

Do we need Biomarkers in Gynecologic Oncology

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Professor of Medicine and Ob/Gyn
University of California Los Angeles



Annual Survivor-Caregiver Summit

What are Biomarkers



Biomarkers tell you....

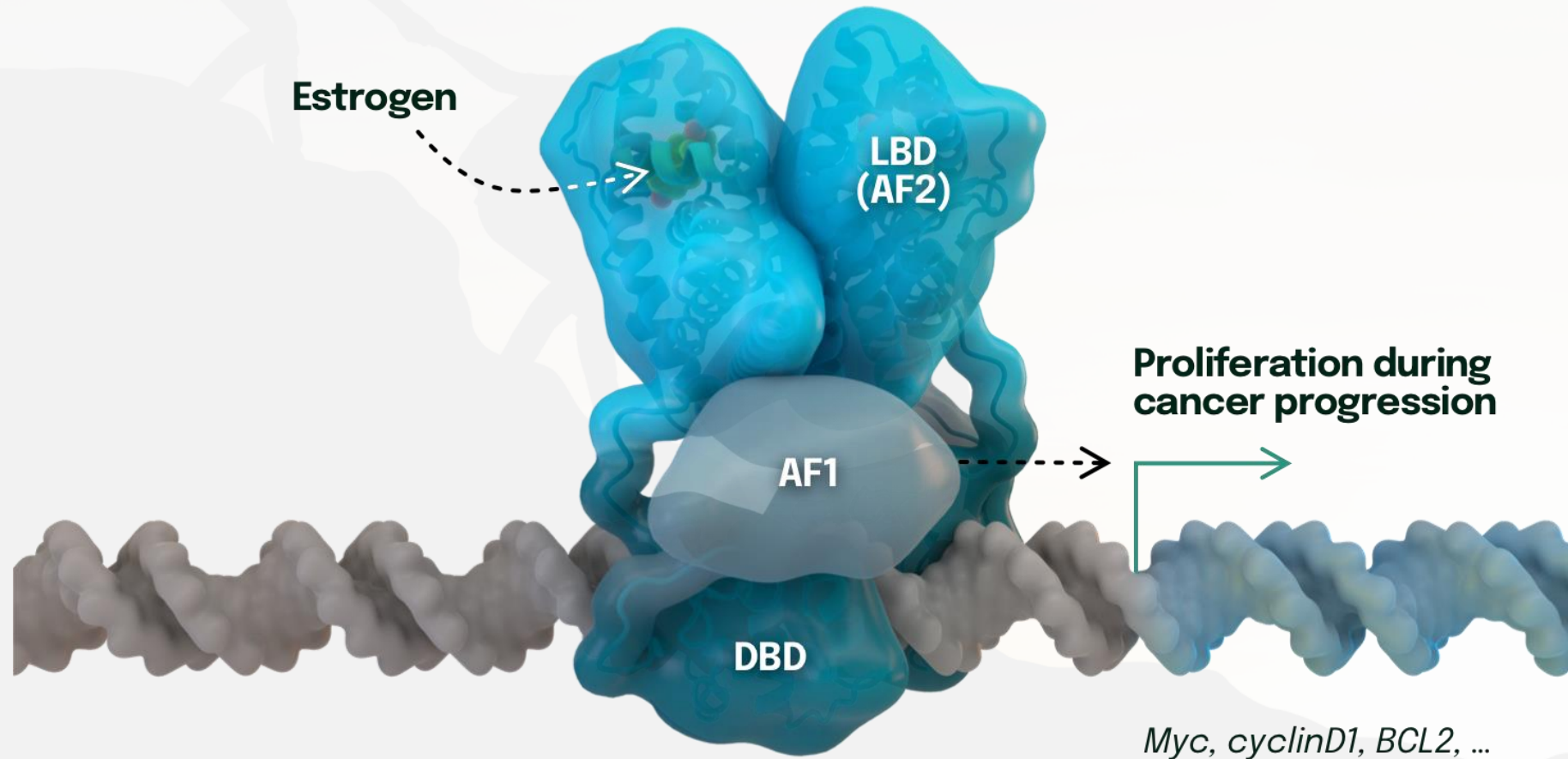
...of an association

...of the likelihood of an event



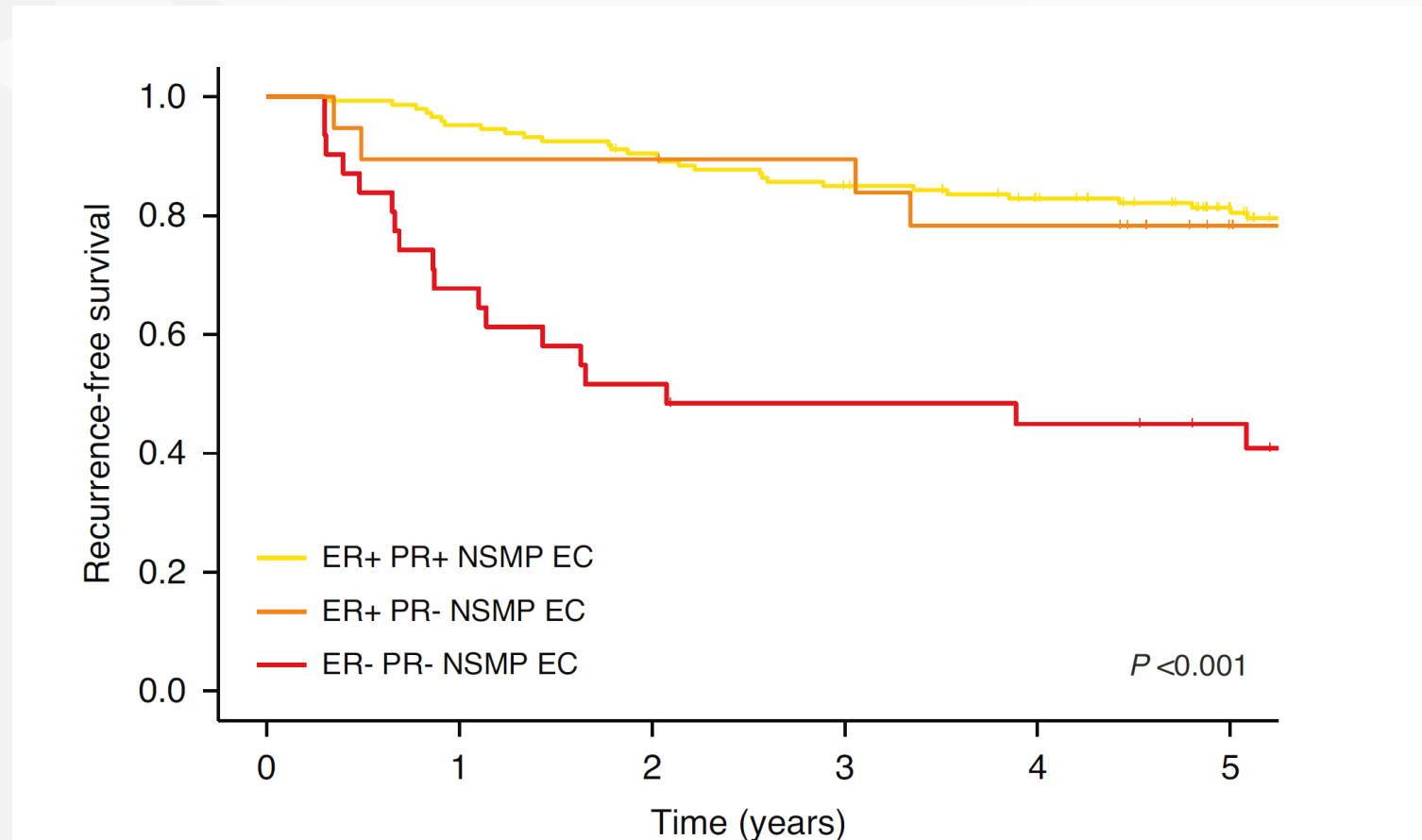
Estrogen Receptor as a Biomarker

Single-agent Immunotherapy efficacy



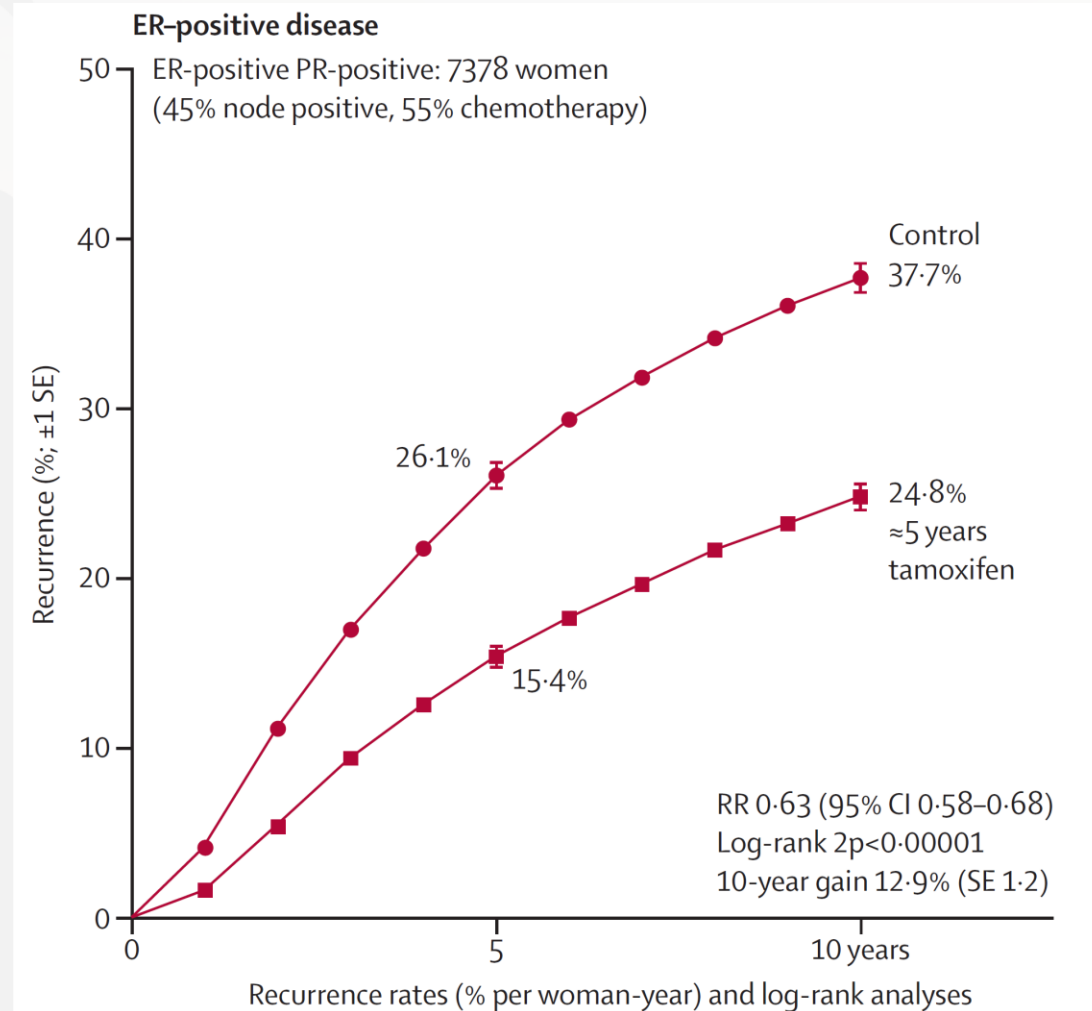
Estrogen Receptor as a Biomarker

Prognostic Marker in Endometrial Cancer

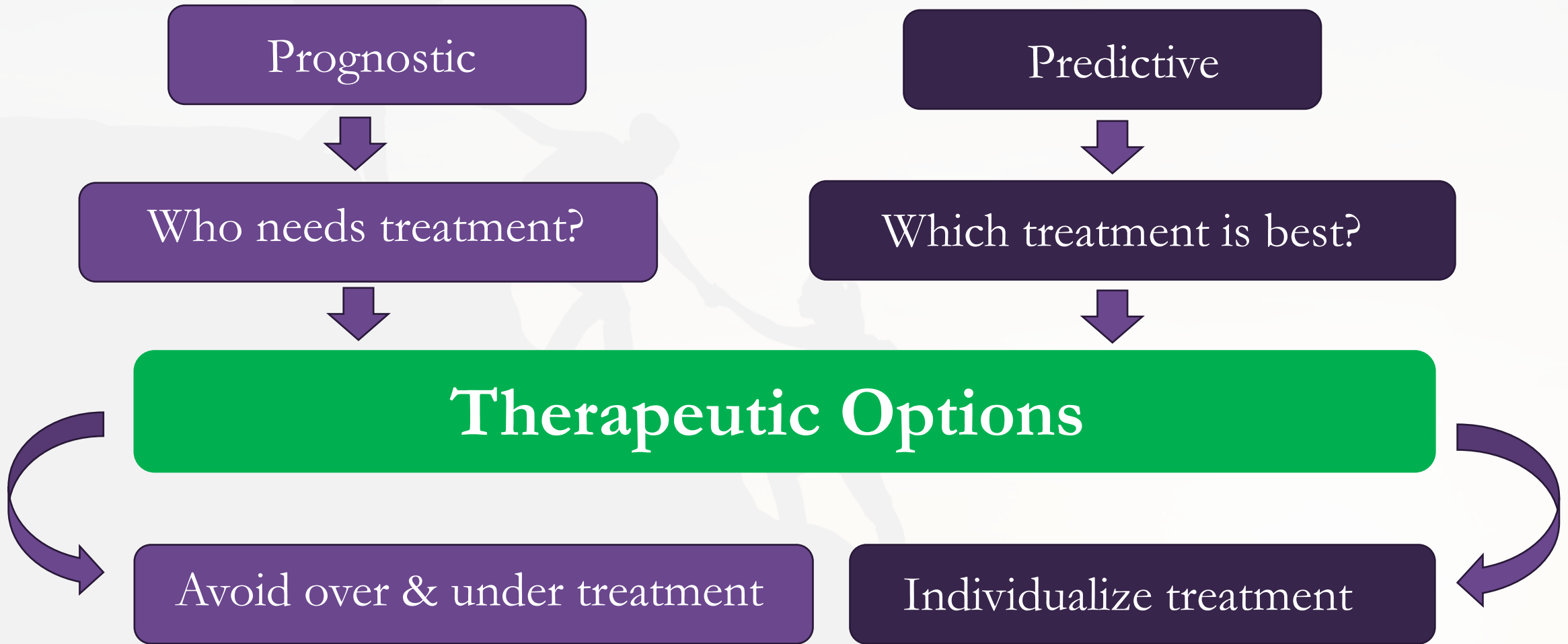


Estrogen Receptor as a Biomarker

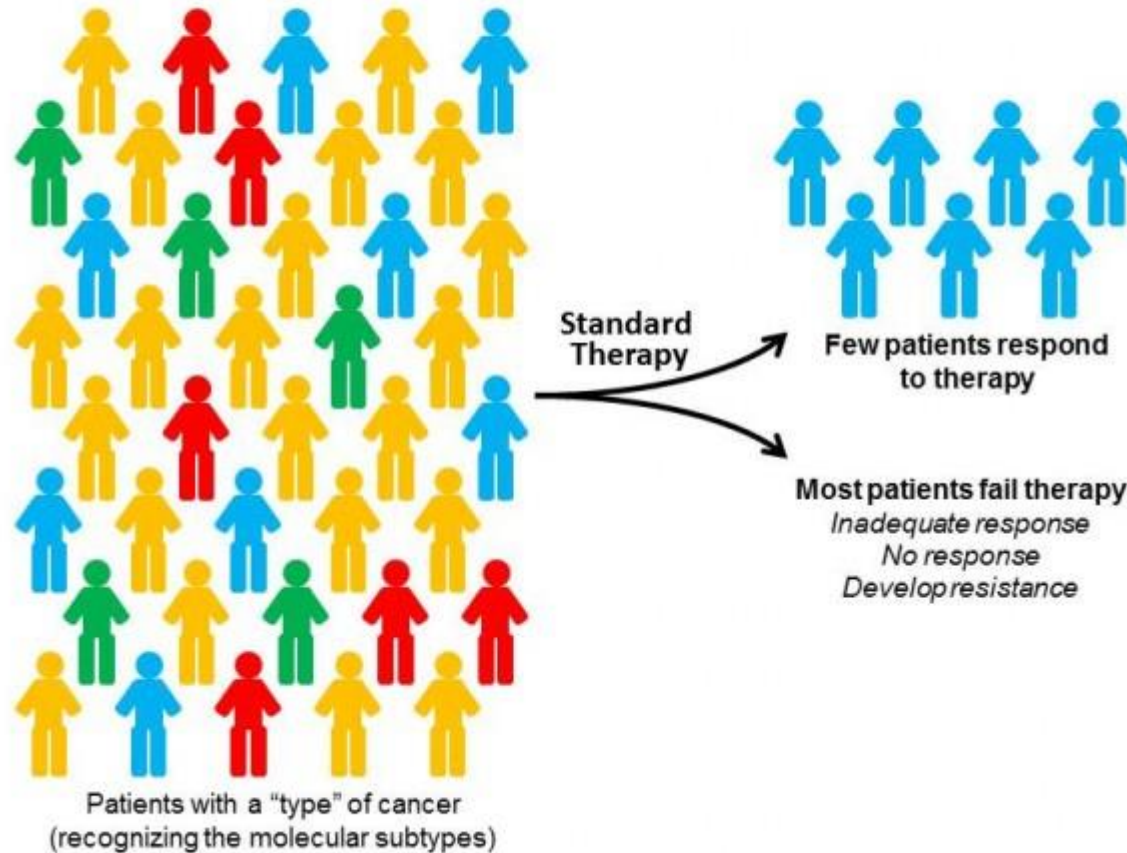
Predictive Marker for Response to Anti-Hormonal Therapy



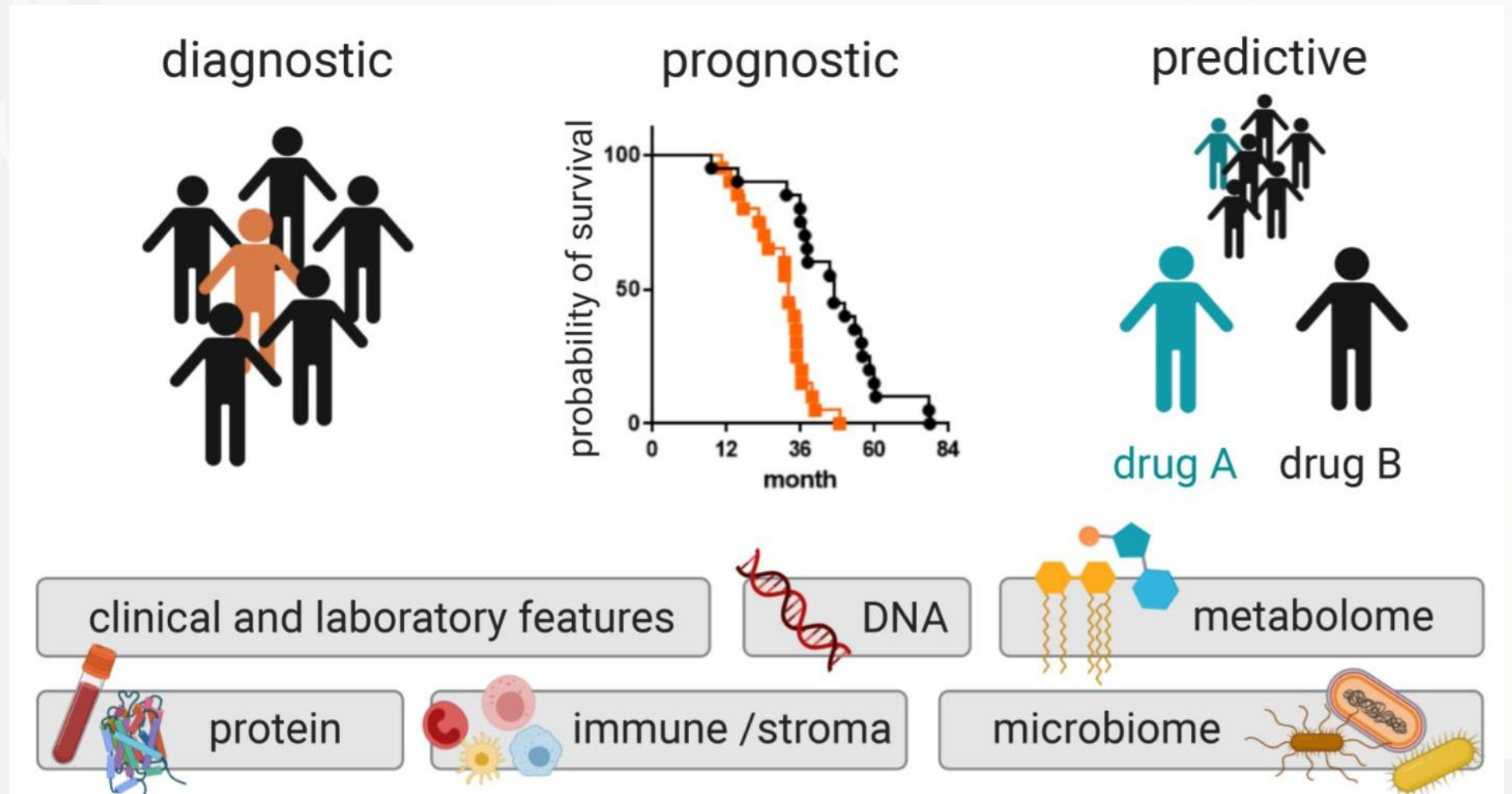
Why do we need *Prognostic* or *Predictive* Markers?



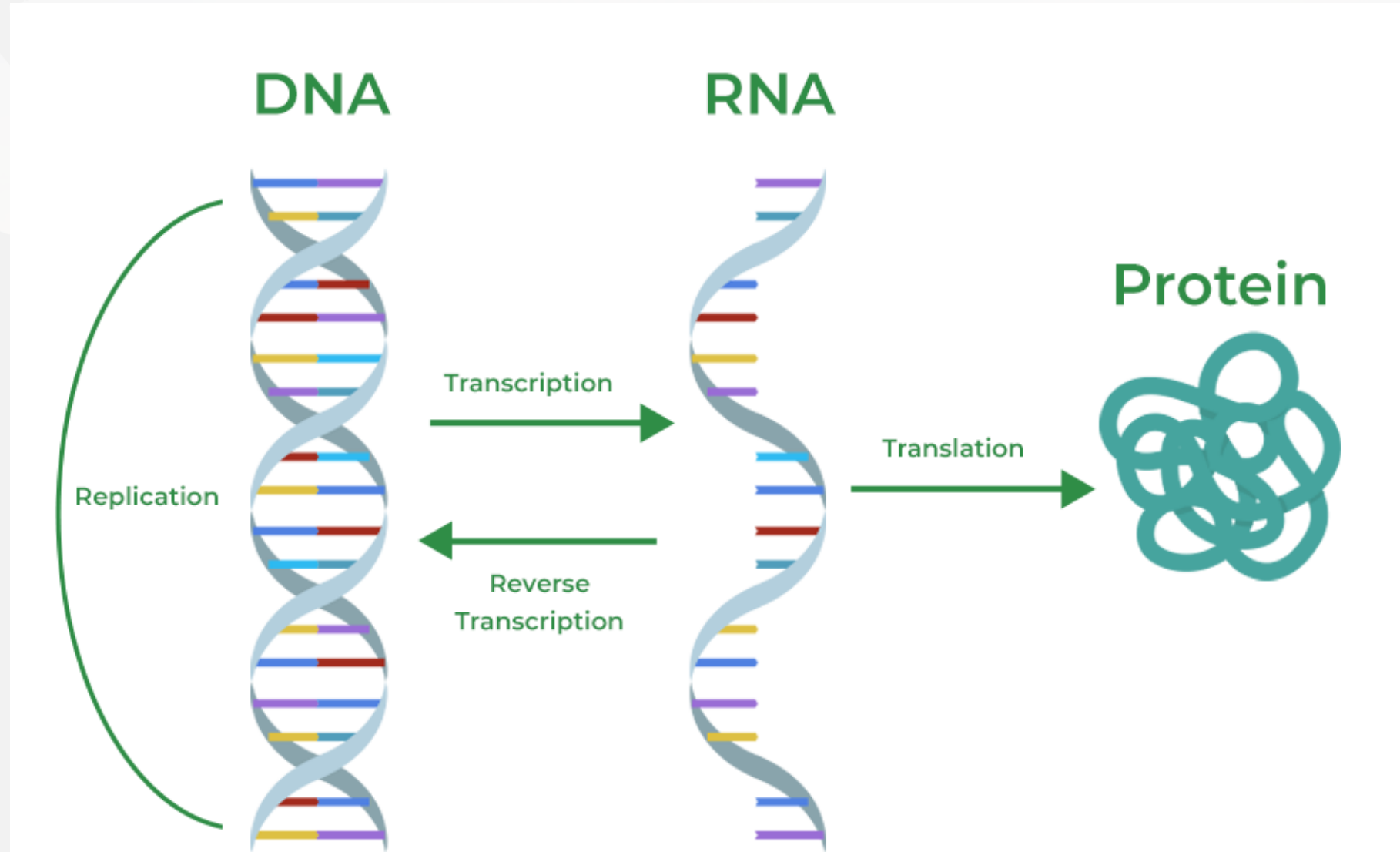
Predictive Markers help individualize Treatments



How do we measure Biomarkers?



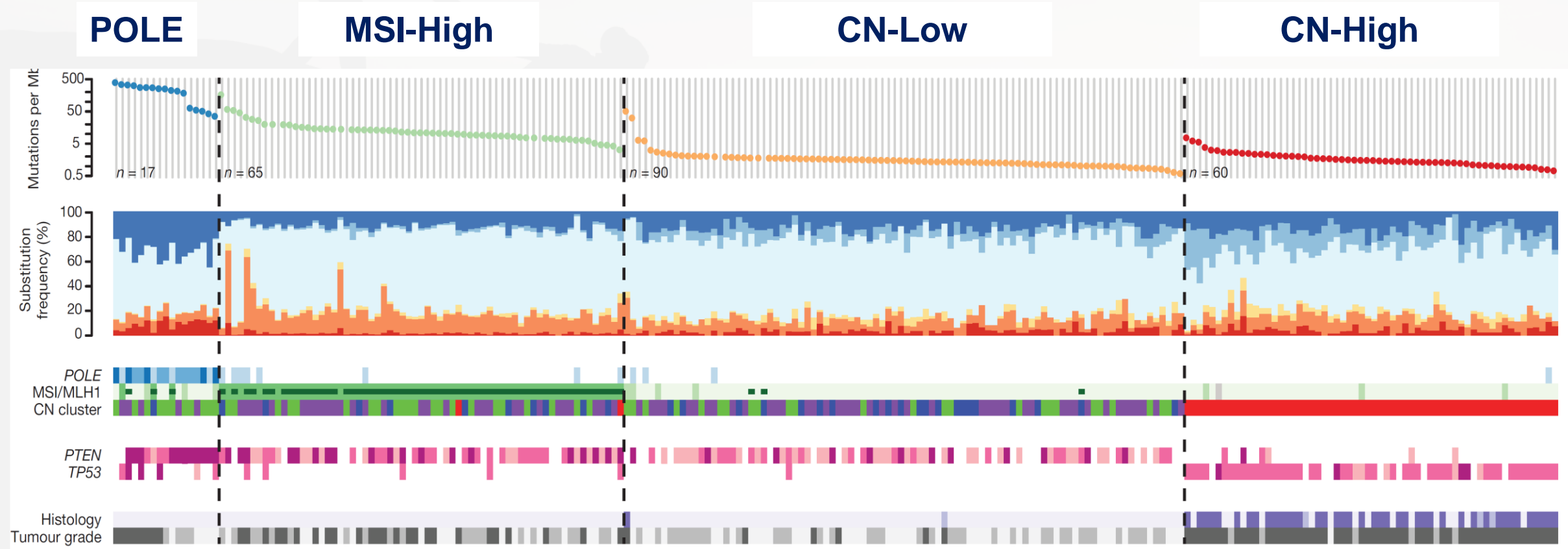
How do we measure Biomarkers?



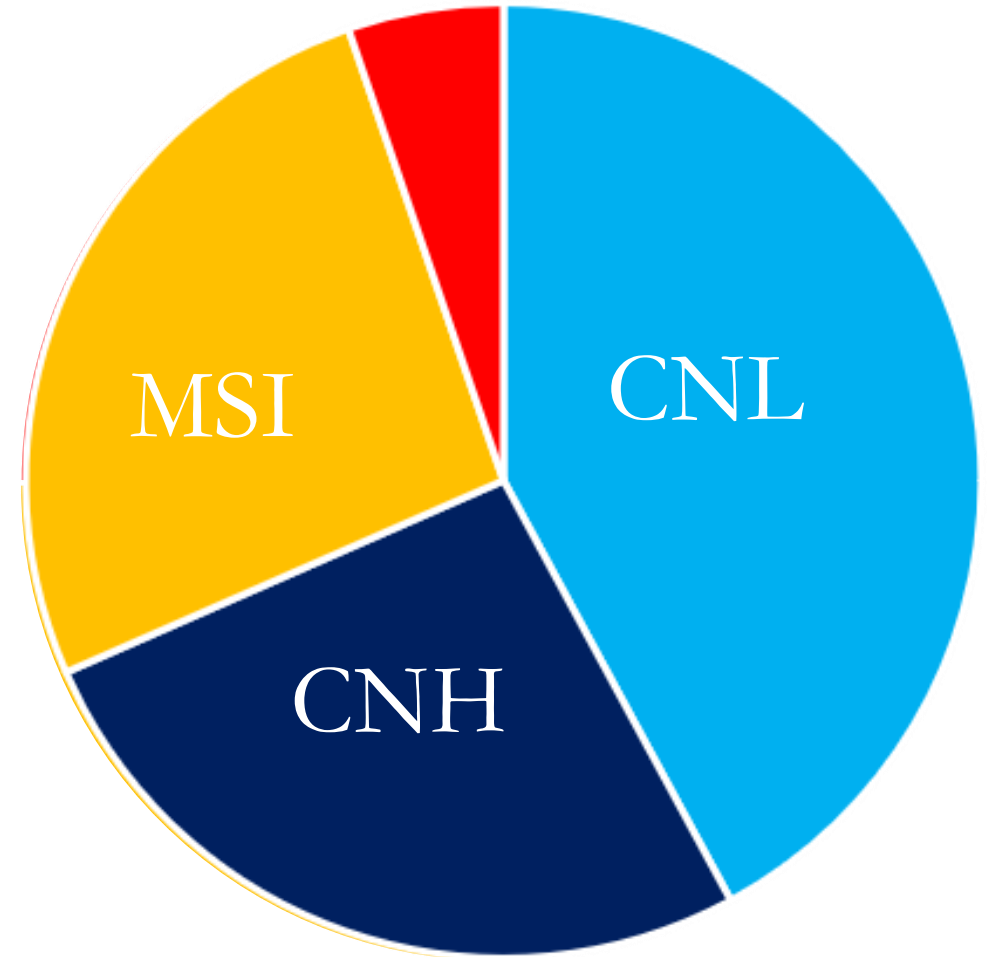
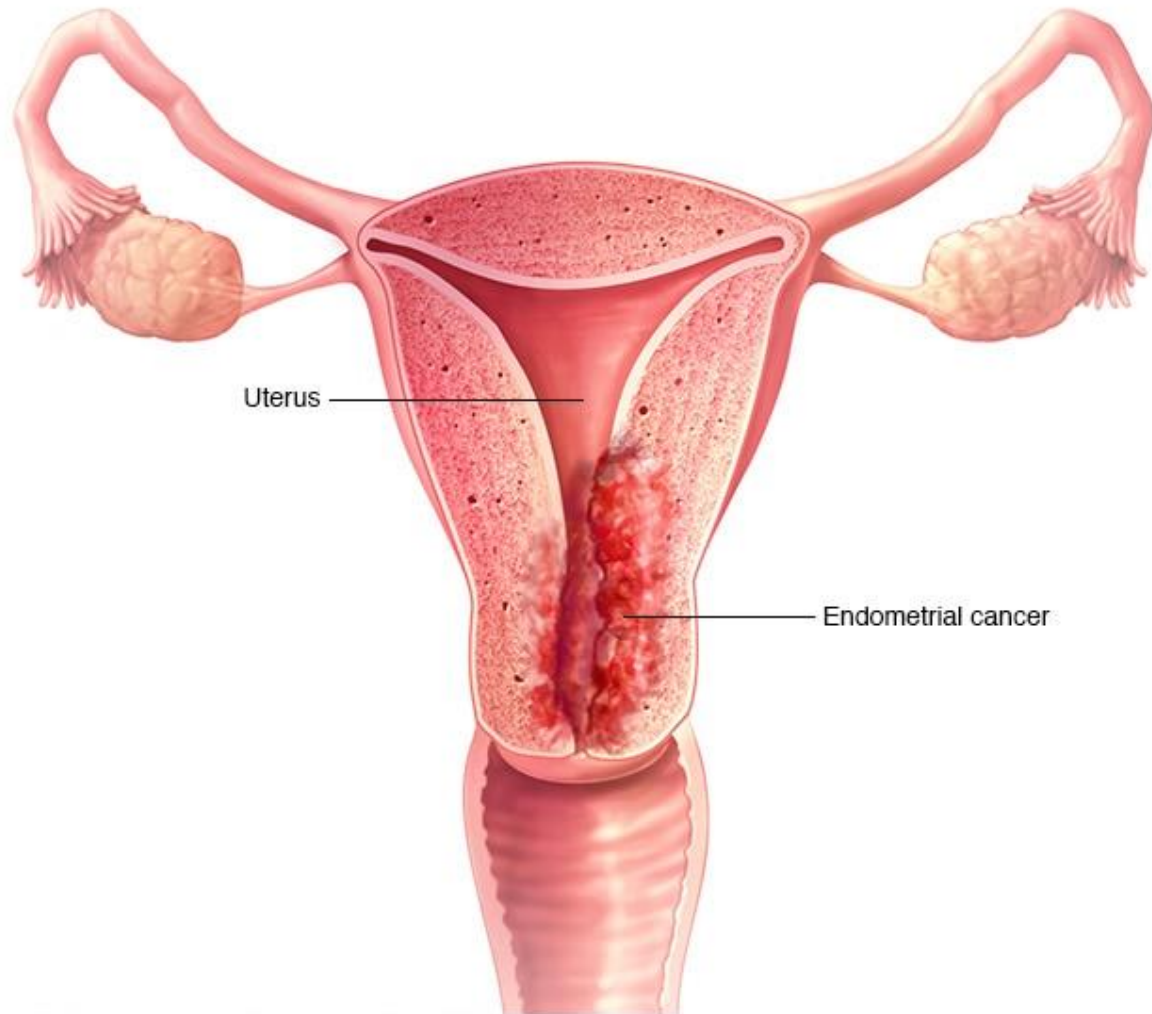
Biomarkers in Endometrial Cancer

Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

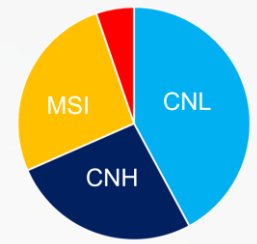


4 Molecular Subtypes



Managing MSI-high disease

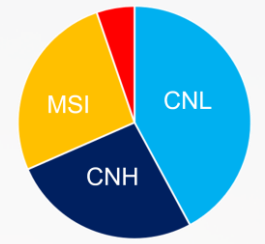
Single-agent Immunotherapy efficacy



Study	Drug	N	Patient Selection	ORR (%)
KEYNOTE-158	Pembrolizumab	49	Advanced / metastatic dMMR	57%
GARNET	Dostarlimab	103	Previously treated Recurrent / advanced dMMR	45%
PHAEDRA	Durvalumab	35	Advanced / metastatic dMMR	43%
NCT02912572	Avelumab	15	Advanced / persistent dMMR	27%

Managing MSS disease:

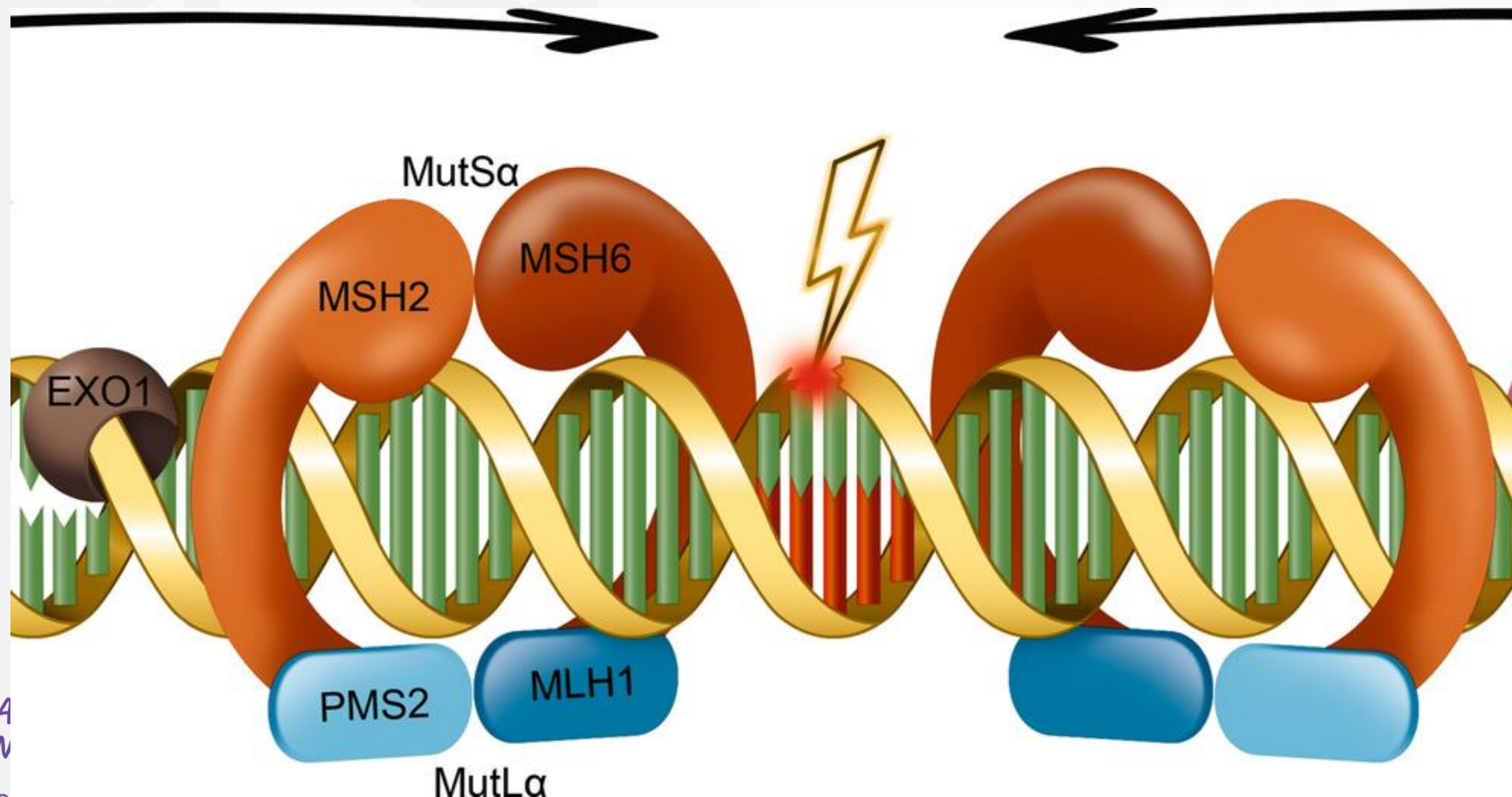
Single Agent IO Efficacy in Biomarker Negative Endometrial Cancer



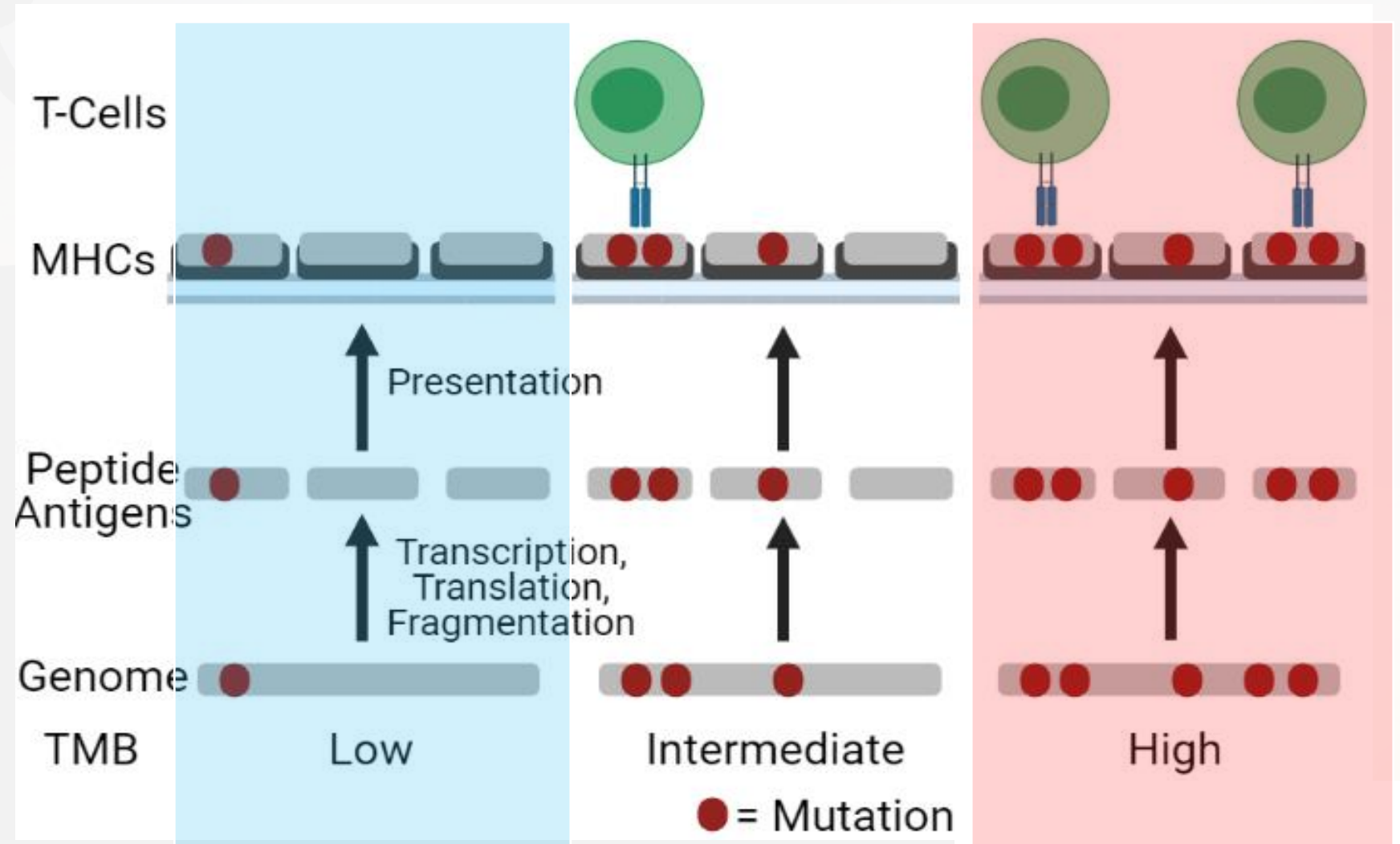
Study	Drug	N	Patient Selection	ORR (%)
KEYNOTE-28	Pembrolizumab	24	Advanced/metastatic PD-L1+	13%
Garnet	Dostarlimab	142	Previously treated Recurrent/advanced pMMR	13.4%
PHAEDRA	Durvalumab	36	Advanced/metastatic pMMR	3%
Konstantinopoulos	Avelumab	16	Advanced/metastatic pMMR	6%

Managing MSI-high disease

Mismatch Repair Deficiency or Microsatellite Instability



MSI-high \rightarrow TMB high \rightarrow Neo-Antigens

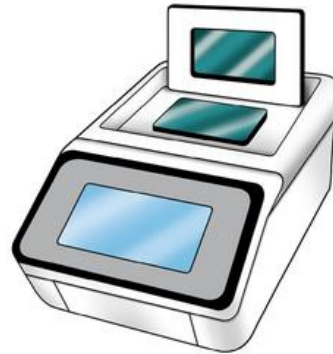


Biomarkers for MSI-high disease

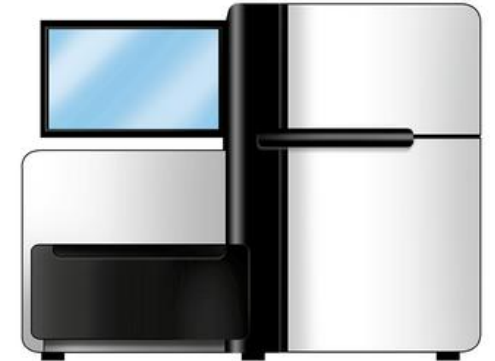
Mismatch Repair Deficiency or Microsatellite Instability



Immunohistochemistry

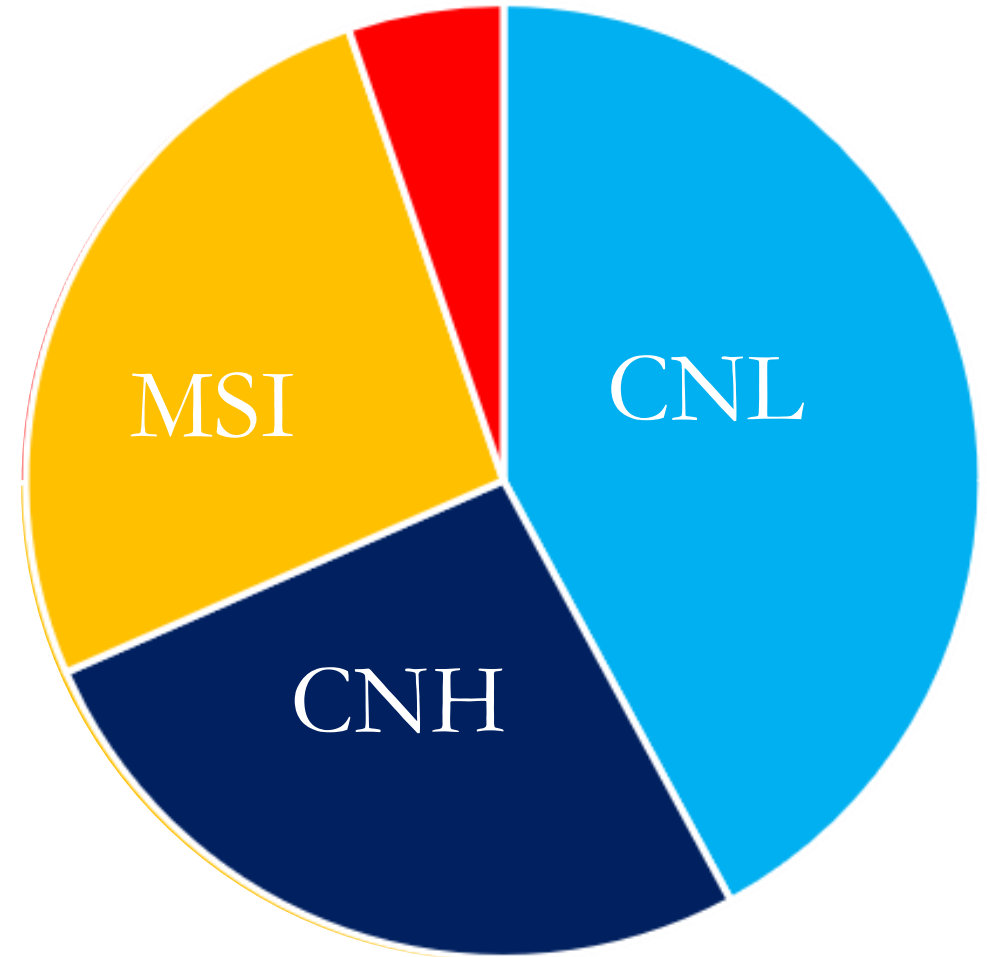
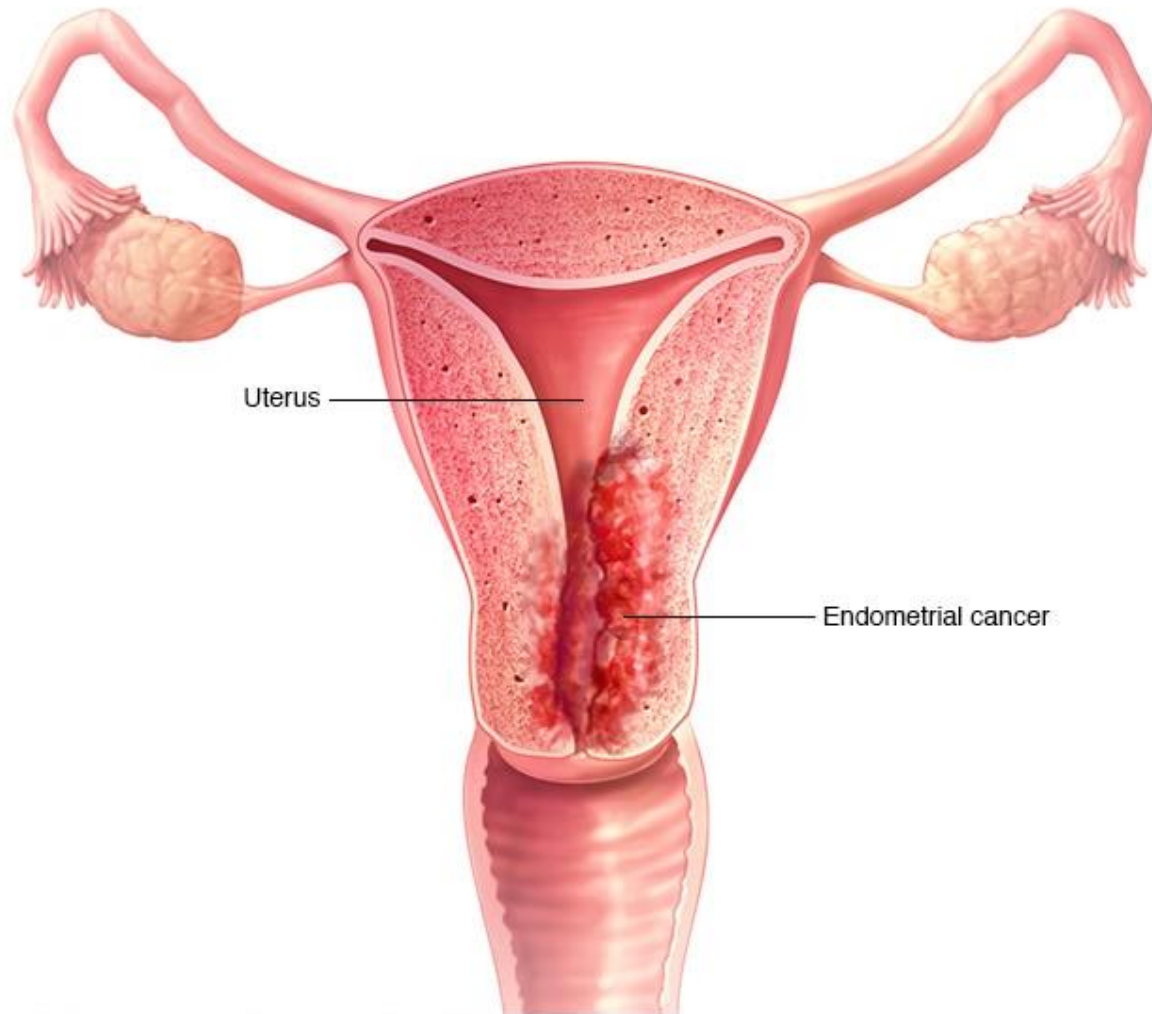


qPCR-based MSI analysis



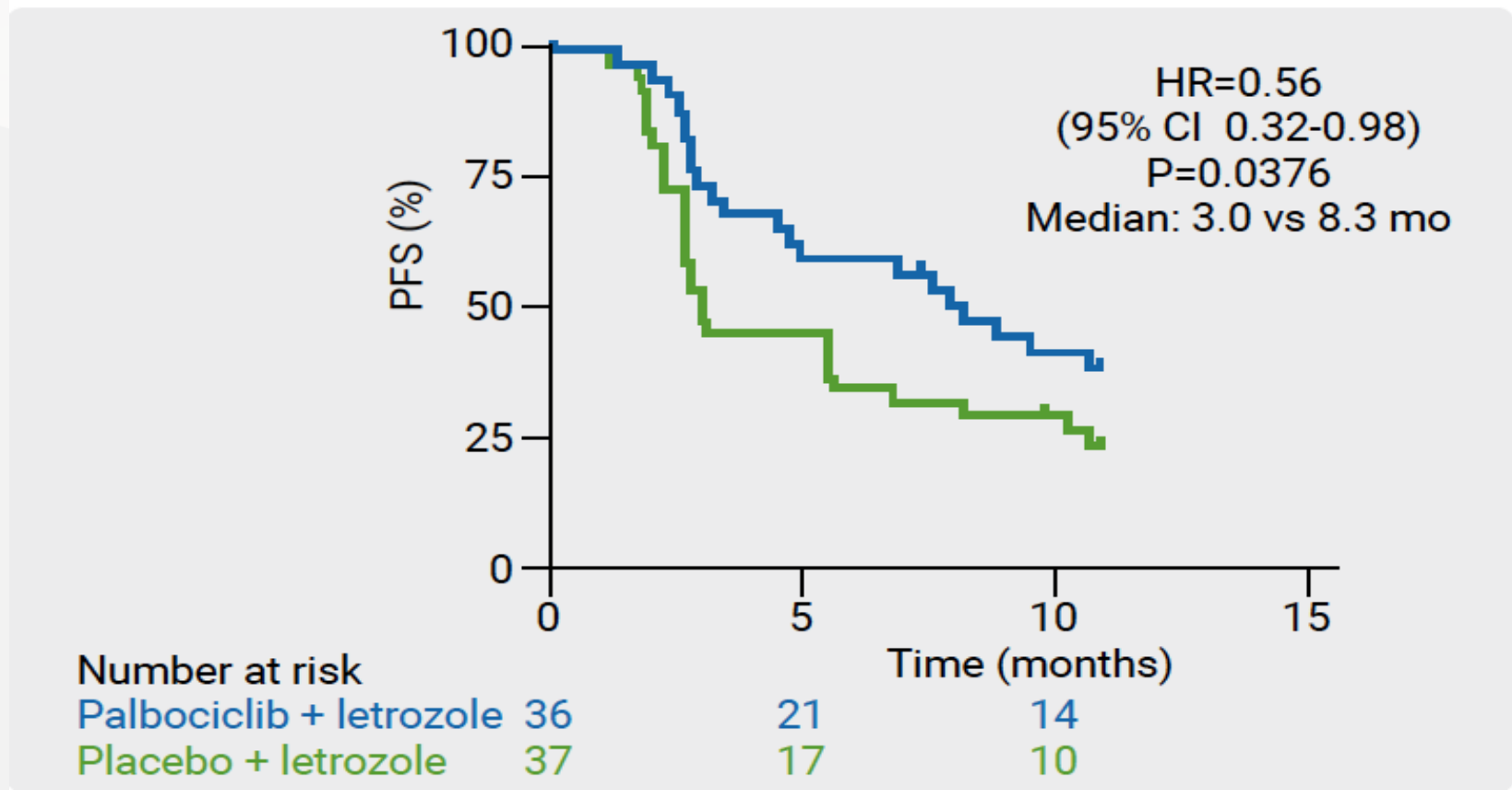
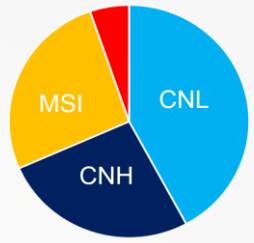
Next-Generation Sequencing

4 Molecular Subtypes



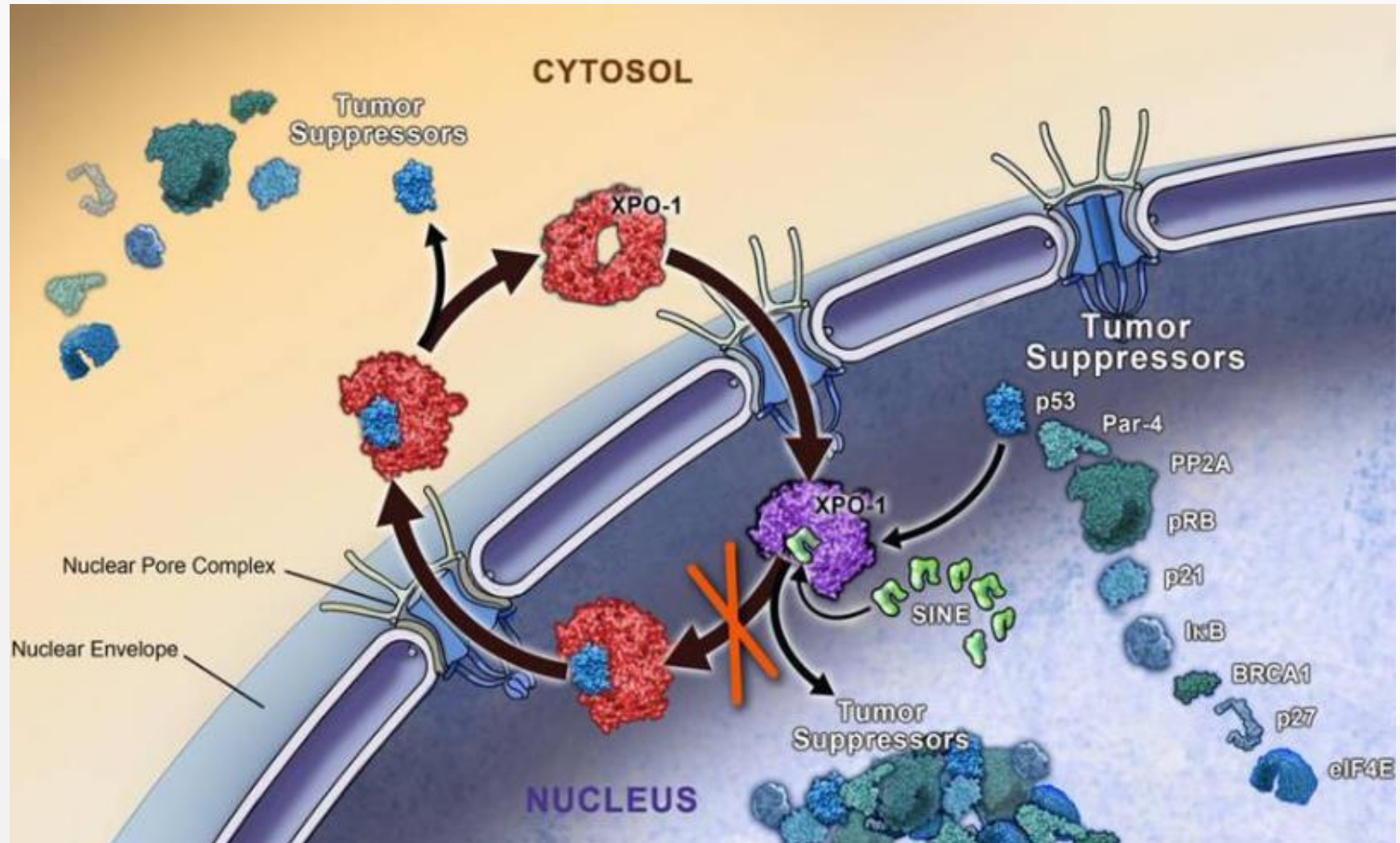
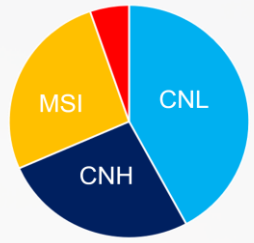
Estrogen Receptor as a Biomarker

Letrozole and Palbociclib in ER+ Endometrial cancer

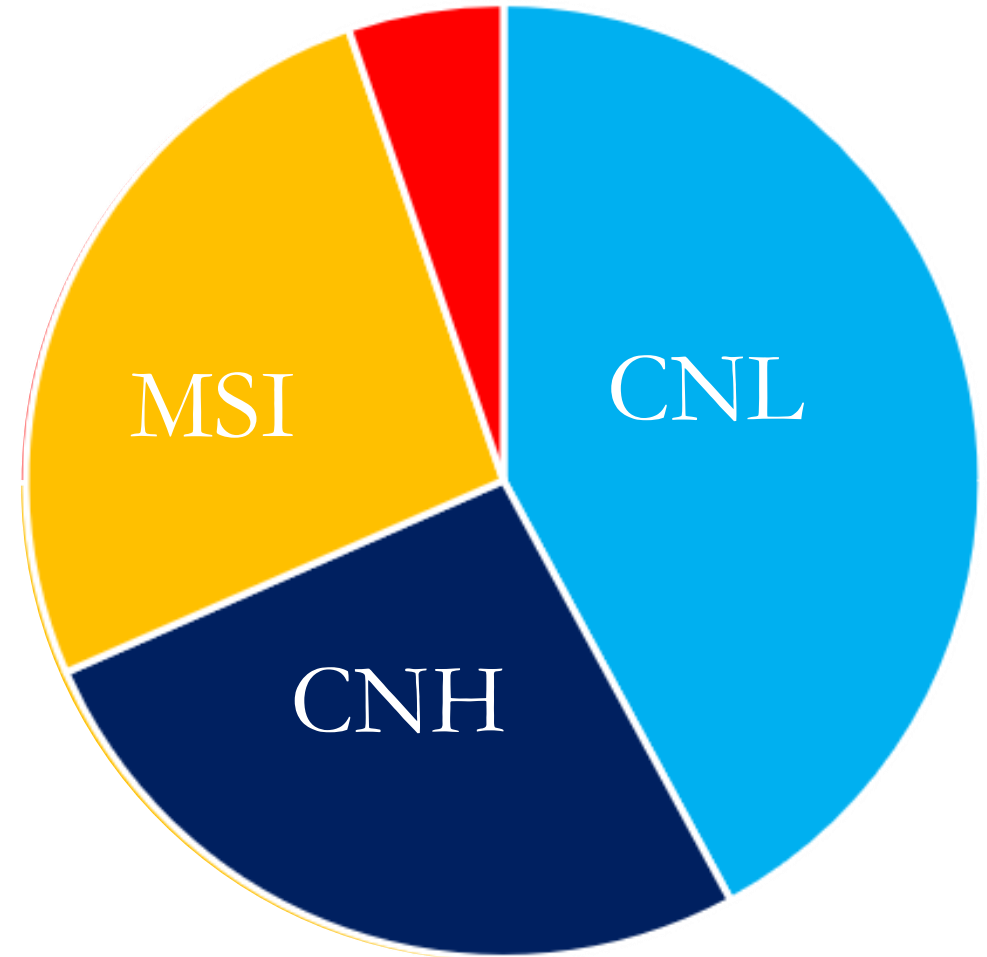
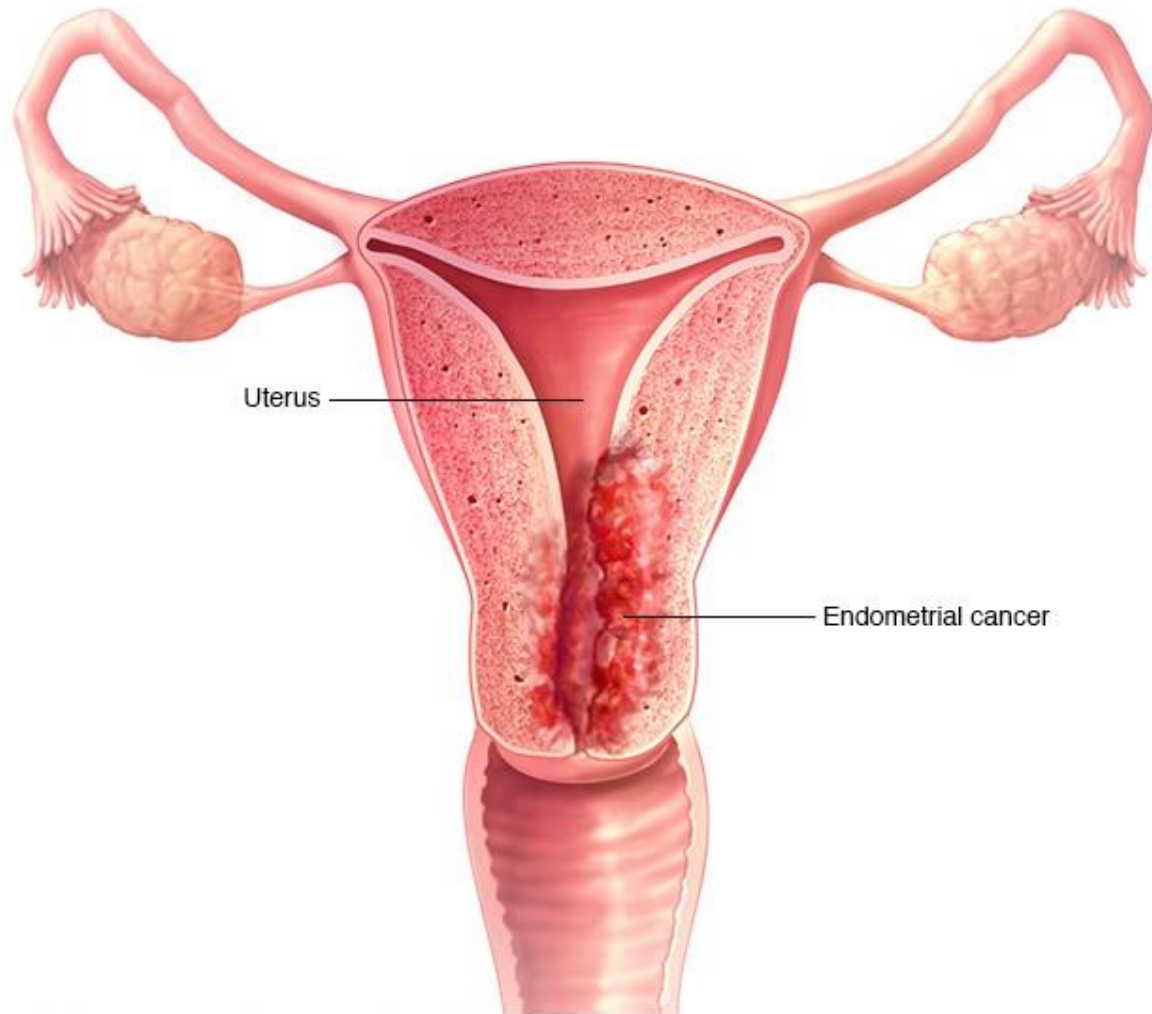


p53 as a Biomarker

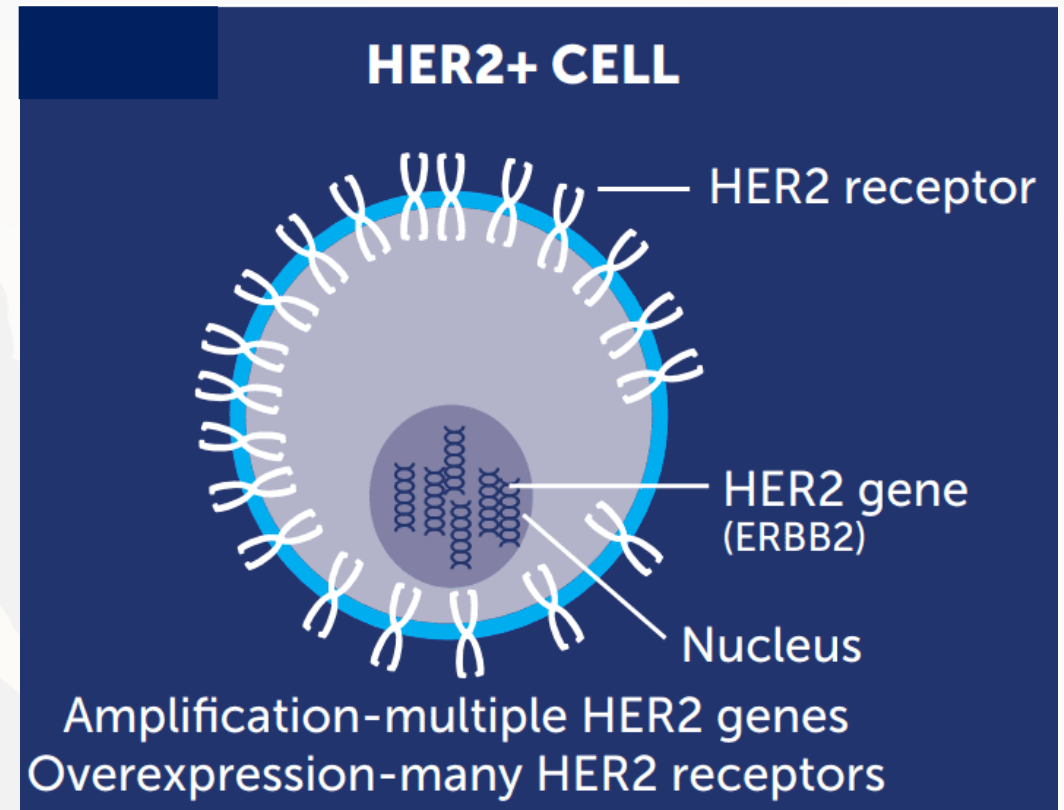
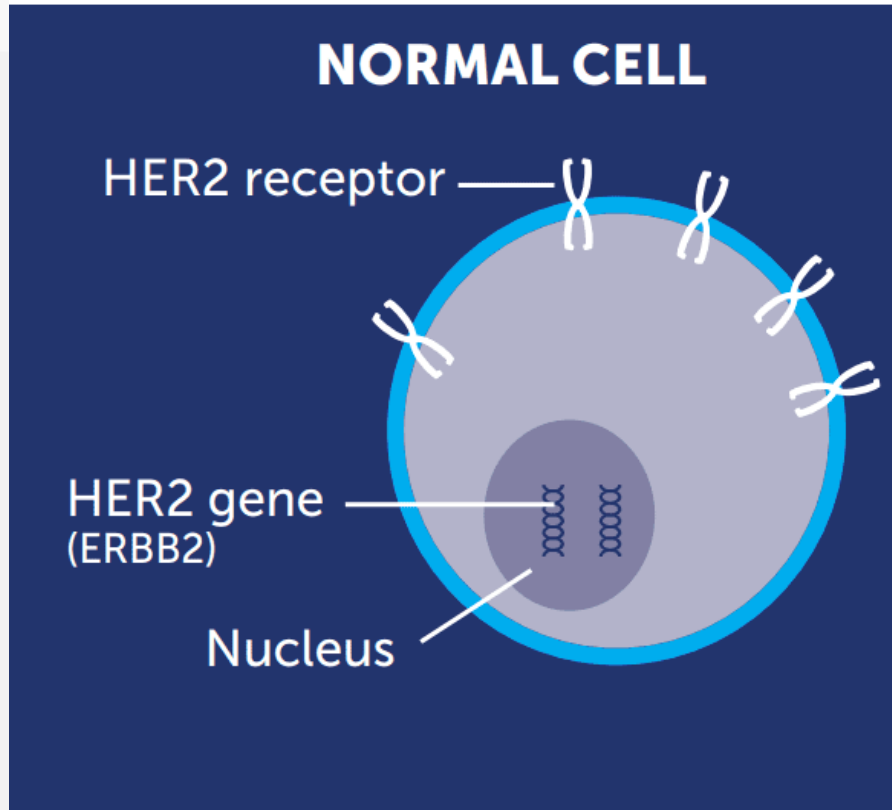
Slenexor in p53 wild-type Endometrial Cancer



4 Molecular Subtypes

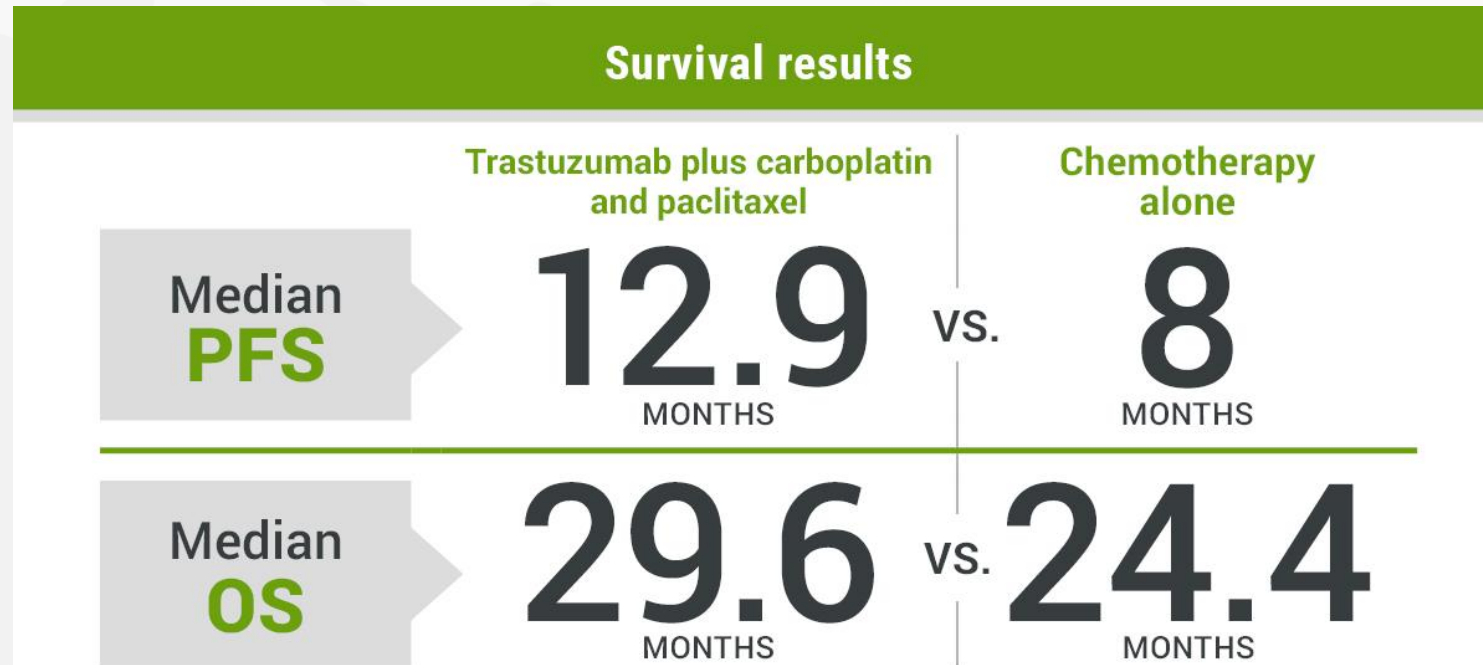


HER2 as a Biomarker *in Endometrial or Ovarian Cancer*



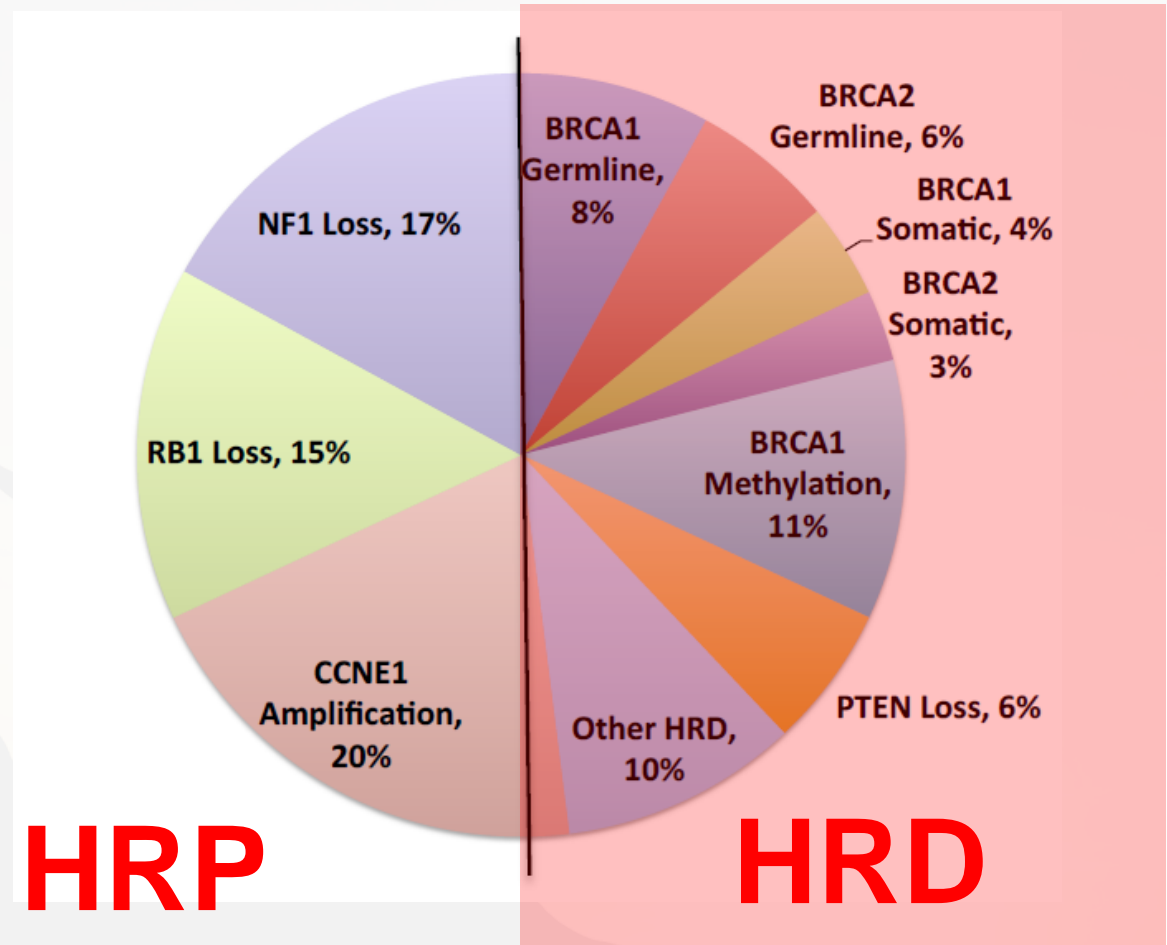
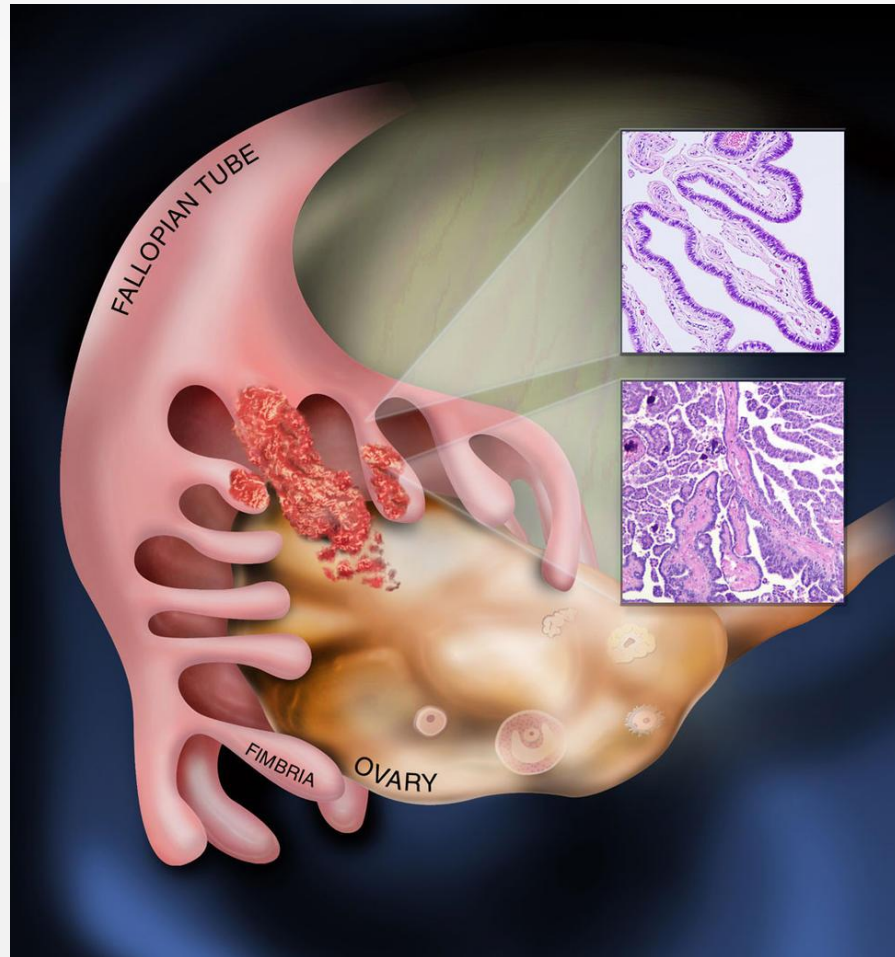
HER2 as a Biomarker

Trastuzumab + Chemotherapy in HER2 + Endometrial Cancer

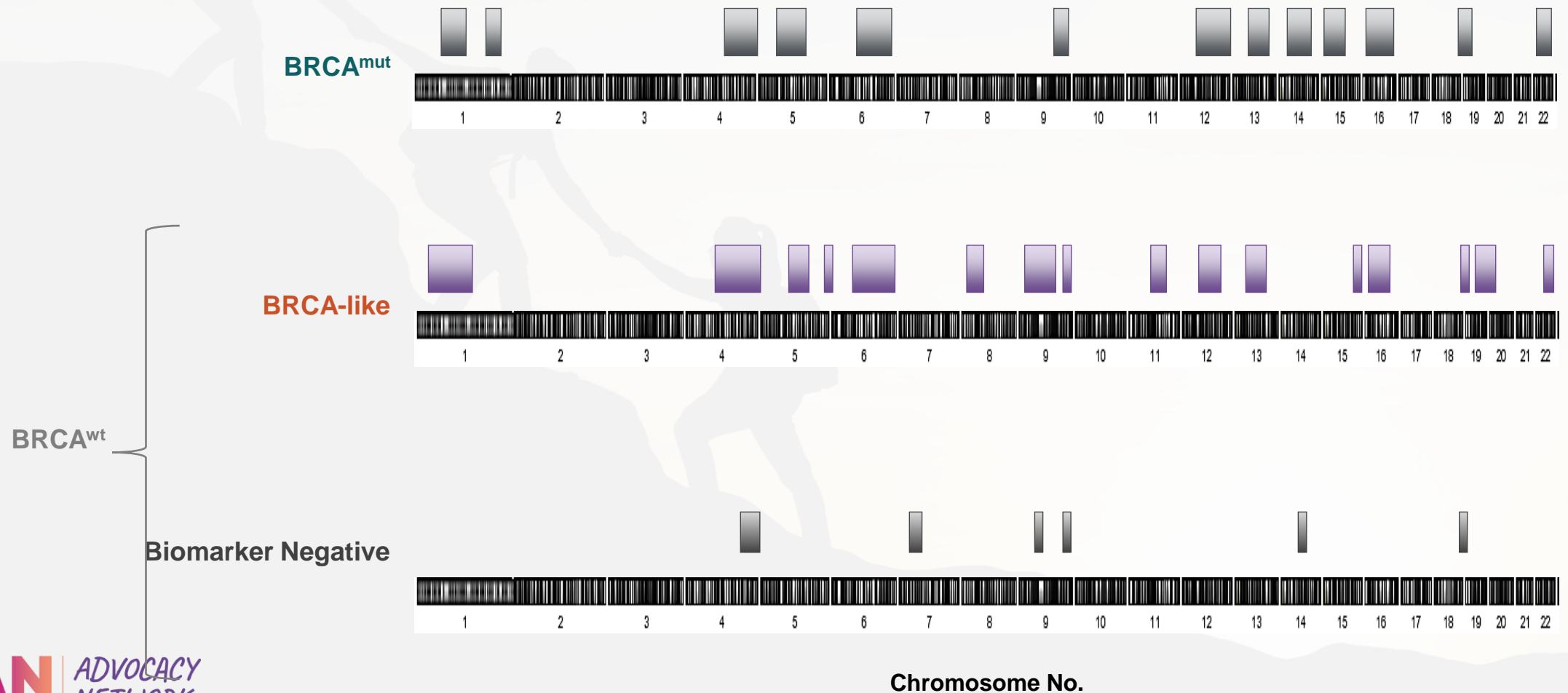


Biomarkers in Ovarian Cancer

Homologous Recombination (HR) Deficiency

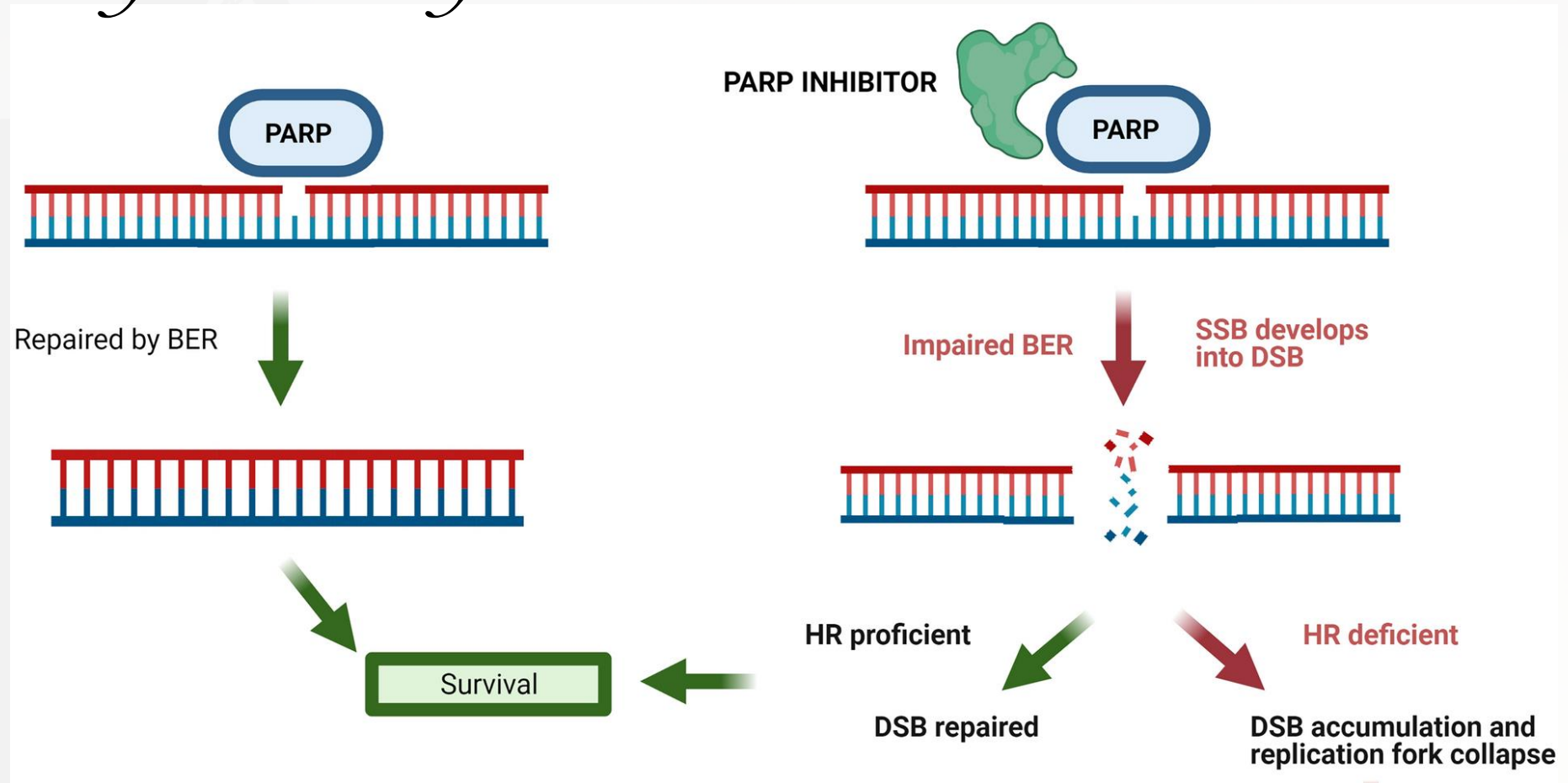


Homologous Recombination (HR) Deficiency

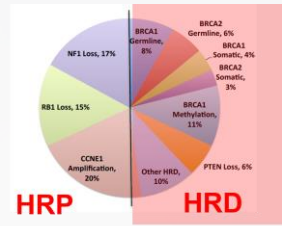


BRCA Mutations and HRD as a Biomarkers

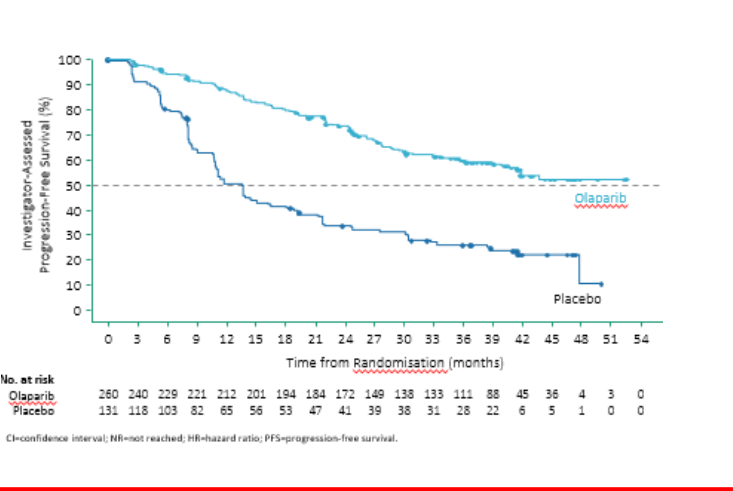
PARPi synthetically lethal



Significant progress for *BRC*A associated cancers



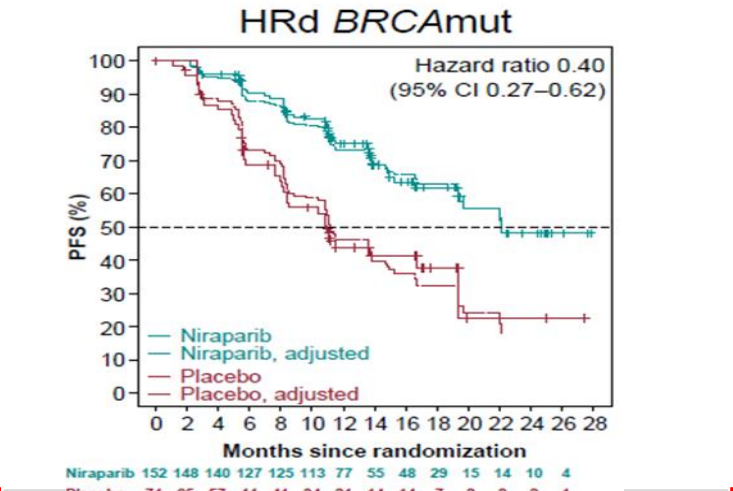
SOLO1 - g*BRC*Am



NR mo vs 13 mo
HR 0.30 (95% CI: 0.23, 0.41)

NR vs. 14.1 mo
HR 0.28 (95% CI 0.2-0.39)

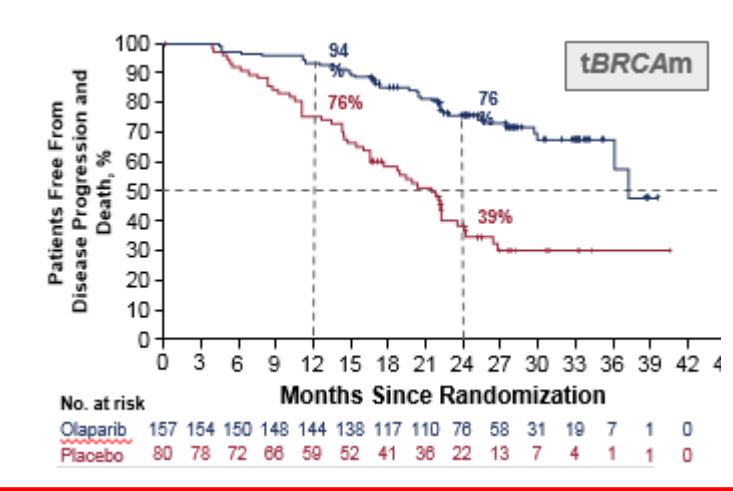
PRIMA



HR 0.40 (95% CI .27-0.62)

HR 0.40 (95% CI .27-0.62)

PAOLA-1



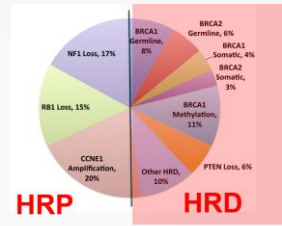
37.2 vs 17.7 mo
HR 0.33 (95% CI 0.25-0.45)

HR 0.33 (95% CI 0.25-0.45)

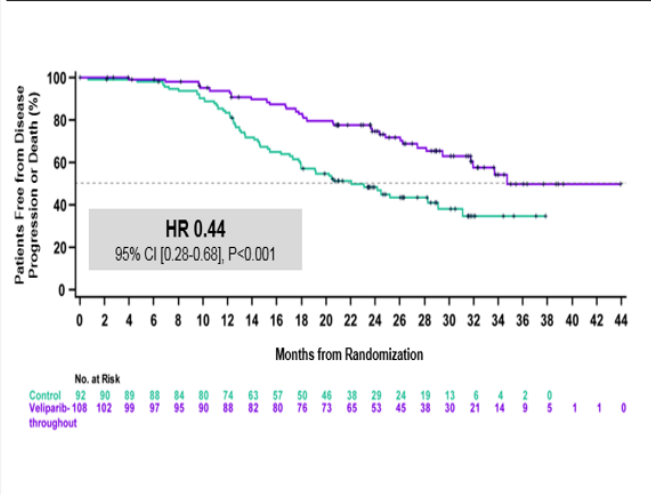
INV
REVIEW

BICR
REVIEW

And for those women with HRD +/- BRCAwt tumors - not perfect but good

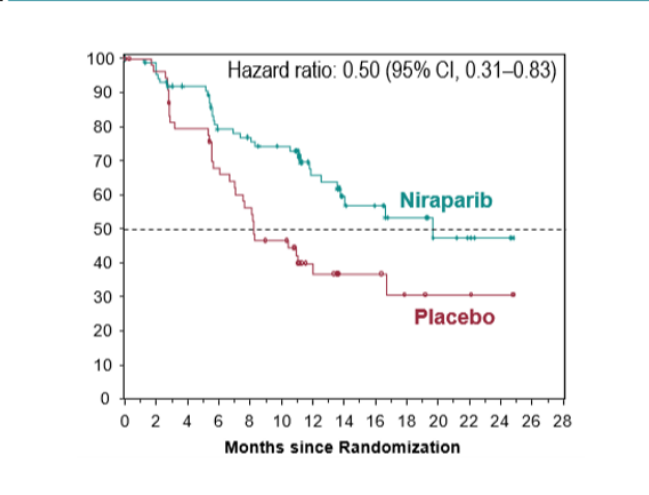


VELIA



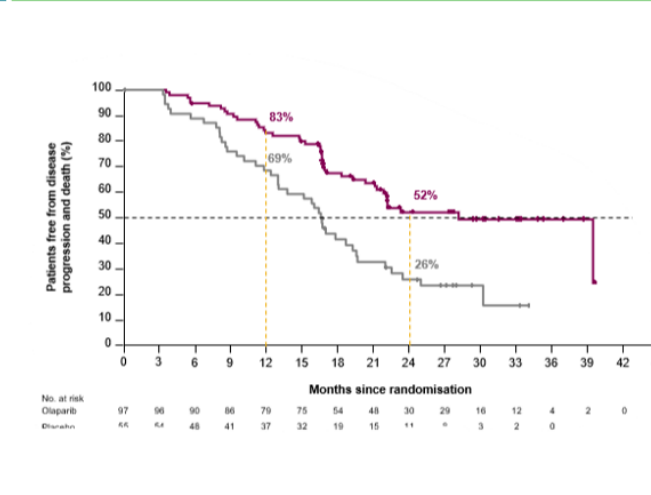
34.7 vs 22 months
HR 0.44 (95% CI: 0.28-0.68)

PRIMA



HR 0.50 (95% CI 0.31-0.83)

PAOLA-1

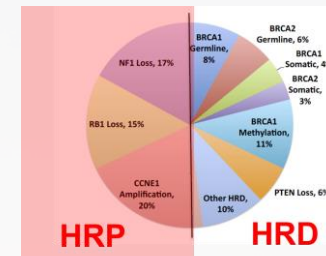


28 vs 16.6 months
HR 0.43 (95% CI 0.28 - 0.66)

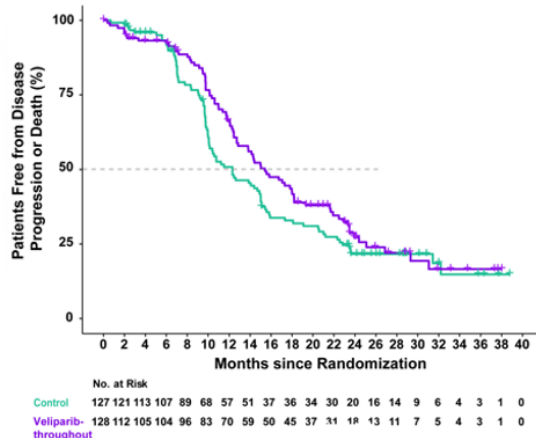
INV
REVIEW

BICR
REVIEW

HRP tumors are the big focus now

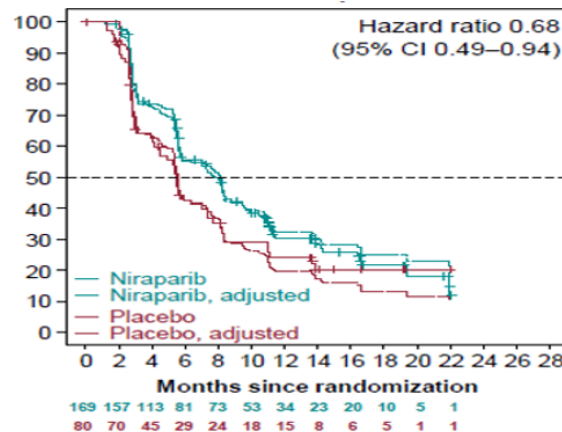


VELIA¹



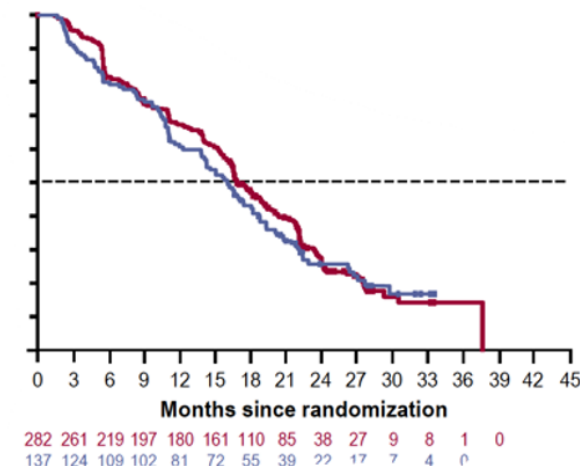
15.4 vs. 12.3 months
HR 0.76 (95% CI 0.55-1.03)

PRIMA²



HR 0.68 (95% CI 0.49-0.94)

PAOLA-1³

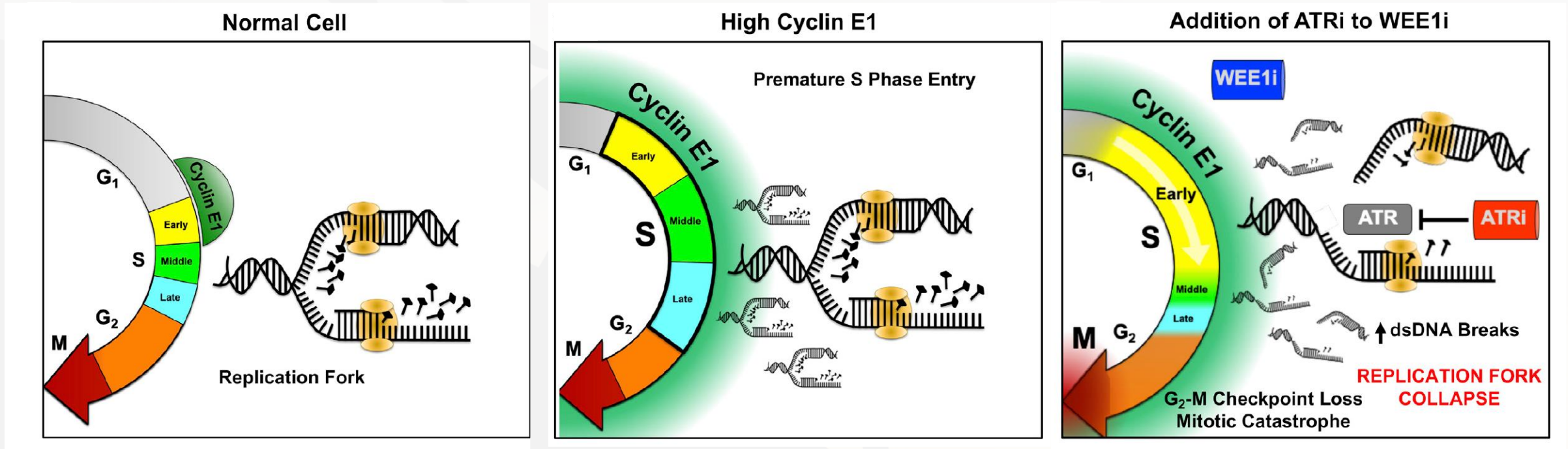


16.9 vs. 16.0 months
HR 0.92 (95% CI :0.72-1.17)

INV
REVIEW

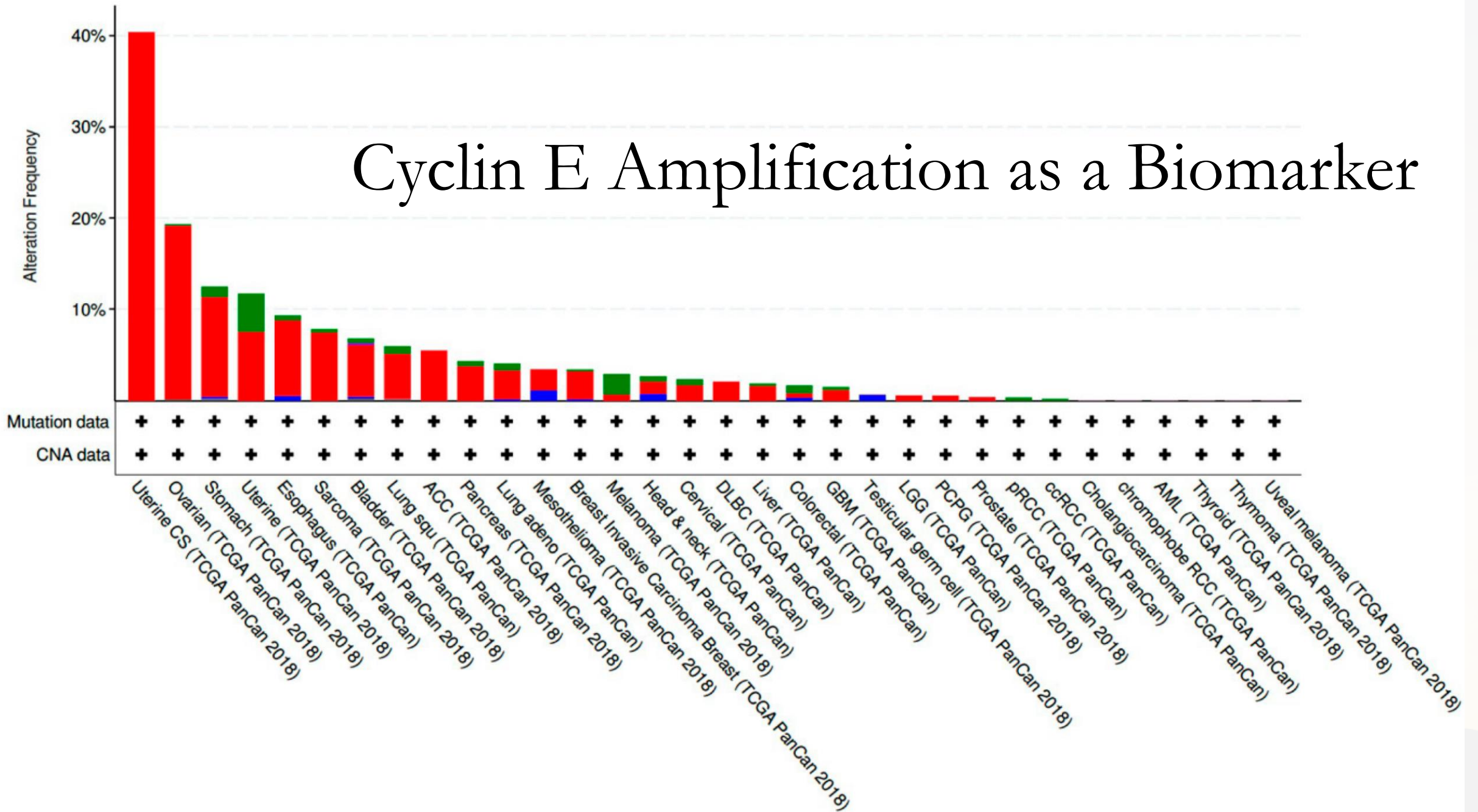
BICR
REVIEW

Cyclin E Amplification as a Biomarker

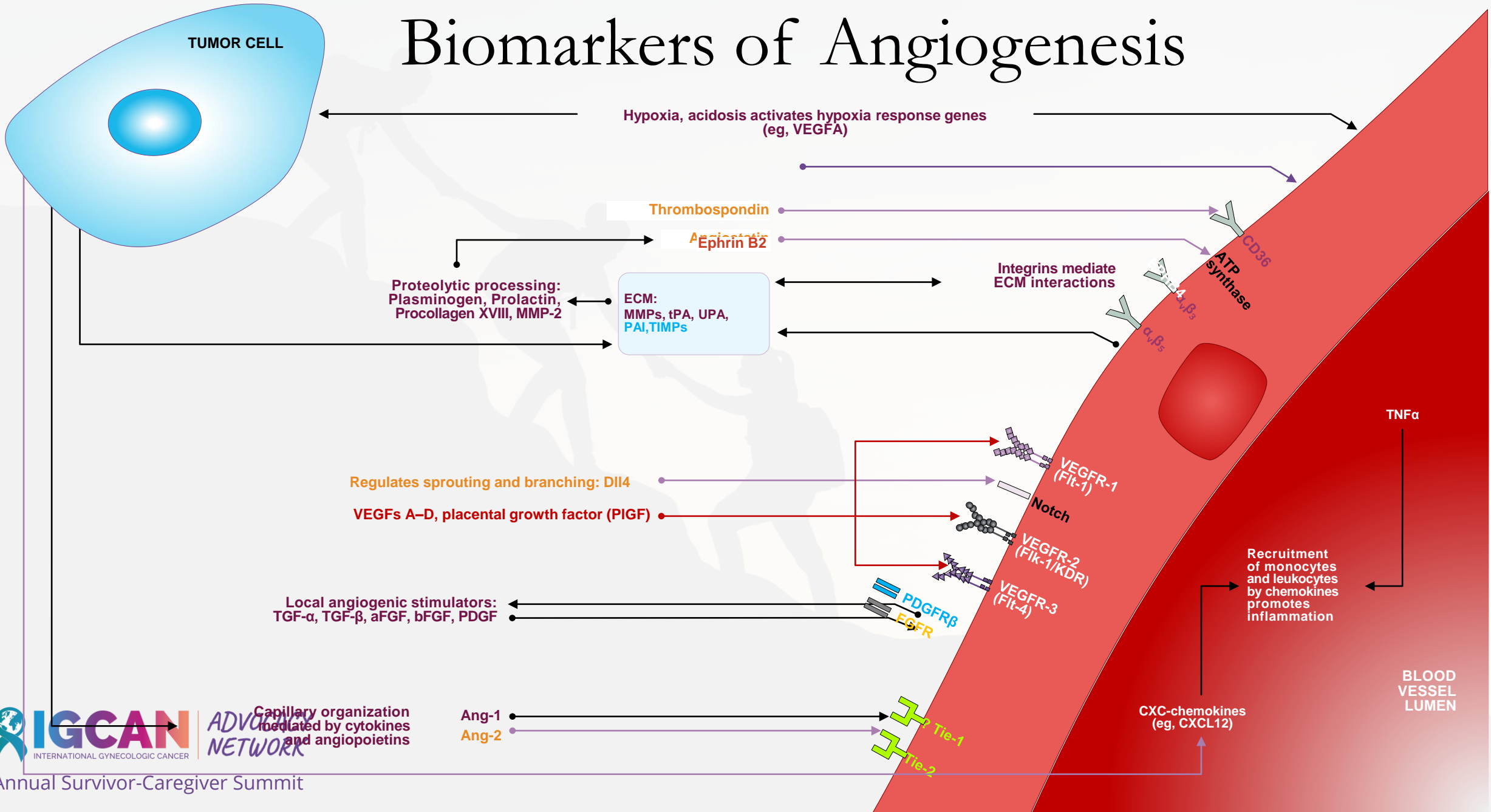


New Targets: WEE1, ATR, PKMYTH

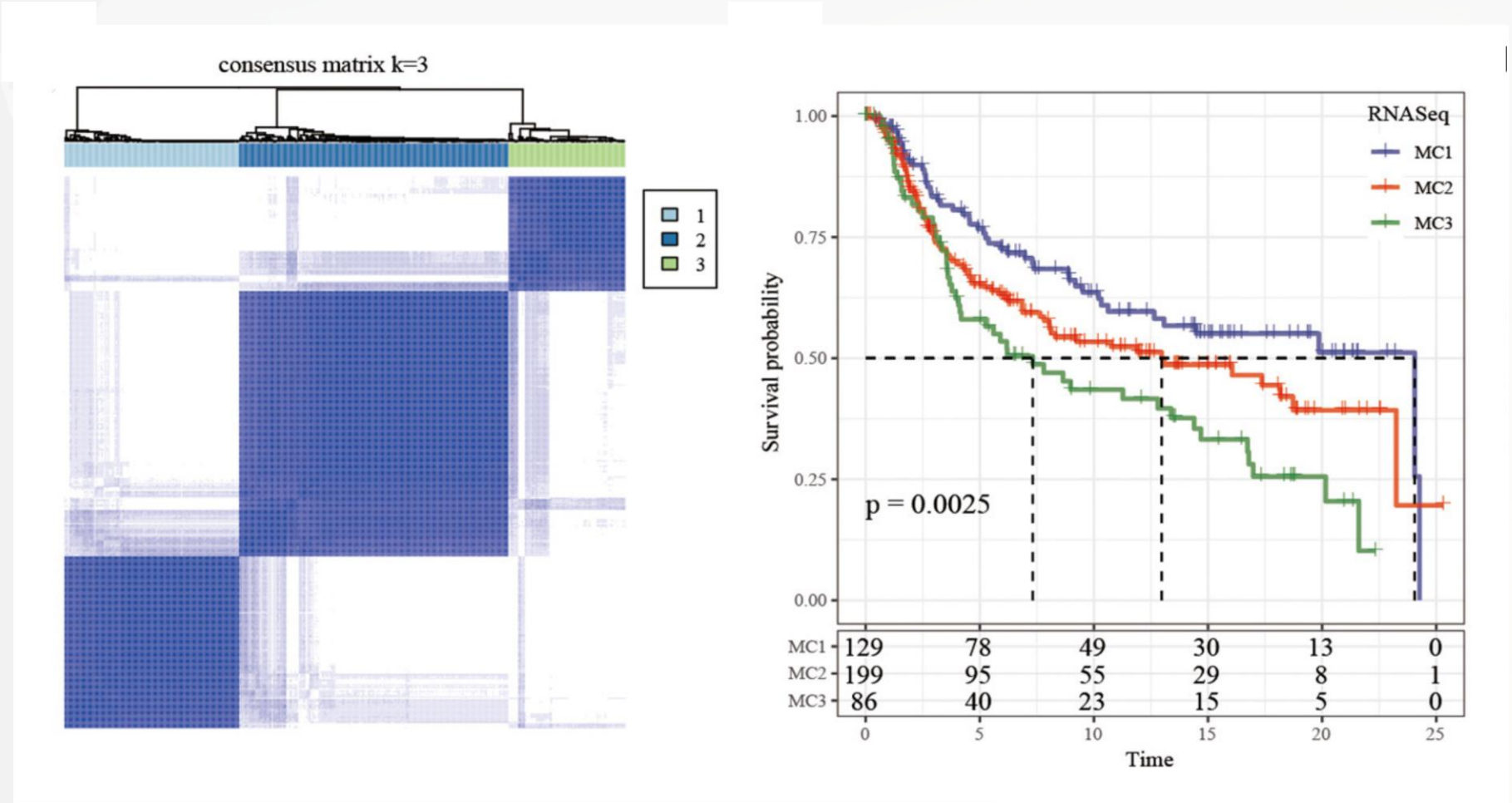
Cyclin E Amplification as a Biomarker



Biomarkers of Angiogenesis



Gene Expression Profiles as a Biomarkers



Gene Signatures and Bevacizumab Response

ICON7/AGO-OVAR11

n=1528

- FIGO stage I-IIA (clear cell or grade 3) or FIGO stage IIB-IV
- Surgically debulked histologically confirmed OC

1:1
R

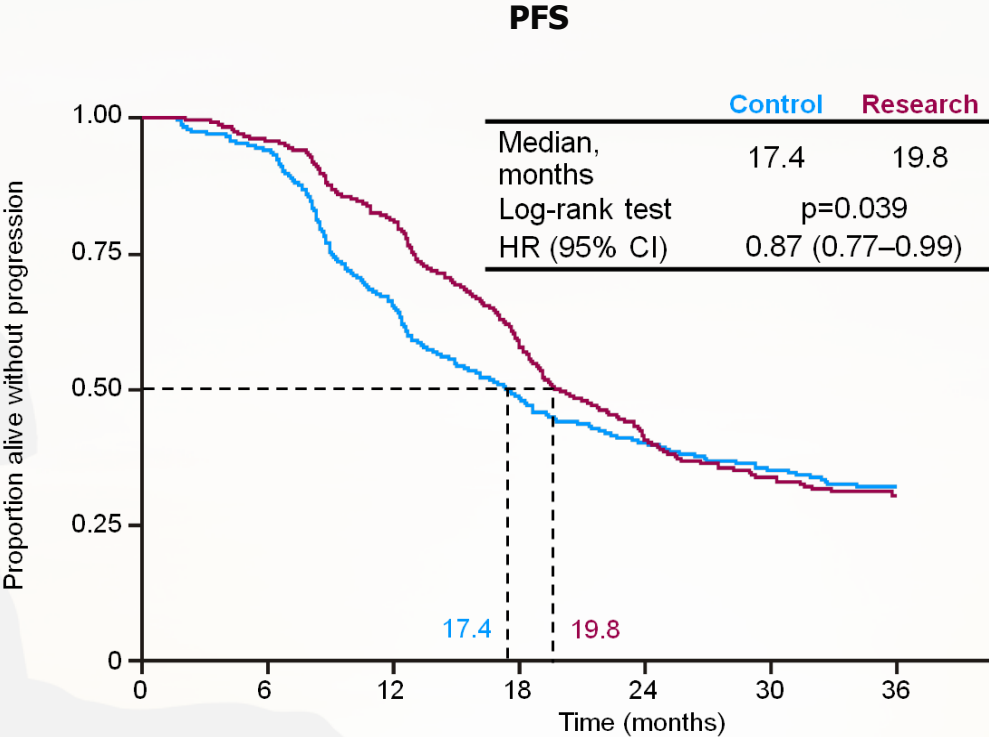
Carboplatin AUC 5 or 6

Paclitaxel 175 mg/m²

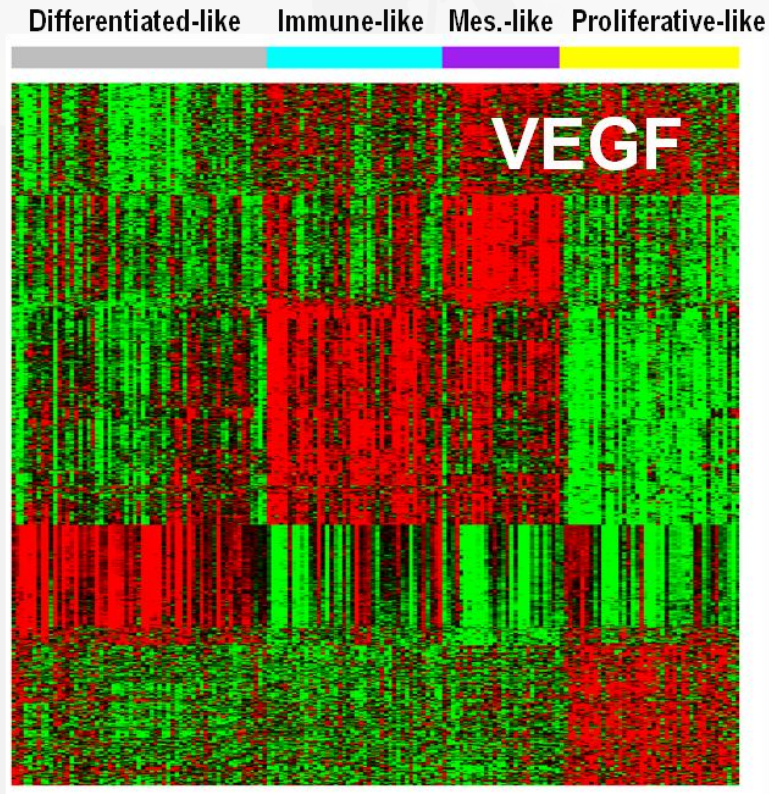
Carboplatin AUC 5 or 6

Paclitaxel 175 mg/m²

Bevacizumab 7.5 mg/kg q3w
18 cycles (12 months)



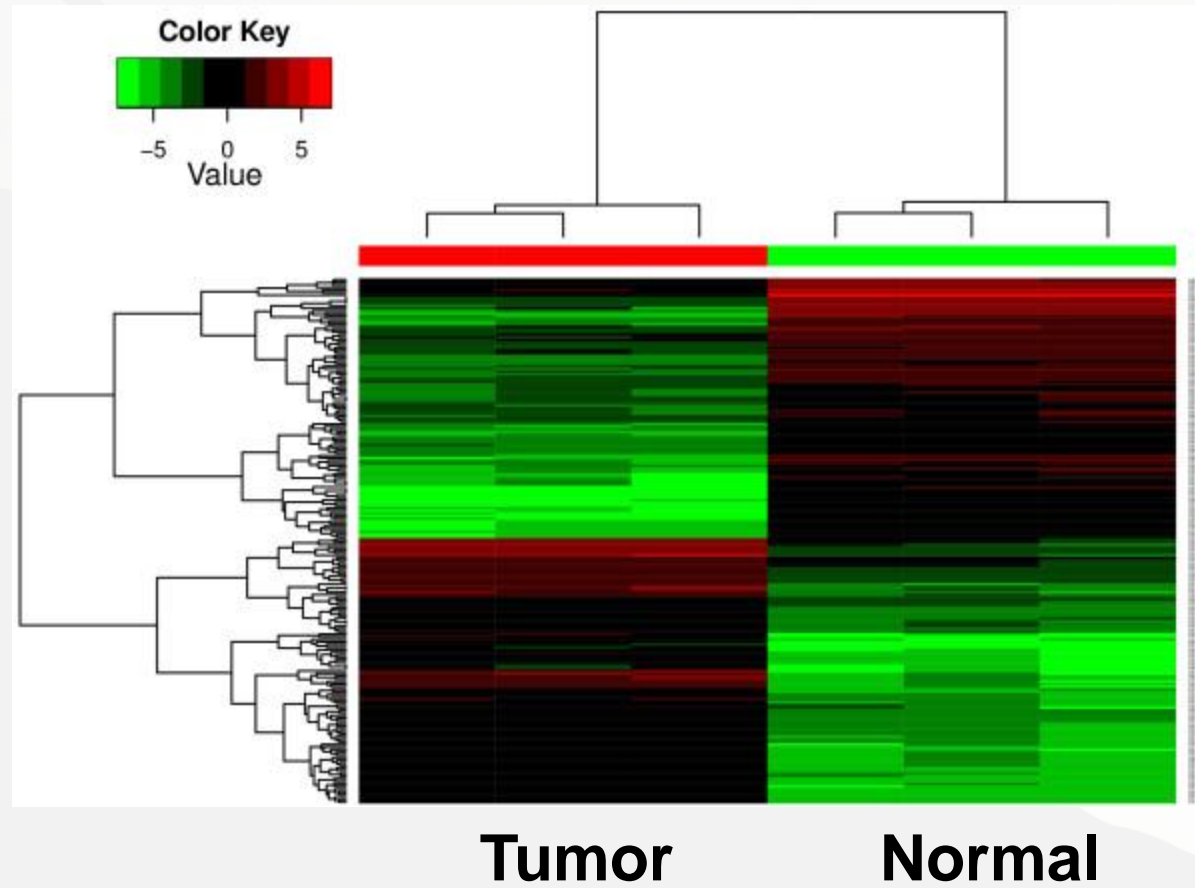
Gene Signatures and Bevacizumab Response



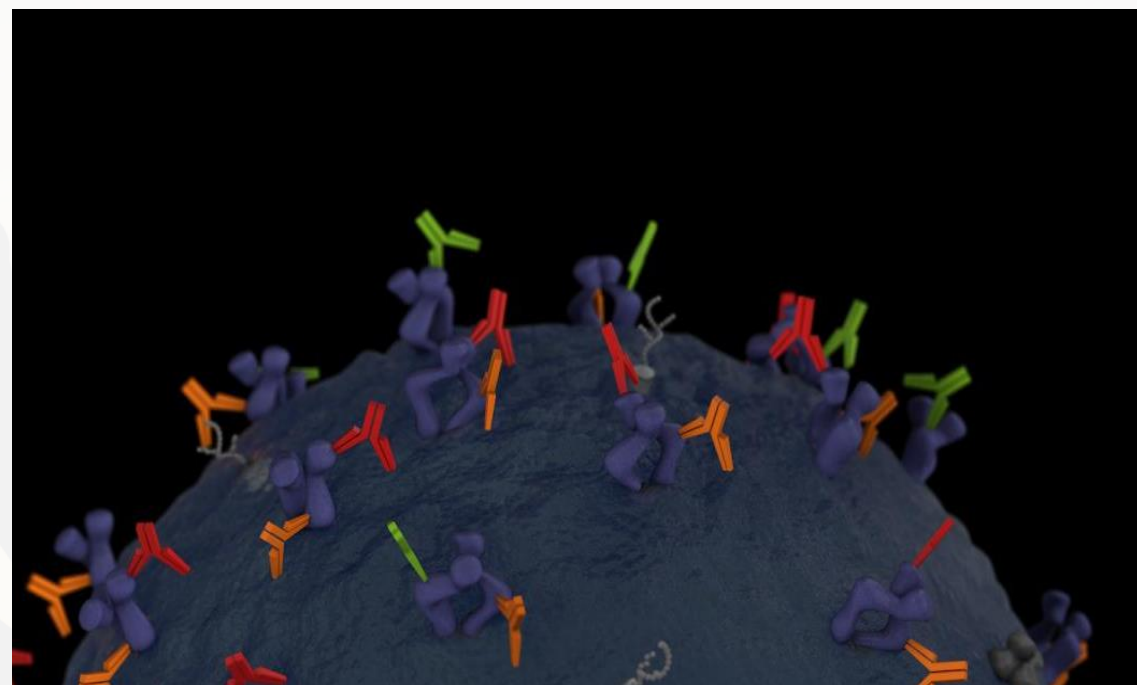
Group	Median Δ PFS in Months
All	6.5, $p=0.004$
Immunoreactive	3.8, $p=0.080$
Differentiated	3.7, $p=0.610$
Proliferative	10.1, $p=0.015$
Mesenchymal	8.2, $p=0.405$

Cell Surface Markers as Biomarkers

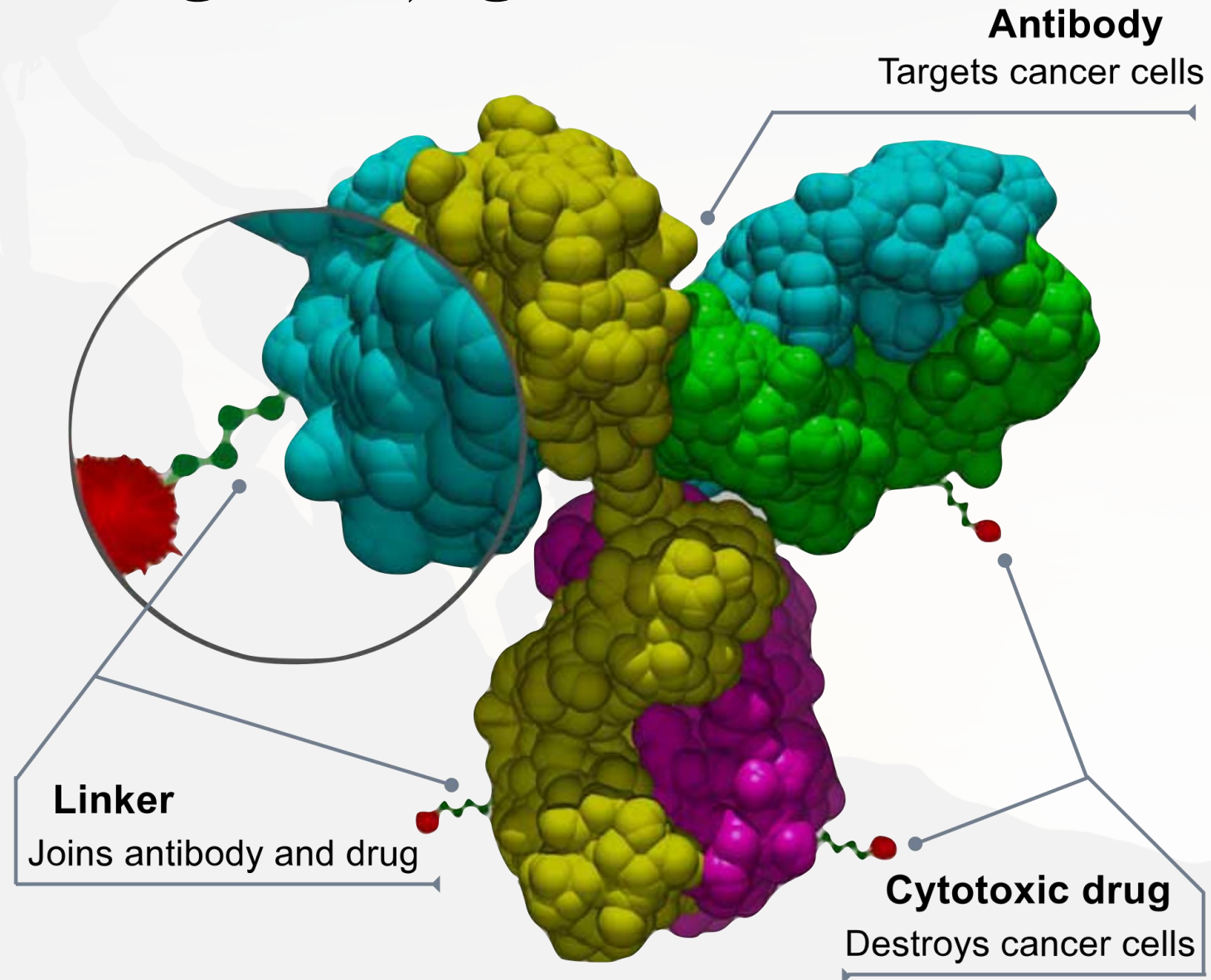
Tumor Specific Biomarker



Identify Proteins on the Cell Surface which can be targeted with Monoclonal Antibodies



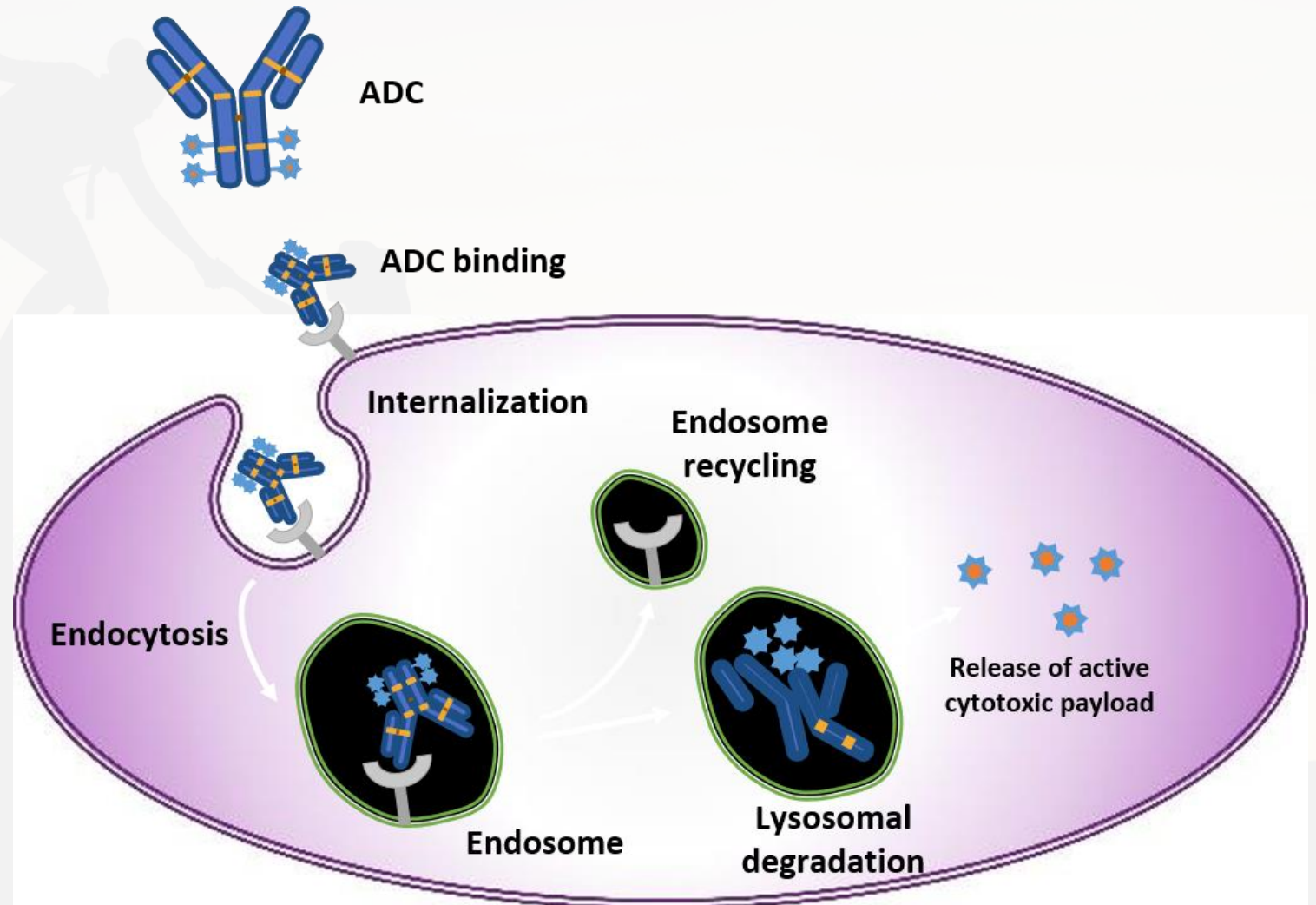
Antibody Drug Conjugates



FOLR1 as a Biomarker in Ovarian Cancer

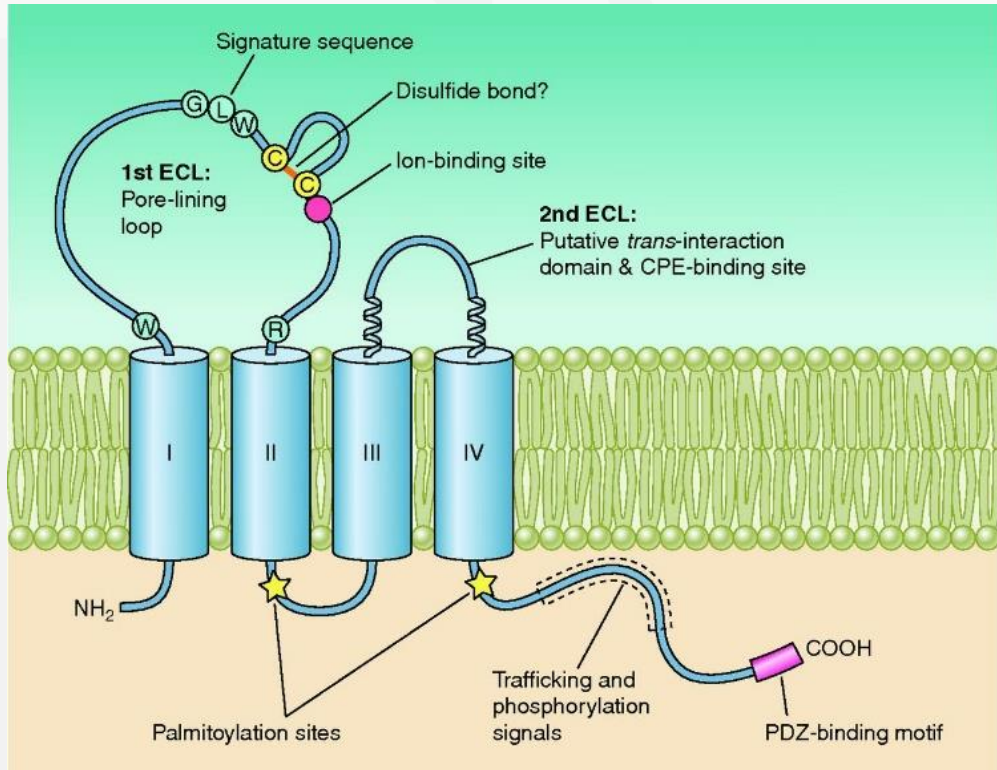
Based on their overall efficacy and adverse event profile → paradigm shift.

Mirvetuximab
Soravtansine

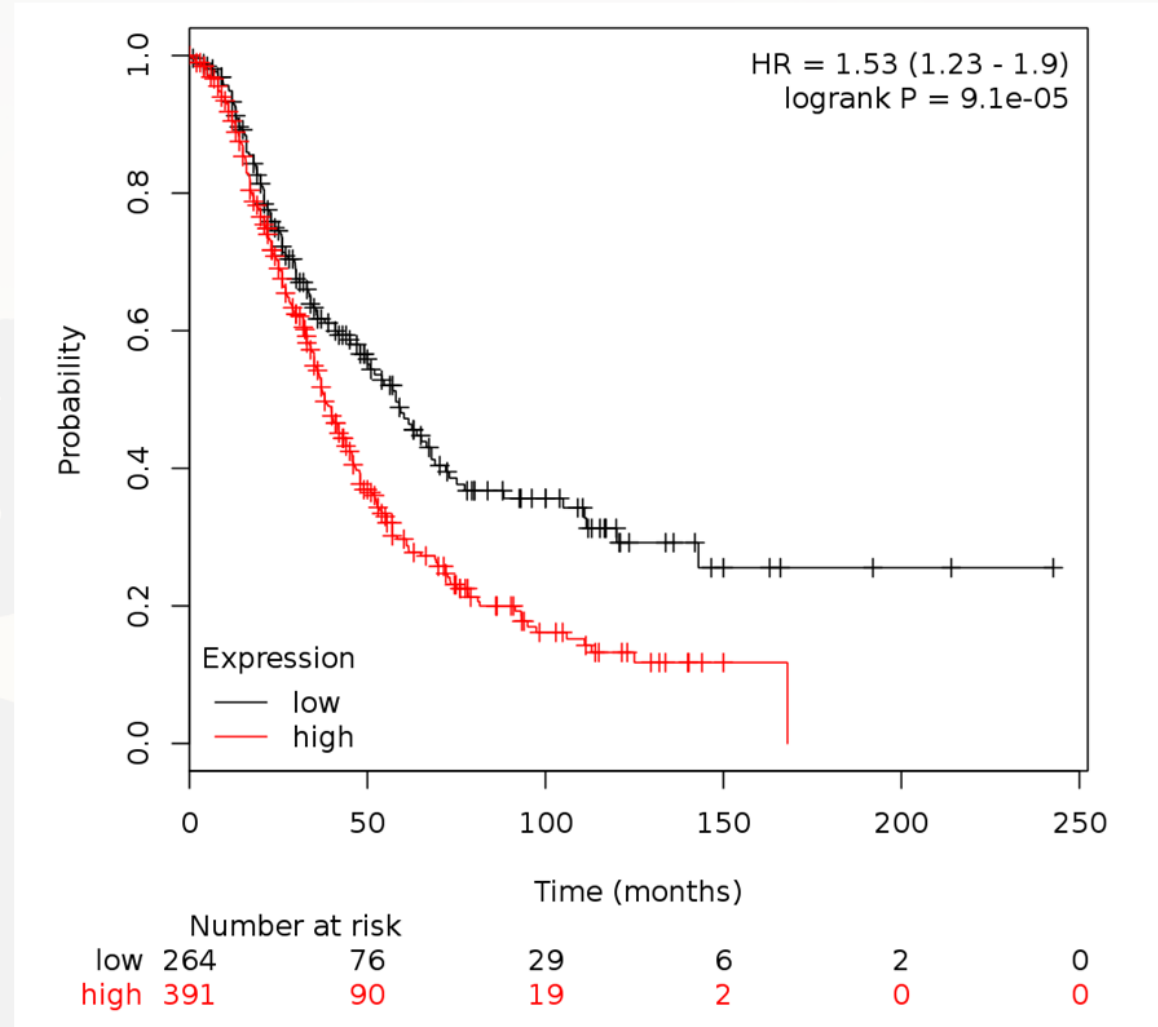


Novel Biomarker and ADC Target at UCLA

CLAUDIN 6

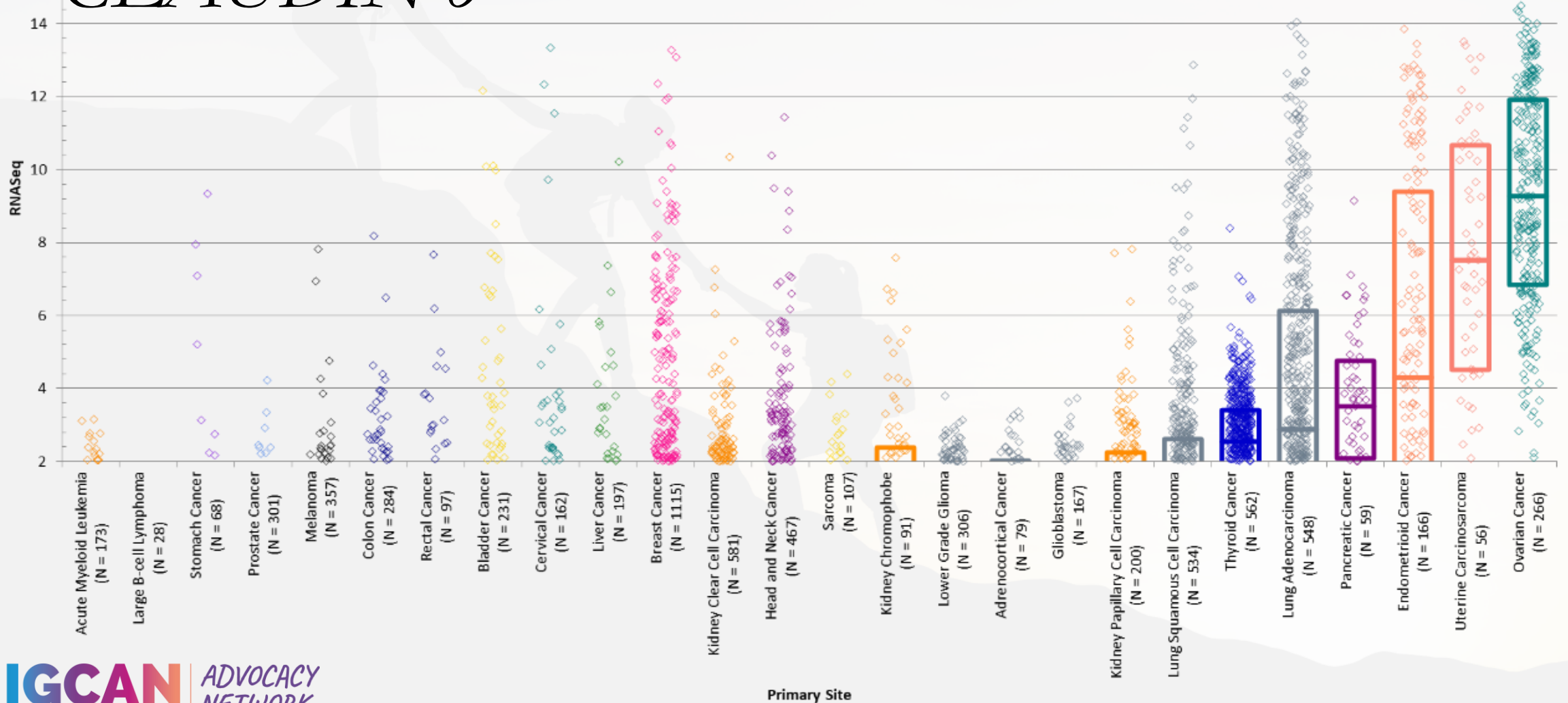


Overall survival - Ovarian Cancer

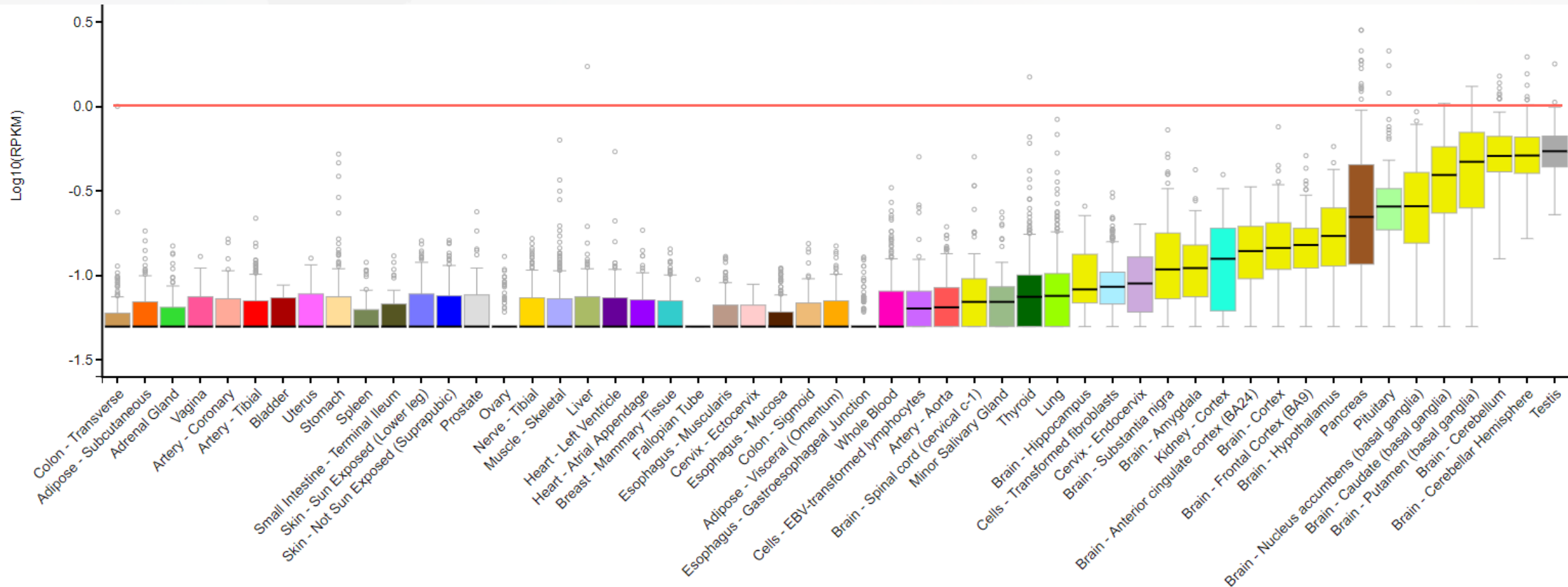


Novel Biomarker and ADC Target

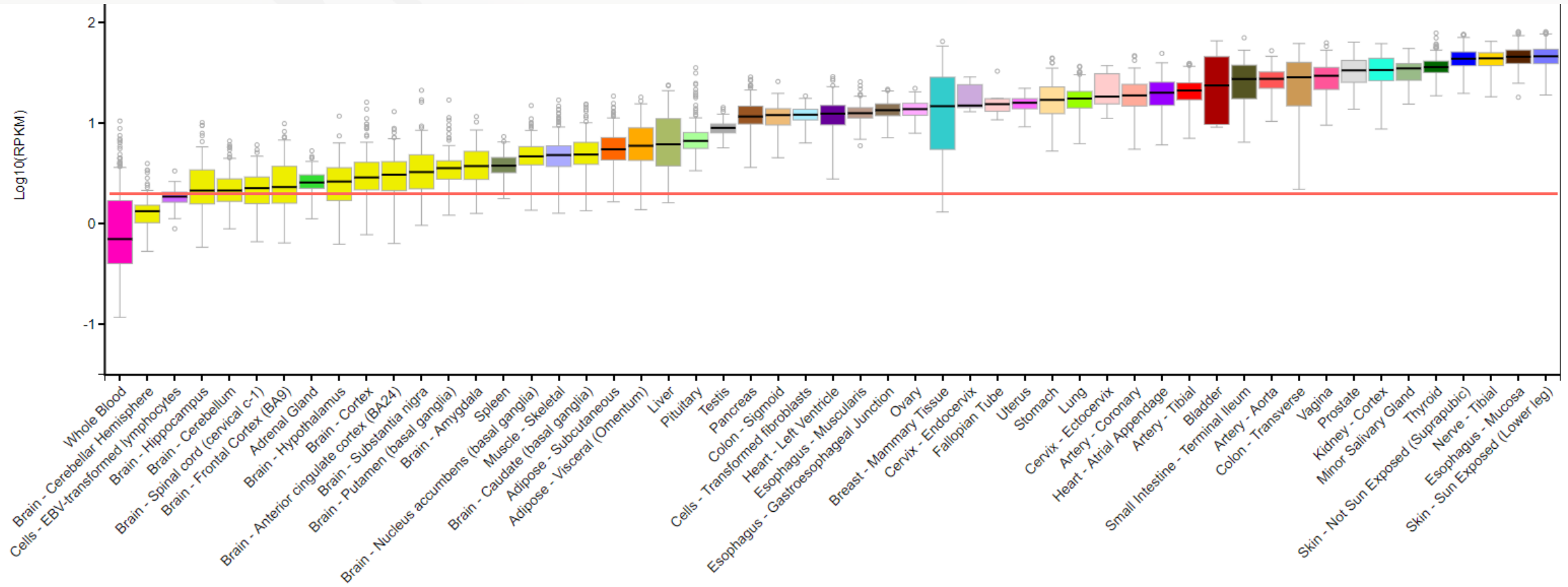
CLAUDIN 6



Expression of Claudin 6 in Normal Tissues (GTEx)

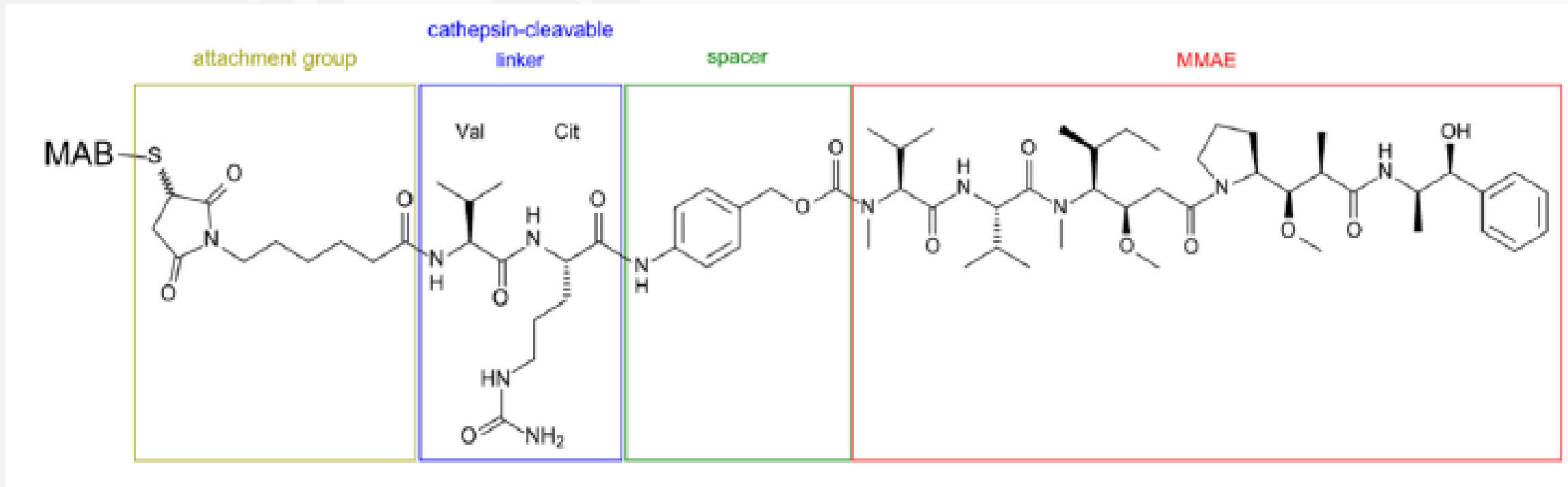


Expression of HER2 in Normal Tissues (GTEx)

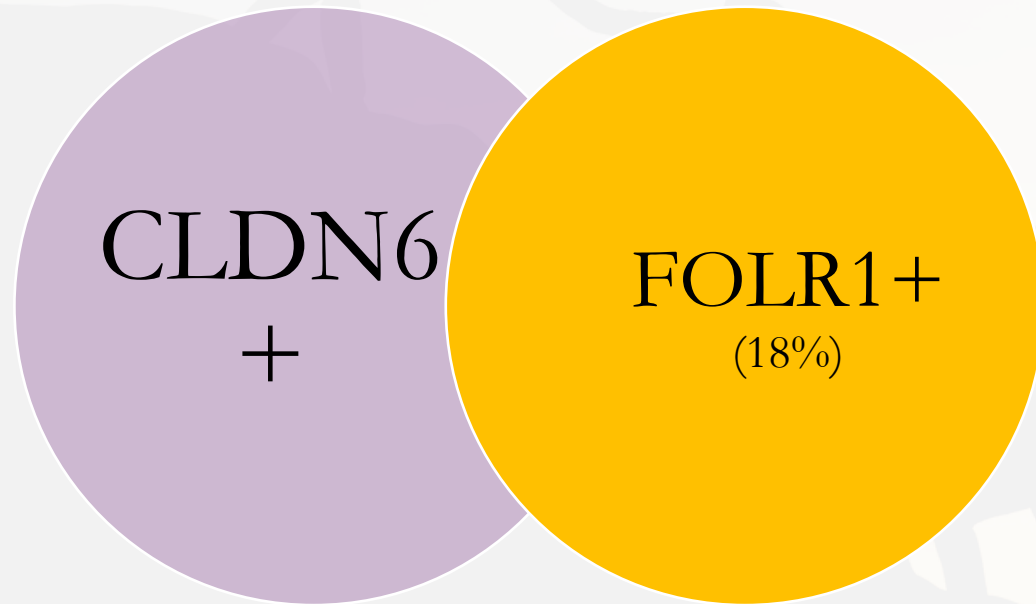


Claudin 6 a New Biomarker

- TORL-1-23 is an ADC with a fully humanized IgG1 (TORL-1-23-MAB) linked to MMAE through a cathepsin hydrolysable dipeptide VC linker (vc-MMAE).



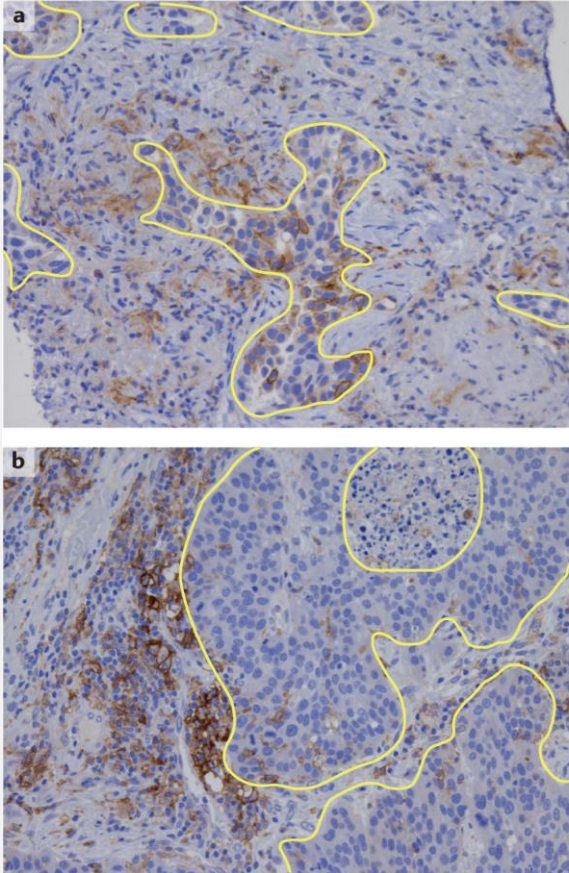
The higher the CLDN6 positivity, the lower the likelihood that patients are FOLR1 positive



CLDN 6+ high (upper half of CLDN 6 mid/high) population appears to be distinct

Immunotherapy Biomarkers

PD-L1 is a Weak Biomarker for Immunotherapy



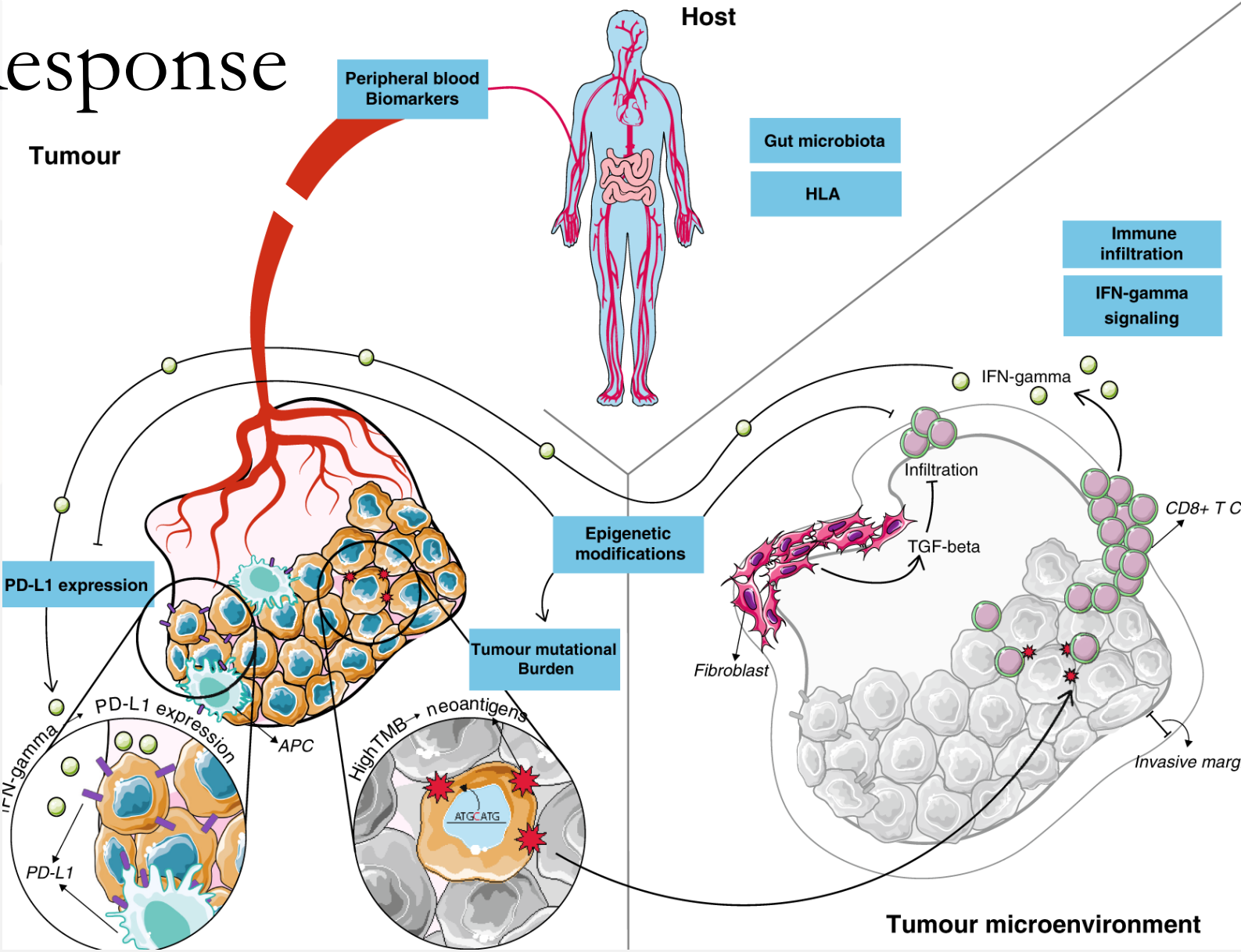
$$\text{TPS (\%)} = \frac{\text{Number of PD-L1-stained tumour cells}}{\text{Total number of viable tumour cells}} \times 100\% \text{ (for 22C3 or SP263)}$$

$$\text{TC (\%)} = \frac{\text{Number of PD-L1-stained tumour cells}}{\text{Total number of viable tumour cells}} \times 100\% \text{ (for SP142)}$$

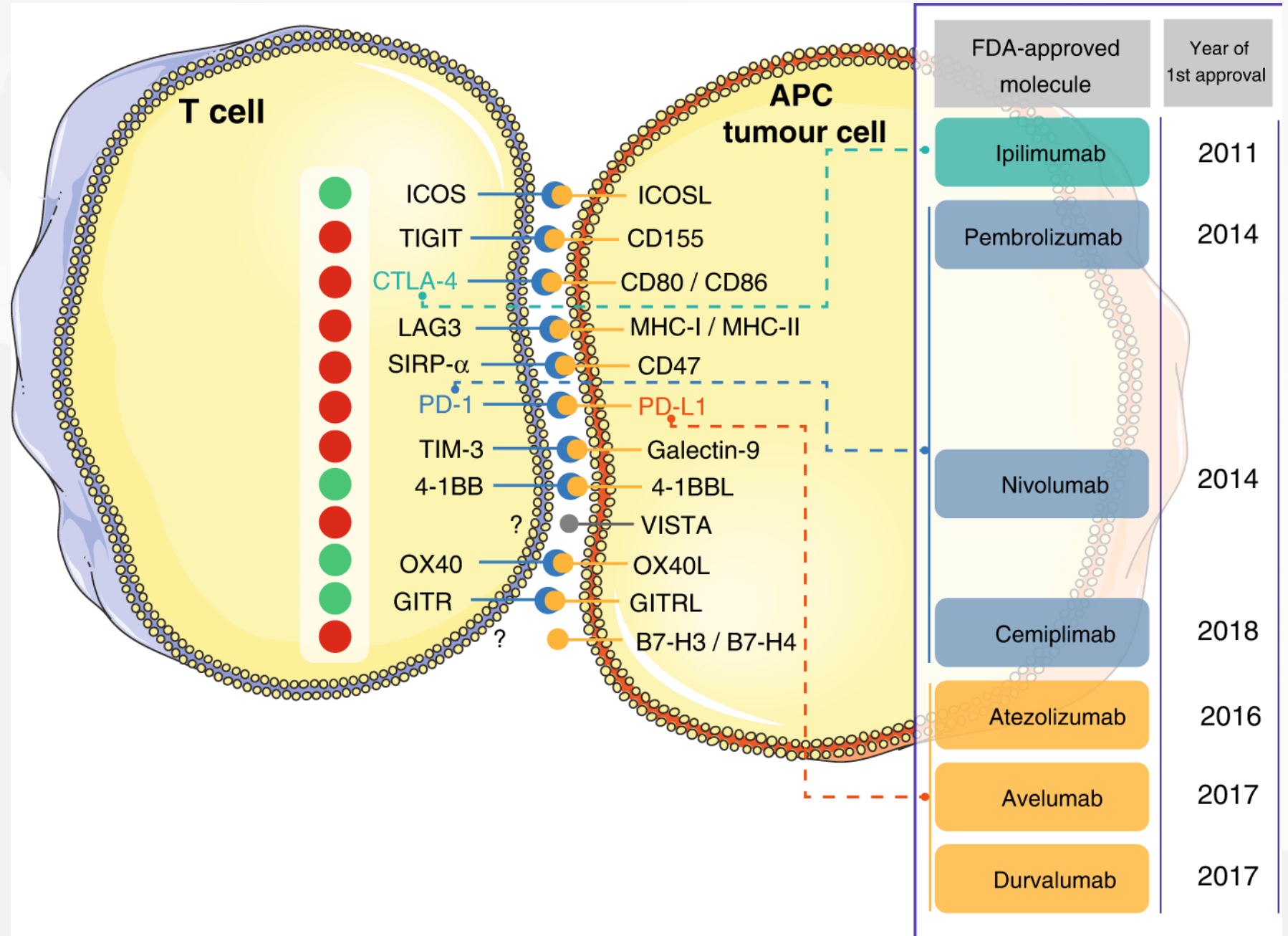
$$\text{IC (\%)} = \frac{\text{Area of tumour infiltrated by PD-L1-stained immune cells}}{\text{Total tumour area}} \times 100\% \text{ (for SP142)}$$

$$\text{CPS} = \frac{\text{Number of PD-L1-stained cells (tumour cells, lymphocytes and macrophages)}}{\text{Total number of viable tumour cells}} \times 100 \text{ (for 22C3)}$$

Evolving Biomarkers for Immunotherapy Response

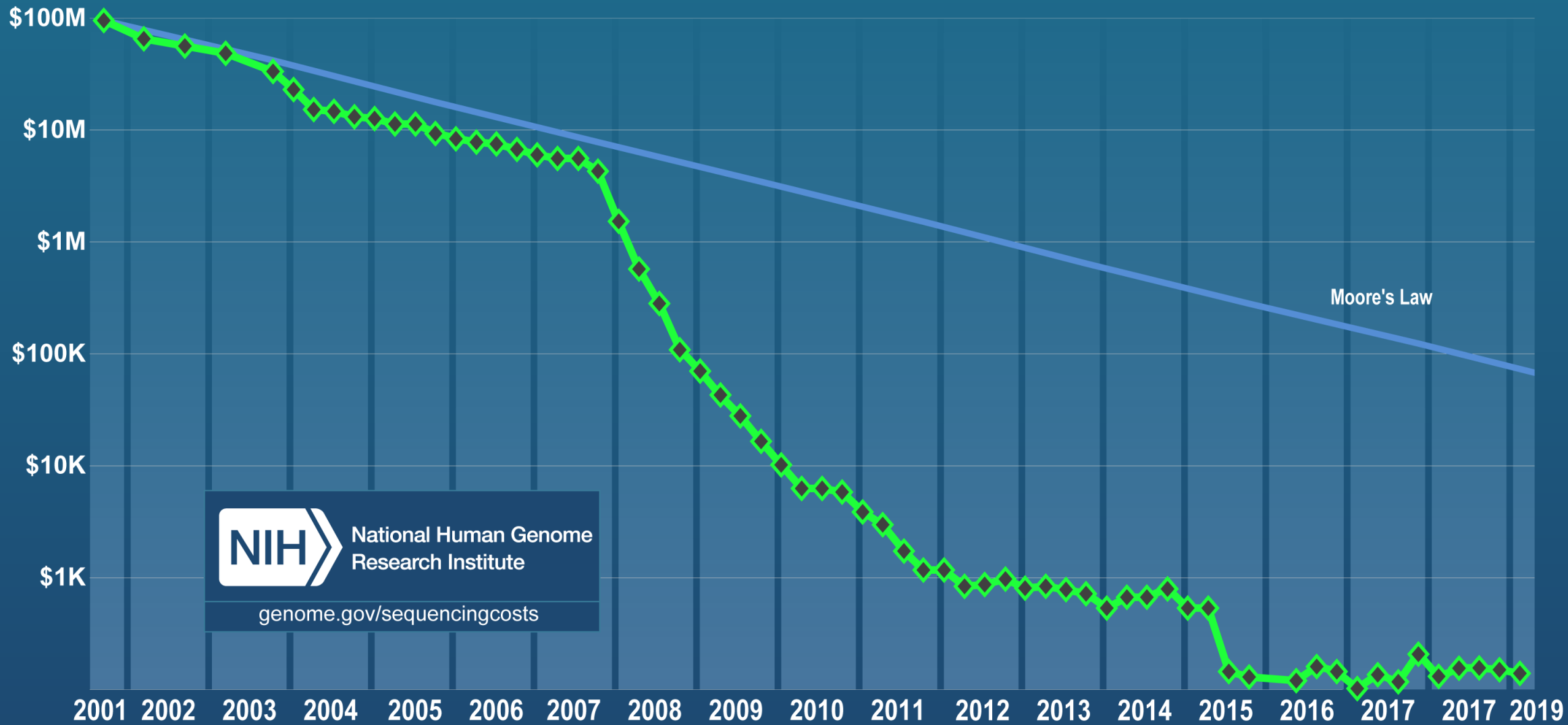


Redundancy of Immune-Checkpoints

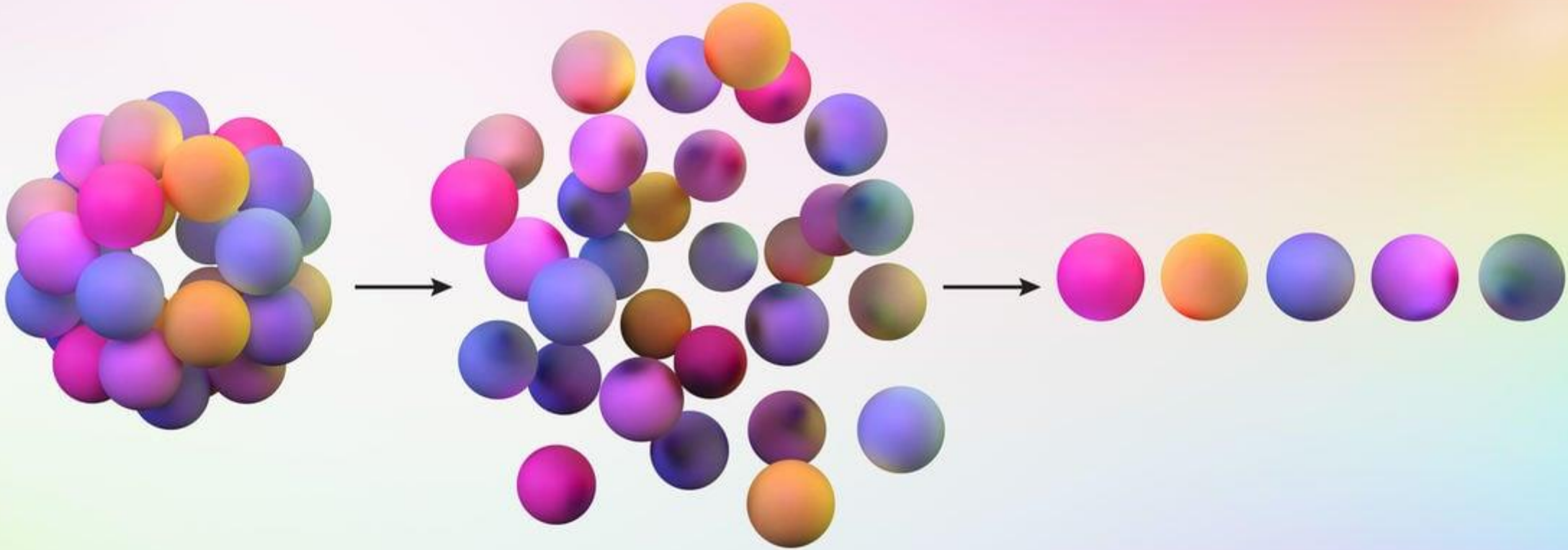


**Biomarker Development with
Single Cell Sequencing
and
Multiplexed Immunohistochemistry**

Cost per Genome



Single Cell RNAseq



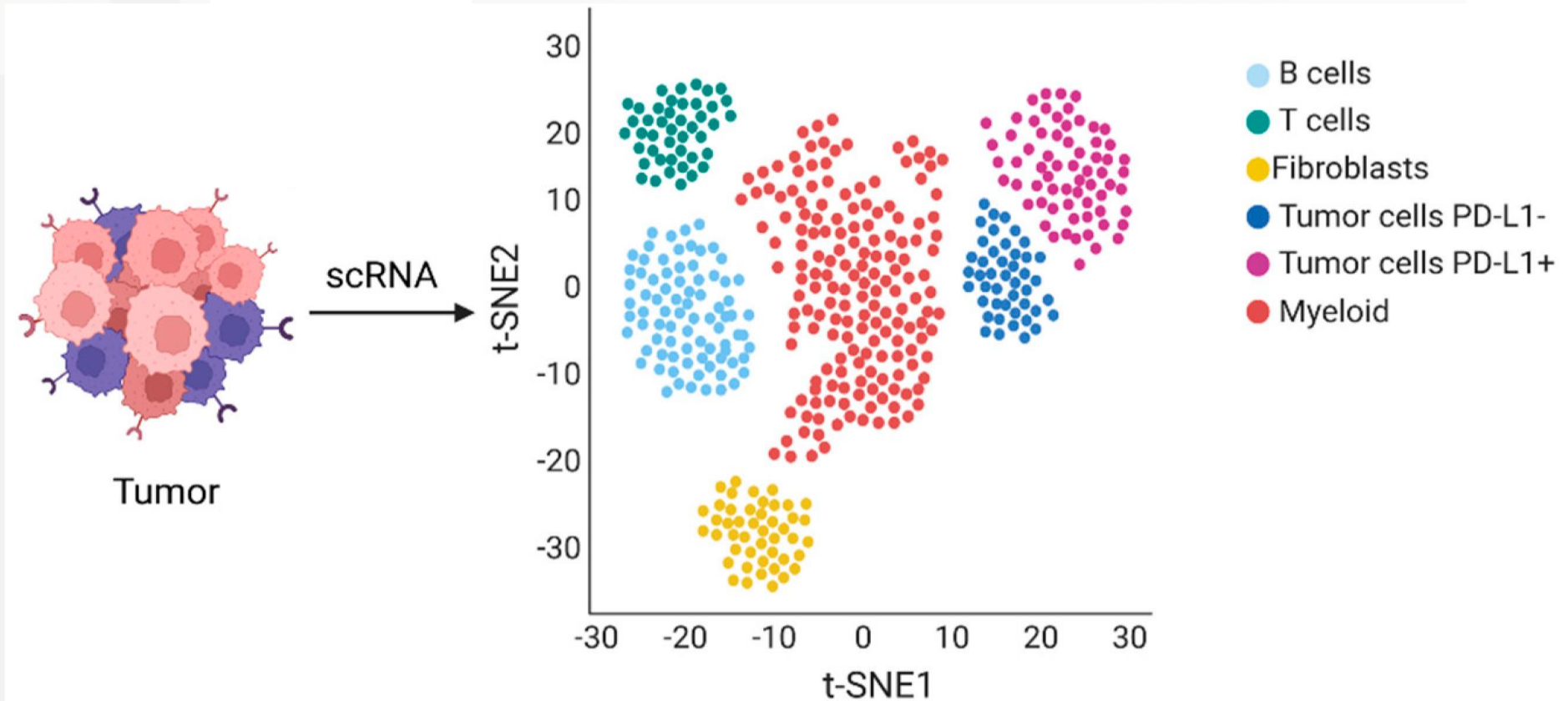
Heterogeneous tissue

Dissociated cells

Single cells ready for scRNA-seq

Single Cell RNAseq for Biomarker Studies

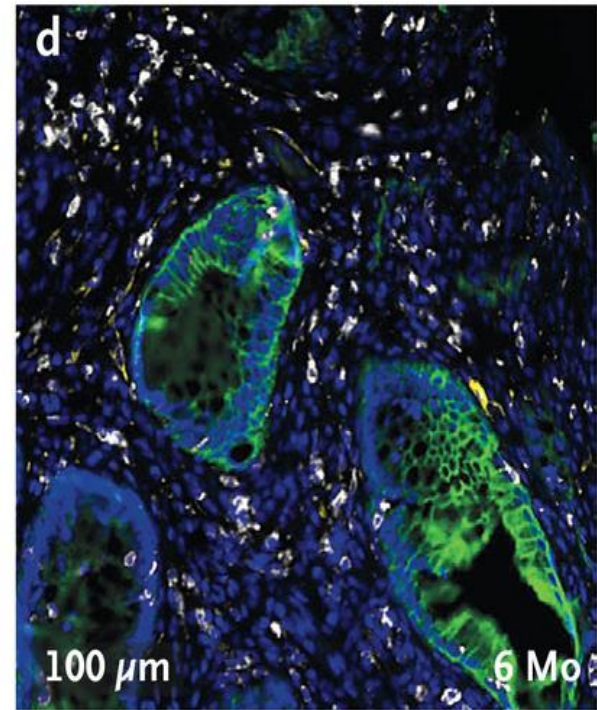
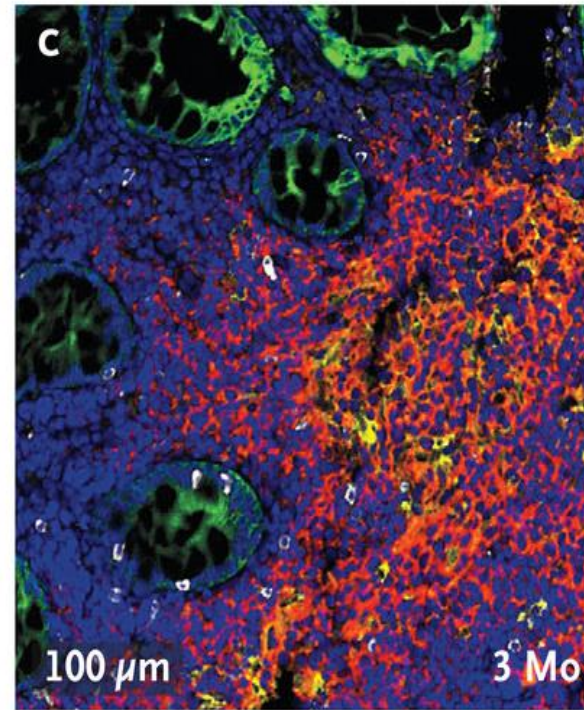
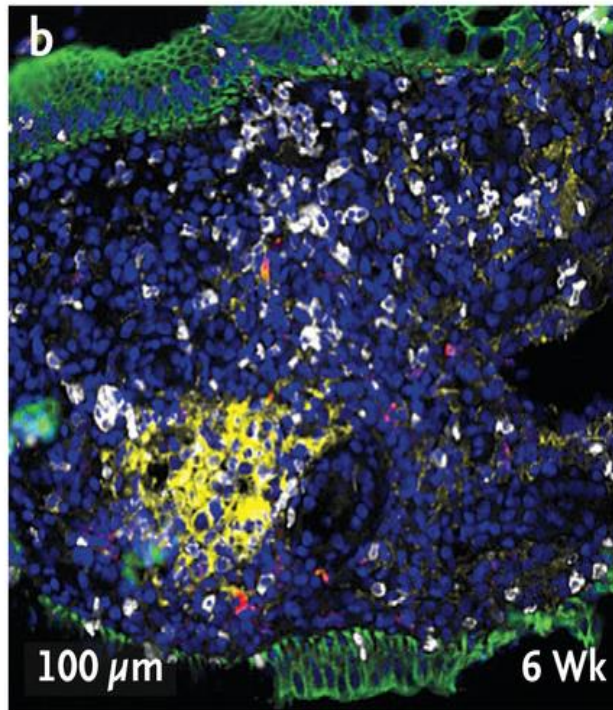
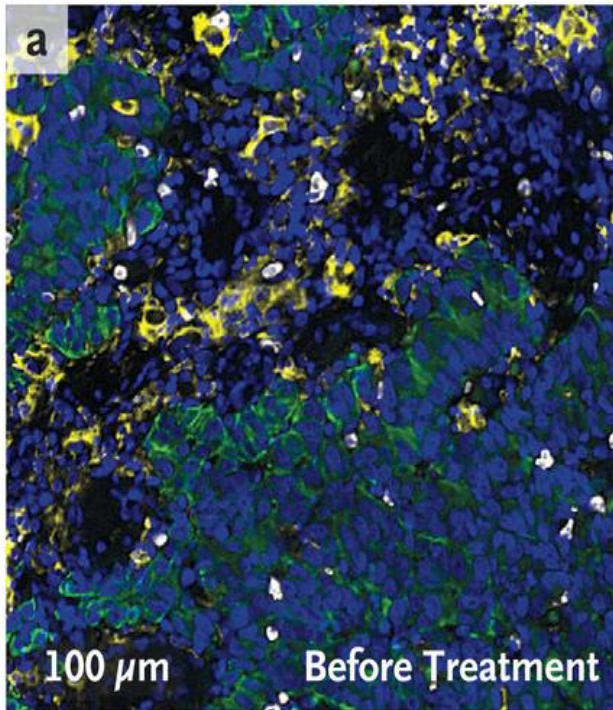
Zoom in to the Single Cell Level



Multiplexed Immunohistochemistry

High Spacial Resolution of Biomarkers

■ DAPI ■ Cytokeratin ■ PD-L1 □ CD8 ■ CD20



Biomarker Testing

Interpretive content on this page and subsequent pages is provided as a professional service, and is not retrieved or approved by the FDA.

PATIENT
 DISEASE: Lung non-small cell lung carcinoma (NOS)
 NAME: [REDACTED]
 DATE OF BIRTH: [REDACTED]
 SEX: [REDACTED]
 MEDICAL RECORD #: [REDACTED]

PHYSICIAN
 ORDERING PHYSICIAN: [REDACTED]
 MEDICAL FACILITY: [REDACTED]
 ADDITIONAL RECIPIENT: [REDACTED]
 MEDICAL FACILITY ID: [REDACTED]
 PATHOLOGIST: [REDACTED]

SPECIMEN
 SPECIMEN SITE: [REDACTED]
 SPECIMEN ID: [REDACTED]
 SPECIMEN TYPE: [REDACTED]
 DATE OF COLLECTION: [REDACTED]
 SPECIMEN RECEIVED: [REDACTED]

Sensitivity for the detection of copy number alterations is reduced due to sample quality.

Biomarker Findings
 Tumor Mutation Burden - TMB-High (20 Mut/Mb)
 Microsatellite Status - MS-Stable

Genomic Findings
 For a complete list of the genes sequenced, please refer to the Appendix.

KRAS G12D
 CDKN2A/B loss
 ATRX loss exons 2-8
 TP53 H168L
 7 Disease relevant genes with no reportable alterations: EGFR, ALK, BRAF, MET, ERBB2, RET, ROS1

3 Therapies with Clinical Benefit in patient's tumor type 20 Clinical Trials
 2 Therapies with Clinical Benefit in other tumor type

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT ON PATIENT'S TUMOR TYPE	THERAPIES WITH CLINICAL BENEFIT ON OTHER TUMOR TYPE
Tumor Mutation Burden - TMB-High (20 Mut/Mb)	Atezolizumab Nivolumab Pembrolizumab	Avelumab Durvalumab
10 Trials see p. 10	No therapies or clinical trials, see Biomarker Findings section	
Microsatellite status - MS-Stable	No therapies or clinical trials, see Biomarker Findings section	
GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT ON PATIENT'S TUMOR TYPE	THERAPIES WITH CLINICAL BENEFIT ON OTHER TUMOR TYPE
KRAS - G12D	none	none
10 Trials see p. 14		

GENOMIC FINDINGS AND BIOMARKERS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS
 For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemopreventive implications, see the Genomic Alterations section.

CDKN2A/B loss p. 4 **TP53 H168L** p. 5
ATRX loss exons 2-8 p. 4

Note: Genomic alterations identified may be associated with activity of certain FDA-approved drugs; however, the agents listed within report may have varied clinical evidence in the patient's tumor type, and the therapeutic agents listed are not intended as a recommendation for use. For more information on clinical evidence for the patient's tumor type, see the Therapeutic Options section.

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"T'EMPUS

Lung Sample Patient 22024

Diagnosis: Adenocarcinoma Accession No: Lung 22024

Date of Birth: 11/22/1961
 Sex: Male
 Physician: Dr. Patel
 Institution: Chicago Cancer Center

GENOMIC VARIANTS

Somatic - Potentially Actionable

- KRAS p.G12C Missense variant (exon 2) - GOF 23.8%

Somatic - Biologically Relevant

- ARID2 p.W256* Stop gain - LOF 26.7%
- RBM10 p.E808* Stop gain - LOF 25.5%
- STK11 p.R331fs Frameshift - LOF 15.7%
- NFE2L2 p.G81V Missense variant - GOF 12.6%
- FAT1 c.13139-1G>T Splice region variant - LOF 10.7%
- BCL11B p.T502fs Frameshift - LOF 8.0%

Germline - Pathogenic / Likely Pathogenic
 No germline pathogenic variants were found in the limited set of genes on which we report.

Pertinent Negatives
 No pathogenic single nucleotide variants, indels, or copy number changes found:



myRisk Genetic Result

RECEIVING HEALTHCARE PROVIDER
 Test HCP, MD
 Test Medical Center
 123 Main St
 Testville, TX 55555

SPECIMEN
 Specimen Type: Blood
 Draw Date: Aug 08, 2017
 Accession Date: Aug 08, 2017
 Report Date: Aug 30, 2017

PATIENT
 Name: PI Last Name, PI First Name
 Date of Birth: Aug 08, 1980
 Patient ID: Patient ID
 Gender: Female
 Accession #: 07778921-BLD
 Requestion #: 7778921

GENETIC RESULT: NEGATIVE - NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED
 Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

BREAST CANCER RISKSORE™: REMAINING LIFETIME RISK 23.7%
 This level of risk is at or above 20% threshold for consideration of modified medical management. See riskScore™ Interpretation Section for more information.

CLINICAL HISTORY ANALYSIS: NO MODIFIED MANAGEMENT GUIDELINES IDENTIFIED BASED ON THE CLINICAL HISTORY PROVIDED
 Other clinical factors may influence individualized management. This analysis may be incomplete if details about cancer diagnoses, ages, family relationships or other factors were omitted or ambiguous.

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

Details About Non-Clinically Significant Variants: All individuals carry DNA changes (e.g., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Variant Classification: Myriad's myRisk™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report.

ADDITIONAL INFORMATION

GENES ANALYZED
 Unless otherwise noted sequencing and large rearrangement analyses were performed on the following genes:
 APC, ATM, BARD1, BMP1YA, BRCA1, BRCA2, BRP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM (large rearrangement only), MHH, MSH2, MSH6, MLH1, NBN, PALB2, PMS2, PIK3R, RAD51C, RAD51D, SMAD4, STK11, TP53. Sequencing was performed for select regions of POLR1 and POLR2, and large rearrangement analysis was performed for select regions of GREM1 (see technical specifications).

Indication for Testing: It is our understanding that this individual was identified for testing due to a personal or family history suggestive of a hereditary predisposition for cancer.

Associated Cancer Risks and Clinical Management: Please see the "myRisk Management Tool" associated with this report for a summary of cancer risk and professional society medical management guidelines that may be useful in developing a plan for this patient based on test results and reported personal/family history, if applicable. Testing of other family members may assist in the interpretation of this patient's test result.

Analysis Description: The Technical Specifications summary (https://www.myriadpro.com/documents-and-forms/technical-specifications) describes the analysis, method, performance, nomenclature, and interpretive criteria of this test. Current testing technologies are unable to definitively determine whether a variant is germline or somatic in origin, which may significantly impact risk estimates and medical management; therefore, these results should be correlated with this patient's personal and family history. The interpretation of this test may also be impacted if the patient has a hematologic malignancy or an allogeneic bone marrow transplant.

**** Other genes not analyzed with this test may also be associated with cancer.**



Final Report CARIS LIFE SCIENCES

Patient
 Name: [REDACTED]
 Date of Birth: [REDACTED]
 Sex: Female
 Case Number: TN23-
 Diagnosis: Carcinoma, metastatic, NOS

Specimen Information
 Primary Tumor Site: Lower lobe, lung
 Specimen Site: Mediastinal lymph node
 Specimen ID: [REDACTED]
 Specimen Collected: [REDACTED]
 Test Report Date: [REDACTED]

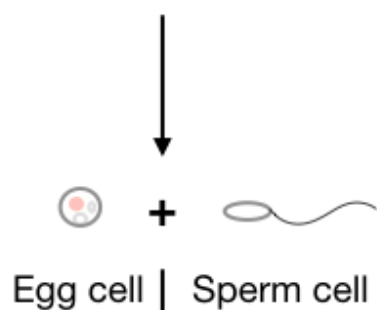
Ordered By

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION	BIOMARKER LEVEL*
PD-L1 (22c3)	IHC	Protein	Positive, TPS: 80%	BENEFIT cemiplimab, pembrolizumab	Level 1
PD-L1 (28-8)	IHC	Protein	Positive 1+, 60%	BENEFIT nivolumab/ipilimumab combination	Level 1
PD-L1 (SP263)	IHC	Protein	Positive, TC: 1+, 60%	BENEFIT atezolizumab (adjuvant)	Level 1
KRAS	Seq	DNA-Tumor	Pathogenic Variant Exon 2 p.G12C	BENEFIT adagrzib, sotorasib	Level 2
				LACK OF BENEFIT erlotinib, gefitinib	Level 2
TMB	Seq	DNA-Tumor	High, 14 mut/Mb	BENEFIT pembrolizumab	Level 2
ALK	IHC	Protein	Negative 0	LACK OF BENEFIT alectinib, ceritinib, crizotinib, lorlatinib	Level 1
				LACK OF BENEFIT brigatinib	Level 2
Seq	RNA-Tumor	Fusion Not Detected		LACK OF BENEFIT alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	Level 2
				LACK OF BENEFIT dabrafenib and trametinib combination therapy, vemurafenib	Level 2
BRAF	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT erlotinib, gefitinib	Level 2
EGR2	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT pralsetinib, selipratinib	Level 2
RET	Seq	RNA-Tumor	Fusion Not Detected	LACK OF BENEFIT ceritinib, crizotinib, entrectinib, lorlatinib	Level 2
ROS1	Seq	RNA-Tumor	Fusion Not Detected	LACK OF BENEFIT crizotinib	Level 3
MET	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT	Level 3

* Biomarker reporting classification: Level 1 - Companion diagnostic (CDx); Level 2 - Strong evidence of clinical significance or is endorsed by standard clinical guidelines; Level 3 - Potential clinical significance. Bolded benefit therapies; if present, highlight the most clinically significant findings.

Germline Testing

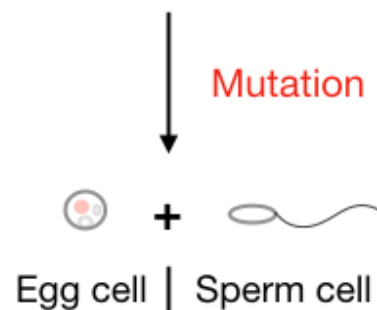


Embryo

Mutation



Somatic mutation

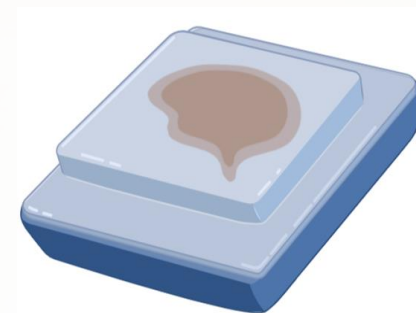


Embryo

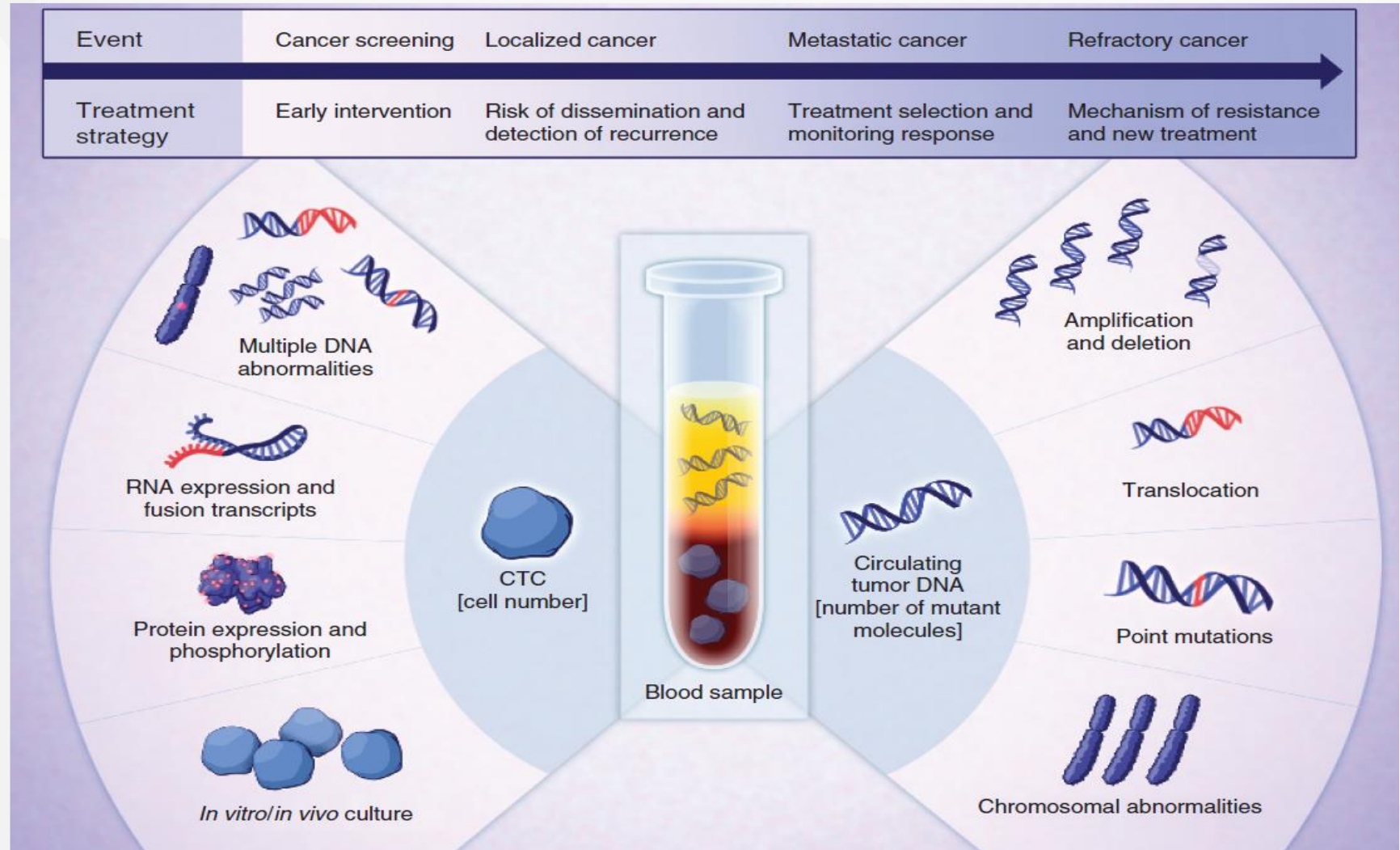


Germline mutation

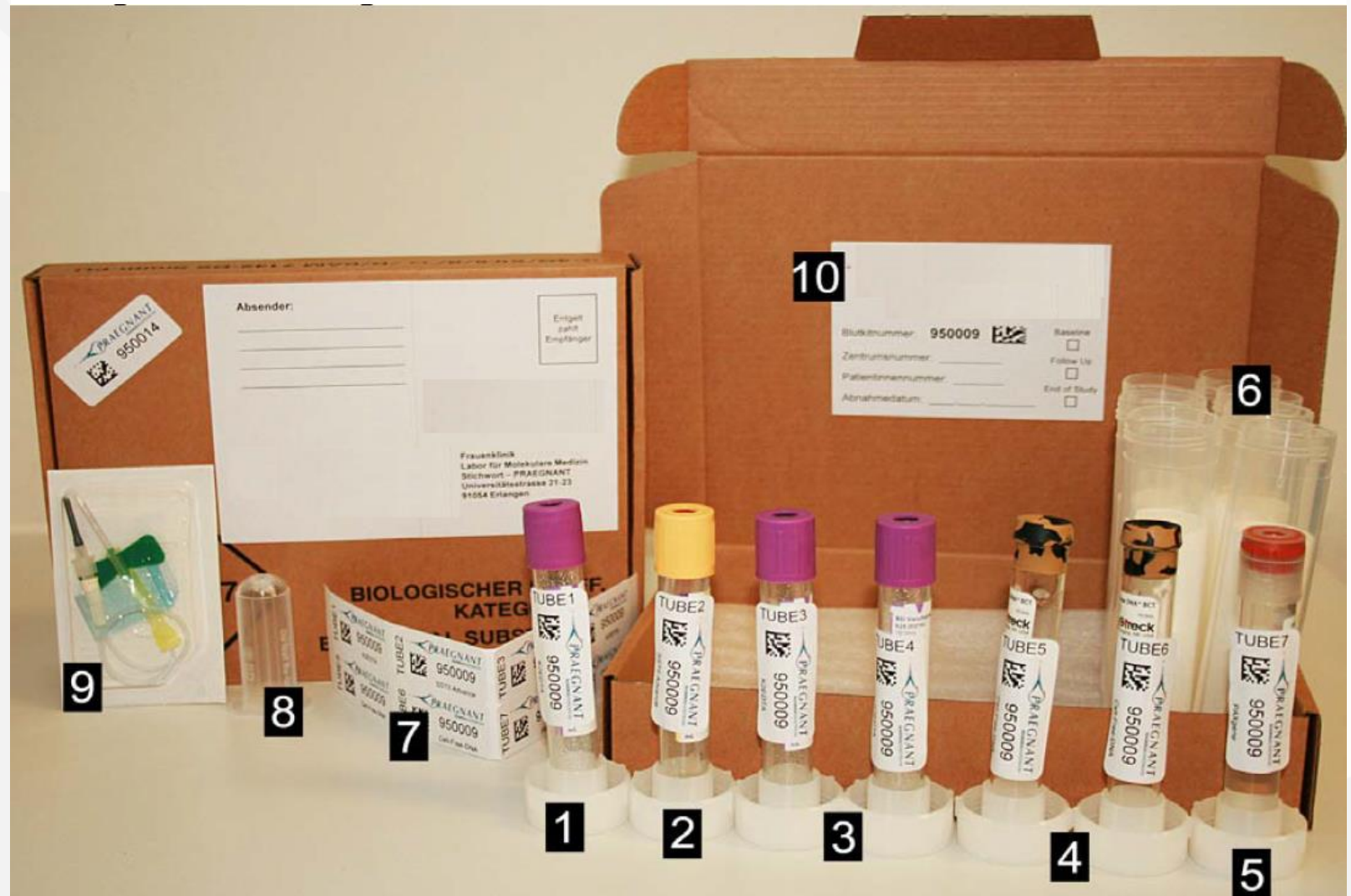
Somatic Testing



Biomarker Testing in circulating cell-free DNA (cfDNA)



Biomarker Testing will help us Understand Treatment Response and Failure



We need Biomarkers in Gynecologic Oncology

- ER
- BRCA1/2
- HRD
- MSI
- TMB
- FOLR1
- CLDN6

- HER2
- PDL1
- CCNE1
- P53
- KRAS
- NTRK
- B7H4

