Window-of-Opportunity Trial of Ulixertinib for MAPK-Activated Lower Grade Gliomas in Adults

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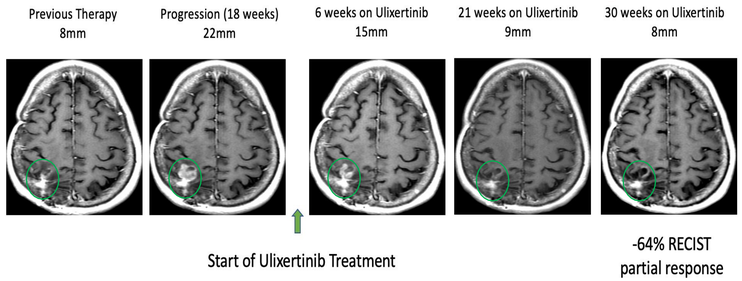
Background

- Ulixertinib is a small molecule inhibitor of extracellular signal-regulated kinase family kinases (ERK1 and ERK2) that is being developed as a novel anti-cancer drug.
- In a phase I/II studies of ulixertinib in advanced solid malignancies, central nervous system (CNS) antitumor responses have been seen.
- We hypothesized that ulixertinib crosses the intact blood-brain barrier (BBB) and it will result in improved responses in MAPK-activated gliomas.
- The trial initially included adult NF1 associated gliomas and CIC-mutated oligodendrogliomas as we have previously demonstrated increased MAPK signaling in NF1 tumors and increased susceptibility to MAPK inhibition in preclinical models of CIC-mutated vs. CIC-wild-type oligodendroglioma.
- Given slow accrual, the trial is now amended to include all gliomas with MAPK activation.

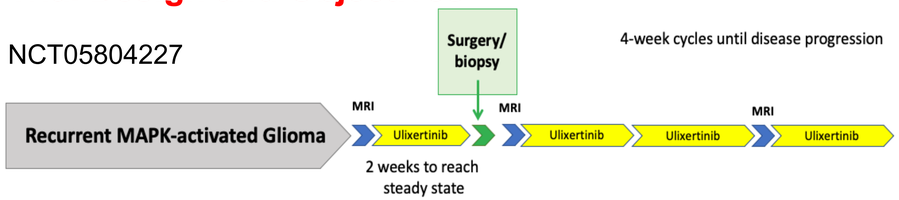
Clinical Evidence- Ulixertinib Activity in CNS



- Phase I trial in MAPK activated solid cancers - adults
  - One $BRAF^{V600E}$ GBM patient with partial response (PR) and on study for 81 weeks (above images)
  - One $BRAF^{V600E}$ GBM patient stable disease (SD) and was on study for 10 weeks
- Phase II trial in MAPK activated solid cancers – paediatrics MATCH
  - One $BRAF^{V600E}$ GNT patient with (SD) for 36 weeks
  - One LGG patient with BRAF fusion (SD) for 60 weeks
  - One LGG patient with BRAF fusion (SD) for 64 weeks
- Expanded Access Program
  - One NRAS GBM patient on study for 15 weeks
  - One $BRAF^{V600E}$ GBM patient on study for 18 weeks
  - One NF1 GBM patient on study for 33 weeks (ongoing)

Trial Design and Objectives

NCT05804227



Primary Objective:

1. To evaluate the ability of ulixertinib to penetrate the BBB (ulixertinib tumor concentration, tumor/plasma ratio)

Secondary Objectives:

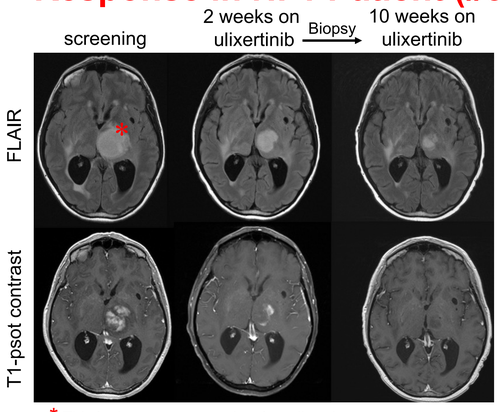
1. To assess anti-tumor activity of ulixertinib based on mPFS, ORR-12, DCR-12, DOR, TTR, TTN
2. To assess safety and tolerability of ulixertinib
3. To evaluate the ability of ulixertinib to reach cerebrospinal fluid (ulixertinib CSF concentration, tumor/CSF ratio)

Patient Characteristics and Early Outcomes

Patient ID	Diagnosis	Relevant somatic molecular alteration	Prior lines of systemic therapy	Number of adjuvant cycles	Best response	Duration of response
1	Oligodendroglioma	CIC p.R1515C	4	0	N/A	N/A
2	Oligodendroglioma	CIC p.S333fs*36 4459_4459+1GG>AA	2	6	SD	53 days
3	Pilocytic astrocytoma in NF1	NF1 p.R1306*	1	4	PR	99 days - ongoing
4	Oligodendroglioma	CIC p.Q1469*	2	5	SD	103 days - ongoing
5	Pleomorphic xanthroastrocytoma in NF1	N/A	1	0	N/A	N/A

as of 10/29/24

Response in NF1 Patient (#3)



* This lesion was not previously radiated

Safety

Adverse events (n)	Grade 2	Grade 3
Diarrhea	2	0
Anemia	1	1
Confusion	1	1
Rash	1	0
Dysgeusia	1	0
ALT increase	1	0
Lymphopenia	1	0

CNS Penetration of Ulixertinib

Cerebrospinal Fluid

Patient ID	Total plasma conc (ng/ml)	Free plasma conc (ng/ml)	CSF conc (ng/ml)	CSF/Free plasma ratio
1	2800	5.60	NA	NA
2	1970	3.94	4.45	1.13
3	2060	4.12	5.98	1.45
4	1320	2.64	4.91	1.86
5	1430	2.86	2.51	0.878
Mean	1920	3.83	4.46	**1.33**
SD	591	1.18	1.45	0.42
Median	1970	3.94	4.68	1.29

Brain Tumor

Patient ID	Total plasma conc (ng/ml)	Free plasma conc (ng/ml)	non-enhancing tumor conc (ng/g)*	non-enhancing tumor/plasma ratio	Enhancing tumor conc (ng/g)*	Enhancing tumor/plasma ratio
1	1430	2.86	241	0.169	407	0.285
2	2310	4.62	769	0.333	2000	0.866
3	2940	5.88	245	0.0833	605	0.206
4	1400	2.80	96.9	0.0692	NA	NA
5	1410	2.82	NA	NA	747	0.530
Mean	1900	3.80	338	**0.163**	940	**0.471**
SD	700	1.40	295	0.121	720	0.297
Median	1430	2.86	243	0.126	676	0.407

*ng/g assumes 1:1 conversation of gram to ml

Conclusions

- Ulixertinib demonstrates CNS activity in MAPK-activated high-grade gliomas based on prior phase I study and ongoing expanded access program.
- Ulixertinib mean CSF / plasma ratio is 1.33.
- Ulixertinib mean tumor / plasma ratio in non-enhancing and enhancing tumors is 0.163 and 0.471 respectively, which is similar to other CNS penetrant drugs in neuro-oncology (temozolomide brain / plasma ratio is 0.2).
- Out of 3 evaluable patients, one partial response was seen in an NF1-associated pilocytic astrocytoma.
- The trial now accepts all MAPK-activated gliomas for further confirmation of CNS penetration and evidence of early efficacy in a larger glioma patient population.

References

Sullivan et al, Cancer Discov, 2018. Siguad et al, Neuro-Oncol, 2022. Vo et al, JCO Precis Oncol, 2024

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