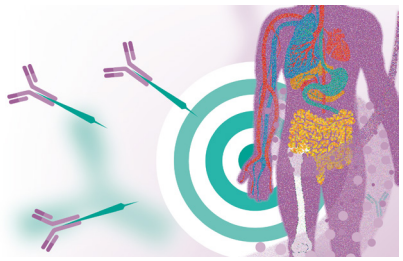
JUNE 2022 Volume 3, Issue 6

IMMUNO-ONCOLOGY INSIGHTS

SPOTLIGHT ON:

0306SL Safety: what progress in understanding and addressing immune-related adverse events?

IMMUNO-ONCOLOGY INSIGHTS Volume 3, Issue 6



SAFETY: WHAT PROGRESS IN UNDERSTANDING & ADDRESSING IMMUNE-RELATED ADVERSE EVENTS?

SAFETY: WHAT PROGRESS IN UNDERSTANDING & ADDRESSING IMMUNE-RELATED ADVERSE EVENTS?

SPOTLIGHT

FOREWORD

Putting the patient first

Róisin McGuigan

"This month, we focus on a topic that is undoubtedly front of mind for everyone working in the I-O space – safety."

FOREWORD

Immuno-Oncology Insights 2022; 3(6), 345–346

DOI: 10.18609/ioi.2022.035

Welcome to the June issue of *Immuno-Oncology Insights*. This month, we focus on a topic that is undoubtedly front of mind for everyone working in the I-O space – safety.

Within the larger subject of safety, a theme has emerged from the contributors in this issue: the importance of ensuring patients with cancer are both involved in and fully

informed about their care; i.e., the concept of patient-centricity.

Our Guest Editor Céline Adessi (Senior Group Director, Oncology, Clinical Safety Science, *Roche*), along with Dominik Rüettinger (*Bayer*) discuss the increasing focus on patient-centric approaches to safety and tolerability within I-O, while Genentech's Anjali Vaze and Peter Kuebler provide insights on the management of cytokine release syndrome (CRS) induced by bispecific monoclonal antibodies – and why centering on the patient in CRS should serve as a roadmap for the future.

Also in this issue, Elaine Murray (*Allogene Therapeutics*) reflects on the safety and accessibility challenges facing CAR-T cell therapies, while Joanne Weidhaas (*UCLA Health*) speaks about her own work on identifying biomarkers to predict risk of autoimmune toxicity with checkpoint inhibitor therapy.

Safety continues to pose a considerable challenge to the I-O field, but one thing is clear –progress in understanding and addressing adverse events, and eventually identifying risk factors, will be best made in close partnership with the only people who experience them firsthand: patients.

AFFILIATION

Róisin McGuigan
Editor
Immuno-Oncology Insights

DOI: 10.18609/ioi.2022.035

IMMUNO-ONCOLOGY INSIGHTS

SAFETY: WHAT PROGRESS IN UNDERSTANDING & ADDRESSING IMMUNE-RELATED ADVERSE EVENTS?

SPOTLIGHT

COMMENTARY

Patient-centered care in immuno-oncology: current progress & opportunities when considering safety & tolerability

Céline Adessi & Dominik Rüttinger

Patient centricity has previously been defined as "putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family" [1] – or more succinctly: "No decision about me, without me". But what does patient centricity look like in practice, and what benefits can it bring – both to the patient themselves and to other stakeholders in the cancer immunotherapy space?

Immuno-Oncology Insights 2022; 3(6), 305–310

DOI: 10.18609/ioi.2022.029

On April 1 2022, Róisin McGuigan, Editor, *Immuno-Oncology Insights*, spoke to Céline Adessi and Dominik Rüttinger, who discussed patient-centered approaches with regards to safety and tolerability of I-O therapies, and identified further opportunities for improving patient centricity. This article has been written based on that interview.

AN INCREASING FOCUS ON PATIENT CENTRICITY

Despite the progress made by the field, the safety profiles of immuno-oncology therapeutics remain less well-characterized compared to classical and well-known anti-cancer treatments like cytotoxic drugs such as chemotherapies, cancer cell targeted therapies, and protein kinase inhibitors.

This creates a significant burden for patients and trial participants treated with I-O therapies due to the clinical assessments required to monitor and further characterize these toxicities. As a result, cumbersome clinical management and surveillance is necessary to ensure patient safety and optimize tolerability.

Patients may not be familiar with I-O mediated toxicities and may not be well equipped to identify the early signs and symptoms. Further, some of these toxicities may worsen already life-threatening conditions, and contribute to patients' anxiety while they are already dealing with cancer treatment. Short and even long-term hospitalization may be required to prevent or treat I-O mediated toxicities, greatly impacting quality of life.

The patient perspective has traditionally been viewed through the lens of the physician, but incorporating patient perspectives is increasingly being recognized as important to the development of high quality, safe, and effective fit-for-patient medicines [2]. In the context of I-O therapies, patient centricity activities should primarily focus on understanding the patients' experience and needs, and on the development and use of supportive tools.

Safety concerns can also result in eligibility criteria for I-O treatments remaining highly restrictive to some subsets of participants. This leads to the exclusion of patients who may potentially benefit from these new treatments because they are considered to be at risk – this includes patients with brain metastases, patients taking immunosuppressive agents, and patients with auto-immune disorders or certain infections such as HIV or hepatitis.

Another question to consider is whether we fully inform patients of what we already know. When considering checkpoint inhibitors (CIs), ipilimumab was approved by the FDA in 2011 for the treatment of melanoma. This was followed by PD-1/PD-L1 antibodies which began seeing approval in 2014. While there is still innovation happening in this space to understand tolerability, is the field currently doing enough to inform patients of the knowledge we have gained from a decade of clinical experience?

CONSIDERING THE RISK/BENEFIT QUESTION

An important component of the patient safety equation is the prediction and prevention of toxicity. If we can predict which patients are at increased risk, we can choose not to expose them to a drug in the first place, or to implement specific monitoring measures and proceed with increased caution. There is innovation happening in this space – for example, a recent study looking at the HLA gene cluster and what it can predict in terms of immune response [3].

One question which still remains is whether patients who experience immune-related adverse events (AEs) are also more likely to experience a benefit from their treatment – this correlation is still up for debate, and presents a great opportunity to learn from real-world data. The more data we gather, the easier it will be to establish or refute this correlation.

We are also still refining our treatments in the clinic. The regulatory authorities are asking I-O therapy providers to think not only about maximum dose and reaching the ceiling for efficacy, but the benefits and risks in regards to optimizing the dose and schedule. Is a weekly schedule needed, or one every two weeks sufficient? How can you best facilitate the life of the patient? Patient centricity should also be considered in this regard – even if a molecule is approved on a certain schedule, we should still be asking what dose and schedule is truly best for the patient.

Overly restrictive clinical trial criteria must also be considered. While every care must

DOI: 10.18609/ioi.2022.029

be taken when broadening enrolment criteria to avoid unacceptable risk, the field has a tendency to automatically exclude certain patients. A more nuanced approach may be needed, and as we acquire more knowledge around efficacy and safety we must keep the door open to the re-evaluation of risk. Constant reassessment is needed, rather than allowing our assessments and eligibility criteria to remain static and continuing excluding patients who could benefit.

Looking beyond clinical trials, the clinical reality is not whether to exclude or not, it's a decision of whether to treat or not – potentially keeping a patient from receiving an approved treatment. Addressing this issue requires expertise, time and money. However, the need is there and this issue being driven by patient advocates – they will not let us remain static in our patient risk assessment, and they are challenging potentially overly restrictive criteria.

MONITORING & ADDRESSING ADVERSE EVENTS

When it comes to mitigating and treating AEs, one of the biggest learnings has been that we cannot extrapolate from established cancer treatments like chemotherapy, where we have a very good idea of what to expect in terms of AEs and can often predict the timing of onset very well.

This is vastly different from immunotherapies. These toxicities can hit any organ and arrive at almost any time – while AEs happen most frequently within the first 6 weeks, late-onset events and persistent autoimmune reactions have also been observed.

The patient-centric answer to this issue is to bring in the right experts. An interdisciplinary problem requires an interdisciplinary solution, rather than leaving these issues solely to the treating oncologist. Steroids remain the mainstay of treatment, but we are still learning how to treat steroid refractory patients, and what additional cytokines to counteract. There are randomized trials ongoing, and there is still a lot to learn, not only for CIs but also for CAR T therapies – the complexity of quicky recognizing, addressing and managing toxicity triggers by complex inflammatory mechanisms that may affect a number of organs remains a critical challenge for the field to address.

Solutions which can help to enable more patient-centric monitoring and management of AEs include:

- Educational materials for healthcare professionals (HCPs) which focus on the specific important risks I-O therapies pose, the need for any additional risk minimization measures, and details of what information is most important for them to explain to patients.
- The development of patient wallet cards describing the main risks associated with I-O treatments, the signs and symptoms associated, and treating physician contact details for direct access to HCPs support as needed.
- Implementation of patient reporting outcome instruments to facilitate the systematic collection of how patients feel, function, and experience their treatment daily throughout the treatment lifecycle.
- Wearable devices for outpatient monitoring of key vital signs parameters such as temperature, ECG, respiration and activity that can alert in case of any early abnormalities. Ultimately, outpatient monitoring may reduce hospitalization and the frequency of hospital visits.
- Providing tools and educational material to patients to monitor, detect, diagnose, or even quantify the severity of I-O toxicities.

BRINGING ALL STAKEHOLDERS TO THE TABLE

It is crucial for trial sponsors to educate not only HCPs, but patients themselves. They

should be given all the tools and materials available, as they will be the person to experience the AE, and likely the first to notice the signs. For example, if a patient is given a drug that carries a risk of neurotoxicity but this is not explained, then they may not make a connection to their treatment if they begin to feel dizzy. The more information patients have, the better armed they will be to identify signs and symptoms that something is wrong. This empowers them to speak to their HCP as quickly as possible, allowing for the appropriate treatment to begin from the onset of the earliest signs of an AE.

For events that might be considered less serious by the HCP, it is still important to acknowledge them. For example, one of the most frequent adverse events experienced with immunotherapy treatment is fatigue. If they are used to dealing with high grade AEs, there may be a risk that HCPs will not appreciate the impact this has on the patient. But if you experience a grade 2 (CTCAE criteria) fatigue for weeks, or even months, this has a huge impact on quality of life. The patient is suffering, even if they are not experiencing a life-threatening AE.

Another example is skin toxicity with rash – there are some skin toxicities that are "only" grade 1 or grade 2, but if someone experiences them for a long time and must avoid exposure to sunlight, this again limits their ability to live a normal life. A patient-centric approach means working to understand how these experiences impacts a patient's life. Even if there is little that can be done to alleviate fatigue or rash, it is important to appreciate and listen to the patient.

This is a concept that may have not been as critical with treatments such as chemotherapy – nausea, diarrhea, and alopecia are all easily visible and widely recognized side effects of this type of treatment. With I-O modalities, the AE may be silent, complex, and much less easily recognizable. As novel treatments continue to emerge in the cancer immunotherapy space, patient education efforts must remain at the forefront of our minds.

PARTNERING WITH PATIENTS FOR SUCCESS

The COVID-19 pandemic has in some ways forced the issue of patient-centricity to the foreground. There were times in the early pandemic when some patients wouldn't go to hospital because they were afraid of contracting the virus. This triggered a lot of efforts around remote monitoring of health. Novel digital tools and remote recording and monitoring approaches have shown great potential for the field. The ALpha-T trial sponsored by Roche is an excellent example of an innovative decentralized approach that takes the trial to the patient [4]. While this approach may not be applicable for the early days after treatment with immunotherapy, where hospitalization is sometimes the standard, it could prove invaluable in particular for late-onset events.

With the right education, our patients are our first and best sensor for detecting any AEs they might be experiencing. But they cannot necessarily recognize what has not been explained to them. Better understanding of safety and risk may also have the additional benefit of increasing the number of patients who enter oncology clinical trials in the first place – a number that continues to be very low particularly in low-socioeconomic and minority populations [5].

We know we can reach out and educate a very broad population of people. They are concerned and they are interested to learn. There is sometimes an attitude within the I-O space that this information is too scientific, too complex, too clinical – but this is not true. If you can present safety and toxicity information in a clear and simple manner, people are able to capture that information and integrate it into their daily lives.

A key part of the solution to the safety challenges still facing I-O therapies is to engage patients by improving their own experience and awareness of their disease management and the risks associated with their treatment, with the aim of helping patients better understand their treatment and care options. The better we educate our patients

DOI: 10.18609/ioi.2022.029

and support them in their treatment journey, the better they in turn will enable us to characterize safety, toxicity, and tolerability – and the better we will ultimately understand cancer immunotherapies and their associated safety risks.

BIOGRAPHIES

CÉLINE ADESSI has more than 20 years of experience in pharmaceutical companies and holding various positions in different therapeutic areas including oncology, neuroscience, and metabolism. Céline Adessi's main center of interest and passion remain in the clinical drug development, toxicology and clinical safety science fields, aiming to provide rapidly to patients new and best treatment modalities. Céline Adessi earned her PhD in Biology, in fundamental research, at the National Research Center "CEA" (University of Grenoble, France) and completed a postdoctoral fellowship at the Geneva Biomedical Research Institute, Glaxo-Wellcome, in the Genomic department. During this time, Céline contributed to the development of a new generation of high-throughput DNA sequencing technology, used nowadays for the sequencing of the Covid-19 DNA, and as authors to patents recognized as breakthrough scientific discovery in the field. Then, Céline Adessi joined the Serono Pharmaceutical Research Institute in Geneva, as Head of Lead Optimization, Biomarkers and Diagnostics of several development programs and pursued her career at F. Hoffmann-La Roche Ltd, in Basel, has Laboratory Head and Projects Leader, working on the development of disease modifying therapies for the treatment of neurodegenerative disorders. More than 10 years ago, Céline's interest refocused on toxicology, pharmacovigilance and clinical safety, joining the Product Development Clinical Safety Oncology department of Roche where she held positions of increasing responsibility. Currently, Céline is Senior Group Director in the Early Clinical Safety Department, working on novel generation of oncology programs, particularly cancer immunotherapies, helping to bring the value of the translational safety and risk mitigation strategies to patients.

DOMINIK RÜTTINGER spent 12 years in academia receiving his clinical training in the US and Germany, the latter at the Ludwig-Maximilians-University in Munich (LMU). After fellowships within the Tumor Immunology Training Program at the Earle A. Chiles Research Institute, Oregon Health and Sciences University (OHSU), Portland, USA and the Surgical Oncology Program at LMU, Prof. Rüttinger received his PhD in Tumor Immunology at LMU, where he still teaches and holds a faculty position. During his career in academia Prof. Rüttinger focused his translational research on cancer immunotherapy and served as principal investigator on multiple international Phase 1–3 clinical trials investigating active-specific immunotherapy and antibody-based therapies. Prof. Rüttinger is co-chairman of the German Society of Immunotherapy and Targeted Therapy (DGFIT). He served as ad hoc reviewer/board member for several oncology journals and has published more than 80 original articles and chapters. Prof. Rüttinger joined Bayer in October 2021 from Roche/Genentech, where he lastly served as the Global Head of Oncology (Pharma Research and Early Development, pRED). Before he joined Roche in 2011, he was at Micromet Inc. (now Amgen Inc.), where he led all solid tumor development programs and supported the development of Blinatumumab (Blincyto™), eventually resulting in the approval of this first CD19-directed T-cell bispecific in 2014.

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AFFILIATIONS

Céline Adessi
Senior Group Director
Oncology
Clinical Safety Science
Roche

Dominik Rüttinger
Global Head Research and Early Development Oncology
Bayer Pharmaceuticals

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *Adessi C is an employe of Hoffman La Roche, participation to internal DSMB. Adessi C also holds stock options in Hoffman La Roche. Rüttinger D is an employee of Bayer AG and a Co-chair German Society for Immune- and Targeted Therapy (DGFIT). Rüttinger D holds stock or stock options in Bayer AG. The authors declare that they have no other conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *This article was written based on an interview. On April 1st 2022, Róisin McGuigan, Editor, Immuno-Oncology Insights, spoke to Céline Adessi and Dominik Rüttinger.*

Submitted: *Apr 01 2022*; ***Revised manuscript received:*** *May 16 2022*; ***Publication date:*** *May 25 2022.*

COMMENTARY

Addressing the challenges of CRS in bispecific monoclonal antibody cancer therapy

Anjali Vaze & Peter Kuebler

The benefit/risk ratio of immuno-oncology (I–O) agents is crucial when considering treatment options for cancer patients. Highly potent and targeted oncology agents come with high hopes of patient benefit. The tradeoff that comes with greater potency is the potential for serious and life-threatening toxicity, such as cytokine release syndrome (CRS). It is incumbent upon physicians, drug developers, and all other stakeholders to ensure a benefit/risk profile for these drugs that optimizes the patient experience throughout their treatment journey, iterating on mitigation measures that work while continuing to explore interventions that might further reduce risk of CRS.

Immuno-Oncology Insights 2022; 3(6), 315–318

DOI: 10.18609/ioi.2022.031

On May 4 2022, Róisin McGuigan, Editor, *Immuno-Oncology Insights*, spoke to Anjali Vaze and Peter Kuebler about the challenges facing the field in addressing bispecific monoclonal antibody-induced cytokine release syndrome. This article has been written based on that interview.

Experience with CAR-T cell therapies and the BiTE blinatumomab present both opportunities and challenges for today's I–O field. They have raised the awareness of CRS as being part of the benefit/risk profile of these highly potent molecules while also setting expectations of patients, physicians, and health authorities. However, CRS induced by molecules with different mechanisms of action and different pharmacology will, to some degree, have different clinical presentations in patients and therefore require different approaches. As novel treatment modalities enter the clinical trial landscape and post-approval space, it will

be necessary to both leverage commonalities and exploit differences in order to not only meet the currently accepted benchmarks for benefit/risk, but also to improve upon them as much as is feasible. In this commentary we will focus on the current challenges facing the emerging modality of bispecific monoclonal antibodies (BiSp MAbs) in I–O applications, and more broadly, opportunities for the I-O field as a whole to better address CRS.

CURRENT CHALLENGES IN ADDRESSING CYTOKINE RELEASE SYNDROME

We are continuously learning about CRS, but it remains complex due to the heterogeneity of clinical presentation – from a fever to requiring admission to the ICU. The underlying cause is also challenging due to immune pathways influenced by the disease under treatment, pharmacology of the drug, patient level characteristics and other variables. Harmonization in describing CRS is perhaps the first hurdle in better management. Fortunately, collaborative efforts such as the consensus recommendations on grading at the meeting supported by the American Society for Transplantation and Cellular Therapy in 2018 and the White Paper published by the Friends of Cancer Research in 2021 provide a foundation for stakeholders to more consistently characterize CRS [1–3].This will be critical if we are to tackle the biologic complexity of CRS and make strides in better treating our patients.

CRS is a consequence of the immune response we wish to elicit, yet what specifically drives CRS across different treatment modalities and among patients is not completely understood. We have learned a great deal from CAR-Ts and BiTEs [4,5]. BiSp MAbs however have unique properties (association with first dose, lower rates, lower frequency of high-grade CRS, etc.) that differentiate them from other I–O molecules not only on the basis of the CRS phenotype, but also by how we can manage CRS [6,7]. Understanding the biology and pathophysiology of CRS is important for learning how to manage it. We have the opportunity and ever-improving tools to push further on the science underlying CRS to prevent it from occurring, predict which patients may experience it, and to better manage symptoms and avoid progression of CRS in whom it develops.

CENTERING ON THE PATIENT IN CRS IS THE ROADMAP FOR THE FUTURE

Patients are at the center of what we do. While as sponsors we may categorize symptoms as 'mild' or 'severe', we shouldn't lose sight of the patient's perspective and look holistically at their experiences, including burdens such as prolonged symptoms and mandatory hospital-based observation. As more treatment and management approaches become available, innovative approaches to education for healthcare providers (HCPs) and patients will be increasingly helpful. We must consider what data generation and regulatory paths will look like to better enable innovation in this area.

Understanding, predicting and managing CRS on an individual patient level is the next frontier. The multifactorial nature of CRS points to the need to integrate patient-level drivers of response, the disease under treatment, and the pharmacology of a given drug. Personalization of healthcare is becoming ever more embedded across the pharmaceutical industry with increasing use of genomics and other patient profiling approaches, and *in vitro* model systems like organoids and digital medicine. Personalized safety risk management for CRS is within our collective reach with drug safety organizations ideally suited to help identify and navigate the path.

TACKLING CRS TOGETHER

Eliminating CRS risk may be difficult, yet it is ultimately what drives us forward. In this

DOI: 10.18609/ioi.2022.031

regard, CAR-Ts and BiTEs have made great progress in managing CRS risk. The addition of BiSp molecules to the therapeutic landscape presents an opportunity to build upon the existing knowledge base and work across stakeholder groups to put innovative and well-researched risk mitigation and minimization strategies into the hands of HCPs and patients.

The scope of the CRS problem can only be addressed synergistically. Drug developers should work with each other, academia, HCPs, patient stakeholders, and the health authorities. Collaboration is the best path to generating meaningful solutions at the right scale. We have an invaluable opportunity to break down barriers that will benefit all of us – and particularly our patients.

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AFFILIATIONS

Anjali Vaze
Genentech
South San Francisco, CA, USA

Peter Kuebler
Genentech,
South San Francisco, CA, USA

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *On May 4 2022, Róisin McGuigan, Editor,* Immuno-Oncology Insights, *spoke to Anjali Vaze and Peter Kuebler. This article has been written based on that interview.*

Interview conducted: *May 4 2022;* ***Publication date:*** *Jun 07 2022.*

DOI: 10.18609/ioi.2022.031

IMMUNO-ONCOLOGY INSIGHTS

SAFETY: WHAT PROGRESS IN UNDERSTANDING & ADDRESSING IMMUNE-RELATED ADVERSE EVENTS?

SPOTLIGHT

VIEWPOINT

Redefining success: predicting checkpoint inhibitor toxicity to improve patient outcomes

Joanne Weidhaas
UCLA Health

"Immunotherapy represents a new era in which toxicity has become an incredibly important consideration in treatment... harnessing immunity can be very powerful, but can lead to very severe sequelae and toxicity, and these toxicities can be life ending."

VIEWPOINT

Immuno-Oncology Insights 2022; 3(6), 311–314

DOI: 10.18609/ioi.2022.030

On April 6 2022, Róisin McGuigan, Editor, *Immuno-Oncology Insights*, spoke to Joanne Weidhaas about her work identifying biomarkers to predict risk of autoimmune toxicity with checkpoint inhibitor therapy. This article has been written based on that interview.

As a radiation oncologist, balancing efficacy and toxicity is always at the forefront of my mind. In oncology generally and with chemotherapy specifically, toxicity has been less of a concern – the focus has been on response, because toxicity has historically been managed well with medication.

Immunotherapy represents a new era in which toxicity has become an incredibly important consideration in treatment. As we have seen in some of the CAR-T trials, harnessing immunity can be very powerful, but can lead to very severe sequelae and toxicity, and these toxicities can be life ending. The importance of toxicity cannot be overlooked, and is a crucial consideration for any clinician using immunotherapy to treat patients.

The excellent responses seen in some patients when using immunotherapy have to be balanced against negative side effects, and it is very difficult to predict which direction these responses will take. We may see short-term toxicity, which often can be treated, but long-term toxicity is with the patient forever. Immune-related adverse events, since they are a form of autoimmunity, often don't go away. This can include diabetes, hyperthyroidism, cardiomyopathies, and hepatoxicity, and many of these toxicities can result in lifelong impacts on the organs that have been affected.

The key question is how we can better predict which patients will experience serious side effects. You can treat a group of people who have the same type of cancer, who look and seem exactly the same, and see vastly different responses, including toxicities. It has always been clear that there is something the patient is bringing to the treatment that significantly affects their personal outcome.

Along with my colleagues, I discovered a new class of germline, or inherited, biomarkers based on studies focusing on microRNAs. Through years of work on these germline biomarkers, we have shown they can predict a stress response. So if a person who has one biomarker is put under stress, versus another person who doesn't have that biomarker, they are going to respond quite differently. We can therefore use them as a way to personalize cancer therapy decisions, as cancer therapy by definition puts stress on the entire body. It therefore made sense that these biomarkers would have some answers and help us separate people into good responders versus bad.

When I joined UCLA I was recruited to use these biomarkers in radiation therapy, and I was collaborating with various groups. I started talking to Antoni Ribas; a world leader in immunotherapy who has worked closely with our department. We had a fruitful meeting where we discussed the science behind these germline biomarkers, their application in radiation oncology, and the similar challenges he was finding in immunotherapy. He said that similar to what I was dealing with in radiation oncology, he had no idea how to predict which patients would experience immune toxicity. One in four people will have these autoimmunities, and there is no way to identify them beforehand.

We began a collaboration studying some of his original datasets. We discovered that these biomarkers are quite accurate in identifying people who will have autoimmune responses to immune therapy. We identified a germline signature using a group of these biomarkers that predicts up to a tenfold increased risk of these autoimmune toxicity in response to single-agent checkpoint therapy [1]. That is a 1000% increased risk, which is really astounding.

We took this toxicity signature and tested different groups of patients treated with similar therapies – single agent anti-PD-1/PD-L1 – and found that regardless of cancer type this signature predicted which patient was going to develop autoimmunity. The beauty of this approach is that you could test a person before they started therapy and know they have a highly increased risk of this type of toxicity. This is particularly important when people are considering one therapy compared to their other options.

We now have had a prospective study underway looking at use of the signature in a group of patients with metastatic prostate cancer – their alternative is an anti-testosterone therapy with known side effects, and

DOI: 10.18609/ioi.2022.030

they may only want to consider checkpoint therapy if they won't be at high risk of these autoimmune toxicities. It has proven very useful for this group of patients in making an informed treatment decision about proceeding with a therapy or not.

For this specific first toxicity signature to PD-1/PD-L1, which we refer to as IMUDX, our next step is to figure out which patients this will be most useful for, and those are conversations that are important to have with thought leaders that deliver this type of therapy. There are also ongoing studies of combination checkpoint therapies and other new classes of immune therapies, and I am optimistic that our biomarkers will also be able to identify who will have toxicity when receiving these therapies.

Looking further ahead, understanding some of the germline genetics that predict autoimmunity may be a path to then developing ways to block that poor response. My hope is that the work we have done could lead to identifying those genes that, when dysregulated, can lead to these autoimmunities. This could in turn lead to the development of approaches that modulate those specific genes.

As oncologists, we are seeing great advances that are leading to cures or to very long remissions, meaning that some cancers may become more of a chronic disease. In this setting it becomes absolutely crucial to balance therapy decisions by considering both tumor response and toxicity for patients. Living with long-term, life-altering toxicity should be considered a poor outcome, not a great success. To date, this balance has perhaps not been pursued as diligently as it could or should be. I would encourage therapy developers to pay greater attention to toxicity issues, and make more efforts to use biomarkers to better personalize therapies, in order to achieve the best outcomes possible for our patients.

BIOGRAPHY

DR WEIDHAAS is a physician-scientist who trained as a Radiation Oncologist at Memorial Sloan Kettering, with broad exposure to the clinical and biological behavior of cancer of all types. Her MD and PHD training was at Tufts University in molecular biology, with post-doctoral work in genetics and radiobiology. Dr Weidhaas's clinical work has primarily focused on women's cancers, and she was the head of the Breast Radiation Oncology Services at Yale before moving to UCLA in 2014. Additionally, Dr Weidhaas founded a molecular diagnostics company in 2010, MiraDx, and subsequently earned her MSM at Stanford in 2013, after which she also founded a non-profit, MiraKind. The fundamental purpose of her work is to break down the barriers between science and clinical cancer care, to significantly improve personalized treatment and ultimately outcome for cancer patients. In January 2015, Dr Weidhaas became the Director of the Division of Molecular and Cellular Oncology and head of translational research at UCLA. Dr Weidhaas's scientific focus has been on the genetics behind cancer risk as well as the personal response to cancer therapy. Much of her current work focuses on the discovery and characterization of functional germ-line genetic biomarkers disrupting microRNA circuitry. Her early work on microRNAs (miRNAs) found that these global genetic regulators are dynamically altered in response to cancer treatment. This insight led to her group's discovery of the first germ-line miRNA binding site mutation, which is an inherited variant in the 3' untranslated region (3'UTR) of the KRAS oncogene. This mutation, now referred to as the KRAS-variant, increases cancer risk, and also predicts unique tumor biology, partly through conserved miRNA and gene expression changes in the tumors of patients that harbor it. It has been broadly shown that patients with the KRAS-variant respond uniquely to cancer therapy, regardless of tumor type, supporting the hypothesis that this class of genetic difference can be used as a pan-cancer predictive biomarker. Dr Weidhaas has expanded her investigations of such germ-line variants and has found numerous mutations in this class that are strongly predictive of response to cancer therapies, including newly developing immune therapies, as well as radiation therapy. By applying this novel class of baseline difference between patients which predict their systemic stress response, her laboratory hopes to facilitate insight into ways to significantly improve and advance personalized cancer care.

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AFFILIATION

Joanne Weidhaas
Vice Chair
Department of Radiation Oncology
Director
Division of Molecular and
Cellular Oncology
UCLA Health

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *Dr Weidhaas is co-founder of MiraDx, a company that has created IP and has a patent regarding signatures of immune toxicity. Dr Weidhaas holds equity in miraDx. The author declares that they have no other conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *On April 6 2022, Róisin McGuigan, Editor, Immuno-Oncology Insights, spoke to Joanne Weidhaas. This article has been written based on that interview.*

Submitted: *Apr 06 2022;* ***Revised manuscript received:*** *May 23 2022;* ***Publication date:*** *Jun 07 2022.*

DOI: 10.18609/ioi.2022.030

IMMUNO-ONCOLOGY INSIGHTS

SAFETY: WHAT PROGRESS IN UNDERSTANDING & ADDRESSING IMMUNE-RELATED ADVERSE EVENTS?

SPOTLIGHT

Understanding the evolving safety landscape in autologous and allogeneic CAR-T therapy

Elaine Murray McCracken
VP, Head of Pharmacovigilance and Epidemiology,
Allogene Therapeutics

"There is a huge – and understandable – focus on efficacy, but we must also keep our eyes on safety."

VIEWPOINT

Immuno-Oncology Insights 2022; 3(6), 339–343

DOI: 10.18609/ioi.2022.034

On April 25, 2022, Róisin McGuigan, Editor, *Immuno-Oncology Insights*, spoke to Elaine Murray McCracken about the current safety and accessibility challenges facing CAR-T cell therapies. This article has been written based on that interview.

TEN YEARS OF EVOLUTION IN CAR-T

Allogene Therapeutics is developing its allogeneic chimeric antigen receptor T cell (AlloCAR T™) products in hematological malignancies and solid tumors, and we are currently poised to start pivotal Phase 2 studies in relapsed/refractory non-Hodgkin lymphoma.

It has been 10 years since Emily Whitehead became the first pediatric patient to receive autologous CAR-T cell therapy, and Carl June had the profound insight to consider inhibiting the action of interleukin-6 (IL-6) which led to both her survival and our understanding and treatment of post-autologous CAR-T cytokine storm and cytokine release syndrome (CRS) [1]. From a safety perspective, this breakthrough allowed for the further development and expansion of the use of what were at that time experimental CARs.

It has only been 5 years since the first health authority approval of autologous CAR-T therapy, and in that short time we now have four approved anti-CD19 autologous CARs and two targeting B-cell maturation antigen (BCMA). In those intervening years, we have learnt and continue to learn more about the safety profiles and risk mitigation. CRS and immune effector cell-associated neurotoxicity syndrome (ICANs) have been in the limelight for safety with autologous CARs. CRS can range from mild, with fever and chills, to life-threatening with end organ damage requiring cardiopulmonary support, and more rarely to hemophagocytic lymphohistiocytosis (HLH); a severe systemic inflammatory syndrome that can be fatal. ICANS manifests as expressive aphasia, tremor, dysgraphia, and lethargy, progressing to seizures and in rare cases fatal brain edema. More recently neurocognitive and movement disorders consistent with parkinsonism have emerged as a potential on-target toxicity of the autologous BCMA CAR-Ts [2].

Understanding the etiology and treatments for CRS and ICANs have driven great collaboration across academia and industry. This led to tocilizumab, an IL-6 receptor antagonists (IL-6ra), being the first FDA-approved treatment for severe or life-threatening CRS induced by CAR-T cell therapy [3] and the creation of an aligned treatment-based grading scale, the ASTCT Consensus Grading Scale for CRS [4]. This global language to communicate and understand the severity of CRS and ICANs, coupled with staff training and consistent earlier treatment of CRS and ICANs, has allowed for the safe and efficacious use of autologous CARs – although still with the need for administration in specialized centers and close outpatient monitoring. Emerging data suggests that Allogenic CAR-T therapy may have a slightly different profile with less CRS and ICANs, no graft-versus-host-disease (GVHD), and comparable infections and cytopenias [5]. This may allow more community-based administration in the future.

CYTOPENIAS: AN EMERGING CHALLENGE

Since these initial approvals, cytopenias – and particularly prolonged and recurrent cytopenias – have emerged as a safety issue for autologous CAR-T therapy. In the FDA review for the initial autologous CARs, cytopenias were noted, but they were felt to be an inherent part of the lymphodepletion chemotherapy and were not at the forefront in the way that CRS and neurotoxicity were [6]. Now, with 5 years of real-world use and with CRS treatments in place, physicians are finding themselves supporting patients with cytopenias, including bone marrow failure, during follow up and some requiring stem cell rescue transplants [7]. There is much more awareness and discussion on the topic, but we do not yet fully know whether they are cytokine mediated and caused by ongoing CAR-T cell activity, the effect of the CAR on the marrow, post CRS with toxicity from steroids and/or tocilizumab, concomitant infections and their treatments or a lingering effect of the lymphodepletion regimens that are used in preparation for cells.

DOI: 10.18609/ioi.2021.034

Patient characteristics associated with cytopenias are now somewhat understood in the autologous CAR space, and we have a published prediction score for hematological toxicity and poorer outcomes in patients with large B-cell lymphoma receiving CD-19 [8,9]. With the approval of the first anti-BCMA autologous CAR approved for treatment of adult patients with relapsed or refractory multiple myeloma (ABECMA), prolonged cytopenias were first included as a black box warning in the US prescribing information.

With the most recent approval of Carvykti™ (ciltacabtagene autoleucel), the second anti-BCMA autologous CAR approved for treatment of adult patients with relapsed or refractory multiple myeloma, the FDA reviewer commented on the occurrence of recurrent Grade 3 or 4 cytopenia and noted that this "has not been reported in other approved CAR-T products … possibly because such analyses were not carried out" [10]. We are watching this closely at Allogene, and are actively pursuing the sweet spot between optimal lymphodepletion for cell expansion, recovery of the immune system, and avoidance of prolonged cytopenias.

ALLOGENEIC VS AUTOLOGOUS SAFETY CONSIDERATIONS

The safety profile of allogeneic CARs versus autologous CARs is evolving. One of the primary concerns is GvHD and graft rejection. There are a number of ways that developers are tackling this. At Allogene we are using TALEN® gene editing to knock out the T-cell receptors (TCR) and CD52 which allows us to optimize our lymphodepletion regimen with an anti-CD52 antibody. This gene editing seems to have made GvHD a 'settled' issue for our AlloCAR T products, as to date at Allogene we have dosed >140 patients without any instance of GvHD. CRS and neurotoxicity are seen, but not with the frequency or severity as was seen with the earlier autologous CARs. The hope is that this will open the door for easier access to patients, as less high-level supportive care may be needed.

However, autologous CAR therapies by their very nature have a turnaround time before they can be manufactured and delivered to patients. This factor, along with the need for administration in mostly academic settings, means that they will never be able to fulfill the unmet medical need. It would therefore be beneficial to be able to get therapies to patients much quicker using an off-the-shelf approach. Allogeneic CARS obviate the need for leukapheresis, which while perhaps not having many safety risks, does reduce access and increase inconvenience for patients. Many patients see their cancers progress whilst waiting for autologous CARs, and require toxic chemotherapy as bridging therapy to manage their disease as they await treatment, which we are also hoping to minimize.

The Center for International Blood and Marrow Transplant Research (CIBMTR) is currently collecting all the long-term safety data for autologous CARs, and companies are also doing post-marketing safety studies. As we pull this data together, we will start to have a deeper understanding of the safety issues at play. Regulatory authorities are worried about long-term effects on the immune system and the development of secondary malignancies, and have put in place 15-year follow-up requirements. We will have to wait to see how this data pans out.

FUTURE DIRECTIONS

We want to get our approach right across the allogeneic platforms so we can bring these therapies to more people. Currently, the field is focused on academic centers, and access is a problem as patients are forced to travel. They must stay close to the area, for up to four weeks in some cases, which can be a heavy burden and is not providing inclusive cancer care.

Our overall aim is to have an outpatient product that does not leave the patient with

a debilitated immune system. Many developers have tried using off switches, but without much success. One potential future avenue could be an easy off switch that did not come with its own toxicities – this would allow you to treat the patient, get the cancer under control, and then turn off the treatment. This would be helpful if the ongoing CAR activity is what is driving the cytotoxicity.

Ultimately, CAR-T cell therapies are revolutionizing cancer care for patients, and my passion is to make them safer and more accessible to patients. There is a huge – and understandable – focus on efficacy, but we must also keep our eyes on safety. One thing we are exploring at Allogene is a chemo-free lymphodepletion regimen to reduce side-effects and improve the patient's experience. As developers, if we have a therapy that is incredibly efficacious but leaves patients with no immune system and in need of a transplant, then we are not moving in the right direction. With allogenic CAR-T therapies the future should bring more therapies closer to patients, without delays for manufacturing and a safety profile that allows them to receive care in their local cancer center without having to travel great distances and stay away from home. Molecular engineering is blazing the trail for safer and more active CAR products in the future.

BIOGRAPHY

ELAINE MURRAY McCRACKEN Driven, dedicated. Patient Focused. Gets it done. Gives back. She/Her, mother, wife, sister, daughter, immigrant, first -generation college graduate. Ally. Head of Pharmacovigilance and Epidemiology at Allogene Therapeutics.

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AFFILIATION

Elaine Murray McCracken
VP, Head of Pharmacovigilance and Epidemiology, Allogene Therapeutics

DOI: 10.18609/ioi.2021.034

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The author declares that they have no conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited.*

Interview conducted: *Apr 25 2022;* ***Publication date:*** *Jun 9 2022.*