
Article:
Jones, R.P. orcid.org/0000-0001-5608-001X, Lee, L.Y.W., Corrie, P.G. et al. (2 more authors) (2023) Individualized cancer vaccines versus surveillance after adjuvant chemotherapy for surgically resected high-risk stage 2 and stage 3 colorectal cancer: protocol for a randomized trial. British Journal of Surgery, 110 (12). pp. 1883-1884. ISSN 0007-1323

https://doi.org/10.1093/bjs/znad332

A randomized clinical trial of Individualised Neoantigen Specific mRNA Vaccine versus surveillance after adjuvant chemotherapy for surgically resected high risk stage 2 and stage 3 colorectal cancer

Robert P. Jones, Lennard W. Lee, Pippa Corrie, Sarah Danson, Dale Vimalachandran

Colorectal cancer remains a major cause of death, accounting for around 9% of global cancer mortality.[1] Surgery is the primary curative treatment, with adjuvant cytotoxic chemotherapy offered to reduce recurrence and improve long term survival. However, which patients receiving adjuvant chemotherapy truly benefit from it remains unclear. The role of circulating tumour DNA (ctDNA) in selecting patients for adjuvant chemotherapy is increasingly recognised. The GALAXY trial reported that patients with detectable ctDNA 4 weeks after primary colorectal surgery had a much higher recurrence risk (hazard ratio (HR) 10.0, $P < 0.0001$) and detectable ctDNA was the most significant prognostic factor associated with disease recurrence (HR 10.82, $P < 0.001$).[2]

Cancer vaccines offer an innovative approach to reducing recurrence after surgery by driving anti-tumour immune response, promoting tumour infiltrating lymphocytes (TIL) into residual disease, targeting cells expressing the relevant tumour antigens. Development of messenger RNA (mRNA) vaccine technology surged during the COVID pandemic. The BioNTech iNEST (Individualized Neoantigen Specific Immunotherapy) platform builds on these advances by taking resected tumour tissue and performing whole exome sequencing before generating bioinformatically predicted and ranked neoantigens specific for an individual patient's cancer.[3] Bespoke mRNA vaccine is delivered in a uridine-lipid envelope, preferentially taken up by dendritic cells with cancer antigens synthesisedand expressed via MHC class 1 & 2 receptors. CD8+ and CD4+ calls are then activated via TLR7 and TLR8, driving an immune reaction specific to the individual patient's cancer. These personalised vaccines can be generated within 9 weeks of specimen collection and integrated into complex surgical and oncological patient pathways.[4]

Colorectal cancer is classically an immune-cold cancer, limiting the impact of novel immunotherapies in all but a minority of cases and is potentially an attractive setting for vaccine technology. Secondary prevention in the adjuvant setting makes sense, since more advanced cancers may be more challenging, show marked immune system dysregulation and antigen variation between metastatic clones.[5]

BNT-122-01 is the first of a series of clinical trials being rolled out across UK sites as part of a national partnership brokered by the Department of Health and Social Care and entering the National Institute of Health and Care Research (NIHR) portfolio. The NIHR Vaccines Innovation Pathway is supporting its delivery. The primary objective of the BNT-122-01 randomised phase II trial is to see whether the addition of iNEST mRNA vaccines improve disease-free survival in high-risk stage 2 & stage 3 R0 resected colorectal cancer treated with adjuvant chemotherapy as standard of care. Secondary endpoints will include overall survival and change in ctDNA status during treatment. Patients with MSI-high tumours or who have received neoadjuvant chemo/radiotherapy will not be eligible. The study is open in 90 sites around the world, with 13 in the United Kingdom, aiming to randomise164

patients. Although a seemingly modest recruitment target, the study has 3 screening steps prior to randomisation. Real world data suggests around 6% of patients entering screening will reach randomisation, suggesting a screening target of around 2750. Interim analysis for futility will take place after 50 events, with final analysis after 124 events in total.

A multi-step consent process ensures is the study concept, risks and potential benefits are explained in a coherent and stepwise approach. Initial consent is for a blood test to check for ctDNA positivity after surgical resection and before start of adjuvant chemotherapy. Routine adjuvant chemotherapy (lasting 3-6 months) is then started within 8 weeks of surgery, as per standard of care. Whilst the patient is on chemotherapy, those who are ctDNA positive are further consented for DNA retrieval from their surgical specimen to be used for vaccine production. At the end of chemotherapy, a baseline CT scan is performed and eligible patients who remain disease-free on imaging are then consented a final time for randomisation. Those randomised to vaccine will then receive mRNA vaccine starting 7 weeks after finishing chemotherapy. The vaccine is delivered as a 2ml intravenous injection, and each patient will receive 15 doses. Patients in both arms of the study will then undergo CT surveillance every 3 months until either disease recurrence or the end of trial (48 months after final randomisation).

Surgeons are playing a pivotal role in the success of this study, leveraging established clinical referral networks between surgical and oncology teams, developing a hub and spoke model, with multiple surgical sites (the spokes) feeding into regional vaccine delivery hubs. Surgical teams discuss the trial with patients before surgery, and provide them with digital patient information in the form of animations and patient-facing websites in their post-operative visit, and perform an eligibility check before referring on to the trial site. Consent to phase 1 screening and ctDNA testing will then be performed by trial site research staff ahead of the patient's initial appointment with the oncologist.

The study is also functioning as a pilot for the NHSEngland Cancer Vaccine Launchpad (CVLP) – a platform designed to accelerate the development of personalised cancer vaccine treatments by providing a defined and expanded standard of care pathway for tumour molecular analysis and sequencing, incorporating elements of the NHS Genomic Medicine Service, as well as reducing redundancy and repetition in research infrastructure. Phase 1 of the CVLP will support identification and recruitment of eligible patients from sites that aren't part of a hub-and-spoke network of BNT-122-01 trial sites, by screening and referring patients on to trial teams for those that are potentially eligible. This model aims to enhance patient access to novel trials, promoting equity of access across the UK.

It is anticipated that the findings from BNT-122-01 will determine the role of mRNA personalised vaccines in resected stage 2/3 colorectal cancer, and will inform future national and international guidelines for the management of these patients. As the first randomised trial of this novel anticancer approach, BNT-122-01 will also provide key feasibility data for the national CVLP, creating opportunities for programme expansion across multiple cancer types in the very near future.