CDRB436BTR01 Study Results Abstract for Public Disclosure

Title

A real-life study to evaluate the use of adjuvant treatment with Dabrafenib and Trametinib in routine practice in patients with completely resected high-risk stage III melanoma

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NIS Type

NIS with Primary Data Collection

Keywords

Dabrafenib, Trametinib, melanoma, adjuvant, recurrence free survival

Rationale and background

Melanoma is one of the most aggressive type of skin cancer and is associated with high mortality rates (Siegel, Miller and Jemal, 2018). The survival of melanoma is mainly related with disease stage at diagnosis with 5-year survival rates varying from 92% for all melanoma patients to 10 % for stage IV patients (Balch *et al.*, 2009). Disease prognosis is also associated with several different gene mutations such as BRAF mutation (Thomas *et al.*, 2015).

Dabrafenib + trametinib was recently approved for adjuvant treatment of patients with early stage melanoma (stage III) with BRAF V600E mutation after complete surgical resection in Turkey (*Tafinlar | Avrupa İlaç Ajansı (EMA)*, 2018). COMBI-AD phase III pivotal study demonstrated that adjuvant dabrafenib plus trametinib therapy significantly reduced the risk of melanoma recurrence in patients with high-risk, stage III BRAF V600–mutant melanoma, with improvements in OS, DMFS, and FFR, and a manageable toxicity profile (Long *et al.*, 2017). Based on these promising clinical trial results, adjuvant treatment with dabrafenib and trametinib was recently recommended by ESMO and NCCN guidelines to use in fully resected high-risk stage III BRAF-mutated melanoma patients, considering it in the same time as one of the standards of care for this group of patients (Coit *et al.*, 2019; Michielin *et al.*, 2019).

This study aimed to evaluate the use of adjuvant dabrafenib and trametinib combination therapy in routine practice in completely resected stage 3 melanoma in patients in Türkiye. As only BRAF V600E mutation was approved to be treated with adjuvant dabrafenib and trametinib combination in Türkiye, the patient population targetted only this group of patients.

In COMBI-AD study, treatment discontinuation rate was 26% and the relapse rate during the treatment period was 12% (Long *et al.*, 2017). However, 7% of these relapses occured after treatment cessation. The nature of randomized controlled clinical study and strict protocol criteria might have influenced these outcomes and a real life study may help confirmation such hypothesis. Additionally, the duration of adjuvant dabrafenib and trametinib treatment is limited to 1 year. It is usually though that treatment compliance rate may be differ in real life. For that reason, in order to get sufficient benefit from the treatment, patients' compliance to treatment during this 1 year is very crucial. Compliance to adjuvant dabrafenib and trametinib treatment may influence the benefit of this combination and eventually may have an impact on relapse-free-survival (RFS) rate 12 months during routine clinical practice. Therefore, rather than the time period after completion of the treatment, our study primarily focused on active treatment period and so that RFS rate at 12 months was selected as primary endpoint.

Research question and objectives

Research question: What is the 12 month recurrence-free survival rate in patients with BRAF-mutant melanoma treated with dabrafenib plus trametinib in routine clinical practice in Türkiye?

Primary objective was to assess the proportion of patients with stage III completely resected BRAF V600E-mutant melanoma who remain recurrence-free at 12 months following initiation of dabrafenib plus trametinib in real-world clinical settings in Türkiye.Secondary objective was to assess the safety and tolerability of dabrafenib and trametinib during adjuvant melanoma treatment.

Study design

This was a 12-month, non-interventional, prospective, observational cohort study conducted in a real-world setting in Türkiye. The study included adult patients receiving adjuvant dabrafenib plus trametinib following complete resection of high-risk stage III BRAF V600E-mutant melanoma. Primary and secondary data were collected prospectively during routine clinical practice.

Setting

The study was conducted between 01 December 2021 and 05 December 2024 across 9 Medical Oncology clinics in Türkiye, all recognized as national centers of excellence for melanoma management. Patient recruitment occurred in the routine clinical setting. Treatment decisions were made independently by oncologists prior to enrolment, in accordance with local regulations for non-interventional studies. RFS was assessed at 12 months from treatment initiation.

Subjects and study size, including dropouts

Eligible patients were adults (≥18 years) with completely resected stage III BRAF V600E-positive melanoma for whom a decision to initiate adjuvant dabrafenib plus trametinib had been made. Key exclusion criteria included missing baseline data, pregnancy or breastfeeding, concurrent primary malignancy requiring treatment, or participation in an interventional melanoma trial. It was planned to include up to 12 centers and to anroll a minimum of 84 patients during the 12 months of recruitment period. However, a total of 9 centers actively participated in the study, and 39 patients were included in the full analysis set (FAS).

Variables and data sources

Demographic, clinical, and pathological characteristics; treatment data; relapse-free survival; and adverse events were collected. Variables included age, sex, ECOG performance status, AJCC stage, primary tumor and histopathologic features, lymph node involvement, Breslow depth, ulceration, comorbidities, treatment regimen, dose modifications, relapse type, and time to relapse.

Data were obtained from hospital medical records and real-life clinical documentation. All patients provided written informed consent, and data were anonymized.

Statistical methods

All analyses were conducted on the FAS, including patients with informed consent and at least one visit with available data. Statistical analyses were performed using IBM SPSS Statistics 24.0. Continuous variables were summarized using descriptive statistics, and categorical variables as frequencies and percentages. No imputation was applied, and analyses were based solely on observed data.

RFS was analyzed using the Kaplan–Meier method, with 12-month estimates and 95% confidence intervals derived from survival analysis outputs. Relapse events, censored observations, and time-to-relapse distributions were summarized descriptively. Adverse events were coded using MedDRA v28.1.

Results

A total of 39 patients were enrolled in the study, of whom 29 (74.4%) completed the 12-month follow-up and 10 (25.6%) discontinued early. The 12-month RFS rate was 79.0% (95% CI: 65.0–93.0), with 8 patients (20.5%) experiencing an RFS event (relapse or death). Among the 5 relapsed patients, the median time to relapse was 5.97 months.The median treatment duration was 381 days among patients who completed the study and 91 days among those who discontinued early. Dose reductions or temporary interruptions occurred in 7 patients, primarily due to adverse events (AEs). Overall, 35 AEs were reported in 19 patients, including 15 serious adverse events. The most common treatment-related

AEs were pyrexia, rash, and pneumonitis. No new or unexpected safety signals were identified during the study.

Discussion

The 12-month relapse-free survival observed in this real-world cohort was consistent with the expected effectiveness of adjuvant dabrafenib plus trametinib in patients with resected, high-risk stage III BRAF V600–mutant melanoma. Safety findings reflected the known profile of the combination, with no new or unexpected toxicities identified, and most adverse events managed with standard clinical measures. Although interpretation is limited by the observational design and sample size, the results align with evidence from randomized clinical trials and other real-world experiences, supporting the established benefit–risk profile of dabrafenib plus trametinib in routine clinical practice.

Conclusion

In this real-world, non-interventional study conducted in Türkiye, adjuvant dabrafenib plus trametinib demonstrated a 12-month relapse-free survival outcome consistent with expectations for patients with completely resected, high-risk stage III BRAF V600–mutant melanoma. The treatment was generally well tolerated, and no new safety signals were identified. Adverse events were manageable with standard clinical interventions, including dose adjustments and temporary treatment interruptions. Overall, the findings support the established benefit–risk profile of dabrafenib plus trametinib in routine clinical practice, while acknowledging that conclusions are limited by the observational design and sample size.

1 List of abbreviations

Abbreviation	Full Term
OS	Overall Survival
DMFS	Distant Metastasis–Free Survival
FFR	Freedom From Recurrence
ESMO	European Society for Medical Oncology
NCCN	National Comprehensive Cancer Network
RFS	Relapse-Free Survival
FAS	Full Analysis Set
ECOG	Eastern Cooperative Oncology Group Performance Status
AJCC	American Joint Committee on Cancer
AE	Adverse Event
BRAF	B-Raf Serine-Threonine Kinase
EMA	European Medicines Agency
MedDRA	Medical Dictionary for Regulatory Activities