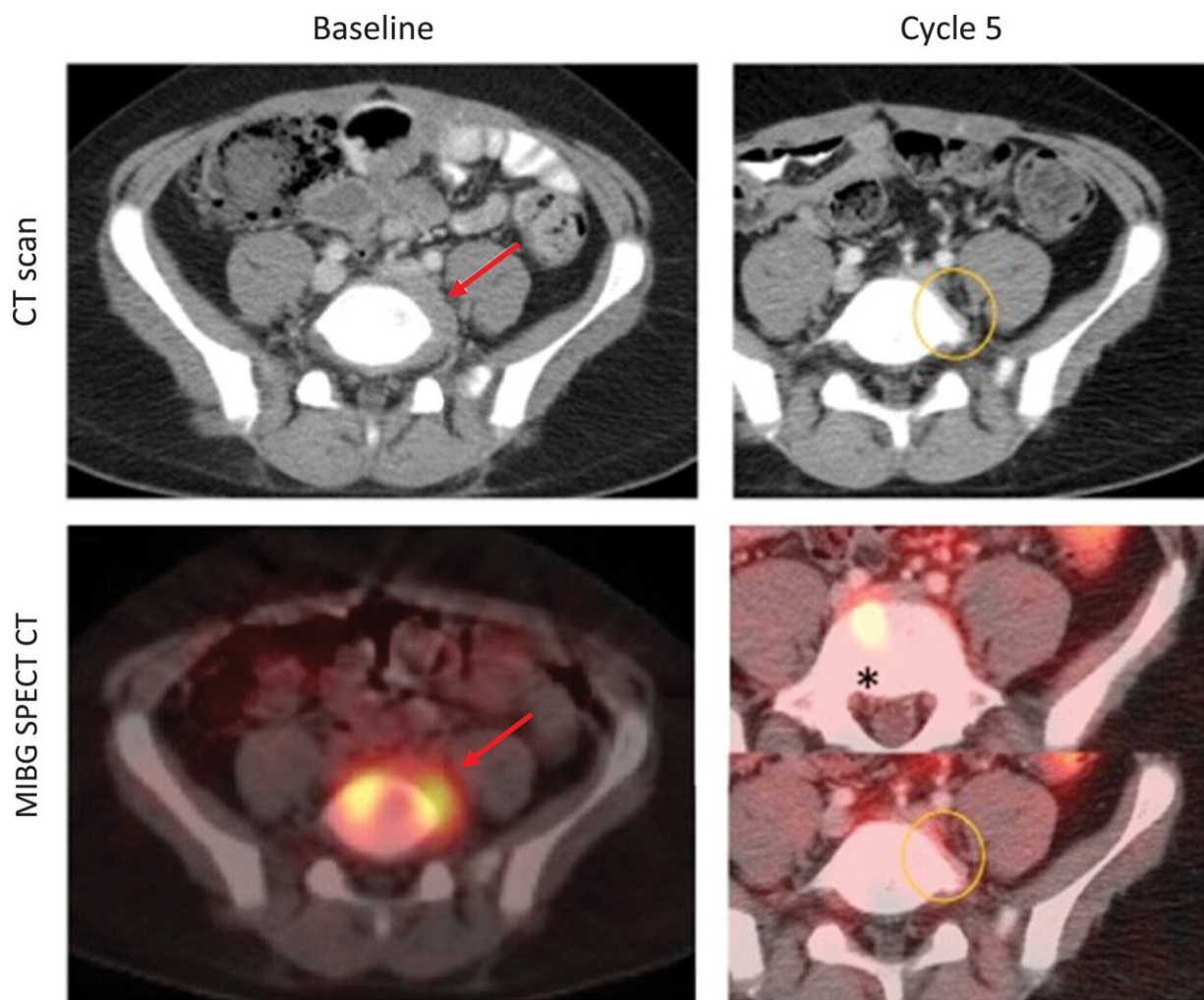


# Two studies find role for alternative lengthening of telomeres in treatment-resistant tumors

April 27 2023



Representative images from subject 3 who had both measurable and MIBG-evaluable neuroblastoma and an overall central radiology reviewed PR from

cycles 3 through 8, and PD at cycle 11. This patient enrolled with a history of progressive disease on a prior irinotecan-containing regimen. The left top panel shows the baseline 3.5-cm paraspinal mass (denoted by the red arrow), which is absent in cycle 5 in the top right panel. The bottom panels demonstrate the corresponding MIBG imaging. The bottom left panel shows the baseline pretherapy MIBG imaging of the paraspinal mass. Although the cycle 5 MIBG paraspinal mass demonstrated a CR (lower half, bottom right panel), there remained a small focus of residual MIBG-avid disease at the L5 vertebrae at cycle 5 (denoted by the \* on the upper half bottom right panel), so the overall response was a PR. CR, complete response; MIBG, metaiodobenzylguanidine; PD, progressive disease; PR, partial response. Credit: *Cancer* (2023). DOI: 10.1002/cncr.34786

Two recent papers from researchers in the Children's Hospital of Philadelphia (CHOP) Cancer Center have advanced the understanding of treatment-resistant pediatric tumors, both in assessing a novel treatment and in characterizing the role of alternative lengthening of telomeres (ALT) in these refractory tumors.

The first paper, published recently in the journal *Cancer*, provided data from a phase 1/2 Children's Oncology Group (COG) clinical trial led by CHOP researchers that investigated the use of a combined therapy of adavosertib and irinotecan for relapsed neuroblastoma, medulloblastoma and rhabdomyosarcoma. Adavosertib is a cell cycle checkpoint inhibitor that blocks the tyrosine kinase WEE1, which is involved in DNA replication, and by doing so sensitizes [tumor cells](#) to cytotoxic agents and replication stress. The trial combined adavosertib with irinotecan, with the aim of enhancing tumor shrinkage and allowing for a prolonged exposure to the treatments.

Although only the neuroblastoma cohort met the protocol defined efficacy endpoint, the results were the first positive signal of clinical

activity in [pediatric oncology](#) for a small molecule inhibitor of the DNA damage repair and cell cycle checkpoint. The neuroblastoma group had an estimated 16.7% objective response rate.

As part of the trial, the researchers explored potential predictors of response to treatment. One predictor they focused on was whether the tumors being treated had alternative lengthening of telomeres (ALT), a phenomenon that allows tumors to replicate uncontrollably; whereas telomeres in [normal cells](#) shorten as cells divide, the telomeres in some tumors lengthen, allowing cells to become effectively immortal. ALT is found in tumors of older pediatric and adolescent patients with neuroblastoma, and preclinical laboratory studies had suggested that ALT tumors may be sensitive to irinotecan and/or adavosertib.

Using a novel research test involving single cell immunofluorescence, the researchers found that 25% of patients whose tumors had ultrabright telomeres—indicating ALT—demonstrated tumor shrinkage when taking adavosertib and irinotecan, while no patients (0 of 4) whose tumors were not ultrabright had shrinkage. This finding requires further study as the cohort size was small and tumor tissue was not available from all enrolled on the trial.

The second study, published in *Neuro-Oncology*, sought to validate the ALT test used in the Cancer study in [tumor](#) tissues. With the help of the Children's Brain Tumor Network (CBTN) and CHOP's Center for Single Cell Biology, the researchers used laboratory and computational approaches to catalog ALT in approximately 900 pediatric brain tumors.

Among 579 pediatric brain tumors that had corresponding whole genome sequencing through the Open Pediatric Brain Tumor Atlas (OpenPBTA), the researchers detected ALT in 6.9% of these tumors. Using the same assay as the *Cancer* paper, they completed additional validation by ultrabright telomeric foci in situ on a subset of these

tumors.

The researchers confirmed that ALT is common (38.1%) in pediatric high-grade glioma (pHGG), but uncommon in other [pediatric brain tumors](#) (

Citation: Two studies find role for alternative lengthening of telomeres in treatment-resistant tumors (2023, April 27) retrieved 19 April 2024 from <https://medicalxpress.com/news/2023-04-role-alternative-lengthening-telomeres-treatment-resistant.html>

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