RAF-kinase pathway inhibitors in the treatment of metastatic melanoma: when compliance doesn't match with tolerance

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Background and Importance

Malignant melanoma (MM) occurs tipically from melanocytes responsible for pigmentation, which are located in the skin, mucosa, central nervous system or uveal tract of the eye. Worldwide, cutaneous MM comprises 1.7% cases of all newly diagnosed primary malignant cancers. [1]

Almost 45-50% of cases of MM are characterised by mutations in BRAF gene: the most common is V600E.[2] Therefore pathway RAS/RAF/MEK/ERK is overactivated, causing continuous and uncontrolled cell proliferation.

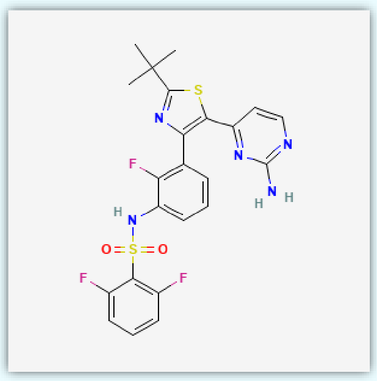
In these cases targeted-therapies with thyrosine-kinases inhibitors (TKI) are the best choice beacause of their specificity.

Aim and Objectives

The analysis considered the two most prescribed oral therapies for unresectable or metastatic MM with a BRAF V600 mutation in Candiolo Cancer Institute FPO IRCCS, Piemonte, Italy:

- **dabrafenib + trametinib**
- **encorafenib + binimetinib**

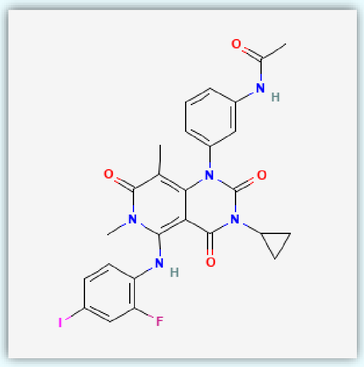
The aim of this study is to compare the two combination therapies, describing their use and patient tolerability using real life data.



dabrafenib
BRAF-inhibitor

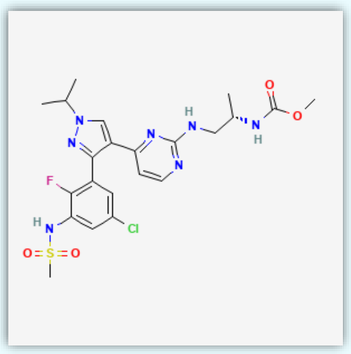
+

trametinib
MEK-inhibitor



	Capsules or tablets/die	mg/die
dabrafenib 75mg capsules	4	300
trametinib 2mg film-coated tablets	1	2

encorafenib
BRAF-inhibitor



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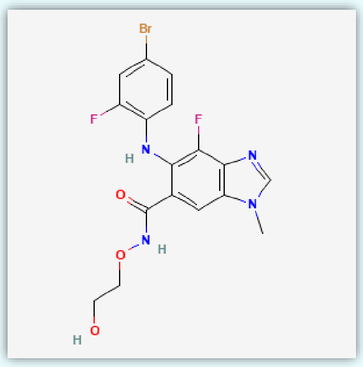


binimetinib
MEK-inhibitor

	Capsules or tablets/die	mg/die
encorafenib 75mg capsules	6	450
binimetinib 15mg film-coated tablets	6	90

Materials and methods

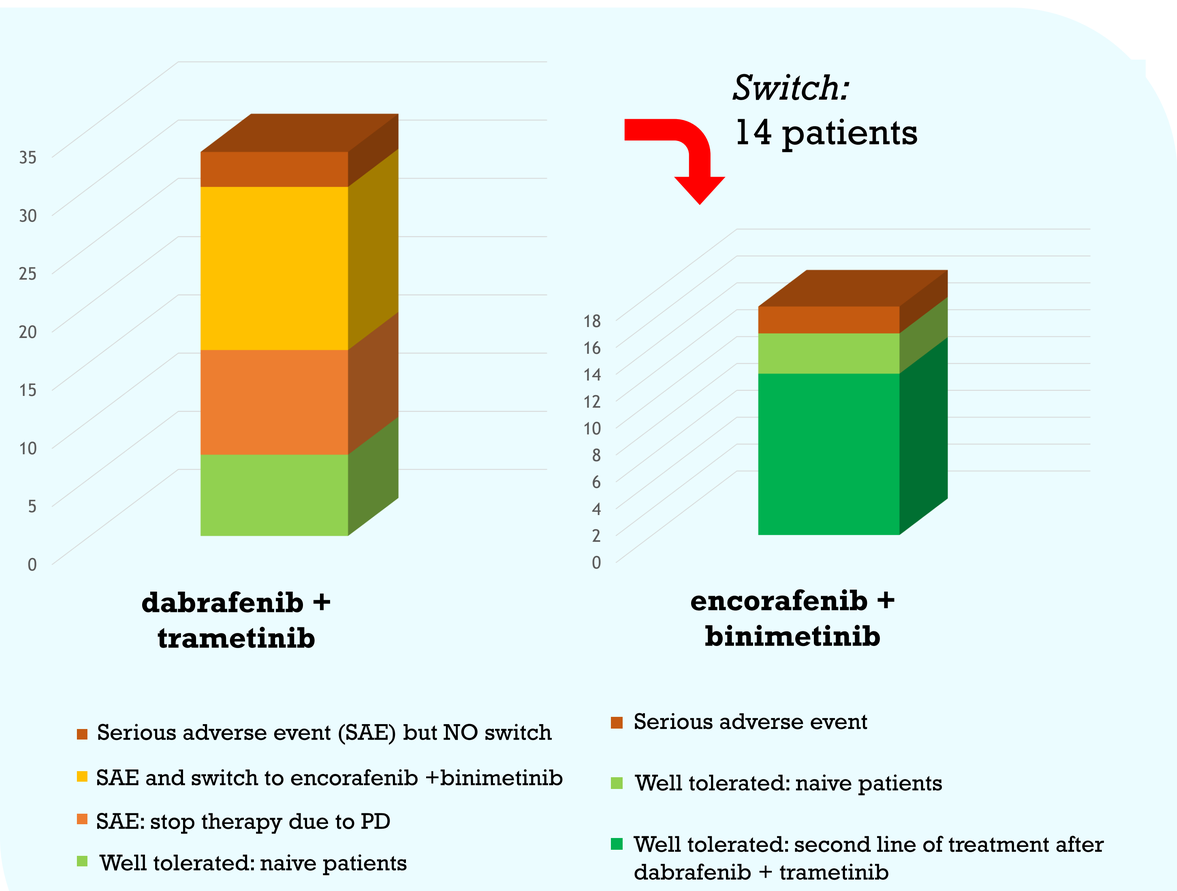
Data were collected from Candiolo Cancer Institute FPO IRCCS prescribing software and from medical records of patients from January 2019 to May 2022.

Results

36 patients were considered for the analysis.
Dabrafenib + trametinib were prescribed firstly to 33 patients.
Only 7 of them (21 %) had no serious adverse events. The adverse events of the remaining 26 patients (79%) were different:

- pyrexia (40%)
- cutaneous disorders (25%)
- gastrointestinal disorders (12,5%)
- fatigue (8%).

9 patients (27%) were forced to stop therapy because of **progressive disease (PD).**
14 patients (42%) facing serious adverse events and/or progressive disease switched to encorafenib + binimetinib therapy. Only 2 of them underwent serious adverse events (fatigue G1-G3, nausea G2) and stopped the new treatment.
Encorafenib + binimetinib were prescribed firstly to 3 patients and they did not experience serious adverse events.
In conclusion, **88% of patients receiving encorafenib + binimetinib did not undergo serious adverse events**.



Conclusion and Relevance

Data collected from January 2019 to May 2022 show that the most prescribed therapy was dabrafenib + trametinib (approved by EMA almost four years earlier than encorafenib + binimetinib). This therapy is characterised by better patient compliance because of the simpler posology; however serious adverse events were more frequent than in the other therapy described.
On the other hand encorafenib + binimetinib combination therapy is the best tolerated treatment, despite a complex therapeutic scheme with possible issues of patient compliance. Therefore encorafenib + binimetinib may provide continuity of care and better clinical outcome.
Moreover for the Regional Health System the therapy with encorafenib + binimetinib is more cost saving, because its cost is 13% lower than the other combination therapy considered in this study.[3]

1: Melanoma & Other Skin Cancers: Essentials for Clinicians, ESMO, 2021
2: Raccomandazioni 2019 per l'implementazione dell'analisi mutazionale e la gestione del paziente con melanoma maligno, Associazione Italiana di Oncologia Medica
3: SCR Piemonte, gara 095-2021, III As
4: Structural formulas: pubchem.ncbi.nlm.nih.gov

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