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Adverse side effects of cancer agents are of great concern in the context of childhood tumors where they can reduce the quality of life in young patients and cause life-long adverse effects. Synergistic drug combinations can lessen potential toxic side effects through lower dosing and simultaneously help to overcome drug resistance. Neuroblastoma is the most common cancer in infancy and extremely heterogeneous in clinical presentation and features. Applying a systematic pairwise drug combination screen we observed a highly potent synergy in neuroblastoma cells between the EGFR kinase inhibitor lapatinib and the anticancer compound YM155 that is preserved across several neuroblastoma variants. Mechanistically, the synergy was based on a lapatinib induced inhibition of the multidrug-resistance efflux transporter ABCB1, which is frequently expressed in resistant neuroblastoma cells, which allowed prolonged and elevated cytotoxicity of YM155. In addition, the drug combination (i.e. lapatinib plus YM155) decreased neuroblastoma tumor size in an in vivo model.

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