

Table 2: Prioritised targets, agents and ongoing/planned clinical trials

Target	Priority for neuroblastoma	Drugs
ALK	High	Crizotinib paediatric Phase I COG completed, Phase II in neuroblastoma ongoing. Ceritinib (LDK378) and entrectinib paediatric Phase I ongoing. Lorlatinib has been activated for IRB approval Combination studies and third generation inhibitor trials under discussion.
MEK	High	Ongoing paediatric trials with selumetinib (Phase II), cobimetinib (Phase I) and trametinib (Phase I).
CDK4/6	High	Ribociclib (LEE011)(CDK4/6 inhibitor) paediatric Phase I recently completed internationally. Abemaciclib (LY2835219) and palbociclib ongoing.
MDM2	High	Nutlin derivatives (RG7112/RG7338) in adult Phase I/II trials.
BET/BARD4	High	Adult Phase I trials of GSK525762 and OTX015 ongoing.
AURKA	High	Alisertib paediatric Phase I (COG) completed, alisertib combined with irinotecan and temozolomide (NANT) and Phase II completed. AT9283 Phase I (CCLG) in solid tumours completed. Neither compound is ideal structurally, further studies await new compounds.
mTORC1/2	High	Rapamycin derivatives have completed paediatric Phase I (oral and iv ridaforolimus, temsirolimus, everolimus) and II studies (temsirolimus). Paediatric combination trials of rapalogues with IGF-1R monoclonal antibodies and other therapies are ongoing. Combined TORC1/2 inhibitors in adult clinical trials (AZD2014, OSI027 and CC-115 a dual TORC/DNA PK inhibitor). Paediatric trial of TORC1/2 inhibitor - AZD2014 open.
BIRC5	High	YM155 in adult clinical trials.
CHK1	High	GDC0575 and CCT245737 in adult development, other compounds starting clinical development. No paediatric studies open yet.
PLK1	Intermediate	GSK461364, BI6727 in adult clinical trials.
BCL2	Intermediate	Obatoclox (GX15-070 63) and navitoclax (ABT263) development discontinued. Venetoclax (BT199) in adult trials; no paediatric studies open yet.
LSD1	Intermediate	No drugs in clinical development yet.
CDK2	Intermediate	SCH727965 in adult clinical trials.
IGF-1R	Intermediate	Several agents tested in paediatric Phase I/II studies (figitumumab, R1507, SCH717454, IMC-A12, dalotuzumab) but development of all of them has stopped.
DNAPK	Low	CC-115 (dual mTOR/DNA-PK inhibitor) first-in-human Phase I completed.
LIN28B	Low	No drugs are currently available. Drugs targeting LIN28B should be developed.
TRKb	Low	Lestaurtinib tested in COG paediatric Phase I/II studies. Entrectinib paediatric Phase I ongoing
BRAF	Low	Vemurafenib and dabrafenib paediatric Phase I studies ongoing for BRAF mutated malignancies.
SHH	Low	LDE225 and vismodegib, paediatric Phase II/III ongoing.
PI3K	Low	Several inhibitors in adult development. Paediatric Phase I of pan PI3K inhibitor SF1126 ongoing in NANT.
AKT	Low	MK-2206 and perifosine in paediatric Phase I in the US completed.

This list is aimed to provide examples of agents in development in each pathway but is not a systematic review of all agents in development. The drug development landscape is subject to dynamic changes. Abbreviations: COG: Children's Oncology Group, NANT: New Approaches to Neuroblastoma Therapy, NCI: US National Cancer Institute