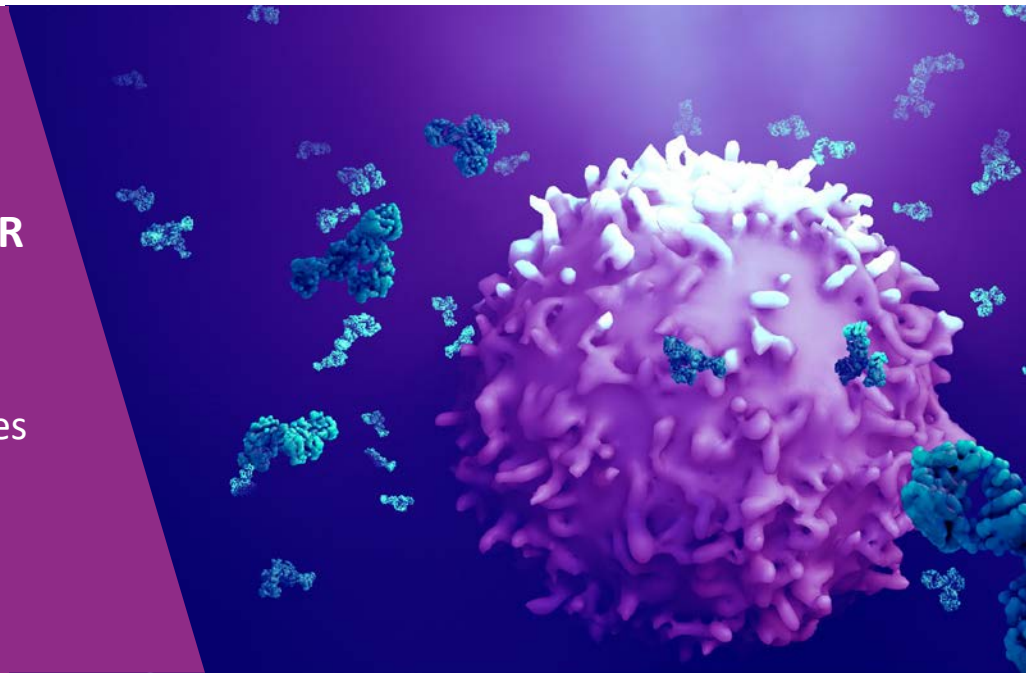
imSAVAR

IMMUNE SAFETY AVATAR

Nonclinical mimicking of the immune system effects of immunomodulatory therapies



Deliverable 1.9
Summary of Patient Engagement

DELIVERABLE 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.

innovative medicines initiative

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JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Abstract

The project imSAVAR has taken significant steps to increase patient involvement in the project, as defined in deliverable 1.9. The project has utilized various strategies to engage patient stakeholders, including the co-design of a workshop entitled “Integrating Patient Preferences in Nonclinical Assessment of Immunomodulatory Therapies – Shifting the Paradigm” with representatives of patient advocacy organizations such as Melanoma Patient Network Europe, Lung Cancer Europe, CML Advocates Network, and Patvocates. This workshop involved key opinion leaders representing stakeholders such as patient advocates, clinicians, toxicologists, immunologists, researchers, and experts in patient preferences. Additionally, a series of workshops was developed, similar to Science Café’s, where scientists presented the work of imSAVAR followed by facilitated dialogues between patient stakeholders and researchers. The project also focused on identifying clinical scenarios where more granular information on toxicity risk would be helpful, establishing patient-derived phenotypes for each identified scenario, and consulting with modeling experts on the feasibility of modeling phenotypes to support clinical decision making. Furthermore, the project aimed to integrate patient preferences into nonclinical safety assessment strategies to inform drug development and approval, with a vision of eliciting patient preferences concerning relevant immune-related adverse events (irAEs) using appropriate methodologies. The project also sought to improve access to clinical outcomes data to inform nonclinical safety strategies and eventually improve their predictivity, aligning with the larger vision of the consortium to build better preclinical models that predict clinically relevant outcomes. Overall, imSAVAR has demonstrated a commitment to engaging patient stakeholders and integrating patient preferences into the nonclinical phase of the project to ensure it is patient-centered and impactful.

Document Information

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1. 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.

Patient engagement, also known as Patient and Public Involvement (PPI), is recognized as crucial in biomedical research to ensure the relevance and impact of research outcomes[1]. While patient involvement in preclinical research, specifically toxicology testing, is still emerging, there are examples of PPI being used in this context[2].

In preclinical research, patient input can be valuable in identifying issues such as data protection and operational factors that can impact patient participation in trials. Patient input can also help evaluate the relevance of a study to the target population and its potential to deliver meaningful outcomes.

Researchers have reported benefits of involving patients in preclinical research, including improving the relevance of the research, gaining patient perspectives and insights, and enhancing study design and outcomes[3]. However, formal evaluation of the impact of PPI in preclinical research is limited.

Challenges in preclinical PPI include ensuring the narrow focus of research needs while allowing patients to contribute based on their own experiences. There are also differences between patient engagement, community-based participatory research, and PPI in terms of definition, approach, and researcher ownership.

Involving patients in preclinical research can be achieved through various methods, such as identifying patients through existing organizations, conducting interviews and focus groups, and using exercises to articulate patient needs.

While there are limitations and challenges, patient engagement in preclinical research is seen as an important aspect to improve the quality and relevance of research outcomes. Collaborative efforts between researchers and patients can lead to improved communication, understanding, and relationship-building.

The debate around genetically modified organisms (GMOs) made it apparent that simply having a dialogue with patient stakeholders is not enough. The European Commission developed the concept of Responsible Research and Innovation (RRI) as an approach that can move beyond dialogue to embedding societal norms and values into research. This call for a deeper level of involvement than focus groups, workshops, or interview-based consultations. It also requires the engagement of experts. When the topic of research requires a high degree of technical or technological knowledge it is important to have non-experts work closely with experts[4]. This is challenging to achieve, but we can look to an example where non-expert and expert interaction has been successful.

2. Science Cafés

Science Café's are an informal two-way learning process that serves to stimulate engagement between the public and expert scientists by building up confidence. The format is typically based upon a brief scientific presentation followed by an open discussion. Moderators aim to attain robust engagement of all participants[5]. Science Café's have gained a degree of following with more than 350 listed on site dedicated to Science Café's. Science Café's offer a safe environment helping people climb the ladder of

participation. They are particularly useful for topics where public awareness is low as they provide a format for the interaction of the public and scientists. The value becomes two way because citizen and the general public have differing perspectives (Rep and Matchos). While Science Café's provide a safe environment which helps to get citizens involved their format leaves little room to advance beyond the lowest rungs of the citizen empowerment ladder.

The citizen empowerment ladder is a framework that was developed to categorize different types of citizen involvement. The lowest rungs, categorized as non-participation, consist of manipulation and therapy. The next level, tokenism, includes informing, consultation, and placation. Science Café's that stop at just a dialogue will be limited to this low category of participation. The top rungs of the ladder are categorized as citizen power and include partnership, delegated power, and citizen control. So, if we are to push for more than just dialogue and one wants to adhere to the principles of RRI there needs to be a way to advance patient engagement beyond tokenism.
In a previous Innovative Medicines Initiative, U-BIOPRED, the patient stakeholder engagement was more as a partnership aiming to move beyond tokenism[6]. Using that experience as a model we sought to achieve true partnership with the patient engagement in imSAVAR.

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.

Accordingly, a series of workshops was developed similar to Science Café's where scientists presented the work of imSAVAR followed by a facilitated dialogue between the patient stakeholders and the researchers. The first additional feature of this Science + Café approach compared to standard Science Café's was that the researchers brought questions for the patient stakeholders to the workshop. While this is an advancement it still falls under tokenism on the participation ladder because it is in effect a consultation.

The dialogue was structured around a problem map. Problems that need to be solved by preclinical model of immune toxicity were identified by the group. For each of the problems discussed the discussion then centered on the causes, effects, and consequences of the problems. This led to a common understanding of the problems between the attendees.

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

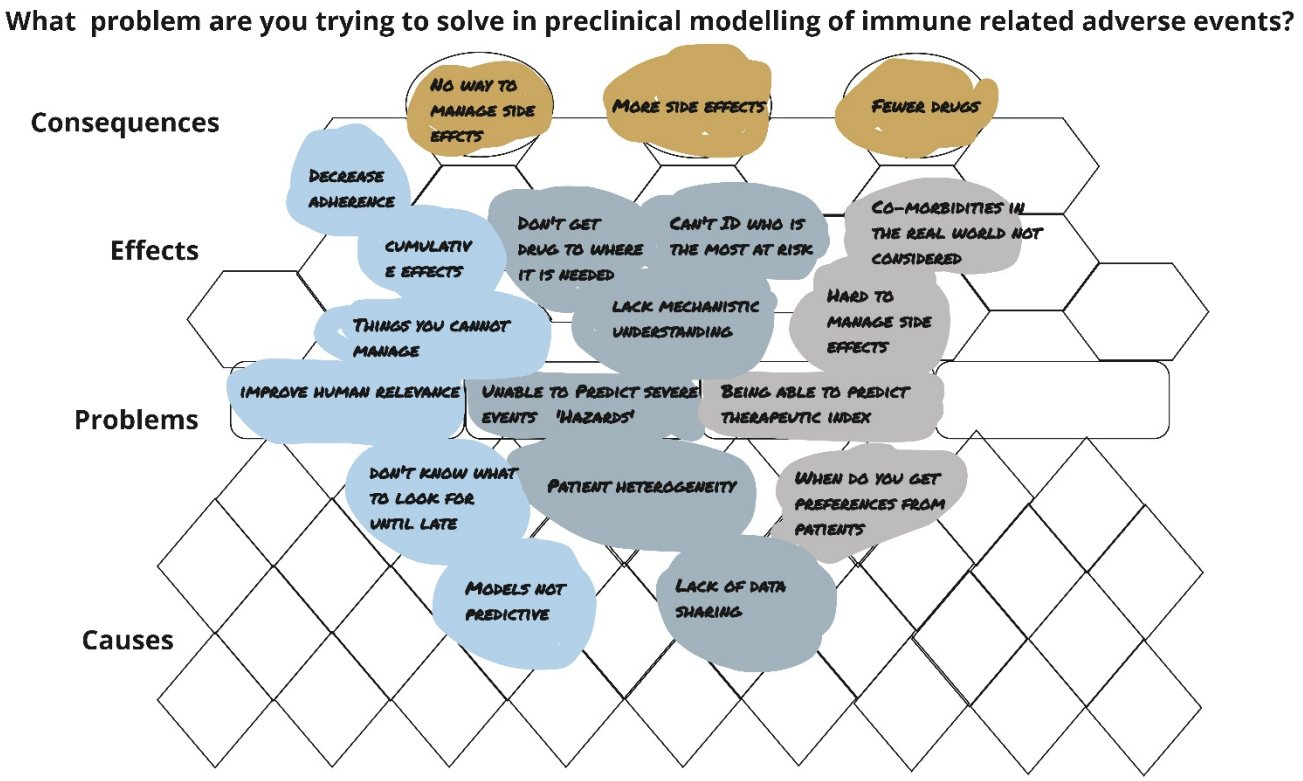

Exhibit 1 Problem Mapping

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 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. The three most important problems were the need to improve human relevance of preclinical models, the inability to predict severe events or 'hazards' and the lack of ability to determine the therapeutic index of a new therapy in the preclinical phase of development.

In order to move beyond consultative tokenism, the issues around preclinical safety testing were mapped in a participative manner between the researchers and the patient stakeholders. The issue map was developed in an iterative manner with feedback from both patient and scientist stakeholders. extending from the problems identified. Issues were formulated into a series of questions:

- Can we predict who is going to have a given toxicity?
    - What do we need to make better predictions?
- What toxicities do we need to predict?
- Are there important things to decide early that need to brought to phase III? When are you ready to quantify what is important to patients?
- What is the unmet need and how do you manage the unmet needs
    - context is important
- Do irAOPs need to be disease specific?
- Does patient centeredness need to be part of the model grading?
- Can long term toxicity be modelled?
- What about impact of prophylaxsis?
- Should toxicity prediction be more stratified/personalized?

These questions where also mapped against the scientific presentations that happened at the start of the workshop.

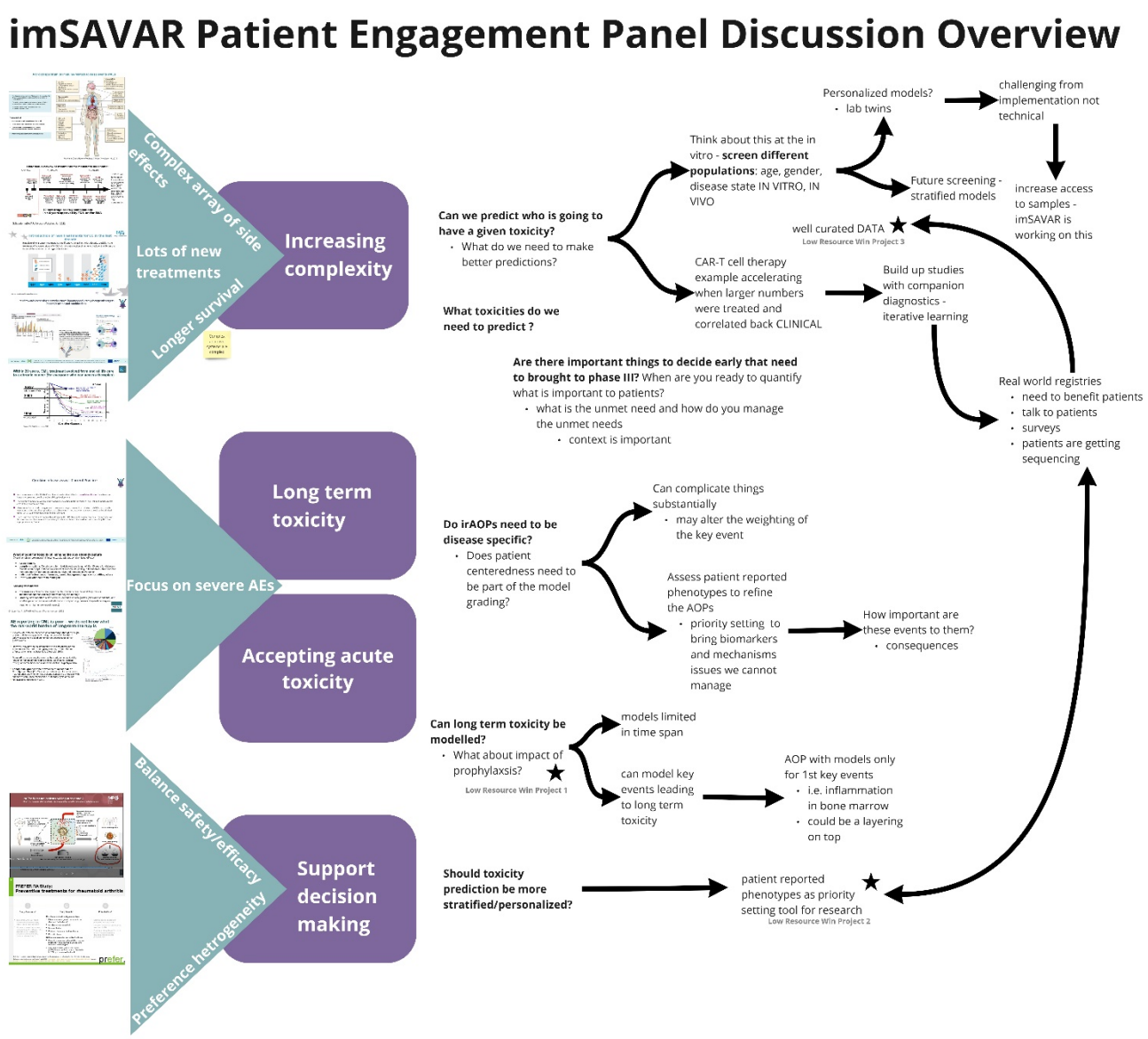

Exhibit 2 Discussions Diagram

3. Low Resource Win Projects

This issue tree was then used to design three different low resource win projects:

1. Supporting patient decision making with preclinical toxicity modelling
2. Identifying immune related adverse effects (irAEs) prioritized through a patient preference study
3. Improving access to clinical outcomes data

The first project was developed to a degree of detail and a working group was convened to initiate the effort around this project.

Low Resource Win Project 1: Supporting patient decision making with preclinical toxicity modelling

Type: Proof of Concept (initiation, pilot, proof of concept etc.)

Problem: Patients are often faced with deciding whether to initiate a therapy. The risk of side effects in some clinical scenarios is important to them. Often the symptoms that are modeled in toxicity studies are not the ones that are most important to patients and therefore patients do not have any assessment of the risk of developing a particular symptom. Having such an assessment in some clinical scenarios would help them to decide their clinical course of action.

What is the longer term change you are trying to make: Preclinical toxicity predictions are used by patients to make clinical decisions. Vision of the future: Patient has the option to initiate a therapy with potential toxicity such as a life-long diarrhea but has to decide to start the therapy or take a more palliative approach. The preclinical predictions help the patient to balance risk of toxicity with efficacy.

Fit to larger vision of the consortium: Ability to predict clinically relevant toxicity for immunomodulatory therapies in the nonclinical phase.

Patients are important stakeholders and their preferences are now required to be included in new therapy development (e.g., by regulatory bodies, for HTA). Therefore, finding a way to reflect their preferences will fulfill the vision of 'clinically relevant' toxicity modelling.

Successful outcome: Clinical scenarios where knowing the risk of certain toxicities would help patient stakeholders in their decision making are identified. These scenarios influence the imSAVAR roadmap for model development.

Unsuccessful outcome: No clinical scenarios are identified where additional toxicity risk prediction would help patient stakeholders in their decision making. The described scenarios do not influence imSAVAR model development priority setting.

Strategic considerations:

- For this accelerant project focus on identifying the simplest clinical decision scenario and set of patient derived phenotypes as possible
- Document the process so that it could be used as a future method

Research/Innovation questions:

1. Are there clinical decision scenarios where the risk of toxicity would influence a patient's decision to initiate therapy?
2. Can we define patient relevant phenotypes that are different than the currently modeled toxicity phenotypes?
3. Are the combined decision scenarios and patient derived phenotypes something which current modelling approaches could support?
4. What would the resulting output look like? A percentage (%) chance of developing a particular toxicity? A balance between toxicity and efficacy?

Design:

- Work with patient groups to define clinical scenarios where more granular information on toxicity risk would be helpful
- Establish the patient derived phenotypes for each identified scenario

- Consult with modelling experts on the feasibility of modelling phenotypes and supporting clinical decision making
- Detail how the imSAVAR model development campaigns will be prioritised to support the generation of models that can support patient clinical decision making

Goals:

Phase 1

- Identify clinical scenario
- Identify teams to be involved
- Generate initial list of scenarios

Phase 2

- Map the patient derived phenotypes for each scenario
- Choose a scenario with patient derived phenotypes that are not currently modelled
- Check with modelling teams about feasibility of modelling

Phase 3

- Determine in what form the output will be given to patients (percent risk, risk/benefit score etc.)
- Decide how this would affect priority setting in imSAVAR
- Initiate experimental campaign and share initial results with patient stakeholders

Participants:

imSAVAR modelers

- *Give:* time to consider the feasibility of developing models to support the clinical scenarios and incorporate that into the priority setting in imSAVAR
- *Get:* opportunity to be part of novel way of engaging patient stakeholders and doing work that will directly benefit patients in difficult clinical situations

Patient stakeholders

- *Give:* their time and effort to define clinical scenarios where additional toxicity risk information on the symptoms they care about the most would help them make decisions
- *Get:* potential to influence research agenda to make it more patient-centered

Low Resource Win Project 2: Identifying irAEs prioritised by patients through a patient preference study

Type: Initiation (initiation, pilot, proof of concept etc.)

Problem: Currently, patient involvement in drug development exists but is unstructured and limited to the later stages which raises questions on actual impact. It is not uncommon for clinicians and patients to have diverging perspectives on treatment outcomes with patients balancing efficacy versus impact on quality of life whilst clinicians and researchers emphasizing severe toxicities and their management. Integrating patient preferences into nonclinical phase can be seen as unprecedented but important in re-shaping the drug development narrative to ensure it is patient centered at the point of setting research priorities. Patient preference studies can play an important role; the IMI project PREFER has developed a methodology that will likely be recognised by the EMA as a framework to elicit patient preferences. Such a structured approach could be used to understand preferences either in terms of

which toxicities linked to immunomodulatory therapies are most important for a patient population, or to understand patient preferences in regards to benefit-risk trade-offs. One example of its application could be for genotoxicity. Genotoxicity refers to the capability of a substance to damage genetic material 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 the disease. A preference study could help define the risk tolerance, to what extent genotoxicity will need to be modelled and its influence on regulatory approval of a therapy.

What is the longer term change you are trying to make: Patient preferences are integrated into nonclinical safety assessment strategies to inform drug development and approval. Vision of the future: For a novel MoA, patient preferences are elicited concerning relevant irAEs using the appropriate methodology. This is an integral part of the nonclinical safety assessment strategy to be implemented. This leads to development of "patient-centered" irAOPs for use in regulatory submissions.

Fit to larger vision of the consortium: Ability to focus efforts and resources to MoAs for which patient preferences have been derived for feedback loops for enhancing the testing battery.

Successful outcome: Defining a patient preference study research question on genotoxicity of CAR T therapy (or other prioritised toxicity of concern) with multistakeholder and multi-initiative alignment considered impactful. This can lead to potential for additional funding to conduct a study.

Unsuccessful outcome: Inability to define an impactful patient preference study research question on genotoxicity of CAR T therapy (or other prioritised toxicity of concern) due to lack of stakeholder alignment.

Strategic considerations:

- Identification of a multistakeholder and multi-initiative aligned research questions is critical for potential funding to run the study
- Document the process of defining the research questions for future use

Research/Innovation questions:

1. What is the risk tolerance of a certain patient population towards genotoxicity (or other identified irAE)?
2. How does the risk tolerance impact to what level genotoxicity needs to be modelled?
3. How can a patient preference study and "patient-centered" irAOP influence regulatory acceptance pathways?

Design:

- Work with IMI PREFER and IMI T2EVOLVE
- Work with stakeholders and relevant disciplines to define list of topics of interest for patient preference study CAR T therapies
- Consult with imSAVAR and T2EVOLVE modelling experts
- Consult with Patient Stakeholders
- Consult with imSAVAR and T2EVOLVE regulatory experts

Goals:

Phase 1

- Identify team to be involved

- Define initial list of irAEs considered impactful
- imSAVAR and T2EVOLVE modelling expert feedback on initial list of irAEs
- Patient and Regulatory Stakeholder feedback on initial list of irAEs

Phase 2

- Define initial patient preference research question
- imSAVAR and T2EVOLVE modelling expert feedback on initial list of irAEs
- Patient and Regulatory Stakeholder feedback on initial list of irAEs

Phase 3

- Develop a study proposal
- Seek funding for the proposal

Participants:

imSAVAR modelers

- *Give:* time to consider the feasibility of developing testing battery to support "patient-centered" irAOP development and incorporate that into the priority setting in imSAVAR
- *Get:* opportunity to be part of new way of with engaging patient stakeholders to define novel nonclinical safety assessment strategy

T2EVOLVE modeler

- *Give:* time to consider the feasibility of developing testing battery to support "patient-centered" irAOP development and incorporate that into the priority setting in T2EVOLVE
- *Get:* opportunity to be part of new way of with engaging patient stakeholders to define novel nonclinical safety assessment strategy

PREFER patient preference study experts

- *Give:* time to help define a novel patient preference study
- *Get:* opportunity to be part of a conducting a novel case study for patient preference elicitation

Patient Stakeholders

- *Give:* their time and effort to define a patient preference study research questions where they would have the ability to be involved at the high impact stage of drug development and influence programmes
- *Get:* potential to influence research priority setting and drug development processes

Regulatory Stakeholders

- *Give:* their time and effort to provide feedback on patient preference research questions
- *Get:* potential to receive detailed consolidated information in the form of "patient-centered" irAOPs for future regulatory assessment

Low Resource Win Project 3: Improving access to clinical outcomes data

Type: Initiation (initiation, pilot, proof of concept etc.)

Problem: Data sharing from industry is very minimal which limits the ability to develop preclinical models with biomarkers that relate to clinical outcomes

What is the longer term change you are trying to make: More streamlined sharing of outcome data helps inform nonclinical safety strategies and eventually improve their predictivity leading to potential for better outcomes.

Fit to larger vision of the consortium: imSAVAR looks to build better preclinical models that predict clinically relevant outcomes. A success in doing that even on a small scale would be hugely beneficial.

Successful outcome: Data from a clinical study is shared with imSAVAR and then used to inform model or biomarker development.

Unsuccessful outcome: No clinical study is identified where its data can be shared with imSAVAR further perpetuating the barrier of data sharing

Strategic considerations:

- Focus on an example within the imSAVAR consortium to demonstrate that sharing of outcome date from a study is feasible
- Document the process required to enable the sharing

4. Low Resource Win Project: Initiation and progress towards citizen/scientist partnership

Subsequently Low Resource Project 1 met three times and the Low Resource Project 2 was initiated with members of the T2EVOLVE project. The concept of low Resource Win project 3: increasing access to clinical outcome data for prediction has been taken up as a core effort for the sustainability model of imSAVAR.

In LRWP 1 a robust discussion was carried out regarding patient preferences for toxicity modelling. For patient stakeholders the most important toxicities to model are those for which there is no treatment. For some patient stakeholders being able to predict toxicity for complex clinical scenarios is the most important. There is a balance between side effects and the efficacy of treatment. The most important consideration is when to switch to a new treatment and the additional or lack of risk that will entail (see CML example insert). The challenge with many different toxicities is that they happen rarely, and it is therefore difficult to obtain samples or compare model outcomes to clinical scenarios. One area where there it would be feasible to modify the current modelling efforts is regarding gender. Gender considerations are rarely included in preclinical modelling efforts. Yet, patient stakeholders point out that there is a prominent concern that women have more immune related adverse outcomes which obviously will influence decision making. The subsequent plan is for imSAVAR researchers to conduct a thorough literature review to understand what is known about gender and immune related adverse events. This will then be brought back to the patient stakeholders to design subsequent efforts to reanalysis datasets that are available with consideration of gender and possibly conduct experiments to determine the impact of models. At a minimum this effort will be able to make recommendations about the best practices around experimental design and data collection in regard to gender.

For LRWP 2 a joint workshop was held with T2EVOLVE researchers. Genotoxicity is a challenging topic to model in the preclinical setting. Ideally the risk of significant genotoxicity is determined before a therapy is approved, however the recent FDA watch on CAR-T therapy is an example of the importance of this topic. It also highlights some of the most important challenges such as the fact with previous or conditioning chemotherapy the risk of a secondary malignancy increases making linking genotoxicity to

the effects of a therapy difficult. T2EVOLVE is conducting a patient survey which may reveal some insights on patient preferences or the perspective on genotoxicity. T2EVOLVE is also planning a spotlight session on genotoxicity. This group will be reconvened as the results of the T2EVOLVE patient survey are analysed.

For LRWP 3 as imSAVAR is in its last two years there is currently ongoing efforts to define a sustainability model. This is planned to be a form of a community where different organisations and projects continue to work together on the topic of immune safety prediction. One of the main areas of interest that has emerged is building a clinical reference dataset to enable more clinically relevant prediction of immune safety outcomes. This project aligns well with this emerging focus. The imSAVAR sustainability working group has been formed and will meet in early 2024 at which point we will look to engage patient stakeholders in via this LRWP.

5. Conclusion

In the imSAVAR project we are aiming to move beyond simple patient stakeholder consultation towards a level of engagement that is true partnership. To date we have achieved robust engagement with patient stakeholder participation in dialogue that is shaping the research and innovation within imSAVAR. The inclusion of gender into the research of imSAVAR demonstrates how deeper patient stakeholder engagement can help to instill societal values and norms into research which is one of the goals the European Union's push for responsible research and innovation.

The next phase of the project will see the deepening of this effort into true partnership as there are concrete plans to conduct research on gender in preclinical immune toxicology with patient stakeholders as part of the team. The Science + Café concept will be further developed with the input of the analysis to make a template for conducting similar Science Cafes. The concept and the process will also be utilized by BioSci Consulting in other projects and will provide support of the development and implementation of Science + Café's as a commercial offering.

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