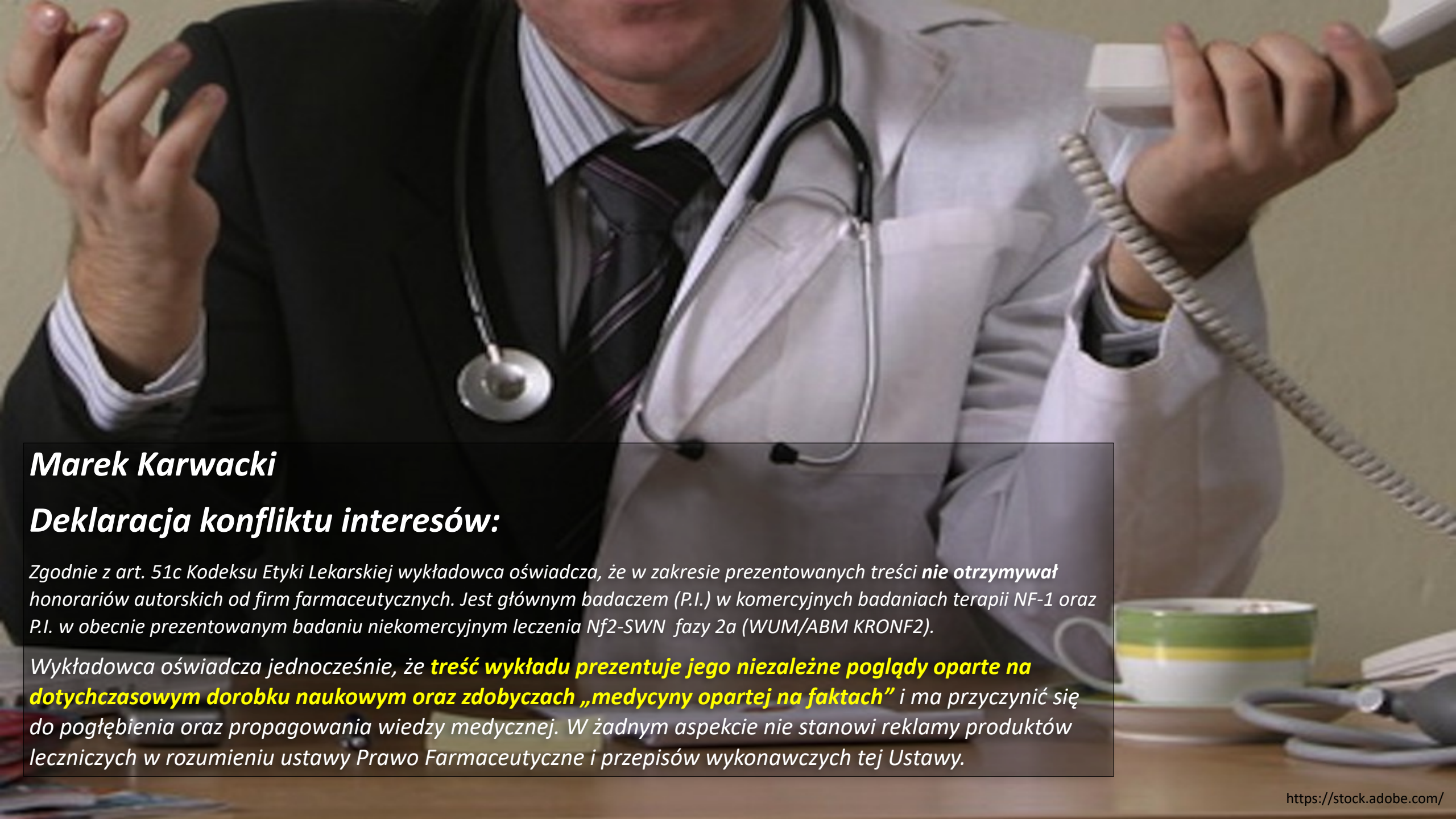


Marek Karwacki

Deklaracja konfliktu interesów:

Zgodnie z art. 51c Kodeksu Etyki Lekarskiej wykładowca oświadcza, że w zakresie prezentowanych treści ***nie otrzymywał*** *honorariów autorskich od firm farmaceutycznych. Jest głównym badaczem (P.I.) w komercyjnych badaniach terapii NF-1 oraz P.I. w obecnie prezentowanym badaniu niekomercyjnym leczenia Nf2-SWN fazy 2a (WUM/ABM KRONF2).*

Wykładowca oświadcza jednocześnie, że ***treść wykładu prezentuje jego niezależne poglądy oparte na dotychczasowym dorobku naukowym oraz zdobyczach „medycyny opartej na faktach”*** *i ma przyczynić się do pogłębienia oraz propagowania wiedzy medycznej. W żadnym aspekcie nie stanowi reklamy produktów leczniczych w rozumieniu ustawy Prawo Farmaceutyczne i przepisów wykonawczych tej Ustawy.*

https://stock.adobe.com/

Centrum Koordynowanej Opieki Medycznej
nad Pacjentami z Neurofibromatozami
i pochodnymi im RASopatiami,
CKOM NF/RAS, UCK-DSK-WUM, Warszawa

Marek Karwacki

Katedra i Klinika Onkologii,
Hematologii Dziecięcej,
Transplantologii Klinicznej i
Pediatrii,
Warszawski Uniwersytet
Medyczny

Czy w *Nf2*-SWN

jesteśmy skazani na chirurga,

czy jednak można

zrobić coś więcej?

KONFERENCJA NF-POLSKA: „*Nauka, klinika, opieka nad chorym*”
Warszawa, 14-15 grudnia 2024 roku

Czym są neurofibromatozy?

M.W. Karwacki i wsp.; Przegląd Pediiatryczny; 2019, 48(3):152-172

RODZINA NEUROFIBROMATOZ

GRUPA NF-1 (RASopatie)

- Pełnoobjawowa NF-1
- Postaci alleliczne NF-1
- Postaci mozaikowe NF-1
- Choroby przyległych genów (17q11del)
- Zespół Legiusa

Co je łączy?

- Plamy CAL
- GUZY OSŁONOWE NERWÓW OBWODOWYCH *historia*

Co je dzieli?

- Odmienna GENETYKA
- BARDZO ODMIENNY PRZEBIEG KLINICZNY

GRUPA SCHWANNOMATOZ

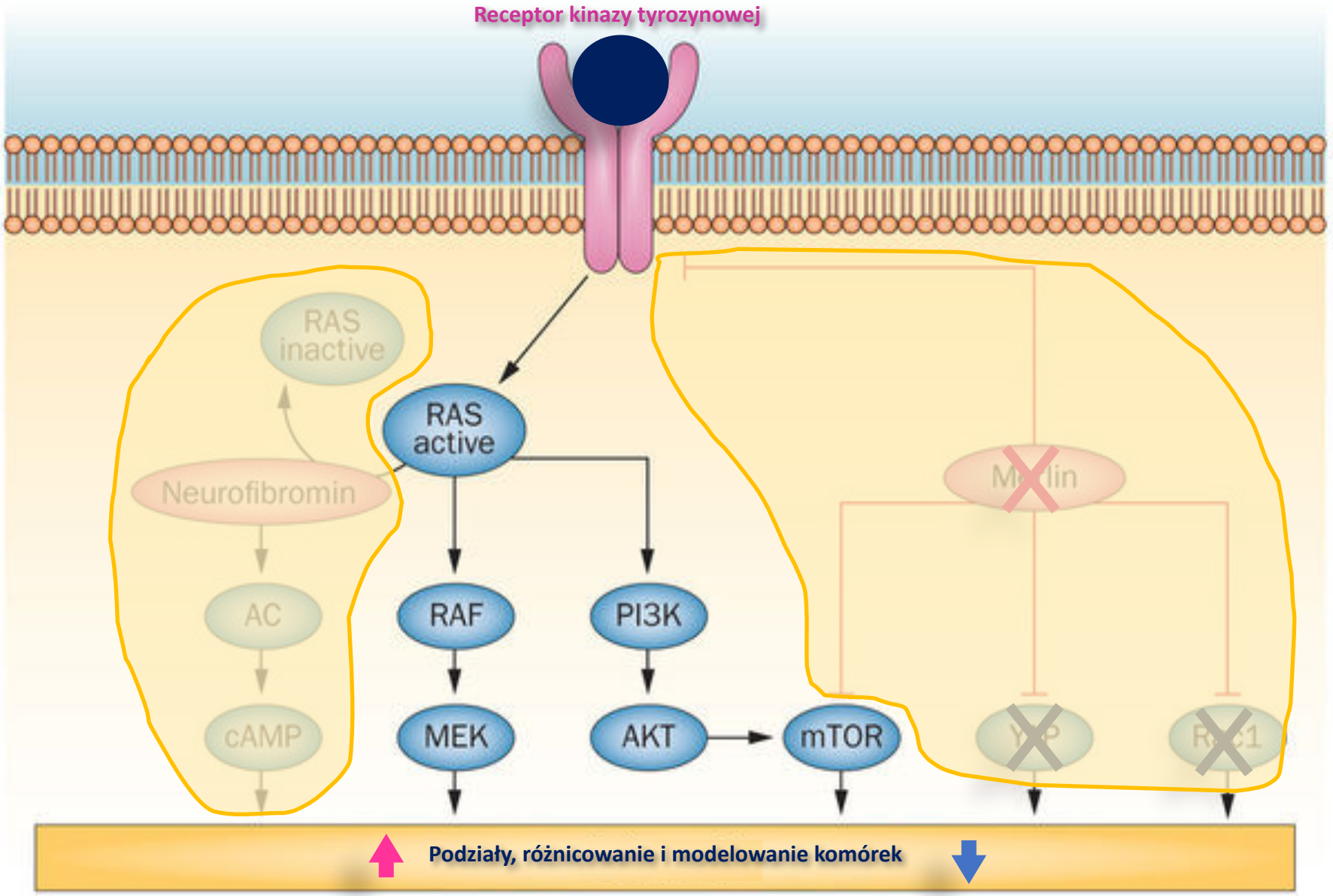
- Pełnoobjawowa *Nf2*-SWN *(NF-2)*
- Postaci mozaikowe *Nf2*-SWN
- Non *Nf2*-SWN *(Schwannomatoza - NF-3)*
- Postaci mozaikowe NF-3
- Zespoły pochodne
- Choroby przyległych genów Ring 22 chromosomu

CHOROBY PIERWOTNIE NOWOTWOROWE!

NF-1 - nerwiakowłókniakowatość typu 1, NF-2 - nerwiakowłókniakowatość typu 2, NF-3 - Schwannomatoza, plamy CAL - skórne plamy o typie „kawy z mlekiem”

Grafika własna autora

NF-y: dlaczego tak różne a jednak razem?

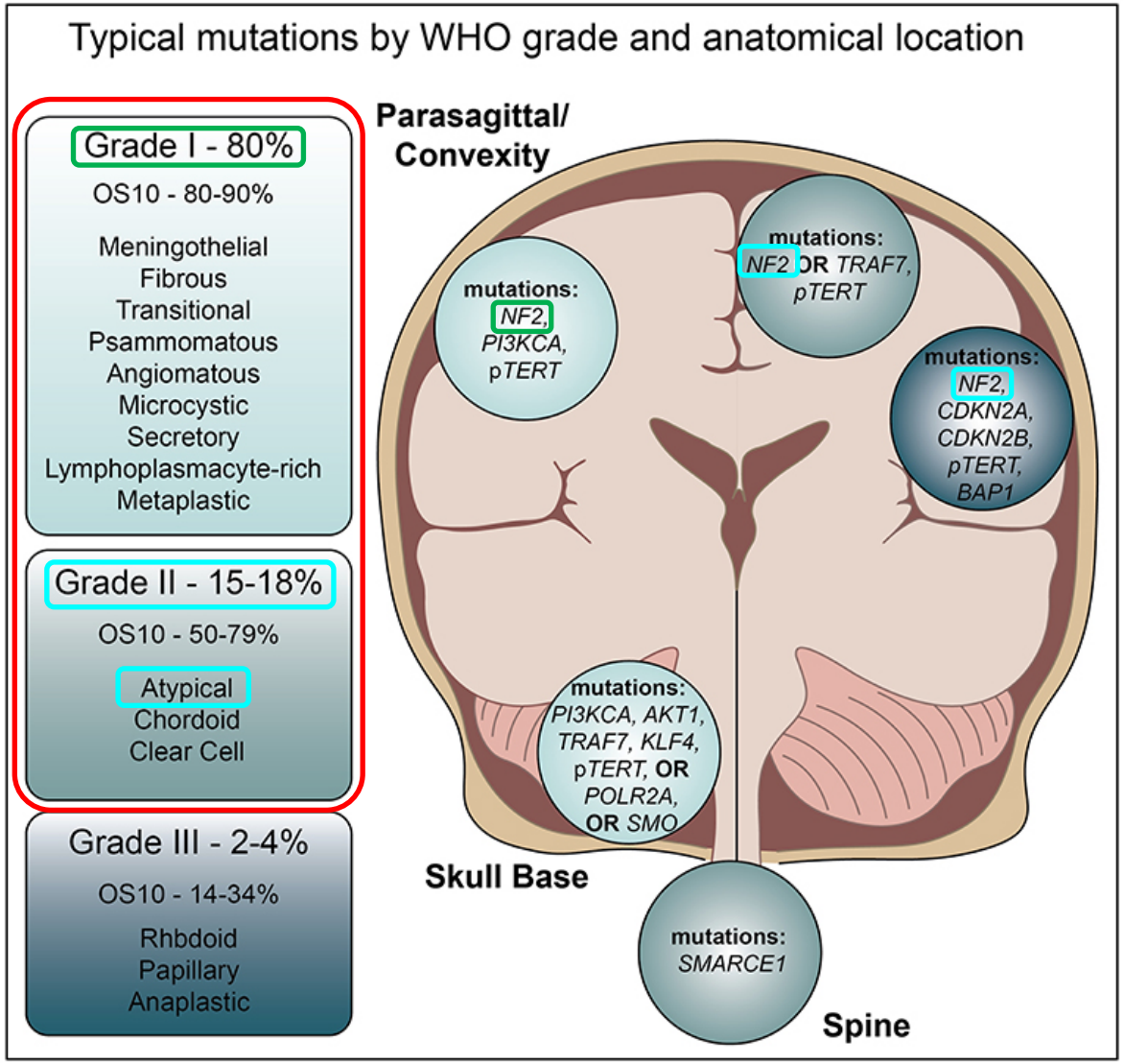


Nf1 i ***Nf2*** to ważne antyonkogeny ustrojowe!

Karwacki M W, at al. Coordinated medical care for children with neurofibromatosis type 1 and related RASopathies in Poland. Archives of Medical Science. 2021;17(5):1221-1231

Opracowanie własne Autora

Znaczenie genu *Nf2* w onkologii człowieka (sporadyczne *vs*. zespołowe oponiaki)



GENOMICS NGS

NF2-Mutated Meningioma

As high grade meningiomas are associated with rapid disease progression and poor prognosis as compared to low grade, recent efforts in next-generation sequencing have sought to identify prognostic biomarker to differentiate between tumors of varying grades, and those that may correlate with treatment response. With a low mutation rate (~3.5 mutations per megabase) compared to other cancers (17), these efforts highlight the challenges in managing these heterogeneous tumors. Similar to cytogenetic analysis, these studies identified *NF2* mutations as the predominant alteration in both spontaneous (~60%) and Neurofibromatosis syndrome associated (~40%) of tumors (16), at a frequency of 43% in low grade, and nearly 80% in high grade tumors (11).

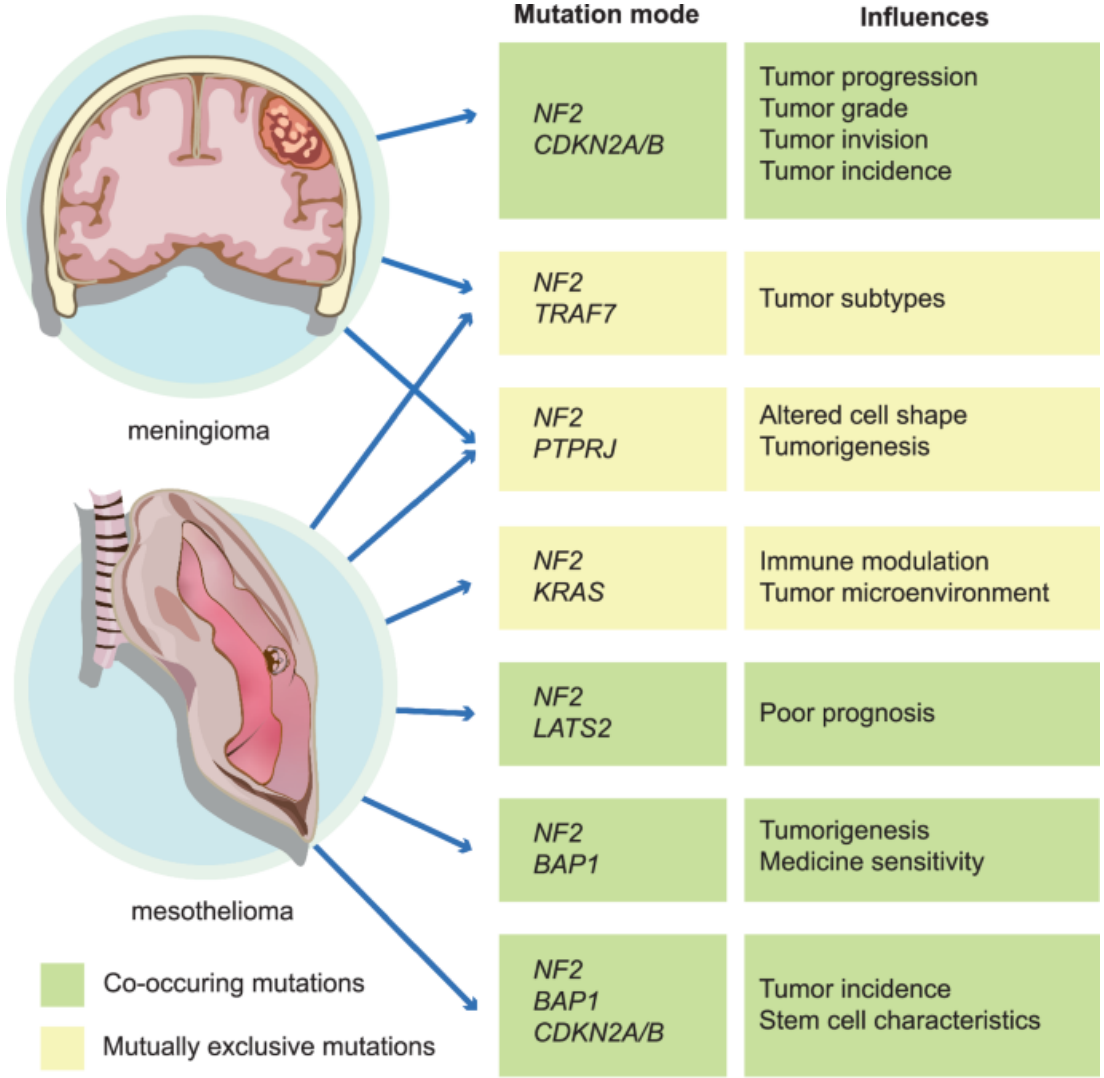
Recent Advances in Meningioma Immunogenetics

*May Al-Rashed[1], Kara Foshay[2,3] and Malak Abedalthagafi[4]**

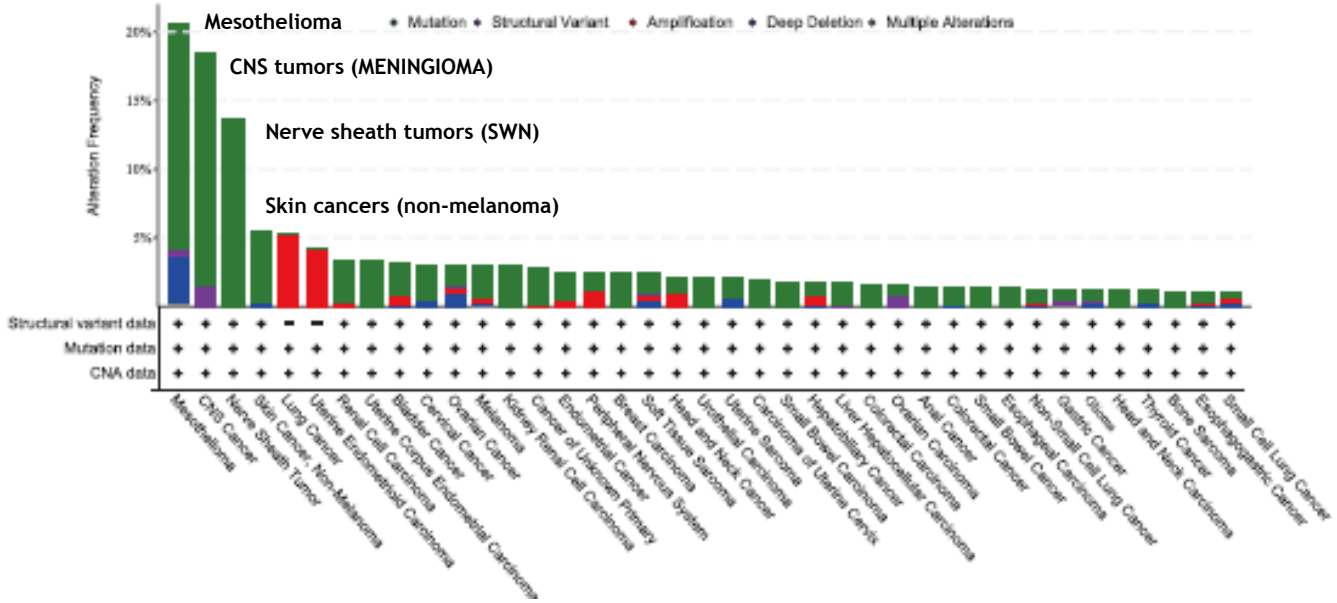
frontiers in Oncology

REVIEW
published: 08 January 2020
doi: 10.3389/fonc.2019.01472

Znaczenie genu *Nf2* w onkologii człowieka (non-Nf2-SWN - kom. somatyczne)



Mutation mode	Influences
NF2 *CDKN2A/B*	Tumor progression Tumor grade Tumor invision Tumor incidence
NF2 *TRAF7*	Tumor subtypes
NF2 *PTPRJ*	Altered cell shape Tumorigenesis
NF2 *KRAS*	Immune modulation Tumor microenvironment
NF2 *LATS2*	Poor prognosis
NF2 *BAP1*	Tumorigenesis Medicine sensitivity
NF2 *BAP1* *CDKN2A/B*	Tumor incidence Stem cell characteristics

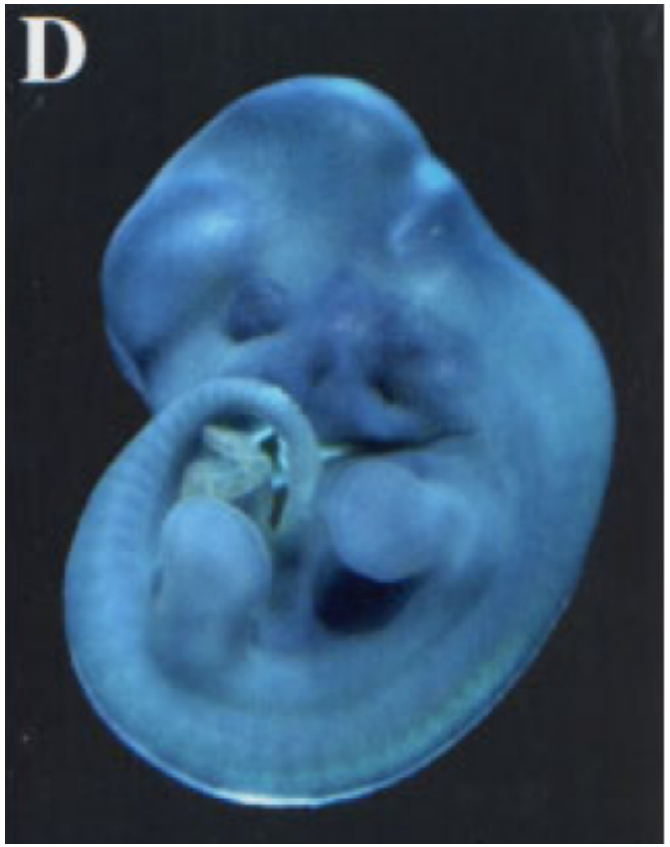


npj | precision oncology
Review article
Published in partnership with The Hormel Institute, University of Minnesota
npj Precision Oncology | (2024)8:133
https://doi.org/10.1038/s41698-024-00627-5

NF2: An underestimated player in cancer metabolic reprogramming and tumor immunity

Duo Xu[1,2], Shiyuan Yin[1,2] & Yongqian Shu[1]

Znaczenie genu *Nf2* w embriogenezie układu nerwowego



In addition, we detected considerable *NF2* promoter activity in various NF2-affected tissues such as acoustic ganglion, trigeminal ganglion, spinal ganglia, optic chiasma, the ependymal cell-containing tela choroidea, and the pigmented epithelium of the retina. The *NF2* promoter expression pattern during embryogenesis suggests a specific regulation of the *NF2* gene during neural crest cell migration and further supports the role of merlin in cell adhesion, motility, and proliferation during development.

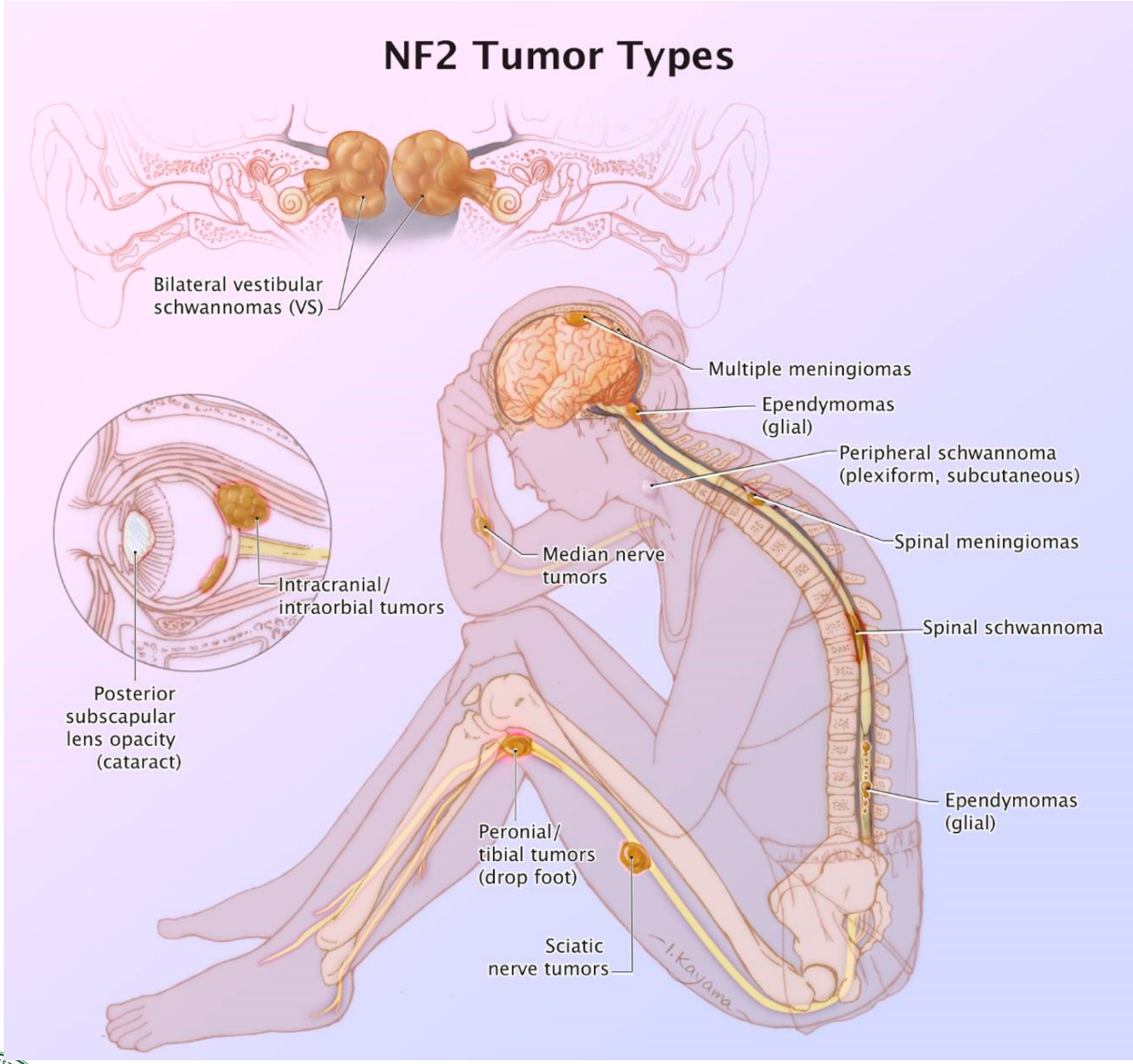
DEVELOPMENTAL DYNAMICS 235:2771–2785, 2006

DISEASE CONNECTIONS

Regulation of the *Neurofibromatosis 2* Gene Promoter Expression During Embryonic Development

Elena M. Akhmametyeva,[1,2] Maria M. Mihaylova,[1,2] Huijun Luo,[1,2] Sadeq Kharzai,[1] D. Bradley Welling,[3] and Long-Sheng Chang[1–4]*

Nf2 zależna Schwannomatoza: spektrum objawów



TYPOWE GRUPY OBJAWÓW Nf2-SWN

- Schwannoma nerwu przedsionkowo-ślimakowego
  - **NIEDOSŁUCH/ GŁUCHOTA**
- Guzy MÓZGU (gwiaździaki ; ASTROCYTOMA)
- Guzy RDZENIA (wyściółczaki; EPENDYMOMA)
- Guzy wewnątrzczaszkowe i wewnątrzkanałowe
  - OPONIAKI (!)
  - OPONIAKI ATYPOWE (wewnątrzoczodołowe)
- Guzy OBWODOWEGO UN (SWN)
  - Schwannoma każdej lokalizacji (OCZODOŁU, przykręgosłupowa, NERWÓW czaszkowych)
- Młodzieńcza zaćma podtorebkowa i hamartomaty siatkówki, błona przedsiatkówkowa
- *POWIKŁANIA NEUROLOGICZNE (niedowłady i porażenia, ból neuropatyczny itp.)*
- ZMIANY SKÓRNE (! dzieci)

REVIEW Open Access
the genetic landscape and possible therapeutics of neurofibromatosis type 2
Mohammad Amin Ghalavand[1,2†], Alimohamad Asghari[3,1†], Mohammad Farhadi[1], Farzad Taghizadeh-Hesary[1,4], Masoud Garshasbi[2*] and Masoumeh Falah[1*]
Ghalavand *et al. Cancer Cell International* (2023) 23:99
https://doi.org/10.1186/s12935-023-02940-8

Revised Diagnostic Criteria for NF2-Related Schwannomatosis

Diagnostic criteria for NF2-related schwannomatosis

A diagnosis of NF2-related schwannomatosis (previously termed neurofibromatosis 2, NF2) can be made when an individual has one of the following:

1. Bilateral vestibular schwannomas (VS)
2. An identical NF2 pathogenic variant in at least 2 anatomically distinct NF2-related tumors (schwannoma, meningioma, and/or ependymoma). (Note: if the variant allele fraction (VAF) in unaffected tissues such as blood is clearly <50%, the diagnosis is mosaic NF2-related schwannomatosis)
3. Either 2 major or 1 major and 2 minor criteria as described in the following:

Major criteria:

a. Unilateral VS
b. First-degree relative other than sibling with NF2-related schwannomatosis
c. 2 or more meningiomas (Note: single meningioma qualifies as minor criteria).
d. NF2 pathogenic variant[a] in an unaffected tissue such as blood (Note: if the VAF is clearly <50%, the diagnosis is mosaic NF2-related schwannomatosis)

Minor criteria:

a. Can count >1 of a type (eg, 2 distinct schwannomas would count as 2 minor criteria)
   - Ependymoma, meningioma (Note: multiple meningiomas qualify as a major criteria), schwannoma (Note: if the major criterion is unilateral VS, at least 1 schwannoma must be dermal in location)

b. Can count only once (eg, bilateral cortical cataracts count as a single minor criterion)
   - Juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane in a person aged <40 years, meningioma

c. Pattern of genetic changes in unaffected and tumor tissue in NF2-related schwannomatosis

Gene locus	Unaffected Tissue[b]	Tumor 1	Tumor 2	Comment
NF2				
Allele 1	PV1[c]	PV1	PV1	Shared NF2 pathogenic variant
Allele 2	WT	LOH or NF2 PV2	LOH or NF2 PV3	Tumor-specific partial loss of 22q in transposition or a different NF2 somatic second PV in every anatomically unrelated tumor

Plotkin SR, Messiaen L, Legius E, Pancza P, Avery RA, Blakeley JO, et al.
Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: an international consensus recommendation.
Genet Med. 2022; 24(9): 1967-77.
https://doi.org/10.1016/j.gim.2022.05.007

Nf2 zależna Schwannomatoza: genotyp-fenotyp i rokowanie

Table 1 Neurofibromatosis type 2 (NF2) mutations based on location and their clinical manifestations [16, 26]

Mutation Type	Location	Mosaic† mutation	Germline mutation
Truncating mutation	Exon 1	Moderate	Moderate-Severe
	Exon 2–13	Moderate-Severe	Severe
	Exon 14–15	Moderate	Moderate-Severe
Splice site mutation	Exon 1–7 (in frame)	Mild	Moderate
	Exon 1–7 (frameshift)	Moderate	Moderate-Severe
	Exon 8–13 (in frame)	Mild	Moderate
	Exon 8–13 (frameshift)	Moderate	Moderate-Severe
	Exon 14–17	Mild	Moderate
Large and small deletions	Small in-frame deletion or duplication	Very mild phenotype	Mild
	Large deletion (> 1 exon) including promoter or exon 1		
	Maintaining reading frame	Very mild phenotype	Mild
	Causing frameshift alteration	Mild	Moderate
	Whole NF2 gene	Mild	Moderate
	Large deletion (> 1 exon) excluding promoter or exon 1		
	Maintaining reading frame	Very mild phenotype	Mild
	Causing frameshift alteration	Mild	Moderate
Missense variants		Very mild phenotype	Mild

† NF2 gene pathogenic variant in an unaffected tissue such as blood saliva samples with variant allele frequency < 50%

BEZ GENETYKI ANI RUSZ!

REVIEW

The genetic landscape and possible therapeutics of neurofibromatosis type 2

Mohammad Amin Ghalavand[1,2†], Alimohamad Asghari[3†], Mohammad Farhadi[1], Farzad Taghizadeh-Hesary[1,4], Masoud Garshasbi[2*] and Masoumeh Falah[1*]

Open Access

Ghalavand et al. Cancer Cell International (2023) 23:99
https://doi.org/10.1186/s12935-023-02940-8

Objawy NF-2 w zależności od wieku *(typowo od 16-22 r.ż.; niedosłuch)*

Glejaki HG (?)

MPNST (??)

Postać dziecięca NF-2:

zmiany oczne, guzy OUN i rdzenia, oponiaki w tym atypowe (oczodół), długo jednostronne VS, mnogie Schwannoma obwodowe i specyficzne skórne (PSS), padaczka, obj. neuropatyczne i porażenia, głuchota, itp. itd.

Schwannoma n. przedsionkowego

Schwannoma n. czaszkowych

MNOGIE oponiaki wewnątrzczaszkowe (LG)
MNOGIE oponiaki wewnątrzkanałowe (LG)
Gwiaździaki OUN (LG)
Wyściółczaki rdzenia kręgowego (LG)

Urodziny — Wczesne dzieciństwo — Okres szkolny — **16-22 r.ż. (!)** — Dorosłość

Plamy CAL (pojedyncze)

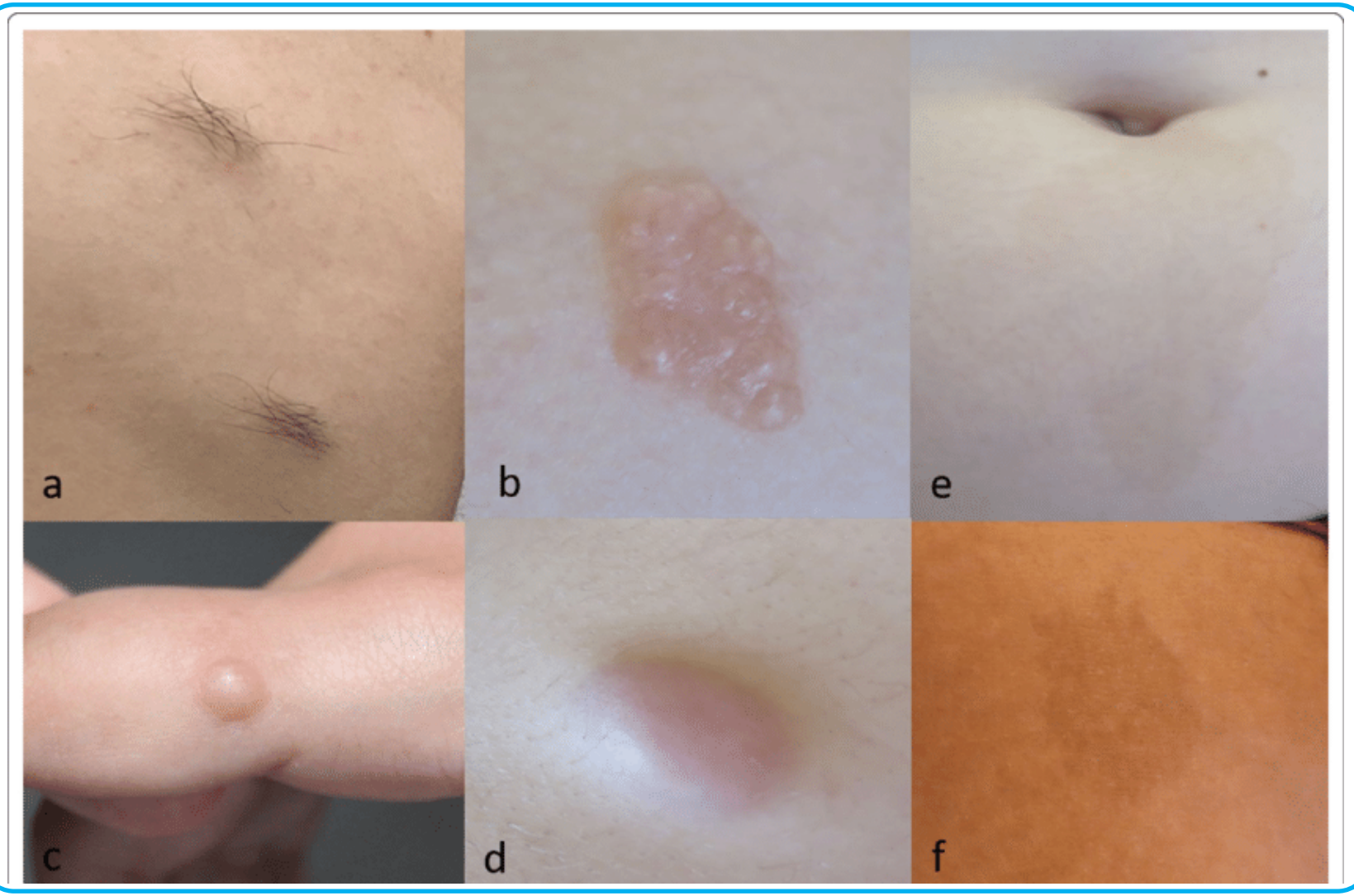
Schwannoma różnych okolic ciała

PSS „*Plaque skin Schwannoma*” (PN-podobne zmiany skórne jak w NF-1)

Zmętnienie podtorebkowe soczewki i różne formy zaćmy
Przerost barwnikowy siatkówki
Hamartomaty siatkówki

Plotkin SR, Messiaen L, Legius E, Pancza P, Avery RA, Blakeley JO, et al.
Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: an international consensus recommendation.
Genet Med. 2022; 24(9): 1967-77. https://doi.org/10.1016/j.gim.2022.05.007

Nf2 zależna Schwannomatoza: jak nie pomylić z NF-1?



Conclusions

Dermatological and ophthalmic lesions are frequent and early in children with sporadic severe NF2 but rarely lead to the diagnosis because of lack of clear guidelines. Cutaneous tumours, and in particular schwannomas, are the most frequent dermatological lesions but are often underdiagnosed. CALMs are frequent, but atypical, and mostly in small numbers. Multiple HPM lesions seem suggestive although inconsistent. The sensitivity of reticulated capillary malformation-like lesions remains to be assessed by further studies.

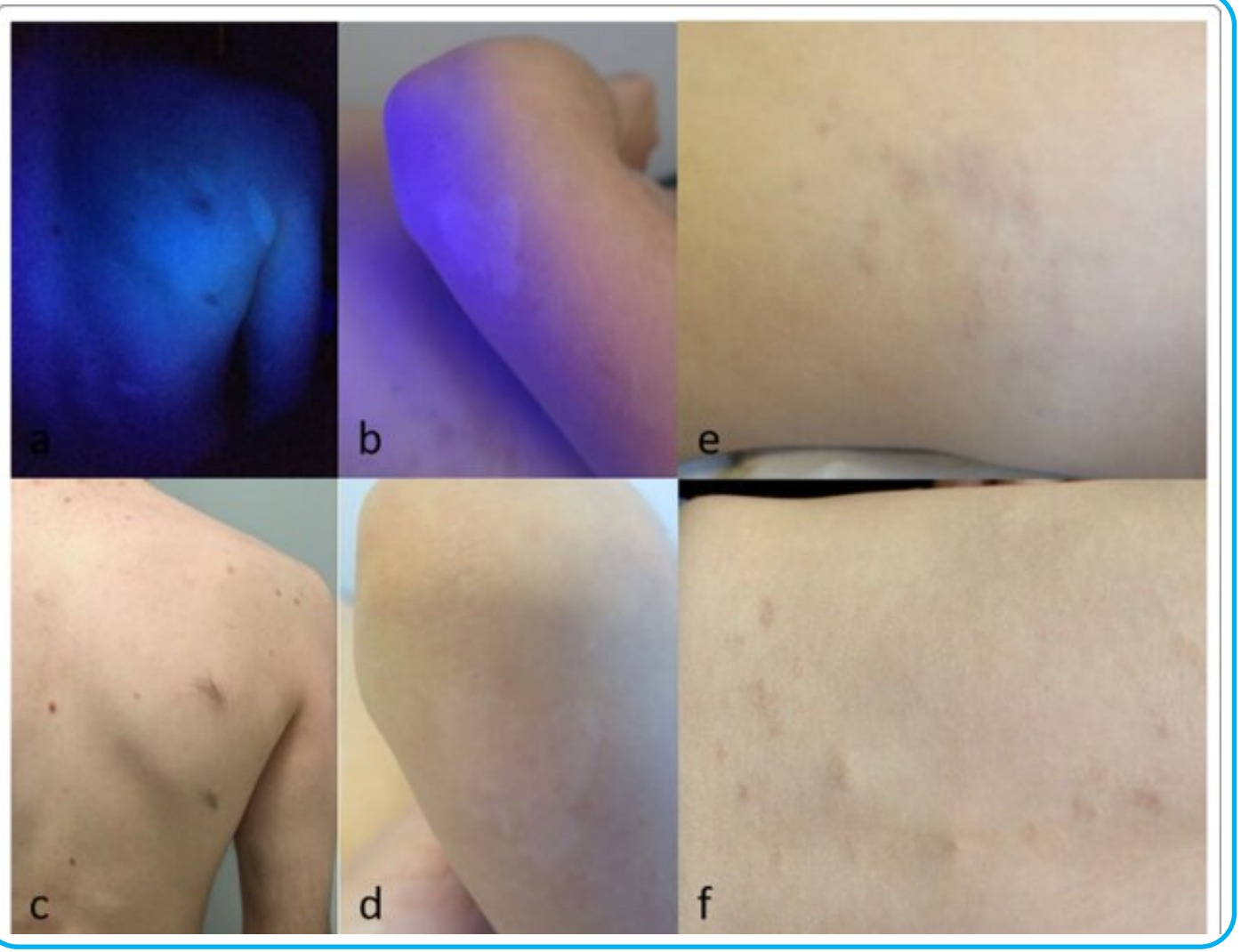
RESEARCH Open Access

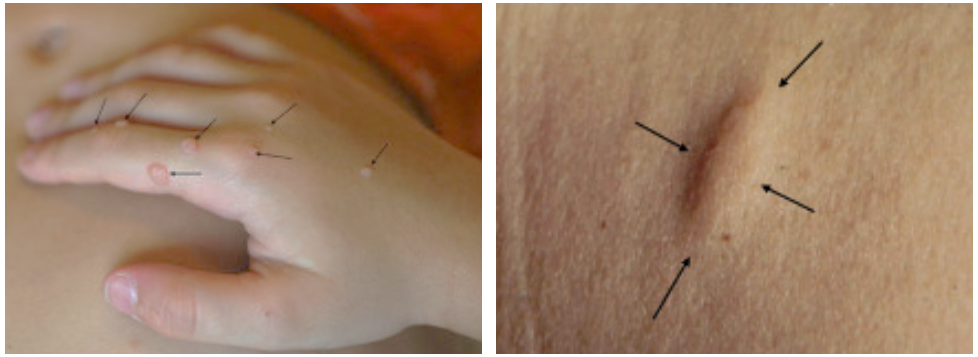
Dermatologic manifestations in paediatric neurofibromatosis type 2: a cross sectional descriptive multicentric study

S. Legoupil[1,2], D. Bessis[3], F. Picard[4], S. Mallet[5], J. Mazereeuw[6], A. Phan[7], D. Dupin-Deguine[8], M. Kalamarides[9,10], Research Group of the French Society of Paediatric Dermatology and C. Chiaverini[1,2*]

Legoupil *et al.*
Orphanet Journal of Rare Diseases (2022) 17:242
https://doi.org/10.1186/s13023-022-02379-6

Nf2 zależna Schwannomatoza: jak nie pomylić z NF-1?





Martino Ruggieri, Andrea Domenico Praticò, Dafydd Gareth Evans.
Diagnosis, Management, and New Therapeutic Options in Childhood Neurofibromatosis Type 2 and Related Forms,
Seminars in Pediatric Neurology,Volume 22, Issue 4,2015,Pages 240-258

RESEARCH Open Access

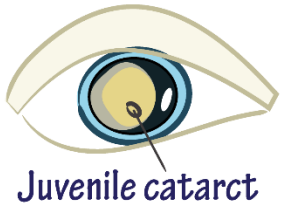
Dermatologic manifestations in paediatric neurofibromatosis type 2: a cross sectional descriptive multicentric study

S. Legoupil[1,2], D. Bessis[3], F. Picard[4], S. Mallet[5], J. Mazereeuw[6], A. Phan[7], D. Dupin-Deguine[8], M. Kalamarides[9,10], Research Group of the French Society of Paediatric Dermatology and C. Chiaverini[1,2*]

Legoupil *et al.*
Orphanet Journal of Rare Diseases (2022) 17:242
https://doi.org/10.1186/s13023-022-02379-6

Nf2 zależna Schwannomatoza: spektrum objawów

Neurofibromatosis Type 2
Autosomal Dominant, Chr 22

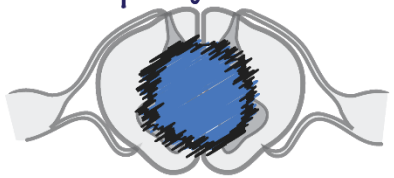


Juvenile catarct

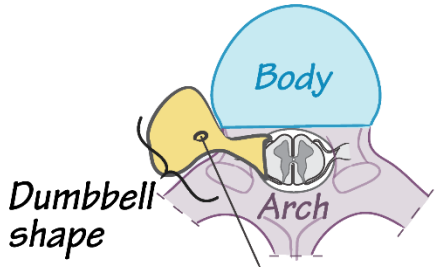
Multiple Meningiomas

Bilateral Acoustic Schwannomas

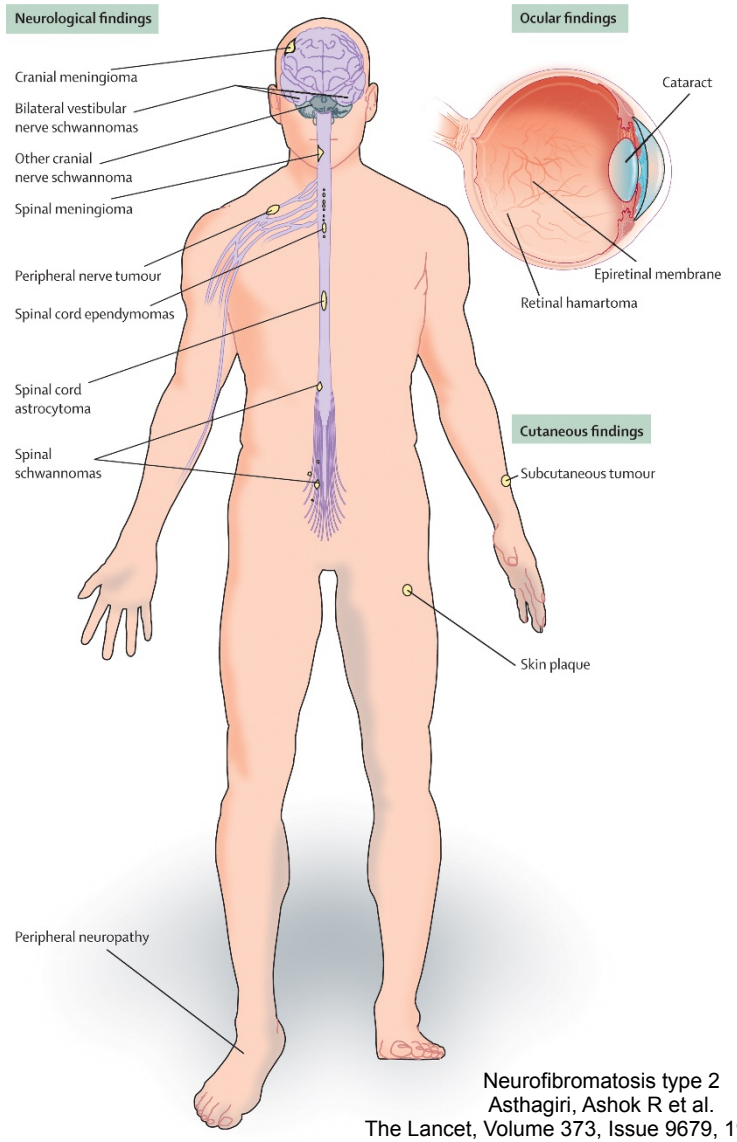
Ependymoma



NF-1 & NF-2



NERVE SHEATH TUMOR
Schwannoma vs. Neurofibroma



Neurofibromatosis type 2
Asthagiri, Ashok R et al.
The Lancet, Volume 373, Issue 9679, 1974 - 1986

https://ditki.com/course/pathology/glossary/pathophysiologic-disorder/familial-tumor-syndromes-neurofibromatosis-type-2

NF2-related Schwannomatosis

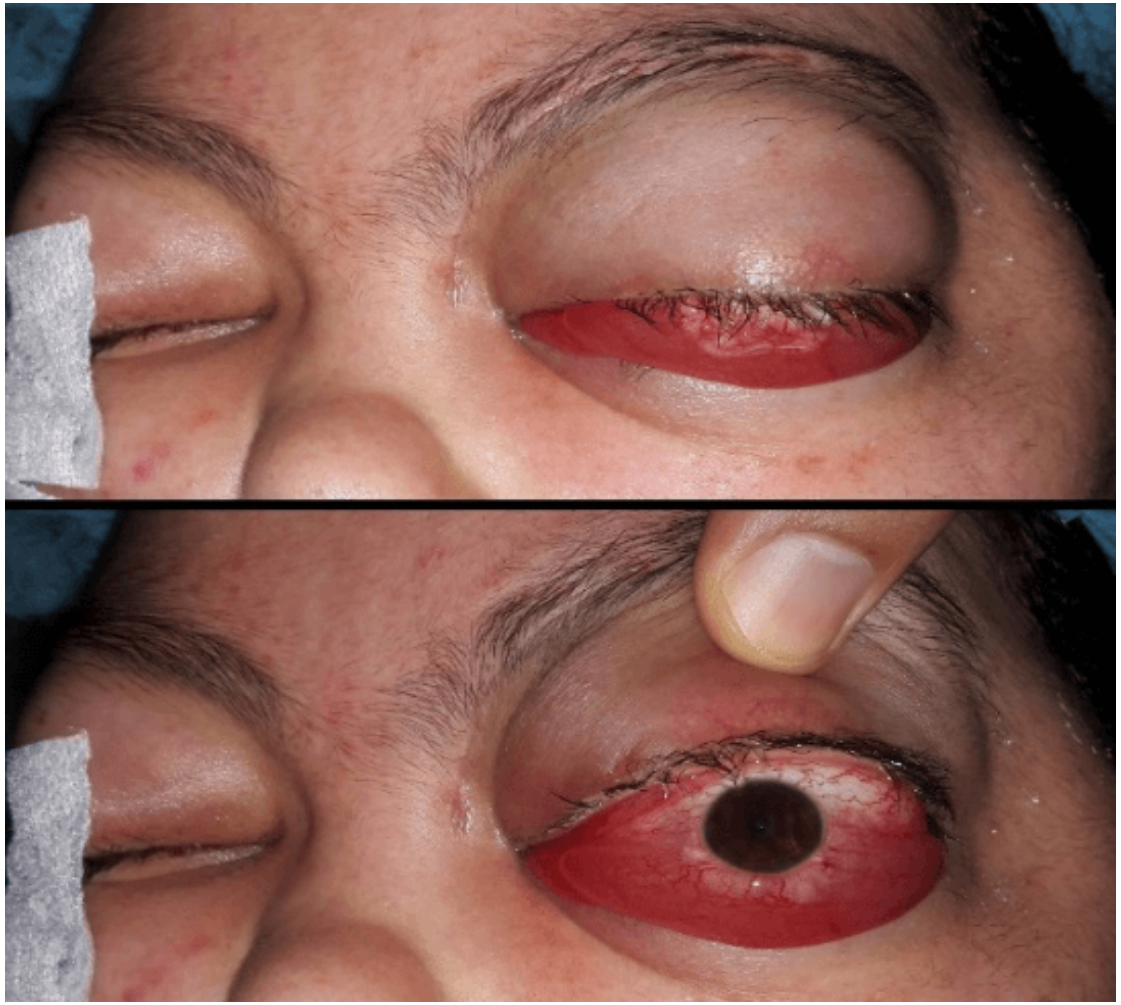
- Caused by disease-causing variants in the *NF2* gene
- Incidence: 1 in 28,000 live births
- Typical Presentation:
  - Adults:
    - Average onset of symptoms: 22 years
    - Hearing loss (44%), tinnitus (10%), imbalance (8%)
  - Children:
    - Average onset of symptoms: 6 years
    - Skin tumors, eye findings, seizures
- Multiple tumors and tumor types
- Benign histology but not benign clinical course

Data was published simultaneously in PLOTKIN, ET AL. N ENGL J MED. 2024. DOI:10.1056/NEJMoa2400985].

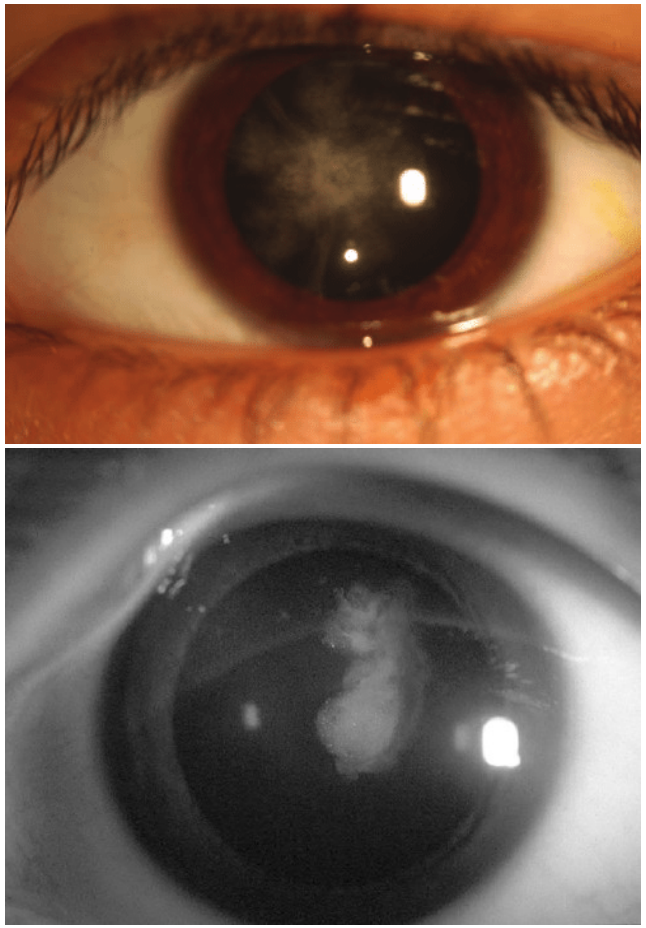
OncLive Rapid Readout

Scott Plotkin, MD, PhD
Massachusetts General Hospital
Boston, Massachusetts

Nf2 zależna Schwannomatoza: objawy oczne

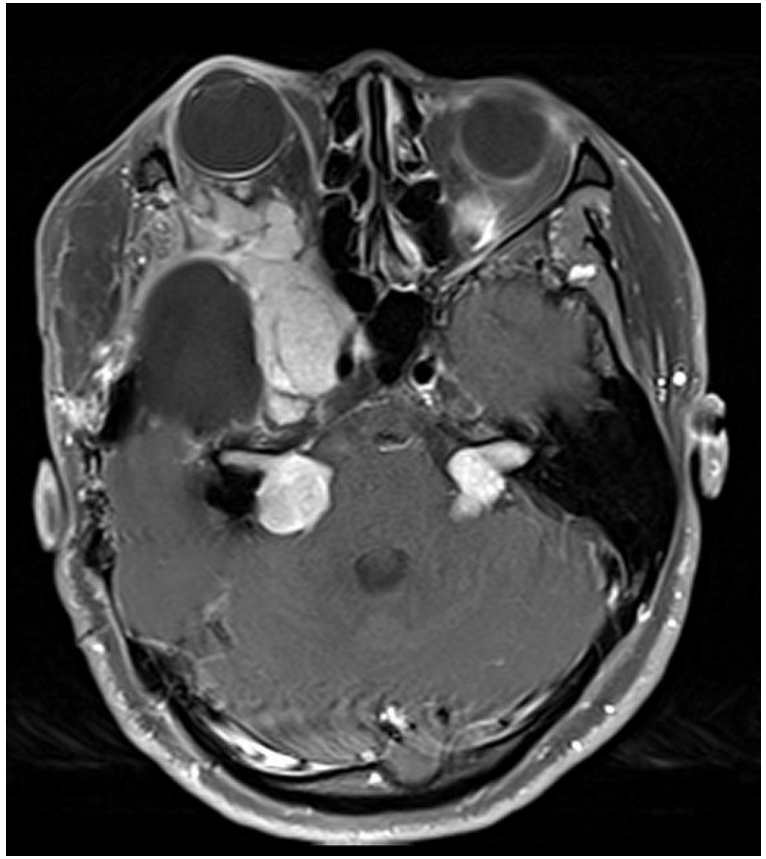


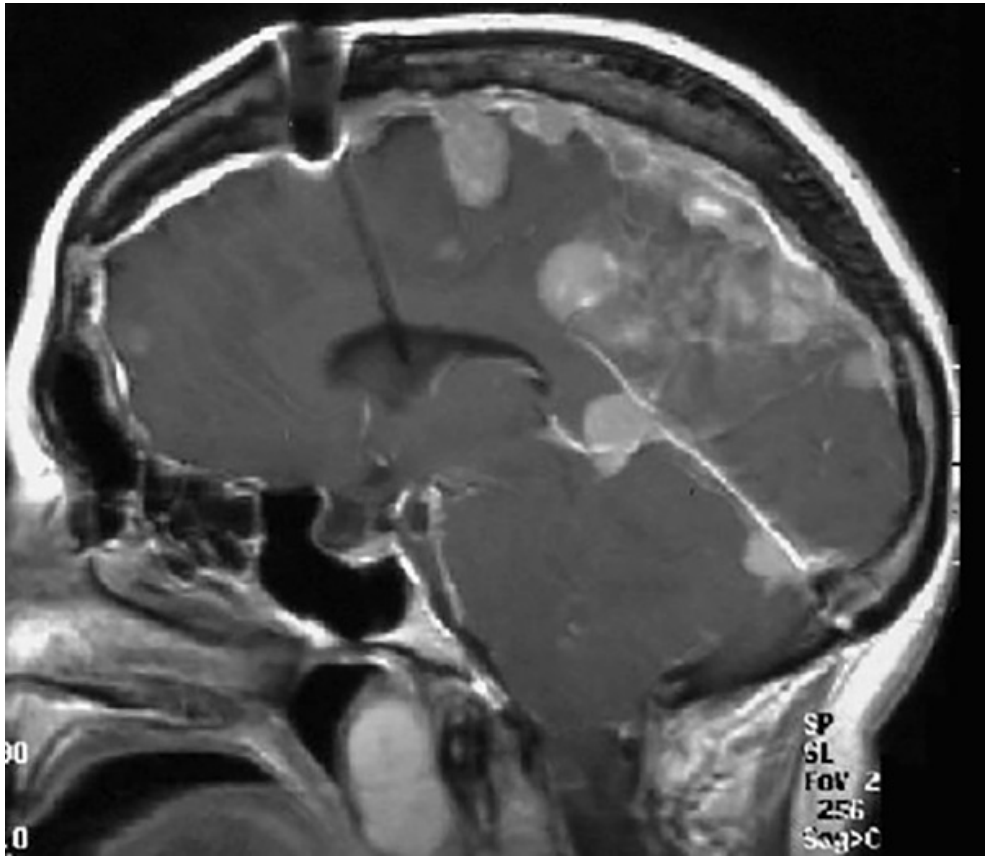
Taoufik Abdellaoui, Soukaina Belfaiza, Yassine Malek, Fouad Elasri, Karim Reda, Abdelbarre Oubaaz.
Large Orbital Tumor in a Patient with Neurofibromatosis Type 2.
American Journal of Surgical Case Reports, 2020, 2674-5046



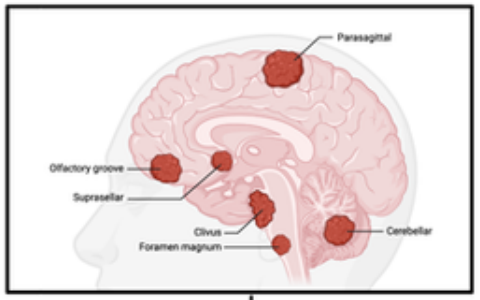
Bosch, M., Mironov, A. & Killer, H.
Atypical manifestation of neurofibromatosis type 2 in a boy.
Eye **19**, 705–706 (2005)

Nf2 zależna Schwannomatoza: mnogie oponiaki





Nf2 zależna Schwannomatoza: mnogie oponiaki



- NF2-mutations
  - Chr 22 loss or no CNA
    - No TERT mutations or CDKN2A/B loss → Better Prognosis
    - TERT mutations/ CDKN2A/B loss → Early recurrence with poor prognosis
  - Chr 22, 1p losses → Early recurrence with poor prognosis
- No NF2-mutations
  - TERT mutations/ CDKN2A/B loss → Early recurrence with poor prognosis
  - AKT/PIK3CA, Hedgehog (SMO, SUFU), TRAF7, ARID1A → Early recurrence with intermediate prognosis
  - KLF4, POLR2A, SMARCB1 → Better Prognosis

Hsieh AL, Bi WL, Ramesh V, Brastianos PK, Plotkin SR. Evolving concepts in meningioma management in the era of genomics. Cancer. 2024 Aug 1;130(15):2586-2600.

Zdjęcie z:https://stock.adobe.com/

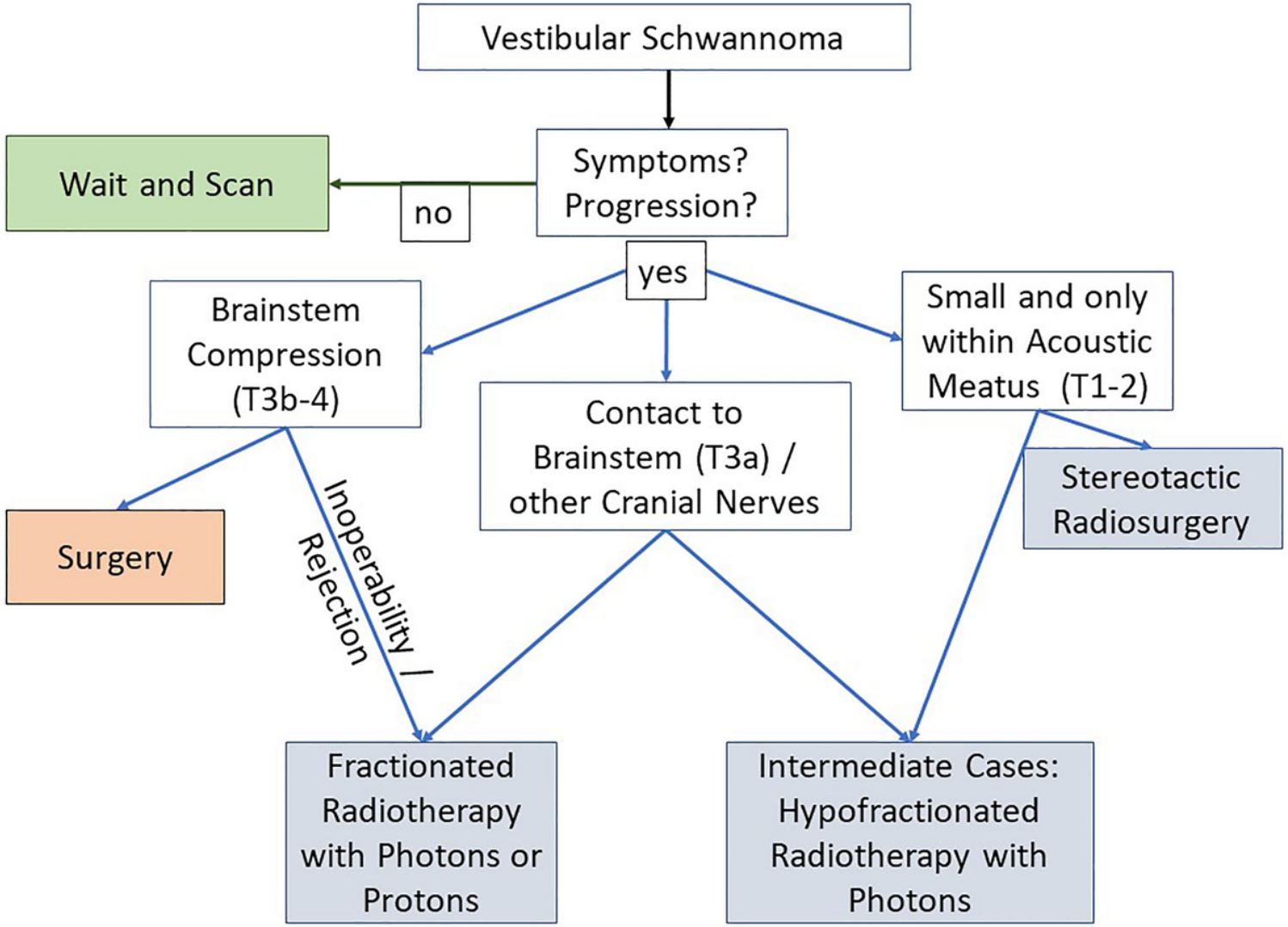
Leczenie NF2-zależnej Schwannomatozy: zasady i filozofia

- **Leczenie neurochirurgiczne**
  - o ograniczanej skuteczności
    - radykalne wycięcie guza osłonkowego n. obwodowych zawsze wiąże się porażeniem unerwianej przez niego struktury
      - możliwość uszkodzenia struktur okolicznych (np. niedowłady czy porażenia n. czaszkowych po wycięciu VS)
    - praktycznie nieoperacyjność guzów wewnątrzrdzeniowych i znacznej części guzów mózgu
    - ograniczone powikłaniami oraz warunkami anatomicznymi możliwości („radykalnego”?) wycięcia oponiaków
- **Radioterapia**
  - o bardzo małej skuteczności, znaczącej toksyczności i ryzyku indukowania transformacji złośliwej (zwłaszcza gwiaździaków)
  - wysokoprecyzyjne i wysokodawkowane terapie stereotaktyczne („GammaKnife” czy bezpieczniej „CyberKnife”) wykorzystuje się w leczeniu oponiaków i VS (!)
    - dowiedziono, że mogą opóźniać postęp niedosłuchu, ale nie zapobiegają utracie słuchu
    - Wykazują przewagę w odniesieniu do zabiegów mikrochirurgicznych z odniesieniu do wyników uzyskiwanych poprzez wszczepianie implantów ślomakowych
- **Leczenie ukierunkowane na cel molekularny**

Chirurgia w NF-ach…

Zdjęcie z: https://arthive.com/artists/9667~Francisco_Jose_Perez_Macedo/works/308034~Surgeon

Leczenie NF2-zależnej Schwannomatozy: (radio)chirurgia



frontiers in Oncology
ORIGINAL RESEARCH
published: 17 November 2021
doi: 10.3389/fonc.2021.772831

Effectiveness and Toxicity of Fractionated Proton Beam Radiotherapy for Cranial Nerve Schwannoma Unsuitable for Stereotactic Radiosurgery

Tanja Eichkorn[1,2], Sebastian Regnery[1,2], Thomas Held[1,2], Dorothea Kronsteiner[3], Juliane Hörner-Rieber[1,2], Rami A. El Shafie[1,2], Klaus Herfarth[1,2], Jürgen Debus[1,2,4,5,6] and Laila König[1,2]*

Leczenie NF2-zależnej Schwannomatozy: leczenie a implant ślimakowy

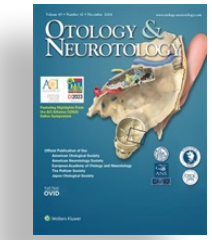
Abstract

Objective

Compare cochlear implant (CI) performance between patients with ipsilateral sporadic vestibular schwannoma (VS) and NF2-related schwannomatosis (NF2). Compare CI performance according to VS management modality.

Conclusion

Select patients with VS achieve successful hearing rehabilitation with a CI. In this cohort, tumor management strategy significantly influenced CI performance, whereas differences in NF2 status exhibited less effect. Specifically, all patients managed with observation or radiosurgery achieved open-set speech perception, whereas approximately half of people with NF2-related VS and two-thirds of people with sporadic VS achieved this outcome after tumor microsurgery. When disease permits, observation and radiosurgery should be considered in patients who may later pursue a CI.

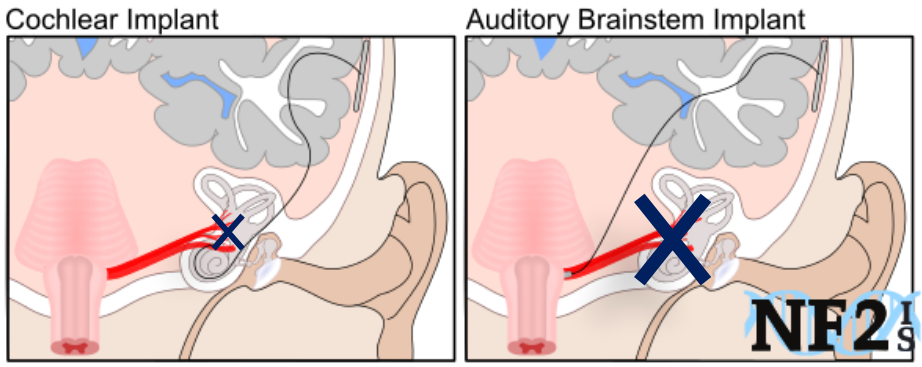


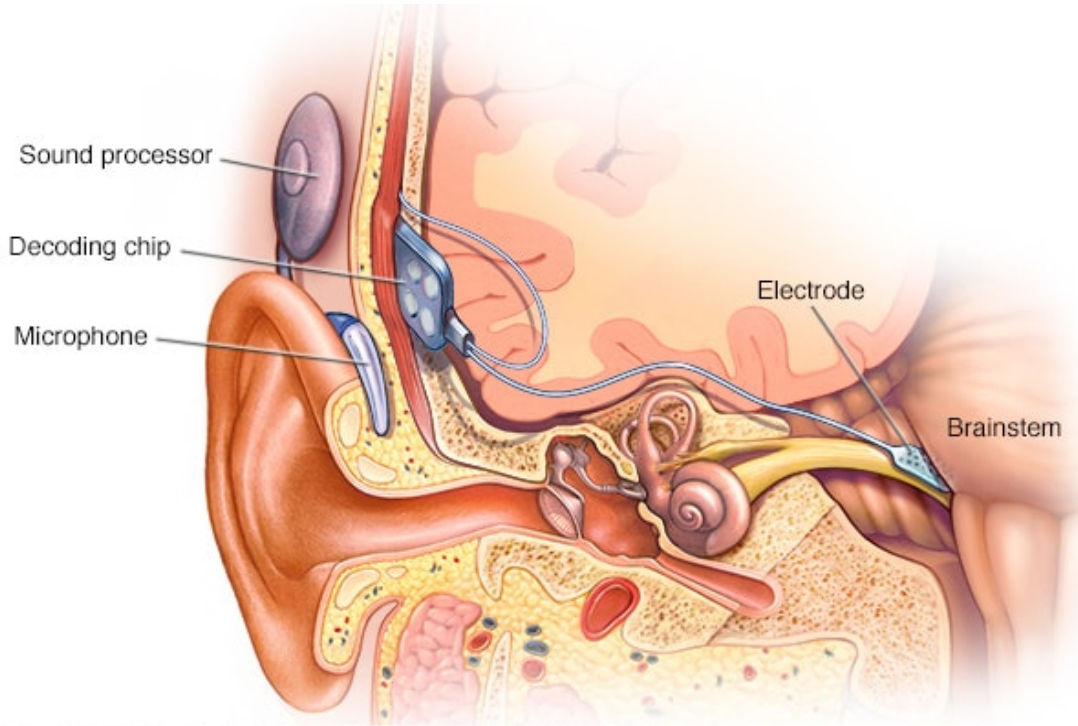
COCHLEAR IMPLANTS

Cochlear Implant Outcomes between Patients with Sporadic and Neurofibromatosis Type 2–Associated Vestibular Schwannoma

Dornhoffer, James R.*; Haller, Travis*; Lohse, Christine M. MS†; Driscoll, Colin L.W.*‡; Neff, Brian A.*‡; Saoji, Aniket*; Link, Michael J.*‡; Carlson, Matthew L.*‡

Otology & Neurotology 44(8):p 791-797, September 2023. | **DOI:** 10.1097/MAO.0000000000003963





Leczenie NF2-zależnej Schwannomatozy: leczenie a implant ślimakowy

European Archives of Oto-Rhino-Laryngology (2018) 275:2667–2674
https://doi.org/10.1007/s00405-018-5127-9

Impact of cochlear implantation on the management strategy of patients with neurofibromatosis type 2

Haoyue Tan[1,2,3] · Huan Jia[1,2,3] · Yun Li[1,2,3] · Zhihua Zhang[1,2,3] · Weidong Zhu[1,2,3] · Yun Cai[1] · Zhaoyan Wang[1,2,3] · Hao WU[1,2,3]

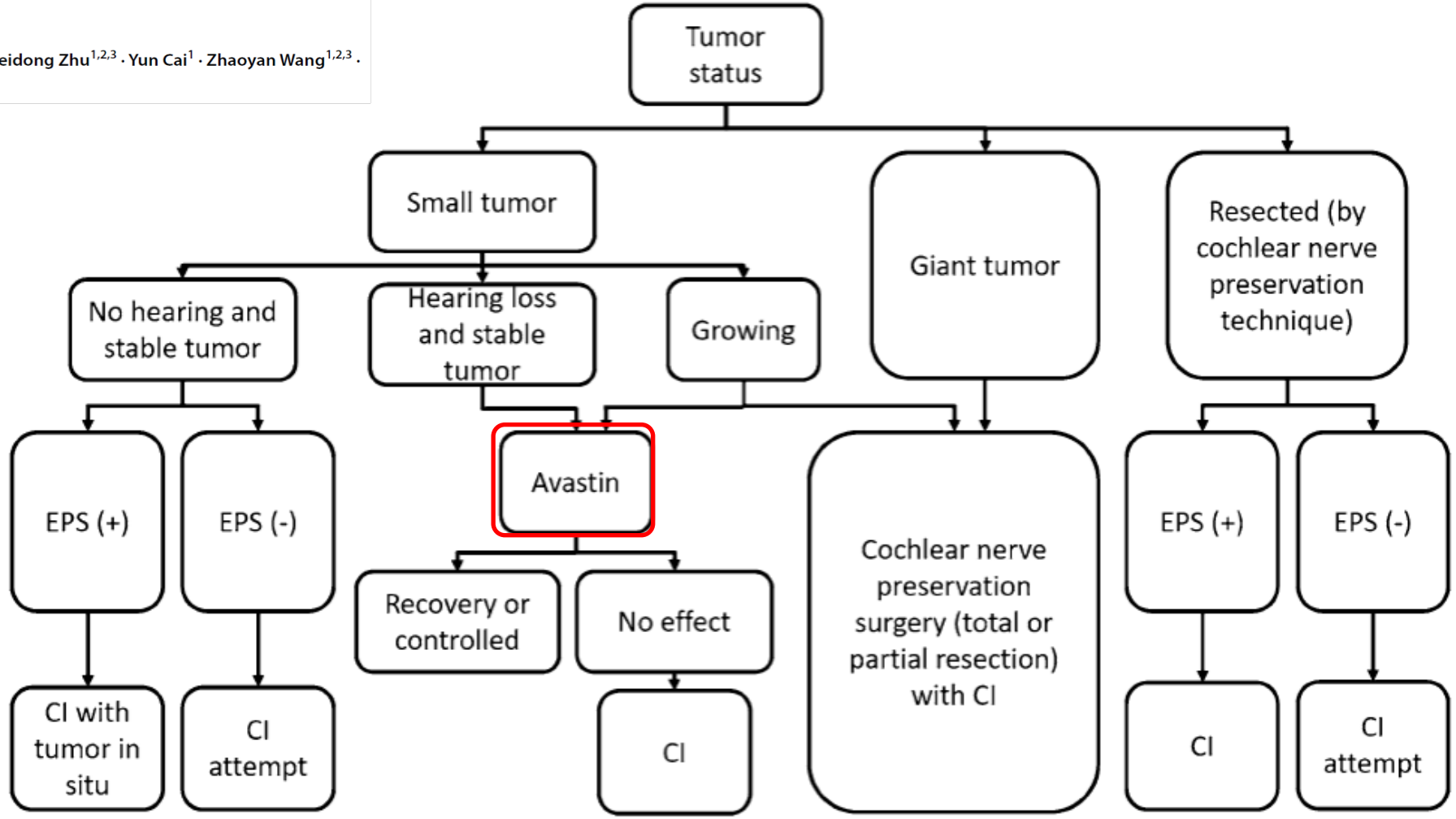
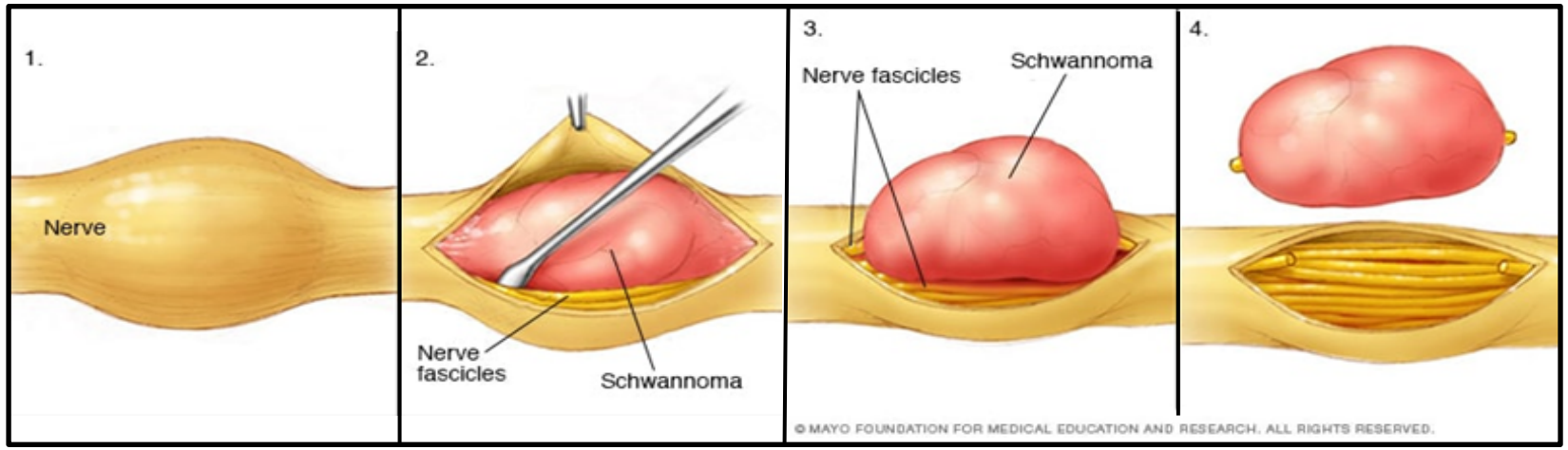


Fig. 3 Decision-making flow-chart for cochlear implantation in NF2 patients. EPS, electrical promontory stimulation

Leczenie NF2-zależnej Schwannomatozy: zasady i filozofia



SWN

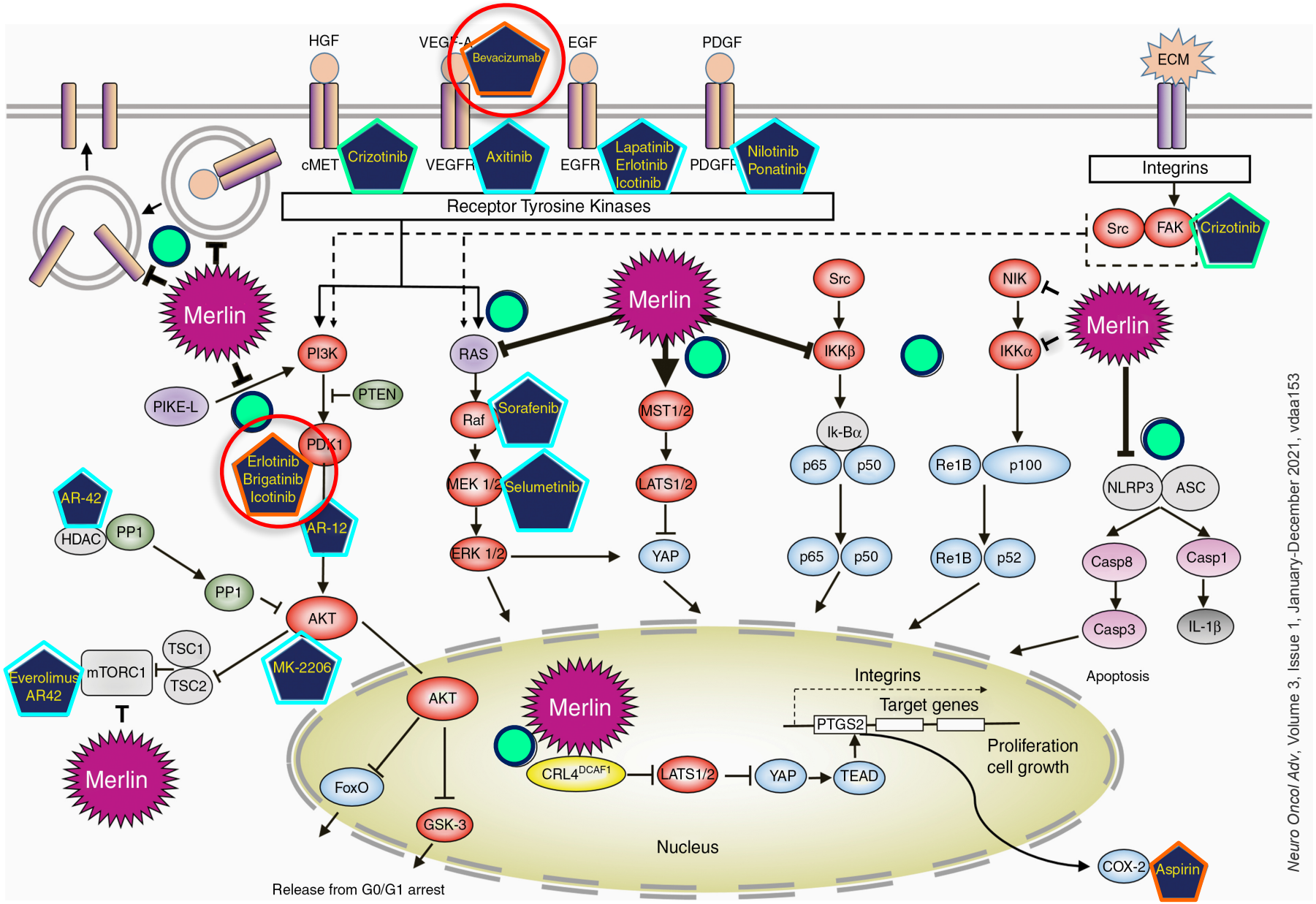
Metody leczenia guzów złośliwych w onkologii

- Chirurgia
- Radioterapia
- Chemioterapia
- **Terapie ukierunkowane na cel molekularny**
  - **warunek**: *somatyczna mutacja genowa*
- Immunoterapia
- Terapie genowe

Metody leczenia guzów łagodnych w onkologii

- **Chirurgia**
- Radioterapia? (=> gest rozpaczy?)
- ~~Chemioterapia~~
- *? Terapie ukierunkowane na cel molekularny*
- *? Immunoterapia*
- *? Terapie genowe*

Cele molekularne do wykorzystania w *Nf2*-SWN



Neuro Oncol Adv, Volume 3, Issue 1, January-December 2021, vdaa153

Nf2- merlina: 7 punktów oddziaływania

Badania kliniczne w Nf2-SWN u dzieci w USA

BADANIA KLINICZNE W GRUPIE Nf2-SWN

- Prowadzone są od 2002 roku
- *Ogółem zarejestrowano 58 badań*
- *Przy czy 19 prowadzono u dzieci 0-17 r.ż.*
  - *17 miało charakter interwencyjny*
  - *16 dotyczyło leków*

Search Results

Viewing 1-19 out of 19 studies

Showing results for: **NF2 | Child (birth - 17) | Phase: 1, 2, 3 | Interventional studies**

— Synonyms of conditions or disease (4)

nf2 ; Neurofibromatosis 2 ; Neurofibromatosis type 2 ; Neurofibromatosis type II ; type 2 neurofibromatosis

	Study Title	NCT Number	Status	Conditions	Interventions
1	Phase II Study of FCN-159 in NF2 Nerve Sheath Tumors	NCT06553365	Not yet recruiting	Nerve Sheath Tumor	FCN-159
2	Doxycycline in Cutaneous Schwannoma (NF2)	NCT05521048	Recruiting	Neurofibromatosis Type 2	Doxycycline
3	Efficacy and Safety of REC-2282 in Patients With Progressive Neurofibromatosis Type 2 (NF2) Mutated Meningiomas	NCT05130866	Recruiting	Neurofibromatosis Type 2	REC-2282; Pb
4	Innovative Trial for Understanding the Impact of Targeted Therapies in NF2-Related Schwannomatosis (INTUITT-NF2)	NCT04374305	Active, not recruiting	Neurofibromatosis Type 2	Brigatinib
5	Phase 2 Clinical Trial of Crizotinib for Children and Adults with Neurofibromatosis Type 2 and Progressive Vestibular	NCT04283669	Active, not recruiting	Vestibular Schwannoma	Crizotinib
6	Trial of Selumetinib in Patients With Neurofibromatosis Type II Related Tumors	NCT03095248	Completed	Neurofibromatosis 2	Selumetinib
7	Study of Aspirin in Patients with Vestibular Schwannoma	NCT03079999	(?), Recruiting	Vestibular Schwannoma	Aspiri; Placeb
8	Icotinib Study for Patients With Neurofibromatosis Type 2 (NF2) and NF2-Related Tumors	NCT02934256	Completed	Vestibular Schwannoma	Icotinib
9	Endostatin Study for Patients With Neurofibromatosis Type 2 (NF2) and NF2-Related Tumors	NCT02104323	Completed	Vestibular Schwannoma	Endostatin
10	Phase 2 Study of Bevacizumab in Children and Young Adults With NF 2 and Progressive Vestibular Schwannomas	NCT01767792	Completed, results	Vestibular Schwannomas	Bevacizumab
11	Bevacizumab and Temsirolimus Alone or in Combination with Valproic Acid or Cetuximab in Treating Patients with Advanced or	NCT01552434	Active, not recruiting	Advanced Mal. Neoplasm	
12	Efficacy and Safety Study of RAD001 in the Growth of the Vestibular Schwannoma(s) in Neurofibromatosis 2 (NF2) Patients	NCT01490476	Completed	Neurofibromatosis 2	Everolimus
13	Phase II Study of Everolimus (RAD001) in Children and Adults With Neurofibromatosis Type 2	NCT01419639	Completed, results	Neurofibromatosis Type II	Everolimus
14	Study of RAD001 for Treatment of NF2-related Vestibular Schwannoma	NCT01345136	Terminated	Neuroma, Acoustic	everolimus
15	Bevacizumab for Symptomatic Vestibular Schwannoma in Neurofibromatosis Type 2 (NF2)	NCT01207687	Completed, results	Vestibular Schwannoma	bevacizumab
16	Lapatinib Study for Children and Adults With Neurofibromatosis Type 2 (NF2) and NF2-Related Tumors	NCT00973739	Completed, results	Vestibular Schwannoma	Lapatinib

Aktywne: 7 (?) (wczesna faza przed rekrutacją: 1; zawieszone: 3, niejasny staus:1)

Zakończone: 7

(w tym z publikacją wyników): 4

PRZERWANE: 1

Badania kliniczne w Nf2-SWN u dzieci w EU

Clinical Trials

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2 results found Modify my search

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2024-512860-75-00 - (NFPET) '89Zr-Bevacizumab PET/CT imaging of vestibular schwannomas for the prediction of bevacizumab treatment effect in patients with symptomatic neurofibromatosis type 2 - Authorised, recruitment pending

Decision date: 01/10/2024 | Start date: N/A | End date: N/A | Medical condition: NF2-related schwannomatosis

Location(s): Netherlands: Authorised, recruitment pending

2024-516607-16-00 - KRONF2 - Phase 2a non-commercial and non-randomized intervention study evaluating the efficacy of crizotinib in the treatment of children with severe type 2 neurofibromatosis, in particular those excluded from surgery and / or radiotherapy - Authorised, recruitment pending

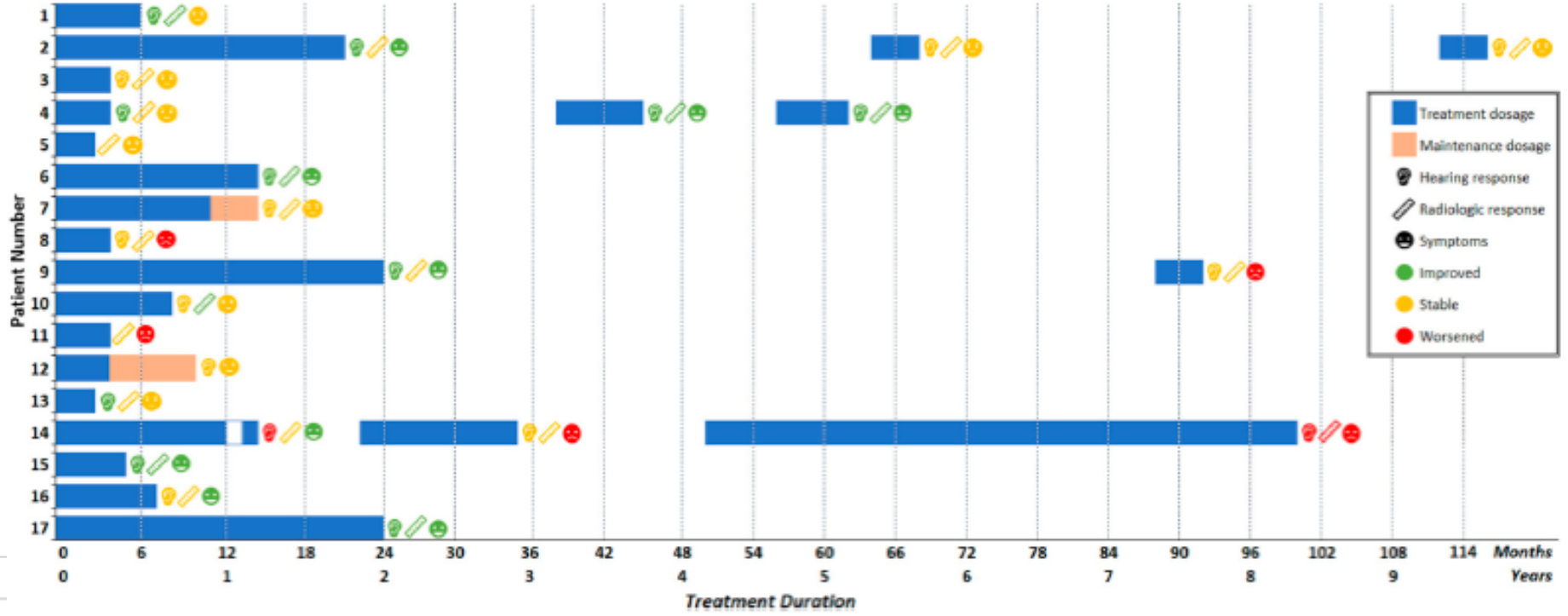
Decision date: 26/08/2024 | Start date: N/A | End date: N/A | Medical condition: Neurofibromatosis type 2 is a genetically determined primary malignancy resulting from a mutation that disables the function of the cell division control gene and leads to neoplasia such as benign peripheral nervous system tumors and various benign or locally malignant tumors of the central nervous system. Many complications occur in children more often than in adults and significantly shorten the survival period of affected children.

Location(s): Poland: Authorised, recruitment pending

Completed Trials for *NF2*-related Schwannomatosis

- Dominant *NF2* trial design: 1 tumor type, 1 drug

Drug	Clinicaltrials.gov	NCT	Phase	Target	N	Age (y)	Tumor/Endpoint	Results
PTC299	NCT00911248	6/2009	2	VEGFR	25	>=18	VS: tumor reduction	Terminated
Lapatinib	NCT00973739	8/2009	2	EGFR/ErbB1/2	17	4-80	VS: 15% volume reduction	12% RR
Everolimus	NCT01164939	3/2011	2	mTORC1	12	>=10	VS: 15% volume reduction	0% RR
Everolimus	NCT01490416	12/2011	2	mTORC1	28	>=15	VS: 20% volume reduction	0% RR
AR-42	NCT01372489	1/2011	1	HDAC	8	>=18	S-M: target inhibition	0% RR
Bevacizumab	NCT01024967	12/2009	2	VEGF	25	>=18	VS: hearing response	43% RR, 36% HR
Everolimus	NCT01334536	4/2012	2	mTORC1	22	>=18	VS: 20% volume reduction	Complete
Bevacizumab	NCT01767792	1/2013	2	VEGF	22	>=12	VS: hearing response	38% RR, 43% HR
Everolimus	NCT01880749	8/2013	2	mTORC1	22	>=12	S-M: target inhibition	Incomplete inhibition, PS
Endostatin	NCT02194333	12/2013	2	Angiogenesis	20	>=18	VS: tumor reduction	Complete
Axitinib	NCT02129647	5/2014	2	VEGFR1/2	16	>=18	VS: 20% volume reduction	Complete
Vistusertib	NCT02831257	7/2016	2	mTORC1/2	18	>=18	M: 20% volume reduction	6% RR
Icotinib	NCT02934256	10/2016	2	EGFR	10	8-16	VS: volume reduction	10% RR, 43% HR



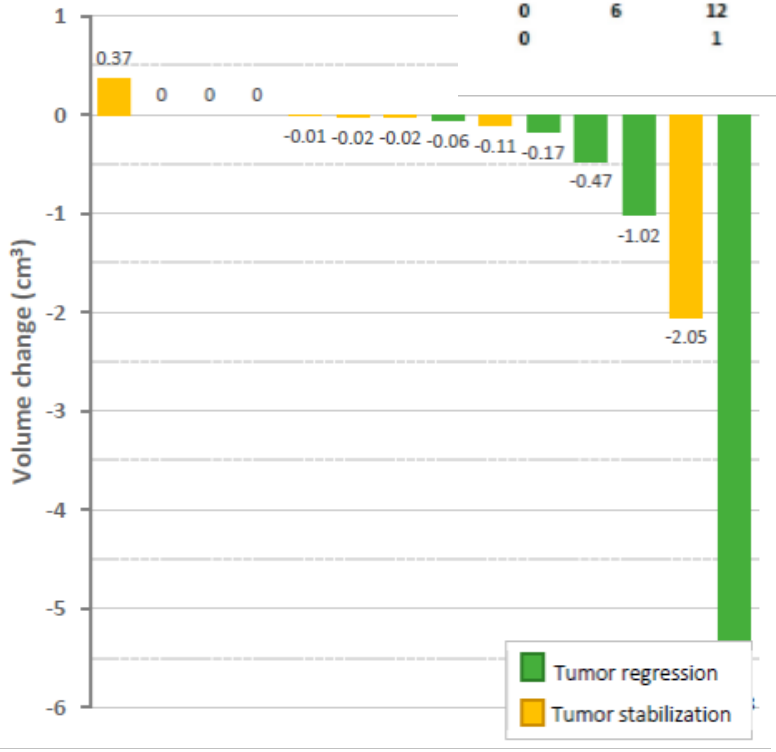


Figure 3. Change in absolute extracanicular volume (cm^3) of vestibular schwannomas after bevacizumab treatment. Vertical bars represent the target vestibular schwannoma of a patient. Coloring of the bars indicate the corresponding tumor response: green for tumor regression (volume change ≥20%), yellow for stable tumor (volume change between −20% and 20%). Three target vestibular schwannomas are not shown: one tumor was confined to the internal auditory canal, two other tumors were not followed up with MRI at the end of treatment.

cancers

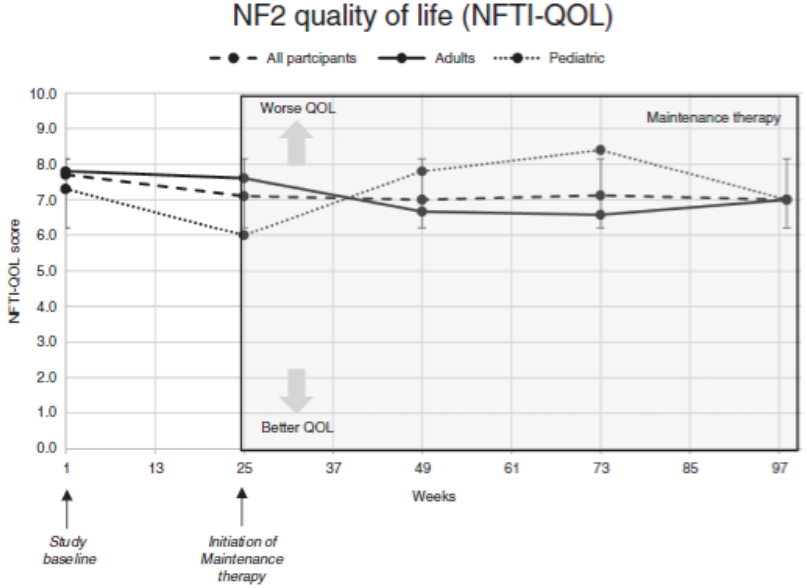
MDPI

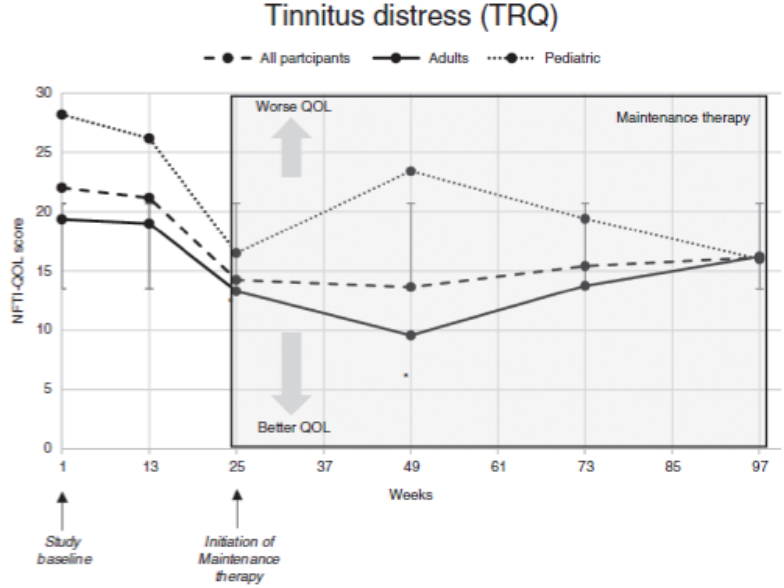
Article

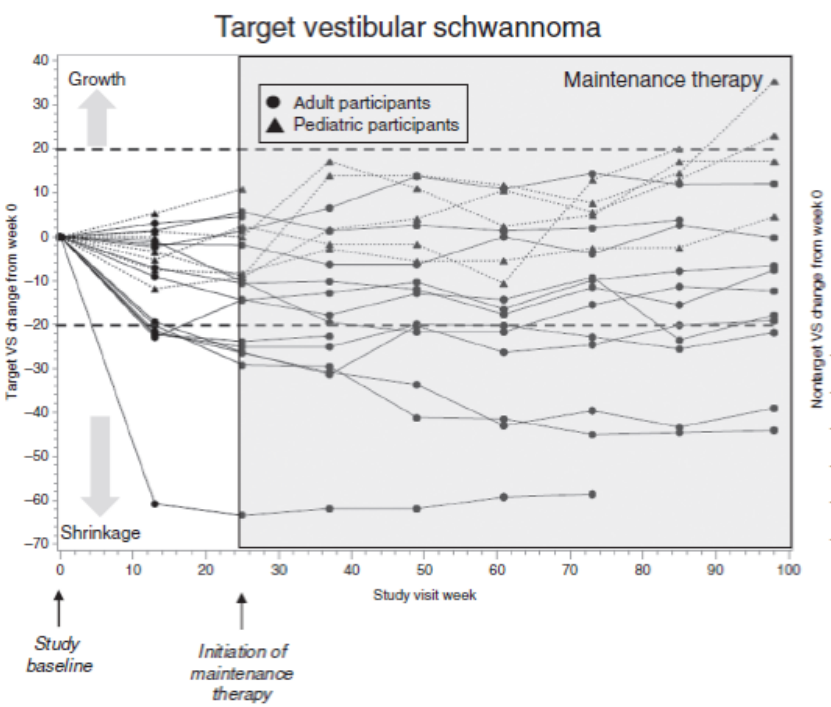
Bevacizumab Treatment for Patients with *NF2*-Related Schwannomatosis: A Single Center Experience

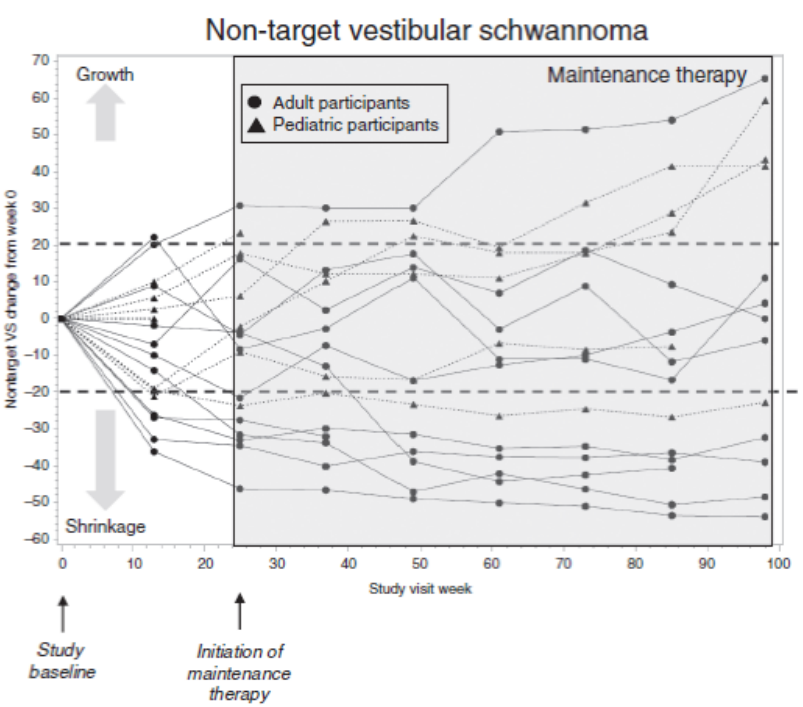
Jules P. J. Douwes [1,*], Erik F. Hensen [1], Jeroen C. Jansen [1], Hans Gelderblom [2] and Josefine E. Schopman [2]

Cancers **2024**, *16*, 1479. https://doi.org/10.3390/cancers16081479









Neuro-Oncology
25(8), 1498–1506, 2023 | https://doi.org/10.1093/neuonc/noad066 | Advance Access date 3 April 2023

Multicenter, prospective, phase II study of maintenance bevacizumab for children and adults with *NF2*-related schwannomatosis and progressive vestibular schwannoma

Scott R. Plotkin, Jeffrey Allen, Girish Dhall[1,a], Jian L. Campian, D. Wade Clapp, Michael J. Fisher, Rakesh K. Jain, James Tonsgard, Nicole J. Ullrich, Coretta Thomas, Lloyd J. Edwards, Bruce Korf, Roger Packer, Matthias A. Karajannis[2,a], and Jaishri O. Blakeley

ASCO 2024 • Chicago, IL • June 2024

BRIGATINIB IN *NF2*-RELATED SCHWANNOMATOSIS WITH PROGRESSIVE TUMORS

Scott R. Plotkin, MD, PhD; Kaleb H. Yohay, MD; Phioanh L. Nghiemphu, MD; Christine T. Dinh, MD, PhD; Dusica Babovic-Vuksanovic, MD; Vanessa L. Merker, PhD; Annette Bakker, PhD; Geoffrey Fell, MS; Lorenzo Trippa, PhD; Jaishri O. Blakeley, MD

N Engl J Med
Volume 390(24):2284-2294
June 27, 2024

OncLive Rapid Readout

Scott Plotkin, MD, PhD
Massachusetts General Hospital
Boston, Massachusetts

The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

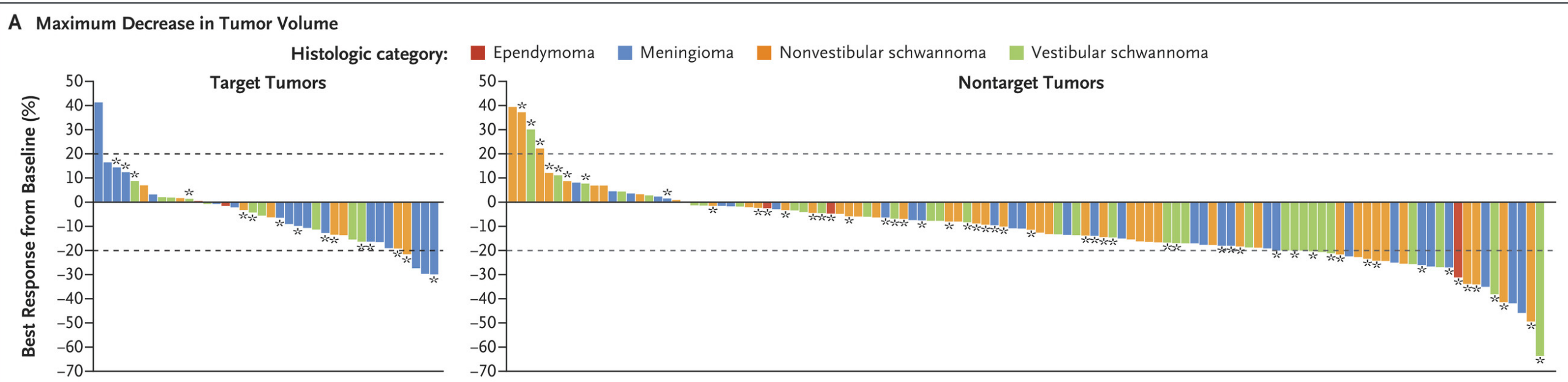
Brigatinib in NF2-Related Schwannomatosis with Progressive Tumors

Authors: Scott R. Plotkin, M.D., Ph.D., Kaleb H. Yohay, M.D., Phioanh L. Nghiemphu, M.D., Christine T. Dinh, M.D., Ph.D., Dusica Babovic-Vuksanovic, M.D., Vanessa L. Merker, Ph.D., Annette Bakker, Ph.D., Geoffrey Fell, M.S., Lorenzo Trippa, Ph.D., and Jaishri O. Blakeley, M.D., for the INTUITT-NF2 Consortium* Author Info & Affiliations

Published June 20, 2024 | N Engl J Med 2024;390:2284-2294 | DOI: 10.1056/NEJMoa2400985 | VOL. 390 NO. 24

RESULTS

A total of 40 patients (median age, 26 years) with progressive target tumors (10 vestibular schwannomas, 8 nonvestibular schwannomas, 20 meningiomas, and 2 ependymomas) received treatment with brigatinib. After a median follow-up of 10.4 months, the percentage of tumors with a radiographic response was 10% (95% confidence interval [CI], 3 to 24) for target tumors and 23% (95% CI, 16 to 30) for all tumors; meningiomas and nonvestibular schwannomas had the greatest benefit. Annualized growth rates decreased for all tumor types during treatment. Hearing improvement occurred in 35% (95% CI, 20 to 53) of eligible ears. Exploratory analyses suggested a decrease in self-reported pain severity during treatment (−0.013 units per month; 95% CI, −0.002 to −0.029) on a scale from 0 (no pain) to 3 (severe pain). No grade 4 or 5 treatment-related adverse events were reported.



The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

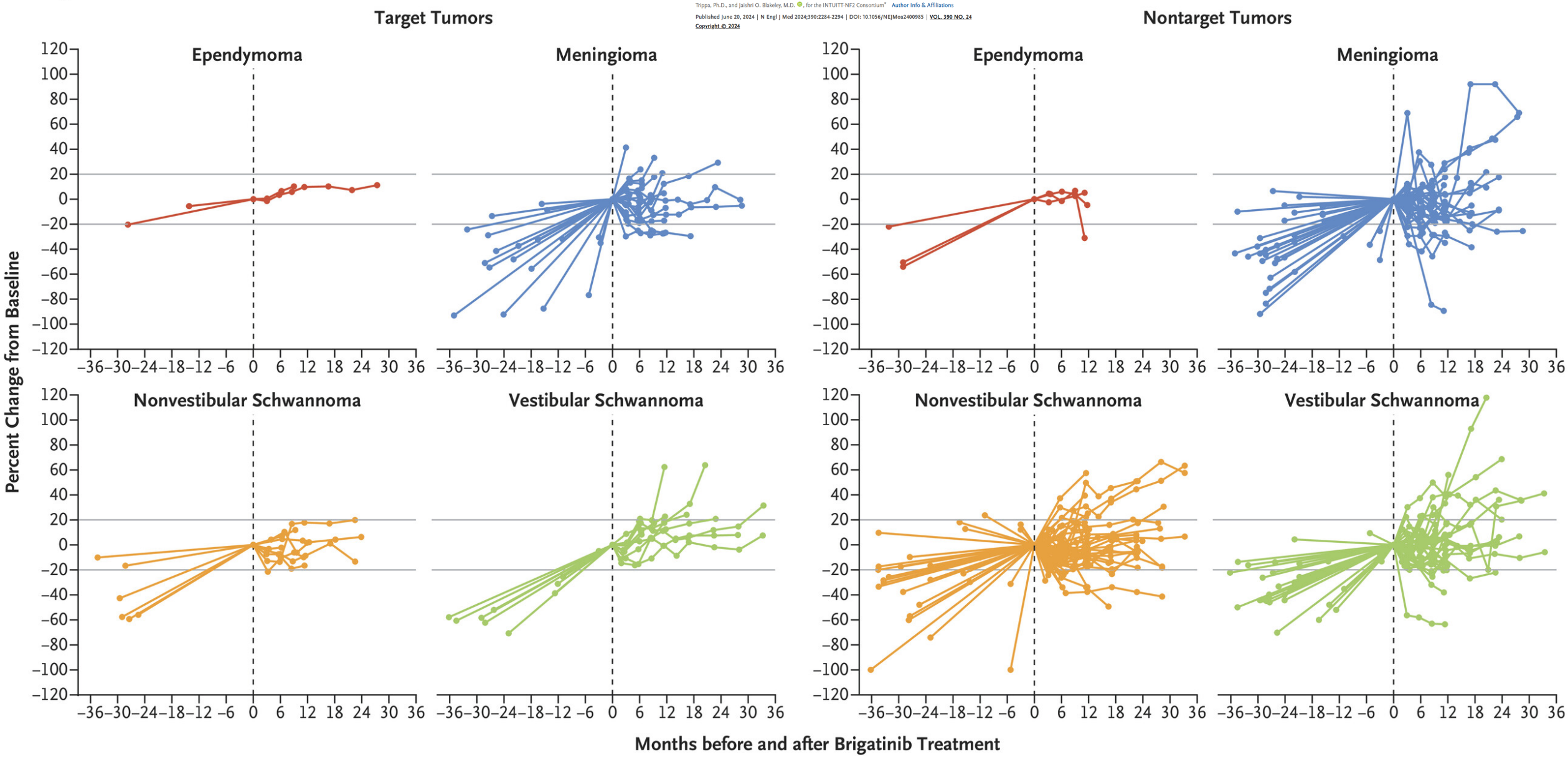
ORIGINAL ARTICLE

Brigatinib in NF2-Related Schwannomatosis with Progressive Tumors

Authors: Scott R. Plotkin, M.D., Ph.D., Kaleb H. Yohay, M.D., Phioanh L. Nghiemphu, M.D., Christine T. Dinh, M.D., Ph.D., Dusica Babovic-Vuksanovic, M.D., Vanessa L. Merker, Ph.D., Annette Bakker, Ph.D., Geoffrey Fell, M.S., Lorenzo Trippa, Ph.D., and Jaishri O. Blakeley, M.D., for the INTUITT-NF2 Consortium* Author Info & Affiliations

Published June 20, 2024 | N Engl J Med 2024;390:2284-2294 | DOI: 10.1056/NEJMoa2400985 | VOL. 390 NO. 24

B Change in Tumor Size



Median Annual Change in Growth Rate: Pre-Treatment vs. Post-Treatment

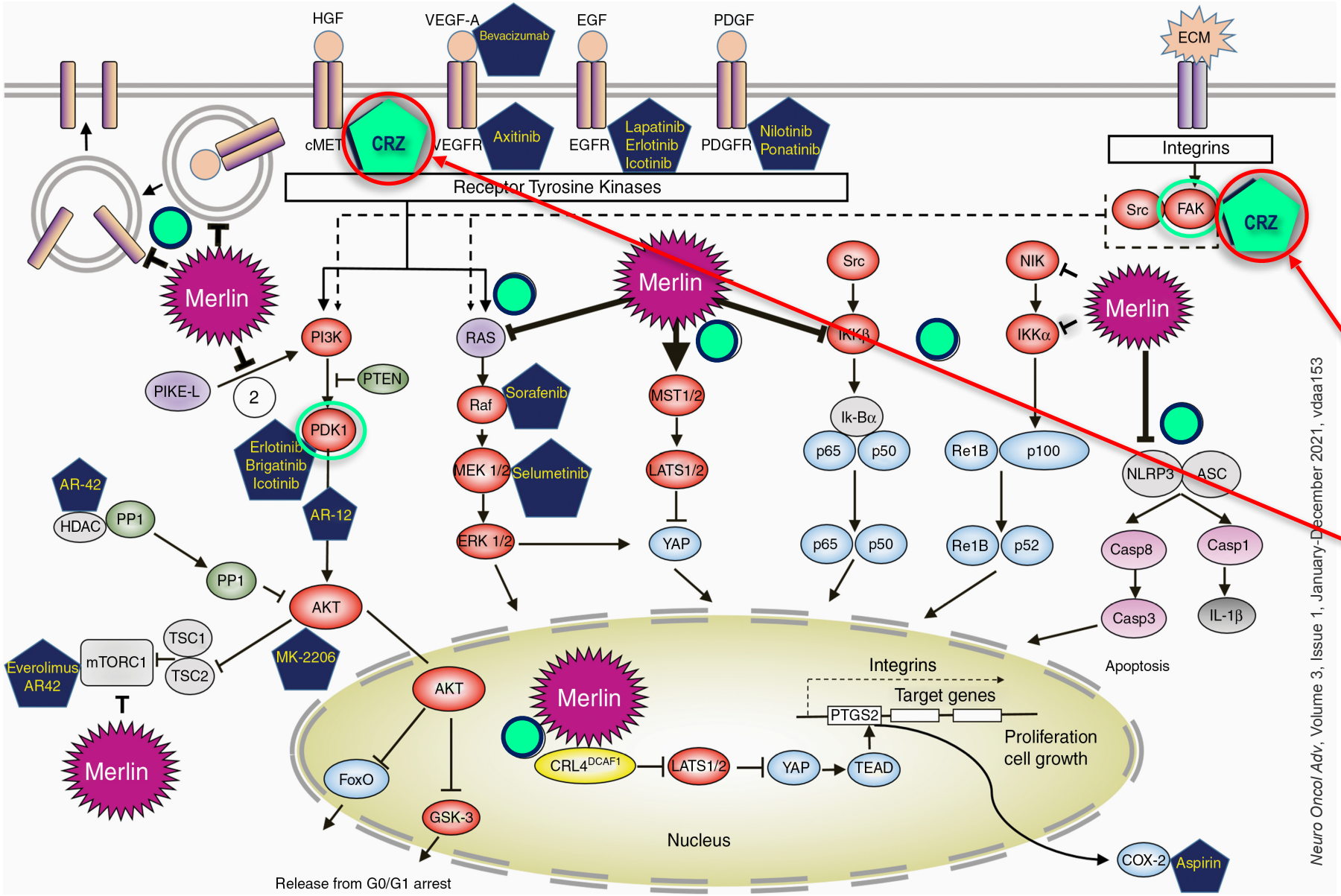
- **Total Tumors Analyzed: 88 tumors**
- **Data Breakdown by Tumor Type:**
  - **Vestibular Schwannoma (N=28)**
    - **Pre-treatment:** ~35% median growth rate
    - **Post-treatment:** ~20% median growth rate
    - **Response Rate (RR):** 1/28 (4%)
  - **Non-vestibular Schwannoma (N=39)**
    - **Pre-treatment:** ~25% median growth rate
    - **Post-treatment:** ~10% median growth rate
    - **Response Rate (RR):** 10/39 (26%)
  - **Meningioma (N=19)**
    - **Pre-treatment:** ~30% median growth rate
    - **Post-treatment:** ~-20% (indicating tumor shrinkage)
    - **Response Rate (RR):** 5/19 (26%)
  - **Ependymoma (N=2)**
    - **Pre-treatment:** ~10% median growth rate
    - **Post-treatment:** ~5% median growth rate
    - **Response Rate (RR):** 0/2 (0%)

Data was published simultaneously in PLOTKIN, ET AL. N ENGL J MED. 2024. DOI:10.1056/NEJMoa2400985].

OncLive Rapid Readout

Scott Plotkin, MD, PhD
Massachusetts General Hospital
Boston, Massachusetts

Cele molekularne do wykorzystania w *Nf2*-SWN



Neuro Oncol Adv, Volume 3, Issue 1, January-December 2021, vdaa153

Nf2- merlina: 7 punktów oddziaływania

PROJEKT **Warszawskiego Uniwersytetu Medycznego**: „Niekomercyjne i nierandomizowane badanie interwencyjne fazy 2a. oceniające skuteczność produktu leczniczego kryzotynib w terapii dzieci z ciężką postacią neurofibromatozy typu 2., w szczególności niepoddających się leczeniu chirurgicznemu oraz/lub radioterapii”
Akronim badania: KRONF2
5 263 510,00 zł

KRYZOTYNIB w Nf2-SWN u dzieci?

Search Results

Viewing 1 result

Showing results for: **NF2** | **Other terms: Crizotinib**

+ Synonyms of conditions or disease (2)

Card View

Focus Your Search
(all filters optional)

<< Hide

Condition/disease

NF2

Other terms

Crizotinib

Intervention/treatment

None Selected

	Study Title	NCT Number	Status	Conditions	Interventions	Sponsor
1	Phase 2 Clinical Trial of **Crizotinib** for Children and Adults with **Neurofibromatosis Type 2** and Progressive Vestibular Schwannomas Added to My Studies	NCT04283669	Active, not recruiting	• **Neurofibromatosis 2** • Progressive Vestibular Schwannoma (VS)	• Drug: **Crizotinib**	University of Alabama at Birmingham

Search Criteria | Search results | Display options

1 results found Modify my search

Sort by: Decision date DESC Sort

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Clinical Trials

2024-516607-16-00 - KRONF2 - Phase 2a non-commercial and non-randomized intervention study evaluating the efficacy of crizotinib in the treatment of children with severe type 2 neurofibromatosis, in particular those excluded from surgery and / or radiotherapy - Authorised, recruitment pending

Decision date: 26/08/2024 | Start date: N/A | End date: N/A | Medical condition: Neurofibromatosis type 2 is a genetically determined primary malignancy resulting from a mutation that disables the function of the cell division control gene and leads to neoplasia such as benign peripheral nervous system tumors and various benign or locally malignant tumors of the central nervous system. Many complications occur in children more often than in adults and significantly shorten the survival period of affected children.

Location(s): Poland: Authorised, recruitment pending

KRONF2 w Polsce *(sponsor - WUM; płatnik ABM)*

Lek wybrano na podstawie **modelu teoretycznego** (przedstawiony poprzednio) w oparciu o wyniki **badań podstawowych** z linii komórkowych i mysich modeli eksperymentalnych, opierając się dodatkowo (choć przede wszystkim) na **znanym profilu bezpieczeństwa** u pacjentów dorosłych (rak płuca) oraz **dzieci** (ultrarzadkie nowotwory dziecięce)

KRONF2 jest **niekomercyjnym**, jednoośrodkowym, nierandomizowanym badaniem interwencyjnym fazy 2b, oceniającym bezpieczeństwo i skuteczność kryzotynibu (XALKORI™, Pfizer) w terapii ciężkich postaci *Nf2*-SWN u dzieci, u których leczenie chirurgiczne i/lub radioterapia nie są skuteczne lub są przeciwwskazane

Głównym **CELEM** badania jest ocena **skuteczności**, **bezpieczeństwa** i **przydatności** kryzotynibu w uzyskaniu i utrzymaniu **przynajmniej stabilności** lub **zmniejszenia wymiarów guza (guzów)** o stwierdzonej progresji lub nieoperacyjnych u dzieci z Nf2-SWN, powodujących określoną i znaczną niepełnosprawność złożoną w porównaniu do okresu sprzed badania

Po zakwalifikowaniu do badania okres podawania leku badanego będzie **nie dłuższy niż 15 miesięcy** z następczą obserwacją do 6 miesięcy (całkowity maksymalny okres pozostawania w badaniu to 21 miesięcy)

Ze względu na specyficzne uwarunkowania projektu (połknięcie kapsułki w całości) oraz czas jego trwania (36 miesięcy w założeniu oraz możliwość udzielania świadczeń dzieciom tylko do ukończenia 17. r.ż.), do badania będą kwalifikowani pacjenci w wieku od 5 roku życia (ukończony 4. r.ż.) do ukończenia 15. roku życia (wartość nieprzekraczalna)

Ze względu na ultrarzadki charakter *Nf2*-SWN oraz jej unikalność w populacji dziecięcej, a tym samym - małą liczebność próby, wyniki badania będą głównie analizowane z zastosowaniem metod statystyki opisowej, a grupa badawcza obejmie

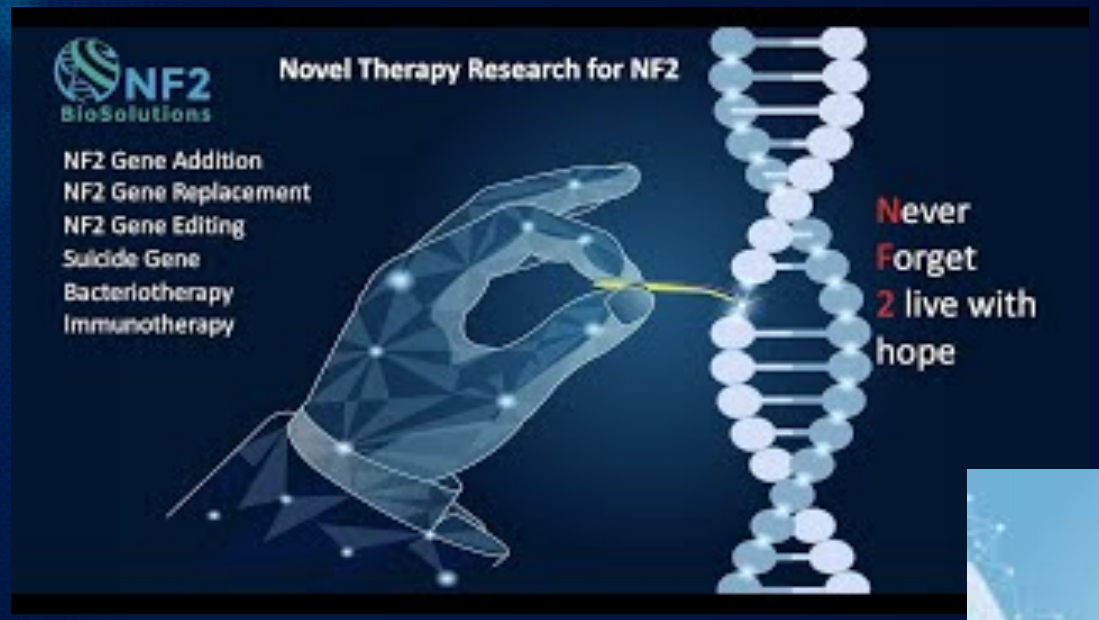
KRONF2 w Polsce *(sponsor - WUM; płatnik ABM)*

- Dotychczas skryning do badania przeprowadzono u 3-ga dzieci
  - u jednego chłopca ustalono konieczność wycięcia atypowego oponiaka (mała szansa powikłań pooperacyjnych z powodu korzystnej lokalizacji guza)
    - zgodnie z protokołem będzie podlegał rewaluacji za 4 miesiące
  - Dwie pacjentki płci żeńskiej **aktywnie uczestniczą w badaniu**
    - jedna, w wieku 15 lat, od 24.05.2024
    - druga, w wieku 14 lat, od 25.10.2024
    - u żadnej z nich nie wystąpiły istotne SAE, a do podstawowych AE związanych z podaniem leku należały luźniejsze stolce i sporadyczne nudności, które ustąpiły do 10 dnia terapii
    - ocena dynamiki zmian objętości guza wskaźnikowego (VS) oraz innych SWN nie jest obecnie jeszcze

      możliwa ze względu na krótki czas terapii eksperymentalnej

      (tylko u jednej wykonano 2-gi kontrolny MR - po 6. miesiącach terapii)
  - Dwoje kolejnych pacjentów oczekuje na skryning (12.2024/01.2025)

Cele molekularne dla NF-2



N*ever*
F*orget*
2 *live with hope*

Terapia genowa w NF-2:
przyszłość a nie

Leczenie NF2-zależnej Schwannomatozy: to się dzieje!

Prior to 2010: No reported preclinical study on gene therapy for *NF2*-related schwannomatosis

2010: HSV-based delivery of ICE led to *NF2*-related schwannomatosis schwannoma regression in a subcutaneous xenograft mouse model.

2013: AAV1-based delivery of ICE led to *NF2*-related schwannomatosis schwannoma regression in a sciatic nerve xenograft mouse model.

2019: AAV1-based delivery of ASC led to *NF2*-related schwannomatosis schwannoma regression in a sciatic nerve xenograft mouse model.

2019: AAV1-based delivery of the pore-forming protein Gasdermin-D led to *NF2*-related schwannomatosis schwannoma regression in a sciatic nerve xenograft mouse model.

2022: AAV1-based delivery of merlin protein led to *NF2*-related schwannomatosis schwannoma regression in a sciatic nerve xenograft mouse model.

2022: Materials and methods for neurofibromin 2/merlin (NF2) gene therapy are disclosed in the international patent application No. PCT/US2022/024680 published as WO 2022/221447A1, filed by RES INST nationwide children's hospital on April 13, 2022, which claims the priority to US provisional patent application No. 63/174,803, filed on April 14, 2021.

2023: Further preclinical studies on gene therapy for *NF2*-related schwannomatosis are ongoing.

Oncol Ther (2024) 12:257–276
https://doi.org/10.1007/s40487-024-00279-2

REVIEW

Gene Therapy for Neurofibromatosis Type 2-Related Schwannomatosis: Recent Progress, Challenges, and Future Directions

Ruofei Yuan · Bo Wang · Ying Wang · Pinan Liu

Leczenie NF2-zależnej Schwannomatozy: terapie genowe

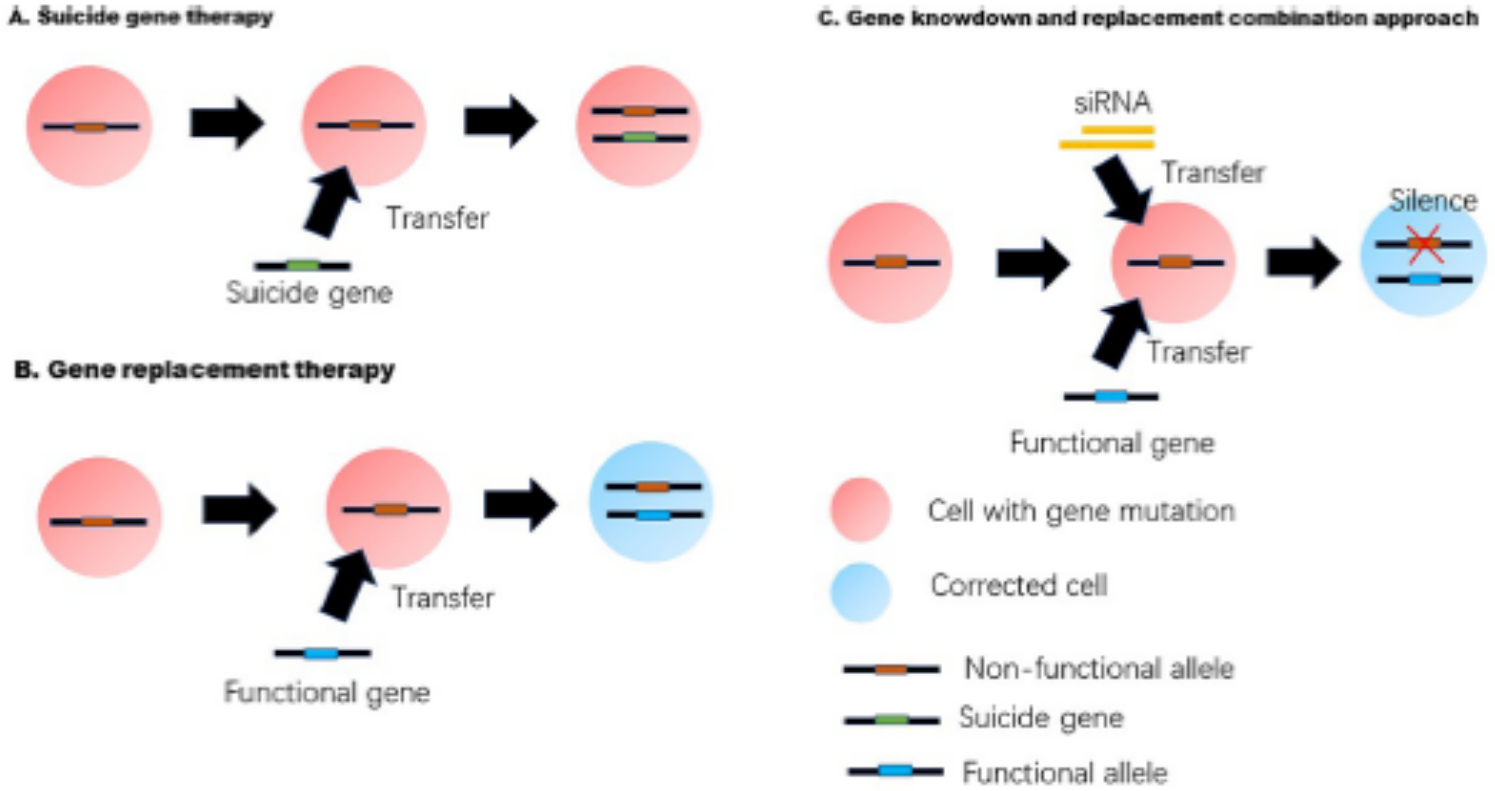


Fig. 3 Gene therapy approaches for neurofibromatosis type 2 (*NF2*)-related schwannomatosis. **A** Suicide gene therapy refers to the specific introduction of a gene into tumor cells to cause tumor cell death without affecting the healthy nearby cells. **B** Gene replacement therapy directly supplies a functional copy of the mutated or inactivated *NF2* gene to augment functional merlin protein re-expression in *NF2*-deficient tumor cells. **C** Gene knockdown and replacement combination approach refers to using small RNAs to silence the mutated *NF2* gene while supplying a functional copy of the *NF2* gene to produce normal merlin protein

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REVIEW

Gene Therapy for Neurofibromatosis Type 2-Related Schwannomatosis: Recent Progress, Challenges, and Future Directions

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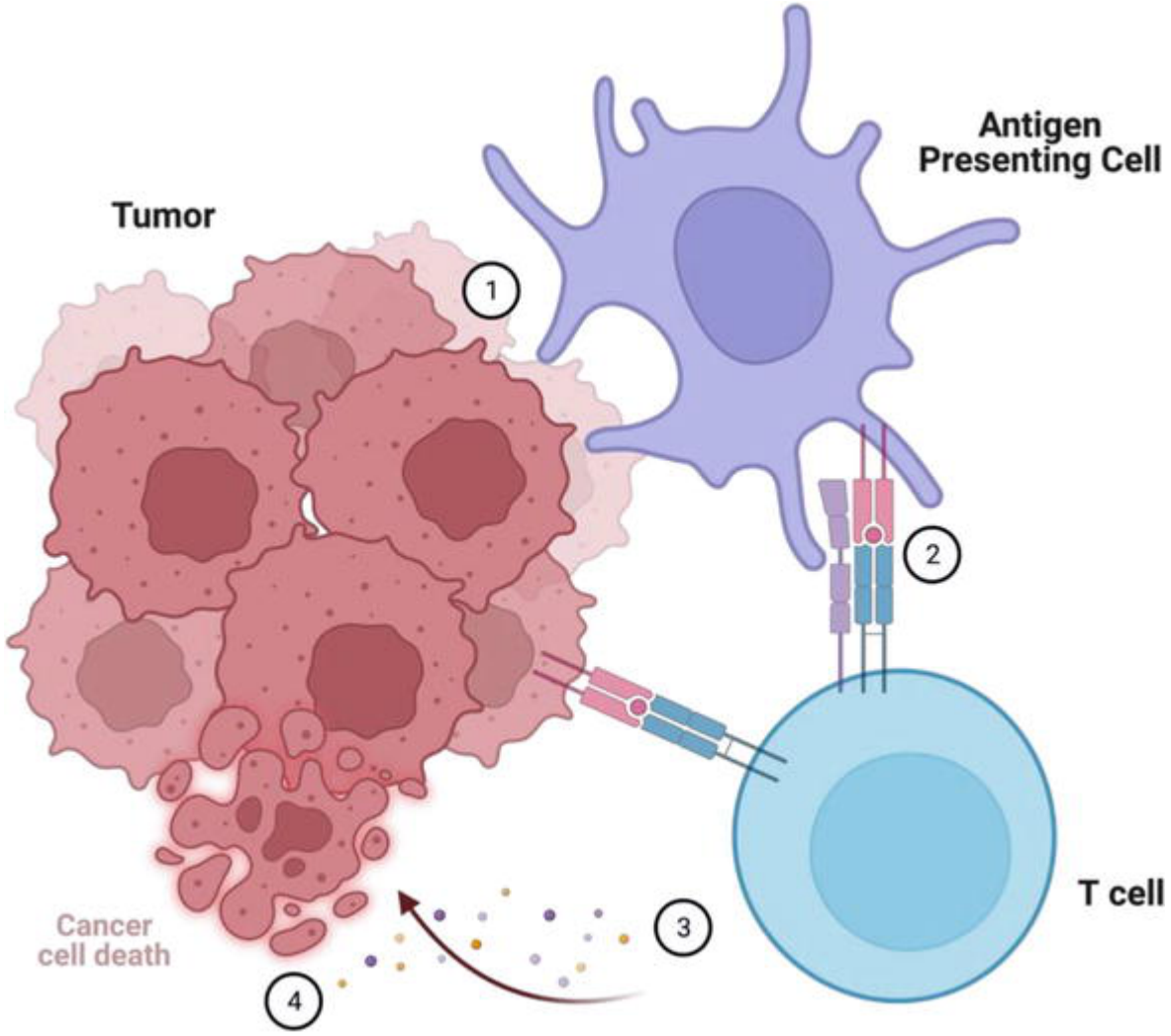
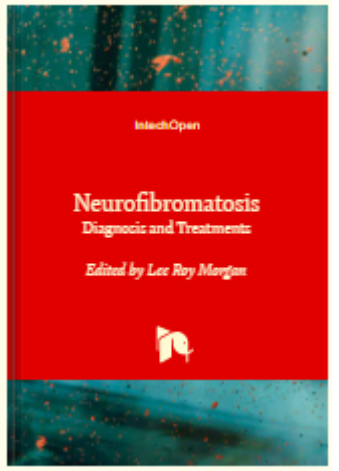
Leczenie NF2-zależnej Schwannomatozy: „immunoterapia przeciwnowotworowa”





Chapter

Immunotherapy Strategies for NF2-Associated Tumors

Shyam Patel, Thomas C. Chen and Frances E. Chow

Submitted: 24 February 2023 Reviewed: 02 March 2023
Published: 28 March 2023
DOI: 10.5772/intechopen.1001348

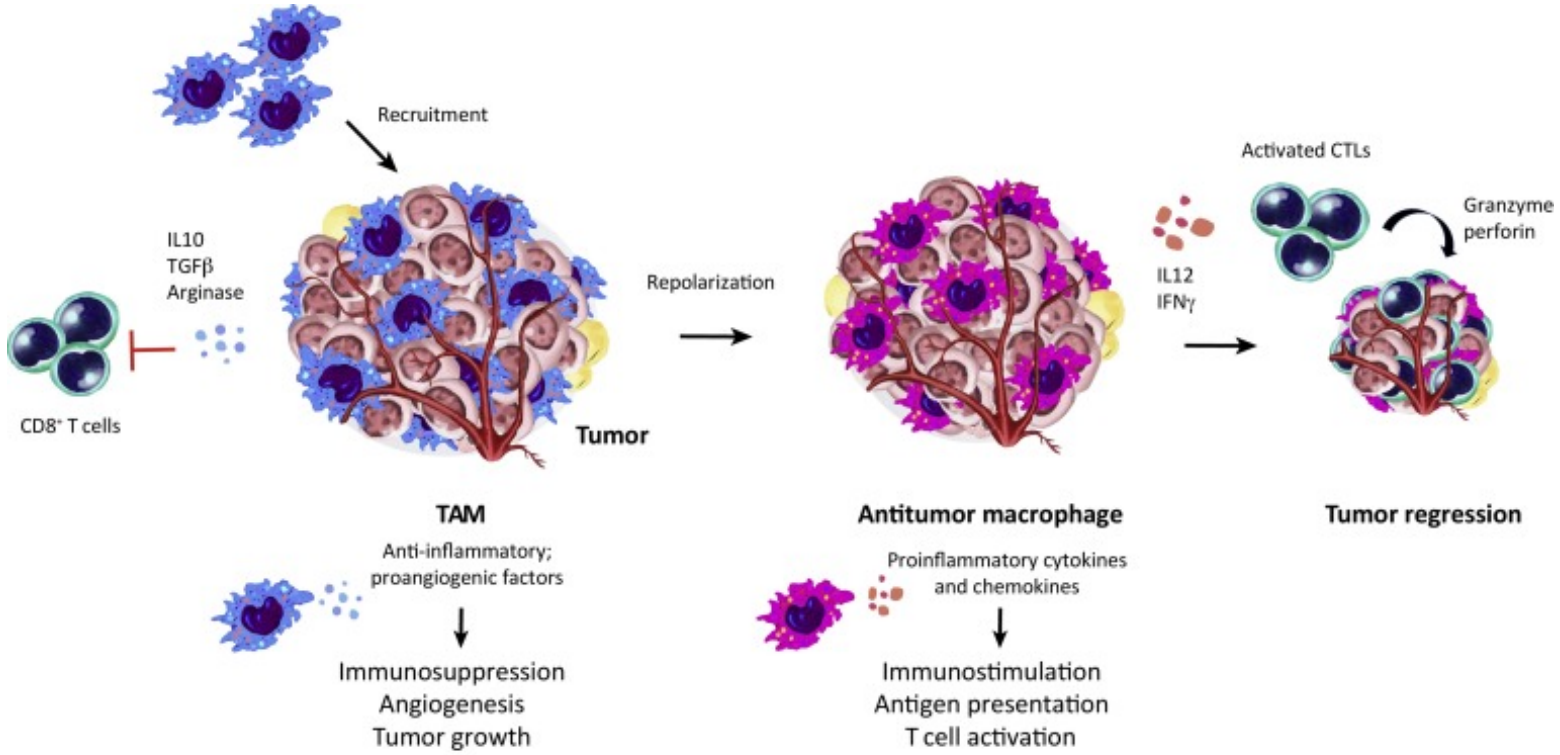
Także bakterie onkolityczne

Figure 1.
*Cancer immunology and principles of immunotherapy. (1) Tumor cells undergo phagocytosis by an antigen presenting cell (APC). (2) The APC presents tumor associated antigens on an MHC molecule to a naïve T cell. Dendritic cells have the most effective antigen presentation and T cell activation. Macrophages are subtyped into M1 anti-tumor and M2 pro-tumor/anti-inflammatory. Natural killer cells are part of the innate immune system and are capable of both antigen presentation and T cell activation. (3) T cell activation occurs when the appropriate T cell receptor (TCR) pairs with a matching tumor-associated antigen. Additional costimulatory signals such as B7-CD28 and cytokines are necessary to guide the differentiation and expansion of effector cells into cytotoxic T cells, helper T cells, regulatory T cells, and B cells. Each of these effector cells have unique markers and functions (**Table 1**). (4) The cytotoxic T cell eliminates the cancer cell in a process involving perforins, granzymes, and lysozymes.*

Leczenie NF2-zależnej Schwannomatozy: terapie „manipulacyjne”

Immunoterapia przeciwnowotworowa w NF-2:

TAM -niedaleka (?!) przyszłość a nie fikcja



Zhang, Q., Cheng, S., Wang, Y. *et al.* Interrogation of the microenvironmental landscape in spinal ependymoma reveals dual functions of tumor-associated macrophages. *Nat Commun* 12, 6867 (2021). https://doi.org/10.1038/s41467-021-27018-9

Uff...!

To wreszcie

ko[illegible]e!

N *ever*

F *orget*

2 *live with*

hope

Dziękuję za

Państwa uwagę


... i za cierpliwość
https://stock.adobe.com/