Molecular Targeted Therapies in Gynecologic Cancer.

Which one matters living longer or living better?

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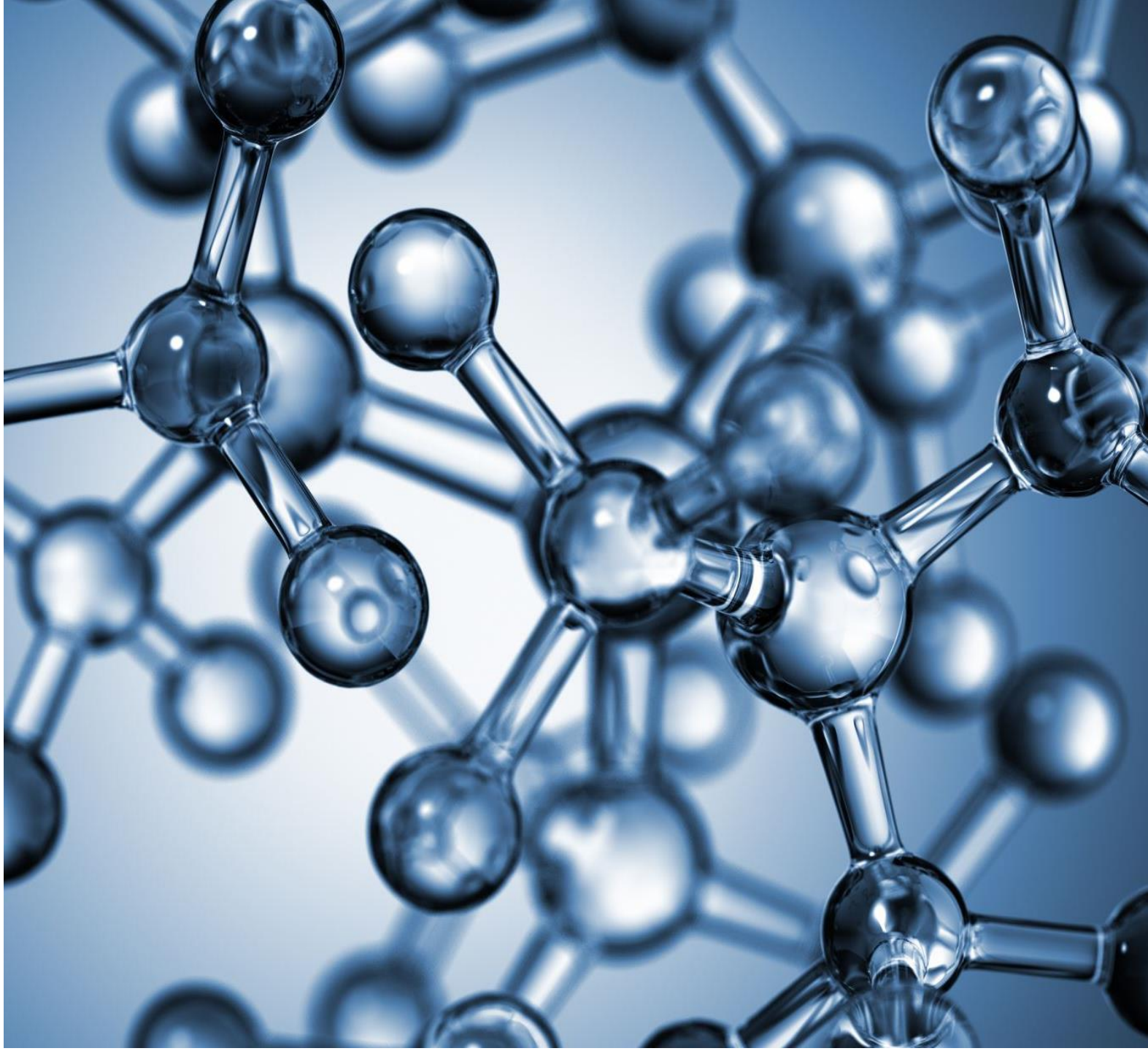


2019

- Where are we now?
- Did we improve our care?
- Is it the biology of tumor?
- Or is it something unseen?

Where are we now?

- Despite recent advances in cancer treatment, the number of deaths from gynecologic cancers remains substantial worldwide.

- In 2012, there were an estimated 527 624 new cases of cervical cancer and 265 672 deaths, 319 605 new cases of endometrial cancer and 76 160 deaths, 238 719 new cases of ovarian cancer and 151 917 deaths.

Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. [Internet]. Lyon: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr/Default.aspx. Accessed May 29, 2018

Did we improve our care?

- Higher center referral with dedicated Gynecology Oncology Unit YES
- Multidisciplinary team approach and multimodal management YES
- Cytoreductive surgery and cytotoxic drugs YES
- First line , second and third lines YES
- IP, HIPEC, PIPAC YES
- Clinical trials YES
- Targeted therapy in the era of precision medicine YES
- Still we have relapse YES

IS it tumor biology?

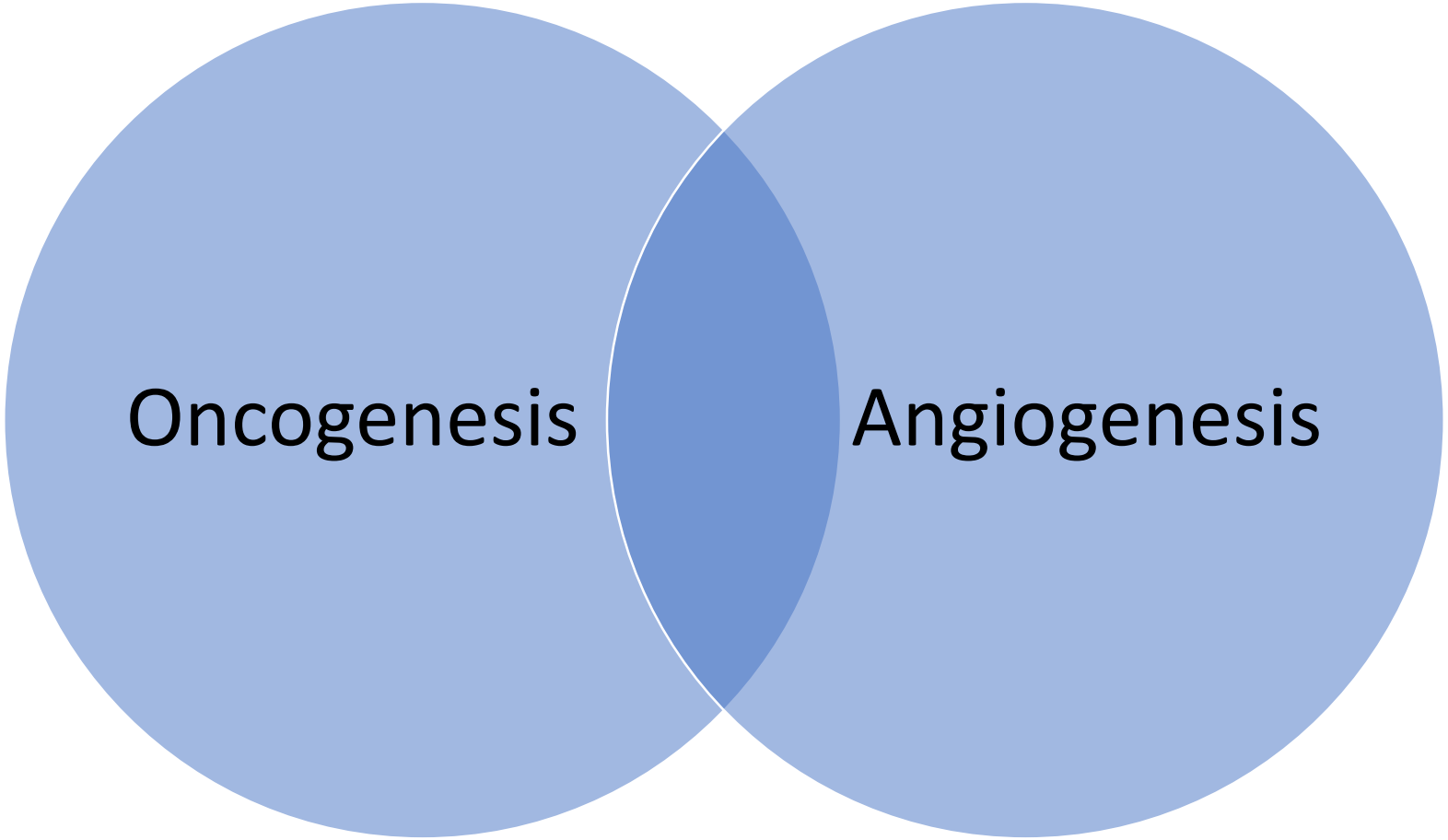
Cancer cells are genetically unstable, and this leads to an accumulation of numerous secondary molecular alterations that play a role in the evolution of malignant transformation.

Cancer cells are

- **Immortal**
- **Invading**
- **Metastasize**
- **Resistance**

Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011

Is it something unseen?



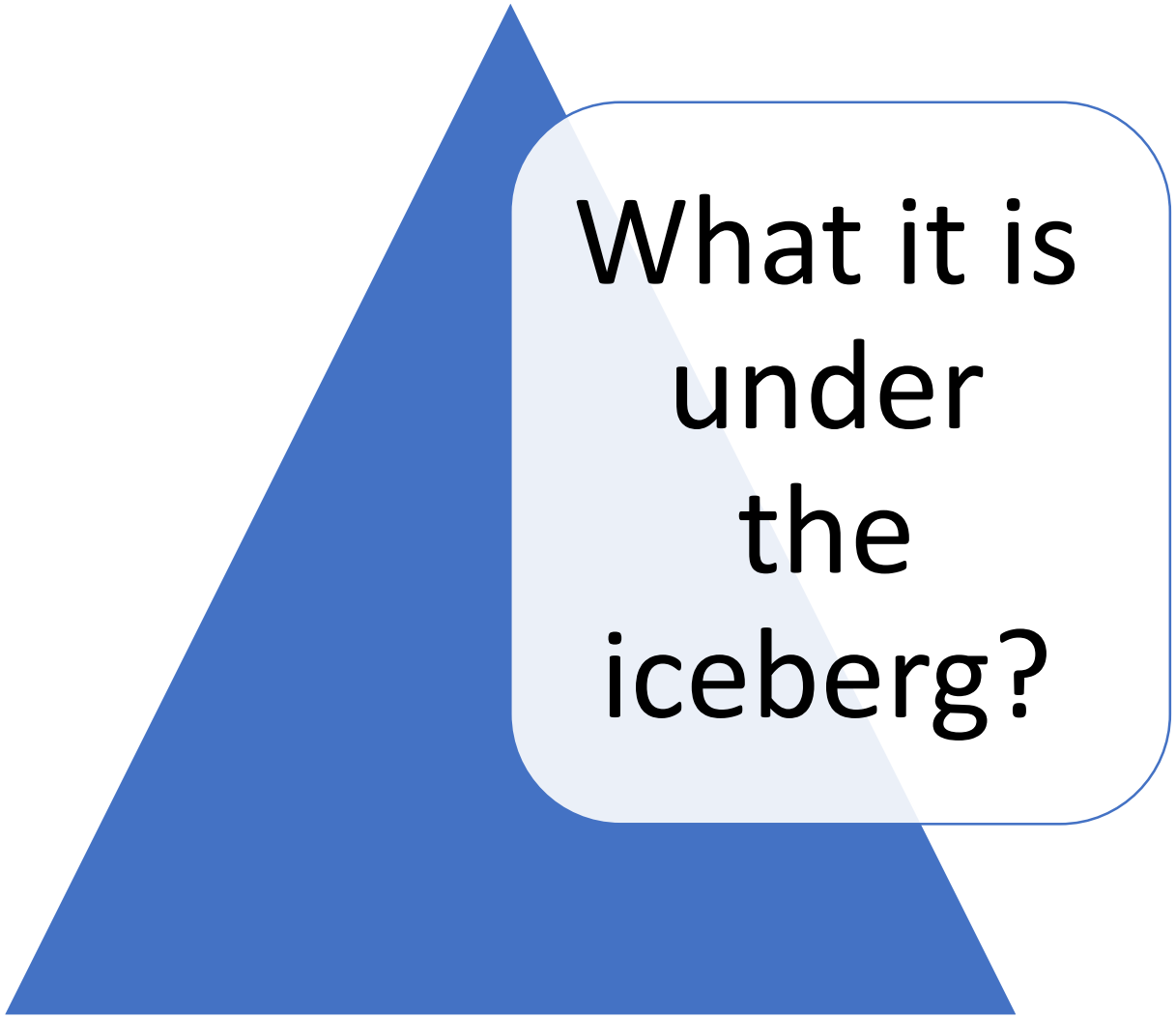
Oncogenesis and angiogenesis.

- Oncogenesis : alterations in genes that stimulate cellular growth (oncogenes) are able to cause the malignant transformation of cells .

- Oncogenes are activated by several mechanisms :
  - First, through amplification which results in overexpression of the corresponding proteins.
  - Second, point mutations may over activate oncogenes.
  - Third, oncogenes may be translocated from one chromosome to another, affecting the promoter regions and resulting in overexpression of the gene.

- Angiogenesis : Various mediators of angiogenesis have been reported, including vascular endothelial growth factor (VEGF), interleukin-8 and matrix metalloproteinases (MMP).

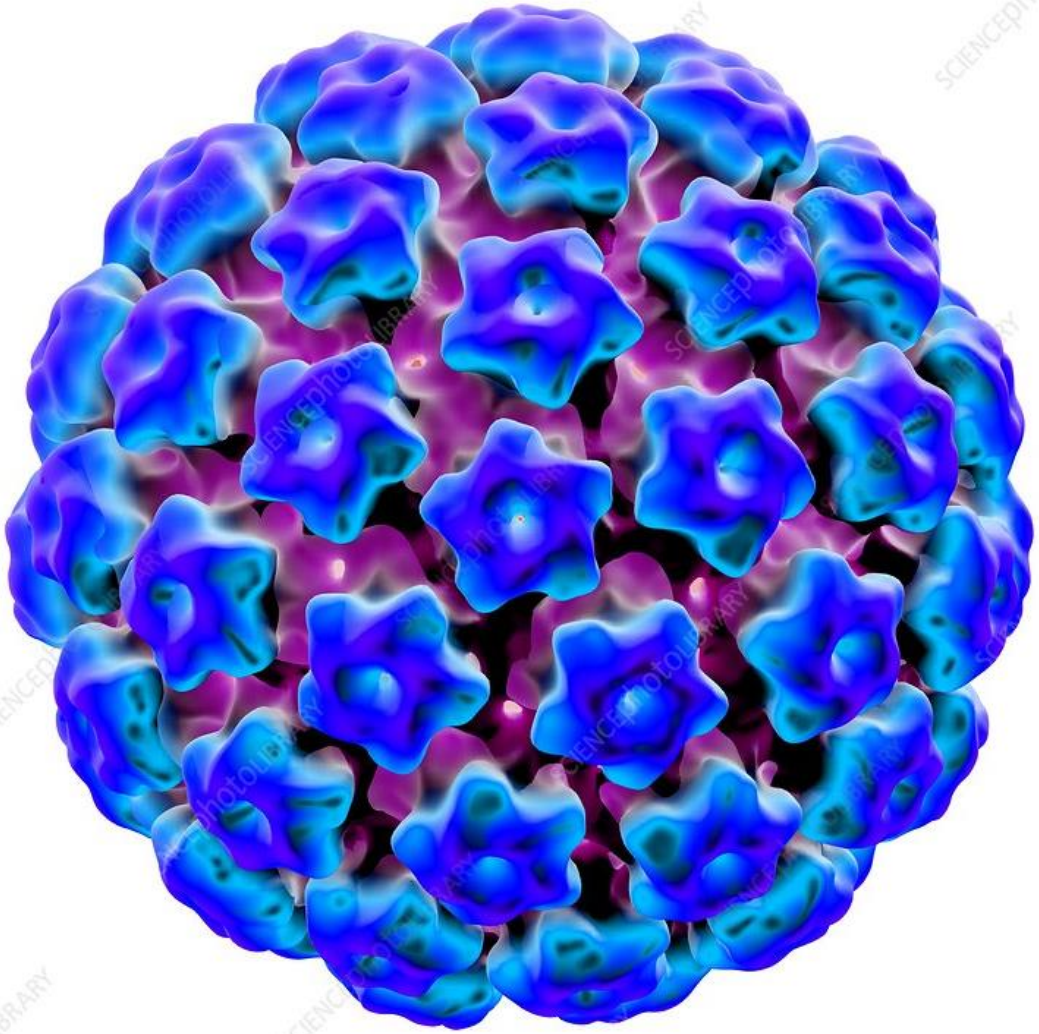
Negrini S, Gorgoulis VG and Halazonetis TD: Genomic instability - an evolving hallmark of cancer. Nat Rev Mol Cell Biol 11: 220-228, 2010

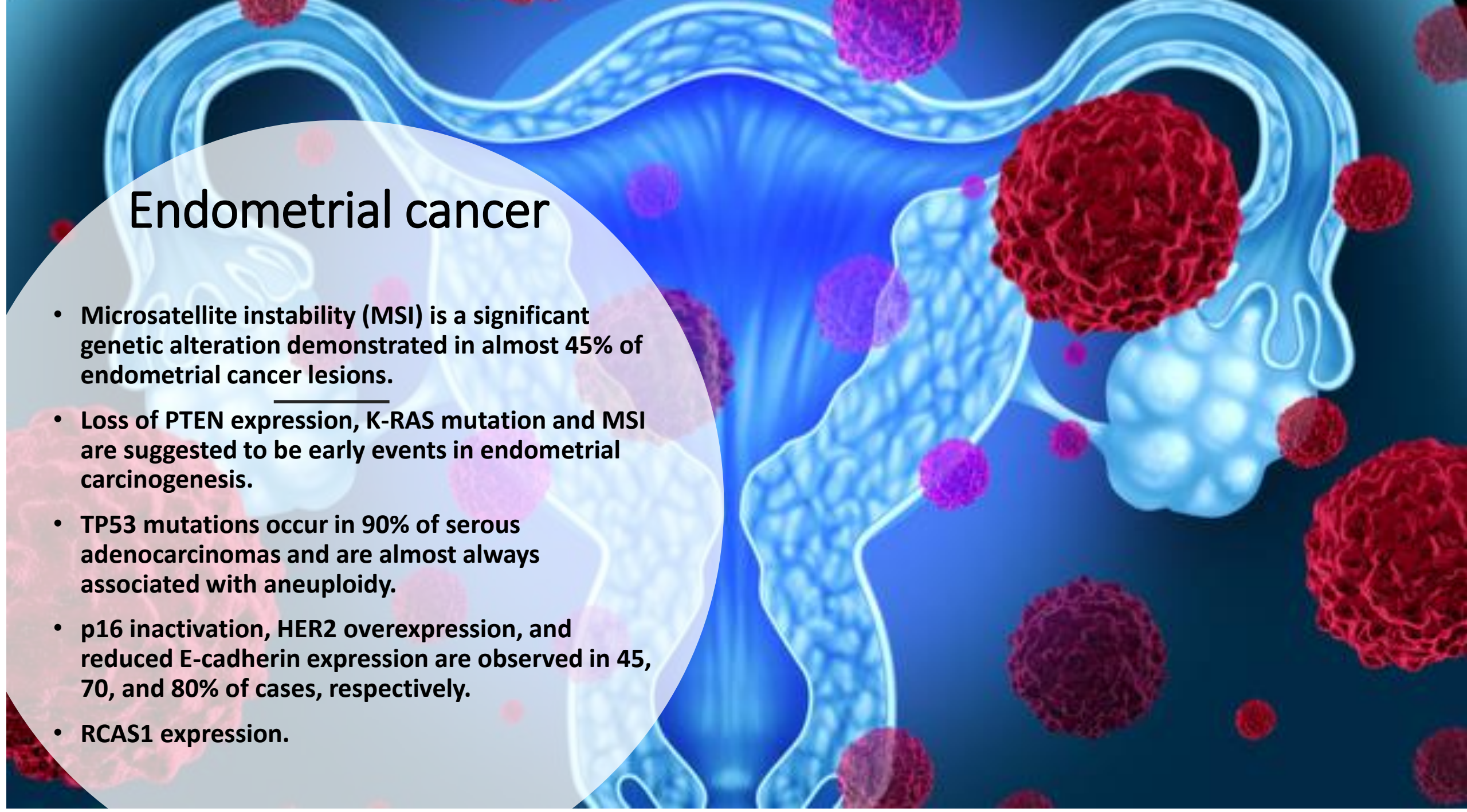

What it is under the iceberg?

Each Gynecological cancer has distinctive biology and molecular signature ……

Cervical cancer.

- HPV
- HPV DNA is composed of 7,800 nucleotides that include early and late open reading frames (ORFs).
- Early ORFs encode 7 proteins, termed E1-7, that are involved in viral replication and host cell transformation. Late ORFs encode structural protein of the virion, such as L1 and 2.
- Cellular transformation may be associated with the integration of HPV DNA into the host genome, for example E6 and 7 bind to and inactivate p53 and Rb respectively, resulting in transformation.
- Additive molecular alterations to HPV infections are considered to be required for the progression to cervical cancer, but these changes are not yet fully understood.



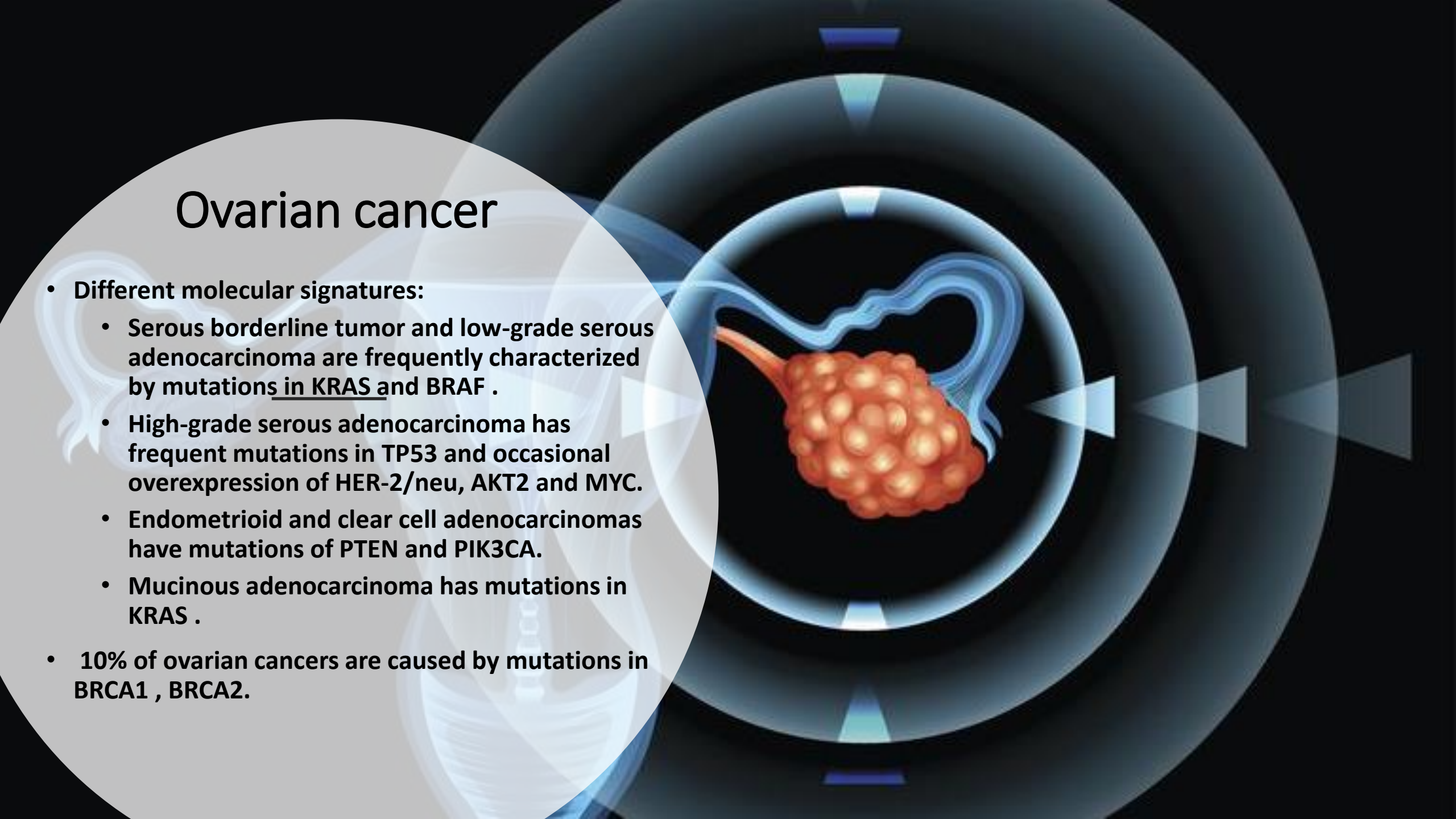


Endometrial cancer

- **Microsatellite instability (MSI) is a significant genetic alteration demonstrated in almost 45% of endometrial cancer lesions.**
- **Loss of PTEN expression, K-RAS mutation and MSI are suggested to be early events in endometrial carcinogenesis.**
- **TP53 mutations occur in 90% of serous adenocarcinomas and are almost always associated with aneuploidy.**
- **p16 inactivation, HER2 overexpression, and reduced E-cadherin expression are observed in 45, 70, and 80% of cases, respectively.**
- **RCAS1 expression.**

Ovarian cancer

- **Different molecular signatures:**
  - **Serous borderline tumor and low-grade serous adenocarcinoma are frequently characterized by mutations in KRAS and BRAF .**
  - **High-grade serous adenocarcinoma has frequent mutations in TP53 and occasional overexpression of HER-2/neu, AKT2 and MYC.**
  - **Endometrioid and clear cell adenocarcinomas have mutations of PTEN and PIK3CA.**
  - **Mucinous adenocarcinoma has mutations in KRAS .**
- **10% of ovarian cancers are caused by mutations in BRCA1 , BRCA2.**



Novel molecular signature of ovarian cancer.

- Lysophosphatidic acid, heparin-binding EGF (HB-EGF) and amphiregulin, have been reported to play pivotal roles in proliferation and dissemination of ovarian cancer(1,2) .

- Yagi et al reported that inhibitory agents against HB-EGF, including CRM197, were possible chemotherapeutic and chemo sensitizing agents for ovarian cancer (3).

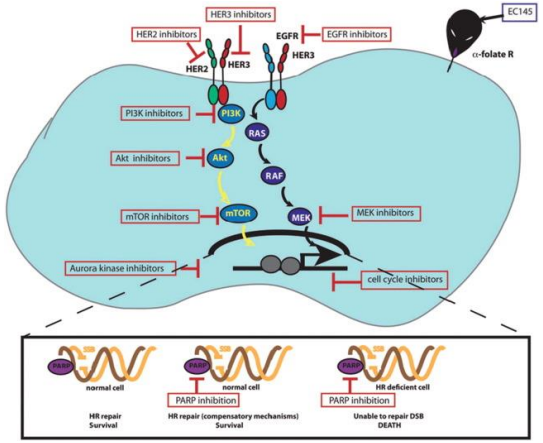
- The clinical application of novel treatments which target these molecules is expected in the future.

1.Fujita T, Miyamoto S, Onoyama I, et al: Expression of lysophosphatidic acid receptors and vascular endothelial growth factor mediating lysophosphatidic acid in the development of human ovarian cancer. Cancer Lett 192: 161-169, 2003. 2.Yotsumoto F, Yagi H, Suzuki SO, et al: Validation of HB-EGF and amphiregulin as targets for human cancer therapy. Biochem Biophys Res Commun 365: 555-561, 2008. 3.Yagi H, Yotsumoto F, Sonoda K, et al: Synergistic anti-tumor effect of paclitaxel with CRM197, an inhibitor of HB-EGF, in ovarian cancer. Int J Cancer 124: 1429-1439, 2009

What it is molecular targeted therapy?

Targeted therapy utilizes the molecular profile of a patient's cancer to design a more efficacious plan for treating the disease.

Defined biomarkers can be targeted to create an antitumor response or as a mechanism for tumor-specific delivery of certain traditional chemotherapeutic drugs.



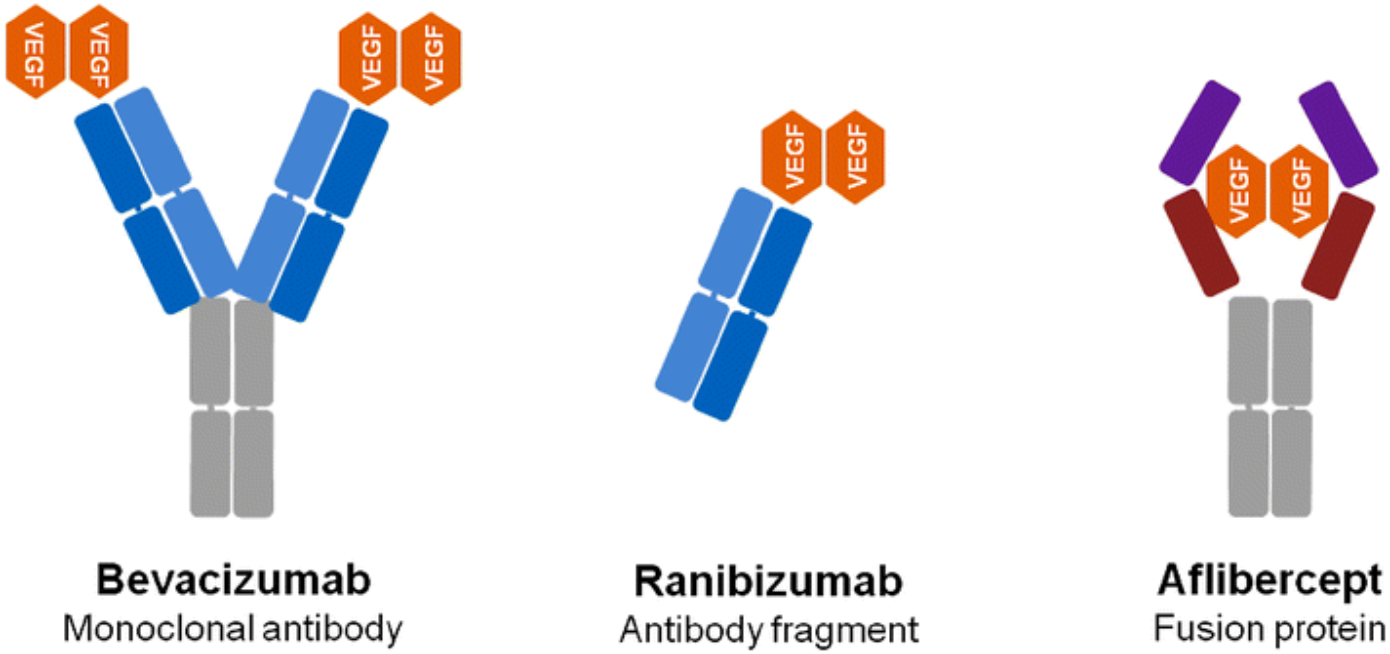
Targeted therapy in Gynecological cancer.

Drugs for targeted therapy are currently divided into two categories:

- Monoclonal antibodies, which do not penetrate cell membranes but bind with ligands and receptors of the specific growth factors to induce the killing of tumors by stimulating monocytes, macrophages, natural killer (NK) cells, killer T cells, and granulocytes

- Low molecular organic compounds, which can enter the cytoplasm and act on targets such as tyrosine kinases, PI3K/AKT/mTOR pathways, and DNA repair mechanisms.

Anti-VEGF antibodies



The anti-VEGF antibody, bevacizumab, is a recombinant humanized monoclonal immunoglobulin G antibody that binds to circulating VEGF and prevents it from binding to its receptors.

This drug also normalizes tumor vessels that are structurally and functionally abnormal, leading to their reversal that may enhance the effects of chemotherapy.

Anti-VEGF antibodies in ovarian cancer

- Common pathway of tumor progression in ovarian carcinomas is peritoneal dissemination, and the progressive accumulation of ascites.

- It has been reported that ovarian carcinomas express VEGF mRNA and VEGF protein (Olson et al, 1994; Boocock et al, 1995; Abu-Jawdeh et al, 1996).

- Examined the expression of VEGF in various types of epithelial ovarian neoplasm by immunohistochemistry and analyzed the correlation with various clinicopathological factors and patient survival. In the 70 patients with ovarian carcinoma, the prognostic significance of VEGF immunostaining was analyzed using the Kaplan-Meier method. Patients with strong VEGF immunostaining showed poorer survival that those with weak or no immunoreactivity for VEGF ($P < 0.01$).

Yamamoto S, Konishi I, Mandai M, et al. Expression of vascular endothelial growth factor (VEGF) in epithelial ovarian neoplaspms: Correlation with clinicopathology and patient survival, and analysis of serum VEGF levels. Br J Cancer. 1997;76:1221–1227

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Strong level of evidence of the survival benefits of Anti VEGF in primary and recurrent settings…….

Positive P3 RCT

1. Burger RA, et al. N Engl J Med. 2011;365(26):2473-2483. 2. Perren TJ, et al. N Engl J Med. 2011;365(26):2484-2496. 3. Aghajanian C, et al. J Clin Oncol. 2012;30(17):2039-2045. 4. Pujade-Lauraine E, et al. J Clin Oncol. 2012;30(15S): Abstract LBA5002.

Primary settings

Two phase II trials evaluated bevacizumab as monotherapy for ovarian cancer and yielded favorable results with response rates of 16%–21%. Gastrointestinal perforation was observed in 11% of patients.

Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A Gynecologic Oncology Group Study. J Clin Oncol. 2007;25:5165–5171. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of beva-cizumab in patients with platinum- resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol. 2007;25:5180–5186.

Primary settings

- Two phase III trials with bevacizumab for ovarian cancer were conducted (GOG218, ICON7), and in both trials, paclitaxel and carboplatin chemotherapy plus bevacizumab and maintenance with bevacizumab showed a significantly longer progression- free survival than chemotherapy alone (GOG218: 14.1 vs 10.3 months,P<0.001; ICON7: 19.8 vs 17.4 months, P<0.001).

- Although statistically significant improvement was not demonstrated in overall survival, the benefit in overall survival was obtained in higher- risk women with incomplete surgery or Stage IV disease (ICON7: 39.7 vs 30.2 months, P=0.03).

Burger RA, Brady MF, Bookman MA, et al. Incorporation of bev-acizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365:2473–2483. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Me2011;365:24842496.

Recurrent settings.

AURELIA	OCEANS
Adding bevacizumab to chemotherapy statistically significantly improved PFS and ORR; the OS trend was not significant. No new safety signals were observed.	GC plus BV followed by BV until progression resulted in a statistically significant improvement in PFS compared with GC plus PL in platinum-sensitive ROC.

Cervical cancer and anti VEGF.

For cervical cancer, a phase III clinical trial was conducted in patients with metastatic, persistent, or recurrent disease, and showed overall survival improvement by addition of bevacizumab to chemotherapy. Fistula occurred in 15% of patients in the bevacizumab group.

Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: Final overall survival and adverse event analysis of a randomised, controlled, open- label, phase 3 trial (Gynecologic Oncology Group 240). Lancet. 2017;390:1654–1663.

Endometrial cancer and anti VEGF.

In a phase 2 trial in patients with persistent or recurrent EC after receiving one to two prior cytotoxic regimens, BEV yielded an OR rate of 13.5%, with 40% of patients attaining a PFS of at least 6 months. The median PFS was 4.2 months, and the OS was 10.5 months.

Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol 2011;29:2259–65

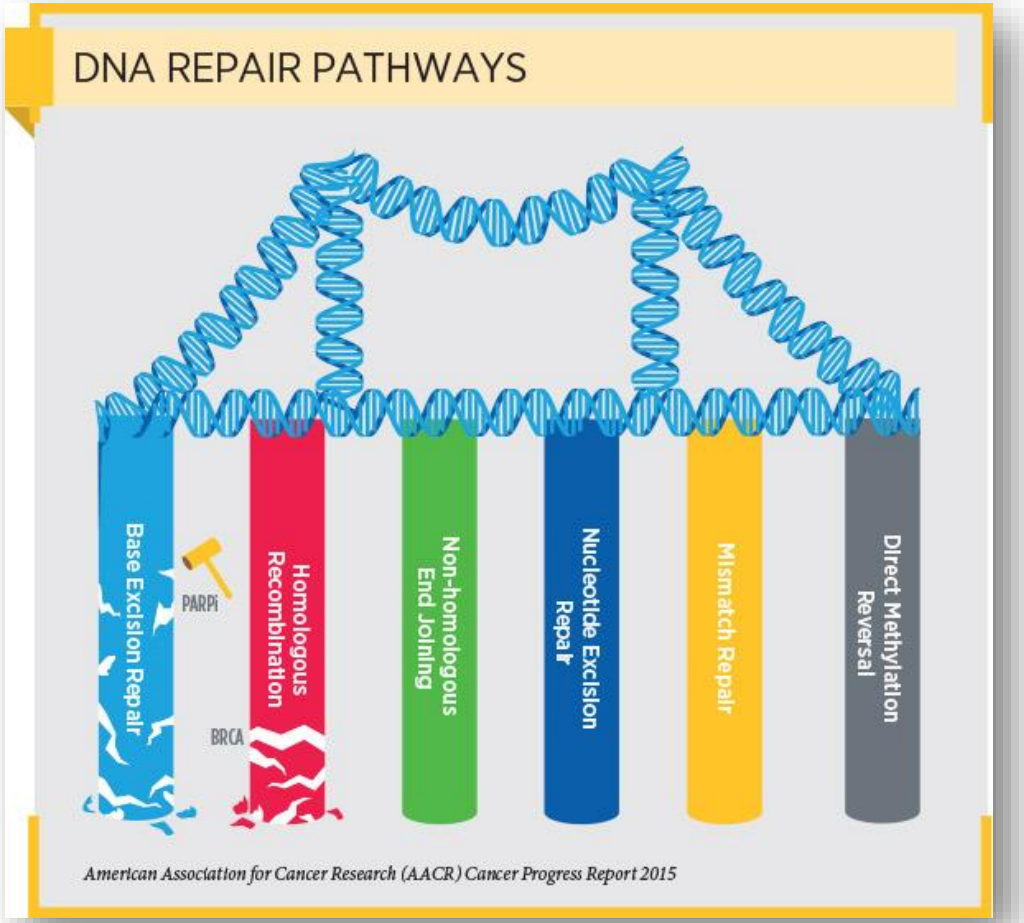
The phase 2 GOG86P trial compared the combination of paclitaxel/carboplatin (TC)/BEV, TC/temsirolimus and ixabepilone/carboplatin/BEV as initial therapy for measurable stage III or IVA, stage IVB or recurrent EC (NCT00977574). a significant improvement in the OS in comparison to historical controls.

Aghajanian C, Filiaci VL, Dizon DS, et al. A randomized phase II study of paclitaxel/carboplatin/bevacizumab,

A phase 2 trial in patients with advanced or recurrent stage III–IV disease (progression >6 months after the completion of previous platinum chemotherapy), and no more than 1 prior chemotherapy lines EC demonstrated that the addition of BEV to TC significantly prolonged the PFS from 8.7 to 13 months. Grade 3 cardiac toxicities were documented in four cases in the TC/ BEV arm (vs no cases in TC arm) .

Lorusso D, Ferrandina G, Colombo N, et al. Randomized phase II trial of carboplatin-paclitaxel (CP) compared to carboplatin-paclitaxelbevacizumab (CP-B) in advanced (stage III-IV) or recurrent endometrial cancer: The MITO END-2 trial. J Clin Oncol 2015;33:5502.

PARPi


DNA REPAIR PATHWAYS
Base Excision Repair
PARPi
Homologous Recombination
BRCA
Non-homologous End Joining
Nucleotide Excision Repair
Mismatch Repair
Direct Methylation Reversal
American Association for Cancer Research (AACR) Cancer Progress Report 2015

Homologous recombination repair defects: Role of BRCA genes and PARPs

- DNA is continuously subjected to injuries by environmental and endogenous exposures that cause a variety of DNA lesions, including double-strand breaks (DSBs) and single-strand breaks (SSBs).
- DNA repair systems are critical to maintain genomic integrity by allowing cells to replicate and survive.
- Homologous recombination repair (HRR) is the most important instrument of reparation of DSBs.
- The BRCA1/2 genes, together with several other genes, code proteins that are necessary for this process.
- When either BRCA1 or BRCA2 is defective, homologous recombination is dysfunctional and the reparation of DSBs is performed through alternative repair mechanisms such as nonhomologous end-joining (NHEJ) and single-strand repair.
- SSBs repair involves a variety of mechanisms such as base excision repair (BER) and nucleotide excision repair, all of which are supported by poly(ADP-ribose) polymerases (PARPs).

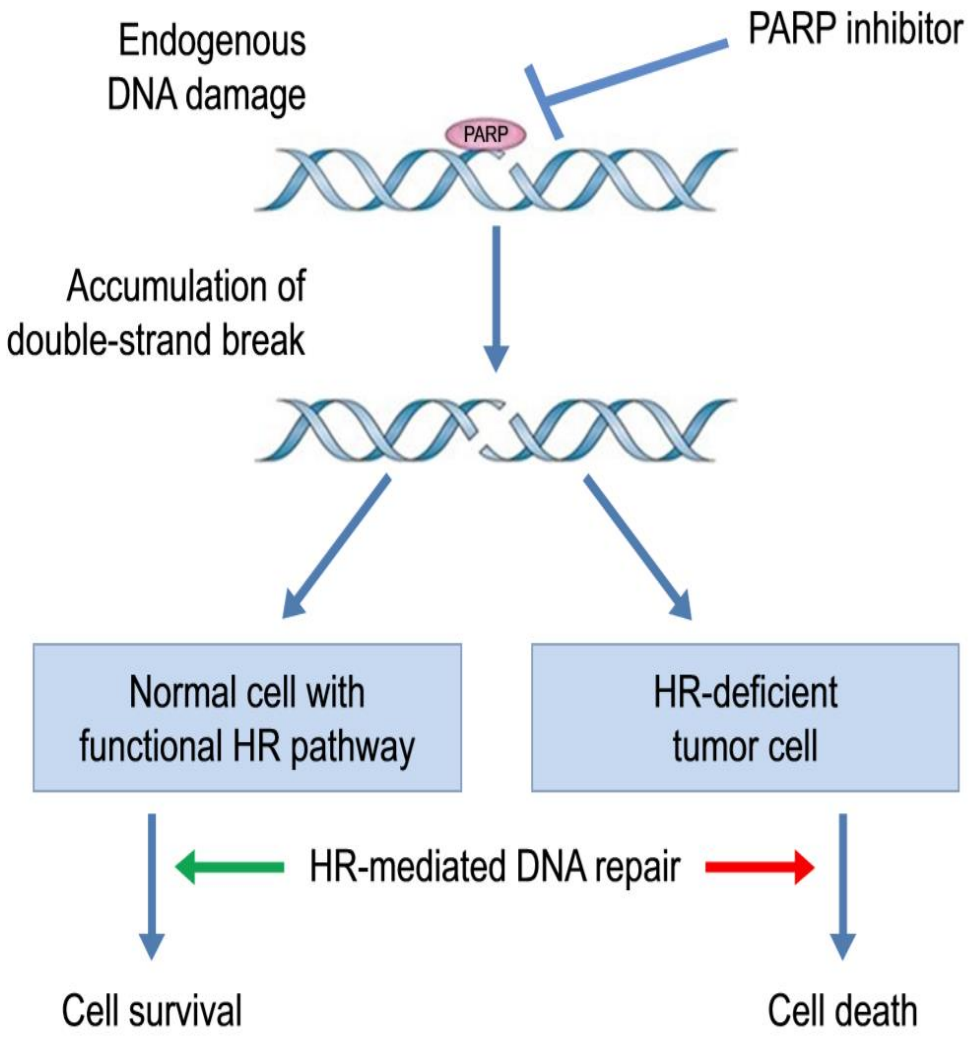
PARPs in depth.

PARPs constitute a family of 18 proteins.PARP1 and PARP2 are enzymes involved in SSBs and BER, which are activated by DNA damage and facilitate DNA repair. PARP1 becomes activated when an SSB occurs and, after binding to the damaged area, increases its catalytic activity and recruits various other proteins to the site of the DNA damage, initiating a repair complex.

If a cell is not able to repair SSB before initiating replication, a single break is transformed into a double strand during replication process.

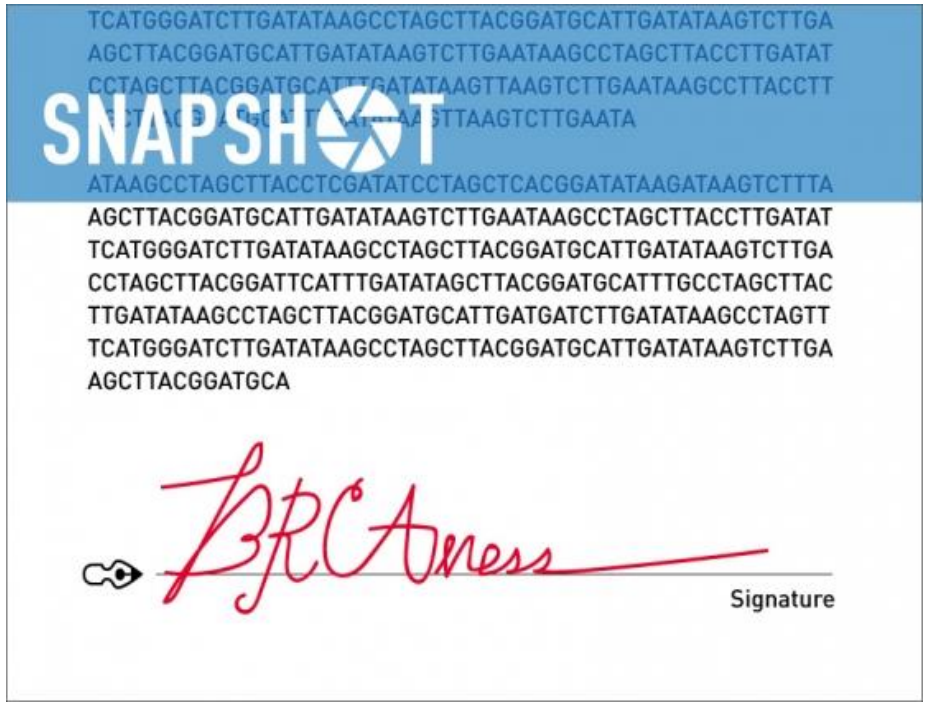
Several studies proposed the model of synthetic lethality, a process by which cancer cells are contemporarily targeted by the inactivation of two genes when the deficiency of either gene alone is nonlethal. This model can be applied to homologous recombination deficient (HRD) cells; in this case, in fact, PARP inhibitors inhibit the repair of DNA SSBs, thus transforming them into DNA DSBs.

When homologous recombination is not functional (HRD), as it is in patients with BRCA mutations, the DNA DSBs cannot be repaired and the PARP inhibition ultimately results in cell death.



BRCAness

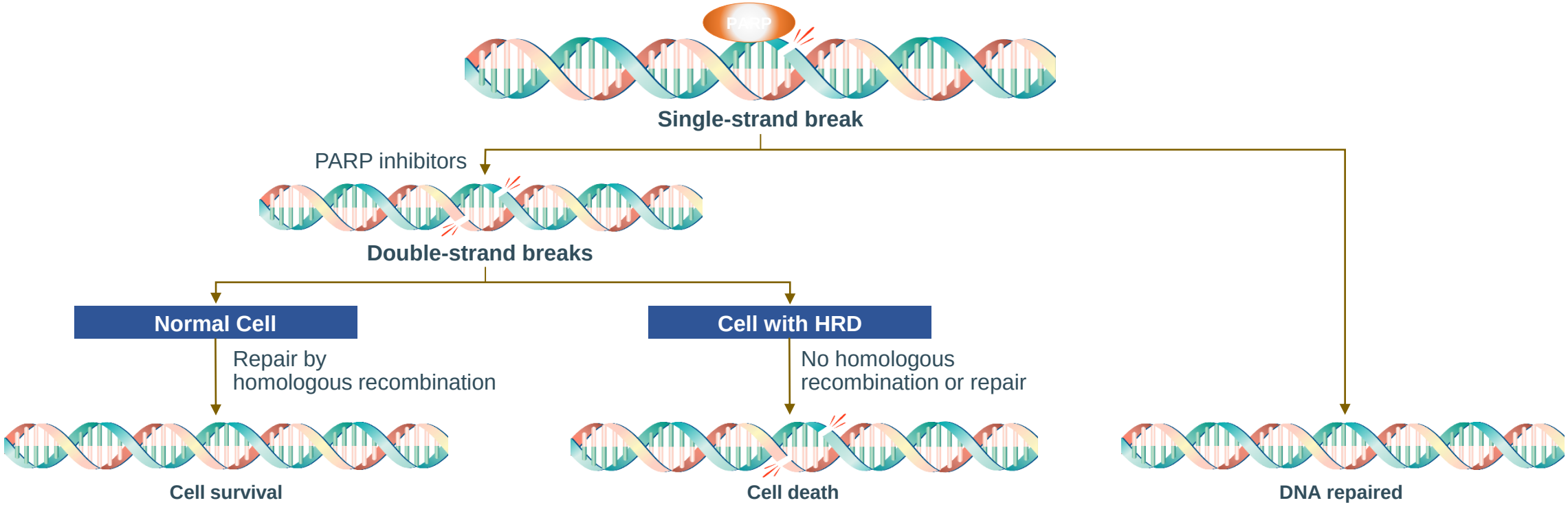
BRCA deficiency and the extended spectrum of HRD phenotype, known as “BRCAness”, associated with improved platinum sensitivity and survival.



Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer. 2016;16: 110–120

PARPi MOA

PARP inhibitors block the other major complementary and back- up DNA repair pathways, thereby leading to cell death referred to as "**synthetic lethality**"



Sonnenblick A, et al. *Nat Rev Clin Oncol.* 2015;12(1):27-41

PARPi Efficacy.

Several landmark phase II/III clinical trials, including the NOVA, SOLO, and ARIEL series that showed significant improvement in the progression- free survival of patients after recurrence.

Three PARP inhibitors (olaparib, rucaparib,and niraparib) were approved for use in ovarian cancer between2014 and 2016.

Summary of FDA-Approved PARP Inhibitors for Use in Ovarian Cancer.

Drug	Registrational Clinical Trial(s)	Indication
Olaparib[1,2]	SOLO-1	Maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*^{mut} or s*BRCA*^{mut} advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to 1L platinum-based chemotherapy. Select patients with g*BRCA*^{mut} for therapy based on an FDA-approved companion diagnostic for olaparib
	SOLO-2 Study 19	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy
	Study 42	Treatment of adult patients with deleterious or suspected deleterious g*BRCA*^{mut} advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for olaparib
Rucaparib[3]	ARIEL3	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy
	ARIEL2 Study 10	Treatment of adult patients with deleterious *BRCA* mutation (germline and/or somatic)–associated epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer who have been treated with ≥2 chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for rucaparib
Niraparib[4]	NOVA	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; December 2018. **2.** FDA. Summary Review for Regulatory Action: Olaparib.https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000SumR.pdf. Published December 16, 2014. Accessed January 14, 2019. **3**. Rucaparib package insert. Clovis Oncology, Inc; April 2018. **4.** Niraparib package insert. TESARO, Inc; February 2019.

SOLO-1 reported a 70% lower risk of disease progression or death with olaparib maintenance therapy than with placebo among women with newly diagnosed advanced ovarian cancer and a *BRCA* mutation

		SOLO-1 (NCT01844986)	
		Olaparib	**Placebo**
N		260	131
Design		Phase 3	
Patients		Newly diagnosed advanced (stage III or IV) high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer with a *BRCA* mutation, in CR or PR after platinum-based chemotherapy	
Treatment		300 mg (two 150-mg tablets) bid	Placebo
Results	mPFS	NR	13.8 mo
	PFS at 36 mo and HR (95% CI)	60%	27%
		0.30 (0.23–0.41); *P*<0.001	
Safety: Most common grade 3 or 4 AEs in active treatment group		Anemia (22%) Neutropenia (9%) Fatigue/asthenia (4%)	Anemia (2%) Neutropenia (5%) Fatigue/asthenia (2%)

Moore K, et al. *N Engl J Med*. 2018;379(26):2495-505

SOLO-2, a double-blind phase 3 clinical trial, reported improved PFS in response to olaparib compared with placebo in patients who had platinum-sensitive, relapsed ovarian cancer and a germline *BRCA* mutation

	SOLO-2 (NCT01874353)	
	Olaparib	**Placebo**
N	195	99
Design	Phase 3	
Patients	Platinum-sensitive, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer including primary peritoneal or fallopian tube cancer, g*BRCA1/2* mutation, ≥2 prior lines of platinum-based chemotherapy, in response to last chemotherapy	
Treatment	300 mg (two 150-mg tablets) bid	Placebo
Results: mPFS and HR (95% CI)	19.1 mo	5.5 mo
	0.30 (0.22–0.41); *P*<0.0001	
Safety: Most common grade 3 or 4 AEs in active treatment group	Anemia (19%) Neutropenia (5%) Fatigue/asthenia (4%)	Anemia (2%) Neutropenia (4%) Fatigue/asthenia (2%)

Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18(9):1274-84

Study 19 reported improved PFS in response to olaparib compared with placebo in patients with platinum-sensitive, relapsed, HGSOC with or without g*BRCA*^{mut}

	Study 19 (NCT00753545)[1,2]	
	Olaparib	**Placebo**
N	136	129
Design	Phase 2	
Patients	Platinum-sensitive, recurrent ovarian or fallopian tube or primary peritoneal cancer with high-grade serous features or a serous component, with or without g*BRCA1/2* mutation, ≥2 prior lines of platinum-based chemotherapy, CR or PR in response to last chemotherapy	
Treatment	400 mg (eight 50-mg capsules) bid	Placebo
Results: mPFS and HR (95% CI)	8.4 mo	4.8 mo
	0.35 (0.25–0.49); *P*<0.001	
Safety: Most common grade 3 or 4 AEs in active treatment group	Fatigue (6.6%) Anemia (5.1%) Nausea (2.2%) Vomiting (2.2%) Diarrhea (2.2%) Back pain (2.2%)	Fatigue (3.1%) Anemia (0.8%) Nausea (0) Vomiting (0.8%) Diarrhea (2.3%) Back pain (0)

Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-92**.** Ledermann JA, et al. *Lancet Oncol.* 2016;17(11):1579-89.

Study 42 reported promising responses to olaparib in patients who had recurrent cancer, g*BRCA* mutation, and progressed after ≥3 prior lines of chemotherapy

	Study 42 (NCT01078662)[1,2]
N	137[a]
Design	Phase 2
Patients	Advanced solid tumors with g*BRCA1/2* mutation (N=298)
	Recurrent ovarian cancer cohort (n=193): Platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer
Treatment	Olaparib 400 mg (eight 50-mg capsules) bid
Results	ORR: 34% mPFS: 6.7 mo
Safety: Most common grade ≥3 AEs in ovarian cancer cohort	Anemia (20%) Abdominal pain (8%) Fatigue (7%)

Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-50. **2.** Domchek SM, et al. *Gynecol Oncol*. 2016;140(2):199-203

Olaparib Currently Has 3 FDA-Approved Ovarian Cancer Indications

Registrational Clinical Trial(s)	Indication	Biomarker Testing Required?	Recommended Dosing
SOLO-1	Maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*^{mut} or s*BRCA*^{mut} advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to 1L platinum-based chemotherapy	Yes, FDA-approved companion diagnostic to select patients with g*BRCA*^{mut} disease[a]	300 mg (two 150-mg tablets) bid
SOLO-2 / Study 19	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy	No	300 mg (two 150-mg tablets) bid
Study 42	Treatment of adult patients with deleterious or suspected deleterious g*BRCA*^{mut} advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy	Yes, FDA-approved companion diagnostic to select patients with g*BRCA*^{mut} disease	300 mg (two 150-mg tablets) bid

Study 10 reported promising responses to rucaparib in patients with platinum-sensitive ovarian cancer and a g*BRCA* mutation, who had received 2–4 prior lines of therapy

	Study 10 (NCT01482715)[1]	
	Part 1	**Part 2**
N	56	42
Design	Phase 1 dose escalation	Phase 2 expansion
Patients	Advanced solid tumor, progressed on treatment	Platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer, with g*BRCA1/2* mutation, 2–4 prior regimens
Treatment	Rucaparib 40–840 mg daily or bid (3+3)	Rucaparib 600 mg bid
Results	**RP2D:** 600 mg bid	**ORR:** 59.5%
Safety: Most common grade 3 or 4 AEs	NR	Anemia (38.1%) Fatigue/asthenia (26.2%) Neutropenia (16.6%)

Kristeleit R, et al. *Clin Cancer Res*. 2017;23(15):4095-106.

ARIEL2 measured PFS in response to rucaparib in patients with platinum-sensitive ovarian cancer, stratified by *BRCA*^{mut} status and extent of HRD (as assessed by LOH[a]), who had received 1–4 prior lines of therapy

	ARIEL2 (NCT01891344)			
	***BRCA*^{mut} (all)**	**s*BRCA*^{mut*}**	***BRCA*^{wt}, LOH high**	***BRCA*^{wt}, LOH low**
N	40	19	82	70
Design	Phase 2			
Patients	**Part 1:** Platinum-sensitive, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer with ≥1 prior line of platinum therapy **Part 2 (ongoing):** Platinum-sensitive, -resistant, or -refractory; 3–4 prior lines of chemotherapy			
Treatment	Rucaparib 600 mg bid			
Results (Part 1)	**mPFS:** 12.8 mo	**Confirmed ORR:** 74%	**mPFS:** 5.7 mo	**mPFS:** 5.2 mo
	HR 0.27, *P*<0.0001 vs LOH low		HR 0.62, *P*=0.011 vs LOH low	
Safety (Part 1): Most common grade ≥3 AEs	Anemia (22%) Elevated ALT/AST (12%) Fatigue/asthenia (9%)			

Swisher EM, et al. *Lancet Oncol.* 2017;18(1):75-87.

ARIEL3 Supported Subsequent FDA Approval for Rucaparib as 2L+ Maintenance Therapy in Patients With Recurrent Ovarian Cancer, With or Without a *BRCA* Mutation

	ARIEL3 (NCT01968213)							
	Rucaparib				Placebo			
N	375[a]				189			
Design	Phase 3							
Patients	Platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer, ≥2 prior lines of platinum chemotherapy							
Treatment	Rucaparib 600 mg bid				Placebo			
Results: mPFS HR (95% CI) [*P* value]	***BRCA*^{mut}**	**HRD**	***BRCA*^{wt} LOH$_{low}$**	**ITT (all pts)**	***BRCA*^{mut}**	**HRD**	***BRCA*^{wt} LOH$_{low}$**	**ITT (all pts)**
	16.6 mo	13.6 mo	6.7 mo	10.8 mo	5.4 mo	5.4 mo	5.4 mo	5.4 mo
	0.23 (0.16–0.34) [<0.0001]	0.32 (0.24–0.42) [<0.0001]	0.58 (0.40–0.85) [0.0049]	0.36 (0.30–0.45) [<0.0001]				
Safety: Most common grade ≥3 AEs in active treatment group	Anemia (19%) Elevated ALT/AST (10%) Fatigue/asthenia (7%)				Anemia (1%) Elevated ALT/AST (0) Fatigue/asthenia (3%)			

Coleman RL, et al. *Lancet.* 2017;390(10106):1949-61.

Rucaparib Currently Has 2 FDA-Approved Ovarian Cancer Indications[1]

Registrational Clinical Trial(s)	Indication	Biomarker Testing Requirement	Recommended Dosing
ARIEL3	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy	No	600 mg (two 300-mg tablets) bid
ARIEL2 / Study 10	Treatment of adult patients with deleterious *BRCA* mutation (germline and/or somatic)–associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥2 chemotherapies	FDA-approved companion diagnostic to select patients with g*BRCA*^{mut} or s*BRCA*^{mut} disease	600 mg (two 300-mg tablets) bid

NOVA Supported FDA Approval for Niraparib as 2L+ Maintenance Therapy in Patients With Recurrent Platinum-Sensitive Ovarian Cancer

	NOVA (NCT01847274)			
	g*BRCA*^{mut}		Non-g*BRCA*^{mut}	
N	203		350	
Design	Phase 3			
Patients	Platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer with predominantly high-grade serous features, ≥2 prior lines of platinum therapy, in CR or PR to most recent platinum therapy			
Treatment	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo
Results: mPFS and HR (95% CI)	21.0 mo	5.5 mo	9.3 mo	3.9 mo
	0.27 (0.17–0.41); *P*<0.001		0.45 (0.34–0.61); *P*<0.001	
Safety: Most common grade 3 or 4 AEs in patients treated with niraparib	Thrombocytopenia (33.8%) Anemia (25.3%) Neutropenia (19.6%)			

	NOVA (NCT01847274) Non-g*BRCA*^{mut}					
	Non-g*BRCA*^{mut} HRD-positive		*sBRCA*^{mut}		HRD-negative	
N	162		47		134	
Treatment	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo
Results: mPFS and HR (95% CI)	12.9 mo	3.8 mo	20.9 mo	11.0 mo	6.9 mo	3.8 mo
	0.38 (0.24–0.59); *P*<0.001		0.27 (0.08–0.90); *P*=0.02		0.58 (0.36–0.92); *P*=0.02	

Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-64

Efficacy is proven, what about SE?

Adverse Events Associated With Approved PARP Inhibitors in Clinical Trials: Grade 1–4 Occurring in ≥20% of Treated Patients

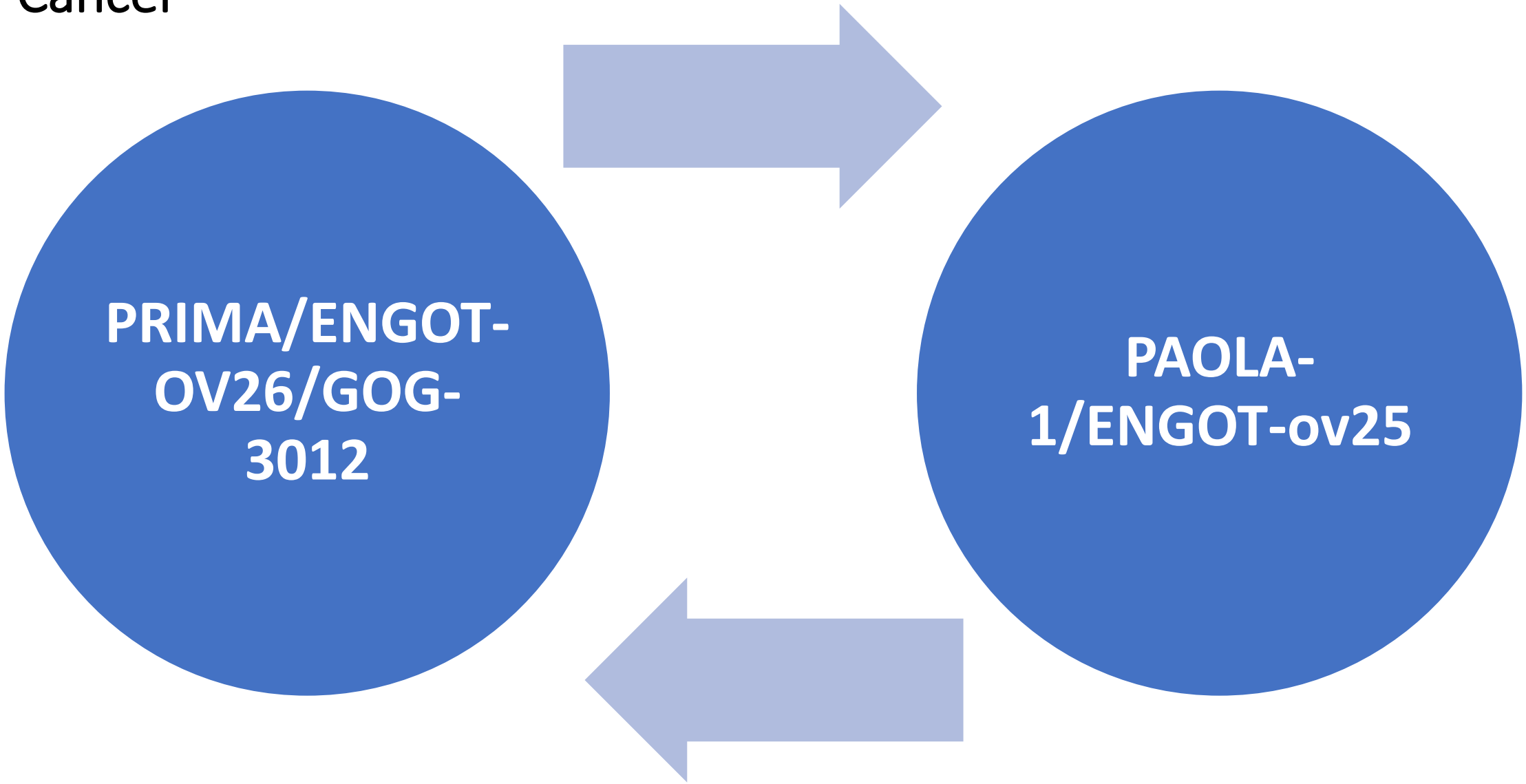
Drug	Olaparib						Rucaparib				Niraparib	
Line of therapy (Study)	1L Maintenance (SOLO-1)		2L+ Maintenance (SOLO-2)		4L+ Treatment (Pooled 6)		2L+ Maintenance (ARIEL3)		3L+ Treatment (Study 10, ARIEL2)		2L+ Maintenance (NOVA)	
N	260		195		223		372		377		367	
Grade	All	3/4	1–4	3/4	1–4	3/4	1–4	3/4	1–4	3/4	1–4	3/4
Blood and lymphatic system disorders, %												
Anemia	**38**	21	**44**	20	**34**	18	**39**	21	**44**	25	**50**	25
Thrombocytopenia	–	–	–	–	–	–	**29**	5	**21**	5	**61**	29
Neutropenia	–	–	–	–	–	–	**20**	8	–	–	**30**	20
Gastrointestinal disorders, %												
Decreased appetite	**20**	0	**22**	0	**22**	1	**23**	1	**39**	3	**25**	0.3
Nausea	**77**	1	**76**	3	**64**	3	**76**	4	**77**	5	**74**	3
Vomiting	**40**	0	**37**	3	**43**	4	**37**	4	**46**	4	**34**	2
Diarrhea	**37**	3	**33**	2	**31**	1	**32**	0.5	**34**	2	**20**	0.3
Dyspepsia	–	–	–	–	**25**	0	–	–	–	–	–	–
Constipation	**28**	0	–	–	–	–	**37**	2	**40**	2	**40**	0.8
Abdominal pain/distension	**45**[c]	2[c]	–	–	–	–	**46**	3	**32**[d]	3[d]	**33**	2
Mucositis/stomatitis	–	–	**20**[e]	1[e]	–	–	**28**[f]	1[f]	–	–	**20**	0.5
Respiratory, thoracic, and mediastinal disorders, %												
Nasopharyngitis/upper respiratory tract infection	**28**[g]	0[g]	**36**[h]	0[h]	**26**	0	**29**	0.3	–	–	**23**[i]	0[i]
Dyspnea	–	–	–	–	–	–	–	–	**21**	0.5	**20**	1
Insomnia	–	–	–	–	–	–	–	–	–	–	**27**	0.3
Rash	–	–	–	–	–	–	**43**	1	–	–	**21**	0.5
Hypertension	–	–	–	–	–	–	–	–	–	–	**20**	9
ALT/AST elevation	–	–	–	–	–	–	**38**	11	–	–	–	–
Nervous system disorders, %												
Dysgeusia	**26**	0	**27**	0	–	–	**40**	0	**39**	0.3	–	–
Dizziness	**20**	0	–	–	–	–	–	–	–	–	–	–
Headache	–	–	**26**	1	–	–	–	–	–	–	**26**	0.3
Musculoskeletal disorders, %												
Arthralgia/musculoskeletal pain	–	–	**30**[c]	0[c]	**21**	0	–	–	–	–	–	–
Myalgia	–	–			**22**	0	–	–	–	–	–	–

MDS and AML Have Been Reported in Patients Treated With PARP Inhibitors

	Olaparib	Rucaparib	Niraparib
Rates of MDS/AML in clinical trials	<1.5%	1.1%	1.4%
MDS/AML incidence in clinical trial(s), n / N	26 / 2258	12 / approx. 1100	5 / 367
Monitoring	Monitor for hematological toxicity at baseline and monthly thereafter	Monitor for hematological toxicity at baseline and monthly thereafter	Monitor for hematological toxicity: test CBC weekly for the first month, then monthly for the next 11 months, and then periodically

Two landscapes trial

Studies Show PARP Inhibitors Improve Survival, Reduce Risk of Disease Recurrence or Death in Newly Diagnosed Ovarian Cancer



PRIMA/ENGOT-OV26/GOG-3012

PRIMA is the first study to show a PARP inhibitor significantly improves PFS, regardless of biomarker status, when given as monotherapy in women with first-line platinum responsive advanced ovarian cancer.

PRIMA AT GLANCE

PRIMA Evaluates Niraparib Maintenance Following First-Line Chemotherapy in Patients With Advanced Ovarian Cancer

- **PRIMA is a global, randomized, multicenter, placebo-controlled phase III study**

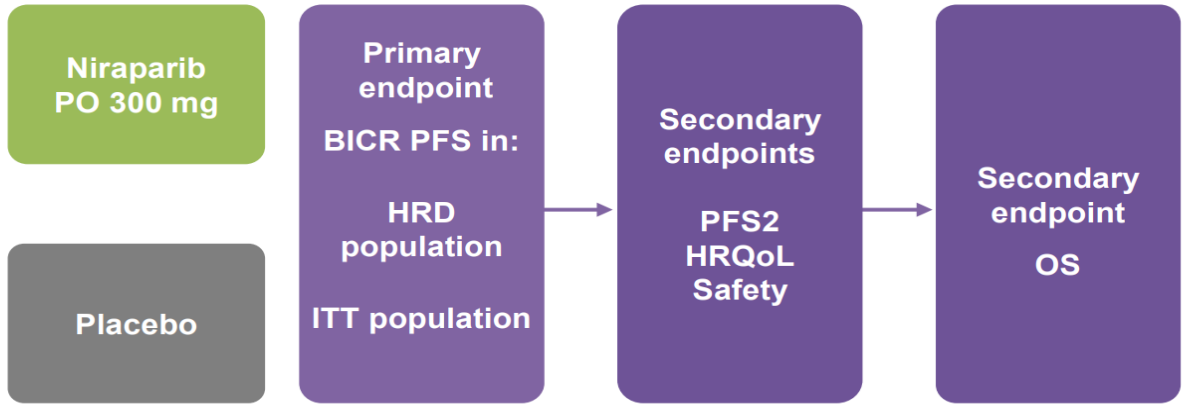
- Newly diagnosed FIGO III-IV HGSOC or high-grade endometrioid ovarian cancer*
- CR or PR following first-line (adjuvant or neoadjuvant) platinum-based CTX
- Patients with stage III disease should have residual disease after primary surgery; all stage IV disease eligible
- Agree to undergo central tumor HRD testing

Randomize within 12 weeks of first day of last chemotherapy cycle

Randomize
2:1
Planned N ≈ 620

Stratification by:
- *Use of NACT*
- *Response (CR/PR) to first-line platinum-based chemotherapy*
- *HRD status*

Global study in 20 countries and 195 trial sites



Clinicaltrials.gov identifier: NCT02655016
Status: Enrollment complete

*Including ovarian, fallopian or primary peritoneal cancer

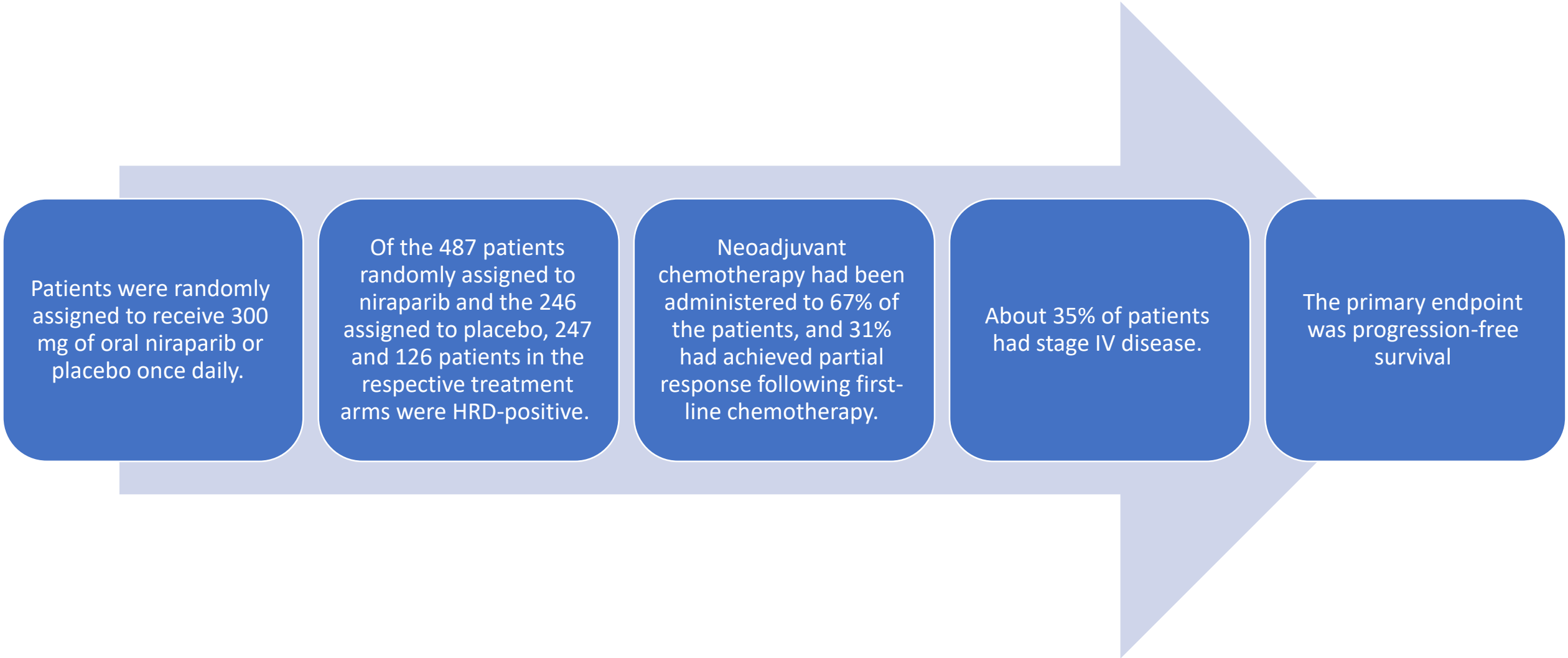
PRIMA/ENGOT-OV26/GOG-3012

Double-blind, placebo-controlled phase III of niraparib in patients who had been newly diagnosed with HGSC.

Eligible patients had achieved a complete or partial response to first-line platinum-based chemotherapy.

Stratification factors included best response to the first-line chemotherapy, receipt of neoadjuvant chemotherapy, and HRD status

PRIMA/ENGOT-OV26/GOG-3012



PRIMA/ENGOT-OV26/GOG-3012

- Patients in the overall population treated with niraparib demonstrated improvement in progression-free survival compared to patients on placebo that was even greater in the HRD-positive subgroup.
- Median progression-free survival in the overall population was 13.8 months (95% confidence interval [CI] = 11.5–14.9) with niraparib compared to 8.2 months (95% CI = 7.3–8.5) with placebo (hazard ratio [HR] = 0.62, 95% CI = 0.5–0.75; *P* < .0001).
- In the HRD-positive subgroup, median progression-free survival was 21.9 months (95% CI = 19.3–not reached) vs 10.4 months (95% CI = 8.1–12.1), with a hazard ratio of 0.43 (95% CI = 0.31–0.59; *P* < .0001).
- The most commonly reported grade ≥ 3 adverse events were anemia in 31% of patients, thrombocytopenia in 29%, and neutropenia in 13% of patients overall.
- No treatment-related deaths occurred.

PAOLA-1

Evaluates Addition of Maintenance Olaparib to Standard of Care in Patients With Newly Diagnosed Advanced Ovarian Cancer.
PAOLA-1 is an ENGOT/GCIG sponsored, randomized, placebo-controlled phase III trial.

PAOLA AT GLANCE

- FIGO stage III–IV high-grade ovarian cancer (serous or endometrioid)* or nonmucinous *BRCA*m
- No evidence of disease or CR or PR following first-line platinum-based chemotherapy plus bevacizumab
- A minimum of 3 cycles of platinum-based chemotherapy plus bevacizumab (2 after interval debulking)
- ECOG PS 0–1

***BRCA* testing prior to randomization**

Randomize 2:1
N = 806

Stratification by tumor BRCA status and first-line outcome

Olaparib
300 mg† PO bid +
Bevacizumab**
15 mg/kg q 3 w
15 months

Placebo
+
Bevacizumab**
15 mg/kg q 3 w
15 months

Primary endpoint
- **PFS1 (RECIST 1.1)**

Secondary endpoints
- **PFS2**
- **TSST**
- **OS**
- **Safety**
- **PRO/HRQoL**

Clinicaltrials.gov identifier: NCT02477644

PAOLA-1/ENGOT-ov25

- Randomized, double-blind, international phase III trial that enrolled patients with newly diagnosed stage III to IV, high-grade serous or endometrioid ovarian cancer.
- Patients in clinical complete or partial response following platinum-based chemotherapy plus bevacizumab were randomly assigned 2:1 to receive oral olaparib at 300 mg twice daily for up to 24 months or placebo plus bevacizumab at 15 mg/kg on day 1 every 3 weeks for 15 months, which included doses received during chemotherapy.
- The patients were stratified by first-line treatment outcome and somatic *BRCA* mutation status.

PAOLA-1/ENGOT-ov25

- The primary endpoint was investigator-assessed progression-free survival.
- The median follow-up was 24.0 months for 537 patients in the olaparib/bevacizumab arm and 22.7 months for 269 patients/bevacizumab in the placebo arm.
- Analysis of the data at 59% maturity demonstrated a median progression-free survival of 22.1 months with olaparib/bevacizumab vs 16.6 months with placebo/bevacizumab (hazard ratio [HR] 0.59, 95% confidence interval [CI] = 0.49–0.72; *P* < .0001).
- Among patients with a *BRCA* mutation, median progression-free survival for patients treated with olaparib/bevacizumab was 37.2 months vs 21.7 months with placebo/bevacizumab (HR = 0.31, 95% CI = 0.20–0.47).
- Patients without a *BRCA* mutation demonstrated a median progression-free survival of 18.9 months with olaparib/bevacizumab vs 16.0 months with placebo/bevacizumab (HR = 0.71, 95% CI = 0.58–0.88).
- In HRD-positive patients, the median progression-free survival with olaparib/bevacizumab was 37.2 months vs 17.7 months with placebo/bevacizumab (HR = 0.33, 95% CI = 0.25–0.45).
- Median progression-free survival in HRD-positive patients without a *BRCA* mutation treated with olaparib/bevacizumab was 28.1 months vs 16.6 months with placebo/bevacizumab (HR = 0.43, 95% CI = 0.28–0.66).
- In patients with negative or unknown HRD status treated with olaparib, median progression-free survival was 16.9 months vs 16.0 months with placebo (HR = 0.92, 95% CI = 0.72–1.17).

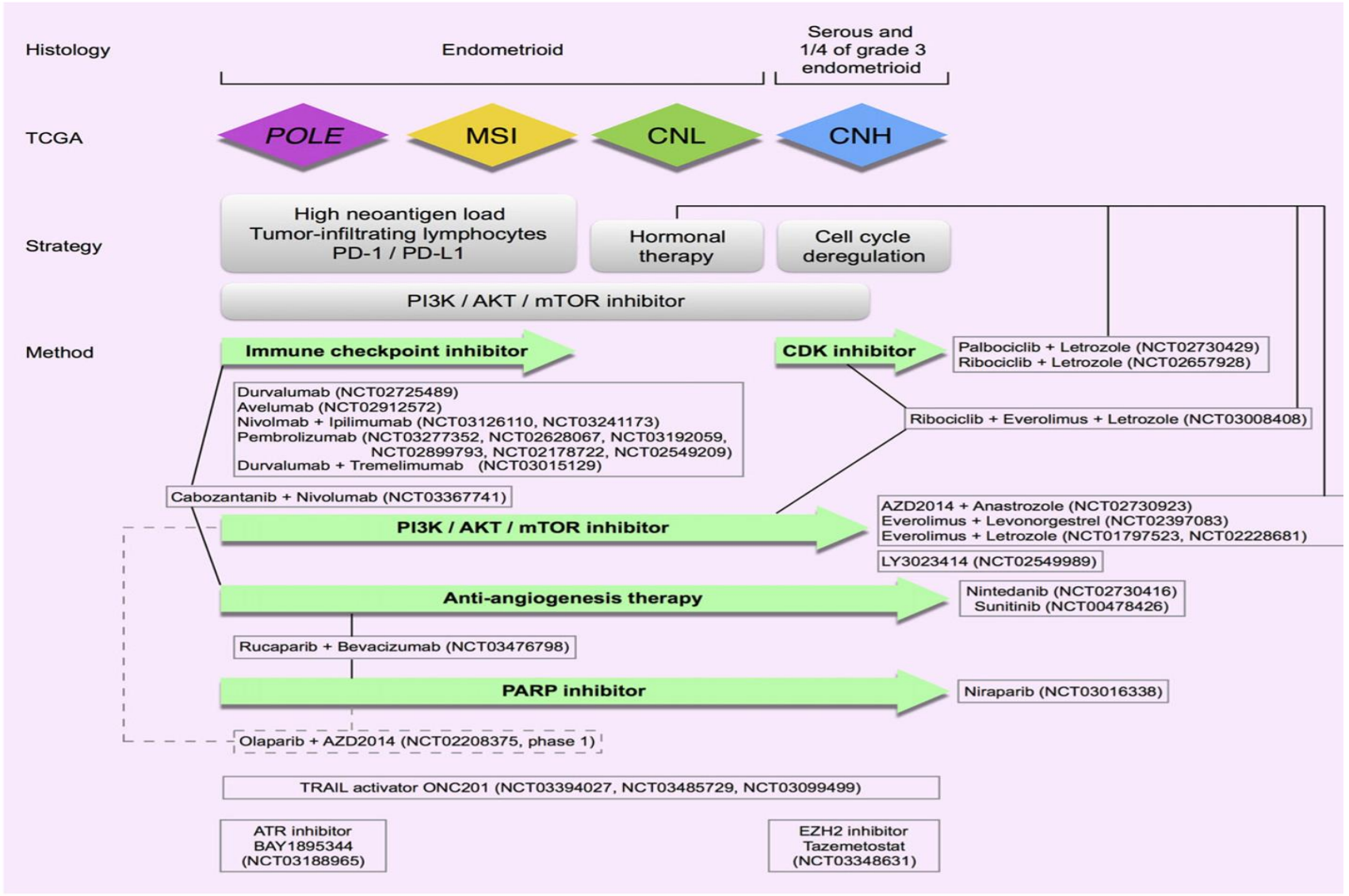
PARPs In Cervical cancer

The PARP inhibitor veliparib was studied in combination with cytotoxic therapy in women with recurrent or persistent cervical cancer after receiving pelvic radiation (with or without cisplatin).

Of the 29 patients with measurable disease, 2 patients (6.9%) had a complete response and 8 patients (27.6%) had a partial response. Additionally, 12 patients (41.4%) had stable disease.

Thaker PH, Brady WE, Lankes HA. Limited access phase I trial of paclitaxel, cisplatin and ABT-888 in the treatment of advanced, persistent, or recurrent carcinoma of the cervix: an NRG/GOG study 2015

PARPs in Endometrial cancer



In short……..

In short, the development of molecularly-targeted drugs for the treatment of cancer is a promising and rapidly-moving field.

Conclusion

Since it is challenging to treat advanced or recurrent cancers using conventional treatments, the development of novel and highly specific targets for therapy is required.

An exponential growth in the collection of genomic and proteomic data in the past 20 years has provided major advances in understanding the molecular mechanisms of human cancer.

This progress has resulted in the development of targeted therapies tailored to an individual molecular profile.

Recent advances in biochemical engineering should contribute to major evolution in diagnosis and treatment of human cancer.

Take home messages

1. Targeted therapies, including the anti-angiogenic agent bevacizumab and PARP i , have been recently approved for the treatment of many gynecological cancer.
2. Based on the results from randomized clinical trials showing significant benefits in terms of progression-free survival.
3. Most of them have acceptable tolerability and no detrimental effects on quality of life.
4. More collaboration is needed in the area of understanding molecular basis of tumor itself.
5. **Precision medicine and targeted therapy** ARE THE FUTURE.

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