Clinical Perspectives on Key Evaluation Elements in Early Phase Oncology Trials

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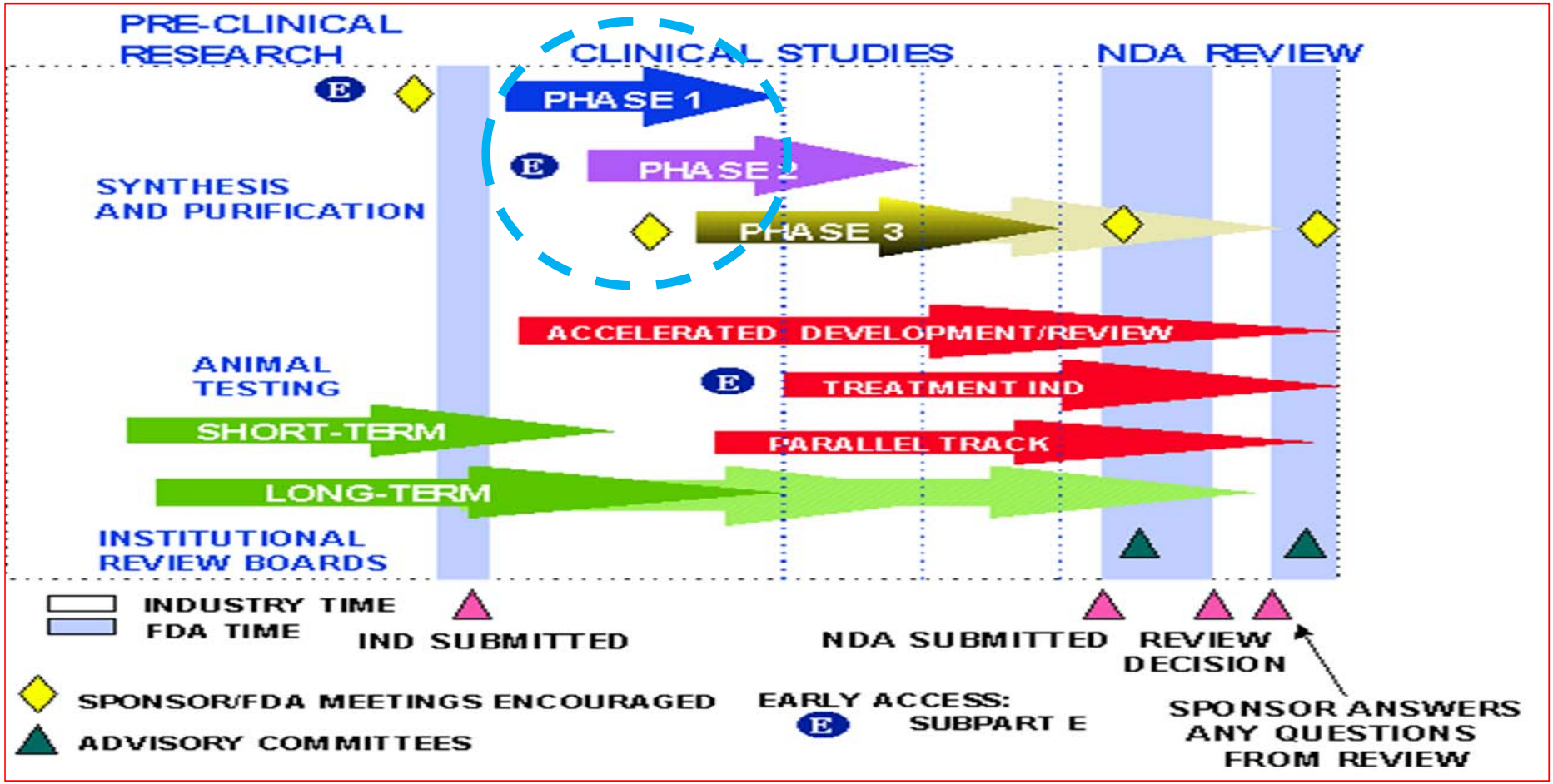
Role of Early Phase Trials



Successful Development Related to Adequate Conduct and Reliable Results of Early Phase Trials

- Many large Phase 3 trials have failed to demonstrate clinical benefits
- Example: in advanced prostate cancer
  - ~30% succeeded, leading to the approval of docetaxel, cabazitaxel, abiraterone, enzalutamide, radium-223, apalutamide
  - ~70% failed: including GVAX + docetaxel, DN-101+docetaxel, atrasentan +docetaxel, dasatinib + docetaxel; sunitinib, bevacizumab + docetaxel, afibercept + docetaxel; lenalidomide + docetaxel; satraplatin + prednisone; TAK-700, tasquinimod, ipilimumab, zibotentan +docetaxel, cabozantinib, custirsen + docetaxel, galeterone, ProstVac +GM-CSF, etc.
- Conduct and results of Phase 1 and/or 2 matter

Key Considerations for Phase 1 Trials

- Objectives
  - To evaluate the safety and tolerability, to determine DLTs, MTD, and obtain PK data, etc.
  - To ensure human subjects protection
  - To assess preliminary antitumor activity
  - To generate reliable and interpretable results for evaluation of future development

- Key Elements
  - Study product
  - Clinical protocol, design, and investigational plan
  - Clinical Investigator and site selection
  - Conduct monitoring, documentation, and reporting
  - Data management and analyses

Pre-clinical Requirements

- CMC [composition, manufacture, and control]
  - Proper identification, quality, purity, and strength
  - Sufficient information on new investigational product
  - Requirements relate to the scope of investigations
- Non-clinical evidence
  - Adequate information about pharmacological and toxicological studies
  - Full tabulation of data expected for detailed review
- Prior Human Experience
  - Summary of prior experience in different use or regions
  - Reasons for withdrawal if applicable
- Refer to Guidance Documents

Study Design, Protocol, Investigational Plan, &Investigator Brochure

- Design and Protocol
  - Statement of objectives and purpose
  - Specification of the design
  - Criteria for patient selection and safety exclusion
  - Detailed dosing plans (starting dose, duration, modifications, definition of the MTD)
  - Detailed monitoring plans (clinical monitoring procedures, safety assessments) to minimize risks
  - Estimated number of patients to be enrolled
- Investigational Plan
  - Rationale for the product, intended studies and potential indication(s)
  - General approaches for evaluation
  - Risks expected per pharmatox data or prior human use
- Investigator Brochure
  - Brief description of study product
  - Summary of non-clinical data
  - Description of expected risks in human use, including prior identified risks

Study Population in Phase 1 Trials

- Well-specified group(s) of patients
  - Patients with refractory/relapse cancer
  - Patients who have received pre-specified treatments
  - Patients with certain tumor marker(s)

- Ethical Issue: in the best interest of patients?
  - Enroll patients who have not received any standard treatment(s) of care?
  - Enroll patients whose disease does not have a well-established therapy?
  - Enroll patients into a first-line combination trial using approved second-line treatment(s)?

Definition for DLTs and MTD

- Dose-Limiting Toxicity (DLT): study product related in a specified time
  - ➢ Clearly pre-specified, but variable and modifiable
  - ➢ General used
    - o Hematological: Grade 3 or Grade 4 with clinical risks (duration, bleeding, febrile neutropenia)
    - o Non-hematological: ≥Grade 3 toxicity (few exceptions: e.g., manageable N/V lasting <48 hrs)
  - ➢ Product-specific
    - o Inclusion of Grade 2 toxicity (e.g., elevated Cr for >2 weeks, irAEs requiring steroid treatment)
    - o Toxicity leading to treatment delay for >2weeks (unexpected toxicities occur!)
- Maximum Tolerated Dose (MTD)
  - Commonly used: the highest dose with <33% probability of causing a DLT
  - Can vary with study product (e.g., no MTD observed after the proposed high dose)
  - Expansion cohort generally used to verify and help determine the dose for further studies

Dose Escalation/De-escalation and Dose Modifications

- Starting Dose
  - Reasonably defined per non-clinical pharmtox data
- Dose Escalation Plan
  - ➢ Varying with study product and its non-clinical data (e.g., toxicity windows)
  - ➢ 100%, 50%, 33%, and/or 25%?
  - ➢ Toxicity-driven (e.g., 100% until a Grade 2 adverse reaction); DLT-based treatment plan (e.g., 50% or 33% if a DLT observed in a 3+3 design)
- Dose De-escalation Plan
  - ➢ Specified in case the starting dose is not tolerated with >1 DLTs
- Dose Modification Plan
  - Pre-specified dose delay and/or reductions for continuation of study treatment
  - Pre-specified criteria for discontinuation of study product

Monitoring Plans and Reporting

- Detailed listing of safety and tumor response assessments
  - Study calendar or assessment schedules: from screening to post-study follow-up
  - Requirements for initiation and continuation of study treatment
  - Adequate inclusion of monitored parameters (e.g., LVEF for some TKIs, TSH for TKIs and immunotherapeutic)

- Criteria for toxicity determination, grading, recording, and reporting
  - Definition for SAEs
  - Reporting to respective regulatory bodies: Serious and unexpected suspected adverse reaction; unexpected fatal or life-threatening suspected adverse reaction

Selection of Qualified Investigators

- Qualified by training and experience as appropriate experts
  - Investigator's statement (e.g., signed relevant form), supported by C.V.
  - Investigator's local IRB information for evaluation of the protocol (assurance to start)
  - Commitment to
    - Adherence to study protocol
    - Protection of the welfare of study patients
    - Compliance with all GCP requirements and local IRB requirements
    - Personal conduct and supervision of the study (sub-investigators, associates, etc.)
    - Understandings of the Investigator Brochure (potential risks) and reporting of adverse experiences to the sponsor
  - Financial disclosure information
- Only qualified participating investigators/study sites should receive the shipment of the investigational product(s)
- Addition of new investigators to the study should be reported

Trial Conduct Monitoring

- Clinical monitoring and quality control
  - Selection of qualified trial monitors
  - Training on all study-related monitoring requirements and procedures
    - Characteristics of the study disease and product
    - Study protocol procedures, investigator brochure
    - Monitoring plan and documentation
    - Case Report Form (CRF or eCRF) and completion requirements
    - Safety reporting process
    - Study product accountability and destruction procedure
  - Review and validation of data consistency between CRF and source data (data integrity!)
  - Reporting to IRB and continuing IRB evaluation and approval of amendments
- Data monitoring and management
  - SOPs for data flow, data analysis plan, and database
- Use of Independent Data Monitoring Committee
  - Varying by study product and study disease, risk-based monitoring strategty

New Trends in Early Phase Trials

- Eligibility Criteria
  - Patients with treated or clinically stable brain metastases should be included unless strong rationale for exclusion
  - Patients with prior or concurrent malignancies should be included when the risk of the malignancies interfering with either safety or efficacy is very low.
  - In initial dose-finding trials, pediatric-specific cohorts should be included based on strong scientific rationale for benefit

- Expansion cohorts
  - Super expansion cohorts: observed in the recent immunotherapy development
  - New Guidance issued in August 2018: 3 or more additional cohorts with specific objectives
    - Specific disease setting to explore antitumor activity
    - Alternative doses or schedules
    - Specific patient population (e.g., organ impairment, biomarker)

- Varying combination cohorts
  - Compelling rationale needed
  - Lead-in phase and expansion studies are important

Kim ES, et al. JCO 35; 2017; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM616325.pdf

Example 1: Safety signals > MTD

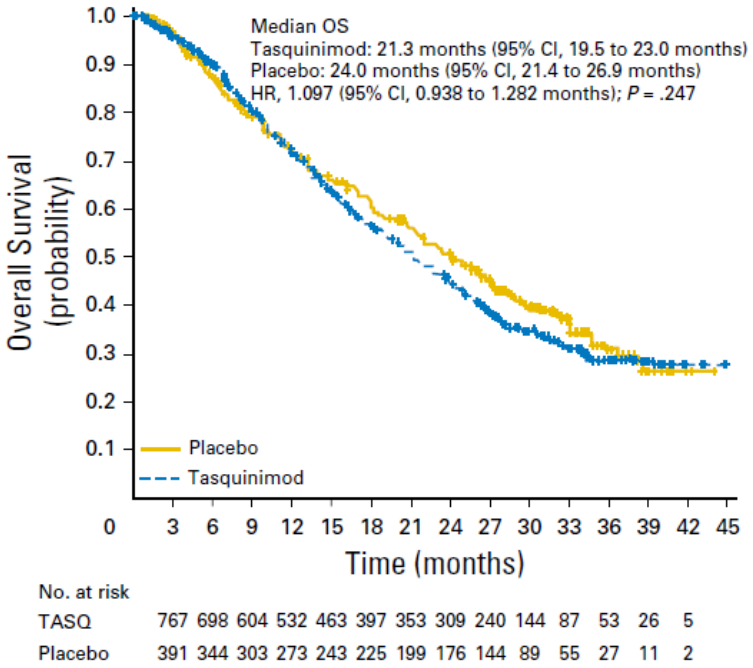
- Tasquinimod: an antiangiogenic product with activity in xenograft models
- Phase 1 trial: DLTs: sinus tachycardia, hyperamylasemia; MTD=1.0 mg/day;
- Phase 2 trial: 0.25 mg/day escalating to 1.0 mg/day over 4 weeks

Important safety observation: More incidences of severe cardiovascular AEs (DVT, MI)

Moderate antitumor activity: PFS 7.6 vs 3.3 mos in the placebo control

Pili R, et al. JCO 29; 2011

Phase 3 Results



"Cardiac disorders were more frequent with tasquinimod (all grades, 10% v 6.8%; grades 3 to 5, 3.4% v 1.6%; serious AEs, 3.9% v 1.9%), which "may have contributed to the lack of survival benefit due to early drug discontinuation".

Sternberg C et al. JCO 34; 2016

Example 2: Rational Phase 1 Combination -(rather combination intended for bundling)

- Phase 1b Trial of Avelumab + Axitinib in Treatment-naïve, Advanced RCC
  - ➢ Similar combinations appeared active and tolerable
  - ➢ Avelumab: starting dose at 10 mg/kg q2wks; de-escalated to 5 mg if the 10 mg not tolerated
  - ➢ Axitinib: 5 mg Bid at the lead-in and combination; de-escalated to 3 mg Bid if needed
  - ➢ Dose-finding in 6 pts that established the MTDs; additional expansion in 49 pts
  - ➢ The safety profile similar to each product
  - ➢ Confirmed ORR: 58% in the expansion cohort

Choueiri TK, et al. Lancet Oncol. 19; 2018

- Phase 3 Trial Results
  - ❖ Median PFS: 13.8 vs 8.4 months in the combination arm compared to the sunitinib arm in the patients irrespective of PD-L1 expression
  - ❖ Confirmed ORR: 55.2% vs. 25.5%
  - ❖ Grade 3 and over TEAEs: 71.2% vs. 71.5%
  - ❖ OS: not reported

Motzer, R et al. ESMO Annual Meeting 2018

Summary of Key Points

- Adequate conduct and reliable results/analyses
  - The key to objective development
- Protection of study subjects
  - Informed Consent
  - IRB evaluation and regulatory feedback
- Compliance with well-implemented regulatory standards
  - Procedures in place
  - Training and monitoring
  - Reporting in a timely manner
- Data management and analyses
  - Complete and accurate documentation
  - Objective assessments of safety and antitumor data
- Communications with stakeholders
  - Feedback matters to successful development