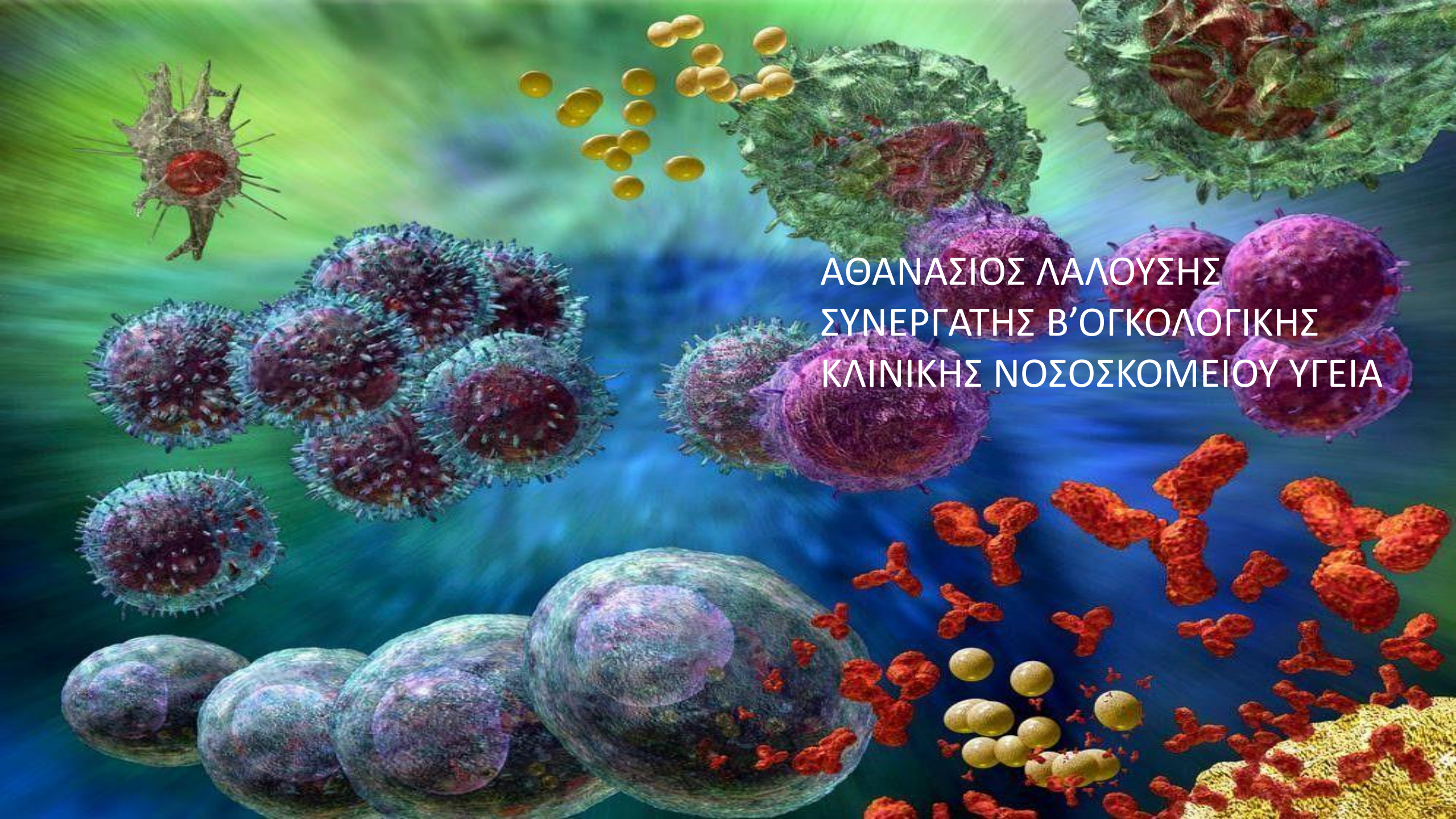
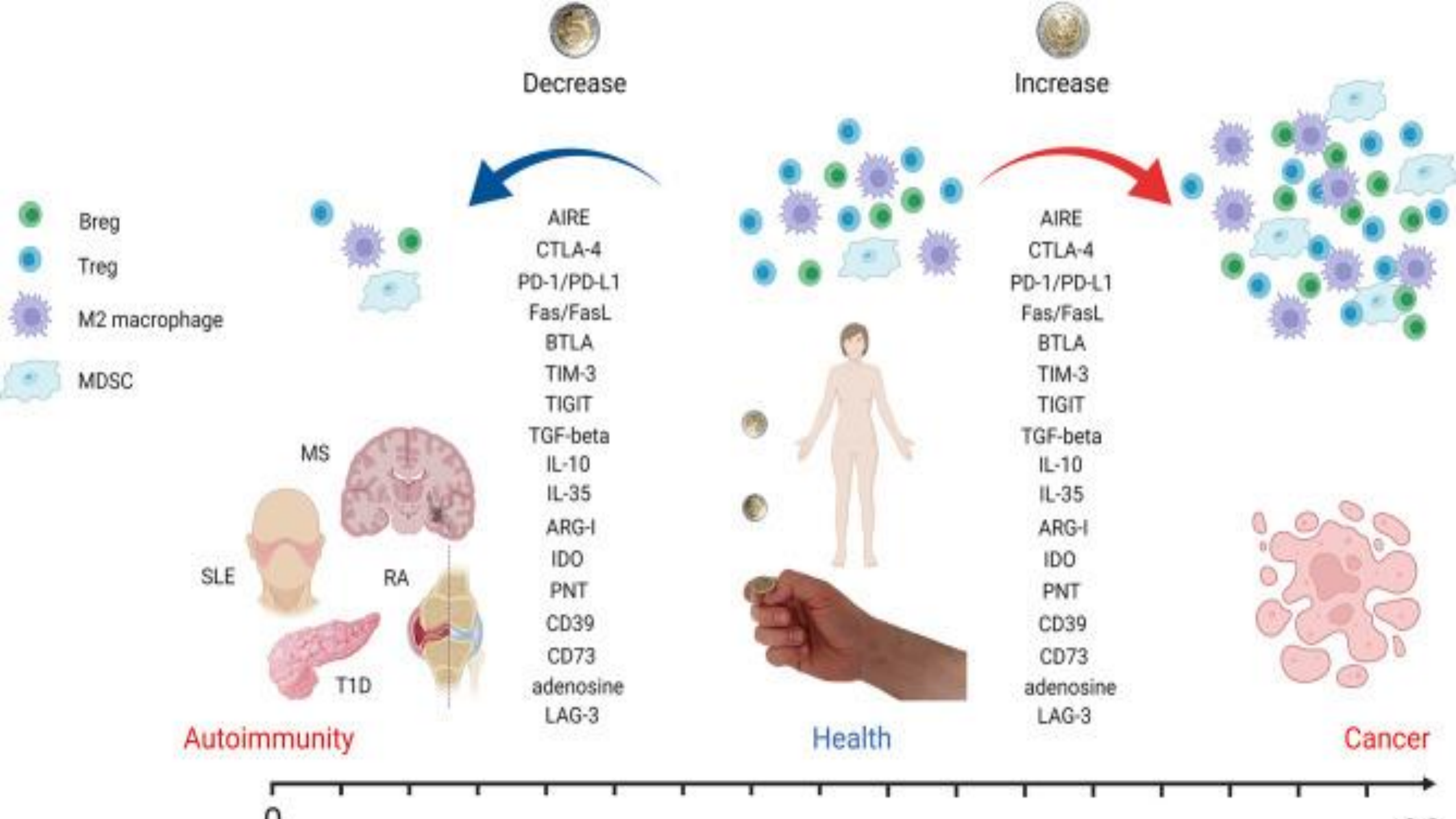

ΑΘΑΝΑΣΙΟΣ ΛΑΛΟΥΣΗΣ
ΣΥΝΕΡΓΑΤΗΣ Β'ΟΓΚΟΛΟΓΙΚΗΣ
ΚΛΙΝΙΚΗΣ ΝΟΣΟΣΚΟΜΕΙΟΥ ΥΓΕΙΑ

- Δεν έχω καμιά σύγκρουση συμφερόντων.


Decrease
Increase
Breg
Treg
M2 macrophage
MDSC
AIRE
CTLA-4
PD-1/PD-L1
Fas/FasL
BTLA
TIM-3
TIGIT
TGF-beta
IL-10
IL-35
ARG-I
IDO
PNT
CD39
CD73
adenosine
LAG-3
MS
SLE
RA
T1D
Autoimmunity
Health
Cancer

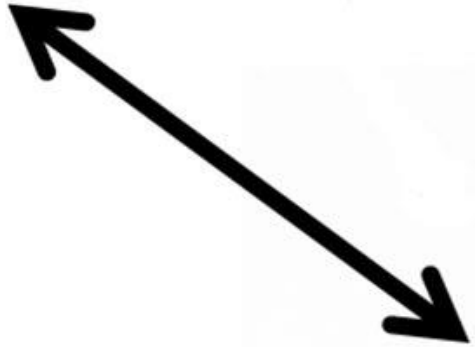
Chronic inflammation and immune activation

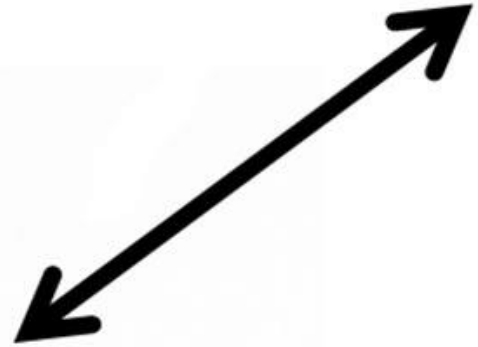
DNA damage, genomic instabiliity

Increased malignancy risk

Immune surveillance dysfunction

Failure to eliminate malignant cells





Autoimmune drug exposure

Treatment-related oncogenic effects

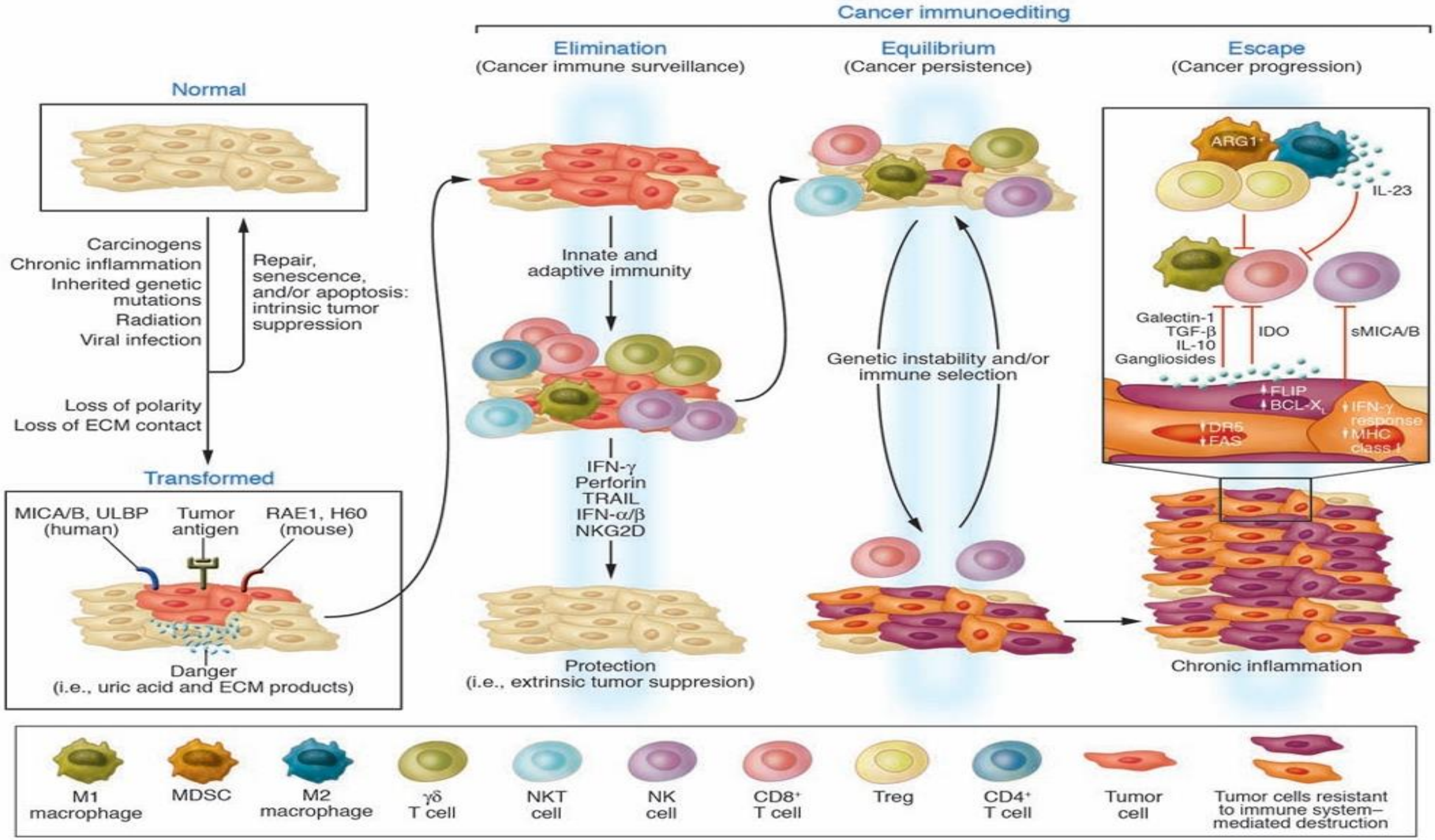

Cancer immunoediting
Elimination
(Cancer immune surveillance)
Equilibrium
(Cancer persistence)
Escape
(Cancer progression)
Normal
Carcinogens
Chronic inflammation
Inherited genetic mutations
Radiation
Viral infection
Repair, senescence, and/or apoptosis: intrinsic tumor suppression
Loss of polarity
Loss of ECM contact
Transformed
MICA/B, ULBP (human)
Tumor antigen
RAE1, H60 (mouse)
Danger
(i.e., uric acid and ECM products)
Innate and adaptive immunity
IFN-γ
Perforin
TRAIL
IFN-α/β
NKG2D
Protection
(i.e., extrinsic tumor suppresion)
Genetic instability and/or immune selection
ARG1
IL-23
Galectin-1
TGF-β
IL-10
Gangliosides
IDO
sMICA/B
FLIP
BCL-X
IFN-γ response
MHC class
DR5
FAS
Chronic inflammation
M1 macrophage
MDSC
M2 macrophage
γδ T cell
NKT cell
NK cell
CD8+ T cell
Treg
CD4+ T cell
Tumor cell
Tumor cells resistant to immune system–mediated destruction

TABLE 1 | Patients with autoimmune diseases may have an increased risk of developing cancer.

Autoimmune disease	Associated cancer	Risk metric (95%CI where available)	Reference
Rheumatoid arthritis	Multiple	SIR: 1.09 (1.06–1.13)	Simon et al. (2015)
Psoriasis	Multiple	RR: 1.21 (1.11–1.33)	Geller et al. (2018) Vaengebjerg et al. (2020)
Systemic lupus erythematosus	Multiple	RR: 1.28 (1.16–1.42)	Cao et al. (2015) Song et al. (2018)
Inflammatory bowel disease	Colorectal cancer	SIR: 1.7 (1.2–2.2)	Lutgens et al. (2013)
Sjogren's syndrome	Multiple	RR: 1.53 (1.17–1.88)	Liang et al. (2014)
Autoimmune gastritis	Gastric adenocarcinoma	OR: 2.18 (1.94–2.45)	Massironi et al. (2019)
Dermatomyositis	Multiple	OR: 14.5 (2.35–89.3)	Lau et al. (2021)

Disease	Age, Sex	Clinical Findings	Serum Findings
IIMs *	>40 at diagnosis Male	Dysphagia Skin ulceration or necrosis Refractory or aggressive disease	TIF1γ, NXP2
Sjögren's Syndrome		Persistent parotid enlargement Lymphadenopathy	Low C4 complement levels Monoclonal gammopathy Cryoglobulins, rheumatoid factor
Systemic Sclerosis	Onset > 65	Aggressive, atypical, or treatment-refractory disease course. Significant weight loss or other constitutional symptoms (disproportionate to the severity of the autoimmune disease). ILD (for lung cancer).	ARA Negative for ACA and ATA in SSc-diffuse disease
SLE		Significant weight loss or other constitutional symptoms (disproportionate to the severity of the autoimmune disease). Persistent HPV infection Prior cyclophosphamide exposure or long-term immunosuppression	
Rheumatoid Arthritis	Older age Male	Persistent inflammation or high disease activity ILD (for lung cancer) Felty's syndrome (for large granular lymphocyte leukaemia)	Seropositivity
Antiphospholipid Syndrome		Unexplained or recurrent thrombosis despite therapy Refractory disease	
AAV	Older age Male	High cumulative exposure to cyclophosphamide	Anti-PR3 positivity
GCA/PMR	Older age Male	Atypical (e.g., absence of morning stiffness) or disproportionate symptoms Poor response to steroids	

- Ανάγκη για νέα φάρμακα....΄΄έξυπνα φάρμακα στην ογκολογία΄΄
  Σε ασθενή με αυτοάνοσο νόσημα?

ΣΤΟΧΕΥΜΕΝΕΣ ΘΕΡΑΠΕΙΕΣ

Μονοκλωνικά αντισώματα

TKIs

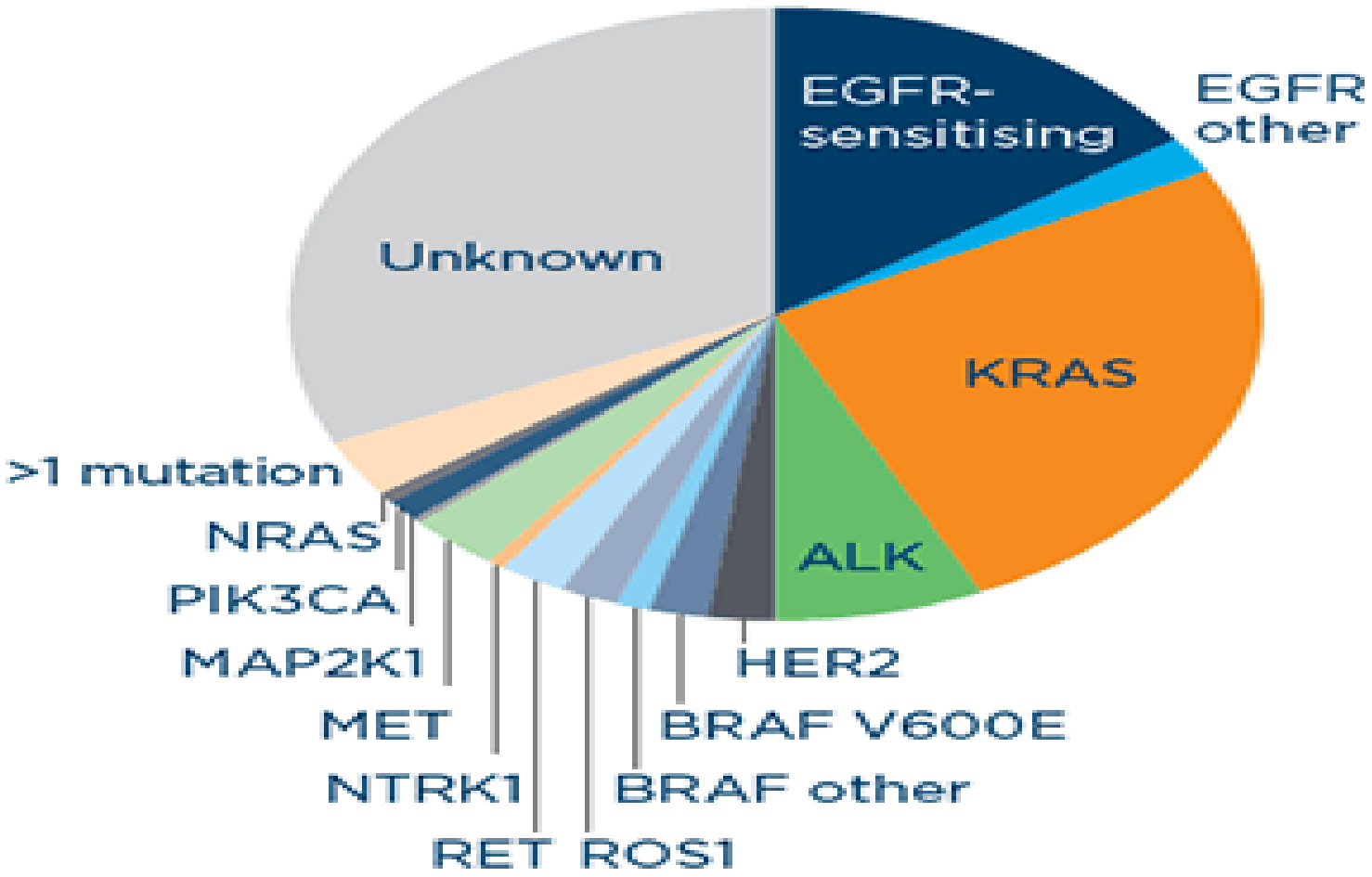
Ανοσοθεραπεία

ADC(συζευγμένα φάρμακα)

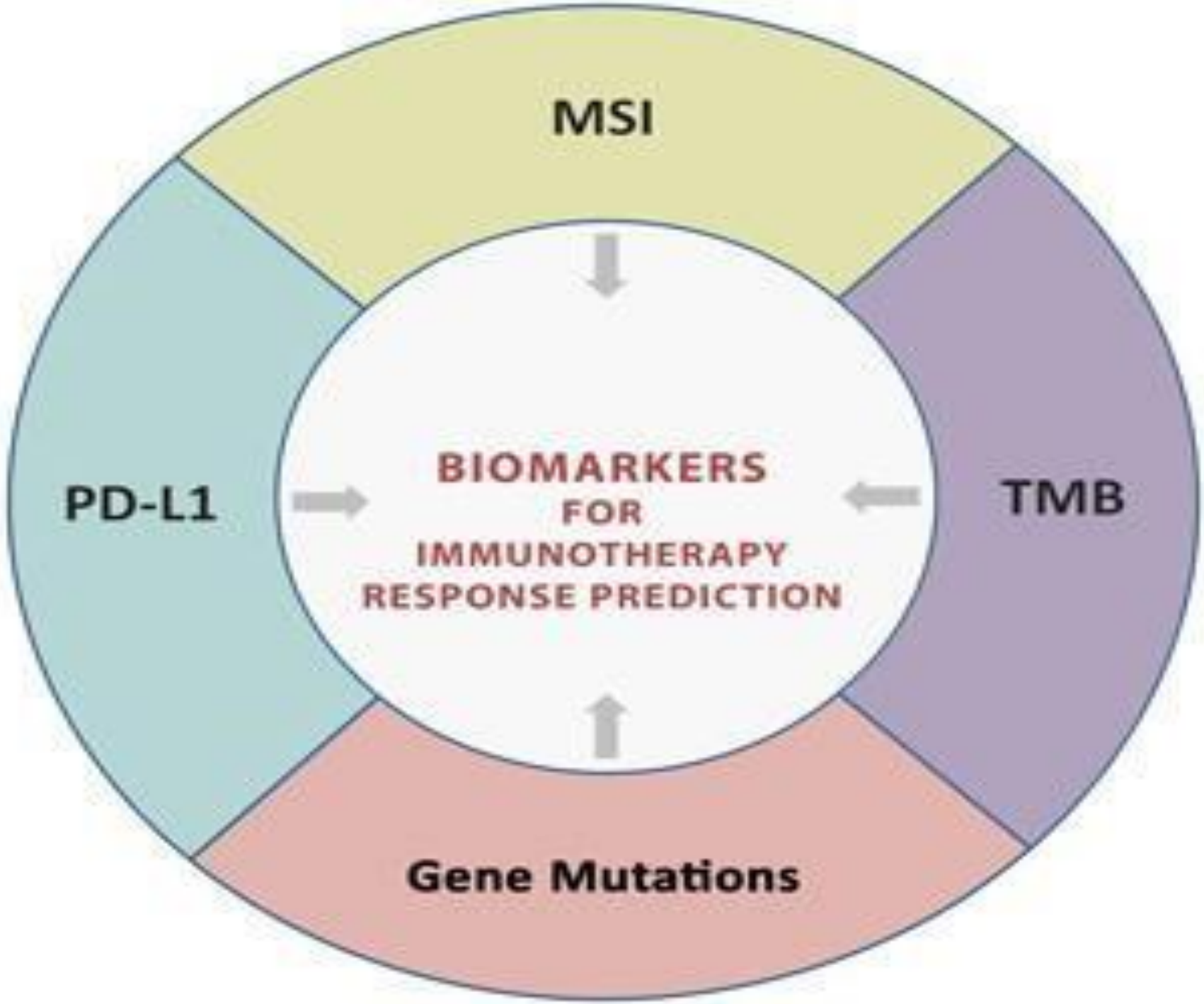
ΑΝΟΣΟΘΕΡΑΠΕΙΑ.....

- Μείωση Κινδύνου Θανάτου: Η χρήση συγκεκριμένων αναστολέων σημείων ελέγχου έχει δείξει μείωση του κινδύνου θανάτου κατά 30% έως 40% σε επιθετικές μορφές καρκίνου.
- Μεταστατικό **Μελάνωμα**: Η 5ετής επιβίωση έχει αυξηθεί από 16% (στα μέσα της δεκαετίας του '90) σε 35% το 2026. Σε ασθενείς που ανταποκρίνονται καλά στη συνδυαστική ανοσοθεραπεία και παραμένουν χωρίς εξέλιξη της νόσου για 3 χρόνια, το ποσοστό επιβίωσης στα 10 χρόνια αγγίζει το 96%.
- Καρκίνος του **Πνεύμονα (ΜΜΚΠ)Σταδιου 4**:η 5ετής επιβίωση έχει πενταπλασιαστεί
- Επίπτωση θανατηφόρων συμβάντων απο ανοσοθεραπεία 0,3% vs 0,9% από χημειοθεραπεία vs 15% απο μεταμόσχευση μυελού.
- Στοχευμενη δραση/**καλύτερη ποιότητα ζωής**.

DRIVER MUTATIONS IN LUNG ADENOCARCINOMA

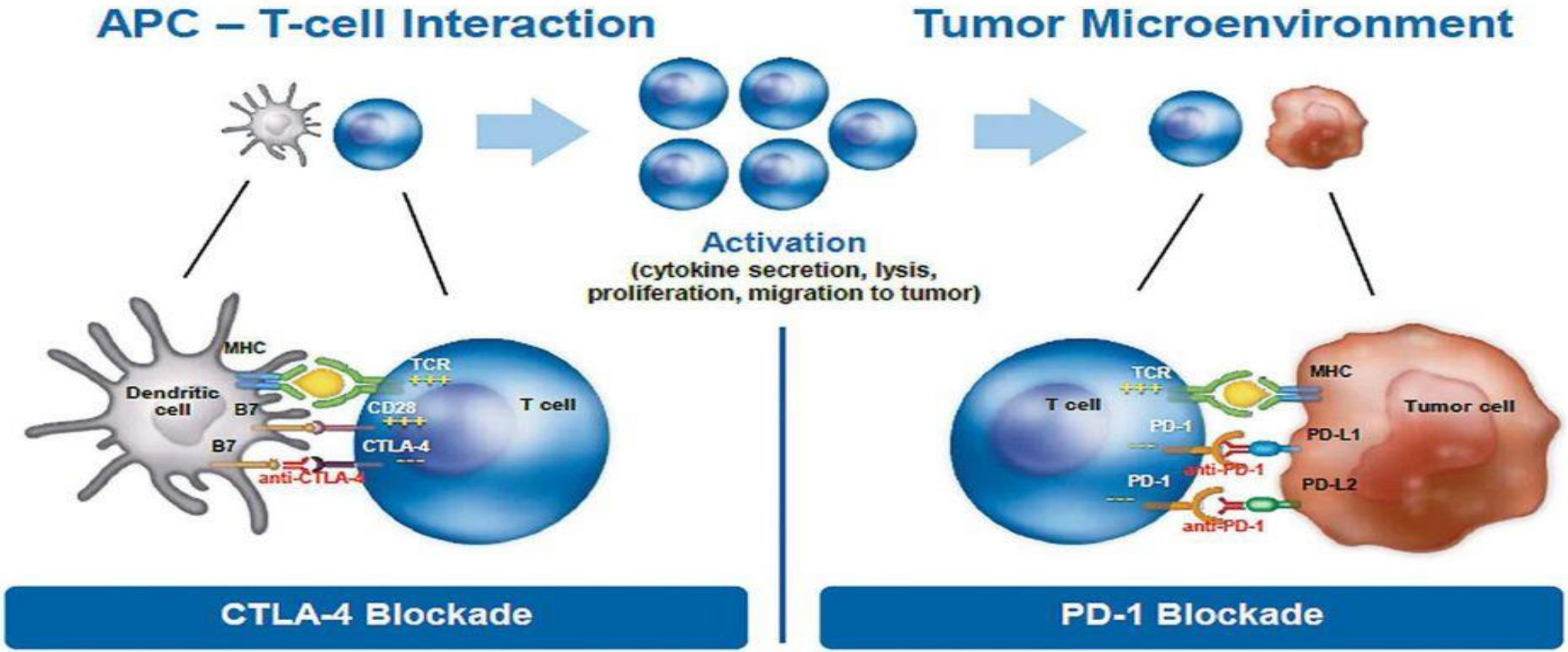


Driver mutations in lung adenocarcinoma	
EGFR-sensitizing	15%
EGFR other	2%
KRAS	25%
ALK	7%
HER2	2%
BRAF V600E	2%
BRAF other	1%
ROS1	2%
RET	2%
NTRK1	0–5%
MET	3%
MAP2K1	0–5%
PIK3CA	1%
NRAS	0–5%
>1 mutation	3%
Unknown	31%


MSI
PD-L1
BIOMARKERS
FOR
IMMUNOTHERAPY
RESPONSE PREDICTION
TMB
Gene Mutations

Στόχευση δενδριτικών για θεραπεία

Απαλοιφή αρνητικής συνδιέγερσης οδηγεί στην ενεργοποίηση των Τ κυττάρων



Ipilimumab, tremelimumab

Nivolumab, pidilizumab, Pembrolizumab

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 7, e2145102 (13 pages)
https://doi.org/10.1080/21645515.2022.2145102

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RESEARCH ARTICLE

OPEN ACCESS Check for updates

Safety and efficacy of immune checkpoint inhibitors in advanced cancer patients with autoimmune disease: A meta-analysis

Qi Cai*, Geng-wei Huo*, Fu-yi Zhu*, Ping Yue, Dong-qi Yuan, and Peng Chen

Department of Thoracic Oncology, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin Lung Cancer Center, Key Laboratory of Cancer Immunology and Biotherapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

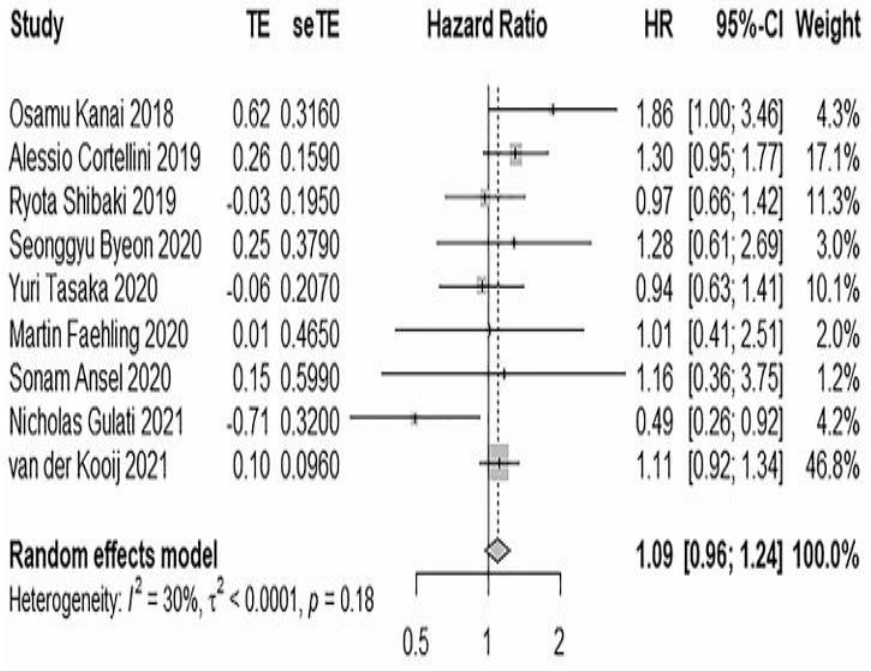


Figure 10. Forest plot of PFS in patients with and without AID receiving ICIs.

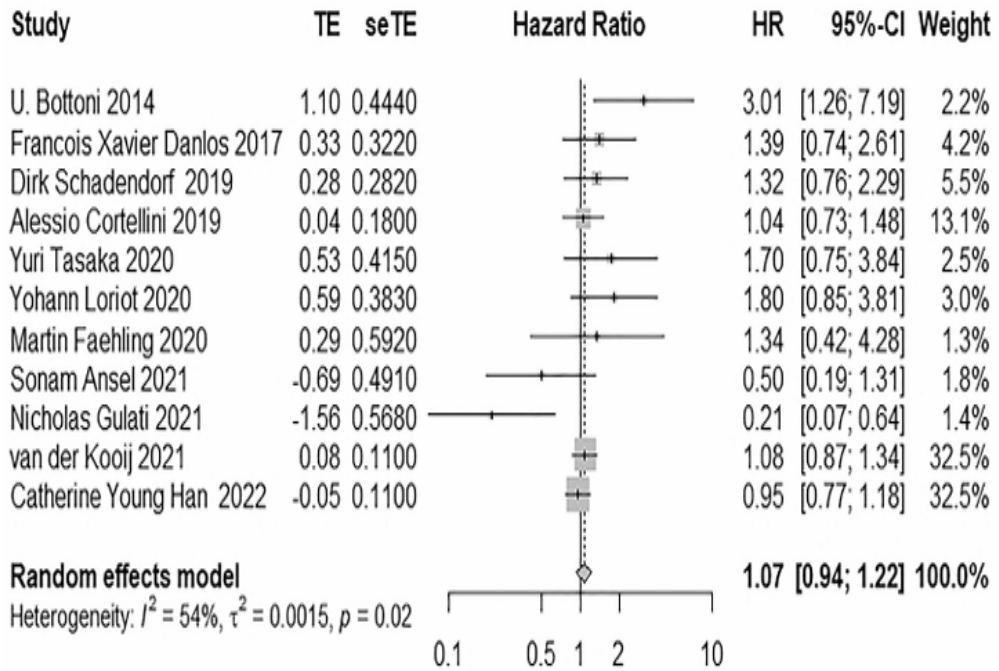


Figure 11. Forest plot of OS in patients with and without AID receiving ICIs.

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[1]*, Konstantinos Melissaropoulos[2]*, Alexandra Filippopoulou[3]*, Dimitrios Daoussis[4]

*These authors contributed equally

[1]Department of Rheumatology, "Asklepieion" General Hospital, Athens, Greece, [2]Department of Rheumatology, Agios Andreas Hospital, Patras, Greece, [3]Clinical Immunology-Rheumatology Unit, 2nd Department of Medicine and Laboratory, Hippokration General Hospital, National and Kapodistrian University of Athens, Athens, Greece, [4]Department of Rheumatology, Patras University Hospital, University of Patras Medical School, Patras, Greece

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]

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 71, No. 12, December 2019, pp 2100–2111
DOI 10.1002/art.41068

Safety and Efficacy of Immune Checkpoint Inhibitors in Patients With Cancer and Preexisting Autoimmune Disease: A Nationwide, Multicenter Cohort Study

Alice Tison,[1] Gilles Quéré,[1] Laurent Misery,[1] Elisa Funck-Brentano,[2] François-Xavier Danlos,[3] Emilie Routier,[3] Caroline Robert,[3] Yohann Loriot,[3] Olivier Lambotte,[4] Bertille Bonniaud,[5] Camille Scalbert,[6] Sarah Maanaoui,[6] Thierry Lesimple,[7] Stéphanie Martinez,[8] Marie Marcq,[9] Christos Chouaid,[10] Catherine Dubos,[11] Florence Brunet-Possenti,[12] Chloé Stavris,[13] Laurent Chiche,[13] Nathalie Beneton,[14] Sandrine Mansard,[15] Florian Guisier,[16] Hélène Doubre,[17] François Skowron,[18] François Aubin,[19] Ouidad Zehou,[20] Christophe Roge,[21] Mickaël Lambert,[21] Anne Pham-Ledard,[22] Marie Beylot-Barry,[22] Rémi Veillon,[22] Nora Kramkimel,[23] Damien Giacchero,[24] Julie De Quatrebarbes,[25] Catherine Michel,[26] Jean-Bernard Auliac,[27] Gilles Gonzales,[28] Chantal Decroisette,[25] Gwenaelle Le Garff,[29] Ioana Carpiuc,[30] Hervé Vallerand,[31] Emmanuel Nowak,[1] Divi Cornec,[1] and Marie Kostine,[22] on behalf of Groupe de Cancérologie Cutanée, Groupe Français de Pneumo-Cancérologie, and Club Rhumatismes et Inflammations

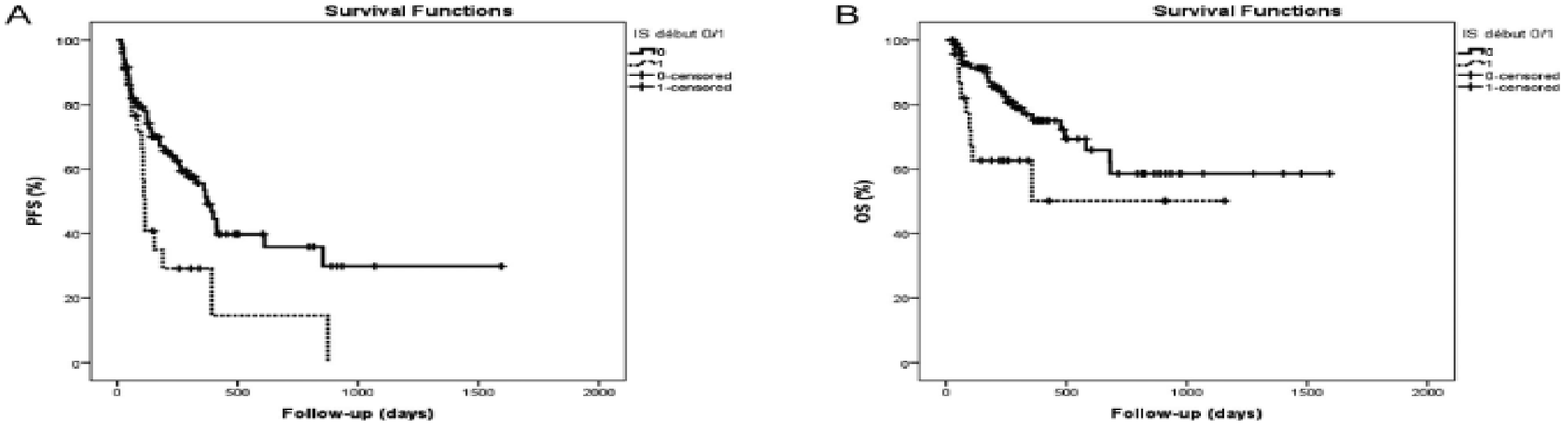


Figure 1. Progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) for patients not receiving immunosuppressive (IS) therapy at initiation of immune checkpoint inhibitor (ICI) treatment (indicated by 0) and patients receiving ongoing immunosuppressive therapy at initiation of ICI treatment (indicated by 1).

ABSTRACT NUMBER: 1732

Incidence of Flares in Pre-existing Rheumatologic Diseases Among Patients with Solid Tumors Undergoing Cancer Immunotherapy: A Systematic Review and Meta-analysis

Takemichi Matsui[1], Kenji Yamada[2], Toshiaki Takahashi[3], Yoshito Nishimura[4] and Yu Fujiwara[5], [1]Department of Medicine, Mount Sinai Morningside/West Hospitals, Icahn School of Medicine at Mount Sinai, New York, NY, [2]Department of Allergy and Rheumatology, Kameda Medical Center, Chiba, Japan, [3]Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, [4]Division of Hematology/Oncology, Mayo Clinic, Rochester, MN, [5]Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Meeting: ACR Convergence 2025

Keywords: autoimmune diseases, meta-analysis, rheumatoid arthritis

Flare Incidences of Pre-existing Rheumatologic Diseases in Patients with Solid Tumors Receiving Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis

Backgrounds

The effect of immune checkpoint inhibitors (ICIs) on pre-existing rheumatologic diseases remains unclear.

Objectives

To evaluate the incidence and severity of rheumatologic disease flares in patients with solid tumors treated with ICIs.

Methods

PubMed
Embase

2,599 articles screened
31 studies identified
More than **700** patients included

Results

Flare incidence

- **Overall flare incidence: 33.8%**
(95% confidence interval [CI]: 25.8–42.2%)
- **Severe flare: 4.2%**
(95% CI: 0.6–9.6%)

✓ Rheumatoid arthritis: **40.9%**
✓ Psoriatic arthritis: **46.4%**
✓ Systemic sclerosis: **11.3%**
✓ Systemic lupus erythematosus: **3.8%**

Flare course

- Onset of flares after ICI initiation: **38.5 days** (interquartile range: 30.0–52.6 days)
- Systemic corticosteroid use: **83%**

- Clinical improvement after treatment: **81%**
- Permanent discontinuation of ICIs: **17%**

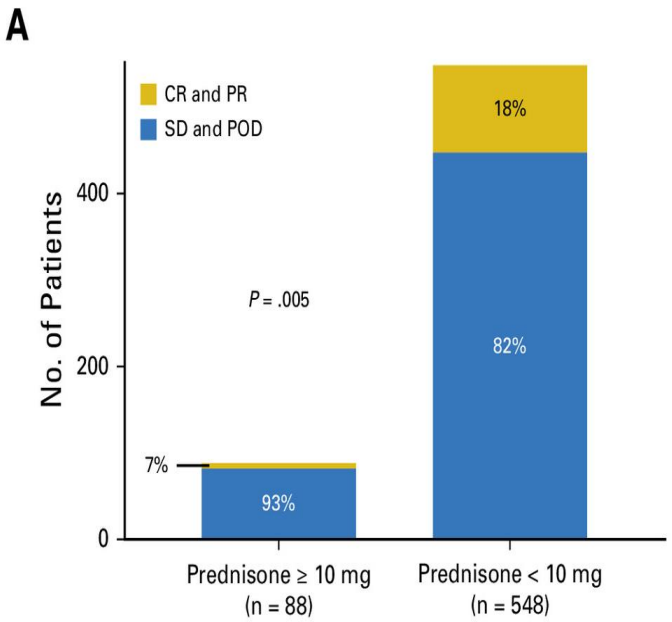
Conclusions: Incidences of flare from ICIs vary depending on the underlying rheumatologic condition. Close communication between rheumatologists and oncologists is important.

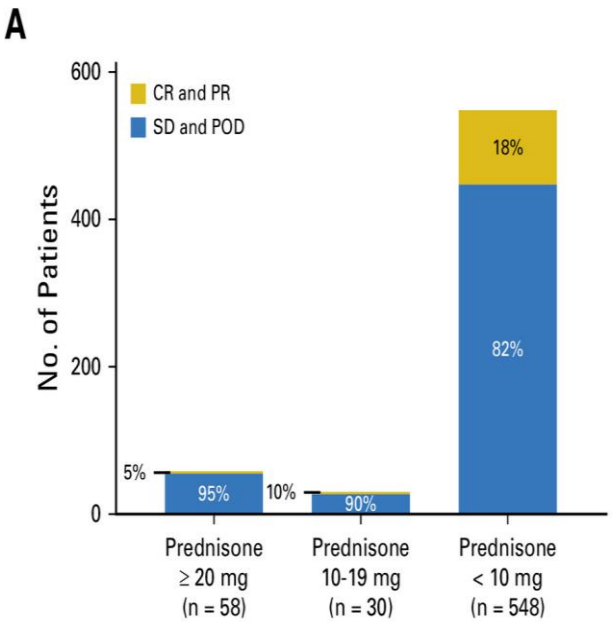
Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non–Small-Cell Lung Cancer

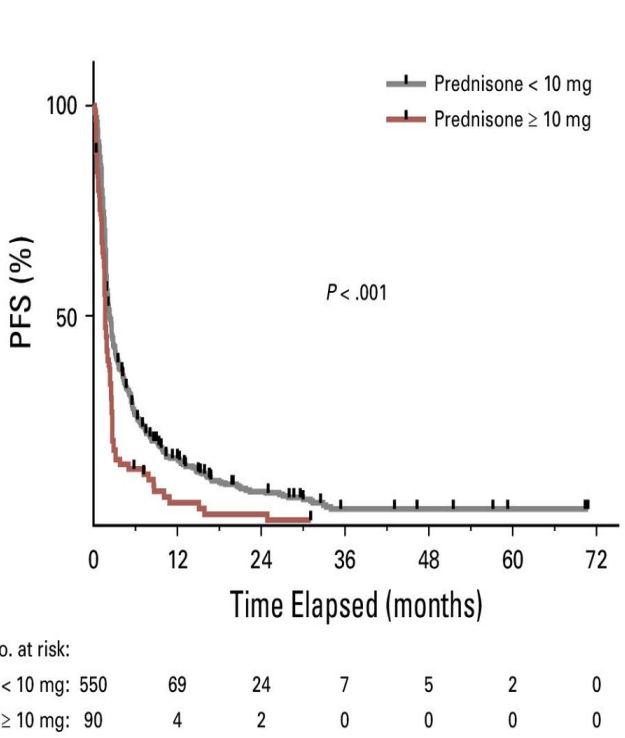
Authors: Kathryn C. Arbour, Laura Mezquita, Niamh Long, Hira Rizvi, Edouard Auclin, Andy Ni, Gala Martínez-Bernal, ... SHOW ALL ... , and Matthew D. Hellmann

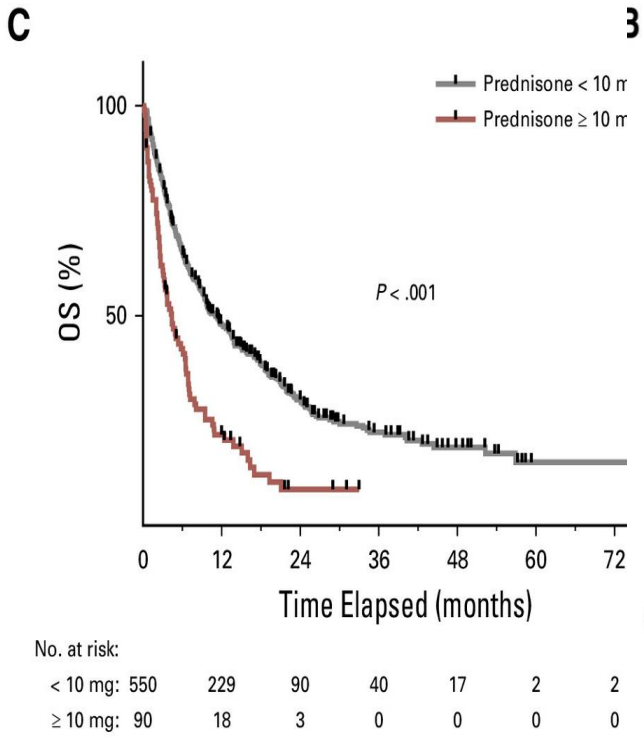
AUTHORS INFO & AFFILIATIONS

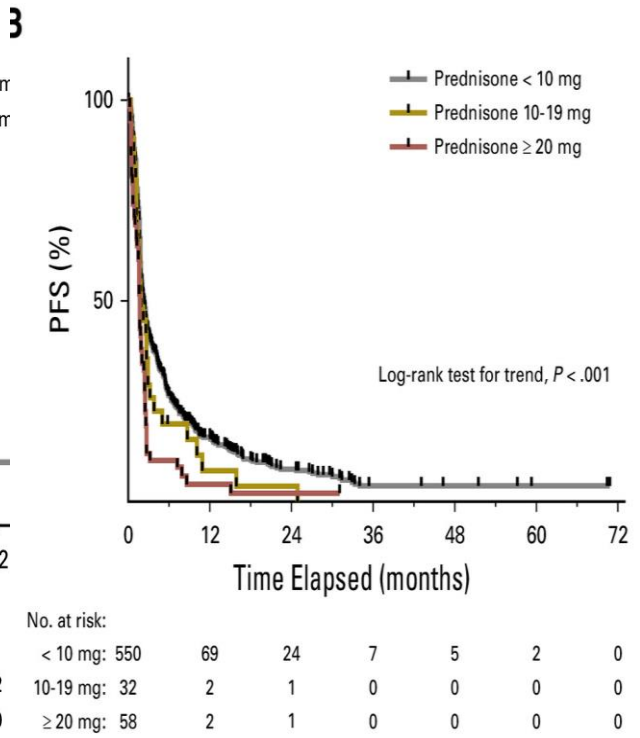
J Clin Oncol 36, 2872-2878(2018) • Volume 36, Number 28 • DOI: 10.1200/JCO.2018.79.0006

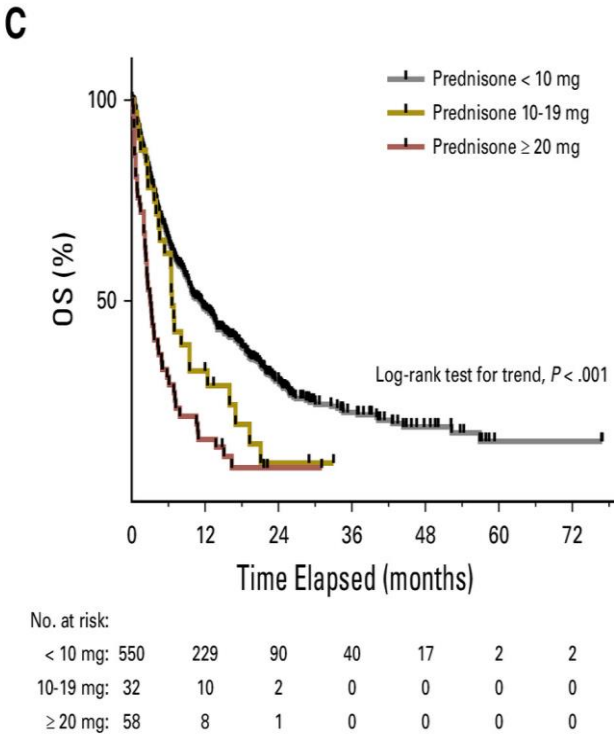

A
CR and PR
SD and POD
No. of Patients
400
200
0
P = .005
18%
82%
7%
93%
Prednisone ≥ 10 mg
(n = 88)
Prednisone < 10 mg
(n = 548)

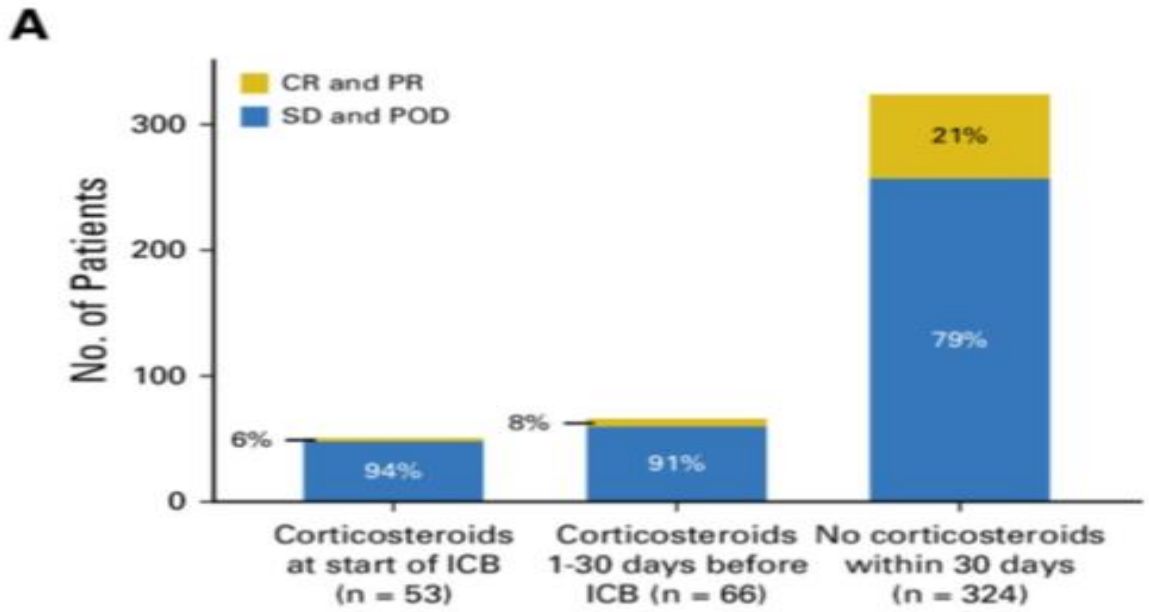

A
600
CR and PR
SD and POD
No. of Patients
400
200
0
18%
82%
5%
95%
10%
90%
Prednisone
≥ 20 mg
(n = 58)
Prednisone
10-19 mg
(n = 30)
Prednisone
< 10 mg
(n = 548)

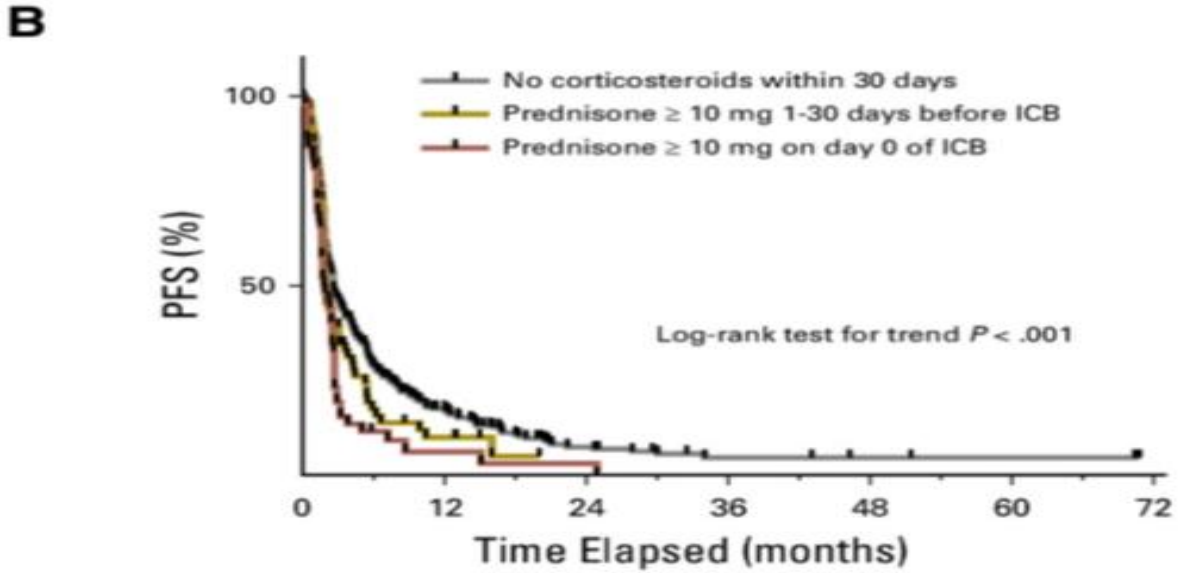

Prednisone < 10 mg
Prednisone ≥ 10 mg
100
50
PFS (%)
P < .001
0
12
24
36
48
60
72
Time Elapsed (months)
o. at risk:
< 10 mg: 550 69 24 7 5 2 0
≥ 10 mg: 90 4 2 0 0 0 0


C
Prednisone < 10 m
Prednisone ≥ 10 m
100
50
OS (%)
P < .001
0
12
24
36
48
60
72
Time Elapsed (months)
No. at risk:
< 10 mg: 550 229 90 40 17 2 2
≥ 10 mg: 90 18 3 0 0 0 0

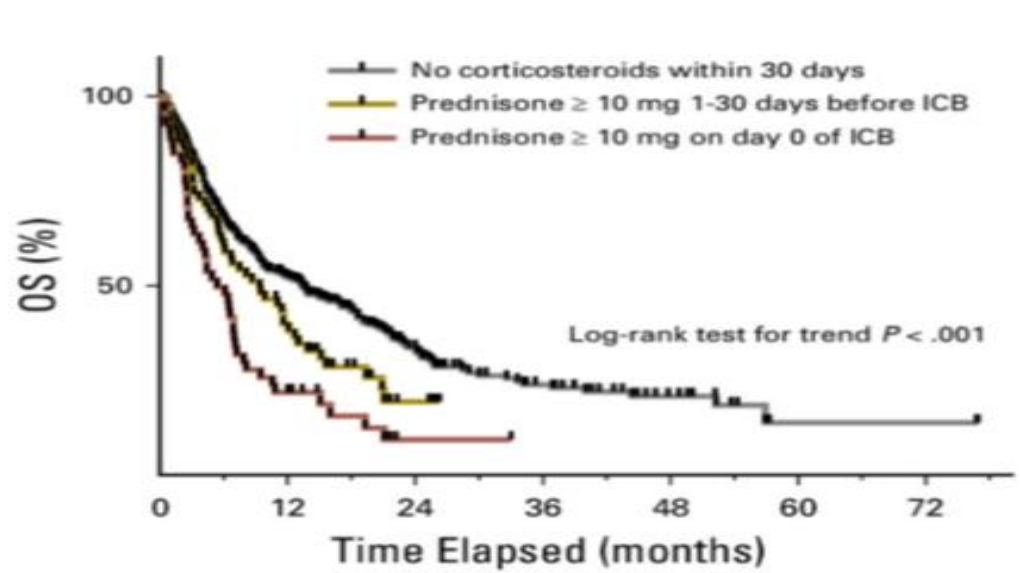

B
Prednisone < 10 mg
Prednisone 10-19 mg
Prednisone ≥ 20 mg
100
50
PFS (%)
Log-rank test for trend, P < .001
0
12
24
36
48
60
72
Time Elapsed (months)
No. at risk:
< 10 mg: 550 69 24 7 5 2 0
10-19 mg: 32 2 1 0 0 0 0
≥ 20 mg: 58 2 1 0 0 0 0


C
Prednisone < 10 mg
Prednisone 10-19 mg
Prednisone ≥ 20 mg
100
50
OS (%)
Log-rank test for trend, P < .001
0
12
24
36
48
60
72
Time Elapsed (months)
No. at risk:
< 10 mg: 550 229 90 40 17 2 2
10-19 mg: 32 10 2 0 0 0 0
≥ 20 mg: 58 8 1 0 0 0 0





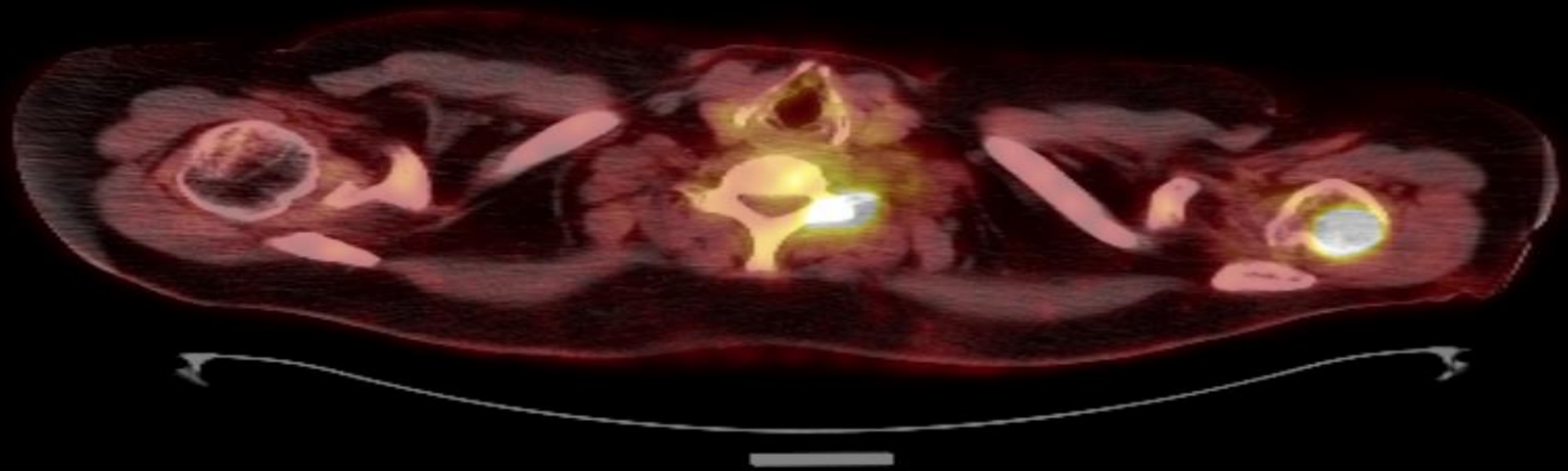
No. at risk:							
No corticosteroids:	336	45	13	5	3	2	0
≥ 10 mg (1-30 days):	66	5	0	0	0	0	0
≥ 10 mg (day 0):	53	2	1	0	0	0	0

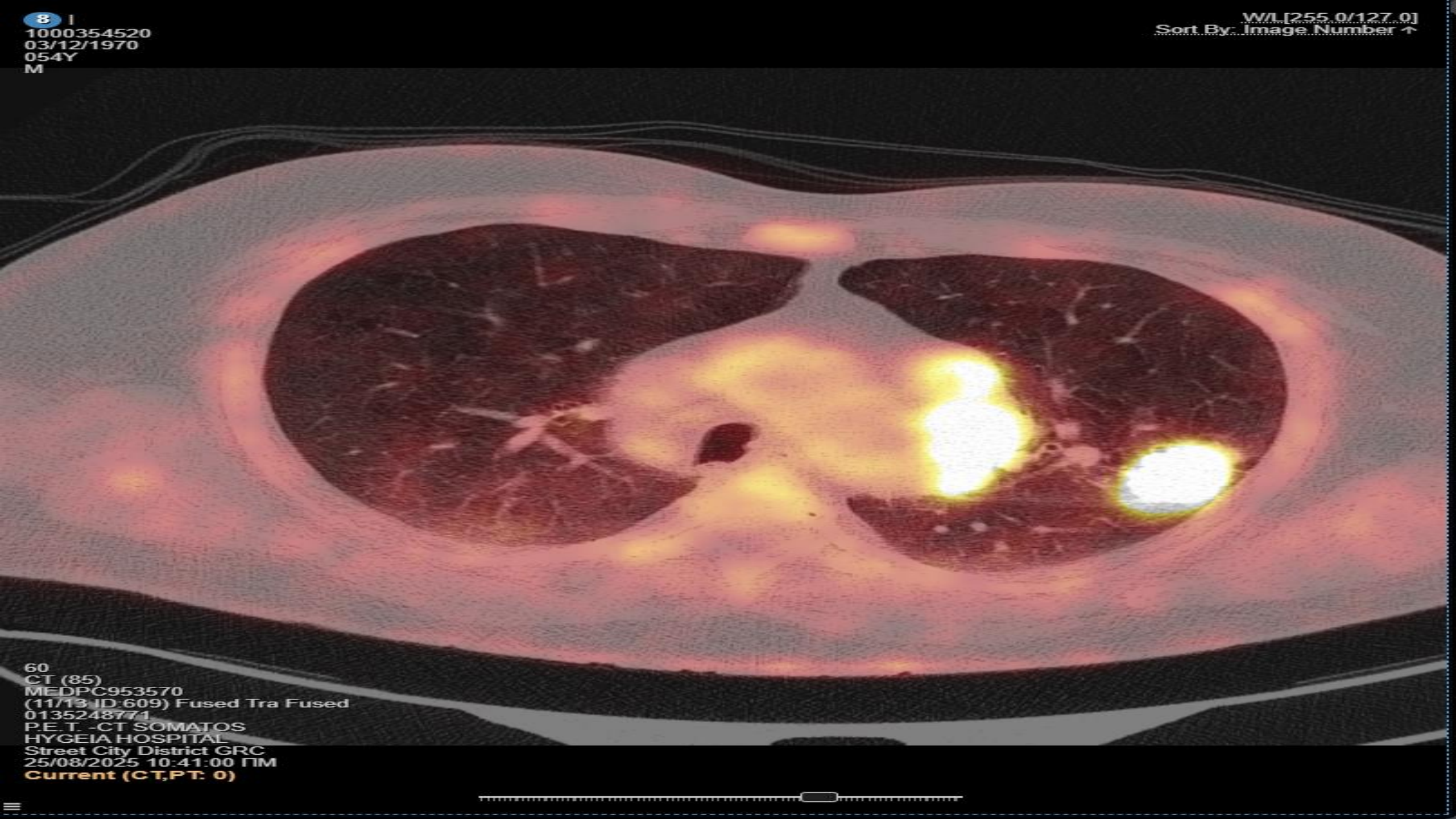


No. at risk:							
No corticosteroids:	336	157	63	28	13	2	2
≥ 10 mg (1-30 days):	66	23	4	0	0	0	0
≥ 10 mg (day 0):	53	11	1	0	0	0	0

1ο Περιστατικο.

- Άνδρας 55 ετών με ιστορικό ρευματοειδούς αρθρίτιδας υπό μεθοτρεξάτη και adalimumab. Αυχεναλγία 12 εβδομάδων.
- MRI ΑΜΣΣ = Οστική μετάσταση
- Pet/ct scan= ΑΡ άνω λοβό , λεμφαδενοπάθεια μεσοθωρακίου , οστική εντόπιση αρ βραχιόνο οστό, Α7.
- Βιοψια =αδενοκαρκίνωμα πνευμονα.
- Μοριακός έλεγχος: Αρνητικός για γονιδιακή μετάλλαξη και PDL-1<1%.
- Έναρξη αγωγής με χημειο-ανοσοθεραπεία (nivolumab-ipilimumab)
- Σε 8 εβδομάδες έντονη κόπωση με εικόνα ρευματικής πολυμυαλγίας

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- Μέτρηση κορτιζόλης ορού
- χορήγηση υδροκορτιζόνης.

2ο Περιστατικο

- Γυναίκα 65 ετων με κόπωση δεκατική πυρετική κίνηση και μυαλγίες ήπιας έντασης.(ΤΚΕ=60,CRP=7)
- Ro θωρακος =κφ, u/s κοιλιας = κφ.
- Pet/ct scan= αλλοίωση αρ νεφρό?
- MRI κοιλίας =βλάβη αρ νεφρό
- Βιοψία =ca νεφρού.
- Αφαίρεση αρ νεφρού/ κακούς προγνωστικούς παράγοντες
- Έναρξη ανοσοθεραπεία (pembrolizumab) για ένα έτος .

- 6 μήνες μετα την έναρξη χορήγησης αρθριτίδα πηχεοκαρπικής άμφω.
- Οροαρνητική
- Χορήγηση 10mg κορτικοειδούς

3ο Περιστατικο

- Άνδρας 70 ετών με ιστορικό ψωριασικής αρθριτίδας και ΣΔ/ΧΝΑ υπό αγωγή με ustekinumab.
- Βλάβη μεσοθωρακίου.
- Βιοψία υποτροπιδικού λεμφαδένα
- Μικροκυτταρικό καρκίνωμα πνευμονα
- Έναρξη αγωγής με χημειοθεραπεία -ανοσοθεραπεία(carboplatin-etoposide-durvalumab)x6.
- Συνέχιση ανοσοθεραπείας ως συντήρηση.

- Υποτροπή της νόσου με έξαρση του εξανθήματος και αρθρίτιδα δε γόνατο , αρ πηχεοκαρπικής άρθρωσης
- Νεφρική ανεπάρκεια (κρεατινίνη=2mg/dl)
- Επαναχορήγηση ustekinumab?

Grading	Management
All grades	Clinicians should follow reports of new joint pain to determine if IA is present. Question whether symptoms new since receiving ICPi.
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi. Initiate analgesia with acetaminophen and/or NSAIDs.
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Consider holding ICPi. Escalate analgesia and consider higher doses of NSAIDS as needed. If inadequately controlled, initiate prednisone 10-20 mg/d or equivalent. If improvement, slow taper according to response during the next 4-6 weeks. If no improvement after initial 4 weeks treat as G3. If unable to lower corticosteroid dose to below 10 mg/d after 6-8 weeks, consider DMARD. Consider intra-articular steroid injections for large joints. Referral to rheumatology.
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; and limiting self-care ADL	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to ≤ G1. Initiate oral prednisone 0.5-1 mg/kg. If failure of improvement after 2 weeks or worsening in meantime, consider synthetic or biologic DMARD. Synthetic: methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine alone or in combination. Biologic: Consider anticytokine therapy such as TNFα or IL-6 antagonists. Note: As a caution, IL6 inhibition can cause intestinal perforation.[141] Although this is extremely rare, it should not be used in patients with concomitant immune-related colitis. Referral to rheumatology.
Additional considerations Early recognition is critical to avoid erosive joint damage. Corticosteroids can be used as part of initial therapy in IA, but because of likely prolonged treatment requirements, physicians should consider starting steroid-sparing agents earlier than one would with other irAEs. Oligoarthritis can be treated early on with intra-articular steroids, consider early referral.	

Tips...

- Χαμηλή δόση κορτικοειδών(max 10mg πρενδιζολόνης).
- Την λιγότερο δυνατόν ανοσοκαταστολή για τον έλεγχο του αυτοάνοσου νοσήματος.
- Χορήγηση μεθοτρεξάτης με σημαντικό προφίλ ασφαλείας.
- Χρονική στιγμή χορήγηση κορτικοειδών.
- Κόπωση σε ασθενή υπό ανοσοθεραπεία.
- Δύσπνοια σε ασθενή υπο ανοσοθεραπεία(Anti-PDL-1>Anti-CTLA4).
- Διαρροικές κενώσεις.

ΧΡΟΝΟΔΙΑΓΡΑΜΜΑ ΕΜΦΑΝΙΣΗΣ

- Πολύ νωρίς (ημέρες έως **4 εβδομάδες**): Δερματικές αντιδράσεις (εξάνθημα, κνησμός), κοπωση.

- Ενδιάμεσα (**5 έως 10 εβδομάδες**): Γαστρεντερικές διαταραχές (διάρροια, κολίτιδα) αρθρίτιδα και ηπατίτιδα.

- Αργότερα (**9 εβδομάδες και μετά**): Ενδοκρινολογικά προβλήματα (θυρεοειδής, υπόφυση) και πνευμονίτιδα.

- Καθυστερημένη εμφάνιση αρθρίτιδας-αυτοάνοσου νοσήματος ακόμα μετά το τέλος της ανοσοθεραπείας!!


Σας ευχαριστώ.