2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-888; veliparib		
Name of Active Ingredient: 1H-Benzimidazole-7-carboxamide, 2-[(2R)-2-methyl-2-pyrrolidinyl]		
Title of Study: A Phase 2 Randomized Clinical Trial of ABT-888 in Combination with Temozolomide Versus Pegylated Liposomal Doxorubicin Alone in Subjects with Recurrent High Grade Serous Ovarian Cancer		
Coordinating Investigator: Joan Walker, MD		
Study Sites: Subjects were enrolled at 30 sites in the United States, Australia, Israel, Canada, New Zealand, Great Britain, Hungary, and Poland.		
Publications: There are no publications based on this study.		
Studied Period (Years): First Subject First Visit: 09 March 2010 Last Subject Last Visit: 25 June 2013	**Phase of Development:** 2	

Objectives:

Primary Objective:

The primary objective of this study was to evaluate the objective response rate (ORR) of ABT-888 (veliparib) in combination with temozolomide (TMZ) compared to pegylated liposomal doxorubicin (PLD) alone in subjects with recurrent high-grade serous ovarian cancer.

Secondary Objectives:

The secondary objectives of the study were to evaluate progression-free survival (PFS), time to progression (TTP), overall survival (OS), 12-month survival rate, 6-month PFS rate, duration of response, safety, and tolerability.

Tertiary Objectives:

The tertiary objectives of the study were to evaluate the quality of life (QoL) and performance status assessment of subjects enrolled.

Methodology:

This was a Phase 2 multicenter, open-label, 2-arm, randomized study of veliparib in combination with TMZ versus PLD alone to evaluate the objective response rate in approximately 150 subjects with recurrent high-grade serous ovarian carcinoma.

Subjects were randomized into one of the 2 treatment arms with a randomization ratio of 2:1. There were to be approximately 100 subjects in the veliparib + TMZ arm and approximately 50 subjects in the PLD alone arm. Subjects were randomized to receive the following:

- Arm A – veliparib 40 mg twice a day (BID) on Days 1 through 7 + TMZ daily (QD) on Days 1 through 5 of each 28-day cycle;
- Arm B – PLD was administered intravenously (IV) at a dose of 50 mg/m^2 on Day 1 of each 28-day cycle.

Subjects who discontinued treatment with veliparib + TMZ or PLD prior to reaching an event of disease progression were to remain on study and continue to follow the schedule for study visits and procedures until disease progression was experienced.

Study visits were to be performed until either disease progression or until subjects met the removal criteria.

When a subject discontinued the study, a Final Visit was to be conducted (preferably prior to the initiation of another anticancer therapy). However, these procedures were not to interfere with the initiation of any new treatments or therapeutic modalities that the investigator felt were necessary to treat the subject's condition. Following discontinuation of the study drug, the subject was to be treated in accordance with the investigator's best clinical judgment.

All subjects were to have one Follow-up Visit approximately 30 days after the Final Visit. This Follow-up Visit did not need to be performed for subjects who had a Final Visit conducted ≥ 30 days after discontinuation of veliparib.

Information pertaining to survival and post-treatment therapy was to be collected approximately every 12 weeks (Months 3, 6, 9, 12, 15, and 18) or as needed to allow for more frequent data collection beginning on the date the subject was registered as discontinued for a period of up to 3 years. Survival information and post-treatment therapy were collected using the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) and submitted to AbbVie.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 150 subjects.

Actual: 168 subjects were enrolled. 165 subjects were treated.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

1. Subject was at least 18 years of age.
2. Subject had histologically (or cytologically) confirmed recurrent high grade serous ovarian, fallopian tube, or primary peritoneal cancer.
3. Subject had at least 1 platinum-containing chemotherapy regimen for ovarian cancer and no more than a total of 3 DNA-damaging or cytotoxic regimens in the past 5 years. Less than a full dose of a DNA-damaging agent, possibly due to reasons such as toxicity or documented allergic reaction, were not counted toward the limit of 3. Previous treatments with biologic agents (including catumaxomab, tigatuzuzumab, abagovomab, and bevacizumab), vaccines, immunostimulants, hormonal agents, and signal transduction inhibitors (e.g., pazoparib, sorafenib, sunitinib, temsirolimus) were allowed and were not counted towards the limit of 3.
4. Subject was resistant to platinum-based therapy or sensitive to, but unable to tolerate, platinum-based therapy (i.e., deemed toxic or had a documented platinum allergy). Subject had at least a ≥ 3-month treatment-free interval from the last dose of platinum based therapy. She may have received other therapy since her last platinum therapy prior to enrolling in this study.
5. Subject was eligible to receive PLD treatment (e.g., no allergic reaction, normal cardiac function).
6. Subject had either:
   - Measurable disease, defined as at least 1 unidimensionally measurable lesion on a computed tomography (CT) scan as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.19 OR
   - Nonmeasurable disease with an elevation of serum CA-125 level by Gynecologic Cancer Intergroup (GCIG) criteria (baseline sample is at least twice the upper limit of normal and within 2 weeks prior to starting treatment).

Main Exclusion Criteria: Redacted information – 03Sep2015

1. Subject was previously treated with a PARP inhibitor except as a single dose from the Cancer Therapy Evaluation Program (CTEP) Phase 0 ([redacted]) study of veliparib.
2. Subjects who had a history of hypersensitivity reaction to the conventional formulation of doxorubicin HCl or the components of PLD.
3. Subject received anticancer agent(s) or an investigational agent within 28 days prior to study drug administration. Subjects who had not recovered to within one grade level (not to exceed Grade 2) of their baseline following a significant adverse event (AE) or toxicity attributed to previous anticancer treatment are excluded.
4. Subject underwent major surgery within the previous 28 days prior to study drug administration.
5. Subject with prior radiotherapy to any portion of the abdominal cavity and pelvis, unless for the treatment of ovarian, fallopian tube, or primary peritoneal cancer. Subject completed radiation at least 28 days prior to study drug administration and had measurable disease outside the radiation field or documented progression of lesions within a previously radiated field.
6. Subject had a known history of brain metastases.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Veliparib 10-mg capsules for oral administration (bulk lot numbers: 08-019658, 09-022737, 08-019658, 10-001885, 10-001372).

TMZ for oral administration: 5-mg capsules (bulk lot numbers: 09-024585, 10-000312, 09-025259, 09-025201, 10-001692, 10-003988, 10-001486, 12-000629, 12-000629); 20-mg capsules (bulk lot numbers: 09-024583, 10-000314, 09-024583, 09-025202, 10-001668, 10-001668, 10-005650, 10-001487, 11-002200, 11-002193); and 100-mg capsules (bulk lot numbers: 09-024817, 10-000315, 09-024817, 09-026049, 09-025203, 10-002777, 10-003990, 10-001488, 11-003508, 11-003508)

Duration of Treatment:

Subjects were to continue to receive treatment until reaching a protocol-defined event of disease progression or experiencing toxicities that warranted discontinuation. Subjects in the PLD arm who met the protocol definition of disease progression and met the eligibility criteria may have crossed over to receive treatment with veliparib + TMZ at the discretion of the investigator.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

PLD for intravenous administration: 20-mg vials (bulk lot numbers: 09-025191, 10-001094, 10-001753, 10-001753, 10-003347, 10-005137) and 50-mg vials (bulk lot numbers: 09-025193, 10-001095, 10-001754, 10-001754, 10-003346, 11-001405)

Criteria for Evaluation

Efficacy: Tumor response and/or disease progression were assessed by combining CT scan using RECIST Version 1.1 with CA-125 measurement according to the GCIG criteria. Radiographic and CA-125 assessments were to be performed at Screening, every 8 weeks after Cycle 1 Day 1, and at the Final Visit, if not performed within the previous four weeks. Disease progression was based on either radiographic or clinical assessment, and was not based on CA-125 elevation alone without radiographic or clinical evidence.

Safety: AbbVie assessed AEs, laboratory data, and vital signs throughout the study. AEs were assessed according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

During the conduct of the study, the AbbVie medical and safety team monitored subject laboratory results, AEs, and serious adverse events (SAEs) data as they were reported.

Statistical Methods

Efficacy:

Primary Analysis of Efficacy

ORR was estimated and compared between the treatment arms (veliparib + TMZ versus PLD) using the Cochran–Mantel–Haenszel test, stratified by number of disease sites (≤ 2 versus > 2 or diffuse peritoneal carcinamatosis) and measurable versus non-measurable disease. In addition, 95% confidence intervals were constructed for the estimated ORR.

Secondary Analysis of Efficacy

For the stratified analyses mentioned below, the stratification factor was to be the number of disease sites (≤ 2 versus > 2 or diffuse peritoneal carcinamatosis) and measurable versus non-measurable disease.

Statistical Methods (Continued)

Efficacy (Continued):

Progression-Free Survival

The distribution of PFS (radiographic progression, clinical progression, or death) was estimated for each treatment arm using Kaplan-Meier methodology and compared between the veliparib + TMZ and PLD treatment arms using the stratified log-rank test.

Time to Progression

The distribution of TTP (radiographic or clinical progression) was estimated for each treatment arm using Kaplan-Meier methodology and compared between the veliparib + TMZ and PLD treatment arms using the stratified log-rank test.

Overall Survival

The distribution of the time to death was estimated for each treatment arm using Kaplan-Meier methodology and compared between the veliparib + TMZ and PLD treatment arms using the stratified log-rank test.

Twelve-month Overall Survival Rate

The 12-month OS rate was estimated using Kaplan-Meier methodology and 95% confidence interval was constructed for the estimated 12-month OS rate for each treatment group. A test statistic based on complementary log–log transformations of the survival probability was constructed to test the null hypothesis that the 12-month OS rates for veliparib + TMZ and PLD are the same.

Six-month Progression Free Survival Rate

The 6-month PFS rate was estimated using Kaplan-Meier methodology and 95% confidence interval was constructed for the estimated 6-month progression-free survival rate for each treatment arm. A test statistic based on complementary log-log transformations of the survival probability was constructed to test the null hypothesis that the 6-month PFS rates for veliparib + TMZ and PLD are the same.

Duration of Response

The distribution of the duration of response was to be estimated for each treatment arm using Kaplan-Meier methodology and compared between the veliparib + TMZ and PLD treatment arms using the stratified log-rank test. If the estimated objective response rate was less than 20% overall, then this analysis was not to be performed.

Tertiary Analysis of Efficacy

Quality of Life

QoL data collected during the study were analyzed using appropriate statistical methodology.

Performance Status

Changes and/or percent changes from baseline were summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for Eastern Cooperative Oncology Group (ECOG) performance status. Post-baseline measurements more than 30 days after the last dose of study drug were not included. Subjects who did not have a baseline measurement or did not have any post-baseline measurements were not included.

Statistical Methods (Continued)

Additional Efficacy Analyses

For ORR, OS, and PFS, additional analyses may have been performed, such as (1) including only data and events that occurred on treatment or within 30 days of the last dose of study drug, (2) subgroup analysis by breast cancer gene status, and others.

Safety:

The safety of veliparib + TMZ and PLD was assessed by evaluating study drug exposure, AEs, SAEs, all deaths, as well as changes in laboratory determinations and vital sign parameters. Subjects who were randomized but did not receive study drug were not included in the analyses of safety.

Duration of Study Drug

A summary of the number of days and/or cycles subjects were exposed to study drug were provided.

Adverse Events

Analyses of AEs included only treatment-emergent events, i.e., those that have an onset on or after the day of the first dose of study drug. Analyses did not include those that had an onset > 30 days after the last dose of study drug. Treatment-emergent AEs were summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) AE coding dictionary. The percentage of subjects experiencing an AE at a NCI CTCAE toxicity grade, and relationship to study drug were provided.

Comparisons of the percentages of subjects who experienced an AE between veliparib + TMZ and PLD treatment arms were performed using Fisher's exact test.

Serious Adverse Events

SAEs were summarized using the same methods as AEs described above.

Deaths

The number of subject deaths was summarized: (1) for deaths that occurred while the subject was still receiving study drug in this study, (2) for deaths that occurred off treatment within 30 days after the last dose of study drug, and (3) for all deaths in this study regardless of the number of days after the last dose of study drug.

Longitudinal Analyses of Laboratory and Vital Signs Data

Analyses of changes and/or percent changes from baseline were analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement existed for a subject on a particular day, then an arithmetic average was calculated. This average was considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of study drug were not included. Subjects who did not have a baseline measurement or did not have any post-baseline measurements were not included.

Statistical Methods (Continued)

Analyses of Laboratory Data Using NCI CTCAE

Where applicable, blood chemistry and hematology determinations were categorized according to NCI CTCAE Version 4.0 grades, and shifts from baseline NCI CTCAE grades to maximum and final post-baseline grades were assessed.

The baseline and final grades were defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the last post-baseline measurement collected no more than 30 days after the last dose of study drug.

Comparisons of the number of subjects who experienced a shift from baseline grades of 0 or 2 to maximum post-baseline grades of 3 or 4, and from baseline grades of 0 or 2 to final post-baseline grades of 3 or 4 between veliparib + TMZ versus PLD were performed using Fisher's exact test.

Additional analyses, including all measurements collected, regardless of the number of days after the last dose of study drug, were performed.

Summary/Conclusions

Efficacy Results:

Primary Efficacy:

The primary efficacy variable was ORR. Tumor response was evaluated in 112 subjects in the veliparib + TMZ arm and 56 subjects in the PLD arm.

For subjects in the intent-to-treat population:

- Overall, 28 subjects (25.0%) in the veliparib + TMZ arm (0 complete response [CR], 28 partial response [PR]) and 21 subjects (37.5%) in the PLD arm (4 CR , 17 PR) achieved objective response based on GCIG (stratified $P = 0.089$).
- A total of 9 of 88 subjects (10.2%) in the veliparib + TMZ arm (1 CR, 8 PR) and 15 of 44 subjects (34.1%) in the PLD arm (4 CR, 11 PR) achieved objective response based on radiographic response (stratified $P = 0.001$).
- A total of 28 of 99 subjects (28.3%) in the veliparib + TMZ arm (8 CR, 20 PR) and 17 of 47 subjects (36.2%) in the PLD arm (4 CR, 13 PR) achieved objective response based on CA-125 response (stratified $P = 0.241$).

The *P* value for difference of ORR between treatment groups is from the Cochran-Mantel-Haenszel stratified by the treatment-free interval between the last platinum-based therapy and starting other chemotherapy agents or anti-cancer treatment (3 to 6 months versus > 6 months) and measurable versus non-measurable disease.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Secondary Efficacy:

Median PFS was 161 days (95% CI: 120 – 174 days) for the veliparib/TMZ arm, and 159 days (95% CI: 113 – 254 days) for the PLD arm. The 6-month PFS rate was 38.3% (95% CI: 29.1% - 47.4%) for the veliparib/TMZ arm, and 43.3% (95% CI: 29.7% – 56.2%) in the PLD arm. The veliparib/TMZ vs. PLD hazard ratio for PFS was 1.305 (95% CI: 0.903 – 1.887; stratified log-rank *P* value = 0.153), when stratified by the treatment free interval between the last platinum-based therapy and starting other chemotherapy agents or anti-cancer treatment (3 to 6 months versus > 6 months) and measurable versus non-measurable disease.

Median TTP was 161 days (95% CI: 120 – 174 days) for the veliparib/TMZ arm, and 164 days (95% CI: 113 – 276 days) for the PLD arm. The 6-month progression-free rate was 38.3% (29.1% - 47.4%) for the veliparib/TMZ arm and 45.0% (95% CI: 31.0% – 58.0%) for the PLD arm. The veliparib/TMZ vs. PLD hazard ratio for TTP was 1.365 (95% CI: 0.938 – 1.986; stratified log-rank *P* value = 0.101), when stratified by the treatment free interval between the last platinum-based therapy and starting other chemotherapy agents or anti-cancer treatment (3 to 6 months versus > 6 months) and measurable versus non-measurable disease.

Median OS was 560 days (95% CI: 446 – 685 days) for the veliparib/TMZ arm, and 508 days (95% CI: 377 – 782 days) for the PLD arm. The 12-month survival rate was 64.8% (55.0% – 73.0%) for the veliparib/TMZ arm and 66.8% (95% CI: 52.6% – 77.7%) for the PLD arm. The veliparib/TMZ versus PLD hazard ratio for OS was 1.044 (95% CI: 0.712 – 1.531; stratified log-rank *P* value = 0.822), when stratified by the treatment free interval between the last platinum based therapy and starting other chemotherapy agents or anti-cancer treatment (3 to 6 months versus > 6 months) and measurable versus non measurable disease.

Median duration of response was 210 days (95% CI: 162 – 256 days) for the veliparib/TMZ arm, and 322 days (95% CI: 198 – 419 days) for the PLD arm. The 6-month duration of overall response rate was 59.6% (39.0% – 75.3%) for the veliparib/TMZ arm and 80.0% (95% CI: 55.1% – 92.0%) for the PLD arm. The veliparib/TMZ vs. PLD hazard ratio for duration of response was 2.479 (95% CI: 1.156- 5.313; stratified log-rank *P* value = 0.017), when stratified by the treatment free interval between the last platinum based therapy and starting other chemotherapy agents or anti-cancer treatment (3 to 6 months versus > 6 months) and measurable versus non measurable disease.

Tertiary Efficacy:

The tertiary efficacy variables were QoL and performance status.

There was no statistically significant difference in change from baseline to final visit in QoL scores between the veliparib/TMZ and PLD arms, as measured by the FACT-O tool and EQ-5D Questionnaire.

There was no statistically significant difference in change from baseline to final visit in ECOG performance status between the veliparib/TMZ and PLD arms.

Summary/Conclusions (Continued)

Safety Results:

All 147 subjects who received veliparib/TMZ and all 55 subjects who received PLD experienced at least 1 treatment-emergent adverse event, with 102 subjects (69.4%) who received veliparib/TMZ and 35 subjects (63.6%) who received PLD having a grade 3 or grade 4 adverse event(s). Adverse events considered by the investigator to be possibly or probably related to veliparib were reported for 133 subjects (90.5%), possibly or probably related to TMZ for 144 subjects (98.0%), and possibly or probably related to PLD for 53 subjects (96.4%). Serious adverse events were reported for 58 subjects (39.5%) who received veliparib/TMZ and 21 subjects (38.2%) who received PLD. Adverse events led to discontinuation of veliparib/TMZ in 33 subjects (22.4%). A total of 24 subjects (16.3%) reported an adverse event leading to discontinuation of veliparib/TMZ due to progression. Adverse events led to discontinuation of PLD in 10 subjects (18.2%).

A total of 133 subjects (90.5%) who received veliparib/TMZ experienced adverse events considered possibly or probably related to veliparib. The most frequently reported (≥ 20% of all subjects) adverse events possibly or probably related to veliparib were nausea (87 subjects, 59.2%), fatigue (74 subjects, 50.3%), thrombocytopenia (57 subjects, 38.8%), neutropenia (40 subjects, 27.2%), vomiting (39 subjects, 26.5%), and decreased appetite (34 subjects, 23.1%).

A total of 144 subjects (98.0%) who received veliparib/TMZ experienced adverse events considered possibly or probably related to TMZ. The most frequently reported (≥ 20% of all subjects) adverse events possibly or probably related to TMZ were nausea (102 subjects, 69.4%), fatigue (83 subjects, 56.5%), thrombocytopenia (69 subjects, 46.9%), neutropenia (50 subjects, 34.0%), vomiting (47 subjects, 32.0%), decreased appetite (43 subjects, 29.3%), anaemia (39 subjects, 26.5%), and constipation (31 subjects, 21.1%).

A total of 53 subjects (96.4%) who received PLD experienced adverse events considered possibly or probably related to PLD. The most frequently reported (≥ 20% of all subjects) adverse events possibly or probably related to PLD were nausea (38 subjects, 69.1%), fatigue (34 subjects, 61.8%), palmar-plantar erythrodysaesthesia syndrome (26 subjects, 47.3%), stomatitis (24 subjects, 43.6%), rash (22 subjects, 40.0%), decreased appetite (20 subjects, 36.4%), vomiting (16 subjects, 29.1%), constipation and neutropenia (15 subjects, 27.3%, each), and mucosal inflammation (12 subjects, 21.8%).

Grade 3 or 4 adverse events reported in more than 2 of the 147 subjects who received veliparib/TMZ (> 1.4%) were thrombocytopenia (45 subjects, 30.6%); neutropenia (29 subjects, 19.7%); fatigue and nausea (15 subjects, 10.2%, each); anaemia (12 subjects, 8.2%); ascites (11 subjects, 7.5%); vomiting (10 subjects, 6.8%); leukopenia (9 subjects, 6.1%); small intestinal obstruction (8 subjects, 5.4%); abdominal pain (6 subjects, 4.1%); constipation (5 subjects, 3.4%); diarrhoea, decreased appetite, decreased neutrophil count, and decreased white blood cell count (4 subjects, 2.7%, each); and dyspnoea, back pain and decreased platelet count (3 subjects, 2.0%, each).

Grade 3 or 4 adverse events reported in more than 2 of the 55 subjects who received PLD (> 3.6%) were palmar-plantar erythrodysaesthesia syndrome (9 subjects, 16.4%), neutropenia (8 subjects, 14.5%), anaemia (5 subjects, 9.1%), abdominal pain and stomatitis (4 subjects, 7.3%, each), burning sensation and vomiting (3 subjects, 5.5%, each).

Summary/Conclusions (Continued)

Safety Results:

One or more grade 3 or grade 4 adverse events were considered possibly or probably related to veliparib for 65 subjects. The most common of these events were thrombocytopenia (37 subjects, 25.2%), neutropenia (23 subjects, 15.6%), nausea and vomiting (8 subjects, 5.4%, each), fatigue and leukopenia (7 subjects, 4.8%, each), anaemia and decreased white blood cell count (4 subjects, 2.7%, each), and decreased neutrophil count and decreased platelet count (3 subjects, 2.0%).

One or more grade 3 or grade 4 adverse events were considered possibly or probably related to TMZ for 84 subjects. The most common of these events were thrombocytopenia (45 subjects, 30.6%); neutropenia (29 subjects, 19.7%); nausea (11 subjects, 7.5%); anaemia (10 subjects, 6.8%); leukopenia (9 subjects, 6.1%); fatigue and vomiting (8 subjects, 5.4%, each); decreased neutrophil count, decreased white blood cell count, and constipation (4 subjects, 2.7%, each); abdominal pain, decreased appetite, and decreased platelet count (3 subjects, 2.0%,each); and increased alanine aminotransferase, decreased granulocyte count, and decreased lymphocyte count (2 subjects, 1.4%, each).

One or more grade 3 or grade 4 adverse events were considered possibly or probably related to PLD for 29 subjects. The most common of these events were palmar plantar erythrodysaesthesia syndrome (9 subjects, 16.4%); neutropenia (8 subjects, 14.5%); anaemia and stomatitis (4 subjects, 7.3%); burning sensation (3 subjects, 5.5%); and abdominal pain, fatigue, leukopenia, rash, and vomiting (2 subjects, 3.6%, each).

Conclusions:

The objective response rate was 25.0% for the veliparib + TMZ arm and 37.5% for the PLD arm. The study failed to meet the primary efficacy endpoint.

Oral veliparib was well tolerated in combination with TMZ, with common toxicities of hematologic cytopenias and gastrointestinal symptoms.