Summary of Discussion

Cancer Drug Development Forum (CDDF) 11th Spring Conference 2020

Current and Future Challenges of Innovative Oncology Drugs Development

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SESSION 1: THE RELEVANCE OF INDIVIDUAL COMPONENTS IN COMBINATION THERAPIES

Novel Preclinical Models to Assess the Value of New Drug Combinations

James Doroshow (National Cancer Institute, US)

The National Cancer Institute (NCI) in 2017 published the "NCI Almanac: A Comprehensive Screening Resource for the Detection of Anticancer Drug Pairs with Enhanced Therapeutic Activity (*Cancer Res*. 77: 3564, 2017)" in vitro studies of drug combinations. This systematic study of 5000 pair-wise combinations of all FDA-approved oncology drugs across NCI-60, discovered over 1200 more than additive combinations. Subsequently the NCI decided to perform a very extensive in vivo experiment on promising combos that were never before studied in human trials. Two examples of very unexpected combination therapies were highlighted: a) Bortezomib and clofarabine were both inactive in HT-29 Colon carcinoma xenografts, but when given together had impressive activity, which was actually confirmed in other in vivo models. B) Similarly, Nilotinib was ineffective as a single agent in Glioblastoma and Breast cancer models, but when added to paclitaxel induced this induced cure! The combination was taken into clinic 24 patients in Taxol resistant breast cancer patients, and yielded 4 long lasting partial remissions, and 12 stable diseases, without any additive toxicity. Even though there is no biological explanation for the observed effect, the principle of this in vivo panel experiment resembles the NCI-60 in vitro panel data, and creates a new standard in selecting combinations for clinical assessment.

NCI has now embarked on the development of Creation of NCI-PDMR (NCI – Patient Derived Models Repository, aiming to have 1000 models, with a focus on Rare cancer models. The first results were briefly presented. In an initial assessment of 39 rare cancer models it turned out that only 2 of 56 potentially active combinations had been tested in clinical trials. Dr. Doroshow stressed the difficulty of assessing response in a PDX, and concluded that likely anything less than prolonged stable disease in the model, has no value. Currently NCI is using a Bin-grouping, of which the relevant Bins are defined as follows:

Bin 1	**CR Achieved >1 timepoint (<60mm^3)**
Bin 2	**Tumor regressed ~30%, durable response (0.5-1c)**
Bin 3	**Tumor regressed ~30%, regrew at drug removal**
Bin 4	**Stable, durable response (0.5-1 cycle)**

It was concluded that

- systematic in vitro screening with in vivo follow-up of FDA approved anticancer drugs has produced multiple, novel, active therapeutic combinations, at least one of which is effective in the clinic.
- In vivo combination investigational drug screening of rare tumor PDX models has demonstrated an unexpected number of active drug pairs that are now undergoing

both therapeutic and mechanistic deconvolution which should form the basis of a public database that will support a wide range of novel clinical trials .

This model might provide major guidance in selecting combinations for clinical studies.

The Relevance of Individual Components in Combination Therapies: Pharmacological and Clinical Trial Design Aspects

Ruth Plummer (Newcastle University, UK)

Despite all recent improvements, we still have to realize that development of novel agents for oncology in general has a limited success rate, with only 14% of new agents that enter clinical trials making it to the market. And development takes a very long time.

An additional challenge is found in the observation that some of the newer classes of agents will unlikely have significant single agent activity, and combination studies becomes more common, and are performed earlier in the development cycle.

While traditionally, development of single agents has circled around toxicity, and only in later stages at efficacy, this may not be relevant with targeted agents, and is certainly not needed in chronic dosing.

Taking these single agents into combination is challenging. The identified hallmarks of cancer all provide potential drug targets, and therewith an enormous potential of combination therapies. It is desirable, to be asking the right questions, and select based on scientific evidence. To assess the relevance of the individual components in combinations, adequate data on single agent activity will be needed, as will be data on the mechanistic interaction to gain additional activity. A preclinical scientific hypothesis for mechanistic rational combinations seems recommendable. Currently, particularly in immune-oncology, many combinations under investigation are not based on such evidence of additive or synergistic effect, but rather on pragmatism.

Proper preclinical pharmacology studies can thus provide guidance. The example of the unexpected findings in a study combining a FAK inhibitor with a MEK inhibitor was discussed. Based upon experience from preclinical pharmacology, modular adaptive design clinical trials have been proposed and meanwhile successfully exploited.

Since the latter may have consequences for additional toxicity, as indicated above, such data should also be collected.

It was concluded that, to be more efficient, we should

- focus more on preclinical data,
- take fewer speculative combinations into the clinic,
- create better preclinical models

Isolation of Effect of the Individual Compounds in a Combination Regimen: The Industry Perspective

Stefan Schwoch (Lilly, UK)

It is crucial to try to isolate the individual contribution in a combination of drugs A + B, to establish the benefit/risk profile of that combination. Can you skip A+B vs A or B, if C is the standard? Also, if there is no good reason to develop A and/or B individually?

In such case, the June 2013 FDA guidance indicates that a clear biological rationale is needed. And states that "If contribution of each individual compound has been *adequately demonstrated in vivo, in vitro and/or in ph2 studies*, … then ph3 studies comparing the combination vs placebo or SOC … could be sufficient to establish effectiveness". The

CHMP guidance (EU) (EMA/CHMP/158268/2017) is a little less comprehensive, and indicates: "If the experimental agent (A) is added to an established regimen (B), superiority of AB vs. B should be demonstrated, traditionally, not include A alone arm…. Uncommonly, an entirely new combination AB is tested against a reference regimen. In these cases, solid non-clinical and clinical phase I/II data should support the need for both components in the experimental regimen"

Some recent experiences challenge the guidelines, at least in part. For instance

Pembrolizumab + axitinib or Avelumab + axitinib or Ipilimumab + Nivolumab respectively vs standard of care sunitinib in 1st line renal cell cancer. In all examples single agent activity had been confirmed first, and the need of first providing single agent superiority over sunitinib could be questioned. For Ipilimumab + Nivolumab approval had already been obtained in Melanoma, but this is clearly a different disease and thus activity in renal cancer could not be guaranteed to be similar, even though preclinical and phase I data were quite convincing.

The issue of use of different doses between phase 2 and phase 3 studies is another interesting point of discussion, as illustrated in the development of the combination of Encorafenib and Binimetinib.

In addition, one could debate if "borrowing" from non-clinical studies, early phase clinical studies, studies in other tumor types, or other lines of disease would be possible. And address the question whether dropping of arms after an interim analysis would enable "shortcuts" toward non-fully powered evidence. This was however also seen as a concern.

The Relevance of Individual Components in Combination Therapies: Regulatory Aspects

Jorge Camarero (Spanish Agency of Medicines and Medical Devices, ES)

We are developing combinations to yield better efficacy and/or improved safety (due to enabled reduced doses), over single agents. A stepwise approach is recommended, starting with a good rationale for the combination, via providing suggestive evidence for the contribution of all active substances in the combination to the desired effect, and of a positive

benefit-risk, to finally providing evidence of that the activity is relevant to the fixed combination of the medicinal products in the application. This could be assessed as an "add-on therapy" (design hardly ever used), "substitution", or "initial combination treatment" (for instance Nivolumab + Ipilimumab in Melanoma; or Pembrolizumab ± chemotherapy in NSCLC). In absence of single agent data, one cannot be sure that adding drugs to each other is any better than the individual components would be. Yet there are examples of approvals in such instances (Ipilimumab + Nivolumab in renal cell cancer). If one cannot show a survival benefit in such cases then maybe showing better response data can be used as convincing evidence. The guidelines have been stretched in such cases.

The contribution of each individual agent to the overall activity of a combination can be justified on cross study comparisons (same disease and setting) in terms of pharmacodynamic activity (ORR).

N important improvement in survival along with mechanism of action data and non-clinical data can justify a new combination.

Whatever the combination and suggested trial design, Scientific Advice is always recommendable.

Discussion:

- FDA and EMA guidelines on combinations are more or less aligned.
- "Science before speculation". The mechanisms of action should provide a sensible rationale to combine drugs. Even in case of Immunotherapies it is important to provide such data.
- Plea to look for synergy, rather than additivity.
- So, check mechanism → if there is synergy then check Pharmacology (if possible) → if OK, move ahead
- With the above:
    - Overall Survival + Mechanism > sufficient for evidence
    - RR or Progression Free Survival + Mechanism > need additional evidence
- Some seem averse to clinical translational research. The suggestion is to use the patient voice up front, to see if the designed translational elements of the protocol are justifiable.
- For adjuvant treatment development, data from metastatic disease on treatment activity, will remain crucial before starting the adjuvant development. Sometimes neoadjuvant response data could help.
- There is no easy answer on trial design for a true anti-metastatic drug.
- "Surrogacy" assumes that from a specific treatment effect you can anticipate another treatment effect. In the context of the total complexity of cancer, this is a complex concept.
- Control arms cannot be dropped in randomized trials, after interim analysis.

- We certainly need trial designs that avoid exposing patients to unnecessary treatment.
- It was suggested to have a specific workshop on the design (science, options, endpoints, comparison) of combination treatment trials

SESSION 2: REFLECTIONS ON CDDF WORKSHOPS OF THE LAST 18 MONTHS

Biomarkers and Patient´s Access to Personalized Oncology Drugs in Europe

Annie Pannelay (Romanian Health Observatory, UK)

Take home messages:

- There is no magic bullet.
- Innovative and validated methodologies to design trials are needed
- A pro-active approach to harmonise HTA processes (from Eunethta) is important
- Innovative access strategies to support timely patient access, while need from payers and providers to assess value, is important
- A specific data privacy framework to keep, protect and share patient data for research purposes and identify suitable biomarkers, would be helpful.
- Leadership or ownership of the theme to support concerted stakeholders' approach

Minimal Residual Disease (AML/CLL)

Irmela Radtke (Roche, CH)

Take home messages:

- EMA confirmed that CLL-MRD can be used as intermediate endpoint for approval, in RCTs designed to show superiority in terms of PFS as described in CLL specific guidance from 2015. EMA confirmed that approval on an intermediate MRD endpoint was explicitly not tied to conditional marketing authorization (CMA) in the guidance to allow flexibility (or avoid legal complexity around eligibility for CMA).
- In November 2018 EMA only had three drugs (Mylotarg, Vyxeos, Rydapt) reviewed and eagerly awaited further phase 3 trials conducted after ELN recommendations to answer open questions in regard to: mutations associated with relapse, timing for MRD, appropriate threshold, validated tests, can results be extrapolated across risk groups within a subtype, can results be extrapolated across different treatments (transplant, non-intensive treatment, how to get statistical power in subtypes with low prevalence.
- It was flagged that even draft guidance on MRD in AML was not expected in the near future in EU
- FDA guidance for CLL is similar to EMA (in regard to threshold) and meaningful MRD results have been included in USPIs (e.g. Venetoclax)
- FDA draft guidance for MRD in AML asked for measurement of MRD at CR with recovery of blood counts, BM preferred substrate, timepoint of measurement was

debated. Since the November 2018 workshop FDA released the final guidance and clarified positions

- Collaboration across industry to obtain appropriate data sets for Meta analyses to demonstrate surrogacy is key and was applauded by regulators (FDA, EMA).
- Efforts to collaborate across industry and academic groups to contribute to a meta-analysis to establish surrogacy are ongoing
- Further workshop on surrogacy planned in September 2020

Involving Patients in Oncology Drug Development

Claudia Hey (Merck Healthcare KGaA, DE)

Take home messages

- Multi-stakeholder discussions drive change.
- Patient advocacy perspective: a political will for change is important to establish the right framework for PFDD at the EU level.
- Standardized outcome assessments can improve informed decision making and the quality of care
- From the Regulator perspective, significant progress has been made. Current priorities are advancement and standardization of Patient Reported Outcomes (PRO), and patient experience data collection, analysis, and communication.
- Time pressure for industry to move fast - may not always allow for patient involvement in a meaningful way.
- Use the multi-stakeholder network within CDDF to periodically share information and perspectives to drive progress.
- Monitoring of the global regulatory environment on patient involvement in (oncology) drug development

The Use of Real-World Data to Optimize Oncology Drug Development and Access

Axel Glasmacher/John Smyth (CDDF, DE)

Take home messages:

- Regulatory/HTA frameworks on the use of RWE for drug development featuring key considerations for decision-making.
- Harmonization, ideally led by European Commission or ICH. Establishment of best practices for RW study conduct.

- Categorization of evidence of RWE to help prioritize and plan studies according to the hierarchy of evidence (e.g. establishing the gold standard of RWE)
- Data quality standards and strategies to ensure data consistency and completeness (endpoint definitions and assessment, linkage to genomic data, capturing of comorbidities)
- Guidelines on data collection and analysis, including (minimum set of) sensitivity analyses and adjustment for confounders
- Efforts to overcome fragmentation of data and access to data through a common data model.
- A new concept of informed consent may be required
- Clearly specify study objectives and rigorous statistical analysis plan aimed at testing and adjusting for bias prior to study initiation, mitigation of missing data and false positive results
- Plan RWE studies prospectively (e.g. pragmatic clinical trials, observational studies), especially if conditional approval is the goal. Engage with regulators early on.
- Preferably use contemporaneous control (vs historic) in RCTs for rare cancers where external control is the only option
- Ensure early patient involvement in study design – patient input on relevant outcomes is critical
- Engage in early and ongoing dialogue with regulators and payers on RWE requirements
- Seek early scientific advice to support qualification procedures for novel methodologies to harmonize approaches in the EU
- Make an inventory of existing registries to optimize use of existing frameworks both at the national and international level
- Share success stories and learning

SESSION 3: TUMOR AGNOSTIC DRUG DEVELOPMENT

Tumor Agnostic Drug Development: Medical Aspects

Irene Braña (Vall d'Hebron Institute of Oncology, ES)

Herceptin may have been the very first drug for which, after an initial full focus on breast cancer, a tumor agnostic development was also performed. Imatinib was developed in parallel for CML and GIST. So, tumor agnostic development is around since some 20 years, but has considerably evolved since. It aims at tumors harboring the target of the drug, rather than at specific histologies, and has led to so called "basket studies" (same drug(s) for different histologies). FDA defined these as "A master protocol, designed to test a single investigational drug or drug combination in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics". They can be non-biomarker selected (example: Pembrolizumab (Keynote-001 study) or Biomarker-selected (Example: Vemurafenib (combinations) in V600E-mutant non-melanoma; and Larotrectinib in NTRK fusion tumors). Challenges in such studies are the quality and validation of the selection marker (which can lead to long delays prior to allowing study entry), the statistical design, and an in-depth understanding of biology across tumor types.
For the biomarker it is proposed to use less stringent requirements in early development studies.
In very rare tumors, the ethics and feasibility of randomization can be an issue, and single arm studies might be acceptable. In such cases basket studies are multiple single arm studies.
A basket study should be clearly distinguished from an "umbrella" study, in which a single tumor type is treated with different drugs, based on expression of different biomarkers.
With the number of drugs in development and the enormous number of rare indications, there are ample opportunities for collaborations between academia and pharmaceutical industry. The Cancer Core Europe Basket of Basket study exemplifies this.

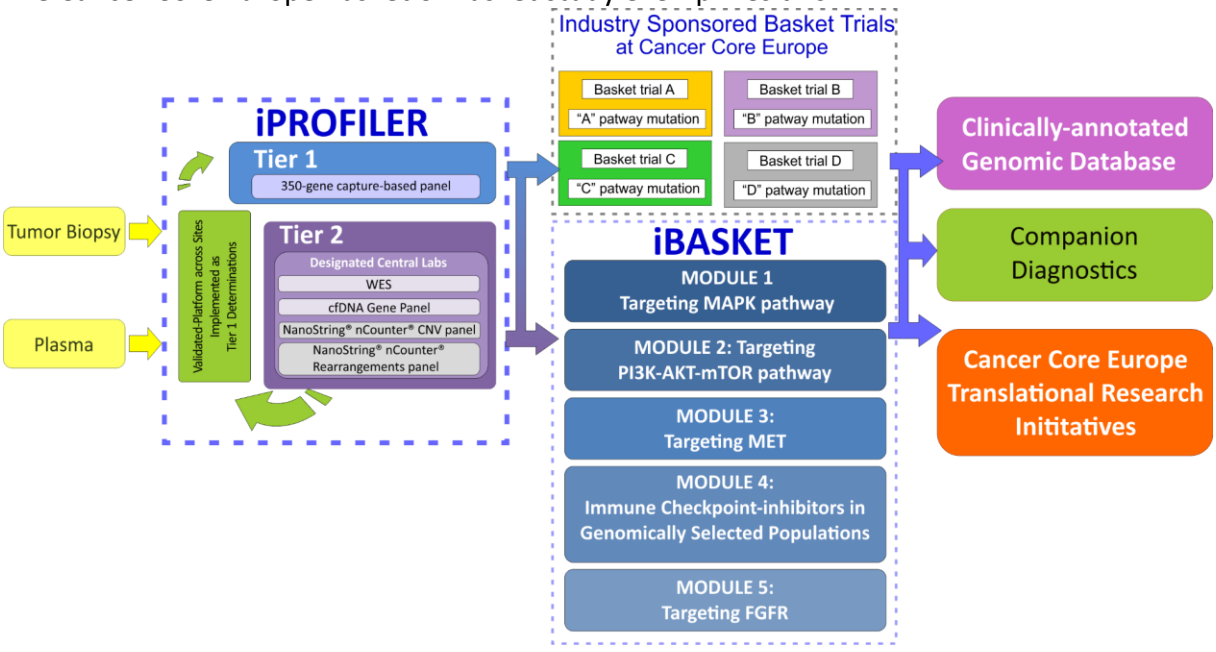


Fig: The Cancer Core Europe Basket of Basket Study

Personalized Healthcare and Tumor Agnostic Development: Requirement for Innovation and Collaboration

Todd Riehl (Genentech, US)

Genome studies have enabled a greater understanding of the heterogeneity of tumors, and a targeting of the molecular cancer cause in subpopulations. In parallel, improved technologies enabled a better patient selection to the therapeutic targeting of the molecular cause. For both the previously mentioned basket- and umbrella trials, genetic testing is key. This leads to small distinct populations, the rarity of which precludes traditional statistical significance approaches. It has been suggested to use Real World Data (RWD) and Real-World Evidence (RWE) for comparison, instead of using Randomized trials. But given the yet poor quality of RWD, and the issue of contemporaneousness, the feasibility of using them remains highly questionable. Instead, single arm cohorts and overall response rates, without the use of a control arm, may be necessary. In such cases intra-patient comparison to the last prior therapy, may help to disclose real benefit of the trial therapy. Particularly if two-tiered futility analysis are used in statistical planning, and new variant labelling approaches are being considered. In order to move ahead, we will need agreement within stakeholders (Health Authorities, HTA bodies, industry, and academia) on mentioned issues, on the approach to providing appropriate supportive data, on the use of Real world/registry data for mutation/biomarker-selected populations with SOC treatment(s). And we need pragmatic new solutions in these new paradigms, rather than adherence to current standards.

Case-Study: Tumor Agnostic Approval of Vitrakvi ® (Larotrectinib)

Chitkala Kalidas (Bayer, US)

In September 2019 EMA issued its first conditional approval for a tumor agnostic indication, involving Vitrakvi ® (Larotrectinib) for tumors displaying a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion. Such gene fusions, of which a variety have been described, were found to drive oncogenic signaling through canonical downstream pathways. They result in a constitutively active and aberrantly expressed TRK fusion protein. NTRK fusions mainly occur in certain rare tumors. Preclinical studies had shown larotrectinib to be active in models expressing NTRK fusions. The phase I study population was tumor agnostic, but target selected, and impressive responses were seen. In the path to registration, scientific advice from EU agencies was extensively gathered, and the EMA 2017 workshop on “histologic-independent indications” provided guidance. The pivotal pooled efficacy data set was composed of 3 studies, including the phase I study in adults, a phase I/II study in pediatrics and a phase 2 basket study, yielding 93 patients (in only 10 there was no decrease in tumor size), and an additional 9 patients with CNS tumors. On top of this there was a support data set of 55 patients from other programs. There were no severe adverse reactions. CHMP considered the efficacy data to show “outstanding effect in this late stage disease setting”, and provided approval for NTRK fusion tumors in patients “who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and

who have not satisfactory treatment options". CHMP deemed that the data set was supportive of conditional rather than regular approval, and recommended that additional data had to be generated as a post-approval measure in order to make the dataset more comprehensive and to confirm the histology-independent efficacy as well as to investigate the primary and secondary resistance mechanisms. The numbers for this were specified. These additional data should also provide additional safety data on an additional consecutively enrolled set of 200 patients, and the applicant also committed to build a 5-year follow-up safety data set in pediatric patients, and an updated (population) pharmacokinetic model and more pediatric PK data.

Key success factors for this first tumor agnostic approval were:

- Clear and consistent assessment/feedback from the regulators during the review
- Robust scientific discussions combined with pragmatic assessments
- The guidance of the above mentioned EMA workshop

and these could provide metrics for future tumor agnostic applications.

Histology-Independent Indications: Regulatory Aspects

Elias Pean (EMA, NL)

In regulatory perspectives an indication is a "description of patient, disease and treatment characteristics that describes a population in whom the balance of benefits and harms has been established to be positive". A specified tumor type or histology is not really necessary, as long as the benefit-risk balance in a well-defined population is positive.
Taking this into account, the concept of histology-independent indications: requires in-depth knowledge about the mechanism of action and at least a strong plausibility across subgroups; requires the need to explore heterogeneity of effects (interactions; resistance mechanisms) ; requires the evidence of positive benefit-risk balance within multiple therapeutic contexts. All of this is easier when high unmet need is present across subgroups, and challenging when competing against available options with established clinical utility in some subgroups.
Even though the benefit-risk assessment is absolute, it requires contextualization, which is challenging in the histology-independent setting when the evidence is based on uncontrolled data. One of the potential risks related to development of a histology-independent indication is "Orphanization" (one unique marker artificially selected to justify ultra-orphan development despite the drug (or the marker) not being that specific of the driver/disease), which is the reason why there is a need for a strong biological rationale for a histology-independent activity of the drug before entering clinical developments. All of these aspects were considered in the EMA review on Larotrectinib.

Given initial divergent views within the CHMP it requested expert input on scientific issues on whether NTRK gene mutations were driver mutations regardless of tissue of origin, whether they had a prognostic impact, whether there was a justification of treatment with larotrectinib in certain conditions, and what additional data would be relevant. All of the recommendations

received helped to further define the uncertainties in the benefit-risk, adjusting the indication and other elements of the product information but also the data required to be provided post authorization in the context of a conditional approval.
The experience further stressed the importance for developers to consider CHMP scientific advice as early as possible in the development when innovative approaches are being explored. The challenges with histology-independent development is that it will require a different approach to patient selection and evidence generation, and the role of Registries to support benefit/risk evaluation should be explored.
There is an ongoing dialogue between EMA, FDA (international cluster; workshops), EUnetHTA, EFPIA, CHMP biostatistics and oncology working parties on these issues.

Discussion:

- The bar on efficacy will be higher in earlier lines of treatment, and the timeliness of marker assay even more important. The discussion on randomization should occur early in those cases. Sometimes a single arm study in first line might still be an important option. Larotrectinib approvals did not insist on randomized studies.
- The definition of agnostic would be “Activity in a diverse set of tumor types”. This does not have to be very high throughout. Resistance mechanisms may be different, while driver mechanisms are the same. We should learn from experience.
- The risk of tumor agnostic approval may be underpowered evidence or even lack of evidence in small subgroups in the study.
- There is no consensus yet on the definition of “clinically meaningful”.

SESSION 4: CELLULAR THERAPIES INCLUDING CAR-T CELL THERAPIES

CAR T cells – Regulatory Aspects from the EMA Committee for Advanced Therapies

Martina Schüssler-Lenz (Chair Committee for Advanced Therapies (CAT), EMA, NL)

Advance Therapy Medicinal Products are regulated under EC1394/2007, and include Gene therapy or genetically modified cells (such as CAR-T cells), Somatic cell therapy, or a Tissue engineered product. They are considered as medicines and authorized via a centralized procedure. The Committee for Advanced Therapies (CAT) is responsible for the assessment of quality, safety and efficacy and prepares a draft opinion, for subsequent final opinion provided by CHMP. Recent assessments included CAR-T cells as well as TCR modified T-cells. Two CAR-T cell products were authorized in 2018: Axicabtagene ciloleucel, and Tisagenlecleucel. Seven further products are expected for marketing authorization in the next 2 years. They mostly cluster around CD19 and BCMA targets.

These seven CAR T cell products in development have entered the EMA Priority Medicines (PRIME) scheme. In the PRIME kick-off contact with the applicant quality, non-clinical, clinical as well as regulatory aspects are discussed. This includes potential changes to commercial manufacturing processes and comparability analysis, the clinical data package required for marketing authorization, the options of full versus conditional approval, the required interaction with Health Technology Assessment bodies (HTAs), and the availability of disease registries and strategy details for post-authorization evidence generation (including a contextualization of the results). In addition, specific regulatory topics are discussed, such as a pediatrics investigation plan, and orphan designations. For authorized CAR-T cell treatments there have been conditions on restrictions for supply and use (only in specialized centers), and restrictions on safe and effective use (including educational programs).

With regard to the EU orphan legislation and implications for market access of CAR T cells targeting the same antigen, e,g, BCMA, developers are advised to develop strategies for prove of “non-similarity” versus other CAR T cell products.

A gap analysis is performed as result of the PRIME kick-off meeting, and identified gaps are addressed in EMA scientific advice procedures. The CAT has developed various specific guidelines, that can be found on the EMA home page.

Cell Therapy in Solid Tumors

Victor Moreno Garcia (START Madrid FJD, ES)

For solid tumors there are currently 3 types of cell therapies under investigation: 1) Tumor infiltrating lymphocytes (TIL), 2) T-cell receptor (TCR) therapies, and 3) CAR-T cells. The number of studies is rapidly increasing, as is the number of involved malignancies, despite the difficult path of development.

It started with TIL harvested from excised tumors. The complexity of the treatments initially limited development to academic sites. More recently, industry became involved. The example of Lifeleucel (LN-144) in melanoma is discussed. For LN-145 in cervical cancer, recently FDA breakthrough designation was granted. Response rates are in the range of 40%. There are now also efforts to stimulate responsiveness by combining with PD-1 related agents.

More recently efforts have started to use CAR-T cells in solid tumors as well. Target selection was a challenge. Solid tumors do not have many extracellular antigens that are only expressed in malignant cells.

A slightly different approach of local administration of CAR-T in Mesothelin expressing mesothelioma (in combination with systemic PD-1 directed therapy), avoids the systemic toxicity of CAR-T cell therapy. Despite the local therapy, CAR-T cells could be detected in peripheral blood, but yet there was not severe systemic toxicity. The response rate of 41% is compelling.

Given the lack of specific extracellular antigens, modified T-cell receptor treatments have been given more attention. They can be targeted against intracellular proteins, and specific mutant proteins. The targeted antigens have to be very selective, otherwise severe organ toxicity may occur. So, the current approach focuses on public antigens in germline cancer cells. NY-ESO is the first example, and NY-ESO-1^{c259} TCR in synovial sarcoma has now been submitted for approval. With a response rate of 50%. Also, in liposarcoma the response rate is high. The number of cells has been shown to be important for effect. Another example involves the use of MAGE-A4 as antigen in synovial sarcoma, again yielding a 58% response in a very small study.

More recently approaches towards patient specific neo-antigens have also been reported.

The clinical trial designs are quickly changing this cellular therapy approaches. Randomized are difficult to perform, and single arm trials are increasingly important. Logistics of the involved therapies still pose a challenge to those trials.

CAR-T cells: Progress in Hematological Malignancies

Gerhard Ehninger (Cellex, DE)

CAR-T cell therapies involve approximately 50% of all cell therapies in development of hematological malignancies. The number of successful developments is minimal, if compared to the total numbers being explored.

After apheresis, the T-cells are selected, ex-vivo the involved gene is inserted and the cells are cultivated, and after lymphocyte depletion therapy they are reinfused into the patient. After attachment to the tumor cells in vivo, malignant cell destruction should result. The complexity cannot enough be stressed. The total process can take several weeks.

The first approval was on Axicaptagen-ciloleucel in diffuse large B-cell lymphoma (DLBCL). The study included 119 patients. Overall response rate was 83% with complete remissions in 58%. Side effects are considerable, partly due to cytokine release. Survival seems to plateau at 50% after 2 years. A retrospective registry study showed similar results, albeit that the OS plateau

was at 20%. Important observation is that effect seems to be related to number of cells infused, but also to the mass of the tumor. Tisagen-lecleucel, also in DLBCL, directed against CD137, was similarly effective. Problem in that study was the time to apheresis. This treatment was also effective in B-cell lymphoblastic leukemia.

Newer treatments seem to yield less severe toxicity.

BCMA directed CAR-T cell therapies have been explored in multiple myeloma. In these studies, the survival curves do not show plateauing. Likely due to target shedding, and therewith antigen loss.

The concept of Adapter CARs was also briefly discussed. They have a switch module between the CAR-T cell and the tumor cell. The switch has to be given separately.

HTA Challenges for Cell and Gene Therapies

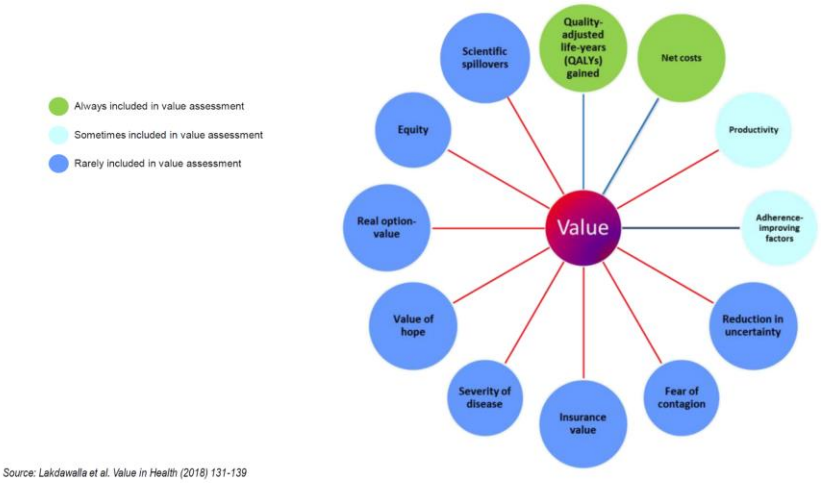
Stephen Palmer (York University, UK)

A separate HTA process for Cell and Gene (C&G) therapies has not yet been developed, and it is questionable if the existing ones are fit for purpose. The technologies present a high level of clinical uncertainty, but also concerns on affordability and budget impact. Health Technology Assessment (HTA) assesses the added value of a new health technology compared to the current standard of care. It considers the therapeutic effect, side-effects, impact on quality of life and costs, in a systematic and multidisciplinary process. This provides policy-makers with evidence-based information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective.

The HTA challenges of C&G therapies are evidential (use of surrogate endpoints, small trials, historical comparisons), on price and affordability (one-time administrations of treatment that might fail, yet has a high upfront price, and requires infrastructure costs), both leading into high levels of uncertainty. The HTA organizations have come up with conclusion on the existing HTA procedures in assessing G&C therapies. They felt that core elements of the methodologies are suitable, but adaptations will be needed. Learnings from the initial experience in the UK were that description of the target population and proposed positioning is critical, that the violation of ITT principle creates issues, that the need for extrapolation approaches is central, that resource and cost uncertainties related to adjunct therapies and treatment administration and adverse event management need to be dealt with, and finally there are a number of issues with implementation. In the HTA process observed short time survivals are being extrapolated with parametric models, to estimate longer term survivals. However, the resulting data still have a high level of variations and heterogeneity, which can have important consequences in the predications on HTA aspects.

In the UK, from an HTA perspective, Quality-Adjusted Life Year (QALY) serves as a reference case, and a health service perspective is used for costs. Costs per QALY have strengths and limitations. But other elements of added value may have to be include in the HTA assessment.

Additional elements of value for C&G therapies?



Source: Lakdawalla et al. Value in Health (2018) 131-139

Augmented cost-effectiveness analysis (trying to understand the net-costs or net-values), and multi-criteria decision analysis (providing weight to each of the attributes of value) are 2 ways to think about additional attributes of value. As yet, no of the existing methods of aggregation is considered perfect. Cost per QALY is still a widely used starting point in the deliberative process. Currently, checklists are being used to assess elements of value.

Managing uncertainty and risk sharing are, and budget impact and affordability complete the list of important elements of consideration.

CAR-T is a ground-breaking therapy. Conventional value/HTA frameworks have been successfully applied to CAR-T but many challenges from study designs, and further research needed on distinctive features that are not captured in QALY. There is an Important role for a structured deliberative process.

Managed entry and flexible pricing are important for initial approvals. There is a need for constructive dialogue between stakeholders – and for progressive reflection of value as knowledge increases. As well as a scope to better communicate benefits of access vs risks/uncertainties under different scenarios.

Discussion:

- Microenvironment in solid tumors provides another challenge for T-cell related therapies. The responses seen however, indicate that the cells reach their target.
- Concern is raised on the issue of allowance-to-treat approval by insurance companies, on top of marketing approval and reimbursement approval by regulatory authorities. Patient advocates feel they could be consulted earlier in such discussions. For patients the most important issue is access to treatment. Involving them in the issue of pricing would help. They are as worried about sustainability as the authorities. The view was expressed that the decision to treat should remain with the involved treatment teams.

- The authorizations of the two CAR T cell products were based on single arm trials, (response rate, duration of response, etc.),. It was questioned whether these provide an adequate basis to judge efficacy.. Yet, it will be difficult to completely ignore the high response rates etc. seen in patients that have exhausted standard of care treatments, and insist on a randomized trial, that might not be doable because of patient refusal to participate. If effects in single arm studies are extremely good, way beyond expectations, we should be able to use these.

Ongoing Revision of EMA Anticancer Guideline and Thoughts on Future Evidence Requirements

Sigrid Klaar (Swedish Medical Products Agency, SE, and EMA Oncology Working Party)

The EMA Anticancer guideline is a continuous work in progress. The current version dates back to September 2017, and in 2019 a concept paper on the need for an update was published. The revision is needed due to developments in e.g. technology and biomarkers, leading to small patient populations and difficulties in performing randomized controlled trials (RCTs). It is expected to soon be published for public consultation.

In the updated guideline, the biomarkers section is being expanded, with focus on quality and validation issues, ensuring a representative biomarker-evaluable population, pre-planning of subgroup analyses, biomarker-based patient selection in confirmatory studies, the fact that new biomarkers with unknown prognostic effect will require controlled data, and finally co-development of drug and companion diagnostic.

The changes in the section on phase 3 trials involve explanation of the regulatory thinking on PFS and OS, patient reported outcomes as primary endpoints, the acceptability of early interruption for efficacy, and terminology requirements on “data maturity”.

There will be a new section on study designs for special situations, such as very rare cancers and basket- and/or umbrella trials. Important issues are underpowered studies, justification of single arm trials (SATs), use of real-world data and historical controls, the different purposes of basket trials and consequent different requirements, and the acceptability of pooling of baskets in a trial (e.g. for a histology-independent indication).

What about future evidence requirements?

Possibly, some degree of future increased alignment between stakeholders in terms of evidence requirements might be envisaged. The current basis for market authorization is a positive benefit-risk balance, formally without consideration of how this relates to other drugs. In conditional market approvals, applied for many single-arm trials, relative efficacy and safety are, however, also considered. With an increasing use of SATs, we may therefore see a shift from absolute to more of relative benefit-risk balances, which might require new methods as well as guidance on the requirements thereof. Such development could make parts of the regulatory and HTA assessments more similar.

The importance of the patient perspective is being increasingly recognized and the subjective data from patient-reported outcomes (PROs) may have increased impact on the benefit-risk balance in the future. Guidance on PROs is already provided in the Guideline.

Real-world data (RWD) may potentially also, after refinement and validation of methods, become a more important component in future approvals, thereby possibly further reducing the gap between regulators and HTAs. Finally, the currently somewhat different regulatory evidence standards for approvals based on SATs versus RCTs might need to become more aligned.

Cancer Medicine Development and Use – EMA Regulatory Science Strategy 2025

Ralf Herold (EMA, NL)

The purpose of the EMA Regulatory Science Strategy is to harness the regulatory science for the purpose of translating patient´s access to medicines into better healthcare systems and provisions overall.

The strategy sets out 5 goals for human medicines regulation:

- Catalyzing the integration of science and technology in medicines development
- Driving collaborative evidence generation – improving scientific quality of evaluations
- Advancing patient-centered access to medicines in partnership with healthcare systems
- Addressing emerging health threats and availability/therapeutic challenges
- Enabling and leveraging research and innovation in regulatory science

Public consultation in 2018 resulted in a ranking of priorities:

1. Foster innovation in clinical trials
2. Promote use of high-quality real-world data in decision making
3. Reinforce patient relevance in evidence generation
4. Contribute to HTA´s preparedness and downstream decision making for innovative medicines
5. Support development in precision medicine, biomarker and `omics.

In just a few months the definitive strategy will be published.

Examples of underlying actions with relevance for oncology are:

- Expand the B/R assessment by incorporating patient preferences and PRO´s.
- Apply structured B/R assessment to improve communication to the public.
- Improve communication with HTA and payers.
- Progress implementing pediatric medicines action plan and geriatric strategic plan.
- Assess clinical value of new endpoints and role in patients´ access to new medicines.
- Promote more integrated development aligning Scientific Advice, Clinical Trial approval, and GCP oversight.
- Support developments in precision medicine, biomarker and `omics.

The strategy has broadly been supported, and will be a motor for improving oncology drug development.

Oncology Center of Excellence: Envisioning Product Development for 2025

Richard Pazdur (FDA, US)

The Oncology Center of Excellence (OCE) was established to coordinate regulatory processes in the development of Devices, Drugs, and Biologics for Oncology, all three of which are used by patients in their treatments. There has been enormous growth in the past decades and, given the increase of drugs in development, it has become important to rethink how the applications are evaluated.

Several oncology regulatory review pilots have been started to streamline the review process. OCE implemented the Assessment Aid, which is prepared by the Sponsor and is organized to present the data, the Sponsor's interpretation, and the FDA assessment. This approach reduces the time spent preparing multiple reviews for an application and focuses the review effort on critical aspects of the application.

The next OCE Project is Real-time Oncology Review (RTOR), which allows for early submission of electronic files and datasets while the study reports are being written. RTOR allows FDA to start the review of the datasets and other key information prior to the full application submission.

OCE also implemented Project Orbis, in which participating countries (Australia, Canada, Singapore, Switzerland, USA) review applications in collaboration. Each regulatory authority will make their own regulatory decision for the application. To date, 2 applications have been approved and multiple applications are in the queue for Project Orbis.

Project Renewal focuses on updating the indications and dosing for existing standard agents that have been approved for decades and have gone off-patent.

The views of patients have become increasingly important and integrated into the system, including educational programs on regulatory science for patient advocates. The OCE plans to set up a website (Project Patient Voice) this year describing patient-reported adverse event data collected in registrational cancer trials.

OCE continues to use the various FDA Expedited Programs (Accelerated Approval, Breakthrough Therapy Designation, Fast Track Designation, Priority Review) to facilitate drug development in oncology. In the last 10 years, 85-90% of the accelerated approvals involved oncology indications. The initial approvals were based on endpoints that are reasonably likely to predict for clinical benefit. More recently, there has been a shift from surrogacy towards early determination of risk-benefit with use of intermediate endpoints other than irreversible morbidity or mortality.

Similar to EMA, FDA is also looking ahead with Project 2025. Key considerations include the shift from site- or tumor-specific indications to tissue agnostic indications, challenging the historical concept on the definition of a disease. Another aspect is the increasing use of neoadjuvant systemic treatments for local disease, which may redefine the primary therapy for the disease and involves development of appropriate endpoints to define clinical benefit.

The traditional sequence of phase 1-3 trials has already disappeared, and with the emergence of small specific populations for targeted therapies, the feasibility of performing randomized

trials may not be possible for these small populations. So, we will have to work with smaller data sets, and there is an urgent need to look into different designs such as Bayesian designs.

One of the challenges we face is the performance of platform trials with common controls, that may require cooperation among pharmaceutical companies.

Finally, we are aware of global challenges with reimbursement, and requirement for demonstration of survival benefit in some areas. FDA notes that the multiple incremental improvements in a therapeutic area may ultimately translate to improvement in survival. This is being observed in multiple myeloma (MM), where approvals based on progression-free survival or response rate have led to a marked improvement in survival in the overall MM population.

Innovation and Current Topics in Oncology Drug Development: Industry Perspective

Eric Rubin (Merck, US)

One of the recent innovations in clinical trials, has been the use of umbrella/platform studies to efficiently evaluate matches between predictive biomarkers and drugs.

The early and lasting example is the ISPY 2 study in breast cancer, initiated in 2010 and involving multiple sponsors. With a common control arm and some 10 prespecified arms defined by predictive biomarkers. The endpoint is pCR. The study involves an adaptive randomization to minimize the numbers of patients needed to determine efficacy. One of the arms involved Pembrolizumab combinations, that graduated in all Her-2 negative signatures.

Another study that involved Pembrolizumab used a clinical genomics database to select combination targets for the drug. It evaluated pre-treatment biopsies from > 300 patients from 22 cancer types, all treated with Pembrolizumab. A gene signature was identified with distinct patterns in relation of T-cell inflamed gene expression profile (GEP) and tumor mutational burden (TMB). These were predictive biomarkers. And looking at the various phenotypes enable identification of combination partners in studies such as KEYNOTE-495 in NSCLC, with an adaptive randomization design.

Another approach aimed to define a patient population refractory to immunotherapy. “Pseudo-progression” due to infiltration with inflamed cells, can confound such characterization. To address the concerns over pseudo-progression, these observations lead to the requirement of *confirmation* of progression on an immunotherapy, and were also used as entrance criteria for subsequent studies. This was used in KEYNOTE-001, and led to the first approval of Pembrolizumab in an ipilimumab refractory population.

Further examples of innovation are in the use of external data to support single arm submissions. As example Enfortumab Vedotin antibody-drug conjugate therapy was discussed. This is a Nectin-4 targeted antibody loaded with aurastatin as warhead. It was studied in a single arm trial in PD-1 failing bladder cancer patients, with striking results (44% ORR, median duration 7.6 months), which lead to drug approval. Another example involves the combination of Pembrolizumab + Lenvatinib, based on the predictive geno- and phenotype, yielding a high response rate and durable responses in endometrial cancer. Using

historical data for comparison, lead to approval by FDA. and through project Orbis in parallel in Australia and Canada. This is a nice example of a combination that involved 2 drugs, 1 biomarker, 2 sponsors, 3 countries, 2 FDA pilot programs and 3 expedited FDA pathways.

Simplification and harmonization of companion diagnostics development also has yielded important examples. The different Immunohistochemistry assays available for PD-L1 testing, urged the need for algorithms to compare outcomes cross tests and studies. An AACR initiated project Blueprint provided such data.

Something similar is important for TMB. It is used as a surrogate for neoantigen load. And actually, microsatellite instability high (MSI-H) is a subtype of TMB-H. While Pembrolizumab is approved for MSI-H tumors, we may miss out on a patient category in TMB-H due to lack of harmonization on tests. A Friends of Cancer Research project has paved the way in this direction. This has been used in KEYNOTE-158, were TMB-H excluding MSI-H tumors, yielded relevant responses throughout tumor types.

All of the above clearly indicates that innovative approaches enabled rapid drug development and access for advanced cancer populations, and should be further pursued.

Panel discussion

Moderator: John Smyth (CDDF, UK)

Panelists: Sigrid Klaar (Swedish Medical Products Agency, SE, and EMA Oncology Working Party), Ralf Herold (EMA, NL), Richard Pazdur (FDA, US), Eric Rubin (Merck, US), Paul Stockman (Astrazeneca, UK), Francesco de Lorenzo (CDDF, IT) and Hans Scheurer (Myeloma Patients Europe, NL)

- Consensus among speakers that involving patients and PRO´s is important.
    - Need to educate patients and advocates to help them understand the essence of the issues.
    - The complexity in EU from a patient perspective is not with EMA, but with 27 different HTA institutions, one in each of the member states. This leads to tremendous disparity for patients access to drugs throughout EU. Fortunately, EU has designed a new HTA legislation, that might hopefully lead to more alignment across member states, if such legislation is eventually agreed and passed.
    - As far as regulatory procedures, from a patient perspective it is difficult to understand why there is such a difference in speed of these procedure between US and EU. This is due to the fact that the Centralized Procedure for market approvals in the EU still requires agreement and peer-reviewing by the member states. Only a truly centralized regulatory assessment, i.e. by a single agency, could ever solve this problem. There was a strong plea for an EMA option for a Real-time Oncology Review. But the current European system, requiring agreement between all Member States, is not likely to be able provide this.

- From patient's perspective there is felt a need to involve drug related Quality of Life more in regulatory assessments. But it needs to be differentiated from other elements contributing to Quality of Life.

- Strategies and changes initiated by the regulators deserve compliments.
  - FDA felt to be ahead of EMA in innovative thinking, and closer to the patient perspective, in the approval of drugs based on relatively preliminary of activity, where EU approvals generally are based on somewhat more data on efficacy and safety. But very early approvals may present disadvantages to patients, as the limited data on early endpoints may not be sufficient for reimbursement, depending on payer system.
  - "Just jump", and take a leap of faith, will stimulate innovation. Changes should be mission-driven. The best-interest of the patients should be core in that mission. The agencies are tasked to help patients, and not to stand in their way. Balancing this, agencies also have the responsibility to ensure that the benefit-risk balance is positive. Currently, differences between US end EU agencies can be discerned regarding the amount of data considered needed to establish a positive benefit-risk balance.
  - Project Orbis overall is considered by industry to be a good thing, even though there are some cons as well. Harmonization of regulatory systems would save work, and therewith money and time, and speed up worldwide procedures. Project Orbis is still a pilot, that will have to be improved based on experience.
  - European procedures in general are lengthier. EMA strategy 2025 and its openness, might also help in this sense.
  - The Benefit-risk balance remains a driver in assessments.

The Cancer Drug Development Forum would like to take a moment to thank all the speakers, program committee members and panelists, session chairs who contributed greatly to our insightful discussions and the success of the meeting.

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