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Final analysis of open-label single-arm study on dabrafenib + trametinib in Chinese patients with *BRAF* V600E-mutant metastatic non-small cell lung cancer

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INTRODUCTION

- *BRAF* V600E mutations are a significant oncogenic activator in metastatic non-small cell lung cancer (NSCLC), leading to activation of the extracellular signal–regulated kinase signaling pathway which promotes cell growth, proliferation, and survival[1]
- *BRAF* V600E mutations have been identified in approximately 1% to 3% of NSCLC cases in Chinese patients[1, 2]
- Dabrafenib + trametinib was the first approved targeted therapy by the National Medical Products Administration in China for patients with NSCLC harboring *BRAF* V600 mutations[2]
- This study evaluated dabrafenib + trametinib in improving clinical responses in terms of overall response rates (ORR), progression-free survival (PFS), and overall survival (OS), and safety in *BRAF* V600E-mutant metastatic NSCLC

METHODS

- This single-arm, open-label, multicenter phase II study evaluated the combination of dabrafenib + trametinib in 40 Chinese patients, with inclusion criteria of being aged ≥18 having *BRAF* V600E-mutant stage IV NSCLC, and being treated with ≤3 prior systemic therapies (including platinum-based chemotherapy, anti-PD-1/PD-L1, or EGFR/ALK inhibitors) or untreated for metastatic disease
- Dabrafenib 150 mg twice daily and trametinib 2 mg once daily were administered orally. Patients were treated until disease progression, new therapy initiation, unacceptable toxicity, pregnancy, consent withdrawal, loss to follow-up, physician's decision, or death. Data cut-off date was November 07, 2024
- The full analysis set (FAS) included all patients who received ≥1 dose of study drug, serving as the primary population for efficacy and safety analysis. PK analysis set (PAS) comprised FAS patients with analyzed PK sample
- Primary endpoint was to assess ORR by central independent review using the FAS. Secondary endpoints included assessing ORR by investigator assessment, PFS, duration of response (DoR), OS, safety and tolerability, quality of life (QoL), all analysed using the FAS and pharmacokinetics (PK) analyzed using the PAS

RESULTS

- In the all lines population, the median (range) age was 63 years (46–77) and 75.0% had an ECOG performance status of 1 at screening
- 20 patients (50.0%) received prior antineoplastic medications, of which 18 patients (45.0%) received antineoplastic medications in metastatic setting

Efficacy Results

- For the all lines population (N=40), ORR was 75.0% (95% CI: 58.8, 87.3) by central independent review and 77.5% (95% CI: 61.5, 89.2) by local review, whereas for patients on first line (1L, N=22) treatment, ORR was 90.9% (95% CI: 70.8, 98.9) and 95.5% (95% CI: 77.2, 99.9), respectively (**Table 1**)

Table 1. ORR based on central independent and local review assessment using RECIST 1.1 criteria (full analysis set)

Dabrafenib + Trametinib	Central independent review, n (%), (95% CI)		Local review, n (%) (95% CI)	
	1L N=22	All lines N=40	1L N=22	All lines N=40
Best Overall Response				
Complete Response (CR)	5 (22.7)	6 (15.0)	1 (4.5)	1 (2.5)
Partial Response (PR)	15 (68.2)	24 (60.0)	20 (90.9)	30 (75.0)
Non-CR/Non-Progressive Disease (PD)	0	1 (2.5)	N/A	N/A
Stable Disease	2 (9.1)	7 (17.5)	1 (4.5)	5 (12.5)
PD	0	1 (2.5)	0	3 (7.5)
Overall Response Rate (ORR:CR+PR)	20 (90.9) (70.8, 98.9)	30 (75.0) (58.8, 87.3)	21 (95.5) (77.2, 99.9)	31 (77.5) (61.5, 89.2)
Disease Control Rate (DCR: CR +PR+SD+ Non-CR/Non-PD)	22 (100.0) (84.6, 100.0)	38 (95.0) (83.1, 99.4)	22 (100.0) (84.6, 100.0)	36 (90.0) (76.3, 97.2)

The exact binomial 95% CI (Clopper and Pearson 1934) is presented ORR, defined as the percentage of patients with a confirmed CR or PR by central independent assessment as per RECIST 1.1 criteria. DCR is the proportion of patients with a best ORR of CR or PR or a SD or non-CR/Non-PD.
1L, first line; CI, confidence interval; N, total number of patients in the treatment group; n, number of patients who are at the corresponding category; N/A, not available.

- Values for disease control rate (DCR), median PFS, and median DoR for all lines population and 1L treatment population are summarized in **Table 2**

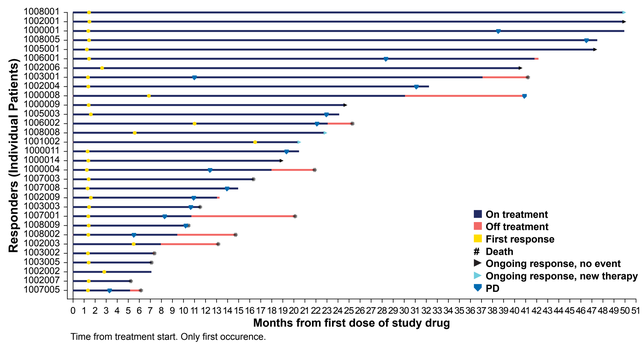
Table 2. PFS, DoR, OS based on investigator assessed response (full analysis set)

Estimates	Dabrafenib + Trametinib	
	1L (N=22)	All lines (N=40)
Progression-Free Survival		
Events, n(%)	15 (68.2)	28 (70.0)
Median (95% CI)	22.1 (10.2, 38.5)	13.9 (10.2, 28.3)
K-M event -free estimates (95% CI) at 48 months	18.6 (3.8, 41.9)	14.3 (4.1, 30.6)
Duration of Response		
Responders*, n(%)	21 (95.5)	31 (77.5)
Median (95% CI)	18.0 (9.2, 45.1)	14.9 (9.2, 29.7)
K-M event -free estimates (95% CI) at 48 months	17.9 (3.4, 41.7)	16.1 (4.5, 34.1)
Overall survival		
Deaths, n(%)	9 (40.9)	18 (45.0)
Median (95% CI)	NE (14.7, NE)	25.3 (16.2, NE)
K-M event -free estimates (95% CI) at		
12 months	77.3 (53.7, 89.8)	73.5 (56.3, 84.8)
48 months	52.1 (26.3, 72.7)	42.2 (22.4, 60.8)

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). *Responders were patients with a best overall response of CR or PR. OS was defined as the time from first dose until death due to any cause. Greenwood formula is used for CIs of KM event-free estimates.
1L, first line; CI, confidence interval; CR, complete response; DoR, duration of response; K-M, Kaplan-Meier; NE, not estimable; OS, overall survival; PR, partial response; PFS, progression-free survival.

- For the all lines population, CR was observed in 2.5% and PR in 75% of patients, as assessed by local review (**Figure 1** and **Table 1**)
- In the all lines population, central radiology review showed a response in 34 patients (85.0%) with a decrease in target lesion size from baseline, including 6 achieving complete response (CR) and 1 with progressive disease (PD) due to a new lesion despite target lesion reduction (**Figure 2**). Local radiology review showed target lesion reduction in 36 patients (90.0%), with 1 achieving CR (**Figure 3**)

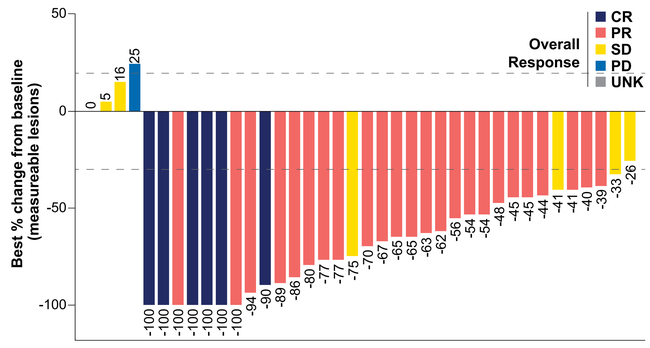
Figure 1. Swimmer plot for time to onset and DoR based on local investigator assessment using RECIST 1.1 criteria (full analysis set for responders)



Time from treatment start. Only first occurence.

CR, complete; DoR, duration of response; PR, partial response; PD, progressive disease.

Figure 2. Waterfall plot for best percentage change from baseline in the sum of longest diameters of lesions based on central radiology review (full analysis set for responders)

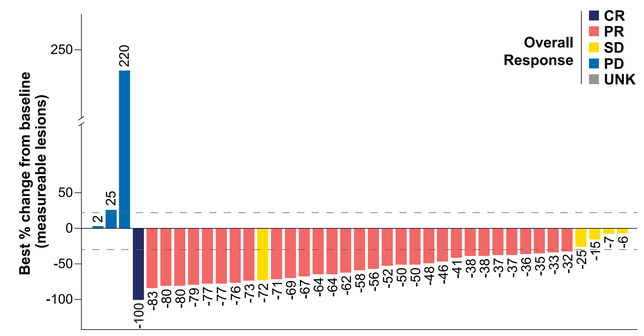


	Dabrafenib + Trametinib
Decrease in best percentage change from baseline	85.0%
Increase/zero in best percentage change from baseline	10.0%
PD due to new lesion despite target reduction	2.5%

Patients for whom the best % change in target lesions was not available were excluded from the analysis, percentages above use n as denominator

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UNK, unknown.

Figure 3. Waterfall plot for best percentage change from baseline in the sum of longest diameters based on local radiology review (full analysis set for responders)



	Dabrafenib + Trametinib
Decrease in best percentage change from baseline	90.0%
Increase/zero in best percentage change from baseline	7.5%
PD due to new lesion despite target reduction	7.5%

Patients for whom the best % change in target lesions was not available were excluded from the analysis, percentages above use n as denominator

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UNK, unknown.

Pharmacokinetic Results

- In this study, the enrolled Chinese all lines population had geometric mean of dabrafenib pre-dose trough concentrations were 74.4 ng/mL at week 3, 91.5 ng/mL at week 6 and 93.9 ng/mL at week 12 with geometric coefficient of variation percentages of 74.9%, 109.7%, and 212.0% respectively
- Trametinib pre-dose trough concentrations remained highly consistent over timepoints, with geometric means of 13.5 ng/mL at week 3, 13.6 ng/mL at week 6, and 12.5 ng/mL at week 12, and corresponding geometric coefficients of variation of 35.0%, 29.5%, and 37.0%, respectively
- No significant effect of race on the PK of dabrafenib and trametinib was observed

Patient-Reported Outcome Results

- In the all lines population, the mean scores for overall health, QoL, and visual analogue scale in QLQ-C30 and EQ-5D-5L questionnaires increased at week 12 and at the end of treatment compared to baseline. Additionally, the mean scores for four items (trouble taking short walk outside, limited doing work/daily activity, overall health during past week, QoL during past week) showed an increase from baseline at week 12
- Given the small sample size, the magnitude of changes observed cannot be used to determine Minimal Clinically Important Difference threshold

Safety Results

- In the all lines population, the median duration of exposure was 16.03 months for dabrafenib and 11.48 months for trametinib
- Overall, 97.5% (n=39) of patients experienced at least one adverse event (AE). 92.5% (n=37) had treatment-related AEs (**Table 3**), with most frequent treatment-related AEs included pyrexia (45.0%), increased aspartate aminotransferase (AST) (40.0%), anemia (37.5%) and decreased neutrophil count (35.0%)
- Grade ≥3 treatment-related AEs were observed in 18 patients (45.0%). Treatment-related AEs led to discontinuation in 5 patients (12.5%) and to dose adjustments or interruptions in 25 patients (62.5%) (**Table 3**)
- Grade ≥3 adverse event of special interest were observed in 15 patients (37.5%); events included pancreatitis (10.0%), hepatic disorders (7.5%), neutropenia (7.5%), and pyrexia (5.0%)
- A total of 6 (15.0%) deaths occurred on-treatment and 12 (30.0%) during follow-up, with no fatal AEs related to the treatment (**Table 3**)
- Serious adverse events (SAEs) were observed in 20 patients (50.0%) (**Table 3**); SAEs suspected to be related to dabrafenib and/or trametinib included pyrexia (10.0%) and increased blood creatinine (5.0%)
- No clinically significant changes were observed in vital signs or ECG parameters, and no patient was seen with a QTcF interval ≥481 msec during the study

Table 3. Overview of adverse events (full analysis set)

	Dabrafenib + Trametinib (N=40) n (%)
AE	39 (97.5)
Treatment-related	37 (92.5)
AEs with grade ≥3	27 (67.5)
Treatment-related	18 (45.0)
SAEs	20 (50.0)
Treatment-related	11 (27.5)
Fatal SAEs	1 (2.5)
Treatment-related	0
AEs leading to discontinuation	7 (17.5)
Treatment-related	5 (12.5)
AEs leading to dose adjustment/interruption	30 (75.0)
Treatment-related	25 (62.5)
AEs requiring additional therapy	38 (95.0)

Number (n) represent number of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication. MedDRA version 27.1, CTCAE version 4.03.
AE, adverse event; n, number of patients; SAE, serious adverse event.

KEY FINDINGS & CONCLUSIONS

- This final analysis demonstrated that dabrafenib plus trametinib provided consistent, long-term efficacy (ORR, DoR, PFS) and prolonged survival, along with significant anti-tumor activity, in Chinese patients with advanced/metastatic *BRAF* V600-mutant NSCLC
- The safety profile was manageable and none of the fatalities were related to the study treatment
- PK profiles in Chinese patients from this study were comparable to the previously described ones in the overall study population, with no evidence of race-related differences in PK parameters
- Efficacy and safety outcomes were consistent with those observed in the global Phase II NSCLC study (NCT01336634)[3] and the primary analysis (NCT04452877)[4], with no identification of new safety signals

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Disclosures

Dr. Jianya Zhou has no conflicts of interest to declare.