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Effectiveness of dabrafenib plus trametinib in melanoma stage III adjuvant setting: results from the first interim analysis of the observational Italian study MADAM

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Background

Adjuvant therapy has shown improvement in the outcome of patients (pts) with resected stage III melanoma, reducing the risk of recurrence by elimination of residual disease after surgery. Considerable experience in the use of dabrafenib plus trametinib (D+T) for the treatment of pts with BRAF mutant disease was acquired from clinical trials (COMBI-AD, COMBI Aplus), that demonstrated the efficacy in reducing relapse and in increasing overall survival. Limited data are available on the impact of the D+T in a real-world setting. [1,2]

The Managed Access Program (MAP) was run in Italy from June 2018 to December 2019 to provide D+T as adjuvant treatment to patients with *BRAF* V600 stage III melanoma following complete tumor resection and without alternative treatment options.

Roughly 550 patients were involved in this program.

Study design and methods

This was an Italian **retrospective-prospective observational study**, involving patients treated with at least one dose of D+T within the melanoma adjuvant Managed Access Program (MAP) from June 2018 to December 2019 in Italy (MADAM study). Data were collected for 5 years starting from the time of completion/discontinuation of adjuvant D+T treatment for any reason.

The primary endpoints were:

- **Relapse-free survival** (RFS) defined as the time, in months, from the start of D+T combination to disease relapse or death from any cause
- **Overall survival** (OS) defined as the time, in months, from the start of combination to death from any cause.

Both functions were estimated using the Kaplan-Meier product-limit method.

Results

This was an interim analysis run after 24 months from study initiation at the cut-off date 30th September 2022.

310 patients included in MADAM study

240 patients completed the 12-month treatment with D+T

70 patients discontinued D +T
14 for relapse
33 for drug-related toxicities
5 for unrelated toxicities
18 for other or missed reasons

Table 1. Baseline characteristics

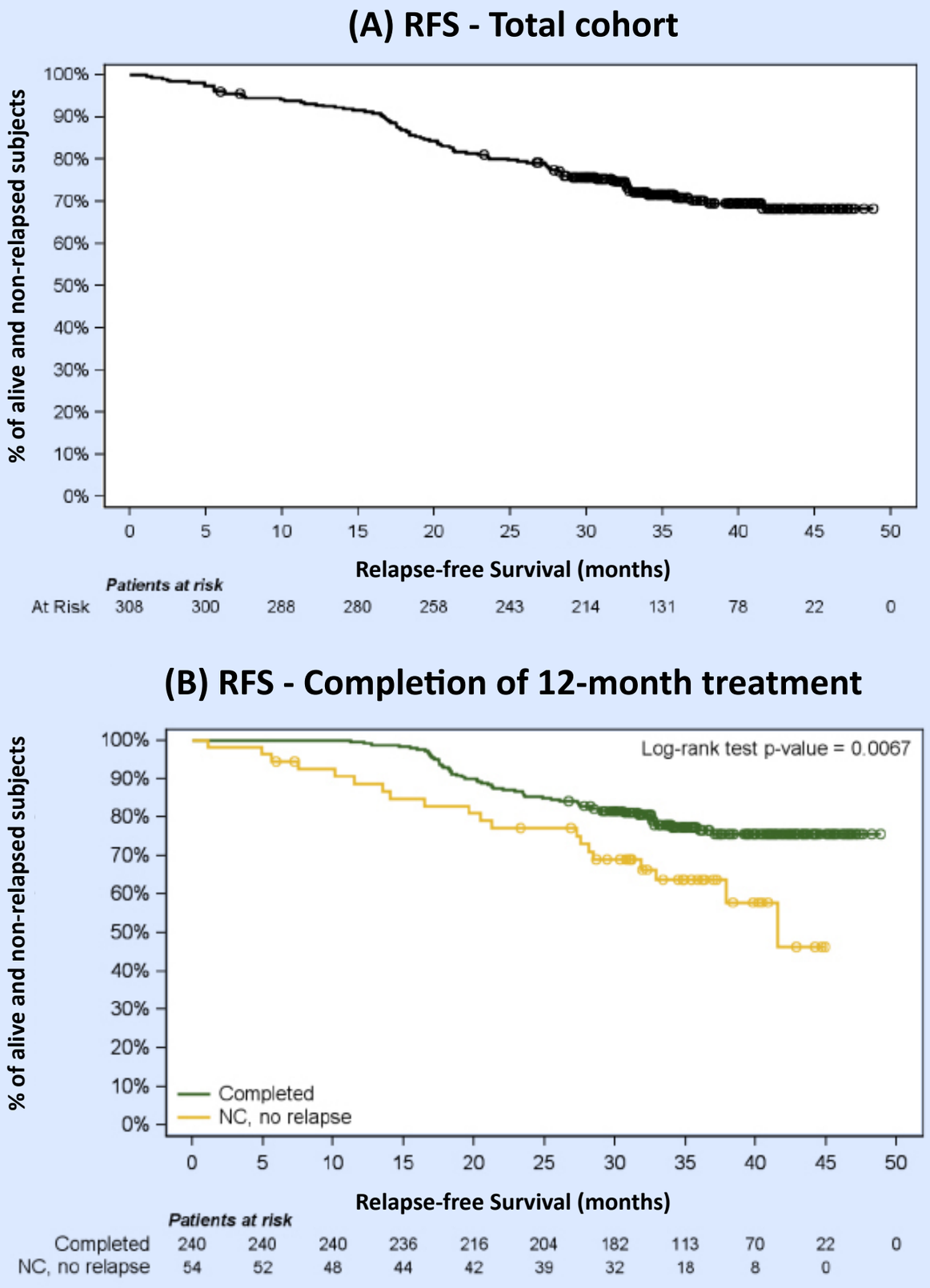
	Cohort (n=310)	Completed (n=240)	Not completed (n=70)
Age (years), mean (SD)	55.1 (13.6)	53.7 (13.3)	60.0 (13.7)
Female, n (%)	128 (41.3)	97 (40.4)	31 (44.3)
Time (months) from diagnosis to D+T initiation, mean (SD)	13.1 (27.4)	14.2 (27.9)	9.3 (25.0)
AJCC 8 Stage*, n (%)			
III	15 (4.8)	13 (5.4)	2 (2.8)
IIIA	75 (24.2)	58 (24.1)	17 (24.3)
IIIB	76 (24.5)	63 (26.2)	13 (18.5)
IIIC	129 (41.6)	98 (40.8)	31 (44.3)
IIID	15 (4.8)	8 (3.3)	7 (10.0)
ECOG PS, n (%)			
0	183 (95.8)	144 (96.0)	39 (95.1)
1	7 (3.7)	5 (3.3)	2 (4.9)
2	1 (0.5)	1 (0.7)	0
Predominant BRAF mutation, n (%)			
V600E	270 (87.10)	-	-
V600K	25 (8.06)		
Other	14 (4.52)		
Missing	1 (0.32)		

***at time of start of combination therapy with D+T**
D+T, dabrafenib + trametinib; SD, standard deviation; AJCC, American Joint Committee on Cancer

- **Median duration of exposure** to D+T was 366 days (range 8-634)

86 patients had at least **one relapse**:
64 patients had at least one systemic relapse
33 had at least one local relapse

Figure 1. Relapse Free Survival (RFS): K-M curve



Dots represent censors. Subjects at risk are patients who have no censored observation and do not experience the event (i.e., the first tumour relapse or death) at the considered timepoint yet. P-value is obtained from stratified two-sided log-rank test. Log-rank test is used instead of Wilcoxon test as specified in the SAP to give equal weight to all time points.

Conclusion

Adjuvant treatment with D+T confers significant relapse free survival benefit also in a real-world heterogeneous patient population, in all patients and greater in patients who completed the treatment. The benefit is sustained after the end of treatment. The results of this interim analysis are consistent with the efficacy of D+T observed in the pivotal phase 3 clinical trials and consolidate the efficacy results in term of RFS in an uncontrolled setting in all stage III subpopulations, including IIIA.

References | 1. Dummer R, et al. N Engl J Med. 2020 Sep 17;383(12):1139-1148; 2. Atkinson V.et al Eur J Cancer. 2022 Mar;163:79-87
Acknowledgement | Authors thank the patients and their family for their participation in the study; Opis s.r.l. for statistical support, Elisa Grassi of Fortrea Inc. for the support in the study management. The authors would also like to thank Vincenza Vinaccia of Novartis Farma SpA for support in the medical review process, and Elisa Sala on behalf of Content Ed Net for providing editorial support. This study and editorial support were funded by Novartis Farma SpA.
Disclosures | IM and DV are employed by Novartis Farma S.p.A; MDV has been advisor and/ or consultant for BMS, MSD, Novartis, PierreFabre, Immunocore; FG reports personal fees for advisory role, speaker engagements and travel and accommodation expenses from Merck Sharp & Dohme, Novocure, Bristol Myers Squibb, Boehringer Ingelheim, Pharmamar, Novartis and Pierre Fabre; FM has been advisor for Novartis, BMS, Sunpharma, Sanofi, Pierre-Fabre, Ipsen e MSD;FS declares to have received fees from BMS, MSD, Novartis,Pierre Fabre, Merck, Sanofi, Sun Pharma and has been advisor for MSD, Novartis, Pierre Fabre, Philogen; PQ received speaker fees and has been advisor for Novartis, BMS, MSD, Pierre Fabre; PQ received speaker fees and has been advisor for Novartis, BMS, MSD, Pierre Fabre;TT has been advisor for Amgen, Novartis, BMS, Roche, Servier Pierrefabre, MSD. No other COIs have been disclosed.
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