

Clinical Trials in Ovarian Cancer

Daniela Matei, MD

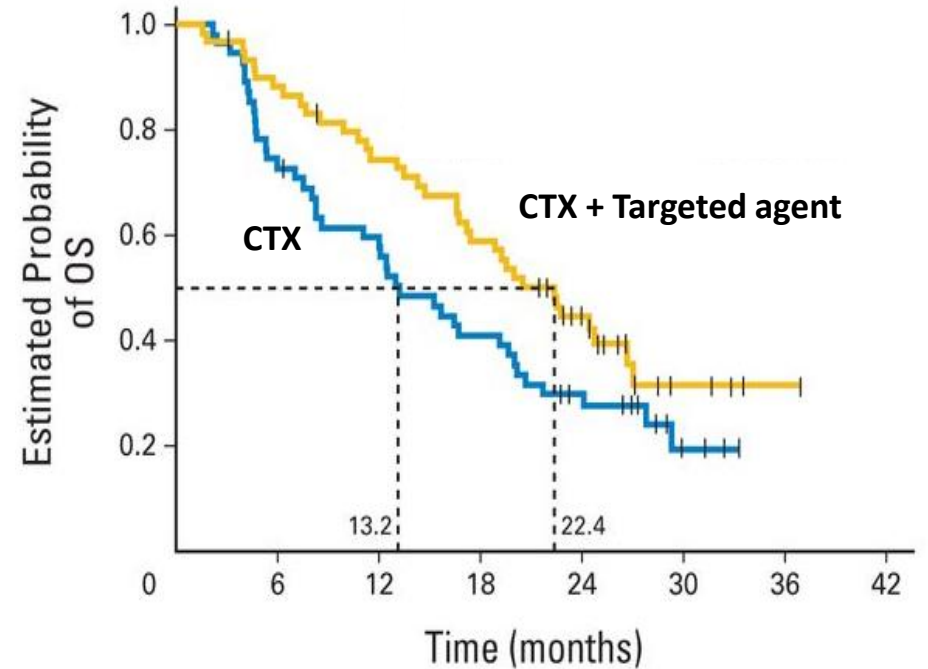
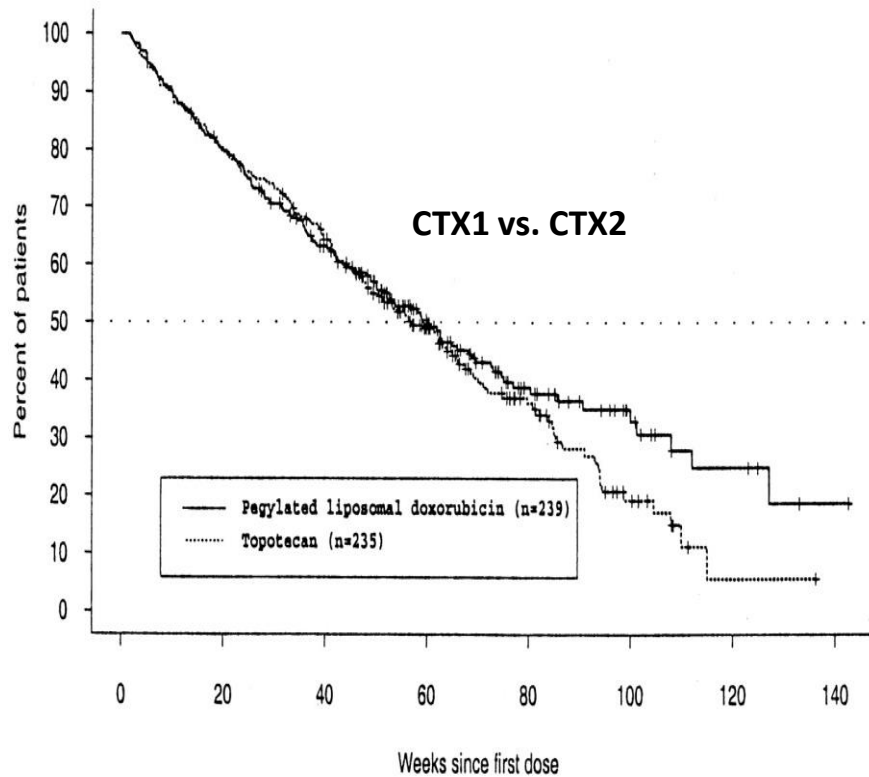
The News

- **Dec 19, 2014:** FDA approved **olaparib** for recurrent OC with mutant BRCA.
- **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
- **2020:** Approval of bevacizumab+Olaparib for upfront treatment of HRD+ ov. cancer
- **2020:** Approval of niraparib for upfront treatment of ovarian cancer
- **November 2022:** US FDA approval for Mirvetuximab for platinum resistant ov. ca ca
- **April 2024:** FDA approved Trastuzumab Deruxtecan for Her2+ ovarian cancer.

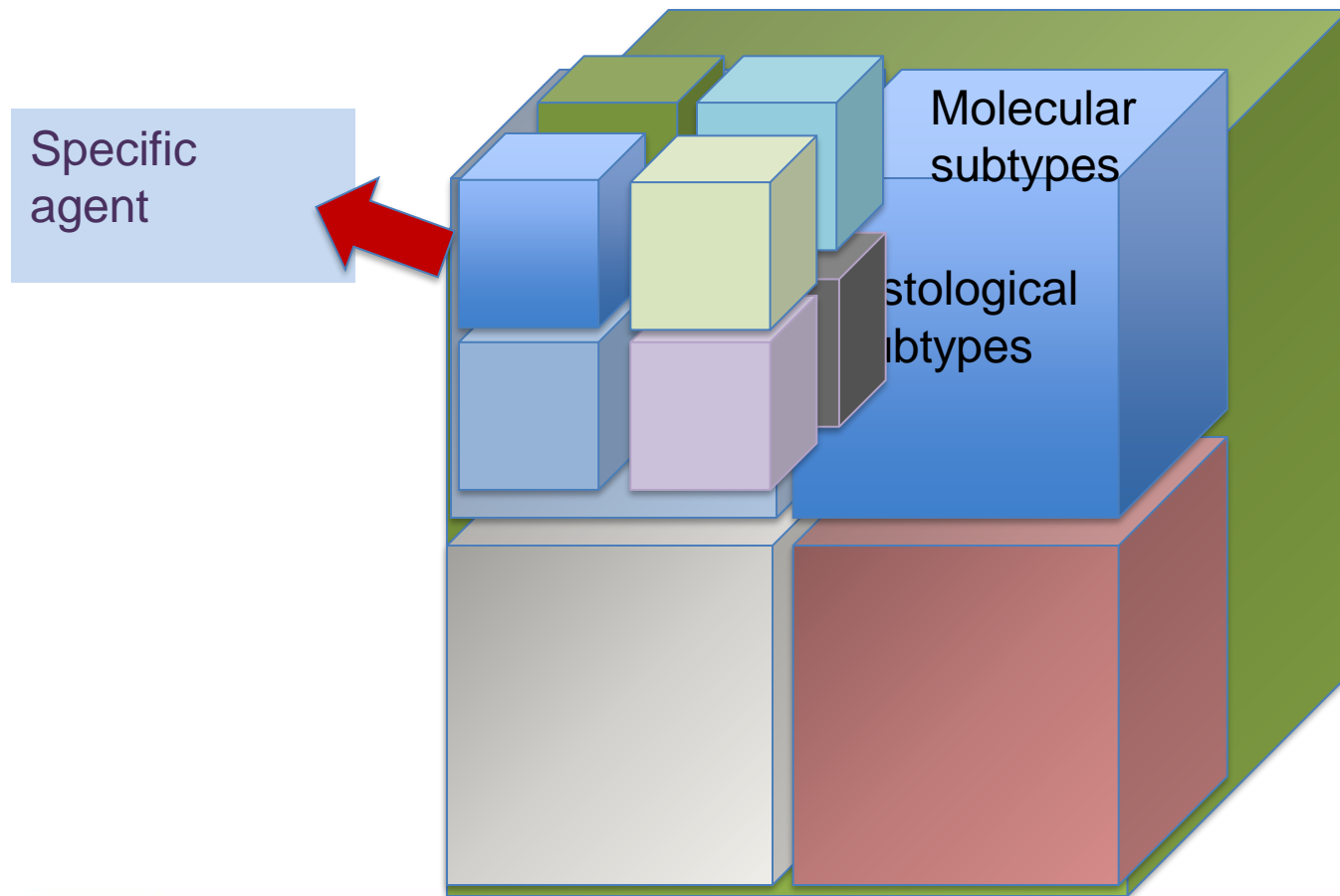
The news

- **Moment of celebration!**—these approvals follow a long drought period(>20 years)
 - 1995: liposomal doxorubicin
 - 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.

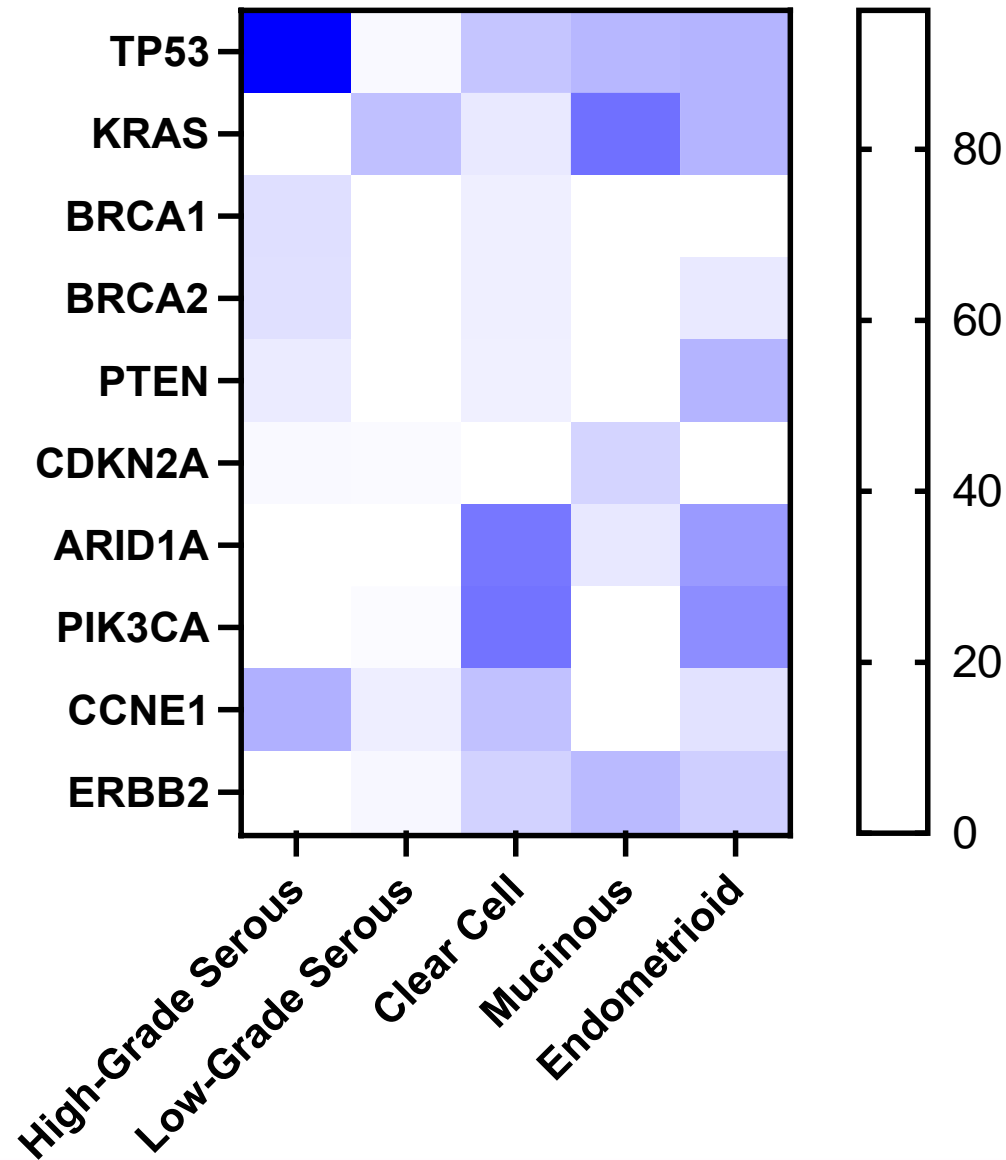
A change in the course of the disease—longer survival!



Is Personalized Treatment Achievable in Gynecologic Cancer?



Personalized Therapy in Ovarian Cancer



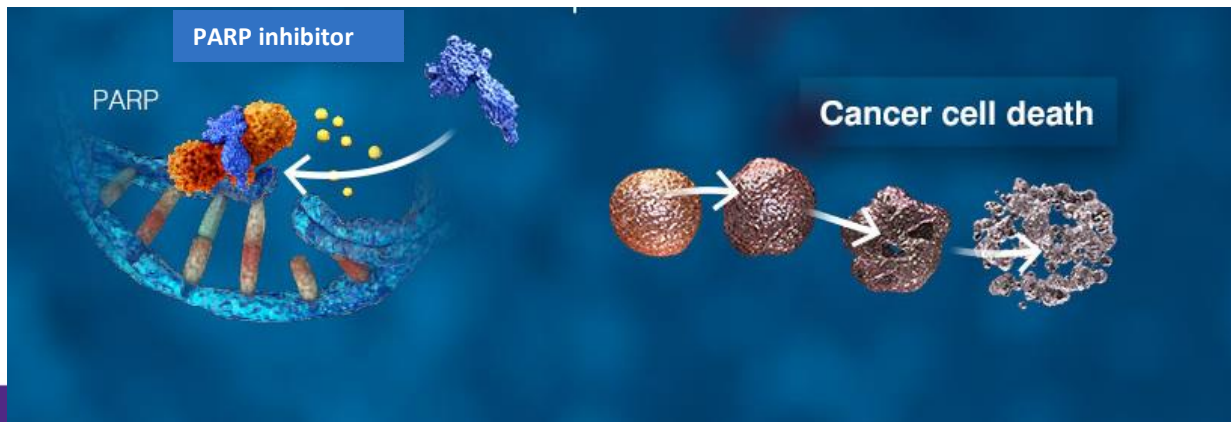
Personalized Therapy in Ovarian Cancer

- High grade serous cancer: BRCA and HRD
- High grade serous ovarian cancer: Folate receptor
- High grade serous ovarian cancer: Cyclin E
- Low grade cancer: Ras/Raf/MAPK
- Clear cell cancer and other types (MSI High or High tumor burden): immunotherapy

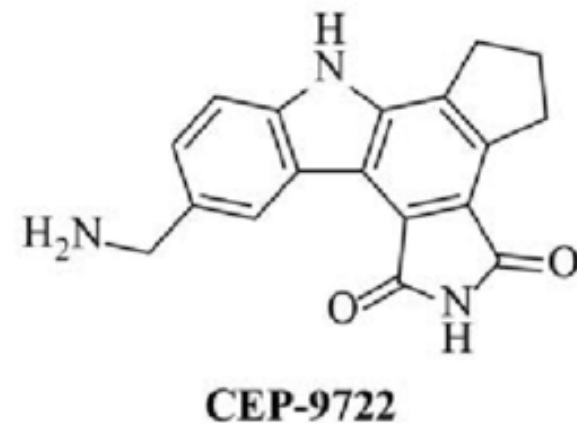
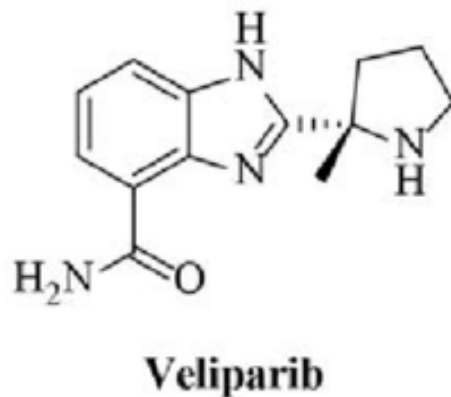
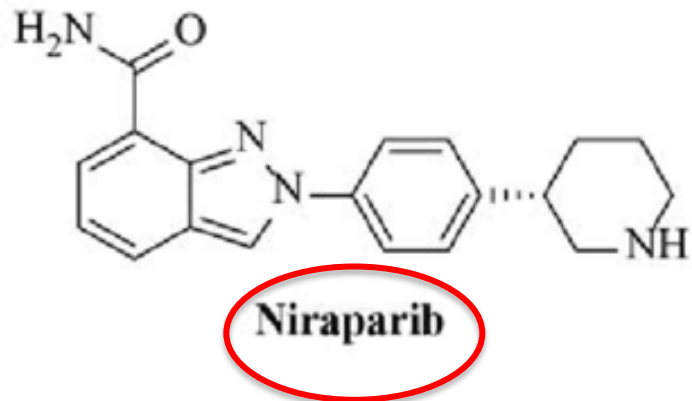
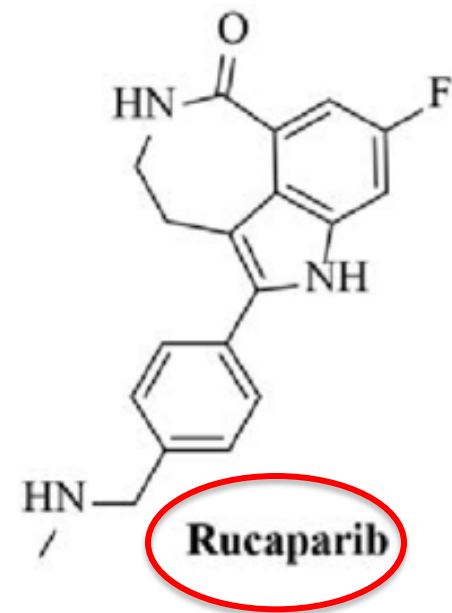
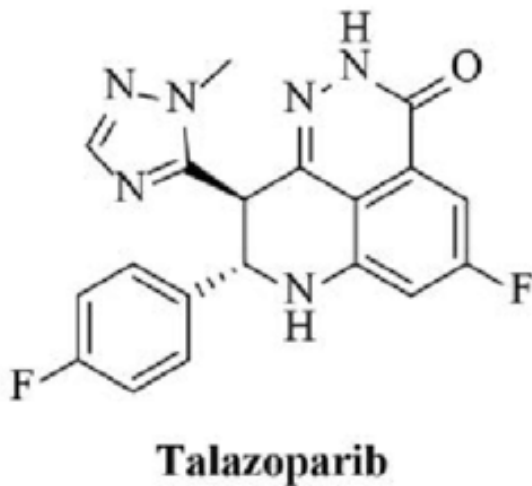
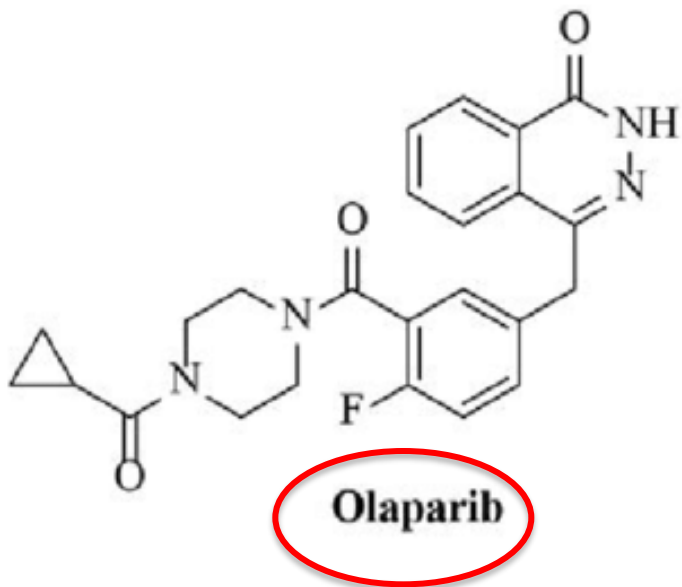
DNA Repair—What is PARP?



PARP enzyme repairs single strand DNA breaks



PARP Inhibitors Bind to PARP Enzyme



PARP inhibition in BRCA deficient cells

BRCA intact



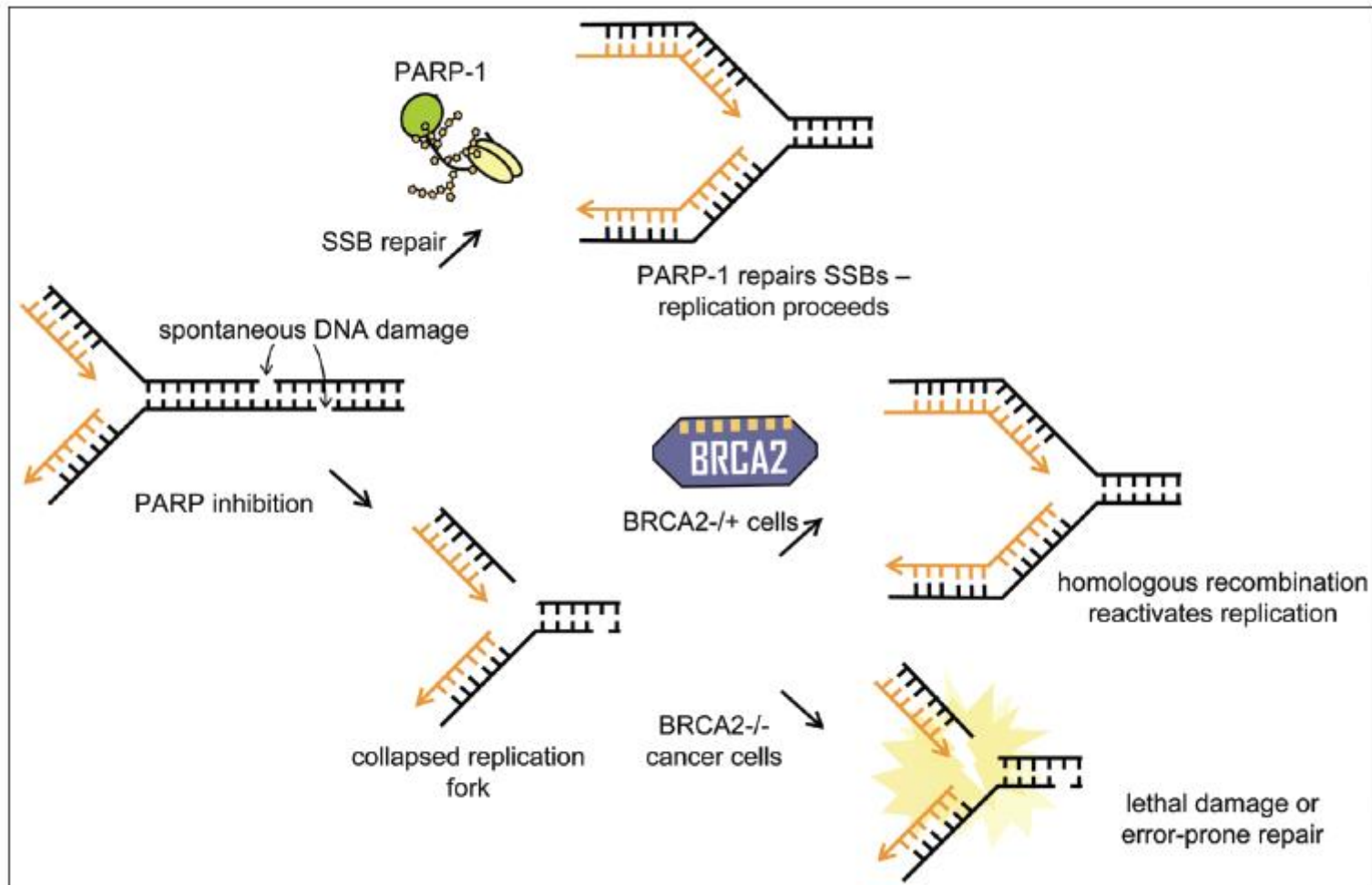
BRCA mutated



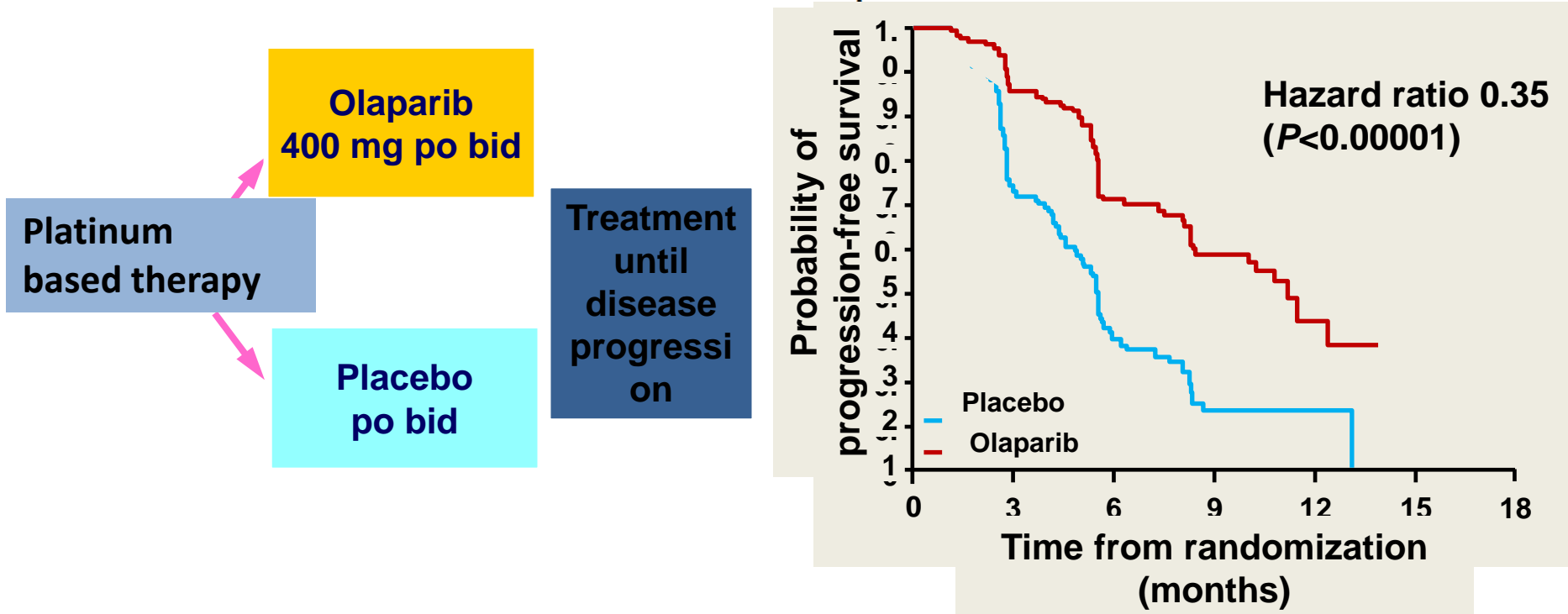
BRCA2-mutant cells treated with a PARP inhibitor undergo massive chromosomal crisis due to the defect in DNA repair mechanisms.

How do PARP Inhibitors Work?

Synthetic Lethality

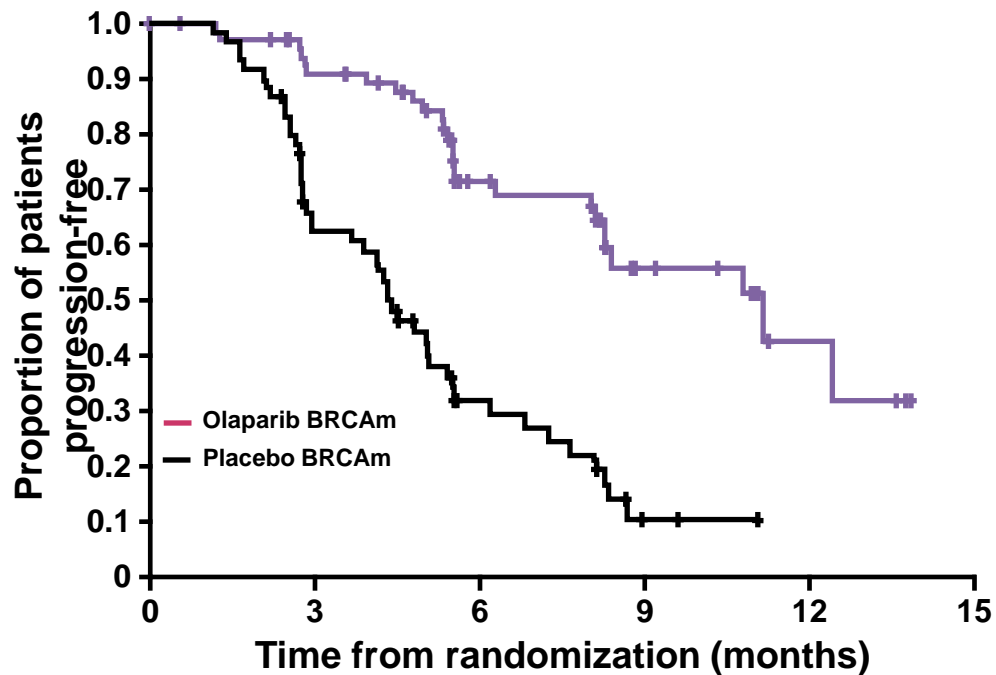


Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer



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

Survival by BRCA mutated status

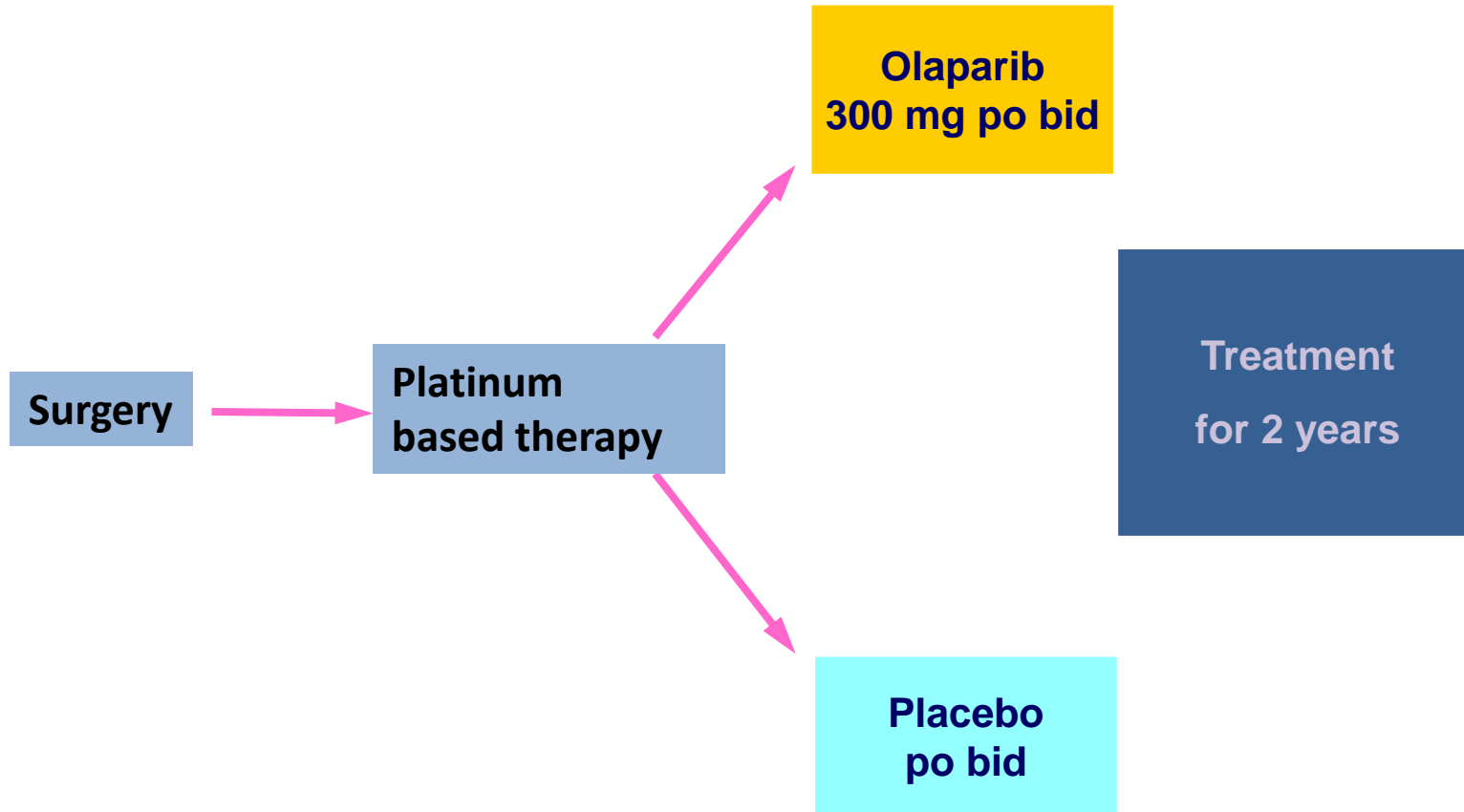


Highest benefit in patients with BRCA mutated tumors

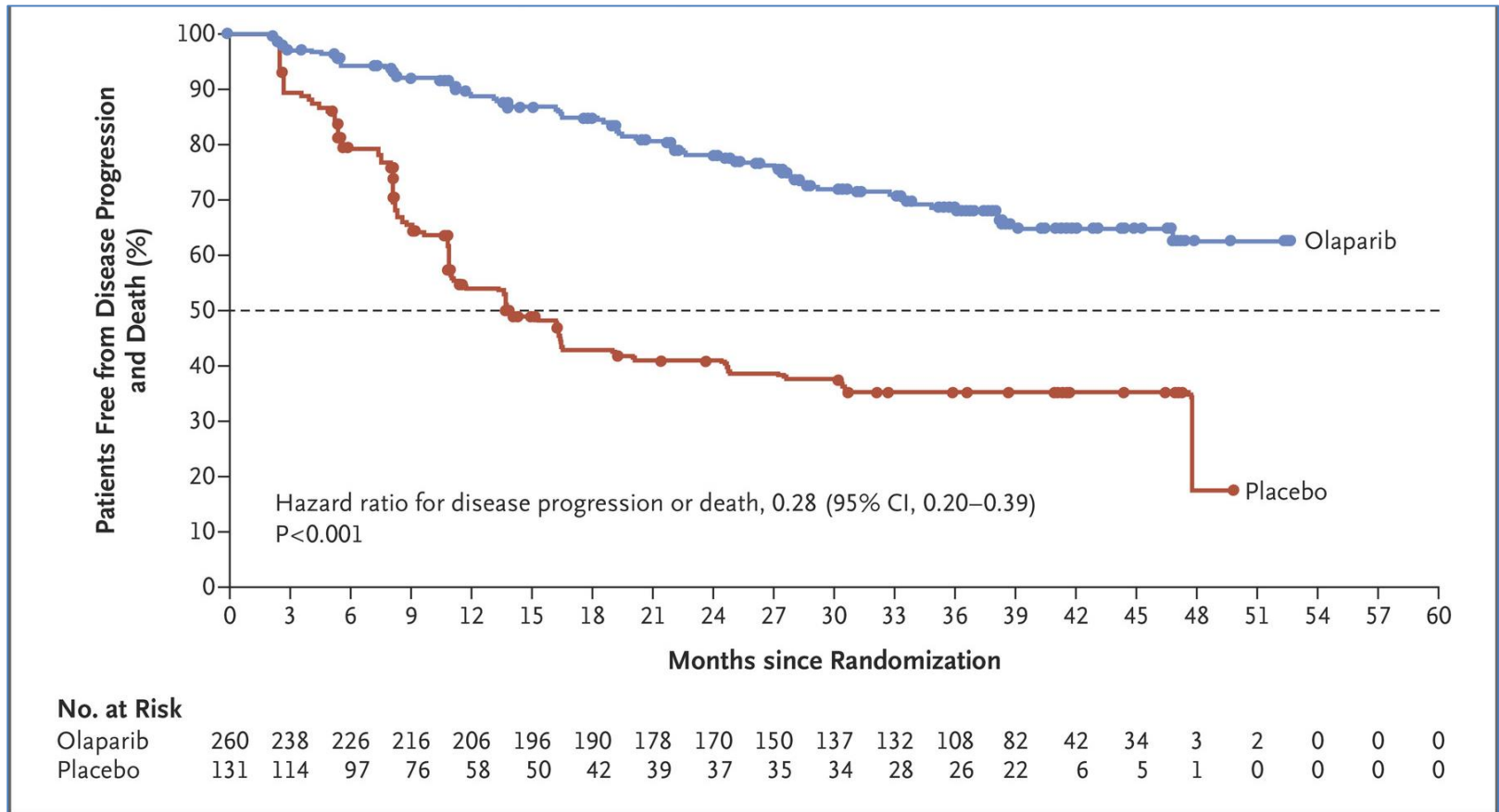
Lederman, NEMJ, 2014
Lederman, Lancet Oncology 2016

PARP Inhibitors in BRCA Mutated Tumors

FIRST LINE SOLO1



PARP Inhibitors in BRCA Mutated Tumors FIRST LINE SOLO1



Is a cure possible?

Who will respond to PARPi?

- Tumors with BRCA 1,2 mutations
- Other mutations in genes that regulate DNA damage response
- Tumors with epigenetic changes in genes that control DNA repair (BRCA1, MLH1 methylation)
- HR Deficient tumors
- Platinum sensitive tumors

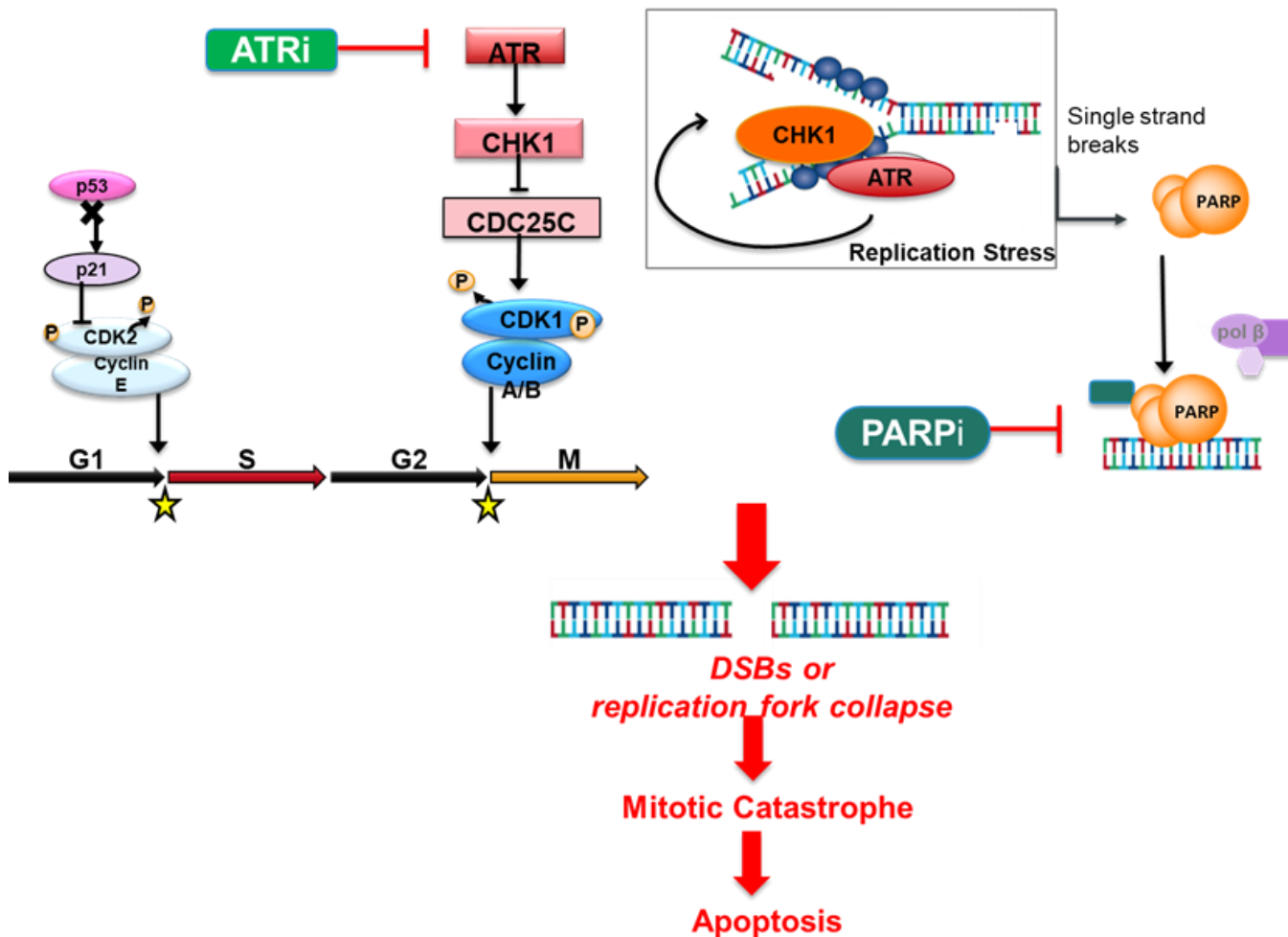
PARP inhibitor approvals

- First line maintenance treatment (after surgery and chemotherapy): tumors with BRCA 1,2 mutations
- Other mutations in genes that regulate DNA damage response
- Tumors with epigenetic changes in genes that control DNA repair (BRCA1, MLH1 methylation)
- HR Deficient tumors
- Platinum sensitive tumors

Who does not respond to PARP inhibitors?

- New mutations (BRCA, RAD51) that make tumors resistant
- Upregulation of growth pathways that stimulate cancer cell growth (e.g. Wnt)
- Loss of DNA repair mechanisms (Sheldin, PTIP).
- Drug efflux
- Area of outmost interest for research

New PARP Inhibitor Combinations

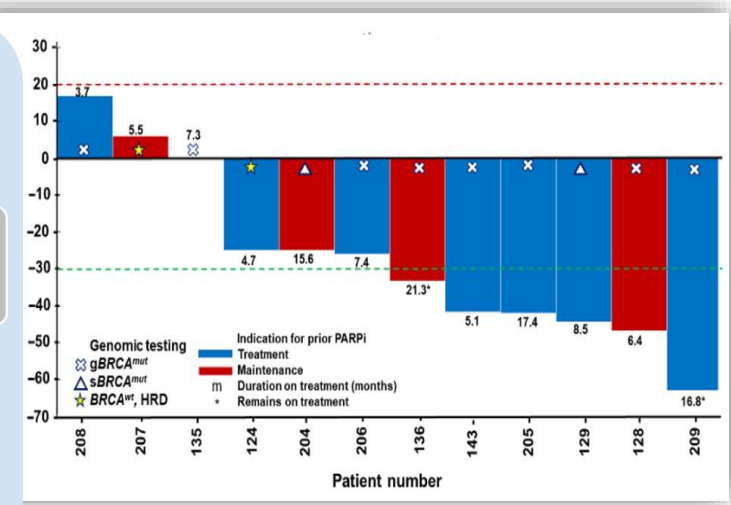
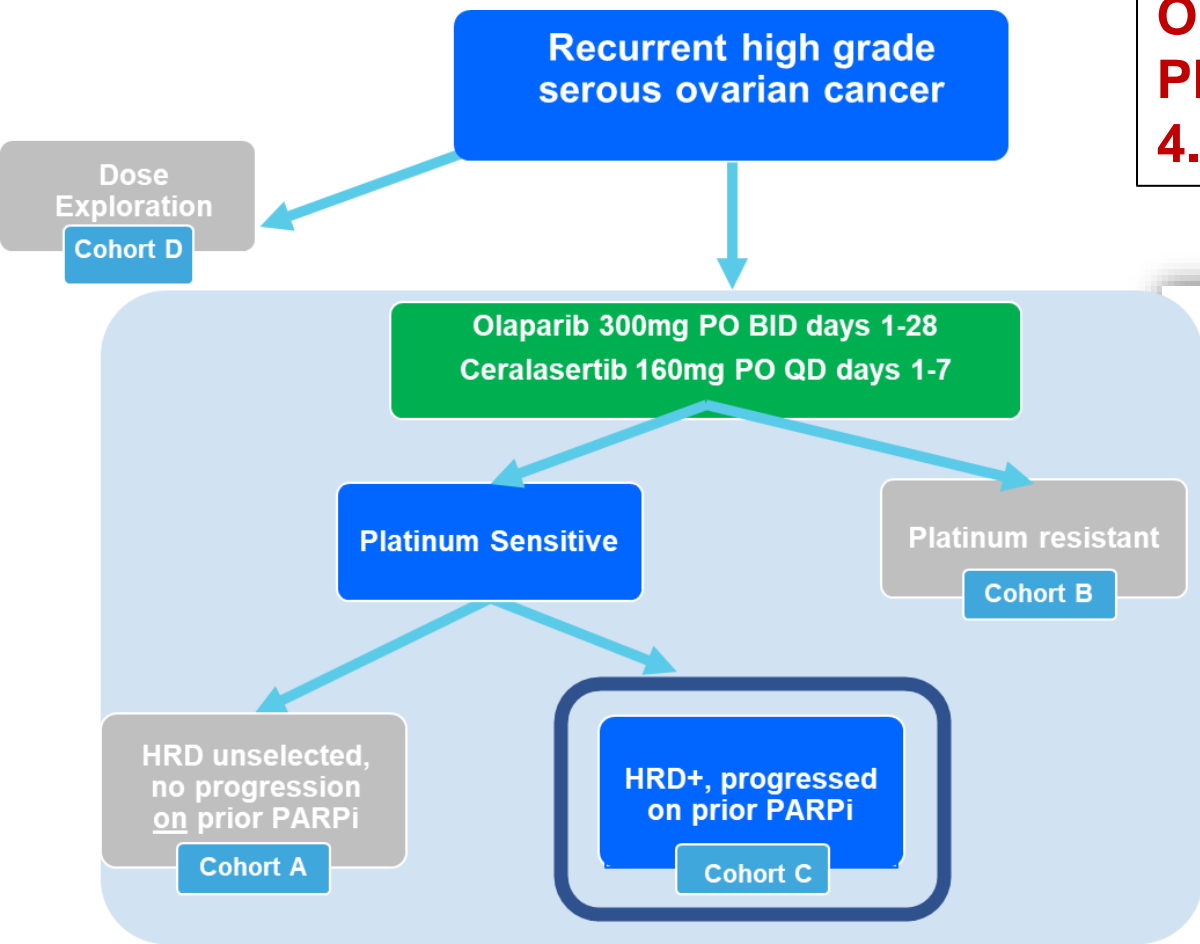


Hypothesis: targeting 2 unique DNA repair pathways by combination PARPi and ATRi, will lead to increased DSB and prevent or overcome PARPi resistance

New PARP Inhibitor Combinations

Ceralasertib + Olaparib

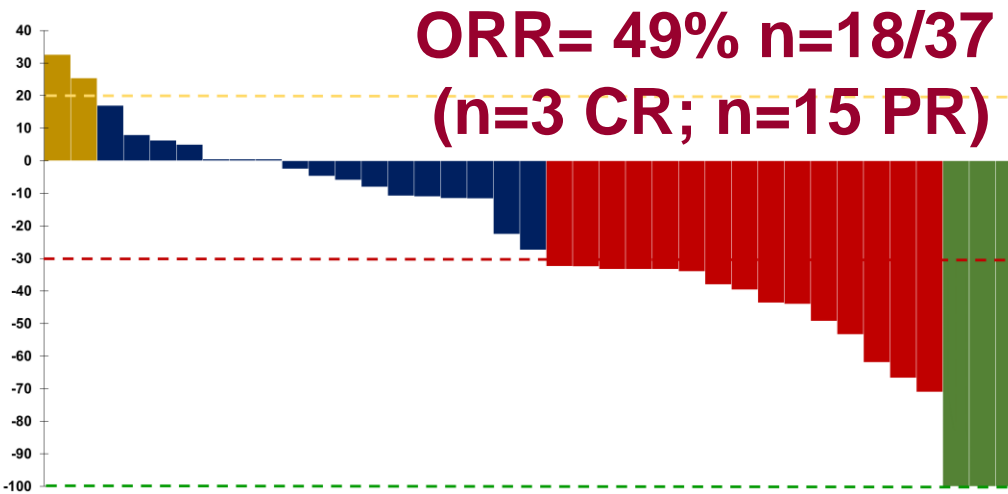
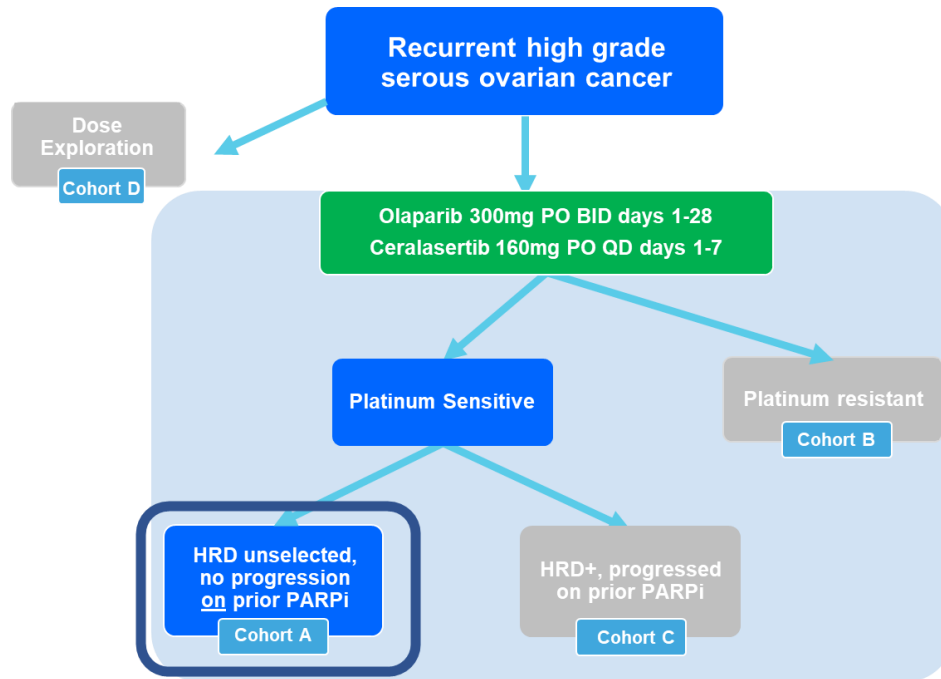
ORR 50% (n=6/12)
PFS 7.5 months (95% CI 4.7-15.1)



ASCO, 2021; Wethington et al., Clin Can Res, 2023

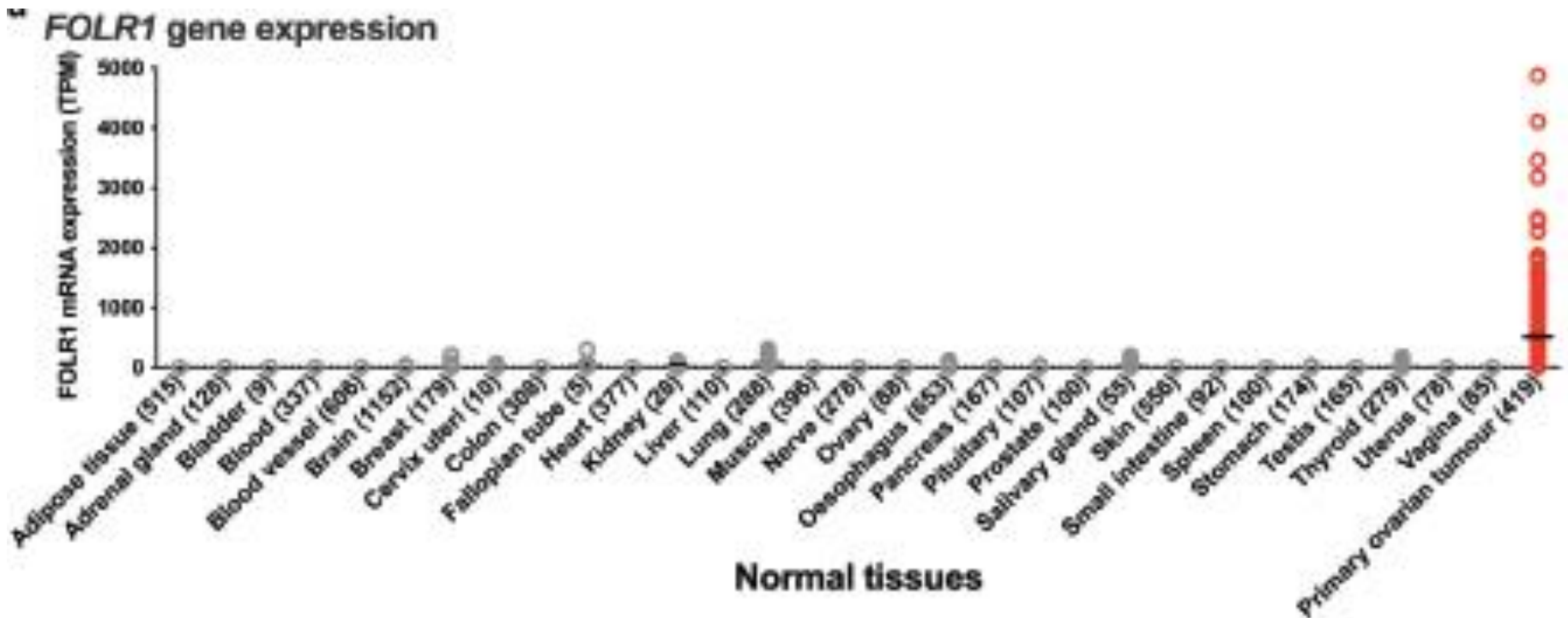
New PARP Inhibitor Combinations

Ceralasertib + Olaparib



ASCO 2024

Folate receptor



Bax, British J of Cancer, 2022

Folate receptor alpha

Ovarian tumour FR α staining

Membrane +ve / cytoplasmic +ve



Membrane +ve / cytoplasmic -ve



Membrane -ve / cytoplasmic +ve

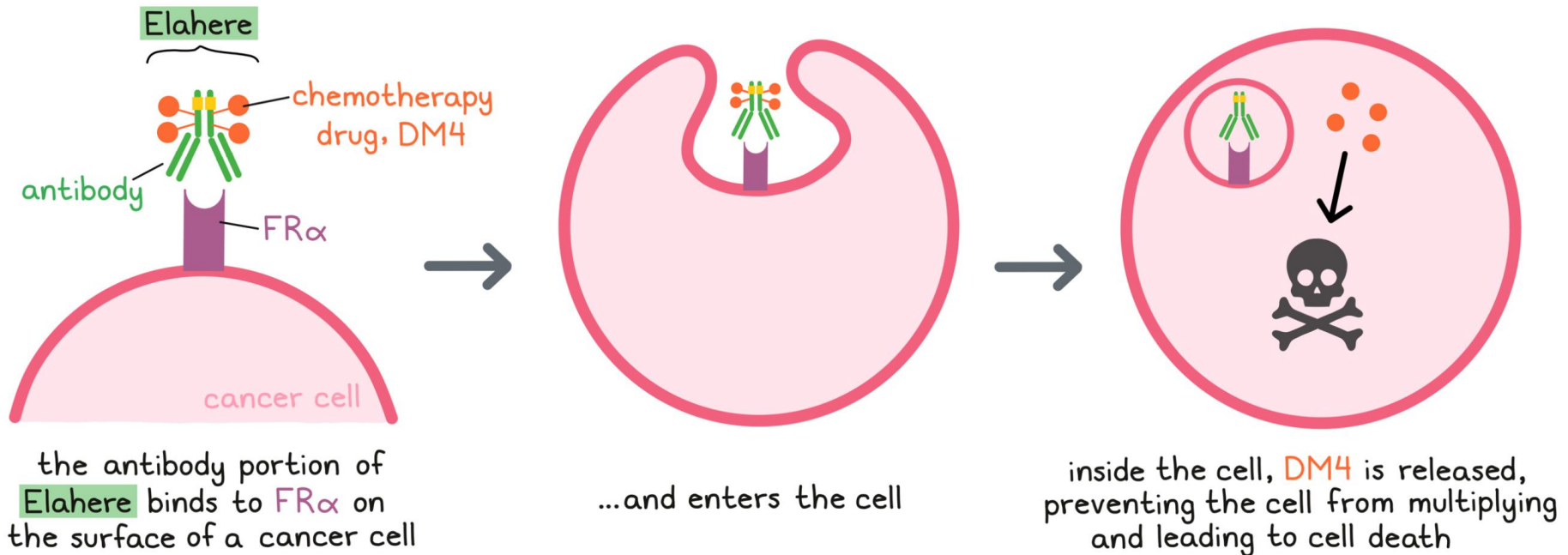


Membrane -ve / cytoplasmic -ve



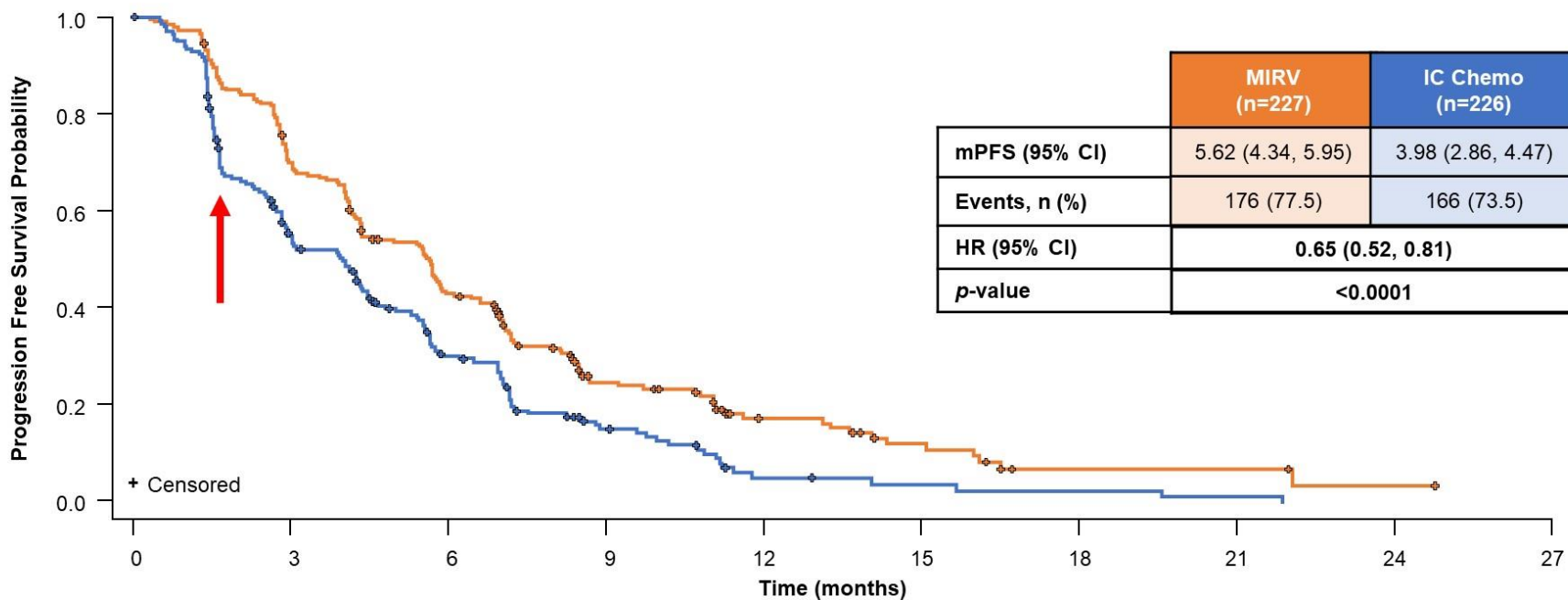
Bax, British J of
Cancer, 2022

Mirvetuximab soravtansine —Mechanism of action



Mirvetuximab soravtansine Clinical Activity

Primary Endpoint: Progression-Free Survival by Investigator



No. Participants at Risk

	0	3	6	9	12	15	18	21	24	27
MIRV 227	227	151	89	38	18	10	3	3	1	0
IC Chemo 226	226	98	48	19	5	3	2	1	0	0

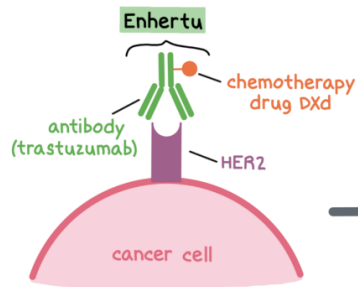
Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

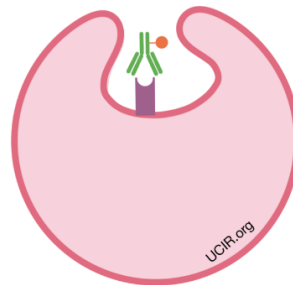
Her 2 neu positive tumors

Trastuzumab Deruxtecan (Enhertu)

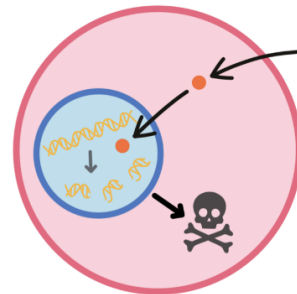
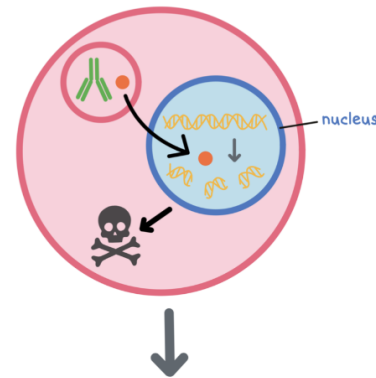
Using its antibody part, **Enhertu** binds to **HER2** on the surface of a **cancer cell**...



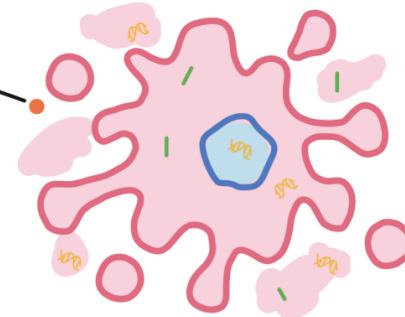
...and enters the cell.



Inside the cell, the **chemotherapy drug DXd** gets released and travels to the **nucleus** of the cell, where it leads to **DNA damage** and results in **cell death**

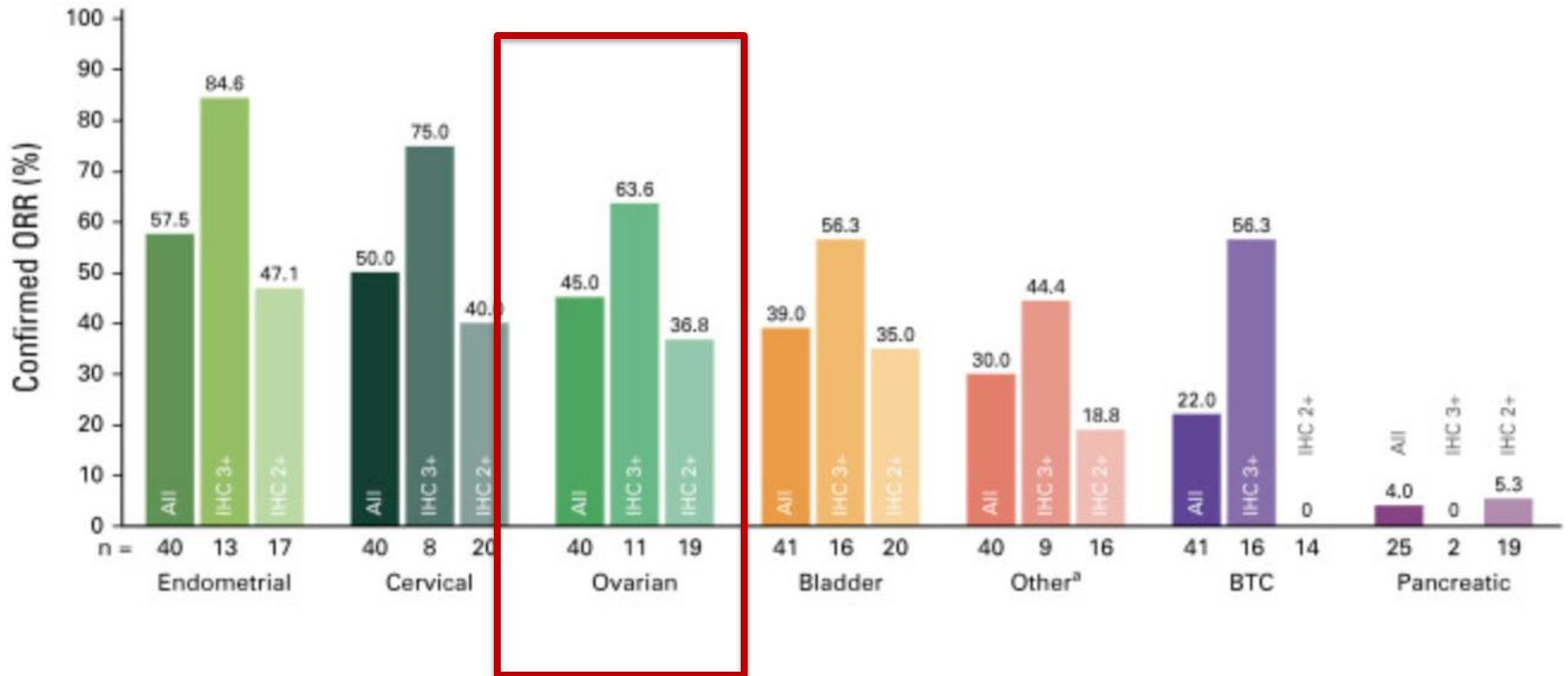


when the **cancer cell** dies, the **chemotherapy drug DXd** may be freed, going on to kill neighboring **cancer cells**

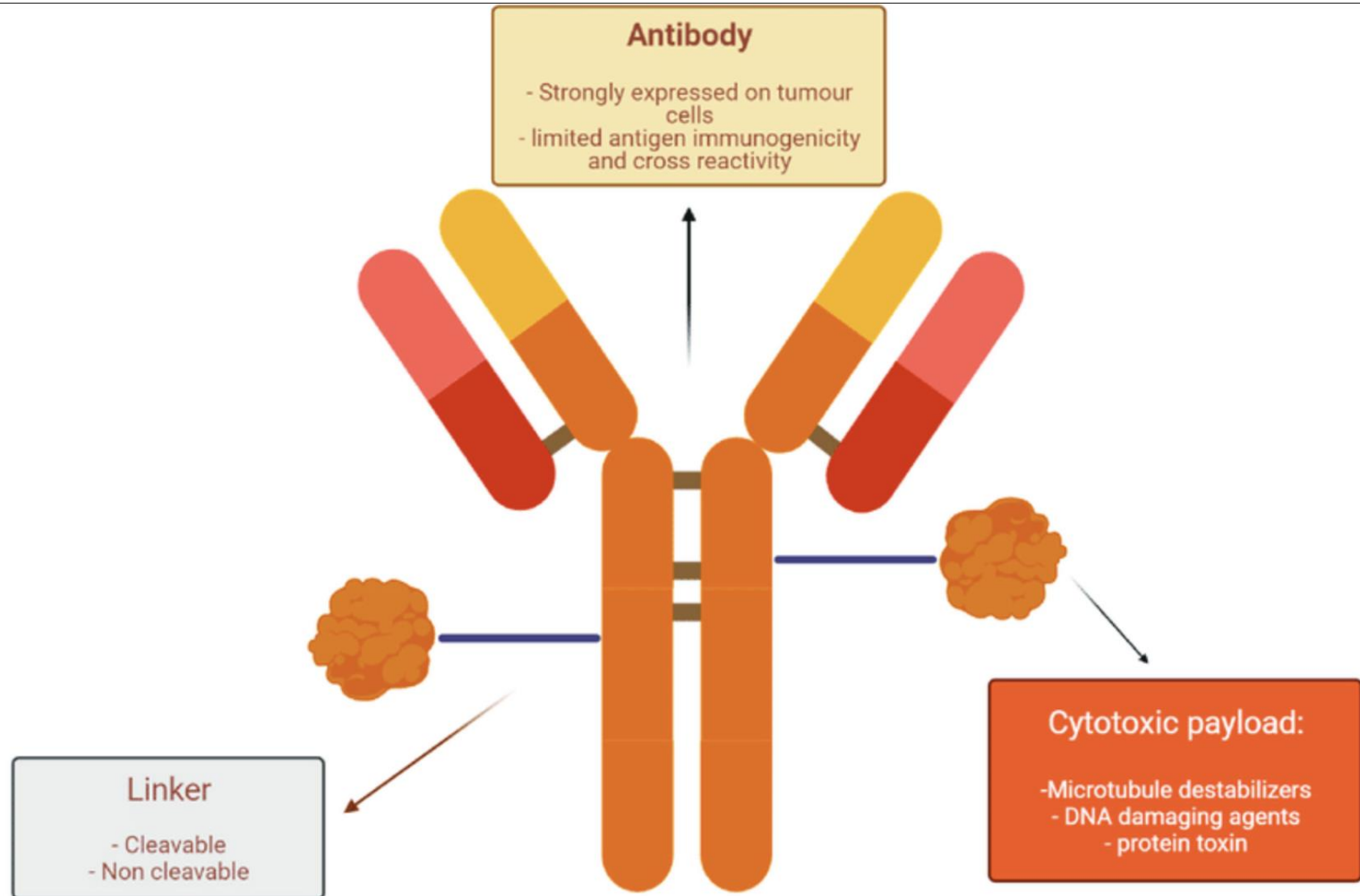


Her 2 neu positive tumors

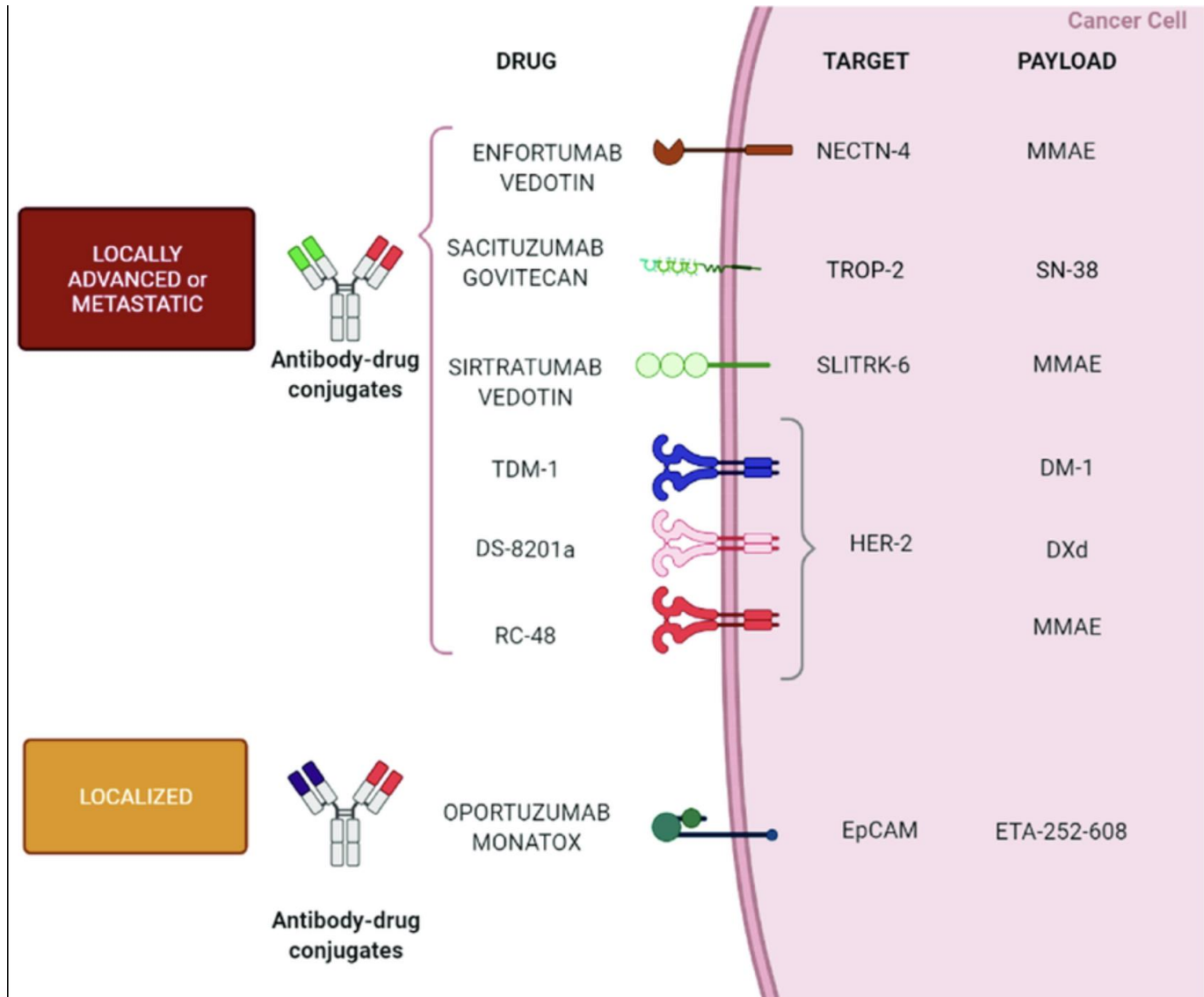
Trastuzumab Deruxtecan (Enhertu)



New Era: Antibody Drug Conjugates



New Era: Antibody Drug Conjugates



Other new drugs

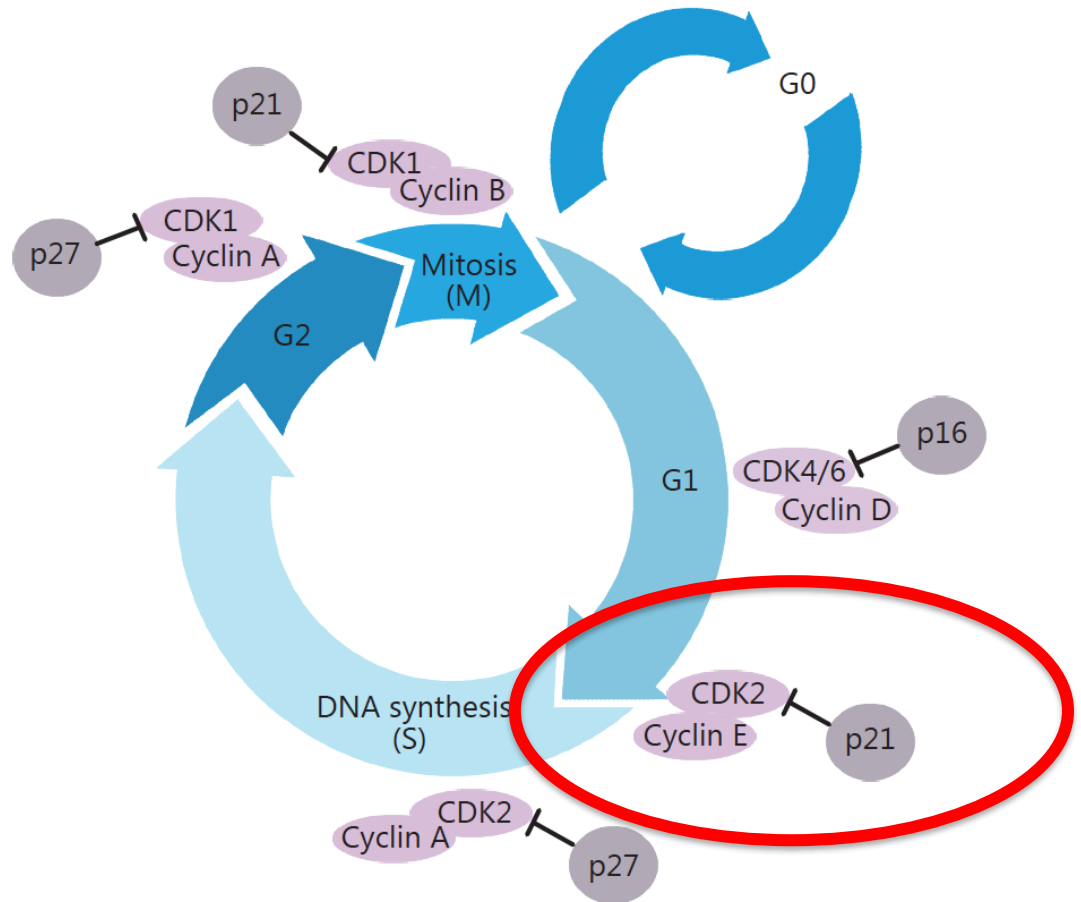
Cyclin E Overexpression

Cyclin E overexpression

- in 10% of ovarian cancers
- aggressive cancers
- resistant to chemotherapy



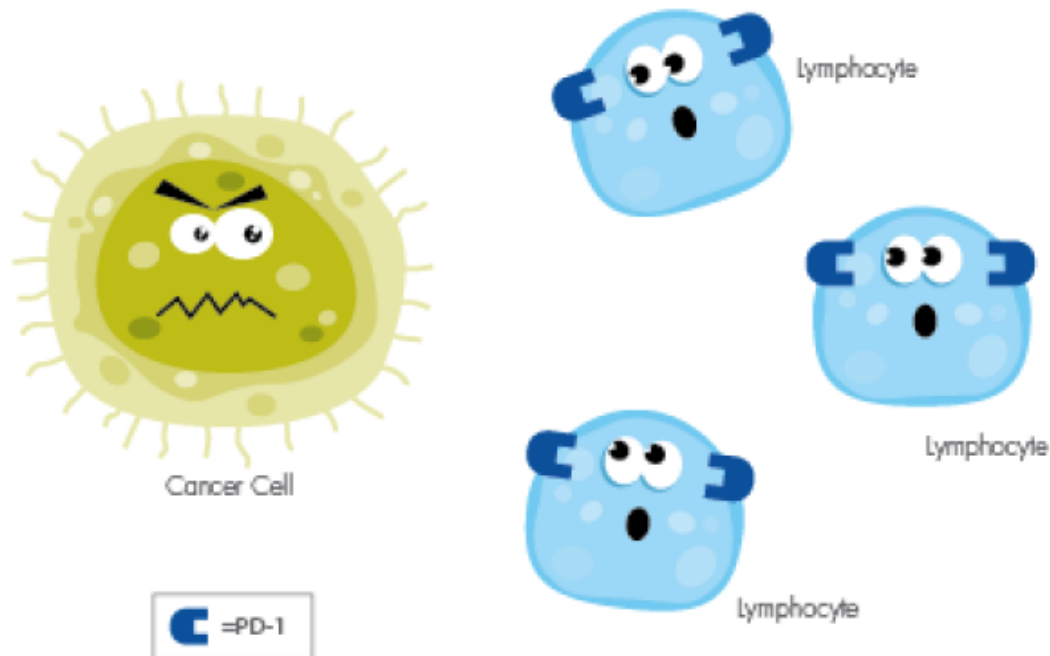
Testing of new
agents that block
CDK2



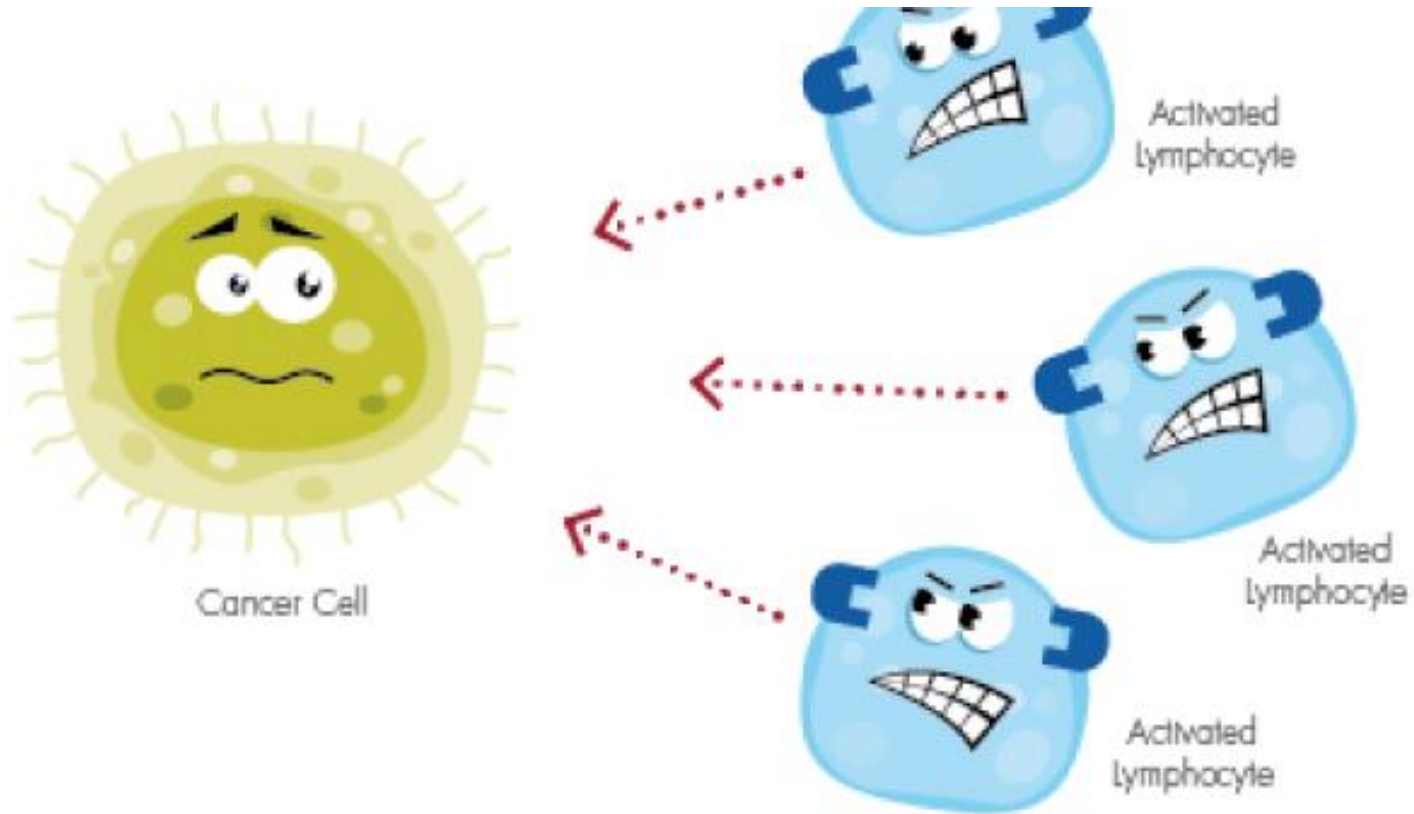
Immunotherapy:

How does the immune system work?

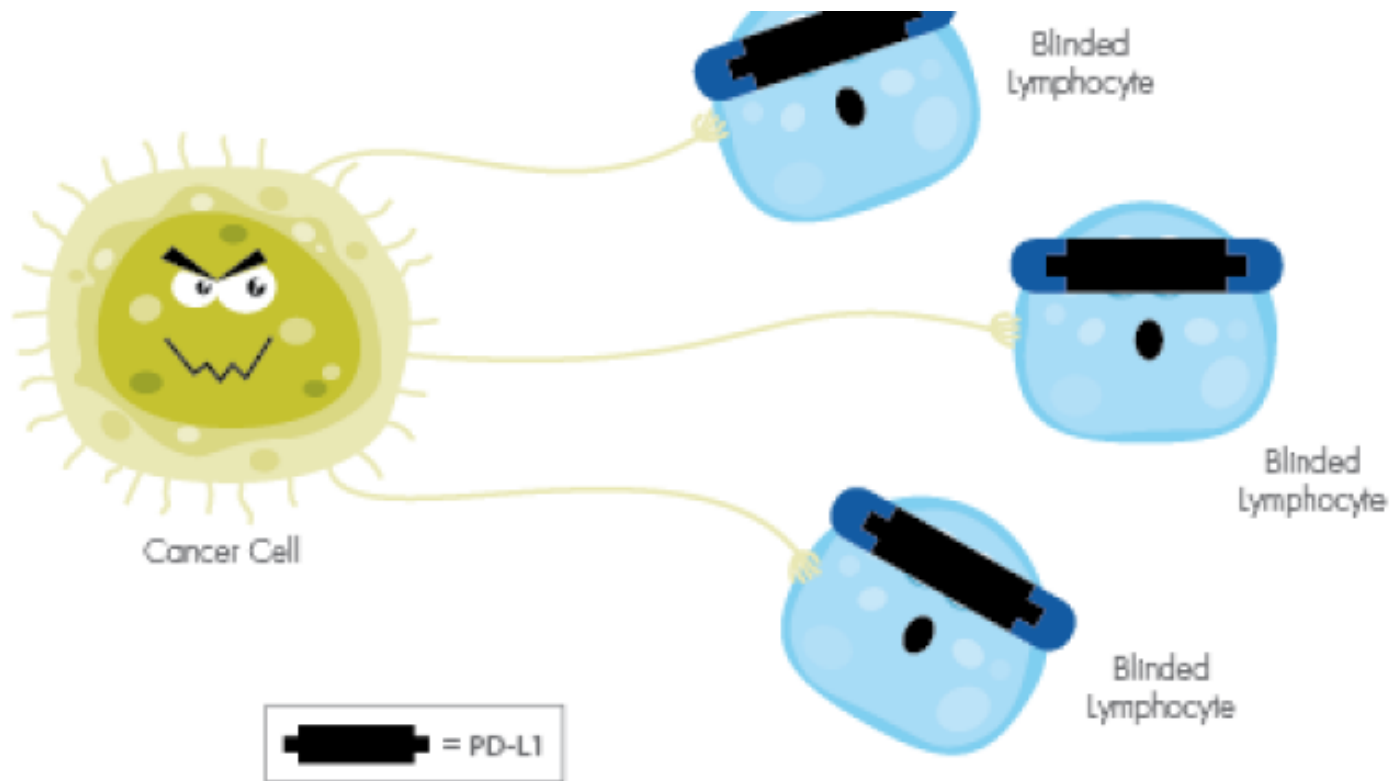
Figure 1A. Lymphocytes recognize the cancer cell as something that is not supposed to be there...



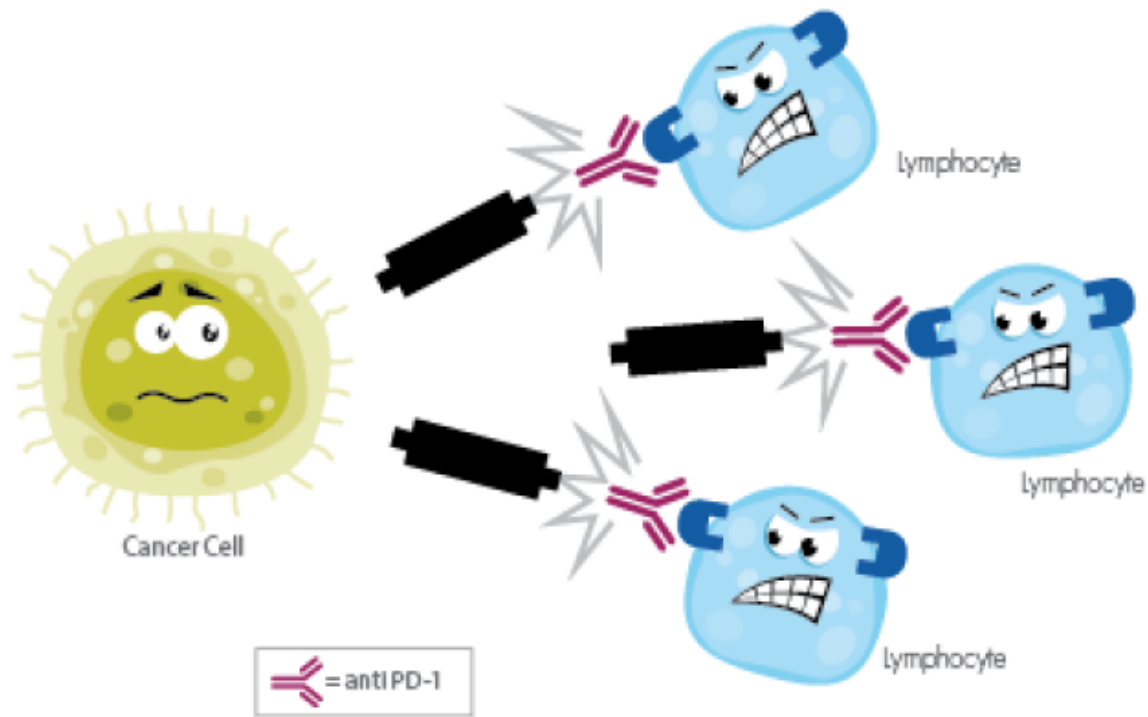
How does the immune system work?



Mechanism by which tumor cells evade the immune system

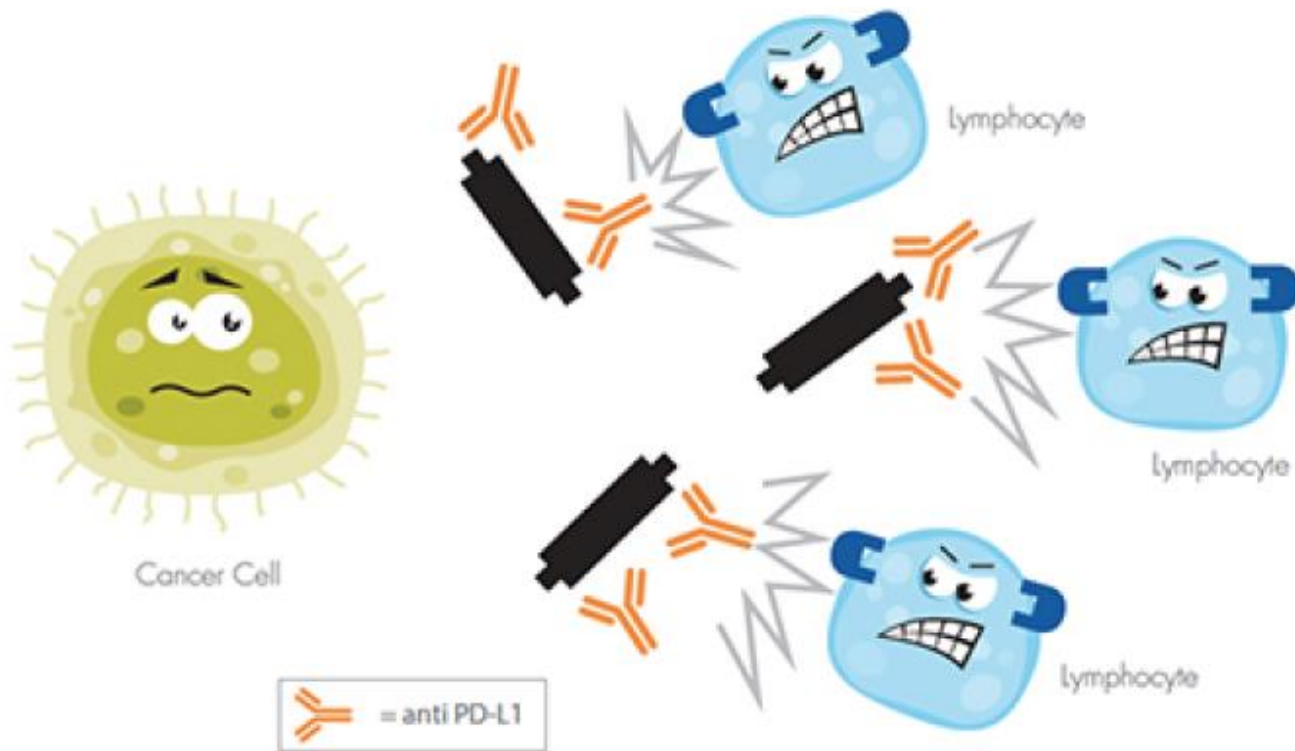


How to unblock anti-tumor immunity: **Anti-PD1**



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

How to unblock anti-cancer immunity anti-PDL1



Examples: pembrolizumab or dostarlimab —approved for endometrial cancer

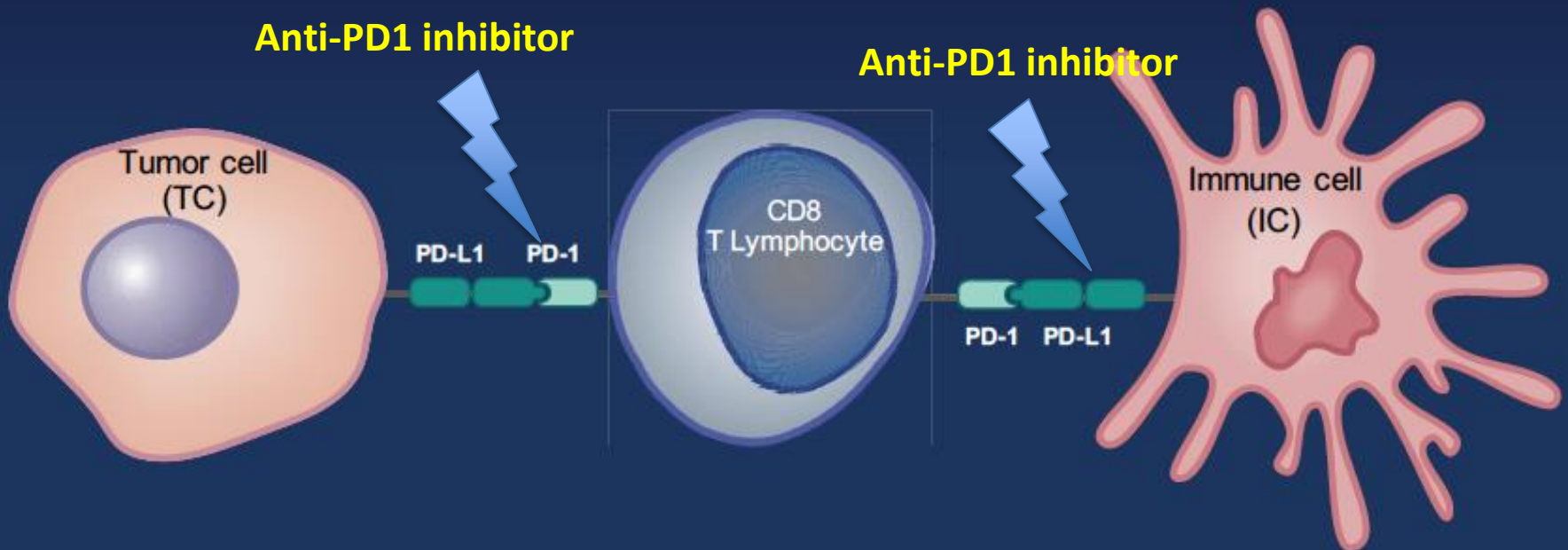
PD-L1 expression by tumor infiltrating immune cells (IC)

PD-L1 expression by tumor cells (TC)

PD-L1 expression in the tumor microenvironment can inhibit anti-tumor T-cell activity

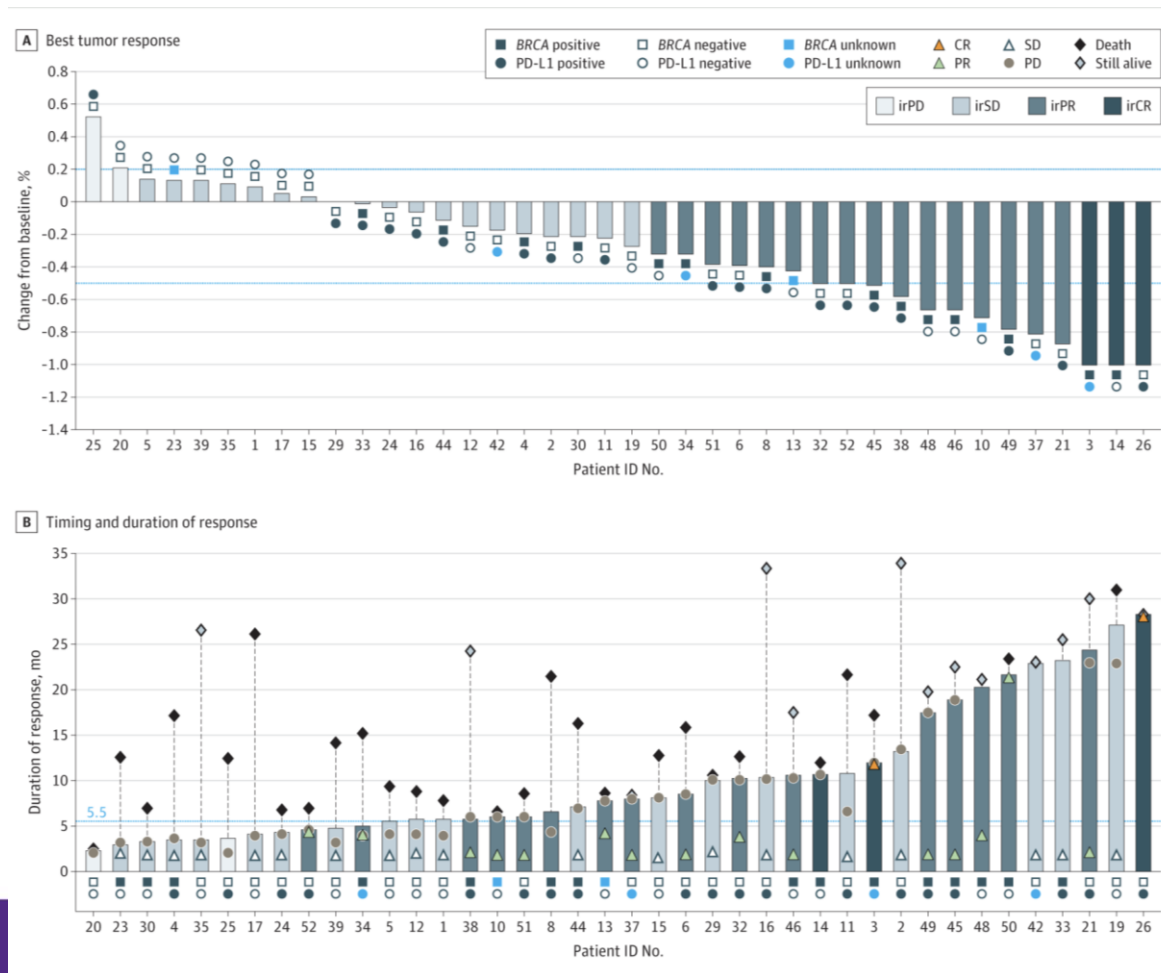
Anti-PD1 inhibitor

Anti-PD1 inhibitor



Immunotherapy combination for ovarian cancer

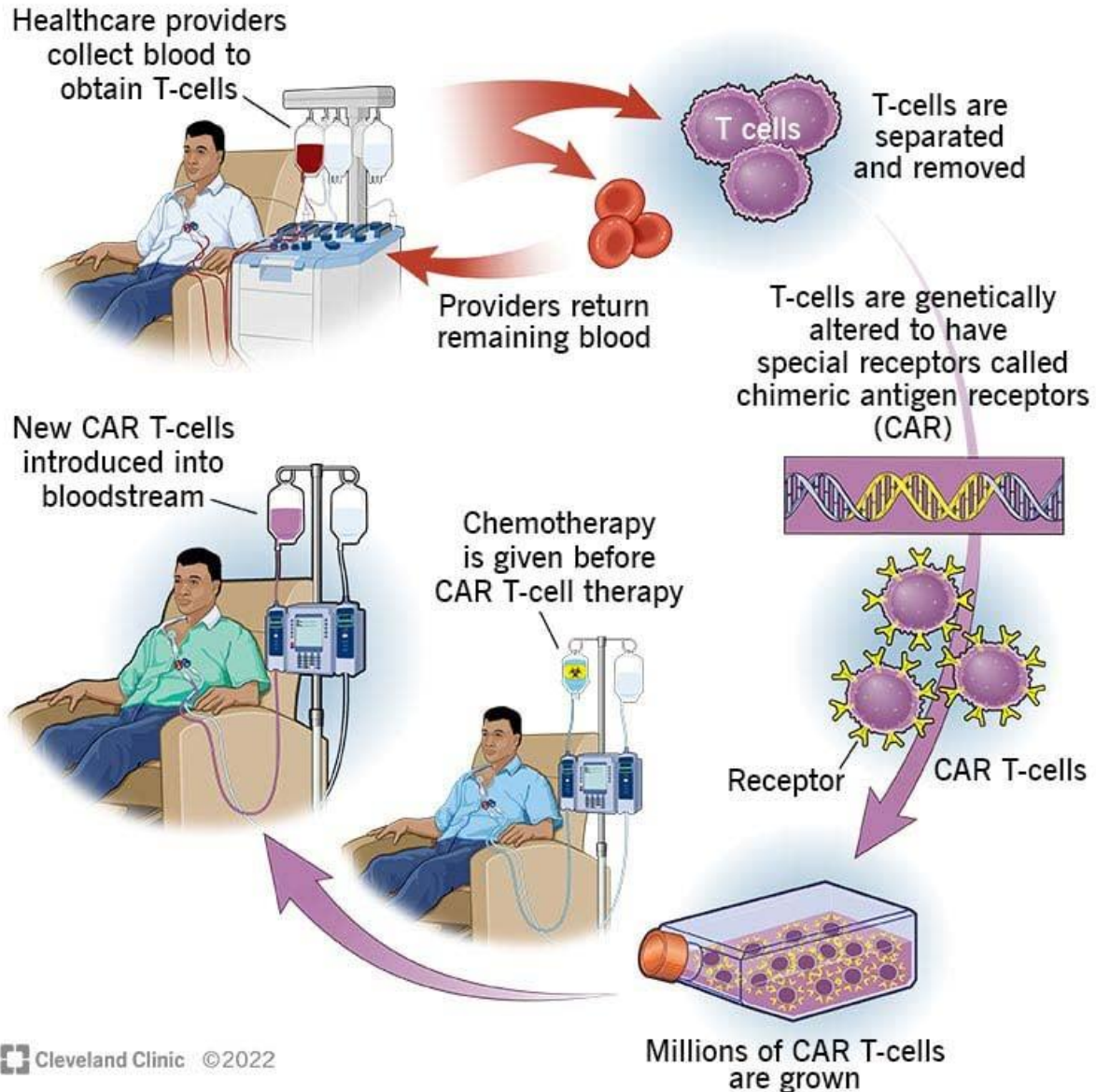
Pembrolizumab, 200 mg, and bevacizumab, 15 mg/kg, every 3 weeks and 50 mg of oral cyclophosphamide once daily during a 21-day treatment cycle



Zsiros, JAMA
Oncology 2020

OTHER FORMS OF IMMUNOTHERAPY

How CAR T-cell therapy is used to treat cancer



CAR T Cell Trials in Ovarian Cancer

Study ID and description	Study phase	Intervention	Target
NCT03017131 ("Genetically Modified T Cells and Decitabine in Treating Patients With Recurrent or Refractory Ovarian, Primary Peritoneal, or Fallopian Tube Cancer")	I	TCR therapy	NY-ESO-1
NCT03691376 ("Genetically Engineered Cells (NY-ESO-1 TCR Engineered T Cells and HSCs) After Melphalan Conditioning Regimen in Treating Patients With Recurrent or Refractory Ovarian, Fallopian Tube, or Primary Peritoneal Cancer")	I	TCR therapy	NY-ESO-1
NCT01567891 ("CT Antigen TCR-redirected T Cells for Ovarian Cancer")	I/IIa	TCR therapy	NY-ESO-1
NCT02650986 ("Gene-Modified T Cells with or Without Decitabine in Treating Patients with Advanced Malignancies Expressing NY-ESO-1")	I/IIa	TCR therapy	NY-ESO-1
NCT02096614 ("Investigator Initiated Phase 1 Study of TBI-1201")	I	TCR therapy	MAGE-A4
NCT03412877 ("Administration of Autologous T-cells Genetically Engineered to Express T-cell Receptors Reactive Against Mutated Neoantigens in People with Metastatic Cancer")	II	TCR therapy	Unspecified

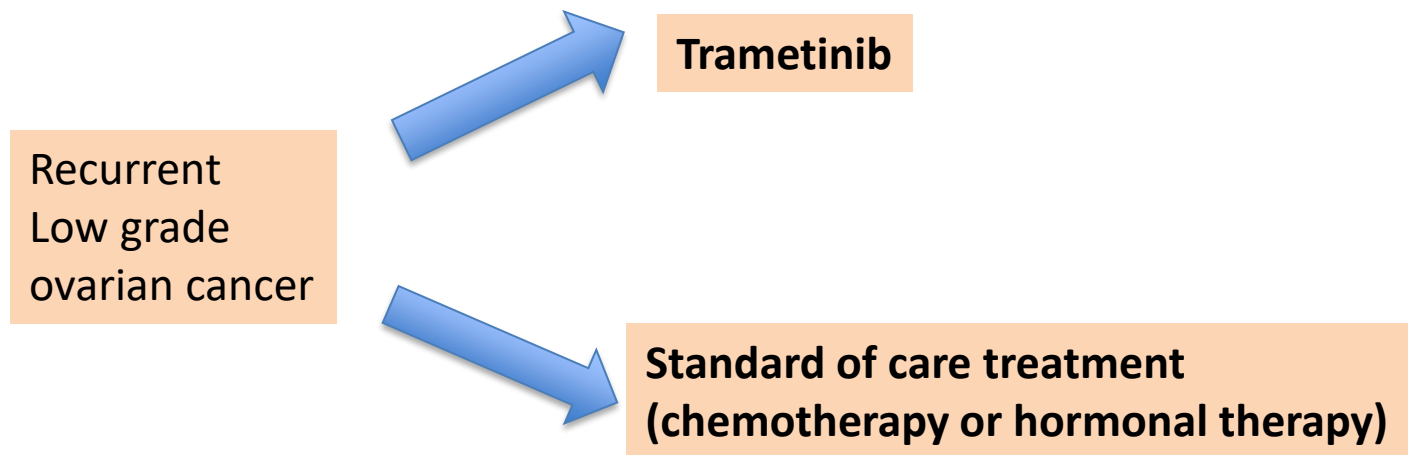
TCR, T-cell receptor; NY-ESO-1, New York esophageal-1; MAGE-A4, melanoma-associated antigen 4.

Immunotherapy-take home message

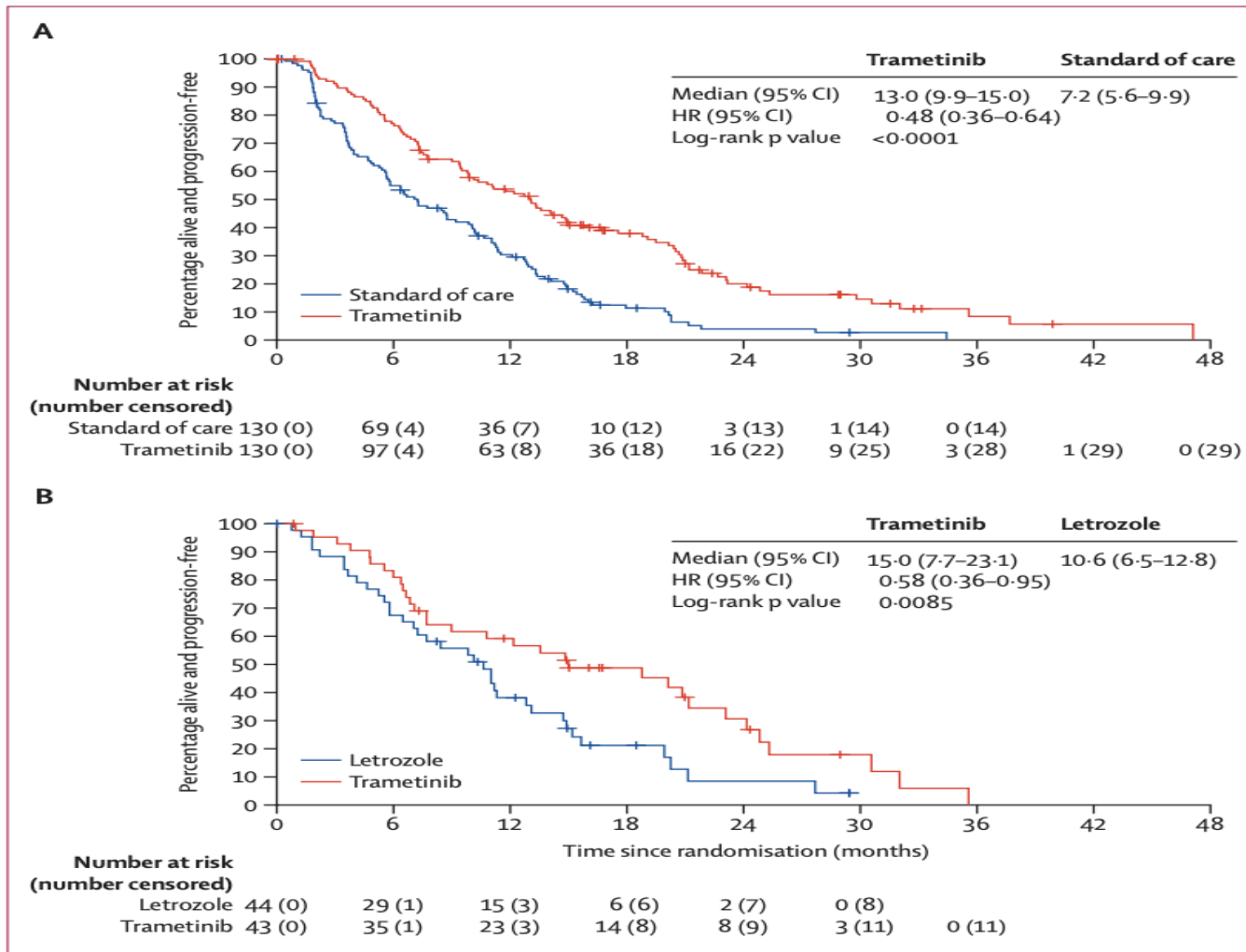
- New class of drugs very active in cancer
- Toxicity profiles includes immune effects (rash, arthritis, diarrhea)
- Efficacy in ovarian cancer is modest, but immune therapies are active in endometrial cancer and cervical cancer
- High MSI or High tumor mutation burden are predictors of response to immunotherapy (rare in ovarian cancer)
- Patients who respond have **long remissions**
- 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.

Low grade serous ovarian cancer

- Rare subtype of ovarian cancer.
- Slow tumor growth
- Poor response to chemotherapy
- Present estrogen receptor, response to anti-estrogens.
- Present mutations in the growth pathway RAS-RAF-MAPK

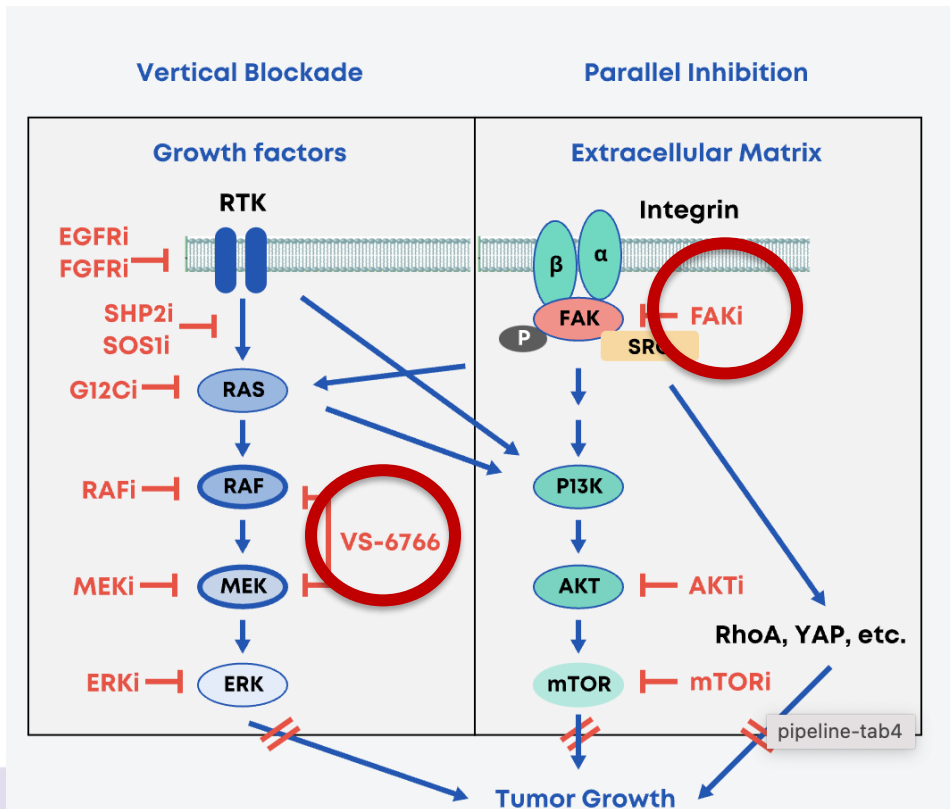


Low grade serous ovarian cancer



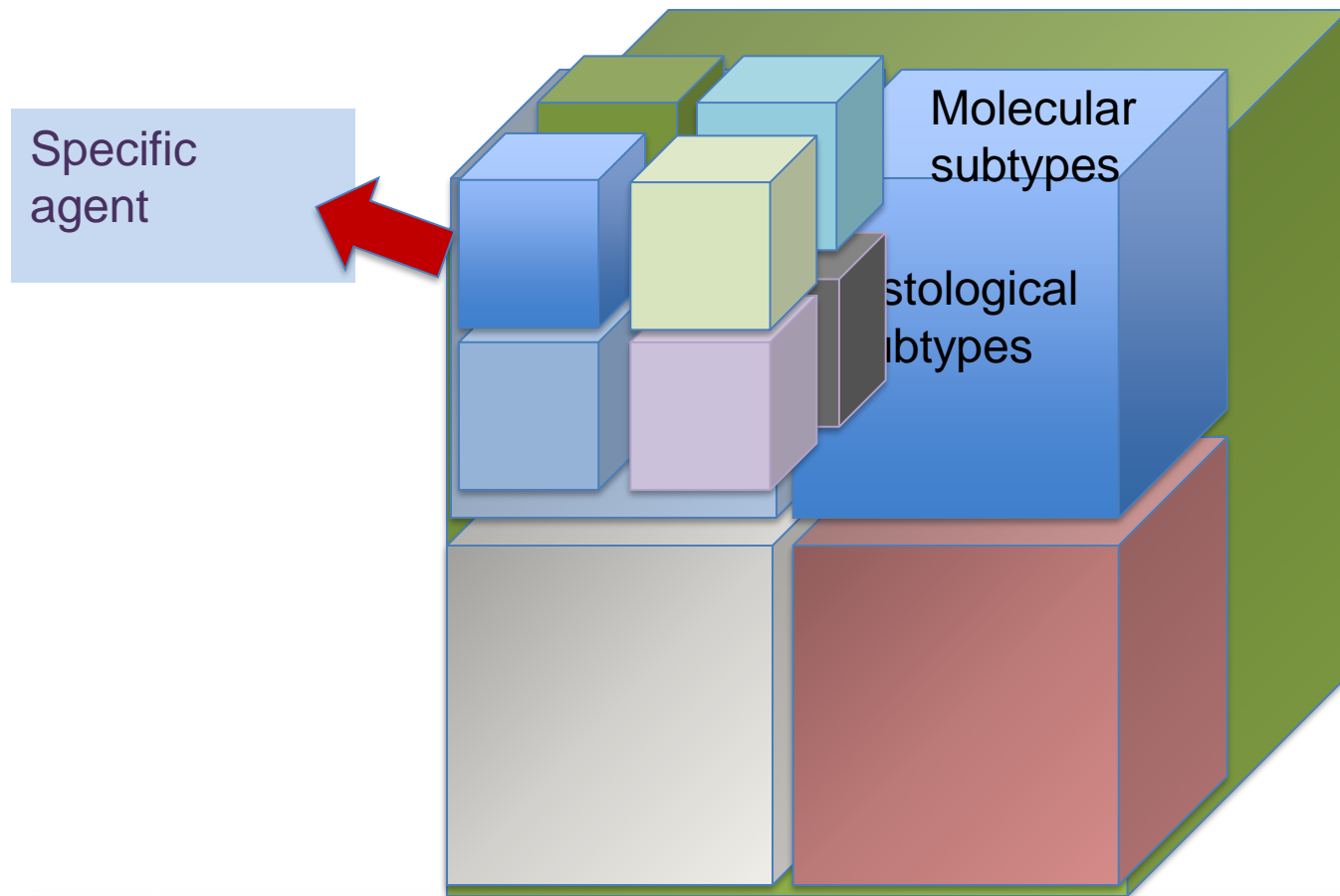
New trials for LGSOC

- GOG-3097/ENGOT-ov81/NCRI/RAMP 301: A Phase 3, Randomized, Study of Combination Therapy with Avutometinib plus Defactinib Versus Investigator's Choice for LGSOC **ONGOING**



Previous results phase II:
response rate 45%
KRAS mutations RR: 60%
KRAS not mutated: RR 29%

Is Personalized Treatment Achievable in Gynecologic Cancer?



Lessons learned: Clinical Trials

“Like quite a few patients, I live and breathe today because of cutting-edge research. With conventional medicine, I would have died back in 2013. When before the start of my trial I read the 20 or 30 pages of boilerplate, I signed on the dotted line, even though the document informed me that the drug might kill me and that its administrators would not be held accountable. I signed because I wanted to see if a new approach might save me from the miseries of standard treatments that had proven ineffective. I also signed because I wanted to help other people with cancer.” **Susan Gubar, *The New York Times***

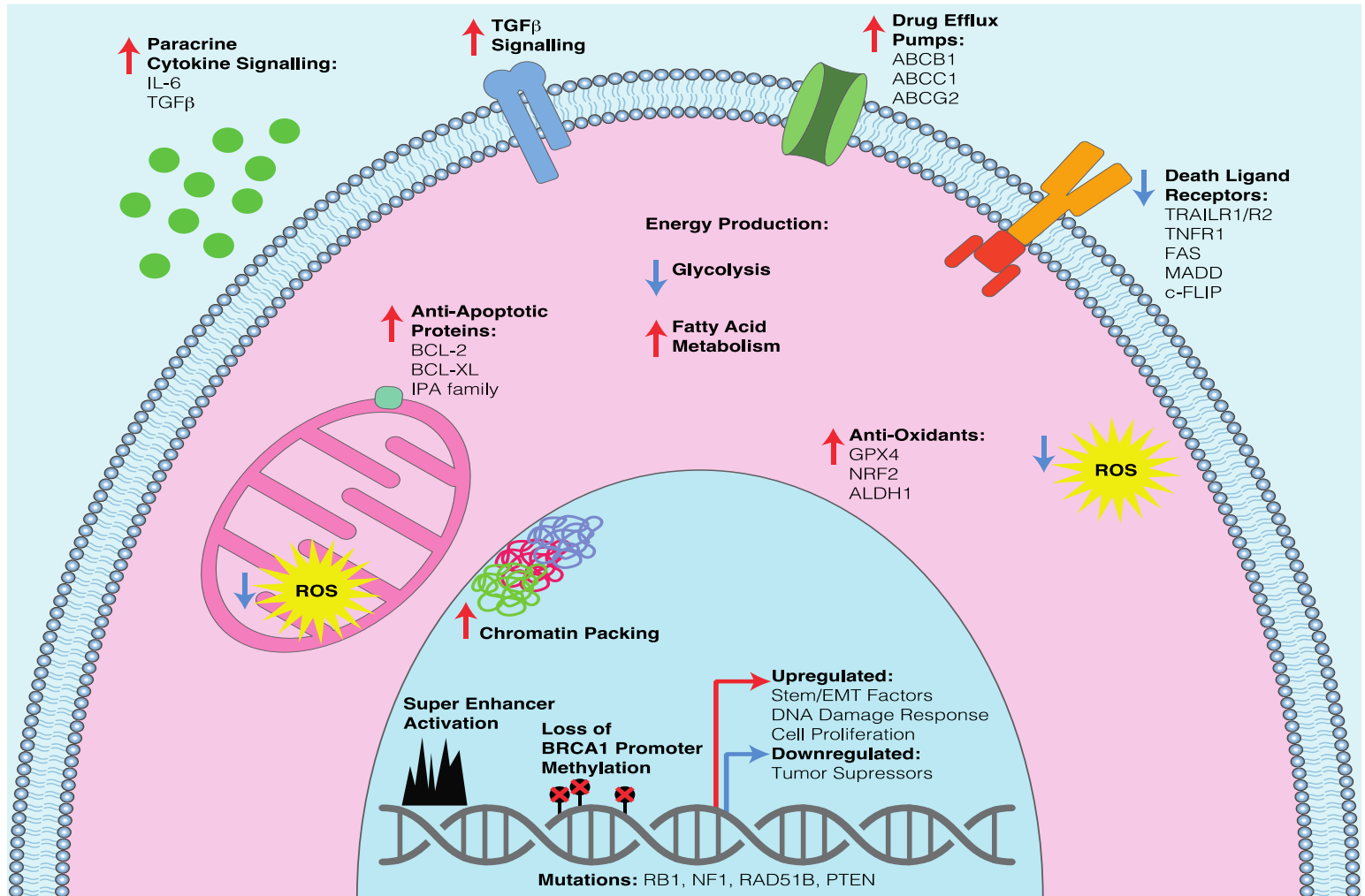


Picture by Fabio Consoli, *NYT*



Matei Research Update

Platinum Resistance—Molecular Mechanisms

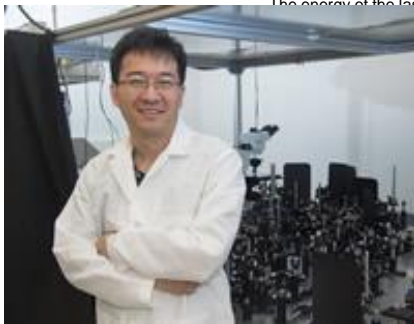
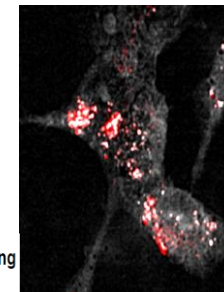
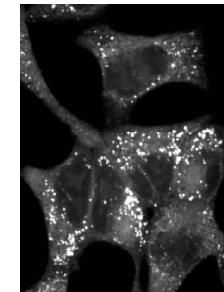
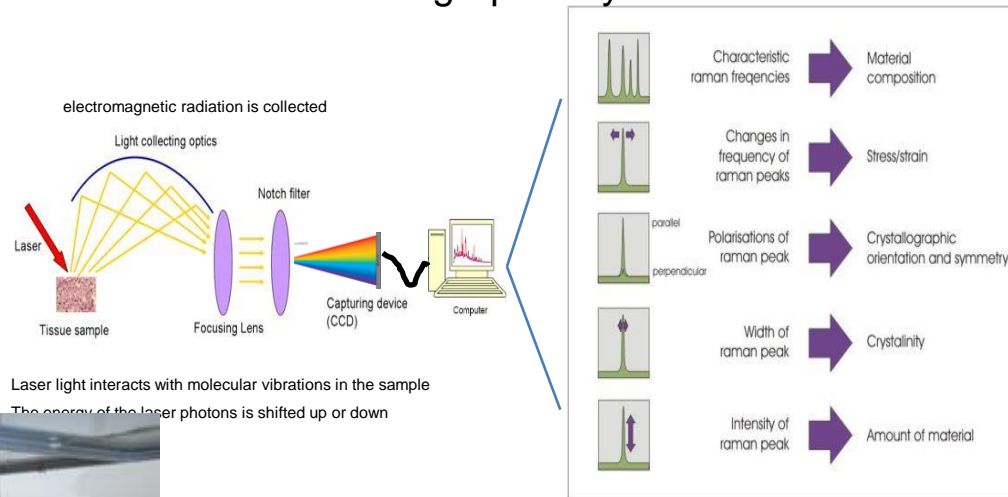


Wang,...,Matei, JCI, 2024

Hyperspectral Stimulated Raman Scattering (SRS) Microscopy

Raman spectroscopy:

- Detects low-frequency modes in a system (vibrational, rotational)
- Provides molecular fingerprint by which molecules can be identified



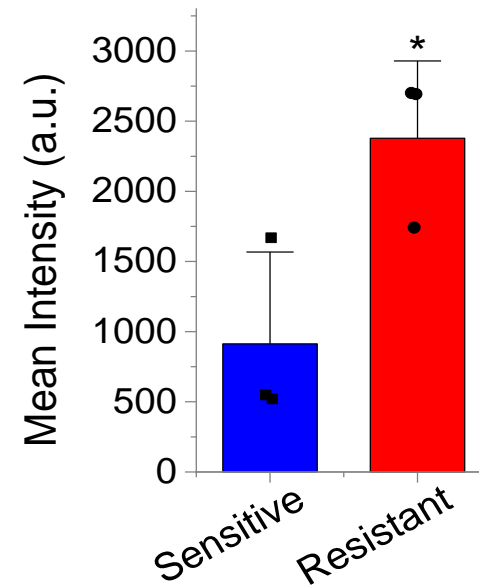
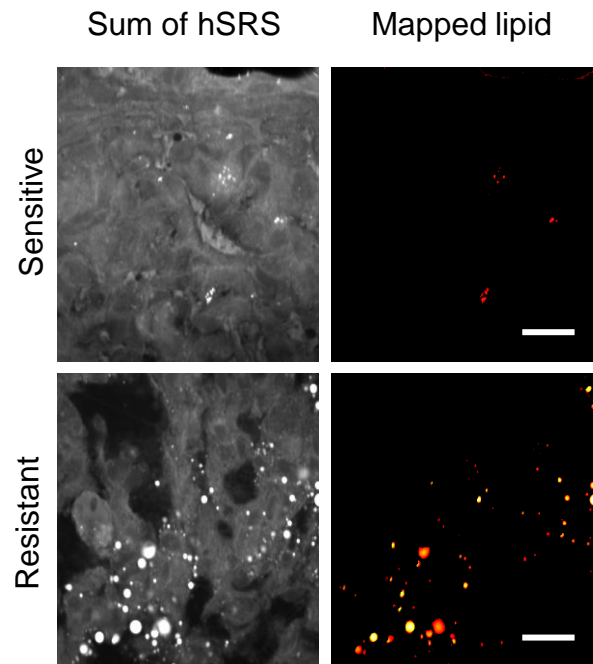
Ji Xin Cheng, Boston University



Vibrational spectroscopic imaging of living systems: An emerging platform for biology and medicine

Ji-Xin Cheng and X. Sunney Xie
Science **350**, (2015);
DOI: 10.1126/science.aaa8870

Single cell lipid profiling on sensitive/resistant ovarian cancer cells



Tan, Zhao, Matei and Cheng, Nature Communications, 2022

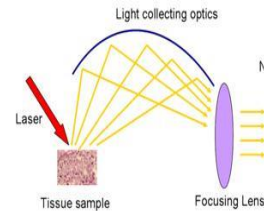
Human Tumor Samples Analyzed with SRS Microscopy



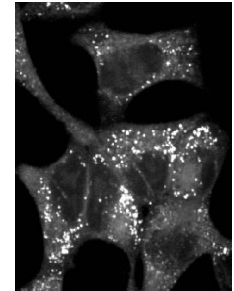
Sample collection
Operating room
Clinical annotation



Cell dissociation
Incubation with
D7 Glu and ODYA

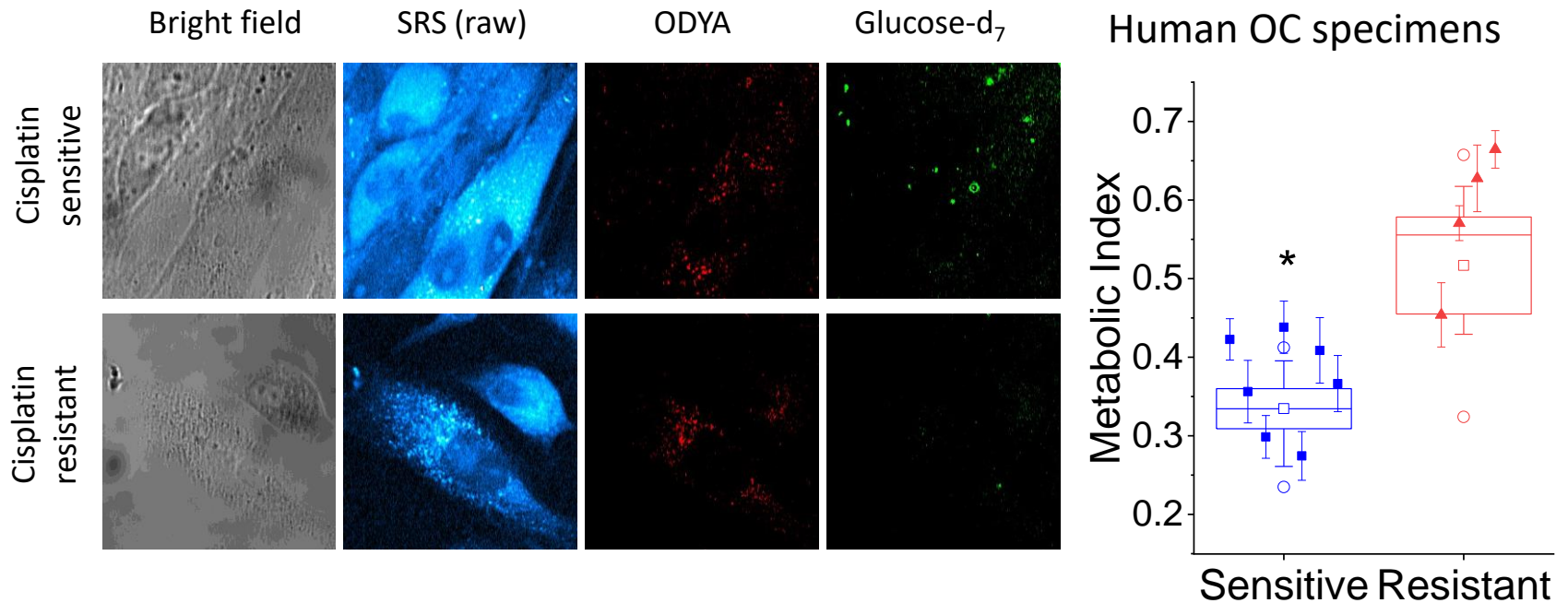


hSRS Microscopy



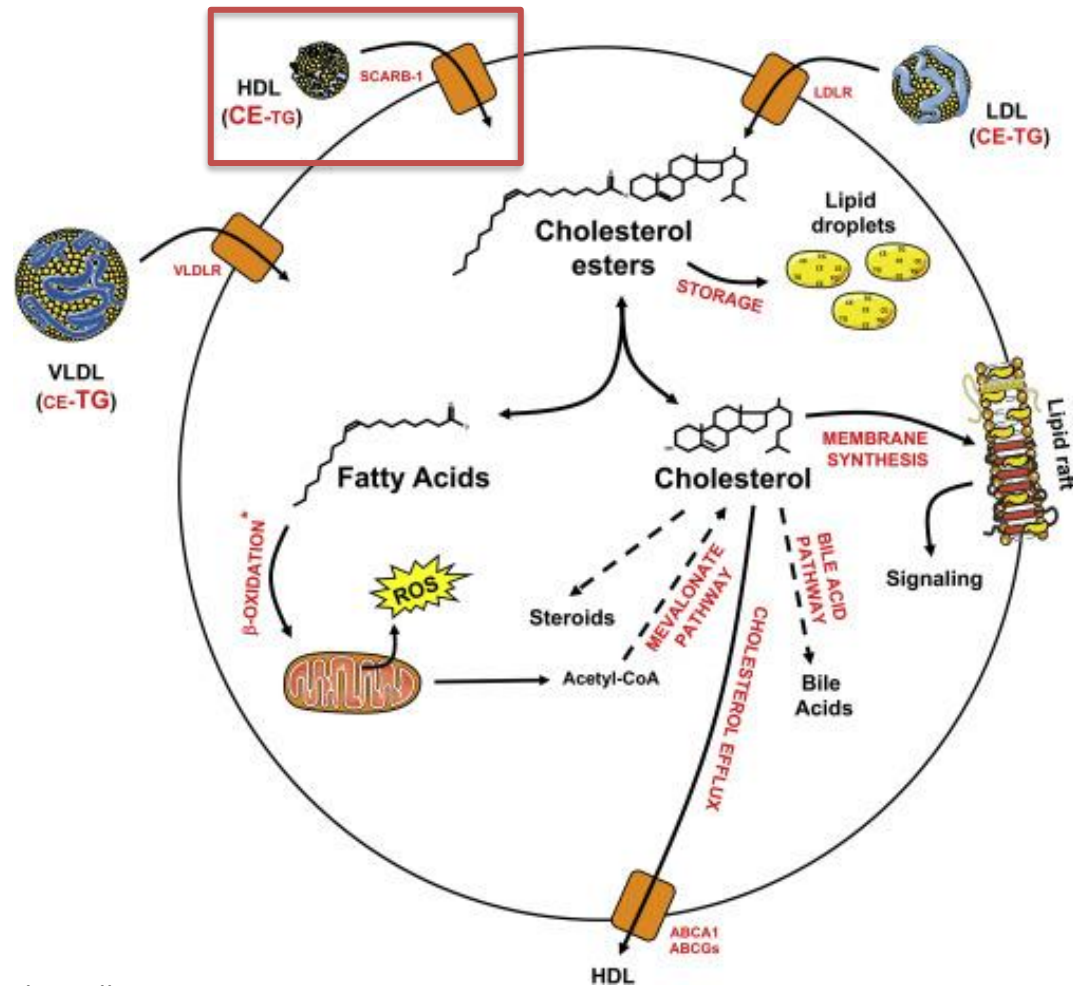
Metabolic Index
determined

Metabolic Index Correlated with Responsiveness to Platinum



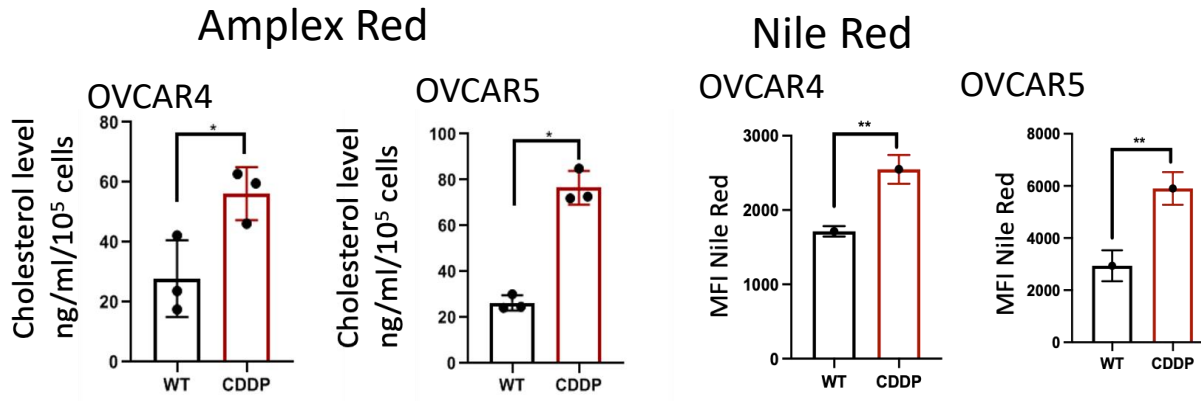
Tan, Zhao, Matei, Cheng, Nature Communications, 2022

Cholesterol and Cancer Cells

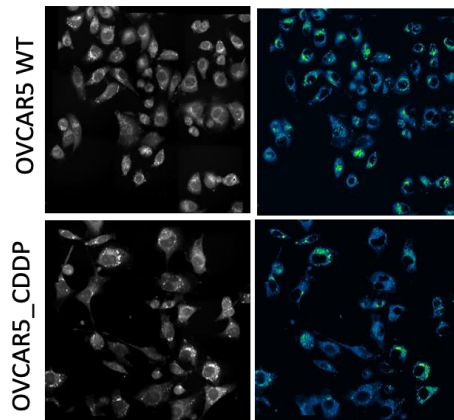


Riscal and Simon, Molecular Cell 2019

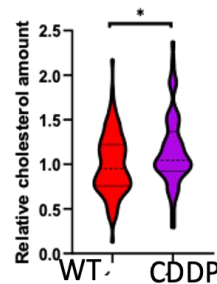
Cholesterol in Resistant Cancer Cells



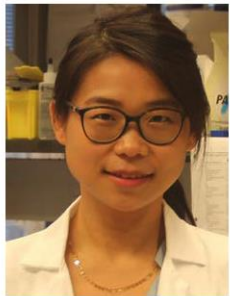
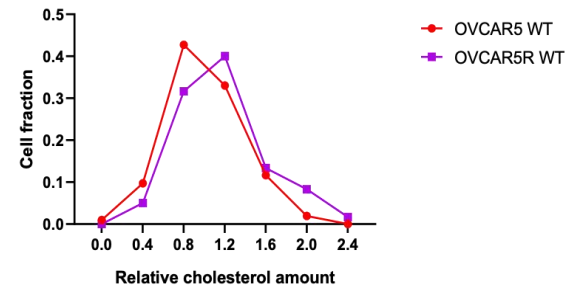
Stack Cholesterol



SRS Imaging



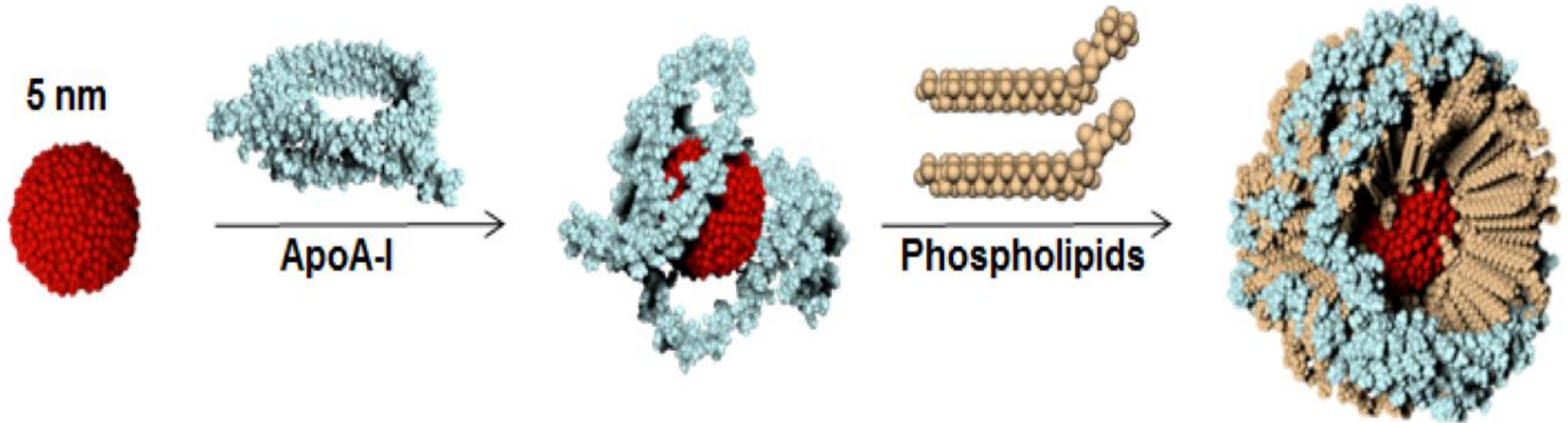
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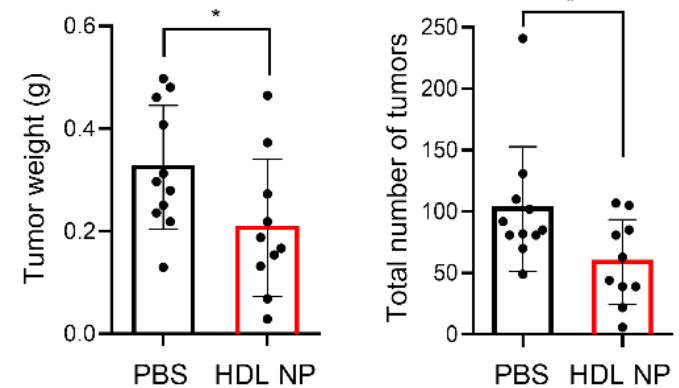
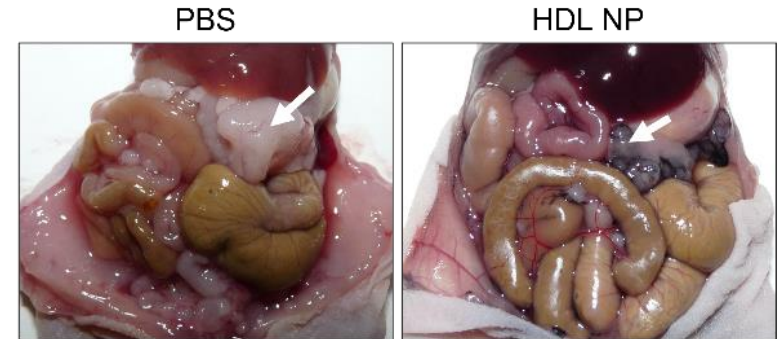
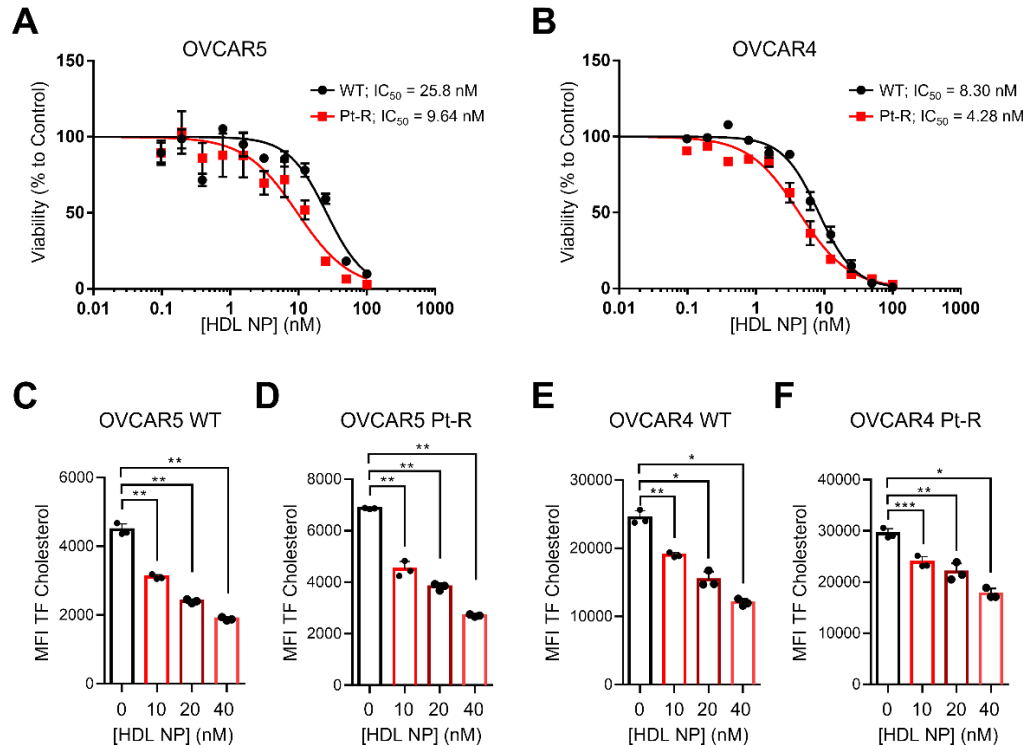
Cholesterol Targeting using HDL Nanoparticles



Collaboration Shad Thaxton

Cholesterol Targeting using HDL Nanoparticles

In Vivo



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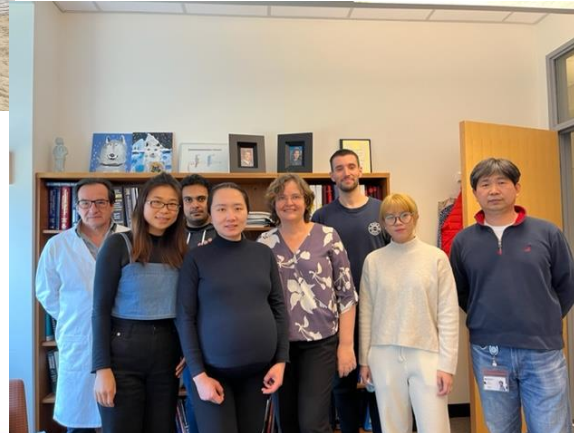
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