

UCL Cancer Institute



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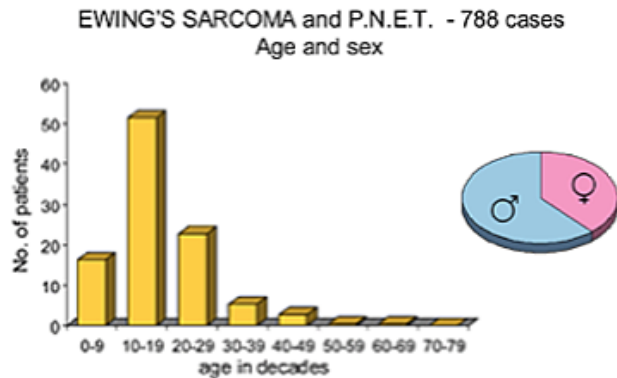
ErbB4 is a novel driver of metastasis and chemoresistance in Ewing sarcoma

Ariadna Mendoza

Childhood Cancer 2012

Ewing sarcoma

Ewing sarcoma (ES) is the second most common type of bone tumour in children and adolescents



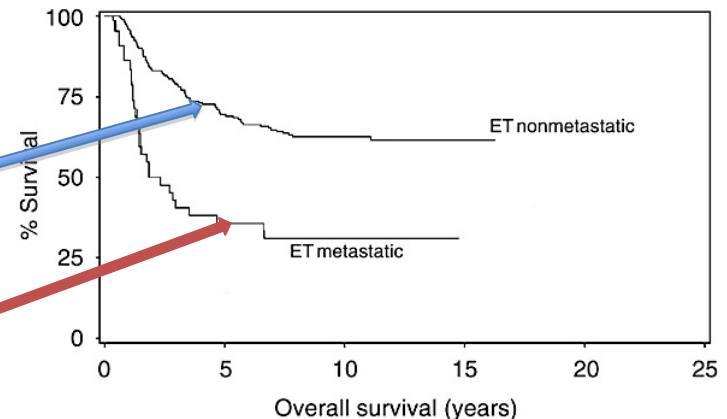
It can occur anywhere in the body, but it is most frequently found in the long bones of lower limb, as well as pelvis. Lungs, bones and bone marrow are the most common metastasis locations.



Clinical outcome

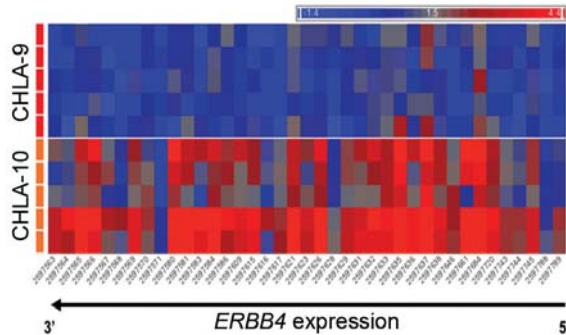
- The 5 year survival for patients with localized disease is ~ 70%
- Prognosis for patients with metastatic disease is poor, with less than 30% surviving 5 years after diagnosis

Kaplan–Meier estimates of survival of ES patients by presence of metastases at diagnosis

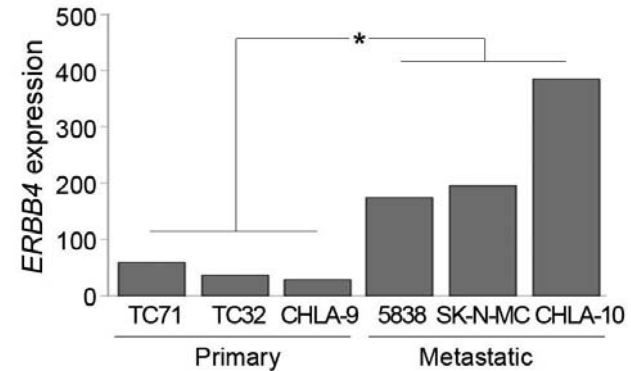


Weston *et al.*, 2004

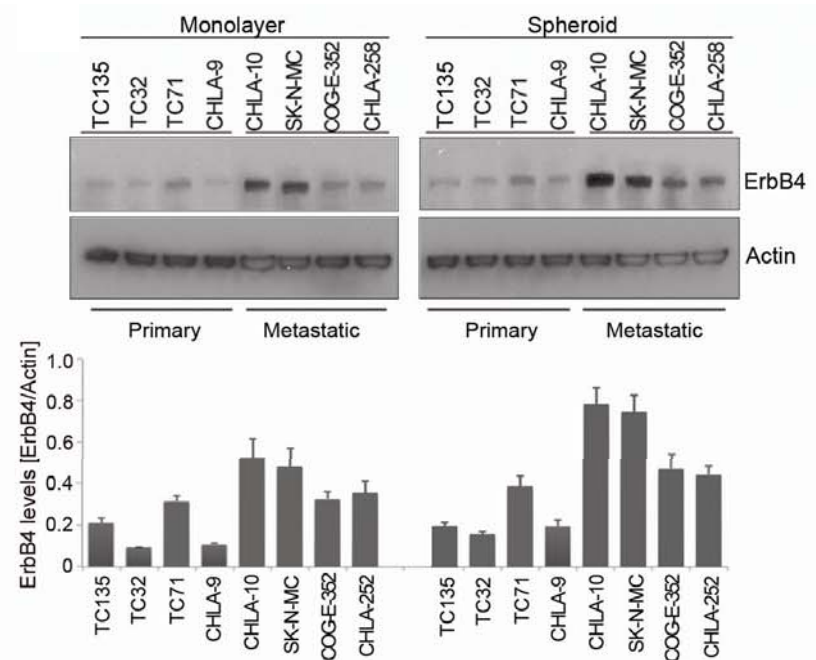
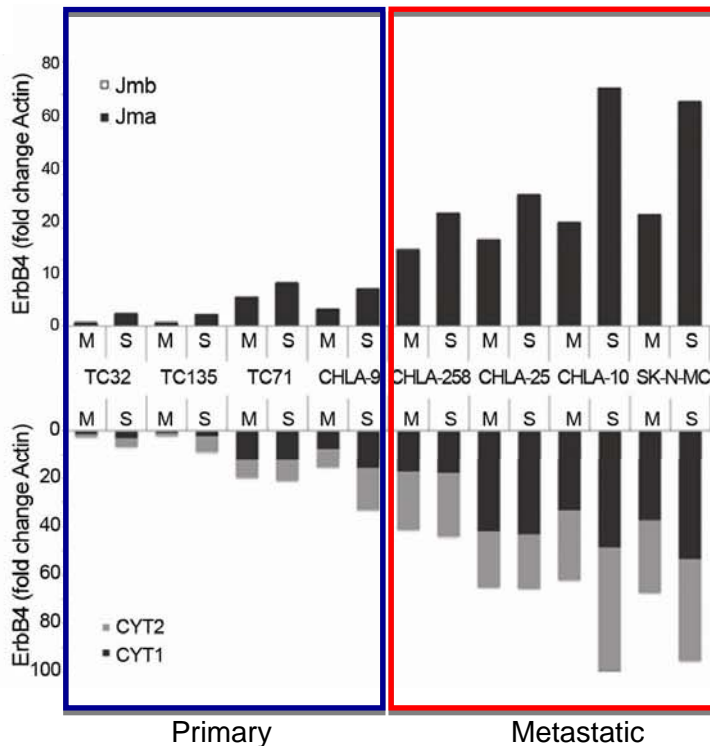
Increased ErbB4 expression in metastatic vs. primary ES cell lines



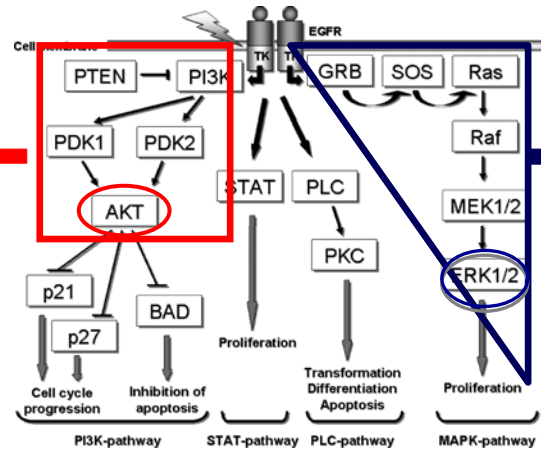
Matched pairs tumour cell lines: The **primary CHLA-9** cell line was established at diagnosis, and the **metastatic/chemoresistant CHLA-10**, from the same **patient**, was established after four cycles of induction chemotherapy: etoposide/doxorubicin/cyclophosphamide/cisplatin)



Daniel Wai, Children's Hospital, LA

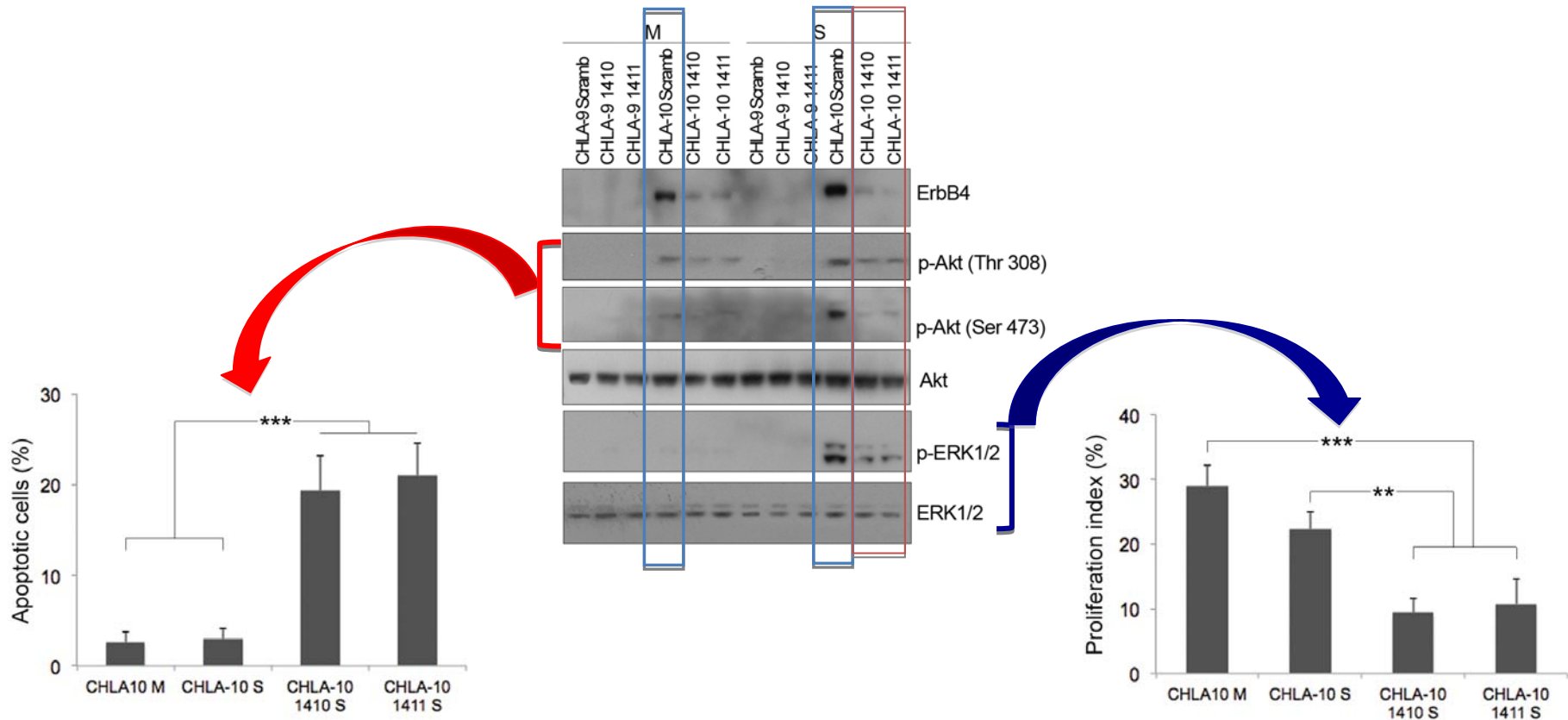


ErbB4 regulates Akt and ERK1/2 activation, and cell survival and proliferation in metastatic ES

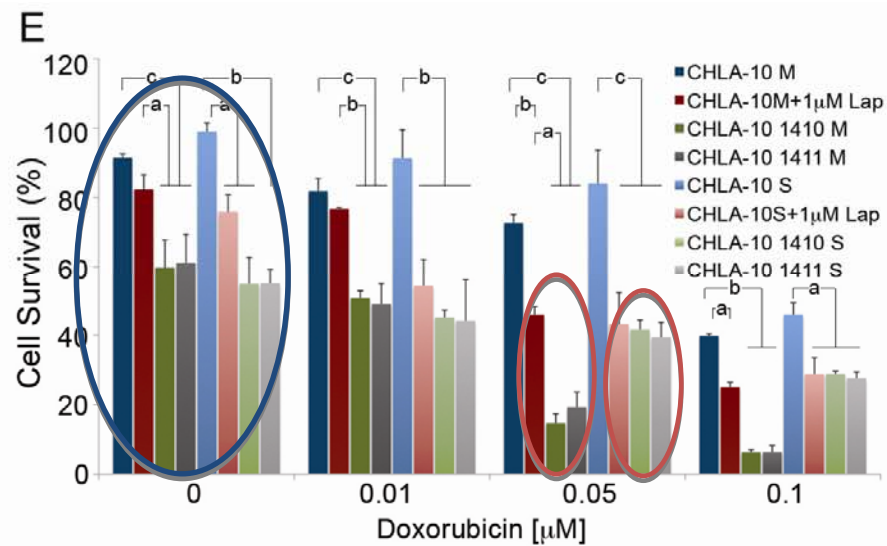
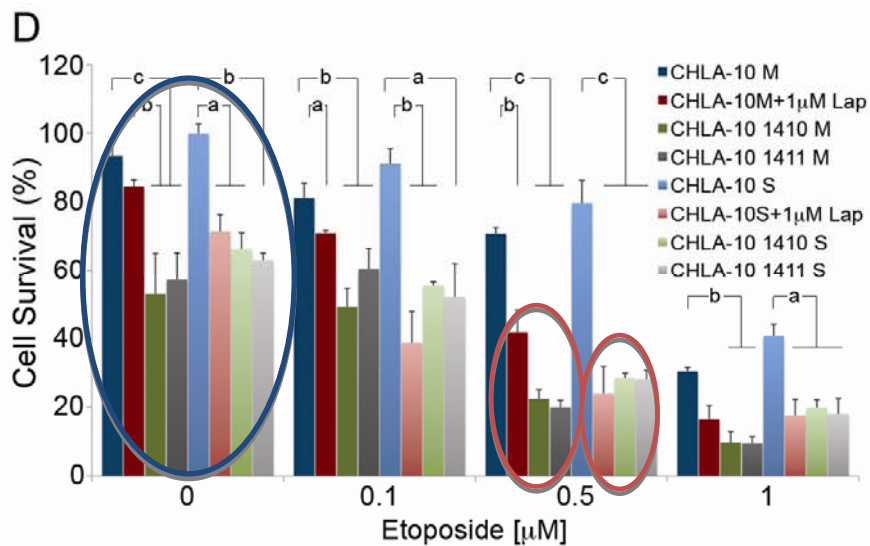


Tumour **survival**,
among other functions

Tumour **proliferation**,
among other functions



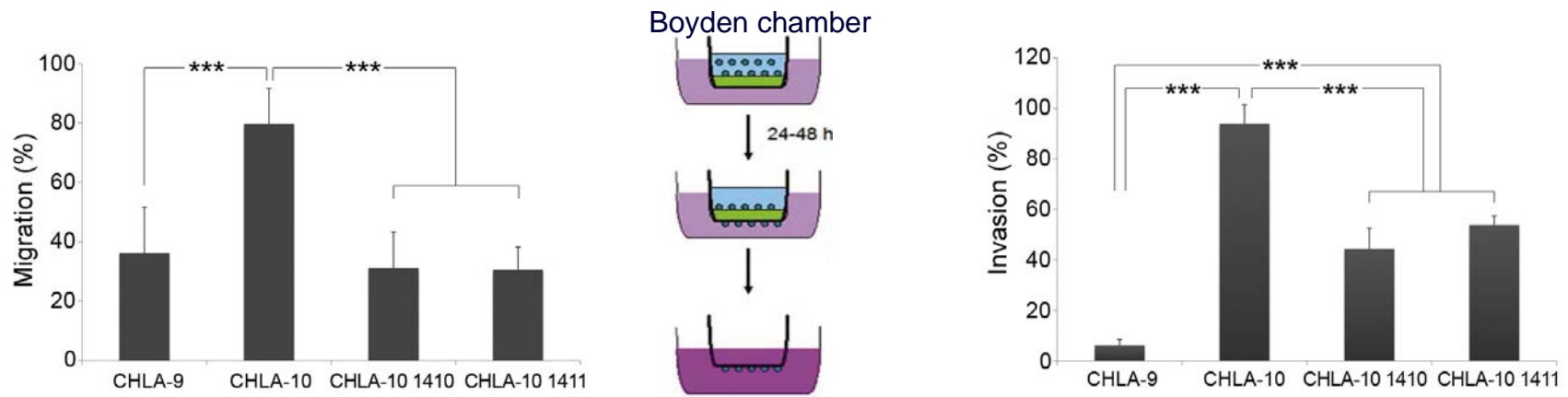
Silencing of ErbB4 or treatment with Lapatinib sensitize metastatic/chemoresistant ES cells to chemotherapeutic drugs



a: $p < 0.05$
b: $p < 0.01$
c: $p < 0.005$

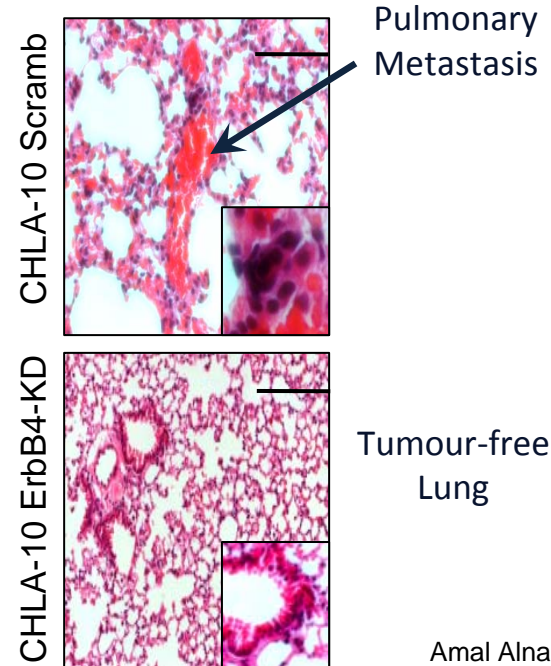
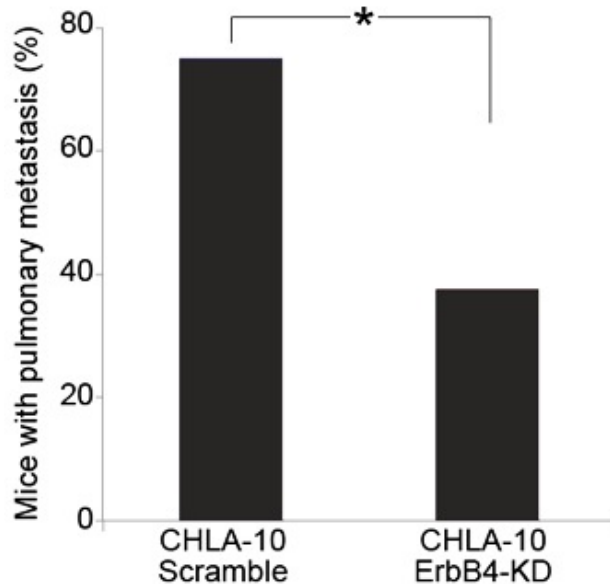
Cell survival was analyzed in ErbB4-KD, or in cells incubated with Lapatinib (FDA-approved pan-ErbB pharmacologic inhibitor), alone or in combination with Etoposide or Doxorubicin, in both monolayer and spheroid cultures

ErbB4 silencing impairs migration and invasion in metastatic ES cells

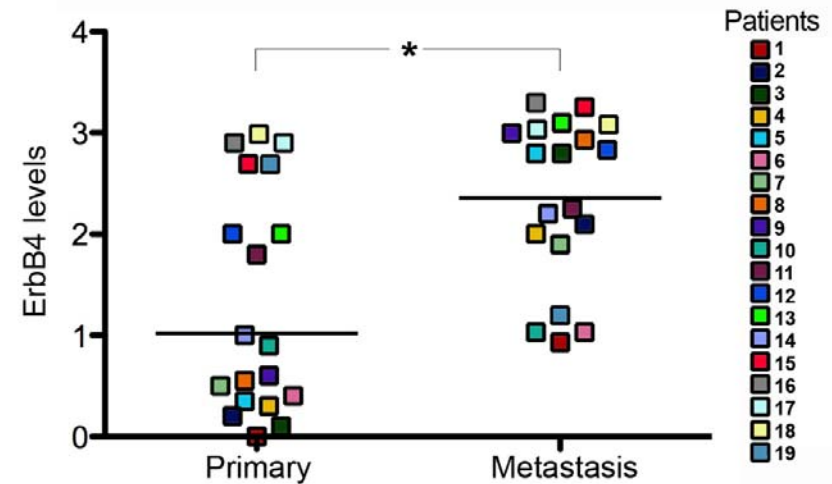
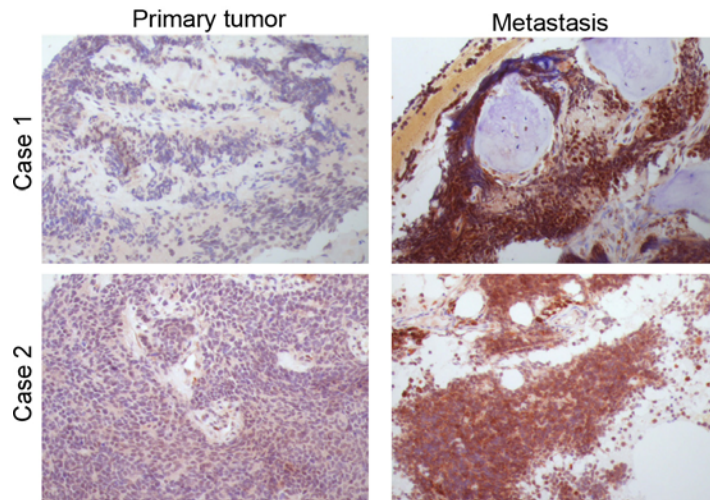


Knockdown of ErbB4 in metastatic ES cells significantly reduced metastasis formation *in vivo*

Renal Subcapsular mouse model

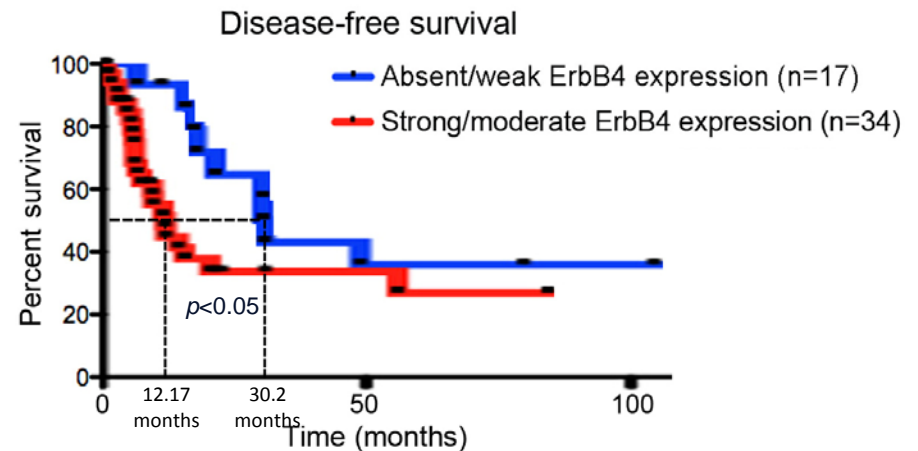
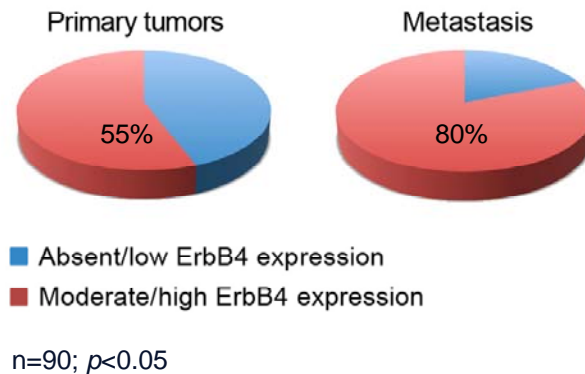


Clinical relevance: ErbB4 expression is higher in metastatic tumour samples and correlates with disease progression in Ewing sarcoma



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Percentage of ErbB4 expression in EFT patients



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Increased ErbB4 expression in metastatic lesion vs. primary tumours from patients

ErbB4 silencing reduces metastasis formation *in vivo*

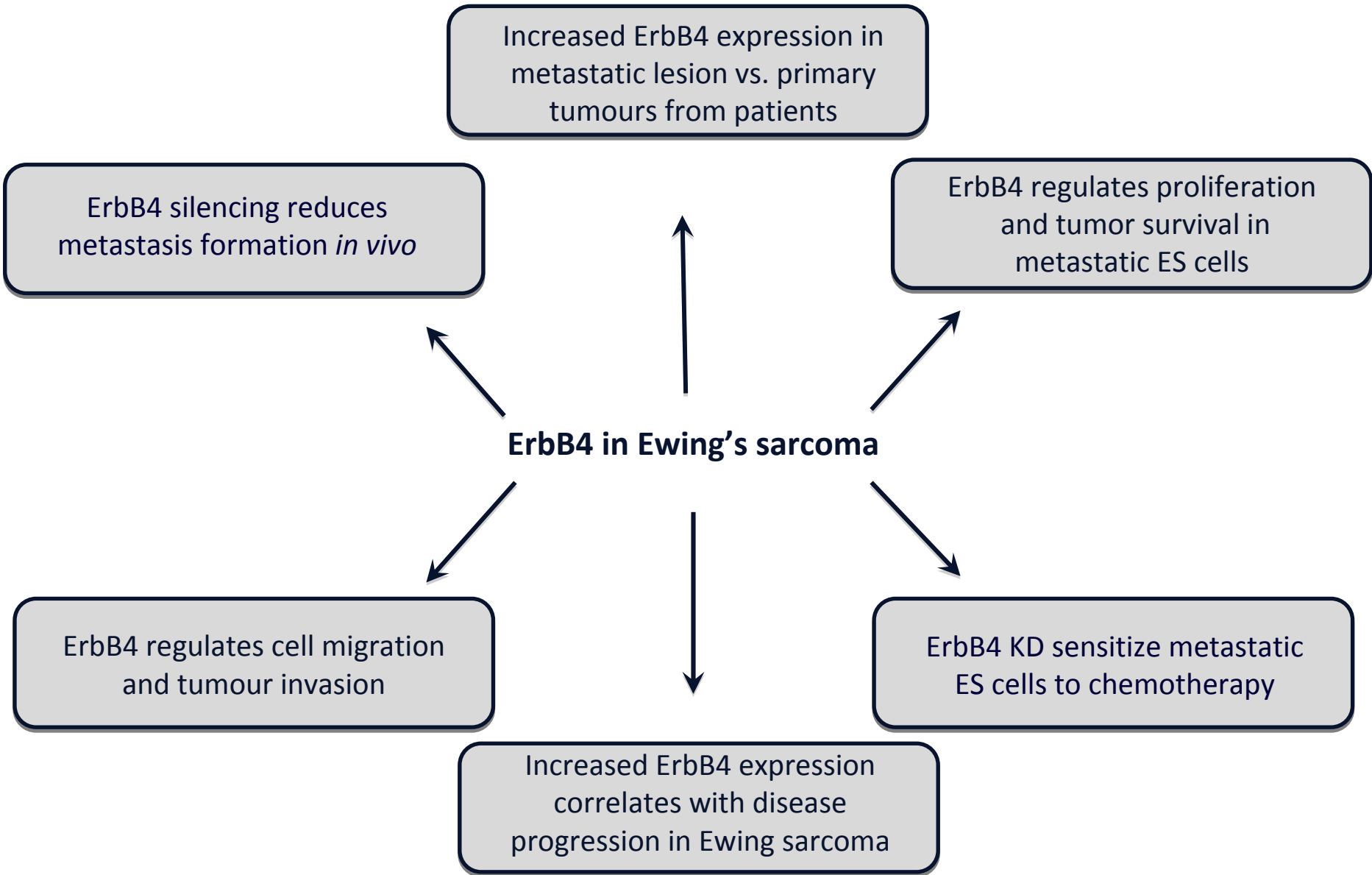
ErbB4 regulates proliferation and tumor survival in metastatic ES cells

ErbB4 in Ewing's sarcoma

ErbB4 regulates cell migration and tumour invasion

ErbB4 KD sensitize metastatic ES cells to chemotherapy

Increased ErbB4 expression correlates with disease progression in Ewing sarcoma



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