

INTRODUCTION

- Lorlatinib, a third generation ALK tyrosine kinase inhibitor (TKI), is the only approved ALK-directed therapy for patients with ALK NSCLC who progress on prior TKIs
- Median progression-free survival (PFS) is 7 months,¹ suggesting rapid development of resistance
- Resistance mechanisms to lorlatinib are diverse and can be broadly categorized as ALK-dependent or ALK-independent
 - ALK-dependent mechanisms involve development of resistant single or compound ALK mutations^{2,3}
 - ALK-independent mechanisms occur by activation of bypass pathways or histologic transformation⁴
- Gilteritinib is FDA-approved for relapsed/refractory FLT3 mutated acute myeloid leukemia. It has *in vitro* and *in vivo* activity against resistant ALK mutations (ie. I1171N compound mutations)⁵ and ALK-independent driver pathways such as AXL, LTK and c-KIT^{6,7}
- We therefore hypothesize that gilteritinib could have activity post-lorlatinib through targeting both ALK-dependent and independent mechanisms

METHODS

- This is a phase I, single-arm, investigator-initiated study at the University of Michigan enrolling patients with stage IV ALK+ NSCLC that have progressed on ALK TKI(s) (must include lorlatinib) and any other number of anti-neoplastic therapies (including prior investigational agents)
- Patients must have ECOG PS 0-2 and measurable disease per RECIST v1.1
- Asymptomatic untreated brain metastases are allowed
- This study utilizes a dose de-escalation design, starting at the approved gilteritinib dose of 120 mg/day. Dose is adjusted based on a two-stage continual reassessment method (CRM) design informed by dose-limiting toxicities (DLTs) and patients' prior treatment history
- Gilteritinib 120mg is given orally every day; each cycle is 21 days in duration
- Response assessment scans are obtained every 6 weeks for 12 weeks then every 9 weeks until progression
- The primary objectives are safety and tolerability
- Secondary objectives include objective response rate (ORR), PFS, and overall survival (OS)
- Translational correlatives include comprehensive whole exome sequencing to evaluate mechanisms of resistance from pre-treatment biopsy and/or circulating tumor cells (CTCs), analysis of CTC kinetics during therapy, and *ex-vivo* drug testing of patient-derived organoids
- This study is registered on clinicaltrials.gov, NCT06225427

DISCUSSION AND CONCLUSION

- Gilteritinib is safe and tolerable for patients with stage IV ALK NSCLC; no dose reductions or interruptions were needed and no DLTs occurred at the currently approved dose of 120mg per day
- Adverse events were all low grade (grade 1 or 2)
- Preliminary efficacy in a small number of patients suggest that patients with progressive disease after multiple lines of therapy including chemotherapy and currently available ALK TKIs can derive clinical benefit from gilteritinib

Future Direction for Research

- The safety and tolerability need to be evaluated in a larger number of patients; trial enrollment is ongoing
- In depth molecular characterization of patients who progress on and who respond to gilteritinib are underway to understand molecular determinants of response
- Additional data is needed regarding intracranial efficacy of gilteritinib, given the burden of brain metastases in ALK NSCLC
- Efforts are underway to expand this study to a multi-site to increase patient accrual and access
- A concurrent global study to evaluate the safety and efficacy of gilteritinib post alectinib and post lorlatinib is also active and accruing (NCT07140016)

REFERENCES & ACKNOWLEDGEMENTS

References

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Acknowledgements

We would like to acknowledge Lungevity and ALK Positive for providing the funding for this study and Astellas for providing gilteritinib. We would like to acknowledge all the members of the Judith Tam ALK Research Initiative (JTARI) and the Oncology Clinical Support Unit at the University of Michigan. Finally, we want to acknowledge and thank the patients and caregivers for participating in the study.

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RESULTS

- This study opened to accrual in 4/2024. As of the data cut-off date 3/5/2026, 11 of 30 planned patients have been enrolled and have received drug; seven patients are evaluable for response and two remain on treatment
- The median duration of follow-up is 2.8 months

Table 1: Patient characteristics

Characteristic	Enrolled patients (n=11)	Response evaluable patients (n=7)
Age at enrollment: median (range)	55 (28-76)	55 (33-76)
Female sex: N (%)	8 (73%)	6 (86%)
ECOG PS 0 N (%)	9 (82%)	6 (86%)
Prior lines of systemic therapy: median (range)	3 (2-7)	4 (2-7)
Prior systemic chemotherapy: N (%)	4 (36%)	5 (71%)
Prior NVL-655 N (%)	4 (36%)	2 (43%)
Adenocarcinoma histology: N (%)	9 (82%)	6 (86%)

Response evaluable defined as received and completed one cycle of gilteritinib and had a response assessment scan performed

Table 2: Adverse Events in 11 toxicity-evaluable patients

Event name	Grade 1 (n, %)	Grade 2 (n, %)
Dysesthesia	3 (27%)	1 (9%)
Fatigue	2 (18%)	1 (9%)
Myalgia	2 (18%)	1 (9%)
Restlessness	2 (18%)	0

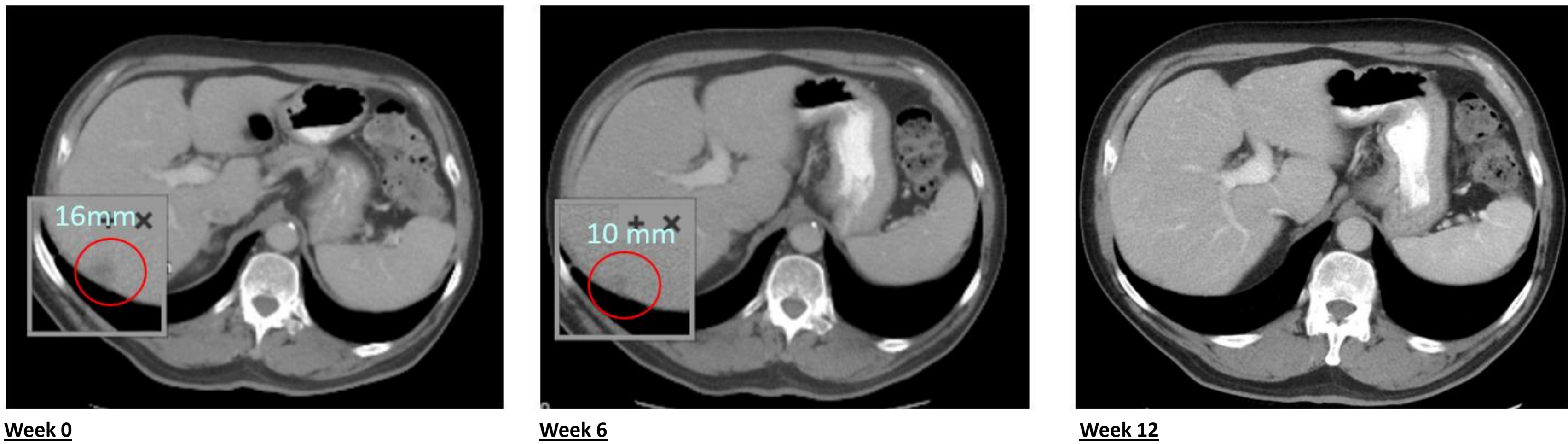
Toxicity-evaluable defined as having received at least one dose of gilteritinib. There were no ≥Grade 3 TRAEs. There were five ≥ Grade 3 AEs observed in two patients, but all were unrelated to gilteritinib

Table 3: Efficacy outcomes in 7 response-evaluable patients

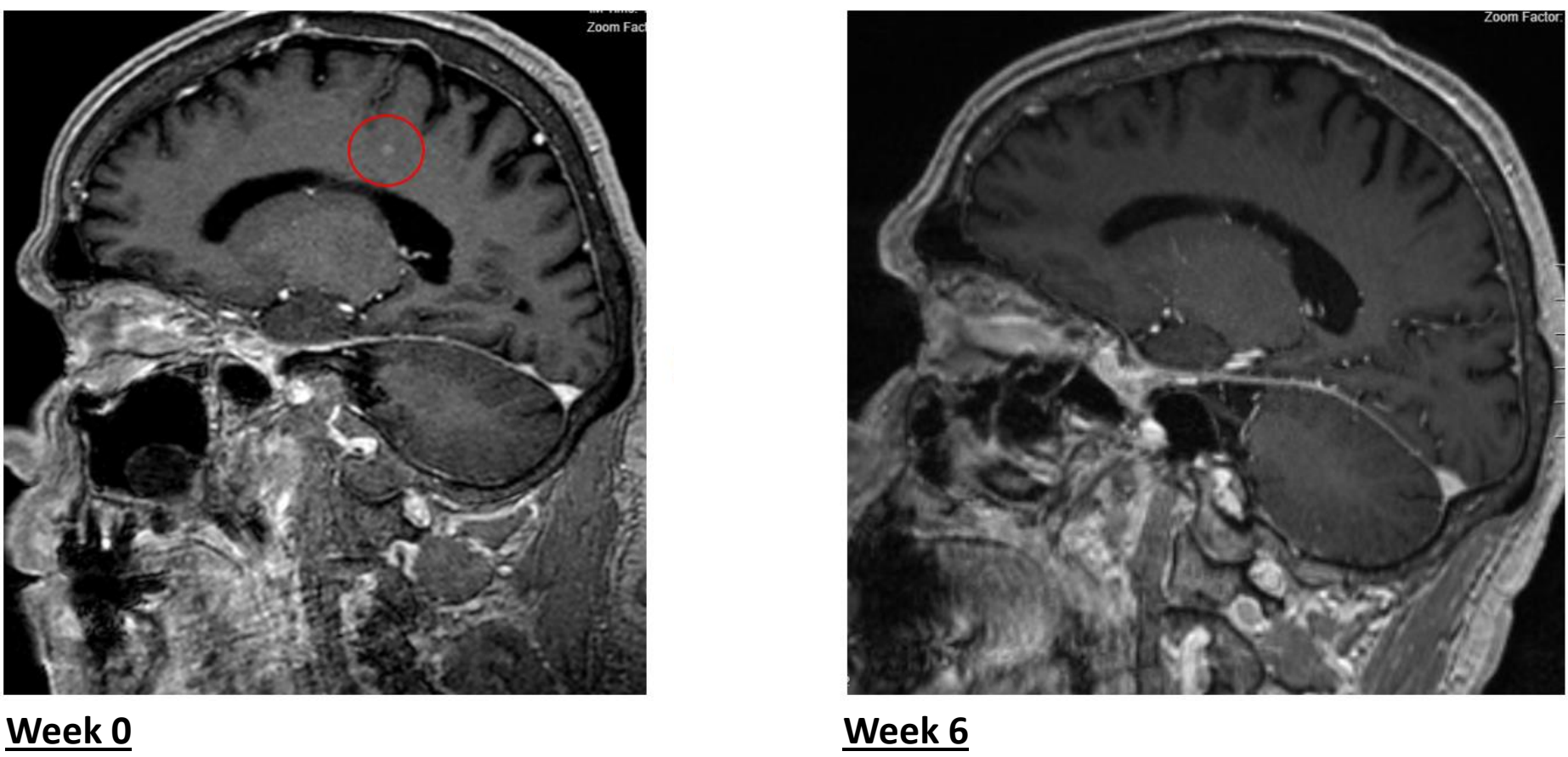
Efficacy	
ORR	29% (2/7)
mPFS	2.0 months (95% CI, 1.4 – NR)
mOS	3.7 months (95% CI, 2.7 – NR)

Confirmed objective response. mPFS median progression free survival; mOS median overall survival; ORR objective response rate

Figure 1. A patient case: 76yo M with Stage IV ALK-EML4 fusion (variant 1) NSCLC with progression on alectinib, lorlatinib, carboplatin/pemetrexed who enrolled on the gilteritinib study.



On the left is a peripheral segment VI/VII liver metastasis prior to gilteritinib. In the middle is response of the metastasis on first response scans after 6 weeks on therapy. On the right is resolution of metastasis after 12 weeks. The patient ultimately remained on drug for 9 months prior to disease progression.



This is the same patient who had an asymptomatic 3mm punctate right frontal metastatic deposit at enrollment. After 6 weeks of gilteritinib, the metastasis resolved. There was no recurrence of brain metastases for an additional 3 months on gilteritinib.