Cancer of Unknown Primary (CUP) Molecular Profile. Real Contribution of NGS Studies to Establish the Primary Site and Target Therapy Indication in a Clinical Laboratory.

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INTRODUCTION

Cancer of unknown primary (CUP) is an aggressive neoplasia with a high mortality rate. Analyzing CUP molecular profiles with a NGS-based panel could be helpful as some molecular alterations may provide clues regarding the putative primary site of each tumor. Moreover, knowing these alterations could benefit patients as they may direct a specific target therapy or being an inclusion criterion for clinical trials. In the present study, the real contribution of tumor molecular profiles to establish the primary site and it's capability to indicate a target therapy in a clinical diagnostics laboratory was analyzed.

METHODS

A retrospective study was designed. All CUP analyzed in our center between August 2022 and August 2023 were included. The morphological diagnosis included a wide panel of immunohistochemical studies. The molecular profile was performed with an NGS panel analyzing alterations in 161 genes at DNA and RNA level (Oncomine Comprehensive v3 Panel. ThermoFisher) Mutations, indels, CNV and gene fusions were recorded.

RESULTS

Sixty-three patients with a CUP diagnosis were included (55.6% males. Median age 73.5), 48 corresponding to biopsies and 15 to cytological samples. Liver (23.8%) was the organ most represented followed by peritoneum (17.4%) and lung (15.8%). In 2 (3.2%) specimens a molecular profile was not established due to a low yield of the DNA and RNA extracted. In 45 (73.8%) cases at least one molecular alteration was detected (range 1 to 6 coexisting alterations). Only 3 fusions affecting ALK, FGFR3 and TMPRSS2 were detected in 3 different patients. Eighty-six mutations were detected in 30 different genes, being TP53 (20.9%), KRAS (16.3%) and ARID1A (5.8%) the most prevalent. Twenty-three amplifications were detected in 14 different genes, being MDM2 (21.7%) and CDK4 (13%) the most prevalent. Figure one shows the molecular profile of each single patient. The molecular profile helped to establish the primary tumor site in 23 patients (51.1%) and could indicate a target therapy or the inclusion of the patient in a clinical trial in 44 (97.8%) of the 45 patients who presented molecular alterations.

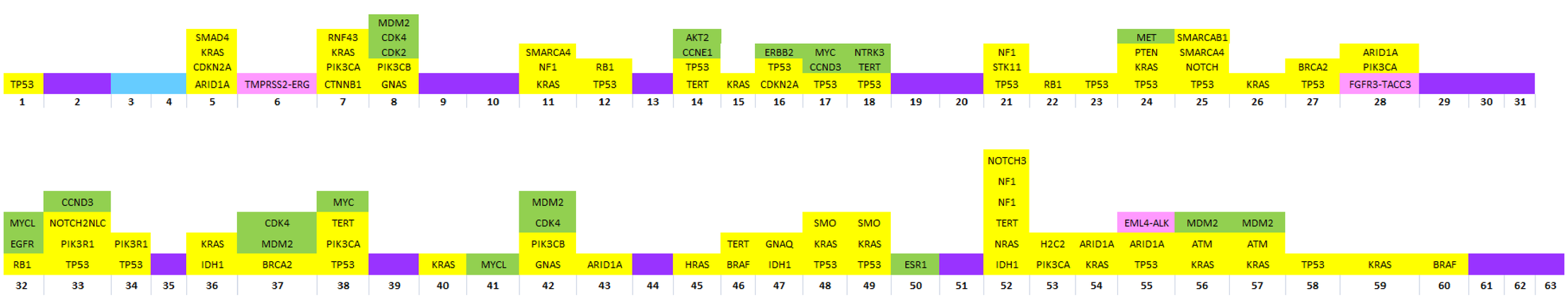

Figure 1. Graphical representation of each patient's molecular profile. Each column represents a single patient with the altered genes identified. Patients with no alteration detected are showed in violet, mutations are shown in yellow, amplifications in green, translocations in pink and patients with a non informative molecular result are shown in blue.

CONCLUSIONS

NGS-based panel molecular profiling of CUP allows the high sensitivity detection of DNA and RNA alterations in a broad number of genes, simultaneously. The molecular alterations detected reports clinically relevant information for a wide range of CUP patients in this series. Molecular profile could help establish the primary tumor site and/or direct a specific target therapy either by clinical guidelines indication or by being an inclusion criterion in a clinical trial.

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