Regulatory Considerations for Seamless Oncology Drug Development – Expansion Cohorts

National Cancer Policy Forum - The Drug Development Paradigm in Oncology: Managing Benefit and Risk in Seamless Cancer Drug Development Session

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Outline

• Background - Changing Drug Development Paradigm in Oncology
• Example of Seamless Expansion Cohort Trial
• Regulatory Considerations for Expansion Cohort Trials
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"Phased" Drug Development Paradigm

Nonclinical Studies

Clinical Trials

SAFETY

Pharmacology → Therapeutic Exploratory → Confirmatory

EFFICACY

IND

Theoret et. al., Clinical Cancer Research, 2015

www.fda.gov
Regular Approval

• Substantial Evidence of Safety And Efficacy
  – Adequate and Well-controlled Clinical Trials

• Direct Evidence of Clinical Benefit
  – Improvement in survival, physical functioning, tumor-related symptoms

• Established Surrogate for Clinical Benefit

• No Comparative Efficacy Requirement for Regular Approval
Accelerated Approval

• One of Four FDA Expedited Programs for Serious or Life-Threatening Illnesses

• Meaningful Therapeutic Benefit “Over Existing Treatments”

• Based on “Surrogate” or Intermediate Endpoint Reasonably Likely to Predict Clinical Benefit

• Confirmatory Trials to Verify and Describe Clinical Benefit
FDA Expedited Programs for Serious Conditions - Drugs & Biologics

- Accelerated Approval
- Priority Review Designation
- Breakthrough Therapy Designation
- Fast Track Designation

All consider the available therapies to treat the serious condition for the disease context to determine whether there is an unmet medical need, or if the new therapy appears to provide an improvement or advantage over available therapies.
FDA Expedited Programs – ORR

- **Breakthrough Therapy** Designation Requests
  - CDER Analysis of BTDR from 9/2012 to 12/2014*
  - Hematology/Oncology – 86 (42%) of the 203 requests
    - 27 (31%) Grant; 18 (21%) Withdrawn; 41 (48%) Denied
    - 18 (67%) of 27 Granted Based on ORR

- **NME Approvals (Oncology)** in OHOP 2014-5
  - Of the 24 NME Approvals, 12 were Accelerated Approvals
  - ORR → Primary Endpoint in 9 of the 12 Accelerated Approvals

*Breakthrough Therapy Designation: Exploring the Qualifying Criteria; 4/24/15
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## MK-3475: PN001 Trial

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>IND Submit</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
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</tbody>
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KN-001 Treatment Cohorts

- **All Patients**
  - N = 1235
  - **Advanced NSCLC** n = 550
    - **Cohort F1 (Randomized)**
      - PD-L1+ Treatment naive n = 101
        - 2 mg/kg Q3W n = 6
        - 10 mg/kg Q3W n = 49
        - 10 mg/kg Q2W n = 46
      - Nonrandomized PD-L1+ ≥2 prior therapies
        - 10 mg/kg Q3W n = 33
        - 10 mg/kg Q2W n = 43
    - **Cohort F2**
      - Previously Treated n = 356
        - Randomized PD-L1+ ≥1 prior therapy
          - 10 mg/kg Q2W n = 167
        - 10 mg/kg Q3W n = 113
    - **Cohort F3**
      - PD-L1+ ≥1 prior therapy
        - 2 mg/kg Q3W n = 55

- **Advanced Melanoma** n = 655
  - **Cohort B1** Nonrandomized n = 135
    - IPI Naive n = 87
      - 10 mg/kg Q2W n = 41
      - 10 mg/kg Q3W n = 24
      - 2 mg/kg Q3W n = 22
    - IPI treated n = 48
      - 10 mg/kg Q2W n = 16
      - 10 mg/kg Q3W n = 32

- **Cohorts B2, B3, D** Randomized n = 520
  - **Cohort D**
    - IPI naive n = 103
      - 2 mg/kg Q3W n = 51
      - 10 mg/kg Q3W n = 51
    - IPI refractory n = 173
      - 2 mg/kg Q3W n = 89
      - 10 mg/kg Q3W n = 84

- **Cohort A**
  - Advanced solid tumors n = 30
    - 1 mg/kg Q2W n = 4
    - 3 mg/kg Q2W n = 3
    - 10 mg/kg Q2W n = 10
    - 2 mg/kg Q3W n = 7
    - 10 mg/kg Q3W n = 6

- **Cohort C**
  - Any PD-L1 ≥2 prior therapies
    - 10 mg/kg Q3W n = 38
  - 10 mg/kg Q2W n = 6

- **Cohort B2** IPI Naive or IPI treated n = 244
  - 10 mg/kg Q3W n = 122
  - 10 mg/kg Q2W n = 122

- **Cohort B3** IPI naive or IPI treated n = 244
  - 10 mg/kg Q3W n = 122

*Slide courtesy of Eric Rubin, National Cancer Policy Forum, 12/12/16*
MK-3475: PN001 Trial

Part A
- 2011: 0
- 2012: 0

Part B
- 2011: 0
- 2012: 0

Amendment
- 2011: 0
- 2012: 1

Number of Patients

www.fda.gov
MK-3475: PN001 Trial

Number of Patients

Part A
Part B

Amendment
1
2

www.fda.gov
MK-3475: PN001 Trial

Number of Patients

Part A
- A1
- A2

Part B

Part C

Amendment
- 1
- 2
- 3

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MK-3475: PN001 Trial

Number of Patients

Part A
- A1
- A2

Part B

Part C

Amendment
- 1
- 2
- 3
- 4

179
MK-3475: PN001 Trial

Number of Patients

1,047

www.fda.gov
MK-3475: PN001 Trial and Selected Melanoma Development Program Milestones

- **IND Submit** (2011)
- **Breakthrough** (2012)
- **Multi-D** (2013)
- **Exp Access** (2013)
- **Pre-BLA Priority Review** (2014)
- **BLA** (2014)
- **AA** (2014)

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# Expansion Cohorts

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<th><strong>Opportunities</strong></th>
<th><strong>Challenges</strong></th>
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| • Adaptable – single protocol  
  – IND in effect  
  – IRB(s) in place  
• Earlier evaluation of efficacy endpoints  
• Standardized data collection  
• Existing trial networks | • Safety  
• Heterogeneous populations  
• Adequate statistical plan  
• No pre-defined milestone meetings with FDA  
• Adequate data collection  
• Independent oversight  
• Products appropriate for expansion cohort designs |

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Theoret et. al., Clin Cancer Res, 2015
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Marketing Application

www.fda.gov
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