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A Phase II Randomized, Double-Blind Trial of a Polyvalent Vaccine-KLH Conjugate (NSC 748933 IND# 14384) + OPT-821 versus OPT-821 in Patients with Epithelial Ovarian, Fallopian Tube, or Peritoneal Cancer Who Are in Second or Third Complete Remission: An NRG Oncology/GOG study

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AUTHOR CONTRIBUTION

All authors provided data, were involved in writing the manuscript as well as the critical review of this manuscript and approved the final manuscript. Dr. Wei Deng performed the statistical analyses of this study. Dr O'Cearbhaill and Dr Sabbatini wrote the manuscript.

CONFLICTS OF INTEREST

The authors wish to report that they have no Conflicts of interest with the exception of Dr. O'Cearbhaill who wishes to report that she has received personal fees from Clovis for serving on an Advisory Board in 2016, from Tesaro for serving on an Advisory Board in both 2017 and 2018 and from GlaxoSmithKline for serving on an Advisory Board in 2019, outside the submitted work. Dr. Benigno wishes to report that he is a member of the Speaker Bureau for AstraZeneca, Tesaro and Clovis. Dr. Powell reports personal fees from Tesaro, personal fees from Merck, personal fees from Roche/Genentech, personal fees from Clovis Oncology, personal fees from AstraZeneca and personal fees from Johnson & Johnson, outside the submitted work. Dr. Aghajanian reports personal fees from Tesaro, personal fees from Immunogen, personal fees from Clovis, personal fees from Mateon Therapeutics, personal fees from Cerulean Pharma, outside the submitted work. Dr. Sabbatini reports grants from BMS, during the conduct of the study.

Trial registration:

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Abstract

Objective: Early-phase data have demonstrated induction of antibody responses to a polyvalent vaccine conjugate (Globo-H, GM2, MUC1-TN, TF) with adjuvant OPT-821. We sought to determine if this combination decreases the hazard of progression or death compared to OPT-821 alone in patients with ovarian cancer in second/third clinical complete remission following chemotherapy. Secondary and translational objectives were overall survival (OS), safety, and immunogenicity.

Methods: From 2010–2013, patients were randomized (1:1) to receive OPT-821±vaccine-KLH conjugate subcutaneously at weeks 1, 2, 3, 7, 11, and then every 12 weeks (total 11). Dose delay or reduction was not permitted. Patients were removed for pre-defined dose-limiting toxicity.

Results: Of 171 patients randomized, 170 were treated. Most had disease of serous histology (85%), stage 3 disease at diagnosis (77%), and had received 2 prior regimens (68%). 32% received >6 treatment cycles [median 6, each arm (p=0.33)]. 77% discontinued due to progression, 4% due to toxicity, and 1 due to myeloid dysplastic syndrome (MDS). Maximum toxicity was grade 4 MDS and depression/personality change (1 each, unlikely related) and others including grade 3 gastrointestinal disorders (n=21, 4 related). Lesser adverse events were injection site reactions (82%) and fever (11%). Estimated HR for progression-free survival (PFS) of the vaccine+OPT-821 to OPT-821 arm was 0.98 (95% CI: 0.71–1.36). At a median follow-up of 60 months, median OS was 47 and 46 months, respectively.

Conclusions: Vaccine+OPT-821 compared to OPT-821 alone was modestly immunogenic and did not prolong PFS or OS. Multi-remission patients are a viable, well-defined population for exploring innovative consolidation and maintenance approaches.

Keywords

Randomized; Vaccine; Ovarian; Remission

INTRODUCTION

Many patients with advanced-stage serous ovarian carcinoma will enter a complete remission following the completion of cytoreductive surgery and platinum-based chemotherapy. The majority of patients will relapse, although a proportion will experience a second or later complete clinical remission with additional chemotherapy. [1] Each subsequent remission tends to be of shorter duration until broad chemotherapy resistance develops. [2] Effective maintenance strategies to prevent relapse or prolong remission are needed.

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Both antibodies and anti-tumoral T cells have been associated with longer survival in patients with epithelial ovarian cancer. [3] Ovarian cancers express a rich array of cell-surface antigens including carbohydrate epitopes such as GM2, Globo-H Lewis, sialyl Tn, Tn, Thompson Friedrich antigen (TF) and mucin 1 (MUC1). [4] Preclinical data supports the hypothesis that polyvalent vaccines will likely be required due to tumor heterogeneity as well as heterogeneity of the immune response. Chemical conjugation of antigens to an immunogenic carrier protein and the use of a potent immunological adjuvant has previously been shown to generate antibodies against defined cell-surface antigens. Keyhole limpet hemocyanin (KLH) is a highly immunogenic carrier protein. A phase I study previously demonstrated the safety and humoral immunogenicity of a polyvalent vaccine-KLH conjugate with the immunological adjuvant QS-21 in patients with ovarian, fallopian tube, or peritoneal cancer in remission. [4]. OPT-821 is an immunological adjuvant that is derived from the same soapbark tree *Quillaja saponaria* as QS-21. The purpose of this multicenter Gynecologic Oncology Group (GOG) 255 study was to determine if the polyvalent vaccine-KLH conjugate (including Globo-H-KLH, GM2-KLH, Tn-MUC1–32mer-KLH, TF-KLH) given with adjuvant OPT-821 (KLH+OPT-821) versus OPT-821 alone (OPT-821) could prolong progression-free survival (PFS) or overall survival (OS) in patients with epithelial ovarian cancer in a second or third complete clinical remission. OPT-821, was selected as the control arm to test if non-specific immune stimulation by an adjuvant was similar in outcome to a more targeted immunization with polyvalent vaccine-KLH+OPT-821.

MATERIALS AND METHODS

Eligibility Criteria

Patients with histologically documented epithelial carcinoma arising in the ovary, fallopian tube, or peritoneum, of any stage and grade at diagnosis, were eligible. All patients were required to have had cytoreductive surgery and at least one platinum-based chemotherapy regimen as part of primary treatment. Eligible patients had recurred on or after initial therapy and were currently in a second or third complete clinical remission after additional chemotherapy. Patients had to start vaccine treatment within 4 months of last chemotherapy. Complete clinical remission was defined as serum CA-125 within institutional normal limits, negative physical examination, and no definitive evidence of disease by computed tomography (CT) of the abdomen and pelvis. Lymph nodes and/or soft tissue abnormalities ≤1.0 cm are often present in the pelvis, and patients were eligible if these were not thought to be objective evidence of persistent disease. Other eligibility criteria included a GOG performance status of 0–2, absolute neutrophil count ≥1,000/mm^3, platelet count >≥100,000/mm^3, serum creatinine ≤1.5x institutional upper limit of normal (ULN), Common Terminology Criteria Adverse Events (CTCAE) grade 1, and hepatic function tests ≤2.5x ULN. Patients with a shellfish allergy were not eligible. The study was approved by the individual participating Institutional Review Boards, and all patients signed informed consent.

Treatment Plan

Patients were randomly assigned with equal probability to receive either polyvalent antigen-KLH + OPT-821 vaccine or non-specific immunization with OPT-821 alone. The study drug

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was to be administered for a total of 11 vaccinations, subcutaneously supplied as a 1.2 mL vial in rotating sites on weeks 1, 2, 3, 7, 11, and then every 12 weeks from week 23 to week 83. Patients were to remain on study treatment until disease progression, unacceptable toxicity, or completion of the planned treatment program (last vaccination at 83 weeks with an additional 4 weeks of follow-up).

Vaccine Preparation

The patient grade vaccine was assembled using Good manufacturing practices (GMP) in the core facility at Memorial Sloan Kettering Cancer Center (MSK) using constructs with preparation and doses as referenced: Glycosylated MUC-1 termed Tn-MUC1 (3 μg) was synthesized by Pepceuticals LLD (Leicester, England). The Globo-H hexasaccharide-KLH (30 μg) was synthesized and conjugated under GMP by Optimer Pharmaceuticals, Inc. (San Diego, CA). The ganglioside GM2 (30 μg) was extracted by Matreya, Inc. (Philadelphia, PA). It was conjugated to KLH by Althea Technologies (San Diego, CA). TF (c) (3 μg) was synthesized by the MSK Carbohydrate Synthesis Core. [4].

Conjugation to KLH was achieved by the following methods: covalent attachment of KLH to TF(c) and Tn-MUC1, achieved with m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), which couples the free SH group of cysteine on the antigen to the N terminus and lysine side chains on KLH. Conjugation of KLH to the glycolipid antigens Globo H is by attachment with the MMCCH linker 4-(4-N-maleimidomethyl) cyclohexane-1-carboxyl hydrazide. Conjugation of GM2 to KLH is achieved directly using reductive amination methods.

OPT-821 is an immunological adjuvant derived from *Quillaja saponaria* Molina and was obtained from Optimer Pharmaceuticals, Inc. (San Diego, CA). Sterility, immunogenicity, and safety testing was performed for each produced lot. The vaccine was distributed to sites for administration by the MSK investigational pharmacy.

Dose Adjustment

Dose reduction or delay was not permitted. Toxicity was evaluated according to the National Cancer Institute CTCAE version 4. [5] Study treatment was discontinued for dose-limiting toxicity (DLT). DLT was defined as follows: 1) grade 2 or higher allergic reaction, with the exception of fever (grade 2 allergic reaction is defined as rash, flushing, urticaria, or dyspnea; grade 3 allergic reaction is defined as symptomatic bronchospasm, requiring parenteral medications, with or without urticaria, allergy-related edema or angioedema; grade 4 allergic reaction is defined as anaphylaxis); 2) grade 2 or higher autoimmune reaction (grade 2 is defined as evidence of autoimmune reaction involving a nonessential organ or function (e.g., hypothyroidism) requiring treatment other than immunosuppressive drugs; grade 3 is a reversible autoimmune reaction involving a major organ [e.g., colitis]); 3) grade 3 or higher hematologic or non-hematologic toxicity, including fever (grade 3 fever is >40°C for <24 hours); and 4) grade 3 injection site reaction (grade 3 is defined as ulceration or necrosis that is severe or prolonged, or requires surgery).

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Evaluation during Study

History, physical examination, and toxicity assessment were performed at weeks 1 and 3 and all subsequent scheduled vaccination appointments. Interval laboratory studies to include complete blood count, comprehensive panel, thyroid-stimulating hormone, prothrombin time, and urinalysis were performed to assess for laboratory evidence of toxicity. Routine imaging with CT scan (or MRI and chest x-ray) were performed every 3 months for the first two years and then every 6 months for the next 3 years while on study, with CA-125 assessment. If CA-125 increased to 2x ULN on a visit in which a CT scan was not scheduled, repeat imaging could be performed at the discretion of the investigator. Patients were not removed from study treatment for rising CA-125 in the absence of radiographic progression.

Statistical Considerations

This was a randomized, double-blinded phase II superiority trial with a reference arm of OPT-821 and an experimental arm of KLH+OPT-821. The primary objective was to determine whether the KLH+OPT-821 treatment decreases the hazard of progression or death compared to the OPT-821 treatment. Progression was defined as either radiological evidence of disease or increasing clinical/histological evidence of disease on CT scan of the abdomen and pelvis. The primary endpoint was PFS, defined as the duration of time from randomization to time of disease progression, death, or the date of last contact, whichever occurs first. PFS was censored in patients who were alive and had not experienced disease progression. The secondary objectives included evaluation of toxicities (among all treated patients) and OS, defined as the duration of time from study entry to the time of death due to any cause or the date of last contact. The intent to treat principle was used in the analyses for the primary objective and OS.

A total of 148 PFS events was required for this study to have an approximately 80% power to detect a 34% reduction of the hazard for PFS in the KLH-OPT-821 experimental arm compared to the OPT-821 reference arm by a one-sided log-rank test while limiting the overall type I error rate to 5%. The final analysis was to occur when 77 PFS events were reported in the reference arm, which would give the expected total number of PFS events as 148 if the experimental arm truly reduced the PFS hazard by 34% (i.e. HR=0.66). One planned interim efficacy and futility analysis was to be performed when at least 39 PFS events were reported in the OPT-821 reference arm, where the efficacy used O'Brien-Fleming alpha spending function and the futility followed the method provided by Wieand et al. [12] The nominal significance level for the interim analysis and final analysis was 0.00557 and 0.04825, respectively. To assure data maturation in a timely manner, this study targeted an accrual of 164 patients.

Cox proportional hazards (PH) model was used to estimate the hazard ratio (HR) and its corresponding Wald confidence interval (CI). For secondary and exploratory analyses, two-sided tests were performed except for OS analysis (one-sided test) at the significance level of 0.05, and no adjustment for multiple tests was made.

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The objective of the translational research was to characterize the immune response (by ELISA) in participants, in order to determine if the outcome correlated with antigen-specific immune titers. ELISA assays against the target antigens were measured as previously described. [4]. Titers were considered "positive" or "negative" using pre-defined cutoffs of 1:40 or higher, or a two-fold increase over baseline titers.

Analyses were conducted on the measures of immune response to assess the effects of the study regimens on these endpoints and to determine whether these endpoints are associated with clinical outcomes (PFS and OS). Immune response was measured at repeated time points (week 1 [prior to treatment] and weeks 11, 17, 23, 35, 47, 59, 71, and 83). Therefore, the relationship of immune response with PFS and OS was examined with Cox proportional hazards models with immune response as a time-dependent covariate. Decisions regarding how to model immune response (e.g., categorizing or transforming) were made based on examination of its distribution and relationship to the outcomes.

RESULTS

Patient Characteristics

From 2010 to 2013, 171 participants were enrolled onto this study and received a blinded random treatment assignment; 86 patients were assigned to the KLH+OPT-821experimental arm and 85 to the OPT-821 reference arm. One patient in the OPT-821 arm did not receive the randomly assigned study regimen, and 1 patient in the KLH+OPT-821 arm withdrew study consent after receiving 6 cycles.

The patient and tumor characteristics are summarized in Table 1. Over 85% of patients were age 50 or older. Approximately 92% had a performance status of 0, reflecting the required remission population. Most had tumor with site of origin assigned to ovary. Most patients had disease of serous histology. Sixty-eight percent had 2 prior regimens, ranging up to 4 in total for some patients. Most patients had International Federation of Gynecology and Obstetrics (FIGO) stage 3 disease at diagnosis, all had prior surgery, 33% had received prior bevacizumab therapy, and 69% were in second complete remission.

Adverse Events

Maximum adverse events were grade 4 MDS (n=1, unlikely related), depression, and personality change (n=1, unlikely related) as well as grade 3 gastrointestinal disorders and others (n=21, 4 related). As expected, the most common lesser adverse events were injection site reactions and fevers. Although the incidence of injection site reactions was similar in both arms (84% for the KLH+OPT-821 arm versus 81% for the OPT-821 reference arm), the combination arm was associated with more grade 2 reactions (35% versus 13%). One-fifth of the patients in the combination arm reported a fever compared with only 2% of the patients in the OPT-821 reference arm (p-value <0.01 by Fisher exact test at 0.05 significance level). Table 2 lists the selected adverse events with a maximum grade of 2 or higher regardless of attribution to study treatment.

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Immune Response

The percentage of patients who met the predefined definition of immunogenicity is shown in Table 3. Using these definitions, less than 50% of patients were found to have a positive IgM response to the individual antigens. Positive IgG responses ranged from 7% to 45%. MUC1 was the most immunogenic antigen, with 49% and 45% of patients developing a positive IgM and IgG response, respectively, when comparing the pre- and post-titers.

Efficacy Analysis

The planned interim efficacy and futility analysis was conducted when 40 PFS events were reported in the OPT-821 reference arm based on data as of December 10, 2012. A one-sided log-rank test had a p-value of 0.5592, and the standardized log-rank test statistic for the KLH+OPT-821 treatment was 0.1489 indicating a slightly higher PFS event rate in KLH +OPT-821 treatment compared to OPT-821 alone. At that time, the study had accrued 148 patients out of the targeted accrual of 164 patients. Therefore, this study continued to the targeted accrual.

The final analysis was conducted after 150 PFS events (75 in each arm) were reported in both arms. A one-sided log-rank test for the primary objective resulted in a p-value of 0.46 (HR = 0.98; 2-sided 95% CI, 0.71 – 1.36). There was no statistically significant evidence to support that the KLH+OPT-821 treatment decreases the hazard of progression or death compared to the OPT-821 treatment. The median PFS for the experimental and reference arms were 5.9 and 6.5 months, respectively (Figure 1). At the time of this analysis, 71 deaths were reported in both arms, with a median follow-up of 34 months; the median OS for the KLH+OPT-821 arm was not reached. An additional analysis was performed after 96 deaths reported in both arms based on data as of May 31 2018, with a median follow-up of 60 months. A one-sided log-rank test for OS had a p-value of 0.18. The HR for death was 0.83 (2-sided 95% CI, 0.55 – 1.24) in KLH+OPT-821 compared to OPT-821 alone, and the median OS for the experimental and reference arms were 47 and 46 months, respectively (Figure 2).

At 0.05 significance level, an exploratory analysis did not support an association of treatment with PFS using log-rank tests after stratification by complete remission status (p = 0.98; HR = 1; 95% CI, 0.71 – 1.43; Figure 3, online only) and prior bevacizumab (p = 0.54; HR = 0.9; 95% CI, 0.65 – 1.25; Figure 4), respectively. Furthermore, Cox PH model was implemented to evaluate the associations of PFS with prior bevacizumab, treatment, and their interaction. The p-values of joint tests for treatment, prior bevacizumab, and their interaction were 0.49, 0.001 and 0.06, respectively, indicating there was an interesting association between prior bevacizumab and PFS and a borderline interesting interaction between them. In patients without prior bevacizumab treatment, the PFS HR was 1.15 (95% CI, 0.77 – 1.71) for KLH+OPT-821 compared to OPT-821 alone; in patients with prior bevacizumab treatment, the PFS HR was 0.61 (95% CI, 0.36 – 1.05) for KLH+OPT-821 compared to OPT-821 alone. In patients treated with KLH+OPT-821, the PFS HR was 0.85 (95% CI, 0.54 – 1.36) for a patient without prior bevacizumab compared to a patient with prior bevacizumab; in patients treated with OPT-821 alone, the PFS HR was 0.46 (95% CI,

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0.28 – 0.74) for a patient without prior bevacizumab compared to a patient with prior bevacizumab.

All of the 171 randomized patients were off study treatment at the time of the final analysis: 13% completed assigned treatment, 77% discontinued due to progression, 6% due to refusal of further treatment, 4% due to toxicity, and 1 due to MDS. Fifty-four patients (24 in the KLH+OPT-821 and 30 in the OPT-821 arms) had more than 6 vaccines; the median number of vaccines per patient was 6 in each arm. Overall, there was no significant difference between the two arms for the distribution in the number of vaccines the patients received ($p = 0.33$ by exact chi-square test). The reason for being taken off study treatment was unrelated to the treatment randomized ($p = 0.14$ by exact chi-square test).

DISCUSSION

The natural history of patients with epithelial ovarian cancer is well suited for the application of maintenance therapies in an effort to extend the disease-free interval. [2] Observational studies have suggested that both antibodies and T cell infiltrates with certain characteristics impact outcomes. [3, 6] This study evaluated the potential efficacy of a carbohydrate-based vaccine with antibodies as the primary immune effectors in the pre-checkpoint inhibitor era. [7] Patient characteristics were typical of those of patients with advanced ovarian cancer. The vaccine was well tolerated, with mild toxicity largely confined to the injection site. Given the composite nature of the vaccine injection it was not possible to distinguish if these were related to KLH or the conjugated antigens. Despite the demonstration of reasonable immunogenicity, this approach did not prolong PFS or OS when compared to patients receiving the non-specific immune adjuvant OPT-821. This study confirms that the induction of antibodies in the absence of other immune effectors or modification of the immune response is ineffective.

In order to return to complete clinical remission, which was an eligibility criterion for the study, nearly all patients had received a median of 6 cycles of a platinum-based doublet. Nearly one-third of patients were receiving third-line therapy, representing a heavily treated group. There was a hypothetical concern that such patients may not mount an adequate immune response, but that was not the case. In addition, approximately one-third of patients received prior bevacizumab. Neither of these characteristics appeared to influence immune response.

The concept of maintenance therapy has been resurrected in the era of poly ADP ribose polymerase (PARP) inhibitors, anti-vascular therapy, and immune-directed treatment. [8] This study shows the feasibility of enrolling second and third complete remission patients to clinical trials investigating modalities best suited for a population with minimal residual disease. It also illustrates the continuously improving OS (likely due to improvements in subsequent anti-cancer therapy) in this patient population. [9] For example, the median OS in both arms of this study was 34 months. This is similar to the OS in the final analysis of the OCEANS study (33 months in the placebo arm) but remarkably longer than the original AGO-OVAR study (18 months). [10, 11] The unexpected length of OS in this population required a much longer analysis time than initially expected for this study. This estimate

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should be kept in mind when designing future studies. One initial criticism of our study was the lack of randomization to placebo, but the survival estimate here is similar to that found in contemporary platinum-based doublet studies, and this suggests that OPT-821 did not have independent activity

The eligibility criteria did not include an assessment of immunocompetence. In our study 50% of the patients did not demonstrate an IgM response which may indicate that half of the patients potentially represented a "non-responder" group and could have adversely impacted our ability to determine the study endpoints. Therefore, future vaccine trials should incorporate an assessment of baseline immunocompetence as well as consideration of a preplanned analysis to correlate outcomes with induction of an immune response. While checkpoint inhibitors have shown remarkable responses in certain tumor types, single-agent activity in patients with ovarian cancer has been disappointing. The next generation of vaccine studies, with T cell or combined effectors, will take advantage of these advances, and combination studies of a variety of vaccine approaches with one or more checkpoint inhibitors are underway.

Conclusions

Vaccination with this polyvalent construct with antibody effectors was modestly immunogenic but did not prolong PFS or OS when compared to OPT-821 alone. In this second and third remission cohort, a well-defined population with minimal residual disease, it is feasible to explore innovative consolidation and maintenance approaches.

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RESEARCH HIGHLIGHTS

- Polyvalent vaccine with adjuvant OPT-821 compared to adjuvant alone was modestly immunogenic and did not prolong survival.
- The vaccine with adjuvant OPT-821 was well tolerated, with mild toxicity largely confined to the injection site reactions
- Multi-remission patients are a distinct population in which to explore innovative consolidation/maintenance approaches.

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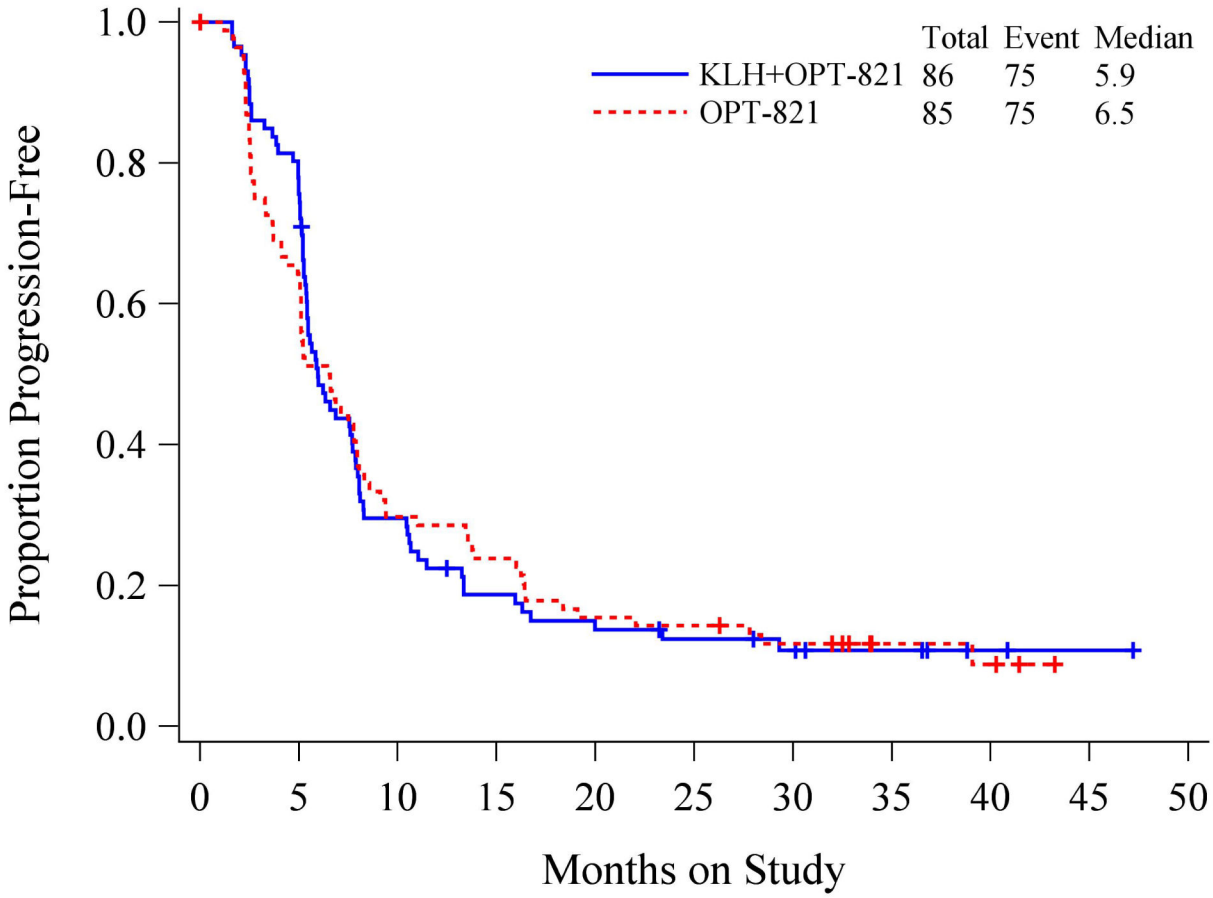

Figure 1.
Kaplan-Meier curves of progression-free survival (PFS) for Vaccine KLH + OPT-821 versus OPT-821 alone

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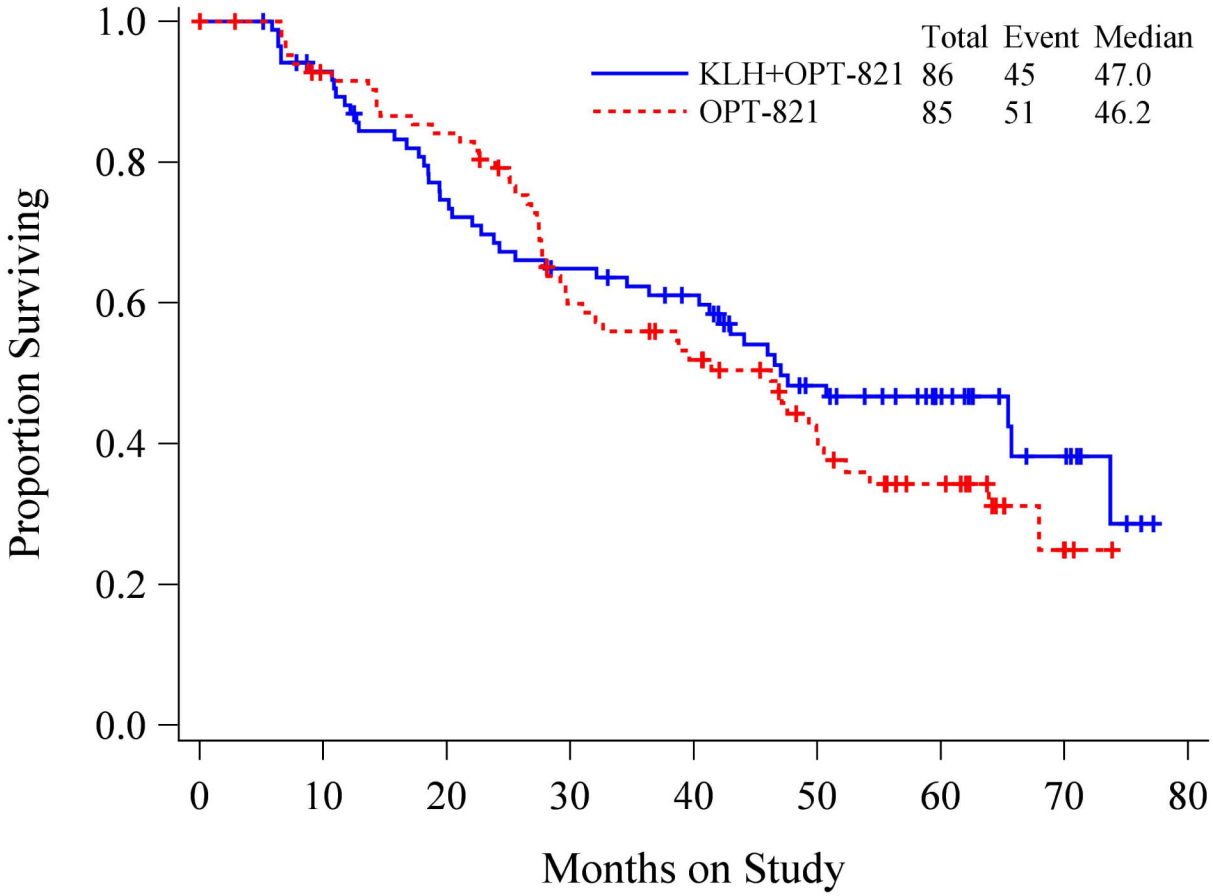

Figure 2.
Kaplan-Meier curves of overall survival for Vaccine KLH + OPT-821 versus OPT-821 alone

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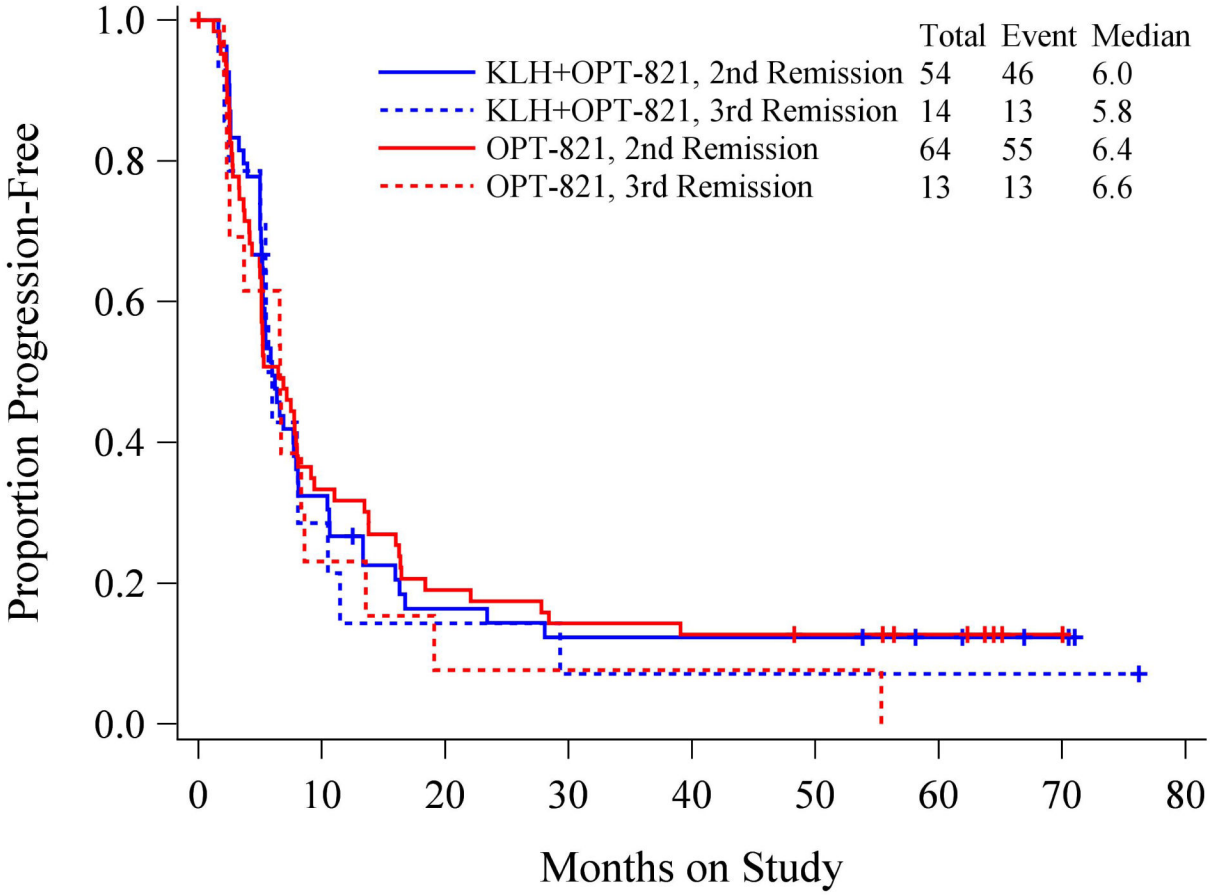

Figure 3.

(Available online only) Kaplan-Meier curves of PFS for Vaccine KLH + OPT-821 versus OPT-821 alone by complete remission status

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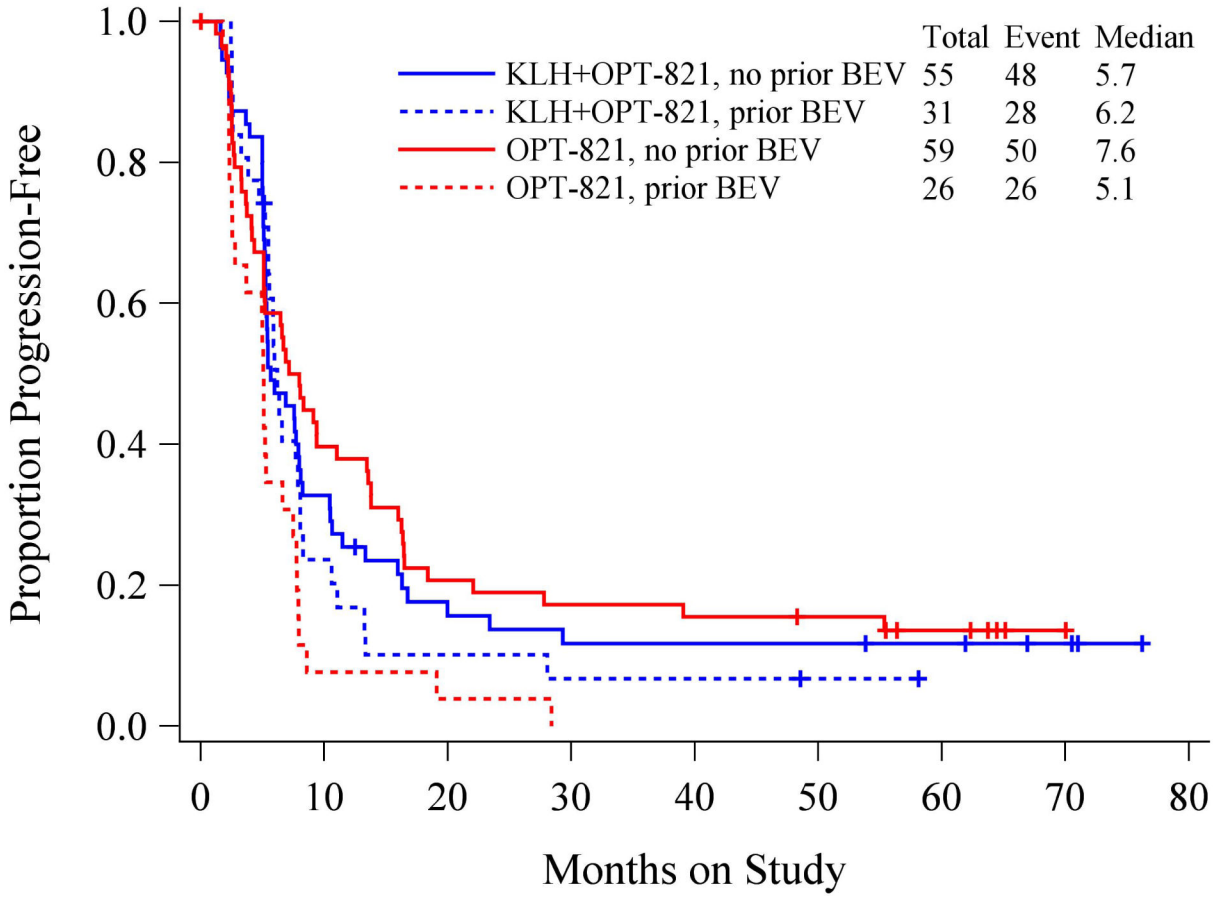

Figure 4.
Kaplan-Meier curves of PFS for Vaccine KLH + OPT-821 versus OPT-821 alone by prior bevacizumab (BEV) treatment

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Table 1:

Patient and tumor characteristics

	KLH+OPT-821		OPT-821		Total	
Patient or Tumor Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age (Years)						
40–49	8	9.3	14	16.5	22	12.9
50–59	29	33.7	31	36.5	60	35.1
60–69	37	43.0	26	30.6	63	36.8
70–79	10	11.6	14	16.5	24	14.0
80–89	2	2.3	0	0.0	2	1.2
Ethnicity						
Hispanic or Latino	1	1.2	1	1.2	2	1.2
Not Hispanic or Latino	78	90.7	77	90.6	155	90.6
Not Reported/Unknown	7	8.1	7	8.2	14	8.2
Race						
Asian	3	3.5	6	7.1	9	5.3
Black/African American	2	2.3	1	1.2	3	1.8
American Indian/Alaskan	0	0.0	1	1.2	1	0.6
White	80	93.0	76	89.4	156	91.2
Not Reported/Unknown	1	1.2	1	1.2	2	1.2
Performance Status						
0	78	90.7	79	92.9	157	91.8
1	7	8.1	6	7.1	13	7.6
2	1	1.2	0	0.0	1	0.6
Site of Disease						
Ovary	64	74.4	70	82.4	134	78.4
Fallopian tube	11	12.8	4	4.7	15	8.8
Other	11	12.8	11	12.9	22	12.9
Cell Type/Grade						
Endometrioid, grade 2	1	1.2	1	1.2	2	1.2
Endometrioid, grade 3	5	5.8	0	0.0	5	2.9
High grade Serous	67	77.9	75	88.2	142	83.0
Low grade Serous	2	2.3	1	1.2	3	1.8
Clear Cell	1	1.2	1	1.2	2	1.2
Adenosquamous	0	0.0	1	1.2	1	0.6
Mixed Epithelial	2	2.3	2	2.4	4	2.3
Undifferentiated	1	1.2	1	1.2	2	1.2
Adenocarcinoma, NOS	3	3.5	1	1.2	4	2.3
Transitional Cell	0	0.0	2	2.4	2	1.2
Other	4	4.7	0	0.0	4	2.3
Number of Prior Regimens						
2	61	70.9	55	64.7	116	67.8

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	KLH+OPT-821		OPT-821		Total	
Patient or Tumor Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
3	24	27.9	29	34.1	53	31.0
4	1	1.2	1	1.2	2	1.2
Prior Radiation						
Yes	6	7.0	5	5.9	11	6.4
No	80	93.0	80	94.1	160	93.6
Prior Immunotherapy						
Yes	3	3.5	2	2.4	5	2.9
No	83	96.5	83	97.6	166	97.1
Prior Surgery						
Yes	86	100.0	85	100.0	171	100.0
FIGO Stage at Diagnosis						
1	4	4.7	3	3.5	7	4.1
2	7	8.1	7	8.2	14	8.2
3	67	77.9	65	76.5	132	77.2
4	8	9.3	10	11.8	18	10.5
Prior Bevacizumab						
Yes	31	36.0	26	30.6	57	33.3
No	55	64.0	59	69.4	114	66.7
Complete remission status						
2nd	54	62.8	64	75.3	118	69.0
3rd	14	16.3	13	15.3	27	15.8
missing	18	20.9	8	9.4	26	15.2
Total	86	100.0	85	100.0	171	100.0

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Table 2:

Distribution of patients by highest grade of adverse event as 2 or worse by specific adverse events term regardless of attribution to treatment

	KLH+OPT-821 (n=86) n (%) of Patients by Grade				OPT-821 (n=84) n (%) of Patients by Grade			
Adverse event	**2**	**3**	**4**	**5**	**2**	**3**	**4**	**5**
Anemia	4 (4.7)	0	0	0	2 (2.4)	1 (1.2)	0	0
Abdominal Pain	3 (3.5)	1 (1.2)	0	0	3 (3–6)	5 (6.0)	0	0
Constipation	4 (4.7)	0	0	0	3 (3.6)	0	0	0
Nausea	4 (4.7)	1 (1.2)	0	0	1 (1.2)	0	0	0
Fatigue	10 (11.6)	0	0	0	3 (3.6)	0	0	0
Fever	1 (1.2)	0	0	0	0	0	0	0
Injection Site Reaction	30 (34.9)	0	0	0	11 (13.1)	0	0	0
Alkaline Phosphatase Increase	0	0	0	0	0	0	0	0
Neutrophil Count Decreased	8 (8.1)	1 (1.2)	0	0	5 (6–0)	1 (1.2)	0	0
Platelet Count Decreased	0	0	0	0	0	0	0	0
White Blood Cell Decreased	4 (4.7)	0	0	0	5 (6.0)	0	0	0
Hyperglycemia	0	1 (1.2)	0	0	0	0	0	0
Myalgia	0	0	0	0	0	0	0	0
Headache	3 (3.5)	0	0	0	1 (1.2)	0	0	0
Peripheral Sensory Neuropathy	2 (2.3)	0	0	0	3 (3.6)	0	0	0

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Table 3:

Immune response

Positive titer change (Patients with pre and post titers) n = 148									
GLOBO-H		**GM2**		**MUC1- TN**		**MUC 1**		**TF**	
IgG	**IgM**	**IgG**	**IgM**	**IgG**	**IgM**	**IgG**	**IgM**	**IgG**	**IgM**
7%	*21%*	*8%*	*26%*	*32%*	*40%*	*45%*	*49%*	*13%*	*22%*