# *On the Path to Individualizing Treatment for Ovarian Cancer Patients*

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UCSF Gynecological Oncology
Symposium
Breakout Session

September 25, 2021

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## *Ovarian Cancer Biology and Treatment Advances*

- Basic Biology/Genomics
- MEK Inhibitors
- PARP Inhibitors
- Antibody Drug Conjugates

## *The Clearity Foundation*

- Who we are
- Individualized Treatment Information
- Tumor Profile Interpretation
- Clinical Trial Identification
- Psychosocial Support (Steps Through OC)



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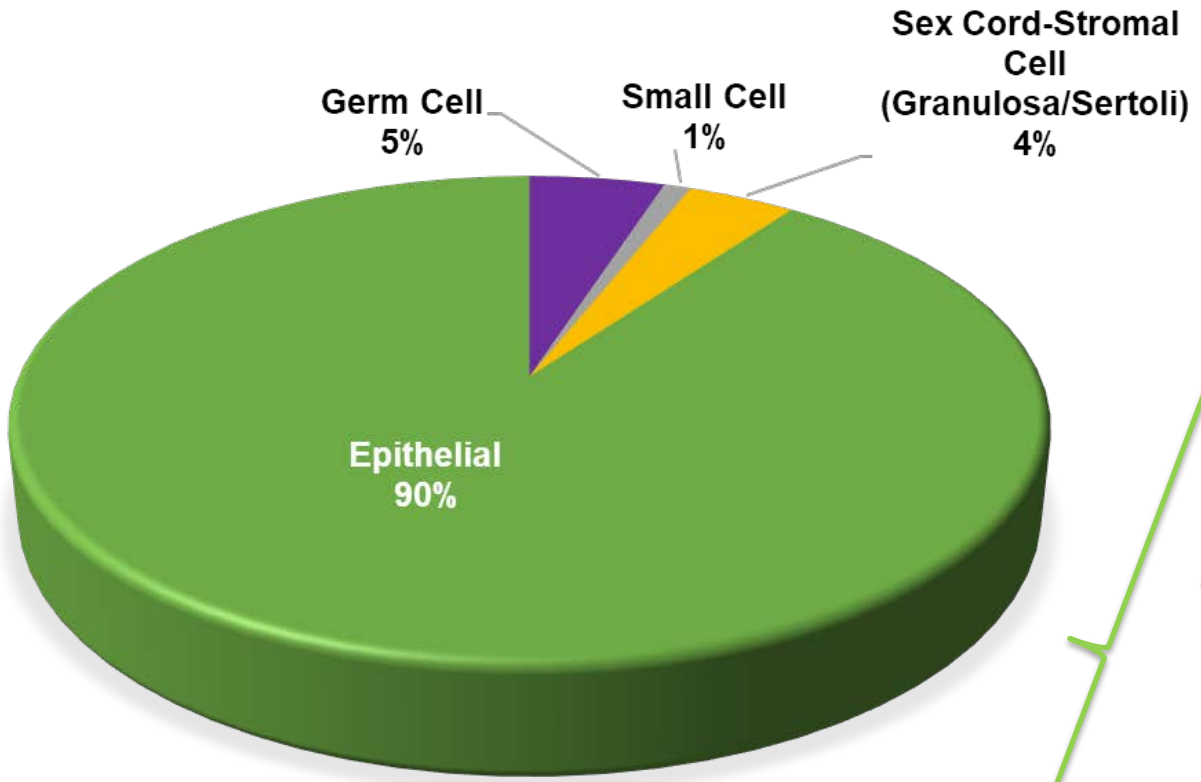
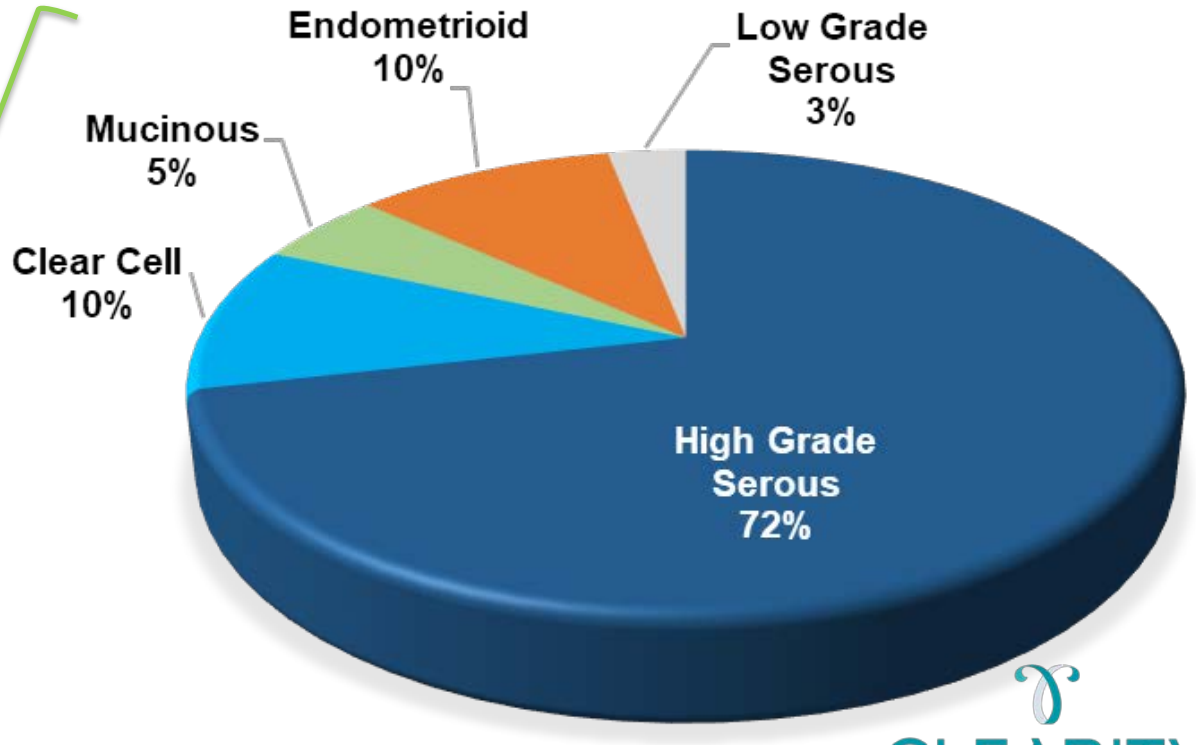
# Most Ovarian, Fallopian Tube, and Primary Peritoneal Cancers are Epithelial

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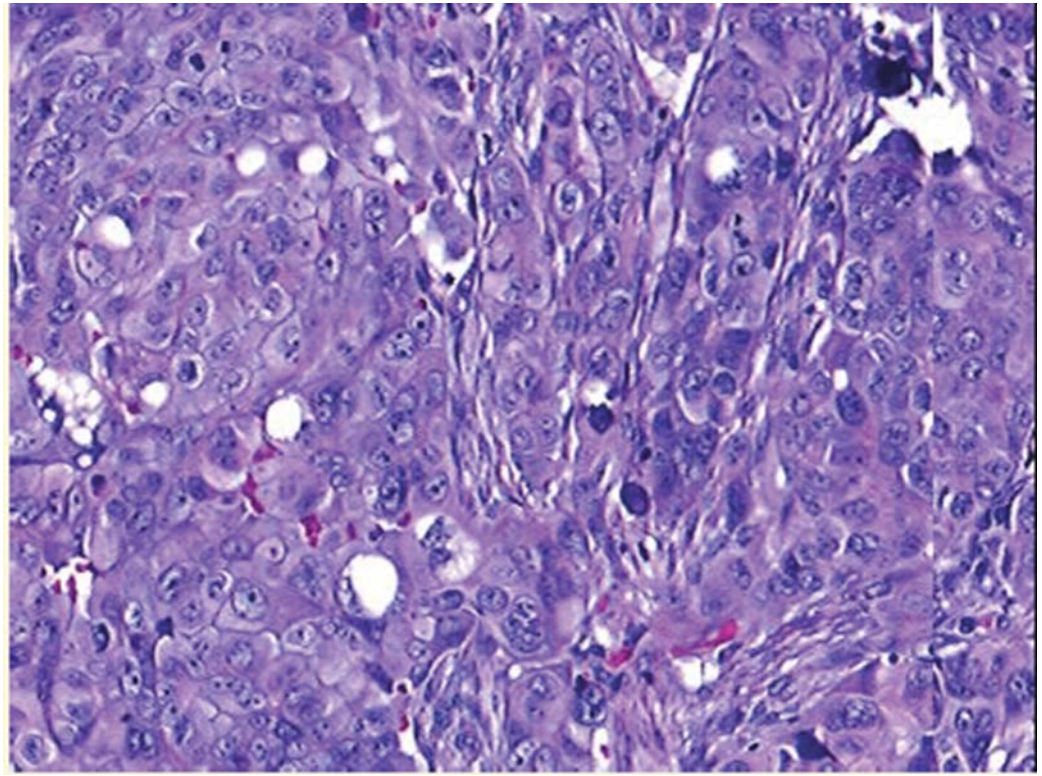
# *Hallmarks of cancer are similar in all advanced stage tumors*

Self-sufficient

Evades immune system



Protected from death-inducing signals

Genomic Instability and Mutation

Develops blood vessels to obtain nutrients and oxygen

Unlimited cell replication

Invades into surrounding tissue and spreads to other parts of the body



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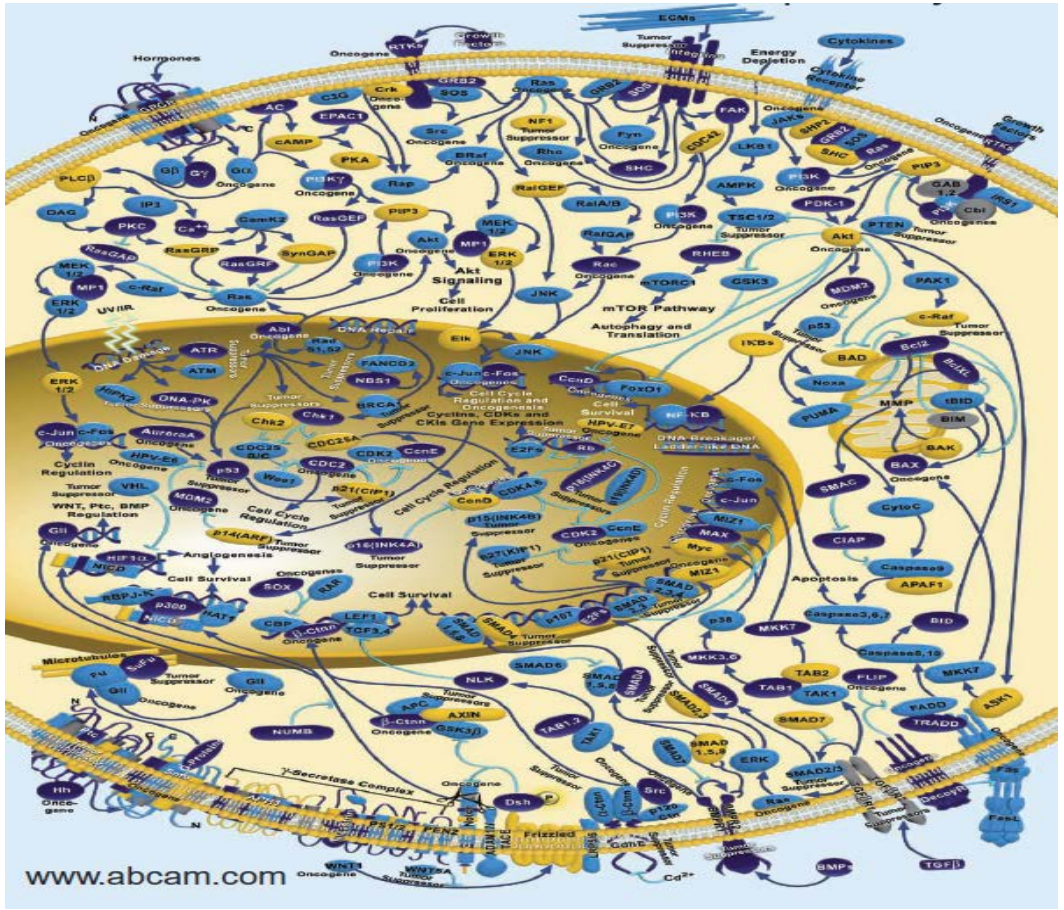
# *Many molecular pathways drive these processes so each tumor can be different*

Self-sufficient

Evades immune system




Protected from death-inducing signals

Genomic Instability and Mutation

Develops blood vessels to obtain nutrients and oxygen

Unlimited cell replication

Invades into surrounding tissue and spreads to other parts of the body



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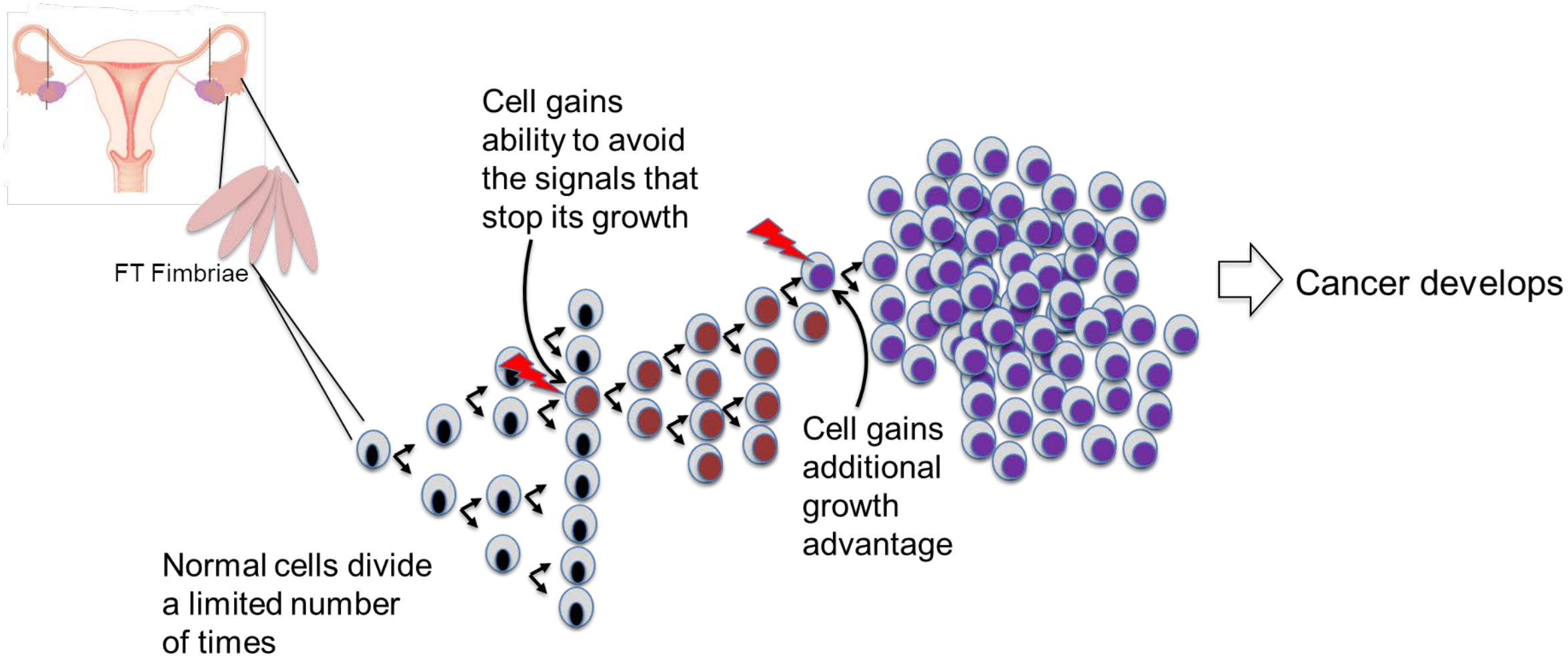
# *Gene mutations drive ovarian cancer development*



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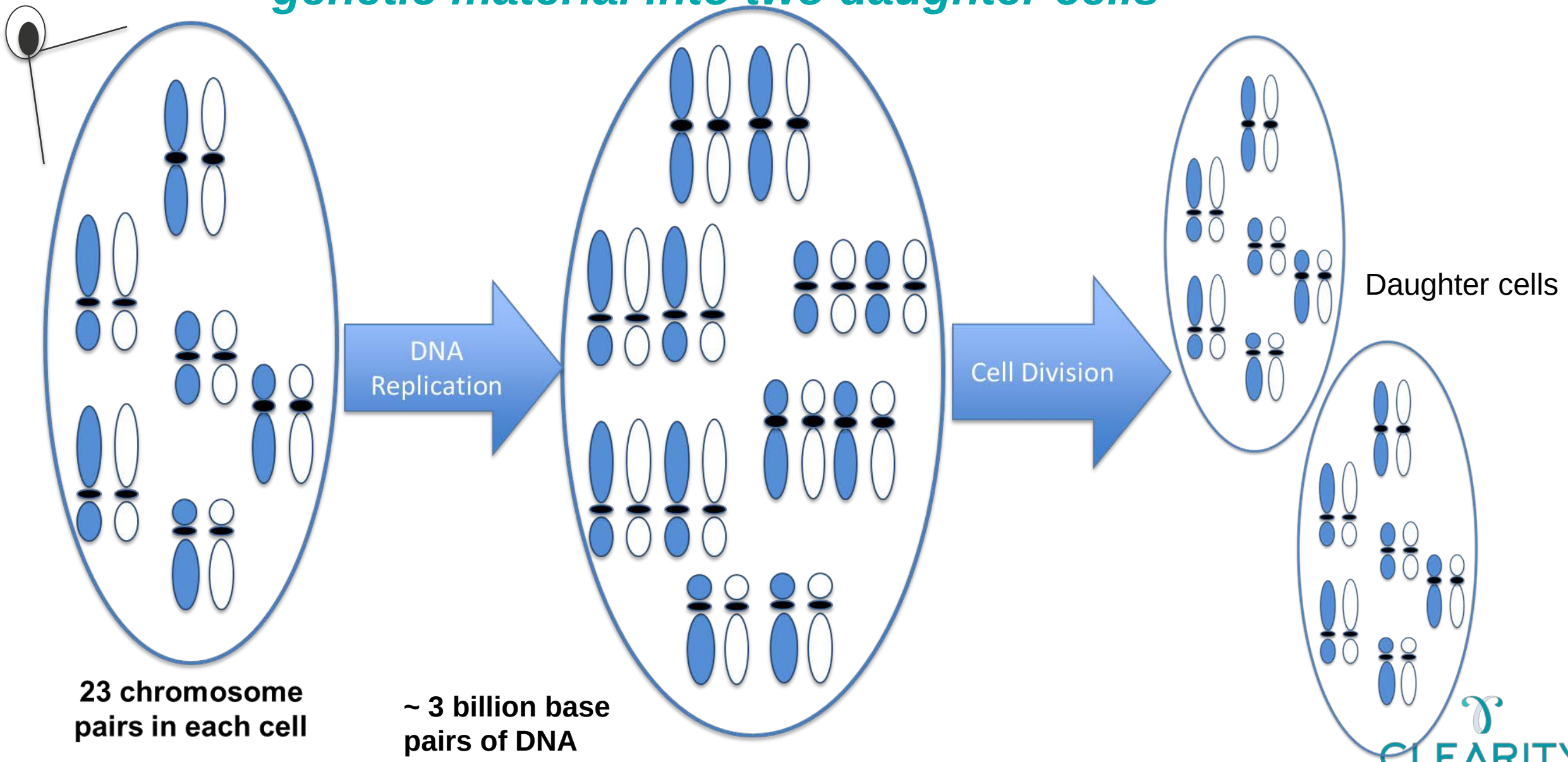
# *Normal cell proliferation requires accurate copying of genetic material into two daughter cells*

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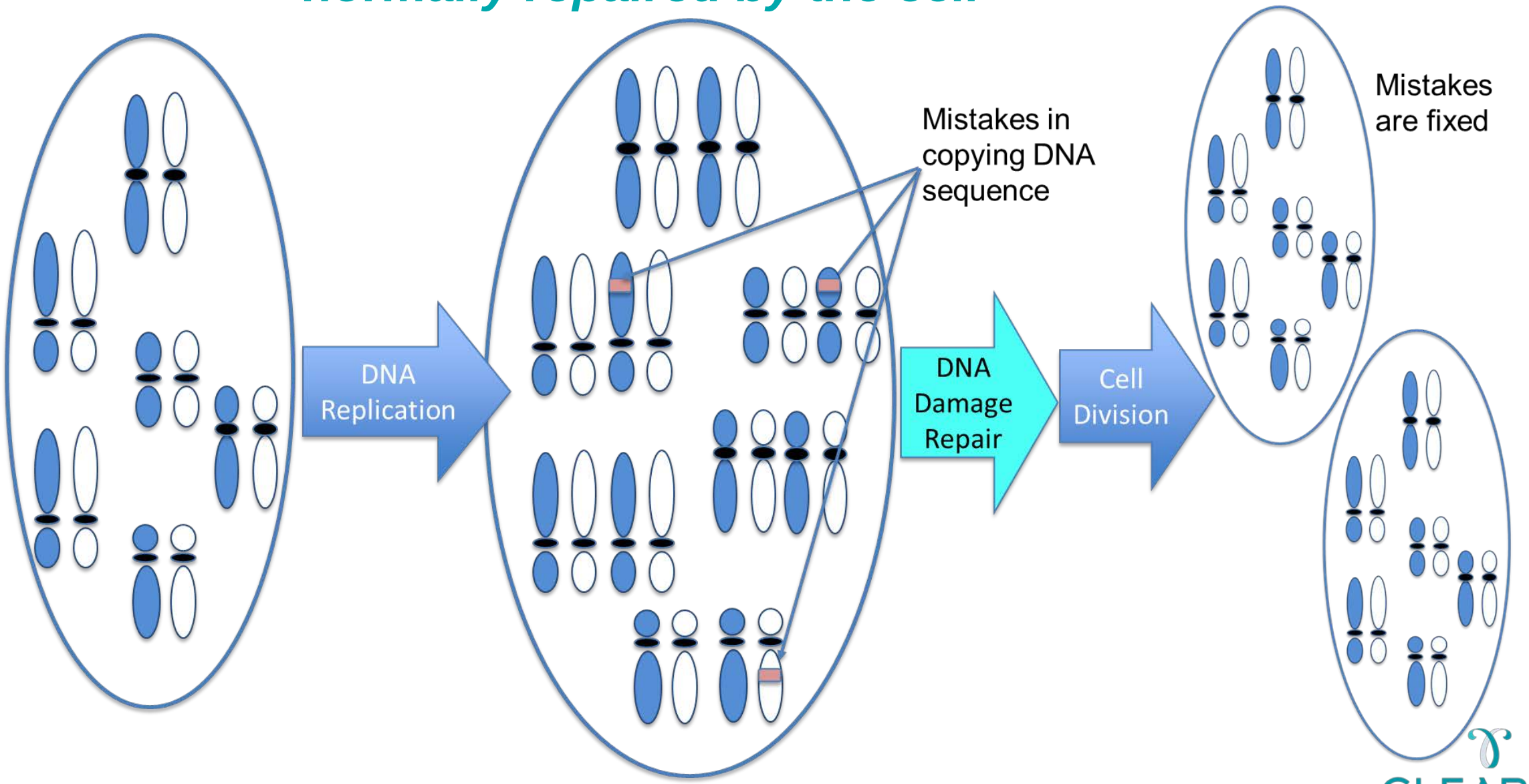
# *Mistakes during the replication process are normally repaired by the cell*



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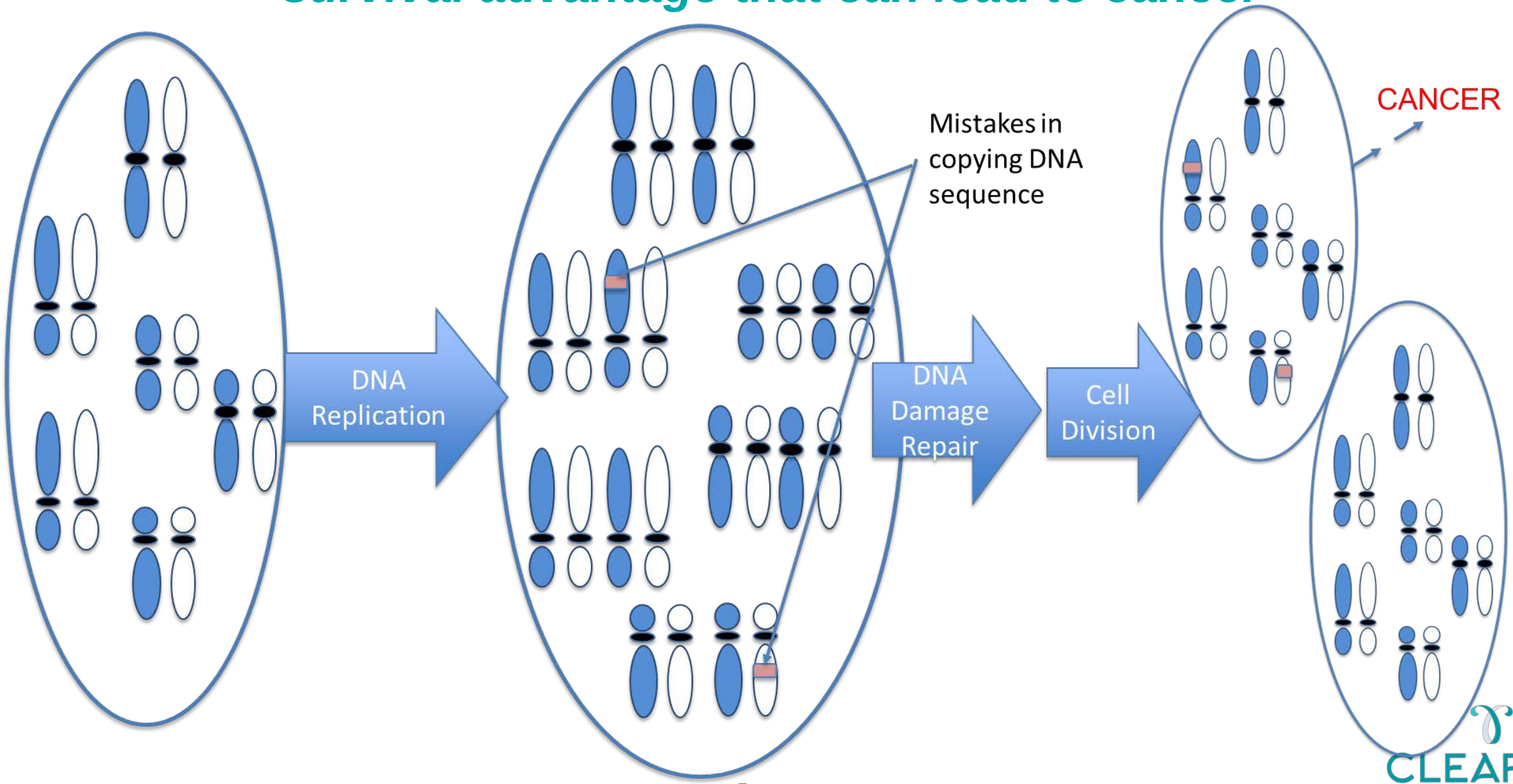
# *In rare cases, a gene mutation is not repaired and can give that cell a survival advantage that can lead to cancer*



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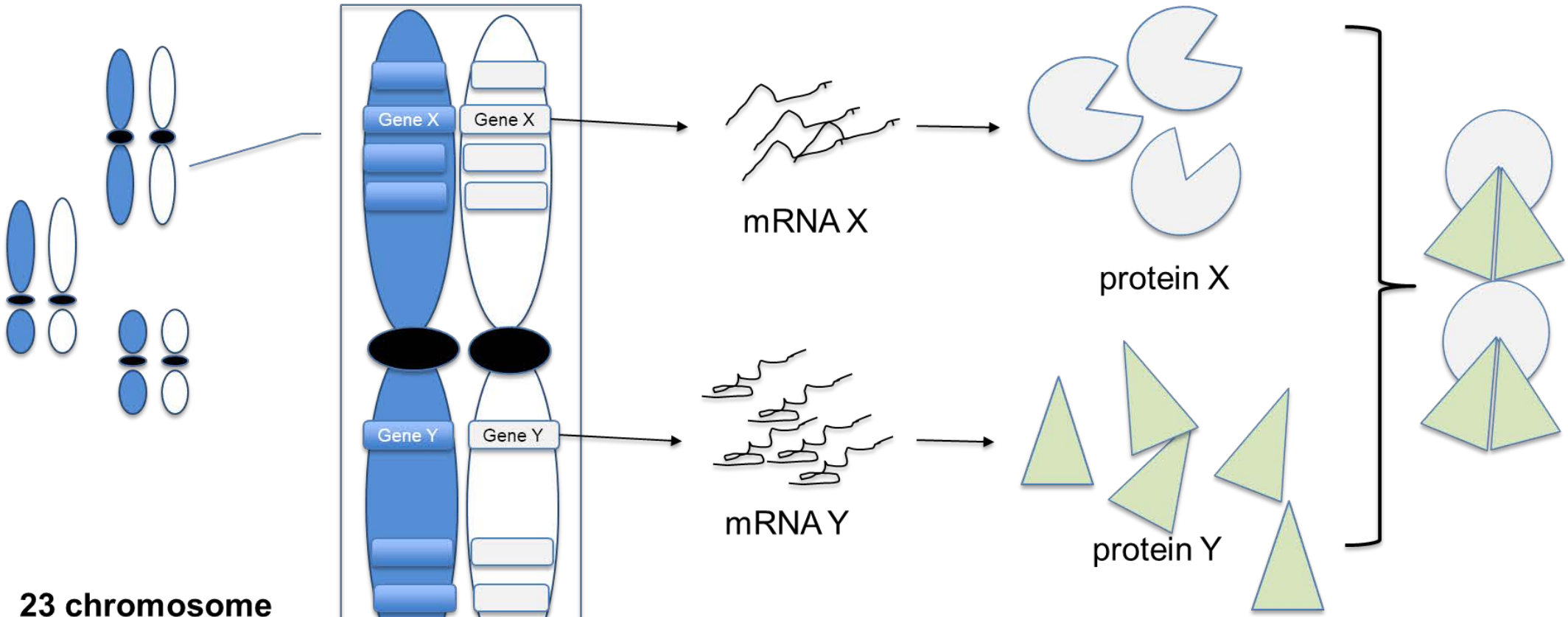
# Genes encode proteins and enzymes important for cell activities, growth, and survival



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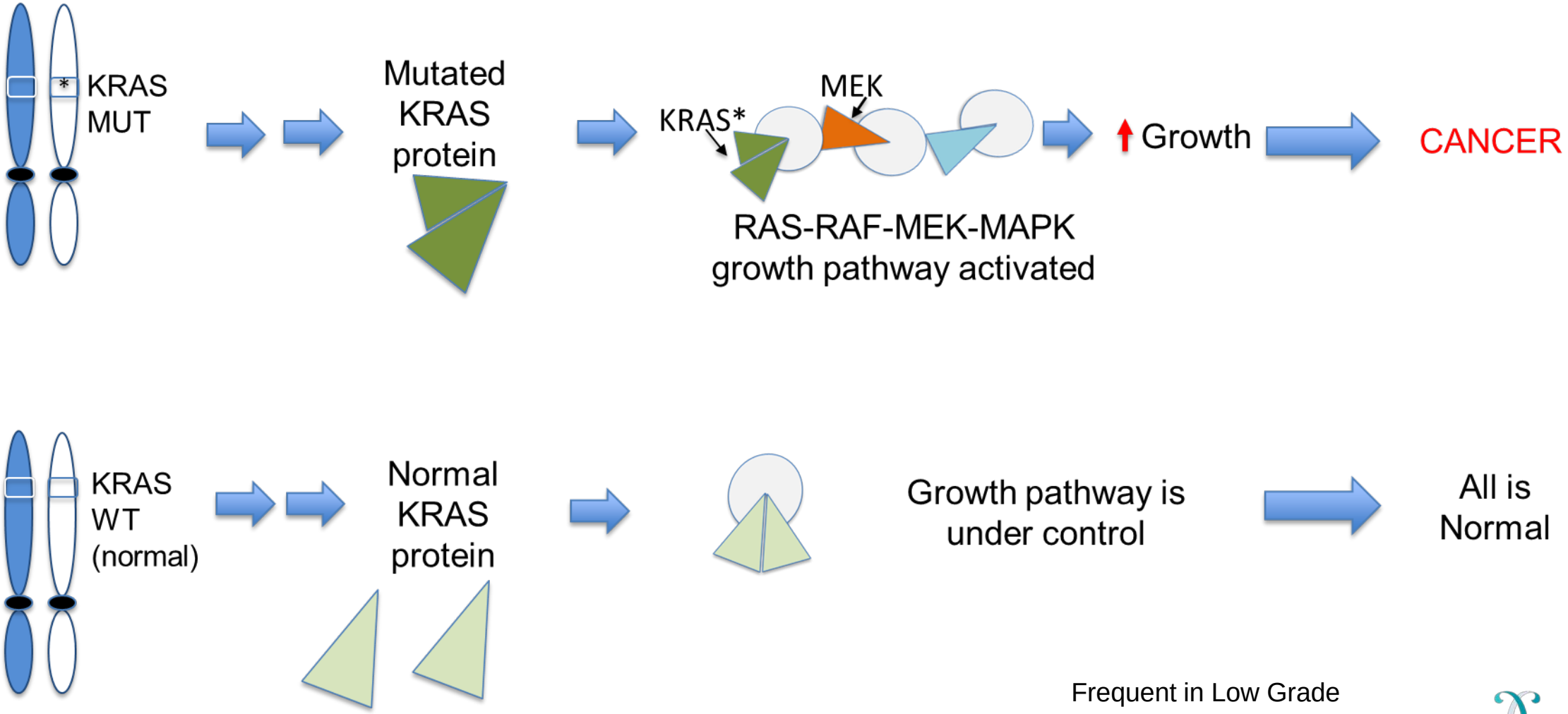
# *Gene mutations can determine the processes that drive tumor growth and survival: KRAS example*




Frequent in Low Grade
Serous Ovarian Cancer



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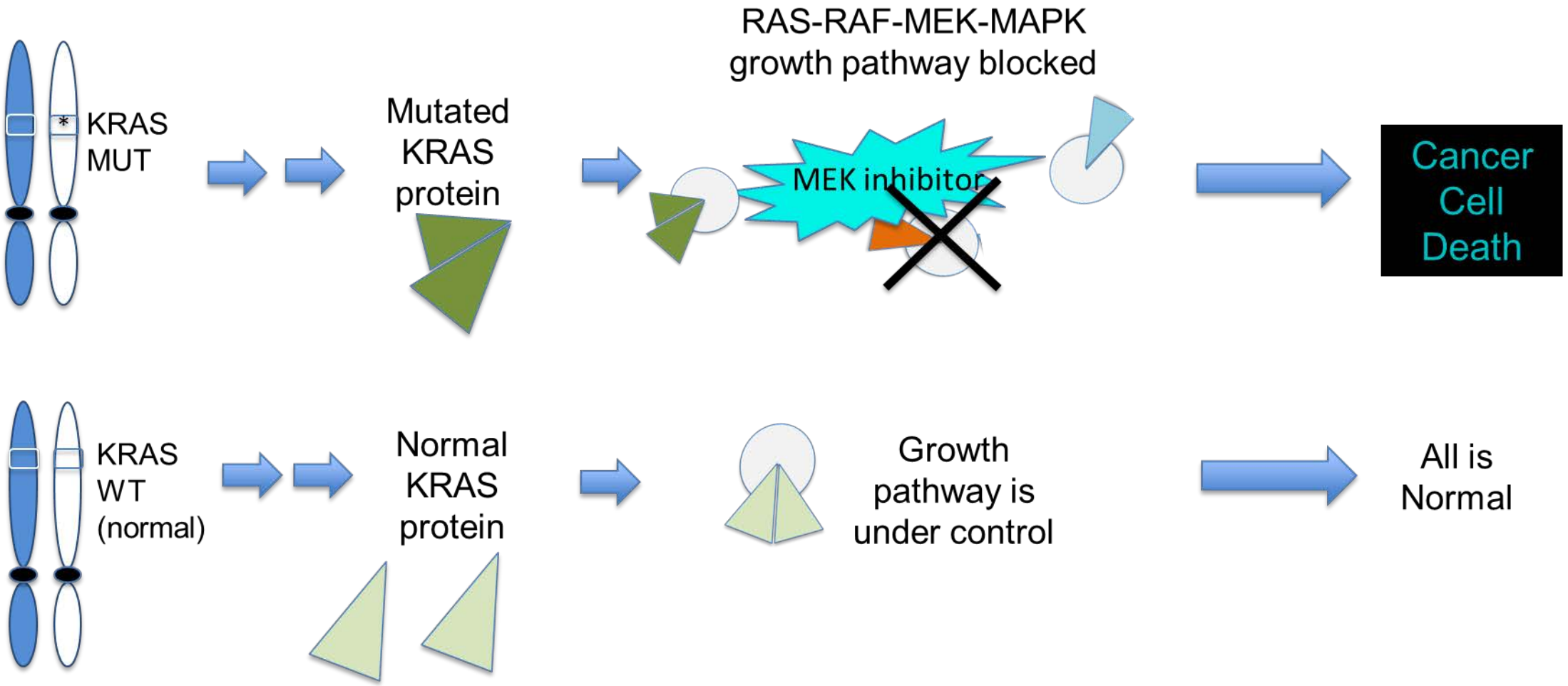
# *KRAS activates RAS-RAF-MEK-MAPK pathway →Inhibiting pathway can cause cell death*



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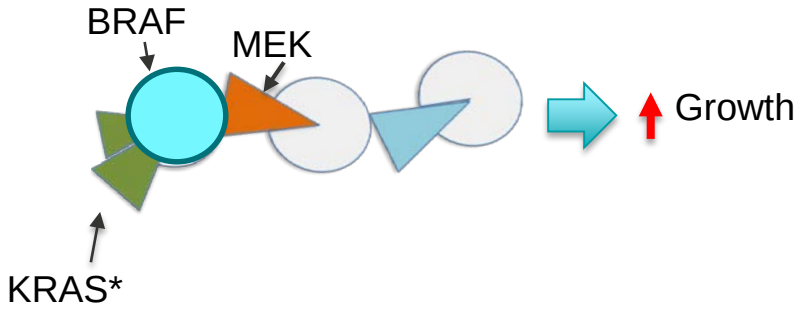
# *Low Grade Serous OC patients benefit from MEK inhibitor treatment*

Frequent BRAF, KRAS, or NRAS mutations→ RAS-RAF-MEK-MAPK growth pathway activated



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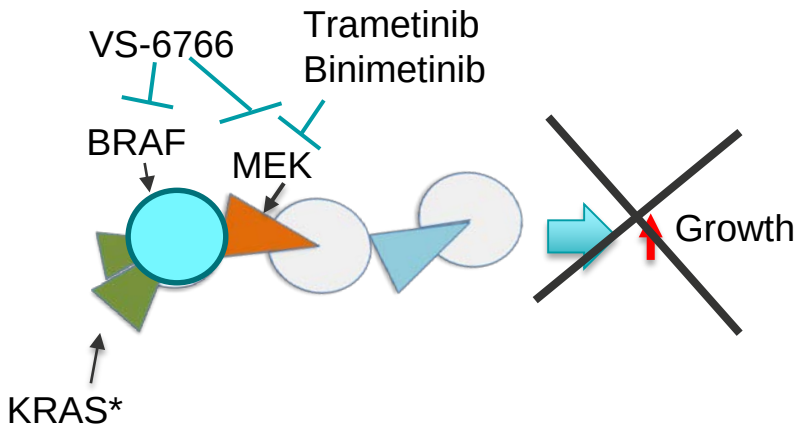


<u>Trametinib (MEKi) vs SoC:</u> Twice the time before recurrence compared to those with standard of care chemo or hormone therapy (NCT02101788)

<u>Binimetinib (MEKi) vs SoC:</u> Increased time to recurrence in patients with KRAS mutations (NCT01849874)

<u>VS-6766 (RAF/MEK inhibitor) + Defactinib (FAKi):</u>
Ongoing trial with promising results particularly in patients with KRAS mutations (NCT03875820)



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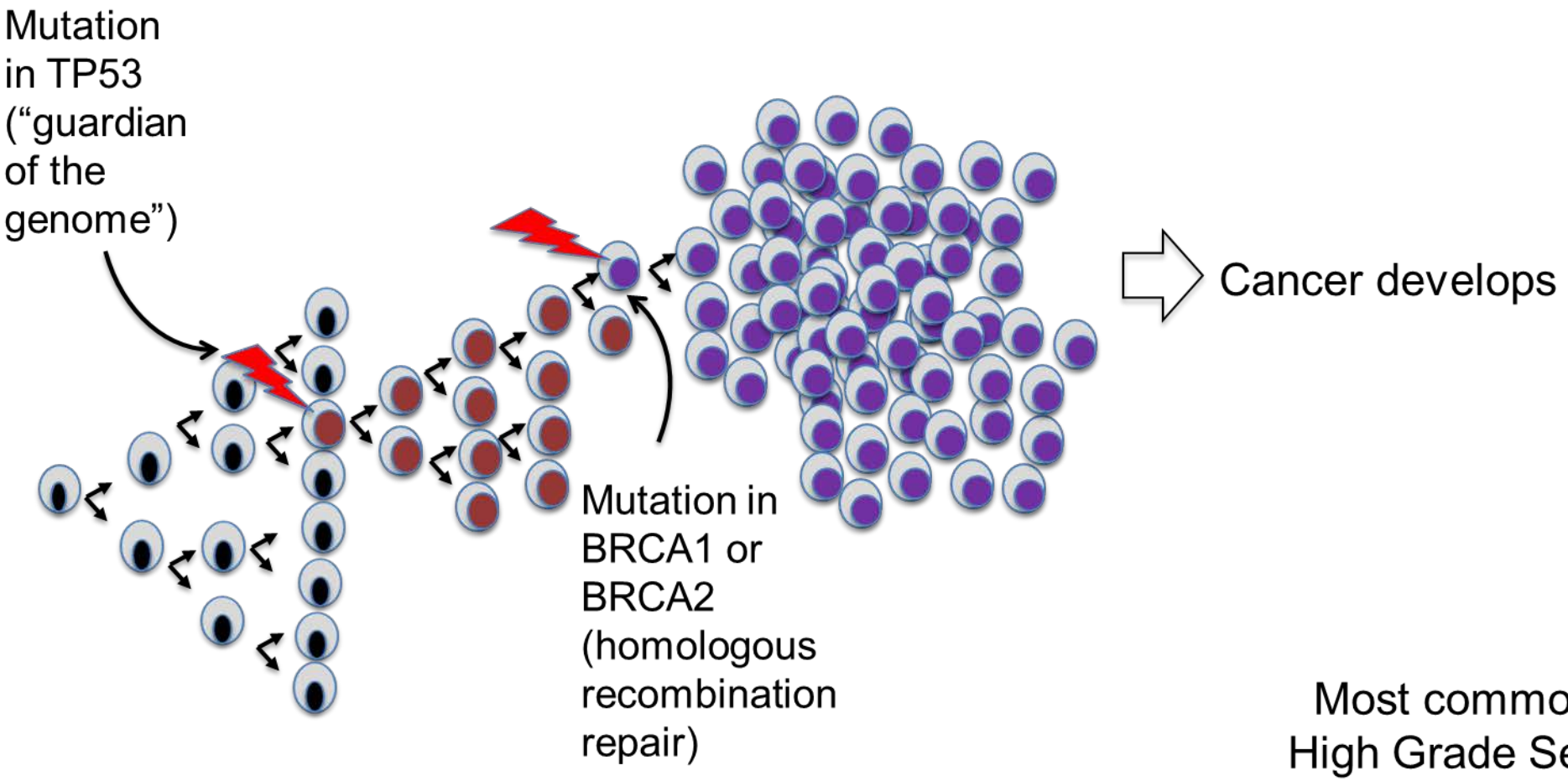
# EOC Histology Subtypes: Distinct Genomic Profiles, Chemo-responsiveness, and Therapeutic Strategies

| Histology | Prevalence | Origin | Platinum Response | Frequent Genomic Alterations | Drug Targets |
|---|---|---|---|---|---|
| High Grade Serous | 70-75% | Fallopian Tube | Sensitive, then resistant | TP53, BRCA1/2, HRD**, CCNE1 AMP | PARP* Angiogenesis* |
| Low Grade Serous | 1-3% | Fallopian Tube | Resistant | BRAF, KRAS, NRAS | ER*, BRAF, MEK |
| Endometrioid | ~10% | Endometriosis | Sensitive | PIK3CA, PTEN, CTNNB1, ARIDA, MSI*** | ER*, PD-1* PI3K-AKT-mTOR |
| Clear Cell | ~10% | Endometriosis | Resistant | TP53, PIK3CA, ARID1A, MSI*** | PD-1* PI3K-AKT-mTOR |
| Mucinous | ~5% | Unknown | Resistant | KRAS, ERBB2 AMP | MEK, HER2 |

*Targets for approved therapies for ovarian cancer
**HRD, homologous recombination deficiency
***MSI, microsatellite instability

# *Mutations in genes that encode proteins critical for genome surveillance or repairing DNA damage can drive cancer development*




Most common in High Grade Serous Ovarian Cancers

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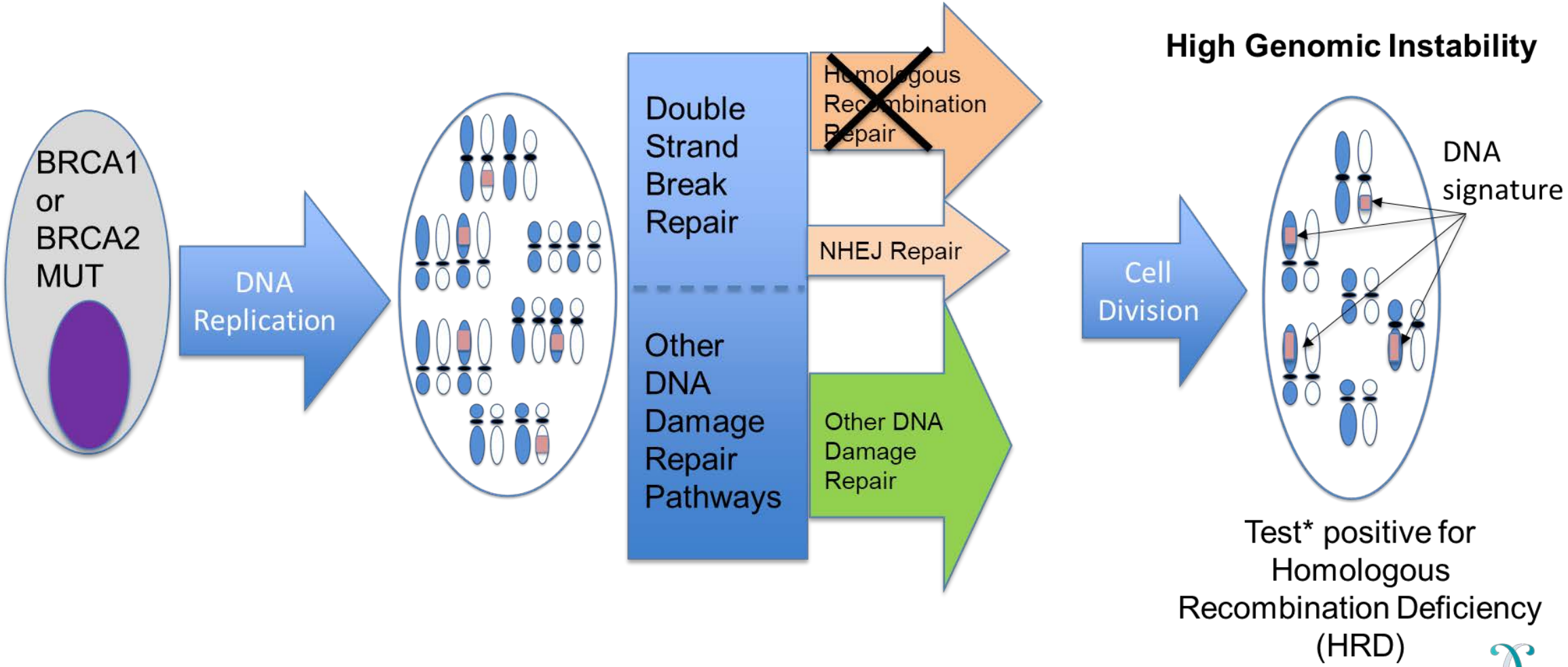
# *Cancer cells have reduced ability to repair DNA damage: BRCA1/2 mutation example*

## *Inaccurate DNA damage repair results in High Genomic Instability*




*HRD Test can measure Loss of heterozygosity (LOH), as well as large scale phase transitions and telomere imbalance



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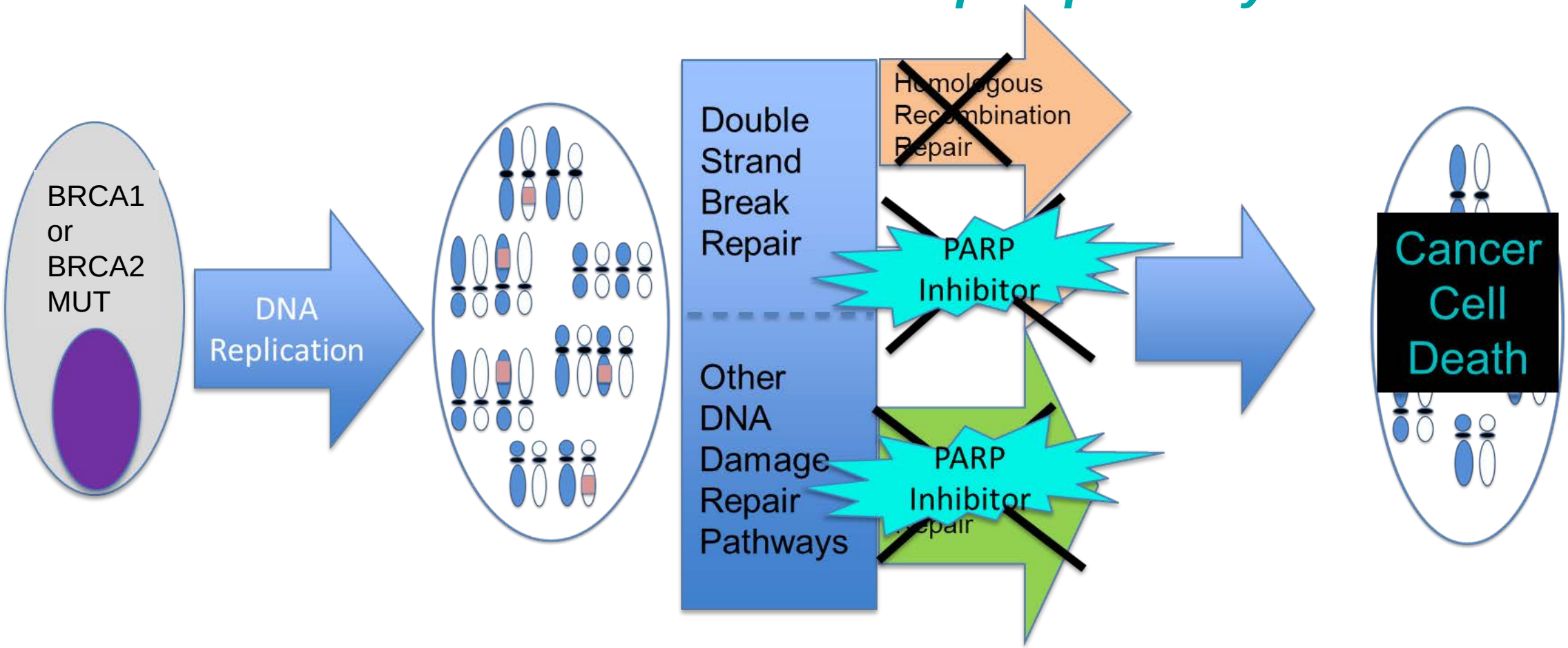
# *BRCA-mutated cancer cells are sensitive to PARP inhibitors that inhibit alternative DNA repair pathway*




PARP=Poly ADP Ribose Polymerase

HRD, homologous recombination deficient



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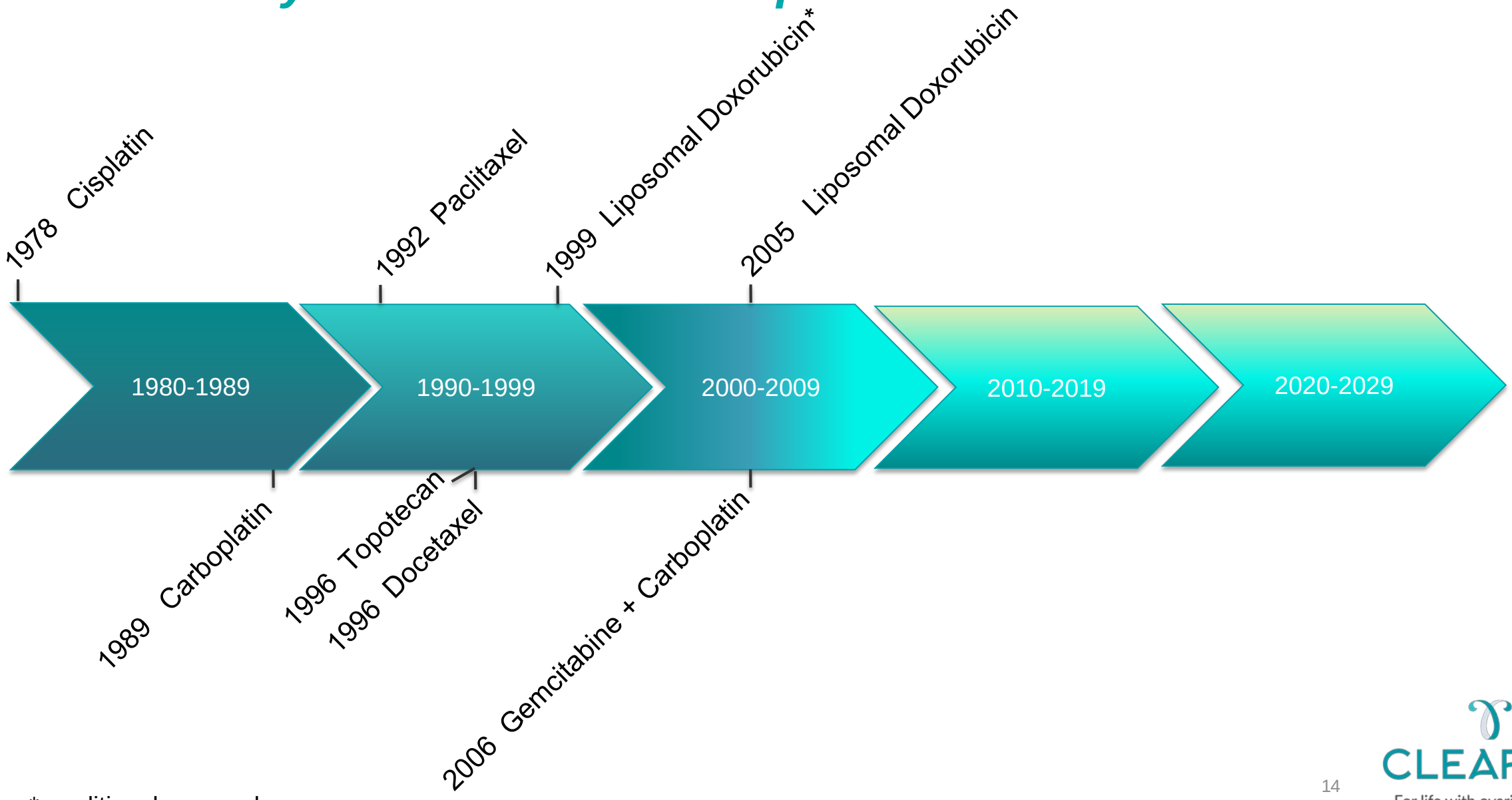
# Ovarian Cancer Drug Approvals: Cytotoxic Chemotherapies until 2014




*conditional approval



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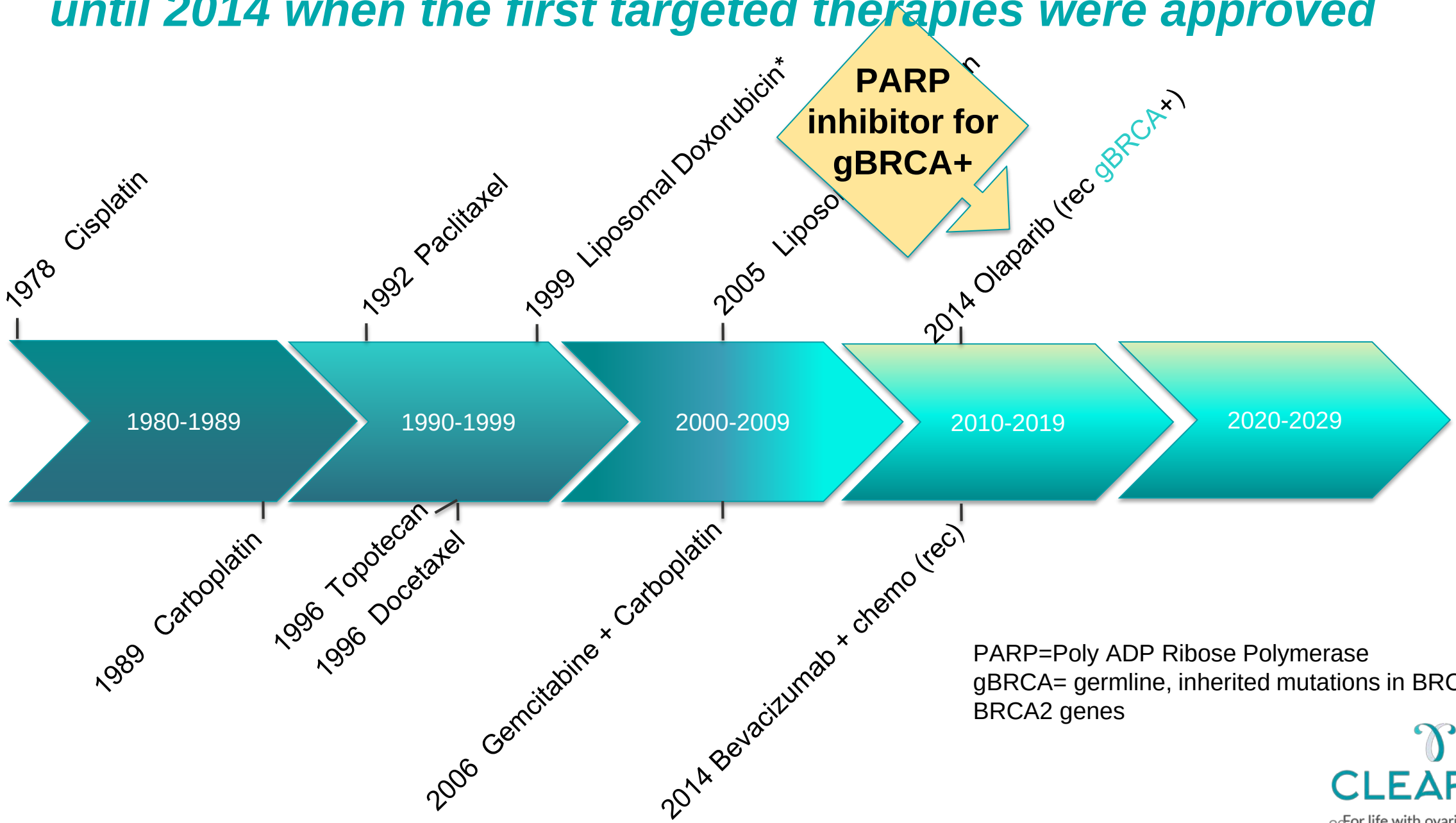
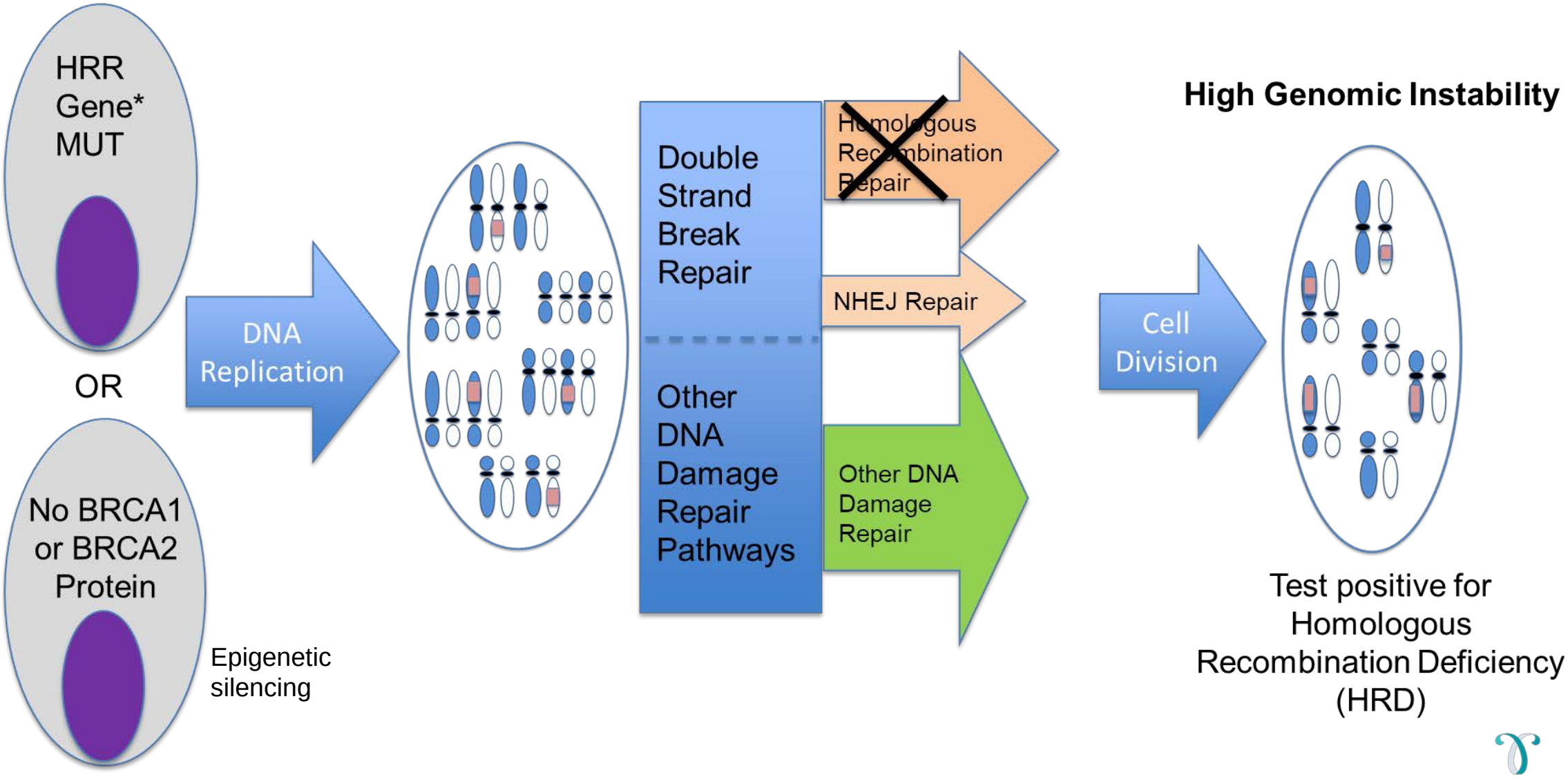
# *Ovarian Cancer Drug Approvals: Cytotoxic chemotherapies until 2014 when the first targeted therapies were approved*




PARP=Poly ADP Ribose Polymerase
gBRCA= germline, inherited mutations in BRCA1 or BRCA2 genes

*conditional approval; rec, recurrent

# *High Genomic Instability also results when BRCA1 or BRCA2 proteins are not made or with mutations in other HRR* genes*




*Homologous recombination repair; e.g., PALB2, RAD51C/D

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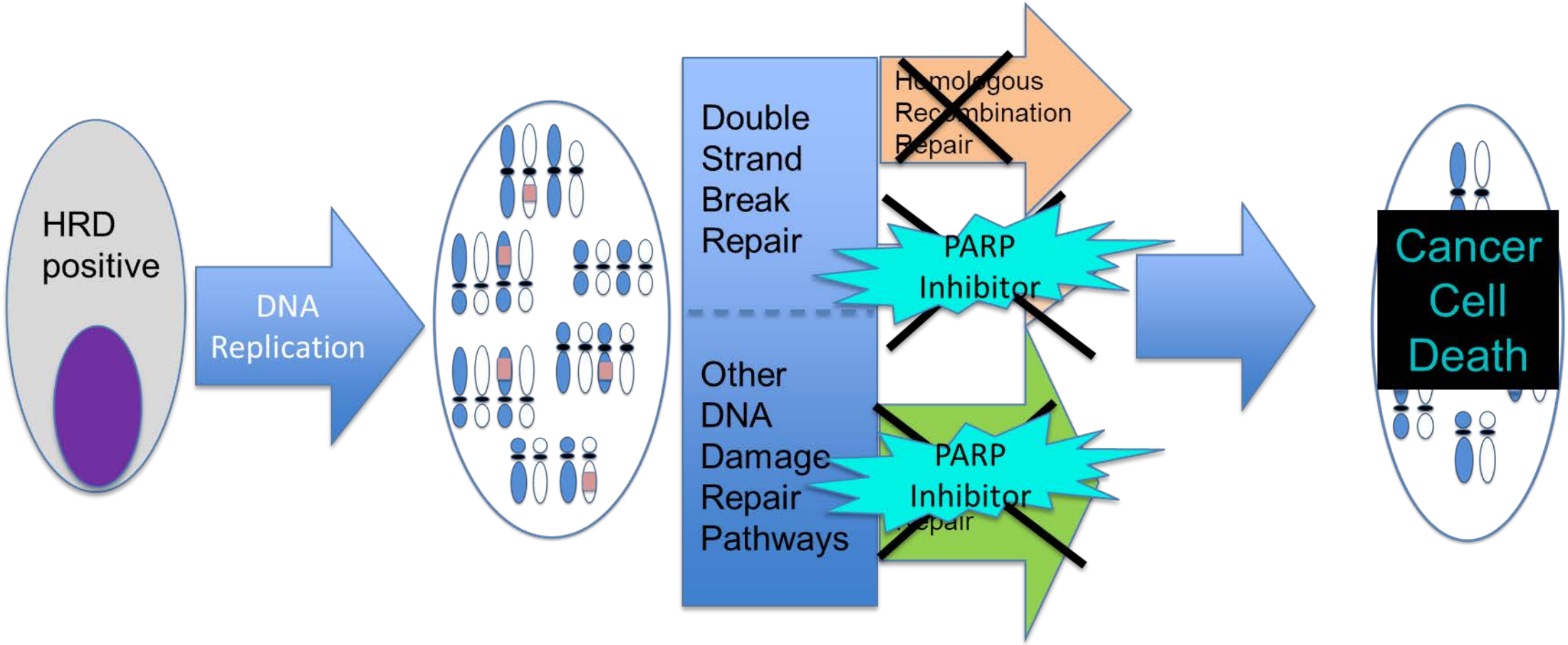
# *HRD (including BRCA) positive cancers are sensitive to PARP inhibitors that inhibit alternative DNA repair pathway*




HRD, homologous recombination deficient



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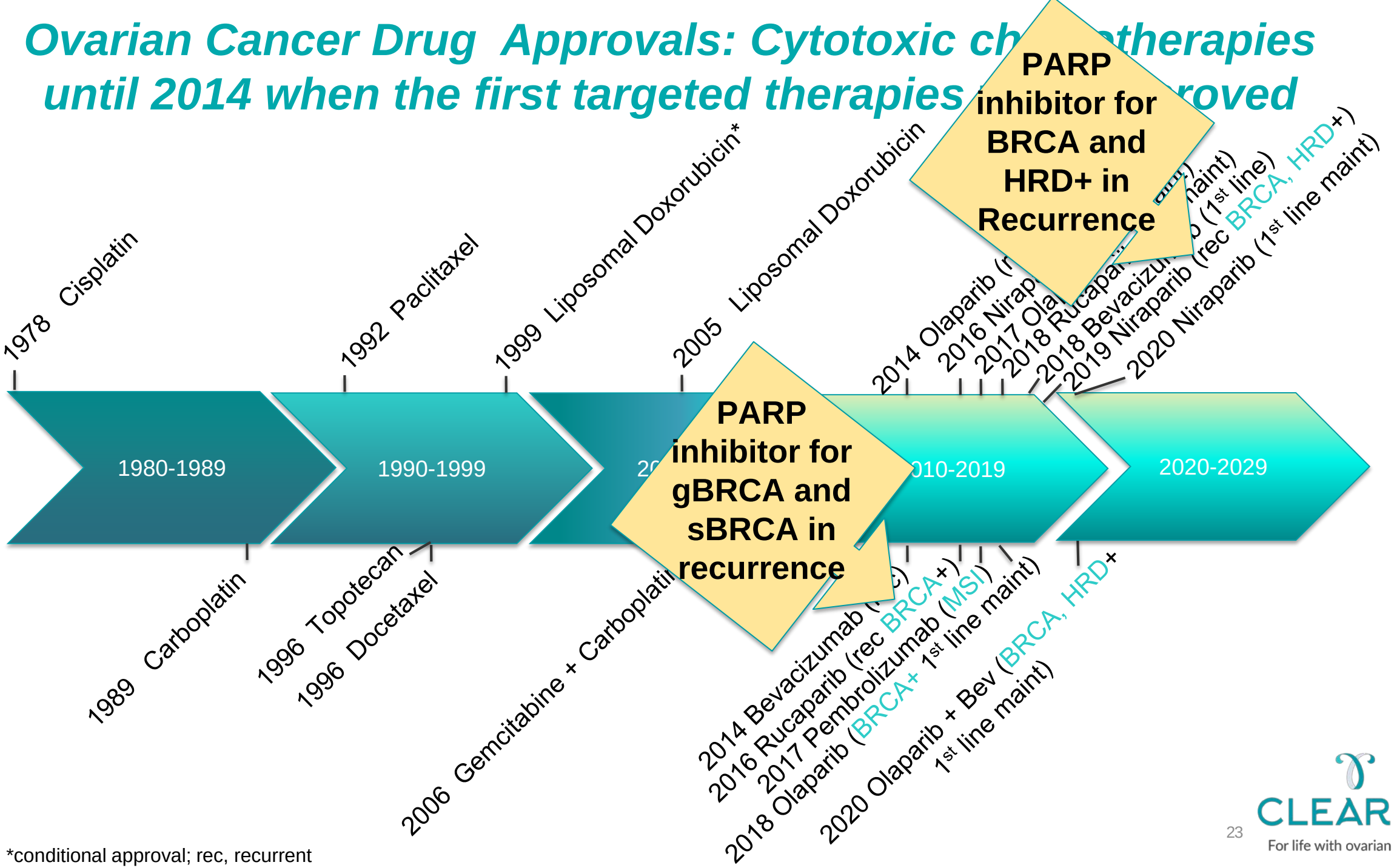


*conditional approval; rec, recurrent



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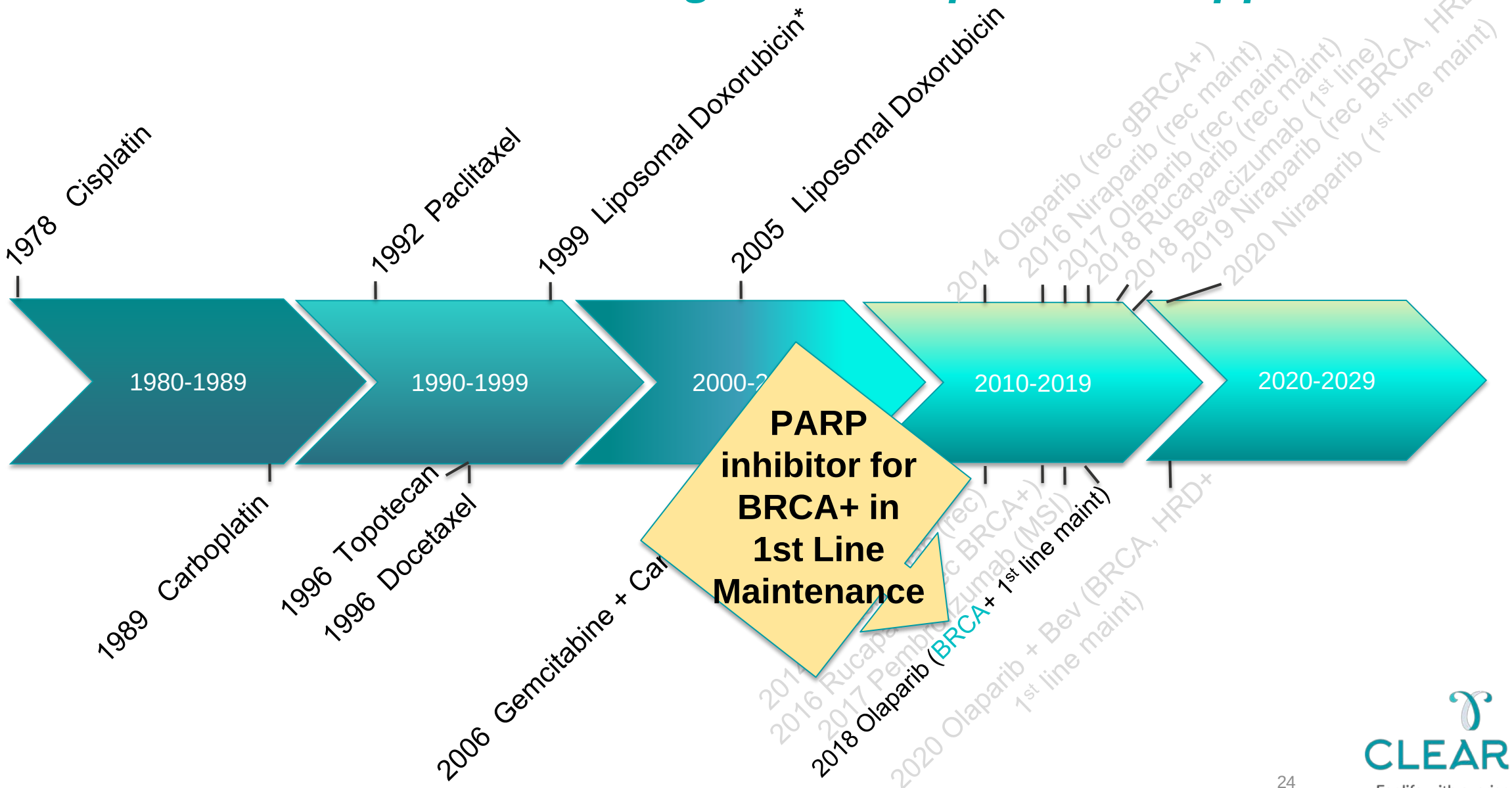


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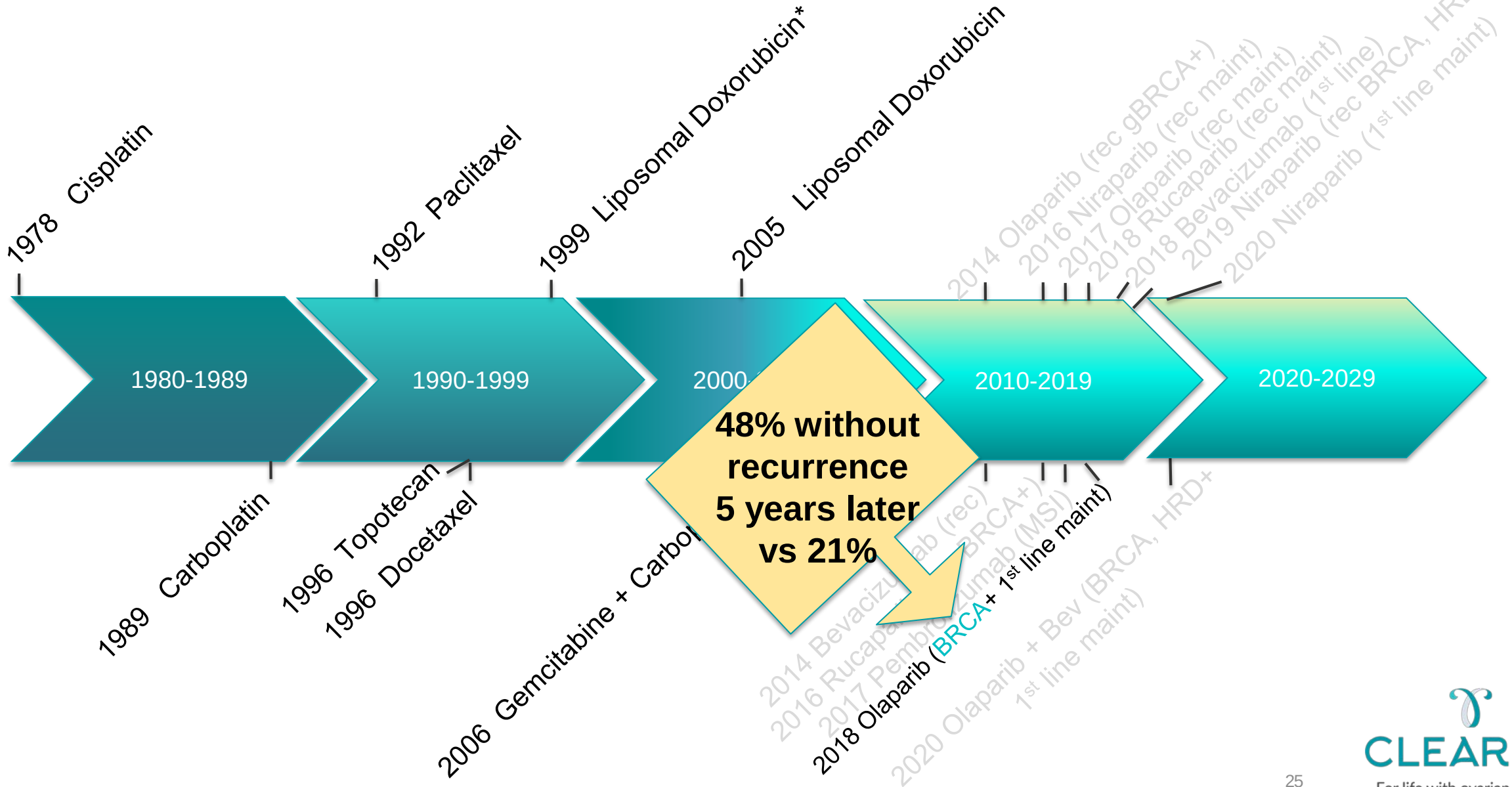


*conditional approval; rec, recurrent



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# *PARP Inhibitors are approved for maintenance and recurrence*

1. New Diagnosis: Maintenance treatment after response to first line platinum-taxol therapy
   a. Olaparib (Lynparza) - BRCA+
   b. Niraparib (Zejula) – all women
   c. Olaparib + bevacizumab (Avastin) – BRCA+ and HRD+

2. Maintenance after platinum-sensitive recurrence that responds to platinum-based chemotherapy
   a. Olaparib (Lynparza) - all women
   b. Niraparib (Zejula) - all women
   c. Rucaparib (Rubraca) – all women

3. Recurrence treatment
   a. Olaparib (Lynparza) - BRCA+ (≥3 prior therapies)
   b. Rucaparib (Rubraca) – BRCA+ (≥2 prior therapies)
   c. Niraparib (Zejula) – BRCA+ and HRD+ (≥3 prior therapies)

HRD, homologous recombination deficiency

# *Tumor Biomarker Testing Identifies the Right Drug for the Right Patient → Better Outcomes*




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# *Next: Precision Medicine for those who are not BRCA or HRD+ or Progress on PARP Inhibitors*




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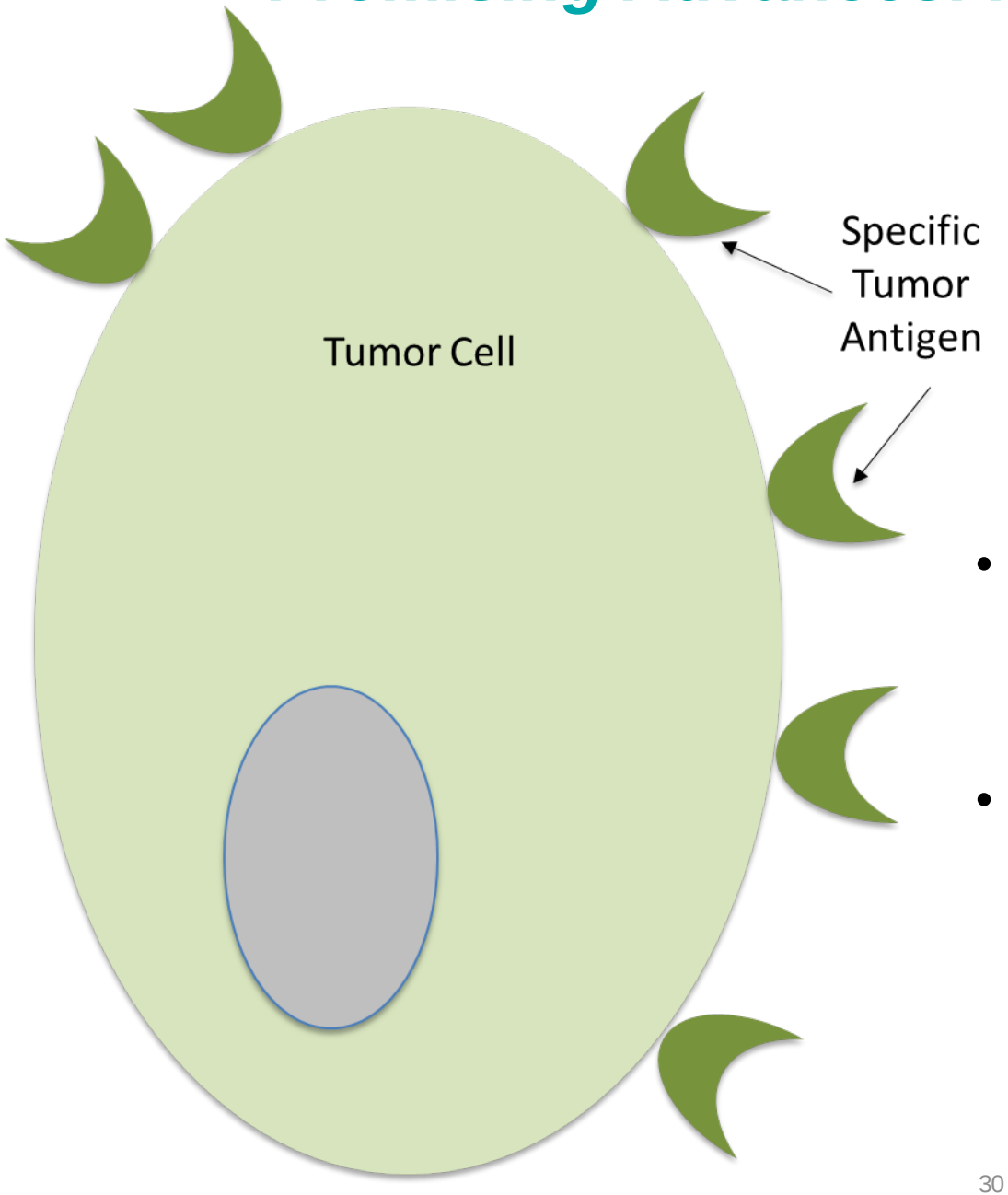
# *PARP Inhibitors are in clinical trials in combination with other drugs to increase their effectiveness (beyond BRCA+ and HRD+)*

| PARP Inhibitor Combination | Drugs | Phase | Trial ID |
|---|---|---|---|
| | | | |
| + Angiogenesis inhibitors (e.g., VEGF/R) | Olaparib + cediranib | II/III | NCT02502266 |
| | | | |
| + Immune checkpoint inhibitors (e.g., PD-1 or PD-L1) + Angiogenesis (VEGF/R) inhibitors | Olaparib + durvalumab + cediranib | II | NCT04739800 and NCT02484404 |
| | Olaparib + pembrolizumab | II | NCT04123366 |
| | Rucaparib + nivolumab + bevacizumab | II | NCT02873962 |
| | Niraparib + dostarlimab | II | NCT04983745 |
| | | | |
| + Cell cycle (Wee1 or ATR) or PI3Kinase inhibitors | Olaparib + ceralasertib (ATR) | II | NCT03462342 and NCT03682289 |
| | Olaparib + alpelisib (PI3Kalpha) | III | NCT04729387 |

# Promising Advances: Antibody Drug Conjugates




Antibody Drug Conjugate (ADC)


- Antibody specifically recognizes a protein made by tumor cells (e.g., Folate Receptor, Mesothelin, NaPi2b, Tissue Factor)
- Drug is a cytotoxic molecule (e.g, MMAE, Auristatin, Eribulin, Exotecan)



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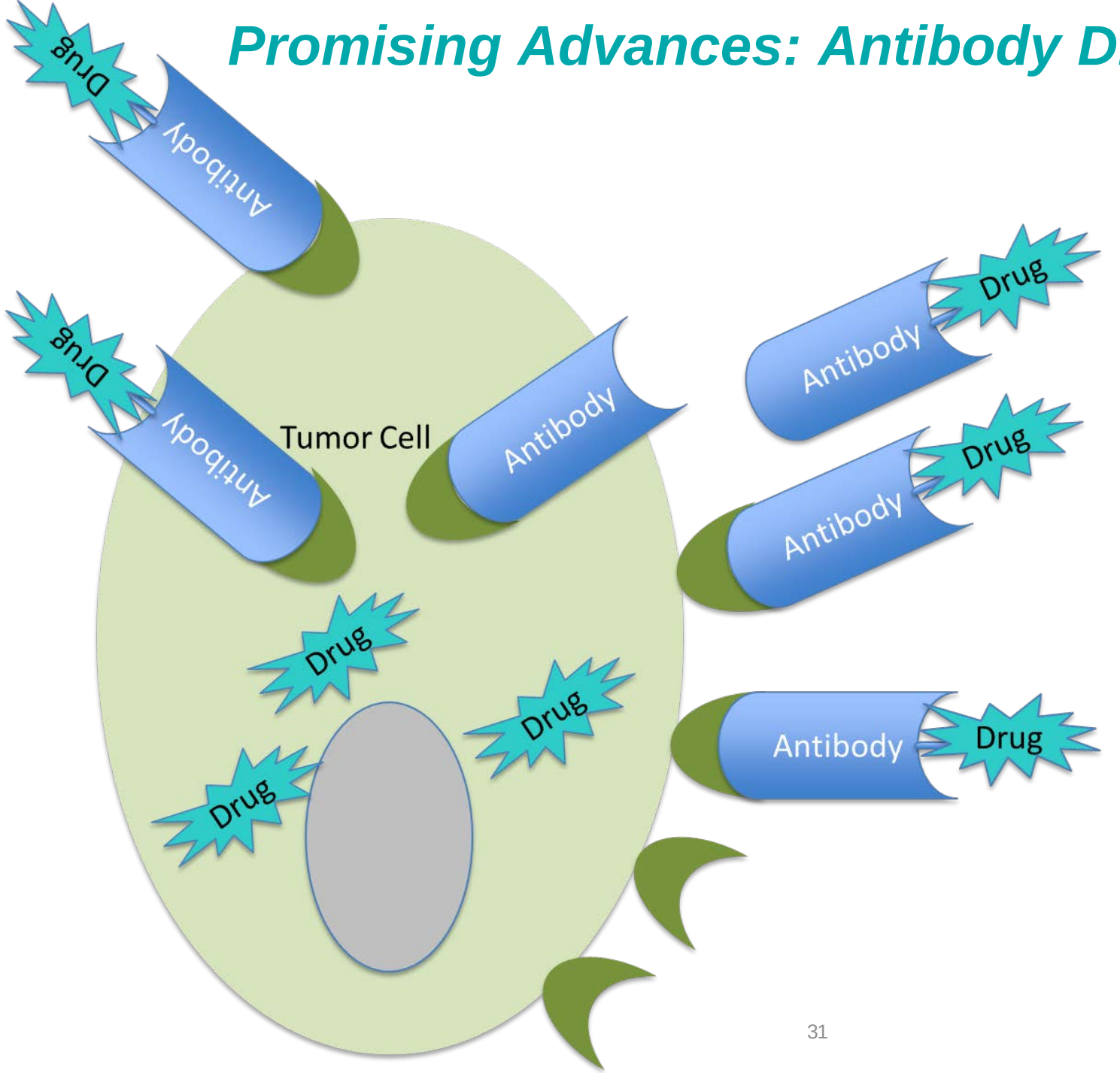
# Promising Advances: Antibody Drug Conjugates




1. ADC binds tumor cells that express specific proteins
2. Tumor cell takes up the ADC and releases the cytotoxic drug inside
3. High levels of specific protein will bind more ADC → more drug in cell
4. Tumor cell dies and can release the cytotoxic drug to kill nearby cells
5. Side effects are different and less than with a similar cytotoxic drug



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# *Promising Advances: Antibody Drug Conjugates*

ADC in clinical development for ovarian cancer
All of these cytotoxic drugs bind to microtubules to kill cancer cells (like Taxol)
→ may be less toxic substitute for taxanes

| Phase | Trial ID (Name) | Drug | Target Protein | Cytotoxic Molecule |
|---|---|---|---|---|
| III | NCT04209855 (MIRASOL) | Mirvetuximab soravtansine | Folate Receptor alpha | Maytansinoid |
| II | NCT03657043 (innovaTV 208) | Tisotumab vedotin | Tissue Factor | MMAE |
| II | NCT03587311 | Anetumab ravtansine + Avastin | Mesothelin | Maytansinoid |
| II | NCT03319628 | Upifitamab rilsodotin (XMT-1536) | NaPi2b | Auristatin |
| I (expansion) | NCT03748186 | STRO-002 | Folate Receptor alpha | SC209 |

Tumor Biomarkers for patient selection = ADC Target Proteins

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# *Clearity Mission and Services*

Founded in 2008 by Laura Shawver, PhD, two years after her ovarian cancer diagnosis

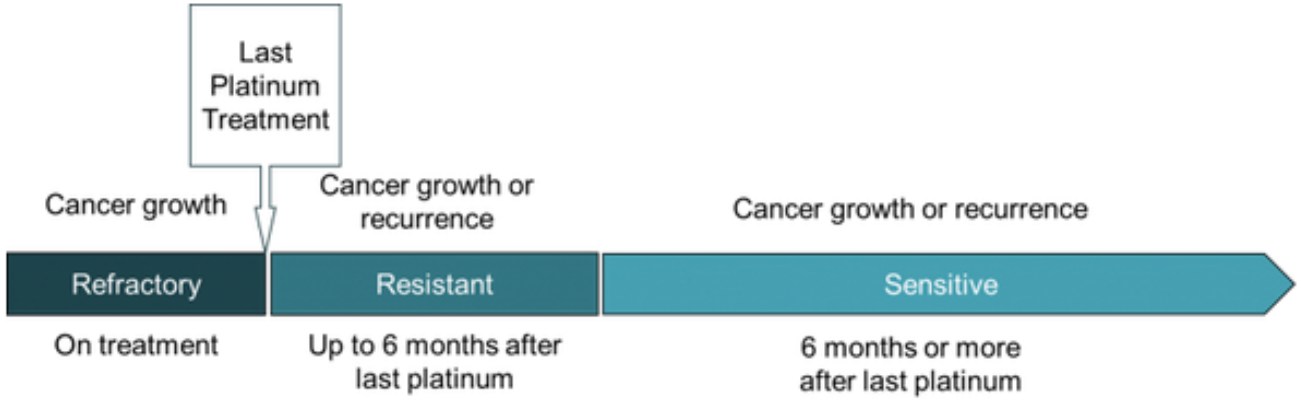
Mission is to improve the survival and quality of life of those with ovarian cancer

Provide  individualized information about standard treatments and clinical trials based on tumor biomarkers, clinical situation, and personal preferences

Provide psychosocial support through one-on-one guidance based on assessment of each participant's needs

# *Standard of care treatment information based on clinical situation —provided on our website*


Platinum Response Status Defined




→ Information on effectiveness of SoC also accessible



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# *All NCCN guideline treatments for each clinical situation are described on our website – with links for more details*

## Recurrent or Progressive Disease

The Basics | Treatments for Platinum-Sensitive Recurrence | Treatments for Platinum-Resistant or Refractory Recurrence

**− Standard of Care Treatments**

| Drug(s) | Clinical Notes |
|---|---|
| Carboplatin or Cisplatin | Standard of care is Carboplatin or Cisplatin combined with Gemzar, Doxil or Taxol.<br><br>Adding Avastin to platinum-based chemo (and continuing as maintenance) can increase the time before cancer returns or gets worse.<br>To see how effective these drugs are, click here.<br>To see side effects for these drugs, click here.<br>To see prescribing information, click here. |
| Carboplatin or Cisplatin<br>Gemcitabine (Gemzar)<br>Bevacizumab (Avastin) | |
| Carboplatin or Cisplatin<br>Paclitaxel (Taxol)<br>Bevacizumab (Avastin) | |
| Carboplatin or Cisplatin<br>Liposomal doxorubicin (Doxil)<br>Bevacizumab (Avastin) | |

**+ Treatments for BRCA or HRD-positive* Patients**

**+ Additional Options for Low Grade Serous Cancer Patients**

**− Promising Drugs in Clinical Trials**

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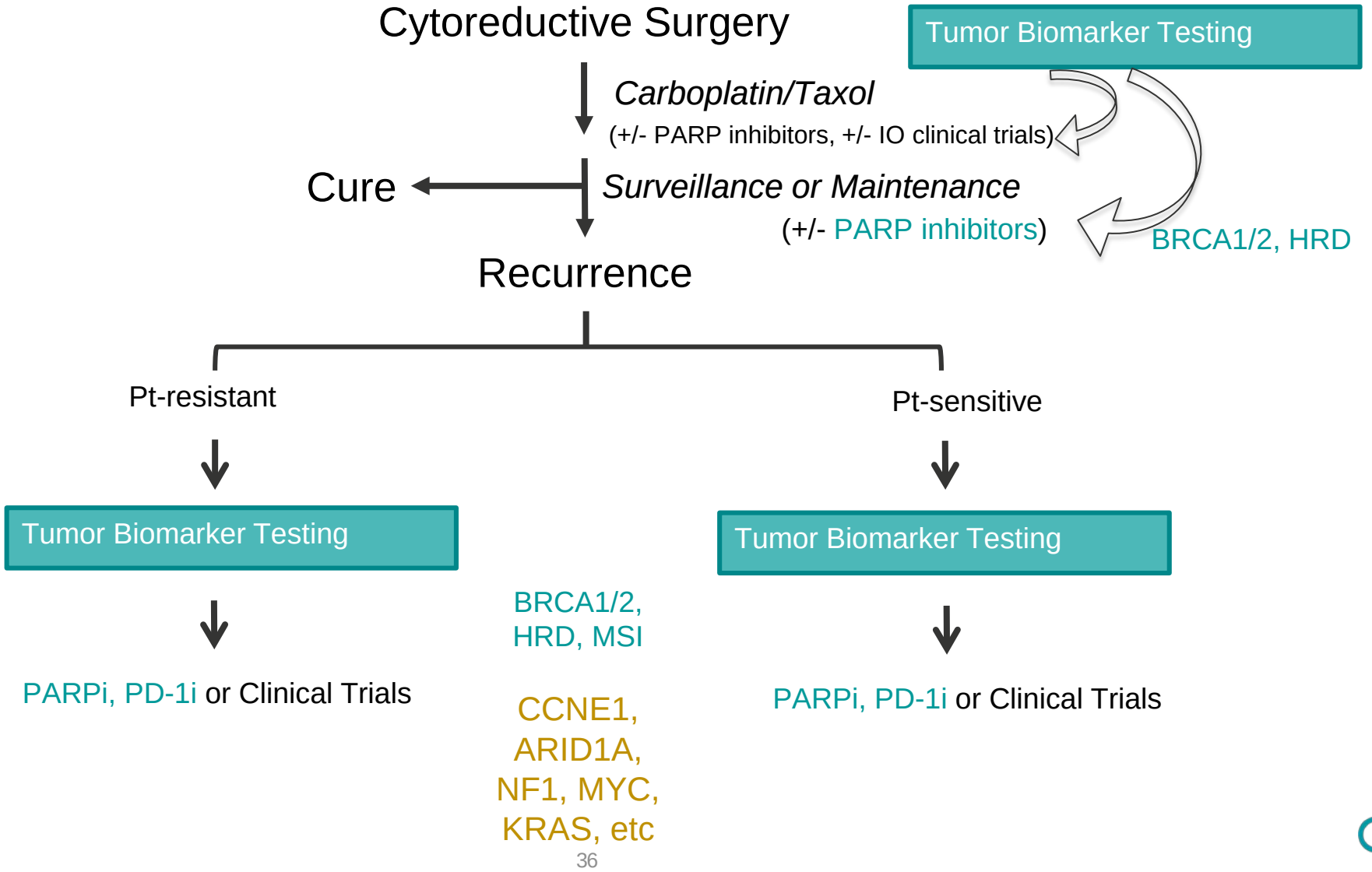
# *Tumor profile/biomarkers can inform selection of approved targeted therapies or clinical trials*



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# Tumor profiling results delivered through an online interactive interpretive report

| DRUGS WITH POTENTIAL BENEFIT | DRUG CLASS | TREATMENT SETTING |
|---|---|---|
| Olaparib, Niraparib, Rucaparib | PARP Inhibitors | NCCN guideline for the treatment of recurrent ovarian cancer |
| Talazoparib | | |
| Talazoparib, PARP Inhibitors | | |
| ATR Inhibitors | ATR Inhibitors | |
| BET Inhibitors | BET Inhibitors | |
| CDK1/2 Inhibitors | CDK1/2 Inhibitors | |


| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ATR Inhibitors | ATR Inhibitors | BRCA1 | NGS | FMI | | - | - | - | DEL | E880* |
| BET Inhibitors | BET Inhibitors | MYC | NGS | FMI | | - | - | - | AMP | 10 |
| CDK1/2 Inhibitors | CDK1/2 Inhibitors | MYC | NGS | FMI | | - | - | - | AMP | 10 |
| WEE1 Inhibitors | WEE1 Inhibitors | TP53 | NGS | FMI | | - | - | - | MUT | R280K |



https://www.youtube.com/watch?v=M4rvqR5QnFE

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# …with links to biomarker information and evidence…

## BRCA1

**Drug:**
Carboplatin, Cisplatin, Oxaliplatin, Olaparib, Niraparib, Rucaparib, PARP Inhibitors

**Test:**
Gene

**Protein Name:**
Breast cancer 1 (Breast and ovarian cancer susceptibility gene)

**Function:**
Maintains genome stability by enabling repair of double stranded DNA breaks by homologous recombination

### CARBOPLATIN, CISPLATIN, OXALIPLATIN

**What clinical and/or pre-clinical evidence supports this interpretation?**

**Clinical:** Germline deleterious mutations in BRCA1 are associated with platinum sensitivity in ovarian cancer patients.

**References**

Yang D, Khan S, Sun Y, et al. (2011) Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA 306(14):1557-65
http://www.ncbi.nlm.nih.gov/pubmed/21990299

Gallagher DJ, Konner JA, Bell-McGuinn KM, et al. (2011) Survival in epithelial ovarian cancer: a multivariate analysis incorporating BRCA mutation status and platinum sensitivity. Ann Oncol 22(5):1127-32.
http://www.ncbi.nlm.nih.gov/pubmed/21084428

### OLAPARIB, NIRAPARIB, RUCAPARIB, PARP INHIBITORS

**What clinical and/or pre-clinical evidence supports this interpretation?**

**Clinical:** Ovarian cancer patients with germline or somatic BRCA1 mutations had improved outcomes following treatment with PARP

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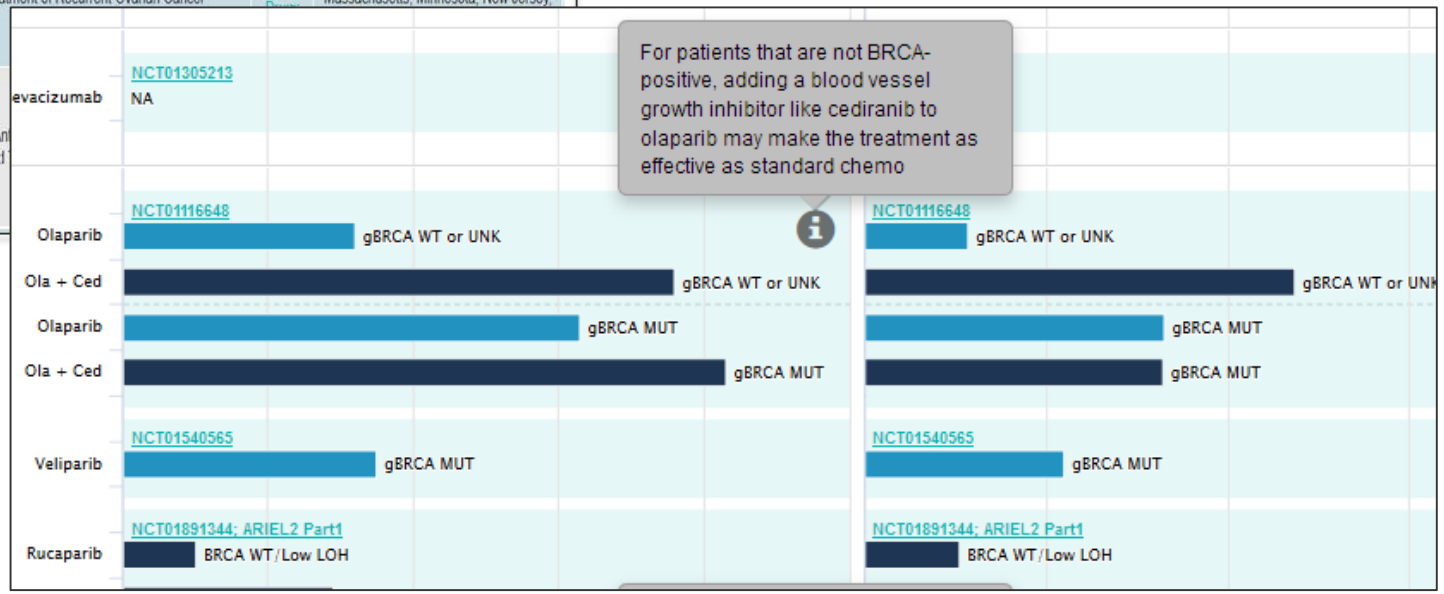
# .....linked to matching clinical trials....

| Clinical Trial | Phase | Eligible Participant | Official Title | Drugs in Trial | Location |
|---|---|---|---|---|---|
| NCT02446600 | III | Platinum sensitive high grade serous or endometrioid ovarian cancer or germline BRCA1/2-mutated ovarian cancer | A Phase III Study Comparing Single-Agent Olaparib or the Combination of Cediranib and Olaparib to Standard Platinum-Based Chemotherapy in Women With Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer | View Drugs | Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Illinois, Iowa, Kansas, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Texas, Utah, Washington, West Virginia, Wisconsin |
| NCT02345265 | II | Recurrent high grade serous or endometrioid ovarian cancer or germline BRCA1/2-mutated ovarian cancer | A Phase 2 Study of Olaparib and Cediranib for the Treatment of Recurrent Ovarian Cancer | View | Arizona, California, Florida, Maryland, Massachusetts, Minnesota, New Jersey, |
| NCT02484404 | I/II | Advanced solid tumors (phase I) and Platinum resistant or refractory or > 2 platinum regimens for ovarian cancer (phase II) | Phase I/II Study of the Anti-Programmed Death Ligand-1 An Combination With Olaparib or Cediranib for Advanced Solid | | |

# and results...




# ...and offer of a phone consultation for more information



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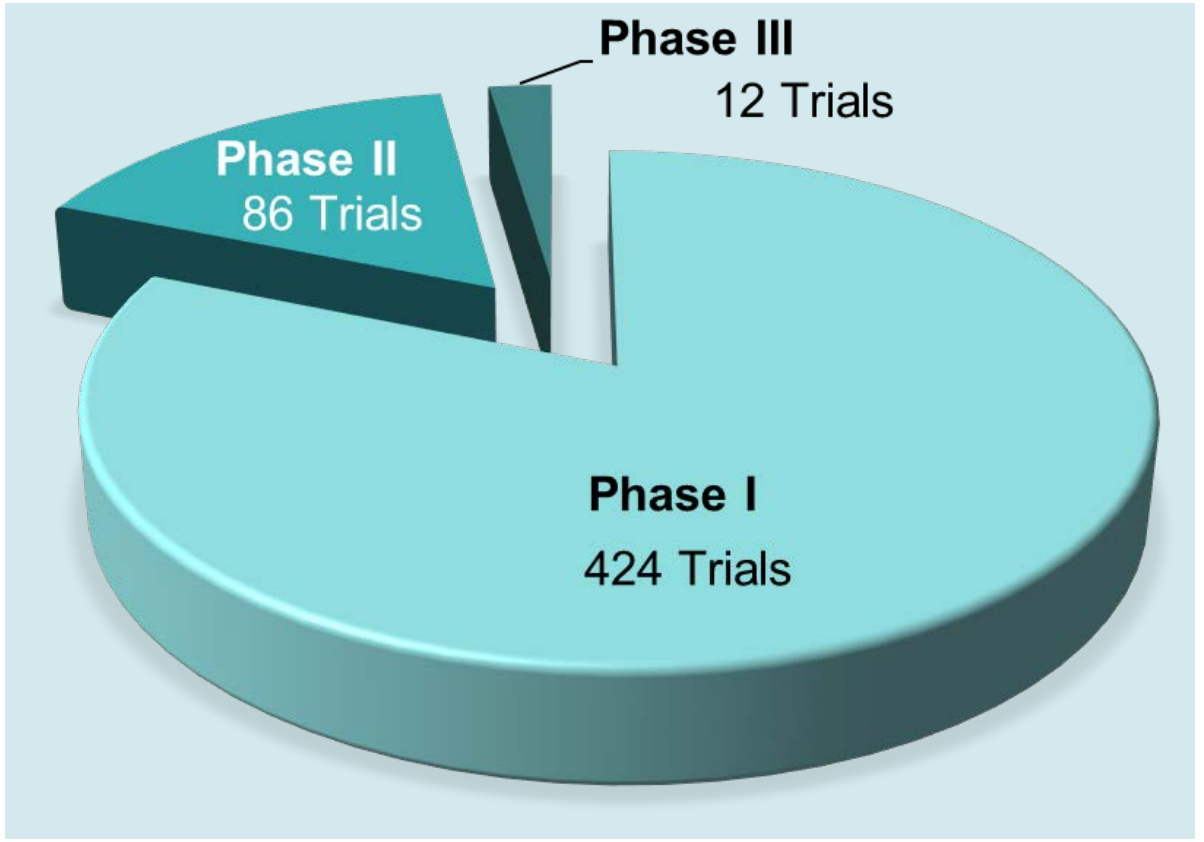
# Search 500+ Trials Available to Ovarian Cancer Patients

## Match to Clinical Situation, Tumor Biomarkers, Location and More


**Prioritize**

50% (262) linked to reported results for drugs in the same or another trial

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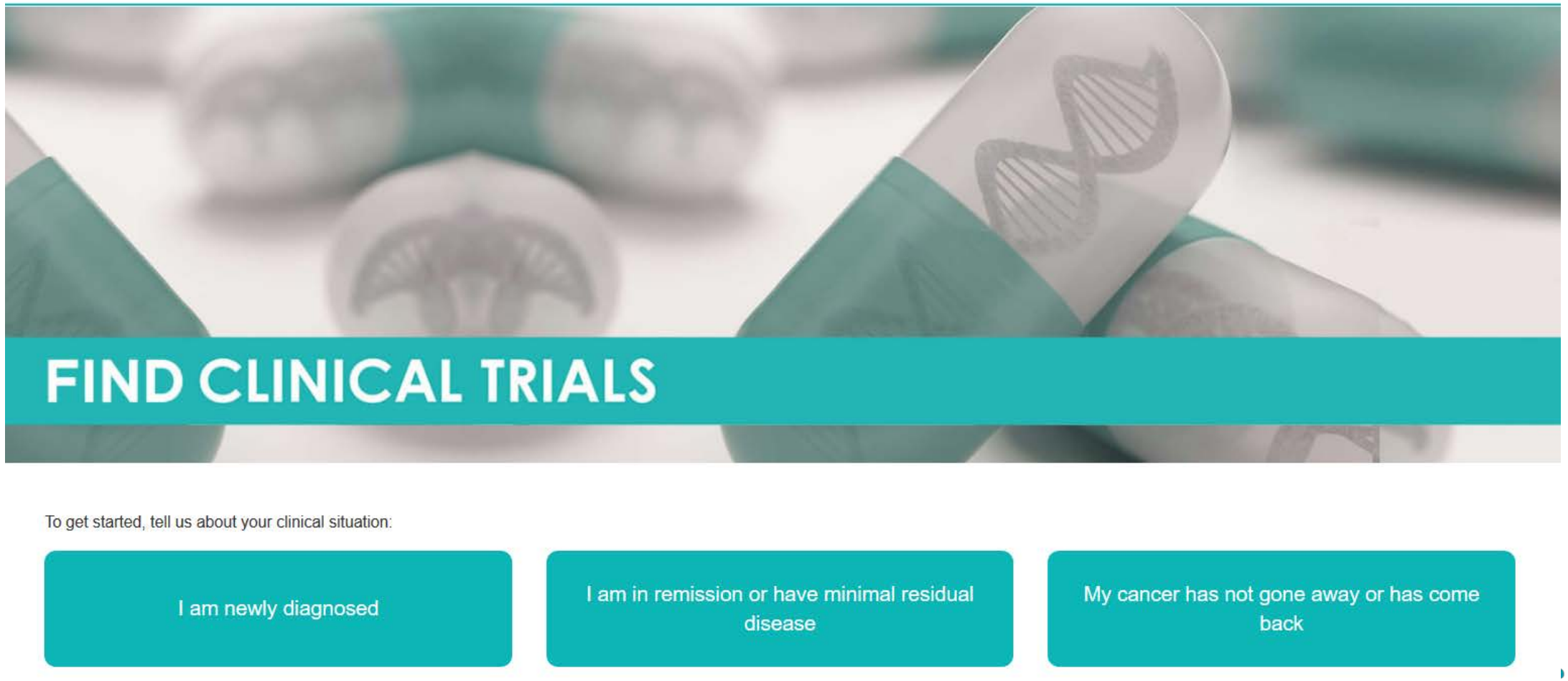
# *Ovarian cancer-specific clinical trial finder helps identify trials for which patient is likely to be eligible*




https://forms.clearityfoundation.org/find-clinical-trials/



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# *User answers questions about their cancer, treatments, platinum response, BRCA status, tumor profile, etc*

I want to enter information about my cancer and treatments

Select if you know the histology type of your cancer.

Which drugs did you get in your first treatment regimen?

Which drugs did you get after your cancer came back or progressed?

How many different chemotherapy regimens have you had?

How long did it take for your cancer to come back (or grow) after your last platinum treatment?

Do you have "measurable" or "evaluable" disease?

Select if you have (or had) brain metastases or a cancer other than ovarian.

I want to enter information about my genetic testing (e.g, BRCA) and/or tumor testing results

I want to filter the trials based on location, phase of development, or drug name, category or target

SEARCH

# *Search output includes a link to Clinical Trials.gov as well as any reported drug effectiveness results*

SAVE TRIALS

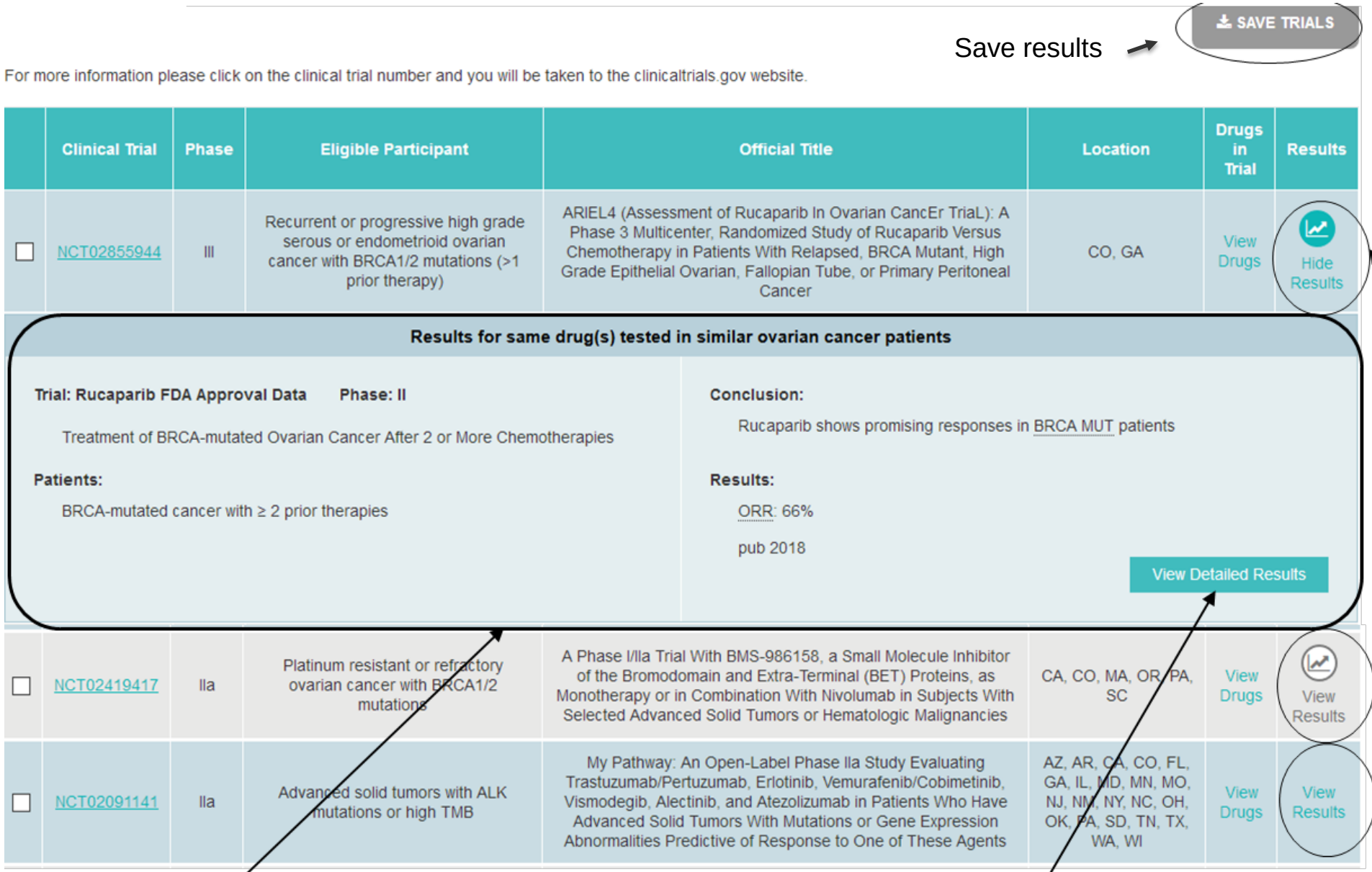
For more detailed information please click on the clinical trial number and you will be taken to the clinicaltrials.gov website.

For a key to the icons and text used in the Results column, please click here.

To learn more about our trial annotation process, results assignments, and the criteria used to highlight drugs with promising results, please click here.

| | Clinical Trial | Phase | Eligible Participant | Official Title | Location | Drugs in Trial | Results |
|---|---|---|---|---|---|---|---|
| ☐ | NCT02855944 | III | Recurrent or progressive high grade serous or endometrioid ovarian cancer with BRCA1/2 mutations (>1 prior therapy) | ARIEL4 (Assessment of Rucaparib In Ovarian CancEr TriaL): A Phase 3 Multicenter, Randomized Study of Rucaparib Versus Chemotherapy in Patients With Relapsed, BRCA Mutant, High Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer | CO, GA | View Drugs | View Results |
| ☐ | NCT03398655 | III | Platinum resistant ovarian cancer | A Randomized, Controlled, Double-Arm, Double-Blind, Multi-Center Study of Ofranergene Obadenovec (VB-111) Combined With Paclitaxel vs. Paclitaxel Combined With Placebo for the Treatment of Recurrent Platinum-Resistant Ovarian Cancer | AZ, CA, CT, FL, GA, IL, IN, KS, KY, LA, MD, MA, MI, NH, NJ, NM, NY, NC, ND, OH, OK, PA, SC, SD, TN, TX, VT, WI | View Drugs | View Results |
| ☐ | NCT04209855 | III | Platinum resistant or refractory FRalpha+ high grade serous ovarian cancer, excluding primary platinum-refractory | MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers With High Folate Receptor-Alpha Expression | AZ, CO, FL, IL, LA, MD, MA, MI, MN, NJ, NC, OH, OR, TX, VA, WA, WV | View Drugs | View Results |
| ☐ | NCT04296890 | III | Platinum resistant or refractory FRalpha+ ovarian cancer, excluding primary platinum-refractory, with prior bevacizumab | SORAYA: A Phase 3, Single Arm Study of Mirvetuximab Soravtansine in Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers With High Folate Receptor-Alpha Expression | NJ | View Drugs | View Results |

# Results summarized and promising drug trials are highlighted

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# *Psychosocial Support Program*

**Provides customized support based on individual needs**

STEPS THROUGH OC

For Patients, Survivors, Active Caregivers

One on one counseling based on emotional needs identified in “OC Coordinates” assessment



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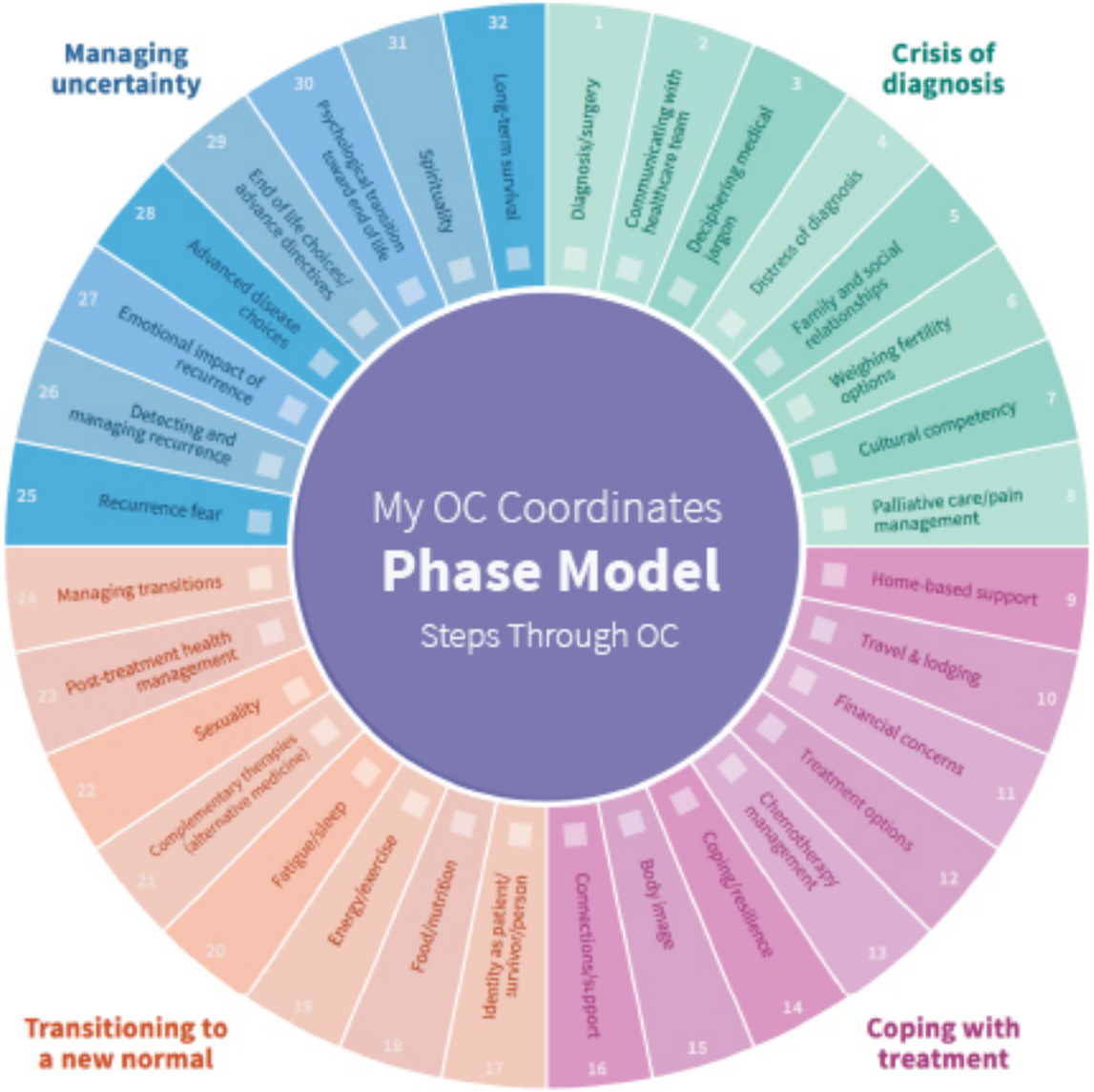


**OC Coordinates**
32-point survey

**OC Counseling Support**
10 sessions over the course of six months and available on an as-needed basis after six months

**Education** and other **OC resources** are available as needed, by request

**Supplemental support** includes a “Graduate Group” and Ambassador program

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# *Summary*

- Ovarian cancer has multiple histology types and molecular characteristics that differ for each tumor so profiling/biomarker testing can provide insights into optimal treatment approaches
- New treatments (i.e., PARP inhibitors) have been approved based on such biomarkers (i.e., BRCA, HRD) and will likely increase overall survival
- New options are also available for those with low grade serous (i.e., Trametinib) and some with clear cell and endometrioid histology (i.e., MSI+, Pembrolizumab)
- Novel therapies directly targeted to the tumor (e.g., antibody drug conjugates) have fewer side effects than cytotoxic drugs and are showing promise in clinical trials
- Our psychosocial support program (STOC) provides one-on-one counseling to anyone with ovarian cancer and their family members
- Clearity stays current on new treatment approaches and provides individualized information about those options on our website and through direct interactions with anyone who come to us for support



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# THANK YOU!!!

# QUESTIONS?

**Committed** to science,

**devoted** to patients,

Clearity is your **trusted partner** for the journey.

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***Treatment Decision Support Program***
*https://www.clearity.org/treatmentdecisionsupport/*

***Steps Through OC***
***Psychosocial Support Program***

*https://www.clearity.org/psychosocial-support/*



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