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OPINION PAPER

Addressing current challenges and future directions in immuno-oncology: expert perspectives from the 2017 NIBIT Foundation Think Tank, Siena, Italy

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Abstract

A collaborative think tank involving panellists from immuno-oncology networks, clinical/translational investigators and the pharmaceutical industry was held in Siena, Italy, in October 2017 to discuss the evolving immune-oncology landscape, identify selected key challenges, and provide a perspective on the next steps required in the translation of current research and knowledge to clinical reality. While there is a trend of combining new agents (e.g., co-stimulator agonists) with a PD-1/PD-L1 treatment backbone, use of alternative combination therapy approaches should also be considered. While the rapid evolution in systems biology provides a deeper understanding of tumor and tumor microenvironment heterogeneity, there remains the need to identify and define genuinely predictive biomarkers to guide treatment and patient selection. Cross-specialty and cross-sector collaboration, along with a broader collective data-sharing approach are key to optimizing immuno-oncology therapy in clinical practice. Continued support of younger research-clinicians is essential for future success in clinical, translational and basic science investigations.

Keywords Immunotherapy · PD-1 · PD-L1 · CTLA-4 · OX-40 · Biomarkers

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Abbreviations

ALC	Absolute lymphocyte count
AMC	Absolute monocyte count
ANC	Absolute neutrophil count
GITR	Glucocorticoid-induced tumor necrosis factor receptor
Hi-TIDe	Human integrated tumor immunology discovery engine
MEK	Mitogen-activated protein kinase kinase
NIBIT	"Network Italiano per la Bioterapia dei Tumori" (Italian Network for Tumor Biotherapy)
BRAF	Proto-oncogene B-Raf
SLiPs	Short-lived proteins
SITC	Society for Immunotherapy of Cancer
TIL	Tumor-infiltrating lymphocyte
TME	Tumor microenvironment

Introduction

The Italian Network for Tumor Biotherapy (NIBIT; http://www.nibit.org/index.php) provides a platform for individuals working within different immuno-oncology communities (academic, clinical, industry, philanthropic and regulatory) to interact to develop novel cancer therapies and treatment strategies through collaborative preclinical and clinical studies at a national and international level [1, 2]. This year's 15th annual NIBIT meeting was held in Siena between October 5 and 7, 2017 with the meeting proceedings recently published [3].

Immediately following the congress, and to coincide with the launch of a new Center for Immuno-Oncology in Siena, a special panel convened by Professor Michele Maio and the NIBIT Foundation took place, entitled "A Vision of I-O: The Siena Consensus". In recognition of the rapid advances and ever-changing landscape in immuno-oncology research and therapy, opinions were sought from individuals drawn from different sectors, including immuno-oncology networks, clinical/translational investigators and the pharmaceutical industry. The format was an appraisal of relevant data, then an informal 'think tank' to allow this diverse group to brainstorm the evolving landscape, identify selected key challenges, and provide perspective on potential solutions and the next steps required in the translation of current research and knowledge to clinical reality.

Scientific background

Targeting immune checkpoints with antagonistic mAbs such as pembrolizumab, nivolumab (anti-PD-1), atezolizumab (anti-PD-L1), avelumab (anti-PD-L1) and ipilimumab (anti-CTLA-4) to boost tumor antigen-specific immune responses is a successful strategy. Although effective in a wide range of solid and hematologic cancer types, the therapeutic efficacy of this strategy is limited to patients whose cancer demonstrates a receptive tumor microenvironment (TME).

An alternative and/or adjunctive strategy is promoting CD4+ and CD8+ T-cell activation and proliferation within the TME by targeting T-cell co-stimulatory receptors, many belonging to the TNFR family (OX40, glucocorticoid-induced tumor necrosis factor receptor [GITR] and 4-1BB). Some representative examples of novel co-stimulator studies and other combination studies are presented in Table 1. For example, MOXR0916, a humanized agonist mAb targeting OX40 is being evaluated for use in a dose-escalation study as monotherapy in patients with locally advanced or metastatic solid tumors (NCT02219724); preliminary data indicate that MOXR0916 is well tolerated at all studied doses [4]. The INDUCE-1 study is a phase I open-label study of GSK3359609, an inducible co-stimulator (ICOS) agonist antibody, currently being investigated for use as monotherapy and in combination with PD-1 blockade (pembrolizumab) in patients with advanced solid tumors (NCT02723955) [5]. The effect of PD-L1 blockade with atezolizumab when used in combination with MAPK kinase (MEK) inhibition (cobimetinib) and proto-oncogene B-Raf (BRAF) inhibition (vemurafenib) is being investigated

Table 1 Examples of ongoing immunotherapy treatment approaches

Drug(s) and/or combinations	Target	Disease	Design	Clinical trials gov
MOXR0916	OX40	Advanced, metastatic cancer	Phase 1 with cohort extension	NCT02219724 [4]
GSK3359609 ± pembrolizumab	ICOS	Advanced, metastatic cancer with subsequent patient selection	Phase 1 with cohort extension including combination with PD-1 inhibitor	NCT02723955 [5]
Atezolizumab + cobimetinib + vemurafenib	BRAFv600 mutations	BRAFv600 mutation-positive metastatic or unresectable locally advanced melanoma	Phase 3 (randomized, blinded)	NCT02908672 [6]
Atezolizumab ± bevacizumab versus sunitinib	PD-L1	Renal cell carcinoma	Phase 2 (randomized)	NCT01984242 [7, 8]

Ongoing in October 2017

in patients in BRAFV600-mutant metastatic melanoma (NCT02908672) [6]. Data from the IMmotion150 study (NCT01984242) comparing atezolizumab as a single agent or in combination with bevacizumab with sunitinib in patients with renal cancer is also encouraging [7, 8].

However, selection of the most appropriate co-stimulatory targets, dosing strategies and timing when used alongside or in sequence with existing (and novel) checkpoint inhibitors represents one of a number of significant challenges.

Challenge 1. Agonist antibodies in the era of antagonist antibodies: monotherapy, combination and/or sequence

Understanding the effect of co-stimulatory agonists on different T-cell populations—both in the TME and in the periphery—and the kinetics of these effects is essential in developing a strategy for use, especially if a combination sequential strategy is being considered. In general, as the relative impact of specific agents on specific T-cell fractions is dictated by such kinetics, each agent may have a time-critical 'window of opportunity' for optimal benefit.

A range of co-stimulatory agonists had been investigated in preclinical and phase I clinical studies. The co-stimulatory immunoreceptor OX40 (CD134) is upregulated on CD4+ (and to a lesser extent on CD8+ T cells) following TCR binding, with subsequent OX40-mediated signaling promoting CD4+/CD8+ proliferation and effector function and crucially, T_{reg} inhibition [9]. Induction of tumor regression with OX40 agonists is seen in different animal models and preliminary clinical data report promising clinical responses [9, 10]. Further clinical studies either as monotherapy or in combination with other immunomodulators are ongoing [11]. Another target is GITR; in animal melanoma models and in humans with advanced cancers, treatment with the GITR agonist TRX-518 results in substantial reductions in the number of T_{reg} cells, both in the peripheral blood and in the TME [12]. Phase I studies of TRX-518 as monotherapy are ongoing, including a dose-escalation study and another evaluating this GITR agonist in combination with pembrolizumab is being planned.

For a combination approach (i.e., use of an OX40 agonist plus a checkpoint inhibitor such as anti-PD-1) the sequence of investigational treatments may be crucial. Data from animal models of mammary cancer have shown that, when given concurrently, the use of anti-PD-1 has a negative impact upon anti-tumoral T-cell responses (e.g., antigen-specific CD8+ T-cell infiltration) compared to use of OX40 agonist alone or OX40 agonist plus vaccine [13, 14]. However, when used in sequence, i.e., initially with OX40 agonist then adding anti-PD-1, the delayed use of anti-PD-1 has a positive effect on T-cell responses, and tumor regression, with substantially increased disease-free survival (30%) and overall survival. Notably, the converse sequence (anti-PD-1 then OX40 agonist) had no such benefits [13]. These data suggest that checkpoint inhibition may have a more important role after T-cell expansion following initial T-cell co-stimulation, acting to reduce contraction of the expanded effector cell component. It should be realized that these data are from two animal models and one co-stimulatory agonist/checkpoint inhibitor combination. These two animal models, namely MC38 and CT26 tumors, are perhaps exceptionally immunogenic and thus differ from other animal models. In addition, mechanisms observed in such models may differ from those that exist in patients. Data on other agent combinations in this and other animal models are required to better define the impact of sequence of administration and optimize sequence and agent combination aspects, allied with evaluation in clinical studies. In such clinical studies, early monitoring of immune responses may be critical in deciding whether to continue with clinical evaluation of specific combinations.

Another factor, of particular importance from a safety perspective, is evaluation of effective dosing and dose escalation with minimal/acceptable toxicity. T-cell priming against tumor-specific antigens via tumor vaccines to increase the available T-cell repertoire and generate robust tumor antigen-specific T-cell responses is an important consideration. While clinical results with cancer vaccines used as single agents have generally been disappointing, their use alongside other immune-oncology agents may be more promising. To date, many preclinical studies of co-stimulatory agonists have been investigated in conjunction with such vaccines.

Measuring humoral IgG antibody responses to tumor antigens also provides an opportunity to evaluate and monitor the effects of vaccination at different time-points and has recently been shown to correlate with specific T-cell responses to the same protein [15, 16]. This can allow assessment of the impact of repeated vaccination. A wide range of tumor-associated peptide vaccine platforms and vaccine vectors have been used. Moving forward, identifying the principal peptide targets will be important; whether these are a restricted set of recognized dominant tumor antigen epitopes [short-lived proteins (SLiPs)], a wider range of longer-lived peptides derived from tumor cell lysates, or indeed those derived from individual tumors; screening a large range of candidate vaccine antigens can be facilitated by seromic assay platforms [17–19].

Recent data by Tripathi et al. has shown that in lung cancer immune evasion is facilitated by downregulation of the 'immunoproteasome' with reduced MHC class I antigen-presentation of tumor antigens on the cell surface [15]. The potential effect of such altered 'immunoproteasome' function (and in turn an altered and more restricted set of

effector T-cell tumor targets, which will vary in individual tumors), requires consideration. Additional aspects include augmenting vaccine responses using adjuvants and or additional immunomodulators (e.g., CD40 or TLR agonists), and indeed site of vaccine administration such as intra-tumoral inoculation may also have value.

The evaluation of effective dosing and dose-escalation strategies with minimal/acceptable toxicity is another important issue that requires further investigation. Future studies should learn from previous investigational programs; for example, while urelumab, a 4-1BB (CD137) agonist shows encouraging anti-tumor activity in animal and clinical studies, significant dose-dependent toxicities were seen which have impeded clinical development [20]. More recent data however indicates acceptable safety with some anti-tumor activity at lower doses [21]. Another 4-1BB agonist (utomilumab) has a more favorable safety profile although with lower activity and clinical investigation continues with both agents [22].

Integrating all these aspects into clinical trials is a challenge and requires development of clinical trials evaluating dose finding and dose-optimization for immune-oncology treatments (and in particular combination regimens), and the use of biomarkers and imaging to guide and evaluate dosing and clinical responses [23]. While much can be learned from animal studies, in particular from a mechanistic perspective, it is essential to move forward with clinical investigations to characterize the effect in humans (in whom most investigational agents have currently limited data). The move into the clinic is particularly needed when the target is not present in animals. A list of differences between human and mouse immunology has been reviewed and published in the early 2000s and needs to be continuously updated to allow for better interpretation of animal models [24]. The large number of novel agents and novel agent combinations is such that alternative approaches to conventional trial design will also be necessary given the limitation of recruiting patients to complex clinical trials.

Clearly, identifying those combinations most likely to deliver synergistic benefit across different time-points in the evolving TME is important; in most likelihood the checkpoint inhibitors will be the principal backbone therapy to which other agents such as co-stimulator agonists could be added. In addition, there may be a role for using different co-stimulatory agonists (e.g., OX-40 and ICOS or GITR agonists) at different points within the treatment strategies; a flexible approach with the agent of choice determined by the individual's tumor and TME characteristics could be considered, requiring the evaluation of numerous investigational agents. As these agents with synergistic potential may be developed by different pharmaceutical companies, a broad cross-industry collaboration will be crucial, and appropriate intellectual property aspects reviewed (although ideally such studies would not be commercially competitive). As the available patient pool is highly heterogeneous both in terms of tumor type and TME, which may be heavily influenced by previous therapy (or therapies), collaboration across multiple centers is essential to ensure adequate numbers of a more homogeneous population for meaningful analysis. Furthermore, capturing, collating and interpreting all data generated from such studies will require considerable resources (including financial support), ideally with such data and analyses shared within and across an open collaborative framework.

Think-tank perspective:

- While there is a trend of combining new agents with a PD-1/PD-L1 treatment backbone, use of alternative combination therapy approaches should also be considered.
- Optimizing patient selection and use of tailored treatment approaches in prospective studies is essential, involving extensive outcomes data collection to inform subsequent treatment decisions.
- This may involve increased translational correlatives in existing studies, and also longitudinal individual patient follow-up over the entire disease course, with tissue sampling (tumor specimens and blood samples) at key times.
- There is a need for 'window of opportunity studies' (mainly in the setting of a neoadjuvant study) in well-defined patient populations, using both standard immune monitoring and cutting-edge approaches.
- Creation of a working group (involving cross-specialty and cross-sector collaboration) would be one avenue that can guide development of future clinical trials.

Challenge 2. Is there a unifying "-omics" systems biology approach that can help drive the future of immunotherapy: a reachable goal or a vision of utopia?

Our understanding of newer approaches to characterize tumor and TME heterogeneity has evolved considerably in recent years. Conventional tumor analyses such as tumor immune-phenotype, mutational status, and other molecular signatures are now supported by a wider variety of tools that allow dissection of tumor and TME biology from a broader perspective. While a range of descriptive terminology may be used to characterize and categorize these tools and associated data-sets, creating an abundant suite of 'omics' (genomics, proteomics, peptidomics, immuno-peptidomics and beyond), they should be seen as complementary to each other and indeed to the broader tumor biology.

For example, in Lausanne an integrated approach to capitalize on and across different 'omic' platforms is fostered by open collaboration of multidisciplinary teams

(scientists, clinicians and bioinformaticians), working in close-proximity to each other, under a common framework, the 'Human integrated tumor immunology discovery engine' (Hi-TIDe). Using these tools, and the ability to harvest personalized tumor xenografts for ex vivo evaluation [25], individual cancers and their TME can be analysed and interrogated from multiple perspectives, generating individualized tumor profiles. Current experience in Lausanne (with more than 60 ovarian, lung and breast tumors analysed) is that substantial heterogeneity is seen across individual tumor/TME profiles. These ex vivo tumors can be treated with different immuno-oncology agents, sequentially and in combinations, and at each step tumor response and the evolution in tumoral T-cell responses can be examined. This allows potential personalized treatment strategies to be identified, while evaluation of responses in the context of the original baseline tumor profile can provide invaluable information to inform putative prediction profiles. This approach can be harnessed in 'window of opportunity' studies.

Newer technologies can also assist development of adoptive T-cell transfer (i.e., ex vivo isolation, expansion and selective stimulation of antigen-specific T cells, followed by autologous administration), a therapeutic avenue with great potential [26]. In ovarian cancer, where the presence of CD4+ and CD8+ tumor-infiltrating lymphocytes (TILs) in the TME indicate a more favorable prognosis [27, 28], adoptive immunotherapy has shown good results in both animal models and in the clinic [29, 30]. Deep analysis of the immune-peptidome by using mass spectroscopy, which allows the identification of an individual patient's tumor antigenic 'signature', including neoantigens, can complement and improve existing in silico predictive approaches to select and evaluate candidate epitopes for use in T-cell manipulation [31, 32].

Think-tank perspective:

- This rapid evolution in systems biology provides a deeper understanding of tumor and TME heterogeneity and assists in translation of research to the clinic. Initiatives to achieve this goal should consider:
- A holistic approach, integrating patient characteristics with their individual tumor/TME profile could be an important strategy, e.g., by incorporating the wider immunological profile, and accounting for any associated etiological aspects (the tumor 'microbiome') to better define the dominant mechanisms driving tumor/TME dynamics. For these assays (and indeed for any putative biomarker), guidelines for sample collection—including time-points, storage, processing and analytical assay validation—should be developed and endorsed across relevant bodies.
- The formation of an international cancer immunotherapy biomarker consortium to provide some oversight and/or direction is one such avenue that could be pursued [33].
- Capturing and synthesizing the increasing quantity of data will be demanding, but it is important to consider this in future studies.
- Broader data sharing will be essential, ideally within a collective open framework, although this may bring logistical challenges. A substantial amount of gene expression data is already being shared in such a manner and adoption of similar initiatives across the broader 'omics' spectrum is welcome.

Challenge 3. Pharmacodynamic biomarkers in peripheral blood: should we continue exploring this field?

As an adjunct to tumor and TME analyses, evaluation of the peripheral blood can provide an inherently more flexible source of additional information on patient responses to immunotherapy. The role of peripheral biomarkers and how best to take advantage of the increasing array of reported data to contribute to ongoing studies and eventual clinical practice continue to evolve.

Pharmacodynamic changes in a wide array of peripheral markers following checkpoint inhibitor treatment have been reported in many studies with a number of excellent recent reviews [34–36]. Markers evaluated range from relatively broad measures such as absolute lymphocyte counts (ALCs) and other systemic markers (e.g., LDH) to assays of specific T-cell fractions, and other immune cells, e.g., NK cells and MDSCs (Table 2). For example, in patients treated with ipilimumab (anti-CTLA-4), improved survival is associated with an early increase in the ALC (at 2–3 weeks after treatment initiation) and delayed (at 8–14 weeks) increases in the frequency of CD4+ and CD8+ T cells [37]. Low baseline levels of MDSCs may also correlate with survival in melanoma patients receiving ipilimumab [38]. Low pretreatment LDH levels is associated with better overall survival in patients with melanoma treated with pembrolizumab [39], and in those patients with elevated baseline LDH, subsequent increases in LDH during treatment with PD-1 inhibitors is associated with disease progression [40, 41].

While such data are informative (and also those reporting additional assays such as antibody titers to tumor antigens, and serum cytokine levels), most data are derived on relatively small cohorts (and often retrospective in nature). At present, more data are reported for studies in melanoma [36], in which other assays such as the measurement of T-cell reinvigoration via Ki67 expression also shows promise (with the increase in circulating Ki67 + PD-1 + CD8+ T cells in relation to pretreatment tumor burden correlating

Table 2 Summary of observations for biomarkers in peripheral blood

Biomarkers	Tumor types	Agent(s)	Outcome
Putative predictive			
Increase in ALC	Melanoma	Ipilimumab	Improved OS [37]
Increase in Ki67 + PD-1 + CD8+ T cells	NSCLC	Pembrolizumab	Improved OS [42]
Increased serum IL-6	Melanoma	Ipilimumab	Low OS [43]
Increase in CD4+ and CD8+ memory T-cell subsets	Melanoma	Ipilimumab	Improved OS [44]
Increase in NK cell subsets	Melanoma	Pembrolizumab	Improved OS [44]
Increase in LDH	Melanoma	PD-1 inhibitors	Clinical progression [40, 41]
High baseline AMC and low post-treatment ANC	NSCLC	PD-1 inhibitors	Clinical response [45]
Putative prognostic			
High baseline LDH	Melanoma	Pembrolizumab	Low OS [39]
Normal/high eosinophils	Melanoma	Pembrolizumab	Improved OS [39]
Low MDSCs	Melanoma	Ipilimumab	Improved OS [38]
Increase in Ki67 + PD-1 + CD8+ T cells	Melanoma	Pembrolizumab	Improved PFS [46]

with clinical response) [46]. However, data in other cancers (e.g., NSCLC) are emerging. An increase in peripheral Ki67 + PD-1 + CD8+ T-cell responses has also recently been reported in patients with NSCLC with clinical response to PD-1 or PD-L1 blockade [42], while higher baseline absolute monocyte counts (AMCs) and lower post-treatment absolute neutrophil counts (ANCs) may be predictive of clinical responses to PD-1 inhibitors in NSCLC patients [45].

Think-tank perspective:

- There is a need to identify and define genuinely predictive biomarkers to guide treatment and patient selection [34, 35].
- This aspect is the focus of a number of dedicated Working Groups from specialist organisations, such as the Immune Biomarkers Task Force from the Society for Immunotherapy of Cancer (SITC) who have recently reported their latest key recommendations on how best to evaluate and validate predictive biomarkers (both in the tumor/TME and in the peripheral blood) [47]. Other expert groups have also reported recommendations [33].
- It important to consolidate approaches in this area to realize greatest benefit.

Challenge 4. Harnessing the motivation and innovative ideas coming from your scientists and research

At present a number of immune-oncology organisations/associations (including the NIBIT, the NIBIT Foundation, the Parker Institute for Cancer Immunotherapy, the Cancer Research Institute and the SITC) actively organise and promote initiatives to nurture younger colleagues and encourage their proposals for novel clinical, translational and basic science investigations. Nevertheless, it may still be difficult to receive appropriate recognition and identify sources of funding or resource support, with a risk that some highly innovative ideas could be missed due to inadequate evaluation.

Think-tank perspective:

- An open and easily accessible forum which provides an opportunity for young researchers to pitch, share and debate ideas; to each other, and to experienced colleagues and potential collaborators could heighten project awareness and attract potential project sponsors.
- Specific meetings incorporating relevant workshops with project development support is one approach, while initiatives from other industries and entrepreneurial business models can be adapted for this setting.

Conclusions

Immuno-oncology is a complex area, and this complexity is accompanied by challenges in developing the next phase of agents and combination strategies. While great strides have already been made by many different research groups and research networks, such efforts are at present somewhat fragmented, which could hamper attempts to accelerate translation to clinical practice in a timely manner. When feasible, sharing of data across different investigator groups should be encouraged. While cross-sector collaboration across academia, clinical researchers, research networks and industry already exist, these efforts should be further consolidated, and more fully harmonized.

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Compliance with ethical standards

Conflict of interest Michel Lahn was an employee of Incyte Biosciences International Sarl, Geneva, Switzerland, at the time of this panel and holds stocks of Incyte. Dominik Reuttinger is an employee of Roche Pharmaceuticals. Patrick L Garcia is an employee of Merck KGaA. Olivier Provendier is an employee of Laboratoires Pierre Fabre. Michele Maio is a consultant/advisory board member for Bristol-Myers Squibb, Incyte, Merck Sharp & Dohme Oncology, Roche, Astex Pharmaceuticals, Amgen, AstraZeneca and Merck Serono. Ramy Ibrahim is an advisory board member for Harpoon, Arcus, Immunovaccine and ImaginAB. Aiman Shalabi was a consultant at the Cancer Research Institute, New York, NY, USA, at the time of this panel. All other authors declare that they have no conflict of interest.

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