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Nonnegotiable Central Laboratory Capabilities for I/O Clinical Trial Success

The right treatment to the right patient: a complex endeavor evolves

Delivering the right treatment to the right patient at the right time in immuno-oncology (I/O) requires experienced laboratory expertise for complex evaluations. Since the 2011 FDA approval of the first checkpoint inhibitor ipilimumab, immuno-oncology has gained momentum as a premier therapeutic strategy within precision medicine. Improvement in patient stratification with increasing clinical efficacy and survival rates is increasing the prospects for regulatory approval. With such promise, the number of pipeline drugs rose from 399 to 1,875 between 2016 and 2019 (Fig. 1), and the market is expected to expand at a compound annual growth rate (CAGR) of 10.4%[1] between 2018 and 2025, surpassing $115 billion by 2023.[2]

Immuno-Oncology Pipeline Drug Counts by Year

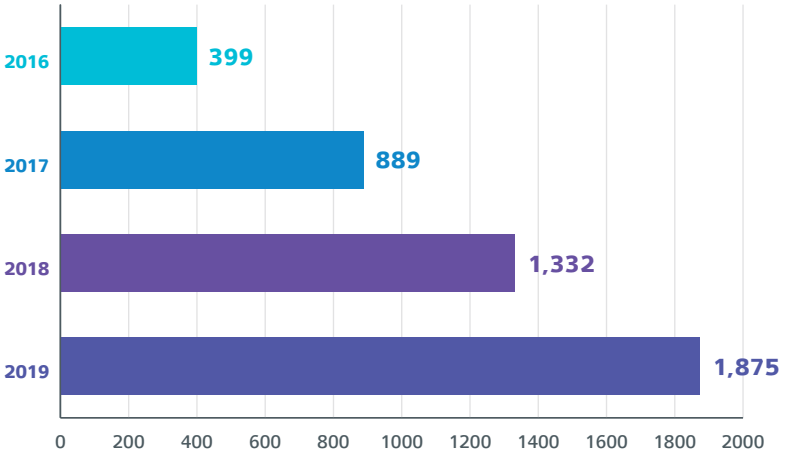

Figure 1: From 2016 to 2019, the immuno-oncology pipeline grew more than 350%. (Source: Pharmaprojects Pharma R&D Annual Review: 2019)

In this burgeoning field, adept, integrated clinical laboratory and diagnostic solutions are needed for the challenging journey from translational research to commercialization. Scientific expertise for insightful protocol advice, operational expertise, speed, agility, and the right diagnostic tools must be forthcoming if these therapies are to achieve their full potential. Access to a sizable patient database is desirable to enable additional early insight through analysis.

EXECUTIVE SUMMARY

- With ever-expanding possibilities for specificity and design, immune-based therapies are pouring into the clinical research funnel.
- In immuno-oncology clinical trials, finding the proper resources to achieve your goals can be a challenge.
- Three main testing methodologies are needed for immuno-oncology: multiplex immunohistochemistry (IHC) for solid tumors, flow cytometry for cells in suspension, and genetic studies (NGS).
- Partnering with a specialty central lab that can help you generate early insights for protocol optimization and can ramp up to commercial scale will enable you to minimize expenditures while keeping timelines intact — resulting in bringing groundbreaking therapies to patients sooner.
- With over 35 years of experience, Cerba Research is a leader in immuno-oncology clinical trials, wielding global solutions including a vast range of biomarker assays.

Furthermore, global multicenter trials require that complex testing must be performed impeccably and in harmony at diverse global locations. To ensure the best experience and outcomes, sponsors need to partner with specialty central labs specifically experienced in immuno-oncology clinical trials. This white paper discusses three mandatory testing capabilities and other company features drug developers should consider when selecting a suitable laboratory partner for an immuno-oncology trial.

Immuno-oncology demands a comprehensive specialty laboratory solution that delivers early biological insights

Careful, knowledgeable planning and execution are required for immuno-oncology trials. Researchers must manage toxicity, demonstrate efficacy, and engage in lengthy follow-up. At the same time, for a developer, the value of obtaining early biological insights that help identify the right patients, the right treatments, the right dosages — and the right durations to optimize protocols and streamline complex trials — cannot be overstated. At the heart of this activity are biomarkers.

It takes global access to proven laboratories and demographically rich data to drive the development of advanced biomarker strategies that facilitate downstream decisions. Accessible scientists who are dedicated experts and understand the I/O space are key. Open communication, transparency, and a commitment to one-on-one relationships ensure that each study is regarded as a unique opportunity, from translational research through commercialization. At Cerba Research, where half of our studies are in oncology, clients engage early to our global network of scientific experts along with custom assays, protocol advice, and other integrated solutions, including scaled-up capacity to build in efficiencies and accelerate programs to market. Cerba's access to biobanked human specimens provides a clear advantage when identifying novel and existing I/O-related pathways, including tumor morphology, tumor genetics, tumor protein and gene expression, and tumor infiltrating lymphocytes (TILs). Such biomarkers can then be developed further to stratify patients into treatment groups, measure treatment efficacy, formulate hypotheses, and increase the trial's probability of success.

Biomarker strategies continue to advance, increasing precision in immunotherapy

The push and pull between immune activation and dampening of the immune response toward malignancies determines cancer outcomes. The results of these complex interactions within the tumor microenvironment and the response to immunotherapies are hard to predict, so measurements of multiple biomarkers are often required.[3] Some therapeutics prove ineffective in as many as 75% of the patients they are expected to help.[4, 5] More approaches must be developed to identify which patients are likely to benefit from any given therapy. The right biomarkers can streamline immunotherapeutic and personalized medicine programs and enhance drug development success rates.[6]

Biomarkers are increasing in importance and evolving quickly in immunotherapeutics to:

- Guide dose selection
- Characterize mode of action or resistance
- Stratify patients/determine inclusion-exclusion
- Predict drug efficacy and safety profiles
- Aid in prognosis
- Monitor disease

Cerba scientists may recommend off-the-shelf biomarkers or propose well-established, research-use-only, or laboratory-developed tests with clinical validation. They can then walk the investigator through the necessary steps, guiding design and customization to provide innovative, flexible solutions. Our large assay portfolio enables targeted approaches or broad immune profiling with multifactorial biomarkers.

Immuno-oncology's necessary trio of tests supports constellations of biomarkers

For precision medicine, a single platform will not suffice for clinical trials in immuno-oncology. A complete program that allows for a holistic understanding of patient status and tumor susceptibility provides experienced guidance and customization for three types of testing: flow cytometry, tissue immunohistochemistry (IHC), and genetic screening (next-generation sequencing, NGS).

Flow cytometry

Flow cytometry is a powerful tool capable of rapidly detecting and measuring thousands of cells with high sensitivity and specificity, providing a snapshot of the immune response. In addition to cell surface markers, flow cytometry can also detect intracellular antigens such as cytokines and phosphorylated signaling proteins. This methodology allows functional analysis and helps with therapeutic strategies and prediction of therapeutic response. The simultaneous use of many biomarkers generates data that is multifaceted, highly complex, and dimensional.

Immune profiling by flow cytometry produces a large amount of information from a single blood sample. The result is a very granular breakdown, for example, of lymphocytes and subtypes, down to T cell memory subsets and activated versus nonactivated markers (Fig. 2). Clinical researchers can utilize this technology to understand how patients are responding and what kind of therapies are suitable for patient-specific treatment plans.

These studies demand highly skilled staff scientists to develop and validate both off-the-shelf and novel biomarkers. Therefore, the lead time for assay development to validation must be considered. Further, for global trials, a standardized approach is critical, including instrument standardization and assay process standardization (same SOP).

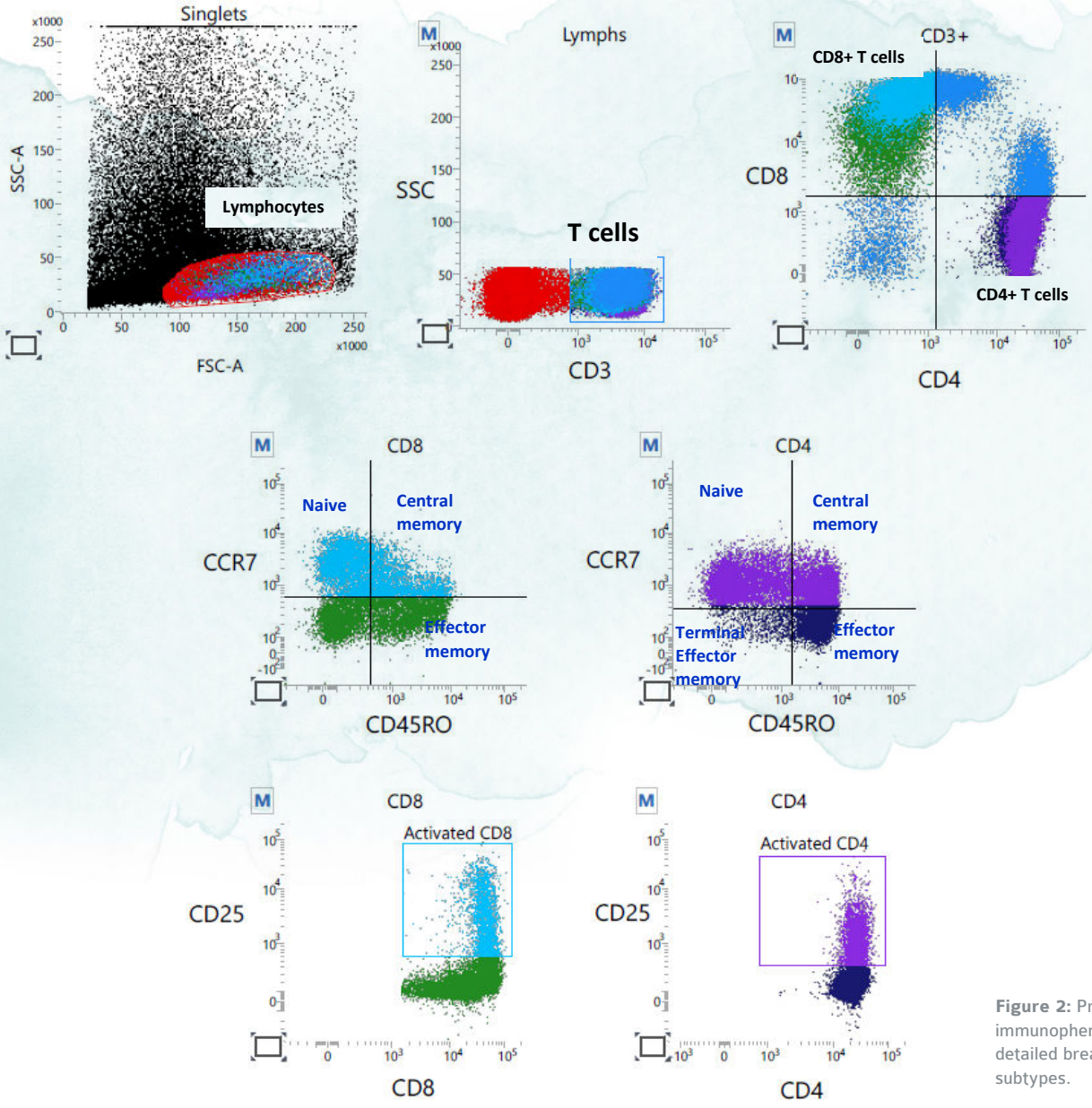

Figure 2: Profiling via 10-color immunophenotyping provides a detailed breakdown of lymphocyte subtypes.

Immunohistochemistry (IHC)

IHC is a cost-effective assay that profiles tissue biomarkers to individualize a patient's therapy. It is an antibody-mediated approach that allows detection of the target of interest in the tissue through fluorescent or chromogenic revelation for quantification and cellular localization. This technique has typically been used for the diagnosis and classification of tumors such as lymphomas and breast cancer. In addition, IHC conveys structural information about the tumor and the tumor microenvironment, demonstrating the localization of immune cells in relation to the tumor or other immune cell populations. It can also reveal the expression of activation/deactivation biomarkers as part of immune cell profiling and oncogene evaluation. Cerba Research offers sponsors an ever-increasing number of novel I/O biomarkers. These include hard-to-develop, customized IHC assays for the preclinical phase, with subsequent validation for use in clinical trials.

Multiplex IHC, the combination of several biomarkers on a single slide/section, is an advanced version that allows for the detection of up to eight biomarkers in one precious tissue section. The ability to detect more biomarkers per slide is increasingly important as:

- Demand for more biomarkers is growing
- Accurate phenotyping requires several markers
- Biopsy size limits the number of sections
- Some data cannot be obtained from circulating markers, such as spatial context and organization and distances between populations of cells

NGS for genetic screening

Genetic screening measures changes in nucleic acid sequences associated with disease susceptibility or resistance. Next generation sequencing (NGS) enables a wide range of new applications and investigations in genetics, including analysis of solid and hematologic tumor genomes as well as in-depth analysis of the patient's immune repertoire pre- and post-treatment, including T cell receptor (TCR) analysis.

Cerba Research's capacity for high throughput, with the ability to sequence 1,000+ whole human genomes in a week — coupled with one of the largest catalogs of clinical NGS genetic and genomic testing — helps

EXAMPLE:

Multiplex IHC for Complex Phenotyping

The utility of multiplex IHC (mIHC) is demonstrated by its use in an immunophenotyping study focused on myeloid-derived suppressor cells (MDSC). These drivers of the tumor microenvironment are immature myeloid cells that protect cancer from the patient's innate and adaptive immune system[7] — and from immunotherapy. They are distinctly heterogeneous, making phenotyping complex.

For complex phenotyping, flow cytometry is a typical choice. However, it will only provide a view of the circulating immune system status at the whole-body level. This may not reflect the populations at the tumor site. For example, a cell population may be abundant, but because of a casein kinase 1 (CK1) activation, the cells will stay away from the tumor; on the IHC panel, the cells will be present, but stop on the same line a few micrometers from the tumor. While flow cytometry can tell you about the abundance, activation, and variations over time of several finely phenotyped populations, only mIHC can give you information about how the cells behave at the tumor site.

In this case, the Cerba IHC team developed a multiplex IHC panel specifically to investigate the microenvironment of a non-small-cell lung cancer (NSCLC) tumor (Fig. 3). The five-plex panel enables the identification of both polymorphonuclear and mononuclear MDSC on a single, NSCLC specimen.

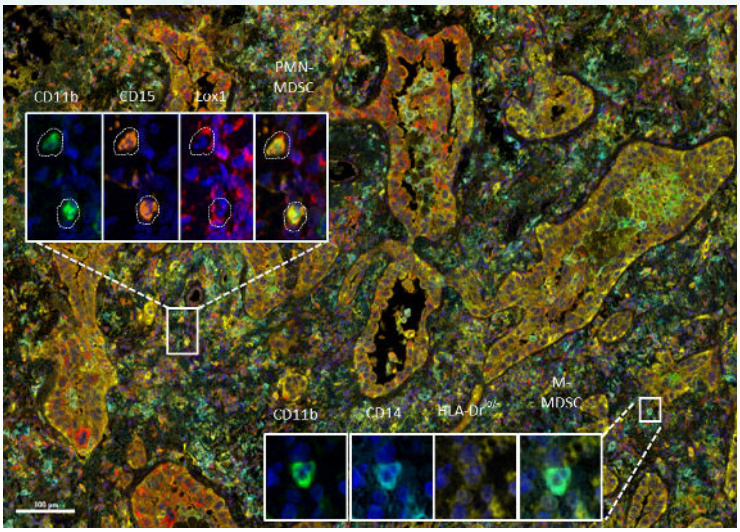

Figure 3: MDSC multiplex IHC panel developed at Cerba Research applied to non-small-cell lung cancer tissue. The high level of phenotyping allows the distinction between subtypes on a single tissue section. Shown: polymorphonuclear (PMN) MDSC and mononuclear (M) MDSC.

ensure that sponsors reach milestones and preserve development timelines, whether they need whole exome sequencing or gene panels customized to suit their protocol.

Applications of genetic insights to look for:

- Biomarker discovery, with comprehensive genomic profiling and customized assays that link mutation to disease
- Prospective patient stratification screening with NGS, PCR, and other assays
- Companion diagnostics development on NGS-based or CHIP-based multiplex qPCR platforms to assess therapeutic suitability
- Cyto- and molecular genetic diagnosis of constitutional and acquired disorders, including developmental disease, predisposition factors, and clotting malfunctions

As an example, the tumor mutational burden (TMB) is a genetic biomarker currently receiving some attention. Cancer is the result of a series of mutations, and cancer cell lines each have between 1 and around 10,000 coding mutations, or .1 to 100 mutations per megabase — the tumor mutational burden. TMB is associated with antitumor response and is a good predictor of response to cancer immunotherapy drugs in some cases, such as melanoma, cutaneous squamous cell carcinoma, and certain colorectal and non-colorectal GI cancers. The reason may be that tumor cells with high TMB have high neoantigen loads, leading to greater T cell reactivity and an enhanced antitumor T cell response. Although the gold standard TMB analysis has been for whole exome sequencing, recent advances in NGS tumor panels have provided consistent results.

Client experience and success hinge on the quality of project management

In immuno-oncology studies, researchers are coordinating variable protocols at multiple study sites and acquiring large quantities of data from many samples that require specialty testing at dispersed locations. This is an intricate process with the potential for delays at every turn. Systematic and global organization is absolutely necessary.

For a successful program and a satisfactory experience, project managers (PM) must be positive, approachable, and highly committed to understanding clients' needs and working with them to deliver their projects on time and on budget. They also need knowledge. Many of Cerba Research's PMs have M.Sc. or Ph.D. degrees, enabling them to develop and implement the right solutions to achieve the right results.

To meet client timelines, whether for a newly initiated or rescue study, an organization must establish seamless communication among sponsors, investigators, labs, shippers, and suppliers. Organizations must also be flexible. Cerba Research typically requires eight weeks for study startup but can be faster, depending on the trial. Recently, a Phase III trial was up and running in less than two weeks in order to meet accelerated timelines.

Experienced advice and record keeping ensure proper validation and assist with regulatory submissions

Study designs in immuno-oncology are often adaptive, multiarmed studies; ensuring proper validation across the spectrum of protocol variations is essential. The typical specialty testing requires detailed sample management at all times, including shipping and associated compliance records, and labeling to maintain sample integrity and chain of custody. Proper interim reports are needed for the product to be considered for fast-track FDA approval. A unified global study database that allows easy access to data anywhere on a secure, user-friendly platform is convenient and saves time. Cerba Research's clinical trial database reports are visible within 30 minutes, allowing sponsors and study teams to search results and address queries in real time. Additionally, reliable biobanking/biospecimen management can help with validation and compliance.

Global footprint and standardization enable clients to stay with the same lab for later-stage trials

Reaching a global patient base can be challenging. Global, harmonized labs are a necessity to achieve timely, comparable processing of samples in multiple locations when the time comes to scale up. While Cerba Research provides the individual attention ideal for early clinical stages, the company also has the global capacity for larger, later-stage clinical trials. A network of scientific experts spanning five continents ensures that everything from sample preparation to instrument setup through data acquisition and analysis is performed consistently at all sites engaged in that study.

Operational support for immuno-oncology trials depends on experience and commitment

Smooth study execution relies on accurate and timely laboratory and fulfillment services. At Cerba, motivated individuals personally committed to improving health via diagnostic services and 35 years of experience handling complex trial logistics equate to fast, dependable turnaround with 24- to 48-hour service, even for remote sites. Custom test kits ensure proper protocol execution across multiple investigator sites and rapid kit manufacturing — reorders taking only five business days. Keeping this function in-house not only speeds up the process, but it also helps guard against shortages or conflicting timelines.

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About Cerba Research

Cerba Research is the result of the merger of Barc Lab, Histalim, and Cerba Xpert. All three entities are part of the Cerba HealthCare group and have decided to join forces under one name.

Cerba Research provides the highest quality specialized laboratory and diagnostic solutions while leveraging patient data and scientific insight to shape and advance clinical trials. With our global footprint and access to leading regional labs, data, patients, technology, and partnered resources, we support global biotech, pharma, and IVD organizations to improve the lives of patients around the world.

From the translation of preclinical to clinical, through commercialization, our expert scientists collaborate with you to optimize your therapeutic development and obtain critical insights earlier. We help accelerate your therapies through the development of highly specialized custom assays, deep biomarker expertise, and a passion for scientific innovation across complex therapeutic areas. Our global network of leading, specialty laboratories ensures you have access to quality data and can reach your patients. Together, we'll improve patients' lives around the globe.

Cerba Research