Ανοσοεπαγόμενες ανεπιθύμητες ενέργειες στα πλαίσια αντικαρκινικής ανοσοθεραπείας Θεραπευτική αντιμετώπιση

ΕΠΕΝΜΥ 2023, Βολος

Δαούσης Δημήτρης
Αναπλ. καθηγητής Παθολογίας/Ρευματολογίας
Ιατρική Σχολή Πανεπιστημίου Πατρών

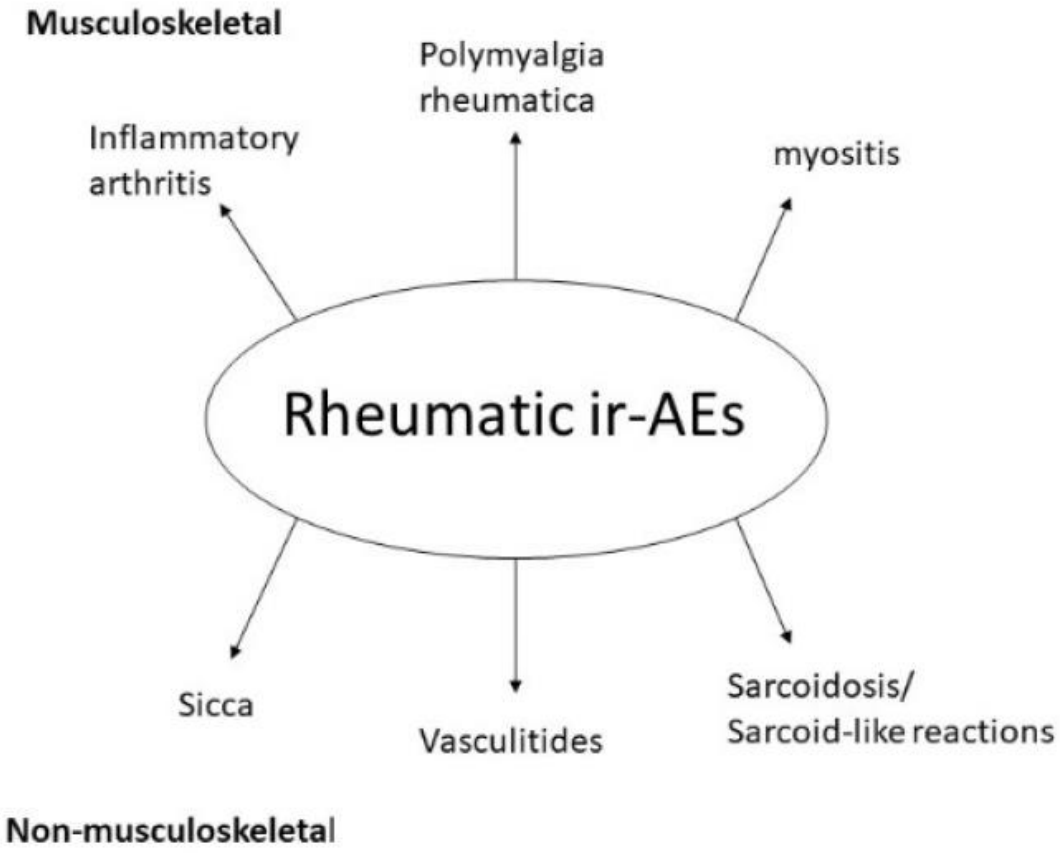
Σύγκρουση συμφερόντων

- Τιμητική αμοιβή για ομιλίες και συμμετοχή σε advisory boards από τις εταιρείες UCB, Pfizer, Novartis, BMS, MSD, Janssen, Abbvie,Lilly, Aenorasis

Οι ρευματικές εκδηλώσεις ποικίλουν…

Πιο συχνές με anti-PD-1/PDL-1

Συνήθως όχι αυτοαντισώματα



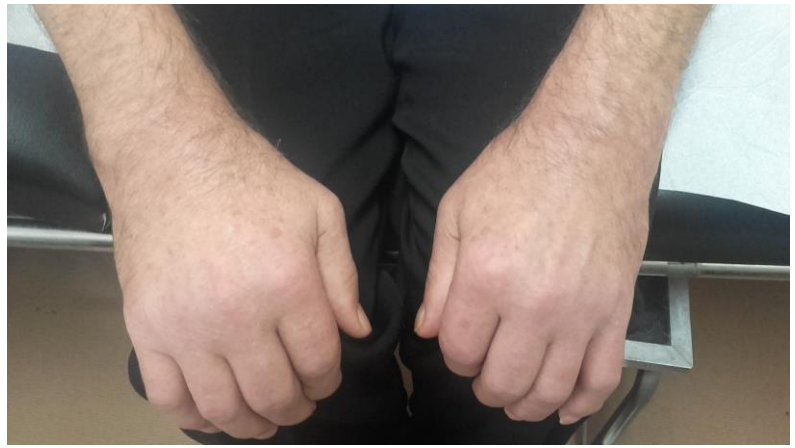
International Journal of *Molecular Sciences*

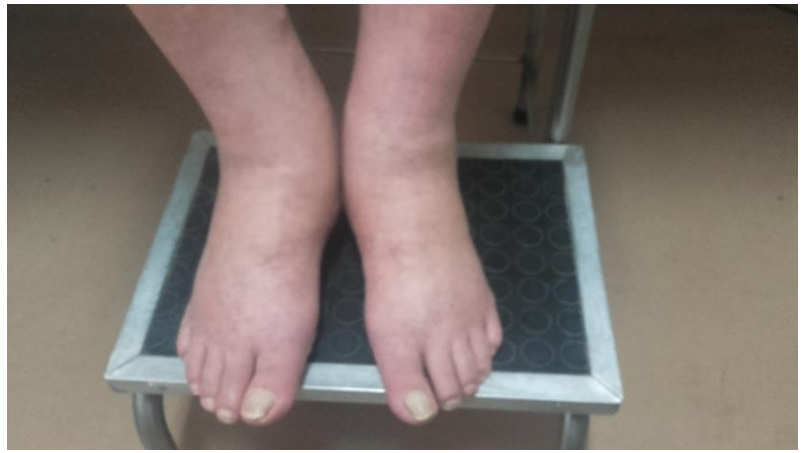
MDPI

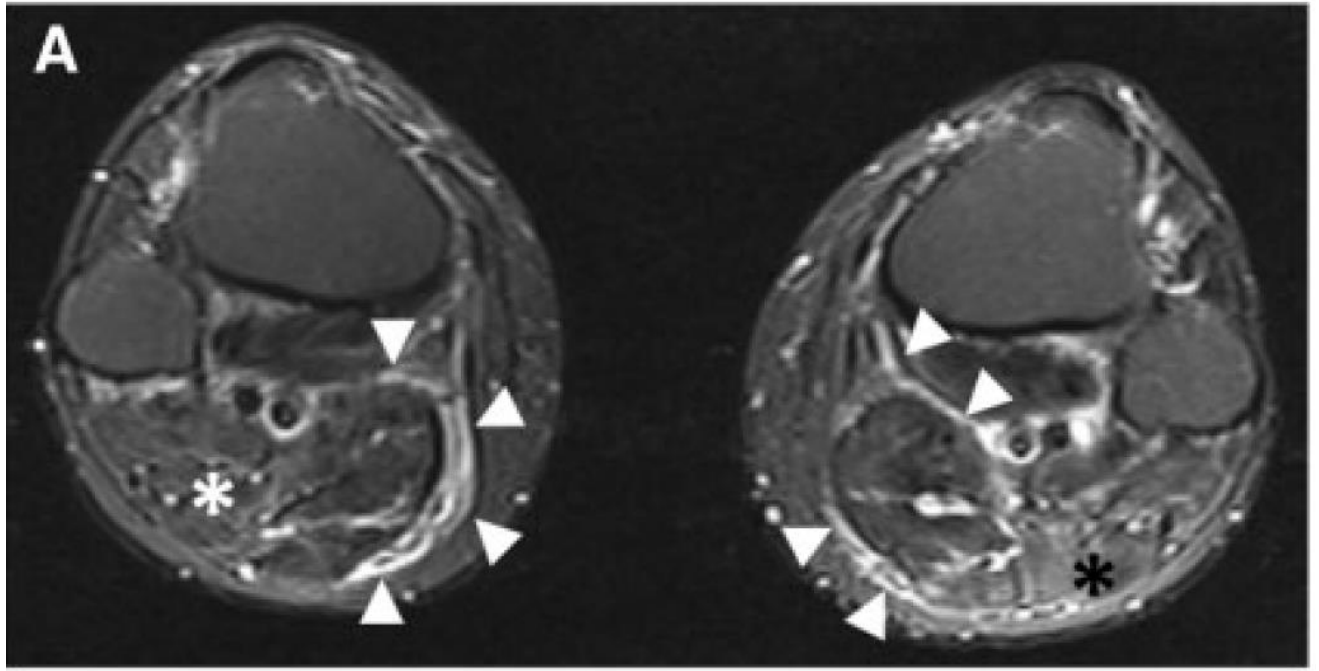
Review

Rheumatic Manifestations in Patients Treated with Immune Checkpoint Inhibitors

Konstantinos Melissaropoulos [1,†], Kalliopi Klavdianou [2,†], Alexandra Filippopoulou [3], Fotini Kalofonou [4], Haralabos Kalofonos [5] and Dimitrios Daoussis [3,*]



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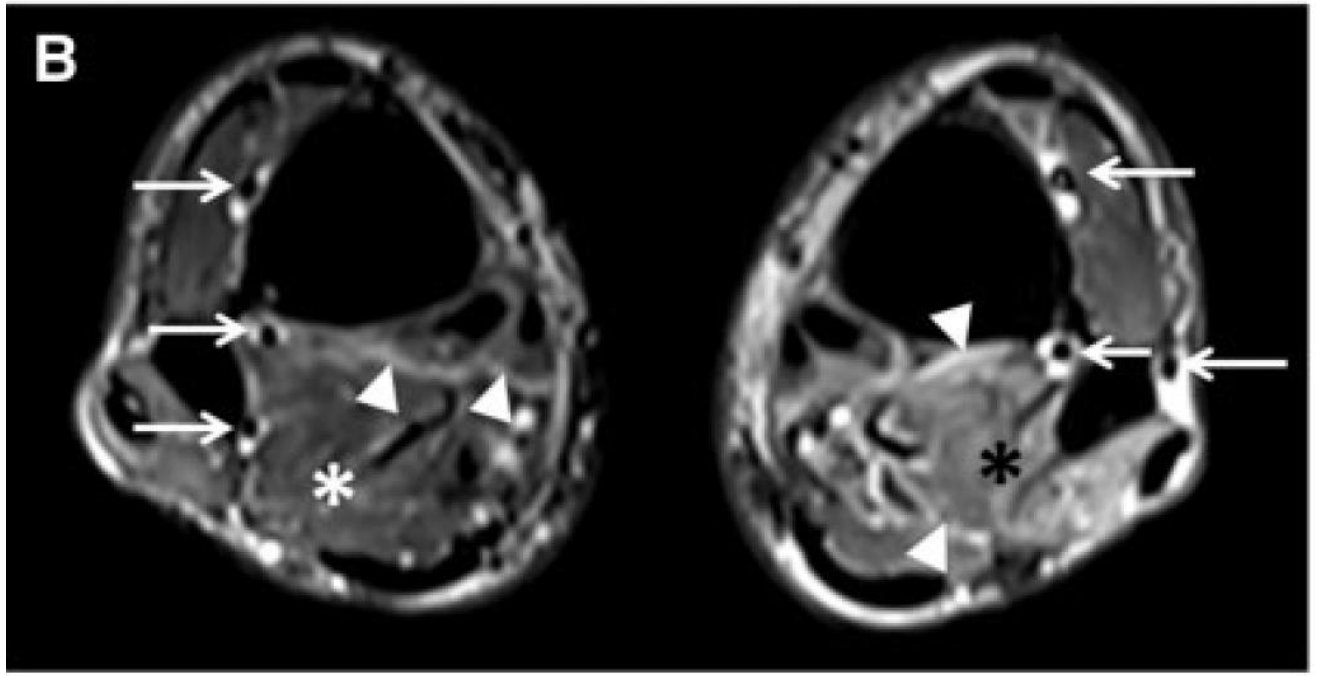

B

RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/kez361

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

Dimitrios Daoussis[1,*], Pantelis Kraniotis[2,*], Alexandra Filippopoulou[1], Rafaella Argiriadi[3], Spyridoula Theodoraki[3], Thomas Makatsoris[3], Angelos Koutras[3], Ioannis Kehagias[4], Dionysios J. Papachristou[5], Aikaterini Solomou[2], Haralabos Kalofonos[3] and Stamatis-Nick Liossis[1]

- **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

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

Ποιοί ασθενείς πρέπει να παραπέμπονται σε ρευματολόγο

- Οι αρθραλγίες/μυαλγίες είναι πολύ συχνές σε ασθενείς με ανοσοθεραπεία. Όχι ιδιαίτερη κλινική σημασία
- Εχει 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/anti-IL6)

Comparative safety and effectiveness of TNF inhibitors, IL6 inhibitors and methotrexate for the treatment of immune checkpoint inhibitor-associated arthritis

Anne R Bass [1,2] Noha Abdel-Wahab,[3] Pankti D Reid [4] Jeffrey A Sparks [5] Cassandra Calabrese [6] Deanna P Jannat-Khah [7,8] Nilasha Ghosh [1,2] Divya Rajesh,[9] Carlos Andres Aude [7] Lydia Gedmintas,[10] Lindsey MacFarlane,[10] Senada Arabelovic,[10] Adewunmi Falohun,[3] Komal Mushtaq,[11] Farah Al Haj,[12] Adi Diab,[13] Ami A Shah,[14] Clifton O Bingham [15] Karmela Kim Chan [1,2] Laura C Cappelli [15]

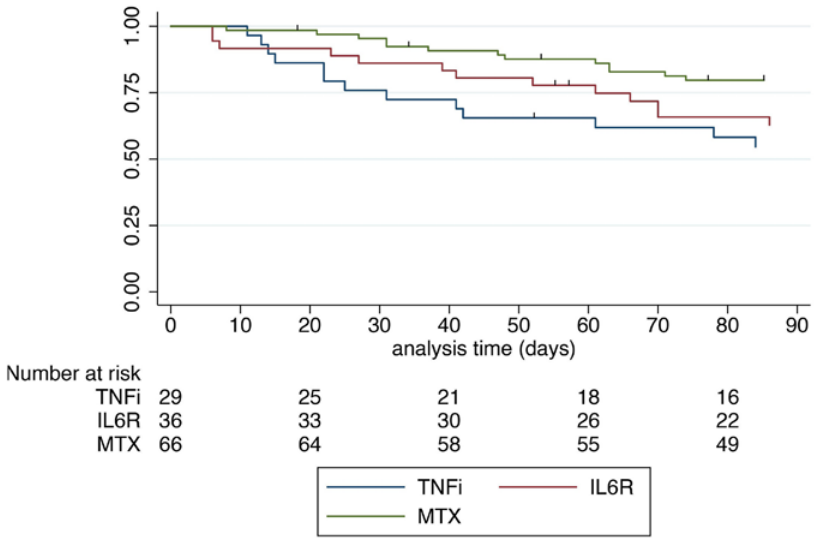
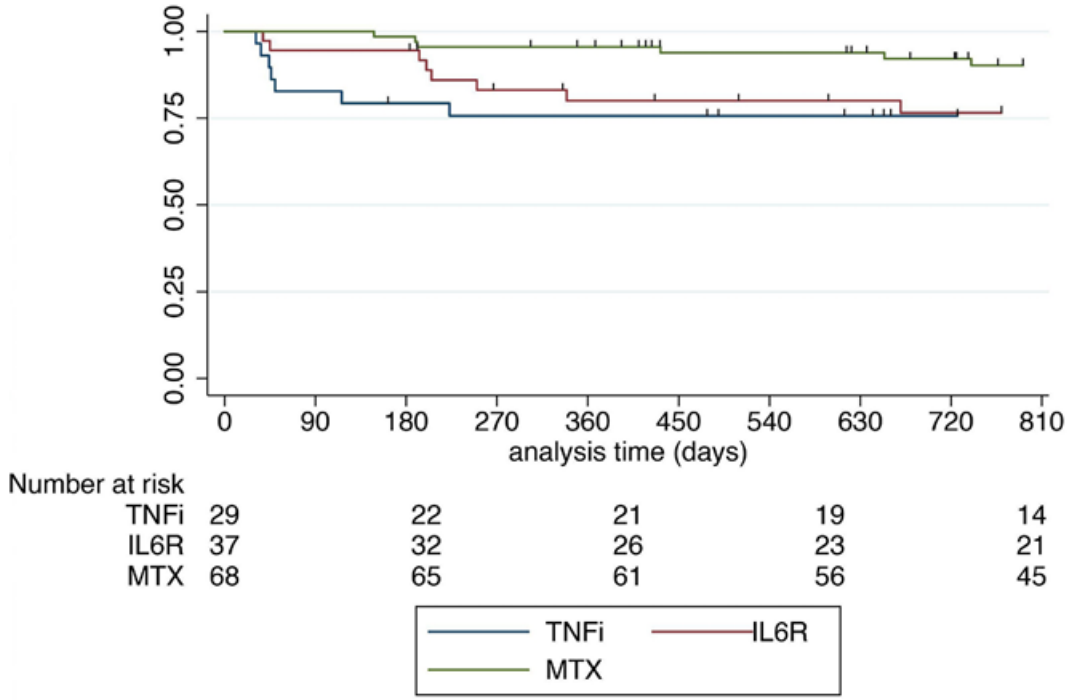


Figure 4 Kaplan-Meier survival estimates: time to arthritis control from disease-modifying antirheumatic drug initiation within the first 90 days. IL6R, interleukin-6 receptor; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor.



Νεότερες θεραπείες για σοβαρές IrAE

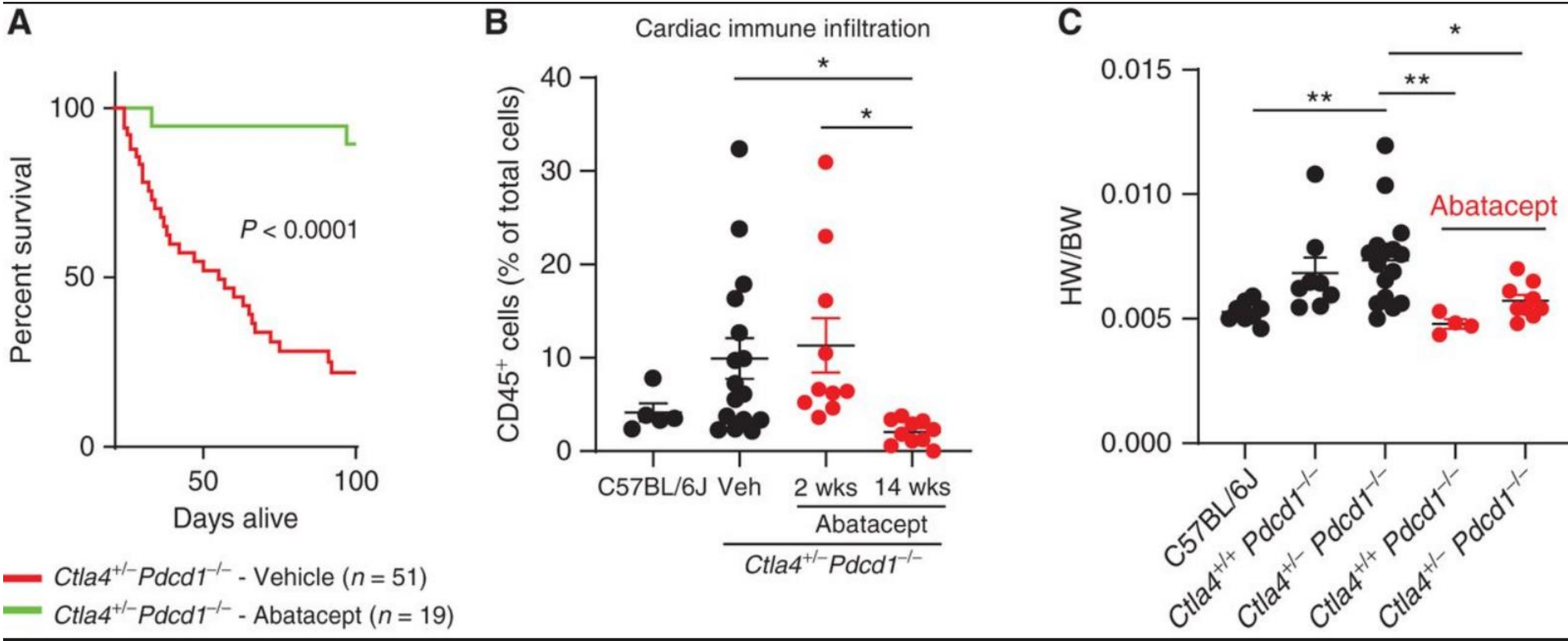
- Κλινικές μελέτες
- Πνευμονίτιδα Infliximab vs IVIG
- Κολίτιδα Infliximab vs vedolizumab

- Νευρολογικά σύνδρομα Rituximab (myasthenia gravis)
- Μυοκαρδίτιδα abatacept/belatacept

RESEARCH BRIEFS | AUTHOR CHOICE | MARCH 02 2021

A Genetic Mouse Model Recapitulates Immune Checkpoint Inhibitor–Associated Myocarditis and Supports a Mechanism-Based Therapeutic Intervention

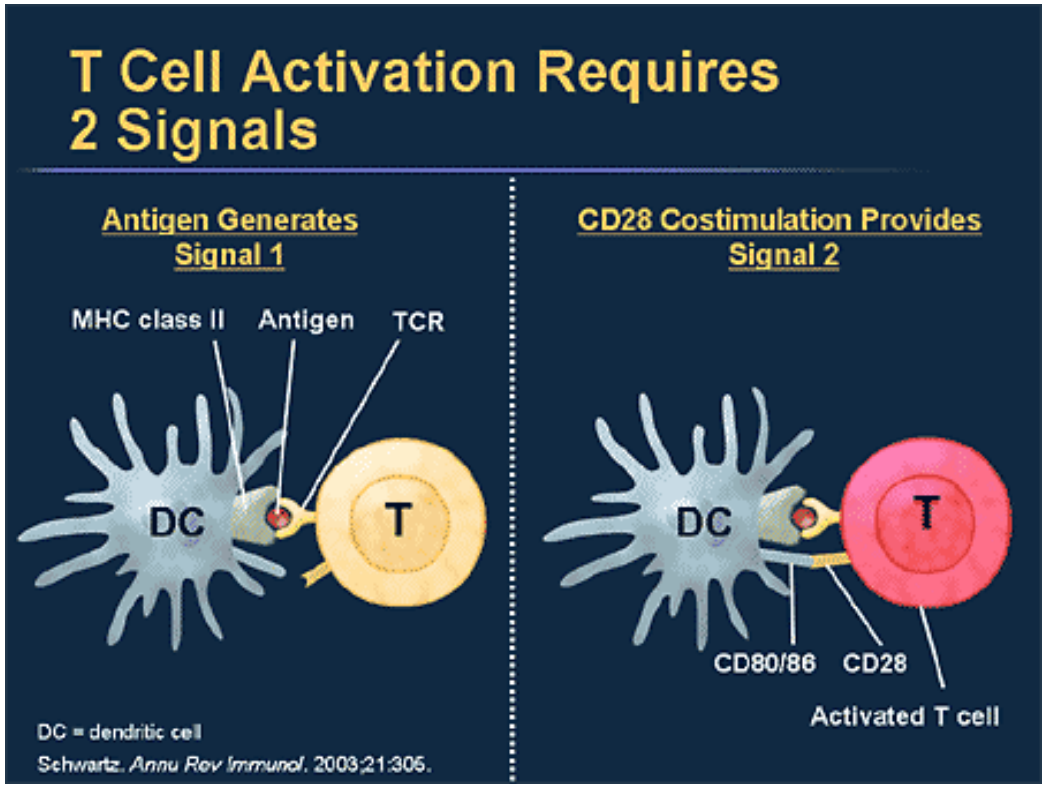
Spencer C. Wei ; Wouter C. Meijers; Margaret L. Axelrod ; Nana-Ama A.S. Anang ; Elles M. Screever; Elizabeth C. Wescott ; Douglas B. Johnson; Elizabeth Whitley; Lorenz Lehmann; Pierre-Yves Courand; James J. Mancuso; Lauren E. Himmel ; Benedicte Lebrun-Vignes; Matthew J. Wieklinski; Bjorn C. Knollmann; Jayashree Srinivasan ; Yu Li; Oluwatomisin T. Atolagbe; Xiayu Rao; Yang Zhao; Jing Wang; Lauren I.R. Ehrlich; Padmanee Sharma; Joe-Elie Salem ; Justin M. Balko ; Javid J. Moslehi ; James P. Allison

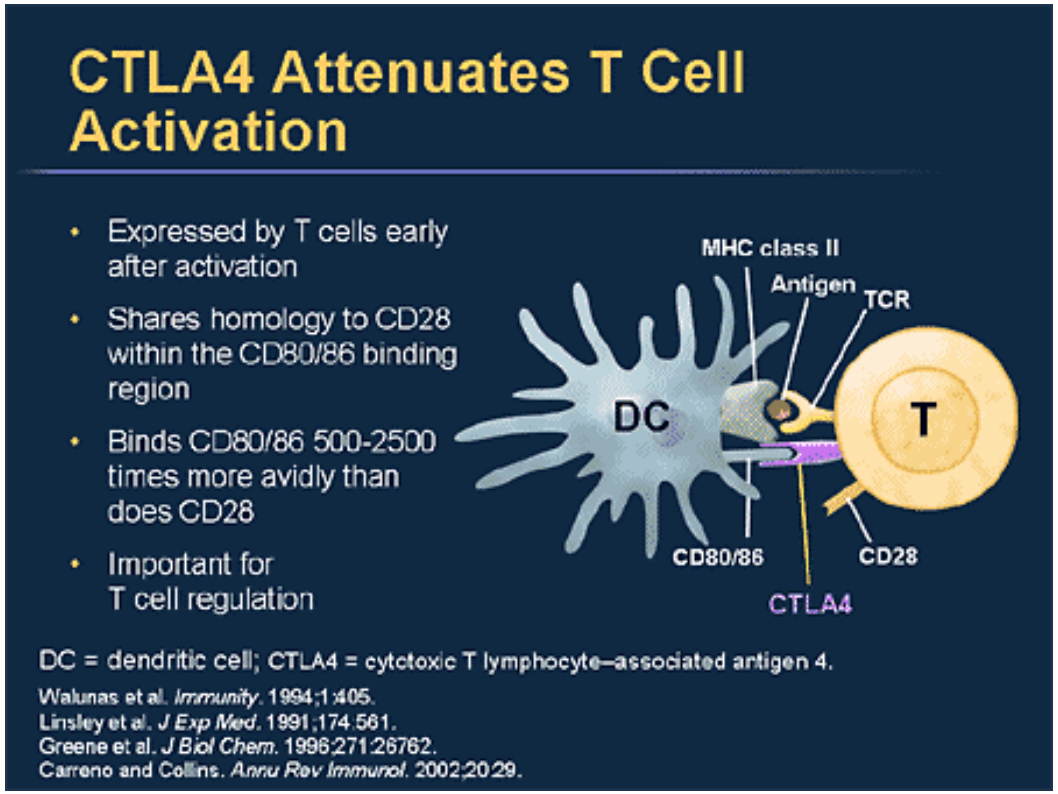


Science Translational Medicine
Current Issue First release papers

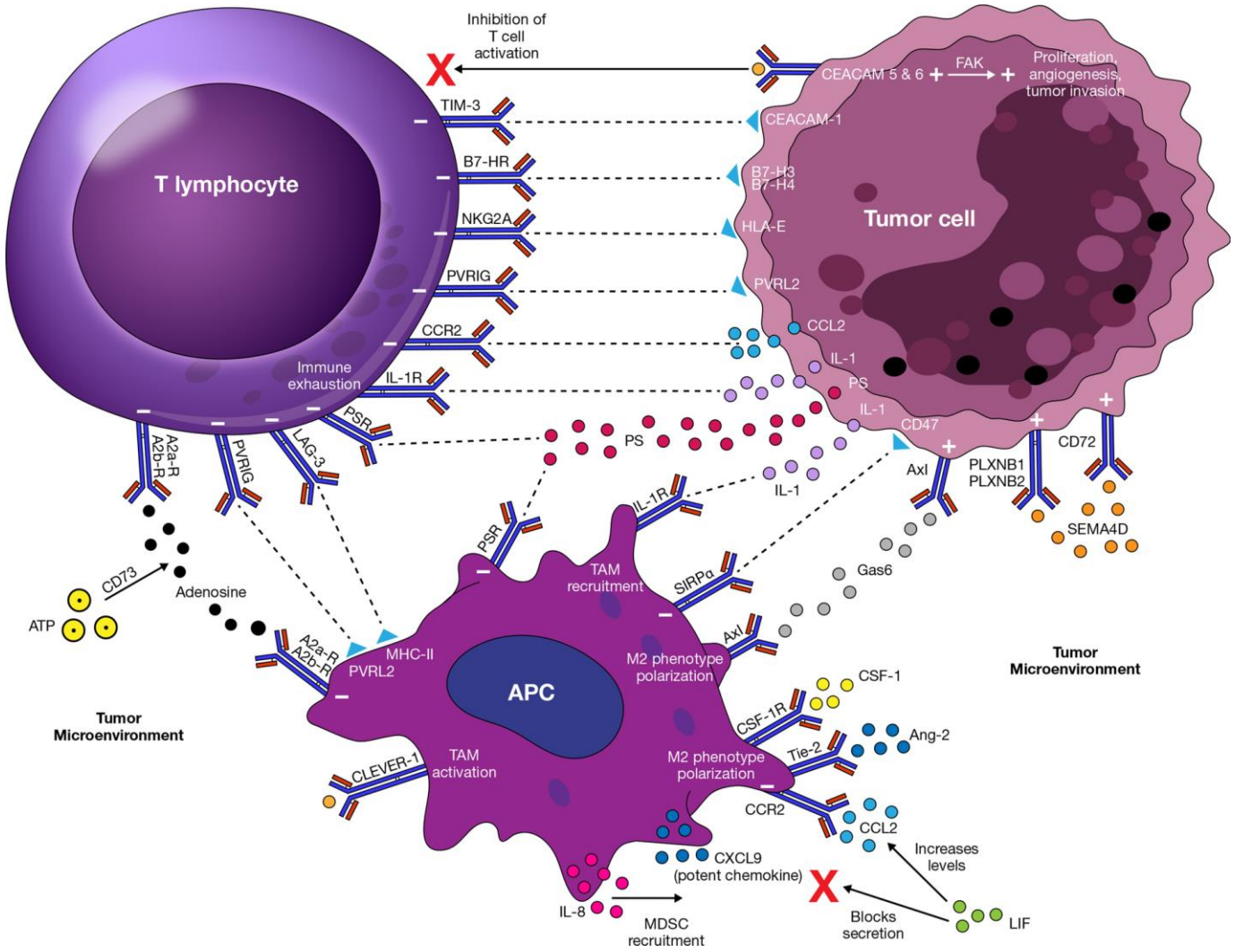
RESEARCH ARTICLE | CANCER IMMUNOTHERAPY

Soluble CTLA-4 mutants ameliorate immune-related adverse events but preserve efficacy of CTLA-4– and PD-1–targeted immunotherapy





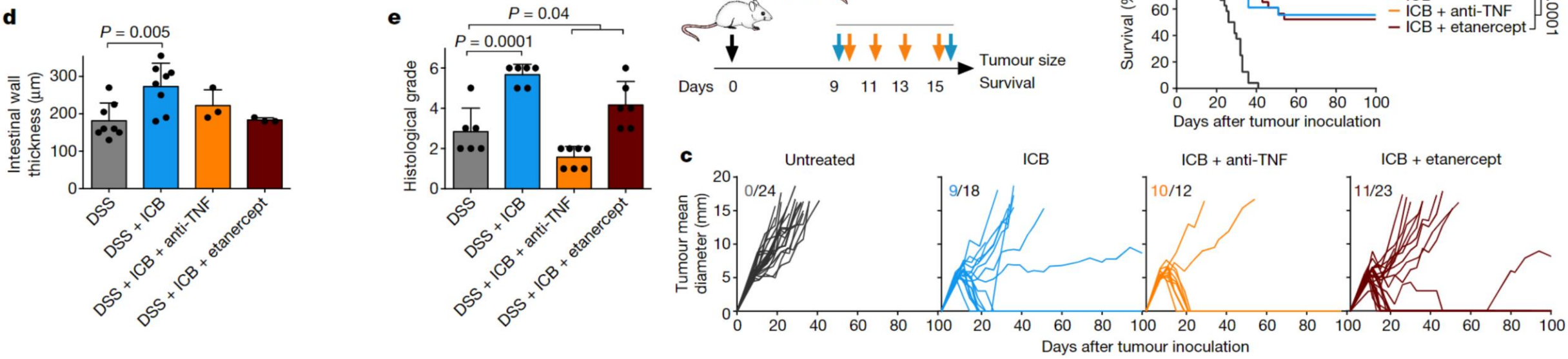
Πολλοί νέοι στόχοι στο άμεσο μέλλον…



https://doi.org/10.1038/s41586-019-1162-y

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 Llacer[9], 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]*



Badran et al. Journal for ImmunoTherapy of Cancer (2019) 7:226
https://doi.org/10.1186/s40425-019-0711-0

Journal for ImmunoTherapy of Cancer

SHORT REPORT Open Access

Concurrent therapy with immune checkpoint inhibitors and TNFα blockade in patients with gastrointestinal immune-related adverse events

Yousef R. Badran[1,2], Justine V. Cohen[2,3], Priscilla K. Brastianos[2,3], Aparna R. Parikh[2,3], Theodore S. Hong[2,4] and Michael Dougan[2,5*]

Case presentations: Five patients with different primary malignancies were treated with ipilimumab/nivolumab (2 patients), pembrolizumab (1 patient), ipilimumab (1 patient), or cemiplimab (1 patient). All patients developed irEC within 40 days of their first ICI dose. The patients presented with a combination of upper and lower gastrointestinal symptoms and subsequently underwent upper endoscopy and/or lower endoscopy. Endoscopy results demonstrated a spectrum of acute inflammatory changes across the gastrointestinal tract. Steroid therapy was used as first line treatment. To prevent prolonged steroid use and recurrence of gastrointestinal inflammation after resumption of cancer therapy, patients were treated concurrently with infliximab and ICI. Patients tolerated further ICI therapy with no recurrence of symptoms. Repeat endoscopies showed resolution of acute inflammation and restaging imaging showed no cancer progression.

Conclusions: Concurrent treatment with anti-TNFα and ICI appears to be safe, facilitates steroid tapering, and prevents irEC. Prospective clinical trials are needed to assess the outcomes of this treatment modality.

Should we be Afraid of Immune Check Point Inhibitors in Cancer Patients with Pre-Existing Rheumatic Diseases? Immunotherapy in Pre-Existing Rheumatic Diseases

Kalliopi Klavdianou, Konstantinos Melissaropoulos, Alexandra Filippopoulou, Dimitrios Daoussis

Mediterr J Rheumatol 2021;32(3):218-26

- Μπορούν ασθενείς με γνωστή ρευματική νόσο να λαβουν ανοσοθεραπεία?
- Μάλλον ΝΑΙ. Λίγα δεδομένα καθώς αποκλείστηκαν από μελέτες
- Καλό να αποφεύγεται η συνδυαστική ανοσοθεραπεία

Table 1. Cases of pre-existing autoimmune diseases (PAD) on immune-checkpoint inhibitor (ICI) therapy retrieved from literature.

PAD	Cases, n	Flare, n (%)	De novo irAE, n (%)	Refs
Rheumatoid arthritis	66	37 (56)	20 (30)	[14-15], [17-22]
Polymyalgia rheumatica	30	17 (57)	10 (33)	[14-15], [17-18], [20-23]
Psoriatic arthritis	14	11 (79)	3 (21)	[14-15], [18], [21], [23], [26], [28-31]
Inflammatory myopathy	3	1 (33)	1 (33)	[17], [22], [33]
Spondyloarthritis	13	3 (23)	1 (8)	[17], [20-22], [29-30]
Vasculitis *ANCA-associated* *Polyarteritis nodosa* *Giant cell arteritis*	 6 1 6	 2 (33) 0 (0) 4 (67)	 2 (33) 0 (0) 5 (83)	 [17-18], [21], [34-38]
Sarcoidosis	16	3 (19)	4 (25)	[14], [17], [20-22], [26], [30], [39-40]
Sicca-Sjögren's	12	3 (25)	1 (8)	[15], [17-18], [20-21]
Systemic lupus erythematosus	15	4 (27)	0 (0)	[14], [17-18], [20], [30], [41-42]
Systemic sclerosis	9	1 (11)	0 (0)	[15], [17-18],[23], [29]

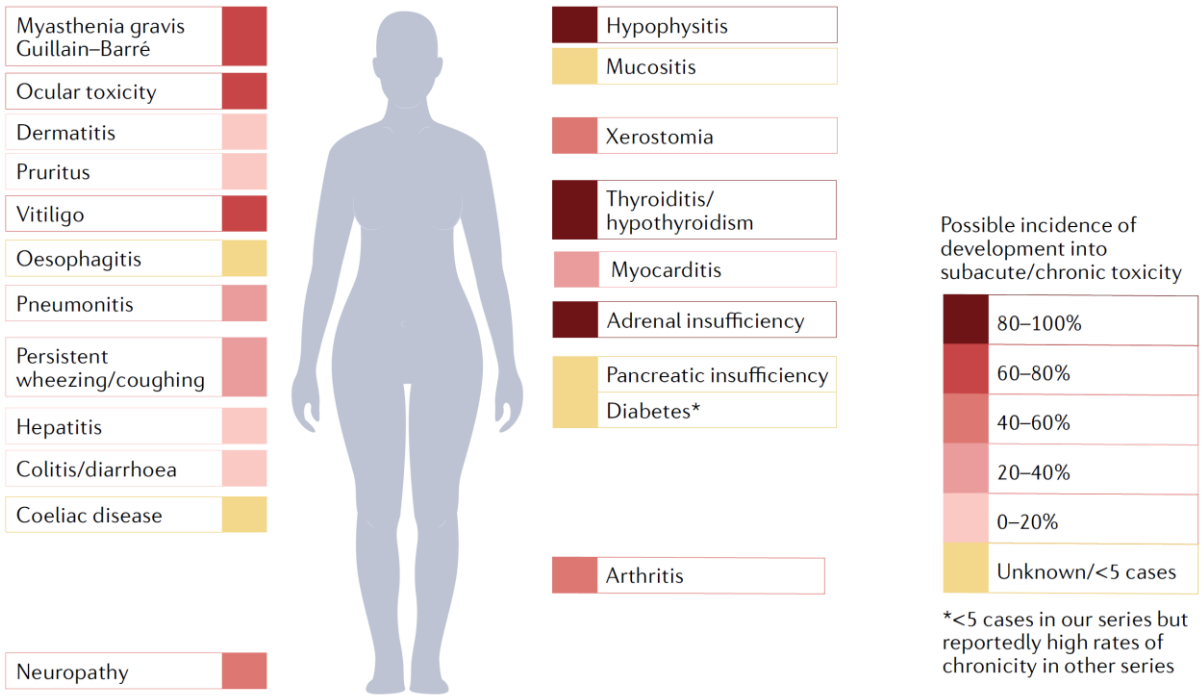
Αντικαρκινική ανοσοθεραπεία και Ρευματολογία

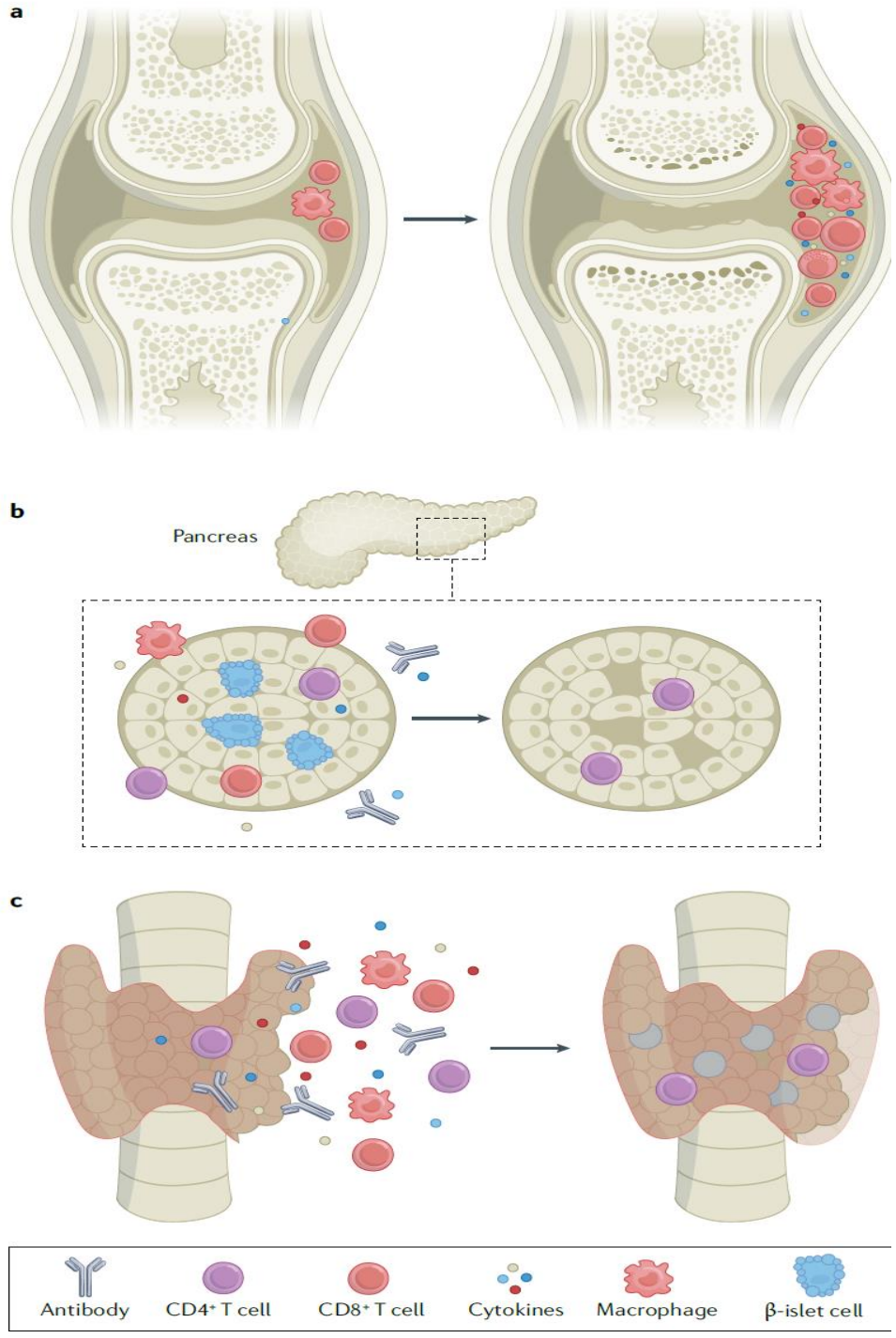
- Μεγάλη αύξηση ασθενών με ανοσοεπαγόμενες ανεπιθύμητες ενέργειες στο αμεσο μέλλον
- Χρήσιμη η συμβολή του ρευματολόγου για την επιλογή ανοκατασταλτικής αγωγής σε ογκολογικούς ασθενείς για αντιμετώπιση IrAE (ρευματικών αλλά και άλλων)
- «Προφυλακτική» χρήση στοχευμένης ανοκατασταλτικής αγωγής για προληψη IrAE??
- Χρόνιες IrAE


Ευχαριστώ

Immune-checkpoint inhibitors: long-term implications of toxicity

Douglas B. Johnson[1] ✉, *Caroline A. Nebhan*[1], *Javid J. Moslehi*[1,2] *and Justin M. Balko*[1]





Arthritis & Rheumatology
Vol. 74, No. 3, March 2022, pp 527–540
DOI 10.1002/art.41949

American College of Rheumatology
Empowering Rheumatology Professionals

Predictors of Rheumatic Immune-Related Adverse Events and De Novo Inflammatory Arthritis After Immune Checkpoint Inhibitor Treatment for Cancer

Amy Cunningham-Bussel,[1] Jiaqi Wang,[2] Lauren C. Prisco,[2] Lily W. Martin,[2] Kathleen M. M. Vanni,[2] Alessandra Zaccardelli,[2] Mazen Nasrallah,[3] Lydia Gedmintas,[1] Lindsey A. MacFarlane,[1] Nancy A. Shadick,[1] Mark M. Awad,[4] Osama Rahma,[4] Nicole R. LeBoeuf,[5] Ellen M. Gravallese,[1] and Jeffrey A. Sparks[1]

Conclusion. We identified novel predictors of rheumatic irAE development in cancer patients, including baseline presence of melanoma, baseline presence of GU tract cancer, preexisting autoimmune disease, receiving or having received combination ICI treatment, and receiving or having received glucocorticoids. The proportion of cancer patients experiencing rheumatic irAEs may be even higher than was reported in the present study, since we used stringent criteria to identify cases of rheumatic irAEs. Our findings could be used to identify cancer patients at risk of developing rheumatic irAEs and de novo inflammatory arthritis and may help further elucidate the pathogenesis of rheumatic irAEs in patients with cancer who are receiving ICI treatment.

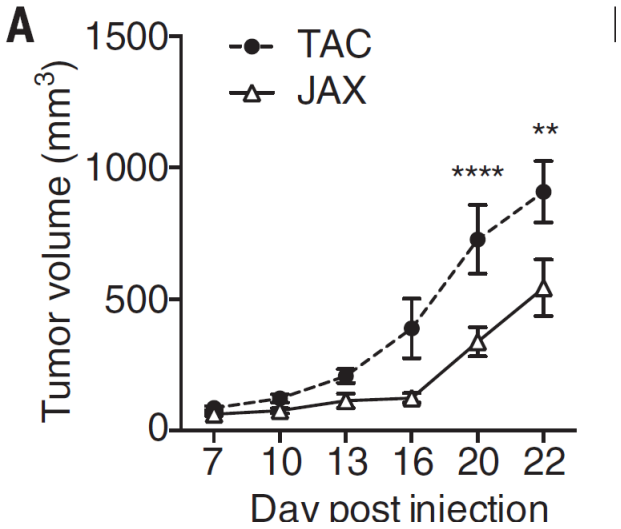
Cell Death and Differentiation (2015) 22, 199–214

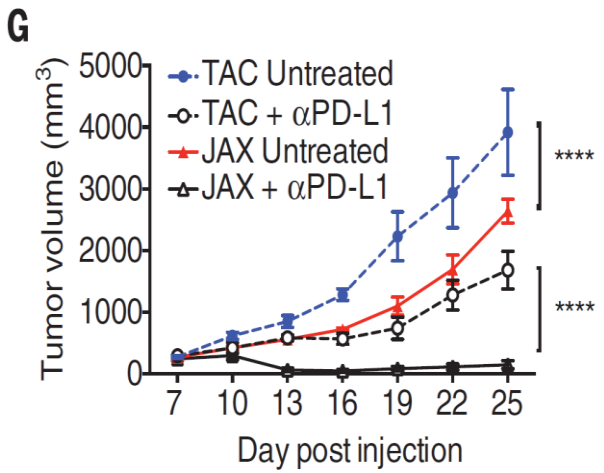
www.nature.com/cdd

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 Pittet[11], F Ghiringhelli[12,13,14], G Trinchieri[15], R Goldszmid[15] and L Zitvogel*[,1,2,16]

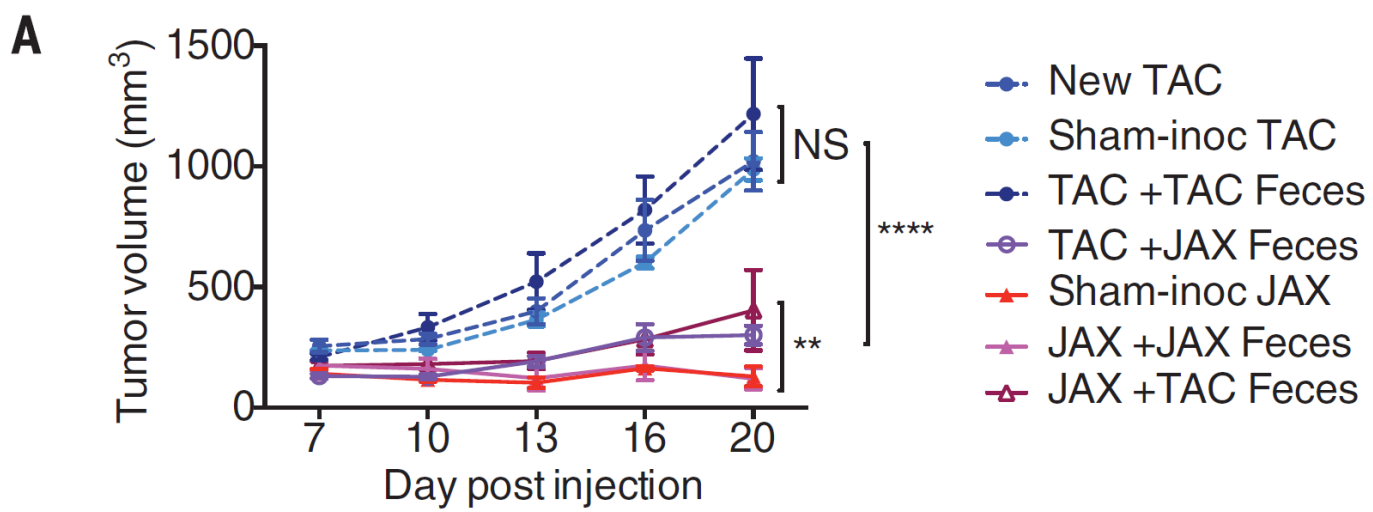


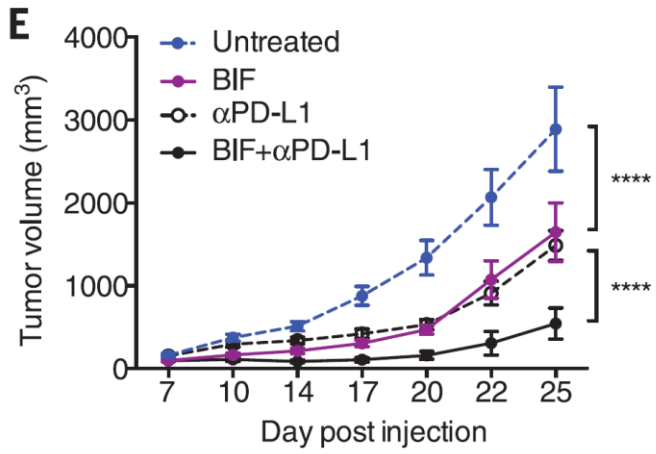


CANCER IMMUNOTHERAPY

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

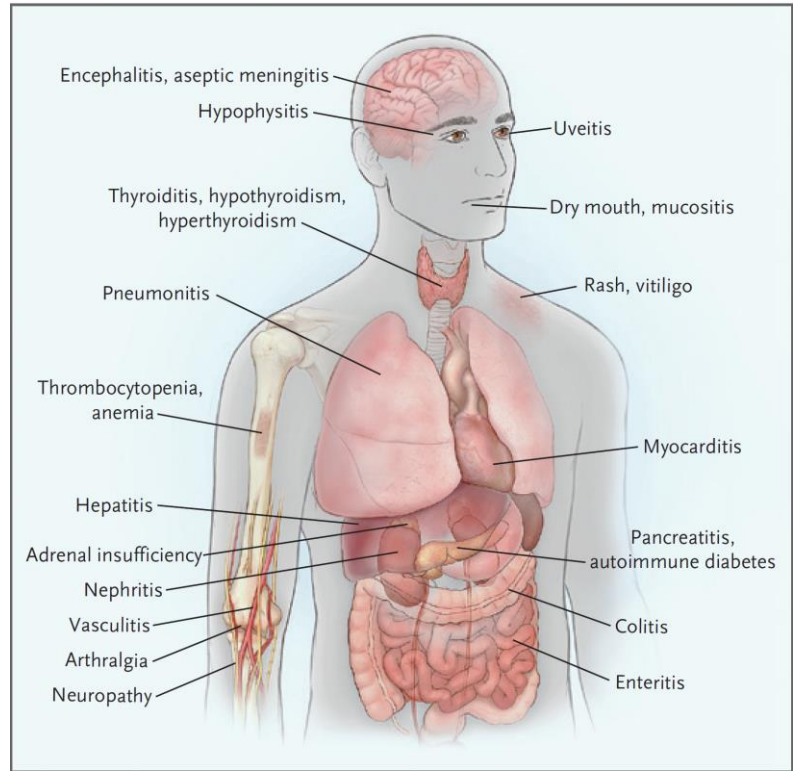
Ayelet Sivan,[1*] Leticia Corrales,[1*] Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[3] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2†]

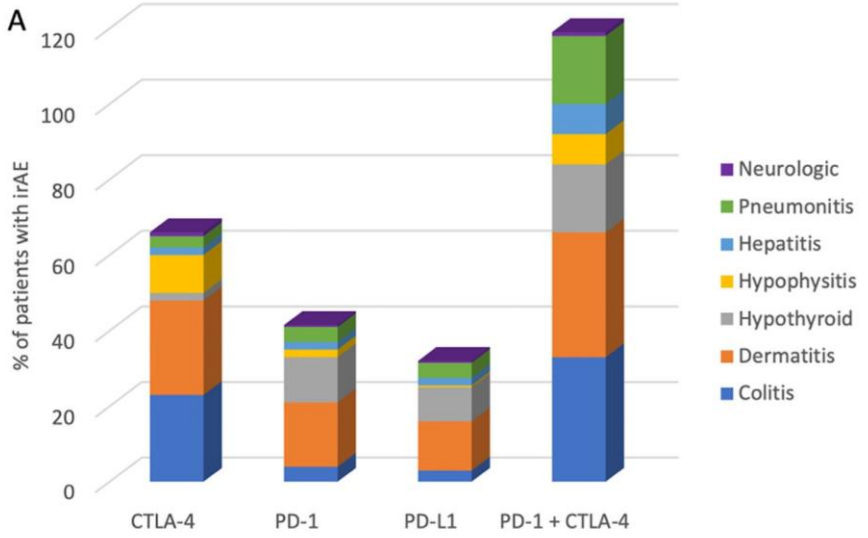




Immune related adverse events (Ir-AE)

- 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%





COMMENT

https://doi.org/10.1038/s41467-022-27960-2 OPEN

Immune-related adverse events and the balancing act of immunotherapy

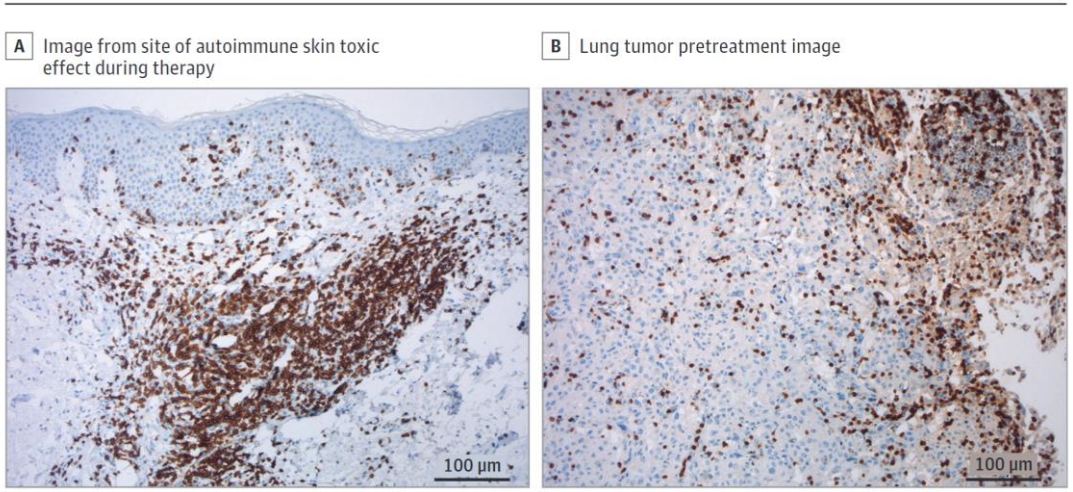
Michael Conroy [1,2,3] & Jarushka Naidoo [1,2,3,4]✉

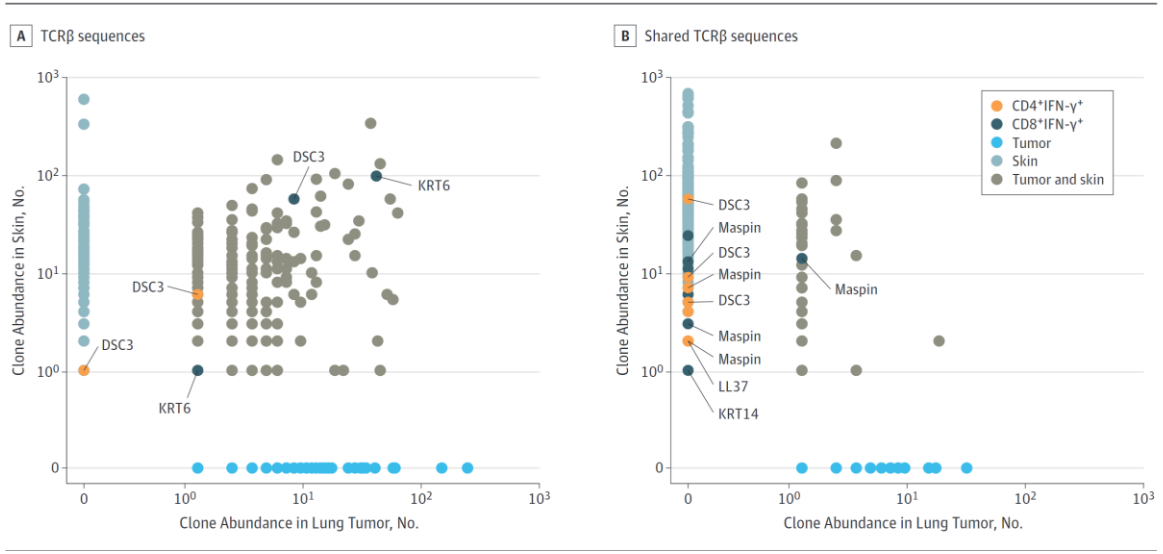
- Μάλλον επιβεβαιώνεται η συσχέτιση μεταξύ IrAE και ογκολογικής απάντησης

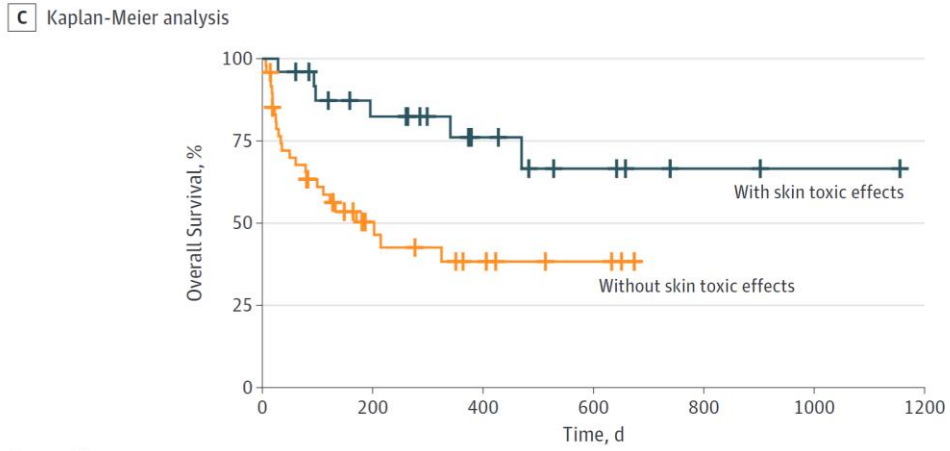
Συσχέτιση ογκολογικής απάντησης και Ir-AE

JAMA Oncology | Brief Report

Association of Checkpoint Inhibitor–Induced Toxic Effects With Shared Cancer and Tissue Antigens in Non–Small Cell Lung Cancer







($\chi^2 = 14.02$, $P < .001$). Nine T-cell antigens shared between tumor tissue and skin were identified. These antigens were able to stimulate $CD8^+$ and $CD4^+$ T cells in vitro. Several of the antigen-specific T cells found in blood samples were also present in autoimmune skin lesions and lung tumors of patients who responded to anti–PD-1 therapy.