

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}

^a IRCCS Istituto Tumori "Giovanni Paolo II" of Bari, Italy

^b Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro", Bari, Italy

^c Medical Oncology Department, Humanitas Gavazzeni, Bergamo, Italy

^d Diabetology Unit, Rete Clinica di Diabetologia Aziendale - Dipartimento, Internistico di Ravenna - AUSL Romagna, Ravenna, Italy

^e Unit of Clinical Pharmacology and Pharmacogenetics, Department of Clinical and Experimental Medicine, University of Pisa, Italy

^f Palliative Care Unit, Istituti Clinici Scientifici Maugeri SPA SB, IRCCS (PV), Italy

^g Oncologia Medica, IRCCS Ospedale Don Calabria-Sacro Cuore di Negrar, Verona, Italy

^h Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Italy

ⁱ Endocrinology Unit, Ospedale Pierantoni-Morgagni, Forlì, Italy

^j Oncological Endocrinology Unit, Department of Medical Sciences, University of Torino, AOU Città della Salute e della Scienza di Torino, Torino, Italy

ARTICLE INFO

Keywords:

metabolic effect
diabetes
targeted therapy
immunotherapy
hyperglycemia
dyslipidemia
hypercholesterolemia
hypertriglyceridemia

ABSTRACT

The growing insights in the next-generation immunotherapy and the state-of-the-art advancement in targeted-agents significantly improved clinical outcome of cancer patients by pointing towards a unexplored Achilles' heel. Novel toxicity profiles have been uncovered, representing unmet medical needs. Thus, a panel of expert provide comprehensive pharmacological and clinical evidence, to provide a patient-tailored approach to metabolic adverse events associated with novel anti-cancer treatments. Prompted by the need of a multidisciplinary cooperation, a working group of Associazione Italiana Oncologia Medica (AIOM), Associazione Medici Diabetologi (AMD) and Società Italiana Farmacologia (SIF) examined the available literature data. The identification of patient risk profile and the characterization of metabolic effects of novel anti-tumour drugs is clearly a clinical challenge that can be addressed by a multidisciplinary clinical approach. Therefore, this review pinpoints the relevance of the challenging profiling of the patient suffering from dysmetabolic conditions induced by the novel therapeutics in medical oncology.

1. Introduction

The increasing knowledge of underlying biology of tumors allowed the development of targeted therapies with enhanced capability to inhibit aberrant signal transduction and restore immune-competence. However, the novel agents uncovered unexpected and unexplored adverse effects to represent an important medical challenges (Niraula et al., 2012; Bedard et al., 2020; Magee et al., 2020). Despite an

improvement in the tolerability over the conventional chemotherapeutic agents, targeted treatments impact on a multitude of biological and homeostatic cell signals (Gharwan and Groninger 2016) resulting in novel adverse events (AEs) and, among them, metabolic alterations whose importance is often underestimated (Kotecki et al., 2015).

Disorders of glucose and lipid homeostasis are reported in a significant number of patients, especially with mTOR-PI3K targeting (Gharwan and Groninger, 2016). Therefore, a deeper knowledge of the

* Corresponding author at: IRCCS Istituto Tumori "Giovanni Paolo II" of Bari, Viale Orazio Flacco, 65, 70124 Bari, Italy.

E-mail address: n.silvestris@oncologico.bari.it (N. Silvestris).

¹ co-first authors.

² co-last authors.

pathophysiological process underlying the target-therapy related AEs is of paramount importance, to decrease the incidence of potentially severe homeostatic and metabolic implications.

The present AIOM/AMD/SIF consensus statement attempts to provide a patient-oriented pathophysiological approach to the metabolic AEs linked to precision oncology driven therapies and immuncheckpoint inhibition. A panel of specialists in medical oncology, endocrinology, and pharmacology examined the implementation of strategies to streamline a multidisciplinary patient-management.

We considered a stepwise approach, dealing with the most relevant pathogenic aspects and the translational pharmacological implications to provide practical recommendations for the medical practitioners. To this end, a broad spectrum of targeted- and immune-therapeutic agents were examined.

2. Bridging the gap between metabolic AEs and targeted/immune-checkpoint treatments: navigating the patient risk

Although type and stage of disease may predispose for a predictable clinical evolution, the true clinical course is often influenced by several other factors related to overall comorbidity and predisposition profile of the patient.

Among the many conditions that can influence the clinical outcomes, the alterations of the carbohydrate and lipid metabolism are undoubtedly significant (Newton et al., 2015; Samuel et al., 2018). Indeed, diabetes and related metabolic disorders may provide a favourable condition for the development and progression of cancer (Tudzarova and Osman 2015).

Several studies showed that metabolic disorders such as prediabetes, diabetes mellitus (DM) and dyslipidaemia are significant comorbidities impacting on mortality and morbidity of cancer patients. (Barone et al., 2008; Zhou et al., 2010; Rao Kondapally Seshasai et al., 2011; Scappaticcio et al., 2017; Tao et al., 2020). Moreover, several antidiabetic agents are supposed to influence cancer development and progression, or to interfere with anticancer therapies. On the other hand, many oncological therapies may affect the endocrine balance (such as glucose homeostasis, dysthyroidism, hypogonadism) and the cardiovascular risk profile. (Kotecki et al., 2015; Jannin et al., 2019; Weickhardt et al., 2012; Weickhardt et al., 2013) Additionally, AEs related to anticancer therapy, such as anti-EGFR and mTOR inhibitors, may impact the clinical outcome, in turn tipping an equilibrium between the management of toxicities and clinical benefit of treatment (Abola and Prasad, 2014; Reig et al., 2014; Dabydeen et al., 2012; Petrelli et al., 2013; Granito et al., 2016; Lacouture et al., 2018). Likewise, an association between immune-related AEs (irAEs) and improved activity of ICIs has also been reported. It is therefore tempting to envision the early onset of irAEs as a potential predictive clinical marker for improved clinical outcome (Attia et al., 2005; Freeman-Keller et al., 2016; Teraoka et al., 2017; Haratani et al., 2018; Indini et al., 2019; Maher et al., 2019; Ricciuti et al., 2019; Eggermont et al., 2020). However, additional data are discordant, thus pinpointing the complexity underlying the impact on the clinical outcome played by irAEs (Freeman-Keller et al., 2016; Weber et al., 2017). Most likely, methodological caveats might have affected the data consistency and warrant *ad hoc* trials aiming to clarify the role of irAEs as surrogate markers of activity. Ancillary, endocrine toxicity appears to significantly contribute to irAEs. However, scanty shreds of evidence highlighted the relevance of the metabolic effect in this regard (Osorio et al., 2017; Teraoka et al., 2017; Haratani et al., 2018; Eggermont et al., 2020).

There is a lack of high quality evidences on factors able to predict the risk of metabolic toxicity. Nonetheless, patients aged < 65 years, preexisting DM and maximum blood glucose > 8.5 mmol/L (153 mg/dl) at baseline, BMI > 25, Asian race are more likely to develop hyperglycaemia when treated with AKT or dual PI3K/mTOR inhibitors (Aggarwal et al., 2014; Goldman et al., 2016; Khan et al., 2016).

Table 1

Current definitions and acknowledged criteria for diagnosing the main alterations of glucose and lipid metabolism.

Criteria defining prediabetes
<ul style="list-style-type: none"> • FPG 100 mg/dl to 125 mg/dl (IFG) Or • 2-h Plasma glucose during 75-g OGTT 140 mg/dl to 199 mg/dl (IGT) Or • HbA_{1c} 39-46 mmol/mol (5.7 – 6.4%)
Criteria defining diabetes*
<ul style="list-style-type: none"> • FPG > 126 mg/dl. Fasting is defined as no caloric intake for at least 8 h. Or • 2-h PG > 200 mg/dl during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. Or • HbA_{1c} > 47 mmol/mol (6.5%). The test should be performed in laboratory using a method that is NGSP certified and standardized to the DCCT assay. Or • In Patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose > 200 mg/dl.
Criteria defining Metabolic Syndrome **
Presence of any three or more of the following: <ul style="list-style-type: none"> Blood glucose greater than 5.6 mmol/L (100 mg/dl) or drug treatment for elevated blood glucose HDL cholesterol < 1.0 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women or drug treatment for low HDL-C Blood triglycerides > 1.7 mmol/L (150 mg/dl) or drug treatment for elevated triglycerides Waist > 102 cm (men) or > 88 cm (women) Blood pressure > 130/85 mmHg or drug treatment for Hypertension

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *American Diabetes Association, 2020; **NCEP (National Cholesterol Education Program) ATP 2005 – National Institute of Health

Moreover, tyrosine kinase inhibitor (TKI), especially nilotinib, are associated with an increased risk of hyperglycaemia in patients with a history of DM and prediabetes at baseline and age > 60 years; furthermore, dyslipidaemia at baseline was identified as an additional risk factor for development of hyperglycaemia on imatinib treatment (Rea et al., 2012). Interestingly, 76% of patients with ICI-related DM harbour polymorphisms of HLA class II on chromosome 6p21, in particular HLA-DR4 genotype. Remarkably, HLA DRB1*04:05-DQB1*04:01 seems to correlate with greater susceptibility for the development of fulminant type 1 DM (Chang et al., 2019). Collectively, validation on statistically powered studies hold the potential to corroborate these findings.

Notably, early and accurate assessment of the presence of prediabetes, DM and/or dyslipidaemia in each patient is important to put in place appropriate management strategies based on specific needs (Gallo et al., 2020).

Table 1 summarizes the current definitions for the diagnosis of main alterations of glucose and lipid metabolism.

3. Molecular mechanism of metabolic AEs: clinical implications from the pathophysiologic standpoint

Fig. 1 illustrates the current understanding of the network of pathways involved in cancer cell growth, as well as some of the targeted cancer therapies that inhibit them. The PI3K/AKT/mTOR pathway is activated by insulin to regulate blood glucose levels and glucose homeostasis in tissues (Busaidy et al., 2012). Agents that target the PI3K/AKT/mTOR pathway may lead to hyperglycaemia by interrupting the intracellular response to insulin, causing decreased glucose transport and glycogen synthesis, and increased glycolysis. In addition, chronic inhibition of mTOR has been linked to decreased proliferation and reduction of insulin producing pancreatic β -cells, contributing to both hyperglycaemia and the development of insulin resistance (Barlow and Nicholson, 2013).

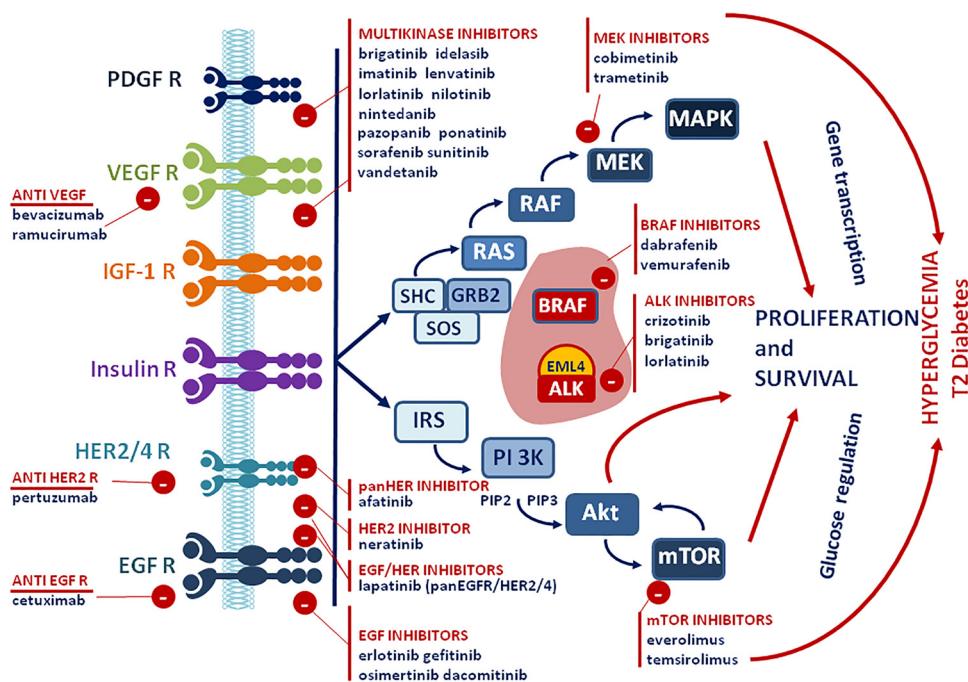


Fig. 1. Schematic diagram showing the main intracellular pathways downstream receptor tyrosine kinases (RTKs) involved in gene transcription, cell growth, differentiation and survival. Specific monoclonal antibodies and targeted therapies designed to inhibit cancer proliferation and promote apoptosis 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.

The search for molecular mechanisms explaining the metabolic effects of multikinase inhibitors is complex since drugs in the same class can be associated with both hypo- and hyperglycaemia. For example, the ABL inhibitor nilotinib causes hyperglycaemia in up to 40% of patients, while imatinib and dasatinib have been reported to cause hypoglycaemia. In part, the effects on glucose metabolism have been related to apoptosis of human β -cells observed *in vitro*, potentially dependent on activation of NF κ B secondary to inhibition of PDGFR (Deangelo 2012). The example of rociletinib suggests that hyperglycaemia or even hyperinsulinemia might be caused by a metabolite with targets other than those of the parent molecule (Sequist et al., 2015). On the other hand, hypoglycaemia has been reported for TKIs such as sorafenib, pazopanib, sunitinib, vandetanib, and ponatinib (Ono et al., 2012; Dy and Adjei 2013). For some of these drugs, chemical structure analysis suggests a potential additional mechanism through modulation of farnesoid X receptor (FXR), involved in glucose and lipid homeostasis (Gabler et al., 2018).

ICIs contribute to immune response by modulating either inhibitory or stimulatory pathways that promote T-cell activation and proliferation (Fig. 2). Interestingly, signaling via both CTLA-4 and PD-1 converge on Akt, although the pathways and consequences of antibody inhibition are distinct (Parry et al., 2005). While PD-1 signaling can directly antagonize PI3K, the effects of CTLA-4 occur via a phosphatase called PP2A. This suggests that molecules inhibiting CTLA-4 or PD-1 follow separate cascades and differ in terms of the stage of T cell activation. Accordingly, anti-CTLA-4 and anti-PD-1/PD-L1 antibodies have recently been termed ‘immune enhancers’ and ‘immune normalizers’, respectively (Sanmamed and Chen 2018). This implies that a combination therapy with PD-1 and CTLA-4 inhibitors might increase the incidence of irAEs (Weinmann and Pisetsky 2019). Indeed, owing to their ability to unleash T cells to fight cancer, ICIs can also trigger autoimmune-like diseases (Barroso-Sousa et al., 2018). While hypophysitis and thyroid disorders are the most frequent endocrine AEs, autoimmune DM is a rare but potentially life-threatening complication, as diabetic ketoacidosis is often the first presentation (Byun et al., 2017; Quandt et al., 2020). In some cases, the hyperglycaemic events may result from concomitant treatments of irAEs with glucocorticoids; nevertheless, autoimmune destruction of pancreatic islet cells and subsequent type 1 DM can occur, leading to decreased insulin levels and hyperglycaemia (Gaudy et al., 2015; Hughes et al., 2015). Similarities

with classic type 1 DM include the presence of islet auto-antibodies and susceptible HLA genotypes (Clotman et al., 2018). According to the mechanisms outlined above, autoimmune DM appears more frequently associated with blockade of PD-1 (nivolumab, pembrolizumab) and PD-L1 (atezolizumab, durvalumab) or combination therapy than with anti-CTLA-4 (ipilimumab) therapy (Haanen et al., 2017; Stamatoouli et al., 2018), highlighting the importance of the PD-1/PD-L pathway in maintaining self-tolerance against pancreatic islets. Interestingly, spectrum and grade of irAEs seem to follow a specific time pattern for anti-CTLA-4 and PD-1/PD-L1 inhibitors (Weber et al., 2012; Weber et al., 2016), which may reflect the stage of T cell activation and the overall disease progression. Importantly, recent studies have started to point out differences in early- versus late-effects to this class of drugs, suggesting that late-irAEs might be correlated with progression-free survival and overall survival in long-term responders (Nigro et al., 2020). The clinical significance of DM resulting from immune checkpoint blockade is expected to increase, as these novel anticancer agents are increasingly employed at an earlier stage of the disease.

4. Novel anti-cancer agents and metabolic toxicities

Despite the strong evidence in the literature regarding the potential AEs of novel anti-cancer agents on lipid and glucose metabolism (Verges et al., 2014; Shariff et al., 2019; Monami et al., 2020), these metabolic toxicities are often underestimated in the clinical practice, with consequent increased risk of inappropriate patient monitoring and late interventions.

The purpose of this section is to explore this phenomenon in a systematic way and summarize clinical data in tables to be quickly consulted by clinicians.

In this regard, we first classified the above-mentioned drugs according to their mechanisms of action and then reviewed the “Summaries of Product Characteristics” (SmPCs) released by the European Medicines Agency (EMA) by October 31, 2019 of the approved drugs belonging to each category.

In particular, we focused on iatrogenic glucose metabolism alterations, including DM, hyper-/hypo-glycaemia and diabetic ketoacidosis (DKA), as well as on the onset of hypercholesterolemia and hypertriglyceridemia as major lipid disorders. Frequencies of such AEs were defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$),

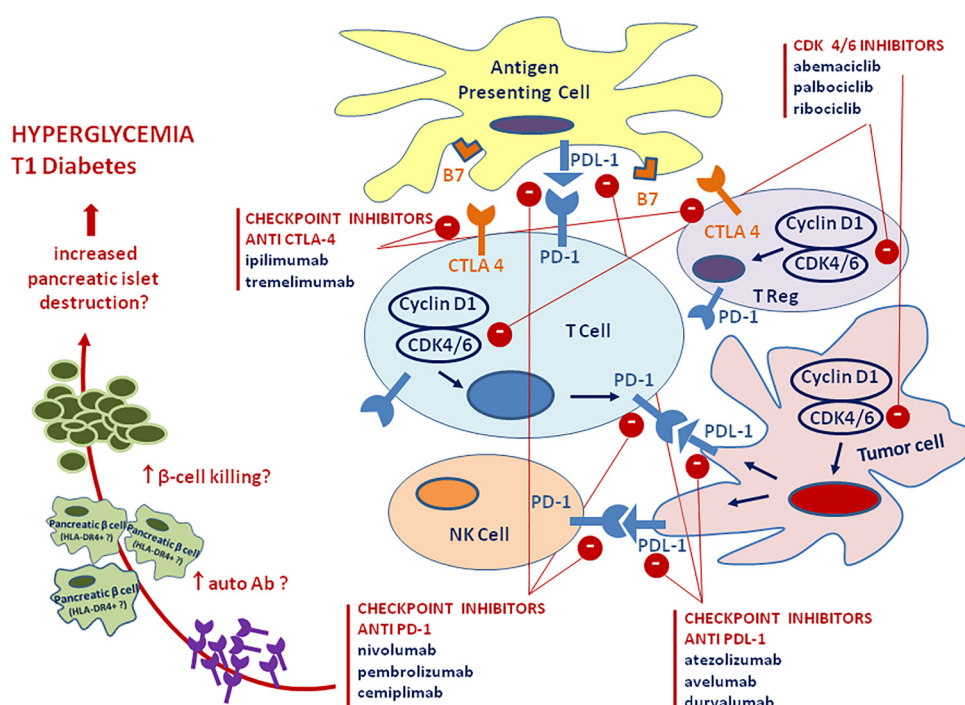


Fig. 2. Schematic diagram recapitulating the main targets of ICIs. These multiple pathways can either trigger immune recognition and killing, or immune tolerance and evasion. Checkpoint inhibitors are regulatory molecules that modulate T cell stimulation or inhibition, thereby preventing inadequate responses and promoting self-tolerance. Some of the most representative molecules and their targets are reported in Fig. 2.

uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) or very rare ($< 1/10,000$), according to the EMA SmPC's indications. "Not reported" (NR) expression was used to define those AEs whose occurrence was described in the SmPC without frequency specification.

Tables 2–6 summarize the agents for which the SmPCs reported at least one of the selected AEs. Indeed, the drug categories shown in Table 2 were all found to be correlated with the onset of at least one metabolic AE, with multikinase inhibitors being associated with the highest number of explored AEs (6 out of 7); on the other hand, the administration of angiogenesis inhibitors correlated with the occurrence of hyperglycaemia only.

With respect to ICIs (Table 3), the onset of hyperglycaemia and DM, with or without development of DKA, was described for most drugs, even if at variable frequencies. In this regard, the incidences of both DM and DKA reported in the SmPCs were apparently lower than those observed in the clinical practice and described by other authors (Wright et al., 2018; Akturk et al., 2019; Stamatouli et al., 2018; Perdigoto et al., 2019). Interestingly, nivolumab monotherapy was found to be associated with glycidic disorders, while no data were available for ipilimumab used as a single agent; however, the administration of the anti-CTLA4 monoclonal antibody in combination with nivolumab correlated with common DM onset.

When focusing on TKIs, we observed a variable incidence of metabolic toxicities (Table 4); for instance, some agents were associated with common/very common glycidic disorders (i.e. brigatinib,

Table 3

Metabolic AEs associated with ICIs.

AGENT	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA
Nivolumab	UC	VC	R	C
Nivolumab + ipilimumab	C	VC	UC	VC
Pembrolizumab	UC	NR	UC	-
Cemiplimab	UC	NR	UC	-
Atezolizumab	UC	C	UC	-
Durvalumab	UC	-	-	-
Avelumab	UC	C	UC	-

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

VC, very common ($\geq 1/10$); C, common ($\geq 1/100$ to $< 1/10$); UC, uncommon ($\geq 1/1,000$ to $< 1/100$); R, rare ($\geq 1/10,000$ to $< 1/1,000$); NR, not reported frequency; -: not reported toxicity.

sorafenib, sunitinib, vandetanib), while lipid metabolism alterations were common/very common for ruxolitinib, idelalisib, lenvatinib and lorlatinib. Notably, both glycidic and lipid disorders have been described during nilotinib and ponatinib administration. In a similar fashion, the incidence of metabolic AEs turned out extremely variable during treatment with other targeted agents, as shown in Table 5 and 6. However, inhibitors of mTOR pathway were not surprisingly associated with the highest frequencies of metabolic disorders (Sivendran et al., 2014).

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
Proteasome inhibitors	YES	YES	NO	NO	NO	NO
Angiogenesis inhibitors	NO	YES	NO	NO	YES	NO

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

Table 4
Metabolic AEs associated with kinase inhibitors.

DRUG CLASS	AGENT	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA	HYPER-CHOLESTEROLEMIA	HYPER-TRIGLYCERIDEMIA
MEK inhibitors	cobimetinib	-	C*	-	-	-	-
	trametinib	-	C*	-	-	-	-
BRAF inhibitors	dabrafenib	-	C	-	-	-	-
JAK inhibitor	ruxolitinib	-	-	-	-	VC	VC
Multi-kinase inhibitors	brigatinib	-	VC	-	-	-	-
	idelasib	-	-	-	-	-	VC
	imatinib	-	UC	-	-	-	-
	lenvatinib	-	-	-	-	C	-
	lorlatinib	-	-	-	-	VC	VC
	nilotinib	C	C	-	UC	C, VC	C, VC
	pazopanib	-	-	-	UC	-	-
	ponatinib	-	C	-	-	-	C
	sorafenib	-	-	-	C	-	-
	sunitinib	-	-	-	C	-	-
	vandetanib	-	C	-	-	-	-

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

VC, very common ($\geq 1/10$); C, common ($\geq 1/100$ to $< 1/10$); UC, uncommon ($\geq 1/1,000$ to $< 1/100$); NO, not reported toxicity. *AEs described in combination with BRAF-inhibitors.

5. Expert panel recommendations

Many of the commonly used target therapies and ICIs exert different effects on glucose and lipid metabolism, as well as on blood pressure and cardiovascular system (Verges et al., 2014; Ruggeri et al., 2019). As a consequence, diabetologists, oncologists and pharmacologists need to co-operate for early patient care and appropriate management (Gallo et al., 2016). The panel of experts identified by AIOM, AMD and SIF put forward some recommendations on the most relevant metabolic AEs of cancer patients who are candidates or are already on treatment with targeted therapies or ICIs.

5.1. Pre-treatment assessment and ongoing monitoring

Appropriate screening at baseline is highly recommended for every patient starting a target therapy or immunotherapy, to identify subjects requiring close monitoring of glucose and lipid metabolism (Table 7) (Breccia et al., 2014; Iurlo et al., 2015). Any patient without previously known DM, especially if at increased risk for, should control fasting plasma glucose every 2 weeks during the first month and then monthly thereafter for the duration of the treatment, i.e., HbA_{1c} at baseline, at 3 months, and therefore annually if normal. In patients with previously known DM, self-monitoring of blood glucose (SMBG) should be proposed or reinforced, alternating fasting and 2-hs post-prandial glucose levels measurements (Verges et al., 2014). Patients should also be appropriately educated to recognize symptomatic hypo- or hyperglycaemias, and to manage these events appropriately. In special circumstances, flash glucose monitoring (FGM) or continuous glucose monitoring (CGM) might enable patients to avoid severe hypoglycaemia and glucose deviations from normal values.

Table 5
Metabolic AEs associated with monoclonal antibodies.

AGENT	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA	HYPER-CHOLESTEROLEMIA	HYPER-TRIGLYCERIDEMIA
Brentuximab (anti-CD30)	-	C	-	-	-	-
Panitumumab (anti-EGFR)	-	C	-	-	-	-
Rituximab (anti-CD20)	-	C	-	-	C	-
Siltuximab (anti-IL6)	-	-	-	-	C	VC

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

VC, very common ($\geq 1/10$); C, common ($\geq 1/100$ to $< 1/10$); NO, not reported toxicity.

Albeit uncommon, the clinical onset of ICIs-induced DM is acute, with an abrupt and steep rise in blood glucose levels, frequently with diabetic ketoacidosis (DKA), manifesting a medical emergency (fulminant diabetes). The median onset of ICI-related DM is 5 months (Stamatouli et al., 2018; Kotwal et al., 2019). Even if blood glucose monitoring for the first 6-12 months of therapy in patients receiving anti-PD-1/PD-L1 therapy is highly recommended by current guidelines, diagnostic delay may be life-threatening. Therefore, patient education for prompt recognition of symptoms of hyperglycaemia (polyuria, polydipsia, blurred vision, weight loss, malaise) and/or DKA (nausea, vomiting, abdominal pain, fatigue) is crucial and urgent medical referral is even more important (Castinetti et al., 2019). Since patients with pre-existing type 2 DM may develop immune-mediated DM when treated with ICIs, this population may benefit from FGM/CGM to early identify a brisk worsening of glucose control (Zezza et al., 2019).

If hyperglycaemia occurs in a patient without well-established risk factors, assessment of urine ketones, auto-antibodies against glutamic acid decarboxylase (anti-GAD), islet cells (ICA) and insulin, as well as serum insulin and C-peptide, is recommended (Ruggeri et al., 2019). Insulin therapy should be promptly started if ICIs-induced DM is suspected, and urgent endocrine consultation is appropriate. Hyperglycaemic hyperosmolar state and diabetic ketoacidosis, which represent the most serious and life-threatening emergencies in subjects with diabetes, should be managed according to the local guidelines. Both disorders are characterized by severe insulinopenia and very high blood glucose levels: as a consequence, aggressive rehydration with intravenous fluids (ie, 0.9% NaCl isotonic saline), insulin therapy, and electrolyte replacement are the cornerstones of their acute management. Pancreatic amylase and lipase may also be of help in cases of fulminant diabetes, whereas diagnostic imaging of the pancreas and

Table 6
Metabolic AEs associated with other targeted agents.

CLASS	AGENT	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA	HYPER-CHOLESTEROLEMIA	HYPER-TRIGLYCERIDEMIA
PARP inhibitors	rucaparib	-	-	-	-	C	-
mTOR inhibitors	everolimus	C	VC	-	-	VC	C
	temsirolimus	C	VC	-	-	VC	VC
proteasome inhibitors	bortezomib	UC	C	-	UC	-	-
	carfilzomib	-	VC	-	-	-	-
angiogenesis inhibitor	bevacizumab	-	NR	-	-	-	-
	aflibercept	-	-	-	-	UC	-

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

VC, very common ($\geq 1/10$); C, common ($\geq 1/100$ to $< 1/10$); UC, uncommon ($\geq 1/1,000$ to $< 1/100$); NR, not reported frequency; NO: not reported toxicity.

Table 7

Recommendations for cancer patients starting a target therapy or immunotherapy.

Pre-treatment assessment
FPG, HbA _{1c} , LDL-C, triglycerides & BP
Ongoing assessment
Patients without previously known DM
FPG & BP every 2 weeks during the 1 st month and then once every month for 6-12 months
HbA _{1c} after 3 months and then every year if normal
Education for early recognition of symptoms of hyperglycemia or DKA, if on ICI
Patients with previously known DM
FPG, HbA _{1c} , LDL-C, triglycerides & BP every 3 months
Reinforce SMBG (FPG & PPG); consider FGM/CGM
Provide diabetes self-management education and support
Consider overall CV risk
Patients who develop hyperglycaemia on ICIs
urine ketones
ICA, anti-GAD, and anti-insulin Ab
Insulin, C-peptide
Pancreatic amylase & lipase

AntiGAD, auto-antibodies against glutamic acid decarboxylase; BP, blood pressure; CGM, continuous glucose monitoring; CV, cardiovascular; DKA, diabetic ketoacidosis; FGM, flash glucose monitoring; FPG, fasting plasma glucose; ICA, anti-islet cells antibodies; ICIs, ICIs; LDL-C, low density lipoprotein cholesterol; PPG, post-prandial glucose; SMBG, self-monitoring of blood glucose.

corticosteroid therapy are not indicated. Patients should not discontinue ICIs therapy while initiating insulin therapy, except in most severe cases (G3-G4), where these drugs could be delayed by a few days until reduction of toxicity to G1 (Haanen et al., 2017; Puzanov et al., 2017; Brahmer et al., 2018; Higham et al., 2018). A 'wallet card' for patients on immunotherapy should be considered to support communication of the risks associated with treatment.

5.2. Glycaemic, blood pressure, and lipid goals

Glycaemic targets for cancer patients with DM should be individualized according to life expectancy, vascular co-morbidities, patient attitude and resources, and expected treatment effects (Inzucchi et al., 2015). Since the prognosis of patients with cancer is longer than in the past, it can be recommended an HbA_{1c} target of 53-58 mmol/mol (7.0-7.5%) for many patients aged less than 75 years, provided that life expectancy will be long enough. In older patients and/or when the prognosis is poor, HbA_{1c} and glucose levels targets should be relaxed with the aim of avoiding symptomatic hypo- hyperglycaemia, DKA, and risk of infection (Gallo et al., 2018). Recommended blood pressure levels for patients with DM are generally < 140 mmHg for systolic and < 90 mmHg for diastolic. Cancer patients with DM and with a prognosis > 1 year may benefit from treatment of hyperlipidaemia, especially if at high risk of cardiovascular AEs based on the SCORE system (<https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts>) (Busaidy et al., 2012; Breccia et al., 2016).

5.3. Antidiabetic therapy

Metformin is typically the first-line agent for the treatment of type 2 DM also for patients with cancer, provided hyperglycaemia is mild, no contraindications subsist, and the patient is not intolerant to the drug. When choosing second-line agent instead of or in association with metformin, the risk profile of each antidiabetic drug (ADD) should be taken into account, together with the most common AEs of target therapies employed for the underlying oncological disease. To cite the most common examples, metformin and GLP1-receptor agonists should be avoided in patients with already existing nausea, diarrhoea, or abdominal pain, whereas the main drawback of thiazolidinediones (pioglitazone, rosiglitazone) is the occurrence of heart failure or peripheral edema. Conversely, patients at increased risk of fluid depletion should not be treated with SGLT2-inhibitors. Finally, sulphonylureas, meglitinides, but also metformin should be avoided in people with liver or renal failure (Gallo et al. 2018).

A possible algorithm for the management of hyperglycaemia induced by cancer therapy is proposed in Fig. 3, with SGLT2-inhibitors and GLP1-receptor agonists suggested as second line therapies if the risk of heart failure or atherosclerotic cardiovascular disease predominates, respectively. Insulin is always a safe option, especially if hyperglycaemia is severe.

Obviously, life-long insulin treatment is the only available therapy for patients with type 1 or ICI-induced DM (with a basal-bolus regimen), as well as the best option for many patients with secondary DM. Appropriate education on SMBG, insulin conservation and use, and an approach for hyper- or hypoglycemia, shall be an integral component of DM management.

Finally, since most oral ADDs and some TKIs are metabolised by the cytochrome P450 system (CYP), cancer patients with DM are at enhanced risk of drug-drug interactions. Combination therapies may therefore affect both the anti-diabetic and the anti-cancer drug levels. In patients with DM treated with imatinib, for example, the tissue exposure to glibenclamide, thiazolidinediones, and meglitinides may increase (Haouala et al., 2011). Furthermore, caution must be taken when prescribing fibrates and lipid-lowering agents (Busaidy et al., 2012). Pravastatin and rosuvastatin should be preferred to other statins (due to the risk of competitive inhibition of CYP 3A4), using fenofibrate in case of statin intolerance or hypertriglyceridemia (Haouala et al., 2011; Wiggins et al., 2016). Ezetimibe could represent a reasonable option as an add-on to statins, when cholesterol is not adequately controlled (Breccia et al., 2016).

6. Conclusions

Growing available options in terms of tailored targeted treatment and immunotherapy deeply improved the clinical outcome of cancer patients, though hijacking the toxicity profile to uncovered landscapes. Therefore, deeper insight aiming to a more comprehensive pathophysiological characterization of the mechanism underlying metabolic AEs is needed in order to support patient management. Meanwhile, a

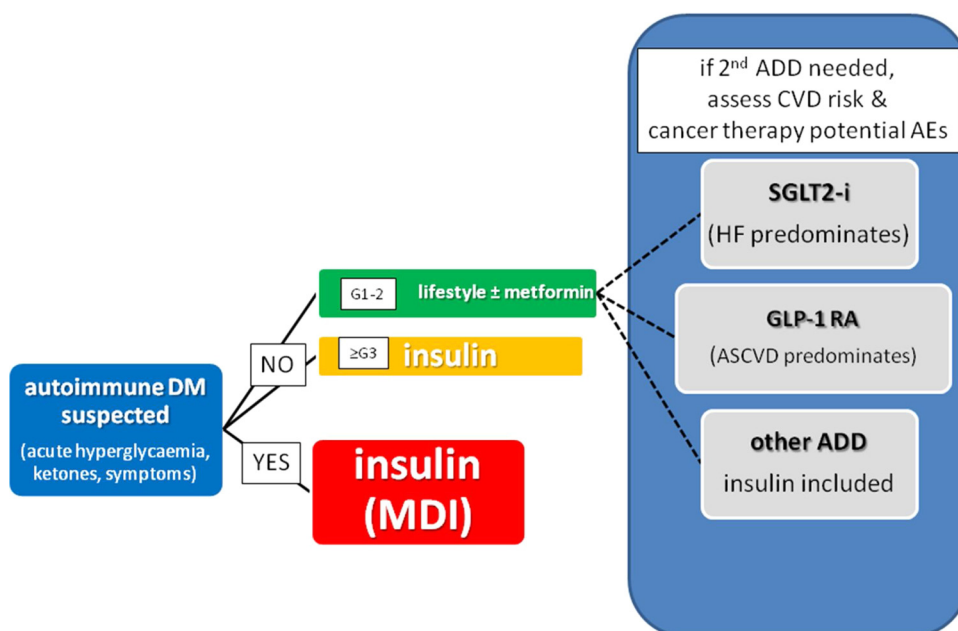


Fig. 3. Management of cancer therapy induced hyperglycaemia.

AES, adverse event; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; SGLT2-i, sodium-glucose transport 2 inhibitors; MDI, multiple daily injections; G1: glycaemia ULN-160 mg/dL; G2: 160-250 mg/dL; G3: 250-500 mg/dL; G4: ≥ 500 mg/dL (from: Common Terminology Criteria for Adverse Events, Version 4.03 - <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>).

stepwise approach to the subjects with targeted- and immune- related metabolic AEs holds the great potential to uncover the complex systemic involvement of novel therapies for optimal management by an integrated multidisciplinary team.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors.

Declaration of Competing Interest

The Authors declare no conflict of interests.

References

- Abola, M.V., Prasad, V., et al., 2014. Association between treatment toxicity and outcomes in oncology clinical trials. *Ann Oncol* 25 (11), 2284–2289.
- Aggarwal, R., Grabowsky, J., et al., 2014. Impact of patient ethnicity on the metabolic and immunologic effects of PI3K-mTOR pathway inhibition in patients with solid tumor malignancies. *Cancer Chemother Pharmacol* 74 (2), 359–365.
- Akturk, H.K., Kahramangil, D., et al., 2019. Immune checkpoint inhibitor-induced Type 1 diabetes: a systematic review and meta-analysis. *Diabet Med* 36 (9), 1075–1081.
- Attia, P., Phan, G.Q., et al., 2005. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. *J Clin Oncol* 23 (25), 6043–6053.
- Barlow, A.D., Nicholson, M.L., et al., 2013. Evidence for rapamycin toxicity in pancreatic beta-cells and a review of the underlying molecular mechanisms. *Diabetes* 62 (8), 2674–2682.
- Barone, B.B., Yeh, H.C., et al., 2008. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 300 (23), 2754–2764.
- Barroso-Sousa, R., Barry, W.T., et al., 2018. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. *JAMA Oncol* 4 (2), 173–182.
- Bedard, P.L., Hyman, D.M., et al., 2020. Small molecules, big impact: 20 years of targeted therapy in oncology. *Lancet* 395 (10229), 1078–1088.
- Brahmer, J.R., Lacchetti, C., et al., 2018. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 36 (17), 1714–1768.
- Breccia, M., Arboscio, E., et al., 2016. Proposal for a tailored stratification at baseline and monitoring of cardiovascular effects during follow-up in chronic phase chronic myeloid leukemia patients treated with nilotinib frontline. *Crit Rev Oncol Hematol* 107, 190–198.
- Breccia, M., Molica, M., et al., 2014. How tyrosine kinase inhibitors impair metabolism and endocrine system function: a systematic updated review. *Leuk Res* 38 (12), 1392–1398.
- Busaidy, N.L., Farooki, A., et al., 2012. Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. *J Clin Oncol* 30 (23), 2919–2928.
- Byun, D.J., Wolchok, J.D., et al., 2017. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. *Nat Rev Endocrinol* 13 (4), 195–207.
- Castinetti, F., Albarel, F., et al., 2019. French Endocrine Society Guidance on endocrine side effects of immunotherapy. *Endocr Relat Cancer* 26 (2), G1–G18.
- Chang, L.S., Barroso-Sousa, R., et al., 2019. Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints. *Endocr Rev* 40 (1), 17–65.
- Clotman, K., Janssens, K., et al., 2018. Programmed Cell Death-1 Inhibitor-Induced Type 1 Diabetes Mellitus. *J Clin Endocrinol Metab* 103 (9), 3144–3154.
- Dabydeen, D.A., Jagannathan, J.P., et al., 2012. Pneumonitis associated with mTOR inhibitors therapy in patients with metastatic renal cell carcinoma: incidence, radiographic findings and correlation with clinical outcome. *Eur J Cancer* 48 (10), 1519–1524.
- Deangelo, D.J., 2012. Managing chronic myeloid leukemia patients intolerant to tyrosine kinase inhibitor therapy. *Blood Cancer J* 2, e95.
- Dy, G.K., Adjei, A.A., 2013. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA Cancer J Clin* 63 (4), 249–279.
- Eggermont, A.M.M., Kicinski, M., et al., 2020. Association Between Immune-Related Adverse Events and Recurrence-Free Survival Among Patients With Stage III Melanoma Randomized to Receive Pembrolizumab or Placebo: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncol*.
- Freeman-Keller, M., Kim, Y., et al., 2016. Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes. *Clin Cancer Res* 22 (4), 886–894.
- Gabler, M., Kramer, J., et al., 2018. Allosteric modulation of the farnesoid X receptor by a small molecule. *Sci Rep* 8 (1), 6846.
- Gallo, M., Clemente, G., et al., 2020. An integrated care pathway for cancer patients with diabetes: A proposal from the Italian experience. *Diabetes Res Clin Pract* 159, 107721.
- Gallo, M., Gentile, L., et al., 2016. Diabetology and oncology meet in a network model: union is strength. *Acta Diabetol* 53 (4), 515–524.
- Gallo, M., Muscogiuri, G., et al., 2018. Adverse glycaemic effects of cancer therapy: indications for a rational approach to cancer patients with diabetes. *Metabolism* 78, 141–154.
- Gaudy, C., Cleve, C., et al., 2015. Anti-PD1 Pembrolizumab Can Induce Exceptional Fulminant Type 1 Diabetes. *Diabetes Care* 38 (11), e182–3.
- Gharwan, H., Groninger, H., 2016. Kinase inhibitors and monoclonal antibodies in oncology: clinical implications. *Nat Rev Clin Oncol* 13 (4), 209–227.
- Goldman, J.W., Mendenhall, M.A., et al., 2016. Hyperglycemia Associated With Targeted Oncologic Treatment: Mechanisms and Management. *Oncologist* 21 (11), 1326–1336.
- Granito, A., Marinelli, S., et al., 2016. Prognostic significance of adverse events in patients with hepatocellular carcinoma treated with sorafenib. *Therap Adv Gastroenterol* 9 (2), 240–249.
- Haanen, J., Carbone, F., et al., 2017. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 28 (suppl.4) iv119–iv142.
- Hauaala, A., Widmer, N., et al., 2011. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. *Blood* 117 (8), e75–87.
- Haratani, K., Hayashi, H., et al., 2018. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. *JAMA Oncol* 4 (3), 374–378.
- Higam, C.E., Olsson-Brown, A., et al., 2018. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Acute management of the endocrine

- complications of checkpoint inhibitor therapy. *Endocr Connect* 7 (7), G1–G7.
- Hughes, J., Vudattu, N., et al., 2015. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. *Diabetes Care* 38 (4), e55–7.
- Indini, A., Di Guardo, L., et al., 2019. Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma. *J Cancer Res Clin Oncol* 145 (2), 511–521.
- Inzucchi, S.E., Bergenstal, R.M., et al., 2015. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 38 (1), 140–149.
- Iurlo, A., Orsi, E., et al., 2015. Effects of first- and second-generation tyrosine kinase inhibitor therapy on glucose and lipid metabolism in chronic myeloid leukemia patients: a real clinical problem? *Oncotarget* 6 (32), 33944–33951.
- Jannin, A., Penel, N., et al., 2019. Tyrosine kinase inhibitors and immune checkpoint inhibitors-induced thyroid disorders. *Crit Rev Oncol Hematol* 141, 23–35.
- Khan, K.H., Wong, M., et al., 2016. Hyperglycemia and Phosphatidylinositol 3-Kinase/Protein Kinase B/Mammalian Target of Rapamycin (PI3K/AKT/mTOR) Inhibitors in Phase I Trials: Incidence, Predictive Factors, and Management. *Oncologist* 21 (7), 855–860.
- Kotecki, N., Penel, N., et al., 2015. Metabolic disorders associated with the use of targeted cancer therapies. *Curr Opin Oncol* 27 (3), 258–266.
- Kotwal, A., Haddox, C., et al., 2019. Immune checkpoint inhibitors: an emerging cause of insulin-dependent diabetes. *BMJ Open Diabetes Res Care* 7 (1), e000591.
- Lacouture, M.E., Anadkat, M., et al., 2018. Dermatologic Toxicity Occurring During Anti-EGFR Monoclonal Inhibitor Therapy in Patients With Metastatic Colorectal Cancer: A Systematic Review. *Clin Colorectal Cancer* 17 (2), 85–96.
- Magee, D.E., Hird, A.E., et al., 2020. Adverse event profile for immunotherapy agents compared with chemotherapy in solid organ tumors: a systematic review and meta-analysis of randomized clinical trials. *Ann Oncol* 31 (1), 50–60.
- Maher, V.E., Fernandes, L.L., et al., 2019. Analysis of the Association Between Adverse Events and Outcome in Patients Receiving a Programmed Death Protein 1 or Programmed Death Ligand 1 Antibody. *J Clin Oncol* 37 (30), 2730–2737.
- Monami, M., Naletto, L., et al., 2020. Immune checkpoints inhibitors and hyperglycemia: A Meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract* 162, 108115.
- Newton, J.N., Briggs, A.D., et al., 2015. Changes in health in England, with analysis by English regions and areas of deprivation, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 386 (10010), 2257–2274.
- Nigro, O., Pinotti, G., et al., 2020. Late immune-related adverse events in long-term responders to PD-1/PD-L1 checkpoint inhibitors: A multicentre study. *Eur J Cancer* 134, 19–28.
- Niraula, S., Seruga, B., et al., 2012. The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. *J Clin Oncol* 30 (24), 3012–3019.
- Ono, K., Suzushima, H., et al., 2012. Rapid amelioration of hyperglycemia facilitated by dasatinib in a chronic myeloid leukemia patient with type 2 diabetes mellitus. *Intern Med* 51 (19), 2763–2766.
- Osorio, J.C., Ni, A., et al., 2017. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann Oncol* 28 (3), 583–589.
- Parry, R.V., Chemnitz, J.M., et al., 2005. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol* 25 (21), 9543–9553.
- Perdigoto, A.L., Quandt, Z., et al., 2019. Checkpoint inhibitor-induced insulin-dependent diabetes: an emerging syndrome. *Lancet Diabetes Endocrinol* 7 (6), 421–423.
- Petrelli, F., Borgonovo, K., et al., 2013. The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. *Target Oncol* 8 (3), 173–181.
- Puzanov, I., Diab, A., et al., 2017. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 5 (1), 95.
- Quandt, Z., Young, A., et al., 2020. Immune checkpoint inhibitor diabetes mellitus: a novel form of autoimmune diabetes. *Clin Exp Immunol* 200 (2), 131–140.
- Rao Kondapally Seshasai, S., Kaptoge, S., et al., 2011. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 364 (9), 829–841.
- Rea, D., Gautier, J., et al., 2012. Incidence of Hyperglycemia by 3 Years in Patients (Pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Nilotinib (NIL) or Imatinib (IM) in ENESTnd. *Blood* 120 (21), 1686.
- Reig, M., Torres, F., et al., 2014. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. *J Hepatol* 61 (2), 318–324.
- Ricciuti, B., Genova, C., et al., 2019. Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis. *J Cancer Res Clin Oncol* 145 (2), 479–485.
- Ruggeri, R.M., Campenni, A., et al., 2019. Endocrine and metabolic adverse effects of immune checkpoint inhibitors: an overview (what endocrinologists should know). *J Endocrinol Invest* 42 (7), 745–756.
- Samuel, S.M., Varghese, E., et al., 2018. Challenges and perspectives in the treatment of diabetes associated breast cancer. *Cancer Treat Rev* 70, 98–111.
- Sanmamed, M.F., Chen, L., 2018. A Paradigm Shift in Cancer Immunotherapy: From Enhancement to Normalization. *Cell* 175 (2), 313–326.
- Scappaticcio, L., Maiorino, M.I., et al., 2017. Insights into the relationships between diabetes, prediabetes, and cancer. *Endocrine* 56 (2), 231–239.
- Sequist, L.V., Soria, J.C., et al., 2015. Rociletinib in EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 372 (18), 1700–1709.
- Shariff, A.I., Syed, S., et al., 2019. Novel cancer therapies and their association with diabetes. *J Mol Endocrinol* 62 (2), R187–R199.
- Sivendran, S., Agarwal, N., et al., 2014. Metabolic complications with the use of mTOR inhibitors for cancer therapy. *Cancer Treat Rev* 40 (1), 190–196.
- Stamatouli, A.M., Quandt, Z., et al., 2018. Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors. *Diabetes* 67 (8), 1471–1480.
- Tao, H., O’Neil, A., et al., 2020. Pre- and Post-diagnosis Diabetes as a Risk Factor for All-Cause and Cancer-Specific Mortality in Breast, Prostate, and Colorectal Cancer Survivors: A Prospective Cohort Study. *J Thorac Oncol* 12 (12), 1798–1805.
- Teraoka, S., Fujimoto, D., et al., 2017. Early Immune-Related Adverse Events and Association with Outcome in Advanced Non-Small Cell Lung Cancer Patients Treated with Nivolumab: A Prospective Cohort Study. *J Thorac Oncol* 12 (12), 1798–1805.
- Tudzarova, S., Osman, M.A., 2015. The double trouble of metabolic diseases: the diabetes-cancer link. *Mol Biol Cell* 26 (18), 3129–3139.
- Verges, B., Walter, T., et al., 2014. Endocrine side effects of anti-cancer drugs: effects of anti-cancer targeted therapies on lipid and glucose metabolism. *Eur J Endocrinol* 170 (2), R43–55.
- Weber, J.S., Hodi, F.S., et al., 2017. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. *J Clin Oncol* 35 (7), 785–792.
- Weber, J.S., Kahler, K.C., et al., 2012. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 30 (21), 2691–2697.
- Weber, J.S., Postow, M., et al., 2016. Management of Adverse Events Following Treatment With Anti-Programmed Death-1 Agents. *Oncologist* 21 (10), 1230–1240.
- Weickhardt, A.J., Doebele, R.C., et al., 2013. Symptomatic reduction in free testosterone levels secondary to crizotinib use in male cancer patients. *Cancer* 119 (13), 2383–2390.
- Weickhardt, A.J., Rothman, M.S., et al., 2012. Rapid-onset hypogonadism secondary to crizotinib use in men with metastatic nonsmall cell lung cancer. *Cancer* 118 (21), 5302–5309.
- Weinmann, S.C., Pisetsky, D.S., 2019. Mechanisms of immune-related adverse events during the treatment of cancer with immune checkpoint inhibitors. *Rheumatology (Oxford)* 58 (Suppl 7), vii59–vii67.
- Wiggins, B.S., Saseen, J.J., et al., 2016. Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation* 134 (21), e468–e495.
- Wright, J.J., Salem, J.E., et al., 2018. Increased Reporting of Immune Checkpoint Inhibitor-Associated Diabetes. *Diabetes Care* 41 (12), e150–e151.
- Zeza, M., Kosinski, C., et al., 2019. Combined immune checkpoint inhibitor therapy with nivolumab and ipilimumab causing acute-onset type 1 diabetes mellitus following a single administration: two case reports. *BMC Endocr Disord* 19 (1), 144.
- Zhou, X.H., Qiao, Q., et al., 2010. Diabetes, prediabetes and cancer mortality. *Diabetologia* 53 (9), 1867–1876.

Nicola Silvestris is an Associate Professor of Medical Oncology at the University of Bari (Italy). He lends his teaching, research and assistance activities at the Department of Internal Medicine and Medical Oncology (DIMO) of the Faculty of Medicine of Bari and at the Cancer Institute “Giovanni Paolo II” of Bari. He was a Scientific Director of the Cancer Center of Bari until June 2019. He is a National Councilor of the Italian Association of Medical Oncology (AIOM). He is an author of over 210 publications in scientific journals with an impact factor. Over the past 15 years he has dedicated a large part of his research and assistance to patients suffering from gastrointestinal malignancies, with particular regard to hepato-biliary-pancreatic tumors. He has also been a speaker at over 300 national and international conferences.

Antonella Argentiero is a medical consultant as clinical oncologist with permanent position as attendant physician at the IRCCS, Istituto Tumori “Giovanni Paolo II” of Bari, Italy. She graduated in medicine and surgery in 2011 and completed her post-graduate residency program in medical oncology at School of Medicine of the University of Bari “Aldo Moro” with Magna cum Laude in 2017. She has been performing routine clinical and medical activities in the area of internal medicine and oncology as interdepartmental shifts and duties. Her main interests of research are represented by medical oncology, with particular focus on the immune-oncology and gastrointestinal cancer. In 2014, she has collaborated in preclinical research at Sbarro Health Research Organization, College of Science and Technology, Temple University of Philadelphia. Since that year, she is an associate member of Italian Association of Medical Oncology (AIOM) as well.

Giordano Domenico Beretta, Graduated in Medicine at Milan University in 1983 with 110/110 and laude. Specialized in Medical Oncology in the same University in 1986 with 70/70 and laude. From December 1980 to March 1983 he attended Medical Oncology Unit of San Carlo Hospital in Milan as student and medical resident. For three years (1986–1988) he had a grant by AIRC (Italian Association in Cancer Research) for a research regarding tumor marker’s study. He worked in Internal Medical Division of Bassini Hospital in Cinisello Balsamo (Milan) from March 1989 to September 1997 (where he was responsible of Oncology Section from May 1990). He was responsible for Oncology Section in Medical Division in Sesto San Giovanni Hospital (Milan) from September 1997 to December 1997. He worked as deputy director in Oncology Unit of Ospedali Riuniti in Bergamo from January 1998 until April 2006, where he was coordinator of GLOG (Gastrointestinal Interdisciplinary Oncology Group) and he was director of Oncology Gastrointestinal Unit since January 2003 until April 2006 in the same hospital. He was Director of Medical Oncology Unit of Sant’Orsola-Fatebenefratelli Hospital in Brescia since May 2006 until April 2010. He was Director of Medical Oncology Unit and Internal Medicine Unit of Humanitas Gavazzeni in Bergamo from May 2010 to April 2018. Now, he is Director of Medical Oncology Unit from April 2018. He is AIOM member from 1985 and Regional Coordinator of Lombardy AIOM section from 2009 to 2013. He was member of AIOM of National Committee from 2013 to 2015 and he was National Secretary of AIOM from 2015 now 2017 and now he is AIOM President. He is member of ESMO since October 1991 and in November 1996 he obtained European Certification of Medical Oncology in Vienna. He is member of ASCO since January 2000. He is author or co-author

of more than 200 publications.

Monica Montagnani Associate Professor of Pharmacology at the Department of Biomedical Sciences and Human Oncology, University of Bari, Medical School. Research interests are focused on diabetes, insulin resistance and vascular complication, cellular and molecular signaling of endocrine mediators in endothelium. Member of Pharmacology and Hypertension Scientific Societies (SIF, SIIA) and editorial board member in scientific Journals. Invited speaker and chairman at National and International congresses; co-author of over 70 scientific publications indexed in PubMed and Scopus (h-index 28, more than 5700 citations).

Romano Danesi is Professor of Pharmacology at the University of Pisa, Italy. He received board certification in Respiratory diseases, Clinical Pharmacology and Oncology from the University of Pisa, Italy. His current research interests are in the field of cancer pharmacogenetics and since 2002 is independent reviewer for the European Commission and many other funding organizations including Academy of Finland, Norwegian Research Council and UK MRC.

Pietro Ferrari is full-time Director of the Palliative Care Unit and Home Care Service at IRCCS Istituti Clinici Scientifici Maugeri Pavia, Italy. Dr Ferrari was born in Pavia on January, 21th 1970. After graduating from medical school at the University of Pavia in 1996, he was board certified in Internal Medicine in 2003. His clinical and research experience include the palliative treatment of advanced oncological and non-oncological diseases with particular attention to their relation to diabetes and other metabolic consequences.

Stella D'Oronzo graduated with honors as a Medical Doctor in 2011 at the University of Bari (Italy) and gained the national certification to the Medical Practice in 2012. At the same University, Dr D'Oronzo completed her post-graduate residency program in Medical Oncology in 2017 and earned a PhD degree in "Biomolecular, Pharmaceutical and Medical Sciences". During her PhD course, Dr D'Oronzo spent about two years at the University of Sheffield (UK) as a Visiting Research Fellow in the "Department of Oncology and Metabolism". In 2018 she gained the "Cancer and Bone Society Young Investigator Award" for her research on osteotropic malignancies, especially focused on mechanisms of breast cancer homing towards bone, identification of predictive/prognostic biomarkers in bone metastatic breast cancer and investigation of cancer-treatment related complications. Since 2019 Dr D'Oronzo is an Assistant Professor in Medical Oncology at the University of Bari.

Antonio Russo is an Associate Professor of Medical Oncology at the University of Palermo (Italy). He is head of the Medical Oncology Unit and of the Reference Center of Rare and Heredo-familial Solid Tumors, Palermo (Italy). In addition, he is Coordinator of the PhD in Oncology at the University of Palermo and Adjunct Full Professor at Temple University's, Philadelphia (USA). He is a medical oncologist and he focuses on translational oncology, hereditary, rare, lung, gastrointestinal and ovarian cancers. Previously he was Director of the Specialization School in Medical Oncology, University of Palermo. He was co-chair of the "CRCP53 International Collaborative Study" project and also member of the international RASCAL II project group. He is an active member of the main scientific oncological groups as ASCO, ESMO, ISBL and AIOM, of which he is a member of the national board of councillors. He was an expert member of INSERM (France), of the Scientific Committee INCA (France) and of the NWCRF (UK). Recently, he has been the recipient of numerous professional accolades, including a Visiting Professor and an Honorary Professor membership for the Peruvian Ricardo Palma University. In 2019 he also received the prestigious NIAF Award for Ethics and creativity in Medical research in Washington (USA). He is the author of more than 300 peer-reviewed publications listed on Medline-PubMed including Journal of Clinical Oncology, Lancet, Annals of Oncology, Oncoimmunology, Lancet Oncology, Oncologist, Cell Stem Cell. He is Editor-in-Chief of several academic textbooks in oncology for Springer Nature.

Silvia Acquati is full-time MD at the Endocrinology Unit of the Hospital Morgagni in Forlì, AUSL Romagna, Italy. She graduated in medicine and surgery in 1999 at the University of Milan and specialized in Endocrinology and Metabolic Diseases in 2004 at the University of Ferrara. She has been performing routine clinical and medical activities in the area of diabetes and diabetic foot. Her clinical and research experience include type 1 and type 2 diabetes, use of technologies in patients affected by diabetes, gestational diabetes and diabetic foot.

Marco Gallo is full-time Assistant Medical Director/Endocrinologist at the Oncological Endocrinology Unit of the University Hospital "Città della Salute e della Scienza di Torino - Molinette", Turin, Italy. Dr Gallo's research interest include diabetes, diabetes and cancer, hormones and cancer, and endocrine cancers. He is author of more than 120 peer-reviewed articles (48 indexed in PubMed) in journals including American Journal of Medicine, British Journal of Cancer, Cancer, Diabetes Care, Endocrine Related Cancer, Lancet Diabetes & Endocrinology, Metabolism, and Thyroid. He is reviewer for several international scientific journals.