

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.

Accelerated approval



- AA regulations* allow for approval of an agent appearing to provide benefit over available therapy for serious, lifethreatening 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



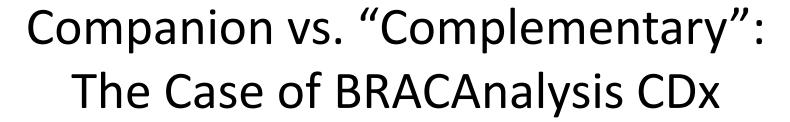
	Treatment		Switch maintenance
Line of	4 th line	3 rd line	≥ 2 prior platinum
therapy			based
Agents and	Olaparib (12/2014)	Rucaparib (12/2016)	Niraparib (3/2017)
approval date			Olaparib (8/2017)
			Rucaparib (4/2018)
Population	gBRCAmut	tBRCAmut	Platinum-sensitive
			recurrent
Approval	Accelerated	Accelerated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

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- 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 HER2negative 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 of 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/GuidanceCompli

anceRegulatoryInformation/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.