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Whole Genome Sequencing for personalized selection of experimental treatment of advanced solid cancer

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Background

Trial specific pre-screenings tests are time and tissue consuming. This complicates personalized experimental treatment of patients who are eligible for early phase clinical trials. In this study, the feasibility of up-front whole genome sequencing (WGS) guided inclusion in early phase trials was investigated.

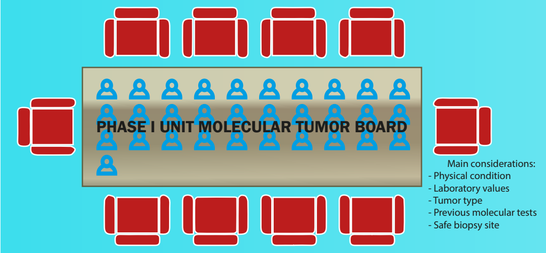

Figure 1. Phase I Unit molecular tumor board discussing patients for WGS based on several considerations

Patients and Methods

The Phase I Unit Molecular Tumor Board (MTB), Erasmus MC Cancer Institute reviewed patients with advanced cancer without standard-of-care treatment (SOC) options for eligibility for a fresh frozen (FF) tumor biopsy for WGS based on clinical-pathological features (fig. 1). The MTB consists of medical oncologists, pathologists, molecular biologists and clinical geneticists. WGS was performed by Hartwig Medical Foundation[1]. Actionability was reported using the ESCAT scale[2]. Multiplex immunofluorescent staining (IF) was performed on simultaneously taken tumor tissue.

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No conflicts of interest to declare

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Results

From September 2019 – March 2021, 31 patients underwent a FF tumor biopsy for WGS (Table 1). The tumor types were highly diverse. Median turnaround time between biopsy and WGS reporting was 15 days (fig. 2). Two samples were not evaluable due to low tumor purity (fig. 3). In 84% of the patients (26/31) at least one actionable alteration or biomarker was found (fig. 4). A third of the patients (11/31) received matched experimental treatment. Reasons for not receiving matched treatment were; absence of a matching trial (n=8), rapid clinical deterioration (n=4) or other (n=2). IF showed tumors with low mutational burden could be highly inflammatory, with high CD8+ cell counts.

N patients	31
Median age in years (range)	59 (32-79)
Male	18 (58%)
Female	13 (42%)
ECOG performance score	
0	8 (26%)
1	23 (74%)
RMH prognostic score	
Median	1
0	4 (13%)
1	6 (19%)
2	8 (26%)
3	0 (0%)
Missing	13 (42%)
Previous systemic treatment	
Yes	27 (87%)
No	4 (13%)
Mean number of treatment lines (range)	2 (0-8)

Table 1. Baseline patient characteristics

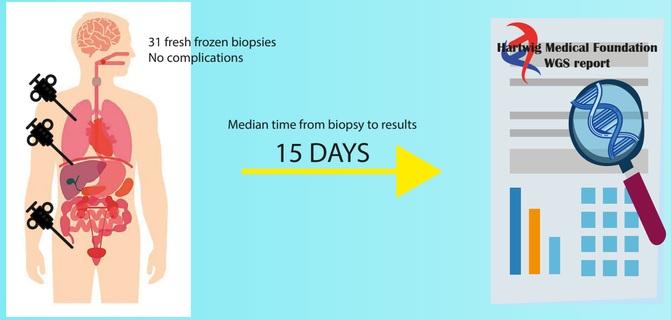

Figure 2. Median time from biopsy to WGS reporting.

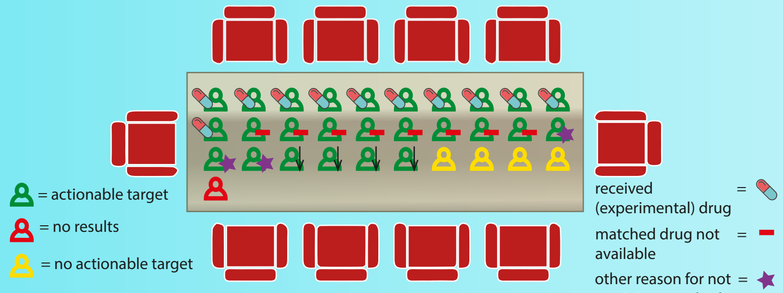

Figure 3. Results and treatment consequences of WGS analysis

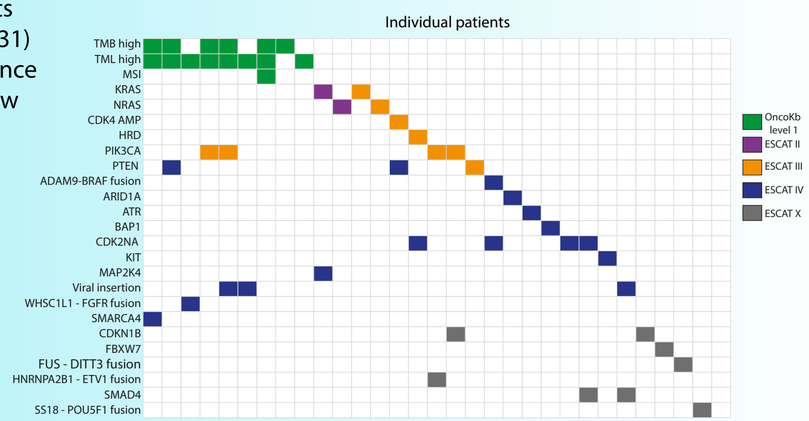

Figure 4. Actionable alterations according to ESCAT scale

Conclusion

WGS on fresh frozen tumor biopsies is a feasible tool for the selection of personalized experimental therapy in patients with advanced cancer without SOC options. WGS could fulfill the role of universal up-front genomic pre-screening test, as WGS is now possible in an acceptable turnaround time (15 days) and the analysis pipeline is open-source. IF had additional value on determining immunogenicity.

[1]P. Roepman et al. Clinical Validation of Whole Genome Sequencing for Cancer Diagnostics. J Mol Diagn. 2021 Jul;23(7):816-833.
[2]J. Mateo et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT), Annals of Oncology, Volume 29, Issue 9, 2018