Comparison of two chemotherapy regimens in newly diagnosed Ewing sarcoma – results of the EURO EWING 2012 (EE2012) randomised phase 3 trial

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Summary

Background Internationally, a single standard chemotherapy treatment for Ewing sarcoma (ES) is not defined. EE2012 compared two different chemotherapy regimens, one used in Europe and one in the United States of America.

Methods EE2012 was a European academic, open label, randomised controlled phase III trial performed in 10 countries, to compare two different induction/consolidation chemotherapy strategies: arm A (VIDE regimen) vincristine, ifosfamide, doxorubicin and etoposide (VIDE) induction, and vincristine, actinomycin D, with ifosfamide or cyclophosphamide, or busulfan and melphalan (VAI/VAC/BuMel) consolidation and arm B (VDC/IE regimen) vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide (VDC/IE) induction,
and ifosfamide and etoposide, vincristine and cyclophosphamide, or vincristine, actinomycin D and ifosfamide, with busulfan and mephalan (IE/VC/VAI/BuMel) consolidation (randomisation R1). Patients were included from age 2 years to less than 50 years, with any histologically and genetically confirmed ES of bone or soft tissue, or ‘Ewing’s-like’ sarcomas. The eligibility criteria originally excluded patients with extrapulmonary metastatic disease, but this was amended in protocol version 3.0 in September 2016. The primary outcome measure was event free survival (EFS). A Bayesian approach was taken for the design, analysis and interpretation of the results. Patients who received at least one dose of study treatment were considered in the safety analysis. The trial was registered with EudraCT number 2012-002107-17 and ISRCTN number 54540667.

Findings Between 21 March 2014 and 1 May 2019, 640 patients were entered into EE2012, 320 allocated to each arm. Median follow-up of surviving patients is 47 months (range 0-84). EFS at 3 years was 61% with arm A-VIDE and 67% with arm B-VDC/IE, with an adjusted hazard ratio (HR)=0.71, 95% credible interval (CrI) 0.55-0.92 in favour of VDC/IE. The probability that the true HR was <1.0 was >0.99. Febrile neutropenia as a grade 3-5 treatment toxicity occurred in 234 (74%) patients receiving VIDE induction but less in those receiving VDC/IE induction 183 (58%). Patients receiving VIDE induction required more platelet transfusions compared to VDC/IE induction, 205 patients with at least 1 versus 138 respectively. Conversely, more blood transfusions were required for VDC/IE arm versus VIDE arm 286 and 277 respectively.

Interpretation Dose intensive chemotherapy with VDC/IE/VC/VAI is more effective, less toxic and more convenient for all stages of newly diagnosed ES and should now be the standard of care for ES.

Funding

This project has received funding from the European Union’s Seventh Framework Programme for research, technological development, and demonstration under grant agreement n°602856. The National Coordinating Centre in France, Centre Léon Bérard, receives additional funding from SFCE and Ligue contre le cancer. The Coordinating Sponsor, United Kingdom is funded by Cancer Research UK (grant award reference C5952/A14745). Funding allowed set up of the study in each country, sponsorship, data collection and analysis.

Research in context

Evidence before this study

We searched PubMed for randomised trials in Ewing sarcoma between 1 January 1990 and 31 December 2010. We searched for published papers with the search terms “Ewing sarcoma” and “chemotherapy trials”. We did
not find any randomised studies comparing different standard regimens of chemotherapy used in Europe and USA.

### Added value of this study

To our knowledge, this is the first randomised study demonstrating that the dose intense USA standard chemotherapy regimen of VDC/IE is more effective than the European non dose intense VIDE regimen.

### Implications of all the available evidence

Dose intensive chemotherapy with VDC/IE regimen is more effective, less toxic and more convenient for all stages of newly diagnosed Ewing sarcoma and should now be the standard of first line care for all patients with Ewing Sarcoma.

### Introduction

Ewing sarcoma (ES) is a cancer of the bone and soft tissue with 80% occurring in adolescents and young adults and a peak incidence in the second decade of life.¹ ES is rare, with fewer than 70 cases per year in the UK, 100 in France and 400 in the rest of Europe, so any randomised trials must be international to yield robust results in a timely manner. With current multimodal programmes, including combination chemotherapy of doxorubicin, etoposide, cyclophosphamide, vincristine and ifosfamide, using different doses and schedules of administration, as well as surgery and radiotherapy, outcome for localised disease is good, with event-free survival (EFS) of 65% and overall survival (OS) of 75% at 3 years with standard chemotherapy regimens.²,³ For metastatic disease, 3-year OS is 68% for patients with isolated pulmonary and/or pleural metastases and only 29% for multi-metastatic disease.⁴–¹⁰

Internationally, a single standard chemotherapy treatment for ES is not defined. The EURO-E.W.I.N.G. 99 trial employed VIDE induction chemotherapy (six cycles of vincristine, ifosfamide, doxorubicin and etoposide given about every 3 weeks prior to local control) followed by risk-adapted randomised treatment of either vincristine, actinomycin D and ifosfamide or cyclophosphamide (VAI/VAC) as consolidation chemotherapy or high-dose busulfan/melphalan. The toxicity of VIDE induction chemotherapy has been published.¹¹

The other widely used treatment regimen for ES, employed mainly in the USA, is from the Children’s Oncology Group (COG) AEWS0031 trial.² In that study, patients with localised ES received alternating cycles of vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide (VDC/IE) as induction chemotherapy and alternating
cycles of ifosfamide-etoposide and vincristine-cyclophosphamide (IE/VC) as consolidation chemotherapy, either
3-weekly or 2-weekly. The 2 weekly schedule was significantly more effective than the 3 weekly schedule and is
now standard of care in USA. As different chemotherapy regimens were standard in Europe and the USA for
newly diagnosed ES, and in the absence of novel agents to investigate, a randomised comparison of these two
strategies was considered worthwhile to establish the regimen of choice, taking account of both clinical outcome
(EFS and OS) and toxicity.

Methods

Study design and participants

EE2012 was a European academic, open label, randomised controlled phase III trial performed in 10 countries
and in 110 sites (appendix for sites and countries). All patients with ES, except widely metastatic disease until
September 2016, were eligible for randomisation (R1) to receive either the European regimen (Arm A) of VIDE
induction and VAI or VAC consolidation or the USA regimen (Arm B) of compressed VDC/IE induction and
IE/VC consolidation. Following induction chemotherapy, all patients were eligible for a second randomisation
(R2) of the addition of zoledronic acid to the consolidation chemotherapy assigned at R1. Furthermore, the R2
randomisation is stratified by allocated treatment in R1, age at R1 randomisation (<14 years; ≥14 years), sex,
disease status (localised disease or regional lymph node involvement of lymph nodes only at diagnosis and good
risk after induction, localised disease or regional lymph node involvement only at diagnosis and of lymph nodes
only poor risk after induction, lung or pleural metastases at diagnosis, other metastasis at diagnosis), and country
(UK, France or other).

The results of R2 will be reported in a future publication. Deviations to the protocol are detailed in the consort
diagram (figure 1)

Patients were eligible from the age of 2 years to less than 50 years with any histologically and genetically
confirmed ES of bone or soft tissue, or ‘Ewing’s-like’ round cell sarcomas but negative for EWSR1 gene
rearrangement, who were medically fit to receive trial treatment. The eligibility criteria originally excluded
patients with extrapulmonary metastatic disease, but this was amended in protocol version 3.0 in September 2016.
The trial was overseen by a trial management and steering groups. An independent data monitoring committee
reviewed safety and efficacy during the trial. The study was conducted in accordance with the Declaration of
Helsinki and the Good Clinical Practice guidelines. Informed written consent was obtained from all patients/parents/legal guardians as per local practice.

**Randomisation**

Patients were allocated in a 1:1 ratio to the two arms. Randomisation was performed by staff at participating centres online by using the randomisation function of the electronic remote data capture (eRDC) system designed and maintained by the coordinating sponsor. The randomisation was stratified using minimisation to ensure a balance between treatments within the strata defined by these key prognostic factors and country. The minimisation factors were age at randomisation (<14 years or ≥14 years), gender, disease type (absence of metastases or involvement of regional lymph nodes only; lung or pleural metastases only; other metastases), volume of tumour at diagnosis (<200 mL or ≥200 mL) and country (the UK, France or other).

**Procedures**

At diagnosis, the work-up consisted of MRI/CT scan of the primary tumour and staging, including bone marrow assessment, CT scan of the chest and radionuclide bone scan (18F-fluorodeoxyglucose PET was an alternative to a bone scan in some trial sites). Resection of the primary tumour at diagnosis was not recommended and for the majority of patients, a biopsy was obtained to establish the diagnosis.

At trial entry, patients were randomised to one of the following treatment arms:

**Arm A (VIDE strategy): VIDE induction, VAI/VAC/BuMel consolidation.**

Induction chemotherapy: six cycles of VIDE.

Consolidation chemotherapy: one cycle of VAI plus seven cycles of VAC (good risk localised disease) - VAC
or one cycle of VAI plus one cycle of BuMel (poor risk localised disease without contraindication to BuMel) – BuMel.

or eight cycles of VAI (poor risk localised disease with contraindication to BuMel, and/or regional lymph node(s) involvement and/or metastatic disease) - VAI


Induction chemotherapy: nine cycles of alternating VDC and IE.

Consolidation chemotherapy: five cycles of alternating IE and VC - (good risk localised disease and/or regional lymph node(s) involvement and/or metastatic disease; or poor risk localised disease with contraindication to BuMel) - IE/VC

or one cycle VAI plus BuMel (poor risk localised disease without contraindication to BuMel) – BuMel.

A summary of the enrolment, interventions and the main assessments has been published, and a SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is supplied in appendix (page 2-6). The full schedule of treatments is provided in appendix (page 7-11) and full details of trial treatments and conduct has been published. Following induction chemotherapy, local control of the primary tumour was performed, where feasible with a complete surgical resection or, if not, definitive radiotherapy. Radiotherapy was recommended to be given concurrently with consolidation chemotherapy to the primary site. In patients with pulmonary and/or pleural metastatic disease, whole lung radiotherapy was recommended to be given on completion of consolidation chemotherapy. Radiotherapy to bony metastases was given either during consolidation or at the end of chemotherapy. Patients who received radiotherapy only as their local control and had measurable disease before radiotherapy had an MRI or CT scan performed at the end of treatment. If the end-of-treatment scan showed residual disease, another scan was performed six months after the end of treatment.

Adverse events were monitored at least weekly and were assessed according to National Cancer Institute Common Toxicity Criteria (NCI CTC) version 4.0. After treatment, patients were followed up with clinical evaluation and scanning for a minimum of five years or until disease progression or death if sooner.

Outcome measures

The primary outcome measure was EFS. EFS was defined as the time from randomisation to first event, where an event was the first of progression without complete or partial response, recurrence (following complete or partial remission), second malignancy or death by any cause without a preceding event; patients who did not
have an event were censored at the date they were last seen. The secondary outcome measures were OS, defined as the time from randomisation to death, irrespective of the cause, with surviving patients censored at their date last seen; adverse events and toxicity; histological response of the primary tumour to induction chemotherapy if surgery was performed; response of the primary tumour, regional lymph nodes and/or metastases, using the volume of the whole primary tumour, diameter of the largest node (or group if not separate), and number of lung and/or pleural and other metastases respectively; and achievement of local control at the end of treatment.

Response data was not complete or of sufficient quality for further analysis and reporting.

**Trial design and statistical analysis**

Due to the rarity of ES and the comparison being between two standard chemotherapy regimens, a Bayesian approach was taken for the design, analysis and interpretation of R1 (see Discussion for a justification of this design). No prior assumptions that one chemotherapy arm was likely to be better than the other were made. With a five-year accrual period, it was anticipated that at least 600 patients could be randomised across participating countries. Hence, the minimum sample size was set at 600 with a minimum of two years and a maximum of seven years’ follow-up, with at least 150 events expected. Non-informative priors were used, so the posterior distribution gives Pr (parameter data) (i.e., the probability of the treatment effect). The ln (hazard ratio [HR]) was assumed to be normally distributed with variance $4/n$, where $n$ is the total number of events in both arms.$^{13}$

Based on the EURO-E.W.I.N.G. 99 data, 3-year EFS was anticipated to be approximately 70% with VIDE.$^3$ A 5% absolute difference in 3-year EFS corresponds to a HR of 1.21 (or inversely 0.81). Different scenarios were considered to establish the probabilities that one treatment was better than the other, or not more than 5% worse, from posterior probability distributions. These were based on a study sample size of 600 patients and a range of observed HRs for the data. The probability that VDC/IE was more than 5% worse or better than VIDE, given an observed HR of 1.00 (i.e., no apparent difference between randomly assigned groups in terms of EFS), would be 10% or 7% respectively. Under the premise of no difference in efficacy (EFS), it would then be reasonable to base the decision on which regimen has a more tolerable toxicity profile. In addition, with an observed HR of 0.81 (i.e., an absolute improvement of approximately 5% in EFS with VDC/IE compared to VIDE, or vice versa), there would be an 8% probability that the apparently better regimen was worse. Finally, with an observed HR of 0.90 (i.e., about a 2.5% absolute difference in EFS in favour of one or other arm), there would be a probability of 25% that the apparently better regimen was worse and a probability of 3% that it was more than 5% worse. The
probabilities from these scenarios were all within the limit of clinical acceptability based on expert opinion at the
design stage, confirming that 600 was an acceptable sample size.

For time-to-event outcome measures, Cox regression models were used to compare the treatment arms, adjusted
for stratification variables. The proportional hazards (PH) assumption was assessed by examining the
Schoenfeld residuals. In addition, Kaplan–Meier survival estimates were obtained at 3 and 5 years. Exploratory
hypothesis-generating subgroup analyses were performed for all stratification variables and interpretation
focused on 95% confidence intervals. Tests for heterogeneity were performed by the likelihood ratio test,
comparing Cox models with and without an interaction term between the treatment variable and stratification
variable. All analyses were intention-to-treat, with all patients analysed in the arm to which assigned at
randomisation.

The statistical software Stata v17.0 was used to perform all statistical analyses.

Role of the funding source.

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing
of the paper or decision to submit the paper.

Results

Between 21 March 2014 and 1 May 2019, 640 patients were entered into EE2012, with 320 allocated to each arm
for the R1 randomisation (figure 1). At the date of data cut off 28 November 2021, median follow-up of surviving
patients is 47 months (range 0-84). Four patients formally withdrew consent for further data collection. Loss to
follow-up is very low and balanced between arms (six patients on VIDE and three on VDC/IE). Baseline clinical
characteristics were well balanced across the two arms (table 1). There were 20 patients with Ewing-like sarcoma,
nine in VIDE arm, and 11 in VDC/IE arm. In the VIDE arm 19 (7%) patients received Bu/Mel and in the VDC/IE
arm six (2%). In the VIDE arm 134 (42%) were randomised in the R2 randomisation, and 183 (44%) in the VDC/IE arm.

99% of patients started their allocated treatment (three withdrawals of consent to treatment, one recurrence prior to starting treatment, one reason not given, one no record to support having treatment or not having treatment). In the VIDE arm, 95% of patients received all six induction courses; in the VDC/IE arm, 91% of patients received all nine induction courses. In the VIDE arm, 58% of patients received all 8 consolidation courses; in the VDC/IE arm, 75% of patients received all five consolidation courses. (figure 1)

The local therapy received to primary tumour is described in table 2. The majority of patients received radiotherapy to the primary tumour, 208 (65%) in VIDE arm and 199 (62%) in VDC/IE arm. In the VIDE arm 34 (64%) with lung and/or pleural metastases received lung radiotherapy and in the VDC/IE arm 30 (57%) with lung and/or pleural metastases received lung radiotherapy.

A total of 240 events was recorded, 131 and 109 in the VIDE and VDC/IE arms respectively. The types of events are shown in table 3. EFS at 3 years was 61% with VIDE and 67% with VDC/IE, with a HR=0.71, 95% CrI 0.55-0.92 (figure 2a) in favour of VDC/IE. The probability that the true HR was <1.0 was >0.99 (figure 3a), while there was a 0.81 probability that the true HR<0.8 in favour of VDC/IE. The PH assumption held.

A total of 163 deaths was recorded, 95 and 68 in the VIDE and VDC/IE arms respectively. The causes of death are shown in table 3. OS at 3 years was 74% with VIDE and 82% with VDC/IE, with a HR=0.62, 95% CrI 0.46-0.85 (figure 2b) in favour of VDC/IE. The probability that the true HR was <1.0 was >0.99 (figure 3b), while there was a 0.94 probability that the true HR<0.8 in favour of VDC/IE. The PH assumption held.

There was no evidence that the treatment effect for VIDE compared to VDC/IE differed across patient and disease subgroups for either EFS or OS (figure 4a and 4b respectively), with all confidence intervals for the interaction
effects including values consistent with no significant subgroup effects. Within all subgroups, the point estimate for the HR was in favour of VDC/IE.

Among patients who started trial treatment, similar numbers experienced grade 3-5 AEs in both arms: for VIDE and VDC/IE respectively, 91% and 90% during induction chemotherapy and 66% and 67% during consolidation. However, febrile neutropenia as a grade 3-5 AE occurred in 234 (74%) patients receiving VIDE induction but less in those receiving VDC/IE induction 183 (58%) (table 4). The difference in febrile neutropenia between the two arms were also seen in E-SARs, again greater in the VIDE arm. There was no difference in gastrointestinal toxicities, and infections and infestations between the two arms. (Table 4)

In-patient stays and supportive care: Patients receiving VIDE induction required more platelet transfusions compared to VDC/IE induction, 205 patients with at least 1 versus 138 respectively. Conversely, more blood transfusions were required for VDC/IE arm versus VIDE arm 286 and 277 respectively. More unscheduled visits were required in the VIDE arm versus VDC/IE arm with the median number of days being 13 and 9 respectively (table 5). The length of treatment for VDC/IE was on average 61 days shorter than VIDE regimen.

In those patients who had surgery after induction chemotherapy, a greater number had good necrosis in the VDC/IE arm compared to VIDE arm 104 versus 82 respectively. (Table 6) Response data was not complete or of sufficient quality for further analysis and reporting.

**Discussion**

The results of this international randomised trial for 2–50-year-old patients with newly diagnosed Ewing sarcoma clearly show that VDC/IE chemotherapy is substantially superior to VIDE for both EFS and OS survival, with a greater than 99% chance that it is better for both outcome measures. This benefit is consistent across all baseline stratification parameters, which are also important prognostic factors. There is no excess toxicity with VDC/IE, fewer supportive care requirements and the total time to complete treatment averages 12 weeks less with VDC/IE. These are all clinically meaningful findings. Hence, these results have led to a practice change in Europe and many other countries. VDC/IE chemotherapy has become the standard regimen for all newly diagnosed Ewing sarcomas in Europe, following its earlier adoption in the USA. Furthermore, the trial used Bayesian statistical
models for what is a rare tumour, which allowed a timely answer to the randomised question as the number of
patients required was smaller than frequentist methodology.

At the time of designing this study, arm B VDC/IE was the standard of care for Ewing sarcoma, for all stages of
disease, in the USA through the COG research group. This followed the COG AEWS0031 trial, which
compared three-weekly chemotherapy VDC/IE versus more intensive two-weekly VDC/IE (arm B in our trial).²
The OS for the comparable arm in AEWS0031 was 83 % at 5 years versus 87 % at 3 years in EE2012 arm B.
While these results seem comparable, the AEWS0031 study only included localised ES versus all stages in
EE2012. Pragmatically VAI/Bu/Mel was allowed in arm B after induction in EE2012, following the results of
EE99 R2 loc randomisation for poor risk localised disease, and therefore differed to AEWS0031 but not
significantly as only 6 (2%) of arm B received Bu/Mel.¹⁸

Furthermore, the median age of subjects in AEWS0031 was lower, known to confer a better prognosis in ES.⁴
The AEWS0031 study had also compared a more dose dense chemotherapy, maintaining the doses but reducing
the interval between chemotherapy.² Their strategy followed Norton’s dose density model and with the use of
granulocyte colony-stimulating factor G-CSF, as in our study, they were able to maintain this dose intensity with
superior results [14]. Arm A – VIDE in this study was standard of care in Europe and other countries from the
EURO-E.W.I.N.G. 99 trial.²⁴⁶¹⁰ It is difficult to make any direct comparisons as no data has been published for
the whole study including all stages of disease.

Previous publications have focused on individual disease types or risk groups related to extent of disease or stage,
either in single arm studies or randomised.²⁴⁶¹⁰ In EE2012, all disease groups of ES were (eventually) included
in the upfront randomisation R1, but there was stratification for these disease groups along with other factors such
as age and tumour volume, for example. The disease type was balanced between the two arms. We performed
subgroup analysis for all baseline parameters and used heterogeneity tests (p-value of the interaction term between
treatment variable and covariate in the adjusted Cox model), visually demonstrated by forest plots, to investigate
whether the treatment effect differed between these groups. For both EFS and OS, the benefit of VDC/IE was not
different for disease type or indeed any other stratification variables. This provides good evidence to treat all ES
with the VDC/IE regimen and hence for it to become the standard of care internationally. This is particularly
important for widely metastatic disease who were not included in the AEWS0031 study. Ewing-like sarcoma were included in the study, but their numbers were small in both arms and therefore unlikely to have had any effect on the outcomes reported.

A limitation of this study was that widely metastatic patients were not included at the start of the study but only from September 2016 (and as there was a competing study in France, they were not entered at all from France). Therefore, the percentage of patients with widely metastatic disease was less than expected from the population data. The group with widely metastatic disease was, however, balanced between the two arms and subgroup analysis showed that the benefit of VDC/IE was consistent for this disease group along with other disease groups.

As a randomised study, the type of local therapy and hence radiation or not received was balanced, and although there was guidance for the dose of, and indications for radiotherapy, it is likely there was variability for this amongst sites and countries both on indications and dose received, as this was not mandatory. Going forward, the ES research community needs to develop an evidence base for radiotherapy doses in ES, as currently there is variability in practice.

A Bayesian approach was chosen because two standard chemotherapy regimens – one European, one North American – were to be compared. Therefore, a less stringent decision criterion for accepting one as being better than the other was considered appropriate compared to a conventional frequentist p=0.05. An informal survey of the trial’s lead clinicians revealed that they would be happy to accept a regimen as the standard going forward if there were an 80% chance that it was better than the other. Furthermore, had a frequentist design been used, it was not clear whether superiority (and which arm would be the control) or equivalence should be demonstrated.

It should be noted that, with the use of non-informative priors, the Bayesian design is entirely equivalent to a frequentist one, with one minus the posterior probability being the one-sided p-value – i.e. 1 – Prob(trueHR<1.0|data) = 1p. Given the 80% decision guideline, it was considered that a Phase III trial with a two-sided alpha of 0.4 might be deemed unacceptable to funders and regulators. We also believe that Bayesian presentation of the results as probabilities that one arm is better than the other is more intuitive and easier for clinicians and patients to understand than p-values, which are often misinterpreted. It transpired that a relaxed decision criterion was not relevant, given that the posterior probabilities for both EFS and OS were 100% – i.e., equivalent to a one-sided p<0.01 – thereby providing very strong evidence that VDC/IE is superior to VIDE. Another advantage of a Bayesian design is that alternative probabilities can be generated, not just the probability that one arm is better than the other. In this case, there is a 94% chance that the true HR for OS is <0.8, i.e., a
94% chance that there is a reduction in the risk of death with VDC/IE compared with VIDE. Advancements in the utilisation of Bayesian methodology since the design of EE2012 means that if the trial were to be designed again, using a minimally (or weakly) informative prior rather than a non-informative prior would preferable to exclude unrealistic values for the log(HR). However, this would not have altered the conclusion of our trial given the large sample size and event rate.

There appears to be little difference in toxicity between the two chemotherapy arms from evaluation of any grade 3-5 events, in both induction and consolidation. However, on review of specific events, there is less overall haematological toxicity in VDC/IE arm B and hence reduced requirement for blood product transfusions, more blood transfusions were required in the VDC/IE arm, but even more platelet transfusions were required in the VIDE arm. This difference is also apparent in infection events, with admissions for both fever alone and episodes associated with neutropenia less in the VDC/IE arm. Overall, there were more unscheduled visits for VIDE arm A. Gastrointestinal events, however, were similar. These findings are not unexpected, as the toxicity of the two arms had been previously described in publications.2,11 In terms of the feasibility of delivering the different chemotherapy arms only 58% of the VIDE arm A received all 8 consolidation courses but for VDC/IE arm B, 75% of patients received all 5 consolidation courses. The 12-week average reduction in total time to complete treatment with VDC/IE is also very important factor supporting this as standard of care.

The success of the VDC/IE arm B and the lower toxicity allows us to think about adding in other non-chemotherapy targeted therapies; in combination, these may have tolerable toxicity and they are certainly needed in the poor prognostic ES such as those with metastatic disease, to hopefully improve outcomes.5,6,18 Early clinical data suggest that strategies adding a multiple tyrosine kinase inhibiter (MTKI) with anti-angiogenic activities may be beneficial in ES.19-21 These drugs have been combined with chemotherapy in ARST1321 trial (ifosfamide/doxorubicin) which included younger patients and reported no major toxicities.22

In summary, dose intensive chemotherapy with VDC/IE is more effective, less toxic and more convenient for all stages of newly diagnosed ES and should now be the standard of first line care for all patients with ES.

Contributors

BB, PMB, NG, VL, JMB, AS, HG, CO, NF, SS, JW, and KW contributed to the study design, data collection, and interpretation, management of the clinical trial, writing and review of the paper, and approval of the final version. LK contributed to the data collection, and interpretation, management of the clinical trial, writing and
review of the paper, and approval of the final version. VM contributed to the study design, data collection, and interpretation, management of the clinical trial, review of the paper, and approval of the final version. BB acted as chief investigator and was part of the TMG, along with PMB, NG, VL, JMB, AS, HG, NF, SS, JW, LK, VM and KW, wrote the protocol and organised the data management. BB, PMB, JMB, HG and CO coordinated the protocol in participating countries. NF coordinated the data centre and LK, VM and KW did the statistical analysis.

Declaration of interests

SS has received honoraria and consulting fees from GSK, Lilly and Ceridwen Oncology.

JMB has the following interests

Institutional Grants from Adaptimmune, Amgen, AROG,

Bayer, Blueprint, BMS, Celgene, Daichii-Sankyo,

Deciphera, Eisai, FORMA, GSK, IMMIX Biopharma, Karyopharm, Lilly, Nektar, Novartis, Pfizer, PharmaMar

Honoraria from PharmaMar, Tecnofarma

Payment for expert testimony from Bayer, Eisai, Lilly, PharmaMar

Support for attending meetings and/or travel from PharmaMar, Asofarma

Participation on a Data Safety Monitoring Board or Advisory Boards for Asofarma; PharmaMar; Boheringer, Tecnofarma, Roche, Bayer.

We declare no other competing interests.

Data sharing

Individual participant data are not publicly available as this was not anticipated in the study protocol

The link to the protocol:


Acknowledgements
We would like to acknowledge all the patients who agreed to take part in this study, as well as the EE2012 investigators and trial staff at participating trial centres. We also acknowledge other colleagues at partner organisations (University of Birmingham, Centre Léon Bérard, Grupo Español de Investigación en Sarcomas, Our Lady's Children's Hospital, European Organisation for Research and Treatment of Cancer (EORTC-1402-STBSG) who supported the trial within their institution.

Funding

This project has received funding from the European Union’s Seventh Framework Programme for research, technological development, and demonstration under grant agreement n°602856. The National Coordinating Centre in France, Centre Léon Bérard, receives additional funding from SFCE and Ligue contre le cancer. The Coordinating Sponsor, United Kingdom is funded by Cancer Research UK (grant award reference C5952/A14745). Funding allowed set up of the study in each country, sponsorship, data collection and analysis.

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