Mini Review

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.

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 paradoxical activation of the MAPK pathway [8-14]. 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. 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.)

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

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

<table>
<thead>
<tr>
<th>Clinical Trial Information</th>
<th>Phase</th>
<th>Stage</th>
<th>Patients Status</th>
<th>ECOG PS</th>
<th>Prior BRAFi</th>
<th>ORR(%)</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td>NCT01072175 [9]</td>
<td>Phase I/II trial</td>
<td>IIIc, IV</td>
<td>PD</td>
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</tbody>
</table>
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