CDDF Multi-stakeholder Workshop

Innovative oncology trial designs

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CDDF
ANNUAL CONFERENCE

Changing paradigms to accelerate
oncology drug development
5 - 7 February 2024

Disclaimer

-Speaker, consultancy, advisory role (non remunerated)
Apogen, Roche, Mylan, Lilly, Pfizer, Novartis, Medicines for Europe, mAbxience, European Access Academy (EAA)

-Speaker (fee)
Astra Zeneca, EAA

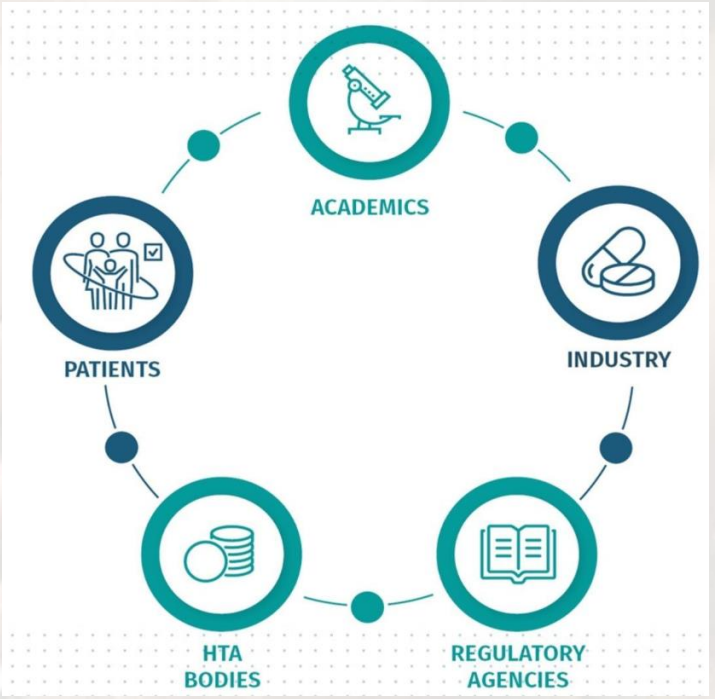
-Research funding paid to Institution: MSD; Novartis,

-Other roles
Co-chair of the Healthcare Professional Working Party of the European Medicines Agency (EMA), 2022-2025
Member of the EMA Cancer Medicine Forum

Former core member of the EMA Scientific Advisory Group-Oncology (2012-2021)
Past Director of the ESMO Public Policy (2020-2022)

Cancer Drug Development Forum (CDDF) member
EAA faculty member
Access to Oncology Medicines Coalition (ATOM) advisory group member
European Coalition for Access to Comprehensive Genomic Profiling (ECGP) member

Genuine and open multistakeholder-discussion



Scientific Committee:

-Stefan Symeonides (CDDF, UK);
-Rosa Giuliani (UK)

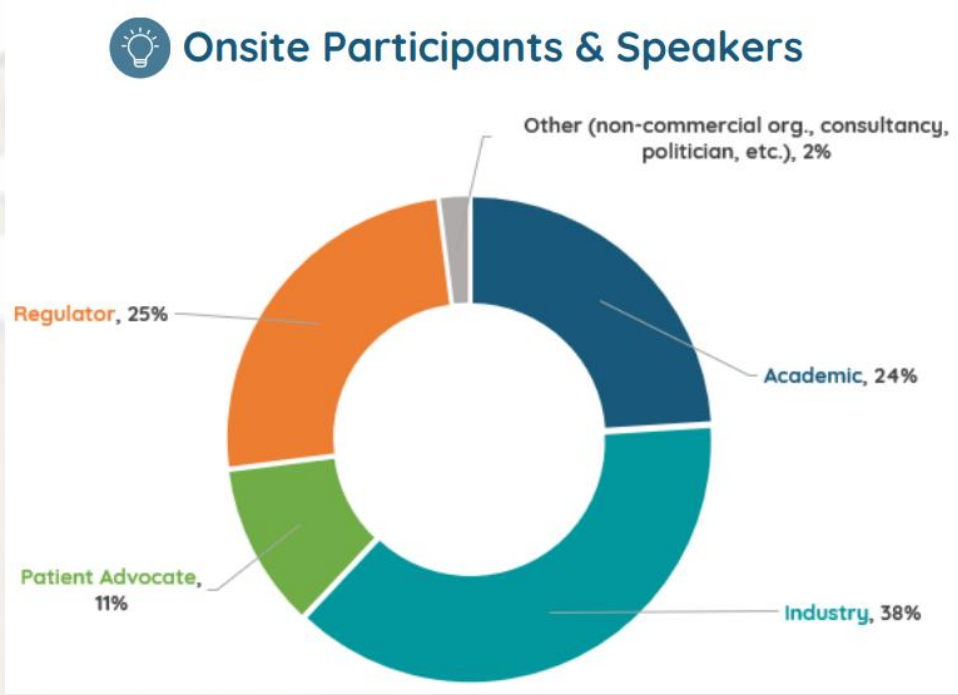
-Jeannette Borregaard (Genmab, DK)
-Lada Leyens (Roche, CH)
-Rachel Giles (International Kidney Cancer Coalition, NL)

SESSION 1: Endpoints for innovative clinical trials

SESSION 2: Innovative trial designs and estimands

SESSION 3: Towards patient-centric evidence generation

SESSION 4: Practicalities on innovative clinical trials



The workshop addressed a range of topics, from novel and surrogate endpoints, patient-reported outcomes and harnessing real-world data, to novel statistical designs and methods.

With the ultimate goal of designing trials in Europe that are more

Efficient

Adaptive

Inclusive

Informative

Fit for purpose: ask the right questions, obtain the answers within a reasonable amount of time, and are robust enough for regulators/HTA/payers to take into account

HOW innovative trials should look like, and HOW they can be PRIORITISED and IMPLEMENTED within Europe

SESSION 1: ENDPOINTS FOR INNOVATIVE CLINICAL TRIALS

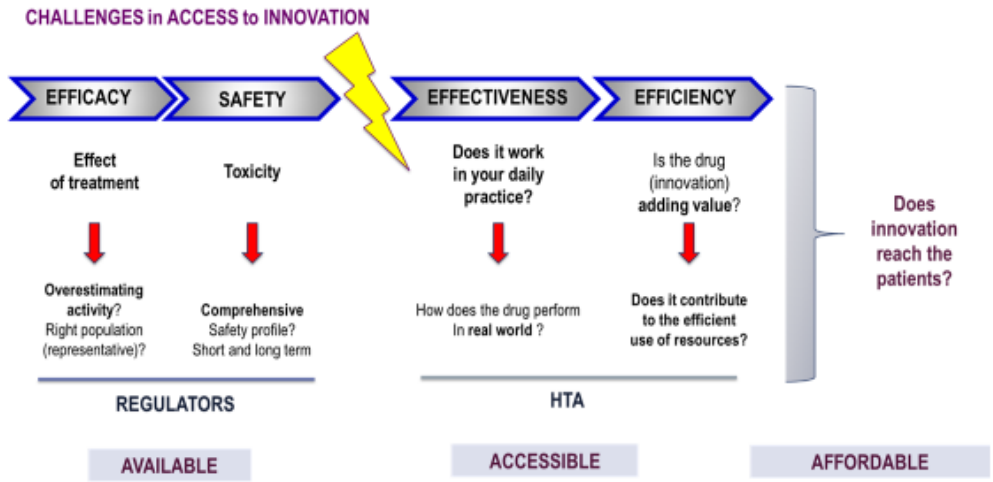
KEY TAKEAWAYS

- ·**RECIST** are validated, and **adaptable/evolvable**, e.g. iRECIST for immunotherapy. Current considerations are **ctDNA and radiometric assessments**, but **not yet been validated**.
- ·It takes **8-10 trials to validate a surrogate endpoint**; there are no novel validated surrogate endpoints at this time.
- ·**Distinct early- and late- endpoints** for conditional approvals may be considered – e.g. ORR.
- ·Ensure **maturity of data** - e.g. for PFS to imply OS.
- ·**Patient-meaningful endpoints** are considered at the **individual level** for quality and robustness; it is accepted that they may not be statistically powered.

-Tension between "acceleration" in regulatory approval and "deceleration" in HTA/payer validation
-MCBS

NEXT STEPS

- ·Harmonise **HTA, regulatory**, and **patient needs**.
- ·**Artificial Intelligence** will likely revolutionise endpoints, but will require confirmation and validation.



KEY TAKEAWAYS

- ·When **designing clinical trials**, it is essential to precisely **define the objective** of the trial, **formulate the research question** in a clear way and **consider the population** as well as the research context when selecting the most appropriate study design. Study design, outcomes collected and analysis methods need to be predefined and **allow answering of the research question formulated**.

- ·**Good planning** from the start and writing the protocol in a clear way that provides **clear arguments** for the selected design is essential both for **standard and innovative design**. This also applies to the good reporting of clinical trials.

- ·**Adaptive trial methodology** can be used to increase the **efficiency of clinical trial designs** and has been applied successfully in the **early-phase** setting.

- ·**Innovation of methodology** should not be for its own sake, its added value should be in **facilitating the answering** of the research question.

- ·**The estimands framework** is an essential framework for all future studies, to ensure the design starts by focusing on the research question and **frames the five components (population, endpoints, summary measure, treatment conditions,** and **handling of intercurrent events)** clearly. This subsequently guides data collection and statistical analysis.

- ·**The estimands framework** should be used for scientific advice and other interactions with regulators. It **requires a cross-functional approach** and **input from other experts** beyond statisticians.

- ·**The estimands framework** affects all aspects of clinical trial design, conduct and analysis and s**hould become the norm in future conversations on clinical trials.** We need all experts to adopt it.

SESSION 2: INNOVATIVE TRIAL DESIGNS AND ESTIMANDS

NEXT STEPS

- ·Ensure **any conversation on clinical trial innovation starts** with asking "**What is the scientific question?**"; define the estimand and select the methods to fit the question and the context.

- ·Share **more examples and learnings** from the use of **adaptive trial designs** as well as the **use of the estimands framework** to increase awareness and adoption.

- ·**Encourage and enable cross-stakeholder** and cross-functional **collaboration on estimands,** especially in non-statistical fora.

- ·Provide **training to iDMCs and ethics committees** to understand innovative trial designs and the estimands framework.

SESSION 3: TOWARDS PATIENT-CENTRIC EVIDENCE GENERATION

KEY TAKEAWAYS

- ·**Patient Preference Data (PPD)** can impact a wide range of decisions, from clinical development to regulatory approval, access/reimbursement and individualized treatment decision-making: it is not just about clinical efficacy!

- ·Stakeholders should work together to **define, incorporate and collect PPD** without duplicating efforts. Patient involvement is essential (e.g. design and analysis).

- ·External Control ARM (ECA) trials are **alternatives to a trial internal control arm** and can be **considered when RCTs** are **unethical, unfeasible or lack equipoise** (e.g rare indications / molecular subgroups, significant unmet medical need, limited treatment options, paediatric indications).

- ·They are **not a shortcut** and definitely not a low-burden effort: they require a convincing rationale that an RCT is not feasible, large high-quality quality and complete databases, a strong design and analytical plan, and they are less able to detect small/moderate differences. Draft FDA guidance is in place.

- ·High burden to demonstrate that the ECA meets the bar for valid treatment comparison.

- ·Pragmatic trials are meant to **inform decision-makers**, **enhance generalizability** by enrolling a population relevant to the decision in practice, and **streamline data collection** or measure a broader range of outcomes.

- ·Extensive, **multidisciplinary/multistakeholder discussions**, including **regulatory guidance**, are key to their design (feasibility and clinical context), conduct (operational and logistic aspects) and ultimate success.

NEXT STEPS

- ·Data and endpoints (PPD) that are meaningful to patients should be at the centre of every clinical trial, so **appropriate and regular collection of PPD should be an integral part of trial design**, as per other endpoints (OS, PFS, RR). The original clinical trial is the best time to collect and make good use of PPD.

- ·ECA trials represent a resource, particularly in certain domains, however **hybrid randomized** designs (e.g. phase II single arm and registrational phase III with hybrid control arm[SS1] [GR(2]) may provide more robust results to support drug approval and reimbursement.

- ·Pragmatic trials are instrumental in increasing **generalizability**, granting appropriate **flexibilities** and offering **access to trials** to a higher number of patients willing to participate. Constant dialogue with regulators and HTA bodies is key.

SESSION 4: PRACTICALITIES ON INNOVATIVE CLINICAL TRIALS

KEY TAKEAWAYS

- Rational combination therapies aim to maximise efficacy and overcome resistance. But there are important **practical mechanistic and regulatory considerations** for trial design (contribution of components), and its preclinical package (activity, interaction), that can differ between the FDA and EMA. **Cellular therapies may open new challenges**.

- For **rare cancers** (and rare subtypes), we need to **identify and engage with the population**, minimise heterogeneity, and **work in collaborative networks**. Regulators understand that size constraints inevitably limit Phase 3 endpoints. Surrogate end-points can be important and higher uncertainty must be expected while maximising the robustness of the data and external validation. www.rarecancerseurope.org has established consensus recommendations.

- **Platform studies improve the efficiency of trials** with shared design, documentation, reference appendices, populations, selection, costs/contracting, data, biomarkers and even control arms. **However, practicalities and planning ahead are essential for central deliverability,** site manageability and patient accessibility. **Simplicity**, where possible, **is key**. Master protocols effectively run multiple trials through one document and need to align their data delivery/cleaning/analysis, and handle evolving arms and populations.

- **Updates to ICH E6 (GCP) and E8** (General Considerations for Clinical Studies) **are designed to improve the design**, conduct and value of clinical trials. Ethics, scientific approach and patient involvement are the general underlying principles. **Stakeholder** (participant and investigator) **involvement**, in a quality continuum, using a proportionate and efficient risk-based approach, aims to better focus efforts on ensuring that **results support useful decision-making**.

NEXT STEPS

- **Combination and platform studies** would benefit from guidance such was developed for rare cancer studies.

- Please read ICH E8 (R1) and E6 (R3) together and please respond to the ICH E6 (R3) GCP consultations by 30th September. Note ICH E6 Annex 1, with Annex 2 drafting underway.

- Explore **how to address the accessibility of patient information sheets** and the consent process within Europe.

- Explore **how to support training of ethics committees** and IDMCs.

CDDF Annual Conference 2024

RATIONAL DRUG DEVELOPMENT

CANCER TYPE/
MOLECULAR TARGET

PATIENTS SELECTION

STUDY DESIGN

-MECHANISMS
Of PROGRESSION/
RESISTANCE
-TIME

TARGETS

DRIVERS

vs

PASSENGERS

CLINICAL DEVELOPMENT
TAILORED TO MOLECULAR
PHENOTYPES

PATHWAYS

BIOMARKERS

INNOVATIVE TRIALS

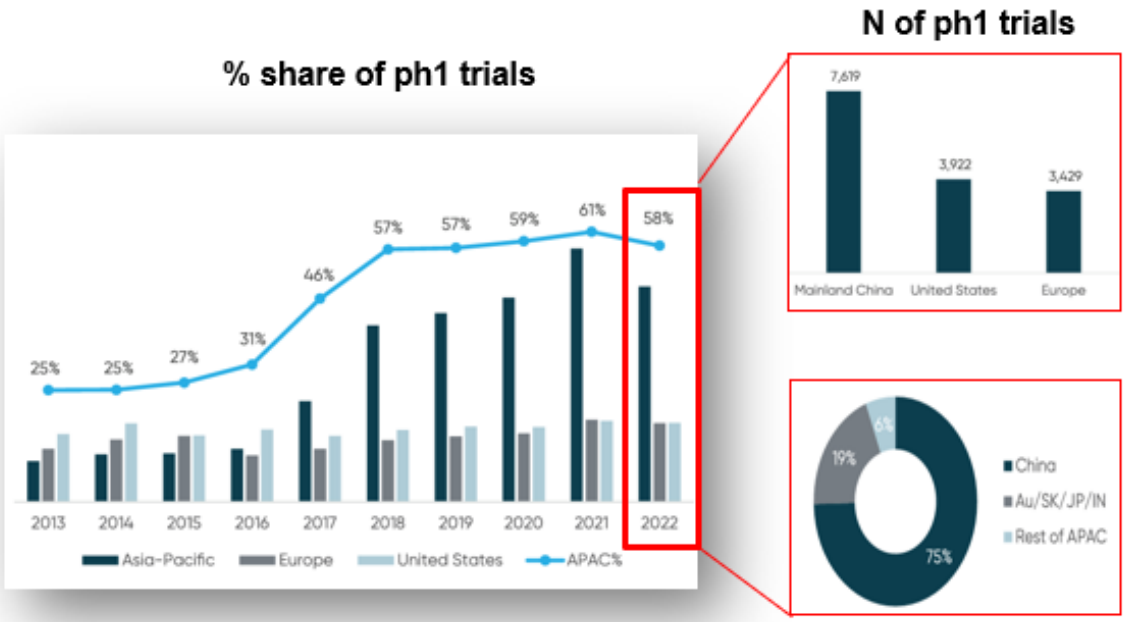
Spatial and
temporal
HETEROGENEITY

Access to test

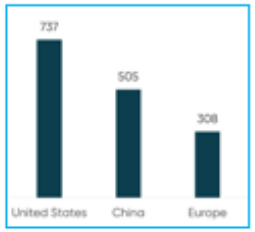
Complexity of study
design

10-y of (early) drug development looks at *East*!

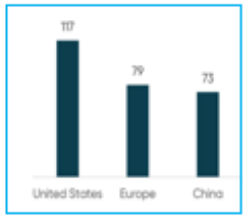
Ph1 activated in 2018-2022



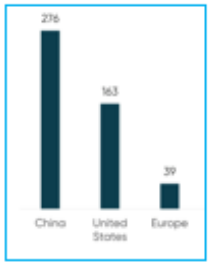
Immunoncology ph1



Bi-specific MABs ph1



Cell-based Th ph1



Novotech (CRO) Report on phase 1 trial (Jan 2023)

MADRID 2023 ESMO congress

Courtesy of D. Trapani

ACT EU Clinical Trials Analytics Workshop

25-26 January 2024

Launched in 2022: Accelerating Clinical Trials in the EU

ACT EU was partly a response to COVID
to get **bigger** trials off the ground **faster**

As the programme formed there were natural categories:

- GCP
- Methodologies
- Clinical trials regulation

Where should we discuss data about clinical trials?

ACCESS TO INNOVATION and CANCER CARE

DRUG DEVELOPMENT/EVIDENCE GENERATION

UNMET NEED

RESEARCH/ TRIALS

PRECLINICAL DEVELOPMENT

EARLY PHASE

ADVANCED PHASE

CLINICAL DEVELOPMENT

SUBMISSION for APPROVAL

HTA/ Price& reimbursement

Further evidence

?

MODERN, INCLUSIVE, REFLECTING THE PT POPULATION THAT WILL BE TREATED POST-APPROVAL

Access starts in the lab

RELEVANCE OF engagement

Early interaction

POLITICAL DRIVE

EARLY DIALOGUE

COLLABORATION (LIFE CYCLE)

Political driving engine

-Trial population not representative (incl/excl criteria)

-Not inclusive (race, social status, age, urban areas…)

-Dose optimisation

-Place in therapy (what proceeds and follows the cancer medicine in study)

Medical devices?

Changing paradig
oncology dr

5 - 7 February 2024

Happy to continue the discussion

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Highlights of the Discussion

- Please provide highlights of the discussion in bullet points and also present **multi-stakeholder perspectives** discussed if applicable

- Point 1
- Point 2
- Point 3
- Point 4

Take-home Message

- Please provide take-home messages in three to four bullet points and present **multi-stakeholder perspectives** discussed during the meeting
- Point 1
- Point 2
- Point 3
- Point 4

Next Steps

- Considering the discussion, please provide next steps to be taken in bullet points
- Point 1
- Point 2
- Point 3