ISSN: 2574-1241
DOI: 10.26717/BJSTR.2018.12.002205
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Mini Review | Open Access

The Clinical Efficacy of Dabrafenib Plus Trametinib Combination Treatment in Stage III/IV BRAF-Mutated Melanoma

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Received: December 04, 2018; **Published:** December 13, 2018

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Abstract

The morbidity of cutaneous melanoma has continued to increase in recent years. Patients with stage III disease are at higher risk for recurrence after locoregional resection and many will ultimately die from metastatic melanoma. BRAF inhibitors vemurafenib and dabrafenib have significantly improved progression-free survival (PFS) and overall survival (OS) as single agents compared with cytotoxic chemotherapy. Acquired resistance to BRAF inhibitors inevitably develops, resulting in a median progression-free survival of 6 to 8 months. Several clinical trials with combination treatment of dabrafenib(150 mg twice daily) plus trametinib(2 mg once daily) in stage III/IV BRAF-mutated melanoma have been reported. These clinical trials identify combination treatment of dabrafenib plus trametinib as front-line therapy in stage III/IV BRAF-mutated melanoma.

Keywords: Dabrafenib; Trametinib; Braf; Mek; Mutant; Melanoma

Mini Review

The morbidity of cutaneous melanoma has continued to increase in recent years [1]. Patients with stage III disease are at higher risk for recurrence after locoregional resection and many will ultimately die from metastatic melanoma [2]. Oncogenic driver mutations in BRAF are found in approximately 40% to 50% of cutaneous melanomas and induce constitutive activation of the MAPK signaling pathway, driving melanoma growth and progression [3]. BRAF inhibitors vemurafenib and dabrafenib have significantly improved progression-free survival (PFS) and overall survival (OS) as single agents compared with cytotoxic chemotherapy [4,5]. Despite these advances, acquired resistance to BRAF inhibitors inevitably develops, resulting in a median progression-free survival of 6 to 8 months [6].

Mechanisms of acquired resistance include secondary NRAS or MEK mutations [7]. In preclinical models, combined BRAF and MEK inhibition achieves more via abrogation of MAPK signaling, thereby forestalling the development of acquired resistance and suppressing paradoxic activation of the MAPK pathway [8-14]. Several clinical trials with combination treatment of dabrafenib(150mg twice daily) plus trametinib(2mg once daily) in stage III/IV BRAF-mutated melanoma have been reported. Here, we review the clinical efficacy of these clinical trials. (Inclusion criteria for these studies included age ≥16 years, histologically confirmed BRAFV600E- or BRAFV600K-mutant melanoma, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2.)

Table 1: The Fundamental Parameters and Efficacy of Clinical Trials.

Clinical Trial Information	Phase	Stage	Patients Status	ECOG PS	Prior BRAFi	ORR(%)	Efficacy
NCT01072175 [9]	phase I/II trial	IIIc,IV	PD	0 to 1	Yes	CohortB:15; CohortC:13	yes
NCT01619774 [10]	Phase 2 trial	IIIc,IV	refractory	0 to 2	yes	10	yes
NCT02039947 [11]	phase 2 trial	III,IV	brain metastases	0, 1, or 2	no	intracranial response:44-59	yes

NCT02296996 [12]	phase 2 trial	IIIc,IV	PD	0, 1, or 2	yes	32	Yes(Re-challenge)
NCT01597908 [13]	phase 3 trial	IIIc,IV	untreated patients	0 or 1	no	64	yes
NCT01682083 [14]	phase 3 trial	III	Complete resected	0 or 1	no	3-year OS rate:86	yes

Result

Table 1 the fundamental parameters and efficacy of clinical trials.

Conclusion

These clinical trials identify combination treatment of dabrafenib(150mg twice daily) plus trametinib(2 mg once daily) as front-line therapy in stage III//IV BRAF-mutated melanoma.

References

1. (2017) National Comprehensive Cancer Network. Clinical practice guidelines in oncology melanoma. V1.
2. Siege RL, Miller KD, Jemal A (2017) Cancer statistics. CA Cancer J Clin 67(1): 7-30.
3. Long GV, Menzies AM, Nagrial AM, Haydu LE, Hamilton AL, et al. (2011) Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol 29(10): 1239-1246.
4. Chapman PB, Hauschild A, Robert C, John B Haanen, Paolo Ascierto, et al. (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364(26): 2507-2516.
5. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, et al. (2012) Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 380(9839): 358-365.
6. Solit DB, Rosen N (2011) Resistance to BRAF inhibition in melanomas. N Engl J Med 364(8): 772-774.
7. Nazarian R, Shi H, Wang Q, Kong X, Koya RC, et al. (2010) Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature 468(7326): 973-977.
8. Shi H, Moriceau G, Kong X, Lee MK, Lee H, et al. (2012) Melanoma whole-exome sequencing identifies (V600E)B-RAF amplification-mediated acquired B-RAF inhibitor resistance. Nat Commun 3: 724.
9. Johnson DB, Flaherty KT, Weber JS, Jeffrey R Infante, Kevin B Kim, et al. (2014) Combined BRAF (Dabrafenib) and MEK Inhibition (Trametinib) in Patients with $BRAF^{V600}$-Mutant Melanoma Experiencing Progression with Single-Agent BRAF Inhibitor. J Clin Oncol 32(33): 3697-3704.
10. Chen G, Mc Quade JL, Panka DJ, Hudgens CW, Amin Mansour A, et al. (2016) Clinical, Molecular, and Immune Analysis of Dabrafenib-Trametinib Combination Treatment for BRAF Inhibitor–Refractory Metastatic Melanoma A Phase 2 Clinical Trial [J]. JAMA Oncol 2(8): 1056-1064.
11. Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, et al. (2017) Dabrafenib plus trametinib in patients with $BRAF^{V600}$-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol 18(7): 863-873.
12. Schreuer M, Jansen Y, Planken S, Chevolet I, Seremet T, et al. (2017) Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced $BRAF^{V600}$-mutant melanoma: an open-label, single arm, dual-centre, phase 2 clinical trial. Lancet Oncol 8(4): 464-472.
13. Robert C, Karaszewska B, Schachter J, Piotr Rutkowski, Andrzej Mackiewicz, et al. (2015) Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. N Engl J Med 372(1): 30-39.
14. Long GV, Hauschild A, Santinami M, Victoria Atkinson, Mario Mandalà, et al. (2017) Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med 377(19): 1813-1823.

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