New Developments in Ovarian Cancer

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Outline

- Recent and ongoing developments in ovarian cancer
- PARP inhibitors
- Antiangiogenic drugs
- Immunotherapy
- Clinical trials--Are clinical trials for you?

The News

- **Dec 19, 2014**: The U.S. FDA granted accelerated approval to **olaparib** for women with recurrent OC with defective BRCA genes (>3 lines).
- **Dec 2014**: US FDA approved **bevacizumab** for recurrent platinum resistant OC in combination with chemotherapy
- **Dec 19 2016**: US FDA approved **rucaparib** for women with recurrent ovarian cancer associated with defective BRCA genes (>2 lines).
- **December 2016**: FDA approved **bevacizumab** for recurrent platinum sensitive OC in combination with Ctx
- **March 2017:** US FDA approves **niraparib** for recurrent OC after response to platinum
- **August 2017**: US FDA approved **olaparib** for recurrent OC after response to platinum
- **October 2018:** US FDA approved **olaparib** for upfront treatment of OC associated with BRCA1 or 2 mutations

The news

- **Moment of celebration**!—these approvals follow a long drought period(>20 years)

  -1995: liposomal doxorubycin

  -1996: topotecan

  -2006: gemcitabine

- The new drug approvals follow **decades of basic science and clinical research**.

- **Long way forward!**

  -Bring these discoveries to upfront treatment of ovarian cancer!

  -Find a cure.

  -Find new pathways to target refractory, resistant tumors.

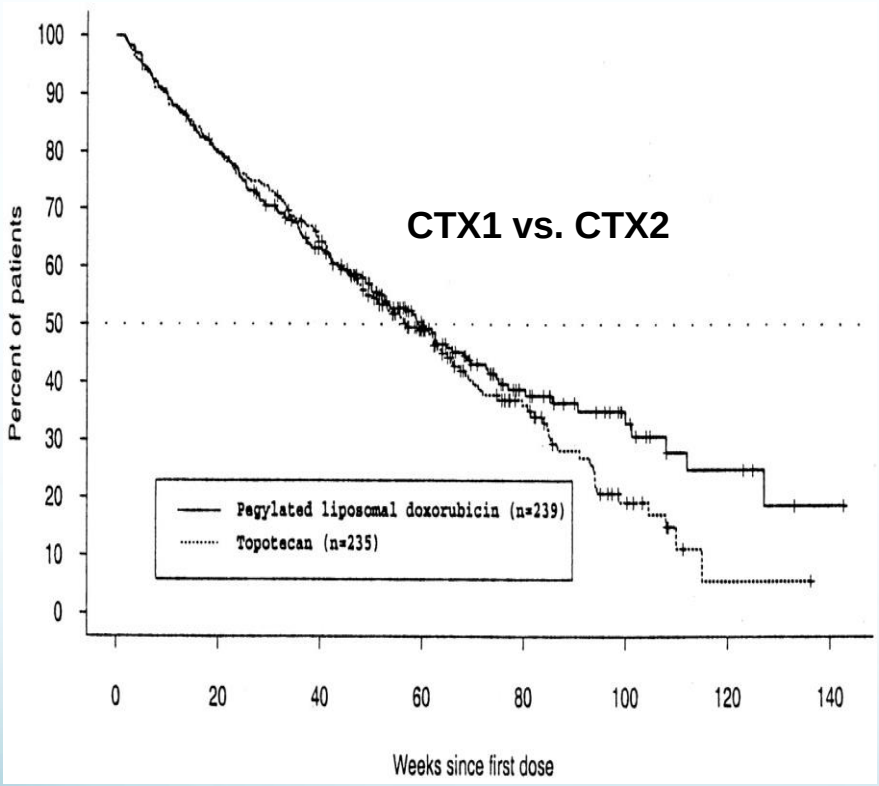
The expectations

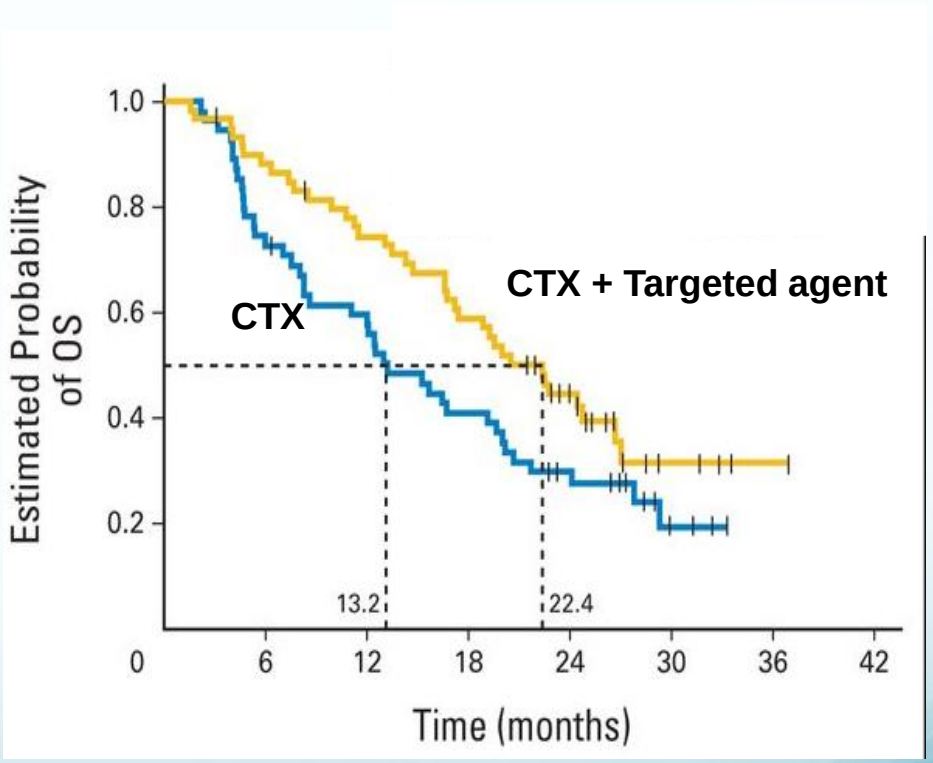
- More data are expected **THIS MONTH** on use of PARP inhibitors as maintenance therapy after the upfront treatment of ovarian cancer with surgery and chemotherapy—Look out for new information

  --For BRCA mutated tumor AND non-mutated

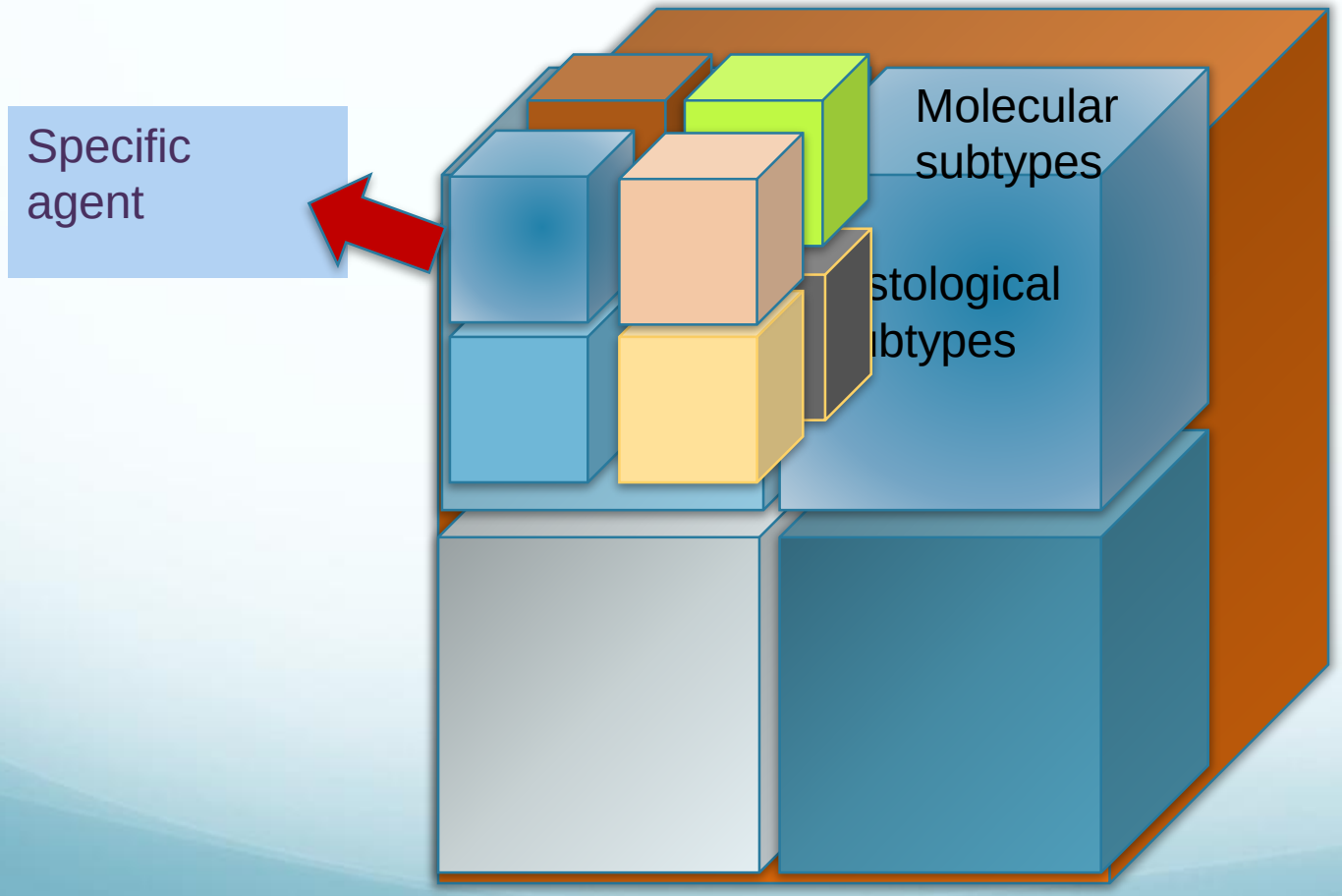
  --In combination with anti-angiogenic agents.

A change in the course of the disease—longer survival!

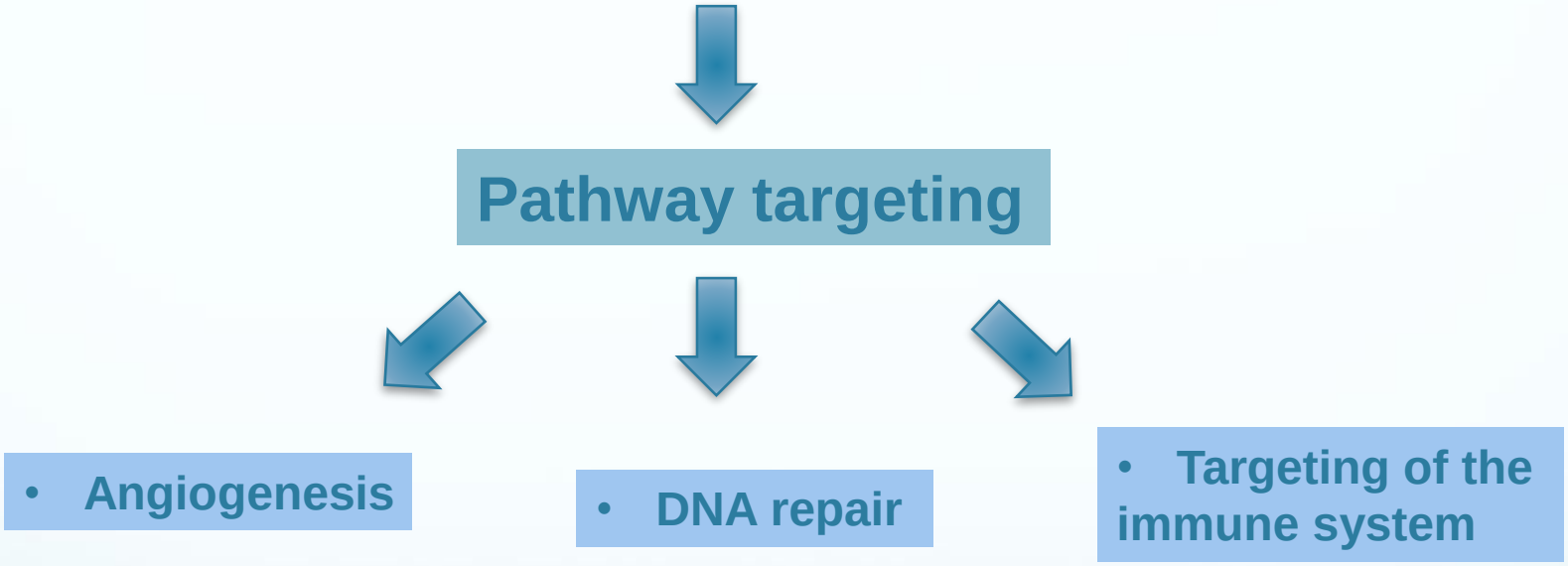




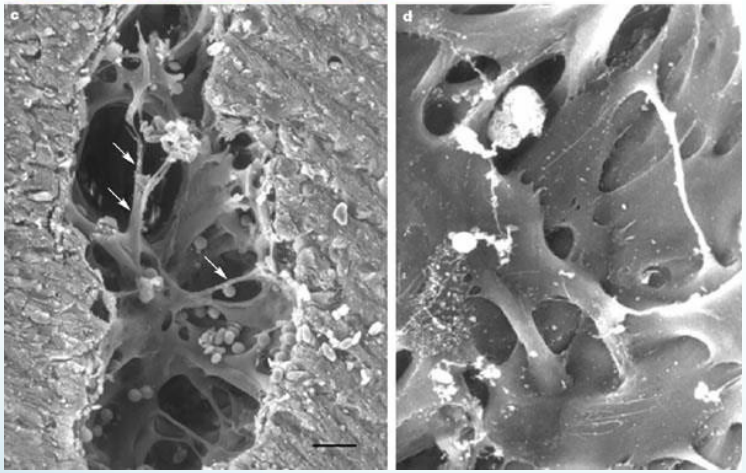
Is Personalized Treatment Achievable in Gynecologic Cancer?



Mutation driven therapy in ovarian cancer is challenging because tumors are heterogenous

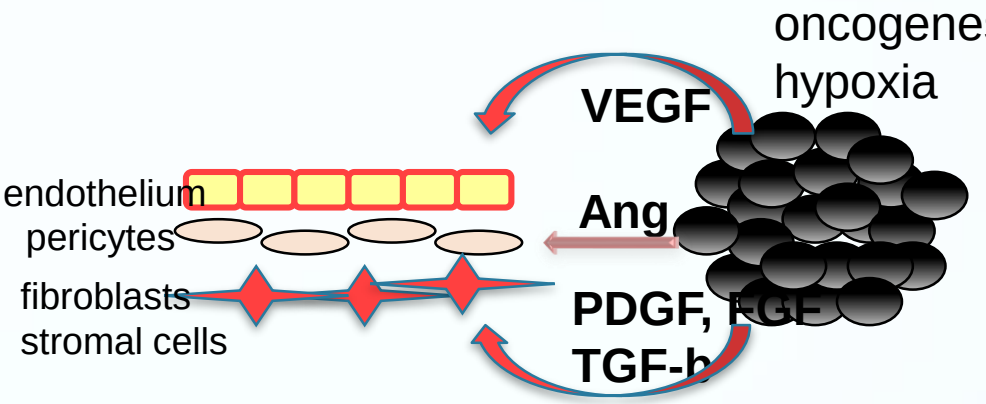


Angiogenesis in Ovarian Cancer

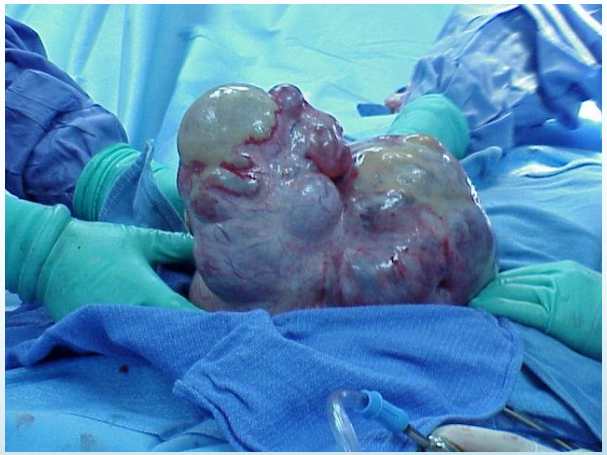


Abnormal vascular structures form and nurture tumor growth.

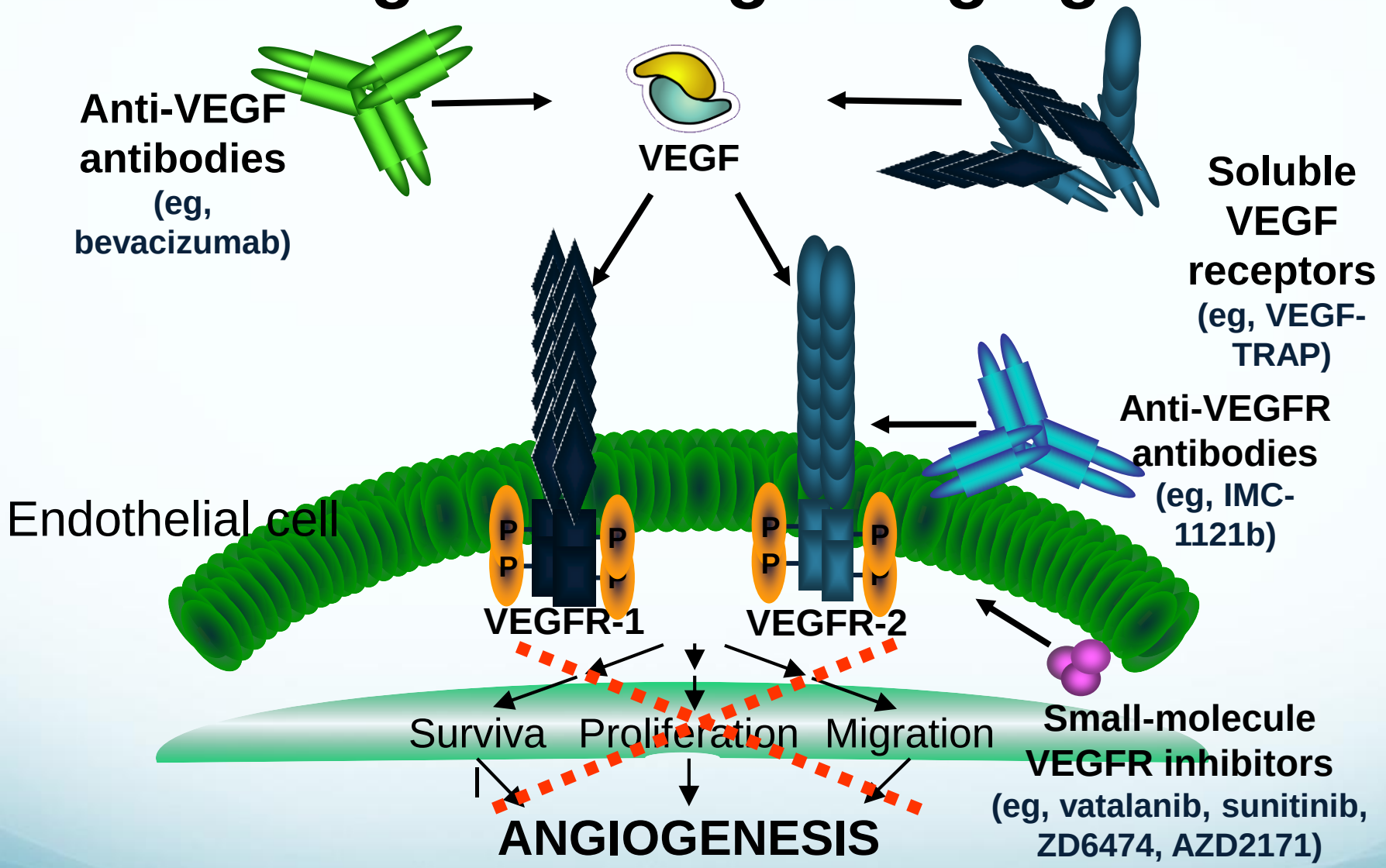
Carmeliet and Jain, Nature, 2000



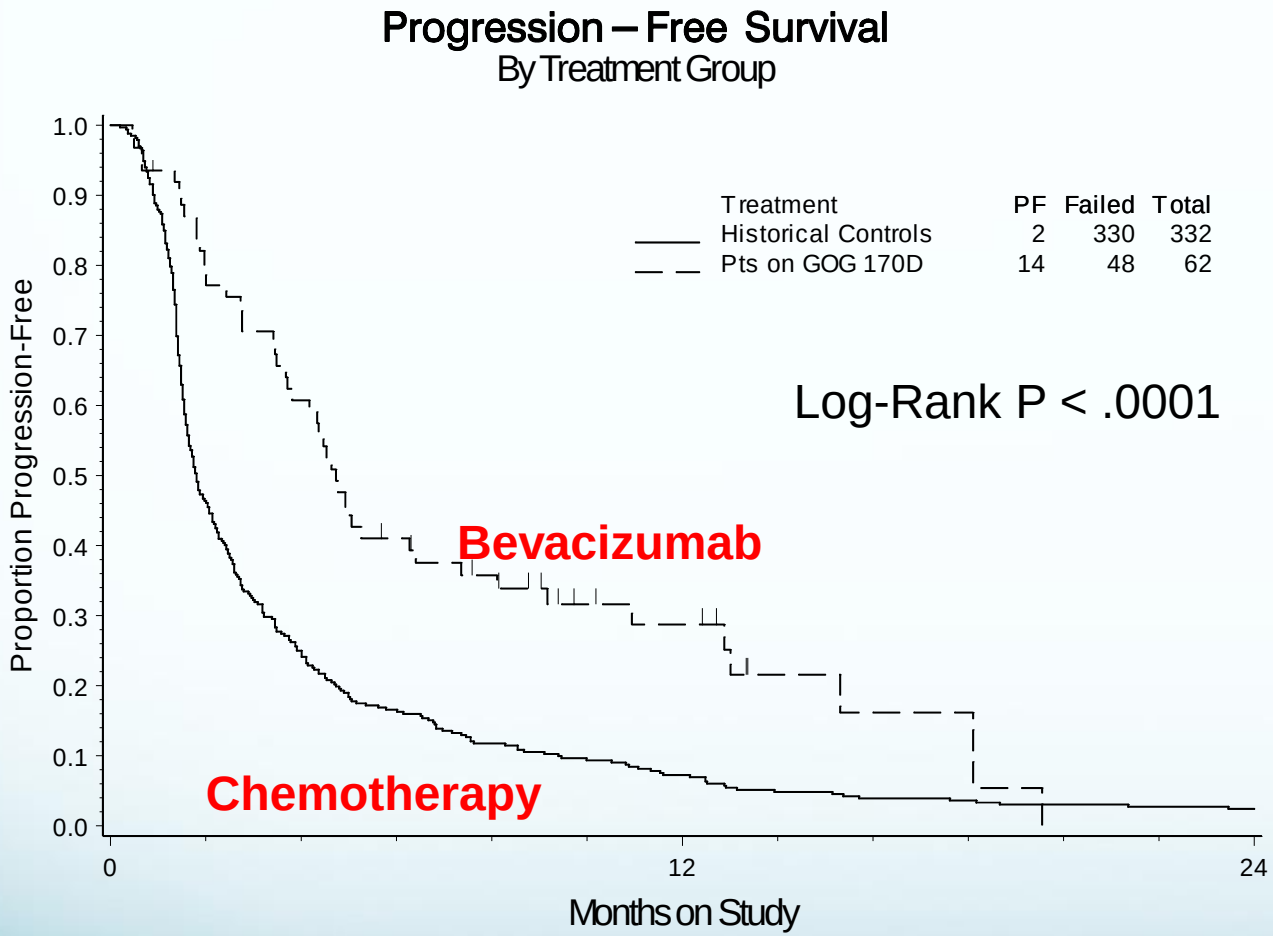
Angiogenesis regulation



Strategies to target angiogenesis



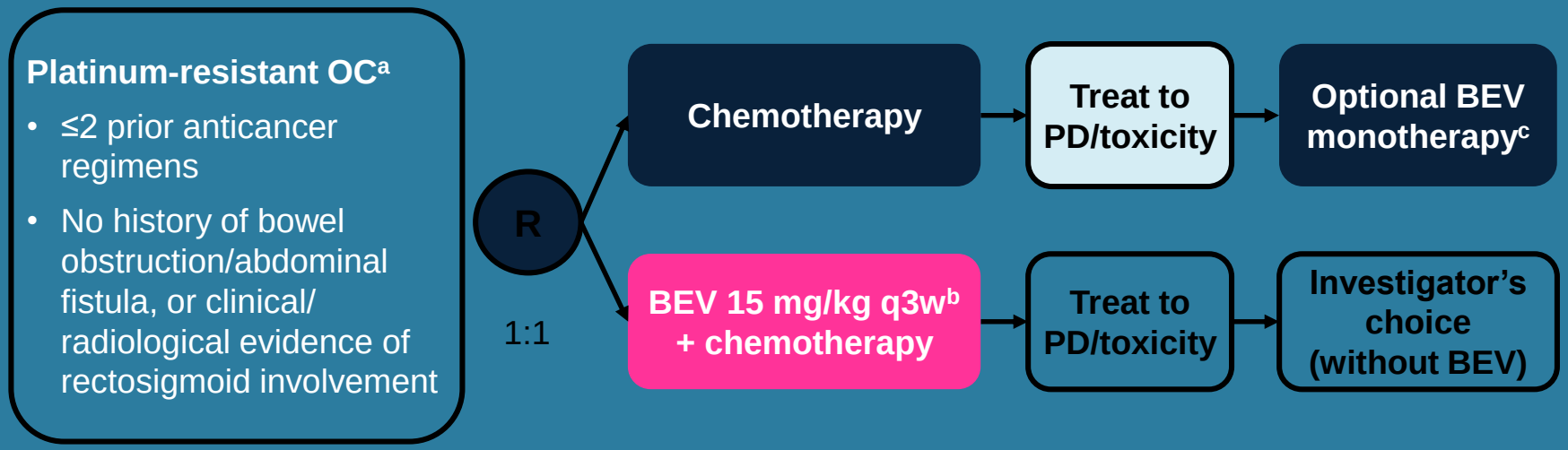
Bevacizumab single agent in recurrent ovarian cancer GOG 170D



N=62
Response Rate: 21% (2CR, 11PR)
6 months PFS: 40.7%
Median response duration 10 months

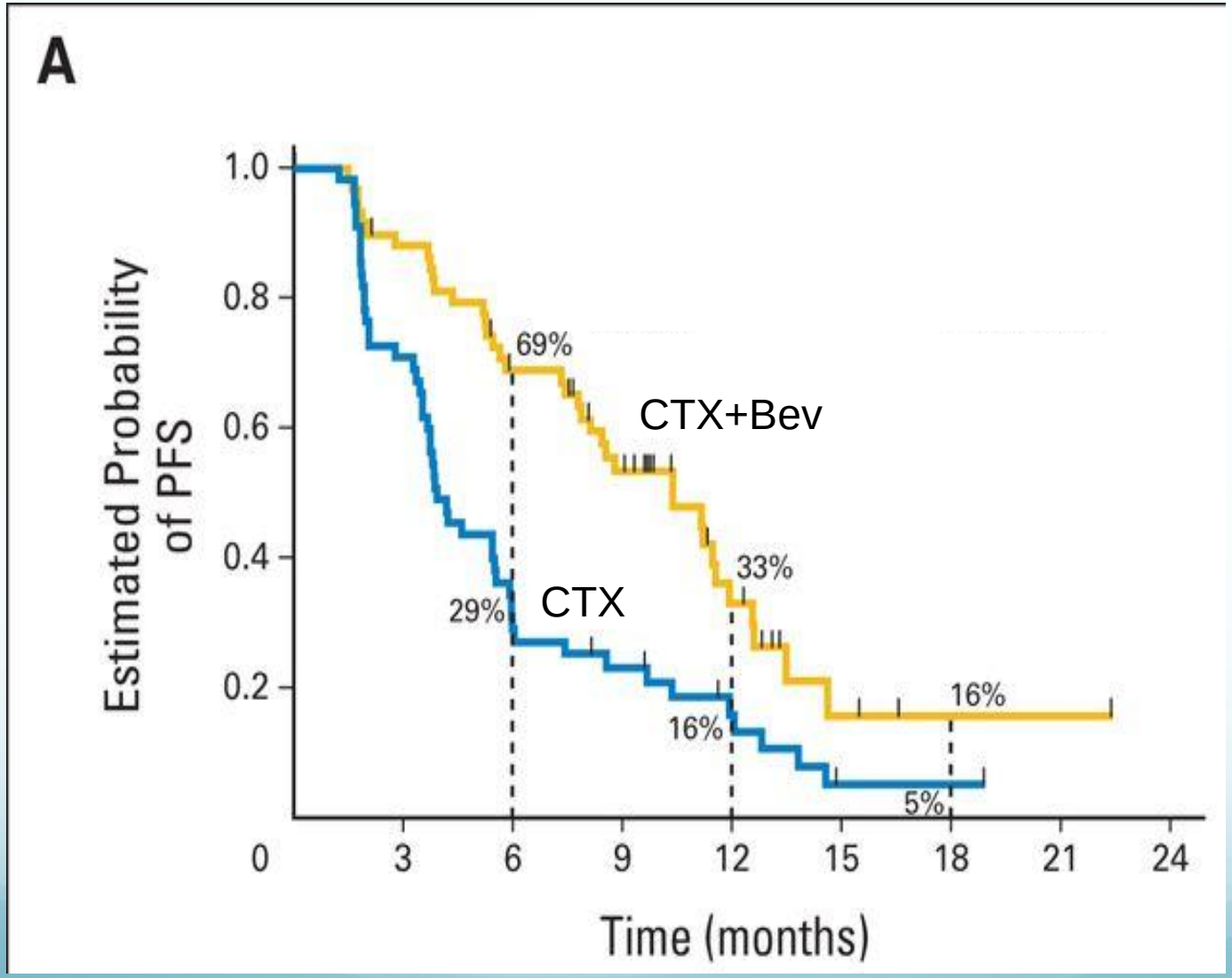
Burger, JCO, 2007

Bevacizumab in combination with chemotherapy



Eric Pujade-Lauraine, JCO, 2014 and 2015

Bevacizumab for ovarian cancer—survival improvement

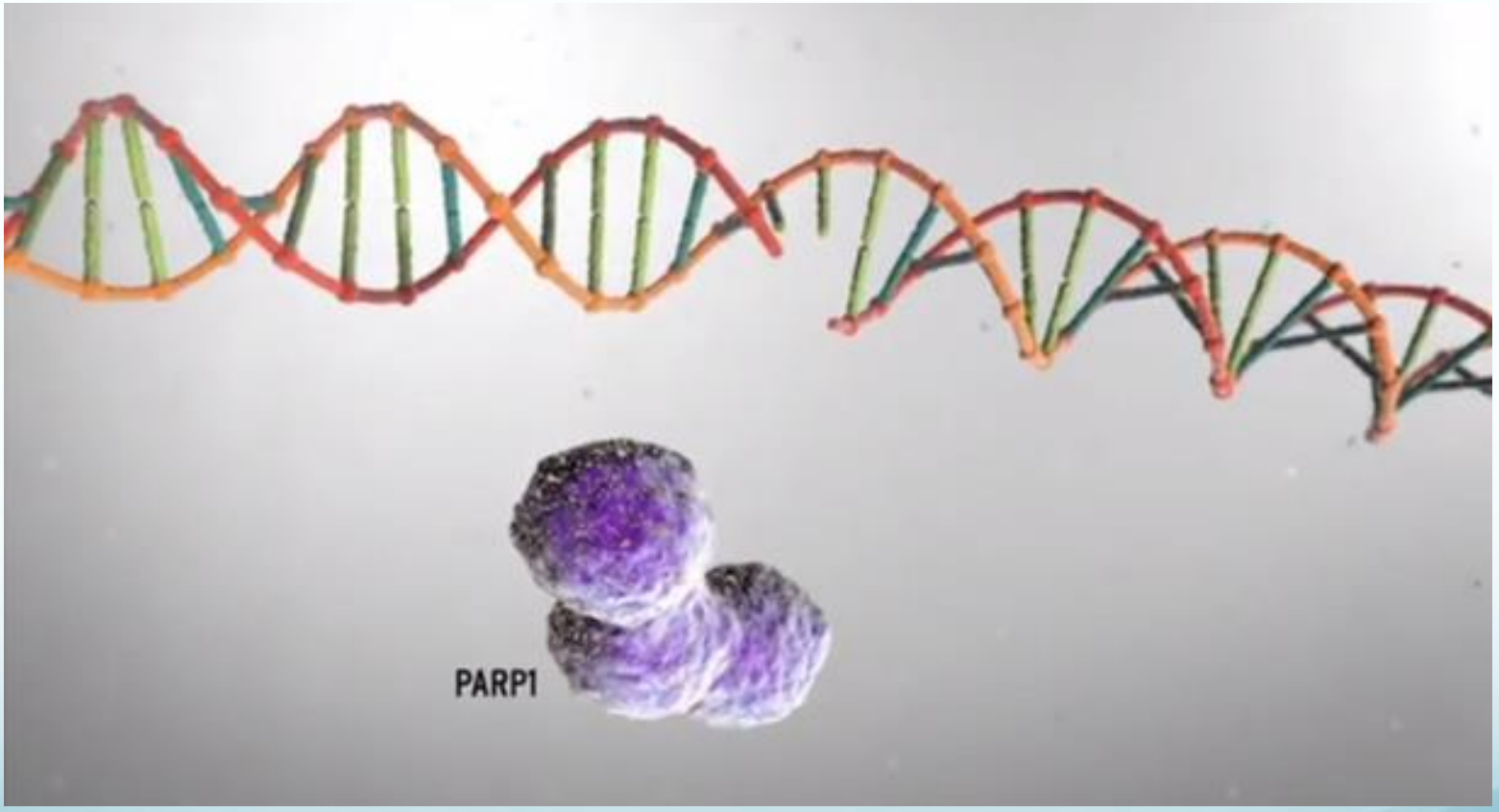


Andres M. Poveda et al. JCO 2015;33:3836-3838

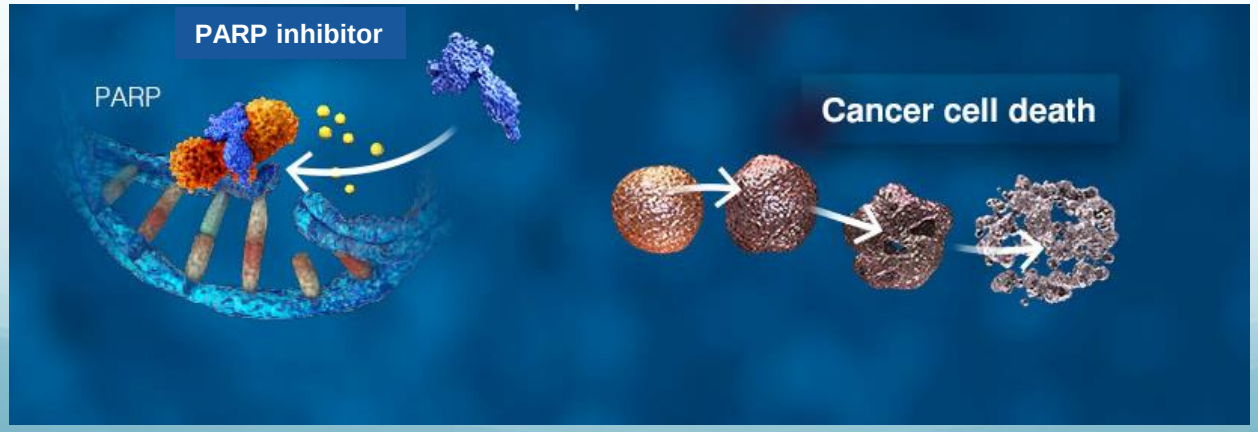
Bevacizumab in ovarian cancer take home message

- Active agent in recurrent ovarian cancer
- Works as a single agent and in combination with chemotherapy
- Induces responses and stabilizes disease
- Long remissions
- Controls ascites
- Toxicities: high blood pressure, protein spill in the urine, stroke, blood clots, and bowel perforation

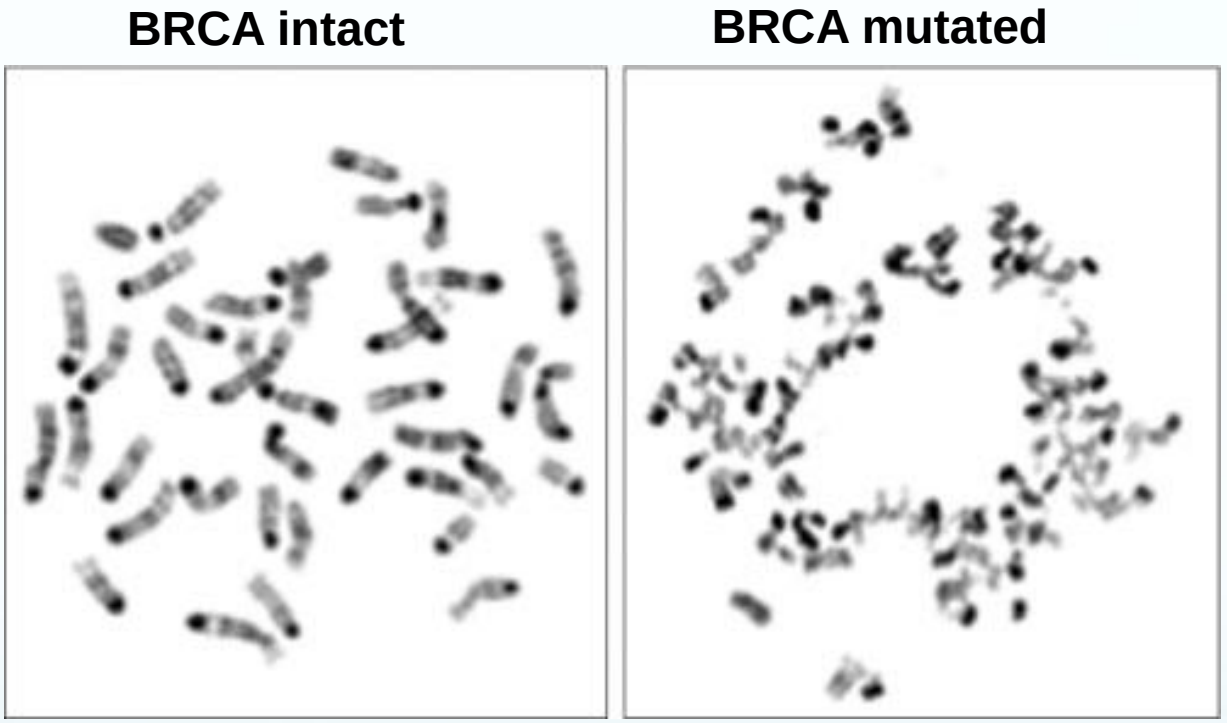
DNA Repair—What is PARP?



PARP enzyme repairs single strand DNA breaks



PARP inhibition in BRCA deficient cells



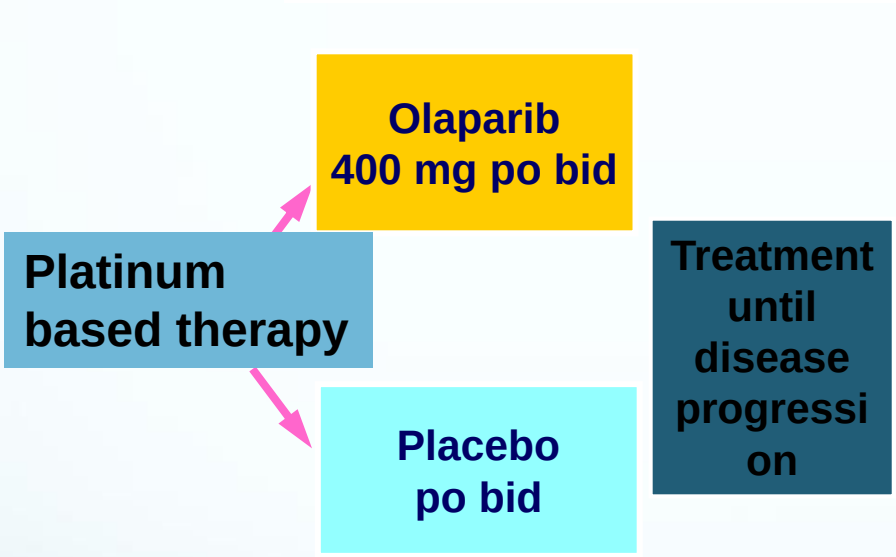
BRCA2-mutant cells treated with a PARP inhibitor undergo massive chromosomal crisis due to the defect in DNA repair mechanisms.

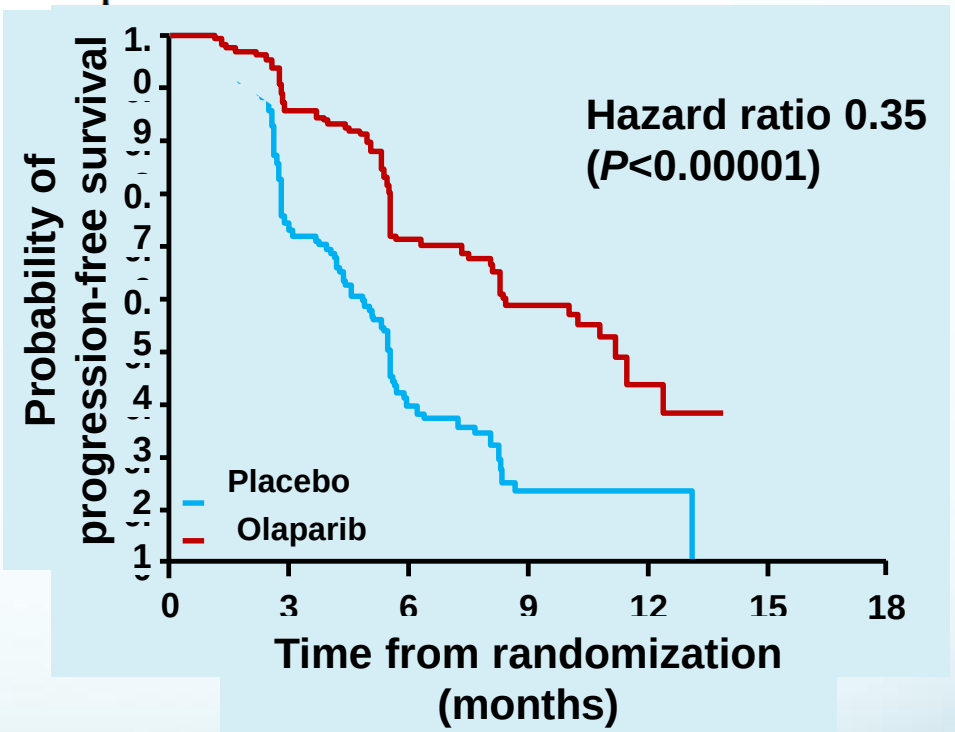
Banerjee, Nature Reviews Clinical Oncology, 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

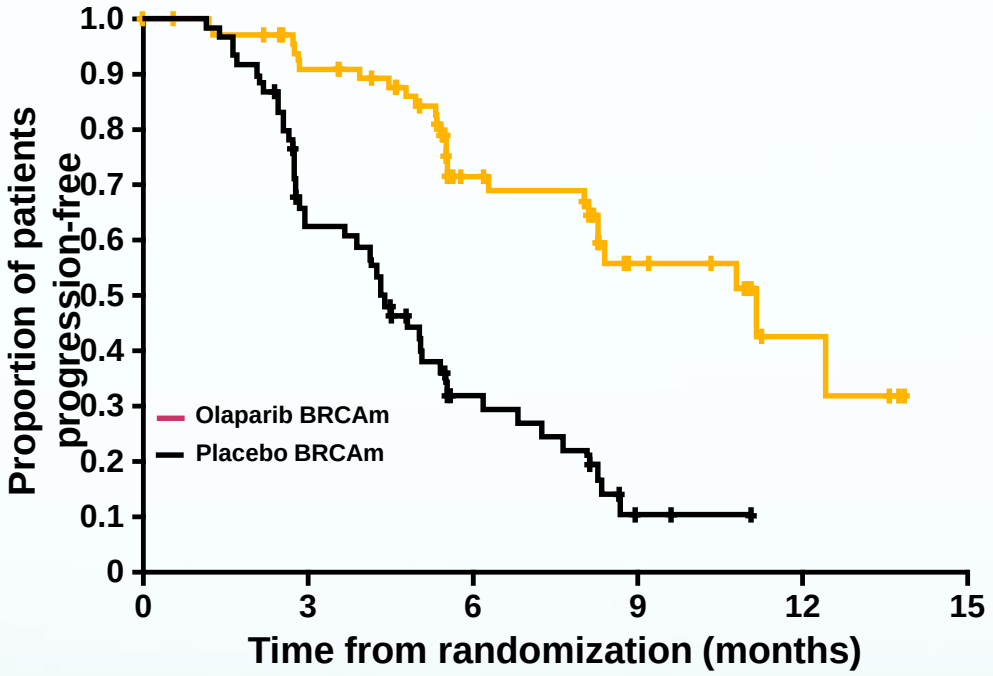




- Olaparib was the first approved PARP inhibitor
- Side effects include: fatigue, anemia, nausea
- Recent conversion from capsules to tablets: easier to tolerate

Ledermann J *et al*. *N Engl J Med* 2012;366:1382–1392

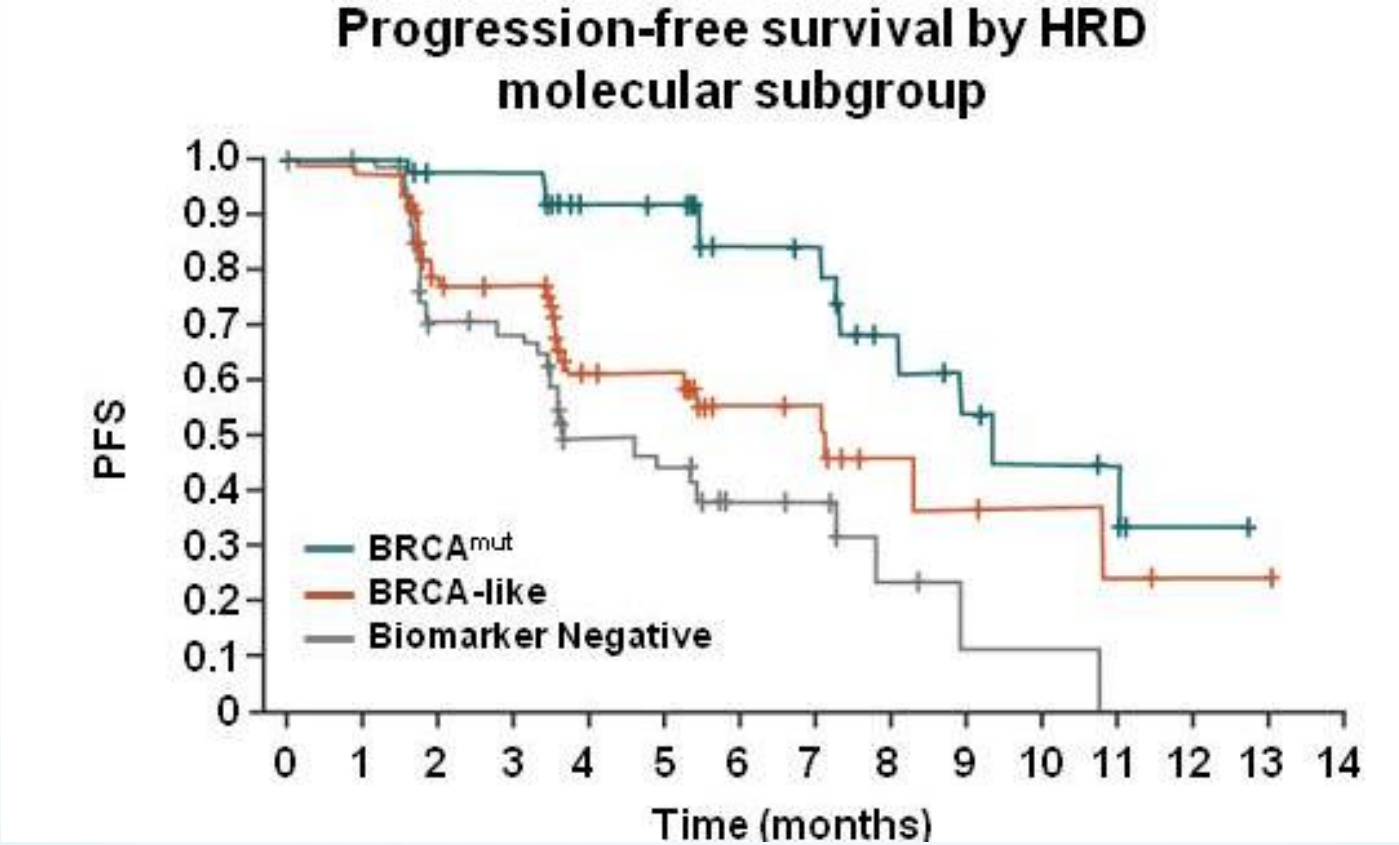
Survival by BRCA mutated status



Highest benefit in patients with BRCA mutated tumors

Lederman, NEMJ, 2014
Lederman, Lancet Oncology 2016

Rucaparib in ovarian cancer



- Second PARP inhibitor to be approved in BRCA mutated tumors
- Best effects observed in BRCA mutated tumors, but benefit also noted in patients identified using a genetic test.
- Impressive response rates in tumor with BRCA mutations (80%)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

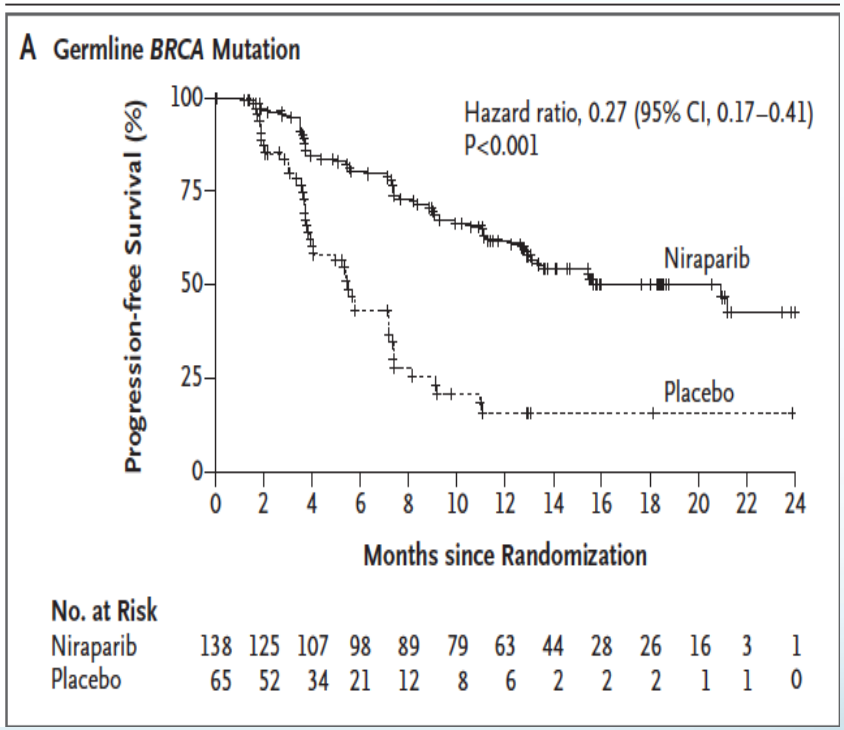
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

Platinum based therapy

Niraparib 300 mg po qd

Placebo po qd

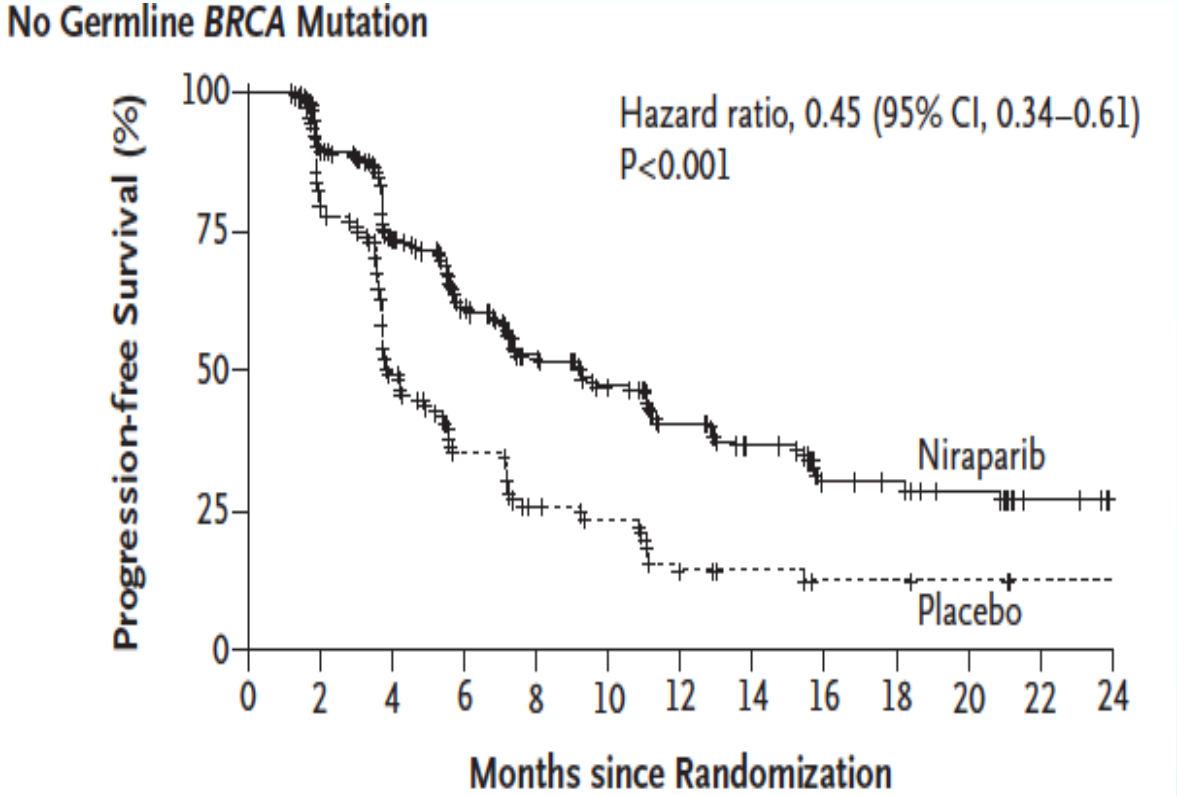
Treatment until disease progression



- Third PARP inhibitor to be approved
- Side effects include low blood counts, fatigue
- Effects observed in BRCA mutated patients, but also in ALL patients

Mirza, NEJM, 2016

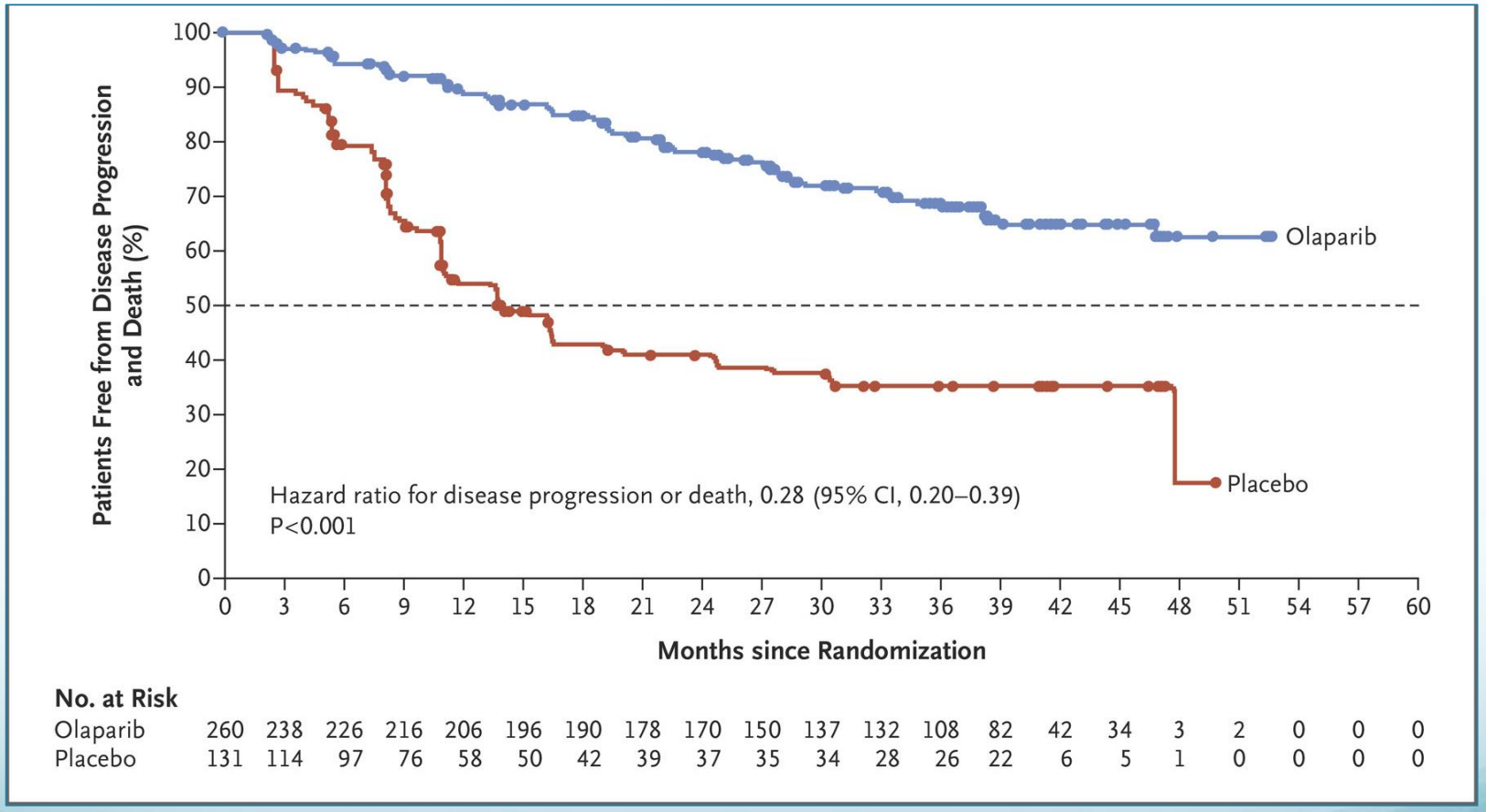
PARP inhibitors beyond BRCA mutations



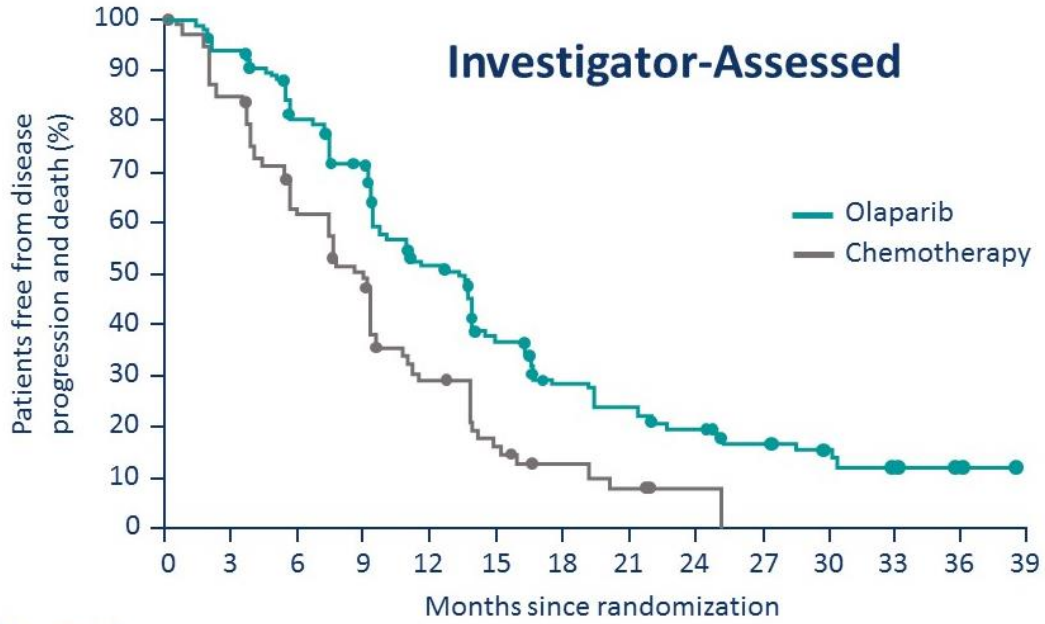
Unexpected results show positive effects of niraparib in tumors without BRCA mutations; leading to its unrestricted FDA approval

Mirza, NEJM, 2016

PARP Inhibitors in the upfront setting



PARP inhibitors vs. Chemotherapy SOLO 3 trial



	Olaparib (n=178)	Chemotherapy (n=88)
PFS events, n (%)	123 (69)	63 (72)
Median PFS, months	**13.2**	**8.5**
HR (95% CI), *P* value	**0.49 (0.35, 0.70); *P*<0.001**	

Ongoing PARP inhibitors Clinical Trials

- **GOG3005:** Carboplatin + paclitaxel +/- veliparib after surgery (No BRCA mutation selection)—accrual completed

- **NRG GY004**: Olaparib, olaparib + cediranib vs. standard of care chemotherapy for platinum sensitive recurrent ovarian cancer

- **NRG GY005: O**laparib, olaparib + cediranib vs. standard of care chemotherapy for platinum resistant ovarian cancer

- **FIRST** trial: Niraparib in upfront setting (BRCA mutated and not mutated)

- **PAOLA** trial: olaparib and bevacizumab in the upfront setting (BRCA mutated and not mutated)
- **Other combinations**: PARP inhibitors and immunotherapy

PARP inhibitors take home message

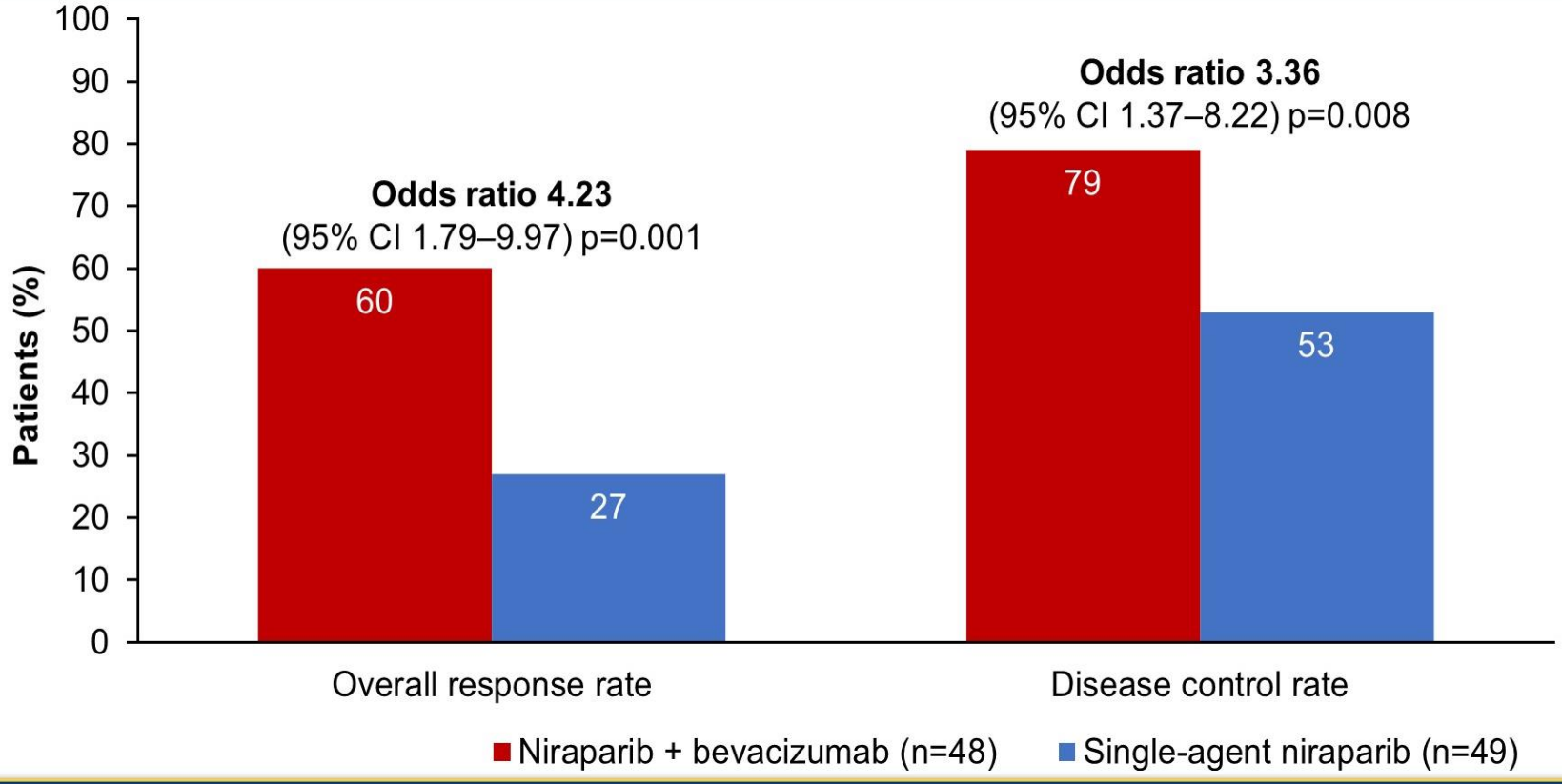
- New class of drugs very active in ovarian cancer
- Three inhibitors approved: olaparib, rucaparib and niraparib
- Slight differences in indication profiles (active treatment vs. maintenance treatment)
- Differences in toxicity profiles
- Highest activity in patients carrying BRCA mutations
- A new test may become available to identify patients who could respond to PARP inhibitors in the absence of a BRCA mutation.
- Research is ongoing

The future is here

- FIRST and PAOLA Trial being reported this weekend

at ESMO in Barcelona—anticipation is high!

Combination niraparib+bevacizumab vs. niraparib alone in ovarian cancer

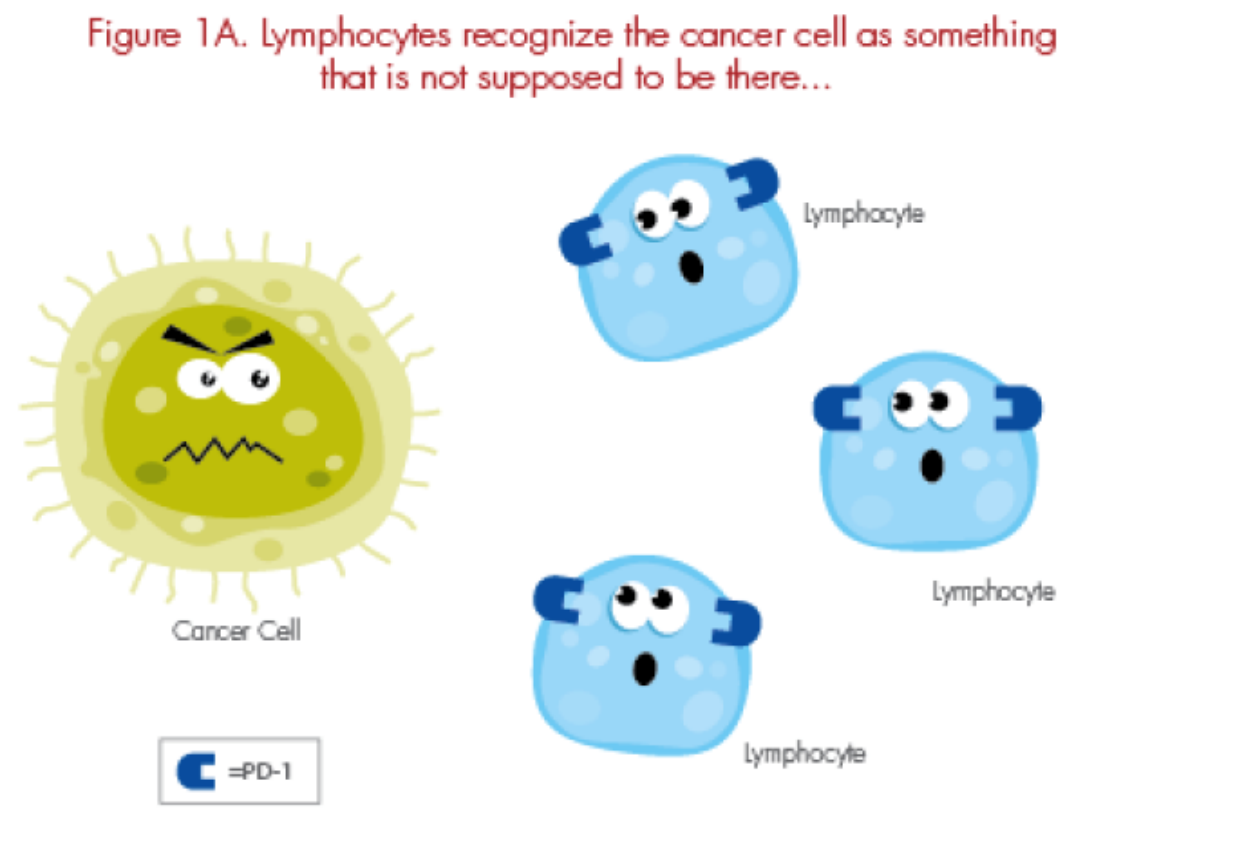


ASCO 2019

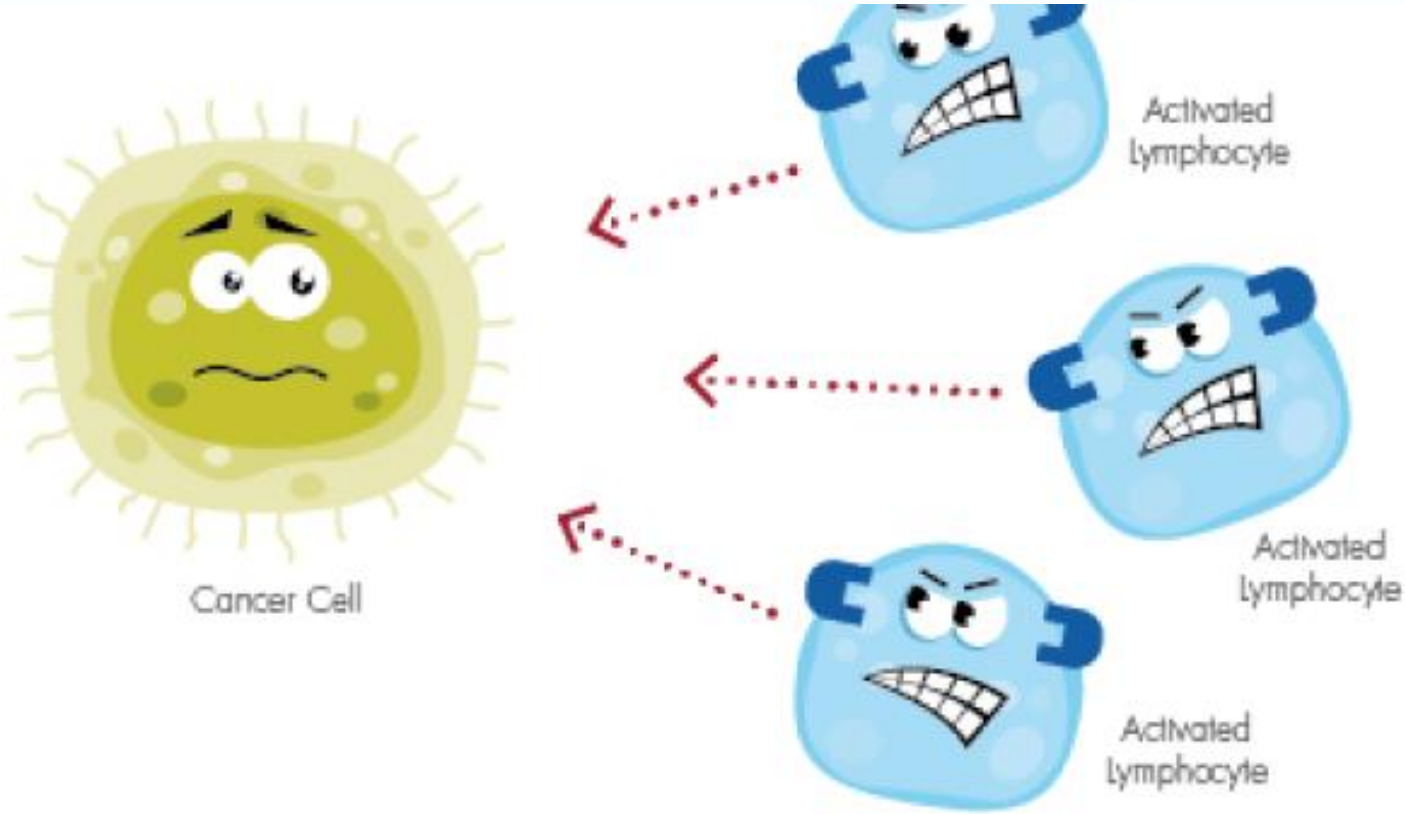
PARP inhibitors: Questions for the future

- Which PARP inhibitor to use?
- Which patients benefit form PARP inhibitors and when?
- Can PARP inhibitors be combined with other drugs?
- How toxic are PARP inhibitors?
- Are there long term side effects?
- Do tumors become resistant to PARP inhibitors?
- What options are there beyond the PARPs?

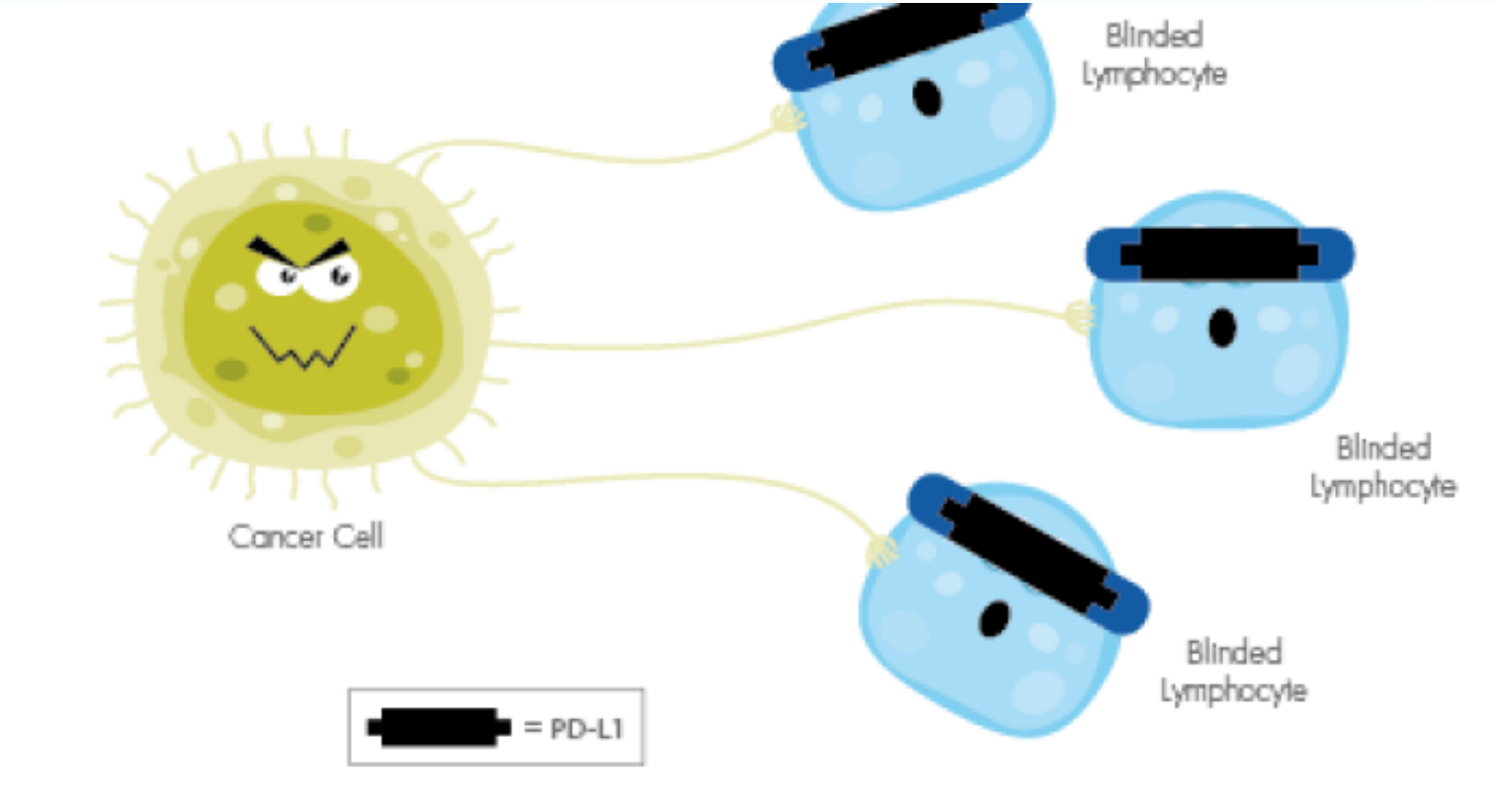
Immunotherapy:
How does the immune system work?



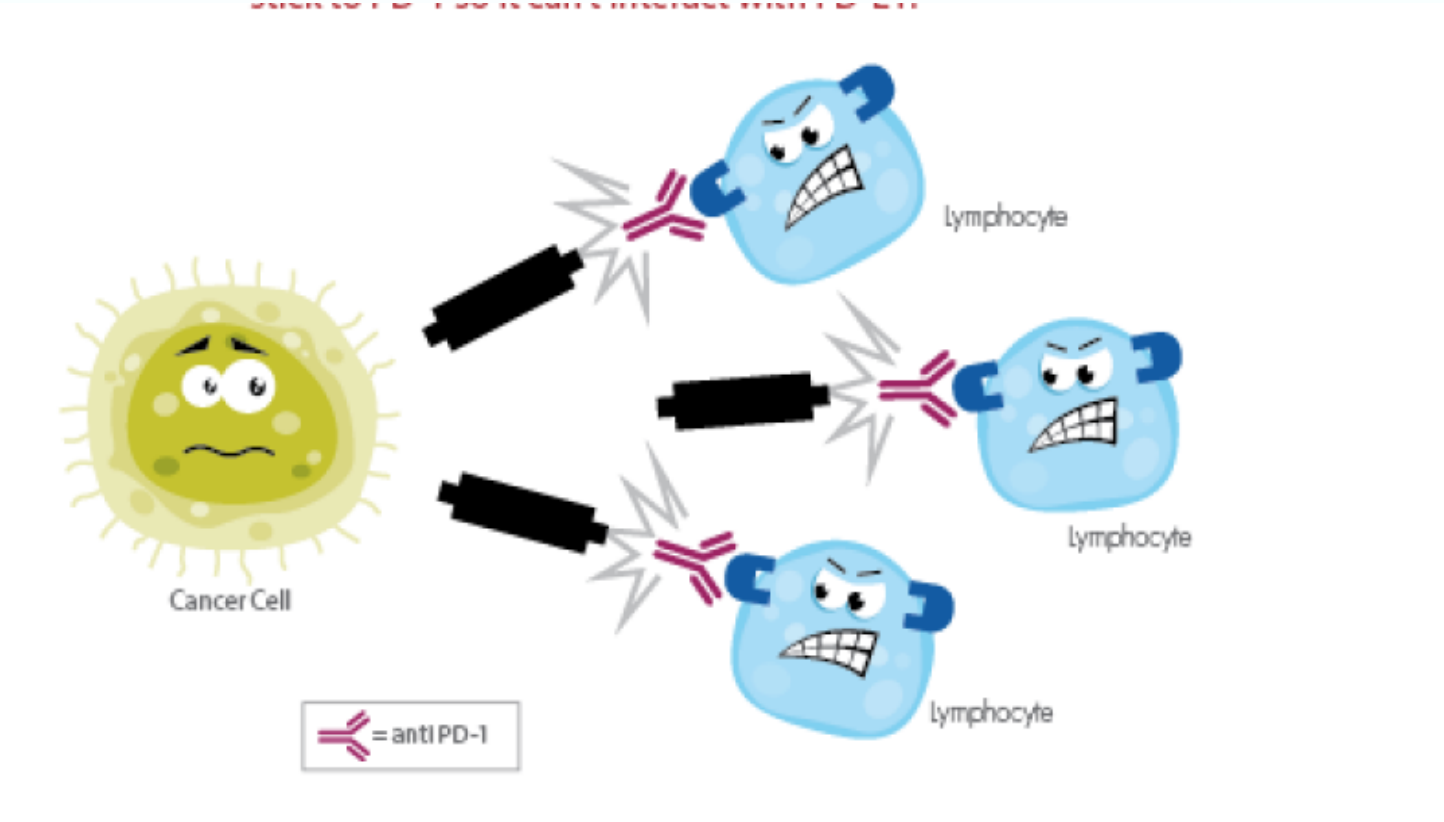
How does the immune system work?



Mechanism by which tumor cells evade the immune system

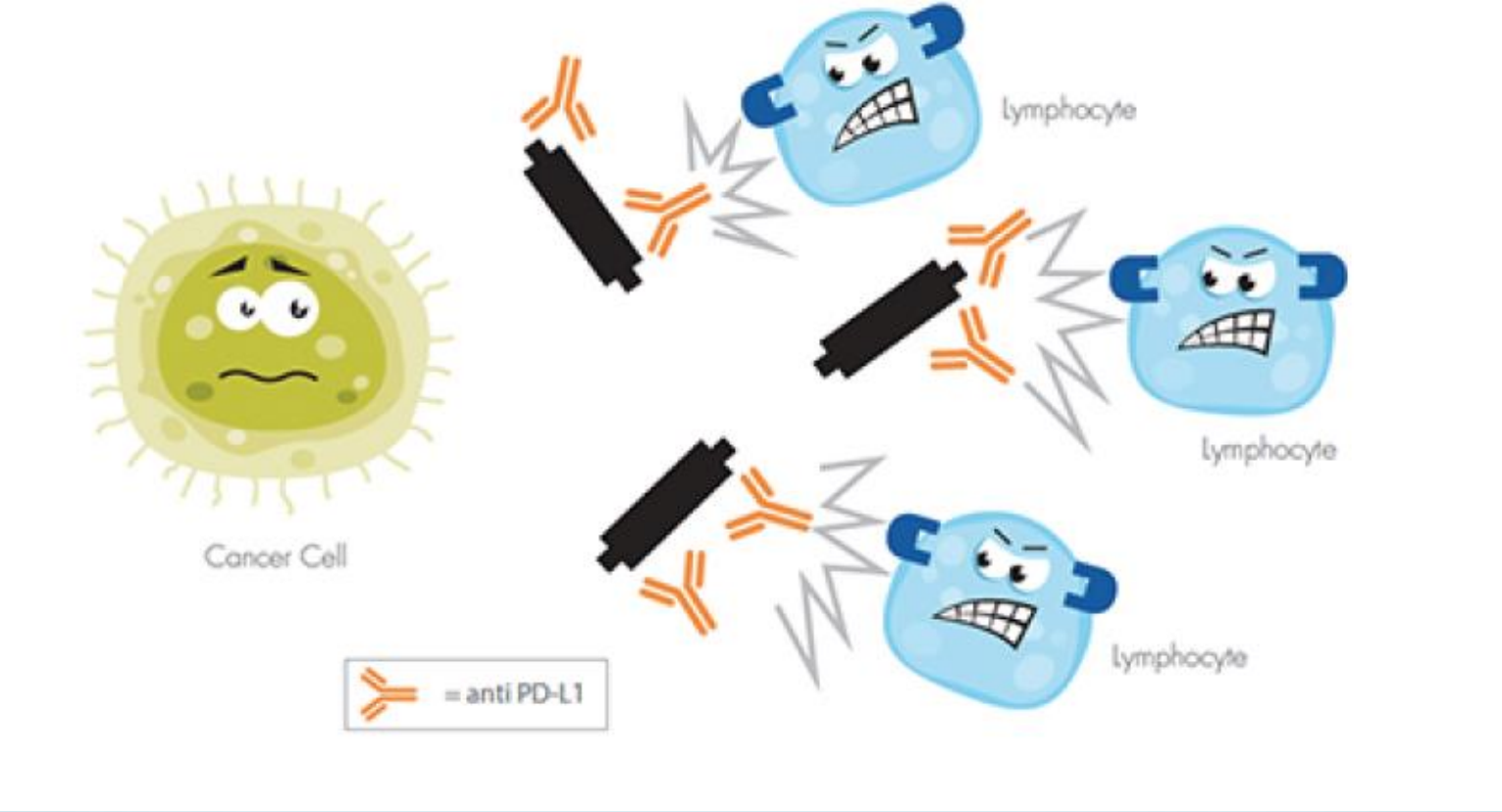


How to unblock anti-tumor immunity: **Anti-PD1**



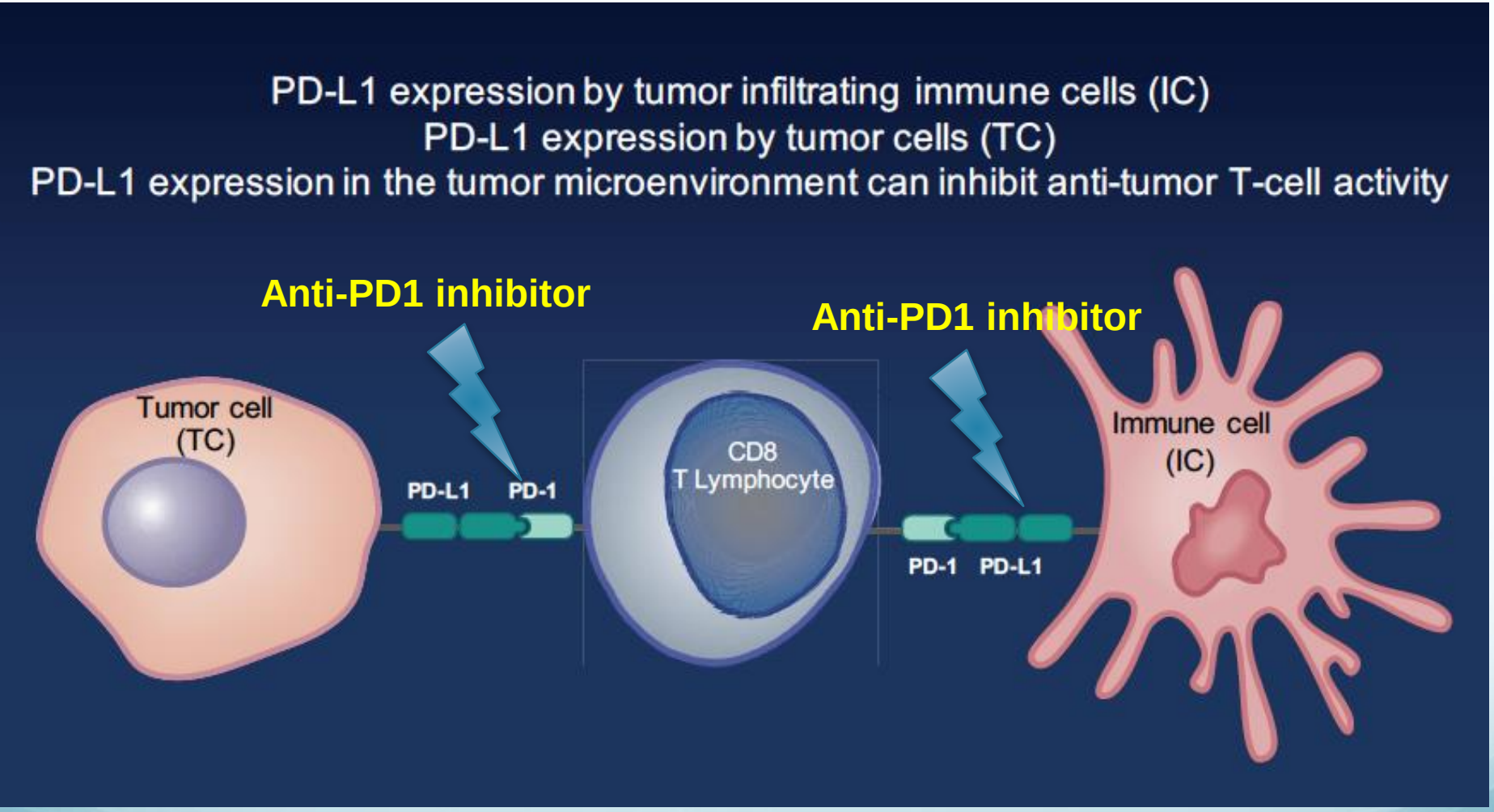
Examples: Pembrolizumab approved for lung cancer, melanoma, renal cancer,
Nivolumab

How to unblock anti-cancer immunity anti-PDL1



Examples: atezolizumab—approved for bladder cancer

PD-L1 expression by tumor infiltrating immune cells (IC)
PD-L1 expression by tumor cells (TC)
PD-L1 expression in the tumor microenvironment can inhibit anti-tumor T-cell activity



Immunotherapy in Ovarian Cancer

- **Avelumab: anti PD-L1**
- Recurrent ovarian cancer
- N=75
- Response rate: 8 (10%)
- Stable disease: 44%
- Serious toxicity: 6

- **Pembrolizumab: anti PD1**
- Recurrent ovarian cancer
- N=26
- Response Rate: 3 (11%)
- Stable disease: 23%
- Serious toxicity: 2

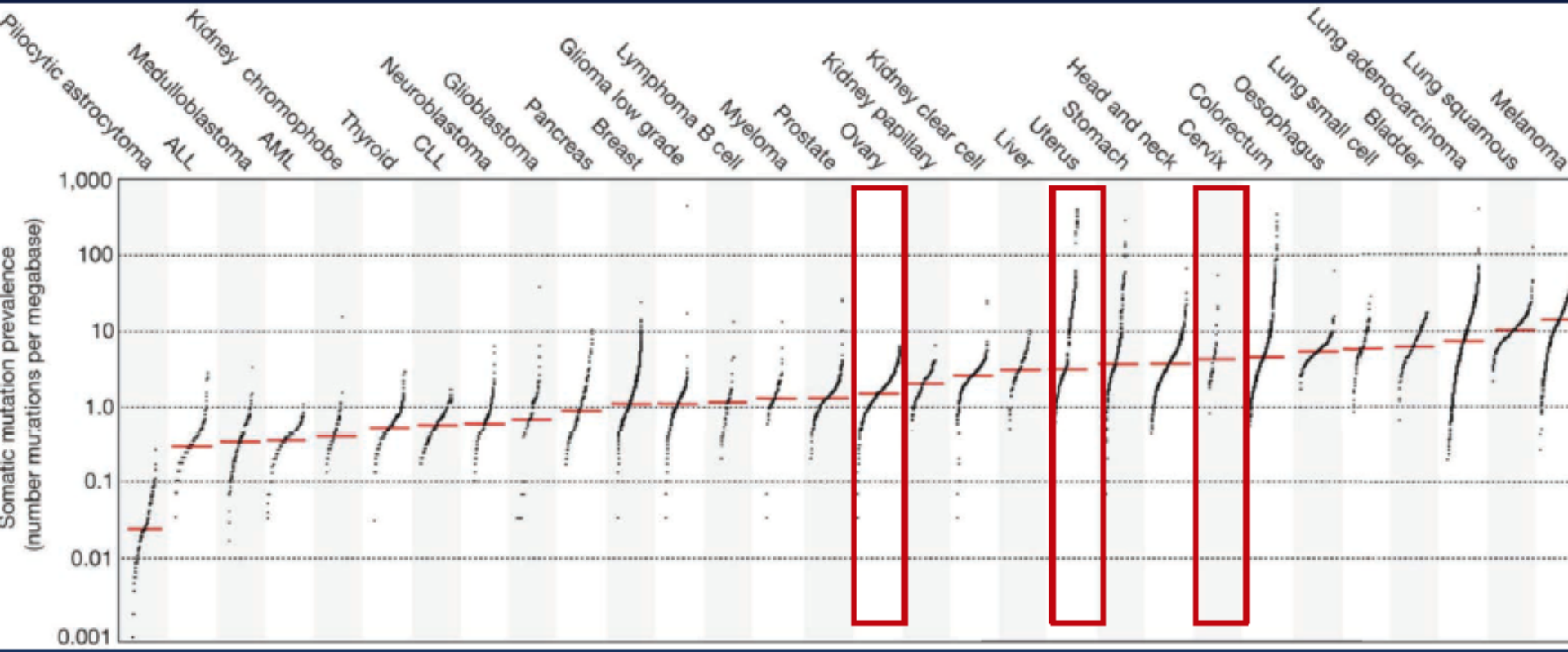
Modest activity: need to boost effects of immunotherapy by using novel combinations

Mary Disis, ASCO 2015

Andrea Varga, ASCO 2015

Mutations in Cancer Cells Make Them Appear Different to the Immune System

High mutational rates may contribute to increased immunogenicity



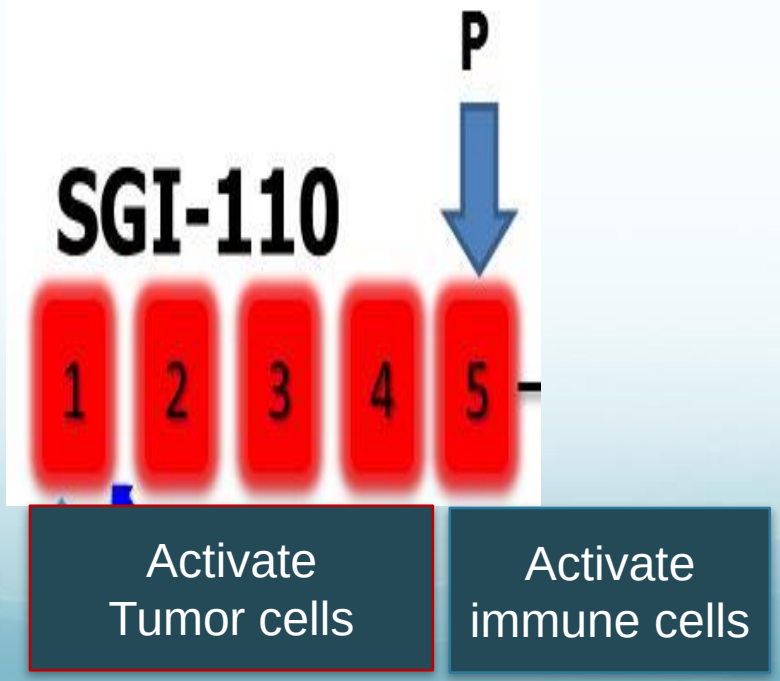
Some GYN tumors are noted to have high mutation load

Alexandrov LB, et al. *Nature*. 2013;500:415-421.

Novel combinations with immunotherapy at Northwestern University and Univ. of Chicago

Hypothesis: Use of drugs that affect the genomic make up of tumors can elicit immune responses to enhance effects of immune therapy.

Trial: An open label phase II trial of guadecitabine and pembrolizumab in platinum resistant recurrent ovarian cancer:



Daniela Matei, PI

Phase II study of pembrolizumab in combination with carboplatin and paclitaxel for advanced endometrial adenocarcinoma
Big Ten Cancer Research Consortium BTCRC-GYN15-013

Hypothesis:

Combination chemotherapy and immunotherapy is more effective than chemotherapy alone for patients with advanced endometrial cancer.

Study design:

Standard chemotherapy + pembrolizumab in recurrent or advanced endometrial cancer

Objectives:

- To estimate the response rate
- To determine the toxicities
- To measure immune response in tumor samples

PI: Dr. Pineda/Matei

Immunotherapy-take home message

- New class of drugs very active in cancer
- Toxicity profiles includes immune effects (rash, arthritis, diarrhea)
- Efficacy in gynecologic tumors is modest at this time
- Patients who respond have **long remissions**
- Duration of treatment remains unclear
- Research ongoing to identify combinations that may boost the effects of immunotherapy in ovarian cancer and to define ways to find patients likely to benefit from immunotherapy.

What are clinical trials?

- Clinical trials are research studies that explore whether a **medical strategy, treatment, or device is safe and effective for humans**.
- These studies also may show which medical approaches work best for certain illnesses or groups of people.
- Clinical trials produce the best data available for health care decision-making.

- The purpose of clinical trials is **research, so the studies follow strict scientific standards**. These standards protect patients and help produce reliable study results.

National Institute of Health

What are clinical trials?
Type of clinical trials

- **Interventional clinical trials:**

  -A new intervention is tested (new drug, new device, new test, new procedure).

  -There are risks and inconvenience associated with new interventions (side effects, doctor visits)

  -There are potential benefits (longer survival)

  -**Informed Consent Form: risks/benefits**

What are clinical trials?

- **Interventional clinical trials types: Phase I**

  Drug or device tested in humans for the first time

  Main goal: determine tolerable dose

  Toxicity and efficacy are NOT known

  Correct dose is not known: **dose escalation**

  High risk, benefit is unknown (response rates <10%)

  Intense monitoring: visits, blood draws

  All participants receive the drug: incremental doses

  Open eligibility, any cancer, any number of prior therapies

What are clinical trials?

- **Interventional clinical trials types: Phase II**

  Dose and toxicity are known

  Main goal: testing efficacy in specific disease

  Risk is smaller, benefit higher

  All participants receive the intervention

  May require additional testing (biopsies, scans)

  Restrictive eligibility: strict criteria for enrollment

What are clinical trials?

- **Interventional clinical trials types: Phase III**:

  Dose, toxicity are known

  Efficacy in specific disease is known (phase II)

  Definitive proof before approval by the FDA

  Very restrictive eligibility criteria

  Randomized design:

  ½ participants receive intervention;

  ½ participants receive control (approved treatment or intervention). If no approved treatment exists, then **placebo** is the control.

What are clinical trials?

- **Interventional clinical trials types: Phase IV**

  Dose, toxicity are known

  Efficacy in specific disease is known (phase III)

  Approval by the FDA has been granted, subject to acquisition of additional information

  Post approval observation and data collection

  Very low risk, low benefit

What are clinical trials?

Observational clinical trials:

Data collection from medical records

Use of tissue already collected and archived, or tissue that would be otherwise discarded

Questionnaires, surveys

Low risk, no benefit to the study participant

Can help test a preliminary idea

Can lead to new scientific hypothesis

Vocabulary of cancer clinical trials

- **Response rate:** how many participants respond to the intervention out of all the participants
- **Progression free survival**: the period from starting the intervention until the cancer progresses (remission)
- **Overall survival:** duration of survival
- **Toxicity**: number of reported side effects
- **Quality of life**: questionnaires assess function—social, psychological, sexual, reproductive, etc.

Are clinical trials for you?

- **Benefits:**

  --Access to new drugs, otherwise not available

  --Potential benefit: “unknown”

  --Increased monitoring, more frequent visits

  --Advance knowledge, help future patients have access to novel therapies

- **Risks/Cons:**

  --Potential toxicities which are not anticipated

  --Potential lack of benefit: “unknown”

  --Time commitment, additional testing which is not required outside of a clinical trial

Are clinical trials for you?

- **Resources:**

  --Clinicaltrials.gov (NIH sponsored website)

  --American Cancer Society

  --Your oncologist

- **Northwestern University Gynecology Oncology Clinical Trials:**

  Deanna Taiym and Andreea Gavrilescu:

  312-695-1337 312-695-0963

Current Research at Northwestern University in Ovarian Cancer

- **Clinical Trials for Recurrent Ovarian Cancer**

  -GOG-NCI sponsored clinical trials:

  -PARP inhibitors + anti-angiogenesis inhibitors

  -Epigenetic therapy + immunotherapy

  -New trials upcoming

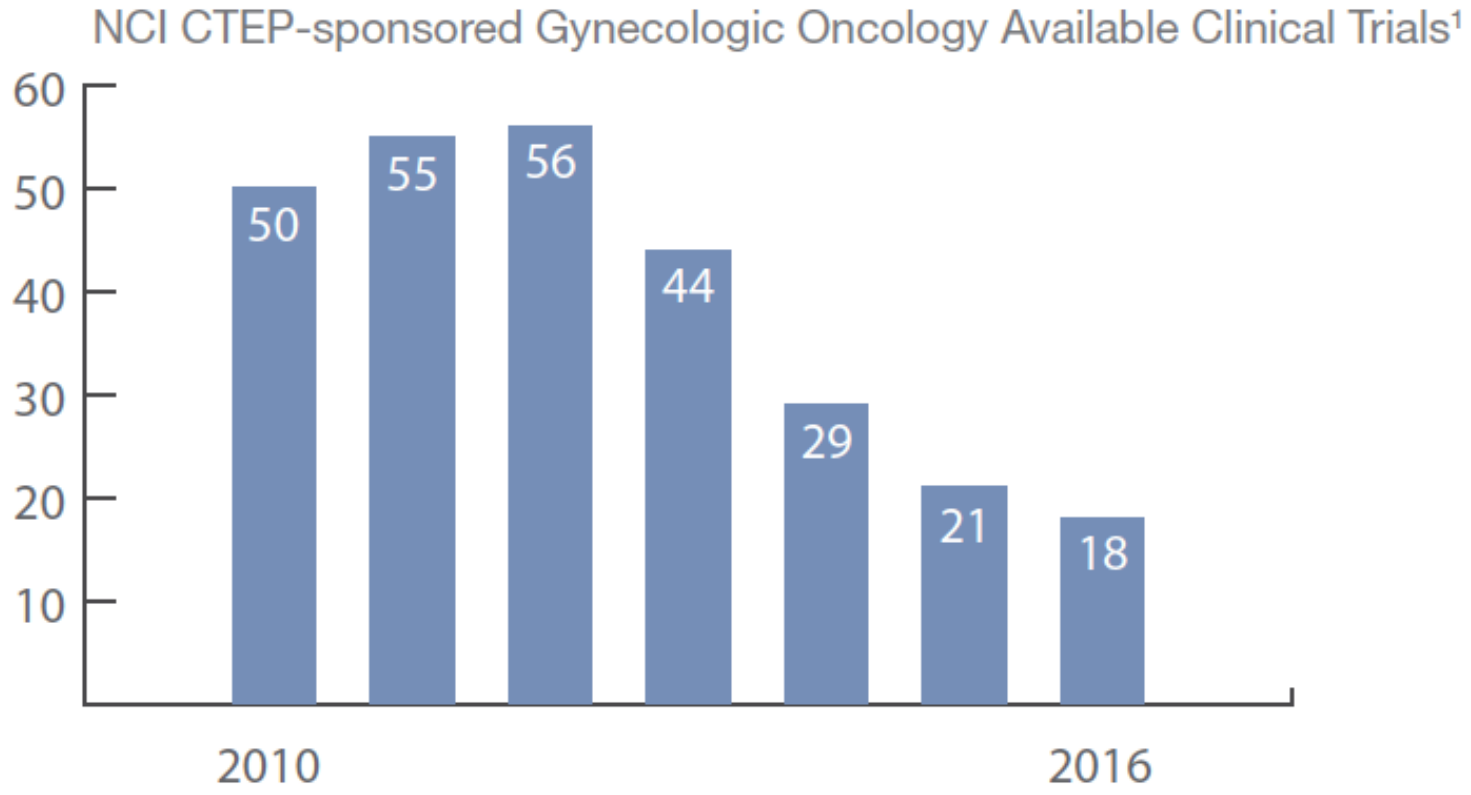
Endometrial cancer: first line therapy:

--Carboplatin/paclitaxel+ pembolizumab. BIG Ten Trial

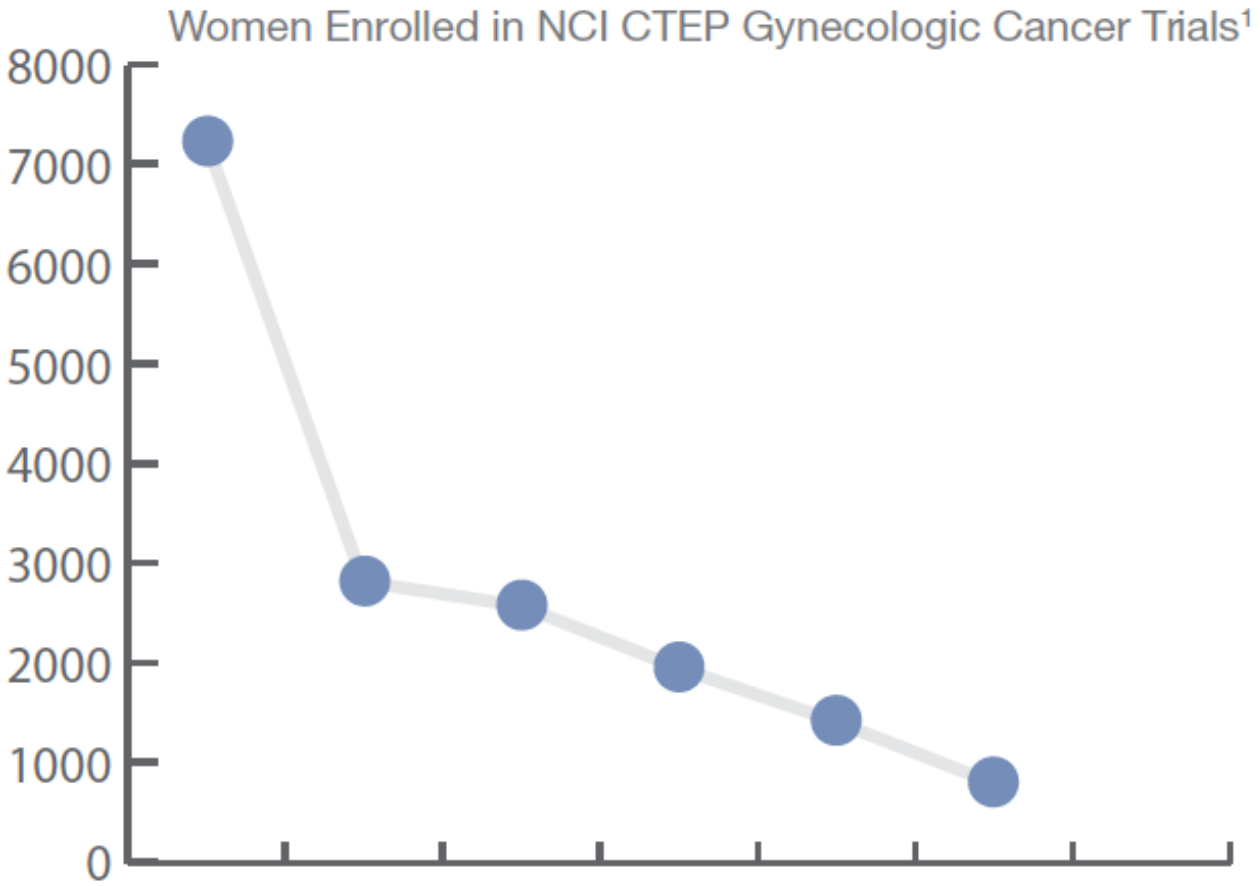
--Carboplatin/paclitaxel +/- pembrolizumab: GOG trial

Deanna Taiym or Andreea Gavrilescu 312-695-1337

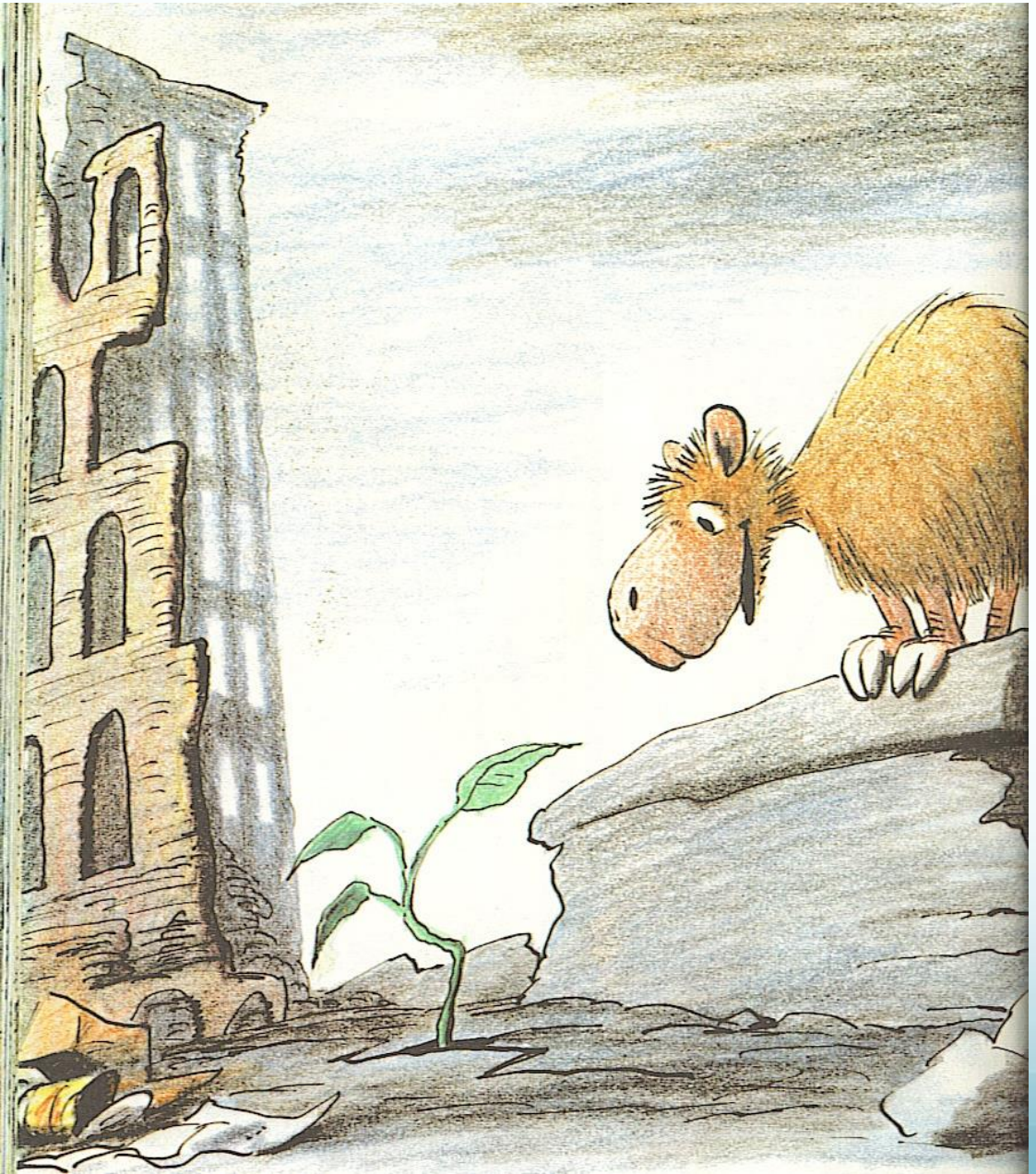
State of clinical trials



State of clinical trials



The future is possible



"In time the murky skies would clear up and the green growth would wind its way up through the rubble. Now there was new hope for the Wumps."

Bill Peet:
"The Wump World"