Abstract #1025

Phase IB Trial Efficacy Estimates via a Clinical Trial Synthetic Control Arm

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ABSTRACT

Background

To inform further development of the novel agent GEN-1, we compared patient outcomes from an early single-arm phase trial of GEN-1 plus standard chemotherapy in ovarian cancer to those of similar historical clinical trial patients treated with standard chemotherapy alone.

Methods

Applying OVATION-1 trial (N=18) inclusion and exclusion criteria to the Medidata Enterprise Data Store (MEDS) data, we identified candidate historical trial patients for comparison (N=41). With propensity score methods we identified just those MEDS patients who most resembled OVATION-1 patients to form a synthetic control arm (SCA).

Results

Fifteen OVATION-1 patients (15/18, 83%) were matched to 15 (37%, 15/41) MEDS historical trial patients. The median PFS time was not reached by OVATION-1 patients and was 15.8 months for the SCA patients (HR 0.53, 95% CI 0.16, 1.73). The toxicity experience was similar in both groups.

Conclusion

Comparing early phase trial results to a historical clinical trial SCA provided informative estimates of efficacy and toxicity which informed GEN-1's subsequent development in ovarian cancer.

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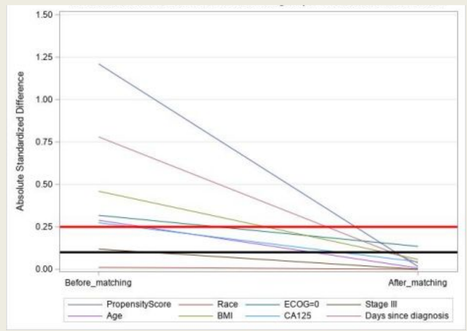
INTRODUCTION

Innovations in data science and trial design have catalyzed novel clinical research methods which may inform the future success of new experimental therapies more efficiently than previously believed. To direct development of the novel immune agent GEN-1 in advance of a randomized controlled trial, we compared endpoints experienced by patients from a recent neoadjuvant single-arm phase IB study of GEN-1 plus standard neoadjuvant chemotherapy (OVATION-1, NCT02480374)[1] to those of similar historical clinical trial patients in receipt of standard neoadjuvant chemotherapy alone.

METHODS AND MATERIALS

To compare safety and efficacy endpoints following first-line neoadjuvant weekly intraperitoneal GEN-1 immunotherapy with systemic carboplatin and paclitaxel to standard first-line systemic neoadjuvant carboplatin and paclitaxel in women with advanced ovarian cancer, we applied key OVATION-1 trial (NCT02480374) inclusion and exclusion criteria to the Medidata Enterprise Data Store (MEDS) data to identify candidate historical clinical trial patients for comparison. We standardized and integrated patient-level MEDS data (N=41) from distinct phase I-III trials (enrollment years 2015-2016) with patient-level OVATION-1 data (N=18). We used standard propensity score methods to identify MEDS patients who appeared similar to OVATION-1 patients to create a synthetic control arm (SCA).

Figure 1. Evaluation of Covariate Balance Pre- and Post-Matching



Legend: Plot of standardized differences before and after matching. Thick horizontal lines indicate the standardized difference of acceptable threshold 0.25 (red) and negligible threshold 0.10 (black).

RESULTS

Fifteen OVATION-1 patients (15/18, 83%) were matched to 15 (37%, 15/41) MEDS historical trial control patients. Matching attenuated pre-existing differences in attributes between the OVATION-1 and MEDS patients. The median progression-free survival time was not reached by the OVATION-1 group and was 15.8 months for the SCA. The hazard of progression for the OVATION-1 group relative to the SCA was 0.53 (95% CI 0.16, 1.73). Fourteen of 15 OVATION-1 patients (93.3%) and all 15 of the SCA patients (100%, 15/15) had at least one MedDRA toxicity. Compared to SCA patients, OVATION-1 patients had a higher incidence in nausea (OVATION-1 73.3%; SCA 53.3%), fatigue (OVATION-1 73.3%; SCA 33.3%), anorexia (OVATION-1 46.7%; SCA 13.3%), chills (OVATION-1 26.7%; SCA 6.7%), and infusion-related reaction (OVATION-1 26.7%; SCA 0%).

Table. Attributes of OVATION-1 and Historic Clinical Trial Patients

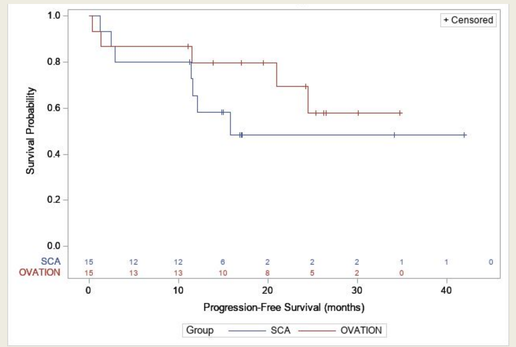
.	Before Matching		After Matching	
	OVATION-1	Historic Trial	OVATION-1	SCA
Variables	**N=18**	**N=41**	**N=15**	**N=15**
ECOG=0*	6 (33%)	20 (49%)	6 (40%)	7 (47%)
White Race	15 (83%)	34 (83%)	13 (87%)	13 (87%)
Stage III	12 (67%)	25 (61%)	9 (60%)	9 (60%)
Age (mean, +/- SD)	64.5 +/- 7.5	62.2 +/- 11.1	62.8 +/- 7.0	63.3 +/- 10.7
BMI (mean, +/- SD)	30.4 +/- 6.6	27.6 +/- 7.4	29.5 +/- 6.1	30.4 +/- 9.0
ln(CA-125) (mean, +/- SD)	6.4 +/- 0.9	6.7 +/- 1.1	6.5 +/- 0.7	6.6 +/- 1.1
Days Since Dx (mean, +/- SD)	10.1 +/- 4.8	16.9 +/- 11.4	8.9 +/- 3.9	8.6 +/- 6.8

Legend. Comparison of attributes of patients in OVATION-1 trial and candidate SCA patients prior to and following propensity score selection of OVATION-1 analytic sample and SCA patients.
*Patient ECOG scores were ≤ 2.
SCA = synthetic control arm; ECOG = Eastern Cooperative Oncology Group performance status; +/- SD = plus or minus one standard deviation; BMI = body mass index in kilograms per meter squared; ln(CA-125) = natural log transformation of cancer antigen 125 (U/ml)

DISCUSSION

The comparison of patient endpoints from a single-arm phase IB trial to a historical clinical trial SCA yielded estimates of efficacy endpoints which informed a decision to continue development of GEN-1 and the design of the subsequent randomized phase II trial. Specifically, the effect size estimate led to a decrease in the number of planned patients for the subsequent randomized phase II trial (NCT 03393884).[2]

Figure 2. PFS of Matched OVATION-1 and SCA Patients (N=30)



Legend: Intent-to-treat product-limit progression-free survival time estimates of patients with ovarian cancer following first-line neoadjuvant treatment with intraperitoneal GEN-1 and systemic chemotherapy therapy (OVATION-1 patients) vs systemic chemotherapy therapy alone (SCA patients). SCA = synthetic control arm.

CONCLUSIONS

More broadly, this approach supports the ability of historical clinical trial patient comparisons to inform drug development via novel trial design, something which may further increase the scientific value of early phase trials.

REFERENCES

1. Thaker PH, Bradley WH, Leath CA, Jackson CG, Borys N, Anwer K, Musso L, Matsuzaki J, Bshara W, Odunsi K, Alvarez RD. GEN-1 in combination with neoadjuvant chemotherapy for patients with advanced epithelial ovarian cancer: a phase I dose-escalation study. Clin Cancer Res 2021.
2. Study of GEN-1 With NACT for Treatment of Ovarian Cancer (OVATION 2) https://clinicaltrials.gov/ct2/show/NCT03393884