Summary

CDDF 10th Alpine Conference

Current and Future Challenges of Innovative Oncology Drug Development

Innsbruck, Austria

26-28 February 2018

The Alpine conference is a unique forum organized by the Cancer Drug Development Forum that convenes every 18 months and gathers the leaders in the world of innovative cancer therapy development.

The 10th edition was held from 26 to 28 February 2018, in Innsbruck, Austria. This multi-stakeholder, interactive meeting offered plenary sessions with lectures on a subject of interest in oncology drug development, including case studies, followed by moderated discussions, and ample networking opportunities.

The audience consisted of representatives from academia, pharmaceutical industry, regulatory agencies and patient group organizations.

The program focused on the latest and future challenges and opportunities in oncology, with special emphasis on horizontal drug development, novel clinical trial design, biomarkers, rare cancers, patients' reported outcomes, and cell therapy. All topics and discussions emphasized the genuine importance of increased collaboration and dialogue among all players, academia, regulators, patients representatives, drug and diagnostic developers.

After the opening of and introduction to the 10th Alpine Conference, Prof J. Verweij (Erasmus MC, Rotterdam, NL) gave the keynote lecture on Clinical Trials Design in 2050, in which he argued that clinical trials will largely be replaced by personalized medicine through continuous profiling of cancer patients via implanted sensors, smart algorithms and individual drug production tailored to the patient's need.

Plenary session 1: Clinical Trials Design in an Era of Horizontal Drug Development

Larotrectinib (LOXO-101) is a pan neurotrophic tyrosine receptor kinase (NTRK) inhibitor that acts in a broad variety of tumor types only when the rare NTRK fusion genes are expressed. The clinical development of larotrectinib is an example of a new approach in early clinical trial design: a biomarker-based phase I study followed by a phase 2 basket study in children and adults. Further presentations focused on the pros and cons of basket (multiple parallel groups, each consisting of one type of cancer with the same mutation) and umbrella (parallel groups of one type of cancer, each with another mutation) trials, including statistical, regulatory, industry considerations. These type of trials become more popular and needed, because traditional trials becoming less realistic to derive robust outcomes with low patient numbers in rare molecular subtypes, due to developers' ability to better define

biomarker-driven subsets early in development. The approval of pembrolizumab by the FDA in 2017 based on a molecular biomarker instead of tumor histology, based on data from five phase I/II trials, might the beginning of a new era of tissue-agnostic oncology drug development. The upcoming latrotrectinib and entrectinib regulatory filings will help illustrate opportunities and challenges of prospective novel designs for registration.

Plenary sessions 2: Rare Cancers

Rare cancers are defined as arising in ≤6 patients per 100.000 persons/year. Collectively, rare cancers affect more than 20% of all cancer patients and 30% of cancer deaths. Rare cancers may not only be defined as rare tumor types including pediatric cancers, but also as a subgroup derived from a more common cancer that has become resistant to a treatment via a specific mutation. This was illustrated with the clinical development of osimertinib, for T790m EGFR mutated NSCLC.

The challenge is how to evaluate the effectiveness of treatments in rare cancers since, due to a low number of patients, conventional trial design is unsuited. As a first step, stake-holders, including patient organizations have to join forces in international collaborations such as the European Joint Action on Rare Cancers, EU Reference Networks and the CRUK/EORTC/NCI/NIH international rare cancer initiative, to share knowledge, encourage use and a true dialogue around innovative trials designs, and improve access to care for patients. It also requires another way of thinking for trials in rare cancer: use of progression free survival as a surrogate endpoint rather than overall survival and acceptance of a higher level of uncertainty instead of providing a definitive answer to potentially change clinical practice.

The various ways to provide access to (novel) therapeutics for children with cancer as early as possible were presented and exemplified.

Plenary session 3: Development and Approval Pathway for Changes in Dosing Regimens

Successful dose and schedule finding begins before phase I clinical studies are initiated. In the era of targeted therapy, Phase I studies underwent an evolution towards testing fewer dose levels and schedules, involving more intense PK/PD modeling, assessing BED instead of MTD, and using additional surrogate endpoints and expansion cohorts. Suboptimal dose and schedule will add extra costs to the already high costs and high attrition rates in oncology drug development. This was illustrated by examples of a change in dosing schedule and change in route of administration due to PK and safety considerations.

In the regulatory experience of the MHRA (2010-2014), 10% of major objectives raised on centrally approved oncology drugs during their evaluation were related to dose and schedule. For instance, due to uncertainties regarding the dose rationale of cabazitaxel, EMA asked for a Phase 3 study to demonstrate non-inferiority in OS of 20 vs. 25 mg/m². It was recommended to use PK tools to simulate different formulation, schedules or route of administration during the development to reduce such problems.

Plenary session 4: Patients' Reported Outcomes (PRO) in Oncology Patient-Centered Drug Development: Opportunities and Challenges

The format of the session (one panelist to introduce a topic briefly) enabled lively discussions between panel and audience. The objective of the session was to inform and discuss progress in the use of PRO to document clinical benefit in oncology drug development made in the last 15-20 years. PROs provide data on the health condition of cancer patients in a trial and compare the outcome in the experimental and control arm. The patient's perspective is not necessarily the same as that from the physician. Several measurement systems are available with different scopes: symptoms, function, quality of life and symptom not cancer-specific, and cancer-specific symptoms. PRO data are very complex and difficult to analyze and interpret. Discussions focused on baseline measurements, historical controls, lack of consistency in endpoints, standardization, reduction of the completion burden and redundancy, also for the patient, without jeopardizing the quality of PRO data.

Although PROs are a field recognized by EMA in 2016 in drug development (Appendix 2: PRO measures), the audience recognized the need for further education and engagement with EMA and FDA on how to best develop, validate and implement PROs towards use in registration programs . In view of the increasing importance of the field and to contribute to the development of the field, CDDF plans to organize a PRO workshop in the near future.

Plenary session 5: Translation of Cancer Biomarkers into Clinical Practice

The session covered a broad array of issues from biomarker development to financial implications of their use on the health system. Biomarkers can be used in oncology drug development and clinical care for e.g. diagnosis, prognosis, patient selection for personalized or individualized medicine, and therapy monitoring. The development of companion diagnostic tests is essential for robust treatment decisions, and safe, effective use of a treatment and should start early in drug development. Predictive enrichment is critical to the feasibility and success of trials when responders constitute a small proportion of the overall population. However, one must consider both the prevalence of the biomarker and the likelihood of response in biomarker-negative patients for rational, ethical trial design. This in mind, developers can avoid a possible loss of opportunity for patients represented by excluding a biomarker-defined subset before strong evidence/proof of concept is generated.

Pharmacogenetics is one of the main pillars of personalized medicine. Approximately, 35% of all drugs that EMA has granted market authorization mention pharmacogenetic relevant biomarkers in their summary of product characteristics. The value of pharmacogenetics was shown for the dosing of cancer patients treated with 5FU or capecitabine. 3-5% of the patients are poor metabolizers of the drugs based on the expression of genes coding for dihydropyrimidine dehydrogenase. They require an alternative drug to avoid serious side effects.

A 2016-survey of the European Cancer Patient Coalition highlighted that despite the global use of biomarker testing regional variations exists in Europe reflecting cultural and local practice in which biomarkers are not used. In addition, the accessibility of biomarker testing varies from country to country. This also holds for variations in delays for testing due to administrative barriers and reimbursement of biomarker testing. These hurdles will more and more affect cancer patients as they may not receive the optimal treatment.

General challenges in development and commercialization of biomarker diagnostics were discussed. The assays are frequently developed and manufactured by companies not belonging to the

pharmaceutical industry, which impedes access to the market. Solutions could be to strengthen collaboration with providers to access clinical samples, use accelerators, and academic incubators, and try to convince key opinion leaders. Engagement in early dialogue with HTA agencies will be key as well as to find support to develop systems perspective economic analysis of the benefit of the test. It is worth noting that not all regions can/will be able to afford some of the new technologies currently being used in clinical trials (e.g. NGS).

Plenary session 6: Report from CDDF Multi-Stakeholder Workshops

In this session the reports on the CDDF Multi-Stakeholder Workshops in 2017 were presented:

- ACCELERATE multi-stakeholder pediatric platform (March 2017, Brussels, Belgium),
- Innovation in Oncology Clinical Trial Design (May 2017, Frankfurt, Germany),
- Access to Innovative Oncology Drugs in Europe (September 2017, Madrid Spain),
- Minimal residual Disease (October 2017, London, UK).

Plenary session 7: Cell Therapy

Cell therapy comprises CAR T cells, dendritic cells (DC) and allogeneic transplantation. More than 15-year experience with monocyte-derived DC vaccines has shown that these vaccines are well-tolerated and safe but demonstrate clinical activity only in a minority of tumor patients. A current ongoing Phase III trial in stage IIIB/C melanoma patients will investigate whether response occurs in patients with T cell infiltrated or non-infiltrated tumors. Furthermore, clinical studies are planned with the combination of monocyte- and plasmacytoid-derived DC, because preliminary data indicate that this combination enhances the antitumor response.

The remainder of the session centered around CAR T cells, its technology, clinical data and regulatory issues. The history of the development and clinical application of CAR T cells, starting at Penn State University (Philadelphia, USA) was presented. It included the first clinical results in CLL patients as of 2006, the Penn-Novartis Alliance (2012), the FDA breakthrough designation (2014) and the FDA approval for r/r B-ALL and r/r DLBCL.

Clinical cases were discussed in NHL covering issues as bridge chemotherapy in the period between leukapheresis and infusion, manufacturing problems and side effects (cytokine release syndrome, neurotoxicity, hypogammaglobulinemia) followed by challenges for global multicenter trials, clinical results and Novartis portfolio for CAR T including multiple myeloma, glioblastoma, and mesothelioma.

Although FDA has approved CAR T, it has not yet been approved by EMA, amongst others because CAR T is in Europe considered as genetically modified organisms which make the process more complicated.

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If you have any inquiry about the CDDF Alpine Conference or publications, please contact the CDDF office via email (CDDF@ecco-org.eu) or by phone (+32 2 775 02 15).

Thank you for your interest into the 10th Alpine Conference and please save the date for the CDDF 11th Alpine conference held on 28-30 October 2019!