TEIMURAZ MIKELADZE, GVANTSA ARVELADZE, TEKLA ABESADZE,
*MARIAM MIKELADZE *, GIORGI BARAMIDZE*

NEUROFIBROMATOSIS TYPE 1 WITH PLEXIFORM NEUROFIBROMA OF THE HEAD AND NECK: SIX YEARS OF CONTINUOUS TRAMETINIB THERAPY

Medical Center MZIURIMED; *GZAAT, Tbilisi, Georgia

Doi: https://doi.org/10.52340/jecm.2026.03.07

თეიმურაზ მიქელაძე, გვანცა არველაძე, თეკლა აბესაძე, მარიამ მიქელაძე, გიორგი ბარამიძე

ტიპი I ნეიროფიბრომატოზი, თავისა და კისრის პლექსიფორმული ნეიროფიბრომით: ტრამეტინიბით მკურნალობის ექვსწლიანი დაკვირვება

სამედიცინო ცენტრი „მზიურიმედი“, *GZAAT, თბილისი, საქართველო

რეზიუმე

ექვსი წლის განმავლობაში ტრამეტინიბის (0.5მგ დღეში ერთხელ) უწყვეტი და შემანარჩუნებელი დოზით თერაპიის შემდეგ კისრისა და თავის არეში არსებული მოცულობითი წარმონაქმნი შემცირდა 82.8%-ით საწყისი 161.2 მლ-დან 27.79 მლ-მდე, რაც დასტურდება 2026 წლის მაისის თვეში ჩატარებული, ბოლო მაგნიტო-რეზონანსული ტომოგრაფიით.

პრეპარატის აქტივობა ხასიათდება დადებითი დინამიური პროფილით. გამოვლენილი გვერდითი ეფექტები: ეპისტაქსისი, ჰემატურია, პარონიქია და მუკოზიტი - შეესაბამებოდა MEK-ინჰიბიტორების კლასისთვის დამახასიათებელ მოლოდინს. გვერდითი ეფექტები აღინიშნებოდა პრეპარატის მიღების პირველი წლის განმავლობაში. მათი მართვა ხდებოდა დოზის შემცირების, მკურნალობის შეწყვეტისა და დამხმარე მედიკამენტების მიღების გარეშე. მკურნალობის მეხუთე წლისთვის აღნიშნული სიმპტომები იმდენად გაიშვიათდა, რომ ოჯახმა შეწყვიტა სისტემატიური ჩანაწერების წარმოება დღიურში. ერთადერთი, მუდმივი ლაბორატორიული გადახრა იყო - კრეატინ კინაზას უსიმპტომო მატება, რომელიც არ უკავშირდებოდა კუნთოვან სიმპტომებს ან თირკმლის ფუნქციის დარღვევას. ხდებოდა გულ-სისხლძარღვთა და ოფთალმოლოგიური მონიტორინგი. აღნიშნული პერიოდის განმავლობაში ზრდის ტემპის შენელება არ დაფიქსირებულა.

პროსპექტულად ტრამეტინიბით ექვსწლიანი მკურნალობის საფუძველზე მიღებულ იქნა მდგრადი კლინიკური, დამაკმაყოფილებელი პასუხი.

Longitudinal efficacy and safety summary — 14 September 2020 to 12 September 2026

DATE OF BIRTH	June 2016	**AGE AT REPORT**	10 years 3 months
DIAGNOSIS	Neurofibromatosis type 1 (NF1)	**TARGET LESION**	Plexiform neurofibroma of the head and neck
THERAPY	Trametinib (Mekinist®) 0.5 mg once daily, oral	**EXPOSURE**	14 Sep 2020 – ongoing · 72 months

–82.8% Tumour volume vs. pre-treatment baseline	**72 months** Continuous exposure, no dose modification	**0** Adverse events of CTCAE grade ≥ 3	**1** Missed dose in six years (febrile illness)

1 Summary

At presentation, a 10-year-old boy with neurofibromatosis type 1 had an extensive, surgically unresectable plexiform neurofibroma involving the submandibular region, tongue, right cervical soft tissues and skull base, with a small paravertebral component and a small cervical syrinx. He had been diagnosed clinically at 2–3 months of age on the basis of multiple café-au-lait macules. International

second opinions obtained between 2018 and 2020 advised against attempted resection. Oral MEK1/2-inhibitor therapy with trametinib 0.5 mg once daily was started on 14 September 2020, at the age of 4 years 3 months, and continued unchanged for 72 months.

Efficacy. Tumour volume fell from 161.2 mL (July 2020) to 27.79 mL (May 2026) — a cumulative reduction of 82.8%. A partial response by REiNS volumetric criteria (≥20% decrease) was reached at the first on-treatment MRI and deepened at almost every assessment thereafter.

Tolerability. Adverse events were concentrated in the first treatment year and became progressively rarer: 73 recorded events in year 1, 13 in year 2, 5 in year 3 and 3 in year 4. None required dose reduction, interruption or medical intervention. No adverse event of CTCAE grade 3 or above occurred at any point.

Laboratory safety. Liver function remained normal throughout, apart from one transient transaminase rise in May–June 2021 that resolved without dose modification. The principal persistent deviation was an asymptomatic creatine kinase elevation within a tolerable range (peak 827 U/L, 3.3× the upper limit of normal, CTCAE grade 2), with no muscular symptoms and normal renal function.

Organ surveillance. Nineteen ECG and echocardiography assessments and seventeen ophthalmological assessments were all normal. No cardiac or ocular toxicity occurred.

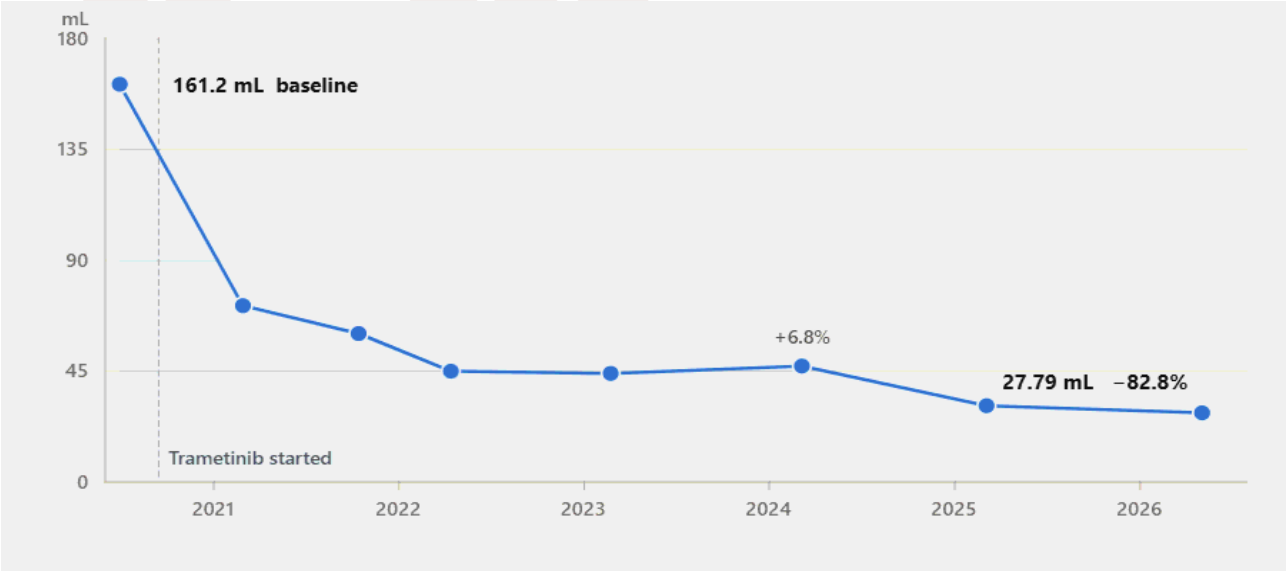
2 Treatment

Table 1 — Treatment details

Agent	Trametinib (Mekinist®), oral MEK1/MEK2 inhibitor
Dose and schedule	0.5 mg once daily — one 0.5 mg tablet
Dose changes	None in 72 months
Start date	14 September 2020 (age:4 years 3 months)
Dose interruptions	None
Missed doses	One, on 28 December 2021, during a febrile illness
Monitoring	Blood tests every 6–8 weeks (49 complete assessments); MRI volumetry annually.

3 Efficacy — tumour volumetry

Figure 1 — Plexiform neurofibroma volume on treatment (mL)



The single interval increase (+6.8%, March 2024) remained far below the ≥20% threshold that defines progressive disease under REiNS volumetric criteria, and was followed by further reduction.

Table 2 — Serial tumour volumetry

MRI DATE	AGE	MONTH OF THERAPY	VOLUME (ML)	VS. PREVIOUS	VS. BASELINE
1 Jul 2020	4 y 0 m	baseline	**161.2**	—	—
1 Mar 2021	4 y 8 m	6	71.3	–55.8%	–55.8%
15 Oct 2021	5 y 4 m	13	59.99	–15.9%	–62.8%
15 Apr 2022	5 y 10 m	19	44.7	–25.5%	–72.3%
24 Feb 2023	6 y 8 m	29	43.8	–2.0%	–72.8%
7 Mar 2024	7 y 8 m	42	46.8	**+6.8%**	–71.0%
6 Mar 2025	8 y 8 m	54	30.7	–34.4%	–81.0%
5 May 2026	9 y 10 m	68	**27.79**	–9.5%	**–82.8%**

Baseline is the MRI of 1 July 2020, obtained 2.5 months before the first dose (upper component 126.3 mL, lower component 34.9 mL). MRI was also performed in July 2018 and July 2019, without volumetric quantification.

4 Tolerability

Figure 2 — Total recorded adverse events by treatment year

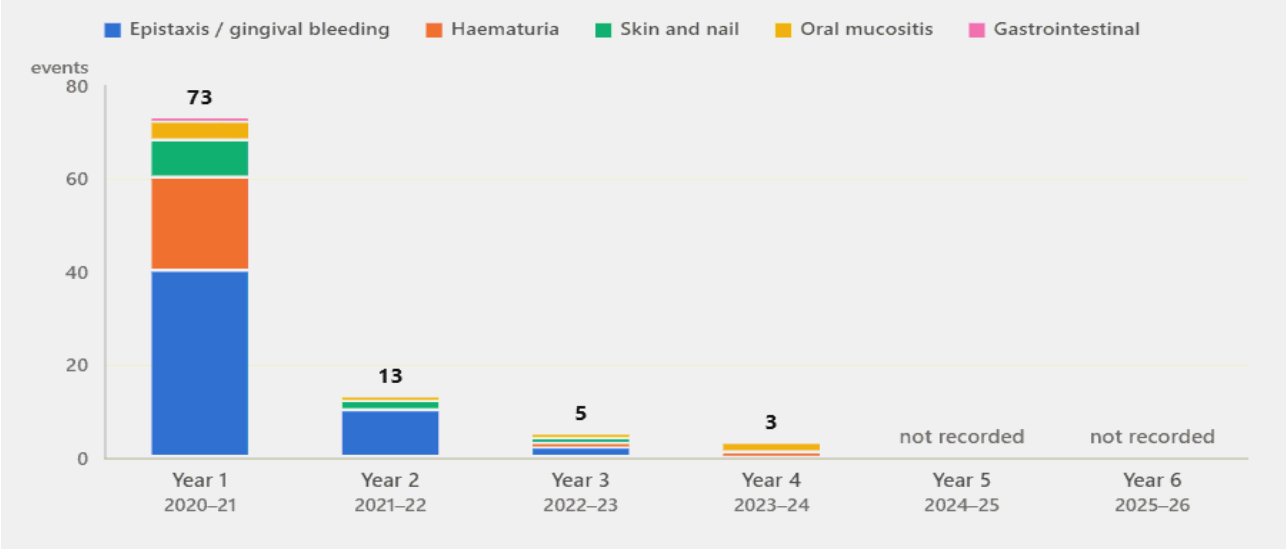


Table 3 — Adverse-event burden by treatment year

CATEGORY	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	YEAR 6
Epistaxis / gingival bleeding	40	10	2	0	—	—
Haematuria	20	0	1	1	—	—
Skin and nail (paronychia, rash)	8	2	1	0	—	—
Oral mucositis	4	1	1	2	—	—
Gastrointestinal upset	1	0	0	0	—	—
Total recorded events	**73**	**13**	**5**	**3**	n.r.	n.r.

n.r. = not recorded: Systematic dairy keeping was discontinued during the fifth year of treatment because adverse events had become infrequent. No adverse event was noted by the family in years 5–6, but these two years are not a complete prospective record and are not reported as a documented zero.

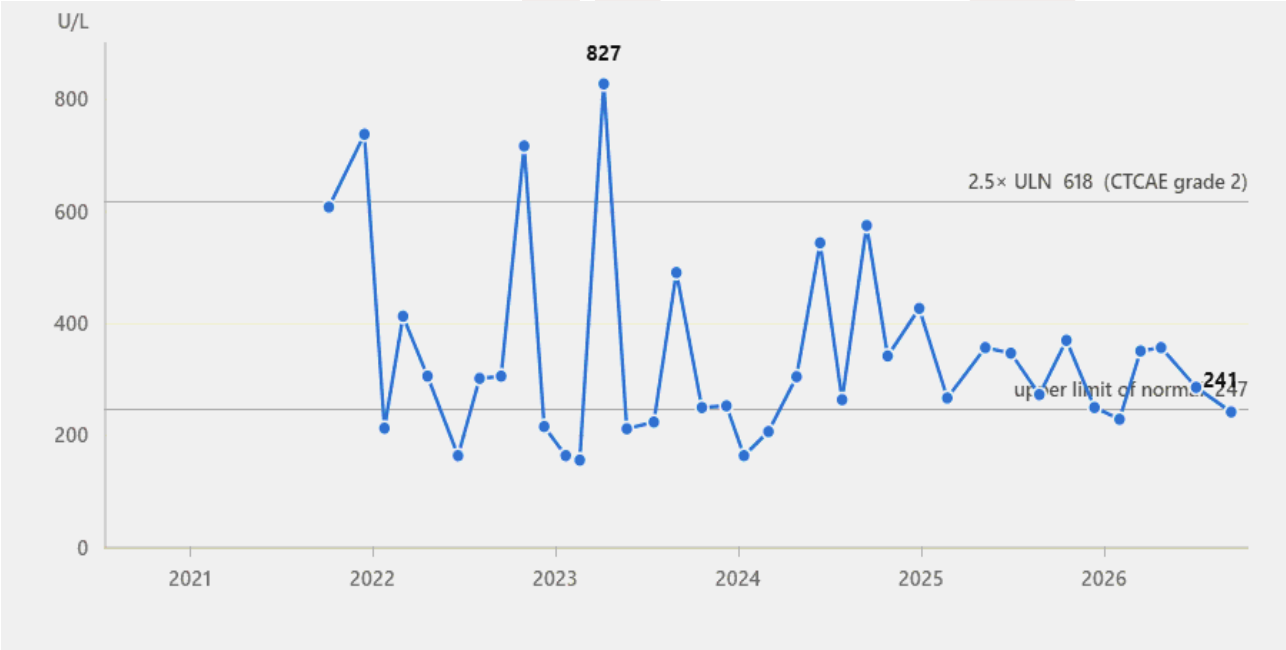
Bleeding. Epistaxis was the dominant early toxicity, beginning on day 16 and recorded on 40 occasions in year 1 — typically a few drops of blood, unilateral, self-limiting, and resolving with simple pressure. No episode required nasal packing, cautery, haemostatic agents, transfusion or medical attendance. The last recorded episode was on 15 October 2022. Macroscopic haematuria occurred as a discrete cluster of 20 entries between 25 May and 13 July 2021, resolving spontaneously without dose interruption; two isolated episodes followed (March 2023 and February 2024), with none thereafter. Coagulation screening from October 2021 onward was essentially normal — fibrinogen was normal at every assessment — and platelet counts were never low, so the bleeding tendency reflected the recognised mucosal-bleeding effect of MEK inhibition rather than any disorder of haemostasis.

Skin, nail and mucosa. Six episodes of paronychia or peri-ungual inflammation occurred between November 2020 and February 2022, each resolving with local care within 2–6 weeks. Two small self-limiting skin rashes (November 2020, January 2022) and one episode of urticaria of unidentified cause were recorded in May 2023. Eight episodes of mild oral mucositis occurred over the six years, all resolving within 3–7 days without affecting oral intake; the last occurred on 3 April 2024.

Gastrointestinal. A single episode of loose stool occurred on day 4 of therapy. No further gastrointestinal adverse event was recorded over the following six years.

5 Laboratory safety

Figure 3 — Highest creatine kinase value recorded in each treatment year (U/L)



Upper limit of normal (ULN) = 247 U/L. The CTCAE grade 2 boundary is 2.5× ULN (618 U/L); the grade 3 boundary is 5× ULN (1 235 U/L) and was never approached. The annual maximum has fallen from 827 U/L to 369 U/L; the latest value (12 Sep 2026) was 241 U/L, within the reference range.

Table 4 — Laboratory parameters across 49 assessments (August 2020 – September 2026)

PARAMETER	REFERENCE	RANGE OBSERVED	LATEST	ASSESSMENT
Alanine aminotransferase	≤ 44 U/L	9–**111**	16	Normal at 47 of 49; one transient rise in May–June 2021, resolved spontaneously without dose change

PARAMETER	REFERENCE	RANGE OBSERVED	LATEST	ASSESSMENT
Aspartate aminotransferase	≤ 48 U/L	26–**110**	39	Same single episode; otherwise, normal or marginal
γ-Glutamyltransferase	≤ 22 U/L	6–16	11	**Normal at every assessment**
Bilirubin, total / direct	< 1.2 / < 0.3 mg/dL	0.1–0.6 / ≤ 0.2	0.5 / 0.2	**Normal at every assessment**
Creatine kinase	< 247 U/L	155–**827**	241	**The principal deviation.** Persistent, asymptomatic; peak 3.3× ULN (grade 2); annual maximum falling; latest value within the reference range
Creatinine	< 0.53 mg/dL	0.28–0.54	0.47	**Normal at 48 of 49.** Renal function preserved — no rhabdomyolysis-associated compromise
Lactate dehydrogenase	112–307 U/L	217–**337**	251	Four marginally raised values, all before November 2021; normal since
Haemoglobin	11.4–14.6 g/dL	11.6–14.1	13.3	**No anaemia at any point**
Mean corpuscular volume	73–87 fL	81.3–**92.0**	**88.0**	Mild persistent macrocytosis without anaemia — expected class effect, clinically silent
Neutrophils, absolute	2–7.5 $\times 10^9$/L	1.43–**13.51**	2.37	**No neutropenia.** Raised values occurred during febrile infections
Platelets	191–426 $\times 10^9$/L	335–**917**	**459**	Intermittent reactive thrombocytosis; **never thrombocytopenic**
Coagulation (PT, INR, aPTT, fibrinogen)	—	see note	normal	Essentially normal; fibrinogen within range at every assessment; only borderline INR deviations
Blood film	—	every visit	—	Findings limited to macrocytosis, occasional toxic granulation of neutrophils and azurophilic granulation of lymphocytes. **No blasts, no dysplasia, no atypical cells**

6 Organ surveillance and growth

Cardiac. ECG and echocardiography were performed on 19 occasions and were reported without pathology every time — with no reduction in left ventricular ejection fraction, no cardiomyopathy, and no arrhythmia. The most recent assessment took place on 25 April 2026.

Ophthalmological. Seventeen examinations were performed, all normal — with no optic pathway glioma, no retinal detachment, no retinal pigment epithelial detachment, and no visual disturbance. The most recent assessment took place on 25 August 2025.

Growth. Height rose from 111 cm at 4 years 5 months (November 2020) to 134 cm at 9 years 10 months (April 2026) — 23 cm over five and a half years. Growth was slower in the middle of the period and faster more recently: 7 cm between December 2024 and April 2026.equivalent to about 3.3 cm per year. Weight rose from 21.3 kg (November 2020) to 34.8 kg (April 2026).

7 Assessment against the known toxicity profile of MEK inhibition

Table 5 — Known class effects versus observed course

KNOWN CLASS EFFECT	OBSERVED IN THIS PATIENT	MAXIMUM SEVERITY
Bleeding events (epistaxis, haemorrhage)	The dominant early toxicity — 40 epistaxis entries in year 1 and a cluster of 20 haematuria entries in months 9–11, all self-limiting without intervention. Epistaxis: none recorded since October 2022; haematuria: none since February 2024	Grade 1 (epistaxis); Grade 2 (macroscopic haematuria)
Raised creatine kinase	Persistent and asymptomatic; the principal ongoing laboratory deviation. Annual maximum has fallen from 827 to 369 U/L	Grade 2 (peak 3.3× ULN)
Paronychia / nail changes	Six episodes between November 2020 and February 2022, all resolving with local care; none since	Grade 1–2
Stomatitis / mucositis	Eight mild episodes, each resolving in 3–7 days; oral intake never affected; none since April 2024	Grade 1
Skin rash (acneiform, maculopapular)	Two small self-limiting rashes and one episode of urticaria; none since May 2023	Grade 1
Hepatotoxicity (raised transaminases)	One transient episode in May–June 2021 with no cholestatic or synthetic component; normal at 47 consecutive assessments over five years since	Grade 1–2
Macrocytosis	Mild, persistent, without anaemia; confirmed on serial blood films	Grade 1
Diarrhoea / gastrointestinal upset	A single episode on day 4 of therapy; nothing since	Grade 1
Left ventricular dysfunction / cardiomyopathy	**Not observed** — 19 serial ECG and echocardiography assessments, all normal	—
Ocular toxicity (retinal pigment epithelial detachment, retinal vein occlusion)	**Not observed** — 17 serial ophthalmological assessments, all normal	—
Myelosuppression	**Not observed** — no neutropenia, anaemia or thrombocytopenia in 49 assessments	—
Nephrotoxicity	**Not observed** — creatinine within reference at 48 of 49 assessments	—
Pneumonitis / interstitial lung disease	**Not observed** — no respiratory adverse event recorded in 72 months	—
Reduced growth velocity	Height rose from 111 cm to 134 cm; the most recent interval measured about 3.3 cm per year	—
Hypertension	No hypertensive episode recorded. Blood pressure is not captured in this dataset	Not recorded

CTCAE v5.0 grades are assigned retrospectively from the descriptive severity recorded in the diary and from the laboratory values against the applicable reference intervals; they were not graded prospectively at the time of the event.

8 Conclusion

After six years of continuous, unmodified trametinib 0.5 mg once daily, the patient achieved and sustained a deep volumetric response in an extensive, unresectable plexiform neurofibroma of the head and neck — a cumulative reduction of 82.8%, from 161.2 mL to 27.79 mL, with the response still deepening at the most recent assessment in May 2026.

The adverse events that occurred — epistaxis, haematuria, paronychia and mucositis — were those expected of the MEK-inhibitor class, were concentrated almost entirely in the first treatment year, and were managed without any dose reduction, interruption or supportive medication. By year 5, events had become infrequent enough that the family discontinued systematic diary recording. No adverse event of CTCAE grade 3 or above occurred at any point. The single persistent laboratory abnormality — asymptomatic creatine kinase elevation — remained within a tolerable range, was never accompanied by muscular symptoms or renal impairment, and improved year on year. Cardiac (19 assessments) and ophthalmological (17 assessments) surveillance was normal throughout.

Taken together, six years of prospectively recorded data document a deep and durable volumetric response achieved on an unchanged paediatric dose, with a toxicity burden that was modest at its peak and diminished steadily thereafter. This case extends the documented duration of continuous single-patient MEK-inhibitor exposure in paediatric NF1-associated plexiform neurofibroma and supports the durability of both efficacy and tolerability with long-term therapy.

9 References:

1. Miller DT, Freedenberg D, Schorry E, et al. Health Supervision for Children With Neurofibromatosis Type 1. *Pediatrics*. 2019;
2. Kotch C, Si SJ, et al. The impact of changes in gadolinium-enhancement on disease progression in children with neurofibromatosis type 1-associated optic pathway glioma: a retrospective analysis. *J Neurooncol*. 2023.
3. Prada CE, Hufnagel RB, Hummel TR, et al. The Use of Magnetic Resonance Imaging Screening for Optic Pathway Gliomas in Children with Neurofibromatosis Type 1. *J Pediatr*. 2015.
4. Carton C, Evans DG, Blanco I, et al. ERN GENTURIS tumour surveillance guidelines for individuals with neurofibromatosis type 1. *EClinicalMedicine*. 2023.
5. Sheerin UM, Holmes P, London NF1 Research Group, et al. Neurovascular complications in adults with neurofibromatosis type 1: a national referral center experience. Am J Med Genet A. 2022.
6. Loponen N, Ylä-Outinen H, Kallionpää RA, Valtanen M, Auranen K, Järveläinen H, Peltonen S, Peltonen J. Hypertension in NF1: a closer look at the primacy of essential hypertension versus secondary causes. Mol Genet Genomic Med. 2024
7. Bizzarri C, Bottaro G. Endocrine implications of neurofibromatosis 1 in childhood. Horm Res Paediatr. 2015;
8. Nix JS, Blakeley J, Rodriguez FJ. An update on the central nervous system manifestations of neurofibromatosis type 1. Acta Neuropathol. 2020
9. Ejerskov C, Krogh K, Ostergaard JR, Joensson I, Haagerup A. Gastrointestinal symptoms in children and adolescents with neurofibromatosis type 1. J Pediatr Gastroenterol Nutr. 2018
10. Carotenuto M, Messina G, Esposito M, Santoro C, Iacono D, Spruyt K. Polysomnographic study in pediatric neurofibromatosis type 1. Front Neurol. 2023

TEIMURAZ MIKELADZE, GVANTSA ARVELADZE, TEKLA ABESADZE,
MARIAM MIKELADZE[*]*, GIORGI BARAMIDZE*

NEUROFIBROMATOSIS TYPE 1 WITH PLEXIFORM NEUROFIBROMA OF THE HEAD AND NECK: SIX YEARS OF CONTINUOUS TRAMETINIB THERAPY

Medical Center MZIURIMED; [*]GZAAT, Tbilisi, Georgia

SUMMARY

Following six years of continuous maintenance therapy with Trametinib (0.5 mg once daily), the volume of the head and neck mass decreased by 82.8%—from a baseline of 161.2 mL to 27.79 mL—as confirmed by the most recent magnetic resonance imaging (MRI) scan performed in May 2026.

The drug demonstrated a favorable clinical response profile. Observed adverse effects—epistaxis, hematuria, paronychia, and mucositis—were consistent with the known safety profile of the MEK inhibitor class. These adverse effects occurred during the first year of treatment and were managed without requiring dose reduction, treatment interruption, or the use of supportive medications. By the fifth year of treatment, the symptoms had become so infrequent that the family discontinued keeping systematic diary records. The only persistent laboratory abnormality was an asymptomatic elevation in creatine kinase, which was not associated with muscular symptoms or renal function impairment. Cardiovascular and ophthalmological monitoring was performed. No slowing of the growth rate was observed during this period.

A sustained, satisfactory clinical response was achieved with six years of prospective treatment with Trametinib.

Keywords: Trametinib, Neurofibromatosis, Plexiform Neurofibroma, Clinical Case