CDDF
Cancer Drug Development Forum

MEETING REPORT

CDDF Multi-Stakeholder Workshop

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

14 - 15 November 2022 Hybrid Workshop

Prepared by Ruth Plummer (CDDF Chairperson)

PROGRAMME COMMITTEE

Chair: Ruth Plummer (CDDF, UK)
Chitkala Kalidas (Bayer, US)
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Introduction

This was an interactive workshop with participants from academia, industry, and the regulators exploring the opportunities and challenges in histology independent cancer drug development.

Sessions over 2 half days discussed the successes and failures of previous trials in this area, explored trial design, and discussed biomarker development for patient stratification as well as patient.

The programme committee of Ruth Plummer (Chair) (CDDF board, UK), Chitkala Kalidas (Bayer, US), Brian Simmons (Roche, US), Sacha Wissink (MSD, NL) and Bettina Ryll (MPNE, SE) developed the workshop programme and speaker faculty to address these elements

The main learning objectives from the workshop were

- To understand the current landscape of tumour agnostic drug development
- To be able to discuss suitable trial designs to deliver such studies
- To develop an understanding of biomarker development and requirements for tumour agnostic registrations
- To understand the regulatory environment around these registrations

The workshop took place over 2 days on 14th and 15th November 2022, with 141 registrants and 34 participants present in person and 89 attending online for the duration of the workshop. The majority of participants were from United Kingdom and United States with additional attendees from multiple European countries.

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

Session chairs:

- **Ruth Plummer (CDDF, UK) & Jaap Verweij (CDDF, NL)**

Speakers:

- **Alastair Greystoke (Newcastle University, UK) Introduction / overview of successes**
- **Elias Pean (EMA, NL) Regulatory perspective**
- **Sahar Barjesteh van Waalwijk van Doorn-Khosrovani (CZ, NL) Moving from experimental phase to evidence-based practice, a payer's perspective**

In this first session of the workshop the three speakers discussed the topics above followed by an in-depth panel discussion where they were joined by **Dr Steven Lemery (FDA, US)**.

Key take away points from speakers

Dr Greystoke – overview of approved histology independent trials

- Noted that response rates and PFS still show a range between tumour sites
- Highlighted the importance of biomarker development or complex/composite biomarkers to identify patients e.g. TMB
- Issues of small cohort numbers and therefore robustness of outcome data remain

Dr Pean – outlined expectations from EMA when evaluating submissions in this area

- Small size of studies remains an issue bringing challenges to contextualise results with lack of randomization
- Conditional marketing approvals used when data not considered comprehensive e.g. Larotrectinib – 93 patients, 14 tumours types, 72% RR
- Trial may be evaluated by tumour type and one arm rejected e.g. pembrolizumab in pancreatic cancer n=22 RR 18%
- Importance of preclinical models and biomarker emphasized
- Success factors – known mechanism of action driven by biomarker, plausibility of activity across tumour types, for subgroups of patients with other options consider as separate cohorts

Dr Barjesteh van Waalwijk van Doorn-Khosrovani – discussed key issues for payers using examples from success DRUP study process in Netherlands

- DRUP trial stage 3embedded in reimbursement system in Netherlands, allowing "personalized reimbursement"
- Off-label requests for funding considered challenging as increases inequity of access
- Lack of structured assessment of benefit remains a challenge

Focus of panel discussion

- Ideal trial endpoints and where in patient pathway such trials may come, and how they move up the pathway
- The challenges of overall survival as an endpoint, however it remains the best and most robust endpoint for regulators and payers of patient benefit

- Powerful advocacy from patient representatives in the audience over the importance of PFS as an outcome for patients

Session 2: Biomarker development and optimisation

Session chairs:

- **Brian Simmons (Roche, US) & Sacha Wissink (MSD, NL)**

Speakers:

- **Sid Mathur (MSD, US) Scene-setting (in a forward looking way)**
- **Lynn Brown (MSD, US) Industry Perspective**
- **Hilke Zander (Paul-Elrich Institut, DE) Regulatory Perspective**
- **David Fabrizio (Foundation Medicine, US) Evolution of comprehensive genomic profiling in precision medicine**
- **Jeff Allen (Friends of Cancer Research, US) Biomarker harmonisation: TMB case study**

Key take away points from speakers

Dr Mathur – set the scene for the session discussing the predictive biomarker and trial leading to successful tumour agnostic licencing of pembrolizumab by FDA

- Underpinned by MSI-H/dMMR being identified as unique biomarker and consistent in its predictive ability across tumour type
- Important to also demonstrate efficacy consistent across dosing regimens for licensed agents
- Extrapolation of data into paediatric cancers
- TMB-H as a biomarker remains challenging as a continuous variable so need to define cut-off
- Considerations for future pan-tumour development are importance of centralised biomarker development, or some defined central validation of local testing where this is available/suitable – especially with EU IVD regulations coming into force in 2023

Dr Brown – gave an overview and industry perspective on recent FDA guidelines in this area

- FDA Guidelines issued October 2022 – first set worldwide, highlight need to understand biology, drug mechanism of action, allowing for possibility of generalisation in some tumour types where low prevalence will preclude cohort recruitment https://www.fda.gov/regulatory-information/search-fda-guidance-documents/tissue-agnostic-drug-development-oncology
- Single arm studies "may be acceptable" but likely then to have post-marketing requirements e.g paediatric cohorts
- Contemporaneous development of tumour agnostic indications with a separate programme for site specific indications allowed
- Pre-clinical considerations – non-clinical pharmacology recommended cell lines from tumours with different origins (but not full range needed)
- Trial justification in some circumstances can supplement data with that from non-clinical or clinical development with different agents in same indication
- Development of a companion diagnostic may be required and there must be sufficient evidence for biomarker across a range of tumour types

Dr Zander discussed biomarkers from a European regulatory perspective

- The clinical indication should be solely defined by the biomarker and there should be a solid rationale for mechanism of action independent of tumour site.
- Adequate selection of patients based on this biomarker is critical
- IVD-R regulations introduced May 2022 to help improve biomarker development/registration – a "companion diagnostic" which is essential for the safe and effective use of IMP identified before and/or during treatment should identify those most likely to benefit. Registration as a class C device. https://ec.europa.eu/commission/presscorner/detail/en/IP_21_5209
- Consequences of recent changes/guidance mean that co-approval will be possible in US but 2 independent approvals needed in EU

Dr Fabrizio outlined the evolution of comprehensive genomic profiling using examples from his experience in the field

- There has been an increasing complexity since BRAF V600E as landmark biomarker defining a treatment group, both in the complexity of the biomarkers and the challenge of those where there is a continuous variable
- Foundation Medicine and Flatiron Health working together to develop real-world clinic-genomic database
- Combinatorial solutions are being developed e.g. immunogenic potential/immune activation/immune resistance biomarkers combined to give IO signature
- Biomarker evolution may allow changes in entry point in patient pathway, potential for prognostic prediction and monitoring

Jeff Allen completed the session by discussing the need for harmonisation of biomarker development, highlighting the challenges of multiple sponsors working independently. He sued the example of TMB harmonisation as a case study with key take homes being:

- Pooled analysis of published data is valuable, however issues remain with differing tests and cut offs used
- Assay alignment can be achieved in 3 stages – in silico, cell lines then clinical samples

Focus of panel discussion

- Practical aspects of validation process
- Challenges of working across industry sponsors to achieve this
- That validation of companion diagnostics remains essential for pivotal studies, and so assay considered "fit for purpose" in initial trials
- Key takeaways from discussion
    - Importance of some centralization during assay development for harmonization of results
    - Within Europe a clinical performance study will be required to achieve CE mark
    - Notified Bodies cannot give advice, EMA can, pathways in EU are quite tortuous with 60 day time line but multiple stakeholders to involve

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

Session chairs:

- **Birgit Wolf (Bayer, DE) & Alastair Greystoke (Newcastle University, UK)**

Speakers:

- **Theodor Framke (EMA, NL) Regulatory perspective**
- **Lucinda Billingham (University of Birmingham, UK) Academic perspective**
- **Richardus Vonk (Bayer, DE) Early phase side of drug development - Industry perspective**

In this session the three speakers discussed the topics above followed by an in-depth panel discussion where they were joined by Dr Steven Lemery (FDA, US).

Key take away points from speakers

Dr Framke discussed trials design from a regulatory perspective, focusing on the advice available within the ACT-EU initiative Accelerating Clinical Trials EU

- This project aims to support the conduct of large multinational trials within the EU, in particular in areas of unmet need – developing the EU for competitive clinical trial delivery and improved development of new medicines. https://www.ema.europa.eu/en/news/accelerating-clinical-trials-eu-act-eu-better-clinical-trials-address-patients-needs
- 10 priority actions identified, unified pan-EU position and active engagement with stakeholders
- Q&A document published May 22 to facilitate development of master protocols for complex trials, EMA, EU Commission and HMA collaboration, 12 months to develop – important issues
    - Trial integrity with focus on precise hypotheses and pre-specification
    - Co-sponsorship of trials considered possible
    - Sub-studies may not be independent, and need to consider controls covered
- Accepted this document will need to evolve and be updated

Prof Billingham discussed complex designs from an academic perspective, bringing her expertise from running a major CTU and developing complex platform trials in adult and paediatric cancers

- Complex Innovative Design paper published in BJC in 2020 outlining strategies for trials incorporating multiple clinical questions – such studies would typically have an adaptive/Bayesian design and require complex statistical modelling https://www.nature.com/articles/s41416-019-0653-9
- Platform trials are dynamic, with sub-trials within a master protocol
- Challenges of basket trials analysis include inefficiencies when conducting independent analyses based on histology if there is homogeneity between groups, however same issues with pooled analyses if heterogeneity between groups. Would suggest assessment of homogeneity at final analysis and pool if appropriate, or use hierarchical modelling "borrowing information from different cohorts"
- DETERMINE study – innovative trial in set up in UK sponsored by CRUK. "Umbrella-basket platform trial – histology and age agnostic testing licensed therapies in rare indications. BOP2 design – Bayesian Optimal Design for Phase II with stop rules defined for each cohort at decision points. Modelled on DRUP study design. Sub-cohort analysis allowed - if at interim analysis defined points a cohort may close, sub-

cohorts will be analysed and may stay open using "predicted probability of success" model
- Take home messages
    - Bayesian approach the "way to go" with these complex trials
    - a priori statistical analysis plan required
    - sub-cohort analysis challenging to plan for

Dr Vonk – completed the review of complex trial design bringing an industry perspective to the discussions focusing again on basket trial designs.

- The discovery of molecular subtypes has meant smaller cohorts of patients are available for recruitment, basket trials have evolved from this based on the assumption that the biomarker/molecular subtype is more important than tumour histology. Evaluation is often based on pooled analysis which can reduce the sample size needed
- Basket trials should answer 2 key questions – does the drug work and if it works when does it work (sup-type)?
- Operational challenges include variation in prevalence of biomarker – low prevalence meaning high screen failure rates and longer recruitment periods
- When pooling/borrowing/information sharing homogeneity of cohorts must be evaluated at interim analysis, evaluate "predicted probability of success" and if a low power close the cohort
- Specification of go/no go decision point important, again need for expert statistical input and significant resource for simulation emphasized
- Take home message – uncertainty based on prevalence needs modelling before trial set up to "predict" recruitment time in a more realistic manner

Focus of panel discussion

- Challenges of uncertainty over numbers and therefore modelling cohort size when costing a study
- Predicted time take to recruit can also influence decisions on cohort sizes, in particular in rare disease setting – consider specifying a minimum number
- Assessment of safety remains a key outcome, for licensed agents in novel settings as well as for novel agents and must be monitored
- What is an unmet need? – no available therapies or if better than available therapies may need to randomize. Usually considered by FDA based on efficacy parameters, can use a safety outcome but generally a higher bar
- DETERMINE and DRUP studies – ground breaking in this area but important to facilitate data sharing – to try and harmonise inclusion criteria where possible
- Bayesian design allows use of other data (even if inclusion criteria not a perfect fit) to estimate priors
- Decentralisation of trials may be needed for rare indications, and this is being proposed by FDA
- EMA exploring use of RWD as contextuality and controls in single arm studies – will give scientific advice pertaining to this, although randomized approach remains preferred option
- Annals of Oncology paper on burden of bureaucracy in trials flagged to audience
- Overall take home "we need to get better at doing single arm trials"

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)**

Speakers:

- **Olga Valcina (OncoAlliance, LV) Why equality and quality matters**
- **Prof Eivind Hovig (University of Oslo, NO) Genomic Standards**
- **Philippe Page (The Human Colossus, SE) Distributed data governance - Addressing the precision public health dilemma**

Key take away points from speakers

Dr Valcina provided both a personal and country-wide view on why equality and equity matter in healthcare provision

- Cancer mortality rates vary considerably across Europe with main factor which appears to influence being government spend per capita on healthcare
- Variation in access means significant challenges to patients – often with lack of reimbursement also being associated with less access to clinical trials in the same location
- Cancer Care Gap across Europe means worse survival, higher symptom burden, reduced public trust in healthcare systems and lower screening uptake rates
- Proposed European Cancer Inequality Registry would enable collection of accurate data to inform political decisions
- Comparable system to EU food quality standards would aid harmonizing of care

Prof Hovig discussed the evolution of pathological techniques from the microscope to multidisciplinary specialty with multiple data types to integrate

- This has led a natural evolution from siloed individual hospital departments to larger centres/networks with a need to share data
- We now need to develop inter-operability of data at a national/international level to enable sharing and research
- Precision medicine emphasizes the need to federate data so small patient numbers at a centre can contribute to building clinical data sets – the importance of the platform studies and DRUP-like trials
- To realise this potential, we need datasets where there is consent for them to be legally accessible, with consents and the metadata being machine readable
- FAIR data – Findable, Accessible, Interoperable, Reusable
- Global Alliance for Genomic Health is helping drive change to develop trusted research environments with standardisation to be implemented by Elixir (European Research Standards Organisation)

Dr Page completed the session by discussing further data governance, with illustrations from his experience across a range of settings, from physics to healthcare

- To manage uncertainty data governance and therefore confidence in the data is key
- Harmonisation of data is important to be able to share and combine datasets

- Accuracy, provenance, and integrity are key elements, and these may best be achieved by a decentralized data storage model
- Distributed data governance provides a framework for data-centric exchange
- We need to achieve a human-centric choice and accountability in the digital space

Focus of panel discussion

- Equality and equity of access to health services is a huge challenge with a major societal impact as well an individual impact in terms of burden of illness
- Barriers to equality of access include test standards and GDPR being not designed for health data sharing
- Good data governance is vital so participants sharing data trust the curators
- Sharing of data sets is a key step needed to improve equity of access to precision medicine

Conclusion

Overall audience enthusiasm and engagement with discussions from academics, pharma, and importantly patient advocates throughout the two days. In depth discussions were had on the challenges of single arm, small cohorts and “certainty of data”. Importance of biomarker development, trial design and statistical input was emphasized in all sessions.