Workstream 1:
The Use of Clinical Endpoints in Cancer Vaccine Trials to Support Efficacy

Summary of Positions

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Background

- Clinical trials for profiling of cancer vaccines should reflect the unique characteristics of the vaccine candidate (esp. in case of autologous vaccines) and the studied patient population
- Traditional measures of efficacy without appropriate adaption may lead to a premature conclusion of ineffectiveness

- Workstream I of the CVCTWG has elaborated on positions regarding endpoints for efficacy trials of cancer vaccines

Time-to-event endpoints: Overall Survival (OS)

- „Gold standard“ of endpoints
- Applicable to advanced/metastatic, adjuvant and preventive setting
- Fully accepted by regulatory authorities
- But: Longest possible study duration
- Two possibly conflicting requirements:
  - Need for optimal patient population: Late stage patients with bulky disease may be immunosuppressed => adjuvant setting ?)
  - Need for reasonable study duration
- Subject to confounding by subsequent therapies

Time-to-event endpoints: Disease-Free Survival (DFS) Progression Free Survival (PFS)

- Delay in the onset of recurrence or progression may lead to improved OS => Surrogate for clinical benefit
- DFS for the adjuvant setting; PFS for the advanced and metastatic setting
- Due to the characteristics of cancer vaccines a delayed onset of activity possible (time required to mount a potentially effective immune response)
- Using traditional definitions may lead to premature study discontinuation
- Modification of definition of progression suggested (to be discussed):
  $\geq$2 observations, if ultimate response seen after initial progression (to be defined quantitatively), DFS or TTP should be based on date of start of therapy

Response Rate (RR)

- Commonly used efficacy measure for cytotoxic therapies
- Can be used in single-arm setting
- May not reflect properly clinical efficacy characteristics of cancer vaccines, reasons:
  - Early progression before onset of effective immune response
  - No tumor shrinking but progression retarded
- RR may be more useful in hematologic malignancies
- Modification of definition of response rate suggested (to be discussed):
  If ultimate regression is seen after initial progression, evaluation should be based on largest tumor volume seen after start of treatment

Design issues relating to endpoints

- Cancer vaccines usually have a very low toxicity profile
- Risk / benefit ratio very different to that of cytotoxic drugs
- => Continuation of vaccination therapy may be justified at the time of first progression
  - If no other therapy immediately required
  - If no effective therapy available
- Continuation of vaccination may be considered also in addition to other therapy (see WS4)

Patient Reported Outcomes (PRO)
Quality of Life (QOL)

- Improvement in PRO`s can be considered clinical benefit (not a surrogate)
- Relevant, since they reflect the patient´s perspective
- Improved QOL accepted as clinical benefit by regulatory authorities

but

- Very difficult to measure, since they are very subjective
- Need to agree on and pre-specify what is a meaningful clinical benefit
- Double-blind study designs needed to avoid bias

Biomarkers

- Objectively measured parameter to indicate normal or abnormal biological processes
- Properly validated biomarker could serve as „surrogate endpoint“ and potentially substitute for a clinical endpoint
- Up to date no sufficiently validated biomarker exist for determination of efficacy of drugs in oncology (except paraprotein in myeloma)
- Use of biomarkers in proof-of-principle cancer vaccine trials to establish biologic activity and to support the conduct of larger efficacy trials
- Use of biomarkers in controlled Phase III trials may eventually lead to validation

Minimal Residual Disease (MRD)

- Biomarker with particular relevance for the biology of cancer
- MRD detected by different methodologies:
  - Immunocytochemistry
  - Flow cytometry
  - PCR-based methods
- MRD has shown prognostic value in certain diseases (e.g. breast cancer, CML)
- Value of eliminating MRD by immunotherapy in investigation
- Molecular responses not yet fully validated as surrogate for clinical benefit

Immune Response Assays

- Adequate immune response is a measure of biologic activity
- Immune responses should be assessed before start of vaccinations and then at several time points with at least two established reproducible assays
- Validation as surrogate for clinical efficacy is mostly missing
- A variety of immunologic assays are available
  - Antibody assays
  - Other serological assays (eg cytokine patterns)
  - Cell-based assays (with focus on assessment of T-cells)
    - Tetramer assays
    - Elispot
    - Intracellular cytokines
    - Cytotoxicity assays
    - Other assays (eg NK-cells)