Phase 2 Study of Dabrafenib Plus Trametinib in Patients With BRAF V600E-Mutant Metastatic NSCLC: Updated 5-Year Survival Rates and Genomic Analysis

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Journal of Thoracic Oncology

Volume 17 Issue 1 Pages 103-115 (January 2022)

DOI: 10.1016/j.jtho.2021.08.011

Introduction

- $BRAF^{V600E}$ mutation occurs in 1-2% of lung adenocarcinomas and acts as an oncogenic driver.

- Dabrafenib plus trametinib was found to have robust antitumor activity in patients with BRAF V600E-mutant metastatic NSCLC (mNSCLC).

- This is an updated survival analysis of a phase 2 study (NCT01336634) with a minimum of 5-year follow-up and updated genomic data

Study Design

- Phase 2, multicohort, multicenter, nonrandomized, open-label study
- Patients (aged ≥18 y) with locally determined BRAF V600E mutation in mNSCLC were sequentially enrolled.
- Stage IV mNSCLC with measurable disease as per RECIST v.1.1, an ECOG PS of less than or equal to 2

- Patients with documented tumor progression after more than or equal to one platinum-based chemotherapy regimen (based on medical history) and less than or equal to three previous systemic treatments were included in one cohort (cohort B)

- Patients without previous systemic treatment were included in another cohort (cohort C).

- Received dabrafenib 150 mg twice daily and trametinib 2 mg once daily.

- Primary end point: Overall response rate
- Secondary end points: DOR, PFS, OS, Safety

Results

Results

- At data cutoff, for cohorts B (57 patients) and C (36 patients)
- the median follow-up was 16.6 (range: 0.5–78.5) and 16.3 (range: 0.4–80) months
- overall response rate (95% confidence interval [CI]) was 68.4% (54.8–80.1) and 63.9% (46.2–79.2)
- median progression-free survival (95% CI) was 10.2 (6.9–16.7) and 10.8 (7.0–14.5) months
- median overall survival (95% CI) was 18.2 (14.3–28.6) and 17.3 (12.3–40.2) months.

Overall Response

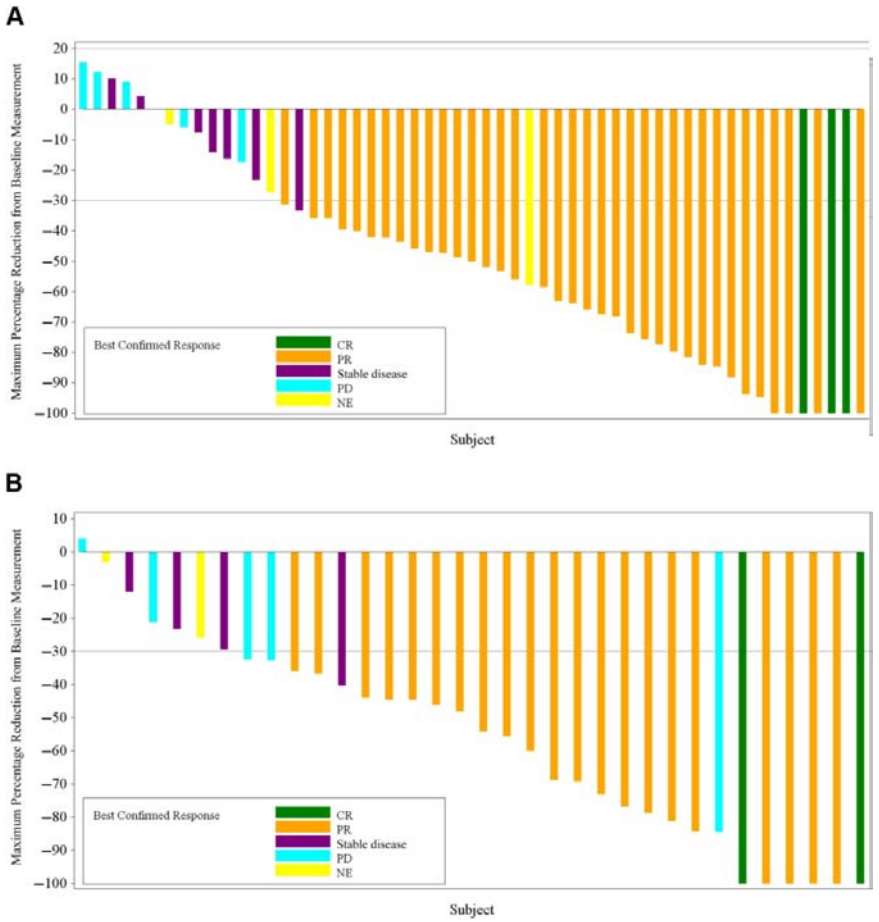
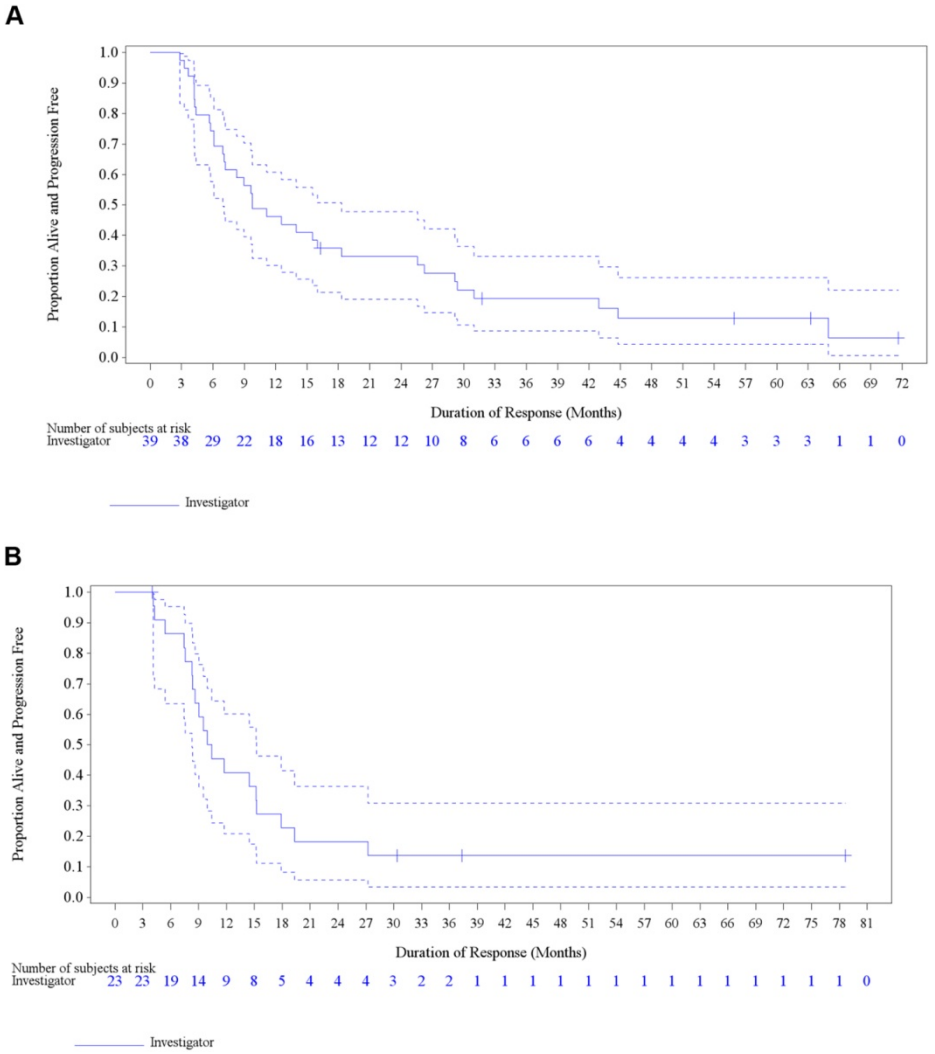


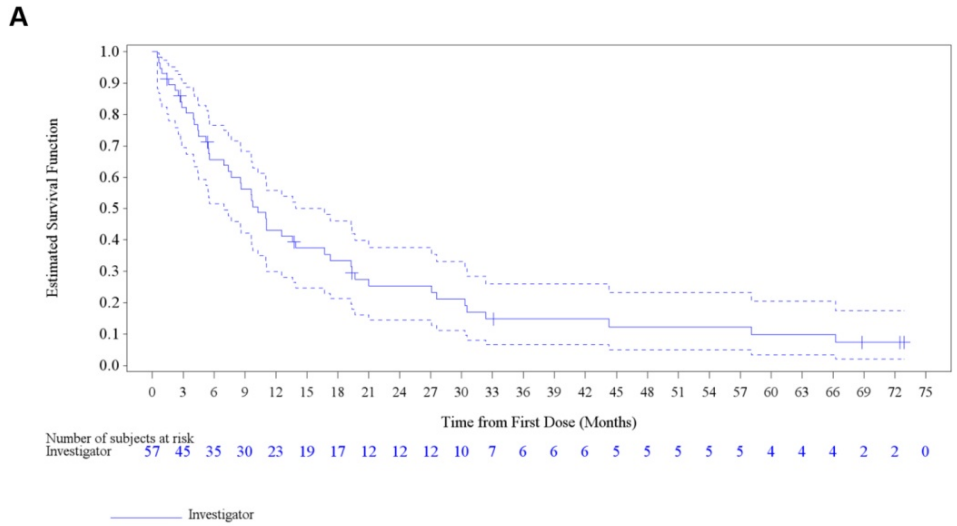
Table 2. Summary of Investigator-Assessed Best Response (RECIST Version 1.1 Criteria)

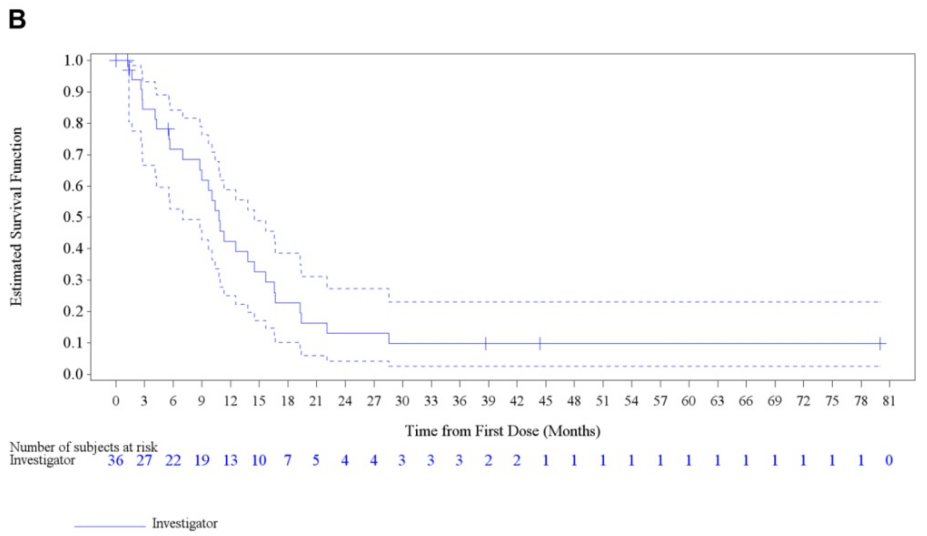
	Pretreated (Cohort B), n = 57	Treatment Naive (Cohort C), n = 36
Best response, n (%)		
CR	3 (5)	2 (6)
PR	36 (63)	21 (58)
Stable disease	7 (12)	4 (11)
PD	7 (12)	5 (14)
NE	4 (7)	4 (11)
Response rate		
CR + PR, n (%)	39 (68.4)	23 (63.9)
95% CI, %	(54.8-80.1)	(46.2-79.2)
Disease control rate		
CR + PR + stable disease, n (%)	46 (80.7)	27 (75.0)
95% CI, %	(68.1-90.0)	(57.8-87.9)

Duration Of Response



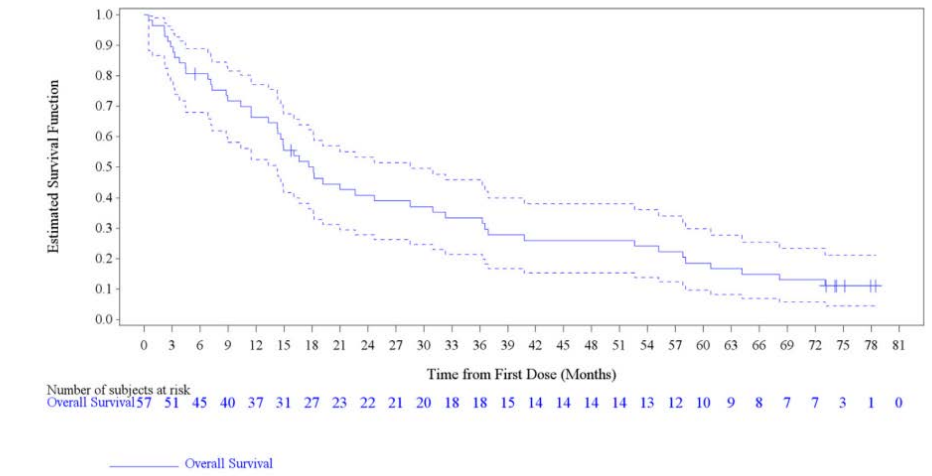
Progression Free Survival





Overall Survival

C



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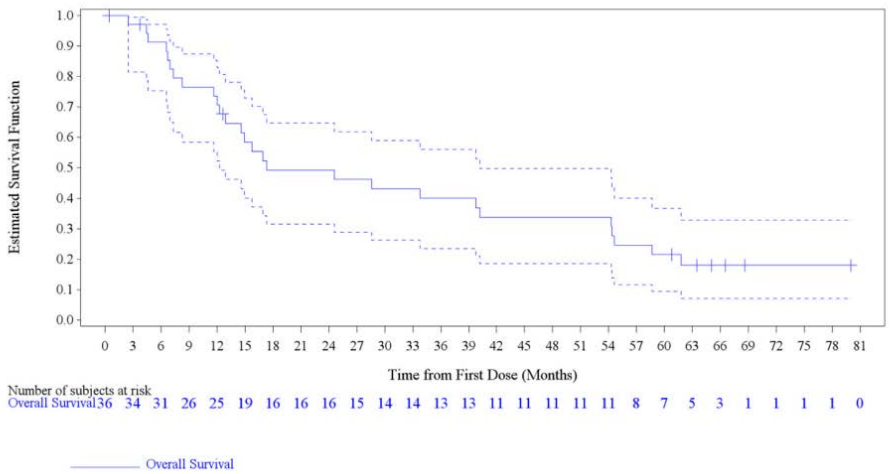

- The 4- and 5-year survival rates were 26% and 19% in pretreated patients and 34% and 22% in treatment-naive patients, respectively. A total of 17 patients (18%) were still alive.

- The most frequent adverse events: pyrexia (56%), nausea (51%), vomiting (41%), dry skin (39%), peripheral edema (38%), diarrhea (37%), decreased appetite (33%)

Retrospective Genomic Analysis

- Revealed the presence of concomitant alterations in addition to the BRAF V600E mutation in 22% of the patients.

- Despite the relatively small number of tumors analyzed and moderate number of genes evaluated, patients with the BRAF V600E mutation and concomitant mutations in the PI3K pathway had a trend toward a decreased OS.

- However, these results require further investigation.

Table 3. Genomic Alterations Detected by NGS in Archival Biopsies From Patients With Metastatic NSCLC Treated With Dabrafenib and Trametinib and Association With Clinical Outcomes

Cohort	Genetic Alterations	Cohort	Best Response	PFS, mo	OS, mo
Dabrafenib plus trametinib (cohort B; ORR, 68.4%; mPFS, 10.2 mo; mOS, 18.2 mo)	*BRAF* V600E+*IDH1*R132C	B	CR	6.9	40.7
	BRAF V600E+*KRAS*G13C	B	PR	58.1	58.1
	BRAF V600E+*IDH1*R132L[a,b]	B	PR	32.4	32.4
	BRAF V600E+*PIK3CA*E542K[c]	B	PR	16.7	55.2
	BRAF V600E+*cMET*ex14 skipping	B	PR	10.2	18.2
	BRAF V600E+*PIK3CA*E545K[c]	B	NE	1.4	3.8
	BRAF V600E+*PIK3CA*E545K[c]	B	PD	1.4	3.1
	*cMET*T1010I[d]	B	PR	27.6	59.4
	*JAK3*S493C[d]	B	PR	5.6	10.3
	*KRAS*G12V[d]	B	PD	2.9	4.4
Dabrafenib plus trametinib (cohort C; ORR, 63.9%; mPFS, 10.8 mo; mOS, 17.3 mo)	*BRAF* V600E+*mTOR*T1977K[c]	C	PR	7.0	7.0
	BRAF V600E+*IDH1*R132C	C	PR	10.4	17.3
	BRAF V600E+*IDH1*R132L	C	PR	5.5	8.2
	BRAF V600E+*BRAF*G466V	C	Stable disease	19.4	40.2
	ALK fusion[d,e]	C	Stable disease	13.8	40.9[f]
	*JAK3*S493C[d]	C	PR	19.3	51.2[f]

Conclusion

- Dabrafenib plus trametinib therapy was found to have substantial and durable clinical benefit, with a manageable safety profile, in patients with BRAF V600E-mutant mNSCLC, regardless of previous treatment

Thank You ☺