Current and Future Directions in PARP Inhibition

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Financial Disclosure

- Ms. Grudem has nothing to disclose.
- Dr. Wahner Hendrickson has nothing to disclose.

Learning Objectives

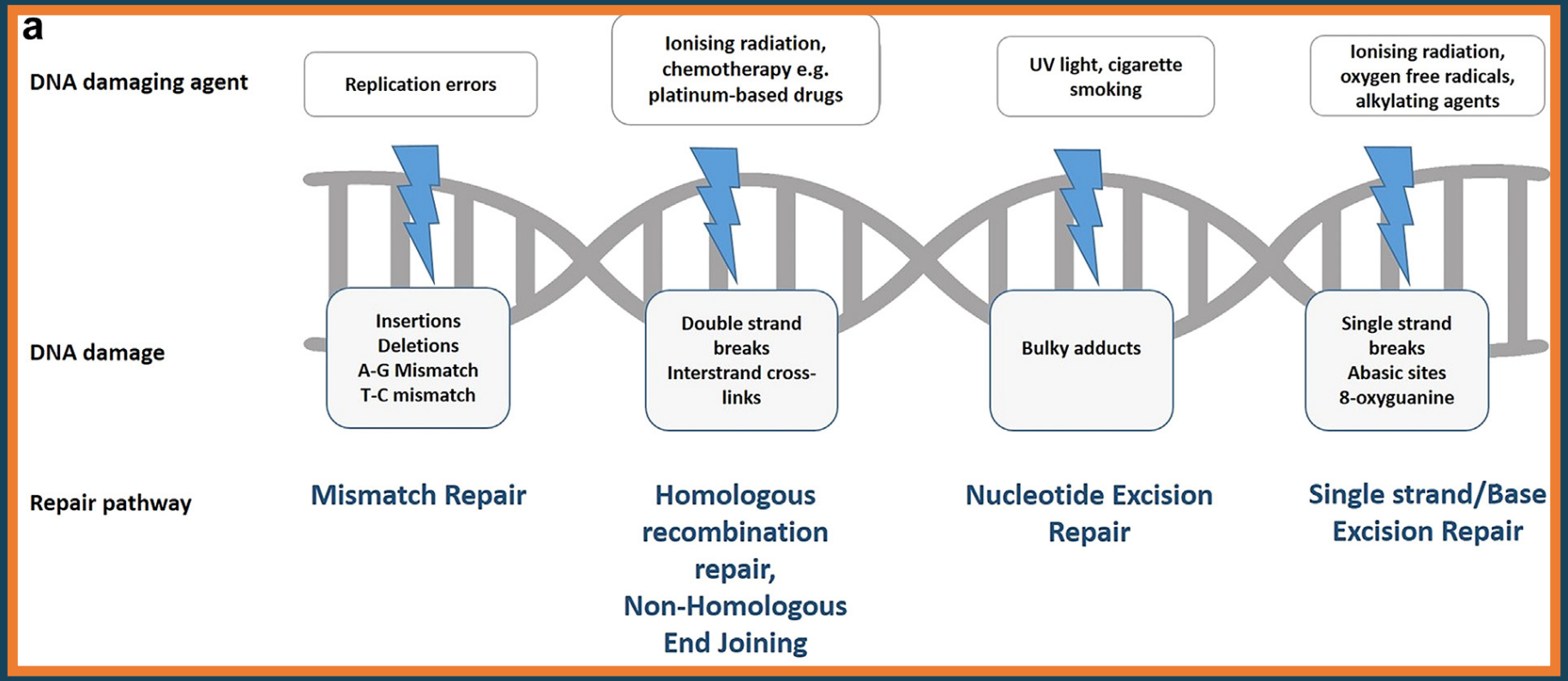
1. Relate the mechanisms of PARP inhibition to the potential role of PARP inhibitors in various malignancies
2. Identify patients who are appropriate candidates for PARP inhibitor therapy in light of genetics, disease biology, and other key factors
3. Devise treatment plans for patients with ovarian or breast cancer that include PARP inhibitor therapy based on genetic profiles, tolerability, dosing schedules, and other factors

PARP Inhibitors

Mechanism of action

DNA Repair Mechanisms

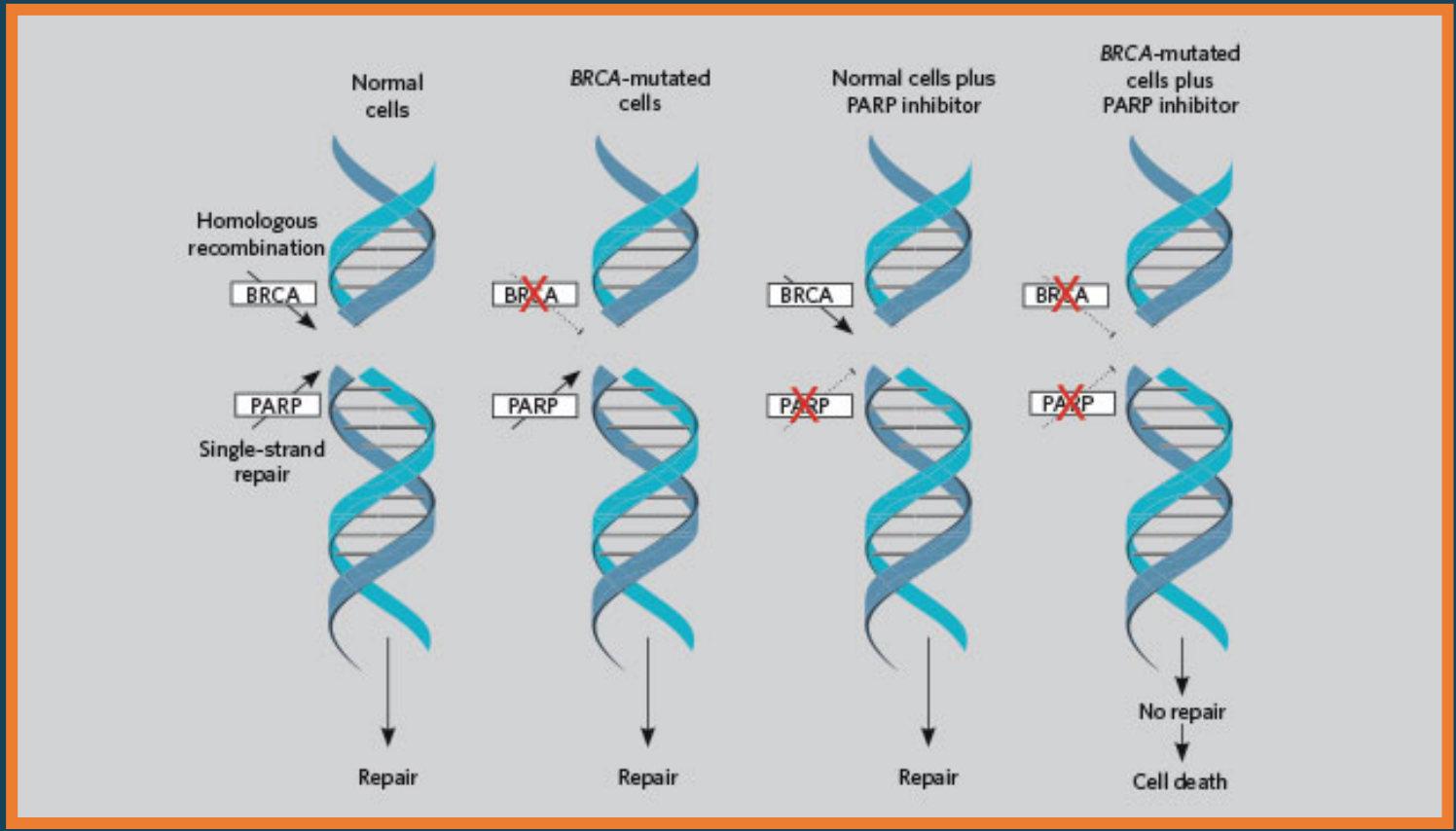
5 Major Pathways



Ledermann JA, et al. *Eur J Cancer.* 2016;60:49-58

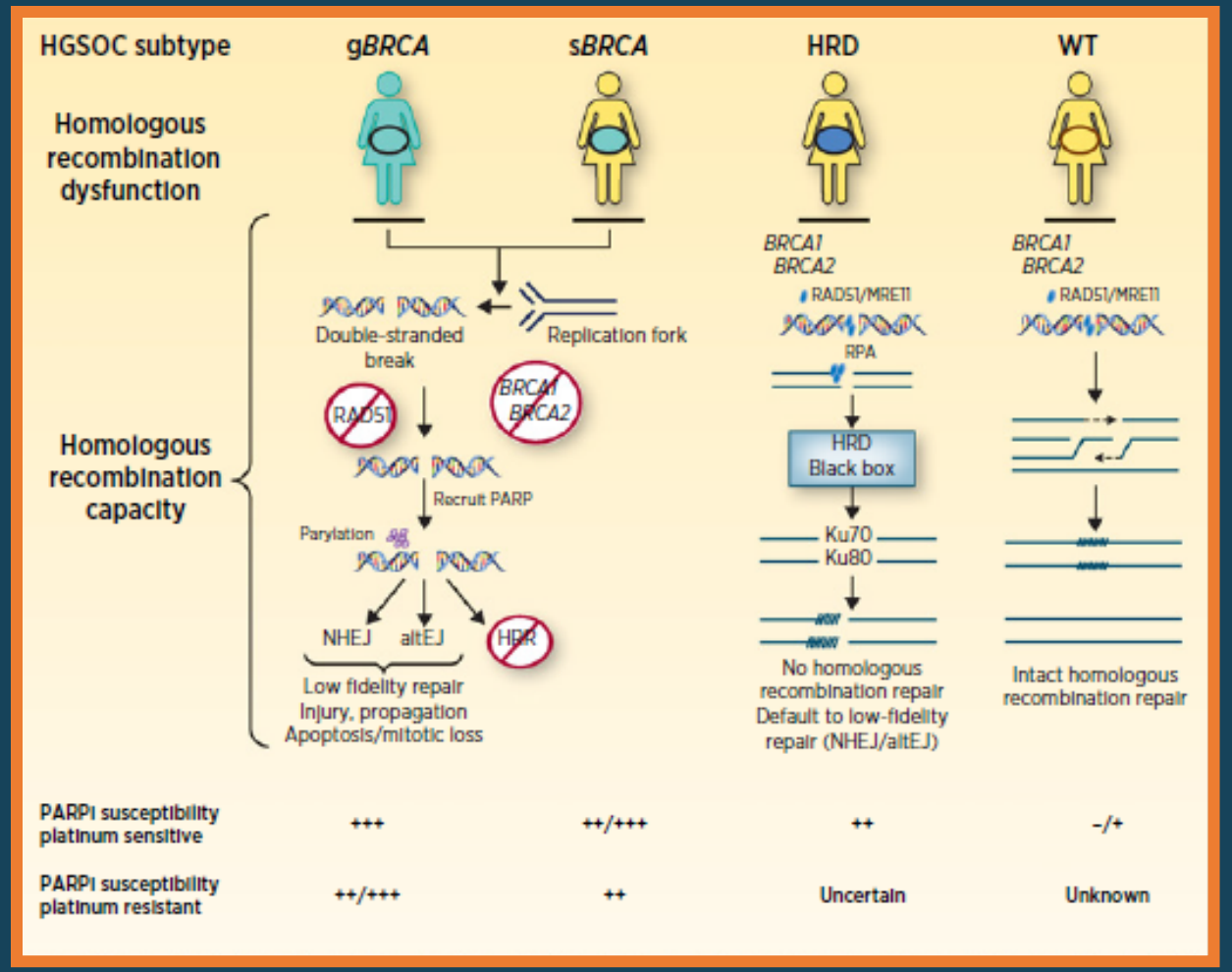
PARP Inhibitor Sensitivity

The Role of *BRCA* Mutations



Bower V, *The Scientist*. April 2018

Why do they work better in some tumors?



Kohn EC, et al. *Clin Cancer Res*. 2017;23(23):7155-57.

Tumors Associated With *BRCA1/2* Mutations

- Breast cancer
- Ovarian cancer
- Prostate cancer
- Pancreatic cancer

Summary

PARP inhibitors work best in tumors with defective DNA repair

- These mutations lead to difficulty in repairing DNA damage
- PARP inhibitors enhance that difficulty
- Can be a germline (inherited) mutation or a somatic (tumor only) mutation
- BRCA1/BRCA2
- “HRD high”

FDA-Approved PARP Inhibitors

Generic Name	Brand Name
niraparib	Zejula
olaparib	Lynparza
rucaparib	Rubraca
talazoparib	Talzenna

A Few Words on Each of the Four PARP Inhibitors

Olaparib

FDA approval in breast and ovarian cancers

Olaparib

FDA-Approved Indication: BREAST

- January 12, 2018
- Treatment of patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy, either in the neoadjuvant, adjuvant, or metastatic setting

OlympiAD: Trial Design

- HER2- metastatic breast cancer
- Hormone pos or neg
- gBRCAm
- No more than 2 prior chemo regimens for recurrent disease

RANDOMIZE 2:1

Olaparib (n=205)

Standard:

Capecitabine (n=41)

Eribulin (n=34)

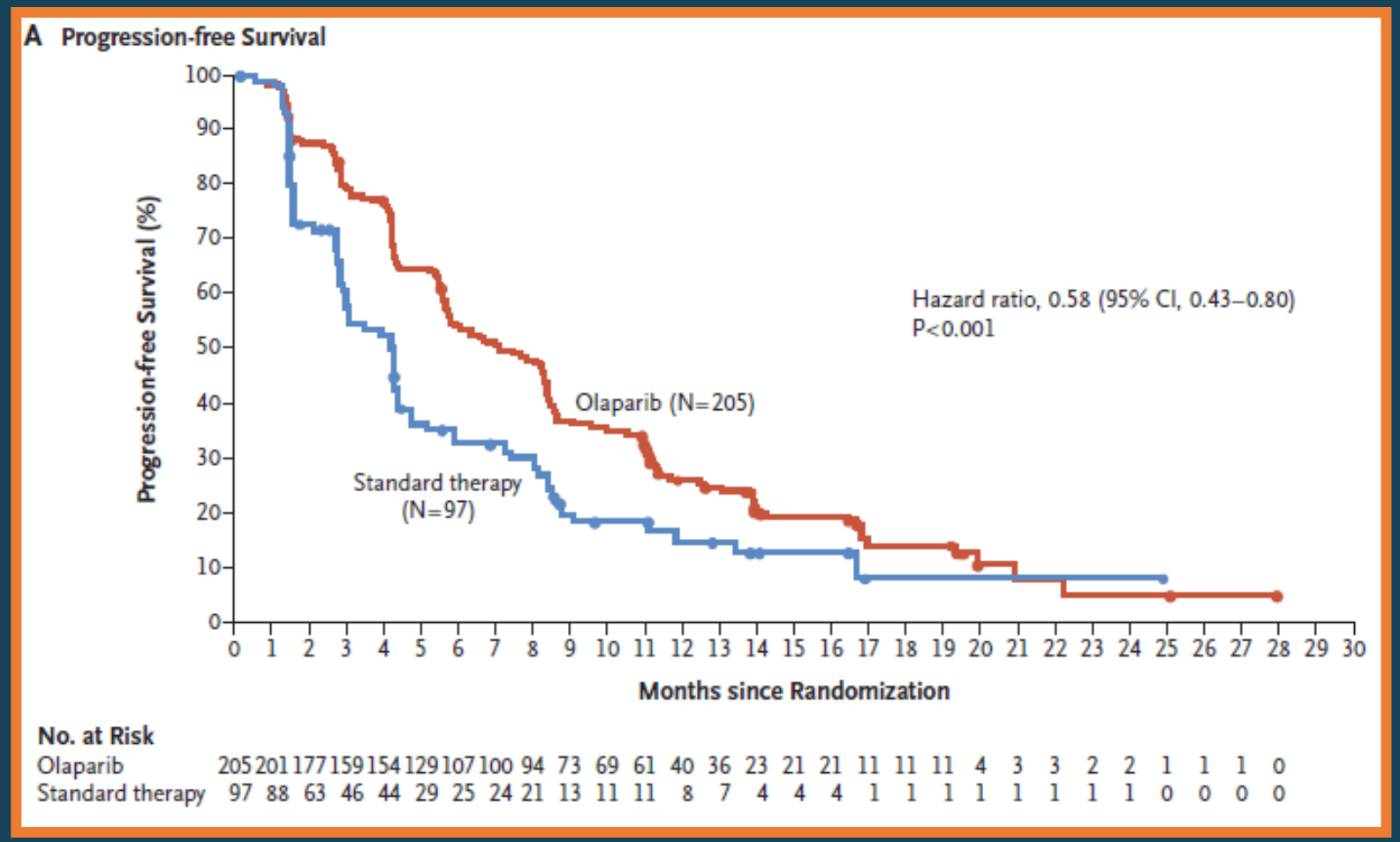
Vinorelbine (n=16)

Stratified:
Prior chemo for metastatic disease
HR status
Prior platinum

Primary Endpoint: PFS
Secondary Endpoint: OS

Robson M, et al. *N Engl J Med*. 2017;377:523-533

OlympiAD: Progression-Free Survival



Robson M, et al. *N Engl J Med*. 2017;377:523-533

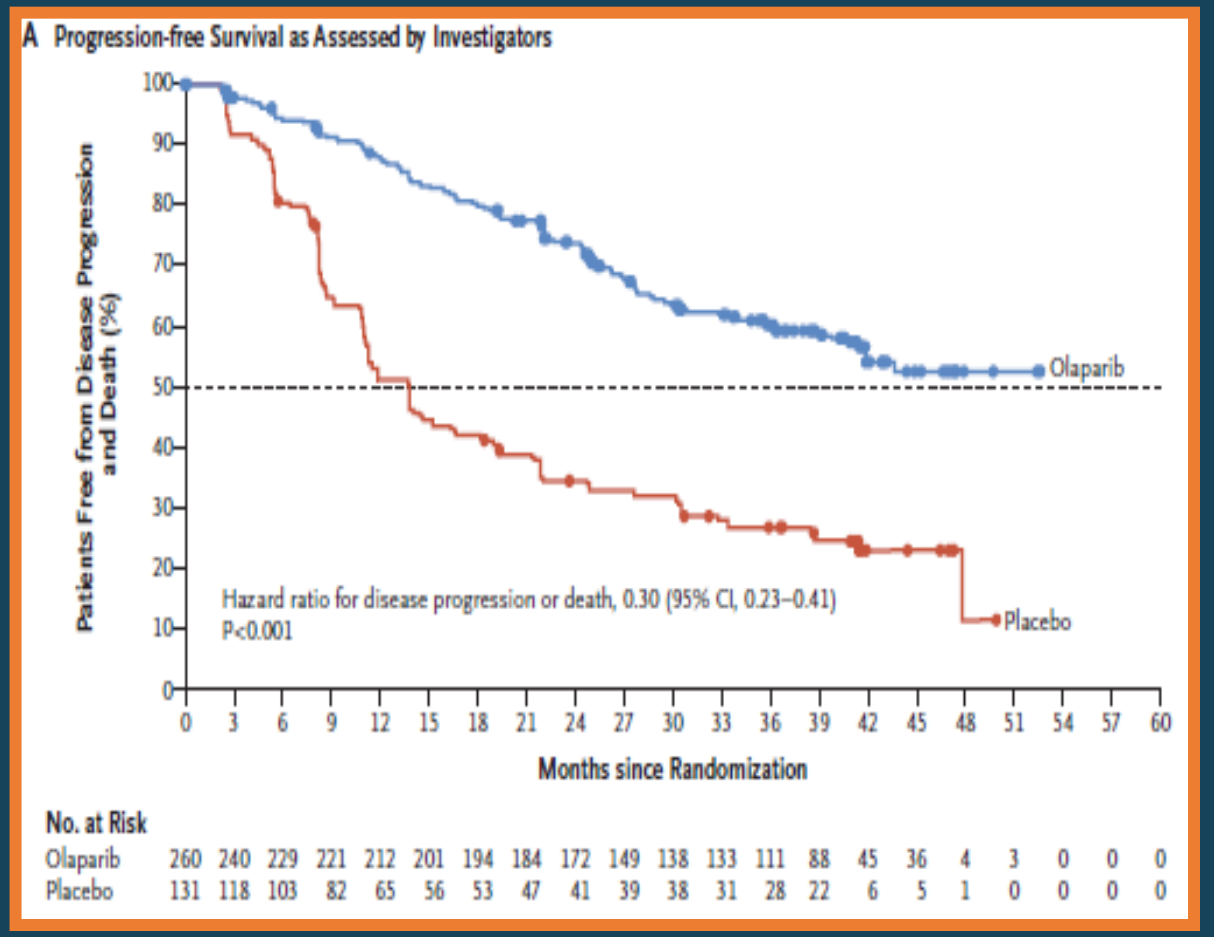
Olaparib
FDA-Approved Indications: OVARIAN

- Maintenance therapy
  - Initial therapy if germline or somatic *BRCA* mutations
  - Recurrent platinum sensitive disease in all women regardless of mutations

- Treatment
  - Germline (inherited) *BRCA*-mutated ovarian cancer who have been treated with 3 or more prior lines of platinum therapy

Olaparib
Ovarian Cancer

- FDA approval December 2018
- Maintenance treatment of adult patients with *gBRCAm or sBRCAm* advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy



N Engl J Med 2018;376:26

Olaparib: Common Side Effects

- Nausea
- Vomiting
- Fatigue
- Diarrhea
- Decreased appetite
- Anemia

Rucaparib

FDA approval in ovarian cancer

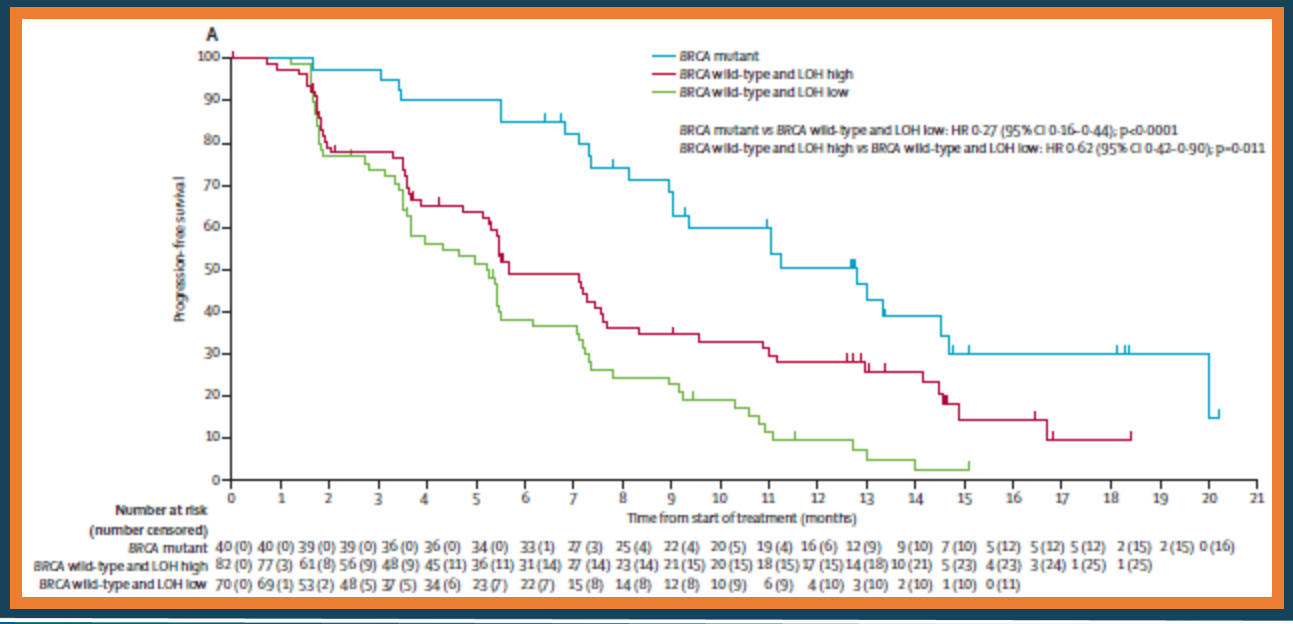
Rucaparib

FDA-Approved Indications: OVARIAN

- Treatment (2016)
  - *BRCA* mutation (germline or somatic)
  - FoundationFocus CDxBRCA test
  - 2 or more prior therapies
- Maintenance therapy (2018)
  - Recurrent ovarian cancer who are in complete or partial remission to platinum-based therapy
  - Regardless of mutation status

Rucaparib
Ovarian Cancer

- Data from Study 10, ARIEL Part 1 and Part 2
  - ARIEL 2 Part 1
    - Platinum sensitive, 1 prior regimen
      - 80% RR in BRCA mut
      - 29% RR in BRCAwt/LOH^{hi}
      - 10% RR in BRCAwt/LOH^{low}



Swisher EM, et al. *Lancet Oncol*. 2017;18:75-87

Rucaparib: Most Common Side Effects

- Nausea
- Vomiting
- Fatigue (including weakness)
- Anemia
- Abdominal pain
- Changes in taste

Niraparib

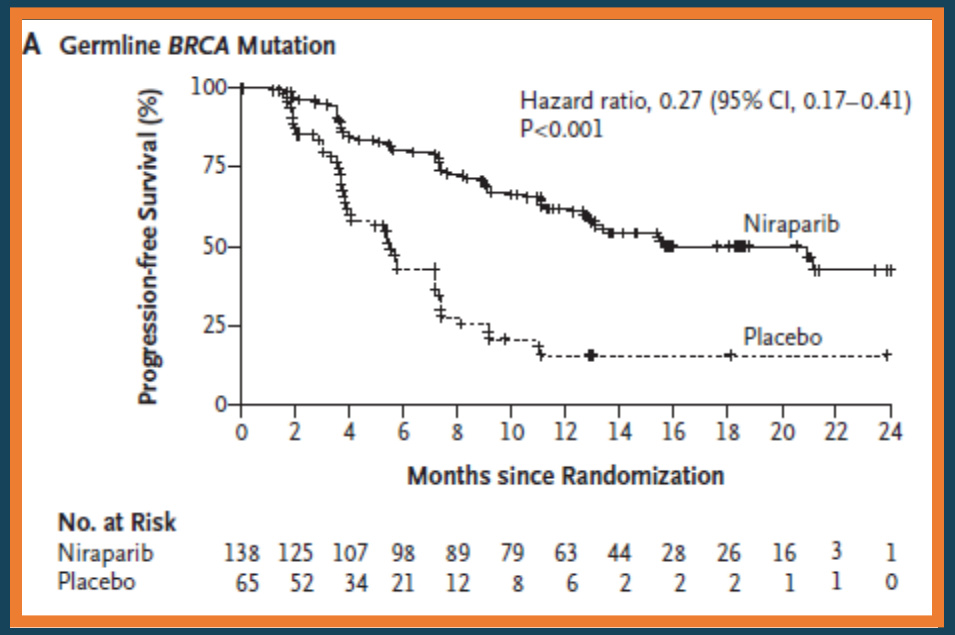
FDA approval in ovarian cancer

Niraparib
FDA-Approved Indications

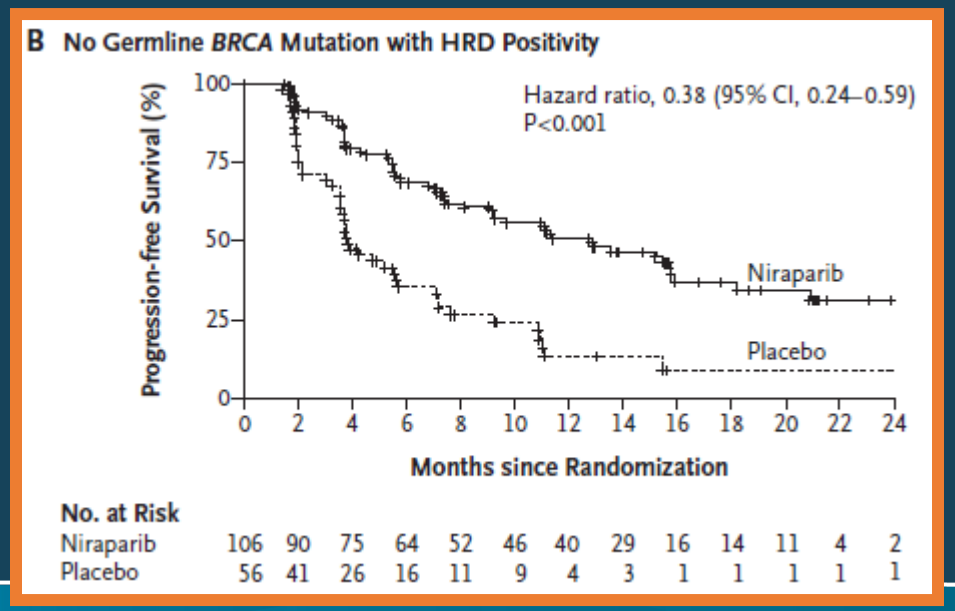
- Maintenance therapy
  - Recurrent (not after first chemotherapy)
  - Tumor has partially or completely “responded” to the most recent platinum chemotherapy
  - All women regardless of mutations
  - Once daily dosing
  - Front line clinical trial presented just published (Gonzalez-Martin NEJM 2019)

- Treatment
  - Currently under review

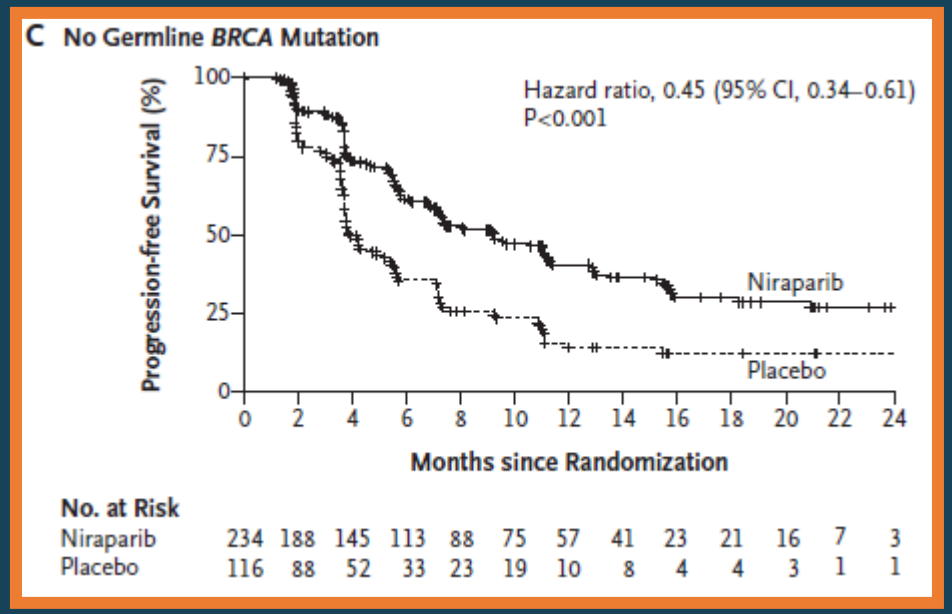
Niraparib Maintenance Therapy



21.0 vs 5.5 mo



12.9 vs 3.8 mo



9.3 vs 3.9 mo

HRD-negative: 6.9 mo vs 3.8 mo

Mirza MR, et al. *N Engl J Med*. 2016;375:2154-64

Niraparib: Most Common Side Effects

- Nausea
- Thrombocytopenia
  - Dose modification based on weight (<77kg) and baseline platelet count (<150,000/uL)
- Fatigue/asthenia
- Anemia
- Vomiting
- Neutropenia

Talazoparib

FDA approval in breast cancer

Talazoparib

- October 2018: FDA approval for gBRCAm HER2-negative locally advanced or metastatic breast cancer
- Once-daily dosing

Trial Design

EMBRACA

- HER2 neg locally advanced or metastatic breast cancer
- Hormone pos or neg
- gBRCAm
- No more than 3 prior chemo regimens for recurrent disease

RANDOMIZE 2:1

Talazoparib (n=287)

Standard (n=144):

Capecitabine (44%)

Eribulin (40%)

Gemcitabine (10%)

Vinorelbine (7%)

Stratified:

prior chemo regimens

HR status (pos/neg)

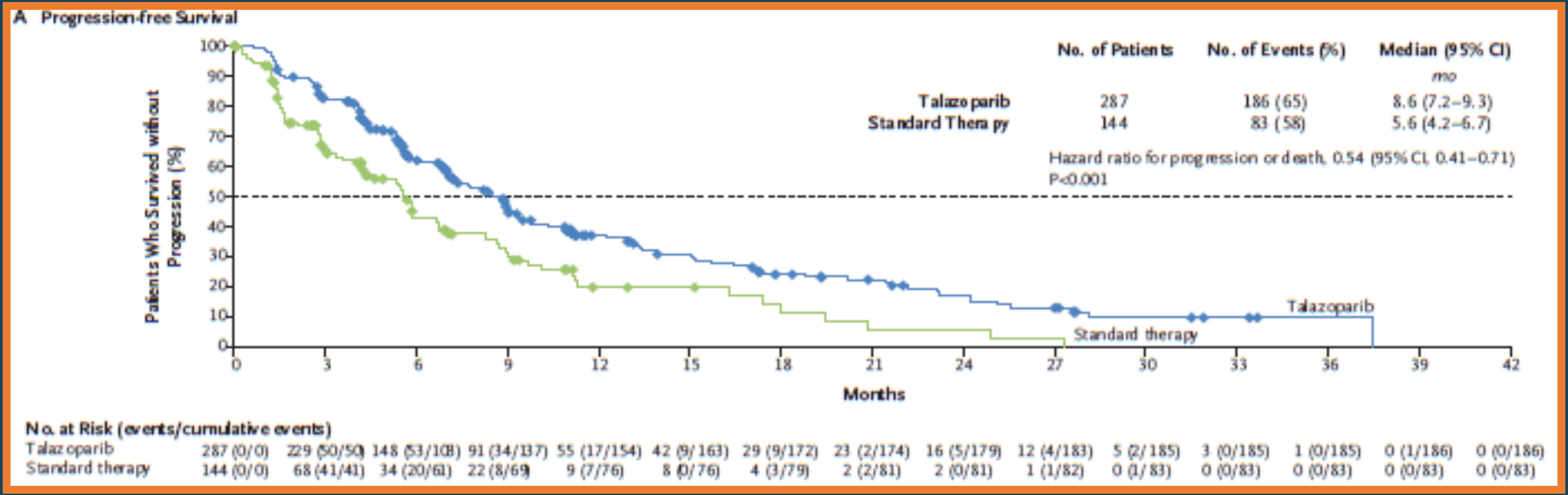
History of CNS mets

Primary Endpoint: PFS

Secondary Endpoint: OS

Litton JK, et al. *N Engl J Med*. 2018;379:753-63

EMBRACA



Litton JK, et al. *N Engl J Med*. 2018;379:753-63

Talazoparib: Side-Effect Profile

- Fatigue
- Anemia
- Nausea
- Neutropenia
- Headache
- Thrombocytopenia
- P-gp inhibitor: Need to reduce dose due to interactions
  - Amiodarone, carvedilol, itraconazole, and verapamil

PARP Inhibitor Side Effects

- All have a similar side effects, but some are more common and/or more severe in one versus another
- All can cause AML/MDS

Myelodysplastic Syndrome (MDS)

- Heterogeneous group of malignant hematopoietic stem cell disorders
  - Older adults
  - Can occur de novo or after mutagenic exposure (chemotherapy, radiation)
- Common presentation
  - Anemia
  - Thrombocytopenia and/or neutropenia
- Dysplasia on blood smear or bone marrow

Myelodysplastic Syndrome: Therapy-related

- Alkylating agents
  - Carboplatin
  - Cisplatin
  - Cyclophosphamide
- Topoisomerase II inhibitors
  - Etoposide
  - Doxorubicin
- PARP inhibitors

Other Side Effects

- Pneumonitis
  - Olaparib
- Increase in cholesterol
  - Rucaparib
- Rash/photosensitivity
  - Rucaparib
  - Olaparib
- Elevation in creatinine
  - Rucaparib
  - Olaparib
- Elevation in LFTs
  - Rucaparib
- Hypertension
  - Niraparib

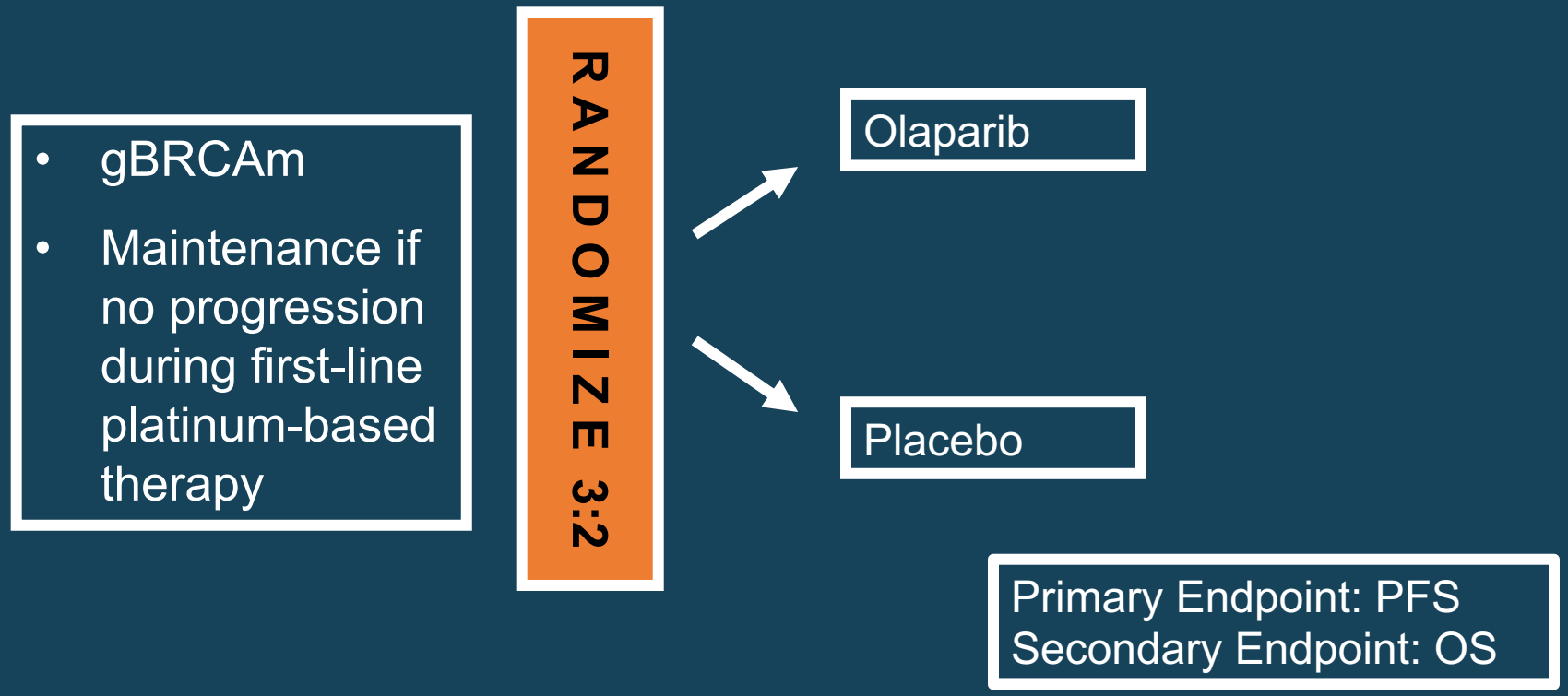
FDA inserts, NOVA NEJM2016

PARP Inhibitors: Agents and Indications in Ovarian Cancer

Agent	Maintenance therapy	Monotherapy
Olaparib	• Front line (BRCAm) • First recurrence, platinum-sensitive	Third recurrence gBRCA
Rucaparib	• First recurrence, platinum-sensitive	Second recurrence gBRCA or sBRCA
Niraparib	• First recurrence, platinum-sensitive	

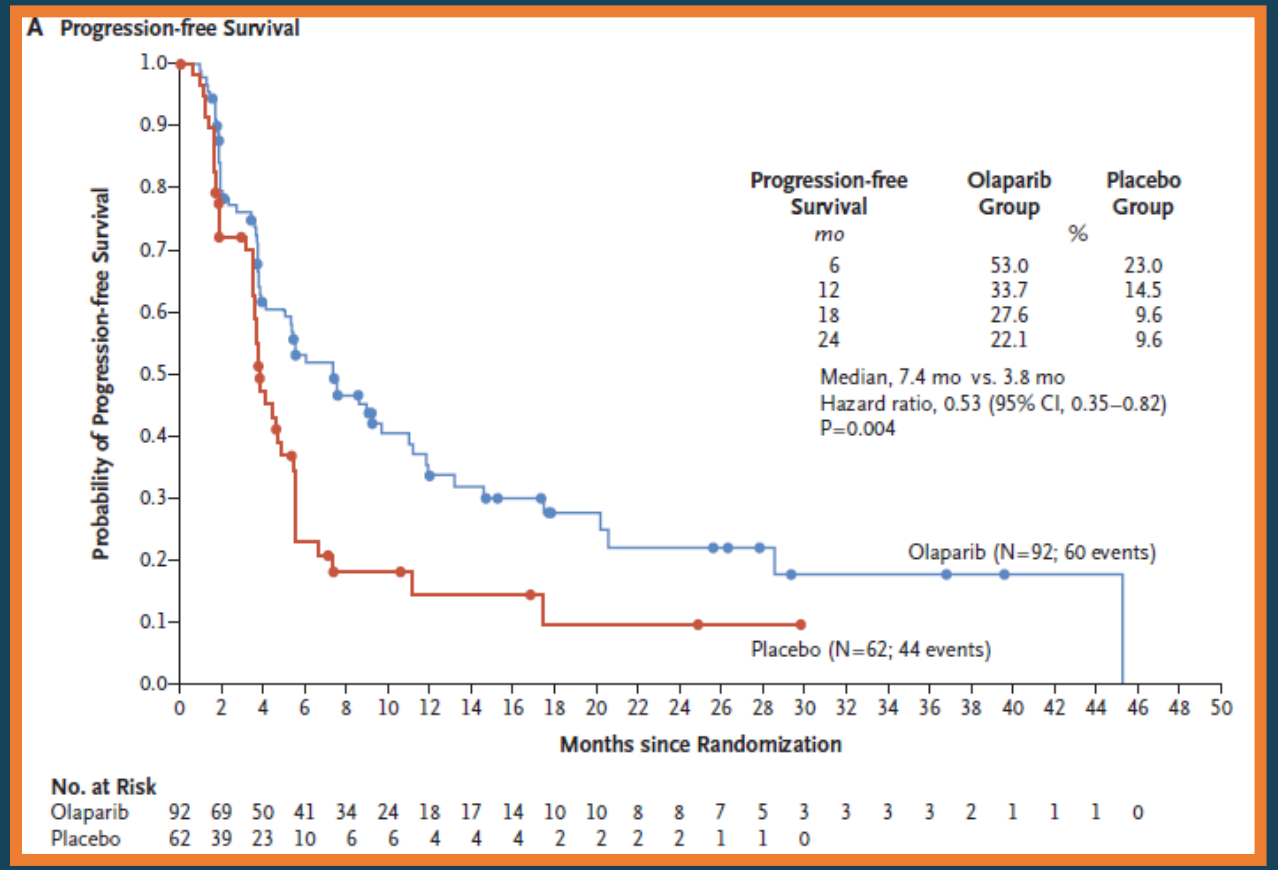
Where Do We Stand in Pancreatic Cancer?

Metastatic Pancreatic Cancer: Trial Design



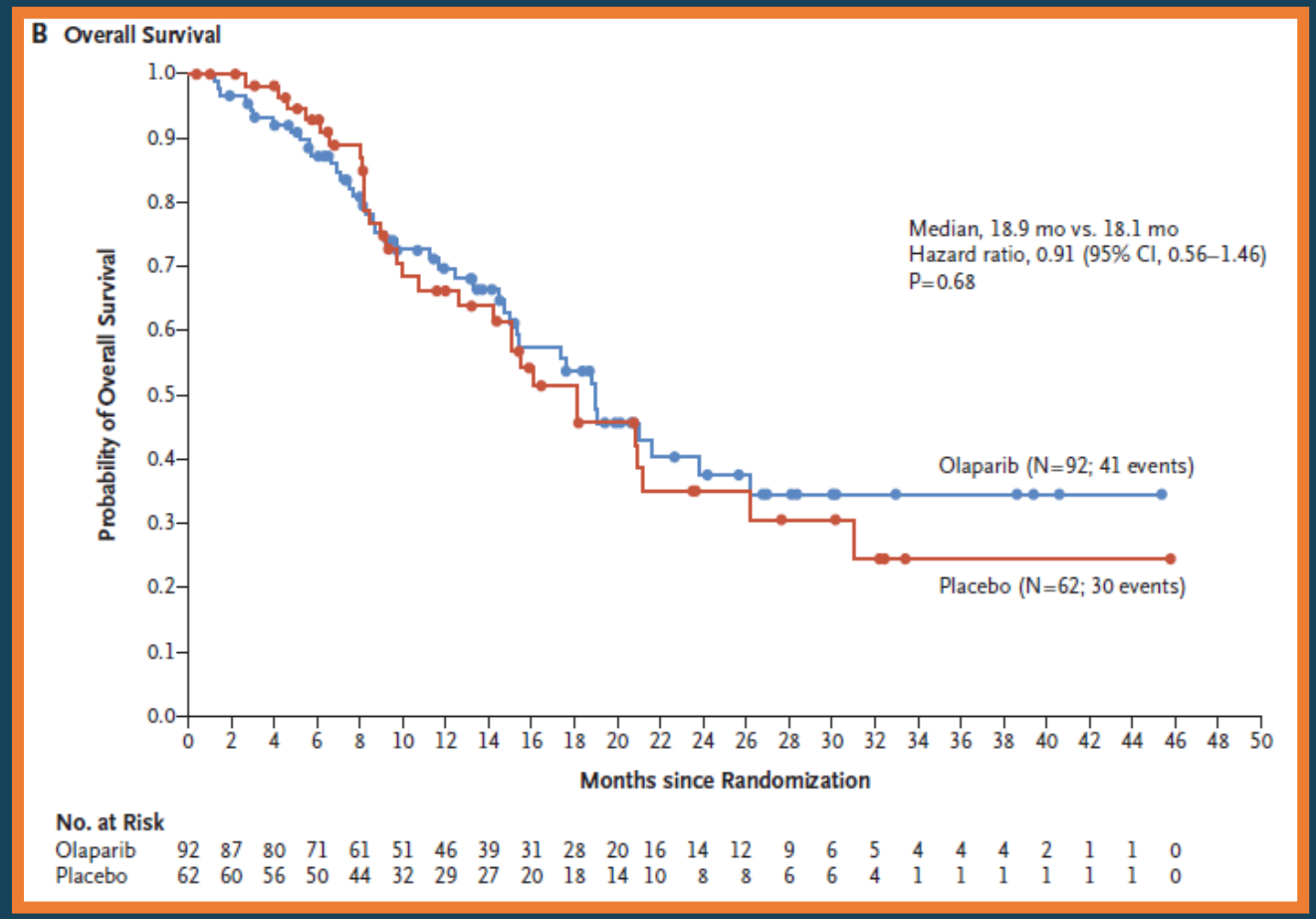
Golan T, et al. *N Engl J Med*. 2019;381:317-27

Metastatic Pancreatic Cancer: Progression-Free Survival



Golan T, et al. *N Engl J Med*. 2019;381:317-27

Metastatic Pancreatic Cancer: Overall Survival



Golan T, et al. *N Engl J Med*. 2019;381:317-27

Ongoing Areas

Genitourinary Cancers

- Prostate cancer
- Renal cell carcinoma

Case Presentations

Case Presentation #1

A 36-year-old woman with stage IIIC high-grade serous ovarian cancer sees you in clinic. She has undergone an optimal surgical resection and is close to finishing her adjuvant chemotherapy with carboplatin and paclitaxel. She has seen a genetic counselor and she tested negative for a germline *BRCA* mutation.

She has seen the advertisements about a new class of oral medications for ovarian cancer and is interested in learning more.

You confirm the patient is talking about PARP inhibitors. What is your next step?

A. You inform her that this class of drugs is only available if her cancer comes back in the future.
B. You inform her she is not eligible for this therapy because she does not have a germline *BRCA* mutation.
C. You recommend somatic tumor testing to assess whether her tumor expresses a *BRCA* mutation.
D. You inform her she is not eligible for this therapy because it is only recommended in those women whose tumor progresses through front-line therapy.

The patient agrees to have her tumor tested for a somatic *BRCA1/2* mutation, and the results are consistent with a somatic *BRCA2* mutation. You review the role of maintenance therapy, and she is interested in proceeding. You recommend which of the following PARP inhibitors for her?

A. Olaparib
B. Niraparib
C. Rucaparib
D. Talazoparib

Risks/Benefits of Maintenance Therapy

- Benefits
  - Improvement in progression-free survival
  - Overall survival data pending
- Disadvantages
  - Side effects
  - Treatment cost
  - More doctor visits
  - Long-term impact on bone marrow

You prescribe olaparib maintenance therapy and review the required blood testing involved with the patient. You relay which of the following information?

A. She will need a weekly CBC
B. She will need a weekly CBC and monthly LFTs, Cr
C. She will require a weekly CBC and creatinine
D. She will not require any bloodwork

Recommended Bloodwork

PARP Inhibitors

Weekly (first month)*	Monthly
CBC with differential	CBC with differential
	LFTs: AST, ALT, Alk Phos
	Creatinine

* Continue weekly until tolerated dose established and counts stable for 1 month

Case Presentation #2

A 57-year-old woman with platinum-sensitive recurrent ovarian cancer has just finished her course of chemotherapy with carboplatin and liposomal doxorubicin. Her CT scans show a complete response. The plan was to initiate PARPi maintenance therapy. Which of the following are options for her?

A. Olaparib
B. Rucaparib
C. Niraparib
D. Talazoparib
E. A, B, and C
F. All of the above

The patient begins therapy with niraparib. She returns for bloodwork 1 week later, which reveals the following:

- Hgb 10.0 g/dL
- WBC 3.6 x 10^9/L
- ANC 1.1 x 10^9/L
- Platelets 80 x 10^9/L

Per prescribing guidelines, you recommend which of the following?

A. Discontinue the niraparib
B. Hold niraparib until counts recover, then restart the niraparib at the same dose (300 mg PO daily)
C. Hold niraparib until the counts recover, then modify the dose of niraparib from 300 mg to 200 mg PO daily
D. Hold the niraparib until the counts recover, then modify the dose of niraparib from 300 mg to 100 mg PO daily

Niraparib Dosing

- Beginning dose: 300 mg daily (comes in 100 mg tablets)
- First dose reduction: 200 mg daily
- Second dose reduction: 100 mg daily
- Reduced initial dosing strategy: Patients weighing <77 kg and/or with baseline platelets <150,000/mm^3: Initial: 200 mg once daily; after 2 to 3 months, in the absence of hematologic toxicity, may consider escalation to usual dose of 300 mg once daily (ARIEL 3)

PARP Dosing

	Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Niraparib (100 mg capsules)	300 mg daily	200 mg daily	100 mg daily	
Olaparib (100 mg and 150 mg tablets)	300 mg twice daily	250 mg twice daily	200 mg twice daily	
Rucaparib (300 mg, 250 mg, and 200 mg tablets)	600 mg twice daily	500 mg twice daily	400 mg twice daily	300 mg twice daily
Talazoparib (0.25 mg and 1 mg capsules)	1 mg daily*	0.75 mg daily	0.5 mg daily	0.25 mg daily

Case Study #3

A 55-year-old woman diagnosed with germline *BRCA1*-positive, HER2-negative, ER-positive breast cancer. She was treated with chemotherapy followed by hormonal therapy, and then her disease recurred within 2 years. She is feeling well with an ECOG PS of 0.

She is interested in her treatment options and would prefer an oral medication. You recommend PARP inhibitor therapy.

Which of the following PARP inhibitors are FDA-approved options for your patient?

A. Niraparib
B. Rucaparib
C. Olaparib
D. Talazoparib
E. C and D only
F. All of the above

She starts olaparib therapy and calls a few days later noting significant nausea. She has not had any emesis, but is not eating well due to the nausea. She is not taking any additional medications. You recommend which of the following?

A. Hold the medication until her next appointment in 3 weeks
B. Recommend taking an antiemetic approximately 30-45 minutes before taking the medication
C. Recommend switching to talazoparib therapy

Conclusions

- PARP inhibitors are becoming a widely used class of agents
- They appear to work best in tumors with dysfunctional DNA repair
  - BRCA1 and BRCA2
- Common side effects
  - GI side effects, fatigue, some cytopenia
- Refer to charts regarding indications and dosing

More Questions?

Come see us at Booth #829 (next to the APSHO Booth)
in the Exhibit Hall from **12:10 to 1:00** today.

This has been a SMARTIE presentation.

To access your post-session questions, you can:

- Click on the link that was sent to you via email
- Visit the SMARTIE station
- Go to jadprolive.com/smartie2019