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FOCUSSED RESEARCH REVIEW

The Italian Network for Tumor Bio-Immunotherapy (NIBIT) Foundation: ongoing and prospective activities in immuno-oncology

Anna Maria Di Giacomo[1] · Alessia Covre[1] · Gianluca Giacobini[1] · Ramy Ibrahim[2] · Jaclyn Lyman[2] · Pier Giorgio Natali[3] · Michele Maio[1]

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Abstract

The ongoing revolution in cancer immunotherapy stems from the knowledge that distinct immune-checkpoints regulate the physiological crosstalk between and among immune cells by delivering inhibitory or activating signals. These notions, and the availability of mAb directed to diverse immune-checkpoint molecules, have led to a significant clinical improvement in cancer treatment. In this scenario, further achievements are undoubtedly to be expected from the contribution of novel, proof-of-principle clinical trials designed to explore the therapeutic efficacy of new immunotherapy-based combinations and treatment sequences. Along these lines, the clinical translation of pre-clinical evidence generated by non-profit research entities is likely to provide a significant contribution to gaining new insights that will further boost the field of cancer immunotherapy. To pursue this goal, and to provide comprehensive educational programs in immune-oncology (I-O), several national and global networks have been revitalized or newly established in recent years. This rapidly evolving scenario led the Board of Directors of the Italian Network of Tumor Bio-Immunotherapy (NIBIT) to establish the NIBIT Foundation. This Focused Research Review summarizes the main ongoing and prospective I-O activities of the NIBIT Foundation.

Keywords Immunotherapy · Immune-oncology · Melanoma · Mesothelioma · Clinical trials · NIBIT

Abbreviations

BM	Brain metastasis
CII	Cancer immunology, immunotherapy
CIO	Center for immuno-oncology
CNS	Central nervous system
CRI	Cancer research institute
DCR	Disease control rate
DHA	DNA hypomethylating agents
DL	Dose level
DOR	Duration of response
IITs	Investigator-initiated trials
I-O	Immuno-Oncology
ir	Immune-related
MM	Metastatic melanoma
MMESO	Malignant mesothelioma
MTD	Maximum tolerated dose
NIBIT	Network Italiano per la Bioterapia dei Tumori (Italian Network for Tumor Bio-Immunotherapy)
ORR	Objective response rate
PFS	Progression-free survival
PICI	Parker Institute for Cancer Immunotherapy
TESLA	Tumor neoantigEn SeLection Alliance
UHS	University Hospital of Siena
W	Week
WIC	World Immunotherapy Council

This paper is a Focussed Research Review based on a presentation given at the *Fifteenth Meeting of the Network Italiano per la Bioterapia dei Tumori (NIBIT) on Cancer Bio-Immunotherapy*, held in Siena, Italy, 5th–7th October 2017. It is part of a series of Focussed Research Reviews and meeting report in *Cancer Immunology, Immunotherapy*.

✉ Anna Maria Di Giacomo
a.m.digiacomo@ao-siena.toscana.it

[1] Center for Immuno-Oncology, Medical Oncology and Immunotherapy, University Hospital of Siena, Istituto Toscano Tumori, Viale Mario Bracci, 16, 53100 Siena, Italy

[2] Parker Institute for Cancer Immunotherapy, San Francisco, CA, USA

[3] Center on Aging Sciences and Translational Medicine (CeSI-MeT), Gabriele d' Annunzio University, Chieti, Italy

NIBIT Foundation

The Network Italiano per la Bioterapia dei Tumori (Italian Network for Tumor Bio-Immunotherapy) (NIBIT) Foundation was established in 2012 as a non-profit legal entity, with the main goal to design and conduct highly innovative clinical trials in cancer immunotherapy. The clinical studies that have been developed so far have stemmed mainly from pre-clinical findings generated by the NIBIT Foundation, in the context of new clinical observations and unmet medical needs. The President of the NIBIT Foundation is Michele Maio, MD and members of the scientific Board of Directors are at present: Anna Maria Di Giacomo, MD, Giorgio Parmiani, MD, Roberto Camerini, MD, Pier Giorgio Natali, MD, and Ruggero Ridolfi, MD. According to its statutes, Principal Investigators of clinical trials sponsored by the NIBIT Foundation become temporary members of its Board of Directors for the whole duration of the study. The NIBIT Foundation has its own laboratory facilities located at the Toscana Life Sciences bio-incubator (http://www.toscanalifesciences.org) in Siena, Italy, in which operate several basic and clinical scientists. The comprehensive research programs of the NIBIT Foundation share in the benefits of the close interactions between clinical and pre-clinical researchers and with the infrastructure belonging to the Center for Immuno-Oncology (CIO) of the University Hospital of Siena (UHS), Italy. In addition, the NIBIT Foundation has multiple ongoing collaborations with academic institutions, scientific societies, and pharmaceutical companies worldwide.

Educational activities

Upon its establishment, the NIBIT Foundation organized the "Cancer Bio-Immunotherapy in Siena - NIBIT annual meetings" in collaboration with the NIBIT. This is an international meeting that has been held in Siena since 2004 (http://www.sienameeting-nibit.org). The meeting represents the major scientific annual NIBIT event that allows sharing of the most recent pre-clinical and clinical results obtained by the NIBIT groups with a high-level international audience. Attendance to the meeting has steadily increased with over 250 participants in 2017, and its Scientific Reports have been hosted in Cancer Immunology, Immunotherapy (CII) since 2013, when CII became the NIBIT official scientific journal [1, 2]. To promote the commitment of young investigators to the immuno-oncology (I-O) field, three NIBIT awards are assigned yearly to the best scientific contributions in basic, translational, and clinical research presented at the meeting by researchers < 40 years old.

On October 7th, 2017 the NIBIT Foundation promoted the first Think Tank titled "A vision of I-O: the Siena consensus" in which highly selected experts from international I-O networks (eg. the Parker Institute for Cancer Immunotherapy (PICI) San Francisco, CA; Cancer Research Institute (CRI) New York, NY; World Immunotherapy Council (WIC) and NIBIT, pharmaceutical companies, and Academia gathered to address current challenges and future directions in I-O (see article published in Cancer Immunology, Immunotherapy: "Addressing current challenges and future directions in immuno-oncology: expert perspectives from the 2017 NIBIT Foundation Think Tank, Siena, Italy" by Michele Maio et al. 2018). The second Siena I-O Think Tank was organized by the NIBIT Foundation in collaboration with the PICI and the CRI, and took place in Siena, Italy, on October 25th–27th, 2018 (https://www.thinktank-nibitfoundation.org/).

Among the multifaceted national and international I-O educational activities designed and developed by the NIBIT Foundation are: first and second level Master-classes for medical oncologists, as well as courses for biologists, radiologists, employees from pharmaceutical companies, nurses, and research nurses. These are all Continuing Medical Education-certified activities, involve internationally renowned pre-clinical and clinical faculty, and provide a unique learning opportunity, being generally held as highly interactive peer-to-peer events. Within their own professional fields, participants improve their comprehensive theoretical and practical knowledge of I-O; specifically, optimize their multi-disciplinary team working skills, familiarize themselves with strategies to improve the recruitment of patients into clinical studies, and/or refine their communication skills with diverse stakeholders including key opinion leaders, treating physicians, payers, and patients' advocacy groups. To date, over 600 professionals have attended these different programs. Detailed information on the educational activities organized by the NIBIT Foundation can be found at http://www.fondazionenibit.org. To keep the larger I-O community updated on advances in the field, in April 2015 the Foundation also launched the website http://www.immunoncologia.org, contributing to update its main sections dedicated to cancer patients and to I-O professionals. To date, the website has about 1500 registered users, and more than 700,000 contacts have been recorded.

Clinical research activities: the ongoing NIBIT Foundation clinical studies

The NIBIT Foundation has designed, and is presently coordinating as a non-profit sponsor, different mono- and multicenter phase I-to-phase III investigator-initiated trials (IITs) exploring new immune checkpoint-based combinations and

treatment sequences in metastatic melanoma (MM) and malignant mesothelioma (MMESO) patients. These clinical trials are aimed at: (i) defining the role of new immune checkpoint-based combinations and sequences in poorly explored clinical settings; (ii) improving the overall efficacy of available immunotherapies; and (iii) identifying early pharmacodynamic biomarkers predictive of response to therapy.

Immune-checkpoint combinations in MM patients with brain metastases (BM): the NIBIT-M1 and -M2 clinical trials

Melanoma is the third most common tumor metastasizing to the brain after lung and breast cancer; BM develop in nearly half of MM patients and represent the major cause of tumor-related deaths, making this clinical setting amongst the most daunting problems in oncology [3]. This notion is enforced by the well-known limited efficacy of "standard" chemotherapeutic agents due to their poor central nervous system (CNS) penetration, and to the relative resistance of melanoma BM to radiotherapy. However, in spite of the notion that the blood–brain barrier generally limits CNS penetration of systemic treatments, earlier evidence supported the possible efficacy of the anti-CTLA-4 mAb ipilimumab in melanoma BM as a single agent [4].

The notions above prompted the development of the multi-center phase II, open-label, NIBIT-M1 trial, the first study that combined ipilimumab with the alkylating agent fotemustine in MM patients, allowing subjects with BM to be enrolled. Twenty of the 86 treated patients had asymptomatic BM at study entry; among those, 50% achieved an immune-related (ir) disease control rate (ir-DCR) as compared to 46.5% in the whole population of treated subjects. The combination was found to be safe and well tolerated, with no unexpected and/or overlapping toxicities. Of note, among the 10 patients with multiple BM at baseline who achieved an ir-DCR, only 3 had received previous radiotherapy for brain disease [5]. Prompted by the emerging results on the long-term efficacy of ipilimumab in concurrent clinical trials in MM patients [5], an updated analysis of the NIBIT-M1 study was performed. The 1- and 2-year survival rates were 51.2% and 30.7% and 55.0% and 38.9%, in the whole patient population and in patients with BM, respectively [5]. Furthermore, a 3-year milestone follow-up analysis continued to support the efficacy of the combination in MM patients with BM: at a median follow-up of 39.9 months, the 3-year survival rates were 28.5% and 27.8%, respectively, for the whole study population and for patients with BM [6, 7]. Building on these promising initial findings, and on upcoming data on the efficacy of ipilimumab combined with the anti-PD-1 mAb nivolumab [8], the NIBIT Foundation subsequently designed the ongoing, multi-center, Phase 3, open-label, NIBIT-M2 trial (NCT02460068). The study enrolls first-line MM patients with asymptomatic, untreated BM that will be randomized to receive fotemustine, the combination of ipilimumab and fotemustine, or the combination of ipilimumab and nivolumab (Fig. 1). Primary objective of the NIBIT-M2 study is OS; secondary objectives are safety, DCR in the brain and at extracranial sites, objective response rate (ORR) and duration of response (DOR), evaluated using both the modified-WHO criteria and the ir-response criteria [9]. To date, 79 of the 168 planned patients have been enrolled. Increasing interest in exploring the efficacy of immunotherapy in BM is exemplified by the initiation of additional clinical trials in this dismal clinical setting. Most recently, first results from the randomized phase II ABC (Anti-PD-1 Brain Collaboration for Patients With Melanoma Brain Metastases) trial suggest that nivolumab combined with ipilimumab, and nivolumab, is active in melanoma brain metastases, with 46% of patients achieving an intracranial response with the combination [10]. Further insights on the efficacy of immunotherapy combinations in MM patients bearing BM will also be derived from the ongoing single-arm phase II CheckMate CA209204 study in which nivolumab in combination with ipilimumab has shown clinically meaningful efficacy with an intracranial ORR of 55%, and 21% of patients achieving a complete response [11] More comprehensively, the results of these trials focusing on MM patients with BM will undoubtedly open the way to new studies exploring the efficacy of I-O combinations in patients with BM from different tumor histotypes.

An epigenetic immuno-sequencing study: the NIBIT-M4 clinical trial

Epigenetic events are acknowledged to be involved in all cellular pathways associated with tumorigenesis and cancer progression [12]. More recently, epigenetic modifications have also been clearly shown to play a major role in down-regulating the immunogenicity of cancer cells and their efficient recognition by the host's immune system [13]. Based on this comprehensive evidence, and on the dynamic and pharmacologically reversible nature of epigenetic modifications, epigenetic remodelling of cancer with diverse DNA hypomethylating agents (DHA) has been shown to improve the immunogenicity and immune recognition of neoplastic cells [13, 14]. These results prompted the hypothesis that DHA could represent an ideal "partner drug" to improve the efficacy of diverse immunotherapeutic agents, including therapeutic mAb to immune checkpoint(s) [13]. This notion has been further supported by studies in syngeneic mouse models demonstrating an improved antitumor activity

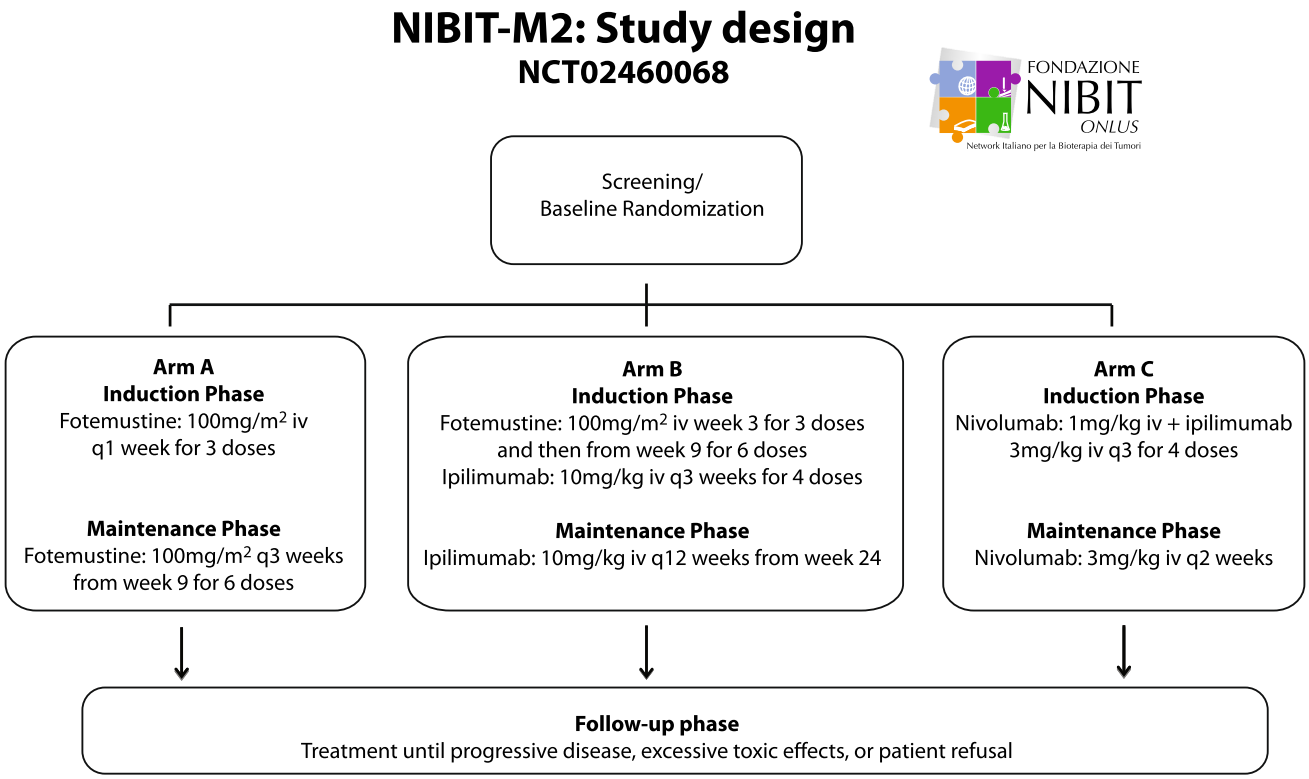

Fig. 1 NIBIT-M2 study design. Melanoma patients with asymptomatic, untreated brain metastases will be randomized to receive fotemustine (ARM A), the combination of ipilimumab and fotemustine (ARM B), or the combination of ipilimumab and nivolumab (ARM C)

of two different DHA (i.e., decitabine and guadecitabine) combined with anti-CTLA-4 and -PD-L1 mAb, compared to either agent alone [15]. These comprehensive findings that were originally generated through the collaboration between the NIBIT Foundation and the CIO of the UHS, are now being translated in the clinic through the ongoing proof-of-principle NIBIT-M4 study (Fig. 2). This study was conceived and developed by the NIBIT Foundation to provide clinical evidence of the potential efficacy of an "epigenetic immune-sequencing" approach in cancer [16]. The NIBIT-M4 trial (NCT02608437) is a phase 1b, dose-escalation study in treatment-naïve or pretreated, unresectable Stage III or Stage IV MM patients, amenable to serial tumor biopsies. The primary objective of the trial is to assess the maximum tolerated dose (MTD) and safety of the next-generation DHA guadecitabine [15] in sequence with ipilimumab; secondary objectives are ir-DCR, -ORR, -progression-free survival (PFS), median OS, and survival rate at 1 and 2 years. Immune-biologic correlates will be exploratory objectives including patient-wise genome-wide methylation, RNA sequencing, and analysis of the tumor immune contexture on tumor biopsies surgically removed at baseline, week (W) 4 and week 12. The dose escalation of guadecitabine follows a 3 + 3 design: cohorts of 3–6 patients receive guadecitabine s.c. on W0, 3, 6, 9, days 1–5 q21d at the one of following doses: Dose Level (DL) − 1: 15 mg/m^2 day; DL 0: 30 mg/m^2 day; DL + 1: 45 mg/m^2 day; DL + 2: 60 mg/m^2 day, and ipilimumab i.v.at 3 mg/kg on W1, 4, 7 and 10, day 1 q21d. Fifteen of the 19 planned patients have been enrolled already and no dose-limiting toxicities have been observed. Preliminary results of the NIBIT-M4 study have been presented as a Late Breaking Abstract at the Annual Meeting of the American Association for Cancer Research, 2018 [17]. Of note, reduced representation bisulfite sequencing analysis of tumor samples from the initial eight patients enrolled in the study demonstrated a reduction in tumor CpG sites' methylation compared to pre-treatment [17]. The efficacy of guadecitabine is currently being investigated in ongoing phase III studies in hematopoietic malignancies (NCT03306264), and earlier evidence showed its demethylating [18] and immunomodulatory activity in patients affected by myelodysplastic syndrome and acute myeloid leukemia [15]. The NIBIT-M4 study foresees extensive translational next generation sequencing studies that will hopefully provide in-depth support to the immunomodulatory activity of guadecitabine also in cancer patients with solid tumors, likely fostering additional clinical trials aimed at improving the therapeutic efficacy of I-O drugs currently available or under clinical development.

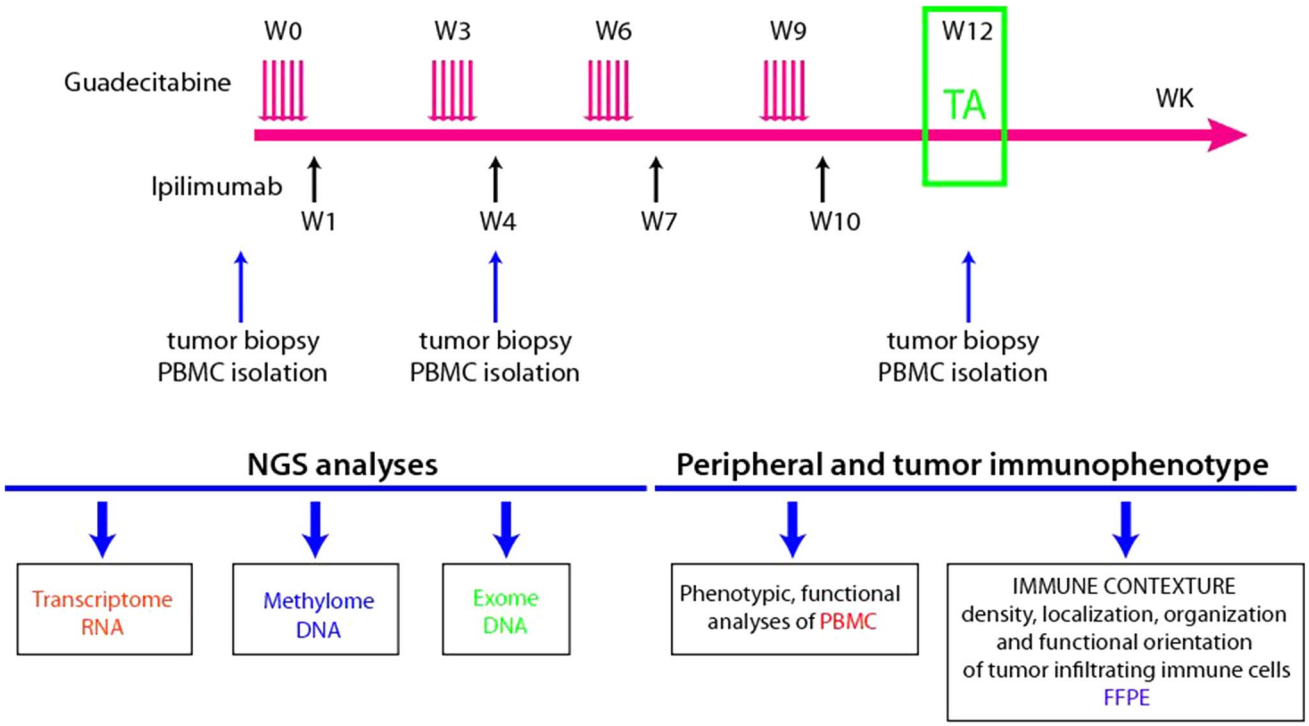

Fig. 2 NIBIT-M4 study design. The NIBIT-M4 trial is a phase 1b, dose-escalation study in unresectable Stage III or Stage IV MM patients, amenable to serial tumor biopsies. The dose escalation of guadecitabine follows a 3 + 3 design: cohorts of 3–6 patients receive guadecitabine s.c. on W 0, 3, 6, 9, days 1–5 q21d and ipilimumab i.v.at 3 mg/kg on W 1, 4, 7 and 10, day 1 q21d. Translational studies on tumor biopsies and on blood samples, planned in the study, are illustrated

Immune-checkpoint combinations in MMESO patients: the NIBIT-MESO-1 clinical trial

Clinical trials investigating the therapeutic potential of immune-checkpoints in patients with MMESO were first developed through joint efforts of the NIBIT, NIBIT Foundation, and the CIO of the UHS. The MESOT-TREM 2008 (NCT01649024) and MESOT-TREM 2012 (NCT01655888) IITs initially explored the activity of the anti-CTLA-4 mAb tremelimumab as a single agent in pretreated MMESO patients [19, 20]. The promising signs of activity identified in these two studies suggested that further exploring the efficacy of immune checkpoint(s) in MMESO was a strategy to be actively pursued and subsequent clinical trials with anti-PD-1/L1 mAb as single agents corroborated this notion [21, 22]. In this rapidly evolving scenario, the NIBIT Foundation developed the IIT NIBIT-MESO-1, the first clinical trial to explore the activity and safety in MMESO patients of the simultaneous targeting of two inhibitory immune-checkpoint molecules (i.e., CTLA-4 and PD-L1) by tremelimumab and durvalumab. Of the 40 treated patients, 11 achieved an ir-ORR and 26 an ir-DCR [23]; comprehensively, the results of the NIBIT-MESO-1 study demonstrate that the combination of tremelimumab and durvalumab is active and has a good safety profile in MMESO patients. This evidence warrants further exploration of combined treatment of MMESO patients, as planned in novel IIT studies being designed by the NIBIT Foundation. An in-depth review of the NIBIT studies above, in the context of the ongoing trials exploring the activity of immune-checkpoint(s) in MMESO, has been recently published [24] as part of a CII series of Focused Research Review based on oral presentations delivered at the XIV Annual Meeting of the NIBIT [25].

Collaboration with the Parker Institute for Cancer Immunotherapy

Within its multiple collaborations with national and international entities (please see the Educational Activities paragraph), the NIBIT Foundation is among the world's leading, academic, non-profit, and industry partners participating in the Tumor neoantigEn SeLection Alliance (TESLA), co-sponsored by the PICI in San Francisco, CA and the CRI in New York, NY. The alliance, announced in December 2016, aims to blindly compare existing and developing methodologies to identify tumor epitopes that may function as optimal targets for cancer immunotherapies, as well as to advance the development of safe and efficacious neo-antigen vaccines.

Analyses will firstly address advanced malignancies expected to harbor high mutational loads such as advanced melanoma, colorectal cancer and non-small cell lung cancer (NSCLC). As the project unfolds, the alliance hopes to move into additional disease areas and stages. Matched normal and tumor tissue are being collected centrally by PICI for DNA and RNA sequencing. The Institute's dedicated team of data scientists is providing a standardized list of sequences for the participating groups to analyze using their local, predictive models. The resulting neo-epitope candidates will be validated centrally by PICI and Sage Bionetworks, a leader in open science data collaboration. Though the neo-antigen alliance hopes to develop novel vaccine targets and treatments, it will be groundbreaking in fostering the collaborative use of bioinformatics. In addition to harnessing the analytical power of the participating research groups, this approach will provide an assessment of each group's algorithm. All partners benefit from the composite data as well as the opportunity to improve upon their predictive models through comparison. This sort of bold, innovative and collaborative approach showcases the founding principles of PICI: an unprecedented partnership between the United States' leading academic, non-profit and industry partners.

PICI research areas of focus

In addition to neo-antigen discovery, PICI is focused on three other major areas of scientific inquiry. The first is on new pathways and synergistic combinations to improve survival rates and broaden the disease areas impacted by checkpoint blockade therapies. Specifically, the institute aims to better understand the mechanisms of resistance around I-O agents, such as PD-1. The second focus centers on developing a new generation of best-in-class cellular therapies and researching new pathways to modulate their activity. This is exemplified by the team's co-funding of what is anticipated to be the United States' first-in-human study utilizing the CRISPR/Cas-9 system. The investigators are striving to engineer more efficient and effective T-cell therapies while minimizing adverse effects, such as autoimmune disorders. Lastly, member scientists of the PICI are focused on establishing a better understanding of the tumor microenvironment through basic and clinical research. The hostile nature of the tumor microenvironment can negatively affect the ability of immune cells and checkpoint inhibitors to work at their fullest, particularly in solid tumors. Creating a broader knowledge base about the tumor microenvironment should help inform the development of effective immunotherapy solutions for solid tumors.

As we are currently in the I-O era, PICI's vision and timing could not be more critical to unlocking the field's unlimited potential. First-generation I-O agents such as CTLA-4, PD-1 and PD-L1 inhibitors are becoming mainstays in the clinic and are increasingly used in a multi-disciplinary approach. According to the Cancer Research Institute, there are approximately 970 immuno-oncology agents in clinical development, with more than 1,100 clinical trials involving anti-PD-1 or anti-PD-L1 agents in combination with other therapies.

With each discovery, and quickly-advancing technologies, it is clear researchers are facing the challenge of an increasingly complex field. We have reached an inflection point in how biomedical research is conducted. Pharmaceutical companies are collaborating and investigating novel combinations based on the emerging science; however, the current research structure has not allowed the knowledge and expertise of academic centers to participate in such open collaboration. These hurdles are compounded by the limitations and instability of strained resources, insufficient funding and time-consuming reporting.

A new model to support I-O research

PICI offers a solution: the centralization and leveraging of resources to overcome these barriers. Over 40 industry and non-profit partners, more than 60 labs and more than 170 of the United States' top researchers have come together to join efforts on PICI's projects and trials. PICI's strengths include coordinated trial management, biorepository development and standardization, access to novel investigational agents (in novel combinations), as well as open data sharing and robust analytics. These provisions, combined with the centralization of funding and intellectual property management, have created an ecosystem within which to establish long-term relationships with industry and academic partners, as well as provide flexibility and support around licensing and research decisions. The result is unified research management, freeing researchers to focus on their discoveries. For clinical trials, PICI also utilizes in-house resources, with the aim of taking the additional burden of multi-center trial management off their academic center partners and providing greater efficiency as well as continuity across trials.

Since its launch in April 2016, PICI has already met several key partnership and clinical development milestones. In 2017, PICI began a strategic, multi-year clinical collaboration with Bristol-Myers Squibb and CRI. The partnership has greatly contributed to the Institute's capacity for developing and managing multi-center clinical trials. Working together with those partners, PICI launched a groundbreaking trial to evaluate the safety and efficacy of combining an anti-CD40 agent, a PD-1 inhibitor and standard of care chemotherapy to treat metastatic pancreatic cancer.

As the number of industry partnerships increases, it will allow for a less limited degree of clinical exploration, no longer restricted to a single pipeline. In addition to these industry, academic, and start-up partnerships, the institute is

investing in developing novel modes of bioinformatics analysis. These technologies will allow for the generation of more robust, translational data at the single cell level and will be made available to all members. Through its partnerships and areas of focus, it is clear PICI is uniquely positioned to truly shift the paradigm of how biomedical research is conducted. With such a concerted effort behind the mission, the implication is great for the number of patients they stand to impact through their efforts.

Perspectives

In the years to come, I-O will undoubtedly stay at the forefront of cancer treatment. However, its optimal exploitation in clinical trials investigating novel targets and new therapeutic combinations and in daily practice, will undoubtedly require significant efforts by the multifaceted I-O community. From this perspective, non-profit entities such as the NIBIT Foundation will continue to play a major role through the development of scientifically sound, proof-of-principle clinical trials and through the conception and implementation of high-level educational activities.

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Author contributions AMDG and MM wrote the first draft of this paper based in part on the talks of RI at the NIBIT 2017 meeting in Siena. AC and GG wrote the section "Educational Activities". JL and RI wrote the section "Collaboration with the Parker Institute for Cancer Immunotherapy" PGN revised the manuscript. All authors critically discussed the manuscript, contributed to its contents, and checked and approved the final version.

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Compliance with ethical standards

Conflict of interest Anna Maria Di Giacomo served on the advisory board of Bristol-Myers Squibb, Incyte, Pierre Fabre, Glaxo Smith Kline and she is a member of the scientific board of directors of the NIBIT Foundation; Ramy Ibrahim is a member of the scientific advisory board of: Arcus, Harpoon, Immunovaccine and ImaginAB;Jaclyn Lyman is a PICI employee; Pier Giorgio Natali is a member of the scientific board of directors of the NIBIT Foundation; Michele Maio served on advisory boards of Bristol-Myers Squibb, Roche-Genentech, Merck Sharp Dohme and AstraZeneca-MedImmune, and he is the president of the NIBIT Foundation. The authors declare that there are no other conflicts of interest.

References

1. Maio M, Fonsatti E (2014) The Italian Network for Tumor Biotherapy (NIBIT): past, present and future goals. Rev Health Care 5(1):3–6. https://doi.org/10.7175/rhc.v5i1.896
2. Maio M, Lofiego MF, Fazio C, Cannito S, Chiarucci C, Giacobini G, Valente M, Tunici P, Covre A, Russo V (2018) Fifteenth Meeting of the Network Italiano per la Bioterapia dei Tumori (NIBIT) on Cancer Bio-Immunotherapy, Siena, Italy, October 5–7, 2017. Cancer Immunol Immunother. https://doi.org/10.1007/s00262-018-2222-0
3. Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, Moon J, Sondak VK, Atkins MB, Eisenhauer EA, Parulekar W, Markovic SN, Saxman S, Kirkwood JM (2008) Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 1 26(4):527–534. https://doi.org/10.1200/JCO.2007.12.7837
4. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, Wolchok JD, Clark JI, Sznol M, Logan TF, Richards J, Michener T, Balogh A, Heller KN, Hodi FS (2012) Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 13:459–465. https://doi.org/10.1016/S1470-2045(12)70090-6
5. Di Giacomo AM, Ascierto PA, Pilla L, Santinami M, Ferrucci PF, Giannarelli D, Marasco A, Rivoltini L, Simeone E, Nicoletti SV, Fonsatti E, Annesi D, Queirolo P, Testori A, Ridolfi R, Parmiani G, Maio M (2012) Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. Lancet Oncol 13:879–886. https://doi.org/10.1016/S1470-2045(12)70324-8
6. Maio M, Grob JJ, Aamdal S, Bondarenko I, Robert C, Thomas L, Garbe C, Chiarion-Sileni V, Testori A, Chen TT, Tschaika M, Wolchok JD (2015) Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol. 33(10):1191–1196. https://doi.org/10.1200/JCO.2014.56.6018
7. Di Giacomo AM, Ascierto PA, Queirolo P, Pilla L, Ridolfi R, Santinami M, Testori A, Simeone E, Guidoboni M, Maurichi A, Orgiano L, Spadola G, Del Vecchio M, Danielli R, Calabrò L, Annesi D, Giannarelli D, Maccalli C, Fonsatti E, Parmiani G, Maio M (2015) Three-year follow-up of advanced melanoma patients who received ipilimumab plus fotemustine in the Italian Network for Tumor Biotherapy (NIBIT)-M1 phase II study. Ann Oncol 26(4):798–803. https://doi.org/10.1093/annonc/mdu577
8. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2 373(1):23–34. https://doi.org/10.1056/NEJMoa1504030
9. Di Giacomo AM (2015) A randomized, phase III study of fotemustine versus the combination of fotemustine and ipilimumab or the combination of ipilimumab and nivolumab in patients with metastatic melanoma with brain metastasis: the NIBIT-M2 trial. J Clin Oncol. https://doi.org/10.1200/jco.2015.33.15_suppl.tps9090
10. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, Wilmott JS, Edwards J, Gonzalez M, Scolyer RA, Menzies AM, McArthur GA (2018) Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multi centre randomised phase 2 study. Lancet Oncol 19(5):672–681. https://doi.org/10.1016/S1470-2045(18)30139-6
11. Tawbi HAH, Forsyth PAJ, Algazi AP, Hamid O, Hodi FS, Moschos SJ, Khushalani N, Gonzalez R, Lao C, Postow M, Atkins MB, Ernstoff M, Puzanov I, Kudchadkar R, Thomas R, Tarhini A, Jiang J, Avila A, Demelo S, Margolin K (2017) Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with

melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204. J Clin Oncol. https://doi.org/10.1200/JCO.2017.35.15_suppl.9507
12. Chatterjee A, Rodger EJ, Eccles MR (2017) Epigenetic drivers of tumourigenesis and cancer metastasis. Semin Cancer Biolpii. https://doi.org/10.1016/j.semcancer.2017.08.004
13. Maio M, Covre A, Fratta E, Di Giacomo AM, Taverna P, Natali PG, Coral S, Sigalotti L (2015) Molecular pathways: at the crossroads of cancer epigenetics and immunotherapy. Clin Cancer Res 21(18):4040–4047. https://doi.org/10.1158/1078-0432.CCR-14-2914
14. Sigalotti L, Fratta E, Coral S, Maio M (2014) Epigenetic drugs as immunomodulators for combination therapies in solid tumors. Pharmacol Ther 142(3):339–350. https://doi.org/10.1016/j.pharmthera.2013.12.015
15. Covre A, Coral S, Di Giacomo AM, Taverna P, Azab M, Maio M (2015) Epigenetics meets immune checkpoints. Semin Oncol 42(3):506–513. https://doi.org/10.1053/j.seminoncol.2015.02.003
16. Di Giacomo AM, Covre A, Taverna P, Coral S, Amato G, Keer HN, Lowder J, Giannarelli D, Azab M, Maio M (2016) A phase Ib study combining the second-generation DNA hypomethylating agent (DHA) guadecitabine (SGI-110) and ipilimumab in patients with metastatic melanoma: The NIBIT-M4 study. J Clin Oncol. https://doi.org/10.1200/JCO.2016.34.15_suppl.TPS9595
17. Di Giacomo AM, Covre A, Finotello F, Rieder D, Sigalotti L, Fazio C, Cutaia O, Bock C, Petitprez F, Lacroix L, Lowder J, Fridman WH, Sautès-Fridman C, Trajanoski Z, Maio M (2018) Epigenetic tumor remodelling to improve the efficacy of immune checkpoint blockade: the NIBIT-M4 clinical trial. Cancer Res 78(13 Supplement):CT059. https://doi.org/10.1158/1538-7445.AM2018-CT059
18. Issa JJ, Roboz G, Rizzieri D, Jabbour E, Stock W, O'Connell C, Yee K, Tibes R, Griffiths EA, Walsh K, Daver N, Chung W, Naim S, Taverna P, Oganesian A, Hao Y, Lowder JN, Azab M, Kantarjian H (2015) Safety and tolerability of guadecitabine (SGI-110) in patients with myelodysplastic syndrome and acute myeloid leukaemia: a multicentre, randomised, dose-escalation phase 1 study. Lancet Oncol 16(9):1099–1110. https://doi.org/10.1016/S1470-2045(15)00038-8
19. Calabrò L, Morra A, Fonsatti E, Cutaia O, Amato G, Giannarelli D, Di Giacomo AM, Danielli R, Altomonte M, Mutti L, Maio M (2013) Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. Lancet Oncol 14(11):1104–1111. https://doi.org/10.1016/S1470-2045(13)70381-4
20. Calabrò L, Morra A, Fonsatti E, Cutaia O, Fazio C, Annesi D, Lenoci M, Amato G, Danielli R, Altomonte M, Giannarelli D, Di Giacomo AM, Maio M (2015) Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Lancet Respir Med 3(4):301–309. https://doi.org/10.1016/S2213-2600(15)00092-2
21. Alley EW, Lopez J, Santoro A, Morosky A, Saraf S, Piperdi B, van Brummelen E (2018) Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncol 18(5):623–630. https://doi.org/10.1016/S1470-2045(17)30169-9
22. Quispel-Janssen J, van der Noort V, de Vries JF, Zimmerman M, Lalezari F, Thunnissen E, Monkhorst K, Schouten R, Schunselaar L, Disselhorst M, Klomp H, Hartemink K, Burgers S, Buikhuisen W, Baas P (2018) PD-1 blockade with nivolumab in patients with recurrent Malignant Pleural Mesothelioma. J Thorac Oncol. https://doi.org/10.1016/j.jtho.2018.05.038
23. Calabrò L, Morra A, Giannarelli D, Amato G, D'Incecco A, Covre A, Lewis A, Rebelatto MC, Danielli R, Altomonte M, Di Giacomo AM, Maio M (2018) Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2study. Lancet Respir Med 6(6):451–460. https://doi.org/10.1016/S2213-2600(18)30151-6
24. Calabrò L, Morra A, Cornelissen R, Aerts J, Maio M (2018) Immune checkpoint blockade therapy of mesothelioma: a clinical and radiological challenge. Cancer Immunol Immunother. https://doi.org/10.1007/s00262-018-2191-3
25. Russo V, Chiarucci C, Lofiego MF, Fazio C, Bertocci E, Cutaia O, Giacobini G, Lazzeri A, Lamboglia A, Altomonte M, Tunici P, Covre A, Maio M (2018) Fourteenth meeting of the network Italiano per la Bioterapia dei Tumori (NIBIT) on cancer bio-immunotherapy, Siena, Italy, October 13–15, 2016. Cancer Immunol Immunother 67(6):1023–1030. https://doi.org/10.1007/s00262-017-2078-8