CDDF
Cancer Drug Development Forum

MEETING REPORT

CDDF Annual Conference

Challenges in clinical trial performance

6 – 8 February 2023

Hybrid Conference

Prepared by Jaap Verweij

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Learning Objectives

- How to best ensure the relevant population diversity aspects in clinical trial for regulatory purposes;
- Awareness on the various aspect of performing clinical trials in a de-centrale mode;
- Which aspects are important to know for those in their early career related to clinical trials for registration purposes.

Session 1: Diversity In Clinical Trial Data

Diversity issues from the perspective of health technology assessment

Carole Longson (NICE, UK)

Given the complexity of the issues, some simplifications seem justified in the following. This will make it easier to take hold of them.

To optimize the process, we need to think about what HTA (Health Technology Assessments) aims to achieve.

- HTA seeks to establish the relative effectiveness of technologies;
- The relative effectiveness is the incremental benefit of a technology for a specific indication under general or routine conditions of use;
- Establishing the relative effectiveness requires use of the technology in the most representative way possible;
- Clinical trials are therefore most useful in an HTA context if they include the population most likely to be treated in routine clinical practice.

Including diversity into this brings in another dimension: one of equity, equality and fairness. These are especially important when it comes to making decisions but are not further discussed here.

In the context of HTA, diversity means **generalizability** and **representativeness**. They are related, but also distinct. Generalizability focuses on trying to make the clinical trial *population* as representative as possible of the routine clinical practice population. The representativeness focuses on the *outcome* data of the clinical trial. Even if generalizability has been taken care of in trial design, this does not fully guarantee that outcome data fully reflect clinical practice populations.

So, diversity includes an entire range of particularly complex issues. There are 3 populations of interest, when we think of generalizability of clinical trials:

- The **target population**, i.e. patients to whom the clinical study results are intended to be applied in real-world;
- The **clinical study population**, i.e. Patients who are eligible for the study based on study inclusion and exclusion criteria. etc.;
- The **clinical study sample**, i.e., participants who are enrolled.

Generalizability can be viewed as the portability of the effects of an intervention observed in a controlled setting to the population in the real world setting and it is influenced by all the above, and even more. Portability means ensuring the greatest possible adequate transfer between the trial environment and the real world.

To improve generalizability for HTA one can map various issues that can be addressed:

- Dialogue: across all the stakeholders involved;
- Advice: in different domains, i.e., from both the regulator and the HTA simultaneously;
- Influence: the balance of power between those planning the clinical trial design and those that need to assess the results of those trials, also within these domains inside a pharmaceutical company;
- Collaboration: needs to be balanced and 360 degrees.

Useful guidance on this is now available via the GetReal Trial Tool (www.getrealtrialtool.eu)[1]

Patient Perspective

Gilliosa Spurrier Bernard (MelanomeFrance; MPNE, FR)

Diversity includes a myriad of varieties that make up humankind, and it really matters. And clinical trial populations should therefore reflect the real-world populations.

For melanoma for instance, there are various gaps in diversity:

- BRAF status;
- Presence of brain metastases;
- Mucosal-, acral and uveal melanoma;
- Toxicities, e.g., women that suffer more from side effects than man.

that all need to be considered when designing a clinical trial and assessing its outcome.[2]

It is therefore important that external validation should be brought into the negotiation of pricing of novel treatments.

In general one can say that **"Absence of evidence of the efficacy data, does not mean evidence of the absence of efficacy"**.

We have to match the trial data to the patients that exist in the real-world, and not the other way around. Trials that do not match should be penalized, for instance in price negotiation on the treatment involved. We also should accommodate the trial design to allow access to patient populations that need the trial as treatment options.

Reflections on how to ensure diversity in clinical practice and clinical trials

Marie von Lilienfeld-Toal (University of Jena, DE)

Ensuring diversity in clinical trials is a tool that helps to provide the best possible care to patients based upon the outcome of these trials. Which is different from the current provision of the same care to every possible patient.

The number of **inter-individual characteristics** is large, as expressed in the "Wheel of Power/Privilege" (www.ccrweb.ca), and involves both biological and societal factors, many of which have turned out to be important in care delivery. Examples are:

- Race;3
- Gender;4
- Body Mass Index;5
- Socio-economic status;6

[1] Zuidgeest et all: *https://www.sciencedirect.com/journal/journal-of-clinical-epidemiology*; and *https://doi.org/10.1016/j.jclinepi.2021.12.019*

[2] Sharma A. et al: Improving diversity in medical research; Nat. Rev. Dis .Primers 7 : 74, 2021; https://doi.org/10.1038/s41572-021-00316-8

[3] Waxman et al, Blood 2010

[4] Heinrich et al, Eur. J.Cancer 2021

[5] Fuerstenau, Leukemia, 2020

[6] Jansen, Lancet Reg.Health Eur 2021

- Biogeography;7
- Microbiome subtypes, that differ geographically, and have dietary consequences.8

All these lead to potential further complexities due to the various possible sub-classifications. There are **toolkits one can use that help to make distinctions in such variables, when designing a clinical trial**.[9] We might need detailed granularity, to get the best possible distinction.

We also need to carefully reassess the validity of in- and exclusion criteria. For instance, the quite usual exclusion of patients with a neutrophil count < 1.5 x 10^9 cell/L, leads to exclusion of 10% of the healthy population of black Americans.[10] In this context, ASCO (American Society of Clinical Oncology) has released a report on **options to improve clinical research and cancer care**[11]. The specific recommendations were:

- Ensure that clinical research is accessible, affordable, and equitable;
- Design of more pragmatic (think of: washout periods, concomitant medications, prior therapies, laboratory ranges, performance status) and efficient clinical trials;
- Minimize administrative and regulatory burdens on research sites;
- Recruit, retain, and support well-trained clinical research workforce;
- Promote appropriate oversight and review of clinical trial conduct and results.

Major barriers for patients to enter clinical trials are a.o:[12]

- No trial available (56%);
- Ineligibility (22%);
- Physician related (15%).

Only 8% of patients enrolled was enrolled in this example, reflecting that trial populations frequently do not match the total patient population. Importantly, and despite previous concerns, it turned out that patient acceptance rates to participate in a trial are rather high (56-67%, if at least offered the option). Reasons for physicians to not offer a trial to a patient can be time constraints, limited resources and implicit bias and lack of awareness.

An incredibly reliable source for support is in the publication "Achieving diversity, inclusion and equity in clinical research".[13]

Ensuring data diversity in big data platforms and building AI algorithms

David Cahané (Owkin, FR)

AI models are built across to help accelerate medical research and improve patient outcomes. They span the full development cycle, from target discovery, via biomarker models, and design of external controls, and covariate adjustment therapeutic decision recommendations, in the performance of a the clinical study. It is important to realize that AI models are as good as the quality, quantity, diversity, and representativeness of the training

[7] www.pharmgkb.org
[8] McCullock, Nat. Med 2022; Simpson, Nat. Med. 2022
[9] https://mrctcenter.org/diversity-in-clinical-trials/
[10] Hsieh et al, Ann. Int. Med. 2007
[11] Pennell et al., J Clin Oncol 2020, doi: 10.1200/JCO.20.02953
[12] Unger et al JNCI 2019
[13] htpps://mrctcenter.org/diversity-in-clinical-trials/

data used in input. If these are not appropriate/balanced, this increases the likelihood of bias in the model.

Strategies to address data diversity and improve AI models include:

- At the level of data collection: Actively pursue to collect data from a wide range of individuals and groups. And use of federated learning models;
- At patient level: Ensure multimodal data involving various aspects of information on the patient, for instance clinical + imaging data;
- Pre-processing: by resampling underrepresented groups, and augment data to artificially increase diversity;
- Model training and evaluation:
    - by external validation on diverse data sets,
    - by blind/prospective data validation,
    - interpretation,
    - and causal inference.

The status quo with AI can be challenged by for instance using AI driven patient diagnostics, screening, and enrollment, for instance based on biomarker pre-screening.

This way we can create AI models that work well for diverse populations and help to ensure that the benefits of AI are accessible to all.

Panel Discussion

Q: How can we balance the tensions between rapid development and involving populations that span the totality of diversity?

A: By learning the various aspects involved in patients harboring similar (but maybe not the same) genetic change in their tumors. In the end, for outcome it all comes down to the effect size. To completely catch the covariates within the patient populations, AI models can help to identify these. Covariate adjustment is one of the possible ways for defining.

Q: Should mathematical models not be prospectively validated in a randomized trial? At least to show that this works?

A: Yes, this should be done.

Q: How do you see the role of RWE, access, and diversity?

A: If clinical trials and RWE data collection can be made to look more similar, Real-world data can help to confirm or question the validity of the outcome of clinical trials. AI models can help in RWE data collection, and outcome validation.

Q: How can we ensure that all factors potentially involved in diversity are covered in clinical trials?

A: A simple answer cannot be given. We may have to accept to decrease speed of development a bit, and look back and look for the places where gaps may be identified. We need to find the balance between speed, safety, and objectivity. Decentral performed trials (see session 4) can also help in this regard.

Q: The regulator can only give marketing authorization for a drug for the population as it was included in the trial(s) that constitute the dossier. So, the regulator is bided. Another regulatory issue may be that the more diversity is included, the smaller the subgroups will become. Which may affect overall results. At what point turns the absence of evidence for

efficacy in a subgroup, to evidence of absence, which would lead to exclusion of the subgroup in the marketing authorization?

A: The dilemma is acknowledged. It may be a solution to use AI to indicate what is a determinator, and what is not.

Q: How will diversity be affected in clinical trials, now a large contingent is excluded from Russia and Ukraine?

A: Trials were not stopped in those countries, so outcomes should not be affected in mentioned perspective. But new trials were not started in those countries.

Q: Some important aspects are never included in the in- and exclusion criteria of trials. How can we data-mine other datasets and supplement available data for regulatory submission. It is important not to slow down trial performance by affecting subgroup issues.

A: It is crucial to think on all these aspects in the process of trial design, and at the same time think of diverse ways that may help to gather data. Large data sets and AI may be a helpful armamentarium for this purpose.

Session 1 Key Takeaways

- There is a definite need to well define variable to capture diversity in clinical trials.
- Diversity can be understood as the combinations of generalizability and representativeness of the clinical trial results.
- Absence of evidence for efficacy, is different from evidence for absence of efficacy.
- Improving data diversity improves artificial intelligence utility tools

Session 2: Reflections on Cddf Workshops and Joint Activities In 2022

Workshop on Measurable Residual Disease (MRD) and Circulating Tumour Nucleotides (ctDNA) in oncology drug development

Axel Glasmacher (CDDF, DE)

This workshop was the 4th in a row on the topic, since 2014.

Measurable residual disease (MRD) is usually analysed in bone marrow samples and involves a detection of malignant cells down to the level of $1:10^4$ – $1:10^6$ (depending on the technique used: NGS (Next Generation Sequencing) is the most sensitive of these). For obvious reasons, its use is limited to hematological malignancies.

In a huge meta-analysis on over 11.000 patients with Acute Myeloid Leukaemia (AML) there was a clear and highly significant survival benefit up to 12 years, for patients that were MRD negative.[14] In AML, Acute Lymphatic Leukaemia (ALL) and Chronic Myeloid Leukaemia (CML) treatment decisions ca now be based on MRD assessments.

Circulating (Cell-free) tumor DNA (ctDNA) is usually analysed in peripheral blood samples and allows to detect tumor-specific nucleotides (= liquid biopsy).

In a study in muscle invasive urothelial cancer (MIUC), comparing adjuvant Atezolizumab to observation, there was no survival benefit for the total group of patients. However, when

[14] Short NJ, JAMA Oncol 2020; 6:1890

assessed according to ctDNA status (+ or -) there was a significant benefit for patients with a ctDNA(+) status.[15]

ctDNA now has a substantial potential to be used throughout the patient journey:

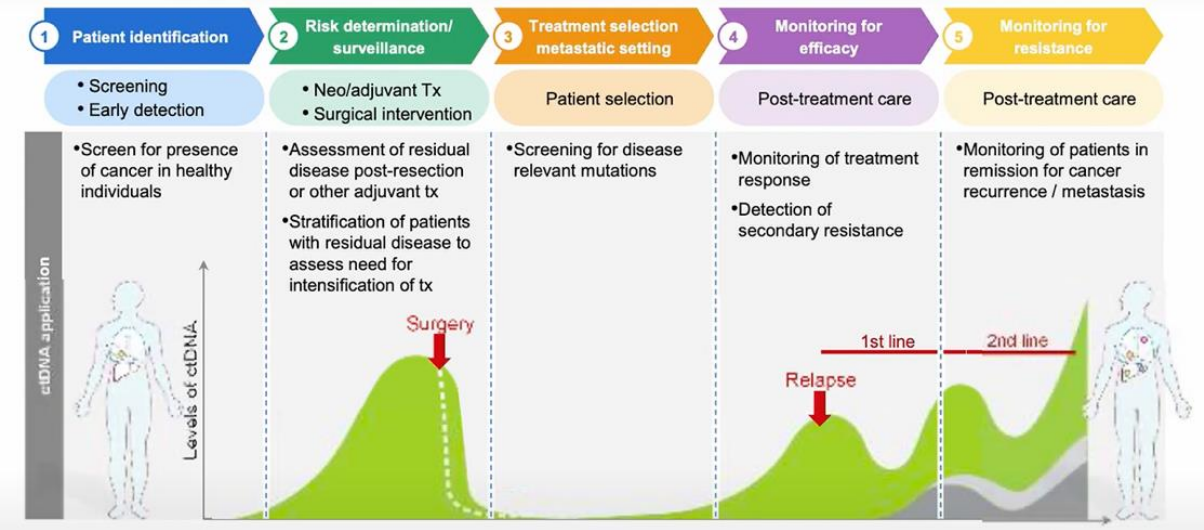


Figure 1. Adapted from Wan et al, Nat. Rev. Cancer, 2017

While MRD and ctDNA can clinically be used for screening and early detection, monitoring for relapse and to guide therapeutic decisions, the FDA now recognizes potential regulatory use of MRD and ctDNA as a prognostic biomarker, but also for patient stratification, patient selection/enrichment, risk-based treatment assignment (escalation or de-escalation), and as intermediate or surrogate endpoint. Accelerated approval are possible with use of MRD or ctDNA, if meta-analyses have confirmed individual-, trial level-surrogacy, with a surrogate threshold effect (minimum treatment effect on the surrogate necessary to predict an effect on the true clinical endpoint). Even in a single trial model.

Figure 2. Single Trial Model

The MRD Partnership and Alliance in AML Clinical Treatment (MPAACT) consortium of 7 pharmaceutical companies is actively jointly performing a meta-analysis on the use of MRD as a surrogate endpoint in AML related drug development. This will generate valuable information.

Method standards, and quality controls in evaluation are especially important and topic of a large study involving a.o NIH (National Institutes of Health) (National Institutes of Health) and FDA.

Another large 3-step project in Non-small cell lung cancer (NSCLC) and the use of PD(L)-1 inhibitors (ctMoniTR), coordinated by Friends of Cancer Research, indicated that PFS and OS were significantly related to ctDNA levels.

Finally, there still is an urgent need for models that allow HTA assessment after regulatory approval based on surrogate endpoints such as MRD and ctDNA.

[15] Bellmunt J, Lancet Oncology 2021; 22:525

Workshop on patient access and engagement in oncology drug development

Mark Lawler (CDDF, UK)

Learning objectives prior to this meeting were:

- To appreciate and understand how patients and the patient voice are best integrated into cancer research, with particular emphasis on cancer drug development and its delivery for the benefit of patients;
- To determine how patients can best contribute to regulatory decision making;
- To understand the complexities of patient access to innovative medicines and reimbursement of innovative medicines and what constitutes best practice;
- To be informed on the key role that data intelligence plays in the delivery of patient focussed oncology medicines for the benefit of patients;
- To appreciate the need and how cross border access to oncology clinical trials can enhance patient access to the latest innovative.

Resulting from this, the **key discussion points** were as follows:

- The Why and the How of empowering patient involvement in oncology drug development research;
- Ensuring that the patient voice is embedded in both clinical oncology research and regulatory decision making;
- Finding the best path to ensure both early access to, and reimbursement of, innovative oncology medicines for patients;
- Ensuring that appropriate data are collected and turned into the intelligence required to inform patient focussed oncology drug development;
- Ensuring cross-border access for oncology clinical trials.

Take home messages of the meeting were formulated as follows:

- Patients must be at the heart of the oncology drug development pathway and be active participants in all stages of the research, from design to delivery;
- Data informed intelligence must underpin the oncology drug development effort;
- Patients must have more involvement in the regulatory decision making process.
- Partnership approaches to ensure the best value for all stakeholders should be explored and encouraged

There was a series of **recommendations** that will be the basis for a white paper that will be produced:

- Absolute primacy of patient involvement;
- Representation of different (underserved) patient voices;
- Appropriate financially compensation (including recognition for their consulting role) for patient contributions;
- Co-authorship on publications that ensue from patient involvement;
- Appropriate training provided for patients depending on the area involved;

- Research to evaluate barriers to PPIE (Patient and Public Involvement and Engagement) in cancer research;
- Research to evaluate the benefit of PPIE in oncology drug development;
- Grant awarding bodies should be giving higher priority to research that provide meaningful patient involvement;
- Guidelines around methodology of patient generated evidence in regulatory decision making.

Workshop on histology independent drug development

Ruth Plummer (CDDF, UK)

The main **learning objectives** from the workshop were:

- To understand the current landscape of histology independent (=tumour agnostic) drug development;
- To be able to discuss suitable trial designs to deliver such studies;
- To develop an understanding of biomarker development and need for tumour agnostic registrations;
- To understand the regulatory environment around these registrations.

The first session was on lessons learned in the recent past, in which there were several marketing approvals for histology independent drug use. Examples are Pembrolizumab and Dostarlimab in Microsatellite instability, Larotrectinib and Entrectinib for NTRK, Dabrafenib and Trametinib in BRAF driven disease, and Selpercatinib for RET mutation disease. With major questions on biomarker prevalence across malignancies, whether there is activity of the drug across malignancies, and how easy is it to identify these patients. In addition, from a regulatory perspective it is crucial to have an in-depth knowledge on mechanism of action, to explore the heterogeneity of effects, and assess the specifics of a positive benefit-risk balance as well as other available treatment options (if any). The Dutch DRUP study is a nice example of an integrated approach, where from the payer's perspective the relevance of studying personalize reimbursement is highlighted.

The discussion on the ideal trial-endpoints was not conclusive. But while OS is admittedly the most robust endpoint, there was powerful advocacy for PFS te as an important outcome for patients.

Obviously, biomarkers are of crucial importance in histology independent drug development, and will require legislative support. Both EMA and FDA are incredibly open to this development and have issued guidance. A problem in Europe is that medicinal product, and the companion diagnostic are following two different regulatory tracks.

As discussed above in the workshop on MRD and ctDNA, the patient journey can now be described in more detail with the molecular techniques we have available. And choices of medicinal products to use will be increasingly dependent on these techniques, supported by guidance from tumour molecular board assessments. This also means that it is important to have some centralization during assay development for the harmonization of results.

From the academic perspective, within the complex innovative trial designs (CID), the basket trial design seems to be the ideal design for histology independent drug development:

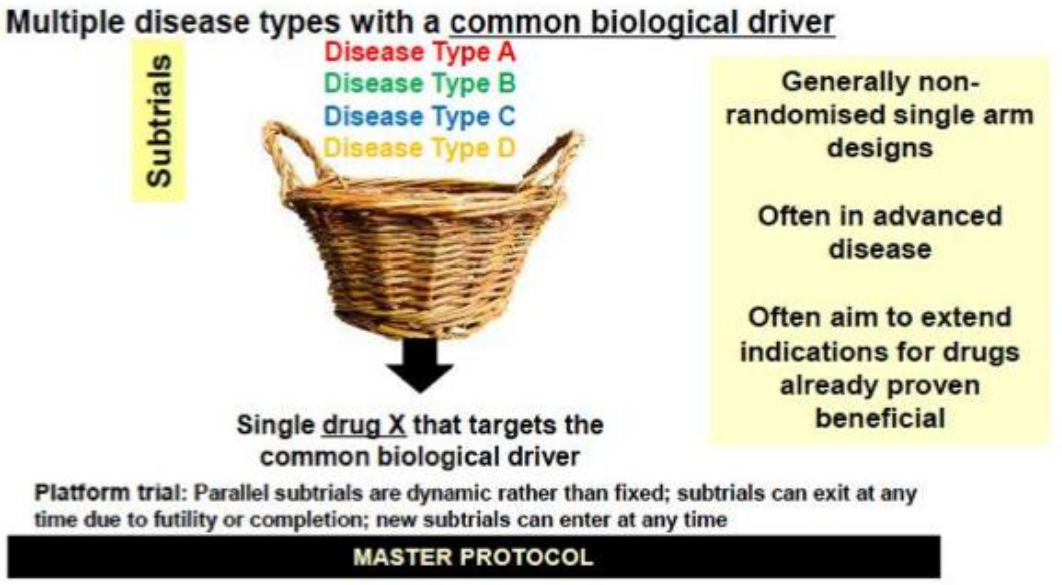


Figure 3. Basket Trials: Key Design for Histology-Independent Drug Evaluation

Ultimately leading to the development of master protocols, in which various statistical methods allow to analyse baskets within baskets. This is supported by regulator views. Just a few days before the workshop the EMA launched the Accelerating Clinical Trials-EU (ACT-EU) initiative,[16] that indicates that basket trials should answer 2 key questions:

1. Does the drug work?
2. If it does work, when does it work?

and that having a statistical plan in place early, is considered of utmost importance. And in this scenario, Bayesian design allows use of other data to estimate priors. Decentralization of trials may be needed for rare indications and currently EMA is exploring the use of RWD as contextuality and controls in single arm trials.

Approvals based on these studies have unfortunately also further widened the cancer car inequalities over the EU countries. Partly because of issues of the testing involved, but also as a negative consequence of GDPD. So, there is a major need to further provide evidence of patient benefit to justify the costs. Being able to share data will stimulate harmonization and support decentralisation.

AAADV-ASCO-CDDF joint workshop on global collaboration

Kim H. Lyerly (AAADV, US)

Given the increasing fragmentation of diseases, due to our increasing knowledge on molecular genetic subtyping, there is an obvious increasing need for global collaboration in cancer drug development. This creates some tension fields due to the differences worldwide on patient data protection, accessibility of data quality for regulators etc. And several aspects were discussed at the meeting, that spanned 3 full days.

There was a full day dedicated for new learners in the field. Informing them of global programs on a variety of topics.

16 https://www.ema.europa.eu/en/news/accelerating-clinical-trials-eu-act-eu-better-clinical-trials-address-patients-needs

The plenary session was fully devoted to global cancer drug development. With topics such as:

- the opportunities and values of global cancer drug development to society (the current lack of socio-economic and QOL (Quality of Life) data at the point of marketing approval, and withdrawals of initial accelerated approval; and the rise of Asia in cancer drug development);
- learnings from infectious diseases in global drug development, the differences in global patient access to therapies post-marketing-approval;
- the assessment of Africa's as well as Latin-America's readiness to participate in global cancer drug development;
- regulatory and health system perspectives of global drug development.

In parallel session two topics were discussed:

- Multi-regional oncology clinical trials (MRCT);
    - If well designed they can deliver better information for regulatory and healthcare decision making;
    - The ICH E17 provides guidance on the general principles of such trials;
    - Such trials usually accrue faster, provide population diversity related data, and enable simultaneous availability to patients by addressing the requirements of different health authorities;
    - Call for simultaneous advice across regional authorities on trial design issues, something which is currently lacking.
- Challenges and opportunities for dose optimization in oncology.[17]

Finally, on the 3rd day there were satellite sessions on:

- The use of ctDNA;
- Innovative computational pathology and proteomics for target quantification;
- Therapeutic drug monitoring for dose optimization;
- Clinical trial diversity and challenges in global cancer drug development;
- Digital patient solutions;
- Improving global capacity to develop medicines and improve care: Targeting paediatric brain tumours.

Session 3: What I Should Have Asked When I Started My Career in Cancer Drug Development

Industry perspective

Theresa Kolben (Bayer, DE)

It is important at the beginning of a career to think where one would like to end up. And then try to work your way towards that final aim. So, begin with the end in mind, along the way be open for change, and always follow your dreams.

Prof. Kolben wanted to study medicine, with the aim to utterly understand medicine. To understand the principles of diseases, in her case, with the aim to develop new medicines to

[17] See also session 4 of this report

treat these diseases. With the dream to make the world a better place, by creating hope for patients in need.

When finishing off her medical training she realized she wanted to combine clinical care with research, and via additional information she realized that her interest would be in early drug development, where science truly meets patient care. And therefor she continued her career in the pharmaceutical industry. She is convinced that the entire process of drug development should start with the patient in mind. So, even at target identification, the aim for result is already considered when designing the full plan.

Throughout the entire process it is important to contact a diversity of people with an open mindset. To realize, that also in pharma a physician will be able to sustain feeling like a physician.

It is important that students, during their medical training, learn to understand the principles of drug development, and are made aware of the options of working in industry. An internship in pharmaceutical industry for medical students might help to achieve this.

Biologist perspective

Steve Wedge (Newcastle University, UK)

Prof. Wedge started his career in academia (where he worked in close collaboration with industry and was involved in the basics of blood sampling as well), then moved to pharmaceutical industry at the time when signal transduction mechanisms became a target for novel agents, and is now back in academia leading a drug discovery group, in close collaboration with Cancer Research UK.

Relevant questions for a biologist starting their work in this field circle around the value of laboratory models:

1. What type of biological data is required to support drug development?
    - So, how robust is the "evidence" provided with the models used?
    - Data reproducibility across researchers and research labs is key, as is model reproducibility across labs;[18]
    - Model diversity, and the breadth of genetics tools used is important;[19]
    - From a drug discovery perspective, target validation involves a progressive development and "de-risking" of a hypothesis;
    - A target is not truly "validated" until a positive phase 3 study has been run.
2. How translatable are cancer efficacy models? And what does the clinical disease that you intend to treat, look like?
    - There is already clinical evidence that activating mutations and/or oncogenic rearrangements can effectively be approached by well tolerated doses of drugs targeting these (EGFR, BRAF, ALK etc). This is well reflected in model data. But this does not mean these models really represent the clinical disease, they merely reflect high target dependency and can be used as PK-PD models.
    - Frequently reality is much more complicated, which can for instance be exemplified by Aurora kinase B, a mitosis regulator. Inhibition of the regulator gave a dose-depending effect in human tumour xenografts.[20] This was

[18] Ben-David U et al, Nature 2018; 560:325

[19] Noble RA et al, Haematologica 102:1247-1257, 2017; Curtis NJ et al, Oncotarget 2017; 8:69219-69236; Noble RA et al, Br.J. Cancer 2022; 127:937-947

[20] Wilkinson R et al. CCR 2007; 13:3682-88

unsuccessfully pursued in clinical studies by a range of companies using a range of agents,[21] possibly since this approach did not target the genetic intrinsic features of tumours, but rather targeted cellular proliferation.
- Another example is the development of drugs inhibiting angiogenesis. They were effective in a wide range of preclinical human tumour xenograft models, suggesting a common phenotype. But it turned out that these models did not commonly represent tumour vascularity in clinical disease,[22] and were not commonly predictive without furthermore detailed assessment.

Clinician perspective

Stefan Symeonides (CDDF, UK)

While being trained at Cambridge medical school, Dr. Symeonides became fascinated with biochemistry and molecular biology in his effort to understand medicine. During the summer holidays he started to become involved in lab-work at Glasgow University. This triggered the direction of his further career part. He then had the opportunity to perform lab research as part of an MD. PhD. program in Cambridge.

The first learning points from that period where:

- The tension between
  - Designing to the problems of yesterday
    - Especially with the long lag-time of drug development
  - Versus chasing blue-sky novelty
    - And academic drive
    - May involve multiple novel dependencies
- And the opportunities in-between

Subsequent learning points involved the drug-development path, which was not at all taught at medical school:

- Consideration of data required for next stage;
- Pre-clinical package;
- Clinical development pathway;
- Line of sight;
- "It takes a village" full of collaborations, with a wide range of expertise.

A third set of learnings involved transferrable skills:

- Self-directed;
- Knowledge;
- Practicalities;
- Critical appraisal.

which avoided disconnects in understanding during the further career.

After medical school Dr. Symeonides joined medical practice, to find out the next set of learnings, related to

[21] Komlodi-Pasztor Ed et al. CCR 2012:51-63
[22] Smith NR eta la. CCR 2014 ; 20 : 5141

- A career in clinical drug development
    - Knowledge of clinical specialties outside of primary and secondary care;
    - About Academic career routes;
    - And about pharmaceutical career routes.

After initial practice in Edinburgh, Australia and New Zealand, he returned to Edinburgh for Medical Oncology specialisation and to pursue an academic career, where further learnings were:

- Diversities in clinical academic career options;
- How do you get funding;
- How can you work in collaboration with pharma;
- How do you run a clinical trial;
- What networks exist to support your work.

He got the opportunity to do a clinical fellowship at industry with AstraZeneca, which lead to further learnings:

- Drug development from industry perspective (trial design, efficiency, decision points, informing online-of-sight)
- Current and emerging landscapes
- Multi-disciplinary project teams
- Project management & delivery
- React to emerging data

Back in academia he now splits his time between the Experimental Cancer Medicine Center in Edinburgh and the CRUK Center for Drug Development (a biotech within CRUK), combining lab and clinical work , bridging discoveries to clinic with clinic to discoveries work

Patient advocacy perspective

Bettina Ryll (Melanoma Patient Network Europe, SE)

Patient advocacy is not really a career one plans for.

Bettina did medical school in Germany, did a year in Paris (which gave a lot of insight in how things are organized differently in various places), and did a PhD on molecular biology in London. She never pursued a path in oncology, but instead fully focused on surgery and molecular biology. She moved to Sweden for a post-doc position in molecular biology, and became involved in paleontology. Unfortunate and sad family circumstances confronted her with oncology, and led to ending up in patient advocacy. Her background helped to explain details of information to others.

Practical personal experience related to the psychological pressures of randomization procedures, and the realization of the limitations of model system where further triggers. Now she spends a lot of time trying to close the gaps between systems. Since the full chain of systems must work, to turn personalized medicine into something real. She now works for the Swedish Cancer Mission.

While patient advocacy, as indicated, is not really a career path one pursues, in hindsight it would have helped to realize:

- It is uncomfortable most of the time;

- For someone who dislikes conflict, it is surprising how much one can end up with it quite readily;
- You do not know what you do not know yet;
- It will take you a decade;
- One has much more space than one thinks one has;
- Systems are not complicated, they are complex;
- There are a lot of convenient "truths" (easy explanations) that hardly ever are the truth;
- Careful observation is key: Everyone has an opinion, few understand the underlying problem, hardly anyone sees long-range dependencies;
- We are all part of the problem, AND part of the solution;
- It is worth working on something one believes in, even when it is hard and unpopular;
- In every stakeholder group, there are always some who genuinely care wherever one goes, people who are generous with their time and their knowledge, and those who want to get it right rather than being right.

Panel Discussion

Q: A common element in the lectures was the somewhat coincidental nature of the career path taken. What are your thoughts on this?

A: There are 2 sides to that: first, the serendipity of what you come across, and the flexibility to adapt to it, remains important, and second knowing that that is an option.

What is also important is the personal urge and willingness to change the status quo. It helps to have a role model, not necessarily to copy, but to serve as mentor.

Q: Was there any disappointment in working for industry?

A: Absolutely not. The multidisciplinary team was just a stimulating environment.

Q: How is one recognized in the various fields, for the work one does? Is there a magic guiding to success?

A: Academics are judged on their publication, and the grants they get. But it is also important to judge yourself, and frequently ask the question "is this what I truly like to do." Similar motivations hold for working in industry. Constructive feedback is always extremely helpful. And witnessing that your work helps others is also extremely rewarding.

Session 3 Key Takeaways

- It is important to early consider where you want your career to land;
- Modern cancer drug development involved basic science, clinical science, and an interplay between patient needs and regulatory trajectories;
- Careers in cancer drug development involve interactions between each of these constituents, but can be focused on an area, or areas, of personal interest and strength, combined with effective communication and management skills;
- Opportunities for more formal exposure to the drug development process, in the form of workshops, internships, and post-doctoral and early career training will have a positive impact on those who experience them.

Session 4: Decentralised Clinical Trials

Medicine trials in 2050: In-clinic or decentral

Jaap Verweij (CDDF, NL)

Since our reality is changing, and the future of care will change, we need to rethink the way we perform our trials to find new treatments. Trying to set the future scene and based upon a story published by the Medical Futurist[23] a forward-looking concept was discussed. When life will be supported digitally, and body and activity detailed will continuously monitored by (implanted) sensors. When there may not be hospitals (clinics) anymore, trials cannot be "clinical"-trials anymore. When data input from sensors will be independent of human activity but will go directly from the sensors to digital storage. When medicine was not at all "personalized."

We must prepare ourselves for that future. And, the COVID-pandemic has, within two years, boosted the use of teleconsulting. This is now an accepted given, but in 2020 was something care givers preferred to avoid. Given the opportunities already available, it is highly likely that future medicine trials will no longer be "clinical" trials but will be performed in a decentral way. And this change has already started since there are already options to do this.

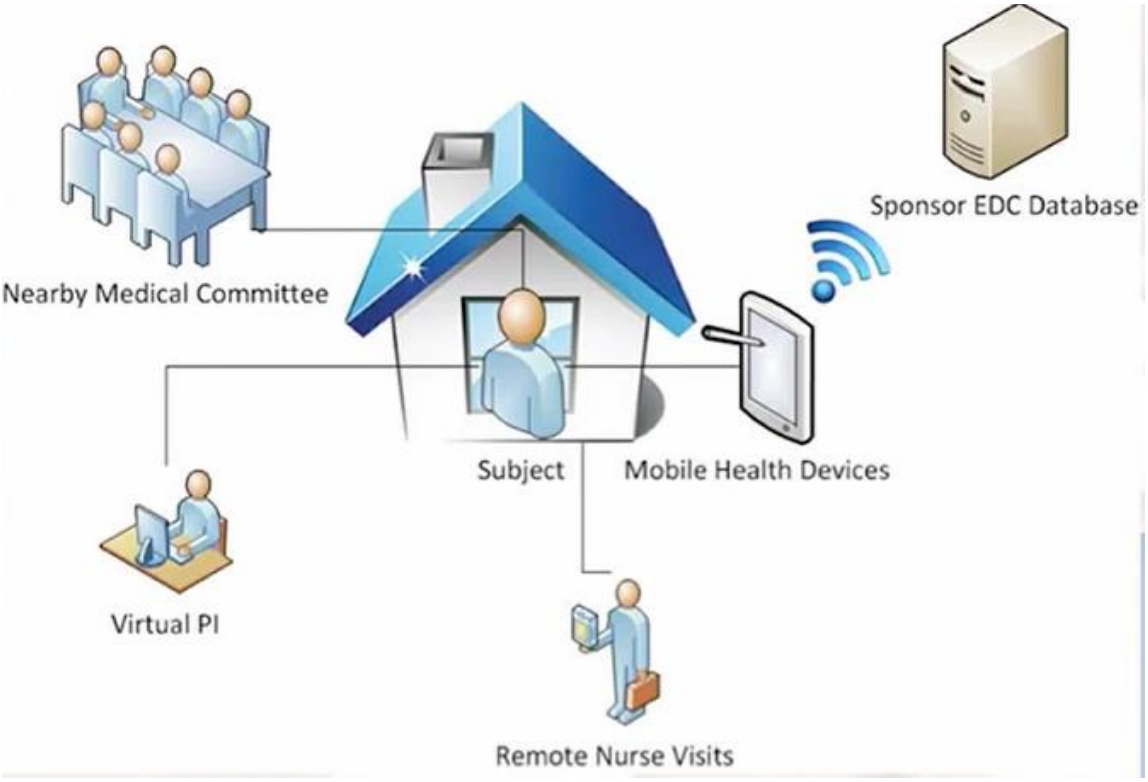


Figure 4. Model for a de-central trial

The decentral trial has become a reality and will be the future. All technical devices are already available. What must be done is ensure data integrity, ensure data validation etc. It will also mean that approvals of tests and tools may even be more important than approvals of the actual drugs.

[23] https://medicalfuturist.com/healthcare-in-2060

Process of decentralised clinical trials. Making clinical trials more patient-friendly: Challenges and opportunities

Jeff Evans (Glasgow Experimental Cancer Medicine Center, UK)

The current challenges and discomforts for patients considering participation to trials a.o include the intensity of procedures and hospital visits (with related travel costs for (long distance travel), the availability of trials in the region, and the knowledge of doctors in that region on the specifics of the increasingly rarer disease subpopulations. In our current reality there is no equity of access to trials.

To conduct trials safely, there are quite a few exclusion criteria, frequently based on outcomes of expensive techniques. So, can we streamline and reduce the burden of trial participation for patients, without compromising safety and scientific integrity?

Just as well, there are many challenges for the investigation site, involving regulatory requirements and bureaucracy, issues with vendors, and workload of staff and support staff, which all slow-down the process and limit recruitment into trials.

So, how can we design trials for patients, whoever they are and wherever they live, and regardless of their societal specifics. This can all be achieved by the "de-central" trial approach. Using remote (virtual) consultation, remote visits at home by (mobile) nursing teams, remote test performance whenever possible, and use of devices to collect remote data, and specialized pharmacy courier services for drug delivery to the patient:

Figure 5. De-centralized approach to trials

The challenges encountered included:

- Study oversight (is this safe for patients, safety reporting requirements, GCP compliance and protocol adherence);
- Resources (infrastructure, mobile teams, training, payment for local imaging etc), and
- What happens if there is a problem? (There would have to be support of local hospitals, in case of required emergency care for the patients involved, and how will his be reimbursed).

In addition, one must ensure:

- PI indemnification;
- Proper description of PI responsibilities (managing mobile teams that are not employed in the PI's institution);
- Financial reimbursements at local sites;
- How patients will be identified, and by whom;
- Academic credit (authorships etc.);
- Best viable way to liaise with local teams.

Advantages of the de-central trial setup also include the following:

- Only sites with eligible patients will enrol;
- There is less redundancy of sites and activities;
- Maximize technology to identify patients;

- Maximize remote site support;
- Sites with less resource and more diverse patient populations can still participate.

All the lessons learned in setting up such a trial in the UK will now be applied to the set-up of the TAPESTRY trial in Scotland.

Industry perspective

Victoria Chiou (AstraZeneca, US)

The pandemic ignited a shift towards decentralized clinical trials. The decentralized trial offers an opportunity for a patient-centric approach to research. Various available digital devices and technologies may enable delivery of decentralized components of clinical trials, such as telemedicine, electronic remote consenting, and patient reported outcomes. For the patient, the decentralized trial is associated with reduced or eliminated travel, and thus, fewer travel inconveniences, such as fewer disruptions of their day-to-day activities, reduced need of childcare, and reduced loss of work. The academic perspectives discussed above overlap with the industry perspectives. Specific advantages for industry are the broadening of access to patients underrepresented in traditional trials, resulting in more diverse patient populations. There will be accelerated recruitment times, improved retention, possibility of frequent or continuous measurements, better representative of real-world outcomes and generalizability of results.

Apart from the fully decentralized trials, there are also options for hybrids between decentral and central trials. Decentralization is in contrast to the centralized model of clinical trials; in fully centralized clinical trials, all trial activities take place at a research site, requiring travel from participants to travel from their home to study sites. The question is now how to best incorporate the available methods in moving forward.

Not only will decentralized trials have advantages for the patients involved, but they will also influence the research community and transform the way we work to accelerate our science, think globally, and accelerate development and delivery of innovative medicines.

Panel Discussion

Q: How do you look at decentralized trials. Have we reached the end of the beginning. There are very many initiatives among all stakeholders.

A: The pushback experienced up to now was mostly from local sites. Once the system has started, the pick-up is not going to be an issue.

Q: Were there any concerns from regulatory side in setting up the UK trial?

A: No, not at all. There was an incredibly good collaboration. And the pandemic in a sense has relieved potential concerns. For instance, remote consent has become much more acceptable.

EORTC has extensive experience with radiation oncology trials where the decentral aspect is considerable. And this works perfectly. So, there is no reason to expect issues with drug trials.

We should also involve the available population registries in identifying the potential patients. But this will not happen in the short run.

Q: Do you really think that drug-development trials are the best trials to start with? Would pragmatic academic trials not be an easier target?

A: Obviously, the more experience we have with the drug, the easier it may become to run a decentralized trial. If we do not yet know anything about the safety of a novel agent, this may be a different setting from the slightly more mature one.

Q: How can we implement this concept in low- and middle- income countries, where many digital tools may not (yet) be affordable?

A: Even in rich countries there is a disparity of wealth, access to many technologies, and the ability to use those technologies. Yet, if we are committed to global (one world) health, we have a responsibility to solve this issue. There are mobile units already in less wealthy countries, that go to communities for care provision. It is surprising to become aware how many capabilities already exist in those countries. We should help them to get the tools, and to help them set up infrastructures, and provide training for use.

Obviously, all clinical research will be conducted within the boundaries of regulatory compliance. It is important to realize that the legal framework that binds the regulators in their work will take time to adjust. Therefore, it is important to carefully evaluate benefits and risks before changes to regulations are recommended or made.

Q: How do you secure patient data privacy and confidentiality, during remote monitoring and consenting?

A: As an example, electronic virtual consent through a secure platform could include video consulting to discuss the content of the study and the form, and then send ing the consent form to the patient for signature.

Q: How can we engage the elderly population, that has an excess presence in rural areas?

A: Elderly populations in cities may also be isolated in practice. We need to make sure that our clinical trials also capture those populations if risks allow, and individualise patient information.

Q: Are organizations already capable of including elements of decentralization into their clinical care?

A: During the pandemic it became evident this could be organized. So, it has become a standard. And there is already evidence that with simple training programs, we can address IT-illiteracy among elderly.

We need a joined legislative action, to help modernize the legislation and help facilitate performance of decentral trials. There is an urgent need. The EU Beating Cancer Plan may offer a good opportunity to start this discussion with the EU Commission.

Session 4 Key Takeaways

- Adopt decentralization of cancer clinical trials to enhance equitable access, diversity of clinical trial population and patient centric drug development;
- Identify the right type of trial to implement decentralization; focus first on pragmatic trials with simpler design and later stage trials;
- Keep the legal framework in mind and legislative actions needed to remove hurdles and enable uptake of decentralized trials;
- Enhance the inclusion of vulnerable populations like the elderly, disabled and rural populations via appropriate decentralization approaches.

Session 5: Treatment-Dose and Schedule Optimisation

FDA Project Optimus

Mirat Shah (FDA, US)

The traditional dosage selection in oncology was developed for cytotoxic drugs. Usually only a few patients are treated in escalating doses cohorts, with the primary aim to identify the dose-limiting toxicity (DLT) and Maximum Tolerated Dose (MTD). Without much refinement the MTD is then carried forward into a registration trial comparing the new drug at MTD to a control arm. If the trial results support approval, the MTD becomes the approved dosage. Lower grades of toxicity are commonly considered less important in dose selection.

Most of the more recently developed drugs are not cytotoxic, but are molecularly targeted agents. These are quite different from cytotoxic products:

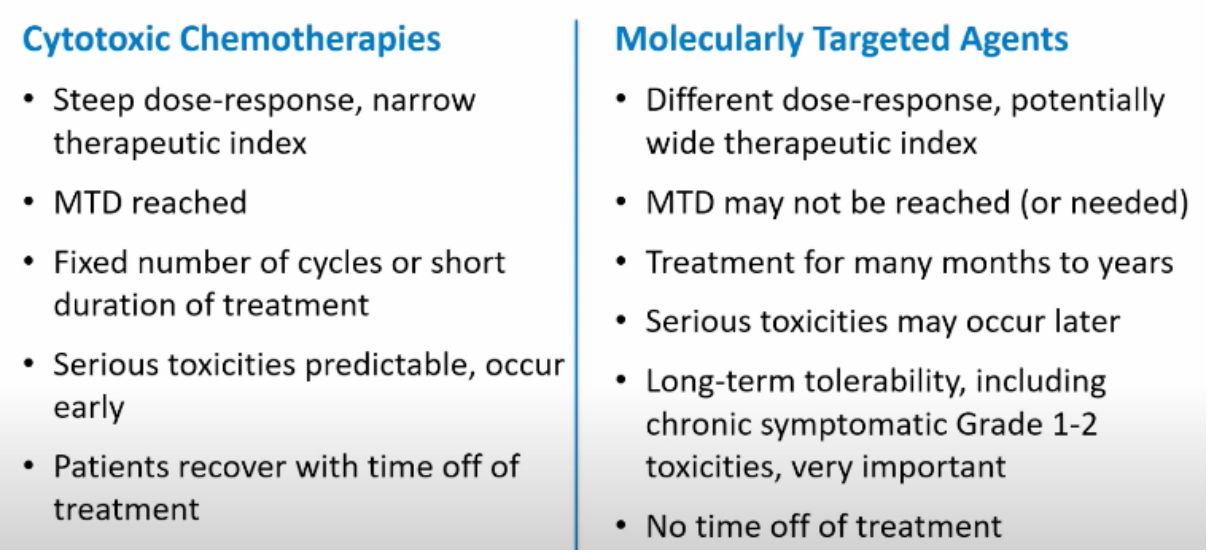


Figure 6. Differences in characteristics between cytotoxic- and molecularly targeted agents

Moreover, the dose-response relationships for targeted therapies are markedly different from dose of cytotoxic drugs. Targeted drugs have an efficacy plateau, and further increase of the dose only yields increased toxicity. So, lower doses may have similar efficacy as higher doses, while they are related to less toxicity. And it may thus be important not only to consider serious toxicities in dose selection, but also the less severe types of toxicities. For instance, grade 1 diarrhoea every day, for an extended period, could jeopardize tolerance.

Project Optimus has the mission to ensure that dosages of cancer drugs are optimized to maximize efficacy as well as safety and tolerability.

Ponatinib, a kinase inhibitor developed for chronic myeloid leukemia in its chronic phase exemplifies the consequences of failing to optimize the dosage in the premarket setting. The drug was approved in 2012 at a dose of 45 mg orally once daily. The limiting toxicity was grade 3 hypertensions. After approval, the incidence of serious vascular events was found to be higher than noted at the time of marketing approval, which lead to voluntary retraction of marketing approval. Subsequently a dose-optimization randomized trial compared 45 mg OD, with 30 mg OD and 15 mg OD, with options for the 2 higher doses to be reduced to 15 mg OD.[24] The highest dose yielded the best efficacy and significantly better than the 2 lower doses, while the number of vascular events was similar across the dose ranges. Based upon

[24] Cortes J, Blood 2021

these results the label was modified (in 2020) to include the option of dose reduction in case of serious vascular events.

If the dosage is not optimized at the time of marketing approval, patients may stop taking a potentially efficacious therapy, or they may choose to try a different therapy. In extreme cases the drug might not even make it to market authorization, or may have to be withdrawn from the market after initial approval.

A new dosing paradigm is needed in oncology, with the emergency of differently targeted novel treatments, so that the dosages of these agents are optimized prior to marketing approval. This will improve decision making for the drug development program, may prevent avoidable toxicity and therewith increase uptake and improve adherence, increase efficiency and feasibility, and allow for a more rapid development of new indications and combination therapies.

FDA has recently (2023) released the Guidance for Industry: "Optimizing the dosage of human prescription drugs and biological products for the treatment of oncologic diseases"[25]. Some of the key principles in the Guidance are:

- Dosages must have justification appropriate to the stage of development;
- The totality of data should be used for dosage selection. Including dose- and exposure- response relationships for both efficacy and safety;
- Randomized comparisons support the identification of optimized dosage(s);
- Safety assessments to include low-grade symptomatic toxicities which affect tolerability;
- Dosage optimization is important for all products, including those with anticipated rapid development timelines.

After selecting several doses randomized comparisons should be performed to optimize dosage. These studies can be underpowered and can be part of phase 1 escalating dosage study. It can also be included in the last step to registration, which should be a (powered) randomized comparison of the selected optimized dosage, to a standard care control arm.

It is highly recommended to discuss the development design early with the FDA.

The EMA Cancer Medicine Forum and dose optimisation

Denis Lacombe (EORTC, BE)

The relevance of academic trials is frequently inappropriately appreciated, which can be displayed by the relevance of many of such trials. Particularly in for instance the fields of rare tumors, drug combinations, or -combinations with radiotherapy and/or surgery academia has yielded practice changing trials. Now that the medicines we use are changing, and the eco-system of the totality of the public sector, the for-profit sector, and the not-for-profit sector is changing, we need to ensure that the academic scientific outputs are appropriately integrated, and to jointly adapt our standards of care and integrate all potential options of care (see figure).

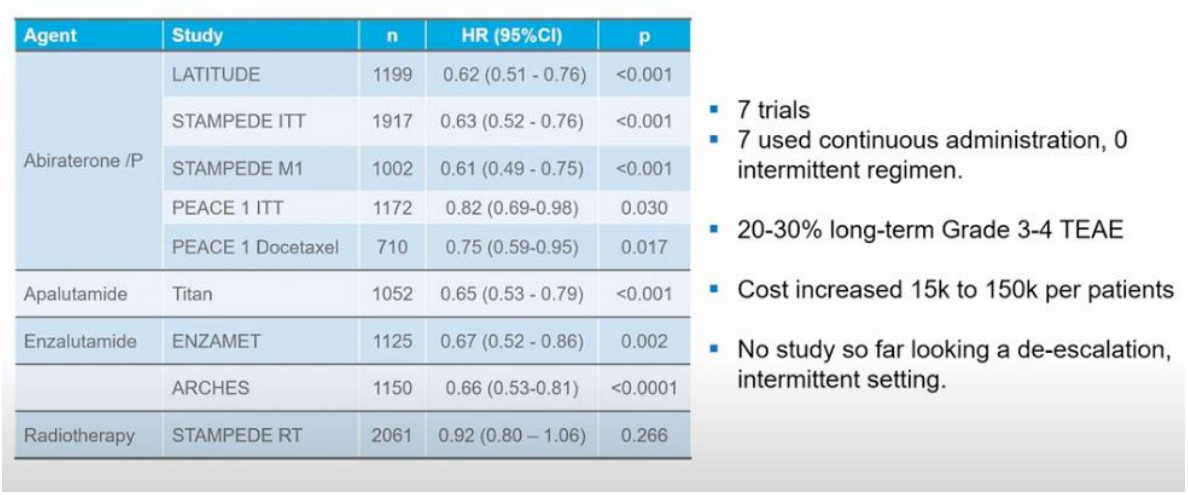
[25] https://www.fda.gov/media/164555/download

Figure 7. Combining the treatment options for cancer

In this picture, we need to realize that the data sets provided for novel agents are frequently no longer the large data sets that were provided previously. Marketing authorization is increasingly based on more limited data sets. This puts an important emphasis on the necessity for post-marketing data acquisitions and studies.

So, how can we optimize treatments in the modern age? It is our opinion that this is a process that starts after market-authorization. There we need to assess optimal dose again, as well as dose reductions, study drug-combinations, and assess specific populations. And balance all information on drugs and effects, against affordability of care for society. This calls for patient-oriented endpoints in research. This is precisely the field where the Cancer Medicines Forum is projected to function.

A good example for the above-described need, can be found in the introduction of new hormonal treatment for metastatic prostate cancer:



Agent	Study	n	HR (95%CI)	p
Abiraterone /P	LATITUDE	1199	0.62 (0.51 - 0.76)	<0.001
	STAMPEDE ITT	1917	0.63 (0.52 - 0.76)	<0.001
	STAMPEDE M1	1002	0.61 (0.49 - 0.75)	<0.001
	PEACE 1 ITT	1172	0.82 (0.69-0.98)	0.030
	PEACE 1 Docetaxel	710	0.75 (0.59-0.95)	0.017
Apalutamide	Titan	1052	0.65 (0.53 - 0.79)	<0.001
Enzalutamide	ENZAMET	1125	0.67 (0.52 - 0.86)	0.002
	ARCHES	1150	0.66 (0.53-0.81)	<0.0001
Radiotherapy	STAMPEDE RT	2061	0.92 (0.80 – 1.06)	0.266

Figure 8. Impact of registration of 4 new hormones

All drugs involved are registered and marketed as continued administration. It is yet unclear if intermittent treatment is equally good and less toxic, an important medical and societal question, also because such an approach would reduce the societal financial burden. The EU commission has commissioned performance of pragmatic trials to answer questions such as these, and in this case EORTC has taken the lead to start such a trial, financed by an EU grant.

Examples such as these, and others from surgical oncology, indicate that there is a major need for adequate randomized controlled (pragmatic) trials, to optimize treatments beyond marketing approvals. Key questions in the discussion with policy makers are therefor:

- How to recognize and structure the independent agenda in the continuum after marketing authorization?
- How to address the gap between supra-national and national competences?
    - After central marketing authorization, patient access in the EU is a national responsibility
- If treatment optimization is to be structured in the process: when how and by whom should this be done?
- How do we re-engineer the sequence of relevant questions from drug development into patient access to these drugs?
- How do we prioritize questions and select the most appropriate methodology?
- How do we finance a required multidisciplinary (not only drug-focused) independent agenda at the European level?

Graphically, the various approaches can be shown as follows:

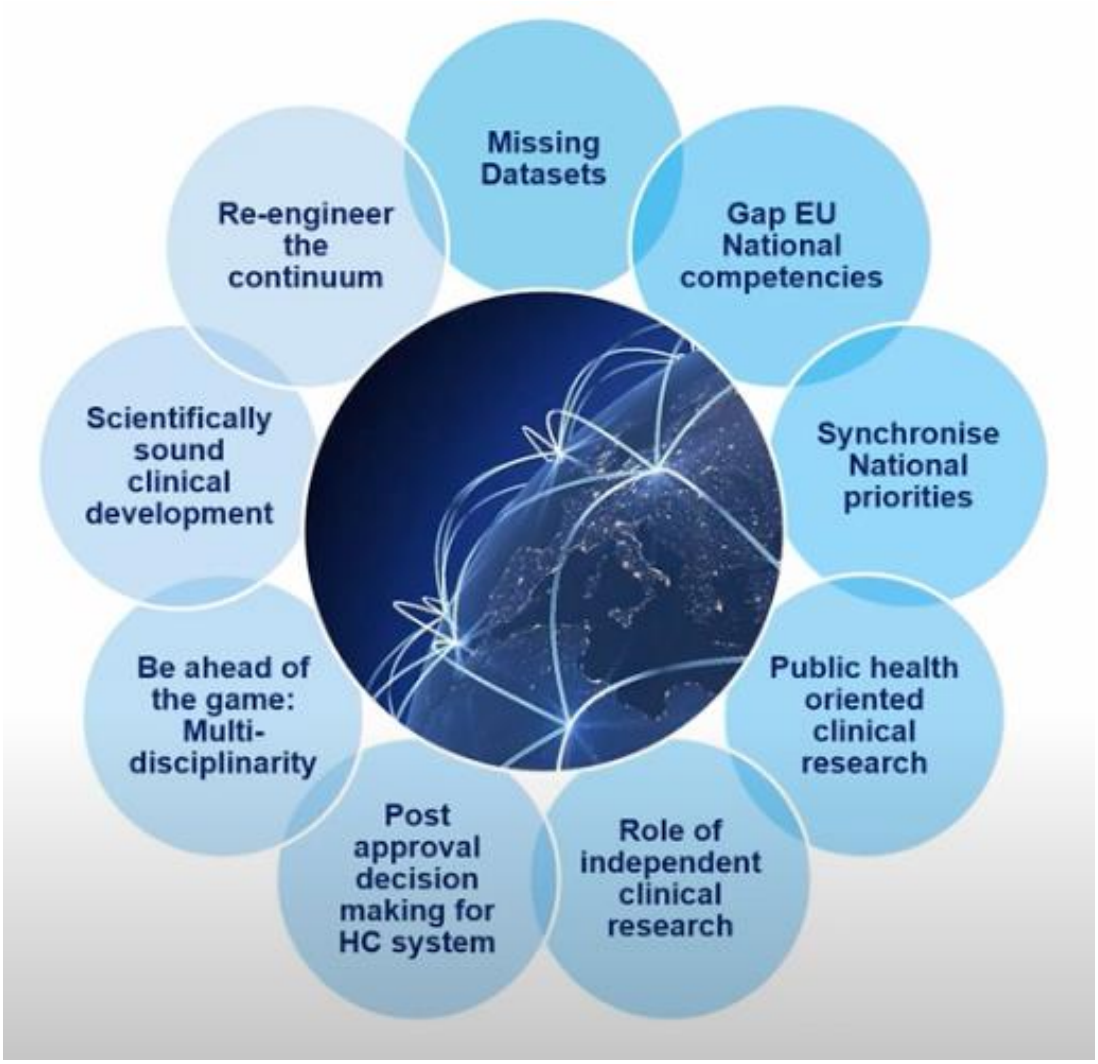


Figure 9. The need for strategic intelligence approaches

These issues were reason for the EMA to establish the Cancer Medicine Forum, with the following objectives:

- To serve as a direct and official communication channel with the academic community in oncology;
- To identify key research questions and best methodological approaches to improve the clinical use of cancer medicines;
- To discuss the uptake of academic work in the wider context of regulatory decision-making in oncology;

all intended to optimize treatments.

The CMF was launched on March 31, 2022, and is chaired by Dr. Denis Lacombe from EORTC and Dr. Francesco Pignatti from EMA. Membership focuses on academia and other stakeholders:

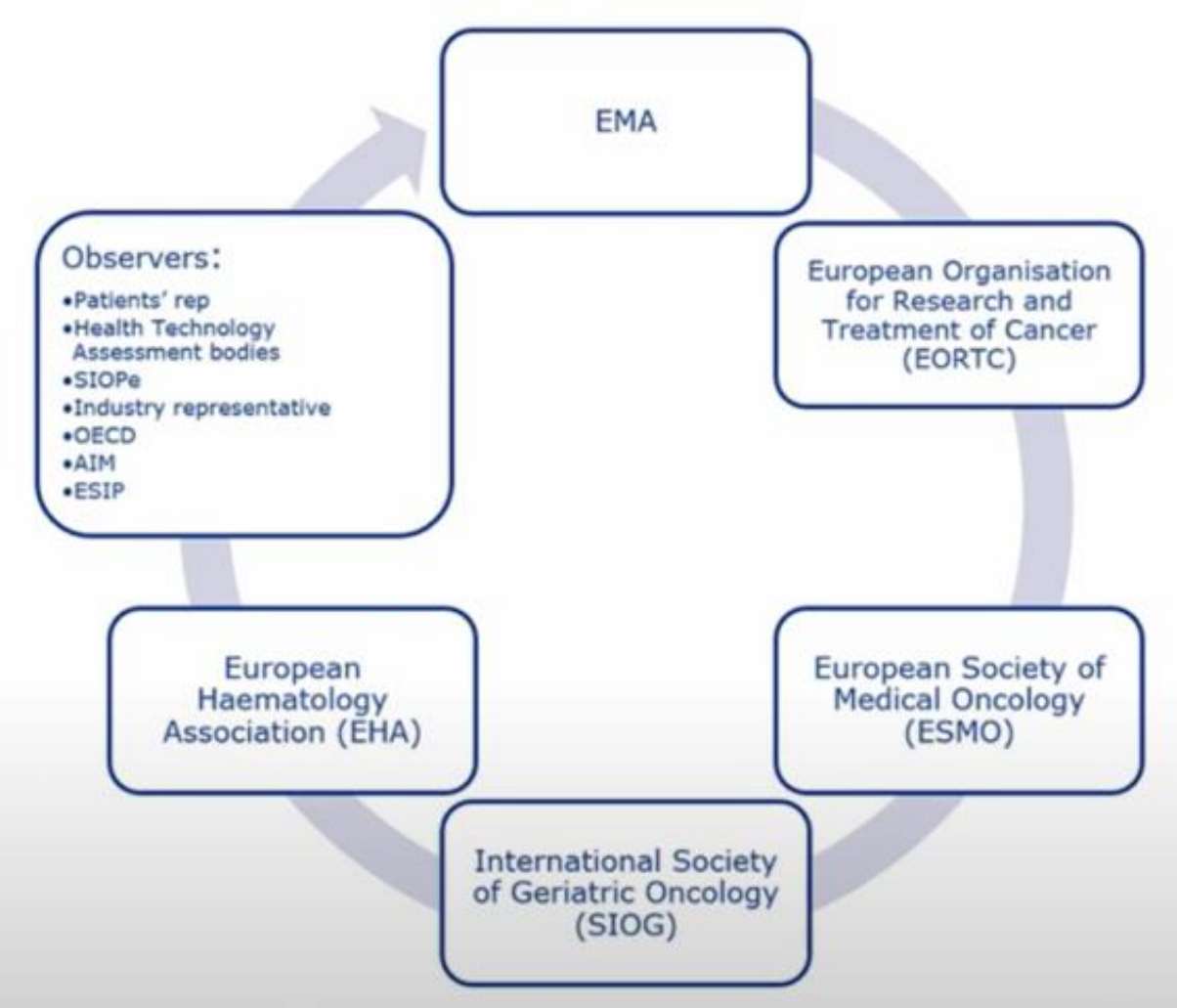


Figure 10. Composition of the Cancer Medicine Forum

Key issues that CMF will need to address are indicated in the following table:

Identification and labelling of TO questions	No structural approach to address the key critical questions for integrating a new drug into treatment strategies.	Set up a "mechanism" where field (patient-doctor- access) priorities are identified and agreed upon
Methodology	Which optimal methodology/design for which questions	Bridge the relevant questions and the methodology to apply Early access to innovation while mandating relevant TO agenda of studies Educate stakeholders to accept large simple pragmatic programs (few eligibility criteria)
Who	Currently nobody is in charge for TO resulting in absence of datasets	Analyze what falls in the remit of the commercial sector or not Build on independent solutions and infrastructure for access decisions into the healthcare systems
How	National: reach and impact not large enough International: organisational challenges	Bring evidence to healthcare systems decisional bodies that patient-centric and society-centric research can go together Ensure collegial endorsement for free access to agents which are already available in the health systems
When	Structuring TO questions in the process around marketing application: the earlier, the better	Explore what can be done pre-marketing (i.e. EMA scientific advice) Ensure expedited processes to run TO optimization trials when components of the trials are already available in the healthcare systems. Control efficiently the window of opportunities
Recruitment	Competition with industry-sponsored trials of novel agents if conducted as separate studies Loss of (perceived) equipoise in the post-approval setting	Structure the process of drug development versus TO trials Pragmatic studies with broad inclusion of participants, more attractive to oncologists Educate stakeholders to understand remaining uncertainty and value of additional trials to optimise patient treatment
Regulatory and legal aspects	High regulatory burden due to lack of separate provision for academic trials in Clinical Trials Regulation High regulatory burden due to the IMP status of the investigational drugs if used outside of the label Adherence to multiple different country-level laws and regulations if conducted as an international study	Legislative changes, e.g. separate provision for academic trials, change in definition of IMP Exemptions from existing laws and regulations Granting free access to IMPs which are already in the healthcare system for a given indication (independent of the stage of the disease independent) Cut red tape of undue bureaucracy
Datasets and reporting	Regulatory and access datasets are complementary Access datasets are not delivered efficiently or at all. Reporting to HTA/payers is not systematically in place	Ensure an appropriate continuum of regulatory into access science with complementarity of stakeholders Deliver efficient TO datasets limited to the key variables of relevance Sponsorship by independent, non-commercial parties to ensure public availability and accessibility of the data generated by TO/access studies
Funding	Lack of industry support due to lack of incentives No reimbursement of the investigational drugs since they are used outside of the label Country-level funding sources difficult to combine and coordinate for international studies Wasted resources in the healthcare systems due to lack of information on TO	New partnership with industry to conduct studies in the post-approval setting, as feasible and relevant Access to the investigational drugs through legislative changes or exemptions (doing a de-escalation study by itself cuts costs of the health care systems) Gain-sharing programs to reward countries that provide funding Public funding of TO trials through the savings by de-escalation of treatments.

Figure 11. Key issues that CMF will need to address

And a major question is, who is going to provide the funds required for all of this?

It is essential that all stakeholders remain involved, and actively contribute. The CMF will contribute to the global aims that were issued by the WHO at its 75th Assembly in 2022.

The Optimal Cancer Care Alliance (OCCA) view and experience

Daniel Goldstein (Davidoff Cancer Center, Rabin Medical Center, IL)

Based upon the observations discussed above, OCCA has put forward the concept of interventional pharmaco-economics (IVPE), actively seeking to disruptively decrease prescribing costs of cancer treatments through the development of new dosing regimens while maintaining equivalent efficacy.[26] This could involve therapeutic substitution, lower dosage, less frequent dosing, and shorter duration of treatment. Most of this work is done in the post-marketing space, which does not take away any of the relevance of pre-marketing initiatives like the FDA Project Optimus.

In the post-marketing space there also is a key role for governments and legislation.

In post-marketing there are almost endless opportunities to improve. To turn these opportunities into impact, there are essentially 2 approaches:

- De-escalation clinical trials;
- Implementing health policies

De-escalation trials can be run in any part of the world. Sometimes the lack of availability of certain drugs due to cost in certain countries turns this into an opportunity to run such trials there and at the same time allow the patients access to drugs they could otherwise not get access to. While in countries with easy patient access, such trials may be more difficult, yet possible. Studies in the EU on drugs such as trastuzumab, denosumab, and pembrolizumab, have shown this.

These trials will also be dependent on the incentive structures in place: if doctors and hospitals are making money from prescribing drugs, the incentive to run de-escalation trials will be less.

Funding for these trials can come from the payers, and mechanisms have been set up in various countries.

The potentials for enormous cost-savings should serve as an incentive for the payers, to finance these trials, as was exemplified by a de-escalation trial design of ibrutinib in chronic lymphatic leukemia.[27] The trial could even make money for society that can be invested in subsequent trials.[28] Obviously the endpoints of such trials need to be considered extensively, since a non-inferiority design is not always the best option. equivalence A viable way forward is to consider near-equivalence, in evidence generation.[29] Without such a pre-discussion on the endpoint, even a study that has quite convincingly shown that when given with food, one can reduce the standard dose of abiraterone in prostate cancer by 75%[30] without loss of effect, has not led to a significant change of practice in the western world. The same holds for the outcome of the Persephone trial on the duration of adjuvant Trastuzumab in breast cancer.[31]

[26] Ratain M et al, JAMA Oncology, 2019
[27] Goldstein et al, Health Affairs Blog 2019
[28] Van Ommen Nijhoff et al, Ann. Oncol, 2021
[29] Tannock et al, JCO 2021
[30] Szmulewitz et al, JCO 2018
[31] Earl et al, Lancet 2019

Running such studies is mostly relevant in the early part of the patent runway, and before the market is already set. A role the regulator in this aspect, could be to only approve drugs conditional to the performance of a de-escalation trial.

Cost-savings are not the only potential importance. Also improving safety is truly relevant.

Policy implementation is also an option, without the need for a large trial. Based on a pharmacokinetic study, the label of Pembrolizumab was changed from bodyweight based dose of 2 mg/kg every 3 weeks, to a fixed dose of 200 mg.

De-escalation of immunotherapy. The example of MOIO phase III clinical trial

Gwenaelle Gravis (Institut Paoli-Calmettes, Marseille, FR)

The recent improvements in immunotherapy for cancer have led to important gains in survival for more than 20 tumor types, but at the registered dose this has come at the cost of relevant toxicities for patients and major financial burdens for society.

Different endpoints and metrics used, have shown a decrease in drug clearance over time, and a related increase in plasma exposures.[32]

A maximum tolerated dose for the involved agents has never been reported, and a clear dose-response relationship has also not been found, and while the lower doses studied seemed to yield similar efficacy, for marketing registration higher doses were pursued.[33] Yet, post-marketing studies in renal cancer have confirmed for instance for Nivolumab, that a low dose of 0.3 mg/kg, yields equal efficacy compared to the registered dose (2 mg/kg) , as well as the highest ever tested dose (10 mg/kg),[34] in terms of progression free survival (PFS), and overall survival (OS).

Initially the immune-checkpoint inhibitors were approved on a weight-based dosing. Later this was changed to a flat dose system.[35] A very recent randomized study in head and neck cancer, where Nivolumab was added to metronomic dosing of methotrexate + celecoxib and erlotinib, showed that adding the low total flat dose of 20 mg every 3 weeks, added a significant benefit in PFS and OS.[36]

Another important question is how long immunotherapy should be continued in case of a positive anti-tumor effect. This is also not yet well defined. In controlled randomized trials in renal cancer for instance, Nivolumab was continued until progression or death, while other studies have limited use to 2 years. In metastatic urothelial cancer, the drugs where used until progression or death. A few discontinuation studies in melanoma suggest that treatment discontinuation at some point is possible, but in other tumor types this is not yet clear.[37] In Non-small cell lung cancer, a small randomized discontinuation study, if anything, seems to favor a stop & go schedule (where the treatment is discontinued, and restarted at subsequent progression), over a continuous dosing schedule.[38]

Pharmacokinetic simulation studies also suggest that, even at low doses, effective steady state levels are maintained for an exceptionally long time.[39] For a combination of Ipilimumab

[32] For instance : Brahmer J.R. et al, JCO 2010 ; 28 :3167-3175
[33] Renner A, J. Glob.Oncol. 2019
[34] Motzer R, JCO 2014
[35] Le Louedec F ; Vaccines 2020
[36] Patil V-M, JCO 2022
[37] ML Gauci, Clin.Cancer. Res. 2018
[38] Zalcman et al ESMO Proc. 2022
[39] Peer CJ, J. Clin.Pharm. 2022

and Nivolumab, an RCT has indicated that infrequent dosing of ipilimumab is significantly less toxic, and yet yields the same efficacy as more frequent dosing.[40] Such immune related toxicities can be long[41][42]

Taken together, the studies suggest that low dose treatment, and/or infrequent dosing, may be preferred in the toxicity/efficacy balance. Such approaches may also reduce the financial burden to society, related to drug costs, by some 90%.[43] In addition there will be major savings in clinic-time related costs, and travel costs.[44]

This is further assessed in the important French MOIO study, a Randomized Comparative Trial that compares the standard dose and dosing schedule of PD- (L)I inhibitors, to the same dose but given only every 3 months:

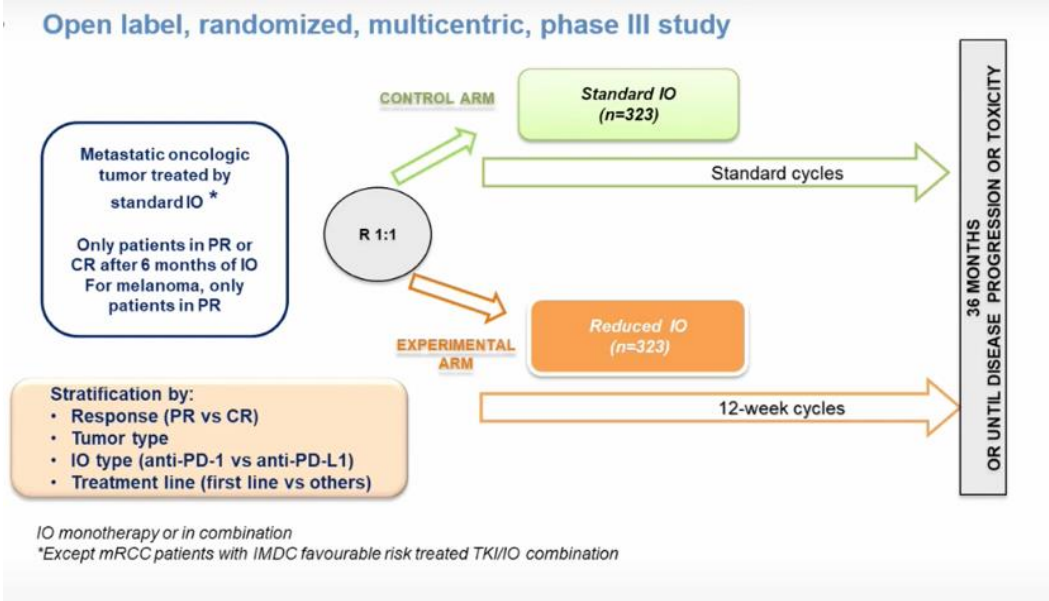


Figure 12. MOIO: study design

This non-inferiority study uses the hazard ratio of progression free survival as primary endpoint.

Panel Discussion and closing remarks

Q: 50% of current approvals are accelerated approvals. Does that impair the options to still perform pre-marketing dose-optimization.

A: A review of FDA accelerated approvals has shown that pushing the dose maximally to yield the highest possible drug activity leads to serious issues in ultimate tolerability, and in some cases with detrimental effect in overall survival. So, even in the accelerated approval pathway, and even if there is a high unmet medical need and no other effective treatment available, a randomized comparison of two doses of the experimental agent

[40] Vasudev et al, ESMO 2021

[42] Johnson DB, Nat.Rev. Clin.Oncol. 2022
[43] Renner A, J. Glob.Oncol. 2019
[44] Tachiki LML, Proc.ASCO 2022, abstr, 2588

to assess the optimal dose, is feasible, frequently without time loss. The randomized study can be underpowered[45], and FDA will still look at the totality of data in there review.

Q: How can we best assess dose in Immune-Oncology?

A: It may be slightly more complex with immunotherapies, and we should not stop assessing optimal dosage, at the point in time of marketing authorization. There are various aspects that likely then still need studying: treatment dose (including ultra-low dose, with a proper PK-PD element, and supported by in-silico data), treatment duration, dose-individualization. Such studies could also help solve the earlier issues on population diversity and inclusivity.

Q: And how can we deal with co-morbidities and frailty in the concept of dose-optimization? There have been some suggestions that stopping treatment early in frail patients leads to a shorter survival.

A: The CMF now includes the International Society for Geriatrics to help tackle this question, but there is no black-and-white answer yet. It makes sense to run such studies funded and supported by the payers. FDA is also advocating broadening the eligibility criteria in the dose-optimization process, to ensure that data on frail populations will be included. And EORTC is now collecting data on populations that are excluded from the trial, in parallel to collection of data on the trial population itself.

Q: Why is SIOP (pediatrics) not a full member of the CMF?

A: Pediatric oncology is way ahead of adult oncology as far as the efficacy of treatment is concerned. And the survival rates in pediatrics are now approaching some 90%. This was achieved by well performed studies on dose-optimization. So, dose-optimization may be less of an issue there, than the actual access to novel drugs.

Q: It is important also to look at societal incentives, in particular the costs of medical costs other than drug costs.

A: Indeed. And the costs of physicians and out-patient hospital care are nowadays just a tiny fraction of current drug costs.

Q: How can we ensure that population specifics are studied in the context of drug-toxicity and drug dosing as well. For instance: Do females need another dose than males? A key element in complexity is, when to do what? Pre-registration, or post-registration?

A: We should aim to have at least an early dose-optimization pre-registration, also since some patients refuse the novel treatments on the perception of poor tolerability. And there should at least be a plan in place on how one wants to guarantee availability of data in respect to population diversity. And we should not only look at dose, but also schedule, treatment duration, gender, elderly. This means not everything can be assessed pre-registration. In addition, the post-marketing space is likely the bigger framework where we will be able to study effects that are completely unexpected and cannot be assessed in vitro or even in vivo.

Q: What is the influence of pharmacokinetics (PK) and pharmacogenetics (PG) in this discussion?

A: With the concept of funding trials from the potential savings the results will provide, there is in principle an endless opportunity to study specific questions, including those on PK and PG. What we need is such a framework and structure.

[45] see FDA guidance: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases

Q: Should we re-consider our definitions on tolerability, for the more novel mechanism of action (MOA) drugs. Being a little nauseated every single day for the rest of your life may well be considered to be not-tolerable. We may have to design different toxicity endpoints for various mechanisms of action.

A: It will indeed be important to do so, and relate this to MOA, and to length of foreseen treatment, and likely also drug administration methods. Patient Reported Outcome (PRO) data may be helpful in this sense, the better characterize actual tolerability. There is a recent white paper from Friend of Cancer Research that addresses this.

Q: How can we find the balance of giving a higher dose to the larger part of the population that tolerates it, and a lower dose to specific populations with poorer tolerance?

A: This is what happened for checkpoint-inhibitors. And it may be the urge to get the highest possible efficacy, to guarantee regulatory approval, that leads the strategy. An aim to be perfect on the highest possible dose, with the highest short term anti-tumor effect. But "the perfect is the enemy of the good"! And for patients' safety and quality of life are extremely important as well, not only best efficacy.

Q: Is the FDA approach on pre-marketing dose-optimization in conflict with the EMA and CMF approach to do most work post-marketing approval?

A: No. The approaches are completely complimentary. Anything that can be addressed pre-marketing should be addressed pre-marketing. But dose-specification should not stop at the point of marketing approval. So, the specifications that can be made in the post-marketing period are also elementary and should be made.

FDA Project PRAGMATICA, is about simplified clinical trial design. It is complimentary to project OPTIMUS, and sometimes the two aspects addressed will be spaced in time, but sometimes they may not.

Session 5 Key Takeaways

- MTD is no longer the holy grail in early studies
- Initial randomized dose optimization studies can be underpowered
- Dose-discontinuation should be an ultimate part of dose optimization studies.