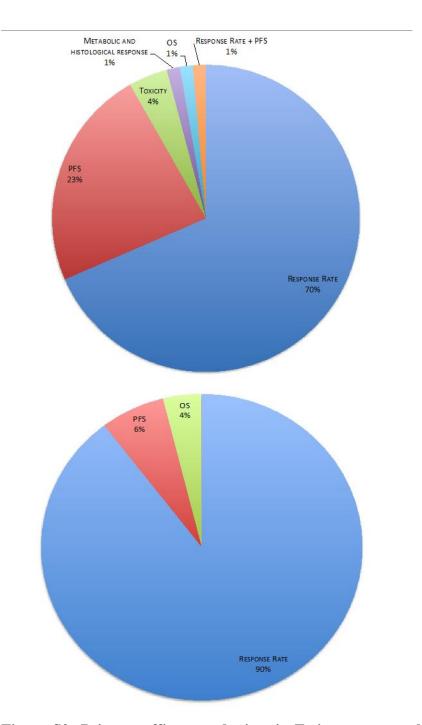
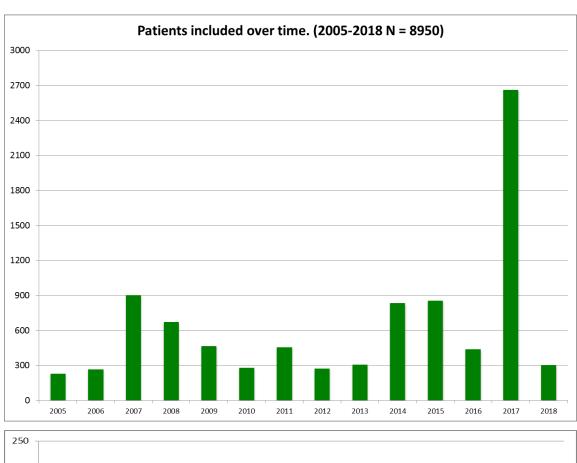
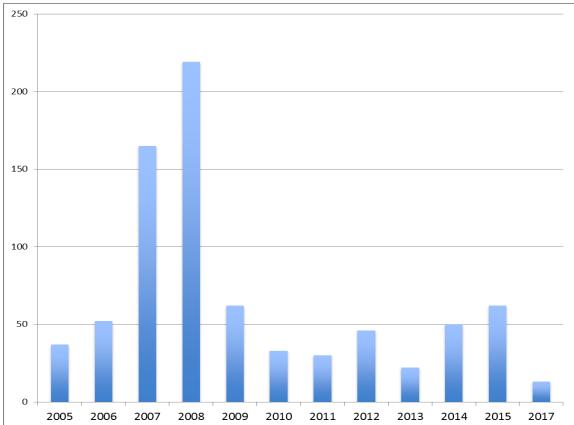


<u>Figure S1:</u> Multi arm randomized phase–II trial design in Ewing sarcoma between 2005-2018 (7 trials). CT: Chemotherapy. VTC: Vincristine, Topotecan, Cyclophosphamide. TEMIRI: Temozolomide + Irinotecan. MAMS: Multi-Arm Multi-Stage.



<u>Figure S2:</u> Primary efficacy endpoints in Ewing sarcoma phase-II trials between 2005 and 2018 (A) In the 67 phase-II and 2 phase-II-III trials and (B) In the phase-II part of the 77 phase-I/II trials.





<u>Figure S3:</u> Patients accrued in Ewing Sarcoma Phase-II trials over time between 2005 and 2018, classified by the year of trial opening. A. In the 146 trials B. ES patients accrued in the 62 published early-phase trials.

Graphical conclusion

Better understanding ES biology/ preclinical model

International trials

1st relapse Multiple relapses Phase-II trial Phase-I/II trial Phase-II trial Children/Adult Adolescent/Adult Adolescent/ Adult Mesurable/evaluable disease, Mesurable/evaluable disease, Mesurable/evaluable disease and MRD and MRD Randomised Randomised Single arm CT vs CT + new TTT New TTT Single / combo New TTT vs (placebo or CT or combo) +/- cross over CT vs combination Basket-trial with Stratified analysis bulky Stratified analysis bulky « sarcomas » and/or disease /MRD disease /MRD « adolescents » cohorts Improve survival Proof of efficacy Tolerance Composite criterion: Composite criterion: First signals of efficacy PFS and RR PFS and RR RR

<u>Figure S4:</u> Graphical conclusion and proposals for future phase-I/II trials enrolling ES recurrent or refractory patients. CT: Chemotherapy, MRD: minimal residual disease, TTT: treatment, Combo: combination.