Real World PFS Outcomes of Bulgarian Patients With BRAF-Positive Melanoma Treated With Dabrafenib and Trametinib

RWD121

B. Ivanova[1], A. Savova[2], L. Bakalivanov[1], B. Zidarova[1], D. Apostolova[1], M. Vasileva[1], S. Terezova[1], M. Manova[2]

1. National Council on Prices and Reimbursement of Medicinal Products, Sofia, Bulgaria 2. Medical University of Sofia, Faculty of Pharmacy, Bulgaria

INTRODUCTION

Skin cancers are the most common form of cancer. More than 1.5 million new diagnoses were recorded in 2020. Melanoma accounts for approximately 1 in 5 of these cases. Approximately half of cutaneous melanomas show mutations in BRAF. Over the past several decades, the treatment of melanoma patients has significantly improved following the developments of immune checkpoint blockers (targeting PD-1 and CTLA-4) and MAPK molecular therapy targeted at BRAF and MEK signaling pathways. Both approaches have been proved effective in the treatment of advanced melanoma.

The combination of dabrafenib and trametinib was the first BRAF-MEK combination approved for metastatic melanoma. Together, dabrafenib and trametinib targets the RAS/RAF/MEK/ERK pathway that is prevalently hyperactivated in cancers. The combination dabrafenib and trametinib is indicated for: the treatment of patients with unresectable (or metastatic) melanoma with BRAF V600E or V600K mutations; adjuvant treatment for patients with BRAF V600E or V600K mutations.

OBJECTIVE

The aim of this research is to analyze the real world data (RWD) outcomes with respect to PFS and to compare those with the outcomes measured in RCTs, COMBI-v and COMBI-d.

The population is Bulgarian patients with BRAF-positive melanoma treated with dabrafenib and trametinib in real therapeutic practice.

METHODS

- Based on secondary usage of anonymized data.
- A retrospective analysis of electronic health records (EHRs) from hospitals in Bulgaria was conducted.
- IT Platform, which integrates large amounts of data using embedded Machine Learning and NLP algorithms, was used for data analysis.
- Iterative proportional fitting (IPF) was applied to the RWD to be weight-adjusted in to match the distributions of the RCTs.
- The survival functions of PFS were estimated using Kaplan-Meier estimator. The confidence interval was calculated using Greenwood's method.
- Ethics committee approval or patient informed consent were not required for this type of research as per Bulgarian national regulations.

RESULTS

The total patients in RWD dataset is 335. About 57% (190/335) of the total patients examined are taking the combination as 1st line - previously untreated in the advanced or metastatic setting. These patients are closest in terms of inclusion/exclusion criteria to the RCTs (COMBI-d and COMBI-v) and are included in treatment group.

The COMBI-d cohort includes 211 patients and the COMBI-v cohort includes of 352 patients. The RWD cohort consists of 190 patients who correspond to the patient characteristics of the RCTs.

In the case of COMBI-d estimates are based on a similar number of events - 95 events for RWD and 103 events for the RCT. The median PFS based on RWD is 16.1 (95% CI: NC-NC) months in comparison to 9.3 months from RCT.

The median PFS for RWD is higher than for COMBI-v at 17.0 (95% CI: NC-NC) months vs 11.4 months.

After the 24th month in both comparisons, confidence intervals of the curve for RWD are rather large due to the small number of patients at risk.

	COMBI-d				COMBI-v			
	RWD		Clinical Trial		RWD		Clinical Trial	
PFS	Patients at risk	N = 190	Patients at risk	N = 211	Patients at risk	N = 190	Patients at risk	N = 352
# events		95 (50.0%)		103 (48.8%)		95 (50.0%)		- -
Median		16.1 months (NC-NC)		9.3 months		17 months (NC-NC)		11.4 months
4 months	134	91% (86 - 95)	164	~ 81%	168	91% (86 - 95)	270	~ 83%
6 months	108	85% (78 - 90)	138	~ 68%	108	85% (79 - 90)	228	~ 71%
8 months	82	68% (60 - 75)	82	~ 58%	82	70% (62 – 77)	194	~ 63%
12 months	58	58% (50 - 66)	9	~ 34%	58	60% (81 - 68)	83	~ 48%
24 months	18	38% (29 - 46)	- -	- -	18	38% (29 - 47)	- -	- -

The weight-adjusted hazard ratio of PFS in the RWD cohort receiving dabrafenib + trametinib was 0.46 (95% CI: 0.29 – 0.74). In COMBI-d, the hazard ratio for dabrafenib + trametinib versus the control group was 0.75. In the RWD group, all subgroups across age, gender and ECOG show more-favorable results in comparison to the RCT.

The weight-adjusted hazard ratio of PFS in the RWD cohort receiving dabrafenib + trametinib was 0.56 (95% CI: 0.35 – 0.89). In COMBI-v, the hazard ratio for dabrafenib + trametinib versus the control group was also 0.56. By the subgroups analysed, more favorable results for the RWD group are estimated for patients below 65 years of age, males, and ECOG 1.

CONCLUSIONS

The research demonstrates that Bulgarian patients with BRAF-positive melanoma treated with dabrafenib and trametinib reach equivalent and even more favourable PFS outcomes compared to RCTs COMBI-d and COMBI-v. The analysis with respect to PFS shows that the results in the real-life therapeutic practice are consistent with those in the clinical trials. In addition, the reported results of the Bulgarian patients are close to the results reported in some reviewed retrospective analyses from real practice. Further analysis on other relative outcomes will be performed.

REFERENCES

Arnold M., Singh D., Laversanne M., Vignat J., Vaccarella S., Meheus F. et al. (2022). Global Burden of Cutaneous Melanoma in 2020 and Projections to 2040, JAMA Dermatol, 158 (5), pp 495-503.

Cancer Genome Atlas Network (2015). Genomic Classification of Cutaneous Melanoma, Cell, 161(7), pp 1681-96.

Jenkins R.W., Fisher D.E., (2021). Treatment of Advanced Melanoma in 2020 and Beyond, Journal of Investigative Dermatology, 141(1), pp 23-31.

European Medicines Agency (2023a). Tafinlar, Amsterdam; European Medicines Agency (2023b). Mekinist, Amsterdam.

El-Khorazaty J.A., Koch G., Preisser J. (2014). The iterative proportional fitting algorithm for adjusted agreement in a non-inferiority diagnostic clinical trial, Pharm Stat, 13(3), pp 173-178.

CONTACT INFORMATION

National Council on Prices and Reimbursement of Medicinal Products

office@ncpr.bg