCTT patients to exclude an MR rate at 2 yr of ≥5%. Despite the unavoidable limitation of being a single-

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**Table 4 – Delayed toxicity: adverse event of worst CTCAE grade per patient**.

| Patients, n (%) | 2–12 mo (n = 233) | 18–24 mo (n = 215) | >24 mo (n = 184) |
|----------------|------------------|------------------|-----------------|
| Any toxicity   |                  |                  |                 |
| Grade 1+       | 137 (59)         | 107 (50)         | 79 (41)         |
| Grade 3+       | 6 (2.6)          | 2 (0.9)          | 3 (1.6)         |
| Specific toxicities of interest |                  |                  |                 |
| Dyspnoea       | 15 (6.4)         | 10 (4.7)         | 8 (4.3)         |
| Ear and labyrinth disorders | 17 (7.3) | 17 (7.9) | 7 (3.8) |
| Psychiatric disorders | 9 (3.9) | 3 (1.4) | 4 (2.2) |
| Fatigue       | 4 (1.7)          | 3 (1.4)          | 1 (0.5)         |
| Insomnia      | 2 (0.9)          | 2 (0.9)          | 1 (0.5)         |

*CTCAE = Common Toxicity Criteria for Adverse Events.

* Details of grade 3–4 toxicities: 2–12 mo: grade 3 anemia, ototoxicity (n = 2), weight increase, and depression, grade 4 thrombocytopenia and osteonecrosis; 18–24 mo: grade 3 osteonecrosis, ototoxicity, and tinnitus; >24 mo: grade 3 diabetes and lethargy, grade 4 deafness.

* For the reporting period of 2–12 mo, emergent toxicities are presented (not present at or worsening from baseline or end of cycle). For the other reporting periods, toxicities were as reported.

* Ototoxicity, deafness, or tinnitus.

* Includes depression, anxiety, depressed mood, and altered mood.
arm study, 111 achieved its aim, with a malignant failure rate of just 1.3% and 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 1 NSCGCTT.

**Author contributions:** Robert Huddart had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Cullen, Huddart, Joffe, Hall.

**Acquisition of data:** Gardiner, Lewis, Witts, Goubar, Maynard.

**Analysis and interpretation of data:** Cullen, Huddart, Joffe, Hall, Porter, Goubar, Maynard.

**Drafting of the manuscript:** Cullen, Huddart, Joffe, Hall, Lewis, Gardiner, Porter, Goubar, Witts, Maynard, Hutton, Mazhar, Shamash, Wheeler, White.

**Critical revision of the manuscript for important intellectual content:** Cullen, Huddart, Joffe, Hall, Lewis, Gardiner, Porter.

**Statistical analysis:** Hall, Porter, Goubar, Maynard.

**Obtaining funding:** Cullen, Huddart, Joffe, Hall.

**Administrative, technical, or material support:** Gardiner, Lewis, Witts.

**Supervision:** Cullen, Huddart, Joffe, Hall.

**Other:** None.

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**Appendix A. Recruiting consultants according to centre (number of patients recruited are shown in bold font)**

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. Wheeler, Dr. P. Simmonds, Dr. G. Mead; Addenbrooke’s Hospital, Cambridge, 9, Dr. D. Mazhar; Castle Hill Hospital, Hull, 9, Dr. M. Butt; Royal Liver Group and 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 Hospital, 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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