How to overcome immunotherapy resistance : the new wave of therapeutic approaches

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November 23 th 2019

What has been learned from first generation ICB ?

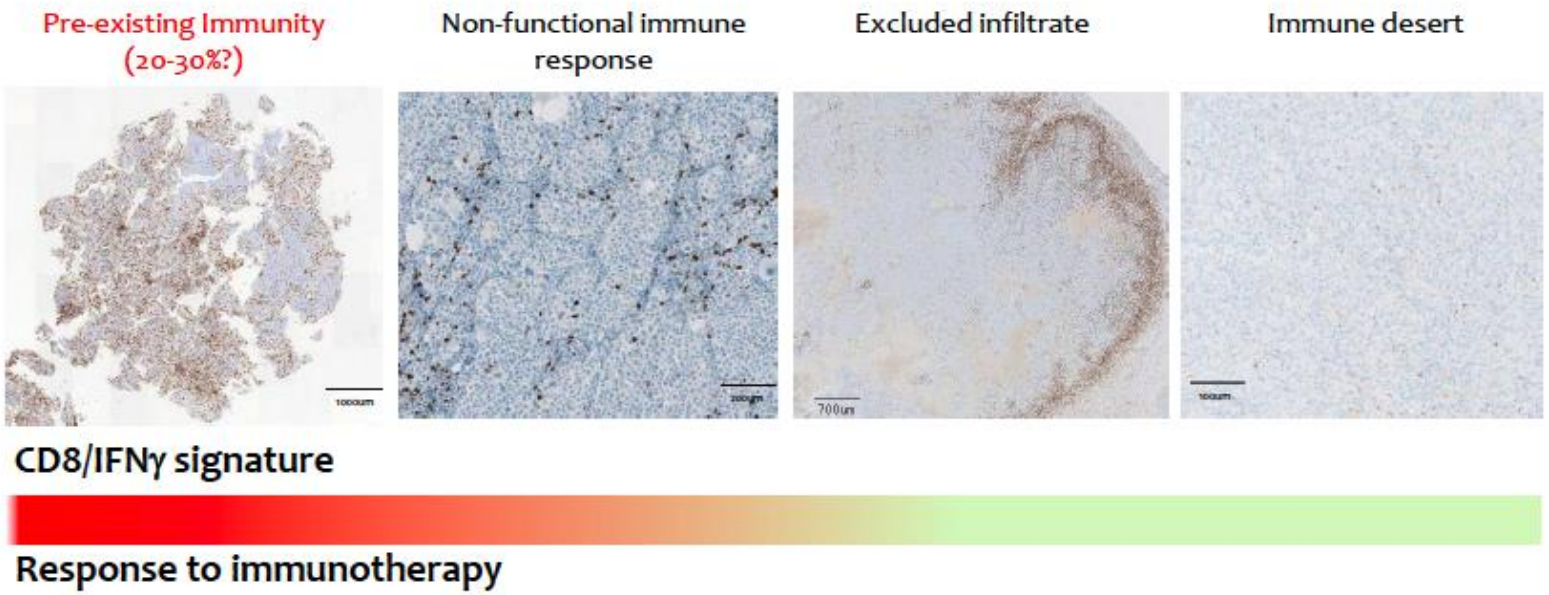
- CTLA-4
- PD-1/PD-L1
- Combo
- Adjuvant versus Neoadjuvant ?
- PD-L1 expression, TMB, neo-antigens

What has (not) been learned from first generation ICB ?

- Exhausted T-Ly: Recruit or reinvigorate ?
- PD-L1 expression: On TCs or ICs ?
- TMB and ITH: are these independent or interchangeable ?

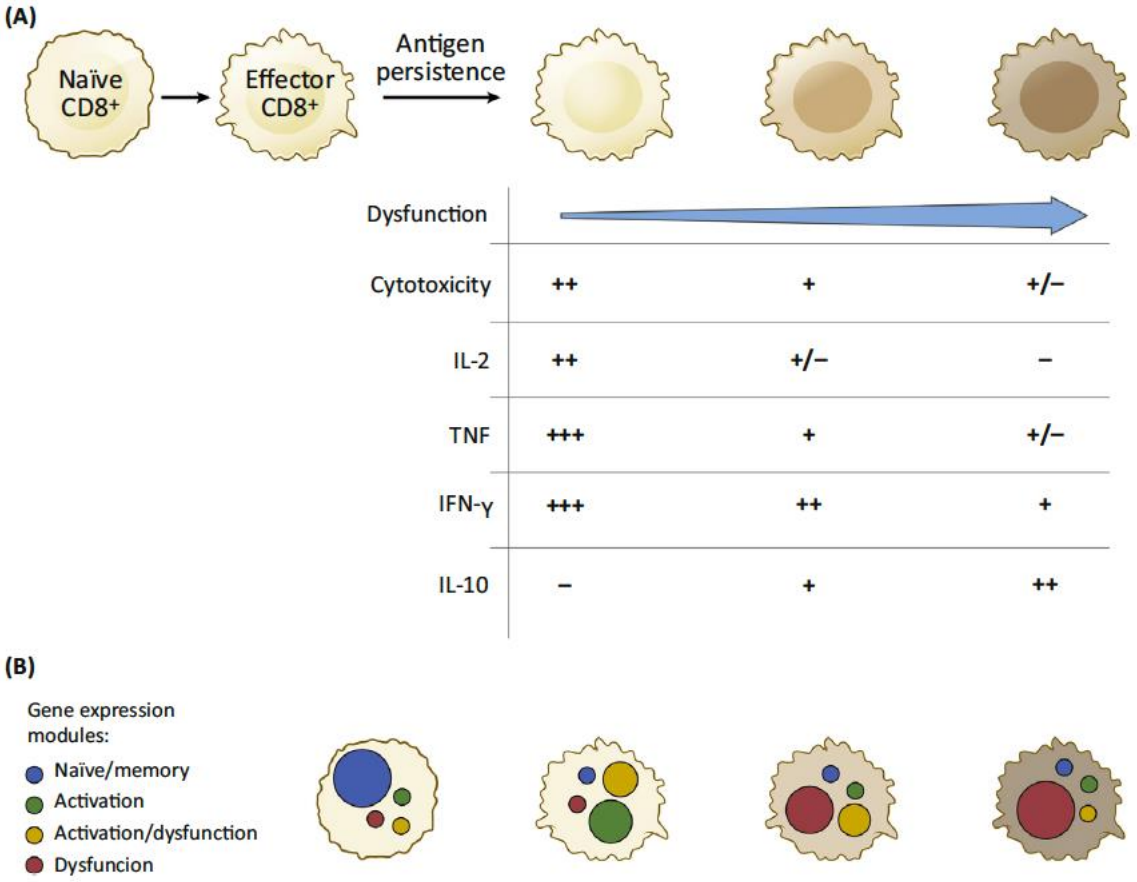
The exhausted T-lymphocyte : Recruit or Reinvigorate?

Current approaches largely address patients with pre-existing immunity

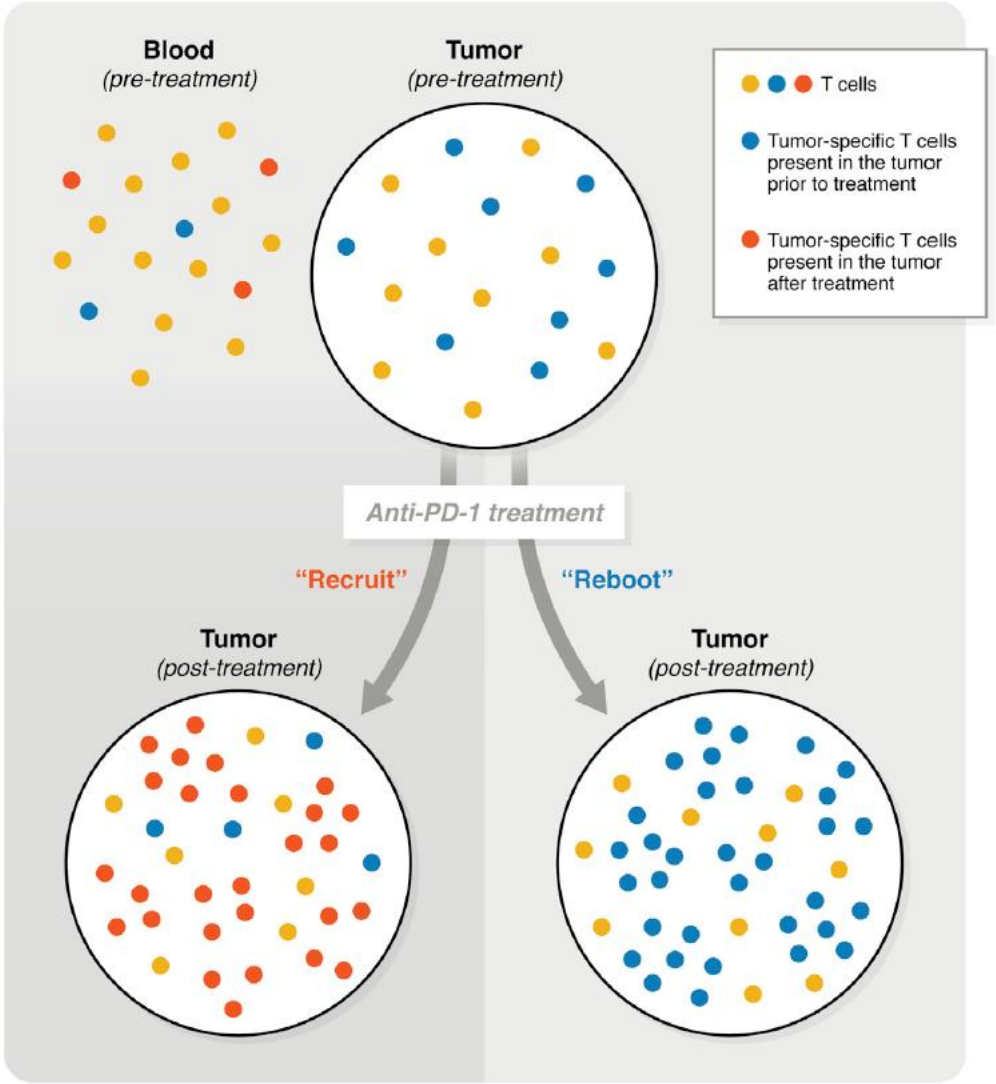


Many or most patients may lack pre-existing immunity

The exhausted T-lymphocyte : Recruit or Reinvigorate?

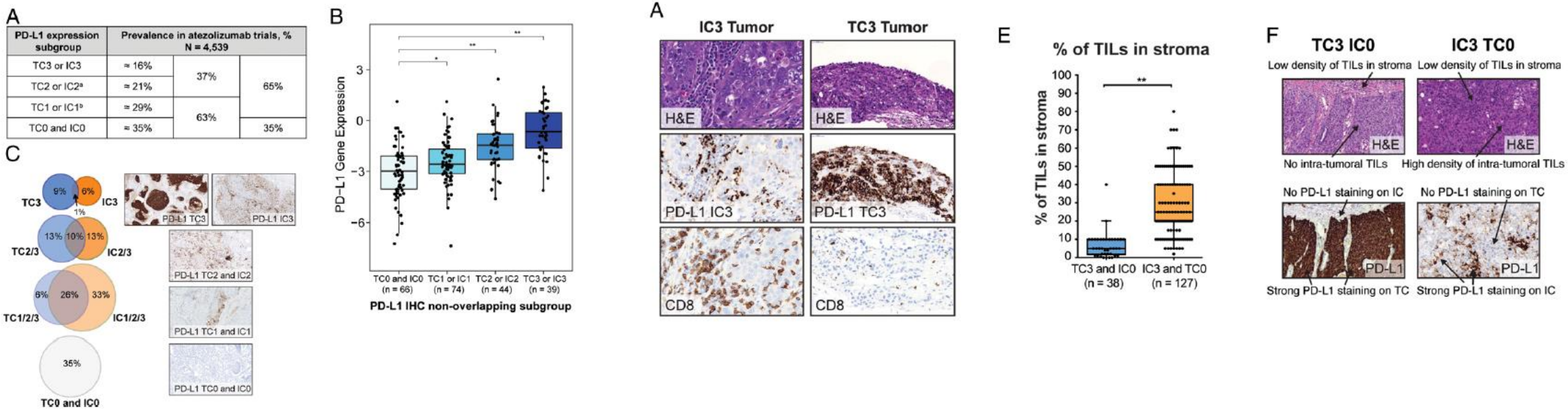


The exhausted T-lymphocyte : Recruit or Reinvigorate?



Yost, KE et al., Nat Med 25,1251.

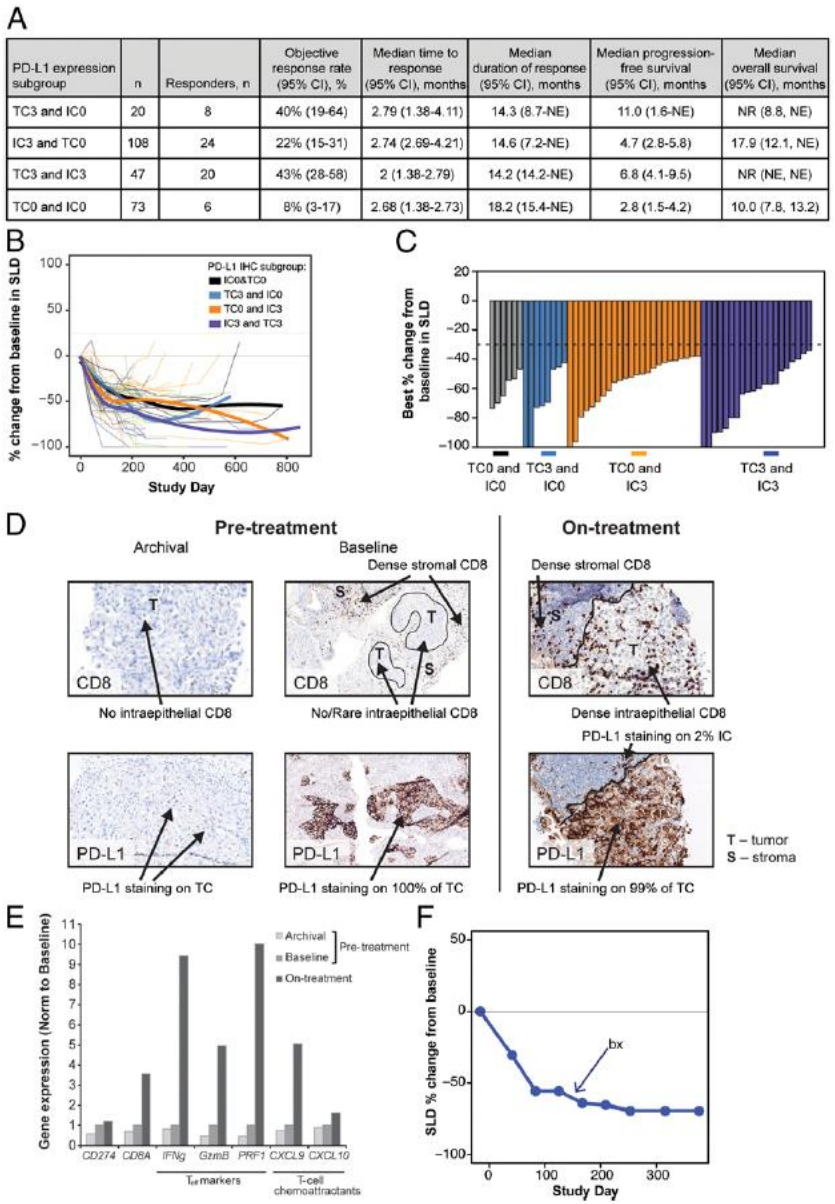
PD-L1 on TC or IC or on both ?



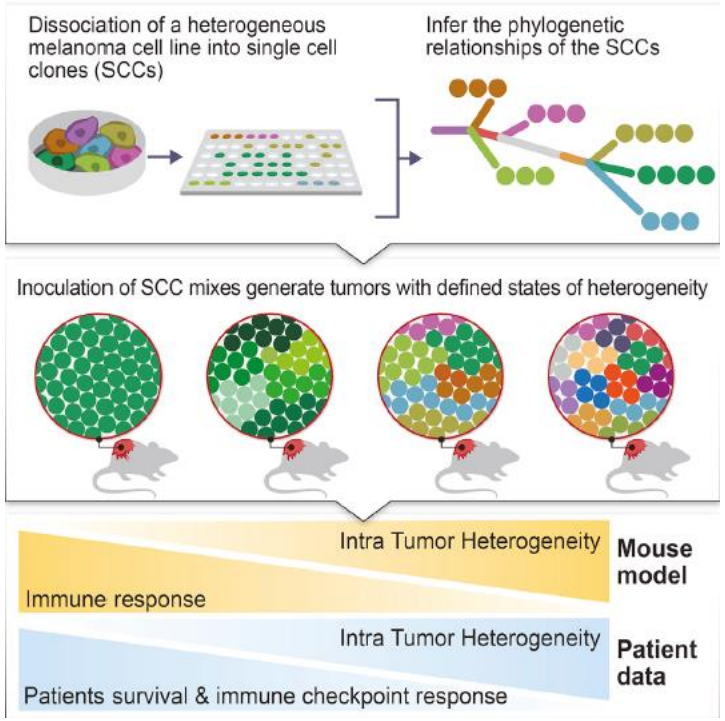
PD-L1 on TC or IC or on both ?

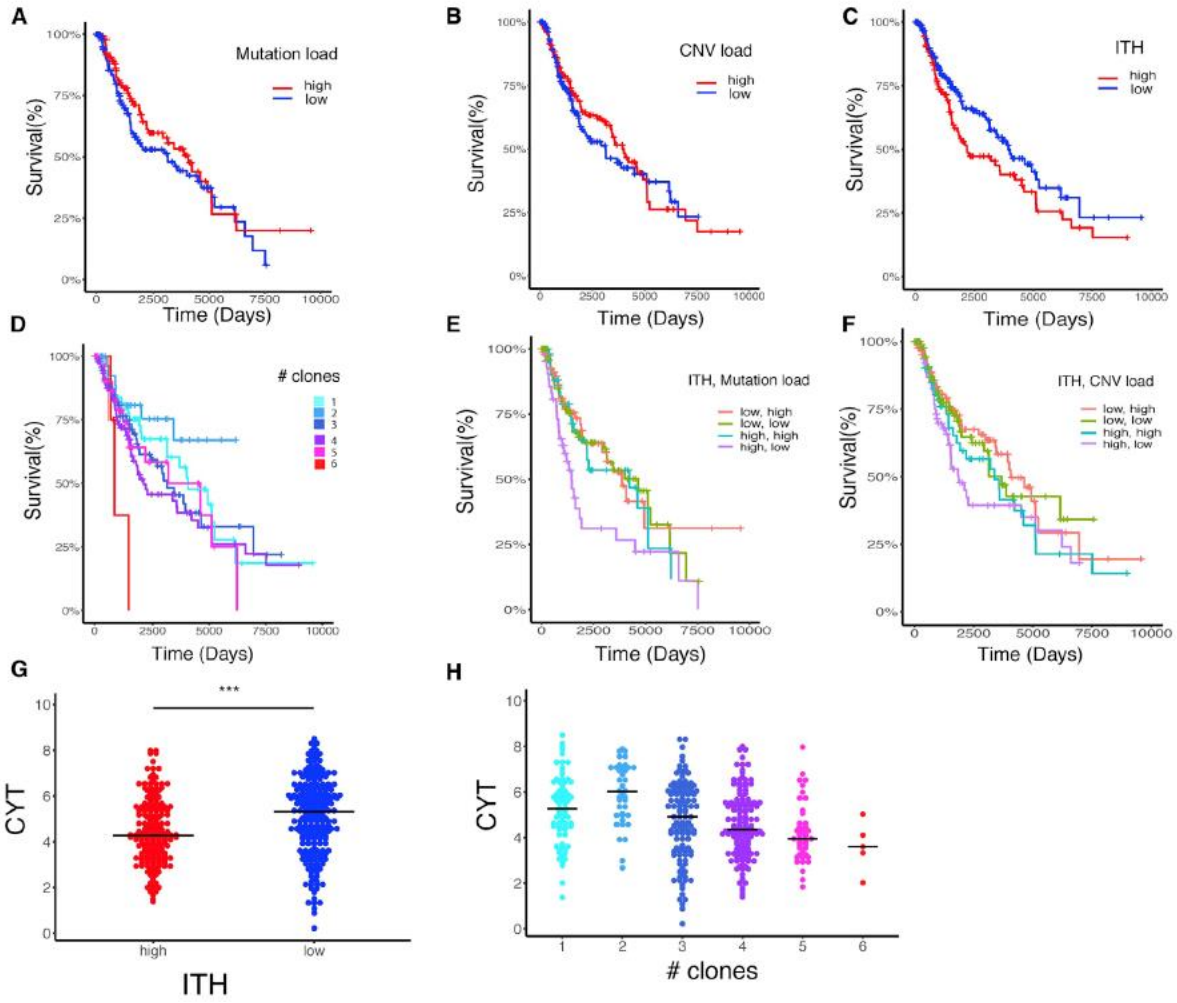
A

PD-L1 expression subgroup	n	Responders, n	Objective response rate (95% CI), %	Median time to response (95% CI), months	Median duration of response (95% CI), months	Median progression-free survival (95% CI), months	Median overall survival (95% CI), months
TC3 and IC0	20	8	40% (19-64)	2.79 (1.38-4.11)	14.3 (8.7-NE)	11.0 (1.6-NE)	NR (8.8, NE)
IC3 and TC0	108	24	22% (15-31)	2.74 (2.69-4.21)	14.6 (7.2-NE)	4.7 (2.8-5.8)	17.9 (12.1, NE)
TC3 and IC3	47	20	43% (28-58)	2 (1.38-2.79)	14.2 (14.2-NE)	6.8 (4.1-9.5)	NR (NE, NE)
TC0 and IC0	73	6	8% (3-17)	2.68 (1.38-2.73)	18.2 (15.4-NE)	2.8 (1.5-4.2)	10.0 (7.8, 13.2)

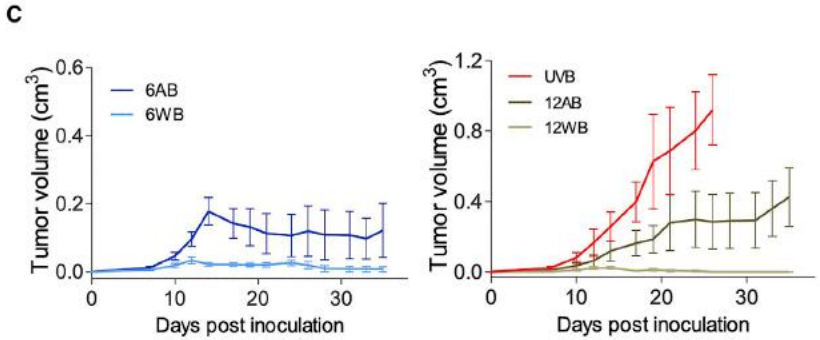


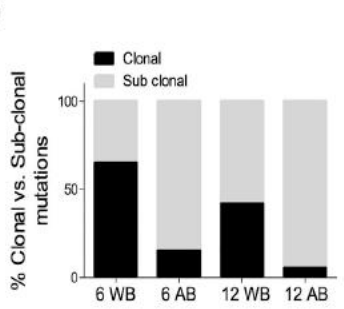
TMB and ITH


Dissociation of a heterogeneous melanoma cell line into single cell clones (SCCs)
Infer the phylogenetic relationships of the SCCs
Inoculation of SCC mixes generate tumors with defined states of heterogeneity
Intra Tumor Heterogeneity
Immune response
Mouse model
Intra Tumor Heterogeneity
Patients survival & immune checkpoint response
Patient data


A
Mutation load
high
low
Survival(%)
Time (Days)
B
CNV load
C
ITH
D
clones
E
ITH, Mutation load
low, high
low, low
high, high
high, low
F
ITH, CNV load
G
***
CYT
high
low
ITH
H
clones

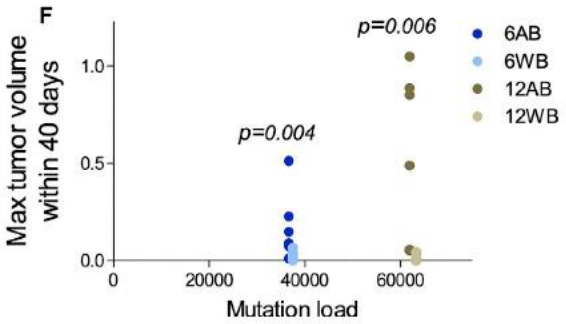
TMB and ITH

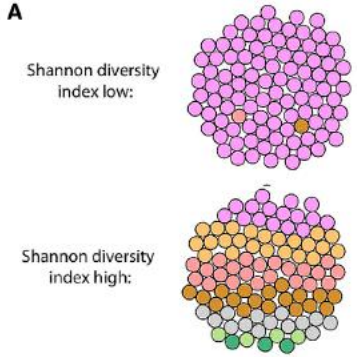


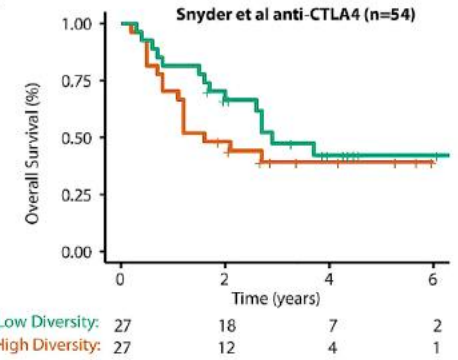


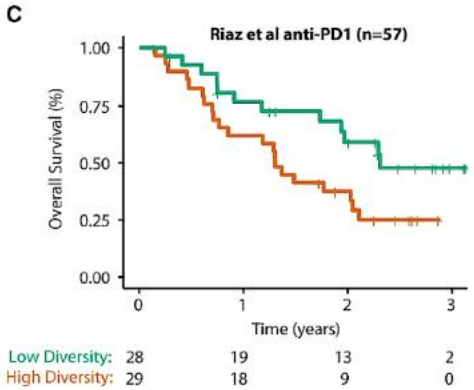
E

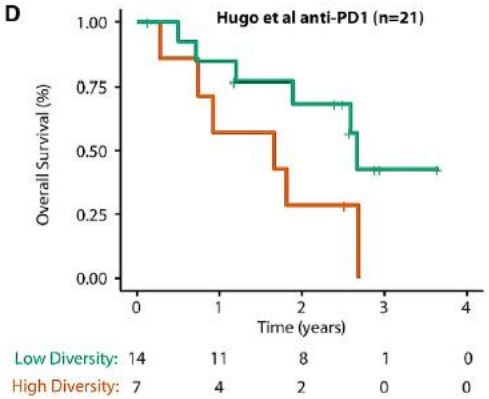
Branch	7	6	7	4	4	8	10	4	8	4	4	7	4	6	10	4	7	4	9	9
SCC	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3AB.1	+	+					+													
3AB.2			+			+														+
3AB.3				+					+						+					
3AB.4														+		+			+	
6WB				+				+		+	+		+			+				
6AB	+						+		+	+				+					+	
12WB	+		+	+	+			+		+	+	+	+			+	+	+		
12AB	+	+	+	+		+	+		+					+	+	+			+	+

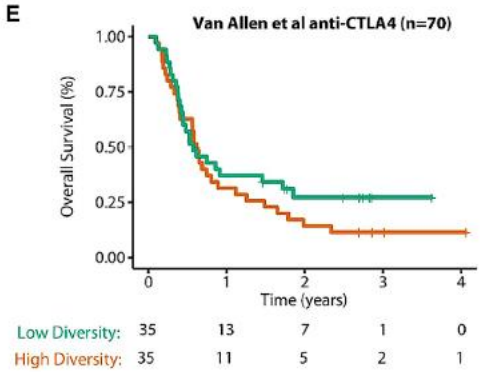


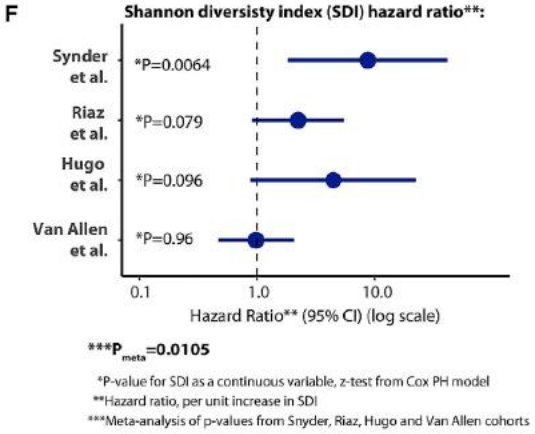






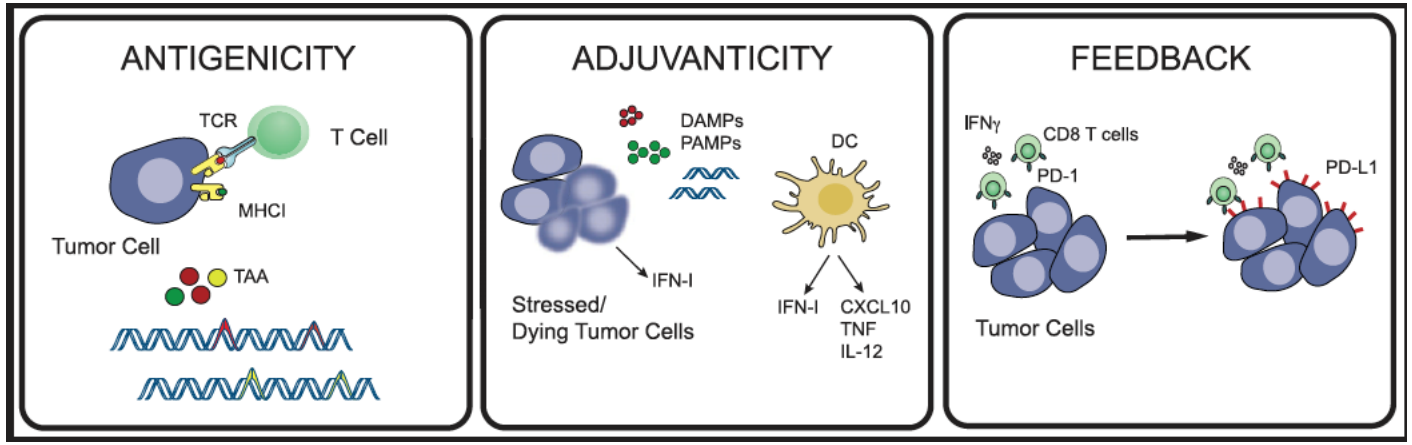






Combination Cancer Therapy with Immune Checkpoint Blockade

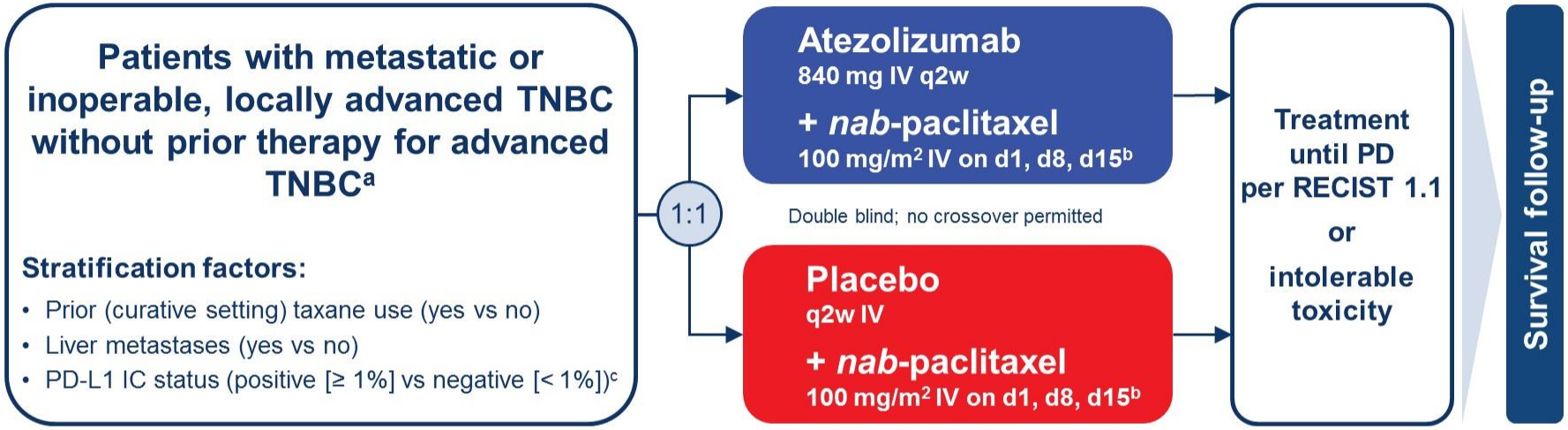
- Genotoxic therapies > 450 trials !!!
  - Chemotherapy
  - Radiation Therapy
- Targeted therapies
- Interfering with Feedback Inhibition in the TME



Combination Cancer Therapy with Immune Checkpoint Blockade: the case for chemotherapy

- Cytotoxic chemotherapy has pleiotropic immunomodulatory effects
- These effects include
  - Expansion or activation of effector cells (NK, DC and T cells)
  - Depletion and/or inhibition of suppressor cells (TAM, MDSC, Tregs)
  - Induction of ICD
  - Increased IFN-g and adaptive PD-L1 upregulation
- But: results are inconsistent across animal models (e.g. cyclophosphamide)
- Different agents have different preponderant effects (e.g. Cyclo Tregs, doxo on ICD)

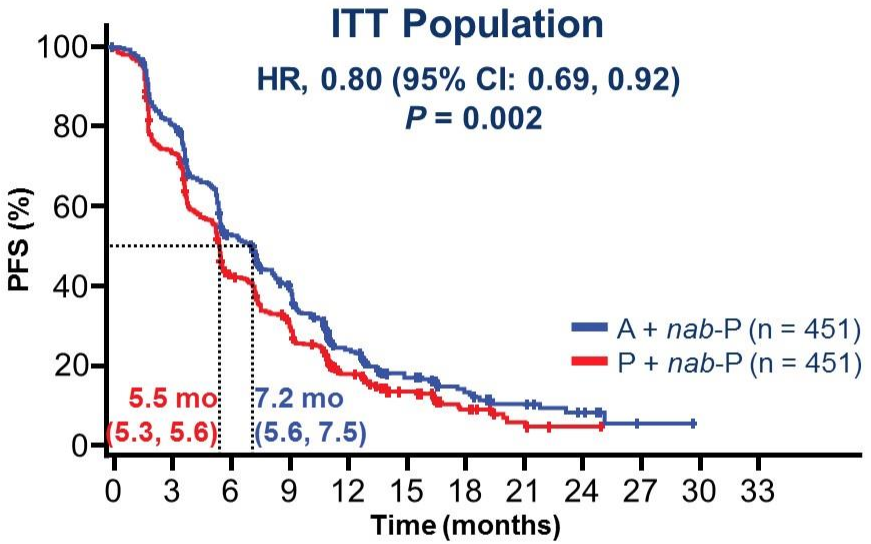
IMpassion130 Study Design

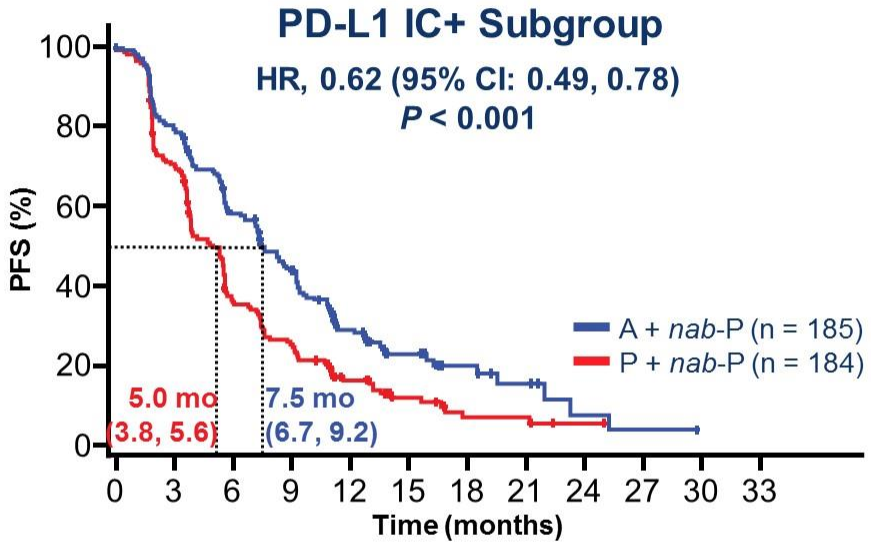


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

[a] Prior chemotherapy in the curative setting allowed if treatment-free interval ≥ 12 months. [b] 28-day cycle. [c] Centrally evaluated per VENTANA SP142 IHC assay.
[d] Efficacy endpoints assessed by investigators per RECIST 1.1. NCT02425891.

Primary PFS Analysis in the ITT and PD-L1 IC+ Subgroup



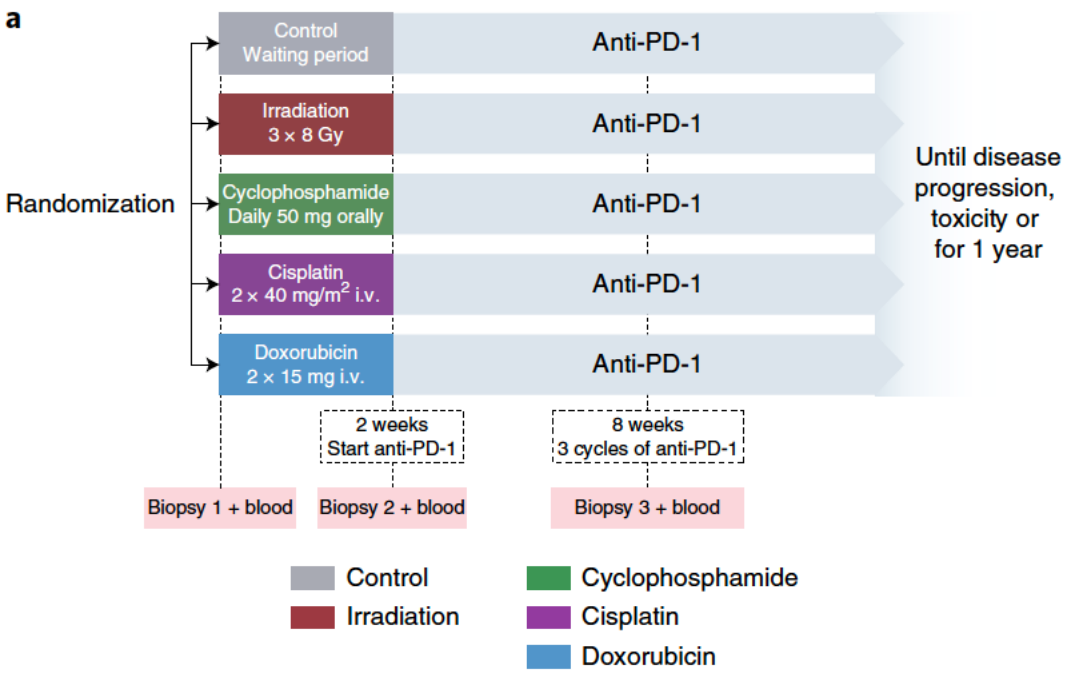


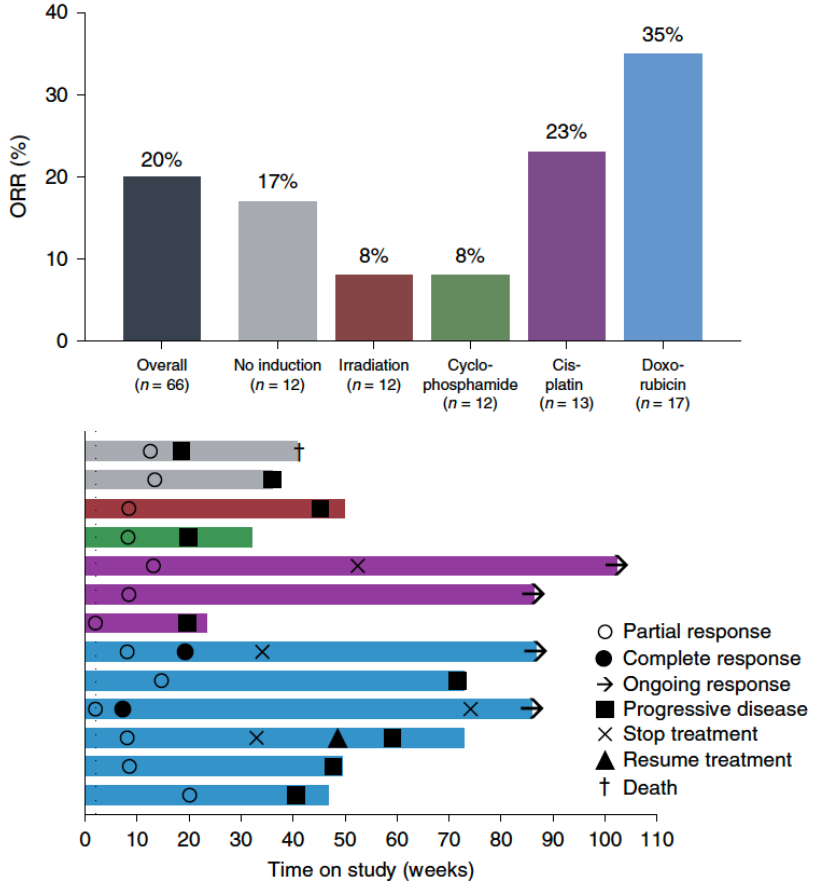
- PFS benefit driven by PD-L1 IC+ patients, as a treatment effect was not observed in PD-L1 IC− patients[1]
- Based on these data,[2] atezolizumab + *nab*-paclitaxel received accelerated approval by the FDA[3] and is recommended for patients with PD-L1 IC+ mTNBC in the NCCN[4] and AGO[5] guidelines

Data cutoff: April 17, 2018. Median follow-up (ITT): 12.9 months.

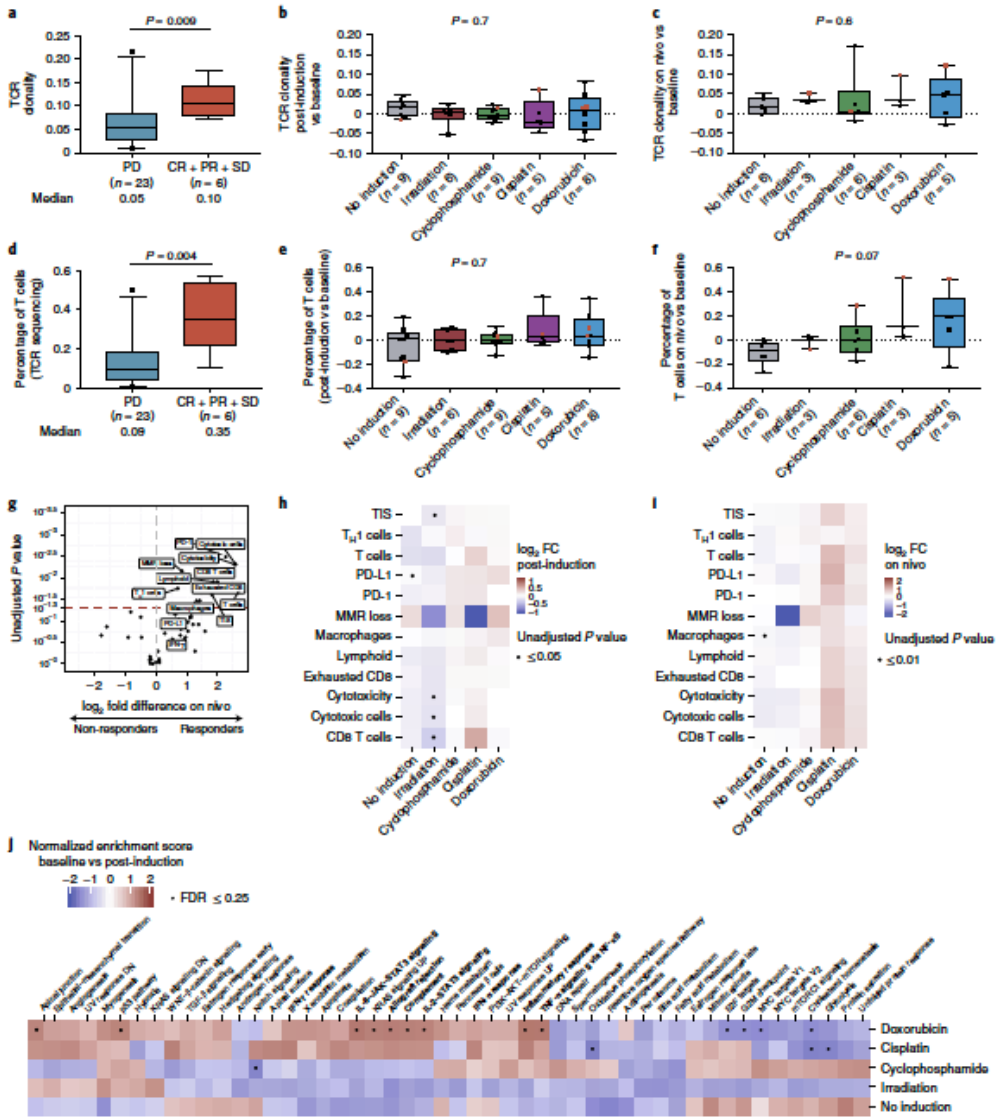
1. Emens SABCS 2018. 2. Schmid *New Engl J Med.* 2018. 3. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019.
4. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 5. AGO Guidelines Breast Version 2019.1.

The TONIC trial





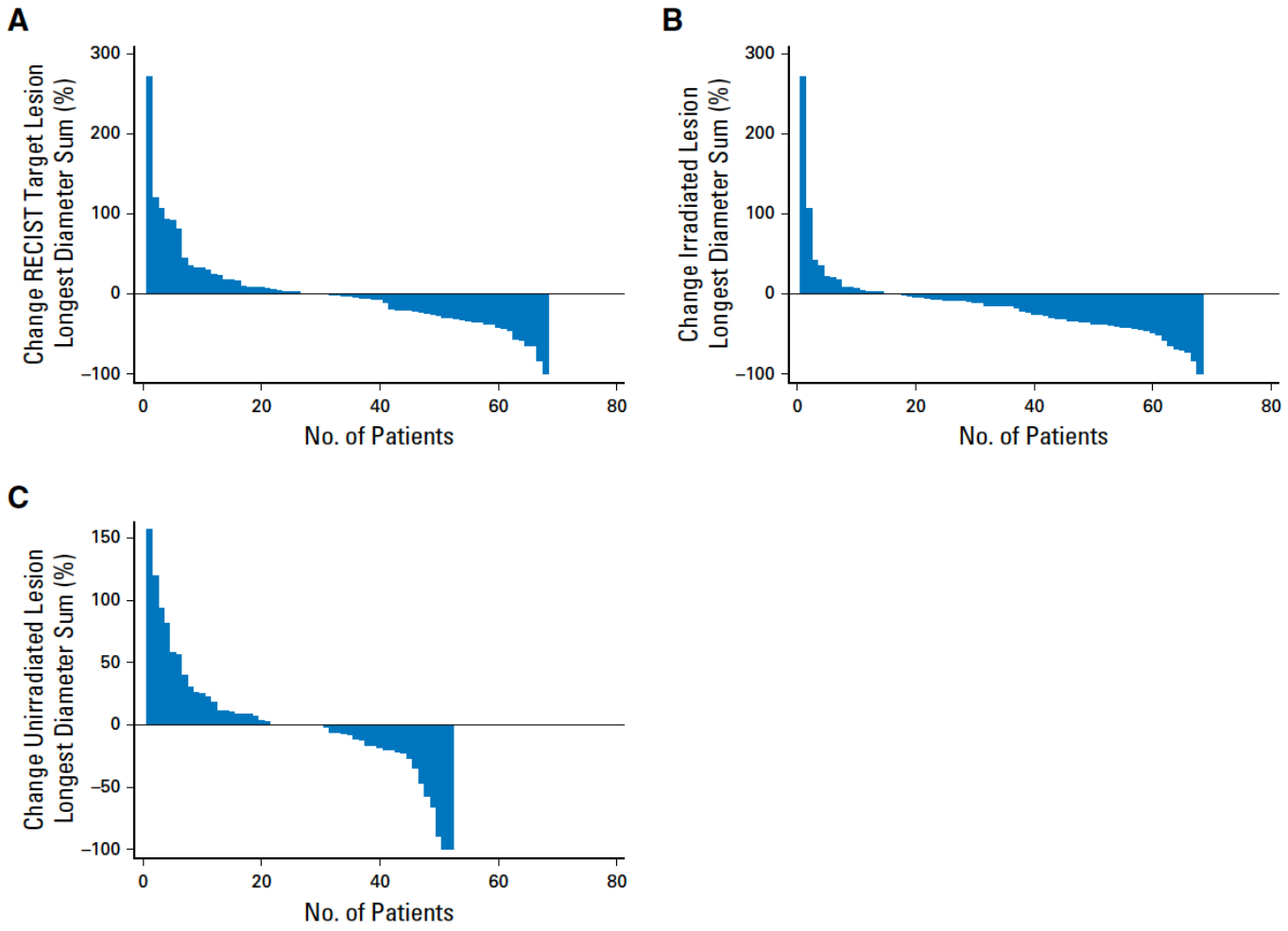
The TONIC trial



Combination Cancer Therapy with Immune Checkpoint Blockade: the case for Radiotherapy

- Principal (?) mechanism of action of RT is induce lethal DNA damage
- RT can enhance innate and adapative antitumor immunity
- RT can cause immonosuppressive effects
- Vaccine effect of RT is modest
- Main effect : adjuvanticity
- Breast cancer models:
  - Hypofractionation 8 Gy x 3 > 1x20-30 Gy
  - 8 Gy x2 > 2 Gy x 10
- Concurrent anti-PD-L1 > sequential
- Case report abscopal effect with anti-CTLA4 melanoma
- Trial result in NSCLC with RT and ipi : RR 18%

Combination Cancer Therapy with Immune Checkpoint Blockade: the case for Pembro and SBRT

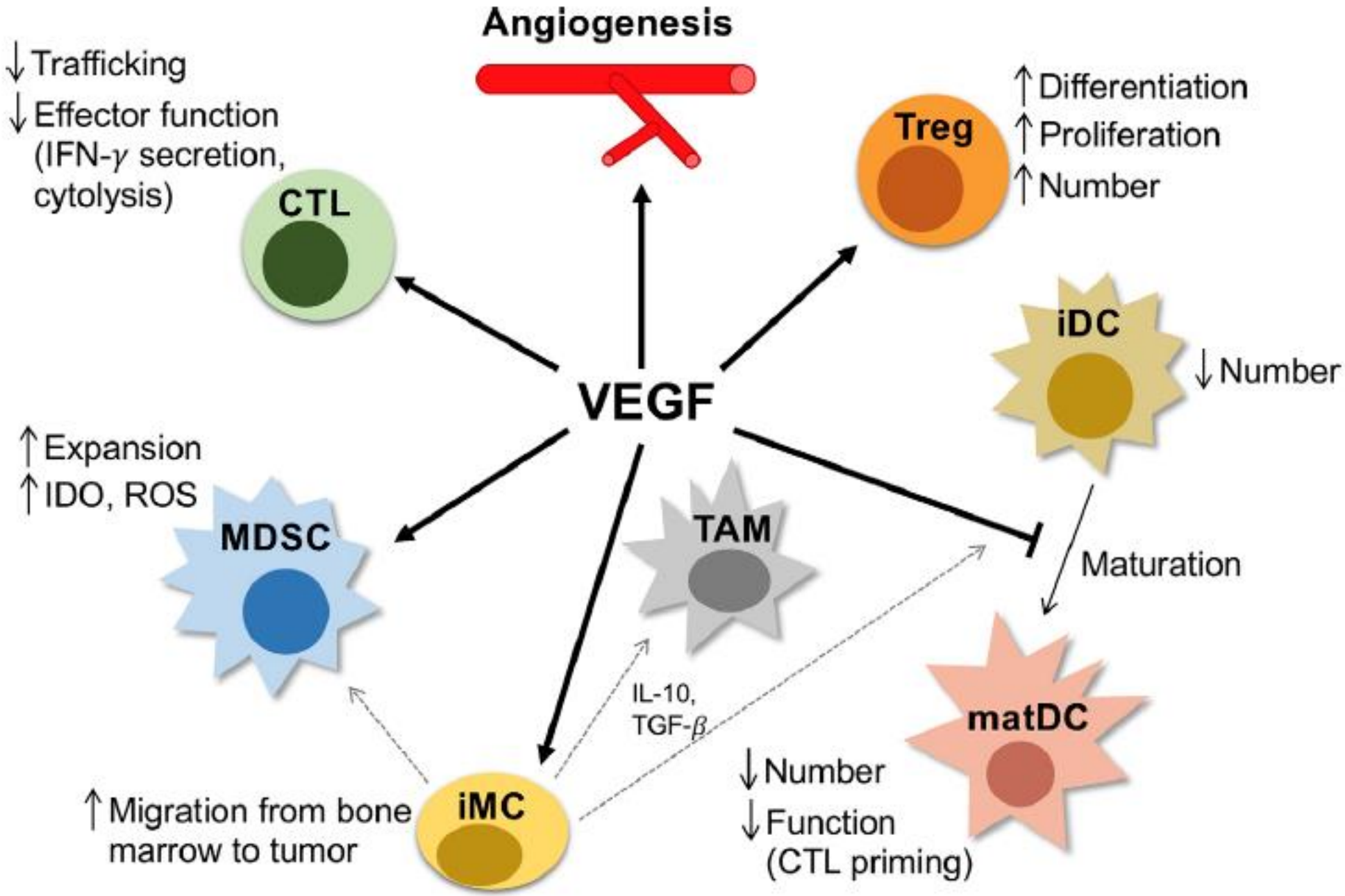


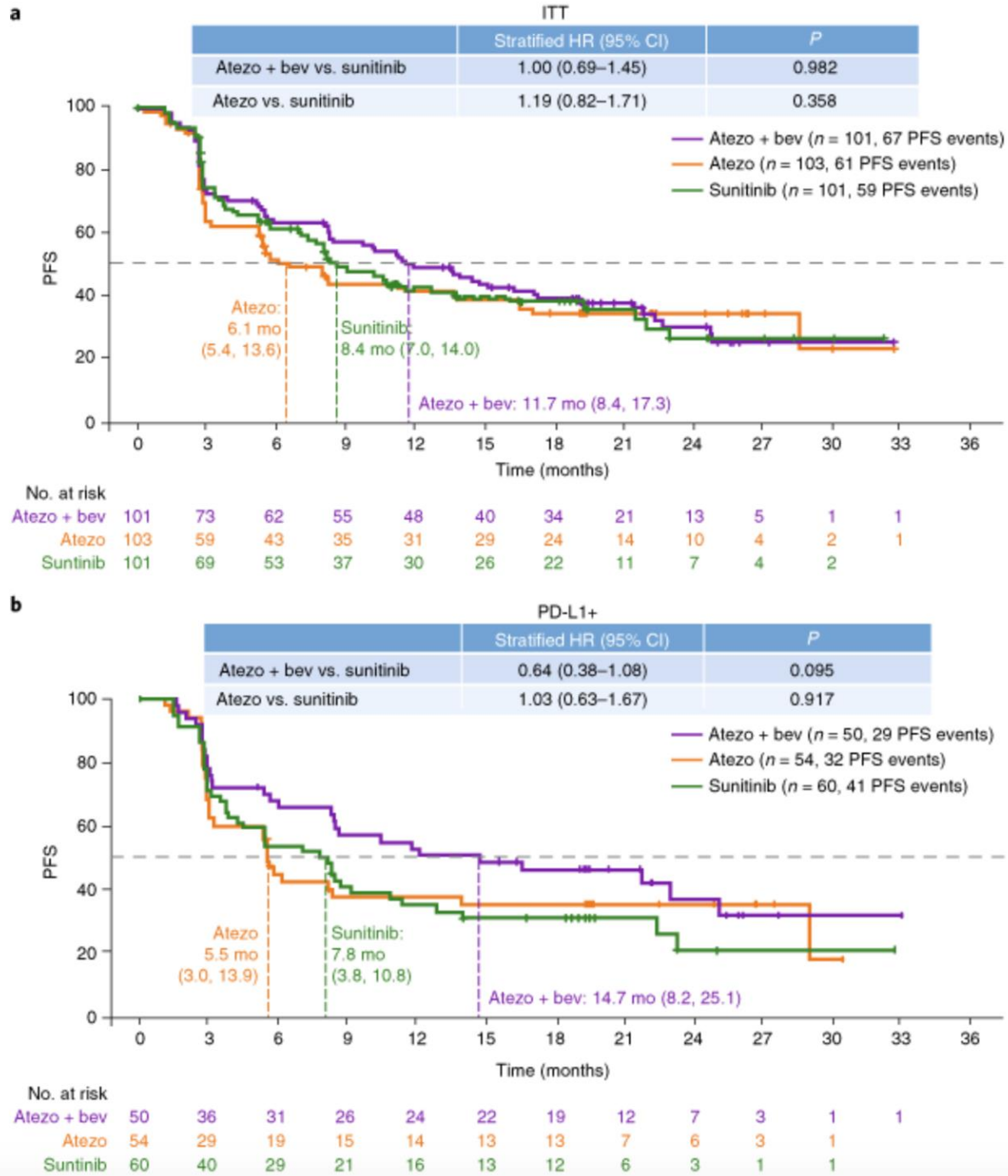
Combination Cancer Therapy with Immune Checkpoint Blockade: targeted therapies: BRAF/MEKi/PD-L1/PD1

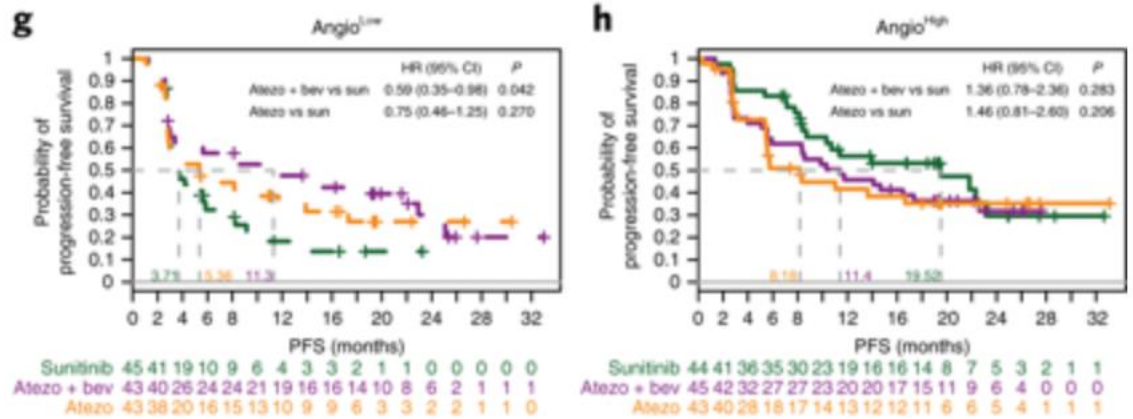
- Preclinical data : BRAF and MEK inhibition increase T cell infiltration
- Vemurafenib and ipilimumab : stop Liver Tox
- Different trials I-II-III combo BRAFi/MEKi/+PD-L1/PD1
- Increased tox
- Suggestion increased PFS in Ph II +/- pembro: increased PFS 16 vs 12
- Increased tox
- Problem in dose reductions
- DREAMSEQ trial

Combination Cancer Therapy with Immune Checkpoint Blockade: the case for targeted therapies

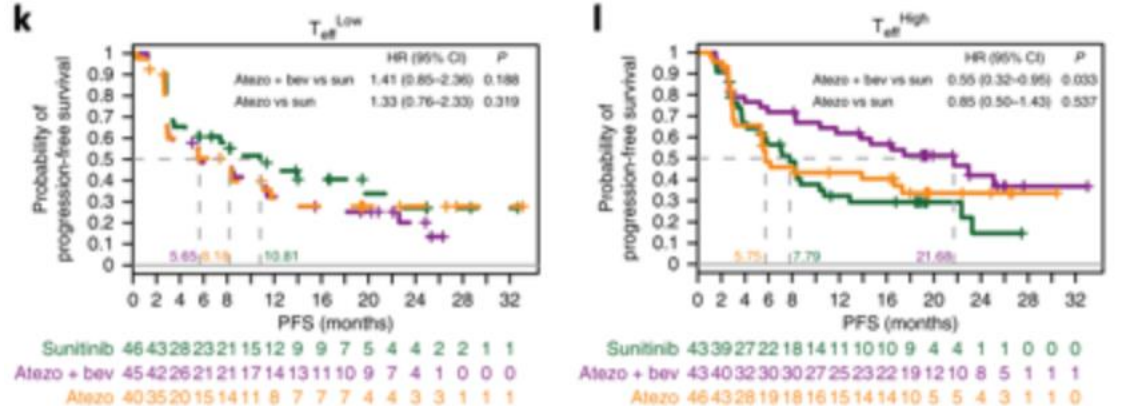
- PARP inhibitors
- CDK4/6 inhibitors
- HER2 inhibitors
- PI3K inhibitors
- IDO inhibitors
- MAPK
- EGFR inhibitors


Angiogenesis
↓Trafficking
↓Effector function (IFN-γ secretion, cytolysis)
CTL
Treg
↑Differentiation
↑Proliferation
↑Number
VEGF
iDC
↓Number
↑Expansion
↑IDO, ROS
MDSC
TAM
Maturation
IL-10, TGF-β
matDC
↓Number
↓Function (CTL priming)
↑Migration from bone marrow to tumor
iMC

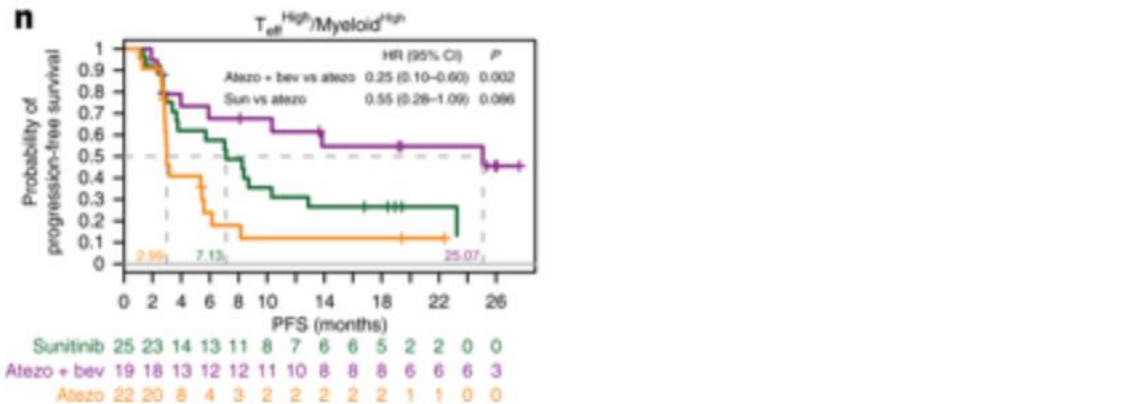

a
ITT
Stratified HR (95% CI)
P
Atezo + bev vs. sunitinib
1.00 (0.69–1.45)
0.982
Atezo vs. sunitinib
1.19 (0.82–1.71)
0.358
Atezo + bev (n = 101, 67 PFS events)
Atezo (n = 103, 61 PFS events)
Sunitinib (n = 101, 59 PFS events)
PFS
Atezo:
6.1 mo
(5.4, 13.6)
Sunitinib:
8.4 mo (7.0, 14.0)
Atezo + bev: 11.7 mo (8.4, 17.3)
Time (months)
No. at risk
Atezo + bev 101 73 62 55 48 40 34 21 13 5 1 1
Atezo 103 59 43 35 31 29 24 14 10 4 2 1
Suntinib 101 69 53 37 30 26 22 11 7 4 2
b
PD-L1+
Stratified HR (95% CI)
P
Atezo + bev vs. sunitinib
0.64 (0.38–1.08)
0.095
Atezo vs. sunitinib
1.03 (0.63–1.67)
0.917
Atezo + bev (n = 50, 29 PFS events)
Atezo (n = 54, 32 PFS events)
Sunitinib (n = 60, 41 PFS events)
PFS
Atezo
5.5 mo
(3.0, 13.9)
Sunitinib:
7.8 mo
(3.8, 10.8)
Atezo + bev: 14.7 mo (8.2, 25.1)
Time (months)
No. at risk
Atezo + bev 50 36 31 26 24 22 19 12 7 3 1 1
Atezo 54 29 19 15 14 13 13 7 6 3 1
Suntinib 60 40 29 21 16 13 12 6 3 1 1


g
Angio^Low
HR (95% CI) P
Atezo + bev vs sun 0.59 (0.35–0.98) 0.042
Atezo vs sun 0.75 (0.46–1.25) 0.270
Probability of progression-free survival
PFS (months)
Sunitinib 45 41 19 10 9 6 4 3 3 2 1 1 0 0 0 0 0
Atezo + bev 43 40 26 24 24 21 19 16 16 14 10 8 6 2 1 1 1
Atezo 43 38 20 16 15 13 10 9 9 6 3 3 2 2 1 1 0

h
Angio^High
HR (95% CI) P
Atezo + bev vs sun 1.36 (0.78–2.36) 0.283
Atezo vs sun 1.46 (0.81–2.60) 0.206
Probability of progression-free survival
PFS (months)
Sunitinib 44 41 36 35 30 23 19 16 16 14 8 7 5 3 2 1 1
Atezo + bev 45 42 32 27 27 23 20 20 17 15 11 9 6 4 0 0 0
Atezo 43 40 28 18 17 14 13 12 12 11 6 6 5 4 1 1 1

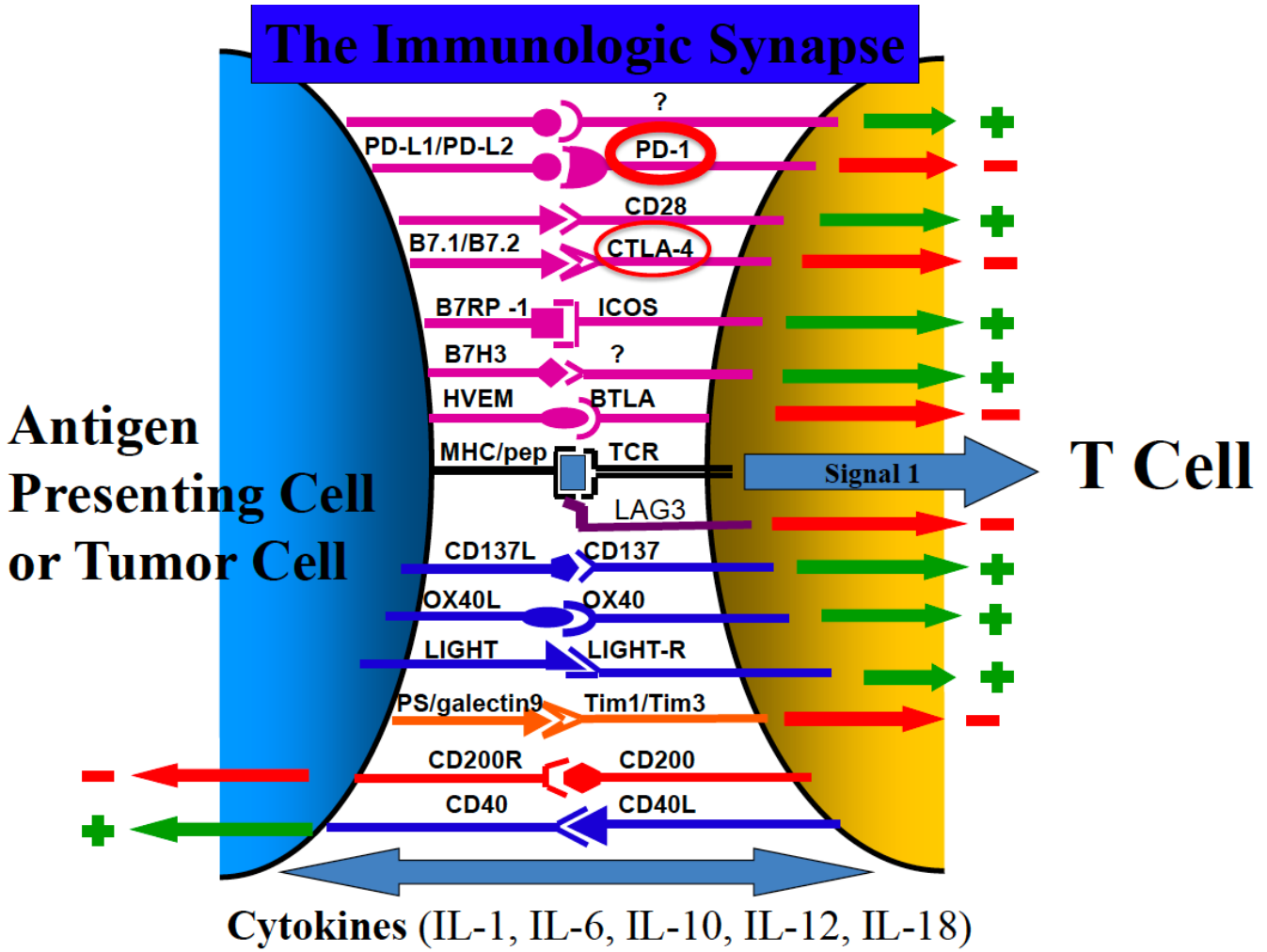

k
T_eff^Low
HR (95% CI) P
Atezo + bev vs sun 1.41 (0.85–2.36) 0.188
Atezo vs sun 1.33 (0.76–2.33) 0.319
Probability of progression-free survival
PFS (months)
Sunitinib 46 43 28 23 21 15 12 9 9 7 5 4 4 2 2 1 1
Atezo + bev 45 42 26 21 21 17 14 13 11 10 9 7 4 1 0 0 0
Atezo 40 35 20 15 14 11 8 7 7 7 4 4 3 3 1 1 1

l
T_eff^High
HR (95% CI) P
Atezo + bev vs sun 0.55 (0.32–0.95) 0.033
Atezo vs sun 0.85 (0.50–1.43) 0.537
Probability of progression-free survival
PFS (months)
Sunitinib 43 39 27 22 18 14 11 10 10 9 4 4 1 1 0 0 0
Atezo + bev 43 40 32 30 30 27 25 23 22 19 12 10 8 5 1 1 1
Atezo 46 43 28 19 18 16 15 14 14 10 5 5 4 3 1 1 0

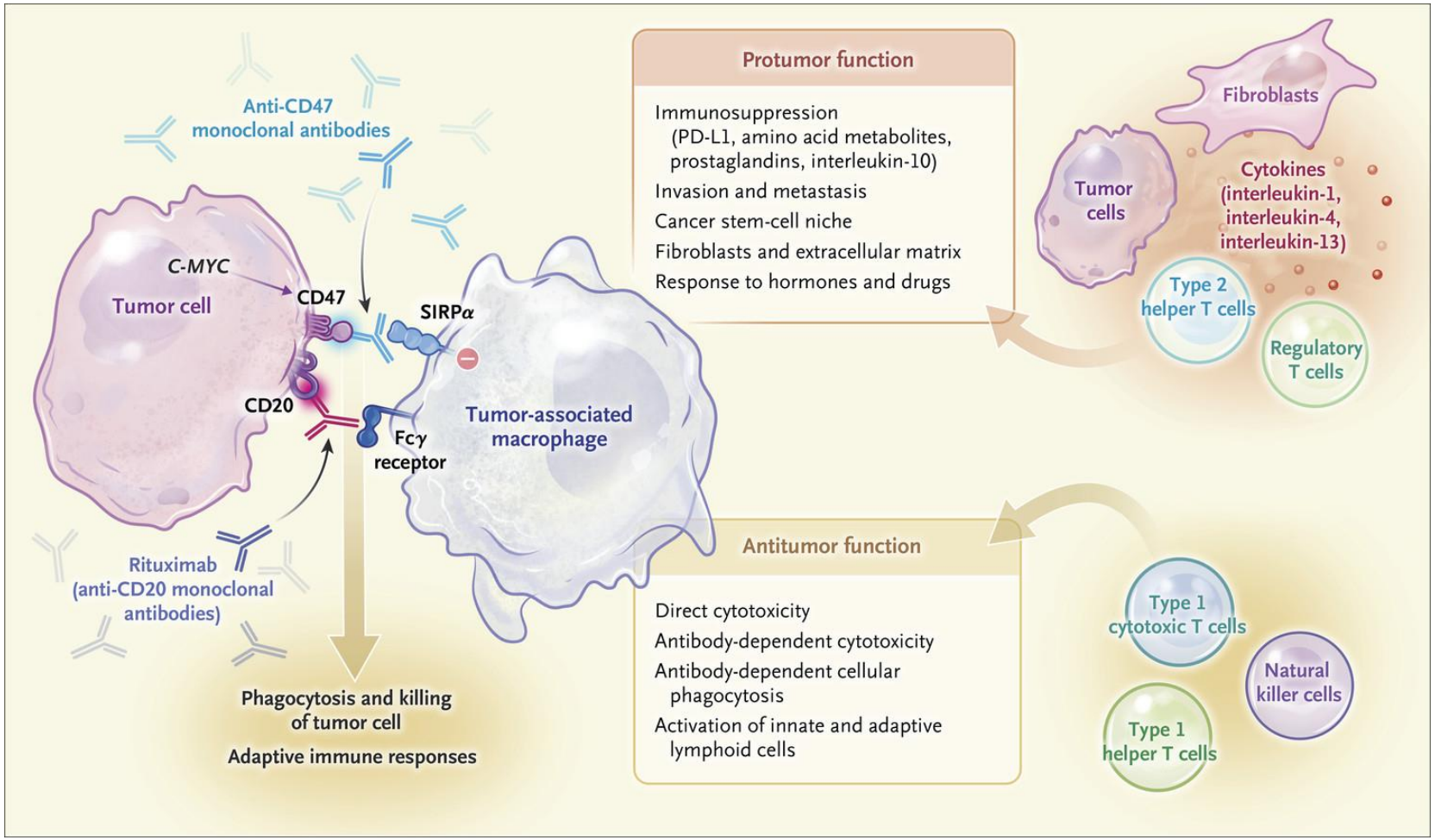

n
T_eff^High/Myeloid^High
HR (95% CI) P
Atezo + bev vs atezo 0.25 (0.10–0.60) 0.002
Sun vs atezo 0.55 (0.29–1.09) 0.086
Probability of progression-free survival
PFS (months)
Sunitinib 25 23 14 13 11 8 7 6 6 5 2 2 0 0
Atezo + bev 19 18 13 12 12 11 10 8 8 8 6 6 6 3
Atezo 22 20 8 4 3 2 2 2 2 2 1 1 0 0

Targeting Feedback Inhibition in the TME

Dual checkpoint blockade	anti-CTLA-4 anti-TIM3 anti-LAG3 anti-TIGIT anti-VISTA	Larkin et al., 2015; Postow et al., 2015; Sakuishi et al., 2010; Koyama et al., 2016; Liu et al., 2015; Wang et al., 2011
Costimulatory agonist	anti-GITR anti-ICOS anti-OX40 anti-CD27	Sanmamed et al., 2015
Regulatory T cells	anti-CD25	Arce Vargas et al., 2017
	IDO1 inhibitors	Prendergast et al., 2017
Epigenetic changes	DNMT inhibitors	Topper et al., 2017
	HDAC inhibitors	Ghoneim et al., 2017
Myeloid suppressor cells	CSF1R inhibitor/ antibodies	Zhu et al., 2014
	PI3Kγ inhibitor	De Henau et al., 2016; Kaneda et al., 2016
	class IIa HDAC inhibitors	Guerriero et al., 2017
Cytokines	JAK inhibitors	Benci et al., 2016
	TGFβ inhibitors/ antibodies	Tauriello et al., 2018; Mariathasan et al., 2018
	MET inhibitors	Glodde et al., 2017
Immunometabolism	IDO1 inhibitors A2AR antagonists arginase inhibitors glutaminase inhibitors	Prendergast et al., 2017; Cekic and Linden, 2016

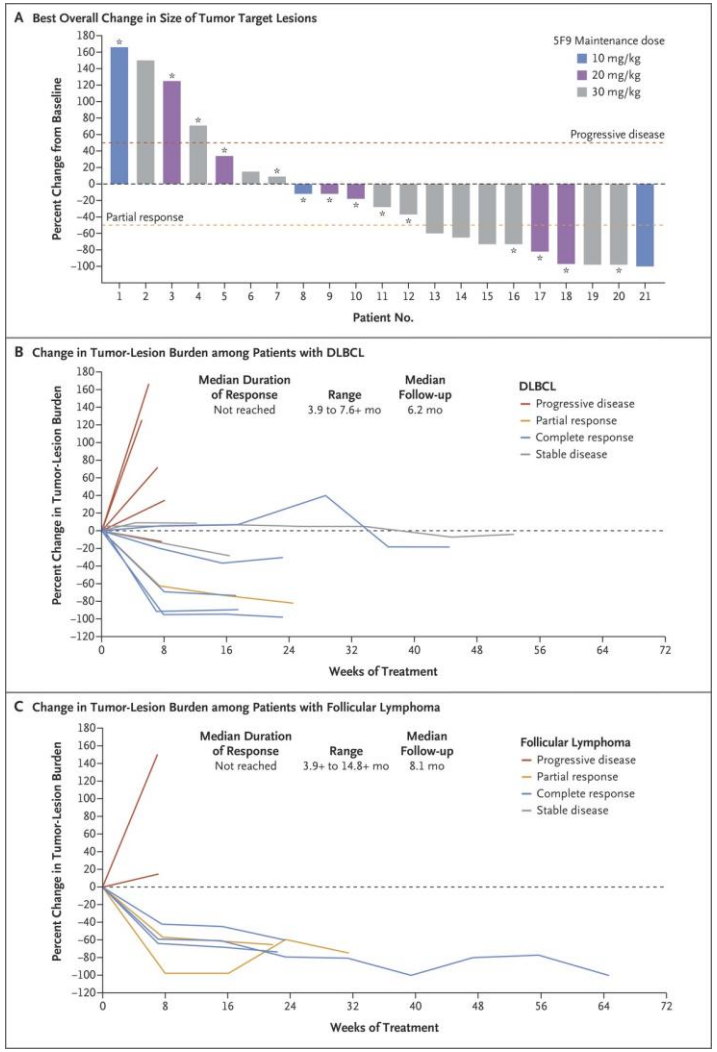


Tumor-Associated Macrophages in Cancer Progression and as Therapeutic Targets.



A Mantovani, DL Longo. N Engl J Med 2018;379:1777-1779.

CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma



How to overcome immunotherapy resistance : the new wave of therapeutic approaches

- Cancer immunotherapy clinical studies have overrun the progress in the understanding the underlying basic science

- This creates opportunity to synergize emerging science with clinical insight

- It creates also the obligation for an integrated, high quality and scientifically sound translational program.