Code of practice needed to ensure good use is made of tissue samples donated by clinical trial participants

Clinical trials provide the opportunity to collect biological samples for translational research in a defined patient population with uniform and detailed follow-up. In the past these have defined the target patient populations for treatment with targeted treatments and immune modulating agents across multiple tumour types[1,2] including breast cancer[3]. The DCARE trial was a placebo-controlled phase III randomised trial of adjuvant denosumab in 4509 women with stage II/III breast cancer, sponsored and funded by Amgen with trial oversight provided by an academic trial steering committee (TSC), a biomarker subcommittee and an independent safety committee. All trial participants were invited to donate primary tumour and serial blood samples for subsequent translational research. Table 1 summarises the remarkably rich resource of >80,000 biological samples that were collected, shipped and stored at biorepositories either owned or funded by Amgen.

The trial failed to achieve both its primary and key secondary endpoints with the results presented in 2018[4] and published in 2020.[5] Once the efficacy results were known, Amgen mandated that all patients discontinue study medication, stopped trial related follow-up and closed the study in 2019. The TSC accepted the decision to terminate the study but, along with the biomarker sub-committee, requested that the biological materials be retained, both to try and identify a potential biological sub-group that may have benefited from study treatment as well as to address more general questions about breast cancer biology. Amgen raised concerns about the costs of sample storage and curation but agreed to consider transfer of the samples to an independent public biobank.

In late 2018, negotiations were initiated with the charity, Breast Cancer Now (BCN) who fund an independent academic tissue bank. Contractual arrangements for the possible transfer of samples from Amgen to BCN were initiated but were complicated by data sharing agreements and intellectual property concerns such that little progress was made throughout 2019 and were then paused due to the Covid-19 pandemic. In September 2020, we requested an update from Amgen who replied that negotiations were "delayed by the pandemic" with no additional information provided.

In September 2021 we again requested an update of progress when it came to light that the transfer of samples from Amgen to BCN was to be limited to a small subset of around 410 tumour blocks and matching cell pellets with a focus on young patients and those with triple negative breast cancer. We were informed that, as far back as early 2019, BCN had indicated to Amgen that they were only interested in taking ownership of specific tumour tissue samples but this decision was not communicated by Amgen to either the TSC or the biomarker sub-committee. Discussions were reactivated with Amgen to try and find a solution to ongoing storage of the remaining samples, only for Amgen to admit that they had made a unilateral decision in 2019 to destroy all the serial blood samples and unstained slides without discussing their intentions with either the TSC or the biomarker sub-committee.

We believe that trial sponsors have a responsibility to make the best use of biological samples collected within the context of a clinical trial. Patients consented to use of their biomaterials believing as the patient information leaflet indicated "*Your tumour tissue samples will be used to help identify genes and other markers that may enhance our understanding of the cancer"* and thus expected good use to be made of their generous donations. The decision by Amgen to destroy the samples completely breaks faith with both the study patients and the investigators who diligently collected, processed and shipped the samples.

Ownership of patient samples is somewhat unclear and the remit of biomarker or translational trial committees poorly specified. Unlike the regulations governing the retention of clinical trial records,

there is no code of practice regulating how long patient samples should be retained or detailing the responsibility of the trial Sponsor in management of biological samples. We urge the international oncology community to address this important issue. With this in mind the signatories are establishing a working group supported by appropriate expertise from within the European Organisation for Research and Treatment of Cancer (EORTC), the National Cancer Research Institute (NCRI), the Breast International Group (BIG) and patient advocates to define minimum standards for retention and curation of biological samples and a model transfer agreement that avoids complex data access and restrictive intellectual property requirements for sponsors to use when transferring samples to an independent biorepository.

735 words

Professor Robert Coleman, University of Sheffield, Sheffield, UK - DCARE Chief Investigator and Co-chair of Trial Steering Committee

Professor Arlene Chan, Curtin University, Perth, Australia - DCARE Investigator and Co-chair of Trial Steering Committee

Professor Carlos Barrios - Centro de Pesquisa em Oncologia, Hospital São Lucas, PUCRS, Porto Alegre, Brazil - DCARE investigator, member of Trial Steering Committee and Latin America Cooperative Oncology Group

Professor David Cameron, University of Edinburgh, Edinburgh, UK. - Chair, Breast International Group

Professor Luis Costa - Hospital de Santa Maria, Lisbon, Portugal - Member of the DCARE Biomarker Sub-committee

Professor Carsten Denkert, Philipps University of Marburg, Germany - Chair of DCARE Biomarker Sub-committee

Professor Mitch Dowsett, Emeritus Professor Institute for Cancer Research and Honorary Clinical Scientist, Royal Marsden Hospital, London, UK.

Professor David Harrison, University of St Andrews, St Andrews, UK - Immediate past-chair of National Cancer Research Institute Cellular Molecular Oncology Initiative (NCRI CMPath)

Professor Anthony Howell – University of Manchester, Manchester, UK - DCARE Data Monitoring and Safety Committee member

Professor Denis Lacombe, European Organisation for Research and Treatment of Cancer (EORTC) Data Centre, Brussels, Belgium - EORTC Director

Mairead MacKenzie, Secretary of Independent Cancer Patients' Voice, UK

Professor Miguel Martin - Hospital General Universitario Gregorio Marañón, Madrid, Spain - DCARE Investigator, member of Trial Steering Committee and on behalf of the Spanish Breast Cancer Research Group (GEICAM)

Professor Stuart McIntosh, Queen's University, Belfast, Northern Ireland - Chair, NCRI Breast Cancer Study Group

Adrienne Morgan, Chair of Independent Cancer Patients' Voice, UK

1. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016; 375:1823.
2. Seymour MT, Brown SR, Middleton G et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol. 2013 Jul;14(8):749-59
3. Andre F, Ciruelos E, Rubovsky G et al. Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med 2019; 380, 1929-1940.
4. Coleman RE, Finklestein D, Barrios C et al. Adjuvant denosumab in early breast cancer: First results from the international multicenter randomized phase III placebo-controlled D-CARE study J Clin Oncol 2018; 36, (suppl), abstr 501
5. Coleman R, Finkelstein DM, Barrios C, et al. Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2020; 21(1):60-72.

Table 1: Number and timing of samples collected within context of DCARE trial

Biomarker type	**Baseline**	**3 months**	**6 months**	**9 months**	**12 months**	**Year 2**	**Year 3**	**Other samples**
Tissue blocks	909							236 on study 37 recurrences
Unstained slides	2526							519 on study
Cell pellets for DNA isolation	3707	3656	3600	3622	3541	3460	2725	177 recurrences
Serum	4230	4092	4012	3977	3869	3770	3130	191 recurrences
Plasma	4229	4080	3998	3963	3865	3769	3122	192 recurrences