

# The Molecular Basis of the Ewing's Sarcoma Family of Tumours

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# Risk-based management individualises care

Improved outcome  
and quality of life

## Molecular Tumour Markers

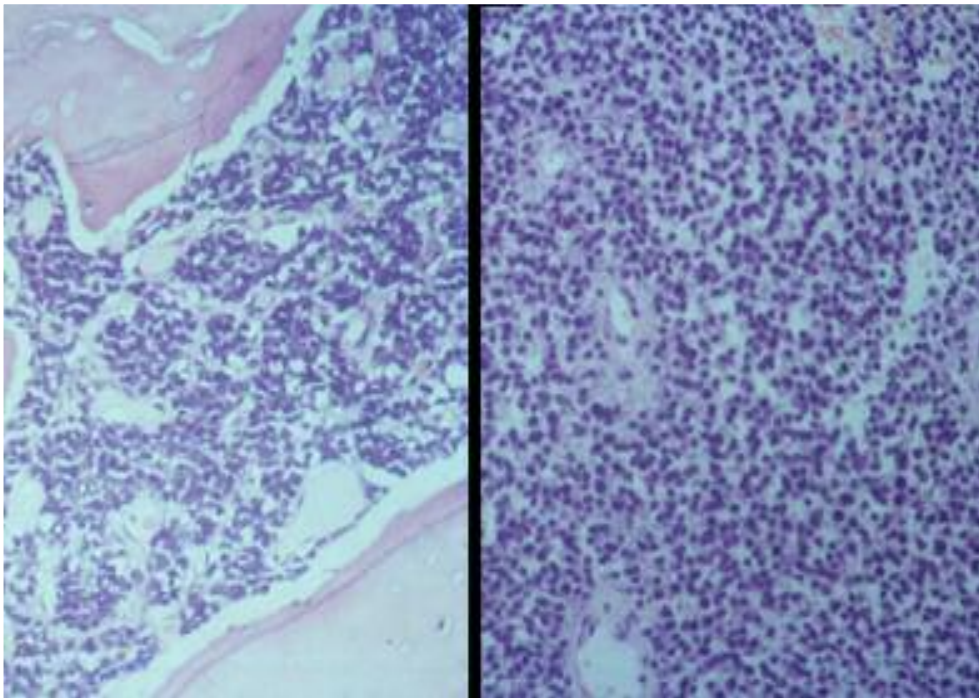
Diagnosis

Prognosis

Monitoring

Treatment

# Ewing's sarcoma family of tumours (ESFT)



Histology

Site of tumour

Age at diagnosis

Immunohistochemistry

Cytogenetics



**EWS gene  
(22q12)**

**ETS gene**

**Frequency**

FLI1 (11q24)

85-90%

ERG (21q22.2)

5-10%

ETV1 (7p22)

< 1%

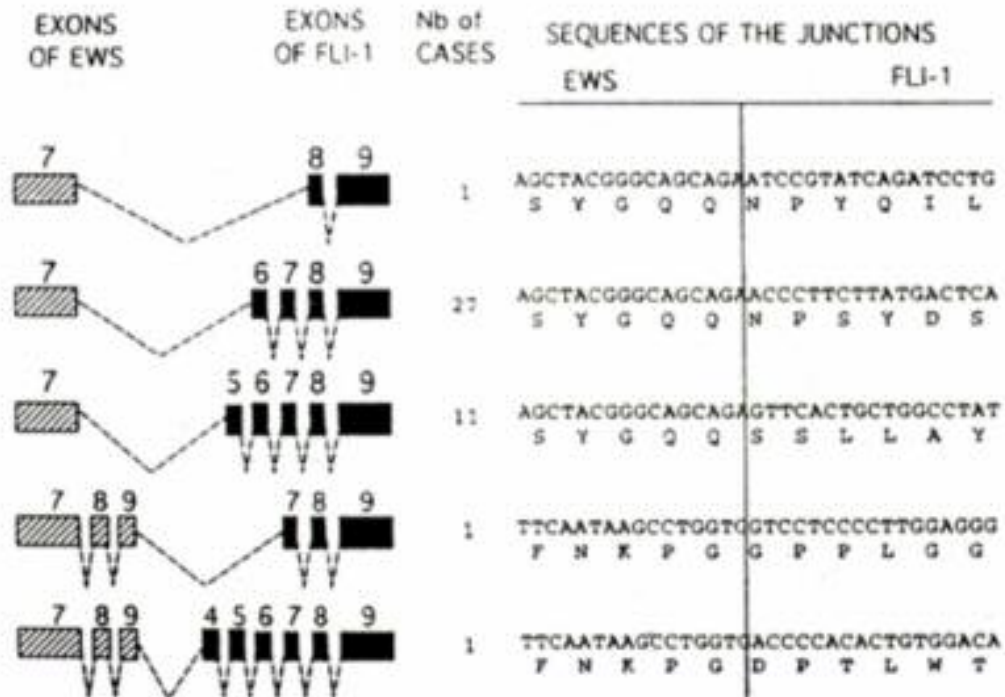
E1AF (17q12)

< 1%

**Diagnosis**



# Different fusion products

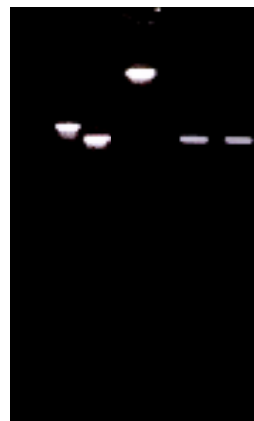


## EWS-ETS RT-PCR

W 1 2 3 4 5  
Tumours PB

EWS-ERG →  
EWS-FLI1 type 2 → RT+  
EWS-FLI1 type 1 →

RT -



# Prognostic significance ?

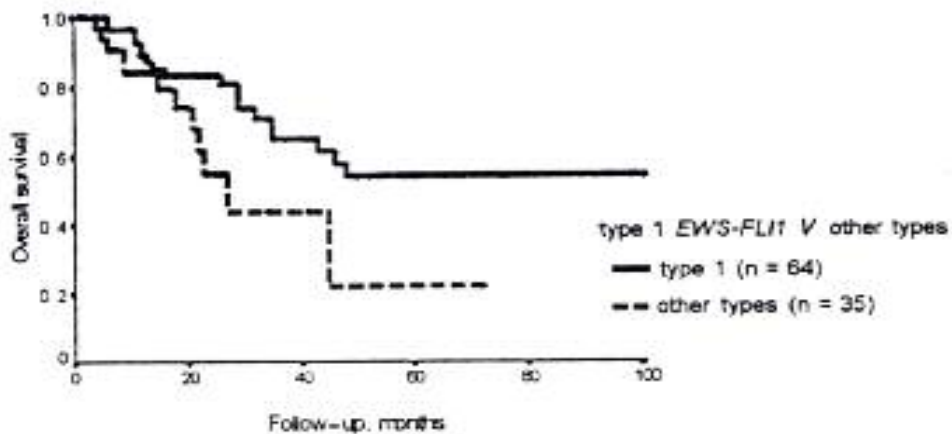


Fig 2. Kaplan-Meier survival plots for all patients regardless of stage with tumors that contain type 1 *EWS-FLI1* fusions versus all other types (multivariate  $P = .014$ ).

EWS-FLI1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. de Alava et al. *J Clin Oncol.* 16:1248-55.1998.

Does expression of different EWS chimeric transcripts define clinically distinct risk groups of Ewing tumor patients? Zoubek et al. *J Clin Oncol.* 14:1245-51.1996.

**EuroE.W.I.N.G. 99**

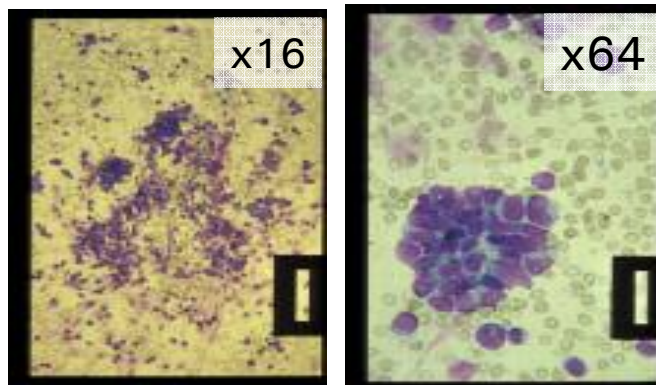
# Metastatic disease is a poor prognostic indicator

Localised disease	70% 5 year survival
Pulmonary metastases	40% 5 year survival
Bone/BM Metastases	<20% 5 year survival

Improved methods for detection

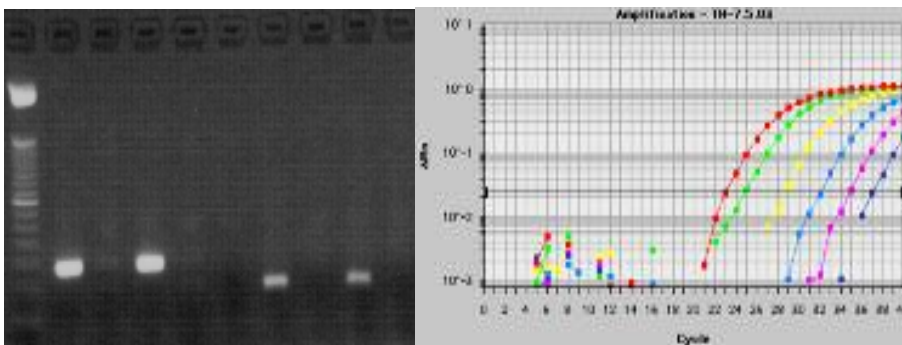
Therapies targeting metastases

# Detect metastatic disease



Cytology

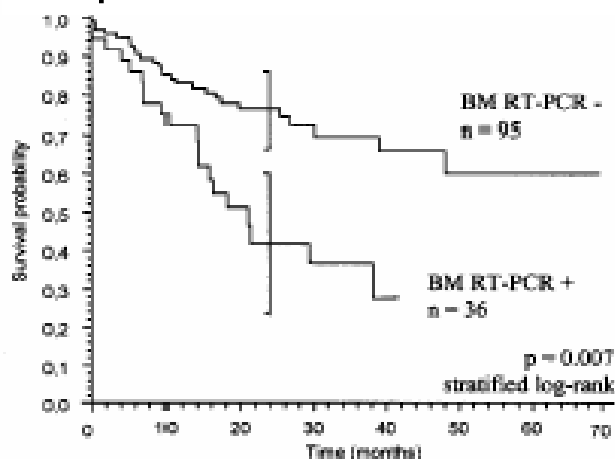
1 tumour cell in  $1 \times 10^2$  normal cells



Reverse transcriptase polymerase chain reaction (RT-PCR).

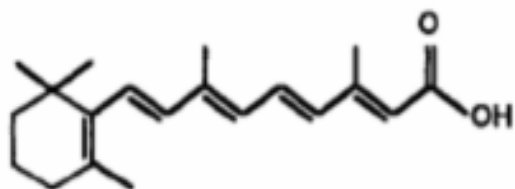
1 tumour cell in  $1 \times 10^6$  normal cells

All patients - disease free survival



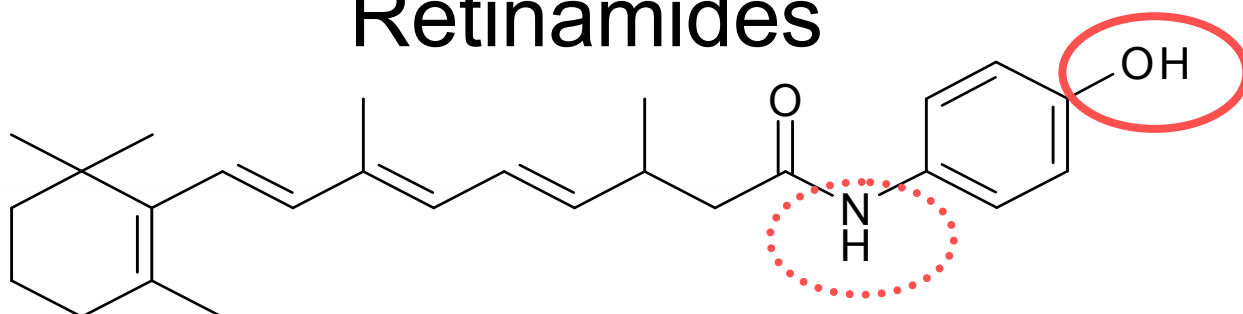
Increased risk of systemic relapses associated with bone marrow micrometastasis and circulating tumour cells in localized Ewing tumour  
Schleiermacher et al. J Clin Oncol. 21:85-91. 2003.

all-trans retinoic acid



~~Retinoids~~

Retinamides



Fenretinide

4-hydroxy(phenyl)retinamide

- Induce death in a number of cancers
- Well tolerated (phase 1 in adult and children): reversible night blindness and dry skin
- Decreases tumour growth in preclinical models of ESFT at plasma concentrations that are achieved in patients

# Fenretinide

## Phase 2 study

- i) Pharmacokinetics of Fenretinide
- ii) Tolerability and compliance with this dose
- iii) Assess response of recurrent ESFT lesions
- iv) Assess biological markers of response

*Dr's Ian Lewis and Andy Proctor*

*CCLG Therapeutics Group  
CR-UK Drug Development Office*

# Molecular Tumour Markers in ESFT

Diagnosis	😊
Prognosis	😐
Monitoring	😐
Treatment	😞

