PRECISION MEDICINE

original reports

Safety, Feasibility, and Merits of Longitudinal Molecular Testing of Multiple Metastatic Sites to Inform mTNBC Patient Treatment in the Intensive Trial of Omics in Cancer

Kimberly A. Burton, PhD[1,2,3,4]; Elisabeth Mahen, BS[2,5,6]; Eric Quentin Konnick, MD, MS[7]; Sibel Blau, MD[2,3]; Michael O. Dorschner, PhD[8,9,10]; Arturo B. Ramirez, PhD[11]; Stephen C. Schmechel, MD[8]; Chaozhong Song, PhD[2,5,6]; Rahul Parulkar, PhD[12]; Stephanie Parker, BA[3,4]; Francis Mark Senecal, MD[3,4]; Colin C. Pritchard, MD, PhD[7]; Brigham H. Mecham, PhD[13]; Christopher Szeto, PhD[12]; Patricia Spilman, MA[14]; Jingchun Zhu, PhD[15]; Vijayakrishna K. Gadi, MD, PhD[16,17]; Roy Ronen, PhD[18]; Jackie Stilwell, PhD[11]; Eric Kaldjian, MD[11]; Janusz Dutkowski, PhD[18]; Stephen Charles Benz, PhD[12]; Shahrooz Rabizadeh, PhD[14]; Patrick Soon-Shiong, MD[12,14]; and C. Anthony Blau, MD[2,5,6,19]

abstract

PURPOSE Patients with metastatic triple-negative breast cancer (mTNBC) have poor outcomes. The Intensive Trial of Omics in Cancer (ITOMIC) sought to determine the feasibility and potential efficacy of informing treatment decisions through multiple biopsies of mTNBC deposits longitudinally over time, accompanied by analysis using a distributed network of experts.

METHODS Thirty-one subjects were enrolled and 432 postenrollment biopsies performed (clinical and study-directed) of which 332 were study-directed. Molecular profiling included whole-genome sequencing or whole-exome sequencing, cancer-associated gene panel sequencing, RNA-sequencing, and immunohistochemistry. To afford time for analysis, subjects were initially treated with cisplatin (19 subjects), or another treatment they had not received previously. The results were discussed at a multi-institutional ITOMIC Tumor Board, and a report transmitted to the subject's oncologist who arrived at the final treatment decision in conjunction with the subject. Assistance was provided to access treatments that were predicted to be effective.

RESULTS Multiple biopsies in single settings and over time were safe, and comprehensive analysis was feasible. Two subjects were found to have lung cancer, one had carcinoma of unknown primary site, tumor samples from three subjects were estrogen receptor–positive and from two others, human epidermal growth factor receptor 2–positive. Two subjects withdrew. Thirty-four of 112 recommended treatments were accessed using approved drugs, clinical trials, and single-patient investigational new drugs. After excluding the three subjects with nonbreast cancers and the two subjects who withdrew, 22 of 26 subjects (84.6%) received at least one ITOMIC Tumor Board–recommended treatment.

CONCLUSION Further exploration of this approach in patients with mTNBC is merited.

JCO Precis Oncol 6:e2100280. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on January 27, 2022 and published at ascopubs.org/journal/po on March 16, 2022: DOI https://doi.org/10.1200/PO.21.00280

INTRODUCTION

Breast cancer (BC) is the most common malignancy in women worldwide excluding skin cancer.[1] Triple-negative BC (TNBC), defined by features that it lacks—overexpression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)—comprises about 10% of BCs in non-Hispanic White women and 21% of BCs in non-Hispanic Black women.[2] TNBC is more aggressive and is associated with a poorer survival at 5 years than other BC subtypes.[3-5] Patients with metastatic TNBC (mTNBC) have especially poor outcomes, with median overall survivals ranging from 8.9 months[6] to 13.3 months.[7,8]

Research advances using next-generation sequencing, computational biology, and other technologies have significantly advanced our understanding of mTNBC[9]; however, insights from these efforts are rarely deployed in a manner that has the potential to immediately benefit patients.[10,11] A growing number of institutions have established molecular tumor boards to recommend treatments on the basis of the results of molecular profiling,[12-15] and clinical trials have assessed the benefits of this approach.[16-21] Multidimensional molecular analysis is typically confined to single tumor samples analyzed at single points in time; however, heterogeneity is inherent to almost all

CONTEXT

Key Objective

To enhance treatment options for patients with metastatic triple-negative breast cancer, we performed molecular analyses that included research as well as approved assays on biopsies of existing and emergent metastases collected over time. Findings were provided to the Intensive Trial of Omics in Cancer Tumor Board, which then made recommendations to the oncologist and patient for their consideration on the basis of identified targets.

Knowledge Generated

Longitudinal molecular testing of biopsies from multiple metastatic sites of patients with metastatic triple-negative breast cancer was found to be safe and feasible, and changes in tumor/metastases molecular profiles over time provided, in some cases, new therapeutic targets.

Relevance

Assessment of changes in tumor/metastasis molecular character during the course of disease is, along with use of research assays and experimental treatments, an approach to precision medicine that has the potential to leverage our increasing knowledge of tumor biology.

cancers and the molecular features of cancers evolve with disease progression[22]; therefore, patients may also benefit from longitudinal profiling. Additionally, the results considered by molecular tumor boards are typically derived from tests performed in Clinical Laboratory Improvement Amendments (CLIA)–approved facilities, limiting the scope of potentially useful information.

We launched the Intensive Trial of Omics in Cancer (ITOMIC; ClinicalTrials.gov identifier: NCT01957514) in October 2013 to capture differences between different tumor samples taken from the same patient at the same time and longitudinally at different times, to access both clinically-validated and research-based tests, to enable analysis by a distributed network of experts, and to provide results to oncologists and their patients. Outside of ITOMIC, the University of Washington Center for Cancer Innovation assisted patients and their oncologists to access treatments that were predicted to be effective. The experience of one subject in this trial has been described previously.[23] Here, we describe the experiences of 31 patients enrolled in the trial.

METHODS

Study Design, Subjects, and Tissue Collection

The design of ITOMIC is depicted schematically in Figure 1. Thirty-one (31) patients with a prestudy diagnosis of mTNBC seen at Northwest Medical Specialties or the Seattle Cancer Care Alliance were enrolled. A diagnosis of mTNBC was established on the basis of the most recent pathology report(s) from clinical specimens.

Upon enrollment, biopsies were taken from multiple metastatic sites, if possible. Archival tissues were analyzed when study biopsies were not feasible (or not successful as occurred in subject 8 whose disease was confined to bone). Archival tissues were either from primary or metastatic sites, and in a few instances, from both. Samples chosen for analysis were based on representativeness and tumor content, and analysis of the most recent biopsy sample was prioritized. Select specimens of sufficient size (typically $>$ 5 mm in length) and tumor content (typically $>$ 50%) were comprehensively analyzed. To afford time for analysis, subjects were initially treated with cisplatin (19 subjects),[24,25] or another treatment that they had not received previously at the discretion of their physician.

The results of analyses across platforms and laboratories were reviewed at a virtual meeting of a multi-institutional ITOMIC Tumor Board (ITB), and a report describing findings was returned to the subject's oncologist who in turn provided the results to the subject for discussion. An example of a report is provided in the Data Supplement. Assistance in accessing a recommended treatment was provided upon request by the University of Washington Center for Cancer Innovation. If the subject declined or was unable to avail themselves of the recommended treatment, the physician provided standard-of-care (SoC) treatment at their discretion or, in some instances and at their discretion, the physician would combine the ITB recommended treatment with SoC therapy at doses and schedules previously demonstrated to be safe.

If disease progressed on the first ITB (or alternative physician-recommended) treatment, the subject underwent additional biopsies for analysis, ITB review, and recommendation. This process was repeated as feasible.

Biopsy-Related Adverse Events

Adverse events (AEs) were graded by the investigator according to the Common Terminology Criteria for Adverse Events (version 4.03) 1 day and 7 days after the study-directed biopsy. A data safety monitoring board reviewed AEs.

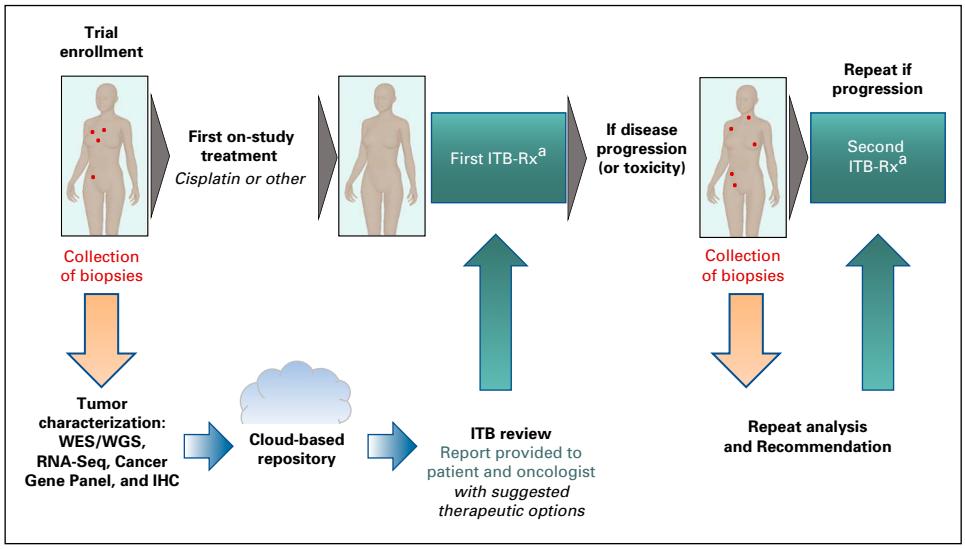

FIG 1. The ITOMIC study. Upon enrollment, biopsies were collected (if possible) from all metastases for tumor characterization; for a few subjects, recent archival primary or metastatic samples were used for the first analyses. To afford time for analysis, subjects received either cisplatin or another therapy that they had not received previously. Biopsy analysis results were stored in a cloud-based repository and underwent review by the ITB, which provided a report to the subject and her physician with treatment recommendations; in most instances, the subject received the recommended treatment; otherwise, the patient received SoC treatment as determined by their physician. Upon disease progression or toxicity the process repeated: collection of biopsies, tumor characterization, ITB review/recommendation, and commencement of a new treatment. [a]The oncologist made the final decision on treatment. Cancer gene panel, University of Washington Oncoplex or Foundation One; IHC, immunohistochemistry; ITB, ITOMIC Tumor Board; ITOMIC, Intensive Trial of Omics in Cancer; RNA-Seq, RNA Sequencing; WES, whole-exome sequencing; WGS, whole-genome sequencing.

Analyses

Selected samples were analyzed using whole-genome sequencing (WGS) or whole-exome sequencing (WES), RNA sequencing (RNA-seq), deep sequencing of panels of cancer-associated genes, immunohistochemistry (IHC) and, in some instances, other studies as described in the Data Supplement. Germline sequencing was performed in all patients and somatic mutations identified by comparing results from germline and tumor sequencing.

RESULTS

Patient Characteristics

Demographics of all 31 subjects who enrolled in ITOMIC and prestudy treatment histories are shown in Table 1. Additional information on subject screening is found in the Data Supplement. The median age at enrollment was 57 years (range: 35-77 years) and 84% of subjects were White. The median number of prior treatments was 2 (range 0-7). All but five participants had received at least one prior therapy.

Study-Directed Biopsies

Figure 2 depicts the timing and anatomic sites for post-enrollment biopsies for all 31 participants. Up to five adequate tumor samples were obtained from a single metastatic site. If an adequate tissue sample could not be obtained, the most recent prestudy clinical specimen was analyzed. Details on biopsy collection numbers and assessments are provided in the Data Supplement.

Adverse Events

AEs related or possibly related to the 332 study-directed biopsies performed on 77 occasions were evaluated one day and 7 days post-biopsy. There were six grade II AEs for pain and one grade III AE for pain associated with extensive cutaneous inflammatory BC; the patient's symptoms had previously been alleviated by bathing, which was temporarily interrupted after she underwent several skin punch biopsies, necessitating a 5-day hospitalization for pain control.

Changes in Diagnosis

Subjects were eligible for enrollment in ITOMIC if the most recent pathologic evaluation of a metastatic site was reported as mTNBC. Subjects 21 and 27 were subsequently determined to have metastatic lung cancer on the basis of analysis of postenrollment biopsies, and subject 30 was determined to have a cancer of unknown primary; all three were removed from the study. Subjects 3 and 7 withdrew following the first set of biopsies. Of the remaining 26 subjects, four (No.s 2, 5, 6, and 18) had prior histories of

TABLE 1. Patient Demographics, Year of Original BC Diagnosis and Receptor Status, Prestudy Treatments, Dates of mTNBC Diagnosis and Trial Enrollment, and Baseline CTC Levels

Subject	Age (years)	Race	BC Diagnosis (year)	Receptor Status at Diagnosis	Therapy Before Enrollment					mTNBC Diagnosis Date	Enrollment Date	Baseline CTC (in 7.5 mL)
					First Line	Second Line	Third Line	Fourth Line	Fifth, Sixth, and Seventh Lines			
1	45	White	2011	TNBC	Paclitaxel, sunitinib, followed by ddAC	Capecitabine	Vinorelbine			May 28, 2013	October 24, 2013	20-40
2	56	White	2007	ER+/PR+	Docetaxel, doxorubicin, cyclophosphamide	Anastrozole	Letrozole, fulvestrant	Capecitabine, paclitaxel		June 25, 2013	October 28, 2013	11,840
3	52	White	2012	TNBC	Paclitaxel, bevacizumab	Cyclophoshamide, fluorouracil, doxorubicin, insulin				April 26, 2012	February 19, 2014	2
4	54	White	2010	TNBC	Docetaxel, cyclophosphamide	Capecitabine	Abraxane			April 25, 2012	February 25, 2014	8
5	77	White	1996	ER+/PR+	Tamoxifen	Anastrozole	Fulvestrant	Paclitaxel, docetaxel, cyclophosphamide	Epirubicin	February 28, 2014	April 7, 2014	7
6	67	White	2006	ER+/PR+	Anastrozole	Exemestane	Abraxane	Capecitabine		April 29, 2013	April 21, 2014	2
7	40	Native Hawaiian or Other Pacific Islander	2006	ER+/PR+	Paclitaxel					May 9, 2014	May 20, 2014	18
8	62	White	2013	TNBC	Docetaxel, doxorubicin, cyclophosphamide					June 11, 2013	September 23, 2014	0 (study day 22)
9	37	Native Hawaiian or Other Pacific Islander	2011	TNBC	Docetaxel, doxorubicin, cyclophosphamide					September 23, 2014	October 13, 2014	0
10	71	White	2014	TNBC	None					December 23, 2014	December 29, 2014	0
11	42	White	2014	TNBC	Docetaxel, doxorubicin, cyclophosphamide					December 17, 2014	January 14, 2015	4
12	46	White	2014	TNBC	Docetaxel, doxorubicin, cyclophosphamide					March 16, 2015	March 24, 2015	2
13	57	White	2014	TNBC	Paclitaxel, doxorubicin, cyclophosphamide					January 14, 2015	February 3, 2016	5
14	54	White	1999	TNBC	Doxorubicin, cyclophosphamide	Paclitaxel plus ipatasertib/ placebo	Eribulin			September 21, 2015	March 7, 2016	0
15	66	White	2003	TNBC	Docetaxel, doxorubicin, cyclophosphamide	Paclitaxel plus ipatasertib/ placebo	Abraxane			July 23, 2015	March 15, 2016	5
16	56	White	2016	TNBC	None					June 27, 2016	July 11, 2016	4
17	35	African American, Asian or Pacific Islander	2016	TNBC	Doxorubicin, cyclophosphamide					May 25, 2016	July 15, 2016	5

(Continued on following page)

TABLE 1. Patient Demographics, Year of Original BC Diagnosis and Receptor Status, Prestudy Treatments, Dates of mTNBC Diagnosis and Trial Enrollment, and Baseline CTC Levels (Continued)

Subject	Age (years)	Race	BC Diagnosis (year)	Receptor Status at Diagnosis	Therapy Before Enrollment					mTNBC Diagnosis Date	Enrollment Date	Baseline CTC (in 7.5 mL)
					First Line	Second Line	Third Line	Fourth Line	Fifth, Sixth, and Seventh Lines			
18	62	White	2013	TNBC (focal ER+)	Cyclophosphamide, methotrexate, fluorouracil, femara	Doxorubicin, cyclophosphamide	Abraxane, carboplatin			September 20, 2016	October 10, 2016	18
19	52	White	2010	TNBC	Doxorubicin, cyclophosphamide, tamoxifen	Paclitaxel plus ipatasertib/ placebo	Paclitaxel, carboplatin			December 14, 2015	October 19, 2016	10
20	67	White	2016	TNBC	None					December 14, 2016	December 29, 2016	0
21	50	White	2016	TNBC	None					December 5, 2016	January 9, 2017	10
22	64	White	2008	TNBC	Doxorubicin, cyclophosphamide	Paclitaxel plus ipatasertib/ placebo	Vinorelbine			November 20, 2015	February 21, 2017	36
23	56	White	2015	TNBC	Docetaxel, doxorubicin, cyclophosphamide	Cisplatin, herceptin				February 9, 2017	March 8, 2017	10
24	58	African American	2016	TNBC	Paclitaxel, doxorubicin, cyclophosphamide					May 23, 2016	March 20, 2017	6
25	60	White	2007	TNBC	Paclitaxel, doxorubicin, cyclophosphamide, herceptin	Vinorelbine, methotrexate, capecitabine				March 20, 2017	March 29, 2017	42
26	64	White	2011	HER2+	Carboplatin, docetaxel, herceptin	Capecitabine, lapatinib	Herceptin, paclitaxel, perjeta	Kadcyla	Fifth: herceptin, navelbine Sixth: gemcitabine, herceptin Seventh: eribulin, herceptin	July 13, 2017	July 18, 2017	Assay failed
27	73	White	2017	TNBC	None					September 1, 2017	September 12, 2017	2
28	36	Asian or Pacific Islander	2014	TNBC	Doxorubin, cyclophosphamide	Cisplatin, paclitaxel	Paclitaxel	Paclitaxel, capecitabine		January 15, 2016	October 26, 2017	0
29	75	White	2017	TNBC	Paclitaxel					December 22, 2016	November 6, 2017	15
30	64	White	2000	HER2+	Perjeta, herceptin, carboplatin, docetaxel	Herceptin				December 4, 2017	December 27, 2017	0
31	61	White	2015	TNBC	Docetaxel, doxorubicin, cyclophosphamide					December 21, 2017	January 18, 2018	0

NOTE. Patients were enrolled in the ITOMIC trial between October 2013 and January 2018. The median age of enrolled subjects was 57 years and race is as listed. Four subjects were ER+/PR+ and two were HER2+ at the time of their original BC diagnosis, but all had a TNBC diagnosis at the time of enrollment. Subjects 10, 16, 20, 21, and 27 presented with mTNBC and were immediately enrolled in the trial.

Abbreviations: BC, breast cancer; CTC, circulating tumor cells; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; mTNBC, metastatic triple-negative breast cancer; PR, progesterone receptor; TNBC, triple-negative breast cancer.

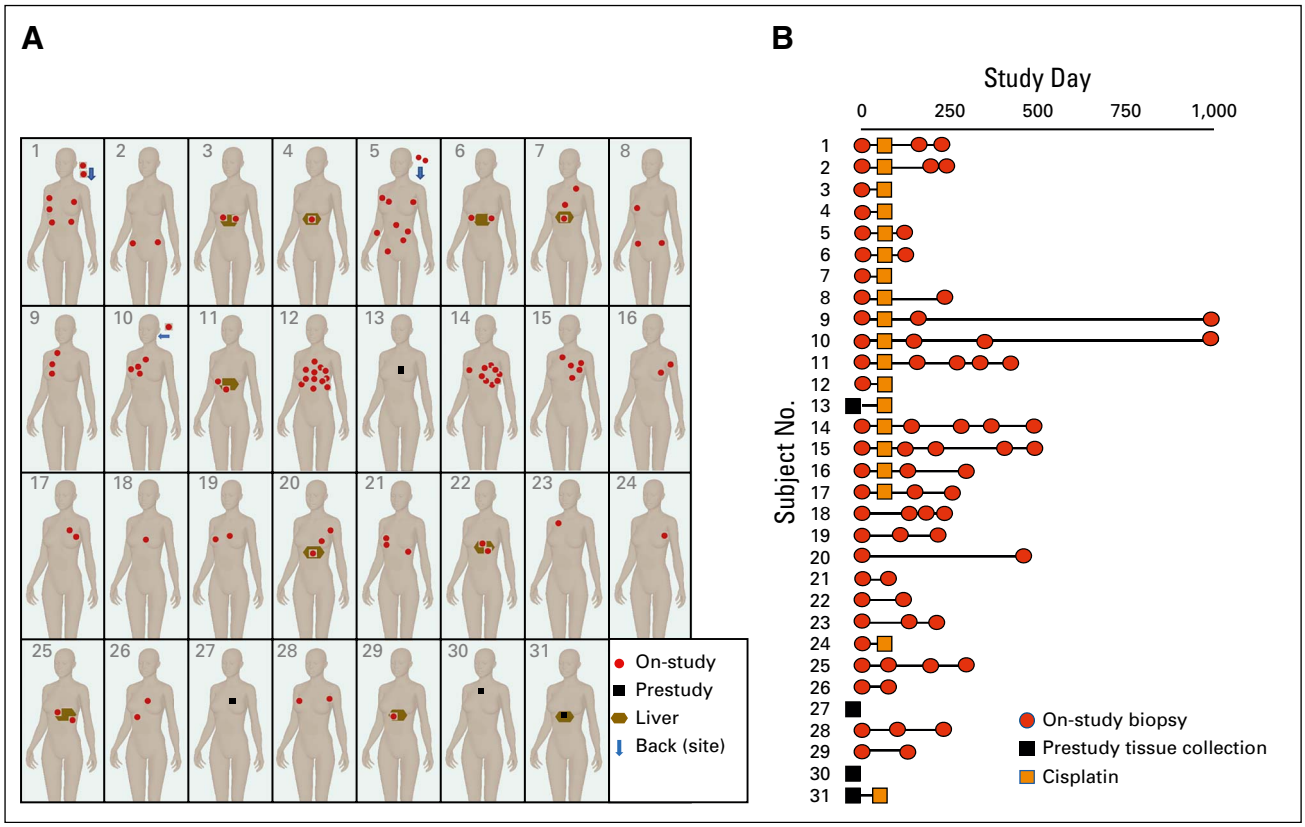

FIG 2. Anatomic sites and timing of postenrollment biopsies. (A) The anatomic locations of postenrollment biopsies (red dots) for all 31 enrolled subjects are shown. Black squares depict instances in which only prestudy biopsies were analyzed. (B) The timing of tissue collections is shown. Black squares depict prestudy tissue collections. Orange squares depict subjects who received cisplatin as the first postenrollment therapy.

ER-positive BC. ER-positivity was again detected in postenrollment biopsies from subject 6, whereas postenrollment biopsies from subjects 2, 5, and 18 were consistently ER-negative. ER-positivity was also detected in postenrollment biopsies from subjects 16 and 17, and weak ER staining affecting 1% of cells was detected in one of six postenrollment biopsies from subject 15 who was categorized as ER-negative. Subject 26 had a prior history of HER2-positive cancer, and persistence of HER2-positivity was confirmed in postenrollment biopsies. Subject 25 had a history of TNBC; however, postenrollment biopsies demonstrated HER2-positivity. Although subject 14 had a history of TNBC, a left BC was documented to be ER/PR- and HER2-positive, whereas a synchronous right BC and metastatic right cervical lymph node were both TNBC. In aggregate, eight of 31 study participants (No.s 6, 16, 17, 21, 25, 26, 27, and 30; 26%) enrolled with a diagnosis of mTNBC were found during postenrollment evaluation to have a different diagnosis.

ITB Recommendations

ITB meetings (Data Supplement) began with a presentation of the patient's relevant medical history, followed by results of IHC, cancer gene panel sequencing, WES, WGS, and RNA-seq from multiple biopsy specimens obtained at the same time from different metastatic sites. The results from research, non-CLIA-approved assays, along with standard assays, were considered by the ITB, as consented to by the patient and permitted in the institutional review board–approved framework. Correlating the variant allele frequency of a somatic mutation with the estimated tumor cell content across samples was taken into consideration in assessing whether a variant was likely to be present in most or all tumor cells, thereby presenting a reasonable therapeutic target. Samples with high tumor content were the most useful in evaluating RNA-seq signatures, and confidence in assessments of the relative expression level of an mRNA transcript increased if the results were similar across different samples. The sequencing depth associated with cancer gene panels provided results when tumor cell frequencies were too low to permit evaluation by WES or WGS. Germline sequencing was used to assess whether variants of undetermined significance identified in cancer gene panels were somatic or germline in origin. Germline sequencing also allowed for predictions of enhanced toxicity in the setting of specific chemotherapeutic agents.[26]

ITB recommendations—on the basis of recent literature, data from preclinical and clinical studies, and the

Subject	ITB Meetings (No.)	ITB Rx Adopted/Total	First Rx Post Enrollment	Duration (weeks)	First Target	First ITB Rx (combined)	Duration (weeks)	Second Target	Second ITB Rx (combined)	Duration (weeks)	Status	Time After Study Enrollment (weeks)	Time After Diagnosis of mTNBC (weeks)	Additional Non–ITB Rx Received
1	2	2/2	Cisplatin	12	BRCA1 p.R1028Qfs*23	Veliparib[1]	10	FGFR2 p.S252W, p.Y375C	Ponatinib[4]	7	Died	35	53	
2	2	1/2	Cisplatin	21	ROS1 Y2092C	Crizotinib[4]	4				Died	39	59	Eribulin
5	2	2/2	Cisplatin	3	CYP3A4 amplification	Cyclophosphamide[3]	10	ATR Y2084H	Veliparib[1]	10	Died	39	76	Doxorubicin
9	2	2/5	Cisplatin	11	BRCA2 L1768fs*5	Veliparib[1] (carboplatin and paclitaxel)	71	Elevated LIV1A RNA	SGN-LIV1A[2]	17	Died	150	152	
10	3	1/2	Cisplatin	6	T-cell receptor clonality and infiltration	Nivolumab[4] (Abraxane); then nivolumab[4] monotherapy	59; 71	Elevated Signature 3	Olaparib[4] (eribulin and nivolumab)	59	Died	279	281	Capecitabine, doxorubicin, and gemcitabine
11	1	2/2	Cisplatin	6	CCND1 amplification, CDKN2A amplification	Ribociclib[2]	8	gpNMB-positive	Glembatumumab vedotin[2]	17	Died	41	45	
12	1	1/3	Cisplatin	3	FGFR1-ADAM32 tandem duplication	Pazopanib[4]	Single dose				Died	17	18	
13	1	1/2	Cisplatin	54	Elevated mutation burden	Nivolumab[4] (Abraxane)	26				Died	129	185	Eribulin and temozolomide
14	4	3/6	Cisplatin	15	ER-positive, PD-L1–positive	Nivolumab[4], Letrozole (Abraxane)	26	HER2-positive	Trastuzumab[3], pertuzumab[3] (docetaxel) followed by trastuzumab[3] (anastrazole)	> 176	Subject still on Rx	237	289	Trastuzumab (nivolumab, docetaxel, and gemcitabine), trastuzumab (nivolumab, capecitabine, everolimus, and exemestane)
15	4	4/7	Cisplatin	9	Amplification and fusion of FGFR2 exons 1-17 with EIF3A exons 14-22	AZD4547[2]	12	Elevated mutation burden	Nivolumab[4] (Abraxane); nivolumab[4] (gemcitabine)	40; 90	Subject still on Rx	236	269	Capecitabine (nivolumab and gemcitabine), Sacituzumab govitecan (nivolumab)
18	2	1/4	Eribulin	10	PD-L1–positive and elevated mutation burden	Nivolumab[4] (capecitabine	4				Died	24	29	
19	2	1/5	Eribulin	7	PD-L1–positive	Nivolumab[4] (Abraxane then capecitabine)	10				Died	30	74	
20	2	0/5	Abraxane	33	NA	NA					Died	65	67	Eribulin and nivolumab
22	1	1/6	Doxorubicin Cyclophosphamide	6	AKT1 p.L52R copy gain	Everolimus[4] (gemcitabine)	4				Died	18	85	
23	1	1/4	Trastuzumab	3	ERBB2 A775_G776insYVMA	Neratinib[3] (gemcitabine and capecitabine)	130				Subject still on Rx	185	188	Neratinib (atezolizumab and Abraxane), tucatinib (atezolizumab, Abraxane, and capecitabine)
24	2	2/6	Cisplatin	15	PD-L1–positive, elevated mutation burden, elevated Signature 3	Durvalumab[4] (olaparib[4])	24				Died	132	355	Eribulin, gemcitabine (nivolumab), capecitabine, and vinorelbine
28	3	1/7	Eribulin	8	PD-L1–positive	Nivolumab[4] (Abraxane)	16				Died	123	216	Gemcitabine, cisplatin, vinorelbine, olaparib, Ixabepilone, and ROR1 CAR T
29	2	1/6	Capecitabine	6	Elevated AKT1 RNA expression	Everolimus[4] (eribulin)	70				Died	85	131	
31	1	0/5	Cisplatin	11	NA	NA					Died	42	180	Eribulin

Extended Table for Subject 15 Below

					Third Target	Third ITB Rx	Duration (weeks)	Fourth Target	Fourth ITB Rx	Duration (weeks)
15					CCND2 amplification	Palbociclib[4] (Abraxane and nivolumab[4])	14	ROR1-positive	ROR1 CAR T[2] (nivolumab)	35; 22

FIG 3. ITB treatment recommendations. Number of ITB meetings, molecular lesions targeted, treatments administered, and duration of therapy for patients enrolled in Intensive Trial of Omics in Cancer (ITOMIC) with confirmed triple-negative breast cancer who received at least one treatment. Numbers in superscript denote method of drug access: [1]Investigational drug accessed via single patient investigational new drug (three instances; light blue); [2]Investigational drug accessed via an existing clinical trial (five instances; beige); [3]On-label indication for an approved drug (three instances; pink); [4]Off-label indication for an approved drug (17 instances; gray). Light green shading indicates a treatment duration of 20-40 weeks, and dark green shading indicates a treatment duration > 40 weeks. Patients came off therapy if there was disease progression, toxicity, or death. Yellow shading denotes subjects who were still alive as of June 1, 2021. Subjects found to show receptor-positivity postenrollment, subjects 3 and 7 who withdrew, and subject 4 who died before the first postenrollment treatment are not shown. Subjects 12, 20, and 31 died before receiving the first ITB-Rx. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; ITB, ITOMIC Tumor Board; ITB Rx, ITOMIC Tumor Board recommended treatment; mTNBC, metastatic triple-negative breast cancer; NA, not applicable; PD-L1, programmed death ligand-1; Rx, recommended treatment.

availability of ongoing clinical trials appropriate for an identified target—uniformly targeted molecular features specific to somatic tissues. When the ITB recommended multiagent regimens, the dose and schedules of component drugs were adopted from published or active clinical trials. For example, subject 23 received a recommendation for combined neratinib and temsirolimus therapy on the basis of a reported clinical trial.[27]

Figure 3 shows recommendations for 19 patients confirmed to have mTNBC, excluding two patients who withdrew (subjects 3 and 7) and one who died before the first postenrollment treatment (subject 4). Significant findings were conveyed to the oncologist ahead of the ITB meeting if indicated by clinical urgency. Details of the numbers of biopsies that underwent assessment can be found in the Data Supplement.

Initially, there was focus on identifying clinical trials across the United States for which a patient might qualify; however, patients were almost uniformly unwilling to travel. For example, subject 12's tumor was found to have two activating mutations affecting the Notch pathway—a *NOTCH2* mutation resulting in a predicted R2400X truncation,[28] and homozygous deletion of exons 3-27 within *NOTCH1*[29]—predicted to confer susceptibility to gamma secretase inhibition. A clinical trial testing a gamma secretase inhibitor at the University of Chicago (ClinicalTrials.gov identifier: NCT02299635) was recommended; however subject 12 did not wish to travel. Subsequently, focus was placed on local clinical trials.

As ITOMIC's processes and areas of emphasis evolved, assessments of RNA-seq results grew in importance, with an emphasis on assessing relative expression levels of transcripts encoding proteins targeted in locally available clinical trials. Assessment of expression level is complicated by variation in the cellular composition of a tumor specimen, tissue processing, and batch effects.[30] Analysis of multiple samples collected over time for comparison and the use of XENA[31] proved especially useful in triaging subjects to locally available trials targeting GPNMB (ClinicalTrials.gov identifier: NCT01997333), LIV-1 (ClinicalTrials.gov identifier: NCT01969643), and ROR-1 (ClinicalTrials.gov identifier: NCT02706392).

Responses to ITB-Recommended Treatments

As a feasibility study, ITOMIC was not designed to demonstrate efficacy, and therefore, assessments of responses using RECIST criteria[32] were not performed. mTNBC has an aggressive clinical course requiring continuous treatment, and the duration of a given therapy provides a useful surrogate for assessing the duration of response. The durations of ITB-recommended treatments are presented in Figure 3. The durations of some ITB-recommended treatments administered to subjects 13, 14, 15, and 24 lasted between 20 and 50 weeks, whereas the durations of some ITB-recommended treatments for subjects 9, 10, 14, 23, 25, and 29 surpassed 50 weeks.

Subjects remained on treatment until disease progression or toxicity. Treatment was not changed solely on the basis of a new recommendation from the ITB. We note that although treatment responses to single agents were observed in some of the first subjects enrolled in ITOMIC, they were short-lived. For example, subject 1 was found to have two somatic activating mutations affecting *FGFR2*, with predicted amino acid substitutions at S252W[33] and Y375C.[34] Off-label treatment with ponatinib produced a significant but short-lived reduction in cutaneous tumor infiltrates, lasting only 7 weeks. These early findings lead to the adoption of multiagent regimens.

Treatments recommended by the ITB sometimes failed. For example, a *ROS1* point mutation identified in subject 2 (encoding Y2092C) failed to confer responsiveness to crizotinib despite the best efforts of domain experts,[23] and an *FGFR2/EIF3A* fusion expressed at high levels failed to confer responsiveness to an investigational FGFR2 inhibitor available through the NCI-MATCH trial.[35]

Although it is not intended to be a presentation of formal assessment of survival, Figure 4 shows the duration of disease pre-enrollment and survival postenrollment up to the end of the 2-year study period and beyond.

Integrating ITB-Recommended Treatments With Clinical Care

Adjustments to ITB treatment recommendations were frequently required because of treatment toxicity and a lack of or loss of treatment responsiveness, as exemplified by subject 10's clinical course, depicted in Figure 5. Subject 10 was age 71 years at the time of mTNBC diagnosis in December 2014. She immediately enrolled in ITOMIC and

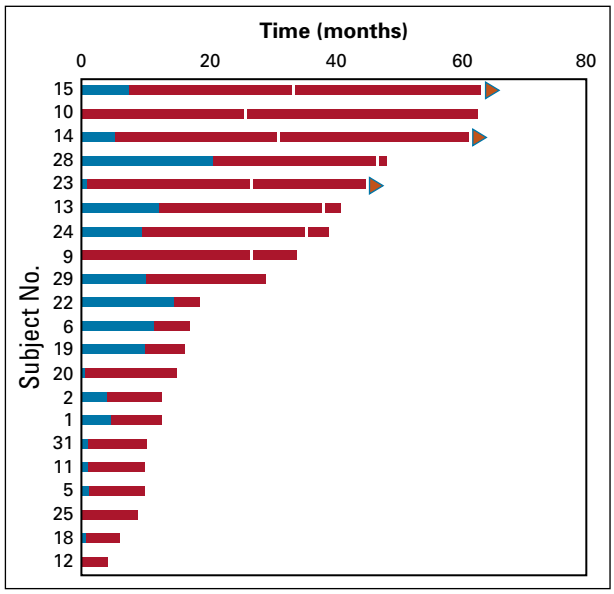

FIG 4. Time from TNBC diagnosis to study enrollment and survival postenrollment. The duration of prestudy disease is shown in blue and poststudy survival in red for the 21 of the 31 enrolled subjects with confirmed metastatic TNBC who received at least one Intensive Trial of Omics in Cancer Tumor Board–recommended treatment. The end of the 2-year Intensive Trial of Omics in Cancer study participation is demarcated in white. Subjects 14, 15, and 23 (orange arrows) were still alive as of June 1, 2021. TNBC, triple-negative breast cancer.

received cisplatin followed by bilateral mastectomies and a right axillary lymphadenectomy. Adjuvant cisplatin was subsequently discontinued because of neuropathy and tinnitus. New metastases were detected in June 2015 and were treated with radiation therapy. Because of disease progression (December 2015), she was treated with ITB-recommended nivolumab and nab-paclitaxel beginning in January 2016. Nivolumab was recommended on the basis of ImmunoSEQ profiling, which identified a dominant clonal population of infiltrating T cells, and research results from metastatic melanoma suggesting that this pattern may be associated with an increased likelihood of responding to programmed cell death protein-1 blockade.[36] A complete response was noted and nivolumab continued while nab-paclitaxel was discontinued because of toxicity. In 2017, several brain metastases were treated with gamma knife radiation/surgery and recurrence in July 2018 prompted the addition of capecitabine and nivolumab. Disease progression in November 2018 prompted discontinuation of capecitabine and initiation of the second ITB recommended treatment, olaparib (because of a signature 3–associated mutation profile[37]) plus eribulin, combined with ongoing nivolumab therapy. Eribulin was discontinued because of infusion-associated dyspnea, substituted by nab-paclitaxel with continued olaparib and nivolumab in September 2019. Continued disease progression prompted a switch back to lower-dose eribulin to January 2020, followed briefly by gemcitibine and doxorubicin treatment before her death in May 2020.

Utility of Serial Biopsies

Although many of molecular features of biopsies remained stable throughout a patient's disease course, there were two ways in which serial biopsies proved useful. The first is related to molecular features only detected in later biopsies. For example, subject 14's first postenrollment biopsies revealed focal ER-positivity, resulting in the inclusion of antiestrogen therapy in her regimen and a second study-related biopsy revealed focal HER2-positivity, resulting in the addition of trastuzumab. Additionally, *CCND2* amplification was first detected in subject 15 in her third post-enrollment biopsy, leading to treatment with palbociclib. Finally, serial biopsies revealed an increase in tumor mutation burden (TMB) over time in subjects 19, 20, 24, 26, 28, and 29. For subjects 24 and 28, the increase in TMB resulted in the incorporation of immune checkpoint inhibitors to their treatment regimens. In subject 24, TMB rose from 4.32 mt/MB and 4.74 mt/MB on initial study biopsies to 12 mt/MB on a later study biopsy, and in subject 28 the TMB increased from 2.6 mt/MB on an initial study biopsy to 16.1 mt/MB in a later biopsy.

A second way in which serial monitoring proved useful was that it allowed for the application of analytic methods not available at the time of previous evaluations. Over the course of ITOMIC, we incorporated methods for estimating levels of mRNA transcripts encoding proteins for which targeted therapies could be accessed via clinical trials. In subject 9, LIV-1A transcript levels were in the 55th percentile of compared with 122 other mTNBC samples, and she was enrolled in ClinicalTrials.gov identifier: NCT01969643. Subject 9 was also found to have high ROR-1 transcript levels (in the 93rd percentile). ROR-1 protein expression was confirmed by IHC, and she was accepted for participation in a CAR-T trial targeting *ROR1;* however, she elected to receive hospice care. In another example, subject 10 was found to have a mutational signature suggestive of loss of *BRCA1* or *BRCA2* on tissue obtained from her third set of biopsies, and a poly (ADP-ribose) polymerase inhibitor was added to her regimen.

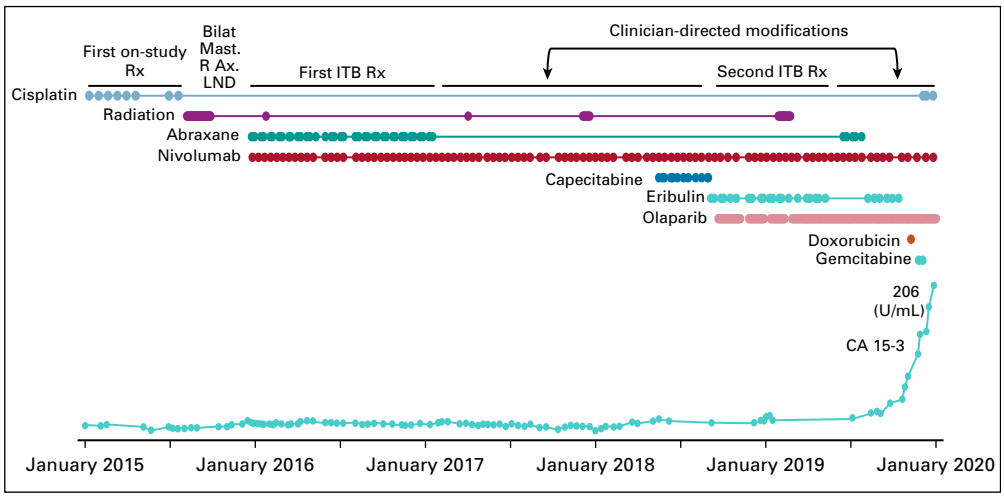

FIG 5. Schematic depiction of the > 5-year clinical course of subject 10. Cancer treatments and CA 15-3 levels (a surrogate marker of tumor burden) are shown. Clinician-directed modifications are described in the Results section. Bilat Mast. R Ax. LND, bilateral mastectomies and right axillary lymph node dissection; CA, cancer antigen; ITB Rx, Intensive Trial of Omics in Cancer Tumor Board–recommended treatment.

DISCUSSION

ITOMIC was a feasibility study and, as such, lacked rigorous, predefined end points. Its aim was to establish and test a framework for delivering a best effort to understand the innerworkings of a patient's cancer that transcended technology platforms, scientific disciplines, and institutions. The addition of research-based tests to clinically validated tests significantly improved the ITB's ability to guide oncologists and their patients to potentially effective therapies, as exemplified by the estimation of relative levels of specific mRNA transcripts for experimental agents targeting the encoded proteins. The results of surveys describing the attitudes of ITOMIC participants, which reflect their overall support for the innovative aspects of the study, have been reported previously.[38]

Surprisingly, ITOMIC analyses revealed that 26% of subjects thought to have mTNBC were subsequently found to have other cancers (three subjects) or other BC subtypes (five subjects). In addition, in some, increases in TMB with time were detected. These observations are clinically significant and point to the merits analyzing multiple biopsy specimens in single settings and over time in patients with mTNBC. These findings underscore the frequent heterogeneity of ER, PR, and HER2 expression in BCs, both spatially and temporally,[39] the frequent difficulty of distinguishing mTNBC from other metastatic cancers, and support the merits of performing multiple biopsies.

Perhaps the greatest success of the work described here was the high frequency with which subjects enrolled in ITOMIC were able to access ITB-recommended therapies. However, despite these successes, many instances remained in which treatments predicted to be effective could not be accessed, as exemplified by subject 2 for whom we were unable to acquire venetoclax.[12]

ITOMIC highlights critical limitations associated with a clinical trial system that is inaccessible to most patients. Urgently needed are mechanisms that afford greater flexibility, allowing patients to access investigational drugs at the point of care, combined with a framework that enables learning by capturing their experiences for the benefit of future patients.

AFFILIATIONS

[1]Department of Medicine, University of Washington, Seattle, WA
[2]Center for Cancer Innovation, University of Washington, Seattle, WA
[3]Northwest Medical Specialties, Puyallup and Tacoma, WA
[4]South Sound CARE Foundation, Seattle, WA
[5]Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA
[6]Department of Medicine/Hematology, University of Washington, Seattle, WA
[7]Department of Laboratory Medicine, University of Washington, Seattle, WA
[8]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA
[9]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA
[10]Center for Precision Diagnostics, University of Washington, Seattle, WA
[11]Rarecyte Inc, Seattle, WA
[12]NantHealth, Culver City, CA
[13]Trialomics, Seattle, WA
[14]ImmunityBio Inc, Culver City, CA
[15]Computational Genomics Lab, University of California at Santa Cruz, Santa Cruz, CA
[16]Department of Medicine, University of Illinois, Chicago, IL
[17]Fred Hutchinson Cancer Research Center, Seattle, WA
[18]Data4Cure Inc, La Jolla, CA
[19]All4Cure Inc, Seattle, WA

CORRESPONDING AUTHOR

C. Anthony Blau, MD, 9435 45th Ave SW, Seattle, WA 98136; e-mail: tony@all4cure.com.

PRIOR PRESENTATION

Presented at the San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX, December 8-11, 2020.

SUPPORT

Supported by The South Sound CARE Foundation, the University of Washington Institute for Stem Cell and Regenerative Medicine, the Washington Research Foundation, and the Chan Soon-Shiong Family Foundation.

AUTHOR CONTRIBUTIONS

Conception and design: Elisabeth Mahen, Sibel Blau, Francis Mark Senecal, Brigham H. Mecham, Shahrooz Rabizadeh, Patrick Soon-Shiong, C. Anthony Blau
Financial support: Patrick Soon-Shiong
Administrative support: Stephanie Parker, Francis Mark Senecal, Patrick Soon-Shiong
Provision of study materials or patients: Francis Mark Senecal, Vijayakrishna K. Gadi, Patrick Soon-Shiong
Collection and assembly of data: Kimberly A. Burton, Elisabeth Mahen, Eric Quentin Konnick, Sibel Blau, Michael O. Dorschner, Arturo B. Ramirez, Stephen C. Schmechel, Chaozhong Song, Rahul Parulkar, Stephanie Parker, Francis Mark Senecal, Colin C. Pritchard, Brigham H. Mecham, Christopher Szeto, Jackie Stilwell, Stephen Charles Benz, C. Anthony Blau
Data analysis and interpretation: Kimberly A. Burton, Elisabeth Mahen, Sibel Blau, Michael O. Dorschner, Arturo B. Ramirez, Rahul Parulkar, Colin C. Pritchard, Brigham H. Mecham, Christopher Szeto, Patricia Spilman, Jingchun Zhu, Vijayakrishna K. Gadi, Roy Ronen, Eric Kaldjian, Janusz Dutkowski, Stephen Charles Benz, Patrick Soon-Shiong, C. Anthony Blau
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the

subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Kimberly A. Burton

Employment: All4Cure, Just Biotherapeutics (I), Northwest Medical Specialties
Leadership: Just Biotherapeutics (I)
Stock and Other Ownership Interests: Just Biotherapeutics (I)
Other Relationship: NantWorks

Eric Quentin Konnick

Honoraria: Ventana Medical Systems, Roche, Clinical Care Options, Medscape, National Comprehensive Cancer Network
Consulting or Advisory Role: River West Meeting Associates
Travel, Accommodations, Expenses: Ventana Medical Systems, Roche, Clinical Care Options LLC, Medscape, National Comprehensive Cancer Network, River West Meeting Associates

Sibel Blau

Employment: Northwest Medical Specialties
Leadership: Northwest Medical Specialties, Quality Cancer Care Alliance
Stock and Other Ownership Interests: Northwest Medical Specialties, All4Cure (I)
Honoraria: Cardinal Health, Novartis, Puma Biotechnology, American Journal of Managed Care
Research Funding: Northwest Medical Specialties
Expert Testimony: Northwest Medical Specialties
Travel, Accommodations, Expenses: Northwest Medical Specialties, Quality Cancer Care Alliance
Other Relationship: Northwest Medical Specialties, All4Cure (I), Quality Cancer Care Alliance

Michael O. Dorschner

Employment: Guardant Health
Stock and Other Ownership Interests: Guardant Health

Arturo B. Ramirez

Employment: RareCyte
Patents, Royalties, Other Intellectual Property: I hold six patents for my work at RareCyte

Stephanie Parker

Employment: IQvia

Colin C. Pritchard

Consulting or Advisory Role: AstraZeneca, Sana Biotechnology
Research Funding: Color Genomics (I)

Christopher Szeto

Employment: NantHealth, Zai Lab, ImmunityBio
Stock and Other Ownership Interests: NantWorks, Zai Lab
Patents, Royalties, Other Intellectual Property: Listed as inventor or coinventor on several patents and patent applications filed with NantOmics; listed as inventor or coinventor on several patents and applications filed with ImmunityBio

Patricia Spilman

Employment: ImmunityBio Inc
Stock and Other Ownership Interests: ImmunityBio Inc
Research Funding: ImmunityBio Inc

Vijayakrishna K. Gadi

Stock and Other Ownership Interests: Sengine Precision Medicine, Novilla, 3rdEyeBio, Phoenix Molecular Designs, New Equilibrium Biosciences
Consulting or Advisory Role: Seattle Genetics, Puma Biotechnology, Novartis, Sanofi
Speakers' Bureau: Seattle Genetics, Hologics, Genentech/Roche, Puma Biotechnology
Research Funding: Genentech/Roche (Inst), SignalOne Bio, Agendia
Travel, Accommodations, Expenses: Seattle Genetics, Genentech/Roche, Puma Biotechnology
Open Payments Link: https://openpaymentsdata.cms.gov/physician/2511

Roy Ronen

Other Relationship: Data4Cure

Jackie Stilwell

Employment: Umoja Biopharma, Seattle Genetics
Stock and Other Ownership Interests: Seattle Genetics

Eric Kaldjian

Employment: RareCyte Inc
Stock and Other Ownership Interests: RareCyte Inc

Janusz Dutkowski

Patents, Royalties, Other Intellectual Property: Patents pending on methods and systems for data analysis including biomedical data analysis (Inst)
Other Relationship: Data4Cure Inc

Stephen Charles Benz

Employment: NantWorks, ImmunityBio, NantHealth
Stock and Other Ownership Interests: Novartis, Celgene, NantWorks, NantHealth, Pfizer, Regeneron, Bluebird Bio
Patents, Royalties, Other Intellectual Property: Patents issued and pending

Shahrooz Rabizadeh

Employment: ImmunityBio, Sagittarius Bio
Leadership: NantBioScience Inc, NantWorks, ImmunityBio, Sagittarius Bio
Stock and Other Ownership Interests: NantHealth, ImmunityBio, Sagittarius Bio
Patents, Royalties, Other Intellectual Property: Made inventions that resulted in IP for NantBioScience and NantOmics; made inventions that resulted in IP for ImmunityBio; made inventions that resulted in IP for Sagittarius Bio

Patrick Soon-Shiong

Employment: ImmunityBio, NantWorks, NantHealth
Leadership: ImmunityBio, NantWorks, NantHealth
Stock and Other Ownership Interests: ImmunityBio, NantWorks, NantHealth
Patents, Royalties, Other Intellectual Property: NantWorks and Affiliates, NantKwest, ImmunityBio

C. Anthony Blau

Employment: All4Cure
Leadership: All4Cure
Stock and Other Ownership Interests: All4Cure
Consulting or Advisory Role: GlaxoSmithKline (Inst)
Travel, Accommodations, Expenses: Novartis (I)

No other potential conflicts of interest were reported.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018
2. ACS: Breast Cancer Facts and Figures 2019-2020. Atlanta, GA, American Cancer Society, 2020, pp 1-38. No. 861019

3. Dent R, Trudeau M, Pritchard KI, et al: Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res 13:4429-4434, 2007
4. Liedtke C, Mazouni C, Hess KR, et al: Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26:1275-1281, 2008
5. Foulkes WD, Smith IE, Reis-Filho JS: Triple-negative breast cancer. N Engl J Med 363:1938-1948, 2010
6. Seung SJ, Traore AN, Pourmirza B, et al: A population-based analysis of breast cancer incidence and survival by subtype in Ontario women. Curr Oncol 27:e191-e198, 2020
7. Gong Y, Liu YR, Ji P, et al: Impact of molecular subtypes on metastatic breast cancer patients: A SEER population-based study. Sci Rep 7:45411, 2017
8. Lin NU, Claus E, Sohl J, et al: Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: High incidence of central nervous system metastases. Cancer 113:2638-2645, 2008
9. Denkert C, Liedtke C, Tutt A, et al: Molecular alterations in triple-negative breast cancer-the road to new treatment strategies. Lancet 389:2430-2442, 2017
10. Blau CA: Can intensive longitudinal monitoring of individuals advance cancer research? Oncologist 17:587-589, 2012
11. Blau CA, Liakopoulou E: Can we deconstruct cancer, one patient at a time? Trends Genet 29:6-10, 2013
12. Kato S, Kim KH, Lim HJ, et al: Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. Nat Commun 11:4965, 2020
13. Luchini C, Lawlor RT, Milella M, et al: Molecular tumor boards in clinical practice. Trends Cancer 6:738-744, 2020
14. Basse C, Morel C, Alt M, et al: Relevance of a molecular tumour board (MTB) for patients' enrolment in clinical trials: Experience of the Institut Curie. ESMO Open 3:e000339, 2018
15. Beaubier N, Bontrager M, Huether R, et al: Integrated genomic profiling expands clinical options for patients with cancer. Nat Biotechnol 37:1351-1360, 2019
16. Hayashi H, Takiguchi Y, Minami H, et al: Site-specific and targeted therapy based on molecular profiling by next-generation sequencing for cancer of unknown primary site: A nonrandomized phase 2 clinical trial. JAMA Oncol 6:1931-1938, 2020
17. Sicklick JK, Kato S, Okamura R, et al: Molecular profiling of cancer patients enables personalized combination therapy: The I-PREDICT study. Nat Med 25:744-750, 2019
18. Hlevnjak M, Schulze M, Elgaafary S, et al: CATCH: A prospective precision oncology trial in metastatic breast cancer. JCO Precis Oncol 10.1200/PO.20.00248
19. Rodon J, Soria JC, Berger R, et al: Genomic and transcriptomic profiling expands precision cancer medicine: The WINTHER trial. Nat Med 25:751-758, 2019
20. Gambardella V, Lombardi P, Carbonell-Asins JA, et al: Molecular profiling of advanced solid tumours. The impact of experimental molecular-matched therapies on cancer patient outcomes in early-phase trials: The MAST study. Br J Cancer 125:1261-1269, 2021
21. Mangat PK, Halabi S, Bruinooge SS, et al: Rationale and design of the Targeted Agent and Profiling Utilization Registry (TAPUR) study. JCO Precis Oncol 10.1200/PO.18.00122
22. Dagogo-Jack I, Shaw AT: Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol 15:81-94, 2018
23. Blau CA, Ramirez AB, Blau S, et al: A distributed network for intensive longitudinal monitoring in metastatic triple-negative breast cancer. J Natl Compr Canc Netw 14:8-17, 2016
24. Pandy JGP, Balolong-Garcia JC, Cruz-Ordinario MVB, et al: Triple negative breast cancer and platinum-based systemic treatment: A meta-analysis and systematic review. BMC Cancer 19:1065, 2019
25. Egger SJ, Willson ML, Morgan J, et al: Platinum-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev 6:CD003374, 2017
26. Hertz DL, Rae J: Pharmacogenetics of cancer drugs. Annu Rev Med 66:65-81, 2015
27. Gandhi L, Bahleda R, Tolaney SM, et al: Phase I study of neratinib in combination with temsirolimus in patients with human epidermal growth factor receptor 2-dependent and other solid tumors. J Clin Oncol 32:68-75, 2014
28. Mašek J, Andersson ER: The developmental biology of genetic Notch disorders. Development 144:1743-1763, 2017
29. Ashworth TD, Pear WS, Chiang MY, et al: Deletion-based mechanisms of Notch1 activation in T-ALL: Key roles for RAG recombinase and a conserved internal translational start site in Notch1. Blood 116:5455-5464, 2010
30. Vaske OM, Bjork I, Salama SR, et al: Comparative tumor RNA sequencing analysis for difficult-to-treat pediatric and young adult patients with cancer. JAMA Netw Open 2:e1913968, 2019
31. UCSC: XENA Functional Genomics Explorer, Xenabrowser. 2018. https://xena.ucsc.edu/
32. Litière S, Isaac G, De Vries EGE, et al: RECIST 1.1 for response evaluation apply not only to chemotherapy-treated patients but also to targeted cancer agents: A pooled database analysis. J Clin Oncol 37:1102-1110, 2019
33. Pollock PM, Gartside MG, Dejeza LC, et al: Frequent activating FGFR2 mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes. Oncogene 26:7158-7162, 2007
34. Fonseca RF, Costa-Lima MA, Pereira ET, et al: Beare-Stevenson cutis gyrata syndrome: A new case of a c.1124C⁀G (Y375C) mutation in the FGFR2 gene. Mol Med Rep 1:753-755, 2008
35. Flaherty KT, Gray R, Chen A, et al: The molecular analysis for therapy choice (NCI-MATCH) trial: Lessons for genomic trial design. J Natl Cancer Inst 112:1021-1029, 2020
36. Tumeh PC, Harview CL, Yearley JH, et al: PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 515:568-571, 2014
37. Nik-Zainal S, Davies H, Staaf J, et al: Landscape of somatic mutations in 560 breast cancer whole-genome sequences. Nature 534:47-54, 2016
38. Kuderer NM, Burton KA, Blau S, et al: Participant attitudes toward an intensive trial of multiple biopsies, multidimensional molecular analysis, and reporting of results in metastatic triple-negative breast cancer. JCO Precis Oncol 10.1200/PO.17.00076
39. Parinyanitikul N, Lei X, Chavez-MacGregor M, et al: Receptor status change from primary to residual breast cancer after neoadjuvant chemotherapy and analysis of survival outcomes. Clin Breast Cancer 15:153-160, 2015