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Perspectives on the role of "-Omics" in predicting response to immunotherapy

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ABSTRACT

The annual Immuno-Oncology "Think Tank" held in October 2023 in Siena reviewed the rapidly evolving systems-biological approaches which are now providing a deeper understanding of tumor and tumor microenvironment heterogeneity. Based on this understanding opportunities for novel therapies may be identified to overcome resistance to immunotherapy. There is increasing evidence that malignant disease processes are not limited to purely intracellular or genetic events but constitute a dynamic interaction between the host and disease. Tumor responses are influenced by many host tissue determinants across different cellular compartments, which can now be investigated by high-throughput molecular profiling technologies, often labelled with a suffix "-omics". "Omics" together with ever increasing computational power, fast developments in machine learning, and high-resolution detection tools offer an unrivalled opportunity to connect high-dimensional data and create a holistic view of disease processes in cancer. This review describes advances in several state-of-the-art "-omics" approaches with perspectives on how these can be applied to the clinical development of new immunotherapeutic strategies and ultimately adopted in clinical practice.

1. Introduction

In 2023, the Siena Think Tank reviewed the achievements of systems biology approaches in cancer and immunotherapy [1]. Like the previous Think Tank meetings [2–5], the members discussed ways to leverage the expanding "Omics-based" technologies for future immunotherapies in cancer. Omics-based biology is the continuation of research conducted by the Italian anatomists Malpighi [6] and Morgagni [7], who in the 17th century regarded organs, tissues and later cells, as the origin of disease [8]. Building on these concepts, Paul Ehrlich developed the

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theory of tailored therapies [9]. Thus, the evaluation of tumor tissue and blood samples remain the key compartments to determine responses to therapy in malignancies. Disease processes are no longer seen as limited to cellular or genetic events, but rather as a continuous interaction between host and disease, leading to the concept of systems biology, which is often labelled with a suffix "-omics" [10]. The availability of ever-increasing computational power, high resolution detection tools, novel mathematical methods and the ability to integrate high-dimensional data have led to an unprecedented ability to create a holistic view of disease processes.

Today, tumor tissues are recognized to consist of different cellular compartments, and depending on the tumor type, the composition and response of the tumor is influenced by important host tissue determinants [11]. Each tumor type differs in the composition of tumor cells, vessels with pericytes, nerves, extracellular matrix (ECM), cancer-associated fibroblasts (CAFs), immune cells (e.g., T, B, NK and myeloid cells) and tertiary lymphoid structures (TLS) [11]. For example, cutaneous melanoma appears to be enriched in immune cells, while pancreatic ductal adenocarcinoma (PDAC) is high in ECM deposition. The composition of the tumor microenvironment (TME) is currently being studied not only for each tumor type, but also for each patient. These host determinants are thought to determine the response to immunotherapy and therefore are targeted by various therapeutic interventions to overcome resistance to immunotherapy. For instance, immune-inflamed tumors are more likely to respond to immunotherapy [12], while fibrotic tumors are less likely to respond and are associated with a poor patient outcome [13]. Recognizing the composition of the TME has led to the development of new therapies to overcome resistance in malignancies [2,14]. During the 2023 Think Tank members reviewed the "-Omics"-based approaches and their utility to better understand tumor progression, detection and potential opportunities for the development and evaluation of novel therapies.

2. The site of metastases indicates important differences in host defenses to tumor progression

Although most malignancies share the ability to metastasize, they do differ by which organ is initially affected and how it influences the overall survival (OS). For example, patients with prostate cancer and metastatic liver disease have a lower OS compared to patients with metastases to other organs [15]. Similar observations are observed for patients with colorectal cancer (CRC) [16,17], non-small cell lung cancer (NSCLC) [18,19] and cutaneous melanoma [20] (Table 1). Patients with liver metastases appear to have a particular poor prognosis, including patients receiving immunotherapy [21]. In CRC, immunotherapy was mostly active in patients with no liver metastases [22]. Underlying specific driver-mutations may render CRC tumors particularly resistant to immunotherapy, perhaps because some of these mutations induce immune suppressive conditions, including in the liver [23]. In fact, patients with liver metastases were found to have reduced peripheral T cell numbers, diminished tumoral T cell diversity and function [24]. Recently a similar observation was reported for NSCLC patients with liver metastases, where a low frequency of $CD8^+$ T cells in the liver and a reduced effector function was observed [25]. These observations have led to exclude patients with liver metastases from clinical trials, regardless of their status on microsatellite stability or other genomic features [26]. Taken together liver appears to be an organ with an immune suppressive microenvironment [27]. Thus, studying the immune suppressive environment in organs like the liver may help to identify factors of immune resistance.

Table 1
Metastases location and overall survival.

Tumor Type	Overall Survival (months) Related to Affected Organs				
	Lymph Node	Bone	Lung	Liver	Reference
Prostate Cancer	31.6	21.3	19.4	13.5	[15]
Colorectal Cancer	ND	5.5	14	9	[16]
Lung Cancer	ND	5	6	4	[18]
Cutaneous Melanoma	13.6	4.8	9.6	3.9	[20]

Based on the observation that organ-associated metastases may have a significant impact on OS, systemic therapies may need to be adapted to overcome resistance mechanisms associated with such metastatic conditions. For example, patients with cutaneous melanoma and brain metastases have improved OS if their immunotherapy is combined with epigenetic modulators [2]. Thus, it is hypothesized that for patients with liver metastases specific inhibitors targeting liver-resident macrophages may remove the immune suppression which prevents immune checkpoint therapies (ICTs) to be effective [28].

3. Radiomics to unlock available data contained in imaging data

Delayed immunotherapy responses have been observed and reported as pseudo-progression. Furthermore, in patients with large tumor burden and metastatic spread, spatial heterogeneity has not yet been sufficiently addressed in current response assessments. With the growing computational power, imaging scans can be analyzed at a greater detail. All tumor lesions can be quantified by size, shape and texture. Some lesions may also contain different metabolically active parts which at baseline appear as merged and subsequently separate after treatment. These changes can be linked to disease and therapeutic outcomes and this forms the basis for radiomic approaches.

Recent examples show that a radiomic approach can predict the outcome of therapy. In a retrospective study of 211 patients with NSCLC who received neoadjuvant chemoimmunotherapy, a radiomic model predicted responses at a similar rate as RECIST [29]. In another retrospective study across multicenter clinical trials (nivolumab, $n = 92$, CheckMate017, CheckMate063; docetaxel, $n = 50$, CheckMate017; gefitinib, $n = 46$]) radiomic signatures and changes predicted tumor sensitivity to treatment in patients with NSCLC [30]. In hepatocellular carcinoma (HCC), quantification of tumor heterogeneity, spatial distribution and relationships of grey levels in medical images was used to predict responses and outcomes [31,32]. In one study the support vector machine (SVM) model was able to differentiate high from low grade HCC [32]. In another study, CT-based texture analyses (CTTA) was significantly correlated with higher tumor grade and disease free survival (DFS) after surgical resection [33].

Based on the success of using radiomics in patients with complex tumor burden, the continued effort to extract additional data from imaging studies (e.g., CT and MRI) may improve response assessments not only in clinical trials, but also in everyday clinical practice. Promising are combinations of radiomic data with other high dimensional datasets (e.g., clinical prognostic data, genomics, transcriptomics) to enhance the predictiveness of radiomics. One such example has been shown to improve prediction of immunotherapy responses in patients with lung cancer [34].

4. "Omics" approaches to characterize immune cells in the tissue microenvironment (TME) of tumors

The tumor microenvironment (TME) is increasingly recognized as an essential player in regulating cancer progression and determining therapeutic outcome [35]. Multiple studies have demonstrated that the composition of the TME is associated with patient prognosis and therapeutic efficacy across several cancer types [36]. Single-cell Omics approaches, and in particular single-cell RNA sequencing (scRNA-seq), offer an unprecedented level of resolution to characterize TME cell populations and explore associated clinical characteristics and endpoints. An essential step towards characterizing the composition of scRNA-seq datasets is cell type annotation – a process that is often a combination of automated tools and manual annotation through clustering and differential expression of marker genes [37]. For broad TME

cell type annotation (e.g., identification of B cells, T cells or myeloid cells), automated tools based on gene signatures have proven to be useful [38,39]. However, at higher levels of resolution (e.g., for the classification of T cell subtypes) several factors can confound cell type annotation. These factors include transient gene expression, different stages of differentiation and cycling phases, as well as technical batch effects. Consequently, high-resolution cell type annotation is often performed manually, resulting in a time-consuming and subjective process. As the understanding of tumor immunology is increasing, so is the need to standardize the descriptions of each cellular subtype. Lack of standardization has led to inconsistent and confusing cell type annotations across studies. This is exemplified by the T cell field, where cell types such as "exhausted", "dysfunctional", "activated", "transitional" and multiple flavors of "memory" subtypes are reported across studies, with no clear mapping across the different reports [40–43]. Such lack of standardization and overreliance on subjective manual annotation stands in the way of recognizing general patterns across studies and tumor types.

A promising approach towards the standardization of cell type annotation is the generation of robust, multi-study reference maps. Single-cell reference maps allow interpreting new datasets in the context of a curated and stable reference and enable large-scale meta-analyses within a controlled vocabulary of high-resolution cell types [44,45]. For example, T cell subtype composition can be evaluated for multiple samples against the same reference and linked to relevant clinical variables such as ICT response. In the future, single-cell reference maps can be used to define "TME types" or " immune archetypes" [46] and to stratify patients for future therapies. It is possible that "TME types" are conserved across tumor types, which may point towards common therapeutic approaches. Patterns of "TME types" may also lead to the development of diagnostic assays. To facilitate such "TME type"-based assays, blood-based biopsies may offer operationally attractive testing platforms if they are representative or predictive of the tumor TME.

5. Digital spatial profiling (DSP) approaches

Gene signatures (e.g., interferon-gamma signature) [47] may offer a more accurate prediction of immunotherapy response compared to standard PD-L1 immunohistochemistry (IHC). However, using two markers in multiplex immunofluorescence (mIF) appears to significantly enhance predictive power for checkpoint blockade responses [48]. A preliminary report suggests that this test can be reliably performed across five different sites with good reproducibility, potentially serving as a clinically applicable tool to determine which patients should receive standard-of-care (SOC) checkpoint inhibitors versus those who should be enrolled in clinical trials [49,50]. Additionally, early data indicate that higher-order mIF may provide deeper insights into a patient's immune status, further supporting the development of advanced profiling techniques [51]. Thus, digital spatial profiling (DSP) was developed to contextualize the content of immune cells in relation to the stroma [52]. Since DSP integrates different data points, complex optical and mathematical methods were developed and tested [53]. Currently, DSP includes multiplex spatial profiling of RNA and proteins on formalin-fixed, paraffin-embedded (FFPE) samples. The application includes the validations of the following reagents and steps: (1) oligonucleotide tags for RNA and/or multiplexed proteins; (2) oligonucleotide tags attached to affinity reagents (antibodies or RNA probes) through a photocleavable (PC) linker; and (3) photocleaving light projected onto the tissue sample to release PC oligonucleotides in any spatial pattern across a region of interest (ROI) covering 1 to ~5000 cells. The development of such reagents is expanding beyond the initial 44 proteins and 96 genes (928 RNA probes) in CRC, lymphoid and other tumors [54].

Identifying the chemokine-like factor (CKLF)-like MARVEL transmembrane domain containing 6 (CMTM6) as a novel predictive biomarker of response to immunotherapy is one example of how DSP can be used to discover novel predictive markers [55]. CMTM6 expression in cutaneous melanoma was positively correlated with protein and mRNA expression of PD-L1, CD3, CD20, and CD68 markers. CMTM6 protein was also associated with longer survival after immunotherapy when measured in the stroma ($P = .007$) and other immune compartments tested (T cells, B cells and macrophages).

Using DSP, CD44 expression in the tumor and not in the immune compartment (panCK$^-$/CD45$^+$) was found to be associated with clinical benefit including extended progression-free survival (PFS) [56]. The effect of tumor cell CD44 expression in predicting PFS was detected independently of other markers, including PD-L1 expression. Intra-tumoral regions with elevated tumor cell CD44 expression showed prominent upregulation of PD-L1, TIM-3, ICOS, and CD40.

In addition to these discoveries for potential predictive assays of immunotherapy, DSP can also uncover novel resistance mechanisms. For example, in PDAC the DSP has found 14 malignant and 4 CAF-associated signaling programs [57]. In this work, a newly identified neural-like progenitor malignant cell program was enriched after chemotherapy and radiotherapy. This novel signaling program was associated with a poor patient prognosis.

Future research may focus on resolving potential discrepancies between RNA and protein expression. To enrich current analyses, the addition and integration of novel platforms such as proteogenomics may lead to greater understanding of the TME. The sole presence of proteins or gene expression may need to be supplemented by molecular analysis, such as T cell receptor (TCR) sequencing. Finally, to cover all aspects related to the hallmarks of cancer, suitable reagents are needed and must be added to the existing portfolio of markers. Thus, the biomarker discovery in drug development and feedback of results to clinical trials will lead to novel target identification in drug development.

6. Cancer antigens targeted for therapeutic effects: an evolving story

The specific cancer antigens that lead to a successful therapeutic effect are still unknown. However, mutations in proteins that generate neoantigens - especially those in oncogenic drivers - have been recognized as promising targets for a destructive immune response [58]. Today, popular thinking often attributes complete responses to T cell immune checkpoint blockade and/or TIL therapy to the recognition of mutation-derived neoantigens. However, early studies also found a significant correlation between objective clinical responses and the presence of T cells targeting tumor-associated antigens (TAAs) [59]. More recent research has revealed that neoantigen-specific T cells constitute only a small subset of the total T cell repertoire within tumors and in many patients who achieve complete remission, neoantigen-specific T cells do not dominate the immune response [60]. Instead, most circulating T cells present during and after remission recognize not only the patient's own tumor but also other HLA-matched melanoma tumor lines, suggesting that long-term tumor control may be sustained by T cells targeting shared antigens.

Shared tumor antigens include TAAs, cancer-testis antigens (CTAs), and viral antigens, but an NCI panel also recognized additional antigens encoded by genes overexpressed in cancer cells as promising therapeutic targets [58]. Recently, a novel class of non-canonical cancer antigens derived from so-called "junk" DNA, also referred to as the Dark Genome, has been identified in the HLA-presented peptidome [61–63]. Some of these non-canonical antigens are linked to malignant properties and appear to be shared within, and occasionally across, different cancer types. A notable early study described HLA-presented non-canonical peptides in acute myeloid leukemia (AML), many of which were associated with epigenetic changes and intron retention [64]. Remarkably, a panel of 58 peptides was identified that could potentially confer immunity against 95 % of AML cases, raising the possibility of a universal AML vaccine [65]. Further findings suggest that elements of the Dark Genome associated with malignant potential may be broadly shared across different cancers, offering new therapeutic possibilities. One

study, for example, identified two T cell receptors (TCRs) targeting epitopes shared among multiple gastric, ovarian, and melanoma cell lines [63]. While further research is needed to assess the expression of these targets in normal tissues, these findings represent a potential breakthrough in cancer immunotherapy.

A question is why non-canonical antigens from the dark genome were not discovered earlier? One reason these antigens were not identified earlier is that most Dark Genome-derived elements give rise to short-lived proteins (SLiPs), which are epigenetically regulated, mediate malignant functions, and have intracellular half-lives of less than 10 min. While rapidly degraded, these proteins are stabilized in class I molecules on the cancer cell surface. Their short intracellular half-life limits their availability for cross-presentation when tumor cells die preventing TILs, or T cells from immunized mice, from being primed to these SLiPs [66]. Achieving immunity against these epitopes appears to require in vitro priming or vaccination with dark matter antigens. With a novel method to capture cancer's short-lived proteins for vaccine development, the first cross-protective vaccine demonstrated therapeutic efficacy against established tumors in murine sarcoma models [67,68]. Building on this work, an "off-the-shelf" clinical vaccine DPV-001 was developed and administered as part of a combination immunotherapy to 18 patients with recurrent metastatic head and neck squamous cell carcinoma (HNSCC) and achieved a response rate three times higher than expected [69]. Mass spectrometry analysis of DPV-001 confirmed the presence of non-canonical proteins from the Dark Genome, along with more than 300 proteins encoded by genes commonly overexpressed in solid tumors. Current studies are evaluating whether patients are responding to dark matter antigens and whether this correlates with response. This understanding will shape the next generation of cancer vaccines and provide insight into the relevance of these targets across different tumor types. Additionally, combining vaccines with immune checkpoint inhibitors is likely to reveal their full therapeutic potential.

7. The role of human leukocyte antigen (HLA) system in tumors

The presence of immune cells in tumor tissues requires a functioning or present HLA system as determined by proteins of the major histocompatibility complex (MHC). Across 33 different tumor types, MHC class I expression significantly varies and is associated with several genomic and immunological features [70]. Immune cell infiltration was generally higher in tumors with higher HLA gene expression and HLA class I losses or downregulation were observed in 93 % of lung cancer, 90 % of cervical cancer and 78 % of CRC [71]. Increased HLA gene expression is associated with a prolonged survival in most cancer types (Table 2). Thus, HLA, neoantigen expression and immune cell infiltration are important factors for studying responses to immunotherapy [72].

Table 2
Examples of cancer types with association of dysfunction of human leukocyte antigen (hla) system and clinical outcome.

Cancer Type	HLA/MHC Component	Clinical Outcome
Bladder	Calreticulin	OS
Breast	HLA-I	DSS
Cervical	HLA-I, LMP7, TAP1, ERAP1	OS, DFS
Colon	HLA-I, Tapasin	OS, DFS
Endometrial	HLA-B/C	OS, PFS
Esophageal	HLA-I, β_2-microglobulin, TAP1	OS
Gastric	Erp57, HLA-II	OS
Hepatocellular Carcinoma (HCC)	HLA-C	OS
Head and Neck Squamous Cell Carcinoma (HNSCC)	HLA-B/C	DFS
Ovarian	HLA-I	PFS
Cutaneous Melanoma	TAP1, TAP2, HLA-B/C	OS, PFS
Non-small cell lung cancer (NSCLC)	HLA-I	OS
Pancreatic ductal adenocarcinoma (PDAC)	HLA-B/C	OS
Prostate	HLA-I	OS
Renal Cell Cancer	HLA-I	OS, RFS

There is growing evidence of several proteins participating in the expression of HLA molecules on the cell surface, which can either alone or in combination contribute to the dysfunction of the HLA antigens [73]. These additional proteins are involved in peptide generation, peptide transport, MHC/HLA class I assembly and antigen presentation. For example, in head and neck squamous cell cancer (HNSCC) the expression of β_2-microglobulin, MHC class I heavy chain and large multifunctional peptidase 10 were downregulated, which was correlated with the patients' outcome [74].

Dysfunction of HLA proteins can be affected by several mechanisms, such as structural alterations, transcriptional regulation, epigenetic modifications, post-transcriptional or translational control. Recognizing the dysfunction of these components has implications for predicting clinical outcome of immunotherapy. Structural alterations of the HLA antigen processing machinery (APM) components are relatively rare events, while changes associated with transcriptional regulation are frequent and likely to be reversed by IFN. Epigenetic modifications may also be treated with effective demethylation agents.

It appears that the increased understanding of the HLA system is on the verge of making HLA class I APM a tool for therapy decisions and patient stratification. This implies that therapeutic strategies are needed to enhance HLA class I surface expression. Given the geographic and ethnic distribution of the HLA system, clinical trials may also need to consider the geographical and ethnic background of patients. This may influence the identification of novel regulators of HLA class I APM molecules and thus require HLA class I as a marker for current and future immunotherapy.

8. Epigenetic immune-modulation in the clinic

Mechanisms of epigenetic modulation include up-regulation or induction of TAA, upregulation of APM components and/or co-stimulatory molecules, up-regulation of the IFN pathway and induction of cytotoxic T cells [75], but also an upregulation of immune inhibitory molecules such as PD-L1 and HLA-G. Therapeutic interventions can reveal the role of epigenetics in malignancies. For example the treatment with 5-aza-2′-deoxycytidine is associated with prolonged up-regulation of HLA class I expression [76]. Additional epigenetic modulators were evaluated, such as DNA methyltransferases (guadecitabine), histone deacetylases (givinostat), BET proteins (JQ1 and OTX-015), and enhancer of zeste homolog 2 (GSK126) [77].

During the combination trial of guadecitabine and ipilimumab in unresectable cutaneous melanoma, the tumor immune contexture showed an upregulation of HLA class I on melanoma cells, an increase in $CD8^+$, $PD\text{-}1^+$ T cells and in $CD20^+$ B cells in post-treatment tumor tissues [78]. In the long-term follow-up additional biomarker changes were detected [79]. With progression of treatment at Week 4 and Week 12, an immunoediting index with an adaptive immunity signature stratifies patients/lesions into four distinct subsets and discriminates 5-year overall survival and progression-free survival. Similarly, a Phase 1 study of guadecitabine and pembrolizumab showed a reduction of methylation in tumor tissues and in PBMCs of patients [80]. A study of guadecitabine and pembrolizumab in ovarian cancer patients found that the long-interspersed element 1 (LINE1) was hypomethylated in post-treatment PBMCs, and methylomic and transcriptomic analyses showed activation of antitumor immunity in post-treatment biopsies [81].

Emerging from the current data, epigenetic immunomodulation is a promising strategy in combination with immunotherapy. However, not all epigenetic drugs are equal (e.g., DHA seem to be best in class) and therefore additional research is needed to identify current and future

epigenetic modulators. In clinical development, randomized studies (e.g., NIBIT-ML1) are needed to better characterize the role of epigenetic modulators compared to standard of care immunotherapy. Finally, the characterization of the epigenetic tumor landscape may help in selecting patients for epigenetically-based immunotherapies.

9. Outlook

Without doubt the convergence of informatics and biology has revealed an unprecedented level of information. This will require an interaction between various disciplines and specialists that until recently were adjunct to the field of clinical research. In some areas, artificial intelligence is already being used to help making medical decisions. For immunotherapy to succeed it appears that "-omics"-based approaches will influence future clinical development of novel therapies, either by identifying novel agents or by selecting the most suitable therapy for a patient.

Author contribitions

Anna Maria Di Giacomo has served as a consultant and/or advisor to Incyte, Pierre Fabre, Glaxo Smith Kline, Bristol-Myers Squibb, Merck Sharp Dohme, Sunpharma, Immunocore and Sanofi and has received compensated educational activities from Bristol Myers Squibb, Merck Sharp Dohme, Pierre Fabre and Sanofi. **Sumit K. Subudhi** reports personal fees from Baird Boxer Capital, Breaking Data, Intellisphere LLC, NoeticInsight, and The Clinical Comms Group; non-financial support from AstraZeneca, BMS, and Janssen Oncology; personal fees and non-financial support from Arcus Biosciences, BMS, DAVA Oncology, Dendreon, Hervolution, Johnson & Johnson, Kahr Medical Ltd, Kiniksa Pharmaceuticals, Merck, Novartis, Pfizer, Portage, Regeneron, Rondo Therapeutics, and Society for Immunotherapy of Cancer; and personal fees and ownership interests from Apricity Health. **Wim Vos** holds stock and is CEO at radiomics.bio **Massimo Andreatta** declares no COI **Santiago J. Carmona** declares no COI **Will McTavish** employed by and holds stocks in NanoString **Barbara Seliger** declares no COI **Ramy Ibrahim** is employed at Georgiamune and holds equity **Michael Lahn** holds stock and is employed by iOnctura **Michael Smith** declares no COI **Alexander M.M. Eggermont** has recieved honoraria for Scientific Advisory Boards or IDMC activities for: Agenus, Boehringer Ingelheim, BioInvent, BioNTech, Brenus, CatalYm, Egle, Eurobio, GSK, Imcheck, Immatics, Ipsen, IO Biotech, IQVIA, Merck&Co, MSD, Oncolytics, Pfizer, Pierre Fabre, QBiotics, Regeneron, Replimune, Sairopa BV, ScanCell, Scorpion therapeutics, Secarna, SkylineDX BV, Thermosome GmbH, Trained Immunity TTX Discovery. Stock or Stock Options: IO Biotech, Sairopa BV, SkylineDX BV, Oncolytics **Bernard A. Fox** has received honoraria for Scientific Advisory Boards for: Abalytics (stock), Calidi, Hookipa, Merck, Pfizer, Primevax (stock), Turnstone (stock). Research support: Akoya, Bristol-Myers Squibb, Hamamatsu, Incyte, Lunaphore, Merck, Navinci, Shimadzu, Ultivue. Board of Directors, Founder, CEO: UbiVac (Stock) **Michele Maio** has served as a consultant and/or advisor to Roche, Bristol-Myers Squibb, Merck Sharp Dohme, Incyte, AstraZeneca, Amgen, Pierre Fabre, Eli Lilly, Glaxo Smith Kline, Sciclone, Sanofi, Alfasigma, Merck Serono and own shares in Epigen Therapeutics srl.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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