Clinical Significance of Fusion in Melanoma: A Real-World Cohort Study

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Background

- Oncogenic gene fusions are rare but clinically relevant events in melanoma, often activating MAPK signaling in the absence of canonical *BRAF*, *NRAS*, or *NF1* mutations.
- The spectrum, co-mutational landscape, and clinical outcomes of such fusions in unselected melanoma cohorts remain incompletely defined.

Methods

- Comprehensive genomic profiling (DNA + RNA sequencing) was performed on 13,835 melanoma cases submitted to Caris Life Sciences between 2015 and 2025.
- Pathogenic and likely pathogenic fusions were detected using whole transcriptome sequencing.
- Tumor mutational burden (TMB)-High was defined as ≥10 mutation/Mb.
- Immune cell infiltration within the tumor microenvironment was estimated by RNA-seq deconvolution approach – quanTIseq.
- Real-world overall survival (rwOS) was derived from insurance claims data and analyzed using Kaplan–Meier estimates from initiation of immune checkpoint inhibitor therapy to last contact.
- Primary melanoma cases were reviewed by 4 dermatopathologists to integrate histopathologic features with molecular characteristics.

Results

Table 1: Fusions Types and Mutations Across Melanoma

Types	Cutaneous	Mucosal	Acral	Spitz	Unknown	Overall
N	287	23	10	15	53	388
			Fusion			
BRAF	119 (41.5%)	10 (43.5%)	4 (40.0%)	1 (6.7%)	19 (35.8%)	153 (39.4%)
RAF1	52 (18.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (7.5%)	56 (14.4%)
ALK	16 (5.6%)	2 (8.7%)	1 (10.0%)	9 (60.0%)	5 (9.4%)	33 (8.5%)
TERT	13 (4.5%)	0 (0.0%)	2 (20.0%)	0 (0.0%)	0 (0.0%)	15 (3.9%)
MET	13 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	14 (3.6%)
NTRK3	12 (4.2%)	1 (4.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	14 (3.6%)
PRKCA	9 (3.1%)	0 (0.00%)	1 (0.0%)	0 (0.0%)	4 (7.5%)	14 (3.6%)
CDK2	8 (2.8%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	2 (3.8%)	11 (2.8%)
PRKCB	6 (2.1%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	3 (5.7%)	10 (2.6%)
Others	39 (13.6%)	8 (34.8%)	2 (20.0%)	4 (26.7%)	15 (28.3%)	68 (17.5%)
			Mutation			
BRAF *V600E/K*	24 (8.4%) n = 19	0 (0.0%)	1 (10.0%) n =1	0.00%	1 (1.9%) n = 1	26 (6.7%)
NF1	29 (11.2%)	1 (4.5%)	0.00%	0.00%	9 (17.3%)	39 (10.9%)
NRAS	13 (4.5%)	1 (4.3%)	1 (10.0%)	0.00%	3 (5.7%)	18 (4.6%)
KIT	7 (2.4%)	2 (8.7%)	0.00%	0.00%	1 (2.4%)	10 (2.6%)
TERT	142 (58.4%)	3 (20.0%)	1 (14.3%)	0.00%	18 (40.0%)	164 (50.6%)
TMB-H	57 (32.0%)	0.00%	0.00%	0.00%	5 (15.6%)	62 (25.6%)

Histopathologic Review of Primary Melanoma Cases (n = 76)

	All Fusion Cases	
Presence of Sheeting Growth	79.70%	59/74
Zonation	9.21%	7/76
Cell size/type	61.80%	47/76
Predominant cytology	84.21%	64/76
Pigmentation status	48.68%	37/76
Bi-/triphenotypic populations	6.58%	5/76
Epidermal changes	38.59%	22/57
Pagetosis/lentiginous spread	43.47%	30/69
Kamino bodies	5.79%	4/69
Host inflammatory response	7.89%	6/76
Necrosis	18.42%	14/76
Regression	2.63%	2/76
Deep dermal mitoses	67.12%	49/73
Ulceration	40.85%	29/71
Mean Mitotic Rate per mm	3.5	

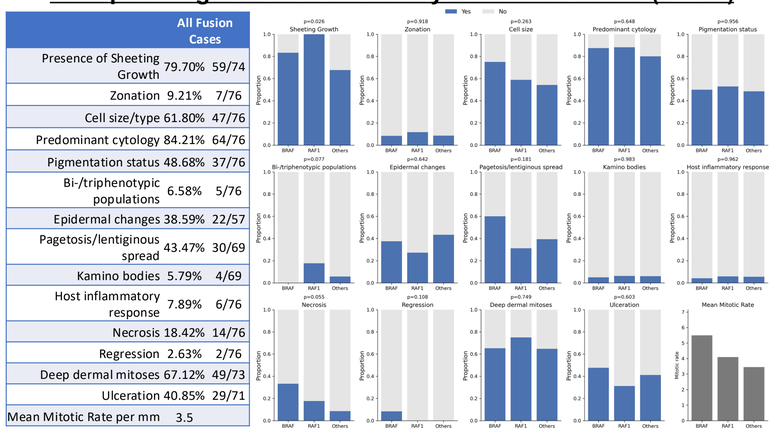

Figure 1: Histopathological review of various fusion types in primary melanoma cases

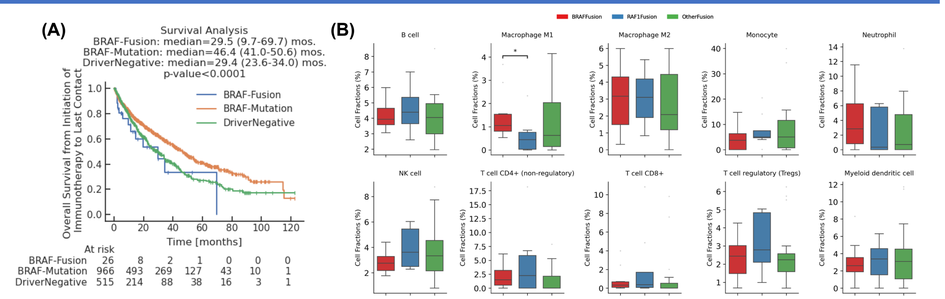

Figure 2: (A). Overall survival from start of immunotherapy to last contact in BRAF Fusion. (B). Characteristics of the tumor microenvironment in histopathologic reviewed cases.

Summary of Result

- A total of 388 cases (2.8%) harbored pathogenic or likely pathogenic fusions.
  - Fusion prevalence was significantly higher in *BRAF/NRAS/NF1* triple-wild-type melanomas (9.7%) compared with mutant cohorts (0.7%; p<0.0001)
  - Fusion prevalence was further enriched in triple-wild-type tumors with *TERT* promoter mutations (14.3% vs 9.7%; p<0.01).
  - Only 26% of fusion-positive melanomas had a high TMB relative to 59% of fusion-negative melanomas.
- Overall, *BRAF* fusions were most prevalent (39%), followed by *RAF1* (14%) and *ALK* (9%) fusions.
  - This pattern held across cutaneous, mucosal, and acral melanomas, whereas ALK fusions predominated in Spitz melanomas (60%), consistent with known Spitz-type molecular signatures.
- Clinical outcome analysis (≈300 cases) demonstrated no overall survival (OS) advantage by fusion type. Patients with *BRAF*-Fusion showed worse survival from initiation of immunotherapy compared with *BRAF*-mutation and not different when compared to DriverNegative (lacking *BRAF/NF1/RAS* mutation) patients.
- There was no statistically significant correlation between various histopathologic features of primary melanoma and specific fusions. The macrophage M1 signature was statistically lower in *RAF1* fusion primary melanoma relative to *BRAF* fusion primary melanomas.

Conclusion

- Pathogenic fusions occur in approximately 3% of melanomas and are enriched in triple-wild-type and TERT promoter–mutant tumors.
- BRAF fusions continue to represent the most frequent pathogenic fusion in melanomas.
- Fusion types may define distinct biological subsets with potential clinical implications.
- This represents the largest clinicogenomic characterization of melanoma fusions to date, providing a foundation for future studies.

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