Mutational and Molecular Landscape of PDTC AND UDTC

MTOS 2022

March 19, 2022

Maria E. Cabanillas, MD, FACE

Professor

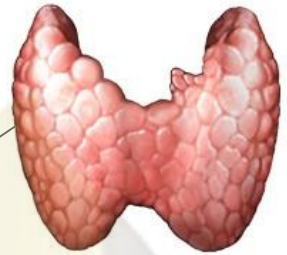
Endocrine Neoplasia & Hormonal Disorders

The University of Texas MD Anderson Cancer Center

Conflicts of Interest

- Grant funding: Eisai, Exelixis, Genentech, Merck and Kura
- Advisory boards: Exelixis, Blueprint, Ignyta, Bayer and LOXO

Origin of Thyroid Cancers



Epithelial follicular cells
(thyroglobulin)

C-cells
(neuroendocrine cells
Calcitonin & CEA)

Differentiated thyroid cancer

PTC

FTC

HTC

MTC

BRAF, RAS mutation; RET, NTRK1&3, ALK & ROS1 fusions

RAS, PTEN, PPARg fusions

RAS (rare), *PPARg fusions*
Often no mutations found

Poorly differentiated (PDTC)

PDTC

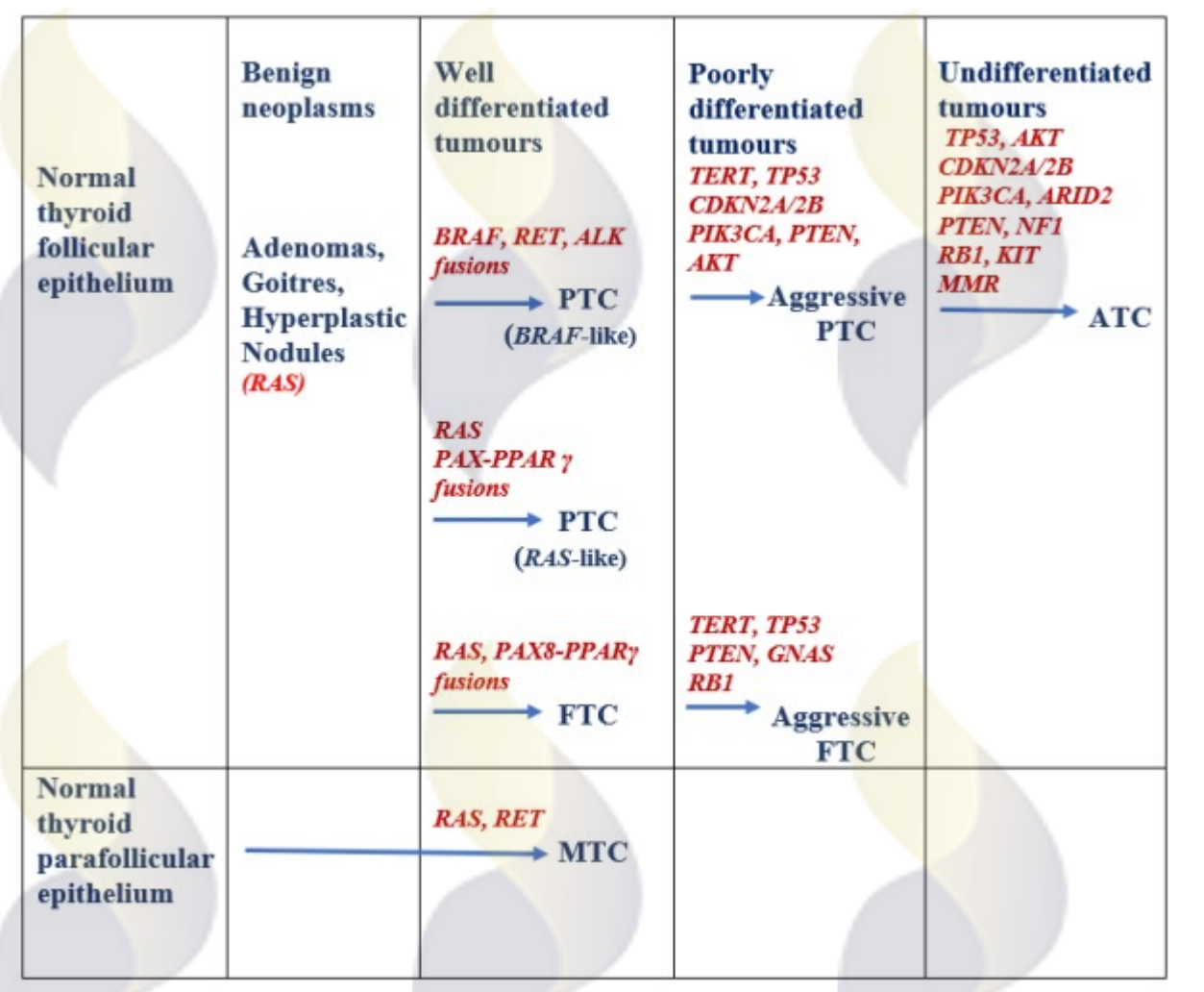
Same driver mutation as parent cell + additional mutations

De novo

ATC (Undifferentiated)

PTC=papillary thyroid cancer; FTC=follicular thyroid cancer; HTC=Hurthle cell thyroid cancer; PDTC=poorly differentiated thyroid cancer; ATC=anaplastic thyroid cancer; MTC=medullary thyroid cancer

Mutations along the spectrum of thyroid cancer

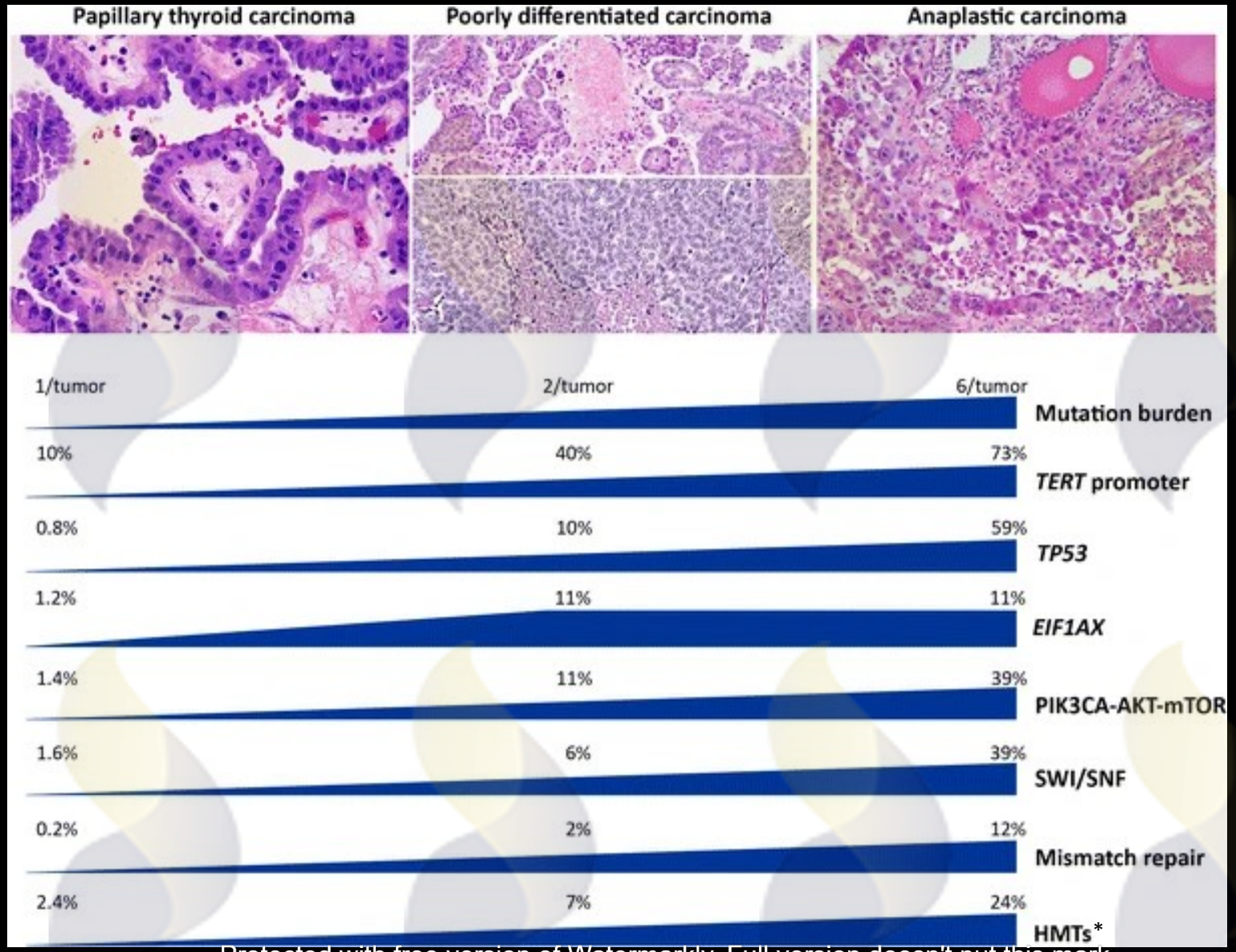


*The driver mutations in the well-differentiated tumors are retained in poorly and undifferentiated

*Acquisition of late event mutations

Singh et al, Cells, 2021

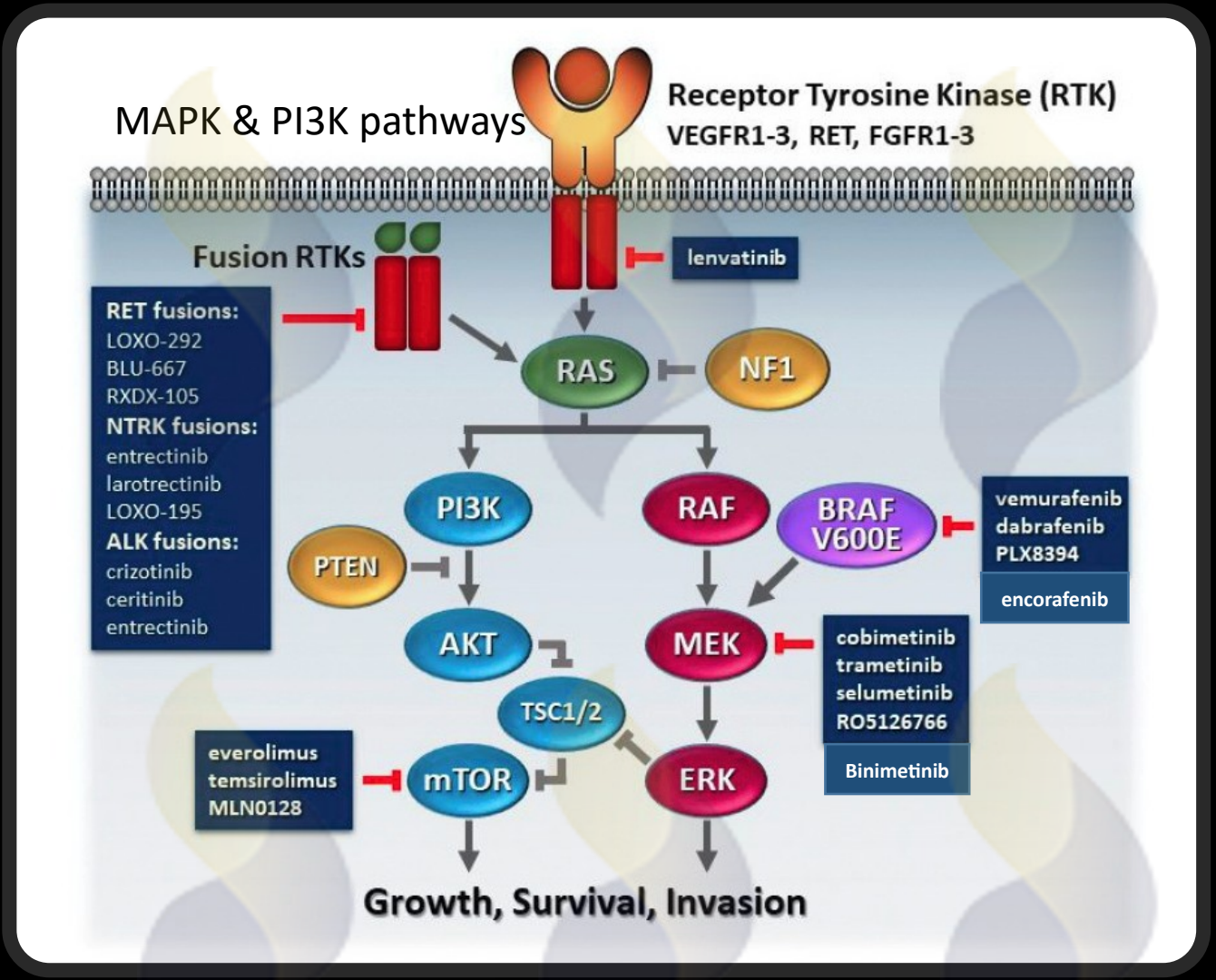
Stepwise molecular pathogenesis of thyroid cancers



Xu B, Ghossein R, Endocrine Pathology 2016

*Histone methyltransferases

Signaling Pathways and Drug Targets in DTC & ATC

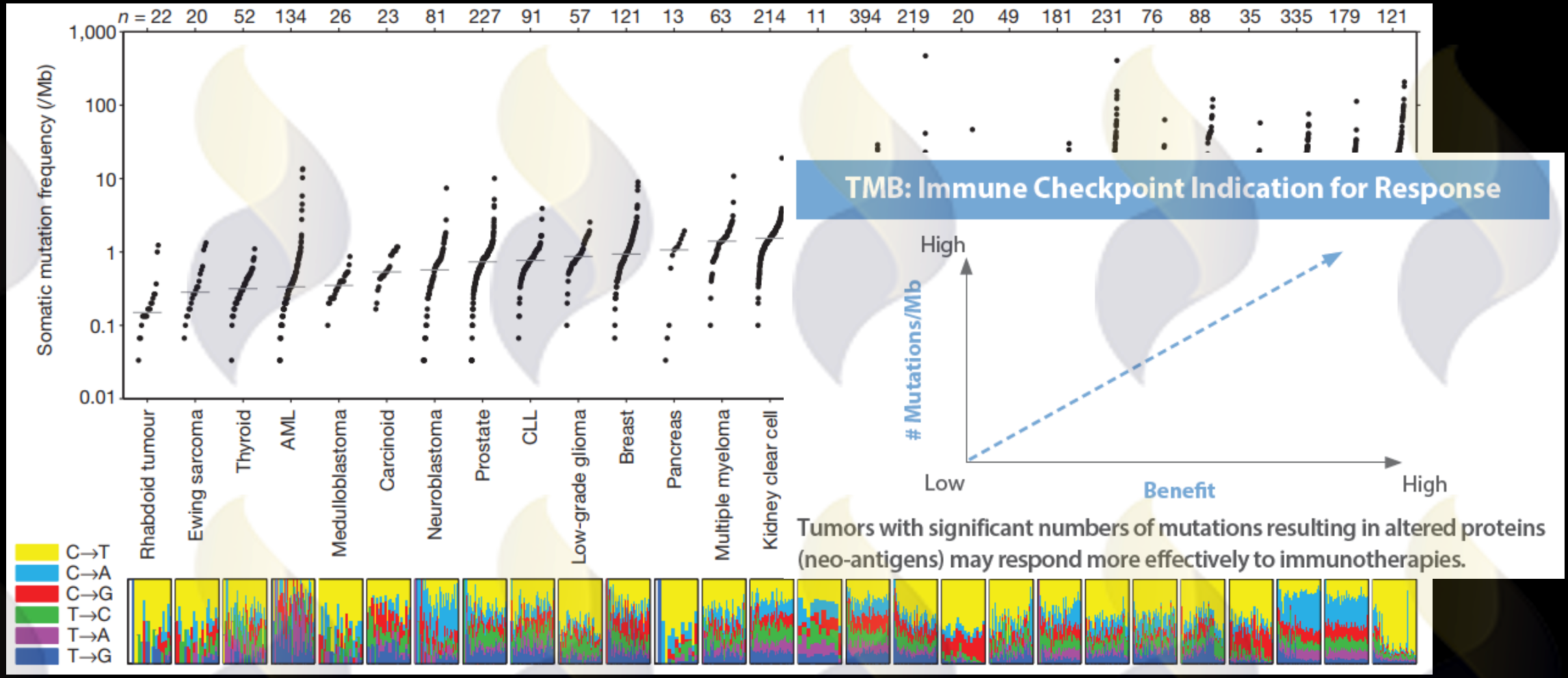


In ATC, we currently use 3 classes of targeted therapy:

- Anti-angiogenic therapy
- Genetic mutation/fusion-driven therapy
- Immunotherapy

Adapted Cabanillas et al, F1000 Reviews, 2018

Tumor Mutation Burden in ATC is Low



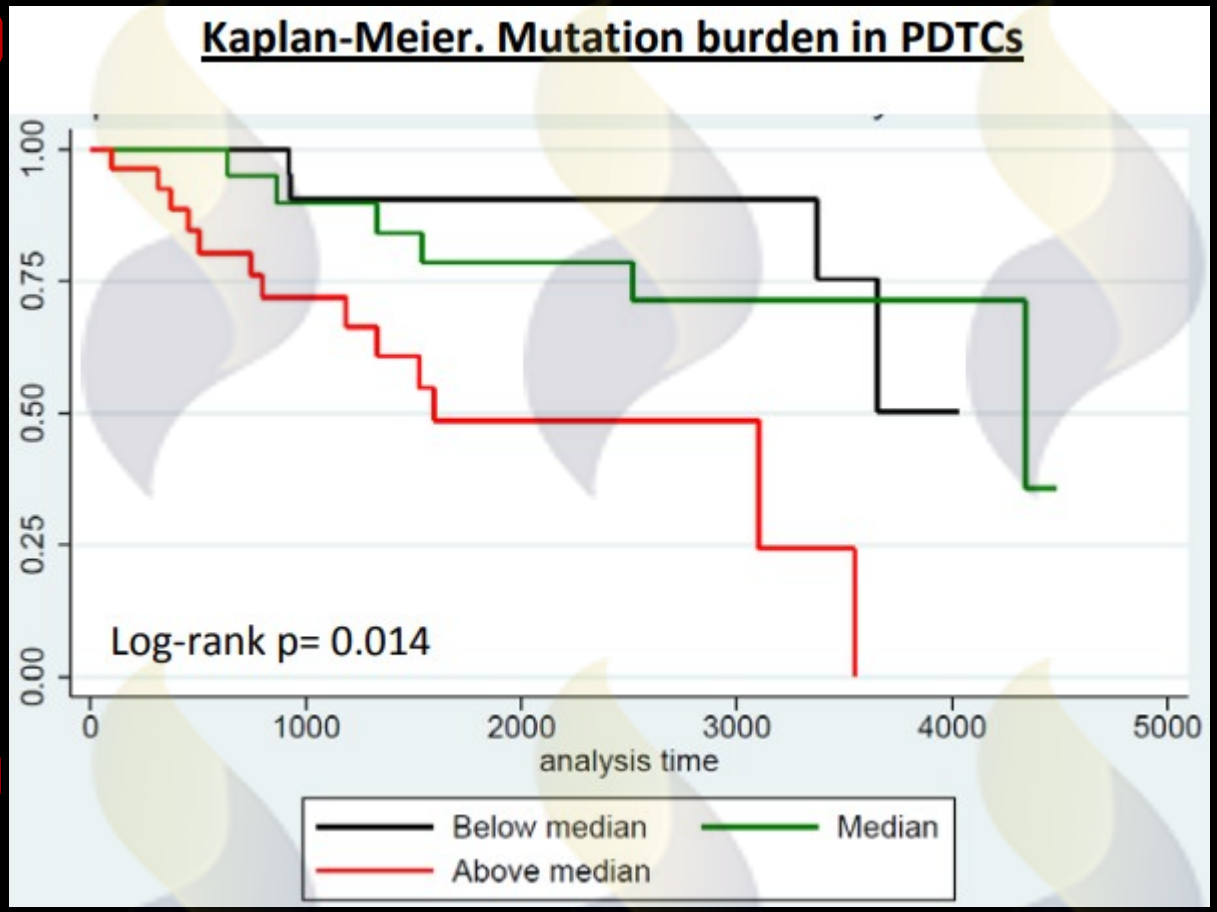
- TMB in ATC is usually low (<5 Mut/Mb) although some are intermediate; rare to find high TMB in ATC

Lawrence et al, Nature 2013

Higher mutation burden in PDTC confers poor prognosis

B. Poorly differentiated thyroid cancers (PDTC)

PDTC = 78	Below median (26)	Median (24)	Above median(28)	p value
Age (y)	47±15	58±15	64±15	<0.001
Gender (%F)	73%	58%	54%	0.314
Family history TC(%yes)	12%	0%	7%	0.452
Tumor size				
≤ 4	64%	57%	29%	
>4	36%	43%	71%	0.038
Pathology staging				
T1/T2	17%	15%	4%	
T3/T4	83%	85%	96%	0.405
Nx/N0	54%	45%	52%	
N1a/N1b	46%	55%	48%	0.822
M0	73%	54%	32%	
M1	8%	29%	57%	
Mx	19%	17%	11%	0.002
RAI				0.874
No	19%	29%	18%	
Yes	73%	63%	75%	
RAI Uptake				
No uptake	8%	4%	0%	
Thyroid bed	38%	29%	21%	
Outside thyroid bed	27%	29%	50%	0.391
Overall survival (died)	19%	25%	46%	0.07
Overall survival time (days±SD)	2242±1332	2181±1406	1469±1158	0.05
Survival analysis: HR (95%CI)			HR:2.03 (1.19-3.47)	0.01
Log rank				0.014

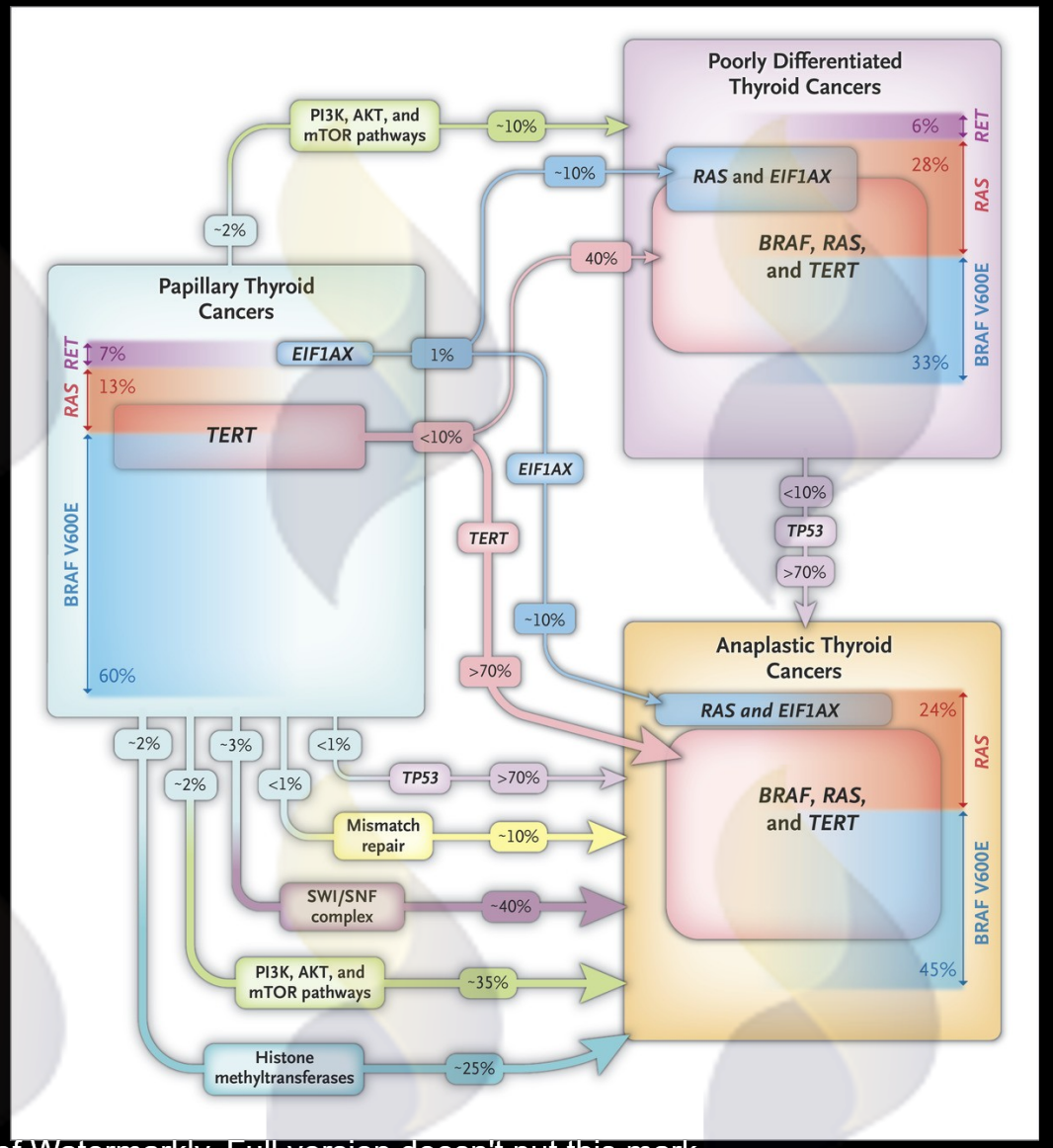


- Mutation burden was greater in older patients and associated with tumor size, presence of distant metastasis, and overall

Landa et al, JCI 2016

Genomic Hallmarks of Advanced Thyroid Cancers

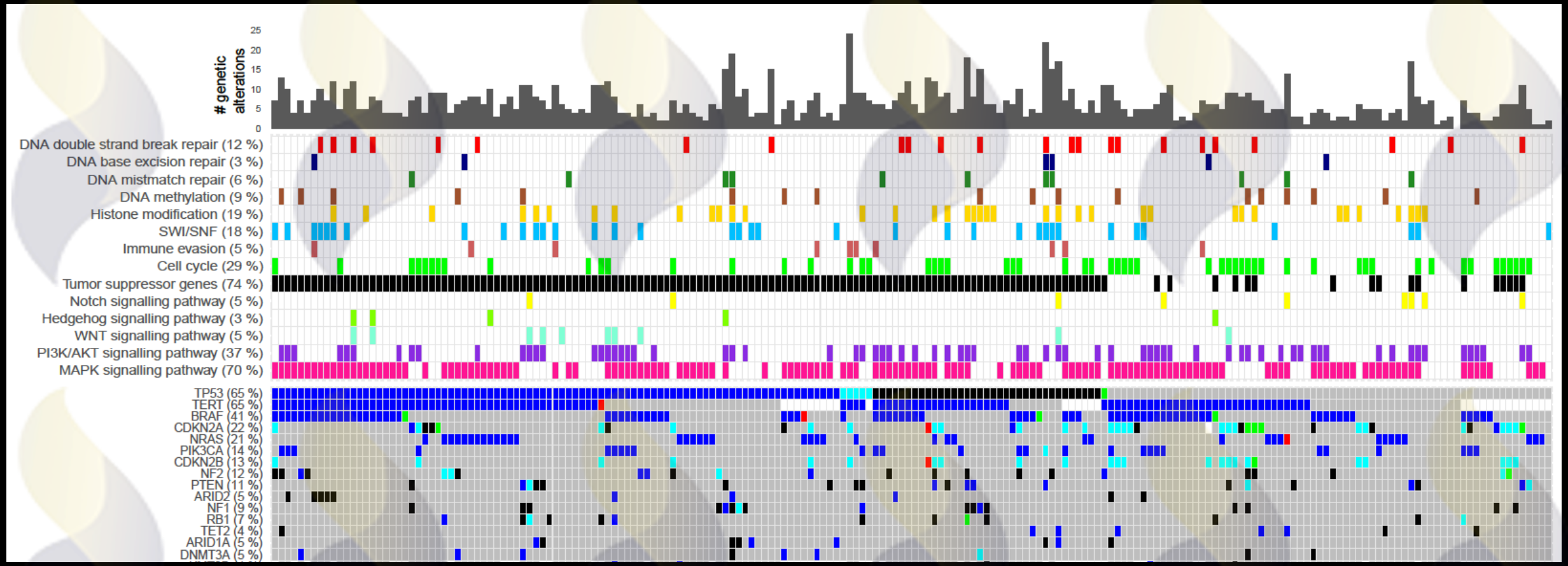
- Driver mutations along MAPK and PI3K pathways are retained
- Acquisition of late event mutations
  - P53, TERT promoter
- SWI/SNF complexes
- Mismatch repair (MSH2, MSH6, MLH1)
- Cell cycle gene alterations (CDKN2A, CDKN2B, CCNE1)
- Tumor immune evasion genes



Fagin JA, Wells SA, NEJM, 2016

NGS Panel Study of 196 ATC tumors

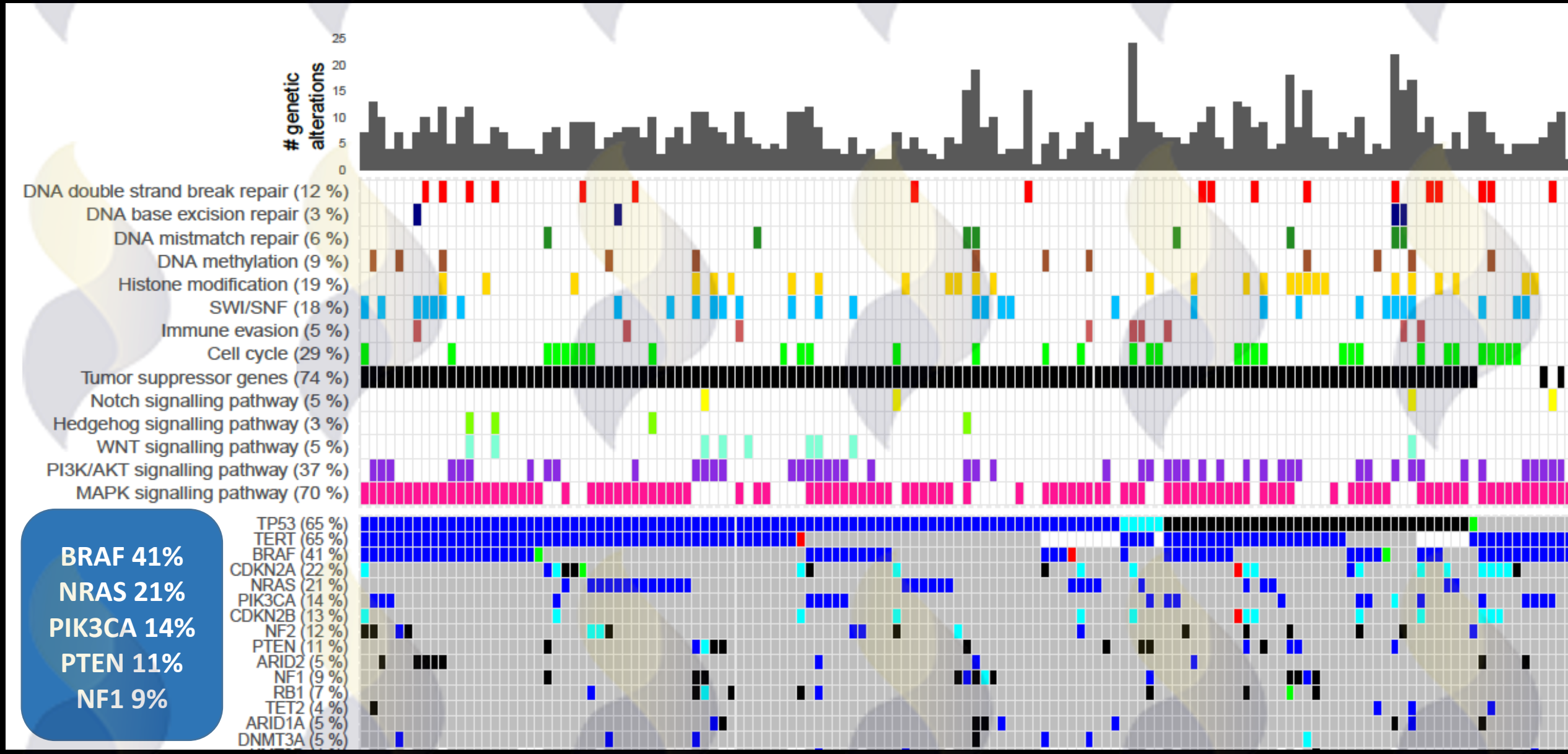
MSK-Impact and Foundation One Panels



(adapted: only most common genes included)
Includes Landa et al ATC data

Pozdeyev et al, CCR 2018

Pozdeyev et al NGS Panel Study 2018 (196 ATCs)

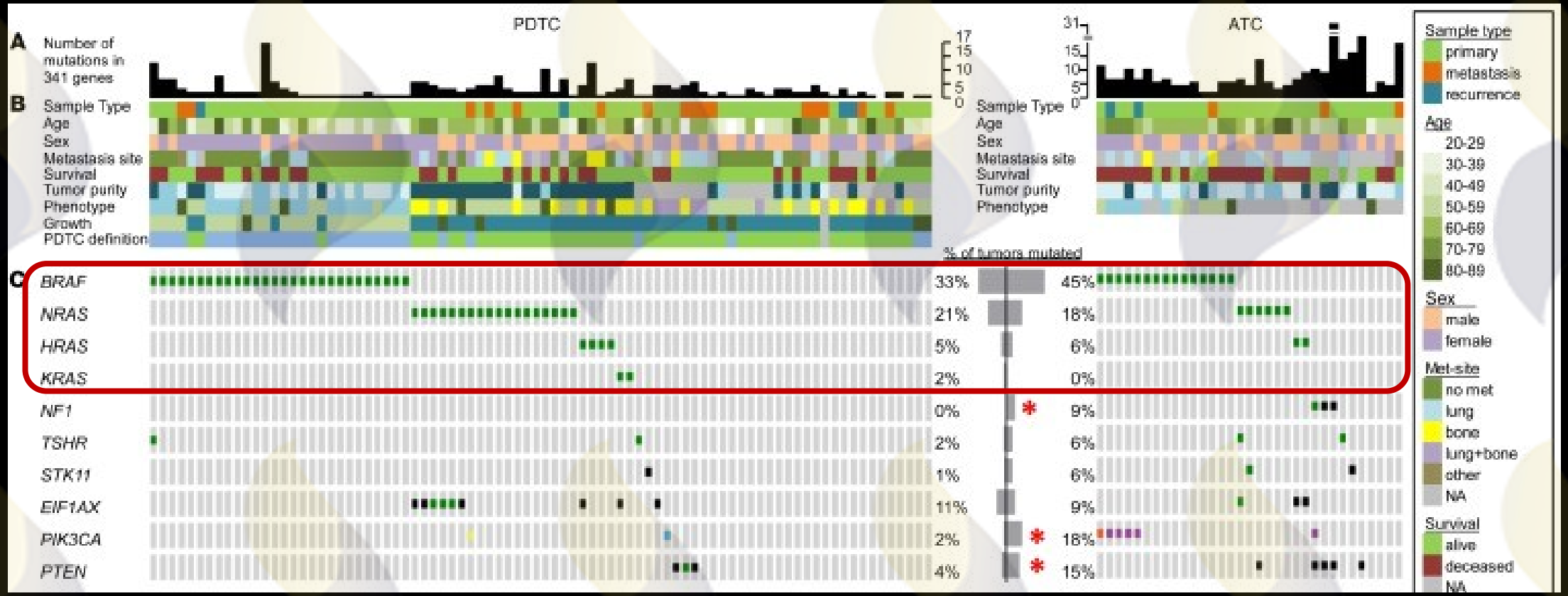


BRAF 41%
NRAS 21%
PIK3CA 14%
PTEN 11%
NF1 9%

(adapted: only most common genes included)
Includes Landa et al ATC data

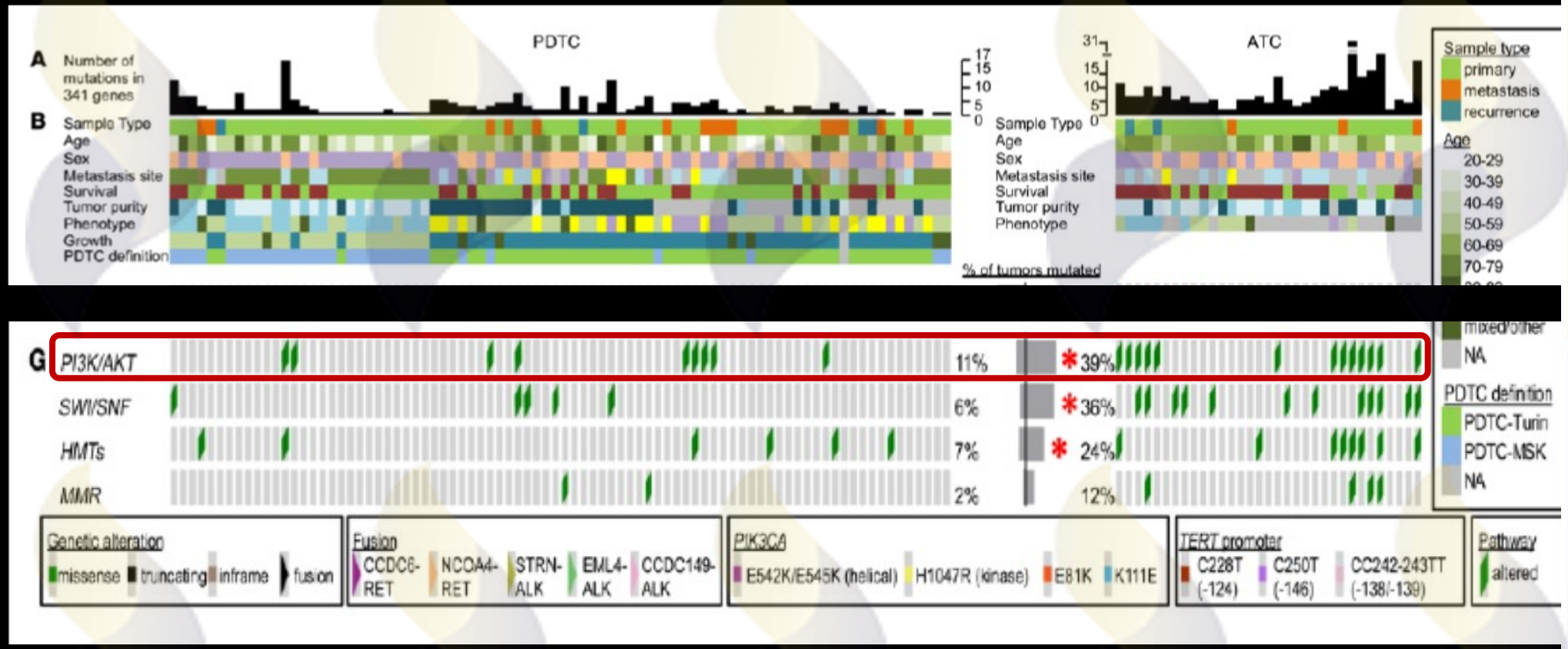
Pozdeyev et al, CCR 2018

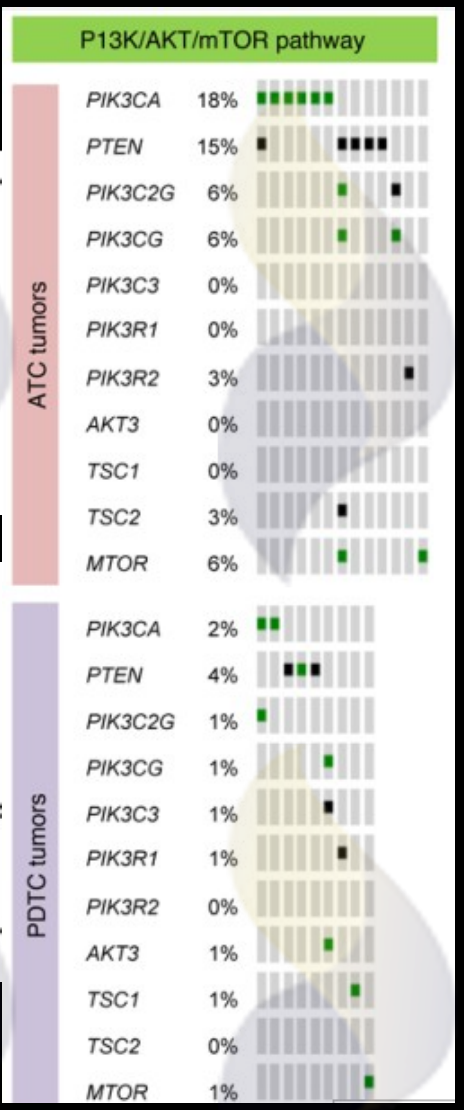
MAPK pathway in PDTC vs ATC



Landa et al, JCI 2016

P13K/AKT/mTOR pathway in PDTC vs ATC

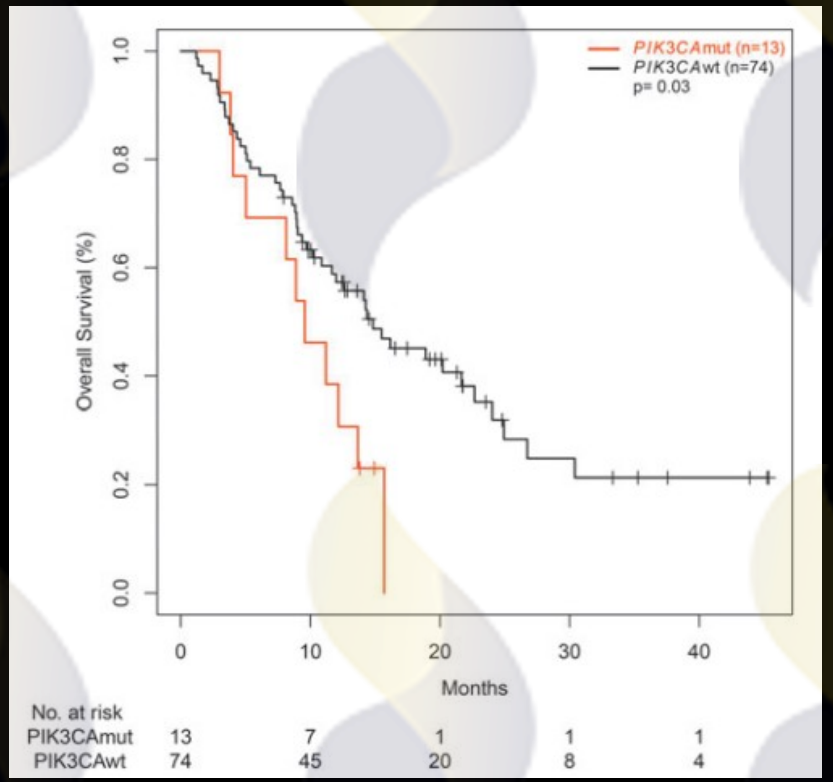




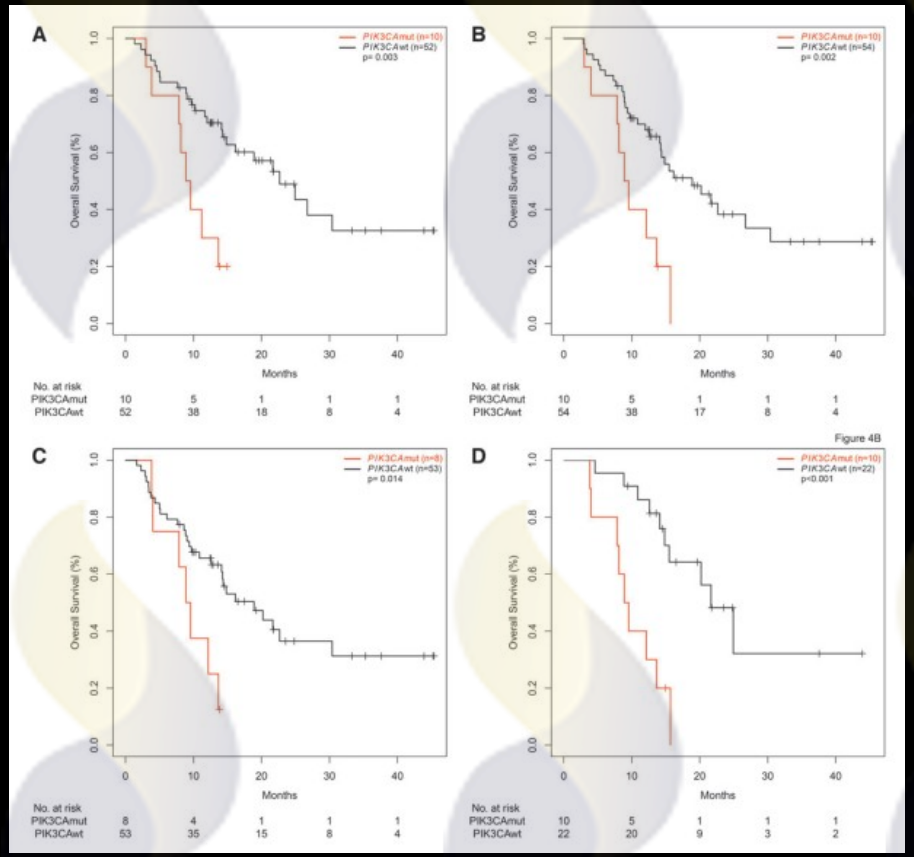
Landa et al, JCI 2016

PIK3CA mutation is prognostic in ATC

- 87 ATC patients with cfDNA
  - 13/87 (15%)with PIK3CA mutation
- Worse OS in PIK3CA mutated vs wild-type

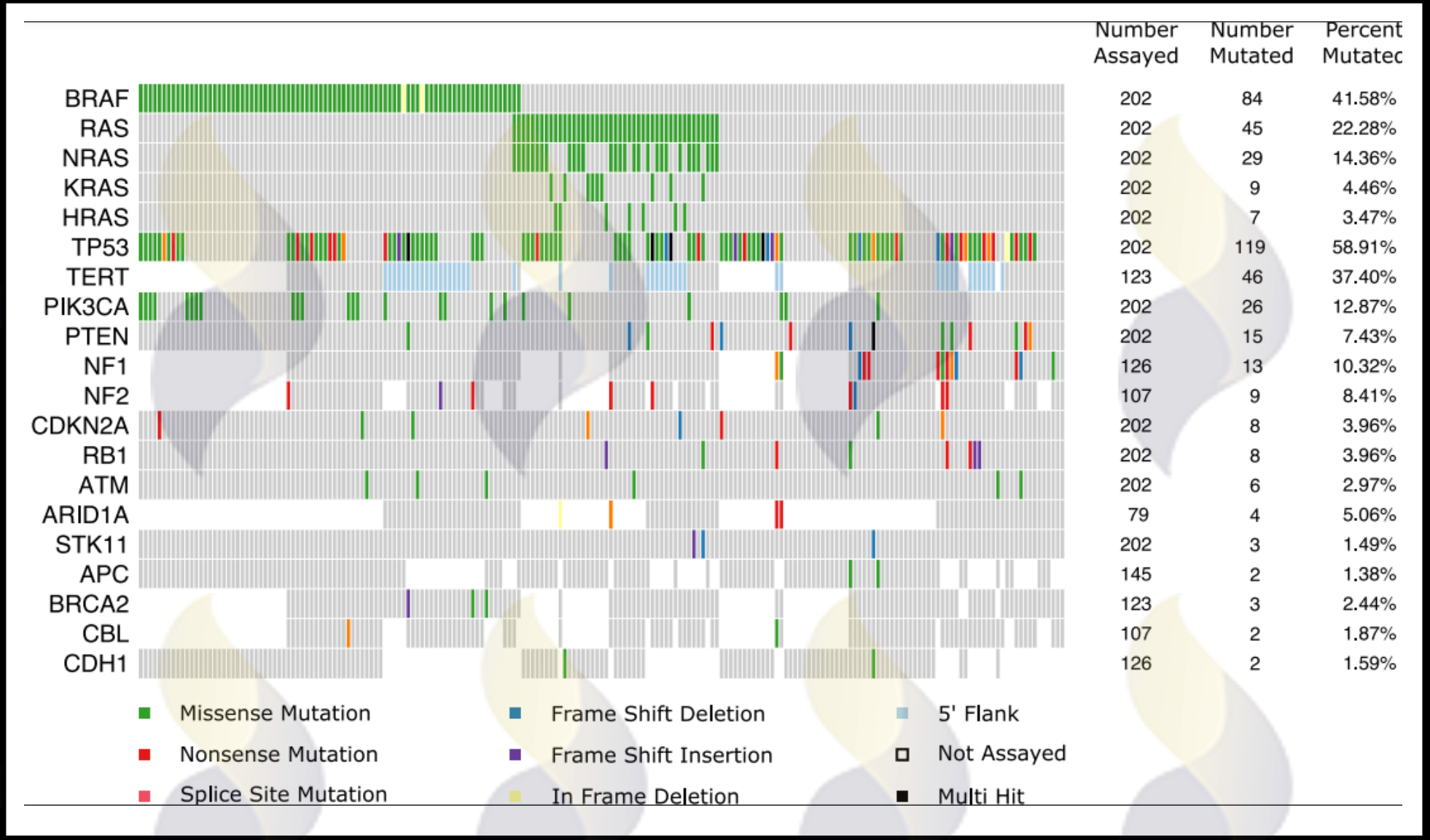


- Worse OS for all types of ATC therapeutic modalities--surgery, cytotoxic chemo, radiation, BRAF inhibitor



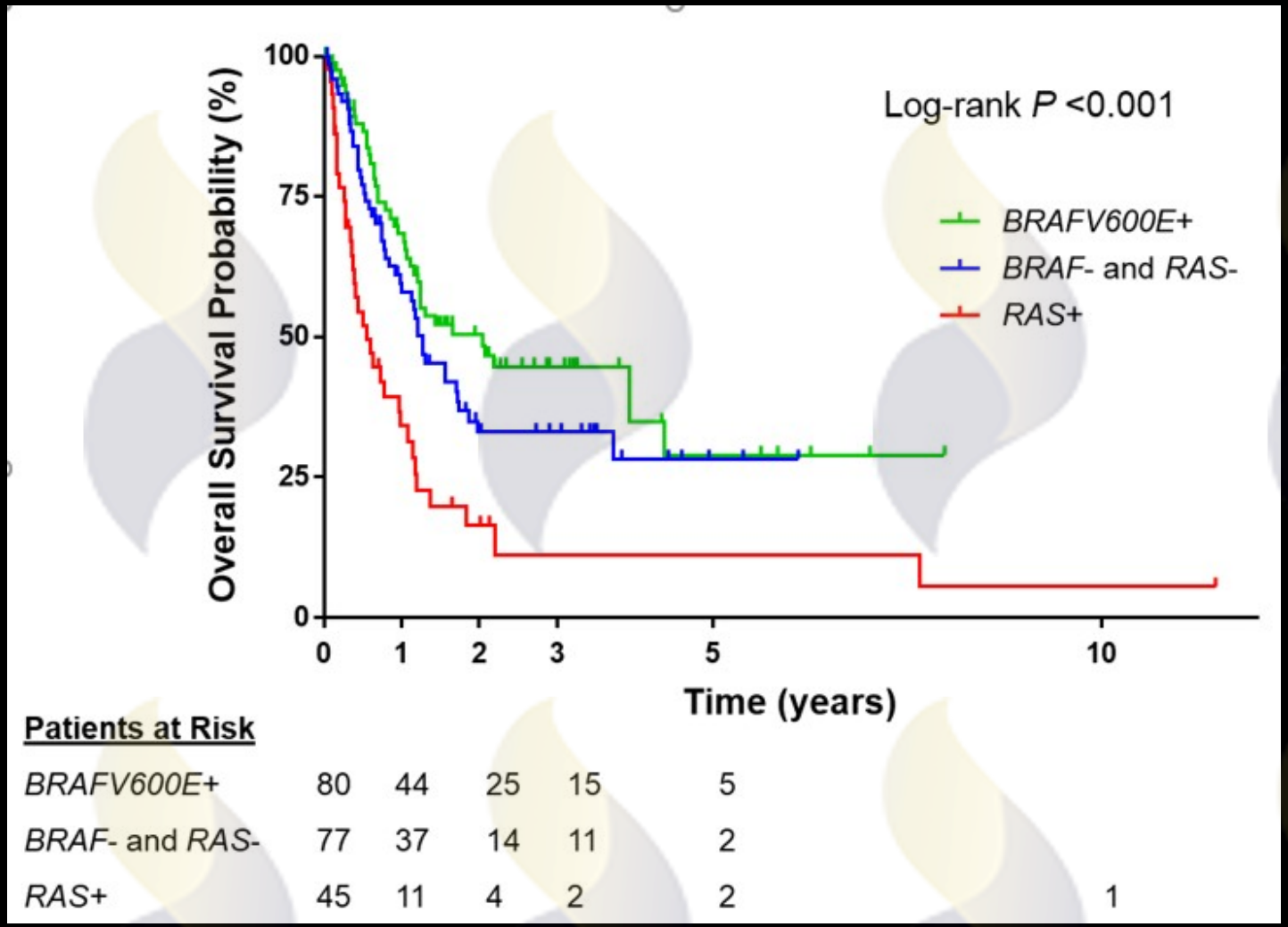
Qin Y, Wang JR, Wang Y, Iyer P, Cote G, Busaidy NL, Dadu R, Zafereo M, Williams MD, Ferrarotto R, Gunn GB, Wei P, Patel K, Hofmann MC, Cabanillas ME, Thyroid 2021

Somatic Mutations in 202 ATC Patients



Wang JR, Montierth M, Li X, Goswami M, Zhao X, Cote G, Wang W, Iyer P, Dadu R, Busaidy NL, Lai SY, Gross ND, Ferrarotto R, Lu C, Gunn GB, Williams MD, Routbort M, Zafereo M, Cabanillas ME, submitted for publication

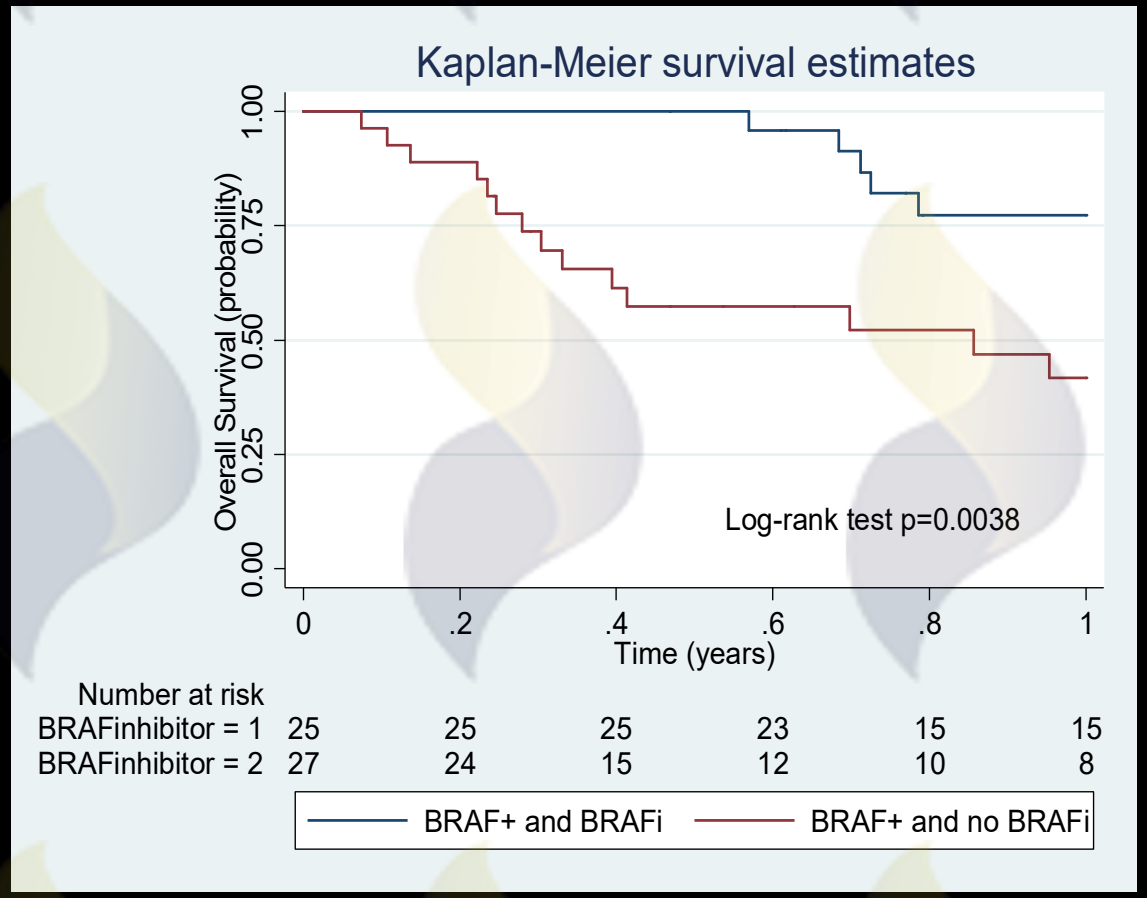
Overall survival of ATC patients by driver mutation status

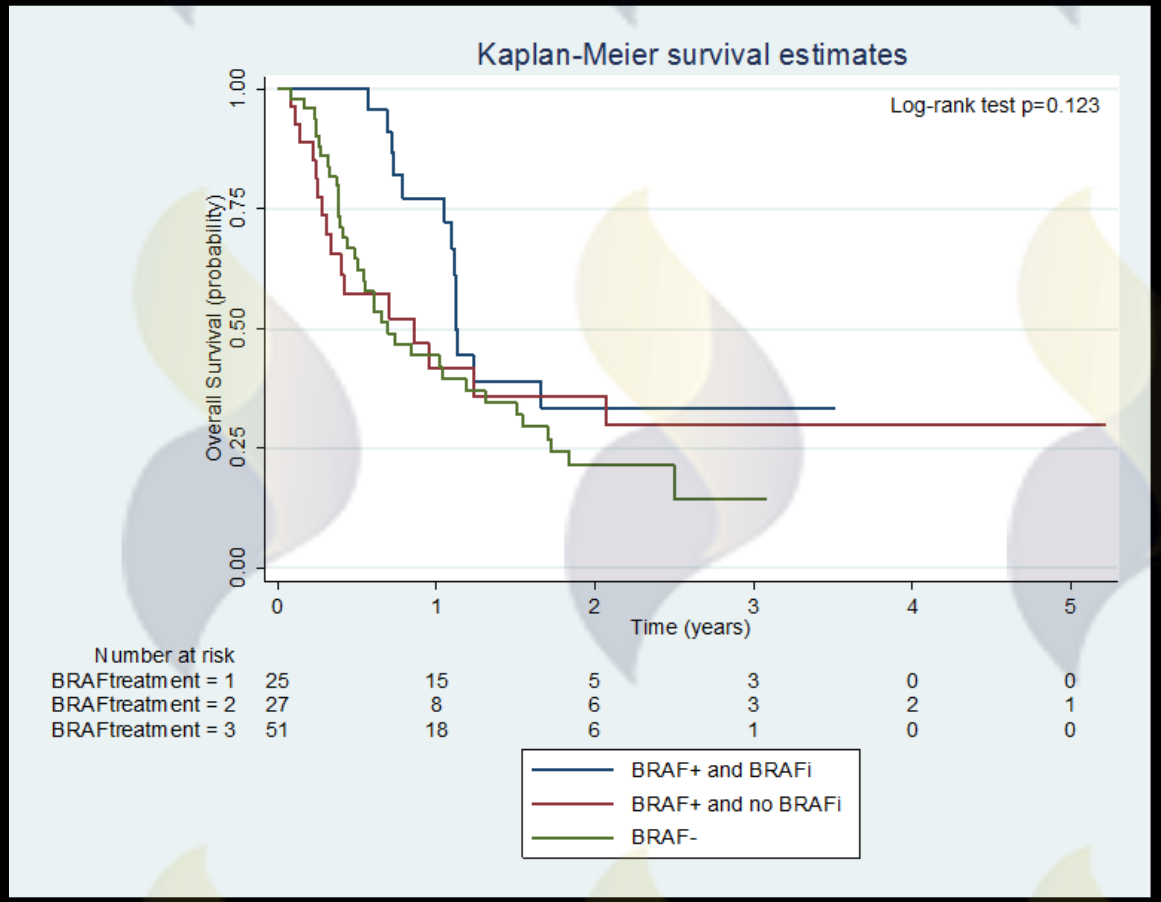


- *RAS* mutations were associated with a more than 2.5-fold higher risk of death (HR 2.64, 95% CI 1.66-4.20) compared to *BRAF*V600E

Wang JR, Montierth M, Li X, Goswami M, Zhao X, Cote G, Wang W, Iyer P, Dadu R, Busaidy NL, Lai SY, Gross ND, Ferrarotto R, Lu C, Gunn GB, Williams MD, Routbort M, Zafereo M, Cabanillas ME, submitted for publication

BRAF inhibitors improve OS…

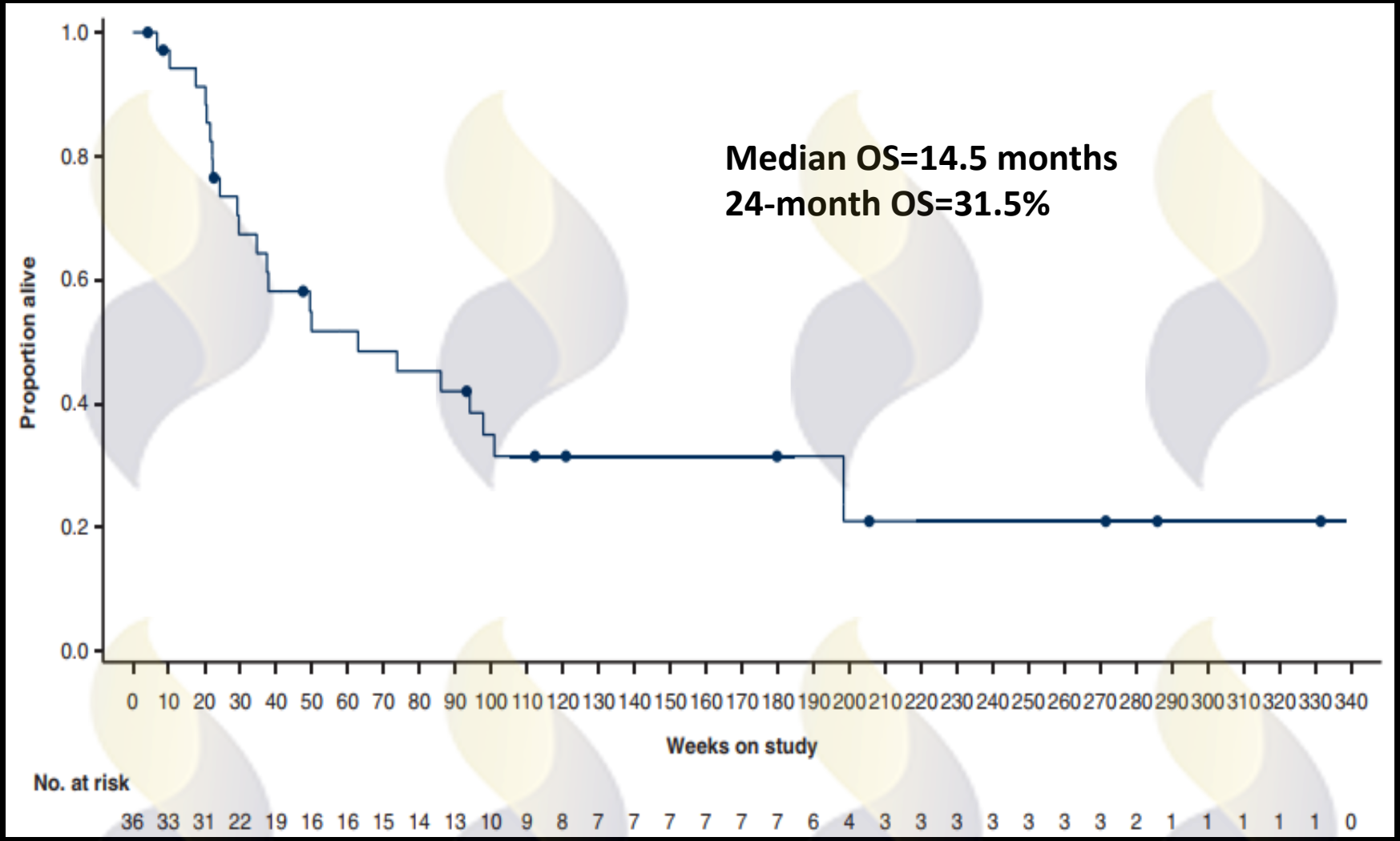




…only the first year or so

Wang et al. Facilitating rapid precision oncology in anaplastic thyroid cancer: Clinical implications of next generation sequencing (NGS) mutation testing and impact on survival. ASCO 2018

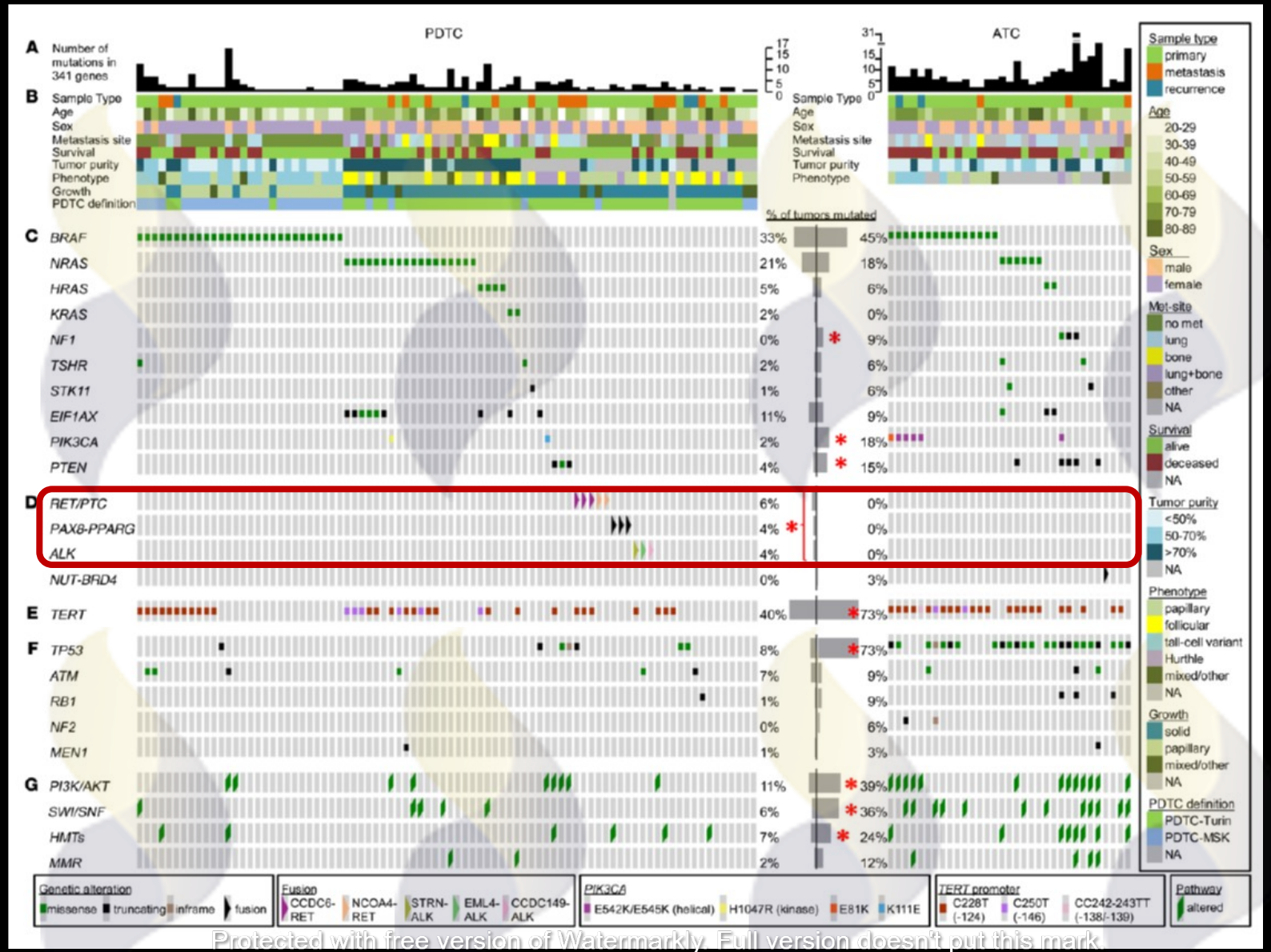
Dabrafenib (BRAFi) + trametinib (MEKi) phase 2



Vivek Subbiah, Robert J. Kreitman, Zev A. Wainberg, Jae Yong Cho, Jan H. M. Schellens, Jean Charles Soria, Patrick Y. Wen, Christoph Zielinski, Maria E. Cabanillas, Boran A, Ilankumaran P, Burgess P, Romero Salas T, Bhumsuk Keam, Annals of Oncology 2021

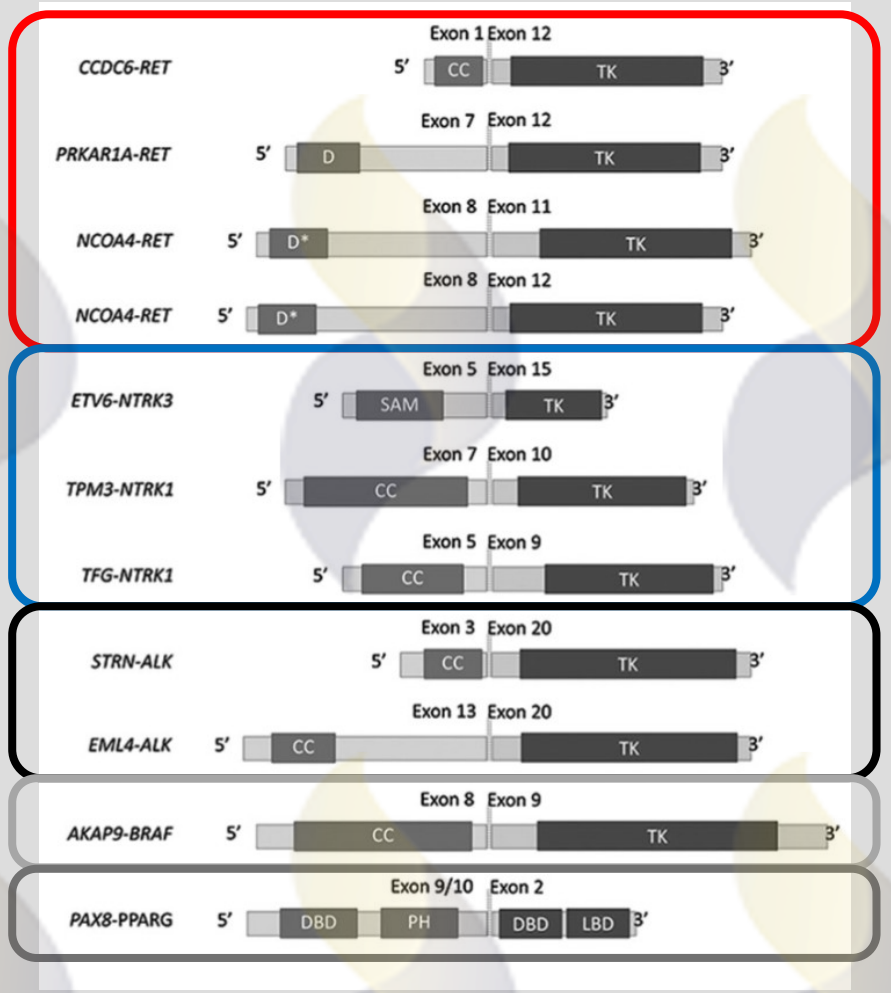
Fusions in PDTC and ATC

NTRK fusions also seen but rare



Landa et al, JCI 2016

Targetable Gene Fusions in Thyroid Cancer



RET

pralsetinib,
selpercatinib

NTRK

larotrectinib
entrectnib

ALK

BRAF

PPARG

ROS1 fusions

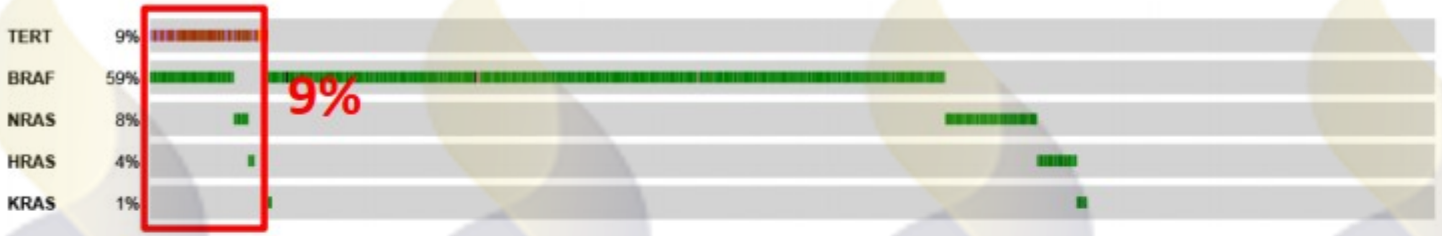
Yakushina VD et al. *Thyroid*. 2018;28:158–167.

Cocco E et al. *Nature Rev Clin Oncol*. 2018;15:731–747.

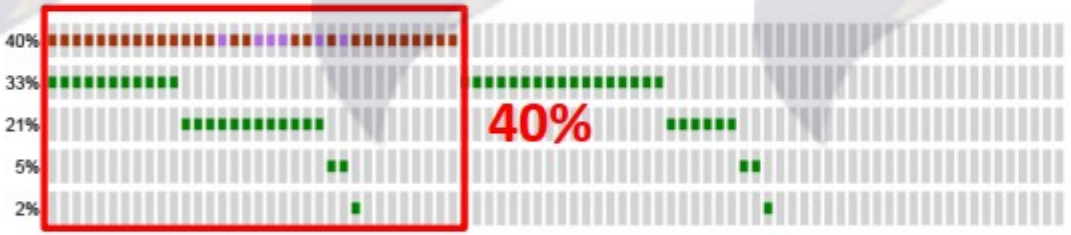
Waguespack et al, presented at ETA 2019, adapted

TERT promoter mutations in thyroid cancers

Papillary thyroid tumors (TCGA)



Poorly-differentiated thyroid tumors

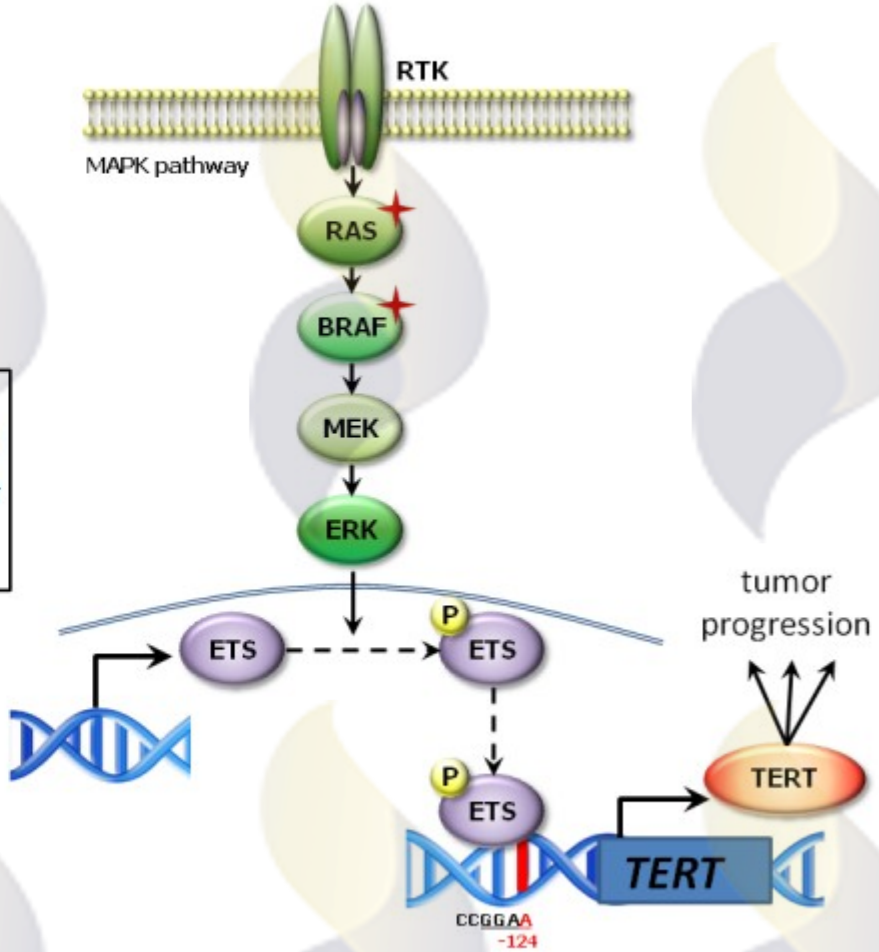


TERT promoter:
C228T (-124) C250T (-146)
C228A (-124) CC242-243TT
BRAF/RAS: missense

Anaplastic thyroid tumors

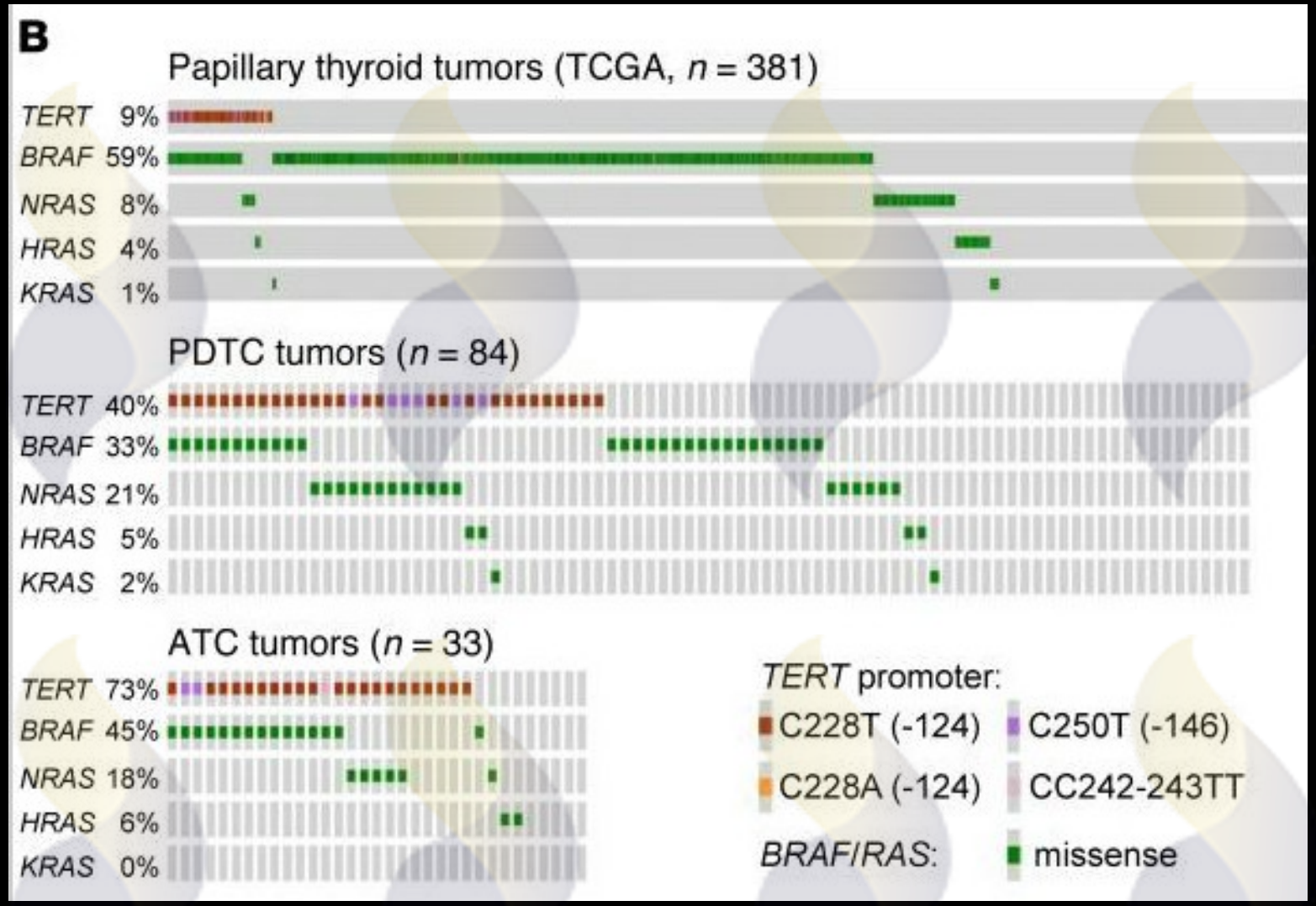
***TERT-BRAF/RAS* association**

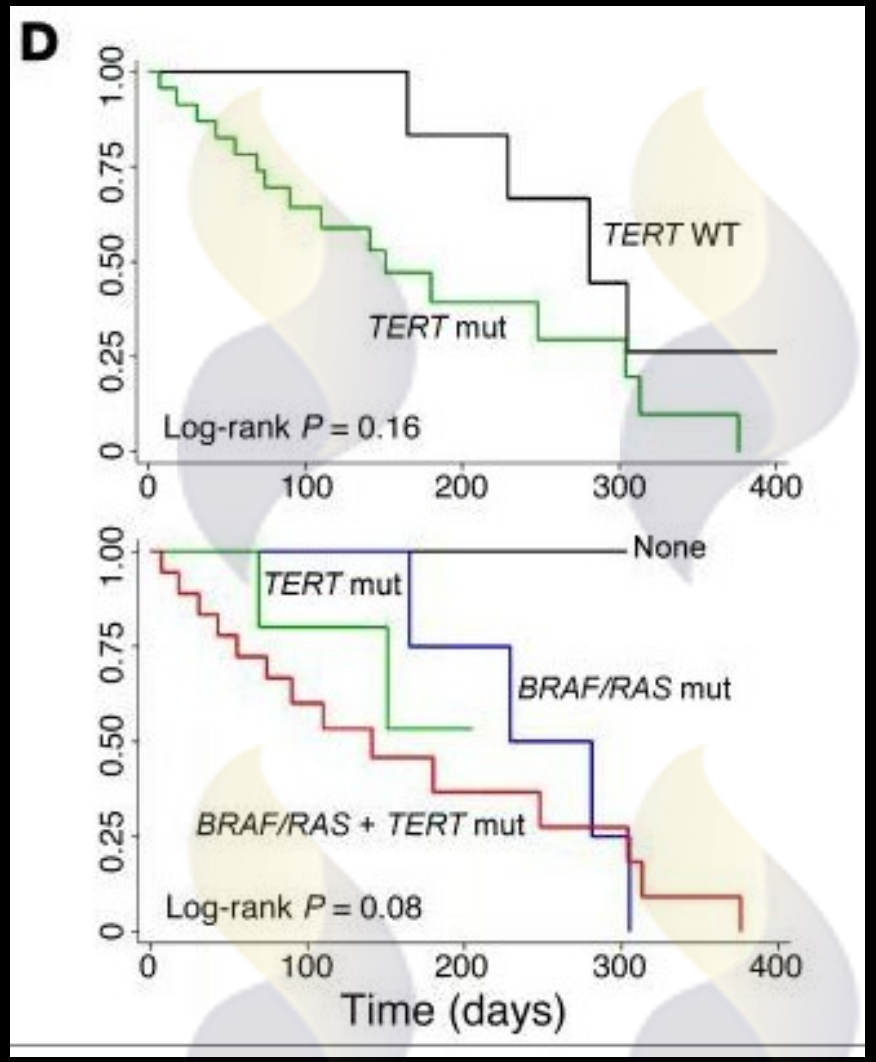
	PTC	PDTC+ATC
OR	3.3	3.4
p-value	0.03	0.004



Slide courtesy of Dr. Fagin, Landa et al, JCI 2016

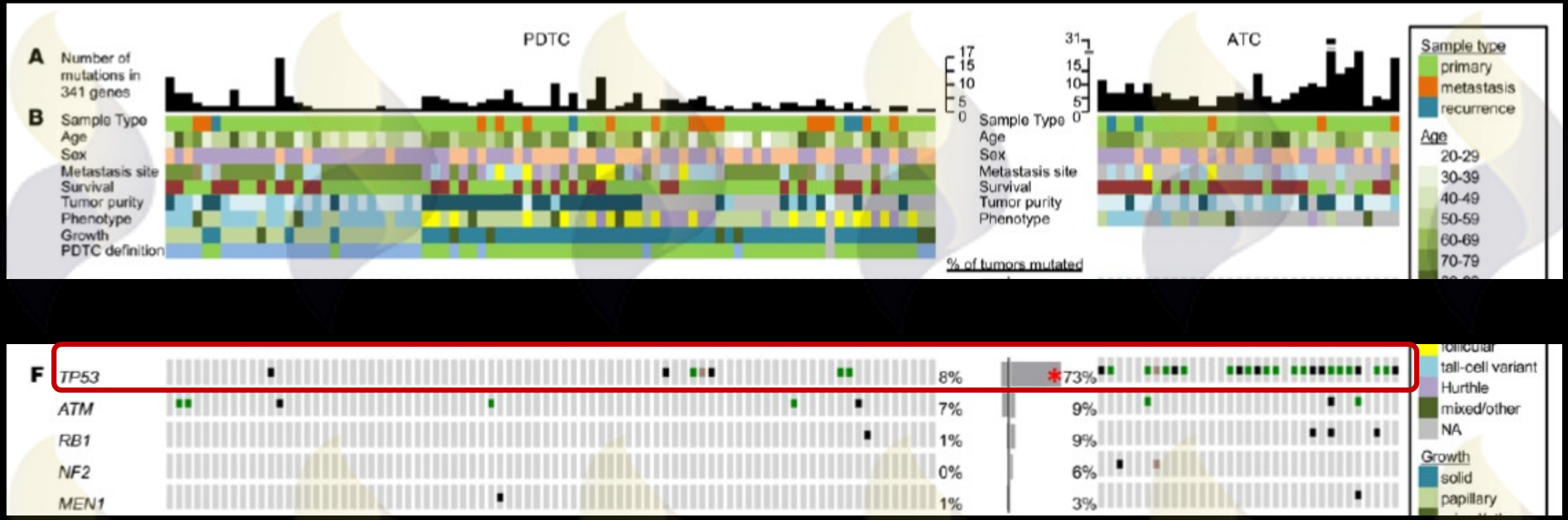
TERT promoter mutations in PDTC vs ATC





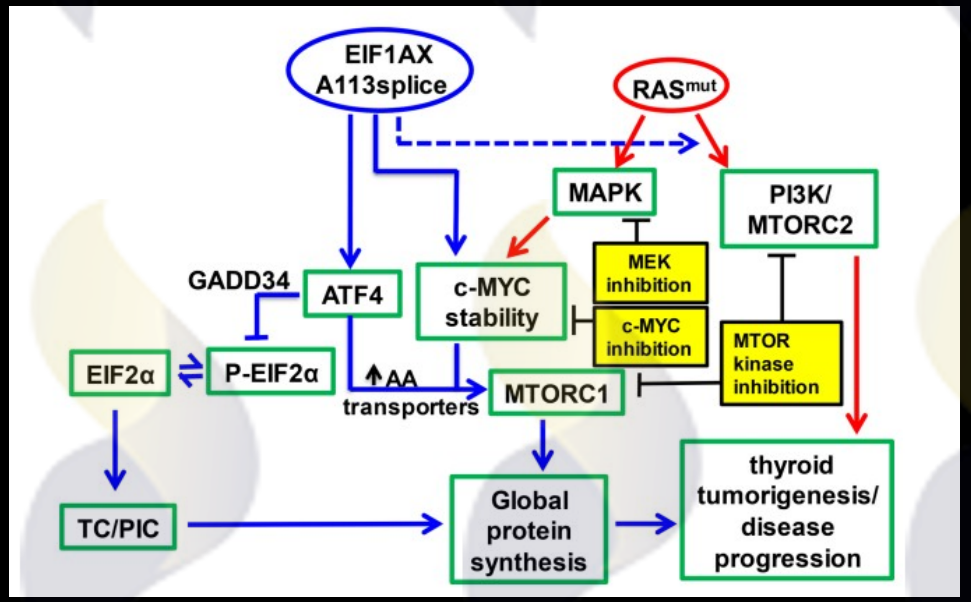
Landa et al, JCI 2016

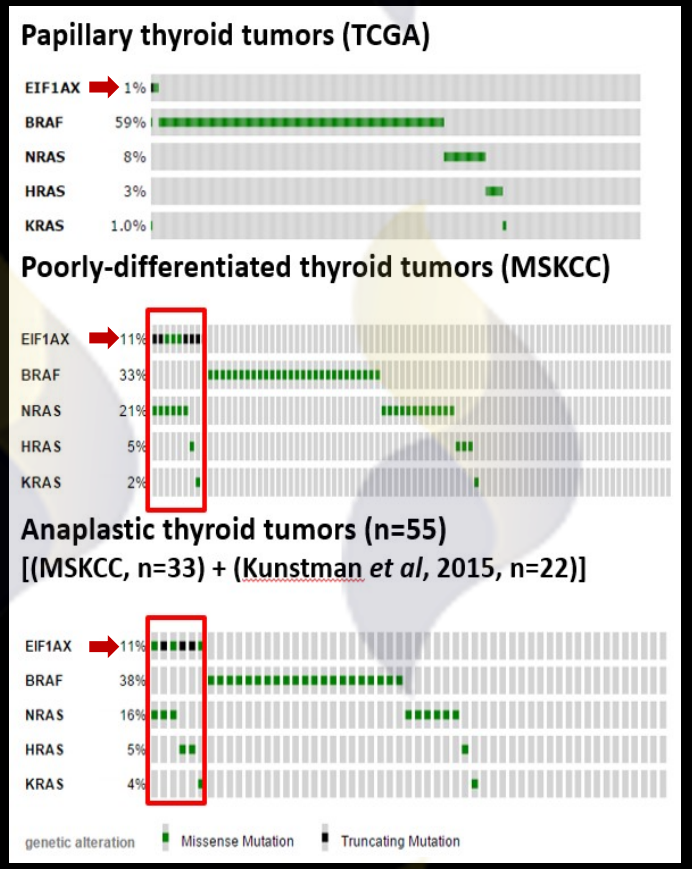
TP53 mutations in PDTC vs ATC



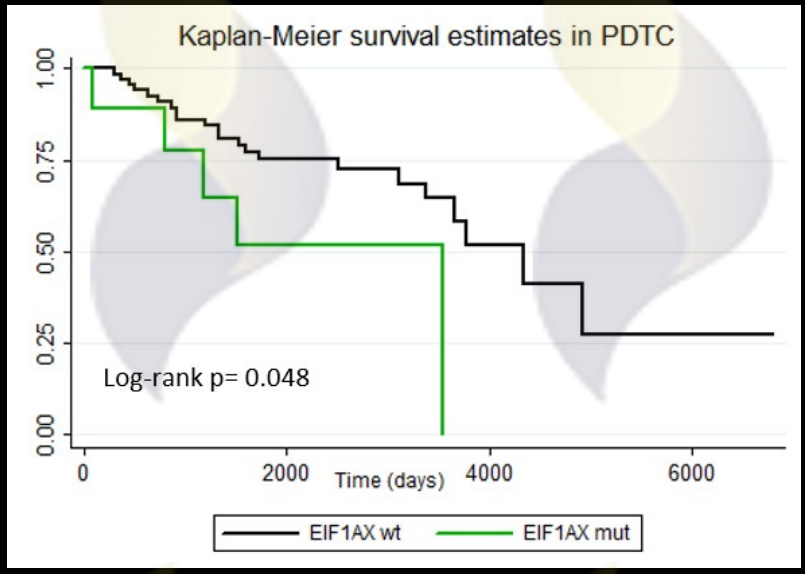
Landa et al, JCI 2016

EIF1AX-RAS association





Landa et al, JCI 2016



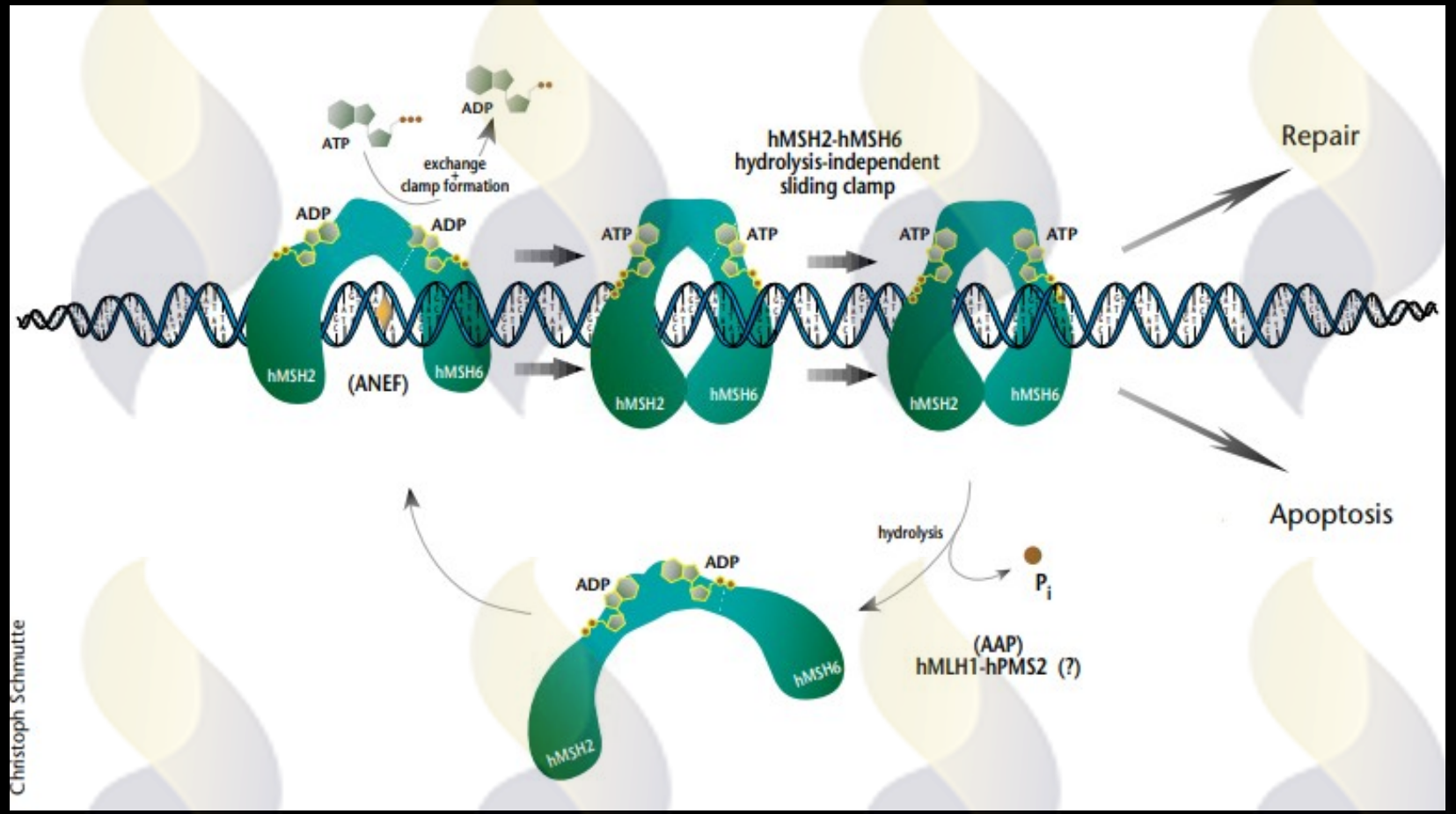
- EIF1AX gene encodes an essential eukaryotic translation initiation factor
  - EIF1AX splice leads to induction of ATF4, inducing global increase in protein synthesis
  - RAS mutation stabilizes c-MYC which is augmented by EIF1AX splice
  - cMYC and ATF4 cooperate to induce transcription of amino acid transporters→ activates mTOR signaling (which is targetable with mTORi)

- Mutations in EIF1AX are markedly enriched in PDTC and ATC
- Striking pattern of co-occurrence of EIF1AX with RAS→ worse prognosis

Krishnamoorthy GP et al, Cancer Discov 2019

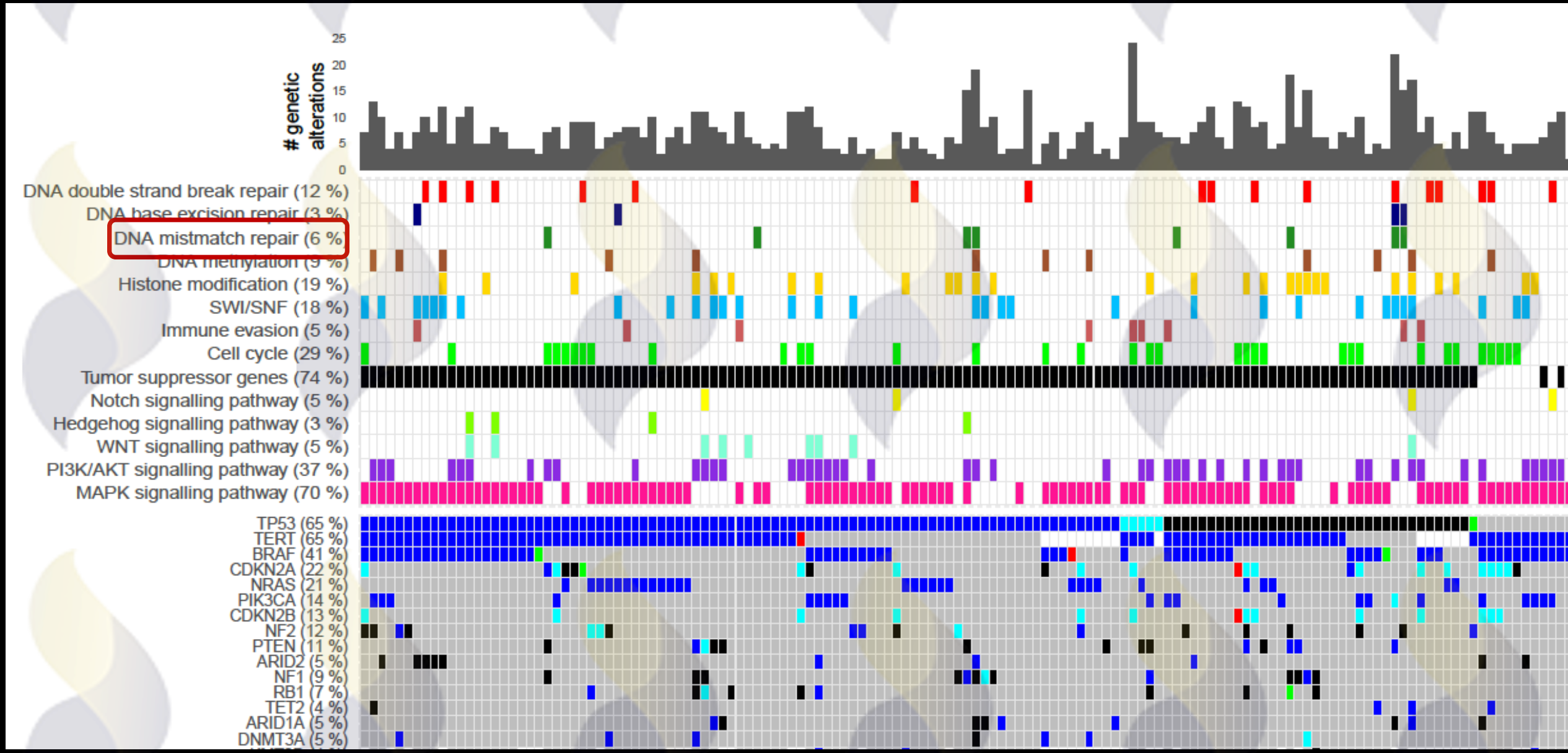
Mismatch repair (MMR)

- DNA damage provokes ADP->ATP exchange that links the sliding clamp to the DNA
- In the ATP-activated form, the sliding clamp transduces a mismatch signal
- In the absence of excision repair or when overwhelming amount of DNA damage→apoptosis occurs



Fischel R, Nature, 1999

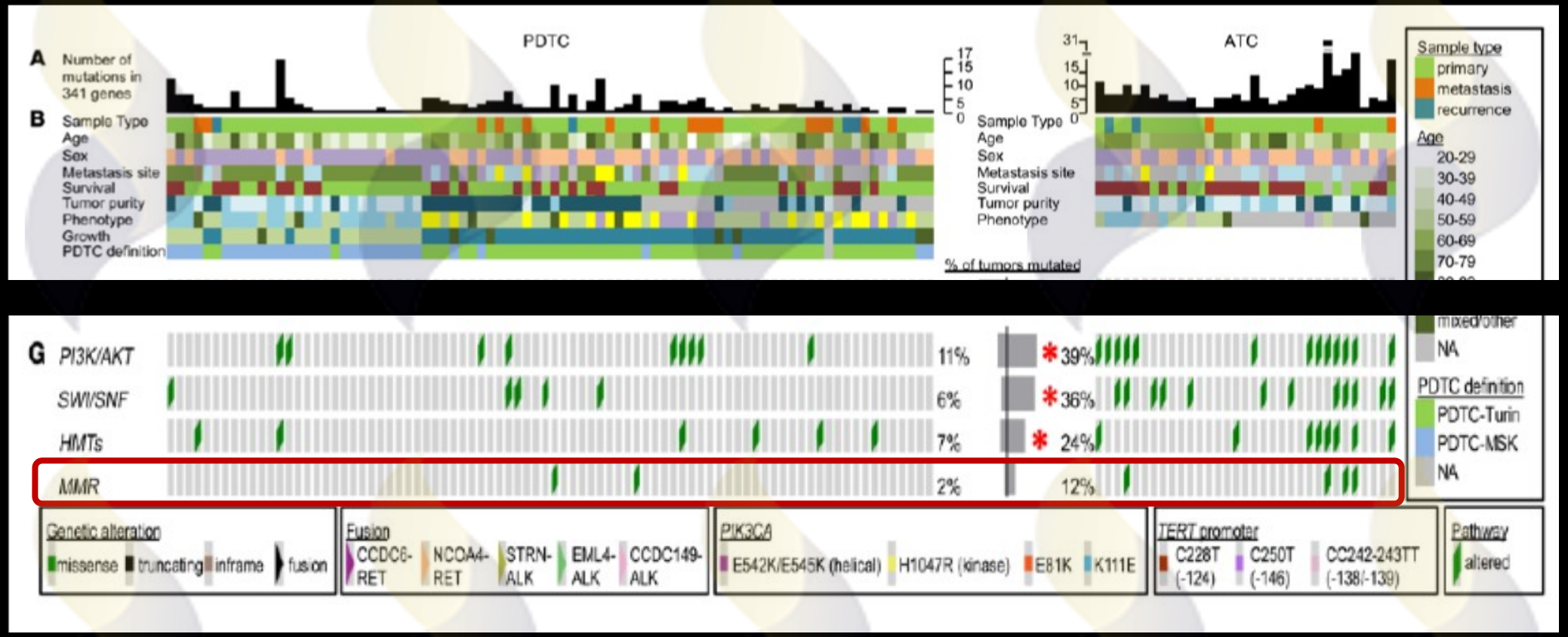
DNA Mismatch Repair Defects in ATC ~6%

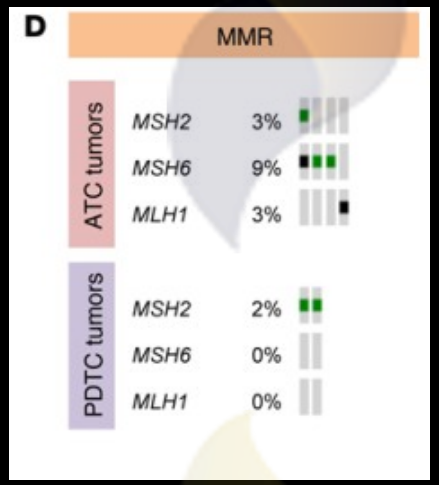


(adapted: only most common genes included)
Includes Landa et al ATC data

Pozdeyev et al, CCR 2018

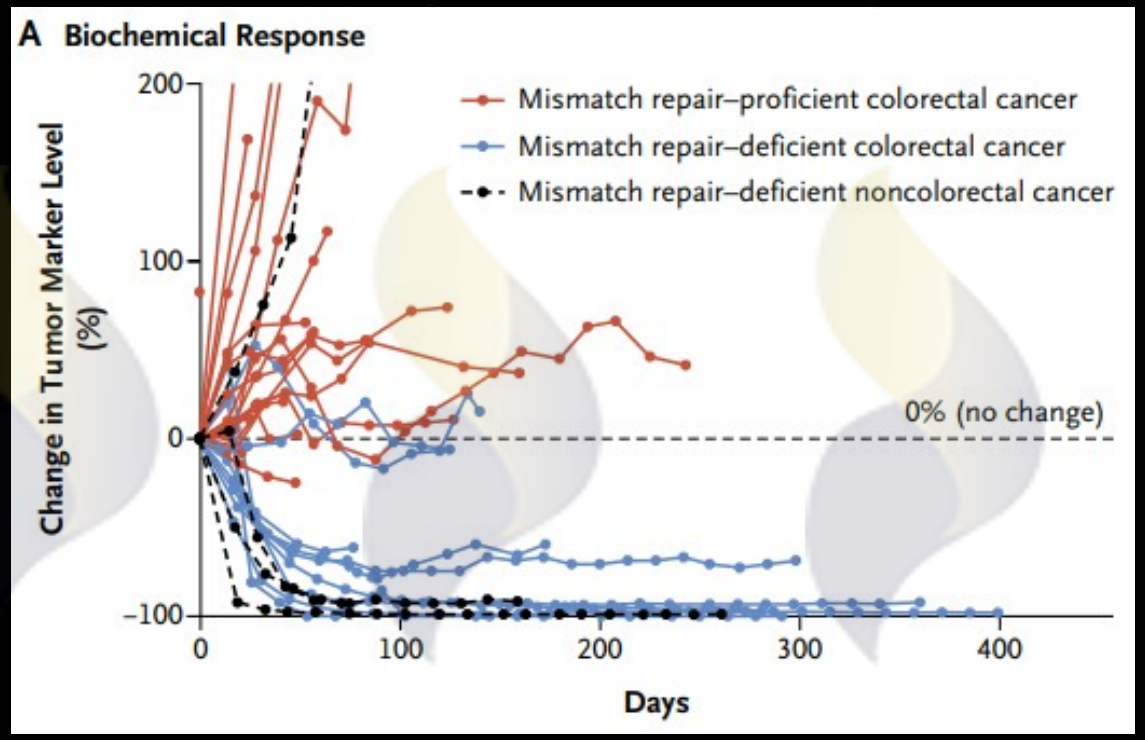
Mismatch repair genes more common in ATC than PDTC





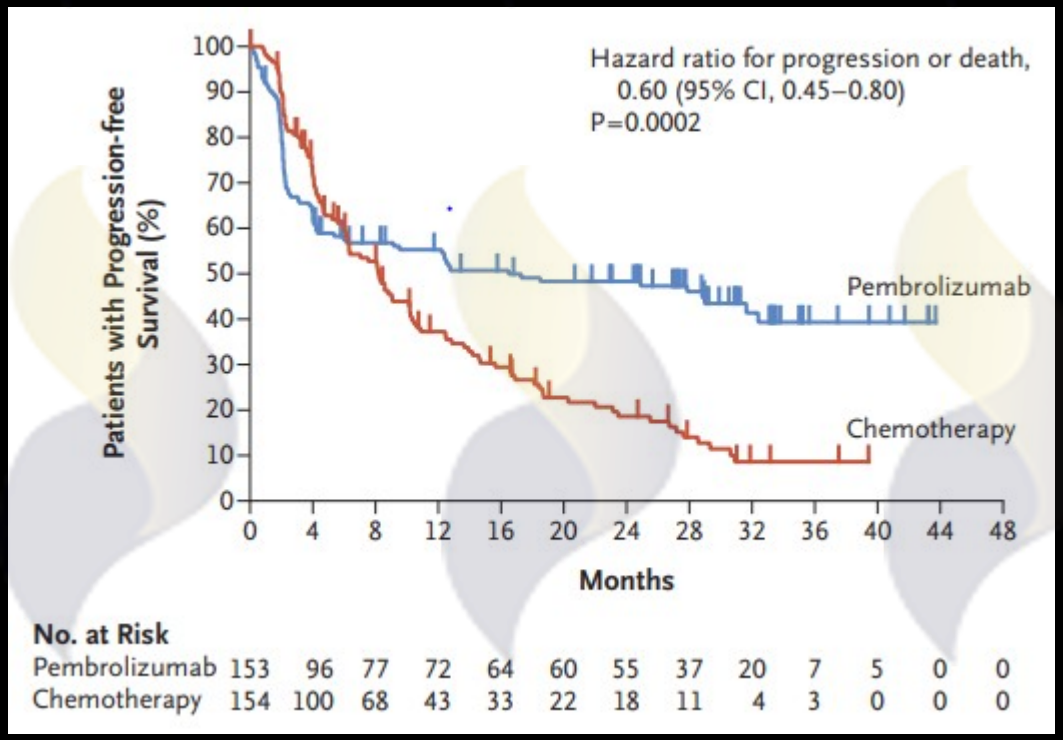
Landa et al, JCI 2016

Mismatch repair and Immunotherapy: CRC



- Phase 2 trial
- Objective response 40% and PFS were 40% (4 of 10 patients) and 78% (7 of 9 patients), respectively, for mismatch repair–deficient colorectal cancers and 0% (0 of 18 patients) and 11% (2 of 18 patients) for mismatch repair–proficient colorectal cancers

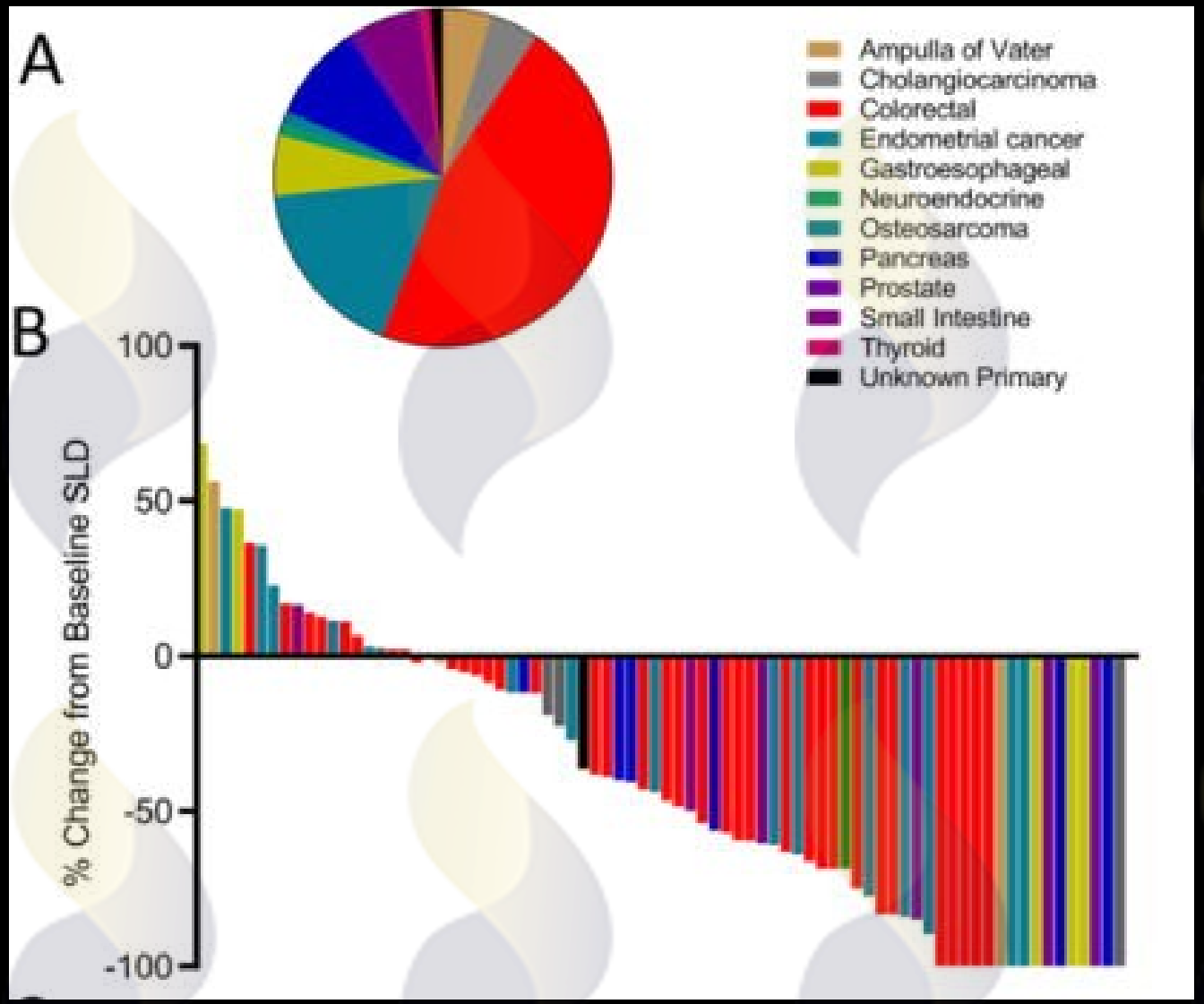
Le DT et al, NEJM 2016

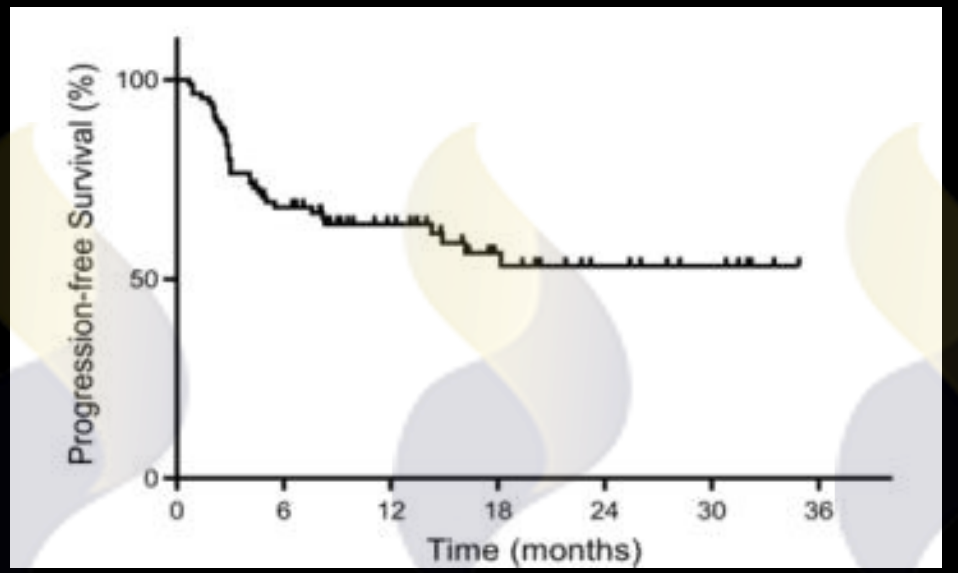


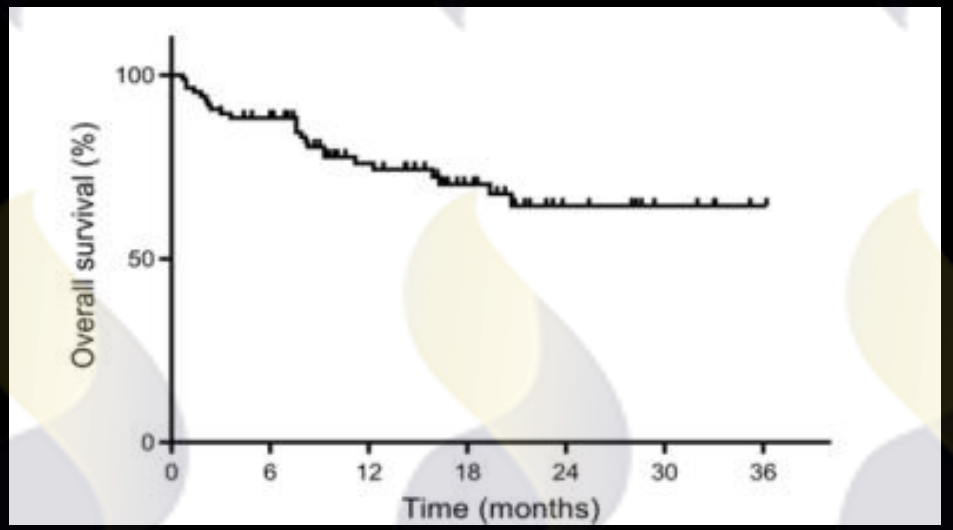
- phase 3 with metastatic MSI-H colorectal cancer randomized to pembrolizumab vs chemo
- Pembrolizumab led to significantly longer PFS than chemotherapy

André T et al, NEJM 2020

Pembrolizumab is FDA approved for MSI-high





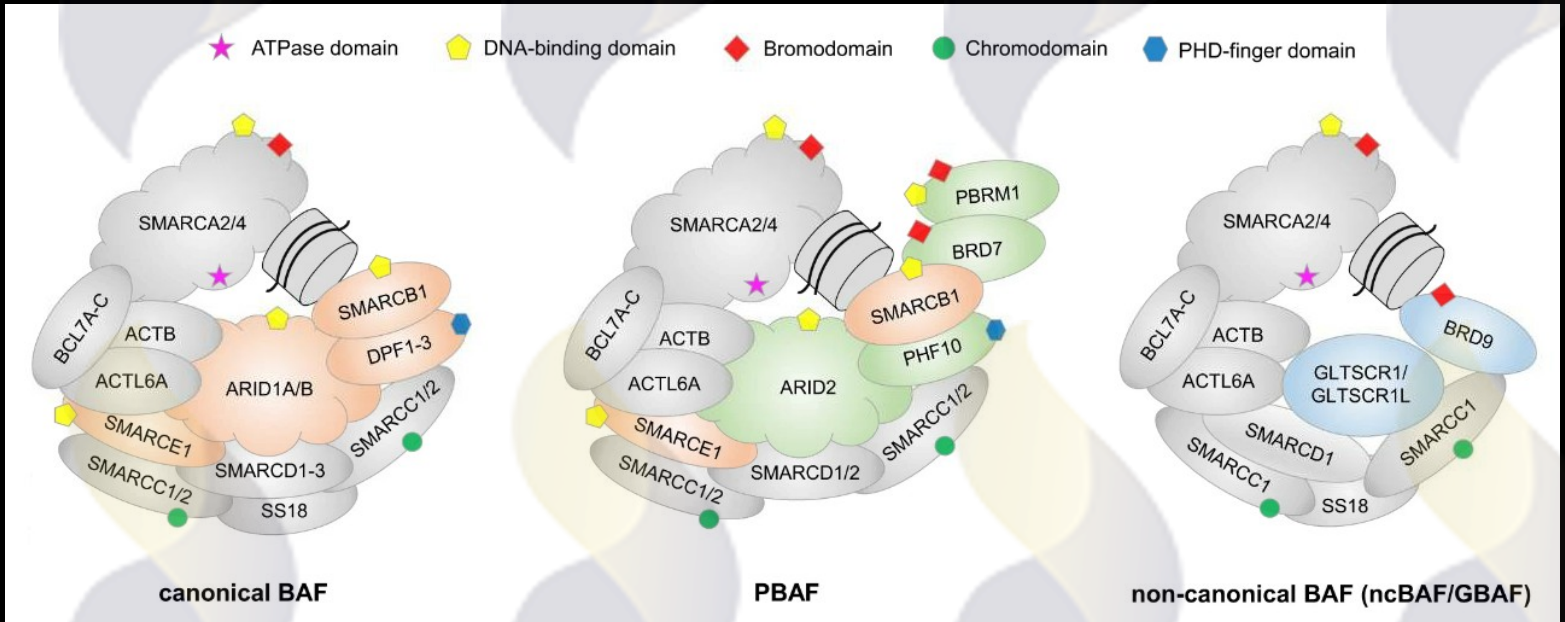


Le DT et al, Science 2017

SWI/SNF Chromatin Remodeling Complex

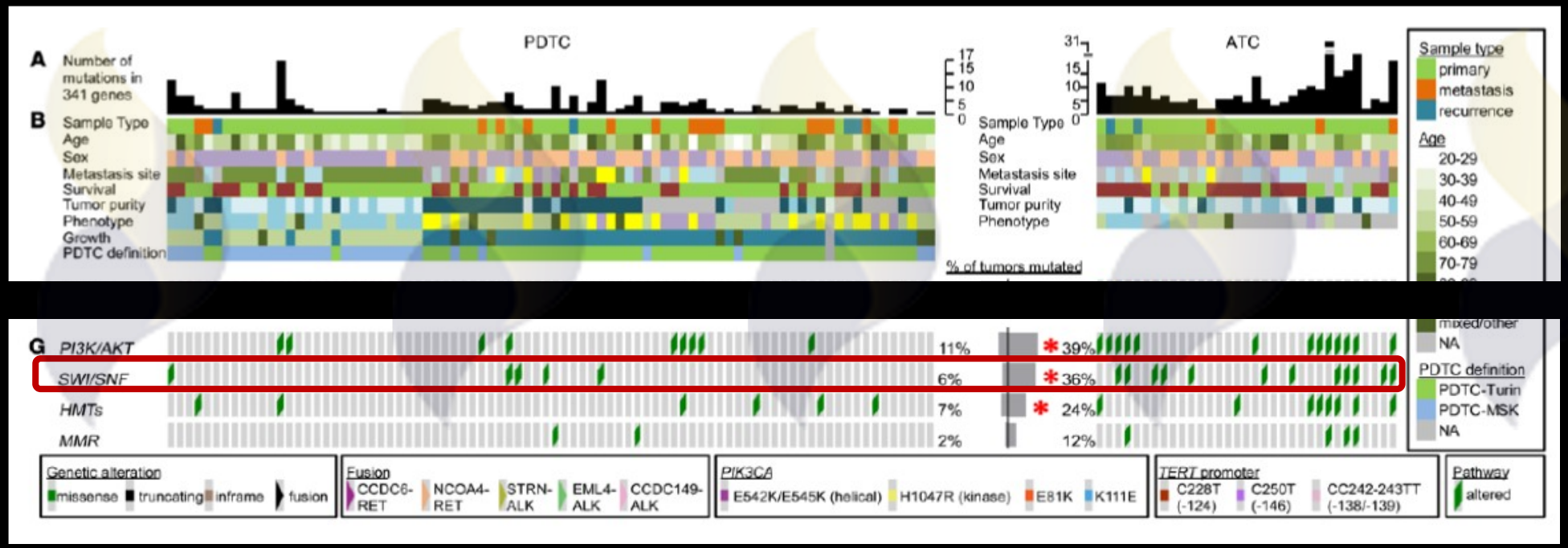
- SWI/SNF complexes consist of 12–15 subunits including ARID1A, ARID1B, ARID2, ARID5B, SMARCB1, SMARCA4, SMARCA2, PBRM1 and ATRX

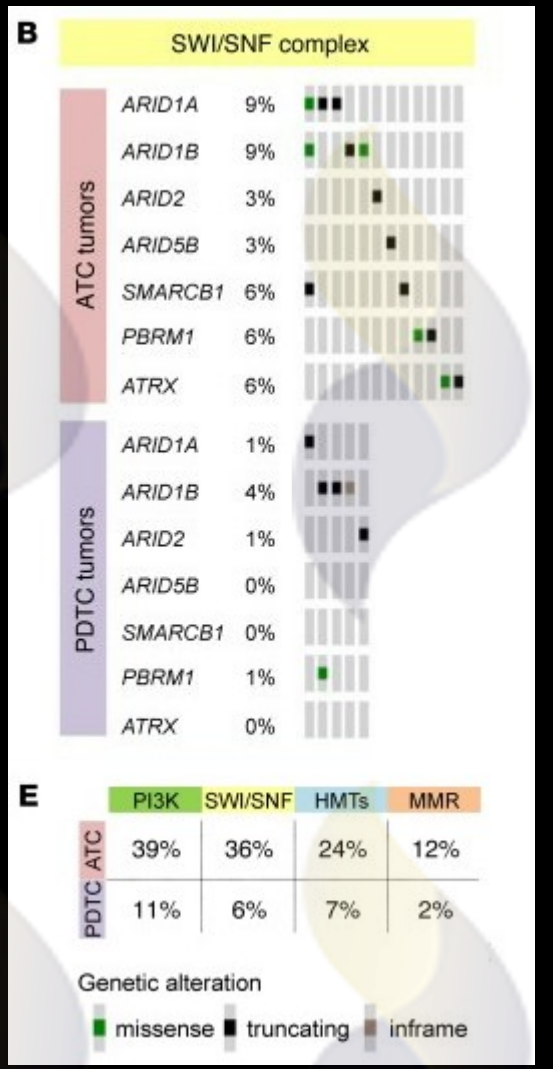
- These complexes interact with co-activators, co-repressors and transcription factors to mobilize nucleosomes, remodel chromatin and repair DNA



Wanior M et al, Oncogene, 2021

SWI/SNF in PDTC vs ATC

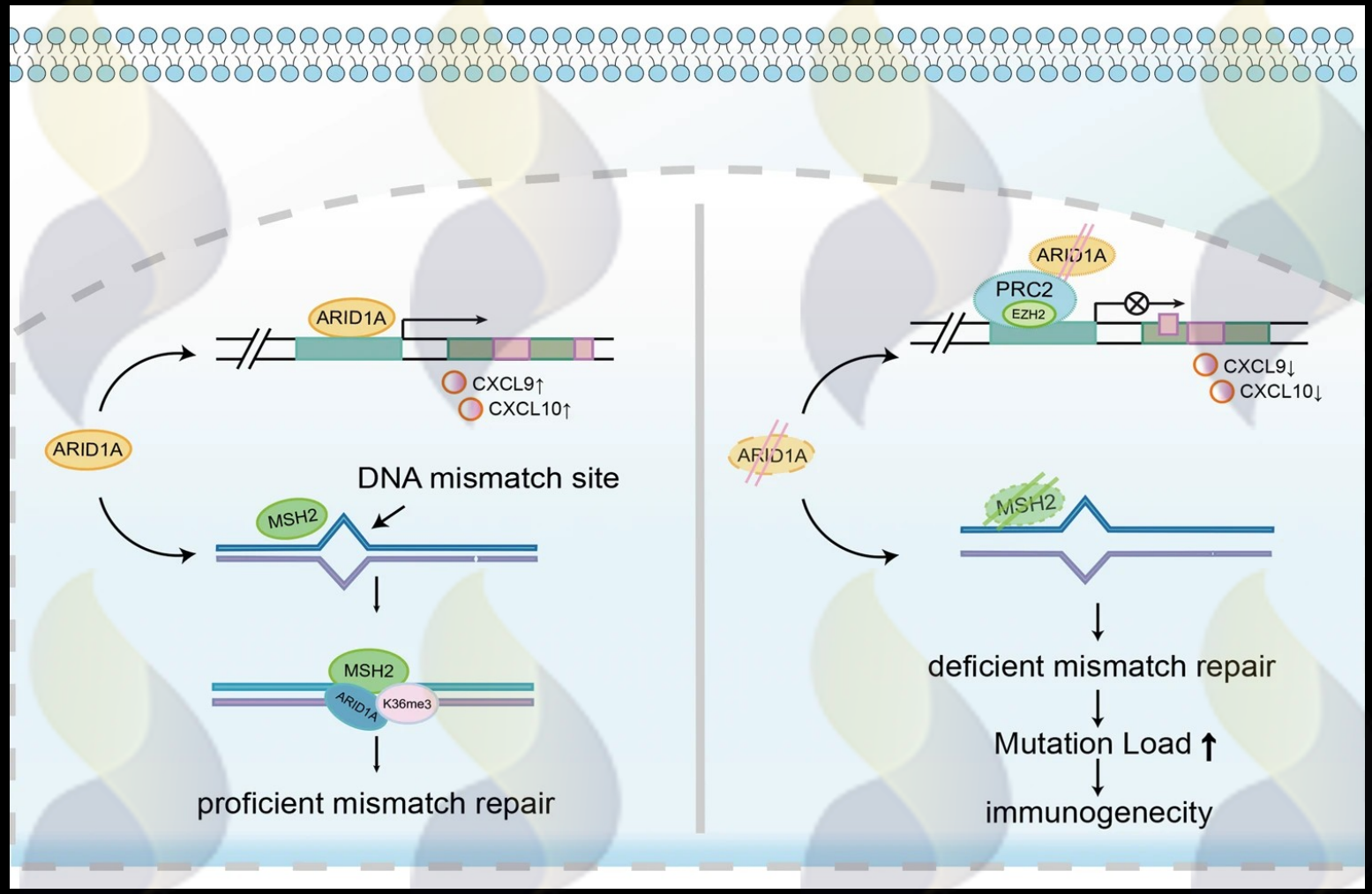




Landa et al, JCI 2016

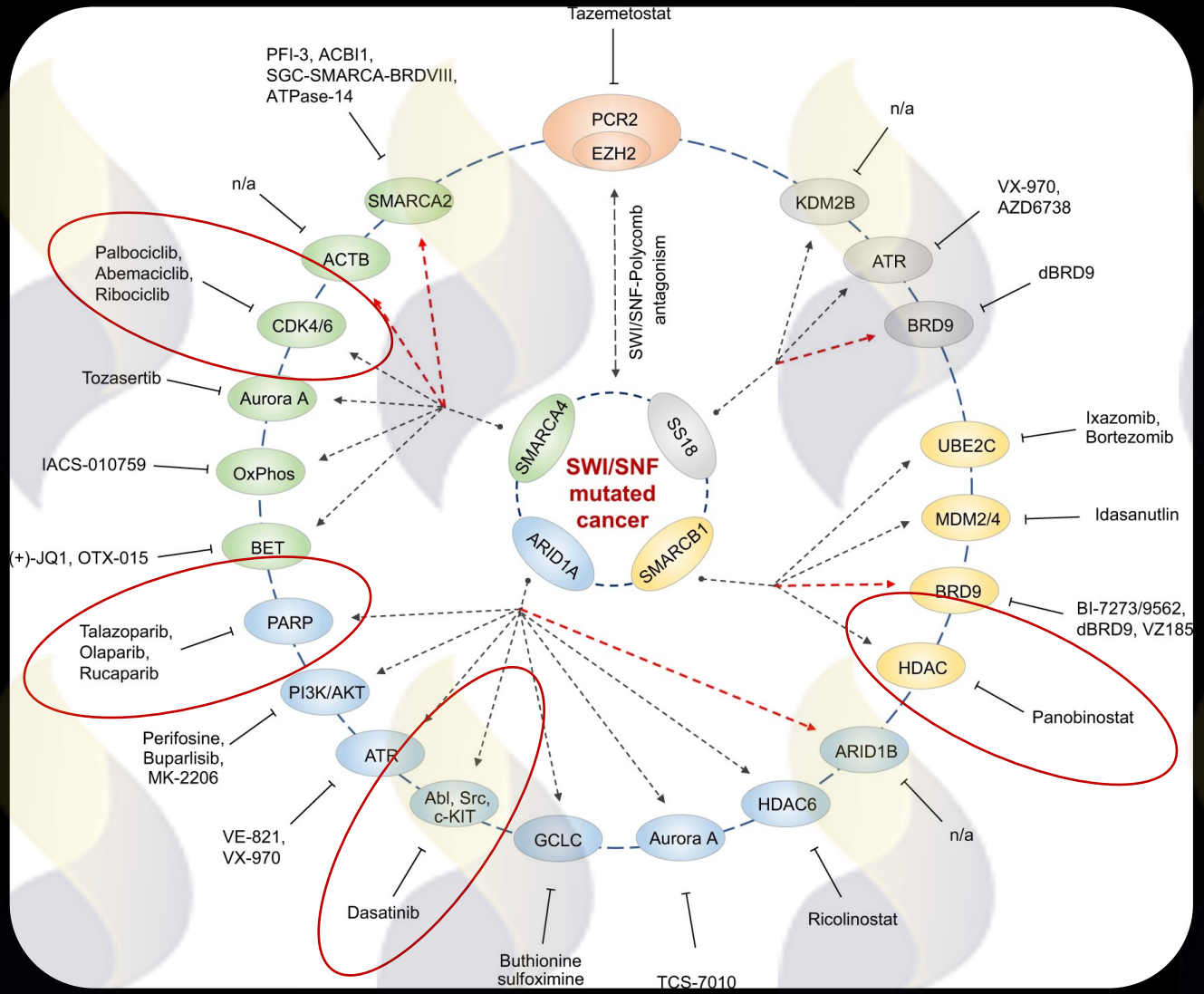
SWI/SNF deficiency is related to sensitivity to immune checkpoint blockade

- ARID1A interacts with MSH2 and regulates MSH2 positioning at DNA mismatch sites→ *functional defects* in MMR



Zhou M et al, Oncogenesis, 2021

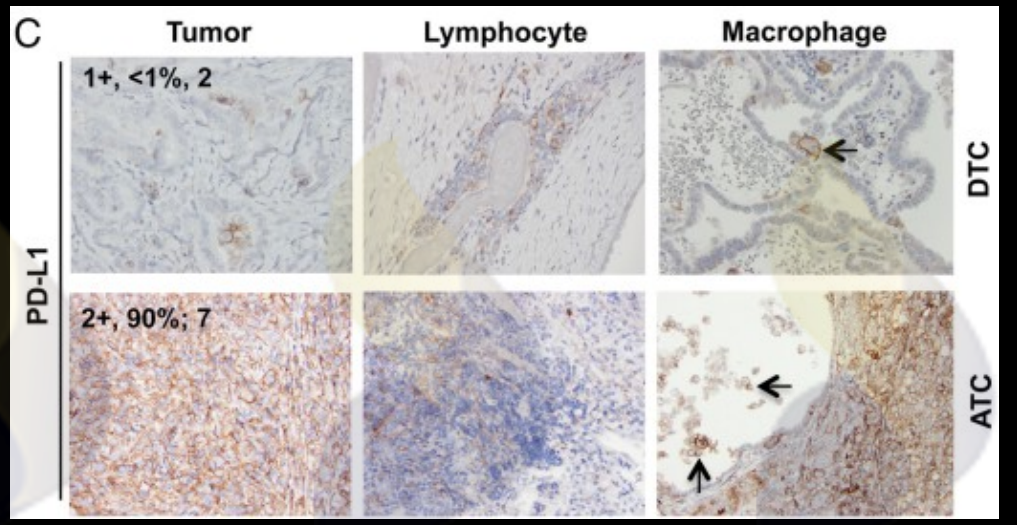
Proposed targeted therapies for SWI/SNF gene mutations



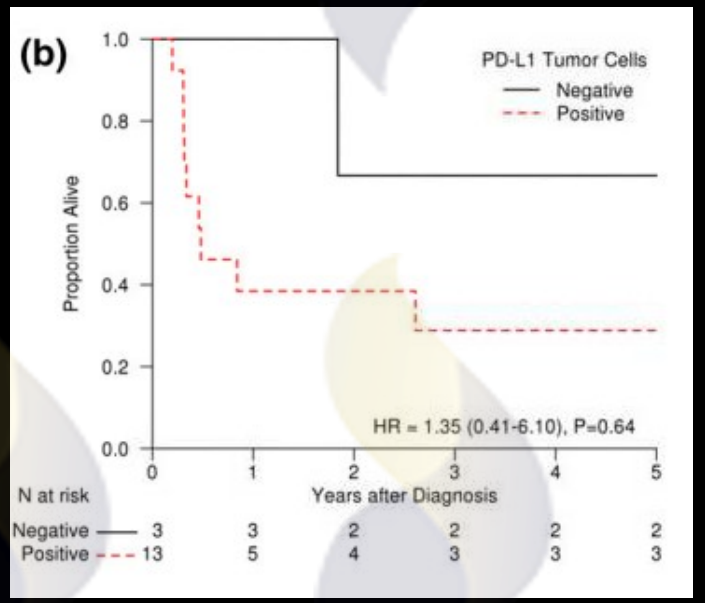
Wanior M et al, Oncogene, 2021

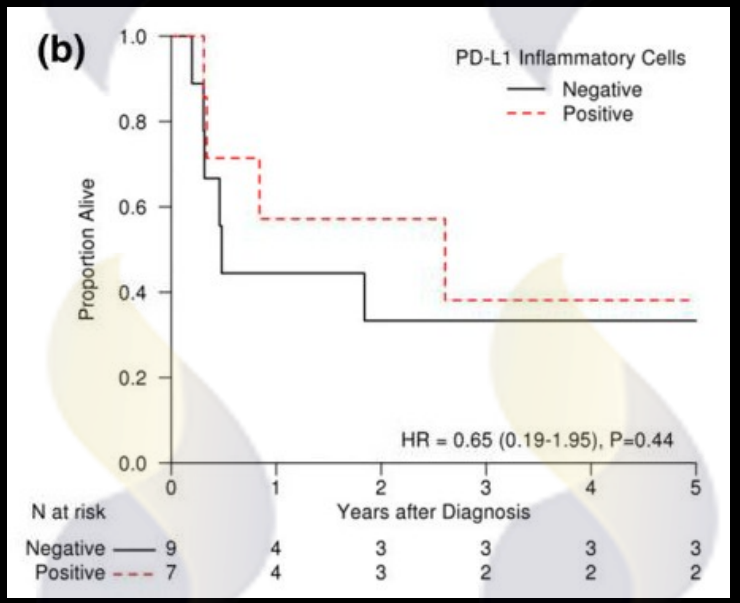
Immune Landscape of ATC

- PDL1 highly expressed in ATC patient tumors compared to DTC
- ATC samples were also infiltrated with CD8^{+}T cells and Tregs
- Positive staining for PD-L1 in tumor cells or PD-1 staining in inflammatory cells appears predictive of prognosis in the ATC patients



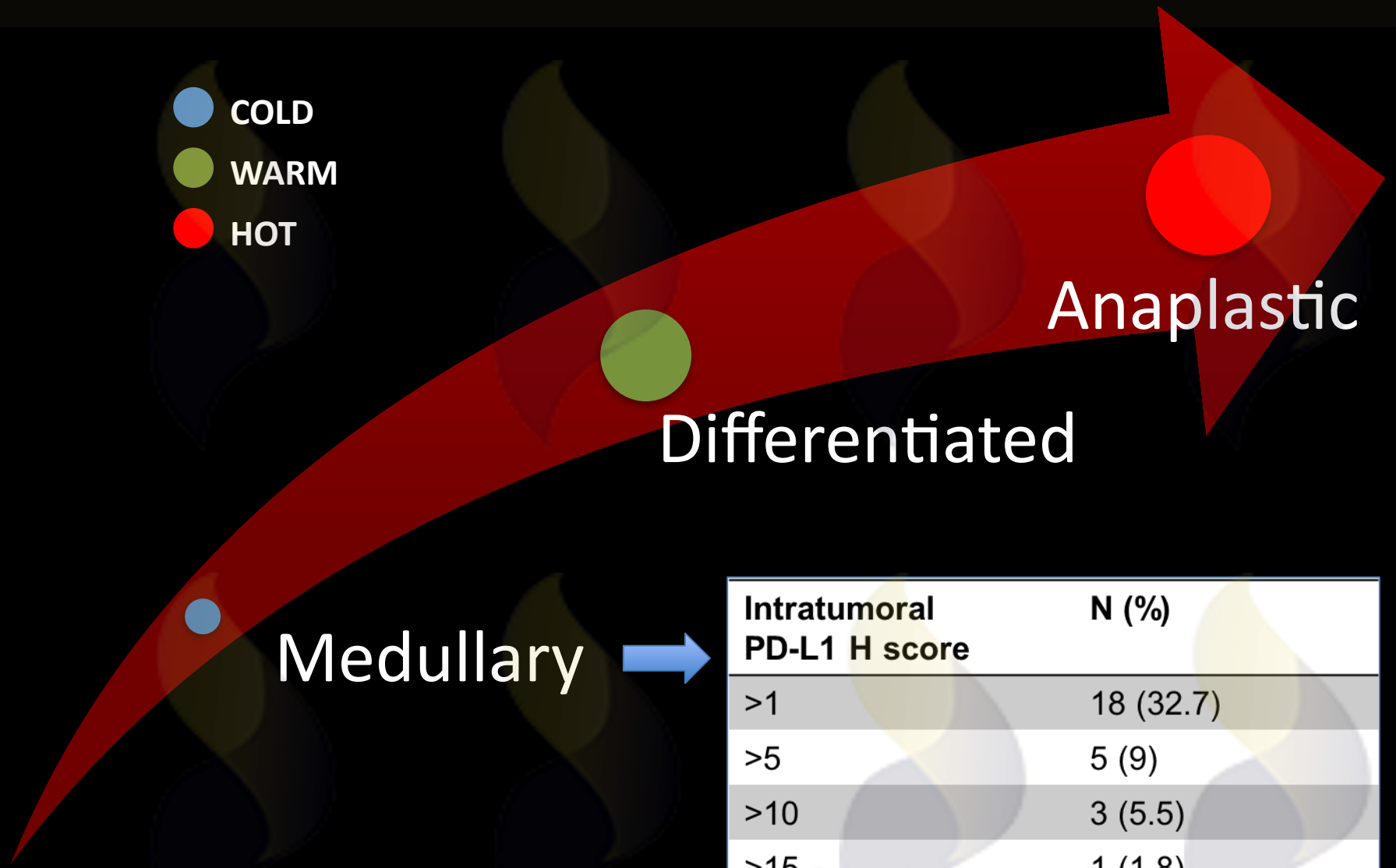
Bastman JJ, JCEM 2016





Chintakuntlawar AV, JCEM 2017

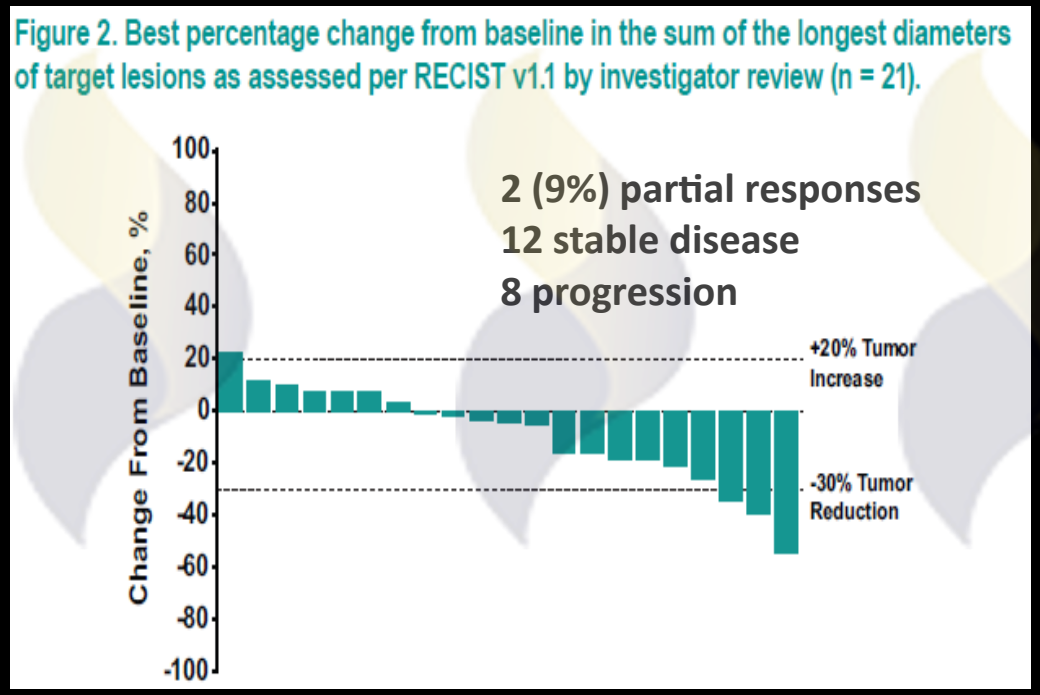
Immune Microenvironment in Thyroid Cancer



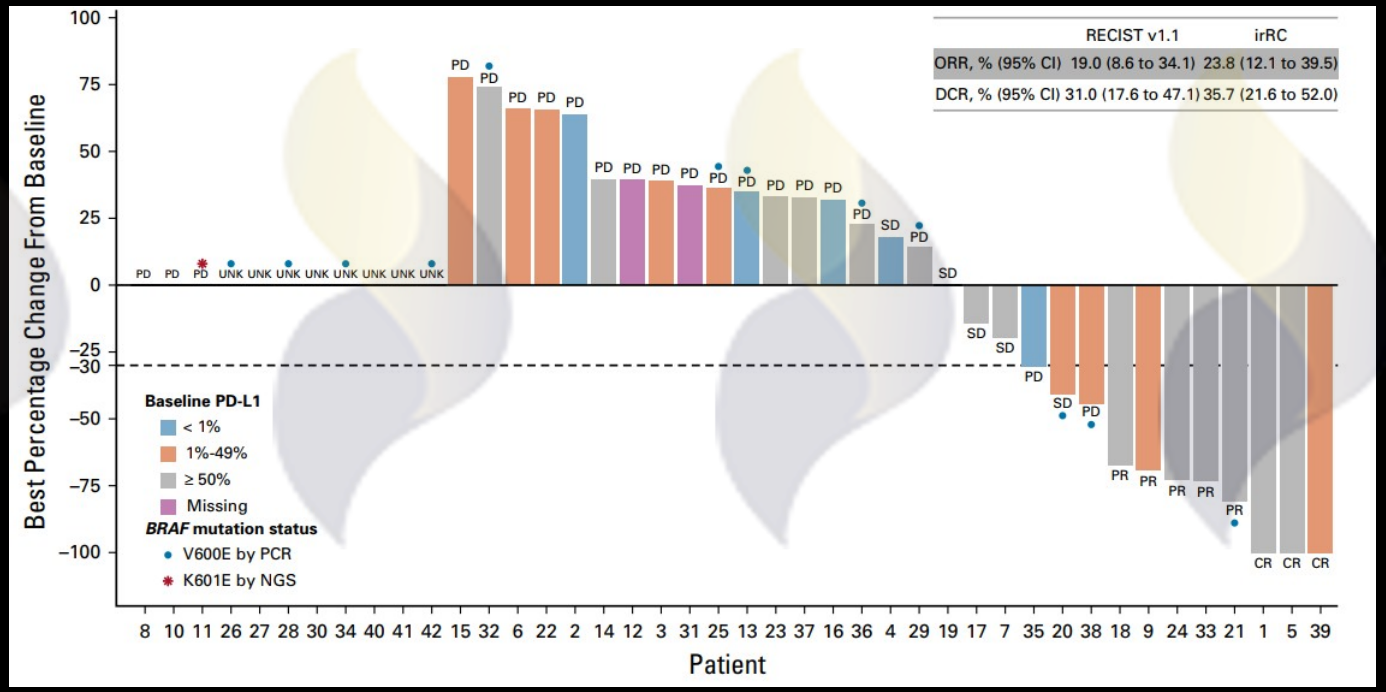
Intratumoral PD-L1 H score	N (%)
>1	18 (32.7)
>5	5 (9)
>10	3 (5.5)
>15	1 (1.8)

Dadu et al, AIA 2016

Checkpoint Inhibitors in DTC vs ATC



Mehnert JM et al, ASCO 2016

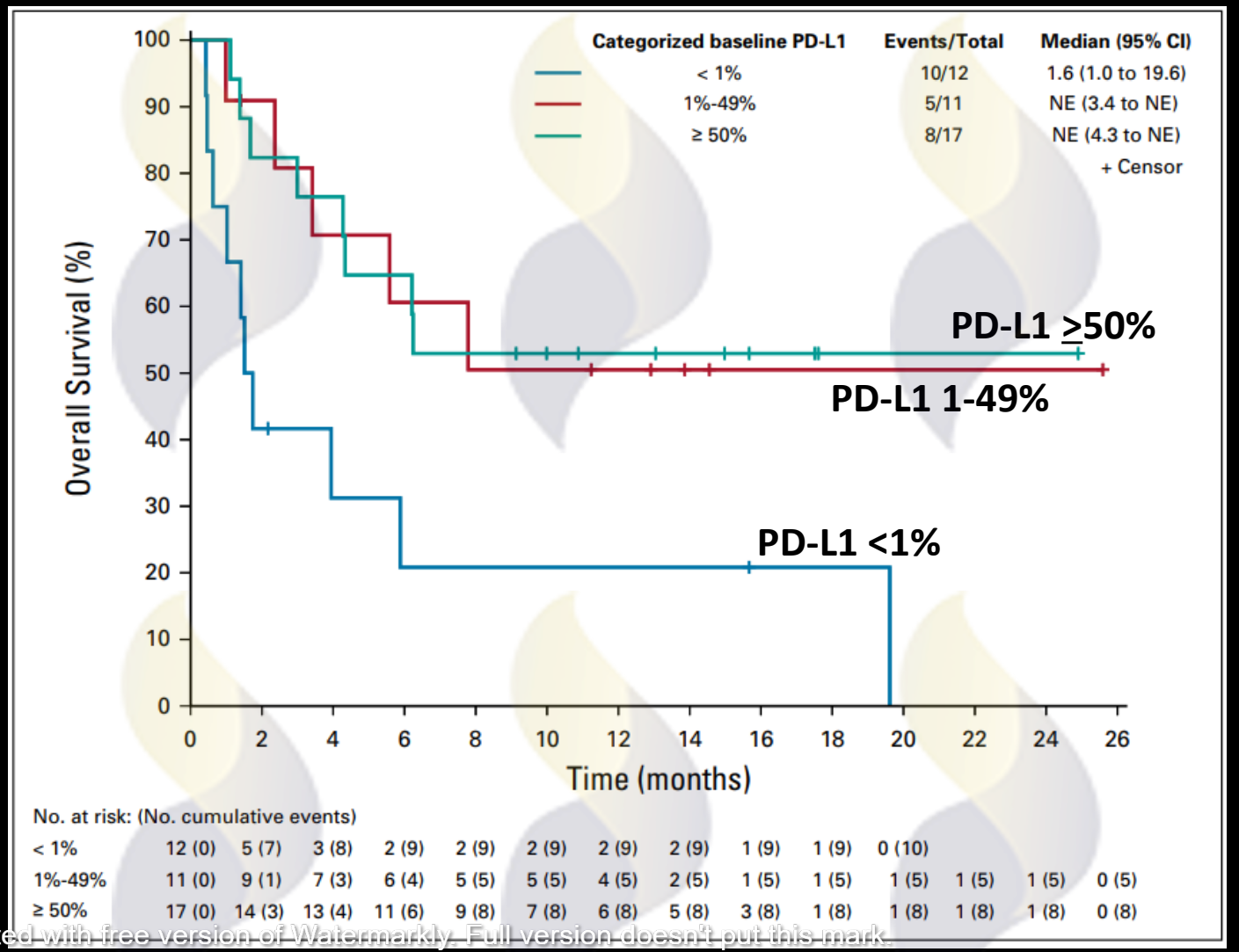


Capdevila et al, JCO, 5/2020

Spartalizumab (anti-PD1/2) in ATC

Biomarker status	ORR – % (n/N) [95% CI]
PD-L1–positive cells by IHC	
<1%	0 (0/12) [0, 26.5]
1–49%	18.2 (2/11) [2.3, 51.8]
≥50%	35.3 (6/17) [14.2, 61.7]
Missing	0 (0/2) [0, 84.2]

- Median PFS was 1.7 months
- Median OS was 5.9 months with 40% of patients alive at 1 year
- In patients with high PD-L1, 52% alive at 1 year (RR 29%)
- Median TMB was low at 3.78 mutations/Mb (range, 0-13.87 mutations/Mb)

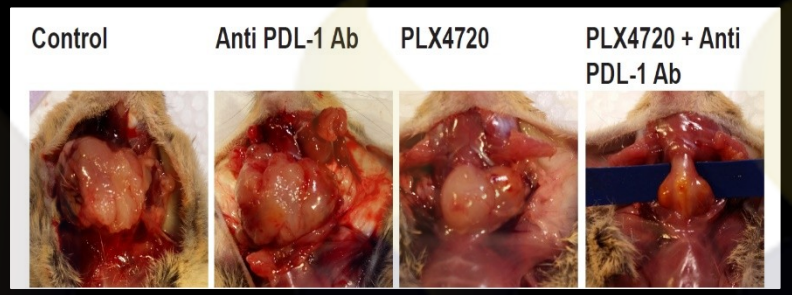


Capdevilla et al, JCO, May 2020

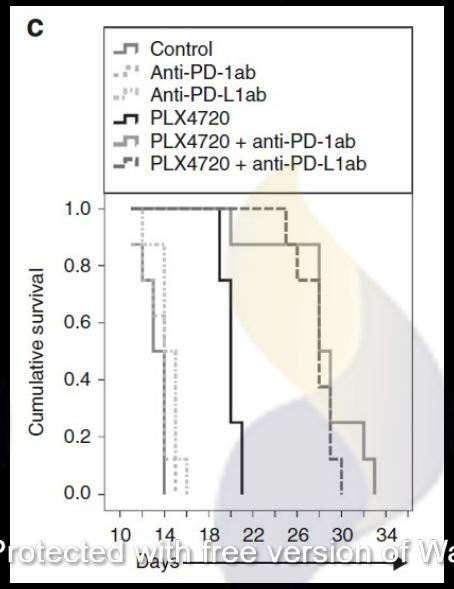
Animal Models of ATC:

(Immunocompetent orthotopic model)

BRAF inhibitor plus immunotherapy

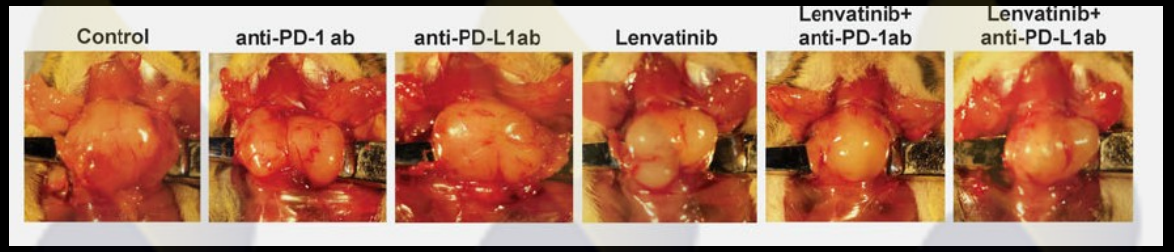


- Immune checkpoint inhibitor potentiates the effect of BRAF inhibitor (PLX4720) on tumor regression and intensifies anti tumor immune response
- A follow-up study showed improved survival with combination therapy

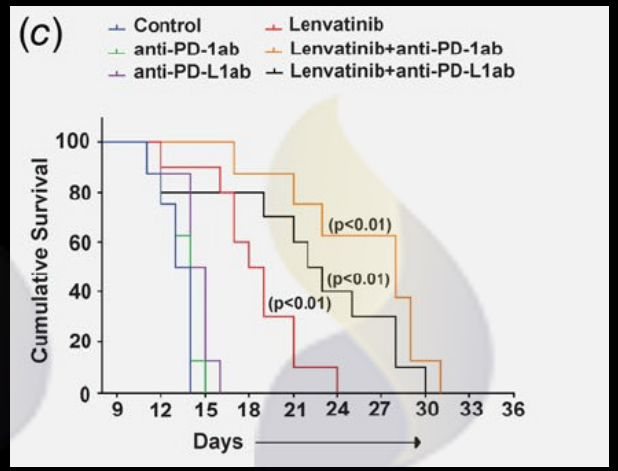


Brauner E et al, Oncotarget 2016
Gunda et al, Br J Cancer, 2018

Lenvatinib plus immunotherapy



- Lenvatinib led to tumor shrinkage and improved survival
- Lenvatinib + checkpoint inhibitor combination therapy led to dramatic improvements in tumor shrinkage and survival compared to monotherapy



Gunda et al, IJC, 2018

All roads lead to combination therapy with immunotherapy in ATC?

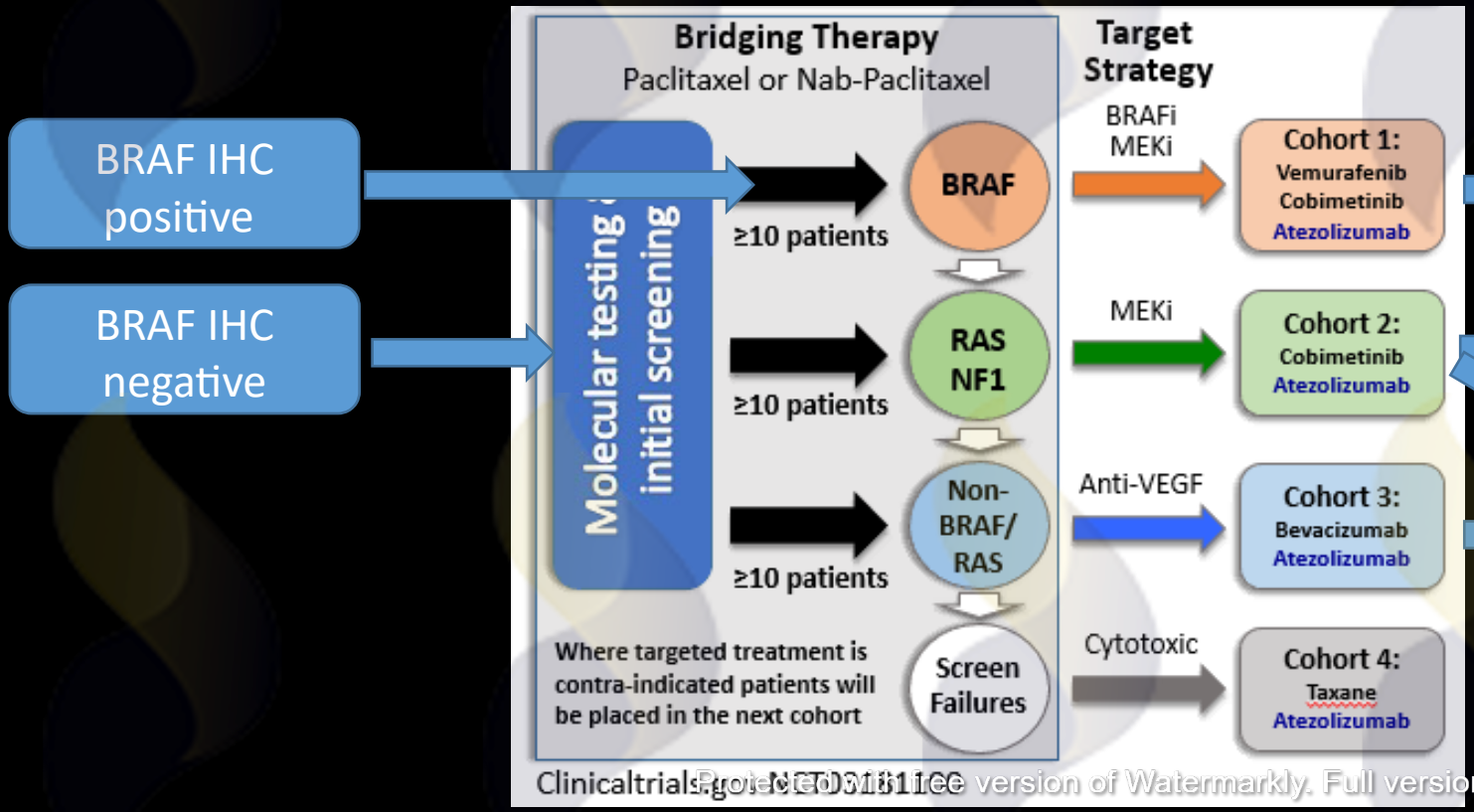
- High PDL1 (~80%)
- Treg and CD8 T cell infiltration
- MMR (12%)
- SWI/SNF mutations (36%)

…all suggest checkpoint inhibitors and other immunotherapies may be logical treatments in the majority of ATC patients

(+ targeted therapy which works very fast but resistance ensues)

Rational Combinatorial Treatment in ATC based on mutational and immune landscape

- Checkpoint inhibitors and other immunotherapies have slow onset of response and act on the immune environment
- Kinase inhibitors responses occur early and act in the cancer cell
- A combination strategy with checkpoint inhib + the right kinase inhibitor is logical strategy

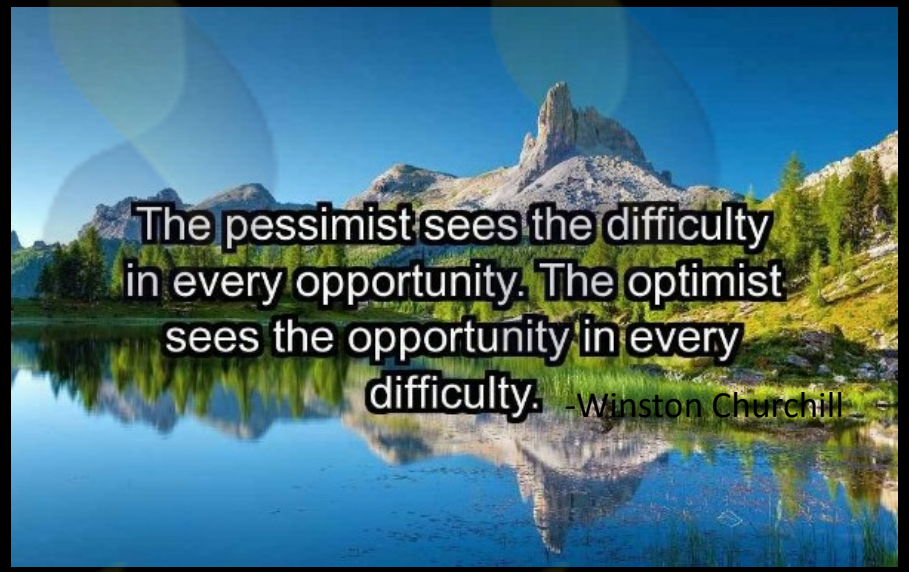


Dabrafenib/trametinib neoadjuvant trial NCT#04675710

? checkpoint inhibitor for RAS…if also EIF1AX then add everolimus

Lenvatinib + pembrolizumab NCT#04171622

Thank you



Anaplastic Thyroid Cancer (“FAST”) Team:
It takes a village and a bunch of optimists!