Immunosurveillance and biomarkers in cancer: the means for more effective therapies

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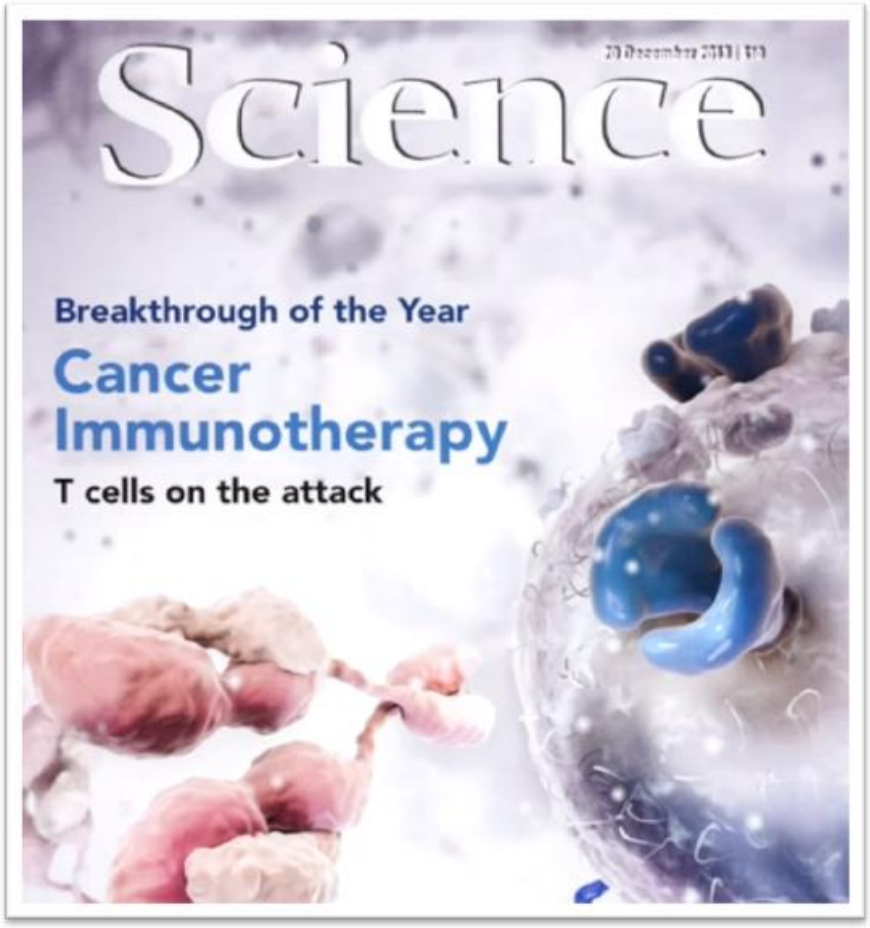
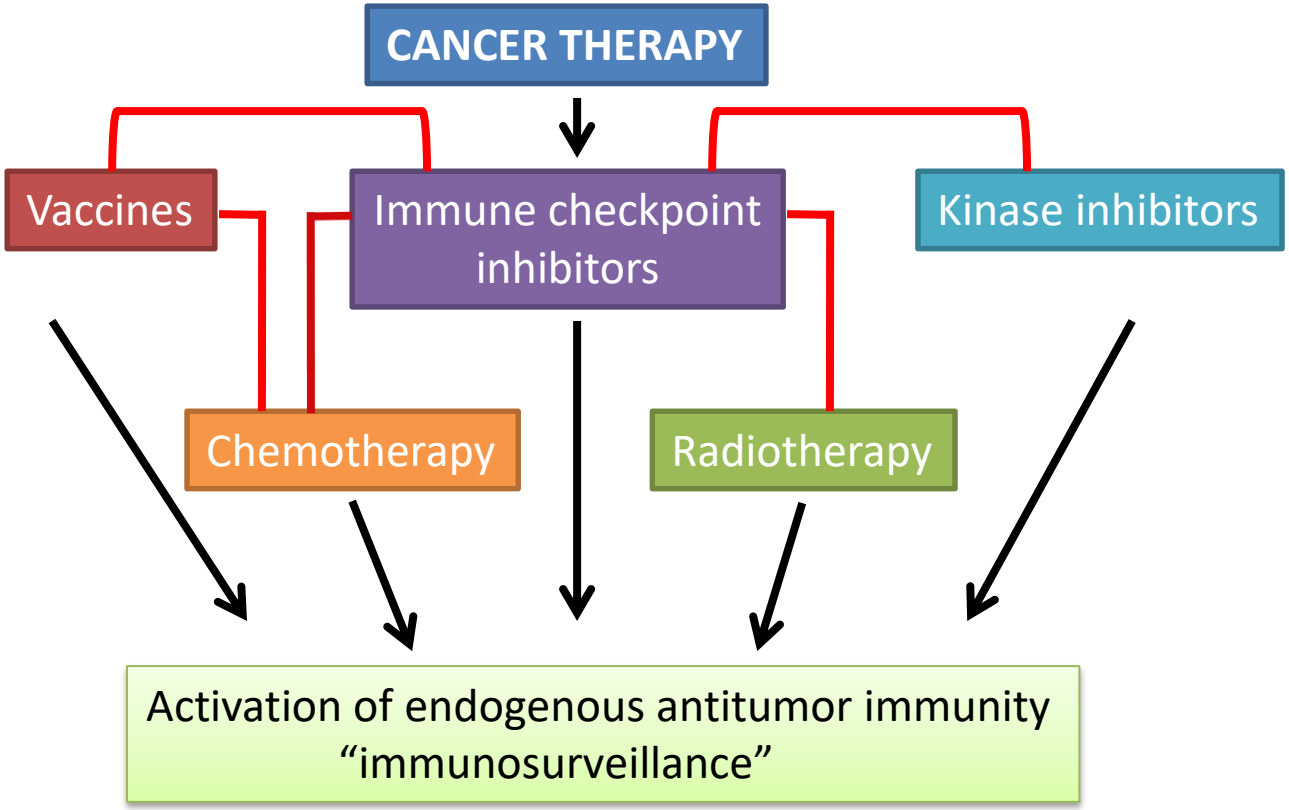
The renaissance of immunotherapy is a revolution for cancer patients



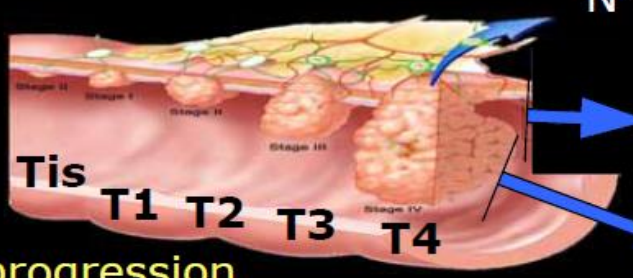
The reactivation of preexisting T cell antitumor immunity is mandatory for the outcome of anticancer therapies


CANCER THERAPY
Vaccines
Immune checkpoint inhibitors
Kinase inhibitors
Chemotherapy
Radiotherapy
Activation of endogenous antitumor immunity
“immunosurveillance”

Definition of cancer

1) A tumor cell DNA disease – Cell-centric paradigm

2) Due to the acquisition of secondary key behavioral characteristics following tumor genomic changes (Hanahan & Weinberg, *Cell* 2000, 2011)



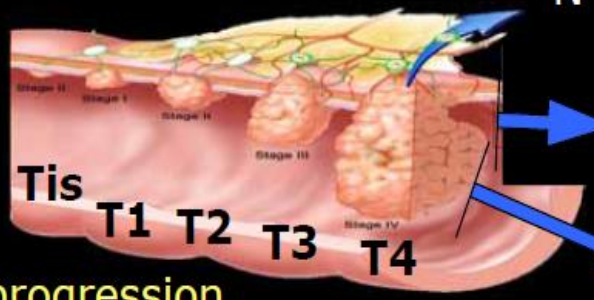
-> Tumor aggressiveness, progression, invasion and recurrence define early and late stage cancers, and the severity of the disease

Novel paradigm

Immunoscore
Immune contexture

Tumor invasion

N-Stage



Early-metastasis
(venous emboli)

T-Stage **Tis** **T1** **T2** **T3** **T4**

M-Stage

Tumor progression

Tumor grade differentiation
Tumor aggressiveness
(driver mutations, CIN, MSI, CIMP…)

-> Tumor recurrence
-> death

- ✓ Tumor progression, invasion and recurrence are dependent on pre-existing immunity and on Immunoscore
- ✓ Pre-existing immunity is determining the fate and survival of the patient
- ✓ Pre-existing immunity is determining the likelihood of response to immunotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

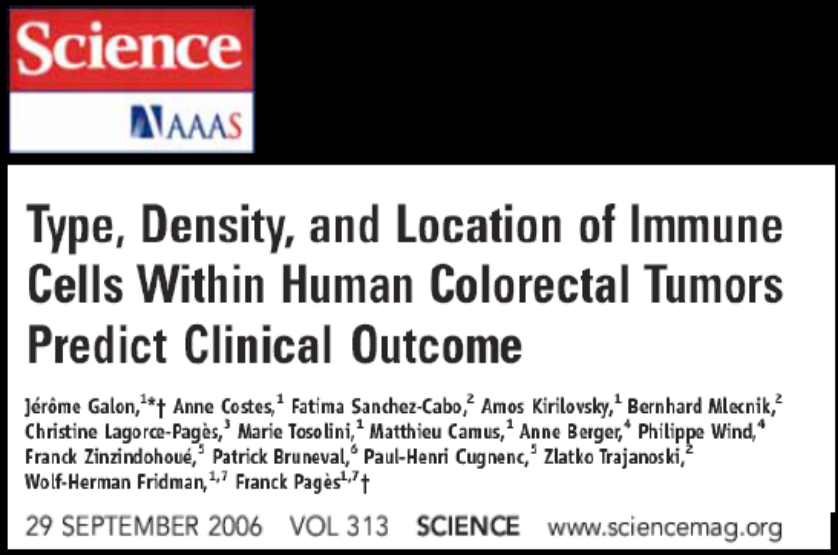
Effector Memory T Cells, Early Metastasis, and Survival in Colorectal Cancer

Franck Pagès, M.D., Ph.D., Anne Berger, M.D., Ph.D., Matthieu Camus, M.Sc., Fatima Sanchez-Cabo, Ph.D., Anne Costes, B.S., Robert Molidor, Ph.D., Bernhard Mlecnik, M.Sc., Amos Kirilovsky, M.Sc., Malin Nilsson, B.S., Diane Damotte, M.D., Ph.D., Tchao Meatchi, M.D., Patrick Bruneval, M.D., Ph.D., Paul-Henri Cugnenc, M.D., Ph.D., Zlatko Trajanoski, Ph.D., Wolf-Herman Fridman, M.D., Ph.D., and Jérôme Galon, Ph.D.*

Memory T cells, in particular, T_{EM} correlate with the absence of early-metastatic invasion, and improved clinical outcome in colorectal carcinoma.

Pagès F, et al. ***N Engl J Med***. 2005
Pagès F & Galon J. ***N Engl J Med***. 2006

A Novel Paradigm for Cancer



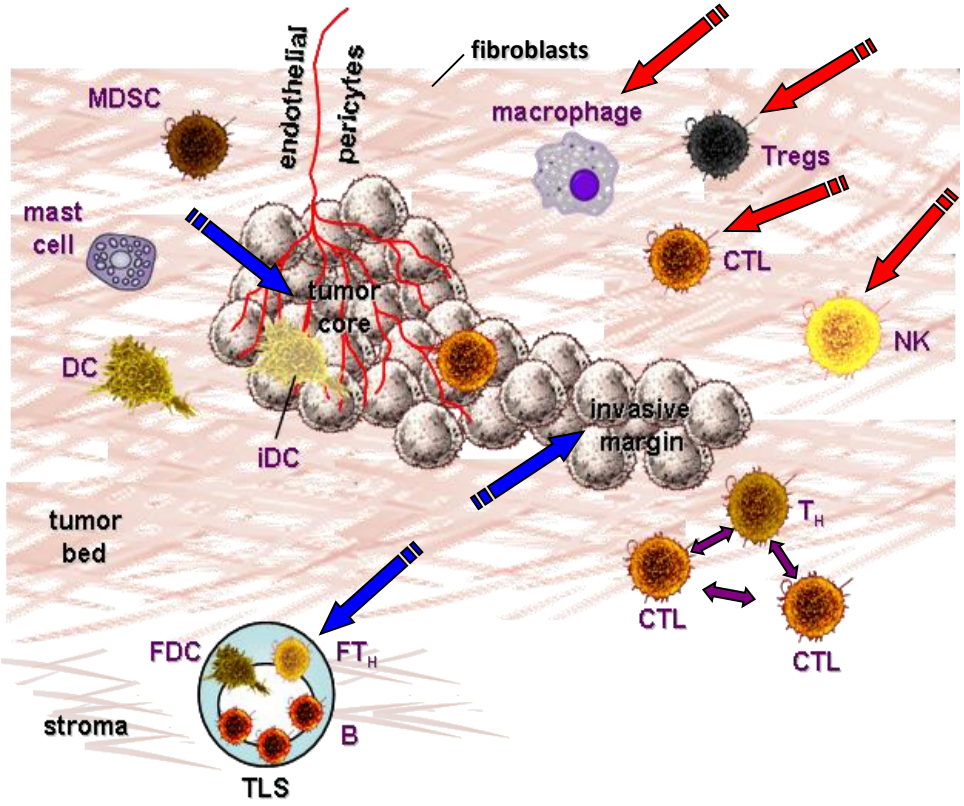
Galon J et al. ***Science*** 2006

The foundation a new concept

Immune contexture ⟷ **Immunoscore**

✓ Quantification of immune cell densities (n=415 Patients, 6640 IHC) revealed the major positive role of cytotoxic and memory T cells for patient's survival

Intratumoral immune signatures as prognostic and predictive markers

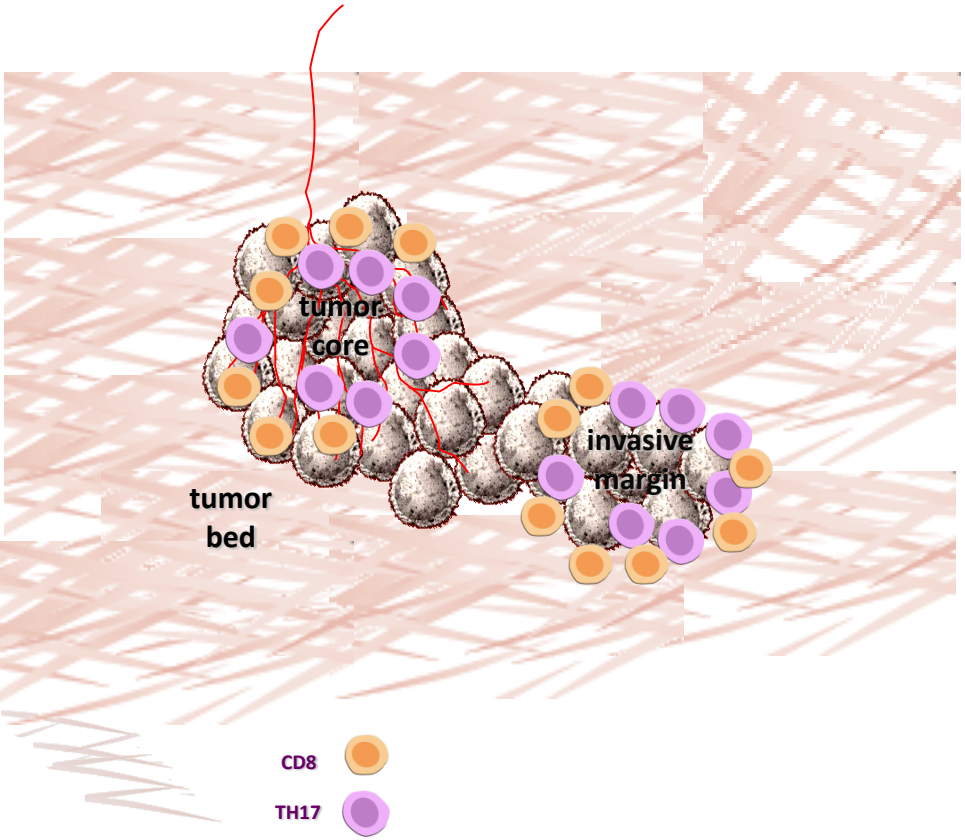


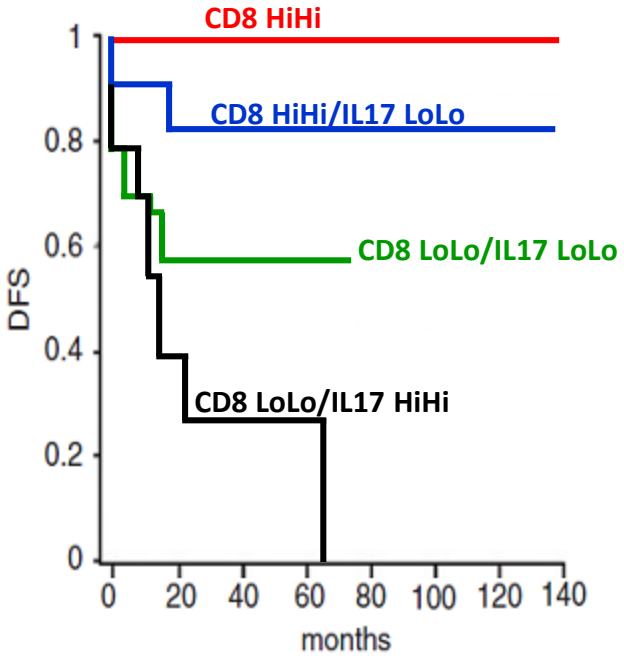
Immune contexture						
Type	Adaptive immunity, cytotoxicity, memory T cells					Immunoscore
Location	Tumor center, margin, tertiary lymphoid islets					
Density	Quantification (cells/mm²)					
Functional orientation	$IL12RB_1$ $IL12RB_2$ CD28 CCR5 CXCR3 TBX21	IRF1 IFNγ G7MB TAP1 IL17 GNLY PRF1 CCL5 CD8A STAT1	IL23R CCL24 RORC IL17A	IL5 IL13 IL4 STAT6 IL4R IL10R $IFN\gamma R_2$ STAT3 $IFN\gamma R_1$	CCL22 CCL17 CTLA4 FOXP3 TGFβ IL10	
	Th_1	cytotoxic	Th_{17}	Th_2	Tregs	

CD8⁺ — **Type 1 microenvironment**

CD4⁺ — **Type 2 microenvironment**

Intratumoral immune signatures as prognostic and predictive markers

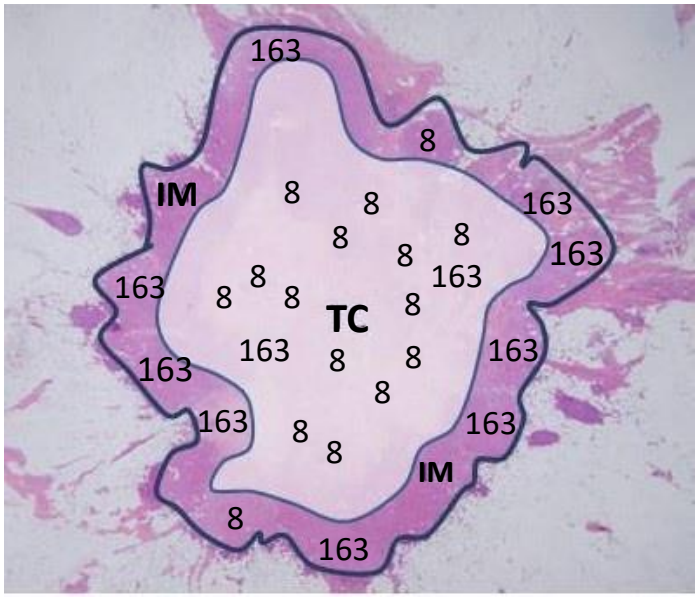




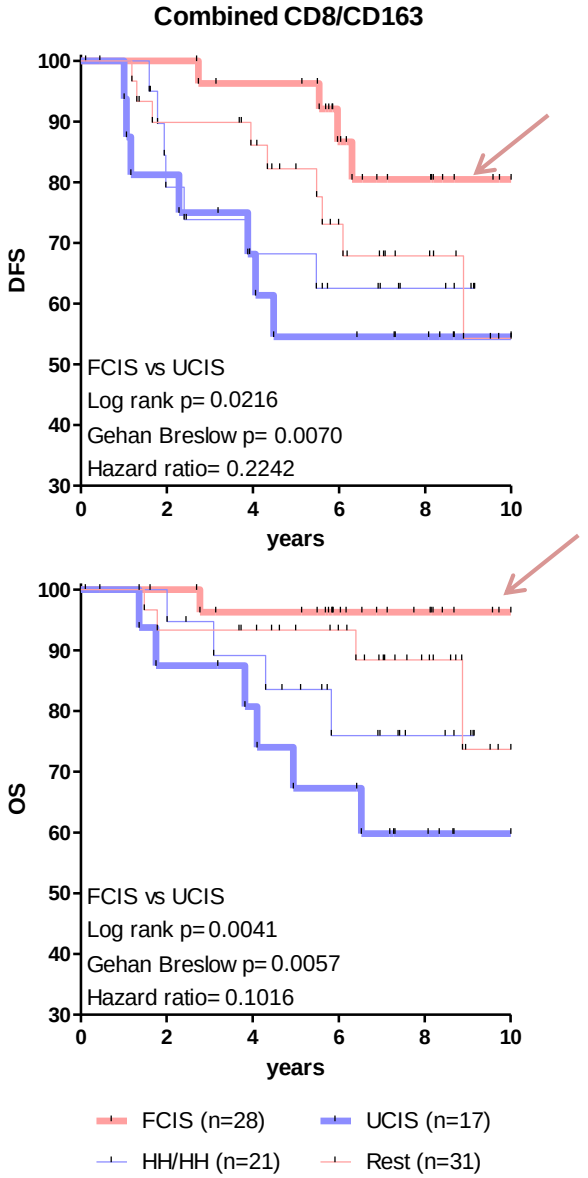
Tosolini M et al. Cancer Res 2011;71:1263

Differential densities of CD8+ and CD163+ cells in different tumor compartments as prognostic biomarkers for DFS and OS in Breast Cancer patients

CD8 HL/ CD163LH



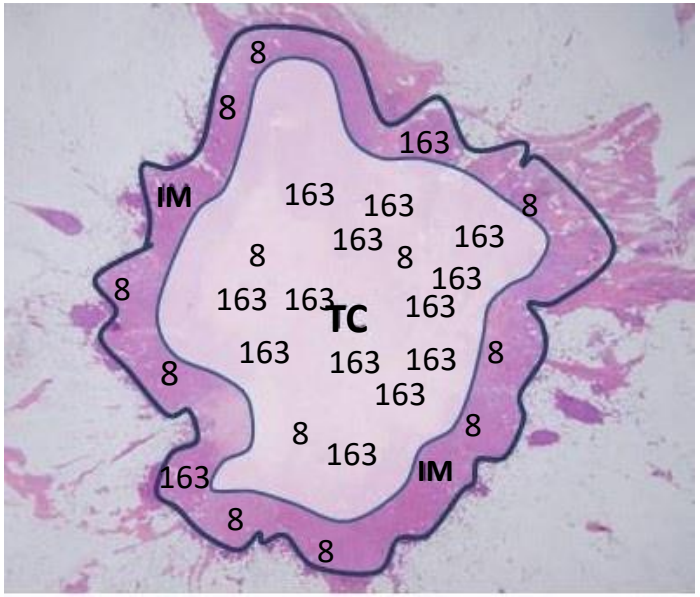
TC: tumor center
IM: invasive margin



Fortis SP et al, J Immunother Cancer. 2017 Apr 18;5:39

Differential densities of CD8+ and CD163+ cells in different tumor compartments as prognostic biomarkers for DFS and OS in Breast Cancer patients

CD8 LH/ CD163HL



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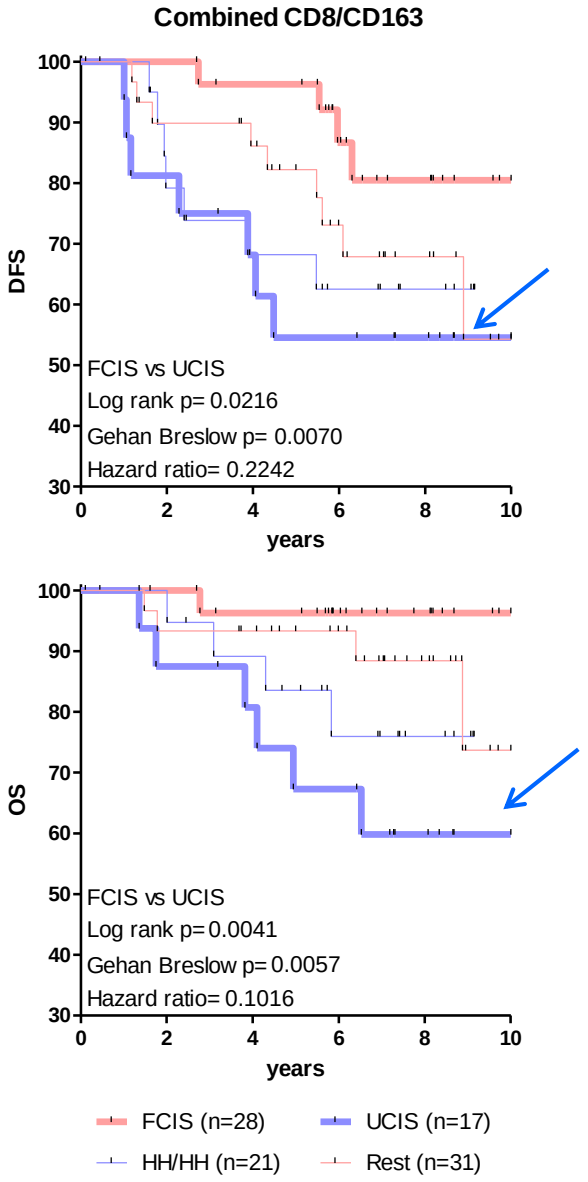

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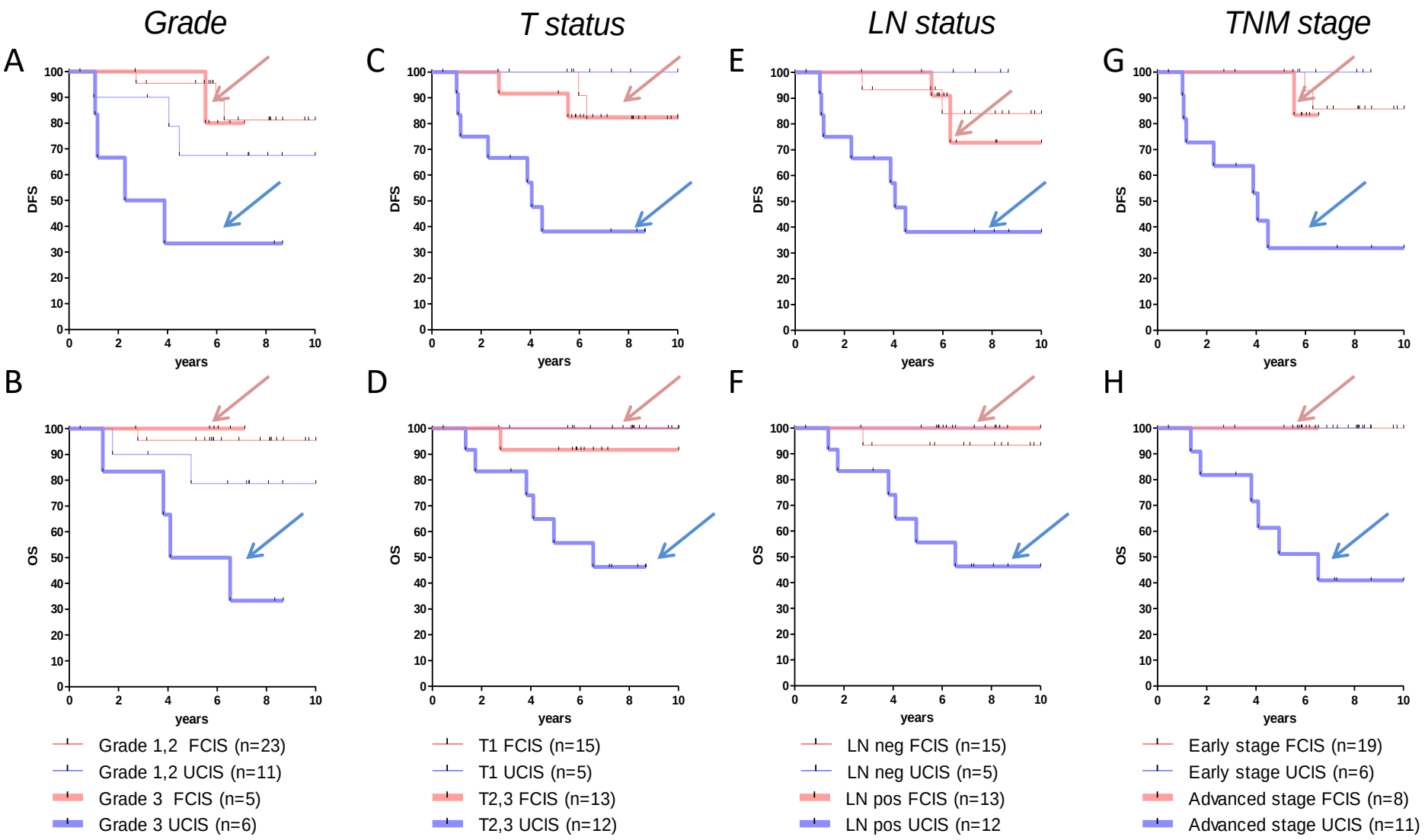
Differential densities of CD8+ and CD163+ cells as prognostic biomarkers for DFS and OS in Breast Cancer patients



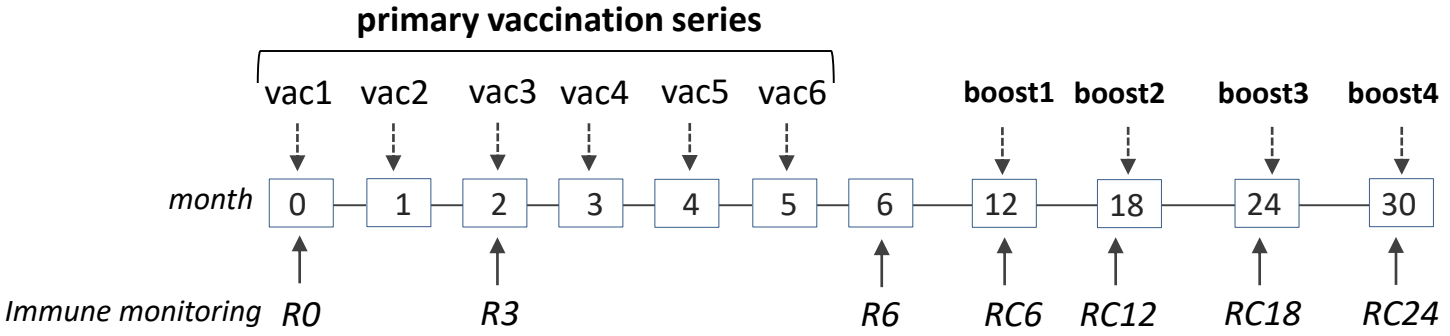
Fortis SP et al, J Immunother Cancer. 2017 Apr 18;5:39

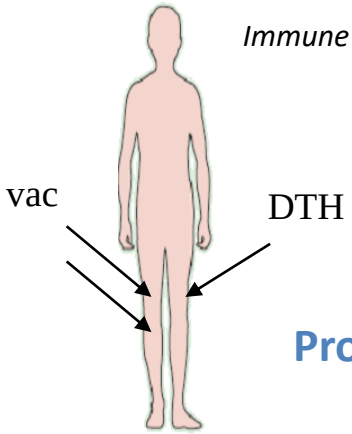
Peripheral and Local reaction to vaccination as predictive biomarker

Holmes JP et al. J Clin Oncol 2008; 23:3426,
Perez SA et al. Clin Cancer Res 2010;16:3495,
Perez SA et al. Cancer Immunol Immunother 2013;62:1599,
Perez SA et al. Cancer Immunol Immunother 2014;63:1141,
Anastasopoulou EA et al. Cancer Immunol Immunother 2015; 64:11239,
Anastasopoulou EA et al. , Oncoimmunology 2016,5(7):e1178439

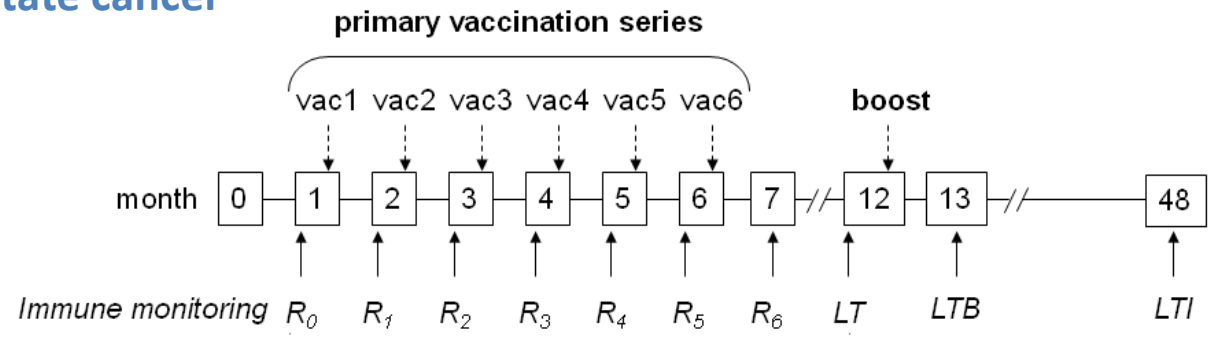
Vaccination schedule with AE37

Breast cancer

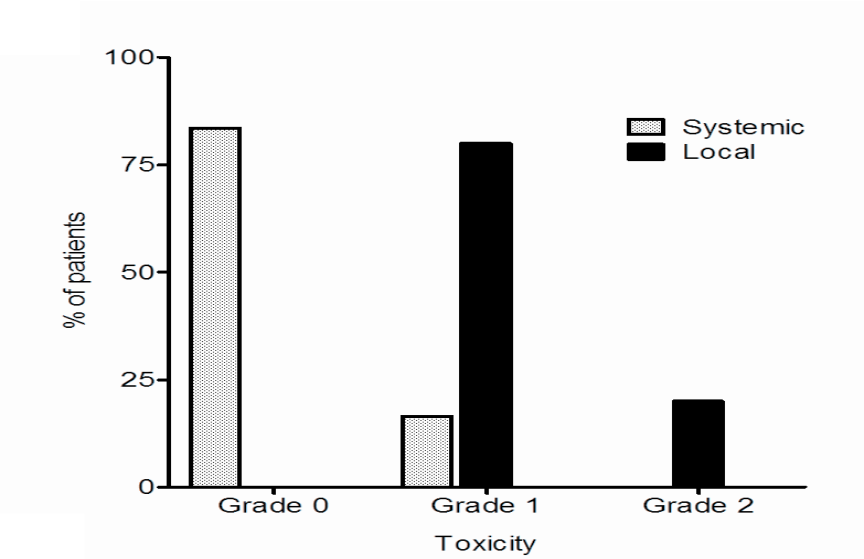




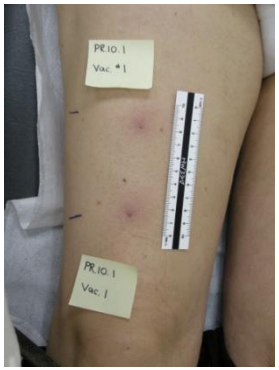
Prostate cancer



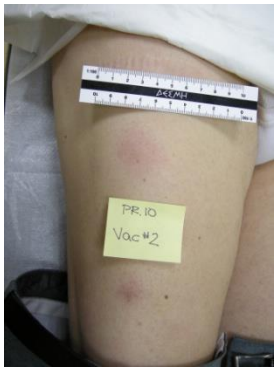
Toxicity profile



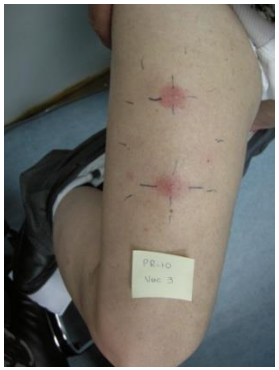
Dermal reactions during vaccinations



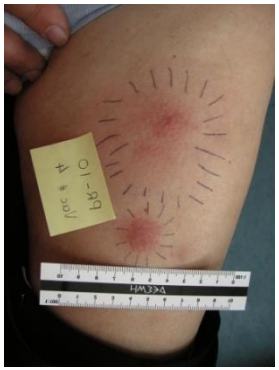
vac 1



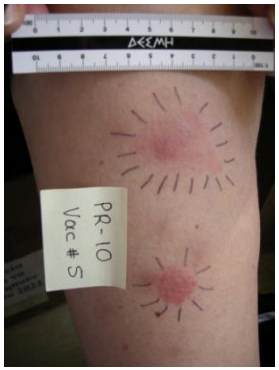
vac 2



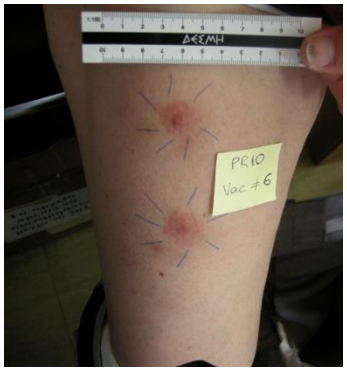
vac 3



vac 4



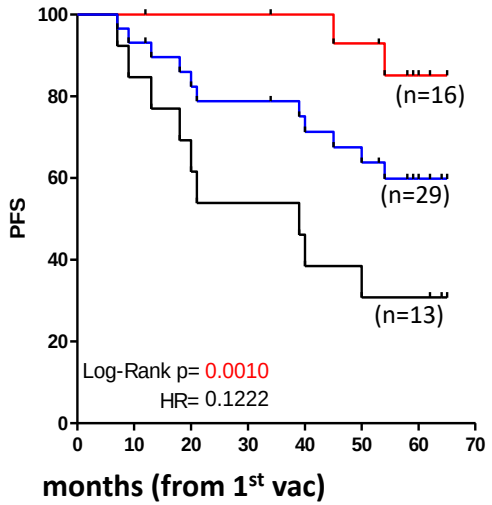
vac 5



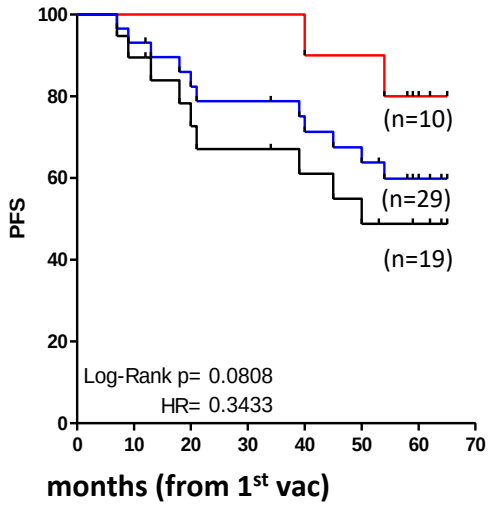
vac 6

Local reaction and IFNγ response to AE36 as predictive biomarkers for PFS in prostate cancer patients

Local Reaction 1 (LR1)



IFNγ-AE36



LR1: after the 1st vaccination
IFNγ-AE36: Preexisting IFNγ response to AE36

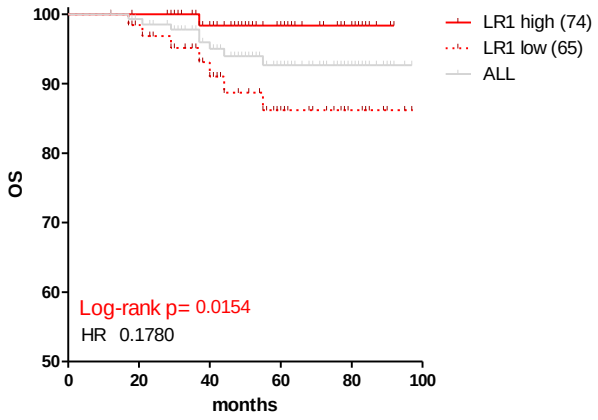
high or low preexisting immunity defined by cutoff finder software (high;≥10 mm or 25 spots)

LR1 as a predictive biomarker of clinical response in vaccinated breast cancer patients

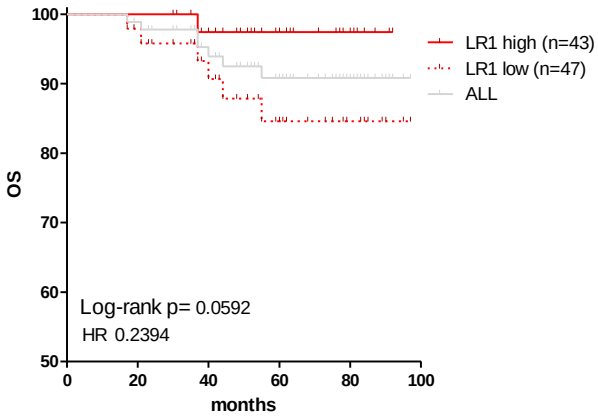
OS of vaccinated patients

median follow up 54 months (range 9-97)

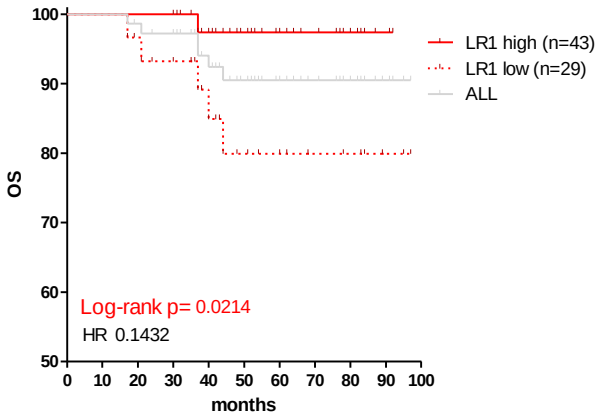
ALL patients



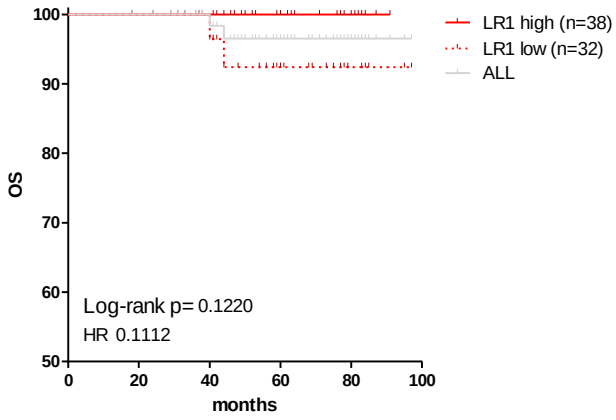
Lymph node positive Pts



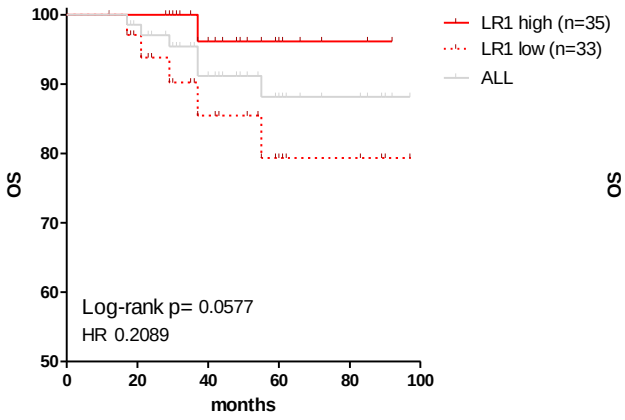
Advanced stage (IIb/III) patients



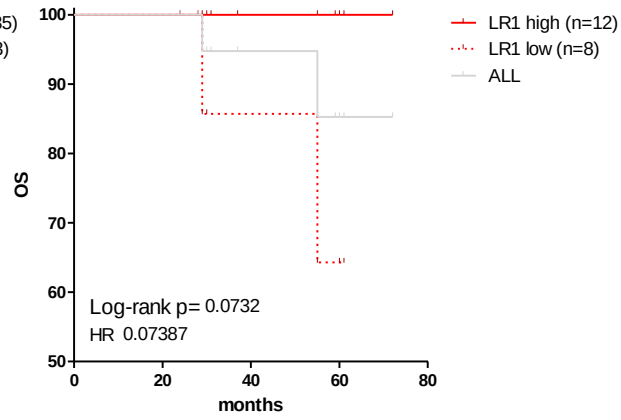
HER2 OE patients



HER2 LE patients



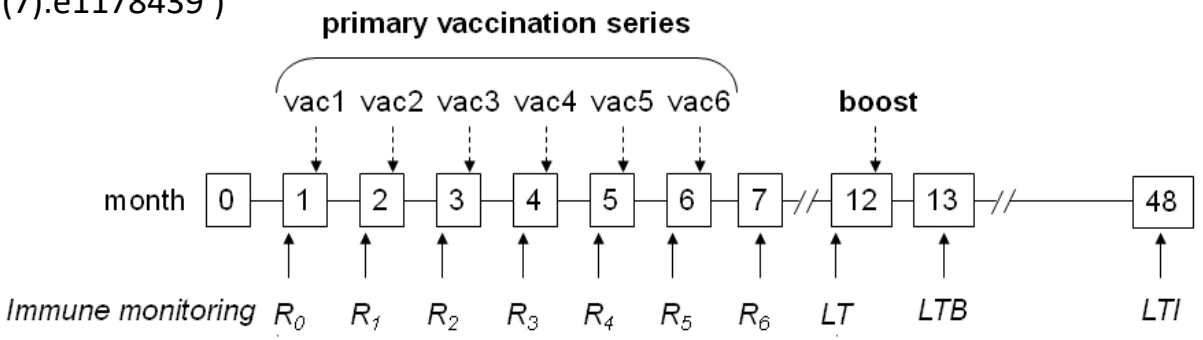
TNBC patients



Peripheral immune biomarkers

The AE37 paradigm for identifying the role of TGFβ, IFNγ and DTH as predictive biomarkers

(Holmes JP et al. J Clin Oncol 2008; 23:3426, Perez SA et al. Clin Cancer Res 2010;16:3495, Perez SA et al. Cancer Immunol Immunother 2013;62:1599, Perez SA et al. Cancer Immunol Immunother 2014;63:1141, Anastasopoulou EA et al. Cancer Immunol Immunother 2015; 64:11239, Anastasopoulou EA et al. , Oncoimmunology 2016,5(7):e1178439)



IFNγ

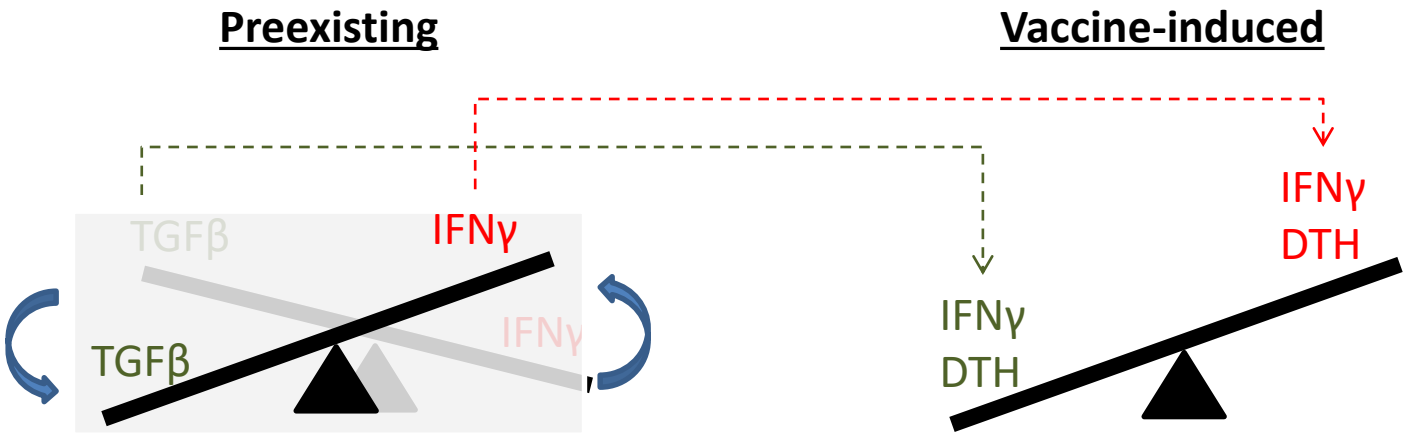
TGFβ

DTH IFNγ | DTH IFNγ | DTH IFNγ | DTH

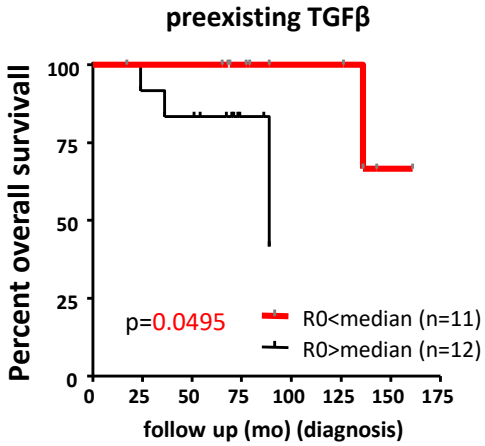
DTH IFNγ | DTH IFNγ | DTH IFNγ

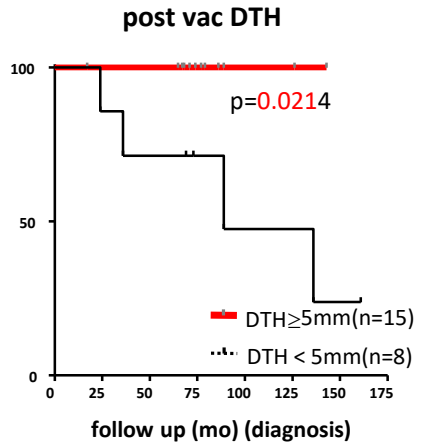
-: direct correlations

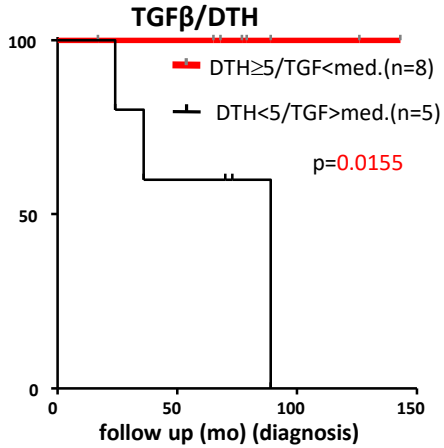
-: inverse correlations

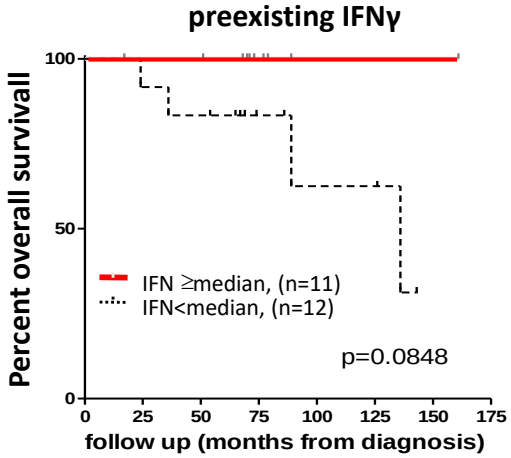


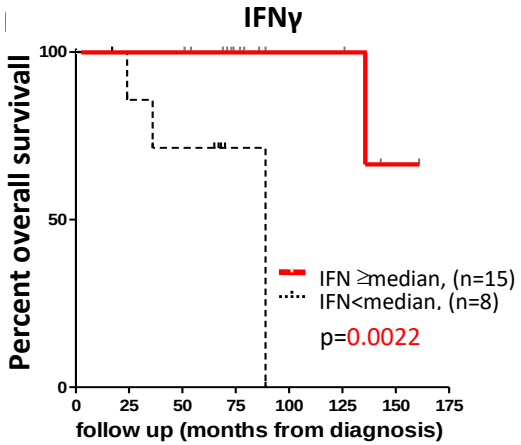
OS in AE37 vaccinated prostate cancer patients











HLA status and response to immunotherapies

Criteria for defining high responders among AE37-vaccinated patients

Pt no	IFNγ	DTH	classification	HLA alleles
8	R1-R5 + R6/LT	-	R	A24/DR11
10	R4-R5 + R6/LT	R6-LTB	HR	DR11
11	R1-R4 + R6/LT	-	R	A2
12	R1-R3 + R6-LTB	LT/LTB	HR	DR11
13	-		NR	A2
14	R2/R3 + LT/LTB	R6-LTB	HR	A24/DR11
15	R3-R5 + R6-LTB	R6-LTB	HR	A24/DR11
16	R1-R5 + R6-LTB	R6-LTB	HR	A24/DR11
17	R2/R3 + R6-LTB	-	R	DR11
19	-	-	NR	A2/A24
20	R1-R5 + R6-LTB	R6-LTB	R	A2/A3
21	R1-R5 + LT/LTB	R6-LTB	R	A2/A3
22	-	R6-LTB	R	A2
23	-	R6-LTB	R	A2
24	R2-R5 + R6-LTB	-	R	A3/DR11
25	-	LT/LTB	R	A24/DR11
26	R1-R3 + LT	R6-LTB	R	A3/A11
27	R1-R5 + R6/LTB	R6-LTB	HR	A24
28	R4/R5 + LT/LTB	LT/LTB	HR	A24/DR11
29	R4/R5 + LTB	R6-LTB	HR	A24/DR11
30	R1-R5 + LTB	R6-LTB	HR	A24/DR11
31	R2-R5 + R6/LTB	R6-LTB	HR	A24/DR11

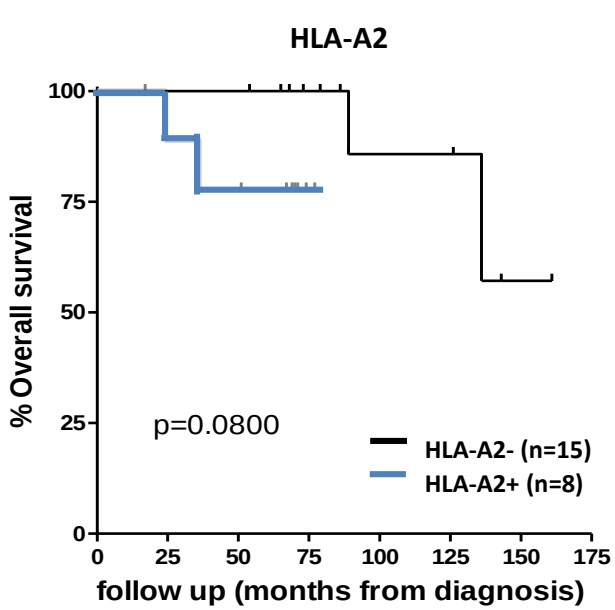
Criteria for response:
HR: IFNγ; SI>4
DTH; >20mm
R: IFNγ; SI>2-4
DTH; >10-20 mm
NR: IFNγ; SI<1.5
DTH; <5mm

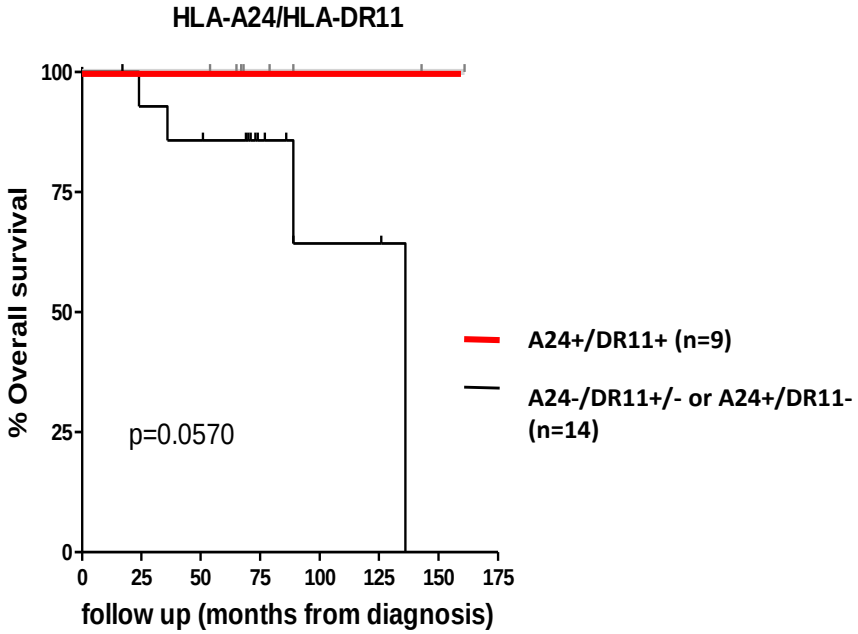
HR: A24/DR11 (n=7)
DR11 (n=2)
A24 (n=1)

R: A24/DR11 (n=2)
A2 (n=3); A2/A3 (n=2)
DR11 (n=1)
A3/DR11 (n=1)
A3/A11 (n=1)

NR: A2 (n=1)
A2/A24 (n=1)

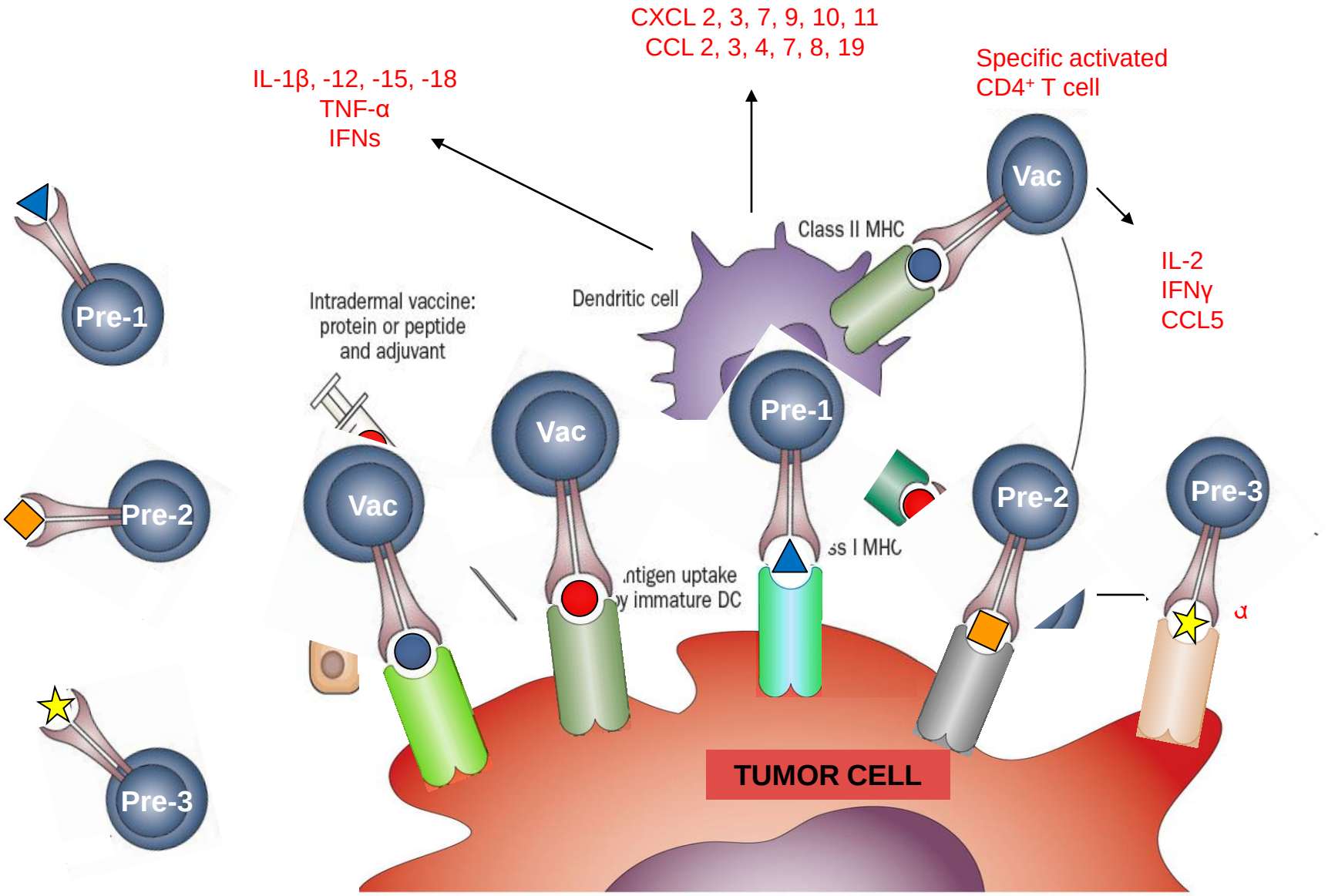
OS in AE37 vaccinated prostate cancer patients



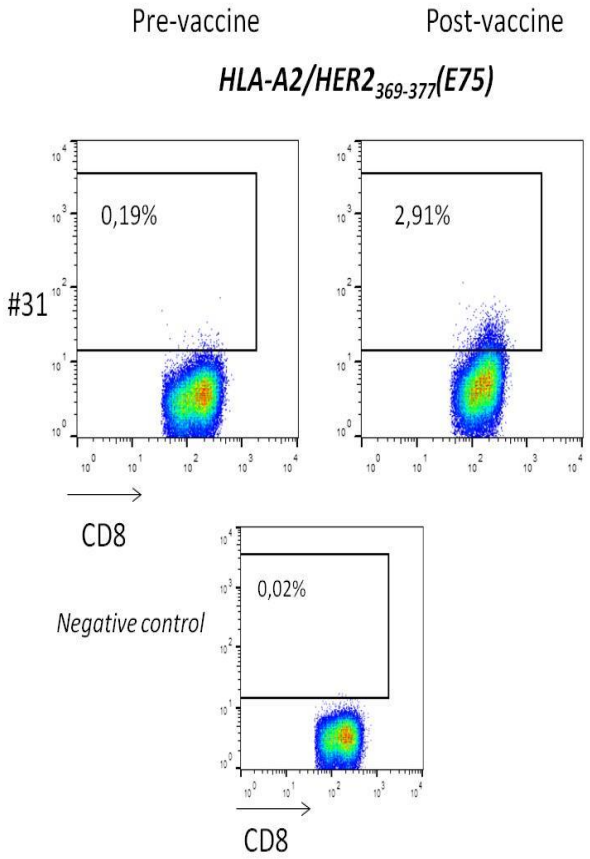


Epitope spreading as peripheral immune biomarker

Targeting multiple epitopes on the tumor cell restricted by various HLA alleles

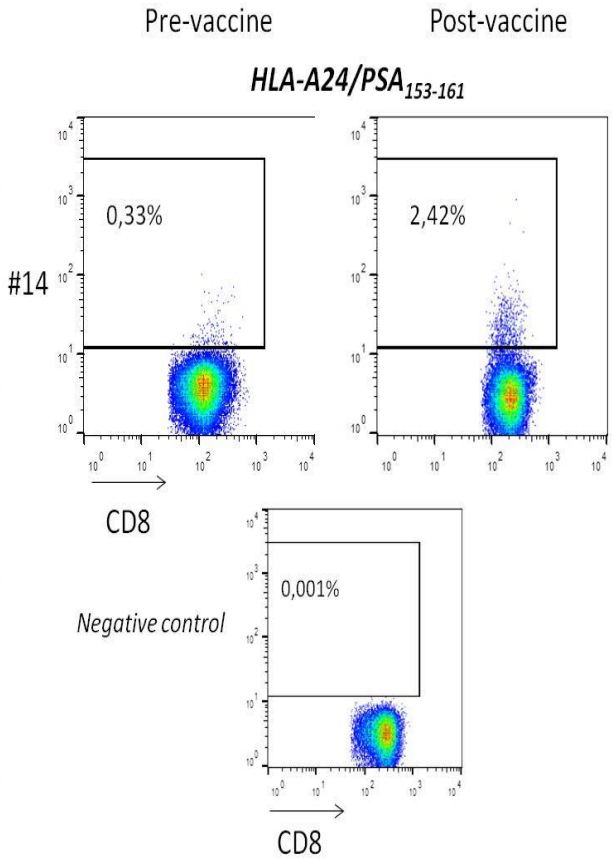


Ex vivo detection of antigen specific CD8⁺ T cells for epitopes not included in the vaccine



HLA-A2⁺

epitope	Induce/ Increase
$HER_{369-377}$ (E75)	9/12 (75%)
HER_{10} 85	6/12 (50%)
HER_{435}	2/12 (16,7%)
$PSA_{146-154}$	8/12 (66,7%)
$TERT_{540-548}$	4/12 (33,3%)
PSMA-27	2/12 (16,7%)
SURV $M2_{96-104}$	5/12 (41,7%)

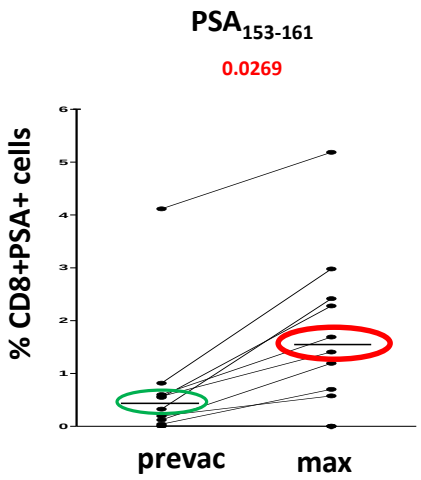


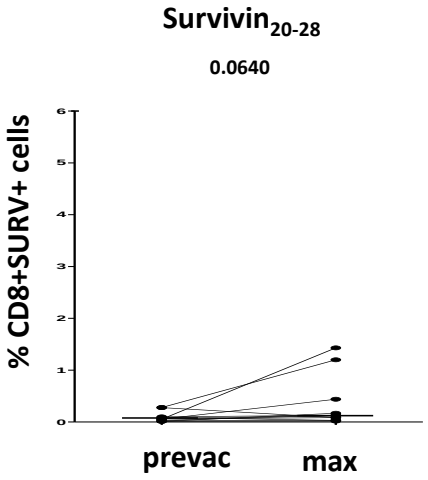
HLA-A24⁺

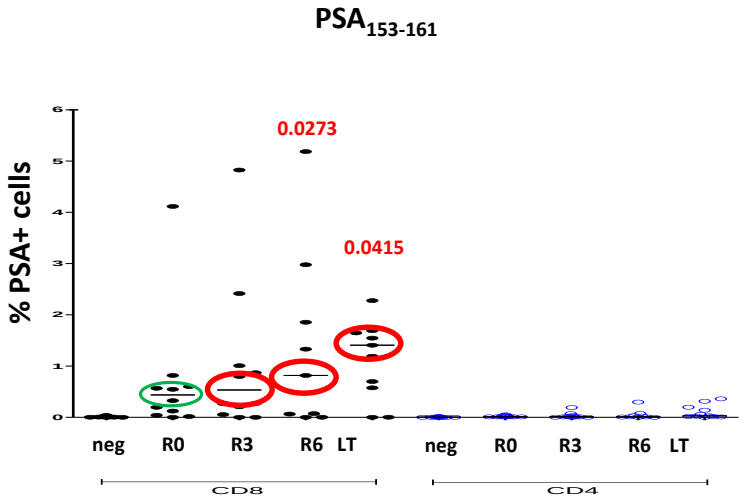
epitope	Induce/ Increase
$PSA_{153-161}$	8/12 (66,7%)
$SURV_{20-28}$	5/12 (41,7%)

Anastasopoulou E. et al, Oncoimmunology 2016,5(7):e1178439
Voutsas I.F. et al , J. Immunother. Cancer 2016,15;4:75

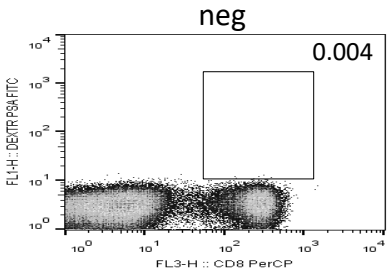
HLA-A24 restricted preexisting immunity and boosting following vaccination with AE37

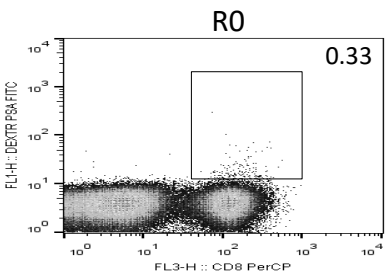


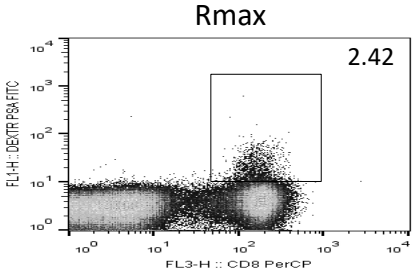




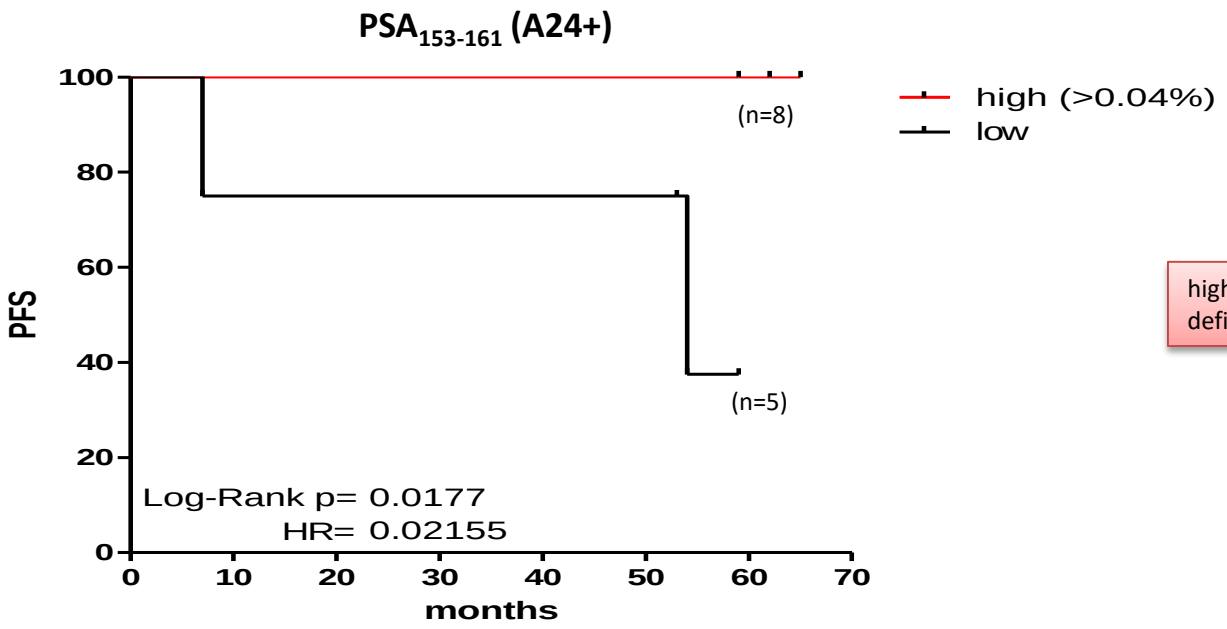
PSA153-161 PR14







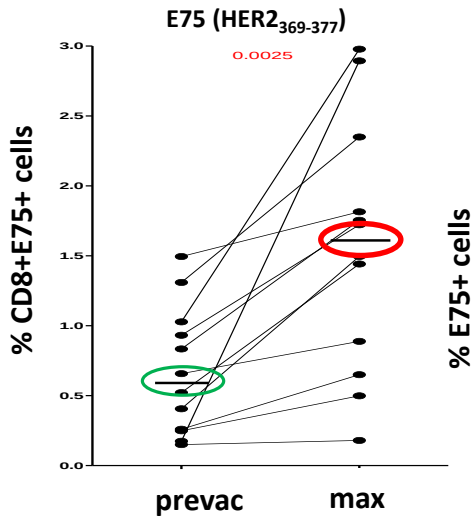
Preexisting immunity in HLA-A24+ vaccinated prostate cancer patients: correlations with PFS

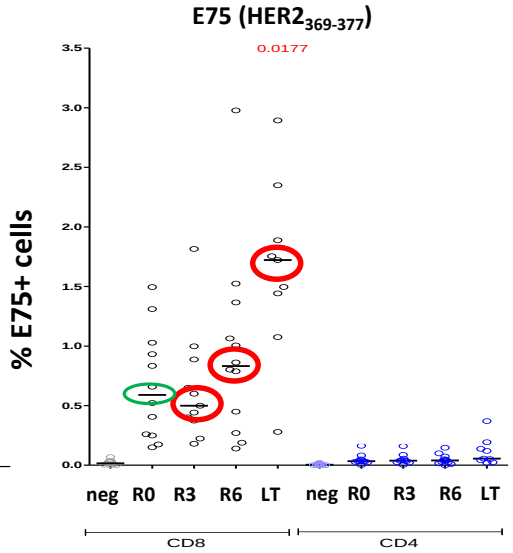


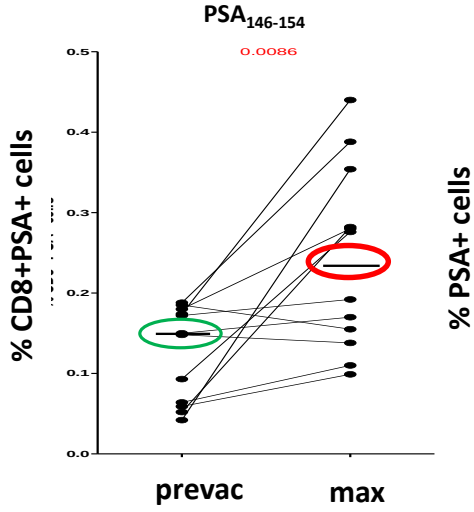
high or low preexisting immunity defined by x-tile software

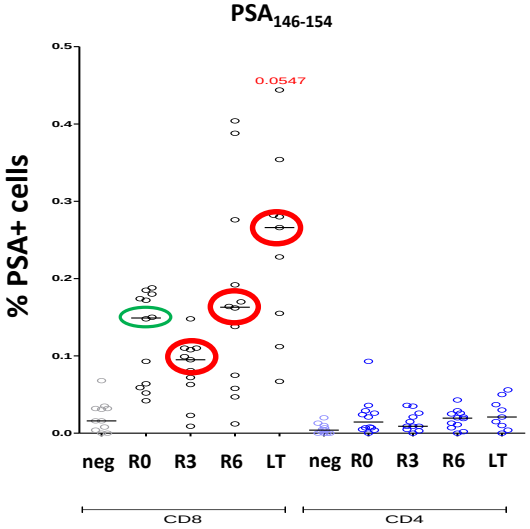
Voutsas I.F. et al , J Immunother. Cancer 2016,15;4:75

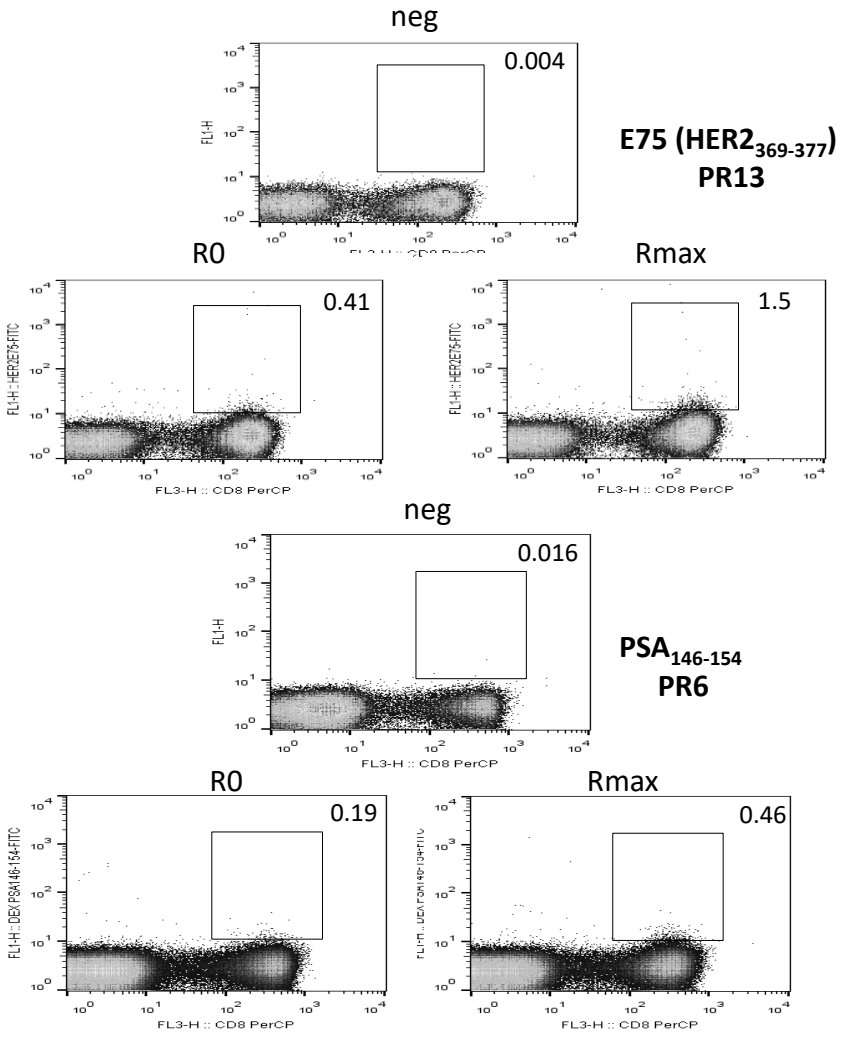
HLA-A2 restricted preexisting immunity and boosting following vaccination with AE37





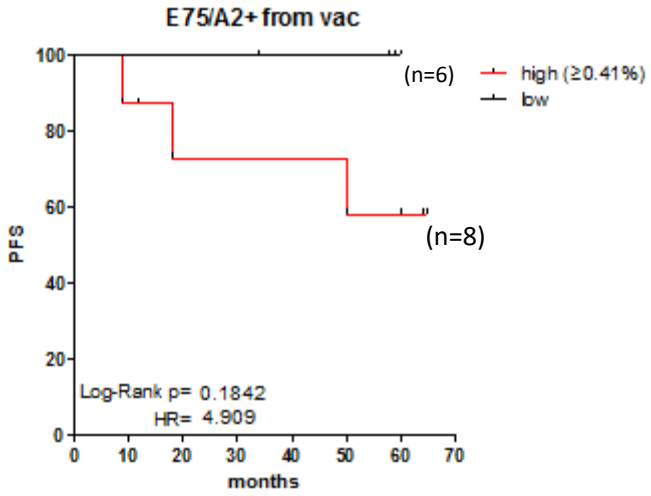






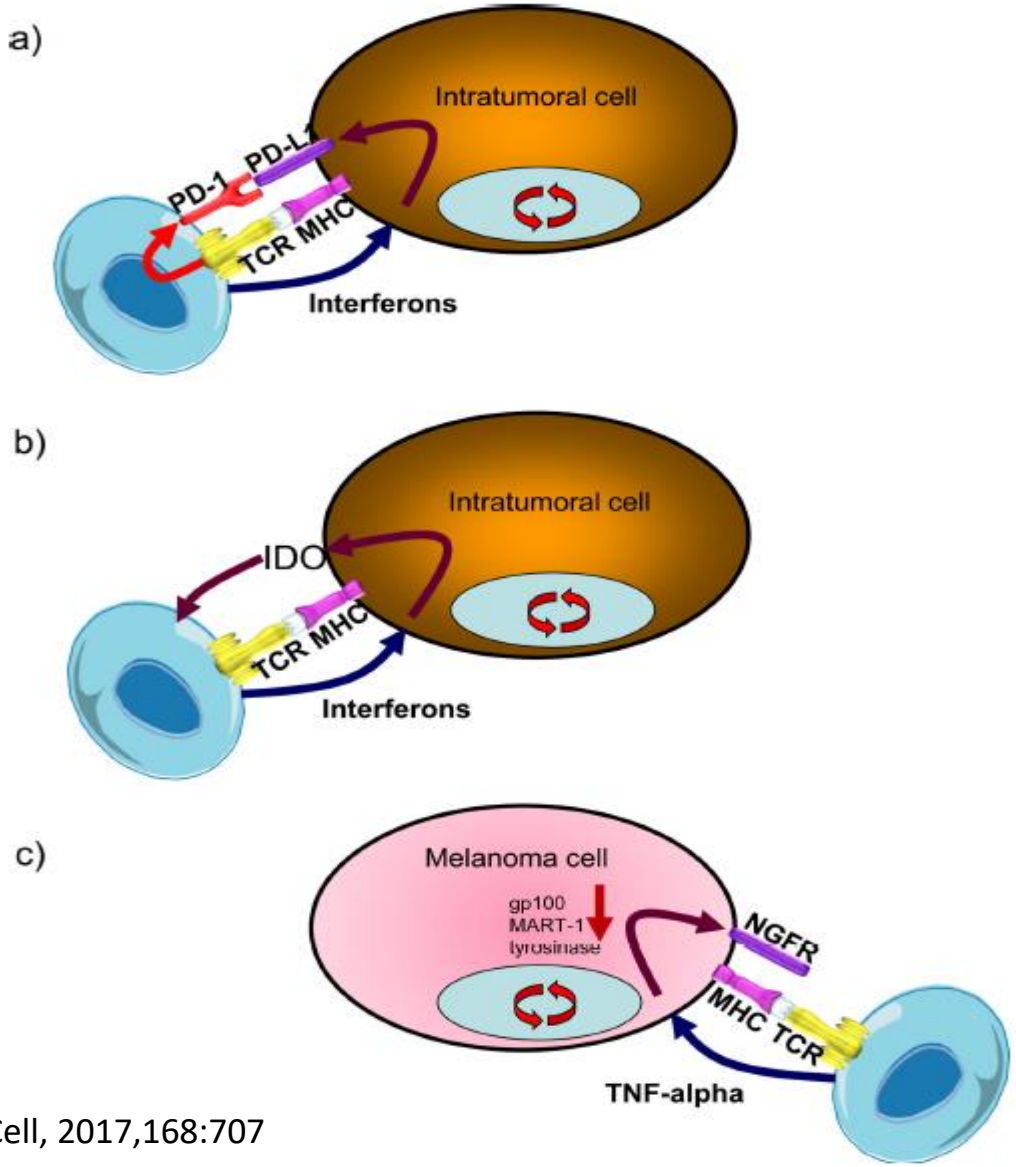
Voutsas I.F. et al , J Immunother. Cancer 2016,15;4:75

Preexisting immunity in HLA-A2+ vaccinated prostate cancer patients: correlations with PFS



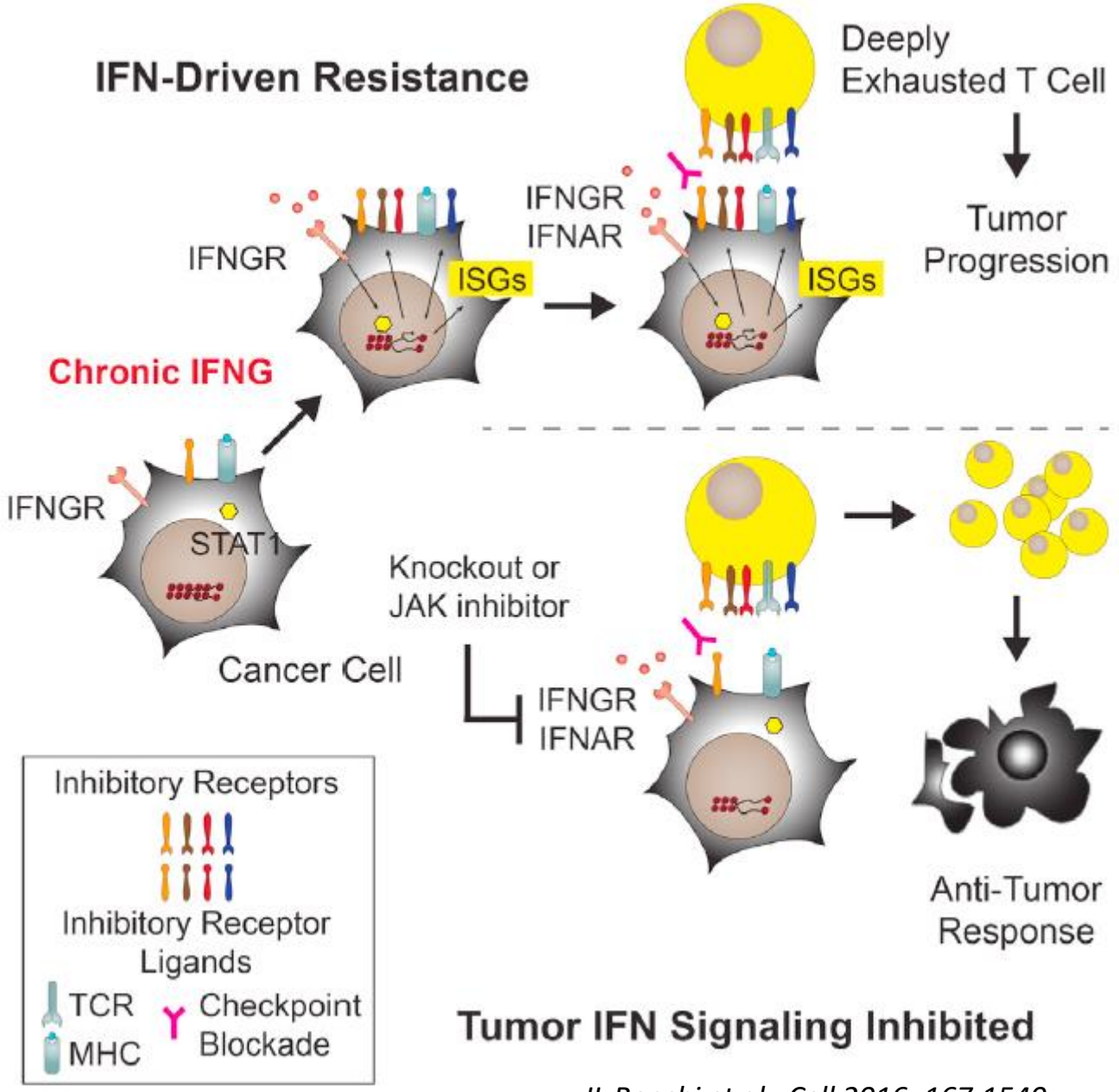
Adaptive immune resistance

Examples of adaptive immune resistance



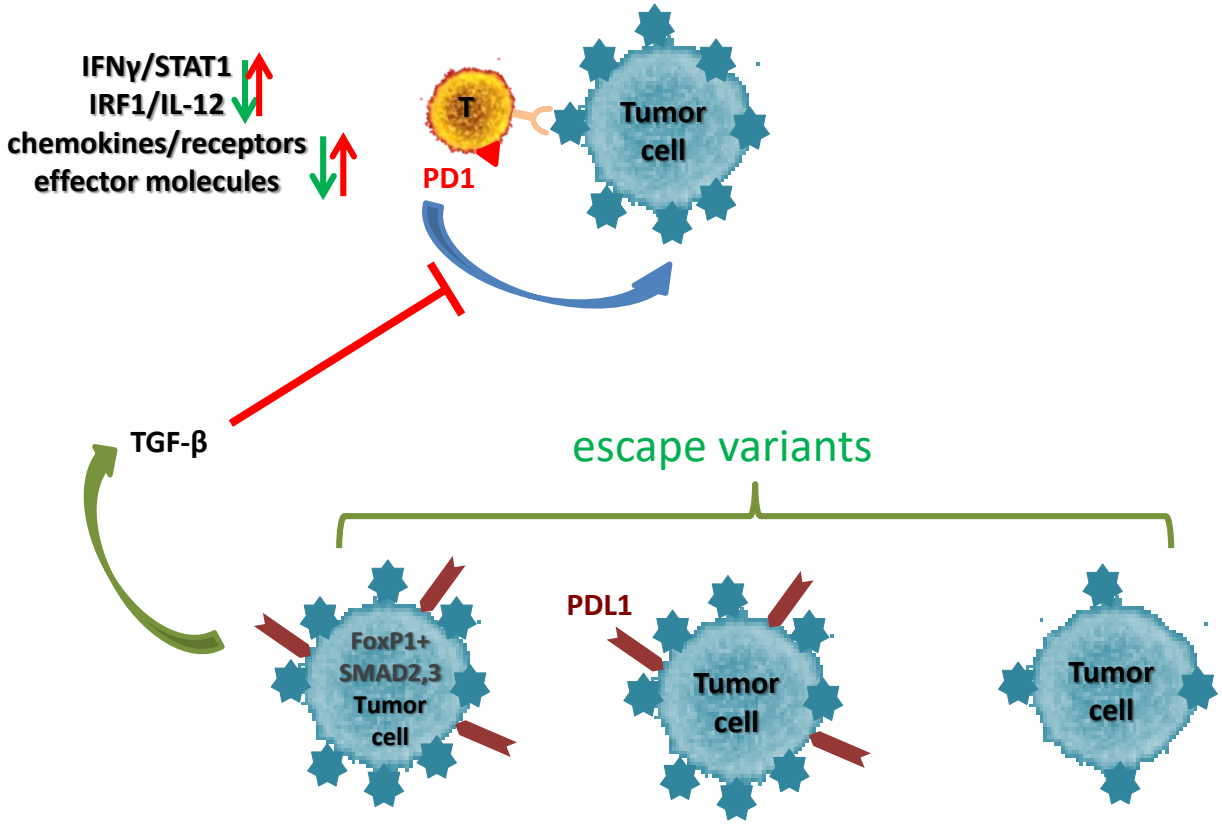
Sharma P et al, Cell, 2017,168:707

Tumor IFNγ signaling regulates multigenic immune checkpoint resistance



JL Benchi et al , Cell 2016; 167;1540

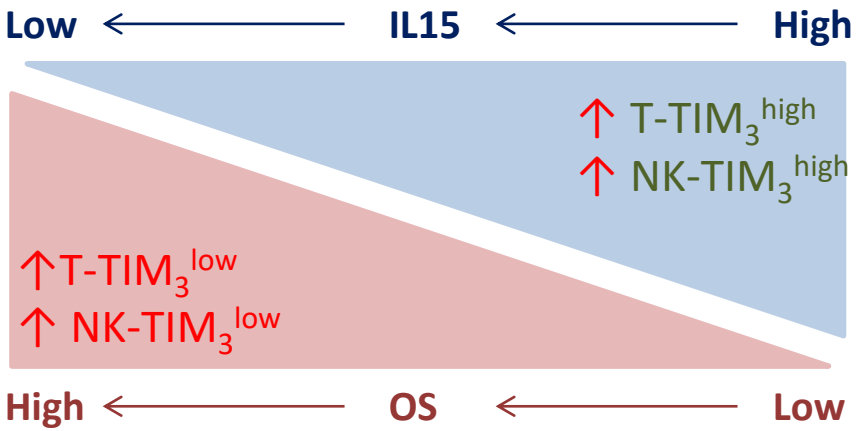
Immune resistance by tumor cells during equilibrium



Zitvogel L and Kroemmer G , Immunity 2014, 41:345

Adaptive immune resistance in the periphery

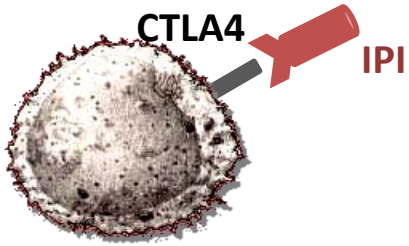
Stage IV melanoma patients receiving IPI as immunotherapy



Tallerico R. et al. Oncoimmunology 2016;6:e1261242

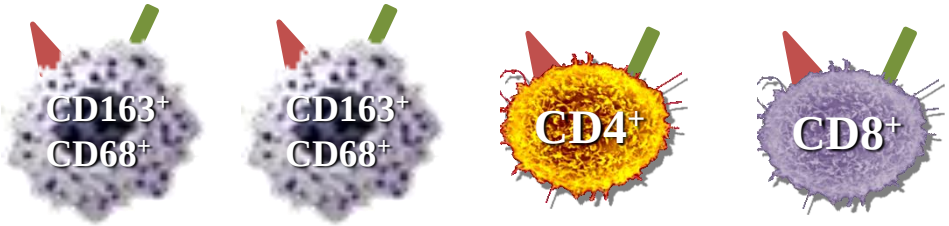
Adaptive immune resistance in the periphery

Localized prostate cancer: pre-surgery ADT ± IPI



: VISTA

: PDL1

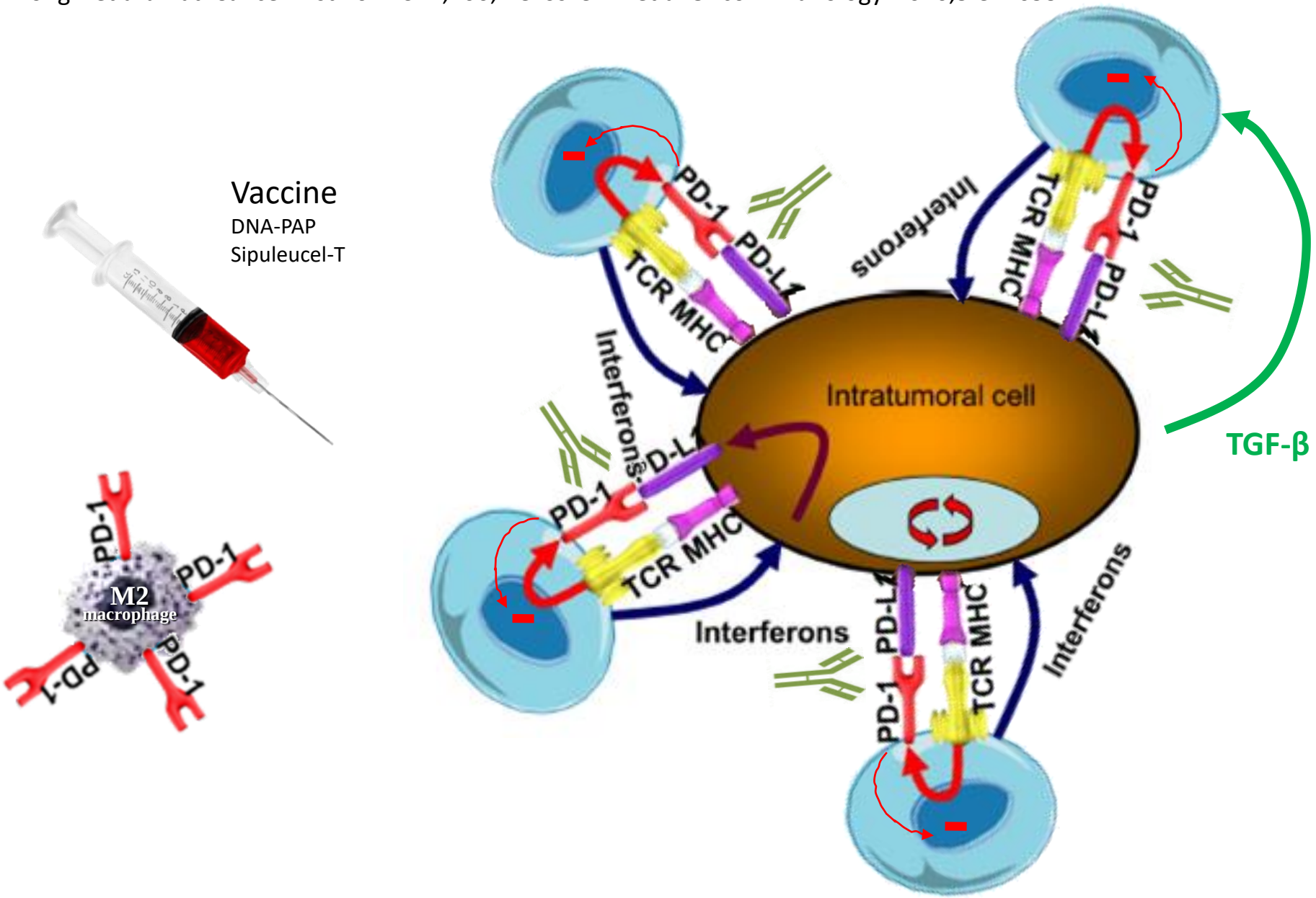


High frequencies of cells

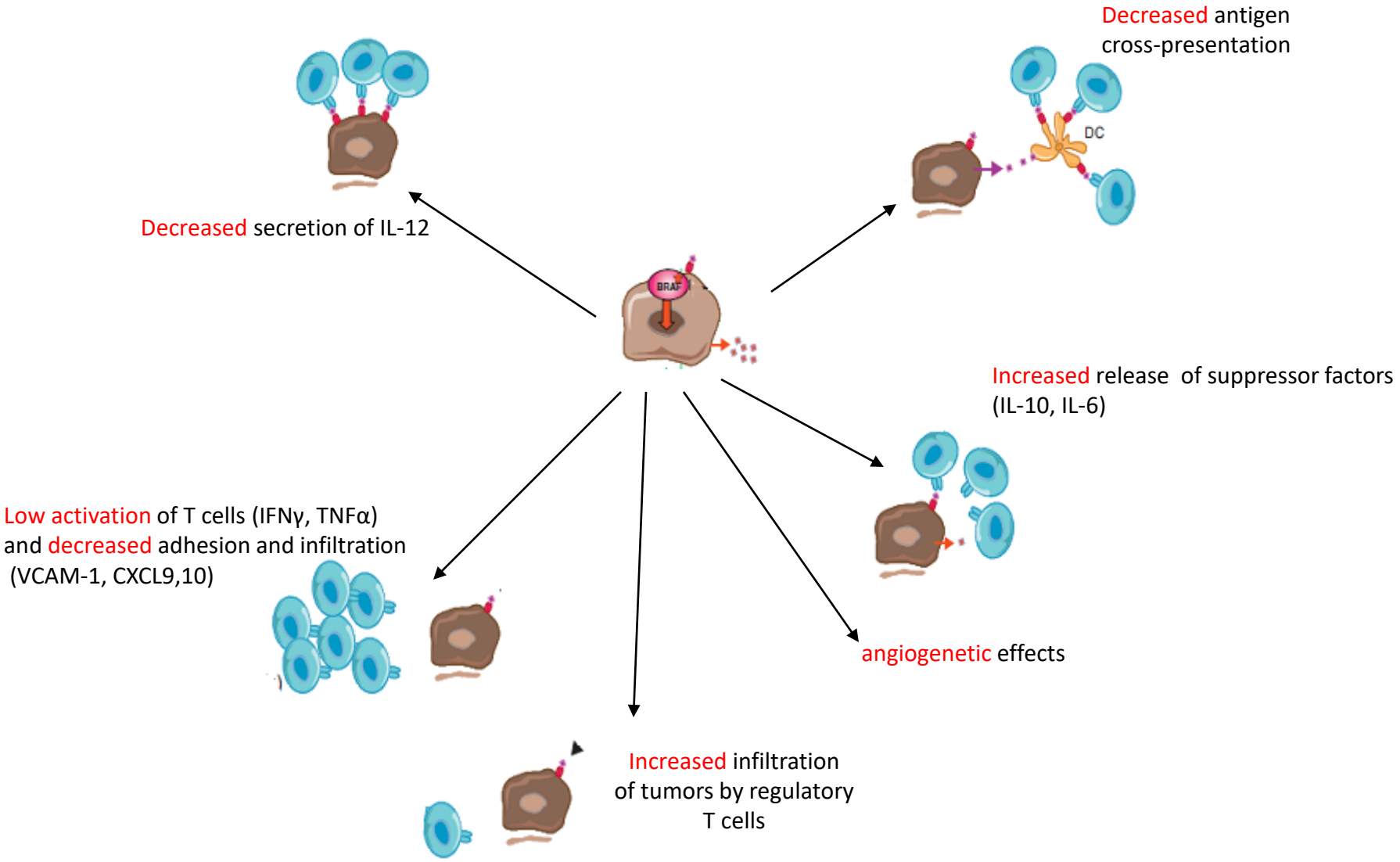
Gao J. et al. Nature Medicine 2017; 27 March

Vaccination induces infiltration of IFNγ producing T-cells within the tumor with up-regulation of PD-L1

Fong L et al J Natl Cancer Inst 2014 S24;106; Rekoske BD et al Oncoimmunology. 2016;5:e1165377



Effects of tumor oriented therapies on the endogenous antitumor immunity: III kinase inhibitors



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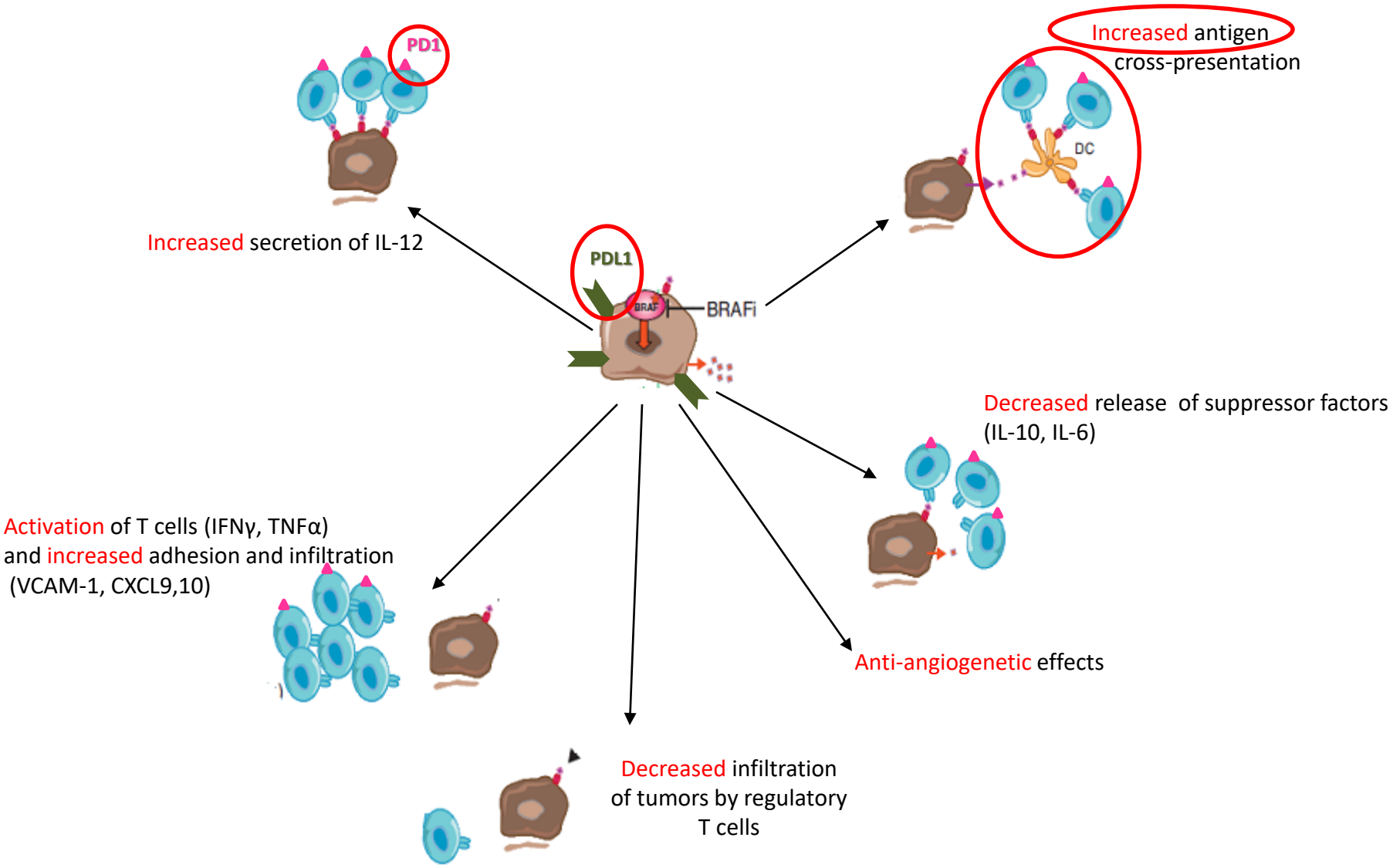
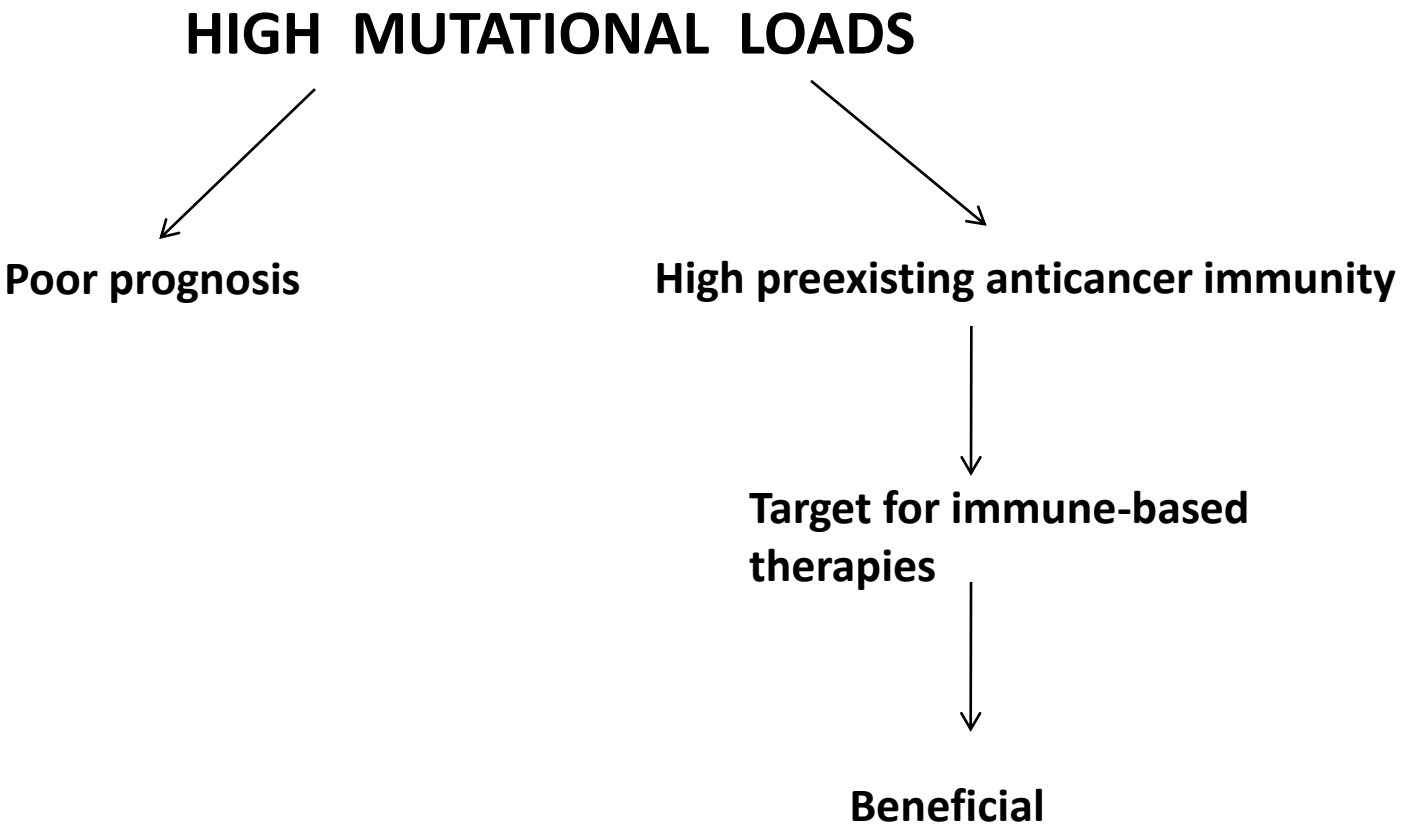
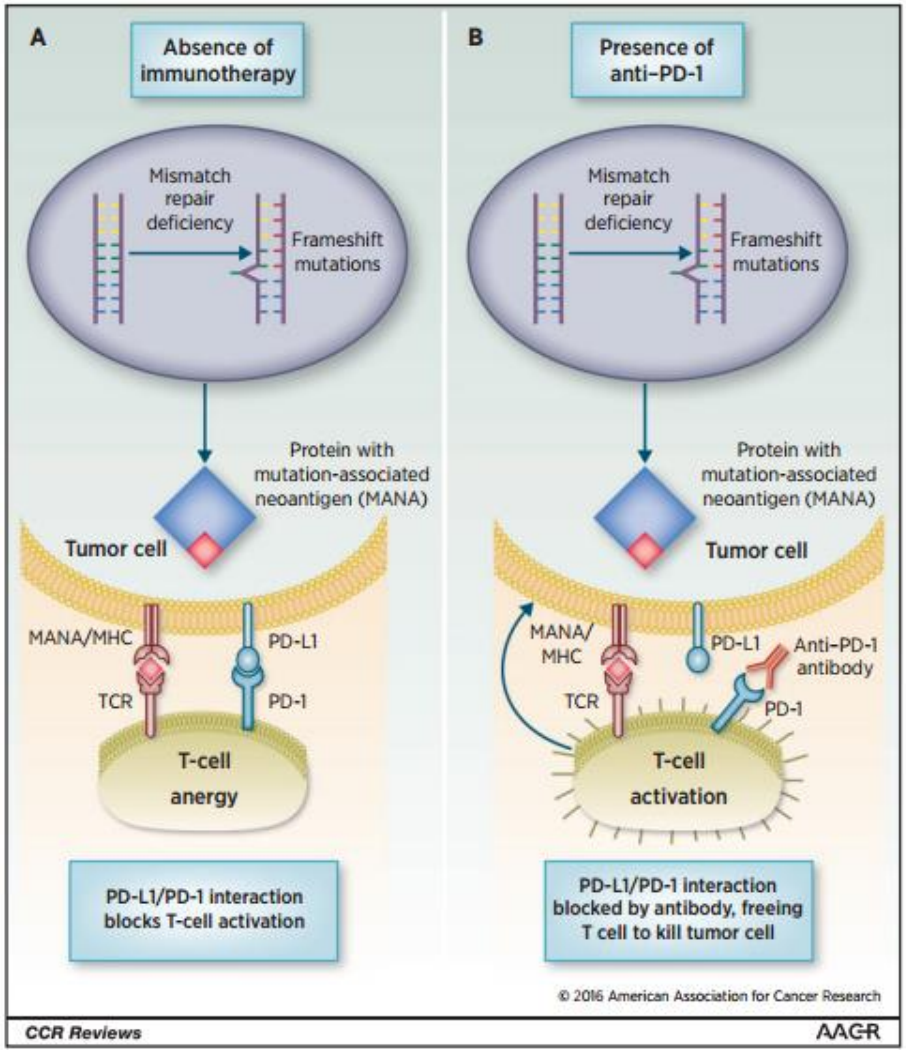


SOMATIC MUTATIONS – NEOANTIGENS – THERAPIES – CLINICAL OUTCOMES



MUTATIONAL LOAD vs CLINICAL RESPONSES: Can neoantigens enhance clinical benefit from immune checkpoint inhibition? Does anti-PD-1 treatment expand preexisting T cells specific for neoantigens?

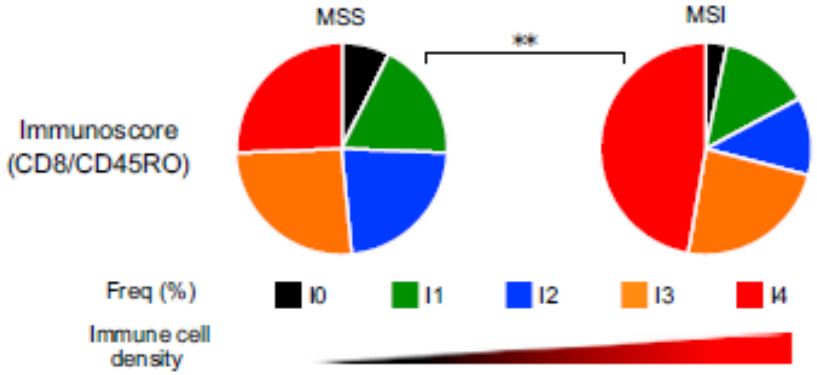


Clin Cancer Res; 22(4) February 15, 2016

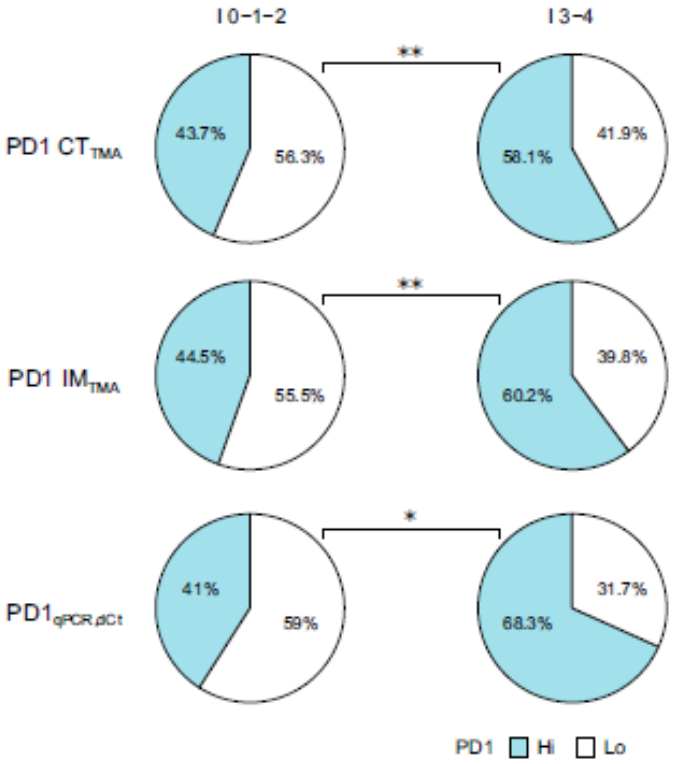
Immunoscore and Microsatellite Instability as Predictors of Patient Survival

Mlecnik B. et al. Immunity, 2016

The frequency of Immunoscore-based groups (I0, I1, I2, I3, I4) in MSS and MSI patients.

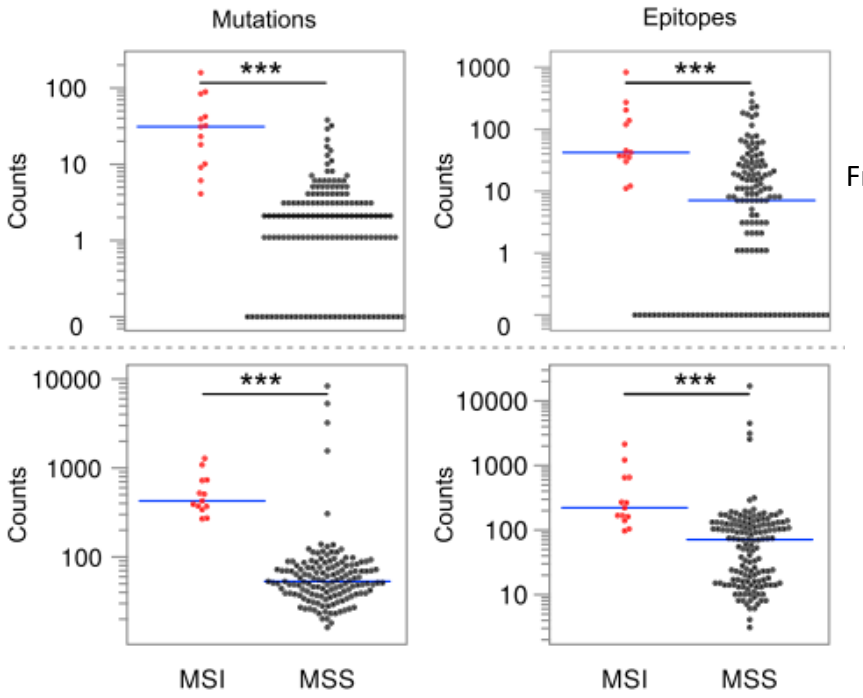


Frequency of the 50% highest PD1 and 50% lowest patients in Immunoscore categories I0–I2 and I3 and I4



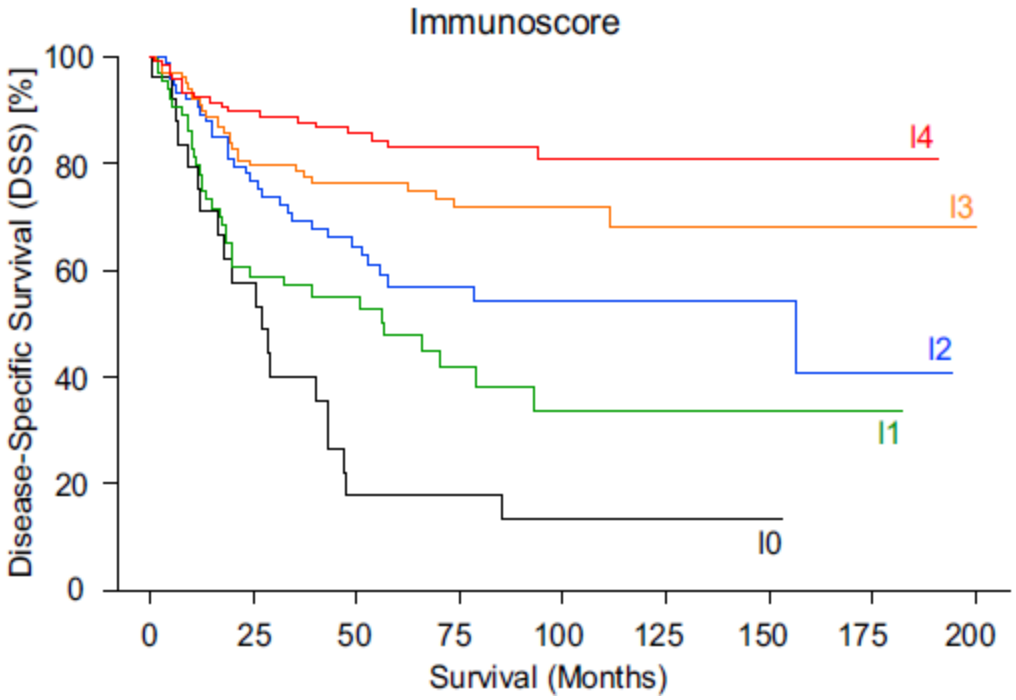
Mlecnik B. et al. Immunity, 2016

Mechanisms Revealing a Higher Immunogenicity of MSI Patients



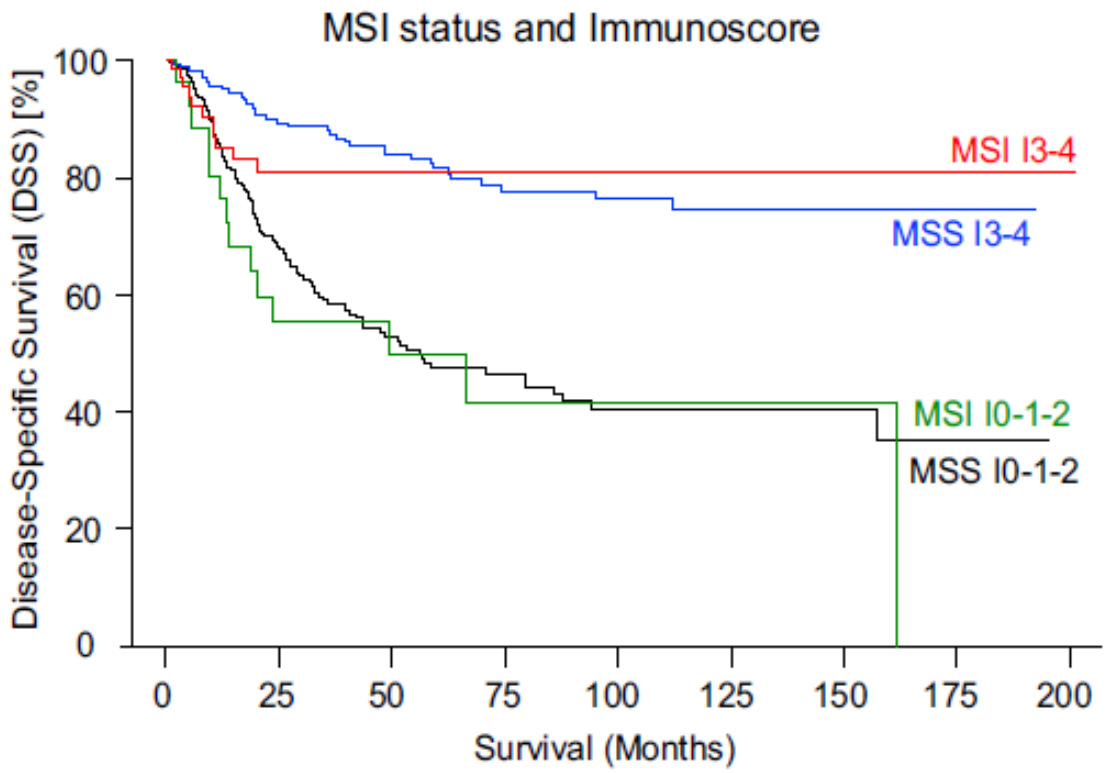
Immunity 44, 698–711, March 15, 2016

Kaplan-Meier estimates of disease-specific survival according to Immunoscore



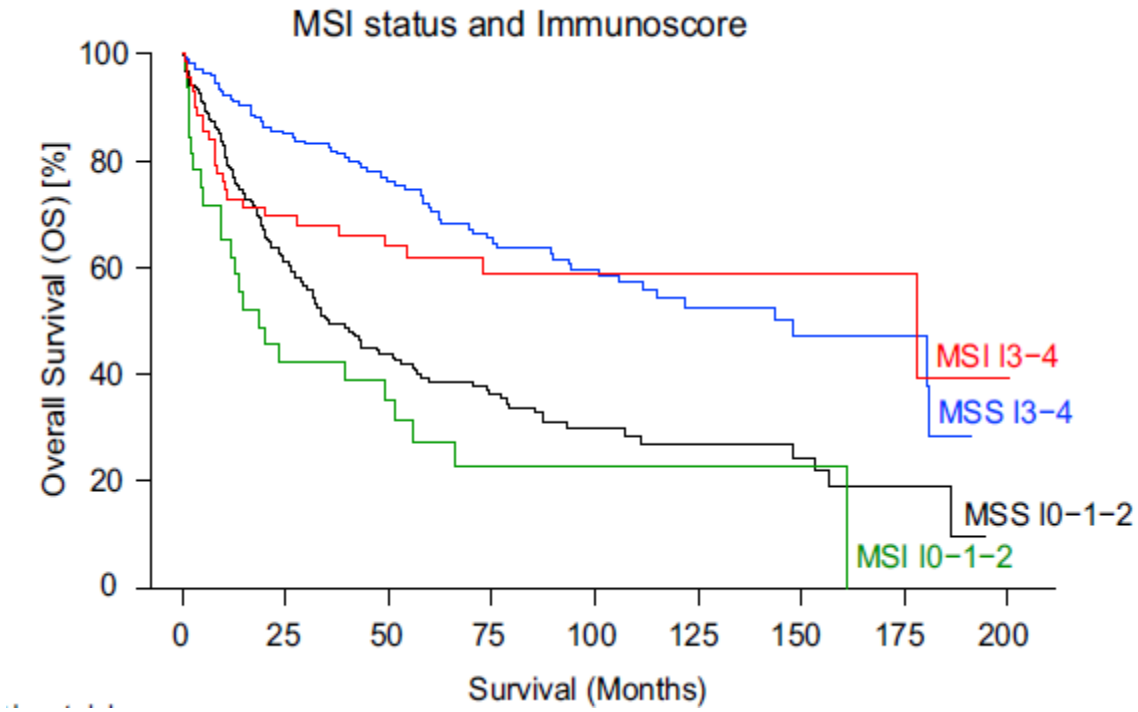
Mlecnik B. et al. Immunity, 2016

Kaplan-Meier estimates of disease-specific survival according to the microsatellite instability status and Immunoscore



Mlecnik B. et al. Immunity, 2016

Kaplan-Meier estimates of overall survival according to the microsatellite instability status and Immunoscore



Mlecnik B. et al. Immunity, 2016

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

(Le DT et al., Science, June, 2017)

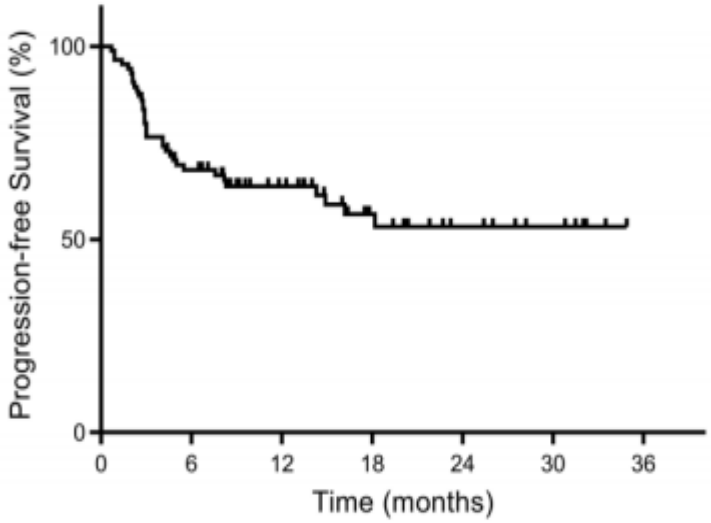
Summary of therapeutic response to Pembrolizumab treatment in patients with MSI and different types of cancer

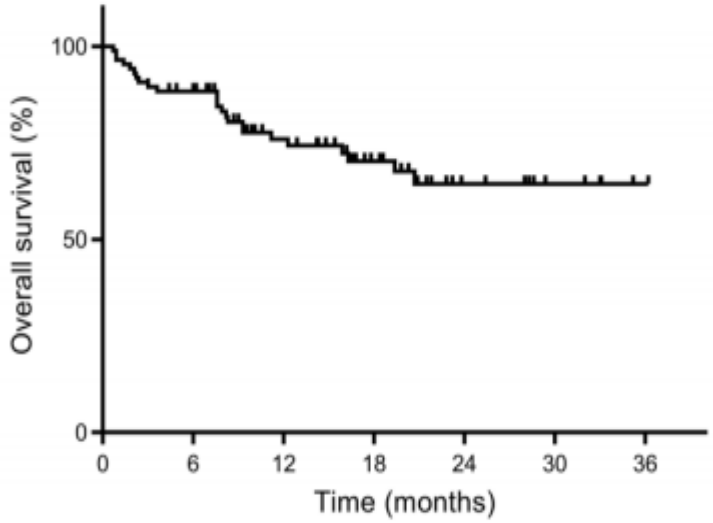
Type of response	Patients (n = 86)
Complete response	18 (21%)
Partial response	28 (33%)
Stable disease	20 (23%)
Progressive disease	12 (14%)
Not evaluable	8 (9%)
Objective response rate 95% CI	53% 42% to 64%
Disease control rate 95% CI	77% 66% to 85%
Median progression-free survival time 95% CI	NR 14.8 months to NR
2-year progression-free survival rate 95% CI	53% 42% to 68%
Median overall survival time 95% CI	NR NR to NR
2-year overall survival rate 95% CI	64% 53% to 78%

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

(Le DT et al., Science, June, 2017)

Summary of therapeutic response to Pembrolizumab treatment in patients with MSI and different types of cancer





Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

(Le DT et al., Science, June, 2017)

1.Oligoclonal transcripts for TCR Vβ CDR3 in peripheral blood in 3 responders

Q1: T cell clones expressing these transcripts were not identified (specificity and function, unknown)

2. Specificity of expanded T cells from 1 responder was tested vs 15 MANAs (mutation-activated neoantigens). IFNγ responses in 7/15 MANAs

Q2: no other tumor antigens were tested for expansion and testing

3. Oligoclonal TCR Vβ CD3 transcripts in peripheral blood after expansion with 3/7 MANAs from the same responder

Q3: T cell clones were not identified. Function, unknown

4.Analyses of T cell frequencies specific for universal tumor antigens before and during treatment were not performed

Q4: Unknown, if anti-PD-1 works through expansion of preexisting immunity to non-mutated antigens

5. No significant differences in the number of Mutations in clinical responders vs non-responders vs progressors after stable-disease

Q5: anti-PD-1 works in the context of a mixed phenotype (immune infiltrates, mutations, tumor antigens, tumor environment, PD-1 expression)

Neoantigen-reactive T cells in the periphery

PD-1+
TCR recognizing the autologous tumor

however

At low frequencies (max. 0.04% - 1.0%)
Recognize approx. 0.5% - 1% of the predicted neoantigens

Questions

- Are computational predictions of neoantigens inadequate?
- Does the tumor suppress reactive T cells or induce their death?
- Can we improve T cell responses to and make them responsive to a greater number of neoantigens?

Reinstating preexistent antitumor immunity: why the most effective therapies are restricted to a limited number of patients?

Response to anti-PD-1

↓

Acquired Immune Resistance

Up-regulation of alternate ICP

HLA loss/down regulation

Jak1/Jak2 mutations

More?

Loss of mutation-associated neoantigens (MANAs) through tumor cell elimination or chromosomal deletion

Anagnostou V et al. Cancer Discov. 7:264, 2017

Conclusions

- Tumor evolution: cross-talk between tumor cells and immune cells.
- Identification of signaling pathways for the interplay between immune system and tumor cells.
- Biomarkers are key-elements regulating immune cell-tumor cell interactions.
- Biomarkers need to be targeted for re-activating pre-existing immunity and pave the way for applying immunotherapies and targeted therapies.
- Tumor cells use various methods to evade immune surveillance. Therefore combinatorial treatments are urgently needed.
- The antitumor immune phenotype may be shaped by multiple parameters including immunoscore, MSI, altered HLA expression, tumor antigens, mutational pathways and microenvironmental factors.

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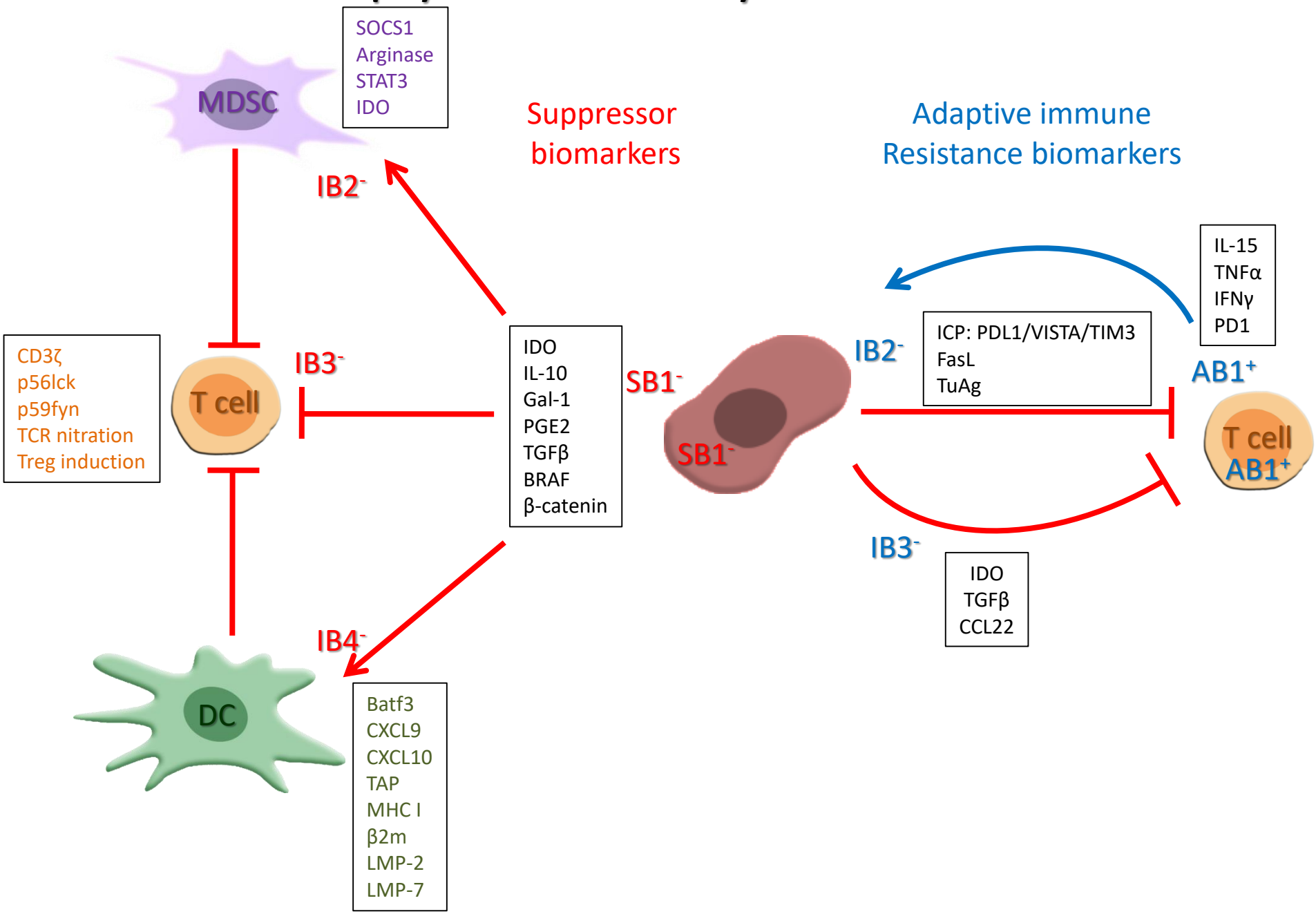
Mittendorf EA
Peoples GE

Progress In Vaccination Against Cancer -17 (PIVAC-17)

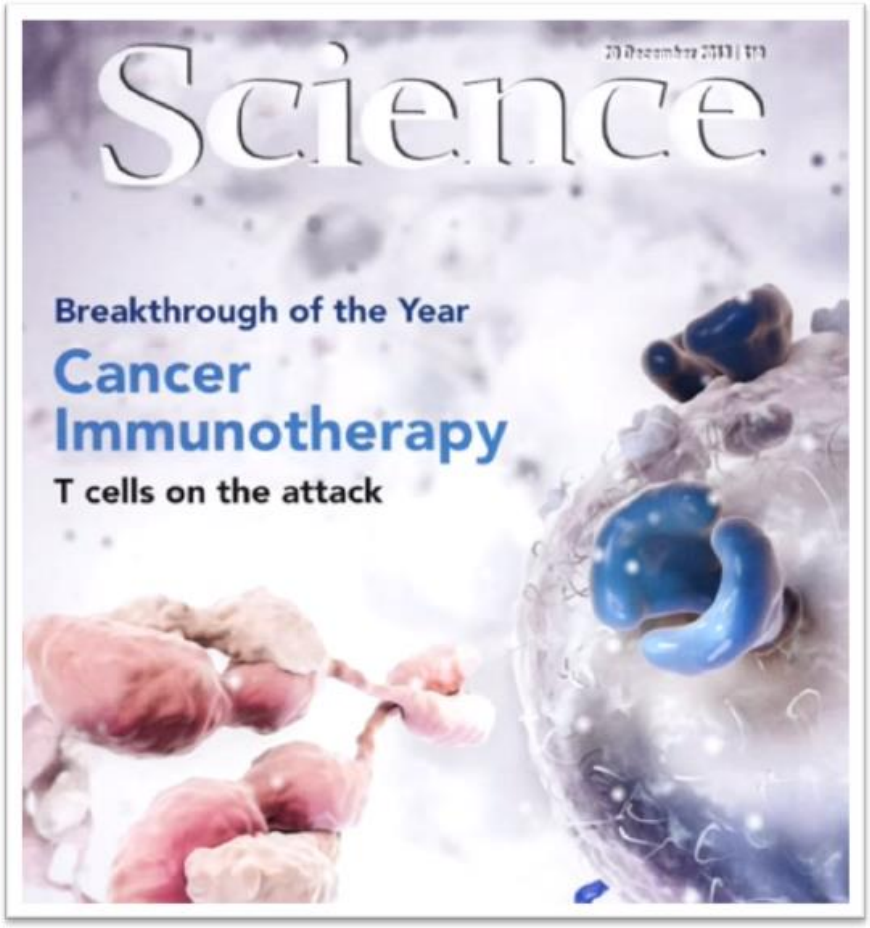
LOUTRAKI 27-30 Sept. 2017

http://pivac17.eu/

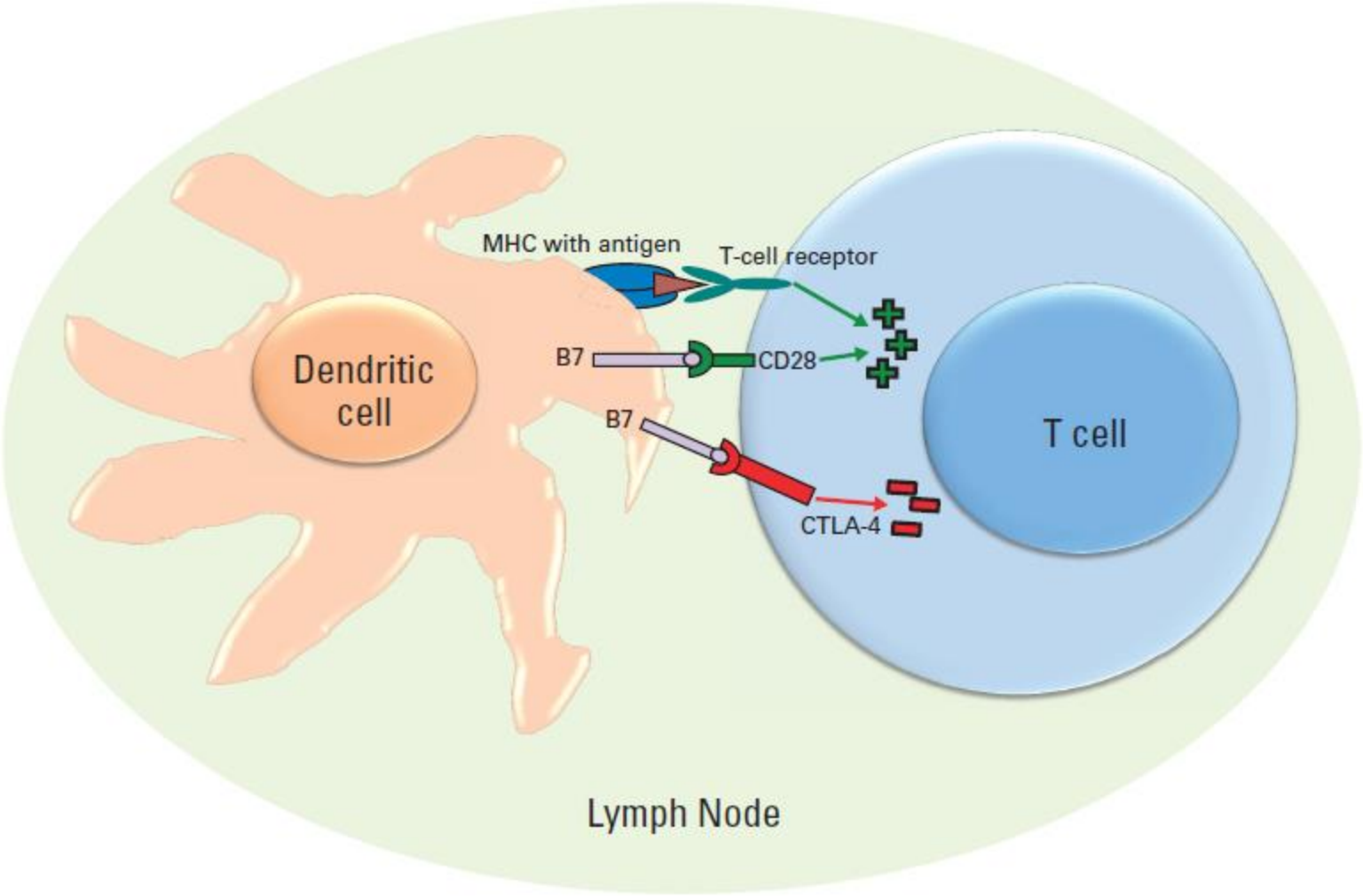
Predictive biomarkers in cancers: an interplay between immune system and tumor cells



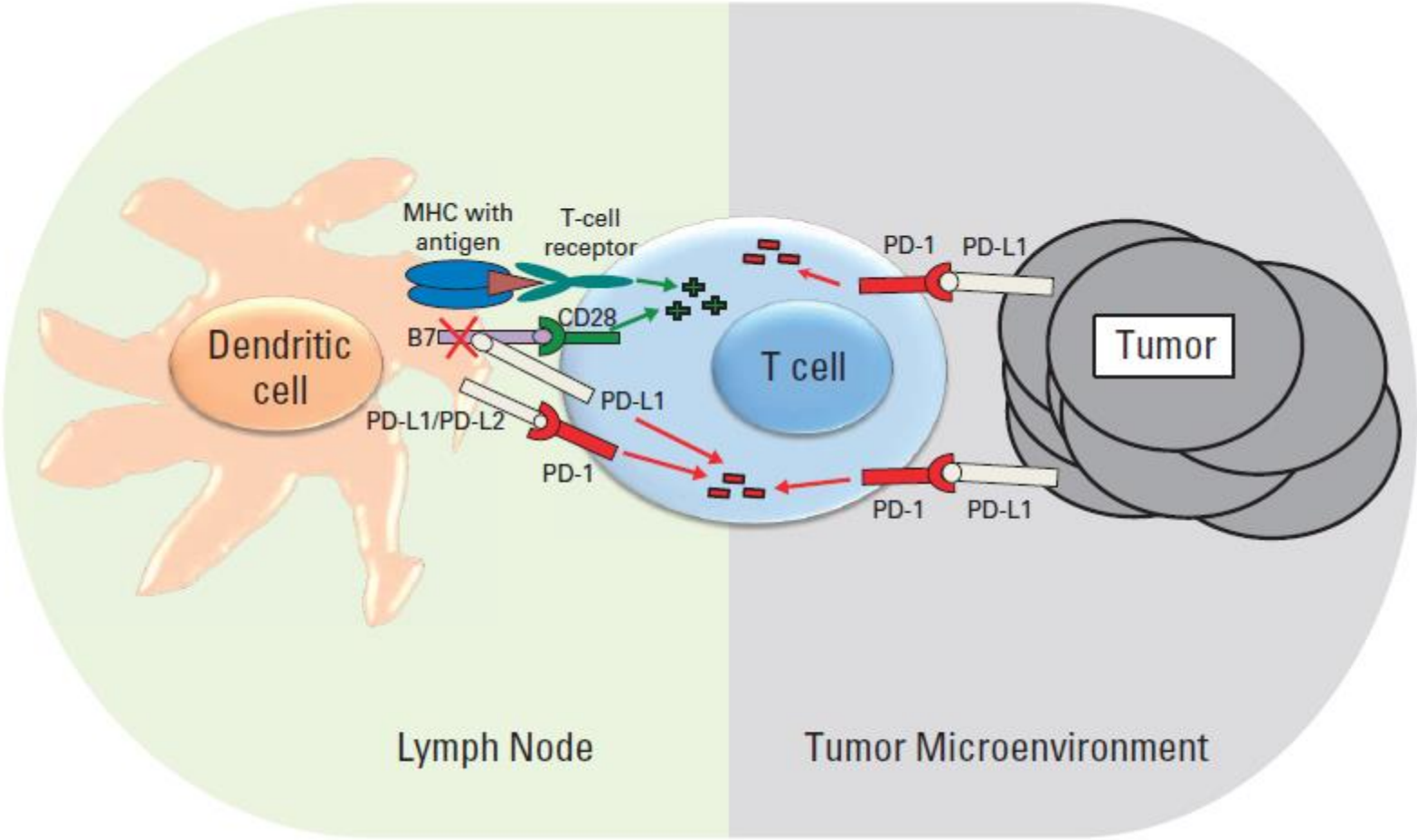
The renaissance of immunotherapy is a revolution for cancer patients



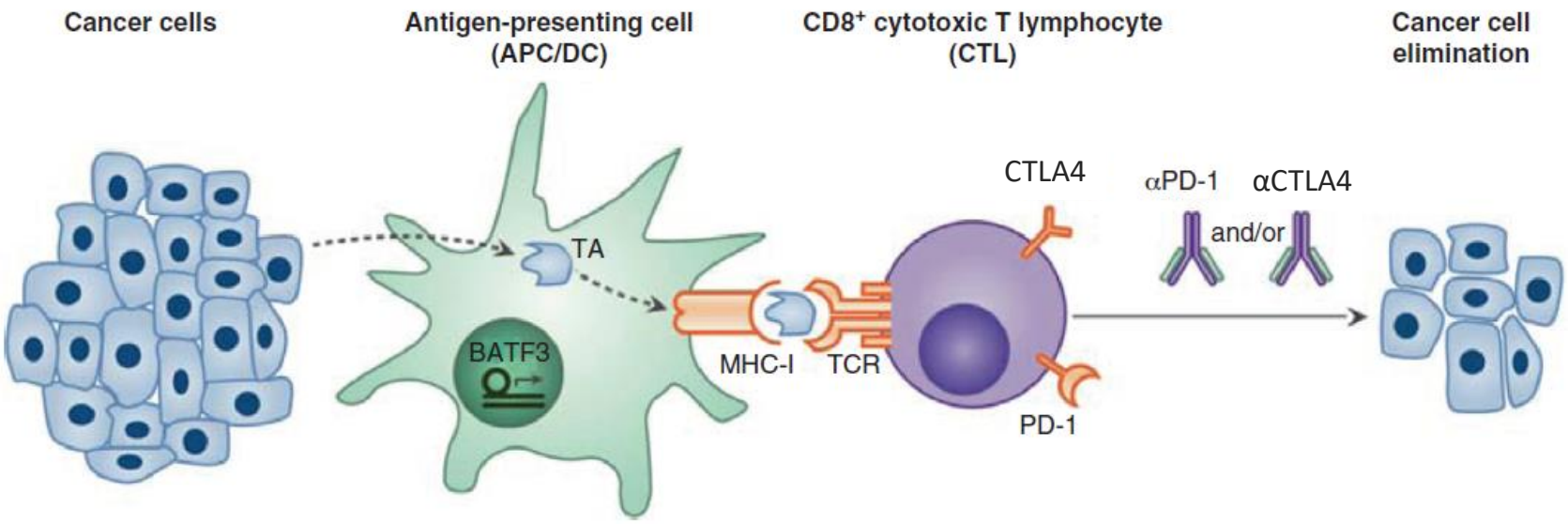
The cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) immunologic checkpoint



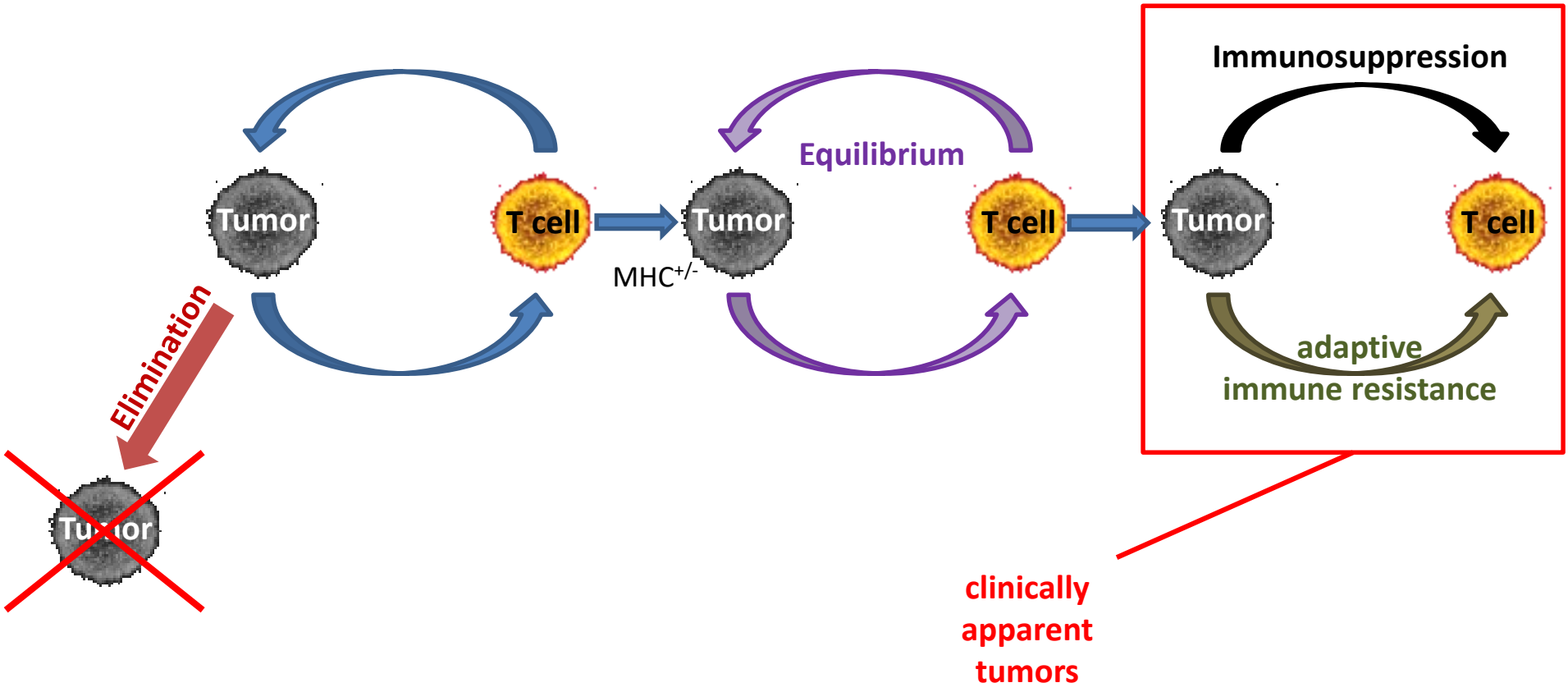
The programmed cell death protein 1 (PD-1) immunologic checkpoint



Antibodies blocking immune checkpoints rescue tumor-reactive T cells from suppression

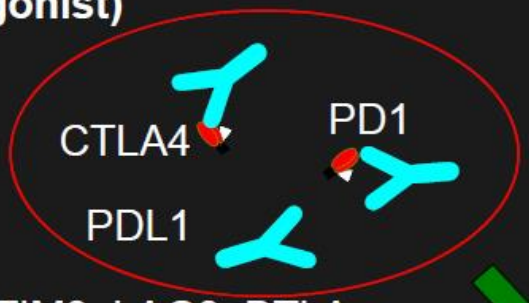


Immunoediting



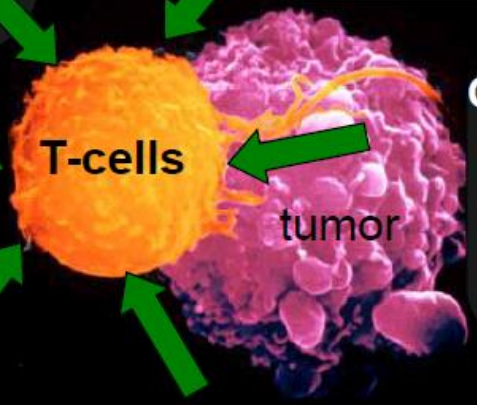
Conclusion: Successful immunotherapies unleash natural pre-existing T cells

Co-inhibitory receptors (antagonist)



TIM3, LAG3, BTLA, …

Costimulatory receptors (agonist)



Peptide vaccine
Genetic vaccine
DC vaccine

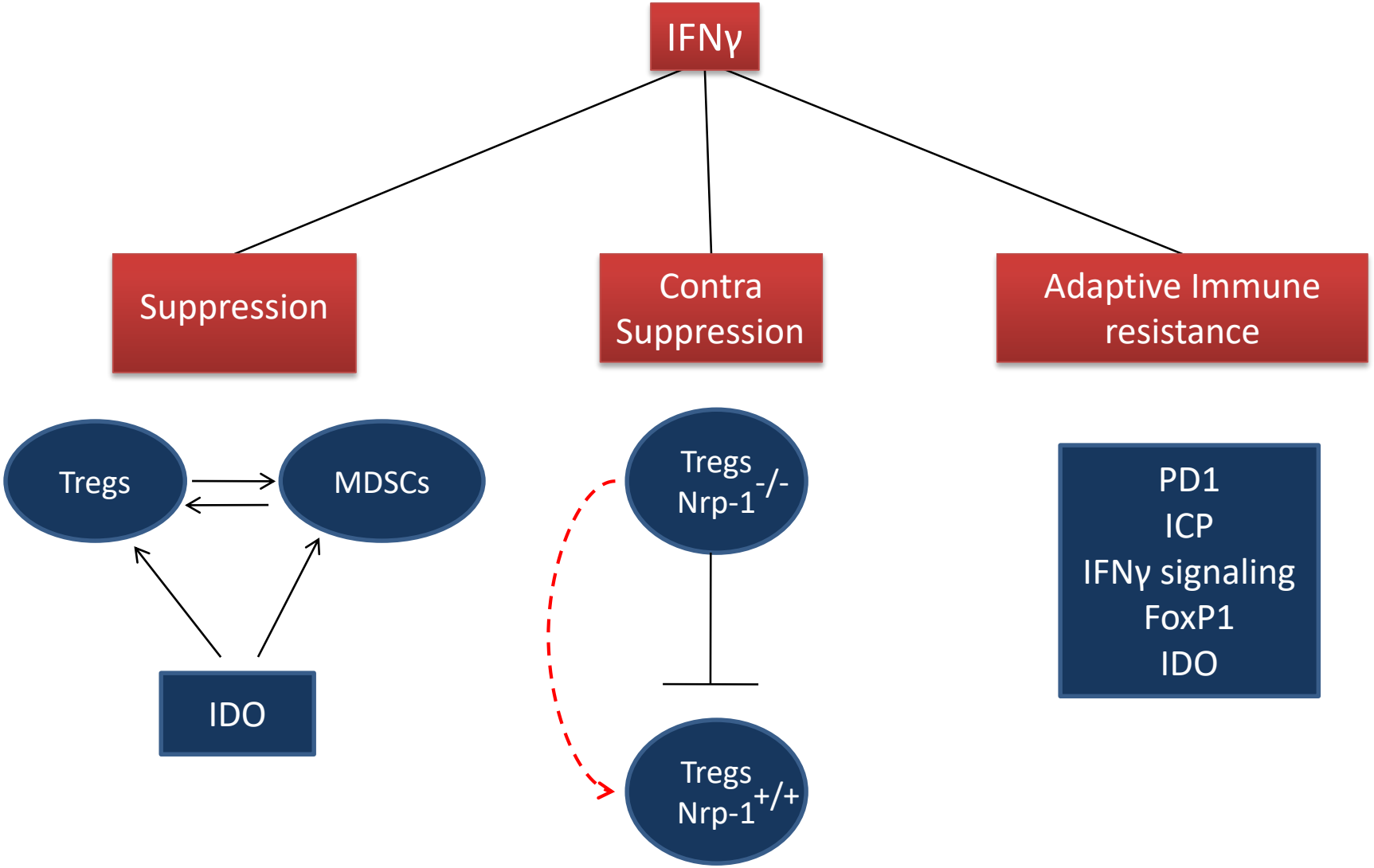
Costimulatory cytokines

IL-2
IFN
IL-15
IL-21

Adoptive Transfert of T cells

Engineered TCR or CAR-T cells

The indispensable role of IFNγ in the landscape of immunoediting

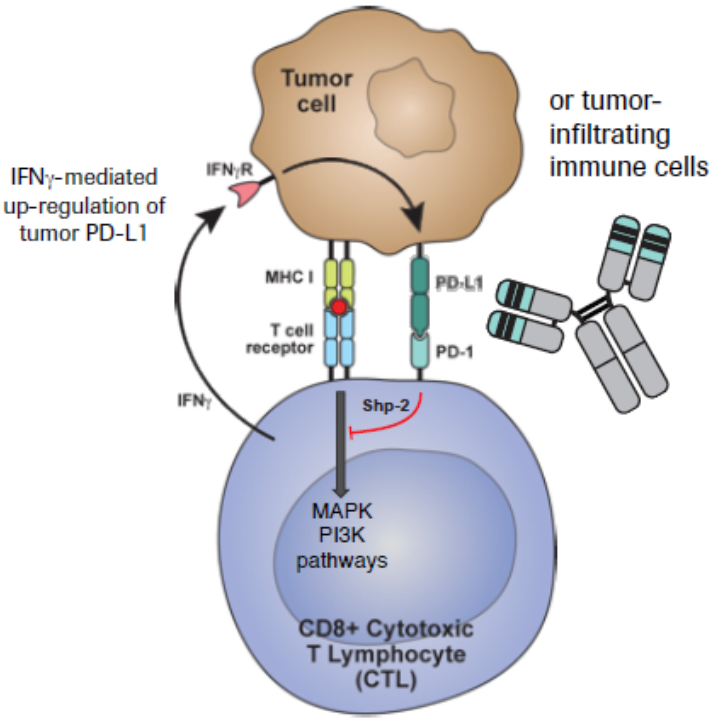


Cell 2017 Jun 1;169:1130-1141
Cell. 2017 Feb 9;168:707-723

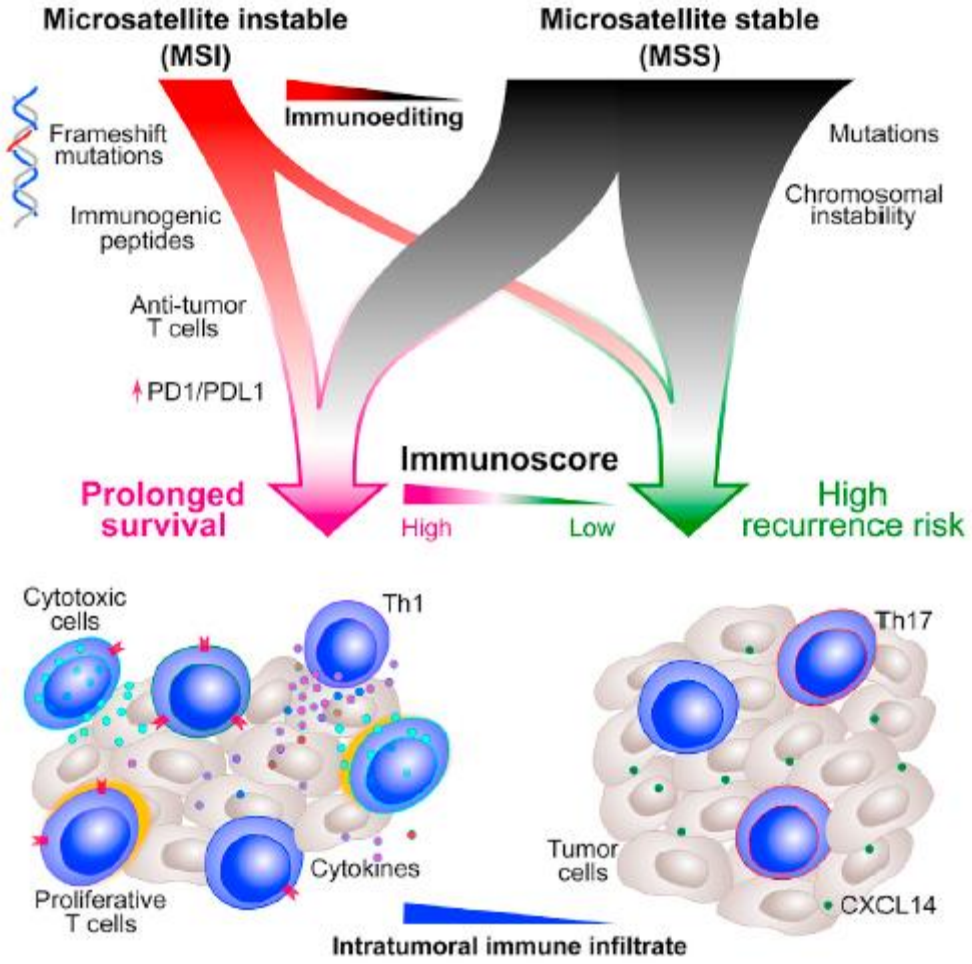
Targeting immuno-supression
PD-1/PD-L1 pathway

- PD-1/PD-L1 interaction inhibits T cell activation, attenuates target killing: **prevents overstimulation of T cells during acute virus infection**
- A large percentage of tumors also up-regulate PD-L1 and evade killing by T cells
- Blocking PD-1 binding restores effector T cell activity

"Adaptive expression" of PD-L1



Immunoscore and Microsatellite Instability as Predictors of Patient Survival



Mlecnik B. et al. Immunity, 2016

Reinstating preexisting (endogenous) cancer-specific immunity is the key for the successful outcome of immunotherapies

Somatic mutation

↓

Neoepitope formation

↓

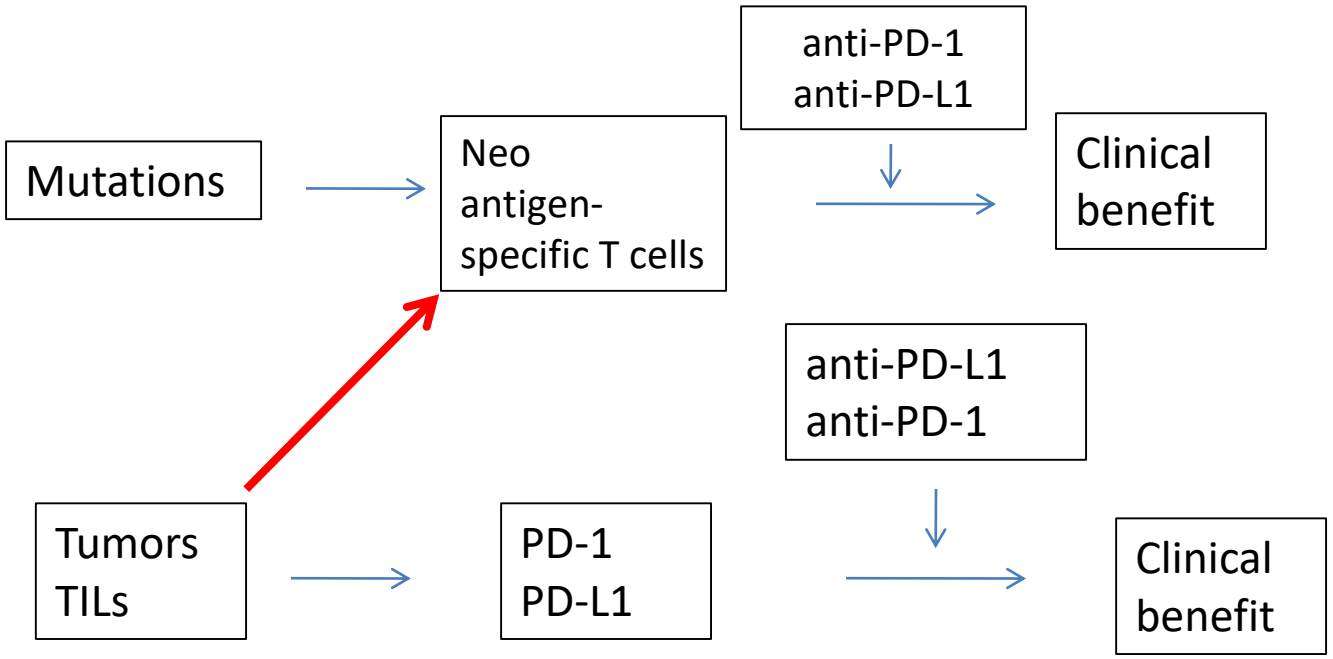
Correlation with Response to immunotherapy

↓

Generation of (i) high frequencies of neoAg-specific T cells; (ii) recognizing a high number of neoAgs

MUTATIONAL LOAD vs CLINICAL RESPONSES

Can high density of neoantigens enhance clinical benefit from immune checkpoint inhibition? Does anti-PD-1 treatment expand preexisting T cells specific for neoantigens?



N E O E P I T O P E S

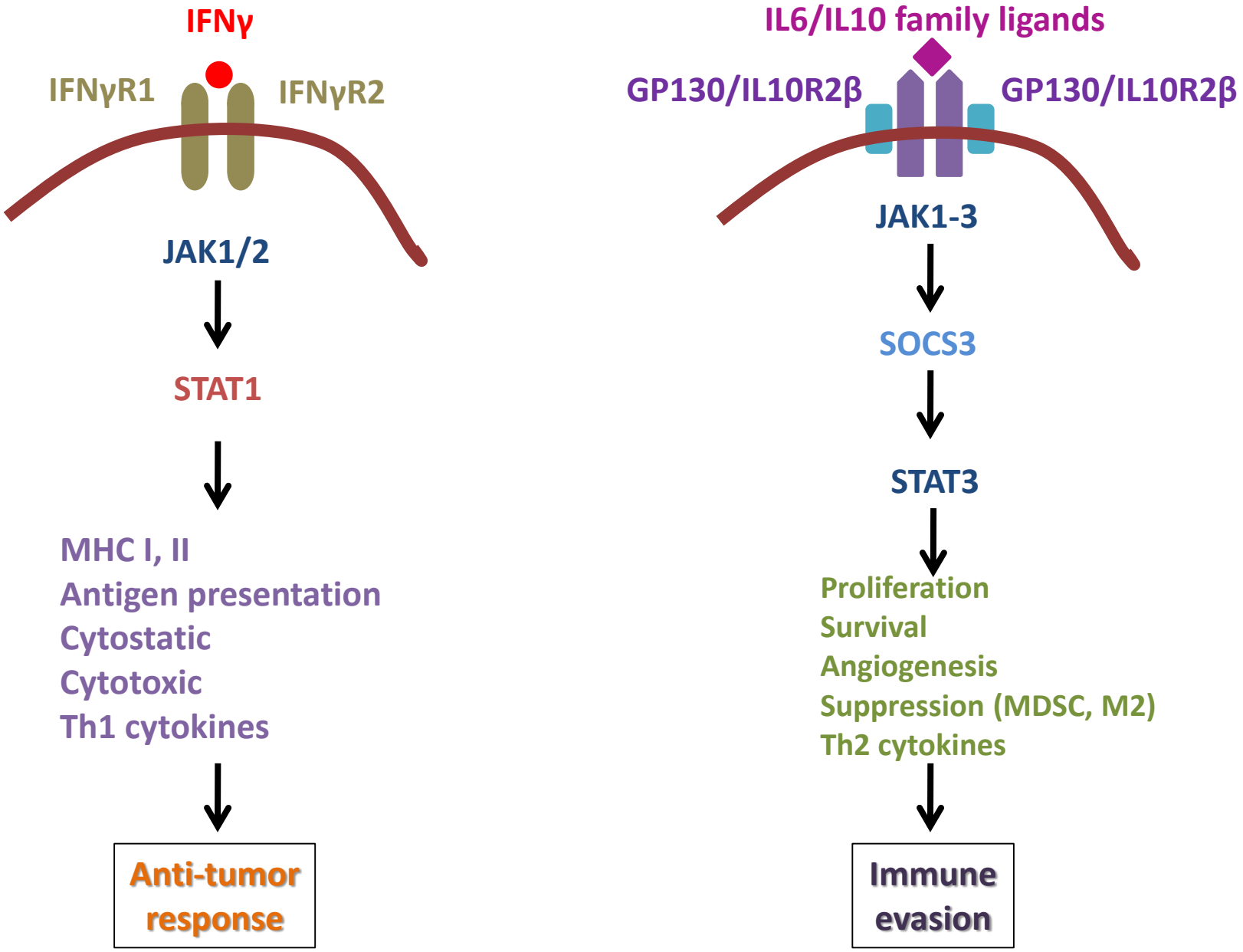
Peptides derived from somatic mutations binding to patient's MHC and recognized by autologous T cells

Why use neoepitopes as therapeutic cancer vaccines?

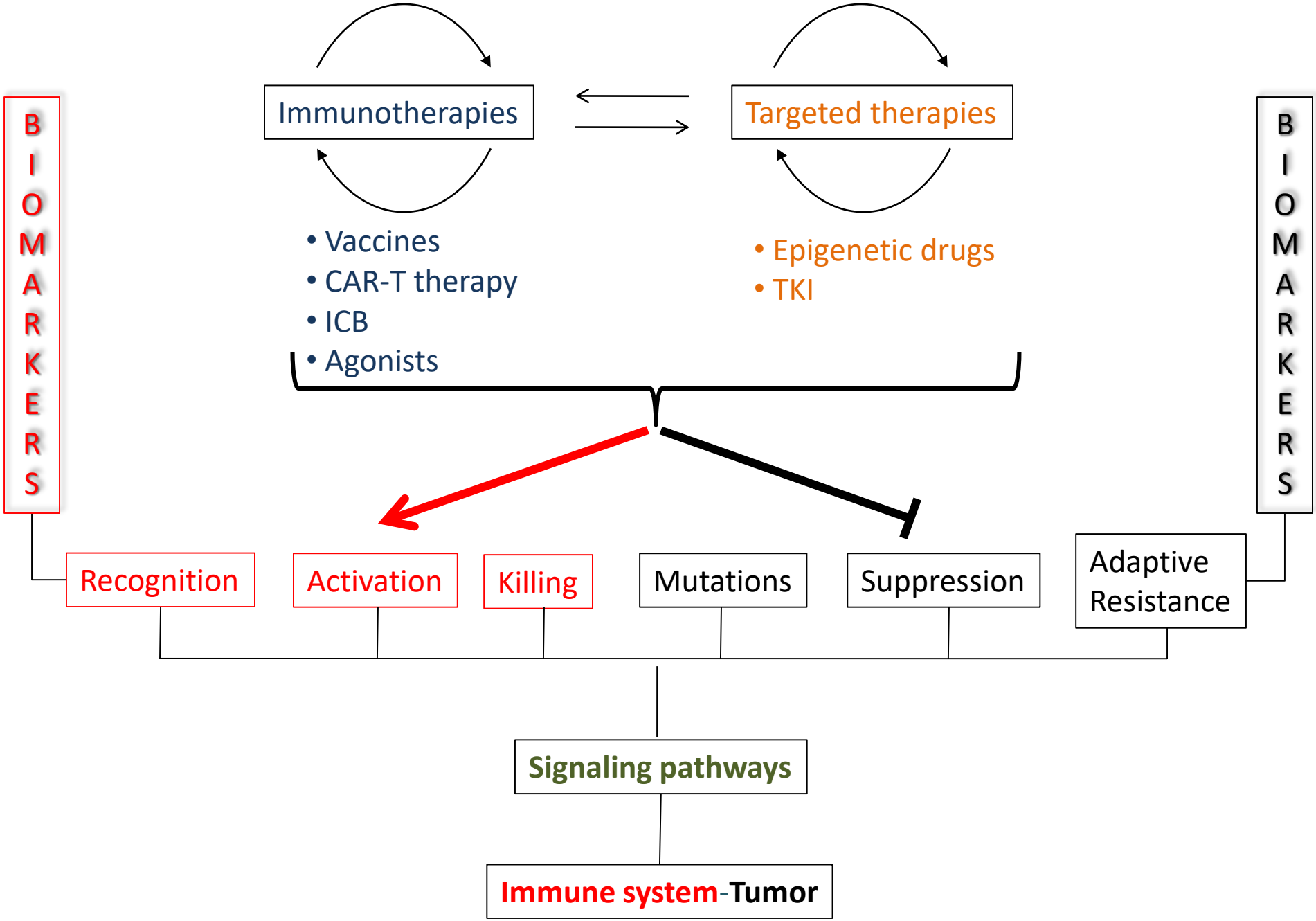
- Favorable safely profile due to lack of expression in healthy tissues

- High likehood of immunogenicity; no subjected to immune tolerance

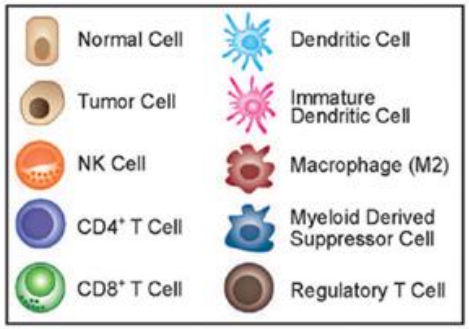
Antagonizing pathways via JAK/STAT signaling



The roadmap to immune-based cancer therapies



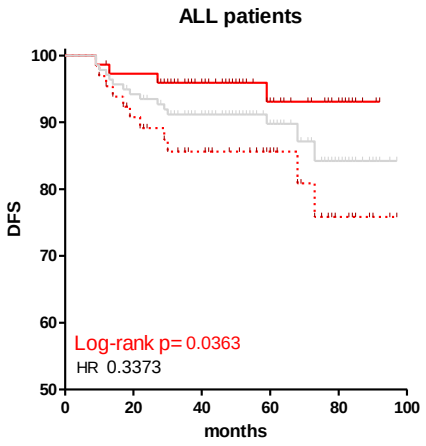
Immunoediting: immune-based elimination of tumor cells selects for MHC-negative tumor escape variants

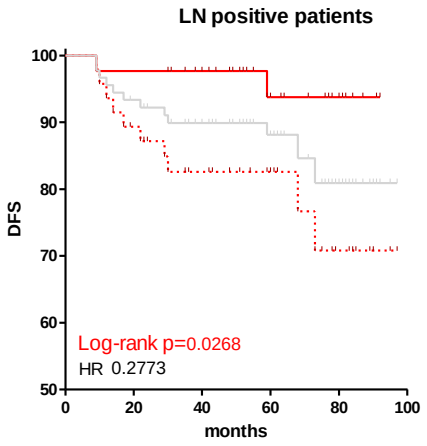


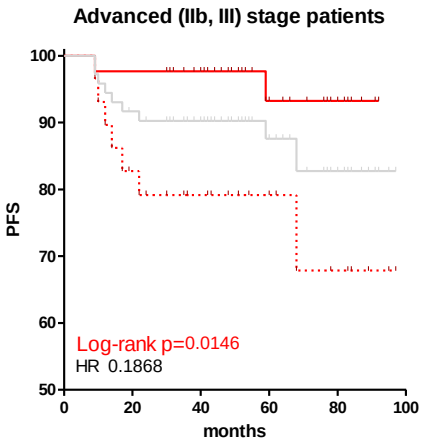
LR1 as a predictive biomarker of clinical response in vaccinated breast cancer patients

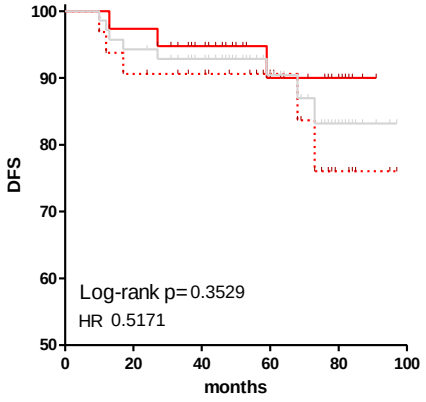
DFS of vaccinated patients

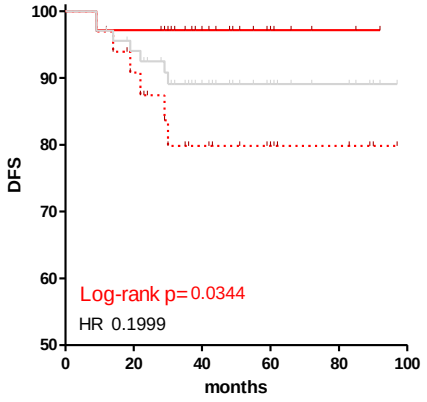
median follow up 54 months (range 9-97)

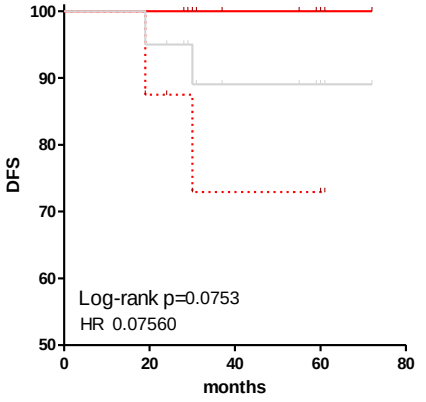




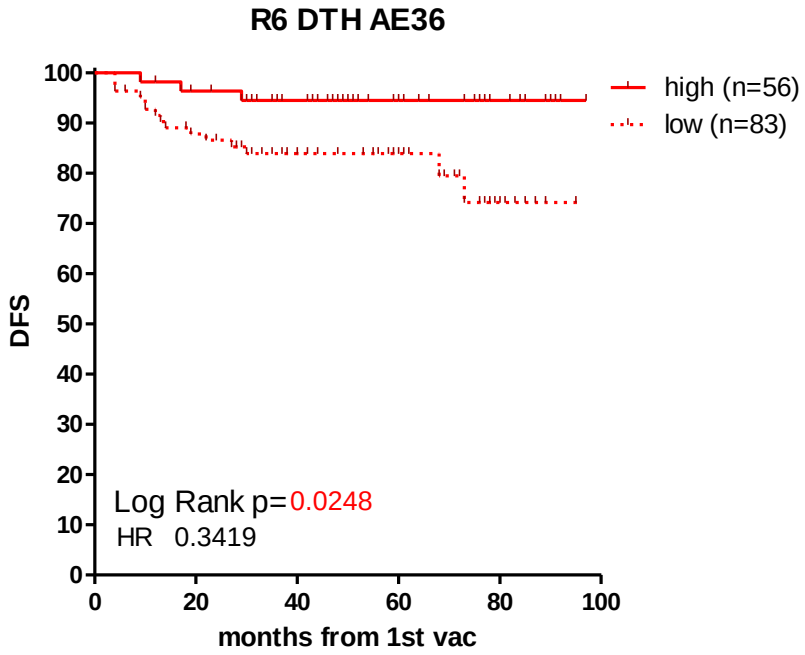






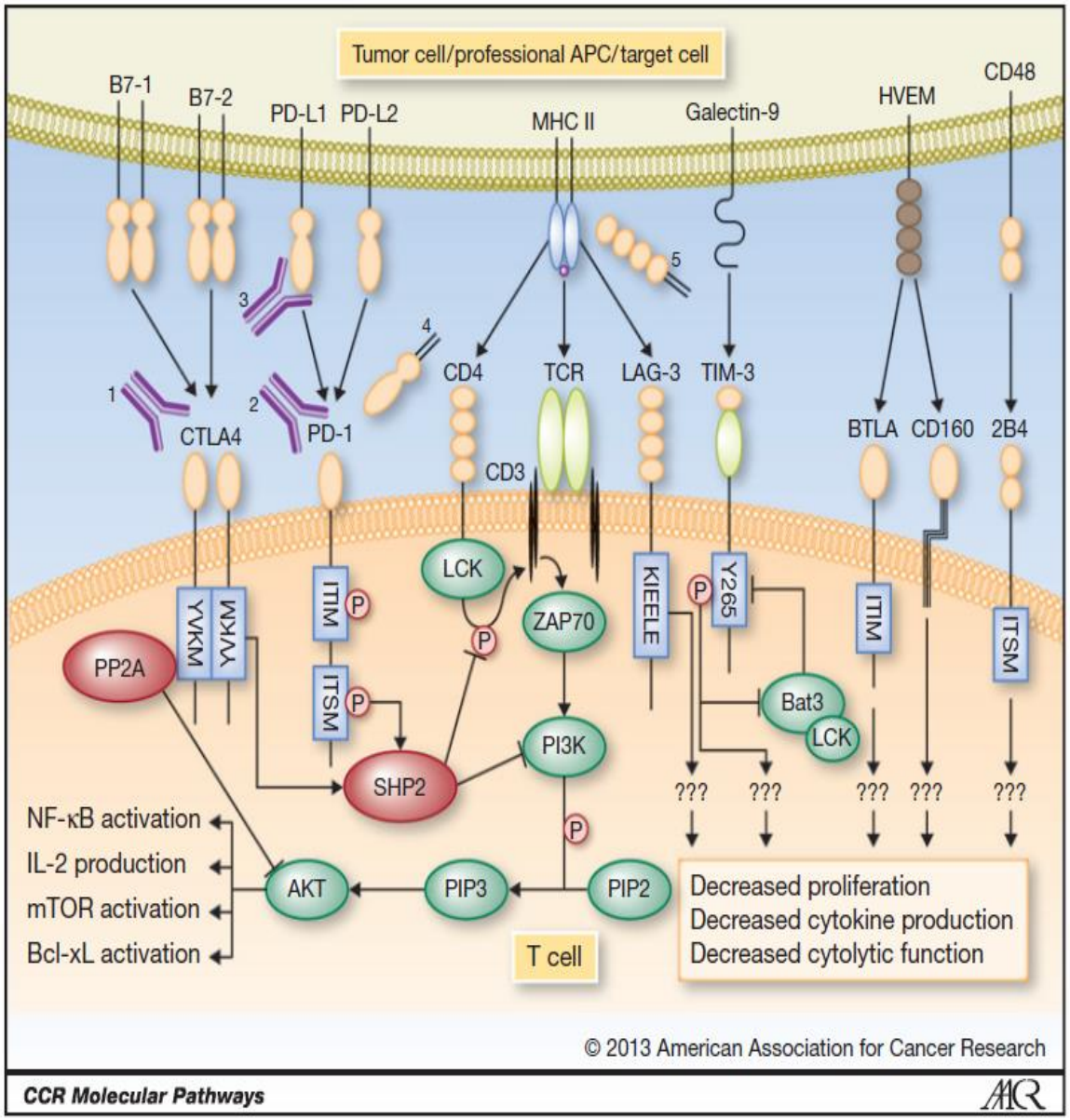


DTH as predictive biomarker of clinical response in vaccinated Breast Cancer patients



high or low DTH
defined by cutoff finder software
(high;>17.5 mm)

Immune checkpoint molecules-signaling pathways



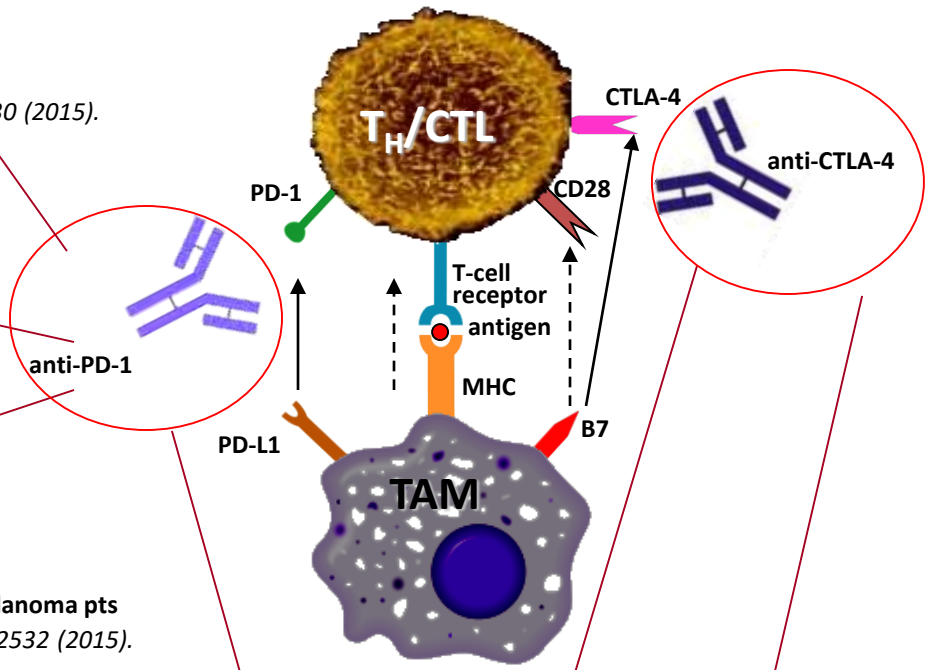
Nirschl CJ et al. Clinical Cancer Research, 2013, 19(18):4917-24

Immune checkpoint blockade

Nivolumab

- **62% and 43%, 1 yr and 2 yr OS in ipi-resistant melanoma pts**
  (Robert, C. et al. N. Engl. J. Med. 372, 320–330 (2015).

- **43% and 32%, 1 yr and 2 yr OS in NSCLC**
  70% and 52%, 1 yr and 2 yr OS in RCC
  (Nishino M. et al, Nat. Rev. Oncol. doi:10.1038/nrclinonc. 2017.88 Published online 27 Jun 2017)



- **Pembrolizumab**
  50% OS (1 yr) in ipi-resistant advanced melanoma pts
  (Robert, C. et al, N. Engl. J. Med. 372, 2521–2532 (2015).

Ipilimumab

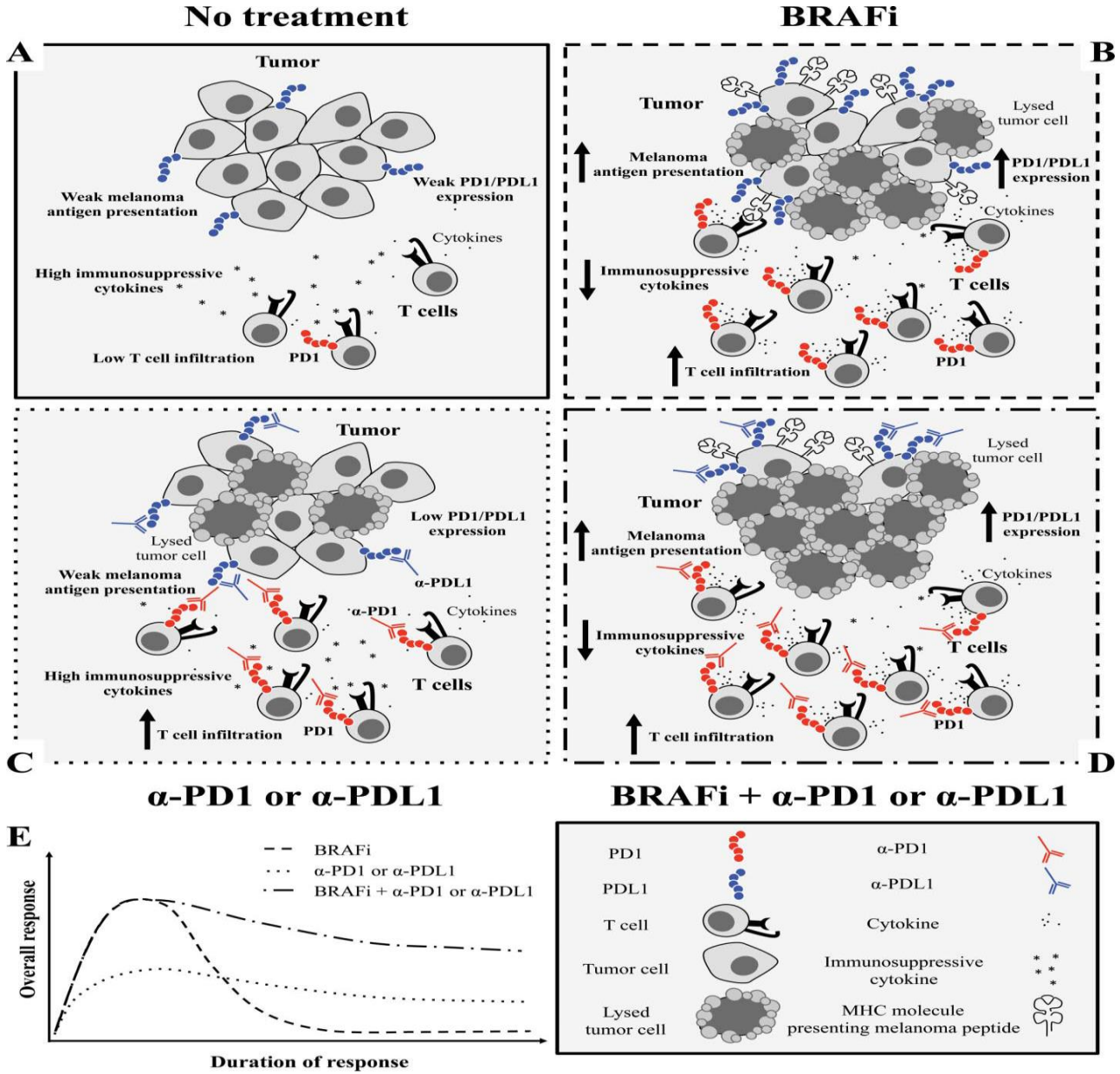
5 yr OS in advanced melanoma pts
(progressed after chemo or treatment naive)
12-50% *(Wolchok, J. D. et al. N. Engl. J. Med. 369, 122–133 (2013)*

Ipilimumab+Nivolumab

53% of pts with advanced, treatment-resistant melanoma had objective tumor response with tumor regression in 80% of them
(Wolchok JD et al. N. Engl. J. Med. 2013;369:122)

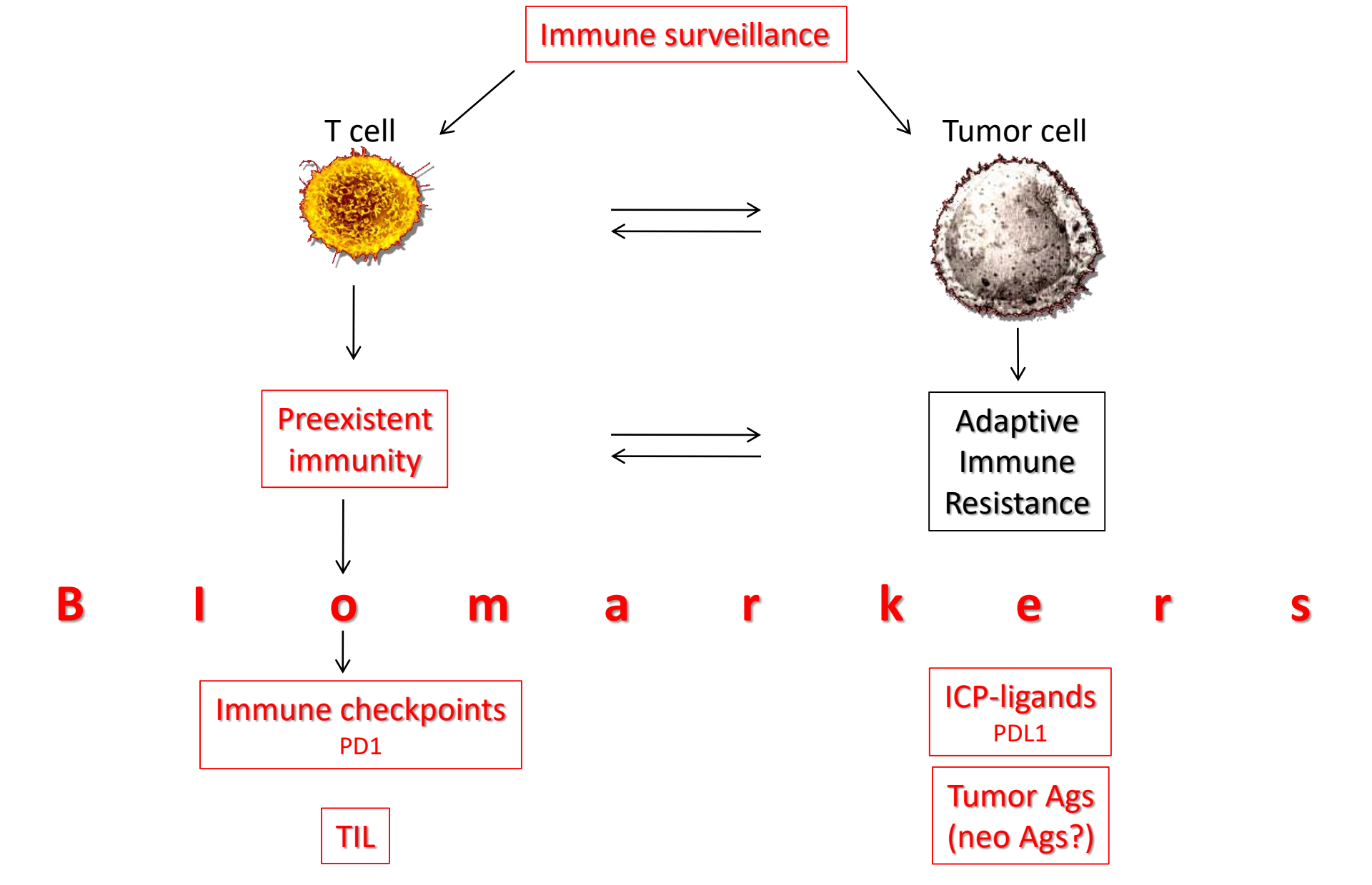
The antitumor phenotype has multiple parameters

Addition of either anti-PD1 or anti-PD-L1 blocking antibody to BRAF inhibitors leads to enhanced antitumor response in melanoma

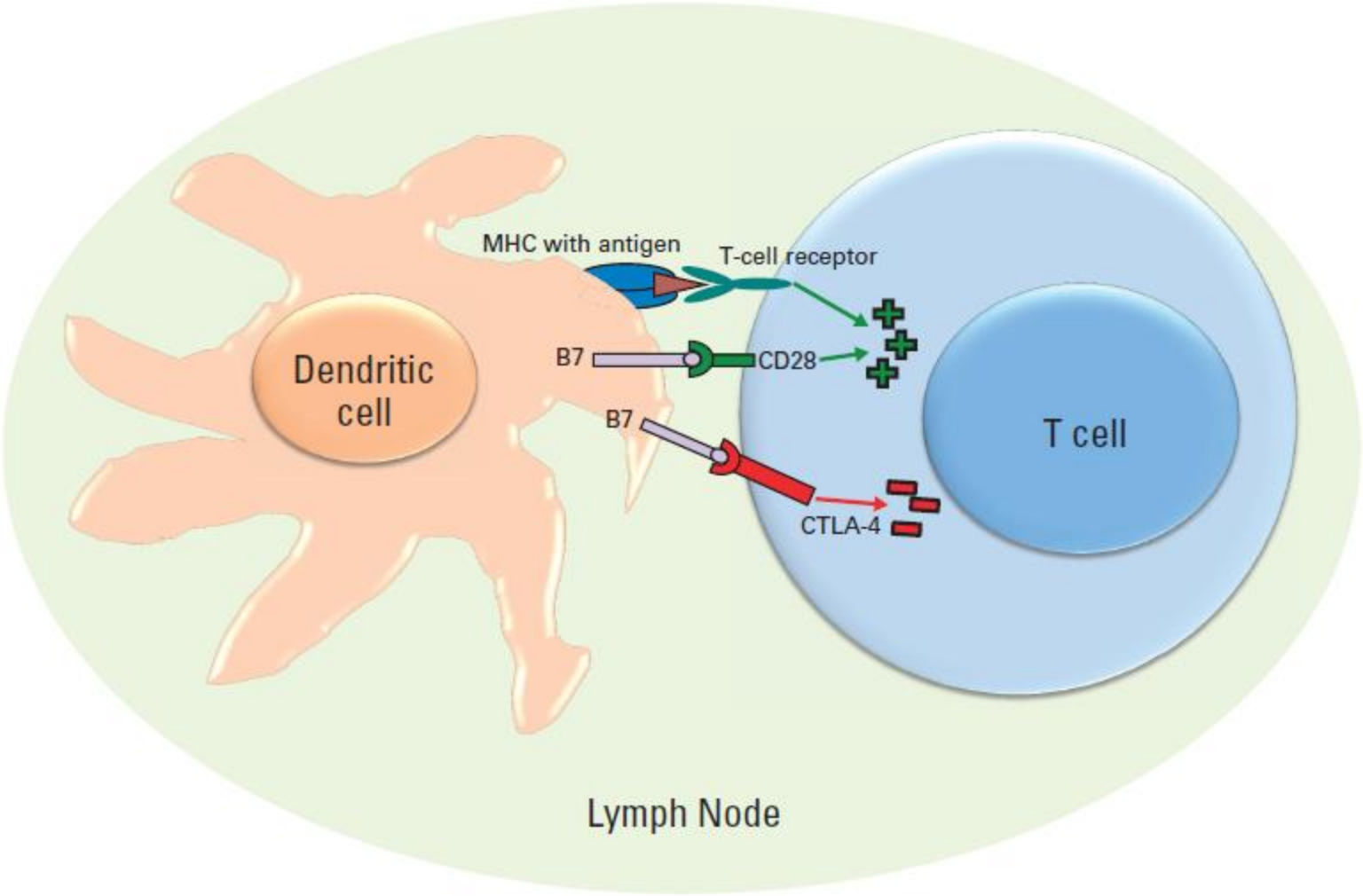


Cooper ZA et al. OncoImmunology 3:9, e954956;2014

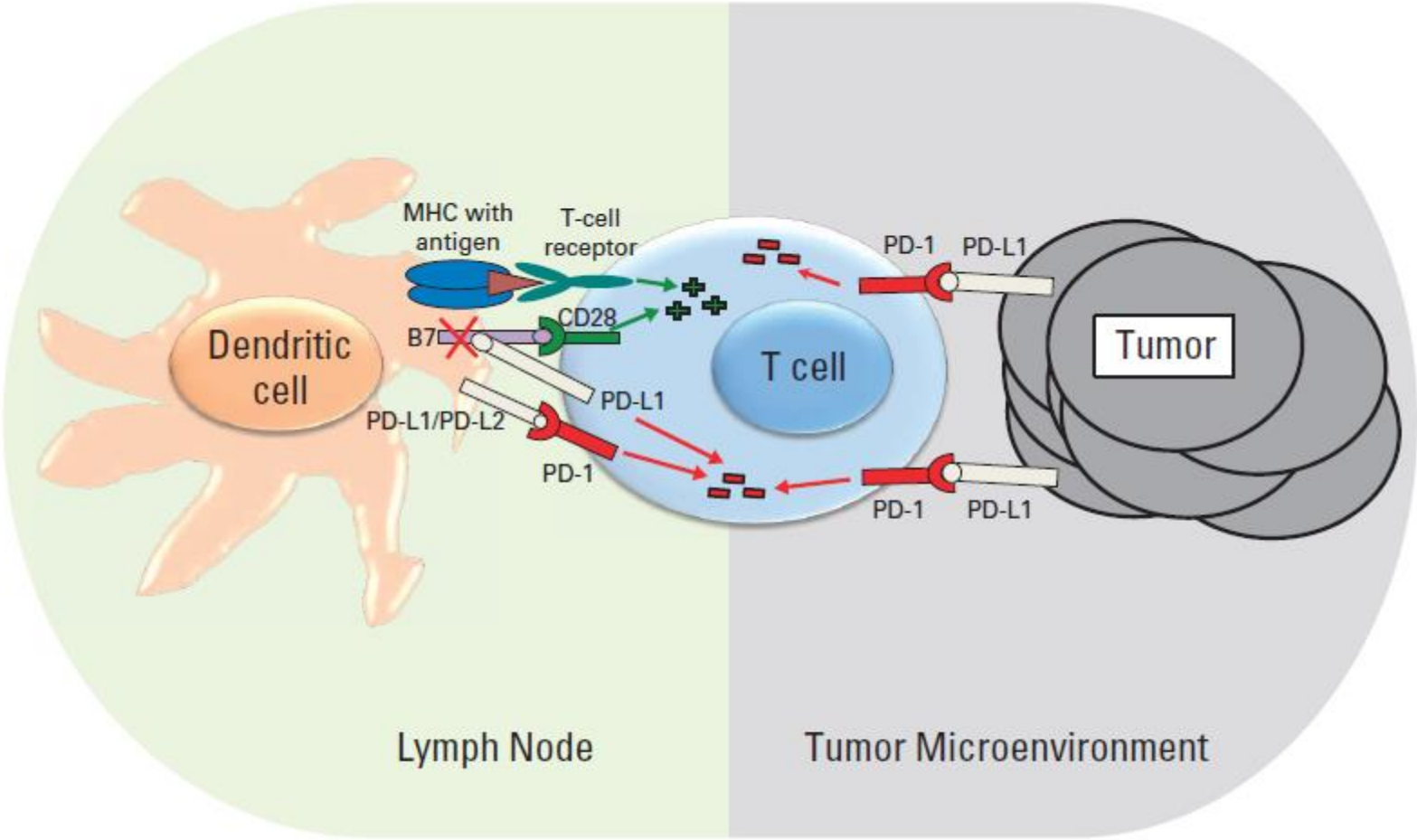
The immune system "shapes" tumor evolution



The cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) immunologic checkpoint



The programmed cell death protein 1 (PD-1) immunologic checkpoint



The Immunoediting cycle