Effetti endocrino-metabolici delle immunoterapie e delle target therapies nel carcinoma mammario e prostatico avanzato

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Disclosure
as of September 10, 2023

UNIVERSITÀ DI TORINO

In the last 3 years I received:

- **Personal** honoraria for acting as consultant or participating to advisory boards:
  - AstraZeneca, Eisai, Janssen, Astellas, Amgen, Pfizer, Roche, Novartis, Boehringer Ingelheim, Merck Serono, MSD

- **Institutional** research grant:
  - Tesaro - GlaxoSmithKline

What we know:
Immune-related adverse events are frequent events

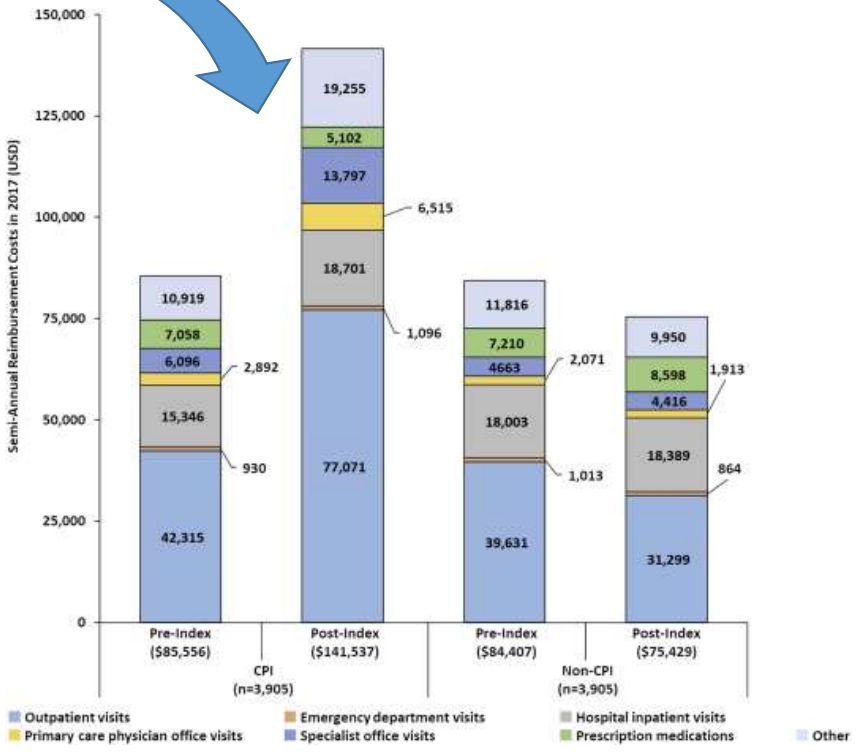
JAMA Oncology | Original Investigation

Use of Immunotherapy With Programmed Cell Death 1 vs Programmed Cell Death Ligand 1 Inhibitors in Patients With Cancer
A Systematic Review and Meta-analysis

Jianchun Duan, MD; Longgang Cui, PhD; Xiaochen Zhao, MD; Hua Bai, MD; Shangli Cai, PhD; Guoqiang Wang, PhD; Zhengyi Zhao, PhD; Jing Zhao, PhD; Shiqing Chen, PhD; Jia Song, PhD; Chuang Qi, PhD; Qing Wang, PhD; Mengli Huang, PhD; Yuzi Zhang, MD; Depei Huang, PhD; Yuezong Bai, PhD; Feng Sun, PhD; J. Jack Lee, PhD, DDS; Zhijie Wang, MD; Jie Wang, MD, PhD

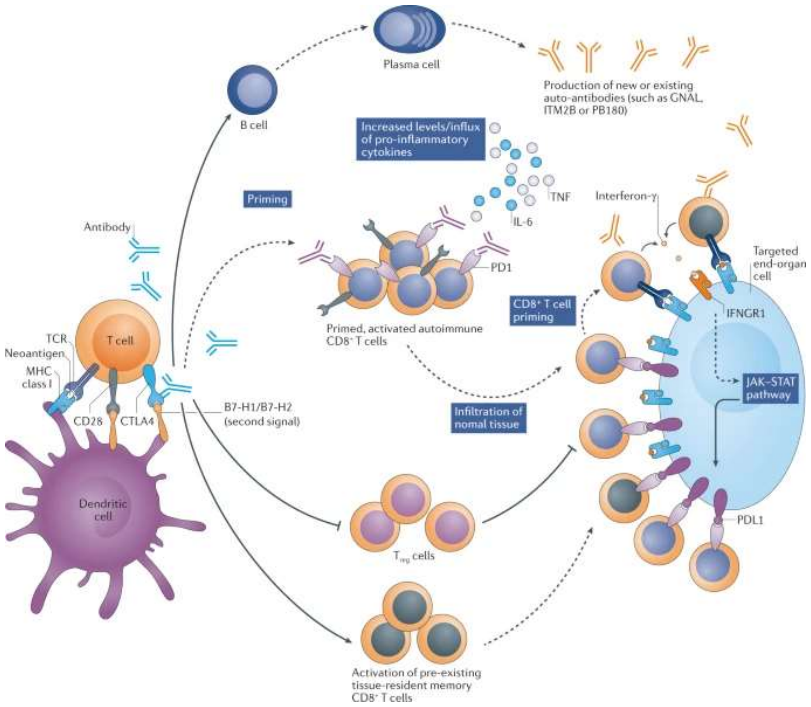
18,000patients:
- **66%** at least one IRAE of any grade
- **14% G3 or higher**

Impact on:
- Our clinical daily routine
- Health-systems



Economic Burden of Checkpoint Inhibitor Immunotherapy for the Treatment of Non–Small Cell Lung Cancer in US Clinical Practice.
https://doi.org/10.1016/j.clinthera.2020.06.018

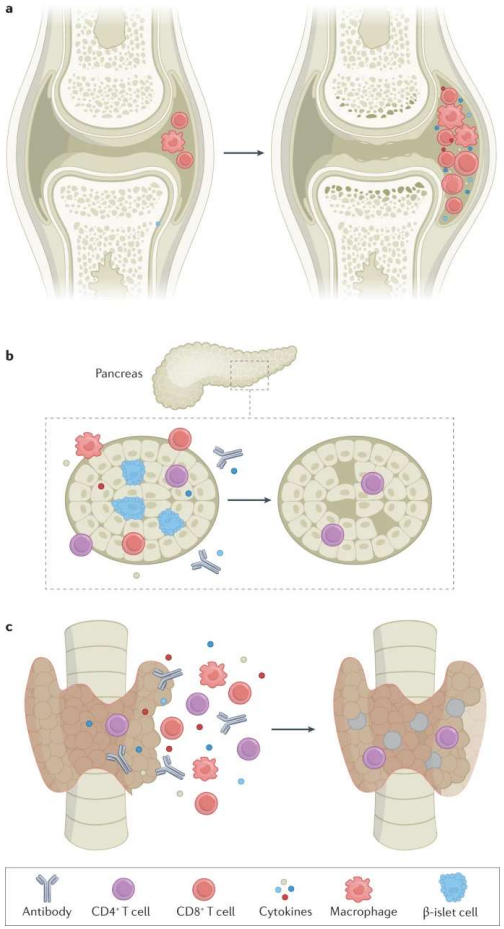
Different mechanisms drive immune-related adverse events



1. Expansion of existing autoantibodies by B cells
2. Disinhibition of T cells that destroy normal tissue
3. Secretion of high levels of cytokines
4. Binding of ICI antibodies to tissue and complement fixation

Sullivan, R.J., Weber, J.S. Immune-related toxicities of checkpoint inhibitors: mechanisms and mitigation strategies. *Nat Rev Drug Discov* (2021). https://doi.org/10.1038/s41573-021-00259-5

Different mechanisms drive immune-related adverse events



1. Expansion of existing autoantibodies by B cells
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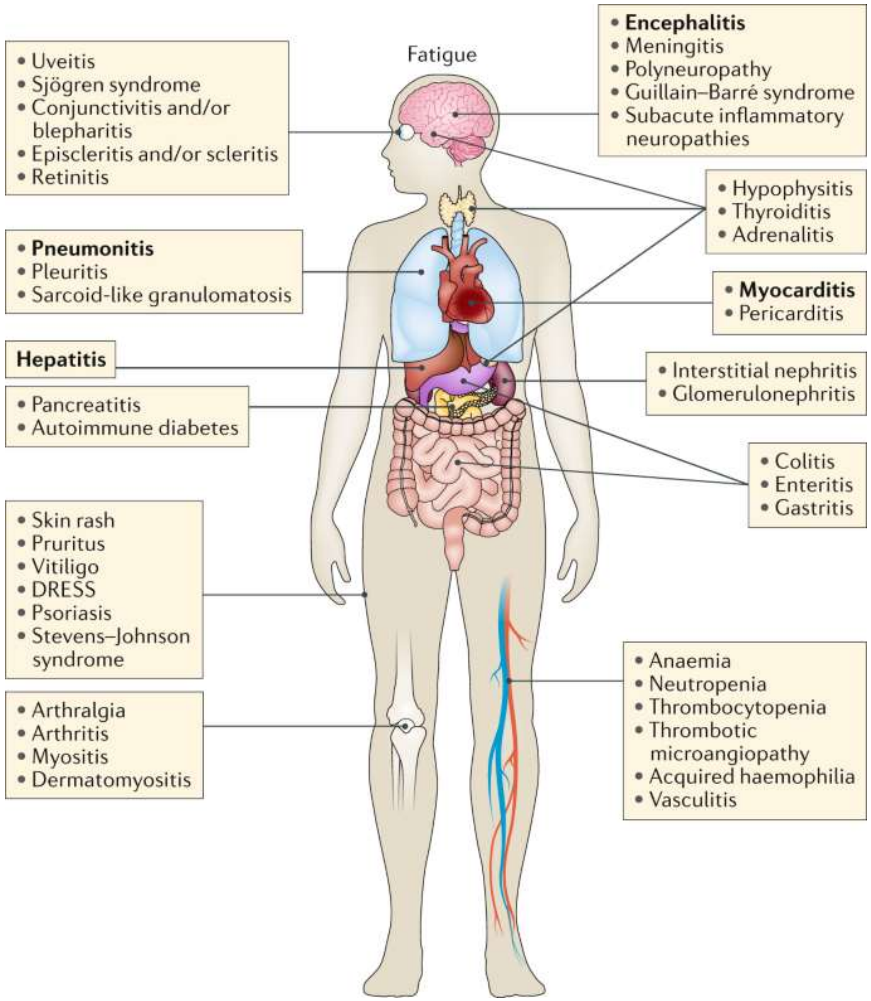
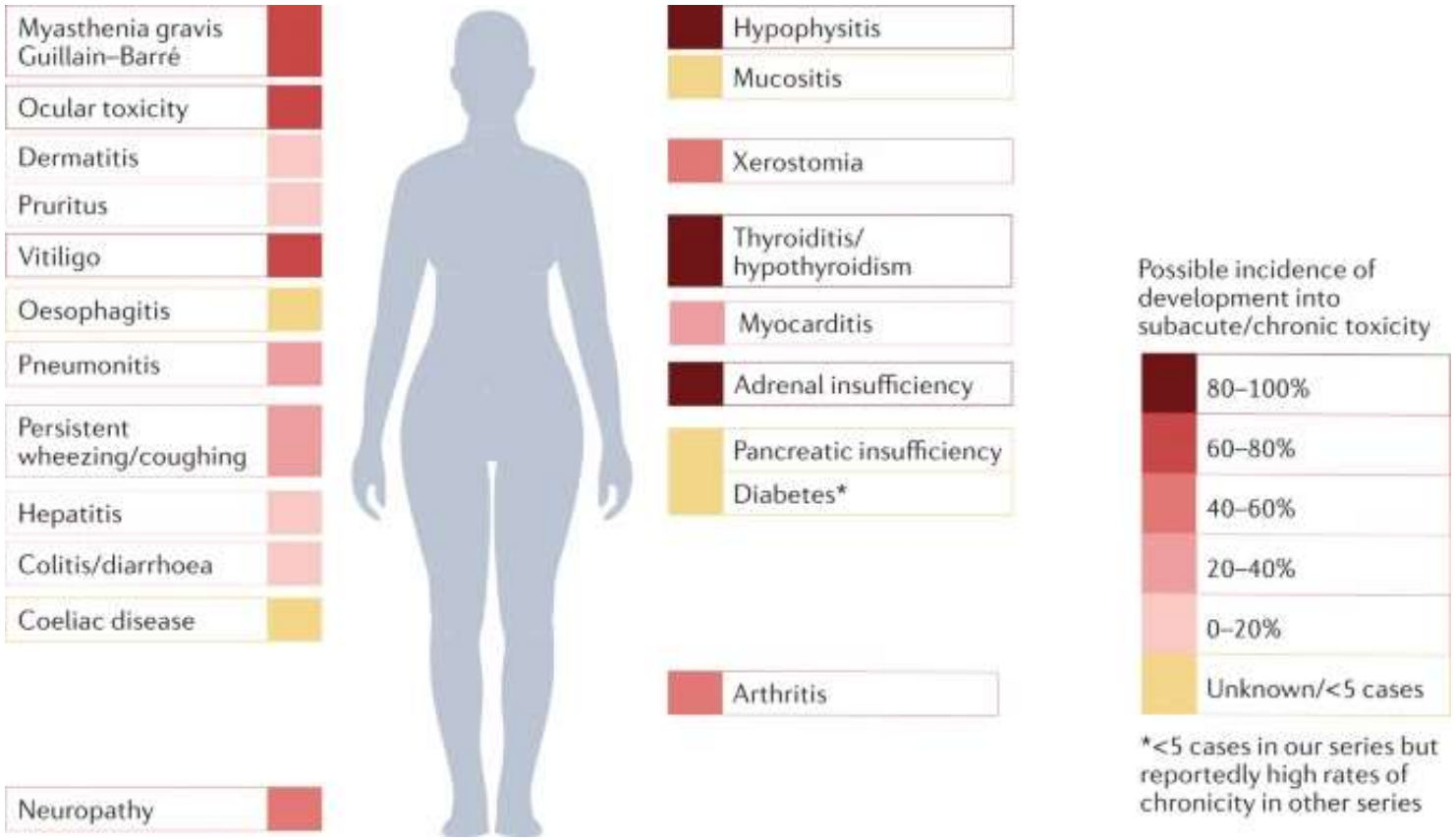
Sullivan, R.J., Weber, J.S. Immune-related toxicities of checkpoint inhibitors: mechanisms and mitigation strategies. *Nat Rev Drug Discov* (2021). https://doi.org/10.1038/s41573-021-00259-5

Broad spectrum of toxicities



Martins, F. *et al.* Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 16, 563–580 (2019). https://doi.org/10.1038/s41571-019-0218-0

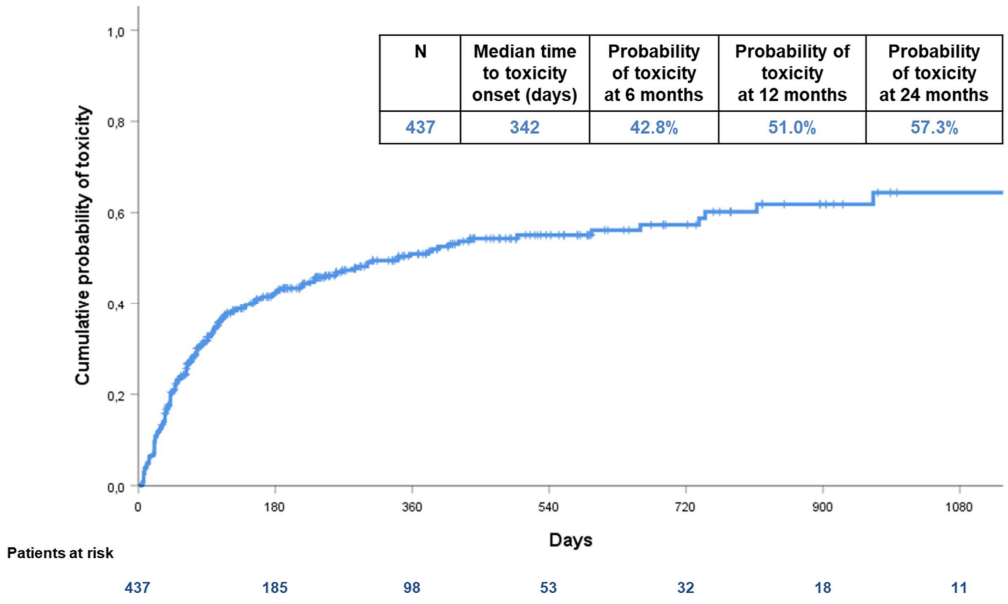
Immune-checkpoint inhibitors: long-term implications of toxicity



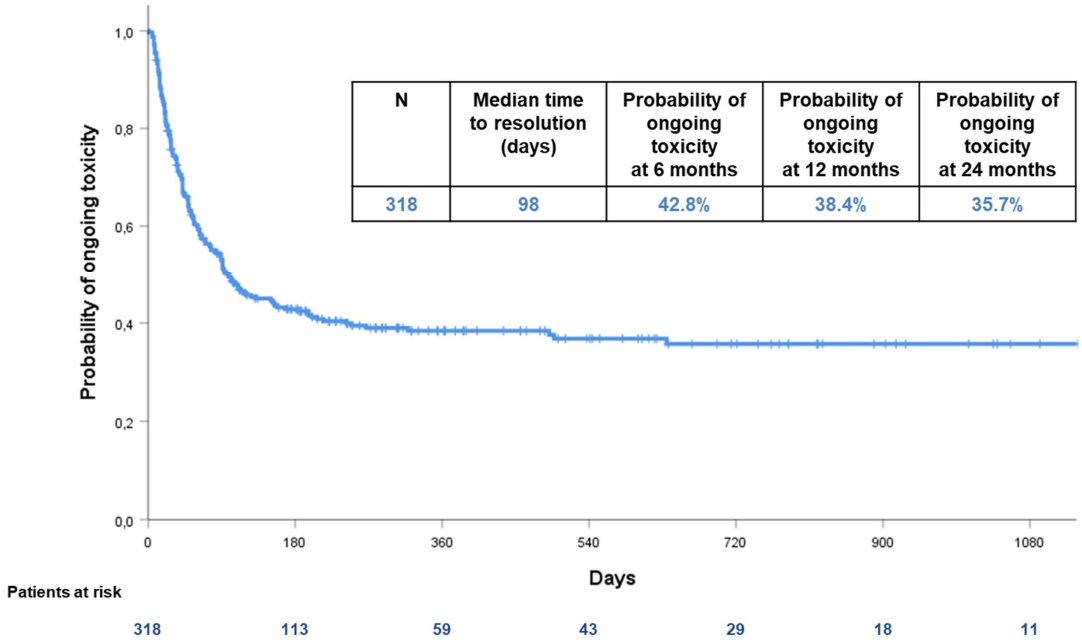
Johnson, D.B., Nebhan, C.A., Moslehi, J.J. *et al.* Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* **19,** 254–267 (2022). https://doi.org/10.1038/s41571-022-00600-w

Late-onset and long-lasting IRAEs

A



B

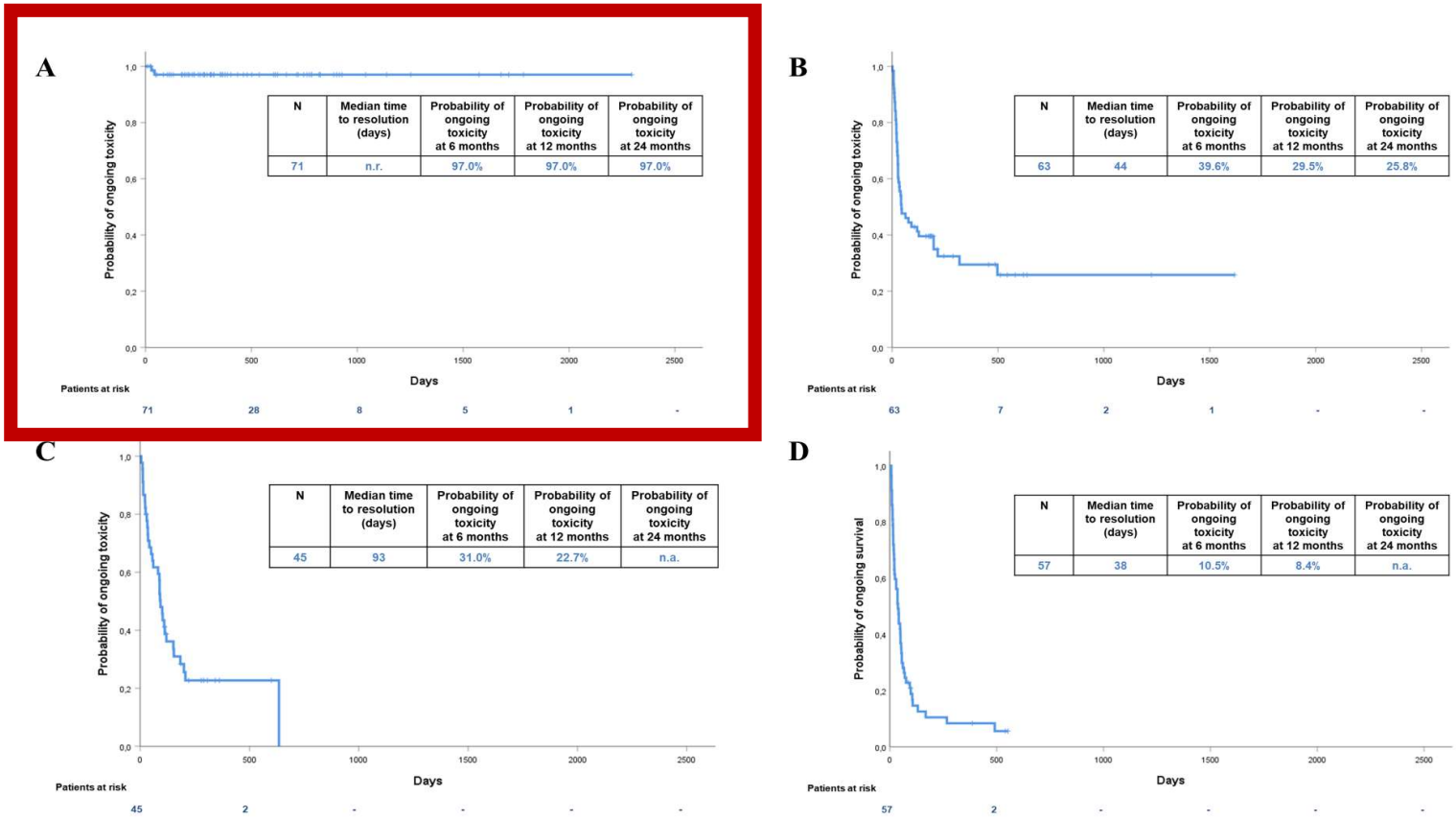


Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy. Ghisoni E. et al. Eur J of Cancer 2021.

Late-onset and long-lasting IRAEs

Probability of ongoing toxicity since toxicity onset according to toxicity type in our study population.

A: endocrine irAEs;
B: skin toxicity;
C: gastro-intestinal irAEs;
D: pulmonary toxicity.



Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy. Ghisoni E. et al. Eur J of Cancer 2021.

IRAEs management

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): i119–i142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

Linee guida
GESTIONE DELLA TOSSICITÀ DA IMMUNOTERAPIA

Edizione 2021
Aggiornata ad agosto 2021

Puzanov *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:95
DOI 10.1186/s40425-017-0300-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES **Open Access**

CrossMark

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov[11], A. Diab[21], K. Abdallah[3], C. O. Bingham III[4], C. Brogdon[5], R. Dadu[2], L. Hamad[1], S. Kim[2], M. E. Lacouture[6], N. R. LeBoeuf[7], D. Lenihan[8], C. Onofrei[9], V. Shannon[2], R. Sharma[1], A. W. Silk[12], D. Skondra[10], M. E. Suarez-Almazor[2], Y. Wang[2], K. Wiley[11], H. L. Kaufman[121], M. S. Ernstoff[1*1] and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

IRAEs management: key-points

1. Patient adequate information and education

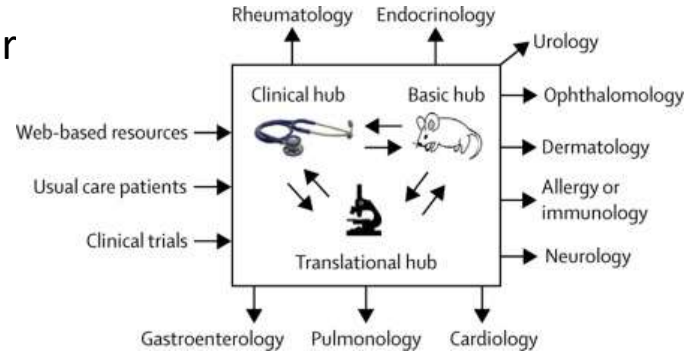
Immunotherapy safety for patients
These are not all the possible side-effects of immunotherapy. Call your oncology team if you have these or other symptoms.

Diarrhoea	Stomach pain
Headache and confusion or both	Extreme tiredness
Chest pain	Shortness of breath
Cough	Severe muscle pain
Severe rash or skin yellowing	Eye pain or blurred vision

XXX-XXX-XXXX to speak with your oncology , 24/7/365

2. Early diagnosis and treatment

3. Multidisciplinary team discussion, especially for steroid-refractor toxicities and in case of ICB re-challenge



AMD-AIOM-SID-SIE-SIF Diabete e tumori

Composizione del gruppo

Coordinatore:

- Nicola Silvestris (AIOM)

Componenti AMD:

- Marco Gallo *(referente per il CDN di AMD)*
- Giampiero Marino
- Lelio Morviducci
- Alberto Ragni
- Valerio Renzelli
- Enzo Tuveri

Componenti AIOM:

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- Romano Danesi
- Stella D'Oronzo
- Tindara Franchina
- Dario Giuffrida
- Stefania Gori
- Antonio Russo

Componenti SIE:

- Francesco Giorgino
- Antongiulio Faggiano
- Annalisa Natalicchio
- Maria Chiara Zatelli

Componenti SIF:

- Stefano Fogli
- Monica Montagnani

Componenti SID:

- Matteo Monami – SID
  Laura Sciacca – SID

RESEARCH ARTICLE

Profilo di cura del paziente oncologico con diabete mellito ricoverato in ospedale

Clinical pathway for inpatients oncologic patients with diabetes

Board di progetto

AMD (Gruppi AMD Diabete e Tumori / Diabete Inpatient): Gennaro Clemente, Marco Gallo, Massimo Michelini, Concetta Suraci, Maria Chantal Ponziani, Riccardo Candido, Nicoletta Musacchio, Domenico Mannino

AIOM: Domenico Corsi, Daniele Farci, Antonio Russo, Carmine Pinto, Stefania Gori

Critical Reviews in Oncology / Hematology 154 (2020) 103066

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journal homepage: www.elsevier.com/locate/critrevonc

Management of metabolic adverse events of targeted therapies and immune checkpoint inhibitors in cancer patients: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Società Italiana Farmacologia (SIF) multidisciplinary consensus position paper

Nicola Silvestris[a,b,*,1], Antonella Argentiero[a,1], Giordano Domenico Beretta[c], Paolo Di Bartolo[d], Monica Montagnani[b], Romano Danesi[e], Pietro Ferrari[f], Stella D'Oronzo[a,b], Stefania Gori[g], Antonio Russo[h], Silvia Acquati[i,2], Marco Gallo[j,2]

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ESMO OPEN CANCER HORIZONS

Volume 6 ■ Issue 3 ■ 2021

REVIEW

Antineoplastic dosing in overweight and obese cancer patients: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Società Italiana Endocrinologia (SIE)/Società Italiana Farmacologia (SIF) multidisciplinary consensus position paper

N. Silvestris[1,2*†], A. Argentiero[1†], A. Natalicchio[3†], S. D'Oronzo[2,17], G. D. Beretta[4], S. Acquati[5], V. Adinolfi[6], P. Di Bartolo[7], R. Danesi[8], A. Faggiano[9], P. Ferrari[10], M. Gallo[11], S. Gori[12], L. Morviducci[13], A. Russo[14], E. Tuveri[15], M. C. Zatelli[16], M. Montagnani[2†] & F. Giorgino[3†]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

REVIEW

Volume 6 ■ Issue 3 ■ 2021

Early prediction of pancreatic cancer from new-onset diabetes: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Società Italiana Endocrinologia (SIE)/Società Italiana Farmacologia (SIF) multidisciplinary consensus position paper

M. Gallo[1*†], V. Adinolfi[2†], L. Morviducci[3†], S. Acquati[4], E. Tuveri[5], P. Ferrari[6], M. C. Zatelli[7], A. Faggiano[8], A. Argentiero[9], A. Natalicchio[10], S. D'Oronzo[11], R. Danesi[12], S. Gori[13], A. Russo[14], M. Montagnani[11], G. D. Beretta[15], P. Di Bartolo[16†], N. Silvestris[9,11†] & F. Giorgino[10†]

Critical Reviews in Oncology/Hematology

Volume 169, January 2022, 103572

Metabolic disorders and gastroenteropancreatic-neuroendocrine tumors (GEP-NETs): How do they influence each other? An Italian Association of Medical Oncology (AIOM)/ Italian Association of Medical Diabetologists (AMD)/ Italian Society of Endocrinology (SIE)/ Italian Society of Pharmacology (SIF) multidisciplinary consensus position paper

Annalisa Natalicchio [a], Antongiulio Faggiano [b], Maria Chiara Zatelli [c], Antonella Argentiero [d], Stella D'Oronzo [e], Nicola Marrano [a], Giordano Domenico Beretta [f], Silvia Acquati [g], Valerio Adinolfi [h], Paolo Di Bartolo [i], Romano Danesi [j], Pietro Ferrari [k], Stefania Gori [l], Lelio Morviducci [m], Antonio Russo [n], Enzo Tuveri [o], Monica Montagnani [e], Marco Gallo [p], Nicola Silvestris [a e 1], Francesco Giorgino [a 1]

SOLAR-1 TRIAL REPORTS OVERALL SURVIVAL BENEFITS IN BREAST CANCER PATIENTS WITH LIMITED OPTIONS OF TREATMENT

Results support the use of alpelisib plus fulvestrant for patients with HR-positive, HER2-negative advanced breast cancer and PI3KCA mutations

Date: 19 Sep 2020
Topics: Breast cancer

Patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer achieved a clinically relevant overall survival (OS) benefit of approximately 8 months when the phosphatidylinositol 3-kinase (PI3K) inhibitor alpelisib was combined with hormonal therapy compared with hormonal therapy alone, as reported in the Late-Breaking presentation at ESMO Virtual Congress 2020 today (LBA18).

Approximately 40% of patients with HR-positive, HER2-negative breast cancer harbour *PI3KCA* gene mutations, resulting in PI3K pathway hyperactivation and endocrine resistance. These patients have a poor prognosis and targeting the PI3K pathway with

More news from the ESMO Congress

Read more on the **ESMO Daily Reporter** and stay up-to-date with the latest findings from the **ESMO Virtual Congress 2020**

Related Links

Encouraging Long-Term Survival Benefits with Atezolizumab Plus Nab-Paclitaxel in Metastatic

Table 2. Most frequently reported adverse events (≥20% incidence of any grade event in either treatment group) in the safety population[a]

AE, *n* (%)	Alpelisib plus fulvestrant (*n* = 284)					Placebo plus fulvestrant (*n* = 287)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AE	282 (99.3)	12 (4.2)	54 (19.0)	183 (64.4)	33 (11.6)	264 (92.0)	69 (24.0)	92 (32.1)	87 (30.3)	15 (5.2)
Hyperglycemia[b]	181 (63.7)	32 (11.3)	45 (15.8)	93 (32.7)	11 (3.9)	28 (9.8)	19 (6.6)	7 (2.4)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	93 (32.7)	52 (18.3)	19 (6.7)	0	45 (15.7)	30 (10.5)	14 (4.9)	1 (0.3)	0
Nausea	127 (44.7)	90 (31.7)	30 (10.6)	7 (2.5)	0	64 (22.3)	49 (17.1)	14 (4.9)	1 (0.3)	0
Decreased appetite	101 (35.6)	75 (26.4)	24 (8.5)	2 (0.7)	0	30 (10.5)	21 (7.3)	8 (2.8)	1 (0.3)	0
Rash[c]	101 (35.6)	48 (16.9)	25 (8.8)	28 (9.9)	0	17 (5.9)	14 (4.9)	2 (0.7)	1 (0.3)	0
Vomiting	77 (27.1)	64 (22.5)	11 (3.9)	2 (0.7)	0	28 (9.8)	18 (6.3)	9 (3.1)	1 (0.3)	0
Decreased weight	76 (26.8)	34 (12.0)	31 (10.9)	11 (3.9)	0	6 (2.1)	1 (0.3)	5 (1.7)	0	0
Stomatitis	70 (24.6)	39 (13.7)	24 (8.5)	7 (2.5)	0	18 (6.3)	15 (5.2)	3 (1.0)	0	0
Fatigue	69 (24.3)	36 (12.7)	23 (8.1)	10 (3.5)	0	49 (17.1)	36 (12.5)	10 (3.5)	3 (1.0)	0
Asthenia	58 (20.4)	25 (8.8)	28 (9.9)	5 (1.8)	0	37 (12.9)	29 (10.1)	8 (2.8)	0	0

AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

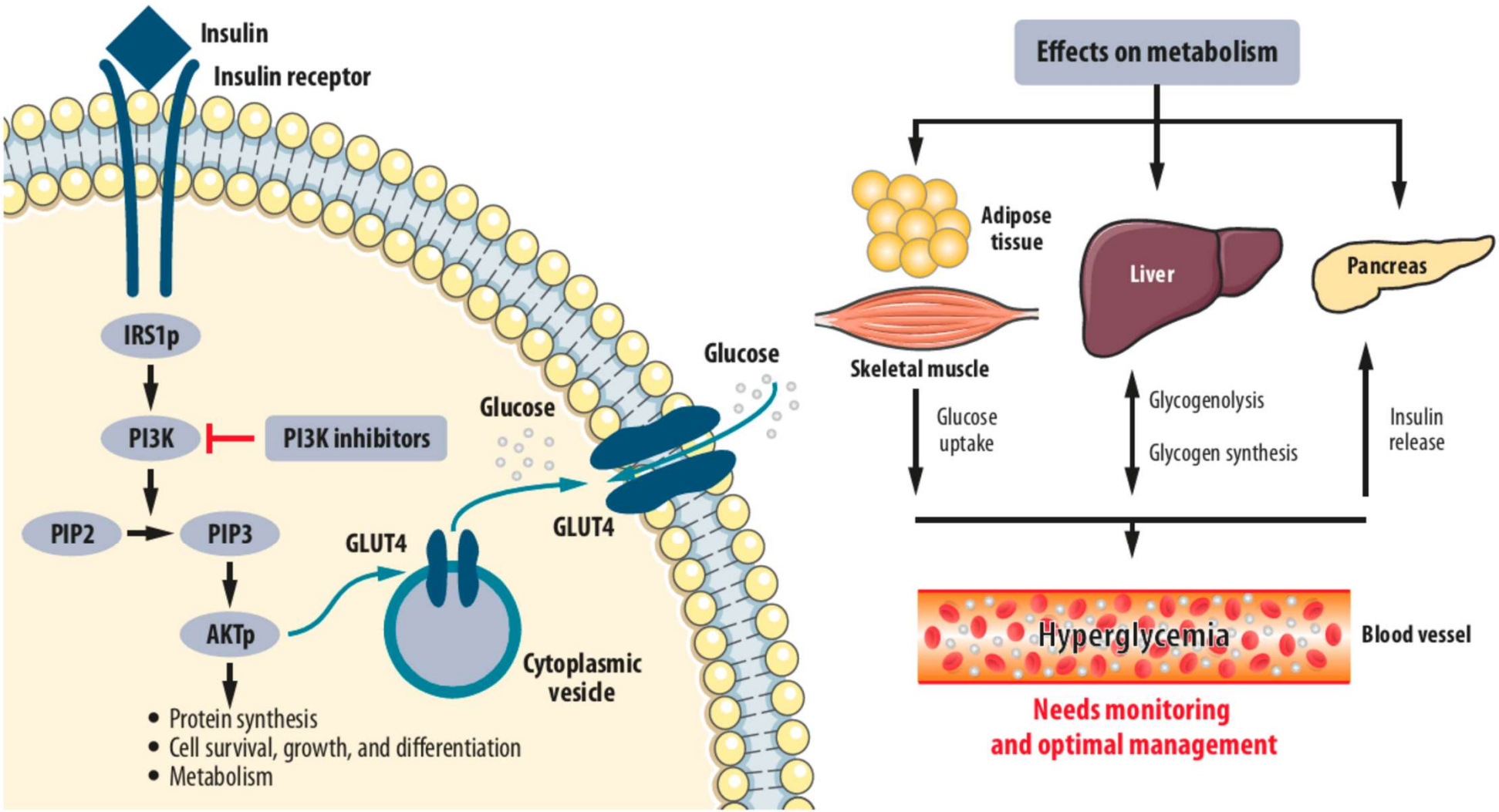
AE, adverse event.

[a] AEs reported as a single preferred term regardless of relationship to study medication.

[b] Hyperglycemia is reported in the table as a preferred term. Hyperglycemia AE of special interest (AESI) (preferred terms listed in supplementary Table S1, available at *Annals of Oncology* online) was reported in 187 (65.8%) patients in the alpelisib plus fulvestrant group [grade ≥3, *n* = 108 (38.0%)] and in 30 (10.5%) of those randomly assigned to receive placebo plus fulvestrant [grade ≥ 3, *n* = 2 (0.7%)].[9]

[c] Rash is reported in the table as a preferred term. Rash AESI (preferred terms listed in supplementary Table S1, available at *Annals of Oncology* online) was reported in 153 (53.9%) of patients in the alpelisib plus fulvestrant group [grade ≥3, *n* = 57 (20.1%)] and in 24 (8.4%) of those randomly assigned to receive placebo plus fulvestrant [grade ≥3, *n* = 1 (0.3%)].[9]

Rugo HS, et al. Ann Oncol. 2020 Aug;31(8):1001-1010.
doi: 10.1016/j.annonc.2020.05.001. Epub 2020 May 13.



Tankova, T.; et al. Management Strategies for Hyperglycemia Associated with the α-Selective PI3K Inhibitor Alpelisib for the Treatment of Breast Cancer. *Cancers* **2022**, *14*, 1598.

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ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer

H. S. Rugo[1*], F. André[2], T. Yamashita[3], H. Cerda[4], I. Toledano[5], S. M. Stemmer[6], J. C. Jurado[7], D. Juric[8], I. Mayer[9], E. M. Ciruelos[10], H. Iwata[11], P. Conte[12], M. Campone[13], C. Wilke[14], D. Mills[14], A. Lteif[15], M. Miller[15], F. Gaudenzi[14] & S. Loibl[16]

[1]Department of Medicine, Division of Hematology and Oncology, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, USA; [2]Department of Medical Oncology, INSERM U981, Gustave Roussy, Université Paris-Sud, Villejuif, France; [3]Department of Breast and Endocrine Surgery, Kanagawa Cancer Center Hospital, Yokohama, Japan; [4]Clinica RedSalud Vitacura, Santiago, Chile; [5]Institut Curie, Paris, France; [6]Institute of Oncology, Davidoff Center, Rabin Medical Center, Tel Aviv University, Tel Aviv, Israel; [7]Hospital Universitario Canarias, S/C Tenerife, Islas Canarias, Spain; [8]Department of Medicine, Massachusetts General Hospital Cancer Center, Boston; [9]Department of Medicine, Hematology and Oncology, Vanderbilt University, Nashville, USA; [10]Medical Oncology Department, Breast Cancer Unit, Hospital Universitario 12 de Octubre, Madrid, Spain; [11]Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [12]Department of Surgery, Oncology and Gastroenterology, University of Padua and Medical Oncology 2, Istituto Oncologico Veneto, IRCCS, Padua, Italy; [13]Department of Medical Oncology, Institut de Cancérologie de l'Ouest, St Herblain, France; [14]Novartis Pharma AG, Basel, Switzerland; [15]Novartis Pharmaceuticals Corporation, East Hanover, USA; [16]Department of Medicine and Research, German Breast Group, Neu-Isenburg; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany

Rugo HS, et al. Ann Oncol. 2020 Aug;31(8):1001-1010.
doi: 10.1016/j.annonc.2020.05.001. Epub 2020 May 13.

Table 1. Management guidance for AESIs based on protocol amendment

Grade	Criteria	Recommendation for alpelisib dosing	Recommendation for management
Hyperglycemia			
1	FPG > ULN to 160 mg/dl or FPG > ULN to 8.9 mmol/l	• No alpelisib dose adjustment required	• If FPG is <140 mg/dl, consider metformin • If FPG is 140–160 mg/dl, start or intensify metformin
2	FPG >160 to 250 mg/dl or FPG >8.9 to 13.9 mmol/l	• No alpelisib dose adjustment required • If FPG does not resolve to grade ≤1 within 21 days after antidiabetic treatment, reduce alpelisib by one dose level[a]	• Start oral antidiabetic treatment (e.g. metformin) • If FPG keeps rising beyond MTD of metformin, add an insulin sensitizer (e.g. pioglitazone)
3	FPG >250 to 500 mg/dl or FPG >13.9 to 27.8 mmol/l	• Discontinue alpelisib • If FPG resolves to grade ≤1 within 3 to 5 days while off alpelisib and on metformin, restart alpelisib and reduce by one dose level[a] • If FPG does not resolve to grade ≤1 within 21 days after antidiabetic treatment, permanently discontinue alpelisib	• Consider consultation with endocrinologist • Start metformin and add pioglitazone • Insulin may be used as rescue medication for 1 to 2 days
4	FPG >500 mg/dl or FPG ≥27.8 mmol/l	• Discontinue alpelisib for 24 H, then: – If grade ≤3, follow specific grade recommendations – If grade 4 persists (with no confounding factors), permanently discontinue alpelisib	• Consult with endocrinologist • See grade 3 recommendations; recheck in 24 H
Diarrhea			

Rugo HS, et al. Ann Oncol. 2020 Aug;31(8):1001-1010.
doi: 10.1016/j.annonc.2020.05.001. Epub 2020 May 13.

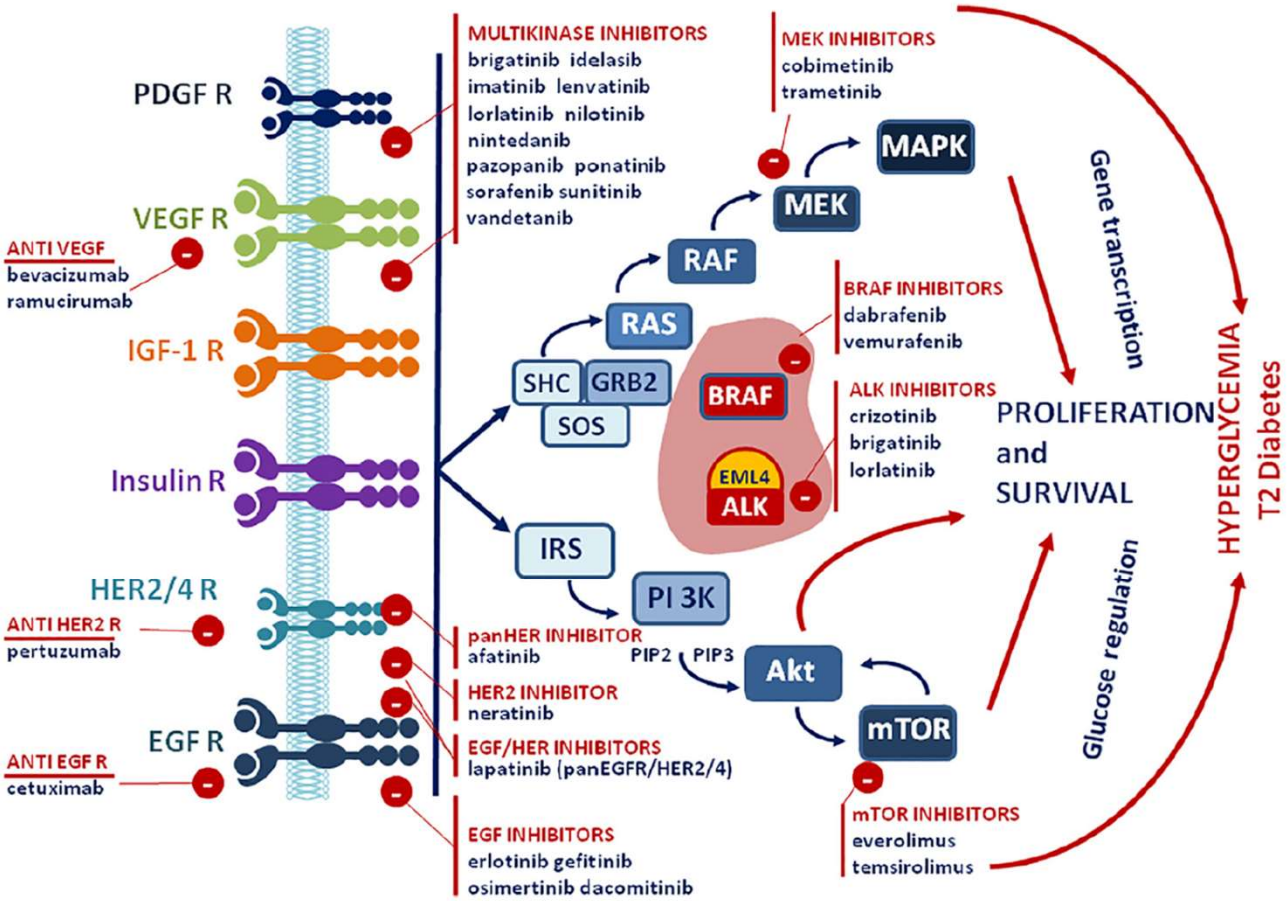
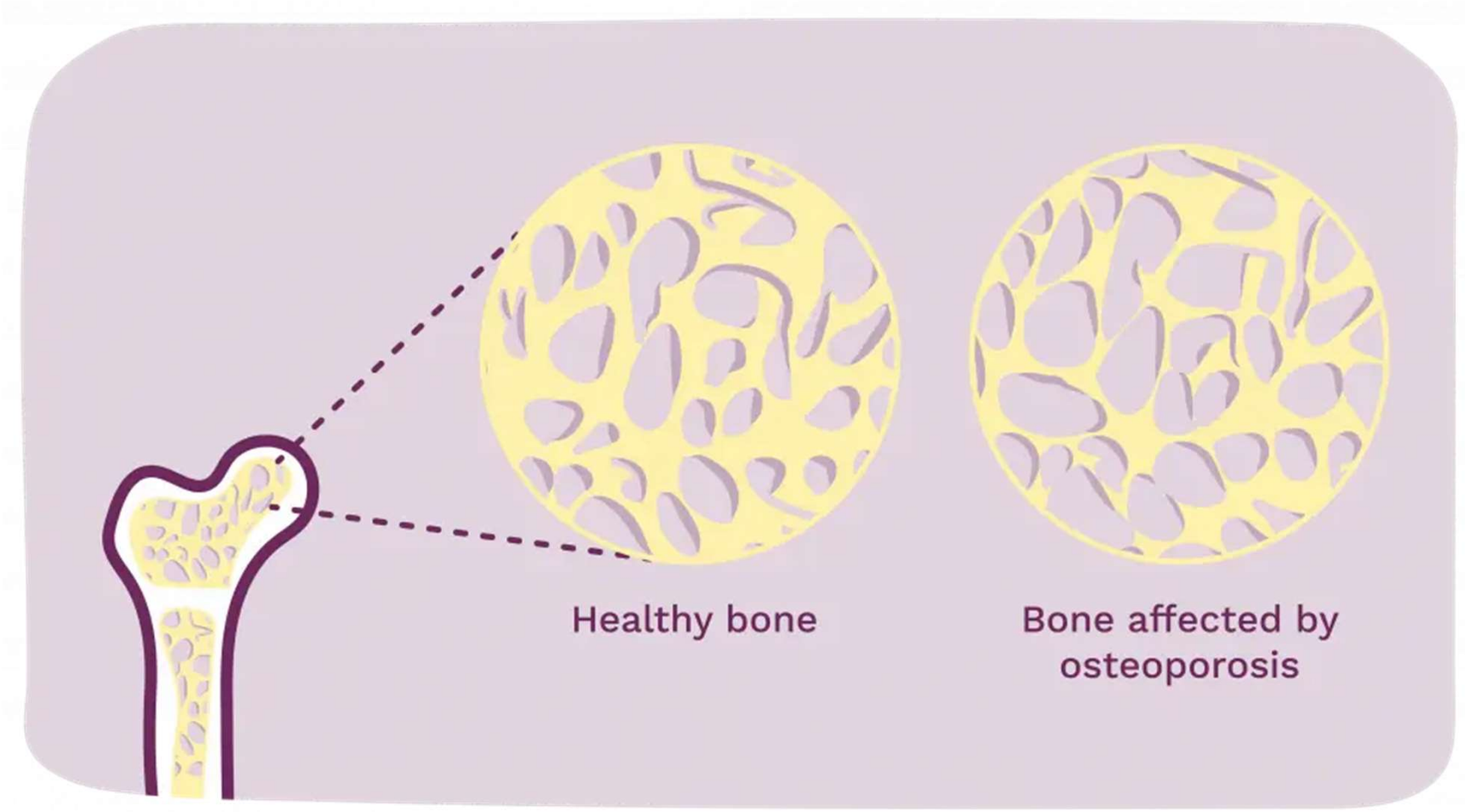


Fig. 1. Schematic diagram showing the main intracellular pathways downstream receptor tyrosine kinases (RTKs) involved in gene transcription, cell growth, differentiation and survival. Specific monoclonal antibodies and targeted therapies designed to inhibit cancer proliferation and promote apoptosis may interfere at multiple points (red circles) on signaling pathways involved in cellular control of glucose homeostasis. Figure reports examples of molecules acting on specific targets.

Silvestris N, et al. Crit Rev Oncol Hematol. 2020 Oct;154:103066.

Terapia ormonale e osso



Exercise is medicine in oncology

TABLE 2. Level of Evidence for the Benefit of Exercise on Cancer-Related Health Outcomes[10]

STRONG EVIDENCE[a]	MODERATE EVIDENCE	INSUFFICIENT EVIDENCE
Reduced anxiety	Sleep	Cardiotoxicity
Fewer depressive symptoms	Bone health (for osteoporosis prevention, not bone metastases)	Chemotherapy-induced peripheral neuropathy
Less fatigue		Cognitive function
Better QOL		Falls
Improved perceived physical function		Nausea
No risk of exacerbating upper extremity lymphedema		Pain
		Sexual function
		Treatment tolerance

Abbreviation: QOL, quality of life.
[a]Effective exercise programs for improving these outcomes are thrice-weekly, moderate-intensity, aerobic and/or resistance training with one exception. Anxiety and depressive symptoms do not appear to be improved by a program of resistance training alone but do improve with aerobic training alone or in combination with resistance training. The scientific evidence review and scheme used for evidence evaluation are described in another article from the American College of Sports Medicine (ACSM) Roundtable.[10]

Schmitz KH, et al CA Cancer J Clin. 2019 Nov;69(6):468-484.

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Ministero della Salute

LINEE DI INDIRIZZO SULL'ATTIVITÀ FISICA

Revisione delle raccomandazioni per le differenti fasce d'età e situazioni fisiologiche
e
nuove raccomandazioni per specifiche patologie

https://www.salute.gov.it/imgs/C_17_notizie_5693_1_file.pdf

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15° Rapporto sulla
condizione assistenziale
dei malati oncologici

14. Attività fisica e cancro: quali raccomandazioni?

a cura di F. Traclò – F.A.V.O.
S. Cinieri, F. Montemurro, E. Stroppa, M. Di Maio – AIOM

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Effetti endocrino-metabolici delle immunoterapie e delle target therapies nel carcinoma mammario e prostatico avanzato

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