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Developing a definition of immune exclusion in cancer: results of a modified Delphi workshop

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ABSTRACT

Checkpoint inhibitors represent an effective treatment approach for a variety of cancers through their inhibition of immune regulatory pathways within the tumor microenvironment (TME). Unfortunately only a minority of patients with cancer achieve clinical benefit from immunotherapy, with the TME emerging as an important predictor of outcomes and sensitivity to therapy. The extent and pattern of T-cell infiltration can vary prominently within/across tumors and represents a biological continuum. Three immune profiles have been identified along this continuum: 'immune-desert' or 'T-cell cold' phenotype, 'immune-active', 'inflamed', or 'T-cell hot' phenotype, and 'immune excluded' phenotype. Of the three profiles, immune excluded remains the most ill-defined with no clear, universally accepted definition even though it is commonly associated with lack of response to immune checkpoint inhibitors and poor clinical outcomes. To address this, 16 multidisciplinary cancer experts from around the world were invited to participate in a symposium using a three-round modified Delphi approach. The first round was an open-ended questionnaire distributed via email and the second was an in-person discussion of the first round results that allowed for statements to be revised as necessary to achieve a maximum consensus (75% agreement) among the rating committee (RC). The final round questionnaire was distributed to the RC via email and had a 100% completion rate. The Delphi process resulted in moving us closer to a consensus definition for immune exclusion that is practical, clinically pertinent, and applicable across a wide range of cancer histologies. A general consensus of the role of immune exclusion in resistance to checkpoint therapy and five research priorities emerged from this process. Together, these tools could help efforts designed to address the underlying mechanisms of immune exclusion that span cancer types and, ultimately, aid in the development of treatments to target these mechanisms to improve patient outcomes.

INTRODUCTION

Immune checkpoint inhibitors have revolutionized the treatments of cancers through their ability to inhibit negative T-cell regulatory pathways, also known as checkpoints.[1] However, only a minority of patients with cancer achieve clinical benefit from immunotherapy. The initial response rates to checkpoint therapies in immunogenic tumors range from 10–60% across different tumor types, and many who initially respond eventually develop clinical resistance and tumor progression.[2] Interestingly, tumor microenvironment (TME) has emerged as a predictor of outcome as well as a marker of sensitivity to therapy.[3–5] As such, immunohistochemistry analyses have identified predominant patterns of immune cell infiltration based on the amount and spatial distribution of T-cells relative to tumor cells, which has led to TME characterization of three distinct immune profiles.[1 6–8] However, it is important to note that these patterns represent states along a biological continuum. First, is the 'immune-active,' 'inflamed' or 'T-cell hot' phenotypes which is defined by lymphocytic infiltration of tumor nests, with the immune cells in close proximity to tumor cells.[6 7 9 10] Second, is the 'immune-desert' or 'T-cell cold' phenotype that is characterized by a lack of lymphocytes in either tumor nests or within the TME as a whole.[6 7 9 10] The third immune profile is the 'immune-excluded' phenotype, characterized by an abundance of immune cells in the stroma immediately surrounding tumor nests but without marked lymphocyte infiltration into tumor nests themselves (figure 1). While the notion of immune exclusion has been described and increasingly reported since 2019, it remains poorly and often inconsistently defined. Compared with highly infiltrated tumors, immune exclusion has been associated with poor prognosis, is evolving as a potential driving force behind primary immunotherapy resistance and may

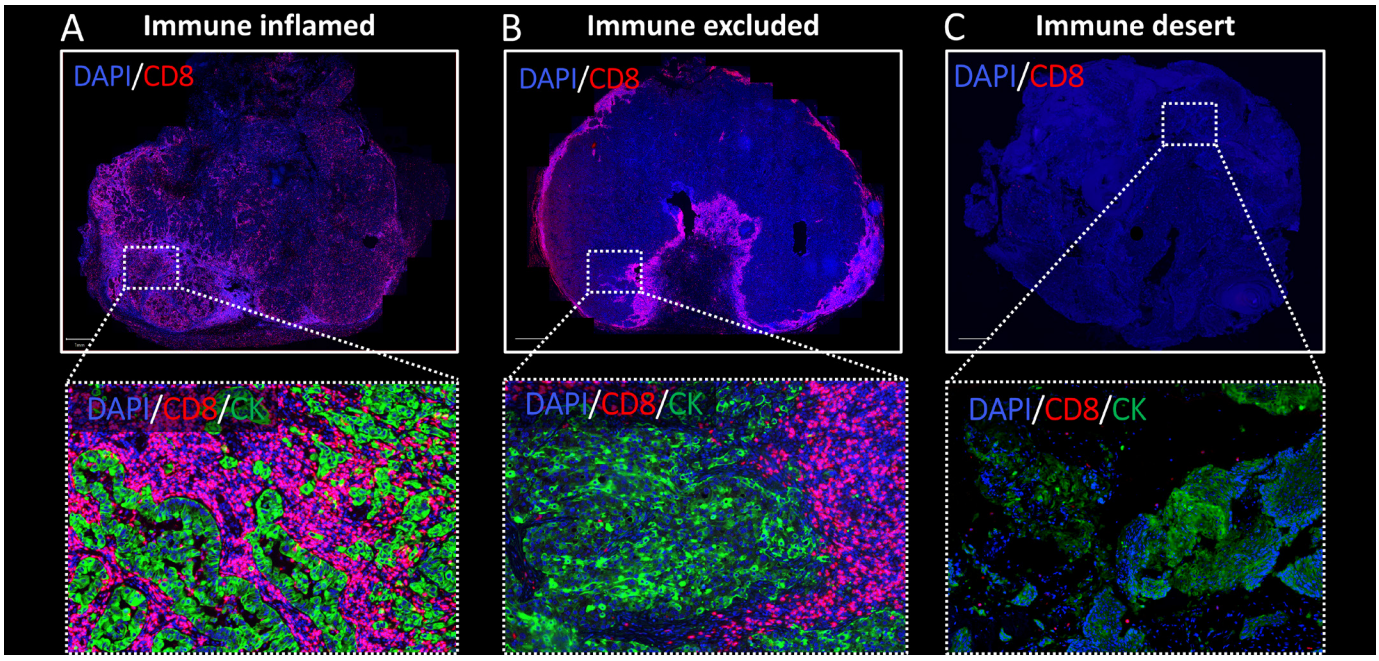

Figure 1 T-cell infiltration patterns in resected human non-small cell lung carcinomas (NSCLCs). (A–C) Representative multicolor immunofluorescence microphotographs of NSCLC sections stained with DAPI for all cells/nuclei (blue), CD8 for cytotoxic T-cells (red) and cytokeratin for tumor epithelial cells (CK, green). The tumor infiltrating lymphocyte patterns represent the extremes of a continuum. Figure was contributed by coauthor Dr Kurt Schalper from Yale University. The multiplexed immunofluorescence staining protocols, including tumor and tumor infiltrating lymphocyte markers, was adapted part of a previously studied retrospective cohort.[26] Bar=1 mm.

occur as a consequence of yet unidentified biologic mechanisms.[11–13] Despite the lack of a single, agreed-upon definition, immune exclusion in cancer is a recognized phenomenon that has prognostic implications, can impact treatment sensitivity, and is potentially actionable.

To identify key characteristics of and issues relevant to immune exclusion in cancer, an international panel of multidisciplinary experts were invited to participate in a symposium using the modified Delphi methodology. The Delphi method is recommended for use in the healthcare setting as a reliable, systematic, and unbiased approach of determining a consensus for a defined clinical problem via rounds of interactive discussions and subsequent voting.[14] Here, this approach was used to develop an initial, consensus definition of immune exclusion, address key issues in immune exclusion biology, and align on priorities for research. This, in turn, would allow for more consistent reporting in the medical literature, help promote research on defining the underlying mechanisms that span cancer types, and aid in the development of approaches to overcome immune exclusion as a cause of immune evasion and treatment resistance across a broad array of cancers.

METHODS

This study used a three-round modified Delphi method[15] to create a consensus definition of immune exclusion in cancer, which took place between October 11, 2021, and July 25, 2022. The study design is provided in online supplemental figure S1. Briefly, the steering committee (SC) consisted of three members (GTC, MR, and WHF). The initial tasks of the SC consisted of an extensive literature search, development of the open-ended first-round questionnaire, and selection of the rating committee (RC) invitees. The potential RC members were selected on the basis of their scientific expertize and record of publication on the topics of immune exclusion, the spatial immune microenvironment, fibroblasts, and immuno-oncology. Efforts were made to include individuals from a variety of fields to include basic science and clinical research from around the globe. A total of 21 individuals were initially invited and of these, 14 accepted (including MR and WHF). Invitees were asked for suggestions for additional experts in the field to invite and as a result, five more invitations were extended, and two accepted; creating an RC expert panel of 16 members. The demographics of both the SC and RC panels is provided in online supplemental table S1.

In the first round, the open-ended remote questionnaire was distributed to the RC by email with a link to a Google document survey. RC members were given 1 month to complete and submit their responses. Synthesis and analysis of the questionnaire by the SC took place via a virtual call among the three members. The second round was a real-time (either in-person or via video conference) consensus meeting to finalize statements. Following a presentation of the first-round questionnaire results to the RC members, there was a series of

Table 1 Consensus on immune exclusion statements

Statement		Panelist agreement n/N (%)
1	Cancer immune exclusion is a descriptive definition of a cancer phenotype characterized by a spatial imbalance with more immunologic cells in proximity to the tumor but fewer immune cells in physical contact with tumor cells.	12/13 (92)
2	The degree of imbalance that is necessary to distinguish immune excluded tumors from immune deserted or immune inflamed tumors is yet to be determined.	13/13 (100)
3	A relative paucity of physical contact between immune cells and tumor cells is a hallmark of this descriptive definition.	13/13 (100)
4	Fibrosis is often present in excluded tumors but not essential to the definition.	12/13 (92)
5	There are multiple mechanisms that likely play a part in immune exclusion to include:	
	A mechanical barrier	11/12 (92)
	Lack of chemotactic factors	12/13 (92)
	Immunosuppressive cytokines	12/13 (92)
	Apoptosis of T cells	9/12 (75)
	Disordered vasculature	11/13 (85)
	Cancer-associated fibroblast subtypes	11/12 (92)

discussions (led by the SC) and statements were revised as necessary to achieve a maximum consensus. For this study, a 75% agreement level was used as the basis for achieving consensus. Prior to round 3, the SC reviewed and refined the consensus statements. The final questionnaire was distributed to members of the RC via email with a link to a Google document survey that was completed by 100% of RC members. Descriptive statistics for the final report was conducted by GTC SC.

RESULTS

The first round consisted of 14 open-ended survey questions that were submitted electronically. Of these, 8 (57.2%) focused on components needed for a consensus definition, 3 (21.4%) focused on identifying mechanisms of immune exclusion, and the remaining 3 (21.4%) addressed research priorities (online supplemental table S2). The second round, real-time discussion of these results led to the development of five statements that included a conceptual definition of immune exclusion, a description of its possible underlying mechanisms, and identification of immune exclusion research priorities. A summary of the consensus of these five statements and research priorities are provided in tables 1 and 2, respectively. Each are individually discussed below:

Statement 1: cancer immune exclusion is characterized by the presence of immunologic cells in proximity to the tumor but with few of those immune cells in direct physical contact with tumor cells

In responses from the open-ended questions from Round 1, the RC described immune exclusion as the lack of functional evidence of an immune response within the tumor (38%, 6/16) and the inability of the immune response outside of the tumor to enter the tumor itself (44%, 7/16). As such, the RC identified the location of immune cells (25%, 4/16), specifically the location of CD8+ lymphocytes (31%, 5/16) as a defining feature. As a result of these responses and supportive discussion in Round 2, the SC derived Statement 1 which was submitted for consensus as part of Round 3 in the remote survey. The RC voted 92.3% (12/13) agreement for the above statement. The dissenting RC member found the description to be confusing and stated that immune cells could be present in the tumor but that the lack of contact between immune cells and tumor cells is more appropriate.

Statement 2: the degree of imbalance that is necessary to distinguish immune excluded tumors from immune desert or immune inflamed tumors is yet to be determined

The open-ended questionnaire responses in Round 1, led to a real-time discussion in Round 2 among the expert panelists surrounding TME and the three

Table 2 Potential research focus areas for immune exclusion

Area of research	Panelist rank of importance
Repulsion/rejection of T cells	2.5±1.2
Spatial profiling of T-cell cancer interaction	2.6±2.3
Understanding the role of cancer-associated fibroblasts	2.8±2.2
Immunosuppressive cytokines	3.3±1.7
Cancer-associated fibroblast subtypes	3.5±2.5
Disordered angiogenesis or vasculature	3.8±1.9
Apoptosis of T cells	3.9±1.8

Panelists were asked to provide a rank based on how important the topic was to the field of immune exclusion with 1 being the most important and 7 being least important. Data presented as mean±SD.

phenotypes (cold or deserted, hot, or excluded). As in the literature, there appears to be controversy on how each is defined and characterized. In response, the SC wrote Statement 2 for consensus as part of Round 3 in the remote survey. The RC voted 100% (13/13) agreement for the above statement, highlighting the need for further clarity in the optimal immune gradient that is functionally and clinically relevant to differentiate immune excluded tumors from other immune spatial phenotypes.

Statement 3: a relative paucity of physical contact between immune cells and tumor cells is a hallmark of this descriptive definition

In Round 1, the RC described a lack of physical contact between immune cells and the tumor (13%, 2/16) and the presence of a physical barrier to be an essential part of the immune exclusion phenomenon (25%, 4/16). The Round 2 real-time discussions supported this as a key component to the immune exclusion definition. Thus, the SC derived Statement 3 for consensus as part of Round 3 in the remote survey. The RC voted 100% (13/13) in agreement for the above statement.

Statement 4: fibrosis is often present in immune excluded tumors but not essential to the definition

In addition to essential components to the immune exclusion definition, Round 1 asked RC members to identify elements that were supportive of immune exclusion definition. The RC largely agreed that a high ratio of CD8+ lymphocytes at the invasive margin relative to the center of tumor was common (60%, 9/16). Other answers included: the presence of fibrosis and lack of clinical response to immunotherapy (13%, 2/16), the lack of tertiary lymphoid structures (6%, 1/16), high levels of immunosuppressive cell populations (6%, 1/16), and gene signatures as described in the literature specific to each cancer type (6%, 1/16). The Round 2 real-time discussion generated the following supportive, though not essential, elements of the definition: fibrosis, lack of clinical response to immunotherapy, the lack of tertiary lymphoid structures, and presence of immunosuppressive cell populations. In response, the SC generated Statement 4 for consensus as part of Round 3 in the remote survey. The RC voted 92.3% (12/13) in agreement. The dissenting RC member had not seen any data linking immune exclusion with fibrosis.

Statement 5: There are multiple mechanisms that likely contribute to immune exclusion including: (1) A mechanical barrier, (2) Lack of chemotactic factors, (3) Immunosuppressive cytokines, (4) Apoptosis of T cells, (5) Disordered vasculature, and (6) Cancer-associated fibroblasts.

The RC members were asked to list the top five mechanisms behind immune exclusion in Round 1. The majority of the panelists listed the mechanical barrier as an important mechanism (56%, 9/16), followed by the lack of chemokine attracting immune cells (31%, 5/16), immunosuppressive cells/T–regulatory cells (31%, 5/16), transforming growth factor-beta (TGFβ) and other immunosuppressive cytokines (31%, 5/16), and disordered angiogenesis (31%, 5/16). Other answers provided included a lack of neoantigens, checkpoints, cancer associated fibroblasts, loss of major histocompatibility complex, metabolic barrier, loss of antigen presentation, low T-cell receptor affinity for antigens, T-cell exhaustion, lack of dendritic cells in tumor, tumor-induced immune cell apoptosis, beta catenin, methylthioadenosine phosphorylase, and cyclin dependent kinase inhibitor 2A. The Round 2, real-time discussion led to the derivation of Statement 5 by the SC, which was added for consensus as part of Round 3 in the remote survey. The panelists were asked for their consensus on the following proposed mechanisms for immune exclusion: (1) A mechanical barrier, 91.7% (11/12) in agreement; (2) Lack of chemotactic factors, 92.3% (12/13) in agreement; (3) Immunosuppressive cytokines, 92.3% (12/13) in agreement; (4) Apoptosis of T cells, 75% (9/12) in agreement; (5) Disordered vasculature, 84.6% (11/13); and (6) Cancer-associated fibroblasts, 91.7% (11/12).

Identification of research priorities to address immune exclusion in cancer

An additional objective of the Delphi process was to identify the top five research priorities to address immune exclusion. In Round 1, the open-ended questionnaire asked for members of the RC to list the top five research priorities to address immune exclusion. That list is provided in online supplemental table S3 and was discussed during Round 2. As a result of those discussions, the SC identified seven areas of investigation that the RC panel of experts felt were important for immune exclusion and were all ranked with a similar level of importance, which are provided in table 2.

The role of a uniform definition of immune exclusion across cancer types

One issue specifically queried in Round 1 was whether the ultimate immune exclusion, and specifically the measurable spatial imbalance of immune cells in proximity to and in contact with tumor cells, should vary for each histologic type of cancer. There was no consensus on this point with 50% (8/16) of the RC voting no, 25% (4/16) voting yes, and 25% (4/16) voting as being unsure. The rationale discussed in Round 2 for a tumor-agnostic or histology-agnostic definition of immune exclusion was based on the position that immune exclusion is a phenomenon seen across cancer types with presumably similar underlying mechanisms. Those who disagreed with this statement cited the fact that cancer types vary and it seemed unreasonable that there would be a ‘one size fits all’ definition. Given that 75% consensus was

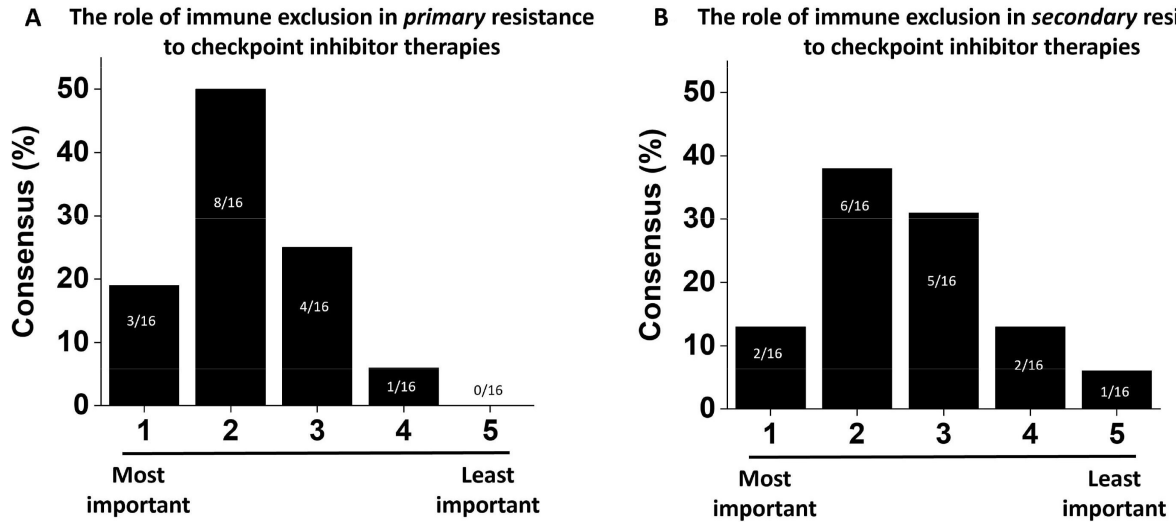

Figure 2 Ranking the role of immune exclusion in checkpoint inhibitor resistance. Members of the rating committee were asked to rank the role immune exclusion plays in primary (A) and secondary resistance (B) to checkpoint inhibitor therapies on a scale of 1 to 5 with 1 being the most important and 5 being the least important.

not achieved in the first two rounds, no statement was generated for Round 3.

The role of immune exclusion in resistance to checkpoint inhibitor therapy

As displayed in figure 2A, members of the RC were also asked to rank what role immune exclusion plays in primary resistance to checkpoint inhibitor therapies on a scale of 1 to 5 (1 being the most important and 5 being the least important). Fifty per cent (8/16) ranked immune exclusion as 2, 19% (3/16) ranked immune exclusion as 1, 25% (4/16) ranked immune exclusion as 3, and 6% (1/16) ranked immune exclusion as 4. On the same scale, the RC was asked to rate the role that immune exclusion plays in secondary resistance, or the loss of initial clinical response, to checkpoint inhibitor therapies (figure 2B). Thirty-eight per cent (6/16) ranked immune exclusion as 2, 31% (5/16) ranked immune exclusion as 3, 13% (2/16) ranked immune exclusion as 1, 13% (2/16) ranked immune exclusion as 4, and 6% (1/16) ranked immune exclusion as 5 for least important player in secondary resistance to checkpoint inhibitors.

DISCUSSION

This multi-institutional, international panel of cancer experts derived a consensus description of key characteristics of immune exclusion and identified research priorities to provide added clarity to an incompletely understood area of scientific and clinical importance. As such, several challenges and areas of controversy surrounding the phenomenon of immune exclusion were revealed from the Delphi process. First, the lack of consistency in the literature to precisely define immune exclusion—either phenotypically or immunologically—initiated a lengthy debate in our virtual and in-person discussions among the SC and RC members in Round 2. Specifically, without an operational definition, the interpretation and cross-study comparison of results is limited even within similar tumor types. Moreover, tumor heterogeneity, such as the variation in composition and spatial distribution of components of the TME that occurs within an individual tumor and within different tumor types is often not accounted for. Many studies evaluating tumor immune phenotypes have divided tumors into either 'immunologically cold' or 'immunologically hot'.[16–18] Grouping immune excluded and immune desert phenotypes together could potentially obscure distinct biological mechanisms and, as a result, hamper progress in understanding and overcoming clinical resistance to immune-based therapies. Complicating matters was the debate on whether the mechanism(s) of immune exclusion differed across tumor types that could necessitate different approaches and criteria based on cancer indication. Taken together, a clear and concise definition could not be achieved via this process but the group was able to identify key characteristics of immune excluded tumors which could serve as the first step towards developing a more precise definition of immune exclusion and ultimately, to understanding the relative impact of the immune excluded phenotype on the prognosis and sensitivity to treatment for different cancer types.

Second, it remains unclear how immune exclusion may contribute to primary-immunotherapy and secondary-immunotherapy resistance. Our expert panelists agreed that a better understanding could facilitate identification of patients that will benefit, and in some cases not benefit, from certain therapies. Given the association between TME and resistance to existing immunotherapies, there is considerable potential for approaches that could overcome immune exclusion by targeting underlying mechanisms to improve patient outcomes and ultimately move toward more personalized treatments. Ultimately, this could allow for a more uniform approach to study patients with immune exclusion in different

clinical contexts, inform study designs, and help identify points of therapeutic intervention. There was disagreement among the panel on the role of fibrosis as a causative event in immune exclusion. In part, it was based on the lack of experimental evidence of causality and the fact that patients with notoriously fibrotic tumors such as desmoplastic melanoma are sensitive to programmed cell death-1 (PD-1) blockers, showing that tumor fibrosis may not be sufficient to restrict T-cell infiltration and tumor-cell killing therapies.[19 20] The composition and architecture of fibrotic stroma may be of greater importance than the quantity present.[21] Along these lines, our RC identified six key mechanisms of interest potentially associated with immune exclusion irrespective of cancer and tumor type. These included: (1) lack of chemotactic factors, (2) a mechanical barrier, (3) immunosuppressive cytokines, (4) cancer-associated fibroblast subtypes, (5) disordered vasculature and (6) apoptosis of T cells.

A third challenge in the current landscape of immune exclusion is that the phenomenon of spatial immune phenotypes is likely to be a continuum, without clear distinctions between categories. It is clear that the spatial location of CD8+ lymphocytes is an essential element to the definition but the degree of immune infiltration in the parenchyma of the tumor and surrounding stroma throughout the TME is variable and efforts should be made to assess many areas of the TME and should also undergo frequent reevaluation. In the continuum between spatial immune phenotypes, the thresholds for the quantity or ratio of immune cells in the tumor center and periphery that distinguishes one phenotype from another should ultimately be made based on clinical relevance such as prognosis or prediction of treatment-specific benefit. A further complicating factor is that variable degrees of heterogeneity are present within individual tumors such that multiple immune phenotypes may be present in one tumor. Further study is needed, but researchers should make raw data available and evaluate for heterogeneity, when feasible, to better address these issues.

Furthermore, the ratio of CD8+ cells and other supportive immune cells, such as T-regulatory cells, natural killer cells, cancer-associated fibroblasts, and tumor-associated macrophages, may be another potential dimension in the response to immunotherapy. Currently, the gold standard for TME characterization remains analysis by immunohistochemistry (IHC). However, becoming less reliant on IHC staining with subjective estimation of cell levels or manually counting cells for immune exclusion characterization will allow large association studies to be performed faster and with increased accuracy. As such, new technical advances in machine learning suggest the potential to evaluate large quantities of data to assess immune exclusion.[22] Gene signatures also appear to hold great promise for quick and accurate evaluation of immune exclusion and may help tease out cancer-specific heterogeneity as well as exploration of possible underlying mechanisms.[11 13 23–25] Taken together, a more streamlined and systematic approach to evaluation of immune exclusion could not only allow for integration into routine clinical settings but could also decrease time to accurate diagnosis and treatment decision with expected positive impact on patients outcomes.[22]

Finally, the virtual-person and in-person discussions among our expert panelists concluded that the biology underpinning immune exclusion is uncertain and may not mirror the other immune phenotypes and as a result requires new tools, insights, and methods to dissect and translate it into an actionable concept. To this end, the RC identified several focus areas of future studies for immune exclusion: repulsion/rejection of T cells; spatial profiling of T-cell cancer interaction, understanding the role of cancer-associated fibroblasts (CAFs); immunosuppressive cytokines, CAF subtypes, defective angiogenesis or vasculature; and exacerbated intratumor T-cell apoptosis.

This modified Delphi study is not without limitations. The members of the symposium may not represent the comprehensive opinions of the scientific community as many of the members selected had previously published about immune exclusion, possibly biasing the group towards overstating the importance of this phenomenon. However, we believe these limitations are outweighed by our diverse internationally recognized expert panelists including clinical trialists, oncologists, pathologists, and biologists with expertize in both research and clinical aspects of disease.

Conclusions

Here, the Delphi process led to the derivation of a consensus description of key elements of immune exclusion that is clear, concise, conceptually sound, clinically pertinent and applicable across a wide range of cancer histologies and study designs. In turn, it is hoped that this will encourage development of a more precise definition of immune exclusion. Such a definition could enable researchers to determine the comparability of studies, the underlying mechanisms of immune exclusion that span cancer types and, ultimately, aid in the development of treatments to target these mechanisms that could improve patient survival and quality of life.

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Contributors GTC was a member of the steering committee and rating committee, helped design the questions, interpret the results, and write the manuscript. MR was a member of the steering committee and rating committee, helped design the questions, interpret the results, and write the manuscript. PAA, GB, MC, JPE, FG, AI, MK, RL, FM-G, SIP, PP, EP, AR, and KAS were members of the rating committee and aided in editing the manuscript. WHF was a member of the steering committee and rating committee, helped design the questions, interpret the results, and write the manuscript.

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Competing interests GTC is an employee of Parthenon Therapeutics. MR is a former Ingram Professor of Cancer Research at the Vanderbilt-Ingram Cancer Center and former Chief Medical Officer of Pfizer; he is also a paid member of the Scientific Advisory Board of Parthenon Therapeutics. PAA has/had a consultant/advisory role for Bristol-Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre-Fabre, AstraZeneca, Sun Pharma, Sanofi, Idera, Sandoz, Immunocore, 4SC, Italfarmaco, Nektar, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, Oncosec, Nouscom, Lunaphore, Seagen, iTeos, Medicenna, Bio-AI Health, ValoTX, Replimmune, Bayer. He also received research funding from Bristol-Myers Squibb, Roche-Genentech, Pfizer, Sanofi. Travel support by Pfizer, Bio-AI Health, Replimmune. GB is a paid consultant of Parthenon Therapeutics. MC has received honoraria from Eisai, Agios Pharmaceuticals, DAVA Oncology, BAYER, Seattle Genetics, Daiichi Sankyo and AstraZeneca, travel/accommodation/expenses from Genentech/Roche and previously received research support as part of the Yale Cancer Center. JPE is an employee of Parthenon Therapeutics. FG received fees for oral communication from Lilly, Sanofi, BMS, AstraZeneca and Amgen, received funding for clinical trials by AstraZeneca, received travel grants from Roche France, Amgen and Servier; and is an advisory board member for Merck Serano, Amgen, Roche France and Sanofi, all outside of the submitted work. AI is on the advisory board: AstraZeneca, Bayer, BMS, Brenus Pharma, Domain Therapeutics, Epizyme, Ipsen, Lilly, Merck, MSD, Novartis, Parthenon, Roche; Research Grant: AstraZeneca, Bayer, BMS, Domain Therapeutics, Ipsen, Merck, MSD, Novartis, Parthenon, Pharmamar, and Roche. MK has none. RL is a paid member of Scientific Advisory Board of Parthenon Therapeutics. FM-G research grants from Innate Pharma, Roche, BMS. SIP has none. PP paid member of Scientific Advisory Board of Parthenon Therapeutics. EP has received research support from Boehringer-Ingelheim, Capstan Therapeutics, Incyte and TMUNITY; co-founder and holds equity in Capstan Therapeutics. AR has received honoraria from consulting with Amgen, Bristol-Myers Squibb and Merck, is or has been a member of the scientific advisory board and holds stock in Advaxis, Appia, Apricity, Arcus, Compugen, CytomX, Highlight, ImaginAb, ImmPact, ImmuneSensor, Inspirna, Isoplexis, Kite-Gilead, Lutris, MapKure, Merus, PACT, Pluto, RAPT, Synthekine and Tango, has received research funding from Agilent and from Bristol-Myers Squibb through Stand Up to Cancer (SU2C), and patent royalties from Arsenal Bio. KAS received research support (last 24 months) from Navigate Biopharma, Tesaro/GSK, Moderna, Takeda, Surface Oncology, Merck, Bristol-Myers Squibb, AstraZeneca, Ribon Therapeutics, Eli Lilly, Boehringer-Ingelheim, Akoya Biosciences and Roche; consulting or advisory board: Clinica Alemana Santiago, Shattuck Labs, AstraZeneca, EMD Serono, Takeda, Agenus, Genmab, OnCusp, Bristol-Myers Squibb, Roche, CDR life, Sensei Therapeutics, Molecular Templates and Merck; Speaking engagements and other: Merck, Parthenon Therapeutics, PeerView, Forefront collaborative. WHF is Professor Emeritus at University Paris Cité working in Immuno-Oncology for more than 50 years. Paid member of the Scienfic Advisory Board and consultant for Parthenon, Ichnos, Oxford Biotherapeutics, Anaveon, Catalym, Genenta and holds patents for Immuoscore.

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REFERENCES

1 Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature* 2017;541:321–30.
2 Schoenfeld AJ, Hellmann MD. Acquired resistance to immune Checkpoint inhibitors. *Cancer Cell* 2020;37:443–55.
3 Galon J, Costes A, Sanchez-Cabo F, *et al*. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006;313:1960–4.
4 Fridman WH, Pagès F, Sautès-Fridman C, *et al*. The immune Contexture in human tumours: Impact on clinical outcome. *Nat Rev Cancer* 2012;12:298–306.
5 Junttila MR, de Sauvage FJ. Influence of tumour micro-environment heterogeneity on therapeutic response. *Nature* 2013;501:346–54.
6 Herbst RS, Soria J-C, Kowanetz M, *et al*. Predictive correlates of response to the anti-PD-L1 antibody Mpdl3280A in cancer patients. *Nature* 2014;515:563–7.
7 Hegde PS, Karanikas V, Evers S. The where, the when, and the how of immune monitoring for cancer Immunotherapies in the era of Checkpoint inhibition. *Clin Cancer Res* 2016;22:1865–74.
8 Kather JN, Suarez-Carmona M, Charoentong P, *et al*. Topography of cancer-associated immune cells in human solid tumors. *Elife* 2018;7:e36967.
9 Gajewski TF. The next hurdle in cancer Immunotherapy: Overcoming the non-T-cell-inflamed tumor Microenvironment. *Semin Oncol* 2015;42:663–71.
10 Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor Microenvironment. *Nat Immunol* 2013;14:1014–22.
11 Hammerl D, Martens JWM, Timmermans M, *et al*. Spatial Immunophenotypes predict response to anti-Pd1 treatment and capture distinct paths of T cell evasion in triple negative breast cancer. *Nat Commun* 2021;12:5668.
12 Echarti A, Hecht M, Büttner-Herold M, *et al*. Cd8+ and regulatory T cells differentiate tumor immune phenotypes and predict survival in locally advanced head and neck cancer. *Cancers (Basel)* 2019;11:1398.
13 Desbois M, Udyavar AR, Ryner L, *et al*. Integrated Digital Pathology and Transcriptome analysis identifies molecular mediators of T-cell exclusion in ovarian cancer. *Nat Commun* 2020;11:5583.
14 Meshkat B, Cowman S, Gethin G, *et al*. Using an E-Delphi technique in achieving consensus across disciplines for developing best practice in day surgery in Ireland. *JHA* 2014;3:1.
15 R Avella J. Delphi panels: Research design, procedures, advantages, and challenges. *IJDS* 2016;11:305–21.
16 Zhou L, Xu Q, Huang L, *et al*. Low-dose carboplatin Reprograms tumor immune Microenvironment through STING signaling pathway and Synergizes with PD-1 inhibitors in lung cancer. *Cancer Lett* 2021;500:163–71.

17 Sobottka B, Moch H, Varga Z. Differential PD-1/LAG-3 expression and immune phenotypes in metastatic sites of breast cancer. *Breast Cancer Res* 2021;23:4.
18 Tsai C-Y, Chi H-C, Wu R-C, *et al*. Combination biomarker of immune checkpoints predict prognosis of urothelial carcinoma. *Biomedicines* 2021;10:8.
19 Eroglu Z, Zaretsky JM, Hu-Lieskovan S, *et al*. High response rate to PD-1 blockade in Desmoplastic Melanomas. *Nature* 2018;553:347–50.
20 Ribas A, Wolchok JD. Cancer Immunotherapy using Checkpoint blockade. *Science* 2018;359:1350–5.
21 Popovic A, Tartare-Deckert S. Role of extracellular matrix architecture and signaling in Melanoma therapeutic resistance. *Front Oncol* 2022;12:924553.
22 Failmezger H, Muralidhar S, Rullan A, *et al*. Topological tumor graphs: A graph-based spatial model to infer Stromal recruitment for immunosuppression in Melanoma histology a C. *Cancer Res* 2020;80:1199–209.
23 Mlynska A, Vaišnorė R, Rafanavičius V, *et al*. A Gene signature for immune Subtyping of desert, excluded, and inflamed ovarian tumors. *Am J Reprod Immunol* 2020;84:e13244.
24 Derks S, de Klerk LK, Xu X, *et al*. Characterizing diversity in the tumor-immune Microenvironment of distinct Subclasses of gastroesophageal adenocarcinomas. *Ann Oncol* 2020;31:1011–20.
25 Xu Q, Chen S, Hu Y, *et al*. Landscape of immune Microenvironment under immune cell infiltration pattern in breast cancer. *Front Immunol* 2021;12.
26 Lopez de Rodas M, Nagineni V, Ravi A, *et al*. Role of tumor infiltrating lymphocytes and spatial immune heterogeneity in sensitivity to PD-1 axis blockers in non-small cell lung cancer. *J Immunother Cancer* 2022;10:e004440.