Florence

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Clinical Cancer Advance: Immunotherapy

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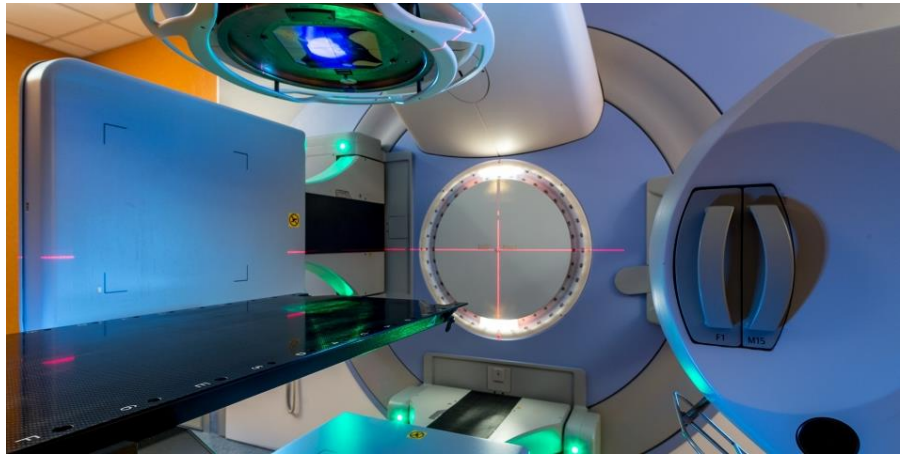
MAIN THERAPEUTIC MODALITIES

SURGERY

RADIOTHERAPY



Peptide Receptor Radionuclide Therapy

MEDICAL THERAPY:

- ***Chemotherapy***
- ***Hormonal therapy***
- ***Biologics*** **(mAb and**
- **small molecules)**
- ***Immunotherapy***

THE REAL IMPACT OF MORE RECENT CLINICAL CANCER ADVANCES

Since 1992 a progressive **decline in overall incidence and mortality** rates for all type of cancers has been observed

The number of **people living 5 years or more** after a cancer diagnosis is excpected to **rise by 31%** in 2026

…Increase of **more than 4 milions survivors** in a decade!!

THE IMPACT OF IMMUNOTHERAPY: A BIG PROGRESS AGAINST CANCER!

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

CANCER IMMUNOTHERAPY

Clinical Cancer Advances 2017: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

CANCER IMMUNOTHERAPY 2.0

Clinical Cancer Advances 2018: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

Chimeric antigen receptor (CAR) T-cell therapy
a type of adoptive cell immunotherapy

Clinical Cancer Advances 2019

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Additional Major Advances

Landmark advances in molecular diagnostics continue, with the most significant achievement made with the TAILORx breast cancer study. This study demonstrated that as many as 70% of women with hormone receptor-positive, node-negative breast cancer could safely forgo adjuvant chemotherapy, based on results from a 21 gene assay.

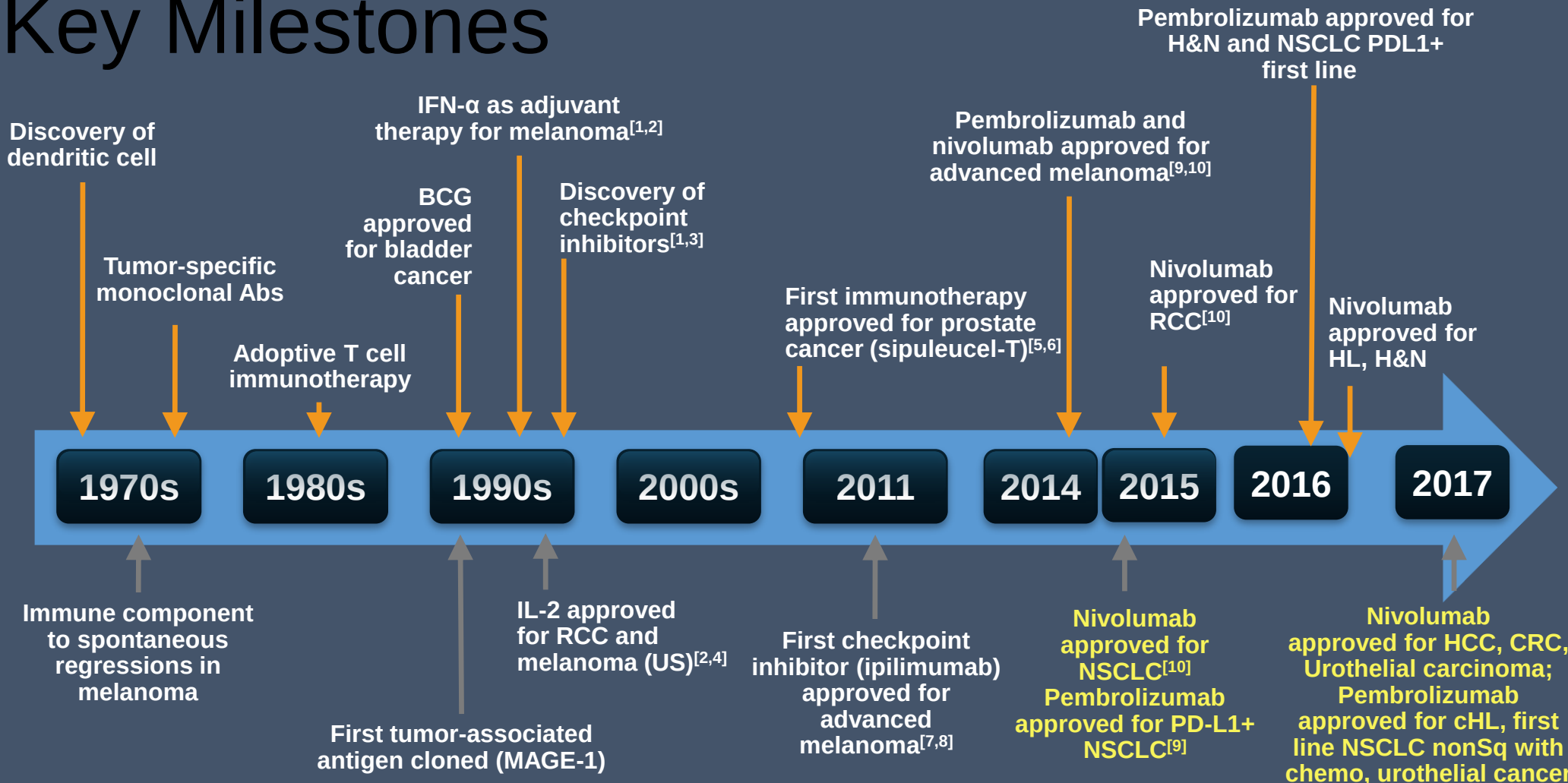
New successes are being achieved with targeted therapies, including the introduction of medicines that delay the progression of breast and lung cancers.

Growing microbiome research field identifies specific bacteria possibly associated with risk for certain head and neck cancers.

Immunotherapy advances continue to grow, expanding to cancers where there have been few immunotherapy treatment successes to date:

- A new combination immunotherapy regimen was proven to boost overall survival in patients with renal cell cancer, gaining Food and Drug Administration (FDA) approval and becoming the new standard of care.
- An investigational PD-1 inhibitor showed promise for advanced squamous cell cancer of the skin, which has few other treatment options.

History of Cancer Immunotherapy: Key Milestones



1. Kirkwood JM, et al. CA Cancer J Clin. 2012;62:309-335. 2. Garbe C, et al. Oncologist. 2011;16:5-24. 3. George S, et al. J Natl Compr Canc Netw. 2011;9:1011-1018. 4. Rosenberg SA. Sci Transl Med. 2012;4:127ps8. 5. Cheever MA, et al. Clin Cancer Res. 2011;17:3520-3526. 6. Kantoff PW, et al. N Engl J Med. 2010;363:411-422. 7. Mansh M. Yale J Biol Med. 2011;84:381-389. 8. Hodi FS, et al. N Engl J Med. 2010;363:711-723. 9. Pembrolizumab [package insert]. 10. Nivolumab [package insert].

THE BIRTH OF IMMUNO-ONCOLOGY

THE PAST: INF-alfa and IL-2

- Chemical mediators that promote immune responses, yet present in the human body
- Essential roles in key functions of the immune system through several pathways

THE MODERN ERA: Immune Check Point inhibitors

- **Immune escape** as a fundamental and conceptual shift
- **Normalizing rather than amplifying** anti-tumor immunity (Sanmamed and Chen, Cell 2018)
- Discovery of **molecular and cellular mechanisms** of cancer immune evasion
- **Development of IO angents** able to restore immunity to fight cancer

Hanahan et al. Cell 2011

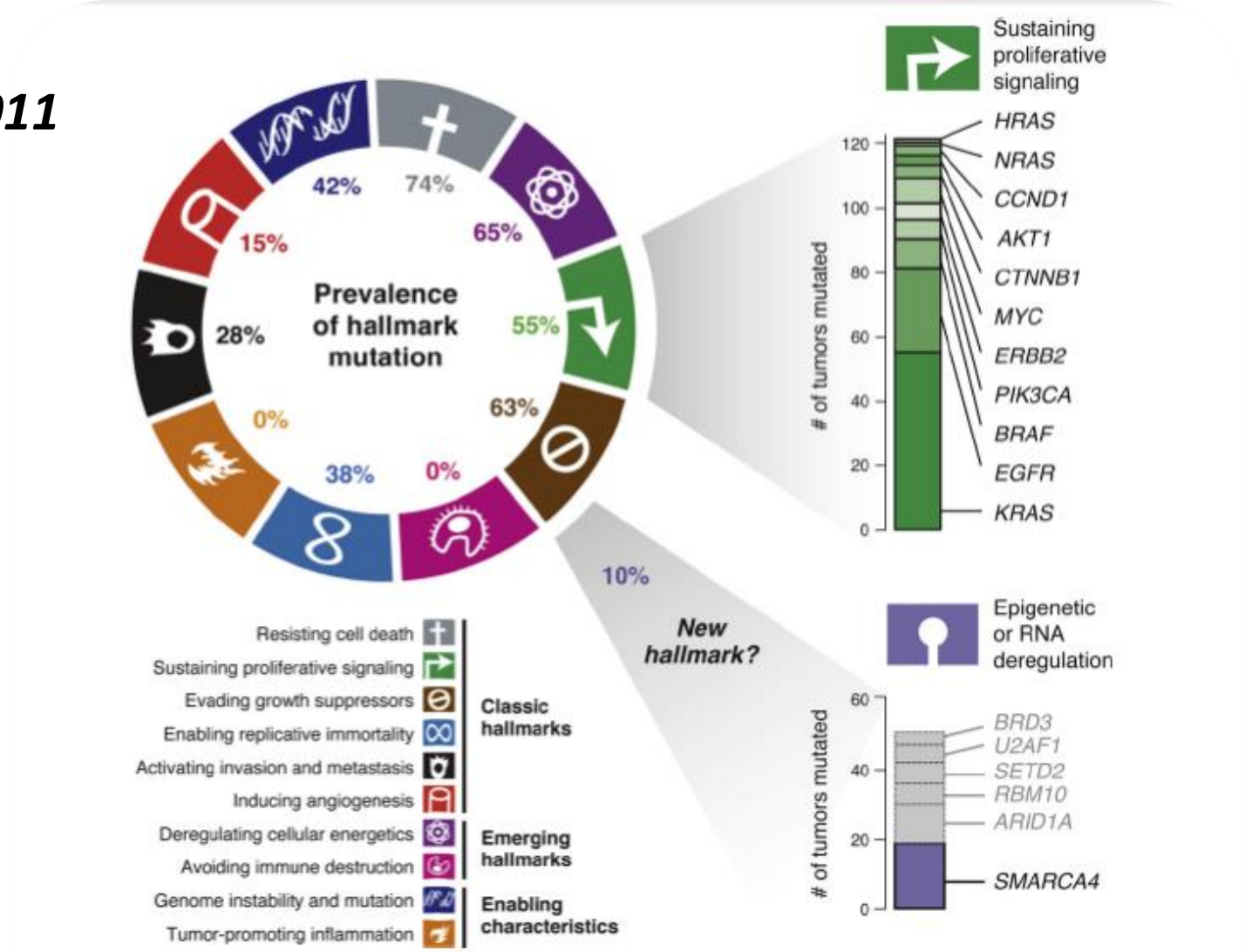


Figure 6. Next-Generation Hallmarks of Lung Adenocarcinoma

Left, the prevalence of mutation or SCNA of Sanger Cancer Gene Census (Futreal et al., 2004) genes mapping to cancer hallmarks defined by Hanahan and Weinberg (2011). Suspected passenger mutations were filtered out of the analysis, as described in Experimental Procedures. Top right, genes comprising the mutated genes in the hallmark of sustaining proliferative signaling are shown. Bottom right, a proposed eleventh hallmark of epigenetic and RNA deregulation is shown, depicted as above. Genes shown in gray are candidate lung adenocarcinoma genes identified in this study that may additionally contribute to the

IMMUNE ESCAPE AS ONE OF THE KEY HALLMARKS OF CANCER!!

SCIENTIFIC RELEVANCE OF IMMUNE ESCAPE

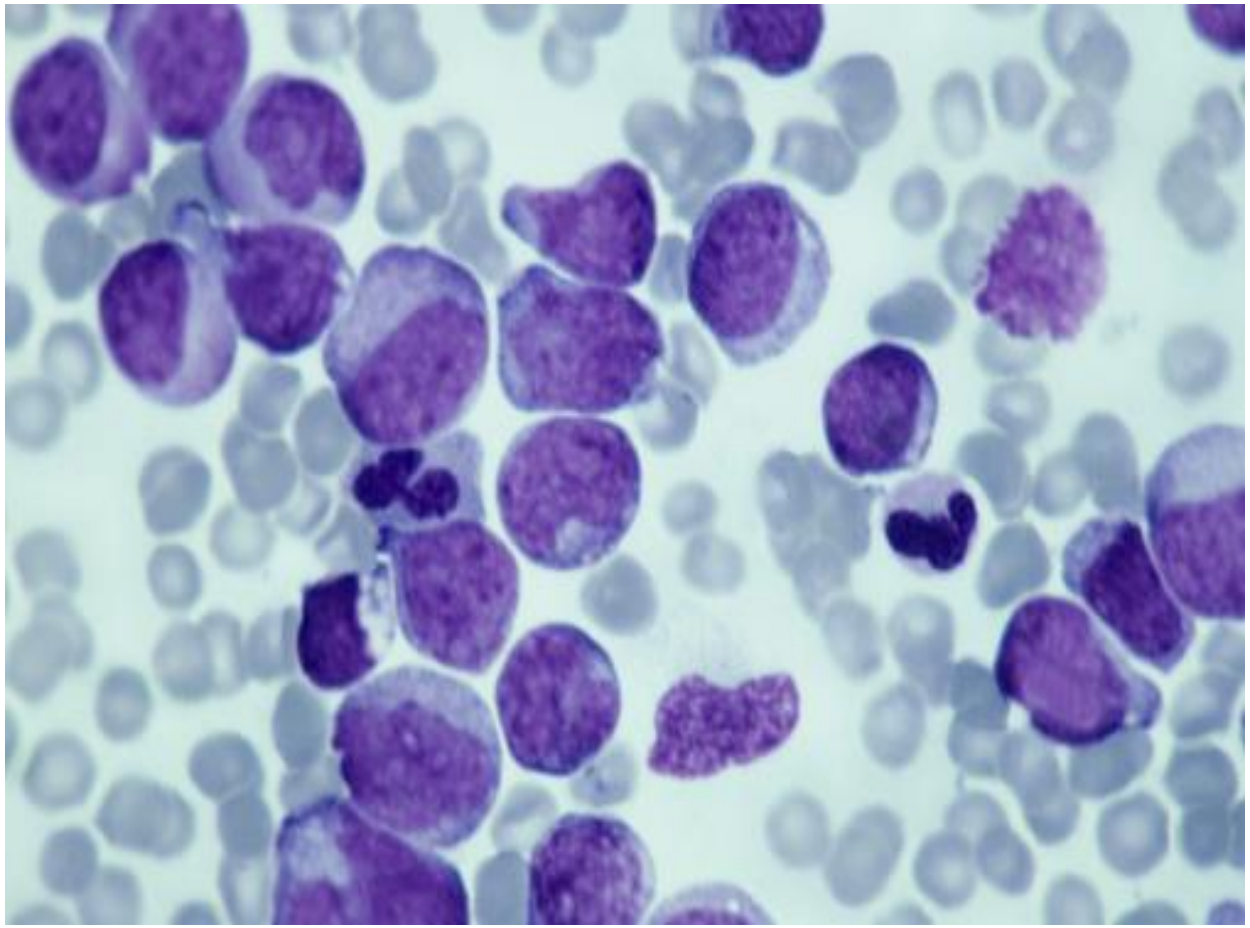
TASUKO HONJO AND JAMES ALLISON

Award of the **2018 Nobel Prize** in Phisiology and Medicine

«for their discovery of cancer medicine by inhibition of negative immune regulation»

THAT IS THE BASE OF MoA of ICIs

…WHAT HAPPENS AT THE CELLULAR LEVEL?



Functional phases cancer progression and immune response: the three Es model

Elimination

Cancer immunosurveillance

- **Effective antigen processing/presentation**
- **Effective activation and function of effector cells**
  - e.g. T cell activation without co-inhibitory signals

Equilibrium

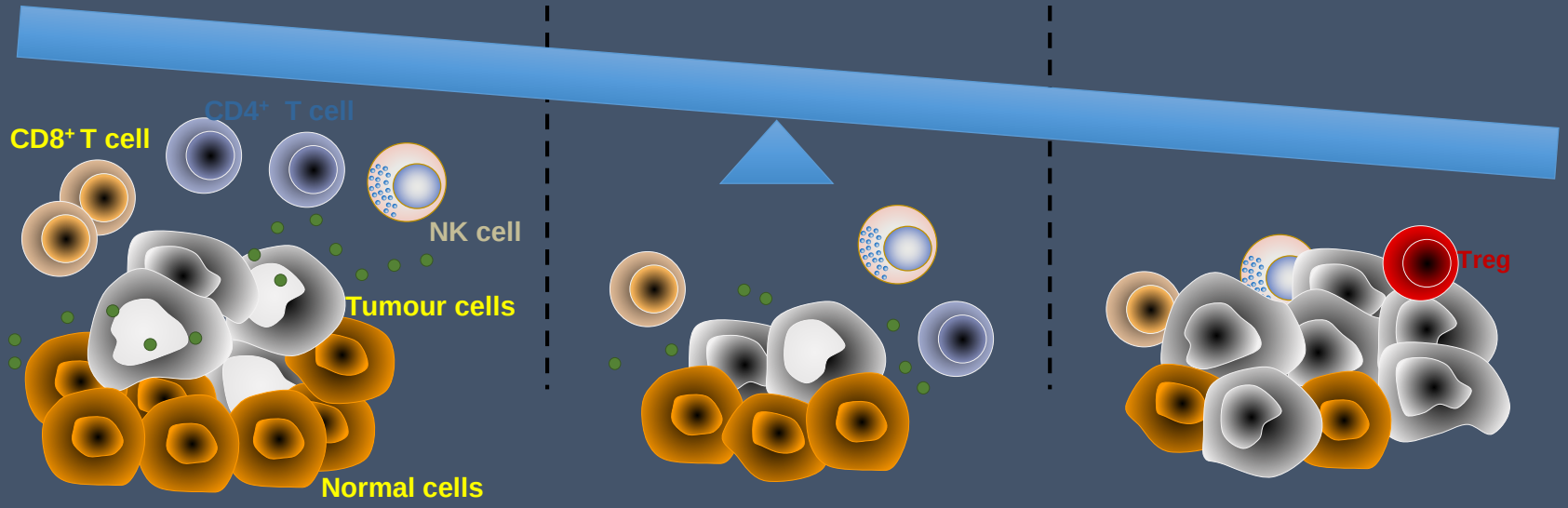
Cancer dormancy

- **Genetic instability**
- **Tumour heterogeneity**
- **Immune selection**
- **Cancer cells are not dividing but survive in a quiescent state**

Escape

Cancer progression

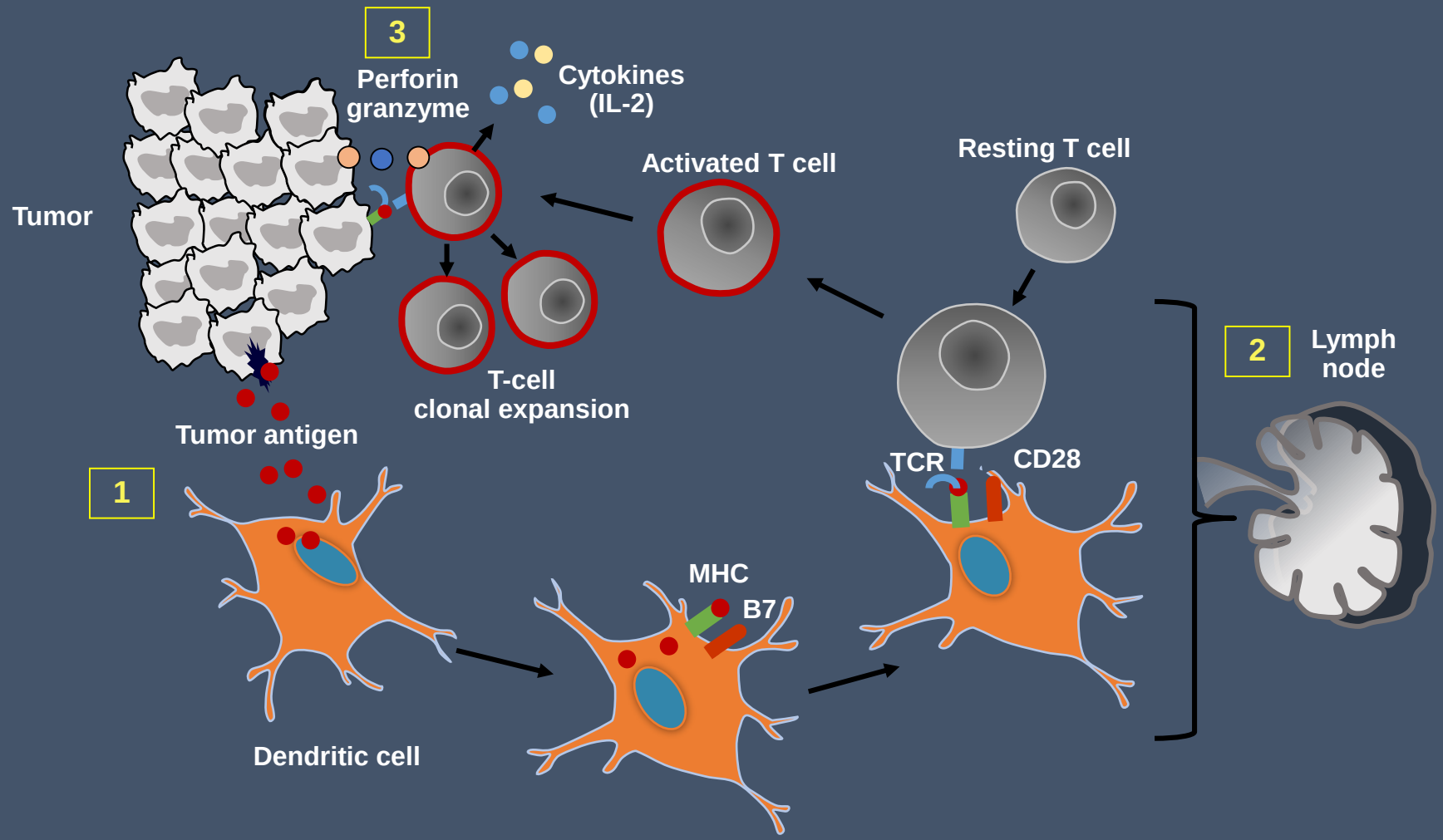
- **Tumours avoid elimination through the outgrowth of tumour cells that can suppress, disrupt or 'escape' the immune system**
- **Reduced immunogenicity**



NK = natural killer; Treg = regulatory T cells.

Vesely M and Schreiber R. *Ann N Y Acad Sci.* 2013;1284:1–5.

THE ELIMINATION PHASE



THE ESCAPE PHASE

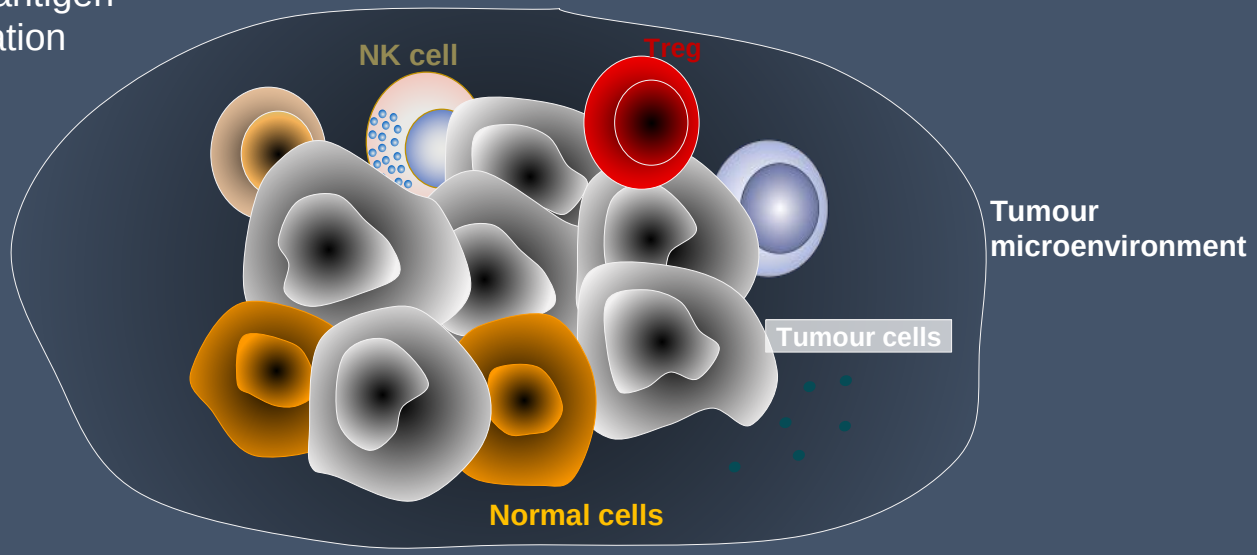
Immune escape mechanisms are complex and frequently overlapping

Ineffective presentation of tumour antigens[1]

e.g. down regulation of MHC I and DC/APC defects in antigen processing/presentation

Recruitment of immunosuppressive cell types[1,2]

e.g. Tregs, MDSC, others



Inhibition of attack by immune cells[1,2]

e.g. disruption of T cell-activating and checkpoint pathways

Secretion of immunosuppressive cytokines[1,2]

e.g. TGF-*B*, IDO, IL-10 inhibiting T cells directly

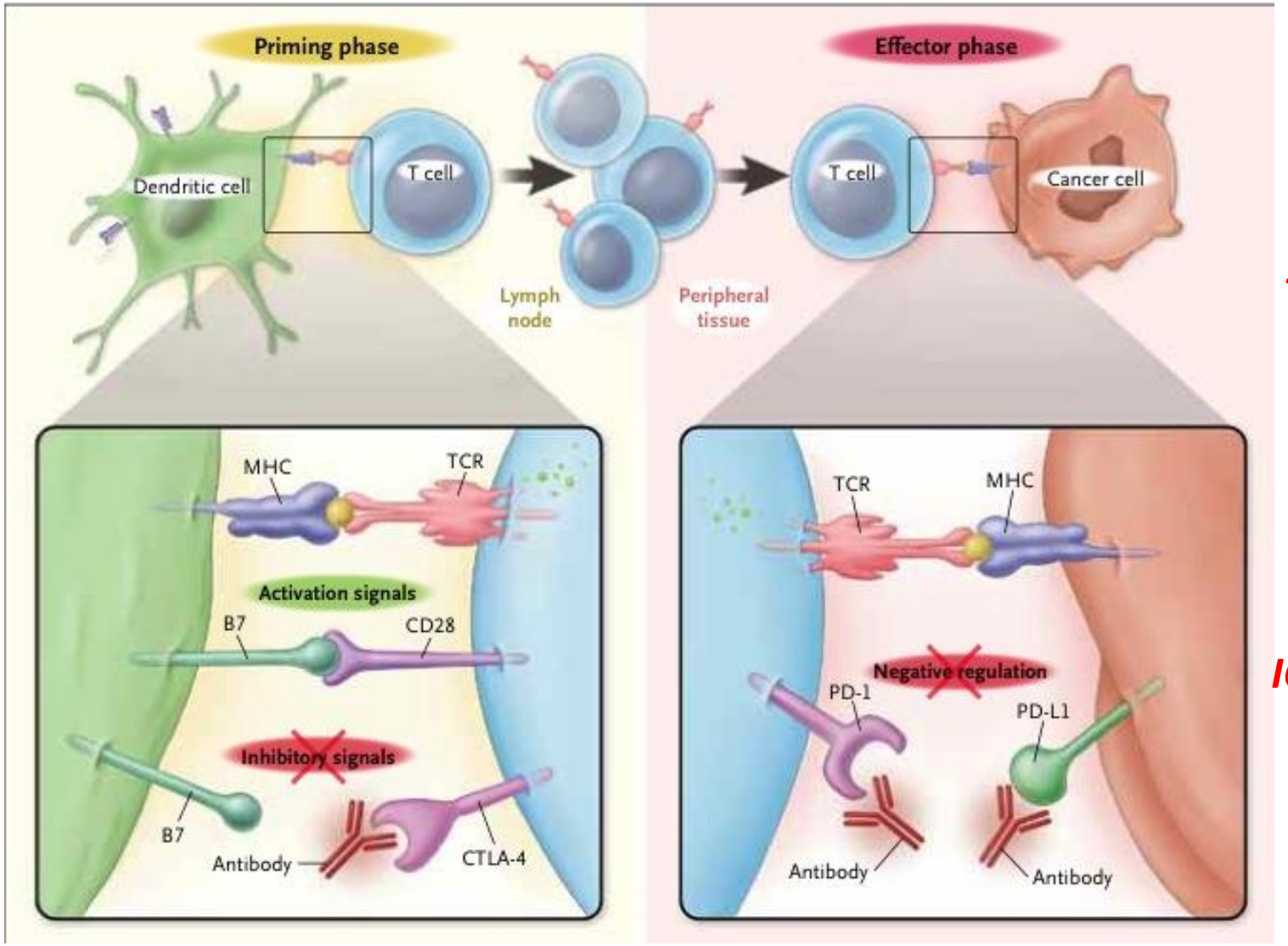
APC = antigen presenting cell; DC = dendritic cell; IDO = indoleamine 2,3-dioxygenase; IL-10 = Interleukin-10; MDSC = myeloid-derived suppressor cells; MHC = major histocompatibility complex; TGF-β = transforming growth factor-β.

1. Jadus M, et al. *Clin Dev Immunol*. 2012:160724; 2. Quezada S, et al. *Immunol Rev.* 2011;241:104–118.

THE MODERN IMMUNO-ONCOLOGY IS BASED ON THE 3 Es MODEL:

IMMUNE CHECK POINT INHIBITORS ARE ABLE TO *PREVENT THE ESCAPE PHASE* AND *TO RESTORE THE ELIMINATION PHASE!!*

PD-1 and CTLA4-signaling in cancer immunotherapy



CTLA4-B7 and PD1-PDL1
Two important check points of the immune system

the more PDL1 is expressed, the more pronounced should be mAb efficacy???

ICIs are definitely a target therapy?

Antoni Ribas, M.D., Ph.D
n engl j med 366;26 nejm.org june 28, 2012

PDL-1 EXPRESSION ON CANCER CELLS

LOGICAL BIOMARKER ……BUT:

✓**It depends on the type of drug** (Pembrolizumab approved only for PDL1+; Nivolumab and Atezolizumab can be admnistered regardless of PDL1; but in any case ICIs efficacy is more enhanced the higher is the positivity score of PD1!!!!)
✓**Heterogeneous intratumoral expression**
✓ **dynamic PDL1 expression** along different phases of the disease
✓**Different staining** tecniques and antibodies
✓**Different tresholds** for defining positivity

…SO, PDL1 EXPRESSION ALONE IS NOT ENOUGH FOR PATIENT SELECTION!!!

Immune Check Point Inhibitors (ICIs)

-**Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) blocker**
(Ipilimumab)
-**Programmed Cell Death Protein 1 (PD1) inhibitors**
(Nivolumab, Pembrolizumab, Cemiplimab)
- **Programmed Cell Death Protein 1 ligand (PDL1) inhibitors**
(Durvalumab, Atezolizumab and Avelumab)

7 ICIs approved by FDA
for the standard treatment of a total **13 cancer types**

ICIs REVOLUTION

Traditionally, a drug is tested in a specific indication for the tretament of a specific cancer site (i.e. brest or colon or lung cancer)

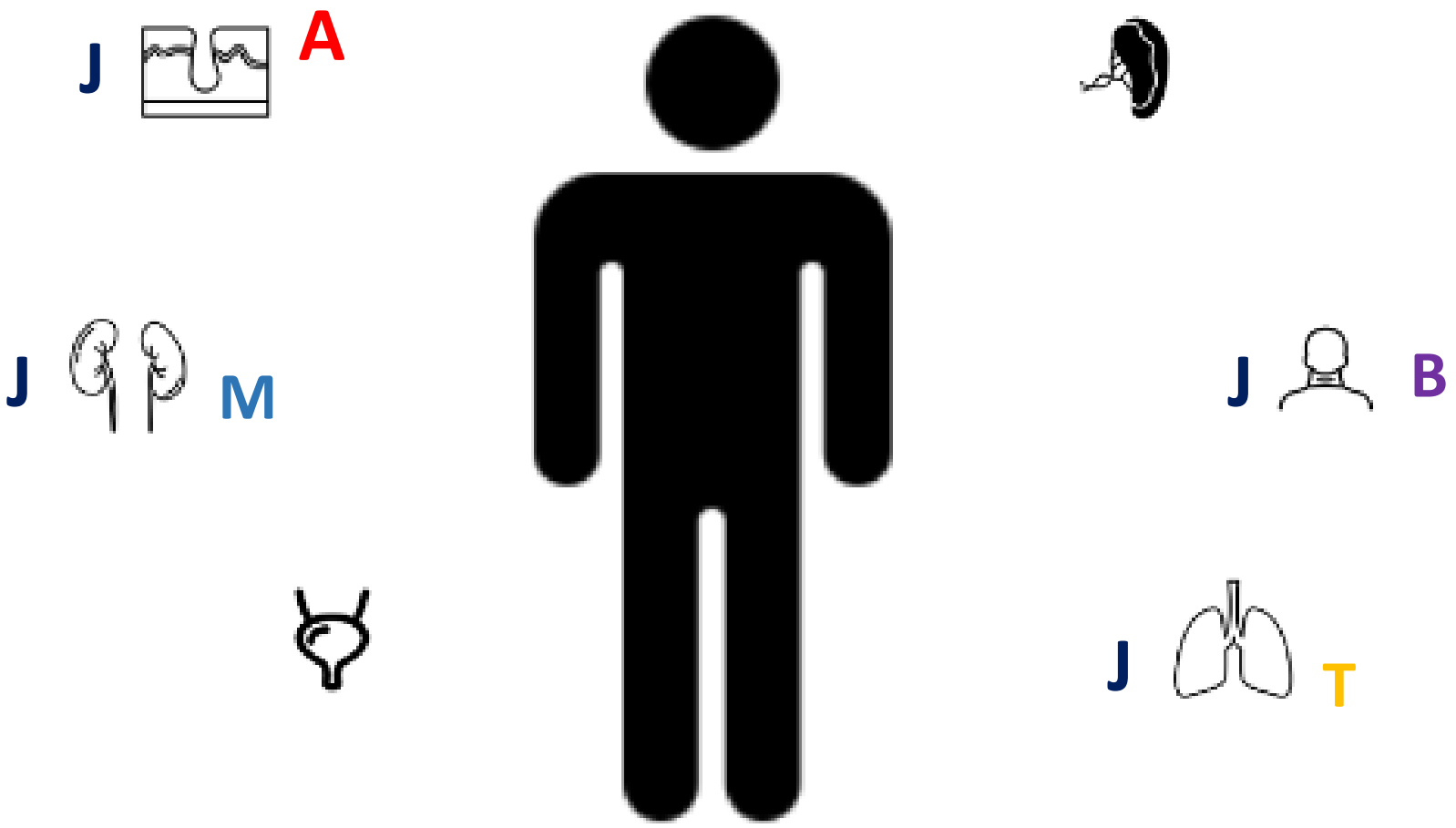
ICIs changed the paradigm!! For the first time a drug has been tested for the treatment of different cancer sites BUT with the same common biomarker that is mismatch-rapair deficiency

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

In May 2017, the FDA approved pembrolizumab, a programmed death 1 inhibitor, for adult and pediatric patients with unresectable or metastatic, microsatellite-instability–high or mismatch-repair–deficient solid tumors, regardless of tumor site or histology.



The drug "J" is effective against different cancer type with the same biomarker → agnostic site approval !!!!

FROM THE BANCH TO THE BEDSIDE…

- ✓ **ICIs are a clinical cancer advance of utmost importance**
- ✓ **To avoid immune escape and restore immune response is the key**

….But which are the clinical effects and implications?

….Which are the main difference with respect to “old” chemotherpy?

MAIN DIFFERENCES WITH RESPECT TO CHEMOTHERAPY

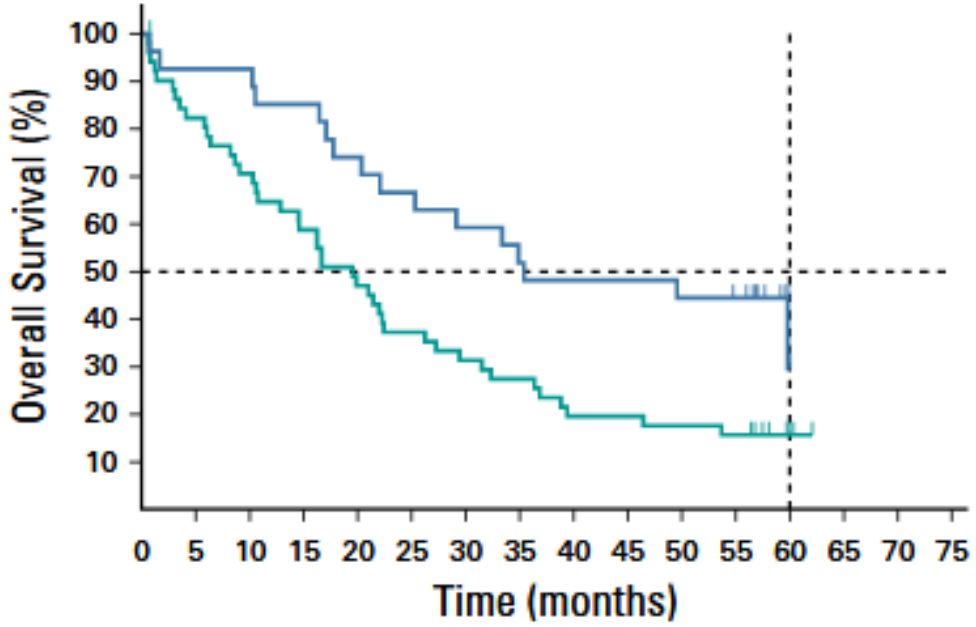
- ✓ *Efficacy*
- ✓ *Pattern of treatment response*
- ✓ *Response Evaluation Criteria*
- ✓ *Toxicity*
- ✓ *Economic sustainability*

EFFICACY of ICIs:

THE LONG TALE SHAPE OF THE SURVIVAL CURVES

C

	Events, n/N	Median OS, mo (95% CI)	5-Year OS Rate, % (95% CI)
TPS ≥ 50%	17/27	35.4 (20.3 to 63.5)	29.6 (7.7 to 56.1)
TPS 1–49%	43/52	19.5 (10.7 to 26.3)	15.7 (7.3 to 26.9)



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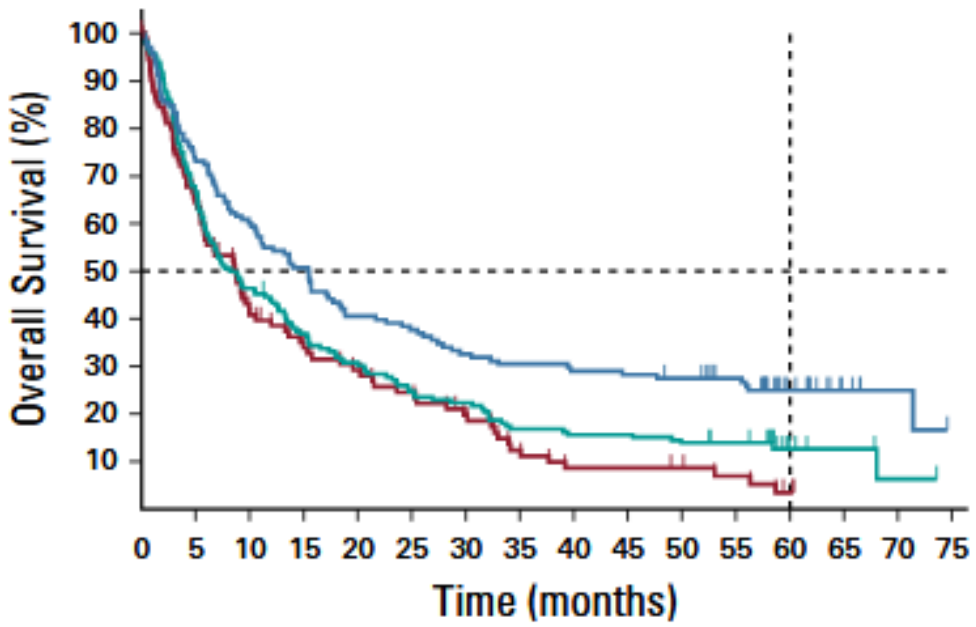
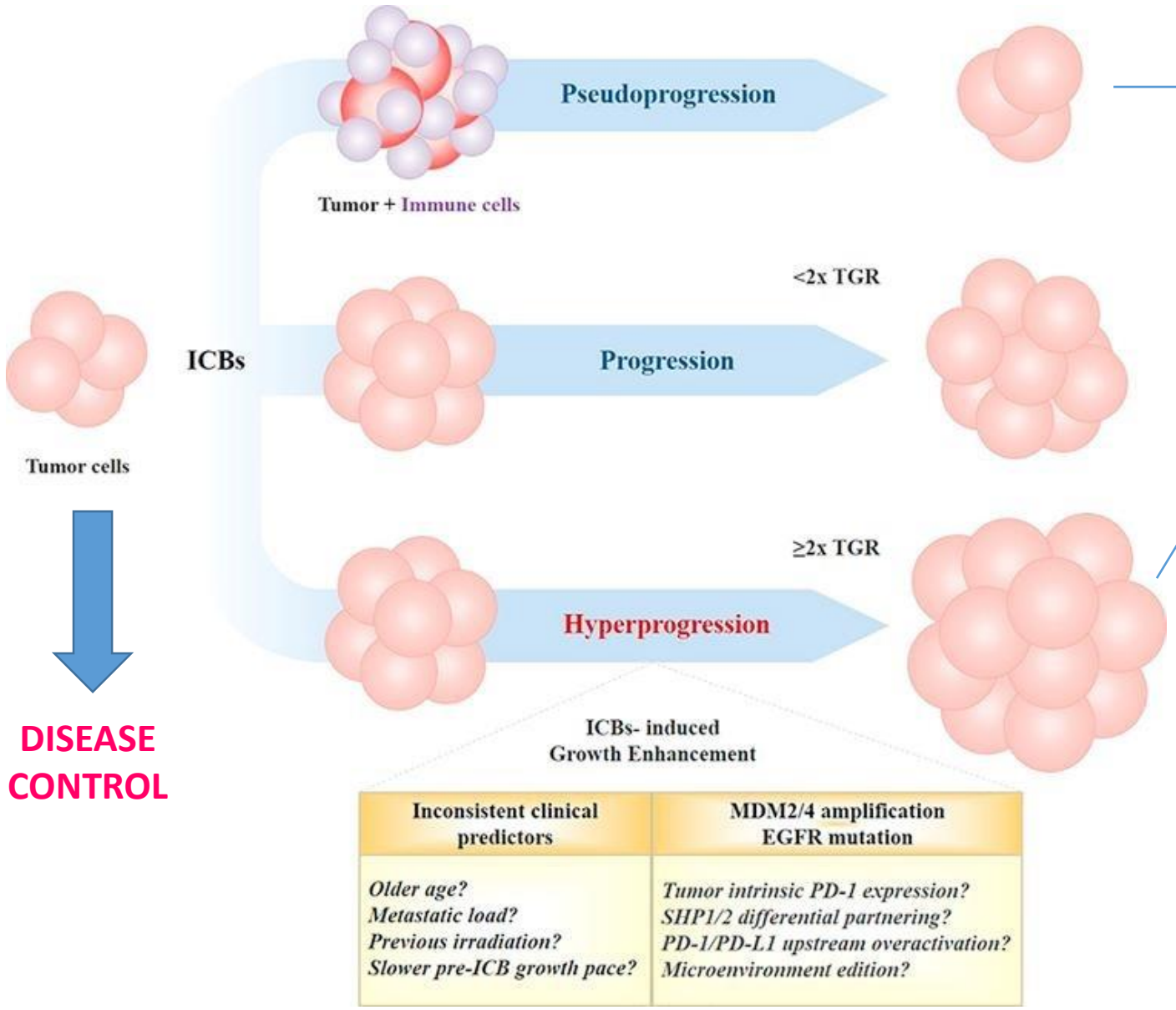
	Events, n/N	Median OS, mo (95% CI)	5-Year OS Rate, % (95% CI)
TPS ≥ 50%	104/138	15.4 (10.6 to 18.8)	25.0 (18.0 to 32.5)
TPS 1–49%	146/168	8.5 (6.0 to 12.6)	12.6 (7.9 to 18.5)
TPS < 1%	83/90	8.6 (5.5 to 10.6)	3.5 (0.7 to 10.0)



5 Year OS in naïve and pre-treated metastatic NSCLC pts: up to 30%!!! Never seen with chemo (6%)!!!

Garon EB, J Clin Oncol 2019

PATTERN OF RESPONSE



Inconsistent clinical predictors	MDM2/4 amplification EGFR mutation
Older age? *Metastatic load?* *Previous irradiation?* *Slower pre-ICB growth pace?*	*Tumor intrinsic PD-1 expression?* *SHP1/2 differential partnering?* *PD-1/PD-L1 upstream overactivation?* *Microenvironment edition?*

Pseudoprogression and Hyperprogression are only immune related kind of response! Never seen with chemo!

HYPERPROGRESSION PHENOMENON (4-29%):

Immunotherapy does not work it is DETRIMENTAL INSTEAD!! with tumor progression at the first on-treatment scan and at least a doubling in tumor pace growth

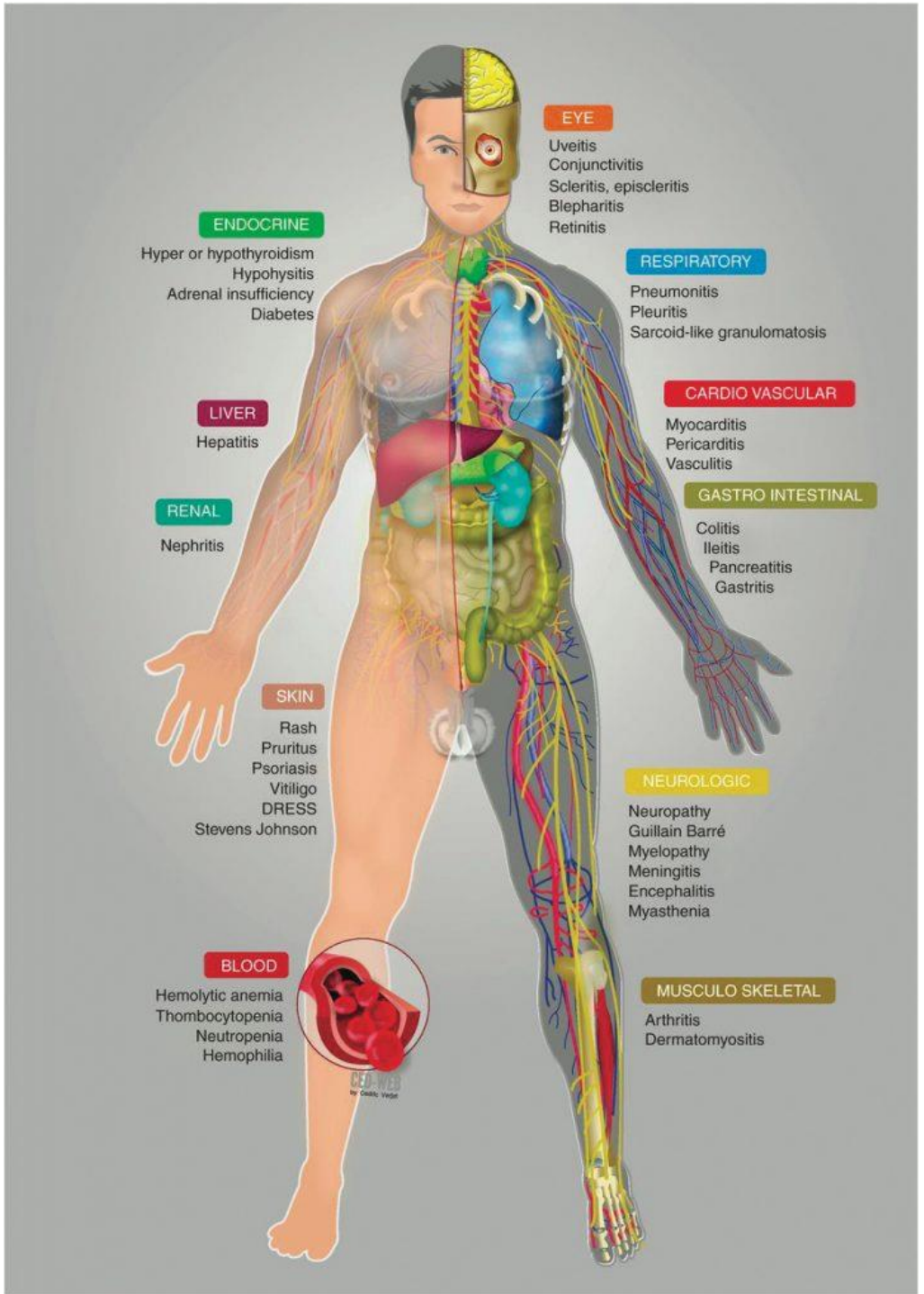
RESPONSE EVALUATION CRITERIA

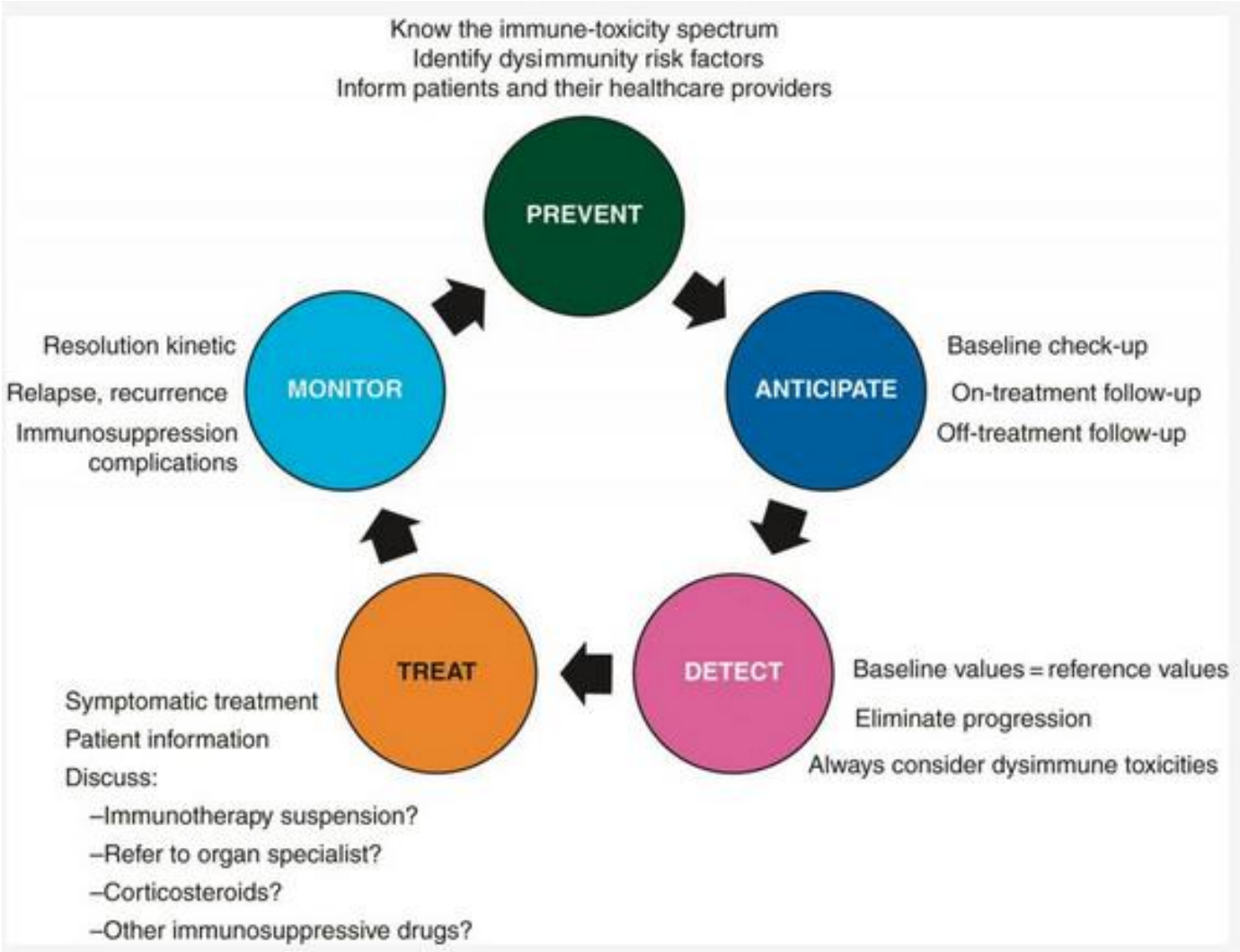
	RECIST ver 1.1	irRC	irRECIST	iRECIST
Introduced	2009	2009	2013	2017
Metrics required	Unidimensional	Bidimensional	Unidimensional	Unidimensional
Total lesions	5	10	5	5
Max lesions per organ	2	2	2	2
New lesions	PD	Add to TTB	Add to TTB	iUPD
Response criteria:				
Complete response (CR)	No lesions	No lesions	No lesions	No lesions
Partial response (PR)	> 30% decrease	> 50% decrease	> 30% decrease	> 30% decrease
Stable disease (SD)	Inbetween	Inbetween	Inbetween	Inbetween
Progressive disease (PD)	> 20% increase	> 25% increase	>20% increase	>20% increase
	FOR CHEMO AND ICIs	*FOR ICIs only*	*FOR ICIs only*	*FOR ICIs only*

Vining DJ 2019

TOXICITY of ICIs

….theoretically any organ could be affected by an immune-related adverse event!!!!





TOXICITY of ICIs

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

ICIs safety profile is more favourable!!!!

✓***Around 60% of cancer patients are eldelry (>70 yrs)***

✓***Quality of life and patient reported outcome***

…AND LAST BUT NOT LEAST :
THE ISSUE OF ECONOMIC SUSTAINABILITY

✓**+ 67%** increase in the number of **active agents in the global IO pipeline**

✓ *All ICIs have indications based on the **accelerated approval mechanism** (faster approval for serious conditions that fill an unmet clinical need).....*

✓*FDA welcomes **seamless trial design** in drug development (adaptive design, interim analysis and surrogate end point).....*

The NEW ENGLAND JOURNAL of MEDICINE

Accelerated Approval and Expensive Drugs — A Challenging Combination

May 25, 2017
N Engl J Med 2017; 376:2001-2004
DOI: 10.1056/NEJMp1700446

IMMUNOTHERAPY: HAILING AS A MIRACLE?

…Why immunotherapy works so well in some cancers and not at all in others?

…Among patients with the same type of cancer, why do some respond to immunotherapy (around 50% overall) while others do not?

WE ARE STILL SEARCHING FOR A PREDICTIVE BIOMARKER!!!!!

CONCLUSIONS

- ✓ Immunotherapy is considered a **relevant clinical cancer advance**.
- ✓ **Several ICIs** have been approved for the treatment of **different tumor types**.
- ✓ ICIs **efficacy can be marked and prolonged**, (such results were unprecedently observed with other medical therapies).
- ✓ Still to be defined the **appropriate biomarker** for an optimal patient selection in order to achieve better outcomes.