Euro Ewing 2012 Trial Synopsis

International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours (ESFT)

Sponsor

University of Birmingham

Trial Design

The Euro Ewing 2012 trial is an international, phase III, open-label, randomised controlled trial.

Objectives

The objective of the induction/consolidation chemotherapy randomisation (R1) is to compare the VIDE strategy (VIDE induction and VAI/VAC/BuMel consolidation) with the VDC/IE strategy (compressed VDC/IE induction and IE/VC/BuMel consolidation). The event-free survival (EFS) of the two chemotherapy regimens will be compared, and also the relative toxicity experienced by patients both before and after local control of the primary tumour.
The objective of the zoledronic acid randomisation (R2) is to determine whether the addition of zoledronic acid to consolidation chemotherapy, as assigned at R1, is associated with improved clinical outcome.
The objective of the biological studies associated with this trial is to identify informative prognostic biomarkers for assessment of disease status and response at diagnosis and throughout the disease course. Whether they are predictive of response to therapy and may be used to improve stratification of patients and whether they might predict those patients that may not tolerate a particular therapy will be explored.

Outcome Measures

Primary outcome measure

- Event-free survival (EFS)

Secondary outcome measures

- Overall Survival (OS)
- Adverse events and toxicity, defined by NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0
- Histological response of the primary tumour to induction chemotherapy if surgery is performed as local control
- Primary tumour and lung, regional lymph nodes and/or metastases
- Achievement of local control at the end of treatment
- Growth parameters and jaw osteonecrosis (R2 only)

Patient Population

Any newly diagnosed patient with ESFT

Sample Size

Randomisation R1 – minimum of 600

Randomisation R2 – minimum of 750 (including 400 from the Ewing 2008 trial)

Trial Duration

Anticipated accrual time for different randomisations:

- Randomisation R1: 5 years
- Randomisation R2: 5 years

After treatment, patients will be followed up with clinical evaluation and scanning for 5 years, or until disease progression or death if sooner. Patients will be followed up for progression and death until all trial objectives have been met.

The first main analysis will be performed once all patients have a minimum of 2 years follow-up.

Treatment Summary

Randomisation R1

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

- **Arm A (VIDE strategy): VIDE induction; VAI/VAC/BuMel consolidation**

  Induction chemotherapy: 6 cycles of VIDE

  Consolidation chemotherapy: 1 cycle of VAI plus 7 cycles of VAC
  (good risk localised disease)

  OR

  1 cycle VAI plus one cycle of BuMel (poor risk localised disease without contraindication to BuMel)

  OR

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

OR

- **Arm B (VDC/IE strategy): VDC/IE induction; IE/VC /BuMel consolidation**

  Induction chemotherapy: 9 cycles of alternating VDC and IE

  Consolidation chemotherapy: 5 cycles of alternating IE and VC
  - R2 IE/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)

OR

1 cycle VAI plus BuMel (poor risk localised disease without contraindication to BuMel)

Randomisation R2

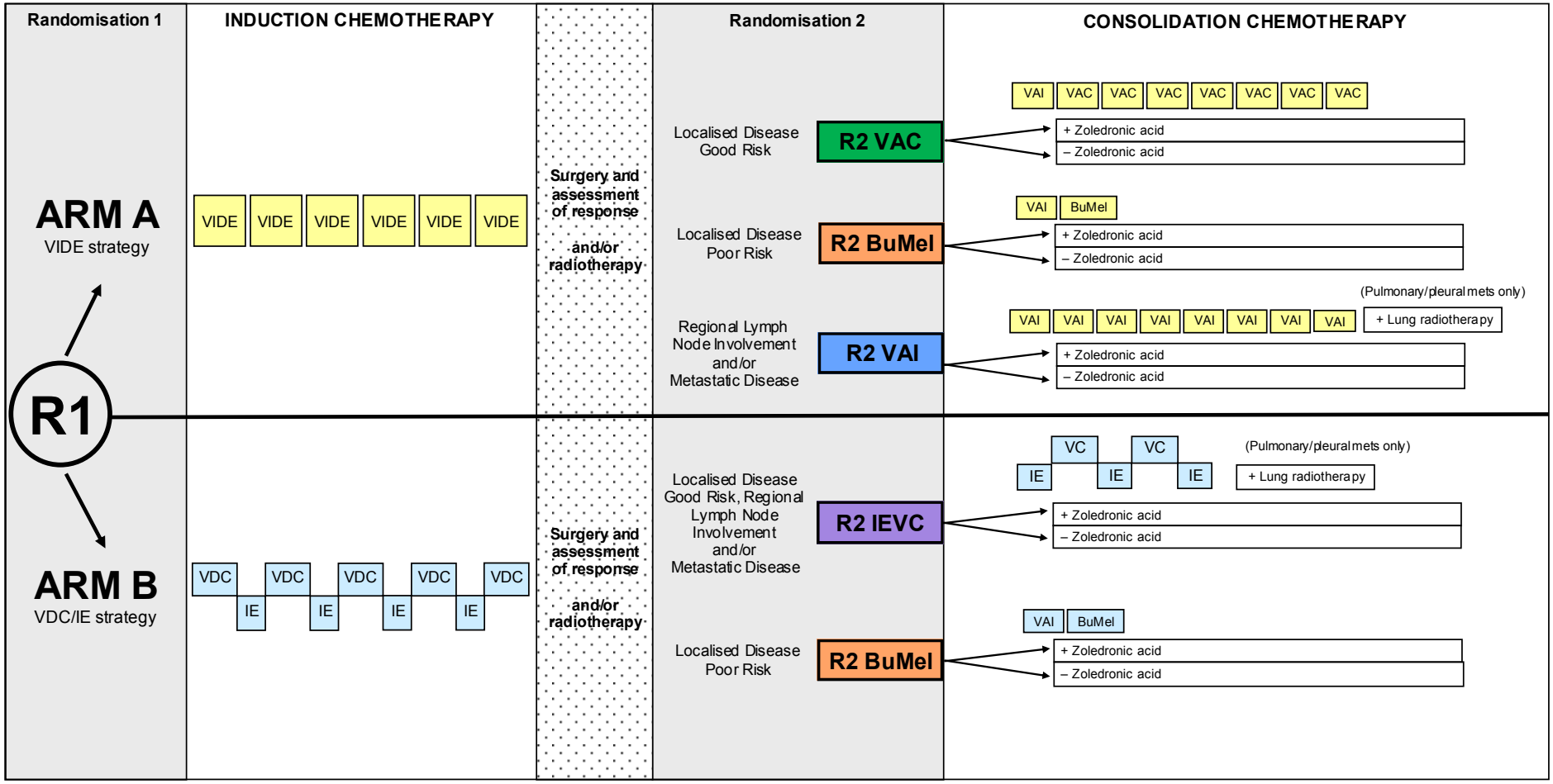
Following induction chemotherapy, patients who fulfil the eligibility criteria for R2 and consent to take part in the randomisation will receive consolidation chemotherapy as allocated at trial entry and be randomised to receive either:

- **9 cycles of zoledronic acid** following the first cycle of consolidation chemotherapy (VAI (Arm A) or IE (Arm B))

OR

- **No zoledronic acid**

Trial Schema



VIDE Vincristine, Ifosfamide, Doxorubicin, Etoposide
VDC Vincristine, Doxorubicin, Cyclophosphamide
IE Ifosfamide, Etoposide

VAI Vincristine, Actinomycin D, Ifosfamide
VAC Vincristine, Actinomycin D, Cyclophosphamide
IE Ifosfamide, Etoposide
VC Vincristine, Cyclophosphamide
Bu Busulfan
Mel Melphalan