Tumorji CŽS s **fuzijami NTRK**

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NTRK

NTRK – neurotrofin tirozin receptor kinaza

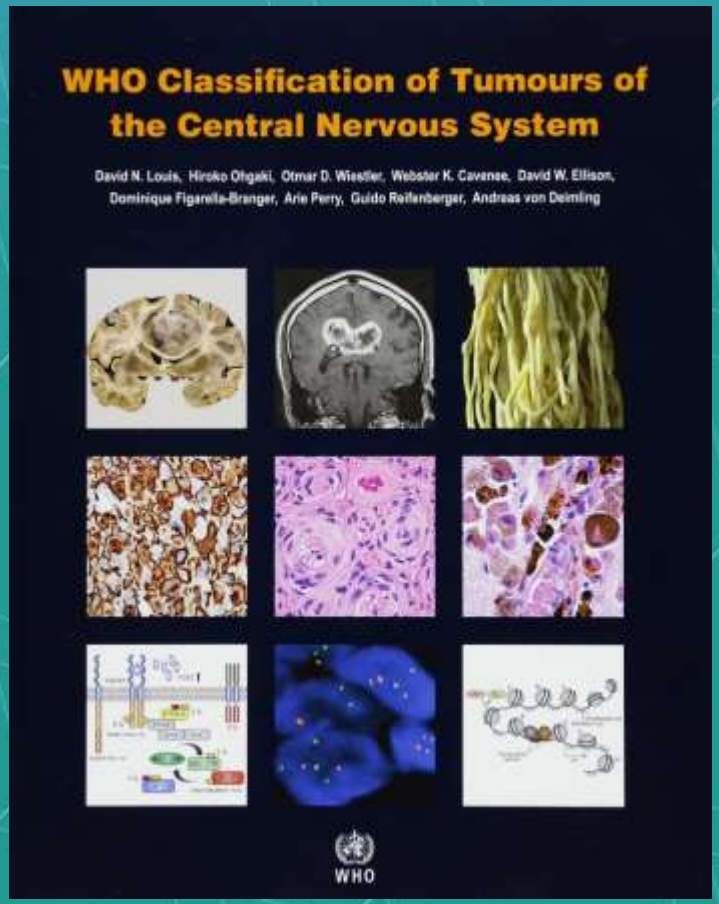
NTRK1/NTRK2/NTRK3 → TrkA/TrkB/TrkC

Receptorji za neurotrofine - rastne faktorje, ki so odgovorni za rast in diferenciacijo živčevja

Za dokazovanje fuzij v CŽS potrebna NGS

Märkl B, et al. Pathol Res Pract 2019

Nove tumorske entitete v CŽS



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Glialni tumorji odraslih z NTRK fuzijami

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Glioblastom in drugi difuzni gliomi

Glioblastom predstavlja približno polovico vseh tumorjev CŽS in približno 4/5 **vseh malignih glialnih tumorjev**.

Relativno pogosto pojavljanje fuzij NTRK (2%) v difuznih gliomih.

NTRK fuzije dvakrat pogostejše pri difuznih gliomih IDH divjega tipa

Ferguson SD, et al. J Neuropathol Exper Neurol, 2018

Glioblastom in drugi difuzni gliomi

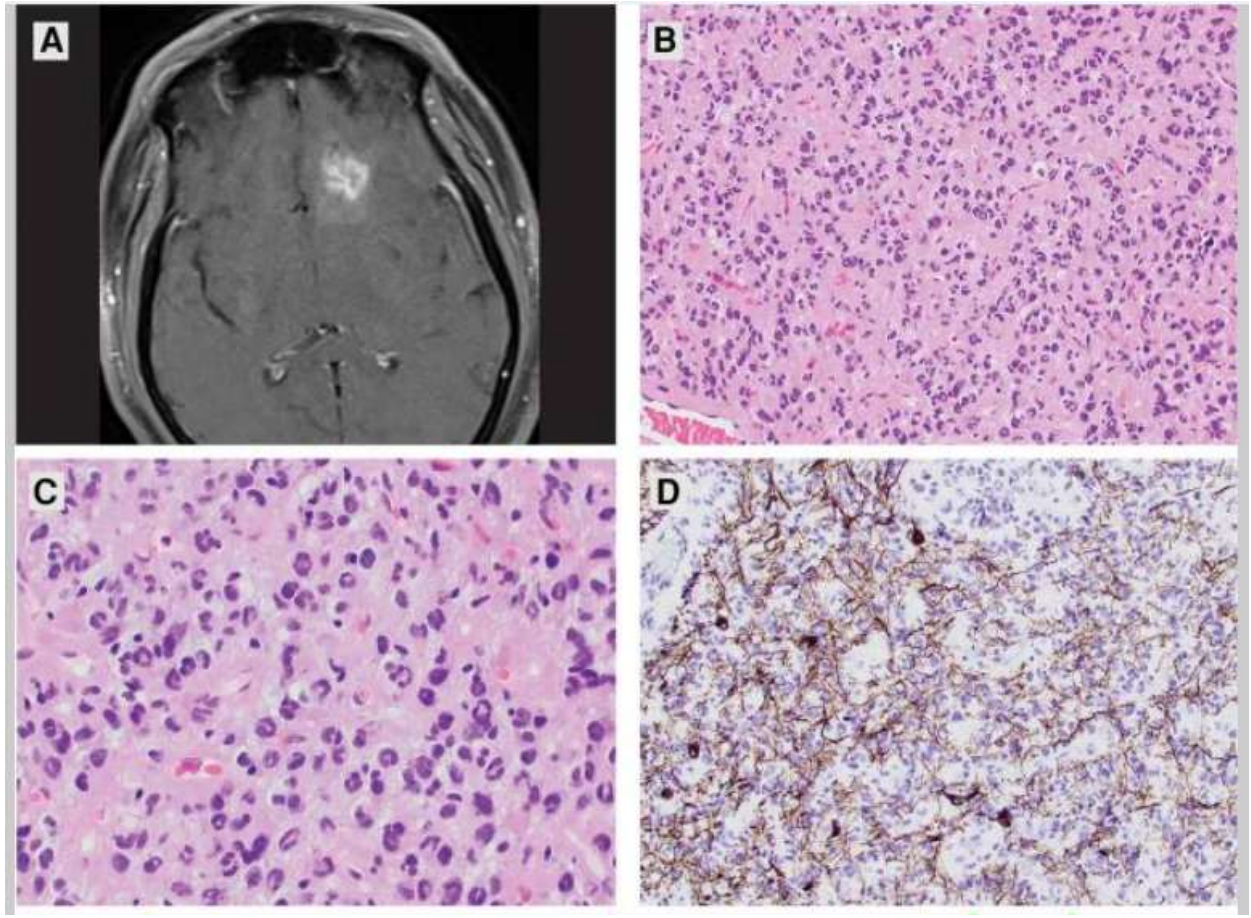
NTRK1-BCAN
NTRK1-CHTOP
NTRK1-ARHGEF2
NTRK1-NFASC
NTRK1-TPM3
NTRK1-AFAP1
NTRK1-MEF2D

NTRK2-GKAP1
NTRK2-KCTD8
NTRK2-NOS1AP
NTRK2-SQSTM1
NTRK2-TBC1D2
NTRK2-VCAN
NTRK2-AFAP1
NTRK2-AGBL4
NTRK2-BTBD1
NTRK2-VCL
NTRK2-BCR
NTRK2-KANK
NTRK2-AGTPBP1
NTRK2-SPECC1L
NTRK2-PRKAR2A

NTRK3-EML4
NTRK3-ZFN710
NTRK3-ETV6
NTRK3-BTBD1

Ferguson SD, et al. J Neuropathol Exper Neurol 2018; Zheng Z, et al. Nat Med 2014; Wu G, et al. Nat Genet 2014; Hechtman JF, et al. Am J Surg Pathol 2017; Drilon AE, et al. J Clin Oncol 2019; Gatalica Z, et al. Modern Pathol 2019;

Gliom nizkega gradusa z BCR-NTRK2 fuzijo



Jones KA, et al. Cold Spring Harb Lab Mol Case Stud 2019.

Glialni tumorji nizkega gradusa in glionevronalni tumorji

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Glialni tumorji nizkega gradusa in glionevronalni tumorji

Pilocitni astrocitom (NTRK1-BCAN, NTRK2-QKI, NTRK2-NACC2)

Dezmoplastični infantilni astrocitom/gangliogliom (NTRK1-TPM3)

Gangliogliom (NTRK2-SLMAP, NTRK2-STRN3)

Drugi glionevronalni tumorji (NTRK2-WNK2, NTRK1-BCAN)

Blessing MM, et al. J Neuropathol Exper Neurol 2019; Alvarez-Breckenridge C, et al. NPJ Precis Oncol 2017; Quaddoumi I, et al. Acta Neropathol 2016; Ferguson SD, et al. J Neuropathol Exper Neurol 2018; Jones DT, et al. Nat Genet, 2013; Wu G, et al. Nat Genet 2014

Pediatrični glialni/glionevronalni tumorji z NTRK fuzijami

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Pediatrični glialni/glionevronalni tumorji visokega gradusa

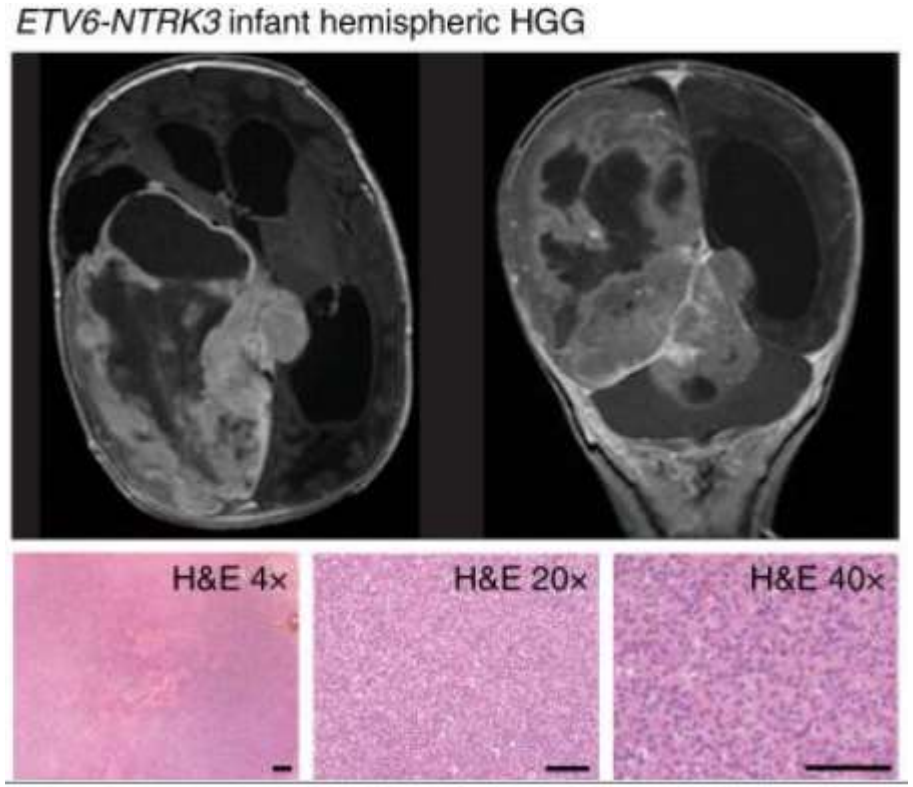
Difuzni leptomeningealni glionevronalni tumor, tip 1

Astrocitni tumorji z mutacijo H3 G34V/F (10%)

Infantilni hemisferični gliomi, skupina 1 (40%)

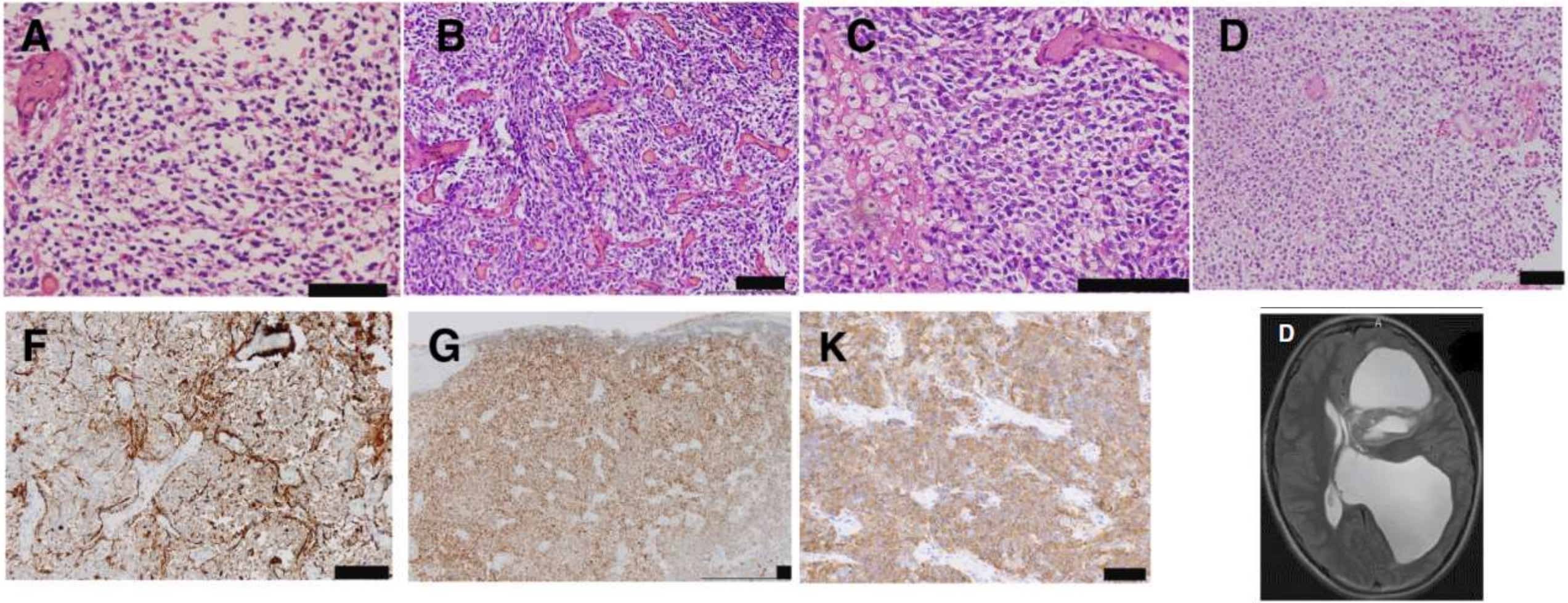
Deng MY, et al. Acta Neuropathol 2018; Vanan MI, et al. Neurotherapeutics 2017; Guerrerio Stucklin AS, et al. Nature Comm 2019; Wu G, et al. Nature Genet 2014

Infantilni hemisferični gliom s fuzijo NTRK3-ETV6



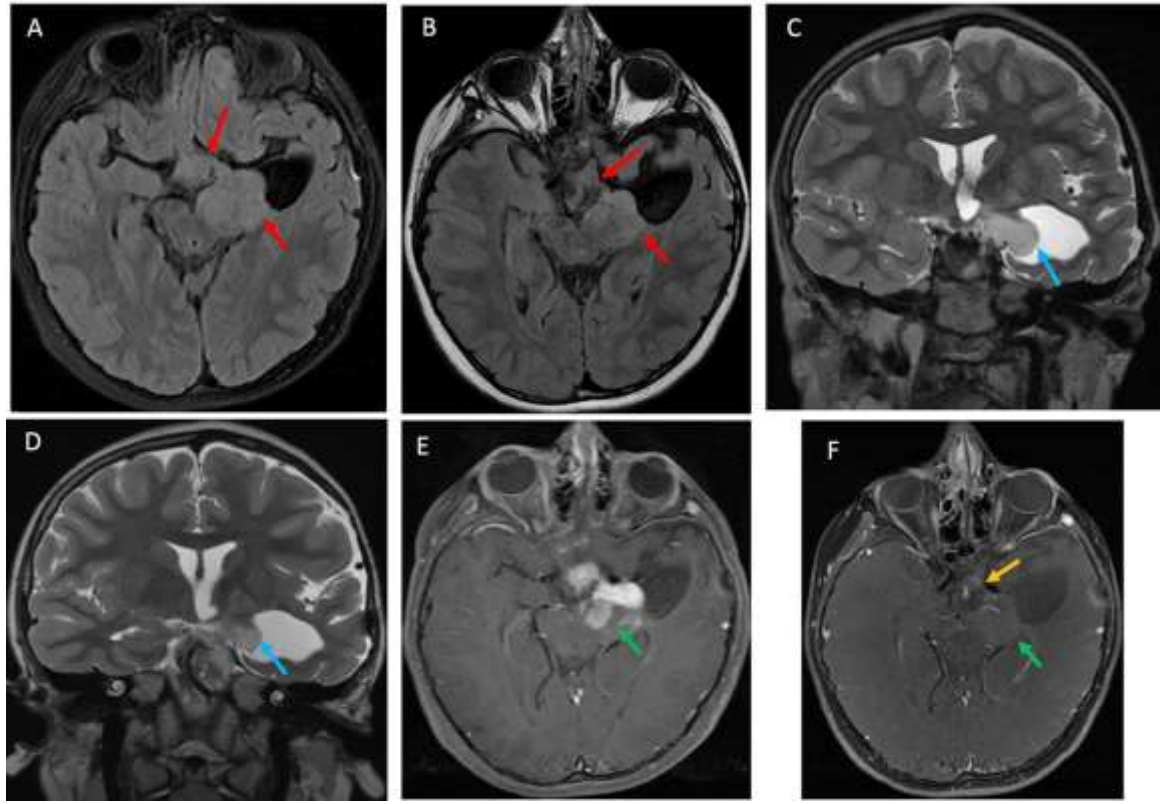
Guerrerio Stucklin AS, et al. Nature Comm 2019

Glionevronalni tumor visokega gradusa s fuzijo ARHGEF2–NTRK1



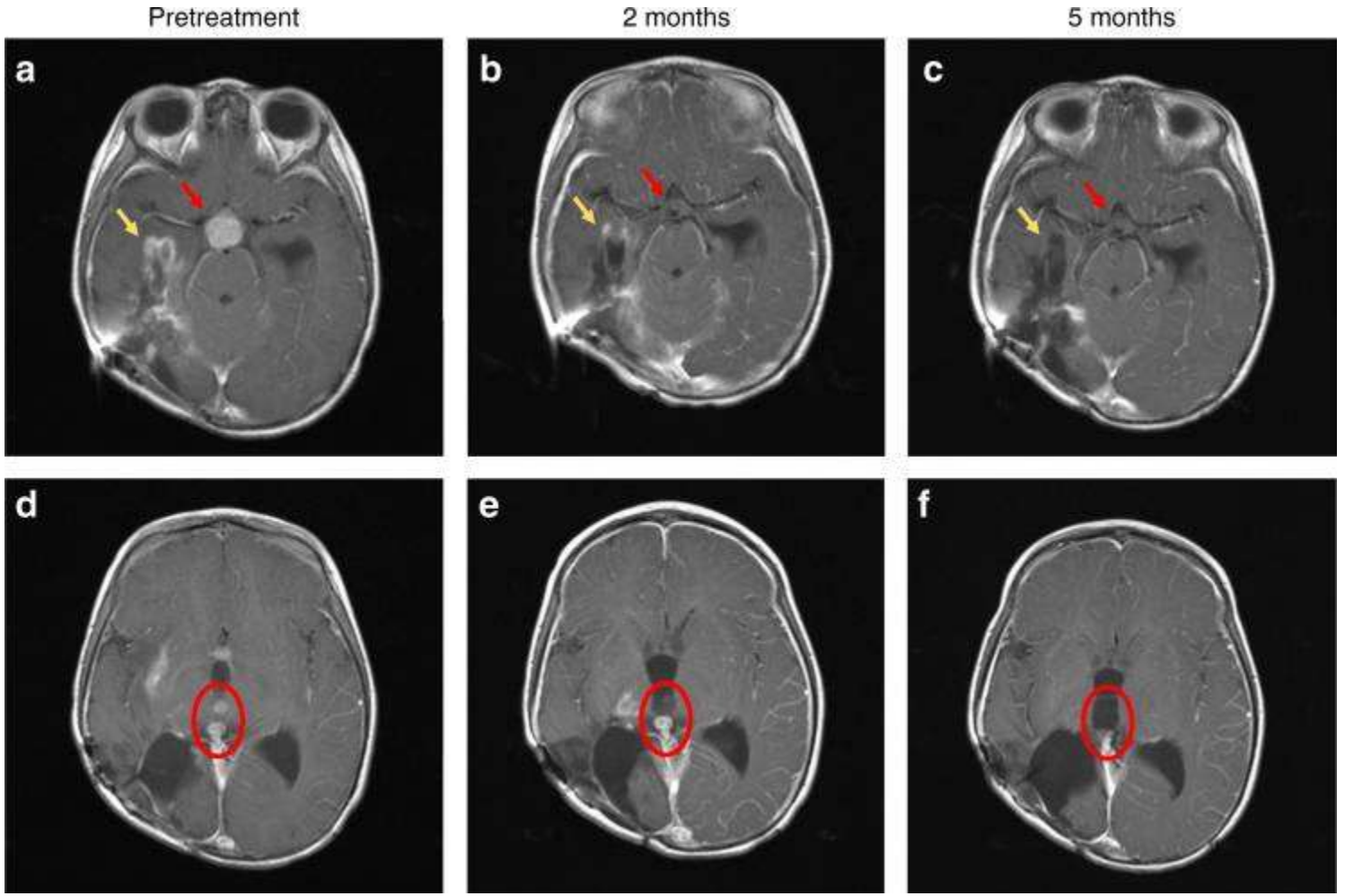
Kurozumi K, et al. Brain Tumor Pathol 2019.

LGG, WHO I, s fuzijo NACC2-NTRK2



Walter AW, et al. Pediatr Blood Cancer 2019.

HGG s fuzijo NTRK3-ETV6



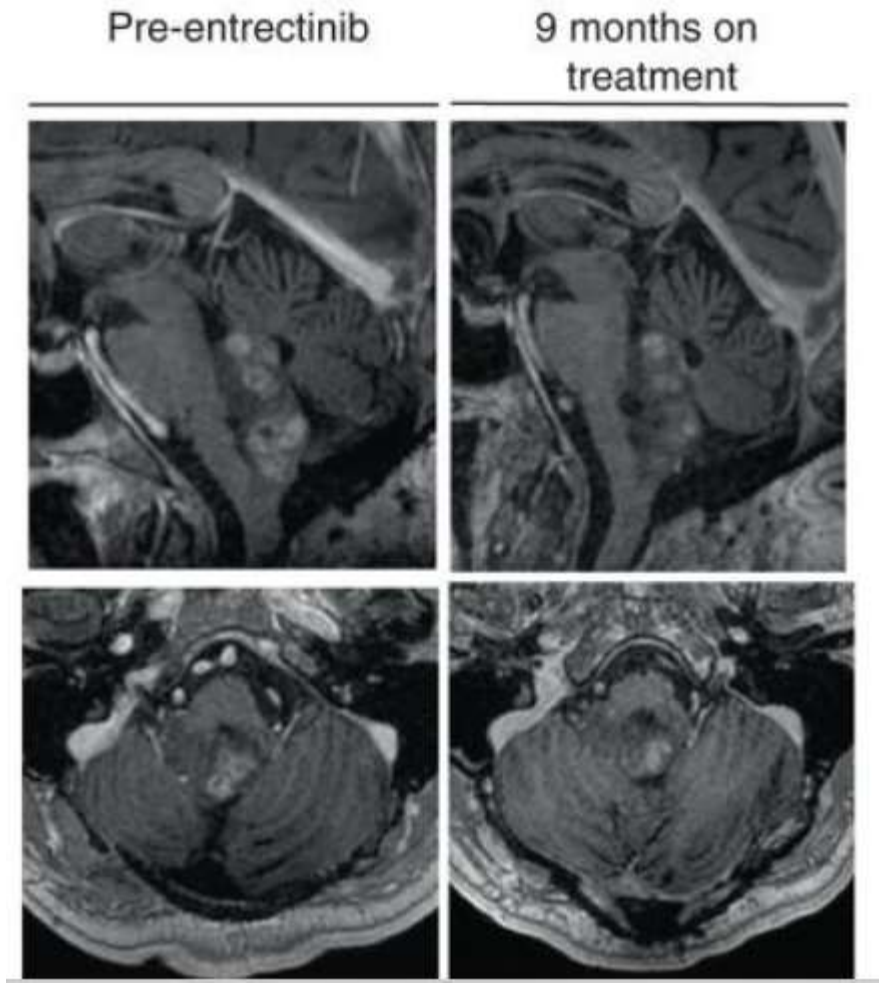
Ziegler DS, et al. Br J Cancer 2018.

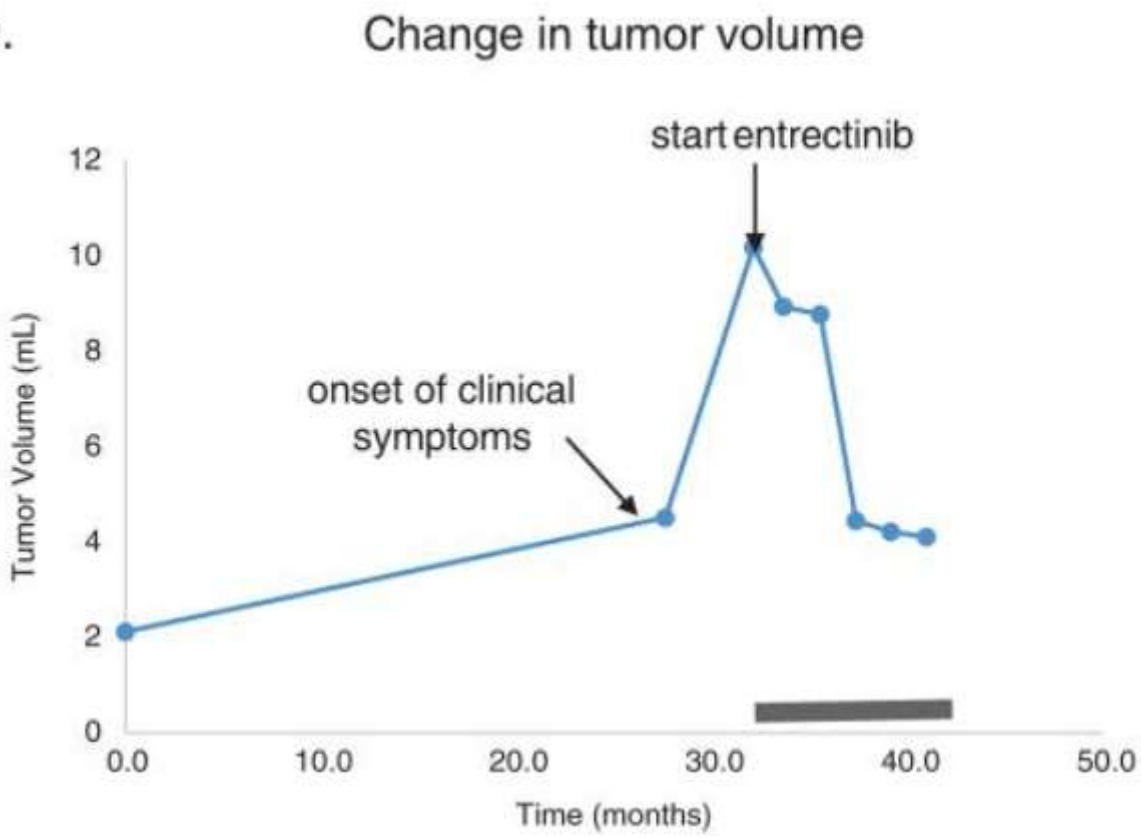
Klinične študije

Larotrektinib: NCT02637687, NCT02576431, NCT03213704, NCT03834961, NCT02465060, NCT03155620

Entrektinib: NCT02568267, NCT02650401

LG Glionevronalni tumor, s fuzijo NTRK1- BCAN





Alvarez-Breckenridge C, et al. NPJ Precis Oncol 2017

NCT02650401

Cancer Discov. 2019 Jul

Entrectinib Shows Pediatric Potential.

Abstract

According to preliminary data from the phase I/Ib STARTRK-NG trial, the investigational multikinase inhibitor entrectinib showed efficacy in children and adolescents with CNS and other tumor types harboring *NTRK1/2/3*, *ROS1*, or *ALK* fusions. Durable responses were seen even in CNS tumors such as high-grade glioma.

NCT02637687, NCT02576431

Drilon AE, et al. J Clin Oncol, 2019

…3 glioma, 2 glioblastoma, 1 astrocytoma, 3 glioma NOS…

…In the 9 pts with primary CNS tumors, disease control was achieved in all evaluable pts (primary PD not observed; 1 pt required dose increase). The best objective response to therapy was PR in 1 (11%; pending confirmation, −55% tumor shrinkage, ongoing at 3.7 mo), SD in 7 (78%; tumor shrinkage range −1% to −24% for pts with measurable disease, 5 had SD > 4 mo), and NE in 1 (11%). Duration of treatment ranged from 2.8–9.2+ mo….

Hvala za pozornost!