Mutational status of superficial spreading and nodular primary melanomas in patients with disease recurrence toward the correlation with clinical, dermoscopic, and histological features: an IMI study (CARAMEL)

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Background

Literature data indicate that more than half of primary cutaneous melanomas (CM) in patients with metastatic disease was superficial spreading (SSM), while the remaining of them had a nodular melanoma (NM) at diagnosis. Moreover, a high proportion of deaths can be attributable to thin melanomas - 1 mm or less - in both the United States (27%) and Australia (23%). Thus, there is a subset of SSM at high risk of metastasis; thin melanomas with worst prognosis seem to be those located on the back and with large regression affecting at least 50% of the lesion. We here investigated the mutational profile in two series of patients with primary SSM or NM who were further stratified for disease progression.

Methods and Materials

Paraffin-embedded tumor tissues of the CM lesions were retrieved from the archives of the institutions participating in the study. NGS was performed using a specific multiple-gene panel constructed by the Italian Melanoma Intergroup (IMI) to explore the mutational status of selected regions (343 amplicons; amplicon range: 125-175 bp; coverage 100%) within the main 25 genes involved in CM pathogenesis (*Fig.1*).

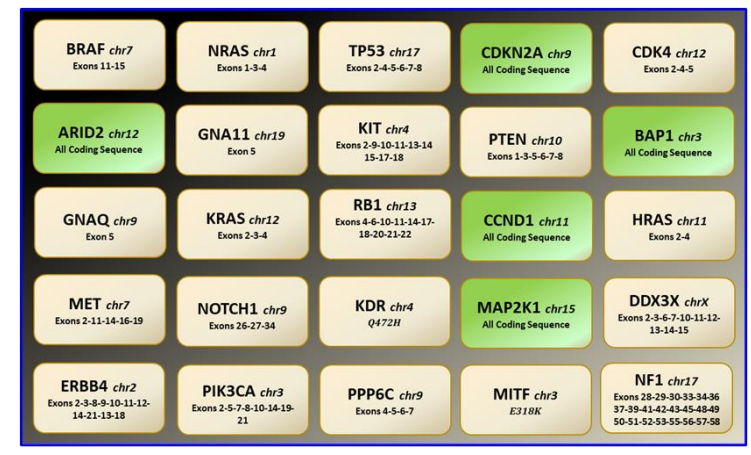


Fig.1 IMI SOMATIC PANEL

Sequencing was performed with the Ion Torrent S5 Studio System (*Fig.2*). For each group of primary SSM and NM, the mutational profile is being compared with dermoscopic and histopathological parameters as well as with clinical outcome within 5 years after the diagnosis.

Fig.2 Run Report

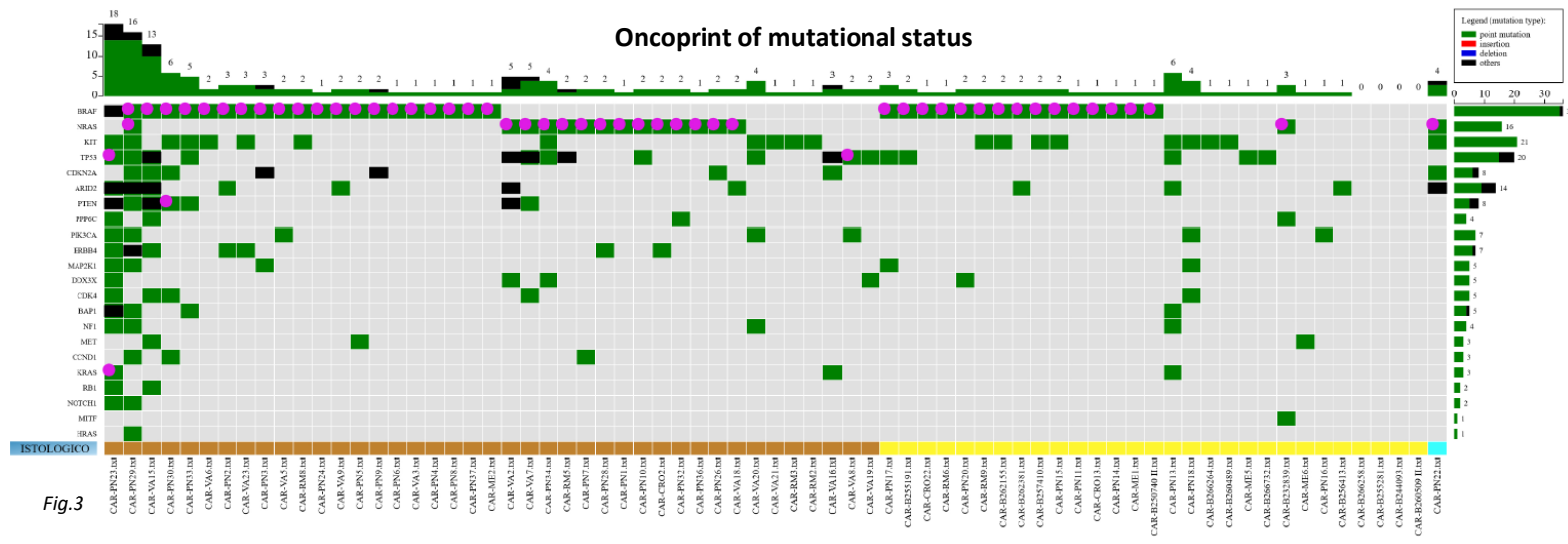


Fig.3

Results

Overall, the median and average rates of pathogenic mutations were 2 and 3,23 for NM samples vs. 1 and 1,42 for SSM samples, respectively (*Fig.3*).

BRAF-V600 mutations were found in 20/42 (47,6%) NM vs. 17/31 (54,8%) SSM; a NRAS mutation was detected in 15/42 (35,7%) NM vs. 1/31 (3,2%) SSM. One cases carried both BRAF-V600E and NRAS-Q61R mutation but with different allele frequencies (6,3% and 18,8%), respectively (*Tab.1a*). The SSM lesions presented a higher frequency of wild-type status in both BRAF and NRAS genes (13/31; 42%) as compared to the NM lesions (8/42; 19%) (*Tab.1b*). Considering the AJCC stage classification, no significant differences were observed in mutation frequency for BRAF or NRAS in NM and SSM samples.

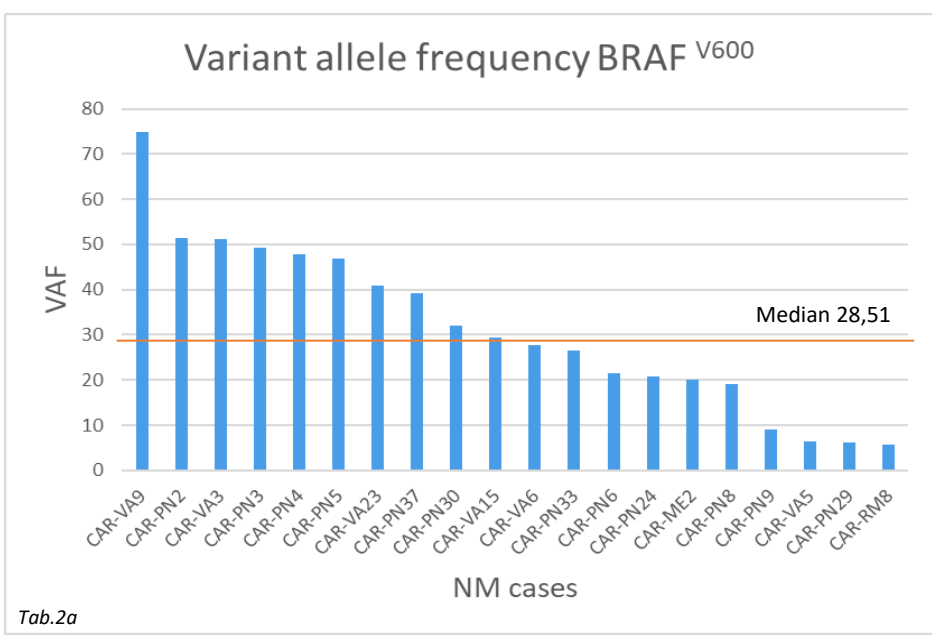
NM					
Stage	**No.**	**BRAF^{V600}**	**%**	**NRAS^{mut}**	**%**
IA/IB-IIA	13	5	38,50%	5	38,50%
IIB/IIC-IIIA	15	6	40,00%	6	40,00%
IIIB/C/D	14	9	64,30%	4	28,60%

Tab.1a

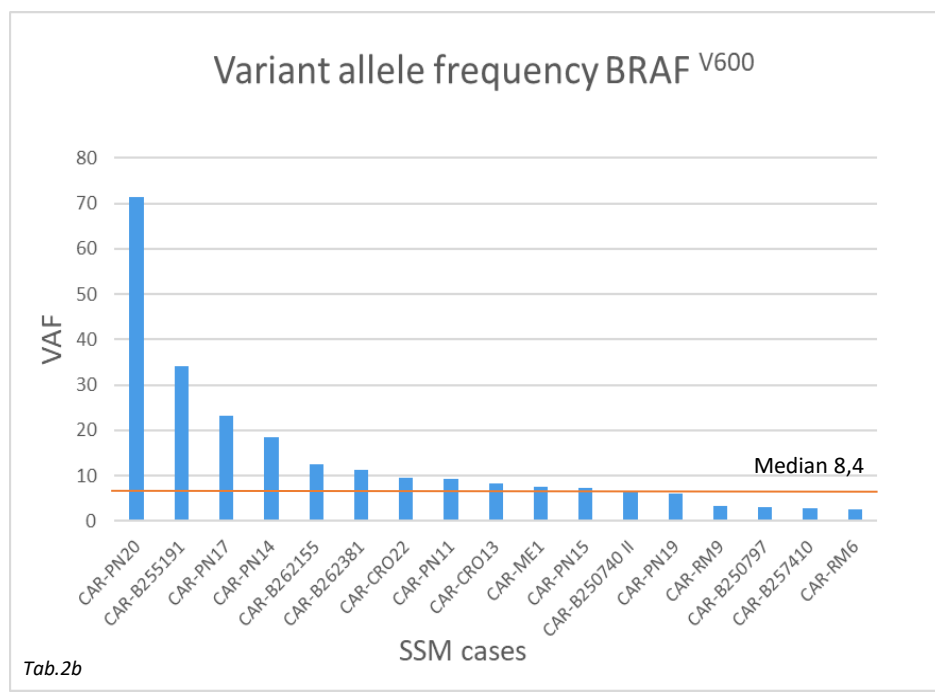
SSM					
Stage	**No.**	**BRAF^{V600}**	**%**	**NRAS^{mut}**	**%**
IA/IB-IIA	26	14	53,80%	1	3,80%
IIB/IIC-IIIA	2	1	50,00%	0	0,00%
IIIB/C/D	3	2	66,70%	0	0,00%

Tab.1b

Interestingly, a variant allele frequency (VAF) ≥ 40% was observed in 9/20 (45%) BRAF-V600 mutated NM cases vs. 2/17 (11,8%) BRAF-V600 mutated SSM cases (*Tab.2a, 2b*).



Tab.2a



Tab.2b

Conclusions

In our series, the SSM lesions were found to lack NRAS mutations. Although the prevalence of BRAF-V600 mutations was similar in both subsets (roughly, half of NM and SSM), a significantly higher level (more than three times) of the BRAF-V600 mutant allele frequency was observed in NM lesions as compared to SSM lesions. Correlation of these different subgroups of mutated cases with clinical and pathological parameters is ongoing.