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MANEJO DE LA TOXICIDAD DE LOS NUEVOS TRATAMIENTOS EN

TUMORES UROLÓGICOS

Valencia, 23 de abril de 2024

Organizado por: GUARD CONSORTIUM

¿Por qué produce toxicidad la inmunoterapia? Mecanismos principales

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Organizado por: GUARD CONSORTIUM

El cáncer y el sistema inmunitario

Las **células tumorales** presentan características diferentes que son **reconocidas por el sistema inmunitario**, que de forma natural tiende a destruirlas. El cáncer desarrolla recursos para evitar ser reconocido por el sistema inmunitario, en algunos casos consigue escapar al control y desarrollarse evitando la respuesta inmunitaria.

dos tipos de mecanismos para **evadir** al sistema inmunitario:

- evitar ser reconocido o

-producir sustancias inmunosupresoras.

Inmunoterapia: **tratamientos que utilizan el sistema inmunitario** del propio paciente para tratar diferentes tipos de enfermedades:

Por lo que respecta a la **inmuno-oncologia** es la administración de inmunoterapia destinada a tratar especialmente el cáncer estimulando el sistema inmunitario del paciente para que sea capaz de reconocer a las células cancerígenas y destruirlas, a diferencia de los demás tratamientos disponibles, que actúan directamente sobre las células del tumor.

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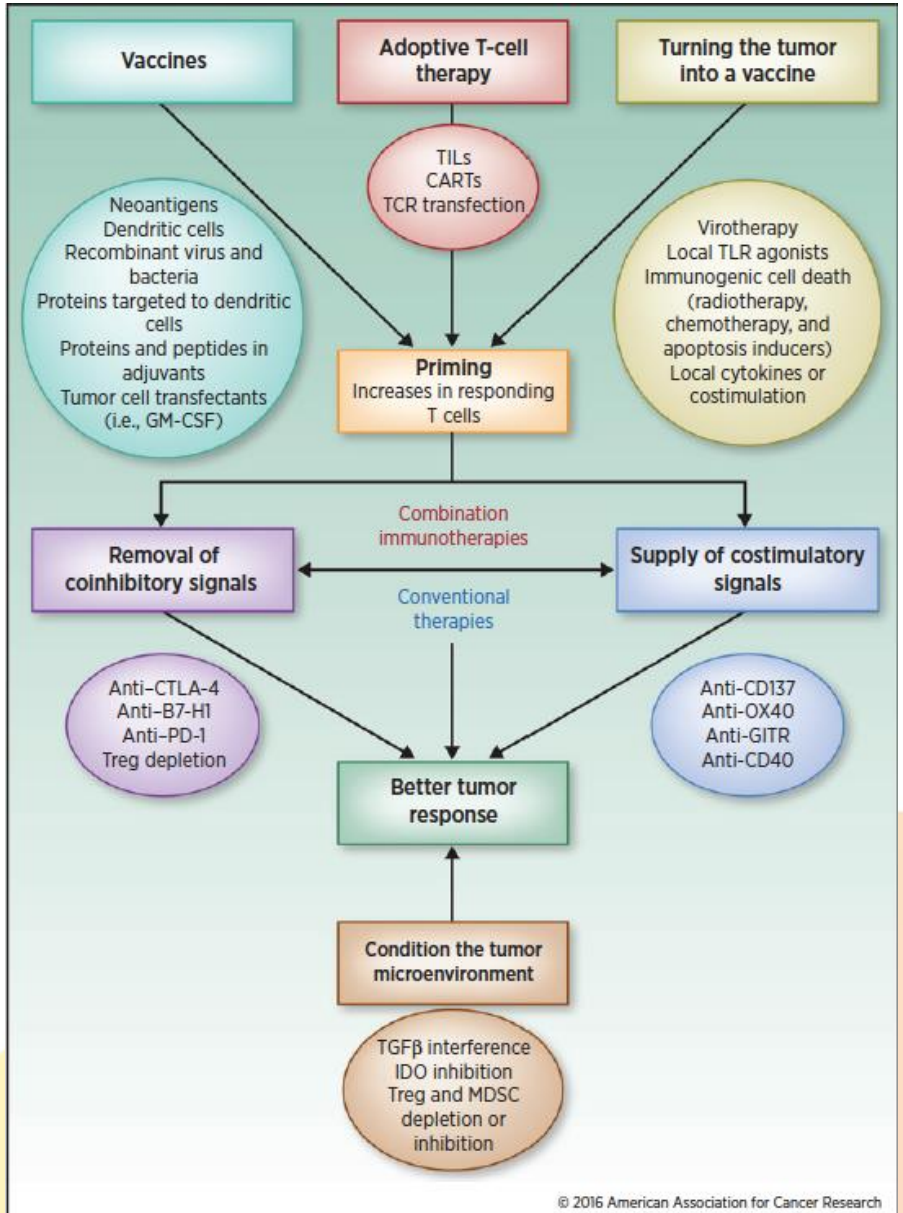
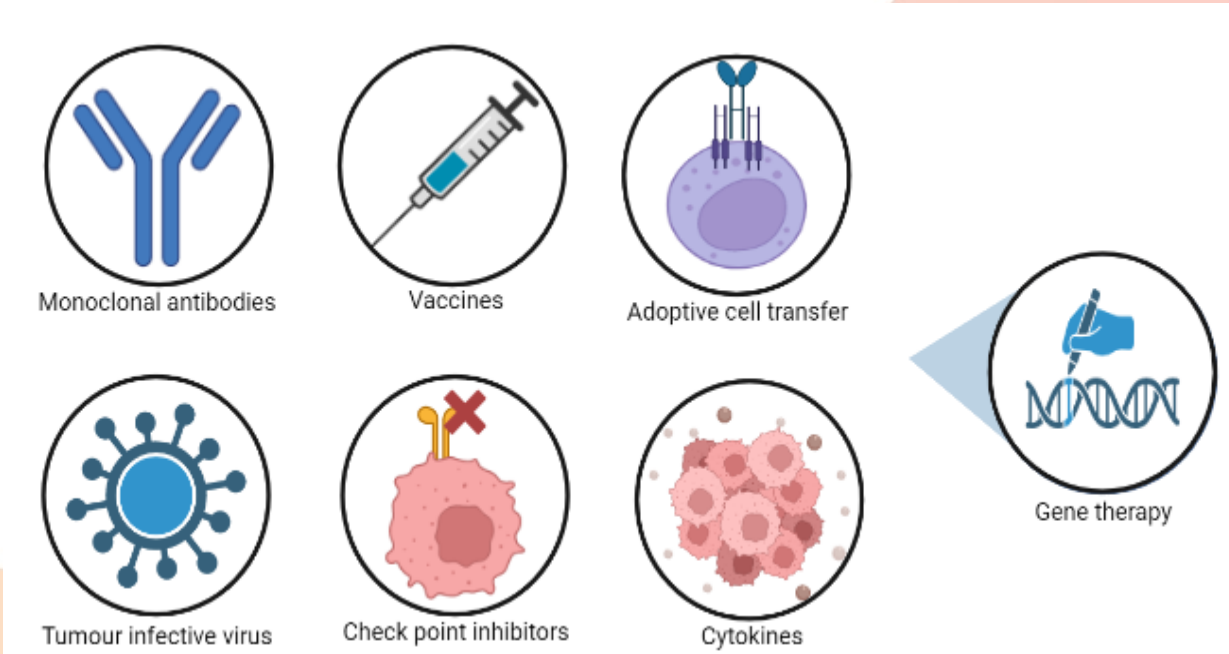
Estrategias generales de inmunoterapia del cáncer





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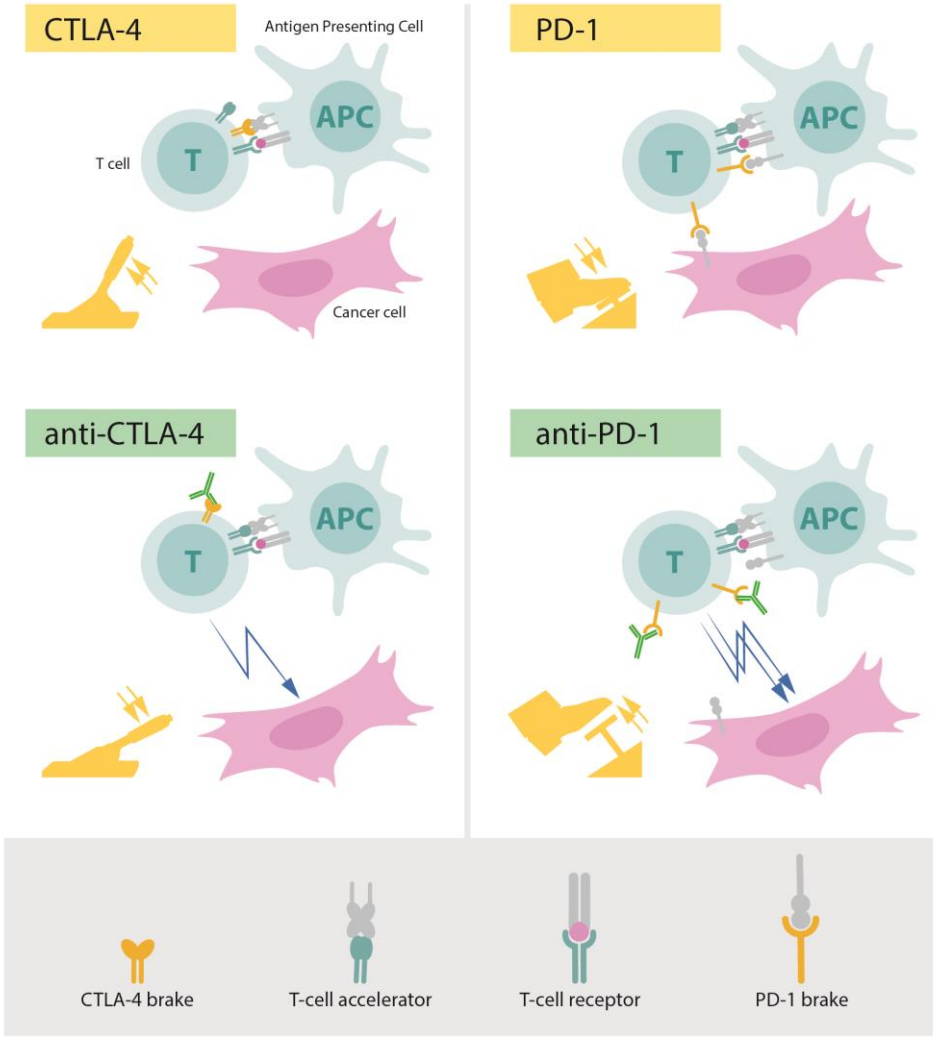
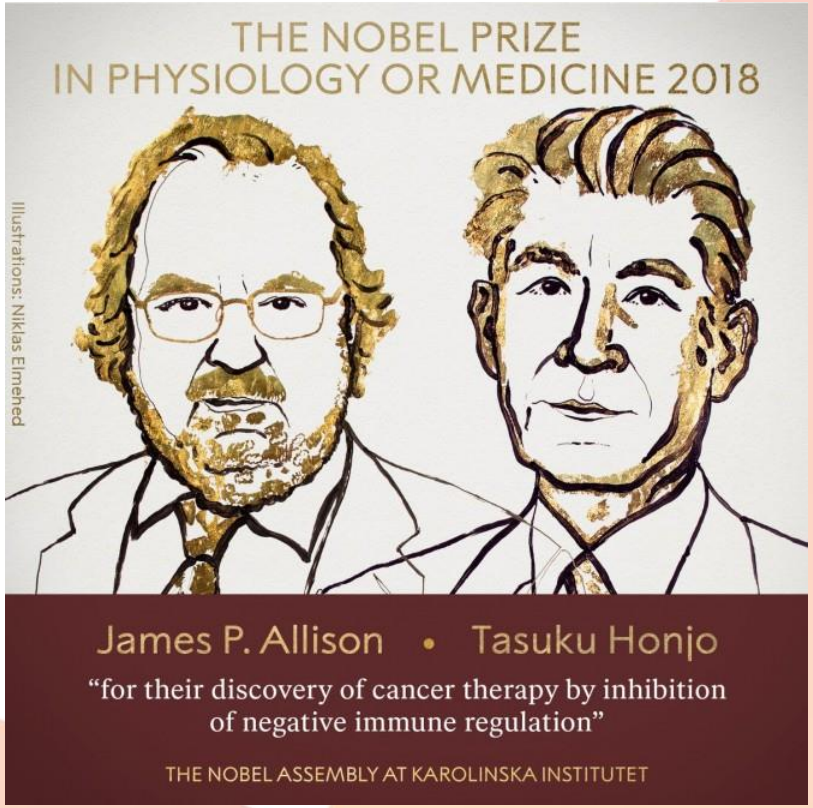
Inhibidores de los puntos control inmunitario (Immune check points)





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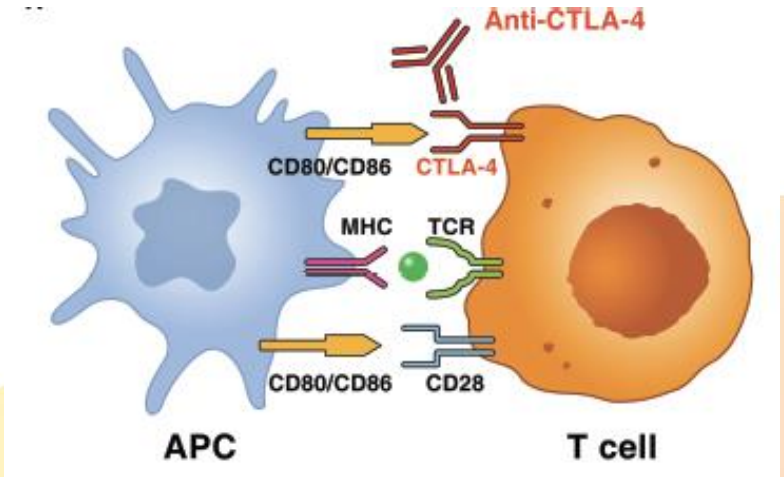
Inhibidores de los puntos control inmunitario (*Immune check point inhibitors-ICIs*)

Cytotoxic T-lymphocyte associated protein (CTLA4)

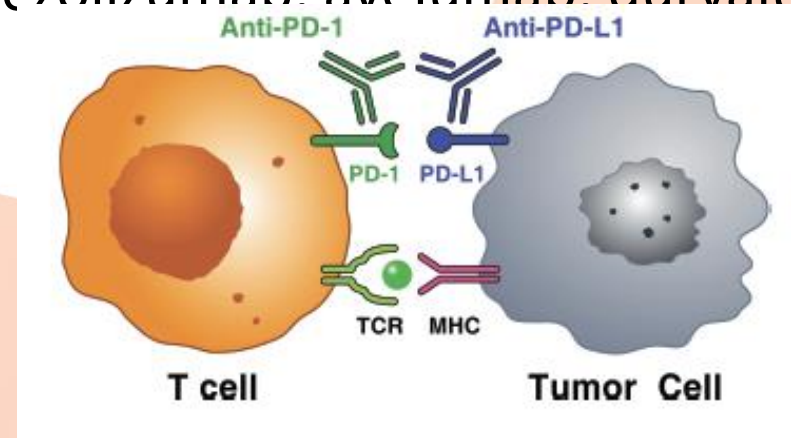
- Ipilimumab (IgG1)



Programmed cell death protein 1 (PD-1)

Programmed cell death protein ligand 1 (PD-L1)

- Nivolumab, prembolizumab (IgG4)
- Cemiplimab
- Atezolizumab, avelumab, durvalumab



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Poto R, Troiani T, Criscuolo G, Marone G, Ciardiello F, Tocchetti CG, Varricchi G. Holistic Approach to Immune Checkpoint Inhibitor-Related Adverse Events. Front Immunol. 2022 Mar 30;13:804597

Dianas principales de los *irAEs*

Box 2 | **Organ-based classification of immune-related adverse events in patients with cancer treated with immune checkpoint inhibitors**

Cardiac
- Myocarditis*
  - Autoimmune myocarditis
  - Myocardial fibrosis
- Pericarditis
  - Autoimmune pericarditis
  - Pericardial effusion
  - Pericardial tamponade

Dermatological
- Alopecia areata/universalis
- Dermatitis herpetiformе
- Erythema multiforme
- Granuloma annulare
- Lichen planopilaris/planus/lichenoid dermatitis
- Panniculitis/erythema nodosum
- Pemphigoid/pemphigus
- Psoriasis
- Pyoderma gangrenosum
- Sweet syndrome
- Vitiligo*

Endocrine
- Adrenitis*
  - Adrenal insufficiency
  - Cortisol deficiency
  - Hypercortisolism
  - Hypoadrenalism
  - Isolated adrenocorticotropic hormone deficiency
- Autoimmune diabetes mellitus
- Hyperparathyroidism
- Hypogonadism
- Hypophysitis*
  - Autoimmune hypophysitis
  - Hypopituitarism
  - Pan-hypopituitarism
- Thyroiditis*
  - Autoimmune thyroiditis
  - Hyperthyroidism
  - Hypothyroidism
  - Graves disease
  - Thyrotoxicosis

Gastrointestinal
- Enterocolitis*
  - Ileitis
  - Ileocolitis
  - Ischaemic colitis
  - Microscopic colitis
  - Ulcerative colitis
- Hepatitis*
  - Autoimmune hepatitis
  - Eosinophilic hepatitis
- Lymphocytic gastritis
- Pancreatitis

Haematological
- Aplastic anaemia/pure red cell aplasia
- Autoimmune haemolytic anaemia
- Autoimmune neutropenia
- Haemophagocytic lymphohistiocytosis
- Immune thrombocytopenic purpura

Muscular
- Myalgias*
- Myositis*
  - Anti-synthetase syndrome
  - Bulbar myopathy
  - Dermatomyositis
  - Diaphragmatic lymphocytic polymyositis
  - Necrotizing myopathy
  - Orbital myositis

Neurological
- Aseptic meningitis
- Encephalitis
- Cranial nerve involvement
  - Bilateral hearing loss
  - Facial palsy
  - Oculomotor paresis
- Motor neuropathy
  - Acute generalized motor neuropathy
  - Multifocal motor block neuropathy
- Myasthenia gravis
- Neuromyelitis optica spectrum disorders
  - Optic neuritis
  - Transverse myelitis
- Polyneuropathies*
  - Axonal sensory motor polyneuropathy
  - Multiplex mononeuritis
  - Peripheral sensory neuropathy
- Polyradiculopathies
  - Chronic inflammatory demyelinating polyneuropathy
  - Guillain–Barré syndrome

Ocular
- Conjunctivitis
- Episcleritis/scleritis
- Orbital inflammation
- Uveitis*
  - Anterior uveitis
  - Chorioretinopathy
  - Iridocyclitis/iritis
  - Panuveitis
  - Posterior uveitis
- Vogt–Koyanagi–Harada syndrome

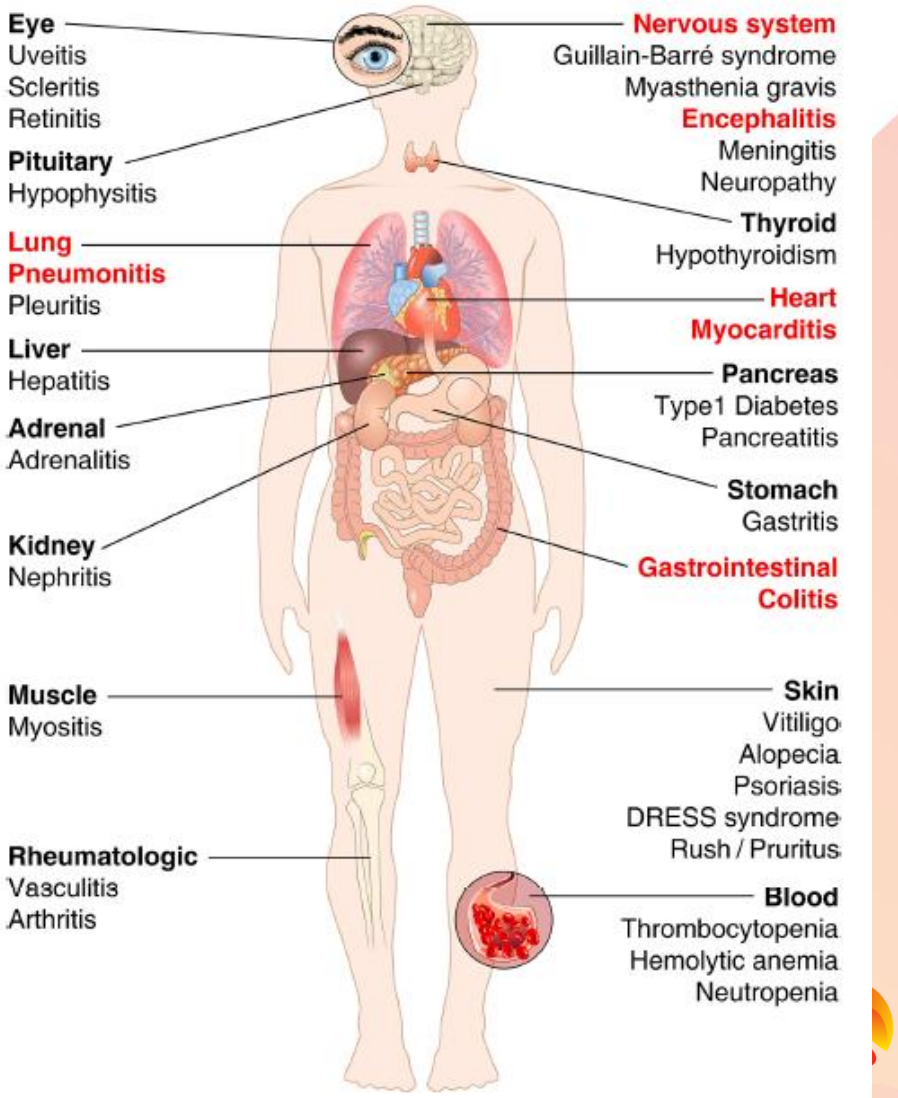
Pulmonary
- Interstitial lung disease*
  - Alveolitis
  - Organizative pneumonitis
  - Pneumonitis
  - Pulmonary fibrosis
  - Pulmonary haemorrhage

Renal
- Acute tubulointerstitial nephritis/renal tubular acidosis
- Glomerulonephritis

Skeletal
- Arthralgia*/polyarthralgia
- Arthritis*
  - Monoarthritis
  - Oligoarthritis
  - Polyarthritis
- Enthesitis
- Fasciitis/eosinophilic fasciitis
- Jaccoud arthropathy
- Polymyalgia rheumatica
- Psoriatic arthritis
- Rheumatoid arthritis
- Spondyloarthropathy
- Tenosynovitis

Systemic
- Antiphospholipid syndrome
- Lupus
  - Lupus nephropathy
  - Subacute cutaneous lupus erythematosus
  - Systemic lupus erythematosus
- Sarcoidosis
  - Cutaneous sarcoidosis
  - Pulmonary sarcoidosis
  - Renal sarcoidosis
- Sicca syndrome*/Sjögren syndrome
- Systemic sclerosis
- Vasculitis*
  - Cerebral vasculitis
  - Cryoglobulinaemia
  - Cutaneous vasculitis
  - Eosinophilic granulomatosis with polyangiitis
  - Giant cell arteritis
  - Pulmonary vasculitis
  - Henoch–Schönlein purpura

*More than 100 cases reported[4].



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Immune-related adverse events (irAEs)

Incidencia

anti-CTLA-4 > anti-PD1, anti-PDL1

Terapia combinada > monoterapia

Diana

anti-CTLA-4 : colitis, hipofisitis

anti-PD1, anti-PDL1: T1DM, pneumonitis.

Colitis, hepatitis, pancreatitis, T1DM mayor tendencia a alto grado

Tiempo

Melanoma anti-CTLA-4:

dermatológicas: 2-3 semanas

gastrointestinales, hepáticas: 6 semanas

endocrinológicas: 6-9 semanas

Immune-related adverse events (irAEs)

Resolución

Alto grado: 2-6 semanas con tratamiento

Artritis: persistente

Alteraciones endocrinas: T1DM, hipotiroidismo: irreversibles

Mortalidad

Aparición temprana, terapia de combinación, 40% miocarditis, 5% colitis

No siempre mismas **características** que sus modelos espontáneos

Clínica, tasa de auto-anticuerpos, respuesta a tratamiento

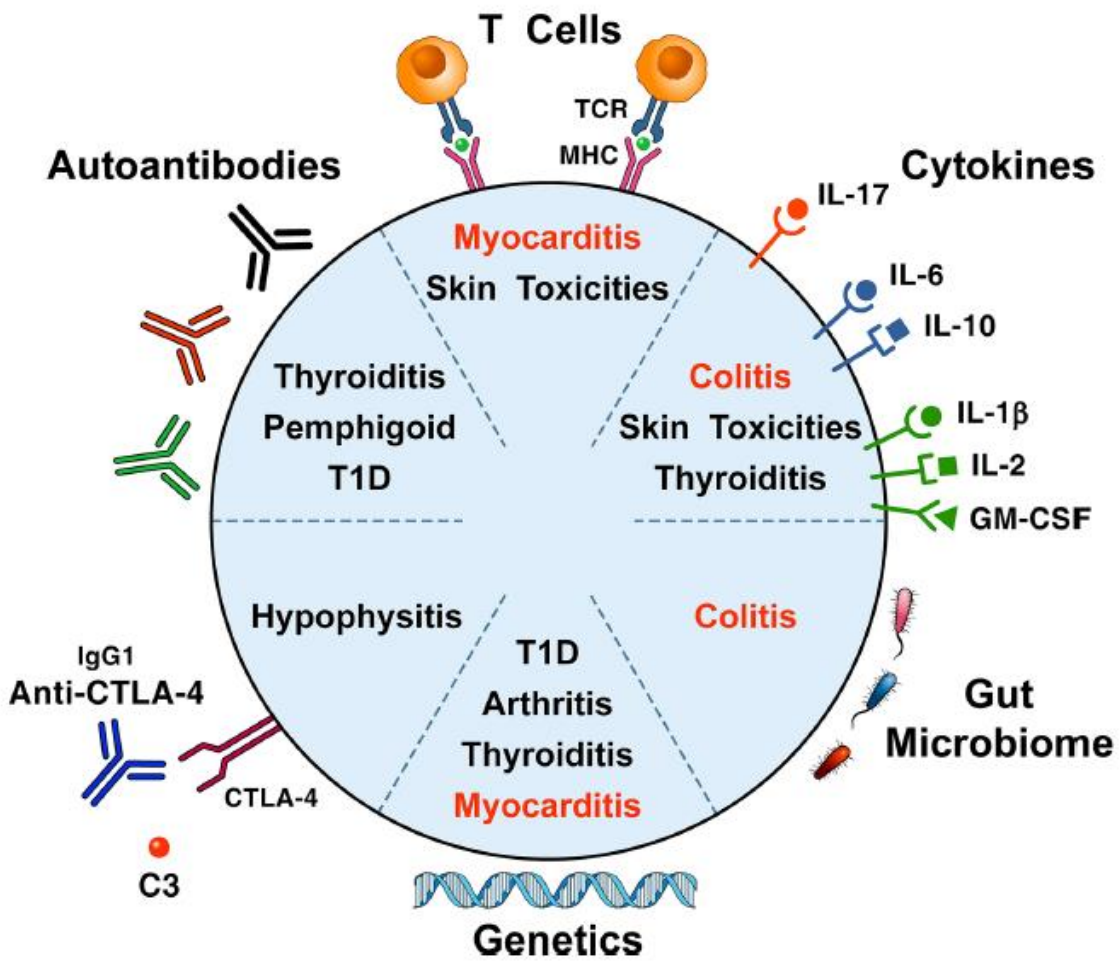
irAEs crónicos

Endocrinopatia, artritis

CTLA-4, PD-1/PDL-1 : reguladores negativos de la ateroesclerosis

Aceleración de eventos cardiovasculares

Immune-related adverse events (irAEs): mecanismos y dianas



Inmunidad celular

Linfocitos T autorreactivos: antígenos compartidos, respuesta clonal

Miocarditis, complicaciones dermatológicas

Alteración de linfocitos T reguladores

Inmunidad de anticuerpos

Anticuerpos anti-tiroideos: hipotoroidismo

Anticuerpos anti-células beta pancreáticas: T1DM

Anticuerpos anti- BP180: en penfigoide bulloso

Anticuerpos anti-acetil colina: MG

Anticuerpos anti-CCP y FR: artritis

Depósito de complemento mediado por IgG1

Glándula pituitarias expresa CTLA-4

Síndrome de liberación de citocinas (CRS)

Leve (fiebre, rash, fatiga) a severo, fatal

IL-17 colitis

IL-6 e IL-10: dermatológicas

IL-1β e TNF-α: grade 3 colitis

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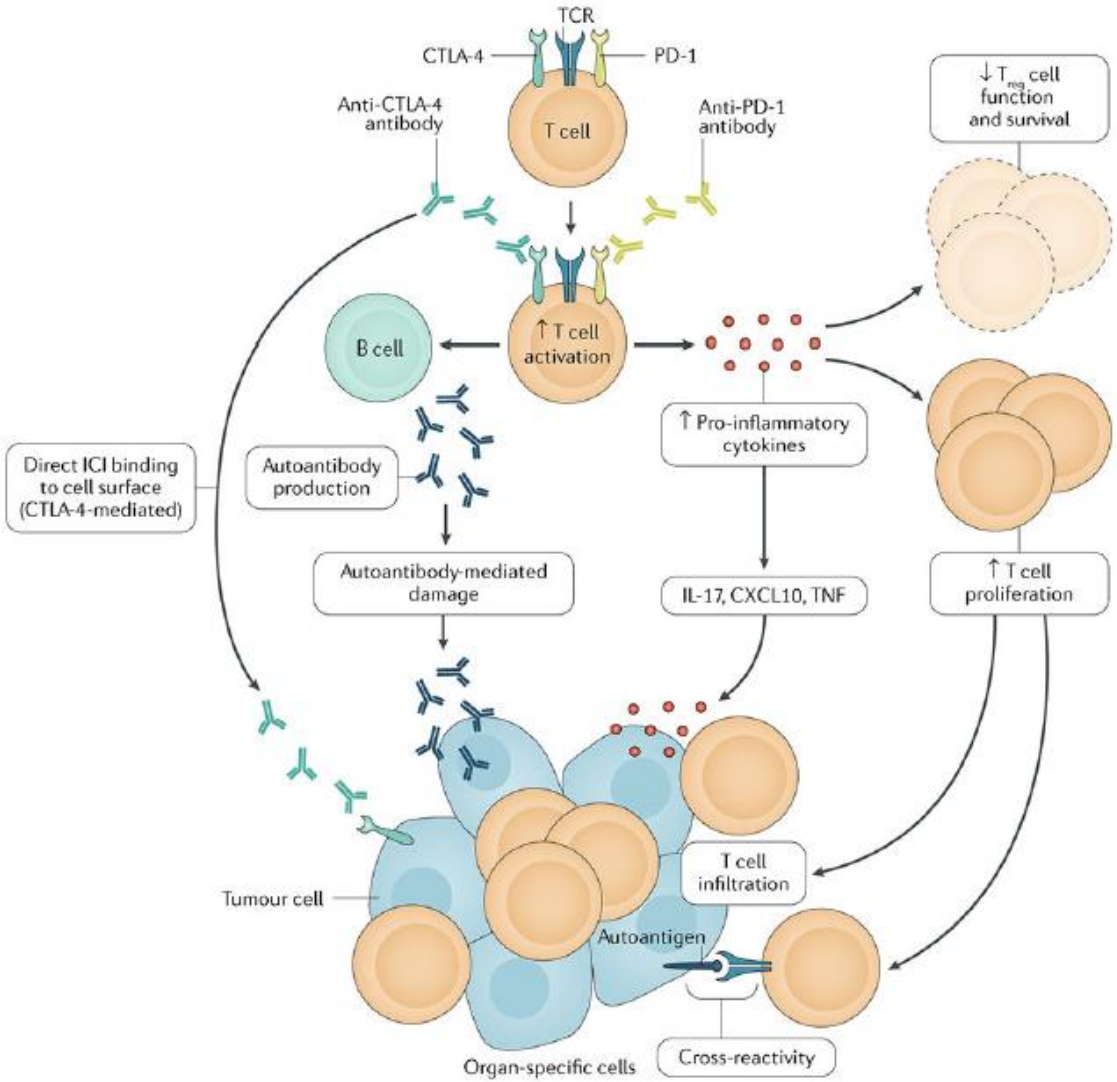
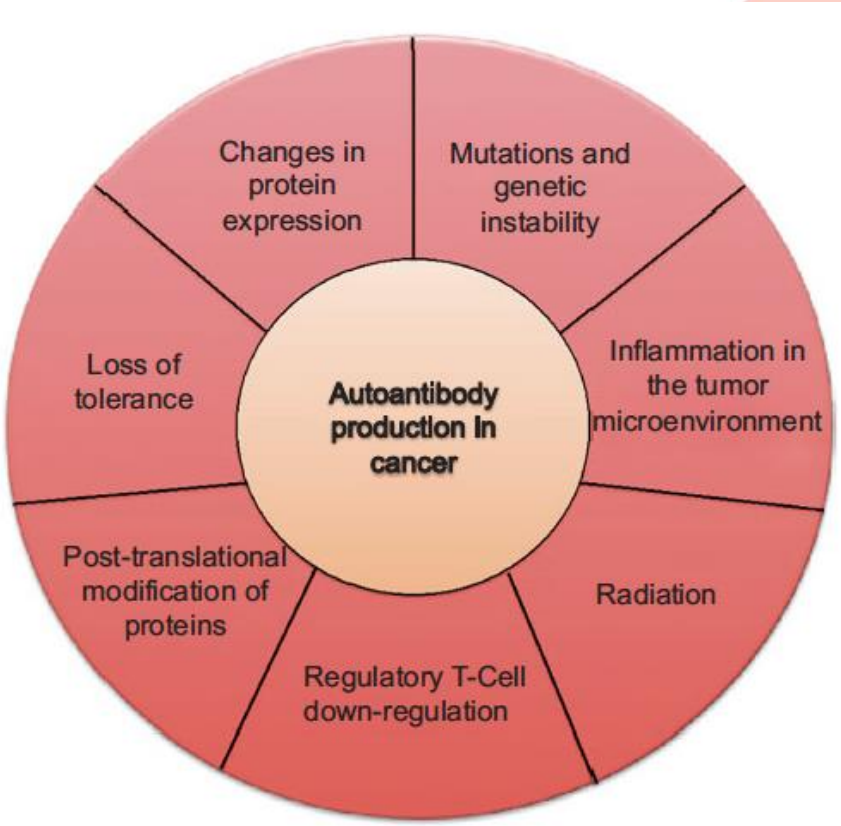
Mecanismos de los *irAEs: linfocitos T y B*





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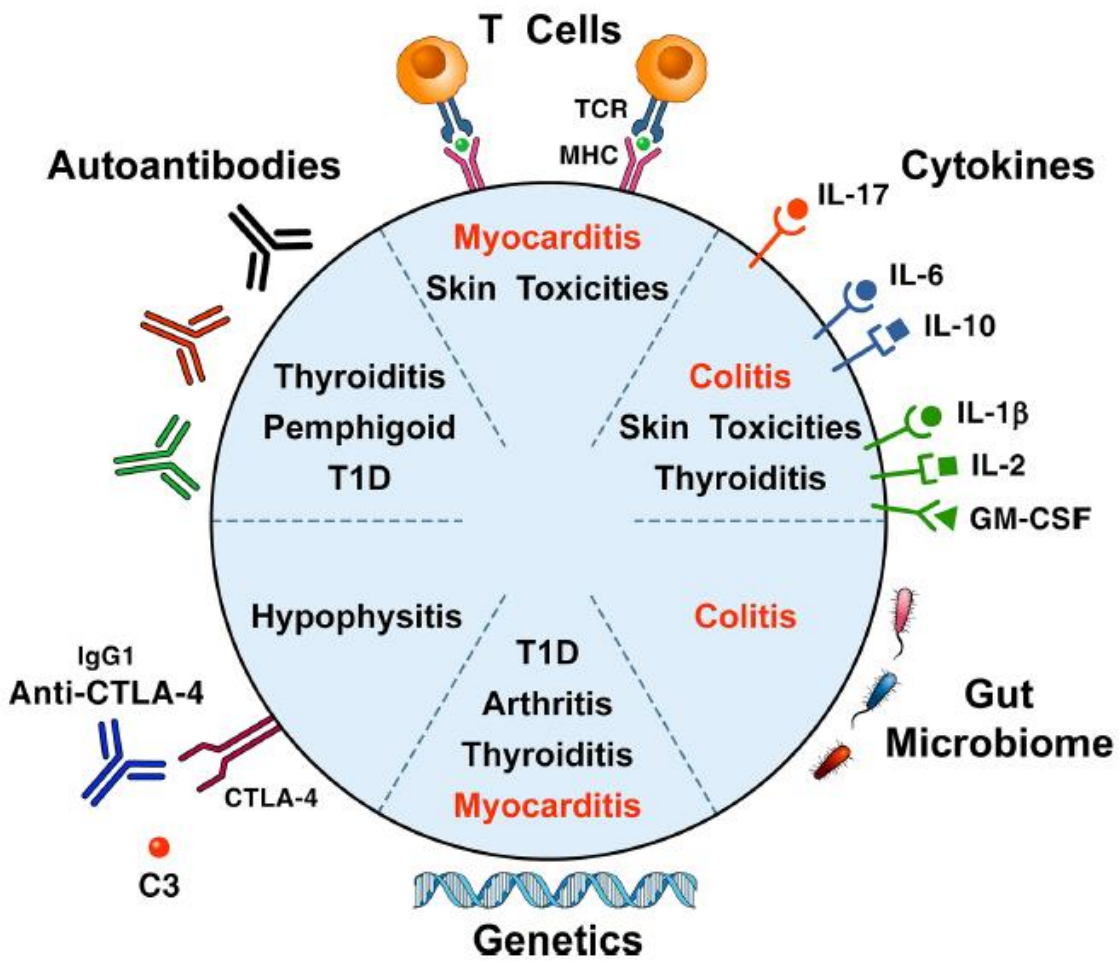
Immune-related adverse events (irAEs): mecanismos y dianas



Predisposición genética

Modelos experimentales

Haplotipos HLA de riesgo: HLA-DR de artritis, T1DM, artritis

Score de riesgo poligénico (PRS) para tiroiditis y alteraciones cutáneas

Microbioma intestinal

Relacionado con eficacia y riesgo de irAEs

Enfermedad autoinmune previa

Psoriasis, AR, EII, LES, vasculitis

Brotes manejados sin discontinuar tratamiento. Manejo multidisciplinar

irAEs: asociado a mejor pronóstico de la respuesta tumoral

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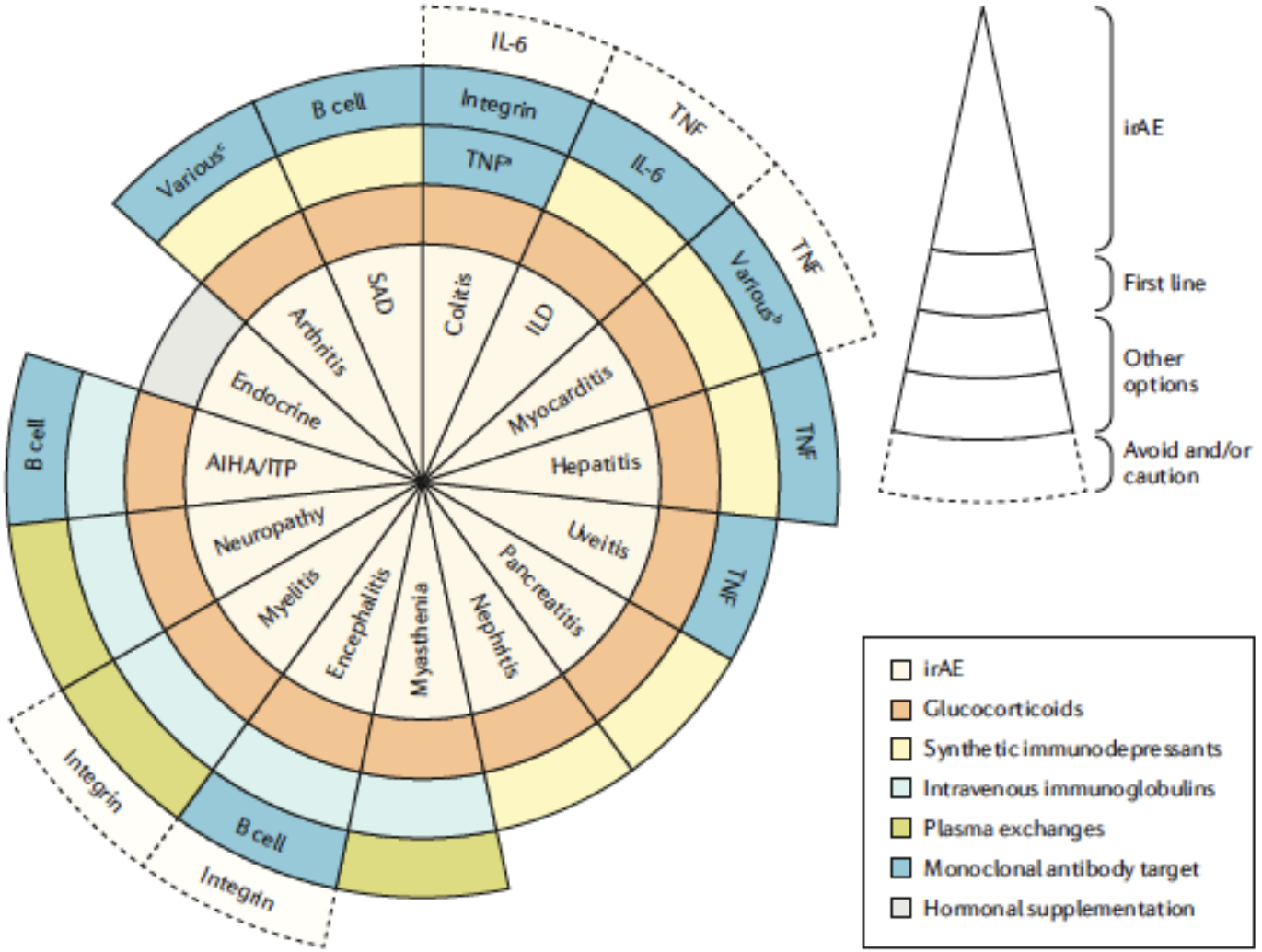
Líneas generales del tratamiento de los *irAEs*



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Terapias emergentes

Drug	Mechanism of action	Efficacy in reversing irAE	Effect on tumor response	Clinical trial
Vedolizumab	Anti-integrin α4β7 mAb	Colitis (137, 248). Prevention of autoimmune flares in patients with IBD (249).	Favorable clinical outcomes (248, 249).	NCT04407247: Comparison of vedolizumab *versus* infliximab for clinical response of ICI-induced diarrhea/colitis. NCT04797325: Comparison of vedolizumab *versus* prednisolone for clinical response of ICI-induced colitis.
Alemtuzumab	CD52 mAb	Myocarditis (198).	Unknown	
Abatacept	CTLA-4 agonist	Myocarditis (250).	Unknown	
Rituximab	Anti-CD20 mAb	Neurological complications (e.g., encephalitis and myasthenia gravis), bullous pemphigoid-like skin disease, renal vasculitis, hematological complications (12, 175, 204, 251–253).	Progression, partial and complete responses reported (251–253).	NCT03719131: Evaluation of rituximab on ICI-induced irAEs.
Tocilizumab	Anti-IL-6 receptor mAb	Pneumonitis, colitis, and pancreatitis (254). Inflammatory arthritis (255).	Clinical improvement with trend towards worse survival with increased doses of tocilizumab (254). 1/3 patients maintained anti-tumor response (255).	NCT03999749: Evaluation of tocilizumab on diarrhea and/or colitis and/or arthritis induced by ICIs. NCT04691817: Evaluation of tocilizumab on irAEs in patients with non-small lung cancer (NSCLC) treated with atezolizumab.
Secukinumab	Anti-IL-17A mAb	Psoriatic rash and colitis (256). Psoriasiform dermatological complication (257).	Tumor progression occurred in one patient (256). No impact on tumor response (257).	
Anakinra	IL-1 receptor antagonist	Experimental intestinal inflammation associated with combined immune checkpoint blockade in mice (96).	Unknown	NCT04576429: Evaluation of anakinra on irAEs and cytokine profile in patients with different cancers.
Fecal microbiota transplant	Possibly increased Tregs and decreased effector T cells (258).	Colitis (258).	Unknown	NCT04038619: Phase I trial of fecal microbiota transplant (FMT) for ICI-induced colitis/diarrhea. NCT04163289: Prevention of irAEs using fecal microbiota transplant. NCT03819296: Prevention of gastrointestinal irAEs by FMT in patients with melanoma or genitourinary cancer.
Certolizumab	anti-TNF-α			NCT03293784: Comparison of infliximab or certolizumab + nivolumab + ipilimumab in patients with melanoma.
Intravenous immunoglobulin (IVIG)				NCT04438382: Comparison of infliximab versus IVIG in patients with pneumonitis.

Tratamiento vs. prevención farmacológica

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Potenciales biomarcadores pronóstico de los *irAEs pre*

Potential biomarker	Determinant	Results	Significance	Accuracy	Cancer type	n	Treatment	Study design	References
Cellular									
Neutrophil to lymphocyte ratio (NLR)	Ratios calculated from peripheral neutrophil, eosinophils and lymphocyte count; and albumin	NLR ≥3 associated with less irAEs	OR_{adj} = 0.37; 95%CI 0.17–0.81; p = 0.012	–	Solid tumor	391	Anti-PD-1	Retrospective cohort	(17)
NLR; prognostic nutrition index (PNI)	Ratio calculated from neutrophil and lymphocyte counts; LDH and serum albumin	Low NLR (<5) and high PNI (≥45) independently associated with irAEs	p < 0.001 | p = 0.001	–	NSCLC	102	Anti-PD-1	Retrospective cohort	(18)
Platelet to lymphocyte ratio (PLR)	Ratios calculated from peripheral neutrophil, lymphocyte, and platelet counts	PLR <180 associated with irAEs	OR_{adj} = 2.3; 95%CI 1.1–4.8; p = 0.027	–	NSCLC	173	Anti-PD-(L)1	Retrospective cohort	(19)
Eosinophils	Peripheral blood cell counts	Eosinophil count associated with grade ≥2 irAEs	OR_{adj} = 1.003; 95%CI 1.000–1.006; p = 0.027	–	Solid tumor	167	Anti-PD-1, combination	Retrospective cohort	(20)
	Peripheral blood cell counts	Eosinophil count of >240/µl associated with endocrine (but not any) irAEs	OR = 7.0; 95%CI 1.50–32.72; p = 0.0134	Sens = 88% Spec = 50%	Advanced melanoma	44	Anti-PD-1	Retrospective cohort	(21)
Lymphocytes	Peripheral blood cell counts	Lymphocyte count >2,000 associated with risk of grade ≥2 irAEs	OR_{adj} = 1.996; 95% CI 1.16–3.49; p = 0.014	–	Solid tumor	167	Anti-PD-1, combination	Retrospective cohort	(20)
	Myeloid and T cell subsets by flow cytometry	Lower % PD-1 expression on CD4+ and CD8+ T cells associated with grade ≥3 irAEs	p = 0.025 | p = 0.022	–	Metastatic melanoma	44	Anti-CTLA-4	Retrospective cohort	(22)
	CD4+ T cells and Treg cells counts at baseline	Lower percentage of Tregs associated with colitis	p = 0.018	–	Metastatic melanoma	18	Anti-CTLA-4	Prospective cohort	(23)

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Hommes JW, Verheijden RJ, Suijkerbuijk KPM, Hamann D. Biomarkers of Checkpoint Inhibitor Induced Immune-Related Adverse Events-A Comprehensive Review. Front Oncol. 2021 Feb 11;10:585311

Potenciales biomarcadores pronóstico de los *irAEs pre*

Potential biomarker	Determinant	Results	Significance	Accuracy	Cancer type	n	Treatment	Study design	References
Cytokines/Chemokines									
IL-6	5 cytokines and lymphocyte subsets	Lower IL-6 levels associated with grade ≥3 irAEs	OR = 2.84; 95%CI 1.34–6.03; p = 0.007	Sens = 70% Spec = 66%	Metastatic melanoma	140	Anti-CTLA-4	Prospective cohort	(24)
IL-6, IL-8, and sCD25	Baseline IL-6, IL-8 and sCD25 in serum	Lower levels of IL-6, IL-8, and sCD25 associated with colitis	p = 0.008 | p = 0.0031 | p = 0.0097	–	Melanoma	18	Anti-CTLA-4	Prospective cohort	(23)
IL-17	Multiplex serum testing for 36 different cytokines and chemokines	Higher IL-17 levels associated with grade ≥3 colitis and grade ≥3 irAEs	p = 0.02 | p = 0.03	–	Advanced melanoma	35	Anti-CTLA-4	Clinical trial	(25)
Various cytokines/ chemokines	65 cytokines/ chemokines profiles; validated in separate cohort	CYTOX score (G-CSF, GM-CSF, fractalkine, FGF-2, IFNα2, IL1a, IL1B, IL1RA, IL2, IL12p70 and IL13) associated with irAEs that required ICI discontinuation or immunosuppression	p = 0.0366	AUC = 0.68	Melanoma	49	Anti-PD-1 or combination	Prospective cohort	(26)
IL-1β, IL-2, GM-CSF	13 cytokines in serum	Increased levels of IL-1β, IL-2, and GM-CSF correlated with thyroid irAEs	p < 0.05	–	Advanced malignancies	26	Anti-PD-1, anti-CTLA-4, or combination	Prospective cohort	(27)
CXCL9, CXCL10, CXCL11, CCL19	40 cytokines in serum	Lower levels of CXCL9, CXCL10, CXCL11, and CCL19 associated with irAEs	p < 0.05	–	Solid tumor	42	Anti-PD-(L)1	Prospective cohort	(28)

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Potenciales biomarcadores pronóstico de los *irAEs pre*

Potential biomarker	Determinant	Results	Significance	Accuracy	Cancer type	n	Treatment	Study design	References
Autoantibodies									
Anti-thyroid antibodies	Thyroid peroxidase and thyroglobulin antibodies in serum	Anti-Tg and anti-TPO associated with thyroid dysfunction	$p < 0.001$ | $p = 0.002$	–	NSCLC	64	Anti-PD-1	Retrospective cohort	(29)
	Anti-thyroid antibodies in serum	Anti-Tg antibody, but not anti-TPO associated with thyroid dysfunction	$OR_{adj} = 26.5$; 95% CI 8.18–85.8; $p < 0.001$ | $p > 0.05$	–	Solid tumor	168	Anti-PD-1	Retrospective cohort	(30)
Anti-BP180 IgG	Serum IgG directed against BP180, BP230, and type VII collagen measured by ELISA	Anti-BP180 IgG levels associated with dermal irAE	$p = 0.04$	–	NSCLC	40	Anti-PD-(L)1	Prospective cohort	(31)
Anti-GNAL and anti-CD74	Identification of autoantibodies using recombinant cDNA expression libraries	Anti-GNAL presence associated with hypophysitis | anti-CD74 presence associated with pneumonitis	OR = 2.66; 95%CI 1.14–7.29; $p = 0.02$ OR = 1.25; 95%CI 1.03–1.52; $p = 0.03$	AUC = 1 for both	Solid tumor	20 32	Anti-CTLA-4, anti-PD-1, combination	Nested prospective cohort	(32)
Various autoantibodies	Autoantibodies tested with HuProt array covering >19,000 proteins	Enrichment of autoantibodies directed against targets in (auto) immunity pathways associated with grade ≥3 irAEs Classification model based on baseline antibody levels predicts risk of developing severe irAEs	$p < 0.05$	- Classification models: Sens≥0.89 Spec≥0.85 for each therapy	Melanoma	75	Anti-CTLA-4, anti-PD-1, combination	Prospective cohort	(33)

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Potenciales biomarcadores pronóstico de los *irAEs pre*

TABLE 1 | Continued

Potential biomarker	Determinant	Results	Significance	Accuracy	Cancer type	n	Treatment	Study design	References
Immunogenetics									
Single-nucleotide polymorphisms (SNPs)	7 SNPs in the *PDCD1*, *PTPN11*, *ZAP70* and *IFNG* genes analyzed using whole blood DNA sequencing	PDCD1 804C>T associated with increased irAE risk in exploration cohort, but not in validation cohort	p = 0.039 | p = 0.828	–	NSCLC	161| 161	Anti-PD-1	Prospective cohort	(34)
	166 SNPs in 86 immune or cancer related genes analyzed using sequenom MassArray iPLEX assay	SNPs in *UNG*, *IFNW1*, *IFNL4*, *PD-L1*, and *CTLA-4* associated with grade ≥3 irAEs	p < 0.05	AUC = 0.89 Sens = 0.8 Spec = 0.85	Solid tumor	94	Anti-PD-(L)1	Retrospective cohort	(35)
	Polygenic risk scores for skin autoimmunity computed with whole-genome germline sequencing	Psoriasis-associated polygenic risk score associated with skin irAEs	p < 0.05	–	Bladder cancer	220	Anti-PD-L1	Retrospective analysis of clinical trial data	(36)
	miR-146a rs2910164 CC genotype	rs2910164 CC genotype associated with grade 3-4 irAEs	OR = 6.78; 95%CI 1.87–24.6; p = 0.004	–	Solid tumor	167	Anti-PD-(L)1	Prospective cohort	(37)
Human leukocyte antigen (HLA)	HLA-A*02:01 subtype	No association between HLA-A*0201 status and irAEs	Not reported	–	Melanoma	450	Anti-CTLA-4	Retrospective analysis of pooled clinical trial data	(38)
	HLA loci with common variants associated with autoimmune disease	No association of HLA and risk of any irAE HLA-DRB1*11:01 associated with pruritis and HLA-DQB1*03:01 with colitis	Not reported OR = 4.53; p = 0.002 | OR = 3.94; p = 0.017	–	Melanoma, NSCLC	102	Anti-CTLA-4, anti-PD-1, combination	Prospective cohort	(39)
	HLA subtypes in patients with ICI-induced diabetes	Higher HLA-DR4 frequency compared to general population and spontaneous type I diabetes is associated with ICI-induced diabetes	p < 0.0001 | p = 0.002	–	Solid tumor	23	Anti-CTLA-4, anti-PD-1, combination	Case series	(40)
	HLA haplotypes in patients with ICI-induced adrenal insufficiency	HLA-DR15 associated with pituitary irAEs	p = 0.0014	–	Advanced cancer	11	Anti-PD-1 or anti-CTLA-4	Case-control study	(41)

GUARD CONSORTIUM

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Potenciales biomarcadores pronóstico de los *irAEs post*

Potential biomarker	Determinant	Results	Significance	Accuracy	Cancer type	n	Treatment	Study design	References
Cellular									
Leukocytes	Peripheral blood cell counts after irAE onset**	Increase in leukocyte count and decrease in relative lymphocyte count associated with grade ≥3 irAEs in univariable, but not multivariable analysis	OR_{adj} = 1.13; 95%CI 0.99–1.29; p = 0.074 | OR_{adj} = 1.18; 95%CI 0.94–1.48; p = 0.15	–	Melanoma	101	Anti-PD-1	Retrospective cohort	(45)
Eosinophils	Leukocyte subsets at 1, 3 and 6 months*	Absolute eosinophil count after 1 month associated with grade ≥2 irAEs	OR_{adj} = 1.002; 95%CI 1.000–1.004; p = 0.027	–	Solid tumor	167	Anti-PD-1, combination	Retrospective cohort	(20)
	Absolute and relative eosinophil counts after 1, 3 and 6 months*	Relative eosinophil count at 1 month >3.2% associated with endocrine irAEs	OR = 5.11; 95%CI 1.23-21.3; p = 0.025	Sens = 67% Spec = 72%	Melanoma	44	Anti-PD-1	Retrospective cohort	(21)
	Relative eosinophil count after onset of dermal irAEs compared with baseline**	Relative eosinophil count increased during treatment in patients with dermal irAEs, but not in those without	p = 0.006 vs. p = 0.19	–	Melanoma	17	Anti-CTLA-4	Nested case control	(46)
Lymphocytes	Leukocyte subsets at 1, 3 and 6 months*	Lymphocyte count >2,000 at 1 month associated with risk of grade ≥2 irAEs, any irAEs and irAEs requiring treatment	OR_{adj} = 1.81; 95%CI 1.03–3.25; p = 0.039 | p < 0.05 | p < 0.01	–	Solid tumor	167	Anti-PD-1, combination	Retrospective cohort	(20)
	T-cell receptor β-chain sequencing in purified T cells from blood at baseline and before irAE occurrence (median 13 days; IQR 2-24)*	Clonal expansion of ≥55 CD8 T-cell clones associated with grade ≥2 irAEs	p < 0.0001	Sens = 100% Spec = 42% AUC = 0.87	Prostate cancer	27	Anti-CTLA-4 + androgen deprivation	Retrospective analysis of clinical trial data	(47)
	T-cell receptor β-chain sequencing in purified T cells from blood at baseline and week 2*	Clonal expansion of more T-cell clones and higher number of newly emerging T-cell clones are associated with irAEs; decline in T-cell clonality in patients with irAEs at week 2 versus baseline	p = 0.028 | p = 0.042; p = 0.023	–	Prostate cancer	21	Anti-CTLA-4 + GM-CSF	Retrospective analysis of clinical trial data	(48)
	Circulating B-cell changes after the first cycle of treatment compared to baseline*	≥30% decline in B cells and doubling of CD21lo cells or plasmablasts associated with grade ≥3 irAEs	p < 0.001	–	Melanoma	23	Combination of anti-CTLA-4 and anti-PD-1	Prospective cohort	(49)

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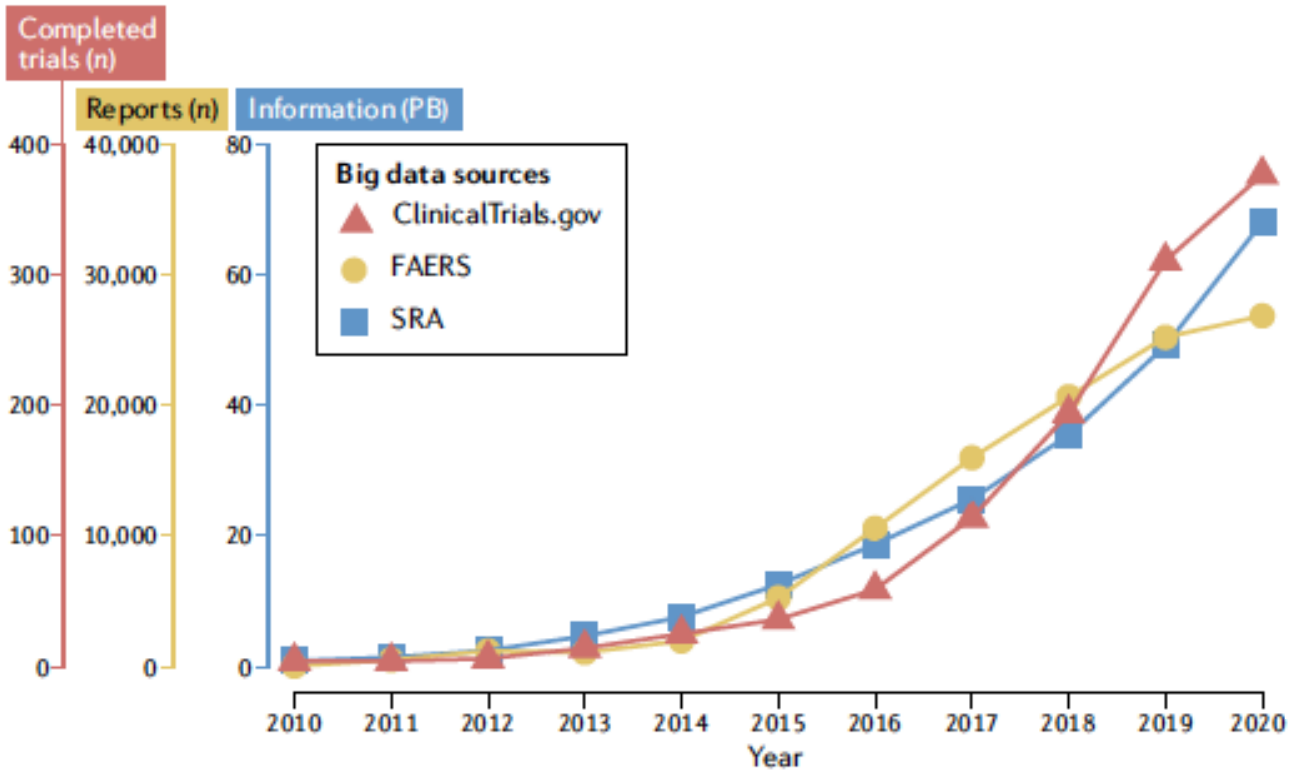
Medicina de precisión en inmunoncología: big data



Type of data source	Advantages	Disadvantages
Aggregate clinical data	Obtained in controlled clinical settings[79,80]	Some key patient-level information (such as sex, treatment history and time of onset of irAEs) and data on rare events might not be published[45]
Real-world data	Encompass information from a tremendously large number of patients[52,54]	The quality and completeness of real-world data can be suboptimal[30,81]
Multi-omics data	Could provide insights on the molecular mechanisms underlying irAEs[66–69]	Often lack comprehensive clinical annotation

GUARD CONSORTIUM

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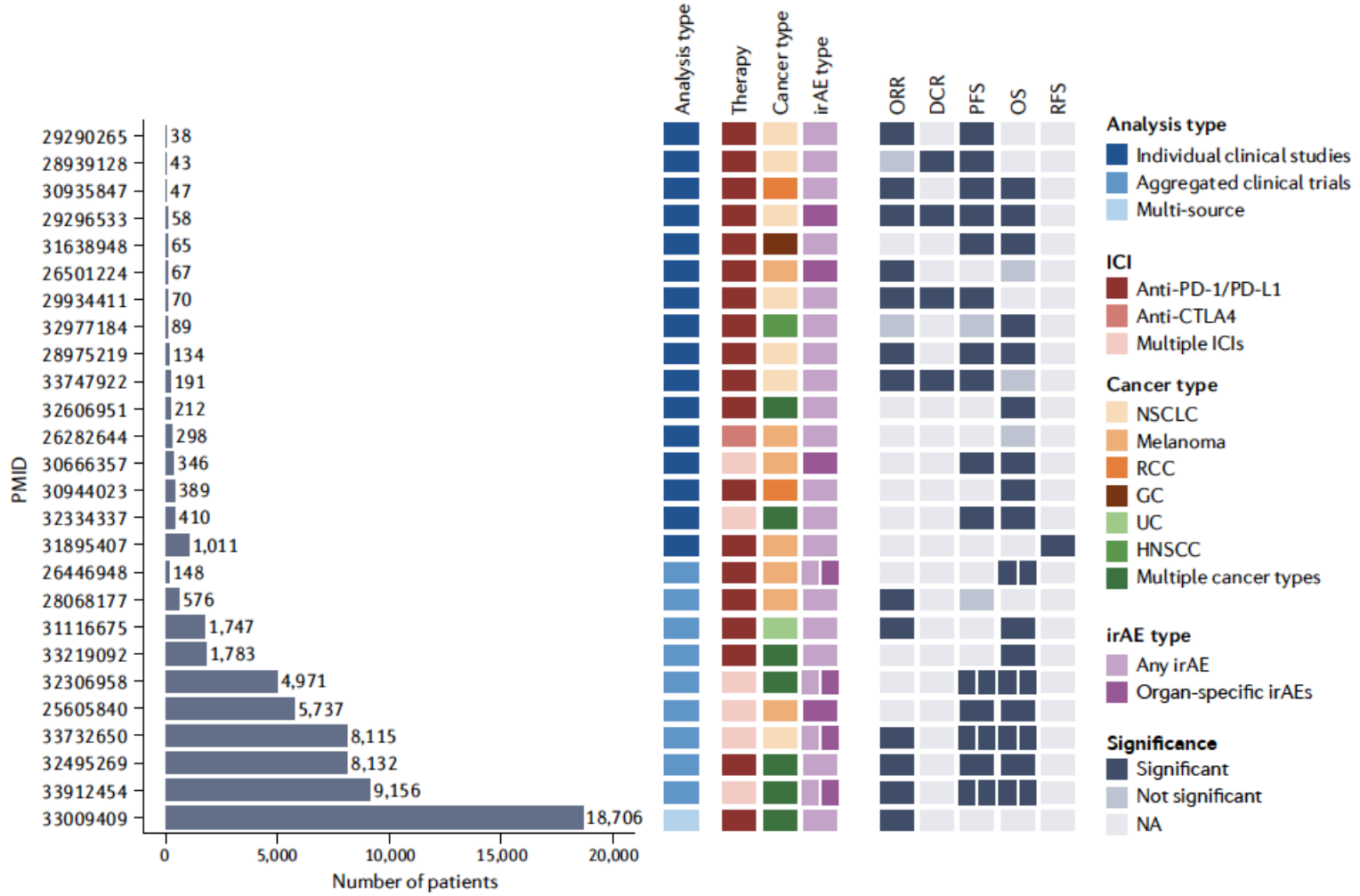

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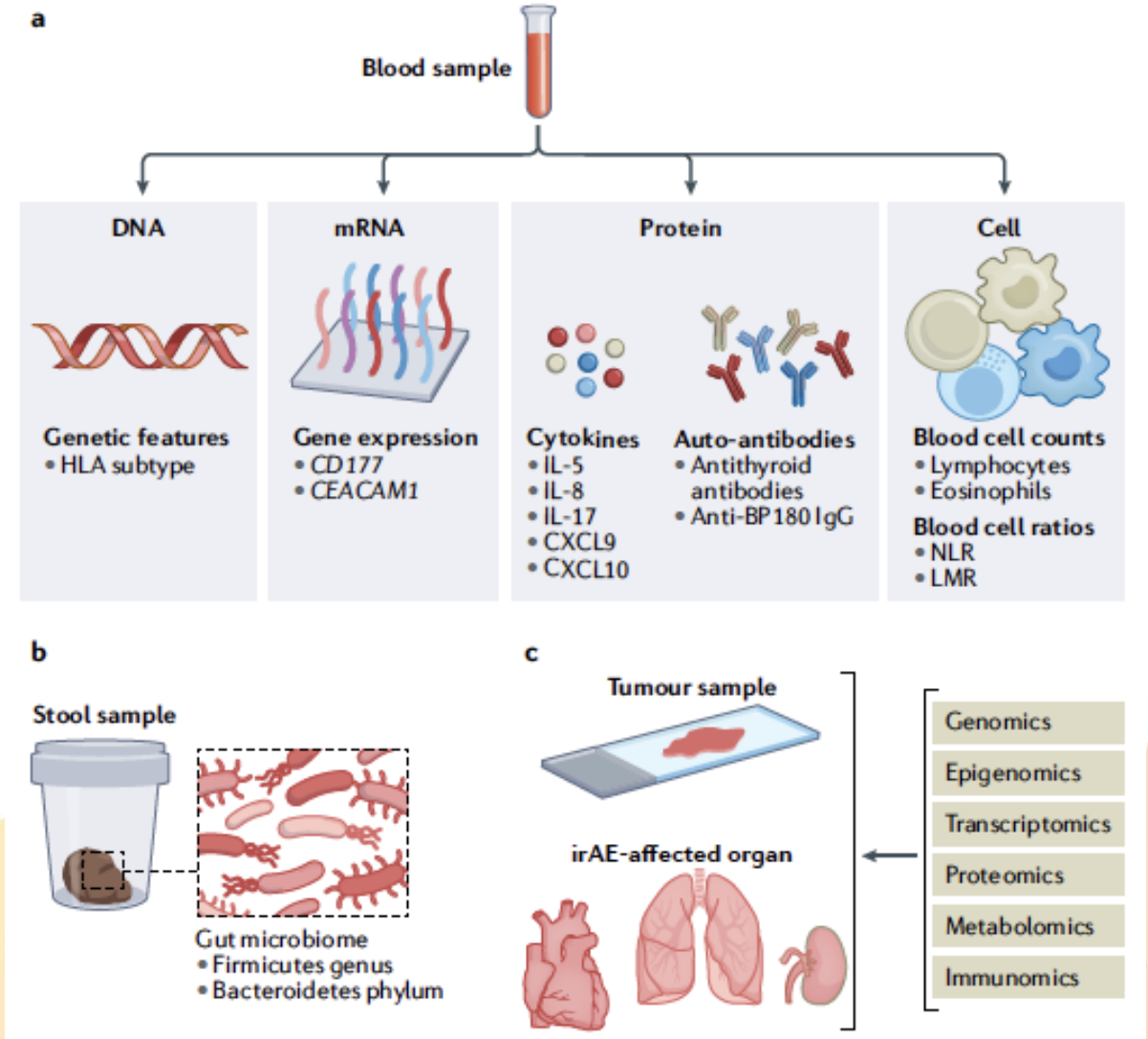
Medicina de precisión en inmunoncología: biomarcadores



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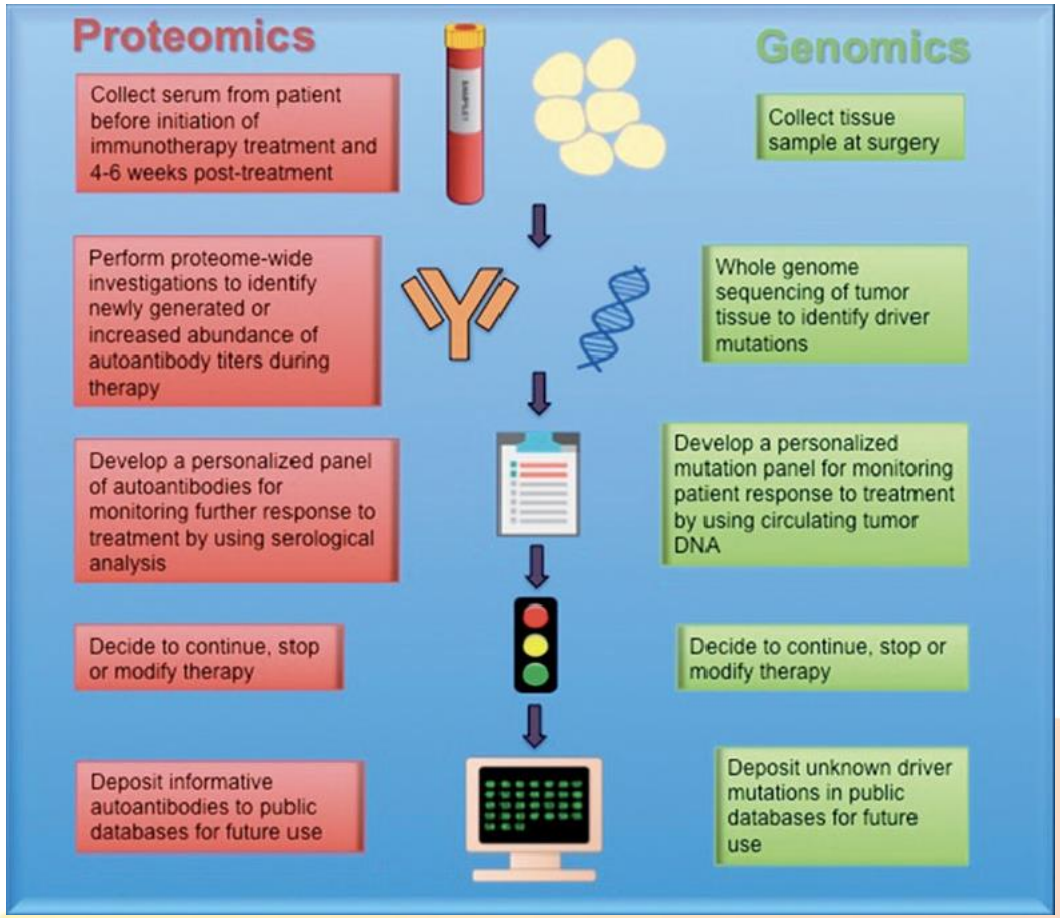

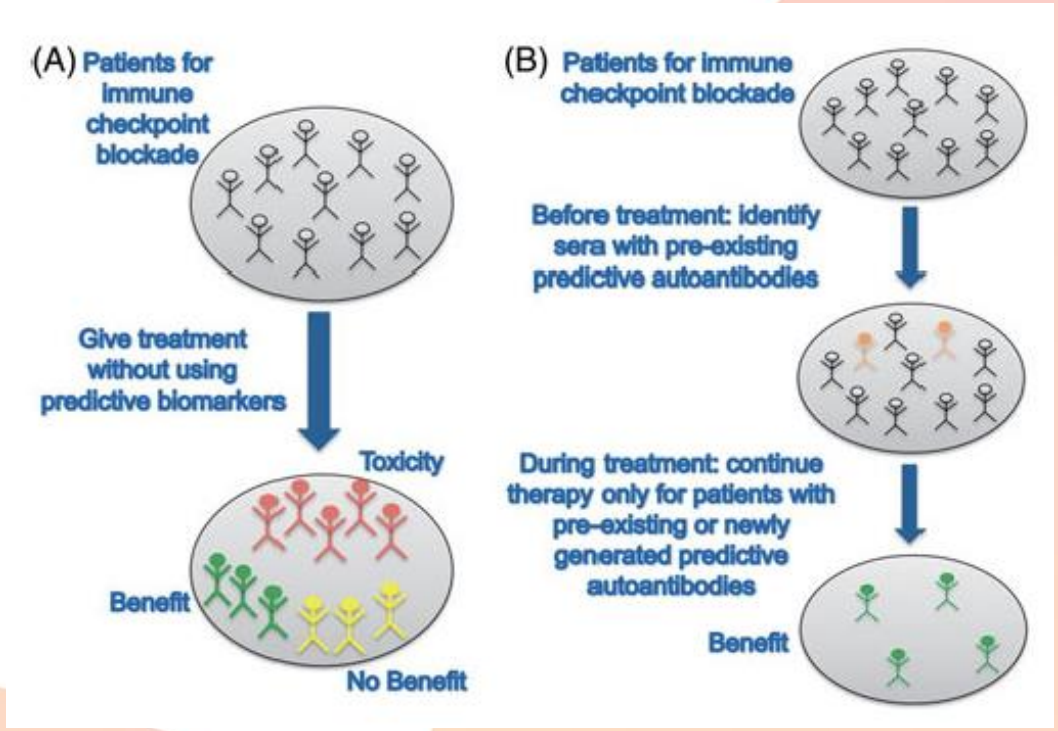

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Potenciales biomarcadores pronóstico de los *irAEs post*

Potential biomarker	Determinant	Results	Significance	Accuracy	Cancer type	n	Treatment	Study design	References
Cytokines/Chemokines									
IL-6	Pre- and post-treatment serum samples tested for IL-6, TNF-α, IFN-γ, IL-8 and IL-17A analysis[7]	Increased IL-6 levels in irAE patients post-treatment compared to pre-treatment, not in patients without irAEs	$p = 0.018$	–	Melanoma	20	Anti-PD-1	Case series	(50)
Various cytokines/ chemokines	65 cytokines/ chemokines profile at week 1-6 validated in separate cohort*	CYTOX score (G-CSF, GM-CSF, fractalkine, FGF-2, IFNα2, IL1a, IL1B, IL1RA, IL2, IL12p70, and IL13) associated with irAEs that required ICI discontinuation or immunosuppression	$p = 0.0168$	AUC = 0.70	Melanoma	49	Anti-PD-1 or combination	Prospective cohort	(26)
CXCL9, CXCL10	40 cytokines in serum tested at baseline and after 2-3 and 6 weeks*	A greater increase of CXCL9 and CXCL10 at week 6 in irAE patients compared to non-irAE patients	$p < 0.05$	–	Solid tumor	42	Anti-PD-(L)1	Prospective cohort	(28)
CCL5	75 serum proteins measured by Millipex MAP assay at baseline and after 4 weeks*	CCL5 levels at 4 weeks in irAE patients increased compared to non-irAE patients	$p < 0.05$	–	NSCLC	32	Anti-PD-1	Prospective cohort	(51)
sCD163	Serum levels of sCD163 and CXCL5 measured at day 0 and day 42*	Change from baseline of sCD163 level at day 42 was higher in irAE patients compared to non-irAE patients	$p = 0.0018$	Sens = 73% Spec = 75%	Melanoma	46	Anti-PD-1	Retrospective cohort	(52)
Autoantibodies									
Anti-thyroid antibodies	Anti-Tg and anti-microsomal antibodies measured at baseline and every cycle during treatment*/**	Anti-Tg present in 80% of patients with thyroid dysfunction compared to 8% of patients without	$p < 0.0001$	–	NSCLC	48	Anti-PD-1	Prospective cohort	(53)
	Autoantibodies tested at baseline and after 4 weeks*	Increased levels of anti-Tg and anti-TPO at 4 weeks compared to baseline associated with thyroid irAEs	$p = 0.012$ | $p = 0.048$	–	Advanced cancer	26	Anti-PD-1, anti-CTLA-4, or combination	Prospective cohort	(27)
Anti-GNAL and anti-ITM2B antibodies	Pre-treatment and post-treatment before irAE analysis with recombinant cDNA libraries	Stronger increase of anti-GNAL and anti-ITM2B in patients with hypophysitis	$p < 0.001$ | $p < 0.001$	AUC = 1 | AUC = 1	Solid tumor	20	Anti-CTLA-4, anti-PD-1, combination	Nested prospective cohort	(32)
Other									
CRP	CRP levels measured at baseline and just before or at irAE onset*/**	CRP levels rose from mean 8.4 mg/L at baseline to 52.7 mg/L at irAE onset	$p < 0.0001$	–	Melanoma	37	Anti-CTLA-4, anti-PD-1, combination	Case series	(12)
	CRP levels at baseline, at irAE onset and after tocilizumab administration**	CRP levels increased from median 23 mg/L at baseline to 109 mg/L at onset of irAEs and decreased to 19 mg/L after irAE treatment	$p < 0.00001$	–	Advanced cancer	34	Anti-PD-1	Case series	(54)
CD177	Gene expression profiling of 9697 non-control probe sets on whole blood samples at baseline, week 3 and 11*	Increased CD177 gene expression at 3 weeks in patients with GI irAEs compared to non-irAE patients and compared to baseline	$p = 0.0076$	–	Melanoma	162	Anti-CTLA-4	Retrospective analysis of clinical trial data	(55)

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Dilemas actuales ICIs

- Bases inmunopatogénicas de los distintos irAEs
- Bases genéticas de predisposición en distintos pacientes: desarrollo
- Bases genéticas y epigenéticas en distintos pacientes: dianas
- Podemos considerar los irAEs versiones de las enfermedades autoinmunes o nuevas entidades
- Aparición temprana vs. tardía
- ¿Se podrían acelerar los efectos cardiovasculares a largo plazo?
- Seguridad a largo plazo en pacientes con autoinmunidad preexistente
- ¿Podremos hacer medicina predictiva asociada al manejo de los ICIs?
- ¿Hay composiciones del microbioma asociado a complicaciones irAEs particulares?
- ¿Puede el estudio del microbioma ayudar a predecir las complicaciones, podemos modificarlo?
- ¿Podemos interceptar los irAEs?

¿Por qué produce toxicidad la inmunoterapia? Mecanismos principales

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