A Phase I/Ib study of the aurora kinase inhibitor alisertib in combination with osimertinib in advanced EGFR-mutated lung cancer

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Background

- Osimertinib is effective for the treatment of advanced EGFR-mutated lung cancer. However, treatment resistance invariably occurs.
- We previously identified Aurora Kinase A (AURKA) activation as a mechanism of resistance to osimertinib. (PMID: 30478424)
- Alisertib is an oral, selective, small-molecule inhibitor of AURKA.
- We evaluated the combination of alisertib with osimertinib in a phase I/Ib study of patients with advanced EGFR-mutated lung cancer who experienced disease progression on prior treatment with osimertinib monotherapy.

Study Design

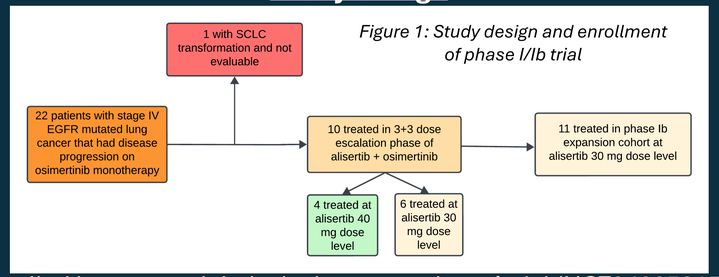


Figure 1: Study design and enrollment of phase I/Ib trial

- 22 patients were enrolled in an open-label, single-center phase I trial (NCT04085315).
- 10 patients were treated in a 3+3 dose escalation phase with alisertib using an intermittent dosing strategy of 30 mg (n = 6) or 40 mg (n = 4) twice daily (BID) in combination with osimertinib 80 mg daily.
- 11 additional patients were treated at the 30 mg alisertib BID intermittent dosing schedule in combination with osimertinib 80 mg daily in a Phase Ib dose expansion.
- Primary endpoints: maximum tolerated dose (MTD), recommended phase II dose (RP2D)
- Secondary endpoints: objective response rate (ORR), disease control rate (DCR), depth of response (DoR), progression free survival (PFS), overall survival (OS)

Table 1: Baseline Characteristics

Characteristic	No.	Percentage(%)
Female	18	85.7
Male	3	14.3
Race/Ethnicity		
Asian	12	57.1
White	8	38.1
Hispanic	1	4.8
Histology		
Adenocarcinoma	17	81
Not Biopsied	3	14.3
Unknown	1	4.8
Driver Mutation		
EGFR Exon 19 deletion	16	76.1
EGFR L858R mutation	3	14.3
EGFR L861Q mutation	2	9.5
Median Age at Diagnosis	70.3 years	

Table 2: Treatment Related Adverse Events

Adverse Event incidence > 5%	Grade 1-2 No. (%)	Grade 3-4 No. (%)	SAE No. (%)	Any Grade No. (%)
Neutropenia	8 (38.1%)	1 (4.8%)	0	9 (42.9%)
Anemia	8 (38.1%)	1 (4.8%)	1 (4.8%)	9 (42.9%)
Diarrhea	5 (23.8%)	3 (14.3%)	0	8 (38.1%)
Lymphopenia	6 (28.6%)	1 (4.8%)	0	7 (33.3%)
Fatigue	6 (28.6%)	1 (4.8%)	0	7 (33.3%)
Thrombocytopenia	5 (23.8%)	1 (4.8%)	0	6 (28.6%)
Nausea	5 (23.8%)	0 (0.0%)	0	5 (23.8%)
Alopecia	5 (23.8%)	0 (0.0%)	0	5 (23.8%)
Decreased Appetite	3 (14.3%)	1 (4.8%)	0	4 (19.0%)
Rash	4 (19.0%)	0 (0.0%)	0	4 (19.0%)
Insomnia	2 (9.5%)	1 (4.8%)	0	3 (14.3%)
Weight loss	3 (14.3%)	0 (0.0%)	0	3 (14.3%)
Constipation	3 (14.3%)	0 (0.0%)	1 (4.8%)	3 (14.3%)
Cough	1 (4.8%)	1 (4.8%)	0	2 (9.5%)
GERD	2 (9.5%)	0 (0.0%)	0	2 (9.5%)
Pruritis	2 (9.5%)	0 (0.0%)	0	2 (9.5%)
QTc Prolongation	2 (9.5%)	0 (0.0%)	0	2 (9.5%)

Efficacy

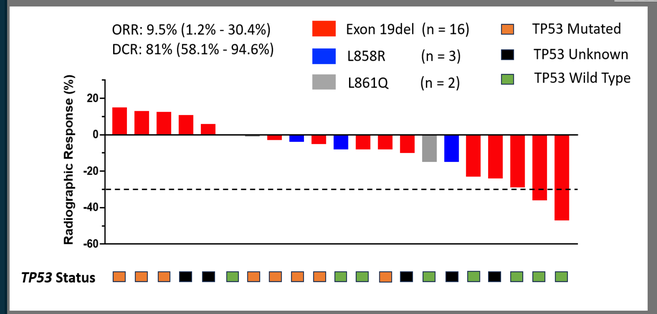


Figure 2: Efficacy of alisertib + osimertinib combination in all patients

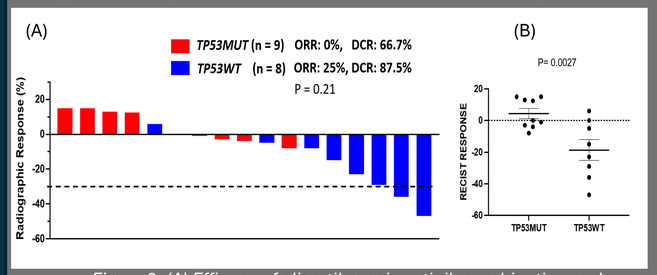


Figure 3: (A) Efficacy of alisertib + osimertinib combination and (B) Scatter plot of RECIST response based on TP53 status

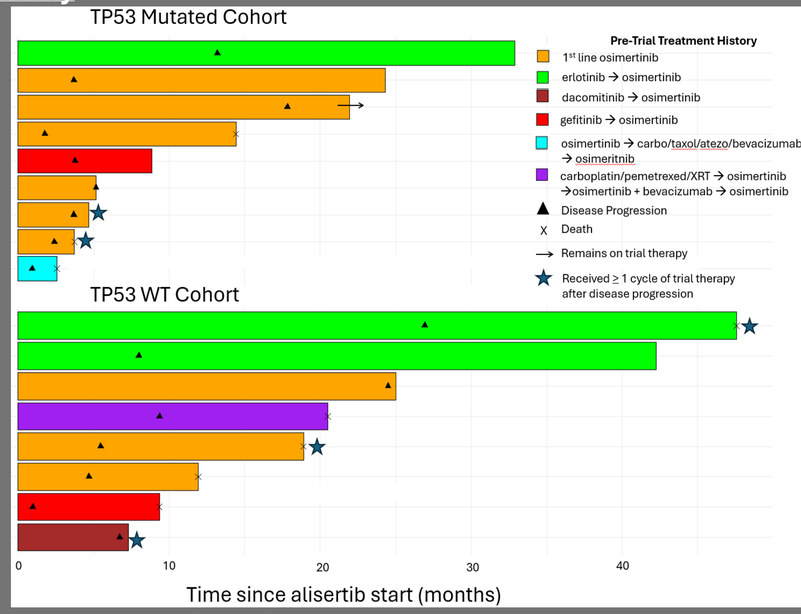
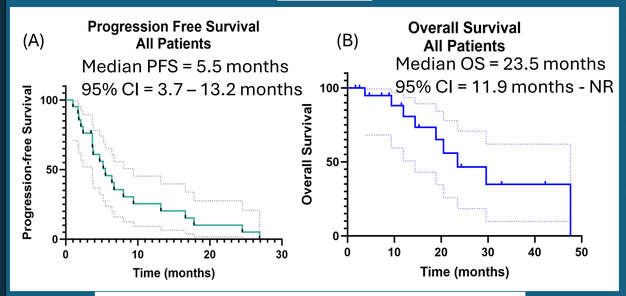


Figure 4: Swimlane plot demonstrating time to event, and pre-trial treatment history based on TP53 status

Survival



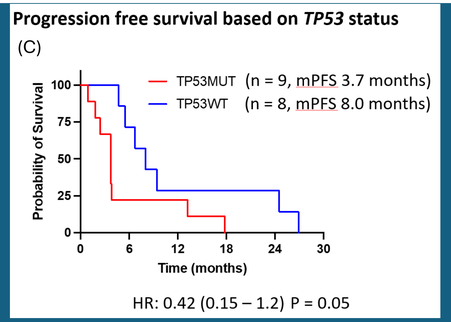


Figure 5: Kaplan Meier curves demonstrating (A) PFS of all patients (B) OS of all patients (C) PFS based on TP53 status

Key Conclusions

- **Optimal Dosing:** Intermittent dosing of alisertib (30mg) BID combined with osimertinib (80mg) daily was established as the MTD and RP2D.
- **Safety:** The treatment was associated with two SAEs, both at the 40 mg BID alisertib dose level, but no deaths.
- **Efficacy:** Although the ORR was < 10%, the DCR >80% suggests effective disease stabilization in a heavily pretreated advanced lung cancer cohort.
- **Comparative Performance:** The median PFS of 5.5 months is comparable to outcomes from other emerging therapies for this patient group.
- **Genetic Insights:** Subgroup analysis revealed that patients with TP53 wild-type status exhibited a superior radiographic response.
- **Limitations:** Small sample size and single-center study limit generalizability.
- **Future Directions:** Our findings warrant further study. Future directions will involve expanding TP53 wild-type cohorts.

Acknowledgments

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