imSAVAR Stakeholder Workshop

Integrating Patient Preferences in Nonclinical Assessment of Immunomodulatory Therapies – Shifting the Paradigm

REPORT

THIS PROJECT HAS RECEIVED FUNDING FROM THE INNOVATIVE MEDICINES INITIATIVE 2 JOINT UNDERTAKING (JU) UNDER GRANT AGREEMENT NO 853988. THE JU RECEIVES SUPPORT FROM THE EUROPEAN UNION'S HORIZON 2020 RESEARCH AND INNOVATION PROGRAMME AND EFPIA AND JDRF INTERNATIONAL.

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Background

Immune-related adverse events (irAEs) are one of the leading causes affecting success rates of immunomodulatory drugs requiring a concerted multistakeholder effort across the drug development process—especially within the nonclinical phase. One of the ways in which the imSAVAR consortium aims to help improve the research and development process and bring a degree of alignment is by creating a Model Grading System through an iterative manner and by leveraging on the imSAVAR Stakeholder Community. A key aspect of imSAVAR is continuing dialogue with patient stakeholders to keep the imSAVAR research agenda patient-centred and maximise outcomes for patients. To better elucidate inclusion of patient preferences within nonclinical assessment of immunomodulatory therapies—specifically toxicity modelling—we co-designed a Workshop entitled "Integrating Patient Preferences in Nonclinical Assessment of Immunomodulatory Therapies – Shifting the Paradigm" with representatives of Melanoma Patient Network Europe (MPNE), Lung Cancer Europe (LuCE), CML Advocates Network and Patvocates. All of these organisations are part of WECAN which is an informal network of leaders of cancer patient umbrella organisations active in Europe. This online imSAVAR Stakeholder Workshop took place on the 26 & 27 January 2022 with a programme composed of various key opinion leaders representing stakeholders such as: Patient Advocates, Clinicians, Toxicologists, Immunologists, Researchers and Experts in patient preferences.

Workshop Summary

The first part of the Workshop focused on presenting the landscape of how immune-related adverse events (irAEs) linked to immune-oncology therapies are managed in clinical practice, complemented by the state of the art in translational safety assessments (i.e., nonclinical models and biomarkers) for predicting these irAEs and challenges and limitations associated with both. This was followed by sharing of patient perspectives on irAEs across different cancers, emphasising not only the heterogeneity in patient preferences regarding treatment outcomes but the risk-benefit trade-offs and treatment choices they struggle with. To culminate, the IMI PREFER evidence-based recommendations on when and how to elicit patient preferences provided an exemplar methodology on capturing the patient voice in medical product decision making, which although deemed vital by most stakeholders lacks guidance.

The second part of the Workshop involved pooling together the captured insights in a multistakeholder deliberation on how to embed patient preferences in the research and nonclinical development phase to better address patient unmet needs. Despite the often diverging stakeholder views on treatment outcomes, there was convergence regarding the need to improve tools to better predict safety and efficacy of immunotherapies—largely stemming from the numerous novel advanced therapies and combinations available, improved long term survival of patients across cancers but offset by an ever growing array of complex and unpredictable irAEs. With patients prioritising long-term and acute toxicities besides just severe toxicities, efforts are needed in modelling for their prediction as well. Whilst managing the risk of immune toxicities is already challenging, it is further intensified by the need to balance the effects of immune toxicity treatments on diminishing the efficacy of cancer treatments. Well curated data linking nonclinical development with clinical experience and utilising "patient reported phenotypes" as a priority setting tool for research were stressed as key considerations to address the issues laid out to reach a balanced immune safety and efficacy profile. Although the pursuit of integrating patient preferences within

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nonclinical safety assessment strategies for immunomodulatory therapies may be unprecedented, its realisation—with all healthcare innovation being a complex endeavour—demands a collaborative approach.

All presentation slides are available through the following link by entering the password *imSAVAR2022*. The workshop recording, is available on the imSAVAR website.

Workshop Outcome

Following the series of presentations (see slides) and interactive panel discussion (see Exhibit 1 and Exhibit 2) various important themes emerged as listed below.

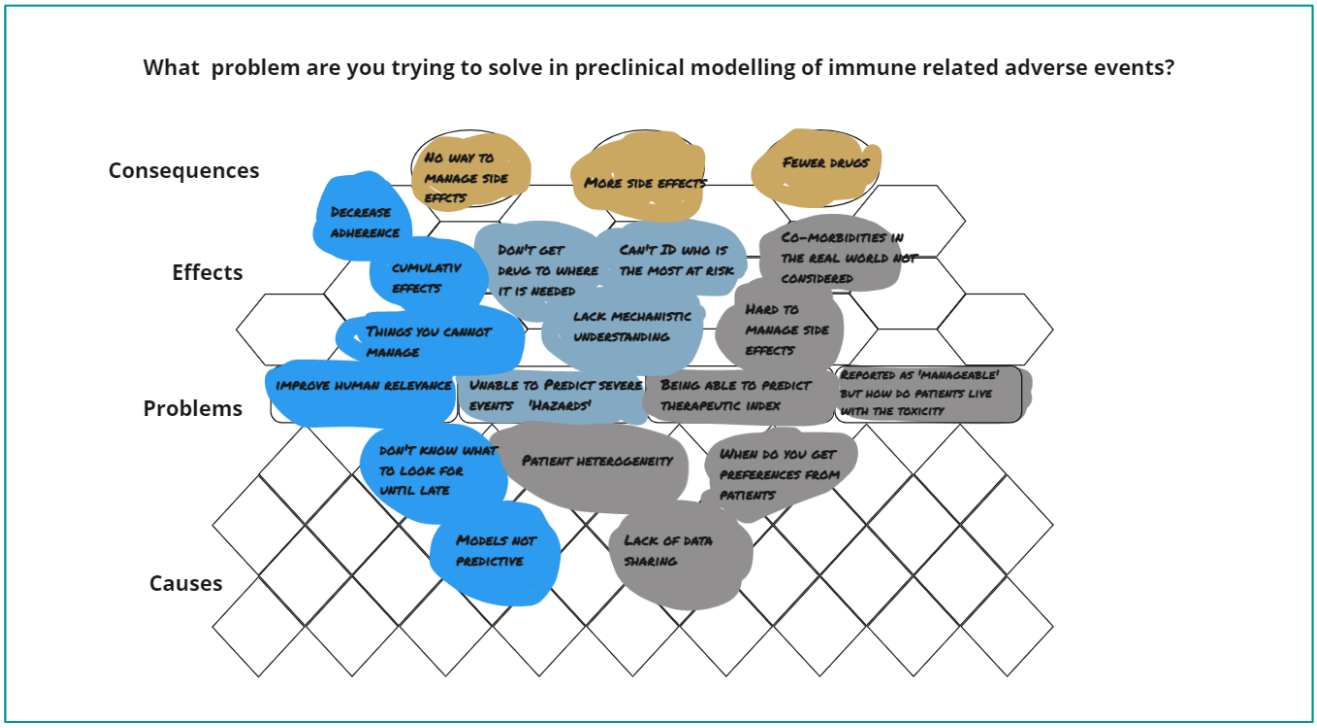

Exhibit 1 Problem Mapping

Patients need support in balancing toxicity and efficacy
Often patients will have to decide if they want to pursue a particular course of therapy. In the case of immunomodulatory therapies the challenge is often that treating toxicity from the drug will diminish its efficacy as well. Having clear guidance on the risk of a given toxicity would be useful in multiple clinical scenarios.

Symptoms and toxicities patients care about the most are not routinely considered
Most toxicity modelling is focused on severe outcomes. However, patients are also concerned about the less severe outcomes especially if this means that they will have to endure a particular symptomology for the rest of their lives. Coupled with the challenge of balancing toxicity and efficacy it is clear that there is a lot of room to improve preclinical toxicology testing from the patient perspective.

Patient preference studies
Patient preference studies can play an important role in shaping drug development. The IMI project

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PREFER has developed a methodology that will likely be recognised by the EMA as a framework to identify and define patient preferences. This could be used to understand preferences either in terms of which toxicities are most important for a patient population, or to understand patient preferences in regards to balancing risk and efficacy. One example of its application could be for genotoxicity. Genotoxicity refers to the capability of a substance to damage genetic materials in cells and cause cancer. It is a concern with immunomodulatory therapies, but it is unclear if genotoxicity should remain a major concern especially if weighed with the risk of dying from a disease. A preference study could help define the risk tolerance, how much genotoxicity will need to be modelled and to what degree it should or should not influence the approval of a therapy.

Access to data limiting the ability to model clinical outcomes

One of the biggest barriers encountered in the imSAVAR consortium is having access to clinical outcome data whilst one of the goals of imSAVAR is to build models that link to a clinical outcome. Therefore, this requires being able to use existing clinical trial data to understand the clinical outcomes and/or biomarkers that relate to toxicity. The sharing of such data is often limited by multiple barriers such as legal and privacy concerns as well as a reluctance to release data that could hinder a current development program. There are efforts to improve the sharing of clinical trial data but to date it remains very challenging. One potential source of data would be real world registries.

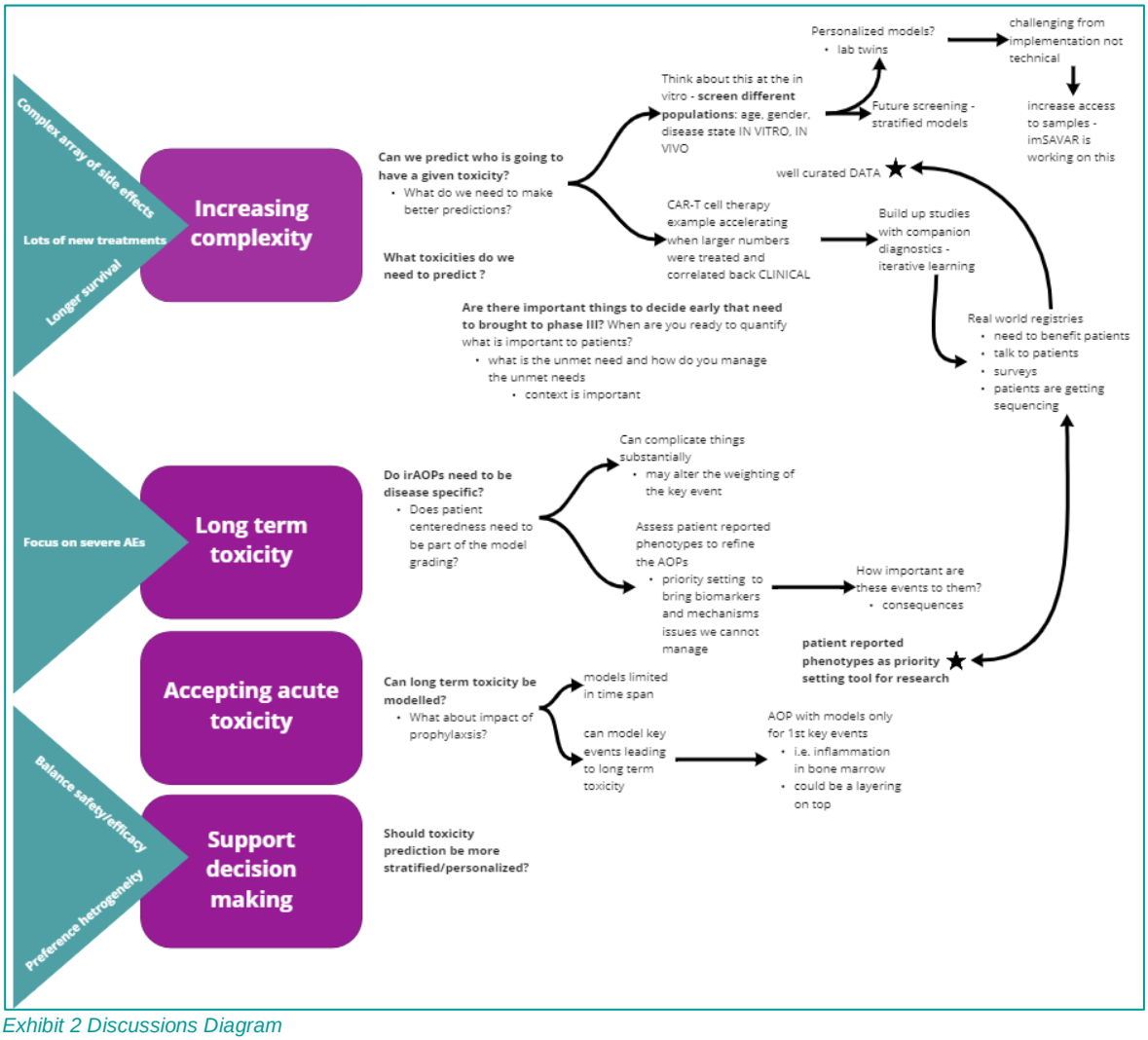

Exhibit 2 Discussions Diagram

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Meaningful Progress

While identifying the challenges and issues presented by speakers and through the panel discussion is an important first step, imSAVAR as a project would like to move forward some of these issues. Often the barriers and challenges to address these issues are linked to requiring additional funding for setting up additional projects.
However, in nearly all cases there at least some 'Fast Mover' projects (FMP) that can be initiated that do not require substantial resources and can be completed quickly to provide proof of concept and to demonstrate the value of working together. Two FMPs have been developed based upon Workshop discussions as shown below and are intended to be continued collaborative endeavours with the stakeholder who participated in the Workshop.
FMP 1: **Supporting patient decision making with preclinical toxicity modelling**
FMP 2: **Identifying irAEs prioritised by patients through a patient preference study**
An FMP on challenges on access to clinical data is under investigation as this is a cross initiative/project issue not limited to imSAVAR alone. Further discussions with key data related experts are needed to better understand the landscape and understand what type of project can be most impactful.

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