



Immune checkpoint inhibitors

Ρευματικές εκδηλώσεις στην ανοσοθεραπεία του καρκίνου

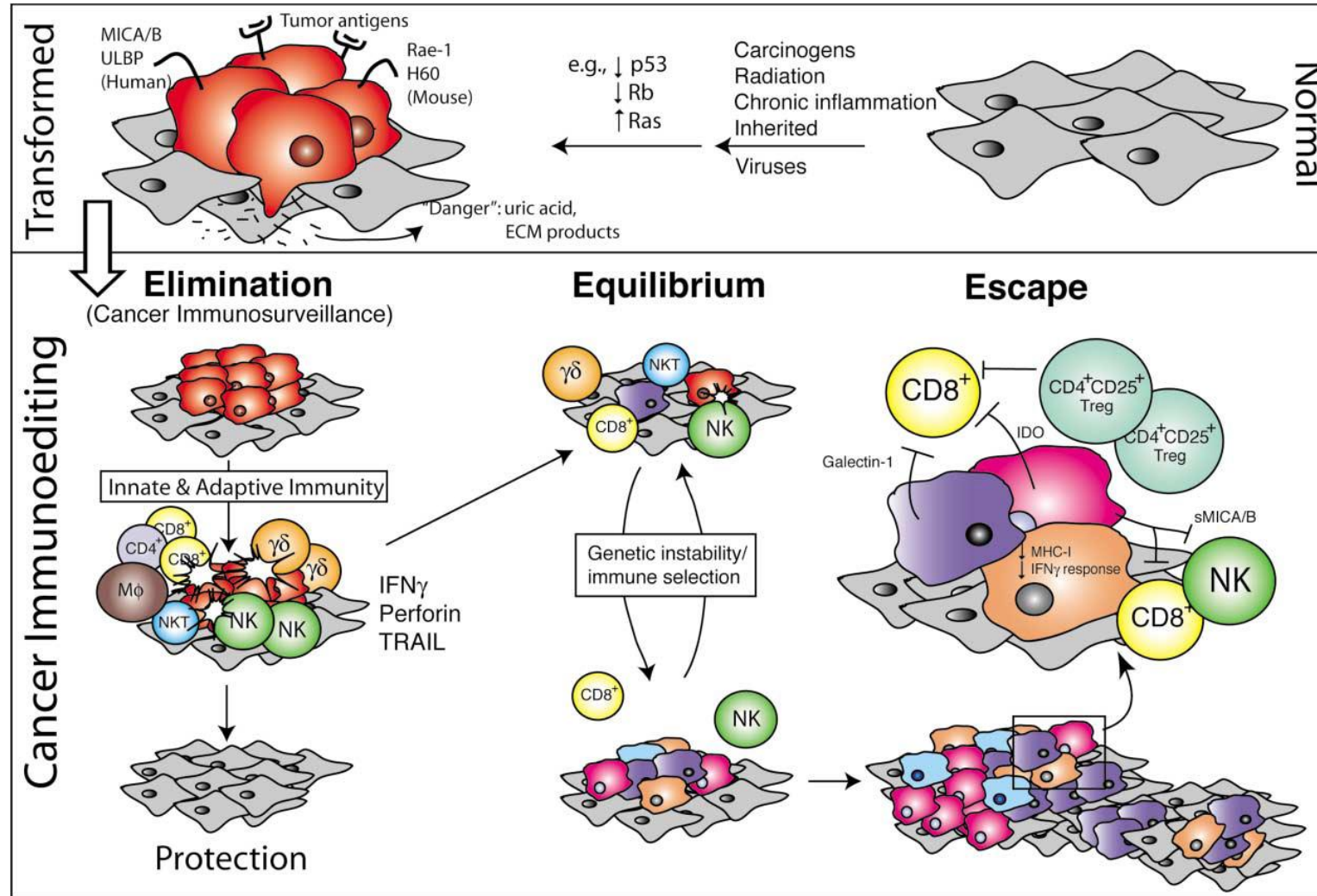


12ο Συνεδριο ΕΠΕΜΥ
Βόλος Οκτ 2020.

Δαούσης Δημήτρης
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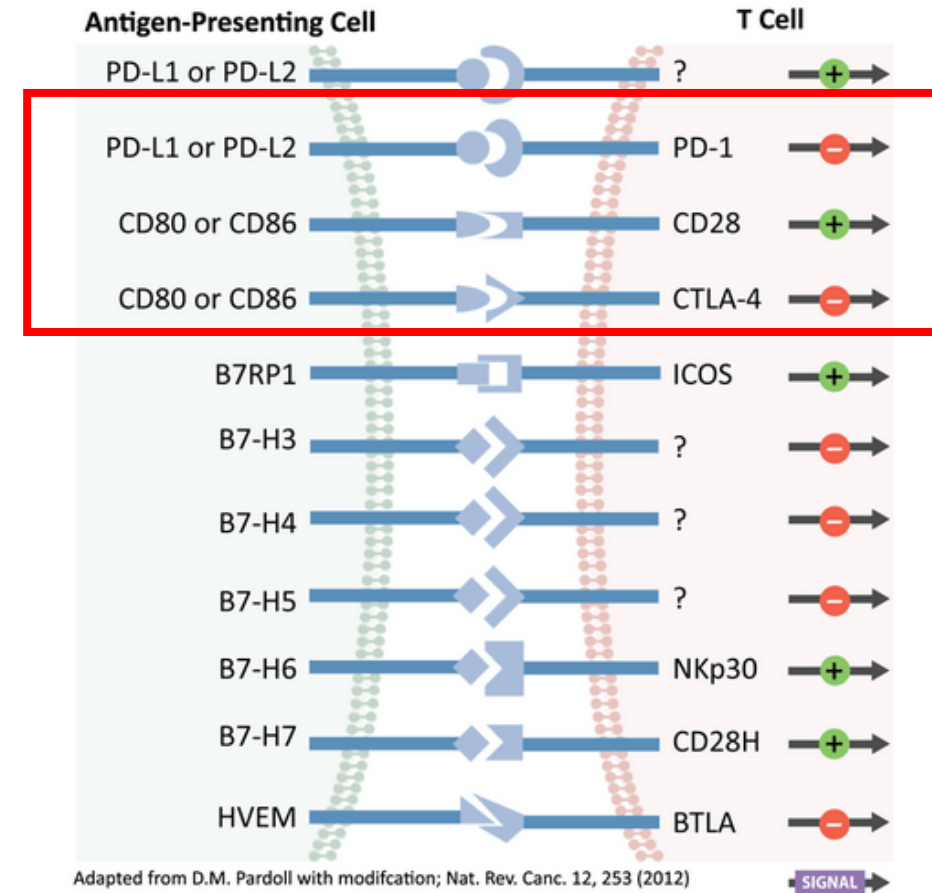
Ανοσολογικό σύστημα και καρκίνος

Μια στενή σχέση



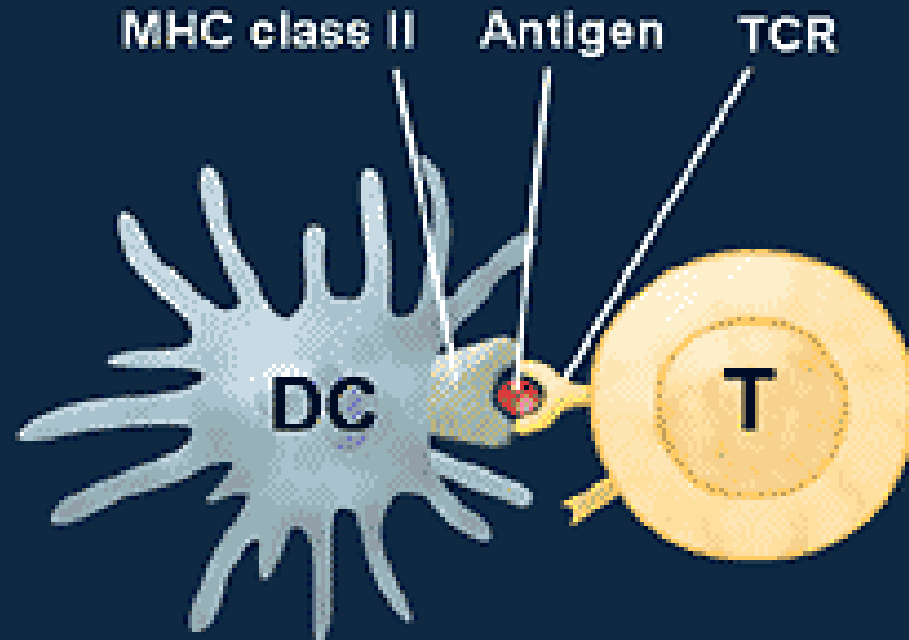
Πως μπορείς να ενεργοποιήσεις το ανοσολογικό σύστημα για να επιτύχεις αντικαρκινική δράση?

- Απελευθερώνοντας τα φυσικά φρένα (immune checkpoints)



T Cell Activation Requires 2 Signals

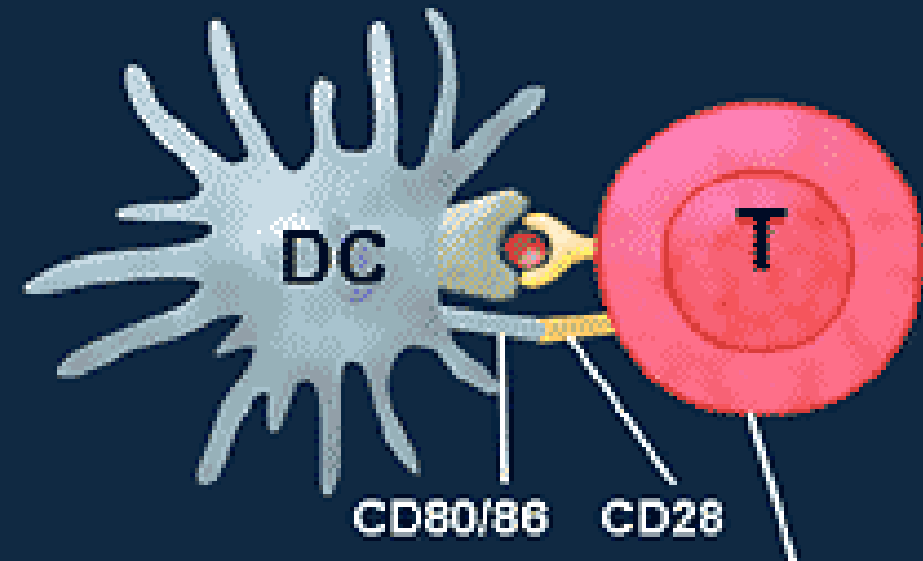
Antigen Generates Signal 1



DC = dendritic cell

Schwartz. *Annu Rev Immunol*. 2003;21:305.

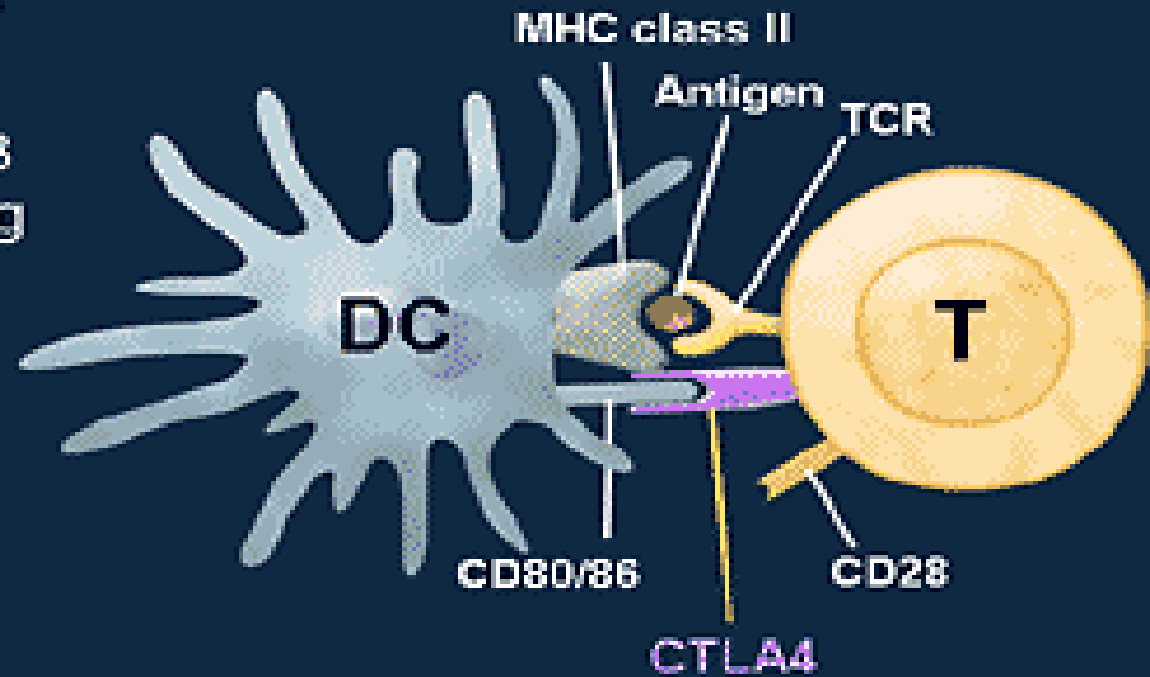
CD28 Costimulation Provides Signal 2



Activated T cell

CTLA4 Attenuates T Cell Activation

- Expressed by T cells early after activation
- Shares homology to CD28 within the CD80/86 binding region
- Binds CD80/86 500-2500 times more avidly than does CD28
- Important for T cell regulation



DC = dendritic cell; CTLA4 = cytotoxic T lymphocyte-associated antigen 4.

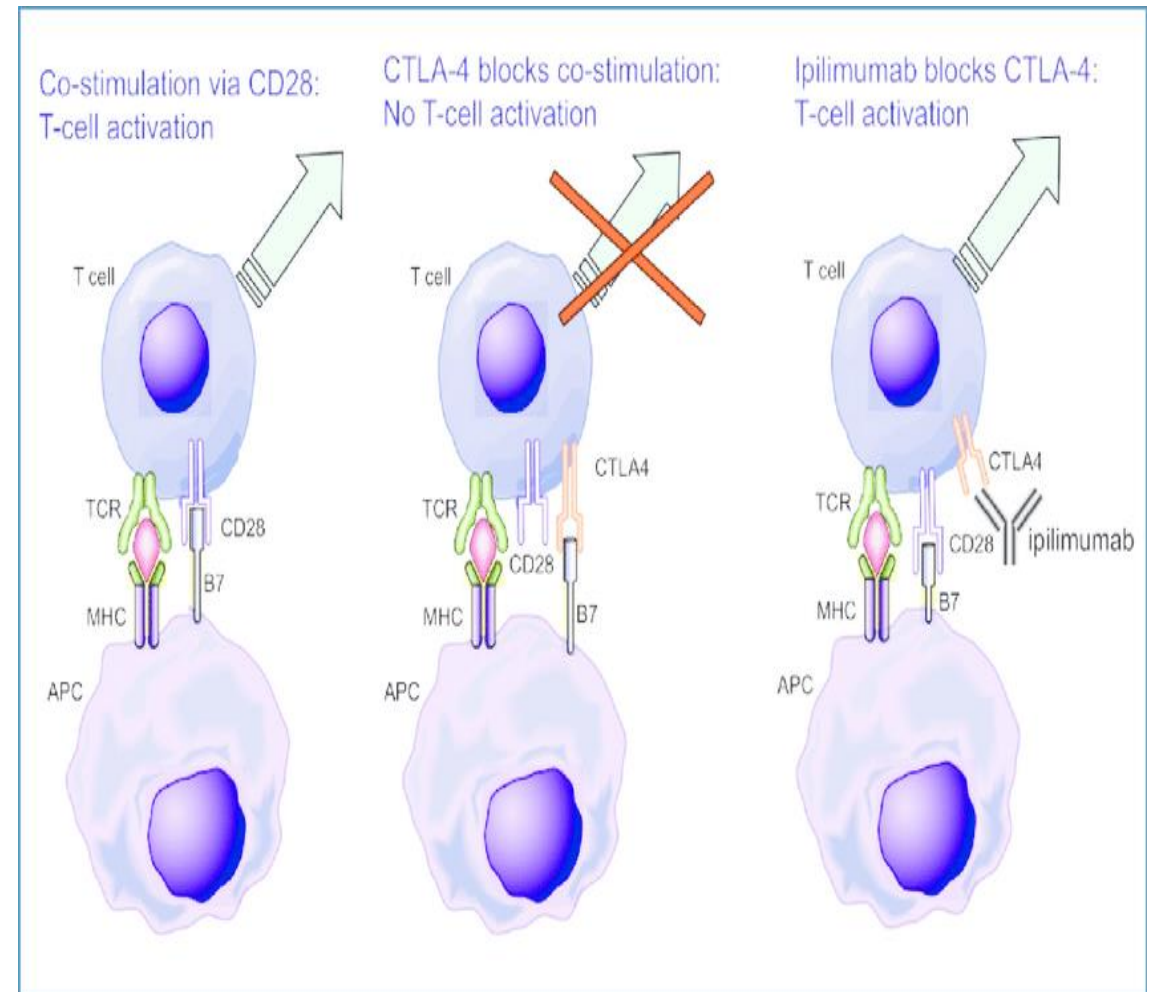
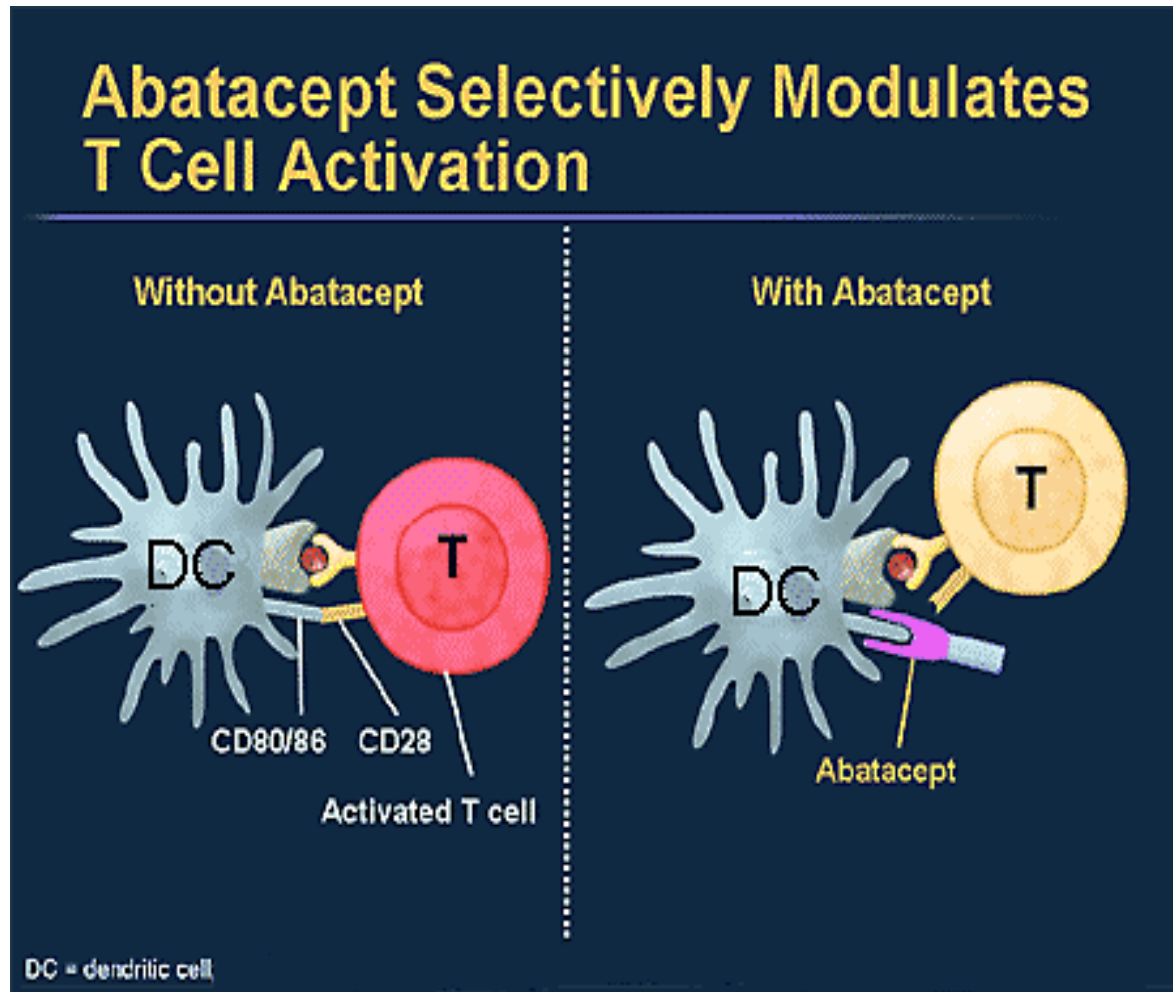
Wakunas et al. *Immunity*. 1994;1:405.

Linsley et al. *J Exp Med*. 1991;174:561.

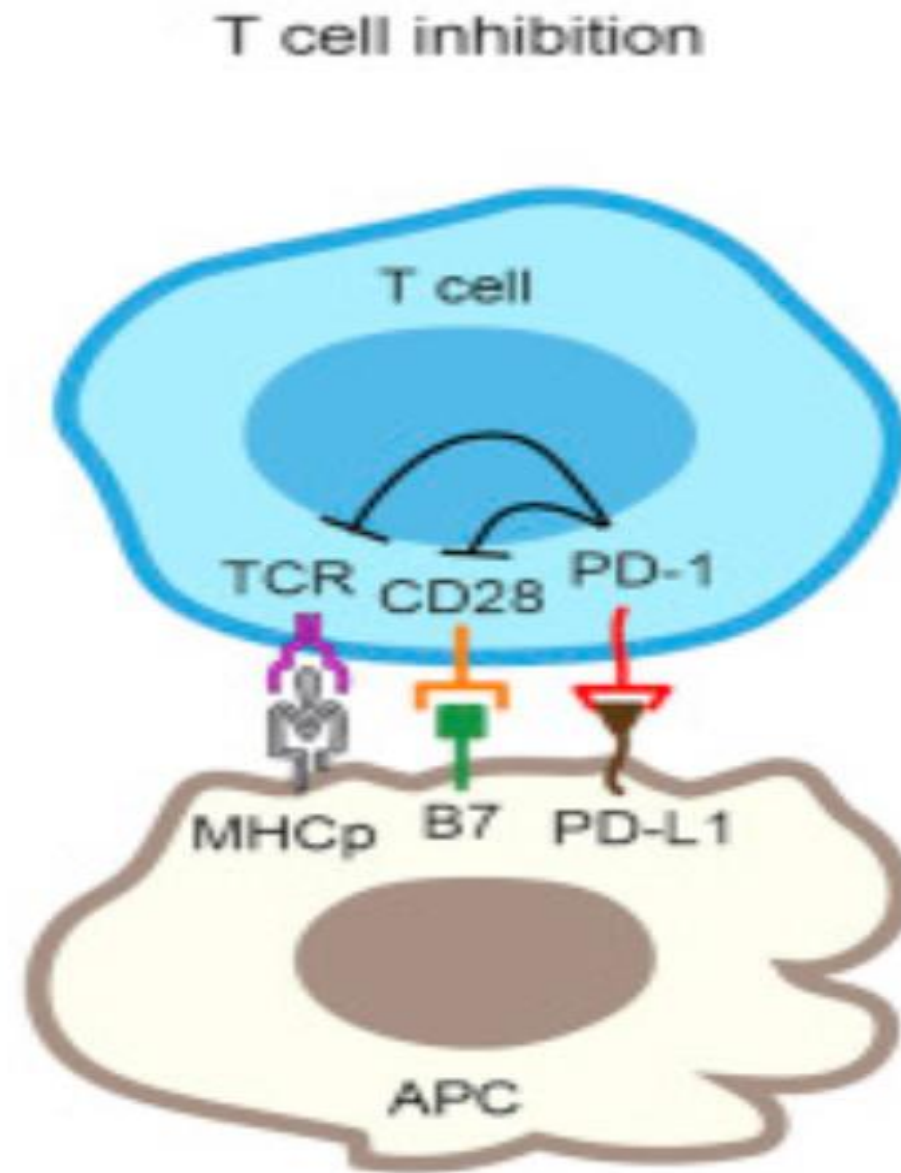
Greene et al. *J Biol Chem*. 1996;271:26762.

Carreno and Collins. *Annu Rev Immunol*. 2002;20:29.

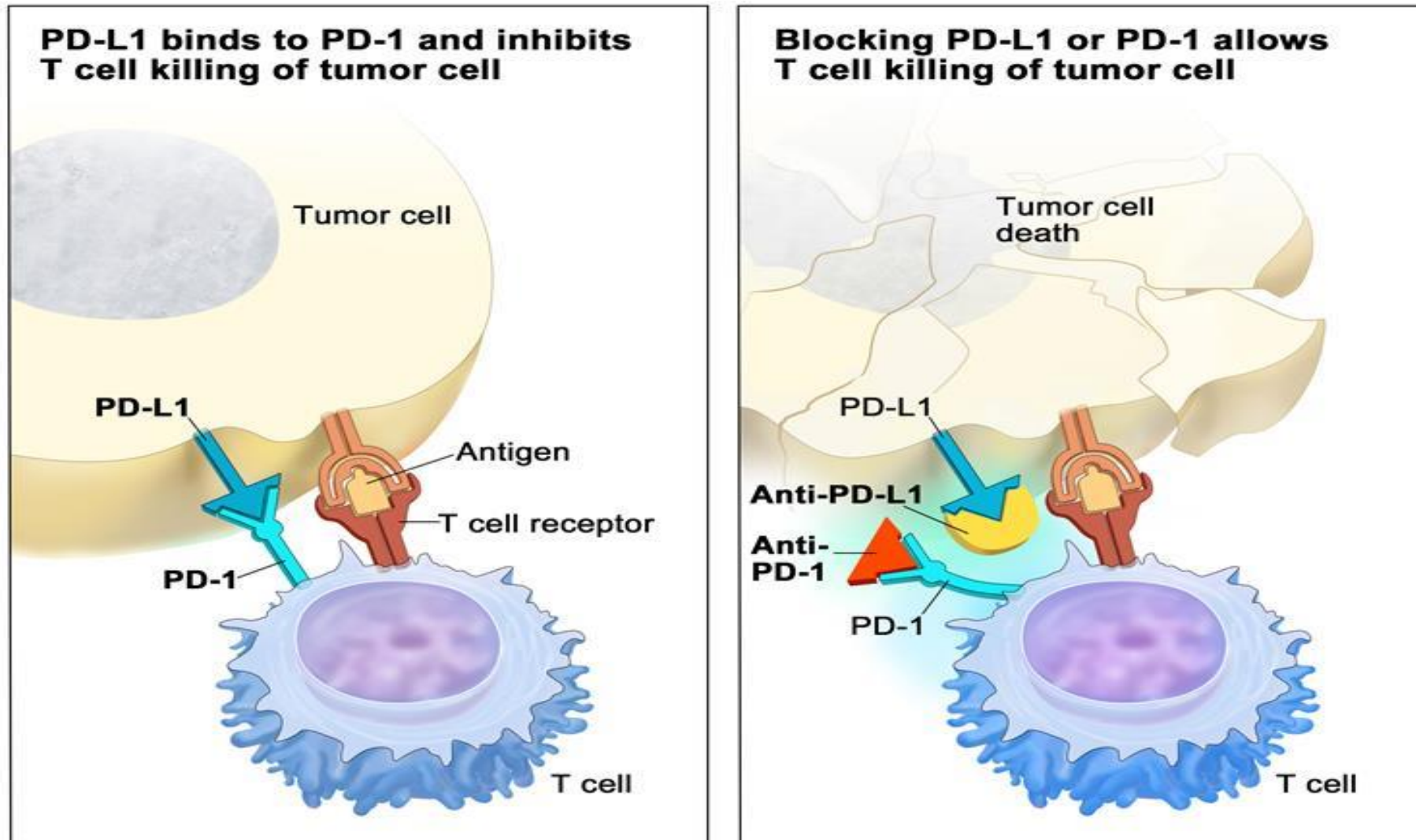
Στοχεύοντας τον ίδιο άξονα με διαφορετικό τρόπο Abatacept Vs Ipilimumab

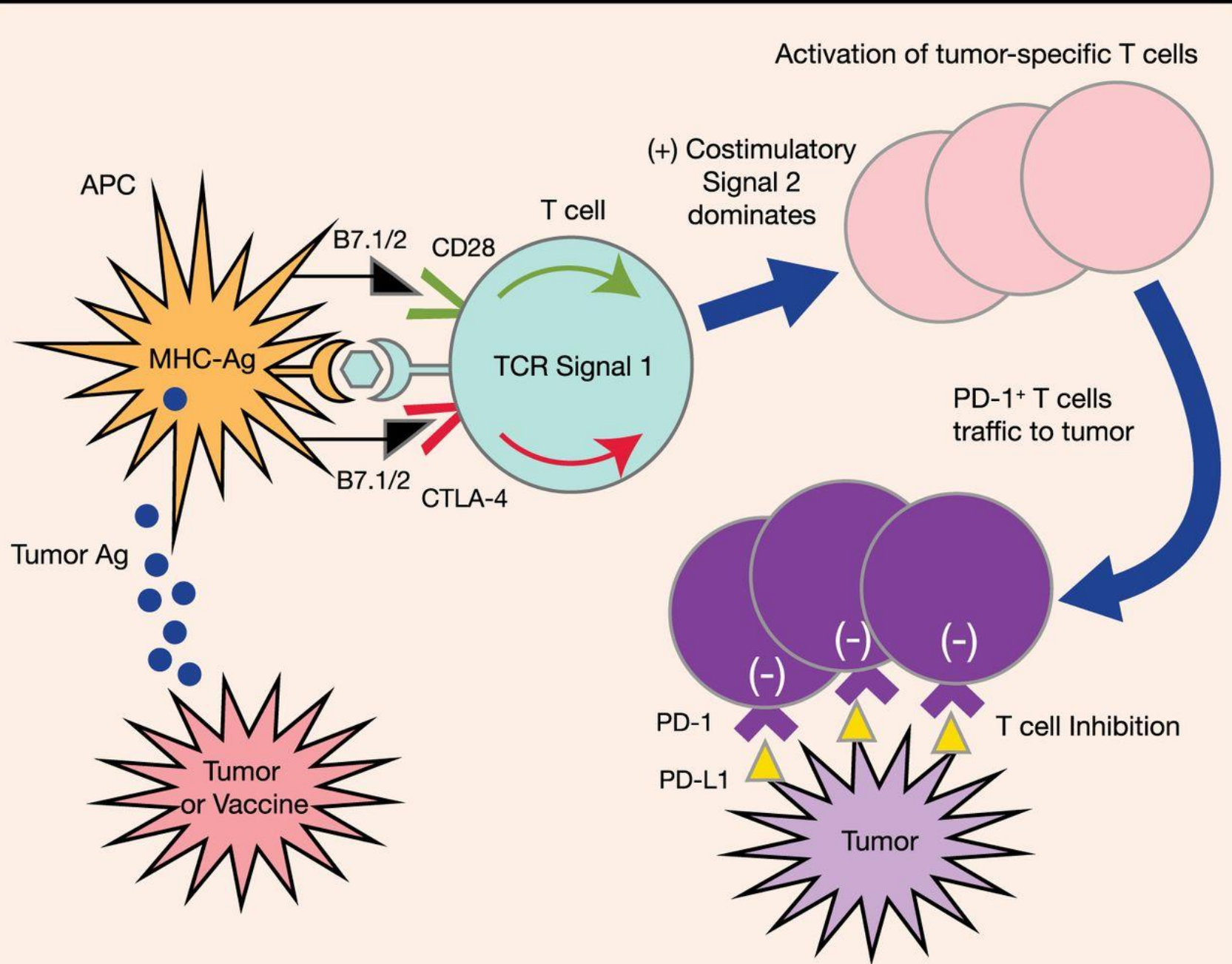


- Ο άξονας PD-1/PD-L1



Πολλοί όγκοι εκφράζουν PD-L1





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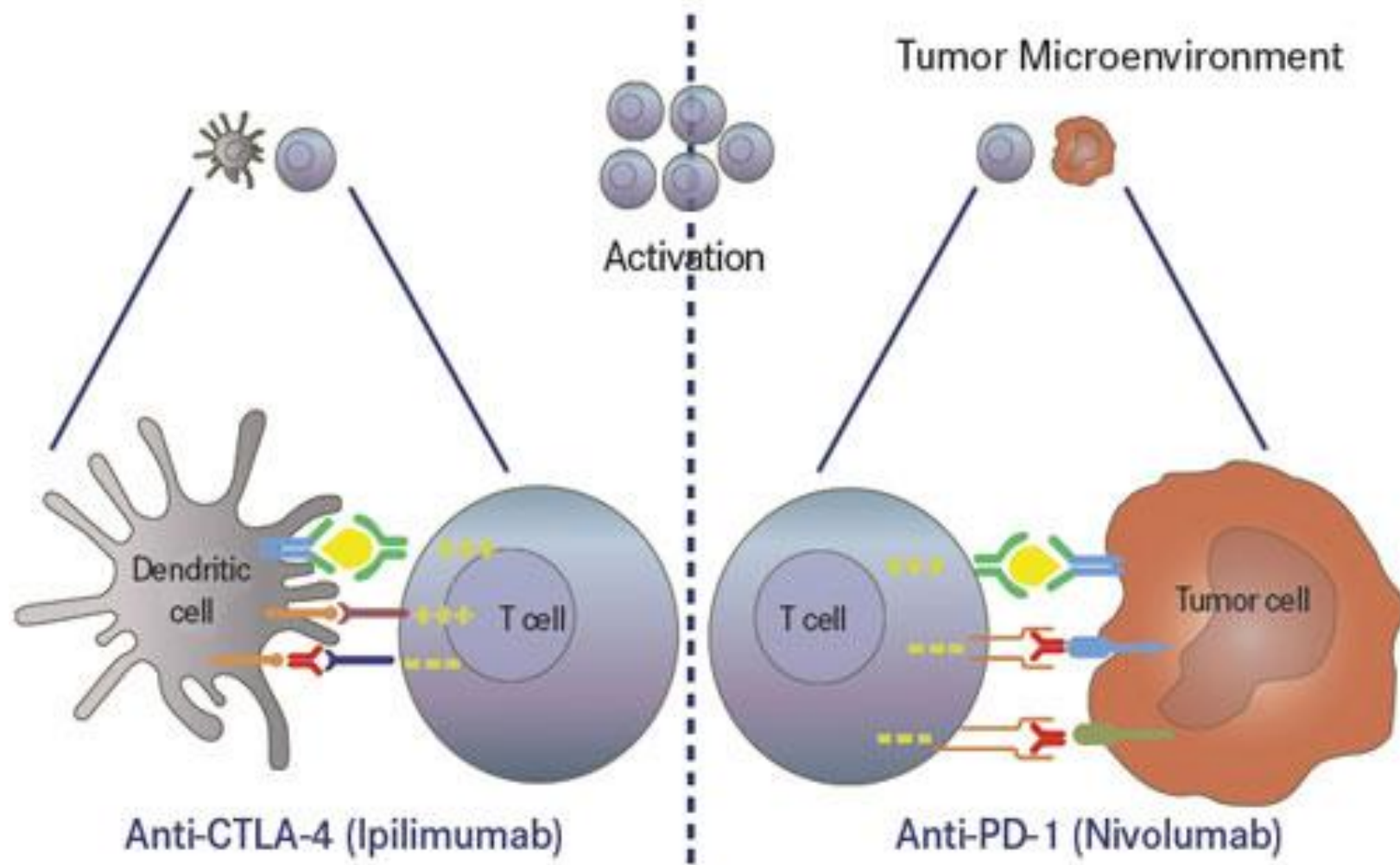


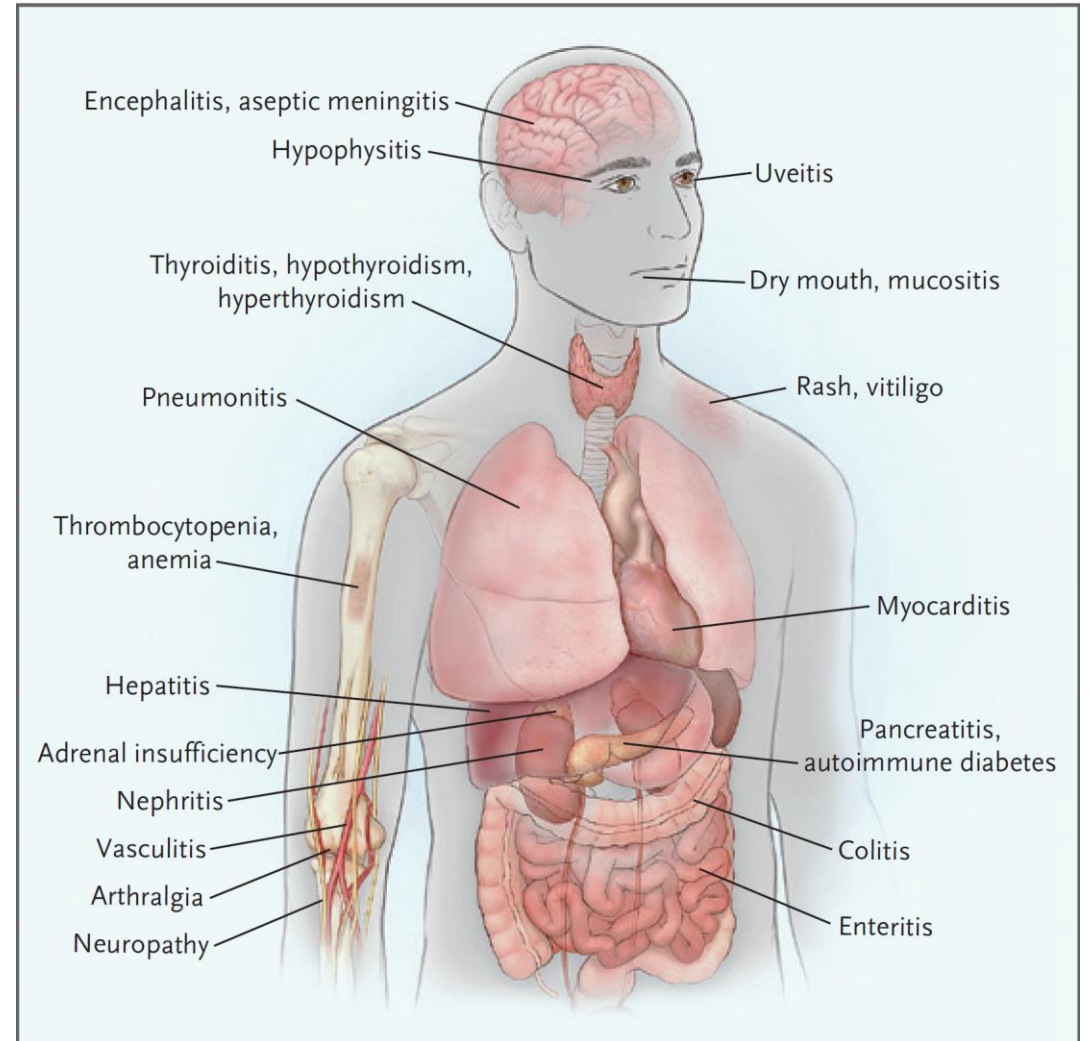
Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

Immune related adverse events (Ir-AE)

- Checkpoint inhibitors associate with immune mediated adverse effects
- Can affect any organ
- Usually skin, gut, endocrine organs and liver
- Serious events in PD-1 blockade 16%
- CTLA4 blockade 27%
- Combined treatment 55%



Παθογένεια

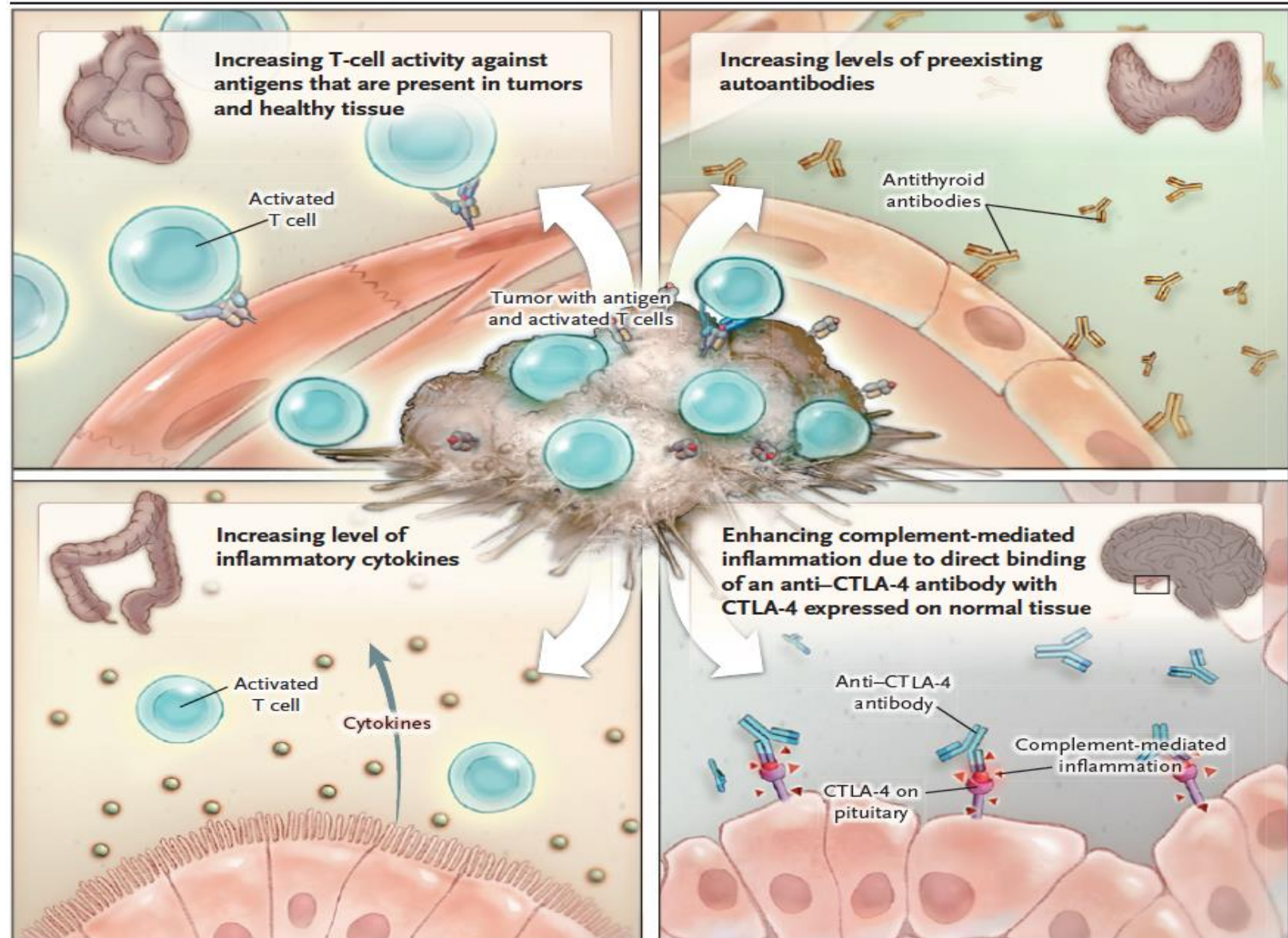
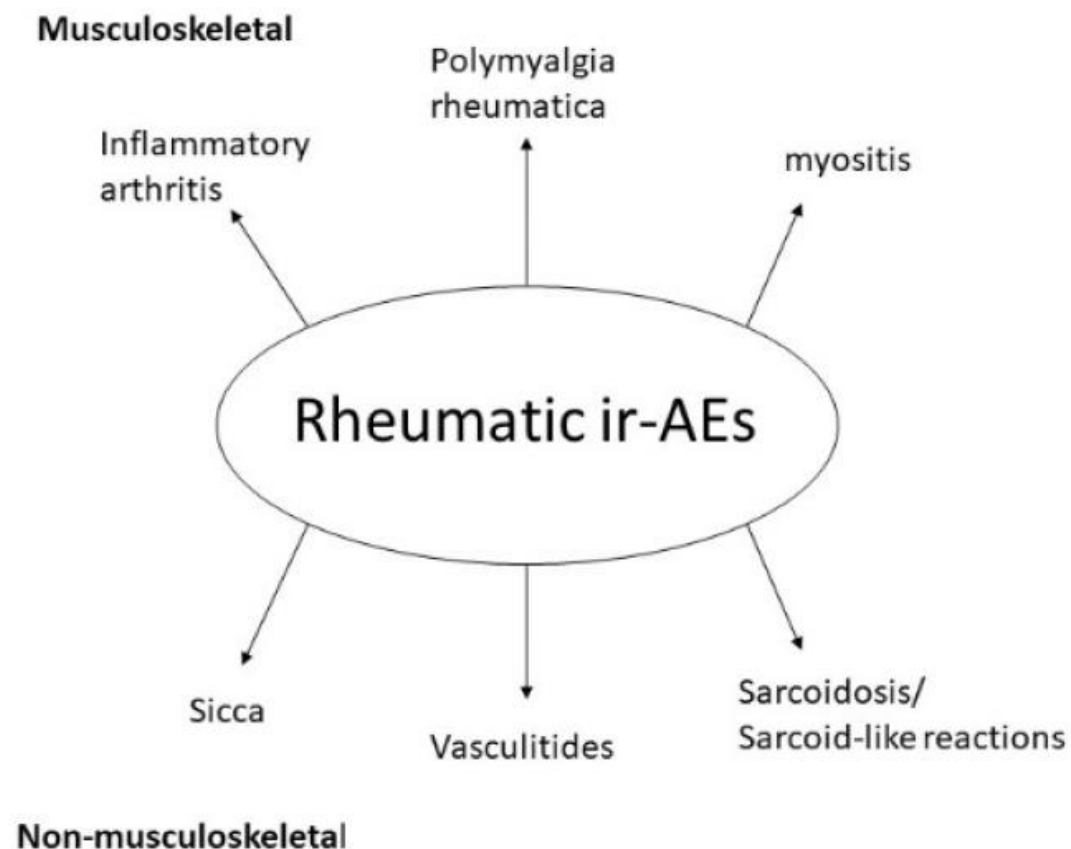


Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.

The mechanisms that result in immune-related adverse events are still being elucidated. Some potential mechanisms include increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies, an increase in the level of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland.

Οι μυοσκελετικές εκδηλώσεις ποικίλουν...

Πιο συχνές με anti-PD-1/PDL-1
Συνήθως όχι αυτοαντισώματα
Όχι έντονη φλεγμονώδη απάντηση



**An MRI study of immune checkpoint inhibitor-induced musculoskeletal manifestations
myofasciitis is the prominent imaging finding**

Dimitrios Daoussis^{1,*}, Pantelis Kraniotis^{2,*}, Alexandra Filippopoulou¹,
Rafaella Argiriadi³, Spyridoula Theodoraki³, Thomas Makatsoris³,
Angelos Koutras³, Ioannis Kehagias⁴, Dionysios J. Papachristou⁵,
Aikaterini Solomou², Haralabos Kalofonos³ and Stamatis-Nick Liossis¹

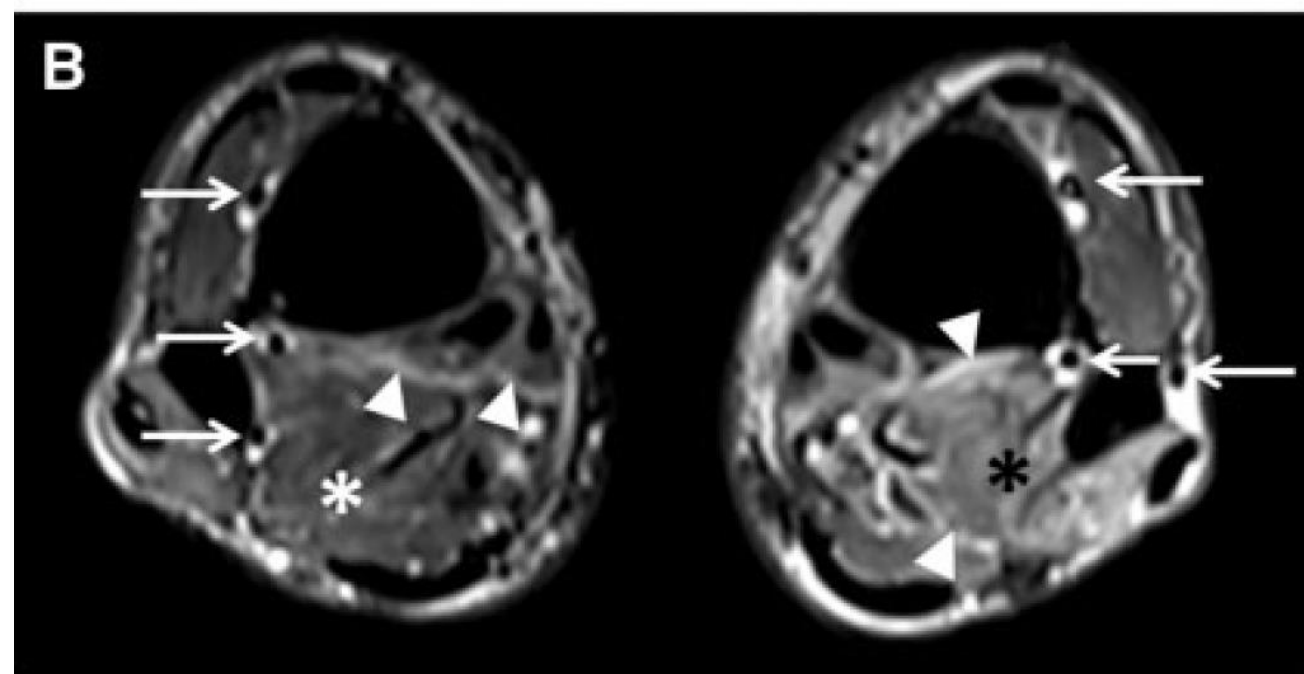
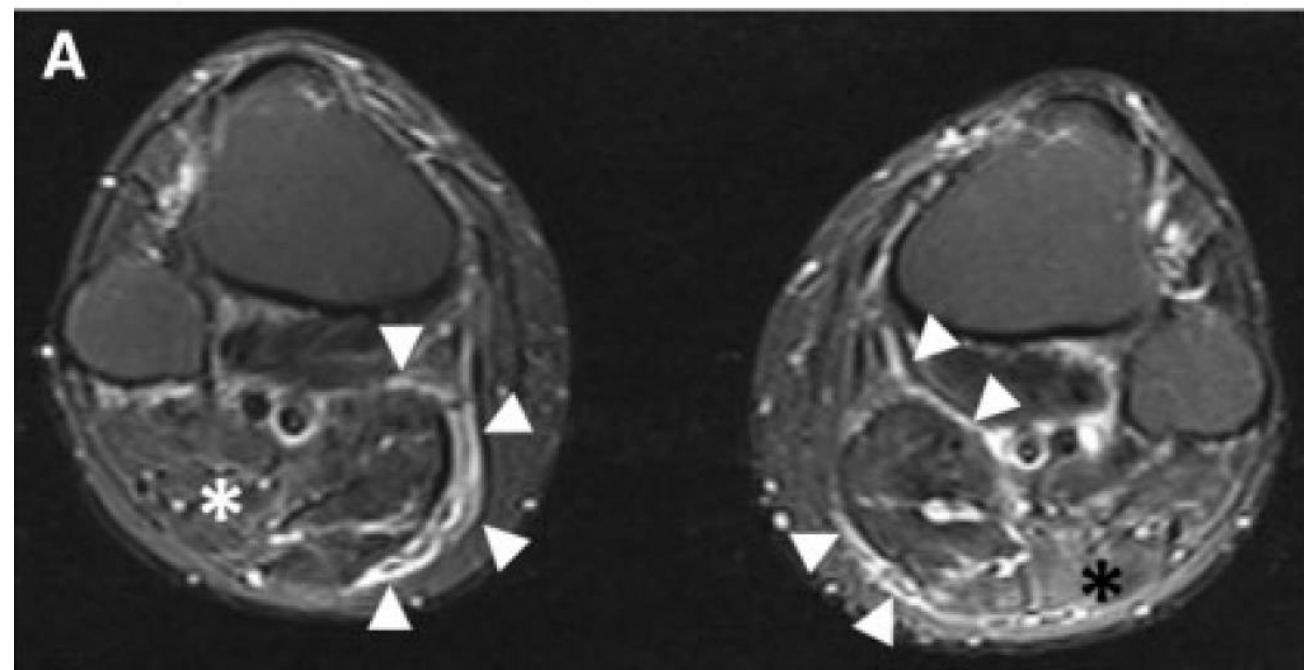
• **Prospective study to assess:**

1. Clinical
 2. **Imaging (MRI)**
- } characteristics of ICI-induced musculoskeletal manifestations
3. To explore potential associations between musculoskeletal manifestations and oncologic response

Demographics

- **male** predominance (80%)
- mean $\pm$ SEM **age** of **66.8 $\pm$ 2.6** years
- The median (range) **time from ICI treatment** since development of symptoms was **2.5 (1-22) months**
- ICI treatment: mostly **nivolumab (n=7)**



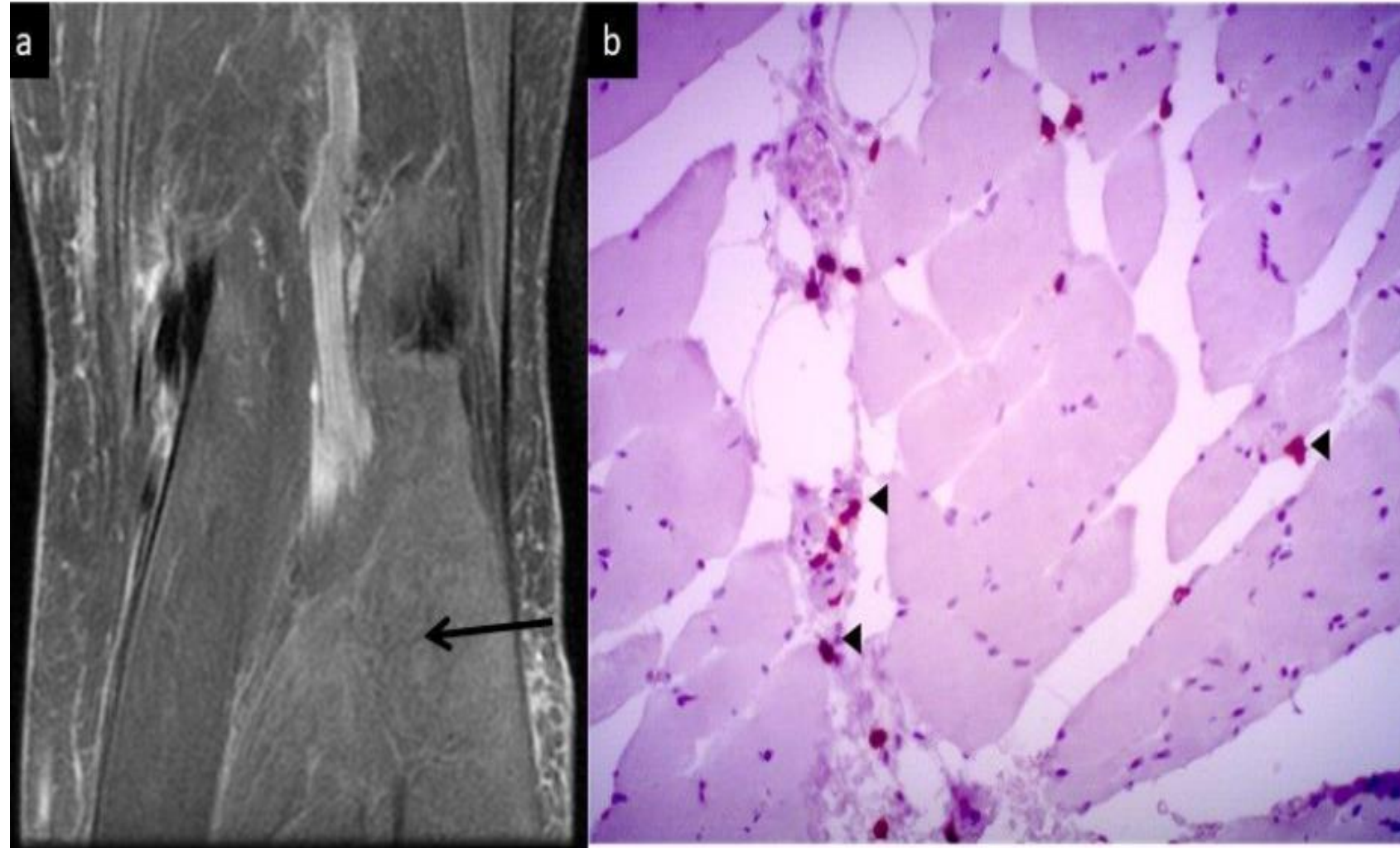


patient 8

- Male
- Age:67
- Nivolumab
- Type of cancer: renal

- Musculoskeletal manifestations:

Pain at left knee/thigh with no signs of arthritis



The imaging findings of myo-fasciitis correspond to tissue inflammatory infiltration at the histology level

Treatment , follow up, oncologic response



- Follow- up 6.5 months (median time)
- Most of patients (n=6) treated with **low/moderate dose of corticosteroids**
 - good clinical response

ONCOLOGIC RESPONSE

- **Favorable oncologic response (partial response or stable disease) in**

50% of patients with musculoskeletal ir-AE related to ICI administration

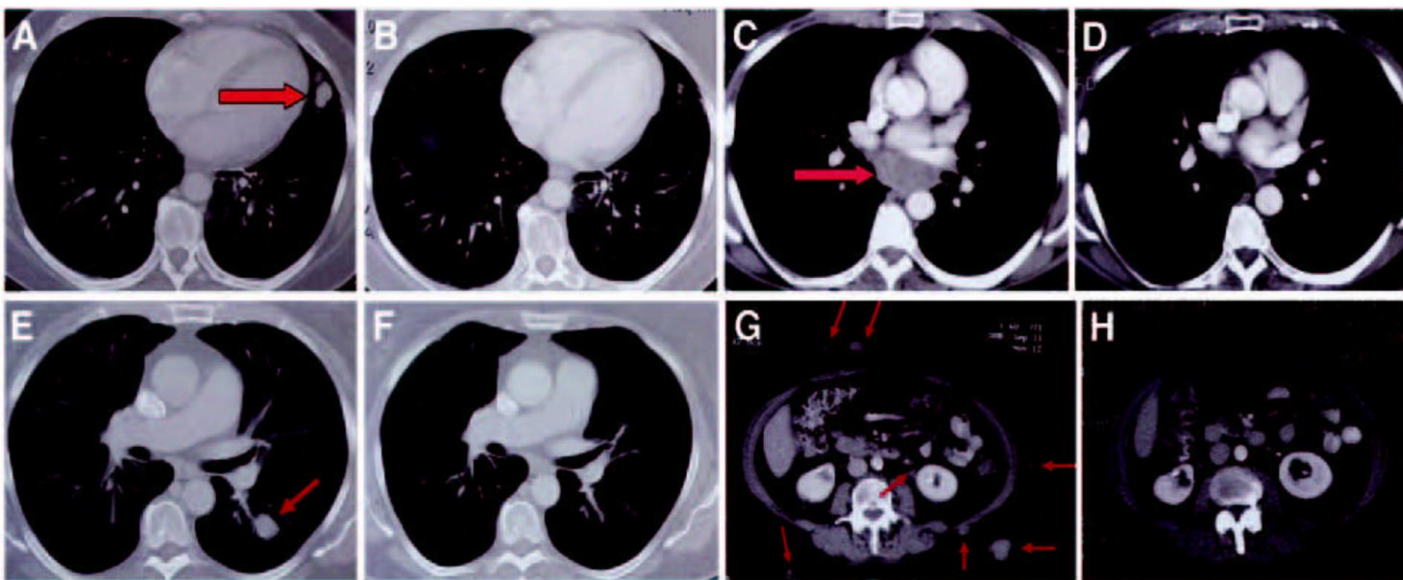
vs

12.5% of patients without musculoskeletal ir-AE

} p=0.0016

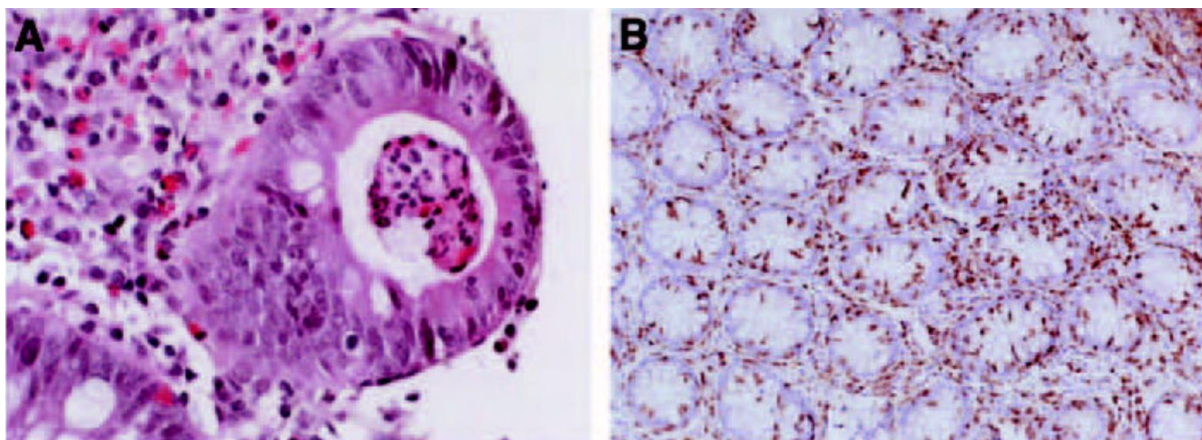
In our cohort

- Musculoskeletal manifestations in **7.7%**
- **Myo-fasciitis** is the prominent imaging finding in **MRI**
- The ICI induced musculoskeletal manifestations mostly involve **periarticular structures** and associate mainly with **myo-fasciitis** and **not** synovium based pathology
- **Favorable oncologic response** in patients with musculoskeletal ir-AE



Συσχέτιση ογκολογικής απάντησης και Ir-AE

- Φαίνεται πως υπάρχει αν και τα δεδομένα δεν είναι ακόμη ξεκάθαρα



NIH Public Access

Author Manuscript

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J Clin Oncol. 2005 September 1; 23(25): 6043–6053.

Autoimmunity Correlates With Tumor Regression in Patients With Metastatic Melanoma Treated With Anti-Cytotoxic T-Lymphocyte Antigen-4

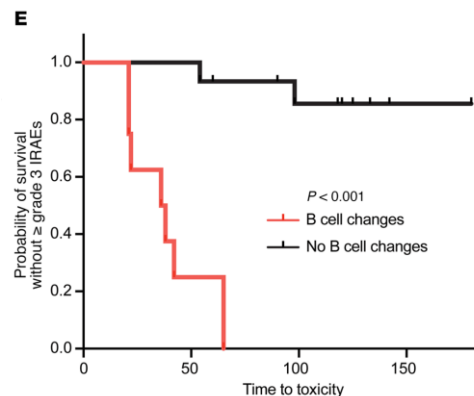
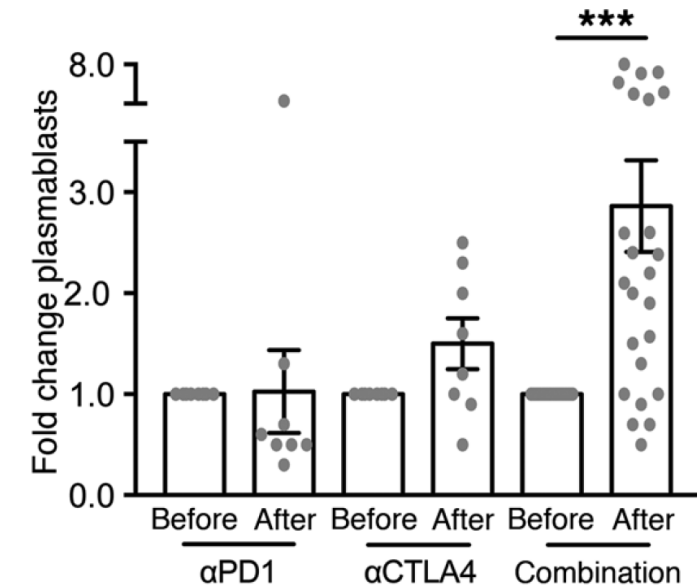
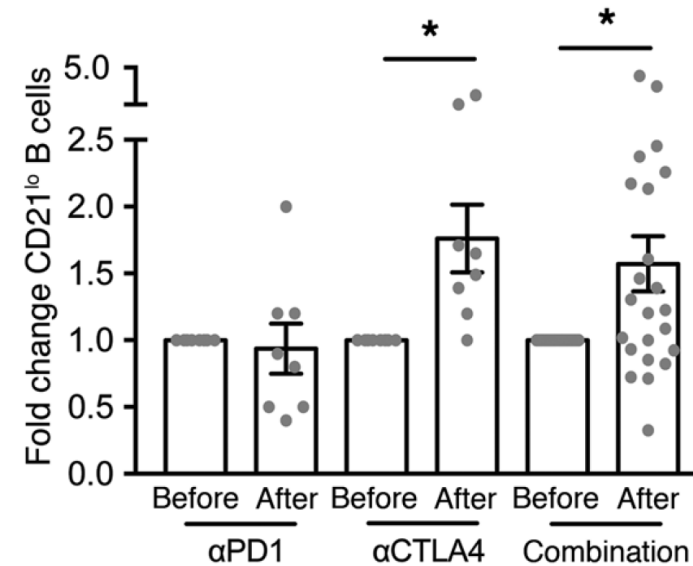
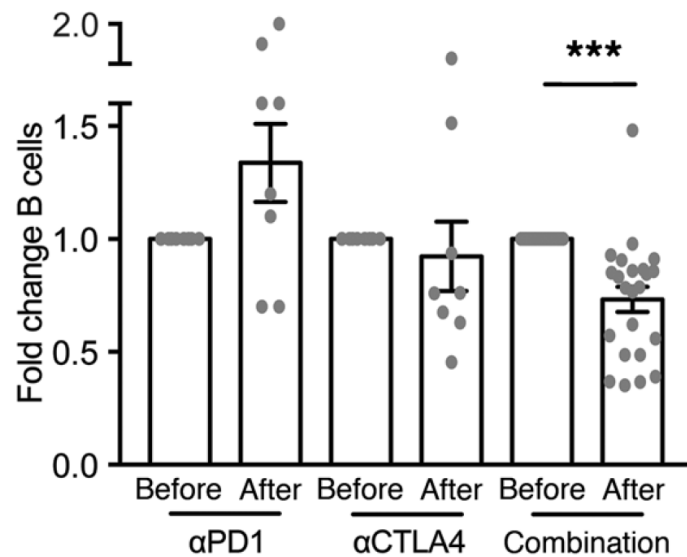
Peter Attia, Giao Q. Phan, Ajay V. Maker, Michael R. Robinson, Martha M. Quezado, James C. Yang, Richard M. Sherry, Suzanne L. Topalian, Udai S. Kammula, Richard E. Royal, Nicholas P. Restifo, Leah R. Haworth, Catherine Levy, Sharon A. Mavroukakis, Geoff Nichol, Michael J. Yellin, and Steven A. Rosenberg

From the Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; and Medarex Inc, Princeton, NJ.

Early B cell changes predict autoimmunity following combination immune checkpoint blockade

Rituparna Das,¹ Noffar Bar,¹ Michelle Ferreira,^{1,2} Aaron M. Newman,^{1,4} Lin Zhang,¹ Jithendra Kini Bailur,¹ Antonella Bacchiocchi,⁵ Harriet Kluger,¹ Wei Wei,⁶ Ruth Halaban,⁵ Mario Sznol,^{1,7} Madhav V. Dhodapkar,^{1,7,8} and Kavita M. Dhodapkar^{2,7}

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Αλλαγές σε B cells «προβλέπουν» Ir-AE
Αλλαγές σε T cells δεν ήταν προγνωστικές!!

Ποιοί ογκολογικοί ασθενείς θα απαντήσουν καλύτερα σε ασοσοθεραπεία?



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Author manuscript

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PD-L1 (B7-H1) and PD-1 Pathway Blockade for Cancer Therapy: Mechanisms, Response Biomarkers and Combinations

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¹Department of Surgery, University of Michigan School of Medicine, Ann Arbor, MI 48109

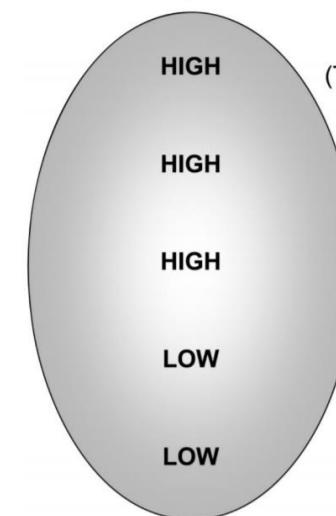
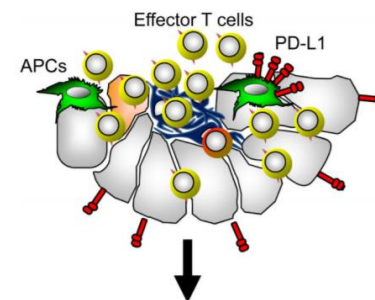
²Department of Medicine and Ludwig Center, Memorial Sloan Kettering Cancer Center, New York, NY 10065

³Department of Immunobiology, Yale University School of Medicine, New Haven, CT

- Προσπάθεια για ποσοτικοποίηση της ανοσολογικής πάντησης στον όγκο (Immunoscore)

Active response to treatment

"inflamed cancer"



Th1 type chemokines, CCL4 and T cells
(Th1 and CD8⁺ T cell trafficking and activation)

Neoantigens
(mutated/specific antigens)

PD-L1 expression
(Tumor, APCs)

immunosuppression
(Tregs, MDSCs)

Stemness
(Cancer stem-like, EMT type)

No or limited response to treatment

"non-inflamed cancer"

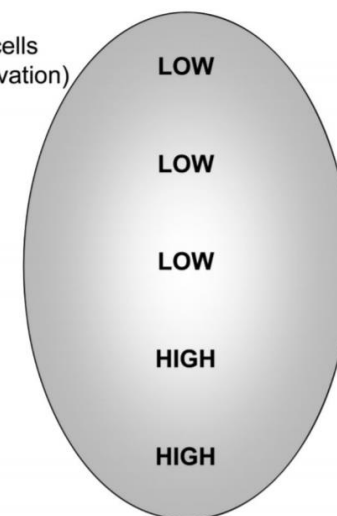
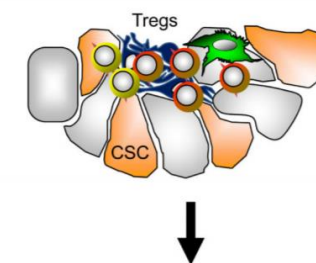
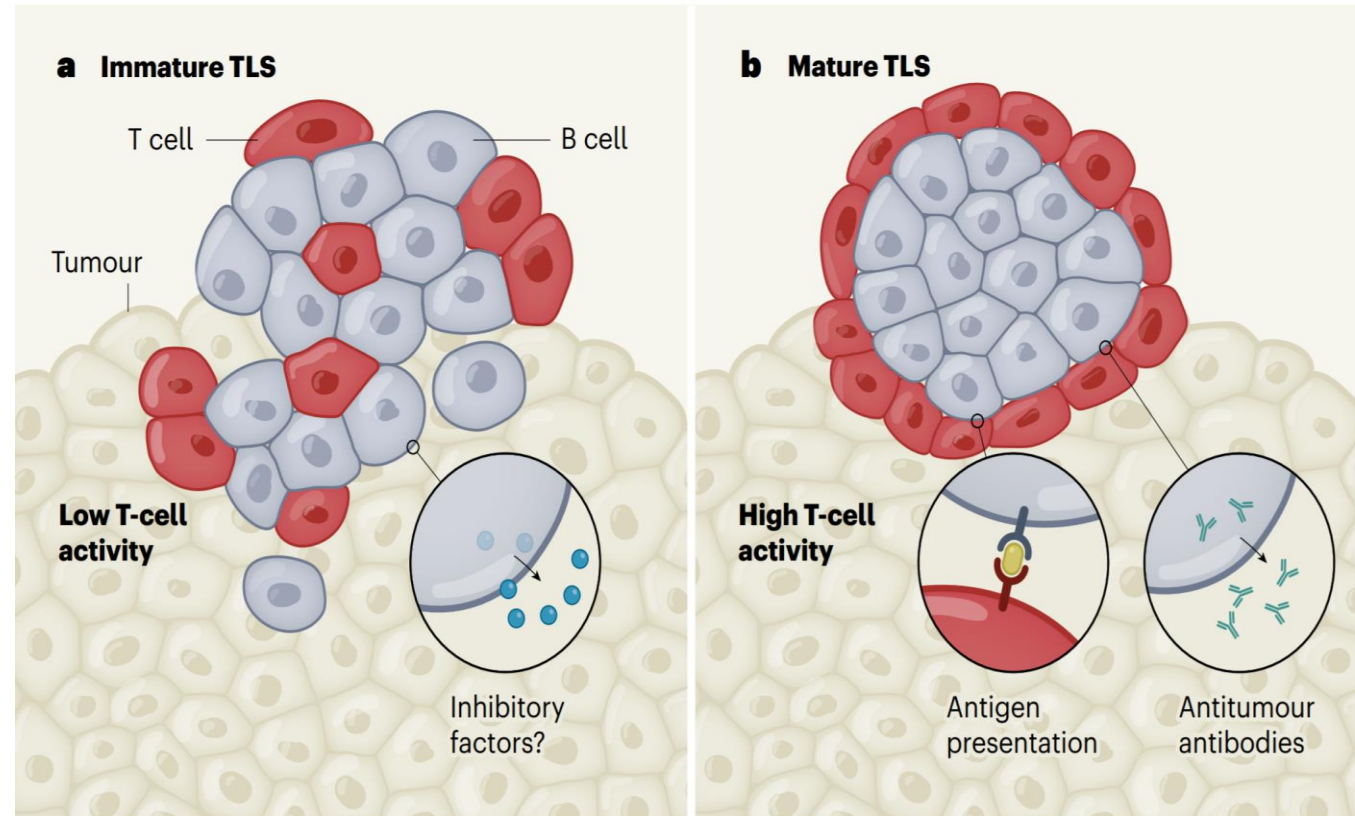


Figure 2

B cells to the forefront of immunotherapy

Tullia C. Bruno

Three studies reveal that the presence in tumours of two key immune components – B cells and tertiary lymphoid structures – is associated with favourable outcomes when individuals undergo immunotherapy. See p.549, p.556 & p.561



Είναι ασφαλής η επανέναρξη της ανοσοθεραπείας μετά από κάποιο συμβάν?

- Μάλλον ναι
- 50% κανένα συμβάν
- 24% το ίδιο συμβάν
- 26% ένα νέο συμβάν
- Σε απειλητική για την ζωή εκδήλωση δεν επαναχορηγούνται

Immune Checkpoint Inhibitors in Challenging Populations

Douglas B. Johnson, MD¹; Ryan J. Sullivan, MD²; and Alexander M. Menzies, MBBS³

- Μπορούν ασθενείς με γνωστή ρευματική νόσο να λαβουν ανοσοθεραπεία?
- Μάλλον ΝΑΙ. Λίγα δεδομένα καθώς αποκλείστηκαν από μελέτες
- 30% θα κάνουν ήπια έξαρση υποκείμενης νόσου
- 29% θα κάνουν ir-AE
- Καλό να αποφεύγεται η συνδυαστική ανοσοθεραπεία

Ποιοί ασθενείς πρέπει να παραπέμπονται σε ρευματολόγο

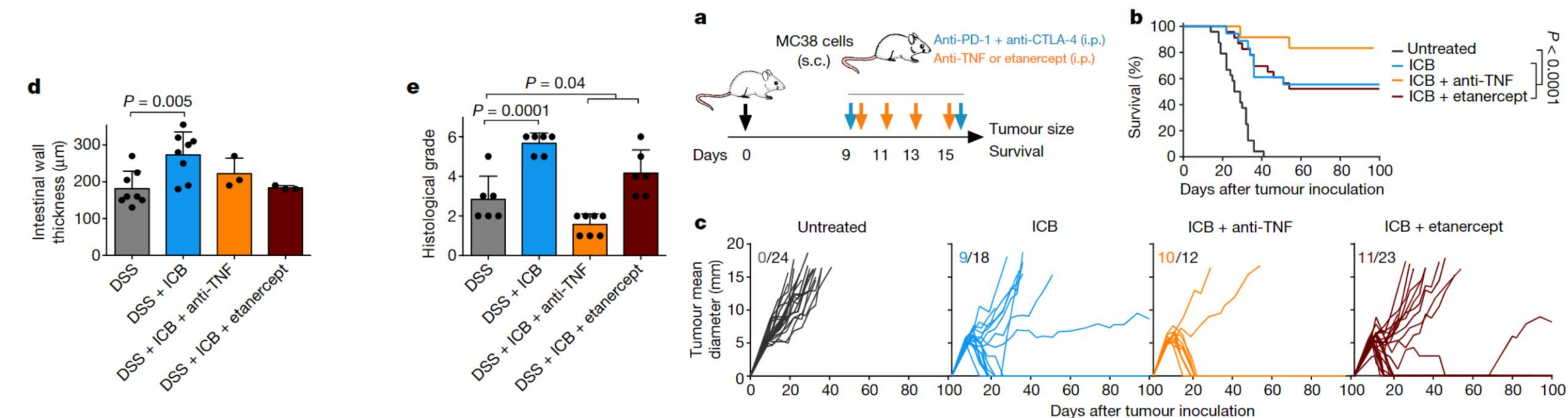
- Οι αρθραλγίες/μυαλγίες είναι πολύ συχνές σε ασθενείς με ανοσοθεραπεία. Όχι ιδιαίτερη κλινική σημασία
- Έχει νόημα η παραπομπή ασθενών με
 - «Φλεγμονώδη» συμπτωματολογία. Πρωινή δυσκαμψία (>30 min).
 - Λειτουργικό περιορισμό
 - Μη τραυματική διόγκωση αρθρώσεων

Πως θεραπεύονται οι μυοσκελετικές εκδηλώσεις?

- Σε ήπιες εκδηλώσεις ΜΣΑΦ/αναλγητικά
- Σε σοβαρότερες εκδηλώσεις
 - Καθυστέρηση επόμενης θεραπείας με check point inhibitors
 - Ανοσοκαταστολή με:
 - Pos στεροειδή-προσπάθεια για χορήγηση της μικρότερης δυνατής δόσης για το μικρότερο δυνατό διάστημα. DMARDs σε εμμένουσες εκδηλώσεις
 - Βιολογικές θεραπείες (anti-TNF)

Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy

Elisabeth Perez-Ruiz^{1,2,3,4,5}, Luna Minute^{1,2}, Itziar Otano^{1,2}, Maite Alvarez^{1,2}, Maria Carmen Ochoa^{1,2,6}, Virginia Belsue^{1,2}, Carlos de Andrea^{2,7}, Maria Esperanza Rodriguez-Ruiz^{1,3}, Jose Luis Perez-Gracia^{2,3,6}, Ivan Marquez-Rodas^{6,8}, Casilda Llacer⁹, Martina Alvarez^{5,10,11}, Vanesa de Luque^{5,10}, Carmen Molina^{1,2}, Alvaro Teijeira^{1,2,6}, Pedro Berraondo^{1,2,6,13*} & Ignacio Melero^{1,2,3,6,12,13*}





Ευχαριστώ

Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—clinical aspects and relationship with tumour response: a single-centre prospective cohort study

Marie Kostine,¹ Léa Rouxel,¹ Thomas Barnetche,¹ Rémi Veillon,² Florent Martin,² Caroline Dutriaux,³ Léa Dousset,³ Anne Pham-Ledard,³ Sorilla Prey,³ Marie Beylot-Barry,³ Amaury Daste,⁴ Marine Gross-Goupil,⁴ Julie Lallier,⁴ Alain Ravaud,⁴ Edouard Forcade,⁵ Bernard Bannwarth,¹ Marie-Elise Truchetet,¹ Christophe Richez,¹ Nadia Mehsen,¹ Thierry Schaevebeke,¹ and on behalf of the FHU ACRONIM

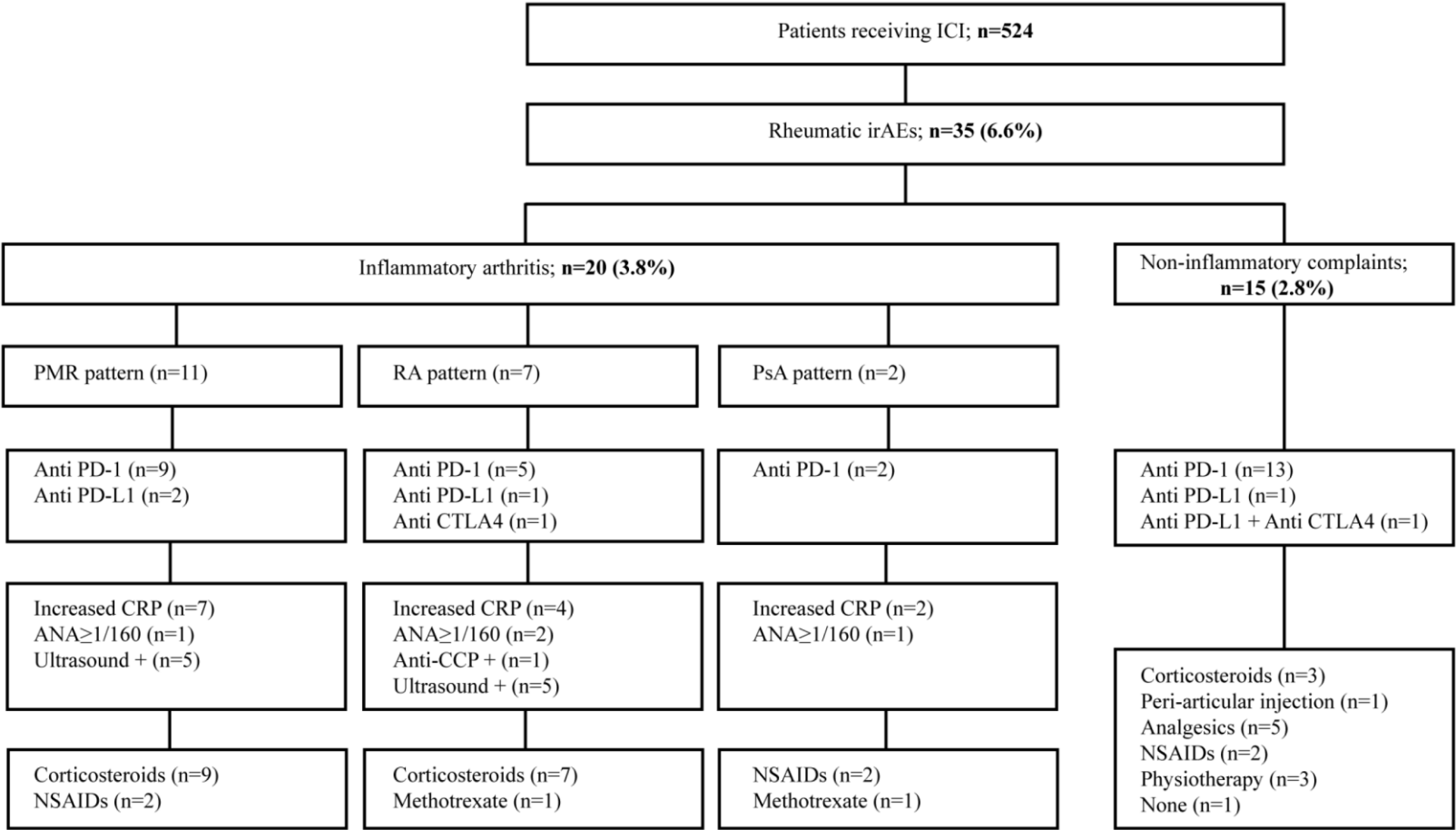
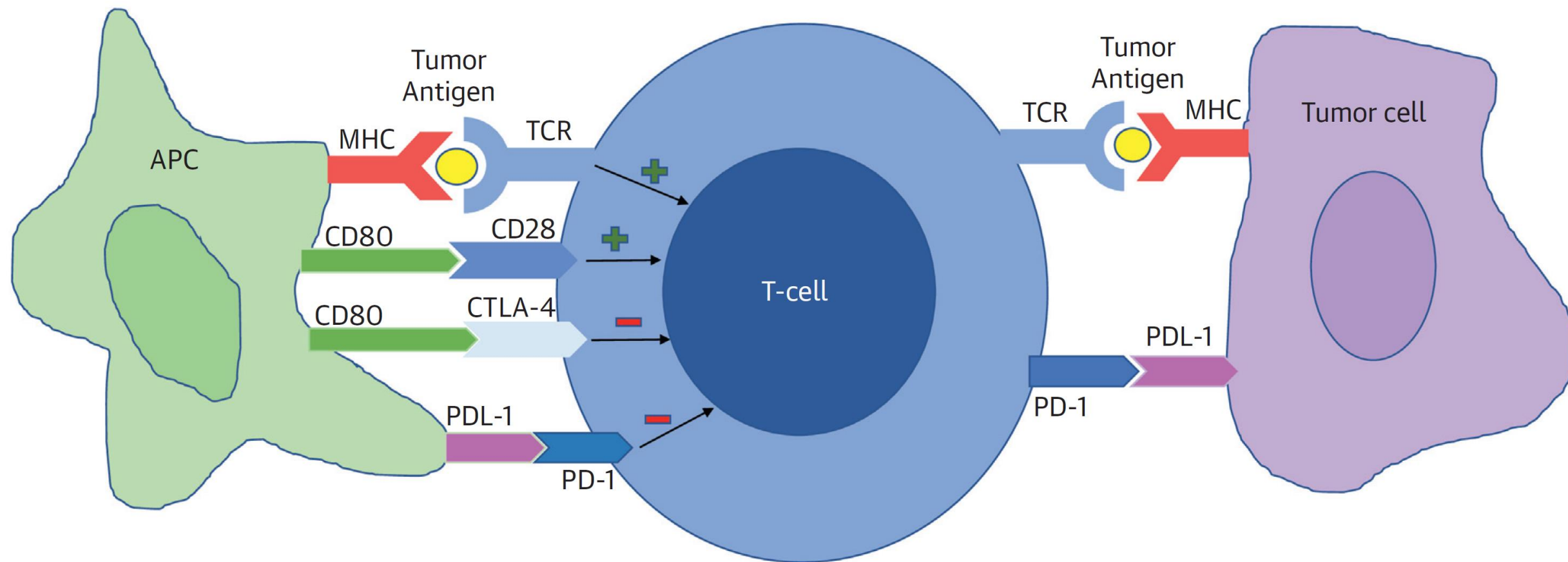
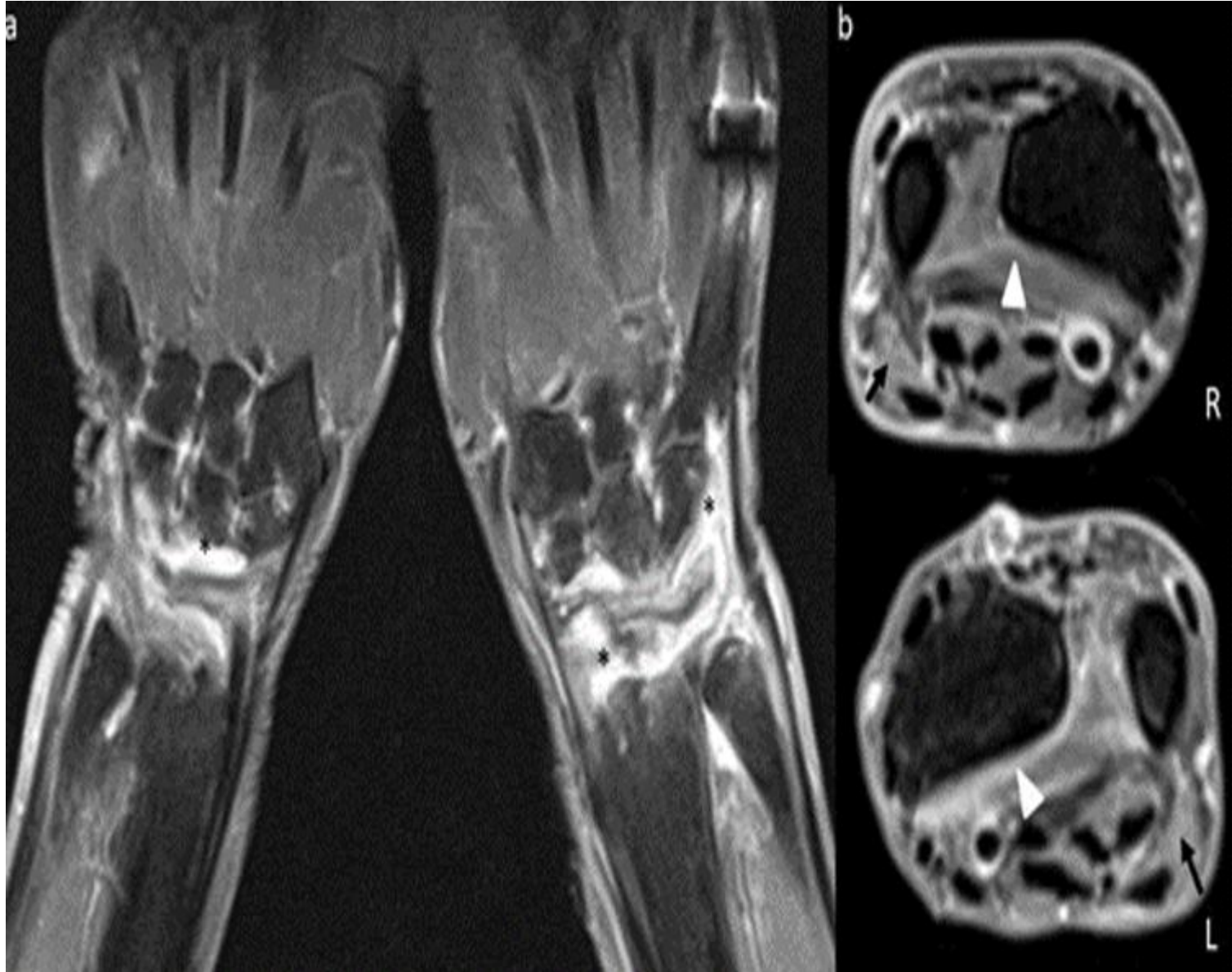


FIGURE 1 Immune Checkpoints in the Tumor Microenvironment



patient 2

- Male
- Age: 71
- Nivolumab
- Type of cancer: Lung
- Musculoskeletal manifestations:
Diffuse painful swelling of hands
and right foot

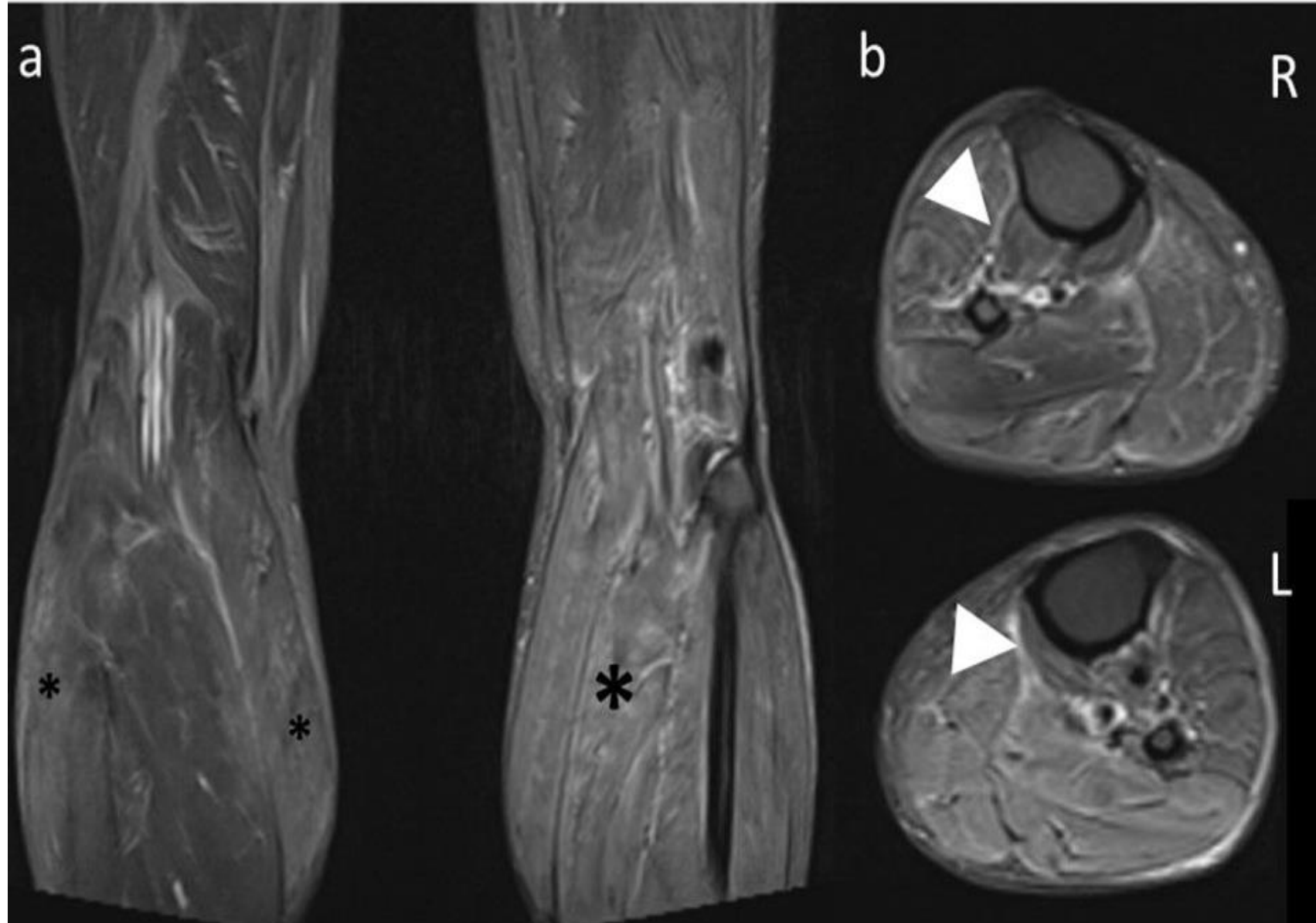


patient 7

- Male
- Age:68
- Nivolumab
- Type of cancer: bladder

- Musculoskeletal manifestations:

Pain of right knee



Πότε και ποιοί θα εμφανίσουν τοξικότητα?



ARTICLE

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OPEN

Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis

Krista Dubin^{1,2,3}, Margaret K. Callahan^{4,5}, Boyu Ren⁶, Raya Khanin⁷, Agnes Viale⁸, Lilan Ling², Daniel No², Asia Gobourne², Eric Littmann², Curtis Huttenhower^{6,9}, Eric G. Pamer^{1,2,10,*} & Jedd D. Wolchok^{4,5,10,11,*}

- Συνήθως στις πρώτες εβδομάδες με μήνες
- Γενετικοί παράγοντες εως τώρα δεν έχουν εντοπιστεί
- Επικράτηση Bacteroidetes phylum σχετίζεται με μειωμένη τοξικότητα (κολίτιδα) από ipilimumab.
- Χρήση προβιοτικών/αντιβιοτικών??

Review

Gut microbiome and anticancer immune response: really hot Sh*t!

S Viaud^{1,2}, R Daillère^{1,2}, IG Boneca^{3,4}, P Lepage^{5,6}, P Langella^{5,6}, M Chamaillard^{7,8,9,10}, MJ Pittet¹¹, F Ghiringhelli^{12,13,14}, G Trinchieri¹⁵, R Goldszmid¹⁵ and L Zitvogel^{1,2,16}

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy

Ayelet Sivan,^{1*} Leticia Corrales,^{1*} Nathaniel Hubert,² Jason B. Williams,¹ Keston Aquino-Michaels,³ Zachary M. Earley,² Franco W. Benyamin,¹ Yuk Man Lei,² Bana Jabri,² Maria-Luisa Alegre,² Eugene B. Chang,² Thomas F. Gajewski^{1,2†}

