20P - Efficacy and safety of AZD3759 in previously untreated EGFR-mutant non-small cell lung cancer with central nervous system metastases in a multi-center, phase 2 umbrella trial (CTONG1702)

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BACKGROUND

Non-small-cell lung cancer (NSCLC) had poor prognosis in patients with central nervous system (CNS) metastases. Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) has changed the treatment paradigm of advanced EGFR-mutant patients. Subgroup analysis of FLAURA study showed clinical activity of osimertinib in untreated patients with EGFR mutation and CNS metastases. Here, we reported the result of a prospective trial with an EGFR-TKI (AZD3759) with high capability to penetrate the blood-brain barrier, in the same population with CNS metastases.

METHODS

We initiated an umbrella trial (CTONG1702), in the 8th arm to access the efficacy and safety of AZD3759 in untreated EGFR-mutant NSCLC with brain or leptomeningeal metastases. Patients received AZD3759 200 mg or 300 mg BID. The primary objective was confirmed objective response rate (ORR). To determine whether AZD3759 has sufficient activity, we used Simon's minimax two-stage to calculate sample size. Here, we observed the clinical response to AZD3759 in different dose and the survival data.

RESULTS

PATIENTS

30 patients were enrolled and received AZD3759 at 200 mg (n = 15) or 300 mg (n = 15) BID . As of June 30 2022, the median follow-up is 29.1 months.

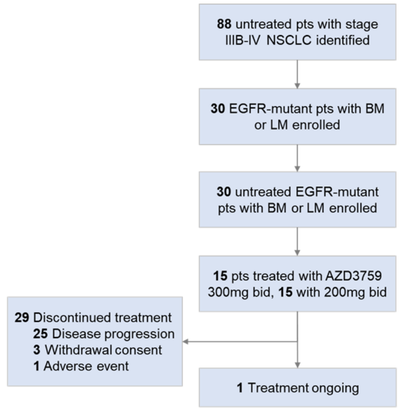

Figure 1 | Patient disposition. A flowchart that illustrates enrollment of patients with EGFR-mutant advanced non-small-cell lung cancer with BM/LM in CTONG1702 (n=30)

Table 1: Demographic and clinical characteristics of the patients.

Characteristics	All pts (n = 30)	200mg (n = 15)	300mg (n = 15)
Age, years, median (range)	58.5 (35, 72)	56 (35, 65)	64 (45, 72)
Sex, No. (%)			
Male	14 (46.7)	7 (46.7)	7 (46.7)
Female	16 (53.3)	8 (53.3)	8 (53.3)
Smoking history, No. (%)			
Current/ Former	12 (40.0)	5 (33.3)	7 (46.7)
Never	18 (60.0)	10 (66.7)	8 (53.3)
ECOG PS, No. (%)			
0	1 (3.3)	0	1 (6.7)
1	29 (96.7)	15 (100)	14 (93.3)
Clinical stage, No. (%)			
IVA	2 (6.7)	1 (6.7)	1 (6.7)
IVB	28 (93.3)	14 (93.3)	14 (93.3)
Pathologic subtypes, No. (%)			
Adenocarcinoma	30 (100)	15 (100%)	15 (100)
BM/LM, No. (%)			
Brain metastasis (BM)	15 (100%)	14 (93.3%)	29 (96.7%)
Leptomeningeal metastasis (LM)	0	1 (6.7%)	1 (3.3%)
EGFR mutation subtypes, No. (%)			
Exon 19 deletion	18 (60.0)	11 (73.3%)	7 (46.7)
Exon 21 L858R mutation	11 (36.7)	4 (26.7%)	7 (46.7)
PD-L1, No. (%)			
positive (1%-49%)	4 (13.3)	4 (26.7)	0 (0.0)
negative (<1%)	5 (16.7)	4 (26.7)	1 (6.7)

Abbreviations:ECOG PS,Eastern Cooperative Oncology Group Performance Status;No.,number.

EFFICACY

The primary endpoint was reached with an ORR of 70% (21/30), which was 80% (12/30) in 200mg group and 60% (9/30) in 300 mg group, respectively. The median progression-free survival (PFS) was 12.9 months (200mg: 15.8 months; 300mg: 10.7 months).

Table 2 : Clinical response to AZD3759.

Parameters	All pts (n = 30)	200mg (n = 15)	300mg (n = 15)
Best overall response, No. (%)			
Confirmed PR	21 (70.0)	12 (80.0)	9 (60.0)
SD	5 (16.7)	2 (13.3)	3 (20.0)
PD	2 (6.7)	0	2 (13.3)
NE	2 (6.7)	1 (6.7)	1 (6.7)
ORR, No. (%, 95%CI)	70.0 (50.6, 85.3)	80.0 (51.9, 95.7)	60.0 (32.3, 83.7)
DCR, No. (%, 95%CI)	86.7 (69.3, 96.2)	93.3 (68.1, 99.8)	80.0 (51.9, 95.7)

Abbreviations:CI,confidence intervals;DCR,disease control rate;ORR,objective response rate;PD,progression disease;PR,partial response;SD,stable disease.

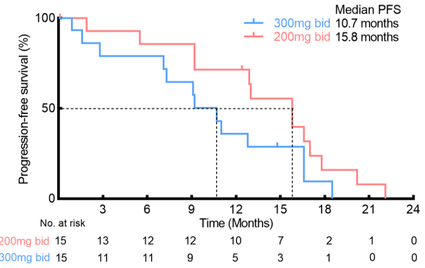

Figure 2 | Survival benefit from different dose of AZD3759 in untreated patients with EGFR mutation and CNS metastasis.

SAFETY

Treatment-related adverse events with grade ≥3 occurred in 21 (70%) patients, which was (60.0%) in 200 mg group and 13 (86.7%) in 300 mg group, respectively. The most common adverse events are rash and diarrhea. Of 16 patients who had tumor or liquid biopsy to analyze acquired resistant mechanism, 10 (62.5%) developed EGFR T790M. Of 30 enrolled patients, 13 received osimertinib as 2nd line therapy.

Table 3 Common TRAEs (≥20%) following AZD3759.

TRAEs, No. (%)	All pts		200mg		300mg	
	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3
Any events	28 (93.3)	22 (73.3)	13 (86.7)	9 (60.0)	15 (100)	13 (86.7)
Rash	25 (83.3)	15 (50.0)	11 (73.3)	6 (40.0)	14 (93.3)	9 (60.0)
Increased AST	18 (60.0)	1 (3.3)	9 (60.0)	1 (6.7)	9 (60.0)	0
Itch	18 (60.0)	0	8 (53.3)	0	10 (66.7)	0
Xerosis cutis	16 (53.3)	0	8 (53.3)	0	8 (53.3)	0
Increased blood bilirubin	10 (33.3)	0	4 (26.7)	0	6 (40.0)	0
Mouth ulcer	10 (33.3)	2 (6.7)	2 (13.3)	0	8 (53.3)	2 (13.3)
Anorexia	9 (30.0)	0	3 (20.0)	0	6 (40.0)	0
Cutaneous fissure	9 (30.0)	1 (3.3)	2 (13.3)	0	7 (46.7)	1 (6.7)
Increased alkaline phosphatase	7 (23.3)	0	5 (33.3)	0	2 (13.3)	0
Increased serum creatinine	7 (23.3)	0	5 (33.3)	0	2 (13.3)	0
Skin exfoliation	6 (20.0)	0	3 (20.0)	0	3 (20.0)	0

CONCLUSIONS

This is the first report to present phase II study outcome of AZD3759 with promising efficacy and tolerable safety in the selected population with CNS metastases. We suggested 200 mg BID was a better dose with superior response and lower toxicity. EGFR T790M was the most common resistant mutation, and these patients still have the opportunity to receive osimertinib after progression of AZD3759.

CONFLICTS OF INTEREST

Prof. Yi-Long Wu reports personal financial interests: consulting and advisory services, speaking engagements of Roche, AstraZeneca, Eli Lilly, Boehringer Ingelheim, Sanofi, MSD, BMS.

Prof. Qing Zhou reports honoraria from AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, MSD, Pfizer, Roche, and Sanofi, outside the submitted work. Other authors declare no competing interest.