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AACR 2019 – Foundation Medicine sets the scene for liquid biopsy approval

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A study of a liquid biopsy and another looking at tumour mutational burden testing give early indications of Foundation's approval strategy.

The Roche subsidiary Foundation Medicine launched its liquid biopsy, FoundationOne Liquid, in the US in September, whereupon the test joined Guardant Health's Guardant360, among others, in a fast-developing market. But none of these pan-cancer blood assays is approved by the FDA – all are marketed as lab-developed tests.

Foundation intends to change this, believing that FoundationOne Liquid could become the first liquid biopsy to gain US approval, and data from a neuroblastoma trial reported today at the AACR meeting suggest that the company might be on the right track. Meanwhile, a separate study has provided an early hint of the suggested importance of tumour mutational burden in breast cancer.

Blood and treasure

In a trial in paediatric neuroblastoma, the group's liquid biopsy was able to identify tumour-associated genetic changes that emerged under the selective pressure of standard and targeted therapies.

Five newly diagnosed and 33 relapsed patients were repeatedly tested with FoundationOne Liquid. The results were compared with tumour sequencing from tissue biopsies taken at the same time as the blood draws.

Serial testing of circulating tumour DNA (ctDNA) with FoundationOne Liquid identified additional pathogenic variants in driver cancer genes – beyond those derived from tissue biopsy – in 45% of the 38 patients. In eight of these patients these included targetable ALK-RAS-MAPK pathway alterations. Among the 18 patients who had three or more ctDNA samples, six developed ALK-RAS-MAPK pathway mutations during therapy.

The fact that Foundation's test pinpointed mutations missed by tissue biopsy raises an interesting point. It will be tempting for Roche investors to take this as evidence of the blood test's superior sensitivity, but if tissue testing is the gold standard these could be regarded as failures of specificity.

Promising though these data are, they will not be used to support the approval submission for the blood test, says Siraj Ali, senior director of clinical development at Foundation Medicine.

"We have a forthcoming version of the liquid biopsy test that has been granted breakthrough device status by the FDA," he told *Vantage*. This version will need to undergo separate clinical trials specifically designed to

prove its worth to the FDA; Foundation will not say how far along these are, or whether an approval submission has yet been made.

“This could be the first FDA-approved liquid biopsy test,” Mr Ali says, though the company later clarifies that FoundationOne Liquid could be the first liquid biopsy approved that includes multiple companion diagnostics and genomic biomarkers, such as tumour mutational burden.

Burden of proof

Unlike the older version tested above, this newer form of the liquid biopsy is also capable of assessing tumour mutational burden (TMB), a marker that some have argued could predict response to checkpoint inhibitors.

The utility of TMB testing has yet to be proven. A recent study published in *Nature Genetics* suggested that high TMB was linked with improved survival in checkpoint inhibitor-treated patients with various cancers, though the TMB cut-offs associated with improved survival varied markedly between tumour types.

Additionally, a trial using Foundation’s blood test presented at last year’s Asco suggested that the biomarker might help predict response to Roche’s PD-L1 inhibitor Tecentriq in first-line non-small cell lung cancer. But these patients can receive Keytruda plus chemo as standard regardless of PD-L1 status, so there is no need to predict their response using TMB testing.

The AACR data concern the use of FoundationOne CDx, which works with tissue samples rather than blood. The assay was used on 14,867 breast carcinoma biopsies; PD-L1 status, detected with an assay developed by Roche’s Ventana subsidiary, was also available for 1,425 samples.

The trial found that PD-L1-positive and TMB-high (defined as more than 10 mutations per megabase) populations were not significantly co-occurrent, except among patients with very high TMB (those with more than 20 mutations per megabase).

The researchers also highlighted a single case report of a stage IIIb breast cancer patient with 40 mutations per megabase and negative PD-L1 status who had progressed on prior drug therapy and achieved durable complete response of more than a year with Opdivo plus chemo.

Correlation

Mr Ali was swift to acknowledge that data from a single patient did not amount to proof that TMB status correlated with survival.

“This patient is really representing the first observation of principle that, if we’re all very fortunate, may extend to a class of patients. But it’s certainly not definitive evidence,” he says.

It is not clear when such evidence might arrive. “There are a lot of efforts ongoing right now, certainly from us, and from large biotechs or pharmaceutical companies, looking at individual drugs and linkages to both tumour mutational burden and other predictors of immunotherapy efficacy,” Mr Ali says.

As the *Nature Genetics* paper points out, however, there is no one accepted definition of high TMB. Foundation Medicine used 10 mutations per megabase in its breast cancer study, but Guardant Health’s liquid biopsy has used 16 mutations per megabase in lung cancer patients (*Astrazeneca plays its tumour mutation burden card, December 13, 2018*).

The conclusion from these trials, as from so many, is that more research needs to be done. FDA approval of FoundationOne Liquid, should it arrive, will be an important validation of liquid biopsy technology. It might also give doctors a reason to use Foundation’s test specifically, possibly giving the company – and its parent, Roche – a sales boost.