

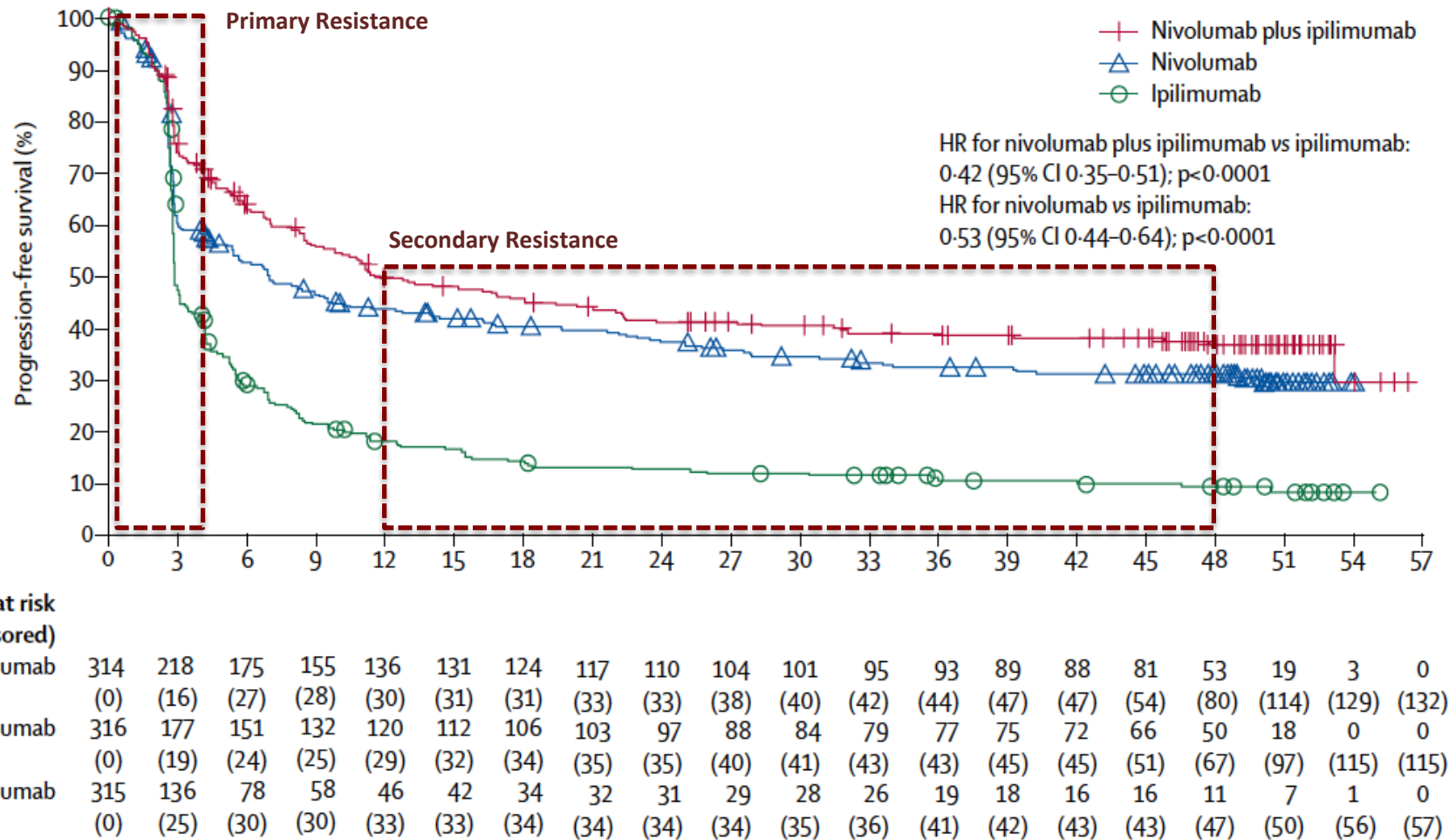
V SIMPOSIO GETHI

CHECKPOINT INHIBITORS: Resistance Mechanisms and how to Overcome Resistance in treatment

Josep M Piulats



Primary vs Secondary Resistance



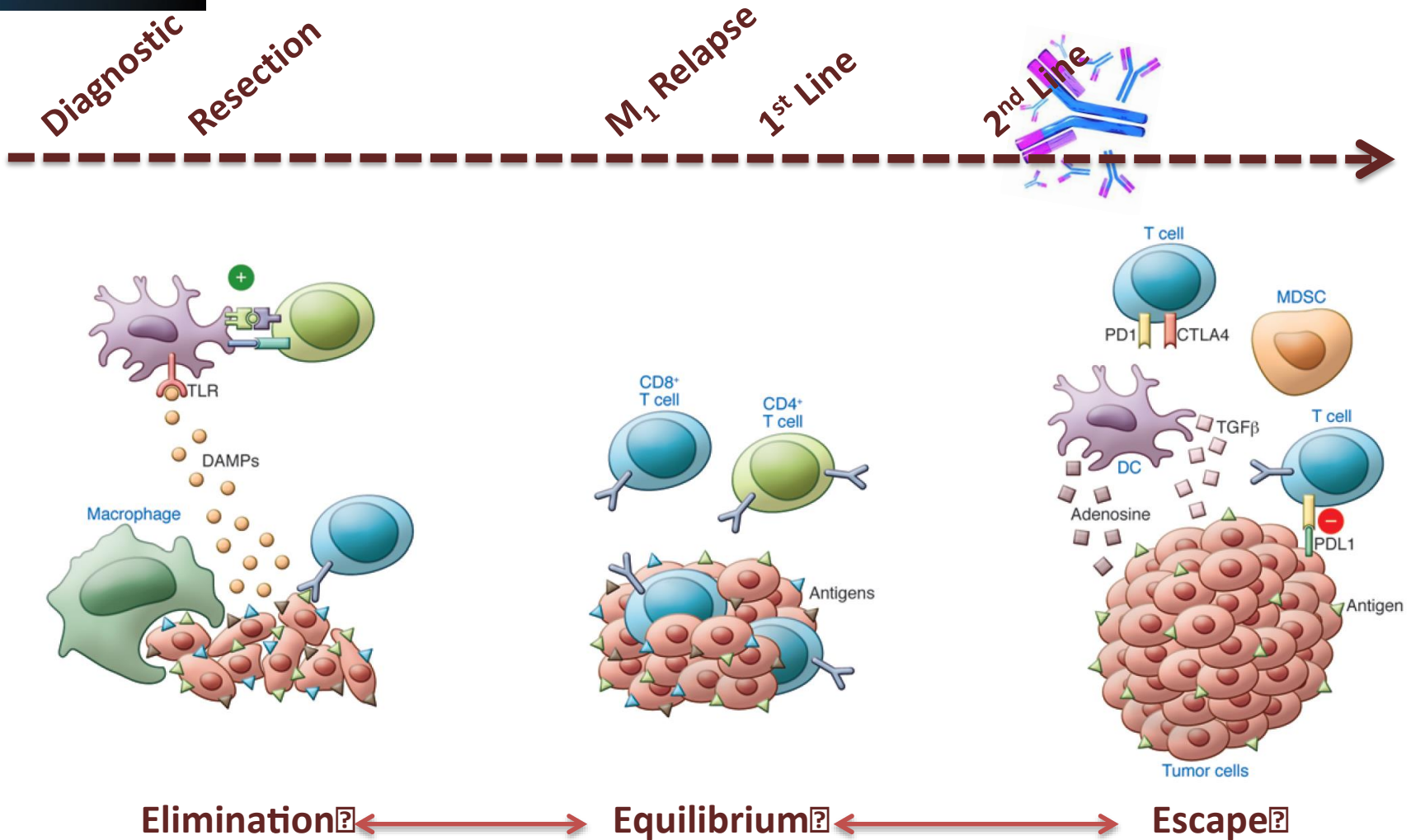


Primary vs Secondary Resistance



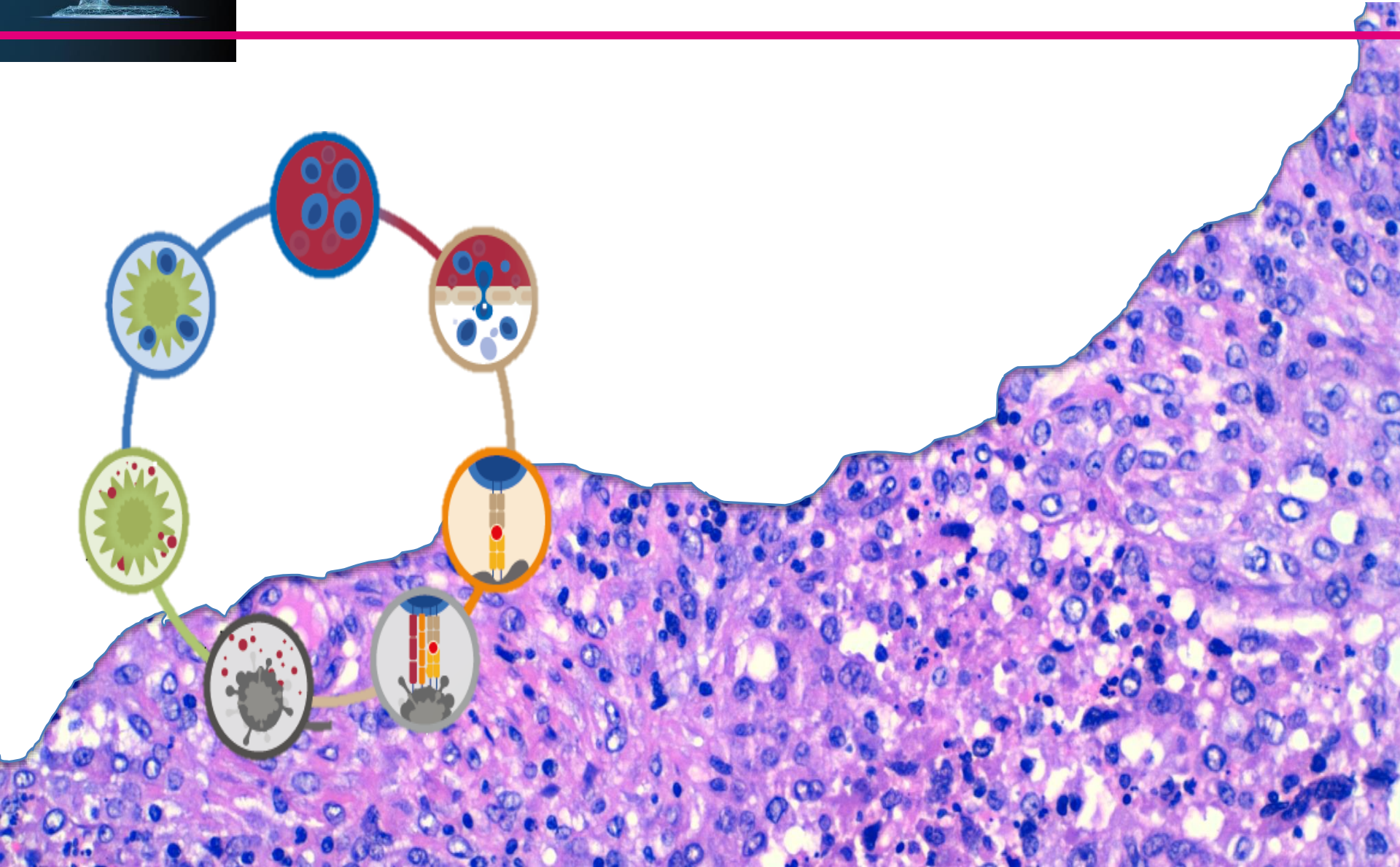


Primary vs Secondary Resistance





Immune-cycle for Oncologists

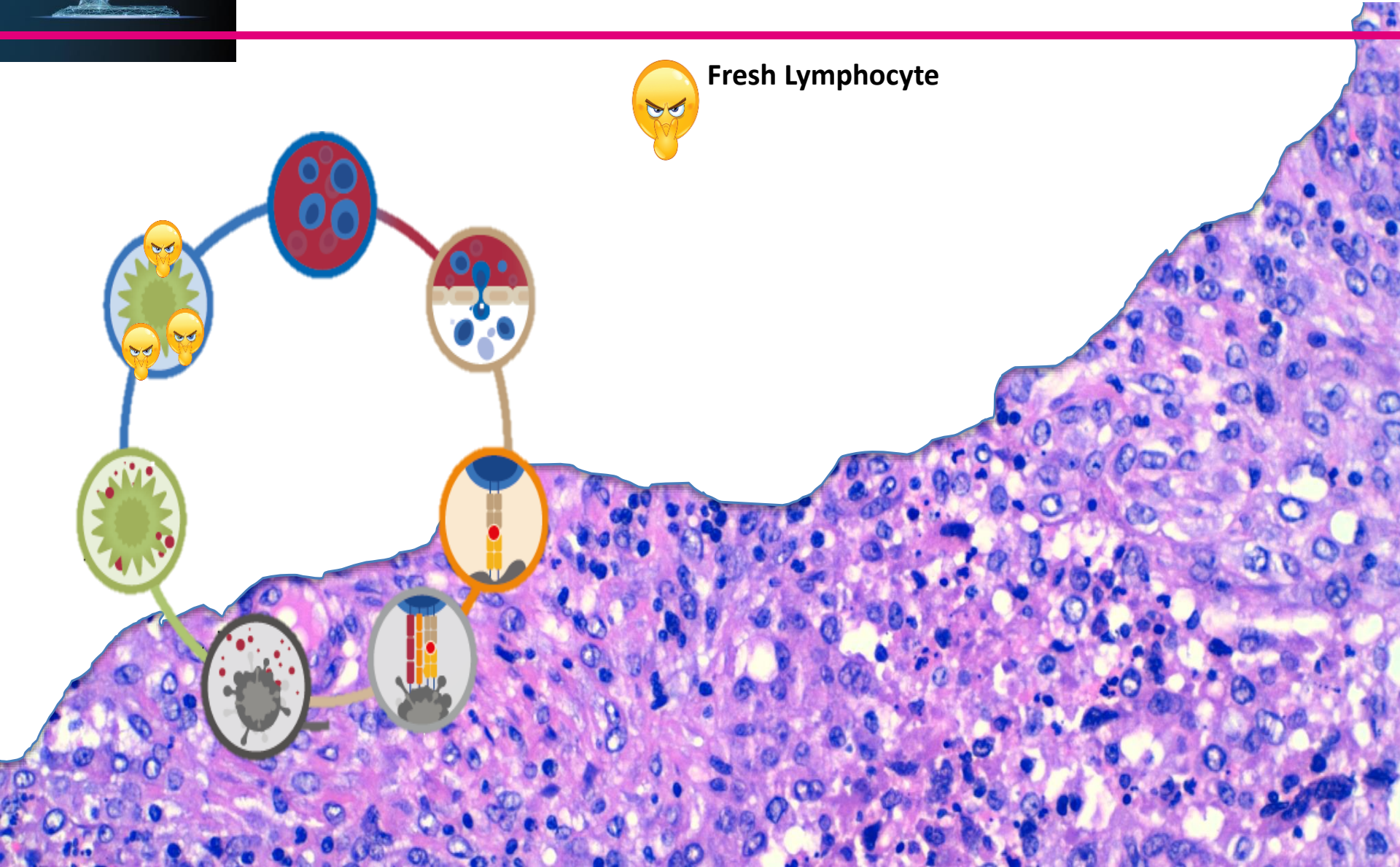




Immune-cycle for Oncologists



Fresh Lymphocyte

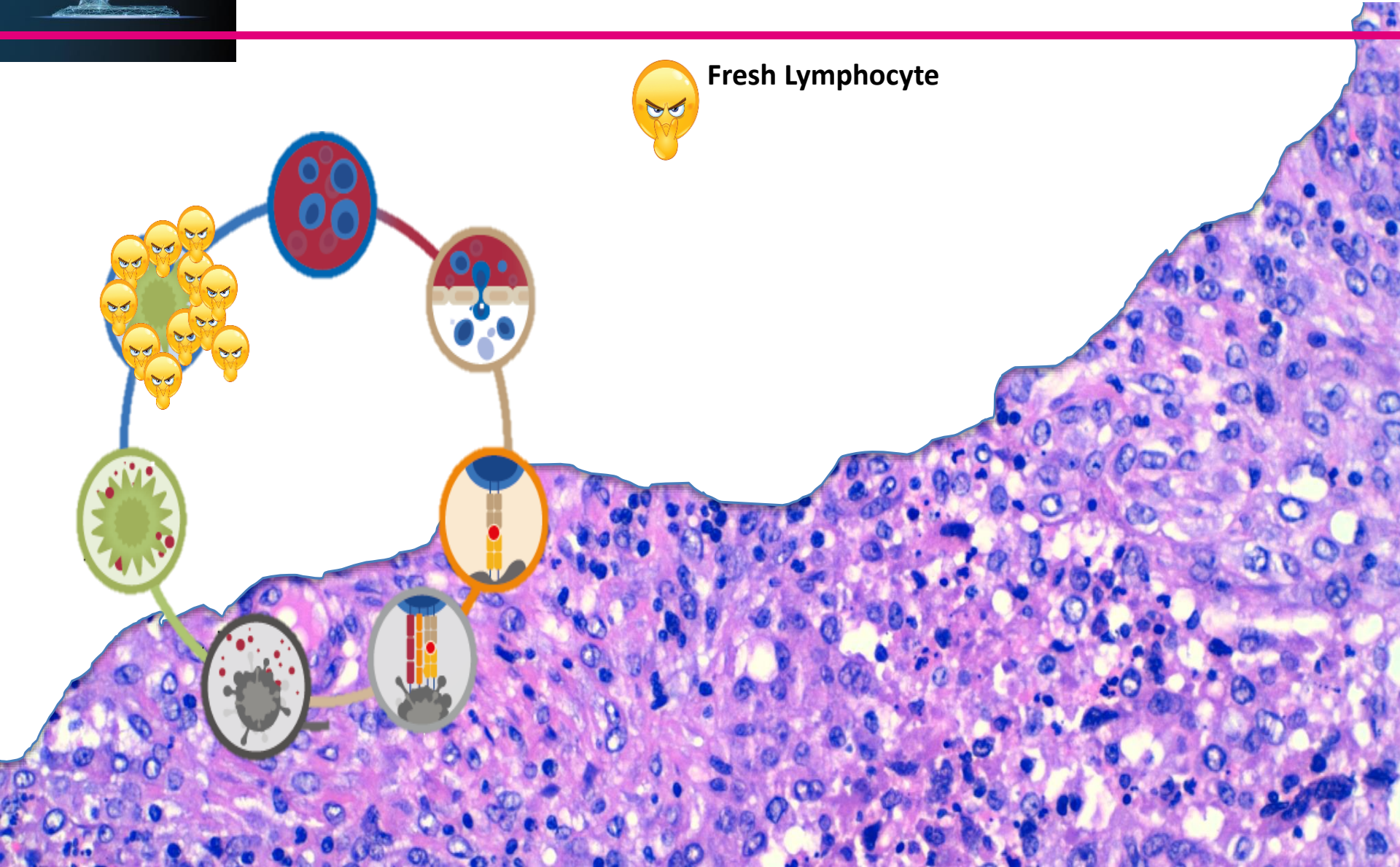




Immune-cycle for Oncologists



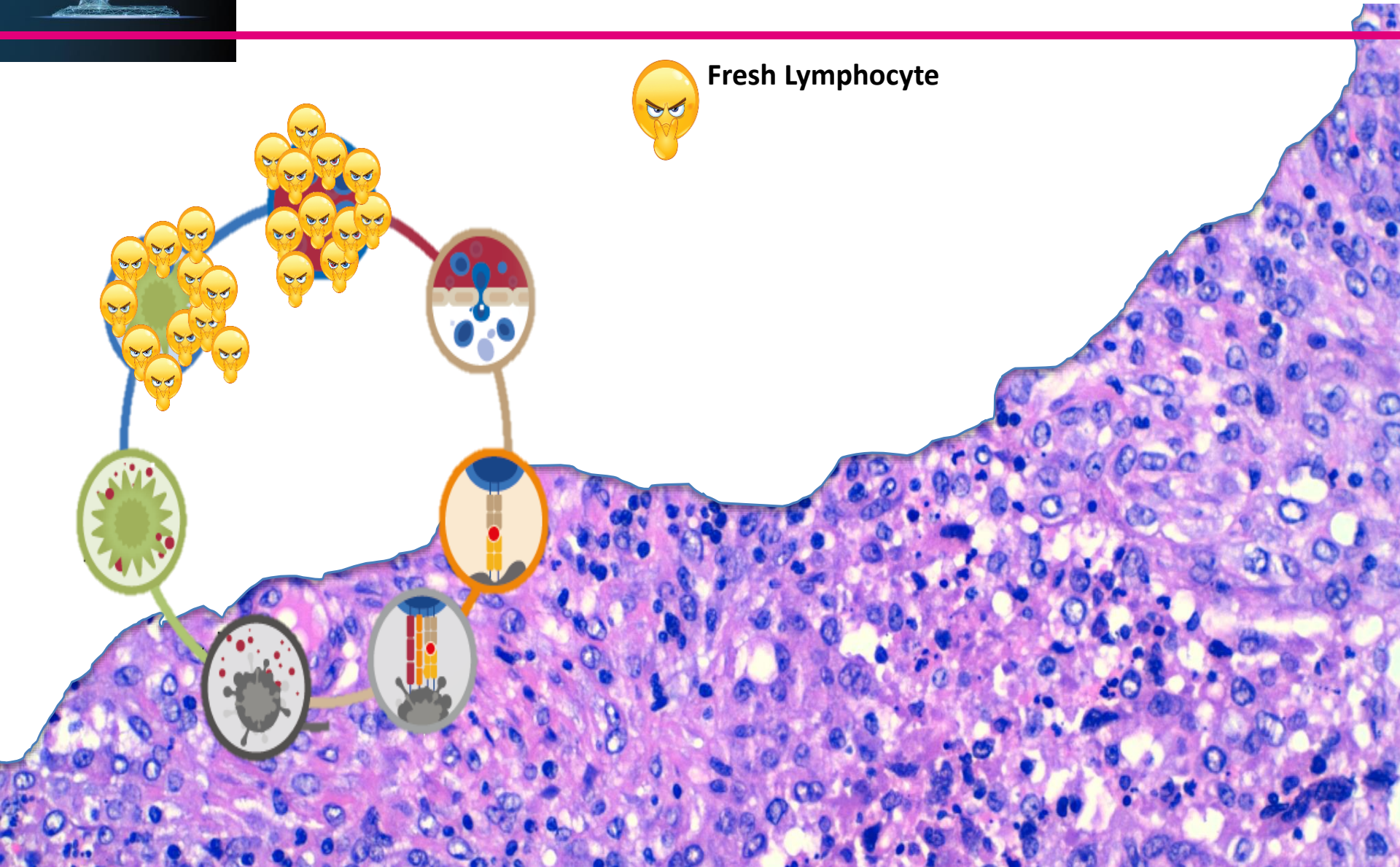
Fresh Lymphocyte





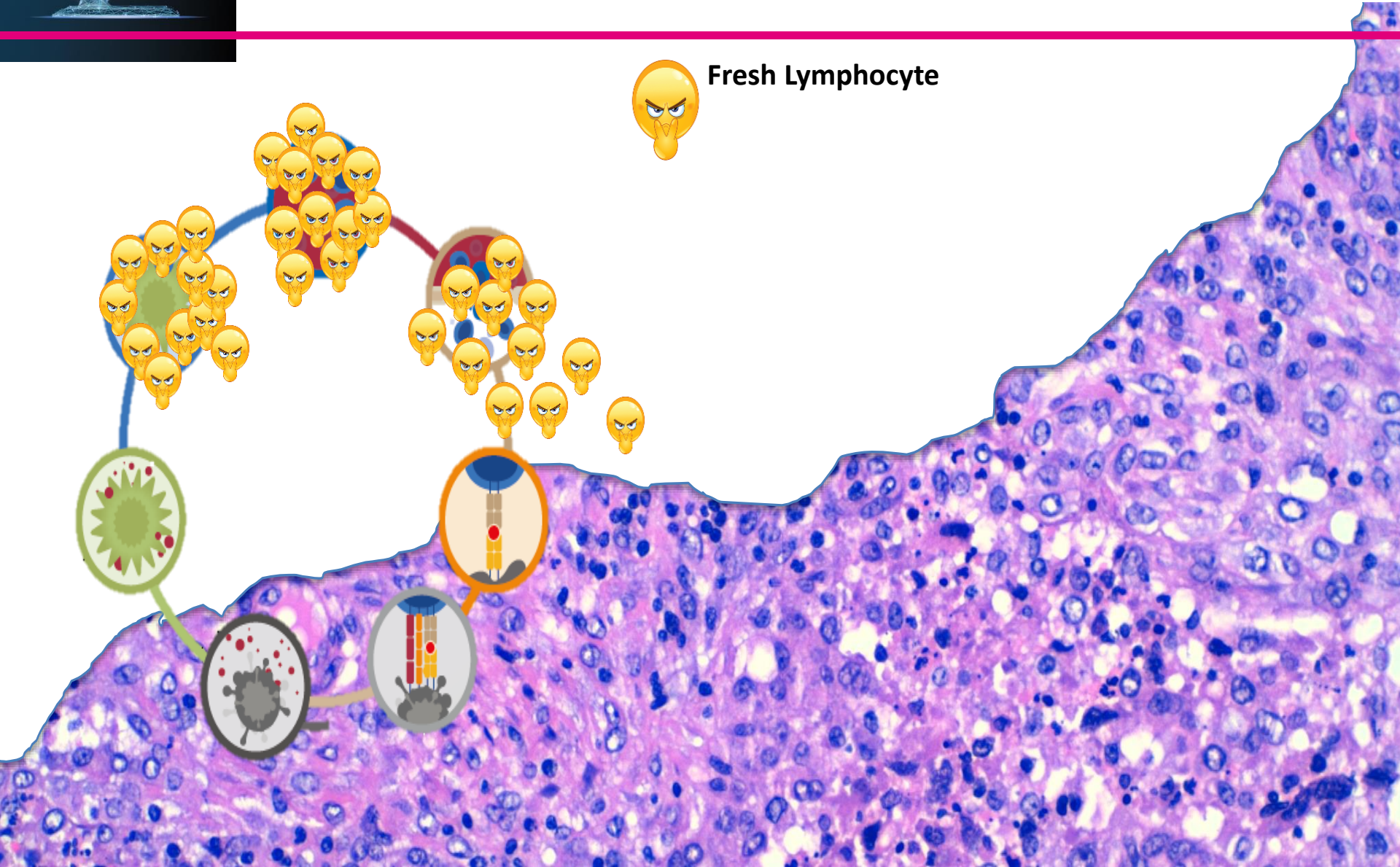
Immune-cycle for Oncologists

 Fresh Lymphocyte



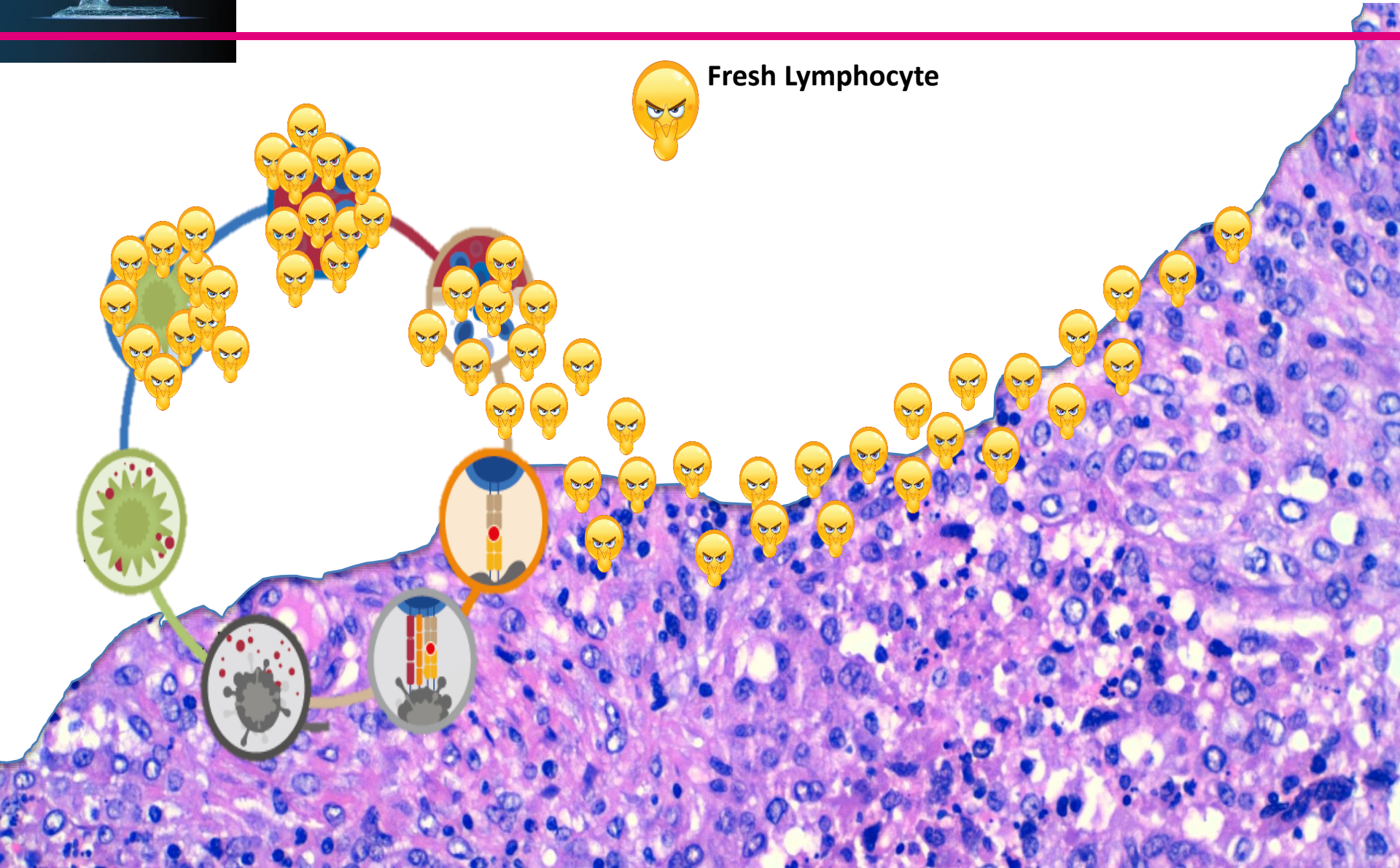


Immune-cycle for Oncologists





Immune-cycle for Oncologists



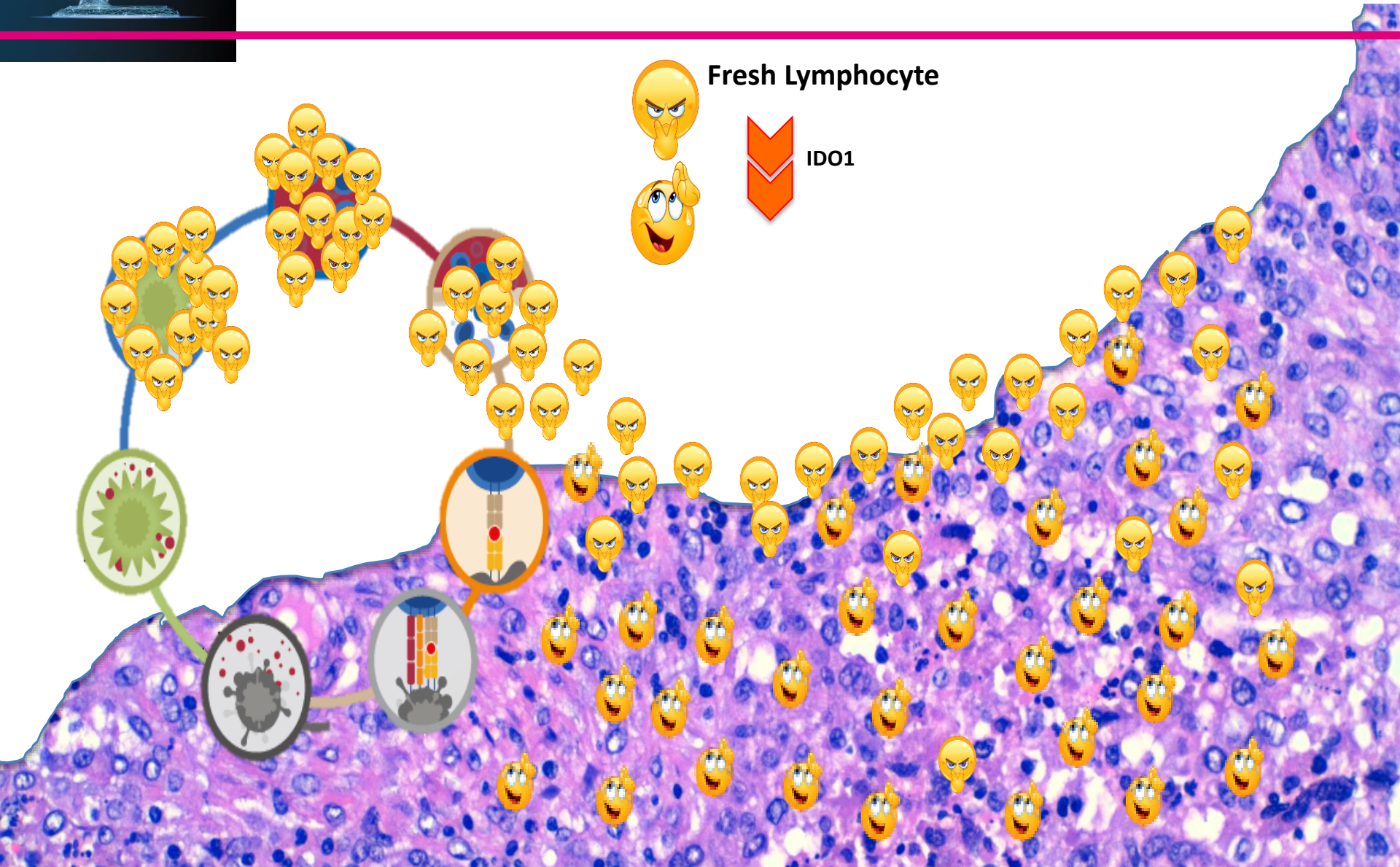


Fresh Lymphocyte

The diagram illustrates the activation and proliferation of lymphocytes. At the top, a single 'Fresh Lymphocyte' (represented by a yellow face with a finger to its mouth) is shown. Below it, a cluster of lymphocytes is depicted, with one cell interacting with a green, star-shaped antigen. This interaction leads to the proliferation of the lymphocyte, resulting in a large population of identical cells. The background is a purple, textured surface, possibly representing a tissue or organ. The diagram is labeled 'Fresh Lymphocyte' at the top.

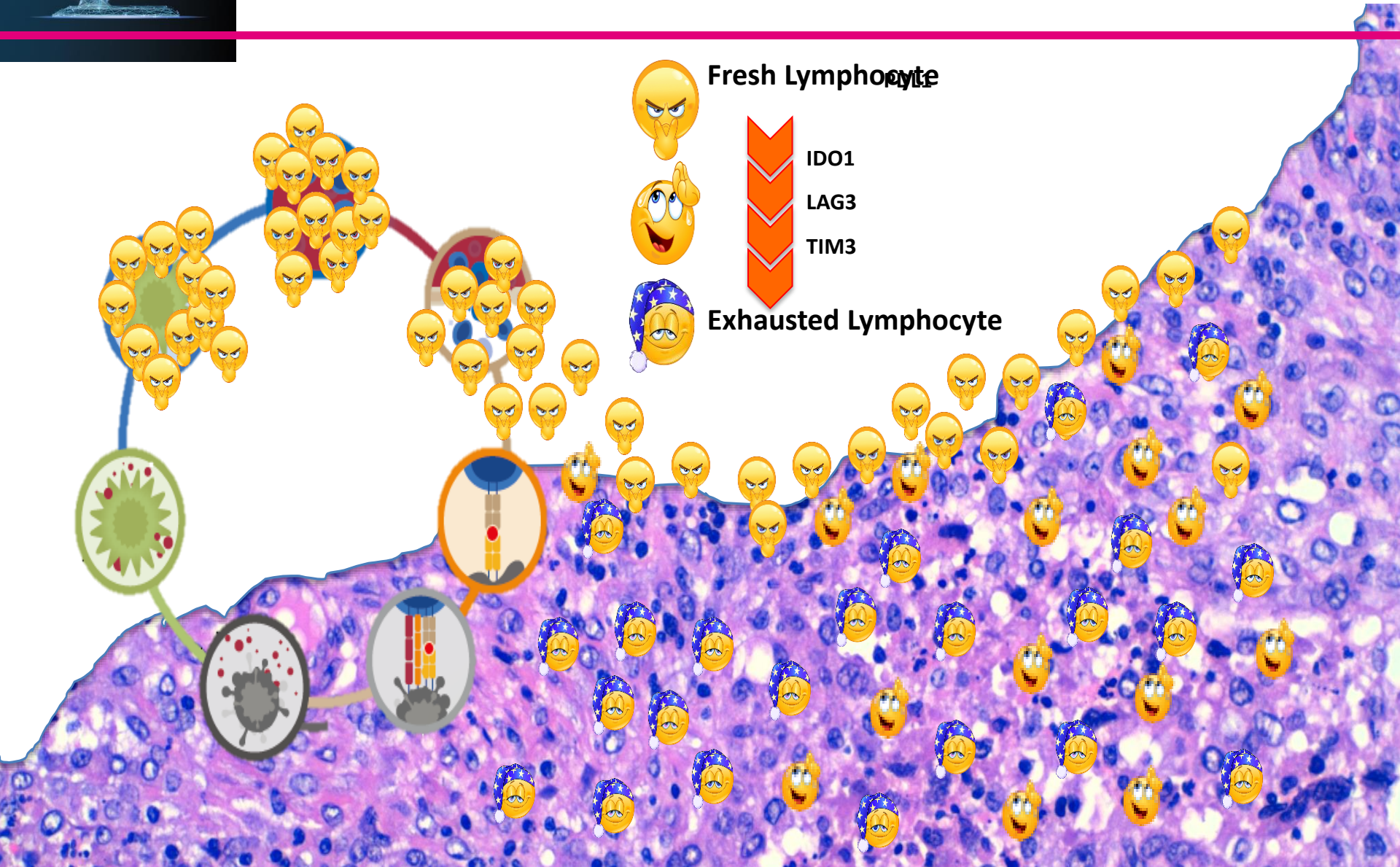


Immune-cycle for Oncologists





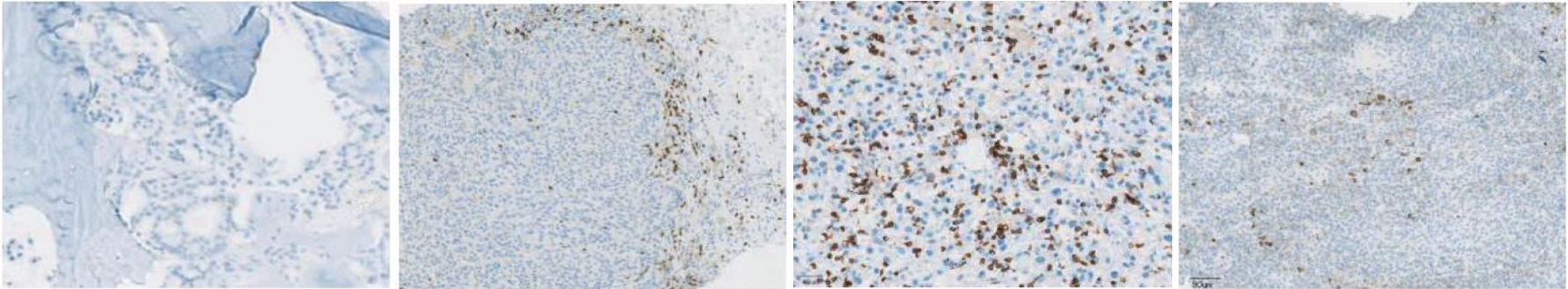
Immune-cycle for Oncologists





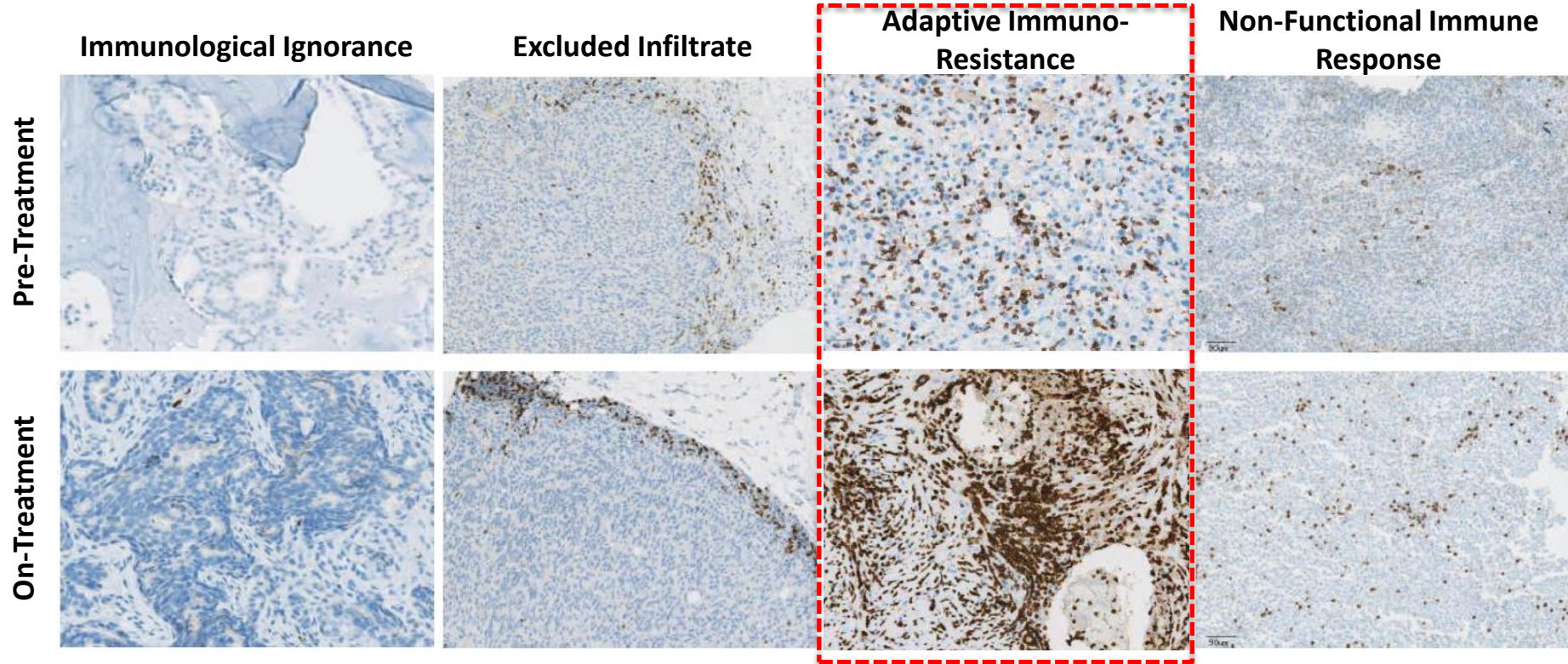
CD8 infiltration patterns

Pre-Treatment



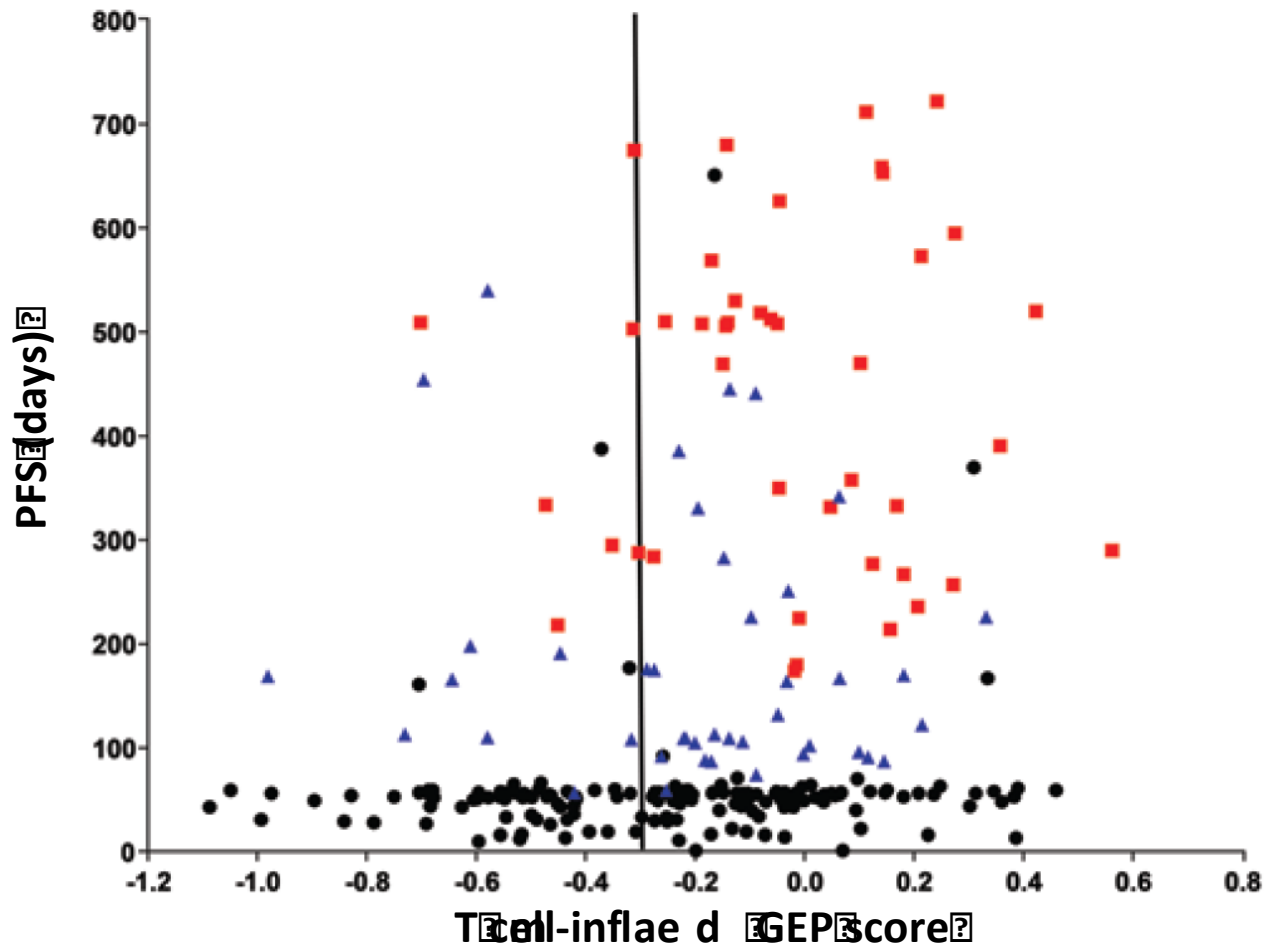


CD8 infiltration patterns





GEP score

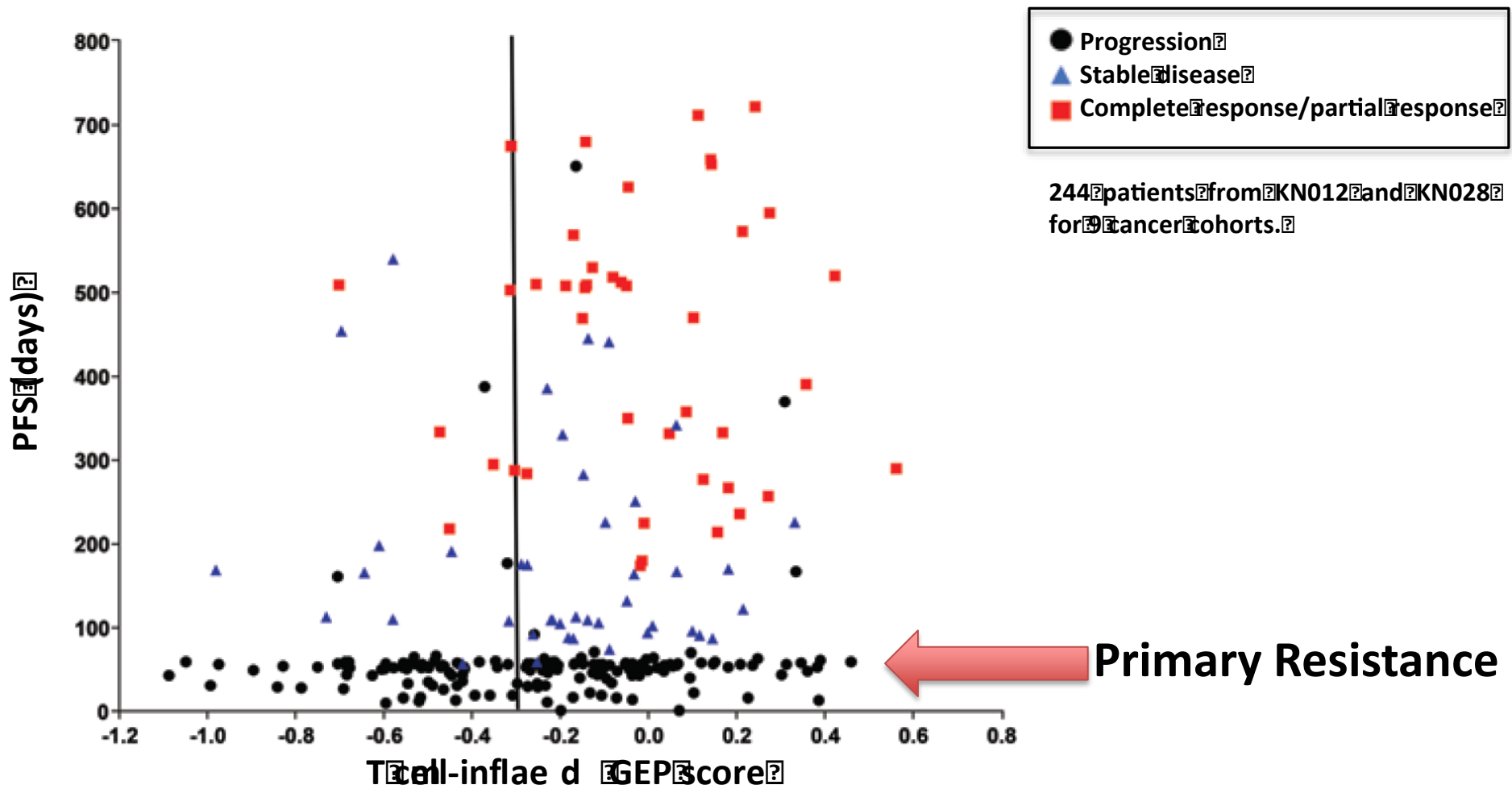


- Progression
- ▲ Stable disease
- Complete response/partial response

244 patients from KN012 and KN028 for Cancer Cohorts.



GEP score





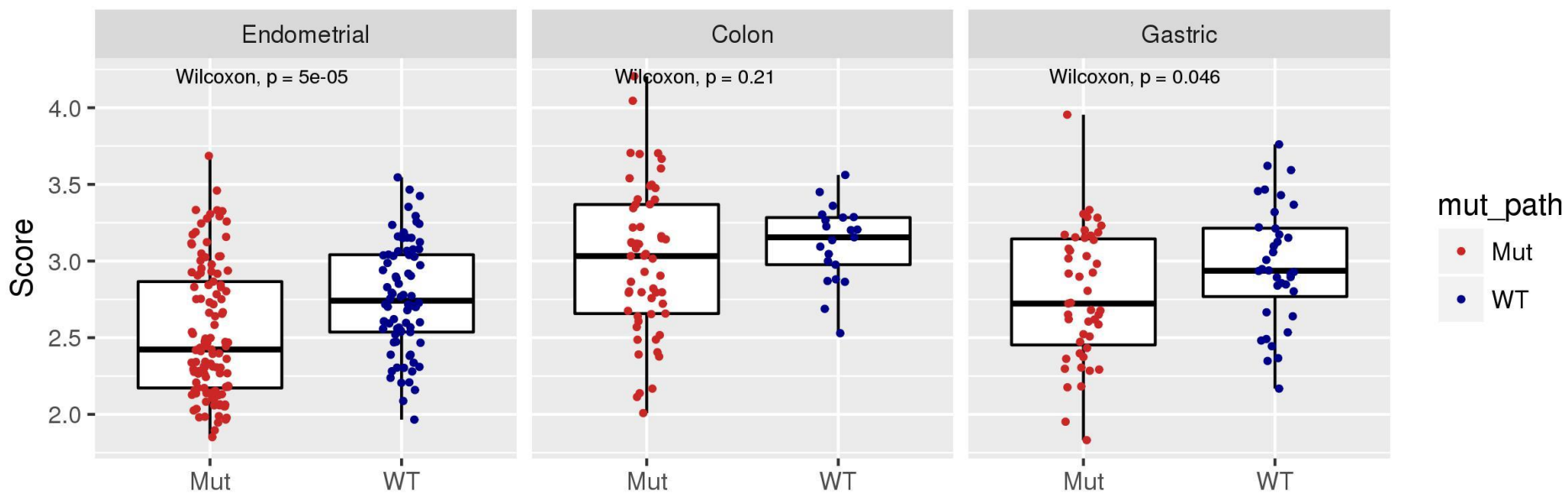
GEP score





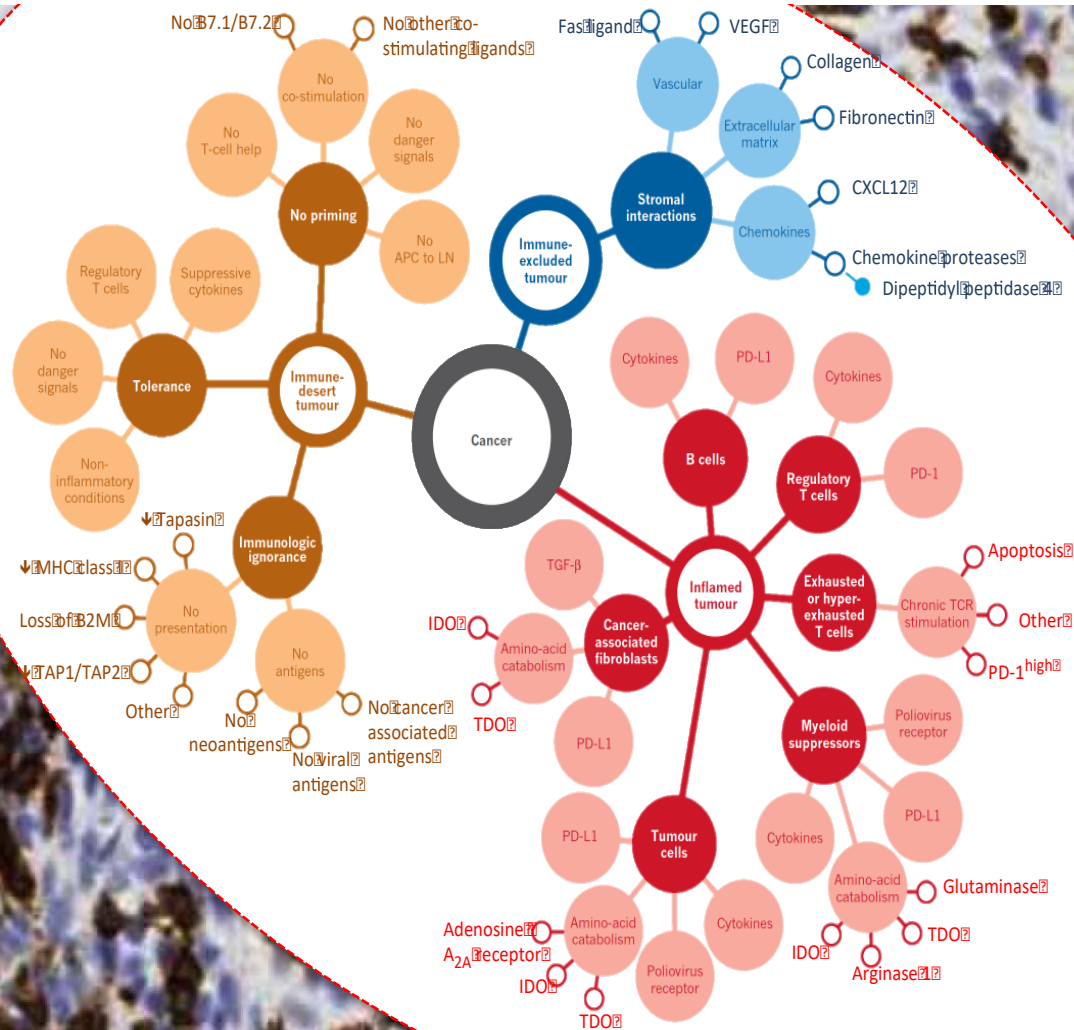
GEP score

Immunophenoscore



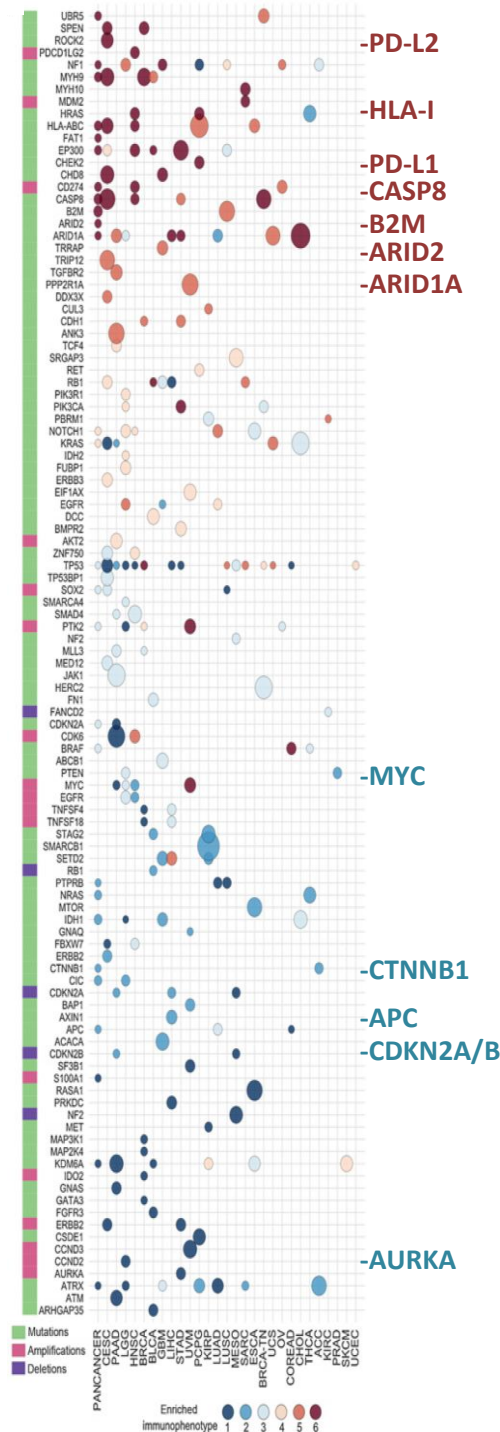


Inflammatory Patterns

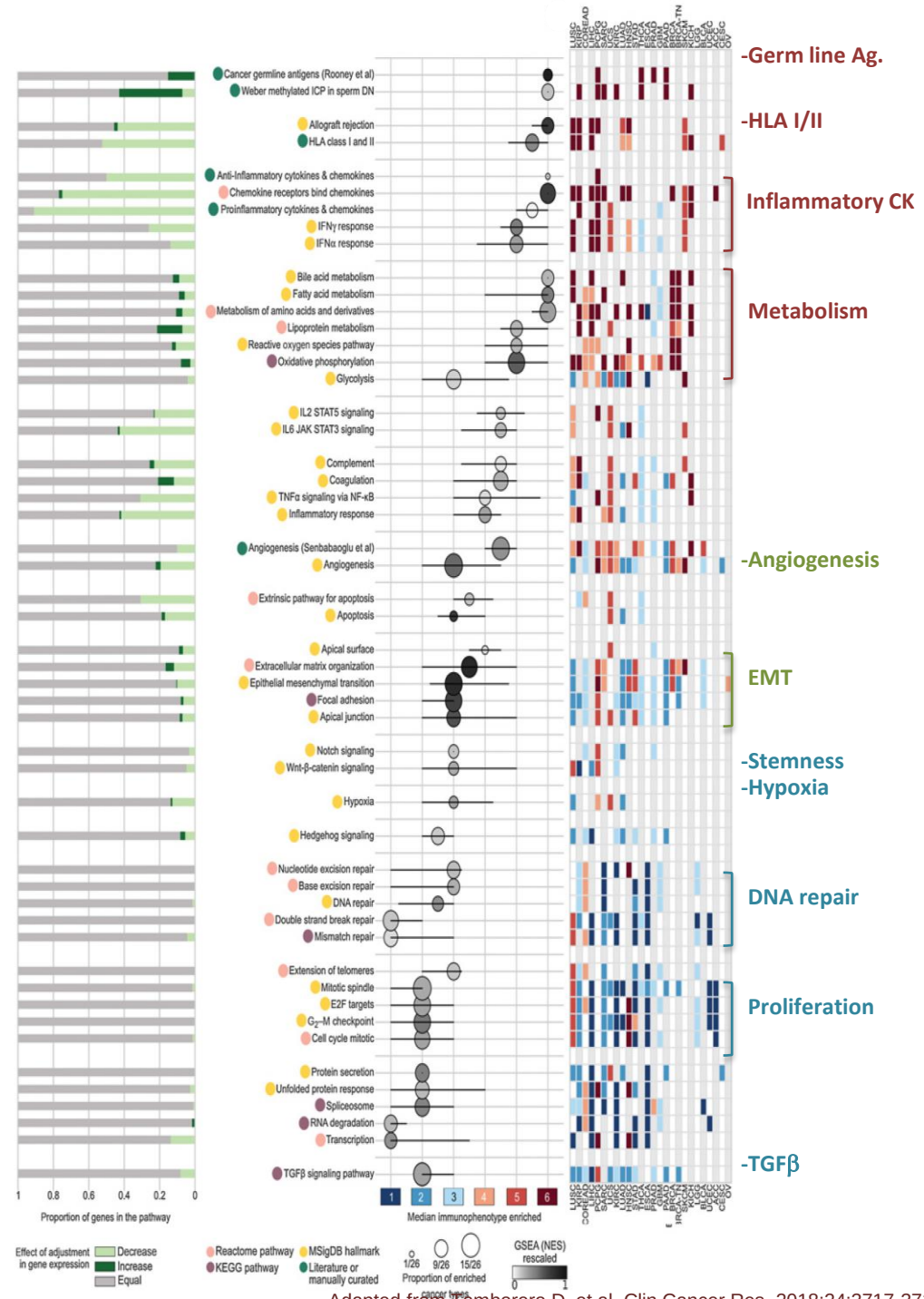


Genes with driver alterations significantly associated to immuno-

phenotypes

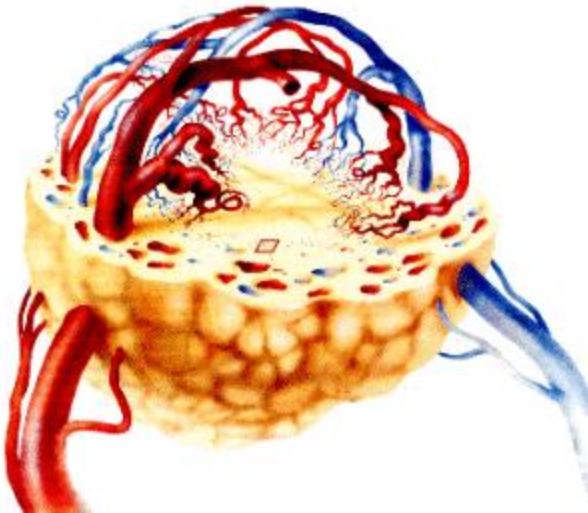


Immuno-phenotypes with enrichment for up-regulated cell pathways across cohorts

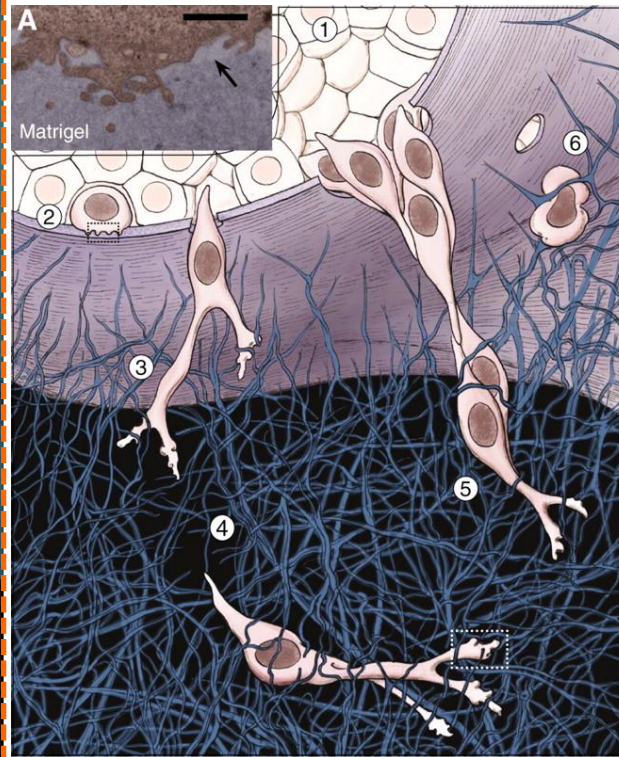


Anti-PD1/PDL1 Resistant Phenotype:

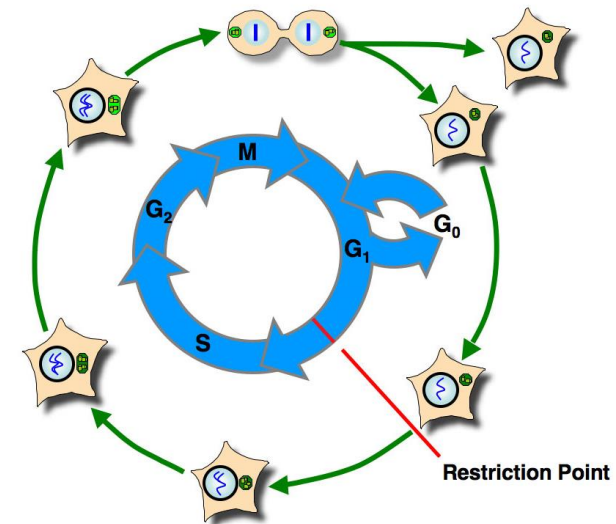
ANGIOGENESIS



EMT

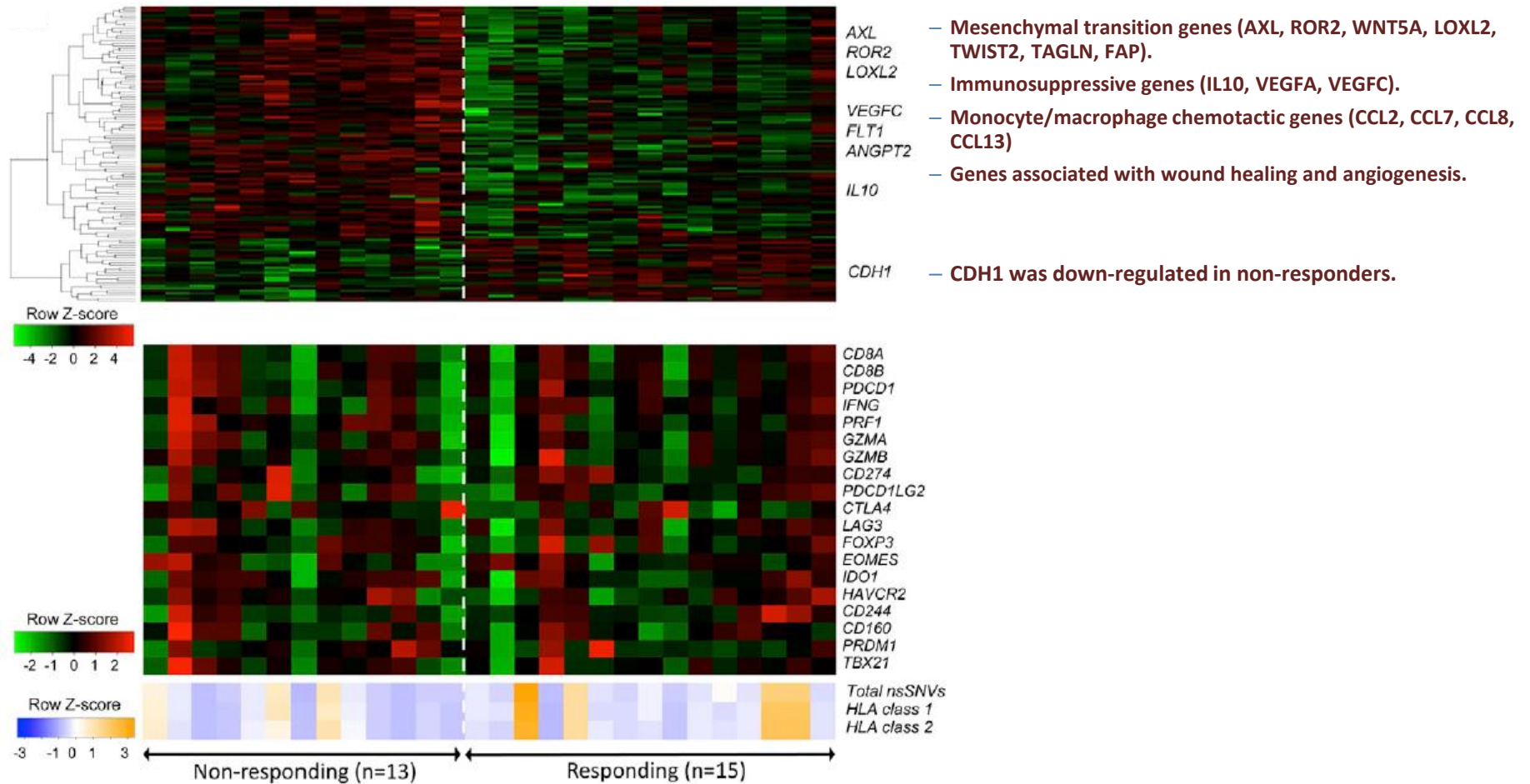


PROLIFERATION





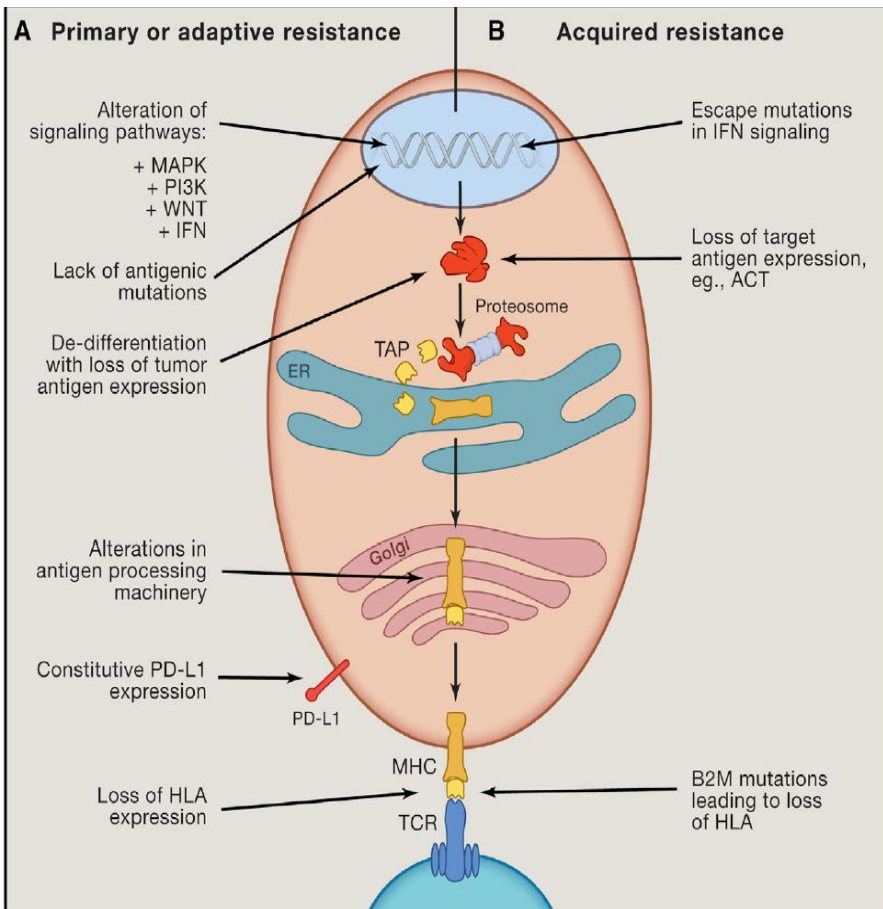
Responders vs Non-Responders





Intrinsic Resistance to ICB

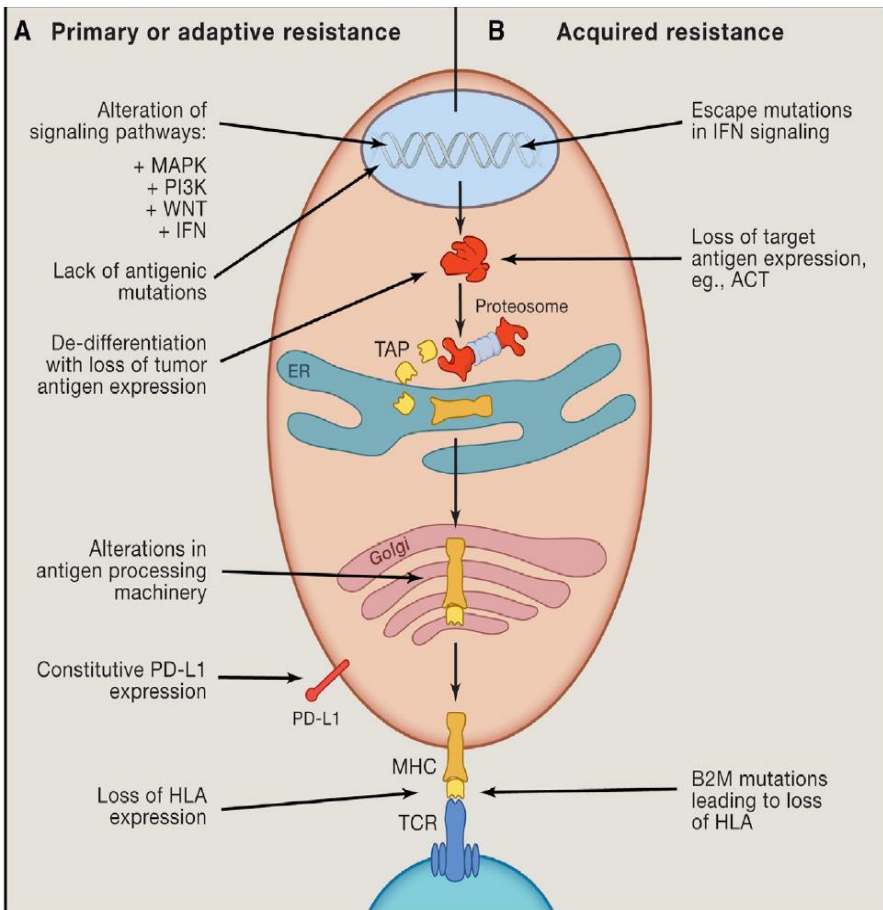
Intrinsic Resistance





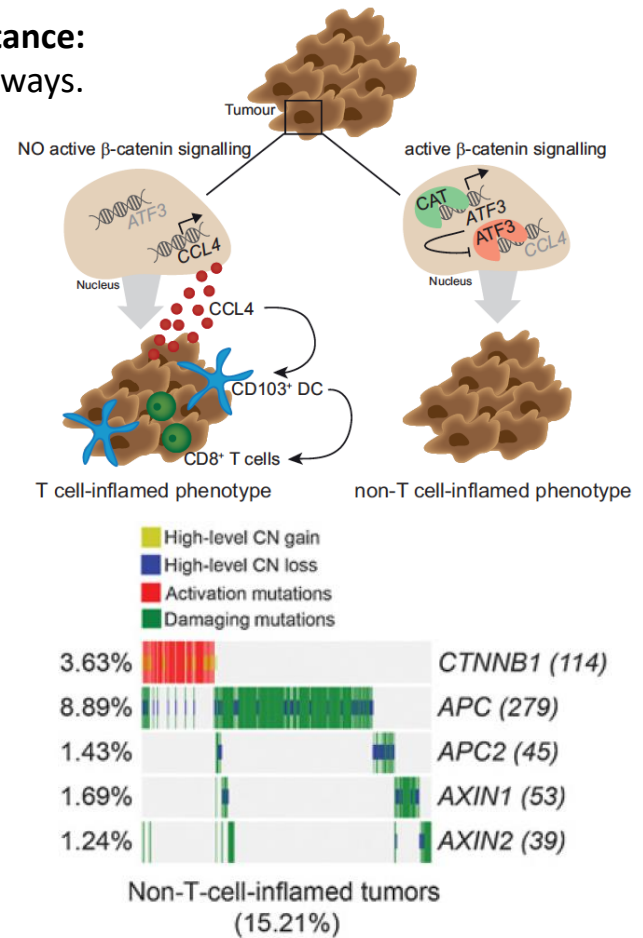
Intrinsic Resistance to ICB

Intrinsic Resistance



Innate Resistance:

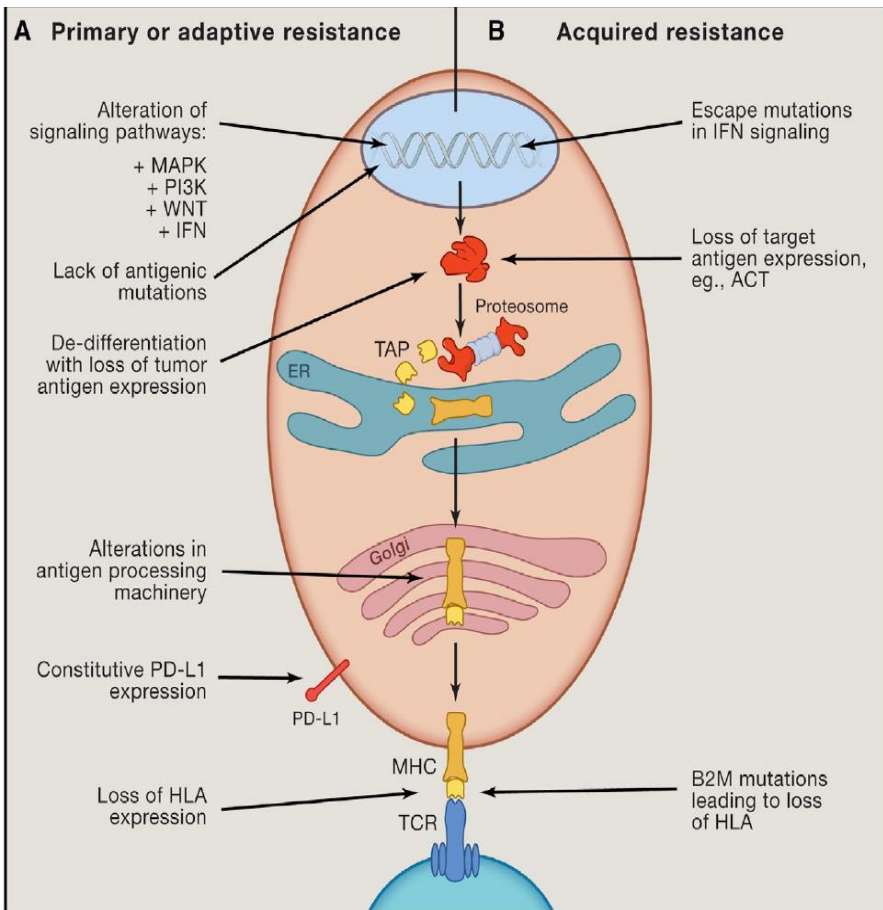
- WNT Pathways.





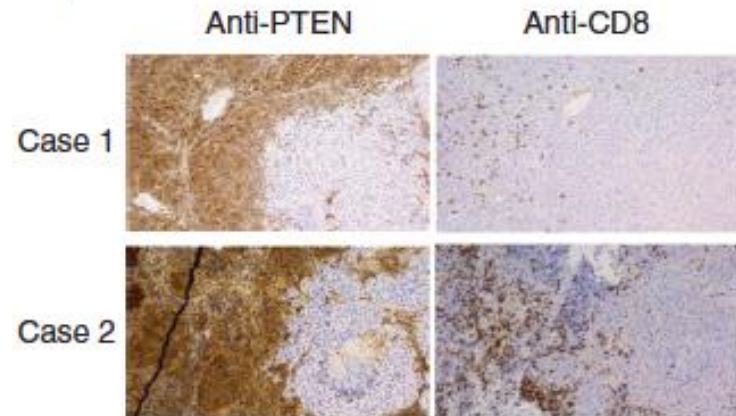
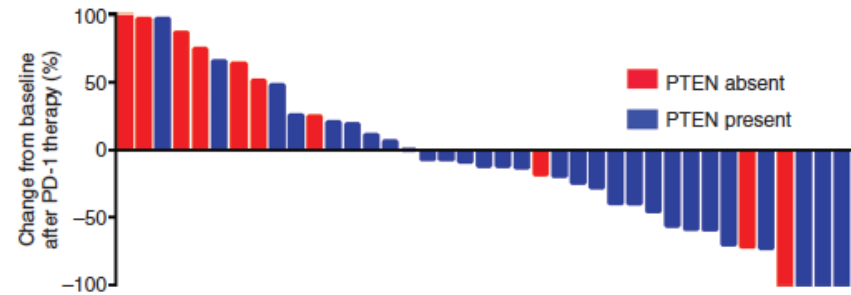
Intrinsic Resistance to ICB

Intrinsic Resistance



Innate Resistance:

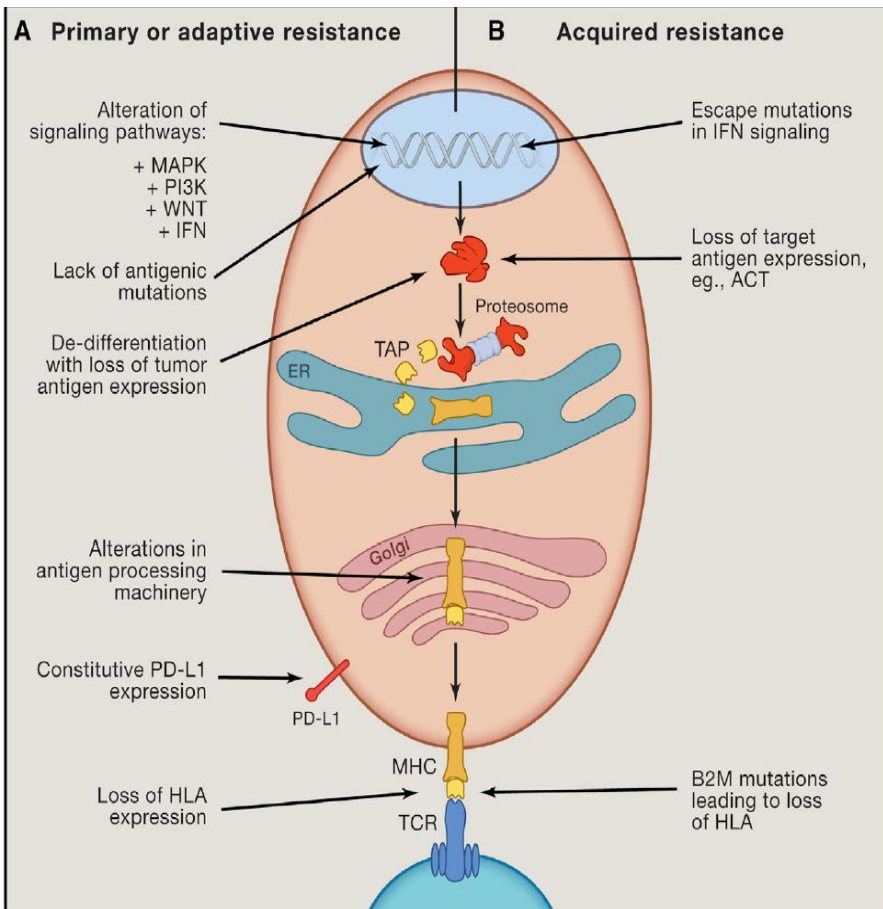
- WNT Pathways.
- PI3K Pathways.





Intrinsic Resistance to ICB

Intrinsic Resistance



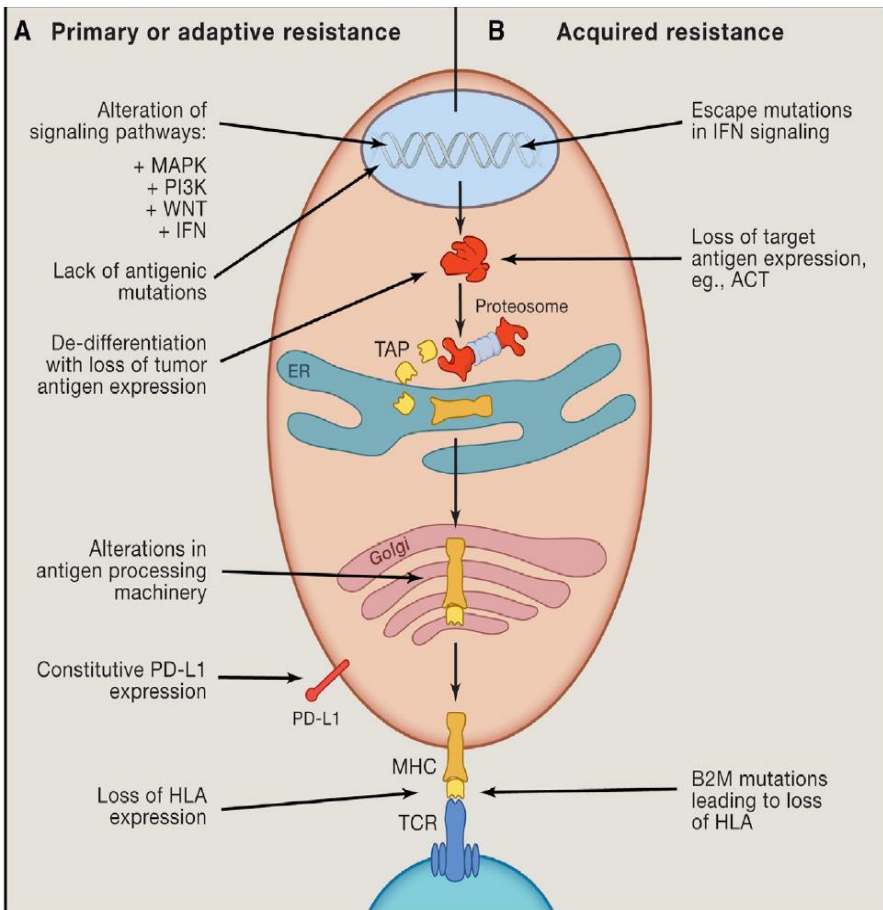
Tumor Antigens:

- Lack of tumor antigens.



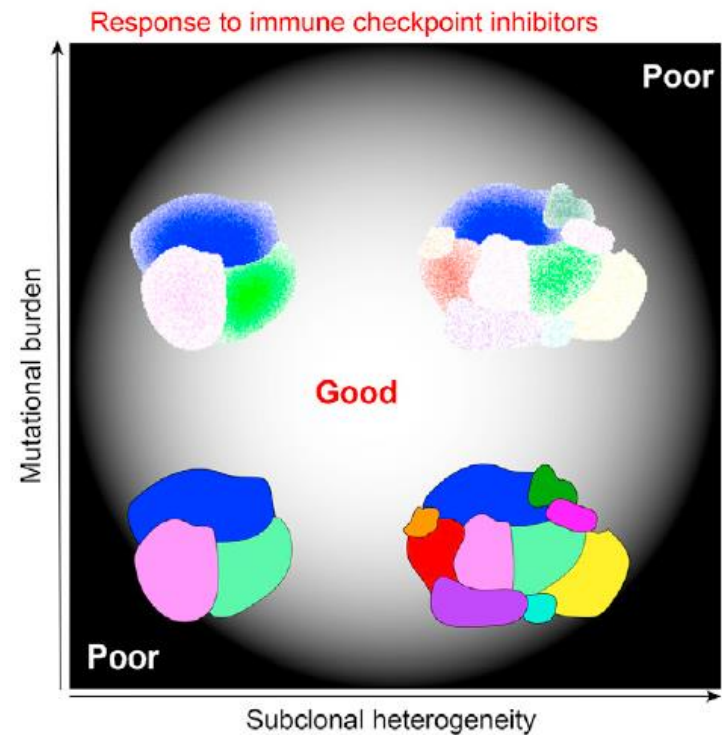
Intrinsic Resistance to ICB

Intrinsic Resistance



Tumor Antigens:

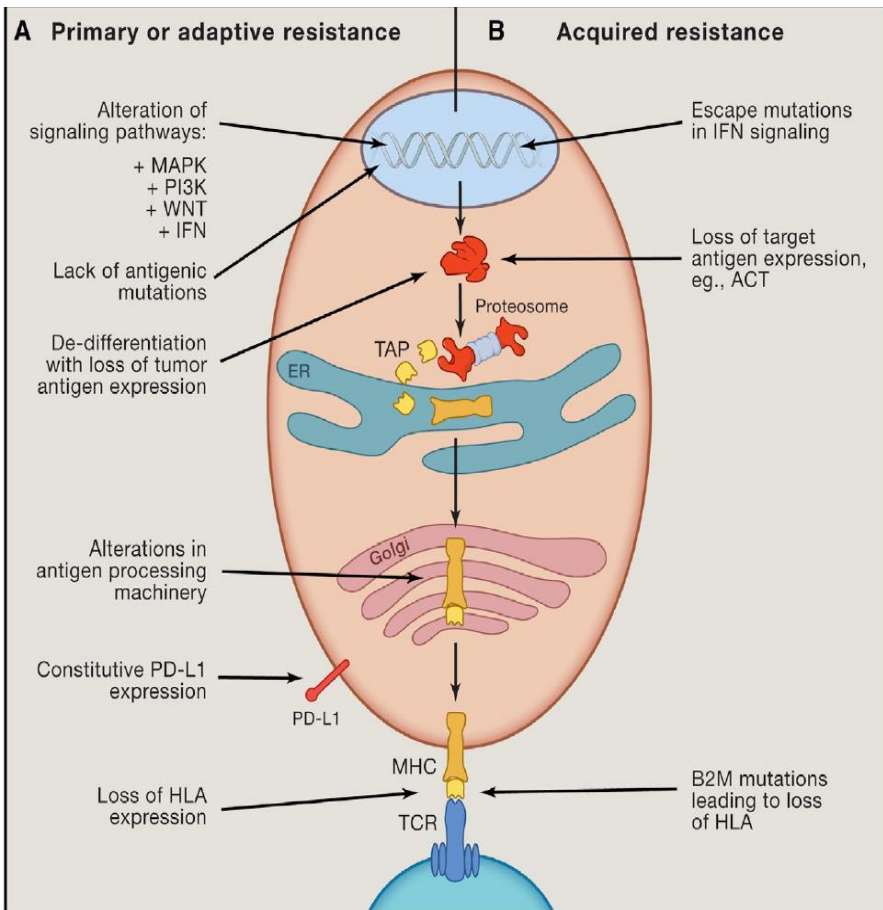
- Lack of tumor antigens.
- Antigen Intra-Tumor Heterogeneity.





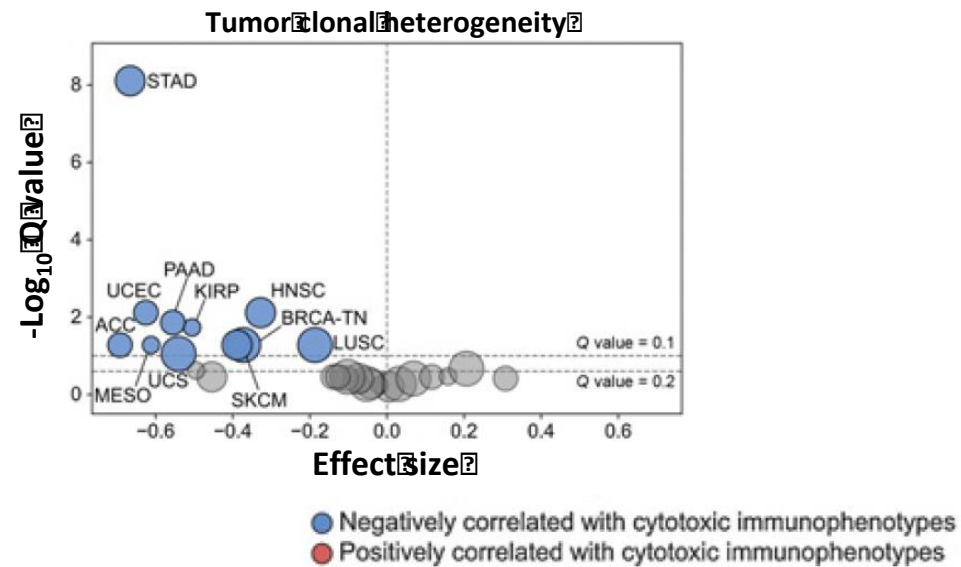
Intrinsic Resistance to ICB

Intrinsic Resistance



Tumor Antigens:

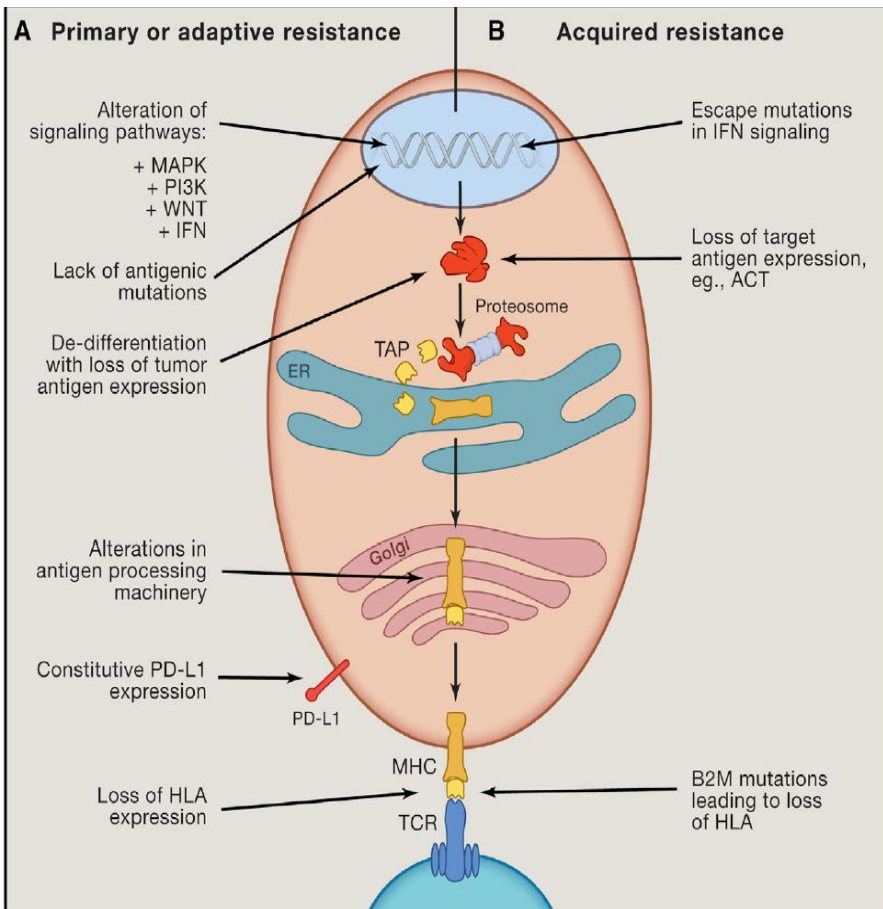
- Lack of tumor antigens.
- Antigen Intra-Tumor Heterogeneity.





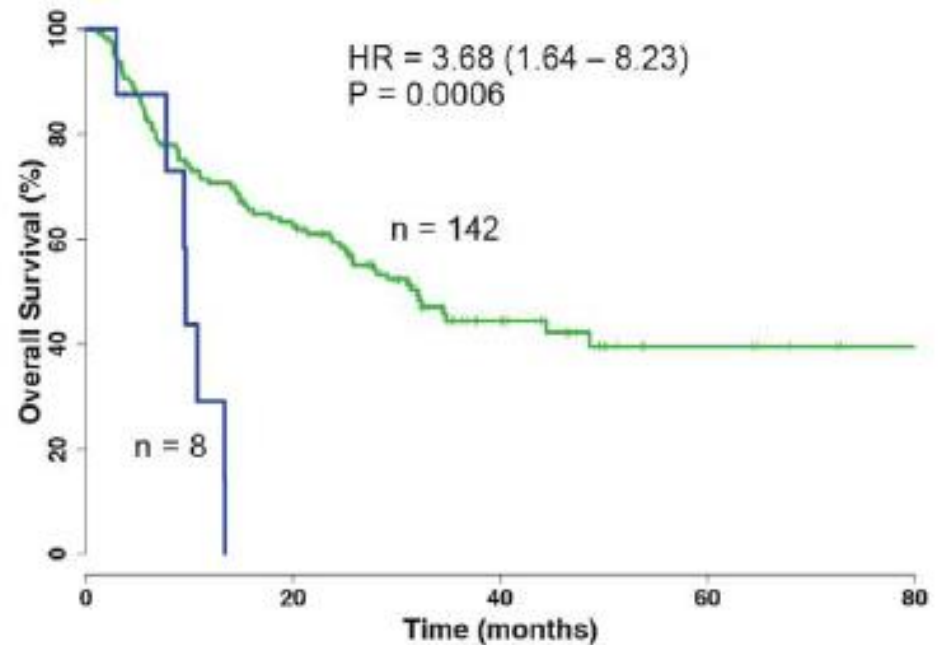
Intrinsic Resistance to ICB

Intrinsic Resistance



Antigen Presentation:

- Loss of HLA.
- B2M mutation.
- Others...

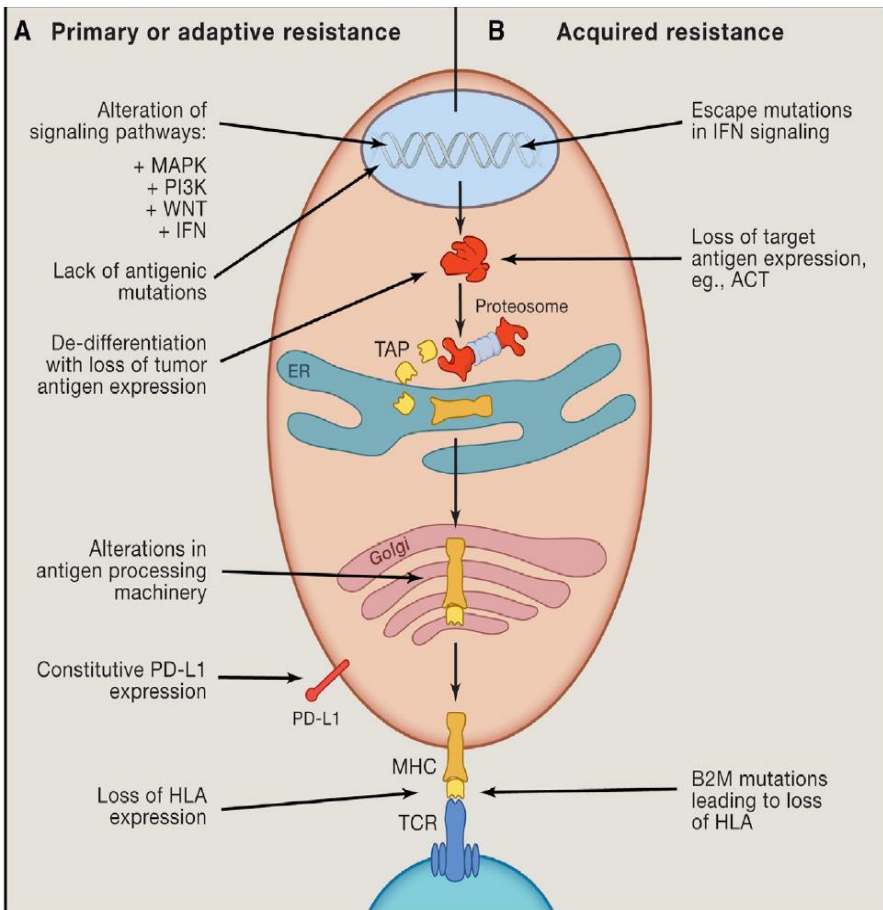


- Heterozygous at all loci, without LOH, and high mutation load
- Heterozygous at all loci, with LOH, and low mutation load



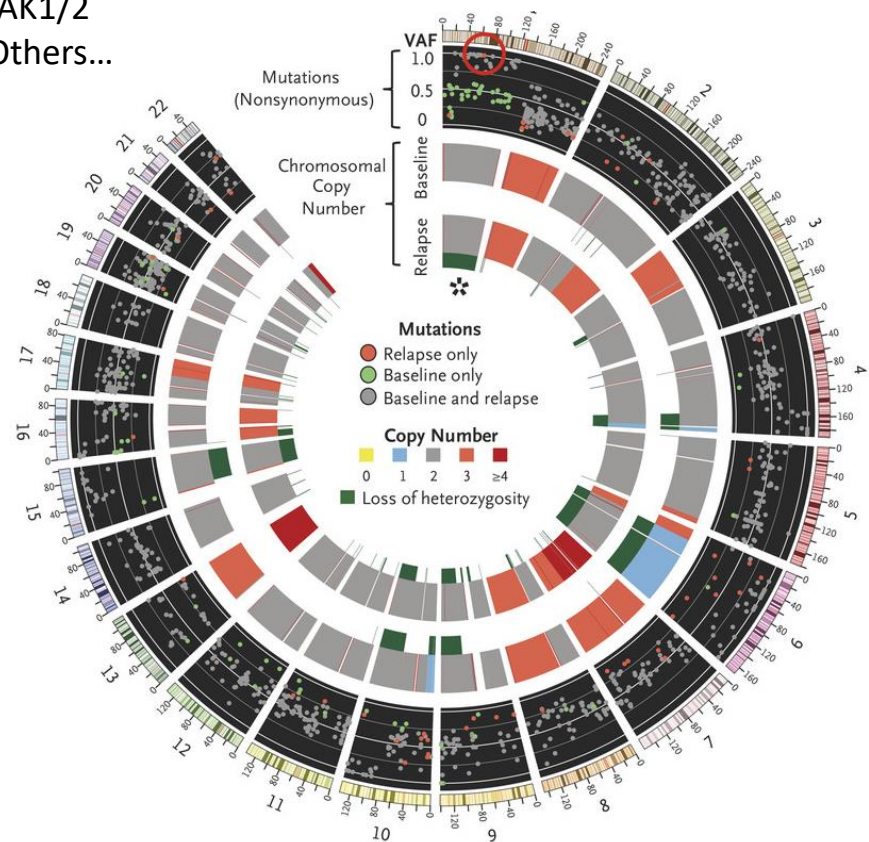
Intrinsic Resistance to ICB

Intrinsic Resistance



Interferon Signaling:

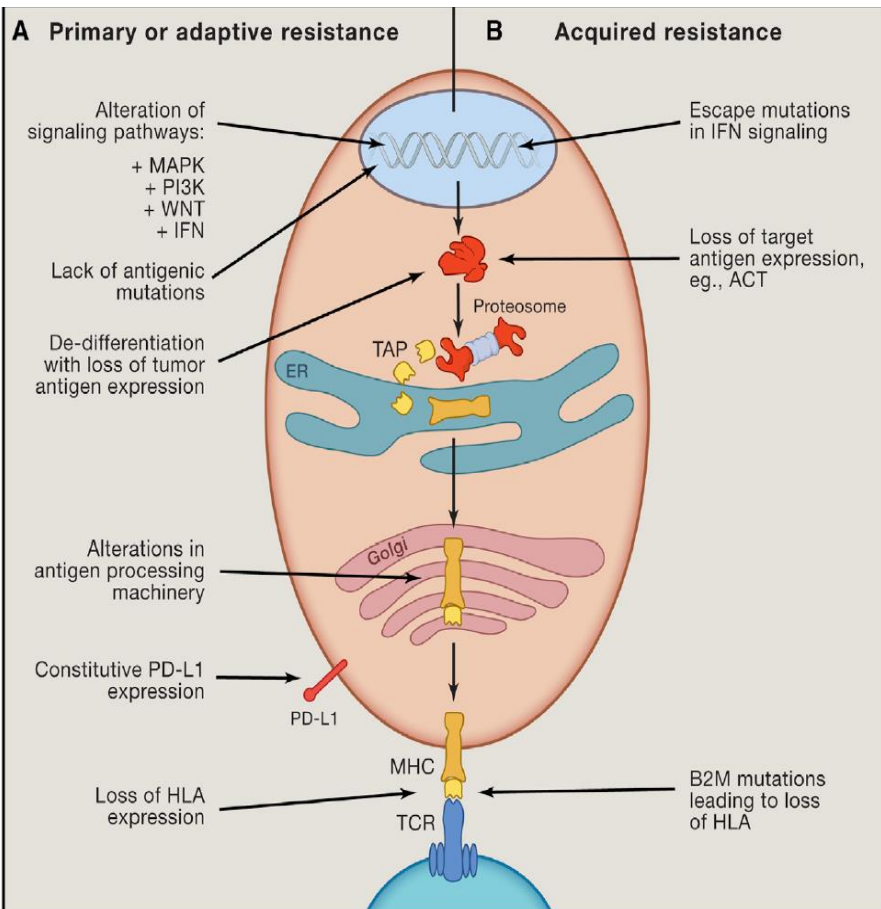
- JAK1/2
- Others...



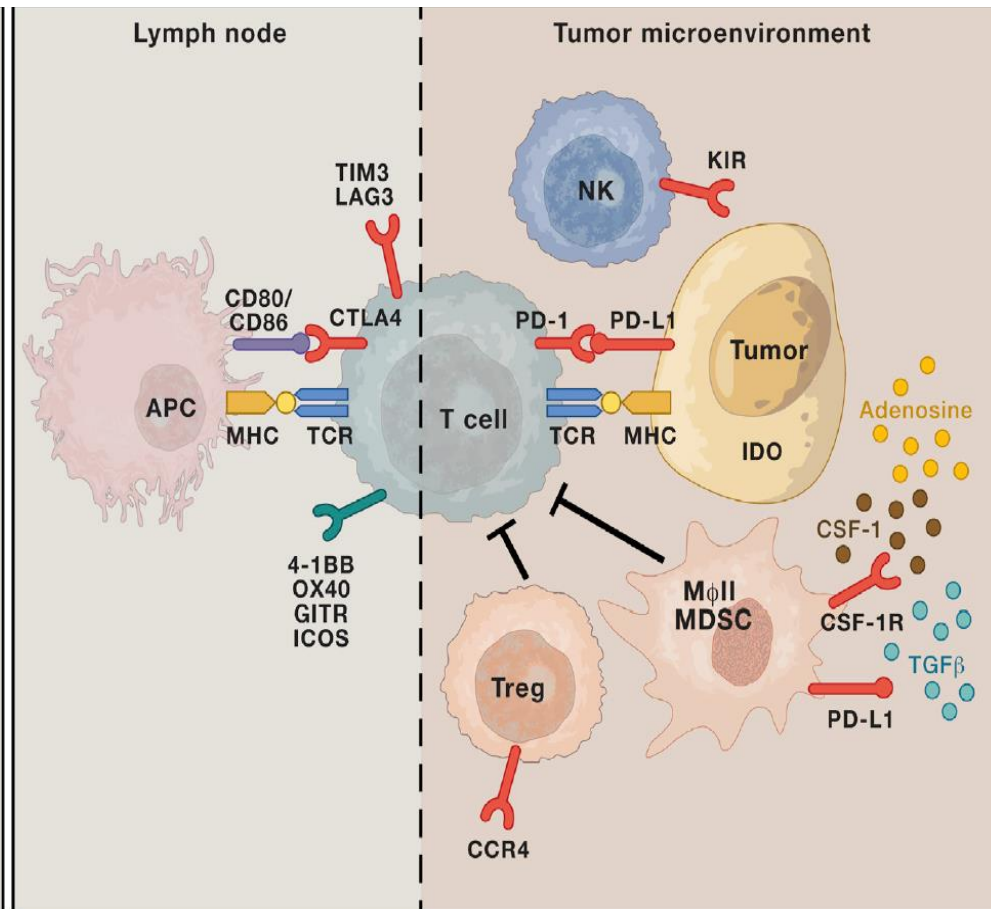


Extrinsic Resistance to ICB

Intrinsic Resistance



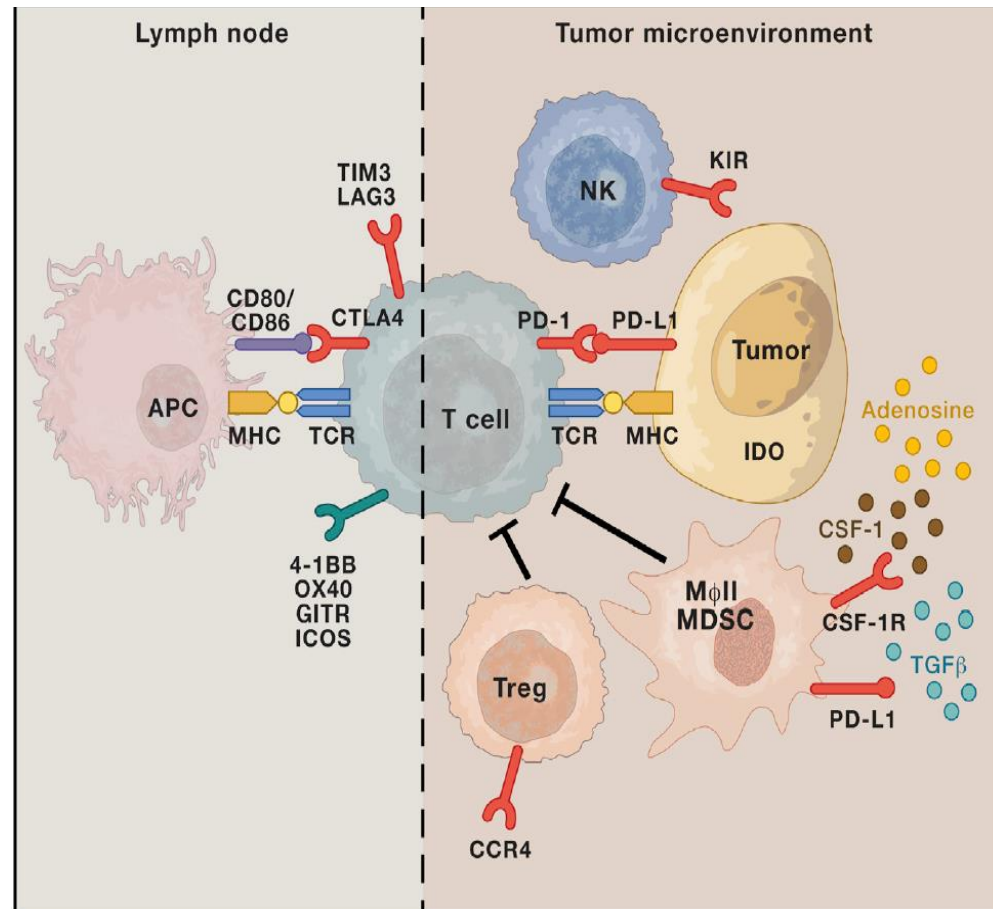
Extrinsic Resistance





Extrinsic Resistance to ICB

Extrinsic Resistance

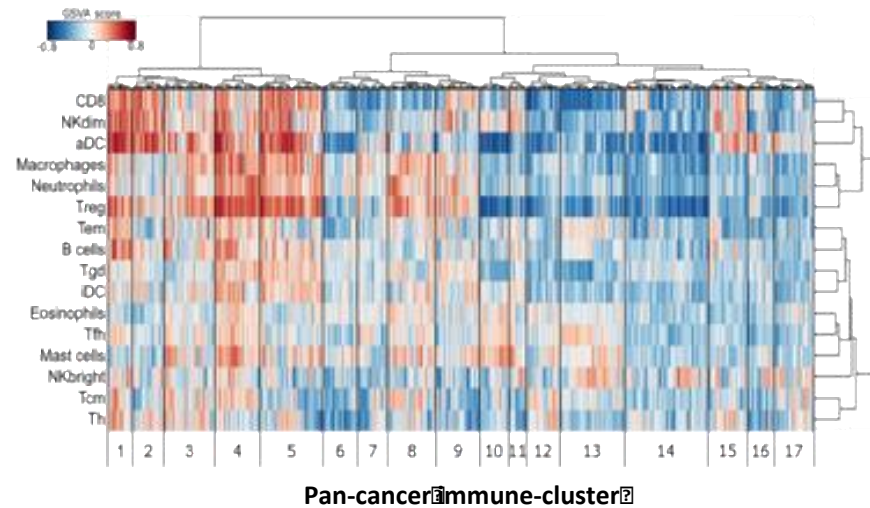




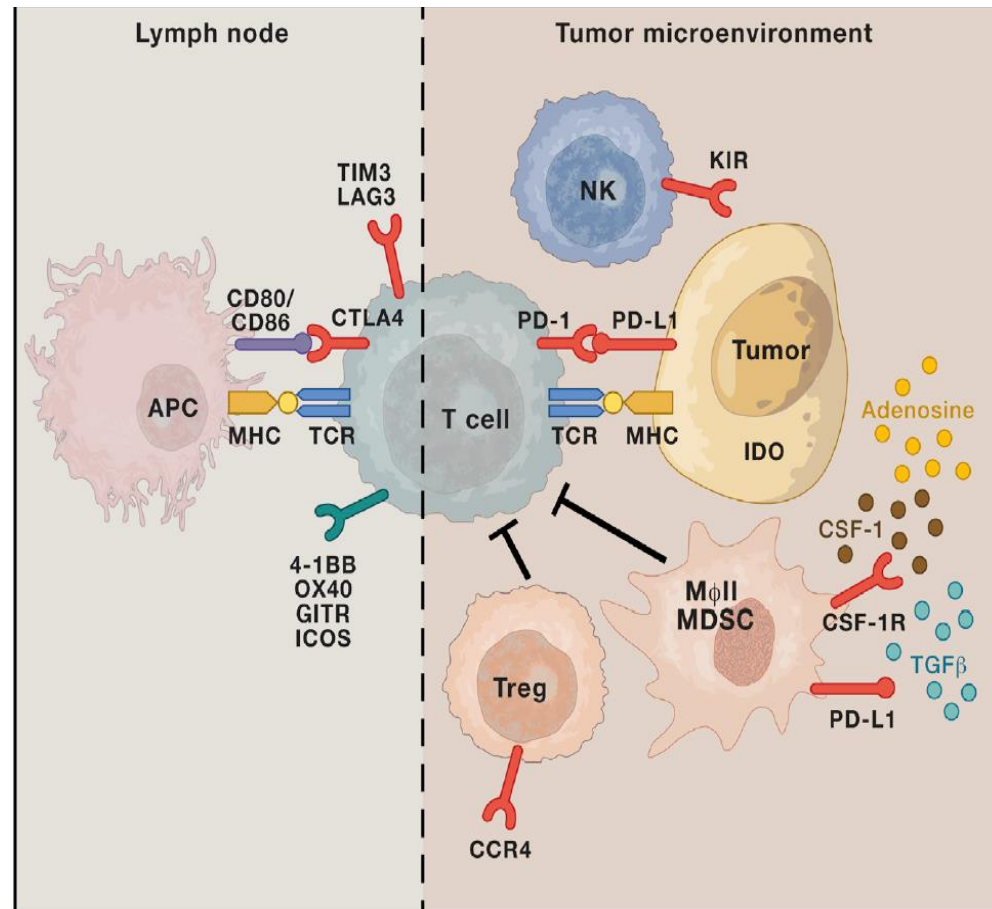
Extrinsic Resistance to ICB

Immune-suppressive cells:

- Tregs.
- MDSCs.
- TAMs.



Extrinsic Resistance

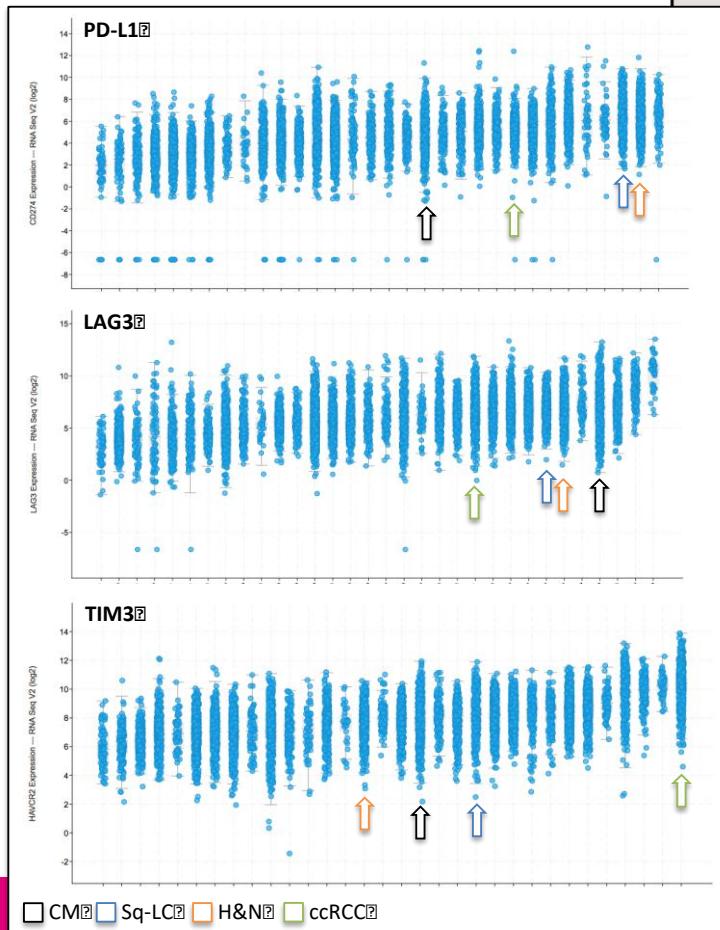




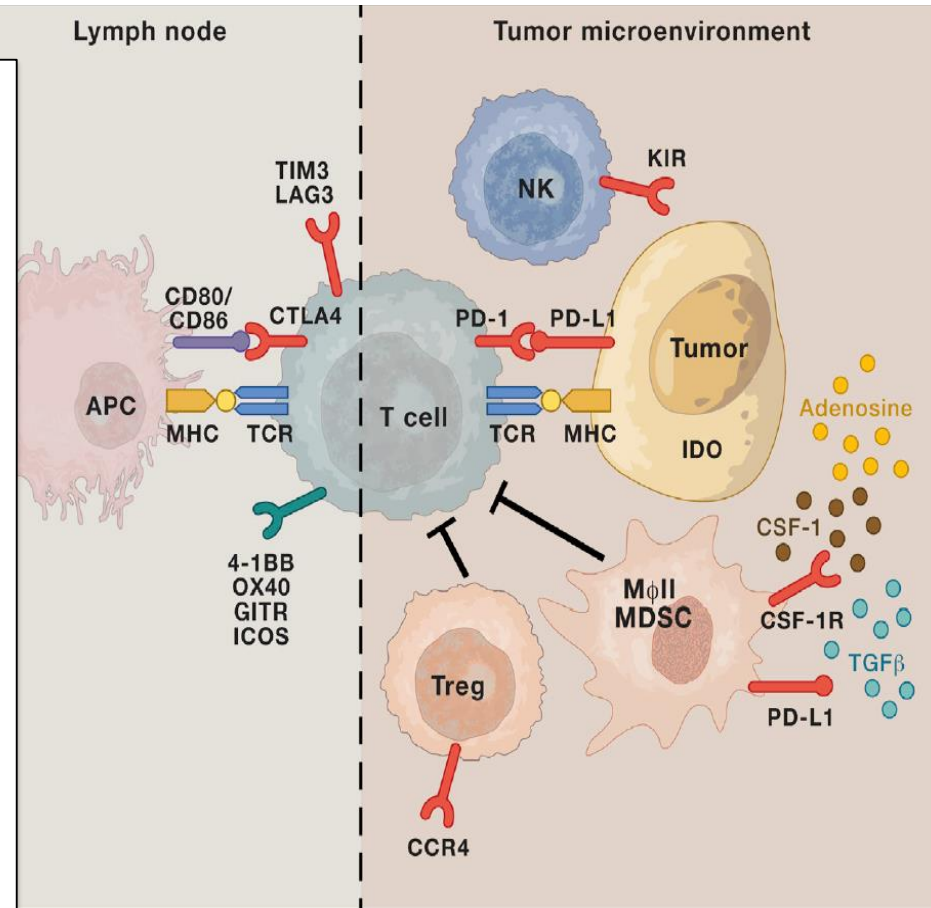
Extrinsic Resistance to ICB

Other Immune Check Point Regulators:

- LAG3.
- TIM3.
- Others.



Extrinsic Resistance

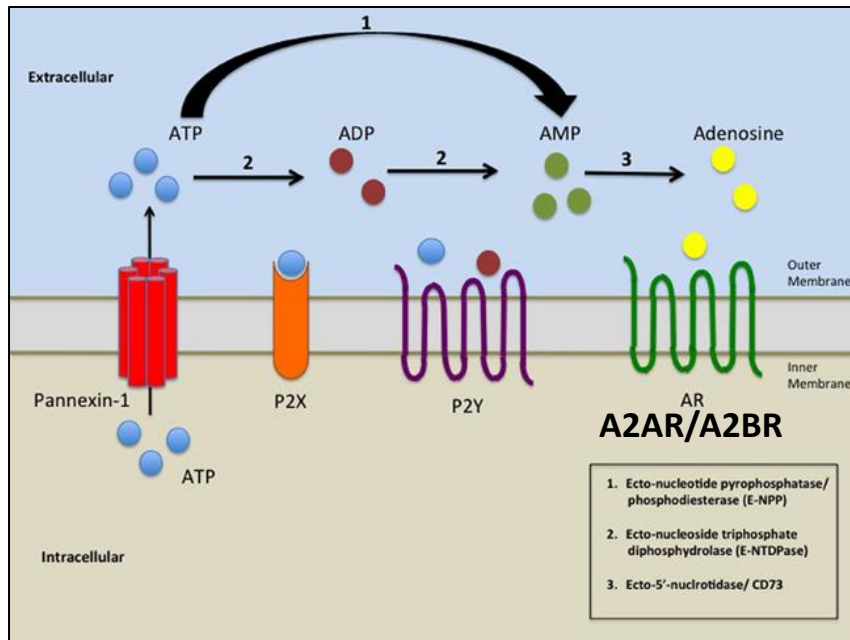




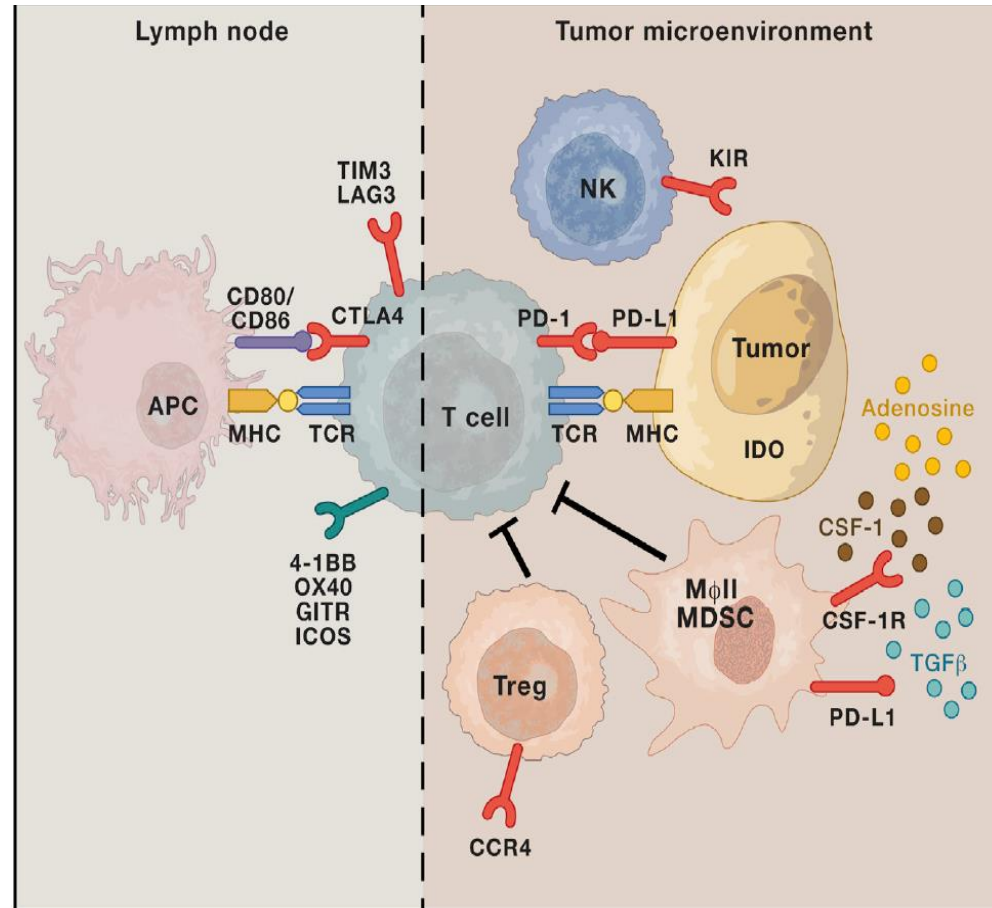
Extrinsic Resistance to ICB

Metabolism:

- Hypoxia.
- Acidosis.
- Glucose metabolism: Glucolytic vs OXPHOS.
- Depletion of essential amino acids: IDO1; ARG.
- Extracellular ATP metabolic pathway: Adenosine.



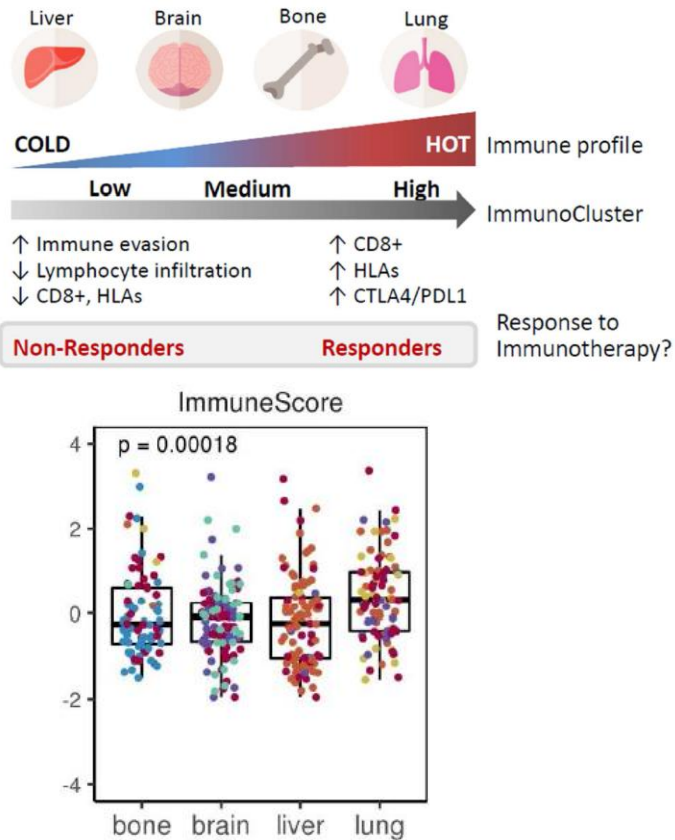
Extrinsic Resistance



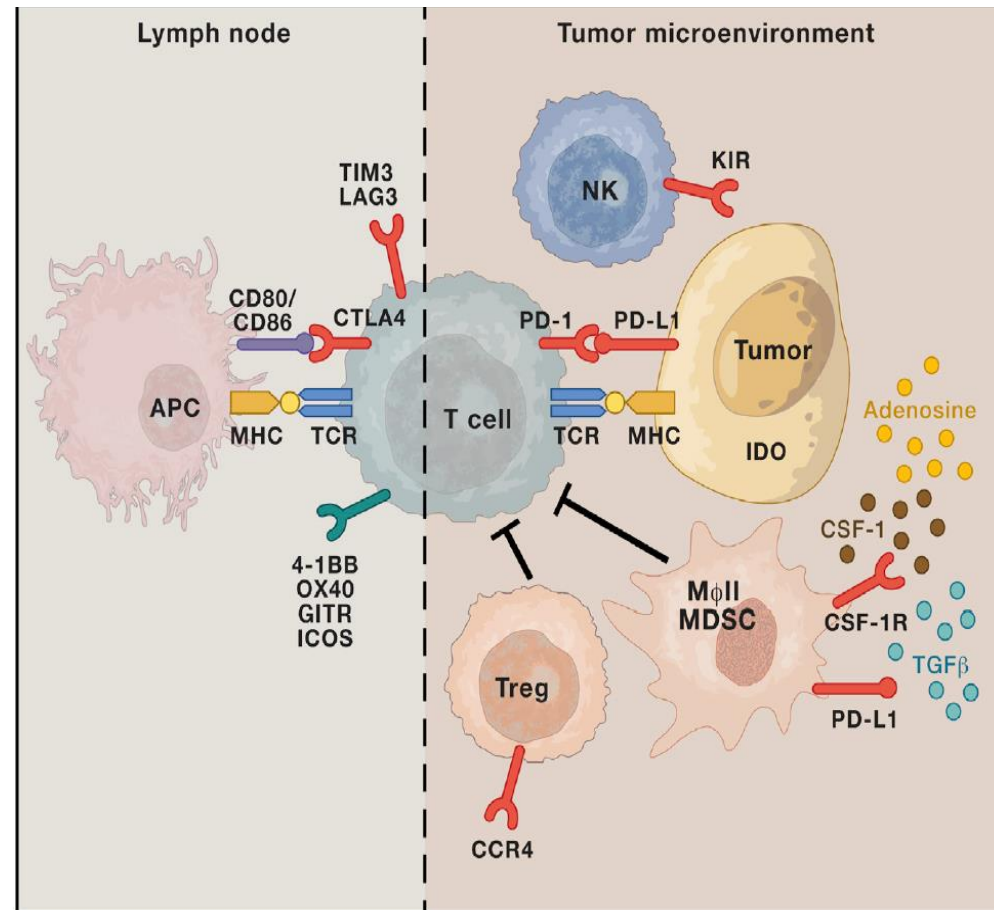


Extrinsic Resistance to ICB

Metastases location:



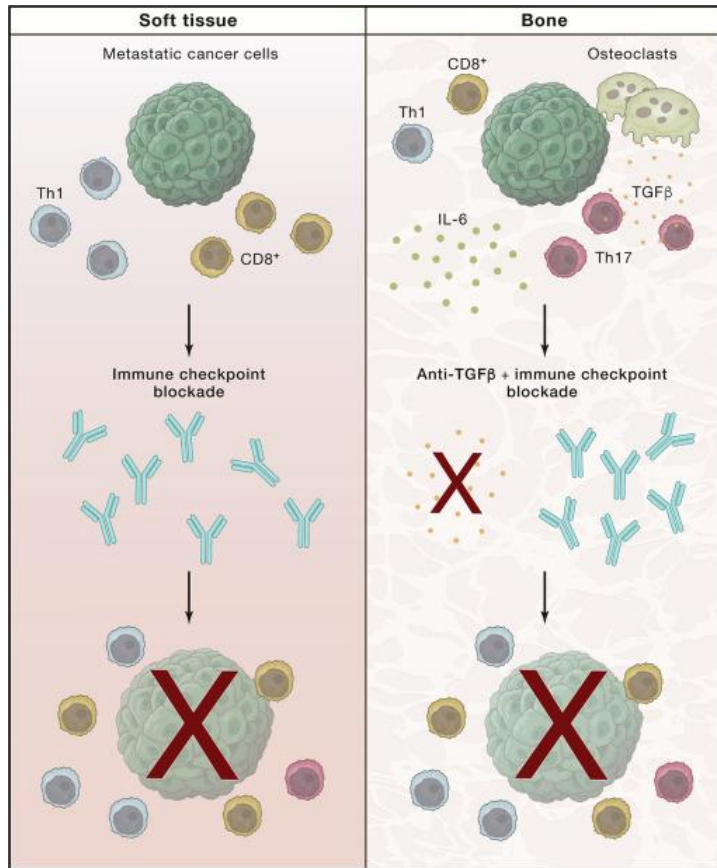
Extrinsic Resistance



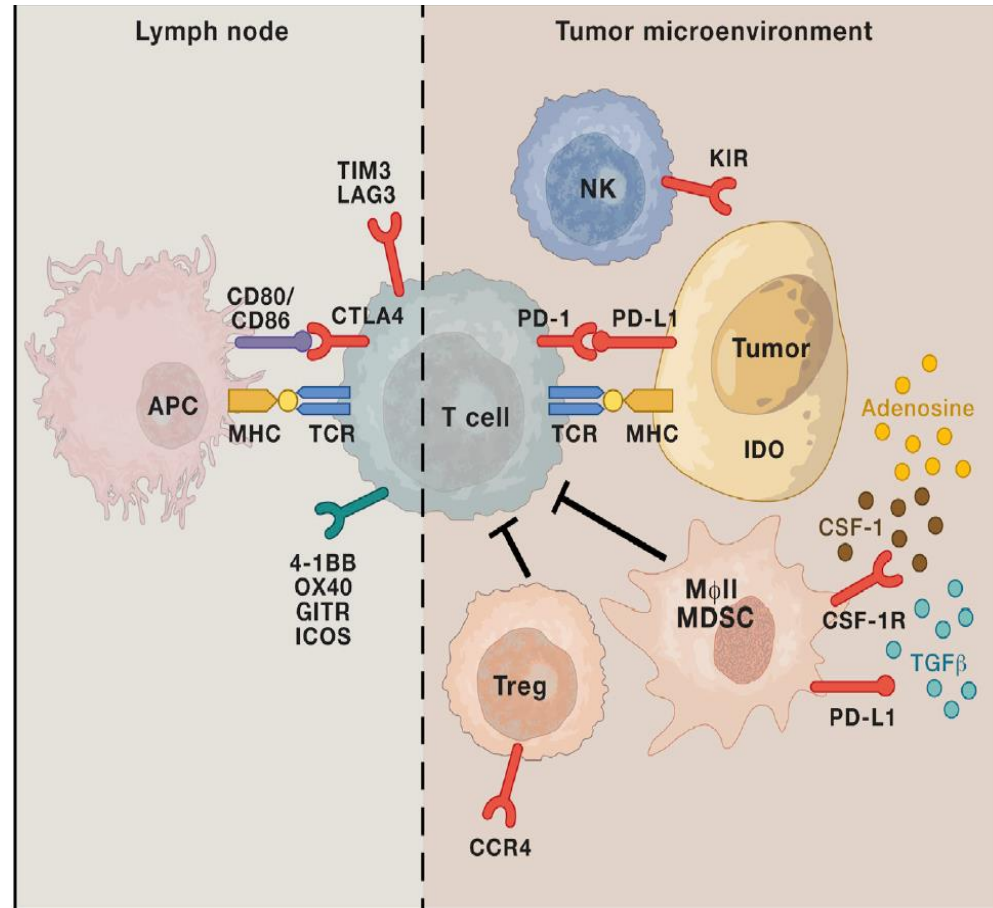


Extrinsic Resistance to ICB

Metastases location:

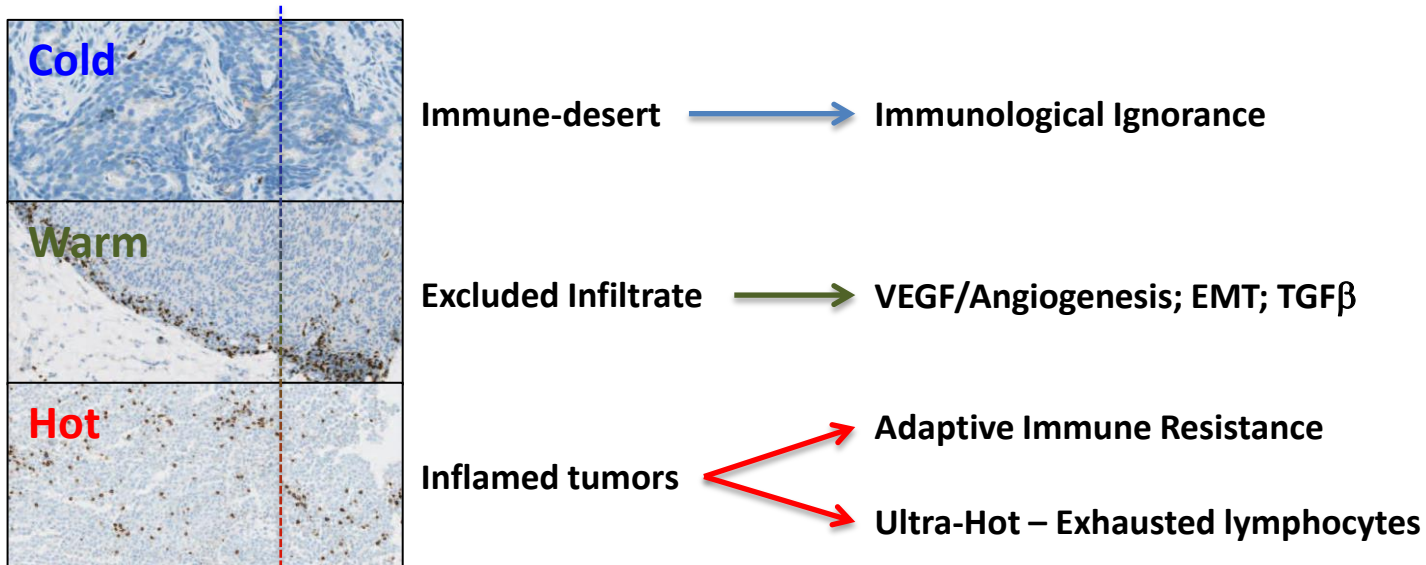


Extrinsic Resistance





Conclusions



No predominant phenotype in common tumors.

COLD: Advanced pathological stage; CN-alterations; Tumor clonal heterogeneity.

HOT: High mutation load; DNA repair defects; virus infection; APOBEC signatures.

*Different Combination
Approaches*