Reflection on CDDF workshop 2021: Endpoints in cancer drug development

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Disclosure

This presentation reflects my personal views and not necessarily those of Bayer

CDDF Endpoints in Cancer Drug Development

3-day Multi-Stakeholder Workshop April 2021

KEY TOPICS

WORKSHOP OBJECTIVE

Address current challenges with the definition and contextualization of endpoints in drug development and commercialization.
Focus on problem-solving aspect through debate and discussion.

- When OS cannot be the primary endpoint
- Endpoints in expedited regulatory pathways
- PRO endpoints – Review of strategies

When OS cannot be primary endpoint (1/2)

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- OS is still the **most important outcome**, however success in the past in achieving long OS duration and larger choice of treatments lead to **challenges** in using OS as the primary endpoint for certain indications

- **Novel endpoints** cannot be assessed in isolation of other endpoints or disease context. They need to be carefully **validated** with evidence across different trials. Still, alternative endpoints do not always correlate with survival

- Alternate endpoints - EU regulatory perspective
  - **PFS** as most common registrational endpoint can be clinically relevant but need to consider no detriment effect on OS
  - Earlier endpoint like **ORR** (with **DoR**) is considered a direct measure of anti-tumor activity, not a clinical benefit *per se*
  - **PRO** can be a valid primary endpoint but often lack of data quality, not subject to type 1 error control, frequently missing data

When OS cannot be primary endpoint (2/2)

DAY 1

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2 CASE STUDIES ON NOVEL ENDPOINTS

Merkel Cell Carcinoma

avelumab

- Alternative endpoint:

Best Overall Response (BOR)

- Initially regulators preferred RCT with PFS endpoint
- Response rate with defined follow-up was accepted (rare disease, high unmet need), approval based on single-arm trial with historical control
- Randomized controlled trial was considered not feasible, totality of evidence supported approval

nmCRPC

apalutamide, enzalutamide, darolutamide

- Novel endpoint:

Metastatic Free Survival (MFS)

- MFS emerged based on multi-stakeholder discussion, OS was considered not feasible for this specific disease stage
- MFS was considered a reasonable endpoint for clinical benefit if of acceptable magnitude, absence of detrimental toxicity, positive trend in OS
- Regulators accepted MFS for full approval

nmCRPC: non metastatic castration-resistant prostate cancer

Endpoints in expedited pathways

DAY 2

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PATIENT

- Expedited pathways are important for patients, still there are challenges
- Earlier endpoints need to be seen in the **context** of novel drugs or treatment, disease over time
- Main challenge seen is the **Regulator-HTA gap** ("earlier *approval is not earlier access*")

REGULATOR (US)

- **OS is the gold standard**
- Earlier endpoints are important, especially **ORR is the main endpoint for accelerated approval (AA)**, ideally for a molecularly defined population
- But **when benefit is not confirmed, AAs may be re-evaluated**
- Various regulatory tools to allow early approval e.g., **RTOR**, **Assessment Aid**

HTA

- Main challenges for HTA in expedited approvals:
  - Unclear **relationship of "surrogate " with key outcome** OS and HRQoL
  - **Lack of comparator,** comparative trials
  - **Small data sets**
- Different approaches are in use to address uncertainty at HTA level, early dialogue is key

PRO endpoint – Review of strategies

DAY 3

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PATIENT

- PRO need to be relevant and **should capture impact of disease** rather than description of side effects
- **Participants need to understand** scoring, questions
- Patients are interested in **results** of PRO data
- Patient organizations can help also with multiregional studies (local language, manuals)

REGULATOR

- Need to discuss PRO **objectives/research questions** early with HAs
- PRO should focus on areas **directly** related to disease / treatment, **meaningful** for patients and provides
- Consider alternative methods to collect data (e.g., wearables, sensors)
- **Data quality** is key

INDUSTRY

- Patient voice can be integrated at **various levels** throughout life-cycle
- This requires early start of planning, increased standardization is helpful
- *de novo* PRO can be challenging especially in expedited pathways

HTA

- Key endpoints for HTA are survival and HRQoL
- **QoL** should be collected earlier in clinical trials and become **routine**
- PRO data should reflect **current** treatment, novel methods key

ACADEMIA

- Successful PRO outcomes require **tailored**, trial-specific PRO hypothesis
- There is a need for better standardization but also allow flexibility
- Option to use computerized **adaptive** testing

Summary

Some reflections on potential solutions

Earlier endpoints are important, and can support expedited approvals, still there are some challenges/opportunities to be addressed

Relationship to OS/QoL: Agree on innovative tools & methodology (and trials) to demonstrate the relationship of a novel / earlier endpoint to OS/QoL

Data: Important to collect post-progression data, understand routine care settings, sequence of treatments (e.g., registries, RWD)

PRO: Utilize novel technologies for data collection, extrapolation, questionnaires, agree on level of standardization

Regulatory pathway: Tools exist that support expedited pathways, e.g., US RTOR, post-approval measures important, leverage global synergies when possible

Regulator/HTA evidence gap: There is a need to discuss early with HA/HTA on pivotal trial design, endpoint, PRO and post-approval data generation

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Thank you!