# Mechanisms of Resistance to Checkpoint Blockade

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# Disclosures

Personal financial interests

- Advisory board: AstraZeneca, Janssen, Syndax, Genentech, BMS, Merck, Eli Lilly, Celgene, Amgen
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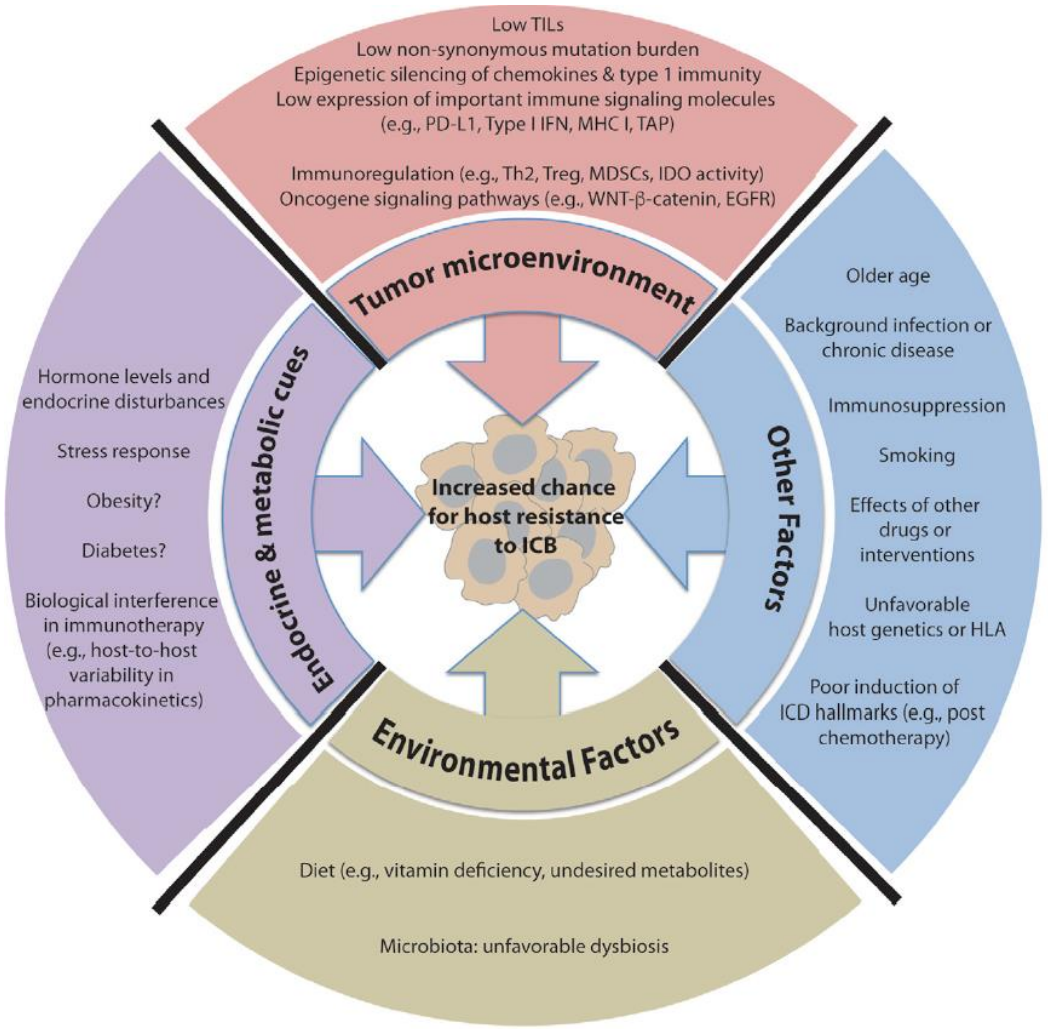
Institutional financial interests

- Clinical trial: Incyte, BMS, MedImmune/AstraZeneca, Janssen, FLXBio

# Types of Resistance

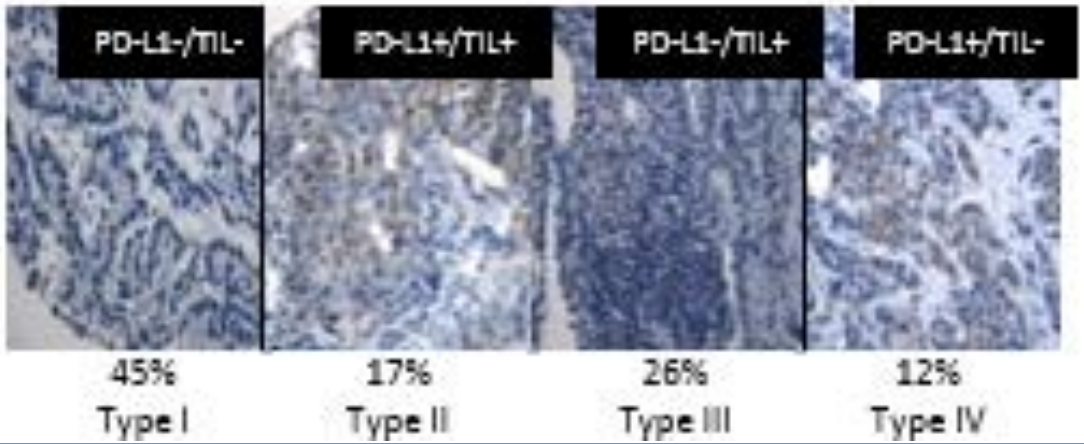
- Primary Resistance – No response
- Acquired Resistance – Progression of disease post response – typically defined as progression after 6 months of therapy

# Primary Resistance Mechanisms to Checkpoint Blockade




Adapted from Zitvogel L et al Immunity Review 2016

# Four Categories of Tumors Based on Presence of PD-L1 and TILS




**Proposed mechanisms associated with NSCLC resistance to anti-PD-1/B7-H1 therapy**

| Subgroup | | Type | Tumor Distribution | Possible Resistance Mechanism(s) | Analysis |
|---|---|---|---|---|---|
| | TIL | | | | |
| - | - | I | 45% | Poor priming of general T cell responses | Peripheral CD4+ and CD8+ T cell responses to autologous tumor cells |
| | | | | Lack of inflammatory cell recruitment | Chemokine expression in biopsy or FFPE samples |
| + | + | II | 17% | Incomplete PD-1/B7-H1 pathway blockade and activation of alternate immune suppressive pathways | CD80 expression on TILs, expression of alternate suppressive pathways in TME |
| - | + | III | 26% | Alternate immune suppressive pathways | Expression of select molecules in pathways with roles in evasion of NSCLC immunity |
| + | - | IV | 12% | Intrinsic induction of B7-H1 by oncogenes | Expression of molecules triggering aberrant signaling events |

Adapted from
L Chen, M Sznol, R Herbst

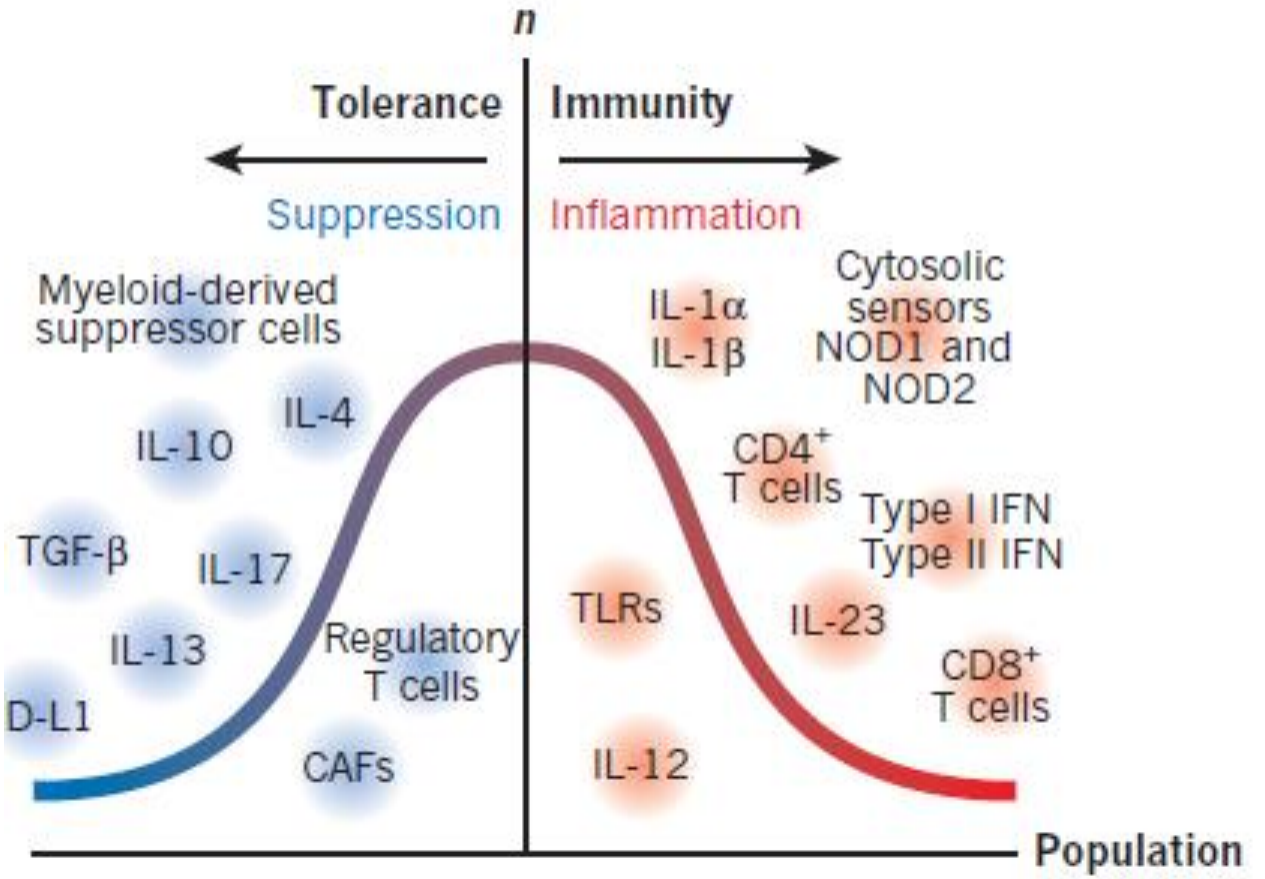
# Classification Based on T-cell Infiltration/PD-L1

| Type I: Adaptive Immune Resistance | Type II: Immunological Ignorance |
|---|---|
| • TIL+ | • TIL- |
| • PD-L1+ | • PD-L1- |

| Type III: Intrinsic Induction | Type IV: Tolerance |
|---|---|
| • TIL- | • TIL+ |
| • PD-L1+ | • PD-L1- |

Teng M, Ngiow SF, Ribas A, Smyth MJ. *Cancer Res*. 2015;75:2139-2145.

# Non-inflamed Tumors “COLD” versus Inflamed “HOT” Tumors

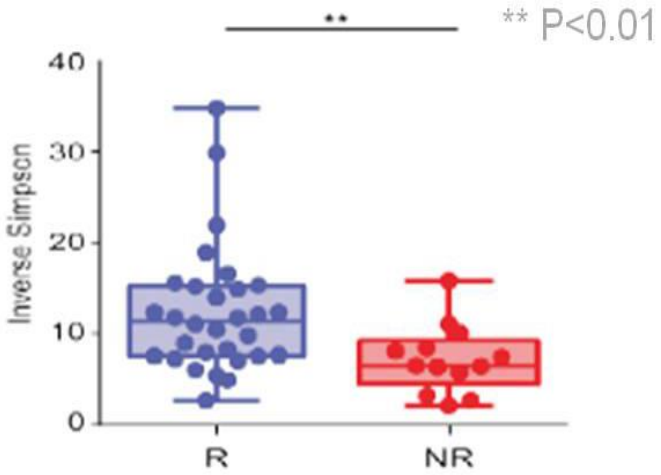



Chen D and Mellman I, Nature 2017

# Microbiome and Immunotherapy for Cancer

- Host factors such as the human microbiome may augment responses to immune checkpoint agents for cancer

Responders to PD-1 had higher gut microbiota diversity than non-responders.




Metastatic melanoma, PD-1 (n=45)

Gopalakrishnan et al, *Science* 2017

# **Microbiome and Immunotherapy**
In NSCLC

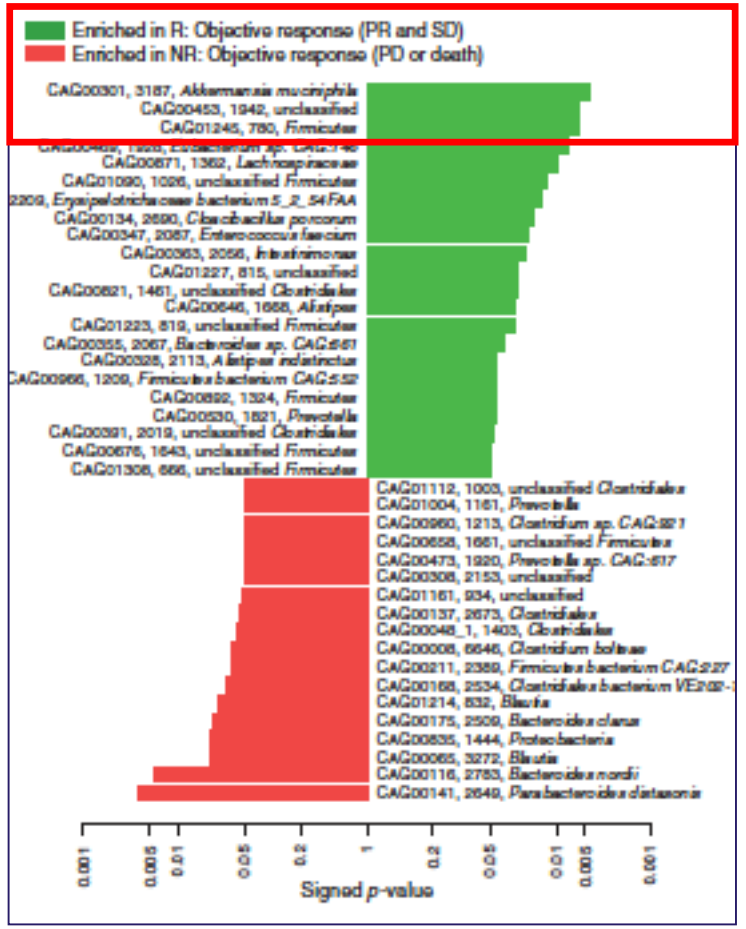
- Microbiota implicated in response may differ by tumor type
- Response may be modulated by prior antibiotic use

- NSCLC (n=60), RCC (n=40)

validation cohort NSCLC (n=27), RCC (n=26)

- **Beneficial (PFS at 3 months)**
- Richness
- s_Akkermansia mucinophila
- s_Enterococcus hirae

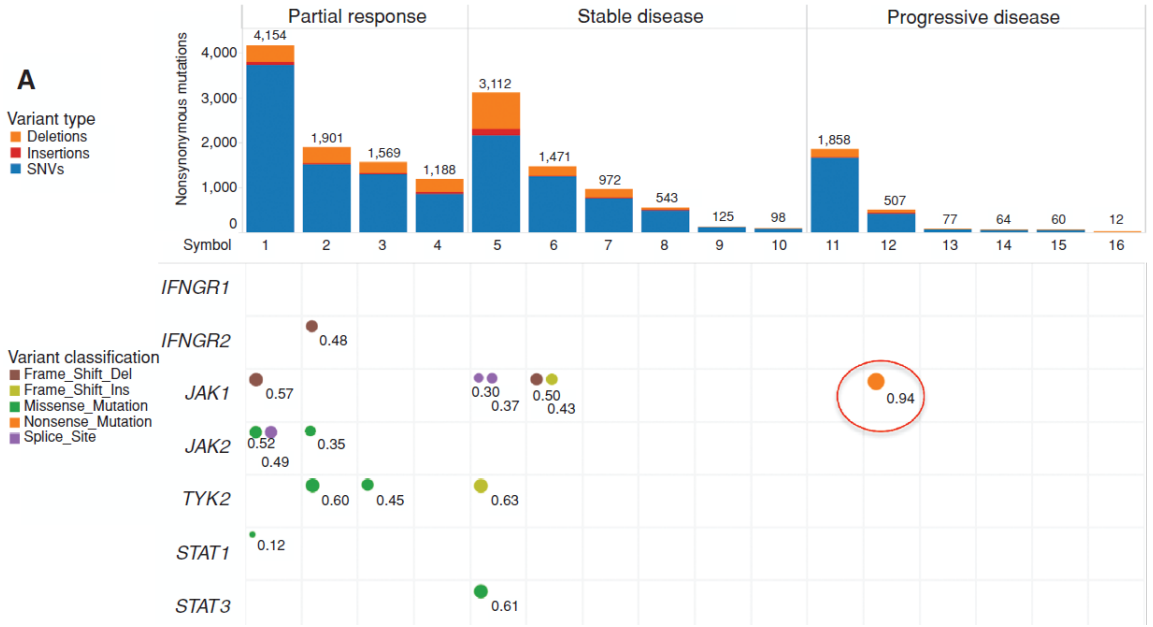
- **Detrimental (PFS at 3 months)**
- Antibiotics

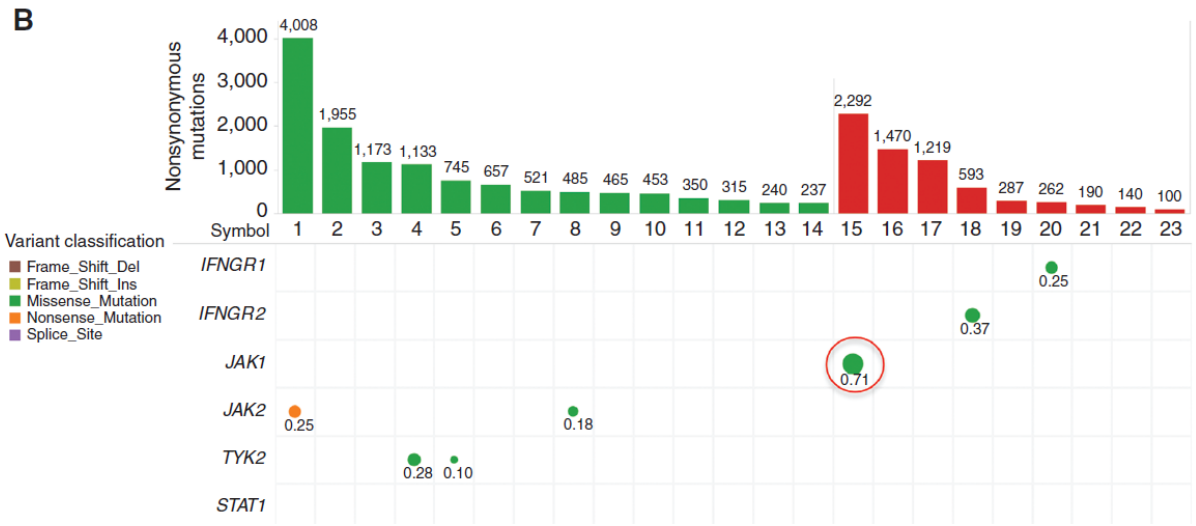



Routy et al, *Science* 2017

# Primary Resistance: Mutations

- Jak 1 and 2 mutations – Examples from melanoma and colon cancer

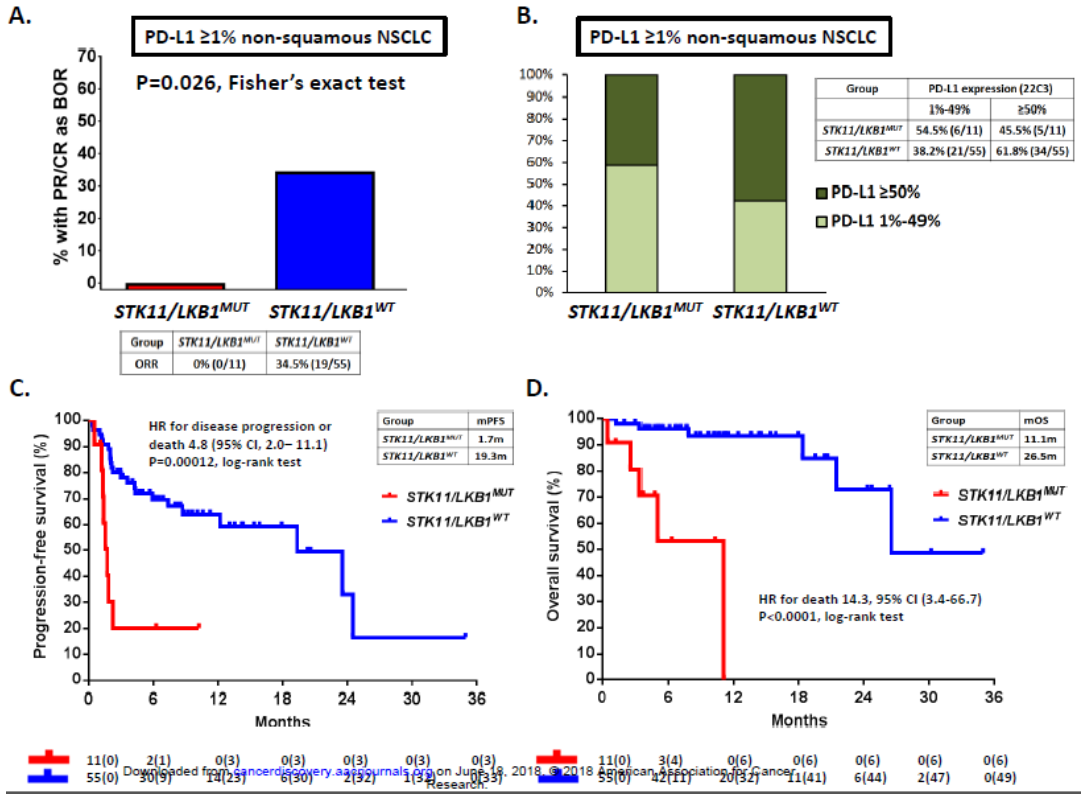


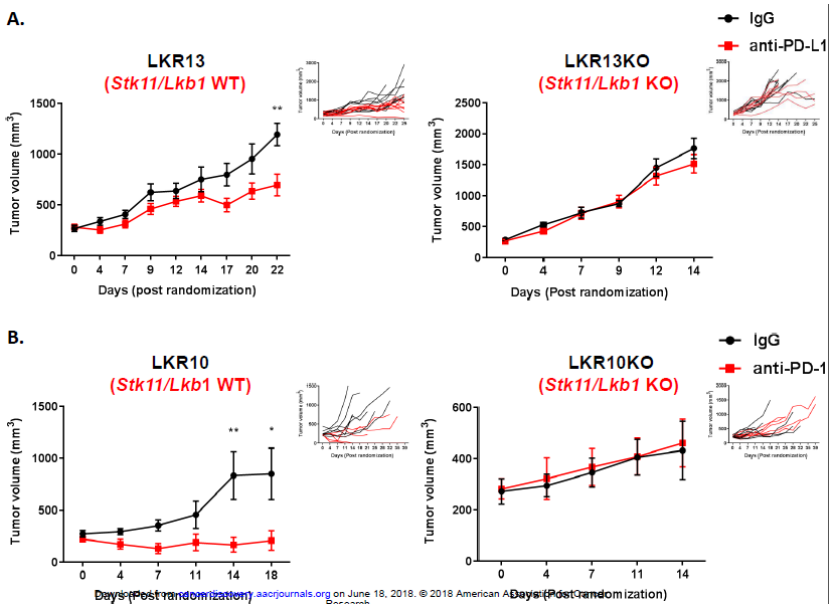

Shin DS et al Cancer Discovery 2016

# Primary Resistance: Mutations

- STK11 in KRAS mutated lung cancers





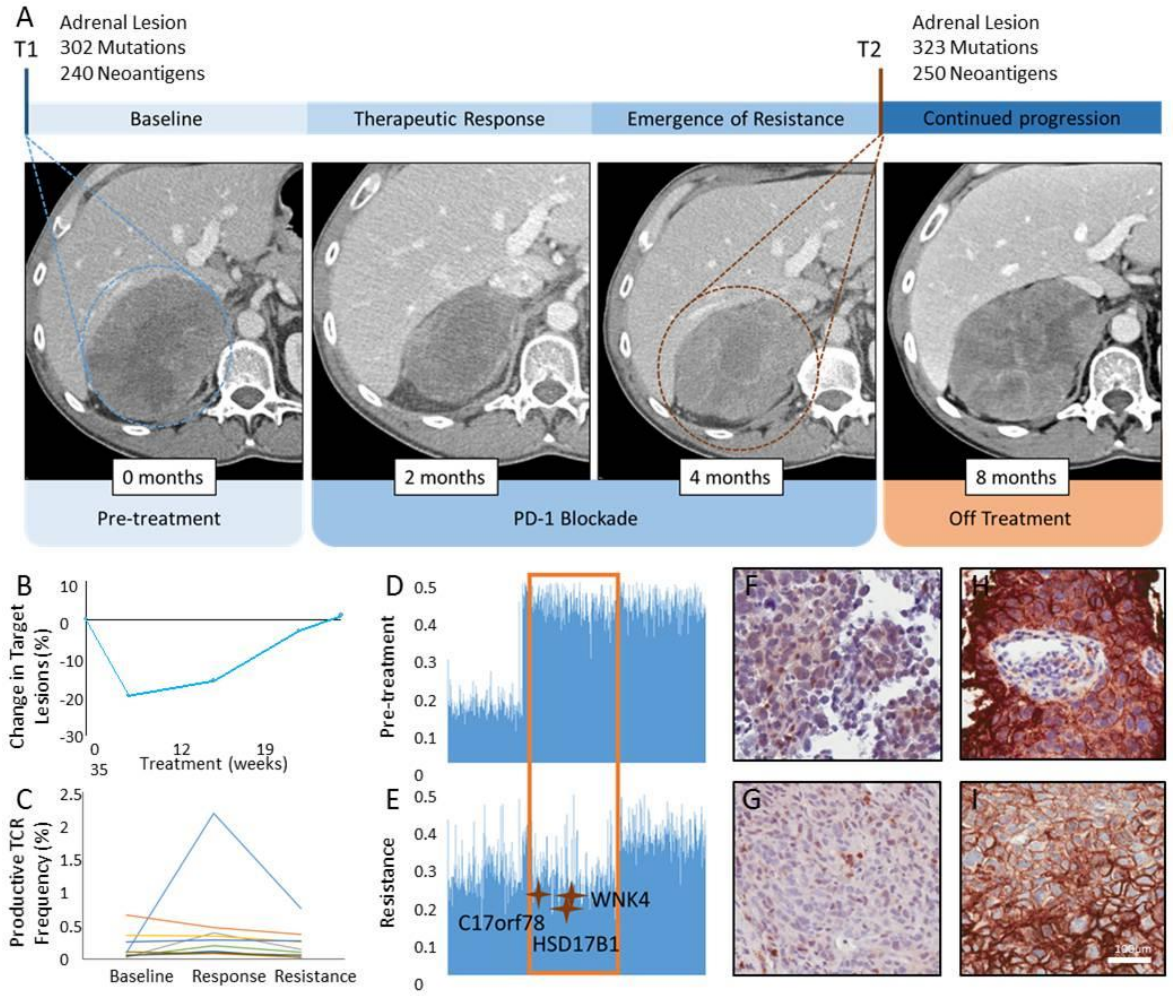






Skoulidis F et al Cancer Discov 2018

# Acquired Resistance:

## Mechanisms of Neoantigen Loss in Resistant Tumors




Anagnostou, Smith et al Cancer Discovery, 2017

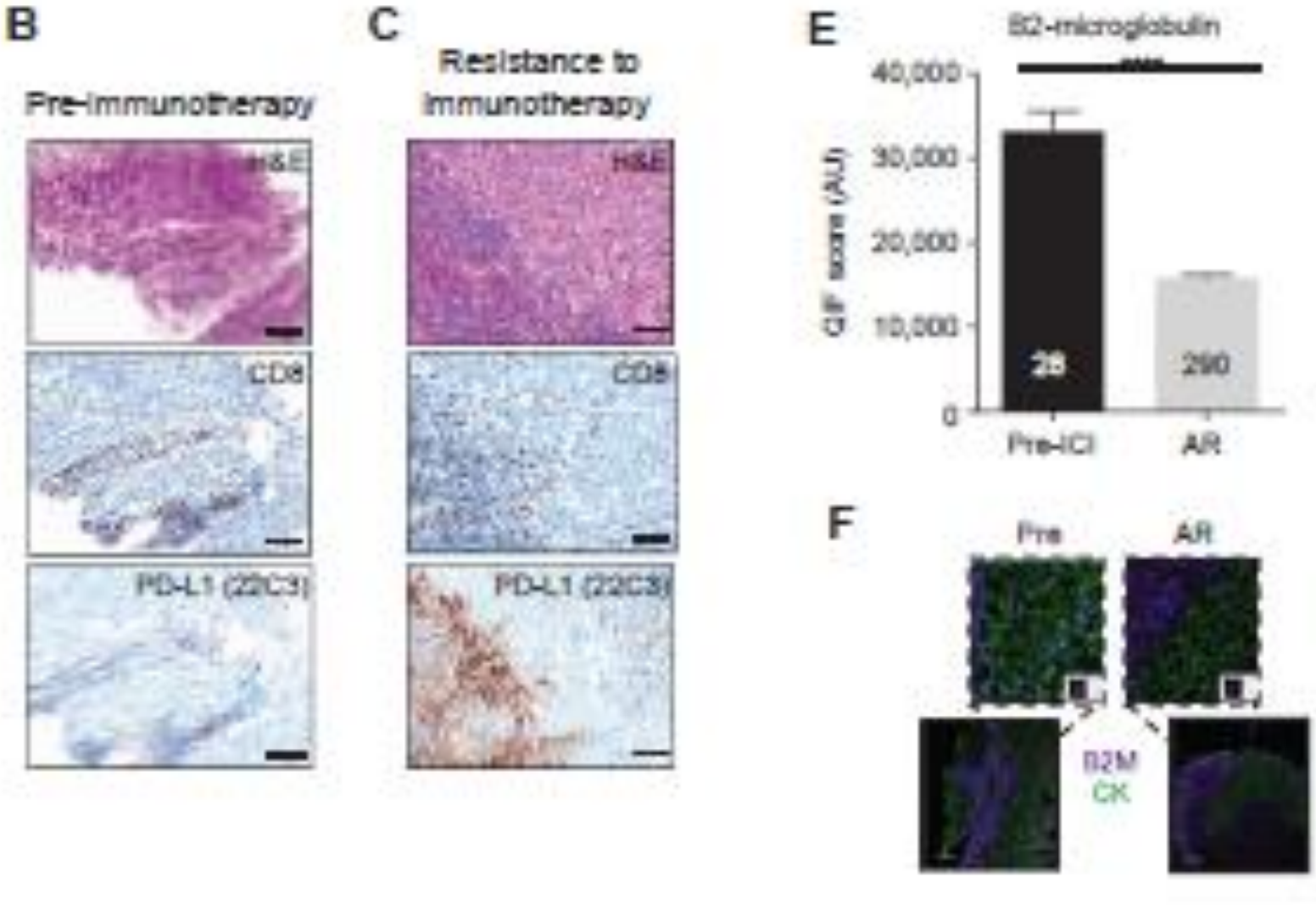
Two mechanisms of neoantigen loss

- The first is through the **immune elimination** of neoantigen-containing tumor cells that represent a **subset** of the tumor cell population, followed by subsequent outgrowth of the remaining cells.

- The second is through the **acquisition** of one or more **genetic events** in a tumor cell that results in neoantigen loss, followed by selection and expansion of the resistant clone.

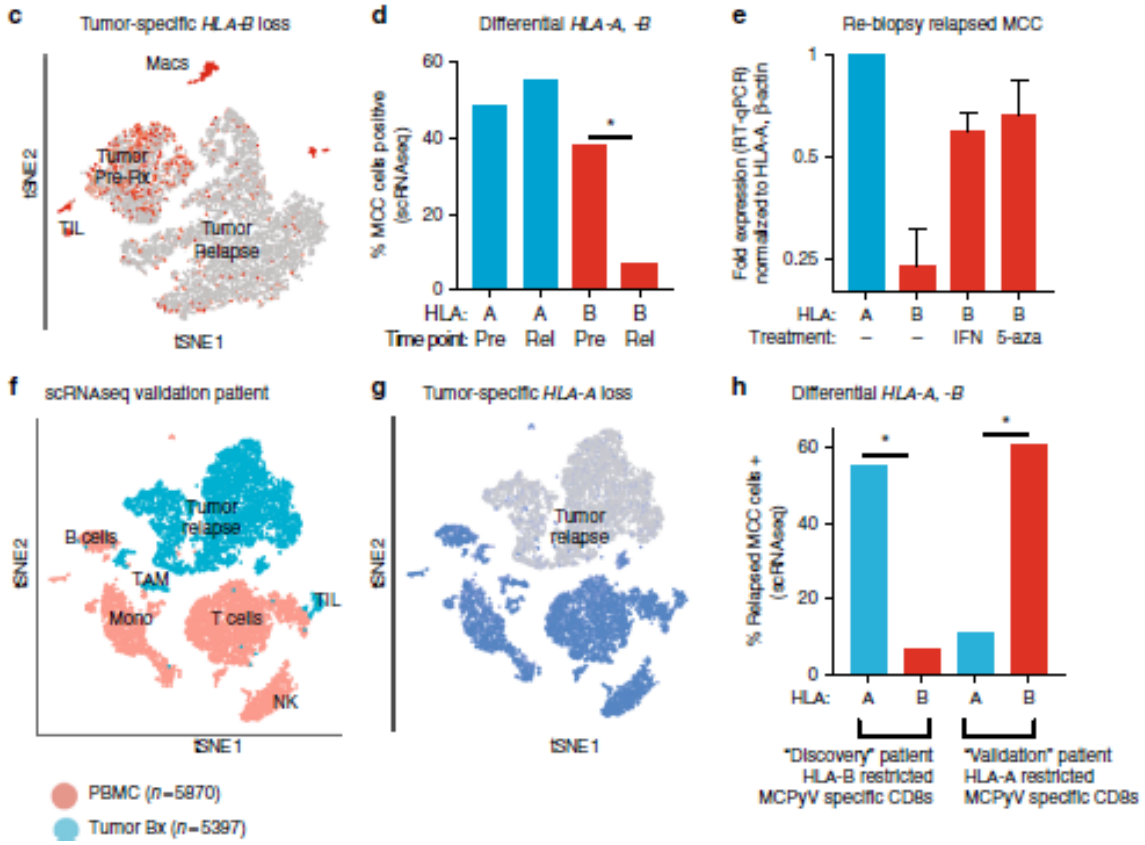
**Slide provided by Dr. Anagnostou**

# Acquired Resistance: B2-microglobulin loss/HLA Class 1 Antigen Processing




Gettinger S Cancer Discovery 2017

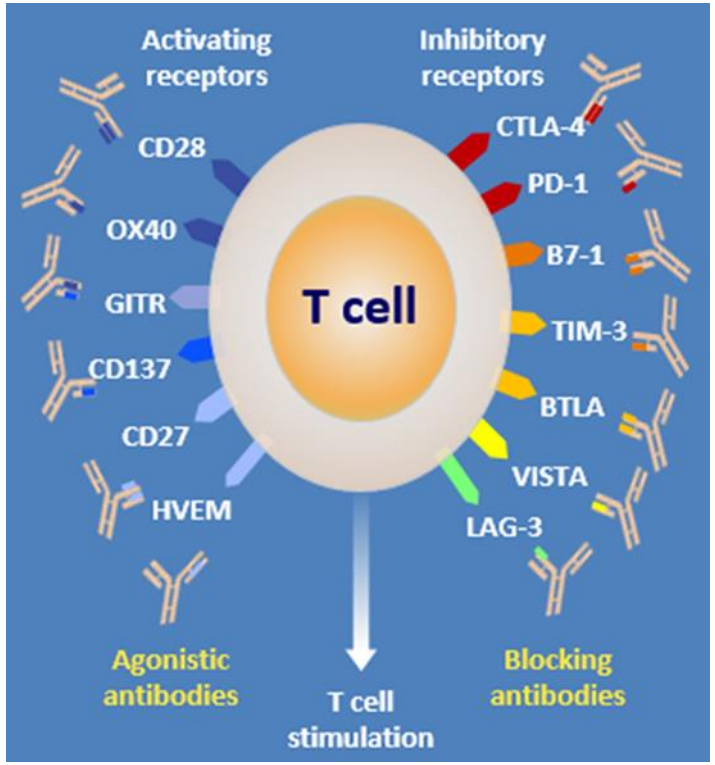
# Acquired Resistance: Class 1 HLA Loss




Paulson KG et al Nature Comm 2018

# Acquired Resistance: Upregulation of Checkpoint Pathways

- LAG3
- TIGIT
- PD-L2
- CTLA4




Gettinger S Cancer Discovery 2017

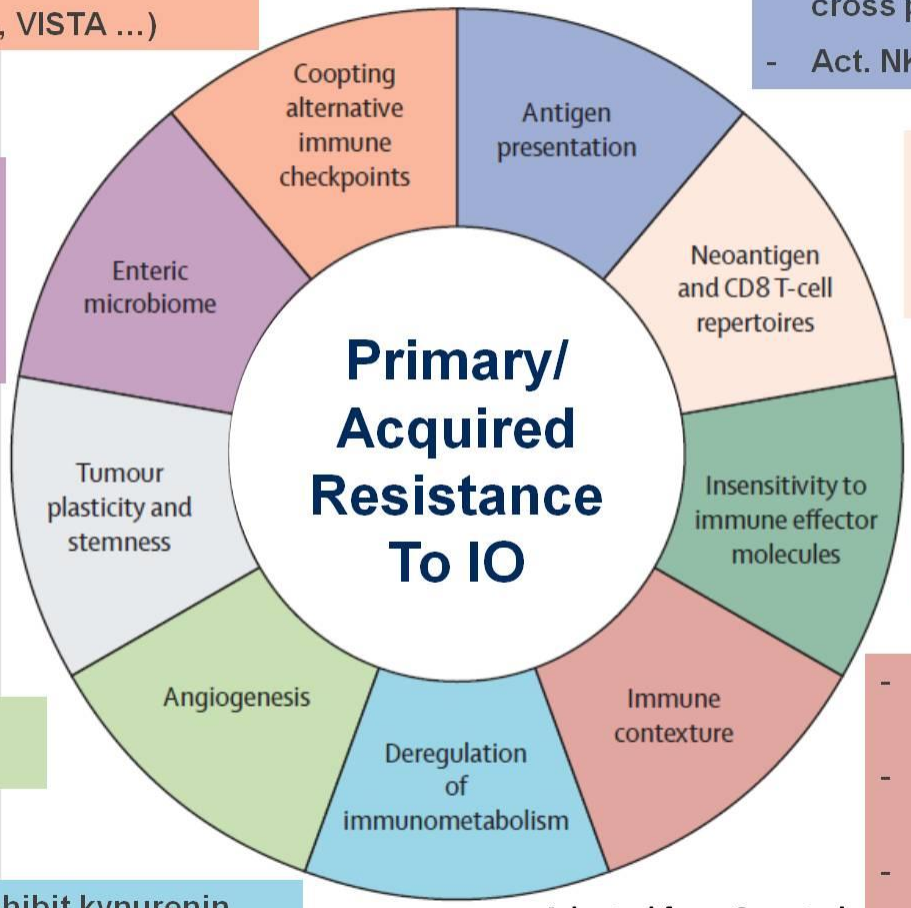
Blockade of multiple T cell inhibitory molecules (e.g anti- LAG3, TIM3, VISTA …)

- Abx that dec gram+, but not gram – Bacteriodales and urkholderiales (Vancomycin)
- Probiotics (Bifidobactrium spp

- TNF signaling Inhibitors
- EMT Inhibitors

Target Neovasculature- e.g VEGF/R antagonists

Modulation of glycolysis, inhibit kynurenin (IDO1 blockade) and adenosinergic pathways




Adapted from Syn et al Lancet Oncol 2016

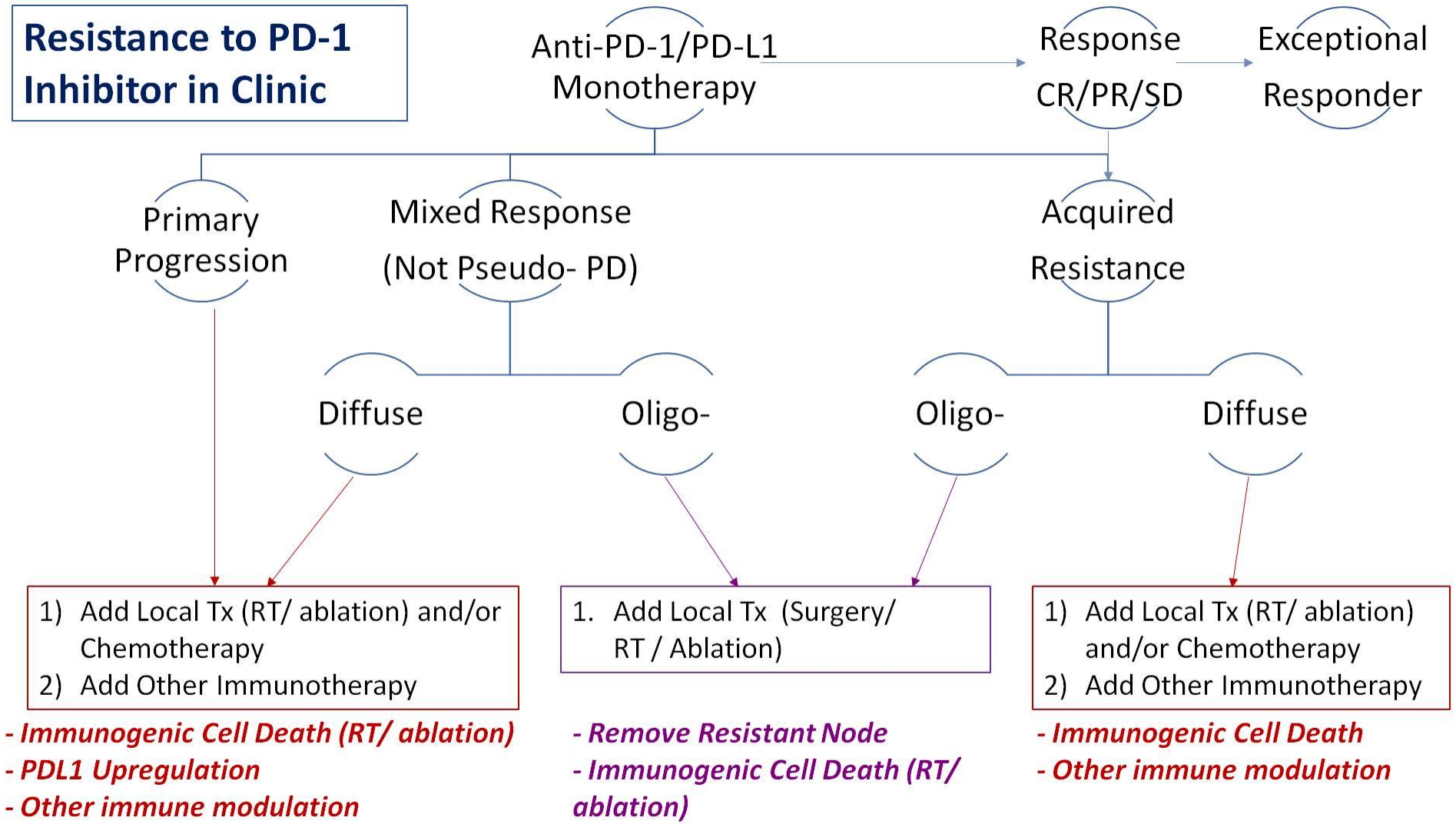
- Target TME myeloid cells (bystander elimination of myeloid cells that cross present tumor epitopes)
- Act. NK cells Harness MHC class II

- Vaccine/ Radiation/ Cytotoxic Chemotherapy
- Epigenetic Tx to induce NeoAg Re-expression

- Stimulator of interferon genes agonists
- Oncolytic viruses that replicate in cells with defective IFN signalling

- Prime intratumoral T cell infiltration (e.g Cytoxan)
- Epigentic Tx (reverese T cell exhaustion/ memory)
- Inhibit immunsuppressive cells (e.g cabozantibin- MDSC, also Treg, TAM)

Slide adapted from Scott Gettinger ASCO-SITC 2018

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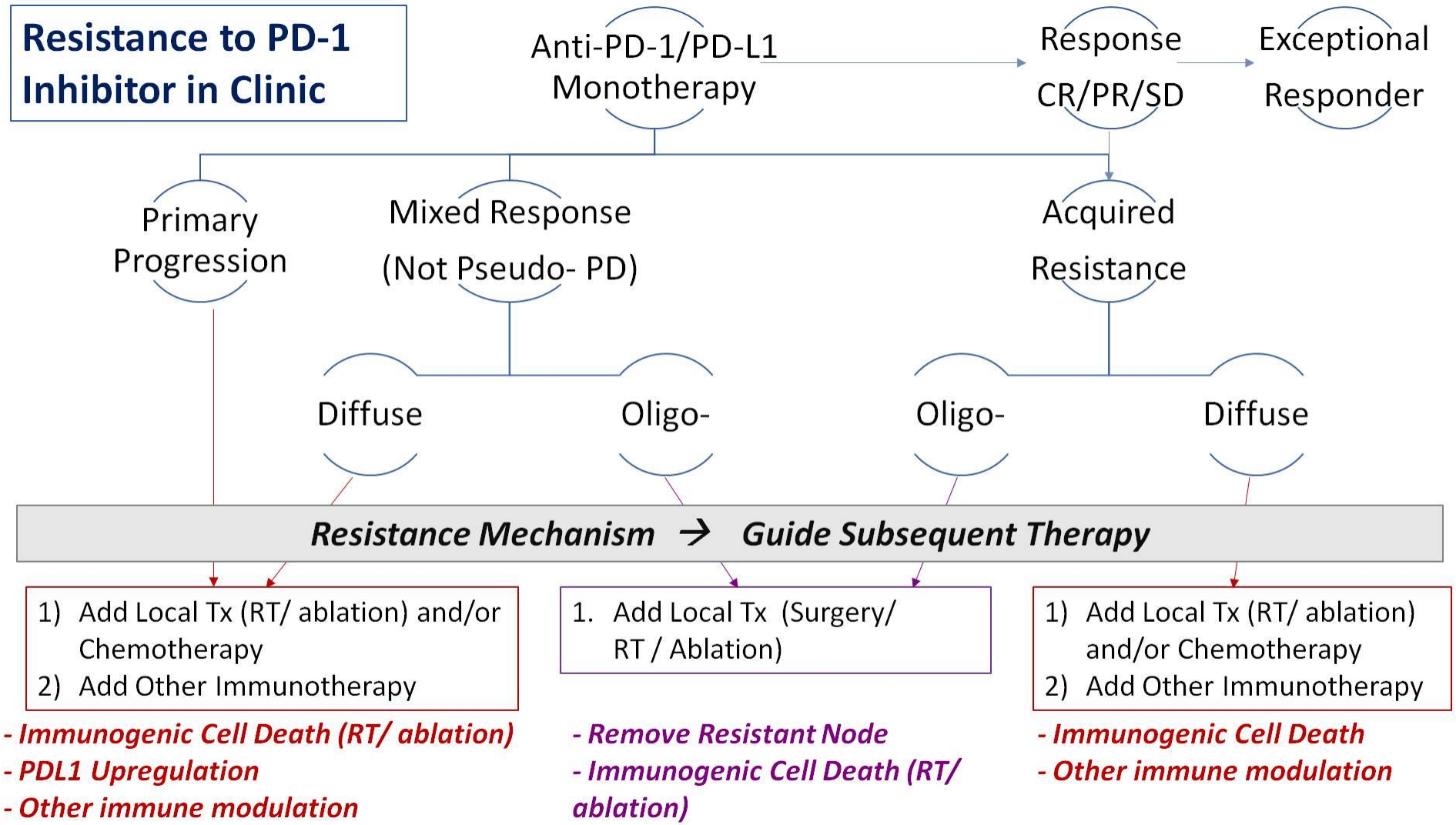


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