Do we need Biomarkers in Gynecologic Oncology

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IGCAN INTERNATIONAL GYNECOLOGIC CANCER | ADVOCACY NETWORK

Annual Survivor-Caregiver Summit

What are Biomarkers

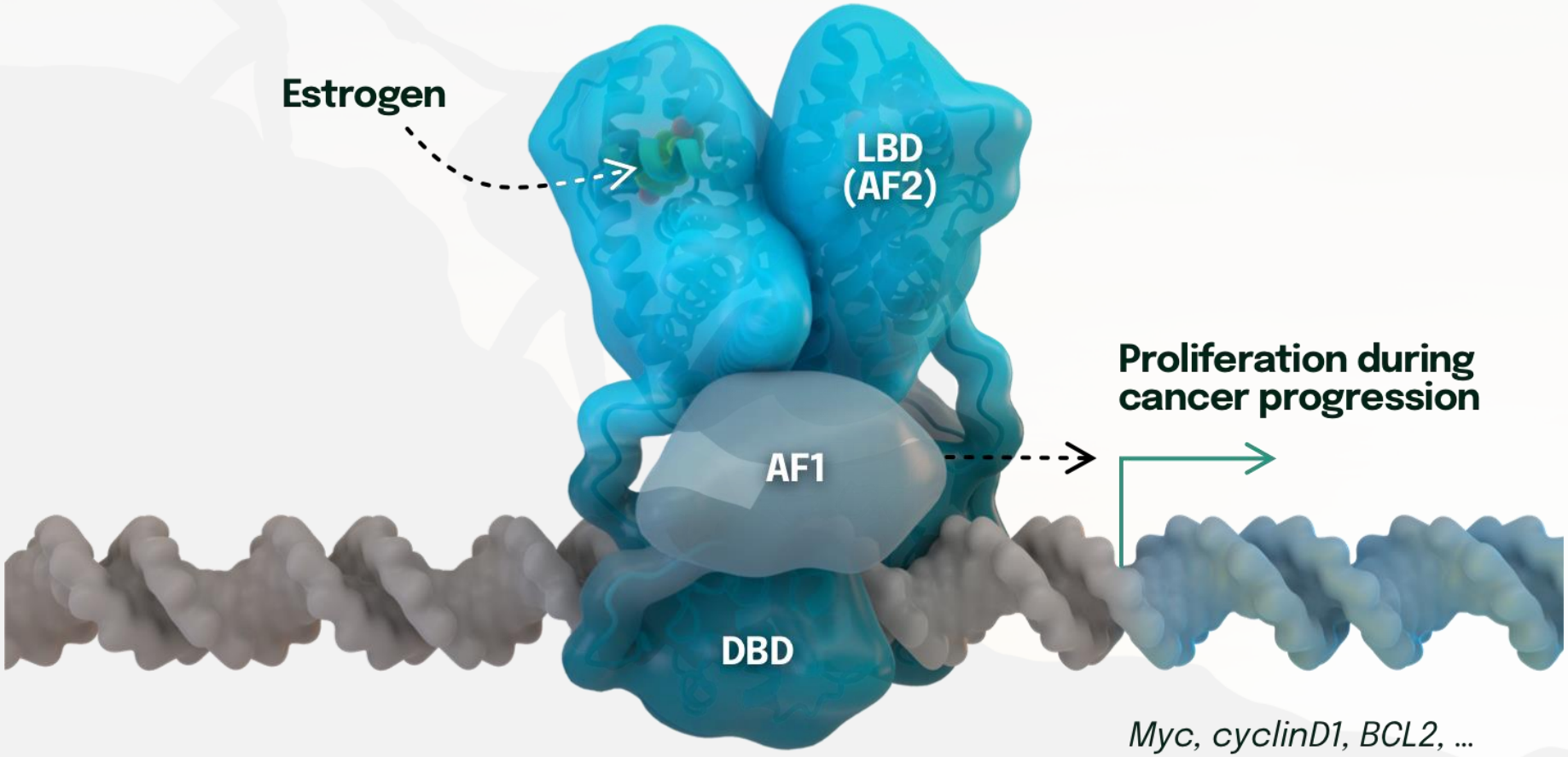
Biomarkers tell you….

…of an association

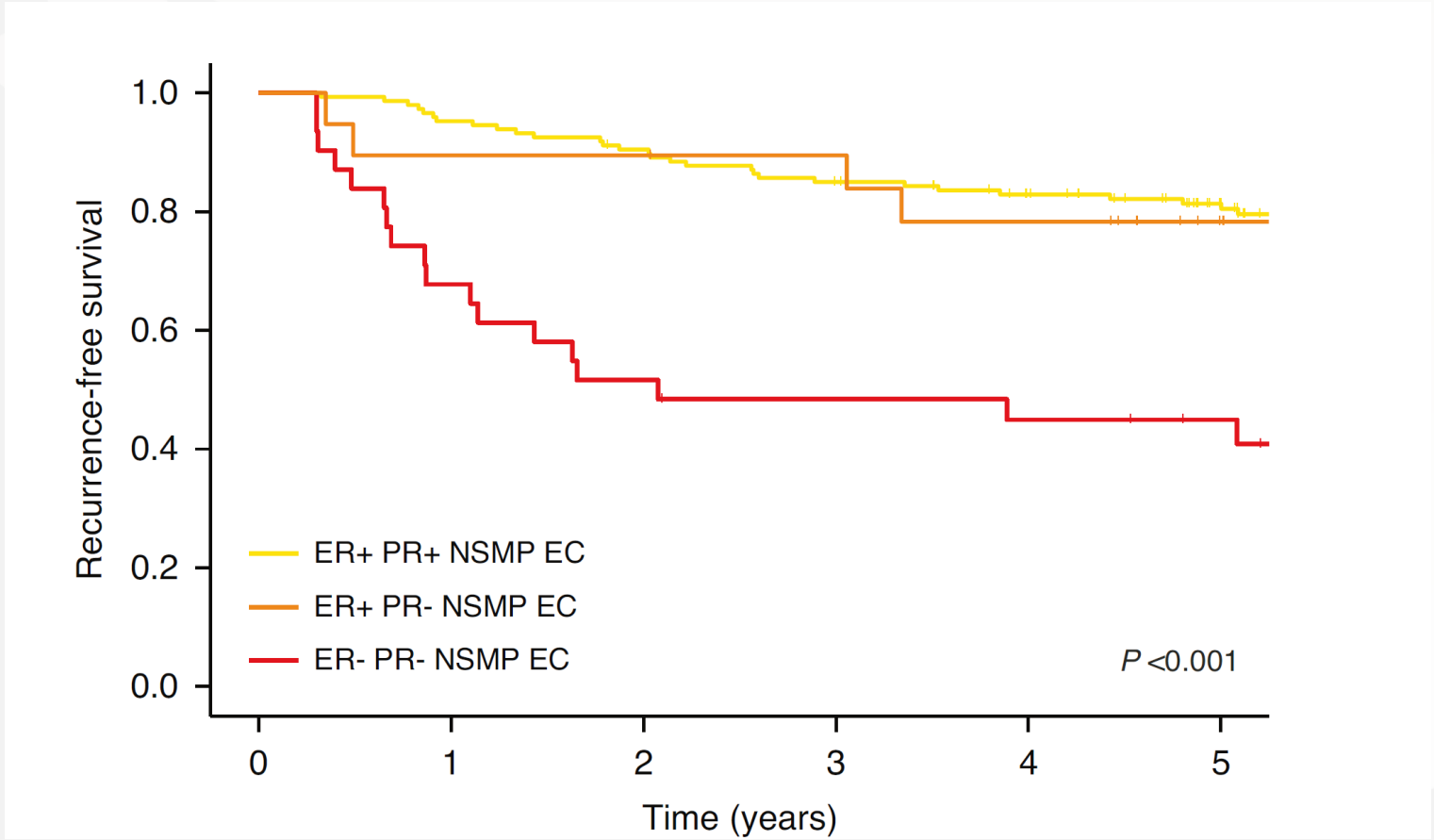
…of the likelihood of an event

Estrogen Receptor as a Biomarker

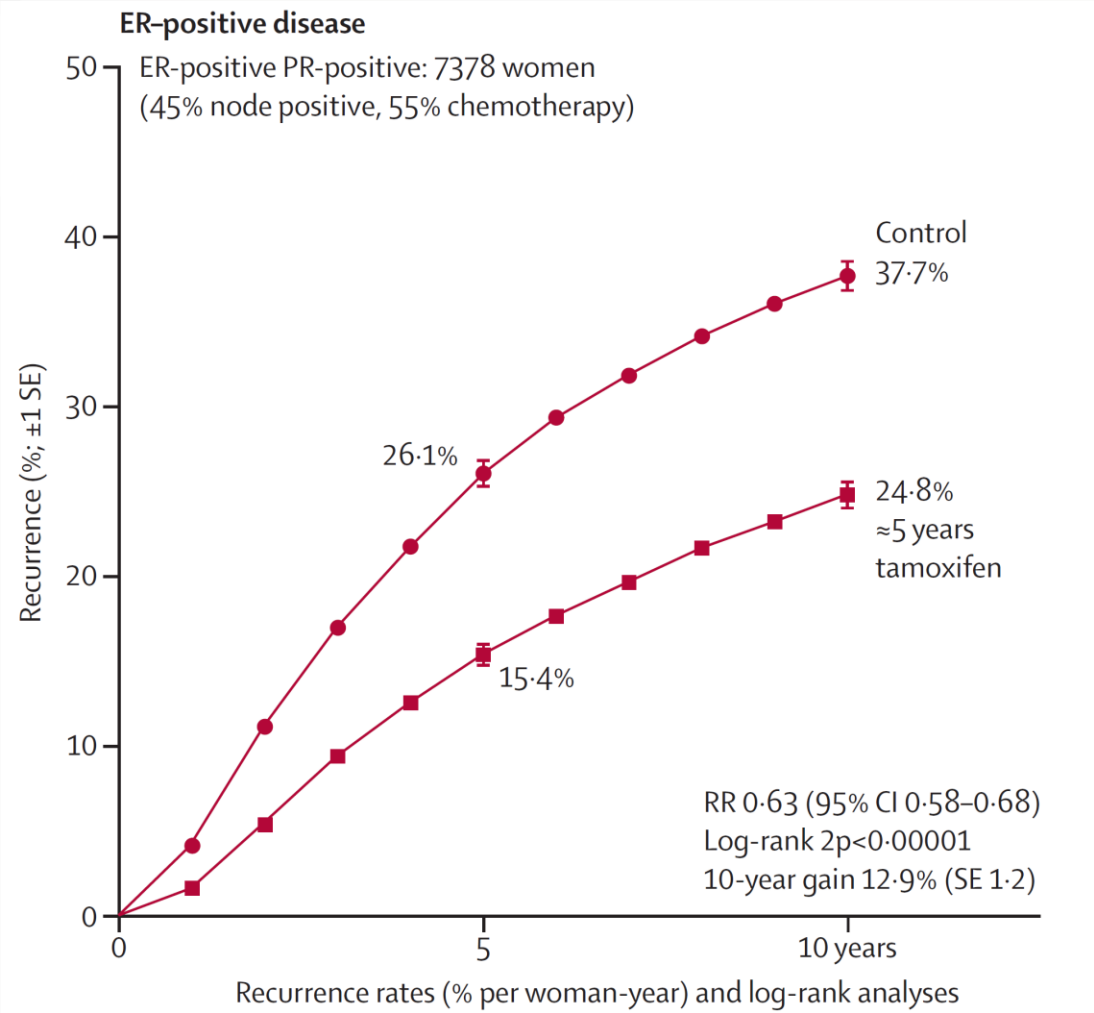
Single-agent Immunotherapy efficacy



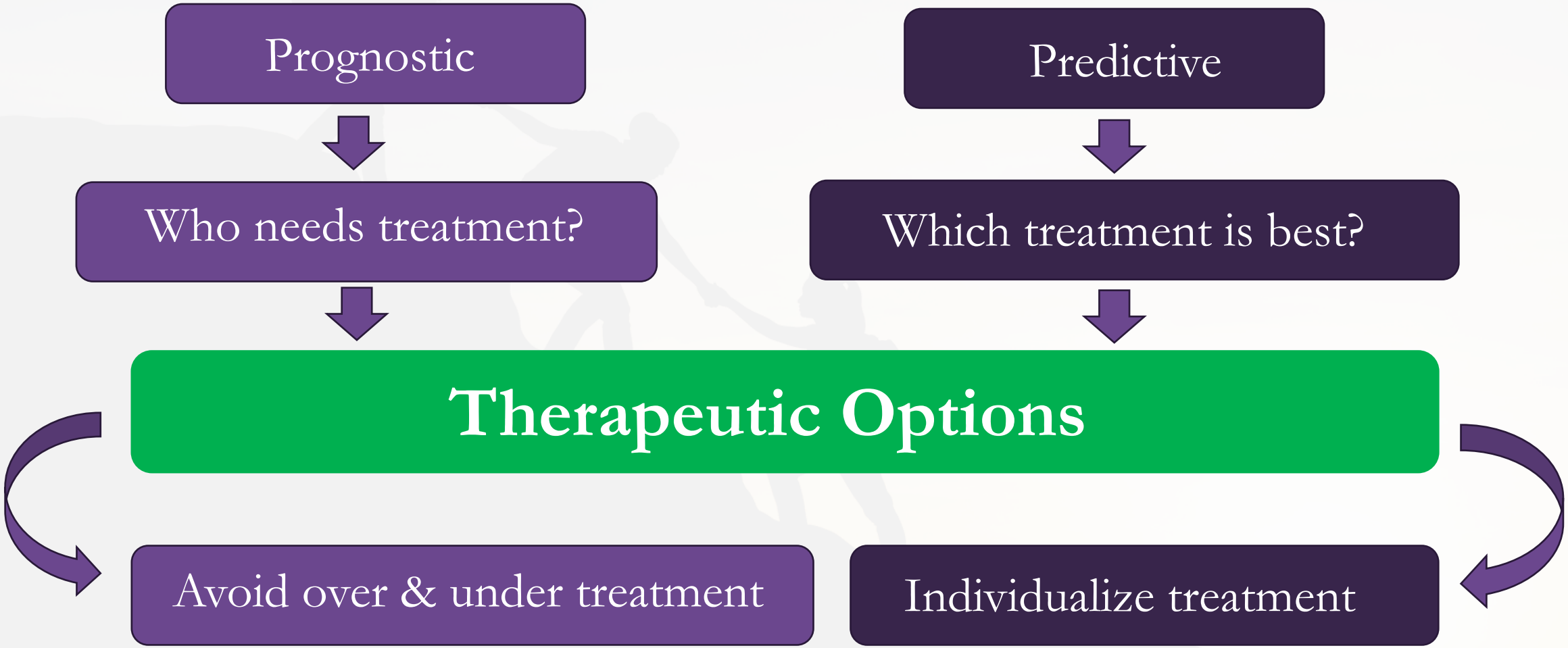
Estrogen Receptor as a Biomarker
Prognostic *Marker in Endometrial Cancer*



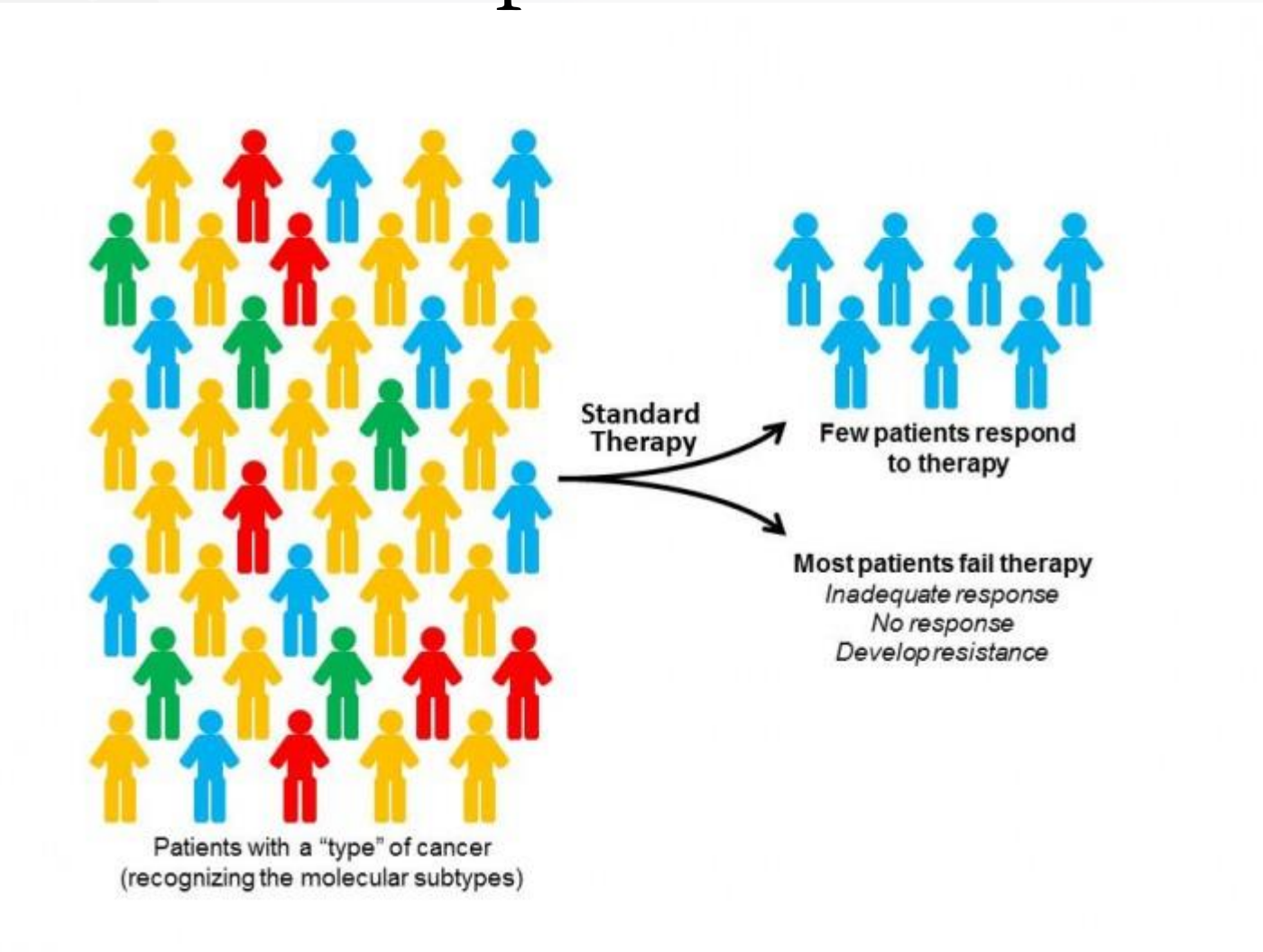
Estrogen Receptor as a Biomarker
Predictive *Marker for Response to Anti-Hormonal Therapy*



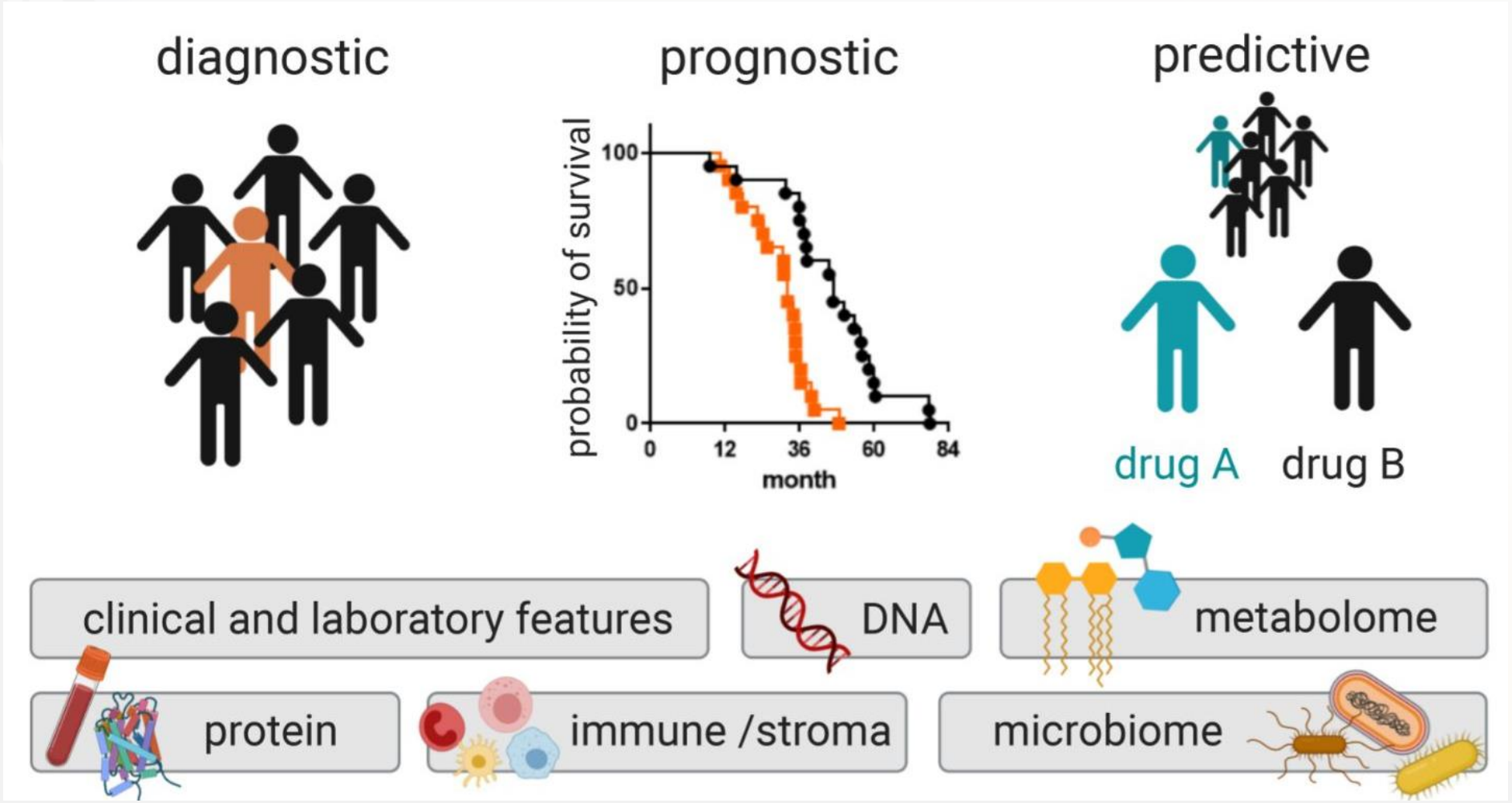
Why do we need ***Prognostic*** or ***Predictive*** Markers?



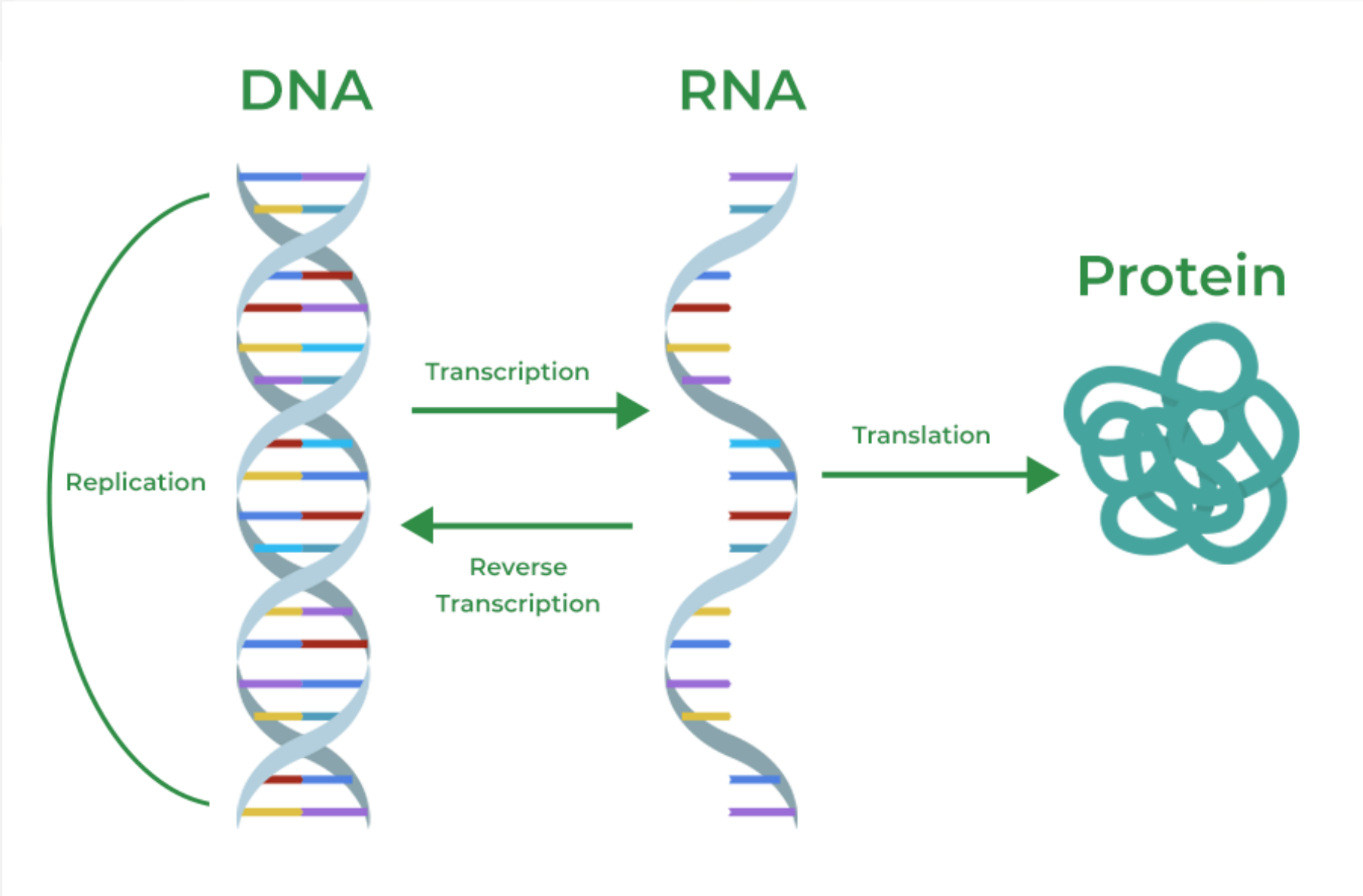
Predictive Markers help individualize Treatments



How do we measure Biomarkers?



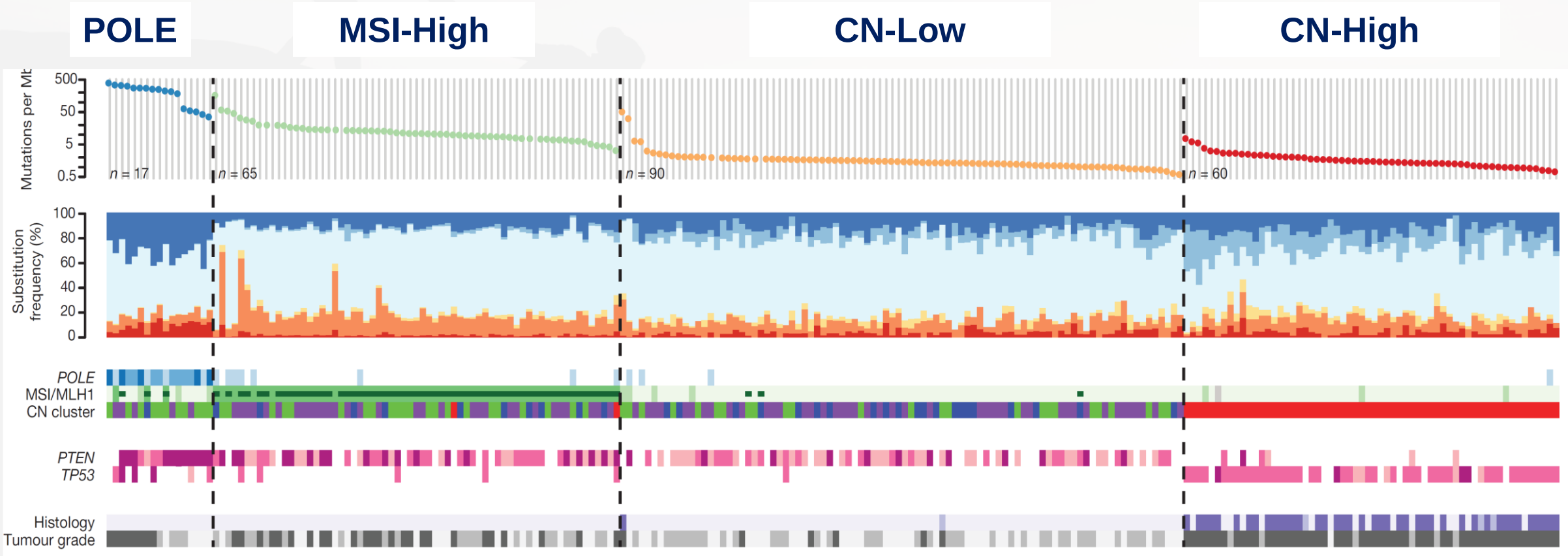
How do we measure Biomarkers?



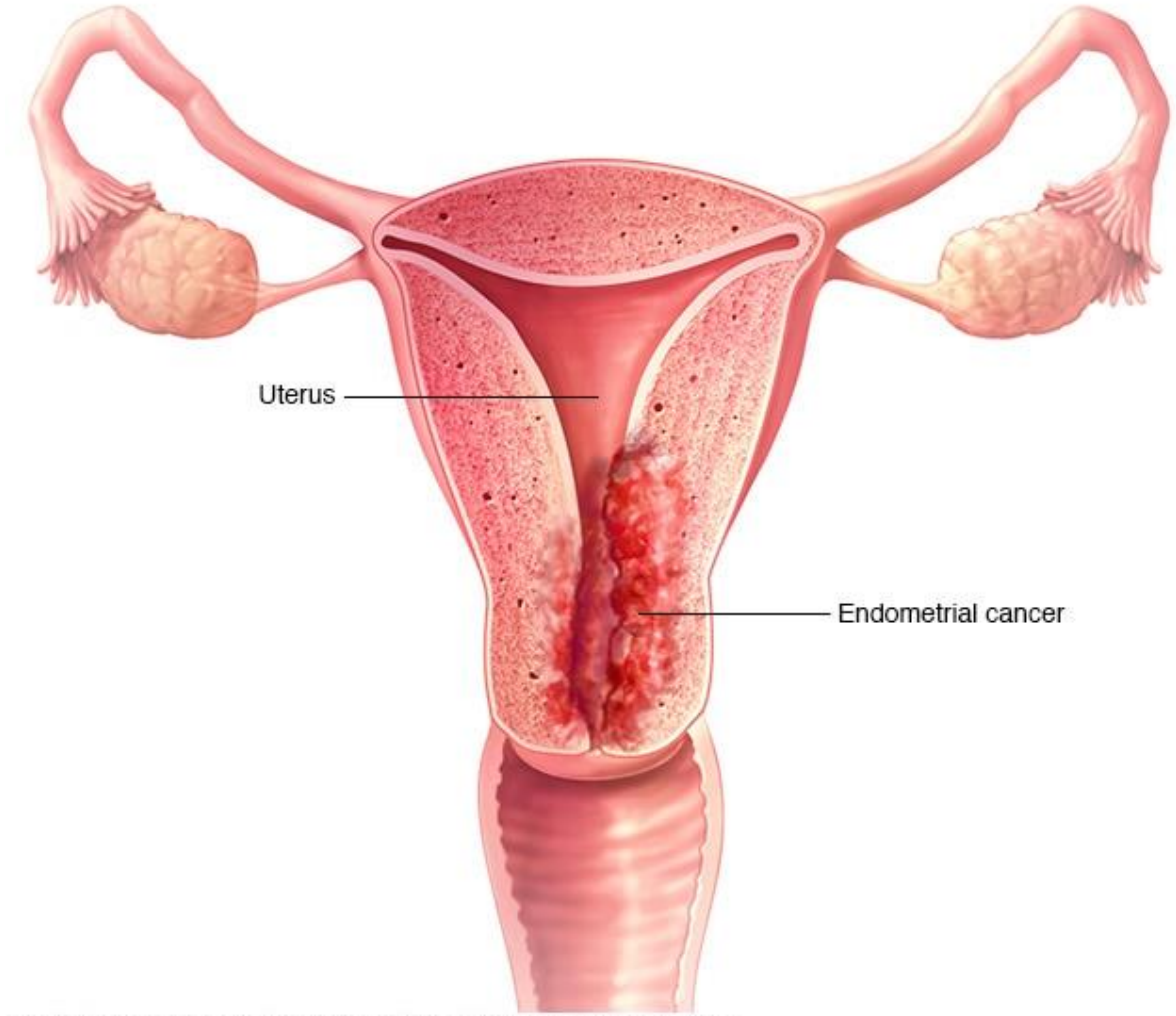
Biomarkers in Endometrial Cancer

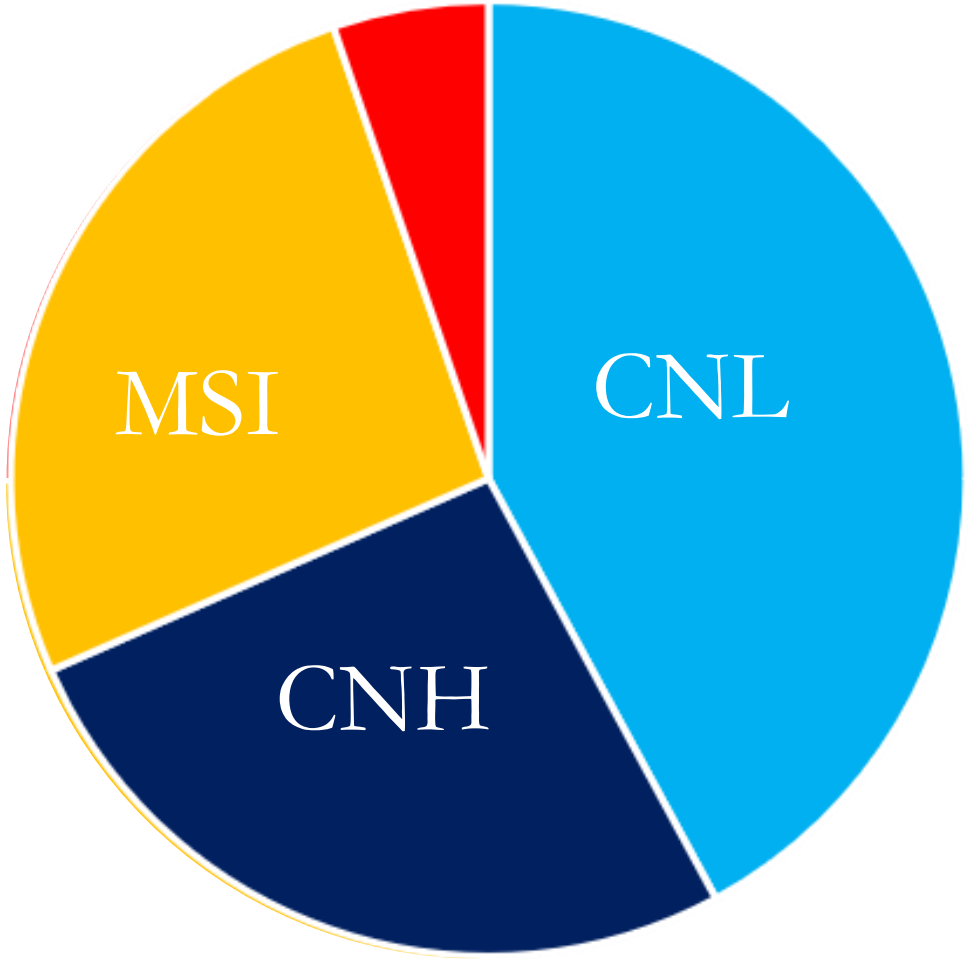
Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

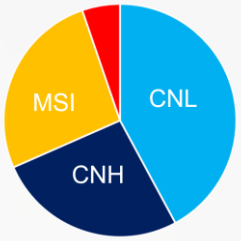


4 Molecular Subtypes





Managing MSI-high disease
Single-agent Immunotherapy efficacy

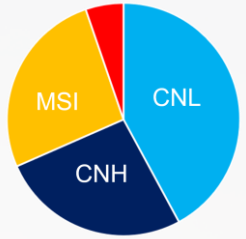


Study	Drug	N	Patient Selection	ORR (%)
KEYNOTE-158	Pembrolizumab	49	Advanced / metastatic dMMR	57%
GARNET	Dostarlimab	103	Previously treated Recurrent / advanced dMMR	45%
PHAEDRA	Durvalumab	35	Advanced / metastatic dMMR	43%
NCT02912572	Avelumab	15	Advanced / persistent dMMR	27%

Marabelle A, et al. *J Clin Oncol.* 2020;38(1):1-10. 2. Oaknin A, et al. Presented at European Society for Medical Oncology Virtual Congress 2020. 3. Antill YC, et al. *J Clin Oncol.* 2019;37(15_suppl):5501. 4. Konstantinopoulos PA, et al. *J Clin Oncol*. 2019;37(30):2786-2794; Bonneville R, et al. *JCO Precis Oncol*. 2017;1:1-15.

Managing MSS disease:

Single Agent IO Efficacy in Biomarker Negative Endometrial Cancer

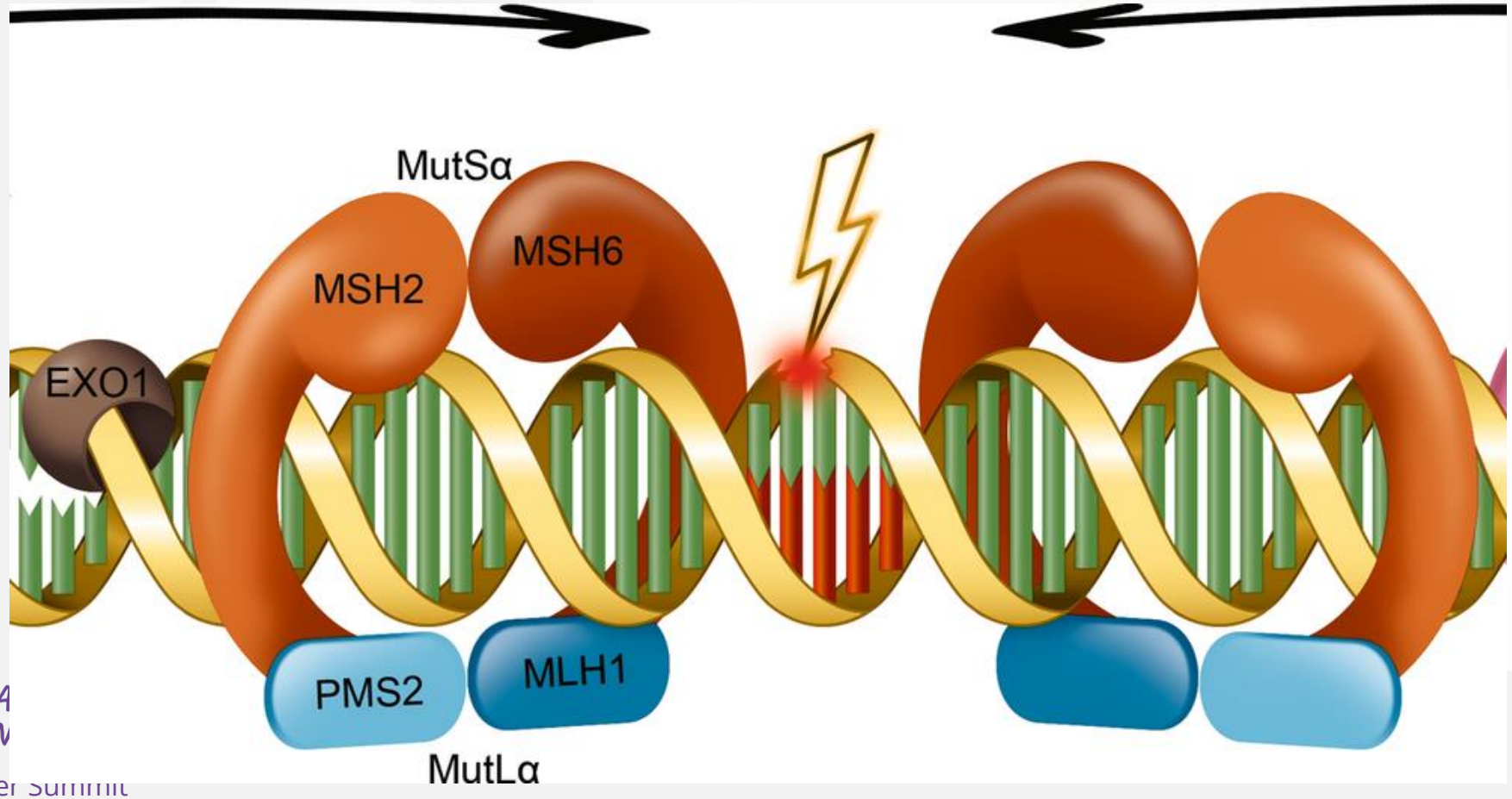


Study	Drug	N	Patient Selection	ORR (%)
KEYNOTE-28	Pembrolizumab	24	Advanced/metastatic PD-L1+	13%
Garnet	Dostarlimab	142	Previously treated Recurrent/advanced pMMR	13.4%
PHAEDRA	Durvalumab	36	Advanced/metastatic pMMR	3%
Konstantinopoulos	Avelumab	16	Advanced/metastatic pMMR	6%

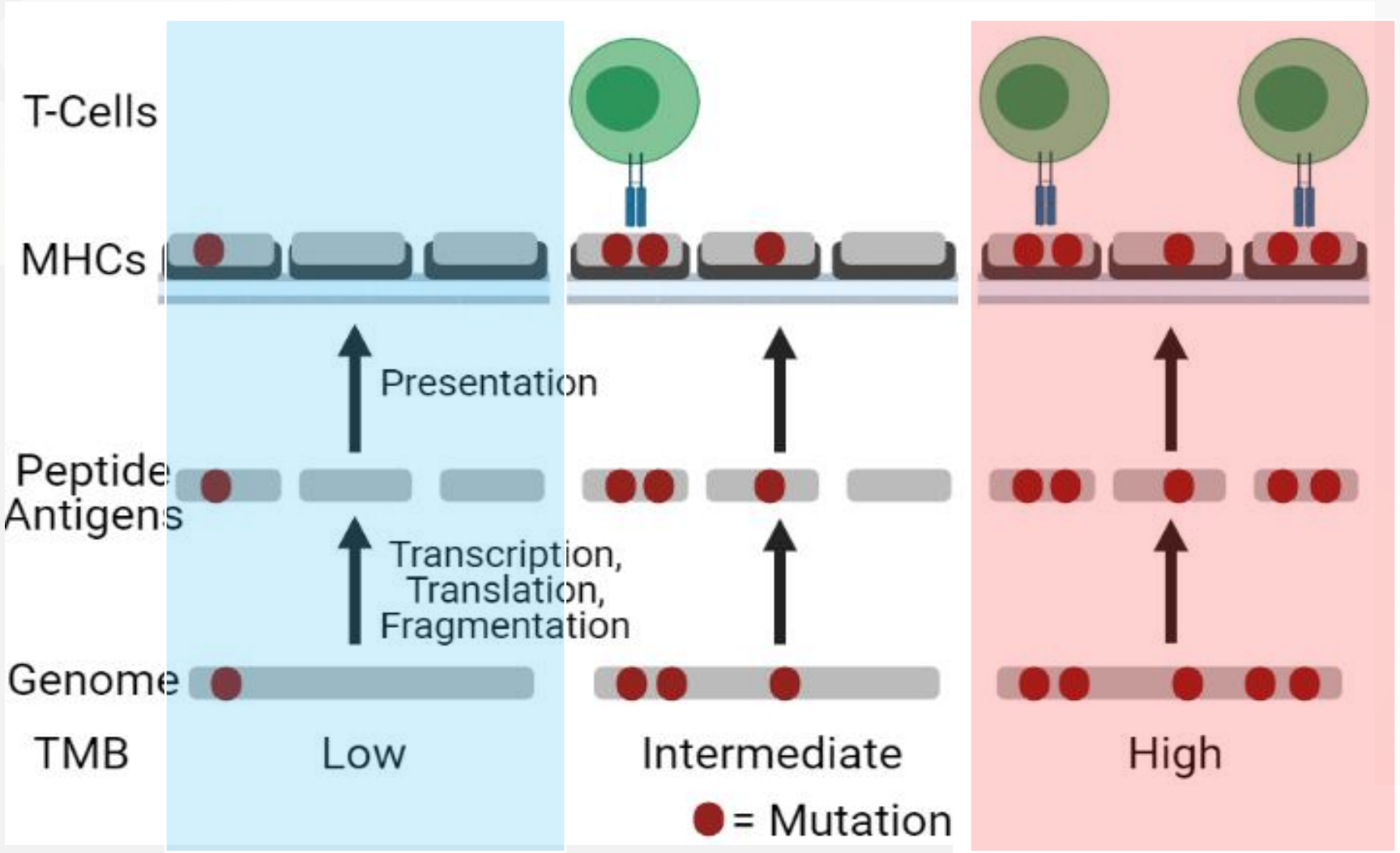
Ott PA et al. *J Clin Oncol.* 2017;35(22):2535-2541. 2. Oaknin A et al. SGO 2020. Abstract LBA 9. 3. Antill Y et al. ASCO 2019. Abstract 5501. 4. Konstantinopoulos PA et al. *J Clin Oncol.* 2019;37(30):2786-2794.

Managing MSI-high disease

Mismatch Repair Deficiency or Microsatelite Instability



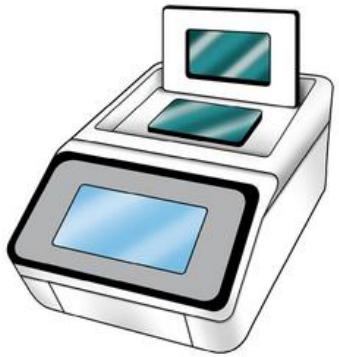
MSI-high ➔TMB high ➔Neo-Antigens



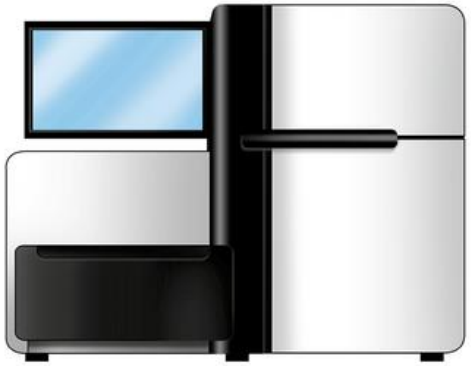
Biomarkers for MSI-high disease

Mismatch Repair Deficiency or Microsatelite Instability

Immunohistochemistry

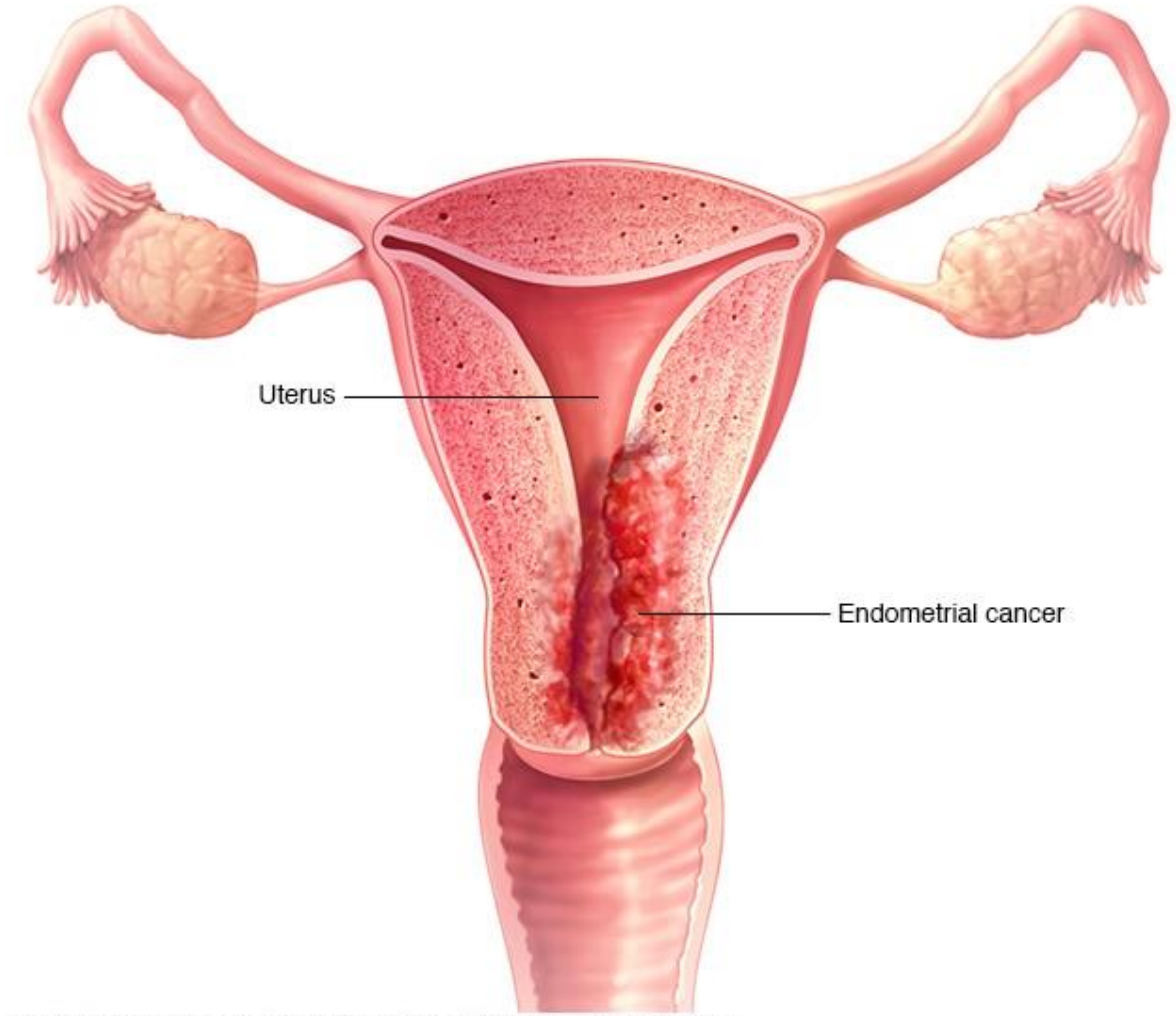


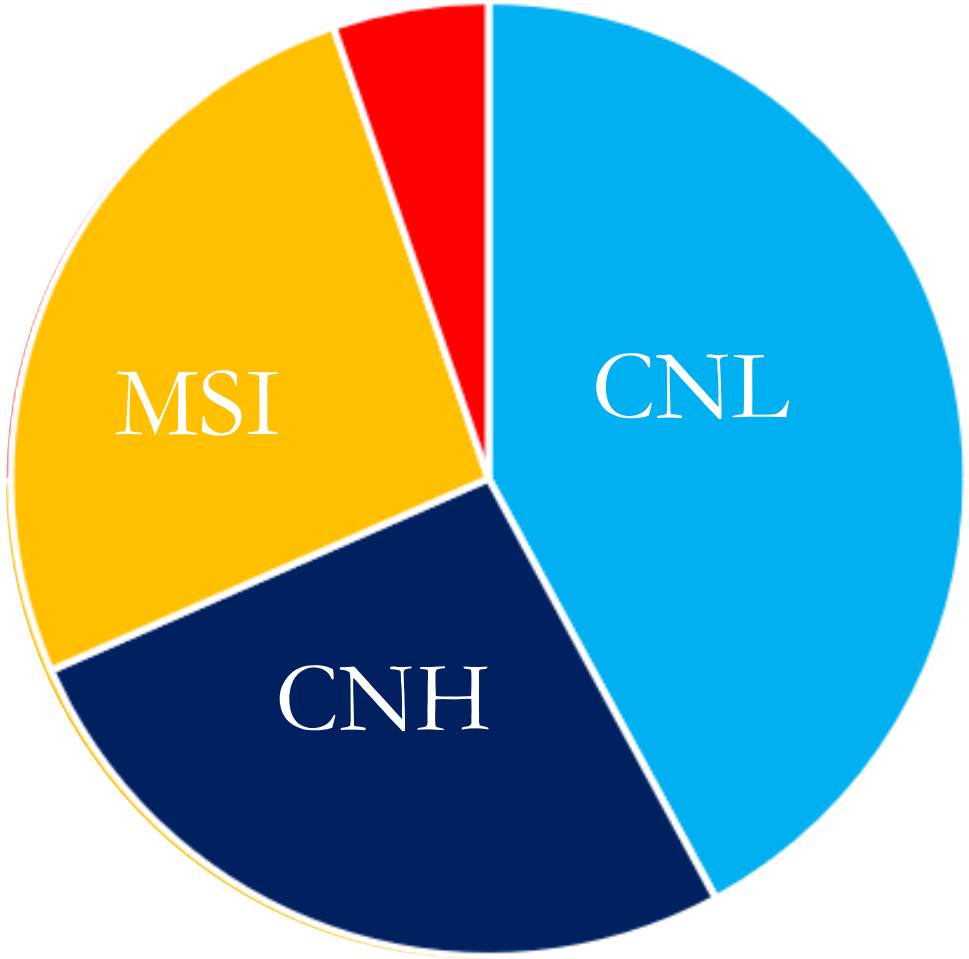
qPCR-based MSI analysis



Next-Generation Sequencing

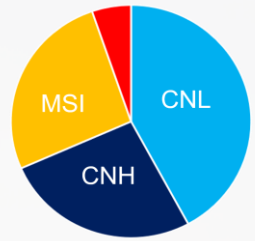
4 Molecular Subtypes

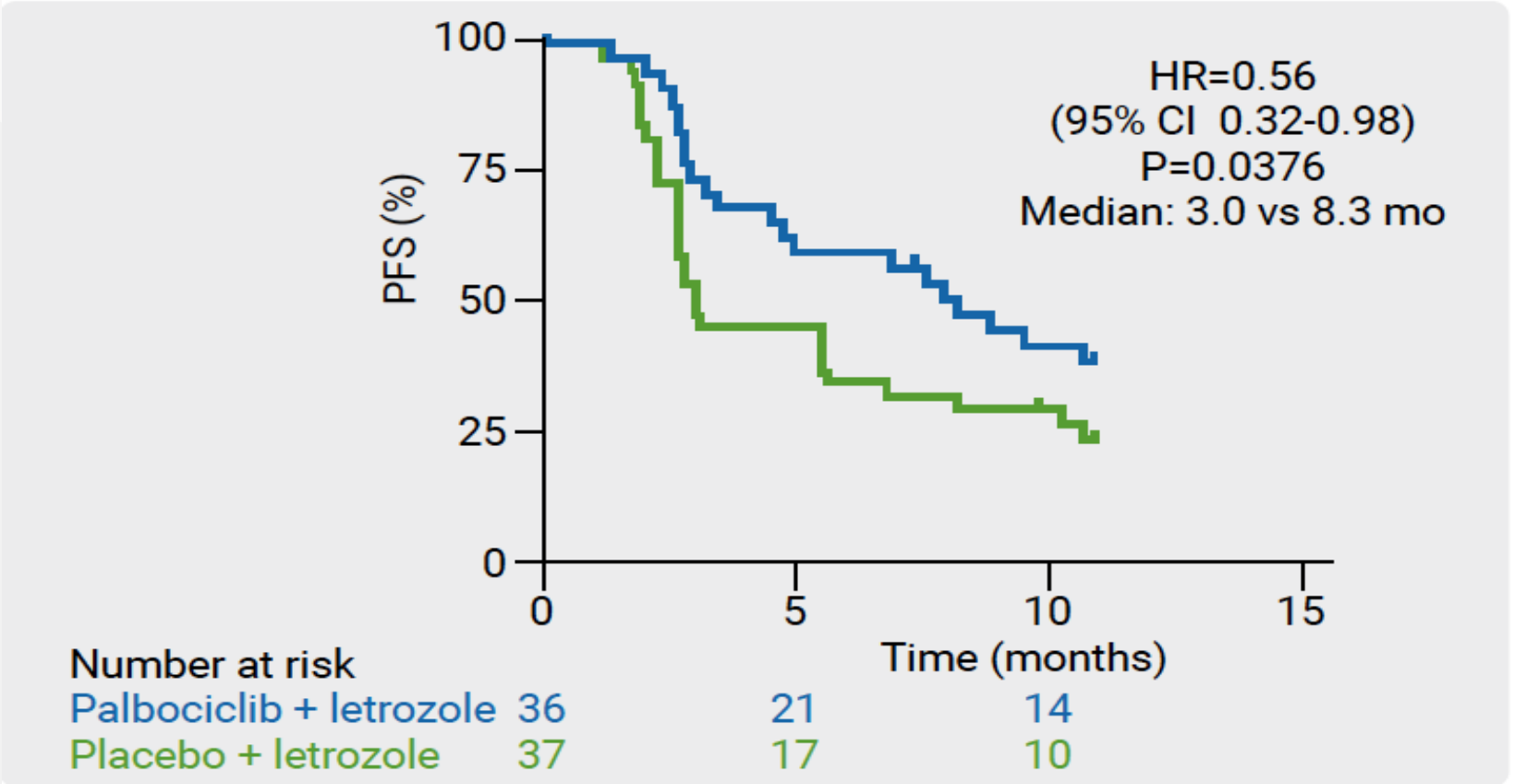




Estrogen Receptor as a Biomarker

Letrozole and Palbociclib in ER+ Endometrial cancer





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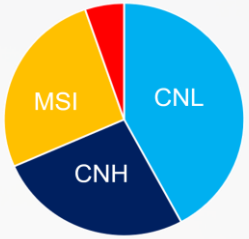
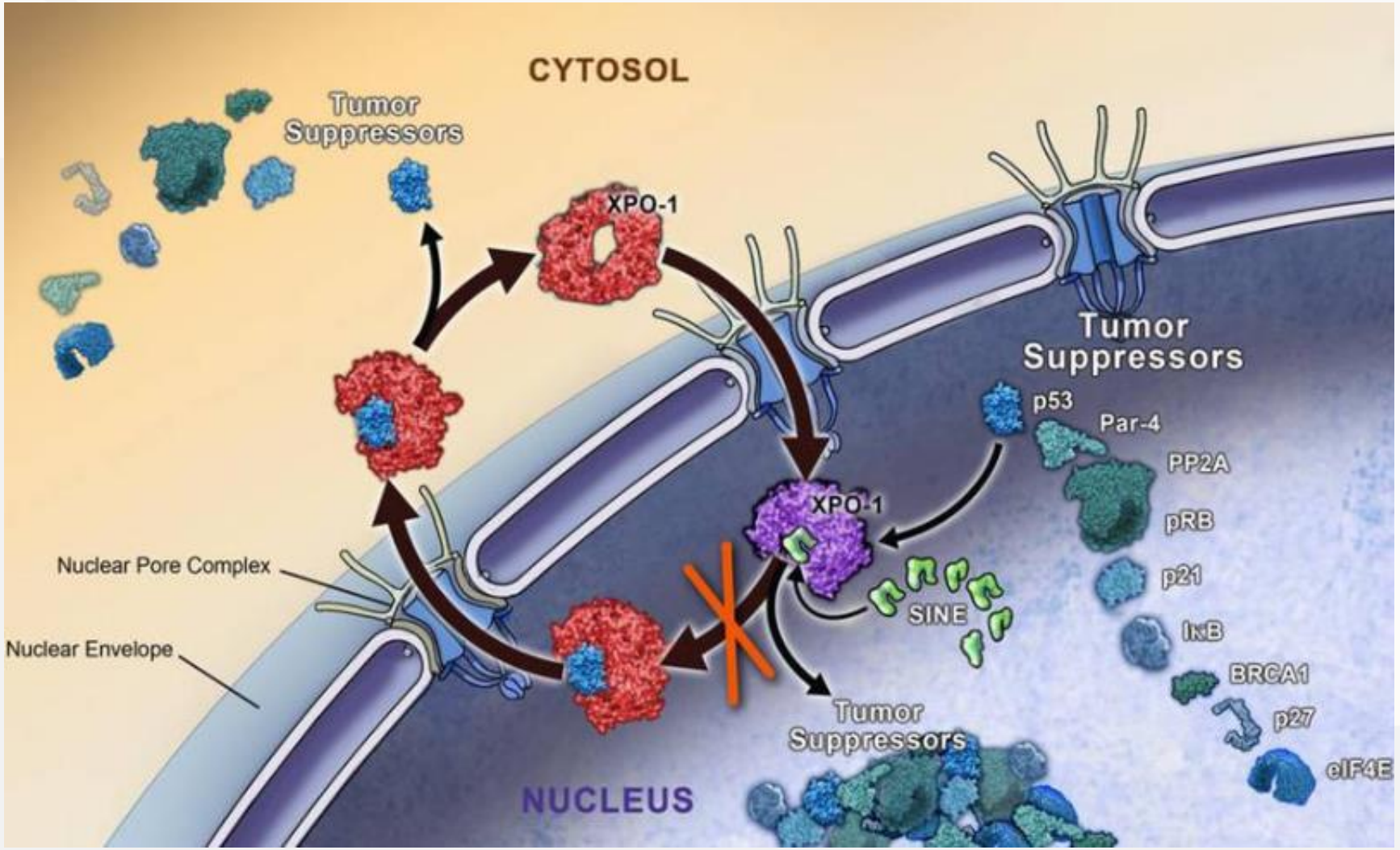
Mirza M et al. ESMO 2020 LBA28

p53 as a Biomarker

*Slenexor in **p53 wild-type** Endometrial Cancer*





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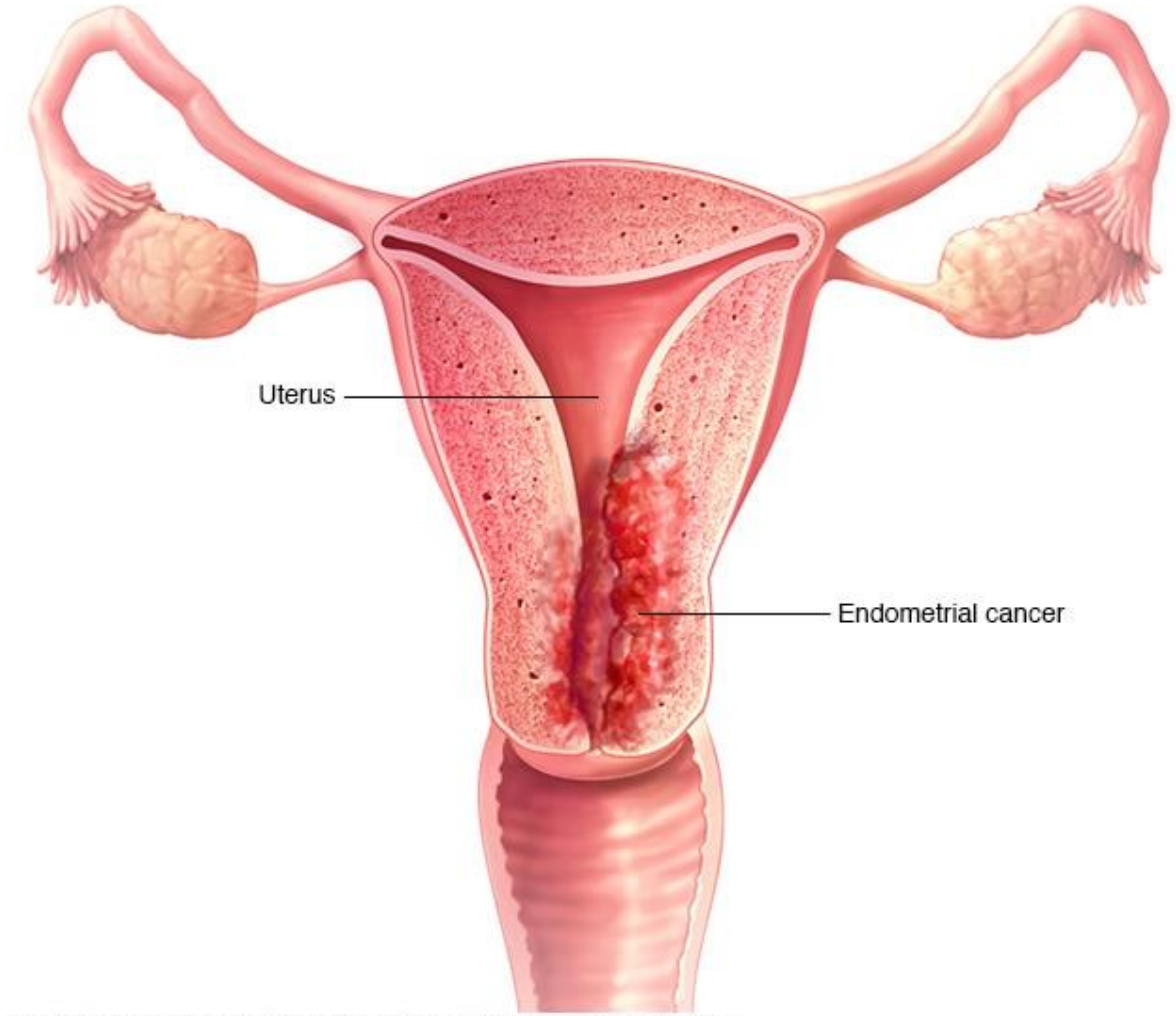
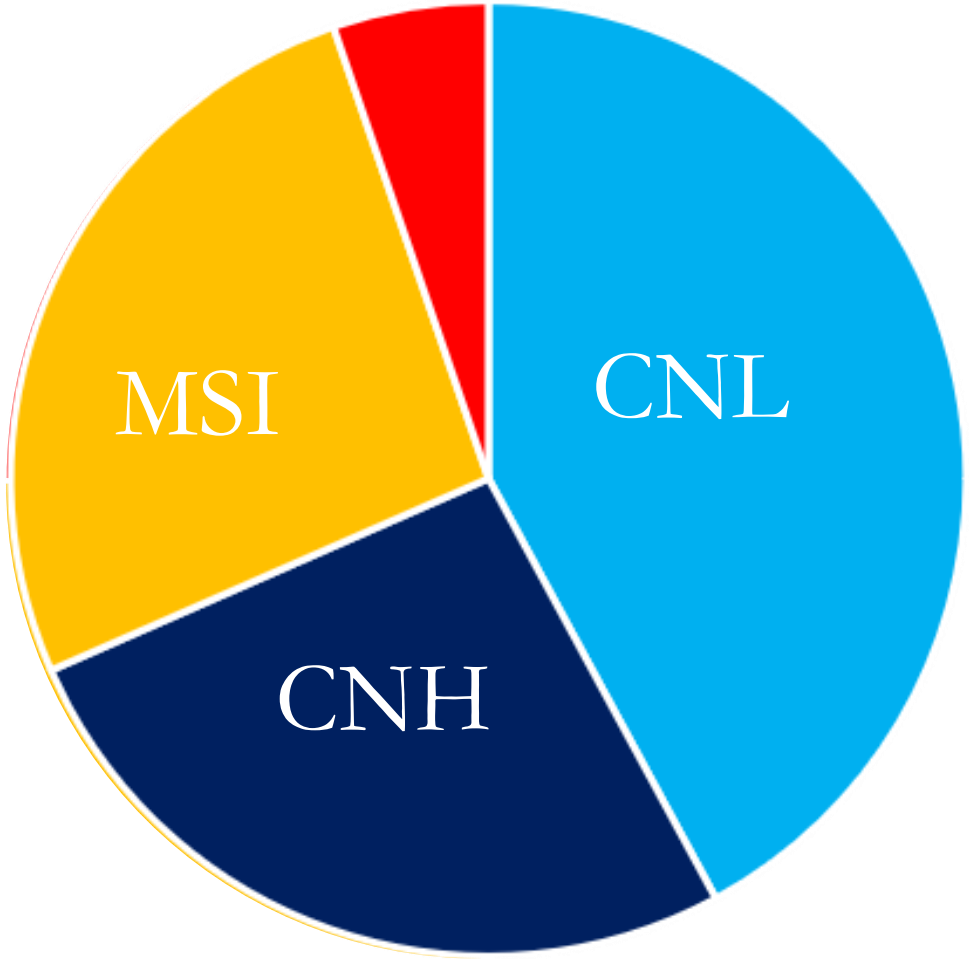
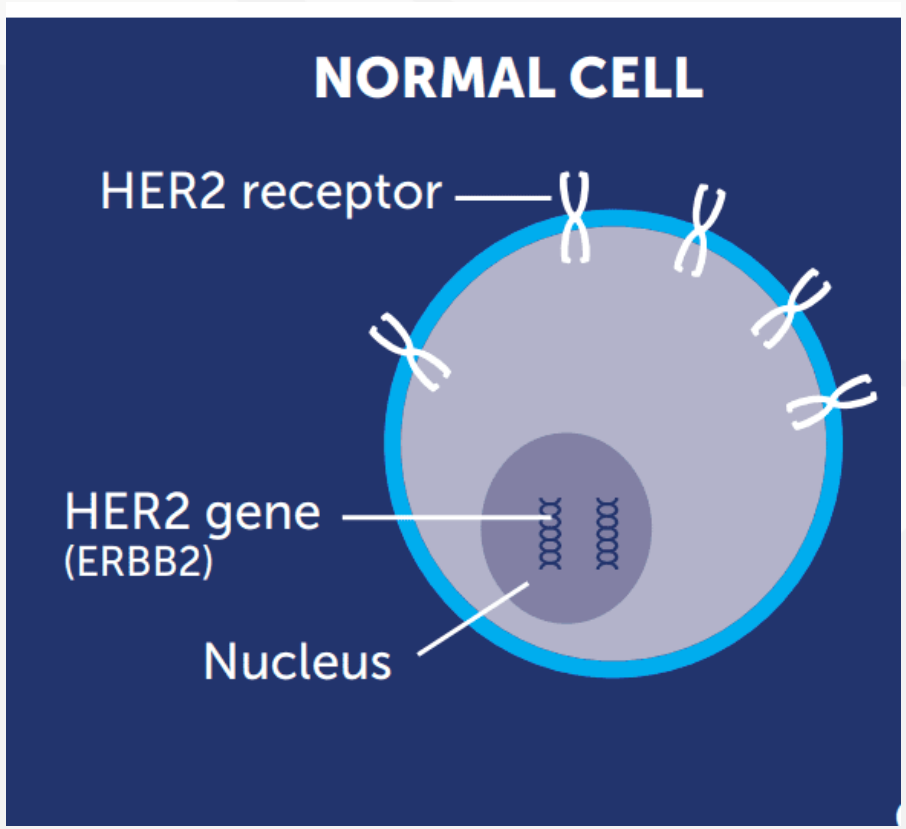
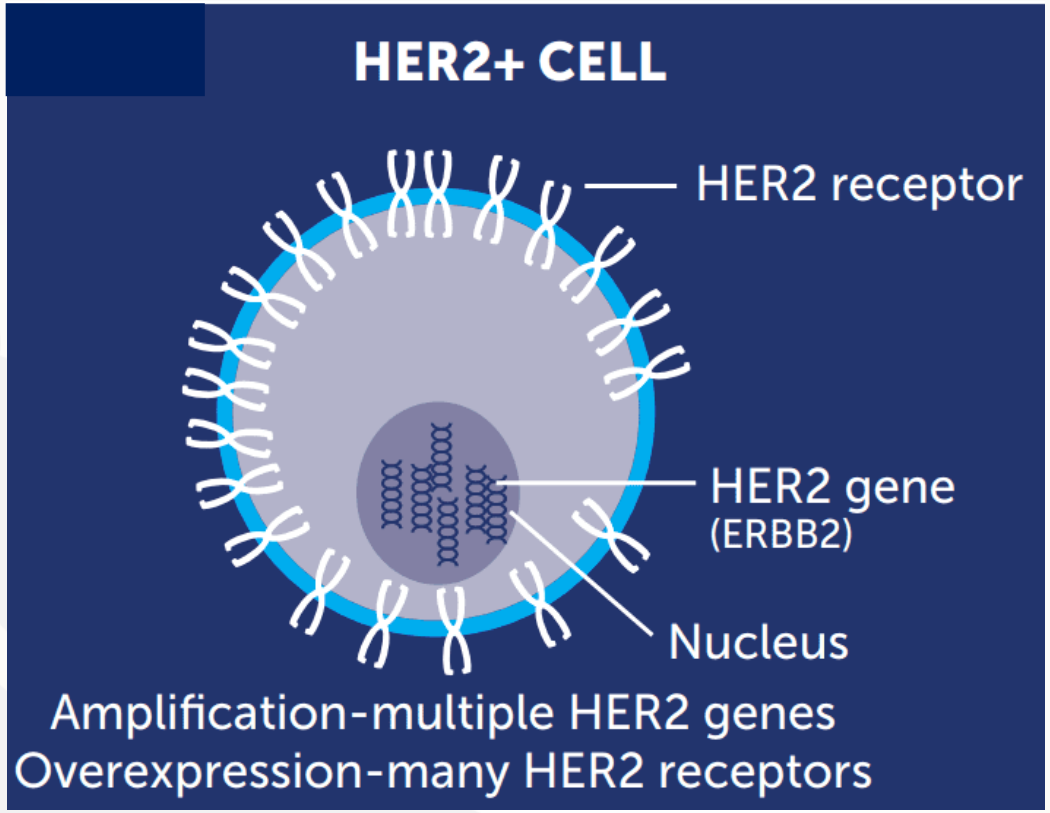
4 Molecular Subtypes





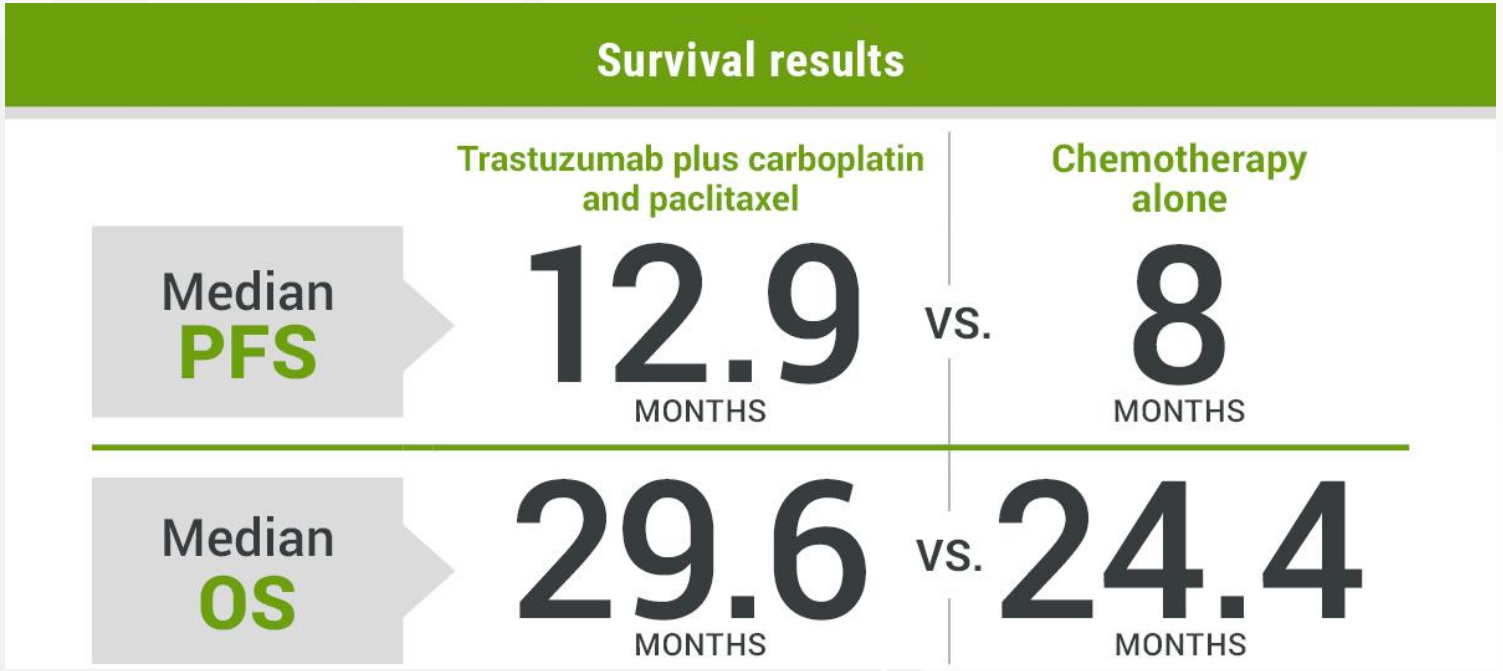
HER2 as a Biomarker
in Endometrial or Ovarian Cancer





HER2 as a Biomarker

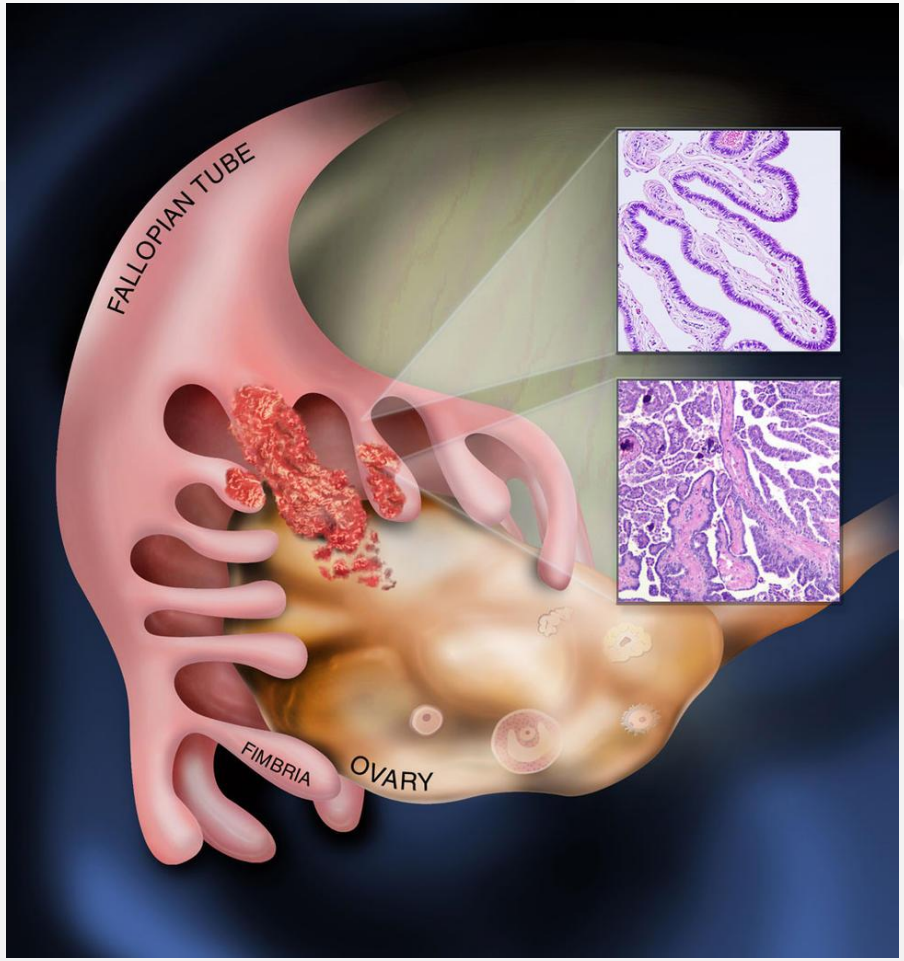
Trastuzumab + *Chemotherapy in* ***HER2 +*** *Endometrial Cancer*

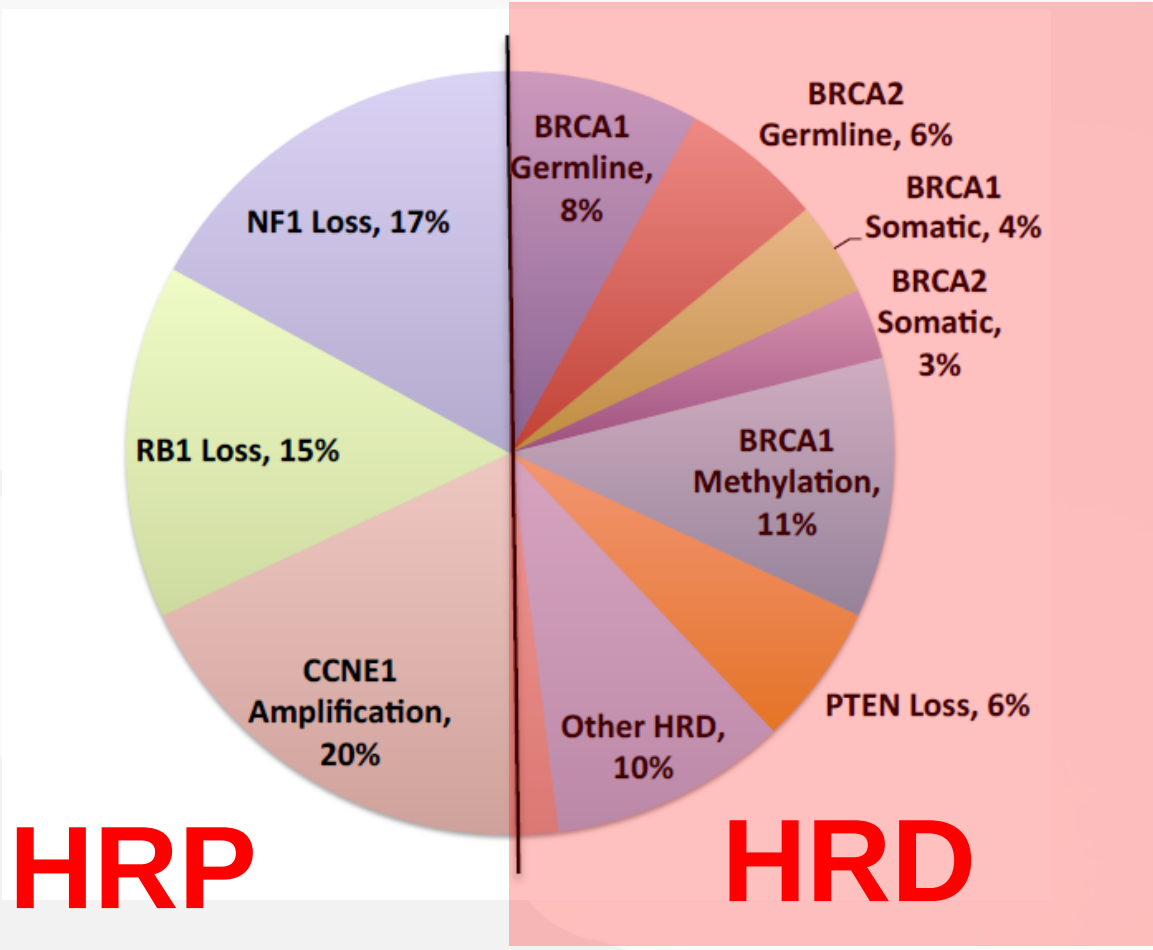


Santin et al, *Journal of Clinical Oncology*

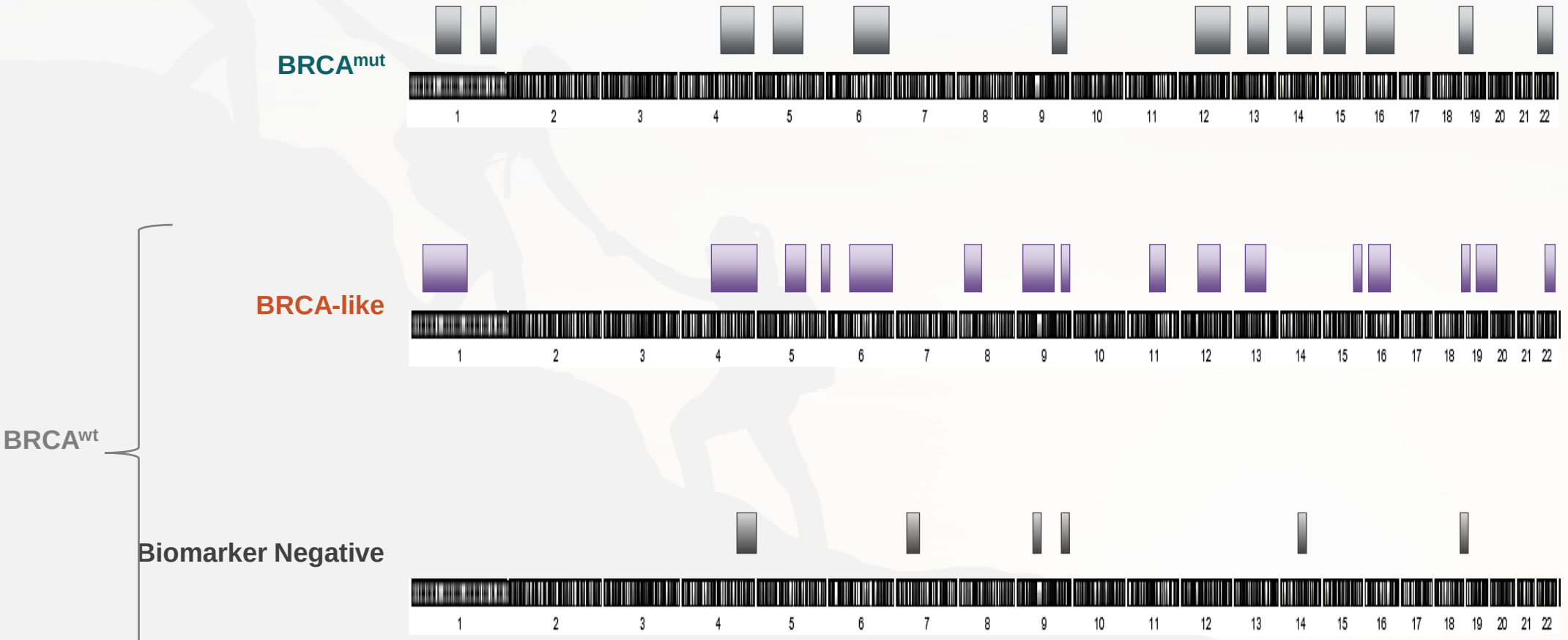
Biomarkers in Ovarian Cancer

Homologous Recombination (HR) Deficiency



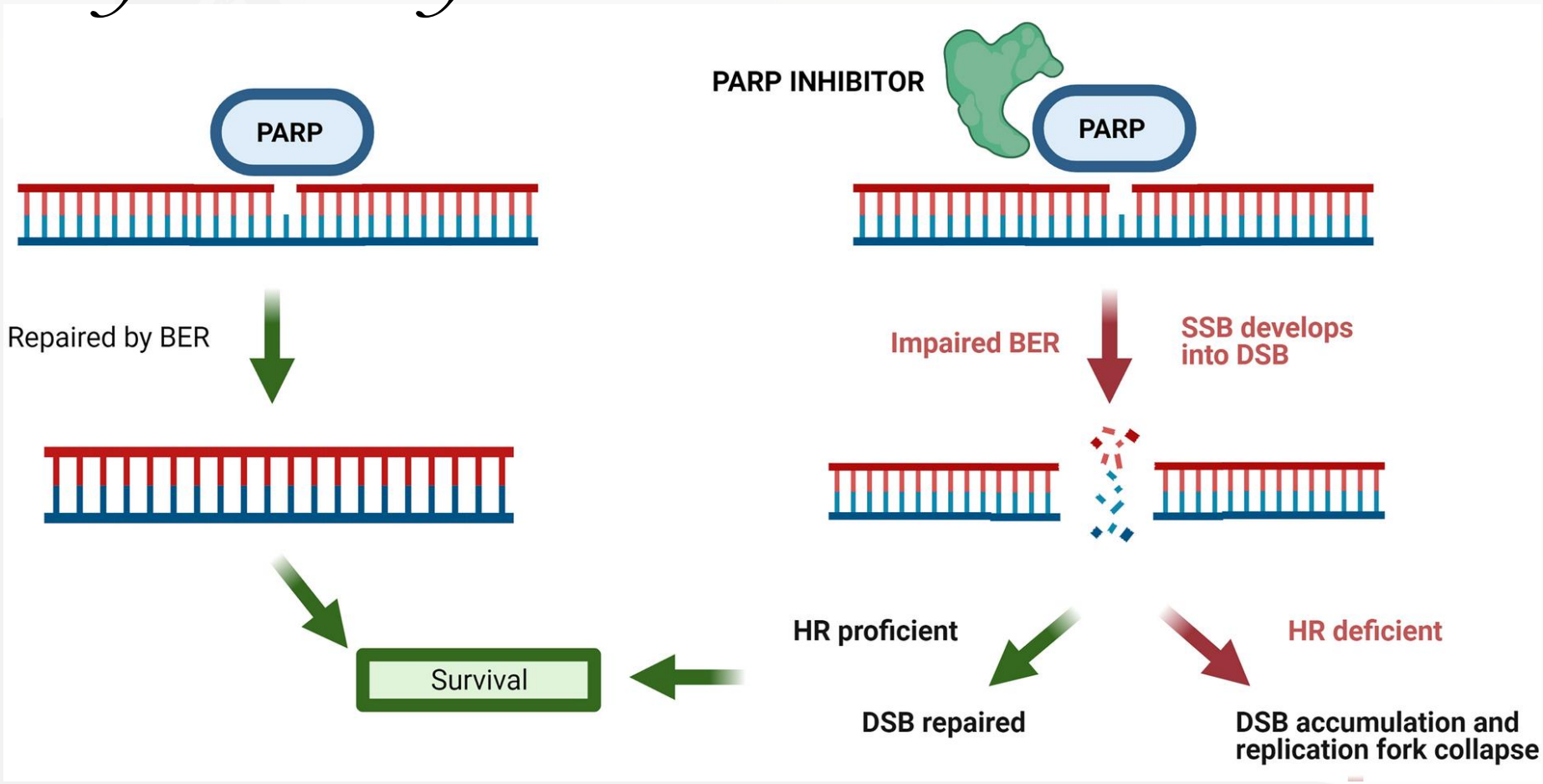


Homologous Recombination (HR) Deficiency

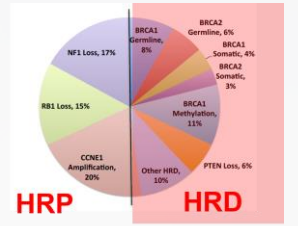


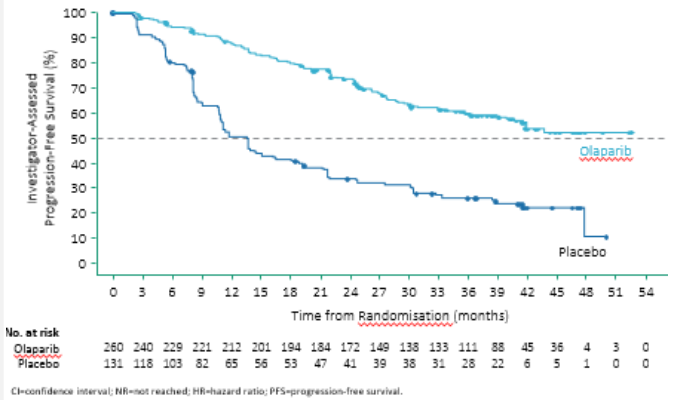
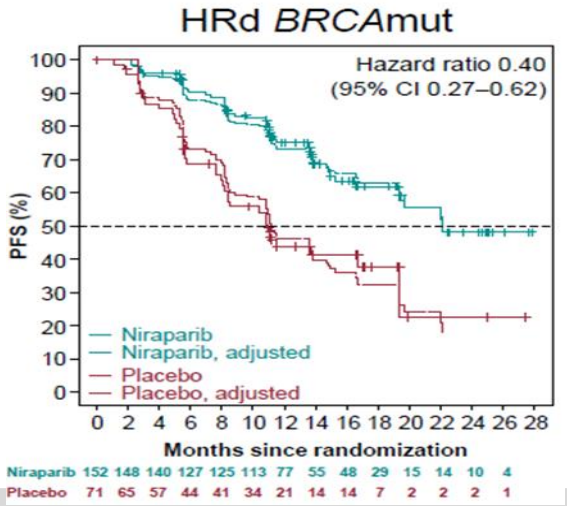
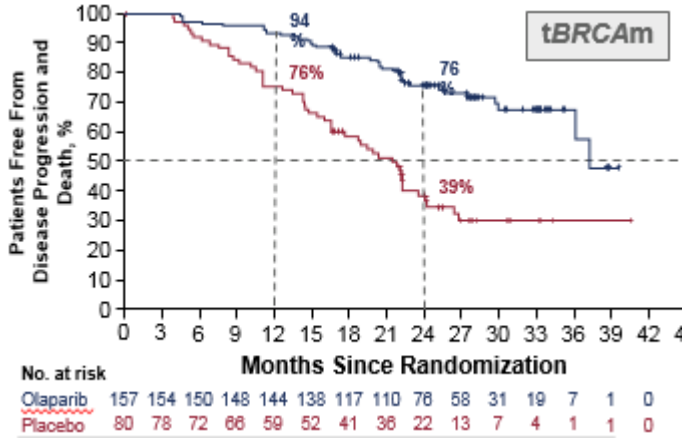
BRCA Mutations and HRD as a Biomarkers

PARPi synthetically lethal



Significant progress for *BRCA* associated cancers



SOLO1 - g*BRCA*m	PRIMA	PAOLA-1	
			
NR mo vs 13 mo HR 0.30 (95% CI: 0.23, 0.41)		**37.2 vs 17.7 mo HR 0.33 (95% CI 0.25-0.45)**	**INV REVIEW**
NR vs. 14.1 mo HR 0.28 (95% CI 0.2-0.39)	**HR 0.40 (95% CI .27-0.62)**		**BICR REVIEW**

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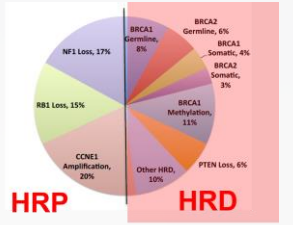
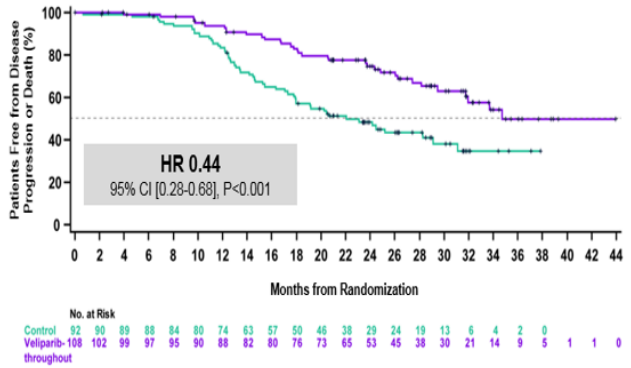
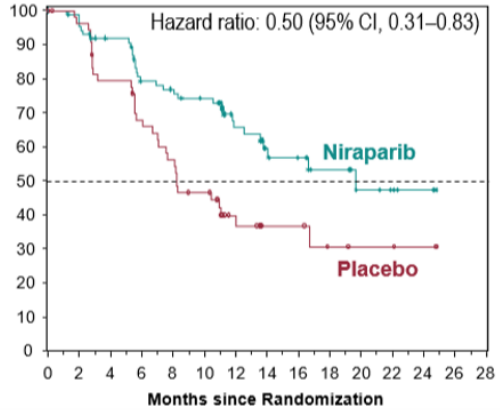
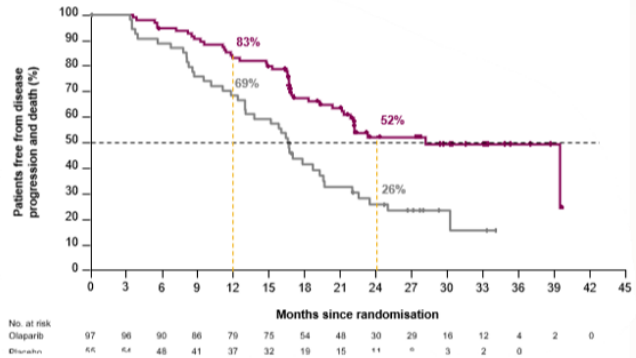
1. Coleman R, et al. *N Engl J Med.* 2019: 381 (25): 2403-2415. 2. Gonzalez Martin A, et al. *N Engl J Med.* 2019: 381(25):2391-2402. 3. Ray-Coquard I, et al. *N Engl J Med.* 2019:381(25):2416-2428.

And for those women with HRD +/*BRCA*wt tumors - not perfect but good



VELIA	PRIMA	PAOLA-1	
			
34.7 vs 22 months HR 0.44 (95% CI: 0.28-0.68)		28 vs 16.6 months HR 0.43 (95% CI 0.28- 0.66)	INV REVIEW
	HR 0.50 (95% CI 0.31-0.83)		BICR REVIEW

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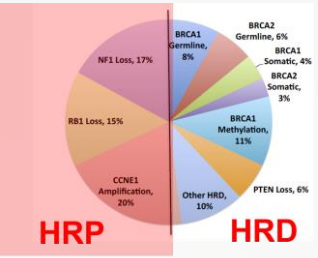
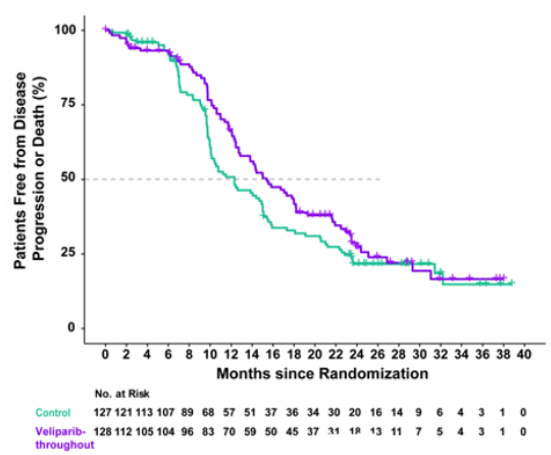
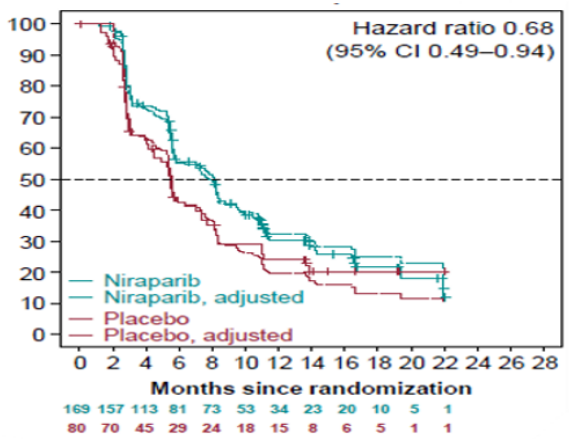
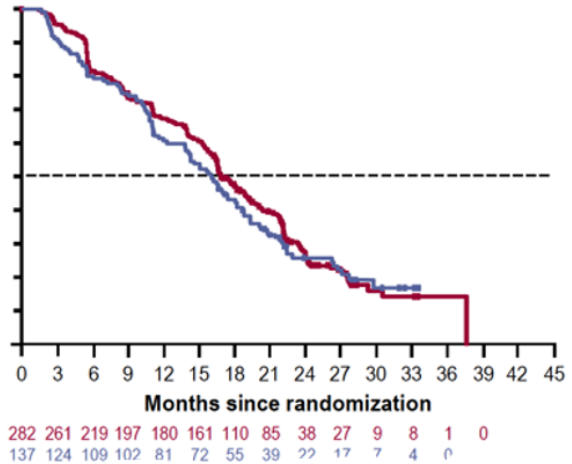
HRP tumors are the big focus now



VELIA[1]	PRIMA[2]	PAOLA-1[3]	
			
15.4 vs. 12.3 months HR 0.76 (95% CI 0.55-1.03)		16.9 vs. 16.0 months HR 0.92 (95% CI :0.72-1.17)	INV REVIEW
	HR 0.68 (95% CI 0.49-0.94)		BICR REVIEW

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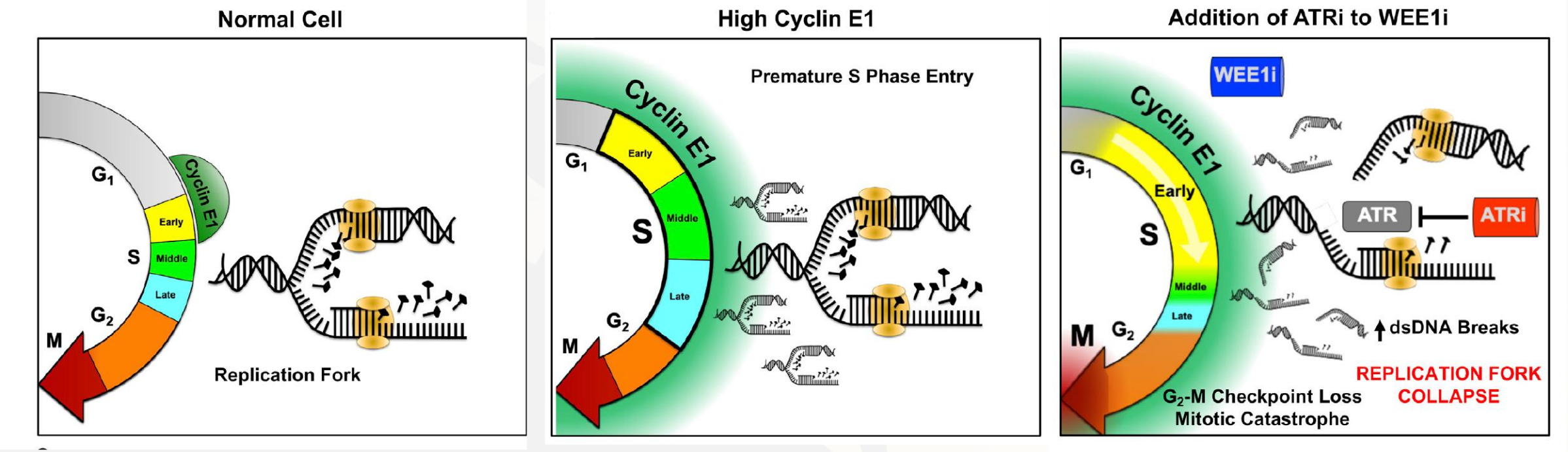
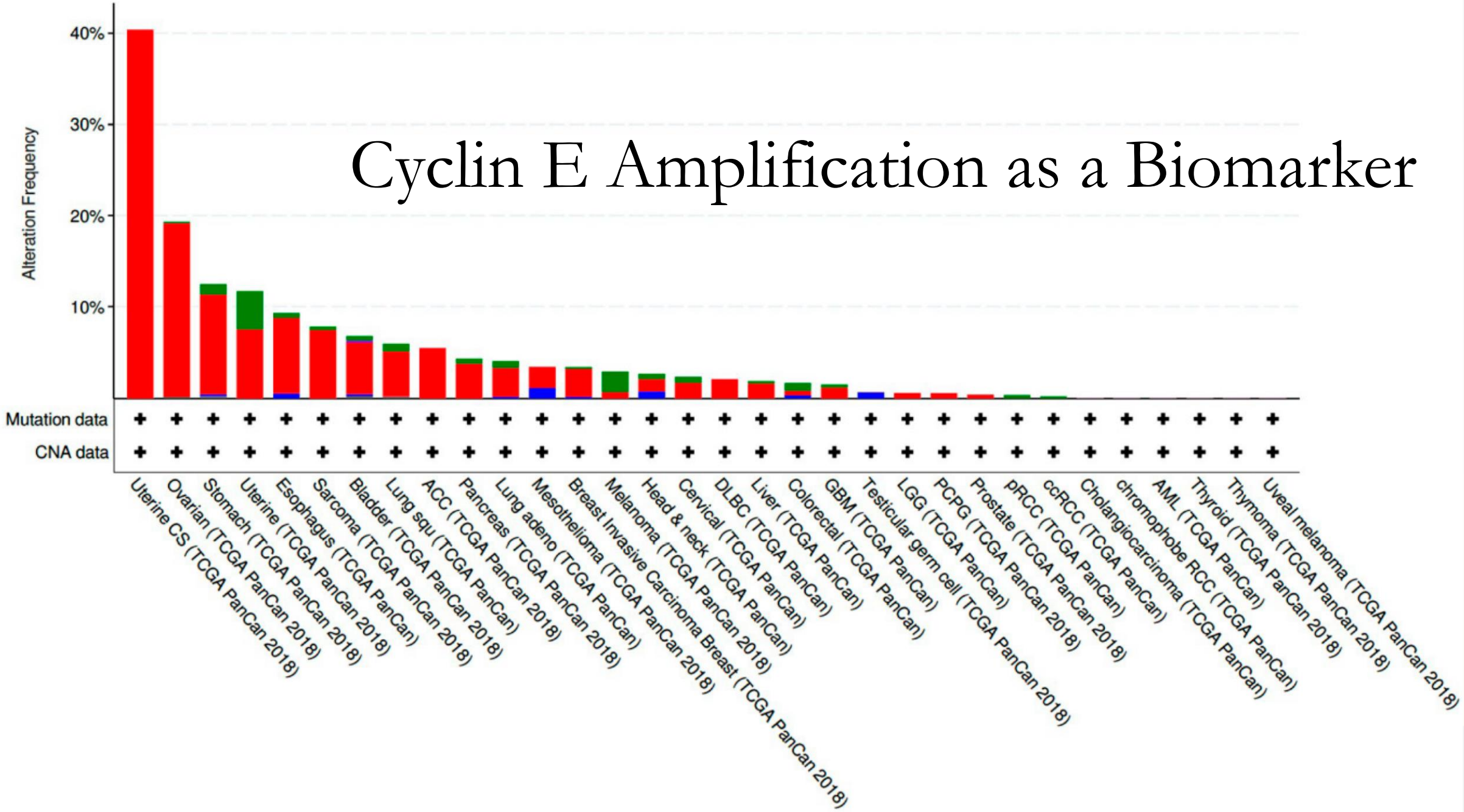
Cyclin E Amplification as a Biomarker

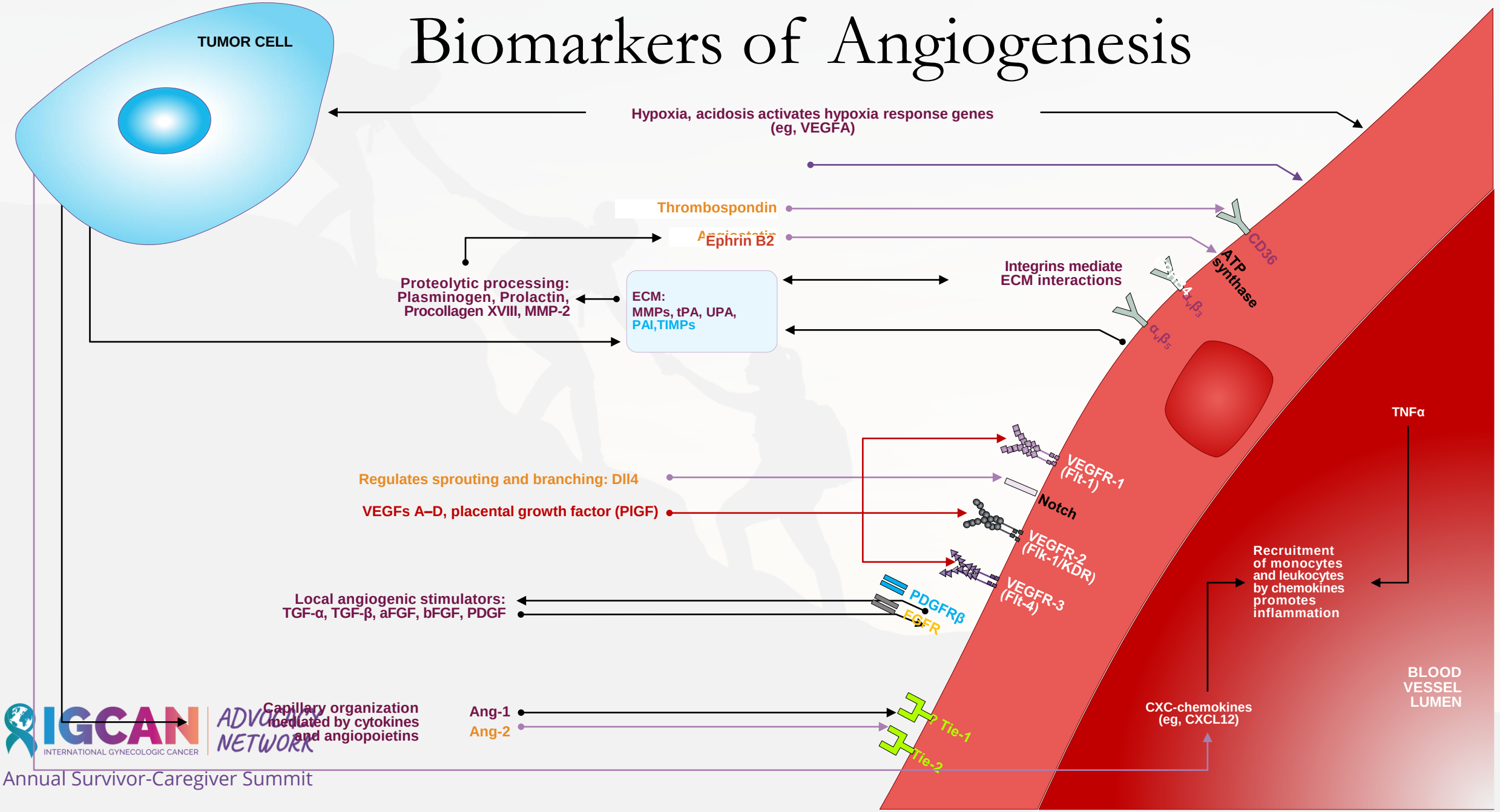


New Targets: WEE1, ATR, PKMYTH

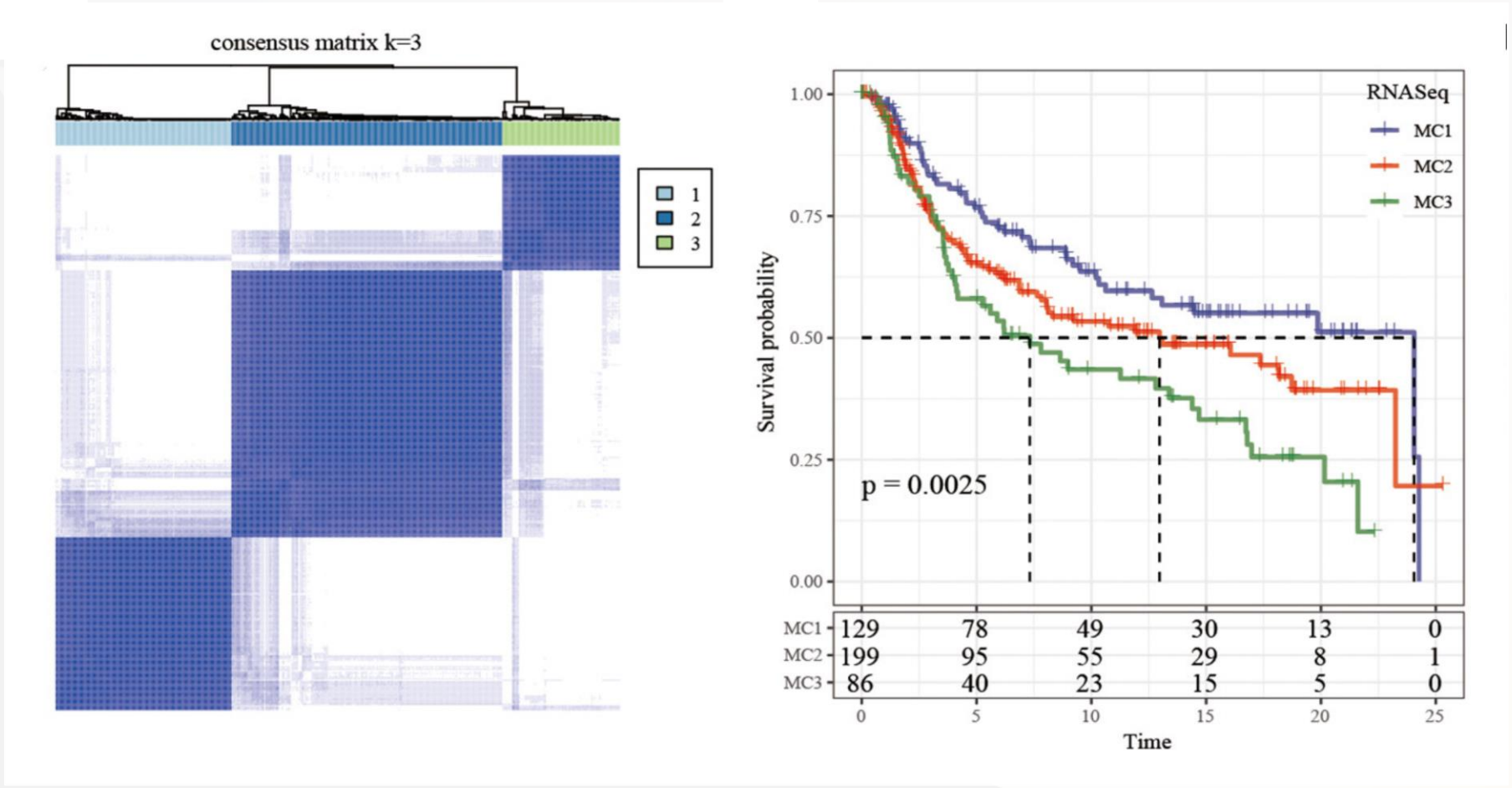
Cyclin E Amplification as a Biomarker



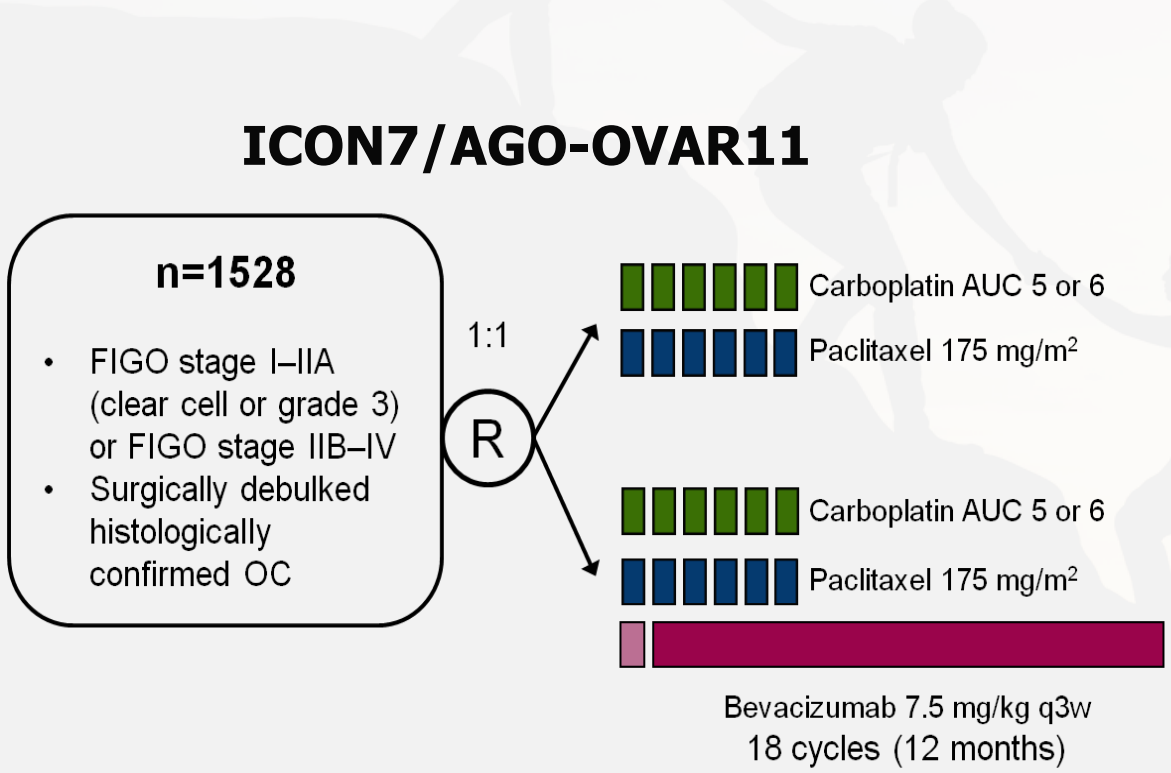
Biomarkers of Angiogenesis

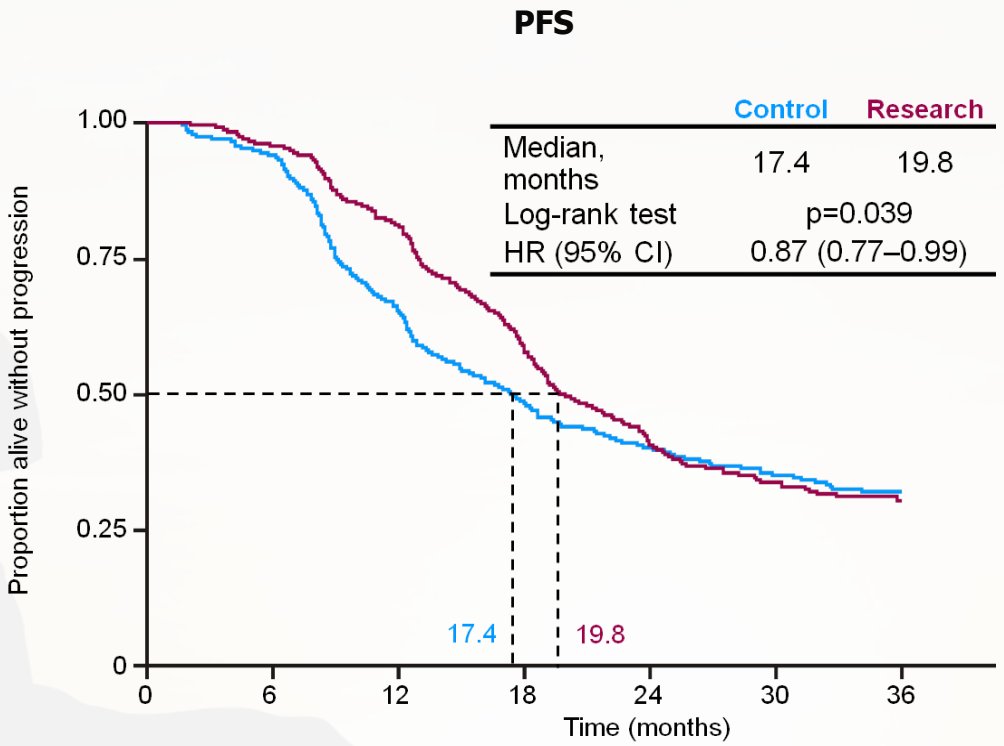


Gene Expression Profiles as a Biomarkers



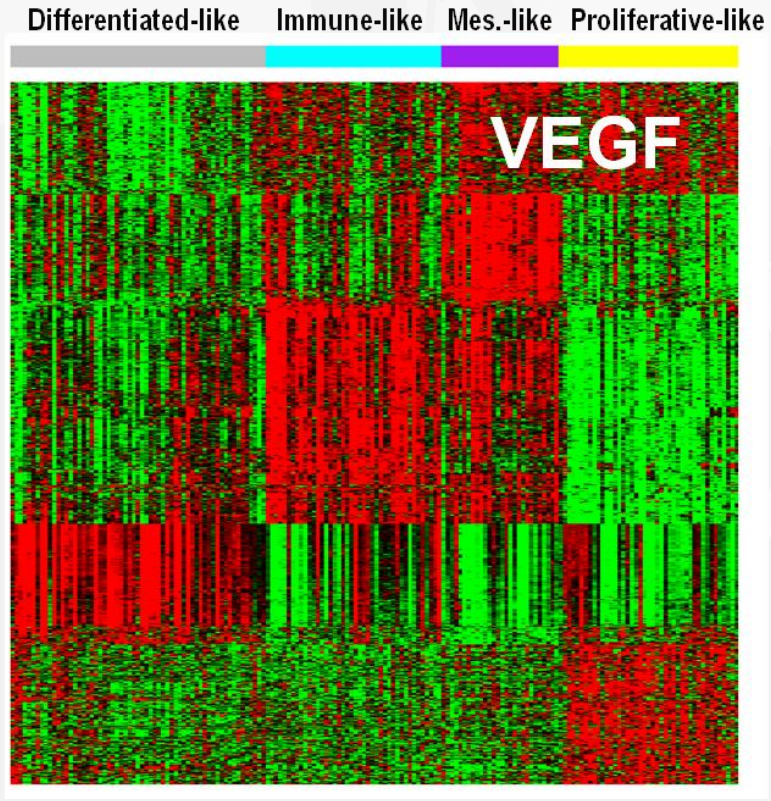
Gene Signatures and Bevacizumab Response





Perren TJ, et al. *N Engl J Med*. 2011 Dec 29;365(26):2484-96

Gene Signatures and Bevacizumab Response

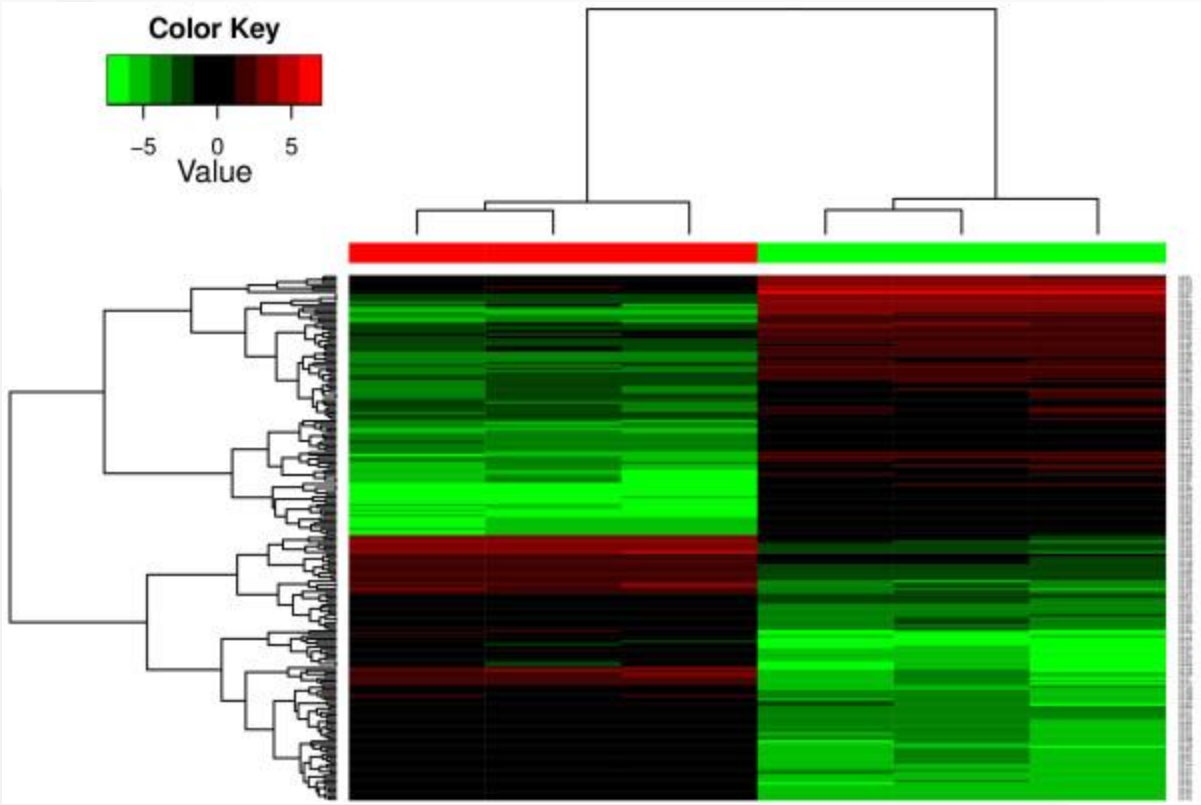


Group	Median Δ PFS in Months
All	6.5, p=0.004
Immunoreactive	**3.8,** p=0.080
Differentiated	**3.7,** p=0.610
Proliferative	**10.1,** p=0.015
Mesenchymal	**8.2,** p=0.405

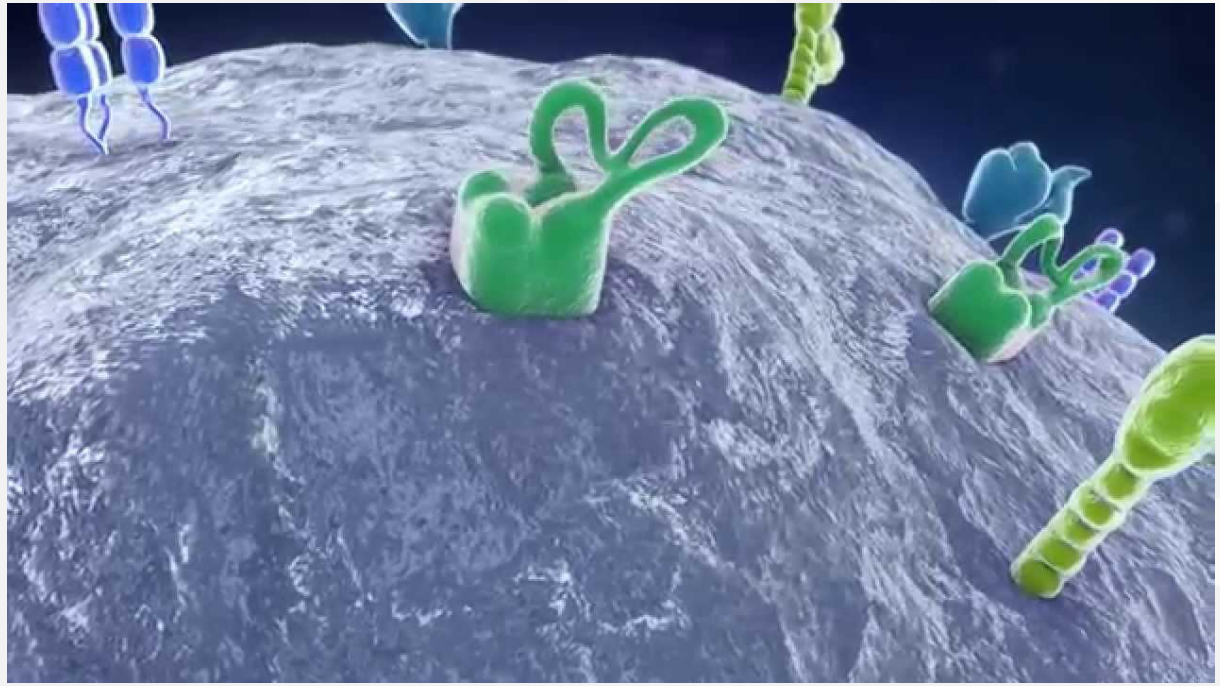
Winterhoff B, Kommoss S, Konecny GE. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5509)

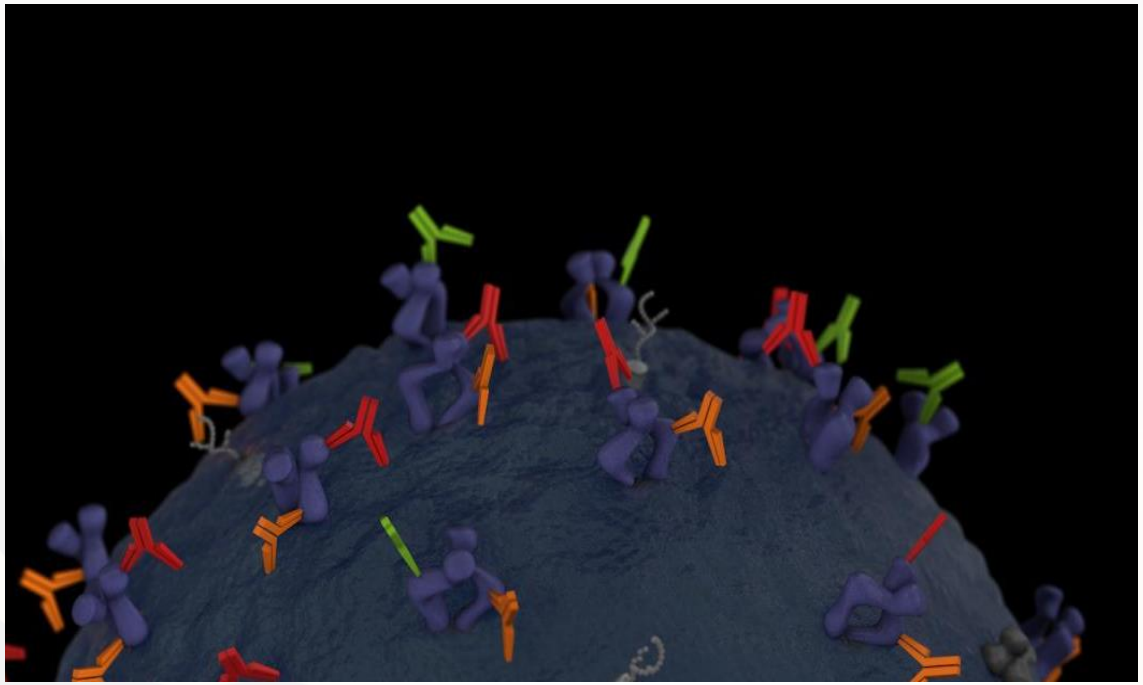
Cell Surface Markers as Biomarkers

Tumor Specific Biomarker

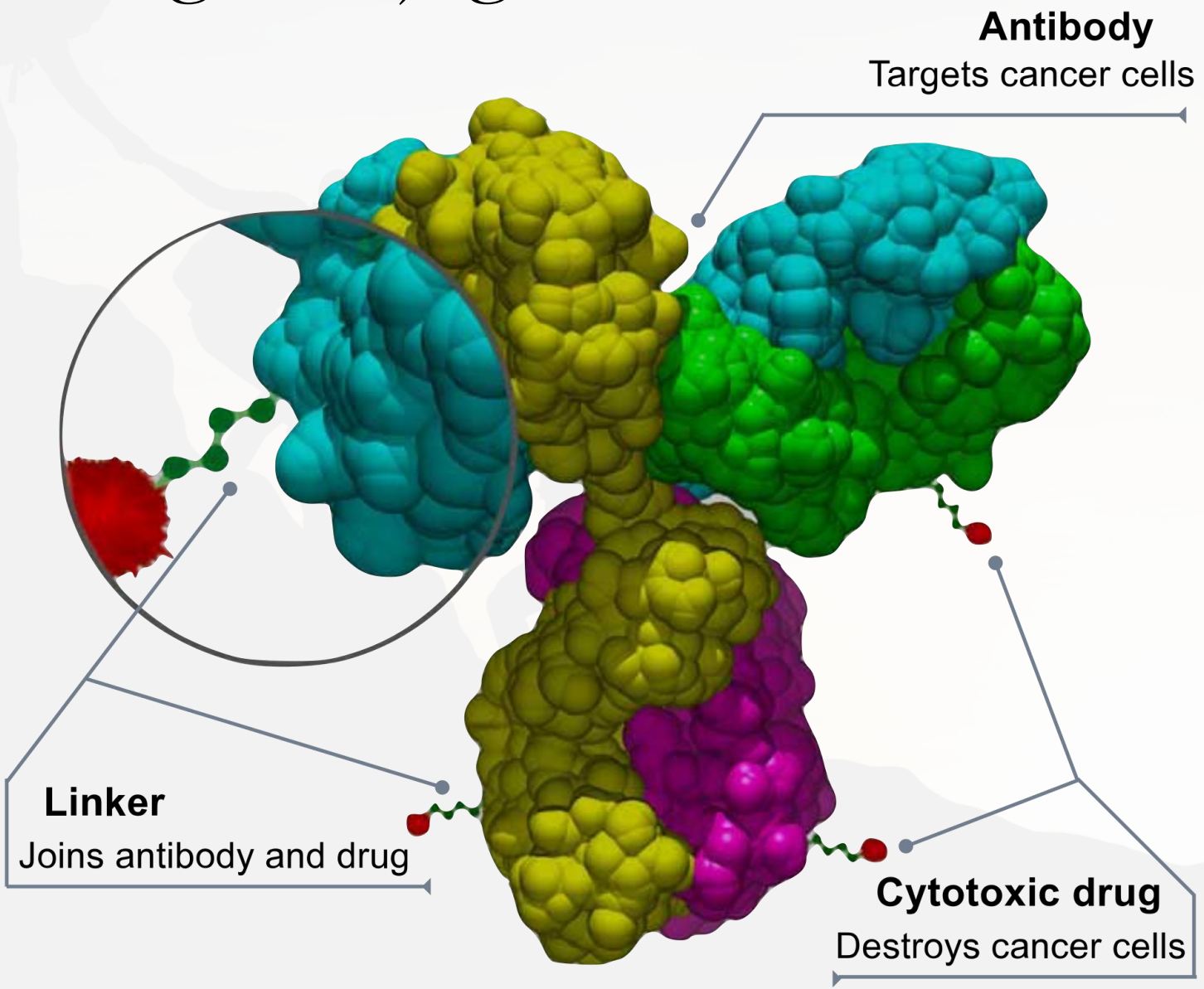


Identify Proteins on the Cell Surface which can be targeted with Monoclonal Anitbodies





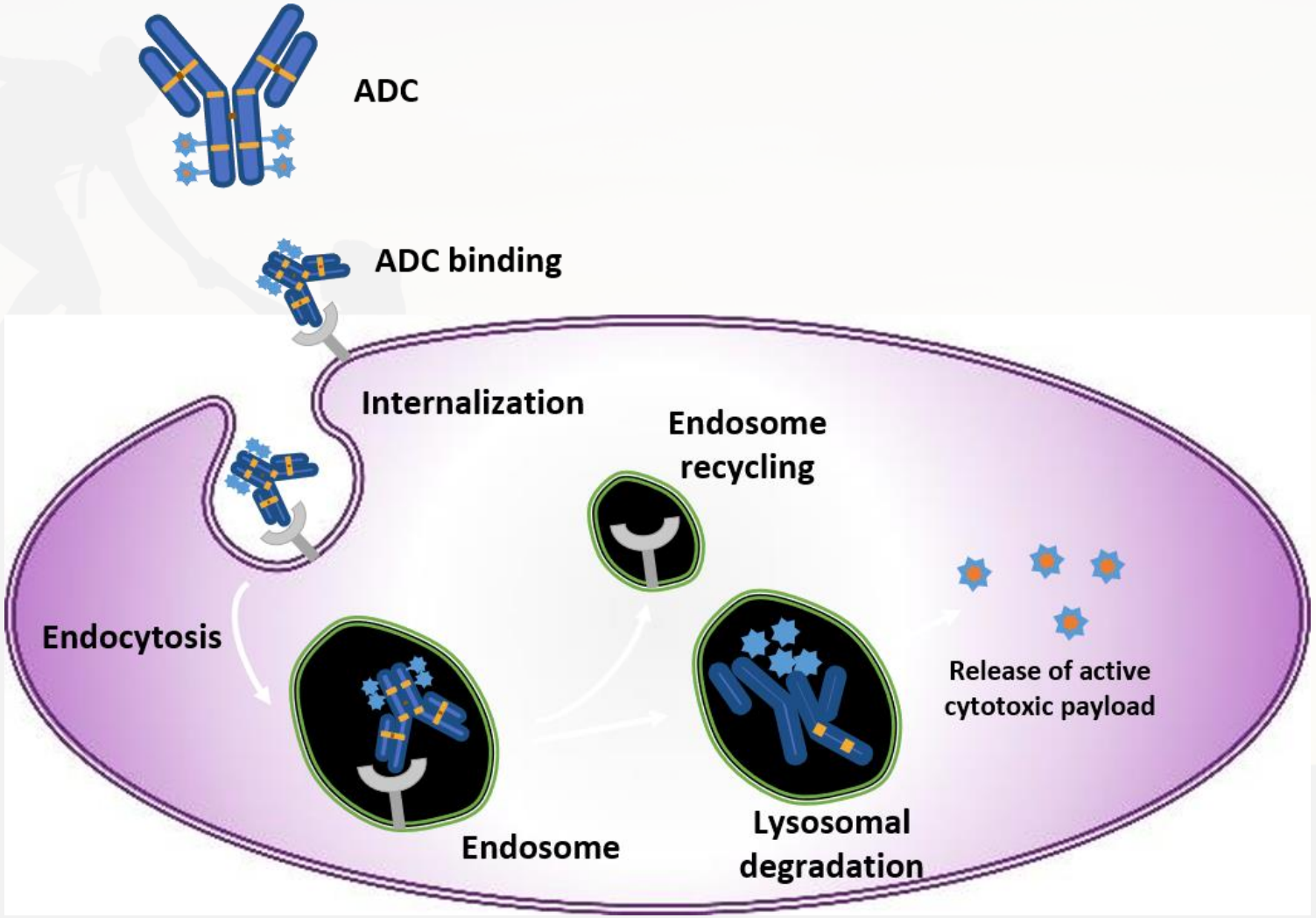
Antibody Drug Conjugates



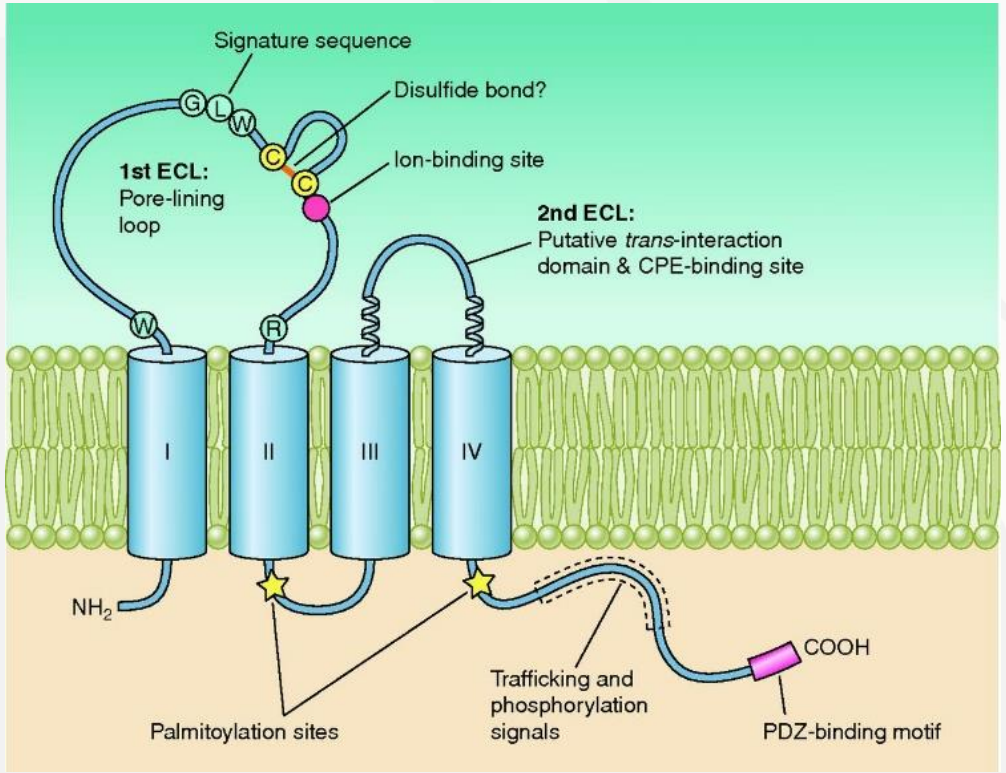
FOLR1 as a Biomarker in Ovarian Cancer

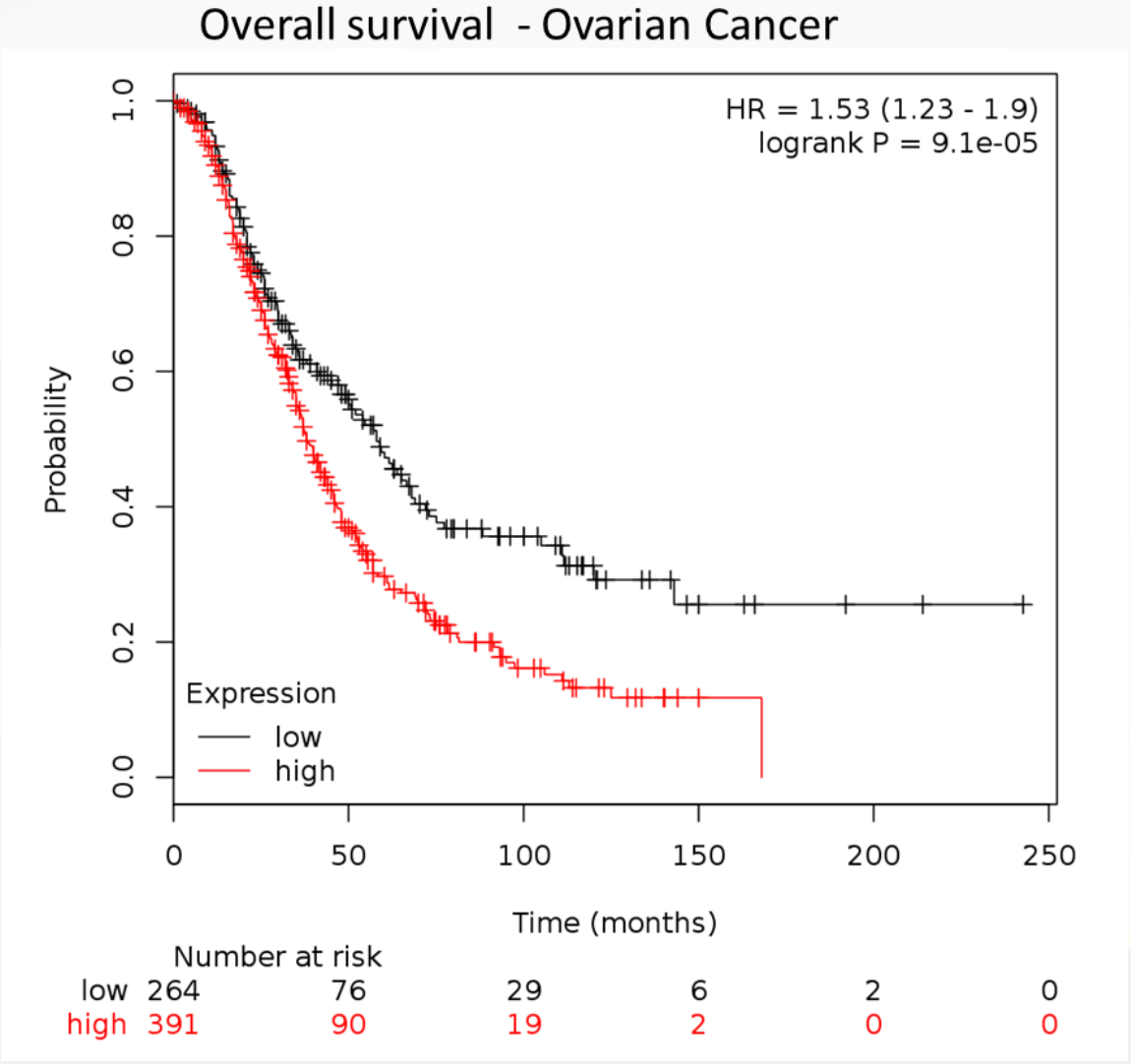
Based on their overall efficacy and adverse event profile → paradigm shift.

Mirvetuximab
Soravtansine



Novel Biomarker and ADC Target
CLAUDIN 6





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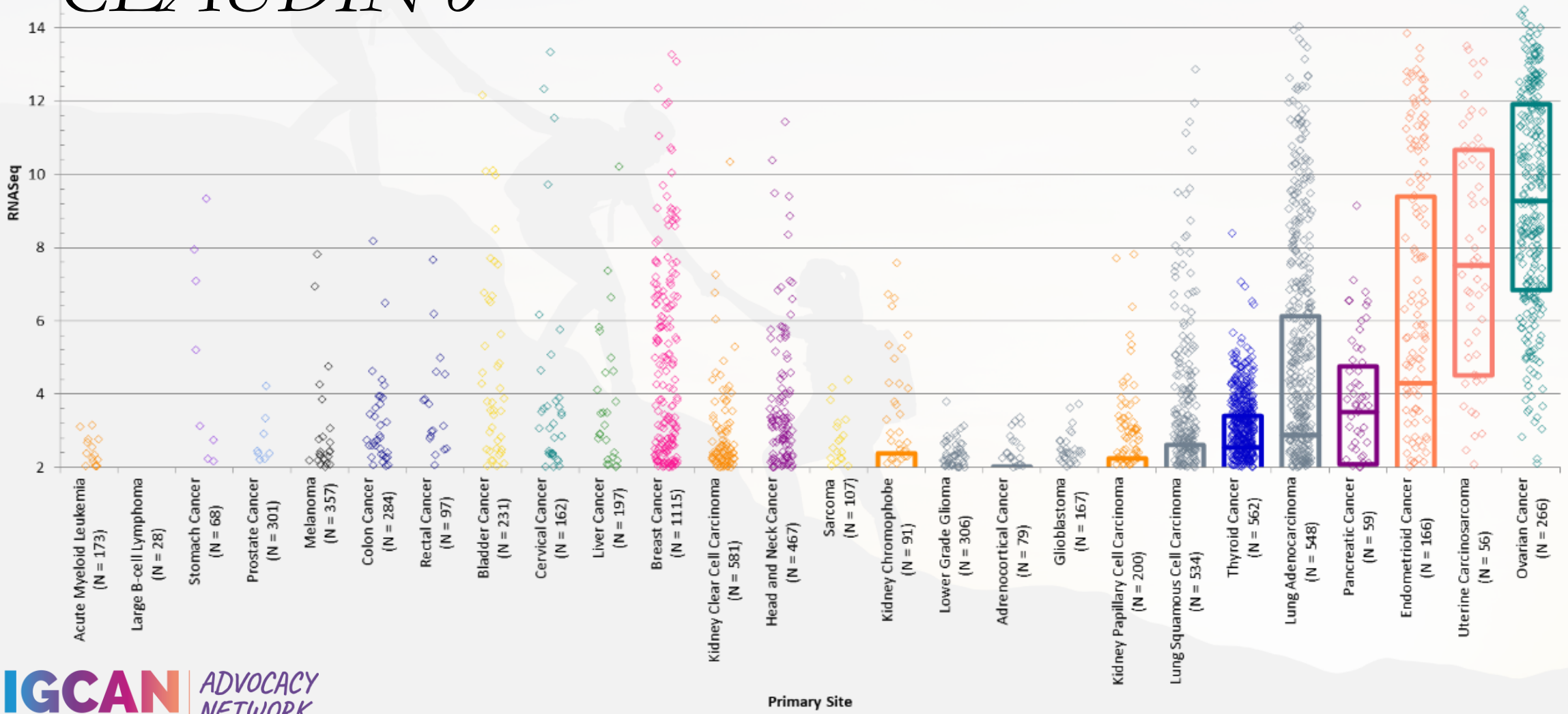
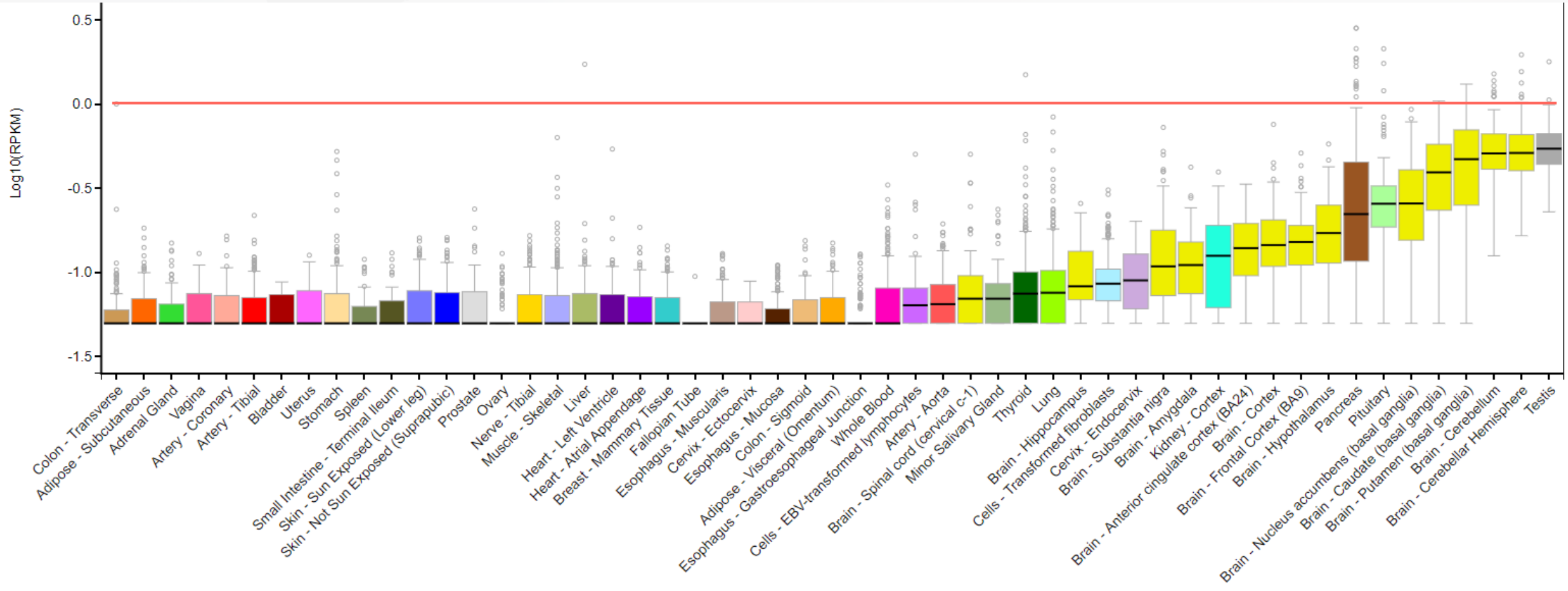
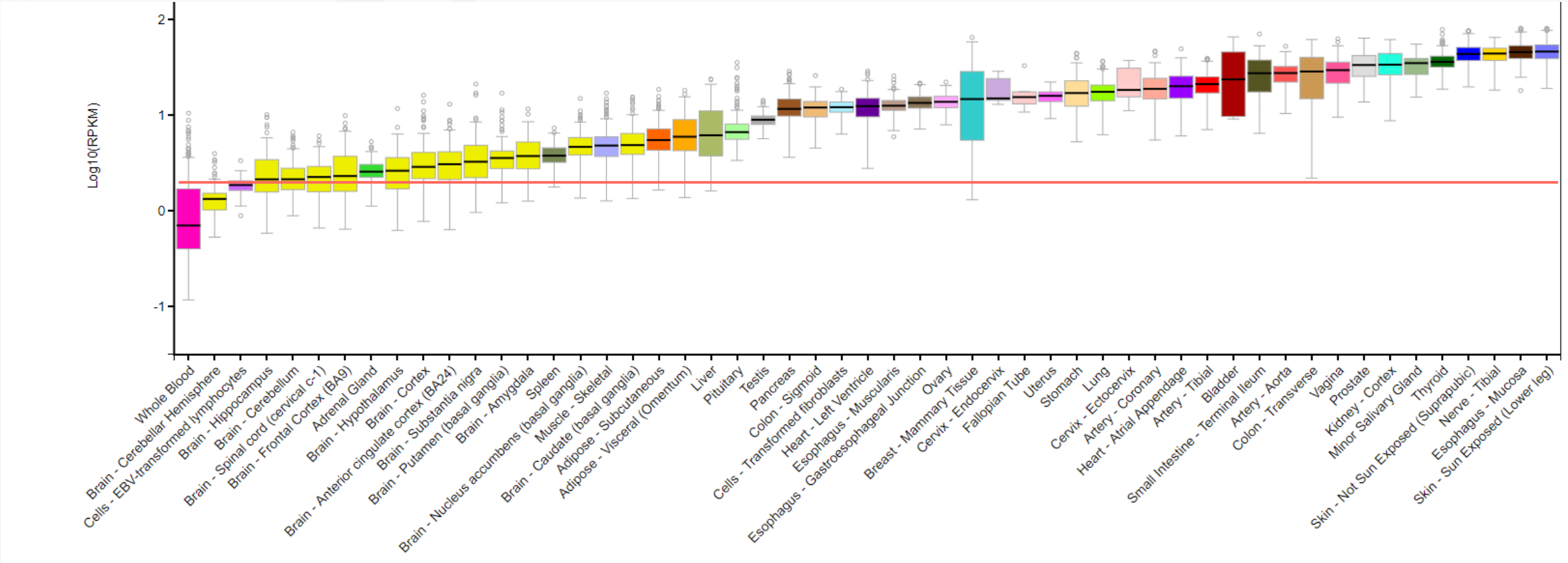
Novel Biomarker and ADC Target
CLAUDIN 6



Expression of Claudin 6 in Normal Tissues (GTEX)

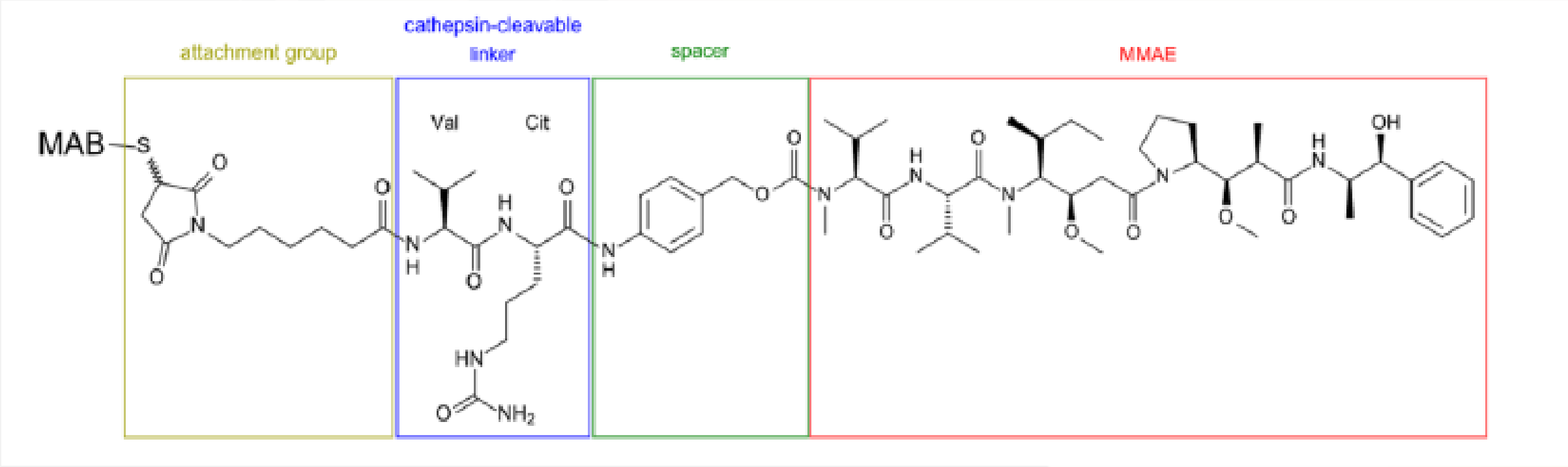


Expression of HER2 in Normal Tissues (GTEX)

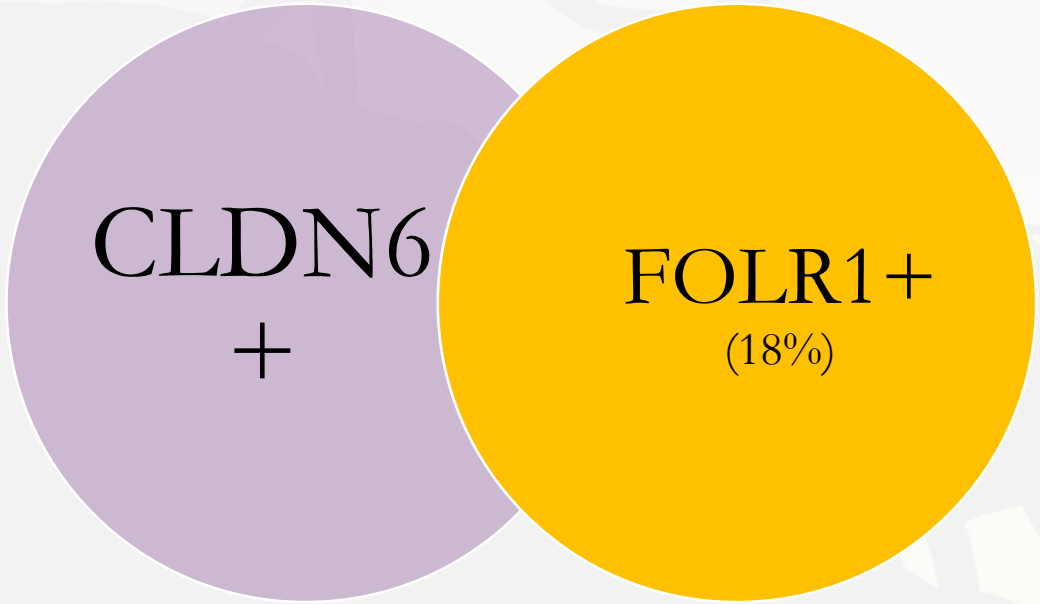


Claudin 6 a New Biomarker

- 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).

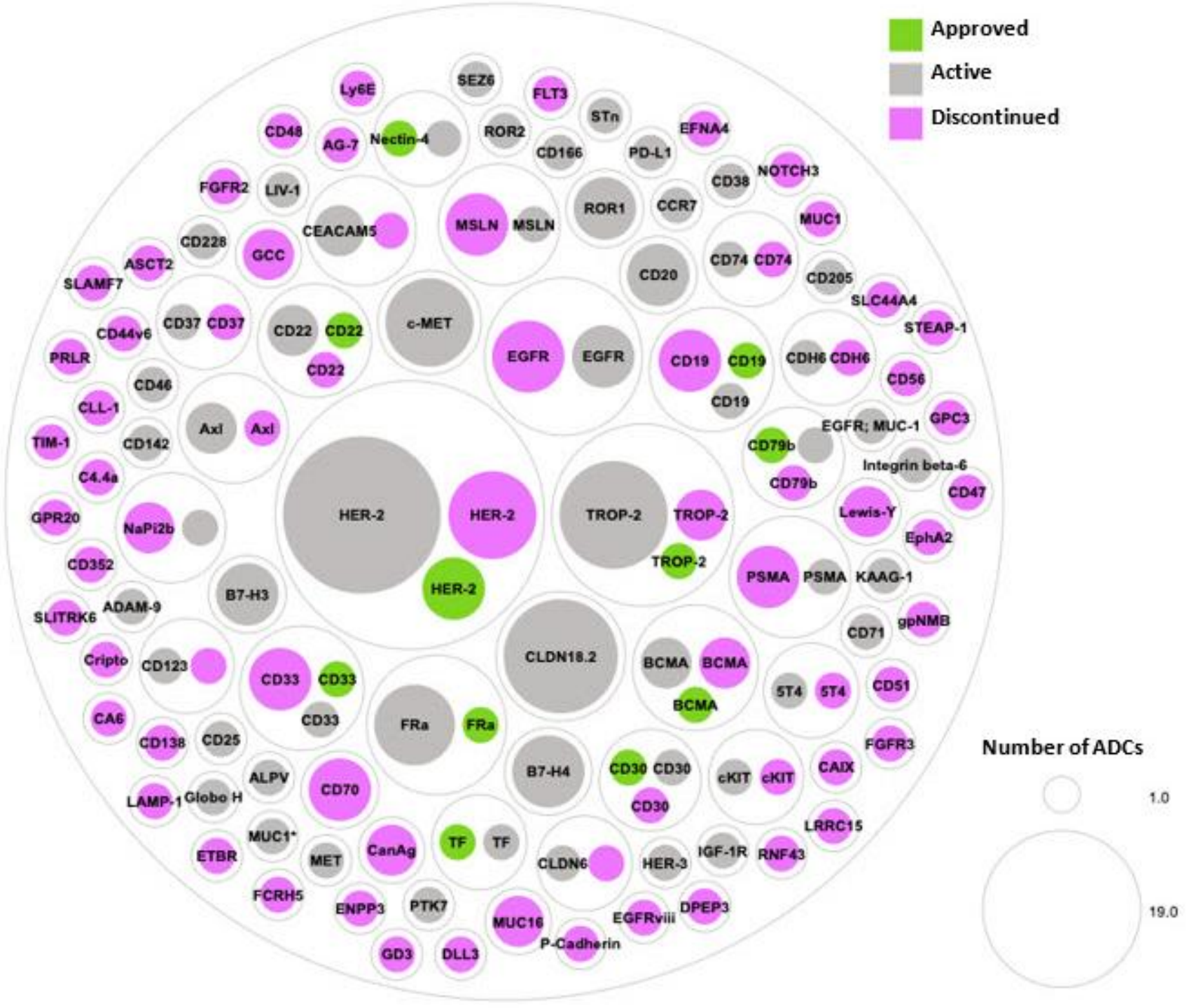


The higher the CLDN6 positivity, the lower the likelihood that patients are FOLR1 positive



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

ADC Landscape 2023



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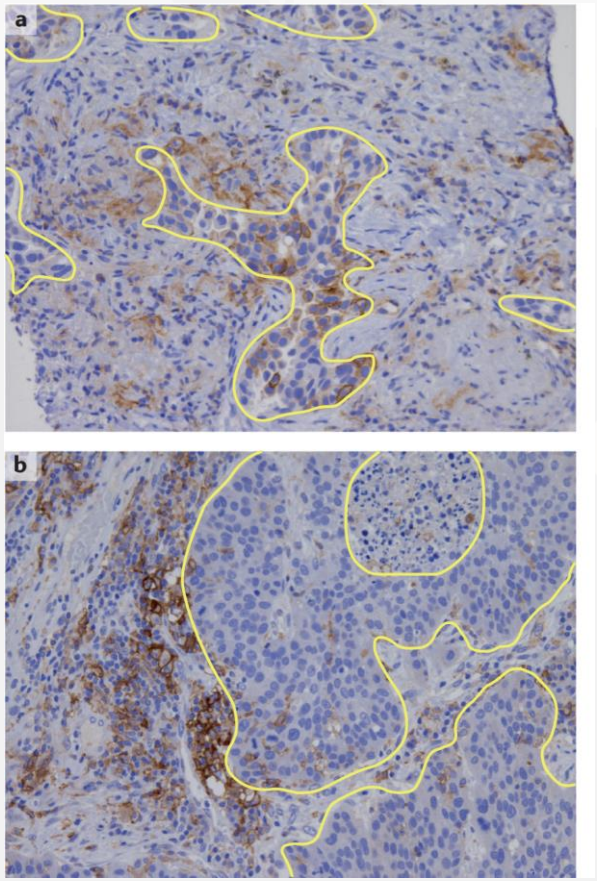
Immunotherapy Biomarkers

PD-L1 is a Weak Biomarker for Immunotherapy



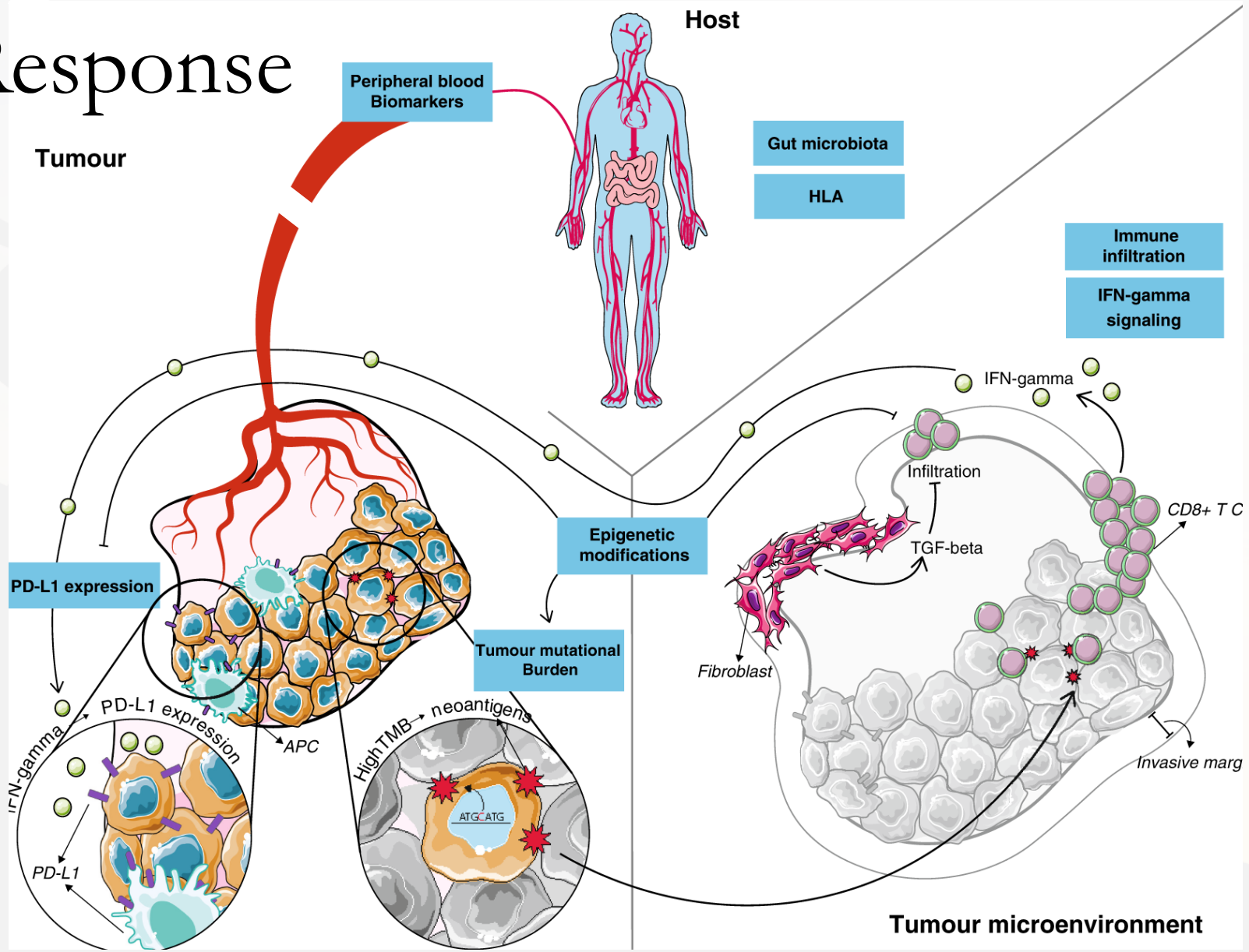
$$\text{TPS (\%)} = \frac{\text{Number of PD-L1-stained tumour cells}}{\text{Total number of viable tumour cells}} \times 100\% \text{ (for 22C3 or SP263)}$$

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

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

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

Evolving Biomarkers for Immunotherapy Response



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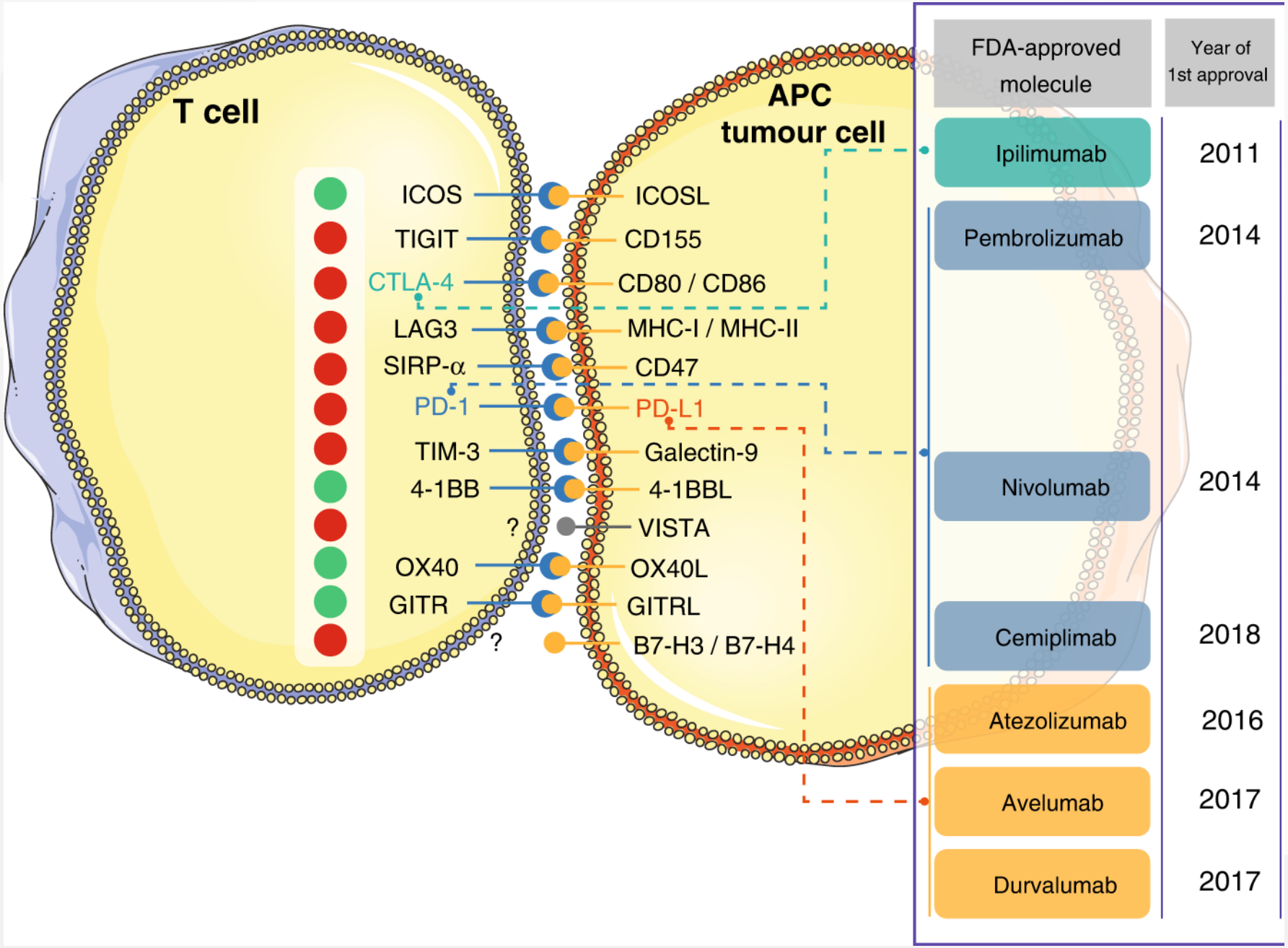
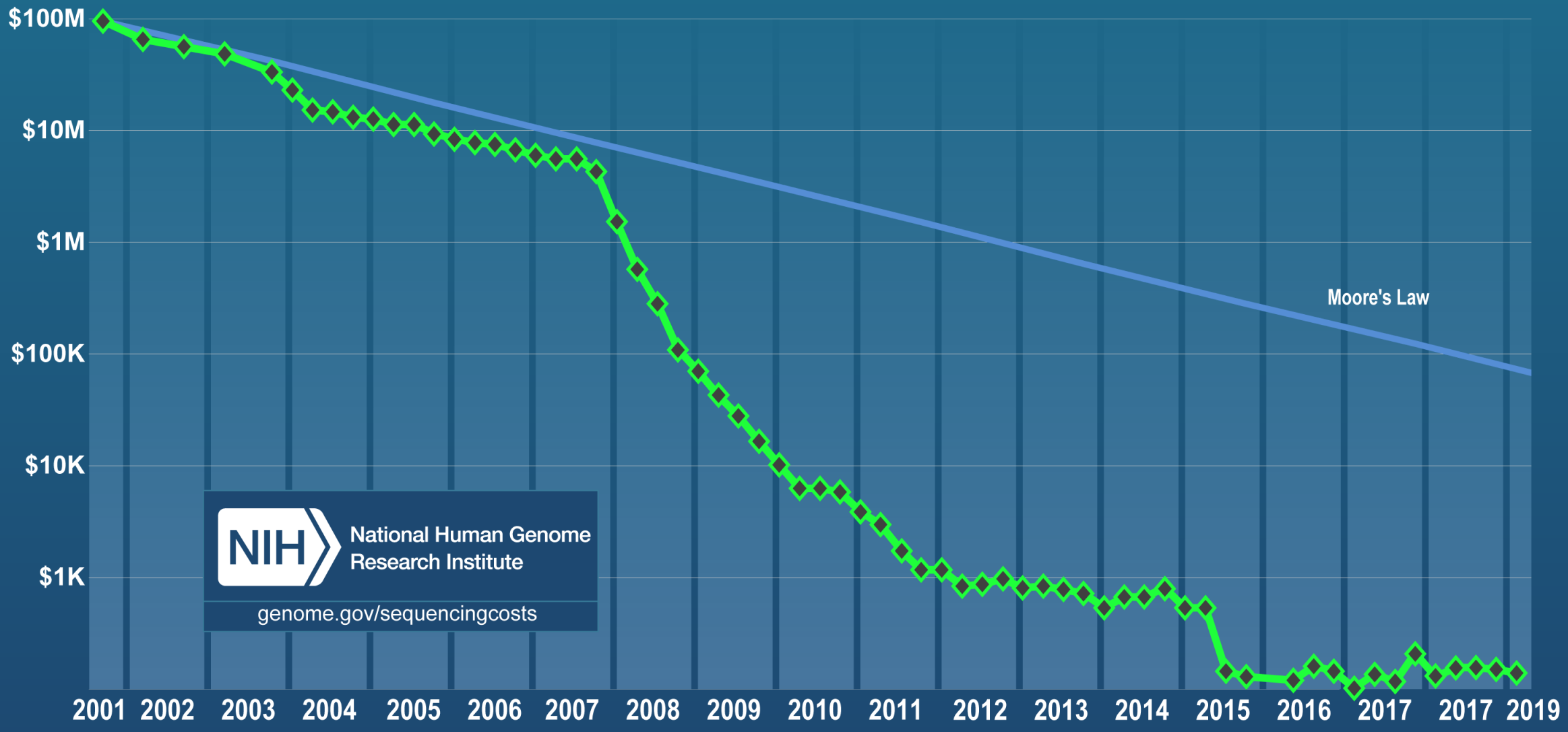
Redundancy of Immune-Checkpoints



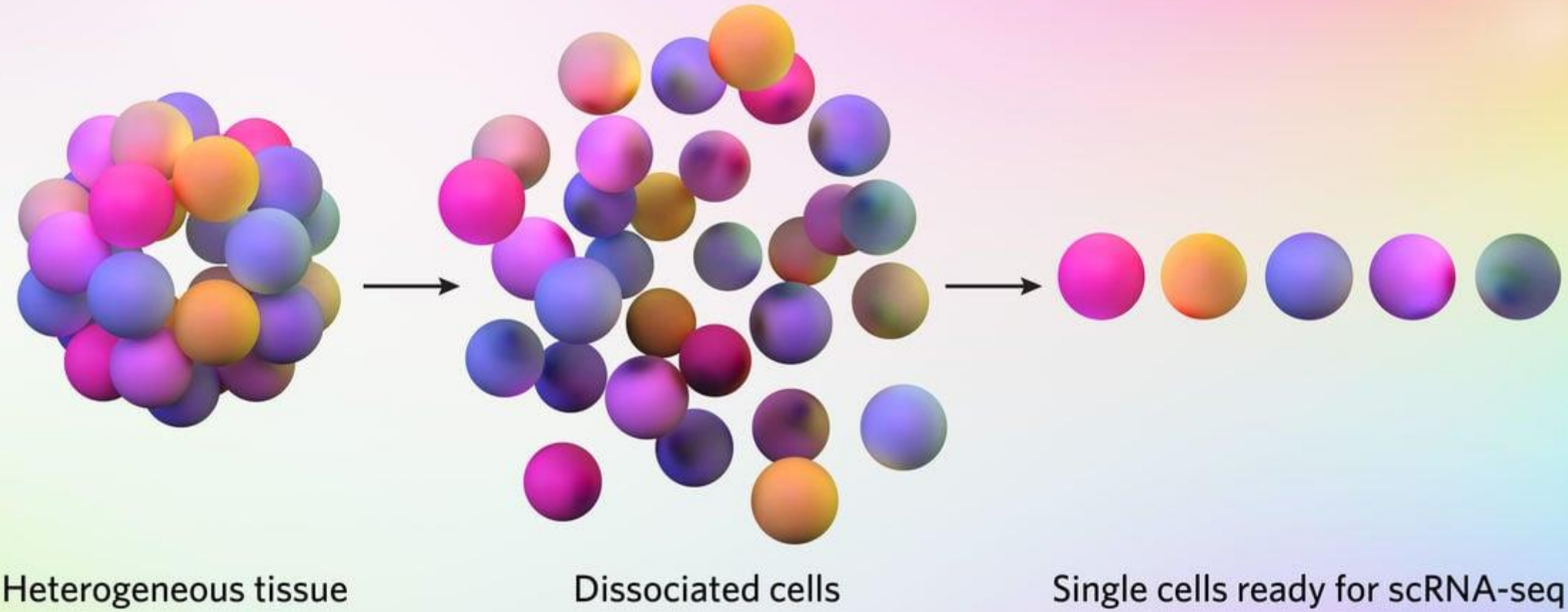
Biomarker Development with

Single Cell Sequencing
and
Multplexed Immunohistochemistry

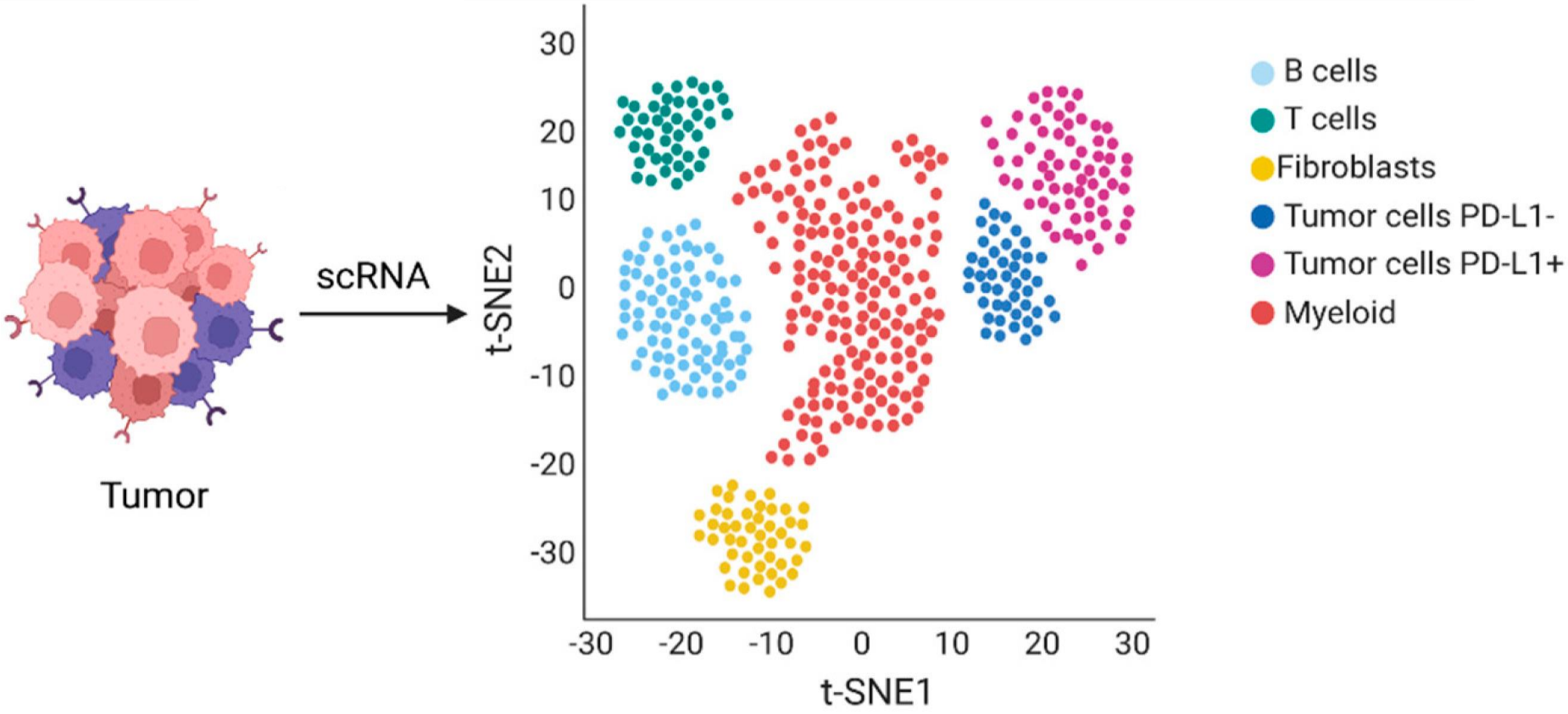
Cost per Genome



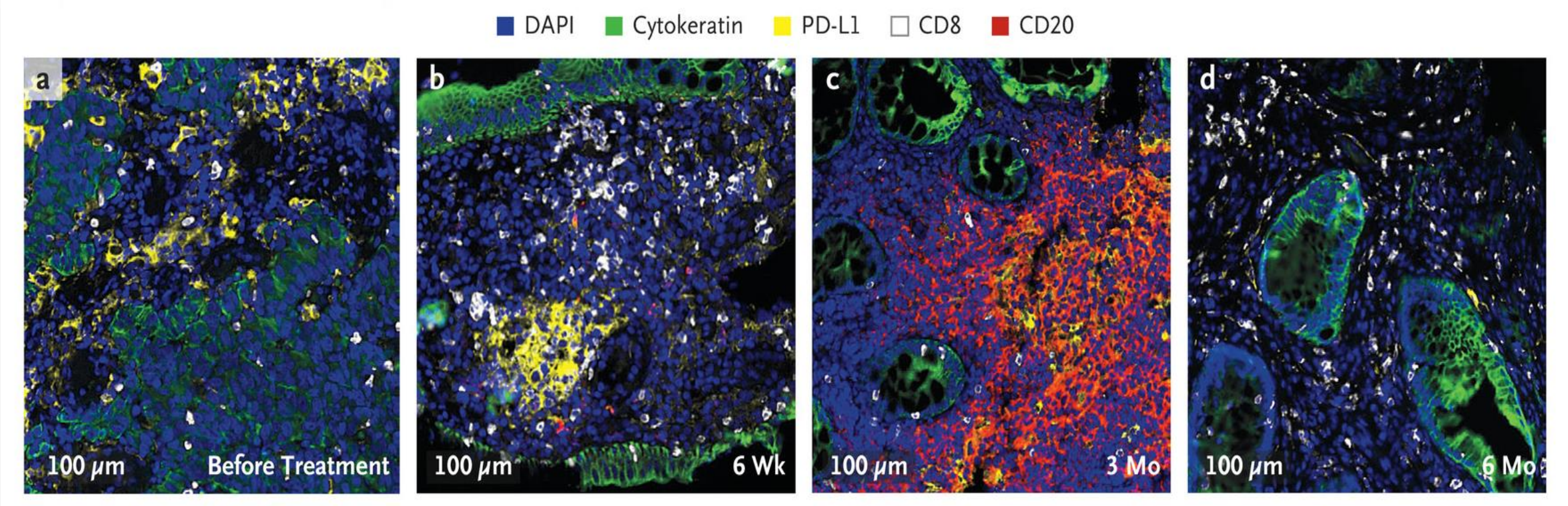
Single Cell RNAseq



Single Cell RNA*seq* for Biomarker Studies
Zoom in to the Single Cell Level

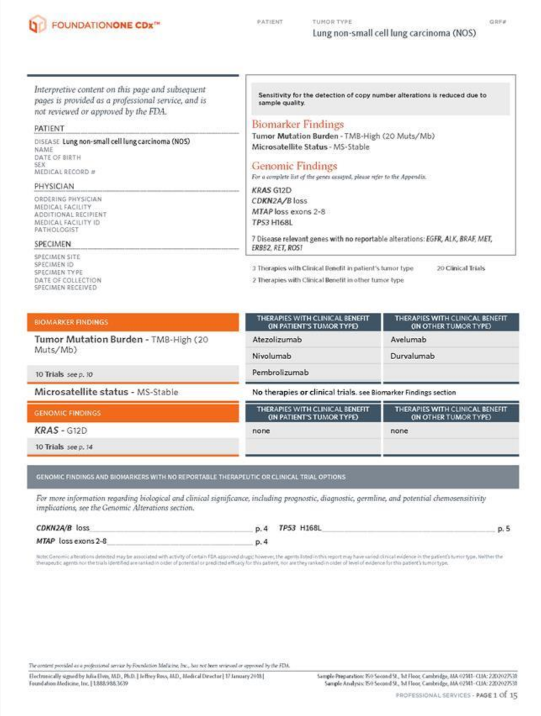


Muliplexed Immunohistochemistry
High Spacial Resolution of Biomarkers

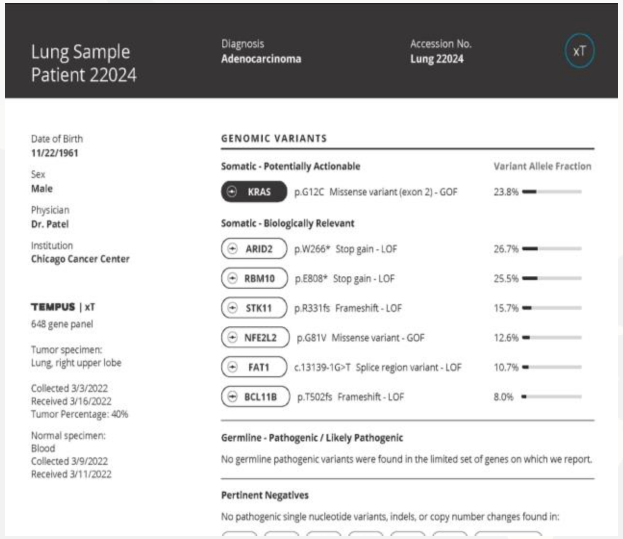


Biomarker Testing

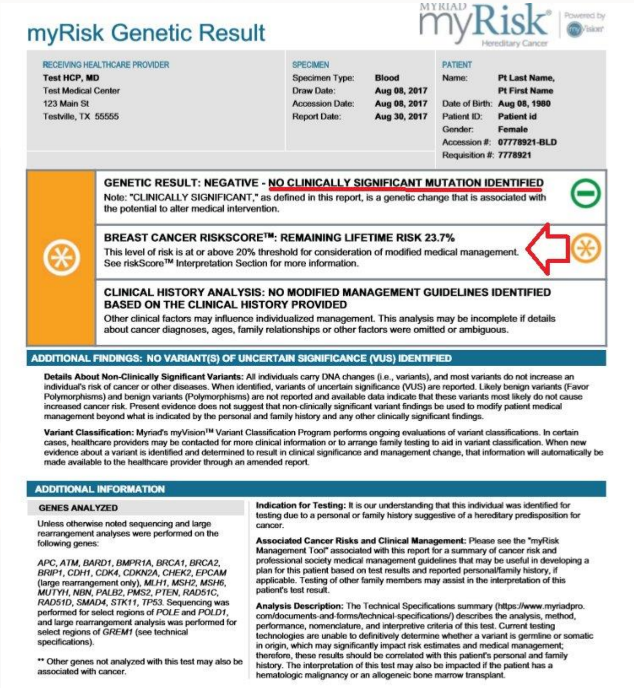
FOUNDATION MEDICINE®



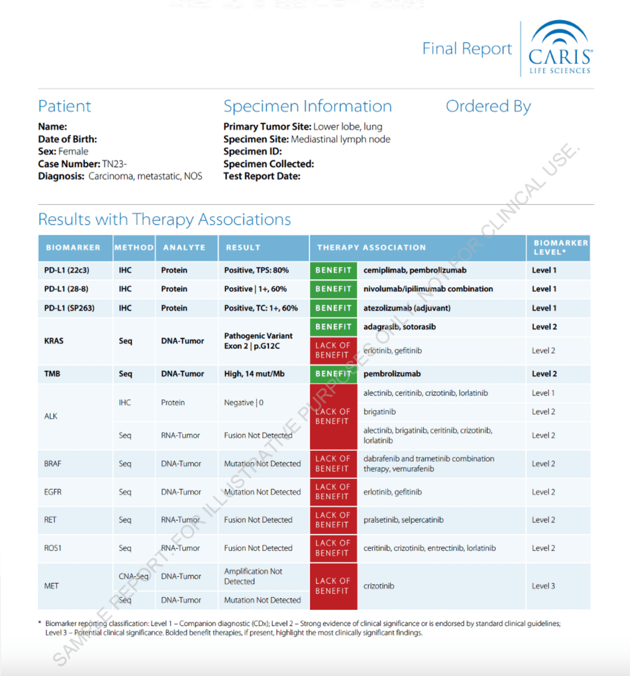
TEMPUS



Myriad genetics



CARIS LIFE SCIENCES



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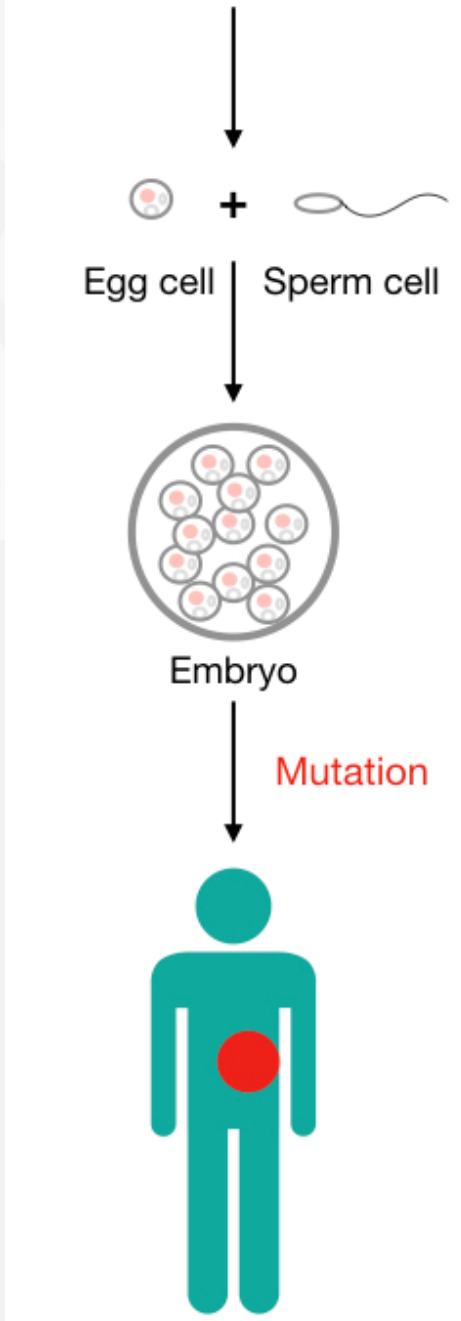
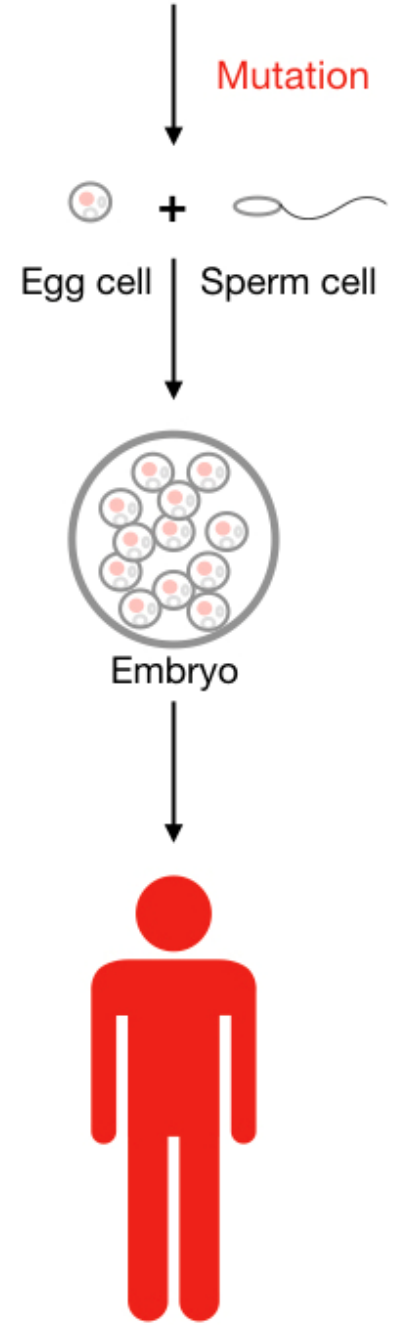
Germline Testing

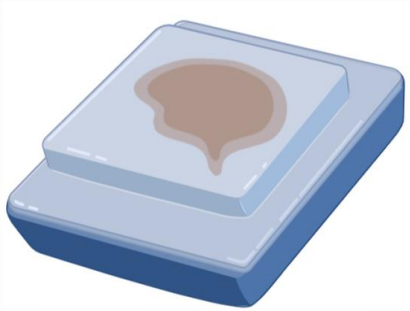


Somatic mutation



Germline mutation

Somatic Testing



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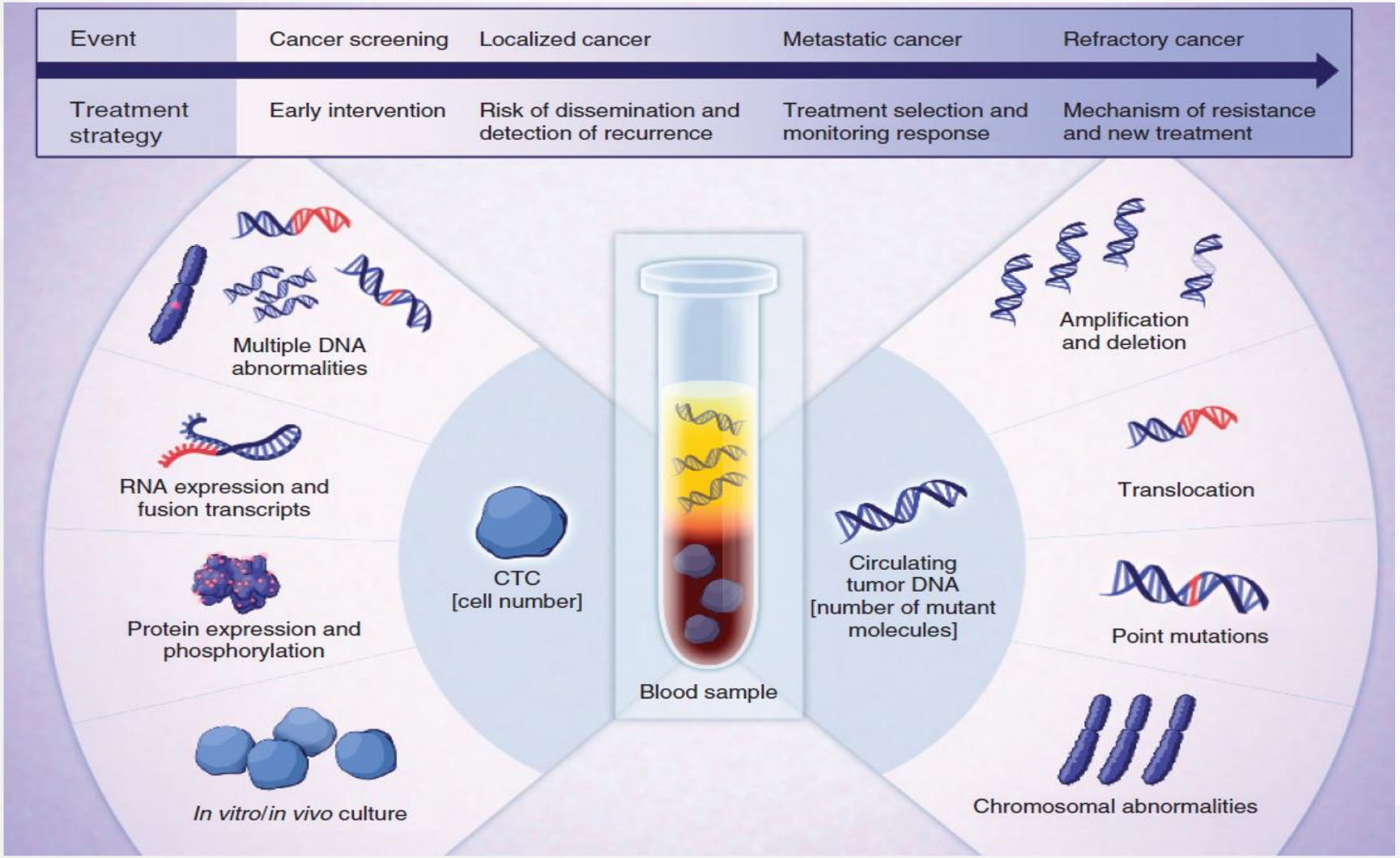
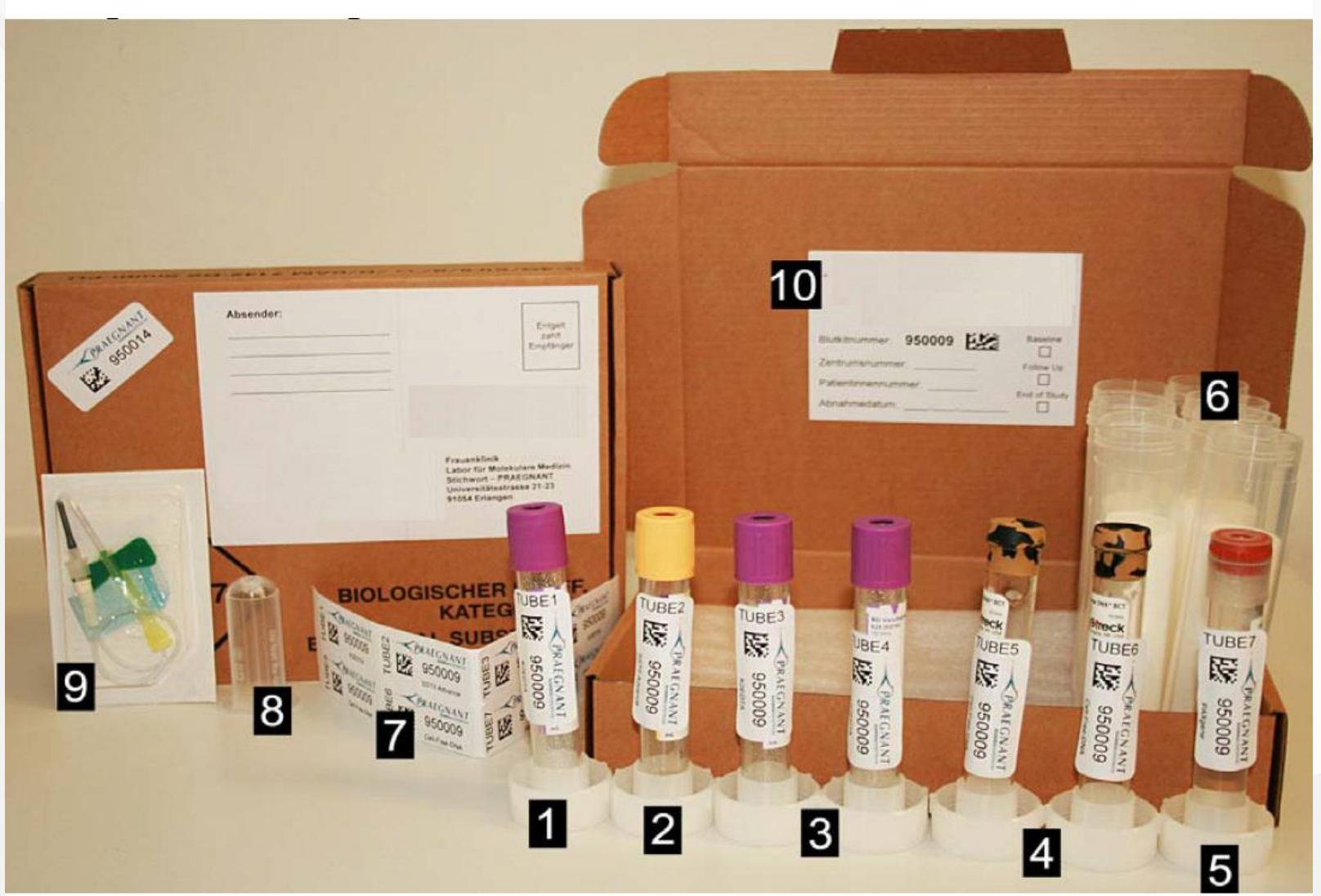
Biomarker Testing in circulating cell-free DNA (cfDNA)



Biomarker Testing will help us Understand Treatment Response and Failure



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We need Biomarkers in Gynecologic Oncology

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

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