# Nilotinib

The efficacy of lapatinib and nilotinib in combination with radiation therapy in a model of NF2 associated peripheral schwannoma.

Neurofibromatosis type 2 (NF2), a neurogenetic condition manifest by peripheral nerve sheath tumors (PNST) throughout the neuroaxis for which there are no approved therapies.

In vitro and in vivo studies presented examine agents targeting signaling pathways, angiogenesis, and DNA repair mechanisms. In vitro dose response assays demonstrated potent activity of lapatinib and nilotinib against the mouse schwannoma SC4 (Nf2 -/-) cell line.

Paldor et al. examined the efficacy of everolimus, nilotinib, lapatinib, bevacizumab and radiotherapy (RT) as mono- and combination therapies in flank and sciatic nerve in vivo NF2-PNST models. Data were analyzed using generalized linear models, two sample T-tests and paired T-tests, and linear regression models. SC4(Nf2 -/-) cells implanted in the flank or sciatic nerve showed similar rates of growth ($p = 0.9748$). Lapatinib, nilotinib and RT significantly reduced tumor growth rate versus controls in the in vivo flank model ($p = 0.0025$, 0.0062, and 0.009, respectively) whereas bevacizumab and everolimus did not. The best performers were tested in the in vivo sciatic nerve model of NF2 associated PNST, where chemoradiation outperformed nilotinib or lapatinib as single agents (nilotinib vs. nilotinib + RT, $p = 0.0001$; lapatinib versus lapatinib + RT, $p < 0.0001$) with no observed toxicity. There was no re-growth of tumors even 14 days after treatment was stopped. The combination of either lapatinib or nilotinib with RT resulted in greater delays in tumor growth rate than any modality alone. This data suggest that concurrent low dose RT and targeted therapy may have a role in addressing progressive PNST in patients with NF2 [1)].

## Case series

In a study, Torchia et al analyzed 191 primary Atypical teratoid rhabdoid tumor ATRTs and 10 ATRT cell lines to define the genomic and epigenomic landscape of ATRTs and identify subgroup-specific therapeutic targets. We found ATRTs segregated into three epigenetic subgroups with distinct genomic profiles, SMARCB1 genotypes, and chromatin landscape that correlated with differential cellular responses to a panel of signaling and epigenetic inhibitors. Significantly, they discovered that differential methylation of a PDGFRB-associated enhancer confers specific sensitivity of group 2 ATRT cells to dasatinib and nilotinib, and suggest that these are promising therapies for this highly lethal ATRT subtype [2)].

1)
Paldor I, Abbadi S, Bonne N, Ye X, Rodriguez FJ, Rowshanshad D, Itzoe M, Vigilar V, Giovannini M, Brem H, Blakeley JO, Tyler BM. The efficacy of lapatinib and nilotinib in combination with radiation therapy in a model of NF2 associated peripheral schwannoma. J Neurooncol. 2017 Jul 22. doi: 10.1007/s11060-017-2567-9. [Epub ahead of print] PubMed PMID: 28735458.
2)
Torchia J, Golbourn B, Feng S, Ho KC, Sin-Chan P, Vasiljevic A, Norman JD, Guilhamon P, Garzia L, Agamez NR, Lu M, Chan TS, Picard D, de Antonellis P, Khuong-Quang DA, Planello AC, Zeller C, Barsyte-Lovejoy D, Lafay-Cousin L, Letourneau L, Bourgey M, Yu M, Gendoo DM, Dzamba M, Barszczyk M, Medina T, Riemenschneider AN, Morrissy AS, Ra YS, Ramaswamy V, Remke M, Dunham CP, Yip S, Ng HK, Lu JQ, Mehta V, Albrecht S, Pimentel J, Chan JA, Somers GR, Faria CC, Roque L, Fouladi M, Hoffman LM, Moore AS, Wang Y, Choi SA, Hansford JR, Catchpoole D, Birks DK, Foreman NK, Strother

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