Clinical trials in bone sarcoma

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Conflicts of interest

I have no conflicts to disclose

Today's talk will focus on:

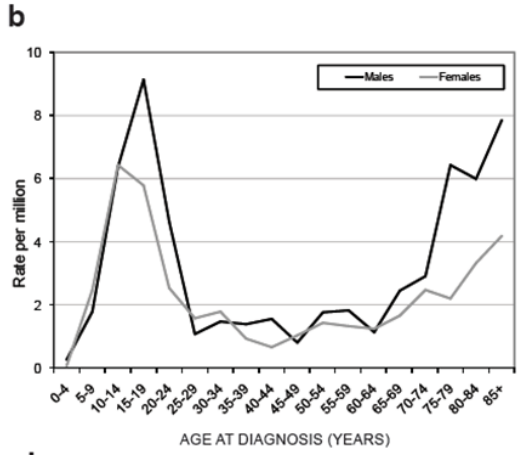
- Clinical trials in bone sarcomas - osteosarcoma, chordoma and Ewing sarcoma
- Influence of Patient advocacy on EEC trials
- What patients want to know / should ask about trials?

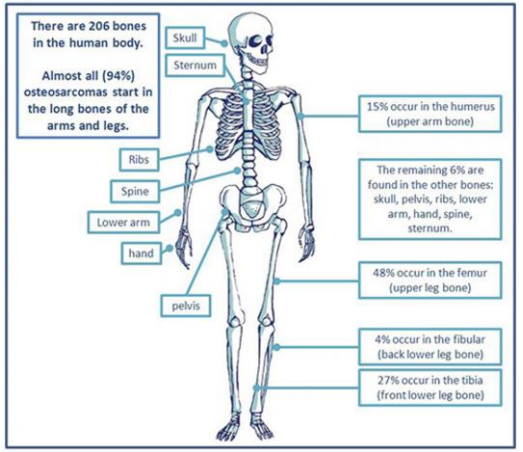
1. OSTEOSARCOMA

- most common primary bone found in adolescents
- second peak in older patients
- Most commonly spreads to the lungs (15%) and bones

Treatment
Complex multi-modality treatment
Expert multi-disciplinary team and must be at specialist centres

For cure:
Require complete surgical resection and chemotherapy





Global international trial

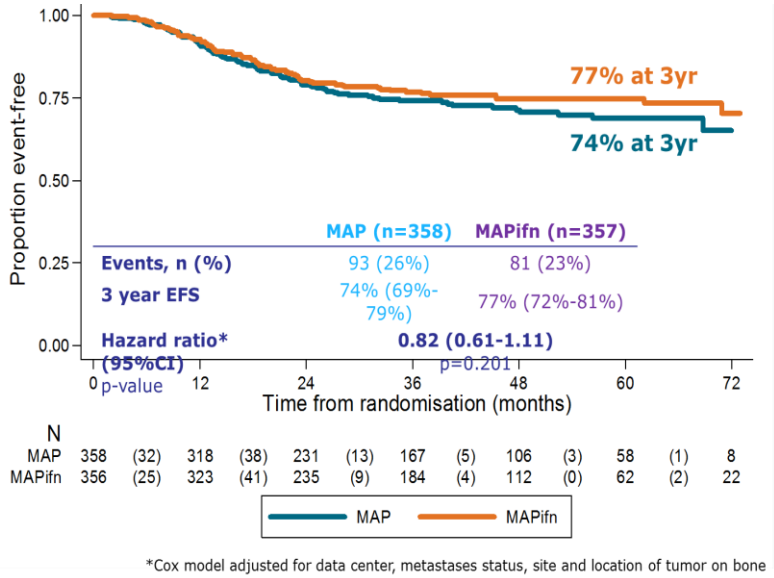
- **≤ 40 years resectable OS**
- does changing treatment based on response to neo-adjuvant chemotherapy (MAP) alter outcome?
- Good response: randomised to maintenance interferon
- Poor response: additional IE

→ demonstrated global collaboration possible, >2200 patients from 17 countries recruited in 6 yrs

→ Closed in 2011 ~ 10 years ago

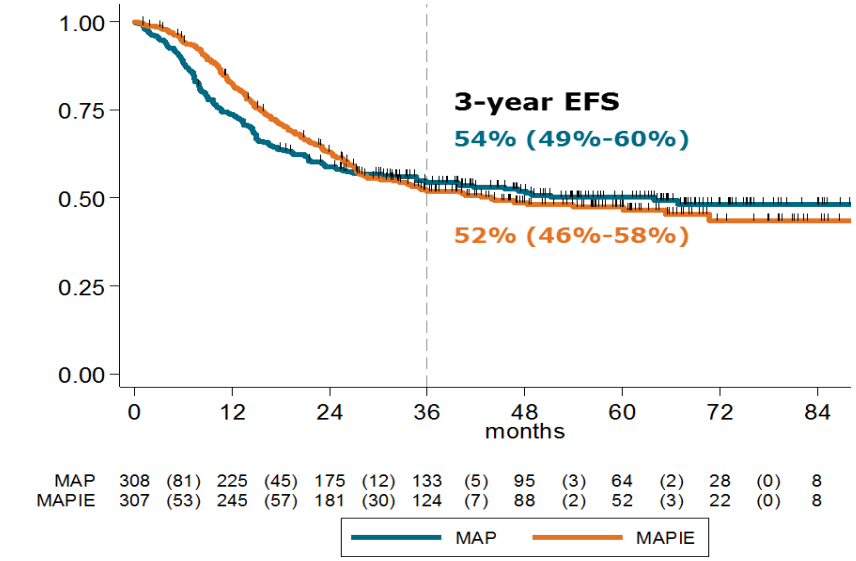
Global international trial-no change in outcome

GOOD RESPONSE[1]



*Cox model adjusted for data center, metastases status, site and location of tumor on bone

POOR RESPONSE[2]



- **standard of care remains MAP chemotherapy**

1. Bielack, et al, J Clin Oncol, 2015
2. Marina, et al, Lancet Oncology, 2017

- No international clinical trials since then as unclear on best question and no new agents

Osteosarcoma: Relapse

Poor prognosis

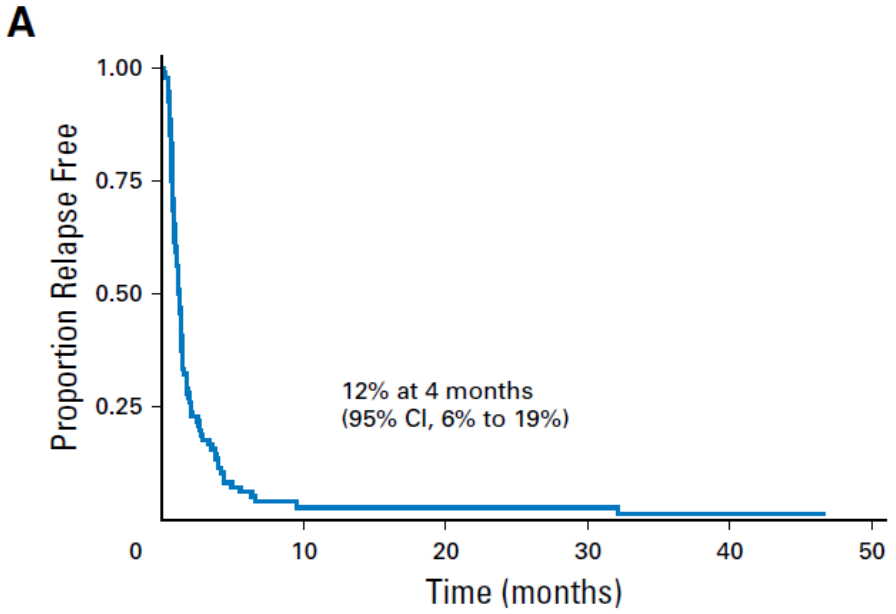
Prognostic factors:

Time to relapse ≤ 2 years vs > 2 years

Lung vs other metastatic sites

No standard of care

Active agents ifosfamide and etoposide



COG analysis of 7 phase II studies[1] :

PFS rate at 4 months- used as std for measurement of activity of new agents – **30% deemed "active"**

Lagmay et al, JCO, 2016

New drugs - Tyrosine kinase inhibitors

	SORAFENIB +/- EVEROLIM [1,2]	REGORAF vs PLACEBO[3]	SARC024[4] (REGORAF vs PLACEBO	CABONE[5]	APATINIB [6]	LENVATINIB[7]
No. pts	35	42	42	45	37	28
Age, med (range)	21 (15-62)	R: 32 (21-50) PL: 40 (29-43)	37 (18-76	34 (20-53)	23 (16-62)	77% (age 6-18) (6-24)
Med. PFS (months)	**4 (2-5)**	**16.4 weeks (8–27)**	**3.6 (CI 2-7.6) vs 1.7 placebo**	**6.7 (CI 5.4 – 7.9)**	**4.5 (CI, 3.5–6.27)**	**3.0 (1.8 -5.5)**
OS (mths)	7 (CI 7–8)	11.3 (CI 5.9–23.9)	11.1 (4.5 – 27)	10.6 (7.4-12.5)	9.7	NR

Interesting and some patients benefit but generally not for long enough and won't cure

1. Grigiani, et la Ann Oncol, 2012;
2. 2. Martin-Broto, et al. Ann Oncol, 2017
3. Duffaud, et al
4. Davis, et al. JCO 2019
5. Italiano, , et al, Lancet Oncol, 2019)
6. Xie, et al. Oncologist, 2019
7. Gaspar, et al, ASCO 2018

What next - Relapsed /refractory OS – ongoing trial

Does combining a TKI with chemotherapy improve outcome?

1. Randomised phase II study of ifosfamide and etoposide +/- lenvatinib in patients aged 2-25 with relapsed/ refractory osteosarcoma (OLIE)
    - Open in many centres across Eu and USA
    - very good study – not everyone gets the TKI but there is a cross over
    - but stops at 25 years

No studies for older patients

No studies for patients with newly diagnosed OS

Very little change in outcome for 10 years

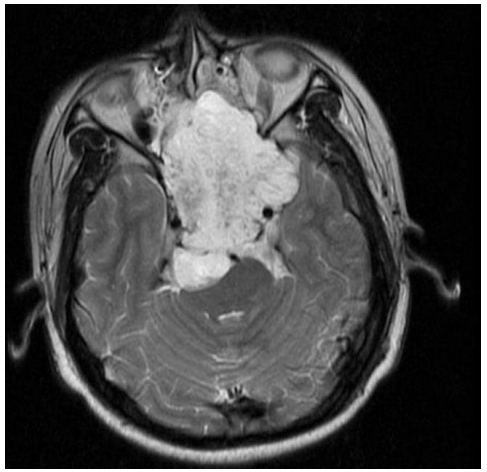
GREAT UNMET NEED – needs an international consortium to work collaboratively to make an impact

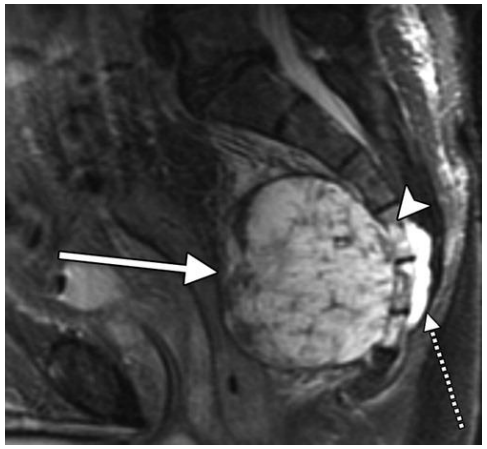
→ Discussion at SIOPE next week

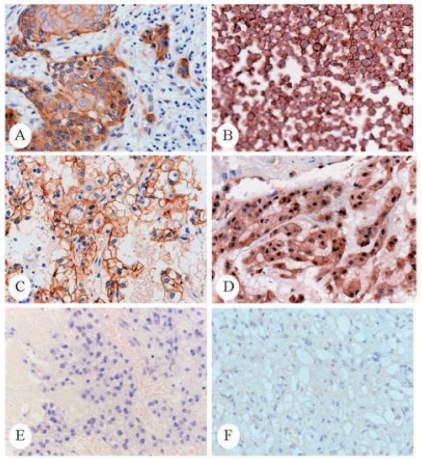
2. CHORDOMA

- Rare bone tumour arising in spine – sacrum or base of skull
- Surgery mainstay of treatment – can be mutilating
- No licenced drugs and no standard of care
- Very few clinical trials

EGFR) signalling important in chordoma, expressed in > 70%







Leiden University Medical Center

UCL

CHORDOMA FOUNDATION

A phase 2, single arm, European multi-center trial evaluating the efficacy of afatinib as first-line or later-line treatment in advanced chordoma

Hans Gelderblom, Lead Investigator LUMC

Chordoma UK
Chordoma action now.
Together we can.

open in:

Leiden

London (Strauss)

Milan (Stacchioti)

Boehringer Ingelheim

Phase II clinical trial-testing if the drug is effective and is tolerated in specific patients

1. **Primary objective:**

-to understand how effective the drug is for patients with EGFR + chordoma
- to understand what effects it has on Quality of life and pain?

2. Secondary objectives:

- how well do patients tolerate the drug, what side effects do patients get?
- does it affect the growth of the tumour?

Which patients?

2 groups of patients

- Patients who have not had any drug treatment before for chordoma (cohort 1) - 12 months
- Patients who have had previous drug treatment (Cohort 2) – 9 months
- Aiming to treat 20 patients in each cohorts, so approx. 40 patients

- Academic study so many challenges
- Opened 3 years ago in Leiden, 2 years ago in London and 1 year ago in Milan

Interim analysis after 20 patients – sufficient activity to continue so currently recruiting

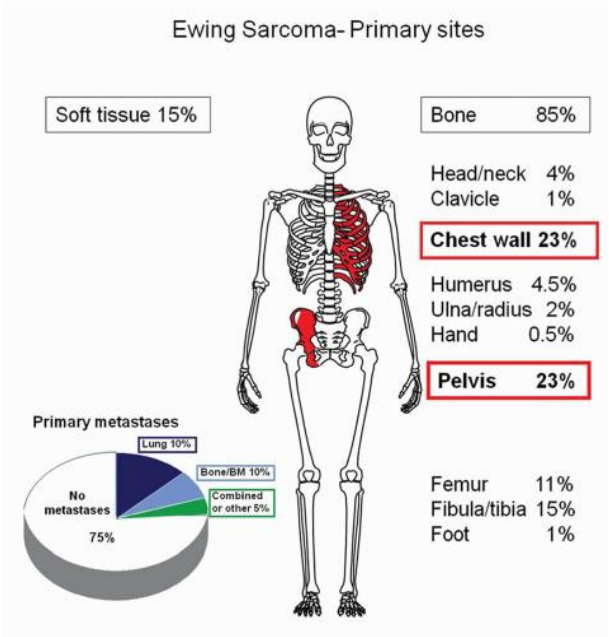
3. EWING SARCOMA

Rare tumour, 2nd most common primary bone tumour in children and teenagers

Majority arise in the bone but can also arise in soft tissue

<u>Management</u>

- Complex chemotherapy + local control (surgery +/- radiotherapy)
- Evolution of therapy through collaborative, international clinical trials



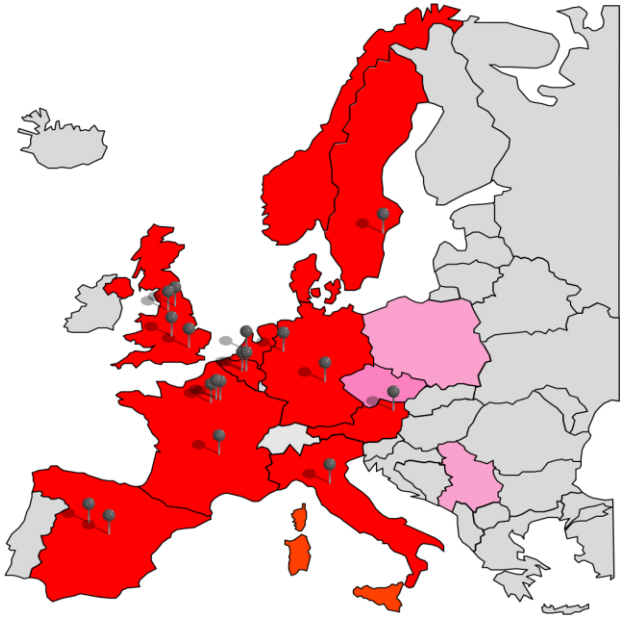
Whelan, et al , Int J Canc 2012

EEC: EURO EWING Consortium – International Clinical Trials to Improve Survival from ES

November 2013 - November 2019; € 5.7m – PI Jeremy Whelan, UCL

21 partners from 9 countries

Work Package 1	**EURO EWING 2012 – First line randomised trial of adjuvant therapy**
Work Package 2	**rEECur – randomised trial of second line chemotherapy**
Work Package 3	Biobanking, reference pathology and molecular characterisation
Work Package 4	Biomarkers of response, toxicity and outcome
Work Package 5	Dissemination and Patient and Public Involvement
Work Package 6	Ethical aspects
Work Package 7	Project management



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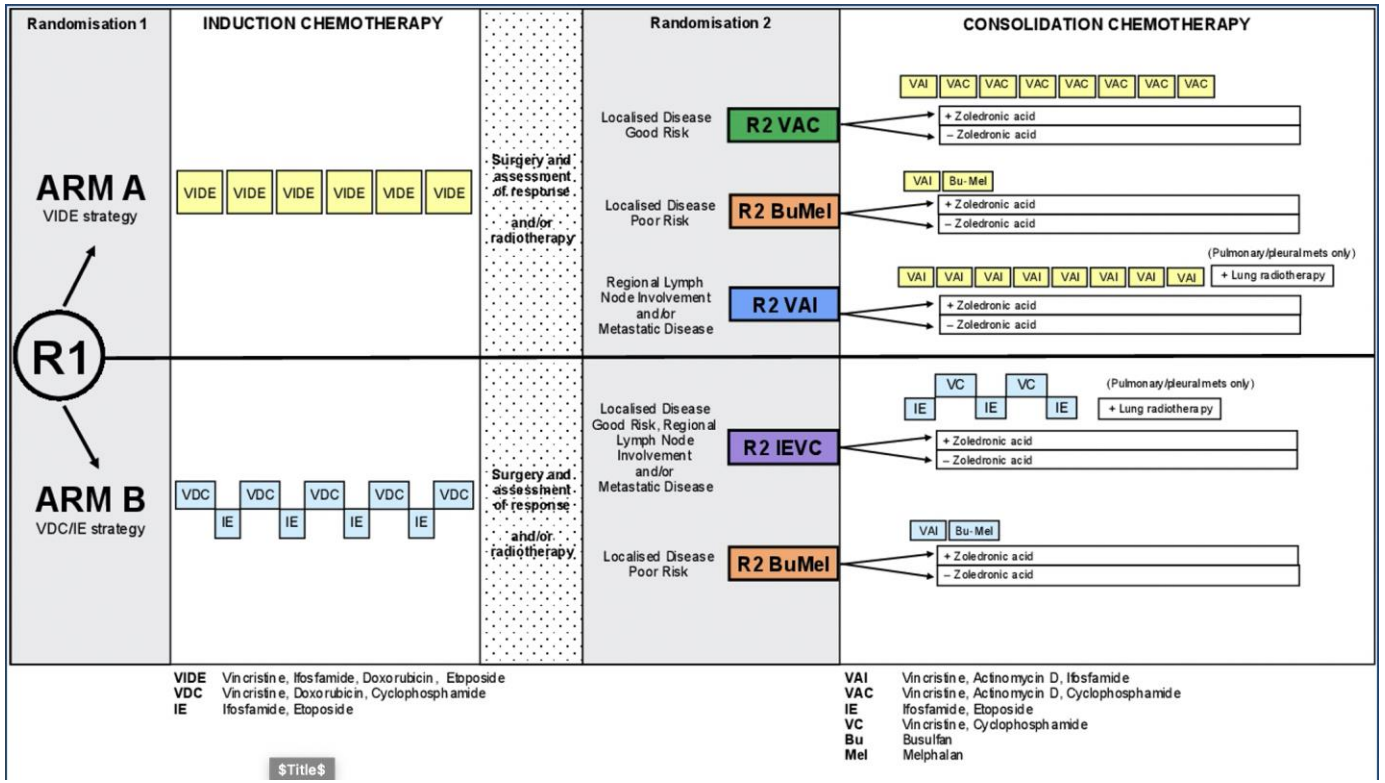
Work Package 6	Ethics aspects
Work Package 7	Project management

- **13 meetings**
- **Multi-national PPI group fully integrated in all activities and integral to the success of EEC**

EuroEwing2012

Randomised trial of chemotherapy in patients with newly diagnosis ES

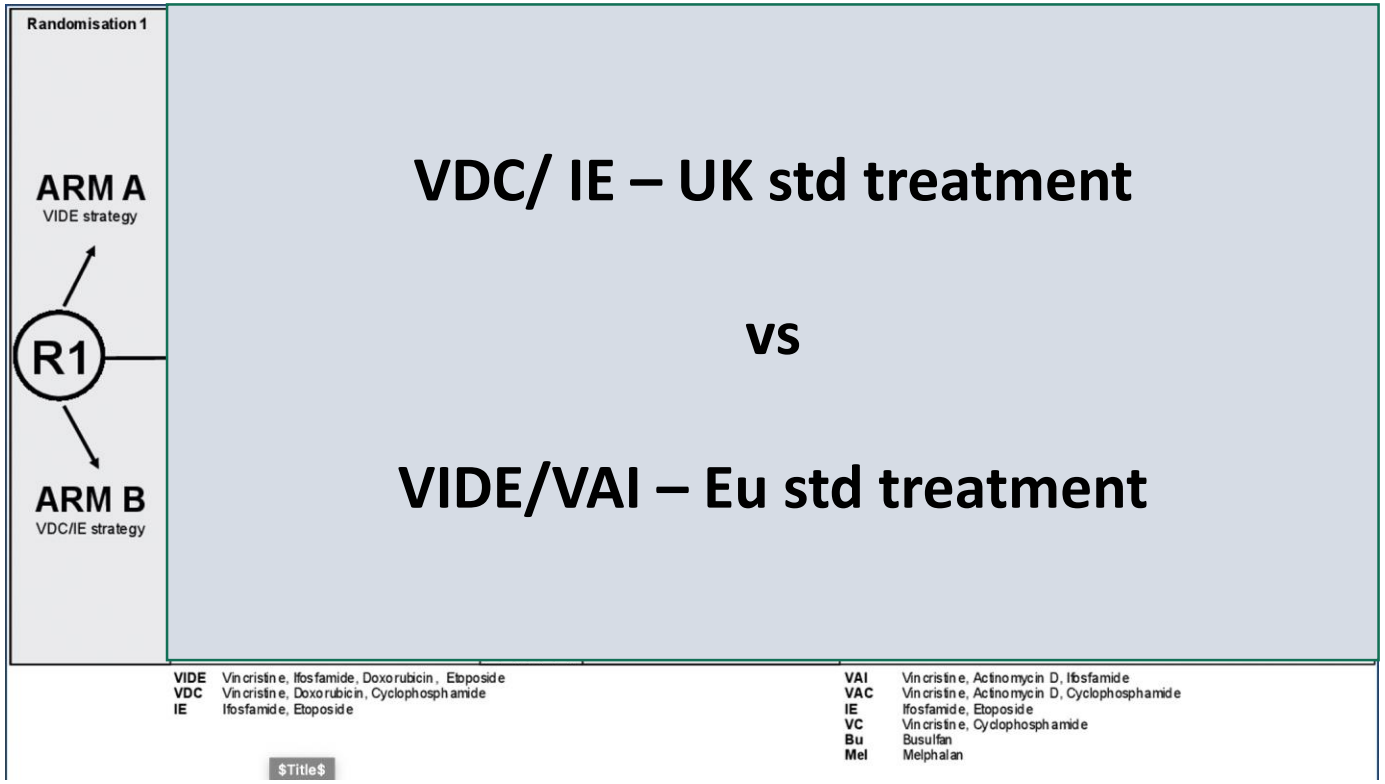


Randomisation 1
between the European standard of care and US

Randomisation 2
+/- zolendronic acid

EuroEwing2012

Randomised trial of chemotherapy in patients with newly diagnosis ES



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EuroEwing2012

Country (and NCC)	Number of patients recruited
UK (CRCTU)	242
France (CLB)	195
Spain (GEIS)	148
Belgium (EORTC)	16
Czech Republic (EORTC)	20
Netherlands (EORTC)	5
Denmark (EORTC)	2
Switzerland (EORTC)	1
Hungary (EORTC)	7
Republic of Ireland (OLCH)	4
Total	640

→ **5.5 years**

EuroEwing2012 → Patients receiving VDC/IE had better survival

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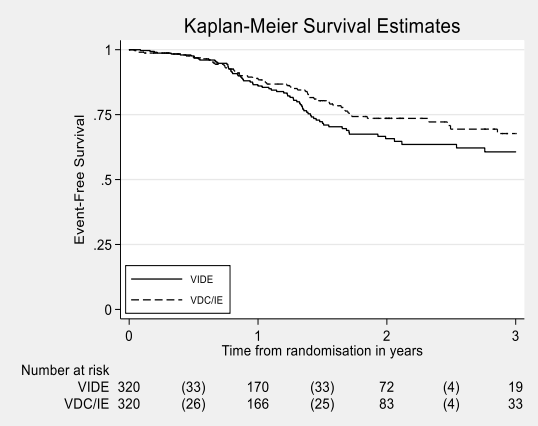
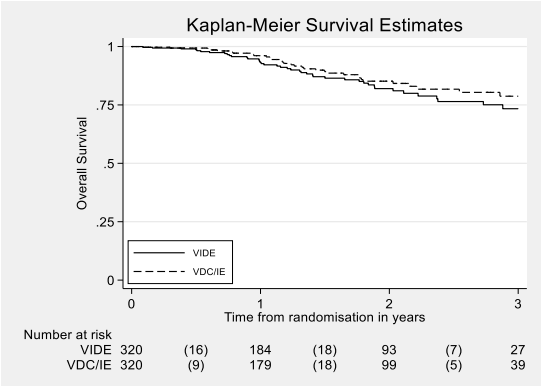
Event-free survival



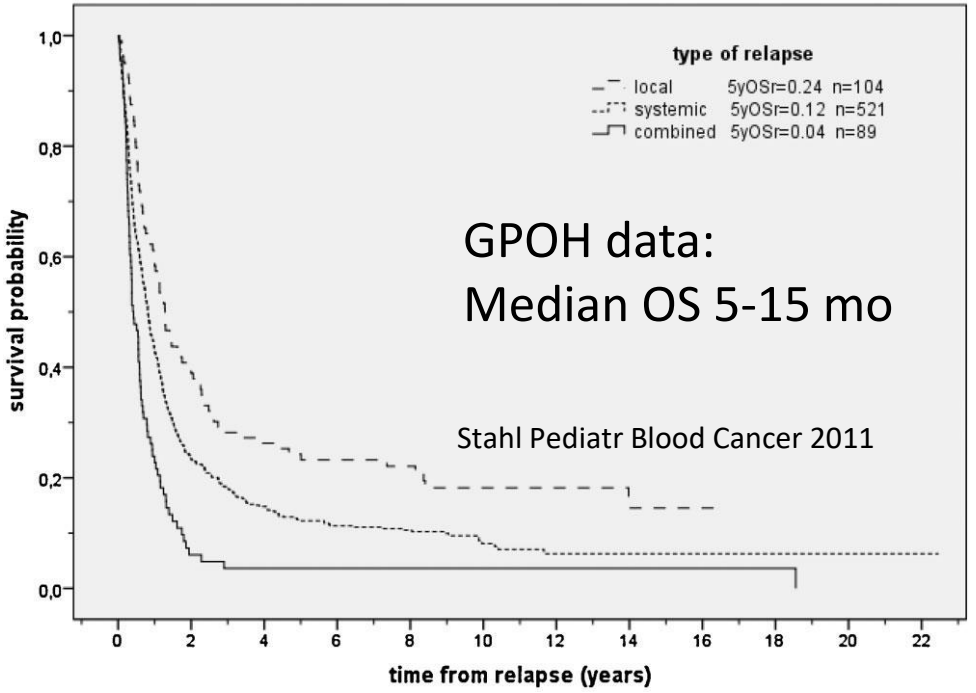
Overall survival



→ VDC / IE is now standard of care for all patients with ES globally

Recurrent/ relapsed ES

- Long term survival poor
- Multiple regimens used at progression
- No prospective evidence from trials
- No standard of care



GPOH data:
Median OS 5-15 mo

Stahl Pediatr Blood Cancer 2011

rEECur: an international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma

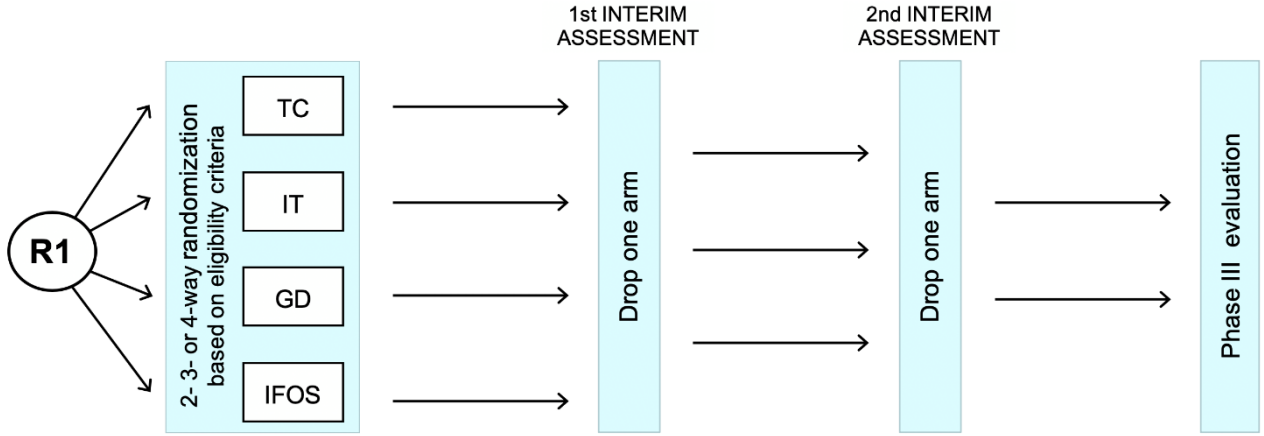
DESIGN

Multi-arm multi-stage (MAMS) seamless phase II / III “drop-a-loser” randomized trial

Bayesian design

Independent Data Monitoring Committee makes recommendations

Independent Trial Steering Committee ratifies them



McCabe et al, ASCO 2019

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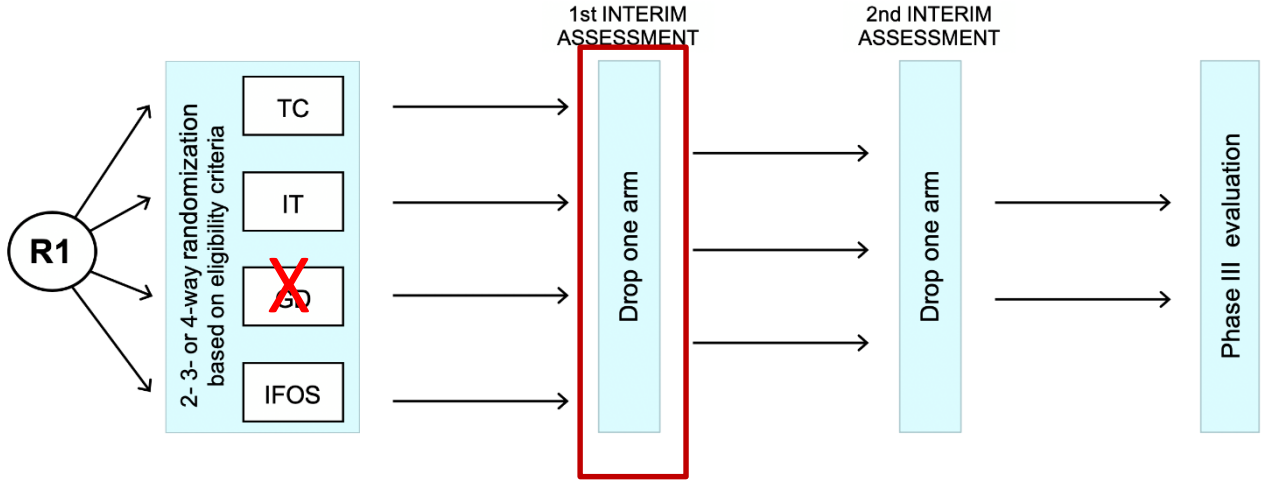

GD - dropped

McCabe et al, ASCO 2019

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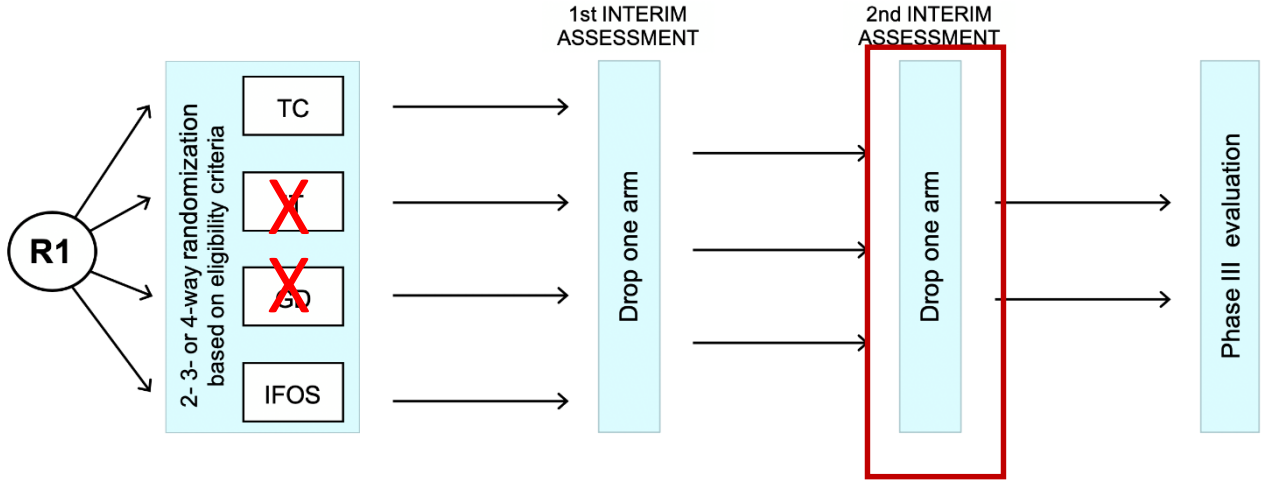
Dropped GD
Then IT

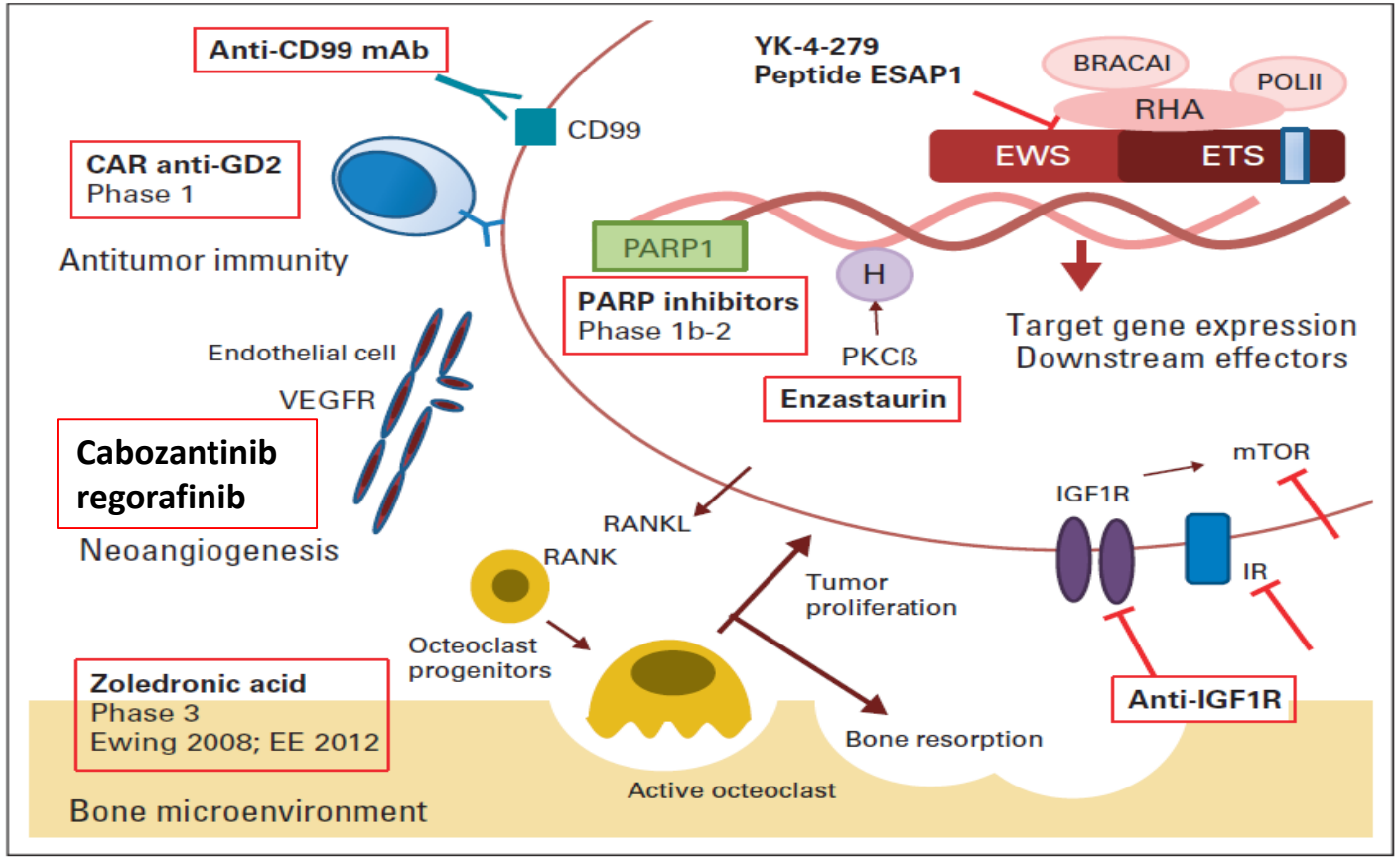


366 pt randomised

New arms coming – std chemotherapy, chemo **+ novel agents**

McCabe et al, ASCO 2020

Novel agents / targets for ES



- **PARP inhibitors – very good science but too toxic**
- **TKIs**
- **Novel agent targeting the fusion protein, YK-4-279 / TK216**

Gaspar, et al, JCO 2015

Other targeted therapy with efficacy - TKI studies in ES

	REGOBONE[1]	SARC024[2]	CABONE[3]
No. pts	46 (23 RG)	30	39
Age inclusion	≥ 10 years	> 18 years	≥ 12 years
Median Age (range)	RG: 32 (18-59) PL: 28 (16-59)	32 (19-65)	33 (16 –53)
Prior therapies Med (range)	1 (17, 37%) 2 (19; 63%)	5 (1-10)	2; > 2 (17 pt (38%)
DCR at 8 weeks	13 / 23 = 54%	18 / 30 = 60%	Not reported
Median PFS	**11.4 wks** **PL 3.9 wks**	**3.6 mths / (15 wks)**	**4.4 mths**

Engagement with Pharma to combine with chemotherapy

1. Defauud, et al , ESMO 2020
2. Attia, et al. ASCO 2017
3. Italiano, et al, Lancet Oncol, 2020

Really helpful responses in some patients but will not cure patients on own

Inter-Ewings-1

- Next EEC trial of patients with newly diagnosed ES
- Builds on EE2012 – using VDC/IE as backbone
- Under review for funding
- Asks question about?
    - i) new agent
    - ii) maintenance treatment
    - iii) radiotherapy

- Extended collaboration outside of Eu
- Developed collaboratively within EEC including PA

Impact of Patient Advocacy on EEC trials

- FP7 grant provided opportunity to form a cohesive international PA group that has grown over time in number and expertise and confidence
- Twice yearly face to face meetings opportunity to become one integrated group

Impact of Patient Advocacy on EEC trials

Study design

- 2014: influenced rEECur protocol to remove mandatory bone marrow biopsies – reduce burden on patients and have a positive effect on recruitment
- Helped write Patient information forms
- PAs were made members of the Trial Steering Committee and Trial management groups for Euro Ewing 2012 and rEECur – integrated into decision-making about design and amendments
- Experience on TMGs given PA knowledge and confidence to be able to input from the very early stages of the next ES trials
- Able to provide a community voice to influence how EEC should evolve and define priorities

- **inclusion of novel agents and looking at quality of life**
- **accountability for sample collection and translational research**

Other important PA contributions

- Andy Westwood carried out survey on social media – further help defining research priorities

 - presented at last EEC meeting
- Link and collaborate with other existing resources and international collaborative projects”
- Chris Copland –Accelerate Platform – FAIR, Peter Pan – support young researchers
- Ornella Gonzato - donated funding to support young ES researchers to work in other labs.
- PA group connected with a key PA in the USA, (Chris Carson) and this has given the EEC links into the charity/ PA groups in the USA

Since 2019 – EEC has evolved:

- Members of ongoing EEC Executive committee –Andy Westwood, Jane Wingrove and Yasmin Uhlenbruch

Major impact of PAs….

- presence at meetings and on committees means that we are always answerable to them, that we have improved transparency, and increased drive to improve the situation for patients. Having PAs involved puts patients at the centre of everything that we do and they push us to be **better and faster.**

What patients should know and ask about clinical trials during their journey'

What patients should know and ask about clinical trials during their journey'

1. *Are there any trials?*
2. *How can I find out about trials?*

- Websites / on-line resources/ are they reliable and up to date?

Sarcoma UK
The bone & soft tissue cancer charity

Clinical Trials Hub

What patients should know and ask about clinical trials at what point during their journey'

We asked the EEC patient advocates what they think patients should know and ask

Does depend on time of journey- 1st line, subsequent, curative, palliative but principles are the same

When discussing a specific trial

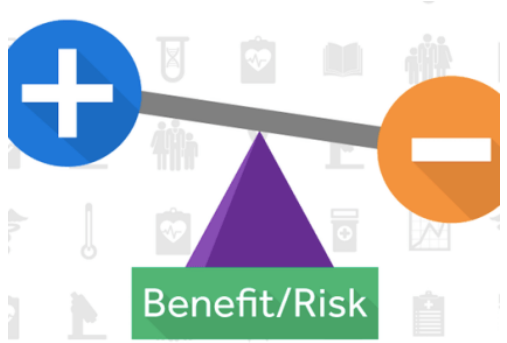
Before enrolling

Why am I being asked to take part in this trial?

Will taking part in the trial give me access to better treatment? – ? NEW DRUGS

Will I be at any greater risk? Is there any increased likelihood of side effects?

Will the length of treatment be different?
Will I have to be an inpatient?
How will samples, biopsies be shared?
Will data collected about me remain private?
Will there be information available in an easily understandable format?
Will I be treated by the same medical staff, at my local hospital – or elsewhere?
Will my I know, and will my doctor know, what drugs I am being given



What patients should know and ask about clinical trials at what point in their journey'

During the trial

- **Will I have access to any information about how the trial is progressing?**
- Will I be able to ask questions of the investigators? What happens if I want to leave the trial early?

After the trial

- **Will I be told the results of the trial?**
- Will there be longer medical follow-ups and do I need to give other information?

What about later in the journey ? - early phase / new drug studies

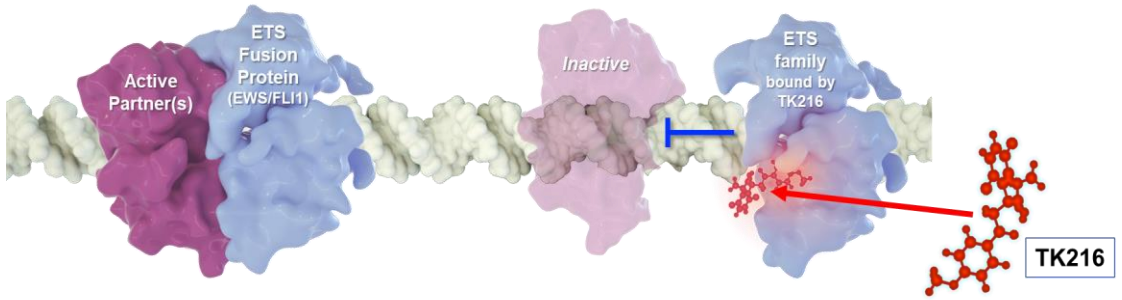
- Patients always want to know there is another treatment/ is there anything new to give hope?
- But also: is there a good scientific rationale, **what is the chance of it helping me?**

“ If I know my child / I have limited time, I don’t want to waste it on something that is not going to work”

Acknowledgements

- Abigail Evans
- Andy Westwood
- Jane Wingrove
- Yasmin Uhlbrecht
- All PAs and patients
- Charities who are willing to fund our difficult work
- ESRT – funds EEC

TK216: A Targeted Inhibitor of ES Fusion Protein



- TK216 is the first clinical candidate targeting the ES fusion protein
- disrupts transcriptome formation mediating:
  - Decreased oncogene and increased tumor suppressor transcription
  - Decreased tumor growth and apoptotic cell death
  - Good results in the laboratory

- **52 patients – safety**
- **15 pts**
- **2 Complete Responses** (including 1 surgical CR), remains on treatment ~1.5 y since enrollment with no evidence of disease, another CR after 6 cycles and remains well, **5 Stable Disease**
- **Disease control rate (CR+PR+SD) = 7 /15 (47%) but short-lived**

Not ready for the next step, so what next?

Ludwig, et al, EMSO 2020