



# METASTATIC BREAST CANCER ALLIANCE **ATYPICAL RESPONDERS ANALYSIS**

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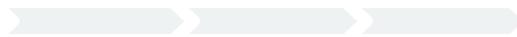
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# ABSTRACT

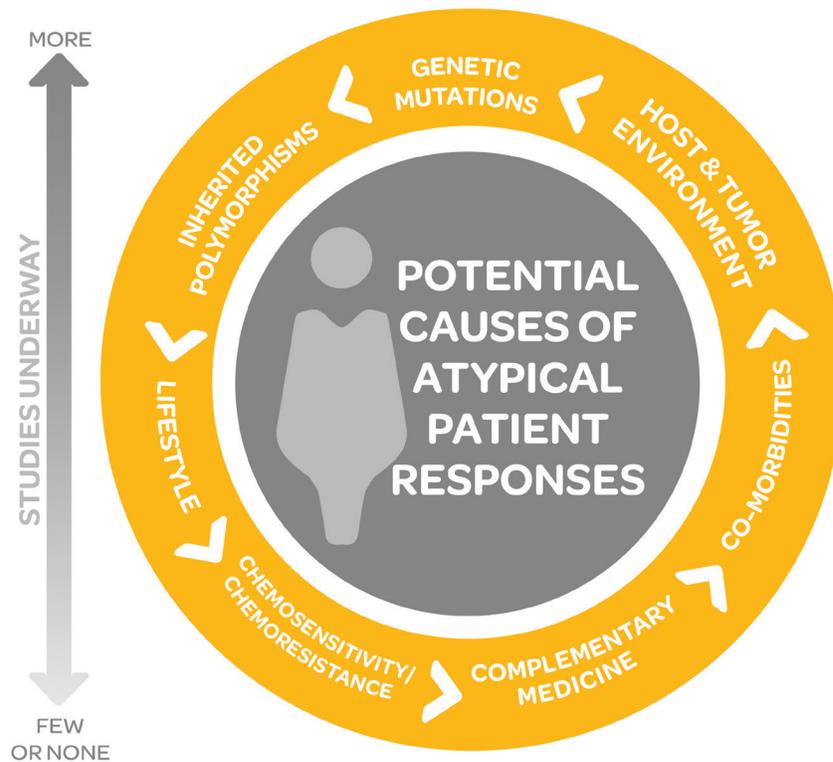
Researchers in clinical oncology and other domains generally focus on results encompassing a statistical mean with little attention to patients undergoing investigational or standard therapies who respond considerably better or worse than the norm. An enormous opportunity exists to explore the reasons underlying an unusual (“atypical”) response, which would increase understanding of the mechanisms involved in cancer progression and treatment resistance, accelerate **biomarker** identification, and improve **personalized medicine** by allowing clinicians to prospectively select optimal treatments while avoiding therapies that would otherwise prove ineffective.

Here we summarize published studies examining the reasons for an atypical response, new research initiatives that are exploring this topic, the strengths and limitations of these endeavors, and a call-to-action for strategic direction. Based on our review, we suggest two ways to move this field forward.



**FIRST,** we propose that clear categorization of “atypical responders” is needed. An “atypical responder” may generally be classified as a patient who responds to a particular treatment in an unusually favorable or an unusually poor manner compared to similar patients undergoing the same regimen. Three sub-categories of patients may be considered: 1. “exceptional responders” (those with an unusually favorable treatment response), 2. “rapid progressors” (patients demonstrating an unusually poor or no therapeutic response), and 3. “exceptional survivors” (advanced stage patients who have far outlived their prognosis for their cancer subtype for reasons that are not fully understood). “Exceptional survivors” may or may not have responded unusually well to a specific therapy, or multiple lines of therapy, yet have fared far better than their counterparts. We propose all three groups of patients be studied in depth.

Second, we suggest that atypical responses may be due to **mutations** present only in tumors (not inheritable; **somatic**), mutations and other genetic changes present in normal tissue (inheritable), the host and tumor environments, lifestyle factors, use of complementary/integrative medicine (CIM), factors that determine chemosensitivity and **chemoresistance**, **co-morbidities**, and the interplay among these elements.



Understanding the reasons underlying atypical responses and exceptional survival is critical to advancing the success of personalized medicine. Therefore, the Metastatic Breast Cancer Alliance calls for:

1. Unified categories of, and criteria for, exceptional responders, rapid progressors, and exceptional survivors
2. Enhancing clinical trial design to study exceptional responders and rapid progressors relative to treatment outcomes. Exceptional survivors who enroll in clinical trials can be readily identified by the date of their MBC diagnosis, and specific methodologies to study these patients are needed.
3. Funding studies that expand upon the role of genetics in atypical responses by integrating other factors including CIM, co-morbidities, and the entire patient, without limiting the study to genetics
4. Sharing standardized, **de-identified** patient information that is generated from these studies in a secure centralized data repository that is accessible to authorized scientists and researchers

Detailed studies of both normal and atypical responses to treatment will be needed to enhance the understanding of the role of non-tumor factors. Clinical trial design for targeted and other types of therapies should be enhanced to collect data in a standardized manner beyond tumor genetics, resulting in a more thorough study of the whole patient.

The objective of studying the multifaceted variables relative to all three categories of atypical response is to enable the scientific community to gain a greater understanding of patient outcomes that will be leveraged to enhance personalized medicine to the point where, in the future, terminally ill patients may be transformed into exceptional survivors who can manage their disease as a chronic condition.

## INTRODUCTION

Whereas the National Cancer Institute (NCI) states “**Precision medicine** uses the genetics of disease to identify effective therapies”[1], we propose that precision medicine should focus on the individual patient using a multifaceted approach. We suggest that as precision medicine becomes more actionable in oncology care, its definition will expand beyond its current focus on treating only the disease (killing cancer cells) to encompass treating the whole patient, considering not only physical health and genetics, but emotional well-being, lifestyle, co-morbidities, and environmental factors during and after treatment.

***We propose that precision medicine should focus on the individual patient using a multi-faceted approach.***

Most clinical studies focus on data derived from patients who fit within a bell curve and often do not examine those who fall significantly outside the average response. Yet these patients, who may be considered “exceptional responders” (i.e., those presenting an unusually favorable treatment response) and “rapid progressors” (i.e., patients demonstrating an unusually poor or no therapeutic response) represent extraordinary potential to increase our understanding of—and improvement upon—human responses to treatment.

Although various investigations have been launched in the US and abroad in an effort to understand atypical treatment-related responses in cancer patients, these studies have limitations in that they:

1. Primarily examine a response to individual treatment regimens, focus on exceptional responders, and do not examine rapid progressors, with the exception of the AURORA trial and the MBC Project
2. Do not investigate the sub-population of patients (“exceptional survivors”) who considerably outlive their prognosis, irrespective of the type and quantity of therapies received, with the exception of the Broad Institute’s MBC Project and the recently initiated University of Wisconsin-Madison Exceptional Survivors study.
3. Develop their own terminology, definitions, and metrics associated with exceptional responders, rapid progressors, and exceptional survivors because no current guidelines exist
4. Focus on the genetic characteristics of tumor cells with limited consideration of inherited **polymorphisms**, the host and tumor environments, lifestyle factors, use of complementary/integrative medicine (CIM), co-morbidities, and other factors that may influence tumor **chemosensitivity** and response to therapy, as well as the interplay among these components
5. Tend not to have stated plans to share de-identified data derived from their investigations that could be leveraged by other researchers in the future

In an effort to address these issues, this analysis examines various ongoing and published studies regarding exceptional responders, rapid progressors, and exceptional survivors, the multiple definitions applied to these patient groups, the possible reasons precipitating an atypical response, and the potential benefits of these studies to metastatic breast cancer (MBC) and other seriously ill patients. This analysis will also address the strengths and limitations of these initiatives while delineating potential action items to be considered by the Metastatic Breast Cancer Alliance and the research community.

Our contention is that studying and sharing information on a common platform about exceptional responders, rapid progressors, and exceptional survivors—and utilizing a standard framework to categorize these populations—will enable the field of personalized medicine to become considerably more precise in developing and utilizing effective protocols for treating patients with cancer and other serious illnesses.

In summary, we suggest that 1. clear categorization of atypical responses is needed, and 2. atypical responses may be due to not only tumor genomic factors but also to **germline-derived** anomalies in normal tissue, the host and tumor environments, lifestyle factors, use of CIM, factors that determine chemosensitivity and chemoresistance, co-morbidities, and the interplay among these factors.

*We suggest that clear categorization of atypical responses is needed, and that atypical responses may be due to multiple factors including:*

- *tumor genomics*
- *normal tissue genomics*
- *the environment in which the tumor is located*
- *co-morbidities and the drugs taken for them*
- *lifestyle factors*
- *practice of complementary and integrative medicine (CIM)*
- *factors that determine chemosensitivity and chemoresistance*

## RESEARCH AND ANALYSIS

### INITIATIVES THAT ARE INVESTIGATING AN “ATYPICAL RESPONSE” AND ASSOCIATED DESCRIPTIONS

Atypical responders encompass groups of patients at either end of the therapeutic spectrum: those who respond to a given therapy either remarkably well or remarkably poorly. In the absence of standard categories, several groups have incorporated a working framework for “exceptional responders” into published or ongoing studies (Table 1, p.31).

Multiple research initiatives are underway in the US and abroad to identify the reasons why some cancer patients respond extraordinarily well to a particular therapy and others do not. Nearly all of these initiatives are studying **molecular aberrations** associated with patients’ tumors in an effort to understand the role these anomalies play in the therapeutic response, and most of them focus solely on exceptional responders. These studies are observational registries and not interventional trials. A list of these studies is provided in Table 2 (p. 33).

## ***The National Cancer Institute's (NCI's) Exceptional Responder Initiative***

**[2]**. NCI has launched a clinical trial to examine the molecular basis of a favorable atypical response ([NCT02243592](#); [NCI News Note: Exceptional Responders Initiative Key Points](#)). The aim is to collect tumor samples from 300 patients with cancer who are considered to be exceptional responders, according to their definition (see Table 1). Researchers will obtain malignant and normal tissue when possible, as well as clinical data. **Whole exome sequencing** and/or mRNA sequencing (**targeted deep sequencing**) of nucleic acids from these tissues will be performed. Samples with sufficient quantities of nucleic acids will be used for additional analyses (e.g., microRNA sequencing, **promoter methylation** analysis, **single nucleotide polymorphism (SNP)** genotyping, and/or **whole genome sequencing**). A potential correlation between molecular profiles and therapeutic responses will be investigated. The stated goal is to determine whether certain molecular features can predict responses to the same or similar drugs. Of note, information gathered in this study will be de-identified and placed in a controlled-access database so other investigators may use it to gain new insights. NCI has funded two [Genome Characterization Centers](#) at The Broad Institute (Boston, MA) and The University of Texas MD Anderson Cancer Center to support this initiative. The strengths of this study include the molecular testing approach, the intent to share de-identified patient data, and a working definition of exceptional responders. Limitations are that no examination of rapid progressors is included, and the study only seeks to perform molecular assessments without addressing lifestyle or other potentially contributing factors that may influence a therapeutic response.

In relation to this initiative, NCI uses the following definition relative to exceptional responders:

- **Complete response (CR)** to a regimen in which CR is expected in <10% of similarly treated patients
- **Partial response (PR)** >6 months in a regimen in which PRs >6 months are expected in <10% of patients with similar disease treated with same or similar regimen
- CR or PR of unusual duration, such that the internal review committee considers it to be an exceptional response; examples below:
  - PR of duration >3× the median expected PR duration (in cases where PR is expected in >10% of patients with the same disease treated with the same regimen)
  - CR or duration >3× the median expected CR duration (in cases where CR may be seen in >10% of patients with same disease treated with same regimen)
  - The observed duration of CR (or PR) is longer than expected for 90% of patients with same disease treated with same regimen

The strengths of these definitions are that they are: 1) quantifiable and 2) utilize commonly measured outcomes such as CR and PR.

***The Broad Institute's MBC Project.*** In addition to playing a role in the NCI initiative above, the Broad Institute has launched a separate endeavor called the MBC Project, which is recruiting patients in a democratized, direct-to-patient approach instead of the traditional approach of working through clinics and institutions. This approach mirrors Dr. Susan Love's ***Army of Women*** project launched in 2008 that recruited 375,000 healthy women, breast cancer survivors, and patients with metastatic disease. The MBC Project seeks to enroll any patient with MBC, including typically and atypically responding patients, to better understand the underlying reasons for their response to treatment. Exceptional responders, rapid progressors, and exceptional survivors present among the population of MBC patients will be identified and studied. The MBC Project is explicitly studying atypical quantitative responses, atypical duration of response, atypical resistance, and long-term survival. MBC Project study participants are asked to submit a questionnaire and provide tumor, saliva, and potentially blood samples. The resulting genomic and medical data will be de-identified before being made available to other researchers. Key strengths of this study are that the criteria defining atypical responders are quantifiable, that tumor mutations will be compared with germline information, and that the resulting data will be made available to other researchers. However, this study does not appear to take into account lifestyle and other factors that may contribute to an unusually favorable therapeutic response.

The MBC Project defines exceptional responders as follows:

1) For patients with estrogen receptor (ER)+/human epidermal growth factor receptor 2 (HER2)- disease or HER2+ MBC:

- Duration with metastatic disease (overall survival), >10 years, OR
- Duration on any one therapy (progression-free survival (PFS)), >3 years, OR
- Any exceptional response to therapy (CR or near CR), as determined by the investigators after review of the answers to the screening questions, OR
- Any other clinical scenario that the investigators believe constitutes an extraordinary response/outcome

2) For patients with triple negative MBC (TNBC):

- Duration with metastatic disease (overall survival), >5 years, OR
- Duration on any one therapy (PFS), >2 years, OR
- Any exceptional response to therapy (CR or near CR), as determined by the investigators after review of the answers to the screening questions, OR
- Any other clinical scenario that the investigators believe constitutes an extraordinary response/outcome [3].

The strengths of this definition are that it is quantifiable and applicable to commonly measured outcomes (CR, PFS, and overall survival) [4].

***The AURORA (Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer) initiative for MBC***

is a program of the Breast Cancer Research Foundation (BCRF) Founder’s Fund for Metastasis Research that includes European and US clinical trials. AURORA EU is a collaborative effort among the Breast International Group, Breast European Adjuvant Studies Team, and Frontier Science & Technology Research Foundation, Inc. Its purpose is to increase genomic and clinical knowledge generated from MBC patients [5]. Initially, 1,300 MBC patients who are either newly diagnosed or have been treated with no more than one line of systemic treatment in the metastatic setting will be recruited to this **prospective** trial. In this study, primary and metastatic tumors as well as blood and plasma samples will be subjected to molecular testing to increase understanding of the molecular evolution of breast cancer. A key goal of this research is to identify predictive biomarkers for response and resistance to commonly applied anticancer agents. Towards that end, a subset of patients in the AURORA study who are characterized as “exceptional responders” or “rapid progressors” will be subjected to more extensive molecular testing to identify prognostic and predictive biomarkers. Another study objective is to provide evidence supporting the feasibility of a global molecular screening platform for MBC. The US-based counterpart to the AURORA project, led by Dr. Nancy Davidson of the University of Pittsburgh and conducted by the Translational Breast Cancer Research Consortium led by **Dr. Antonio C. Wolff** of Johns Hopkins University, will conduct a prospective trial similar to AURORA EU. They will also perform a retrospective analysis of banked paired primary and metastatic specimens, together with a translational laboratory component utilizing patient-derived **xenograft** models to study metastatic disease. The strengths of the AURORA study include the molecular testing approach, the consideration of a possible global molecular screening platform, the incorporation of rapid progressors, and quantifiable definitions of both exceptional responders and rapid progressors. A limitation is not considering lifestyle, co-morbidities, or other potential contributing factors that may impact a therapeutic response.

AURORA endeavors to examine both spectrums of MBC patients exhibiting an atypical response. The study defines exceptional responders as those “showing (nearly) complete response for a duration exceeding 1 year” and rapid progressors as “patients on first- or second-line treatment progressing within the first 3 months since its initiation.” [5]. Notable strengths of this definition are the attempt at quantification and the specific inclusion of rapid progressors.

## **University of Wisconsin–Madison’s Exceptional Survivor Study.**

Recently, the University of Wisconsin–Madison launched the only known study dedicated solely to exceptional survivors to determine why MBC patients have lived an unusually long time since their original early stage breast cancer or **de novo MBC** diagnosis. The underlying hypothesis relating to this definition is that early stage patients have had metastatic disease all along, but their tumor cells have remained dormant or extremely slow growing, and their metastatic disease has been clinically undetectable. This study will also include “de novo” MBC patients who were metastatic from the beginning. *This hypothesis represents a different definition in terms of timing of diagnosis for exceptional survivors. As described in this paper, the MBCA defines exceptional survival as the time from the patient’s advanced stage cancer diagnosis to the current date.* Dr. Mark Burkard, who is leading the University of Wisconsin–Madison study, wants to learn about the contributing factors that have enabled patients to live an unusually long time with breast cancer cells in their bodies. Specifically, Dr. Burkard has employed the following criteria for patient inclusion in his study:

### **For MBC patients with ER+ disease:**

- Duration since early stage or de novo breast cancer diagnosis (overall survival) 10+ years

### **For MBC patients with ER– disease (the study will distinguish between patients with HER2+ vs. TNBC after enrollment):**

- Duration since early stage or de novo breast cancer diagnosis (overall survival) 5+ years.

This study is unique in that it is dedicated to understanding the factors leading to exceptional survival in metastatic patients, and that unlike many other studies, it does not limit the potential causative factors to genetics (although both germline and tumor mutations will be studied). Non-genetic factors will be explored via patient questionnaires, which will solicit information regarding factors such as lifestyle and co-morbidities. Furthermore, Dr. Burkard hopes to share de-identified patient data in as much detail as possible while maintaining patient privacy and anonymity.

**Memorial Sloan Kettering Cancer Center (MSKCC).** Memorial Sloan Kettering Cancer Center is shifting the focus from failed clinical trials in which few patients responded well, and is reexamining the subset of patients in those trials who displayed a positive response (i.e., exceptional responders). MSKCC has established the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, which will be involved in sequencing samples from exceptional responders ([read more](#)). MSKCC is using next-generation sequencing of tumor tissue that allows detection of molecular aberrations in heterogeneous tissue to determine what makes these exceptionally responding tumors unique, and has established a tumor tissue bank that contains samples from thousands of cancer patients. MSKCC hypothesizes that if a particular aberration can be

shown to make a tumor exceptionally vulnerable to a drug, and a pathological explanation can be identified, other patients with the same aberration may benefit from the drug—even if their cancer types are different. In line with this concept, MSKCC and other scientists are also initiating **basket trials** in which small groups of patients with different cancers but the same molecular aberration are studied to look for benefits from one drug across cancer types [6]. MSKCC investigators are leveraging a comprehensive new genomic sequencing test called MSK-IMPACT™ that identifies “actionable”, targetable molecular aberrations in tumor tissue [7]. This test can be capitalized upon to inform physicians about treatments that match an individual patient with a specific drug that may benefit that patient, or identify patients that would be candidates for a basket trial. The MSK-IMPACT™ test is rapid, highly sensitive, and capable of analyzing 410 of the currently most important cancer genes [6]. An advantage of MSKCC’s efforts is the examination of molecular aberrations across different types of cancers relative to a therapeutic response. Limitations include the absence of a clear, quantifiable definition of exceptional responders, no examination of rapid progressors, and no investigation of lifestyle and other factors that may contribute to a therapeutic response.

***InVite Study (NCT01598597; 23andMe and Genentech)***. InVite was a retrospective study to gather self-reported, treatment-related outcomes and genetic data from up to 1,000 cancer patients who received Avastin® (bevacizumab) prior to 2013. The study collected patient questionnaires together with saliva and blood samples to analyze molecular and lifestyle factors relative to bevacizumab response. This study does not specifically define an atypical response, and it is confined exclusively to responses to bevacizumab. However, it appears to analyze lifestyle and other possible contributing factors. No published results could be located.

***Health of Women Study (NCT02334085)***. The Health of Women (HOW) Study, sponsored by the Dr. Susan Love Research Foundation, solicits surveys from women and men with all health statuses. Data collected include information about general health, personal and family health history, weight and exercise, environmental exposure, and **quality of life (QOL)** considerations including digestion, concentration, sex, and mental health. This study may also scrutinize long-term survivors of breast cancer to try to better understand their outcomes. Although not specifically aimed at studying atypical responses, long-term survivors of breast cancer may provide useful information relative to surviving the disease overall, and so attention should be paid to this possibility. A notable strength of this study is that data regarding a variety of lifestyle factors are being gathered.

## Summary of Current Studies of Atypical Responses

Limitations of the majority of studies described above are that they: 1) Generally focus on exceptional responders; 2) Usually do not state a definitive intent to share de-identified data on a secure platform (with a few exceptions); and 3) Potentially overemphasize the role of molecular aberrations while rarely investigating other important factors that may play a key part in an atypical response.

## Other Definitions

In their editorial, *Subbiah and Subbiah* (2015) have defined exceptional responders as patients who obtain “a complete response, showing no radiographic evidence of the cancer where previously widely metastatic cancer was noted” [8]. In another editorial, *Chau and Lorch* (2015) described exceptional responders as “a minority of patients with cancer who respond to drugs in an unexpected and often dramatic degree” [9]. These definitions are not quantifiable. In a short report, *another group* defined exceptionally responding breast cancer patients as those with a “highly durable ( $\geq 5$  years) or ongoing clinical response” [10], a definition that is related only to the chemotherapy drug Xeloda® (capecitabine).

## Summary of Definitions of Atypical Responses

Although multiple attempts have been made to define an atypical response, these definitions vary considerably and focus mainly on exceptional responders. Therefore, a more precise framework for exceptional responders, rapid progressors, and exceptional survivors is needed.

To complete this emerging picture of patients with atypical responses, we propose that the scientific community adopt the following framework:

- “Exceptional responder”: a patient who has an unusually favorable response to a specific treatment protocol compared to other patients on the same protocol
- “Rapid progressor”: a patient who has an unusually poor response, or no response, to a specific treatment protocol compared to other patients on the same protocol
- “Exceptional survivor”: an advanced stage patient who has far outlived his or her prognosis for reasons that are not fully understood irrespective of whether the patient exhibited an atypical response to specific therapy(ies). Such a patient may be considered to have an atypical response to the disease itself by considerably outliving his or her prognosis.

These proposed categories can be customized for the cancer type or subtype and the clinical

# ATYPICAL RESPONDER

## EXCEPTIONAL RESPONDER

A PATIENT WITH AN UNUSUALLY  
**FAVORABLE RESPONSE**  
TO TREATMENT COMPARED  
TO HIS OR HER COUNTERPARTS

## RAPID PROGRESSOR

A PATIENT WITH AN UNUSUALLY  
**POOR RESPONSE**  
TO TREATMENT COMPARED  
TO HIS OR HER COUNTERPARTS

## EXCEPTIONAL SURVIVOR

A PATIENT WHO HAS  
**FAR OUTLIVED**  
**HIS OR HER PROGNOSIS**  
IRRESPECTIVE OF THE NUMBER  
AND TYPES OF TREATMENT

context under investigation. Patients exhibiting an atypical response as per these three categories may have MBC or another life-limiting disease. Exceptional responses may be quantitative (i.e., tumor shrinkage, absence of new metastases) or related to duration of response. Mechanisms of rapid progression may include intrinsic or acquired resistance [11, 12]. Patients on conventional therapy as well as those in clinical trials should be included when studying atypical responses, because a community-based population will generally be more heterogeneous than a population enrolled in a trial.

## BENEFITS OF STUDYING ATYPICAL RESPONSES

Clear categorization of subgroups of atypical responders is needed to allow prospective selection of patients for hypothesis testing and to allow comparison of results across studies. Once the response of the patients being studied is more clearly stated, researchers can then determine the underlying reasons as to why the response occurs. These categories will also improve the potential for data sharing and accelerating research.

Studying patients exhibiting an atypical response may provide mechanistic insight, increase researchers' understanding of tumor and other biomarkers, and lead to novel combinatorial therapeutic strategies [9, 13-15]. Such studies are expected to provide experts with improved information, which in turn will enhance the domain of personalized medicine that is already part of best practices for MBC and many other illnesses. Because a single given therapy may not benefit a large number of patients, studying patients who exhibit an atypical response will likely provide a greater understanding of the phenomenon, identify novel biomarkers that can be used to prospectively identify patients who will [11-14, 16-18] and will not [13] benefit from a particular therapy, and lead

to novel combination therapies [13-15]. Personalized therapies are especially important in groups of patients, such as those with MBC, who have a short life expectancy (2-3 years) and a relatively inferior QOL.

Most studies of atypical responses (Table 2 and Table 3) employ various types of genetic analyses, and the resulting molecular testing is expected to lead to identification of predictive biomarkers and more targeted therapies [8]. In many cases, molecular aberrations (mutations, **insertions, deletions, copy number variations, rearrangements, multi-gene fusions, translocation, truncations**, etc.) can predict a change in a patient such as an alteration in a molecular pathway or an increase in cellular receptors, and hence a potential therapeutic outcome. It is encouraging that rapid genetic analyses are becoming increasingly available and less costly.

The study of atypical responses suggests that routine molecular testing can lead to the selection of patients for multiple types of trials. Examples include “basket trials” whereby researchers test the effect of a single drug on a specific mutation in a variety of cancer types, “**umbrella trials**,” which are designed to test the impact of different drugs on various mutations in a single type of cancer

***The investigation of atypical responses is anticipated to lead to improved selection of therapies for individual patients and avoidance of therapies that are unlikely to work.***

(one example is Lung-MAP, which is enrolling patients with advanced lung cancer; [NCT02154490](#)), and biomarker-driven trials [9]. Differently designed clinical trials may be required to optimize precision medicine [19]. One example is the I-SPY 2 trial in which breast cancer patients with Stage II, III, or “regional” stage IV, in which supraclavicular lymph nodes are the only sites of metastasis, are randomized to treatment based on response to therapy of patients with similar biomarker profiles who were previously enrolled in the same trial ([NCT01042379](#)).

In addition, the investigation of atypical responses is anticipated to lead to improved selection of therapies for individual patients and avoidance of therapies that are unlikely to work, resulting in improved patient outcomes and QOL (Figure 1, p. 36). The initial successes in implementing such a model are illustrated by the published studies of atypical responses outlined in Table 3, p. 34. Published and anticipated results from these studies have identified mechanisms of drug resistance, the **molecular pathways** involved, and multifaceted approaches. Notably, these published studies mainly involved **molecular testing** of the tumor tissue without addressing the roles that normal (non-tumor) tissue, lifestyle, co-morbidities, and other factors play in an atypical response. Furthermore, the results of genetic testing may vary significantly depending on the company

***In patients who underwent genetic testing by both FoundationOne and Guardant 360 labs, only 25% agreement was found regarding their recommended drugs.***

performing the analysis and the method used. As an example, a recent study comparing genetic alterations in patients who underwent testing using two platforms, FoundationOne and Guardant 360, developed by two companies revealed 22% concordance between the two platforms among 45 alterations in eight patients. Although 36 drugs were recommended for these patients, only nine (25%) were recommended for the same patients by both platforms [20] ([read more](#)).

## FACTORS CONTRIBUTING TO ATYPICAL RESPONSES

### **Molecular Aberrations in Tumors**

As described in Table 3 and seen within the aforementioned initiatives studying atypical responses, most researchers focus on identifying molecular aberrations but do not examine other possible contributing factors. Many institutions have developed molecular tumor boards that are collecting molecular information from patients studied at their facilities. Certainly, spectacular successes have occurred in which an identified molecular aberration and a corresponding **targeted therapy** substantially changed the outcome. An excellent example is the BCR-ABL mutation in chronic myelogenous leukemia (CML) and the drug Gleevec® (imatinib) that targets this mutant enzyme. Prior to 2001, less than one in three CML patients survived past 5 years. Now, most cases of CML can be controlled with Gleevec®, and researchers have developed new medications to counter resistance to Gleevec® when it arises. A 2011 study concluded that CML patients whose disease is in remission after 2 years of Gleevec® treatment have the same life expectancy as those who never had this disease [21]. As a result of targeted therapy with Gleevec®, a substantial number of CML patients have been transformed into “exceptional survivors” who are able to manage their disease as a chronic instead of a terminal illness. Gleevec®’s stunning patient outcomes, coupled with successes in other areas, have inspired a multitude of additional efforts to identify and target molecular-based therapies for other cancers and serious diseases.

Unfortunately, not all attempts at therapeutically targeting genetic aberrations have been successful. Although molecular testing of tumors is important, it does not represent the full breadth of reasons governing atypical responses across multiple cancer types. In a presentation at the 2015 San Antonio Breast Cancer Symposium, Gordon B. Mills, PhD, at the University of Texas MD Anderson Cancer Center referred to the “*unexpected high rate of failure of targeted therapeutics* [22].” He indicated that “*For most of our patients with a biomarker, only a sub-population of patients benefit, and that’s usually short-term.*” He contended that the reasons for this outcome include genetics, the therapy selected, and tumor adaptive resistance. Specifically regarding tumor adaptive resistance, Dr. Mills stated that, “*Tumor cells adapt to the targeted therapeutic in a way that allows them to bypass that stress. And that adaptation is almost always mediated at an RNA or protein level rather than a genomic level, and cannot be ascertained by solely studying DNA.*”

Two studies illustrating the failures and prospective dangers of targeted therapies are provided below.

In the first study, results that were published in 2014 from the PALOMA-1 clinical trial showed that MBC patients with mutations that could be targeted fared no better than patients without them. PALOMA-1 had been split into two parts. The first part included 66 patients with ER+, HER2– advanced breast cancer. The second part consisted of 99 patients with ER+, HER2– disease and specific biomarkers, including cyclin D1 amplification, p16 loss, or both. Although preclinical data had suggested that ER+ patients with cyclin D1 amplification and p16 loss may be predicted to respond, this was not observed in the clinical trial [23].

In the second study, researchers found that at least in some cases, targeting single genetic mutations through drugs can occasionally backfire. In a study that targeted the phosphatidylinositol **3-kinase** (PI3K) mutation, **monotherapy** treatment aimed at PI3K inhibition caused **mitochondria** to migrate to the peripheral **cytoskeleton** of the tumor cells, whereas the mitochondria of untreated cells were seen clustered around the cell nucleus [24]. The net result was that PI3K inhibition diverted the mitochondria to specialized regions of the cell membrane that are implicated in cell motility, and the cells could move spontaneously, thus permitting invasion.

Molecular profiling of a patient’s tumor often allows identification of the biological mechanism of a response to therapy, including an exceptionally favorable or poor response [11, 16-18, 25]. However, the contribution of molecular aberrations must be carefully considered, because focusing on molecular aberrations to the exclusion of other potentially contributing factors can, at least in some instances, prove problematic. In addition, non-genetic attributes, including those occurring at the RNA or protein level as described by Dr. Mills, also influence therapeutic responses. Although genomic factors are often clearly important, a genomic explanation for an atypical response is not always identified [26]. Furthermore, factors not directly involving the tumor likely also play a role in therapeutic responses, as described below.

### ***Moving Beyond Analysis of Molecular Aberrations in Tumors***

The studies below that analyze factors other than genetic mutations provide sufficiently intriguing preliminary results that warrant further study in both normally and atypically responding patients, a necessary step toward adopting these practices into the standard of care.

**Genetic anomalies in normal, non-tumor tissue can impact a patient's response to a given therapy.**

### **Impact of Genetic Polymorphisms in Normal Tissue on Pharmacokinetics and Side Effects**

Genetic anomalies in normal, non-tumor tissue may affect the pharmacokinetics in an individual patient, contribute to responses to therapy, and may play a role in an atypical response. For example, **cytochrome** P450 liver enzymes

**metabolize** drugs, and one of these, CYP2D6, is involved in the metabolism of approximately 25% of all prescribed drugs [27]. CYP2D6 may metabolize drugs to inactivate molecules, or metabolize **pro-drugs** into active metabolites. Approximately 75% of people, depending on ethnicity, are “normal metabolizers” and harbor two **wild-type** copies of *CYP2D6*. However, a small percentage of people are “ultra-rapid” or “extensive” metabolizers. Due to *CYP2D6* gene duplication, increased numbers of enzyme molecules are produced, resulting in increased drug metabolism. In contrast, some people are “poor metabolizers”. Due to allelic variants of *CYP2D6*, these individuals produce enzyme molecules with lower than normal CYP2D6 activity.

CYP2D6 is important for breast cancer patients because this enzyme is needed to convert Nolvadex® (tamoxifen) to endoxifen, the active form of the drug. Thus, patients who are ultra-rapid metabolizers are expected to convert high levels of Nolvadex® to endoxifen, and those who are poor metabolizers do not obtain therapeutic levels of the active metabolite and therefore may not experience the expected therapeutic response. Hence, CYP2D6 **phenotype**-adjusted dosing may be required [28, 29]. **Genotype**/phenotype analyses for CYP2D6 are **currently available** (e.g., Genelex, Seattle, WA).

Other cytochrome P450 genes expressed in the liver and small intestine also play a role in drug metabolism. Often drugs metabolized by the same cytochrome P450 can impede one another, and thus, drug interactions need to be carefully monitored to ensure patients receive the intended therapeutic dose [30]. Treatment with a prior CYP inhibitor is sometimes an exclusion criterion in clinical trial design. Multiple clinical trials are examining the contribution of various CYP genotypes to response to therapy. Some natural products consumed as CIM inhibit or activate different cytochrome P450 enzymes [31]. Although tests are available to determine the cytochrome P450 genotype and predicted phenotype, determining the pharmacokinetics profile of an individual patient and predicting a response to therapy can be extremely complex and is not yet incorporated into the standard of care.

Another example in which a genetic mutation in normal tissue affects the response to therapy is dihydropyrimidine dehydrogenase (DPD) deficiency. About 5% of individuals are deficient in this enzyme due to a mutation in its gene, leading to insufficient breakdown of drugs such as Xeloda® (capecitabine) and subsequent severe toxicity [32].

Genetic **polymorphisms** such as SNPs can also predict the development of side effects to therapy. Two SNPs have recently been shown to predict taxane-induced peripheral **neuropathy**. Patients of African descent have a higher risk for this neuropathy [33], and a second SNP is associated with Avastin® (bevacizumab)-induced hypertension [34].

More studies are needed to precisely predict a response to therapy by leveraging **pharmacogenomics**. Tissue analysis of genetic explanations for an atypical response should involve investigation of anomalies in both tumor tissue and non-tumor samples.

### **The Role of the Host Environment**

Response to therapy is impacted not only by the biology of the tumor, but also by the biology of the environment in which the tumor is located (“**microenvironment**”). Tumor cells interact with surroundings that include **vasculature**, immune cells, **extracellular matrix**, **stroma**, hormones, various secreted growth factors, **cytokines**, and **chemokines** [35–37]. These factors are dynamic and are likely to contribute to tumor behavior and response or resistance to therapy [37, 38]. Indeed, therapies such as Nexavar® (sorafenib), Sutent® (sunitinib), Gleevec® (imatinib), and Avastin® (bevacizumab) are aimed in part at modulating these tumor microenvironment factors [39].

***Response to therapy is impacted not only by the biology of the tumor, but also by the biology of the environment in which the tumor is located (“microenvironment”).***

The details of how the tumor microenvironment may specifically mediate an atypical response are not entirely clear, although efforts are currently underway to better understand how tumor surroundings affect progression of different cancer subtypes. In 2015, a research team found that the progression of different types of breast cancer in mice is influenced by the tissue—the tumor microenvironment—in which the tumor is embedded. In this study, matrix metalloproteinase 9 (**MMP9**) was deleted in two mouse models [38]. The absence of the MMP9 protein delayed tumor

onset only in one mouse model (triple-negative/basal-like C3(1)–Simian virus 40 large T antigen), whereas it had no effect in a luminal mouse mammary tumor virus–Neu model. The reason for this inconsistency appeared to be mediated by insulin-like growth factor binding protein (IGFBP)-1. If IGFBP-1 was absent, MMP9 had no effect, but if IGFBP-1 was present, then MMP9 became active. This suggests that IGFBP-1 interacts with MMP9 to promote tumor formation. Thus, trials of MMP inhibitors may need to be focused on patients whose tumor microenvironment contains IGFBPs [38] ([read more](#)). In addition, a recent review described

***Co-morbidities and the drugs that patients take for them may impact atypical responses and survival in cancer patients. Additionally, some co-morbidities preclude MBC patients from taking the very drugs that may be of most benefit to them.***

that the tumor microenvironment can mediate resistance or sensitivity to therapy, and that this effect on efficacy can be intrinsic or acquired [40].

## Co-morbidities

Co-morbidities and the drugs that patients take for them may impact atypical responses and survival in cancer patients. Cardiovascular co-morbidities reduce survival time in patients with ovarian cancer [41]. Other studies have shown variable impacts of cardiovascular [42], autoimmune [43], and diabetic [44] co-morbidities on patient outcomes. Certain diseases or conditions may disqualify patients from taking specific cancer-related medications, as exemplified by patients with heart disease who may be precluded from taking anthracycline drugs. Furthermore, development of treatment-related co-morbidities such as cardiovascular problems induced by anthracyclines and Herceptin® (trastuzumab) may preclude patients from taking the very drugs that may be the most effective for treating their disease [45]. A review of more than 2,500 published articles relating co-morbidity and patients with colon cancer, breast cancer, and lung cancer concluded that patients with a co-morbidity had worse survival than those without a co-morbidity. With 5-year mortality **hazard ratio** is as high as 5.8, some co-morbidities may be associated with rapid cancer progression [46]. These complex situations warrant further studies relative to atypical responses.

*Investigation of whether lifestyle factors can specifically impact the efficacy of a particular cancer treatment has received little attention.*

## Lifestyle Factors

Lifestyle factors include but are not limited to diet, physical activity, body mass index, smoking, alcohol consumption, and social factors such as depression, anxiety, and support. These attributes may play a role in a patient's response to therapy, QOL, and overall survival. Unfortunately, investigation of whether lifestyle factors can specifically impact the efficacy of a particular cancer treatment has received little attention [47, 48]. One example is a study indicating that cancer patients who drank one glass of grapefruit juice per day achieved the same benefits from the mTOR inhibitor Rapamune® (sirolimus) at a dose of 25 mg as they would have obtained with a 90-mg dose of the drug [49]. The researchers noted that grapefruit juice can inhibit enzymes in the intestine that break down Rapamune® and several other drugs. The effects were observed within a few hours of grapefruit juice ingestion and gradually subsided over a few days.

Physical activity and diet can also considerably enhance survival after a breast cancer diagnosis [50]. A **cohort study** of self-reported dietary habits in breast cancer survivors suggested that a combination of a healthy diet (five servings per day of fruits and vegetables) and physical activity (equivalent to walking 30 minutes 6 days per week) is associated with a 50% reduction in mortality over a 7-year follow-up period [51]. Exercise following a cancer diagnosis is associated with reductions

in cancer recurrence and mortality [50]. Researchers reported a study in mice that showed that exercise slows tumor growth [52], but similar to the development and testing of a new cancer drug, rigorous scientific testing in humans is required to test this hypothesis. As a first step, MSKCC recently launched a two-arm randomized, controlled trial to evaluate the safety and tolerability of exercise in women with advanced breast cancer ([NCT01725633](#)). Patients with advanced breast cancer will be randomly assigned to standard of care plus exercise training, or to standard of care plus progressive stretching. This study may potentially be a first step toward the ultimate goal, which is to test whether exercise inhibits tumor growth in women with MBC and perhaps other malignancies. If exercise is safe and tolerable in these patients, MSKCC plans to design the next trial to assess whether exercise affects clinical activity in women with advanced breast cancer ([read more](#)).

Whether a broader variety of lifestyle factors can precipitate or preclude an atypical response to a certain therapy is unknown. Therefore, additional analyses of atypical responses in relation to identified lifestyle factors must be performed. One such study is underway at Radboud University in the Netherlands, where researchers are investigating whether the **pharmacokinetics** of Afinitor® (everolimus) are different in elderly or obese patients compared to controls ([NCT01948960](#)).

Further investigation of the impact of co-morbidities and lifestyle factors on response to therapy, especially in patients with metastatic disease, will elucidate an explanation for the promising results above. Because such data can be obtained from cost-effective patient questionnaires, prospective clinical trials should be designed to capture this information. Such questionnaires should be standardized across trials and should collect information regarding all supplements consumed, CIM therapies practiced by the patient, co-morbidities and drugs specifically taken for them, and other elements. Published studies suggest that factors such as consumption of low-dose aspirin [53] and supplements such as Vitamin D [54] are associated with increased survival following a breast cancer diagnosis. Due to their potential, these factors should also be queried. Analysis of these data may result in hypothesis-generating models that could be tested in a systematic manner. An important aspect of data acquisition is standardization of how data are collected, de-identified, and stored on a secure platform that is accessible to authorized researchers.

## **Complementary/Integrative Medicine (CIM)**

Complementary and alternative practices are those that are used to promote wellness beyond standard medical care [55]. NIH's National Center for Complementary and Integrative Health (NCCIH) defines complementary, integrative, and alternative medicine as follows:

- Complementary Medicine: If a non-mainstream practice and/or product is used together with conventional medicine, it is considered complementary.
- Integrative Medicine/Integrative Health Care: Integrative health care is the practice of combining conventional and complementary approaches in a coordinated manner.

***Complementary and integrative health practices are widely used by breast cancer patients to manage symptoms, mitigate side effects, and improve quality of life.***

• Alternative Medicine: If a non-mainstream practice and/or product is used in place of conventional medicine, it is considered alternative.

Examples of CIM include consumption of natural products, dietary supplements, and substances that are not FDA approved, as well as mind-body holistic practices such as yoga, massage, meditation, acupuncture, and music therapy.

Complementary and integrative health practices are widely used by breast cancer patients to manage symptoms, mitigate side effects, and improve QOL, and several studies have concluded that these interventions play a role in enhanced well-being. Given that the majority of North American women with breast cancer report utilizing some form of integrative medicine [55], specific studies are warranted to determine which complementary and integrative therapies are best suited for specific patient populations.

For example, a randomized study analyzed the role of acupuncture in reducing pain and dysfunction in individuals with cancer of the head or neck who had undergone surgical dissection of the lymph nodes in their neck [56]. The study found that individuals in the group receiving acupuncture experienced significant reduction in pain and dysfunction compared with individuals receiving standard care.

Interestingly, the mistletoe extract Iscador® is widely used in the CIM setting among cancer patients, especially in Germany and elsewhere in Europe. Iscador formulations are labeled based on the tree from which the mistletoe was harvested (M for Malus (apple); P for Pinus (pine); Q for Quercus (oak); and U for Ulmus (elm)), with different therapeutic effects attributed to each. A study in patients with advanced pancreatic cancer reported both survival and symptom improvements [57]. Other studies with cancer patients suggest that chemotherapy regimens may be better tolerated with fewer negative effects when adding a prescribed mistletoe regimen, and that mistletoe can improve symptoms, QOL [58], and survival [59], although such studies may be hampered by publication bias and low internal quality. A Phase II study examined 23 extremely ill cancer patients who had short life expectancies due to peritoneal ascites accumulation that required repeated peritoneal punctures for drainage. Following drainage of fluid, Iscador M® 10 mg was injected **intraperitoneally**, and the interval until the next drainage was measured in comparison with a baseline time interval recorded in the absence of administration of Iscador M®. After the first administration of Iscador M®, the median time interval between drainage events increased from 7 days (baseline) to 12 days. No toxicity was observed [60]. A proposed reason for the positive effects of Iscador® in cancer patients includes beneficial effects on the immune system, and further study is warranted ([read more](#)). Interestingly, one of the 23 patients with ascites showed a clinically objective

improvement that lasted 12 months. This patient may be considered an exceptional survivor because malignant ascites accumulation is associated with a mean survival of about 5 months [61]. However, whether this patient's prolonged survival was due to Iscador®, reduction in ascites accumulation, and/or some other factor(s) is undetermined.

In another CIM study, the effectiveness of mindfulness-based stress reduction (MBSR) for cancer-related fatigue and related symptoms was evaluated in 35 cancer patients. The MBSR group underwent training in mindfulness meditation, yoga, and self-regulatory responses to stress. Compared to the control group, the MBSR group experienced significant improvements in fatigue, energy, depression, and sleep disturbance. Results were maintained or strengthened at the 1-month follow-up, and were also maintained 6 months after completing the training [62]. Other studies are ongoing. For example, researchers at the Osher Center for Integrative Medicine at the University of California at San Francisco are determining the optimal yoga intervention for supportive care for fatigue and other side effects from chemotherapy in patients with breast and other cancers in both the adjuvant and metastatic setting ([read more](#)).

Not only are various CIM interventions associated with QOL outcomes, but these therapies may also play a role in enhanced survival and favorable biological outcomes as described below.

- A randomized clinical trial of 227 women revealed that interventions to reduce psychological stress in patients with breast cancer resulted in a reduced risk of cancer recurrence and death [63].
- Conversely, a **meta-analysis** found that stress-related psychosocial factors were associated with worse survival in patients with cancer [64].
- A meta-analysis concluded that newly diagnosed breast cancer patients with the highest quintile of serum Vitamin D levels had approximately half the death rate of those in the lowest Vitamin D quintile [54].
- A **retrospective** case series of 239 Stage IV lung cancer patients who utilized Pan-Asian medicine and vitamins showed that long-term use of this regimen beyond completion of conventional cancer care decreased deaths by 69% compared to conventional cancer care alone [65].
- A study of MBC patients receiving highly customized CIM regimens showed survival times that were double those of patients receiving only standard medical care [66].

Although the specific biological reasons underlying these remarkable results are not fully understood, physiological evidence has been obtained that may offer at least a partial explanation. A randomized

trial of 88 women showed that **telomere** length is maintained in distressed patients with Stage I-III breast cancer undergoing mindfulness-based cancer recovery or supportive-expressive group therapy compared to controls [67]. A separate randomized trial of 71 women demonstrated that mindful awareness practices reduced stress and pro-inflammatory gene **expression** in young breast cancer patients who had completed cancer treatment [68].

The above studies show that CIM practices influence patient QOL, overall survival, and biological outcomes, and additional clinical trials are warranted to further assess these impacts. Although some funding has been available to investigate the effects of CIM on QOL, capital for the far more expensive **assays** (e.g., blood tests, etc.) needed to test the impact of CIM, supplements, and other non-regulated therapies on biological outcomes is scarce. For these promising **modalities** to become part of the standard of care, considerable funding for a stepwise process leading to large-scale studies in both normal and atypical responders is required.

CUSIOS (NCT02494037) is an observational registry that will compare overall survival outcomes of consecutively recruited advanced stage breast, colorectal, pancreatic, and ovarian cancer patients treated at one of several advanced integrative oncology specialist clinics in North America to those published in the current medical literature and **Surveillance, Epidemiology and End Results** (also known as **SEER**). Advanced integrative oncology (AIO) as well as conventional oncology treatment information will also be collected across the cohort, along with health-related QOL data from a subgroup of Canadian AIO-treated patients. The data obtained from CUSIOS and similar studies may further enhance overall cancer patient care.

## **Alternative Medicine**

Alternative medicine, defined by NCCIH as utilizing a non-mainstream practice and/or product in lieu of standard medical care, has not been well studied. Anecdotes abound regarding patients who far outlive their prognosis when following alternative therapies or whose condition has significantly improved while undergoing an unconventional treatment. Multiple hypotheses have been developed in an attempt to explain these outcomes, including the impact of reducing toxicity in the patient and modulating immune system function. Performing scientific studies to identify the reasons for successes attributed to alternative or unproven treatments is difficult because funding is scarce, many factors may work together to mediate the patient's response, and record-keeping regarding these patients has been minimal. Ethical issues arising from substituting an alternative therapy for conventional therapy are also problematic. As is the case with conventional medicine, clinicians currently cannot accurately predict which cancer patients will respond favorably to specific alternative protocols and which patients will not.

Some terminally ill patients experience an unexpectedly favorable outcome while practicing a variety of alternative therapies as reported by the author in the book, "Radical Remission: Surviving

Cancer Against All Odds” by Kelly A. Turner and the mainstream media Discover Magazine’s “The Body Can Beat Terminal Cancer – Sometimes” ([read more](#)). An important caveat is that due to a dearth of scientific studies, researchers and clinicians do not know how or if the therapy is related to the outcome, or if the same response would be reproducible in other patients. In addition, stories of patients who tried such therapies but did not survive are not readily available, and a recent study from the Yale School of Medicine determined that cancer patients who use only alternative therapies are twice as likely to die as those who undergo conventional treatment [69] ([read more](#)). Whether the alternative product and/or practice itself, the patient’s unique physiology, the placebo effect, or a combination of these factors working together contribute to an unexpectedly favorable (or unfavorable) outcome remains unknown. Further evidence-based studies are warranted.

Some therapies such as the use of certain diets, supplements, and protocols can be adopted in either an integrative or alternative setting. Testing in one setting may validate the use of a given therapy in another setting. One example is Iscador®, which has been used as a CIM therapy as described above, as well as in alternative settings ([read more](#)).

The study of alternative therapies requires careful consideration of whether the patient has exhausted the list of viable available standard therapies, the patient’s willingness to try an unproven therapy, ease of access to the new treatment, funding sources, verification that the new therapy is relatively or completely non-toxic, and valid methodology for measuring and replicating patients’ responses. As with other clinical studies, thoughtful study design must be combined with ethical issues relative to the life expectancy and QOL of the patient. A priori determination of what could be learned about the relationship between the alternative therapy in question and a potential clinical benefit must be carefully considered in conjunction with the patient’s wishes.

### ***Prognostic and Diagnostic Assay Use in Atypical Response Research***

One of the confounding aspects of cancer research is that seemingly similar tumors respond differently to a given therapy. Some tumors are more sensitive to certain drugs than others, and recent studies are beginning to elucidate the mechanisms of chemosensitivity and chemoresistance. For example, breast cancer tumors that express high levels of pyruvate M2 kinase are more sensitive to Ellence® (epirubicin) and Efudex®, Carac®, and Fluoroplex® (5-fluorouracil) than tumors that express low levels of the kinase [70]. A protein called RECK can be **downregulated** in breast cancer cells, and restoration of higher levels of RECK may increase the chemosensitivity of breast cancer cells [71]. The **microRNA** MiR-139-5p regulates drug resistance and the viability of breast cancer cells by regulating expression of its target, Notch 1 [72]. A newly identified gene called **MACROD2** confers resistance to Nolvadex® (tamoxifen) in breast cancer cells and estrogen-independent growth when **overexpressed**. Expression of **MACROD2** can change as breast cancer progresses [73].

Several biological determinants may predict chemosensitivity and chemoresistance. Results from the TAILORx trial recently showed that the 21-gene profile assay, OncotypeDX® (Genomic Health, Inc.), accurately predicts which patients with hormone receptor–positive, HER2–negative, axillary node–negative invasive stage I or II breast cancer can be treated solely with hormone therapy and avoid adjuvant chemotherapy, which would otherwise be recommended based on clinicopathological features alone [74]. Another example is MammaPrint® (Agendia), which uses a score derived from the relative expression of 70 genes [75]. Although these evidence-based decision support tools are useful in early-stage breast cancer patients, similar tools are yet to be developed for MBC.

Non-invasive technologies to detect circulating tumor DNA may be useful for detecting molecular aberrations [76, 77], some of which may confer resistance or sensitivity and suggest new therapeutic targets. Although promising, some of these tools remain preliminary. Key drawbacks are that tumors are **heterogeneous**, the complete tumor (and other tumors within the patient) is not assessed, the tumor’s microenvironment is excluded, and the biological and social/lifestyle determinants that may influence the response are not elucidated. Nevertheless, an atypical response may become more predictable with these assays, allowing optimal selection and avoidance of therapies.

An effort launched in the 1950s to predict an individual patient’s response to treatment by placing their tumor cells in a test tube and exposing them to various chemotherapy agents was not as successful as anticipated because, among other reasons, the tumor’s microenvironment was excluded [78]. This is important because the microenvironment is different **in vivo** compared to **in vitro**. In vitro conditions lack important factors such as macrophages and lymphocytes, which are immune system cells [79]. Recent innovations aim to overcome these obstacles by conducting real-time testing of **ex vivo** cancer cells and including microenvironment attributes. Predicting a clinical response to therapy with these techniques remains controversial [78], and robust studies are warranted.

***An atypical response may become more predictable with chemosensitivity/chemoresistance assays, allowing selection of optimal therapies and avoidance of therapies that are unlikely to work or that are needlessly toxic.***

The [Weisenthal Cancer Group](#) has established a chemosensitivity assay test called “Cytometric Profiling” in which live, whole cancer cells from an individual patient are exposed to a library of chemotherapeutic agents or combinations of agents to determine which drugs/drug combinations will work best for that tumor and which will not [80]. A study of 30 women with ovarian cancer that compared therapies based on chemosensitivity testing with therapies aimed at genetic aberrations revealed that chemosensitivity testing is a superior predictor of treatment

response compared to selection of therapies based on expression levels of a panel of relevant genes [80]. Similarly, **Nagourney Cancer Institute** utilizes a testing platform and process that they refer to as “Functional Profiling” in which tumor cells are kept in 3-D clusters (“microspheroids” that mimic the body’s environment) and are exposed to various drugs and combinations [81]. A study of lung cancer specimens obtained during surgery found that therapy based on functional profiling testing doubled the treatment response rate and more than doubled overall survival in patients receiving assay-directed therapy compared to historical population-directed therapy [81].

To improve patient outcomes, combined and repeated molecular and chemosensitivity testing may be needed because genetic and host attributes can change over time.

## EXCEPTIONAL SURVIVORS

Some patients who considerably outlived their prognosis may have done so as the result of an exceptional response to conventional, integrative, or alternative therapies. Yet some exceptional survivors may not have exhibited an unusually positive response to a specific therapy, and no obvious explanation can be identified. Patients who have fared exceptionally well have cited (among other reasons) good communication with their medical team, strong family support, and a proactive attitude as contributing factors to their unexpected longevity [82, 83]. Next steps in the study of exceptional survivors should ideally integrate data such as demographics, diagnosis, prognosis, treatment history, imaging data, laboratory data, lifestyle factors, practice of CIM and/or alternative medicine, co-morbidities, saliva testing (i.e., genetic analysis of normal tissue), chemosensitivity testing, number and location(s) of metastatic lesions, and sampling of primary and metastatic tumors. The Broad Institute’s MBC Project and the University of Wisconsin-Madison Exceptional Survivors study plan to identify and study exceptional survivors.

***Some exceptional survivors may not have exhibited an unusually positive response to a specific therapy, and no obvious explanation can be identified.***

Registry data should be analyzed to detect survival patterns and to generate a testable series of hypotheses. Constructing a centralized database of not only exceptional responders and rapid progressors, but also exceptional survivors, would help formulate and improve testable theories. Certainly, more rigorous studies of this interesting and vitally important population of long-lived terminally ill patients are warranted.

# CHALLENGES AND FUTURE DIRECTIONS

A number of discoveries and challenges remain regarding the study and interpretation of atypical responses. Learning from exceptional responders, rapid progressors, and exceptional survivors will require the use of standard terminology, qualitative guidelines, and metrics. It will also necessitate collaboration, funding, and the ability to analyze, annotate, store, and share results in a central data repository [8, 9]. Based on the evidence presented in this paper, a clear paradigm shift is needed within the scientific community to embrace and study not only genetic aberrations within tumors, but other factors including—but not limited to—inherited polymorphisms, the host and tumor environments, lifestyle, use of complementary/integrative/alternative medicine, chemosensitivity and chemoresistance, co-morbidities, and the interplay among them.

Financing the above endeavors remains a key consideration, although we anticipate that this investment may be offset by reduced treatment costs as the result of providing seriously ill patients with highly effective, precise, and personalized therapies.

# SUGGESTED ACTION ITEMS

FOR THE MBCA, OTHER ADVOCACY ORGANIZATIONS, AND RESEARCHERS

1

Develop unified categories of exceptional responders, rapid progressors, and exceptional survivors, including qualitative and quantitative criteria (Table 4, p. 35).

3

Encourage funding agencies to accelerate exploration of the underlying factors governing atypical responses including CIM, co-morbidities, and the entire patient, without limiting the study to tumor markers or genetics. These factors should also be investigated in normally responding patients.

4

Investigate why all three subtypes of atypical responders show extraordinary outcomes. Exceptional survivors may or may not be enrolled in a trial, and stakeholders will need to work with experts to develop methodologies to study these patients and the factors contributing to their survival.

2

Enhance clinical trial design to:

- study exceptional responders and rapid progressors relative to specific treatment outcomes;
- capture data about exceptional survivors who enroll in the study;
- obtain data about multiple aspects of a response to therapy;
- encourage collection of a common set of data elements, including health-related quality of life measures, across clinical trials;
- use standardized questionnaires to gather more information about CIM modalities practiced, supplements consumed, co-morbidities and drugs taken for them, etc., look for correlations, and perform retrospective and prospective analyses to test hypotheses about potentially important factors.

5

Standardize how data are captured and de-identified regardless of source to allow accessible mining by authorized researchers across platforms and systems. Leveraging a secure platform for access to data regarding exceptional responders, rapid progressors, and exceptional survivors will help detect survival patterns and formulate and improve testable hypotheses.

6

Establish an MBC patient registry. As discussed in this paper, several disparate studies are underway regarding atypical responses, with more likely to follow. To help facilitate research in a consolidated and coordinated manner, the MBC Alliance envisages creating a registry that would solicit information from MBC patients worldwide about their disease. The entered data will be de-identified and stored on a central platform that will be made available to sanctioned researchers for analysis about atypical response and other issues of importance to the MBC community.

# SUMMARY

Although some investigations have been launched in the US and Europe to study treatment-related responses in cancer patients, they have significant limitations. This paper provides a blueprint to increase researchers' knowledge regarding why some patients experience an atypical response. Due to a dearth of robust studies, we cannot currently predict which factors will be more important and which will be less so. The studies cited in this paper provide information about specific indicators that may prove to be important and warrant further examination (e.g., aspirin [53], Vitamin D [54]), although future research into atypical responses should not be limited solely to the factors described herein. Questionnaires designed to capture and store a wide variety of information such as diet, exercise, psychosocial factors, supplements, CIM, chemosensitivity testing, co-morbidities, etc. may also provide important evidence.

We propose that clinical trials be carefully re-designed to collect and centrally store **de-identified data** in a standardized manner, conduct a more thorough, multifaceted study of the whole patient, and consider ethnic, racial, lifestyle, and social differences [84, 85]. Similarly, physicians in clinical practice are encouraged to capture and store on a common platform de-identified multidimensional patient data, treatments, and outcomes irrespective of whether the patient exhibits an atypical response. Through obtaining, storing, and studying the patient information thus provided, researchers could readily scrutinize a wealth of information regarding exceptional responders, rapid progressors, exceptional survivors, as well as typically responding patients for comparative purposes. From there, hypotheses would be formulated based upon the results of prior studies as well as upon newly emerging observations. These ideas would then lead to rigorous testing, with patterns and trends materializing over time. The outcomes of these studies could ultimately prove practice-changing by transforming a formerly terminal disease into a chronic condition.

# Tables

**TABLE 1**  
**CATEGORIES AND TERMS RELATED TO ATYPICAL RESPONDERS**

STUDY OR INSTITUTE	QUALITATIVE DEFINITION	METRICS/QUANTITATIVE CRITERIA
<p><b>NCI Study: Molecular Profiling in Tissue Samples From Patients With Cancer Who Are Exceptional Responders to Treatment</b></p>	<p>“Exceptional responders” are patients who have a unique response to treatments that are not effective for most other patients.</p>	<ul style="list-style-type: none"> <li>• Complete response to treatment expected in &lt;10% of patients</li> <li>• Partial response to treatment &gt;6 months expected in &lt;10% of patients</li> <li>• Response at least 3 times the duration expected when therapy started</li> <li>• Does not capture rapid progressors</li> </ul>
<p><b>The Broad Institute’s MBC Project</b></p>	<p>Uses the terms “exceptional response”, “extraordinary response”, and “outliers” interchangeably [3].</p>	<p>For patients with estrogen receptor (ER)+/human epidermal growth factor receptor 2 (HER2) – disease or HER2+ MBC:</p> <ul style="list-style-type: none"> <li>• Duration with metastatic disease (overall survival), &gt;10 years, OR</li> <li>• Duration on any one therapy (progression-free survival; PFS), &gt;3 years</li> </ul> <p>For patients with triple negative MBC (TNBC):</p> <ul style="list-style-type: none"> <li>• Duration with metastatic disease (overall survival), &gt;5 years, OR</li> <li>• Duration on any one therapy (PFS), &gt;2 years</li> </ul> <p>OR, for either group:</p> <ul style="list-style-type: none"> <li>• Any complete response, or near complete, to any therapy (for any length of time)</li> <li>• Any other clinical scenario that the investigators believe constitutes an extraordinary response/outcome (The study does not define rapid progressors)</li> </ul>
<p><b>AURORA (Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer)</b></p>	<p>Defines “exceptional responders” as those “showing (nearly) complete response for a duration exceeding 1 year” and “rapid progressors” as “patients on first- or second-line treatment progressing within the first 3 months since its initiation” [5].</p>	<ul style="list-style-type: none"> <li>• Exceptional Responders: Complete response for a duration of ≥1 year</li> <li>• Rapid Progressors: Progressed within &lt;3 months since initiation of 1st or 2nd line of therapy</li> </ul>

**TABLE 1 CONTINUED ON NEXT PAGE**

TABLE 1 CONTINUED

**TABLE 1**  
CATEGORIES AND TERMS RELATED TO ATYPICAL RESPONDERS

STUDY OR INSTITUTE	QUALITATIVE DEFINITION	METRICS/QUANTITATIVE CRITERIA
<b>University of Wisconsin-Madison's Exceptional Survivors Study</b>	Refers to "exceptional survivors" as MBC patients who have lived an unusually long time since their first breast cancer diagnosis (early stage or de novo) to the current date. The underlying hypothesis relating to this definition is that early stage patients have had metastatic disease all along, but their tumor cells have remained dormant or extremely slow growing, and metastatic disease has been clinically undetectable. In contrast, the MBCA defines exceptional survival as the time from the advanced stage diagnosis to the current date.	<p><b>For MBC patients with ER+ disease:</b></p> <ul style="list-style-type: none"> <li>• Duration since early stage or de novo breast cancer diagnosis (overall survival) 10+ years</li> </ul> <p><b>For MBC patients with ER- disease (the study will distinguish between patients with HER2+ vs. TNBC after enrollment):</b></p> <ul style="list-style-type: none"> <li>• Duration since early stage or de novo breast cancer diagnosis (overall survival) 5+ years</li> </ul>
<b>Editorial: Subbiah and Subbiah (2015)</b>	An "exceptional responder" is a patient who obtains "a complete response, showing no radiographic evidence of the cancer where previously widely metastatic cancer was noted" [8].	<ul style="list-style-type: none"> <li>• Not quantifiable</li> <li>• Does not capture rapid progressors</li> </ul>
<b>Editorial: Chau and Lorch (2015)</b>	Described "exceptional responders" as "a minority of patients with cancer who respond to drugs in an unexpected and often dramatic degree" [9].	<ul style="list-style-type: none"> <li>• Not quantifiable</li> <li>• Does not capture rapid progressors</li> </ul>
<b>Short report: Levin et al. (2015)</b>	"Exceptional responders" are those with a "highly durable ( $\geq 5$ years) or ongoing clinical response" [10].	<ul style="list-style-type: none"> <li>• Highly durable (<math>\geq 5</math> years) or ongoing clinical response</li> <li>• Only pertains to the chemotherapy under study Xeloda® (capecitabine)</li> <li>• Patients may be heavily pretreated</li> <li>• Does not capture rapid progressors</li> </ul>

**TABLE 2**  
**CURRENT INITIATIVES STUDYING ATYPICAL RESPONSES**

STUDY OR INSTITUTE	TYPE OF SAMPLE COLLECTED FOR ANALYSIS	TYPE OF ANALYSIS	ANALYSIS OUTPUT
<b>NCI Study: Molecular Profiling in Tissue Samples From Patients With Cancer Who Are Exceptional Responders to Treatments</b>	Tumor tissue prior to treatment; normal tissue	Whole exome sequencing. Targeted next-generation deep sequencing will be performed if sufficient quantities of nucleic acids are available. Other analyses include mRNA sequencing; microRNA sequencing; whole genome sequencing; promoter methylation analysis; SNP genotyping	“Molecular features” of the exceptional response
<b>The Broad Institute’s MBC Project</b>	Tumor biopsy, saliva, and potentially blood samples	Genomic analysis	Shared data containing de-identified genomic and medical information
<b>AURORA (Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer)</b>	Primary tumor; metastatic lesions; blood; serum; plasma	Whole exome sequencing	“Biomarkers of response and/or resistance to systemic therapy”
<b>University of Wisconsin-Madison’s Exceptional Survivors Study</b>	Blood or saliva, plus tumor samples in a subset of patients. Notably, questionnaires regarding lifestyle and other factors will be answered by all patients.	Whole-exome sequencing; questionnaires	In a subset of patients, the team will look for genetic mutations and/or changes in gene expression that are common among “exceptional survivors” and not found in established or published samples from “normal survivors”. The team will analyze germline and tumor genomics, as well as tumor-infiltrating immune cells. Responses to patient questionnaires will be assessed.
<b>Memorial Sloan Kettering Cancer Center</b>	Tumor DNA	MSK-IMPACT™ (genomic sequencing of ~410 cancer genes)	Clinically actionable molecular aberrations; candidates for basket trials

**TABLE 3**  
**SUMMARY OF PUBLISHED STUDIES EXAMINING ATYPICAL RESPONSES**

CANCER TYPE	DRUG(S) PROVIDING AN ATYPICAL RESPONSE (TARGET)	MOLECULAR ABERRATION(S) IDENTIFIED	COMMENTS	REFERENCE(S)
<b>ER-positive, HER2-negative MBC</b>	Xeloda® (capecitabine) (DNA synthesis)	Various DNA repair and/or chromatin remodeling genes	Study included six superior exceptional responders; mechanism of the atypical response suggested: identification of classes of mutated genes	[10]
<b>Ewing's sarcoma</b>	IGFR1 inhibitor	Mutations in PTPRD and GRB10 (germline)	KRAS mutation developed in a resistant tumor; individualized combination therapy may be useful	[86, 87]
<b>Metastatic bladder cancer</b>	Afinitor® (everolimus) (mTOR)	TSC1 loss-of-function mutation	~8% of bladder cancers have this mutation [9]; TSC1 mutation may be a biomarker for everolimus sensitivity: 3/4 of patients with the mutation responded to everolimus, and 8/9 patients whose tumor progressed on everolimus did not have the mutation	[17]
<b>Thyroid cancer</b>	Afinitor® (everolimus)	TSC2 mutation, secondary mutation in MTOR	Identification of the mechanism of acquired resistance	[11]
<b>Small-cell cancer of the ureter</b>	AZD7762 (CHK1 inhibitor) + Camptosar® (irinotecan) (Topoisomerase I inhibitor)	RAD50	This drug combination may be useful in the context of RAD50 mutation.	[15]
<b>Head and neck squamous cell carcinoma</b>	Tarceva® (erlotinib) (EGFR)	Activating MAPK1 mutation	Paradoxical activating mutation predicted resistance to erlotinib; precision oncology may predict indication for erlotinib use	[88]

**TABLE 4**  
**FRAMEWORK FOR THREE CATEGORIES OF ATYPICAL RESPONDERS**

CATEGORY	RESPONSE TO THERAPY	DURATION OF SURVIVAL	METRICS/QUANTITATIVE CRITERIA
<b>Exceptional responder</b>	A patient who has responded unusually favorably (dramatic tumor shrinkage, development of no evidence of disease, or an unusually long progression-free or overall survival) to a particular therapy compared with others on the same therapy who have the same cancer stage and subtype of disease (and possibly a similar number of prior lines of therapy).	The patient may or may not have survived well past his or her prognosis.	A patient within the top [X]* percentile of the mean therapeutic response to a specific treatment protocol as measured by endpoints such as progression free survival, overall survival, tumor shrinkage, etc.
<b>Rapid progressor</b>	A patient who has responded unusually poorly (dramatic tumor growth or an unusually short progression-free or overall survival) to a particular therapy compared with others on the same therapy who have the same cancer stage and subtype of disease (and possibly a similar number of prior lines of therapy).	The patient may or may not have survived well past his or her prognosis.	A patient within the bottom [X]* percentile of the mean therapeutic response to a specific treatment protocol as measured by endpoints such as progression free survival, overall survival, tumor shrinkage, etc.
<b>Exceptional survivor</b>	The patient may or may not have exhibited an atypical response to a specific therapeutic regimen.	An advanced stage patient who has far outlived the prognosis for his or her cancer subtype.	An advanced stage patient who has outlived the average life expectancy for his or her cancer subtype by a factor of [X]* or more, regardless of the type or quantity of therapies received.

Quantitative metrics should be developed by the research community and stated in each published study. Metrics may include standard deviation, percentile, etc. Quantitative criteria may need to be considered in terms of the clinical context including cancer type or subtype, patient population, therapeutic regimen, and number of prior lines of therapy.

\* The most appropriate percentile and factor of survival to apply to a quantitative definition of an atypical response are not known. This lack of a clear definition is one of the problems with the current state of studying atypical responses. Quantitative criteria should be applicable across multiple cancer types, patient populations, and therapeutic regimens.

# FIGURE 1

## OVERVIEW OF ATYPICAL RESPONSE ANALYSES AND RELATED CLINICAL OUTCOMES

IDENTIFY ATYPICAL RESPONSE. THESE DE-IDENTIFIED DATA CAN BE STORED IN A CENTRAL DATABASE.

DETERMINE THE REASON FOR THE ATYPICAL RESPONSE

BY PERFORMING MOLECULAR TESTING OF THE TUMOR OR NORMAL TISSUE

BY DETERMINING AN ASSOCIATION BETWEEN A LIFESTYLE OR OTHER FACTOR AND THE RESPONSE

BY CONDUCTING RIGOROUS SCIENTIFIC AND CLINICAL STUDIES TO COLLECT EVIDENCE FOR A GENOTYPE/ PHENOTYPE/OUTCOME LINK

BY CONDUCTING RIGOROUS SCIENTIFIC AND CLINICAL STUDIES TO COLLECT EVIDENCE FOR A LINK BETWEEN LIFESTYLE OR OTHER FACTOR AND CLINICAL OUTCOME

ESTABLISH A NEW TEST, ASSAY, SURVEY, ETC. OR UTILIZE ONE THAT IS ALREADY AVAILABLE THAT PREDICTS THE REASON FOR THE ATYPICAL RESPONSE. CONSIDER OTHER POTENTIAL CONFOUNDING FACTORS AND UPDATE THE DATABASE ACCORDINGLY.

PROVIDE MULTI-FACTORIAL CRITERIA FOR PHYSICIANS TO A *PRIORI* SELECT THE BEST THERAPEUTIC REGIMEN FOR AN INDIVIDUAL PATIENT AND AVOID THOSE LIKELY TO RESULT IN A POOR OUTCOME.

IMPROVED CLINICAL OUTCOMES AND QUALITY OF LIFE

# Glossary

**Assay:** a measurement performed on a biological sample

**Basket trial:** a clinical trial in which researchers test the effect of a single drug on a specific mutation in a variety of cancer types.

**Biomarker:** a quantifiable biological molecule such as a protein, DNA, RNA, or biological compound that is measured in a biological sample (blood, DNA, a tumor, etc.) and that acts as an indicator for a specific biological state or condition. In the context of personalized cancer therapy, biomarkers are used to determine patient prognosis and predict which patients will have the highest likelihood of responding to selected therapies or have adverse side effects with particular therapies. Biomarker tests are currently being used to predict the likelihood of benefit, which integrates both sensitivity and resistance to targeted therapies [86].

**Chemokines:** cytokines that attract cells to a site of infection or inflammation

**Chemoresistance:** low or no response to a drug that is generally considered effective in many tumors

**Chemosensitivity:** exquisitely high response to a drug in which tumor cells die more quickly or at a much lower drug concentration compared to many other tumors

**Cohort study:** a study of a group of patients with certain similarities, such as a particular disease or treatment at a particular hospital or institute who are followed up over a period of time. In contrast to many clinical trials, cohort studies are observational, meaning that patients in a cohort receive standard of care as determined by their physicians rather than novel treatments such as in a clinical trial; researchers observe a cohort and intervene in a clinical trial. In addition, unlike many clinical trials, cohort studies can be carried out over many years or decades and can thus be used to obtain much longer-term data than typical clinical trials. Cohort studies can be retrospective, meaning that data for a group of patients are examined after the patients have been treated, or prospective, meaning that researchers will enroll patients in their cohort with selected characteristics (for example, all patients with a certain disease treated at a certain institute who underwent a particular imaging technique or received a certain treatment). Carefully defined cohort studies can establish a cause between two events.

**Co-morbidity:** other diseases or conditions the patient may have

**Complete response (CR):** disappearance of all indications of a disease such as cancer following a treatment

**Cytochrome:** proteins that carry iron and that function in metabolism

**Cytokines:** a group of small molecules released by immune cells that affect the nearby cells

**Cytoskeleton:** the scaffold of proteins located inside cells that determines the shape of the cells and that helps cells move

**De-identified data**: information about a patient's medical condition that is anonymous due to removal of personal information such as name, social security number, date of birth, etc. De-identification allows data from an individual patient to be shared among researchers for analysis without compromising the patient's privacy.

**De novo MBC**: breast cancer that is diagnosed as metastatic at the first cancer diagnosis. These patients were not diagnosed with early stage disease, but were considered metastatic at the initial cancer diagnosis.

**Downregulated**: decreased

**Extracellular matrix**: proteins located outside of cells that provide physical support to cells

**Ex vivo**: tissue or cells removed from a person or animal

**Genotype**: the genes carried by an individual that determine the characteristics of proteins, cells, organs, or the entire individual

**Germline-derived polymorphism**: DNA changes that are inheritable (found in egg and sperm cells and thus passed down to offspring). The variants may or may not influence cancer etiology, progression, or metastasis, and are more likely to influence a response to therapy.

**Hazard ratio**: compares the likelihood of an event (such as death) occurring in one population compared to another population (for example, a treated group and a placebo group) over time and is generally shown as a number close to 1.0. A hazard ratio higher than 1.0 means an increased likelihood of an event occurring. For example, a hazard ratio of 2.0 means that the event is twice as likely to occur in one population compared to another population. A hazard ratio less than 1.0 means the event is less likely to occur in one population compared to the other, and a hazard ratio of 1.0 means that the event is equally likely to occur in the two populations.

**Heterogeneous**: different or mixed. A heterogeneous population of patients has many different characteristics. A heterogeneous tumor has cells with different properties.

**In vitro**: in a test tube or culture plate

**In vivo**: in a person's or animal's body

**Intraperitoneal**: within or through the membrane that lines the walls of the abdominal cavity

**Kinase**: A kinase is a type of protein in the body that helps control cell division. Certain drugs such as Ibrance™ (palbociclib), Kisqali™ (ribociclib), and Verzenio™ (abemaciclib) inhibit the cyclin-dependent kinase 4 and 6 (CDK 4/6).

**Meta-analysis**: a systematic process in which similar data collected from multiple studies are re-analyzed to increase statistical power

**Metabolize:** to break down. For example, enzymes in the liver break down or metabolize drugs and other foreign substances so that they can be excreted from the body. Metabolism can activate an inactive drug or inactivate an active drug.

**Microenvironment:** the environment in which a tumor is located. The microenvironment consists of a variety of molecules, cells, and blood vessels, all of which may affect the survival of tumor cells and the response to therapy.

**microRNA:** RNA that is transcribed (i.e., the RNA code is used to make a certain protein) from DNA in the cell's nucleus but that does not encode a protein. microRNAs bind to other RNA molecules called messenger RNA or mRNA that encode proteins and regulate the translation of mRNA into protein.

**Mitochondria:** the part of the cell responsible for energy production

**Modality:** regimen; a series of practices

**Molecular aberrations:** abnormal variations present in DNA that include:

Amplifications and duplications: more copies of a gene or multi-gene region than are normally present

Copy number variation: a different number of copies of a gene

Deletion: removal of DNA from a sequence

Insertion: addition of extra DNA to a sequence

Multi-gene fusion: joining of two genes or parts of genes that are not normally found together

Mutation: a change in the DNA sequence

Rearrangement: a section of DNA that is moved to another location

Translocation: swapping the location of genes, often between two different chromosomes

Truncation: shortening of a gene

**Molecular pathways:** the stepwise process by which different proteins in one or more cells send a message that changes the status or function of another cell

**Molecular testing:** analysis of DNA, RNA, or protein from a biological sample such as blood or a tumor

**Monotherapy:** treatment with a single drug

**Neuropathy:** when one or more parts of the nervous system are not working properly. Neuropathy generally involves "peripheral" nerves, which are those outside the brain and spinal cord. Symptoms of neuropathy include pain, numbness, and weakness.

**Overexpression**: levels, often of a protein or mRNA, that are higher than normal

**Partial response (PR)**: in cancer, a reduction in a tumor following a treatment, but not a complete disappearance

**Pharmacogenomics**: the study of how genes affect a person's response to drugs

**Pharmacokinetics**: the body's processing of drugs

**Phenotype**: the characteristics of a protein, cell, organ, or organism as determined by its genes

**Polymorphisms**: different forms of a gene, which are called "variant alleles".

**Precision medicine /personalized medicine**: using an individual's particular genes and other characteristics to select treatments for a disease

**Pro-drug**: A pro-drug is an inactive drug that you take that the body "activates", usually by the liver. Tamoxifen is one example of a pro-drug that the liver converts to its active form.

**Promoter methylation**: the promoter is a section of a gene that regulates expression of the gene (i.e., if the gene is switched "on" or "off"). Methylation is addition of a chemical group called a methyl group. Addition or removal of a methyl group from a promoter is a common way for cells to temporarily turn genes on or off.

**Prospective**: when used to describe a trial or data, prospective means that the information will be collected in the future according to a specified plan.

**Quality of life (QOL)**: a person's well-being and satisfaction with life that includes the person's ability or desire to participate in social, physical, employment, education, religious, etc. activities

**Retrospective**: when used to describe a trial or data, retrospective means that the information already exists, such as in electronic medical records or banked tumor samples, and will be collected and analyzed as is

**Surveillance, Epidemiology, and End Results (SEER)**: A program of the National Cancer Institute that acts as a repository for cancer statistics concerning incidence and survival in the US

**Single nucleotide polymorphism (SNP)**: a small, single change in the DNA sequence

**Somatic mutations**: changes in DNA that originate in the tumor and are thus not inheritable (not passed down to offspring because they are not present in eggs and sperm). Such changes may impact cancer progression and acquired resistance to therapy.

**Stroma**: connective tissue

**Targeted deep sequencing:** “deep” sequencing refers to sequencing the same region of DNA multiple times (hundreds of times). This is required if the tissue sample contains a mixture of cell types as in a biopsy sample or if a mutation is rare. “Targeted” refers to sequencing a selected DNA region of interest.

**Targeted therapy:** in cancer, a treatment that is aimed at a specific characteristic of a tumor

**Telomere:** the tip of a chromosome that functions to prevent deterioration of the chromosome

**Umbrella trials:** clinical trials that test the impact of different drugs on various mutations in a single type of cancer

**Vasculature:** the arrangement or distribution of blood vessels in an area of the body

**Whole exome sequencing:** sequencing of all regions of DNA that encode proteins

**Whole genome sequencing:** sequencing all DNA of an organism or tissue sample

**Wild type:** Wild type refers to the normal, natural form of your genes. Genes can become mutated during development of offspring and over a life time.

**Xenograft:** transplant of tissue from one type of organism (say a human) into another type of organism (say a mouse) for research or transplantation purposes.

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