Osimertinib plus repotrectinib phase I trial in TKI-resistant non-small cell lung cancer (NSCLC) with EGFR mutations

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BACKGROUND

NSCLC tumors often develop resistance to osimertinib through activation of parallel signaling pathways. [1,2] Repotrectinib is a tyrosine kinase inhibitor (TKI) of Src/FAK/JAK2, in addition to ALK, ROS1 and NTRKs that directly competes with ATP binding, including in the presence of resistance mutations. [3] In preclinical assays, repotrectinib combined with osimertinib, ablated STAT3, paxillin, and YAP1 phosphorylation. [4,5] The combination may have efficacy, surpassing resistance to osimertinib, with no substantial toxicity in patients with EGFR-mut NSCLC. [2-5] These findings prompted us to carry out the TOTEM trial to evaluate the combination of repotrectinib with osimertinib in patients with EGFR-mutant NSCLC.

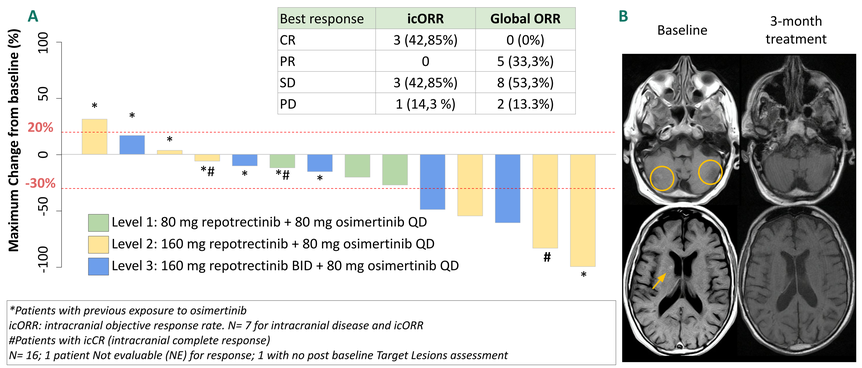
METHODS

TOTEM (NCT04772235) is a phase I, two-part study to assess safety, tolerability, pharmacokinetics, and antitumor activity of repotrectinib plus osimertinib in patients with advanced or metastatic EGFR-mutant (EGFR exon 18, exon 19, exon 21, or T790M mutation) NSCLC resistant to previous lines of treatment. Eligible patients were ≥ 18 years, ECOG 0-1, a creatinine clearance >50 mL/min. Patients with asymptomatic brain metastasis are eligible.

Phase Ia was a dose escalation (3+3) to determine the recommended phase 2 dose (RP2D). Treatment naïve patients were treated with osimertinib 80mg QD plus: repotrectinib 80mg QD (level 1), 160mg QD (level 2) and 160mg BID (level 3). Part B is an expansion phase at RP2D enrolling 20-30 patients that should have received osimertinib or osimertinib plus chemotherapy as first line treatment. Treatment continued until confirmed radiographic disease progression according to RECIST 1.1 criteria or unacceptable toxicity.

Table 1. Patient Characteristics

Patient Characteristics		Part Ia (n = 15)	Level 1 80mg/QD n=3	Level 2 160mg/QD n=6	Level 3 160mg/BID n=6
Median age, years (range)		61 (34 - 71)	60,3 (55 - 64)	55,5 (34 - 71)	57 (45 - 65)
Sex Female; n (%)		10 (66,7%)	1 (33,3%)	4 (66,7%)	5 (83,3%)
ECOG; n (%)	0	6 (40%)	2 (66,7%)	0 (0%)	4 (66,7%)
	1	9 (60%)	1 (33,3%)	6 (100%)	2 (33,3%)
Median sum of lesion diameters, mm (range)		64 (11 - 182,5)	64 (64-71)	46,5 (11 - 122)	64 (35,2 - 182,5)
Brain Metastasis; n (%)		7 (46,7%)	1 (33,3%)	4 (66,7%)	2 (33,3%)
EGFR mutation; n (%)	Exon 19 deletion	8 (53,3%)	1 (33,3%)	5 (83,3%)	2 (33,3%)
	Exon 21 L858R L861Q	5 (33,3%)	2 (66,7%)	0 (0%)	3 (50%)
	Exon 18 / G719X	2 (13,3%)	0 (0%)	1 (16,7%)	1 (16,7%)
Previous osimertinib; n (%)		9 (60%)	1 (33,3%)	4 (66,7%)	4 (66,7%)
N of previous treatment; n (%)	0	6 (40%)	2 (66,7%)	2 (33,3%)	2 (33,3%)
	1	4 (26,7%)	0 (0%)	1 (16,7%)	3 (50%)
	2	1 (6,7%)	0 (0%)	1 (16,7%)	0 (0%)
	3	4 (26,7%)	1 (33,3%)	2 (33,3%)	1 (16,7%)



Best response	icORR	Global ORR
CR	3 (42,85%)	0 (0%)
PR	0	5 (33,3%)
SD	3 (42,85%)	8 (53,3%)
PD	1 (14,3 %)	2 (13.3%)

*Patients with previous exposure to osimertinib
icORR: intracranial objective response rate. N= 7 for intracranial disease and icORR
#Patients with icCR (intracranial complete response)
N= 16; 1 patient Not evaluable (NE) for response; 1 with no post baseline Target Lesions assessment

Figure 1. a) Waterfall plot showing the objective response rate (ORR) and target lesions maximum size reduction. b) Example of intracranial response to repotrectinib plus osimertinib in a patient resistant to osimertinib.

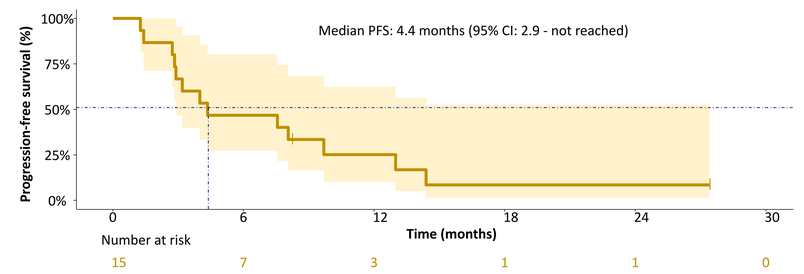
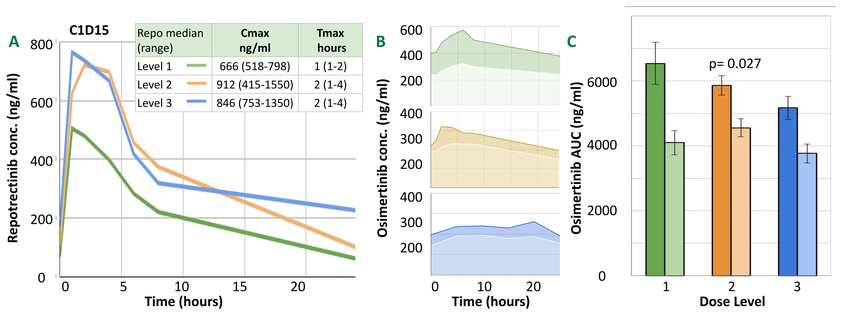


Figure 2. Kaplan-Meier showing the progression-free survival (PFS).



Repo median (range)	Cmax ng/ml	Tmax hours
Level 1	666 (518-798)	1 (1-2)
Level 2	912 (415-1550)	2 (1-4)
Level 3	846 (753-1350)	2 (1-4)

Figure 3. a) Repotrectinib conc. at cycle 1 day 15s. b) Osimertinib conc. in cycle 1 day 15 (dark area) and baseline (bright area) per dose levels. c) reduction in area under the curve os osimertinib between C1D15 and baseline.

RESULTS

Phase Ia included 15 patients with a median age of 61 yrs (34-71). Of these patients: 10 were female (66.7%), 9 had PS1 (60%), and 7 had brain metastasis (48.7%) (**Table 1**). At the time of starting treatment, two patients had exon 18 (G719X) mutations (p.E709_T710delinsD and p.G719A), 5 had exon 21 (4 p.L858R, 1 p.L861Q) and 8 had exon 19 deletion. Eight patients had p53 co-mutations, other co-alterations included PIK3CA, RET, FAT1, FGFR3 and MYC mutations, CDK4 and EGFR amplification, and MET, ROS, EGFR and FGFR3 over-expression. Six patients were treatment-naive, four were osimertinib progressors, and five had received two or more previous lines of treatment.

Intracranial complete response was attained in 3 of the seven patients with brain metastasis (42.85%). The overall objective response rate (ORR) was noted in 5 patients (33.3%), and stable disease in 8 patients (53.3%) (**Figure 1**). Median PFS was 4.4 mo. (95% CI 2.9-NR) (**Figure 2**). Pharmacokinetic analysis indicated a favorable profile of the combination and no concerns regarding drug-drug interactions, despite a non-significant decrease in osimertinib AUC is reported at the RP2D (**Figure 3**).

Of the adverse events, manageable, transient dizziness was observed in 76% of the patients, and dysgeusia occurred in 48% of cases (**Figure 4**). Most side effects were grade 1-2, including anemia, diarrhea, fatigue, and liver enzyme elevation. No DLTs were observed. Dose level 3 (160mg BID) was safe, therefore, part Ib continued with repotrectinib 160mg BID plus osimertinib 80mg QD in 15 additional patients.

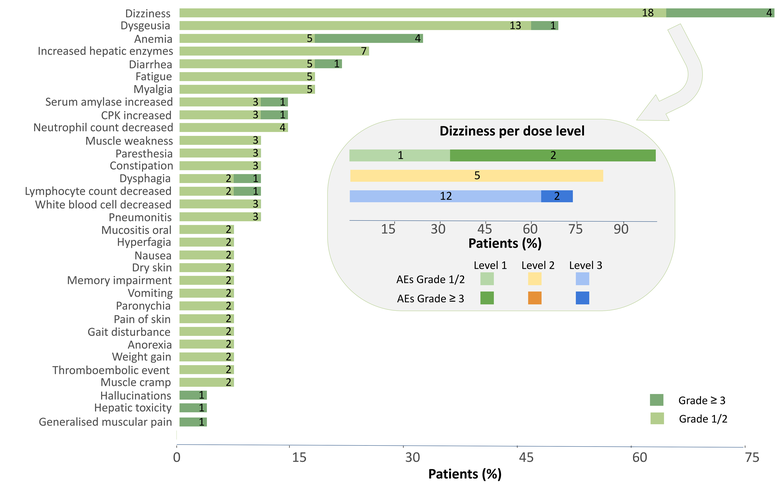


Figure 4. Safety profile of the combination of osimertinib and repotrectinib.

CONCLUSIONS

- In Part Ia osimertinib + repotrectinib showed impressive intracranial ORR with a manageable safety profile.
- Results were in range with recent reports for new combinations and are promising considering that patients were heavily pretreated and some bear EGFR exon 18 and 20 mutations.
- Part Ib with repotrectinib 160 mg BID plus osimertinib 80 mg completed accrual on January 2025 and is ongoing.

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