

PARP Inhibitors For Ovarian Cancer

	OLAPARIB	RUCAPARIB	NIRAPARIB
Target	Pan-PARP inhibitor		PARP 1 and 2
Dose	300 mg BID	600 mg BID	300 mg daily
Dose adjustments	CrCl 31-50 mL/min: 200 mg BID		If < 77 kg or platelets < 150,000/ μ L: 200 mg daily, Titrate up if tolerated
Class ADR	Nausea, diarrhea, fatigue, bone marrow suppression, secondary malignancy		
Unique ADR	Asymptomatic elevation of serum creatinine, pneumonitis	Transaminitis, asymptomatic increase in serum creatinine, GERD, dysgeusia, rash	Insomnia, hypertension
DDIs	Substrate of CYP3A4 Inhibits MATE1 and MATE2-K	Substrate of CYP2D6 Inhibits CYP2C9 Inhibits MATE1 and MATE2-K	
PK	Mean half-life = 14.9 +/- 8.2 hours	Mean half-life = 17-19 hours	Mean half-life = 36 hour
Notes	Tablets and capsules are not interchangeable (capsules are phased out)		Weekly CBC for the first month of therapy then monthly thereafter

CrCl, creatinine clearance; CYP, cytochrome P450; DDIs, drug-drug interactions; PK, pharmacokinetics; GERD, gastroesophageal reflux disease; CBC, complete blood count; ADR, adverse drug reactions

ADVERSE EFFECT MANAGEMENT PEARLS

OLAPARIB

- Consider hold for new or worsening respiratory symptoms
- Consider cystatin C if cancer for true kidney dysfunct

RUCAPARIB

- Sunscreen and sun-protective clothing
- Consider PPI for GERD
- Good oral hygiene for dysgeusia
- Consider statins for hypercholesterolemia
- Consider cystatin C if cancer for true kidney dysfunction

NIRAPARIB

- Weekly CBC for the first month of therapy
- Monitor blood pressure and heart rate weekly for 2 months, then monthly
- May take dose in the morning for insomnia

RUCAPARIB

- Moderately emetogenic
- Ondansetron 4-8 mg with each PARP inhibitor dose (8-16 mg/day)
- May add prochlorperazine as needed as a breakthrough agent
- Non-pharmacologic management of fatigue includes exercise, cognitive behavioral therapy, massage therapy
- Counsel patients to report increases of 4-6 stools per day over baseline (Grade 2) or diarrhea limiting ADLs

NON-HEMATOLOGIC TOXICITY OF PARP INHIBITORS

	OLAPARIB	RUCAPARIB	NIRAPARIB
Fatigue			
Grade ≥ 3	4%	7%	8%
Nausea			
All Grades	76%	75%	74%
Grade ≥ 3	3%	4%	3%
Diarrhea			
All Grades	33%	32%	20%
Grade ≥ 3	1%	1%	< 1%

HEMATOLOGIC TOXICITY OF PARP INHIBITORS

	OLAPARIB	RUCAPARIB	NIRAPARIB
Anemia			
Grade ≥ 3	20%	19%	25%
Thrombocytopenia			
Grade ≥ 3	0%	5%	34%
Neutropenia			
Grade ≥ 3	5%	7%	20%

UNIQUE ADVERSE EFFECTS (ALL GRADE) OF PARP INHIBITORS

OLAPARIB	RUCAPARIB	NIRAPARIB
<ul style="list-style-type: none"> • Pneumonitis (< 1%) • Asymptomatic increase in serum creatinine (11%) 	<ul style="list-style-type: none"> • Transaminitis (34%) • Hypercholesterolemia (40%-84%) • Photosensitivity (17%) • Dyspepsia (15%) • Dysgeusia (39%) • Asymptomatic increase in serum creatinine (15%) 	<ul style="list-style-type: none"> • Insomnia (24%) • Hypertension (19%)

FDA APPROVALS OF PARPI IN OVARIAN CANCER

	Upfront maintenance	Recurrent maintenance	Treatment
Olaparib	X BRCAm	X	X
Olaparib + bevacizumab	X HRD	X	X
Rucaparib		X	X
Niraparib	X	X	X



REFERENCES

- Antolin AA, Ameratunga M, Banerji U, Clarke PA, Workman P, Al-Lazikani B. The kinase polypharmacology landscape of clinical PARP inhibitors. *Scientific reports*. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7026418/>. Published February 17, 2020. Accessed June 25, 2020.
- Berek JS;Matulonis UA;Peen U;Ghatage P;Mahner S;Redondo A;Lesoin A;Colombo N;Vergote I;Rosengarten O;Ledermann J;Pineda M;Ellard S;Sehouli J;Gonzalez-Martin A;Berton-Rigaud D;Madry R;Reinthaller A;Hazard S;Guo W;Mirza MR; Safety and Dose Modification for Patients Receiving Niraparib. *Annals of oncology : official journal of the European Society for Medical Oncology*. <https://pubmed.ncbi.nlm.nih.gov/29767688/>. Published 2018. Accessed June 25, 2020.
- Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* (London, England). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5901715/>. Published October 28, 2017. Accessed June 25, 2020.
- Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Nature News*. <https://www.nature.com/articles/s41416-018-0271-y>. Published October 24, 2018. Accessed June 25, 2020.
- LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. *The Lancet. Oncology*. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7292736/>. Published January 2019. Accessed June 25, 2020.
- Mirza MR, Al. E, Investigators* for the ENGOT-OVNOVA, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer: *NEJM*. *New England Journal of Medicine*. <https://www.nejm.org/doi/full/10.1056/NEJMoa1611310>. Published December 1, 2016. Accessed June 25, 2020.
- Oza AM;Tinker AV;Oaknin A;Shapira-Frommer R;McNeish IA;Swisher EM;Ray-Coquard I;Bell-McGuinn K;Coleman RL;O'Malley DM;Leary A;Chen LM;Provencher D;Ma L;Brenton JD;Konecny GE;Castro CM;Giordano H;Maloney L;Goble S;Lin KK;Sun J;Raponi M;Rolfe L;Kristeleit R. Antitumor Activity and Safety of the PARP Inhibitor Rucaparib in Patients With High-Grade Ovarian Carcinoma and a Germline or Somatic BRCA1 or BRCA2 Mutation: Integrated Analysis of Data From Study 10 and ARIEL2. *Gynecologic oncology*. <https://pubmed.ncbi.nlm.nih.gov/28882436/>. Published 2017. Accessed June 25, 2020.
- Pujade-Lauraine E;Ledermann JA;Selle F;GebSKI V;Penson RT;Oza AM;Korach J;Huzarski T;Poveda A;Pignata S;Friedlander M;Colombo N;Harter P;Fujiwara K;Ray-Coquard I;Banerjee S;Liu J;Lowe ES;Bloomfield R;Pautier P; ; Olaparib Tablets as Maintenance Therapy in Patients With Platinum-Sensitive, Relapsed Ovarian Cancer and a BRCA1/2 Mutation (SOLO2/ENGOT-Ov21): A Double-Blind, Randomised, Placebo-Controlled, Phase 3 Trial. *The Lancet. Oncology*. <https://pubmed.ncbi.nlm.nih.gov/28754483/>. Published 2017. Accessed June 25, 2020.
- Lynparza [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020.
- Rubraca [package insert]. Boulder, CO: Clovis Oncology, Inc.; 2020.
- Zejula [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2020.