Cancer Immunotherapy 2017 (Paris, France). Progress and challenges

Cancer Immunotherapy 2017 (Paris, France). Progrès et défis

The international conference Cancer Immunotherapy 2017 took place in Paris, France, November 27th–28th 2017. This conference was organized by Salem Chouaib (Institut Gustave Roussy, Villejuif, France) and Claude Leclerc (Institute Pasteur, Paris, France), with main financial support from the Institut National du Cancer and Aviesan/ITMO Cancer. The conference brought together an impressive list of renowned national and international speakers and hosted more than 300 registered attendants. Thus, the conference served as a unique comprehensive workshop uniting researchers, clinicians and pharmaceutical partners to discuss the present and future perspectives in the exciting and rapidly evolving field of Cancer Immunotherapy. Over two days, seven sessions and expert round table discussions, a broad range of timely and relevant topics were covered, including immune checkpoint inhibitors (ICI), co-stimulatory molecules and combination therapy regimens. Tumor microenvironment as a mediator of immune suppression and novel approaches to analyze and target the immune-suppressive niche were also covered. Design of cancer vaccines and adoptive T-cell immunotherapy and therapeutic improvements thereof were also presented, as well as the potential benefits of combination therapies and anticancer probiotics to reinvigorate endogenous immune responses. A particular strength of the Conference Cancer Immunotherapy 2017 was the substantial contribution of novel, unpublished data by several speakers.

Immune checkpoint blockers and co-stimulatory molecules

The introduction of immune checkpoint inhibitors, mainly Ipilimumab (anti-CTLA4), and Nivolumab or Pembrolizumab (anti-PD1) and Atezolizumab (anti-PD-L1) marks a prominent paradigm shift in cancer treatment. We have experienced the transformation of metastatic melanoma from an incurable to a curable disease for an important number of patients, with accompanying 5 year-survival rates increasing from less than 5% to more than 50%. Furthermore, the impact of anti-PD1 is surpassing all expectations due to its impact across tumor types and today anti-PD1/PD-L1 agents have been approved for a broad range of tumors, in addition to any type of tumor with extremely high mutational burden due to DNA repair deficiency called microsatellite instability (MSI). Researches are currently focused on establishing predictive biomarkers, to identify the patients who will benefit from ICI, and to understand the mechanisms of failure in the poorly and non-responding tumors. An important clinical challenge now lies within the design of optimal combination regimens with the potential to enhance the fraction of responders and/or improve the extent and durability of patient responses. An additional remaining challenge for clinicians is to find the best appropriate treatment regimen and dosage for combination therapy. Reducing the dosing in order to both diminish the cost and the serious side-effects and toxicities is also to be considered, particularly in regimens involving Ipilimumab (anti-CTLA4). In line with this thinking, there is also a need to identify biomarkers not only to guide treatment decision, but also to better predict when to stop the treatment. This concern was raised particularly by Alexander M. M. Eggermont (Institut Gustave Roussy, Villejuif, France), who also suggested that the combination studies should preferably be guided by agents inducing an immunogenic form of cell death (ICD), such as the Paclitaxel and Carboplatin combinations discussed at the conference. As further pointed out by Professor Eggermont, melanoma will likely lead the way in the exploration of multiple immune-oncology combination regimens, including various combinations of checkpoint-inhibitors plus cytokines, vaccines, or monoclonal antibodies, as well as the combinations with adoptive transfer of T-cells. As we have learned, several approved targeted therapy compounds have unexpected immune modulatory effects which again raises additional hope related to their potential performance in combination with immune checkpoint inhibitors.

Since the introduction of the kinase inhibitors in the treatment of oncogene addicted tumors, a second therapeutic revolution in the treatment of NSCLC is mediated by the emergence of ICI. The question whether there is still a place for ICI in the context of oncogene addiction were discussed by Jacques Cadranel (Hôpital Tenon, Paris, France). Recently, Pembrolizumab has demonstrated its superior efficacy as first line treatment of NSCLC, compared to a platinum-based doublet chemotherapy in patients with strong PD-L1 expression. Alongside clinical and biological factors, PD-L1 expression was associated with greater likelihood of efficacy. Amongst these, the presence of addictive molecular alterations such as EGFR mutation were found to be associated with greater likelihood of ICI efficacy. Preclinical studies also seem to support the notion that EGFR or ALK alterations are associated with an increased PD-L1 expression. Improved preclinical models are needed to better explore the

BULCAN-547

E. Chouaieb, S. Terry, S. Corgnac, AST. Engelsen

specific immune responses and to define the best therapeutic sequence in this context. It remains to be explored if this holds true also for other oncogene addictions found with varying frequencies in other malignancies, and the impact of EGFR mutant and ALK rearranged NSCLC. The ATLANTIC phase-II multi-cohorts trial will likely highlight the impact of EGFR/ALK alterations and their recognition by the immune system. Current situation and challenges for immunotherapy in kidney cancer were discussed by Bernard Escudier (Institut Gustave Roussy, Villejuif, France). Despite standard therapeutic regimen for renal cell carcinoma (RCC) including molecularly targeted agents like VEGFRi, RTKi and mTORi, treatment outcomes are still poor. In this disease PD-L1 expression has proven its value for prognostic purpose and based on a large phase-3 study, PD-1 inhibitor were recently approved as second line therapy for patients who relapsed on anti-angiogenic therapy. With regards to PD-L1 as a predictor of therapy response, discrepancies were noted among studies and therefore, PD-L1 testing deserves further evaluation in this setting. Thus, an important effort in the future will be dedicated to test combination approaches with the abovementioned targeted agents (VEGFRi, RTKi, mTORi) or combining immunotherapies. Exploratory results from the phase III clinical trial "Checkmate 214" suggest improved efficacy of Nivolumab + Ipilimumab as first-line treatment for treatment-naïve advanced or metastatic clear-cell RCC patients. And these results support the use of Nivolumab + Ipilimumab as a new first-line standard of care option for patients with ccRCC. The importance of inducing an immunogenic form of cell death in combination with immune checkpoint inhibitors were highlighted by several speakers over the two days and the promising concept of combining immunogenic chemotherapies with immune oncology (IO) drugs were particularly well covered by Francois Ghiringhelli (Centre de Recherche Inserm-LNC, Dijon, France). As supported by preclinical evidence from this group, some chemotherapy agents could both stimulate effector functions of tumor infiltrating CD8+ lymphocytes and promote an exhaustion state in those potentially targetable by immunotherapies.

Tumor microenvironment and novel approaches to analyze and target the tumor microenvironment to combat immunosuppression

In recent years, it has become increasingly clear that an immunosuppressive tumor microenvironment is one of the major obstacles to an efficient therapy response, not only limiting the IO therapy response but also limiting the clinical efficacy of other conventional therapies. Thus, major research efforts are currently being undertaken to elucidate the cellular and molecular mechanisms involved in the search for novel targets. Gregg L. Semenza (Johns Hopkins University School of Medicine, Baltimore, USA) presented preclinical data to suggest that the addition of an inhibitor of hypoxia inducible factor (HIF) in combination with chemotherapy could counteract the innate and adaptive immune evasion in the setting of triple negative breast cancer (TNBC). It has been shown that TNBC cells that survive chemotherapy have increased expression of HIFs, which in turn increase transcription of genes promoting and maintaining tumor cell with a stem cell like phenotype. Dr. Semenza and his research team observed that several immuno-modulatory molecules such as CD47, PD-L1 and CD73 are direct HIF target genes in TNBC cells. Especially, CD47 which blocks "eat me signals" on cancer cells by interacting with SIRP on macrophages and consequently inhibits phagocytosis. Interestingly, different chemotherapy regimens may have various impact on the expression of these immuno-modulators, adding yet another level of complexity to take into account in further studies.

Another important microenvironmental factor supressing efficient antitumor immune response is the presence of indoleamine 2,3-dioxygenase 1 (IDO1) mediated tryptophan catabolism. Benoit Van den Eynde (Ludwig Institute for Cancer Research, Brussels, Belgium) showed that constitutive IDO1 expression induced by IFNγ can prevent T-cell infiltration and result in immunologically "cold" tumors in preclinical mouse models. His team found that the presence of constitutive IDO1 depends on COX-2 and prostaglandin E2 (PGE2) which in turn activates IDO1 via PKC and PI3K pathways. Furthermore, Celecoxib treatment was shown to promote immune rejection of IDO1-expressing human tumor xenografts in immunodeficient mice reconstituted with human allogeneic lymphocytes. This effect was associated with a reduced IDO1 expression and an increased infiltration of CD8+ T-cells. Phase III clinical trial with an IDO1 inhibitor (Epacadostat) in combination with anti-PD-1 (Pembrolizumab) is currently ongoing for different indications (ECHO trial). Work by Van den Eynde and his research team, further suggested that in an immune-suppressive tumor microenvironment, agents such as anti-IFNγ or agents disrupting the Fas/Fas Ligand signaling axis could be used to improve cancer immunotherapies, as elegantly shown in their preclinical models. In this setting, Anti-Fas Ligand could prevent apoptosis of the tumor infiltrating lymphocytes which is otherwise induced by the high Fas Ligand expression on granulocytic myeloid derived suppressor cells (MDSCs) in the tumor microenvironment. Blocking Fas-ligand increased the anti-tumor efficacy of adoptive cell therapy in their melanoma model and were also shown to increase the efficacy of checkpoint blockade.

It is evident from this meeting that much still remains to be explored regarding the heterogeneity of the immune and inflammatory components of the microenvironment of human tumors and it is clear that this characterization is crucial in order to define new prognostic and theranostic markers. Furthermore, it is becoming increasingly evident that the immune effector cells represent a continuum of cells displaying functional and phenotypic plasticity and as highlighted by several speakers, as these particular subsets of immune cells are poorly defined in terms of

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markers and functional characteristics, there is still an urgent need to characterize the subsets in order to enable clever design of improved cancer immunotherapy regimens. As novel technology enables in-depth analysis of the intratumoral immune responses, the information from single cell molecular signatures will be crucial in order to enable identification of novel and more selective targets for cancer immunotherapy. Regulatory T cells (Treg) are immunosuppressive cells, which generally suppress or downregulate the induction or proliferation of effector T cells. Treg gene signatures have been shown to correlate with poorer survival both in colorectal cancer (CRC) and non-small cell lung cancer (NSCLC) and single cell analysis of the tumor infiltrating CD4+ T cells and Treg populations indicate a certain degree of heterogeneity in these subsets. Sergio Abrigani (INGM, Milan, Italy) also showed that tumor infiltrating CD4+ T cells were enriched in Treg cells and in "unconventional" CD4+ T cell subsets with high immune-suppressive potential. His research team better characterized the tumor infiltrating Treg subsets and demonstrated that surprisingly some Treg subsets lack the immuno-suppressive profile and are unable to prevent the proliferation of cytotoxic T-lymphocytes (CTL). These findings also serve to emphasize that in order to define novel principles, rules and mechanisms of intratumoral immune responses it is of uttermost importance that the immune cells are studied by the refined methodologies and preferably at the single cell level [1,2].

Michele De Palma (ISREC, EPFL, Lausanne, Switzerland) discussed the importance of vascular-borne immunosuppressive mechanisms in the tumor microenvironment, and his novel findings support the rationale for targeting angiogenesis to enhance antitumor immunity. A combination of Angiopoietin-2 (ANGPT2) and vascular endothelial growth factor (VEGF) specific blockade by bispecific antibodies were shown to provide synergistic antitumoral benefits in genetically engineered and transplant tumor mouse models. In addition to vascular normalization and regression, bi-specific antibodies were shown to induce cancer cell death and macrophage reprogramming, as well as increased tumor antigen presentation by intratumoral macrophages.

Janis Marie Taube (Johns Hopkins University School of Medicine, Baltimore, USA) gave a thorough update on PD-L1 as potential biomarker for response to ICI, with an emphasis on the promise of novel technologies like multiplex immunostaining and development of automated precision image analysis tools. She argued that LAG3, another inhibitory receptor, is co-expressed with PD-L1 in melanoma and could also be a potent predictive biomarker. It is becoming increasingly evident that the tremendous complexity of cancers requires comprehensive analysis of the tumor microenvironment. Thus, the concept of cancer immune-contexture and the standardized, simple and powerful digital pathology-based immune stratification system "Immunoscore" were presented and discussed by Jérôme Galon (Centre de recherche des Cordeliers, Paris, France). Immunoscore is a methodology defined to quantify the in situ immune cell

infiltrate in tumors, including cell type, density and location in the tumor [3]. Dr Galonemphasized in his presentation some of the requirements for proper validation of candidate biomarkers in the oncoimmunology field and shared his enthusiasm for the novel enabling technologies for multiplex phenotyping like mass cytometry (CyTof) that allows evaluation of the tumor microenvironment with single cell resolution and spatial information for up to 40 parameters. A worldwide consortium has validated the prognostic value of "Immunoscore" as especially relevant in the setting of colorectal carcinoma and importantly the results are also encouraging for future routine implementation for a wide range of cancers. Furthermore, stratification of patients based on their immune-status requires improved and standardized, objective and quantitative assays allowing a proper immune classification. This need is the very rationale for "Immunoscore", and will in turn allow a better stratification of patients for future clinical trials. The proper multiplex classification tools of prognostic and predictive value will also be particularly important in the clinic in the current era of combination therapies.

Design of therapeutic improvements by oncolytic viruses, cancer vaccines

Using engineered viruses to activate antitumor activity is a promising therapeutic avenue for combination with immune checkpoint inhibitors. Clinical development of Poxvirus based oncolytic viruses (OV) is focused on safety, biodistribution, activity and early proof of concept. Vaccinia virus based OV display a good therapeutic index. An extensive overview of the features of the next generation poxvirus based immunotherapeutics were presented by Eric Quemeneur (Transgène, Strasbourg, France). A benefit of Vaccina based oncolytic viruses compared to OV of other viral origin is the large genome size allowing insertion of more therapeutic "cargo". By the local transgene delivery, armed OV therapy may benefit from the "bystander effect" which is the killing of tumor cells adjacent to the infected cell by spreading of the transgene products to cells adjacent to the infected cell. Recently, it has also been shown that Poxvirus based OV can contribute to warm up cold tumors and induce and immunogenic form of cell death. It is expected that the next generation oncolytic viruses (OV) will work in synergy with other immunotherapy regimens, like adaptive cell therapies. The ability to reprogram the tumor microenvironment is a particularly appealing feature of the armored OV. By secretion of chemokines and enzymes produced in the tumor bed, the armored OV has the potential benefit of altering the immune contexture. Being an exciting new therapeutic class, still the best is probably yet to come for oncolytic viruses, which are currently being tested in a total of 73 ongoing clinical trials [4]. Sjord Van der Burg (Leiden University Medical Center, Leiden, Netherlands) discussed how chemotherapy could be used to improve the therapeutic efficacy of cancer vaccines, partially

Bulletin du CANCER

3

E. Chouaieb, S. Terry, S. Corgnac, AST. Engelsen

through normalization of the myeloid cell compartment and he emphasized that vaccines should be administered during treatment, rather than after treatment whenever possible. Patients with advanced gynecological cancers enrolled in the phase I/II CervISA study receive a combination of chemotherapy (carboplatin-paclitaxel) and vaccination (using synthetic long peptide (SLP) vaccine targeting E6 and E7 of HPV16). Potentiated T-cell responsiveness and improved clinical outcomes in patients with advanced cervical cancer has been shown and extensive immune monitoring revealed that myeloid cell depletion was associated with a robust and sustained induction of HPV16-specific T-cell response. Preliminary overall survival data point to the potential long-term benefit, especially for previously untreated patients.

In recent years, publications have demonstrated the essential role of the Fc part of antibodies in modulating the in vivo activity of checkpoint targeting antibodies. Sergio Quezada (ULC Cancer Institute, London UK) demonstrated that high polymorphism of Fc receptors (FcR) is beneficial for the anti-CTLA-4 response. He presented his work on an optimized anti-CD25 antibody with enhanced binding to FcR, which resulted in higher depletion of immune-suppressive intratumoral Treg cells and a better control of tumor growth. The anti-CD25 antibody therapy were also shown to work in synergy with PD-1 blockade in a murine fibrosarcoma model. A single dose of the optimized anti-CD25 antibody followed by anti-PD-1 therapy was shown to eradicate established tumors in 78.6% of the mice, resulting in long-term survival of more than 100 days.

The fact that the tumors' mutational load correlates with clinical response to immune checkpoint inhibitors has been known for some time. However, a major challenge, even for tumors with high mutational burden is that only a very small fraction of the mutations generate an efficient T-cell response and these are not necessarily the driver mutations. Lélia Delamarre (Genentech – South San Fransisco, USA) reviewed the general properties of immunogenic neoantigens as well as the methods currently used to identify them. Delamarre gave an illustrative example from a melanoma patient who had 1099 identified mutations and 49 predicted neoantigens, but in fact only 9 were verified immunogenic neoantigens, underscoring the fact that we still do not fully understand the peptide processing and that there is still room for improvement of the currently available prediction tools. Delamarre highlighted that prediction strategies to efficiently identify immunogenic neoantigens could facilitate the generation of potent personalized vaccines and also the tracking of tumor-specific T-cells following immunotherapy.

Microbiota and the importance of the recently discovered anticancer probiotics to re-establish the cancer immunology set-point

As highlighted by the keynote-speaker Giorgio Trinchieri (Cancer and Inflammation Program, NIH-NCI, Bethesda, USA),

commensal microorganisms colonize the barrier surfaces of all multicellular organisms and they affect immune – and non-immune functions of their hosts to such an extent that the two together de facto comprise one meta-organism. It has recently been reported that the microbial imbalance may play a crucial role not only in cancer initiation and development, but microbial imbalance also affect the response to various forms of cancer therapy, including chemotherapy and immunotherapy. The high predictive value of microbiota sequencing were demonstrated by Thomas Gajewski [5] (University of Chicago, Chicago, USA), who also revealed that of the 12 signaling pathways currently under active investigation for lack of T-cell infiltration, several pathways are immediately targetable. The progress relating to the classification of the "good" or "favorable" strains of microbiota and the possibility of using probiotics in order to improve the immunotherapy response was well covered and supported by the speakers. The importance of the microbiota in cancer therapy was further discussed in depth by Laurence Zitvogel (Institut Gustave Roussy, Villejuif, France). As shown in a recent study from her group, antibiotics (ATB) regimens could negatively influence the response to anti-PD1 in advanced cancer patients. An elegant follow-up study from her group also indicated that transfer of fecal microbiota from cancer patients who responded well to ICI, but not from non-responding patients into germ-free or ATB-treated mice ameliorated the antitumor effects of PD-1 blockade [6]. A particular strain was identified as especially relevant in mediating these effects, Akkermansia muciniphila. Furthermore, oral supplementation with A.municiphila afterpost-fecal microbiota transplantation with non-responder feces was also able to restore some efficacy of PD-1 blockade in this model.

Chimeric antigen receptor (CAR) T-cell therapies

For chimeric antigen receptor (CAR) T-cell therapies, remarkable achievements in immune cell engineering has fostered synthetically engineered CAR T-cells with improved efficacy that serve as a powerful and promising new class of cancer therapeutics [7]. Recent improvements and strategies were presented by keynote-speaker Carl H. June (Perelman School of Medicine, University of Pennsylvania, USA). The emergence of novel gene engineering tools like the CRISPR/Cas9 platform establishes CAR T-cell therapy as a powerful new class of cancer therapeutics and the design of the next generation T-cell precision therapeutics were discussed. Moreover, the clinical benefit observed in B-cell malignancies have helped define the major challenges ahead that need to be addressed in order to make CAR T-cells a reliable, safe and effective platform for a broader range of cancers, including solid tumors [8]. In this respect, a target activity has been detected by EGFRvIII and IL-13-R-alpha CAR T-cells in recurrent gliomas, although this approach has not yet resulted in complete tumor eradication. In preclinical studies, TCR-specific CAR T-cells have been shown to display higher anti-tumor

activity following disruption of the naïve TCR alpha and beta genes and the PD1 gene using multiplexed CRISPR/Cas9 technology and clinical trials have been initiated. The remaining engineering and biological challenges were discussed, including the need to scale up the manufacturing process, decrease infusion toxicity and to increase the durability of the response [9].

Justin Eyquem (Memorial Sloan Kettering Cancer Center, New York, USA) further presented very interesting and innovative genome editing-based strategies to study CAR immuno-biology and to improve the performance as well as the safety of CAR T-cells. One of the strategies discussed includes optimization of the DNA position for genomic insertion of the CAR gene and Eyquem and his research team has shown that insertion into the T-cell receptor alpha constant (TRAC) locus offers an optimal regulation of the cell surface expression and delays T-cell exhaustion. The optimized CAR expression level, leads to enhanced function and anti-tumor efficacy compared to random integration or integration in different transcriptional configurations. Taken together, much optimism is linked to the further development of CAR T-cell therapy and the safe and efficient implementation of CAR T-cell therapy is expected in a broader range of tumors in the near future.

Roundtable discussion and summary of progress and challenges

The roundtable discussion highlighted the support of broader initiatives to identify and validate novel prognostic, predictive and mechanistic biomarkers, as well as the need to establish combinatorial immune signature markers for better stratification of patients. Multiplex approaches in the pipeline that were discussed during the meeting includes the multiplex qPCR or nanostring monitoring of altered composition of gut microbiota as well as the improved multiplex imaging modalities of tumor samples that also allows for a tracking of the dynamic tumor microenvironment. Assays for improving patient selection algorithms and next generation biomarker assays like multiplex immunohistochemistry/immunofluorescence assays were discussed by Janis Marie Taube (Johns Hopkins University School of Medicine, Baltimore, USA) at this meeting, in addition to the standardized and powerful digital-pathology based immune stratification system immunoscore based on the concept of cancer immune contexture, presented by Jérome Galon (Institute Gustave Roussy, Villejuif, France). The issues of potential sampling bias as well as the aim to better monitor the dynamic alterations over the treatment time-course still needs to be adequately addressed by the research community. Thus, as highlighted at this conference, efforts and approaches of more in-depth monitoring of patients enrolled in clinical trials should be encouraged and aided by the improved technological platforms and state of the art technologies. This issue clearly deserves a stronger focus alongside the initiatives to increase collaboration and sharing of sample material and results obtained in the trials to come. These efforts could collectively benefit faster developments in the field.

Conclusion

The conference "Cancer Immunotherapy 2017 Progress and Challenges'' successfully brought together leading researchers, clinicians and pharmaceutical partners to evaluate the progress and challenges in the field of immunotherapy – the medical revolution we are living today. By sharing the details of the progress made in different areas of the immunotherapy field, as well as witnessing the remarkable benefit for a subset of patients, the organizers concluded the Cancer Immunotherapy 2017 conference by highlighting their huge expectations for the next few years and especially the optimism related to the ongoing efforts discussed as well as to the active clinical trials.

Disclosure of interest: the authors declare that they have no competing interest.

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Elyes Chouaieb[1], Stéphane Terry[2], Stéphanie Corgnac[2], Agnete Svendsen Tenfjord Engelsen[2,3]

[1]Université Paris Sud, faculté de pharmacie, 5, rue Jean-Baptiste-Clément, 92290 Châtenay-Malabry, France
[2]Université Paris-Sud, université Paris-Saclay, faculté de médecine, Integrative Tumor Immunology and Genetic Oncology, Inserm UMR 1186, Gustave-Roussy, 114, rue Edouard-Vaillant, 94805 Villejuif, France
[3]University of Bergen, Centre for Cancer Biomarkers (CCBIO), Department of Biomedicine, Jonas Lies vei 91, 5009 Bergen, Norway

Correspondence: Agnete Svendsen Tenfjord Engelsen, University of Bergen, Centre for Cancer Biomarkers (CCBIO), Department of Biomedicine, Jonas Lies vei 91, 5009 Bergen, Norway
agnete.engelsen@uib.no