Long-term safety and efficacy of plixorafenib in patients with BRAF-altered CNS neoplasms from the Phase 1/2a PLX120-03 study

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Plixorafenib: A First-in-Class Paradox Breaker for BRAF-altered Tumors

Selective activity against BRAF V600 mutations and BRAF fusions, without paradoxical MAPK pathway activation

Investigational agent designed for selective BRAF inhibition

- Targets BRAF V600 monomers and disrupts mutant BRAF dimers without inducing paradoxical MAPK activation
- Robust CNS activity, inhibiting tumor growth by over 90% in animal model of V600E-mutant brain metastasis
- No acquired mutations found in MAPK pathway after progression on plixorafenib

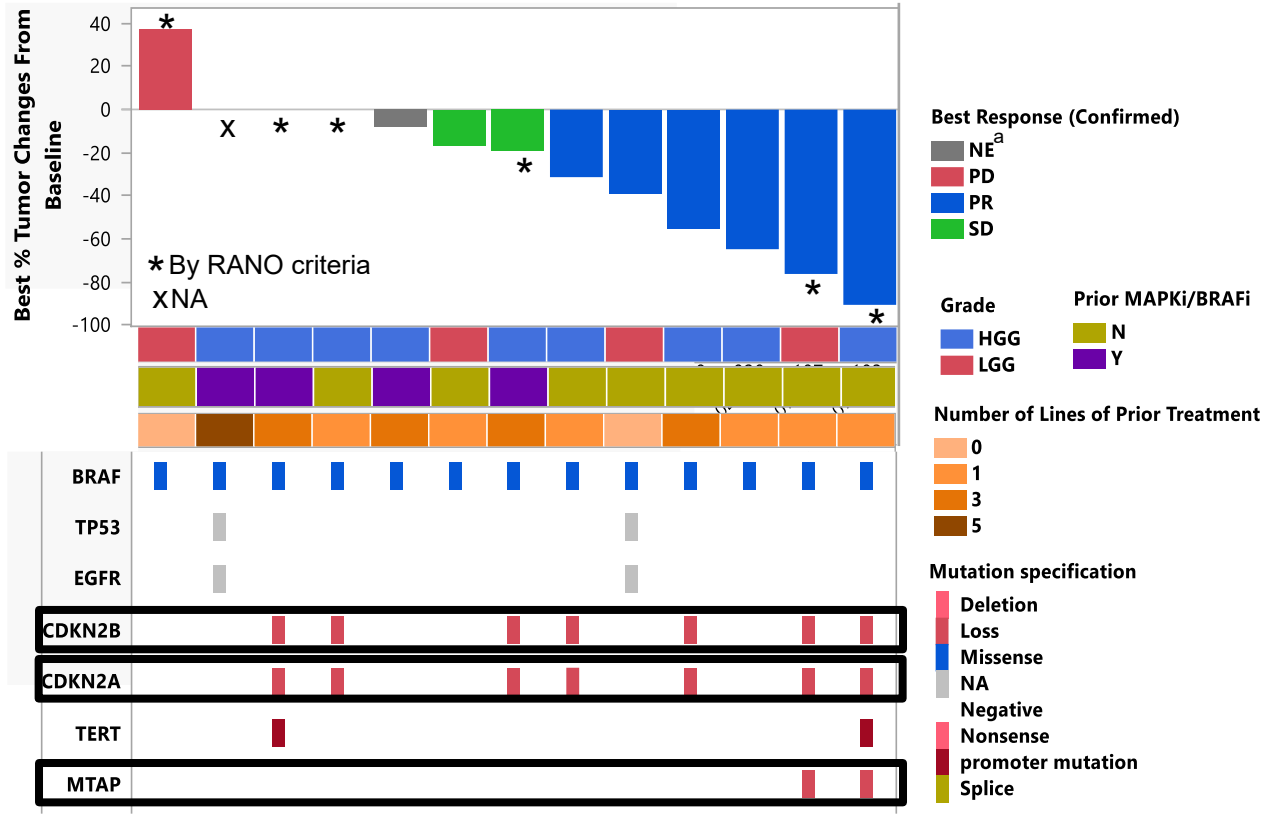
Single-agent activity with differentiated tolerability in a ph1/2a study

- 30% ORR in BRAF V600 tumors (42% in MAPKi-naïve)
- Median DOR ~18 months
- Grade 4-related events were rare and limited to asymptomatic laboratory abnormalities; no fatal treatment-related AEs

Responses observed across HGG and LGG/GNT

- 4 of the 6 responses occurred with CDKN2A/B deletion, with 2 also having MTAP deletion (1 HGG, 1 LGG), known to convey a worse prognosis (figure)

SNO 2023: Phase 1/2a demonstrated clinical activity in BRAF V600-mutated HGG and LGG including CDKN2A/B and MTAP deletion



NE: the only postbaseline assessment was SD and <42 days from baseline.

Here we present long-term follow-up demonstrating sustained clinical benefit with prolonged plixorafenib exposure in BRAF-altered CNS tumors

AA, anaplastic astrocytoma; DOR, duration of response; GBM, glioblastoma; HGG, high-grade glioma; LGG/GNT, low-grade glioma/glioneuronal tumor; MAPKi, MAPK-pathway inhibitor; NE, not evaluable; ORR, objective response rate; PA, pilocytic astrocytoma; PD, progressive disease; PR, partial response; PXA, pleomorphic xanthoastrocytoma; SD, stable disease.

Phase 1/2a Subanalysis: Primary CNS Tumors

Overall safety cohort and prespecified BRAF V600E, MAPK-naïve efficacy subgroup

Primary CNS safety cohort
22

BRAF V600 Efficacy evaluable
13
With post-baseline assessment

MAPKi-naive
9
Prespecified subgroup analysis

Primary CNS safety cohort
N = 22

- **HGG N = 12**
- **LGG/GNT N = 10**
- **Median Age 41.5 yrs (range, 4-80)**

MAPKi-naïve efficacy subgroup
6/9
Partial response
ORR 67%

Median treatment duration
13.8 months
Range 2.8–61.8+ months;
includes 2 ongoing on sIND

Efficacy subgroup composition (N = 9)

HGG (N = 5)	Glioblastoma (n = 4)
	Anaplastic astrocytoma (n = 1)
LGG/GNT (N = 4)	Neuroepithelial-GNT (n = 1) Ganglioglioma-GNT (n = 1) Pilocytic astrocytoma (n = 1) Pleomorphic xanthoastrocytoma (n = 1)

HGG, high-grade glioma; LGG/GNT, low-grade glioma/glioneuronal tumor; MAPKi, MAPK-pathway inhibitor; sIND, single-patient investigational new drug.
Tumor assessments used RECIST 1.1 or RANO /LGG criteria according to the applicable protocol version.

Durable Response Across High- and Low-grade CNS Tumors

BRAF V600E, MAPK-naïve, efficacy-evaluable participants (N = 9)

Overall ORR
67%
6/9

PFS ≥12 mo
56%
5/9

PFS ≥24 mo
33%
3/9

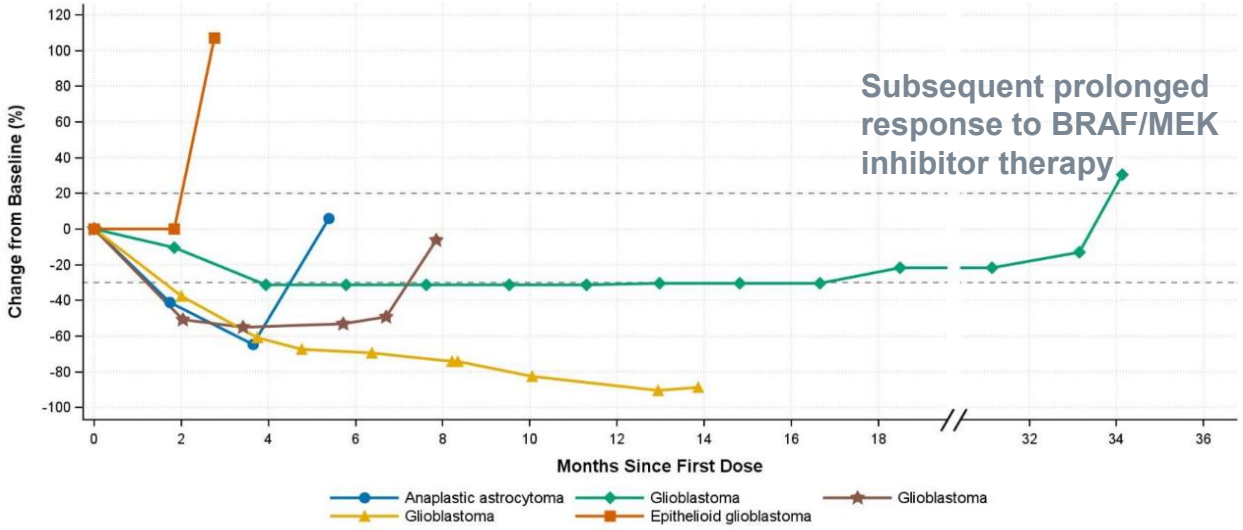
Response by Tumor Type

	PR	ORR
HGG	4/5	80%
LGG/GNT	2/4	50%
Overall	6/9	67%

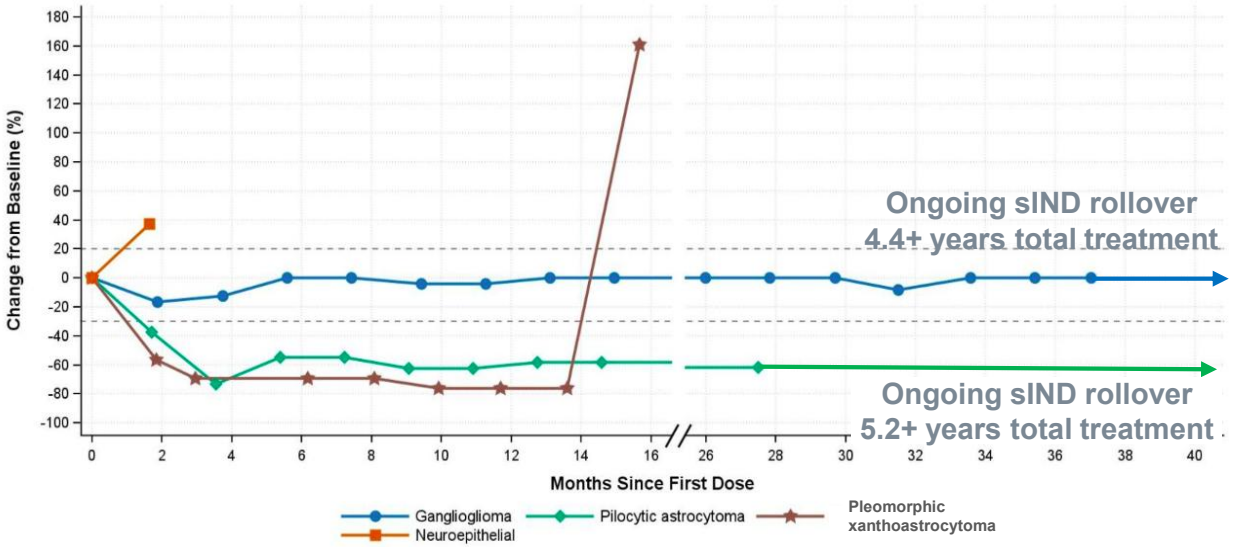
Confirmed PRs by histology

- Glioblastoma (n = 3)
- Pilocytic astrocytoma (n = 1)
- Anaplastic astrocytoma (n = 1)
- Pleomorphic xanthoastrocytoma (n = 1)

Tumor Changes Over Time: HGG (N = 5)



Tumor Changes Over Time: LGG/GNT (N = 4)



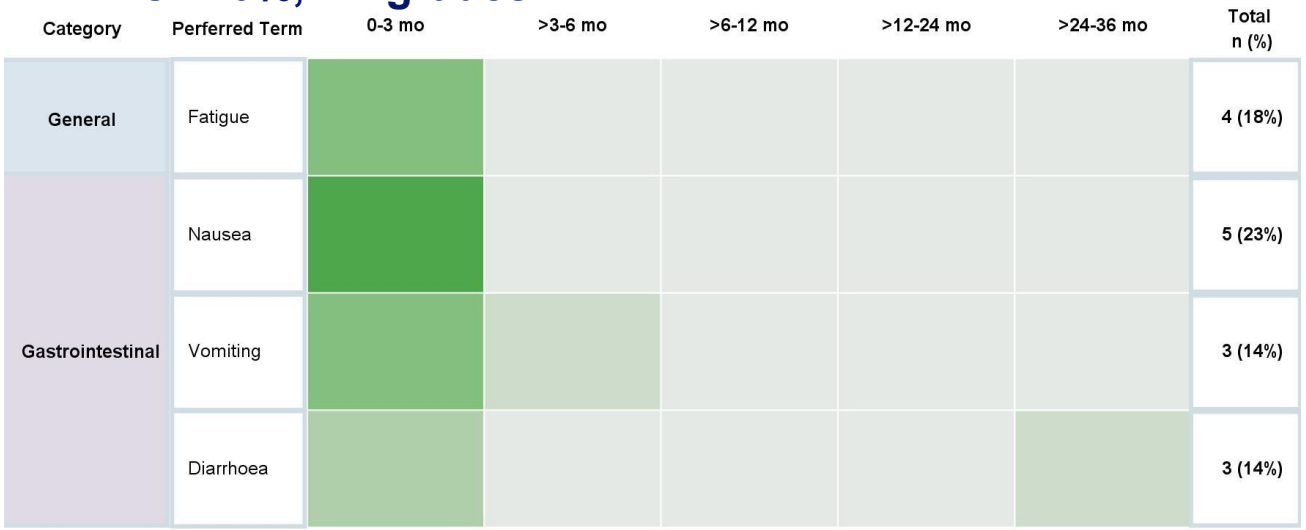
Arrows indicate sIND continuation; no target-lesion measurements were available during sIND treatment.

Responses were observed in both HGG and LGG/GNT, with durable treatment continuation

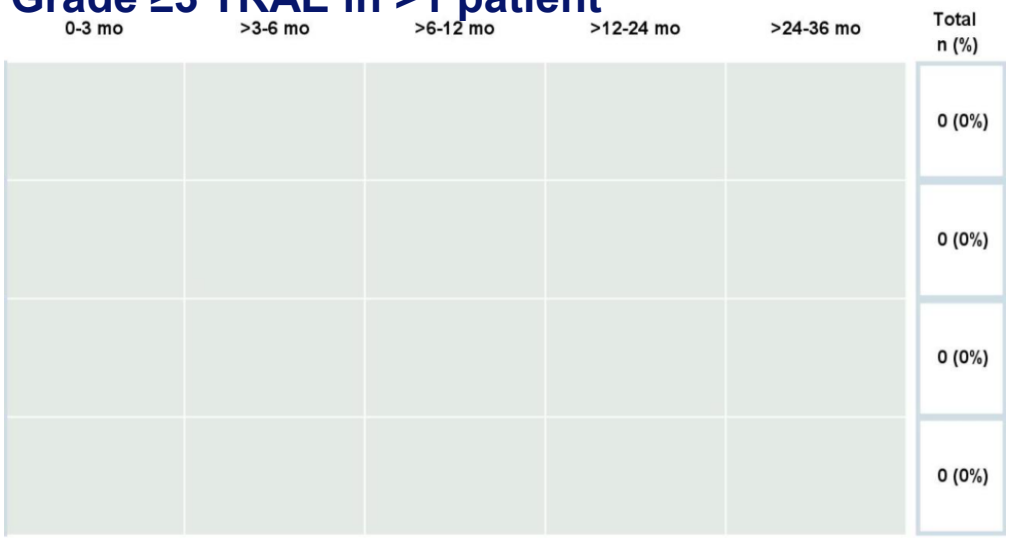
HGG, high-grade glioma; LGG/GNT, low-grade glioma/glioneuronal tumor; MAPKi, MAPK-pathway inhibitor; Mo, month; ORR, overall response rate; PFS, progression-free survival; PR, partial response; sIND, single-patient investigational new drug; Y, year.

Plixorafenib-related TEAEs (≥10%) By Time of Each Event Onset in Patients With Primary CNS Tumors (N = 22)

TRAEs ≥10%; All grades[a]

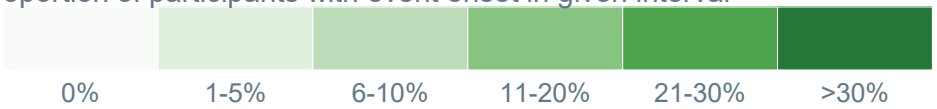


Grade ≥3 TRAE in >1 patient



Events occur early in treatment and generally last 3–5 days

Proportion of participants with event onset in given interval



Majority of events were low grade
No late onset or cumulative events occurred with prolonged exposure

[a]Each event including recurrence is shown, 1 patient with vomiting had 2 events.
Heat map excludes TEAEs of investigations, which is shown on the lower left

TEAEs Independent of Causality

- Gr ≥3 TEAEs >1 patient: ALT increase (n = 4) and headache (n = 2); all Gr 3
- Anemia was infrequent (18%; TRAEs = 0) and Grade 1/2 only

Most Common Laboratory Abnormalities (TRAEs)

Any Grade	Grade ≥3
ALT increased: 15 (68%)	ALT increased: 4 (18%)
AST increased: 14 (64%)	

- Grade ≥3 events limited to LFT increases. Most were with cobicistat and resolved within 1–2 weeks

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; TEAEs, treatment-emergent adverse event; TRAE, treatment-related adverse event.

BRAF Class-relevant TRAEs Over Time in the CNS Cohort

Event onset by time interval and grade

Time from first dose to event onset (n = 22)

Select TRAEs	0–3 mo	>3–6 mo	>6–12 mo	>1–2 y	>1–2 y	>2–3 y	>3 y
Pyrexia	0	0	0	0	0	0	0
Vomiting	1, 2	0	0	0	0	0	0
Nausea	5	0	0	0	0	0	0
Diarrhea	2	0	0	0	0	1	0
Grouped rash	1	0	0	0	0	0	0
Uveitis / retinal detachment	0	0	0	0	0	0	0
Hair/nail effects	0	0	0	0	0	0	0
Hemorrhagic events	0	0	0	0	0	0	0
Cardiovascular/ thromboembolic events	0	0	0	0	0	0	0
Pediatric reduction in growth velocity	0	0	0	0	0	0	0

Grade 1 Grade 2 Grade 3 Grade 4

MANAGEMENT BURDEN

- No Grade 3/4 TRAEs were observed
- Rash was Grade 1 only
- No clinically significant ocular AEs
- No hair/nail effects
- No secondary malignancies
- No treatment-emergent reduction in growth velocity identified (n = 5 children)

TREATMENT IMPACT

The low severity and absence of a late-onset increase support limited treatment burden during long-term plixorafenib exposure.

Low severity • Limited management burden
No increasing late-onset pattern

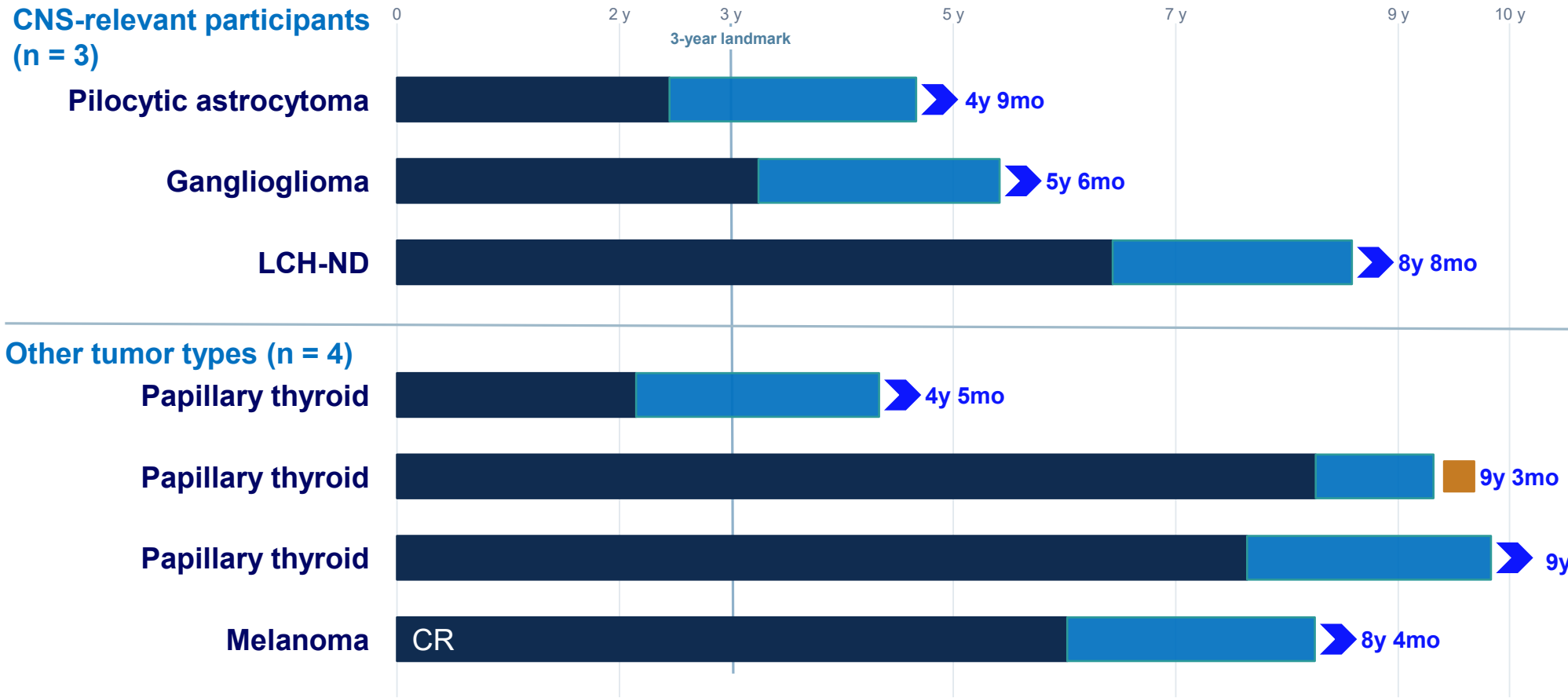
Treatment-related adverse events relevant to BRAF class were all Grade 1/2 and almost all occurred early

Mo, month; TRAE, treatment-related adverse event; Y, year.

Sustained Clinical Benefit (4 to 9+ Years) With Favorable Tolerability

7 sIND rollovers | 6 ongoing | Total treatment exposure: 4.3–9.8 years

On study | Compassionate Use | Ongoing | Stopped



Physician perspectives on the patient experience

- *Remarkable clinical improvement without clinically significant toxicities*
- *Ambulatory and self-caring, tolerating treatment*
- *Dramatic and sustained response together with major cognitive improvement*
- *Clinically stable*
- *Stable for a very long time; 89 years young**
- *Continues full-time employment*
- *Remains completely disease-free*

Clinical benefit maintained in ongoing compassionate use patients following transition to fed dosing ≥6 months ago

*Discontinued for quality-of-life reasons in consideration of advanced age.

CR, complete response; LCH-ND, neurodegenerative Langerhans cell histiocytosis; sIND, single-patient investigational new drug (compassionate use).

Conclusions

- Plixorafenib is a novel, first-in-class paradox breaker designed for use as a single agent
  - No acquired MAPK pathway mutations identified following progression on plixorafenib
- Final Phase 1/2a PLX120-03 (NCT02428712) data presented
  - 22 patients with primary CNS tumors, including 2 continuing plixorafenib through sIND for >4.8 years
- Differentiated safety profile
  - No evidence of cumulative toxicity with long-term treatment
  - No clinically significant ocular, cardiovascular, or dermatologic toxicities requiring dedicated monitoring
  - Lower rate of LFT abnormalities without cobicistat
- Highly encouraging and durable clinical benefit in primary CNS tumors
  - Clinical benefit observed for up to 5 years
  - 8+ years of treatment in a patient with neurodegenerative LCH
- FORTE (NCT05503797), the ongoing registrational basket study, includes patients with primary CNS tumors
  - CNS results anticipated in 2027
  - Plixorafenib administered with food rather than a PK booster, anticipated to improve tolerability
- Breakthrough Therapy Designation granted April 21, 2026 for plixorafenib in BRAF V600E-mutant HGG

We Would Like to Thank

- The patients and their families who made this study possible
- The principal investigators and their institutions for their dedication and support

