PLENARY SESSION 1: CLINICAL TRIAL DESIGN IN AN ERA OF HORIZONTAL DRUG DEVELOPMENT

Industry Perspective

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Disclaimer

The opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of Acerta Pharma.
Drug Discovery and Development Timeline

- **Drug Discovery**: ~5,000 – 10,000 compounds, 3 – 6 years
- **Preclinical**: 250
- **Clinical Trials**
  - Phase 1: 5
  - Number of Volunteers: 20–100
  - Phase 2: 6 – 7 years
  - Number of Volunteers: 100–500
  - Phase 3: 1,000–5,000
  - Number of Volunteers: 1,000–5,000
- **FDA Review**: 0.5 – 2 years
- **Scale-Up to Mfg.**: INDEFINITE
- **Post-Marketing Surveillance**: INDEFINITE

**Pre-IND**, **PoC/EOP2**, **Phase 3**, **Filings**, **Post Approval**

Compress Development Timelines by Combining Phases/Tumor Types Studied?

Standard Drug Development Paradigm:

- FIH
- POC
- Registrational

Alternative Development Paradigms:

- FIH=POC
- Registrational
- Nivolumab
  - Melanoma

- FIH
- POC=Registrational
- Palbociclib
  - HR+ MBC

- FIH=POC=Registrational
- Pembrolizumab
  - Melanoma

- FIH=POC=Registrational
- Pembrolizumab
  - Larotrectinib
  - Entrectinib
  - Multiple tumor types
Tissue-Agnostic Breakthroughs

**Merck's Keytruda (pembrolizumab)**

- MSI-H/dMMR cancers (non-colorectal and colorectal)
- **Status**: FDA approved May 23, 2017 with data from five Phase I/II trials

**Loxo Oncology's larotrectinib**

- NTRK fusion-positive solid tumors
- **Status**: Phase II NAVIGATE basket trial underway, NDA rolling submission initiated in Dec 2017

**Roche/Ignyta's entrectinib**

- NTRK fusion-positive solid tumors
- **Status**: Phase II STARTRK-2 basket trial underway, potential for 2018 US NDA filing
First Tumor Agnostic Approval in May 2017 - Pembrolizumab

Indication of microsatellite instability-high (MSI-H) and Mismatch Repair Deficient (dMMR) Cancers

• Pembrolizumab, a programmed death 1 (PD-1) inhibitor
  – FDA Accelerated Approval granted for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H and dMMR cancers
  – Data from 149 patients with MSI-H or dMMR cancers enrolled across 5 single-arm clinical trials
    • ORR was 39.6% (95% CI, 31.7-47.9), including 11 (7.4%) CRs and 48 (32.2%) PRs
    • ORR was 36% in patients with CRC and 46% in patients with other tumor types
    • The median duration of response was not yet reached (range, 1.6+ months to 22.7+ months) Among patients who responded to pembrolizumab, 78% had responses that lasted for at least 6 months
  – Two Breakthrough therapy designations granted by the FDA in 2015 and 2016, as a treatment for patients with MSI-H metastatic CRC and non-CRC solid tumors
  – No approved test to identify patients with MSI-H or dMMR cancers, at the time of this approval

First drug approval based on a tumor’s biomarker without regard to the tumor’s original location
Shifting from Conventional Development to Tissue-Agnostic Approaches

1. Identification of new targets, biomarkers and development of therapies for new targets
2. Co-development of Rx and Dx
3. Platform / basket trials to optimize identification and enrollment of rare patient populations
4. Increased awareness for diagnostic testing
5. Continued openness by regulatory agencies for novel, science-based approach toward increasing the arsenal of novel effective therapies for cancer patients

➔ Plan early for biomarker/patient population identification
➔ True partnership between regulators, academia, patients advocates and manufacturers
➔ Close collaboration between Rx and Dx developers
1. Identification of New Targets, Biomarkers and Development of Therapies for New Targets

- Reclassification of disease from histopathology-based diagnosis to molecularly-based diagnosis
  - Applicable to precisely targeted cancer drug development, in rare biomarker(+) tumor types
  - Tissue-agnostic (biomarker-defined) vs. conventional tumor type drug development
    - E.g. the pembro development made scientific sense
    - Shared common pathological characteristics
    - Increased mutation load and neo-antigen burden
    - Association of mutation load / neo-antigen burden and improved outcomes to immunotherapy in different tumors

requires early and continuous collaboration between key stakeholders: academia, sponsors, Dx manufacturers, regulators, patients advocates

(Steven Lemery, ASCO 2017)
2. Co-development of Rx and Dx

• Significant investment needed in research to prospectively understand underlying mechanisms and signaling pathways

• Consider biomarkers early in development
  – Incorporation into Phase 1 study designs
  – Get answers early in development where possible, whilst ensuring the broadest patient population is included
  – Secure early collaboration between Rx and Dx developers
  – Speak to FDA and EMA often and early
3. Platform / Basket Trials to Optimize Identification and Enrollment of Rare Patient Populations

Table 1. Types of Master Protocols.

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbrella</td>
<td>To study multiple targeted therapies in the context of a single disease</td>
</tr>
<tr>
<td>Basket</td>
<td>To study a single targeted therapy in the context of multiple diseases or disease subtypes</td>
</tr>
<tr>
<td>Platform</td>
<td>To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm</td>
</tr>
</tbody>
</table>

Examples: NCI-MATCH, TAPUR, STARTRK-2 (NTRK, ROS1 or ALK fusions), NAVIGATE (NTRK fusion)

VE-BASKET (V600E), SUMMIT (HER2/HER3)
3. Platform / Basket Trials to Optimize Identification and Enrollment of Rare Patient Populations

- Platform and basket trials may offer a more cost-effective and logistically feasible approach to developing therapies for rare patient populations and...

- Can slow things down and make drug development more costly
  - Diversion of resources from more common biomarker positive tumor types (e.g. site selection)
  - Increase number of sites, number of patients screened, technology cost

- Enrolment challenges for rare tumors include:
  - Avoid exclusion of patients likely to benefit (validate the biomarker hypothesis)
  - Geographic convenience of trial sites
  - Realistic use of modern tests across regions – Reimbursement/access issues
  - Test results may be complicated and delay enrollment
4. Increased Awareness of Diagnostic Testing

- Opportunities to improve the effectiveness of clinical trials for patients in biomarker-defined trials
  
  - Molecular testing to occur earlier in a patient’s clinical course
    * At a higher frequency,
    * Ideally integrated as a part of standard of care,
    * Via broad genomic test panels
  
  - More informative molecular testing reports for treating physician and patient
    * Reliable next steps, more robust decision making based on test results

Kowak et al. 2017, Journal of Precision Medicines
5. Continued Openness to Novel and Science-based Approaches by Regulatory Agencies, with Caveats

• US Accelerated Approval and EU Conditional Authorization
  – Randomized controlled trials to assess OS in rare biomarker(+) tumor types may not be feasible and / or not ethical in refractory settings
  – Early approvals on single arm data with confirmation of benefit through post approval commitments
    • E.g. Pembrolizumab MSI-H with single arm ORR and DOR F/U
    • Consider the use of Real World Evidence
  – Lack of randomized data can remain a concern e.g. Recent withdrawal of the nivolumab EU filing in MSI-H mCRC

• Evolving companion diagnostic landscape (e.g., PMA=clinical validation vs 510(k)=analytical validation)
  – At the time of pembrolizumab approval for MSI-H and dMMR cancers, no approved test to identify patients with MSI-H or dMMR cancers
  – Upcoming site agnostic filings incorporate early Dx validation strategies (entrectinib, larotrectinib)
Regulatory Considerations – Tumor Agnostic Development

• How many tumor types should be evaluated?
  – No “one size fits all” answer
  – Totality of the data
  – Consistency of effect across tumor types
  – Scientific rationale

• Extrapolation to non-studied tumor types and pediatric tumors
  – E.g. pembrolizumab showed responses in at least 14 MSI-H/dMMR tumor types
  – No pattern indicating a qualitative effect of tumor type on response
  – Pembrolizumab is approved in children

• Accelerated/conditional vs full approval
  – Approval based on single arm data → Importance of post marketing requirements/commitments

• Management of the residual uncertainty pre and post approval
  – Pre-approval – Consider magnitude of effect, tox profile, unmet medical need
  – Leverage Real World Evidence
  – Value of BTD

(Steven Lemery, ASCO 2017)
Shifting from conventional development to tissue-agnostic approach – requires extensive collaboration

1. Identification of new targets, biomarkers and development of therapies for new targets
   – Collaboration between sponsors and academia

2. Co-development of Rx and Dx
   – Sponsors and diagnostic manufacturers

3. Platform / basket trials to optimize identification and enrollment of rare patient populations
   – Collaboration between sponsors and with Investigators

4. Increased awareness for diagnostic testing
   – Treating physicians and patient advocacy groups

5. Continued openness by regulatory agencies for novel, science-based approach toward increasing the arsenal of novel effective therapies for cancer patients
THANK YOU!
Back up
TRADITIONAL

Phase I
A small study assesses a treatment's safety and determines dosage.

Phase II
A mid-size trial in a group of people with the same type of cancer (e.g., lung cancer) provides signals of a treatment's efficacy.

Phase III
A large randomized trial compares a drug to the standard of care in a group of people with the same type of cancer.

Approval
Regulatory authorization is granted to market the drug for people with a specific type of cancer.

BASKET

People with different types of cancer (e.g., lung, colon) respond.

Approval
Regulatory authorization is granted to market the drug for anyone with a specific genetic profile.

Studies welcome anyone harboring the same genetic mutation, regardless of tumor type.

A subset of patients with the same type of cancer responds, potentially leading to studies in a specific tumor type.
Keytruda mmR MSI-H Indication Statement (US PI)

- Microsatellite Instability-High Cancer: for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment in patients who have no satisfactory alternative treatment colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

- This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

- Limitation of Use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design &amp; Patient Population</th>
<th>Number of patients</th>
<th>MSI-H/dMMR testing</th>
<th>Dose</th>
<th>Prior therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-016</td>
<td>prospective, investigator-initiated</td>
<td>28 CRC</td>
<td>local PCR or IHC</td>
<td>10 mg/kg every 2 weeks</td>
<td>CRC: ≥ 2 prior regimens</td>
</tr>
<tr>
<td>NCT01876511</td>
<td>patients with CRC and other tumors</td>
<td>30 non-CRC</td>
<td></td>
<td></td>
<td>Non-CRC: ≥1 prior regimen</td>
</tr>
<tr>
<td>KEYNOTE-164</td>
<td>prospective international multicenter</td>
<td>61</td>
<td>local PCR or IHC</td>
<td>200 mg every 3 weeks</td>
<td>Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- antiVEGF/EGFR mAb</td>
</tr>
<tr>
<td>NCT02460198</td>
<td>CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-012</td>
<td>retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer</td>
<td>6</td>
<td>central PCR</td>
<td>10 mg/kg every 2 weeks</td>
<td>≥1 prior regimen</td>
</tr>
<tr>
<td>NCT01848834</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-028</td>
<td>retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC</td>
<td>5</td>
<td>central PCR</td>
<td>10 mg/kg every 2 weeks</td>
<td>≥1 prior regimen</td>
</tr>
<tr>
<td>NCT02054806</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-158</td>
<td>prospective international multicenter enrollment of patients with MSI-H/dMMR non-CRC retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts</td>
<td>19 l</td>
<td>local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)</td>
<td>200 mg every 3 weeks</td>
<td>≥1 prior regimen</td>
</tr>
<tr>
<td>NCT02628067</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>149</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Pembrolizumab Response Rate by Tumor Type

### MSI-H or dMMR cancers

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Tumors</th>
<th>Patients with a Response</th>
<th>Range of Response Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td>mo</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>90</td>
<td>32 (36)</td>
<td>1.6+ to 22.7+</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>14</td>
<td>5 (36)</td>
<td>4.2+ to 17.3+</td>
</tr>
<tr>
<td>Biliary cancer</td>
<td>11</td>
<td>3 (27)</td>
<td>11.6+ to 19.6+</td>
</tr>
<tr>
<td>Gastric or gastroesophageal junction</td>
<td>9</td>
<td>5 (56)</td>
<td>5.8+ to 22.1+</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>6</td>
<td>5 (83)</td>
<td>2.6+ to 9.2+</td>
</tr>
<tr>
<td>Small-intestine cancer</td>
<td>8</td>
<td>3 (38)</td>
<td>1.9+ to 9.1+</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>2 (100)</td>
<td>7.6 to 15.9</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>1 (50)</td>
<td>9.8+</td>
</tr>
<tr>
<td>Other cancers</td>
<td>7</td>
<td>3 (43)</td>
<td>7.5+ to 18.2+</td>
</tr>
</tbody>
</table>

Lemery et al., 2017 NEJM
STANDARD APPROVAL

PRECLINICAL
Cell & animal studies

PHASE I
Safety testing
~2-4 YRS

PHASE II
Small groups of patients
~1-2 YRS

PHASE III
Large populations of patients
~2-7 YRS

FDA REVIEW
1 YR

APPROVAL

OR

ACCELERATED APPROVAL

If EARLY TRIAL RESULTS are especially promising, the FDA can grant ACCELERATED APPROVAL to an investigational medicine. This allows patients access while ongoing Phase III studies confirm safety and efficacy.

PRECLINICAL

PHASE I

PHASE II

PHASE III

FDA REVIEW

ACCELERATED APPROVAL

POST-MARKETING COMMITMENT TRIAL

Leads to full approval or removal of accelerated approval

www.gene.com
Table 2. Examples of Master Protocols in Cancer.*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
<th>Design</th>
<th>Drug or Drugs</th>
<th>Disease and Target</th>
<th>Study Population</th>
<th>End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>B222S</td>
<td>Basket trial to determine cancers responsive to imatinib</td>
<td>Phase 2, multicenter, open-label, noncomparative trial</td>
<td>Single: imatinib (400 or 800 mg per day)</td>
<td>40 cancers (solid tumors and hematologic cancers) with activation of imatinib target kinases</td>
<td>186 patients ≥15 yr of age</td>
<td>Tumor response (SWOG criteria and investigator’s assessment)</td>
</tr>
<tr>
<td>BRAF V600</td>
<td>Basket trial to evaluate the efficacy of vemurafenib in nonmelanoma cancers</td>
<td>Early phase 2, multi-center, open-label, noncomparative, adaptive trial using Simon’s two-stage design</td>
<td>Vemurafenib monotherapy or (in some patients with colorectal cancer) vemurafenib plus cetuximab</td>
<td>Multiple nonmelanoma cancers with BRAF V600 mutations; eight tumor-specific cohorts plus an “all others” cohort</td>
<td>122 adults (≥18 yr of age)</td>
<td>Response rate (assessed by investigators according to RECIST or IMWG criteria) at wk 8</td>
</tr>
<tr>
<td>NCI-Match</td>
<td>Umbrella trial to determine whether treating cancers according to molecular abnormalities is effective</td>
<td>Exploratory, multicenter, noncomparative trial</td>
<td>Multiple: 30 treatments (as of May 2016), both FDA-approved and investigational, that target gene abnormalities</td>
<td>Advanced solid tumor, lymphoma, or myeloma; DNA sequencing for actionable mutations</td>
<td>35 adults planned per substudy; pediatric study to begin in 2017</td>
<td>Tumor response (primary) and progression-free survival</td>
</tr>
<tr>
<td>BATTLE-1</td>
<td>Umbrella trial to evaluate targeted therapies in chemotherapy-refractory NSCLC</td>
<td>Phase 2, single-center, comparative, adaptive randomization trial</td>
<td>Multiple: three monotherapies (erlotinib, vandetanib, and sorafenib) and one combination (erlotinib plus bexarotene)</td>
<td>Advanced NSCLC; targets included EGFR mutation, KRAS/BRAF mutation, VEGF expression, and RXRs/CyclinD1 expression</td>
<td>255 adults in whom ≥1 chemotherapeutic regimen had failed</td>
<td>Complete or partial response or stable disease according to RECIST criteria at wk 8 (primary), progression-free survival, overall survival, and toxicity</td>
</tr>
<tr>
<td>I-SPY 2</td>
<td>Adaptive platform trial to identify treatment regimens for locally advanced breast cancer in the context of neoadjuvant therapy on the basis of biomarker signatures</td>
<td>Phase 2, multicenter, comparative, adaptive randomization trial</td>
<td>Multiple: standard chemotherapy and five new drugs (initially) as add-on to chemotherapy; 12 treatments tested to date, with latest (patritumab) added October 2016</td>
<td>Early, high-risk breast cancer; three biomarkers (hormone-receptor status, HER2 status, and Mammaprint risk score) define eight genetic subgroups</td>
<td>1920 women (estimated) with invasive tumor ≥2.5 cm in diameter</td>
<td>Pathological complete response</td>
</tr>
<tr>
<td>Lung-MAP</td>
<td>Master protocol to evaluate biomarker-matched therapies in rare squamous-cell subsets of NSCLC</td>
<td>Phase 2–3 comparative trial</td>
<td>Multiple: four investigational drugs plus one therapy for no-match control group (initially); three investigational drugs remain</td>
<td>Squamous-cell NSCLC; multiple targets (four molecular targets initially; three remain)</td>
<td>100–170 patients planned for phase 2 (40 are now enrolled); 300–400 planned for phase 3</td>
<td>Objective response rate, progression-free survival, and overall survival</td>
</tr>
</tbody>
</table>

Other considerations for tissue-agnostic drug development

- How many different tumor types to evaluate
  - Based on totality of evidence to support approval
  - Inclusion of common tumor types
  - Effect generally consistent among tumors
  - Approach scientifically supportable

- Extrapolation to non-studied tumor types/pediatrics
  - Yes, if appropriate
  - Can be approved in children based on extrapolation, biology expected to be similar in children, pediatric dose established, initiate pediatric investigation and formulation work early in development (eg, consider including 12yo and older in adult trials)
  - Pembrolizumab showed no pattern indicating a qualitative effect of tumor type on response (at least 14 tumor types)

*From Dr. Steven Lemery (FDA Division of Oncology 2), 2017 ASCO Annual Meeting*
Trial events

- Trial start
- Continuous screening

Biomarker A
- Biomarker A-positive
  - Investigational drug 1
  - Standard of care A

Biomarker B
- Biomarker B-positive
  - Investigational drug 3
  - Standard of care B

Biomarker-negative
- Biomarker-negative
  - Investigational drug 4
  - Standard of care for biomarker-negative patients

Biomarker C
- Biomarker C-positive
  - Investigational drug 6
  - Standard of care C

Investigational drug 5
- Stop because criteria for success are met
- Recruitment is closed
- Investigational drug 1 becomes new standard of care A
- Stop for futility
- Stratum continues to enroll patients

Time (ongoing)
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Breast, HER2-mutant (n=25)</th>
<th>Bladder, HER2-mutant (n=16)</th>
<th>Lung, HER2-mutant (n=26)</th>
<th>Colorectal, HER2-mutant (n=12)</th>
<th>Biliary Tract, HER2-mutant (n=9)</th>
<th>Cervical, HER2-mutant (n=5)</th>
<th>Solid tumors, HER3-mutant (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR at week 8, n (%)</td>
<td>8 (32%)</td>
<td>0 (0)</td>
<td>1 (3.8%)</td>
<td>0 (0)</td>
<td>2 (22.2%)</td>
<td>1 (20%)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Clinical benefit rate, n (%)</td>
<td>10 (40%)</td>
<td>3 (18.8%)</td>
<td>11 (42.3%)</td>
<td>1(8.3%)</td>
<td>3 (33.3%)</td>
<td>3 (60%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>3.5</td>
<td>1.8</td>
<td>5.5</td>
<td>1.8</td>
<td>2.8</td>
<td>20.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>
**NCI MATCH**

1. **Genetic sequencing**
2. **Actionable mutation detected**
3. **Study agent**
4. **Stable Disease, Complete or partial response (CR+PR)**
5. **Progressive disease (PD)**
6. **Check for additional actionable mutations**
7. **PD**
8. **Continue on study agent until progression**
9. **No additional actionable mutations, or withdraw consent**
10. **On study**

- Conduct across 2400 NCI-supported sites
- Pay for on-study and at progression biopsies
- Screen 5000 patients to complete
  - 30 phase II trials; target 25% ‘rare’ tumors;

https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match