Vision for a Seamless Cancer Drug Development Paradigm

A Perspective from Industry

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Chief Development Officer – Oncology
Challenges to Seamless Drug Development in Industry

- What kind of signal are we looking for to accelerate the development of a new cancer medicine?
- How strong does that signal have to be? How certain do we have to be that the signal is real? How big is our experience?
- If a surrogate signal is being used, how certain must we be that the surrogate signal will translate into clear clinical benefit?
- How confident are we that the right patient population has been defined for accelerated development?
- What investment do we have to make now in order to ensure that the medicine can complete its journey to the market in a rapid fashion?
- Operationally, the same group may not be responsible for preclinical, early clinical, and late clinical/registration/lifecycle development for a single medicine. How do we ensure coordination of efforts across groups?
Signal Detection

- **Kind of Signal**
  - Efficacy: ORR, CBR, waterfall/swimmers plot, spider plot, PFS, OS rate (landmark/milestone analysis), OS, RMST, elevated tail of the curve, ...

- **Strength of Signal**
  - Context of benefit achieved from available therapies (unmet medical need)
  - Context of potential competitor compounds in this space
    - Same MOA vs different MOA
    - Now vs when pivotal study is projected to be completed

- **Confidence in Signal**
  - Chance occurrence
  - Related to patient selection (good prognostic group of patients)
  - Similar to what could be achieved by existing therapies
  - # of pts treated
    - Depth of response
    - Durability of response or disease control
    - Meaningful symptom control or relief (PRO)
    - Safety
Investing at Risk & Opportunity Costs

• Decision to accelerate development is not taken lightly
  – Deployment of human and financial resources
  – Multi-year commitment
  – Risk tolerance of organization
  – Opportunity costs

• Governance
  – May involve multiple layers and committees
  – Opportunity must be understood by leaders not versed in oncology or deviating from “Phase” of drug development
  – Timing of request may be out-of-sync with yearly Operating Plan
Example 1: Crizotinib

2006
- First in Human

2007
- Objective Responses in 3 of 37 patients
- Discovery of EML4-ALK Translocation in Japan

2008
- Identification of ALK Translocations in all 3 Responding Patients
- Engaged FDA, Selected CDx

2009
- Expand ALK+ NSCLC Cohort in Phase I Trial Treated at RP2D
- Initiate Phase II Study in ALK+ NSCLC

2010
- Amend Phase I Study to Enroll ROS1+ NSCLC
- Initiate Phase III Study in 2L ALK+ NSCLC
- Initiate Phase III Study in 1L ALK+ NSCLC

2011
- Complete Accrual
Response to Crizotinib in a Patient with ROS1+ NSCLC

Baseline

After 3 months of crizotinib
### IC\textsubscript{50} Concentrations for Crizotinib

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<th>Kinase</th>
<th>IC\textsubscript{50} (nM) mean</th>
<th>Selectivity ratio</th>
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*Source: Cui et al. J Med Chem 2011;54: 6342-6363*
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Complete Accrual
Example 1: Crizotinib

- **2010** Amend Phase I Study to Enroll ROS1+ NSCLC

- **2011** Crizotinib Approved in ALK+ NSCLC by FDA
- **2012** Crizotinib Approved in ALK+ NSCLC by EMA
- **2013** Initiate Separate Phase II Studies in ROS1+ NSCLC
- **2014** Amend Phase I Study to Enroll cMET Exon 14 mutant NSCLC
- **2016** Crizotinib Approved in ROS1+ NSCLC by FDA and EMA

**Additional Notes:**
- Initiate Phase III Study in 2L ALK+ NSCLC
- Initiate Phase III Study in 1L ALK+ NSCLC
- Complete Accrual
- Discovery of cMET Activation via Exon 14 mutation
Lessons Learned from this Experience

• Strong signals of activity can be observed in Phase I

• Understanding the underlying biology/genomics can alter and enhance confidence in radically shifting clinical development strategy

• Expansion cohorts in Phase I trials can provide unique opportunities to rapidly and efficiently test clinical hypotheses
  – PROFILE 1001 has had 25 amendments in 9 years … and remains open to accrual!

• Phase I, II, and III trials can coexist under the right circumstances

• When strong signals of efficacy are detected and confirmed, regulatory agencies are demonstrating increased willingness to act without Phase III data

• The end result is that new agents with truly transformational levels of activity can reach the market years ahead of schedule
Example 2: Avelumab

2013

First in Human

Multiple Expansion Cohorts Built Into Phase I Trial (n>500)

Class Activity had been Demonstrated for CPIs

2013 - present

Phase II Studies

Phase Ib Studies

Phase Ib → III Studies

Registration

Phase III Studies

Registration

Phase II Studies

Phase III Studies

Registration
Example 2: Avelumab

2013

First in Human

Multiple Expansion Cohorts Built Into Phase I Trial (n>500)

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2013 - present

Registration

Scenario 1
- Very strong signal with single agent (efficacy & safety)
- Adequate experience in sufficient # of patients
- No SoC or inadequate SoC (unmet medical need)
- Example: 2L Merkel Cell Carcinoma

Phase III Studies

Phase II Studies
Example 2: Avelumab

2013

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Multiple Expansion Cohorts Built Into Phase I Trial (n>500)

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2013 - present

Registration

Phase II Studies

Phase III Studies

Registration

Phase III Studies

Registration

Scenario 2

• Signal observed with single agent in Phase I but needs confirmation and/or refinement

• Phase II trial could focus on a specific biomarker-selected group of patients
Example 2: Avelumab

2013

First in Human

Multiple Expansion Cohorts Built Into Phase I Trial (n>500)

Class Activity had been Demonstrated for CPIs

2013 - present

Registration

Phase Ib → III Studies

Registration

Scenario 3
• Strong rationale for combination (Phase I data, single agent activity for each component)
• Low probability of drug-drug interaction or synergistic toxicity
• Accelerated development strategy
• Example: PD-1 + VEGFR in mRCC
Example 2: Avelumab

2013

First in Human

Multiple Expansion Cohorts Built Into Phase I Trial (n>500)

Class Activity had been Demonstrated for CPIs

2013 - present

Scenario 4

• Exploratory combinations
• Safety concerns or patient selection criteria warrant separate Phase Ib study
• Signal observed and specific setting will determine whether Phase II or III trial should be pursued
• Example: IO.IO combinations

Phase Ia Studies

Phase Ib Studies

Phase II Studies

Phase III Studies

Registration

Registration
Lessons Learned from this Experience

• Phase I trials can be designed to be large and include multiple expansion cohorts provided that there are ample and compelling reasons for confidence
  – FDA has taken steps to limit the size of expansion cohorts and require specific hypotheses to be tested (ie, not open-ended)

• Multiple paths may be pursued following Phase I expansion including
  – Formal Phase II evaluation of the single agent
  – Phase Ib testing of combination
  – Integrated Phase Ib → Phase III trial
  – Moving directly to registration

• Significant resources must be committed for a long period of time
  – This approach is not suitable for most new agents

• But successful application of this strategy can shorten clinical development substantially and speed the new medicine to the market