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original reports abstract

Historic Clinical Trial External Control Arm Provides Actionable GEN-1 Efficacy Estimate Before a Randomized Trial

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PURPOSE To inform continued development of the novel immune agent GEN-1, we compared ovarian cancer patients' end points from a neoadjuvant single-arm phase IB study with those of similar historic clinical trial (HCT) patients who received standard neoadjuvant chemotherapy.

METHODS Applying OVATION-1 trial (ClinicalTrials.gov identifier: NCT02480374) inclusion and exclusion criteria to Medidata HCT data, we identified historical trial patients for comparison. Integrating patient-level Medidata historic trial data (N = 41) from distinct neoadjuvant ovarian phase I-III trials with patient-level OVATION-1 data (N = 18), we selected Medidata patients with similar baseline characteristics as OVATION-1 patients using propensity score methods to create an external control arm (ECA).

RESULTS Fifteen OVATION-1 patients (15 of 18, 83%) were matched to 15 (37%, 15 of 41) Medidata historical trial control patients. Matching attenuated preexisting differences in attributes between the groups. The median progression-free survival time was not reached by the OVATION-1 group and was 15.8 months (interquartile range, 11.40 months to nonestimable) for the ECA. The hazard of progression was 0.53 (95% CI, 0.16 to 1.73), favoring GEN-1 patients. Compared with ECA patients, OVATION-1 patients had more nausea, fatigue, chills, and infusion-related reactions.

CONCLUSION Comparing results of a single-arm early-phase trial to those of a rigorously matched HCT ECA yielded insights regarding comparative efficacy prior to a randomized controlled trial. The effect size estimate itself informed both the decision to continue development and the randomized phase II trial (ClinicalTrials.gov identifier: NCT03393884) sample size. The work illustrates the potential of HCT data to inform drug development.

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BACKGROUND

Clinical oncology drug development has historically started with phase I safety and toxicity studies, followed by either single-arm or multiarm phase II efficacy trials and finally by randomized controlled phase III trials where a standard of care is compared with the novel therapy. Randomized phase III clinical trials have been the dominant paradigm for establishing cancer drug efficacy in the United States, one that has been supported by a variety of stakeholders including federal regulators, payers, and physicians. Currently fewer than half of all phase III trials of promising phase II therapies reveal the experimental agent to be superior to the standard of care (ie, the control arm).[1,2] Developing methods to identify which phase I and II therapies have a higher likelihood of success in the phase III setting may minimize trial patients' morbidity and mortality, accelerate new drug development, lower research and development spending, and ultimately increase population health.

Novel methods in data science may be one way to accelerate the drug development cycle through comparative efficacy and safety evaluations of phase I and phase II patient outcomes relative to standard-of-care outcomes of patients from external control arms (ECAs). ECAs represent a collection of patients with the disease of interest who were treated outside of a clinical trial of interest (ie, target trial) and whose outcomes are compared with trial patients' outcomes to make comparative inferences about efficacy. ECAs have historically been assembled from diverse data sources including disease registries, clinical care data, billing claims, and historic clinical trial HCT data.[3,4] ECAs can provide actionable insights for therapies in instances where phase III trials are not possible (eg, ethical concerns or logistic reasons) and when phase

ASSOCIATED CONTENT

Data Supplement

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

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CONTEXT

Key Objective

We sought to contextualize results of an early-phase single-arm curative-intent trial of GEN-1 in ovarian cancer through comparison of GEN-1 patient outcomes with those of patients from historic clinical trial data via a statistically matched external control arm.

Knowledge Generated

The results informed the subsequent development of GEN-1.

Relevance

The relative importance of efficacy findings from early-phase studies of new therapies can be hard to estimate without internal comparators. External control arms composed of historic clinical trial data may support the traditional drug development paradigm.

III trials are possible (eg, early efficacy signals in advance of randomized trial results).[5,6]

For estimating comparative efficacy of drugs studied in early-phase trials, ECAs offer an advantage over static efficacy estimates from the medical literature because they allow contemporaneous comparisons which take into account differences between patients. Furthermore, comparisons of patients on experimental single-arm trials with ECAs of patients treated with standard-of-care therapies also through clinical trials attenuate differences in samples associated with trial enrollment. Balancing baseline patient prognostic factors across a target trial and an ECA via robust statistical methods for subsequent outcome comparison have been termed synthetic control arms.[4] The validity of such historic clinical trial (HCT) ECAs to replicate outcomes of control arms of distinct trials has been established.[5,6] This methodology has the potential to accelerate the drug development cycle through multiple efficiencies. Efficiencies include early inferences regarding both efficacy and safety parameters relative to standard-of-care therapies. These inferences have the potential to inform high-level sponsor decisions regarding continued development of the most promising products and the pathway to new drug development including regulatory body approval of Breakthrough Therapy or Fast Track designations for example.[7,8] Subsequent study design choices such as justification for sample size and power calculations, choice of efficacy end points, and design of eligibility criteria for future trials are also more fully supported, possibly leading to more successful clinical development programs overall. Enhancing control arms with HCT patients' data in the form of hybrid study designs may also accelerate the study life cycle through decreasing the required number of enrolling patients. Furthermore, such a hybrid control design means enrolling patients are more likely to receive the investigational therapy than the control therapy, a fact that may appeal to patients and providers and hasten trial accrual and completion.

A phase IB study was performed to determine the recommended phase II dose of neoadjuvant intraperitoneal (IP) GEN-1 in combination with standard-of-care parenteral neoadjuvant chemotherapy in patients with advanced stage epithelial ovarian cancer. After completion of the study, we compared trial patients' outcomes with those of patients from HCTs to inform whether there was sufficient evidence to justify continued clinical development of GEN-1. Specifically, we compared primary safety outcomes and secondary efficacy outcomes of women with newly diagnosed advanced stage ovarian cancer who were treated with neoadjuvant therapy on the phase I trial with similar women from a HCT ECA who received standard guideline-recommended therapy alone.

METHODS

Patient-level data from two distinct sources were used in this study of patients with newly diagnosed advanced epithelial ovarian cancer who received first-line curative-intent therapy in the clinical research setting. The OVATION-1 study was a single-arm phase IB dose-escalation trial of the safety and biological activity of IP GEN-1 administered in combination with standard neoadjuvant chemotherapy in patients newly diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer.[9] The final version of the data sets from the OVATION-1 study was transferred from Imunon to Medidata to allow comparison of patients with historic trial patients.

Clinical trial data from Medidata Data Fabric was studied to select standard-of-care control arm patients (ie, HCT ECA patients) for comparison with OVATION-1 patients. Medidata Data Fabric data are composed of data from the Rave international clinical trial platform. In the specific area of oncology, Rave hosted 29% of the world's industry-sponsored interventional trials of oncology drugs or biological agents during the study period.[10] We identified patients from completed clinical trials (ie, historic clinical trial data) within Medidata Data Fabric who met OVATION-1 trial eligibility criteria and were treated with a standard systemic chemotherapy regimen such as the regimen used

in OVATION-1. Specifically, we selected patients from Medidata Data Fabric trials who were age 18 years or older at diagnosis; had a diagnosis of previously untreated epithelial ovarian, fallopian tube, or primary peritoneal cancer; had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; had interval debulking surgery planned; and were assigned to receive one of two equally efficacious carboplatin and paclitaxel systemic chemotherapy regimens in the neoadjuvant setting on a Medidata trial (Table 1).[11-13] All patients with these attributes who were treated on a trial within Medidata data and available for study through data sharing agreements were included in the analyses. All selections of studies and patients were made without knowledge of outcomes for the historical patients or trials.

Key outcomes were primarily safety and secondarily efficacy. For all patients, the safety endpoint was operationalized by coding all adverse events to a system organ class and a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) taxonomy.[14] Only adverse events occurring after the first dose date of any study treatment were included. All patients had been monitored for progression, and the percentages of patients experiencing each type of event were reported according to OVATION-1 versus HCT ECA status. Efficacy endpoints were progression-free survival (PFS) (ie, time to ovarian cancer progression or death from any cause) and overall survival (OS). Of note, the prior publication of the OVATION-1 clinical trial results reported endpoints on all 18 patients.[9] In these analyses, OVATION-1 patients were included if they were able to be matched to a HCT patient. This leaves the possibility that fewer than 18 patients would be studied and thus that end point reports would differ from those of the clinical trial report.[9]

TABLE 1. OVATION-1 Trial Eligibility Criteria Applied to Historic Clinical Trial Patients

Inclusion Criteria for Historic Clinical Trial ECA Patients
Women age 18 years or older
ECOG PS of ≤ 2
Advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer
Previous untreated
Planned for interval debulking surgery
Assigned to one of two 21-day neoadjuvant treatment regimens of carboplatin and paclitaxel with an intended duration of six cycles:
Day 1 carboplatin AUC 5 or 6 IV and day 1, 8, 15 paclitaxel 80 mg/m^2
Day 1 carboplatin AUC 5 or 6 IV and paclitaxel 175 mg/m^2

NOTE. Eligibility criteria for identification of potential historic clinical trial ECA patients. Selection criteria mirror both the patient eligibility criteria OVATION-1 and the standard systemic therapy component of the OVATION-1 anticancer treatment regimen.

Abbreviations: AUC, area under the curve; ECA, external control arm; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous.

After identifying candidate historic clinical trial ECA patients on the basis of eligibility requirements for OVATION-1, we used a two-step approach to (1) construct the ECA and (2) compare ECA and OVATION-1 patients with respect to efficacy and safety endpoints. To construct the ECA, we standardized and appended patient-level historic clinical trial data to OVATION-1 data and modeled treatment group membership (ie, OVATION-1 *v* HCT) as a function of prognostically important baseline demographic and disease variables with a logistic regression. These variables were age, race (Caucasian *v* non-Caucasian or unknown), ECOG performance status, body mass index (BMI), Federation of Gynecology and Obstetrics (FIGO) stage of disease, days from ovarian cancer diagnosis and treatment, and the natural log of serum cancer antigen-125 (CA-125) values. We then used the model to estimate the probability of being a member of the OVATION-1 treatment group (ie, the propensity score).

We used the propensity score to match OVATION-1 patients to historic trial patients using greedy nearest-neighbor matching without replacement at a fixed 1:1 ratio. Using Rosenbaum's recommended caliper width of ≤ 0.25 of the pooled standard deviation of logit of the propensity score from the two groups, OVATION-1 patients were matched to HCT patients whose propensity score was closest within the prespecified caliper.[15] By selecting patients for comparison on the basis of their propensity scores, prognostically important covariates are more closely balanced in the two groups (reducing baseline differences) increasing the likelihood that any difference in outcomes between the groups is reliably attributable to the investigational product. The Data Supplement contains a more detailed description of the propensity score methods applied to these data.

We employed an intent-to-treat approach to compare treatment groups. We compared demographic and disease attributes using descriptive statistics; for continuous variables, we describe the number of observations, mean, standard deviation, median, minimum, and maximum, and for dichotomous endpoints, we describe the frequency and percentage for each category. The key outcomes for this study were safety, preliminary antitumor activity, and immunological response to IP GEN-1 in combination with neoadjuvant carboplatin and paclitaxel parenteral chemotherapy in patients with advanced epithelial ovarian cancer. We summarized the subject incidence rate of adverse events in MedDRA preferred terms to describe safety outcomes. Secondary efficacy endpoints of interest were PFS and OS survival. Comparison of treatment groups according to secondary endpoints were carried out with Kaplan-Meier curves and two-sided log-rank tests. Hazard ratios (HRs) between the two groups and the 95% CIs were estimated using a Cox proportional hazard regression model.

All analyses were prespecified in a statistical analysis plan. All analyses were performed using SAS (version 9.4). Legal agreements with the sponsors of the HCTs and Medidata mandate deidentification of the historical control data and aggregation (ie, every analysis must include data from two or more sponsors). All patients treated signed informed consent for receipt of experimental treatment and analysis of associated data. All patients studied had consented to treatment in a clinical trial. The OVATION-1 study was reviewed and approved by the institutional review boards at the four participating institutions. This subsequent study of existing deidentified data from historic clinical trial patients does not meet the definition of human subjects' research and thus did not require institutional review board review under the 2018 revision of 45 Code of Federal Requirements §46.[16]

RESULTS

The OVATION-1 trial enrolled 18 patients from four sites in the United States in 2015. An intent-to-treat analysis was defined to include all enrolled subjects and was the primary population for description of baseline subject characteristics and analysis of efficacy end points. The historic clinical trial ECA was constructed by matching this population. After applying OVATION-1 eligibility criteria to the Medidata database, 41 potential ECA patients were identified from up to five phase II and III trials enrolling patients from multiple countries in 2015-2016. Table 2 describes the extent to which patient demographic and disease attributes varied according to the treatment group (ie, OVATION-1 patients vs Medidata HCT patients) before propensity score matching. Compared with Medidata patients, OVATION-1 patients were slightly older, had higher ECOG scores and BMIs, had lower FIGO stages and natural log of CA-125 values, and had fewer days between cancer diagnosis and treatment.

Through propensity score matching, 15 (15 of 18, 83%) OVATION-1 patients were matched at a 1:1 ratio to 15 (37%, 15 of 41) Medidata historic trial control patients (Fig 1). The remaining three (17%) unmatched OVATION-1 patients were removed from further analysis. The 15 Medidata historic trial control patients represent the HCT ECA. The postmatching cohort composition (Table 2) shows that differences in age, performance status, BMI, FIGO stage, CA-125 values, and time since cancer diagnosis by treatment group noted before matching attenuated after propensity score-driven control patient selection. Figure 2 illustrates the standardized mean differences in the propensity score (and all baseline characteristics examined) within prematched and postmatched samples. After matching, the standardized mean differences were reduced to < 0.25, a commonly used rule of thumb for declaring acceptable balance between groups (Fig 2).[15,17]

With respect to safety endpoints, the number of patients with at least one MedDRA adverse event was 14 (93.3%) of 15 in OVATION-1 patients and 15 (100%, 15 of 15) in the Medidata historic clinical trial ECA patients. Compared with historic clinical trial ECA patients, OVATION-1 patients had a slightly higher incidence in nausea (OVATION-1, 73.3%; ECA, 53.3%), fatigue (OVATION-1, 73.3%; ECA, 33.3%), anorexia (OVATION-1, 46.7%; ECA, 13.3%), chills (OVATION-1, 26.7%; ECA, 6.7%), and infusion-related reaction

TABLE 2. Attributes of OVATION-1 and Prematching and Postmatching Historic Clinical Trial Patients

	Before Matching (N = 59)		After Matching (n = 30)	
Baseline Variables	**OVATION-1 (N = 18)**	**Historic Trial Control (N = 41)**	**OVATION-1 (n = 15)**	**Historic Trial ECA (n = 15)**
ECOG score, No. (%)				
0	6 (33.3)	20 (48.8)	6 (40.0)	7 (46.7)
1	10 (55.6)	20 (48.8)	8 (53.3)	8 (53.3)
2	2 (11.1)	1 (2.4)	1 (6.7)	0 (0.0)
Race, No. (%)				
White	15 (83.3)	34 (82.9)	13 (86.7)	13 (86.7)
FIGO stage III, No. (%)	12 (66.7)	25 (61.0)	9 (60.0)	9 (60.0)
Age at baseline, years, mean (SD)	64.5 (7.5)	62.2 (11.1)	62.8 (7.0)	63.3 (10.7)
BMI, kg/m^2, mean (SD)	30.4 (6.6)	27.6 (7.4)	29.5 (6.1)	30.4 (9.0)
ln(CA-125), U/mL,[a] mean (SD)	6.4 (0.9)	6.7 (1.1)	6.5 (0.7)	6.6 (1.1)
Days since cancer diagnosis, mean (SD)	10.1 (4.8)	16.9 (11.4)	8.9 (3.9)	8.6 (6.8)

NOTE. Comparison of attributes of patients in OVATION-1 trial and candidate ECA patients before and after propensity score selection of OVATION-1 analytic sample and ECA patients.

Abbreviations: BMI, body mass index; CA-125, cancer antigen-125; ECA, external control arm; ECOG, Eastern Cooperative Oncology Group; FIGO, Federation of Gynecology and Obstetrics; SD, standard deviation.

[a]ln(CA-125) = natural log of patient CA-125 value in units per milliliter.

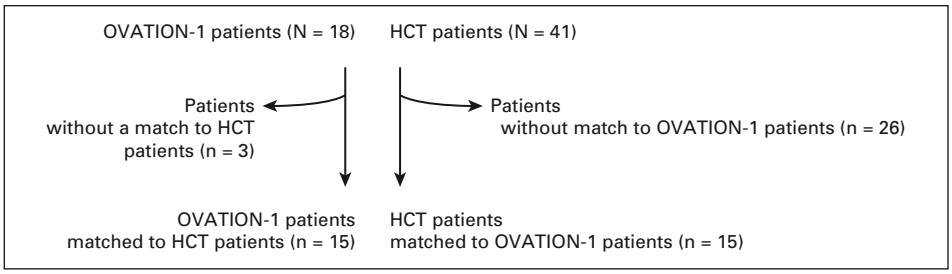

FIG 1. Comparative cohort selection OVATION-1 and HCT patients. Selection of OVATION-1 patients and HCT patients meeting OVATION-1 eligibility criteria via propensity score methods to allow comparison of outcomes after neoadjuvant therapy for advanced epithelial ovarian cancer. HCT, historical clinical trial.

(OVATION-1, 26.7%; ECA, 0%). Table 3 contains results of all comparisons of adverse events.

With respect to efficacy end points, the percentage of patients without progression and/or death events at 2 years was 69.5% (95% CI, 36.5 to 87.7) for the OVATION-1 group and 48.5% (95% CI, 20.4 to 71.9) for the HCT ECA. The median PFS time is not estimable for the OVATION-1 group since its survival probability was maintained above 50% at the end of the observation period; the median PFS time was 15.8 months (interquartile range, 11.40 months to nonestimable) for the HCT ECA (Fig 3). The HR of PFS for the OVATION-1 group relative to HCT ECA was 0.53 (95% CI, 0.16 to 1.73). The median OS time was 34.3 months for the OVATION-1 group and 40.2 months for the HCT ECA. The HR of OS for the OVATION-1 group relative to the HCT ECA was 0.85 (95% CI, 0.26 to 2.80). Figure 3 contains the Kaplan-Meier curve of PFS by matched treatment groups.

DISCUSSION

We found treatment with neoadjuvant IP GEN-1 immunotherapy in combination with standard systemic neoadjuvant chemotherapy in the phase IB OVATION-1 trial was associated with a more favorable PFS point estimate when compared with a HCT ECA composed of similar women with ovarian cancer who had received the same systemic standard neoadjuvant chemotherapy in prior clinical trials. These insights have immediate implications for the development of GEN-1 and also more broadly for the drug development process.

With respect to GEN-1, this study both reinforced the sponsor's decision to pursue a phase II study and the way in which they pursued it. That is, this early information about GEN-1's possible comparative treatment advantage over a standard-of-care regimen both informed the decision to continue development of GEN-1 under FDA Fast Track designation and provided practical information regarding trial design including the appropriate number of patients to enroll in the subsequent randomized phase II trial. In this case, the HCT ECA comparison yielded an effect size estimate which was larger than that which would have otherwise been conservatively employed to design the randomized

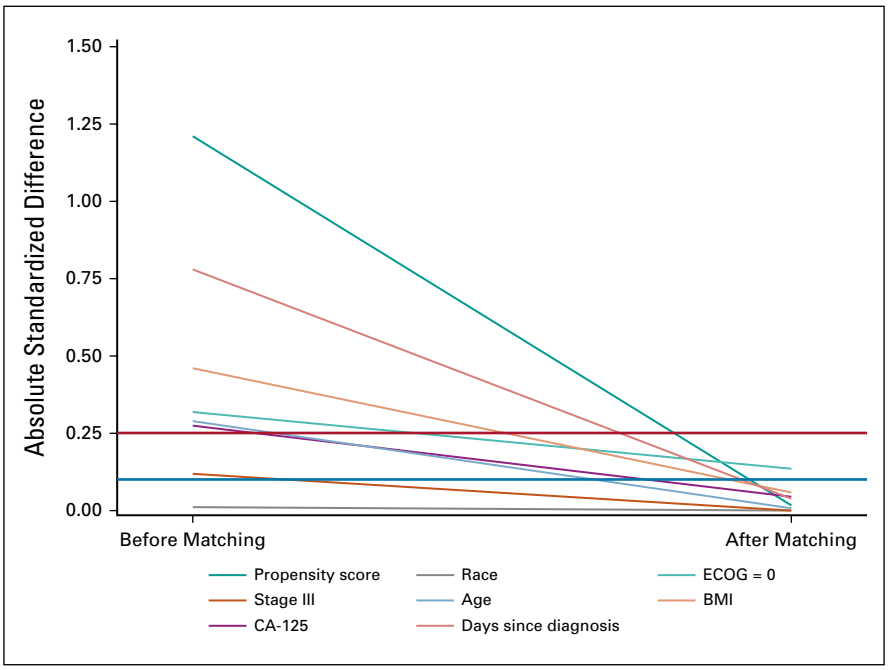

FIG 2. Evaluation of covariate balance between OVATION-1 and historical clinical trial external control arm patient groups before and after propensity score matching. Thick horizontal lines indicate the standardized difference of acceptable threshold 0.25 (red) and negligible threshold 0.10 (black). BMI, body mass index; CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group.

TABLE 3. Incidence of Adverse Event by Treatment Group (n = 30)

Preferred Term	Matched OVATION Group (n = 15), No. (%)	Historic Clinical Trial ECA (n = 15), No. (%)
Any AE	14 (93.3)	15 (100.0)
Nausea	11 (73.3)	8 (53.3)
Fatigue	11 (73.3)	5 (33.3)
Constipation	9 (60.0)	7 (46.7)
Neutropenia	8 (53.3)	9 (60.0)
Anemia	8 (53.3)	8 (53.3)
Diarrhea	7 (46.7)	10 (66.7)
Abdominal pain	7 (46.7)	7 (46.7)
Vomiting	7 (46.7)	7 (46.7)
Decreased appetite	7 (46.7)	2 (13.3)
Alopecia	5 (33.3)	6 (40.0)
Thrombocytopenia	5 (33.3)	4 (26.7)
Pyrexia	5 (33.3)	3 (20.0)
Dyspnea	5 (33.3)	2 (13.3)
WBC count decreased	4 (26.7)	2 (13.3)
Chills	4 (26.7)	1 (6.7)
Infusion-related reaction	4 (26.7)	0 (0.0)
Cough	3 (20.0)	5 (33.3)
Peripheral sensory neuropathy	3 (20.0)	4 (26.7)
Hypomagnesaemia	3 (20.0)	3 (20.0)
Neutrophil count decreased	3 (20.0)	3 (20.0)
Dysgeusia	3 (20.0)	2 (13.3)
Dizziness	3 (20.0)	1 (6.7)
Myalgia	3 (20.0)	1 (6.7)
Blood creatinine increased	3 (20.0)	0 (0.0)
Hypokalemia	2 (13.3)	5 (33.3)
Hyperglycemia	2 (13.3)	3 (20.0)
Hypertension	2 (13.3)	3 (20.0)
Pain	2 (13.3)	3 (20.0)
Weight decreased	2 (13.3)	3 (20.0)
Hypersensitivity	2 (13.3)	2 (13.3)
Leukopenia	2 (13.3)	2 (13.3)
Platelet count decreased	2 (13.3)	2 (13.3)
Rash	2 (13.3)	2 (13.3)
ALT increased	2 (13.3)	1 (6.7)
AST increased	2 (13.3)	1 (6.7)
Epistaxis	2 (13.3)	1 (6.7)
Hot flush	2 (13.3)	1 (6.7)
Hyponatremia	2 (13.3)	1 (6.7)
Abdominal distension	2 (13.3)	0 (0.0)
Dehydration	2 (13.3)	0 (0.0)
Muscular weakness	2 (13.3)	0 (0.0)

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TABLE 3. Incidence of Adverse Event by Treatment Group (n = 30) (Continued)

Preferred Term	Matched OVATION Group (n = 15), No. (%)	Historic Clinical Trial ECA (n = 15), No. (%)
Palpitations	2 (13.3)	0 (0.0)
Sinus disorder	2 (13.3)	0 (0.0)
Headache	1 (6.7)	3 (20.0)
Urinary tract infection	1 (6.7)	3 (20.0)
Arthralgia	1 (6.7)	2 (13.3)
Asthenia	1 (6.7)	2 (13.3)
Depression	1 (6.7)	2 (13.3)
Dyspepsia	1 (6.7)	2 (13.3)
Hypocalcemia	1 (6.7)	2 (13.3)
Vaginal hemorrhage	1 (6.7)	2 (13.3)
Back pain	0 (0.0)	8 (53.3)
Abdominal pain upper	0 (0.0)	2 (13.3)
Dry skin	0 (0.0)	2 (13.3)
Dysuria	0 (0.0)	2 (13.3)
Insomnia	0 (0.0)	2 (13.3)
Limb discomfort	0 (0.0)	2 (13.3)
Malaise	0 (0.0)	2 (13.3)
Mucosal inflammation	0 (0.0)	2 (13.3)
Muscle spasms	0 (0.0)	2 (13.3)
Musculoskeletal pain	0 (0.0)	2 (13.3)
Nasopharyngitis	0 (0.0)	2 (13.3)
Polyneuropathy	0 (0.0)	2 (13.3)
Procedural pain	0 (0.0)	2 (13.3)
Stomatitis	0 (0.0)	2 (13.3)
Urinary incontinence	0 (0.0)	2 (13.3)
Weight increased	0 (0.0)	2 (13.3)

NOTE. The table is shown by AE incidence rates in descending order of the matched OVATION-1 group.
Abbreviations: AE, adverse event; ECA, external control arm.

phase II trial, a fact that led to a follow-up trial requiring 20 fewer patients than originally planned.

More broadly, the research shows that historic clinical trials can be meaningfully used to allow early-phase trials to yield greater information. That is, a comparative clinical trial ECA may facilitate preliminary quantitative understandings of primary safety and secondary efficacy end points from early-phase trials well in advance of a phase III trial. Of critical importance to the approach is the data source studied. Studying patient outcomes from HCT data offers advantages over traditional real-world data ECAs through mitigating bias associated with patient enrollment on clinical trials and the uniformity of protocol-specified methods. Taken together, the findings suggest that HCT ECAs may accelerate the drug development cycle under certain circumstances in a manner that minimizes bias in cohort selection, provides uniformity in data collection through electronic case report forms, and relies on canonical efficacy and toxicity metrics.

There are limitations to the study. The research studied exclusively patients within Medidata Data Fabric data and thus findings may not be generalizable to studies that do not use the Rave platform. OVATION-1 was carried out in the United States, and the candidate ECA pool included patients from four countries. Given that OVATION-1 was a phase IB study, the study's goal was primarily of safety and thus was not powered for efficacy comparisons with ECAs like the HCT ECA developed and studied in this research. Further because results of OVATION-1 were intended to inform the phase II dose, the protocol-defined radiologic evaluation cadence ended with the end of experimental therapy (approximately 6 months from initial treatment) which differed from candidate SCA studies (ie, phase II and phase III studies) where efficacy

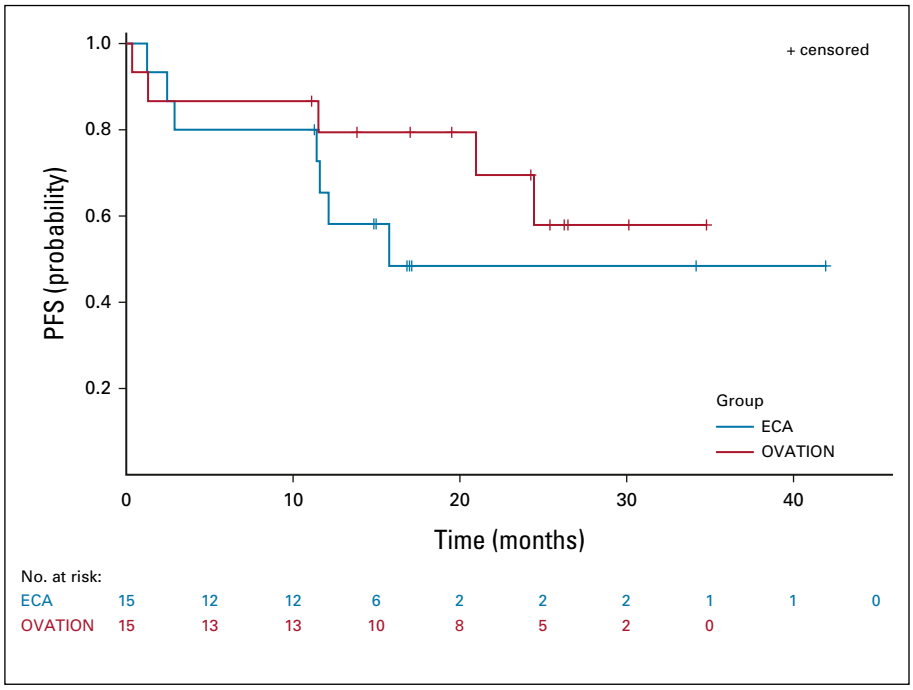

FIG 3. PFS of matched OVATION-1 and historical clinical trial ECA patients (n = 30). Intent-to-treat product limit PFS time estimates of patients with ovarian cancer after first-line neoadjuvant treatment with either combination intraperitoneal GEN-1 and systemic chemotherapy therapy (OVATION-1 patients) or systemic chemotherapy therapy alone (ECA patients). ECA, external control arm; PFS, progression-free survival.

was a key endpoint and all patients were followed with radiologic imaging for 5 years in the absence of relapse or death potentially introducing bias in favor of the alternative hypothesis. The small sample size limits precision of parameter estimates and the CIs for HRs are wide. That is, the study was underpowered to find significant differences in key endpoints. Similarly, because there are few deaths in this small curative-intent trial, the OS estimates are not robust and their reports or estimates of the hazard of death may be misleading. Because patients were not randomly assigned to GEN-1 versus standard of care within a single study, it is possible that unmeasured confounders at the patient, provider, and/or health center level may account for the observed differences between groups. Relatedly, that patients in the two groups were treated in accordance with distinct protocols, follow-up time was not uniform across the groups raising caution in interpretation of HRs. Finally, although observable covariates were generally well-balanced across the two treatment groups, any unmeasured confounders that are not correlated with measured covariates may bias the results.

In conclusion, we found that a HCT ECA provided insights regarding the potential comparative toxicity and efficacy of GEN-1, a novel immunotherapy, in advance of a randomized controlled phase III trial. Such findings have the potential to complement randomized trials and inform drug development decisions (eg, regulatory pathways such as Fast Track designation, subsequent study design including effect sizes for efficacy and safety end points). The results of comparisons of early-stage single-arm trials with HCT ECAs may yield actionable insights in advance of phase III results, something which may increase the scientific value of early-phase trials through improved decision making and accelerated new drug development.

AFFILIATIONS

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PRIOR PRESENTATION

Presented as a poster at American Association for Cancer Research (AACR) annual meeting, New Orleans, LA, April 11, 2022 and at American Association for Cancer Research annual meeting 2022, Philadelphia, PA, April 8-13, 2022 (abstr 1025).

SUPPORT

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AUTHOR CONTRIBUTIONS

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