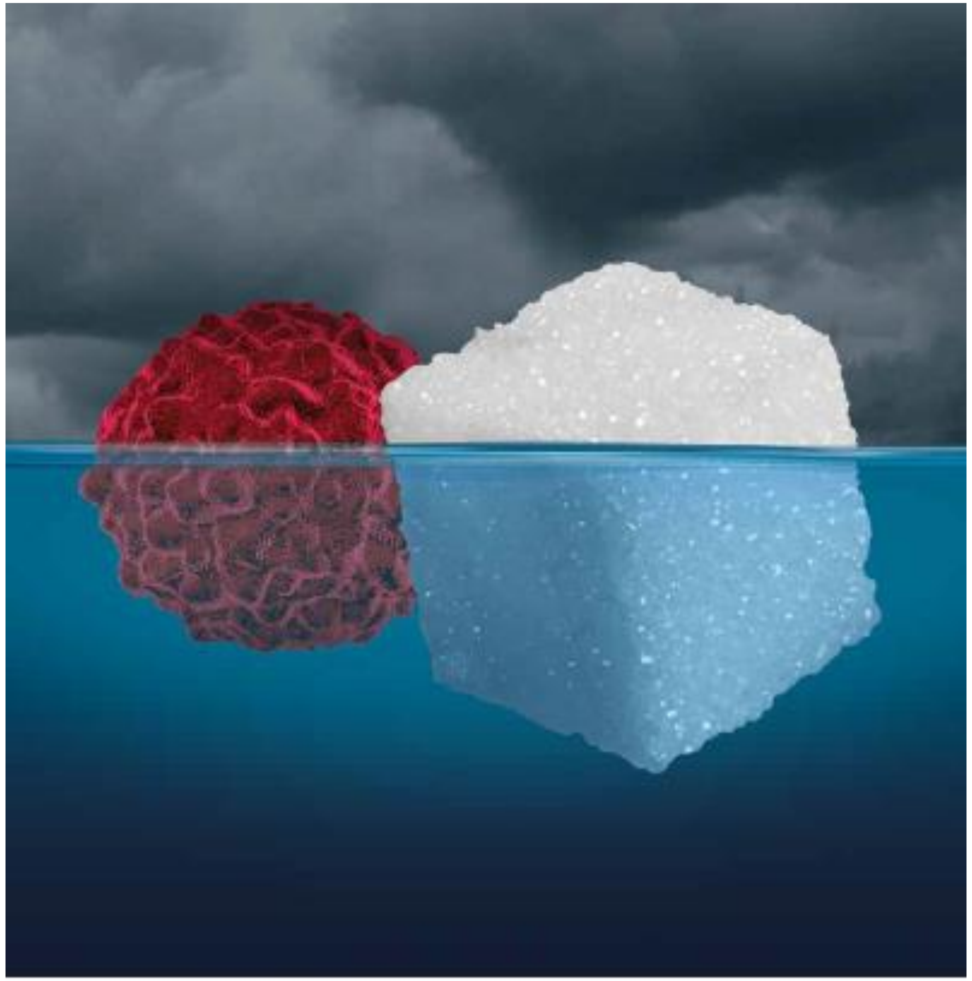


DIABETE E TUMORI NELLA PRATICA CLINICA:
RILEVANZA, CRITICITÀ, SOLUZIONI

ROMA, 9 Novembre 2019

UNAHOTELS DECÒ
Via Giovanni Amendola, 57

AMD 1974 ASSOCIAZIONE MEDICI DIABETOLOGI

AIOM Associazione Italiana di Oncologia Medica

TERAPIE ANTITUMORALI: TOSSICITA' METABOLICHE ACUTE

Dott.ssa Silvia Acquati
UO Endocrinologia e
Mal. Metaboliche, Forlì
AUSL ROMAGNA

CONFLITTO DI INTERESSI

- Ai sensi dell’art. 4.5 su “Docenti e moderatori dell’evento”, pag. 8 del Manuale Nazionale di Accreditamento per l’erogazione di eventi ECM del 06/12/2018, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti, **non** di finanziamento, con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

  - Menarini Diagnostics

TARGETED THERAPIES
IMMUNOTHERAPY

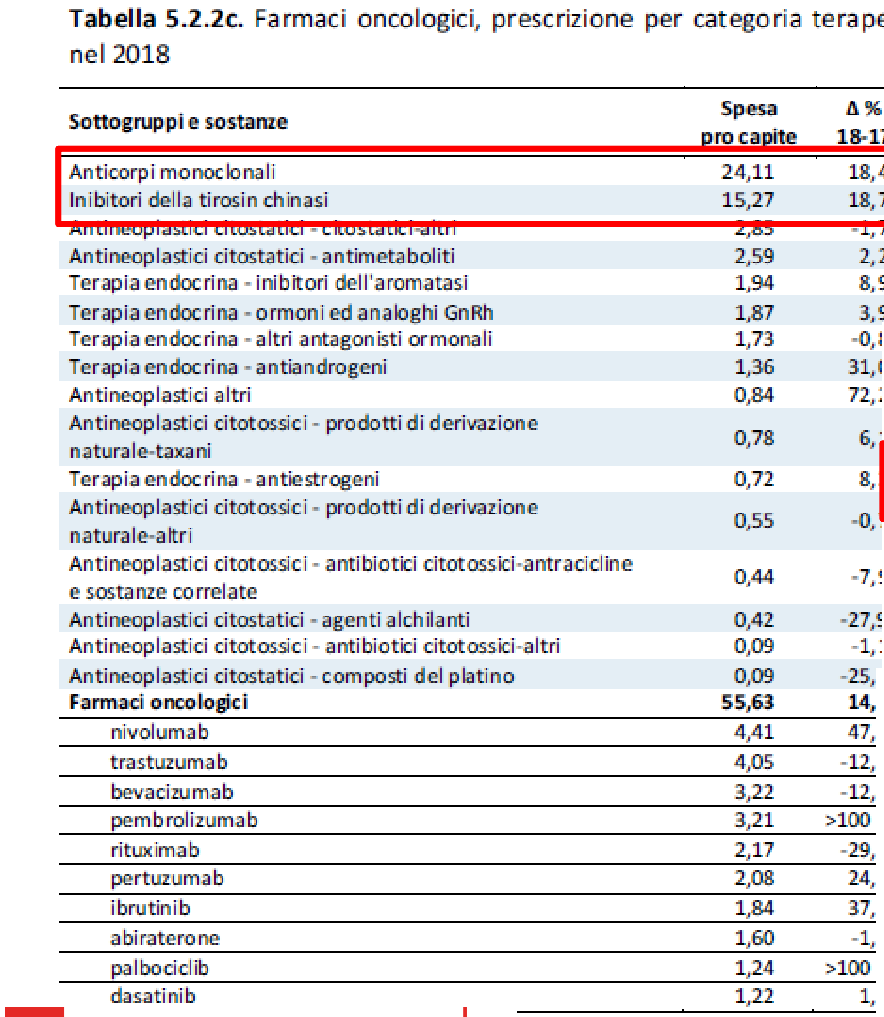


Tabella 5.2.2c. Farmaci oncologici, prescrizione per categoria terapeutica e per sostanza nel 2018

Sottogruppi e sostanze	Spesa pro capite	Δ % 18-17	DDD/1000 ab die	Δ % 18-17
Anticorpi monoclonali	24,11	18,4	1,1	6,8
Inibitori della tirosin chinasi	15,27	18,7	0,4	18,2
Antineoplastici citostatici - citostatici-altri	2,85	-1,7	0,4	1,4
Antineoplastici citostatici - antimetaboliti	2,59	2,2	0,6	-5,2
Terapia endocrina - inibitori dell'aromatasi	1,94	8,9	3,1	7,0
Terapia endocrina - ormoni ed analoghi GnRh	1,87	3,9	1,0	4,8
Terapia endocrina - altri antagonisti ormonali	1,73	-0,		
Terapia endocrina - antiandrogeni	1,36	31,		
Antineoplastici altri	0,84	72,		
Antineoplastici citotossici - prodotti di derivazione naturale-taxani	0,78	6,		
Terapia endocrina - antiestrogeni	0,72	8,		
Antineoplastici citotossici - prodotti di derivazione naturale-altri	0,55	-0,		
Antineoplastici citotossici - antibiotici citotossici-antracicline e sostanze correlate	0,44	-7,		
Antineoplastici citostatici - agenti alchilanti	0,42	-27,		
Antineoplastici citotossici - antibiotici citotossici-altri	0,09	-1,		
Antineoplastici citostatici - composti del platino	0,09	-25,		
Farmaci oncologici	**55,63**	**14,**		
nivolumab	4,41	47,		
trastuzumab	4,05	-12,		
bevacizumab	3,22	-12,		
pembrolizumab	3,21	>100		
rituximab	2,17	-29,		
pertuzumab	2,08	24,		
ibrutinib	1,84	37,		
abiraterone	1,60	-1,		
palbociclib	1,24	>100		
dasatinib	1,22	1,		

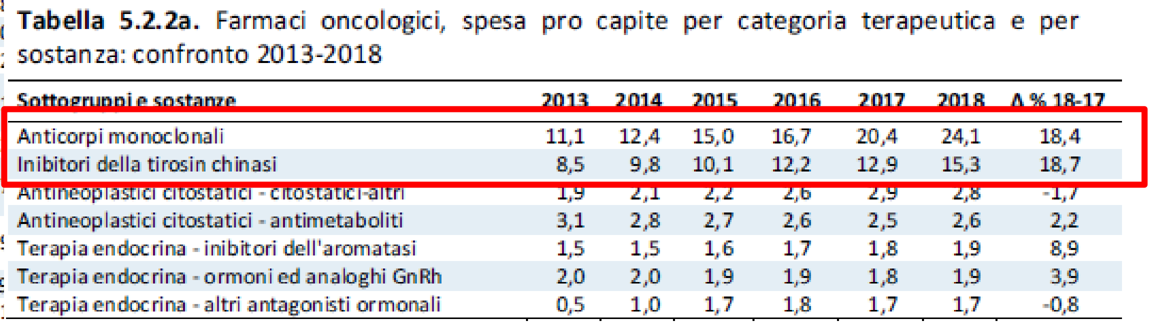
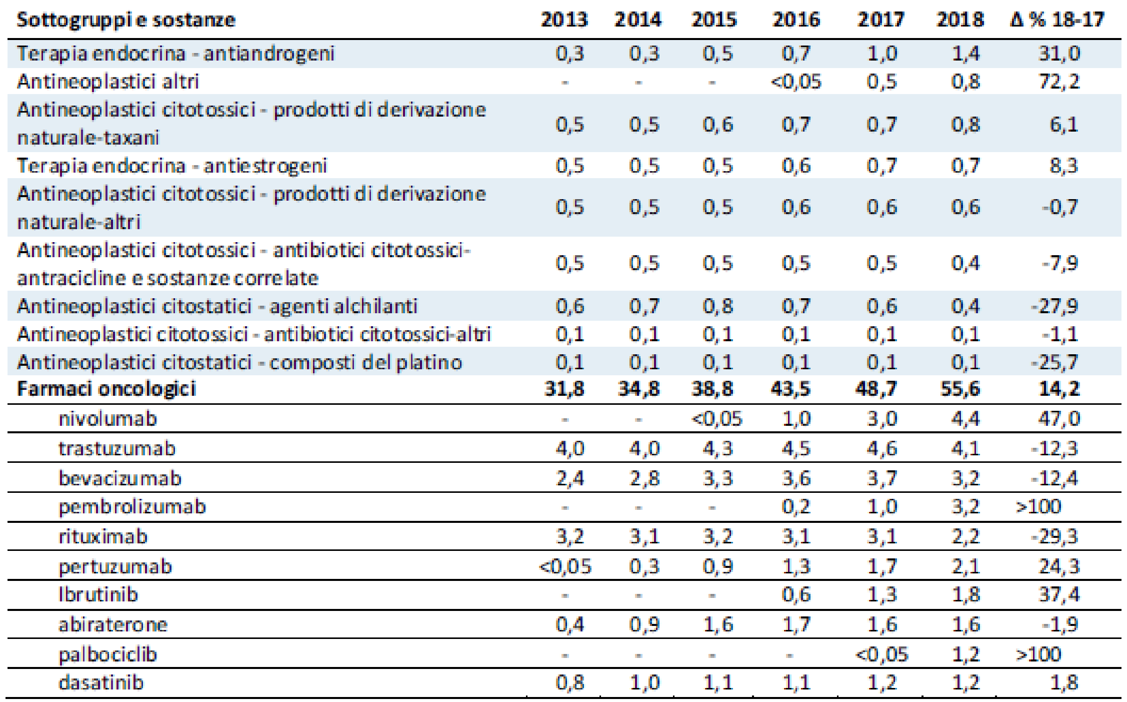


Tabella 5.2.2a. Farmaci oncologici, spesa pro capite per categoria terapeutica e per sostanza: confronto 2013-2018



Sottogruppi e sostanze	2013	2014	2015	2016	2017	2018	Δ % 18-17
Anticorpi monoclonali	11,1	12,4	15,0	16,7	20,4	24,1	18,4
Inibitori della tirosin chinasi	8,5	9,8	10,1	12,2	12,9	15,3	18,7
Antineoplastici citostatici - citostatici-altri	1,9	2,1	2,2	2,6	2,9	2,8	-1,7
Antineoplastici citostatici - antimetaboliti	3,1	2,8	2,7	2,6	2,5	2,6	2,2
Terapia endocrina - inibitori dell'aromatasi	1,5	1,5	1,6	1,7	1,8	1,9	8,9
Terapia endocrina - ormoni ed analoghi GnRh	2,0	2,0	1,9	1,9	1,8	1,9	3,9
Terapia endocrina - altri antagonisti ormonali	0,5	1,0	1,7	1,8	1,7	1,7	-0,8
Terapia endocrina - antiandrogeni	0,3	0,3	0,5	0,7	1,0	1,4	31,0
Antineoplastici altri	-	-	-	<0,05	0,5	0,8	72,2
Antineoplastici citotossici - prodotti di derivazione naturale-taxani	0,5	0,5	0,6	0,7	0,7	0,8	6,1
Terapia endocrina - antiestrogeni	0,5	0,5	0,5	0,6	0,7	0,7	8,3
Antineoplastici citotossici - prodotti di derivazione naturale-altri	0,5	0,5	0,5	0,6	0,6	0,6	-0,7
Antineoplastici citotossici - antibiotici citotossici-antracicline e sostanze correlate	0,5	0,5	0,5	0,5	0,5	0,4	-7,9
Antineoplastici citostatici - agenti alchilanti	0,6	0,7	0,8	0,7	0,6	0,4	-27,9
Antineoplastici citotossici - antibiotici citotossici-altri	0,1	0,1	0,1	0,1	0,1	0,1	-1,1
Antineoplastici citostatici - composti del platino	0,1	0,1	0,1	0,1	0,1	0,1	-25,7
Farmaci oncologici	**31,8**	**34,8**	**38,8**	**43,5**	**48,7**	**55,6**	**14,2**
nivolumab	-	-	<0,05	1,0	3,0	4,4	47,0
trastuzumab	4,0	4,0	4,3	4,5	4,6	4,1	-12,3
bevacizumab	2,4	2,8	3,3	3,6	3,7	3,2	-12,4
pembrolizumab	-	-	-	0,2	1,0	3,2	>100
rituximab	3,2	3,1	3,2	3,1	3,1	2,2	-29,3
pertuzumab	<0,05	0,3	0,9	1,3	1,7	2,1	24,3
Ibrutinib	-	-	-	0,6	1,3	1,8	37,4
abiraterone	0,4	0,9	1,6	1,7	1,6	1,6	-1,9
palbociclib	-	-	-	-	<0,05	1,2	>100
dasatinib	0,8	1,0	1,1	1,1	1,2	1,2	1,8

L'uso dei Farmaci in Italia
Rapporto Nazionale
Anno 2018

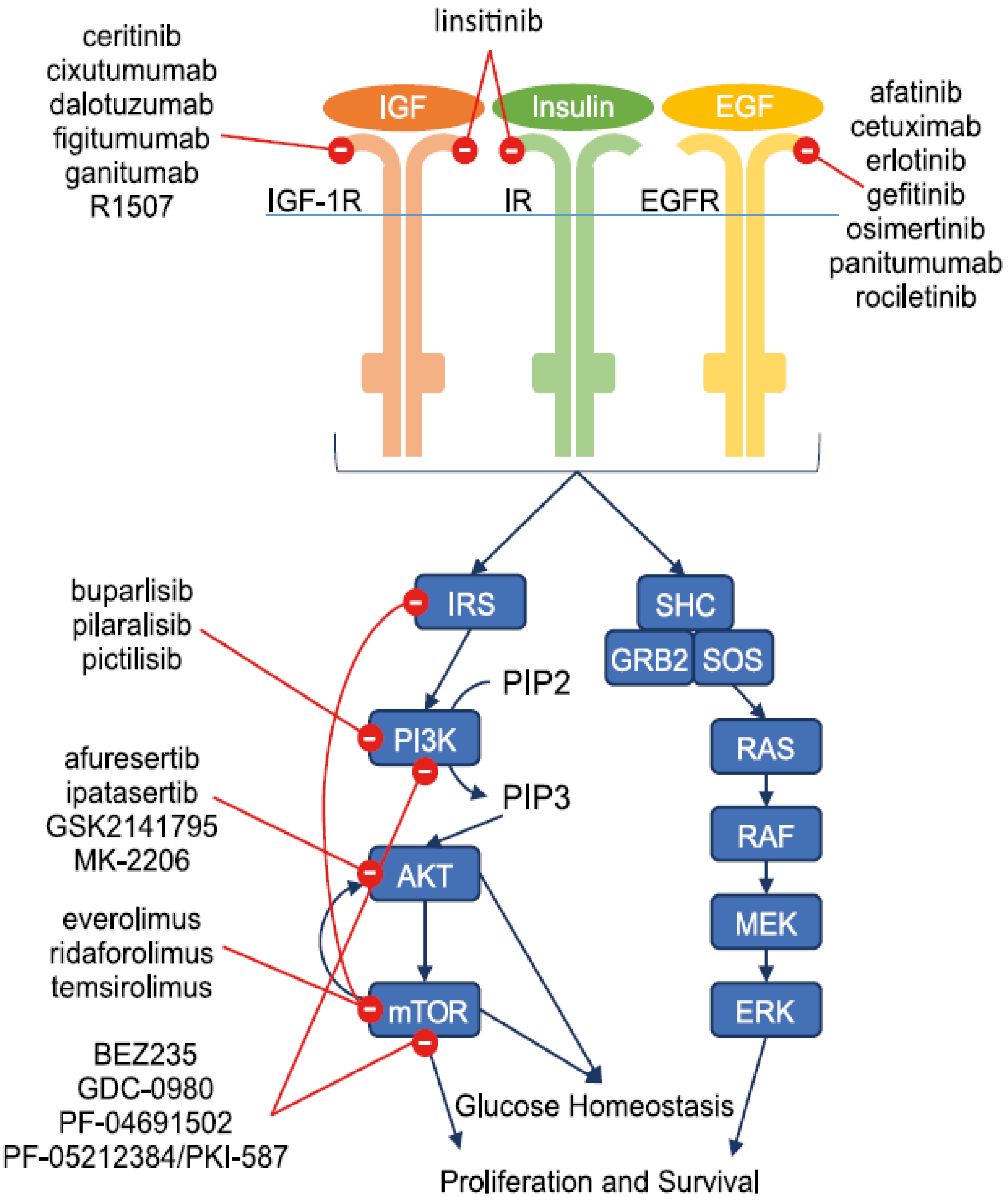
OSSERVATORIO NAZIONALE SULL'IMPIEGO DEI MEDICINALI

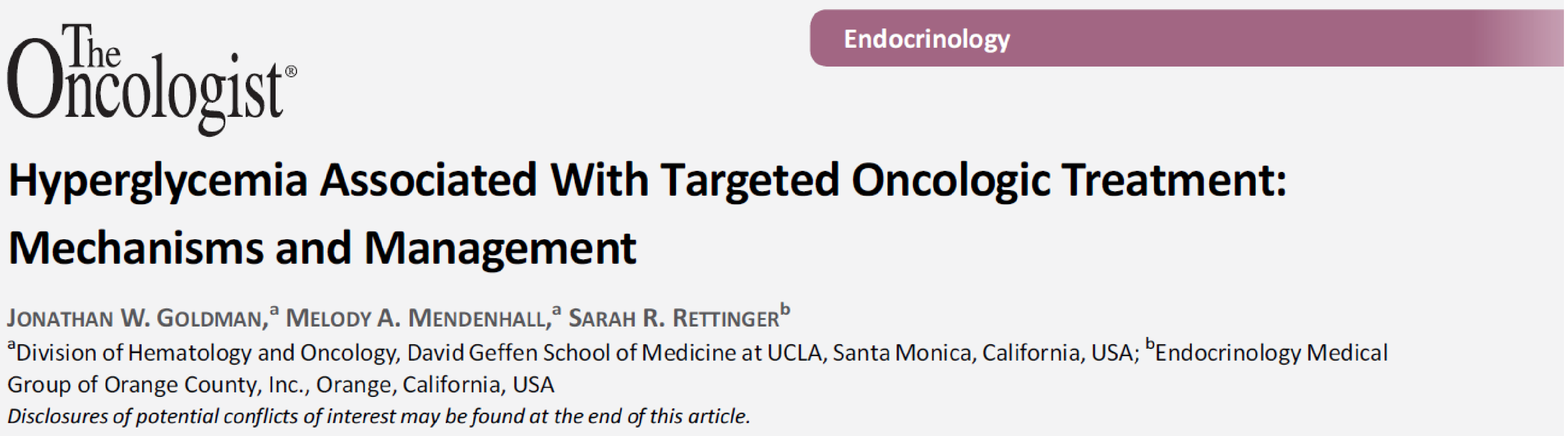
TARGETED THERAPIES

- Inibiscono vie cellulari che promuovono la crescita tumorale
- Molti di questi agenti che bloccano i segnali di proliferazione cellulare sono piccole molecole che inibiscono le tirosin chinasi (MAPK, PI3k/mTOR) bloccando la dimerizzazione del ligando
- Le cellule di superficie possono essere anche inibite da anticorpi monoclonali
- Rispetto alla chemioterapia citotossica tradizionale l'incidenza di leucopenia, nausea, vomito e astenia sono marcatamente ridotti
- Molte di queste proteine inibite sono coinvolte nella regolazione del metabolismo glucidico e lipidico
- Molti di questi targeted agents si associano ad iperglicemia (induced treatment related hyperglycemia)

TARGETED THERAPIES

- Ridotta captazione del glucosio
- Ridotta gliconesintesi
- Aumentata glicolisi
- Sviluppo di insulino resistenza
- La cronica inibizione di mTOR inhibitors si associa a ridotta proliferazione e distruzione beta celllulare
- Alterazione del controllo glicemico in pazienti diabetici noti
- Insorgenza di diabete mellito


ceritinib
cixutumumab
dalotuzumab
figitumumab
ganitumab
R1507
linsitinib
IGF
Insulin
EGF
afatinib
cetuximab
erlotinib
gefitinib
osimertinib
panitumumab
rociletinib
IGF-1R
IR
EGFR
buparlisib
pilaralisib
pictilisib
IRS
SHC
GRB2
SOS
PIP2
PI3K
PIP3
RAS
afuresertib
ipatasertib
GSK2141795
MK-2206
AKT
RAF
MEK
everolimus
ridaforolimus
temsirolimus
mTOR
ERK
BEZ235
GDC-0980
PF-04691502
PF-05212384/PKI-587
Glucose Homeostasis
Proliferation and Survival



The Oncologist®

Endocrinology

Hyperglycemia Associated With Targeted Oncologic Treatment: Mechanisms and Management

Jonathan W. Goldman,[a] Melody A. Mendenhall,[a] Sarah R. Rettinger[b]
[a]Division of Hematology and Oncology, David Geffen School of Medicine at UCLA, Santa Monica, California, USA; [b]Endocrinology Medical Group of Orange County, Inc., Orange, California, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

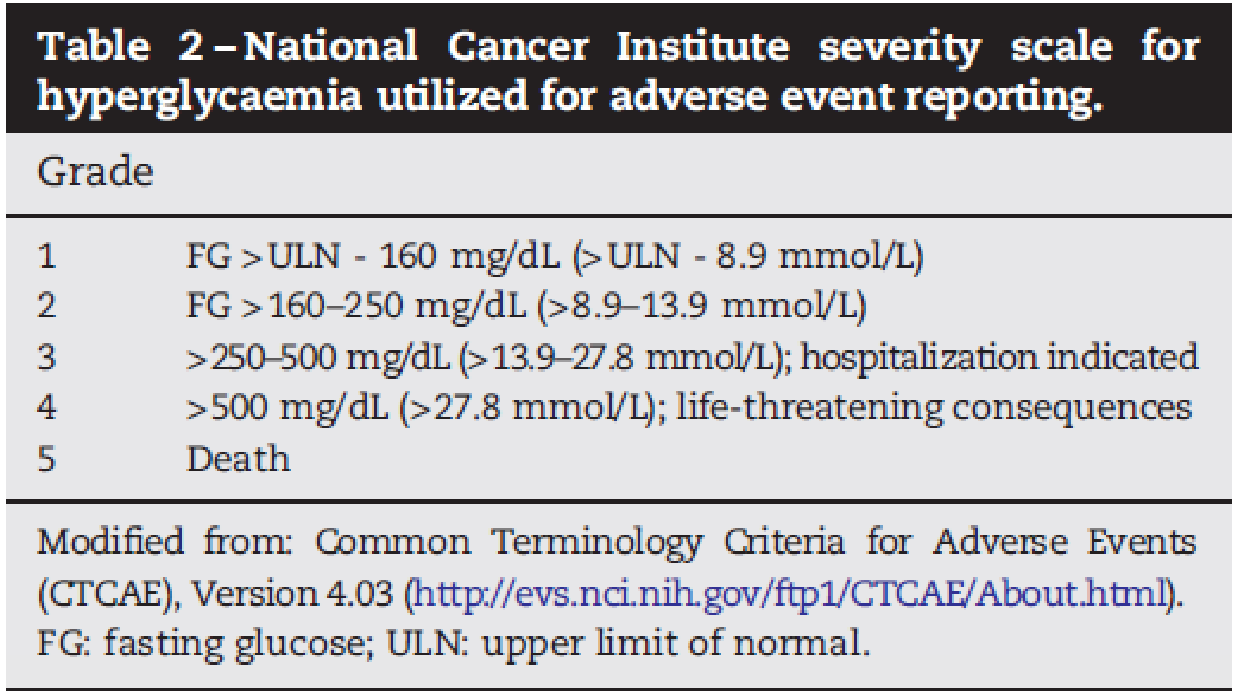


Table 2 – National Cancer Institute severity scale for hyperglycaemia utilized for adverse event reporting.

Grade	
1	FG >ULN - 160 mg/dL (>ULN - 8.9 mmol/L)
2	FG >160–250 mg/dL (>8.9–13.9 mmol/L)
3	>250–500 mg/dL (>13.9–27.8 mmol/L); hospitalization indicated
4	>500 mg/dL (>27.8 mmol/L); life-threatening consequences
5	Death

Modified from: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).
FG: fasting glucose; ULN: upper limit of normal.

The Oncologist 2016;21:1326–1336

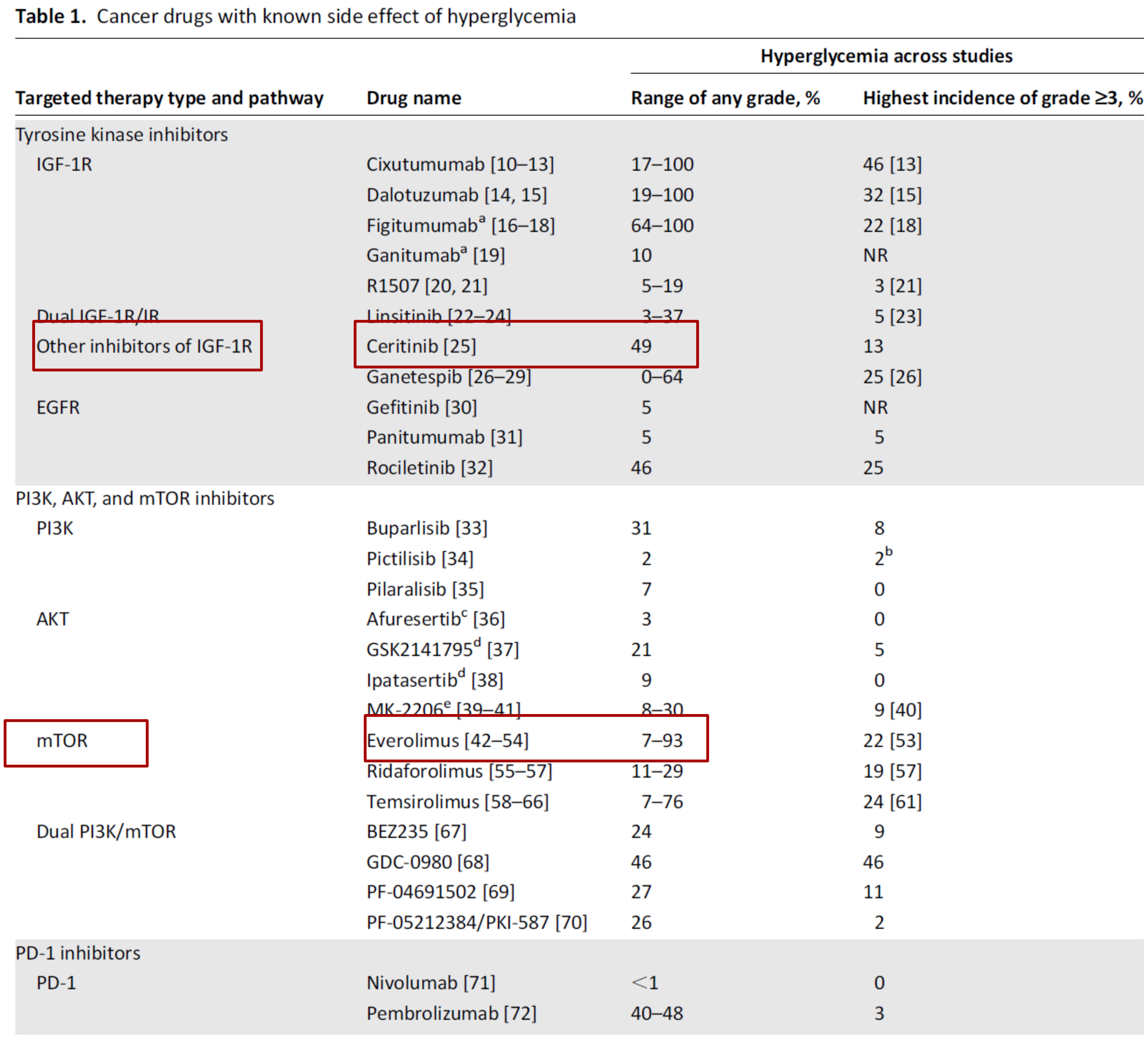
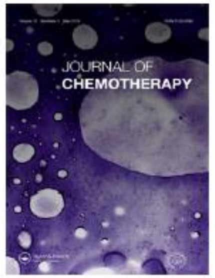


Table 1. Cancer drugs with known side effect of hyperglycemia

		Hyperglycemia across studies	
Targeted therapy type and pathway	**Drug name**	**Range of any grade, %**	**Highest incidence of grade ≥3, %**
Tyrosine kinase inhibitors			
IGF-1R	Cixutumumab [10–13]	17–100	46 [13]
	Dalotuzumab [14, 15]	19–100	32 [15]
	Figitumumab[a] [16–18]	64–100	22 [18]
	Ganitumab[a] [19]	10	NR
	R1507 [20, 21]	5–19	3 [21]
Dual IGF-1R/IR	Linsitinib [22–24]	3–37	5 [23]
Other inhibitors of IGF-1R	Ceritinib [25]	49	13
	Ganetespib [26–29]	0–64	25 [26]
EGFR	Gefitinib [30]	5	NR
	Panitumumab [31]	5	5
	Rociletinib [32]	46	25
PI3K, AKT, and mTOR inhibitors			
PI3K	Buparlisib [33]	31	8
	Pictilisib [34]	2	2[b]
	Pilaralisib [35]	7	0
AKT	Afuresertib[c] [36]	3	0
	GSK2141795[d] [37]	21	5
	Ipatasertib[d] [38]	9	0
	MK-2206[e] [39–41]	8–30	9 [40]
mTOR	Everolimus [42–54]	7–93	22 [53]
	Ridaforolimus [55–57]	11–29	19 [57]
	Temsirolimus [58–66]	7–76	24 [61]
Dual PI3K/mTOR	BEZ235 [67]	24	9
	GDC-0980 [68]	46	46
	PF-04691502 [69]	27	11
	PF-05212384/PKI-587 [70]	26	2
PD-1 inhibitors			
PD-1	Nivolumab [71]	<1	0
	Pembrolizumab [72]	40–48	3

Short-term adverse effects of anticancer drugs in patients with type 2 diabetes

Agostino Milluzzo, Andrea Tumminia, Veronica Vella, Fiorenza Gianì, Livia Manzella, Lucia Frittitta, Antonino Belfiore, Riccardo Vigneri & Laura Sciacca



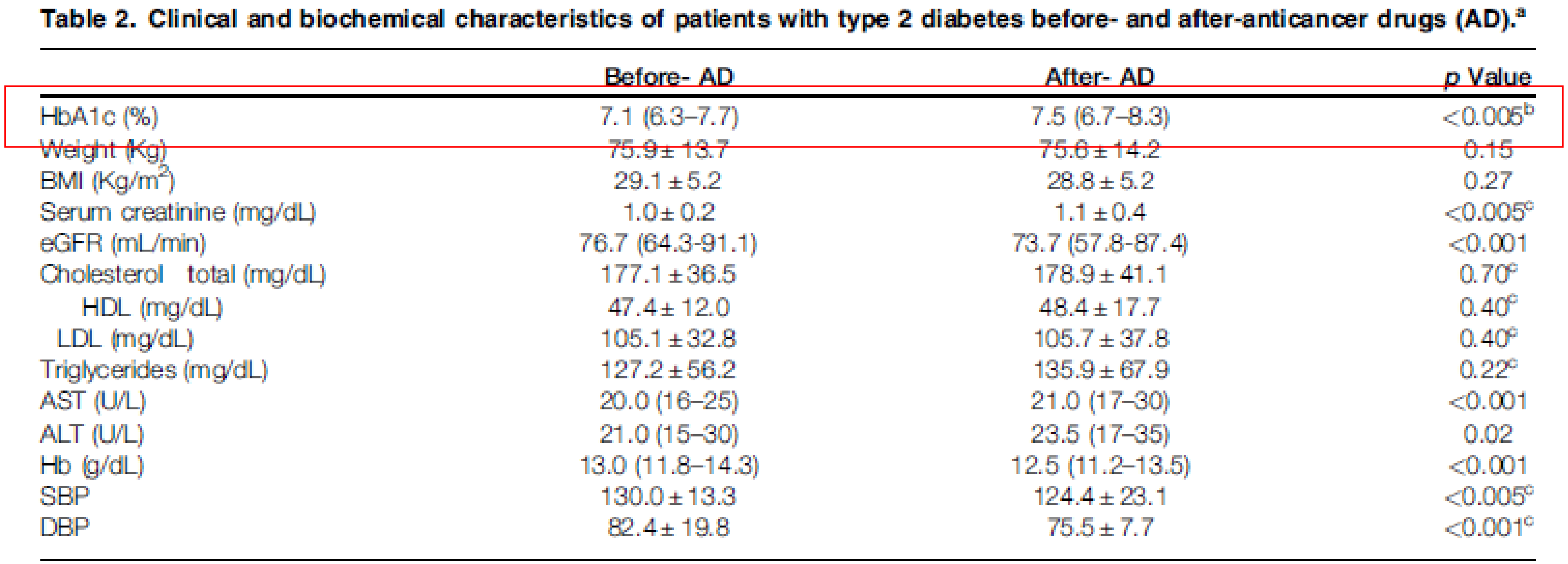


Table 2. Clinical and biochemical characteristics of patients with type 2 diabetes before- and after-anticancer drugs (AD).[a]

	Before- AD	After- AD	*p* Value
HbA1c (%)	7.1 (6.3–7.7)	7.5 (6.7–8.3)	<0.005[b]
Weight (Kg)	75.9 ± 13.7	75.6 ± 14.2	0.15
BMI (Kg/m^2)	29.1 ± 5.2	28.8 ± 5.2	0.27
Serum creatinine (mg/dL)	1.0 ± 0.2	1.1 ± 0.4	<0.005[c]
eGFR (mL/min)	76.7 (64.3-91.1)	73.7 (57.8-87.4)	<0.001
Cholesterol total (mg/dL)	177.1 ± 36.5	178.9 ± 41.1	0.70[c]
HDL (mg/dL)	47.4 ± 12.0	48.4 ± 17.7	0.40[c]
LDL (mg/dL)	105.1 ± 32.8	105.7 ± 37.8	0.40[c]
Triglycerides (mg/dL)	127.2 ± 56.2	135.9 ± 67.9	0.22[c]
AST (U/L)	20.0 (16–25)	21.0 (17–30)	<0.001
ALT (U/L)	21.0 (15–30)	23.5 (17–35)	0.02
Hb (g/dL)	13.0 (11.8–14.3)	12.5 (11.2–13.5)	<0.001
SBP	130.0 ± 13.3	124.4 ± 23.1	<0.005[c]
DBP	82.4 ± 19.8	75.5 ± 7.7	<0.001[c]

Journal of Chemotherapy 2019 VOL. 31 NO. 3

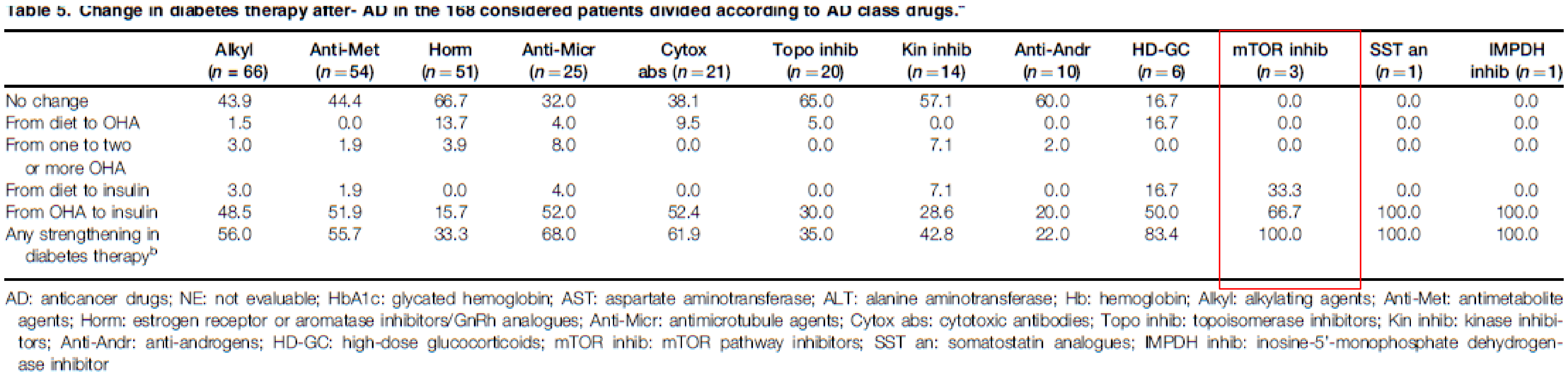
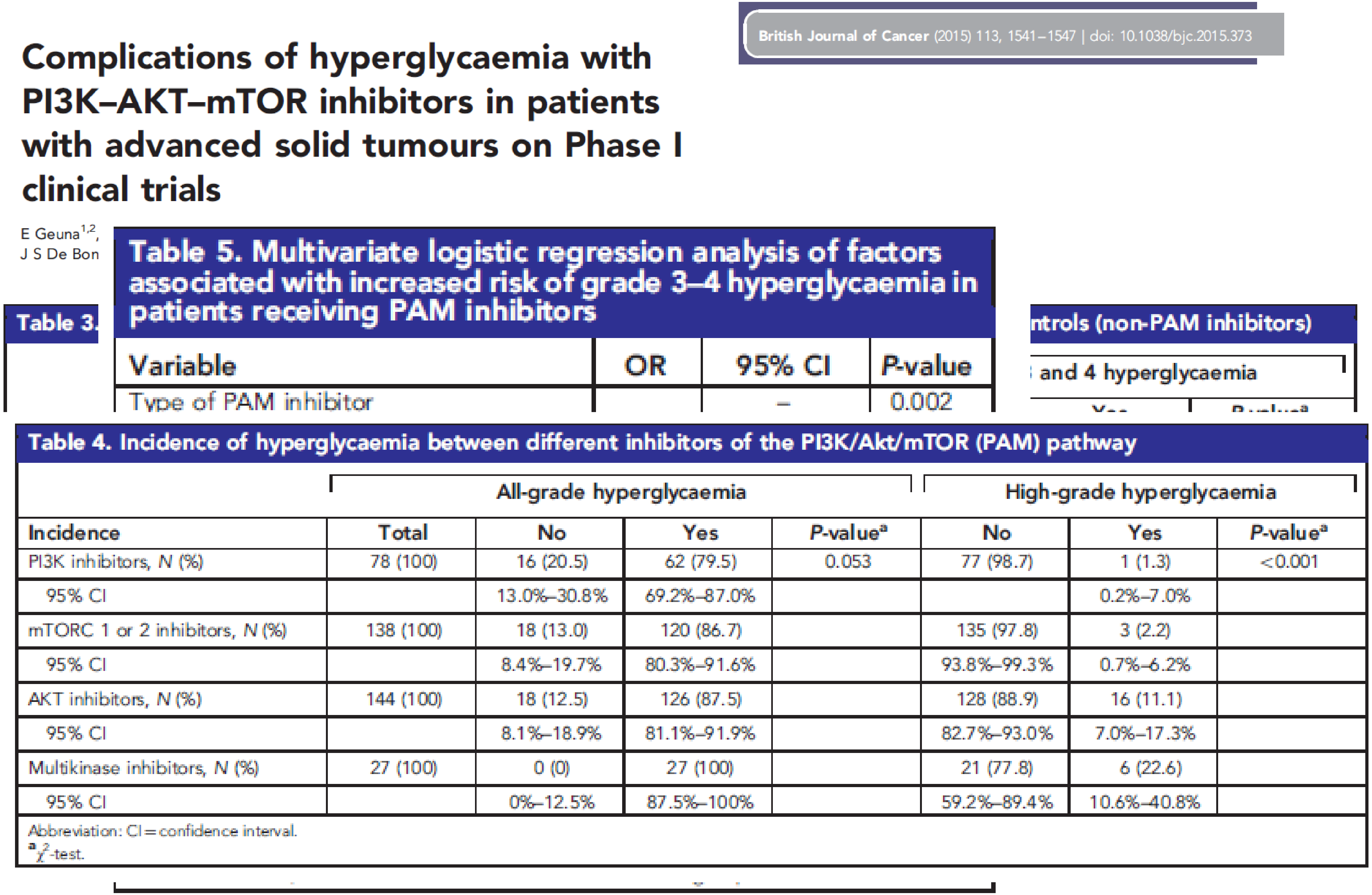


Table 5. Change in diabetes therapy after- AD in the 168 considered patients divided according to AD class drugs.[a]

	Alkyl (*n* = 66)	Anti-Met (*n* = 54)	Horm (*n* = 51)	Anti-Micr (*n* = 25)	Cytox abs (*n* = 21)	Topo inhib (*n* = 20)	Kin inhib (*n* = 14)	Anti-Andr (*n* = 10)	HD-GC (*n* = 6)	mTOR inhib (*n* = 3)	SST an (*n* = 1)	IMPDH inhib (*n* = 1)
No change	43.9	44.4	66.7	32.0	38.1	65.0	57.1	60.0	16.7	0.0	0.0	0.0
From diet to OHA	1.5	0.0	13.7	4.0	9.5	5.0	0.0	0.0	16.7	0.0	0.0	0.0
From one to two or more OHA	3.0	1.9	3.9	8.0	0.0	0.0	7.1	2.0	0.0	0.0	0.0	0.0
From diet to insulin	3.0	1.9	0.0	4.0	0.0	0.0	7.1	0.0	16.7	33.3	0.0	0.0
From OHA to insulin	48.5	51.9	15.7	52.0	52.4	30.0	28.6	20.0	50.0	66.7	100.0	100.0
Any strengthening in diabetes therapy[b]	56.0	55.7	33.3	68.0	61.9	35.0	42.8	22.0	83.4	100.0	100.0	100.0

AD: anticancer drugs; NE: not evaluable; HbA1c: glycated hemoglobin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Hb: hemoglobin; Alkyl: alkylating agents; Anti-Met: antimetabolite agents; Horm: estrogen receptor or aromatase inhibitors/GnRh analogues; Anti-Micr: antimicrotubule agents; Cytox abs: cytotoxic antibodies; Topo inhib: topoisomerase inhibitors; Kin inhib: kinase inhibitors; Anti-Andr: anti-androgens; HD-GC: high-dose glucocorticoids; mTOR inhib: mTOR pathway inhibitors; SST an: somatostatin analogues; IMPDH inhib: inosine-5'-monophosphate dehydrogenase inhibitor

- 168 pz D2 dopo 6 mesi dall’inizio del trattamento
- 36.9% peggioramento di Hba1c
- In tutti i pazienti in terapia con mTOR si è osservata la necessità di potenziare la terapia antidiabetica



British Journal of Cancer (2015) 113, 1541–1547 | doi: 10.1038/bjc.2015.373

Complications of hyperglycaemia with PI3K–AKT–mTOR inhibitors in patients with advanced solid tumours on Phase I clinical trials

E Geuna[1,2],
J S De Bon

Table 3.

ntrols (non-PAM inhibitors)

and 4 hyperglycaemia

Table 5. Multivariate logistic regression analysis of factors associated with increased risk of grade 3–4 hyperglycaemia in patients receiving PAM inhibitors

Variable	OR	95% CI	P-value
Type of PAM inhibitor		–	0.002

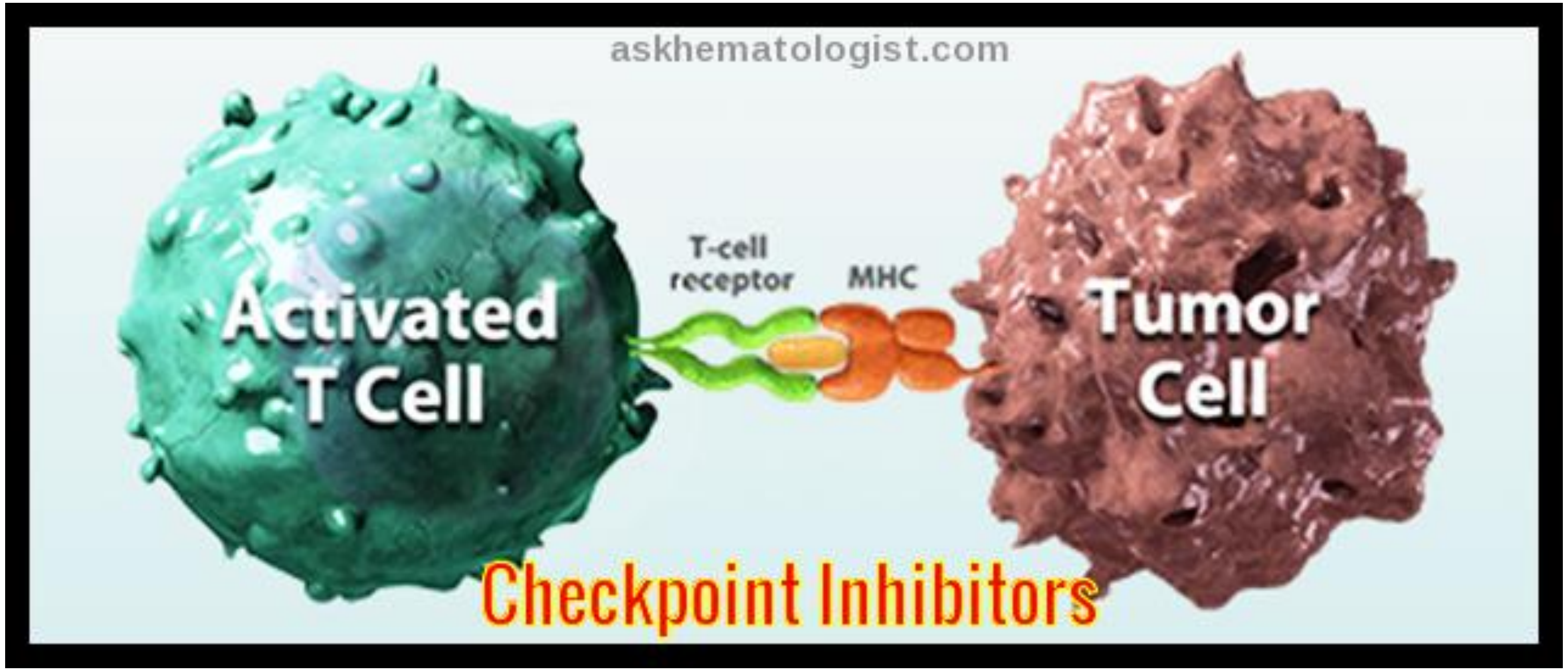
Table 4. Incidence of hyperglycaemia between different inhibitors of the PI3K/Akt/mTOR (PAM) pathway

		All-grade hyperglycaemia			High-grade hyperglycaemia		
Incidence	Total	No	Yes	P-value[a]	No	Yes	P-value[a]
PI3K inhibitors, *N* (%)	78 (100)	16 (20.5)	62 (79.5)	0.053	77 (98.7)	1 (1.3)	<0.001
95% CI		13.0%–30.8%	69.2%–87.0%			0.2%–7.0%	
mTORC 1 or 2 inhibitors, *N* (%)	138 (100)	18 (13.0)	120 (86.7)		135 (97.8)	3 (2.2)	
95% CI		8.4%–19.7%	80.3%–91.6%		93.8%–99.3%	0.7%–6.2%	
AKT inhibitors, *N* (%)	144 (100)	18 (12.5)	126 (87.5)		128 (88.9)	16 (11.1)	
95% CI		8.1%–18.9%	81.1%–91.9%		82.7%–93.0%	7.0%–17.3%	
Multikinase inhibitors, *N* (%)	27 (100)	0 (0)	27 (100)		21 (77.8)	6 (22.6)	
95% CI		0%–12.5%	87.5%–100%		59.2%–89.4%	10.6%–40.8%	

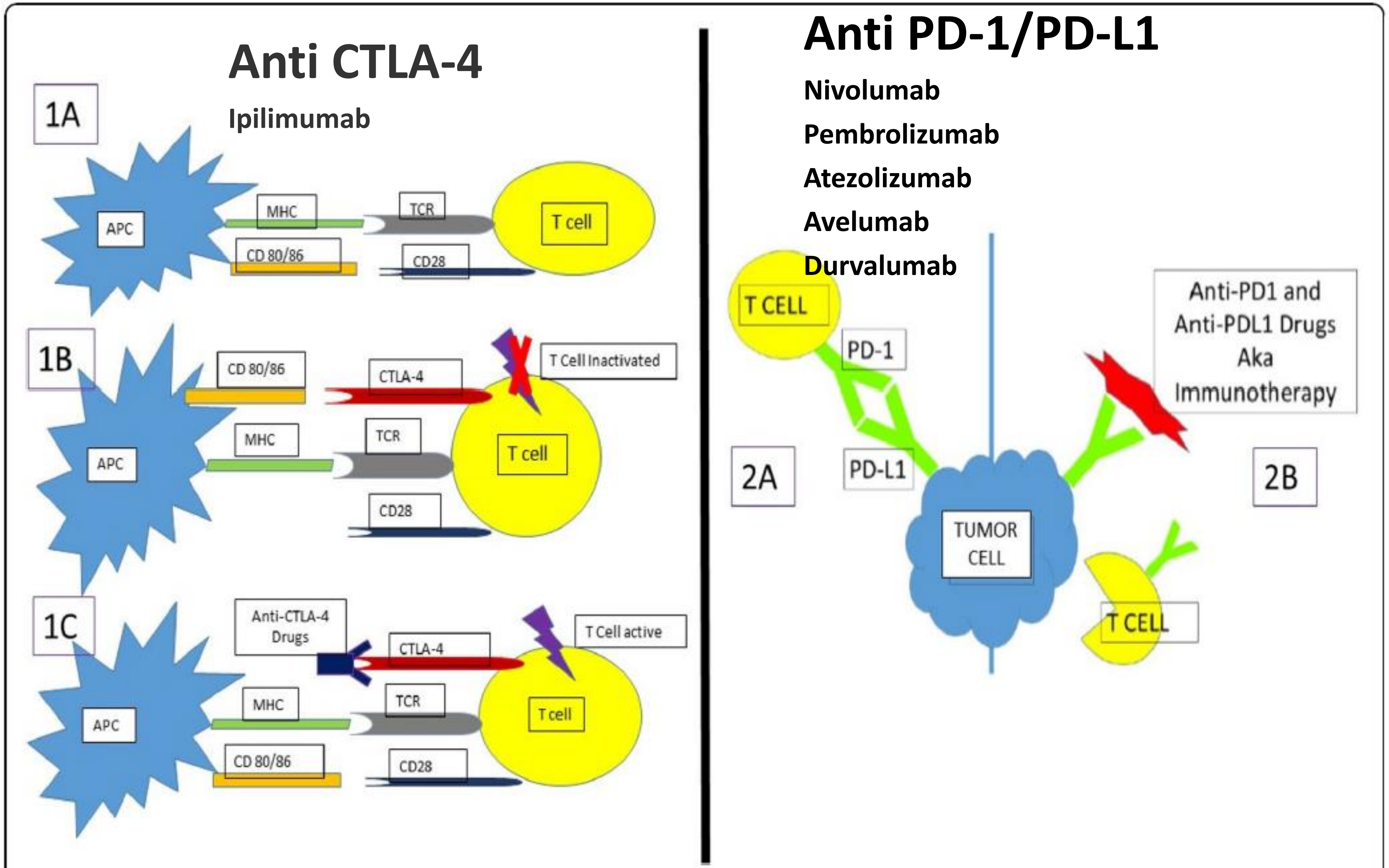
Abbreviation: CI = confidence interval.

[a] χ^2-test.

IMMUNOTHERAPY


askhematologist.com
Activated T Cell
T-cell receptor
MHC
Tumor Cell
Checkpoint Inhibitors

MECCANISMO D’AZIONE DEI CHECKPOINT INHIBITORS



Anti CTLA-4

Ipilimumab

Anti PD-1/PD-L1

Nivolumab

Pembrolizumab

Atezolizumab

Avelumab

Durvalumab

1A
APC
MHC
TCR
T cell
CD 80/86
CD28
1B
CD 80/86
CTLA-4
T Cell Inactivated
APC
MHC
TCR
T cell
CD28
1C
Anti-CTLA-4 Drugs
CTLA-4
T Cell active
APC
MHC
TCR
T cell
CD 80/86
CD28
T CELL
PD-1
PD-L1
2A
TUMOR CELL
Anti-PD1 and Anti-PDL1 Drugs Aka Immunotherapy
2B
T CELL

Fig. 4 Mechanisms of Action of Anti-PD(L)1 and CTLA-4 Drugs. **1a** Normal activation state of T cells after interaction with Antigen presenting cell (APC). TCR = T-Cell receptor. **1b** Inhibition of T cell activation due to CTLA-4 out-competing CD28 for interaction with CD 80/86. **1c** Anti-CTLA-4 drug inhibits CTLA-4 thus CD28 is able to interact with CD80/86 and activate T cell. **2a** PD-L1 on tumor cell prevents T cell activation. **2b** PD-L1 is blocked by anti-PD(L)1 drugs, T cell activation against tumor is possible

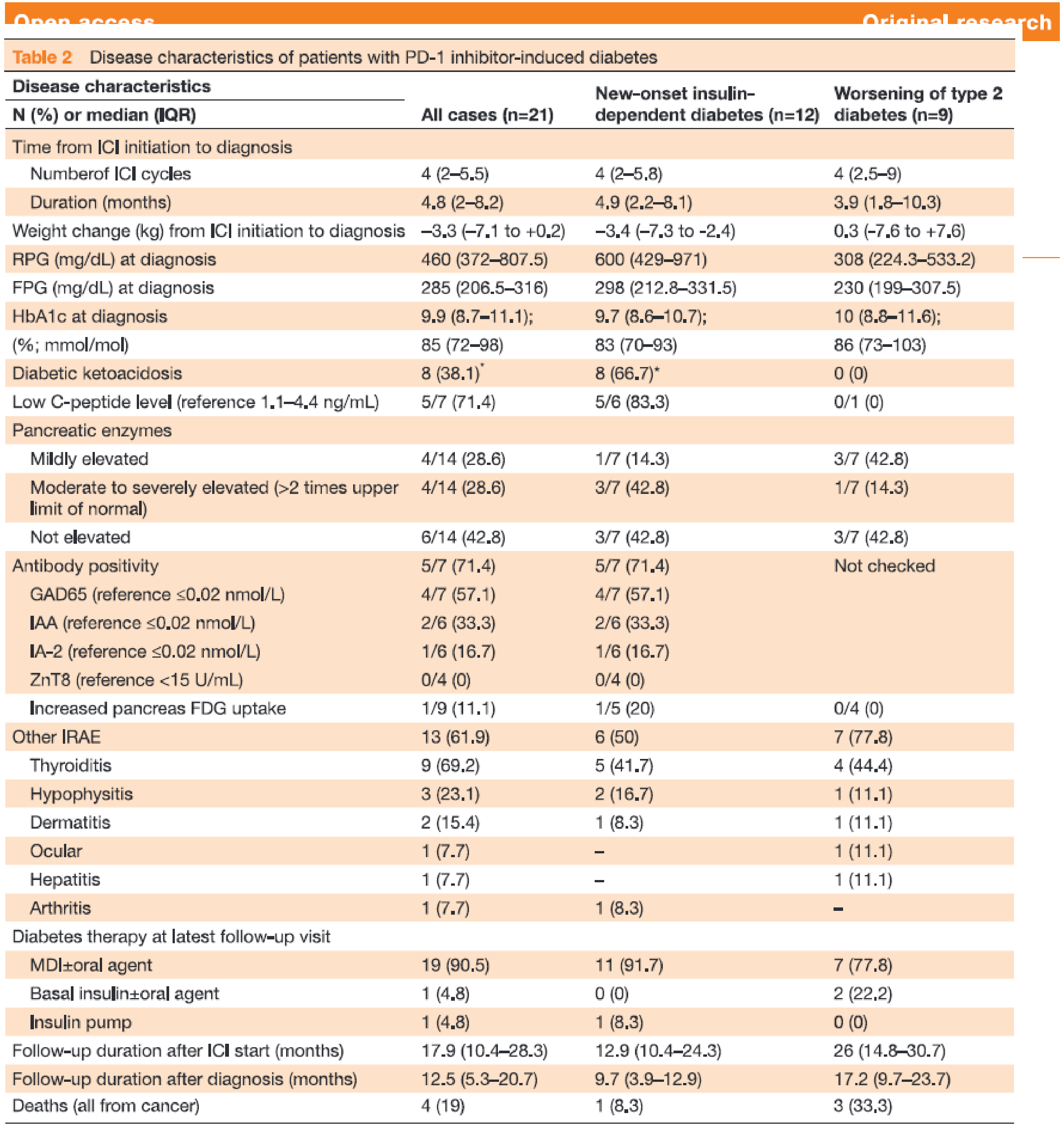


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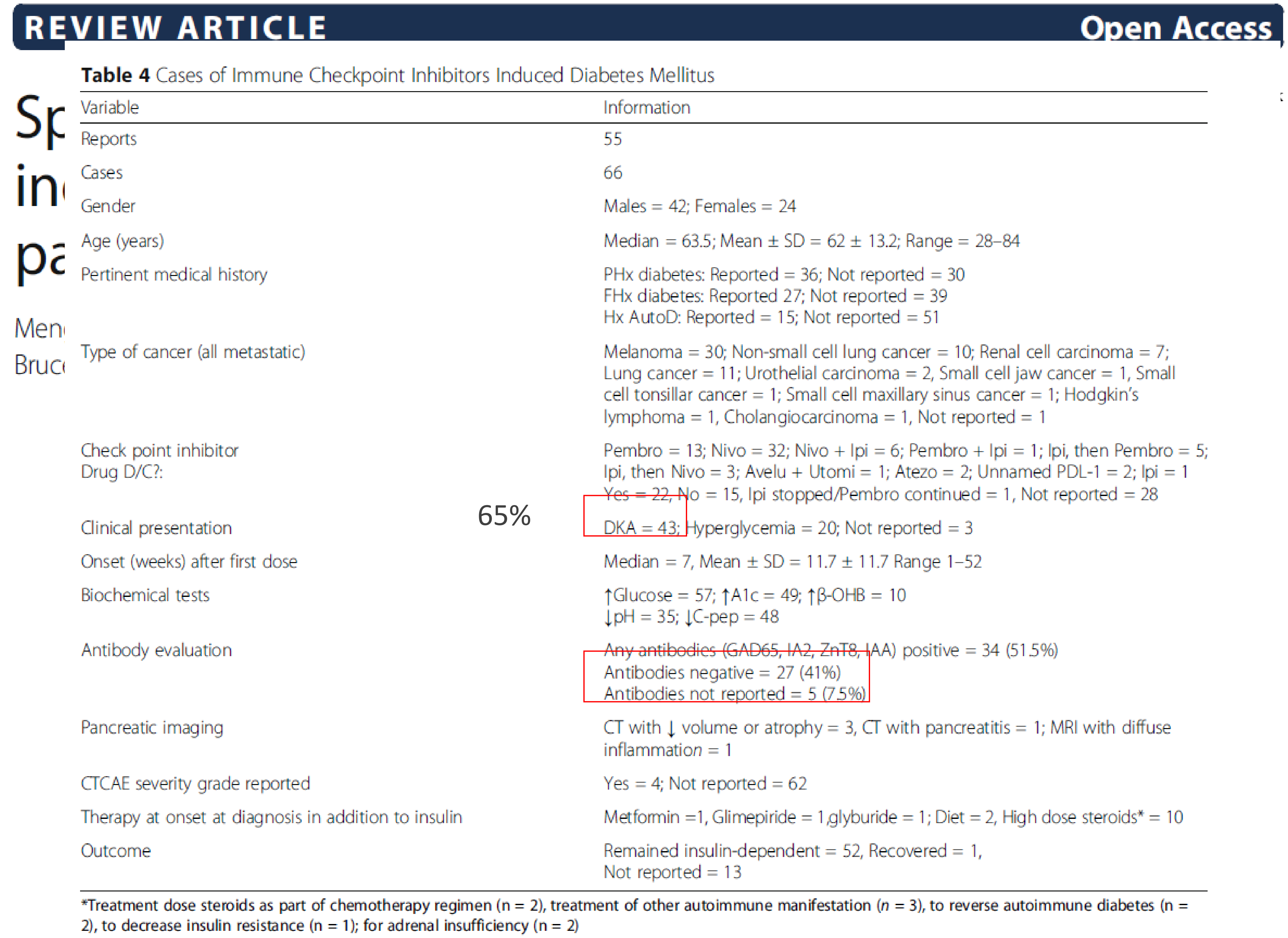
Table 2 Disease characteristics of patients with PD-1 inhibitor-induced diabetes

Disease characteristics N (%) or median (IQR)	All cases (n=21)	New-onset insulin-dependent diabetes (n=12)	Worsening of type 2 diabetes (n=9)
Time from ICI initiation to diagnosis			
Numberof ICI cycles	4 (2–5.5)	4 (2–5.8)	4 (2.5–9)
Duration (months)	4.8 (2–8.2)	4.9 (2.2–8.1)	3.9 (1.8–10.3)
Weight change (kg) from ICI initiation to diagnosis	−3.3 (−7.1 to +0.2)	−3.4 (−7.3 to -2.4)	0.3 (-7.6 to +7.6)
RPG (mg/dL) at diagnosis	460 (372–807.5)	600 (429–971)	308 (224.3–533.2)
FPG (mg/dL) at diagnosis	285 (206.5–316)	298 (212.8–331.5)	230 (199–307.5)
HbA1c at diagnosis	9.9 (8.7–11.1);	9.7 (8.6–10.7);	10 (8.8–11.6);
(%; mmol/mol)	85 (72–98)	83 (70–93)	86 (73–103)
Diabetic ketoacidosis	8 (38.1)*	8 (66.7)*	0 (0)
Low C-peptide level (reference 1.1–4.4 ng/mL)	5/7 (71.4)	5/6 (83.3)	0/1 (0)
Pancreatic enzymes			
Mildly elevated	4/14 (28.6)	1/7 (14.3)	3/7 (42.8)
Moderate to severely elevated (>2 times upper limit of normal)	4/14 (28.6)	3/7 (42.8)	1/7 (14.3)
Not elevated	6/14 (42.8)	3/7 (42.8)	3/7 (42.8)
Antibody positivity	5/7 (71.4)	5/7 (71.4)	Not checked
GAD65 (reference ≤0.02 nmol/L)	4/7 (57.1)	4/7 (57.1)	
IAA (reference ≤0.02 nmol/L)	2/6 (33.3)	2/6 (33.3)	
IA-2 (reference ≤0.02 nmol/L)	1/6 (16.7)	1/6 (16.7)	
ZnT8 (reference <15 U/mL)	0/4 (0)	0/4 (0)	
Increased pancreas FDG uptake	1/9 (11.1)	1/5 (20)	0/4 (0)
Other IRAE	13 (61.9)	6 (50)	7 (77.8)
Thyroiditis	9 (69.2)	5 (41.7)	4 (44.4)
Hypophysitis	3 (23.1)	2 (16.7)	1 (11.1)
Dermatitis	2 (15.4)	1 (8.3)	1 (11.1)
Ocular	1 (7.7)	–	1 (11.1)
Hepatitis	1 (7.7)	–	1 (11.1)
Arthritis	1 (7.7)	1 (8.3)	–
Diabetes therapy at latest follow-up visit			
MDI±oral agent	19 (90.5)	11 (91.7)	7 (77.8)
Basal insulin±oral agent	1 (4.8)	0 (0)	2 (22.2)
Insulin pump	1 (4.8)	1 (8.3)	0 (0)
Follow-up duration after ICI start (months)	17.9 (10.4–28.3)	12.9 (10.4–24.3)	26 (14.8–30.7)
Follow-up duration after diagnosis (months)	12.5 (5.3–20.7)	9.7 (3.9–12.9)	17.2 (9.7–23.7)
Deaths (all from cancer)	4 (19)	1 (8.3)	3 (33.3)

- 1.4% diabete di nuova diagnosi e/o peggioramento di diabete di tipo 2
- Nessun caso con anti CTLA4 in monoterapia
- Comparsa entro 4 mesi
- Chetoacidosi diabetica nel 38% dei casi

BMJ Open Diab Res Care 2019;7:



REVIEW ARTICLE **Open Access**

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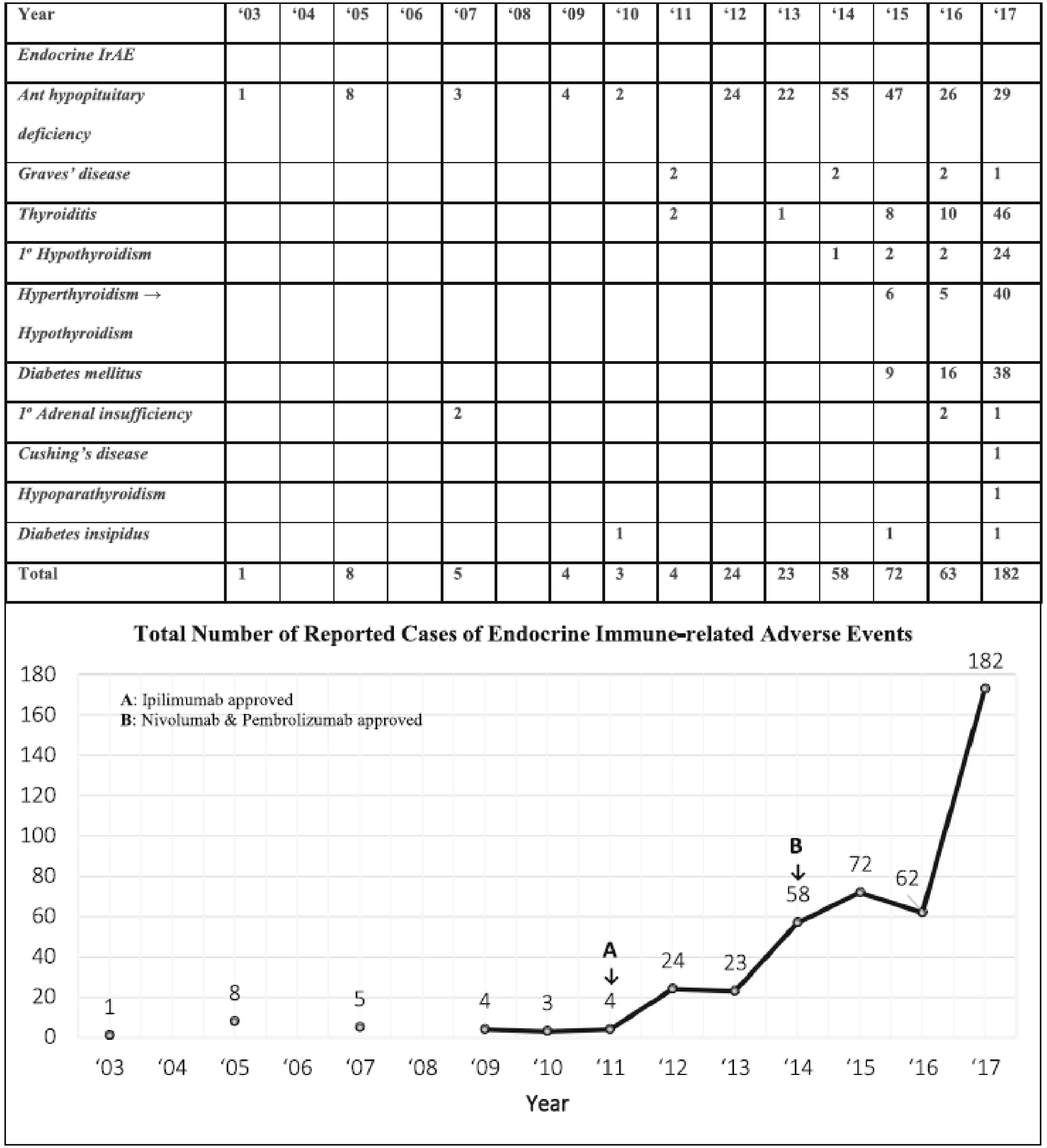
Table 4 Cases of Immune Checkpoint Inhibitors Induced Diabetes Mellitus

Variable	Information
Reports	55
Cases	66
Gender	Males = 42; Females = 24
Age (years)	Median = 63.5; Mean ± SD = 62 ± 13.2; Range = 28–84
Pertinent medical history	PHx diabetes: Reported = 36; Not reported = 30 FHx diabetes: Reported 27; Not reported = 39 Hx AutoD: Reported = 15; Not reported = 51
Type of cancer (all metastatic)	Melanoma = 30; Non-small cell lung cancer = 10; Renal cell carcinoma = 7; Lung cancer = 11; Urothelial carcinoma = 2, Small cell jaw cancer = 1, Small cell tonsillar cancer = 1; Small cell maxillary sinus cancer = 1; Hodgkin's lymphoma = 1, Cholangiocarcinoma = 1, Not reported = 1
Check point inhibitor	Pembro = 13; Nivo = 32; Nivo + Ipi = 6; Pembro + Ipi = 1; Ipi, then Pembro = 5; Ipi, then Nivo = 3; Avelu + Utomi = 1; Atezo = 2; Unnamed PDL-1 = 2; Ipi = 1
Drug D/C?:	Yes = 22, No = 15, Ipi stopped/Pembro continued = 1, Not reported = 28
Clinical presentation	DKA = 43; Hyperglycemia = 20; Not reported = 3
Onset (weeks) after first dose	Median = 7, Mean ± SD = 11.7 ± 11.7 Range 1–52
Biochemical tests	↑Glucose = 57; ↑A1c = 49; ↑β-OHB = 10 ↓pH = 35; ↓C-pep = 48
Antibody evaluation	Any antibodies (GAD65, IA2, ZnT8, IAA) positive = 34 (51.5%) Antibodies negative = 27 (41%) Antibodies not reported = 5 (7.5%)
Pancreatic imaging	CT with ↓ volume or atrophy = 3, CT with pancreatitis = 1; MRI with diffuse inflammation = 1
CTCAE severity grade reported	Yes = 4; Not reported = 62
Therapy at onset at diagnosis in addition to insulin	Metformin =1, Glimepiride = 1,glyburide = 1; Diet = 2, High dose steroids* = 10
Outcome	Remained insulin-dependent = 52, Recovered = 1, Not reported = 13

*Treatment dose steroids as part of chemotherapy regimen (n = 2), treatment of other autoimmune manifestation (*n* = 3), to reverse autoimmune diabetes (n = 2), to decrease insulin resistance (n = 1); for adrenal insufficiency (n = 2)

65%

Tan *et al. Clinical Diabetes and Endocrinology* (2019) 5:1



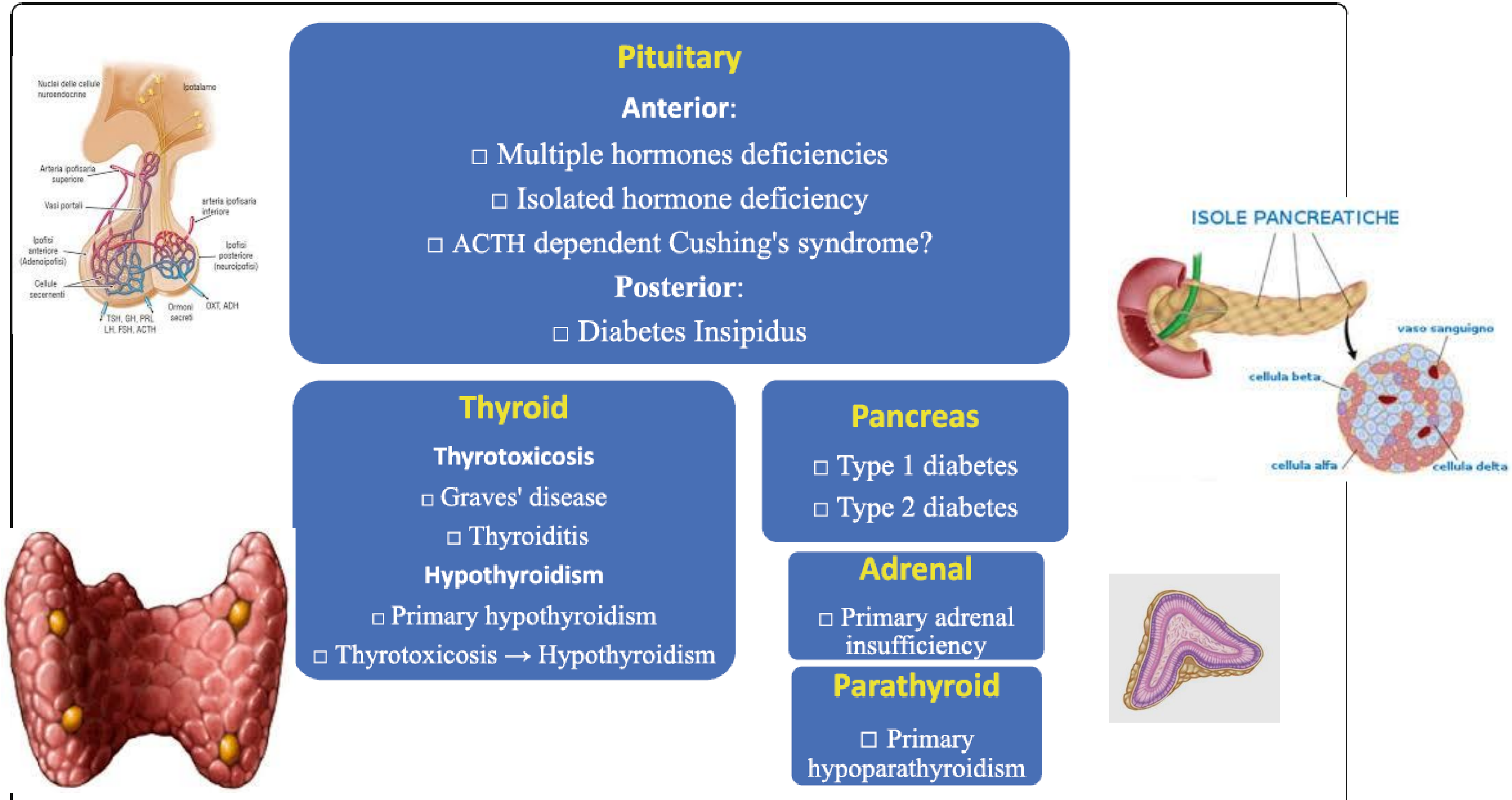
Year	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12	'13	'14	'15	'16	'17
Endocrine IrAE															
Ant hypopituitary deficiency	1		8		3		4	2		24	22	55	47	26	29
Graves' disease									2			2		2	1
Thyroiditis									2		1		8	10	46
1° Hypothyroidism												1	2	2	24
Hyperthyroidism → Hypothyroidism													6	5	40
Diabetes mellitus													9	16	38
1° Adrenal insufficiency					2									2	1
Cushing's disease															1
Hypoparathyroidism															1
Diabetes insipidus								1					1		1
Total	1		8		5		4	3	4	24	23	58	72	63	182

Total Number of Reported Cases of Endocrine Immune-related Adverse Events
A: Ipilimumab approved
B: Nivolumab & Pembrolizumab approved
180
160
140
120
100
80
60
40
20
0
1
8
5
4
3
A
4
24
23
B
58
72
62
182
'03
'04
'05
'06
'07
'08
'09
'10
'11
'12
'13
'14
'15
'16
'17
Year

Fig. 2 Reported cases of immune checkpoint inhibitor-induced endocrinopathies

Tan et al. Clinical Diabetes and Endocrinology (2019) 5:1

RISPOSTA AUTOIMMUNITARIA CELLULO MEDIATA



Pituitary

Anterior:

- ☐ Multiple hormones deficiencies
- ☐ Isolated hormone deficiency
- ☐ ACTH dependent Cushing's syndrome?

Posterior:

- ☐ Diabetes Insipidus

Thyroid

Thyrotoxicosis

- ☐ Graves' disease
- ☐ Thyroiditis

Hypothyroidism

- ☐ Primary hypothyroidism
- ☐ Thyrotoxicosis → Hypothyroidism

Pancreas

- ☐ Type 1 diabetes
- ☐ Type 2 diabetes

Adrenal

- ☐ Primary adrenal insufficiency

Parathyroid

- ☐ Primary hypoparathyroidism

Nuclei delle cellule nuroendocrine
Ipotalamo
Arteria ipofisaria superiore
Vasi portali
arteria ipofisaria inferiore
Ipofisi anteriore (Adenoipofisi)
Ipofisi posteriore (neuroipofisi)
Cellule secernenti
TSH, GH, PRL LH, FSH, ACTH
Ormoni secreti
OXT, ADH
ISOLE PANCREATICHE
vaso sanguigno
cellula beta
cellula alfa
cellula delta

Fig. 3 Spectrum of immune checkpoint inhibitor-induced endocrinopathies

Immune related endocrinopathies: tireopatia fino al 30 % di pazienti in trattamento con terapia combinata ipilimumab e nivolumab ; iofisite nel 20% dei casi in trattamento con ipilimimab

Tan *et al. Clinical Diabetes and Endocrinology* (2019) 5:1

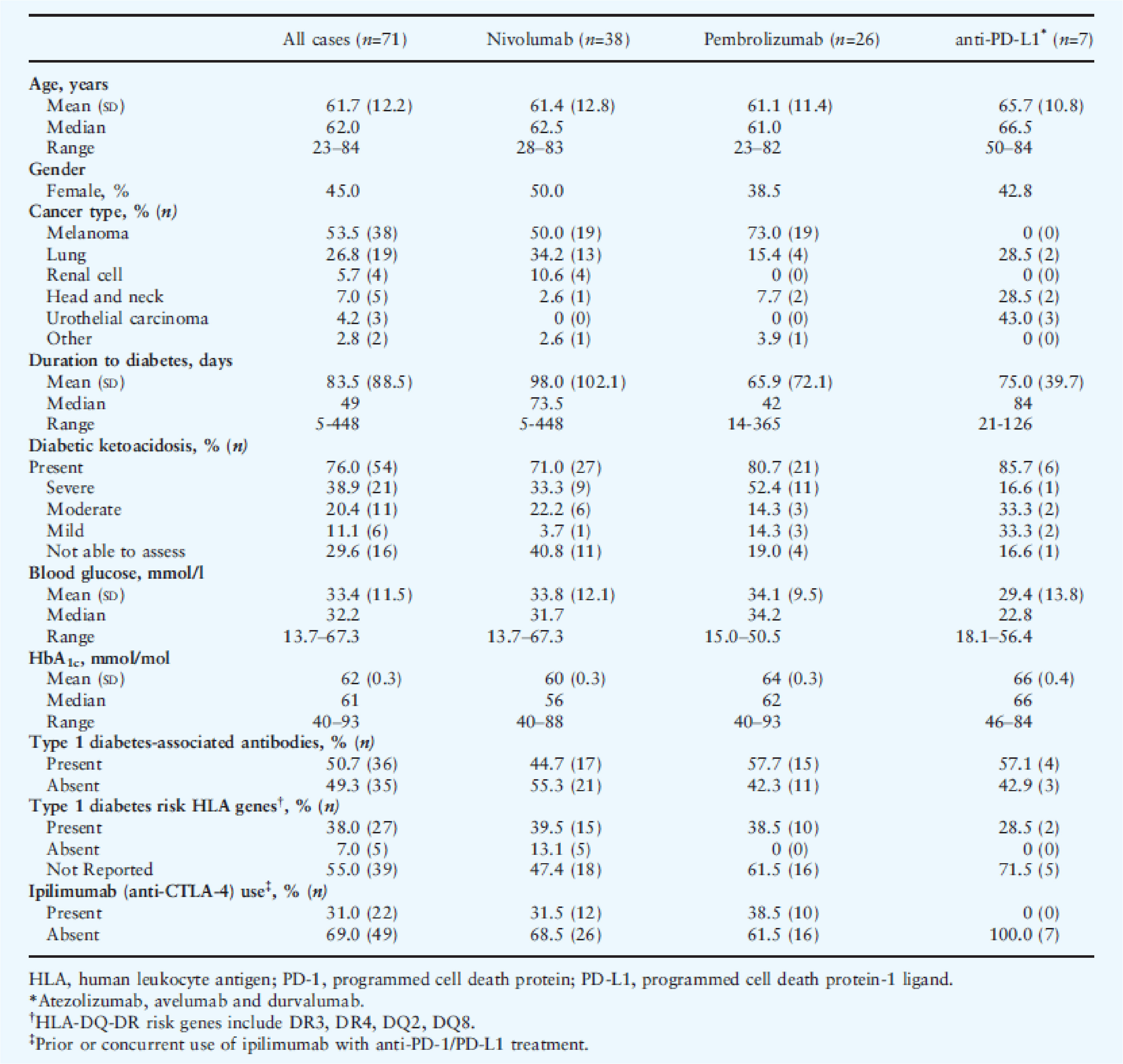
Systematic Review

Immune checkpoin
a systematic revie

H. K. Akturk[1], D. Kahramar
A. W. Michels[1]

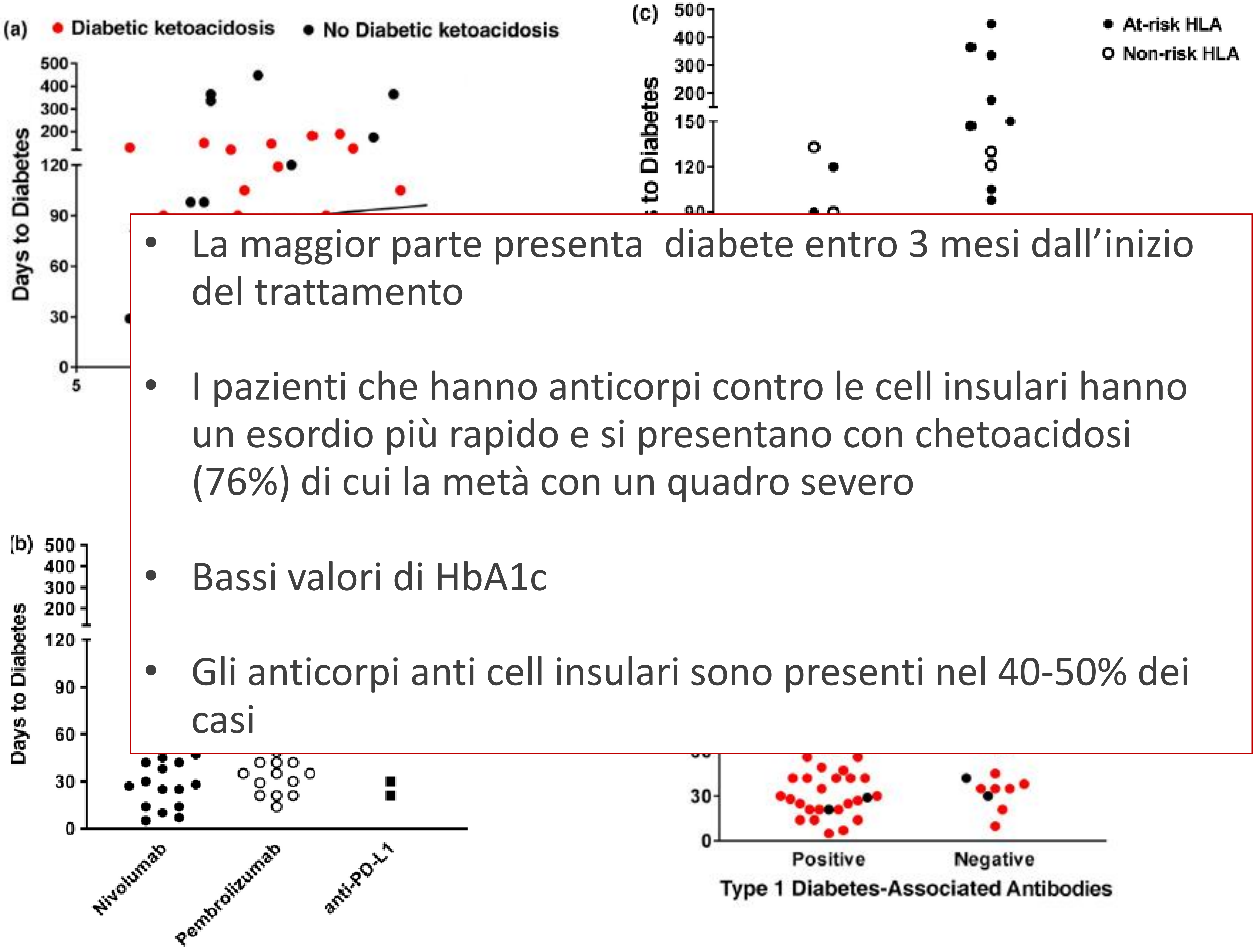
Accepted 11 June 2019

Table 1 Clinical, metabolic and immunological characteristics of anti-programmed cell death protein-1 or anti-programmed cell death protein-1 ligand inhibitor-induced Type 1 diabetes



	All cases (*n*=71)	Nivolumab (*n*=38)	Pembrolizumab (*n*=26)	anti-PD-L1* (*n*=7)
Age, years				
Mean (SD)	61.7 (12.2)	61.4 (12.8)	61.1 (11.4)	65.7 (10.8)
Median	62.0	62.5	61.0	66.5
Range	23–84	28–83	23–82	50–84
Gender				
Female, %	45.0	50.0	38.5	42.8
Cancer type, % (*n*)				
Melanoma	53.5 (38)	50.0 (19)	73.0 (19)	0 (0)
Lung	26.8 (19)	34.2 (13)	15.4 (4)	28.5 (2)
Renal cell	5.7 (4)	10.6 (4)	0 (0)	0 (0)
Head and neck	7.0 (5)	2.6 (1)	7.7 (2)	28.5 (2)
Urothelial carcinoma	4.2 (3)	0 (0)	0 (0)	43.0 (3)
Other	2.8 (2)	2.6 (1)	3.9 (1)	0 (0)
Duration to diabetes, days				
Mean (SD)	83.5 (88.5)	98.0 (102.1)	65.9 (72.1)	75.0 (39.7)
Median	49	73.5	42	84
Range	5-448	5-448	14-365	21-126
Diabetic ketoacidosis, % (*n*)				
Present	76.0 (54)	71.0 (27)	80.7 (21)	85.7 (6)
Severe	38.9 (21)	33.3 (9)	52.4 (11)	16.6 (1)
Moderate	20.4 (11)	22.2 (6)	14.3 (3)	33.3 (2)
Mild	11.1 (6)	3.7 (1)	14.3 (3)	33.3 (2)
Not able to assess	29.6 (16)	40.8 (11)	19.0 (4)	16.6 (1)
Blood glucose, mmol/l				
Mean (SD)	33.4 (11.5)	33.8 (12.1)	34.1 (9.5)	29.4 (13.8)
Median	32.2	31.7	34.2	22.8
Range	13.7–67.3	13.7–67.3	15.0–50.5	18.1–56.4
HbA_{1c}, mmol/mol				
Mean (SD)	62 (0.3)	60 (0.3)	64 (0.3)	66 (0.4)
Median	61	56	62	66
Range	40–93	40–88	40–93	46–84
Type 1 diabetes-associated antibodies, % (*n*)				
Present	50.7 (36)	44.7 (17)	57.7 (15)	57.1 (4)
Absent	49.3 (35)	55.3 (21)	42.3 (11)	42.9 (3)
Type 1 diabetes risk HLA genes†, % (*n*)				
Present	38.0 (27)	39.5 (15)	38.5 (10)	28.5 (2)
Absent	7.0 (5)	13.1 (5)	0 (0)	0 (0)
Not Reported	55.0 (39)	47.4 (18)	61.5 (16)	71.5 (5)
Ipilimumab (anti-CTLA-4) use‡, % (*n*)				
Present	31.0 (22)	31.5 (12)	38.5 (10)	0 (0)
Absent	69.0 (49)	68.5 (26)	61.5 (16)	100.0 (7)

HLA, human leukocyte antigen; PD-1, programmed cell death protein; PD-L1, programmed cell death protein-1 ligand.
*Atezolizumab, avelumab and durvalumab.
†HLA-DQ-DR risk genes include DR3, DR4, DQ2, DQ8.
‡Prior or concurrent use of ipilimumab with anti-PD-1/PD-L1 treatment.



- La maggior parte presenta diabete entro 3 mesi dall’inizio del trattamento

- I pazienti che hanno anticorpi contro le cell insulari hanno un esordio più rapido e si presentano con chetoacidosi (76%) di cui la metà con un quadro severo

- Bassi valori di HbA1c

- Gli anticorpi anti cell insulari sono presenti nel 40-50% dei casi

CASO CLINICO

- Sabina, 40 anni, trattata con ipilimumab e nivolumab per melanoma metastatico (aprile 2018)
- Dopo la terza somministrazione viene inviata per iperglicemia (450 mg/dl)
- Riscontro di chetoacidosi diabetica (PH 7,25, HCO3- -9)
- Concomita tireotossicosi (TSH < 0,05, FT4 24, FT3 5) ed epatite acuta per cui viene interrotto il trattamento
- Agli esami **anticorpiantiGAD >1000**, anticorpianti TPO, anti recTSH e antiTg negativi
- HbA1c 64 mmol/mol
- **C-peptide 0.32** (VN> 0,25)
- Terapia insulinica basal bolus e terapia corticosteroidea e immunosoppressiva

E' nato prima
l'uovo
o
la gallina?

The Journal of Clinical Endocrinology & Metabolism

Checkpoint inhibitor associated autoimmune diabetes (CIADM) is distinct from type 1 diabetes

July 02, 2019

Venessa H. M. Tsang, Rachel T. McGrath, Roderick J. Clifton-Bligh, Richard A. Scolyer, Valerie Jakrot, Alexander D. Guminski, Georgina V. Long, Alexander M. Menzies

- 538 pz in terapia con antiPD1 per melanoma

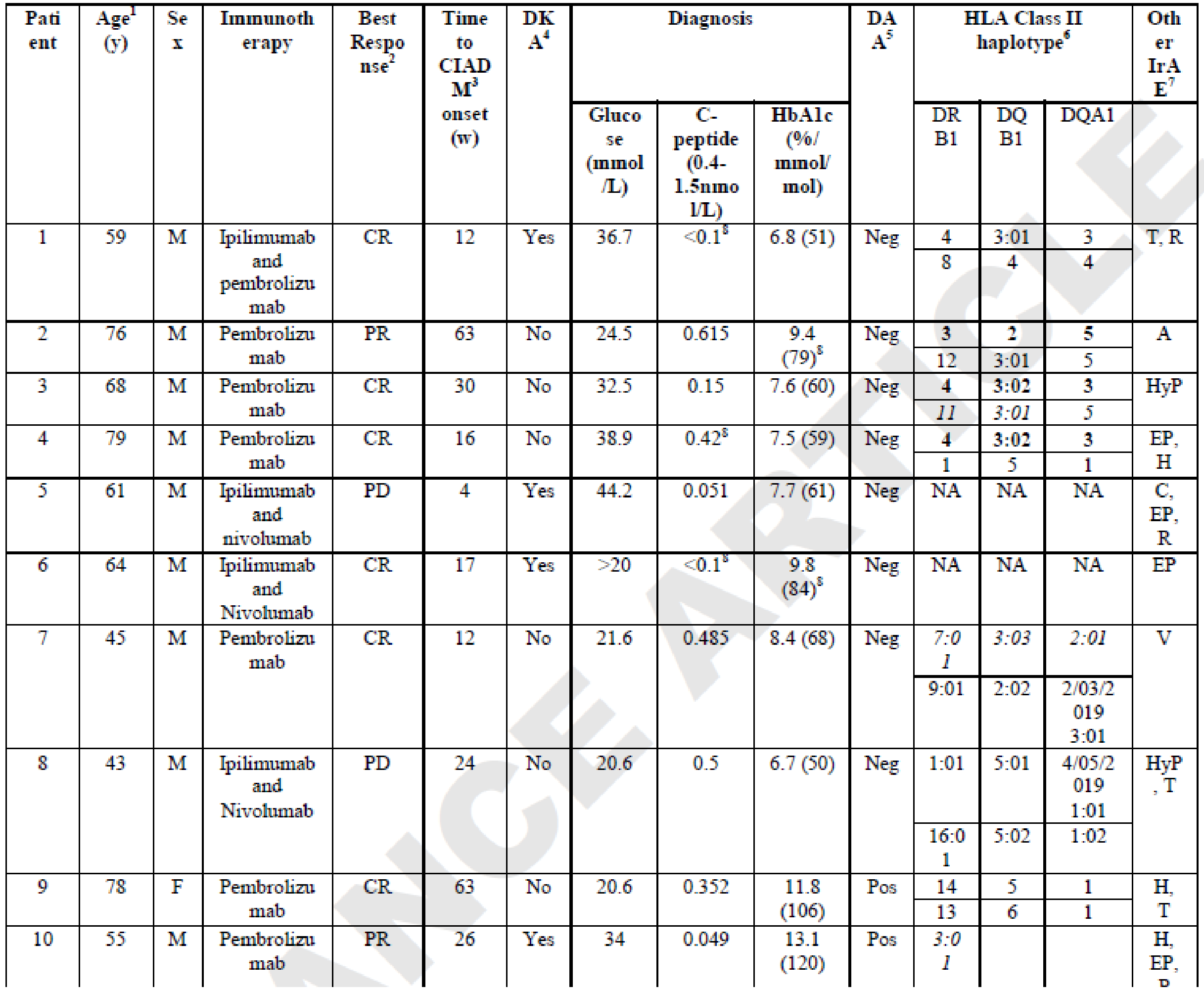
- 10 PZ→ 1,9%

- Media Hba1c 7,6%
- Media C-peptide 0,35 (v.n. > 0,4)

- AnticorpiantiGAD in 2 pz (0 pz con anticorpi antiinsulina, IA2 e ZnT8)

- 3 pz aplotipo HLA a rischio di D1 e 2 aplotipo protettivo per D1

Table 1. Patient characteristics, CIADM features and associated toxicity.



Patient	Age[1] (y)	Sex	Immunotherapy	Best Response[2]	Time to CIADM[3] onset (w)	DKA[4]	Diagnosis			DAA[5]	HLA Class II haplotype[6]			Other IrAE[7]
							Glucose (mmol/L)	C-peptide (0.4-1.5nmol/L)	HbA1c (%/ mmol/ mol)		DRB1	DQB1	DQA1	
1	59	M	Ipilimumab and pembrolizumab	CR	12	Yes	36.7	<0.1[8]	6.8 (51)	Neg	4 8	3:01 4	3 4	T, R
2	76	M	Pembrolizumab	PR	63	No	24.5	0.615	9.4 (79)[8]	Neg	**3** 12	**2** 3:01	**5** 5	A
3	68	M	Pembrolizumab	CR	30	No	32.5	0.15	7.6 (60)	Neg	**4** *11*	**3:02** *3:01*	**3** *5*	HyP
4	79	M	Pembrolizumab	CR	16	No	38.9	0.42[8]	7.5 (59)	Neg	**4** 1	**3:02** 5	**3** 1	EP, H
5	61	M	Ipilimumab and nivolumab	PD	4	Yes	44.2	0.051	7.7 (61)	Neg	NA	NA	NA	C, EP, R
6	64	M	Ipilimumab and Nivolumab	CR	17	Yes	>20	<0.1[8]	9.8 (84)[8]	Neg	NA	NA	NA	EP
7	45	M	Pembrolizumab	CR	12	No	21.6	0.485	8.4 (68)	Neg	*7:01* 9:01	*3:03* 2:02	*2:01* 2/03/2019 3:01	V
8	43	M	Ipilimumab and Nivolumab	PD	24	No	20.6	0.5	6.7 (50)	Neg	1:01 16:01	5:01 5:02	4/05/2019 1:01 1:02	HyP, T
9	78	F	Pembrolizumab	CR	63	No	20.6	0.352	11.8 (106)	Pos	14 13	5 6	1 1	H, T
10	55	M	Pembrolizumab	PR	26	Yes	34	0.049	13.1 (120)	Pos	*3:01*			H, EP,

CASE REP

Anti-pr
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Ashray Gunjur[1*]

Table 1 Summary of Case Reports of anti-PD1/PD-L1 induced APS-2 (at least two components)

Author (year published)	Therapy	Age (years)	Country	Disease	Timing[a] (weeks)	Conditions	auto-Ab found	HLA type	Response
Hakami [7] (2019)	pembrolizumab	52	Ireland	melanoma	21	hypothyroidism T1DM		NR	NR
Lanzolla [8] (2019)	atezolizumab	60	Italy	NSCLC	6	T1DM hypoadrenalism	anti-21-OH	DRB1*04 DQB1*03	PD
Sakurai [9] (2018)	nivolumab	68	Japan	RCC	14	hypothyroidism[b] T1DM	anti-TPO Anti-Tg	DRB1*09:01 DQB1*03:03	NR
Gauci [10] (2017)	nivolumab	73	France	melanoma	6	hyperthyroidism[b] T1DM	anti-GAD anti-IA2 anti-ZnT8	NR	PR
Paepegaey [11] (2017)	pembrolizumab	55	France	melanoma	12	hypothyroidism hypoadrenalism	anti-21-OH	NR	NR
Li [12] (2017)	nivolumab	63	USA	NSCLC	4	T1DM hypothyroidism	anti-GAD anti-TPO	NR	PD
Alhusseini [13] (2017)	pembrolizumab + ipilimumab	65	USA	NSCLC	3	T1DM hyperthyroidism	anti-GAD anti-IA anti-insulin anti-TPO	NR	PR
Lowe [14] (2016)	nivolumab + ipilimumab	54	USA	melanoma	2	hyperthyroidism T1DM	anti-GAD	DQB1*0602	CR
Kong [15] (2016)	pembrolizumab	68	Korea	NSCLC	21	T1DM hyperthyroidism	Nil	DRB1*09:01 DQB1*03:03	PR
Hansen [16] (2016)	pembrolizumab	58	USA	melanoma	NR	hypothyroidism T1DM	anti-GAD	NR	PR
Mellati [17] (2015)	NR	66		SCC jaw	7	T1DM hypothyroidism	anti-TPO anti-GAD	DR3-DQ2 DR4-DQ8	NR
Hughes [18] (2015)	nivolumab + ipilimumab	55	USA	melanoma	20	hypothyroidism[b] T1DM		A2.1 DR4	NR
Hughes (2015)	pembrolizumab	64	USA	melanoma	< 4	hypothyroidism[b] T1DM		DR4	NR

Abbreviations: auto-Ab auto-antibody, *HLA* Human leukocyte antigen, *T1DM* Type 1 diabetes mellitus, *NR* Not reported, *PD* Progressive disease, *21-OH* 21-hydroxylase, *anti-TPO* Anti-thyroid peroxidase, *anti-Tg* anti-thyroglobulin, *anti-GAD* anti-glutamic acid decarboxylase, *anti-IA2* anti-islet antibody 2, *anti-ZnT8* anti-zinc transporter 8, *PR* partial response, *CR* complete response

[a] timing denotes weeks after start of anti-PD1 therapy to onset of APS-2

[b] auto-immune condition preceded treatment with anti-PD1 axis therapy

A case of pembrolizumab-induced severe DKA and hypothyroidism in a patient with metastatic melanoma

Diabetes & Metabolism
CASE REPORTS

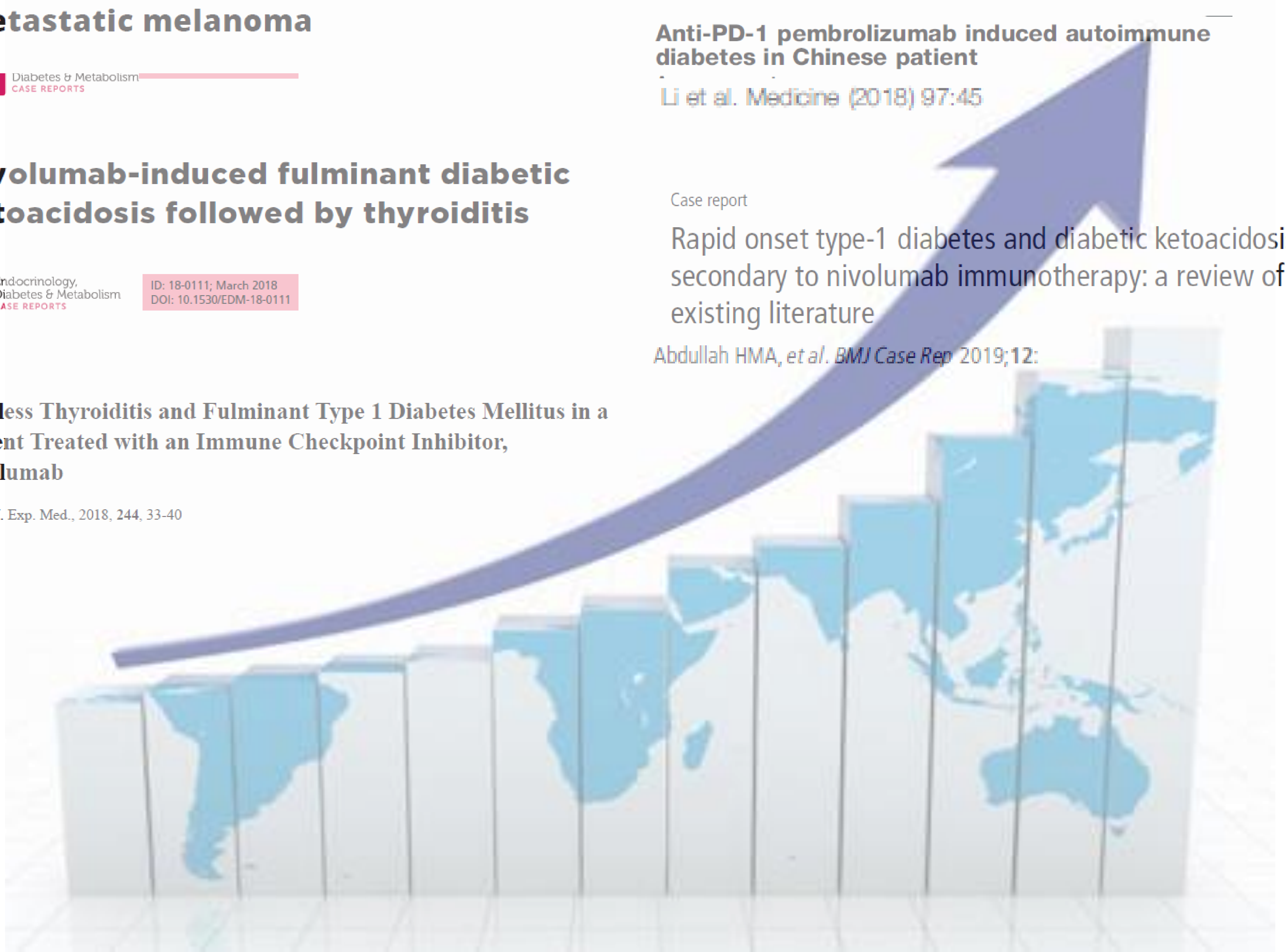
Nivolumab-induced fulminant diabetic ketoacidosis followed by thyroiditis

Endocrinology,
Diabetes & Metabolism
CASE REPORTS

ID: 18-0111; March 2018
DOI: 10.1530/EDM-18-0111

Painless Thyroiditis and Fulminant Type 1 Diabetes Mellitus in a Patient Treated with an Immune Checkpoint Inhibitor, Nivolumab

Tohoku J. Exp. Med., 2018, **244**, 33-40



Anti-PD-1 pembrolizumab induced autoimmune diabetes in Chinese patient

Li et al. Medicine (2018) 97:45

Case report

Rapid onset type-1 diabetes and diabetic ketoacidosis secondary to nivolumab immunotherapy: a review of existing literature

Abdullah HMA, *et al*. *BMJ Case Rep* 2019;**12**:

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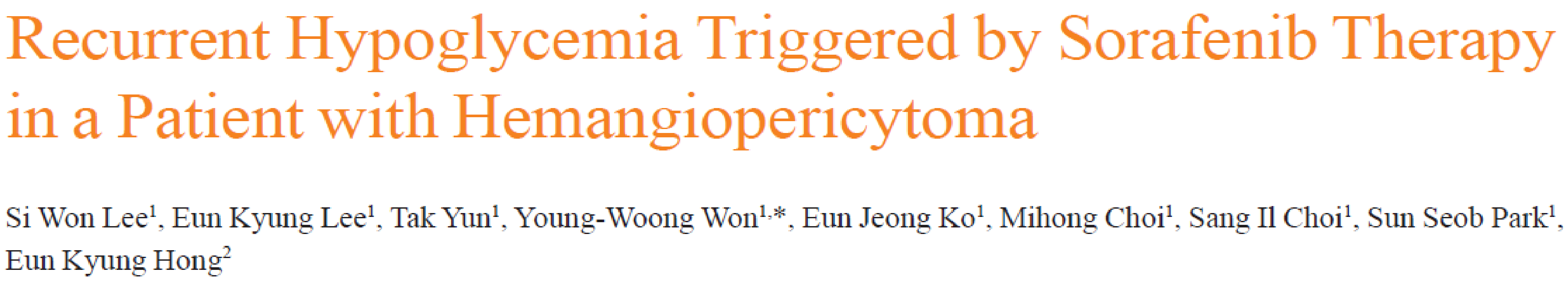
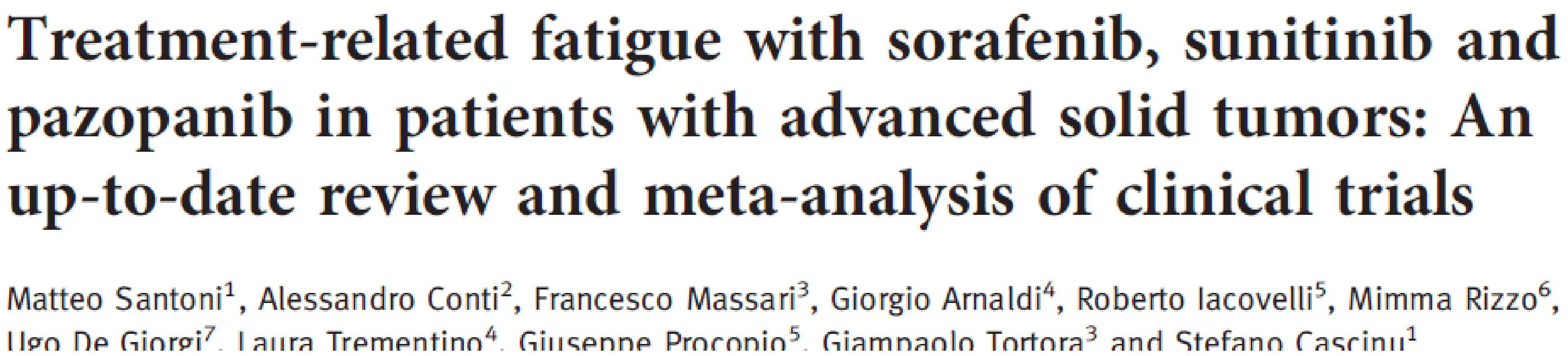


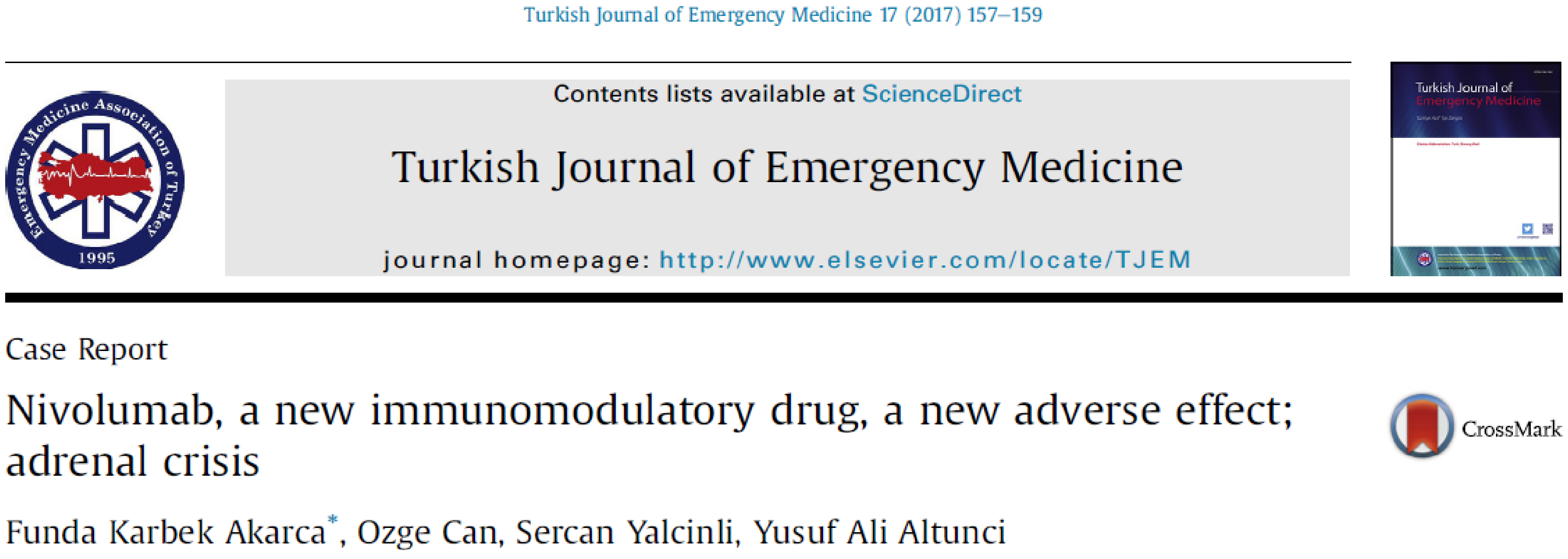
Recurrent Hypoglycemia Triggered by Sorafenib Therapy in a Patient with Hemangiopericytoma

Si Won Lee[1], Eun Kyung Lee[1], Tak Yun[1], Young-Woong Won[1,*], Eun Jeong Ko[1], Mihong Choi[1], Sang Il Choi[1], Sun Seob Park[1], Eun Kyung Hong[2]



Treatment-related fatigue with sorafenib, sunitinib and pazopanib in patients with advanced solid tumors: An up-to-date review and meta-analysis of clinical trials

Matteo Santoni[1], Alessandro Conti[2], Francesco Massari[3], Giorgio Arnaldi[4], Roberto Iacovelli[5], Mimma Rizzo[6], Ugo De Giorgi[7], Laura Trementino[4], Giuseppe Procopio[5], Giampaolo Tortora[3] and Stefano Cascinu[1]



Turkish Journal of Emergency Medicine 17 (2017) 157–159

Contents lists available at ScienceDirect

Turkish Journal of Emergency Medicine

journal homepage: http://www.elsevier.com/locate/TJEM

Case Report

Nivolumab, a new immunomodulatory drug, a new adverse effect; adrenal crisis

Funda Karbek Akarca*, Ozge Can, Sercan Yalcinli, Yusuf Ali Altunci

FARMACI ANTITUMORALI ED IPOGLICEMIA

- Eventi avversi endocrini (iposurrenalismo)
- Gli inibitori delle tirosin chinasi mostrano diversi effetti sul compenso glicemico
- In uno studio retrospettivo 47% dei pazienti trattati con VEGFR TKI (dasatinib, sorafenib, sunatenib imatinib) hanno sospeso la terapia ipoglicemizzante
- Stretto monitoraggio glicemico nei pazienti in trattamento con tirosin chinasi per alto rischio di ipoglicemia
- Meccanismo patogenetico non ben chiaro

ENDOCRINE SIDE EFFECTS OF ANTI-CANCER DRUGS

Effects of anti-cancer targeted therapies on lipid and glucose metabolism

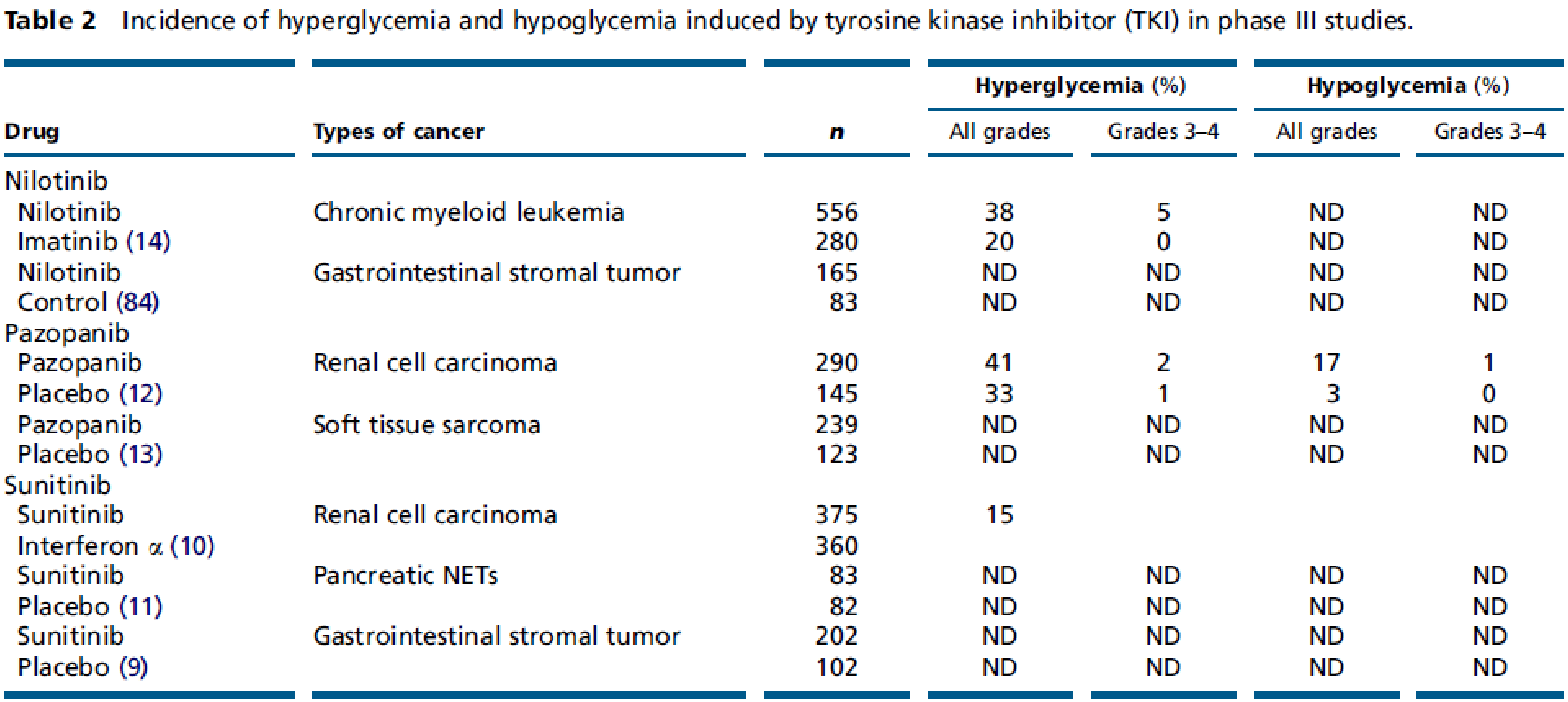
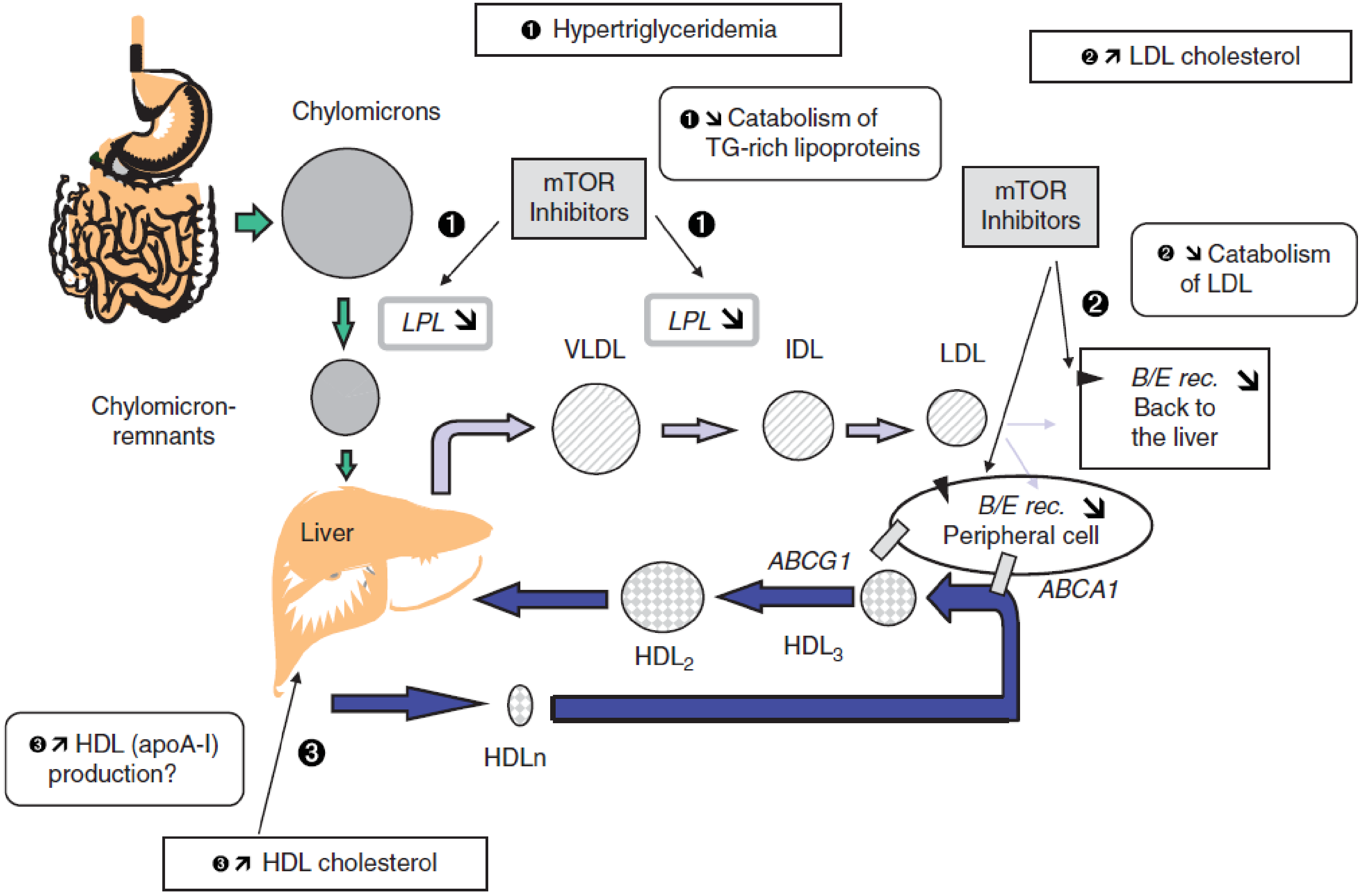


Table 2 Incidence of hyperglycemia and hypoglycemia induced by tyrosine kinase inhibitor (TKI) in phase III studies.

			Hyperglycemia (%)		**Hypoglycemia** (%)	
Drug	**Types of cancer**	***n***	All grades	Grades 3–4	All grades	Grades 3–4
Nilotinib						
Nilotinib	Chronic myeloid leukemia	556	38	5	ND	ND
Imatinib (14)		280	20	0	ND	ND
Nilotinib	Gastrointestinal stromal tumor	165	ND	ND	ND	ND
Control (84)		83	ND	ND	ND	ND
Pazopanib						
Pazopanib	Renal cell carcinoma	290	41	2	17	1
Placebo (12)		145	33	1	3	0
Pazopanib	Soft tissue sarcoma	239	ND	ND	ND	ND
Placebo (13)		123	ND	ND	ND	ND
Sunitinib						
Sunitinib	Renal cell carcinoma	375	15			
Interferon α (10)		360				
Sunitinib	Pancreatic NETs	83	ND	ND	ND	ND
Placebo (11)		82	ND	ND	ND	ND
Sunitinib	Gastrointestinal stromal tumor	202	ND	ND	ND	ND
Placebo (9)		102	ND	ND	ND	ND

B. Verges, Eur J End, 2014, 170.

mTOR inhibitors e dislipidemia


❶ Hypertriglyceridemia
❷ ↗ LDL cholesterol
Chylomicrons
❶ ↘ Catabolism of TG-rich lipoproteins
mTOR Inhibitors
mTOR Inhibitors
❶
❶
❷
❷ ↘ Catabolism of LDL
LPL ↘
LPL ↘
VLDL
IDL
LDL
B/E rec. ↘ Back to the liver
Chylomicron-remnants
B/E rec. ↘ Peripheral cell
Liver
ABCG1
ABCA1
HDL$_2$
HDL$_3$
HDLn
❸ ↗ HDL (apoA-I) production?
❸
❸ ↗ HDL cholesterol

↓ catabolismo delle VLDL e LDL (ridotti LDL rec)

↓ attività della lipoprotein lipasi

↓ Inibizione della lipasi ormone sensibile da parte dell'insulina

↑ Espressione di PCSK9

↑ APO A-I e HDL

B. Verges, Eur J End, 2014, 170.

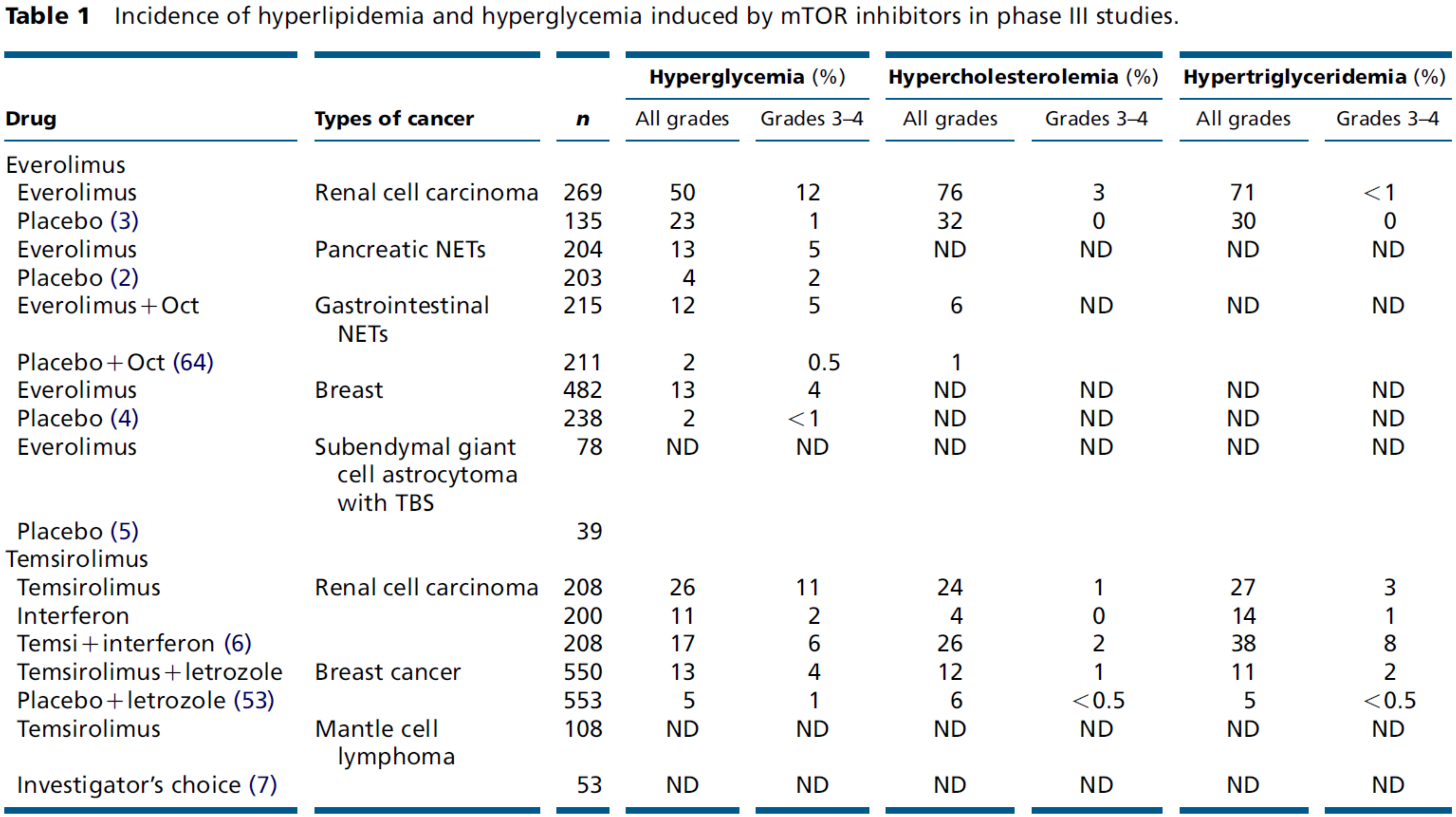


Table 1 Incidence of hyperlipidemia and hyperglycemia induced by mTOR inhibitors in phase III studies.

Drug	**Types of cancer**	***n***	**Hyperglycemia** (%)		**Hypercholesterolemia** (%)		**Hypertriglyceridemia** (%)	
			All grades	Grades 3–4	All grades	Grades 3–4	All grades	Grades 3–4
Everolimus								
Everolimus	Renal cell carcinoma	269	50	12	76	3	71	<1
Placebo (3)		135	23	1	32	0	30	0
Everolimus	Pancreatic NETs	204	13	5	ND	ND	ND	ND
Placebo (2)		203	4	2				
Everolimus + Oct	Gastrointestinal NETs	215	12	5	6	ND	ND	ND
Placebo + Oct (64)		211	2	0.5	1			
Everolimus	Breast	482	13	4	ND	ND	ND	ND
Placebo (4)		238	2	<1	ND	ND	ND	ND
Everolimus	Subendymal giant cell astrocytoma with TBS	78	ND	ND	ND	ND	ND	ND
Placebo (5)		39						
Temsirolimus								
Temsirolimus	Renal cell carcinoma	208	26	11	24	1	27	3
Interferon		200	11	2	4	0	14	1
Temsi + interferon (6)		208	17	6	26	2	38	8
Temsirolimus + letrozole	Breast cancer	550	13	4	12	1	11	2
Placebo + letrozole (53)		553	5	1	6	<0.5	5	<0.5
Temsirolimus	Mantle cell lymphoma	108	ND	ND	ND	ND	ND	ND
Investigator's choice (7)		53	ND	ND	ND	ND	ND	ND

B. Verges, Eur J End, 2014, 170.

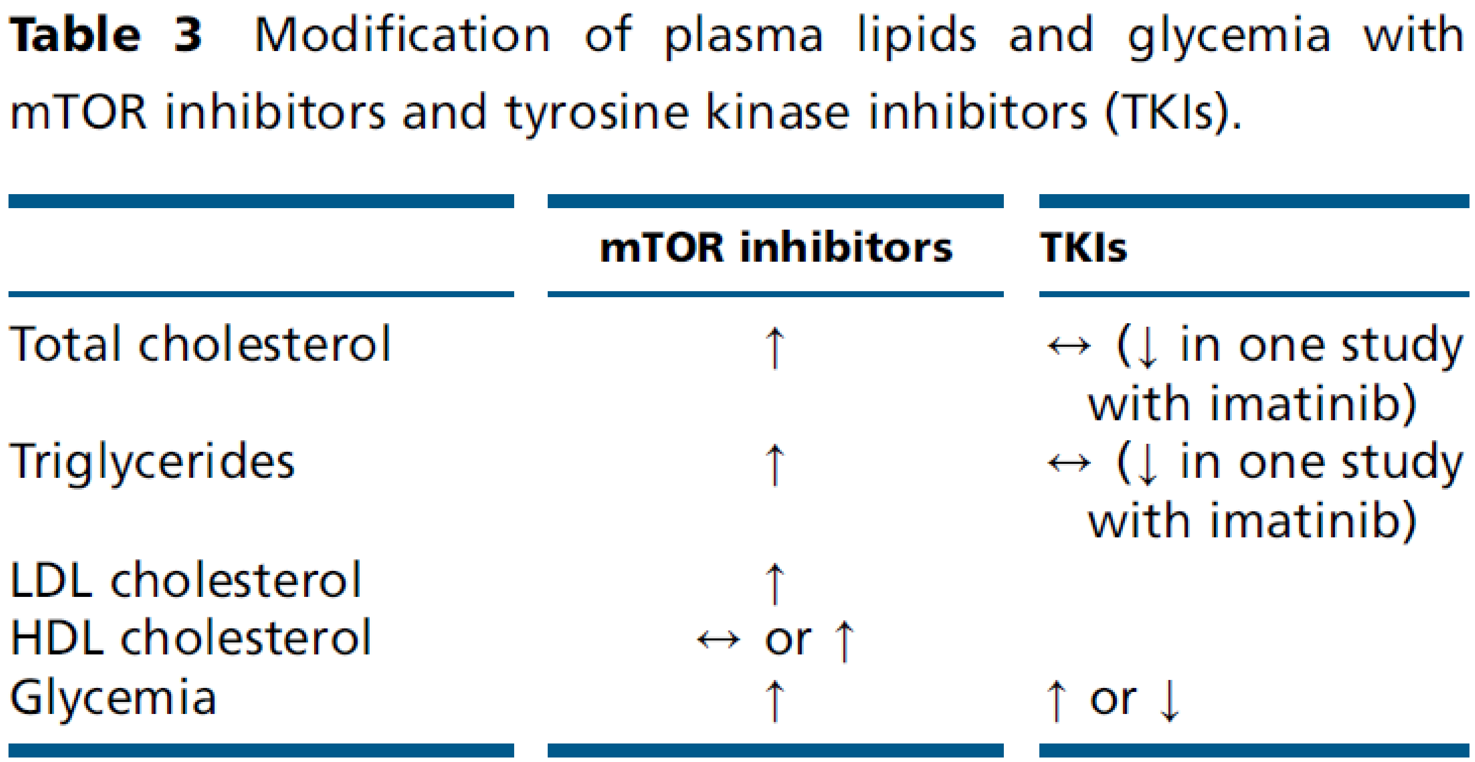


Table 3 Modification of plasma lipids and glycemia with mTOR inhibitors and tyrosine kinase inhibitors (TKIs).

	mTOR inhibitors	**TKIs**
Total cholesterol	↑	↔ (↓ in one study with imatinib)
Triglycerides	↑	↔ (↓ in one study with imatinib)
LDL cholesterol	↑	
HDL cholesterol	↔ or ↑	
Glycemia	↑	↑ or ↓

B. Verges, Eur J End, 2014, 170.

GRUPPO DI STUDIO DIABETE E TUMORI – SOTTOGRUPPO «FARMACI ANTITUMORALI E TOSSICITA' METABOLICA»

Gabriella Piscitelli

Silvia Acquati

Stella D'Oronzo

Pietro Ferrari

Montagnani Monica

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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means

Summary of Product Characteristics

by acronymsandslang.com

Immunotherapies

Checkpoint inhibitors

Anti-CTLA4 (ipilimumab, tremelimumab)

Anti-PD1 (nivolumab, pembrolizumab, cemiplimab)

Anti-PDL1 (atezolizumab, avelumab, durvalumab)

Immunomodulatory drugs (IMIDs) (lenalidomide, pomalidomide, thalidomide)

Targeted therapies

Monoclonal antibodies

Angiogenesis inhibitors (bevacizumab, ramucirumab)

Anti-EGFR (cetuximab, panitumumab)

Anti-HER2 (pertuzumab, trastuzumab, trastuzumab emtansine)

Anti-RANK-L (denosumab)

Monoclonal antibodies for hematological malignancies (alemtuzumab, blinatumomab, brentuximab vedotin, daratumumab, inotuzumab ozogamicin, obinutuzumab, ofatumumab, rituximab)

Kinase inhibitors

ALK inhibitors (alectinib, ceritinib)

BRAF inhibitors (dabrafenib, vemurafenib)

CDK 4/6 inhibitors (abemaciclib, palbociclib, ribociclib)

EGFR inhibitors (erlotinib, gefitinib, osimertinib)

MEK inhibitors (cobimetinib, trametinib)

Multi-kinase inhibitors (afatinib, axitinib, cabozantinib, crizotinib, dasatinib, imatinib, lapatinib, lenvatinib, nilotinib, pazopanib, regorafenib, sorafenib, sunitinib, vandetanib)

mTOR inhibitors (everolimus, temsirolimus)

PARP inhibitors (niraparib, olaparib, rucaparib)

Proteosome inhibitors (bortezomib, carfilzomib)

Other targeted therapies (aflibercept, vismodegib, etc.)

TERAPIE ANTITUMORALI E TOSSICITA' METABOLICA

CLASSE FARMACOLOGICA	DIABETE	IPERGLICEMIA	DKA	IPOGLICEMIA	IPERCOL	IPERTG
Checkpoint inhibitors	**SI**	**SI**	**SI**	**SI**	NO	NO
Immunomodulatory	NO	SI	NO	**SI**	NO	NO
Monoclonal antibodies	NO	**SI**	NO	NO	**SI**	NO
Kinase inhibitors	NO	**SI**	NO	NO	NO	NO
Multikinase inhibitors	**SI**	**SI**	NO	**SI**	**SI**	**SI**
mTOR inhibitors	**SI**	**SI**	NO	NO	**SI**	**SI**
PARP inhibitors	NO	NO	NO	NO	**SI**	NO
Proteosome inhibitors	**SI**	**SI**	NO	NO	NO	NO
Angiogenesis inhibitors	NO	**SI**	NO	NO	NO	NO

CHECKPOINT INHIBITORS E TOSSICITA' METABOLICA

FARMACO	DIABETE	IPERGLICEMIA	DKA	IPOGLICEMIA	IPERCOL	IPERTG
ipilimumab in combination with nivolumab	**C**	NR	**UC**	N	N	N
nivolumab monotherapy	**UC**	**VC**	**R**	**C**	N	N
nivolumab in combination with ipilimumab	**C**	**VC**	**UC**	**VC**	N	N
pembrolizumab	**UC**	NR	**Y**	N	N	N
cemiplimab	**UC**	NR	**Y (NR)**	N	N	N
atezolizumab	**UC**	NR	**Y**	N	N	N
durvalumab	**UC**	NR	**N**	N	N	N
avelumab	**UC**	NR	**Y**	N	N	N

VC (≥ 1/10); C (≥ 1/100 to < 1/10); UC (≥ 1/1,000 to < 1/100); R (≥ 1/10,000 to < 1/1,000); VR (< 1/10,000); NR

KINASE INHIBITORS E PARP INHIBITORS: TOSSICITA' METABOLICA

CLASSE	FARMACO	DIABETE	IPERGLICEMIA	DKA	IPOGLICEMIA	IPERCOL	IPERTG
mek inhibitors	cobimetinib	NO	**C**	NO	NO	NO	NO
mek inhibitors	trametinib	NO	**C**	NO	NO	NO	NO
alk inhibitor	ceritinib	NO	**C**	NO	NO	NO	NO
braf inhib	dabrafenib	NO	**C**	NO	NO	**NO**	NO
parp inhib	rucaparib	NO	NO	NO	NO	**C**	NO

VC (≥ 1/10); C (≥ 1/100 to < 1/10); UC (≥ 1/1,000 to < 1/100); R (≥ 1/10,000 to < 1/1,000); VR (< 1/10,000); NR

MONOCLONAL ANTIBODIES ed mTOR INHIBITORS

CLASSE	FARMACO	DIABETE	IPERGLICEMIA	DKA	IPOGLICEMIA	IPERCOL	IPERTG
MONOCLONAL ANTIBODIES	panitumumab in combination with irinotecan; FOLFOX	NO	**C**	NO	NO	NO	NO
MONOCLONAL ANTIBODIES	brentuximab	NO	**C (pre-existing and not pre-existing diabetes)**	NO	NO	NO	NO
MONOCLONAL ANTIBODIES	rituximab	NO	**C**	NO	NO	**C**	NO
mTOR inhibitors	everolimus	**C**	**VC**	NO	NO	**VC**	**C**
mTOR inhibitors	temsirolimus	**C**	**VC**	NO	NO	**VC**	**VC**

VC (≥ 1/10); C (≥ 1/100 to < 1/10); UC (≥ 1/1,000 to < 1/100); R (≥ 1/10,000 to < 1/1,000); VR (< 1/10,000); NR

PROTEOSOME INHIBITORS E ANGIOGENESIS INHIBITORS: TOSSICITA’ METABOLICA

CLASSE	FARMACO	DIABETE	IPERGLICEMIA	DKA	IPOGLICEMIA	IPERCOL	IPERTG
proteosome inhibitors	bortezomib	**UC**	**C**	NO	NO	NO	NO
proteosome inhibitors	carfilzomib	NO	**VC**	NO	NO	NO	NO
angiogenesis inhibitors	bevacizumab	NO	**Y**	NO	NO	NR	NR

VC (≥ 1/10); C (≥ 1/100 to < 1/10); UC (≥ 1/1,000 to < 1/100); R (≥ 1/10,000 to < 1/1,000); VR (< 1/10,000); NR

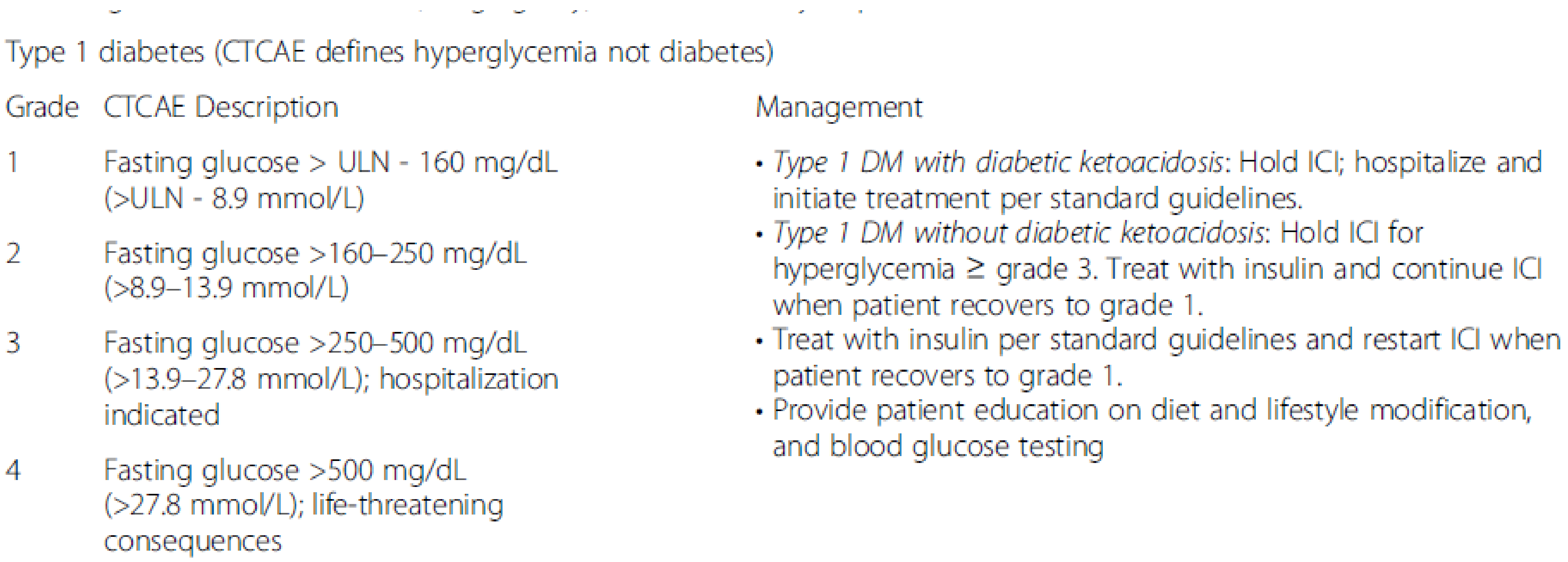
MULTIKINASE INHIBITORS: TOSSICITA' METABOLICA

FARMACO	DIABETE	IPERGLICEMIA	DKA	IPOGLICEMIA	IPERCOL	IPERTG
nilotinib	**C**	**C**	NO	**UC**	**C,VC**	**C,VC**
imatinib	NO	**UC**	NO	NO	NO	NO
idelasib	NO	NO	NO	NO	NO	**VC**
lenvatinib	NO	NO	NO	NO	**C**	NO
pazopanib	NO	NO	NO	UC	NO	NO
ponatinib	NO	**C**	NO	NO	NO	**C**
sorafenib	NO	NO	NO	**C**	NO	NO
sunitinib	NO	NO	NO	**C**	NO	NO
vandetanib	NO	**C**	NO	NO	NO	NO

VC (≥ 1/10); C (≥ 1/100 to < 1/10); UC (≥ 1/1,000 to < 1/100); R (≥ 1/10,000 to < 1/1,000); VR (< 1/10,000); NR

SOCIETY FOR IMMUNOTHERAPY OF CANCER TOXICITY MANAGEMENT WORKING GROUP , 2017

Prima di iniziare ICI:
-TSH, FT4, cortisolo e ACTH 8 am, glicemia, HbA1c
-Glicemia ogni 2 settimane per il primo mese
-Cortisolo e ACTH at 8 am ogni mese per 6 mesi poi ogni 3 mesi per 6 mesi e infine ogni 6 mesi per un anno



Type 1 diabetes (CTCAE defines hyperglycemia not diabetes)

Grade	CTCAE Description	Management
1	Fasting glucose > ULN - 160 mg/dL (>ULN - 8.9 mmol/L)	• *Type 1 DM with diabetic ketoacidosis*: Hold ICI; hospitalize and initiate treatment per standard guidelines. • *Type 1 DM without diabetic ketoacidosis*: Hold ICI for hyperglycemia ≥ grade 3. Treat with insulin and continue ICI when patient recovers to grade 1. • Treat with insulin per standard guidelines and restart ICI when patient recovers to grade 1. • Provide patient education on diet and lifestyle modification, and blood glucose testing
2	Fasting glucose >160–250 mg/dL (>8.9–13.9 mmol/L)	
3	Fasting glucose >250–500 mg/dL (>13.9–27.8 mmol/L); hospitalization indicated	
4	Fasting glucose >500 mg/dL (>27.8 mmol/L); life-threatening consequences	

TARGET THERAPIES: MANAGEMENTE OF HYPERGLYCEMIA

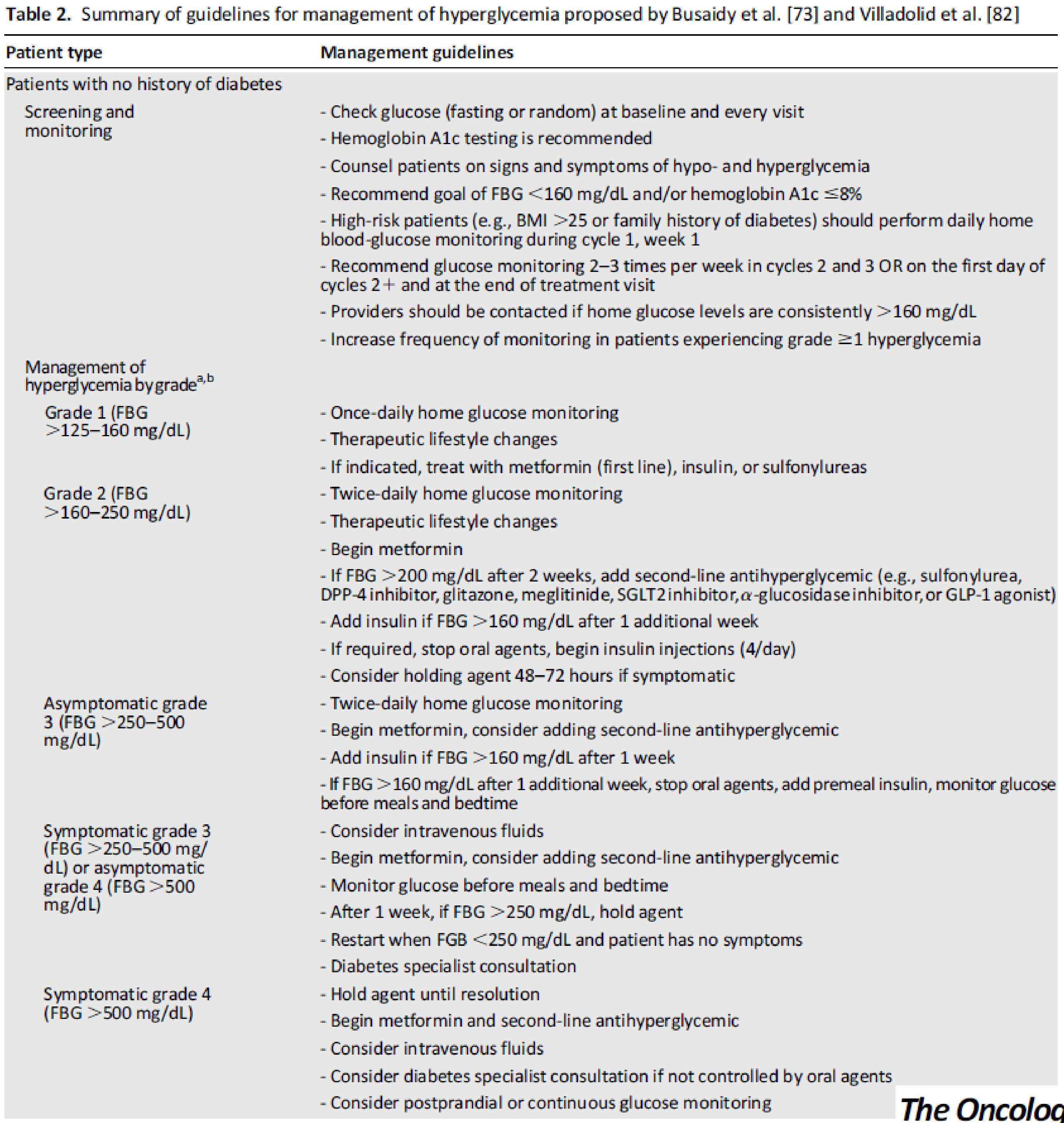
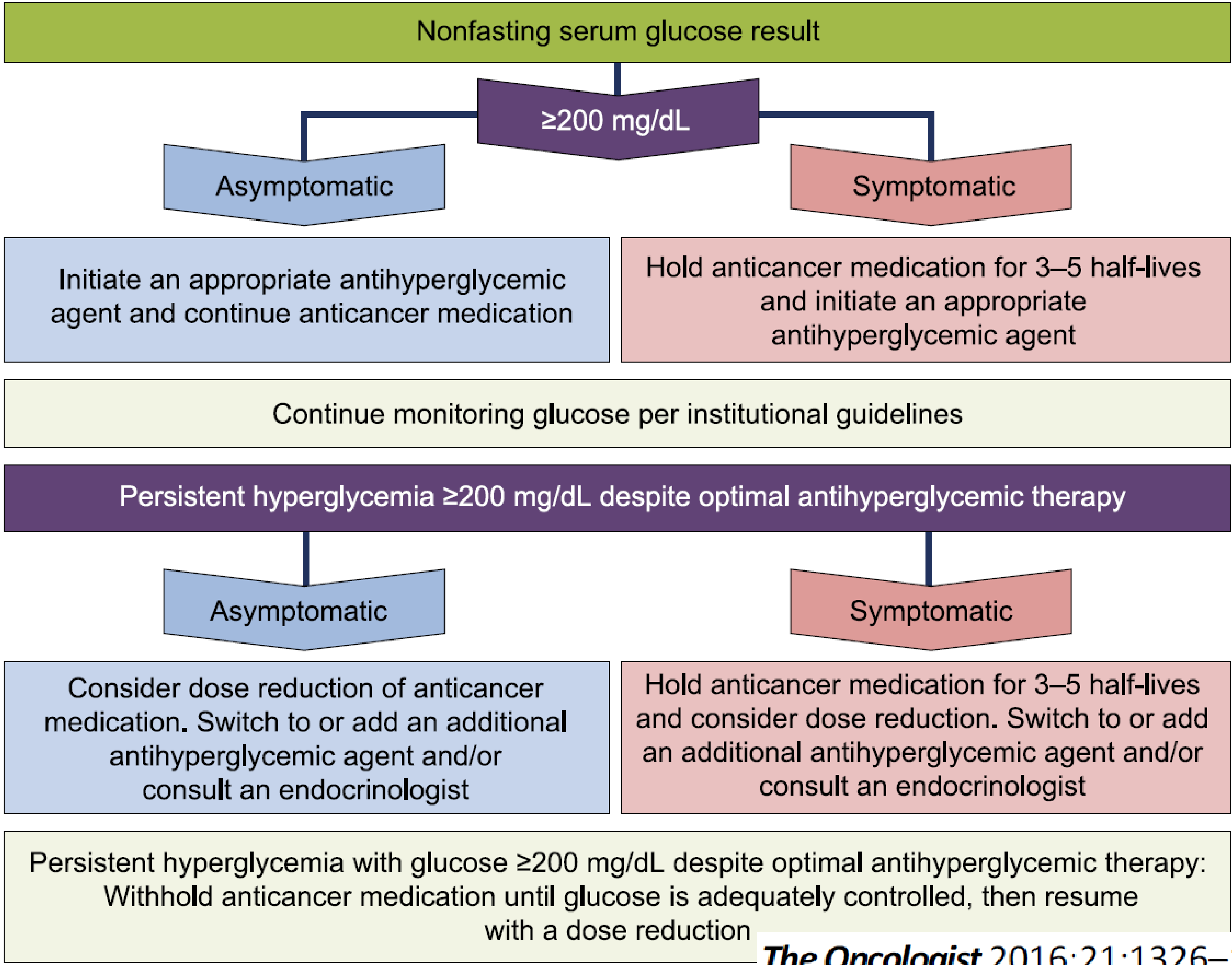


Table 2. Summary of guidelines for management of hyperglycemia proposed by Busaidy et al. [73] and Villadolid et al. [82]

Patient type	Management guidelines
Patients with no history of diabetes	
Screening and monitoring	- Check glucose (fasting or random) at baseline and every visit - Hemoglobin A1c testing is recommended - Counsel patients on signs and symptoms of hypo- and hyperglycemia - Recommend goal of FBG <160 mg/dL and/or hemoglobin A1c ≤8% - High-risk patients (e.g., BMI >25 or family history of diabetes) should perform daily home blood-glucose monitoring during cycle 1, week 1 - Recommend glucose monitoring 2–3 times per week in cycles 2 and 3 OR on the first day of cycles 2+ and at the end of treatment visit - Providers should be contacted if home glucose levels are consistently >160 mg/dL - Increase frequency of monitoring in patients experiencing grade ≥1 hyperglycemia
Management of hyperglycemia by grade[a,b]	
Grade 1 (FBG >125–160 mg/dL)	- Once-daily home glucose monitoring - Therapeutic lifestyle changes - If indicated, treat with metformin (first line), insulin, or sulfonylureas
Grade 2 (FBG >160–250 mg/dL)	- Twice-daily home glucose monitoring - Therapeutic lifestyle changes - Begin metformin - If FBG >200 mg/dL after 2 weeks, add second-line antihyperglycemic (e.g., sulfonylurea, DPP-4 inhibitor, glitazone, meglitinide, SGLT2 inhibitor, α-glucosidase inhibitor, or GLP-1 agonist) - Add insulin if FBG >160 mg/dL after 1 additional week - If required, stop oral agents, begin insulin injections (4/day) - Consider holding agent 48–72 hours if symptomatic
Asymptomatic grade 3 (FBG >250–500 mg/dL)	- Twice-daily home glucose monitoring - Begin metformin, consider adding second-line antihyperglycemic - Add insulin if FBG >160 mg/dL after 1 week - If FBG >160 mg/dL after 1 additional week, stop oral agents, add premeal insulin, monitor glucose before meals and bedtime
Symptomatic grade 3 (FBG >250–500 mg/dL) or asymptomatic grade 4 (FBG >500 mg/dL)	- Consider intravenous fluids - Begin metformin, consider adding second-line antihyperglycemic - Monitor glucose before meals and bedtime - After 1 week, if FBG >250 mg/dL, hold agent - Restart when FGB <250 mg/dL and patient has no symptoms - Diabetes specialist consultation
Symptomatic grade 4 (FBG >500 mg/dL)	- Hold agent until resolution - Begin metformin and second-line antihyperglycemic - Consider intravenous fluids - Consider diabetes specialist consultation if not controlled by oral agents - Consider postprandial or continuous glucose monitoring

The Oncologist 2016;21:1326–1336

Management of hyperglycemia



Nonfasting serum glucose result

≥200 mg/dL

Asymptomatic

Initiate an appropriate antihyperglycemic agent and continue anticancer medication

Symptomatic

Hold anticancer medication for 3–5 half-lives and initiate an appropriate antihyperglycemic agent

Continue monitoring glucose per institutional guidelines

Persistent hyperglycemia ≥200 mg/dL despite optimal antihyperglycemic therapy

Asymptomatic

Consider dose reduction of anticancer medication. Switch to or add an additional antihyperglycemic agent and/or consult an endocrinologist

Symptomatic

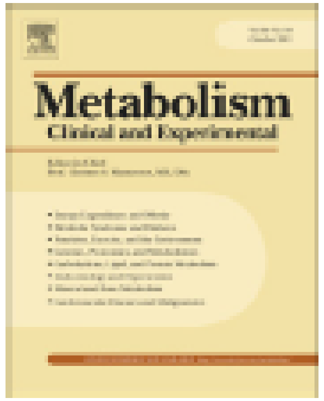
Hold anticancer medication for 3–5 half-lives and consider dose reduction. Switch to or add an additional antihyperglycemic agent and/or consult an endocrinologist

Persistent hyperglycemia with glucose ≥200 mg/dL despite optimal antihyperglycemic therapy: Withhold anticancer medication until glucose is adequately controlled, then resume with a dose reduction

The Oncologist 2016;21:1326–1336

Adverse glycaemic effects of cancer therapy: indications for a rational approach to cancer patients with diabetes

Marco Gallo[a,*], *Giovanna Muscogiuri*[b], *Francesco Felicetti*[c], *Antongiulio Faggiano*[d], *Francesco Trimarchi*[e], *Emanuela Arvat*[a], *Riccardo Vigneri*[f], *Annamaria Colao*[g]



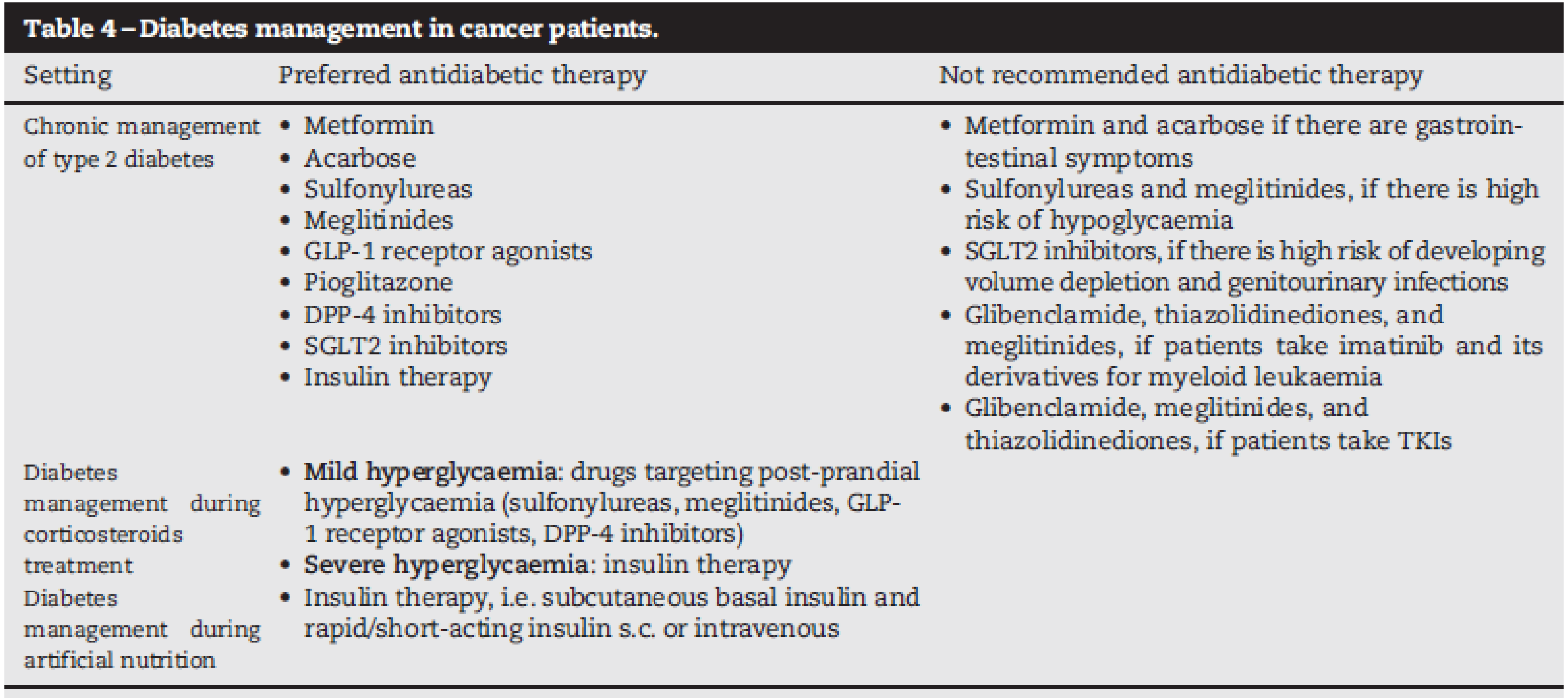


Table 4 – Diabetes management in cancer patients.

Setting	Preferred antidiabetic therapy	Not recommended antidiabetic therapy
Chronic management of type 2 diabetes	• Metformin • Acarbose • Sulfonylureas • Meglitinides • GLP-1 receptor agonists • Pioglitazone • DPP-4 inhibitors • SGLT2 inhibitors • Insulin therapy	• Metformin and acarbose if there are gastrointestinal symptoms • Sulfonylureas and meglitinides, if there is high risk of hypoglycaemia • SGLT2 inhibitors, if there is high risk of developing volume depletion and genitourinary infections • Glibenclamide, thiazolidinediones, and meglitinides, if patients take imatinib and its derivatives for myeloid leukaemia • Glibenclamide, meglitinides, and thiazolidinediones, if patients take TKIs
Diabetes management during corticosteroids treatment	• **Mild hyperglycaemia**: drugs targeting post-prandial hyperglycaemia (sulfonylureas, meglitinides, GLP-1 receptor agonists, DPP-4 inhibitors) • **Severe hyperglycaemia**: insulin therapy	
Diabetes management during artificial nutrition	• Insulin therapy, i.e. subcutaneous basal insulin and rapid/short-acting insulin s.c. or intravenous	

TAKE HOME MESSAGES

- I farmaci antitumorali di nuova generazione (targeted therapy e immunotherapy) mostrano un’elevata incidenza di complicanze acute legate al metabolismo glucidico
- Lo screening dei pazienti diabetici o a rischio di diabete è necessario prima di iniziare questi farmaci per un più attento monitoraggio glicemico

- I checkpoint inhibitors (ICI) si associano a diabete immunomediato caratterizzato da esordio rapido spesso associato a chetoacidosi diabetica
- Studi futuri sono necessari per valutare i potenziali fattori di rischio e nuove strategie di intervento per evitare l’insorgenza di chetoacidosi diabetica
- Il futuro: marker che possano identificare pazienti a rischio e farmaci in grado di ripristinare la funzione beta cellulare

Successful Treatment of Immune Checkpoint Inhibitor–Induced Diabetes With Infliximab

Diabetes Care 2019;42:e153–e154 | https://doi.org/10.2337/dc19-0908

- Recupero della funzione beta cellulare
- Patogenesi diversa rispetto al diabete di tipo 1
- Possibile utilizzo di farmaci che bloccano TNFa