Tracking multiple time point liquid biopsies TARGET National Study: A centre case series of 26 patients matched to clinical trials.

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INTRODUCTION

Detection of genomic aberrations through liquid biopsies (LB) offers a minimally invasive route to enabling access to targeted anticancer therapies.[1] The TARGET National trial aims to expand access to early phase clinical trials through tumour profiling by liquid biopsy in advanced cancers using sequencing of circulating DNA (ctDNA).[2]

We present a case series of 26 patients recruited in Newcastle Hospitals NHS Trust, who had serial blood tests available taken within TARGET national.

METHODS AND COHORT

All patients referred to an early phase trial due to a liquid biopsy, and with multiple liquid biopsy timepoints were included (n=26).

In this cohort 14/26 (54%) were female, with a median age at enrollment of 66 years (IQR 57-76). Patients included had 16 distinct cancer types (*Figure 1*), and at the time of collection, 24/26 patients had completed their trial, with a median length of trial enrolment of 67 days (IQR 28-126) (*Figure 2*).

Patients provided 82 liquid biopsies (median 2, IQR 2-4, max 10). Over these, 600 variants were detected (median of 8 variants detected in each test, IQR 5-10).

These included 82 likely CHIP variants and likely germline variants were displayed in 4/26 patients (BRCA2, MSH2 and ATM).[3,4]

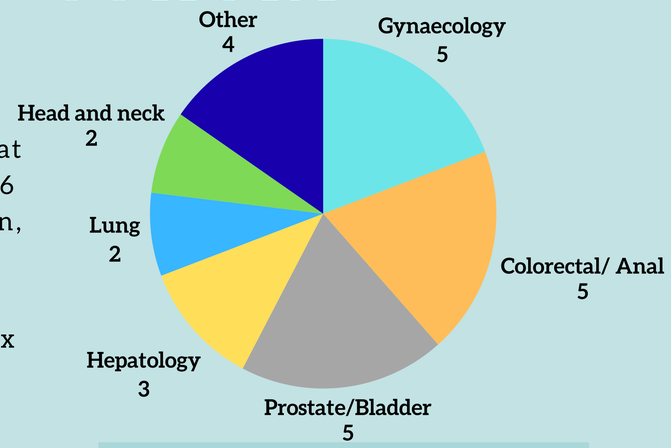

Figure 1 - Pie chart of the groups of cancers included in the study

RESULTS

The 26 patients were enrolled into 13 distinct early phase clinical trials with specific treatment modalities. These included Trials:

- Investigating immunotherapies. Overall, 8 patients enrolled, 3 demonstrated a reduction in tumour mutational burden. While 2 progressed on trial, 1 remained on trial for fifteen months before they withdrew due to toxicities.
- Targeting anti-ERBB2 directed therapies (4 patients). No reduction was found in tumour ERBB2 variant allele frequencies and 3/4 progressed. One patient's trial is ongoing.
- Targeting DNA damage and repair defects (9 patients, including 1 patient treated within the PYNNACLE trial). This patient's cancer remains stable, as does the variant allele fraction (VAF) on LB testing.
- Targeting BRAF therapies (2 patients). Both maintained stable levels of BRAF variants. One progressed on therapy; the other withdrew due to toxicity.
- Therapies targeting other mechanisms were received by 5 patients.

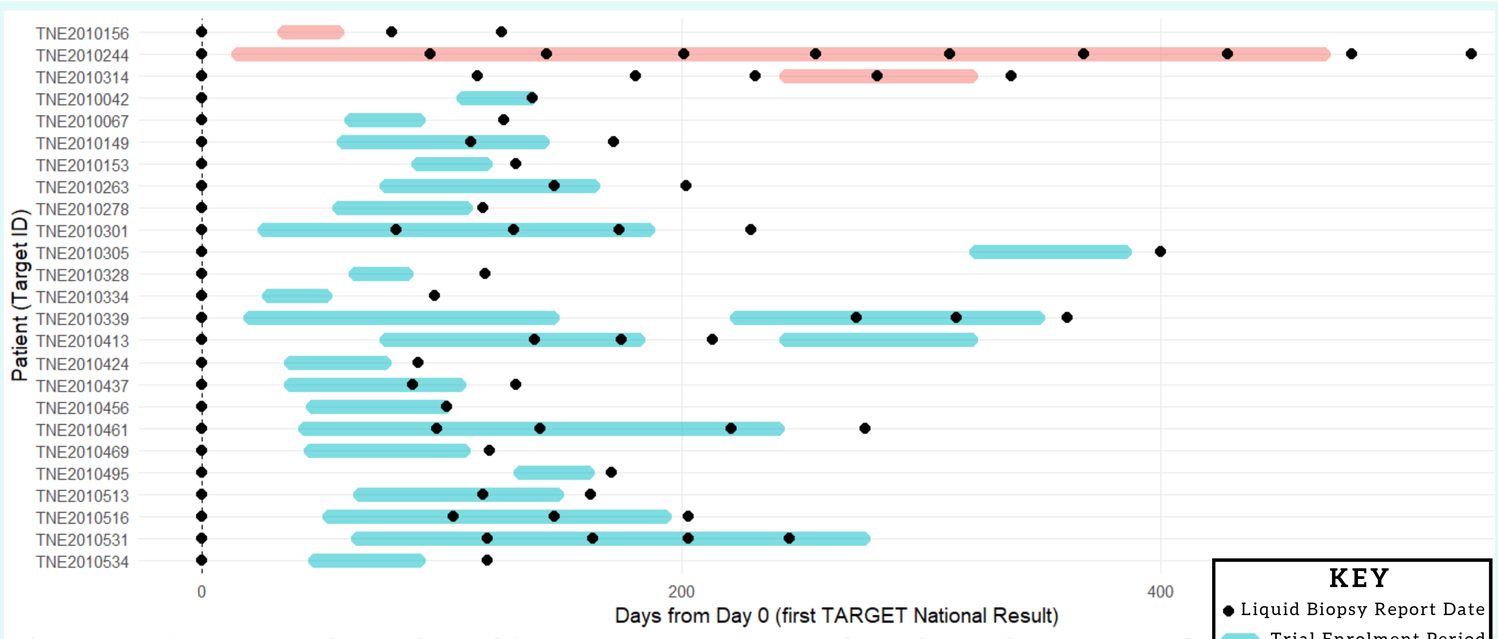

Figure 2 - Swimmer plot of liquid biopsies over time, and trial enrolment periods from day 0 (the first TARGET National Liquid Biopsy report date)

SPECIFIC EXAMPLES

PATIENT 1

Diagnosed with Invasive Ductal carcinoma. Originally treated with Adriamycin, cyclophosphamide and underwent local excision and adjuvant radiotherapy and tamoxifen.

Progressed across 6 lines of treatment.

TARGET CfDNA: high tumour mutational burden (TMB) of 97 - Patient was enrolled to a phase 1 trial of oral PDL-1 inhibitor *(Figure 3)*.

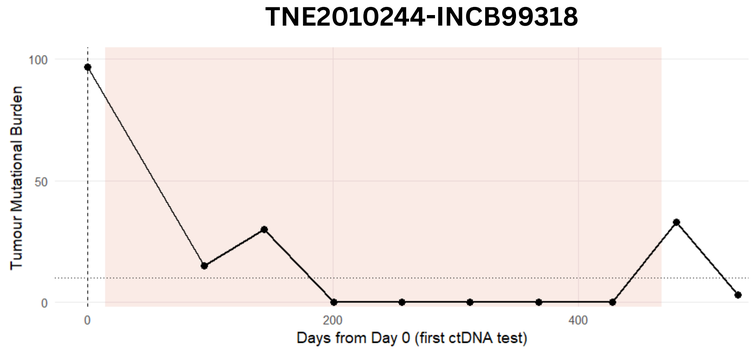

Figure 3 - Tumour Mutational Burden for patient TNE2010244 over time.

She demonstrated a partial response on CT and on serial liquid biopsies by TMB.

However developed anterior uveitis and treatment was discontinued. Started CDK 4/6 inhibitor abemaciclib.

PATIENT 2

Patient diagnosed with melanoma.
Treated with extensive surgery and amputation.
Progressed on 3 different lines of treatment.

In 2022 TARGET CfDNA found BRCA2 Q1701*.
Patient was started on M1774 and Niraparib.

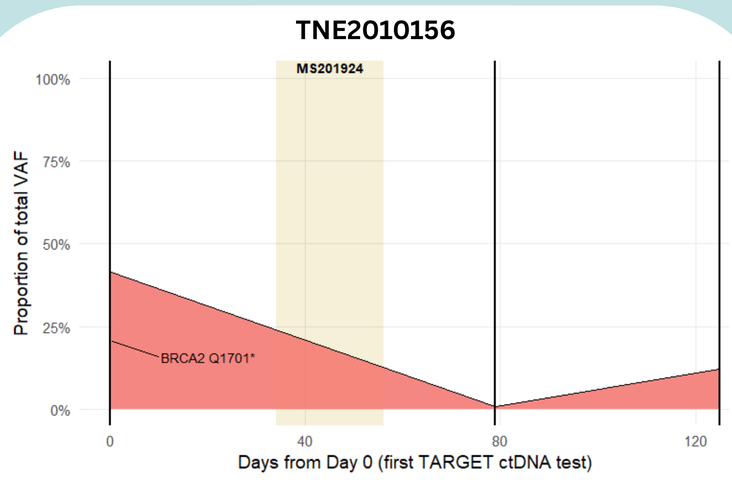

Figure 4 -Variant allele frequency (VAF) derived from liquid biopsies over time for the BRCA2 Q1701* variant over time

ctDNA Level went down 0.14%.

A CT scan showed showed stable disease. The patient elected to come off treatment.
ctDNA retested, with the BRCA2 variant at 0.14%, but was later retested at 12.1% and a following CT demonstrated progression.

PATIENT 3

Patient diagnosed with NSCLC.
Progressed on chemo / immunotherapy.

Treated on the trial on immunotherapy (pembrolizumab) and an aryl hydrocarbon receptor (AhR) inhibitor (BAY 2416964).

Prior to treatment TMB 18 mutations/Mb. During treatment this decreased (*Figure 5*).
However, the patient had to withdraw from trial due to pneumonitis.

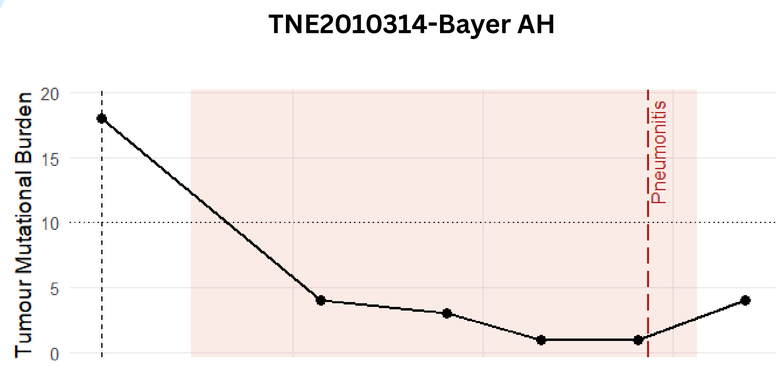

Figure 5 - Tumour Mutational Burden for patient TNE2010314 over time with the date of immunotherapy related pneumonitis noted.

At the time of this data collection the patient is alive on active surveillance.

CONCLUSIONS

This case series highlights the effective recruitment to targeted early phase clinical trials through liquid biopsy based molecular profiling through the TARGET National Trial, and the utility of molecular profile monitoring whilst enrolled in a clinical trial.

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