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Sadal Refae[1], Jocelyn Gal[2], Patrick Brest[3] and Gerard Milano[4,5*].

[1] Centre Antoine Lacassagne, Medical Oncology Department, University Côte d'Azur, Nice, F-06189, France
[2] Centre Antoine Lacassagne, Epidemiology and Biostatistics Department, University Côte d'Azur, Nice, F-06189, France
[3] Centre Antoine Lacassagne, Cnrs, Inserm, Ircan, FHU-Oncoage, University Côte d'Azur, Nice, F-06189, France
[4] Centre Antoine Lacassagne, Oncopharmacology Unit, University Côte d'Azur, Nice, F-06189, France

Corresponding author*: Gerard Milano, Ph.D.
Oncopharmacology Unit
Centre Antoine Lacassagne
University of Cote d'Azur
33, avenue de Valombrose
06189 NICE CEDEX - FRANCE
Tel: 0033.492.031.553
gerard.milano@nice.unicancer.fr

Abstract

Clinical response to checkpoint inhibitors-based (CPIs) therapies can vary among tumor types and between patients. This led to a significant amount of pre-clinical and clinical research into biomarker identification. Biomarkers have been found to cover both the tumor itself and the tumor microenvironment. Entering host-related parameters into the equation should provide a valuable strategy for identifying not only factors predictive of treatment efficacy but also of treatment-related toxicity. It is clear that germline variants can offer efficient and easily-assessable indicators (blood DNA) to enlarge the spectrum of predictive markers for CPI-based treatment. A major issue concerns the real functional significance of the reported single-nucleotide polymorphisms (SNPs) linked to CPI-treatment outcome. Powered calculations should lead to an optimal trade-off between sample size and allele frequency. New molecular technologies and new analytical methods should provide opportunities to bridge the knowledge gap between SNP-CPI treatment associations and the functional impact of these SNPs.

Key words: Immunotherapy, Check-point inhibitors, predictive factors, germinal immunogenetics

1. Immunotherapy-predictive factors-current status in brief

Immunotherapy using the so-called checkpoint inhibitors (CPI) has now reached a high level of clinical evidence in terms of durable antitumor activity and acceptable safety across a spectrum of solid and hematologic malignancies (Ribas and Wolchok 2018; Sharma and Allison 2015). The fact that clinical response to CPI-based therapies can vary among tumor types and between patients has given rise to considerable pre-clinical and clinical research into biomarker identification that may allow greater accuracy in predicting response and resistance to treatment, as recently reported in the excellent review article by Havel and colleagues (Havel, Chowell, and Chan 2019). These biomarkers have been found to cover both the tumor itself and the tumor microenvironment. Expression of PD-L1 has been reported to be predictive of response to CPI targeting PD-1 in several cancers (Ansell et al. 2015; Garon et al. 2015; Havel, Chowell, and Chan 2019; Reck et al. 2016). As T cells recognize immunogenic antigens, it has been shown that tumor antigenicity, such as tumor mutational burden (TMB) or neoantigen load, could be associated with response to CPI (Cristescu et al. 2018; Rizvi et al. 2015). Linked or not to TMB, tumor microsatellite status has been identified as a predictor of CPI antitumor efficacy with a link between the presence of microsatellite instability and enhanced response rate (Le et al. 2015). Interestingly, and logically, a multifactorial approach combining these biomarkers was recently reported (Ott et al. 2019). The biomarker profile covered both the tumor microenvironment and the tumor characteristics including a T-cell-inflamed gene expression profile (GEP), PD-L1 expression and TMB. However, the study was undertaken retrospectively (Keynote – 028 clinical trial) and covered multiple tumor types. It was shown that high levels of TMB, PD-L1 expression and T-cell-inflamed GEP, assessed separately or in combination, were able to predict clinical response to pembrolizumab. More precisely, the highest likelihood of clinical efficacy conferred by pembrolizumab was found in tumors exhibiting both high TMB and elevated levels of inflammation translated by GEP or PD-L1 (Ott et al. 2019). This study calls for prospective confirmation in order to ensure greater precision regarding the strength of the relationships within individual cancer types. Such a multifactorial approach also ensures its wide clinical scale applicability in daily practice although the elevated intrinsic cost may constitute a significant hurdle in clinical practice.

On the other hand, predictive markers are very scarce and even absent as regards side-effects associated with CPI treatment practice. Although toxicity related to CPI use is relatively rare and reversible, its severity is nevertheless challenging, with an approximate 1% of treatment-related deaths reported in a recent meta-analysis (Wang et al. 2018). This review underscores the risk of death due to complications associated with CPI-based therapy as it is present in adjuvant and maintenance therapy strategies (Antonia et al. 2017; Weber et al. 2017). Globally, patients who died of toxic effects were older and patient sex had no influence on the risk of lethal toxic events. Clearly, more reliable predictors are needed to identify the few patients at high risk of toxic death under CPI treatment. On the other hand, there is compelling evidence that some patients under CPI undergo deterioration of their clinical status as a result of the applied therapy itself. This paradoxical phenomenon, called hyperprogression, has recently been well reviewed by Champiat and coworkers (Champiat et al. 2018). Hyperprogression needs to be acknowledged and patients at risk should be identified to improve the management of CPI-based therapy (Champiat et al. 2018). The review also stressed that, among a panel of biomarkers covering PD-L1 status, TMB and lymphocyte infiltration score, none appeared to be appropriate for the detection of hyperprogressive disease at individual level (Champiat et al. 2018).

There is cumulative evidence that pharmacodynamics reactions (both response and toxicity) to conventional anti-cancer therapy, including chemotherapy and targeted therapy, may be linked to intrinsic genomic characteristics generally referred to as pharmacogenetics (Ciccolini et al. 2015; Hertz and McLeod 2013). To date, as summarized above, most research into predicting the clinical efficacy of CPI treatment has focused on tumor-immune phenotype and somatic genomic features. However and surprisingly enough, it is currently unclear how host germline genetics may affect response to immunotherapy by CPI. Host-related parameters entered into the equation should provide a valuable strategy for the identification not only of factors predictive of treatment efficacy but also of treatment-related toxicity. In addition, the present review article will examine the interactions between host and CPI-based treatment outcome related to age, sex, microbiota and, notably, germline genetics.

2. Predicting CPI treatment outcome through host characteristics

2.1. Main host factors unrelated to germline genetics

There is cumulative evidence supporting the role of the microbiome in the modulation of response to CPI treatment across cancer types (Gopalakrishnan et al. 2018; Havel, Chowell, and Chan 2019). It is clear that insights have recently been gained into the influence of the microbiome on immunity and cancer (Abt et al. 2012). Trials aimed at manipulating the gut microbiome are currently being developed to enhance response to cancer immunotherapy (Gopalakrishnan et al. 2018). However, the usefulness of microbiome profiling in patients treated by CPI remains unclear. A likely major difficulty in this context is the vast complexity of the body-wide human microbiome, particularly outside the gut. Other difficulties in this context are populations in different geographical areas and with differing lifestyles (Pasolli et al. 2019). This problem highlights the need to capture microbial molecular mechanisms that can be causal in microbiome-associated health conditions in general and in CPI-treatment responses in particular.

An interesting meta-analysis has recently reported a possible association between gender and CPI-treatment outcome (Wallis et al. 2019). The study covered 23 randomized clinical trials including 9322 men and 4399 women. In brief, meta-analysis of study-level differences in response to treatment by CPI failed to reveal statistically significant differences between males and females. However, this question regarding the influence, or not, of gender on CPI treatment efficacy remains controversial and open to debate since other authors have drawn the conclusion that there is a significant advantage in favor of males (Conforti et al. 2018). It is possible that differences in treatment outcomes between men and women may result from difficulties in detecting interfering factors such as life-style, comorbidities, and the presence or not of autoimmune diseases (Wallis et al. 2019).

Patient age is a host characteristic which cannot be ignored in the context of immunity in general and regarding clinical efficacy of immunotherapy by CPI in particular. However, little is known about age-related differences in patient response efficacy/toxicity to CPI therapy. An age-related impact in lung cancer patients treated by CPI was investigated in a recent report by King-Kallimanis and coworkers (King-Kallimanis et al. 2018). Examining ten of the most commonly reported adverse events (AE) under immunotherapy, the most frequently reported AE was fatigue,

which was slightly more common in patients aged 70 and older. On the other hand, Casaluce and coworkers, also investigating the use of CPI in lung cancer, demonstrated that the elderly population drew greater benefit from CPI, although with contrasting results according to the type of CPI applied (Casaluce et al. 2018). The interaction between aging and individual immunologic status is complex (Alpert et al. 2019). Nevertheless, it can potentially impact key mechanisms governing the responsiveness of CPI treatment in terms of efficacy and toxicity(Castelo-Branco and Soveral 2014). For instance, Kugel and coworkers recently reported that melanoma tumors from older individuals had higher CD8+: FoxP 3 ratios, thus supporting the increased response rate of elderly patients to anti-PD1 (Kugel et al. 2018). Clearly, a better understanding of changes in the aging immune system and their impact on CPI use would be helpful to improve immunotherapy management in advanced age.

2.2. Factors related to germline genetics

Current knowledge in genomic technologies has shed light on the identification of germline DNA alterations possibly associated with treatment outcome under CPI therapy. This vast area of investigation is providing a favorable context in terms of clinical applicability (research into whole genomic DNA) and compares well with more costly and laborious sequencing on available tumor samples. In this second part of the review, we attempt to gather complementary elements which constitute both the background (mainly links between individual SNPs and autoimmune diseases) and current developments (clinical reports on germinal immunogenetics and CPI therapy) including our own contribution in this field. It should be noted that several of the quoted studies are based on a limited number of patients with several SNPs. Such a methodological context may limit the clinical impact of the report data. The recent recommendations from the PAMM group of the EORTC point on the necessity to apply strict rules as concerns clinical pharmacogenetics (Robert et al. 2014). This includes the studied population with the number of studied cases, the assessment of diagnosis and treatments received. The recommendation also included the analyzed polymorphisms with mentioned to be made to an easy identification in the main databases. The authors also pointed to the applied statistical methods with a clear references to the Bonferroni correction, for instance.

Autoimmune diseases are characterized by inflammation and tissue damage largely attributable to general deregulation of immunity cells (Chen et al. 2018). In

this respect, similar mechanisms of cell immunity deregulation can be the origin of autoimmune diseases and of excessive reactivity conferred by immunotherapy by CPI. Interestingly, single-nucleotide polymorphisms (SNPs) in key immune regulatory genes have been reported to be associated with auto-immune syndromes (Chen et al. 2018; Molineros et al. 2013; Visscher et al. 2017). Auto-immune diseases with variants and gene discovery were recently pointed to as an example of GWAS success (Visscher et al. 2017). It was thus logical to examine possible connections between these individual SNP distributions and immunotherapy treatment outcome. Several recent reports have pinpointed such links. Regarding response to treatment, a study by Lima and coworkers (Lima et al. 2015) examined in 204 patients the role of functional polymorphisms in immune response genes as potential biomarkers of BCG therapy in bladder cancer. Their approach merged an initial evaluation of separate genetic variants and subsequent assessment of their combinations (Lima et al. 2015). The focus was placed on 42 functional SNPs in 38 genes of molecules potentially implicated in BCG immunotherapy mechanisms of action. They found that several SNPs in cytokines, chemokines genes and their receptors carried a risk of recurrence after BCG treatment. Interestingly, the authors included SNP-related data in a global predictive approach and established a predictive score of BCG immunotherapy outcome combining clinicopathological characteristics and a range of genetic polymorphisms. Focusing on CPI treatment helps reveal this type of relationship between SNPs-treatment-related effects in terms of both response to treatment and toxicity. There is evidence showing a connection between the efficacy of monoclonal antibody therapy and polymorphisms of their target itself, as recently shown for CD52 (2 SNPs) and alemtuzimab in a group of 108 kidney graft recipients (Oko et al. 2009). Considering more broadly the field of therapeutic monoclonal antibodies and regarding herceptin and HER2 in breast cancer, our group has previously reported on the Ile655Val genetic polymorphism for the risk of developing trastuzumab-related cardiotoxicity in a group 61 patients (Beauclair et al. 2007). Also, in a group of 52 colorectal cancer patients treated by cetuximab-irinotecan, we previously demonstrated that the maximum toxicity grade was linked to the EGFR-191C>A polymorphism (Etienne-Grimaldi et al. 2012). In this context of target polymorphisms and as concerns CPI, Nomizo and coworkers suggested the hypothesis that germline PD-1/PD-L1 SNPs might be potential predictive markers for response to nivolumab in advanced non-small-cell lung cancer (NSCLC) patients

(Nomizo et al. 2017). In this study, five PD-L1 SNPs and two PD-1 SNPs were genotyped in 50 NSCLC patients under nivolumab. The G-allele for PD-L1 *rs2282055* and the C-allele of PD-L1 *rs4143815* were found to be associated with improved clinical response (Nomizo et al. 2017). On the other hand, other authors based on 152 advanced melanoma patients and 7 SNPs, have shown CTLA4 gene polymorphisms to be associated with anti-CTLA4 therapy (Breunis et al. 2008).

HLA class I and class II molecules play a central role in controlling the specificity of antigen presentation (Havel, Chowell, and Chan 2019; Kelly and Trowsdale 2019). The fact that some immune-mediated adverse events under CPI are related to characteristics of well-defined autoimmune diseases linked to HLA risk alleles (Jin et al. 2019; Paternoster et al. 2015) has logically led investigators to explore whether HLA gene polymorphisms might be associated with CPI-related toxicity (Chowell et al. 2018; Hasan Ali et al. 2019). Hassan Ali and coworkers performed HLA haplotyping with complete HLA class I and class II sequencing in a group of 102 patients under CPI (Hasan Ali et al. 2019). They found a significant association between HLA-DRB1*11:01 and pruritus, while a significant association was demonstrated between HLA-DQB1* 03:01 and colitis. However, this study was built on a mix of cancer locations (NSCLC and melanoma) receiving heterogeneous treatments (anti-CTLA4 alone, anti-PD1 alone, a combination of both). This may limit the impact of the findings and requires confirmation studies on larger and clearly-defined groups of patients taking into account treatment and cancer-type. HLA genotype was also recently investigated regarding a possible link with response to CPI-based treatment (Chowell et al. 2018). In this study, the authors effectively characterized the sets of patients according to the type of CPI and tumor location. In brief, the study covered a group of 1535 advanced patients on whom HAL-I genotyping was performed. In two independent melanoma cohorts, patients with the HLA-B44 supertype had extended survival. In contrast, the HLA-B62 genotype was associated with poor outcome. While these reported data may have potential implications for predicting response to CPI, the genetic complexity of the HLA system is such that an easy and generalizable germinal genetic-based tool is difficult to design on the currently available data.

2.3. Personal implication

We recently applied a global germinal immunogenetic approach in an attempt to predict treatment outcome (toxicity and response) in patients under CPI (Refae et al. 2018; Refae et al. 2019). The setting of potentially relevant SNPs was based on an extensive literature search for genes implicated in immune reaction, immunotherapy response and autoimmune diseases (Figure 1). Candidate SNPs with minor allele frequency of ≥ 5% in Caucasians according to SNPpedia (http://www.snppedia.com) and Ensemble databases (http://Ensemble.org) were selected. This led to the constitution of a custom panel of 86 genes and 166 associated SNPs. High-throughput genotyping of germinal DNA was performed by MassArray (Agena Bioscience®). In a group of 48 patients with NSCLC (Refae et al. 2018), a composite score of favorable alleles (zero to five) was found to be markedly associated with progression-free-survival. On a larger group of 94 patients (Refae et al. 2019), it was possible to distinguish between an association with response rate conferred by tumor environment-related gene polymorphisms (CCL2, NOS3, IL1RN, IL12B, CXCR3, IL6R) and grade 3-4 adverse event prediction, which was more closely linked to target-related SNPs (UNG, IFNW1, CTLA-4, PD-L1, IFNL4). It is certain that these promising results based on multi-SNP predictive signatures need larger prospective series (in progress) to reveal their full clinical significance and applicability.

3. Advantages and limits

Germinal immunogenetics, as summarized above for the main current applications in the field of CPI-based treatment, has established its potential clinical usefulness. Germinal immunogenetics constitutes an ideal source of additional information in the area of predictive biomarkers for immunotherapy by CPI, which are generally centered on the tumor itself or on its environment. It is clear that germline variants can provide efficient and easily assessable indicators (blood DNA, at any time) in order to enlarge the range. Is germinal immunogenetics to be ranked at the same decisional level as molecular and cellular predictive biomarkers for immunotherapy by CPI? Probably not, and rightly so. The initial go/no go step, as exemplified by RAS mutation testing in colorectal cancer with anti-EGFR treatment, can be translated to biological predictive parameters for CPI-based therapy with PD-L1 expression, mutational load, microsatellite instability and tumor T cell infiltrate. Once a decision to treat is taken, additional information regarding patient characteristics is useful. This

additional information may be supplied by germinal immunogenetics, thus involving several potential risks, i.e. the risk of the patient being a lesser responder and the risk of him/her being predisposed to adverse events. This second step of dose adjustment is based on the individual germinal immunogenetic profile. Clearly, the two steps, with predictive markers on one hand and germinal immunogenetics on the other, may be ideally complementary (Table 1). However, it is important to take into account certain limitations in the ability of germinal polymorphisms to provide accurate predictions in patients receiving CPI-based therapy. These limitations of germinal polymorphism assessment concern not only CPI-based therapy but also the general field of anticancer treatment. For instance, the pharmacogenetics of anticancer agents has largely proven its clinical utility (DPD and fluoropyrimidines, UGT1A1 for irinotecan) (Henricks et al. 2018; Paez et al. 2019). However, this predictive tool suffers from several inherent drawbacks: the small number of cases on which links between pharmacogenetics and pharmacodynamics are generally established and the lack of independent validation on larger cohorts. The recently reported study by Bins and coworkers is an illustration for CPI-based therapy. The authors assessed the association between seven SNPs in four genes and toxicity under CPI (Bins et al. 2018). A multivariate analysis in an exploration cohort revealed that homozygous variant patients for PDCD1 B04C>T ran a lower risk of toxicity. However, in a prospective validation group this link was no longer observed (Bins et al. 2018). Relatively few prospective controlled trials in which the clinical usefulness of gene polymorphisms was firmly established have been published as concerns DPD (Henricks et al. 2018) and UGT1A1 (Paez et al. 2019).

Another important issue concerns the precise functional significance of the reported SNPs linked to treatment outcome. This lack of information may be explained by the complexity of the investigations needed. Generally, only *in silico* simulations using dedicated software are undertaken to shed light on this important issue of the functional impact of reported predictive SNPs. Table 2 illustrates the main free software programs available in this context. These programs generate hypotheses for future experimental investigations in order to test the biological functionality of the alleles of interest. An illustration of this strategy is found in the study by Chen and coworkers (Kugel et al. 2018). The authors identified a variant of IgG1 with a Gly 396–>Arg (hIgG1-G396R), which positively correlated with systemic lupus erythematosus. Interestingly, the authors generated mice carrying the G396R

homozygous genotypes. They were able to show that the variant impacted the phosphorylation of the ITT motif leading to an alteration of tyrosine kinase signaling on antigen binding.

A clear distinction between a true predictive marker and a prognostic factor should also be defined. In this regard, Rendleman and coworkers reported on the link between IL10 *rs3024493* and clinical outcomes in a population sample of 1022 melanoma patients (Rendleman et al. 2015). They found a significant association of this IL10 gene polymorphism with melanoma survival while no mention of applied CPI-based treatment was made in this study. Thus, there would appear to be a potential risk in concluding that this IL10 gene polymorphism has a predictive value in melanoma patients treated by CPI whereas it only has intrinsic prognostic value independently of an applied therapy. Similarly, Liu and coworkers (Liu et al. 2018) recently reported on the prognostic value of CTLA-4 *rs231775* in patients with renal carcinoma. Patients were treated by antiangiogenic therapy with sunitinib and not by CPI-based treatment. This finding highlights to the need to understand the biological significance of the disclosed alleles in order to establish more clearly their potential link with the drug mechanism of action.

4. Perspectives

It is clear that an understanding of mechanisms underlying the inter-individual variability of immunotherapy sensitivity remains a key challenge for personalized medicine. The identification of reliable immunotherapy biomarkers that provide insights into biological and genetic sources of response variability will be critical to guide personalized-medicine approaches.

The statistical power to establish clinical genetic associations should be revisited, as recently stressed by Vissher and coworkers (Visscher et al. 2017). Carefully-powered calculations should lead to an optimal trade-off between sample size, allele frequency and effect size. A GWAS catalogue from 2008 to 2016 revealed a SNP-trait discovery timeline with an increasing number of SNP-related traits (Welter et al. 2014). New molecular technologies and innovative analytical methods should provide opportunities to bridge the knowledge gap between SNP-CPI treatment associations and the functional impact of these SNPs and the gene level. The design of novel computational methods incorporating machine learning and bioinformatic techniques should make available tools particularly suitable for

predicting immunosensitivity at individual level and for identifying SNP-related biological mechanisms (Oh et al. 2017). The huge power of the emerging CRISPR/cas9-based technologies (Karimian et al. 2019) could offer real opportunities by assisting in the design of appropriate biological models to test the functional impact of the SNPs discovered in germinal immunogenetic studies investigating CPI-based therapy. At this level, a dual approach associating cellular and animal models appears to be particularly relevant to ensure adequate exploration of functional impacts following SNP discovery (Winters, Murray, and Winslow 2018). It must also be borne in mind, in most cases, that the molecular mechanisms by which non-coding genetic variants disrupt gene expression remain unclear. In this respect, it is important to mention the DICE project (database of immune cell expression, expression quantitative trait loci[eQTL] and epigenomics) which is shedding more light on eQTL and the transcriptomic data human immune system (Schmiedel et al. 2018).

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References

Abt, M. C., L. C. Osborne, L. A. Monticelli, T. A. Doering, T. Alenghat, G. F. Sonnenberg, M. A. Paley, M. Antenus, K. L. Williams, J. Erikson, E. J. Wherry, and D. Artis. 2012. 'Commensal bacteria calibrate the activation threshold of innate antiviral immunity', *Immunity*, 37: 158-70.

Alpert, A., Y. Pickman, M. Leipold, Y. Rosenberg-Hasson, X. Ji, R. Gaujoux, H. Rabani, E. Starosvetsky, K. Kveler, S. Schaffert, D. Furman, O. Caspi, U. Rosenschein, P. Khatri, C. L. Dekker, H. T. Maecker, M. M. Davis, and S. S. Shen-Orr. 2019. 'A clinically meaningful metric of immune age derived from high-dimensional longitudinal monitoring', *Nat Med*, 25: 487-95.

Ansell, S. M., A. M. Lesokhin, I. Borrello, A. Halwani, E. C. Scott, M. Gutierrez, S. J. Schuster, M. M. Millenson, D. Cattry, G. J. Freeman, S. J. Rodig, B. Chapuy, A. H. Ligon, L. Zhu, J. F. Grosso, S. Y. Kim, J. M. Timmerman, M. A. Shipp, and P. Armand. 2015. 'PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma', *N Engl J Med*, 372: 311-9.

Antonia, S. J., A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K. H. Lee, M. de Wit, B. C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y. C. Kim, C. S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J. E. Gray, L. Paz-Ares, J. de Castro Carpeno, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P. A. Dennis, M. Ozguroglu, and Pacific Investigators. 2017. 'Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer', *N Engl J Med*, 377: 1919-29.

Beauclair, S., P. Formento, J. L. Fischel, W. Lescaut, R. Largillier, E. Chamorey, P. Hofman, J. M. Ferrero, G. Pages, and G. Milano. 2007. 'Role of the HER2 [Ile655Val] genetic polymorphism in tumorogenesis and in the risk of trastuzumab-related cardiotoxicity', *Ann Oncol*, 18: 1335-41.

Bins, S., E. A. Basak, S. El Bouazzaoui, S. L. W. Koolen, E. Oomen-de Hoop, C. H. van der Leest, A. A. M. van der Veldt, S. Sleijfer, R. Debets, R. H. N. van Schaik, Jgjv Aerts, and R. H. J. Mathijssen. 2018. 'Association between single-nucleotide polymorphisms and adverse events in nivolumab-treated non-small cell lung cancer patients', *Br J Cancer*, 118: 1296-301.

Breunis, W. B., E. Tarazona-Santos, R. Chen, M. Kiley, S. A. Rosenberg, and S. J. Chanock. 2008. 'Influence of cytotoxic T lymphocyte-associated antigen 4 (CTLA4) common polymorphisms on outcome in treatment of melanoma patients with CTLA-4 blockade', *J Immunother*, 31: 586-90.

Casaluce, F., A. Sgambato, P. Maione, A. Spagnuolo, and C. Gridelli. 2018. 'Lung cancer, elderly and immune checkpoint inhibitors', *J Thorac Dis*, 10: S1474-S81.

Castelo-Branco, C., and I. Soveral. 2014. 'The immune system and aging: a review', *Gynecol Endocrinol*, 30: 16-22.

Champiat, S., R. Ferrara, C. Massard, B. Besse, A. Marabelle, J. C. Soria, and C. Ferte. 2018. 'Hyperprogressive disease: recognizing a novel pattern to improve patient management', *Nat Rev Clin Oncol*, 15: 748-62.

Chen, X., X. Sun, W. Yang, B. Yang, X. Zhao, S. Chen, L. He, H. Chen, C. Yang, L. Xiao, Z. Chang, J. Guo, J. He, F. Zhang, F. Zheng, Z. Hu, Z. Yang, J. Lou, W. Zheng, H. Qi, C. Xu, H. Zhang, H. Shan, X. J. Zhou, Q. Wang, Y. Shi, L. Lai, Z. Li, and W. Liu. 2018. 'An autoimmune disease variant of IgG1 modulates B cell activation and differentiation', *Science*, 362: 700-05.

Chowell, D., L. G. T. Morris, C. M. Grigg, J. K. Weber, R. M. Samstein, V. Makarov, F. Kuo, S. M. Kendall, D. Requena, N. Riaz, B. Greenbaum, J. Carroll, E. Garon, D. M. Hyman, A. Zehir, D. Solit, M. Berger, R. Zhou, N. A. Rizvi, and T. A. Chan. 2018. 'Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy', *Science*, 359: 582-87.

Ciccolini, J., R. Fanciullino, C. Serdjebi, and G. Milano. 2015. 'Pharmacogenetics and breast cancer management: current status and perspectives', *Expert Opin Drug Metab Toxicol*, 11: 719-29.

Conforti, F., L. Pala, V. Bagnardi, T. De Pas, M. Martinetti, G. Viale, R. D. Gelber, and A. Goldhirsch. 2018. 'Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis', *Lancet Oncol*, 19: 737-46.

Cristescu, R., R. Mogg, M. Ayers, A. Albright, E. Murphy, J. Yearley, X. Sher, X. Q. Liu, H. Lu, M. Nebozhyn, C. Zhang, J. K. Lunceford, A. Joe, J. Cheng, A. L. Webber, N. Ibrahim, E. R. Plimack, P. A. Ott, T. Y. Seiwert, A. Ribas, T. K. McClanahan, J. E. Tomassini, A. Loboda, and D. Kaufman. 2018. 'Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy', *Science*, 362.

Etienne-Grimaldi, M. C., J. Bennouna, J. L. Formento, J. Y. Douillard, M. Francoual, I. Hennebelle, E. Chatelut, E. Francois, R. Faroux, C. El Hannani, J. H. Jacob, and G. Milano. 2012. 'Multifactorial pharmacogenetic analysis in colorectal cancer patients receiving 5-fluorouracil-based therapy together with cetuximab-irinotecan', *Br J Clin Pharmacol*, 73: 776-85.

Garon, E. B., N. A. Rizvi, R. Hui, N. Leighl, A. S. Balmanoukian, J. P. Eder, A. Patnaik, C. Aggarwal, M. Gubens, L. Horn, E. Carcereny, M. J. Ahn, E. Felip, J. S. Lee, M. D. Hellmann, O. Hamid, J. W. Goldman, J. C. Soria, M. Dolled-Filhart, R. Z. Rutledge, J. Zhang, J. K. Lunceford, R. Rangwala, G. M. Lubiniecki, C. Roach, K. Emancipator, L. Gandhi, and Keynote- Investigators. 2015. 'Pembrolizumab for the treatment of non-small-cell lung cancer', *N Engl J Med*, 372: 2018-28.

Gopalakrishnan, V., B. A. Helmink, C. N. Spencer, A. Reuben, and J. A. Wargo. 2018. 'The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy', *Cancer Cell*, 33: 570-80.

Hasan Ali, O., F. Berner, D. Bomze, M. Fassler, S. Diem, A. Cozzio, M. Jorger, M. Fruh, C. Driessen, T. L. Lenz, and L. Flatz. 2019. 'Human leukocyte antigen variation is associated with adverse events of checkpoint inhibitors', *Eur J Cancer*, 107: 8-14.

Havel, J. J., D. Chowell, and T. A. Chan. 2019. 'The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy', *Nat Rev Cancer*, 19: 133-50.

Henricks, L. M., Catc Lunenburg, F. M. de Man, D. Meulendijks, G. W. J. Frederix, E. Kienhuis, G. J. Creemers, A. Baars, V. O. Dezentje, A. L. T. Imholz, F. J. F. Jeurissen, J. E. A. Portielje, R. L. H. Jansen, P. Hamberg, A. J. Ten Tije, H. J. Droogendijk, M. Koopman, P. Nieboer, M. H. W. van de Poel, Cmpw Mandigers, H. Rosing, J. H. Beijnen, E. V. Werkhoven, A. B. P. van Kuilenburg, R. H. N. van Schaik, R. H. J. Mathijssen, J. J. Swen, H. Gelderblom, A. Cats, H. J. Guchelaar, and J. H. M. Schellens. 2018. 'DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis', *Lancet Oncol*, 19: 1459-67.

Hertz, D. L., and H. L. McLeod. 2013. 'Use of pharmacogenetics for predicting cancer prognosis and treatment exposure, response and toxicity', *J Hum Genet*, 58: 346-52.

Jin, Y., G. H. L. Roberts, T. M. Ferrara, S. Ben, N. van Geel, A. Wolkerstorfer, K. Ezzedine, J. Siebert, C. P. Neff, B. E. Palmer, S. A. Santorico, and R. A. Spritz. 2019. 'Early-onset autoimmune vitiligo associated with an enhancer variant haplotype that upregulates class II HLA expression', *Nat Commun*, 10: 391.

Karimian, A., K. Azizian, H. Parsian, S. Rafieian, V. Shafiei-Irannejad, M. Kheyrollah, M. Yousefi, M. Majidinia, and B. Yousefi. 2019. 'CRISPR/Cas9 technology as a potent molecular tool for gene therapy', *J Cell Physiol*.

Kelly, A., and J. Trowsdale. 2019. 'Genetics of antigen processing and presentation', *Immunogenetics*, 71: 161-70.

King-Kallimanis, B. L., B. Kanapuru, G. M. Blumenthal, M. R. Theoret, and P. G. Kluetz. 2018. 'Age-related differences in patient-reported outcomes in patients with advanced lung cancer receiving anti-PD-1/PD-L1 therapy', *Semin Oncol*, 45: 201-09.

Kugel, C. H., 3rd, S. M. Douglass, M. R. Webster, A. Kaur, Q. Liu, X. Yin, S. A. Weiss, F. Darvishian, R. N. Al-Rohil, A. Ndoye, R. Behera, G. M. Alicea, B. L. Ecker, M. Fane, M. J. Allegrezza, N. Svoronos, V. Kumar, D. Y. Wang, R. Somasundaram, S. Hu-Lieskovan, A. Ozgun, M. Herlyn, J. R. Conejo-Garcia, D. Gabrilovich, E. L. Stone, T. S. Nowicki, J. Sosman, R. Rai, M. S. Carlino, G. V. Long, R. Marais, A. Ribas, Z. Eroglu, M. A. Davies, B. Schilling, D. Schadendorf, W. Xu, R. K. Amaravadi, A. M. Menzies, J. L. McQuade, D. B. Johnson, I. Osman, and A. T. Weeraratna. 2018. 'Age Correlates with Response to Anti-PD1, Reflecting Age-Related Differences in Intratumoral Effector and Regulatory T-Cell Populations', *Clin Cancer Res*, 24: 5347-56.

Le, D. T., J. N. Uram, H. Wang, B. R. Bartlett, H. Kemberling, A. D. Eyring, A. D. Skora, B. S. Luber, N. S. Azad, D. Laheru, B. Biedrzycki, R. C. Donehower, A. Zaheer, G. A. Fisher, T. S. Crocenzi, J. J. Lee, S. M. Duffy, R. M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R. H. Hruban, L. D. Wood, N. Cuka, D. M. Pardoll, N. Papadopoulos, K. W. Kinzler, S. Zhou, T. C. Cornish, J. M. Taube, R. A. Anders, J. R. Eshleman, B. Vogelstein, and L. A. Diaz, Jr. 2015. 'PD-1 Blockade in Tumors with Mismatch-Repair Deficiency', *N Engl J Med*, 372: 2509-20.

Lima, L., D. Oliveira, J. A. Ferreira, A. Tavares, R. Cruz, R. Medeiros, and L. Santos. 2015. 'The role of functional polymorphisms in immune response genes as biomarkers of bacille Calmette-Guerin (BCG) immunotherapy outcome in bladder cancer: establishment of a predictive profile in a Southern Europe population', *BJU Int*, 116: 753-63.

Liu, X., J. J. Swen, M. H. M. Diekstra, E. Boven, D. Castellano, H. Gelderblom, R. H. J. Mathijssen, S. H. Vermeulen, E. Oosterwijk, K. Junker, M. Roessler, K. Alexiusdottir, A. Sverrisdottir, M. T. Radu, V. Ambert, T. Eisen, A. Warren, C. Rodriguez-Antona, J. Garcia-Donas, S. Bohringer, K. K. M. Koudijs, Lalm Kiemeney, B. I. Rini, and H. J. Guchelaar. 2018. 'A Genetic Polymorphism in CTLA-4 Is Associated with Overall Survival in Sunitinib-Treated Patients with Clear Cell Metastatic Renal Cell Carcinoma', *Clin Cancer Res*, 24: 2350-56.

Molineros, J. E., A. K. Maiti, C. Sun, L. L. Looger, S. Han, X. Kim-Howard, S. Glenn, A. Adler, J. A. Kelly, T. B. Niewold, G. S. Gilkeson, E. E. Brown, G. S. Alarcon, J. C. Edberg, M. Petri, R. Ramsey-Goldman, J. D. Reveille, L. M. Vila, B. I.

Freedman, B. P. Tsao, L. A. Criswell, C. O. Jacob, J. H. Moore, T. J. Vyse, C. L. Langefeld, J. M. Guthridge, P. M. Gaffney, K. L. Moser, R. H. Scofield, M. E. Alarcon-Riquelme, Biolupus Network, S. M. Williams, J. T. Merrill, J. A. James, K. M. Kaufman, R. P. Kimberly, J. B. Harley, and S. K. Nath. 2013. 'Admixture mapping in lupus identifies multiple functional variants within IFIH1 associated with apoptosis, inflammation, and autoantibody production', *PLoS Genet*, 9: e1003222.

Nomizo, T., H. Ozasa, T. Tsuji, T. Funazo, Y. Yasuda, H. Yoshida, Y. Yagi, Y. Sakamori, H. Nagai, T. Hirai, and Y. H. Kim. 2017. 'Clinical Impact of Single Nucleotide Polymorphism in PD-L1 on Response to Nivolumab for Advanced Non-Small-Cell Lung Cancer Patients', *Sci Rep*, 7: 45124.

Oh, J. H., S. Kerns, H. Ostrer, S. N. Powell, B. Rosenstein, and J. O. Deasy. 2017. 'Computational methods using genome-wide association studies to predict radiotherapy complications and to identify correlative molecular processes', *Sci Rep*, 7: 43381.

Oko, A., L. S. Wyrwicz, M. Glyda, I. Idasiak-Piechocka, A. Binczak-Kuleta, M. Kaczmarczyk, A. Drozd, A. Ciechanowicz, and S. Czekalski. 2009. 'CD52 gene polymorphism and its potential effect on the response to alemtuzumab in renal transplant recipients', *Ann Acad Med Stetin*, 55: 22-6.

Ott, P. A., Y. J. Bang, S. A. Piha-Paul, A. R. A. Razak, J. Bennouna, J. C. Soria, H. S. Rugo, R. B. Cohen, B. H. O'Neil, J. M. Mehnert, J. Lopez, T. Doi, E. M. J. van Brummelen, R. Cristescu, P. Yang, K. Emancipator, K. Stein, M. Ayers, A. K. Joe, and J. K. Lunceford. 2019. 'T-Cell-Inflamed Gene-Expression Profile, Programmed Death Ligand 1 Expression, and Tumor Mutational Burden Predict Efficacy in Patients Treated With Pembrolizumab Across 20 Cancers: KEYNOTE-028', *J Clin Oncol*, 37: 318-27.

Paez, D., M. Tobena, J. Fernandez-Plana, A. Sebio, A. C. Virgili, L. Cirera, A. Barnadas, P. Riera, I. Sullivan, and J. Salazar. 2019. 'Pharmacogenetic clinical randomised phase II trial to evaluate the efficacy and safety of FOLFIRI with high-dose irinotecan (HD-FOLFIRI) in metastatic colorectal cancer patients according to their UGT1A 1 genotype', *Br J Cancer*, 120: 190-95.

Pasolli, E., F. Asnicar, S. Manara, M. Zolfo, N. Karcher, F. Armanini, F. Beghini, P. Manghi, A. Tett, P. Ghensi, M. C. Collado, B. L. Rice, C. DuLong, X. C. Morgan, C. D. Golden, C. Quince, C. Huttenhower, and N. Segata. 2019. 'Extensive Unexplored Human Microbiome Diversity Revealed by Over 150,000 Genomes from Metagenomes Spanning Age, Geography, and Lifestyle', *Cell*, 176: 649-62 e20.

Paternoster, L., M. Standl, J. Waage, H. Baurecht, M. Hotze, D. P. Strachan, J. A. Curtin, K. Bonnelykke, C. Tian, A. Takahashi, J. Esparza-Gordillo, A. C. Alves, J. P. Thyssen, H. T. den Dekker, M. A. Ferreira, E. Altmaier, P. M. Sleiman, F. L. Xiao, J. R. Gonzalez, I. Marenholz, B. Kalb, M. P. Yanes, C. J. Xu, L. Carstensen, M. M. Groen-Blokhuis, C. Venturini, C. E. Pennell, S. J. Barton, A. M. Levin, I. Curjuric, M. Bustamante, E. Kreiner-Moller, G. A. Lockett, J. Bacelis, S. Bunyavanich, R. A. Myers, A. Matanovic, A. Kumar, J. Y. Tung, T. Hirota, M. Kubo, W. L. McArdle, A. J. Henderson, J. P. Kemp, J. Zheng, G. D. Smith, F. Ruschendorf, A. Bauerfeind, M. A. Lee-Kirsch, A. Arnold, G. Homuth, C. O. Schmidt, E. Mangold, S. Cichon, T. Keil, E. Rodriguez, A. Peters, A. Franke, W. Lieb, N. Novak, R. Folster-Holst, M. Horikoshi, J. Pekkanen, S. Sebert, L. L. Husemoen, N. Grarup, J. C. de Jongste, F.

Rivadeneira, A. Hofman, V. W. Jaddoe, S. G. Pasmans, N. J. Elbert, A. G. Uitterlinden, G. B. Marks, P. J. Thompson, M. C. Matheson, C. F. Robertson, Consortium Australian Asthma Genetics, J. S. Ried, J. Li, X. B. Zuo, X. D. Zheng, X. Y. Yin, L. D. Sun, M. A. McAleer, G. M. O'Regan, C. M. Fahy, L. E. Campbell, M. Macek, M. Kurek, D. Hu, C. Eng, D. S. Postma, B. Feenstra, F. Geller, J. J. Hottenga, C. M. Middeldorp, P. Hysi, V. Bataille, T. Spector, C. M. Tiesler, E. Thiering, B. Pahukasahasram, J. J. Yang, M. Imboden, S. Huntsman, N. Vilor-Tejedor, C. L. Relton, R. Myhre, W. Nystad, A. Custovic, S. T. Weiss, D. A. Meyers, C. Soderhall, E. Melen, C. Ober, B. A. Raby, A. Simpson, B. Jacobsson, J. W. Holloway, H. Bisgaard, J. Sunyer, N. M. P. Hensch, L. K. Williams, K. M. Godfrey, C. A. Wang, D. I. Boomsma, M. Melbye, G. H. Koppelman, D. Jarvis, W. I. McLean, A. D. Irvine, X. J. Zhang, H. Hakonarson, C. Gieger, E. G. Burchard, N. G. Martin, L. Duijts, A. Linneberg, M. R. Jarvelin, M. M. Noethen, S. Lau, N. Hubner, Y. A. Lee, M. Tamari, D. A. Hinds, D. Glass, S. J. Brown, J. Heinrich, D. M. Evans, and S. Weidinger. 2015. 'Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis', *Nat Genet*, 47: 1449-56.

Reck, M., D. Rodriguez-Abreu, A. G. Robinson, R. Hui, T. Csoszi, A. Fulop, M. Gottfried, N. Peled, A. Tafreshi, S. Cuffe, M. O'Brien, S. Rao, K. Hotta, M. A. Leiby, G. M. Lubiniecki, Y. Shentu, R. Rangwala, J. R. Brahmer, and Keynote-Investigators. 2016. 'Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer', *N Engl J Med*, 375: 1823-33.

Refae, Sadal, Nathalie Ebran, Jocelyn Gal, Josiane Otto, Damien Giacchero, Delphine Borchiellini, Joel Guigay, Frederique Peyrade, Gerard Milano, and Esma Saada. 2018. 'Abstract 4548: Host immunogenetics and hyperprogression under PD1/PD-L1 checkpoint inhibitors', *Cancer Research*, 78: 4548-48.

Refae, Sadal, Jocelyn Gal, Nathalie Ebran, Josiane Otto, Delphine Borchiellini, Frederic Peyrade, Emmanuel Chamorey, Patrick Brest, Gérard Milano, and Esma Saada. 2019. 'Abstract 1070: Germinal immunogenetics predicts treatment outcome for PD1 PD-L1 checkpoint inhibitors', *Cancer Research*.

Rendleman, J., M. Vogelsang, A. Bapodra, C. Adaniel, I. Silva, D. Moogk, C. N. Martinez, N. Fleming, J. Shields, R. Shapiro, R. Berman, A. Pavlick, D. Polsky, Y. Shao, I. Osman, M. Krogsgaard, and T. Kirchhoff. 2015. 'Genetic associations of the interleukin locus at 1q32.1 with clinical outcomes of cutaneous melanoma', *J Med Genet*, 52: 231-9.

Ribas, A., and J. D. Wolchok. 2018. 'Cancer immunotherapy using checkpoint blockade', *Science*, 359: 1350-55.

Rizvi, N. A., M. D. Hellmann, A. Snyder, P. Kvistborg, V. Makarov, J. J. Havel, W. Lee, J. Yuan, P. Wong, T. S. Ho, M. L. Miller, N. Rekhtman, A. L. Moreira, F. Ibrahim, C. Bruggeman, B. Gasmi, R. Zappasodi, Y. Maeda, C. Sander, E. B. Garon, T. Merghoub, J. D. Wolchok, T. N. Schumacher, and T. A. Chan. 2015. 'Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer', *Science*, 348: 124-8.

Robert, J., V. Le Morvan, E. Giovannetti, G. J. Peters, and Pamm Group of EORTC. 2014. 'On the use of pharmacogenetics in cancer treatment and clinical trials', *Eur J Cancer*, 50: 2532-43.

Schmiedel, B. J., D. Singh, A. Madrigal, A. G. Valdovino-Gonzalez, B. M. White, J. Zapardiel-Gonzalo, B. Ha, G. Altay, J. A. Greenbaum, G. McVicker, G.

Seumois, A. Rao, M. Kronenberg, B. Peters, and P. Vijayanand. 2018. 'Impact of Genetic Polymorphisms on Human Immune Cell Gene Expression', *Cell*, 175: 1701-15 e16.

Sharma, P., and J. P. Allison. 2015. 'The future of immune checkpoint therapy', *Science*, 348: 56-61.

Visscher, P. M., N. R. Wray, Q. Zhang, P. Sklar, M. I. McCarthy, M. A. Brown, and J. Yang. 2017. '10 Years of GWAS Discovery: Biology, Function, and Translation', *Am J Hum Genet*, 101: 5-22.

Wallis, C. J. D., M. Butaney, R. Satkunasivam, S. J. Freedland, S. P. Patel, O. Hamid, S. K. Pal, and Z. Klaassen. 2019. 'Association of Patient Sex With Efficacy of Immune Checkpoint Inhibitors and Overall Survival in Advanced Cancers: A Systematic Review and Meta-analysis', *JAMA Oncol*.

Wang, D. Y., J. E. Salem, J. V. Cohen, S. Chandra, C. Menzer, F. Ye, S. Zhao, S. Das, K. E. Beckermann, L. Ha, W. K. Rathmell, K. K. Ancell, J. M. Balko, C. Bowman, E. J. Davis, D. D. Chism, L. Horn, G. V. Long, M. S. Carlino, B. Lebrun-Vignes, Z. Eroglu, J. C. Hassel, A. M. Menzies, J. A. Sosman, R. J. Sullivan, J. J. Moslehi, and D. B. Johnson. 2018. 'Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis', *JAMA Oncol*, 4: 1721-28.

Weber, J., M. Mandala, M. Del Vecchio, H. J. Gogas, A. M. Arance, C. L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J. J. Grob, M. O. Butler, M. R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R. R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M. B. Atkins, G. V. Long, S. Bhatia, C. Lebbe, P. Rutkowski, K. Yokota, N. Yamazaki, T. M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, P. A. Ascierto, and Collaborators CheckMate. 2017. 'Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma', *N Engl J Med*, 377: 1824-35.

Welter, D., J. MacArthur, J. Morales, T. Burdett, P. Hall, H. Junkins, A. Klemm, P. Flicek, T. Manolio, L. Hindorff, and H. Parkinson. 2014. 'The NHGRI GWAS Catalog, a curated resource of SNP-trait associations', *Nucleic Acids Res*, 42: D1001-6.

Winters, I. P., C. W. Murray, and M. M. Winslow. 2018. 'Towards quantitative and multiplexed in vivo functional cancer genomics', *Nat Rev Genet*, 19: 741-55.

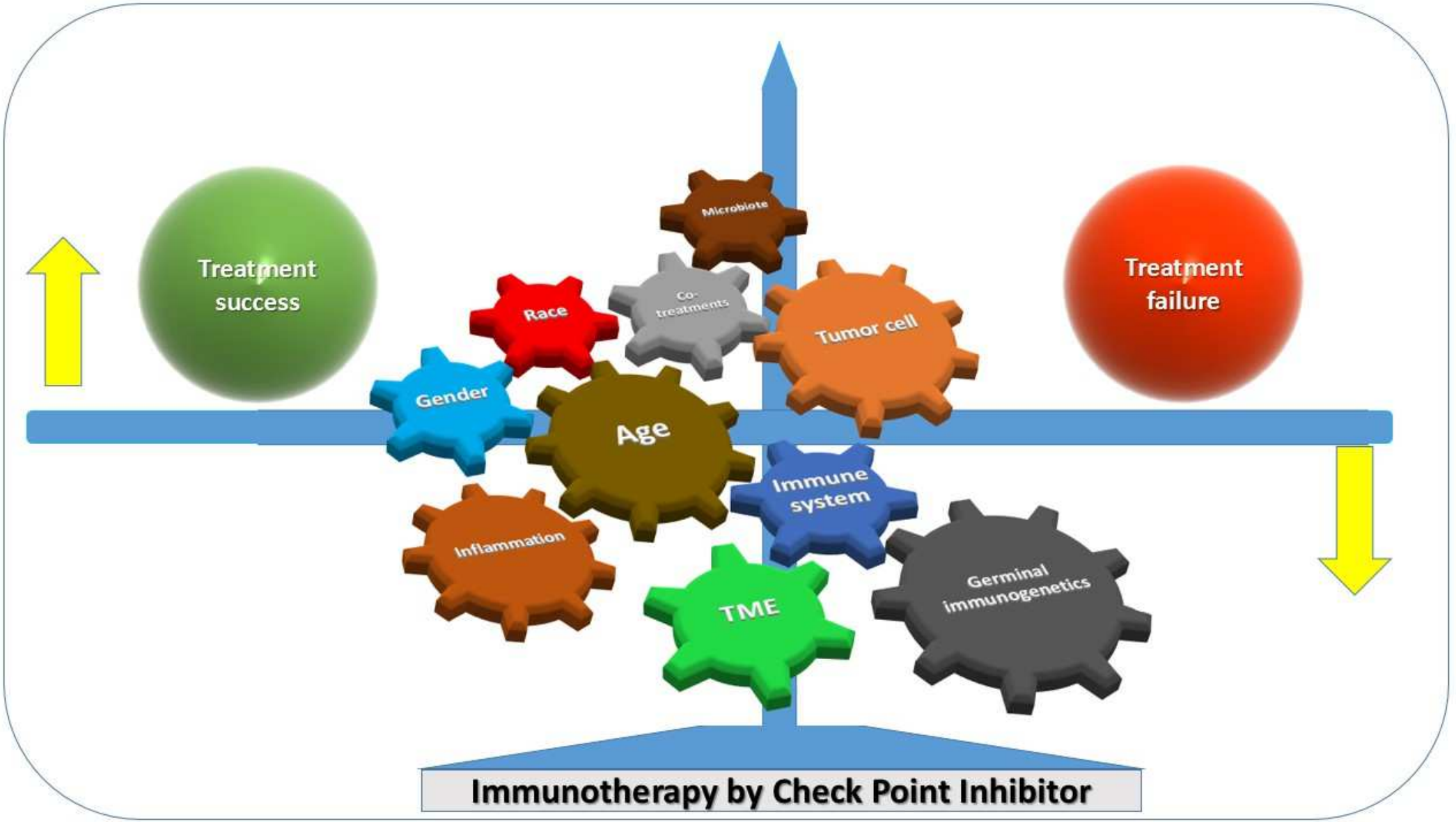


Figure 1: Germinal immunogenetics wheel within the CPI response machinery. SNPs (germinal immunogenetics) hold a place in the global machinery linked to the response to CPI. They can interfere with the immune system itself but also with the microbiota, the tumoral microenvironment (TME) and the tumor. Other potential influencing factors may (non-exclusively) implicate race, sex, age and inflammation.

Table 1: A tentative global approach for optimizing CPI-based treatment

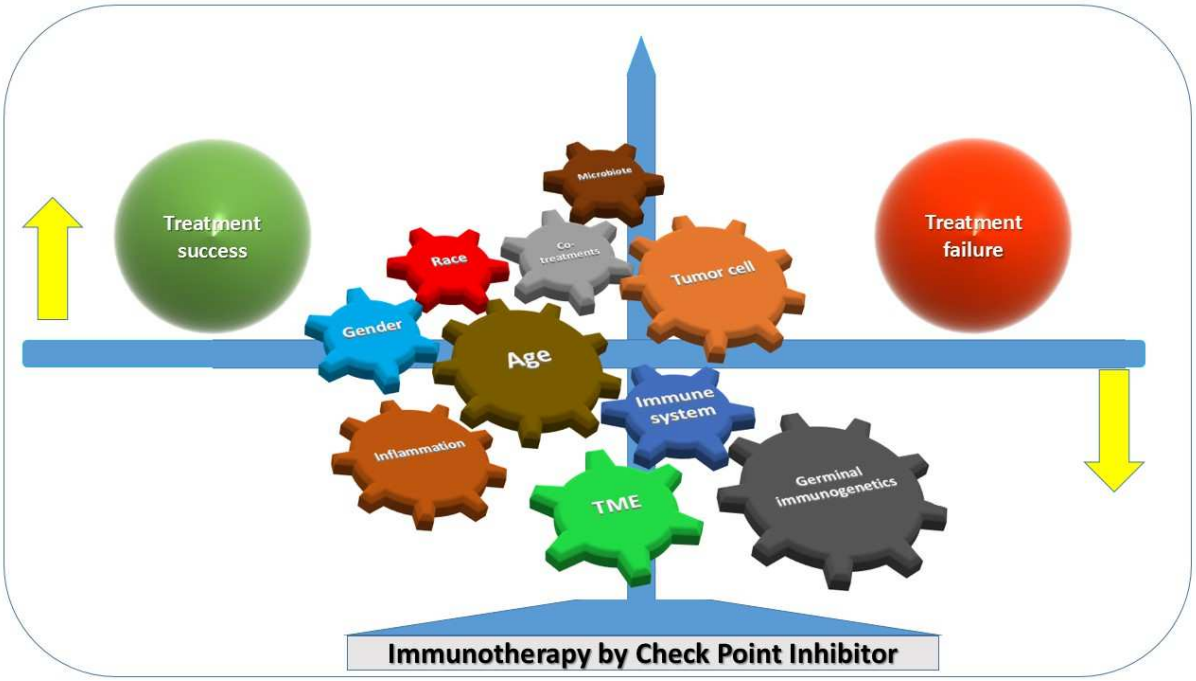
THE CURRENT APPROACH		THE COMPLEMENTARY PART OF THE HOST	
MARKERS	**Tumor and environnement-related** - Target expression (PD-L1) - Tumor mutational load - Tumor T cell infiltrate (quantitative, qualitative) - MSS / MSI	**MARKERS**	**Germinal immunogenetics (SNP score)** - Tumor-related factors (PD-L1, CTLA-4, IDO, HLA…) - Microenvironment-related (INF, TCR…) ↓ Risk Score Calculation
DECISIONS	- Go/No Go - Combine with CPI (plus chemotherapy, plus TKIs…)	**DECISIONS**	- Individual dose adjustment - Schedule adaptation - PK survey incorporation

Table 2: Free available tools to analyze SNPs

NAME	Link	Description
HAPLOREG	https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php	Explores annotations of the noncoding genome at variants on haplotype blocks, such as candidate regulatory SNPs at disease-associated loci. HaploReg returns SNPs in LD with query SNPs, their frequency in 4 populations from 1000 Genomes Phase1, and also tells you what evidence ENCODE has found for regulatory protein binding, chromatin structure, the chromatin state of the region, and putative transcription factor binding motifs that are altered by the variant.
ENSEMBL	https://www.ensembl.org/index.html	Gives the location of the variant on the gene
GTEX	https://gtexportal.org/home/	The Genotype-Tissue Expression (GTEx) project is an ongoing effort to build a comprehensive public resource to study tissue-specific gene expression and regulation. Samples were collected from 53 non-diseased tissue sites across nearly 1000 individuals, primarily for molecular assays including WGS, WES, and RNA-Seq. The GTEx Portal provides open access to data including gene expression, QTLs, and histology images.
REGULOMEDB	http://www.regulomedb.org/index	RegulomeDB is a database that annotates SNPs with known and predicted regulatory elements in the intergenic regions of the H.Sapiens genome. Known and predicted regulatory DNA elements include regions of DNAase hypersensitivity, binding sites of transcription factors, and promoter regions that have been biochemically characterized to regulation transcription. Sources of these data include public datasets from GEO, the ENCODE project, and published literature.
SNIPMIR	http://www.genomique.info:8080/merge/index?action=MISNP	Tests the gain/loss of microRNA binding induced by a SNP

Graphical abstract

Germinal immunogenetics as a predictive factor for immunotherapy



Clinical response to checkpoint inhibitors-based (CPIs) therapies can vary among tumor types and between patients according to several factors.

Entering host-related parameters (germinal immunogenetics) into the biomarker panel of CPI should provide a valuable strategy for identifying not only factors predictive of treatment efficacy but also of treatment-related toxicity.

A major issue concerns the real functional significance of the reported single-nucleotide polymorphisms (SNPs) linked to CPI-treatment outcome.