1088P: Molecular Profiling and Matched Targeted Therapy for Patients with Advanced Melanoma: Results from Part 1 of the MatchMEL Study

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Background

- Immune checkpoint inhibitors (ICIs) have revolutionized outcomes in advanced melanoma[1]. However, about half of the patients exhibit resistance to current immunotherapeutic approaches[1,2].
- While the molecular landscape of melanoma has been defined, the clinicopathological associations of patients with BRAF/NRAS wild-type melanoma and ICIs treatment outcomes are less well understood[3].
- Melanoma genomes typically have the highest mutation load among cancers. However, some melanomas exhibit a lower tumor mutation burden (TMB), which could have significant implications for resistance to ICIs[1,3].

Objectives

- The MatchMEL study (NCT02645149) investigated the mutational profile of BRAF/NRAS wild type melanoma and examined whether targeted treatments could be matched to specific molecular alterations with clinical efficacy.
- In Part 1, clinicopathologic, molecular features and ICI outcomes were examined. In Part 2, we assessed outcomes for patients treated with targeted therapies following FoundationOne® CDx sequencing.

Methods

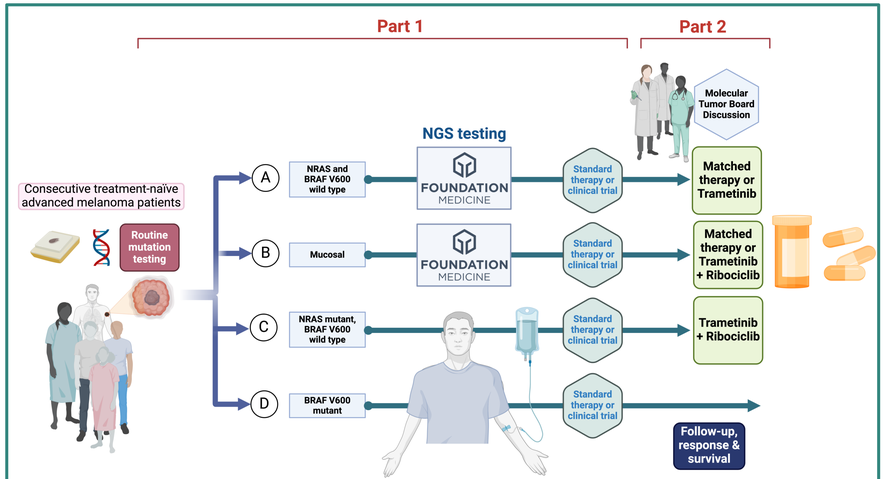

FIGURE 1. The MatchMEL study design. Created with Biorender.com.

- Consecutive patients with newly diagnosed advanced melanoma presenting to two centers in Australia were enrolled. BRAF V600 and NRAS wild type patients underwent tissue sequencing with FoundationOne® CDx, a 324 gene panel.
- All patients received treatment as per clinical practice (standard or in a clinical trial).
- A molecular tumor board analyzed sequencing results to match targeted therapy to molecular alterations.
- In Part 2, following the failure of all the available treatment options, patients could receive matched targeted therapy.

Results

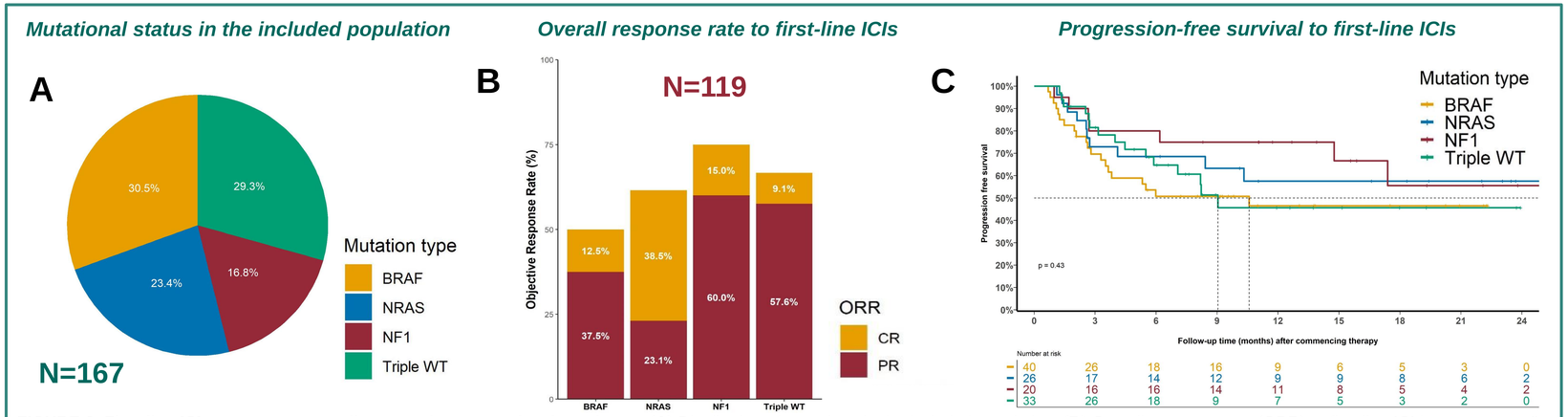

FIGURE 2. First-line ICIs outcomes according to melanoma molecular subtype. (A) Distribution of mutations in the included population. **(B)** Overall response rate (ORR) to first-line ICI in treatment-naïve patients was numerically higher in the NF1 population followed by the NRAS and BRAFV600 (p>0.05). **(C)** Kaplan Meier curves showing PFS to first-line ICIs in neo/adjuvant naïve patients.

- 167 patients: 119 treatment-naïve and 36 received prior neo/adjuvant immunotherapy treatment.
- Median follow-up 11.6 (2.5-29) months follow-up.
- Among BRAF/NRAS wild type patients, lower TMB was seen in neo/adjuvant ICIs progressors compared to treatment-naïve patients (11 vs. 37, p=0.016).

A

Primary melanoma type	N=68
Cutaneous, No. (%)	48 (71)
Sun-exposed, No. (%)	27 (56)
Non sun-exposed, No. (%)	21 (44)
Acral, No. (%)	4 (6)
Mucosal, No. (%)	4 (6)
Unknown, No. (%)	12 (17)
FoundationOne® CDx	**N=63**
NF1, No. (%)	23 (37)*
BRAF non-V600, No. (%)	12 (19), class 2 (n=8), class 3 (n=3)
KIT or PDGFRa, No. (%)	8 (12)
CDKN2A/B; CDK4, No. (%)	30 (48)*
MEK1, No. (%)	5 (8)
NRAS	1
*n=10 overlapping NF1 and CDKN2A/B or CDK4	

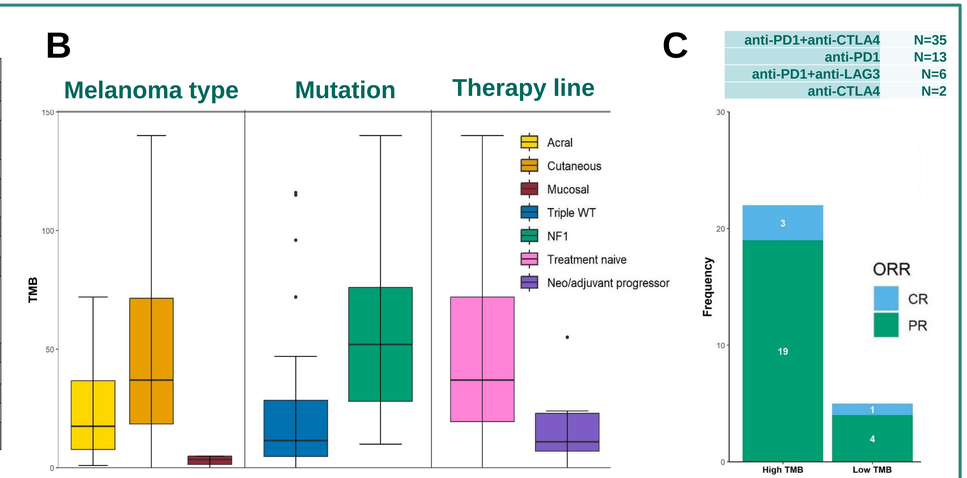

FIGURE 3. Characteristics of the BRAF/NRAS wild type population. (A) Primary melanoma type and FoundationOne® CDx results. **(B)** TMB values in some clinical subcategories. **(C)** ORR to first-line ICI (and the ICI regimens used) according to TMB (high >10, low ≤10).

Conclusions

- **Preliminary results of the MatchMel study revealed a variety of molecular mutations in wild type melanoma patients.**
- **NF1 alterations appeared to be linked with High TMB.**
- **High TMB was associated with higher ORR to immunotherapy.**

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