FDA Perspective:
Evolving Development of Parp Inhibitors
Gwynn Ison, MD
June 14, 2018
• 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

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<thead>
<tr>
<th>Line of therapy</th>
<th>Treatment</th>
<th>Switch maintenance</th>
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<tbody>
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<td>4th line</td>
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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 **do**es **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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<td>Rucaparib (12/2016)</td>
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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/ $\Delta$ 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
Acknowledgments

• Sanjeeve Balasubramaniam
• Julia Beaver
• Gideon Blumenthal
• 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:
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.