Principles of Management of Ewing Sarcoma

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EWING SARCOMA

Today's lecture will focus on:

- Multi-disciplinary management of newly diagnosed patients
  - Chemotherapy
  - Local therapy – radiotherapy and surgery
  - Areas of controversy

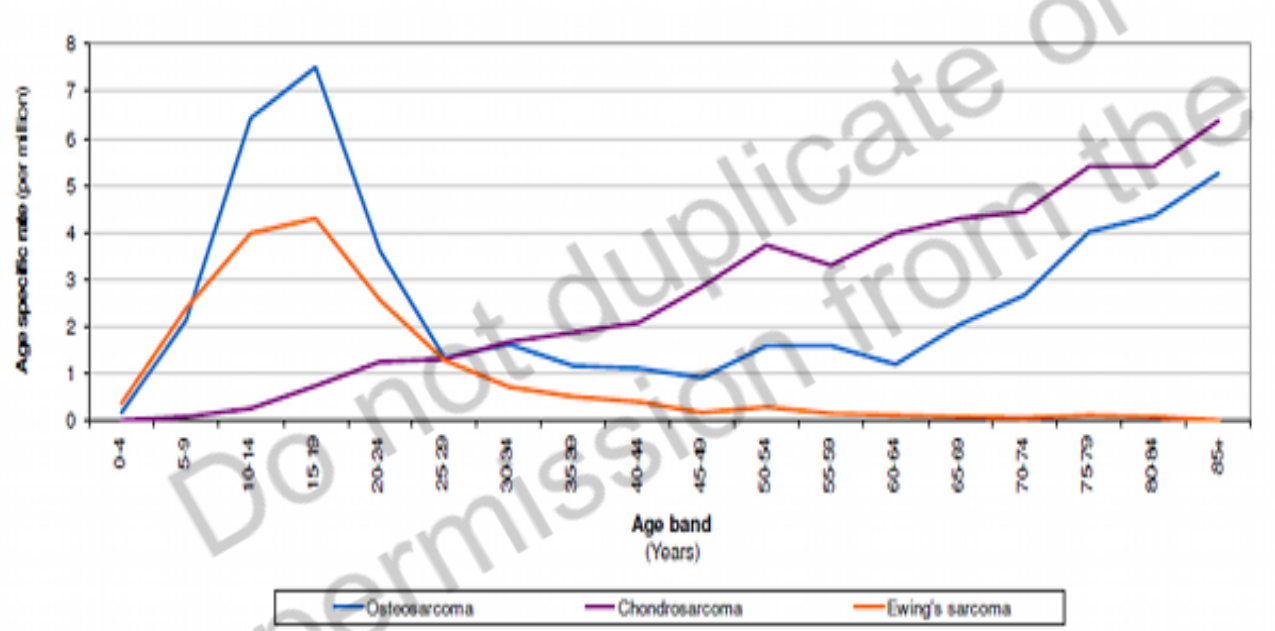
- Relapsed /recurrent disease

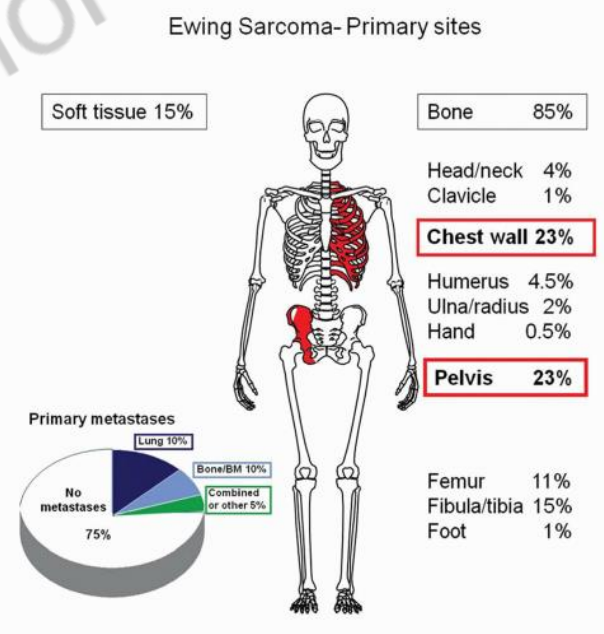
- Novel therapies

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

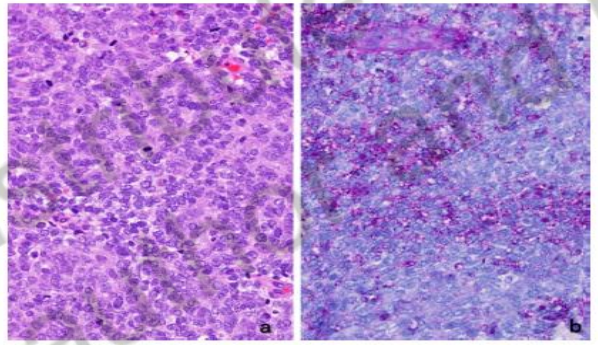




Whelan, et al , Int J Canc 2012

EWING SARCOMA

- Small round blue cells
- CD99 positive
- Characterised by specific rearrangement
- EWSR1 with ETS family of genes



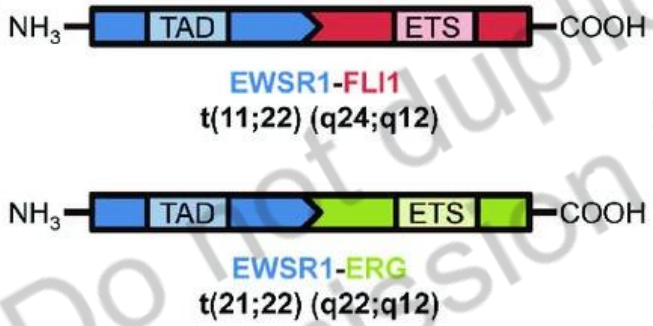


Table 2 Most common types of translocations found in Ewing sarcoma

Translocation	Fusion gene	% of tumors exhibiting EWS gene rearrangement
t(11;22)(q24;q12)	*EWSR1-FLI1*	85
t(21;22)(q22;q12)	*EWSR1-ERG*	10
t(7;22)(q22;q12)	*EWSR1-ETV1*	rare
t(17;22)(q21;q12)	*EWSR1-ETV4*	rare
t(2;22)(q35;q12)	*EWSR1-FEV*	rare

→ Aberrant transcription factor with many down stream targets

EWING SARCOMA

- Management – multi-modality therapy
- Complex chemotherapy + local control (surgery +/- radiotherapy)

<u>Patients risk stratified</u>

- R1 - Standard risk (localised)
- R2 – pulmonary metastases R2 –loc (poor response to chemotherapy)
- R3 – extra pulmonary metastases – Bone and bone marrow

- Evolution of therapy through collaborative, international clinical trials

RCT in PATIENTS WITH LOCALISED EWING SARCOMA

Ref.	Trial	Population	Pts (*n*)	Treatment	Survival outcomes
Standard risk, localized					
Paulussen[49]	EICESS-92	Localized, Tumor volume <100ml	155	Induction (VAIA x4) + Randomization: VAIA x10 vs. VACA x10 (cyclophosphamide vs ifosfamide)	3y EFS 74% vs. 73%, HRs for EFS and overall survival 0.91 VAIA vs. VACA
Le Deley[50]	Euro-Ewing99 R1	<50yo Localized, either good histologic response (>90%) or Tumor volume (<200ml)	856	Induction (VIDE x6, VAI x1) Randomization: VAIx7 vs. VACx7	3y EFS and overall survival for VAI vs. VAC, 78.2% vs. 75.4% and 85.5% vs. 85.9%
Localized					
Grier[48]	INT-0091 (CCG-7881 and POG-8850)	<30yo	398	Standard (VACA) vs experimental (VACA + IE)	5yr EFS and overall survival for standard vs. experimental, 54% vs. 69% (*p* 0.005) and 61% vs. 72% (*p* 0.01)
Granowetter[163]	INT-0154	<30yo Localized, bone + soft tissue	478	VDC/IE (17 cycles, 48 weeks) vs. dose intensified VDC/IE (11 cycles, 30 weeks)	5y EFS and overall survival for standard vs. dose intensified, 72.1% vs. 70.1% and 80.5% vs. 77%
Womer[52]	COG AEWS0031	<50yr age, Localized	568	Randomization: VDC/IE standard (q3/52) vs. VDC/IE intensified (q2/52)	3y EFS and overall survival for std vs. intensified, **65% vs. 73% (*p* 0.048) and 77% vs. 83% (*p* 0.056)** Similar toxicity

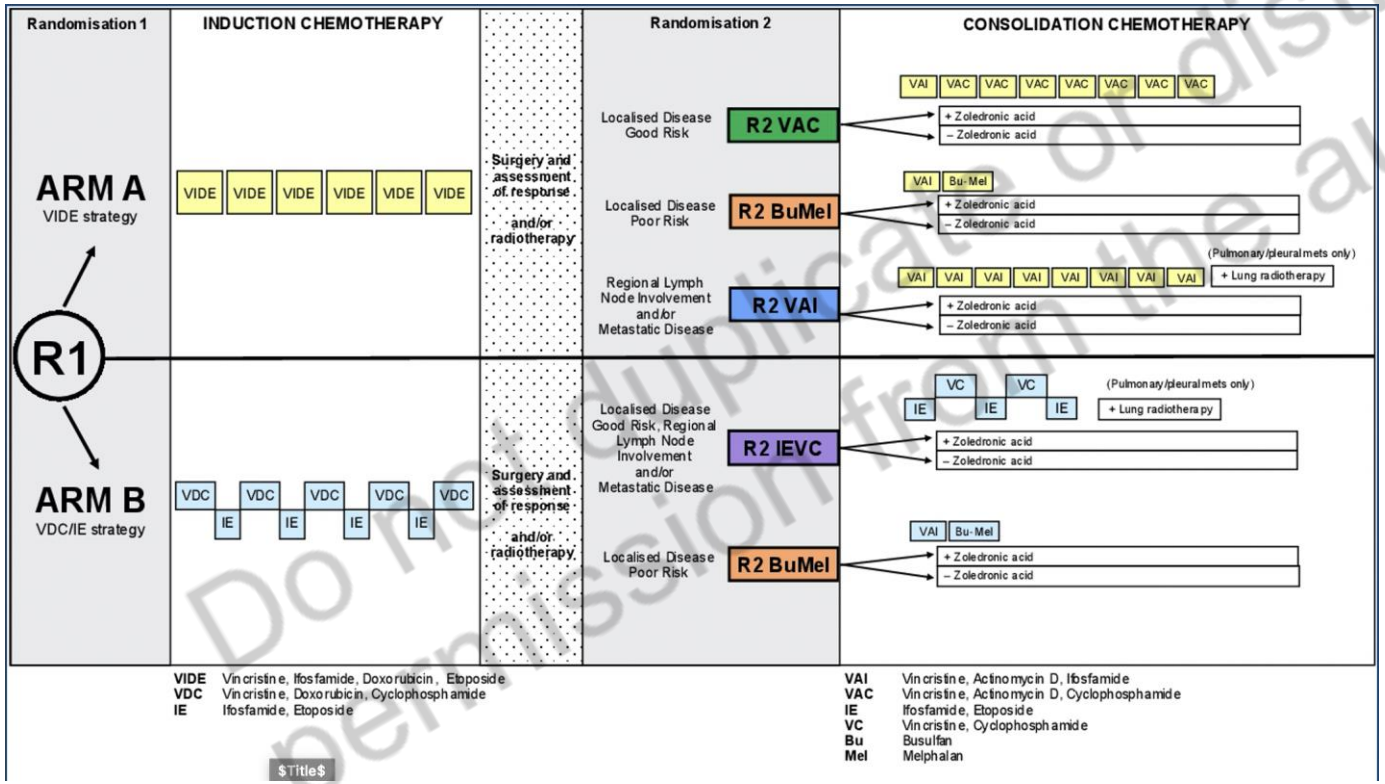
High risk, localized*

HIGH RISK EWING SARCOMA

High risk, localized*					
Whelan[105]	Euro-Ewing99/ Ewing-2008	<50yo Poor histologic response (≤90%), Tumor volume ≥200ml	240	Induction (VIDEx6, VAIx1) Randomization: VAI vs. Bu-Mel/ ASCT	8y EFS and overall survival for VAI vs. Bu-Mel, **47.1% vs. 60.7% (*P* 0.026) and 55.6% vs. 64.5% (*p* 0.028)**
Metastatic (lungs only)					
Dirksen[106]	Euro-Ewing99 R2Pulm/ EWING-2008	<50yo Pulmonary/pleural metastases, nil other	287	VAI + WLI vs. Bu-Mel	No improvement **3y EFS 50.6% vs. 56.6%, HR= 0.79, *p*=0.16** **3yr OS 68% vs. 68.2%, HR=1.00, *p*=0.99**
Multisite-metastatic (other)					
Ladenstein	EuroEwing 99	Mulit-metastaic	281	VIDE/VAI +/- BM	**3 y EFS 27% +/- 3% and 3 y OS 34% +/- 4%**

EuroEwing2012

First line randomised trial of adjuvant therapy



Randomisation 1
between the European standard of care and US

Randomisation 2
+/- zolendronic acid

EuroEwing2012

Trial design

•No assumptions regarding superiority or equivalence

•No conventional sample size calculation; no alpha and no beta (i.e. power) assumed

• **Bayesian likelihood approach** - interpretation based on posterior probabilities (with non-informative priors), i.e. Prob[true HR|data]

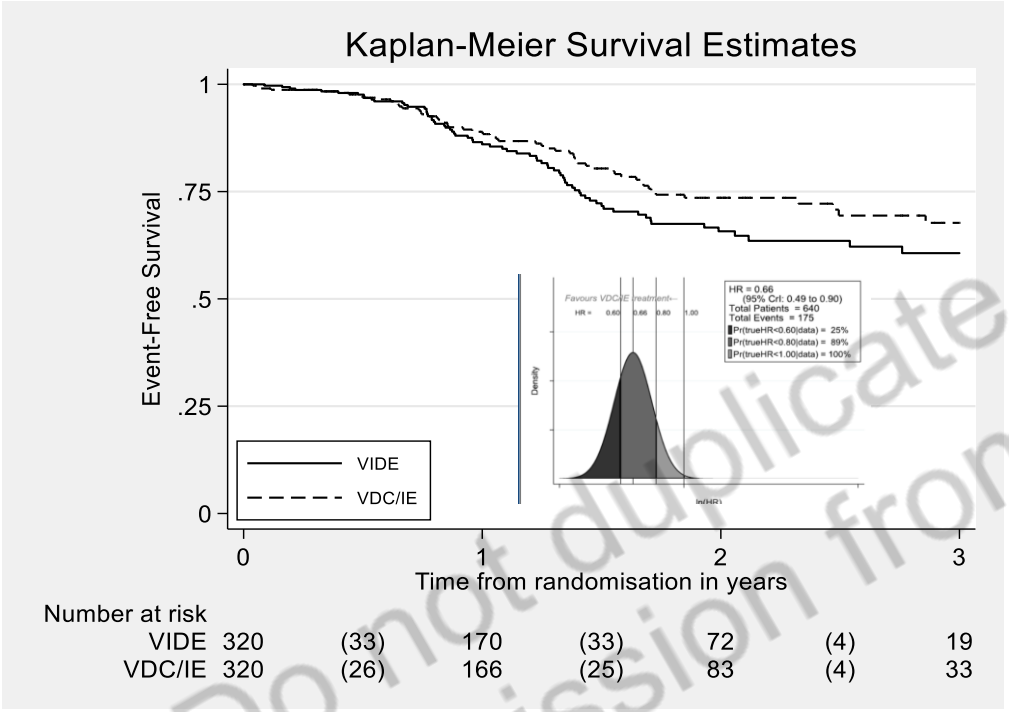
•Hazard ratios (HR) presented, with 95% credible intervals (CrI)

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

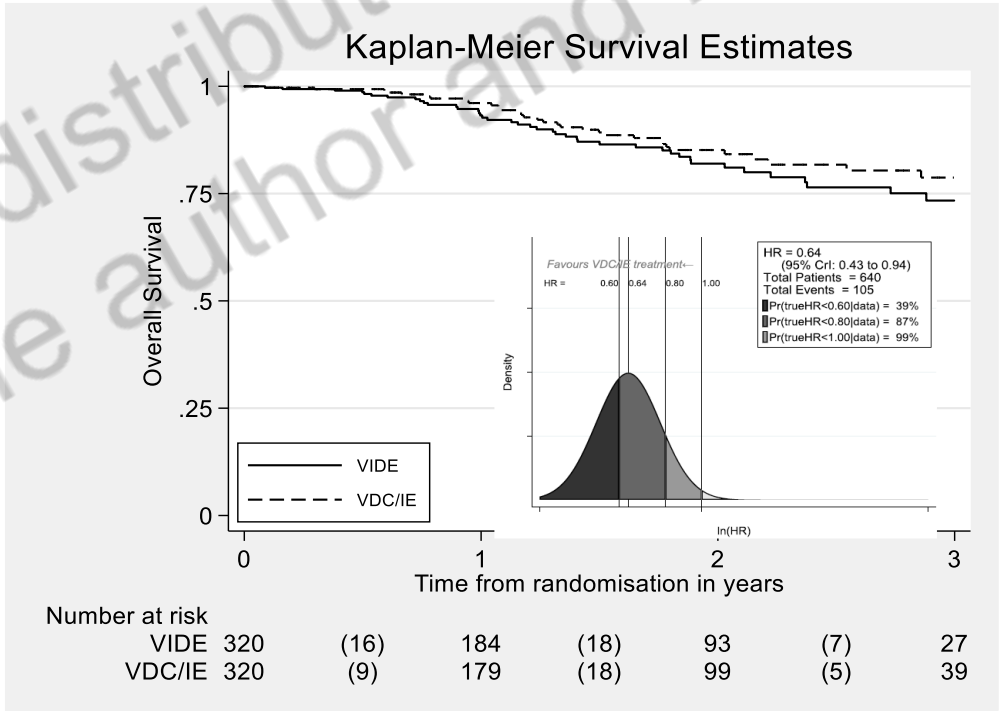
Event-free survival



Number at risk

VIDE	320	(33)	170	(33)	72	(4)	19
VDC/IE	320	(26)	166	(25)	83	(4)	33

Overall survival



Number at risk

VIDE	320	(16)	184	(18)	93	(7)	27
VDC/IE	320	(9)	179	(18)	99	(5)	39

- **VDC / IE standard of care for ES across all risk groups**
- Results of ZA randomisation awaited

Brennan et al, ASCO 2020

EWING SARCOMA-ROLE OF HIGH DOSE CHEMOTHERAPY

Newly diagnosed ES

High risk localised – difficult to extrapolate findings from EE99 to new standard of care VDC/IE

Patients with lung metastases: -no role defined

Multi-metastatic ES: improved outcome in EE9 for patients under 14 years but not randomised

EE2008: Randomised patients between VIDE/VAI and Treo/melph – no statistical difference, trend to improvement for pts < 14 years

Recurrent ES

No randomised evidence
Retrospective series – improved impact > 2 years DFI, complete CR

EWING SARCOMA-LOCAL THERAPY

- Individualised and must be through discussion at expert specialist MDT/ tumour board

Depends on many factors:

- patient age, primary site, size and local extension
- Must be discussed early
- No/ little data comparing surgery and RT in randomised studies

Overall surgery –better outcomes

- Risk of local recurrence weighed against functional outcome and late effects

- Despite response to chemotherapy, need to factor in tumour volume at diagnosis

EWING SARCOMA-LOCAL THERAPY

Surgery

Despite response to chemotherapy, need to factor in tumour volume at diagnosis

Principle – complete excision, with no role for debulking surgery

Amputation can be avoided in the majority of patients

Novel techniques including intraoperative navigation and personalized jigs to guide bone resections are more established and increase safety

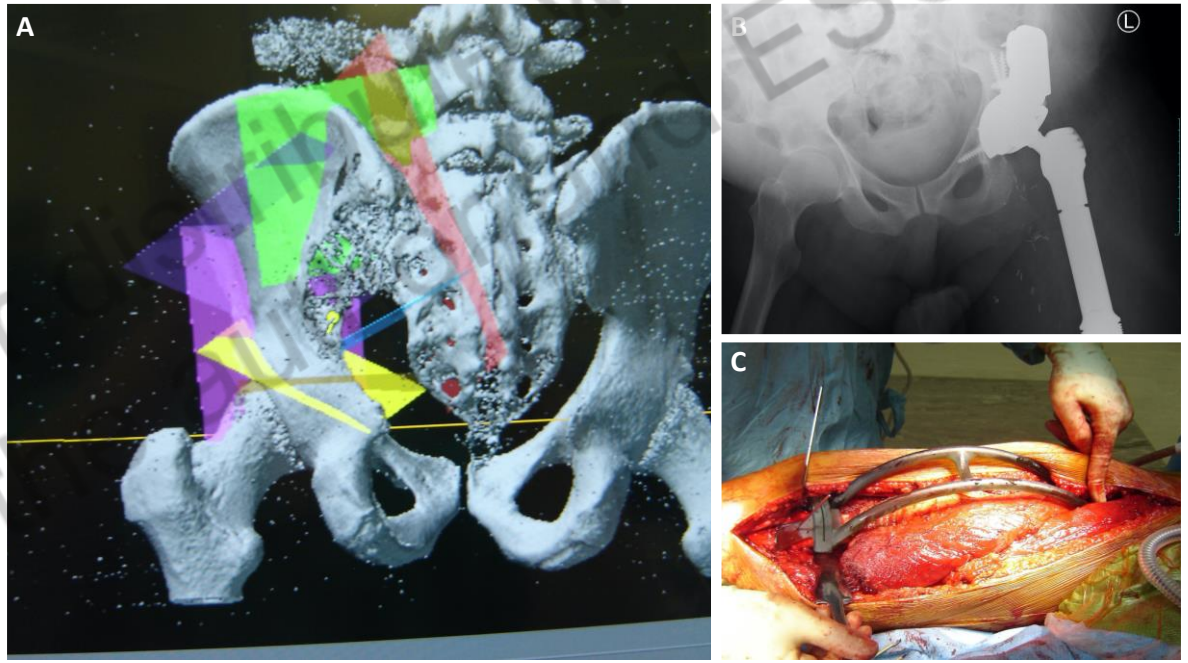


Figure 3. Surgical techniques for Ewing sarcoma.

A. Complex navigation plan showing proposed resection planes for low grade osteosarcoma of the iliac wing. **B**. Reconstruction of the hip after navigated extraarticular resection using modular porous acetabular reconstruction system. **C**. 3D printed customized jig for resection of femoral diaphyseal Ewing sarcoma.

EWING SARCOMA-LOCAL THERAPY

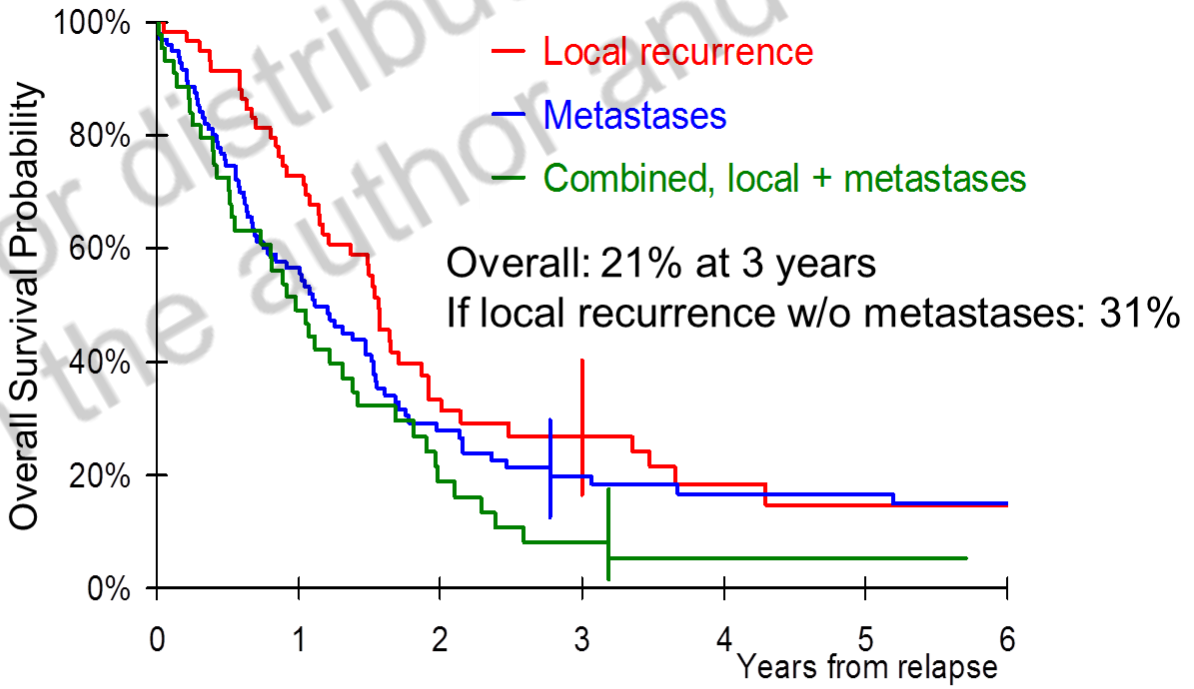
RADIOTHERAPY

1. In combination with surgery
2. Definitive for inoperable tumours
3. New approaches

EWING SARCOMA-LOCAL THERAPY

RADIOTHERAPY

If tumour recurs at the primary site, outcome is poor, so need to optimise treatment at diagnosis



Radiotherapy –important in reducing local recurrence (halves) –only tumours that are not irradiated are small and good response (>90%). If definitely –pre-op. consider PBT

S. Foulon et al. / European Journal of Cancer 61 (2016) 128–136

EWING SARCOMA-LOCAL THERAPY

Can postoperative radiotherapy be omitted in localised standard-risk Ewing sarcoma? An observational study of the Euro-E.W.I.N.G group

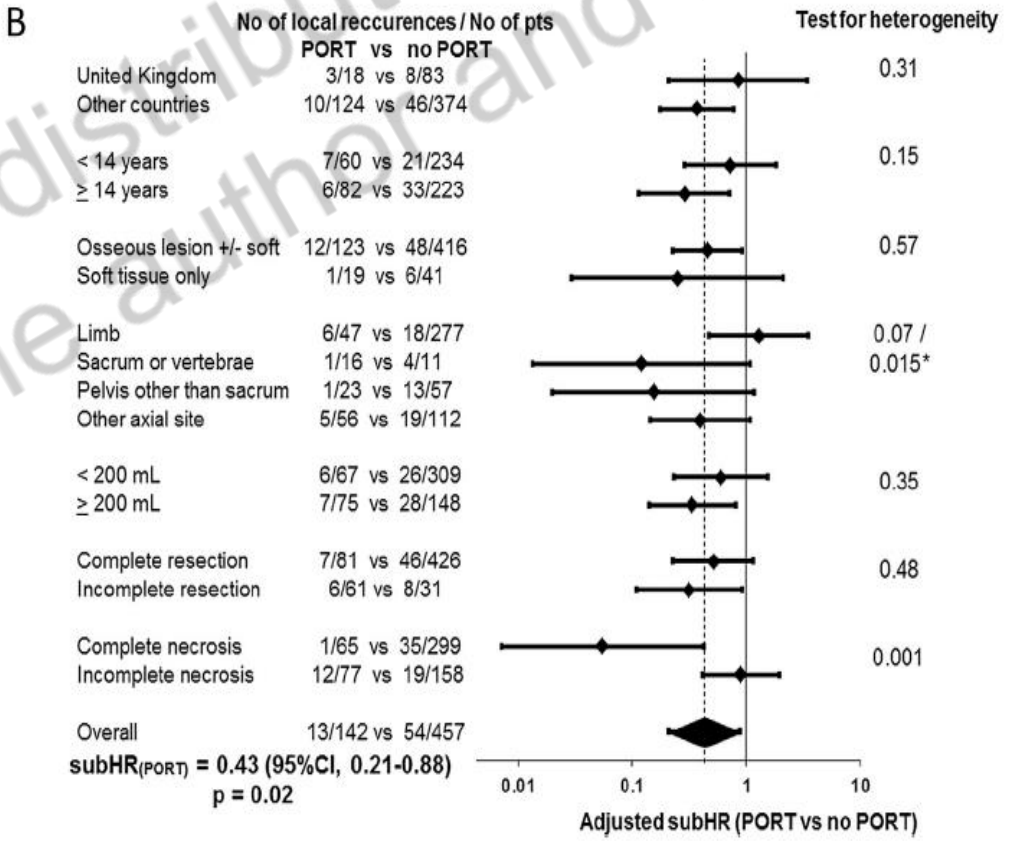
24% received PORT
Median FU 6.2 years; 11.9% LR incidence

Statistical sig reduction in LR if PORT (HR=0.43% (0.21-0.88, p=0.02)

Most marked - large tumours (> 200mL)

→ **Recommended for all patients apart from small tumour with good response**

→ **If definitely having, then often given pre-op**



EWING SARCOMA-LOCAL THERAPY

DEFINITIVE RADIOTHERAPY

- No randomised trials on optimal dose, RT dose ranges from 45Gy to 66Gy– subject of upcoming InterEwings trial
- For inoperable tumours eg: sacrum or pelvic tumours where morbidity too great
- Also spinal- often have decompressive surgery, further surgery not shown to improve outcome

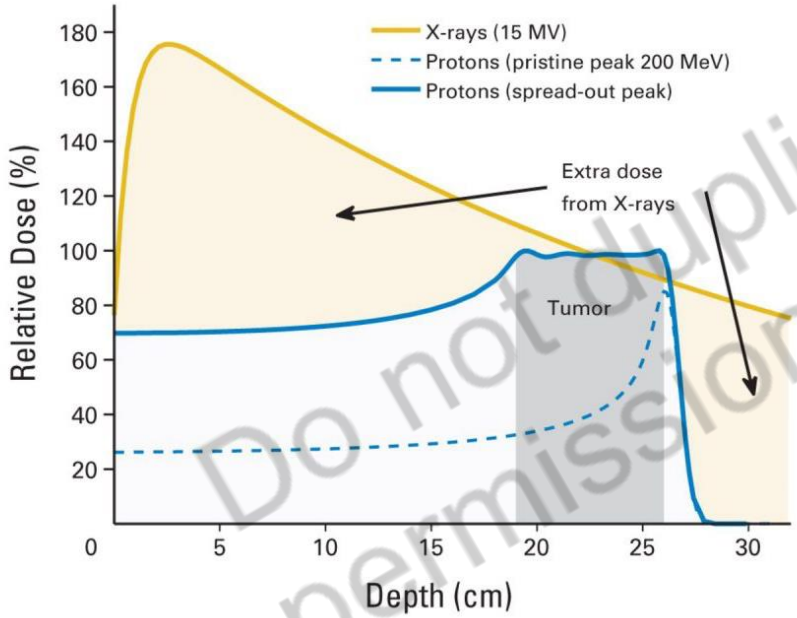
WHOLE LUNG RADIOTHERAPY

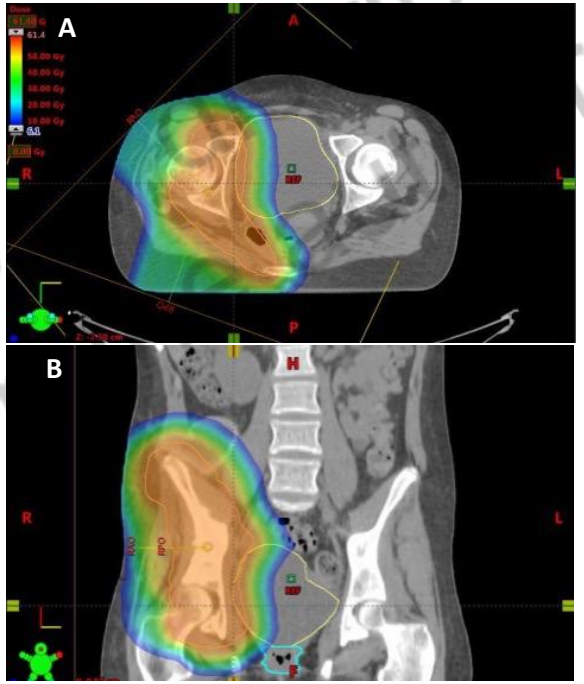
- Consolidate at end of chemotherapy for patients with lung metastases, although no randomised evidence

EWING SARCOMA-LOCAL THERAPY

Proton Beam Therapy

increasingly used particularly for pelvic, spinal and chest wall disease





EWING SARCOMA – NEWLY DIAGNOSED PT

EUROEWING CONSORTIUM - CURRENT QUESTIONS

1. What is optimal dose of RT for patients definitive treatment and post-operatively

2. Is there any role for maintenance chemotherapy?

   -cyclophosphamide / vinorelbine

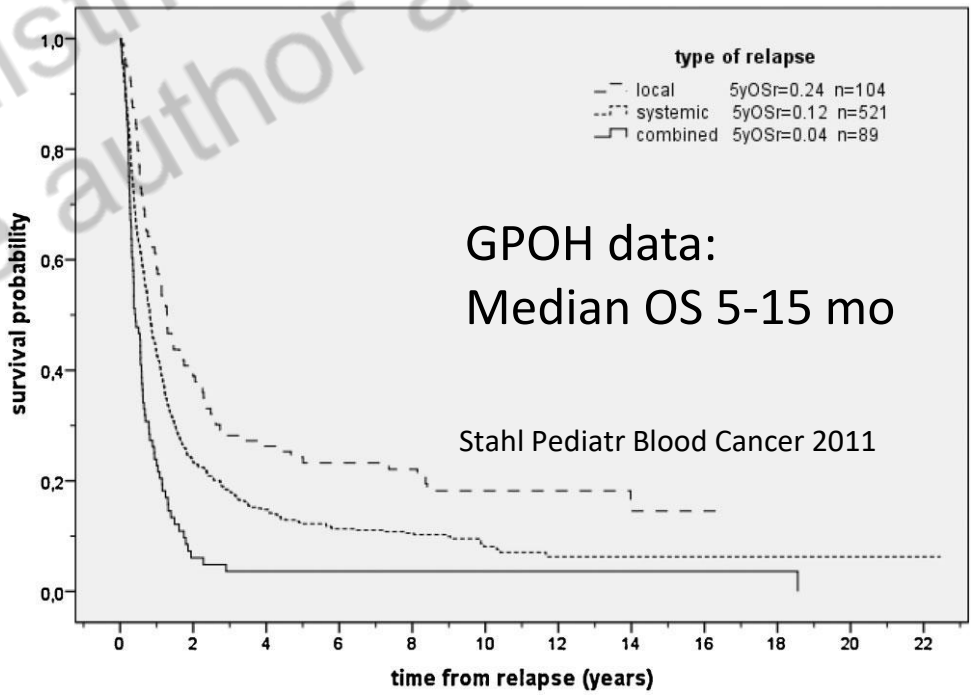
3. Will adding additional targets agents to VDC/IE improve outcome? (TKIs)

→ protocol under funding review - InterEwings-1 – extends collaboration to Australia and NZ and beyond

Recurrent/ relapsed ES

- Long term survival for RR-ES is poor
- Multiple regimens used at progression
- No prospective evidence
- No standard of care

- Outcome depends on
  - Local recurrence
  - Metastatic, lung vs other
  - Disease-free interval



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

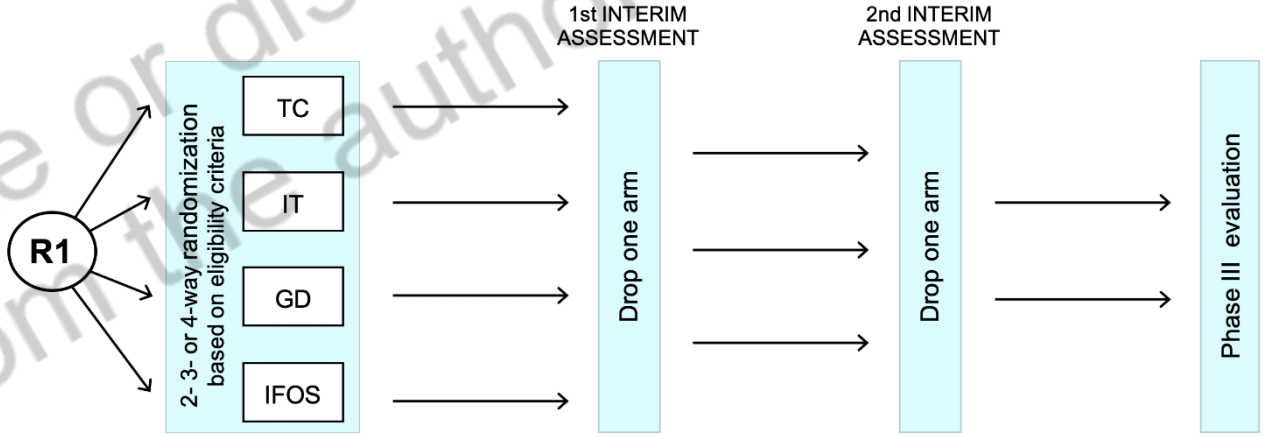
DESIGN

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

Bayesian design with interpretation based on posterior probabilities (with non-informative priors)

Independent Data Monitoring Committee makes recommendations

Independent Trial Steering Committee ratifies them



McCabe et al, ASCO 2019

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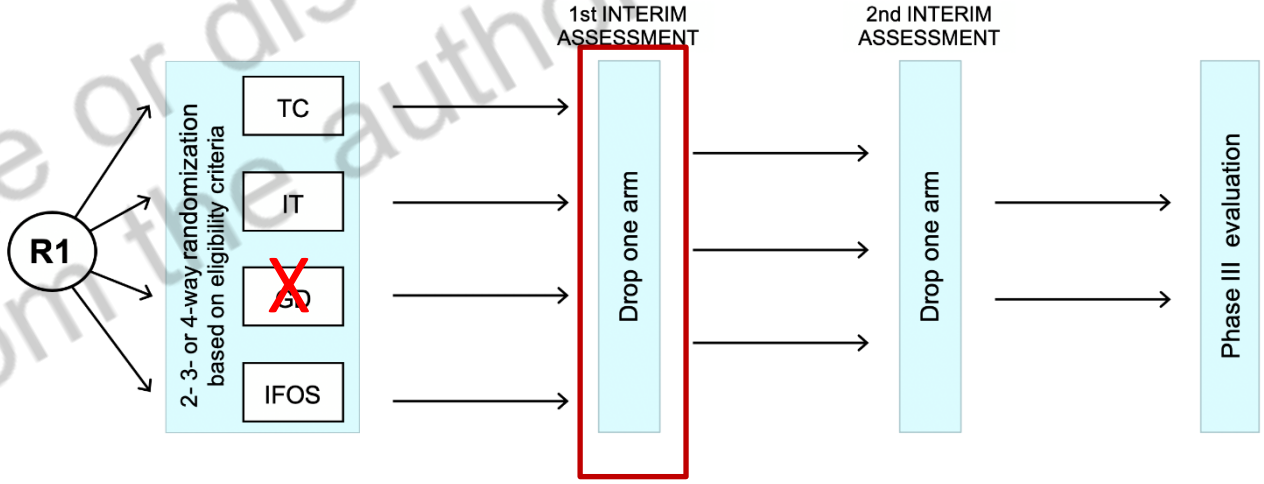

GD - dropped

McCabe et al, ASCO 2019

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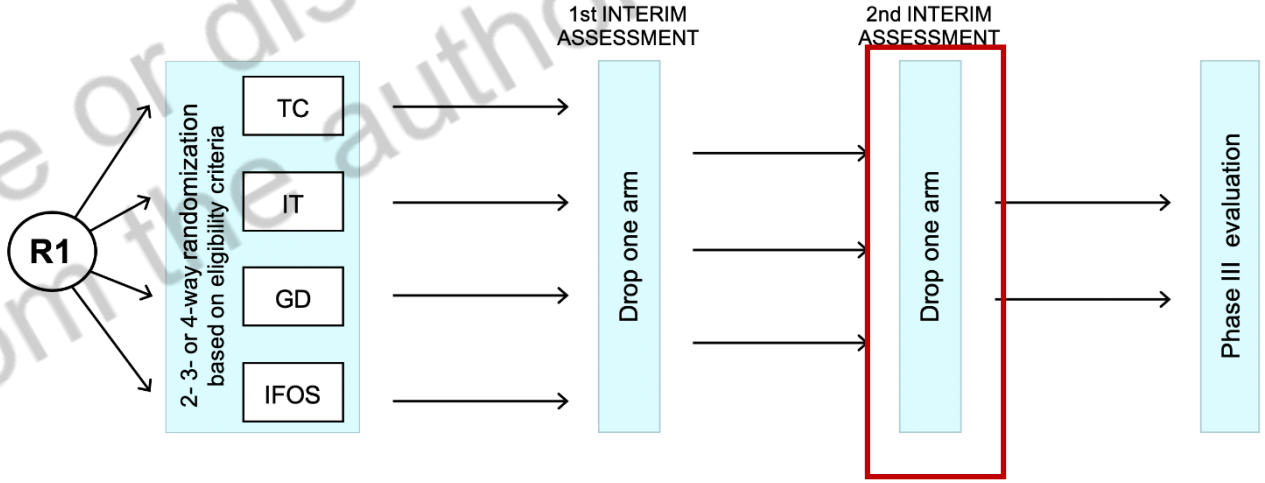
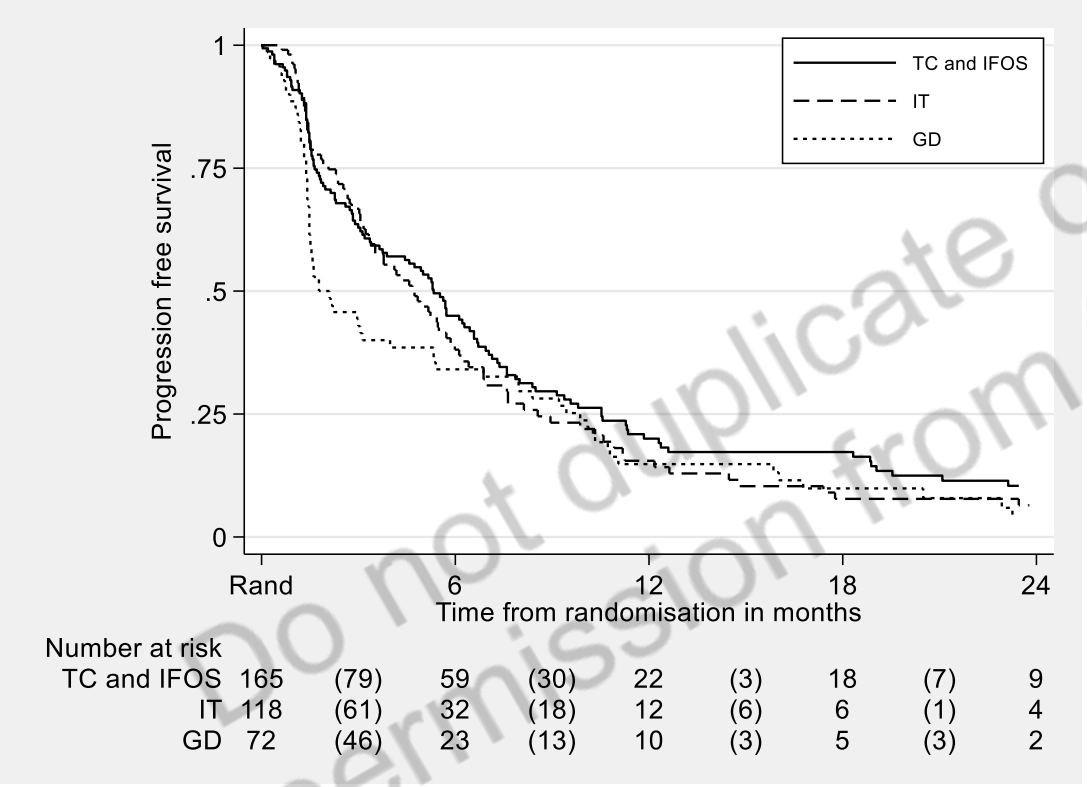


366 pt randomised

McCabe et al, ASCO 2020

Recurrent Ewing Sarcoma - rEECur

Outcomes: PFS by treatment group



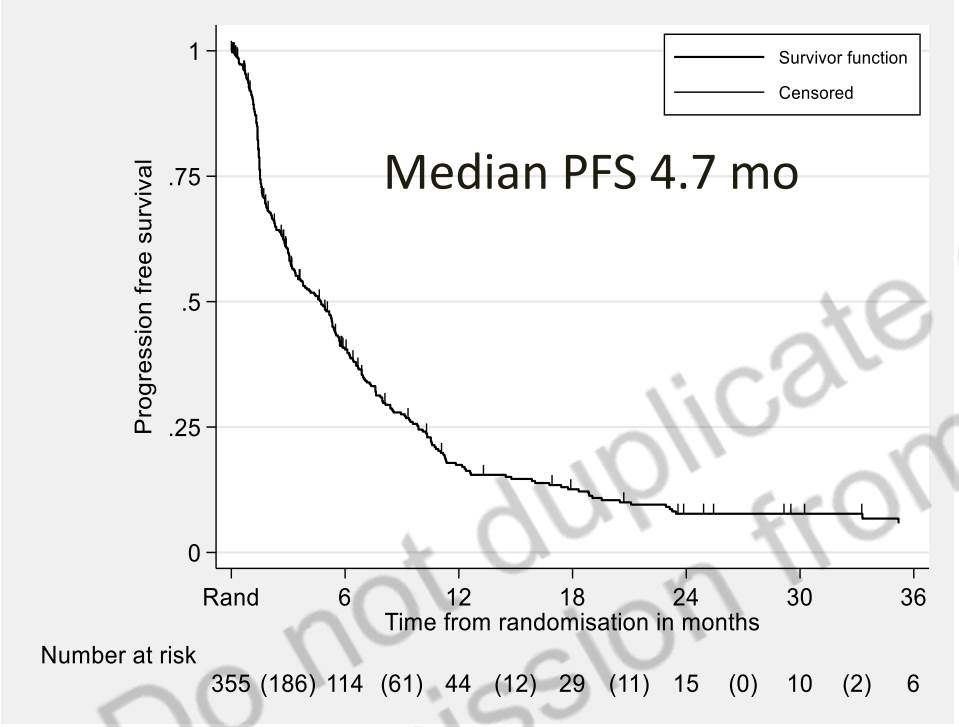
Progressions	GD	IT	TC or IFOS	Overall
No progression	8 (11%)	31 (26%)	45 (27%)	84 (24%)
Progression	64 (89%)	87 (74%)	120 (73%)	271 (76%)
Total	**72**	**118**	**165**	**355**

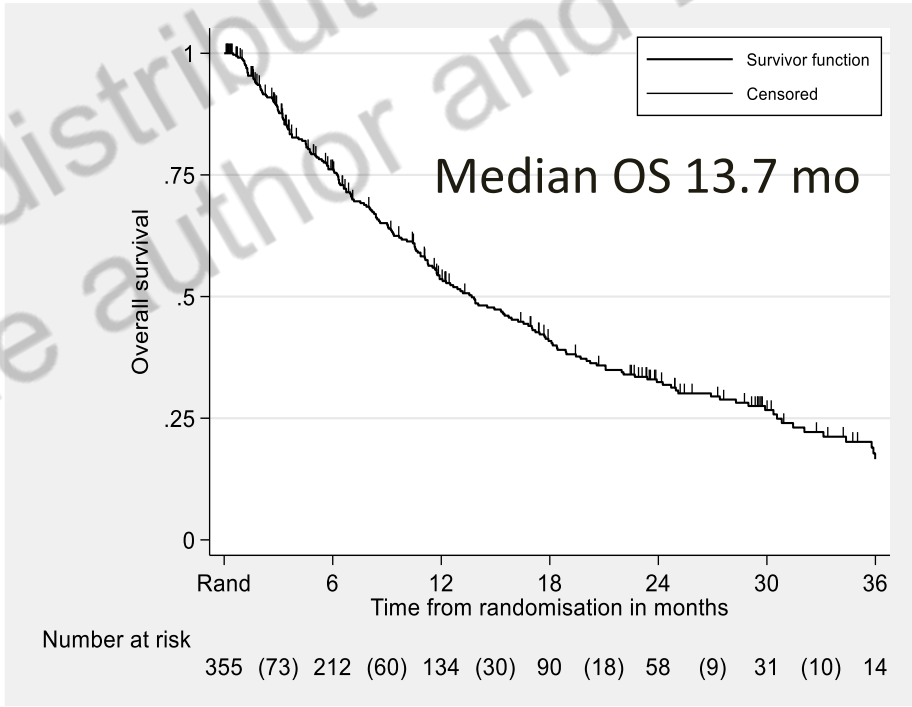
Pairwise comparisons	Progression-free survival Pr(true HR <1 | data)
IT vs 'Arm A'	7%
IT vs 'Arm B'	33%

The probability that PFS favours IT is low

Recurrent Ewing Sarcoma - rEECur

Outcomes: survival across all arms (Median follow up 24.2 months)



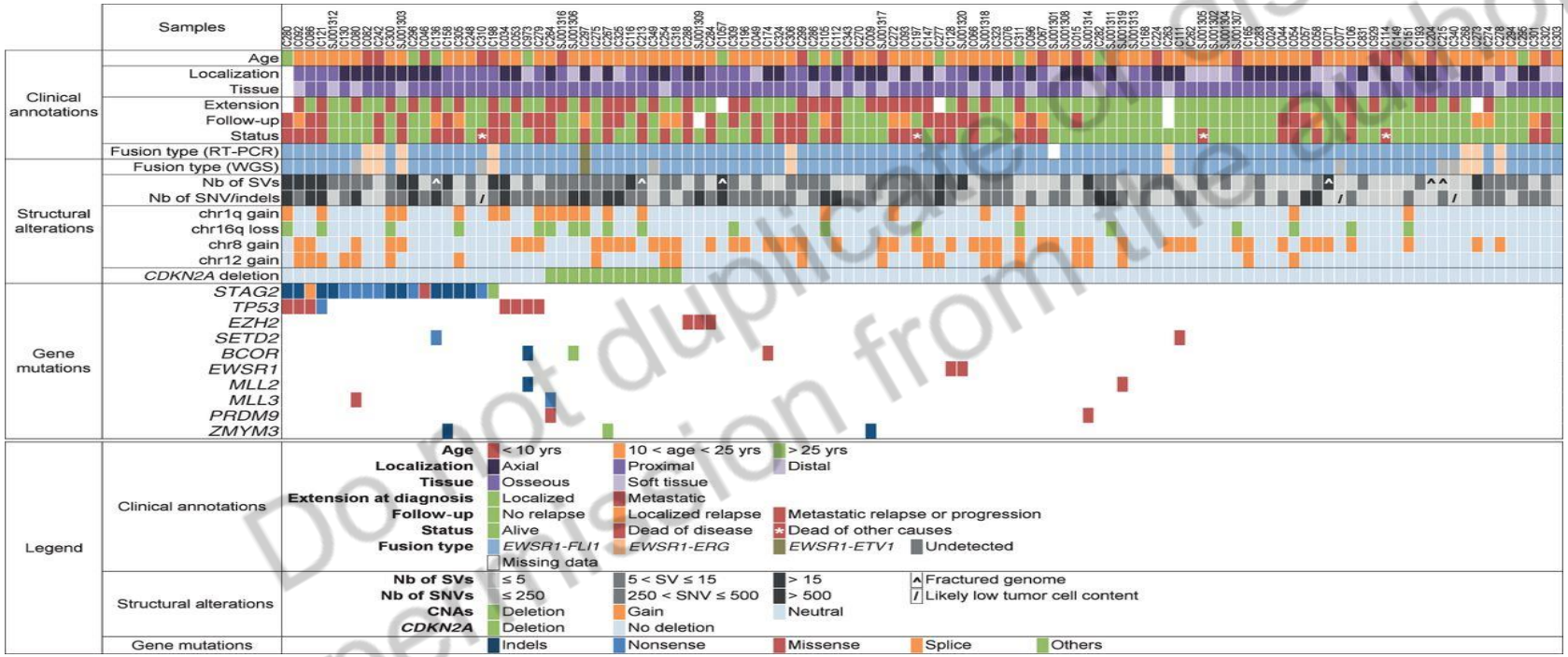


Discussion regarding adding additional arms – std chemotherapy, chemo + novel agents

Novel agents / targets for ES

Genomic Landscape of Ewing Sarcoma Defines an Aggressive Subtype with Co-Association of *STAG2* and *TP53* Mutations

Tirode, et al, Cancer discovery 2014



Low mutation burden

No role for checkpoint inhibitors in small studies

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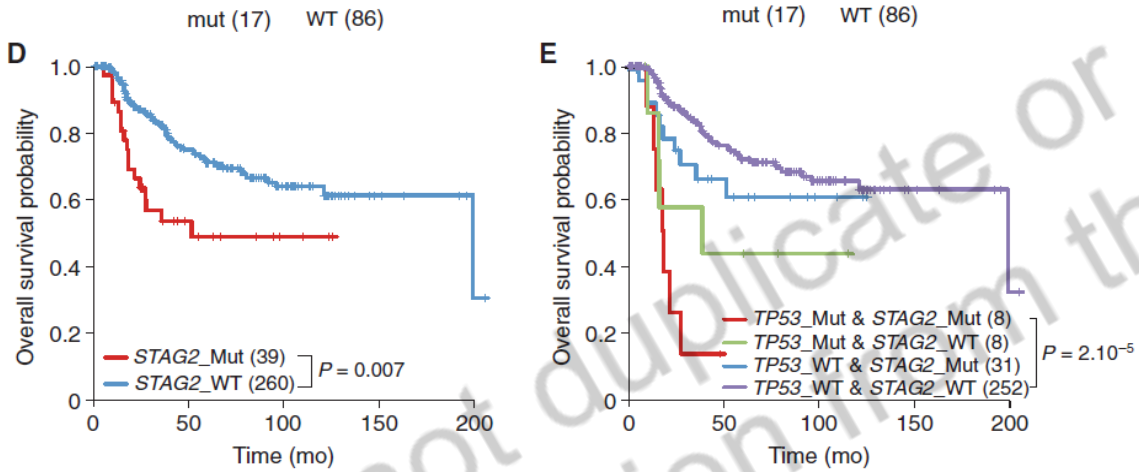


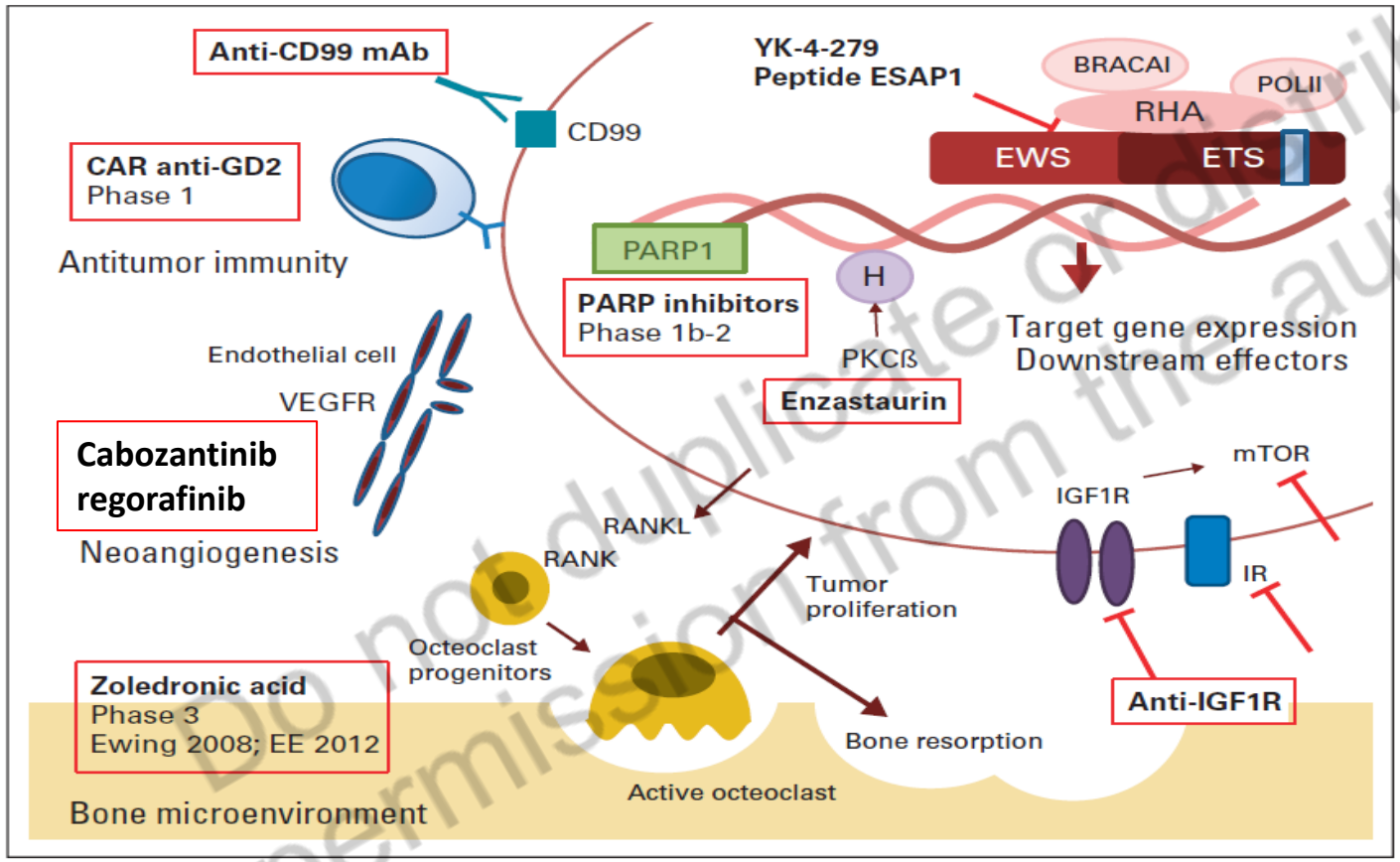
confer a poor prognosis but not currently druggable

Low mutation burden

STAG2 – one of 4 subunits of cohesin

→ cohesion of sister chromatids

Novel agents / targets for ES

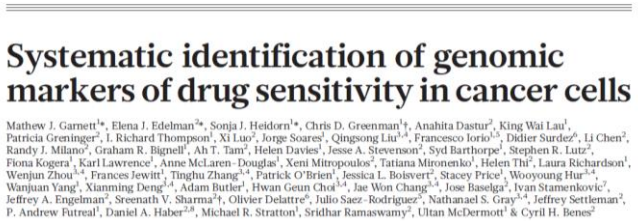


- PARP inhibitors
- TKIs
- Novel agent targeting the fusion protein, YK-4-279 / TK216

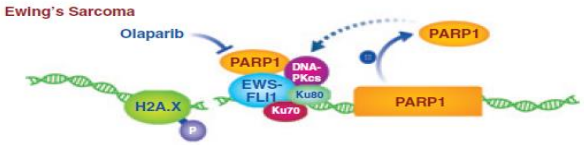
Gaspar, et al, JCO 2015

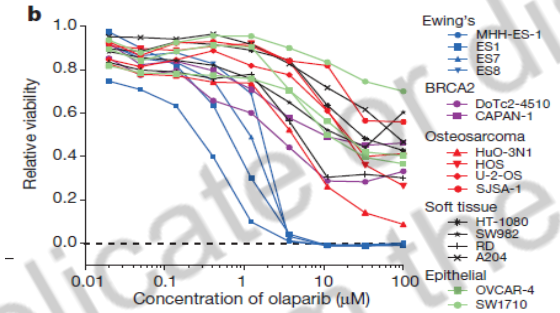
Novel targets: PARP inhibition (PARPi) and Ewing sarcoma (ES)

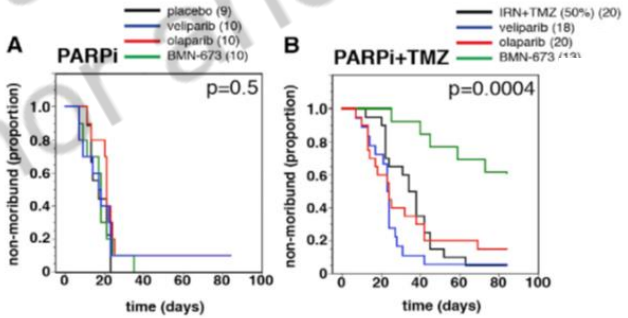
- 2012: PARPi identified as a potential therapeutic target in ES[1,2]


Systematic identification of genomic markers of drug sensitivity in cancer cells

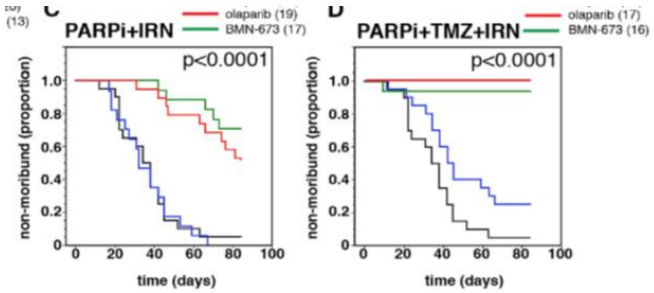
Mathew J. Garnett[1]*, Elena J. Edelman[2]*, Sonja J. Heidorn[1]*, Chris D. Greenman[1]†, Anahita Dastur[2], King Wai Lau[1], Patricia Greninger[2], I. Richard Thompson[1], Xi Luo[2], Jorge Soares[1], Qingsong Liu[3,4], Francesco Iorio[1,5], Didier Surdez[6], Li Chen[2], Randy J. Milano[2], Graham R. Bignell[1], Ah T. Tam[2], Helen Davies[1], Jesse A. Stevenson[2], Syd Barthorpe[1], Stephen R. Lutz[2], Fiona Kogera[1], Karl Lawrence[1], Anne McLaren-Douglas[1], Xeni Mitropoulos[2], Tatiana Mironenko[1], Helen Thi[2], Laura Richardson[1], Wenjun Zhou[3,4], Frances Jewitt[1], Tinghu Zhang[3,4], Patrick O'Brien[1], Jessica L. Boisvert[2], Stacey Price[1], Wooyoung Hur[3,4], Wanjuan Yang[1], Xianming Deng[3,4], Adam Butler[1], Hwan Geun Choi[3,4], Jae Won Chang[3,4], Jose Baselga[2], Ivan Stamenkovic[7], Jeffrey A. Engelman[2], Sreenath V. Sharma[2]†, Olivier Delattre[6], Julio Saez-Rodriguez[2], Nathanael S. Gray[3,4], Jeffrey Settleman[2], P. Andrew Futreal[1], Daniel A. Haber[2,8], Michael R. Stratton[1], Sridhar Ramaswamy[2], Ultan McDermott[1] & Cyril H. Benes[2]







PARP is a transcriptional regulator of EWS-FL1[2]



- Single agent activity in phase II study of olaparib in ES disappointing
- synergy in vitro and benefit of PARPi temozolomide and irinotecan in vivo[3]
- clinical trials undertaken to identify patient groups and PARPi combinations most likely to provide benefit

1. Garnett et al, Nature 2012 2. Brenner, et al. Cancer Research, 2012 3. Stewart et al. Cell Reports, 2014

Summary of PARP inhibitor – Temozolomide combination Studies

Study	Indication	RP2 PARP and dose / schedule	RP2 TMZ dose	DLT	Best response	Ongoing
Children's Oncology Group, Schaefer, et al [1]	Paediatric phase 1. >12 months ≤ 21 years	Talazoparib 600mcg/ m^2 bd D1; 600mcg/ m^2 od, D2-6	30mg/m^2 (D2-6)	**Neutropenia and thrombocytopenia**	Not Reported	Phase II Simon's 2-stage (10+10 in ES).
Dana-Faber Choy, et al[2]	ES Age ≥ 18 years N =14	Olaparib 200mg bd D 1-7	75mg/m^2 (D1-7)	**Neutropenia thrombocytopenia**	SD = 6 /14, (minor responses)	+ irinotecan
ESPRIT/ SARC025-Arm 1 Chugh, et al[3]	ES Age ≥ 13 years N=17	Niraparib 200mg od D 1-7	30mg/m^2 (D2-6)	**Thrombocytopenia Neutropenia**	SD, median PFS = 2.1 months	On hold for Arm 2

1. Schaefer, et al. Eu J Canc, 2016; 2. Choy, et al. *Proc CTOS* 2014 3. Chugh, et al. Cancer (in press)

Summary of PARP inhibitor – Irinotecan combination Studies

Study	Indication	RP2 PARP and dose / schedule	RP2 Irinotecan dose	DLT	ORR in ES	+ Tem
St Judes Frederico, et al[1]	Children and young adults, solid tumours	Talazoparib 1000mcg D1-6	40mg/m^2 D2-6	Neutropenia and thrombocytopenia, GGT, colitis	CR in ES, prolonged SD	3 / 6 PR (but dose-limiting)
ITCC, ESMART study, Arm D	Solid tumours Age < 18 years (DSB repair deficiency)	Olaparib	Not reported			
SARC025-Arm 2 Chugh,, et al	ES Age ≥ 13 years	Niraparib 100mg	20mg/m2 D2-6	GI, GGT colitis	PR, prolonged SD (median PFS = 3.8 months)	ongoing

- **Cytotoxic combinations associated with significant toxicity that limit the dose**
- Do they offer any greater efficacy then std cytotoxic therapy?
- Are there any predictive biomarkers?
- Are there other rationale combinations that may be better tolerated: eg: ATR and PARP

ITCC = Innovative Therapies for Children's Cancer;
ESMART study –European proof of concept therapeutic stratification trial of Molecular abnormalities

1. Frederico, et al, ASCO 2017 2. Chugh, et al, Cancer (in press)

Other targeted therapy with efficacy - TKI studies in ES

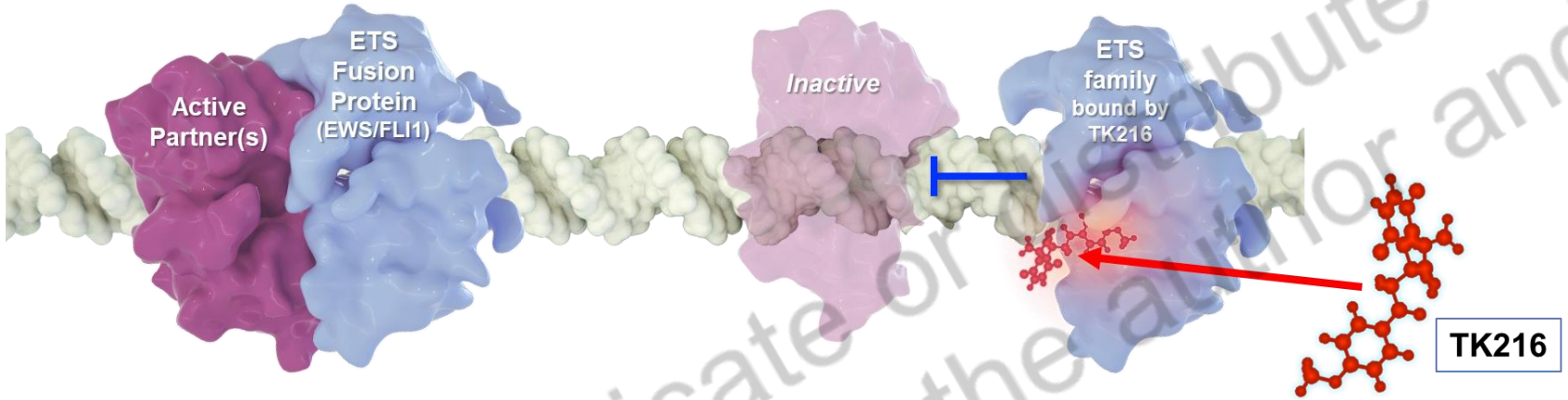
	REGOBONE[1]	SARC024[2]	CABONE[3]
No. pts	46 (23 RG)	30	39
Age inclusion	≥ 10 years	> 18 years	≥ 12 years
Median Age (range)	RG: 32 (18-59) PL: 28 (16-59)	32 (19-65)	33 (16 –53)
Prior therapies Med (range)	1 (17, 37%) 2 (19; 63%)	5 (1-10)	2; > 2 (17 pt (38%)
DCR at 8 weeks	13 / 23 = 54%	18 / 30 = 60%	Not reported
Median PFS	**11.4 wks (Switch 12.9); PL 3.9 wks**	**3.6 mths / (15 wks)**	**4.4 mths**

Engagement with Pharma to combine with chemotherapy in recurrent disease

Could consider as maintenance therapy

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

TK216: A Targeted Inhibitor of ES Fusion Protein



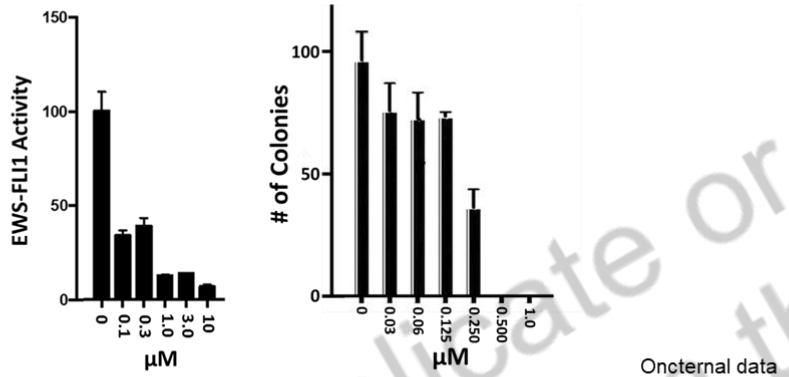
- TK216 is the first clinical candidate targeting the oncogenic ES fusion protein
- Blocks binding of EWS-FLI1 and RNA helicase A which is required to activate the TF
- disrupts transcriptome formation mediating:
  - Decreased oncogene and increased tumor suppressor transcription
  - Decreased tumor growth and apoptotic cell death

ES = Ewing sarcoma
ETS = E26 Transformation-Specific oncogene family

Ludwig, et al, EMSO 2020

Preclinical Activity of ETS inhibitors

TK216 Inhibits Oncogenic Transcription and Cell Proliferation



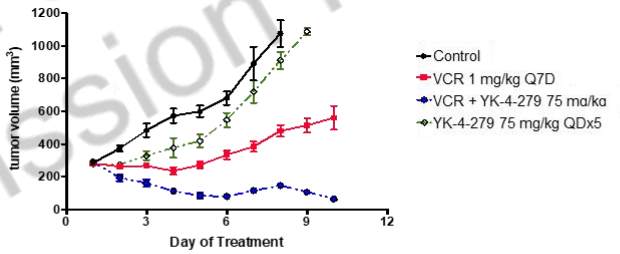
Oncternal data

TK216 Analogue YK-4-279 is Synergistic with Vincristine

In Vitro

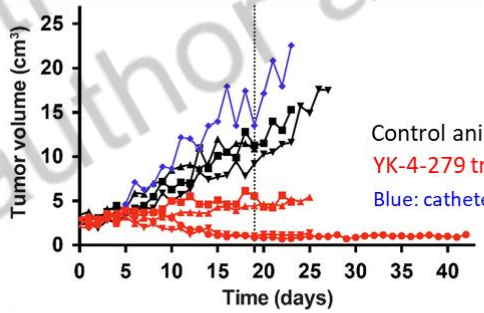
- ↑ G2-M arrest
- ↑ cyclin B1
- ↓ microtubule-associated proteins
- ↑ microtubule depolymerization
- Enhanced apoptosis

In Vivo (A4573 xenograft)

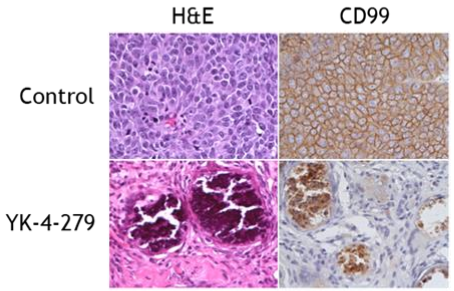


Zollner *et al*, 2017 Science Signaling

TK216 Analogue YK-4-279 Inhibited ES Tumor Growth, Induced Apoptotic Death



Control animals: Black
YK-4-279 treated: Red
Blue: catheter malfunction



Hong *et al*., 2014 Oncotarget

Preclinical data strongly suggested that prolonged continuous infusion provided optimal antitumor activity

TK216 – Safety and Efficacy

N = 52

Age: median 29 (11-77)

Lines of Prior Systemic Therapy:

Median 3 (1-11)

Phase 1: DLT - neutropenia

- RP2D for 14-day infusion: 200 mg/m2/day, vincristine (VCR) allowed starting in cycle 3

Phase 2: dose demonstrated early evidence of activity. (n= 35)

- Well-tolerated and manageable safety profile -transient marrow suppression
- **2 CRs** (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,
- **1 unconfirmed PR , 11 SD**
- **Disease control rate (CR+PR+SD) = 14 /35 (40%) PFS = 1.9 months**

Ludwig, et al, ASCO 2021

Conclusions and future studies

- ES rare malignancy
- Treatment is individualised and requires expert multi-disciplinary team
- VDC/IE is standard of care for patients ≤ 50 years
- Improvement in outcome only through collaboration
- How to we add novel agents to intense chemotherapy in 1st line and relapsed setting?
- How do we determine patients most likely to benefit