U.S. FOOD & DRUG ADMINISTRATION

FDA Perspective:

Evolving Development of Parp Inhibitors

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- I have no financial relationships to disclose
- I will not discuss off label or investigational use of products in my presentation

Outline

- Regulatory background/basics
  - Regulatory approvals
  - Diagnostics
- PARP overview
  - Approvals
- Next steps-
  - Combinations
  - Other gyn malignancies/ other biomarkers?

FDA approval types

- **Regular approval*** based on endpoints that demonstrate that a drug provides longer life, better life, or favorable effect on an established surrogate for longer life or better life.
  - Requires substantial evidence from adequate and well-controlled trial(s).
- **Accelerated approval (AA)** based on surrogate endpoint reasonably likely to predict clinical benefit.

*21 CFR Part 314.126

Accelerated approval

- AA regulations* allow for approval of an agent appearing to provide benefit over available therapy for serious, life-threatening diseases
- Under AA, advantage based on effect on surrogate endpoint reasonably likely to predict clinical benefit, such as response rate, or endpoint measured earlier than irreversible morbidity or mortality
- AA granted instead of regular approval because of uncertainty about ultimate patient outcome.
- Additional trial to confirm clinical benefit required and should be underway at time of AA since surrogate is not direct measure of benefit

*21 CFR, Part 314.510, 21 CFR, Part 601.41

FDA PARP approvals: Summary

	Treatment		Switch maintenance
Line of therapy	4th line	3rd line	≥ 2 prior platinum based
Agents and approval date	Olaparib (12/2014)	Rucaparib (12/2016)	Niraparib (3/2017) Olaparib (8/2017) Rucaparib (4/2018)
Population	gBRCAmut	tBRCAmut	Platinum-sensitive recurrent
Approval type	Accelerated	Accelerated	Regular
Diagnostic	Companion diagnostic	Companion diagnostic	Complementary diagnostic

Companion vs. "Complementary" diagnostic

- Companion- a medical device or test, often an *in vitro* device, provides information **essential** for safe and effective use of a drug or biologic
- Complementary*- a medical device or test that identifies a biomarker-defined subset of patients with a different therapeutic product effect, but does not restrict patients from use of a therapy based upon test result.

***THIS IS NOT AN OFFICIAL DEFINITION**

Companion vs. "Complementary": The Case of BRACAnalysis CDx

- **Olaparib 4th line**
  - **12/19/15**
- Supporting trial only studied BRCAm patients
- **Companion Dx** required; part of drug indication
  - **Example**- Used to identify ovarian cancer patients with del gBRCAm, who may be eligible for treatment with olaparib

- **Niraparib maintenance**
  - **3/27/17**
- Supporting trial enrolled BRCA and non-BRCA
- **Complementary Dx** does not restrict use of drug but may guide use
  - **Example**- Detection of gBRCA variants using the test may predict for patients who may have enhanced PFS in association with niraparib maintenance

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What next?

- Improve upon current data:
  - **PARP combinations?**: cedarinib, bevacizumab, PD-1/PD-L1 agents

Combinations

- 21 CFR 300.50-
  - Two or more drugs may be **combined** (in a single dosage form) when **each component makes a contribution to the claimed effects** and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

Criteria for Codevelopment

- Intended to treat serious disease or condition
- **Strong biologic rationale** for the combination
- Nonclinical model or limited clinical study
  - suggests substantial activity of the combination
  - provides greater than additive activity or more durable response
- Compelling reason for not developing agents individually
  - Rapid resistance with monotherapy (antivirals)
  - One or both agents with very limited activity as monotherapy

Codevelopment Caveats

- Intended to address 2 or more drugs not previously developed for any indication to be used in combination to treat a disease or condition
- Assess the contribution of each component in addition to the combination
- Less information about safety and effectiveness than if individual drugs were developed; how much less will depend on stage of development
- Inherent risk compared to individual development of a drug

Additional Caveats

- No fixed duration/ Δ for PFS/OS improvement
- No fixed ORR
  - Historical controls for comparison may be acceptable
- RISK:BENEFIT is key

What next?

- Improve upon current data:
  - **PARP combinations?**: cedarinib, bevacizumab, PD-1/PD-L1 agents
  - Comparing PARP inhibitors head-to-head?
  - PARP in front line ovarian cancer (SOLO1).
  - Other biomarkers (beyond BRCA and HRD) to predict response?
  - Exploratory subgroups (bulky vs. non-bulky)?
  - **PARP in other malignancies** (Other gynecologic malignancies)?

Parp in other malignancies?

- Olaparib approved Jan 2018 for use in HER2-negative metastatic breast cancer patients with gBRCAm who had received prior chemotherapy and appropriate endocrine therapy for hormone receptor positive cancers.
- Tissue agnostic?

References

- 21 CFR, Part 314.510
- 21 CFR, Part 601.41
- FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics, May 2014
- FDA Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination, June 2013

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- Hisani Madison

Back up

Guidance: Codevelopment of 2 or more Inv drugs in combination

One approved, one unapproved:

- Similar to scenario with two investigational agents
  - Monotherapy trial for approved agent presumably completed
  - Still need to do study to isolate effect of each agent
    - If one agent has little activity on its own, still need to demonstrate combination activity over single agent

Guidance: Codevelopment of 2 or more Inv drugs in combination

Two unapproved agents:

- Recommend Phase 1 monotherapy to find safe doses for each agent alone
- Phase 2 (or extension cohort of Phase 1) to find efficacy signal
- Trial to determine safe dose of combination and establish efficacy of combination
  - **Need to show contribution of each agent for combinations**
- FDA Guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

Guidance: Codevelopment of 2 or more Inv drugs in combination

Two approved agents:

- IND exemption may apply- combining approved agents (even in unapproved indication) in course of medical practice
- Randomized trials evaluating unapproved use of marketed drugs may require IND
- FDA cannot compel Sponsor to conduct trials, but NO marketing claim can be made for increased efficacy over each agent alone

Rationale for PARP inhibition

- PARP inhibition may have a role in tumors in the setting of:
  - Germline or somatic BRCA 1/2 mutation
  - Epigenetic inactivation of BRCA
  - Defect in homologous recombination pathway independent of BRCA 1/2.