Mechanisms of Resistance to Checkpoint Blockade

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Disclosures

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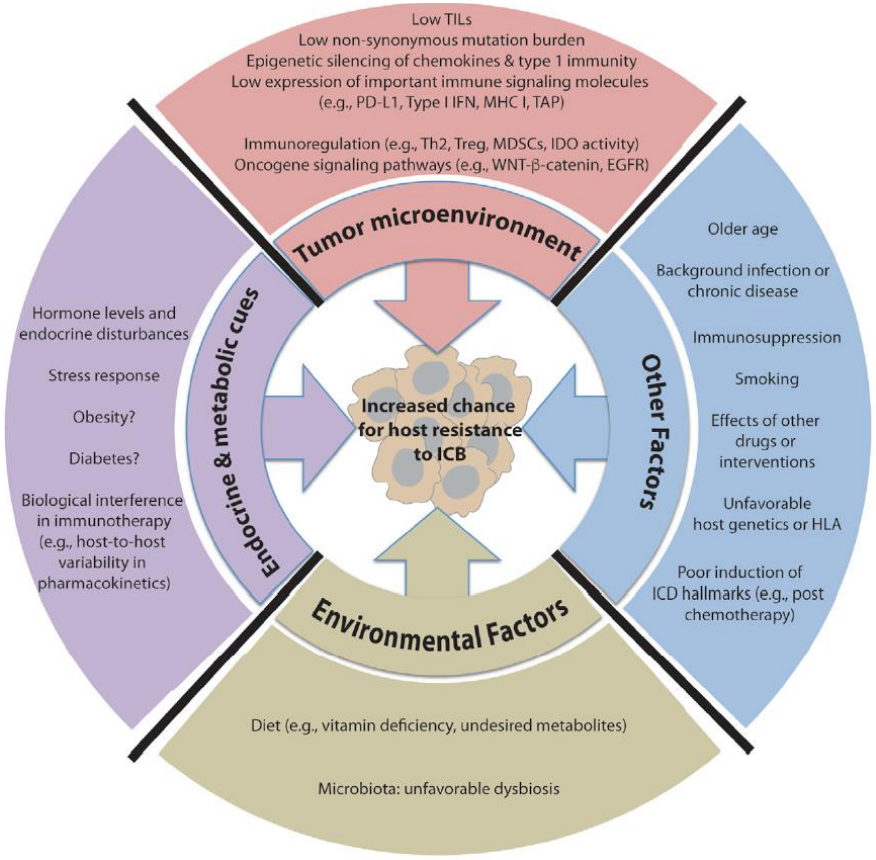
Institutional financial interests

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

Types of Resistance

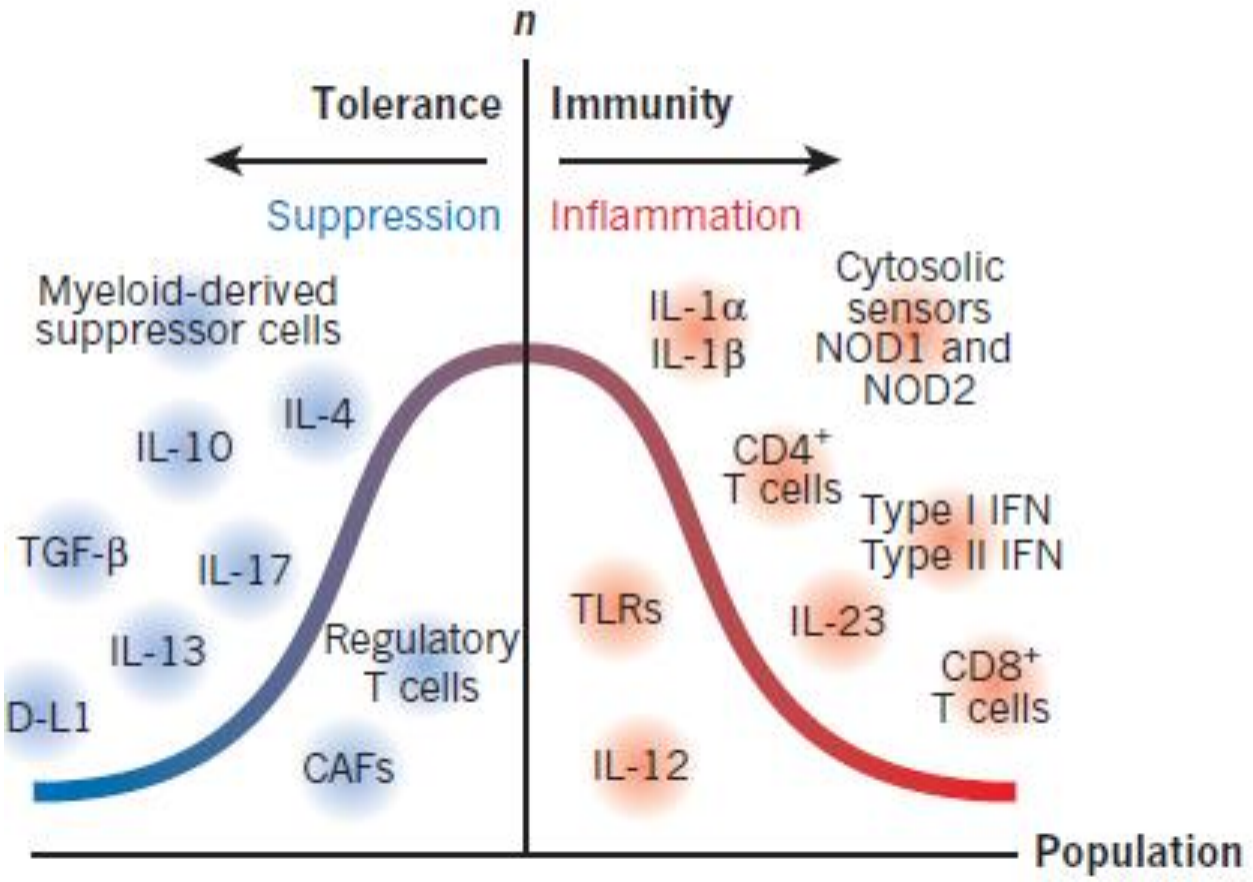
- Primary Resistance – No response
- Acquired Resistance – Progression of disease post response – typically defined as progression after 6 months of therapy

Primary Resistance Mechanisms to Checkpoint Blockade



Adapted from Zitvogel L et al Immunity Review 2016

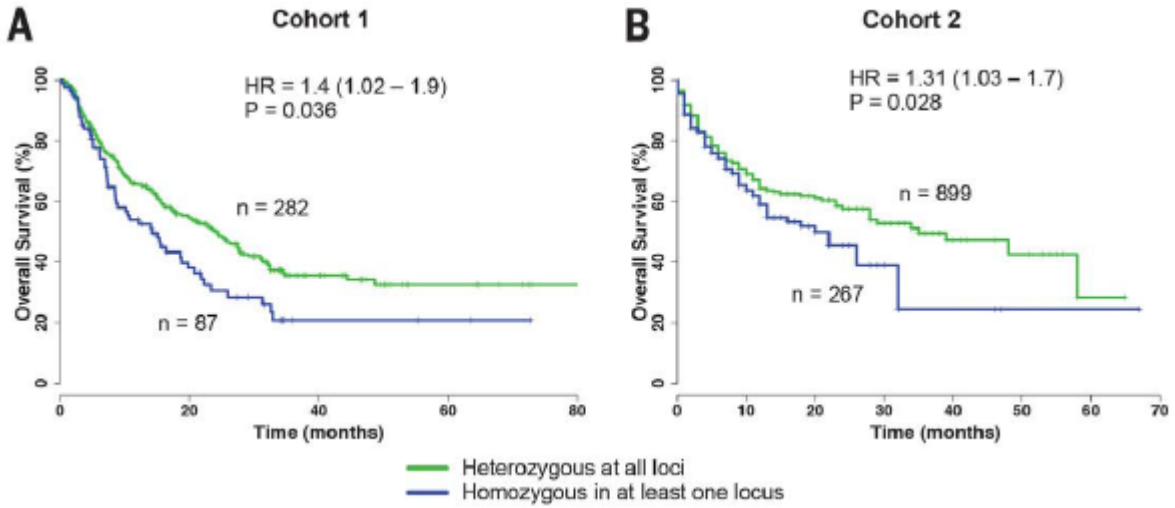
Non-inflamed Tumors “COLD” versus Inflamed “HOT” Tumors



Chen D and Mellman I, Nature 2017

Host Factors Influencing Response/Resistance HLA

- Homozygosity of HLA-B, HLA-A, HLA-DP, and HLA-DPB alleles are associated with poor OS



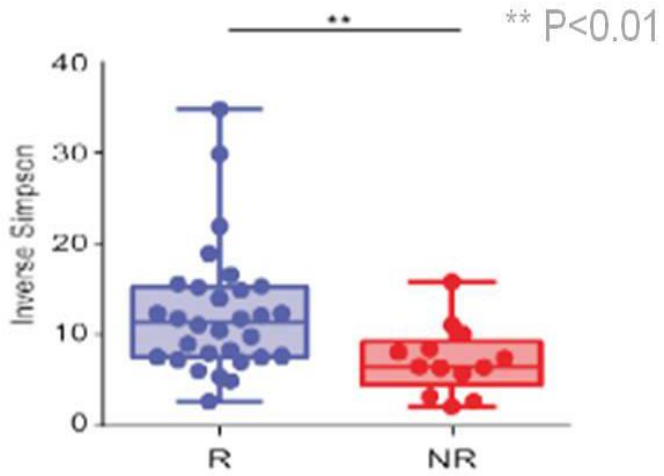
- HLA-B62 associated with poor OS

Chowell D et al Science 2018

Host Factors:
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

Host Factors: Microbiome and Immunotherapy
In NSCLC

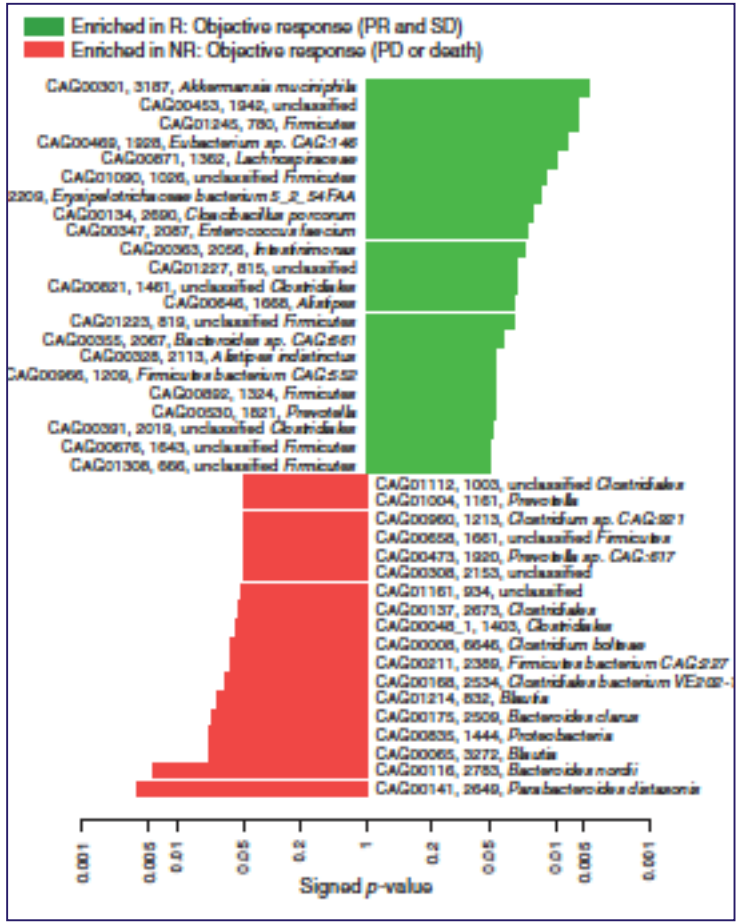
- Microbiota implicated in response may differ by tumor type
- Response may be modulated by prior antibiotic use

- 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

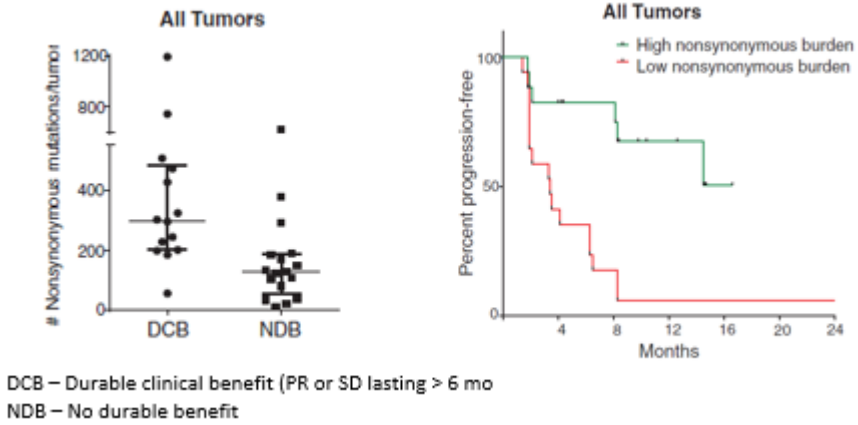
- **Detrimental (PFS at 3 months)**
- Antibiotics



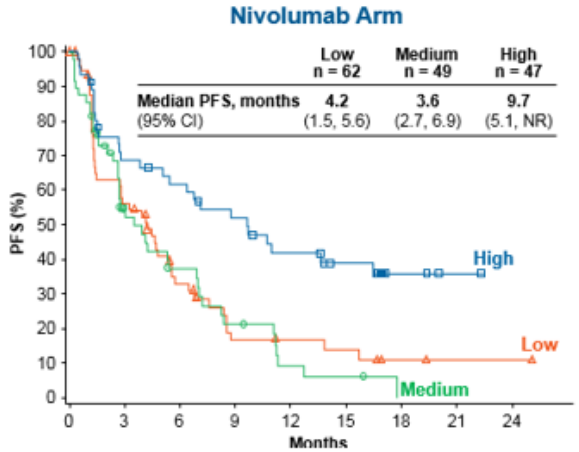
Routy et al, *Science* 2017

Tumor-Intrinsic Factors Influencing Response to Checkpoint Blockade

- Tumor Mutation Load



DCB – Durable clinical benefit (PR or SD lasting > 6 mo
NDB – No durable benefit

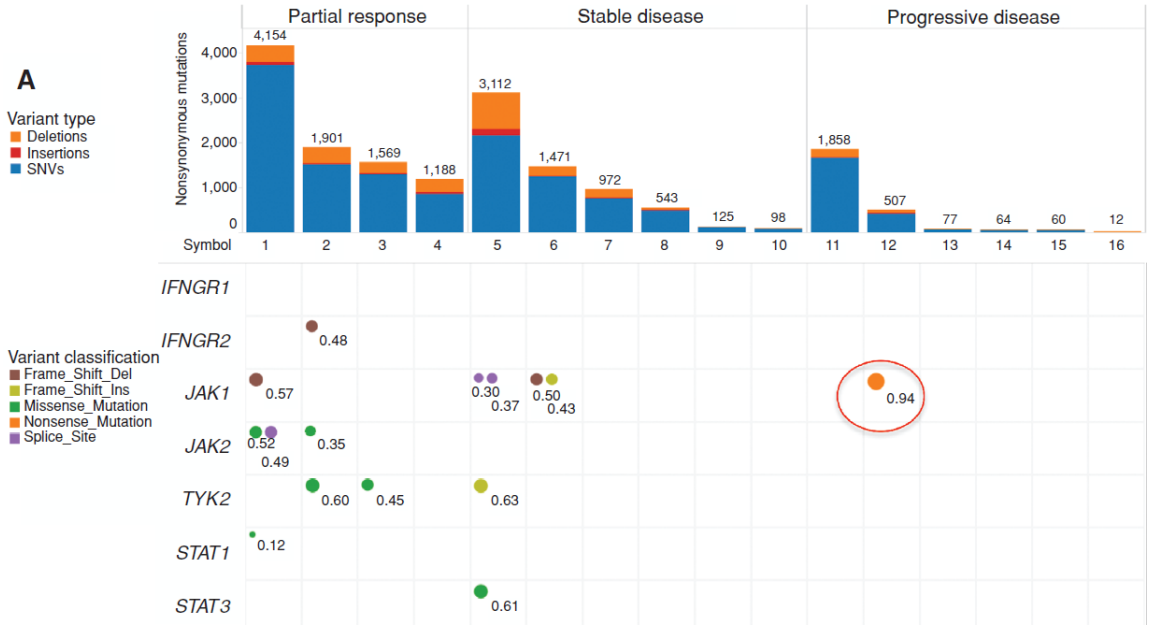


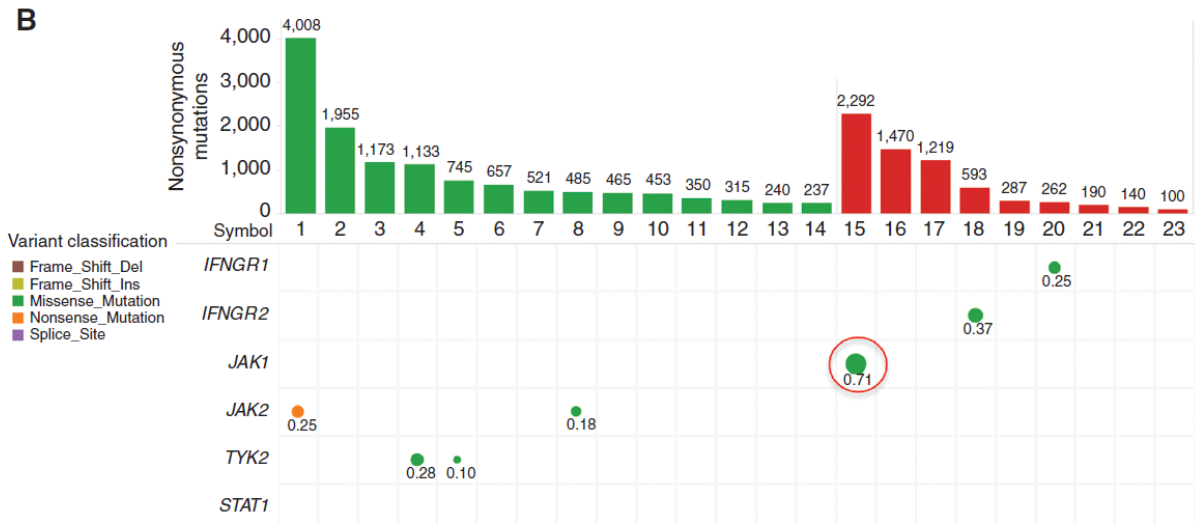
- MSI
- Mutations in DNA repair genes- MLH1, MSH2, BRCA2, POLD1, POLE

Rizvi NA, et al. *Science.* 2015;348:124-128
Peters S et al AACR 2017
Le D et al Science 2017
Borcherding N et al J Mol Biol 2018

Primary Resistance: Mutations

- Jak 1 and 2 mutations – Examples from melanoma, colon cancer, NSCLC
- Major relays in INF-γ signaling
- PD-L1 expression is mediated via activation of JAK/STAT

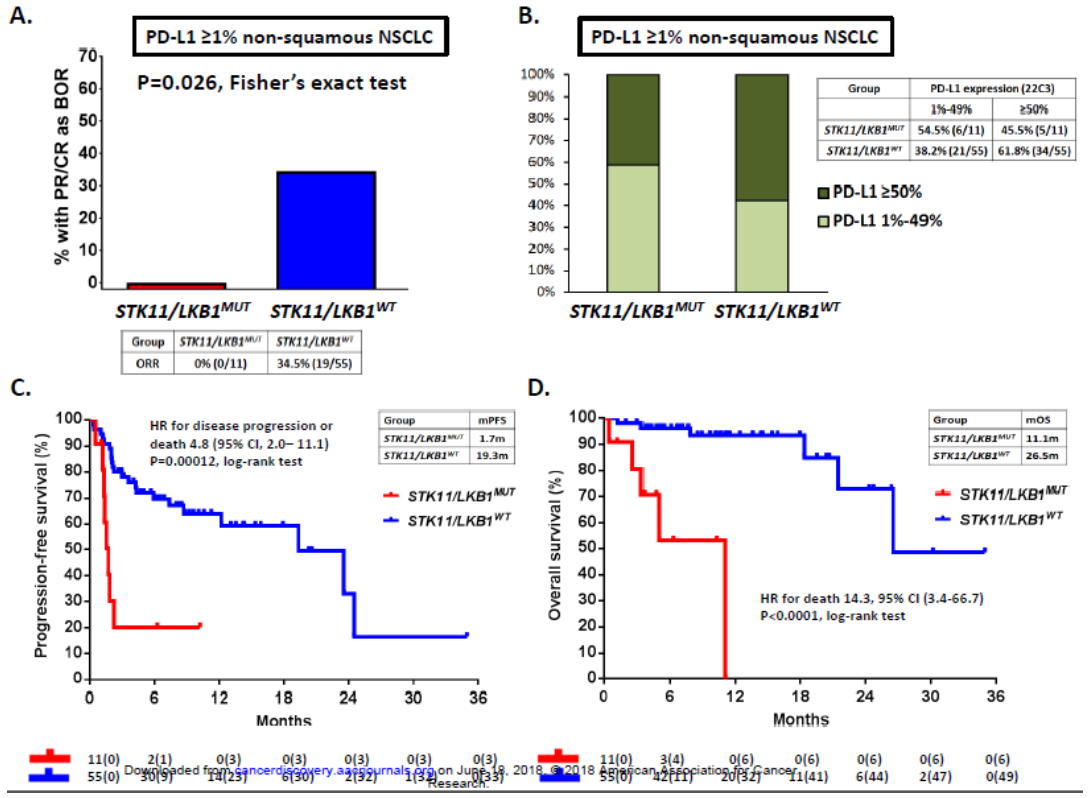


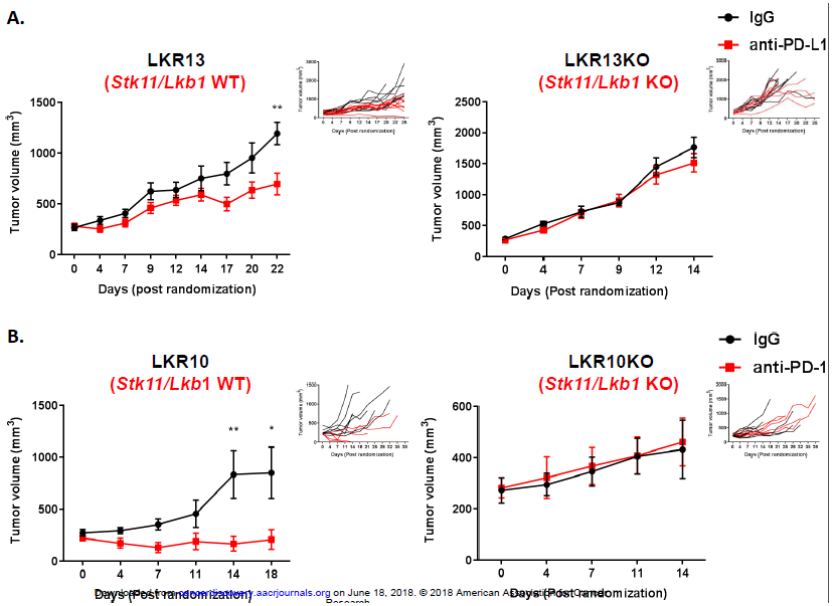


Shin DS et al Cancer Discovery 2016
Riaz N et al Nat Genet 2016
Zaretsky JM, et al NEJM 2016

Primary Resistance: Mutations

- STK11 in KRAS mutated lung cancers



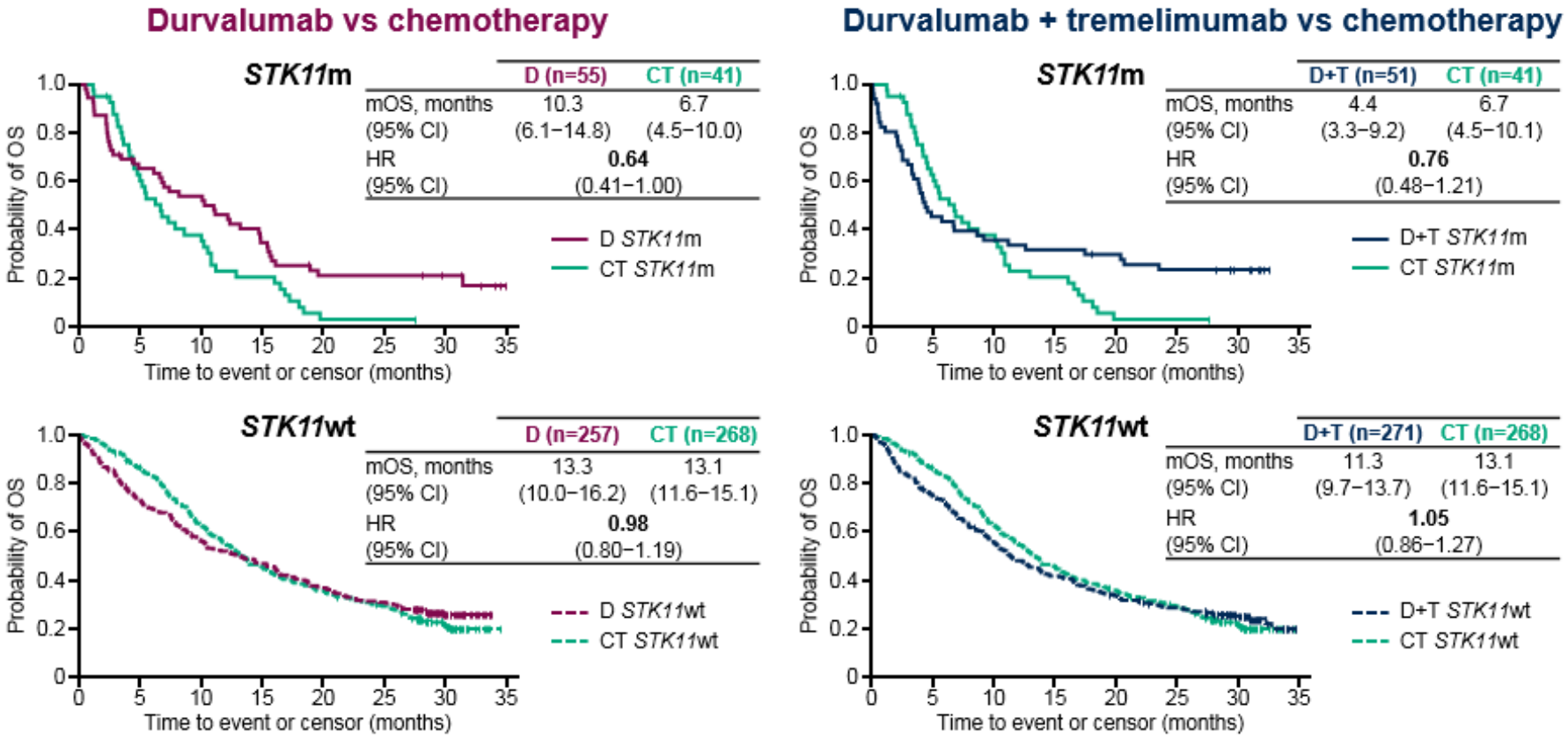


Lack of PD-L1 expression
Upregulation of MYC = decreased T cell infiltrate

Skoulidis F et al Cancer Discov 2018

Primary Resistance: Mutations

- STK11 mutated lung cancers – lessons from PD-L1 and PD-L1 and CTLA-4 combination



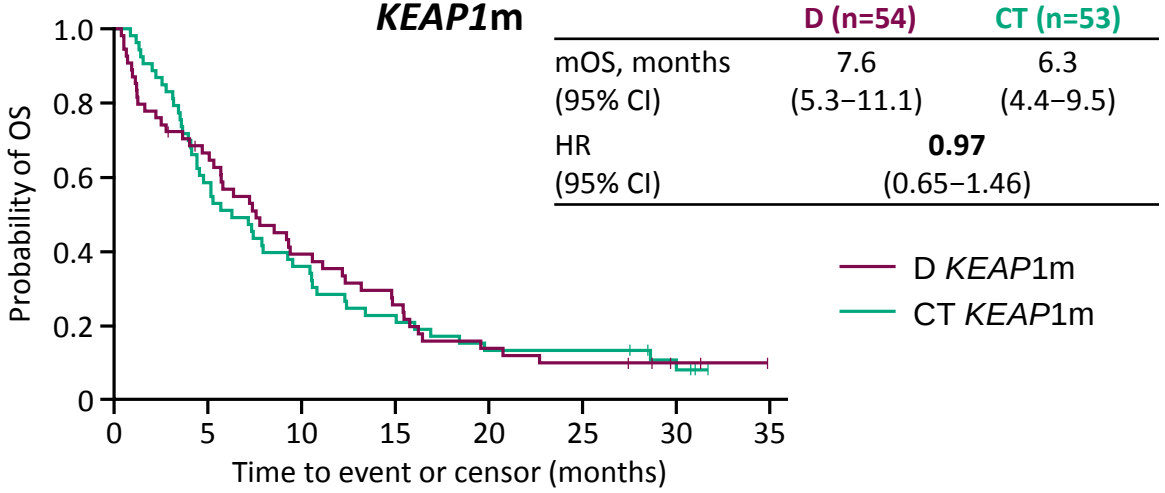
Primary Resistance: Mutations

KEAP1 mutated lung cancers – lessons from PD-L1 and PD-L1 and CTLA-4 combination

Durvalumab vs chemotherapy

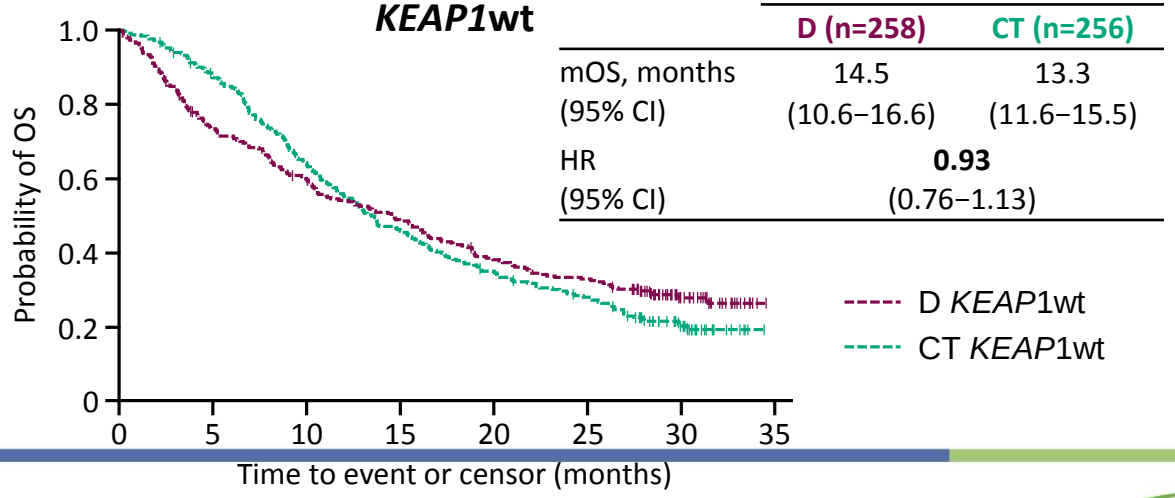
***KEAP1*m**

	D (n=54)	CT (n=53)
mOS, months (95% CI)	7.6 (5.3–11.1)	6.3 (4.4–9.5)
HR (95% CI)	**0.97** (0.65–1.46)	



***KEAP1*wt**

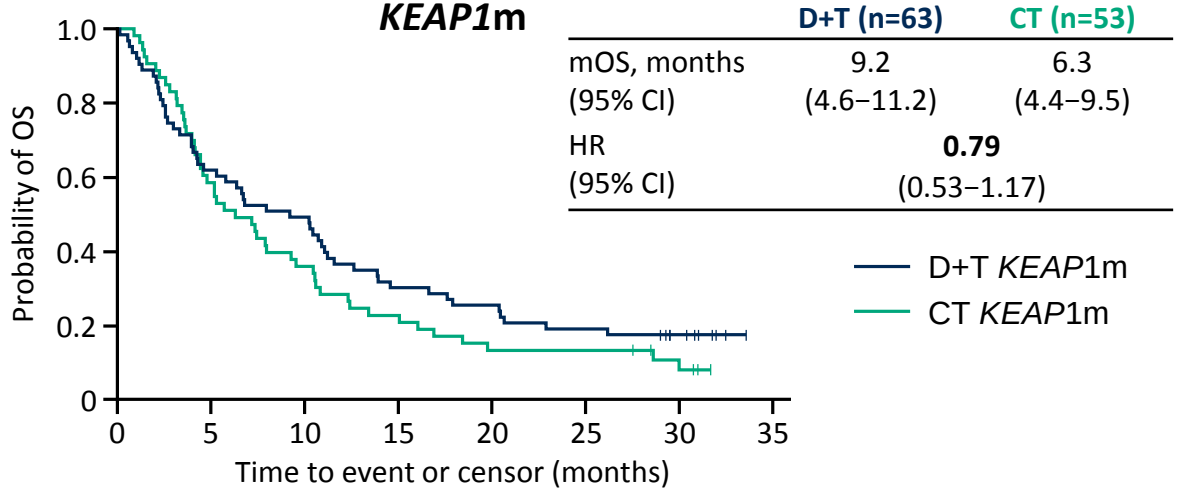
	D (n=258)	CT (n=256)
mOS, months (95% CI)	14.5 (10.6–16.6)	13.3 (11.6–15.5)
HR (95% CI)	**0.93** (0.76–1.13)	



Durvalumab + tremelimumab vs chemotherapy

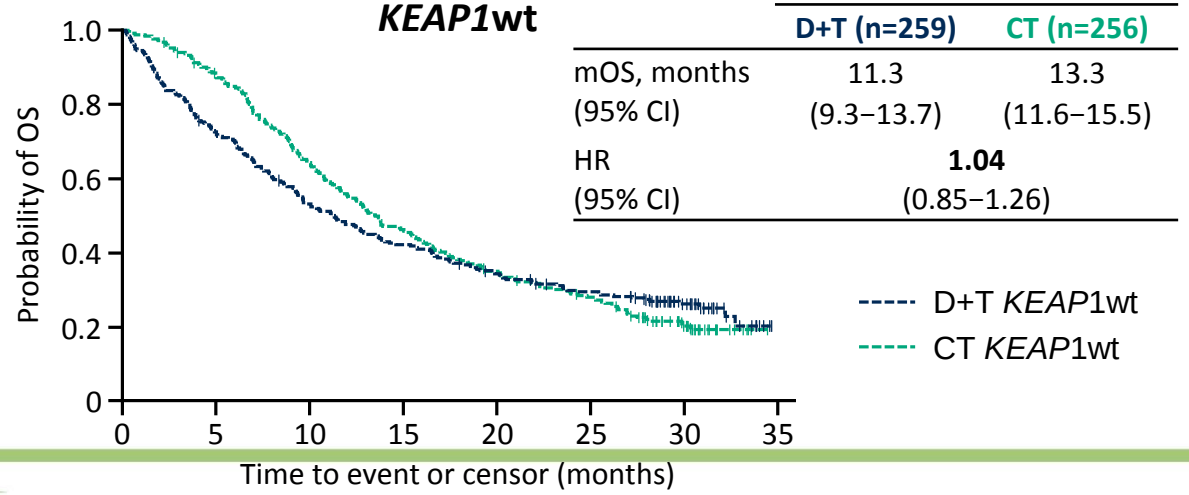
***KEAP1*m**

	D+T (n=63)	CT (n=53)
mOS, months (95% CI)	9.2 (4.6–11.2)	6.3 (4.4–9.5)
HR (95% CI)	**0.79** (0.53–1.17)	



***KEAP1*wt**

	D+T (n=259)	CT (n=256)
mOS, months (95% CI)	11.3 (9.3–13.7)	13.3 (11.6–15.5)
HR (95% CI)	**1.04** (0.85–1.26)	



Primary Resistance: Tumor Intrinsic

- PTEN deletion – upregulation if immune suppressive cytokines - associated with reduced T-cell infiltration and increased immune suppressive cells in the TME.

- WNT-β-catenin signaling upregulation – decreased recruitment of T cells via downregulation of CCL4

- Epithelial-mesenchymal transition (EMT) – gene expression signatures associated with innate resistance to PD-1 blockade

Liu D et al Amer J Clin Derm 2019

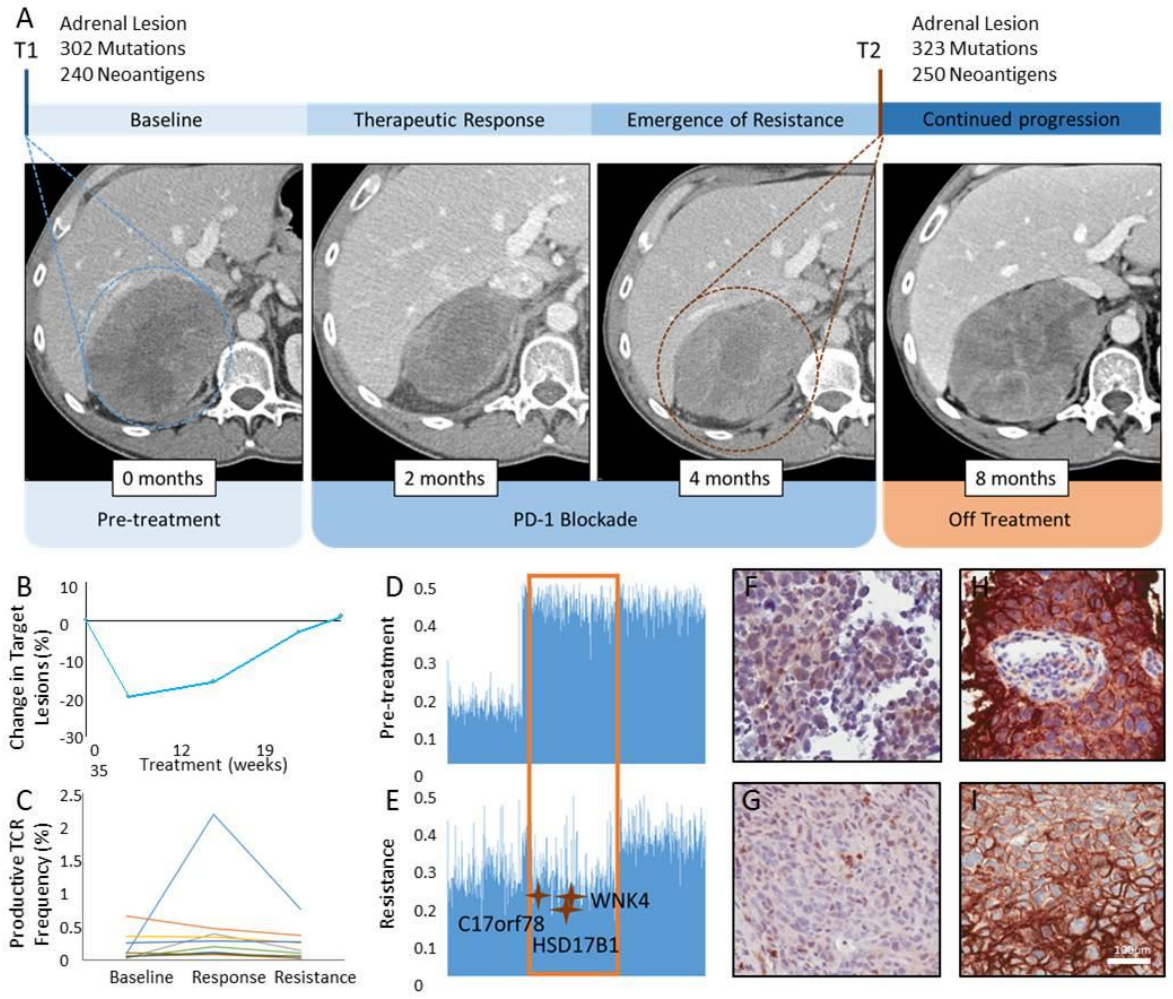
Acquired Resistance

- Selection pressure to reduce mutational load
- Mutations of copy number alterations in Type 1 and Type 2 INF limiting immune activation in the TME
- Other checkpoint upregulation – TIM-3

Riaz N et al Cell 2017, Zaretsky JM NEJM 2016, Gao J et al Cell 2016, Koyama S et al Nat Commun 2016

Acquired Resistance:

Mechanisms of Neoantigen Loss in Resistant Tumors



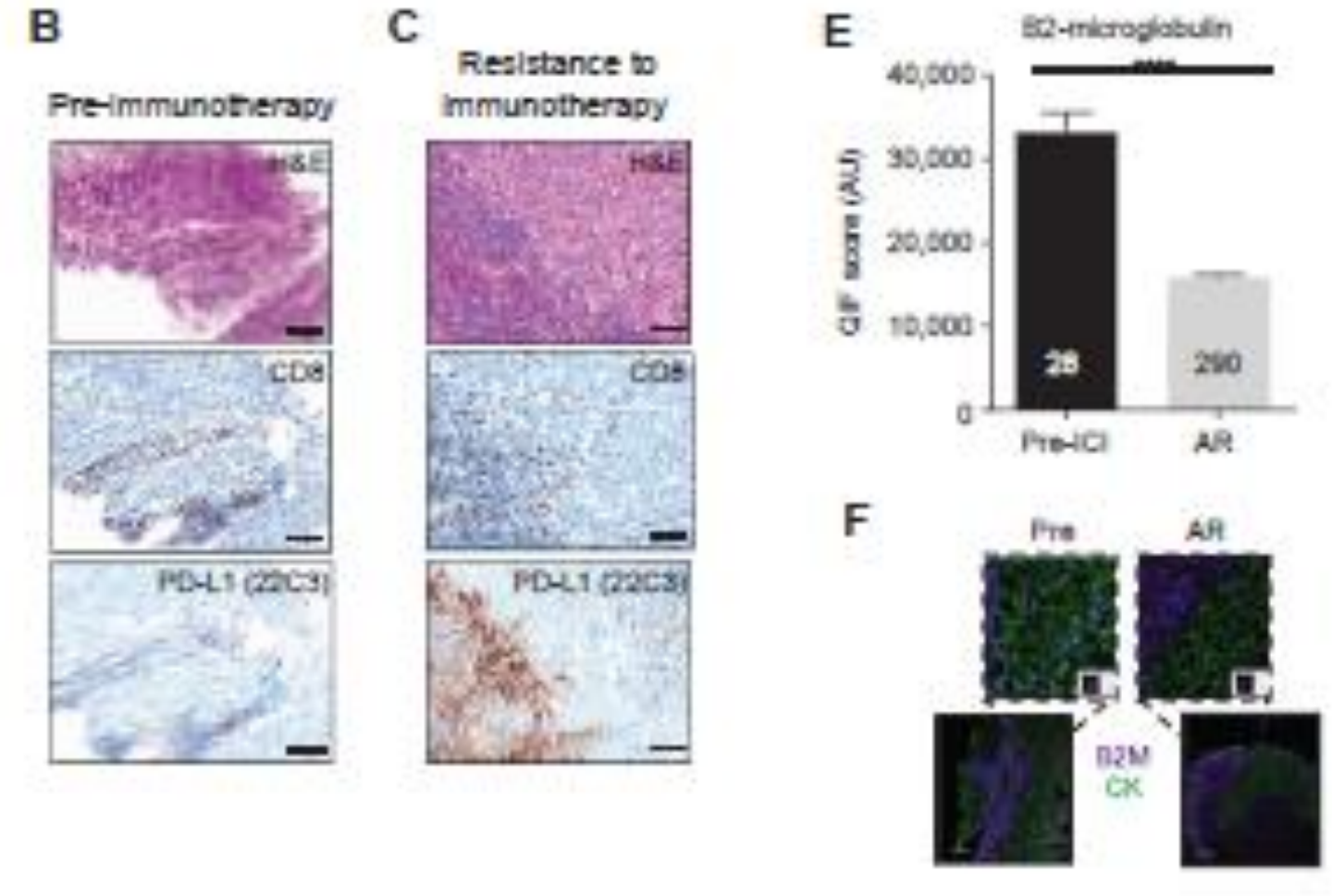
Anagnostou, Smith et al Cancer Discovery, 2017

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.

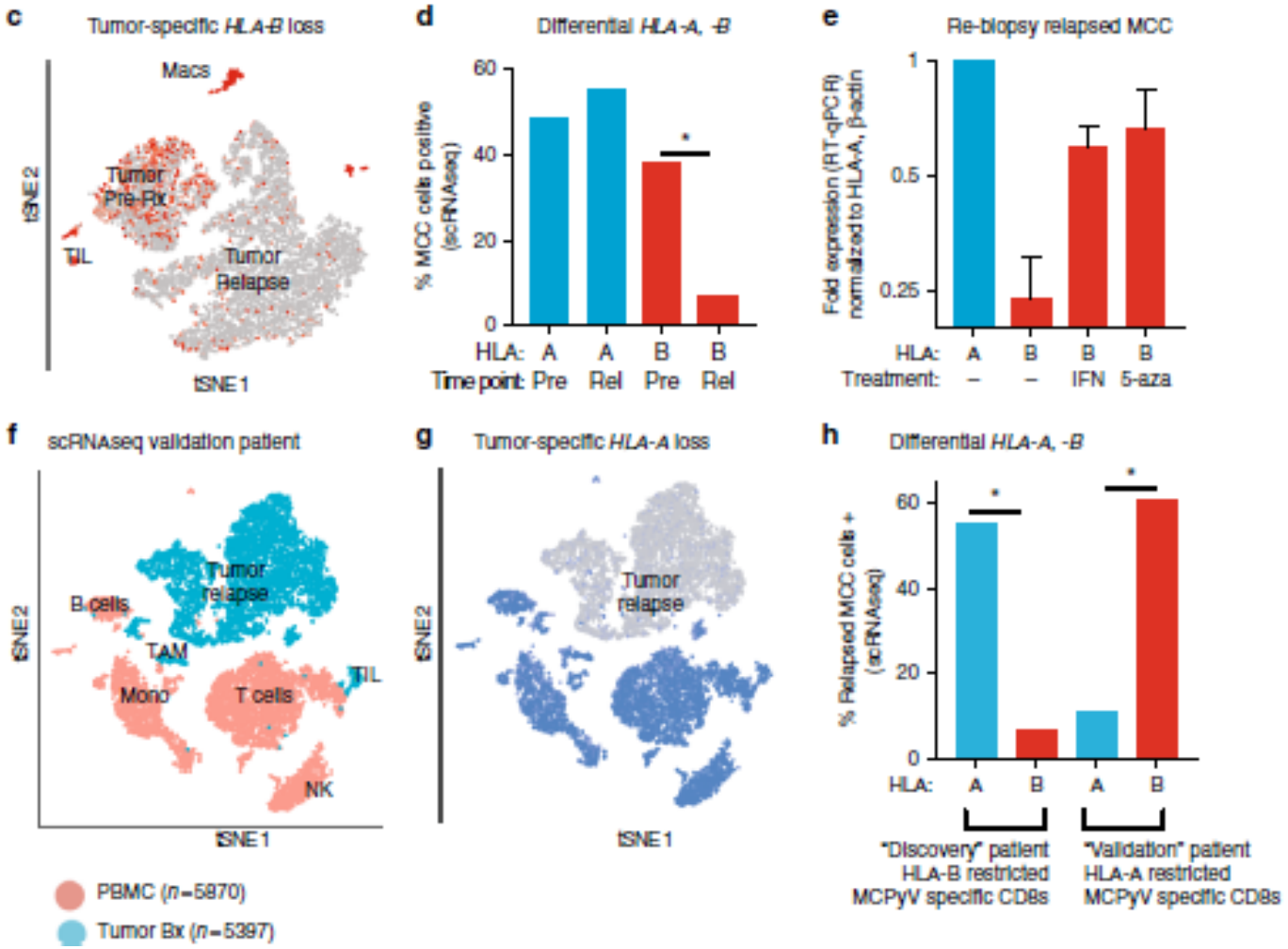
Slide provided by Dr. Anagnostou

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



Gettinger S Cancer Discovery 2017

Acquired Resistance: Class 1 HLA Loss

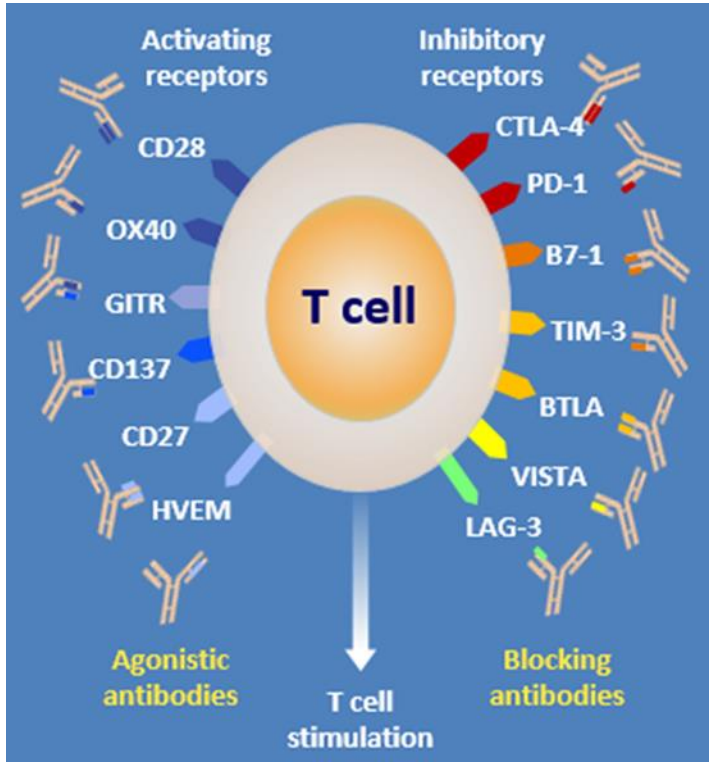


If transcriptional loss, then hypomethylating agents may upregulate Class 1 HLA again.

Paulson KG et al Nature Comm 2018

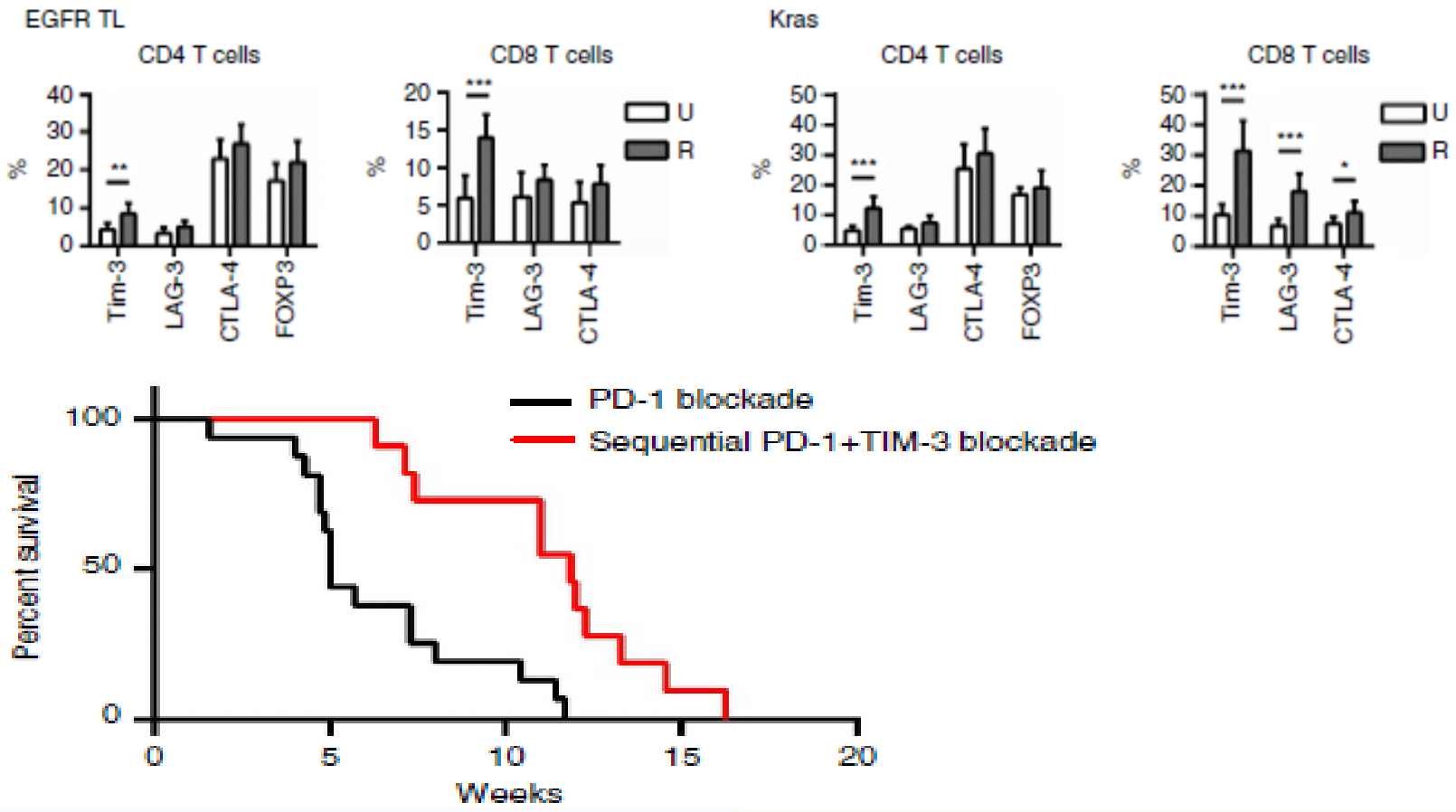
Acquired Resistance: Upregulation of Checkpoint Pathways

- LAG3
- TIGIT
- PD-L2
- CTLA4
- VISTA
- TIM-3



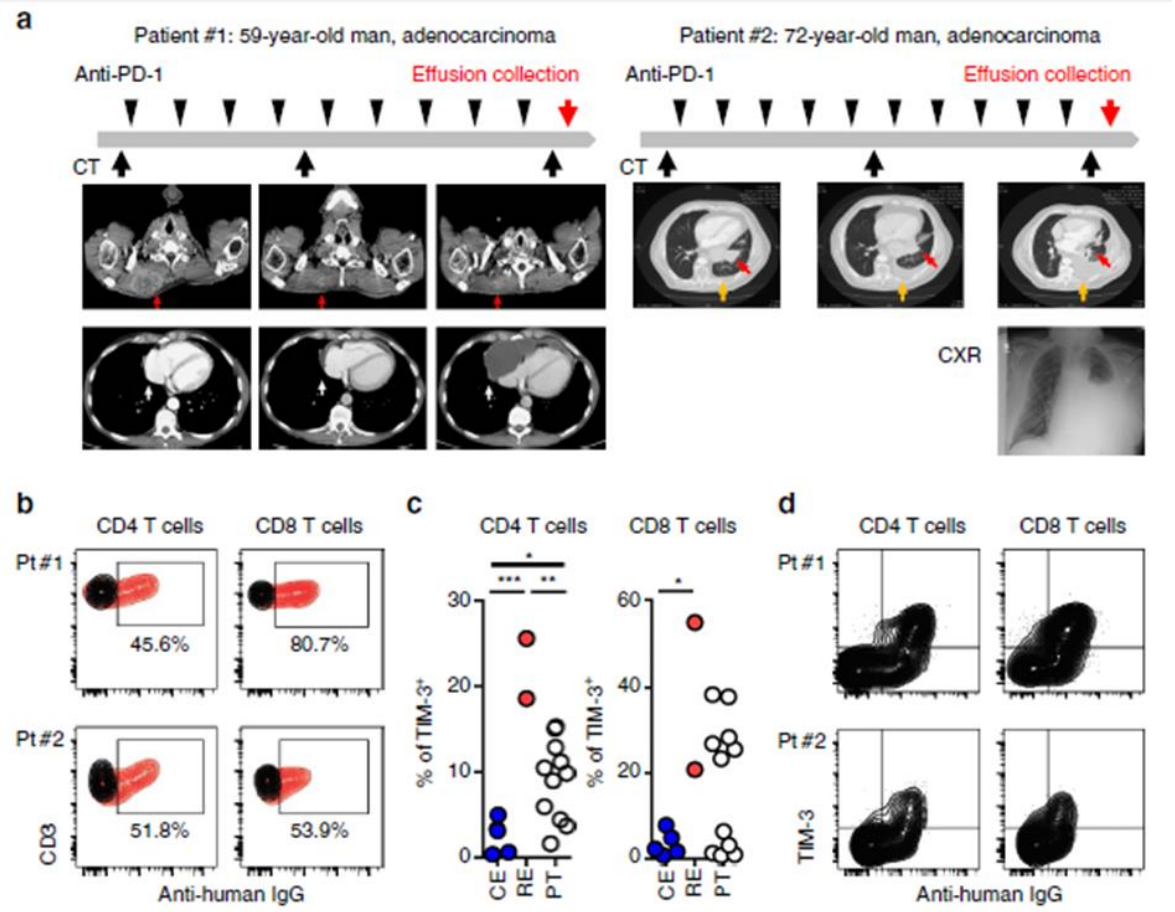
Gettinger S Cancer Discovery 2017

Acquired Resistance: Upregulation of Checkpoint Pathways – TIM-3



Koyama S et al Nat Com 2015

Acquired Resistance: Upregulation of Checkpoint Pathways – TIM-3



Koyama S et al Nat Com 2015

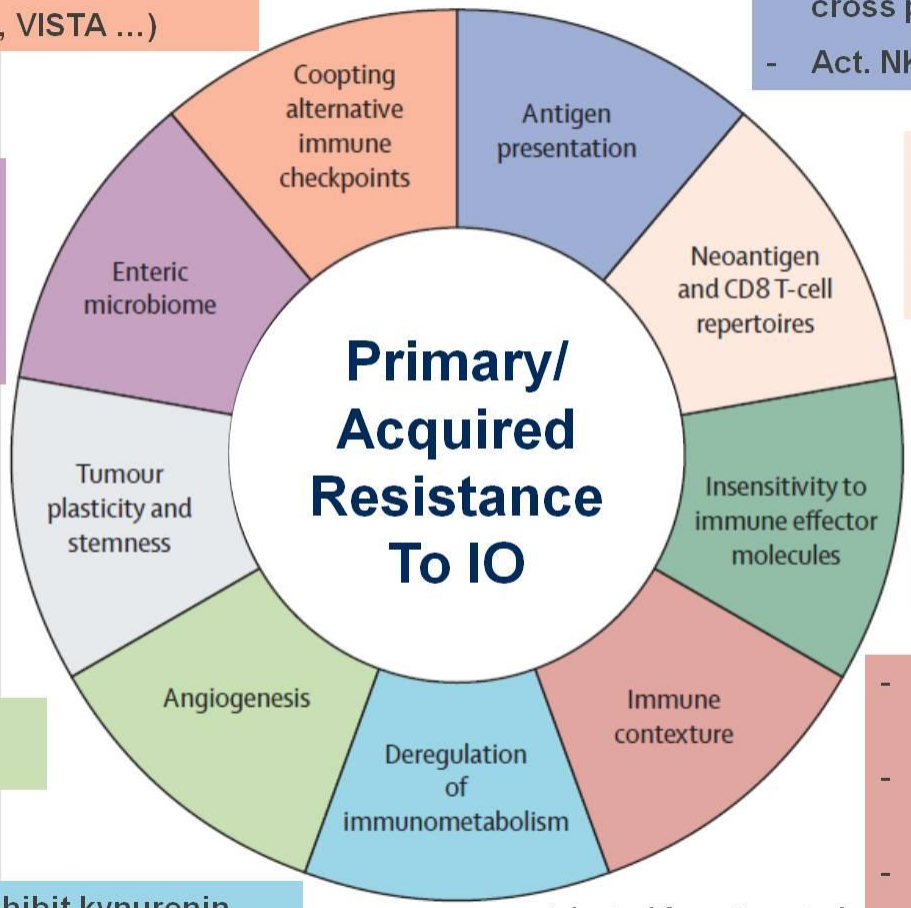
Blockade of multiple T cell inhibitory molecules (e.g anti- LAG3, TIM3, VISTA …)

- 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

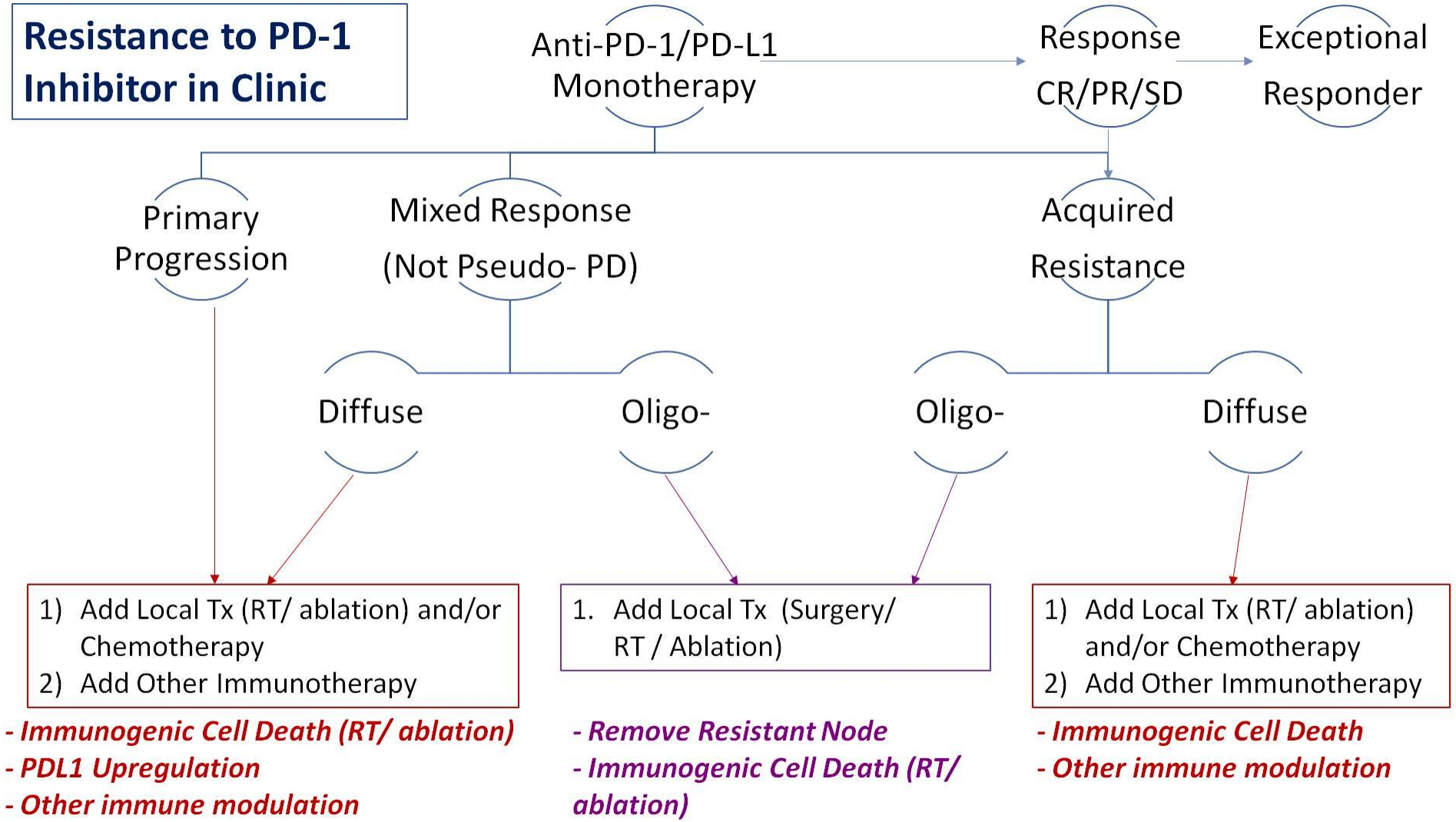
- Vaccine/ Radiation/ Cytotoxic Chemotherapy
- Epigenetic Tx to induce NeoAg Re-expression

- 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

Resistance to PD-1 Inhibitor in Clinic



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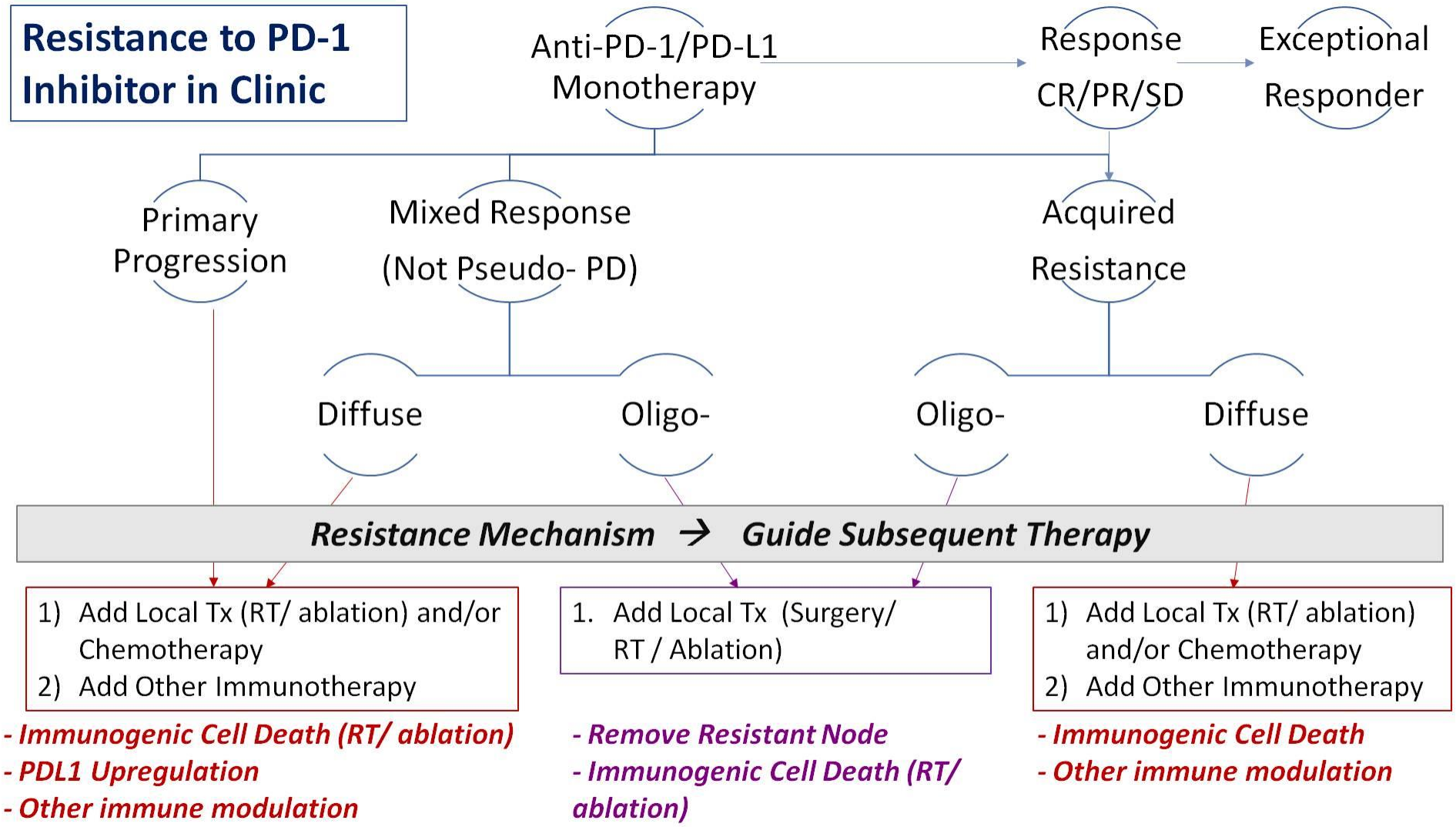

Slide adapted from Scott Gettinger ASCO-SITC 2018

Just the tip of the iceberg……

Johns Hopkins Bloomberg-Kimmel Institute For Cancer Immunotherapy