Histology independent drug development - Is this the future for cancer drugs?

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DOI:
10.1016/j.ctrv.2023.102674

Cancer Treatment Reviews 123 (2024) 102674

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Hot Topic

Histology independent drug development – Is this the future for cancer drugs?

Lucinda Billingham [a], Lynn Brown [b], Theodor Framke [c], Alastair Greystoke [d], Eivind Hovig [e,f], Siddhartha Mathur [b], Philippe Page [g], Elias Pean [h], Sahar Barjesteh van Waalwijk van Doorn-Khosrovani [i,j], Richardus Vonk [k], Sacha Wissink [l], Hilke Zander [m], Ruth Plummer [d,*]

[a] Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Sciences, University of Birmingham, UK
[b] Oncology Division, Merck & Co., Inc., Rahway, NJ, USA
[c] European Medicines Agency, Amsterdam, The Netherlands. Institute for Biostatistics, Hannover Medical School, Hannover, Germany
[d] Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne NE2 4HH, UK
[e] Centre for Bioinformatics, University of Oslo, P.O. Box 1080 Blindern, 0316 OSLO, Norway
[f] Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, PO Box 4950 Nydalen, 0424 Oslo, Norway
[g] Human Colossus Foundation, Switzerland
[h] European Medicines Agency, Amsterdam, the Netherlands
[i] National Funder's Committee for Evaluation of Specialised Medicines and Companion Diagnostics (CieBAG), the Netherlands
[j] Department of Oncology, Leiden University Medical Centre The Netherlands CZ, Postbus 90152, 5000 LD, Tilburg, the Netherlands
[k] Bayer AG 13342 Berlin, Germany
[l] Merck Sharpe Dohme, the Netherlands
[m] Paul-Elrich Institut, Germany

ARTICLE INFO

Keywords:
Cancer trial
Histology independent
Tumour agnostic
Biomarker
Data sharing

ABSTRACT

The Cancer Drug Development Forum (CDDF)'s 'Histology independent drug development – is this the future for cancer drugs?' workshop was set up to explore the current landscape of histology independent drug development, review the current regulatory landscape and propose recommendations for improving the conduct of future trials.

The first session considered lessons learnt from previous trials, including innovative solutions for reimbursement. The session explored why overall survival represents the most valuable endpoint, and the importance of duration of response, which can be captured with swimmer and spider plots.

The second session on biomarker development and treatment optimisation considered current regulations for companion diagnostics, FDA guidance on histology independent drug development in oncology, and the need to establish cut-offs for the biomarker of tumour mutational burden to identify the patients most likely to benefit from PDL1 treatment.

The third session reviewed novel trial designs, including basket, umbrella and platform trials, and statistical approaches of hierarchical modelling where homogeneity between study cohorts enables information to be borrowed between cohorts. The discussion highlighted the need to agree 'common assessment standards' to facilitate pooling of data across studies.

In the fourth session, the sharing of data sets was recognised as a key step for improving equity of access to precision medicines across Europe. The session considered how the European Health Data Space (EHDS) could streamline access to medical records, emphasizing the importance of introducing greater accountability into the digital space.

In conclusion the workshop proposed 11 recommendations to facilitate histology agnostic drug development.

* Corresponding author at: Translational and Clinical research Institute, Newcastle University, Newcastle Upon Tyne NE2 4HH, UK.
E-mail addresses: L.J.Billingham@bham.ac.uk (L. Billingham), lynn.may.brown@merck.com (L. Brown), theodor.framke@ema.europa.eu (T. Framke), Alastair.greystoke@newcastle.ac.uk (A. Greystoke), ehovig@ifi.uio.no (E. Hovig), siddhartha.mathur@merck.com (S. Mathur), philippe.page@humancolossus.org (P. Page), elias.pean@ema.europa.eu (E. Pean), sahar.van.waalwijk@cz.nl (S. Barjesteh van Waalwijk van Doorn-Khosrovani), richardus.vonk@bayer.com (R. Vonk), sacha.wissink@merck.com (S. Wissink), hilke.zander@pei.de (H. Zander), ruth.plummer@ncl.ac.uk (R. Plummer).

https://doi.org/10.1016/j.ctrv.2023.102674
Received 30 October 2023; Received in revised form 18 December 2023; Accepted 21 December 2023
Available online 23 December 2023

Introduction

This White Paper has been developed following the Cancer Drug Development Forum (CDDF)'s 'Histology independent drug development – is this the future for cancer drugs?' workshop, which took place on 14-15th November 2022, in Amsterdam.

The aim of the hybrid meeting, which brought together 141 participants (both in person and remotely) was to understand the current landscape of histology independent drug development, discuss suitable trial design to deliver tumour-type agnostic drugs, develop an understanding of biomarker development and understand their potential and the regulatory environment surrounding such approvals.

The terms histology-independent, tumour-agnostic, and tissue-agnostic drug, refer to a drug that targets (a) specific molecular alteration (s) across multiple cancer types as defined by organ, tissue or tumour type [1]. These terms are used synonymously and for simplicity histology independent is commonly used throughout the article.

A histology independent oncology drug can therefore be used to treat multiple types of cancer carrying the same molecular alterations. The molecular alterations involved include a wide array of molecular changes in DNA, RNA, or proteins, including point mutations, gene fusions, mutational load, antigen or neoantigen burden, epigenetic changes, and protein over or under-expression.

There are some advantages to this strategy, histology-independent approaches can speed up a drug's development, reduce cost and importantly provide early access to novel agents to patients with rare cancers. It allows targeting of key biology parameters regardless of tumour type. The increasing use of large gene panel testing (both on tumour and cfDNA) means that appropriate patient populations can be identified.

In comparison to traditional drug development, where treatment is based on tissue of origin, development of histology independent drugs raises however new challenges. Concerns towards such development include whether the same aberrations in different histologies have similar biological functional and pathological significance; whether common endpoints can be used when each tumour type is likely to have a distinct natural history and different standard of care options, and whether primary drug resistance mechanisms still depend on histology and cellular lineage [2].

Additionally, randomised clinical trials for histology independent drugs are difficult to conduct as only small numbers of patients carry a particular genetic aberration in a specific tumour type. Furthermore, historical data are often not available to compare treatment outcomes of the investigated drug to conventional treatment, as earlier studies have not always taken the genetic profile of tumours into account [3].

Nevertheless, the rationale for the biomarkers and development of such and therapeutic agents needs to be supported by robust clinical trials data that can be translated into clinical decision making.

Lessons learned from previous trials – Successes and failures

The Food and Drug Administration (FDA) has approved seven agents for tumour-agnostic treatment, starting in 2017 with pembrolizumab for patients with cancers that have microsatellite instability (MSI-H). Larotrectinib followed in 2018 for patients harbouring NTRK fusions, entrectinib in 2019 (again for NTRK fusions), dostarlimab in 2021 for adult patients with mismatch repair deficient (dMMR) solid tumors (loss of a mismatch repair protein as determined by the FDA approved immunohistochemistry assay), dabrafenib and trametinib in solid tumours with BRAF V600E tumours (except in colorectal cancer) and in 2022 selpercatinib for solid tumours with RET fusions.

While more cautious to accept tumour-agnostic treatments, the European Medicines Agency (EMA) approved larotrectinib in 2019, followed by entrectinib in 2020.

Tumour-agnostic drugs are not necessarily equally effective in all cancers bearing the same mutation. Although the BRAF inhibitors vemurafenib, dabrafenib, and trametinib have been approved for treating BRAF-mutated metastatic melanoma, these drugs only showed a 5 % response rate when used as monotherapy in a phase II BRAF-mutant colorectal cancer study due to upregulation of EGFR signalling [4]. "The contrast of activity from BRAF inhibition in melanoma and CRC has been an important cautionary tale for the trend toward tumour-agnostic, oncogene defined basket clinical trials," write the study authors [5].

Explanations for such disparate effects come from colon cancer studies showing that BRAF(V600E) inhibition causes a rapid feedback-activation of epidermal growth factor receptor (EGFR), supporting continued proliferation in the presence of BRAF (V600E) inhibition. Melanoma cells, unlike colon cells, express low levels of EGFR and are therefore not subject to such feedback activation [6].

A second example of different tumours showing a range of activity comes from the phase II KEYNOTE-158 study in233 patients with 27 tumour types displaying deficient DNA mismatch repair (dMMR) with high microsatellite instability (MSI-H). The study found that pembrolizumab demonstrated high response rates and median PFS in endometrial and most gastric cancers, lower response rates in pancreatic and ovarian cancer, and no observed responses in brain cancer. Results for the latter two tumour types should however be interpreted with caution as there were fewer patients enrolled with ovarian and brain cancer [7].

Biomarkers may be used to help determine which patients respond better, using tumour mutational burden (TMB) as a predictor of response. A study of 22 patients with colorectal cancer and MSI-H treated with PD-1/L1 check point inhibitors found that those with the highest TMB did significantly better than those with lower TMB, with the optimal predictive cut-point for TMB (present in around 30 % of patients) estimated between 37 and 41 mutations/ MB [8].

With studies demonstrating that not all patients benefit equally from targeted therapies, payers have expressed concerns in reimbursing off-label indications. Issues have therefore arisen from unequal access to treatment and the lack of systematic collection of outcomes when patients are treated off-label.

In the Netherlands, the Drug Access Protocol (DAP), developed by oncologists, insurers, and the healthcare public institute, provides an innovative solution for authorised indications of cancer drugs when there is uncertainty regarding their real-world benefit [9]. The reimbursement scheme in DAP, known as 'personalised reimbursement' is similar to a scheme that was rolled out earlier in the Netherlands for Drug Rediscovery Protocol (DRUP), an adaptive platform trial for repurposing cancer drugs. This scheme involves pharmaceutical companies funding the medication for 16 weeks, then if patients show benefit (stable disease, partial or complete response) they are moved from trial medication to commercial medication reimbursed by health insurance companies [10 3]. Both DAP and DRUP enable early access to potentially promising treatments providing controls on overspending of the healthcare budget while at the same time generating evidence to support future reimbursement. The DRUP trial has recently provided the evidence required by the Dutch HTA body to fully reimburse nivolumab for dMMR- or MSI-H tumours, independent of histology, in cases where these patients do not have any other treatment options [11].

As with all oncology studies, overall survival (OS) is considered the most valuable endpoint. As an example, the phase 3 ARIEL4 study demonstrated that progression free survival (PFS) may not always predict OS benefit. In ARIEL4, primary analysis of median PFS supported rucaparib as an alternative treatment to standard of care chemotherapy in relapsed BRCA1-mutated or BRCA2-mutated ovarian carcinoma - median PFS was 7.4 months for rucaparib vs 5.7 months for chemotherapy (HR 0.67 [95 % CI 0.52–0.86]; p = 0.0017) [12]. However, the final OS results showed that median OS favoured the chemotherapy control arm (19.4 months in the rucaparib arm vs 25.4 months in the chemotherapy arm (HR 1.31 [95 % CI:1.00, 1.73] p = 0.0507) [13]. As a result, the EMA recommended that rucaparib should no longer be used as third-line treatment for cancers of the ovary, fallopian tubes or

peritoneum [14]. In the US, after discussion with the FDA, Clovis Oncology announced a voluntary market withdrawal of rucaparib for treatment of BRCA-mutated ovarian cancer after two or more chemotherapies [15].

The EMA representative suggests that for a drug to be considered for histology independent approval it requires:

- a good understanding of the mechanism of action of the drug
- a strong mechanistic rationale to support the homogenous treatment effect
- pre-clinical data and pharmacodynamics, biological plausibility of the biomarker
- a good knowledge of potential resistance linked to other oncogenic drivers or mutations.

The low prevalence/rarity of target alterations have led to difficulties with performing randomised controlled trials (RCTs). When RCTs are not feasible in the whole population regardless of tumour type, an RCT could be conducted in one tumour type and complemented with uncontrolled trials in the remaining tumour types.

It was also acknowledged that where the EMA has not considered data to be comprehensive, they awarded conditional marketing approval such as Larotrectinib based on a study of 93 patients with 14 tumour types, 72 % response rate across tumour types. However, in some cases, trials may also be evaluated according to tumour type. For example, pembrolizumab was approved in CRC, endometrial, gastric, small intestine and biliary cancer, but not in pancreatic cancer due to a lower ORR of 18.2 %. Additionally, further data on gastric, biliary, and small intestine cancers from KEYNOTE-158 were requested post approval.

The **discussion** considered how greater emphasis should be awarded to the duration of response rather than just the magnitude of response, and the fact that duration can be captured by introducing methods such as swimmer plots and spider plots (as opposed to waterfall plots).

The disadvantage of waterfall plots (where each vertical bar represents an individual patient's tumour response) is provision of static information that only reports on patient 'best response'. In contrast, by introducing clear symbol legends, swimmer plots can overlay the patient's bar with multiple information elements allowing sponsors to determine which patients achieved longer durations of response. Similarly, spider plots can highlight changes in tumour burden over time relative to baseline.

In all cases, the ability to rank patients based on response allows for identification and characterisation of exceptional responders versus normal responders, which ultimately provides additional opportunities to characterise responders to inform later drug development.

Biomarker development and optimisation

For the first time, the **InVitro Diagnostic (IVD)-Regulation 2017/746 (IVDR)**, which came into effect May 2022, defined a companion diagnostic (CDx) as "a device which is essential for the safe and effective use of corresponding medicinal products to a) identify before and/or during treatment patients who are most likely to benefit from the corresponding medicinal product (MP), or (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.".

As a result of CDx being classified as a class C device, conformity assessments are undertaken by Notified Bodies (NBs); this results in two separate processes taking place in Europe for the approval of medicinal products and the CE certification of the CDx. Additionally, the MP and the CDx are usually not linked by the EMA's summary of product characteristics (SmPC), in contrast with the US where the CDx and medicinal product can be co-approved and linked by full prescribing information.

In Europe, interactions occur between the two independent pathways, with the analytical performance of an assay requiring evaluation prior to biomarker-based patient selection for trials or starting pivotal phase 3 trials of the medicinal product, where cut-off confirmations and predictive power evaluations can be assessed. Confirmatory prospective randomised trials are important to distinguish between prognostic and predictive values. Other important considerations include adequate quality of tumour material and liquid biopsies, the use of central testing to deliver reliable data and the establishment of prespecified biomarker cut-off levels or variant classification for mutation-based assays. Importantly, pivotal phase 3 trials evaluating predictive values of biomarkers can also serve as performance studies for the CDx development.

At the time of marketing authorisation, it is important (although not compulsory) for NBs to have finalized their conformity assessments otherwise the CDx would not be available for testing patients. For the conformity assessment additionally, a consultation procedure is required between EMA and NBs prior to the CE certification of aCDx.

The draft FDA guidance "**Tissue Agnostic Development in Oncology**", issued October 2022, represents the first regulatory guidance to have been issued by any health authority [1]. The guidance states that even though it may be necessary to generalize treatment effects from high to low prevalence tumours with the same molecular alterations, it is important to assess potential response differences. The guidance highlights how dose justifications may be required for specific toxicity, e.g. drugs with hepatoxicity may require lower doses for patients with hepatocellular carcinoma (HCC) when used for a histology independent indications. The FDA states willingness to accept single arm histology independent studies to support full approval in patients with advanced metastatic cancers if results are clinically meaningful, accepting the justification that conducting randomised trials in multi tumour settings can be challenging due to differences in standard of care control arms across tumour types. The guidance further states that tissue agnostic clinical studies may enable or expedite development of therapies for rare cancer types where it may not be feasible or practical to conduct clinical trials in each rare cancer with the same molecular alteration.

While pre-clinical pharmacology studies should include cell lines from cancers of different origins, the FDA feels there is no need to conduct such studies in all tumours considered for tumour-agnostic development programmes. They raise the possibility of using data from different drugs with the same molecular action that has been studied in tumours with the same molecular alterations.

Diagnostic considerations highlighted include the need for both tissue agnostic CDx and clinical studies to provide sufficient evidence of performance across a number of tumour types. Analytical validation of CDx tests for a tumour agnostic claim is challenging given that the scoring method/algorithm/cutoff needs to work across tumours. Additionally, sourcing samples, especially in tumour types with low biomarker prevalence can be time and resource intensive. Finally, post marketing commitments for diagnostic development may be imposed, as occurred in the case of pembrolizumab, for its dMMR/MSI-H solid tumour indication, an immunohistochemistry-based diagnostic was requested for identification of dMMR and a nucleic acid based CDx for identification of MSI-H solid tumour patients.

Tumour mutational burden (TMB), defined as the number of somatic mutations per megabase of interrogated genomic sequence, has been used as a biomarker to determine which cancer patients are more likely to respond to immune checkpoint inhibitors. For TMB, different companies worked independently to optimise TMB levels for their specific therapies, with each setting different cut-off points for a tissue-agnostic drug assessment.

A comprehensive review of publicly available studies using PDL1/PD-L1 inhibitors in a range of tumours showed that the response rate of patients with TMB high tumours was significantly better than those with TMB low tumours. To identify the most appropriate cut-off level, a pooled analysis was undertaken across 1732 patients with 15 different

types of cancer treated with immune checkpoint inhibitors. The results showed that using TMB $\geq$ 10 mut/Mb as the cut-off allowed identification of more patients for whom benefit could be achieved than a cut-off of TMB $\geq$ 15 mut/Mb.

A second issue identified was the need to harmonise assays using common reference standards to facilitate their alignment. An analysis of a range of TMB levels by 15 different laboratories showed high variability. Assay alignment can be achieved using a three-stage process involving *in silico* models, then cell lines and finally clinical samples.

To increase the understanding of biomarkers, Foundation Medicine (the company who provides genomic testing to US cancer patients) have collaborated with Flatiron (who provide longitudinal patient data) to provide real world outcomes for patients undergoing biomarker testing. The partnership is exploring biomarkers associated with the potential to mount an immune response and looking at resistance mechanisms.

Data presented at the Society for Immunotherapy of Cancer's meeting in Boston in 2022 demonstrated that combining three signatures was better at predicting OS in lung cancer patients treated with immunotherapy than individual biomarkers.

Biomarker companies are exploring possibilities to expand their platforms to address prognosis and uncover resistance mechanisms in earlier stage disease.

Monitoring circulating tumour DNA spread into the blood stream, for example, can be used to investigate response to therapy or risk of recurrence. Foundation Medicine has developed a tumour informed approach, the FoundationOne® tracker, optimising algorithms to identify patient-specific variants and a personalised assay design allowing detection of circulating tumour DNA (ctDNA) in plasma.

In the PREDATOR study in metastatic CRC, they showed that patients with ctDNA in comparison to those without ctDNA had significantly worse DFS (HR:4.97; $p < 0.001$) and OS (HR 27.05; $p < 0.0001$) [16].

For patients without initial tissue baselines, FoundationOne has developed the Confera DX monitoring assay using low pass whole genome sequencing to assess global copy number changes and methylation patterns as a proxy for ctDNA levels over time. The approach can be used in situations where TMB is not high enough or where tissue baseline material is not accessible.

The **discussion** highlighted the detrimental effects of NBs not being permitted to provide companies with advice. Other challenges in Europe include the wide range of players involved (EMA, NBs and pharmaceutical companies and manufacturers) and the need to reach a decision during the EMA-NB consultation within 60 days.

If local testing is undertaken early in biomarker development, it is important to retain samples so they can be used to test the CDx. Not surprisingly, levels of validation needed for biomarkers were considered less for initiating clinical trials than for achieving marketing authorisation.

Trial design – Basket or umbrella for optimal progress?

Development of molecularly guided therapies has led to the need for novel trial designs with the potential to accelerate drug development and enable patients to get timely access to transformative therapies. Basket, umbrella, and platform trial designs (sometimes collectively referred to as master protocols) have been developed to allow testing of one or more hypothesis within a protocol to accelerate drug development [17].

Basket trials are used to evaluate a single investigational targeted drug (or drug combination) in multiple populations, usually defined by different histologies, that all have the same molecular driver which the drug targets. They can be thought of as multiple independent sub-trials within the basket, allowing the treatment effect in each histology to be considered separately, or the treatment effect can be evaluated across the whole basket. Basket trials frequently have a single arm design with overall response rate used as the primary endpoint [17].

Umbrella trials are used with a single disease or target population stratified into different biological actionable pathways treated with specific therapies. An umbrella trial can be viewed as a logistical tool enabling multiple questions to be addressed within a single protocol [17].

Platform trials (also referred to as multi-arm, multi-stage design trials) may include elements of both umbrella and basket trial design. The protocol is dynamic, rather than fixed, with pre-specified adaption rules allowing dropping ineffective interventions with flexibility to add in new interventions during the trial. Platform trials may be used to provide an additional opportunity for a controlled trial (arms may not be concurrent). However, platform trials have yet to find their place in marketing authorisation applications.

The first successful example of such a complex trial is the Drug Rediscovery Protocol (DRUP) trial, launched by Netherlands Cancer Institute in 2016, where cancer patients who have exhausted standard treatment options, are treated off-label with registered targeted therapies and immune checkpoint inhibitors based on molecular tumour profiles. In DRUP, investigators have agreed on a common set of standards, including recording response at 12 weeks, to enable pooling of data across cohorts. Conformity of approach allows data sharing across countries, leading to increased power, with the Personalised Cancer Medicine for all EU Citizens initiative building towards this [18].

A second example is the DETERMINE trial, which opened in November 2022, and represents an example of an adaptive, umbrella basket platform trial. The study, coordinated by the Cancer Research UK Centre for Drug Development, is enrolling patients with identifiable genetic alterations that can be targeted by treatments already approved for use in other cancer types. DETERMINE has established a joint protocol for childhood, teenage and adult patient populations. Currently five different mutations are being addressed by five different targeted agents on the platform, with each of the five containing baskets of different cancer types, and age groups. In the first instance, Roche has provided the targeted therapies to be evaluated with additional pharmaceutical partners expected to contribute agents as the trial advances [19].

Statistical power can be gained in basket trial designs through the method of analysis. When evaluating the effectiveness of a single drug in a basket of different histologies that share the same molecular driver, hierarchical modelling is an efficient form of analysis. In this approach, rather than evaluating the treatment effect in each histology separately, we consider the histologies as sub-populations of the whole basket, such that the estimate of the treatment effect in any one histology borrows data about the treatment effect on the other histologies in the basket. Such an approach can be problematic if the effect is not homogenous across the sub-populations.

The Accelerating Clinical Trials in the EU (ACT-EU) initiative, launched in January 2022, aims to develop the European Union as a focal point for clinical research and promote the development of high quality, safe and effective medicines and better integrate clinical research into the European health system [20].

ACT EU, co-led by the European Commission (EC), Heads of Medicines Agencies (HMA) and the EMA, builds on the momentum of the Clinical Trials Regulation and CTIS. The ACT EU strategy paper lists six objectives, including the need to provide specific support for trials addressing unmet needs, rare diseases, and medicines for public health while also ensuring a European approach for trial processes and strategic matters at the international level. Furthermore, the document lists 10 priority actions, classified into four domains (governance and integration, engagement, methods and practices, and impact), with a particular focus on the need to 'develop and publish' key methodologies on complex trials.

'The Complex trials -Questions and answers document', published jointly in May 2022 by EC, HMA and EMA, aims to support sponsors, clinical trialists and applicants in different aspects of clinical trials including the analysis and interpretation of complex clinical trials under

EU Clinical Trials Regulation (EU CTR) [21].

The document poses seven questions covering the planning and conduct of complex trials, additional considerations for the design and conduct of master protocol studies, how to describe Bayesian approaches, considerations for planning and collection of data used as control, regulatory pathways to be considered when using biomarkers, considerations related to the safety, rights and wellbeing of participants, and transparency and communication between regulators, sponsors, and investigators. Selected highlights from the document, written by 25 experts from multiple disciplines across the regulatory network, include how to deal with operational complexities, the need to focus on clear and precise hypotheses and pre-specification, considerations on trial integrity, the need for cross-referencing and seamlessly interlinked sub-protocols that are free of inconsistencies. Use of graphical visualisations are encouraged in the cover letter. Outstanding issues such as Type I error control will be addressed in an upcoming reflection paper on platform trials as stated in the published concept paper [22].

The **discussion** highlighted limited knowledge around combining data from trials, with the need recognised for trialists to agree 'common assessment standards', such as undertaking response assessments at 12 weeks. While the DRUP, DETERMINE and other DRUP-like studies were recognised as 'ground-breaking', data sharing across studies needs to further optimised. Small populations may mean slow accrual particularly in rare tumour types, hence data sharing means that evidence of patient benefit can be quicker, cheaper and more robust, and allows evaluation of generalisability across different populations. It was mentioned that in some cases, Bayesian designs might allow use of external data to estimate priors although the appropriateness of this approach is a case-by-case basis. An additional challenge is that a large number of centres are needed to enrol sufficient patients with rare tumours. For efficiency purposes, both financially and to facilitate trial participation of patients being unwilling to travel, hybrid models are needed to facilitate decentralized trials. A multiplatform accrual and data-sharing is expected to speed up recruitment for rare tumours and reduce trial costs for each centre. At present, several countries have initiated or are preparing to launch a 'DRUP-like clinical trial' using the same protocol. The objective is to provide access to precision medicine and jointly gather data [23]. In addition, the EMA is exploring the use of Real World Data to contextualise data from single arm studies, although the randomised approach remains the preferred option.

The overall take home message was the need to improve performance of single arm trials, since this design does not match the evidence levels of a randomised trial. If patients do not wish to be randomised, platform trials may provide an opportunity for concurrent controls. Obtaining scientific advice is however highly recommended to discuss whether the evidence generated from a single arm trial can be considered acceptable for seeking marketing authorisation for a specific development programme.

Leveraging the potential of precision medicine: Ensuring equity of access to precision diagnostics and treatments for patients

Cancer mortality varies across Europe with one of the main causative factors being differences in per capita healthcare expenditures. The ensuing care gaps, both within and between countries, have adverse effects on survival, symptom burden, adherence to appropriate treatment plans, public trust in healthcare systems and screening uptake.

The European Cancer Inequalities Registry, a flagship initiative of Europe's Beating Cancer Plan, was created to provide reliable data on cancer prevention and care and identify trends, disparities and inequalities between member states and regions [24].

The initiative will compare mortality for specific tumours by stage and specific genetic types at the time of cancer diagnosis, with data including access to treatment and genetic tests and financial toxicity (both out of pocket payments and informal payments).

The rarity of different mutations targeted in trials has created the need to 'federate' data allowing small numbers of patients across different centres to contribute to building clinical data sets. Such collaborations between centres could be facilitated by introducing the FAIR data and tools approach, standing for:

- Findable, with data and materials enriched with metadata assigned with a unique identifier,
- Accessible, with data and metadata stored in a trusted repository with open and free protocols, that is accessible by machines and humans,
- Interoperable, with vocabularies and public domain ontologies, the metadata can be referenced and linked,
- Reusable, additional documentation and protocols describe the acquisition of data, licensed with a detailed provenance.

The European Health Data Space (EHDS), launched in May 2022 by the European Commission, combines rules, standards, practices, and infrastructures under a common governance framework. The EHDS concept is to streamline access to medical records for patients and allow researchers, policy-makers and companies to use and study patients' medical records after they receive a permit from one of the health data access body, which will be established in each member state. Information on the platform will include health data from mobile applications, medical devices, or registries, as well as electronic health records [25].

With a multitude of stakeholders having access comes the need to introduce accountability and data protection. Two proposals, currently being investigated, are the possibility to develop mechanisms to provide 'permanent identifiers' allowing detection of anyone transgressing data and 'decentralised semantics' [26] to harmonised data across multiple jurisdictions. Such approaches offer the potential to introduce governance, normally found in the real world, into the digital space. Challenges however remain as some data cannot be easily shared within one common repository, due to current ethical and legal constraints. In some cases, sharing by transferring analytical pipelines, rather than data, is a way to achieve some level of federation.

In the **discussion**, good data governance was considered vital, so that participants sharing data trust the curators. GDPR, it was felt, had not been designed with medical systems in mind, creating enormous challenges for data. The sharing of data sets was felt to be a key step needed to improve equity of access to precision medicine across Europe.

Recommendations

Lessons learned from previous trials – Successes and failures

- Not all cancers harbouring the same mutations have similar response rates. When outstanding response rates are reported there is a need to ensure that the data is not driven by a specific tumour type, and that consistency exists across tumour types.
- Overall survival represents the optimal endpoint, but in some situations may not be feasible, consequently a greater emphasis needs to be placed on duration of response, which can be captured with spider and swimmer plots.
- To inform later developments, both responders and non-responders should be fully characterised.

Biomarker development and optimisation

- A tissue agnostic CDx should provide sufficient evidence of performance across multiple tumour types.
- Paediatric cancer development plans should be included in tissue agnostic programmes.
- A system in Europe should be introduced formally linking the assessment of CDx and medicinal products, to be reflected in the MP prescribing information.

- Tissue agnostic clinical trials could expedite development of new therapies for rare tumours harbouring the same molecular alteration by it circumventing the need to investigate each rare tumour type individually.

Trial design – Basket or umbrella for optimal progress?

- When combining data in different cohorts there is a need to agree on common standards to allow data to be pooled.
- Statistical design and analysis of innovative trials is complex and needs expert input.
- Efforts are needed to ensure high levels of evidence and to improve the performance of single arm trials.

Leveraging the potential of precision medicine: Ensuring equity of access to precision diagnostics and treatments for patients

- Good data governance, based on data-centric technological architectures, is vital, with the need to introduce accountability into the digital space and secure the information as it moves between healthcare platforms.

Conclusions

Tumour histology independent cancer drug development can be appropriate and represents possibly the most expeditious way to develop agents targeting rare driver mutations, or specific tumour phenotypes. However, for such developments to be endorsed by regulators, it does require innovative trial designs with robust statistical plans, timely biomarker validation and implementation; there are also instances where tumour site sub-group analysis of the emerging clinical data remains appropriate. To maximise the potential benefits of this mode of clinical drug development, it is critical that well governed data sharing is enabled across Europe. In addition, ensuring equity of access across all patient groups in Europe remains a challenge to be addressed.

Workshop's programme

Day 1 – Monday 14 November 2022

SESSION 1: Lessons learned from previous trials - successes and failures

Session chairs: Ruth Plummer (CDDF, UK) & Jaap Verweij (CDDF, NL)

13:00–13:15 **Introduction / overview of successes**
Alastair Greystoke (Newcastle University, UK)
13:15–13:30 **Regulatory perspective**
Elias Pean (EMA, NL)
13:30–13:45 **Moving from experimental phase to evidence-based practice, a payer's perspective**
Sahar Barjesteh van Waalwijk van Doorn-Khosrovani (CZ, NL)
13:45–14:35 **Panel discussion**
Moderators: session chairs, Panelists: speakers + Dr Steven Lemery (FDA, US)

SESSION 2: Biomarker development and optimisation

Session chairs: Brian Simmons (Roche, US) & Sacha Wissink (MSD, NL)

15:00–15:15 **Scene-setting (in a forward looking way)**
Sid Mathur (MSD, US)
15:15–15:30 **Industry perspective**
Lynn M. Brown (MSD, US)
15:30–15:45 **Regulatory perspective**
Hilke Zander (Paul-Elrich Institut, DE)
15:45–15:55 **Break**
15:55–16:10 **Evolution of comprehensive genomic profiling in precision medicine**
David Fabrizio (Foundation Medicine, US)
16:10–16:25 **Biomarker harmonisation: TMB case study**
Jeff Allen (Friends of Cancer Research, US)
16:25–17:25 **Panel discussion**
Moderators: session chairs, Panelists: speakers

Day 2 – Tuesday 15 November 2022

SESSION 3: Trials design - basket or umbrella for optimal progress

Session chairs: Chitkala Kalidas (Bayer, US) & Alastair Greystoke (Newcastle University, UK)

10:00–10:05 **Introduction**
Session chairs
10:05–10:20 **Regulatory perspective**
Dr Theodor Framke (EMA, NL)
10:20–10:35 **Academic perspective**
Prof Lucinda Billingham (University of Birmingham, UK)
10:35–10:50 **Early phase side of drug development - Industry perspective**
Richardus Vonk (Bayer, DE)
10:50–11:40 **Panel discussion**
Moderators: session chairs, Panelists: speakers + Dr Steven Lemery (FDA, US)

SESSION 4: Leveraging the potential of precision medicine: Ensuring equity of access to precision diagnostics and treatments for patients

Session chairs: Bettina Ryll (MPNE, SE) & Olga Valcina (Onco Alliance, LV)

12:00–12:05 **Introduction**
Bettina Ryll (MPNE, SE)
12:05–12:20 **Why equality and quality matters**
Olga Valcina (OncoAlliance, LV, Deputy Director on Laboratory Matters, Institute of Food Safety, Animal Health and Environment "BIOR")
12:20–12:35 **Genomic standards**
Eivind Hovig (University of Oslo, NO)
12:35–12:50 **Distributed data governance - Addressing the precision public health dilemma**
Philippe Page (Human Colossus Foundation, CH)
12:50–13:15 **Panel discussion**
Moderators: session chairs, Panelists: speakers
13:15–13:20 **Farewell**
Jaap Verweij (CDDF, NL)

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Funding support

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors acknowledge writing support from Janet Fricker, and administrative support from the CDDF Office staff.

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