Molecular characterization of fast-growing melanomas

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Background: The rate of growth of primary melanoma is a robust predictor of aggressiveness, but the mutational profile of fast-growing melanomas (FGMM) and the potential to stratify patients at high risk of death has not been comprehensively studied.

Objective: To investigate the epidemiologic, clinical, and mutational profile of primary cutaneous melanomas with a thickness ≥ 1 mm, stratified by rate of growth.

Methods: Observational prospective study. Deep-targeted sequencing of 40 melanoma driver genes on formalin fixed, paraffin-embedded primary melanoma samples. Comparison of FGMM (rate of growth > 0.5 mm/month) and nonFGMM (rate of growth ≤ 0.5 mm/month).

Results: Two hundred patients were enrolled, among wom 70 had FGMM. The relapse-free survival was lower in the FGMM group (P = .014). FGMM had a higher number of predicted deleterious mutations within the 40 genes than nonFGMM (P = .033). Ulceration (P = .032), thickness (P = .006), lower sun exposure (P = .049), and fibroblast growth factor receptor 2 (*FGFR2*) mutations (P = .037) were significantly associated with fast growth.

Limitations: Single-center study, cohort size, potential memory bias, number of investigated genes.

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Conclusion: Fast growth is linked to specific tumor biology and environmental factors. Ulceration, thickness, and *FGFR2* mutations are associated with fast growth. Screening for *FGFR2* mutations might provide an additional tool to better identify FGMM, which are probably good candidates for adjuvant therapies. (J Am Acad Dermatol 2022;86:312-21.)

Key words: fast-growth melanoma; FGFR2 mutations; melanoma; mutations of poor prognosis.

INTRODUCTION

The incidence of cutaneous melanoma continues to rise worldwide.[1-4] Prevention campaigns promoting early diagnosis underlie an epidemiologic shift toward earlier recognition of disease[5-10] and most new melanoma cases are diagnosed at localized stages.[8,11,12] Stage II tumors are considered low risk[13]; however, because there is a large prevalence of stage II tumors, the prediction is that they will account for most deaths in the future.[8,11,12]

CAPSULE SUMMARY

- Fast-growing melanomas are aggressive and linked to early death. Rapid growth is more frequent in patients with less accumulated sun exposure and is associated with thicker, ulcerated tumors with fibroblast growth factor receptor 2 mutations.
- Ulceration, thickness, and fibroblast growth factor receptor 2 mutations are biomarkers for aggressive disease and could stratify patients for adjuvant therapy.

Targeted and immunotherapies have transformed the care for metastatic melanomas and adjuvant trials have demonstrated a high efficacy. New trials are testing anti-PD1 in American Joint Committee on Cancer stages IIB/IIC melanomas, expanding the pool of potential candidates for adjuvant immunotherapy. Identification of new biomarkers of aggressiveness is paramount to optimize risk-ratio toxicity and ensure optimal resource allocation.

Primary melanoma growth, defined as the ratio of tumor thickness to patient-reported time of melanoma growth,[14] is a validated robust, reproducible, and independent prognostic factor of outcome.[14-17] Patients with fast-growing melanomas (FGMM) have an aggressive disease that spreads early, leading to shorter survival time.[14-17] Fast growth is associated with nodular subtype, trunk location, male sex, previous nonmelanoma skin cancer, and few sunburns during childhood.[15-17] Furthermore, FGMM displays high mitotic rates[15-17] and frequent *NRAS*[18] and *TERT* promoter mutations[19], highlighting growth kinetics is a relevant feature that accurately represents the aggressiveness of the melanoma. The mutational profile of FGMM has not been comprehensively studied. We compared the epidemiologic, clinical, and mutational profile of a cohort of FGMM and nonFGMM primary cutaneous melanomas.

METHODS

Clinical data

We prospectively enrolled consecutive primary melanoma patients with a thickness ≥1 mm who were referred to the dermato-oncology unit of La Timone Hospital, Marseilles, France between February 2012 and October 2014. We collected epidemiologic and clinical characteristics (Supplemental Methods; available via Mendeley at https://data.mendeley.com/datasets/ysd3vr9yr8/1). Rate of growth (ROG) was calculated as the ratio between thickness and time to melanoma development.[14] FGMM were defined by ROG > 0.5 mm/month and nonFGMM by ROG ≤ 0.5 mm/month.[15-17] Patients filled out a standardized questionnaire to estimate sun exposure (Supplemental Methods). We derived 2 sun exposure scores to estimate lifelong sun exposure and lifelong sunburn.

Molecular analyses

Tumor DNA was extracted from hand-macrodissected FFPE melanoma specimens, and normal DNA from patient-matched peritumoral normal skin or wide local excision. DNA was extracted using the GeneRead DNA FFPE kits (Qiagen) and DNA integrity assessed using the NGS FFPE QC Kit (Agilent Technologies). Histopathologic variables were extracted from routine reports.

We performed deep-targeted sequencing of 40 melanoma genes, selected by frequency of mutation in The Cancer Genome Atlas database (>7%) and/or specific cancer genes of interest (Supplemental Table I). *TERT* promoter was not analyzed in our panel. Three different pipelines were used for variant filtering validation. Manual inspection of the "nonconsensual" variants was performed on Integrative Genomics Viewer to avoid false-positive

Abbreviations used:

DMFS: distant metastasis-free survival
FGMM: fast-growing melanomas
MSS: melanoma specific survival
ROG: rate of growth
RFS: recurrence-free survival

calls (Supplementary Methods). Only single nucleotide variants predicted as pathogenic or likely pathogenic by the Catalogue Of Somatic Mutations In Cancer[20] or Varsome[21] databases were considered in the final analysis.

Analysis of gene expression

Cutaneous primary and metastatic melanomas (SKCM) from The Cancer Genome Atlas[22] were divided into fibroblast growth factor receptor 2 (*FGFR2*), wildtype (WT), and *FGFR2* mutants based on the presence of a deleterious mutation (missense, frame shift insertion/deletion, nonsense mutation) in *FGFR2*. Thirty-five cases with a missense mutation were present with matched clinical and gene expression data, and 437 WT cases. For each sample, the G1/S and G2/M gene expression signature scores were determined by calculating the geometric mean of all genes in each signature. G1/S- and G2/M-specific genes were those used in Tirosh et al[23] to measure proliferating cells.

Somatic mutation and RNA-seq (log_2 transformed RSEM) data were downloaded from The Cancer Genome Atlas Xena database from the University of Santa Cruz (https://xenabrowser.net/datapages/) and statistical analysis was performed in Prism v8.2.0 (GraphPad). The Mann-Whitney test was used to compare expression and scores between *FGFR2* mutants and WT samples.

Statistical analysis

Continuous variables were expressed as means ± SD or as median with range and categorical variables as count and percentages. Means were compared by student t-test and percentages were compared using the chi-square test (or Fisher's exact test, as appropriate). Univariate and stepwise forward multivariate logistic regression models were used to identify factors associated with FGMM. Variables with a $P < .05$ in univariate analysis were included in multivariate analyses. Recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and melanoma specific survival (MSS) were calculated from the melanoma diagnosis. RFS, DMFS, and MSS curves were estimated by the Kaplan-Meier method and the log-rank test. All tests were 2-sided and statistical significance was defined as $P < .05$. The false discovery rate was controlled with a Benjamini-Hochberg procedure.[24] Statistical analyses were performed using SPSS Statistics, version 20 (IBM SPSS Inc). RandomForest algorithm, bootstrap, and multilayer neural perceptron analyses were used to estimate the robustness of the results by using the randomForest and caret packages of R (The R Foundation).

RESULTS

Clinical and epidemiological variables associated with fast growth

Three hundred and fifty-three patients were referred to our institution during the study period. ROG calculation, DNA extraction, and molecular analyses were successfully performed for 200 patients (Supplemental Fig 1). We compared the clinical, epidemiologic, and genetic mutations of FGMM (n = 70, ROG > 0.5 mm/month) to the features of nonFGMM (n = 130, ROG ≤ 0.5/month). The cohort included 112 men and the median age at diagnosis was 62 years.

Most melanomas were located on the trunk (84%) and lower limbs (30.5%). The most common histologic subtype was superficial spreading melanoma (63.5%), followed by nodular melanoma (29.5%). The median Breslow thickness was 2.25 mm. Approximately one third of melanomas were ulcerated and 54% had a mitotic rate ≥ 1/mm^2. Regression was present in 18 samples (9%). A sentinel node biopsy was performed in 170 patients (75%). Twelve patients had clinical node involvement at diagnosis. The American Joint Committee on Cancer[25] distribution was: stage I, 35.5%; stage II, 39%; stage III, 23.5%; and stage IV, 2%. The median ROG was 0.26 (interquartile range, 0.09-0.77; Supplemental Table II).

Univariate analysis showed that FGMM were more frequently thick ($P < .001$), ulcerated ($P < .001$), nodular ($P = .009$), with a positive sentinel node ($P = .01$). FGMM were less frequently located on the upper limb ($P = .047$) and more frequent in patients medicated with beta blockers ($P = .02$). We found an association between FGMM and less lifetime sun exposure ($P = .04$) and sunburns ($P = .034$). (Table I and Supplemental Table III). After multivariate analysis, only ulceration ($P = .016$), thickness ($P = .007$), and less lifelong sun exposure ($P = .043$) were significantly associated with FGMM (Table II).

We studied the association between survival and melanoma ROG, and found 61 patients relapsed after a median follow-up period of 59.67 months (28 in the FGMM and 33 in the nonFGMM group). Although the

Table I. Clinical and epidemiologic variables associated with fast growth[†]

Variable	NonFGMM (n = 130)	FGMM (n = 70)	OR 95%	*P* value
Melanoma location				
Head and neck	11 (8.5%)	9 (12.9%)	1.26 (0.47-3.38)	.640
Trunk	51 (39.2%)	33 (47.1%)	1	
Upper Limb	20 (15.4%)	4 (5.7%)	0.31 (0.10-0.99)	.047
Lower Limb	41 (31.5%)	20 (28.6%)	0.75 (0.38-1.51)	.423
Hands/feet/palm/nail	7 (5.4%)	4 (5.7%)	0.88 (0.24-3.25)	.852
Histological subtype				
SSM	90 (69.2%)	37 (52.9%)	1	
NM	30 (23.1%)	29 (41.4%)	2.35 (1.24-4.45)	.009
Other*	10 (7.7%)	4 (5.7%)	1.08 (0.31-3.73)	.902
Ulceration				
No	92 (73%)	32 (45.7%)	1	
Yes	34 (27%)	38 (54.3%)	3.21 (1.74-5.93)	.001
Missing	4	0		
Thickness (mm)				
Median	1.8 (1.4-3)	4 (2.5-6)	1.61 (1.34-1.93)	.001
Mean	2.4 ± 1.58	5.70 ± 6.68		
1.00-2.00	80 (61.5%)	10 (14.3%)	1	
2.01-4.00	33 (25.4%)	30 (42.9%)	7.27 (3.20-16.56)	.001
>4.00	17 (13.1%)	30 (42.9%)	14.12 (5.82-34.26)	.001
Sentinel node biopsy				
Positive	19 (16.5%)	19 (34.5%)	2.67 (1.27-5.60)	.010
Negative	96 (83.5%)	36 (65.5%)	1	
Missing	16	14		
AJCC (7th classification)				
I	63 (48.5%)	8 (11.4%)	1	
II	43 (33.1%)	35 (50%)	6.41 (2.71-15.11)	.001
III	22 (16.9%)	25 (35.7%)	8.95 (3.52-22.74)	.001
IV	2 (1.5%)	2 (2.9%)	7.88 (0.97-63.89)	.053
Beta blockers				
No	123 (94.6%)	59 (84.3%)	1	
Yes	7 (5.4%)	11 (15.7%)	3.28 (1.21-8.88)	.020
Mean sun exposure score				
During childhood	5.41 ± 1.66	4.71 ± 1.34	0.75 (0.61-0.92)	.005
During adulthood	6.88 ± 2.11	6.34 ± 1.84	0.87 (0.75-1.02)	.008
All life long	12.3 ± 3.42	10.88 ± 2.5	0.86 (0.78-0.96)	.004
Mean sunburn score				
During childhood	1.55 ± 0.9	1.25 ± 0.8	0.68 (0.47-0.97)	.033
During adulthood	1.55 ± 0.9	1.33 ± 0.9	0.77 (0.55-1.08)	.124
Lifelong	3.10 ± 1.6	2.57 ± 1.5	0.80 (0.65-0.98)	.034

FGMM, Fast-growing melanomas; *NM*, nodular melanoma; *OR*, odds ratio; *SSM*, superficial spreading melanoma.
*ALM, acral lentiginous melanoma (n = 6); LM, lentigo maligna (n = 2); desmoplastic (n = 1); spitzoïd (n = 1); malignant blue (n = 1); nonassessable (n = 3); SSM, superficial spreading melanoma; NM, nodular melanoma.
[†]Univariate analysis, *P* value < .05.

median RFS and median DMFS were not reached, the RFS was significantly lower in the FGMM group (5-year FGMM RFS, 58.4%; nonFGMM, 73.7%; *P* = .014; hazard ratio, 1.9 [1.1-3.1]) (Fig 1). We assessed distant recurrences and documented 56 patients (FGMM = 27, nonFGMM = 29). The DMFS was significantly lower in the FGMM cohort (5-year DMFS FGMM, 61%; nonFGMM, 77.2%; *P* = .010; hazard ratio, 1.9 [1.2-3.3]) (Supplemental Fig 2). During the follow-up period, 39 patients died (FGMM = 18; nonFGMM = 21) and we found a trend for lower MSS in the FGMM cohort (5-year FGMM MSS, 74.1%; nonFGMM, 83.5%; *P* = .092).

Pathogenic mutations associated with FGMM

We compared the proportion of samples driven by the common oncogenic melanoma mutations *BRAF*, *RAS* or *NF*1, or WT for *BRAF*, *NRAS*, *NF1*

Table II. Clinical and epidemiologic variables associated with fast growth

Variables*	nonFGMM (n = 130)	FGMM (n = 70)	Univariate OR 95%	*P* value	Multivariate OR 95%	*P* value
Melanoma location						
Head and neck	11 (8.5%)	9 (12.9%)	1.26 (0.47-3.38)	.64		
Trunk	51 (39.2%)	33 (47.1%)	1		1	
Upper Limb	20 (15.4%)	4 (5.7%)	0.31 (0.10-0.99)	.047		
Lower Limb	41 (31.5%)	20 (28.6%)	0.75 (0.38-1.51)	.423		
Hands/feet/palm/nail	7 (5.4%)	4 (5.7%)	0.88 (0.24-3.25)	.852		
Histological subtype						
SSM	90 (69.2%)	37 (52.9%)	1		1	
NM	30 (23.1%)	29 (41.4%)	2.35 (1.24-4.45)	.009		
Other†	10 (7.7%)	4 (5.7%)	1.08 (0.31-3.73)	.902		
Ulceration						
No	92 (73%)	32 (45.7%)	1		1	
Yes	34 (27%)	38 (54.3%)	3.21 (1.74-5.93)	<.001	3.18 (1.2-8.2)	.016
Missing	4	0				
Mitotic rate						
0/mm^2	37 (37.4%)	13 (22.4%)	0.48 (0.23-1.01)	.054		
≥1/mm^2	62 (62.6%)	45 (77.6%)	1		1	
Missing	31	12				
Thickness (mm)						
1.00-2.00	80 (61.5%)	10 (14.3%)	1		1	
2.01-4.00	33 (25.4%)	30 (42.9%)	7.27 (3.20-16.56)	<.001	4.73 (1.55-14.7)	.007
>4.00	17 (13.1%)	30 (42.9%)	14.12 (5.82-34.26)	<.001	7.64 (2.2-27.0)	.002
Sentinel node biopsy						
Positive	19 (16.1%)	19 (33.3%)	2.67 (1.27-5.60)	.01		
Negative	96 (81.4%)	36 (63.2%)	1		1	
Missing	16	14				
Beta blockers						
No	123 (94.6%)	59 (84.3%)	1		1	
Yes	7 (5.4%)	11 (15.7%)	3.28 (1.21-8.88)	.02		
Mean sun exposure score (lifelong)	12.3 (±3.42)	10.88 (±2.5)	0.86 (0.78-0.96)	.004	0.84 (0.7-0.99)	.043
Mean sunburn score (lifelong)	3.10 (±1.6)	2.57 (±1.5)	0.80 (0.65-0.98)	.034		

Multivariate stepwise forward model.

FGMM, Fast-growing melanomas; *OR*, odds ratio.

*Only variables with a *P* value < .05 after univariate analysis were included in the model.

†ALM (acral lentiginous melanoma), LM (lentigo maligna), desmoplastic, spitzoïd, malignant blue, nonassessable.

(triple WT) and confirmed a similar distribution to previous cohorts.[22,26] The most commonly mutated genes were *BRAF* (49%), *NRAS* (23.5%), and *NF1* (17.5%), together with *TP53* (12%), which appeared in similar proportions in FGMM and nonFGMM samples. We explored the association between FGMM and mutation burden in the 40-gene panel. FGMM had a higher number of pathogenic mutations than nonFGMM (mean single nucleotide variants FGMM = 3.17 ± 3.58; nonFGMM = 2.13 ± 1.931; *P* = .033).

We next investigated the association between pathogenic mutations in each gene and FGMM and found at least 1 mutation in 1 of the 40 genes in 179 patients. We performed univariate analyses and found a higher proportion of pathogenic mutations in *FGFR2*, *ALK*, *ERBB4*, *IDH1*, *PDGFRA*, *PREX2* and *RB1* in FGMM. We corrected for multiple comparison, confirmed that *FGFR2* and *IDH1* mutations were associated with fast growth, and noted that 15.7% of FGMM presented *FGFR2* mutations, in contrast to 2.3% in the nonFGMM group (*P* = .0049; hazard ratio, 7.81; 1.96-45.25) (Table III, Supplemental Tables IV and V). *IDH1* mutations were exclusively found in FGMM at a rate of 5.7% (*P* = .049).

We reasoned that if *FGFR2* mutations are associated with fast growth, melanomas with *FGFR2* mutations should present a transcriptional profile of increased cell proliferation.[23] We studied the transcriptional profile of melanomas with *FGFR2* mutations using data from The Cancer Genome

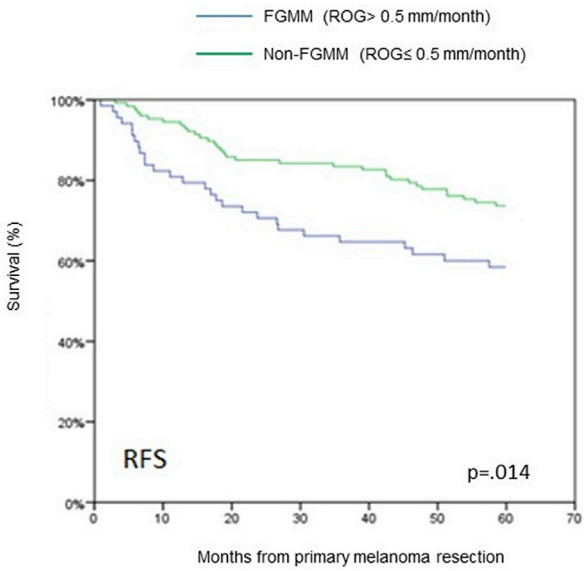

Fig 1. Relapse-free survival by rate of growth in the 200-patient cohort. *FGMM*, Fast-growing melanomas; *ROG*, rate of growth; *RFS*, recurrence-free survival.

Atlas. As the majority of point mutations in melanoma are acquired early and preserved at the metastatic stage,[27] we opted to include both primary and metastatic samples of the SKM cohort in our analysis. We compared the differentially enriched pathways in *FGFR2*-mutated and *FGFR2*-wild type samples and performed unbiased gene set enrichment analysis.[28] Remarkably, the expression of cell cycle genes indicating increased melanoma cell proliferation was significantly higher in *FGFR2*-mutated melanomas (Supplemental Fig 3).

Alterations in genetic pathways associated with fast growth

We analyzed the percentage of samples with protein-affecting aberrations in candidate driver genes, grouped by pathway in our 200 sample cohort (Supplemental Fig 4). FGMM more frequently presented mutations in receptor tyrosine kinases (*ERBB4/PDGFRA/ROS/RET/ALK/KIT/FGFR2*; FGMM = 32.9%/nonFGMM = 18.5%; P = .033), cell cycle pathway (*CDKNA/CDK4/BCLAF1*; FGMM = 10%/nonFGMM = 3.1%, P = .053) and the methylation pathway gene *IDH1* (FGMM = 5.7%/nonFGMM = 0; P = .042) after Benjamini-Hochberg adjustment (Supplemental Fig 4).

Integrating clinical and molecular biomarkers of FGMM

To validate the robustness of our biomarkers, we performed stepwise forward logistic regression analysis, including variables that were statistically significantly associated with FGMM (tumor location, histological subtype, ulceration, mitotic rate, thickness, sentinel node biopsy, betablocker consumption, lifelong sun exposure, lifelong sunburn, and mutations). The final model, which included 114 patients, confirmed ulceration (P = .032), thickness (P = .006), less sun exposure (P = .049), and *FGFR2* mutations (P = .037) are independent features associated with FGMM (Table IV).

To further assess how much *FGFR2* mutations contributed to fast growth relative to ulceration and thickness, we performed a recursive partitioning analysis (Supplemental Fig 5) as well as bootstrapping and a multilayer perception network analysis (Supplemental Figs 6 and 7). All these analyses demonstrated that *FGFR2* mutations allowed additional detection of FGMM beyond the other factors.

DISCUSSION

The rapid growth of primary melanoma is recognized as a marker of poor prognosis, frequently described in tumors with additional hallmarks of aggressive disease.[14-17] We studied the clinical and genetic characteristics of FGMM and confirmed that FGMMs metastasize more rapidly, are frequently ulcerated and thicker, and are inversely associated with lifetime sun exposure.[14-17] Additionally, we observed that FGMM carry an increased number of pathogenic mutations in melanoma driver genes. In a novel finding, we show a strong association with *FGFR2* mutations. These results suggest specific molecular changes and environmental factors affect primary ROG and consequently the disease outcome.

Our study confirms previous data[15-17] and sheds light on possible mechanistic drivers of rapid growth. Extensive studies in cancer research show additive oncogenic mutations increase the severity of cancer[29,30] and we show that a higher number of pathogenic mutations in 40 melanoma driver genes is linked to fast growth. This suggests that additive genetic damage to key genes will move melanoma forward at a faster pace. Additionally, we show environmental factors influence the ROG, as patient-reported high levels of sun exposure protects from rapid growth. Consistent with this finding, previous work revealed a higher burden of sun-induced mutations across the genome affecting primarily nondriver genes is coupled to better outcome.[31] Taken together, these studies validate that additive oncogenic drivers accelerate melanoma, but high levels of sun damage protect from aggressive disease.

Genomic aberrations in melanoma frequently affect key signaling pathways to tumorigenesis. The

Table III. Association of mutations in genes with fast-growing and nonfast growing melanoma (univariate analysis)

Genes mutation	NonFGMM (n = 130)	FGMM (n = 70)	OR 95%	Raw *P value*	Adjusted *P* value Benjamini-Hochberg
ALK mutation					
No	124 (95.4%)	62 (88.6%)	1	.085	.085
Yes	6 (4.6%)	8 (11.4%)	2.67 (0.89-8.02)		
ERBB4 mutation					
No	121 (93.1%)	59 (84.3%)	1	.048	.112
Yes	9 (6.9%)	11 (15.7%)	2.49 (0.88-7.22)		
FGFR2 mutation					
No	127 (97.7%)	59 (84.3%)	1	.0007	.0049
Yes	3 (2.3%)	11 (15.7%)	7.81 (1.96-45.25)		
IDH1 mutation					
No	130 (100%)	66 (94.3%)	1	.014	.049
Yes	0	4 (5.7%)	NE		
PDGFRA mutation					
No	128 (98.5%)	65 (92.9%)	1	.052	.073
Yes	2 (1.5%)	5 (7.1%)	4.92 (0.93-26.07)		
PREX2 mutation					
No	121 (93.1%)	59 (84.3%)	1	.048	.084
Yes	9 (6.9%)	11 (15.7%)	2.51 (0.99-6.38)		
RB1 mutation					
No	127 (97.7%)	64 (91.4%)	1	.068	.079
Yes	3 (2.3%)	6 (8.6%)	3.97 (0.96-16.39)		

FGMM, Fast-growing melanomas; *NE*, nonestimable; *OR*, odds ratio.

most affected pathways are the MAP kinase, PI3 kinase, and upstream receptor tyrosine kinases. In keeping with a faster proliferation, our study revealed FGMM accumulated more mutations in receptor tyrosine kinases and showed a trend for more mutations in genes controlling cell cycle. Significantly, we found a robust association between rapid growth and *FGFR2* mutations. FGFR2 is involved in tumor cell proliferation, angiogenesis, migration, and survival in multiple tissues.[32-34] Selective FGFR2 inhibitors show a decrease in tumor cell proliferation and promising results in early phase trials for multiple cancer types with activating *FGFR2* mutations.[34-37] Cutaneous melanoma, however, can present gain-of-function, oncogenic mutations[32] and loss-of-receptor function mutations[38] through multiple mechanisms, including lower ligand binding affinity, impaired dimerization, and reduced kinase activity.[32,34]

These studies highlight that FGFR2 signaling can exert opposing functions, either promoting growth or driving senescence, so that it is likely that the contribution of FGFR2 varies depending on cellular context and tumor type. The signaling consequences of the majority of *FGFR2* mutations documented in melanoma are unknown[39,40] and further work should address whether rapidly growing melanomas with *FGFR2* mutations are candidates for targeted inhibitor FGFR2 therapies.

Although the number of samples in our cohort is small, we found *IDH1* mutations might associate with fast growth. We identified hotspot oncogenic *IDH1*R132C mutations in 4 patients, exclusively in the FGMM group. *IDH1* mutations drive a variety of human cancers in addition to melanoma.[22,41] In vitro studies show that mutant IDH1 confers growth and metabolic advantage to melanoma and cancer cells,[41-43] and in glioma models, *IDH1/2* mutations may shape the immunologic landscape of the tumor microenvironment.[44,45] These findings support that *IDH1* mutations might drive more aggressive melanomas.

We acknowledge our study has limitations. Twenty percent of patients were not able to provide information required for ROG calculation and were excluded from the study. The size of the population was relatively small and missing data reduced the number of cases included in the multivariate models. Because ROG is calculated prospectively and *FGFR2* is not routinely analyzed, we could not corroborate our data in a validation cohort. Finally, *TERT* promoter sequencing was not included in our panel and is linked to rapid growth.[19] We additionally focused

Table IV. Variables associated with fast growth

Variables*	NonFGMM (n = 130)	FGMM (n = 70)	Univariate		Multivariate (stepwise)	
			OR 95%	*P* value	OR 95%	*P* value
Melanoma location						
Head and neck	11 (8.5%)	9 (12.9%)	1.26 (0.47-3.38)	.64		
Trunk	51 (39.2%)	33 (47.1%)	1			
Upper Limb	20 (15.4%)	4 (5.7%)	0.31 (0.10-0.99)	.047		
Lower Limb	41 (31.5%)	20 (28.6%)	0.75 (0.38-1.51)	.423		
Hands/Feet/palm/nail	7 (5.4%)	4 (5.7%)	0.88 (0.24-3.25)	.852		
Histological subtype						
SSM	90 (69.2%)	37 (52.9%)	1			
NM	30 (23.1%)	29 (41.4%)	2.35 (1.24-4.45)	.009		
Other†	10 (7.7%)	4 (5.7%)	1.08 (0.31-3.73)	.902		
Ulceration						
No	92 (73%)	32 (45.7%)	1		1	
Yes	34 (27%)	38 (54.3%)	3.21 (1.74-5.93)	<.001	2.90 (1.10-7.63)	.032
Missing	4	0				
Mitotic rate						
0/mm^2	37 (37.4%)	13 (22.4%)	0.48 (0.23-1.01)	.054		
≥1/mm^2	62 (62.6%)	45 (77.6%)	1			
Missing	31	12				
Thickness (mm)						
1.00-2.00	80 (61.5%)	10 (14.3%)	1		1	
2.01-4.00	33 (25.4%)	30 (42.9%)	7.27 (3.20-16.56)	<.001	5.41 (1.64-17.82)	.006
>4.00	17 (13.1%)	30 (42.9%)	14.12 (5.82-34.26)	<.001	8.88 (2.37-33.26)	.001
Sentinel node biopsy						
Positive	19 (16.1%)	19 (33.3%)	2.67 (1.27-5.60)	.01		
Negative	96 (81.4%)	36 (63.2%)	1			
Missing	16	14				
Beta blockers						
No	123 (94.6%)	59 (84.3%)	1			
Yes	7 (5.4%)	11 (15.7%)	3.28 (1.21-8.88)	.02		
Mean sun exposure score (lifelong)	12.3 (±3.42)	10.88 (±2.5)	0.86 (0.78-0.96)	.004	0.85 (0.71-0.99)	.049
Mean sunburn score (lifelong)	3.10 (±1.6)	2.57 (±1.5)	0.80 (0.65-0.98)	.034		
FGFR2 mutation						
No	127 (97.7%)	59 (84.3%)	1		1	
Yes	3 (2.3%)	11 (15.7%)	7.81 (1.96-45.25)	.005	8.64 (1.14-65.43)	.037

Multivariate stepwise forward model. Data missing for the following variables: histologic subtype (n = 1); mitotic rate (n = 43); SN biopsy results (n = 30); sunburn score (lifelong) (n = 18); sun exposure score (lifelong) (n = 12); ulceration (n = 4).
FGMM, Fast-growing melanomas; *NM*, nodular melanoma; *OR*, odds ratio; *SSM*, superficial spreading melanoma.
*Only variables with a *P* value < .05 after univariate analysis were included in the model.
†ALM, LM, Desmoplastic, spitzoïd, malignant blue, nonassessable.

on targeted mutational analysis, omitting overall tumor mutation burden, mutational signatures, gene fusions, and expression.

CONCLUSIONS

The multivariate analysis reveals *FGFR2* mutations, thickness, and ulceration remain robust independent predictors of rapid melanoma growth, a strong indicator of poor outcome. Only patients with stages III or IV resected melanomas are currently eligible for adjuvant therapies. Given the ongoing trials in stage II melanomas, 1 of the current challenges is to find biomarkers to identify individuals at highest risk of death who are most likely to benefit from therapies in order to avoid overtreatment and drug toxicity. Screening for *FGFR2* mutations might provide an additional tool to better identify fast-growing tumors, which, given their aggressiveness, undoubtedly should be regarded as strong candidates for adjuvant therapies.

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Conflicts of interest

None disclosed.

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