Tossicità Endocrino-Metabolica: Diagnostica e Terapia

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ALDO MORO

Tossicità Tardive dei Trattamenti Oncologici

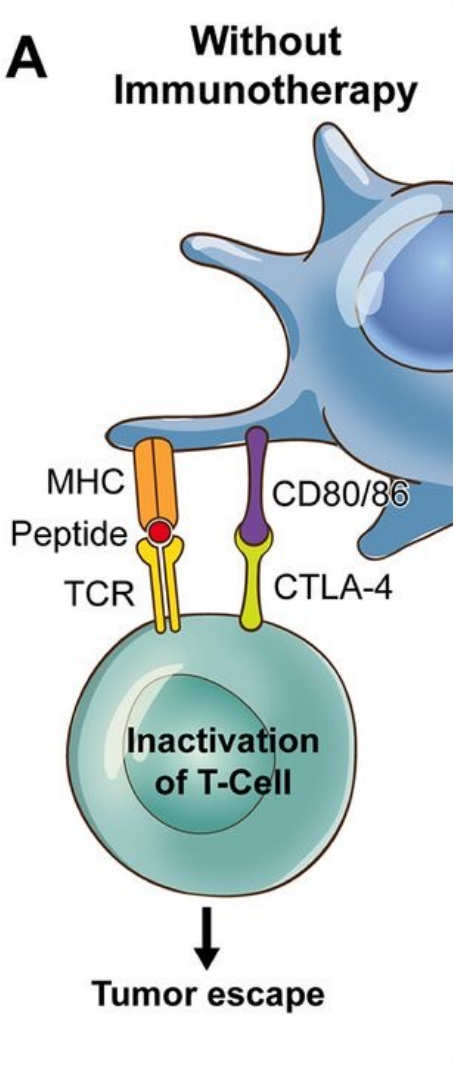
1. Inibitori dei Checkpoint Immunitari (ICIs)

- Inibitori del **CTLA-4** (cytotoxic T-lymphocyte associated protein-4) *(Ipililumab e Tremelimumab)*
- Inibitori del **PD-1** (programmed death-1) *(Nivolumab, Pembrolizumab)*
- Inibitori del **PDL-1** (programmed death ligand-1) *(Atezolizumab, Avelumab e Durvalumab)*

2. Targeted Therapies

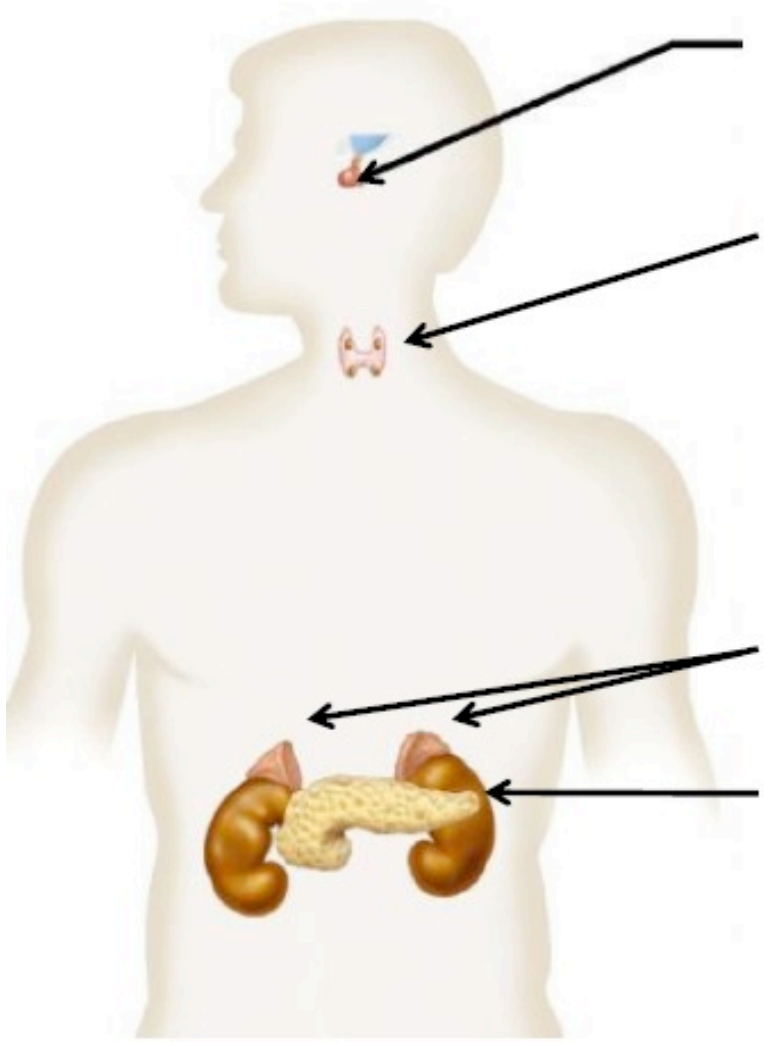
- **Anticorpi monoclonali**: inibitori dell'angiogenesi, anti-EGFR, anti-HER2, anti-RANK-L, anticorpi monolonali per tumori ematologici
- **Inibitori delle tirosin-chinasi (TKIs)**: ALK inibitori, BRAF inibitori, CDK 4/6 inibitori, EGFR inibitori, MEK inibitori, inibitori multi-chinasi
- **Inibitori di mTOR**
- **Inibitori di PARP**
- **Inibitori del proteasoma**

ICIs: Meccanismo di Azione



Gut. 2018 Nov;67(11):2056-2067

Immune-checkpoint Inhibitors and Endocrine Alterations



Pituitary gland ← Ipilimumab / Nivolumab
- Hypophysitis 7%-13%
- Corticotropin (ACTH) decrease
- Secondary adrenal insufficiency[a]

Thyroid gland ← Nivolumab / Pembrolizumab
- Hyperthyroidism 3%-8%
- Hypothyroidism 7%-13%
- TSH increase or decrease
- Thyroiditis
- Free thyroxine increase or decrease
- Autoimmune thyroiditis

Adrenal glands
- Primary adrenal insufficiency[b] rare

Pancreas
- Diabetes mellitus rare

Adapted from Sznol M. et al., *Cancer Treat Rev* 2017

Incidence of thyroid dysfunction following the use of immune checkpoint inhibitors regimens

Figure 2. Incidence of All-Grade Hypothyroidism During Treatment With Different Immune Checkpoint Inhibitor Regimens

Source	Treated Patients, No.[a]	Incidence Rate (95% CI)
PD-L1		
Fehrenbacher et al,[14] 2016	142	5.6 (2.5-10.8)
NCT01375842	558	3.8 (2.3-5.7)
Rosenberg et al,[15] 2016	310	0.0 (0.0-1.2)
RE MODEL		
PD-1		
Hamanishi et al,[16] 2015	20	40.0 (19.1-63.9)
Muro et al,[17] 2016	39	12.8 (4.3-27.4)
Robert et al,[18] 2015	555	9.4 (7.1-12.1)
Larkin et al,[19] 2015	313	8.6 (5.8-12.3)
Herbst et al,[20] 2015	682	8.2 (6.3-10.5)
Weber et al,[21] 2016	61	8.2 (2.7-18.1)
Motzer et al,[22] 2015	406	8.1 (5.7-11.2)
Ribas et al,[23] 2015	357	7.3 (4.8-10.5)
Garon et al,[24] 2015	495	6.9 (4.8-9.5)
Selwert et al,[25] 2016	60	6.7 (1.8-16.2)
Patnaik et al,[26] 2015	30	6.7 (0.8-22.1)
Borghaei et al,[27] 2015	287	6.6 (4.0-10.1)
Motzer et al,[28] 2015	167	6.0 (2.9-10.7)
Gettinger et al,[29] 2016	52	5.8 (1.2-15.9)
Weber et al,[30] 2015	268	5.6 (3.2-9.1)
Robert et al,[31] 2015	206	4.4 (2.0-8.1)
Robert et al,[32] 2014	173	4.0 (1.6-8.2)
Brahmer et al,[33] 2015	131	3.8 (1.3-8.7)
Nanda et al,[34] 2016	32	3.1 (0.1-16.2)
Antonia et al,[35] 2016	98	3.1 (0.6-8.7)
Wolchok et al,[36] 2013	33	3.0 (0.1-15.8)
Rizvi et al,[37] 2015	117	2.6 (0.5-7.3)
Brahmer et al,[38] 2010	39	2.6 (0.1-13.5)
Topalian et al,[39] 2012	296	2.4 (1.0-4.8)
Nghiem et al,[40] 2016	26	0.0 (0.0-13.2)
Shimizu et al,[41] 2016	10	0.0 (0.0-30.8)
RE MODEL		
CTLA-4		
Postow et al,[42] 2015	46	15.2 (6.3-28.9)
Yamazaki et al,[43] 2015	20	5.0 (0.1-24.9)
Larkin et al,[19] 2015	311	4.2 (2.2-7.0)
Robert et al,[31] 2015	256	2.0 (0.6-4.5)
Hodi et al,[44] 2010	131	1.5 (0.2-5.4)
Zimmer et al,[45] 2015	103	1.0 (0.0-5.3)
Zimmer et al,[46] 2015	53	0.0 (0.0-6.7)
Le et al,[47] 2013	15	0.0 (0.0-21.8)
Yang et al,[48] 2007	61	0.0 (0.0-5.9)
O´Mahony et al,[49] 2007	11	0.0 (0.0-28.5)
Maki et al,[50] 2013	6	0.0 (0.0-45.9)
RE MODEL		
Combination		
Postow et al,[42] 2015	94	16.0 (9.2-25.0)
Larkin et al,[19] 2015	313	15.0 (11.2-19.5)
Antonia et al,[35] 2016	115	12.2 (6.8-19.6)
Wolchok et al,[36] 2013	53	3.8 (0.5-13.0)
RE MODEL		

Hypo

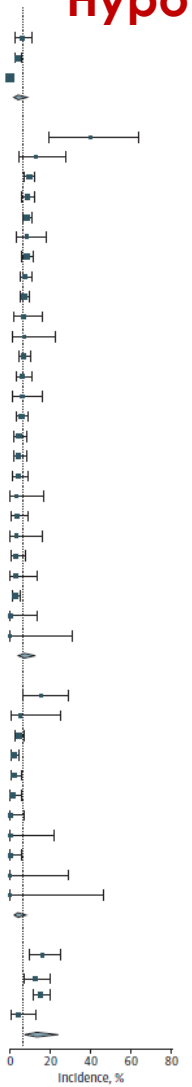


Figure 3. Incidence of All-Grade Hyperthyroidism During Treatment With Different Immune Checkpoint Inhibitor Regimens

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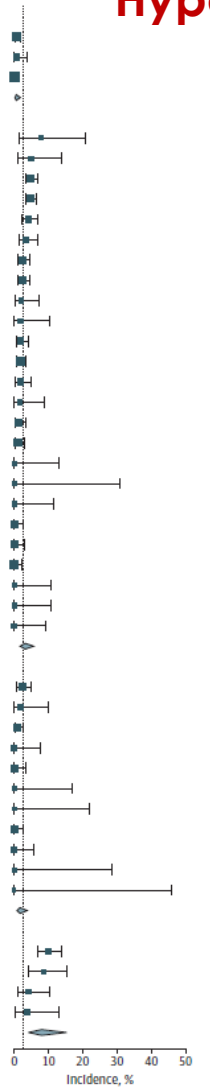
RE MODEL		

Hyper



Barroso-Sousa R. et al., *JAMA* 2018

Timing of Endocrine Adverse Events

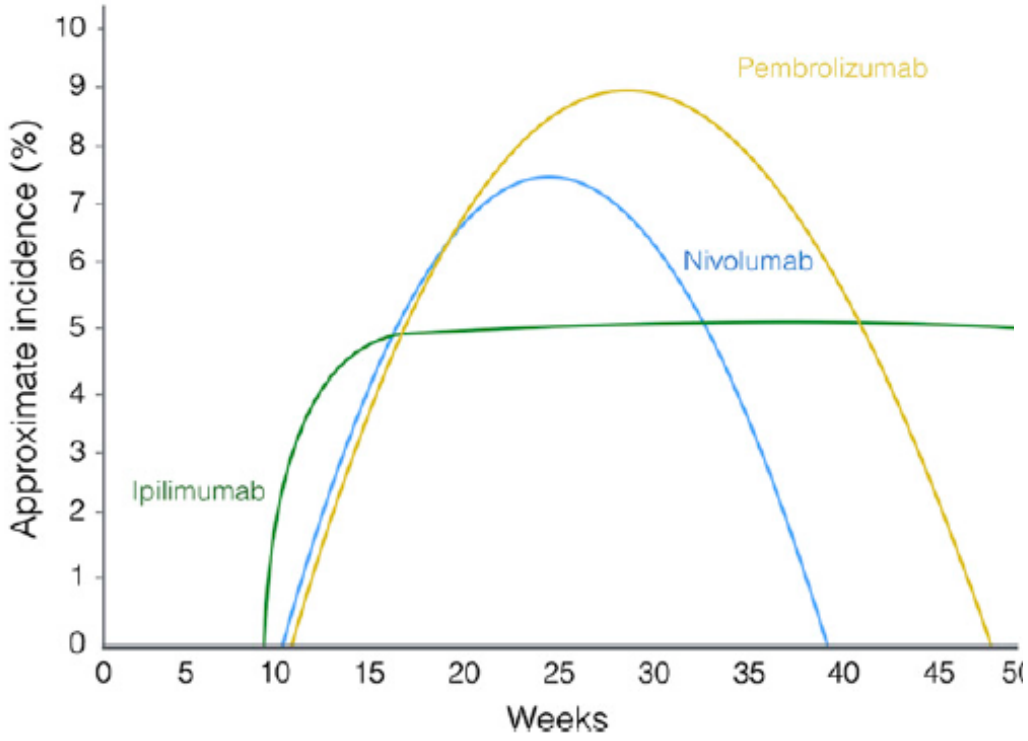
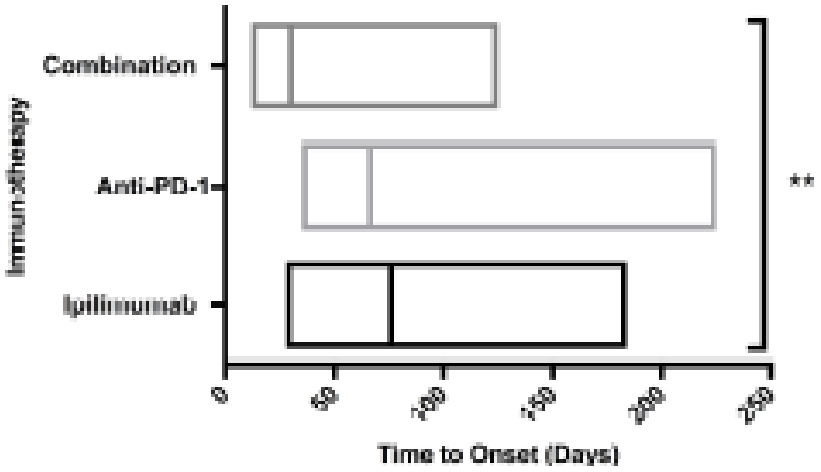


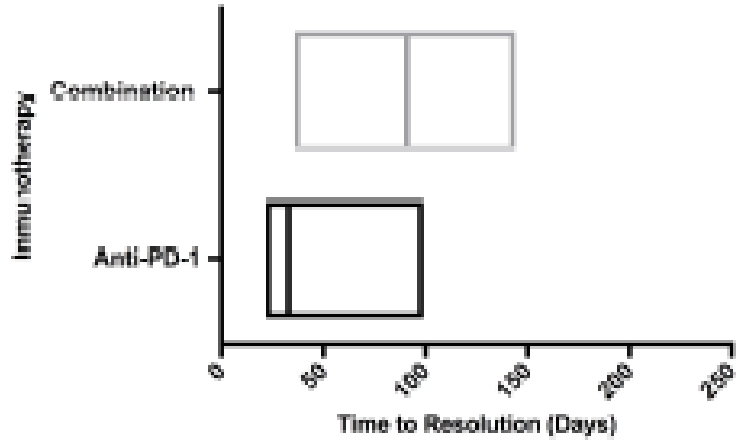
Figure 1. Timing pattern of endocrine adverse events.

Gonzalez-Rodriguez E. et al., *Oncologist* 2016

Time from drug commencement to development of any endocrinopathies



Time to resolution of overt and subclinical hyperthyroidism



Scott E.S. et al., Eur J Endocrinol.2018

Incidence of hypophysitis following the use of immune checkpoint inhibitors regimens

Figure 4. Incidence of All-Grade Hypophysitis During Treatment With Different Immune Checkpoint Inhibitor Regimens[a]

Source	Treated Patients, No.[b]	Incidence Rate (95% CI)
PD-1		
Wolchok et al,[36] 2013	33	3.0 (0.1-15.8)
Robert et al,[32] 2014	173	1.2 (0.1-4.1)
Larkin et al,[19] 2015	313	0.6 (0.1-2.3)
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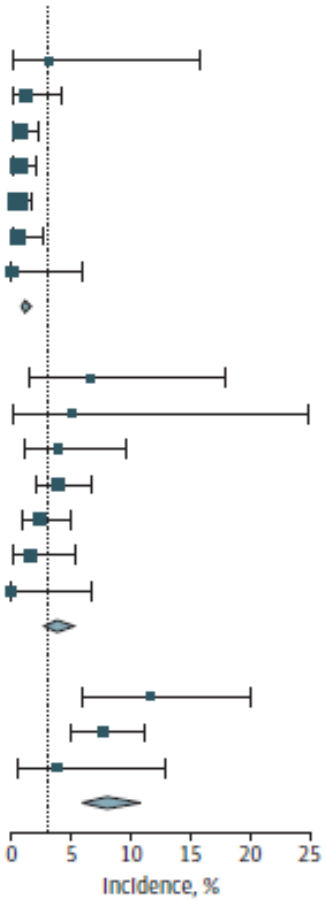
RE MODEL		



Barroso-Sousa R. et al., *JAMA* 2018

Diabete Mellito (DM) Correlato all'Utilizzo di ICIs: Epidemiologia

- Il **DM** può essere considerato un **raro** irAE dovuto alla terapia con ICIs (l'incidenza è < 0.5%).
- La maggior parte dei casi di **DM** sono stati descritti in pazienti in trattamento con **anti-PD-1** (meno in pazienti in trattamento con anti-**PD-L1**; rarissimi casi in pazienti trattati con anti-**CTLA-4**).
- L'età media di insorgenza è di 63 anni (range 31-84 anni).
- Può insorgere già dopo la prima somministrazione di ICIs (mediamente dopo la 4° dose), in un range che va da 1-2 settimane a 16 mesi dopo l'inizio della terapia con ICIs (in media dopo 11-20 settimane).

Endocr Rev. 2019 Feb 1;40(1):17-65; Endocr Relat Cancer. 2018 Oct 1. pii: ERC-18-0320; Lancet Diabetes Endocrinol. 2019 Jun;7(6):421-423; Best Pract Res Clin Endocrinol Metab. 2022 May;36(3):101657

DM Correlato all'Utilizzo di ICIs: Caratteristiche

- Rapida insorgenza di **iperglicemia**, con livelli di HbA1c mediamente bassi se relazionati ai livelli di glicemia (valore mediano di HbA1c all'insorgenza di 7,6% rispetto a una glicemia mediana all'insorgenza di circa 600 mg/dL).

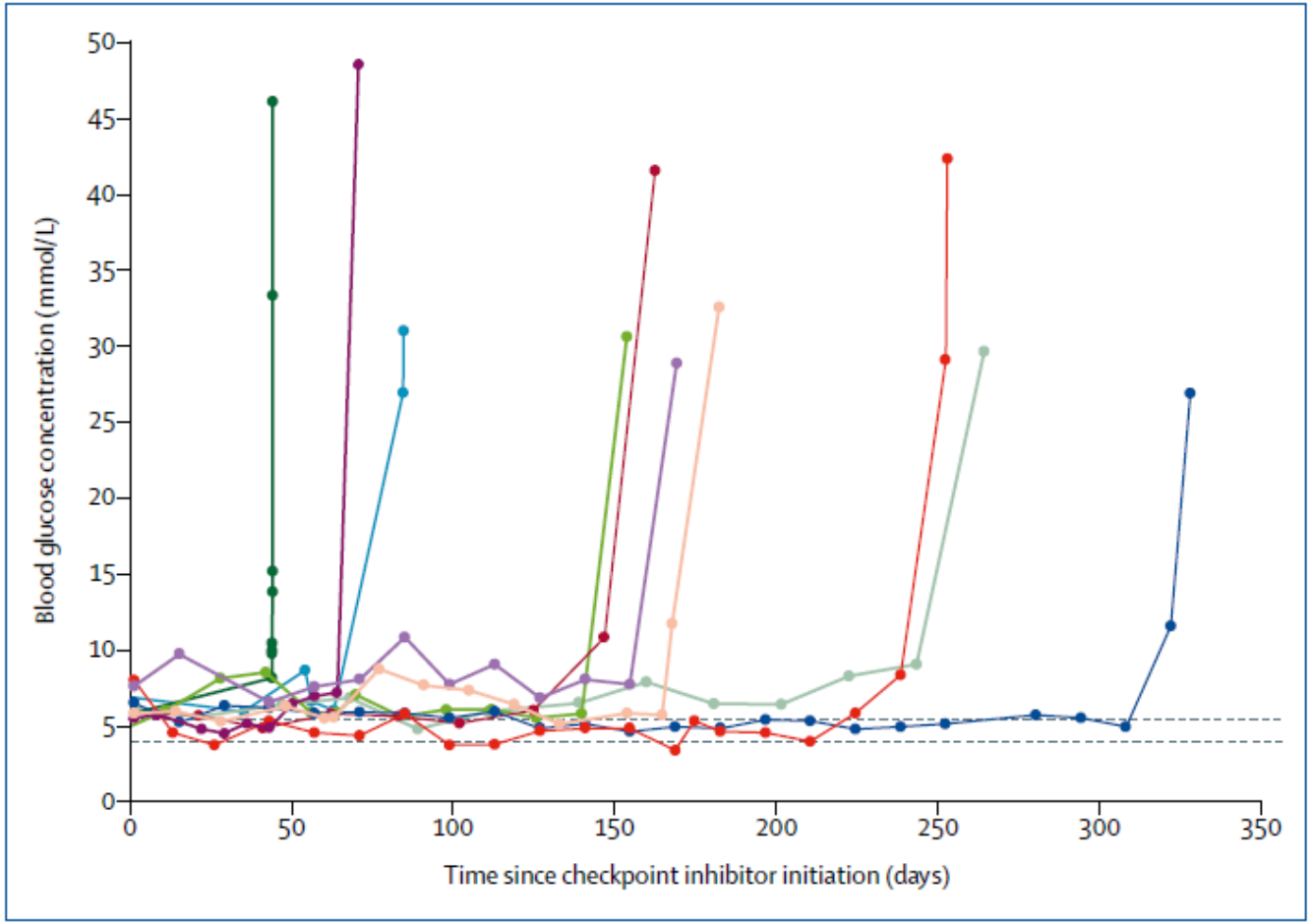
- Rapida progressione della carenza di **insulina** endogena (C-peptide basso in circa il 90% dei pazienti).

- Alto rischio di **chetoacidosi diabetica** se non diagnosticato e trattato prontamente (circa il 60-70% dei casi a seconda degli studi).
  (spesso è l'insorgenza di chetoacidosi a portare alla diagnosi di DM ICIs-correlato).

Diabete Mellito di Tipo 1 Fulminante?

Endocr Rev. 2019 Feb 1;40(1):17-65; J Diabetes Investig. 2012 Dec 20;3(6):536-9; Endocr Relat Cancer. 2018 Oct 1. pii: ERC-18-0320; Lancet Diabetes Endocrinol. 2019 Jun;7(6):421-423; Best Pract Res Clin Endocrinol Metab. 2022 May;36(3):101657.

Checkpoint inhibitor-induced insulin-dependent diabetes: an emerging syndrome



Lancet Diabetes Endocrinol. 2019 Jun;7(6):421-423

Il DM ICIs-correlato: Può Essere Considerato un Diabete Mellito di Tipo 1 Fulminante?

	DM ICIs-correlato	DMT1 fulminante
Autoanticorpi vs. l'isola	Nel 50% dei casi	NO
Innalzamento enzimi pancreatici	Raro	Nel 98% dei casi
Sintomi influenzali	Rari	Comuni

Endocr Rev. 2019 Feb 1;40(1):17-65; J Diabetes Investig. 2012 Dec 20;3(6):536-9

DM Correlato all'Utilizzo di ICIs: Fisiopatologia

- **Autoanticorpi** correlati al diabete sono stati ritrovati in circa il 30-50% dei pazienti affetti da DM ICIs-correlato.

  Di questi, erano tutti anti-GAD+ e in almeno 1 caso sono stati trovati autoanticorpi anti-IA2, IAA, ZnT8

- In alcuni pazienti erano presenti autoanticorpi vs. l'isola prima della terapia con ICIs, mentre in altri pazienti gli autoanticorpi sono stati riscontrati dopo l'inizio della terapia con ICIs (**inutile lo screening degli autoanticorpi prima della terapia con ICIs**).

- Nella maggior parte dei pazienti non vi erano prediabete o diabete preesistenti.

Endocr Rev. 2019 Feb 1;40(1):17-65; Cancer Immunol Immunother. 2017 Nov;66(11):1399-1410; J Immunother Cancer. 2017 May 16;5:40; J Immunother Cancer. 2016 Dec 20;4:89; Endocr Relat Cancer. 2018 Oct 1. pii: ERC-18-0320; Best Pract Res Clin Endocrinol Metab. 2022 May;36(3):101657.

DM Correlato all'Utilizzo di ICIs

Manifestazioni Cliniche	
Iperglicemia	Poliuria, polidipsia, perdita di peso
Chetoacidosi	Nausea, vomito, dolore addominale, iperventilazione/tachipnea, letargia, convulsioni, coma

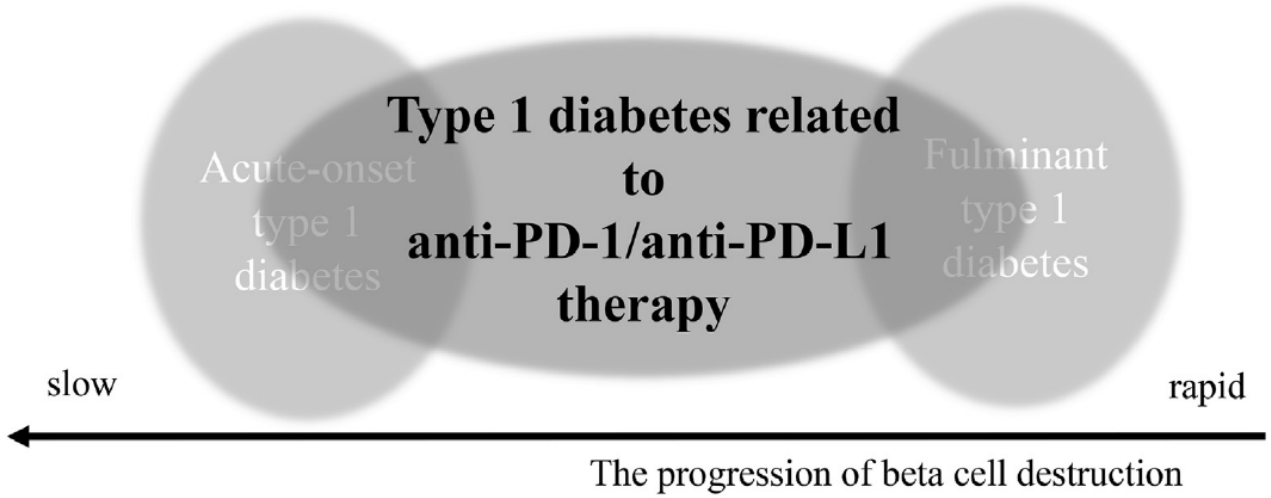
Valori Ematochimici	
HbA1c	Non eccessivamente alti rispetto ai valori di glicemia
C-peptide	Basso o non detectabile (deficienza insulinica)

Imaging del Pancreas
Il pancreas può apparire atrofico, slargato e infiammato, ma anche completamente nella norma

Endocr Rev. 2019 Feb 1;40(1):17-65

Caratteristiche cliniche del DM Correlato all'Utilizzo di ICIs

	Baden et al.	Preiato et al.	Kotwal et al.	Stamatouli et al.
N	22	200	12	27
Race	Japanese	ND	Caucasian	Caucsian
Age	63 ± 12 (mean ± SD)	64 (median)	61.3 (median)	66 (median)
Male %	59%	62.50%	50%	63%
BMI (kg/m^2)	20.7 ± 3.8 (mean ± SD)	ND	32.2 (median)	26.07 (median)
Glucose (mg/dL)	617 ± 248 (mean ± SD)	564.5 (median)	ND	653 (median)
HbA1c (%)	8.1 ± 1.3 (mean ± SD)	7.9 (median)	9.7 (median)	7.95 (median)
DKA/ketosis	39%/85%	67.50%/ND	67%/ND	59%/ND
GAD positive %	5%	43%	57%	36%
HLA DR4/DR9	ND	51.3%/14.1%	ND	76%/ND



Best Pract Res Clin Endocrinol Metab. 2022 May;36(3):101657

Evaluation of Patients on ICIs Immunotherapy for Possible Endocrinopathies

Baseline	• Clinical evaluation for symptoms: Extreme weakness, unusual headache patterns, vision changes, increased sweating, rapid heartbeat, weight loss or weight gain, mood changes, constipation or diarrhea, deepening of the voice, changes in urination, polydipsia, extreme or low hunger, nausea or vomiting, abdominal pain • Laboratory evaluation: Morning TSH, FT4, cortisol, glucose, electrolytes
Every 4-6 weeks and 4-6 weeks after the last cycle	• Clinical evaluation for symptoms • Laboratory evaluation: Morning TSH, FT4, cortisol, glucose, electrolytes

ACTH, adrenocorticotropic hormone; CT, computed tomography; DI, diabetes insipidus; E2, estradiol; FSH, follicle stimulating hormone; FT4, free thyroxine; GADA, glutamic acid decarboxylase autoantibodies; IA2, islet autoantibodies; IAA, insulin autoantibodies; ICI, immune checkpoint inhibitors; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; MRI, magnetic resonance imaging; PRL, prolactin; T3, triiodothyronine; TG, thyroglobulin; TPO, thyroid peroxidase; TRAb, TSH receptor antibodies; TSH, thyroid stimulating hormone; TSI, thyroid stimulating immunoglobulin; ZnT8, zinc transporter.

Paschou SA et al, *ESMO Open* 2021

Evaluation of Patients on ICIs Immunotherapy for Possible Endocrinopathies

Additional tests	
If hypothyroidism suspected	• Anti-TPO, anti-TG
If hyperthyroidism suspected	• T3 • TSH, FT4, T3 every 2-3 weeks to diagnose persistent hyperthyroidism or hypothyroidism (due to destructive thyroiditis) • TRAb (TSI)
If cortisol low	• ACTH • Consider ACTH stimulation test (250 µg i.v.) • Adrenal CT, if primary adrenal insufficiency
If hypophysitis suspected	• ACTH, LH, FSH, testosterone (men) or E2 (women) • PRL, IGF-1 can be also measured • Pituitary MRI, if multiple endocrine abnormalities, headaches or visual defects • DI is rare, but monitoring is important in some cases
If hyperglycemia	• pH, urine ketones • Autoantibodies (GADA, IA2, IAA, anti-ZnT8) • C peptide

ACTH, adrenocorticotropic hormone; CT, computed tomography; DI, diabetes insipidus; E2, estradiol; FSH, follicle stimulating hormone; FT4, free thyroxine; GADA, glutamic acid decarboxylase autoantibodies; IA2, islet autoantibodies; IAA, insulin autoantibodies; ICI, immune checkpoint inhibitors; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; MRI, magnetic resonance imaging; PRL, prolactin; T3, triiodothyronine; TG, thyroglobulin; TPO, thyroid peroxidase; TRAb, TSH receptor antibodies; TSH, thyroid stimulating hormone; TSI, thyroid stimulating immunoglobulin; ZnT8, zinc transporter.

Paschou SA et al, *ESMO Open* 2021

Management of Endocrinopathies after ICIs According to Grading

Endocrinopathies	Grade 1 Asymptomatic or mild symptoms	Grade 2 Moderate symptoms	Grade 3 Severe but not life-threatening symptoms	Grade 4 Life-threatening consequences	Grade 5 Death
Hypophysitis Inflammation of the pituitary gland	• Low cortisol (<5 µg/dl or <18 µg/dl after ACTH stimulation test), low ACTH and asymptomatic or mild symptoms • Consider holding ICIs • Hydrocortisone (15-25 mg/day) in 2-3 doses or equivalent • If central hypothyroidism also present, start levothyroxine always several days after hydrocortisone and monitor with FT4 levels • If hypogonadism also present, testosterone in men or estrogen/progestogen therapy in women, only in those without contra-indications • GH replacement is contraindicated in patients with active malignancy • Endocrine consultation	• Low cortisol and moderate symptoms • Hold ICIs until symptoms resolve • Management as in G1, but ×2-3 initial dose hydrocortisone	• Severe symptoms • Hold ICIs until symptoms resolve • Hospitalize for i.v. fluids and hydrocortisone (100 mg at presentation) • High-dose systemic corticosteroids (prednisolone 1 mg/kg/day) should be reserved for few severe cases	• Life-threatening symptoms • Management as in G3	—

Paschou SA et al, *ESMO Open* 2021

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Endocrinopathies	Grade 1 Asymptomatic or mild symptoms	Grade 2 Moderate symptoms	Grade 3 Severe but not life-threatening symptoms	Grade 4 Life-threatening consequences	Grade 5 Death
Hypothyroidism Decrease in production of thyroid hormones	• TSH 4-10 mIU/l, normal FT4 and asymptomatic • Continue ICIs • TSH every 4-6 weeks	• TSH >10 mIU/l or TSH 4-10 mIU/l with low FT4 and/or with moderate symptoms • Hold ICIs until symptoms resolve • Levothyroxine (starting dose ~1.1 µg/kg/day or 25-50 µg for elderly and patients with CVD) • TSH every 6 weeks while titrating to optimal dose • FT4 can be used in the short term (2 weeks) to ensure adequacy	• Severe symptoms • Management as in G2 • Endocrine consultation	• Life-threatening symptoms • Management as in G3 • Hospitalize patient for i.v. therapy if signs of myxedema	—
Hyperthyroidism Increase in production of thyroid hormones	• TSH <0.4 mIU/l and asymptomatic or mild symptoms • Continue ICIs • TSH, FT4, T3 every 2-3 weeks to diagnose persistent hyperthyroidism or hypothyroidism (due to destructive thyroiditis)	• Low TSH and moderate symptoms • Hold ICIs until symptoms resolve • Beta blockers • TRAb (TSI) measurement • Methimazole if persistent hyperthyroidism • TSH, FT4, T3 every 4-6 weeks • Endocrine consultation	• Severe symptoms • Management as in G2 • Consider corticosteroids	• Life-threatening symptoms • Management as in G3 • Hospitalize patient with concern of thyroid storm	—

Paschou SA et al, *ESMO Open* 2021

Management of Endocrinopathies after ICIs According to Grading

Endocrinopathies	Grade 1 Asymptomatic or mild symptoms	Grade 2 Moderate symptoms	Grade 3 Severe but not life-threatening symptoms	Grade 4 Life-threatening consequences	Grade 5 Death
Primary adrenal insufficiency Disorder of the adrenal cortex	• Low cortisol (<5 µg/dl or <18 µg/dl after ACTH stimulation test), high ACTH (×2 upper limit) and asymptomatic or mild symptoms • Consider holding ICIs • Hydrocortisone (15-25 mg/day) in 2-3 doses or equivalent • Fludrocortisone (starting dose 50-100 µg) • Endocrine consultation	• Low cortisol and moderate symptoms • Hold ICIs until symptoms resolve • Management as in G1, but ×2-3 initial dose hydrocortisone	• Severe symptoms • Hold ICIs until symptoms resolve • Hospitalize for i.v. fluids and hydrocortisone (100 mg at presentation)	• Life-threatening symptoms • Management as in G3	–

Paschou SA et al, *ESMO Open* 2021

Gestione del DM ICIs-correlato

1. **Informare il paziente** in terapia con ICIs e i suoi familiari circa i segni e i sintomi dell'iperglicemia e della chetoacidosi (specialmente i pazienti in terapia con anti-PD-1).
2. In caso di **iperglicemia**:
   - valutare la presenza di chetoacidosi diabetica
   - monitorare costantemente i livelli di glucosio
   - misurare i livelli di C-peptide
   - in caso di bassi livelli di C-peptide, iniziare subito la terapia insulinica
3. In caso di **chetoacidosi diabetica**:
   - somministrare tempestivamente liquidi per via intravenosa
   - correggere eventuali sbilanciamenti elettrolitici
   - iniziare la terapia insulinica
4. Quasi sempre la terapia insulinica va continuata in modo permanente.
5. Considerato che il DM è trattabile e che la terapia insulinica risulta essere permanente, **non c'è bisogno di interrompere la terapia con ICIs**.
6. L'uso dei **corticosteroidi** non apporta alcun beneficio alla terapia del DM ICIs-correlato (potrebbe anzi peggiorare il quadro clinico).

Endocr Rev. 2019 Feb 1;40(1):17-65; Endocr Relat Cancer. 2018 Oct 1. pii: ERC-18-0320

Tossicità Tardive dei Trattamenti Oncologici

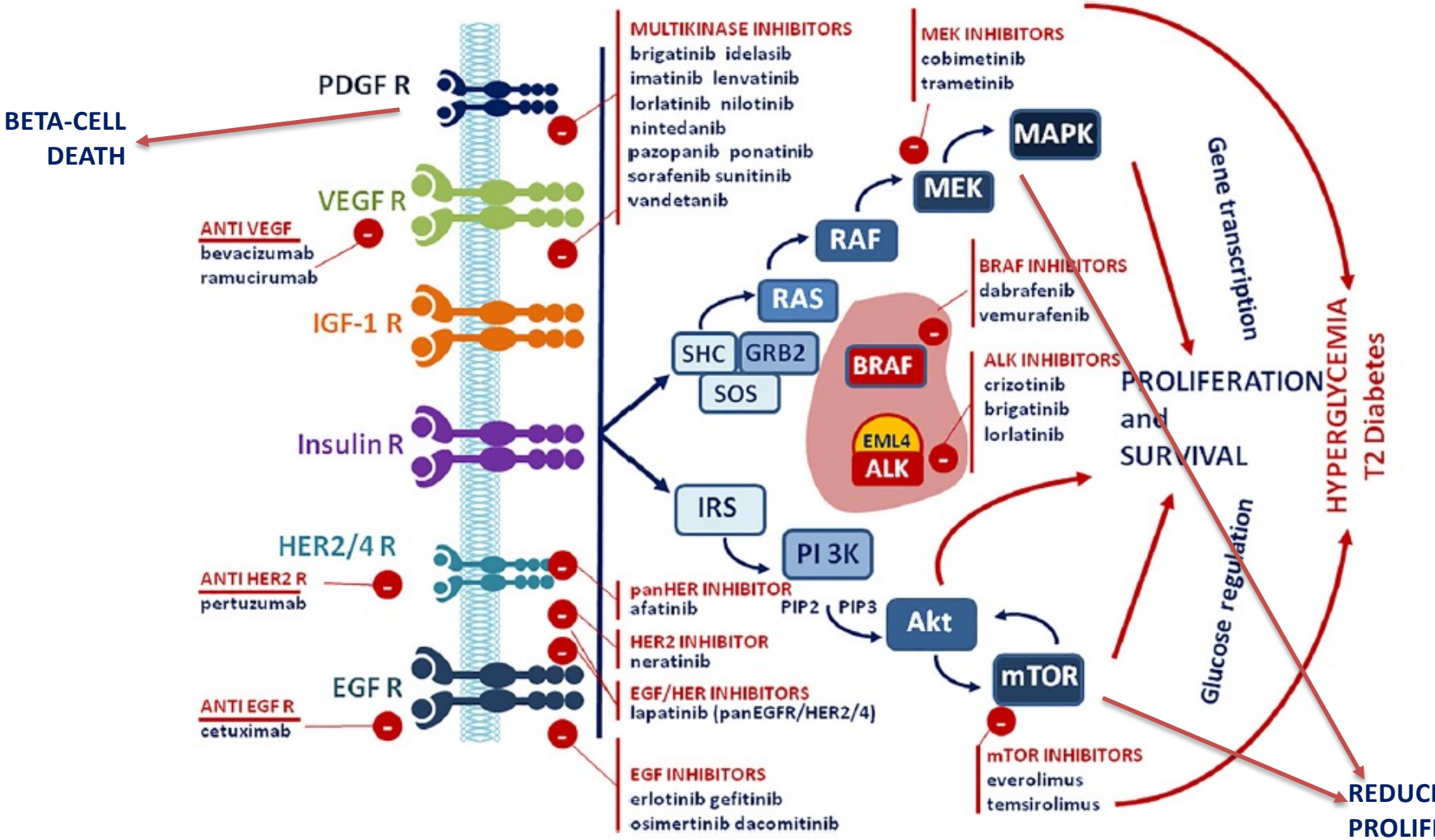
1. Inibitori dei checkpoint immunitari (ICIs)

- Inibitori del **CTLA-4** (cytotoxic T-lymphocyte associated protein-4) *(Ipililumab e tremelimumab)*
- Inibitori del **PD-1** (programmed death-1) *(Nivolumab, pembrolizumab)*
- Inibitori del **PDL-1** (programmed death ligand-1) *(Atezolizumab, avelumab e durvalumab)*

2. Targeted Therapies

- **Anticorpi monoclonali**: inibitori dell'angiogenesi, anti-EGFR, anti-HER2, anti-RANK-L, anticorpi monolonali per tumori ematologici
- **Inibitori delle tirosin-chinasi (TKIs)**: ALK inibitori, BRAF inibitori, CDK 4/6 inibitori, EGFR inibitori, MEK inibitori, inibitori multi-chinasi
- **Inibitori di mTOR**
- **Inibitori di PARP**
- **Inibitori del proteasoma**

Eventi Avversi Metabolici Correlati all'Utilizzo di *Targeted Therapies*: Meccanismi Molecolari



- ↑ Glycogenolysis
- ↑ Gluconeogenesis
- ↓ Glycogenosynthesis
- ↓ Glucose transport
- ↓ Insulin receptor signaling

Crit Rev Oncol Hematol. 2020 Oct;154:103066

Incidenza di Iper- e Ipoglicemie in corso di *Targeted Therapies*

Table 2. Incidence of hyperglycemia/hypoglycemia under targeted therapies

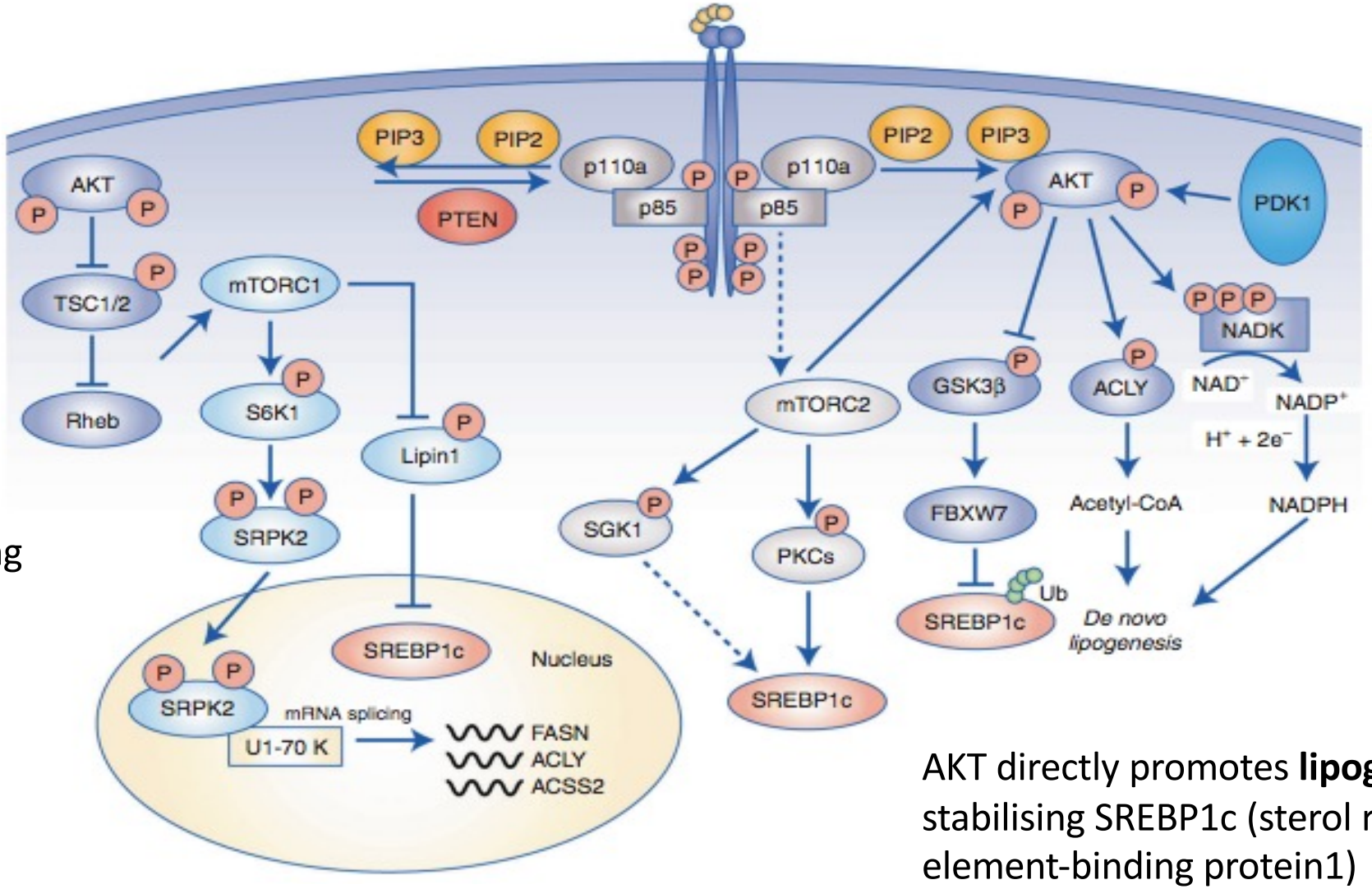
Authors, year [reference]	Study design	Type of targeted therapy	No. of patients	Tumor type	Hyperglycemia, *n* (%)	
					All grades	Grade 3/4
Motzer *et al.*, 2008 [33]	III	Everolimus	269	RCC	135 (50%)	31 (12%)
Motzer *et al.*, 2010 [34]	III	Everolimus	274	RCC	156 (57%)	41 (15%)
Ellard *et al.*, 2009 [35]	II	Everolimus + exemestane	49	BC ER + HER2−	27 (55%)	2 (4%)
Beck *et al.*, 2014 [36▪]	III	Everolimus + exemestane	100	BC ER + HER2−	25 (17%)	8 (8%)
André *et al.*, 2014 [37]	III	Everolimus + vinorelbine + trastuzumab	280	BC HER2+	25 (9%)	6(2%)
Sternberg *et al.*, 2013 [38]	III	Pazopanib	290	Advanced or M+ RCC	120 (43%)	2 (<1%)
Hudes *et al.*, 2007 [39]	III	Temserolimus	208	RCC	26 (12.5%)	1 (<1%)

BC, breast cancer; HER2, human epidermal growth factor 2; M+, metastatic; RCC, renal cell carcinoma; RS, retrospective.

- Uno **stretto monitoraggio della glicemia a digiuno** prima di iniziare il trattamento e periodicamente;
- Grado 1 Inf a 160 nessun trattamento
- Nelle iperglicemie di **grado 2 (160-250)** il paziente andrebbe trattato secondo le linee guida ADA (attenzione ai farmaci che danno nausea);
- In caso di iperglicemia **di grado 3 (>250)**, il trattamento deve essere temporaneamente interrotto e ripreso a dose ridotta;
- In caso di iperglicemia **grado 4 (>500)**, il trattamento deve essere interrotto;
- A causa delle ipoglicemie, alcuni pazienti con diabete pre-esistente sono stati costretti a interrompere la terapia anti-diabete.

Curr Opin Oncol. 2015 May;27(3):258-66; Eur J Cancer. 2011 Jun;47(9):1287-98; Diabetologia. 2008 Jan;51(1):8-11; Hematol Oncol Clin North Am. 2011Aug;25(4):893-915.

PI3K/AKT/mTOR and Lipid Metabolism



mTORC1 regulates lipogenesis promoting the expression of **lipogenic enzymes**

AKT directly promotes **lipogenesis** by stabilising SREBP1c (sterol regulatory element-binding protein1)

Br J Cancer. 2020 Jan;122(1):4-22

Table 3. Incidence of dyslipidemia during targeted therapies

Authors, year [reference]	Study design	Type of targeted therapy	No. of patients	Tumor type	HyperChT, *n* (%)		HyperTG, *n* (%)	
					All grades	Grade 3/4	All grades	Grade 3/4
Motzer *et al.*, 2008 [33]	III	Everolimus	269	RCC	205 (76%)	9 (3%)	191 (71%)	2 (1%)
Motzer *et al.*, 2010 [34]	III	Everolimus	274	RCC	210 (77%)	10 (4%)	200 (73%)	<1%
Ellard *et al.*, 2009 [35]	II	Everolimus + exemestane	49	BC ER + HER2−	40 (81%)	0	22 (44%)	0
Hudes *et al.*, 2007 [39]		Temserolimus	208	RCC	24 (11%)	1 (<1%)	–	–
André *et al.*, 2014 [37]	III	Everolimus + vinorelbine + trastuzumab	280	BC HER2+	–	–	22 (8%)	2 (<1%)

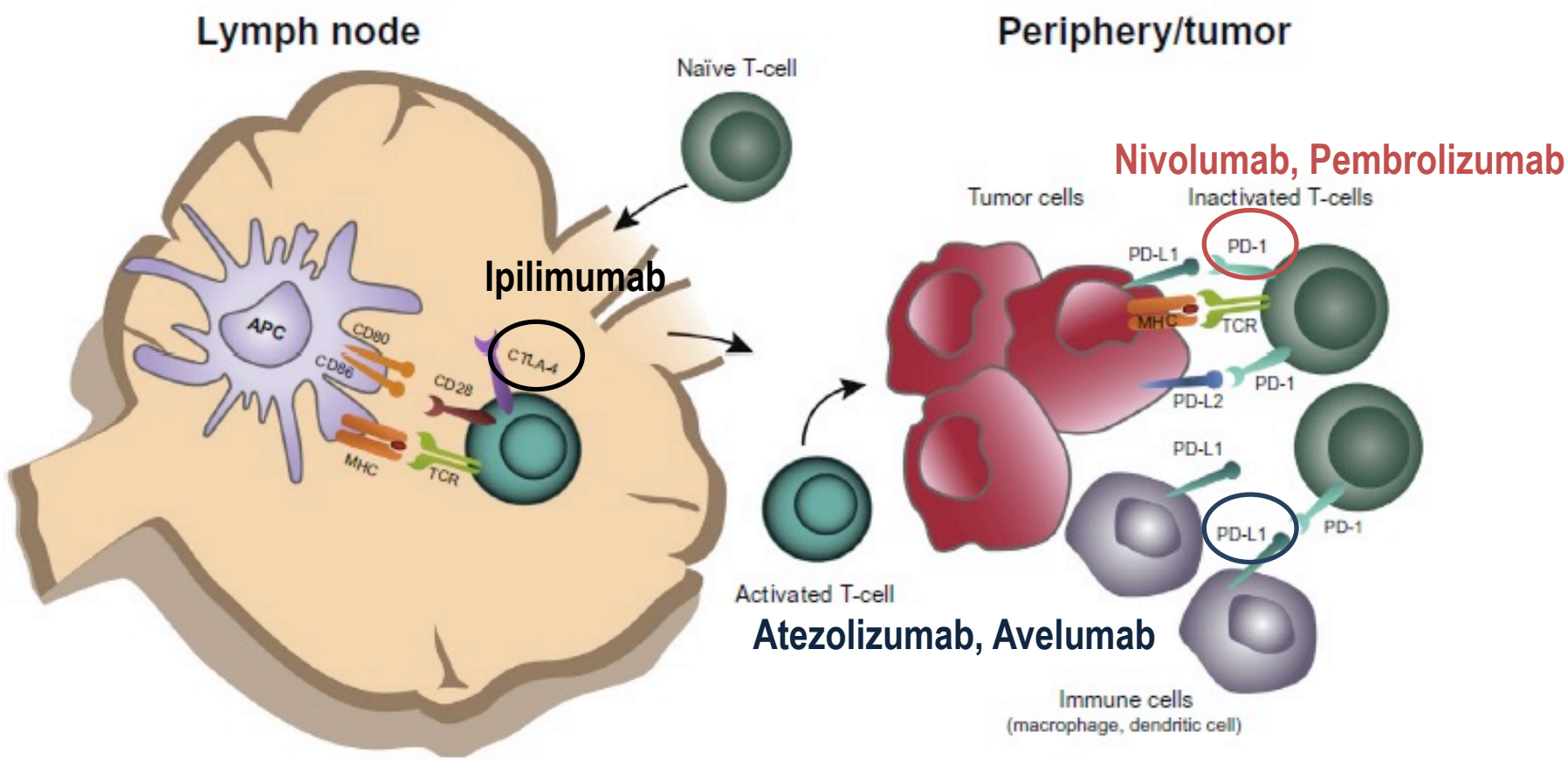
BC, breast cancer; HER2, human epidermal growth factor 2; hyperChT, hypercholesterolemia; hyperTG, hypertriglyceridemia; RCC, renal cell carcinoma.

Curr Opin Oncol. 2015 May;27(3):258-66

Monitoraggio delle Dislipidemie in corso di *Targeted Therapies*

- Un **profilo lipidico** completo deve essere eseguito prima di iniziare il trattamento con l'inibitore di mTOR e deve essere ripetuto ogni 6 settimane durante il trattamento;
- Nelle dislipidemie di **grado 1 (150-300)-2 (300-500)** dovrebbe essere introdotta una terapia ipolipemizzante e attuata una maggiore sorveglianza;
- In caso di **tossicità di grado 3 (500-1000)**, il trattamento deve essere temporaneamente interrotto e ripreso a dose ridotta (50%);
- In caso di **tossicità di grado 4 (>1000)**, il trattamento deve essere interrotto.
- Come ipocolesterolemizzante, utilizzare **statine** o **resine a scambio anionico** in caso di colesterolo elevato; **acido nicotinico** o **fibrato** in caso di trigliceridi elevati.
- **ATTENZIONE: i farmaci ipolipemizzanti e farmaci antitumorali possono avere interazioni farmacologiche che potrebbero comprometterne i benefici terapeutici.**

Curr Opin Oncol. 2015 May;27(3):258-66; Transplant Rev (Orlando). 2014 Jul;28(3):126-33; Cancer Treat Rev. 2013 Jun;39(4):388-401; Clin Pharmacol Ther. 2006 Dec;80(6):565-81.



The most typical adverse events affect the skin, the GI tract, the liver and the **endocrine system**.

modificato da Sznol M. et al., *Cancer Treat Rev* 2017

Incidence of treatment-related endocrine AEs of potential immunological etiology in major melanoma and lung cancer trials of anti-PD-1-based therapy.

Patients reporting event, %	Melanoma						SC-NSCLC		NS-NSCLC	
	Pembrolizumab[a]		NIVO[b,c]		NIVO + IPI[b,c]		NIVO[d]		NIVO[c,e]	
	Any Gr	Gr 3–5	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Any endocrine event	NR	NR	14.4	0.6	30.0	4.8	4.0	0	9.4	0
Pituitary disorders	NR	NR	0.6	0.3	7.7	1.6	NR	NR	NR	NR
Hypophysitis	0.7	0.4	0.6	0.3	7.7	1.6	NR	NR	NR	NR
Corticotropin (ACTH) decreased	NR	NR	0	0	0.6	0	NR	NR	NR	NR
Secondary adrenal insufficiency[f,g]	NR	NR	0	0	0.3	0	NR	NR	NR	NR
Thyroid disorders	NR	NR	13.1	0	25.6	1.9	4.0	0	9.4	0
Hyperthyroidism	3.2	0	4.2	0	9.9	1.0	NR	NR	1.4	0
Hypothyroidism	8.7	0	8.6	0	15.0	0.3	4.0	0	6.6	0
Blood TSH increased	NR	NR	0.3	0	1.0	0	NR	NR	2.1	0
Blood TSH decreased	NR	NR	1.3	0	1.3	0	NR	NR	<1.0	0
Thyroiditis	NR	NR	0.6	0	3.8	0.3	NR	NR	<1.0	0
Autoimmune thyroiditis	NR	NR	0.3	0	0.6	0.6	NR	NR	NR	NR
Thyroxin free increased	NR	NR	0	0	0.3	0	NR	NR	NR	NR
Thyroxin free decreased	NR	NR	0.3	0	0.3	0	NR	NR	NR	NR
Adrenal disorders	NR	NR	0.6	0.3	3.5	1.6	NR	NR	NR	NR
Primary adrenal insufficiency[f,h]	NR	NR	0.6	0.3	2.6	1.6	NR	NR	NR	NR
Diabetes mellitus	0.4	0.4	0	0	0.3	0	NR	NR	0	0

Abbreviations: Gr, grade; IPI, ipilimumab; NIVO, nivolumab; NR, not reported; NS-NSCLC, nonsquamous non–small-cell lung cancer; SC-NSCLC, squamous-cell non–small-cell lung cancer; TSH, thyroid-stimulating hormone.

[a] Data from KEYNOTE-006, every 3 weeks dosing arm. The listed adverse events include related terms and are provided regardless of attribution to a study drug [28].

[b] Data from CheckMate 067 [6].

[c] Data on file [Bristol-Myers Squibb].

[d] Data from CheckMate 017 [29].

[e] Data from CheckMate 057 [30].

[f] Causing decreased cortisol secretion.

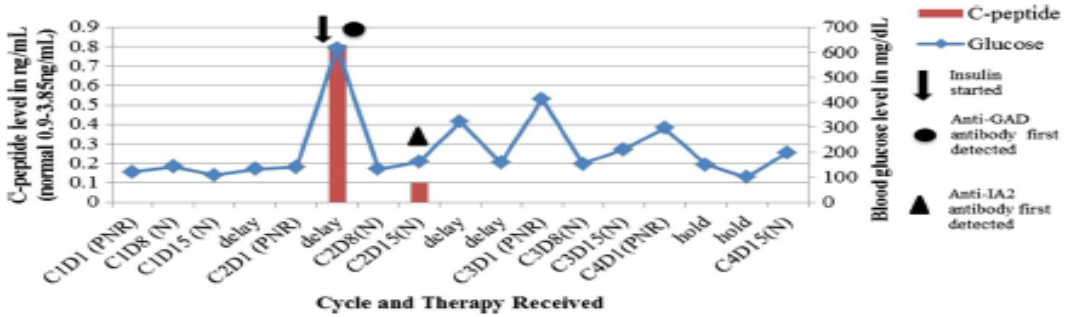
[g] Caused by decreased ACTH secretion by the anterior pituitary gland.

[h] Caused by a disorder of the adrenal glands.

Sznol M. et al., *Cancer Treat Rev* 2017

Immune checkpoint inhibitor-induced Type 1 Diabetes

- Recently, **case reports** have shown an association between T1DM and anti-PD-1 immunomodulating agents.
- PD-1 inhibition should allow autoreactive T-cells to be directly activated and infiltrate pancreatic islet cells.
- Testing HLA genotypes prior to administration of immunotherapy may help to identify patients at risk.
- It is unclear whether patients will have lifelong diabetes.
- Until now, CTLA-4 inhibitor has not been associated with T1DM.



Chae YK et al., Cancer Immunol Immunother 2016

Eventi Avversi Metabolici Correlati all'Utilizzo delle Nuove Terapie Antitumorali

Table 2
Anti-cancer agents and metabolic AEs.

DRUG CLASS	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA	HYPER-CHOLESTEROLEMIA	HYPER-TRIGLYCERIDEMIA
ICIs	YES	YES	YES	YES	NO	NO
Monoclonal antibodies	NO	YES	NO	NO	YES	YES
Kinase inhibitors	NO	YES	NO	NO	YES	YES
Multikinase inhibitors	YES	YES	NO	YES	YES	YES
mTOR inhibitors	YES	YES	NO	NO	YES	YES
PARP inhibitors	NO	NO	NO	NO	YES	NO
Proteosome inhibitors	YES	YES	NO	NO	NO	NO
Angiogenesis inhibitors	NO	YES	NO	NO	YES	NO

Informations available in EMA's "Summaries of Product Characteristics"

Crit Rev Oncol Hematol. 2020 Oct;154:103066