PREVALENCE OF MUTATIONS IN COMMON TUMOUR TYPES IN NORTHERN ENGLAND AND UTILITY OF EXPERIMENTAL CANCER MEDICINE CENTRE (ECMC) CRUK TRIAL FINDER

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BACKGROUND

Genomic profiling of tumours has expanded rapidly and is of increasing importance in early phase trial units in matching patients to targeted clinical trials. It is recognised that mutational signatures vary by demographic group, however, regional differences are not yet characterised. This was investigated by comparing relative prevalence of mutations for common cancers presenting to Newcastle ECMC to The Cancer Genome Atlas (TCGA) and comparative utility of trial matching modalities within and outside the UK.

METHODS

Detailed clinicogenomic outcome data was obtained for patients with advanced cancer presenting to Newcastle ECMC with ctDNA profiling completed September 2017 – December 2020. Prevalence of commonly identified mutations in lung, colorectal, breast and prostate cancer was compared to TCGA GDC Data Portal. Experimental Cancer (EC) Trial Finder utility in matching trials was assessed, compared to Molecular Tumour Boards (MTB) and sequencing reports. Statistical analysis was conducted using SPSS Version 27.0. *P* values <0.05 were considered statistically significant.

RESULTS

The most common tumour types of 311 patients with advanced cancer were lung (n = 131, 42.1%), colorectal (n = 44, 14.1%), breast (n = 36, 11.6%) and prostate (n = 18, 5.6%) (Table 1). ≥1 genomic finding was identified in the majority (n = 260, 84%). Significant differences in prevalence of mutations compared to TCGA were identified, including a high prevalence of EGFR in lung cancer (*P* = 0.001); RB1 in lung and breast (*P* = 0.01, *P* = 0.0002); and multiple mutations in prostate cancer (Table 2). EC Trial Finder demonstrated significantly different utility than sequencing reports in identifying trials for mutations identified at ≥5% prevalence (*P* = 0.007) (Figure 2).

TABLE 1: PROFILED PATIENTS DEMOGRAPHICS NORTHERN ENGLAND

Variable	n = 311 (%)
Sex	
M	129 (41.5)
F	182 (58.5)
Age (years)	
Median (Range)	63 (19 – 97)
Sequencing Method	
Foundation One® FOL Original	151 (48.6)
Foundation One® FOL CDx	80 (25.7)
Qiagen comprehensive cancer panel (PROSPECT-NE)	80 (25.7)
Tumour Type	
Lung	131 (42.1)
Colorectal	44 (14.1)
Breast	36 (11.6)
Prostate	18 (5.6)
Pancreatic	12 (3.9)
Cervical	9 (2.9)
Oesophagogastric	8 (2.6)
Ovarian	5 (1.6)
Cancer of Unknown Primary (CUP)	5 (1.6)
Bladder	5 (1.6)
Other[a]	38 (12.2)

TABLE 2: MUTATIONS IN COMMON TUMOUR TYPES IDENTIFIED COMPARED TO THE CANCER GENOME ATLAS

Mutations commonly identified in Newcastle ECMC	Northern England	Cancer Genome Atlas	*P* (Chi-Squared)
Lung			
	n = 131 (%)	n = 1267 (%)	
TP53	72 (55.0)	887 (69.0)	0.11
EGFR	30 (22.9)	148 (11.7)	**0.001**
KRAS	23 (17.6)	208 (16.4)	0.78
RB1	17 (13.0)	82 (6.5)	**0.01**
STK11	15 (11.5)	117 (9.2)	0.46
ATM	14 (10.7)	104 (8.2)	0.38
CHEK2	11 (8.4)	20 (1.6)	**0.000001**
PIK3CA	11 (8.4)	104 (8.2)	0.95
PTEN	10 (7.6)	89 (7.0)	0.81
DNMT3A	9 (6.9)	44 (3.5)	0.07
Colorectal			
	n = 44 (%)	n = 610 (%)	
TP53	33 (75.0)	386 (63.3)	0.48
APC	28 (63.6)	486 (79.7)	0.37
KRAS	22 (50.0)	255 (41.8)	0.51
PIK3CA	8 (18.2)	165 (27.0)	0.31
MSH6	3 (6.8)	42 (6.9)	0.77
BRAF	3 (6.8)	86 (14.1)	0.22
NRAS	3 (6.8)	32 (5.2)	0.67
ERBB2	2 (4.5)	39 (6.4)	0.64
Breast			
	n = 36 (%)	n = 1306 (%)	
TP53	13 (36.1)	473 (36.2)	0.99
PIK3CA	10 (27.8)	435 (33.3)	0.62
RB1	5 (13.9)	33 (2.5)	**0.0002**
PTEN	4 (11.1)	89 (6.8)	0.35
ATM	3 (8.3)	38 (2.9)	0.08
Prostate			
	n = 18 (%)	n = 527 (%)	
TP53	13 (72.2)	70 (13.3)	**0.00001**
AR	6 (33.3)	4 (0.8)	**0.00001**
PTEN	5 (27.8)	19 (3.6)	**0.00002**
PIK3CA	3 (16.7)	13 (2.5)	**0.00001**
TMPRSS2	3 (16.7)	9 (1.7)	**0.000095**
AKT1	2 (11.1)	3 (0.6)	**0.000013**
CTNNB1	2 (11.1)	12 (2.3)	**0.029**
NF1	2 (11.1)	2 (0.4)	**0.000001**

FIGURE 2 (RIGHT):
Trial exploration for prevalent mutations in most common tumour types.
PROSPECT-NE MTB results were retrospectively interrogated and documented as potentially actionable. Potentially targeted trials were recorded. Foundation One® sequencing reports were retrospectively reviewed. Mutations were recorded as actionable, and trials recorded as YES if a report suggested a matched trial.
All mutations were processed by tumour type using EC Trial Finder. Trials were recorded as YES if open and whether they were 'all comer' or specific to tumour type. Significance testing criteria was not fulfilled for MTB results.

TABLE 1 (LEFT):
[a] Other – Tumour types found in ≤4 patients: Adrenocortical, Appendiceal, Cholangiocarcinoma, Endometrial, Eccrine adenocarcinoma, Gastrointestinal stromal cell tumour (GIST), Liver, Renal, Sarcoma, Thymic, Vulval, No active malignancy.

FIGURE 1: CRUK ECMC Network Map (BELOW)
(www.ecmcnetwork.org.uk)

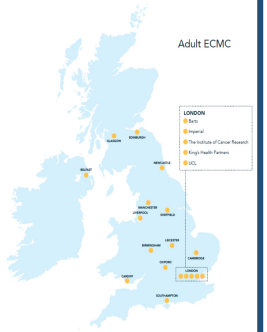
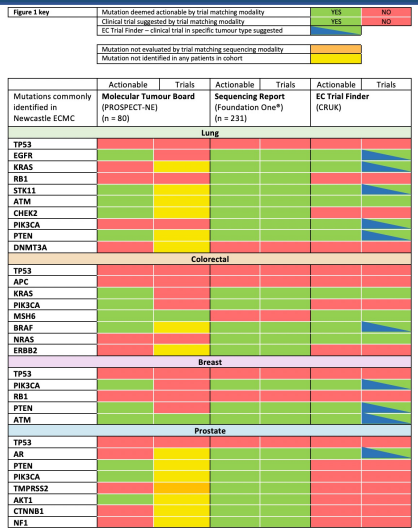


FIGURE 2: UTILITY OF CLINICAL TRIAL GENETIC MATCHING MODALITIES IN COMMON TUMOUR TYPES AND MUTATIONS



CONCLUSIONS

- Regional differences in mutational signatures remain challenging to characterise.
- Advanced disease stage and profiling methods may account for increased prevalence of specific mutations, notably in the prostate cancer cohort.
- EC Trial Finder shows utility in finding targeted trials in the regional population.
- Sequencing reports may over report 'actionable' mutations.
- Understanding local prevalence and trial availability could increase enrollment of patients onto matched clinical trials.
- This may improve patient outcomes in early phase trials.