



A GUIDE FOR CHOOSING THE RIGHT CRO IN IMMUNO- ONCOLOGY STUDIES

MITIGATING RISK IN THE CLINIC

INTRODUCTION

IMMUNOTHERAPY TRIALS IN ONCOLOGY HAVE SHOWN TREMENDOUS PROMISE AND MAY REPRESENT THE MOST PROMISING CANCER TREATMENT APPROACH IN THE PAST 50 YEARS. NEW SCIENTIFIC BREAKTHROUGHS ALWAYS COME WITH A LEARNING CURVE. IT'S NO DIFFERENT WITH CANCER IMMUNOTHERAPY RESEARCH.

To mitigate risk, it's critical for sponsors and investigators — and everyone else working on your immunotherapy trial — to understand how the immune system responds to cancer treatments.

To avoid misinterpreting your data or missing trial deadlines, ensure that your sites and vendors have experience in immunotherapy studies and can help you avoid the numerous potential pitfalls that could cause you to prematurely end your trial ... *when the immunotherapy treatment is actually working.*

This guide provides eight recommendations to keep your immuno-oncology study on track and was developed from our hands-on experience managing complex cancer immunotherapy studies since 2008.



ABOUT MEDELIS

MEDELIS IS A SPECIALTY ONCOLOGY CRO FOCUSED ON PRECLINICAL AND PHASE I THROUGH PHASE IV ONCOLOGY STUDIES IN NORTH AMERICA AND EUROPE. FOUNDED IN 2003, MEDELIS PROVIDES CUSTOMERS WITH ONCOLOGY EXPERTISE FROM DRUG DEVELOPMENT THOUGHT-LEADERSHIP TO A HIGHLY SKILLED CLINICAL OPERATIONS TEAM, HANDLING COMPLEX ONCOLOGY TRIALS IN ALL INDICATIONS, INCLUDING CUTTING-EDGE IMMUNOTHERAPY TREATMENTS.

IMMUNOTHERAPY IN ONCOLOGY — AN ADDED LEVEL OF COMPLEXITY

RAPID ADVANCES IN CANCER IMMUNOTHERAPY TREATMENTS HAVE FUELED
A TREMENDOUS INVESTMENT IN THIS PROMISING AREA OF RESEARCH.



While sponsors and investigators rush to get immunotherapy treatments (such as checkpoint inhibitors, adoptive cell transfer, therapeutic antibodies and immune system modulators) into the clinic, it's important not to overlook the operational considerations associated with cancer immunotherapy studies.

AS WE ALL KNOW, CANCER STUDIES
ARE MORE COMPLEX THAN STUDIES IN
MOST OTHER THERAPEUTIC AREAS.

AND FURTHERMORE, CANCER
IMMUNOTHERAPY STUDIES ARE MORE
COMPLEX THAN MOST TYPICAL
CANCER STUDIES.

This complexity requires an additional level of detailed planning to properly address the nuances of an immunotherapy study. Failure to do so could cause you to prematurely end a study — *even though the therapy is actually working* — or end up with extended timelines, bad data and cost overruns.

[1] SITE SELECTION — THE FIRST CRITICAL OPERATIONAL DECISION

PROPER SITE SELECTION IS CRITICAL TO THE SUCCESS OF ANY ONCOLOGY STUDY. IT'S EVEN MORE CRITICAL IN THE RAPIDLY EXPANDING AREA OF CANCER IMMUNOTHERAPY.



TO GET THE RIGHT DATA WITHIN YOUR TIMELINES, YOU NEED:

1. The investigators who have access to the patients your study requires
.....
2. The right mix of sites (academic, government and community-based) that are able to get patients enrolled within your timeline
.....
3. Sites that are skilled and experienced in handling the type of treatment being administered
.....
4. Sites that understand how to deal with the differences in how the immune system reacts to these types of treatments

THESE VARIABLES DIRECTLY AFFECT YOUR STUDY COST AND DATA QUALITY.

IN ADDITION, IF YOUR STUDY IS PHASE I, YOU WILL ALSO HAVE TO EVALUATE THEIR DOSE-ESCALATION EXPERIENCE.

[2] INVESTIGATIONAL PRODUCT HANDLING

SEVERAL OF THE IMMUNOTHERAPY STUDIES WE'VE MANAGED RECENTLY HAVE REQUIRED US TO FOLLOW THE NIH BIOSAFETY LEVEL 2 (BSL-2) GUIDELINES FOR THE HANDLING OF THERAPIES UTILIZING MICROORGANISMS ASSOCIATED WITH HUMAN DISEASES.

Biosafety levels, or BSLs, are designations to classify the level of danger of a biological agent in an enclosed laboratory facility.

THE DESIGNATIONS AND RISKS ASSOCIATED ARE AS FOLLOWS:

LEVEL 1 — The lowest level, this applies to agents that pose minimal threat to lab workers and the environment.

LEVEL 2 — This includes work with agents that are associated with human disease — pathogenic or infectious organisms posing a moderate health hazard.

LEVEL 3 — Indigenous or exotic agents that cause serious or lethal disease via aerosol transmission.

LEVEL 4 — Extremely dangerous agents that pose risk of life-threatening diseases for which there are no vaccines or cures.

If your treatment is BSL-2, it will affect your site selection. Not all sites have the processes or infrastructure to handle these types of agents, which require the use of surgical gowns, gloves, goggles, safety glasses and possibly a Class II biological safety cabinet.

Additionally, the local investigational biosafety committee (IBC) must approve the site's level of preparation to handle these types of agents. This was a challenge for Medelis during our first cancer immunotherapy studies (back in 2008) because at that time, not all sites had an IBC.

THUS, WE HAD TO WORK WITH THE SITES TO HELP THEM ESTABLISH ONE. AS LEVEL 2 IMMUNOTHERAPY AGENTS BECOME MORE PROMINENT, INSTITUTIONS ARE BECOMING BETTER PREPARED, BUT MANY SITES STILL REQUIRE ASSISTANCE WITH INFRASTRUCTURE ISSUES.





[3] BIOSAMPLE COLLECTION

A KEY GOAL OF CANCER IMMUNOTHERAPY STUDIES IS TO COLLECT AND UTILIZE SPECIMENS FROM PATIENTS FOR IMMUNO MONITORING, AND FOR DEVELOPING AND CREDENTIALING BIOMARKERS THAT WILL ASSESS THE PHARMACODYNAMIC EFFECTS OR THAT CAN SERVE AS PREDICTORS OF RESPONSE.

Thus, it's critical to plan for the logistics of sample collection, processing and shipping during trial planning. Consider:

- **CONTAINERS** — Do you require specialized containers?
- **TRANSPORT** — What requirements should be in place for the couriers? Most immunotherapy treatments require temperature control during transport and storage.

- **CUSTOMS** — If you're running a global study, what are the implications of samples passing through customs? This may impact the countries you select.

In the Aduro Biotech GVAX Pancreas Prime study, we handled this by working closely with the drug distributor to coordinate just-in-time delivery with the vaccine and dry nitrogen shippers. We also worked closely with the site to ensure that there were no patient treatment delays.

[4] PRODUCT STORAGE

MANY OF THE NEW IMMUNOTHERAPY TREATMENTS REQUIRE SPECIALIZED STORAGE PROCEDURES. REVIEW THE SITE'S PHARMACY PROCEDURES FOR MONITORING THE TEMPERATURE OF STORED PRODUCTS, ALONG WITH HOW THEY REPORT DEVIATIONS.



For many therapies, an ultra-low temperature freezer is required, and in recent years, vendors have started producing this type of freezer in sizes that fit in a typical site's pharmacy.

[5] MONITORING irAEs AND SAEs IN ONCOLOGY IMMUNOTHERAPY STUDIES

THE EVALUATION AND HANDLING OF SAEs IN CANCER IMMUNOTHERAPY STUDIES ARE CRITICAL TO THE OUTCOME OF THE STUDY. THE MAJORITY OF THE EVENTS WILL BE AUTOIMMUNE-RELATED, SINCE THE BODY WILL START ATTACKING ITSELF. MANY PATIENTS ENROLLED IN THESE STUDIES HAVE ADVANCED CANCERS AND HAVE FAILED MOST TREATMENTS, SO IT'S COMMON FOR THEM TO HAVE WEAKENED IMMUNE SYSTEMS.

Therapies targeting checkpoint receptors have shown to increase toxicities that can create a unique set of adverse events called immune-related adverse events (irAEs). Research is showing that combinations of different checkpoint inhibitors improve the body's ability to eradicate cancer, but at the cost of an increase in frequency and severity of irAEs.

Patients undergoing immunotherapy treatments may experience reactions like dermatitis (from rashes to toxic epidermal necrolysis), pancreatitis, immunitis, iridocyclitis, hepatotoxicity,

hypophysitis, neuropathies, nephritis and hepatitis. Some patients with underlying autoimmune disorders can experience exacerbations of underlying autoimmune conditions when on therapies blocking CTLA-4 and PD-1. These reactions often start out mild but can become severe and life-threatening if not recognized.

Since multiple studies have shown that there is an association between irAEs and clinical benefit, it's important to have a comprehensive approach for evaluating and treating SAEs.

[6] SAE AND irAE MANAGEMENT

FOR EVERY ONCOLOGY IMMUNOTHERAPY STUDY WE RECOMMEND THE FOLLOWING:

TRAINING FOR EARLY RECOGNITION

Early recognition and AE management is critical to allow the patient to continue on the study treatment per the protocol. This can be addressed during site training by educating the study coordinator research nurses about potential immune-related AE symptoms.

COMBINATION THERAPY EVALUATION

Each therapy's relationship with the AE must be assessed. Recent studies have shown that algorithms designed for specific therapies can help clinicians manage and treat the most common irAEs associated with the treatment.

THESE CAN OFTEN PREDICT THE irAE FREQUENCY AND SEVERITY
BASED ON DOSAGE AND FREQUENCY OF THE TREATMENT.

[7] SPECIALIZED REPORT FORMS

Adverse event report forms must be designed in a way that addresses the possibility for multiple attributions. For example, if there is more than one drug being given, the case report form (CRF) needs to ask about the AE's relationship to each individual drug, rather than the study treatment as a whole.



[8] CRF GUIDELINES

CASE REPORT GUIDELINES MUST INCLUDE SPECIFIC INSTRUCTIONS FOR THE SITE ON HOW TO RECORD THE AE.

The research has made it clear that the preparation for, handling of, and analysis of specific types of SAEs and irAEs are critical for immuno-oncology studies — to accurately measure the success of the treatment, to reduce trial delays that extend timelines and increase costs, and most importantly, to ensure the safety of the patients on protocol.

EXPERIENCE IS THE KEY

FOLLOWING THESE EIGHT GUIDELINES CAN HELP YOU OVERCOME THE NUMEROUS OBSTACLES THAT MANY SPONSORS ENCOUNTER IN THE CLINIC WITH THEIR FIRST IMMUNO-ONCOLOGY STUDY.

CONNECT WITH US IF YOU'D LIKE ASSISTANCE WITH SITE SELECTION OR WITH THE DETAILS OF YOUR UPCOMING IMMUNOTHERAPY STUDY.

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