

# Attrition of Patients on a Precision Oncology Trial: Analysis of the I-PREDICT Experience

SANDY S. BOHAN <sup>a,†</sup> JASON K. SICKLICK,<sup>b,c,d,†</sup> SHUMEI KATO <sup>c,d,†</sup> RYOSUKE OKAMURA,<sup>c,d</sup> VINCENT A. MILLER,<sup>e</sup> BRIAN LEYLAND-JONES,<sup>f</sup> SCOTT M. LIPPMAN,<sup>c,d</sup> RAZELLE KURZROCK <sup>c,d</sup>

<sup>a</sup>San Diego State University/University of California, San Diego, San Diego, California, USA; <sup>b</sup>Department of Surgery, Divisions of Surgical Oncology, <sup>c</sup>Moore's Cancer Center, and <sup>d</sup>Center for Personalized Cancer Therapy, University of California, San Diego, La Jolla, California, USA; <sup>e</sup>Foundation Medicine, Inc., Cambridge, Massachusetts, USA; <sup>f</sup>Avera Cancer Institute, Sioux Falls, South Dakota, USA

<sup>†</sup>Contributed equally

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## ABSTRACT

**Background.** Precision oncology uses molecular profiling of tumors to identify biomarker-tailored therapies for patients in the hope of improving outcomes. Typically, only a minority of patients receives evaluable matched treatment. This study explored the reasons for attrition on a precision medicine trial.

**Materials and Methods.** Study participants were 190 adult patients who consented to the I-PREDICT (Investigation of molecular Profile-Related Evidence Determining Individualized Cancer Therapy) trial. Patients had metastatic and/or unresectable incurable malignancies. Patients who were not evaluable were analyzed.

**Results.** Of consented patients, 44% were not evaluable. Men were twice as likely to be not evaluable as women. Prominently, 45% of patients who were not evaluable dropped off because of death, hospice referral, or decline in organ function.

**Conclusion.** Health deterioration of consented patients is a significant barrier to being evaluable on the I-PREDICT trial. These data suggest that patients are enrolled on precision oncology trials too late in their disease course or with excessive disease burden. *The Oncologist* 2020;25:e1803–e1806

## INTRODUCTION

Genome-driven cancer care is predicated on the presence of actionable alterations for which targeted therapies exist. Molecular profiling of tumors has become more common. Studies have demonstrated that profiling identifies actionable alterations in 40%–95% of patients [1–10]. However, only 5% to ~50% of eligible patients were treated with matched therapies [1–10].

Limited studies have explored this low rate of matching and treatment in precision oncology trials. Common barriers include the discretion of treating oncologists, access to drugs, and the timing of profiling in advanced disease [1–6]. The current study investigated patient attrition in the Investigation of molecular Profile-Related Evidence Determining Individualized Cancer Therapy (I-PREDICT) [10] trial.

## MATERIALS AND METHODS

### I-PREDICT Trial

The I-PREDICT trial (ClinicalTrials.gov Identifier: NCT02534675) uses genomic profiling to match patients to treatment [10]. Next-generation sequencing from Foundation Medicine profiled tumors (Cambridge, MA, <http://www.foundationmedicine.com>). These assays have been previously described [10]. Based on profiling results, a molecular tumor board recommended therapies to treating oncologists. All patients consented to an institutional review board–approved protocol.

### Participants

The first 190 enrolled patients, beginning February 13, 2015, at the University of California, San Diego Moore's Cancer

Correspondence: Razelle Kurzrock, M.D., Division of Hematology-Oncology, Moore's Cancer Center, University of California, San Diego, 3855 Health Sciences Drive, Mail Code 0658, La Jolla, California 92093-0658, USA. Telephone: 858-246-1102; e-mail: rkurzrock@health.ucsd.edu; or Jason K. Sicklick, M.D., Division of Surgical Oncology, Moore's Cancer Center, University of California, San Diego, 3855 Health Sciences Drive, Mail Code 0987, La Jolla, California 92093-0987, USA. Telephone: 858-822-3967; e-mail: jsicklick@health.ucsd.edu Received April 22, 2020; accepted for publication July 10, 2020; published Online First on October 2, 2020. <http://dx.doi.org/10.1002/onco.13532>

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**Table 1.** The I-PREDICT trial: characteristics of consented patients (University of California, San Diego site)

Parameter <sup>a</sup>	Evaluable	Not evaluable	Group difference, <i>p</i> value <sup>g</sup>	Univariable (not evaluable vs. evaluable), OR, 95% CI, <i>p</i> value <sup>g,h</sup>	Multivariable (not evaluable vs. evaluable), OR, 95% CI, <i>p</i> value <sup>g,h</sup>	Awaiting treatment <sup>i</sup>
Consented, <i>n</i> = 190 <sup>b</sup>	99 (52%)	83 (44%)				8 (4%)
Age, years			.51			
Median = 62 (range: 21–93)	62 (21–93)	63 (27–93)				59 (41–82)
<62, <i>n</i> = 94 (49%)	50 (53%)	39 (42%)		reference		5 (5%)
≥62, <i>n</i> = 96 (51%)	49 (51%)	44 (46%)		1.2, 0.6–2.1, .64		3 (3%)
Gender			<b>.04</b>			
Female, <i>n</i> = 112 (59%)	64 (57%)	41 (37%)		reference	reference	7 (6%)
Male, <i>n</i> = 78 (41%)	35 (45%)	42 (54%)		1.9, 1.0–3.4, <b>.04</b>	2.0, 1.1–3.9, <b>.03</b>	1 (1%)
Ethnicity/Race			.34			
White, <i>n</i> = 125 (66%)	68 (54%)	50 (40%)		0.8, 0.4–1.6, .56		7 (6%)
Hispanic, <i>n</i> = 22 (11%)	9 (41%)	13 (59%)		1.6, 0.6–4.6, .38		0
Other, <i>n</i> = 43 (23%) <sup>c</sup>	22 (51%)	20 (47%)		reference		1 (2%)
Tumor type <sup>d</sup>			.36			
Gastrointestinal, <i>n</i> = 103 (54%)	50 (49%)	49 (47%)		1.6, 0.8–3.1, <b>.16</b>	1.5, 0.8–2.9, .24	4 (4%)
Gynecological, <i>n</i> = 27 (14%)	13 (48%)	12 (45%)		1.5, 0.6–3.9, .39		2 (7%)
Other, <i>n</i> = 60 (32%)	36 (60%)	22 (37%)		reference	reference	2 (3%)
Treatment status before trial			.31			
Prior treatment, <i>n</i> = 123 (65%)	68 (55%)	51 (42%)		reference		4 (3%)
Treatment naïve, <i>n</i> = 67 (35%)	31 (46%)	32 (48%)		1.4, 0.7–2.5, .31		4 (6%)
Prior therapies <sup>e</sup>			.94			
Median = 2 (range: 1–11)	2 (1–11)	2 (1–7)				1 (1–4)
<2, <i>n</i> = 94 (49%)	28 (58%)	18 (38%)		reference		2 (4%)
≥2, <i>n</i> = 96 (51%)	40 (53%)	33 (44%)		1.3, 0.6–2.7, .52		2 (3%)
ECOG status <sup>f</sup>			.24			
0, <i>n</i> = 57 (30%)	33 (58%)	21 (37%)		reference		3 (5%)
≥1, <i>n</i> = 133 (70%)	66 (50%)	62 (46%)		1.5, 0.7–2.9, .24		5 (4%)
Death after consent						
<3 months, <i>n</i> = 33 (17%)	16 (48%)	17 (52%)	.45			0
<6 months, <i>n</i> = 56 (29%)	28 (50%)	28 (50%)	.43			0

Data are presented as *n* (%), unless otherwise stated.

<sup>a</sup>All parameters were from the time of consent.

<sup>b</sup>Only patients consented at the University of California, San Diego site. There was a total of 190 patients. These included 182 evaluable and not evaluable patients and 8 awaiting treatment.

<sup>c</sup>Includes non-Hispanic ethnicity of Asian, Black or African American, other, and declined to state races.

<sup>d</sup>Gastrointestinal tumor type includes 28 hepatobiliary and pancreatic cancers. Other tumor types are all tumor types other than gastrointestinal and gynecological. A detailed profile of tumor types is in supplemental online Table 1.

<sup>e</sup>Number of prior systemic therapies, including adjuvant or neoadjuvant, only among patients receiving prior treatment before enrollment in the I-PREDICT trial (*n* = 123, 65%).

<sup>f</sup>ECOG performance status.

<sup>g</sup>Comparison between evaluable and not evaluable patients; excludes eight patients awaiting treatment for less than 6 months.

<sup>h</sup>Association between not evaluable status and parameter. Parameters in the univariable analysis with *p* ≤ .2 were included in the multivariable analysis; evaluable status = outcome reference.

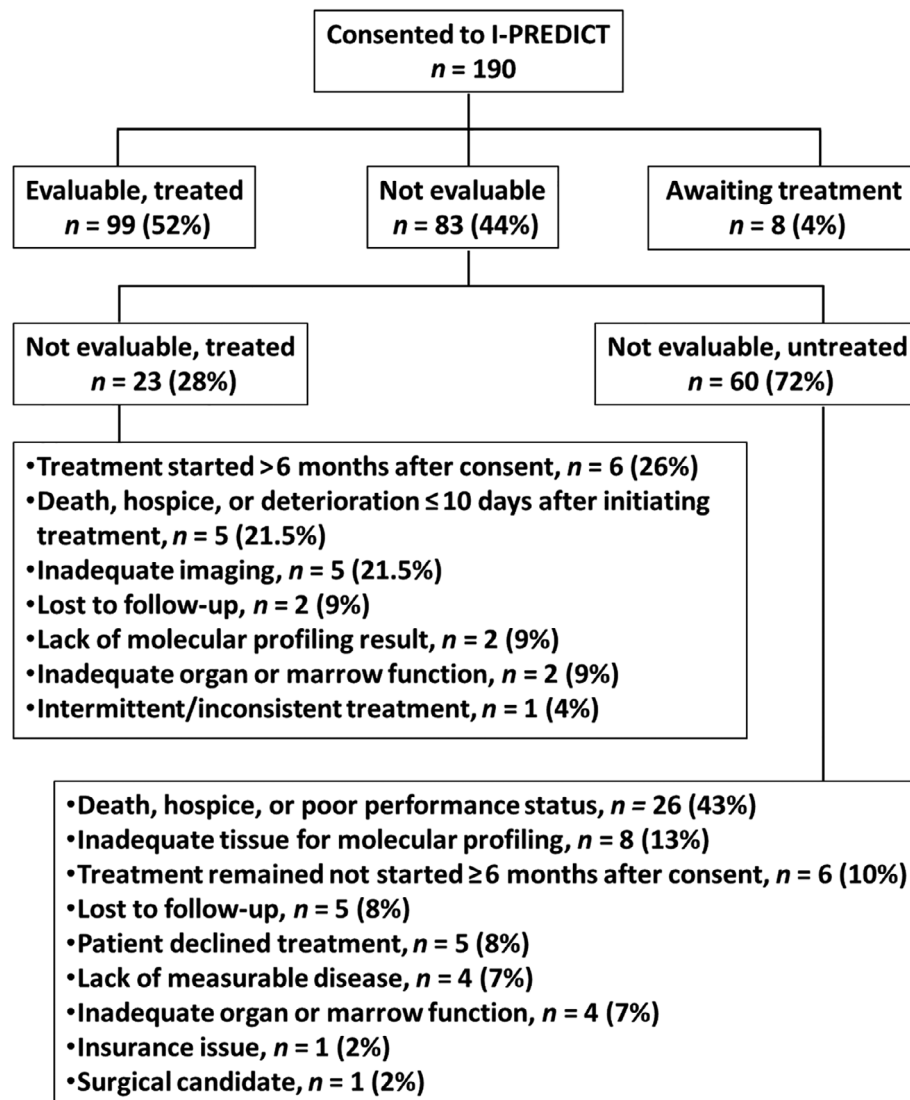
<sup>i</sup>Not yet determined whether evaluable or not evaluable as of September 26, 2017.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio.

Center site were included. Eligibility criteria for the I-PREDICT trial have been previously outlined [10]. Participants were adults (age ≥ 18 years) with an incurable metastatic or unresectable malignancy that was treatment naïve and with ≥50% 2-year mortality, or previously treated that had failed standard therapies or had no standard therapy.

## Data Analysis

A secondary analysis of the I-PREDICT trial data was performed. Demographic and clinicopathologic characteristics were described for patients who were not evaluable and those who were evaluable. Patients who were not evaluable were subdivided: untreated (since



**Figure 1.** Reasons for being not evaluable in the I-PREDICT trial (University of California, San Diego site).

consent) and treated (with  $\geq 1$  dose of anticancer drug after consent; see supplemental online Materials and Methods).

## RESULTS

### Patient Characteristics

Of the 190 total patients, the median age was 62 years (range: 21–93 years); 59% were women ( $n = 112$ ); and 66% were White ( $n = 125$ ). More than half had gastrointestinal cancers ( $n = 103$ , 54%). Most patients had received prior treatment ( $n = 123$ , 65%). Of these, the median number of prior lines of therapy was 2 (range: 1–11 therapies). At enrollment, 57 patients (30%) had excellent performance status. Overall, 56 patients (29%) died within 6 months, and 33 (17%) within 3 months of consent. In this cohort, 4% were awaiting treatment ( $n = 8$ ), 52% were evaluable ( $n = 99$ ), and 44% were not evaluable ( $n = 83$ ). Of the 83 patients who were not evaluable, 28% were treated ( $n = 23$ ) and 72% were untreated ( $n = 60$ ; Table 1; Fig. 1).

### Characteristics Associated with Being Not Evaluable

Of the 83 patients who were not evaluable, there were more men (54%) than women (37%;  $p = .04$ ). Patients with gastrointestinal cancer trended to be not evaluable ( $p = .16$ ). However, only gender was independently associated with not evaluable status; men were twice as likely to be not evaluable as women (odds ratio = 2.0, 95% confidence interval: 1.1–3.9,  $p = .03$ , multivariable analysis; Table 1).

### Reasons for Being Not Evaluable

The most common reason for being not evaluable was the deteriorating health of patients, which led to early discontinuation of treatment, hospice care, or death ( $n = 31$ , 37% of 83 patients who were not evaluable), plus another 7% who had inadequate organ function ( $n = 6$  of 83 patients). Hence, health decline explained 45% of patients who were not evaluable ( $n = 37$  of 83 patients). Treatment delays, usually for personal reasons, accounted for 14% of patients ( $n = 12$  of 83 patients). Only 12% experienced molecular profiling issues ( $n = 10$  of 83 patients), and 8% were lost to

follow-up ( $n = 7$  of 83 patients). Notably, only 1 patient had insufficient insurance coverage (1.2% of 83 patients; Fig. 1).

## DISCUSSION

Growing evidence indicates that matched molecularly targeted therapies may yield improved cancer outcomes [2, 4–7]. Nevertheless, most patients in precision medicine trials remain untreated/unmatched [1–10]. We explored patient attrition in the I-PREDICT trial, which uses genomic sequencing to navigate patients to therapy [10]. Of 190 consecutively enrolled patients, 44% were not evaluable ( $n = 83$ ). Only male gender was independently associated with not evaluable status ( $p = .03$ , multivariable analysis). Prominently, 45% of attrition ( $n = 37$  of the 83 patients who were not evaluable; 19% of 190 consented patients) was attributable to declining health. Other studies also reported that patients were frequently not evaluable on precision medicine trials because of death or hospice transfer [2, 4, 8–9].

Studies have also reported that patient access to matched clinical trials/therapies was hindered by extensive inclusion criteria, insurance denial, travel restrictions, and lack of available protocols [2, 5–7]. In contrast, only one I-PREDICT patient dropped off owing to lack of insurance coverage, and drug access was not a significant barrier in the I-PREDICT trial. Clinical trial navigators and medication acquisition specialists, who are devoted to ensuring that patients receive treatment, and a just-in-time molecular tumor board are incorporated into the workflow of the trial to circumvent these barriers.

The treatment rate in the I-PREDICT cohort was high for a precision medicine trial (52%). This may be partly explained by the few molecular profiling issues experienced in the I-PREDICT trial (5%,  $n = 10$  of 190 consented patients). In addition to the design features of the trial discussed above, identifying actionable alterations in I-PREDICT patients may have been facilitated by using a large gene panel as well as blood-based sequencing. Studies have shown that such assays can identify actionable alterations in up to 90% of patients [2, 4], suggesting that the treatment rate can still be improved.

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## CONCLUSION

Health deterioration of patients after consent is a significant barrier to being evaluable on the current genome-driven precision oncology trial (I-PREDICT) [10]. Studies should investigate tumor burden, pace of progression, and other features that might correlate with imminent worsening. Consideration should be given to ensuring that patients are enrolled on precision medicine studies before their condition is in rapid decline.

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## DISCLOSURES

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