Circulating levels of miR-204-5p predict response to BRAF and MEK inhibitors in metastatic melanoma patients

Ciro F. Ruggiero[1], Irene Terrenato[2] Luigi Fattore[2], Valentina Salvati[2], Francesca Sperati [3] Domenico Liguoro[4] , Vittorio Castaldo[4], Gabriele Madonna[5], Mariaelena Capone [5],Diana Giannarelli[2], Paolo A. Ascierto[5], Rita Mancini[4] and Gennaro Ciliberto[2]

[1]Department of Experimental and Clinical Medicine, University "Magna Graecia" of Catanzaro, Catanzaro, Italy. [2]IRCCS, Regina Elena National Cancer Institute, Rome, Italy. [3]San Gallicano Dermatological Institute, IRCSS, Rome Italy. [4]University of Roma "Sapienza", Department of Clinical and Molecular Medicine Rome, Italy. [5]Istituto Nazionale Tumori IRCCS, "Fondazione G. Pascale", Naples, Italy.

P502

Objective

Metastatic melanomas harboring BRAF-V600 mutations are currently treated with combinations of BRAF and MEK inhibitors (MAPKi) increasing the objective responses, disease free survival and overall survival over monotherapy with BRAF inhibitors. Unfortunately, several patients suffer from ab initio or acquired resistance to these agents. Several efforts have been directed in recent years to understand mechanisms of resistance to MAPK inhibitors. These studies have shown a prominent involvement of non-mutational adaptive events, among which also deregulation of miRNAs expression. In this regard our laboratory has identified several miRNAs which undergo either up- or down-regulation during the development of drug resistance (1). In this study we have started to assess whether circulating levels of one or more of these miRNAs can act as an early predictor of response to therapy. In this retrospective study were involved BRAF-mutated patients All patients were treated with MAPKi therapy in first . Results showed that only miR-204-5p emerged to have a role in predicting both OS and PFS.

Results

Sample description

	N (%)
N° cases	51
BRAF variant	
V600E	49 (96%)
V600K	2 (4%)
Gender	
Male	24 (47%)
Female	27 (53%)
Age	
Median (min-max)	45 yrs (28-79)
Stage	
IV	

Fig.1 In the table are reported all features of this retrospective study which involved metastatic patients with a median age of 45 years. Among them, 27 (53%) were females. All patients were treated with MAPKi therapy in first line except one who received the treatment in second line.

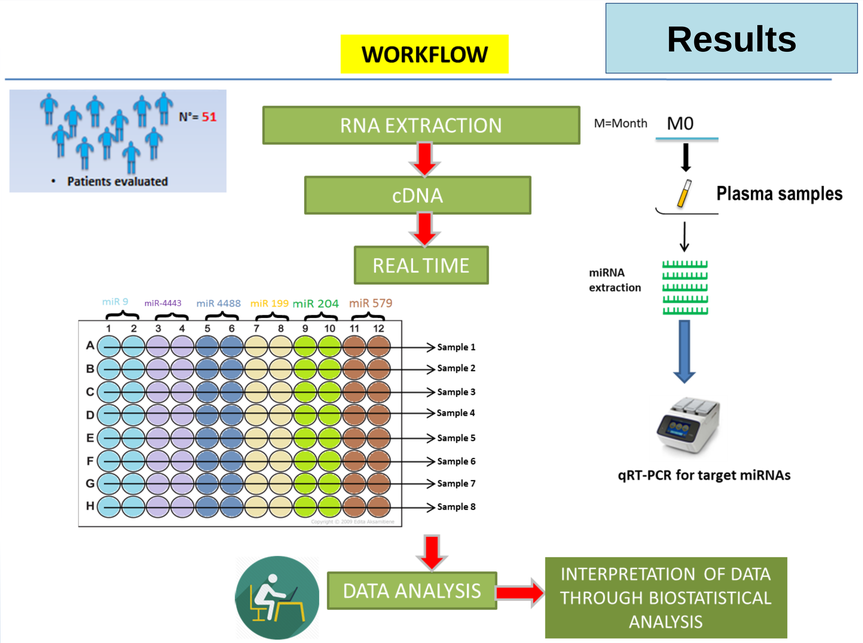


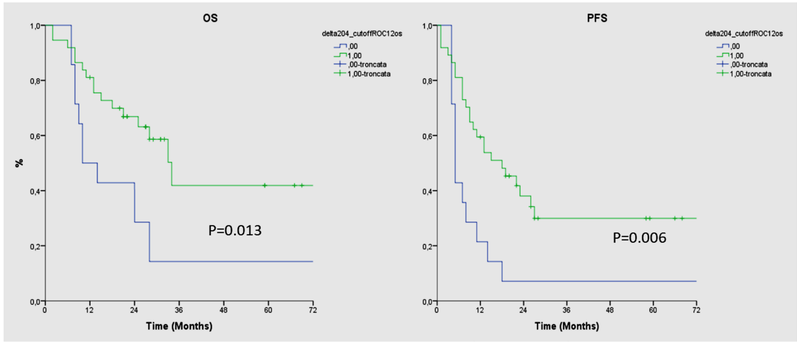
Fig.2 Circulating miRNAs were extracted from the serum of 51 BRAF-mutated melanoma patients before the beginning of therapy through miRNeasy Mini Kit (Qiagen). Real-time PCR for miR-204-5p, miR-199b-5p miR-579-3p, miR-9-5p miR-4443 and miR-4488 was assayed by TaqMan Gene Expression. Data of circulating miRNAs were normalized using Global mean normalization and NormFinder model (2)

Results: ROC ANALYSIS

miRNA	AUC	SE	p-value	Cut-off	Sen	Spec
199	0.515	0.101	0.869	1.6034	0.806	0.400
204	0.581	0.099	0.363	-1.5774	0.806	0.467
579	0.500	0.100	1.000	-1.2357	0.972	0.267
4443	0.570	0.094	0.432	-1-4038	0.472	0.800
4488	0.541	0.086	0.649	-0.6799	0.556	0.600

Results: Survival analysis (Kaplan-Meyer Method)

miRNA204



Median time to death:

DCt 204 under cut-off: 10 months 95%CI=(3.9-16.1)

DCt 204 over cut-off: 34 months 95%CI=(25.7-42.3)

Median time to relapse:

DCt 204 under cut-off: 5 months 95%CI=(4.1-5.9)

DCt 204 over cut-off: 18 months 95%CI=(7.9-28.1)

Fig.3 A) Based on ROC analysis results reported in the table bioinformatic survival analysis (Kaplan-Meyer Method).were performed. B) Kaplan-Meyer curves show that only miR-204-5p emerged to have a role in predicting both OS and PFS. Concerning OS, patients with a ΔCt value under the ROC cut-off show a shorter median time to death in comparison to patients with a ΔCt value over the ROC cut-off (10 months 95% confidence interval (95%CI): (3.9-16.1) vs 34 months 95%CI: (25.7-42.3); p-value=0.013). Concerning PFS analysis, patients with a ΔCt value under the ROC cut-off have a shorter median time to progression in comparison to patients with a ΔCt value over the ROC cut-off (5 months 95%CI: (4.1-5.9) vs 18 months 95%CI: (7.9-28.1); p-value=0.006).

Conclusions

On the basis of these results, miR-204-5p can be a promising predictive biomarker able to discriminate advanced melanoma patients who may benefit of MAPKi treatments. These data warrants of further validation in an extended cohort of patients as well as in prospective following studies

References

1.Fattore L, et al. Cell Death Differ. 2019. doi: 10.1038/s41418-018-0205-5.
2.Fogli S, et al. Tumour Biol. 2017; doi: 10.1177/1010428317701646