

Reference:

1. Sun Y, Liu WZ, Liu T, Feng X, Yang N, Zhou HF. Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis. *Journal of Receptors and Signal Transduction*. 2015;35(6):600-604. doi:10.3109/10799893.2015.1030412
2. Kieran MW. Targeting BRAF in Pediatric Brain Tumors. *American Society of Clinical Oncology Educational Book*. 2014;(34):e436-e440. doi:10.14694/edbook_am.2014.34.e436
3. Jones DTW, Gronych J, Lichter P, Witt O, Pfister SM. MAPK pathway activation in pilocytic astrocytoma. *Cellular and Molecular Life Sciences*. 2012;69(11):1799-1811. doi:10.1007/s00018-011-0898-9
4. Varan A, Şen H, Aydin B, Yalçın B, Kutluk T, Akyüz C. Neurofibromatosis type 1 and malignancy in childhood. *Clinical Genetics*. 2016;89(3):341-345. doi:10.1111/cge.12625
5. Forsheo T, Tatevossian RG, Lawson ARJ, et al. Activation of the ERK/MAPK pathway: A signature genetic defect in posterior fossa pilocytic astrocytomas. *Journal of Pathology*. 2009;218(2):172-181. doi:10.1002/path.2558
6. Kaley T, Touat M, Subbiah V, et al. BRAF inhibition in BRAFV600-mutant gliomas: Results from the VE-BASKET study. In: *Journal of Clinical Oncology*. Vol 36. American Society of Clinical Oncology; 2018:3477-3484. doi:10.1200/JCO.2018.78.9990
7. Daniotti M, Ferrari A, Frigerio S, et al. Cutaneous melanoma in childhood and adolescence shows frequent loss of INK4A and gain of KIT. *Journal of Investigative Dermatology*. 2009;129(7):1759-1768. doi:10.1038/jid.2008.422
8. Durham BH. Molecular characterization of the histiocytoses: Neoplasia of dendritic cells and macrophages. *Seminars in Cell and Developmental Biology*. 2019;86:62-76. doi:10.1016/j.semcdb.2018.03.002
9. Fernandes GS, Girardi DM, Bernardes JPG, Fonseca FP, Fregnani ER. Clinical benefit and radiological response with BRAF inhibitor in a patient with recurrent ameloblastoma harboring V600E mutation. *BMC Cancer*. 2018;18(1). doi:10.1186/s12885-018-4802-y
10. Karajannis MA, Legault G, Fisher MJ, et al. Phase II study of sorafenib in children with recurrent or progressive low-grade astrocytomas. *Neuro-Oncology*. 2014;16(10):1408-1416. doi:10.1093/neuonc/nou059
11. Hauschild A, Grob JJ, Demidov L v., et al. Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. *The Lancet*. 2012;380(9839):358-365. doi:10.1016/S0140-6736(12)60868-X
12. Kieran MW, Geoerger B, Dunkel IJ, et al. A phase I and pharmacokinetic study of oral dabrafenib in children and adolescent patients with recurrent or refractory BRAF V600 mutation-positive solid tumors. *Clinical Cancer Research*. 2019;25(24):7294-7302. doi:10.1158/1078-0432.CCR-17-3572

13. Hargrave DR, Bouffet E, Tabori U, et al. Efficacy and safety of dabrafenib in pediatric patients with BRAF V600 mutation–positive relapsed or refractory low-grade glioma: Results from a phase I/IIa study. *Clinical Cancer Research*. 2019;25(24):7303-7311. doi:10.1158/1078-0432.CCR-19-2177
14. Flaherty KT, Robert C, Hersey P, et al. Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma. *NEJM.org N Engl J Med*. 2012;367:107-121. doi:10.1056/NEJMoa1203421
15. Ramtohul P, Freund KB. Clinical and Morphological Characteristics of Anti-Programmed Death Ligand 1-Associated Retinopathy: Expanding the Spectrum of Acute Macular Neuroretinopathy. *Ophthalmology Retina*. 2020;4(4):446-450. doi:10.1016/j.oret.2019.11.006
16. Georger B, Moertel CL, Whitlock J, et al. Phase 1 trial of trametinib alone and in combination with dabrafenib in children and adolescents with relapsed solid tumors or neurofibromatosis type 1 (NF1) progressive plexiform neurofibromas (PN). *Journal of Clinical Oncology*. 2018;36(15_suppl):10537-10537. doi:10.1200/jco.2018.36.15_suppl.10537
17. Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. *New England Journal of Medicine*. 2020;382(15):1430-1442. doi:10.1056/NEJMoa1912735
18. Goldstein A, Haelyon U, Krolik E, Sack J. Comparison of body weight and height of Israeli schoolchildren with the Tanner and Centers for Disease Control and Prevention growth charts. *Pediatrics*. 2001;108(6). doi:10.1542/peds.108.6.e108
19. Colan SD. Normal Echocardiographic Values for Cardiovascular Structures. In: *Echocardiography in Pediatric and Congenital Heart Disease*. John Wiley & Sons, Ltd; 2016:883-901. doi:10.1002/9781118742440.app1
20. Kieran MW. Targeting BRAF in Pediatric Brain Tumors. *American Society of Clinical Oncology Educational Book*. 2014;(34):e436-e440. doi:10.14694/edbook_am.2014.34.e436
21. Long G v., Stroyakovskiy D, Gogas H, et al. Overall survival in COMBI-d, a randomized, double-blinded, phase III study comparing the combination of dabrafenib and trametinib with dabrafenib and placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/Kmutation-positive cutaneous melanoma. *Journal of Clinical Oncology*. 2015;33(15_suppl):102-102. doi:10.1200/jco.2015.33.15_suppl.102
22. Binder G. Noonan syndrome, the Ras-MAPK signalling pathway and short stature. In: *Hormone Research*. Vol 71. ; 2009:64-70. doi:10.1159/000192439
23. Dumas M, Laly P, Gottlieb J, et al. Osteopenia and fractures associated with long-term therapy with MEK inhibitors. *Melanoma Research*. 2018;28(6):641-644. doi:10.1097/CMR.0000000000000490
24. Kim JM, Yang YS, Park KH, Oh H, Greenblatt MB, Shim JH. The ERK MAPK pathway is essential for skeletal development and homeostasis. *International Journal of Molecular Sciences*. 2019;20(8). doi:10.3390/ijms20081803

25. Emens LA, Davis SL, Oliver SCN, et al. Association of Cancer Immunotherapy with Acute Macular Neuroretinopathy and Diffuse Retinal Venulitis. *JAMA Ophthalmology*. 2019;137(1):96-100. doi:10.1001/jamaophthalmol.2018.5191
26. Dimitriou F, Frauchiger AL, Urosevic-Maiwald M, et al. Sarcoid-like reactions in patients receiving modern melanoma treatment. *Melanoma Research*. 2018;28(3):230-236. doi:10.1097/CMR.0000000000000437
27. Ramani NS, Curry JL, Kapil J, et al. Panniculitis with Necrotizing Granulomata in a Patient on BRAF Inhibitor (Dabrafenib) Therapy for Metastatic Melanoma. *American Journal of Dermatopathology*. 2015;37(8):e96-e99. doi:10.1097/DAD.0000000000000230
28. Callahan MK, Masters G, Pratilas CA, et al. Paradoxical activation of T cells via augmented ERK signaling mediated by a RAF inhibitor. *Cancer immunology research*. 2014;2(1):70-79. doi:10.1158/2326-6066.CIR-13-0160
29. Frederick DT, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clinical Cancer Research*. 2013;19(5):1225-1231. doi:10.1158/1078-0432.CCR-12-1630
30. Boni A, Cogdill AP, Dang P, et al. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. *Cancer Research*. 2010;70(13):5213-5219. doi:10.1158/0008-5472.CAN-10-0118

Legend list

FIGURE 1 – MASSIVE PULMONARY LYMPHADENOPATHY

CT scan revealing Diffuse bi-hilar lymphadenopathy severely compressing the main bronchi and causing secondary atelectasis in addition to bilateral pulmonary infiltrates

FIGURE 2 - GROWTH CHARTS

Growth charts of patents number 5 and 3, showing decreased growth rate while on treatment. Patient number 5 had a decrease in height-SDS from 0.16 before treatment to -1.0. patient number 3 had a decrease in height-SDS from 1.35 to -0.11.

FIGURE 3- RETINAL TOXICITY

Red free fundus photos of the right (a) and left (b) eye showing focal macular lesions nasal to both foveas (white arrows). Optical coherence tomography (OCT) of the right (c) and left (d) eyes of the corresponding macular areas showing absence of the retinal outer layer in the area of the lesions (white asterisks)