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Value of comprehensive genomic profiling in pre-screening patients for *NTRK* fusion in STARTRK2 trial – single centre experience

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BACKGROUND and AIM

Comprehensive genomic profiling (CGP) by next-generation sequencing (NGS) is increasingly used as a pre-screening tool for clinical trials. The aim of this study is to retrospectively determine the scope of alterations identified by CGP that could render patients suitable for alternative early phase clinical trials of genomically-matched/immunotherapy or 'off-label' drug use.

METHOD

Patients were pre-screened for the STARTRK2 study (Entrectinib, NCT02568267) at The Christie using FoundationOneCDx (FM) assay introduced in Jan' 19. Testing is validated for NTRK, ROS1 and ALK fusion detection but all pathogenic alterations are reported on a trial specific FM report. We evaluated on an exploratory basis, potential treatment options on the basis of the full genomic report considering alternative clinical trials, off-label drug use (where a variant was present in a tumour type outside of FDA label) and genomic variants amenable to non-approved drugs with strong clinical evidence ('off-label use of 'pre-license drugs'). Patient with Tumour Mutation Burden (TMB) ≥10 mutations/megabase (mut/Mb) were considered eligible for off-label pembrolizumab.

RESULTS (I): study cohort and clinical characteristics

From Jan '19 to Oct '20, 269 patients were pre-screened for STARTRK2 with FM (Figure 1) their clinical characteristics are described in Table 1.

Figure 1. Consort diagram of study cohort.

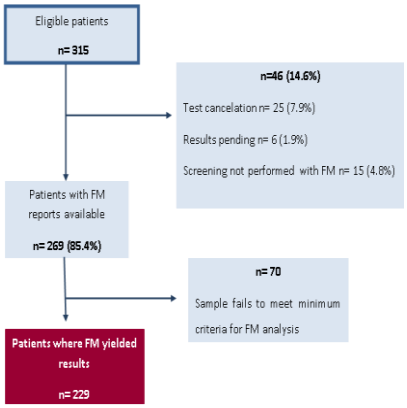


Table 1. Clinical characteristics.

Descriptive (n 269)	n	%
Median age (range)	60 (23-87)	
Male	157	58.4
Prior lines		
0	64	24.2
1-2	123	45.8
≥3	82	29.7
Most prevalent tumour types		
Colorectal (CRC)	71	26.4
Head and neck (HN)	58	21.6
Sarcomas	19	7.1
Pancreas	16	5.9
Breast	15	5.6
NSCLC	11	4.1
Other	10	3.7
Biliary	8	3.0
Prostate	8	3.0

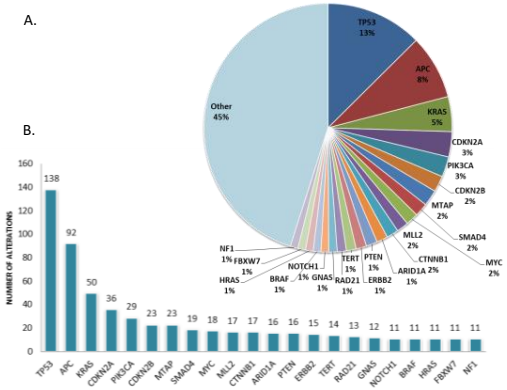
RESULTS (II): Sequencing results

FM testing yielded results in 229 (85.2%) patients. Microsatellite Instability (MSI) status and TMB were evaluable in 204 (75.8%) and 213 (79.1%) patients, respectively (Table 2). A total of 1098 genomic variations were reported. The 20 most prevalent genes represented 603 (55%) of these variants (Figure 2). Type of genomic alterations: gene substitutions/indels (66.3%), amplifications (21.3%), loss (9.4%), truncations (1.8%) and rearrangements/fusions (1.2%). **No oncogenic NTRK 1/2/3 fusions were detected.**

Table 2. NGS and genomic biomarkers results.

Variables	n	%
MSI-High patients	3	1.5
TMB low (1-5 mut/Mb)	128	60.4
TMB intermediate (6-19 mut/Mb)	51	24.1
TMB high (≥20 mut/Mb)	5	2.4
Median number of mutations per patient, (range)	4 (1-54)	
Median time from sample collection to study consent in months (range)	27 (0-123)	

Figure 2. A Percentage distribution of the 20 most prevalent genes and 'other' in the entire cohort. B Number of alterations in 20 most prevalent genes.



First author conflicts of interest: nothing to declare
STARTRK2 is a Roche sponsored study

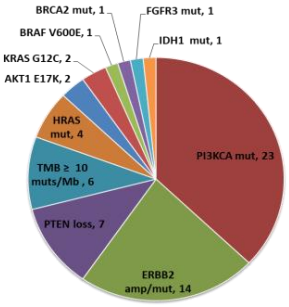
RESULTS (III): potential treatment options

61 (26.6%) patients were potentially eligible for of 'off-label' drug use and 104 (45.4%) for phase I biomarker-selective trials available within our centre (Table 3). *PI3KCA, ERBB2* and *PTEN* were amongst the most frequent genomic variants eligible for off-label drug use (Figure 3).

Table 3. Number of patients eligible for 'off-label' and clinical trials

Variables	n	%
Eligible for any form of 'off-label use'	**61**	**26.6**
Off-label drug use of FDA-approved drugs	42	18.3
Off-label drug use of 'pre-license drugs'	19	8.3
Eligible for biomarker-selected clinical trial	**104**	**45.4**
Genomically-Matched trials	101	44.1
Immunotherapy-trials	3	1.3

Figure 3. Genomic variations reported in the 61 patients eligible for any form of off-label drug use. Amp: amplifications; mut: mutations.



CONCLUSION

Our results highlight the relevance of CGP in identifying patients for clinical trials or off-label drug use. The retrospective nature of this work and the fact that extended FM results provided within STARTRK2 are not intended for clinical use precluded implementing these recommendations. NTRK fusions were not detected in our cohort which highlights the rarity of this event in our population.