TITLE PAGE

Study Title:	A retrospective study of characteristics, patterns of care, healthcare resource utilisation and event histories in subjects with recurrent ovarian cancer in selected European countries TROCADERO (Treatment of Recurrent Ovarian Cancer And Description of Events, Resources and Outcomes)
Product or Therapeutic Area:	Trebananib
Indication:	Recurrent Ovarian Cancer
Brief Description:	This study is a retrospective analysis of subject data as captured in the records of participating centres. It is designed to increase understanding of the recurrent ovarian cancer landscape.
Study Sponsor:	Amgen Ltd, 1 Uxbridge Business Park, Uxbridge, UK
Study No.:	20110178
Study Phase:	Not Applicable: Non interventional Study
Study Initiation Date:	18th October 2012
Interim Analysis:	23rd April 2013
Study Completion Date:	21st August 2013
Principal Investigator(s):	This study was conducted at 36 centres in 3 countries: Germany, France and Spain. Centres and Principal Investigators are listed in Appendix 3.
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Good Clinical / Pharmacoepidemiology Practice:	This study was conducted in accordance with applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP); International Society for PharmacoEpidemiology (ISPE) Good Pharmacoepidemiology Practice (GPP) guidelines; Volume 10 of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use and patients' data protection act in the UK. Essential documents will be retained in accordance with the guidelines.
Report Date:	**31 January 2014**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
ADR	Adverse drug reaction
AE	Adverse event
BSA	Body surface area
CI	Confidence interval
CRF	Case report form. A paper document used for capturing data
CRO	Contract research organisation
eCRF	Electronic case report form
EDC system	Electronic data capture system
EU	European Union
FIGO	International Federation of Gynaecology and Obstetrics
HCRU	Healthcare resource utilisation
ICF	Informed consent form
Index date	The date of the first (index) recurrence
Index recurrence	The diagnosis of first recurrence. It provides the index date for each subject
OC	Ovarian cancer
OI	OptumInsight
OS	Overall survival
PFS	Progression-free survival
PFI	Platinum-free interval
Pre-index period	The period between the primary diagnosis and the index recurrence for each subject
Post-index period	The period between the index date and last contact date for each subject
PPS	Partially platinum sensitive
QC	Quality control
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SAP	Statistical analysis plan
SC	Steering committee
SDV	Source document verification
SMC	Site management centre
SOP	Standard operating procedures
SCC	Study coordinating centre

BODY OF REPORT

Name of Sponsor: Amgen Ltd, 1 Uxbridge Business Park, Uxbridge, United Kingdom

Product or Therapeutic Area: Trebananib

Indication: Recurrent Ovarian Cancer

Title of Study: A retrospective study of characteristics, patterns of care, healthcare resource utilisation and event histories in subjects with recurrent ovarian cancer in selected European countries TROCADERO (Treatment of Recurrent Ovarian Cancer And Description of Events, Resources and Outcomes)

Investigators and Study Centres: This study was conducted at 36 centres in 3 countries: Germany, France and Spain. Centres and Principal Investigators are listed in Appendix 3.

Study administrative structures:

The Study Sponsor was:
Amgen Ltd

Key persons responsible for study at Amgen were:

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Sandrine Cure, Senior Director, HEOR Operations
Medical Advisor:
Jean Siebenaler, Senior Medical Director, Life sciences
Site Management Centre (SMC):
Mansour Aouadj, Site Management Centre Manager

Publication(s): No relevant publications or conference proceedings up to the date of this report.

Study Period: 18th October 2012 – 21st August 2013

Development Phase: Not Applicable

1. INTRODUCTION AND OBJECTIVES

1.1 Disease and therapeutic area

Ovarian cancer (OC) is the sixth most common cancer in women (Garcia et al, 2007) causing more deaths per year than any other cancer of the female reproductive system. In the European Union (EU), 44,483 women were diagnosed with ovarian cancer in 2012 and a total of 30,079 deaths were attributed to ovarian cancer (Ferlay et al, 2013). The case-fatality ratio for ovarian cancer is 68%, making it one of the most deadly cancers.

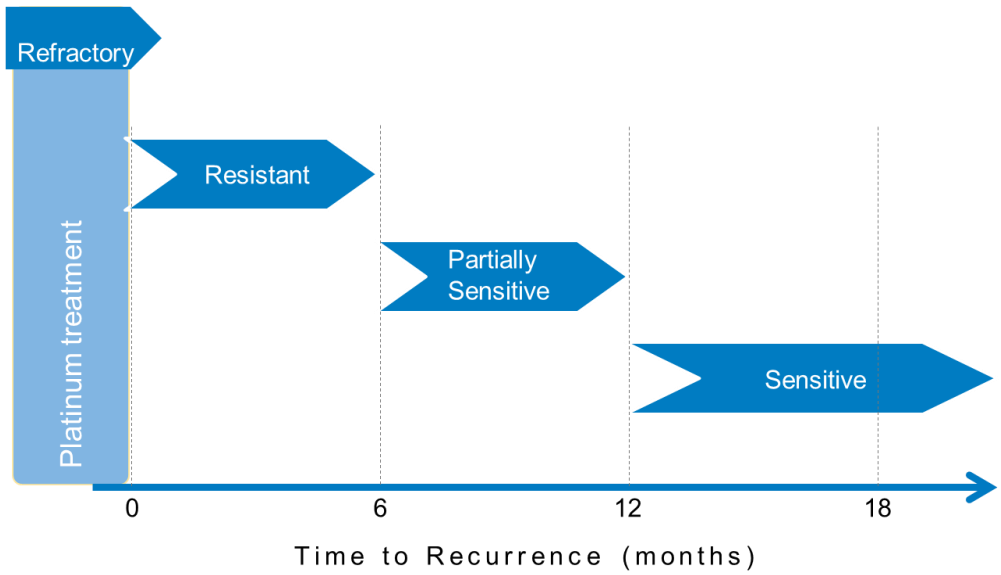
One of the key reasons why ovarian cancer is so deadly is that most patients are diagnosed with advanced disease. Despite receiving a combination of surgery and chemotherapy, about 80% of the patients with advanced stage [International Federation of Gynaecology and Obstetrics (FIGO) IIB–IV] epithelial ovarian cancer will relapse during or after adjuvant taxane/platinum-based chemotherapy, with half of these patients recurring within 12 months (du Bois et al, 2009). Only about 20% of patients with advanced ovarian cancer will be disease-free at 10 years following first-line treatment (du Bois et al, 2009).

The treatment landscape in recurrent ovarian cancer is heterogeneous and the standard of care varies. Treatment decisions may be influenced by factors such as patient age, performance status, comorbidities and prior treatment, notably toxicity. A key factor influencing the selection of second-line regimens is an assessment of the patient's past sensitivity to platinum, which is inferred from the platinum free Interval (PFI). Patients with recurrent disease may be divided into four categories, henceforth referred to as PFI category ("platinum-refractory", "platinum-resistant", "partially platinum-sensitive", and "platinum-sensitive") (Figure 1). The longer the time from the end of platinum based therapy to disease recurrence, the more likely patients are to receive another platinum-based regimen. However, the response to platinum is diminished after each additional line of therapy, highlighting a medical need for an efficacious, non-platinum based therapy.

Recent research has led to a number of promising new treatments for recurrent ovarian cancer. Amgen is developing trebananib (AMG 386), a novel anti-angiogenic agent that inhibits tumour angiogenesis by preventing the interaction of angiopoietins 1/2 with the Tie2 receptor. A possible initial indication for trebananib (AMG 386) will be for patients

with recurrent ovarian cancer who are resistant or partially sensitive to platinum-based regimens.

Figure 1. Relationship between platinum-free interval and platinum sensitivity



Source: Adapted from NICE guidance TA 91 (NICE TA 91 2008)

1.2 Rationale

There is currently little evidence in the published literature on treatment patterns and outcomes associated with recurrent ovarian cancer patients by platinum sensitivity. In particular, for patients whose disease recurs within 6 – 12 months (classified as partially platinum sensitive (PPS)) limited information is available on their treatment history, clinical characteristics, outcomes, demographics and prognosis. Clinical guidelines recommend a platinum based regimen when the disease recurs 6 months or later following platinum based first-line therapy. However, evidence from routine clinical practise indicates that up to one third of patients in the partially platinum-sensitive group actually receive a non-platinum based regimen. The present study offers the opportunity to identify amongst partially platinum-sensitive patients any differences in terms of clinical characteristics, outcomes and prognosis between those patients who do and do not receive further platinum-based therapy.

The clinical characteristics, outcomes and prognosis of patients using weekly taxol vs. the three-weekly regimen will also be identified. Since AMG 386 has been administered weekly with a taxol (taxol is usually administered in a three-weekly schedule) this study

will also help to better understand the future target population for Trebananib (AMG 386).

1.3 Study objectives

1.3.1 Primary study objective

- In recurrent ovarian cancer subjects, to evaluate the platinum-free interval for partially platinum-sensitive subjects who receive platinum-containing treatment at the first recurrence and those who do not.

1.3.2 Secondary study objectives

- To describe at the time of first recurrence the clinical characteristics and demographics of the partially platinum-sensitive subgroup by receipt of a platinum versus a non-platinum based regimen and to describe these characteristics in relation to the other subgroups of platinum-sensitive, resistant and refractory subjects.
- To estimate the incidence and duration of clinical events by platinum subgroups and treatment.
- To estimate key cost-driving components of healthcare resource utilisation (HCRU), such as hospital stays, surgical procedures and anti-tumour therapy.
- To reconstruct anti-tumour treatment histories over the course of disease by documenting successive regimens and components, the duration of each line of treatment, and the interval between treatment lines, and to report same by PFI.
- To investigate the demographic and clinical characteristics of subjects on weekly versus three-weekly taxanes (for platinum-sensitive and partially platinum-sensitive subjects on combination therapy and partially platinum-sensitive and platinum-resistant subjects on single-agent taxane therapy).

1.4 Study hypothesis

The study was descriptive and was not intended to test any pre-specified hypotheses.

1.5 Study management

Amgen, as study sponsor, outsourced the study to a Contract Research Organisation (CRO), OptumInsight (OI). OI was responsible for clinical operations including: creation of an electronic data capture system (EDC), recruitment and management of the relationship with all participating centres through a study coordinating centre (SCC), programming of the study database and transfer of test and final datasets to Amgen. The SCC recorded all aspects of study status, including centre recruitment, construction

of the sampling frame, selection of subjects, centre monitoring and data capture with the aid of an electronic data capture system. OI took primary responsibility for data quality assurance procedures but data review was undertaken by both Amgen and OI. Amgen retained responsibility for the study design, governance, supervision of OI, statistical analysis and reporting. Amgen retained the overall supervision and was responsible for Safety of Adverse Event Reporting.

A Steering Committee (SC) meeting was organised by Amgen once the interim analysis results were available. The SC was composed of functional representatives from Amgen, two Lead Investigators (one from Germany and one from France) and the Study Coordinating Investigator from France. The main aim of the meeting was to share preliminary results with clinical investigators in order to allow the study team to receive feedback on the quality and plausibility of the clinical data collected up to that point.

2. STUDY DESIGN AND METHODOLOGY

This is a retrospective, observational cohort study of subjects with recurrent disease following primary diagnosis of defined types of ovarian cancer. It is a descriptive study of data extracted from anonymised subject records (a "chart review"). Data was extracted from paper and/or electronic records ("charts") retained by the treatment sites into electronic case record forms (eCRFs) to create a study database. Subjects were followed from recurrence to their last date of contact available, in order to construct Healthcare Resource Utilization (HCRU) histories and longitudinal records of clinical events.

2.1 Source population

This chart review included 380 subjects (150 subjects from France, 148 subjects from Germany and 82 subjects from Spain) diagnosed with recurrent epithelial ovarian, peritoneal, or fallopian tube cancer, who had their first disease recurrence between 01 January 2008 and 30 June 2011 and who had been treated with platinum therapy as a first-line treatment.

2.1.1 Site selection

Fifteen sites were selected from Germany, 13 sites from France and 8 sites from Spain, with the goal of selecting approximately 10 subjects per site. Hospital sites with oncology units that retained sufficient medical information in records for treatment of advanced ovarian cancer were eligble for inclusion in this study. In addition, the following site inclusion criteria had to be met:

- All incident cases of recurrent epithelial ovarian, peritoneal or fallopian tube cancer diagnosed and registered at the centre
- Cases recorded at the site since January 2008
- Caseload permitted the identification of approximately 10 potentially eligible cases.

Potential sites were administered a feasibility questionnaire to determine whether they met the above criteria.

2.1.2 Case identification and subject selection

Patients were selected at the site level once each site had completed the screening phase. This phase consisted of collecting initial data for all patients diagnosed with recurrent ovarian cancer, which provided the information necessary to identify eligible patients. The requested inclusion/exclusion criteria were:

- Inclusion criteria
    - Patients were at least 18 years of age at the time of diagnosis
    - Patients received a primary diagnosis of invasive epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
    - Patients received at least one line of platinum therapy after the primary diagnosis date
    - Patients had at least one case of recurrent or progressive epithelial ovarian, primary peritoneal or fallopian tube cancer after first-line platinum therapy
    - Patient's first recurrence (or progression) of ovarian cancer after completion of (or during) first-line therapy occurred within the eligibility period of 1 January 2008 - 30 June 2011
- Exclusion criteria
    - Enrolment during the eligibility period in a clinical trial with a compound without current approval for use in patients with ovarian cancer in the EU

Definition of the end date of the first-line platinum therapy was described in the updated eCRF guidelines v2.0 dated 15 October 2012. If a patient had received more than one platinum therapy during their first-line chemotherapy, the end date of the last platinum agent received in the first-line was used in the definition of PFI and determination of PFI category after first recurrence.

Based on the above-mentioned inclusion and exclusion criteria, all potentially eligible patients were identified from included sites and sent to OI for the second phase of the patient selection process. Supplementary information was used to determine to which platinum subgroup each patient belonged to: i.e. platinum-sensitive, partially platinum-sensitive (treated with or without platinum after their first recurrence), platinum-resistant and platinum-refractory.

- Supplementary information
    - Primary ovarian cancer diagnosis date
    - First platinum chemotherapy (e.g. carboplatin, cisplatin, oxaliplatin, other platinum) start and end dates

- Date of first recurrence or progression after or during first-line platinum therapy
- Whether or not patients did receive platinum agent(s) after the first recurrence and before the second recurrence

Once the PFI category was assigned, patients were selected at random within the PFI category, considering that each site were to fully extract through the eCRF no more than 10 patient records.

In order to ensure adequate representation, the sample sizes were fixed so that at least 126 partially platinum-sensitive subjects could be enrolled into the study, including 63 partially platinum-sensitive subjects treated with platinum at first recurrence and 63 partially platinum-sensitive subjects treated with non-platinum based chemotherapy at first recurrence. It was assumed that the PFI values within each subcategory of the partially platinum-sensitive patient subgroups were normally distributed with common standard deviation of 1 month. Under these assumptions 63 subjects in each partially platinum sensitive subcategory would provide a 95% confidence interval for the true mean PFI of half-width 0.25 months. This level of precision was thought to be sufficient for the descriptive purposes of this study. In addition to the 126 partially platinum sensitive patients, 100 subjects were planned for enrollment into the platinum sensitive subgroup, 90 subjects into the platinum resistant subgroup, and 64 subjects into the platinum refractory subgroup.

During the study period, however, some of the patients that had initially been selected by the site and to whom a PFI category had already been assigned had to be replaced for the following reasons:

- Alive but refused to sign the Informed Consent Form (ICF) or did not complete the ICF in required time period
- Alive but with a loss to follow up or non contactable
- Patients' relatives rejected the ICF
- Deceased patients with no relatives available to sign the ICF
- Selected patients with key incomplete or missing data

Because some of the initially selected patients had to be replaced as the study progressed the final number of patients in the four platinum subgroups was different to

the initial selected study sample cohort. The change in PFI patient distribution was mainly due the unavailability of subjects in the PFI category of interest in the selected sites. However in a few cases, patients had a change in PFI category following a review of their full eCRF data by Amgen which also impacted the final PFI patient distribution.

2.1.3 Number of subjects enrolled

The final number of subjects enrolled into the study is presented by country and by PFI category at first recurrence in Table 1. In total, data abstraction included 39 platinum-refractory, 108 platinum-resistant, 99 partially platinum-sensitive and 134 platinum-sensitive patients.

Table 1. Number of Subjects Enrolled by Country and PFI Category

	Platinum Sensitivity Determined after Receiving First Line of Platinum Therapy				
Country/Site	**Refractory**	**Resistant**	**Partially Sensitive**	**Sensitive**	**All**
France - n (%)	**22 (56.4%)**	**45 (41.7%)**	**34 (34.3%)**	**49 (36.6%)**	**150 (39.5%)**
Germany - n (%)	**11 (28.2%)**	**37 (34.3%)**	**44 (44.4%)**	**56 (41.8%)**	**148 (38.9%)**
Spain - n (%)	**6 (15.4%)**	**26 (24.1%)**	**21 (21.2%)**	**29 (21.6%)**	**82 (21.6%)**
Total	**39 (10.26%)**	**108 (28.24%)**	**99 (26.05%)**	**134 (35.26%)**	**380 (100.0%)**

Source: Table 1.0 Subject Enrollment by Country – (Full Analysis Set, All countries)

Among the 380 subjects enrolled into the study, only 350 subjects received any anti-tumour medication after first-recurrence. Enrolment breakdown of these subjects by country and PFI category is shown in Table 2.

Table 2. Subjects who Received Anti-Tumor Medication after First Recurrence by Country and PFI Category

	Platinum Sensitivity Determined after Receiving First Line of Platinum Therapy						
			Partially Sensitive				
			Received platinum therapy				
Country/Site	Refractory	Resistant	Yes	No	Total	Sensitive	All
France – n (%)	19 (52.8%)	40 (40.8%)	24 (42.9%)	10 (27.8%)	34 (37.0%)	45 (36.3%)	138 (39.4%)
Germany – n (%)	11 (30.6%)	34 (34.7%)	17 (30.4%)	22 (61.1%)	39 (42.4%)	50 (40.3%)	134 (38.3%)
Spain – n (%)	6 (16.7%)	24 (24.5%)	15 (26.8%)	4 (11.1%)	19 (20.7%)	29 (23.4%)	78 (22.3%)
Total	36 (10.3%)	98 (28.0%)	56 (16.0%)	36 (10.3%)	92 (26.3%)	124 (35.4%)	350 (100.0%)

Source: Table 1.1 Subject Enrollment by Country and Investigator - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

2.2 Data collection and extraction methods

Data collection was performed by retrospective review of patient records. During the data collection OI supervised and monitored site staff abstracting data from patient charts into an eCRF. The eCRFs were implemented using OI's web-based electronic data capture (EDC) system. All data entered into the EDC system by site study staff was pseudonymised (key-coded) to ensure patient confidentiality and compliance with country ethical and data regulations. No patient-identifying information was available to Amgen or the CRO. There was no formal source data verification (SDV). However, the structure and programming of the EDC system did permit remote monitoring of the pseudonymised data by Amgen or the CRO, as the study data accrued in real time, allowing data queries to be raised with sites.

OI monitored site performance and carried out a quality control (QC) check on a proportion of records. OI was responsible for compiling SAS datasets using its own database management tool, suitable for potential ad hoc analyses by Amgen Biostatistical Programming and Biostatistical Science teams.

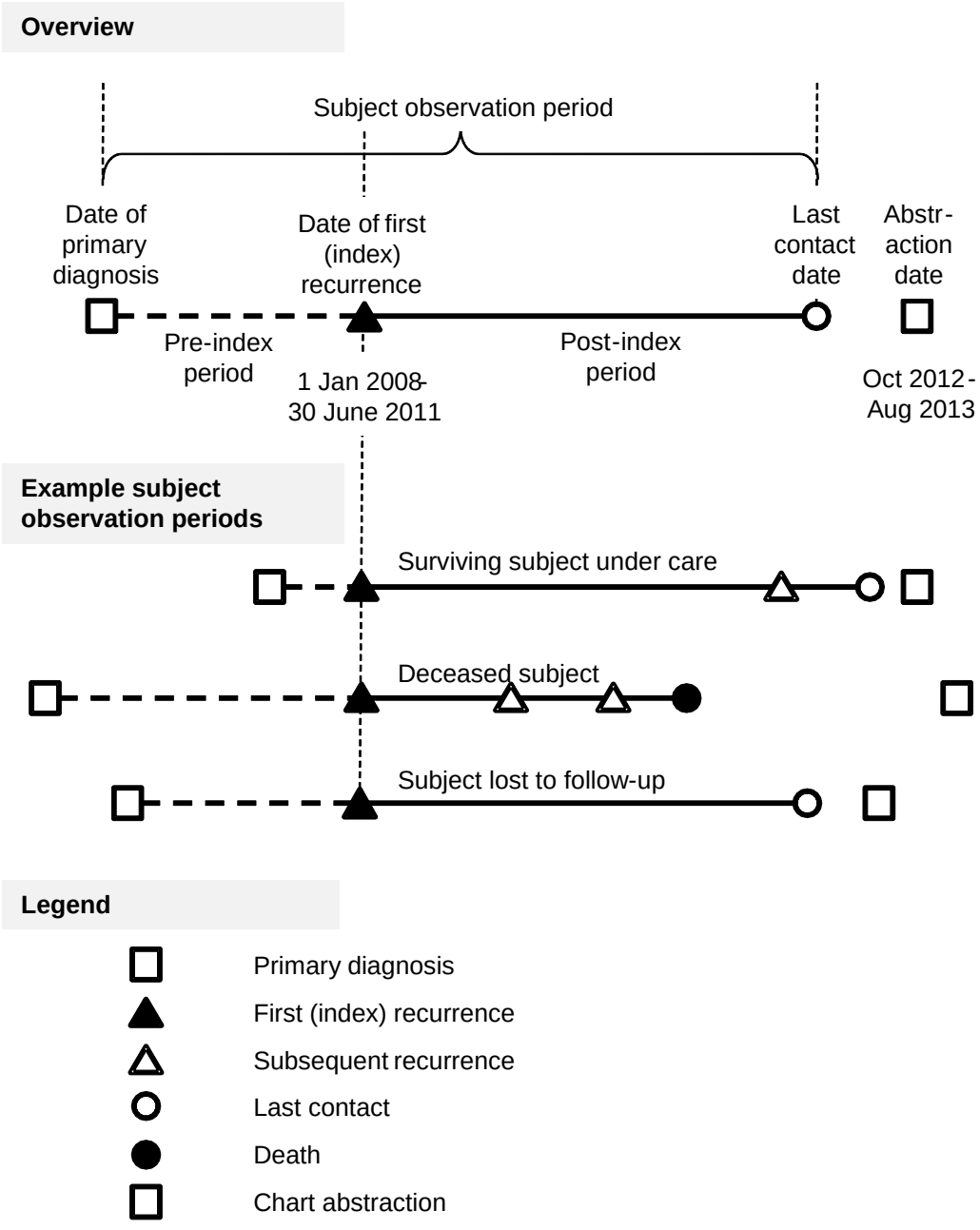
2.2.1 Applicable study period

The subject observation period for data to be abstracted covered two periods either side of the index date, which was defined as the date of index recurrence. The first period (the pre-index period) extended from the date of index recurrence retrospectively, if possible, to the date of primary diagnosis of ovarian cancer, thereby providing information on subject characteristics and first-line treatment received. The second period was defined as the post-index period, which extended prospectively in time from

the date of index recurrence until death, loss to follow up or date of the last recorded data entry. Both periods are shown diagrammatically in Figure 2.

As the figure shows, although the index recurrence was defined as the first recurrence occurring during the eligibility period, defined as 1 January 2008 to 30 June 2011, it was possible that further recurrences occurred during the post-index period. By definition no recurrences occurred during the pre-index period.

Figure 2. Subject observation period and event definitions



Subjects lost to follow-up at the date of chart abstraction were censored at the last contact date.

2.2.2 Pre-index data

Data collected for the pre-index period included details of subject demographics, clinical characteristics, clinical history, hospitalizations, surgical and diagnostic procedures, as summarised in Table 3 below. Chemotherapy data was used to calculate the PFI.

Table 3. Summary of data types collected for the pre-index period

Subject characteristics at the time of diagnosis of primary tumour	• Site(s) of tumour • Primary tumour type: ovarian, primary peritoneal, fallopian tube • Invasive sites • Age, height and weight at diagnosis • Date of diagnosis • Presence of measurable disease and ascites • FIGO stage
Participation in a permissible clinical trial(s)	• Start and end date(s) of participation • Name and type of trial • Name of intervention/s
Clinical history during pre-index period	• Existing comorbidities at or prior to primary diagnosis • History of other cancers • Performance status • Diagnostic imaging dates, procedure types and results • Surgical procedures: Reason, dates and procedure type • Hospitalizations: Admission and discharge dates, ward type and reason for admission
Anti-tumor medications during pre-index period	• Anti-tumor medication name with start and stop dates • Weight and body surface area (BSA) at start of each medication • Details of each platinum-containing regimen such as route, dose, frequency, number of completed cycles, etc.

	• Date of last exposure to platinum • Reason(s) for discontinuation of platinum-containing regimen

2.2.3 Post-index data

Categories of data collected for the post-index period are summarised in Table 4. All data were accompanied by dates when applicable and available.

Table 4. Summary of data types collected for the post-index period

Subject characteristics at index date	• Index date (date of diagnosis of first recurrence)
Platinum-free interval categories	• PFI categories at each recurrence (platinum sensitive, partially platinum sensitive, platinum resistant, platinum refractory). These categories were inferred programmatically from last stop dates of platinum prior to recurrence
Participation in a permissible clinical trial(s)	• Start and end date(s) of participation • Name and type of trial • Name of the interventions
Clinical disease status	• Disease progression (i.e. progressive disease, stable disease, partial response, complete response) • Date of documentation • Measurable disease • Recurrence date • Presence of ascites at recurrence • Diagnostic imaging dates, presence of measurable disease, procedure types and results • Sites of disease • Evidence of progression or recurrence including type of evidence (e.g., physical exam, rising CA-125 level, pelvic ultrasound or CT scan etc.) and date of progression or recurrence
Disease recurrence and progression	• Number of recurrences • Dates of each recurrence • Site(s) of recurrence • Method(s) used to assess recurrence • CA-125 values • Site(s) of metastases

	• Death
Clinical events	• Surgical complications • Chemotherapy side-effects (hospitalised) • Chemotherapy side-effects (not hospitalised) • Dates of admission and discharge • Admission ward entry type (s) • Subsequent ward changes (unit type and transfer date) • Reason for hospitalisation • Type of event • Severity grade (mild, moderate, severe)
Adverse drug reaction (ADR) and serious adverse drug reaction (SADR) reporting event (to comply with Amgen safety SOP)	• Type of Amgen drug and event code • Date of documentation • Adverse event (AE) or adverse drug reaction (ADR), start and stop dates, AE grade, outcome, hospitalised due to the AE, if related to an Amgen product, the product name and if the AE was serious or not.
Anti-tumour medications during post-index period	• Medication name with start and stop dates • Weight and BSA at start of each medication • Details of each regimen such as route, dose, frequency, number of completed cycles etc. • Components of each regimen • Cycle start and stop date(s) • Total number of cycle treatment days (prescribed vs. received) • Total cycle dose (prescribed vs. received) • Route of administration (ROA) • Cycle duration and number of cycles completed • Discontinuations and modifications within or between cycles • Body surface area (BSA) at start of each cycle

Oncology supportive pharmacotherapy	• Major cost-driving categories, e.g. haematopoietics, but not analgesia or antiemetics. Medication name, start and stop dates, dose, route and frequency
Inpatient Hospitalisation (i.e. overnight stays)	• Dates of admission and discharge • Admission ward entry type (s) • Subsequent ward changes (unit type and transfer date) • Reason for admission • Discharge codes - admission and discharge dates, ward type and reason for admission
Surgical procedures	• Type of procedure • Date of procedure • Procedural complications reason, date and procedure type
Diagnostic and imaging procedures	• Type of procedure • Date of procedure
Status at last recorded data entry	• Continuing under care of institution • Known under care of another institution • Lost to follow-up • Death and death date if applicable

2.3 Transformations and operations on the data

2.3.1 Data from non-chart sources

Some study variables required derivation from the primary data abstracted from charts. These are summarised in Table 5. In order to categorise subjects according to platinum sensitivity, the PFI was calculated, defined as the time interval between last exposure to a platinum agent during the line of treatment and the subsequent date of disease progression as noted during or following discontinuation of the prior platinum agent. The post-index period was divided into time-to-recurrence intervals for each subject, defined to correspond with time-to-time intervals between successive recurrences. It was also divided into line-of-therapy intervals. Anti-tumor medications were assigned a line of therapy by considering the receiving period with respect to recurrence dates. For example, a medication received after first recurrence and before the second recurrence was identified as second-line.

Table 5. Summary of variables requiring derivation from primary data

Platinum-free Interval	• PFI category at each recurrence (platinum sensitive, partially platinum sensitive, platinum resistant, platinum refractory). These categories were inferred programmatically from stop dates of platinum prior to recurrence of interest
Recurrence-free Survival	• Time between primary diagnosis and first recurrence, time from first recurrence to the earliest of second recurrence or death, time from second recurrence to the earliest of third recurrence or death, and so on
Line of therapy intervals	• Time between start and stop of successive lines of therapy: decision rules were defined to adjudicate this

2.4 Handling of missing data

For categorical items, if any subjects had missing data, the number and percentage missing (out of the total analysis set) were presented as appropriate. This approach was implemented as missing data were not assumed to be missing at random. For items which had a category of "unknown" collected on the eCRF, the number and percentage of "unknowns" were presented separately from the missing category. In general for analyses which involved dates, if the day of the month was missing then the 15th of the month was used to impute the missing day-part. The primary ovarian cancer diagnosis date, first platinum anti-tumor medication start date, first platinum chemotherapy end date, and first progression date were all required for a subject to be enrolled into the study.

When only the day-part of the start date of an adverse drug reaction was missing, the first day of the month was used to impute the missing day-part. If only the day-part of the stop date of an adverse drug reaction was missing, the last day of the month was used to impute the missing day-part. Regarding the missing start or stop dates of anti-tumour medication regimens, the following rules were implemented to impute the missing dates:

- If both start and stop dates were missing no imputation was performed

- When only the day-part was missing, then the first day of the month was used if it was a start date and last day of the month if it was the stop date that needed to be imputed
- If the start date was non-missing and the stop date was missing, then the number of cycles completed and the dosing frequency, if both available, were used to impute the missing stop date. However, this was done only if the frequency was of the form '**every week**' or '**every x weeks**'. In such cases stop date was imputed by:

  minimum of [start date+nfreq x 7 x (cycles completed -1), death date, final chart entry date],

  where nfreq=1 if dosing frequency was 'every week', nfreq=2 if the dosing frequency was 'every 2 weeks', and in general nfreq=x if the dosing frequency was 'every x weeks'.
- If the stop date was non-missing and start date was missing, then the number of cycles completed and the dosing frequency, if both available, were used to impute the missing start date. Again, this was done only when the dosing frequency was of the form '**every week**' or '**every x weeks**' and the missing start date was imputed by:

  Maximum of (stop date - nfreq*7*(cycles completed-1), primary diagnosis date), where nfreq is defined as above.
- In all other cases, if the start date was available but the stop date was missing, then we imputed the stop date with the start date and if the start date was missing and stop date was available, then we imputed the start date with available stop date.

For data on anti-tumour medication, surgery, hospitalisation, and other events which were entered into the eCRFs as incomplete the following table describes a set of rules that were adopted as the minimum data for entries to be included in the analyses:

Table 6. Data Requirement by Item

Item	Minimum Data Required
Non-platinum anti-tumor medication	To count as Yes, the subject must have had an entry with: (i) a drug name AND (ii) at least one partial (at least month and year

	recorded) start or end date.
Platinum anti-tumor medication	To count as Yes, the subject must have had an entry with: (i) a platinum containing drug name AND (ii) at least one partial (at least month and year recorded) start or end date
Recurrence date	To be counted as having progression, the subject must have had an entry with: (i) a partial (at least month and year recorded) progression date
Adverse event	To be counted as having adverse event, the subject must have had an entry with: (i) adverse event AND (ii) at least one partial (at least month and year recorded) start or end date
Surgery procedure tumor	To count as Yes, the subject must have had an entry with: (i) a procedure type AND (ii) a partial (at least month and year recorded) date
Hospitalisations	For each ward type, to count as admitted, the subject must have had an entry with: (i) Ward type code (ii) at least one partial (at least month and year recorded) date (admin date, discharge date or transfer date)
Oncology supportive pharmacotherapy	For each pharmacotherapy type, to count as Yes, the subject must have had an entry: (i) a drug name AND (ii) at least one partial (at least month and year recorded) start or end date
Death	To be counted as having died, the subject must have had an entry with: (i) a partial (at least month and year recorded) date of death

2.5 Interim analysis

A formal interim analysis was planned in order to assess data quality. The interim data cut-off date was 23rd April 2013. All planned Tables, Figures and Listings for the primary analysis were generated for the interim analysis.

3. STUDY ENDPOINTS AND OUTCOMES

3.1 Baseline patient characteristics

The following baseline characteristics were collected and summarized for all subjects by PFI category at first recurrence:

- Age, height, weight and BSA at primary diagnosis

- Disease and other characteristics (tumour type, presence of measurable disease and ascites, FIGO stage, sites of disease, history of other cancers, clinical trial participation) at primary diagnosis.

3.2 Primary endpoints and outcomes

The primary endpoint of the study was to evaluate the platinum-free interval (PFI) between partially platinum-sensitive subjects who received platinum-containing treatment following first recurrence and those who did not. PFI was also calculated and summarised by PFI category at first recurrence.

3.3 Secondary endpoints and outcomes

The following secondary endpoints and outcomes were collected as specified in the Statistical Analysis Plan (SAP):

- Time from primary diagnosis to first recurrence was calculated for all subjects and summarised. Recurrence-free interval, defined as time from each recurrence to earliest of subsequent recurrence or death, was calculated and summarised by latest PFI category based on the most recent platinum therapy received prior to the recurrence of interest. Subjects whose disease did not recur or died were censored at the last chart entry date. When censored data were present, Kaplan-Meier estimates of median and associated confidence intervals were calculated and presented. Recurrence-free interval prior to first recurrence and each subsequent recurrence were also categorically summarised. Categories included 0-6 months, >6 - <=12 months, and > 12 months. Additionally, overall survival (OS) data were also summarised using the Kaplan-Meier method.

- Co-morbidities at primary diagnosis by system and co-morbidity were categorically summarised. Number of hospitalisations, total time in hospital, ward type (i.e. Oncology Unit) and reasons for hospitalisation were summarised, further breaking down by hospitalisations prior to first recurrence (pre-index period) and that after first recurrence (post-index period). Similar summaries were produced for surgical procedures data. These included reason for surgery, the procedure type, and post-op complications.

- Anti-tumour medications received after primary diagnosis were summarised by line of therapy and medication. Medications received after primary diagnosis and on or prior to first recurrence were considered as first-line therapy. Medications received after first-recurrence and on or prior to earliest of second recurrence or

death were considered as second-line therapy. Other lines of therapy were defined analogously. Based on the primary diagnosis date and subsequent recurrence dates, total data collection period for each subject were broken down into sub-periods; period between primary diagnosis and first-recurrence, first-recurrence and second recurrence, second recurrence and taxane therapy was also summarised by taxane regimen (for example, weekly and three weekly) further breaking down by PFI category at first-recurrence.

- Demographics and clinical characteristics of subjects who received taxane therapy were also summarised by taxane regimen further breaking down by PFI category at first-recurrence.

3.4 Safety monitoring

Safety reporting followed Amgen policy specific to retrospective observational studies.

3.4.1 Definition of adverse events and adverse drug reactions

An adverse event (AE) or adverse drug reaction (ADR) was defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which did not necessarily have to have a causal relationship with the treatment. An AE could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE included worsening of a pre-existing medical condition. For the purpose of this study, AEs and ADRs were considered as synonyms.

A serious adverse event (SAE) was defined as any adverse event that:

- was fatal
- was life threatening (placed the subject at immediate risk of death)
- required inpatient hospitalisation or prolongation of existing hospitalisation
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect
- was some other significant medical hazard

3.4.2 Reporting procedures for adverse drug reactions (ADR)

For the purpose of this study, an adverse drug reaction (ADR) was any adverse event (as defined above) that the treating physician considered to be causally associated with the use of any Amgen product, per the medical record, and was identified in the course

of the retrospective record review. Any clearly documented ADRs for an identifiable subject related to Amgen product(s) was collected and reported on the study data collection form. If an AE was related to an Amgen product(s), the product name (s) and information on whether it was a serious AE was collected and reported on the study data collection form.

3.4.3 Reporting procedures for serious adverse drug reactions (SADRs)

All SADRs related to Amgen product(s) were to be reported to Amgen Global Safety within one business day of discovery or notification. Initial SADR information and all follow-up information were to be recorded on the SADR form and faxed to Amgen Global Safety.

3.4.4 Pregnancy reporting

All pregnancies occurring in female patients while taking Amgen products, and all pregnancies occurring in female partners of male patients taking Amgen products were also to be reported to Amgen's global Pregnancy Surveillance Program. Reporters were to contact the local or nearest Amgen office using the phone number provided in the regional product label.

4. STATISTICAL METHODS

In general, results are presented for the cohort of subjects who received any anti-tumour medication after first recurrence, and include a breakdown by PFI categories at first recurrence. Appropriate descriptive statistics were produced for each parameter. For continuous data, number of subjects, mean, standard deviation, median, minimum and maximum are presented. For categorical data (including yes/no categories), the frequency and percentage in each category are presented as appropriate.

This study was not intended to test any formal pre-specified hypotheses; however, confidence intervals (CI) were constructed as necessary to understand the population characteristics of interest. Two-sided 95% confidence intervals were used to assess endpoints, where relevant.

4.1 Baseline patient characteristics

Demographic and baseline characteristics (endpoints listed in the pre-index period and at the time of primary ovarian cancer diagnosis) were summarised using descriptive statistics and included a breakdown by PFI subgroups.

The time between primary ovarian cancer diagnosis and first progression/recurrence was calculated and reported as a continuous endpoint and also categorized into 3 categories: 0 ≤ 6 months, > 6 to ≤ 12 months, >12.

4.1.1 Analysis of primary endpoint

The PFI (months) as a continuous variable was summarised using descriptive statistics for the PFI categories and partially platinum sensitive subcategories.

4.1.2 Analyses of secondary endpoints and outcomes

Secondary endpoints for this study were categorised according to the following three periods in which they occurred: i) at the time of diagnosis of the primary tumour, ii) during the pre-index period (i.e. from primary diagnosis to first recurrence) or iii) during the post-index period (i.e. after the first recurrence). Many of the variables in the first two categories were of interest primarily for the purposes of categorising and sub-setting the study population for analysis of outcome variables in the post-index period.

The intention of the secondary endpoints listed in section 3.3 is to summarise the clinical characteristics and demographics of the partially platinum sensitive subcategories in relation to other PFI subgroups of platinum sensitive, resistant, and refractory subjects. The clinical characteristics and demographics of taxane subgroups were also summarised. All secondary endpoints in section 3.3 were summarised using descriptive statistics by PFI subgroups and partially platinum sensitive subcategories.

The incidence of receiving first-, second- and third-line pharmacotherapy were summarised using the Full Analysis Set who Received Anti-tumour Medication after First Recurrence, the At Risk of Second Line Pharmacotherapy Analysis Set, and the At Risk of Third Line Pharmacotherapy Analysis Set, respectively. If the number of lines of pharmacotherapy exceeded three, then the number of these analyses was extended as required.

Time-to-event endpoints was summarised using Kaplan-Meier methods by PFI categories including partial platinum sensitive subcategories. For each endpoint, the number and percentage of events and censored subjects were reported, as well as the median and its 80 and 95% confidence interval.

4.2 Safety analyses

4.2.1 Adverse events/Adverse drug reactions

Adverse events data collected during the data collection period were descriptively summarized by PFI category at first recurrence.

If a subject had more than one episode of a particular adverse event and any of these had a missing severity grade, then the maximum severity was calculated from the non-missing severity grade(s). A subject was only to be reported in the tables as having a missing worst grade if all episodes of the adverse event were of unknown severity grade.

The number and percentage of subjects experiencing any ADRs, any serious ADRs and any non-serious ADRs were reported for each Amgen drug.

5. SUMMARY OF RESULTS

Although data were collected in this study for the Full Analysis Set (all subjects enrolled into the study (N=380)), the focus of this report is on the subset of patients who received anti-tumour medication after first recurrence (N=350).

5.1 Subject characteristics

The mean age at primary diagnosis for 350 patients who received anti-tumour medication after first recurrence was 62.6 ± 11.4 [range 20.9, 87.8] years. For the patients in the partially platinum sensitive subgroups who received platinum therapy at first recurrence the mean age at primary diagnosis was 63.4 ± 11.5 [range 35.0, 83.6] years. The partially platinum sensitive subgroup of patients who did not receive a platinum therapy at first recurrence had a mean age at primary diagnosis of 61.5 ± 13.0 [range 22.1, 79.9] years (Table 7).

Table 7. Patient characteristics at primary diagnosis – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	**Yes (N=56)**	**No (N=36)**	Total (N=92)	Sensitive (N=124)	**All (N=350)**
Age (yrs)							
Mean	63.5	63.3	**63.4**	**61.5**	62.6	61.8	**62.6**
SD	10.5	11.2	**11.5**	**13.0**	12.1	11.3	**11.4**
Median	64.5	63.8	**63.3**	**65.7**	63.9	63.1	**63.7**
Q1, Q3	59.6, 71.0	57.3, 70.9	**54.4, 73.3**	**54.4, 71.0**	54.4, 72.0	55.6, 69.7	**56.3, 70.8**
Min, Max	41.3, 82.6	24.8, 87.8	**35.0, 83.6**	**22.1, 79.9**	22.1, 83.6	20.9, 85.6	**20.9, 87.8**

Source: Table 4.1 Demographics at Primary Diagnosis – (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

5.2 Primary endpoint

In the partially platinum-sensitive subgroup of patients who received anti-tumour medication after first recurrence the median PFI was 266 days (Table 8). For the partially platinum-sensitive patients who had received a platinum based therapy after first recurrence the median PFI was 270 days compared to 252.5 days for the patients who had not received a platinum based therapy after first recurrence.

Table 8. Platinum-free interval (in days) after ending platinum therapy as first line – Patients who received anti-tumour medication after first recurrence

Platinum sensitivity determined at the end of line of platinum therapy			
	Partially Sensitive		
	Received platinum therapy		
	Yes	No	Total
Platinum-Free Interval after Ending First Line of Platinum Therapy			
Platinum-Free Interval (days)			
N	56	36	92
Mean	276.2	255.8	268.2
SD	51.0	47.9	50.6
Median	**270.0**	**252.5**	**266.0**
Q1, Q3	237.5, 324.0	211.0, 295.5	224.0, 312.0
Min, Max	184.0, 364.0	183.0, 344.0	183.0, 364.0

Source: Table 16.1.1 Platinum-Free Interval after Ending First Line of Platinum Therapy – (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

5.3 Secondary endpoints

5.3.1 Disease characteristics

Disease characteristics at primary diagnosis for patients who received anti-tumour medication after first recurrence are described by PFI category at first recurrence in Table 9.

5.3.1.1 Tumour type at diagnosis for patients who received anti-tumour medication after first recurrence

The majority of patients who received anti-tumour medication after first recurrence had ovarian cancer (308 patients, 88.0%) with only a smaller proportion presenting with primary peritoneal (24 patients, 6.9%) or fallopian tube cancers (18 patients, 5.1%). A greater proportion of patients had ovarian cancer (34 patients, 94.4%) in the partially platinum-sensitive subgroup of patients who did not receive platinum therapy at first recurrence compared to the subgroup of patients who had received platinum therapy at first recurrence (49 patients, 87.5%) (Table 9).

5.3.1.2 FIGO stage at diagnosis for patients with recurrent ovarian cancer

Of the 350 patients who received anti-tumour medication after first recurrence, the majority of patients (82.0%) had advanced disease at first diagnosis [FIGO stage IIB-IV, 287 patients] and only 9.1% had early disease at diagnosis [FIGO stage IA-IIA, 32 patients]. In the partially platinum-sensitive subgroup, there were more patients with

advanced disease (34 patients, 94.4%) in the group who did not receive platinum therapy at first recurrence compared to those who had received platinum therapy (46 patients, 82.1%) (Table 9).

5.3.1.3 Measurable disease and ascites

Out of the 350 patients who received anti-tumour medication after first recurrence 281 (80.3%) had measurable disease and 167 (47.7%) had ascites. In the partially platinum-sensitive subgroup the proportion of patients with measurable disease was higher in those patients who had not received a platinum-based therapy after first recurrence (31 patients, 86.1%) versus those patients who had received a platinum-based therapy (40 patients, 71.4%). On the other hand, the proportion of patients with ascites was lower in the subgroup of patients who had not received a platinum-based therapy after first recurrence (14 patients, 38.9%) versus those patients who had received a platinum-based therapy (33 patients, 58.9%) (Table 9).

5.3.1.4 History of other cancers at primary diagnosis

A total of 33 patients (9.4%) who received anti-tumour medication after first recurrence had a history of other cancers with breast cancer being the most common (20 patients, 60.6%) (

Table 10). In the partially platinum-sensitive subgroup only 2 patients (5.6%) who had not received a platinum-based therapy after first recurrence had a history of other cancers compared to 5 patients (8.9%) in the subgroup of patients who had received a platinum-based therapy.

5.3.1.5 Performance status at primary diagnosis

In subjects who received anti-tumour medication after first recurrence just over 50% of patients had a performance status score of either 1 (107 patients, 30.6%) or 0 (70 patients, 20.0%). In the partially platinum sensitive subgroup the proportion of patients with performance status score of 1 was higher in those who had received a platinum-based therapy after first recurrence (24 patients, 42.9%) compared to those who had not received a platinum-based therapy (10 patients, 27.8%) therapy (Table 11).

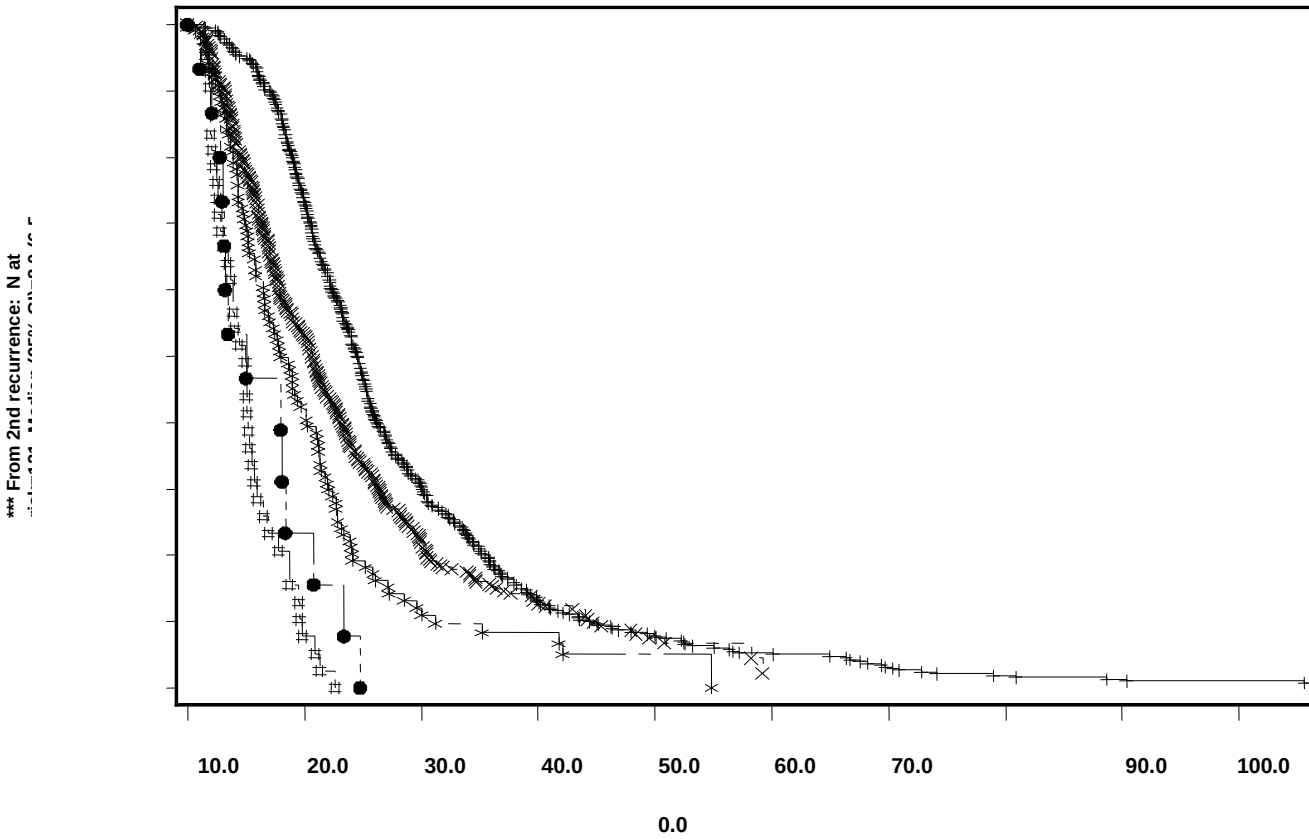
5.3.2 Clinical events

5.3.2.1 Recurrence-free survival

In patients who received anti-tumour medication after first recurrence the median recurrence-free survival time was 10.6 months (CI 9.0, 11.8). The median recurrence-free survival time was the longest among platinum-sensitive patients (15.5 months, CI

13.6, 18.1), followed by partially platinum-sensitive patients (12.0 months, CI 9.9, 14.4), platinum-resistant (6.5 months, CI 5.3, 7.9) and platinum-refractory patients (5.5 months, CI 3.2, 6.9) (Table 12). As the number of recurrences experienced by patients increased the shorter the median recurrence-free survival became. After the second and third recurrences the median recurrence-free survival times were 8.0 months (CI 6.5, 10.2) and 4.9 months (CI 3.1, 5.5), respectively (Figure 3).

Figure 3. Kaplan Meier estimate of recurrence-free survival (in months)



Source: Figure 1 Kaplan-Meier Estimate of Recurrence Free Survival after Primary Diagnosis and Each Subsequent Recurrence

5.3.2.2 Overall survival

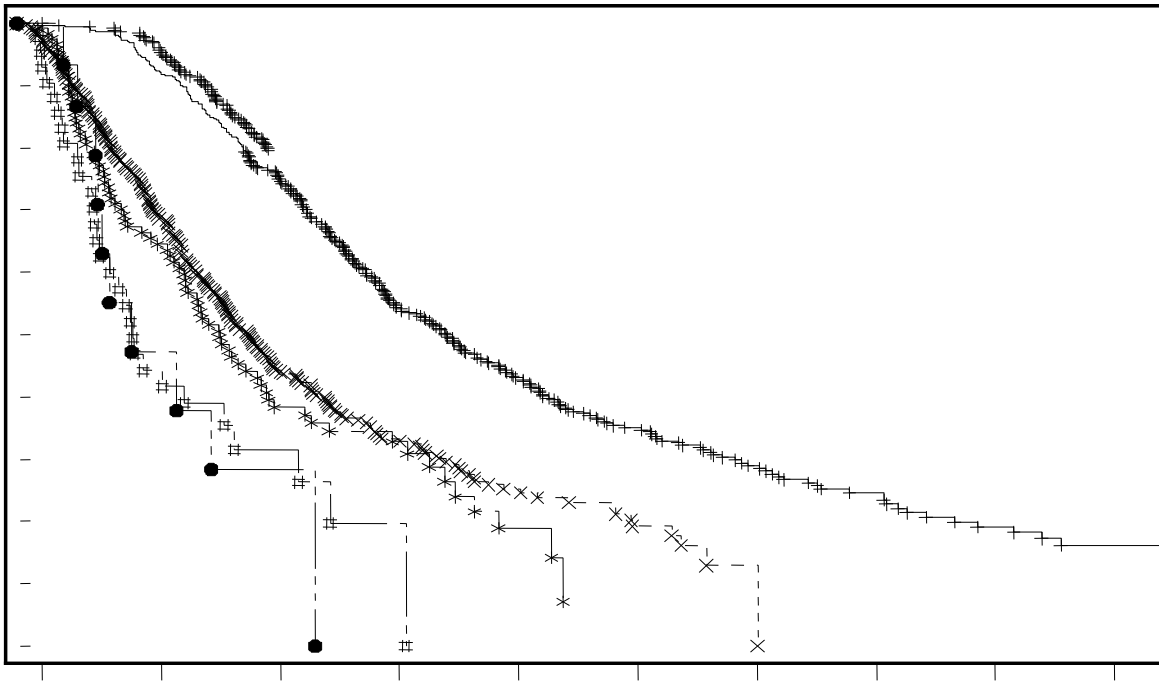
In patients who received anti-tumour medication after first recurrence the median overall survival time after first recurrence was 19.5 months (CI 17.2, 21.5). The median overall survival time was the longest among platinum-sensitive patients (34 months, CI 25.1, 42.3), followed by the partially platinum-sensitive patients (20.5 months, CI 17.7, 24.8), platinum-resistant (12.7 months, CI 10.4, 14.2) and platinum-refractory patients (9.8 months, CI 6.6, 14.9) (***Source: Table 19 Kaplan-Meier Estimate of Recurrence Free Survival after Primary Diagnosis and Each Subsequent Recurrence – (Full Analysis Set, All countries)***

Note: recurrence-free survival time is considered to be the time from primary diagnosis or recurrence of interest to the earliest of recurrence or death from any cause.
If no recurrence or death was observed for a subject, recurrence-free survival time was censored at the last recorded date.
[a] *Status is based on the most recent platinum therapy received.*
[b] *Only the subjects who received treatment after recurrence are considered*

Table 13). As the number of recurrances experienced by patients increased the shorter the median overall survival time became. After the second and third recurrences the median overall survival time were 17.0 months (CI 14.1, 21.1) and 9.7 months (CI 6.7, 18.3) respectively (

Figure **4**).

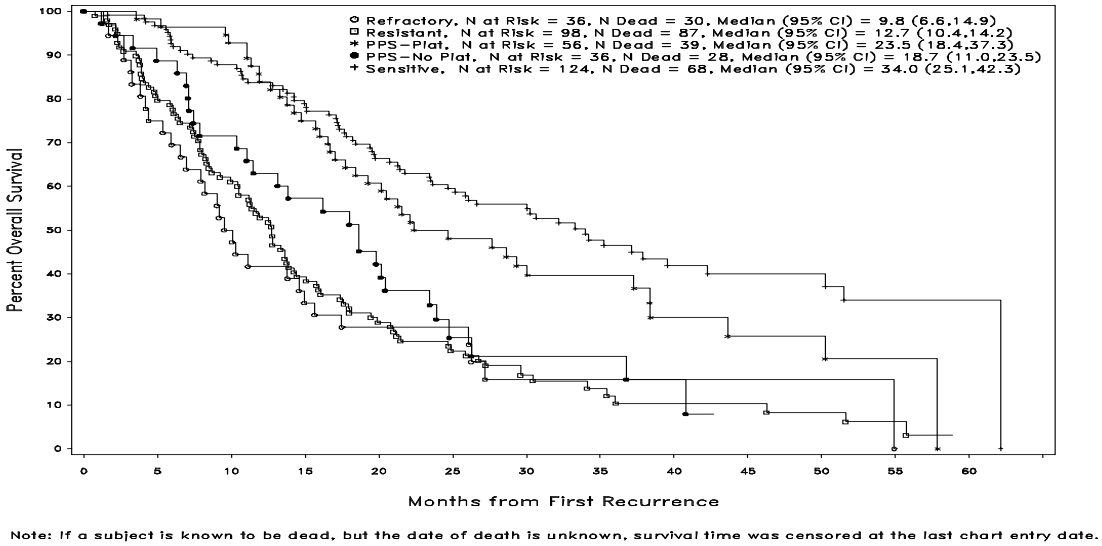
Figure 4. Kaplan Meier estimate of overall survival (in months)



Source: Figure 2 Kaplan-Meier Estimate of Overall Survival after Primary Diagnosis and Each Subsequent Recurrence

The median overall survival after first recurrence in the partially platinum-sensitive patients who had received a platinum-based therapy was 23.5 months (CI 18.4, 37.3) compared to 18.7 months (CI 11.0, 23.5) in those patients who had not received a platinum-based therapy (Table 14) (Figure 5).

Figure 5. Kaplan-Meier plot of Survival After First Recurrance by PFI category at first recurrence.



Source: Figure 3 Kaplan-Meier plot of survival time after first recurrence by PFI category at first recurrence (post hoc analysis)

5.3.2.3 Length of observation

For patients who received anti-tumour medication after first recurrence the median time from primary diagnosis to first recurrence was 14.6 months (range 2.3, 110.0 months). The median time from first recurrence to earliest of death or last record date was 18.4 months (range 0.8, 62.2 months) and the median time from primary diagnosis date to earliest of death or last record date was 35.5 months (range 5.3, 145.5 months). The median time from primary diagnosis to first recurrence was similar between partially platinum-sensitive patients who had (14.5, range 10.2, 19.7 months) vs. who had not (13.7, range 9.9, 19.5 months) received a platinum-based therapy. However the median time from first recurrence to death was longer in the partially platinum-sensitive patients who had received a platinum-based therapy (17.7, range 3.6, 57.9 months) compared to patients who had not received a platinum-based therapy after first recurrence (13.5, range 1.2, 40.8 months) (Table 15).

5.3.2.4 Time to first dose and duration of first line pharmacotherapy

In patients who received anti-tumour medication after first recurrence the median time to first dose from primary diagnosis was 29 days (range 1.0, 378.0 days). The two subgroups of partially platinum-sensitive patients had similar duration of first-line pharmacotherapy (114 vs. 118 days) all drugs considered. However, median time to first dose from primary diagnosis was 8 days higher in the subgroup of patients who did not receive platinum therapy at first recurrence (34.5 days, range 8.0, 205.0) compared to

those who had received platinum therapy at first recurrence (26 days, range 2.0, 150.0) (Table 16).

5.3.3 Co-morbidities

There were small differences between the platinum subgroup categories in the distribution of co-morbidities. The most common co-morbidities among all patients who had received anti-tumour medication after first recurrence were: hypertension (118 patients, 33.7%), followed by diabetes mellitus (25 patients, 7.1%), depression (18 patients, 5.1%) and hyperlipidemia (18 patients, 5.1%) (Table 17).

5.3.4 Hospitalisations

In all subjects who received anti-tumour medication after first recurrence slightly more patients had a hospitalisation after first recurrence (269 patients, 76.9%) compared to before the first recurrence (250 patients, 71.4%). The median total time spent in hospital increased from 15 days (range 1.0, 365.0 days) in those hospitalised before first recurrence to 24 days (range 1.0, 174.0 days) in those hospitalised after first recurrence. While surgery was the main reason for admission to hospital (200 patients, 80%) prior to first recurrence, treatment of ovarian cancer disease complications became the main reason after first recurrence (188 patients, 69.9%). More patients were treated in a general medical ward before their first recurrence (184 patients, 73.6%) than after their first recurrence (133 patients, 49.4%) (Table 18) (Table 19).

5.3.5 Surgery

In all subjects who received anti-tumour medication after first recurrence, a higher proportion of patients had surgery prior to first recurrence (319 patients, 91.1%) compared to after first recurrence (148 patients, 42.3%). The main reason for surgery prior to first recurrence was staging laparotomy at diagnosis (191 patients, 59.9%) whereas after first recurrence it was to resolve disease complications (70 patients, 47.3%). Hysterectomy was performed in 195 patients (61.1%) prior to first recurrence (Table 20) (Table 21).

5.3.6 Diagnostic imaging prior to first recurrence

Most patients (317 patients, 90.6%) who had received anti-tumour medication after first recurrence had at least one diagnostic imaging performed prior to first recurrence. The great majority (280 patients, 88.3%) had measurable disease. More patients in the partially platinum-sensitive subgroup who had received a platinum-based therapy had measurable disease (50 patients, 94.3%) compared to those who had not received a platinum-based therapy (28 patients, 82.4%). Both subgroups however had a similar

proportion of patients who had at least one diagnostic imaging done prior to first recurrence (53 patients, 94.6% vs. 34 patients, 94.4%) respectively (Table 22).

5.3.7 Concomitant treatments

The proportion of patients who had received anti-tumour medication after first recurrence and that used oncology supporting pharmacotherapies after first recurrence was 64.9% (227 patients). The partially platinum-sensitive subgroup was the subgroup that used the most oncology supporting pharmacotherapies (70 patients, 76.1%), although no major differences were observed between the partially platinum-sensitive subgroups who had received a platinum-based therapy and the ones who had not received one (43 patients, 76.8% vs. 27 patients, 75.0% respectively). The majority of patients (130, 37.1%) used corticosteroids (Table 23).

5.3.8 Chemotherapies

In subjects who had received anti-tumour medication after first recurrence a total of 341 patients also received an initial second line therapy. Of these, 21 patients (6.2%) received a platinum monotherapy, 178 patients (52.2%) received a platinum combination therapy and 142 patients (41.6%) a non platinum therapy. For patients receiving a third line therapy the proportion receiving platinum monotherapy was 4.3% (8 patients), those receiving platinum combination therapy was 35.7% (66 patients) and those not receiving any platinum therapy was 60% (111 patients) (Table 24).

5.3.9 Weekly vs. three-weekly taxane regimen

The proportion of patients on weekly vs. three-weekly taxane regimen was 5.79% (22 patients) vs. 77.89% (296 patients), respectively, for first line therapy. For second line therapy the proportion on weekly vs. three-weekly taxane regimen was 8.16% (31 patients) vs. 15.79% (60 patients), respectively, and in third line, it was 6.25% (16 patients) vs. 5.47% (14 patients). In total 58 patients (15.26%) were on a combination three-weekly taxane in second line compared to only 2 patients (0.53%) on monotherapy. In the weekly taxane group 17 patients (4.47%) were on a combination treatment in second line compared to 14 patients (3.68%) on monotherapy (**Error! Reference source not found.**).

5.3.10 Safety

In patients who received anti-tumour medication after first recurrence 308 patients (88%) had at least one AE, of which 174 patients (49.7%) had at least a Grade 3 or higher AE. The most common AEs were: anorexia, nausea, vomiting and/or diarrhoea (192 patients, 54.9%), fatigue (asthenia, lethargy, malaise) (149 patients, 42.6%), anaemia

(148 patients, 42.3%), neutropenia without fever (107 patients, 30.6%), peripheral neuropathy and pain (104 patients, 29.7% each) and thrombocytopenia (86 patients, 24.6%) (Table 26). In regards to Amgen related AEs one subject had two episodes of pain and both were recorded as related to Amgen product Pegfilgrastim (Neulasta). Both episodes were non-serious and of grade 1 and both recovered without sequelae.

6. DISCUSSION

The primary objective of this study was to identify, amongst PPS patients, differences in clinical characteristics, outcomes and prognosis between patients who were treated with platinum-based therapy after their first recurrence and those who were not. A key question informing this objective was to identify clinical parameters or patient characteristics determining why some patients in the PPS group received platinum, while others received a non-platinum based regimen. The median PFI between patients in both groups differed by only 17 days (270 days for those who received a platinum based as second-line versus 253 days for those who received a non-platinum based regimen). This difference of 17 days in terms of the PFI in an interval comprising 180 days seems unlikely to be a major determinant for chosing a second-line therapy.

The prognosis between the four platinum subgroups differed. In regard to differences between the four PFI categories ("platinum-refractory", "platinum-resistant", "partially platinum-sensitive", and "platinum-sensitive"), as expected, both the median recurrence-free survival and overall survival time were the longest among the platinum-sensitive patients followed by the partially platinum-sensitive patients, platinum-resistant and platinum-refractory patients. The shorter the platinum-free interval following platinum based first-line therapy, the worse the prognosis.

Interestingly, within the PPS subgroup, there was a difference in the median overall survival after first recurrence in the partially platinum-sensitive patients who had received a platinum-based therapy (23.5 months) compared to those patients who had not received a platinum-based therapy (18.7 months). Observing the Kaplan Meier estimates, the curve of patients in the PPS subgroup receiving a platinum based treatment is closer to the curve of platinum sensitive patients. Likewise, the curve of patients in the PPS subgroup receiving a non-platinum based treatment is very close to the curve of platinum resistant patients. There were no real differences between the two PPS groups in terms of comorbidities, adverse events or patient characteristics. In light of these findings, physicians are likely to be using other parameters in addition to the PFI to determine when to prescribe non-platinum based treatment in the PPS subgroup. This is currently not acknowledged in clinical guidelines, which recommend a platinum-based treatment for all patients in the PPS subgroup. In fact, clinical guidelines at present do not acknowledge the existence of the PPS subgroup.

In regard to the usage of weekly Taxol, 31 out of 91 patients receiving Taxol as second-line therapy received the weekly regimen. This may indicate that already between Q1

2008 and Q2 2011 physicians decided that the weekly regimen might be beneficial to patients with recurrent disease. Due to the small sample sizes it was not possible to identify any differences by PFI category in terms of comorbidities, adverse events or characteristics in patients using weekly vs. three weekly Taxol.

6.1 Internal Validity

The internal validity of the study depended upon the quality and completeness of the source data and the integrity of its transfer into the study database through the process of chart abstraction. Measures taken to minimise error included careful design of the EDC tool and eCRF, to ensure that they were intuitive and user-friendly. Errors were captured by means of automated validation checks, edit checks, line listing review and site queries, along with an escalation process up to and including rejection of subject records or re-abstraction where error rates exceeded prespecified limits.

6.2 External Validity

The overall findings from the three participating countries (France, Germany and Spain), were not intended to be generalised to Europe or other countries within Europe. Therefore, the design intent was that the selection of sites and subjects within a site were broadly representative of the country to which they belonged. Obtaining a representative sample of recurrent ovarian cancer patients in this study presented a significant challenge and may have been affected by selection bias on several levels: participation of eligible hospitals, medical centres and clinics, case identification at each participating site, and exclusions due to data quality issues. The degree to which a sample of sites was representative of the prevalent recurrent ovarian cancer population in a given country was not clear, as unobservable factors may have influenced the outcomes to be measured, with unknown direction and magnitude. Each of the countries included different types of hospitals and clinics insofar as willingness of sufficient centres to participate permitted. Furthermore, the type of hospitals included may not have been representative of all cancer centres in these three countries.

The proposed method of selecting subjects, requiring sites to identify all cases with a primary diagnosis and placing eligibility assessment and subject selection under the CRO's control, was designed to minimize subject selection bias at the site level. Equally, it allowed the CRO to control quota sampling in order to achieve a minimum sample of

each PFI subgroup. At sites where informed consent was required, selection bias may have arisen from participants' reasons for consenting.

Information bias arises if abstractors are required to make interpretations of data. The CRF was developed to avoid the need for interpretation and abstractors were trained to abstract data only as documented. Decision algorithms were developed when interpretations were required for clinical variables (e.g. determining disease recurrence). Programmatic methods were used where possible and, in other instances, responsible physicians were instructed to provide the clinical interpretations using explicit decision rules.

7. CONCLUSION

The study identified that in ovarian cancer patients with recurrent disease classified as partially platinum sensitive following first-line therapy a group of patients receive a non-platinum based treatment. This is contrary to international clinical guidelines that recommend a platinum-based treatment for this patient group.

Furthermore, the partially platinum based subgroup appears to consist of two groups: a group of patients receiving platinum based therapy and a group of patients receiving non-platinum based treatment. The prognosis of patients between both groups, as measured by either the median overall survival or the time from first recurrent to death, is different. What drives the choice of platinum versus non-platinum treatment in the PPS group could not be clearly identified in this study. The absolute PFI did not stand out as a clear determining factor. It appears that physicians are taking a range of factors into account when choosing a treatment, some of which may not be documented in routine clinical care.

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SUMMARY TABLES AND FIGURES

Table 9. Disease characteristics at primary diagnosis – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Tumour type - n(%)							
- Ovarian	31 (86.1%)	84 (85.7%)	49 (87.5%)	34 (94.4%)	83 (90.2%)	110 (88.7%)	308 (88.0%)
- Primary peritoneal	3 (8.3%)	8 (8.2%)	5 (8.9%)	1 (2.8%)	6 (6.5%)	7 (5.6%)	24 (6.9%)
- Fallopian tube	2 (5.6%)	6 (6.1%)	2 (3.6%)	1 (2.8%)	3 (3.3%)	7 (5.6%)	18 (5.1%)
Measurable disease	33 (91.7%)	80 (81.6%)	40 (71.4%)	31 (86.1%)	71 (77.2%)	97 (78.2%)	281 (80.3%)
Ascites present	21 (58.3%)	51 (52.0%)	33 (58.9%)	14 (38.9%)	47 (51.1%)	48 (38.7%)	167 (47.7%)
FIGO stage - n(%)							
- Early disease (IA-IIA)	-	8 (8.2%)	4 (7.1%)	-	4 (4.3%)	20 (16.1%)	32 (9.1%)
- Advanced disease (IIB-IV)	32 (88.9%)	82 (83.7%)	46 (82.1%)	34 (94.4%)	80 (87.0%)	93 (75.0%)	287 (82.0%)
- Unknown	4 (11.1%)	8 (8.2%)	6 (10.7%)	2 (5.6%)	8 (8.7%)	11 (8.9%)	31 (8.9%)

Source: Table 5.1 Disease and Other Characteristics at Primary Diagnosis - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

Table 10. History of other cancers at primary diagnosis – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
History of other cancers - n(%)							
Yes	4 (11.1%)	12 (12.2%)	5 (8.9%)	2 (5.6%)	7 (7.6%)	10 (8.1%)	33 (9.4%)
- Breast	3 (75.0%)	8 (66.7%)	3 (60.0%)	-	3 (42.9%)	6 (60.0%)	20 (60.6%)
- Lung	-	1 (8.3%)	-	-	-	-	1 (3.0%)
- Colorectal	1 (25.0%)	1 (8.3%)	1 (20.0%)	-	1 (14.3%)	-	3 (9.1%)
- Uterine and/or cervical	-	1 (8.3%)	-	1 (50.0%)	1 (14.3%)	-	2 (6.1%)
- Other	-	1 (8.3%)	1 (20.0%)	1 (50.0%)	2 (28.6%)	4 (40.0%)	7 (21.2%)
No	28 (77.8%)	81 (82.7%)	50 (89.3%)	28 (77.8%)	78 (84.8%)	103 (83.1%)	290 (82.9%)
Unknown	4 (11.1%)	5 (5.1%)	1 (1.8%)	6 (16.7%)	7 (7.6%)	11 (8.9%)	27 (7.7%)

Source: Table 5.1 Disease and Other Characteristics at Primary Diagnosis - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

Table 11. Performance status at primary diagnosis – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Performance Status - n(%)							
0	4 (11.1%)	21 (21.4%)	6 (10.7%)	9 (25.0%)	15 (16.3%)	30 (24.2%)	70 (20.0%)
1	8 (22.2%)	30 (30.6%)	24 (42.9%)	10 (27.8%)	34 (37.0%)	35 (28.2%)	107 (30.6%)
2	7 (19.4%)	11 (11.2%)	4 (7.1%)	1 (2.8%)	5 (5.4%)	9 (7.3%)	32 (9.1%)
3	1 (2.8%)	1 (1.0%)	1 (1.8%)	-	1 (1.1%)	-	3 (0.9%)
Unknown	-	-	2 (3.6%)	1 (2.8%)	3 (3.3%)	2 (1.6%)	5 (1.4%)

Source: Table 5.1 Disease and Other Characteristics at Primary Diagnosis - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

Table 12. Kaplan Meier estimate of recurrence-free survival (in months) – Full analysis set

	Platinum sensitivity[a]				
	Refractory	Resistant	Partially Sensitive	Sensitive	All
From primary diagnosis[b]					
At risk	39	108	99	134	380
Recurred	39	108	99	134	380
Median	5.3	9.6	14.5	26.4	14.6
95% CI of Median	(3.8, 6.0)	(9.2, 10.1)	(13.8, 14.9)	(25.1, 28.6)	(13.5, 15.3)
From first reccurence[b]					
At risk	36	98	92	124	350
Recurred	35	92	84	101	312
Median	5.5	6.5	12.0	15.5	10.6
95% CI of Median	(3.2, 6.9)	(5.3, 7.9)	(9.9, 14.4)	(13.6, 18.1)	(9, 11.8)
From second reccurence[b]					
At risk	32	29	40	20	121
Recurred	32	27	34	11	104
Median	5.2	7.0	9.1	13.9	8.0
95% CI of Median	(3.4, 8.0)	(5.1, 8.6)	(5.3, 11.3)	(10.3, 25.2)	(6.5, 10.2)
From third reccurence[b]					
At risk	15	18	9	1	43
Recurred	15	16	8	1	40
Median	2.5	4.9	9.6	9.8	4.9
95% CI of Median	(1.9, 3.9)	(3.1, 5.1)	(2.8, 11.3)	(., .)	(3.1, 5.5)

Source: Table 19 Kaplan-Meier Estimate of Recurrence Free Survival after Primary Diagnosis and Each Subsequent Recurrence – (Full Analysis Set, All countries)

Note: recurrence-free survival time is considered to be the time from primary diagnosis or recurrence of interest to the earliest of recurrence or death from any cause.
If no recurrence or death was observed for a subject, recurrence-free survival time was censored at the last recorded date.
[a] *Status is based on the most recent platinum therapy received.*
[b] *Only the subjects who received treatment after recurrence are considered*

Table 13. Kaplan Meier estimate of overall survival (in months) – Full analysis set

	Platinum sensitivity[a]				
	Refractory	Resistant	Partially Sensitive	Sensitive	All
From primary diagnosis[b]					
At risk	39	108	99	134	380
Recurred	32	97	73	74	276
Median	14.6	22	34.9	72.7	36
95% CI of Median	(10.4, 17.6)	(19.2, 23.9)	(30.4, 37.6)	(58.4, 80.6)	(31.6, 40.4)
From first reccurence[b]					
At risk	36	98	92	124	350
Recurred	30	87	67	68	252
Median	9.8	12.7	20.5	34.0	19.5
95% CI of Median	(6.6, 14.9)	(10.4, 14.2)	(17.7, 24.8)	(25.1, 42.3)	(17.2, 21.5)
From second reccurence[b]					
At risk	32	29	40	20	121
Recurred	24	24	25	5	78
Median	14.6	12.6	20.1	.	17.0
95% CI of Median	(7.7, 19.2)	(6.9, 18.6)	(13.6, 32.8)	(14.0, .)	(14.1, 21.1)
From third reccurence[b]					
At risk	15	18	9	1	43
Recurred	13	13	3	0	29
Median	6.7	11	26.2	.	9.7
95% CI of Median	(2.1, 9.5)	(5.1, 23.7)	(7.8, .)	(., .)	(6.7, 18.3)

Source: Table 20 Kaplan-Meier Estimate of Overall Survival after Primary Diagnosis and Each Subsequent Recurrence – (Full Analysis Set, All countries)

Note: Survival time is considered to be the time from primary diagnosis or recurrence of interest to death from any cause.
If death was not observed for a subject, survival time was censored at the last recorded date.
[a] *Not applicable at primary diagnosis. Status is based on the most recent platinum therapy received.*
[b] *Only the subjects who received treatment after recurrence are considered*

Table 14. Kaplan Meier Estimates of Overall Survival after First Recurrence - Subjects who Received Anti-Tumor Therapy after First Recurrence

Platinum sensitivity determined after receiving first line of platinum therapy			
	Partially Sensitive		
	Received platinum therapy		
	Yes	No	Total
Parameter	(N=56)	(N=36)	(N=92)
Dead	39	28	67
Alive	17	8	25
Median Survival (months)	**23.5**	**18.7**	**20.5**
95% CI	18.4, 37.3	11.0, 23.5	17.7, 24.8

Source: K M Estimates of Overall Survival after First Recurrence - Subjects who Received Anti-Tumor Therapy after First Recurrence - Post-hoc analyses

Table 15. Length of observation in months – Patients who received anti-tumour medication after first recurrence

Period/Statistic	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Time from primary diagnosis date to first recurrence - N	36	98	56	36	92	124	350
Median	5.3	9.7	14.5	13.7	14.4	26.2	14.6
Min, Max	2.3, 12.7	6.6, 18.9	10.2, 19.7	9.9, 19.5	9.9, 19.7	16.1, 110.0	2.3, 110.0
Time from first recurrence to earliest of death date or last record date - N	36	98	56	36	92	124	350
Median	9.8	12.6	23.1	16.5	20.3	26	18.4
Min, Max	1.3, 54.9	0.8, 58.9	2.5, 57.9	1.2, 42.7	1.2, 57.9	1.3, 62.2	0.8, 62.2
Time from first recurrence to death –N	30	87	39	28	67	68	252
Median	8.6	11.4	17.7	13.5	16.7	17.7	13.8
Min, Max	1.3, 54.9	0.8, 55.7	3.6, 57.9	1.2, 40.8	1.2, 57.9	1.6, 62.2	0.8, 62.2
Time from primary diagnosis date to earliest of death date or last record date - N	36	98	56	36	92	124	350
Median	14.6	22.4	37.5	29.5	34.7	58	35.5
Min, Max	5.3, 63.9	8.2, 68.8	14.7, 72.7	12.1, 59.7	12.1, 72.7	23.7, 145.5	5.3, 145.5

Source: Table 3.1 Length of Observation in Months - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

Table 16. Time to first dose and duration of first line pharmacotherapy – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
All Drugs							
Time to first dose from primary diagnosis (days)							
N	36	98	56	36	92	124	350
Median	28	28.5	26.0	34.5	31.5	29	29
Min, Max	6.0, 256.0	1.0, 378.0	2.0, 150.0	8.0, 205.0	2.0, 205.0	2.0, 223.0	1.0, 378.0
Duration[a] (days)							
N	36	98	56	36	92	124	350
Median	106	164	114.0	118.0	116	125.5	123
Min, Max	35.0, 172.0	85.0, 490.0	1.0, 694.0	106.0, 355.0	1.0, 694.0	71.0, 952.0	1.0, 952.0

Source: Table 13.1 Time to First Dose from Primary Diagnosis, Duration and Cycles of First Line Pharmacotherapy – (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

Note: Includes pharmacotherapy received prior to first recurrence.
[a]Duration is calculated as the time between the first dose and the last dose of therapy.
If a subject received more than one therapy, then the duration is calculated as the time between the earliest first dose of all therapies and the latest last dose of all therapies received during the period of interest.

Table 17. Comorbidities at primary diagnosis – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
Category / Comorbidity[a]	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Mental Health							
Depression	1 (2.8%)	7 (7.1%)	2 (3.6%)	2 (5.6%)	4 (4.3%)	6 (4.8%)	18 (5.1%)
Anxiety disorder	-	1 (1.0%)	2 (3.6%)	-	2 (2.2%)	-	3 (0.9%)
Other	-	-	-	-	-	2 (1.6%)	2 (0.6%)
Central Nervous System							
Cerebrovascular disease	-	1 (1.0%)	-	-	-	-	1 (0.3%)
Chronic pain	1 (2.8%)	-	1 (1.8%)	-	1 (1.1%)	1 (0.8%)	3 (0.9%)
Other	-	3 (3.1%)	-	1 (2.8%)	1 (1.1%)	1 (0.8%)	5 (1.4%)
Respiratory							
Asthma	1 (2.8%)	1 (1.0%)	4 (7.1%)	1 (2.8%)	5 (5.4%)	-	7 (2.0%)
COPD	2 (5.6%)	2 (2.0%)	2 (3.6%)	1 (2.8%)	3 (3.3%)	4 (3.2%)	11 (3.1%)
Other	-	1 (1.0%)	1 (1.8%)	-	1 (1.1%)	1 (0.8%)	3 (0.9%)
Metabolic							
Diabetes Mellitus	3 (8.3%)	10 (10.2%)	5 (8.9%)	2 (5.6%)	7 (7.6%)	5 (4.0%)	25 (7.1%)
Obesity	3 (8.3%)	6 (6.1%)	3 (5.4%)	2 (5.6%)	5 (5.4%)	-	14 (4.0%)
Other	2 (5.6%)	3 (3.1%)	3 (5.4%)	2 (5.6%)	5 (5.4%)	6 (4.8%)	16 (4.6%)
Gastrointestinal							
Constipation	-	2 (2.0%)	2 (3.6%)	-	2 (2.2%)	1 (0.8%)	5 (1.4%)
GERD	1 (2.8%)	4 (4.1%)	1 (1.8%)	-	1 (1.1%)	2 (1.6%)	8 (2.3%)
Inflammatory Bowel Disease	-	1 (1.0%)	-	1 (2.8%)	1 (1.1%)	-	2 (0.6%)
Liver Disease	-	1 (1.0%)	-	-	-	-	1 (0.3%)

Other	4 (11.1%)	4 (4.1%)	2 (3.6%)	2 (5.6%)	4 (4.3%)	6 (4.8%)	18 (5.1%)
Cardiovascular							
Congestive Heart Failure	-	1 (1.0%)	-	2 (5.6%)	2 (2.2%)	2 (1.6%)	5 (1.4%)
Hypertension	15 (41.7%)	35 (35.7%)	17 (30.4%)	14 (38.9%)	31 (33.7%)	37 (29.8%)	118 (33.7%)
Hyperlipidemia	4 (11.1%)	5 (5.1%)	4 (7.1%)	1 (2.8%)	5 (5.4%)	4 (3.2%)	18 (5.1%)
Angina	1 (2.8%)	1 (1.0%)	1 (1.8%)	-	1 (1.1%)	1 (0.8%)	4 (1.1%)
Myocardial Infarction	-	2 (2.0%)	-	-	-	1 (0.8%)	3 (0.9%)
Peripheral Vascular Disease	4 (11.1%)	-	2 (3.6%)	-	2 (2.2%)	-	6 (1.7%)
Venous Thrombosis	1 (2.8%)	2 (2.0%)	4 (7.1%)	-	4 (4.3%)	3 (2.4%)	10 (2.9%)
Other	2 (5.6%)	5 (5.1%)	3 (5.4%)	3 (8.3%)	6 (6.5%)	9 (7.3%)	22 (6.3%)
Renal							
Chronic kidney disease without dialysis	-	3 (3.1%)	-	1 (2.8%)	1 (1.1%)	-	4 (1.1%)
Other	1 (2.8%)	4 (4.1%)	-	-	-	1 (0.8%)	6 (1.7%)
Other	7 (19.4%)	25 (25.5%)	13 (23.2%)	9 (25.0%)	22 (23.9%)	23 (18.5%)	77 (22.0%)

Source: Table 6.1 Co-morbidities at Primary Diagnosis - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

[a]A subject may be counted only once for a category, but may be counted in more than one co-morbidity summary lines

Table 18. Hospitalisations prior to first recurrence – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Had hospitalisation prior to first recurrence – n (%)[a]	19 (52.8%)	74 (75.5%)	41 (73.2%)	28 (77.8%)	69 (75.0%)	88 (71.0%)	250 (71.4%)
Total time in hospital (days)[b], N	19	74	41	28	69	88	250
Median	5	19.5	11	14	14	13	15
Min, Max	1.0, 28.0	1.0, 101.0	1.0, 365.0	1.0, 33.0	1.0, 365.0	1.0, 124.0	1.0, 365.0
Ward type[c]							
General medical	13 (68.4%)	57 (77.0%)	29 (70.7%)	21 (75.0%)	50 (72.5%)	64 (72.7%)	184 (73.6%)
Oncology unit	5 (26.3%)	14 (18.9%)	5 (12.2%)	5 (17.9%)	10 (14.5%)	13 (14.8%)	42 (16.8%)
Reason for admission							
Treatment of ovarian cancer disease complication	4 (21.1%)	18 (24.3%)	9 (22.0%)	7 (25.0%)	16 (23.2%)	21 (23.9%)	59 (23.6%)
Surgery	14 (73.7%)	60 (81.1%)	32 (78.0%)	22 (78.6%)	54 (78.3%)	72 (81.8%)	200 (80.0%)

Source: Table 7.1 Hospitalizations Prior to First Recurrence - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

[a] *A subject may have multiple hospitalisations however, counted only once.*
[b] *If a subject has multiple hospitalisations, total time in hospital is calculated by adding each time period in hospital. Only those subjects with at least one hospitalisation are considered in this summary.*
[c] *A subject is counted only once for each ward type and reason for admission. Percentage is based on the number of subjects who were hospitalised at least once prior to first recurrence.*

Table 19. Hospitalisations after first recurrence – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Had hospitalisation after first recurrence – n (%)[a]	30 (83.3%)	76 (77.6%)	44 (78.6%)	29 (80.6%)	73 (79.3%)	90 (72.6%)	269 (76.9%)
Total time in hospital (days)[b]	30	76	44	29	73	90	269
Median	18.5	26	22	33	25	22	24
Min, Max	1.0, 125.0	1.0, 165.0	6.0, 153.0	2.0, 108.0	2.0, 153.0	1.0, 174.0	1.0, 174.0
Ward type[c]							
Emergency room	3 (10.0%)	5 (6.6%)	7 (15.9%)	2 (6.9%)	9 (12.3%)	12 (13.3%)	29 (10.8%)
General medical	14 (46.7%)	28 (36.8%)	21 (47.7%)	17 (58.6%)	38 (52.1%)	53 (58.9%)	133 (49.4%)
Oncology unit	16 (53.3%)	36 (47.4%)	21 (47.7%)	13 (44.8%)	34 (46.6%)	31 (34.4%)	117 (43.5%)
Reason for admission							
Treatment of chemo AE	4 (13.3%)	13 (17.1%)	8 (18.2%)	10 (34.5%)	18 (24.7%)	15 (16.7%)	50 (18.6%)
Treatment of ovarian cancer disease complication	23 (76.7%)	52 (68.4%)	36 (81.8%)	21 (72.4%)	57 (78.1%)	56 (62.2%)	188 (69.9%)
Surgery	9 (30.0%)	19 (25.0%)	15 (34.1%)	13 (44.8%)	28 (38.4%)	44 (48.9%)	100 (37.2%)

Source: Table 8.1 Hospitalizations After First Recurrence - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

[a] *A subject may have multiple hospitalisations however, counted only once.*
[b] *If a subject has multiple hospitalisations, total time in hospital is calculated by adding each time period in hospital. Only those subjects with at least one hospitalisation are considered in this summary.*
[c] *A subject is counted only once for each ward type and reason for admission. Percentage is based on the number of subjects who were hospitalised at least once prior to first recurrence.*

Table 20. Surgeries prior to first recurrence – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Had surgery prior to first recurrence – n (%)[a]	30 (83.3%)	86 (87.8%)	51 (91.1%)	36 (100.0%)	87 (94.6%)	116 (93.5%)	319 (91.1%)
Reason for surgery – n (%)[b]							
- Staging laparotomy[c] at diagnosis	22 (73.3%)	46 (53.5%)	31 (60.8%)	24 (66.7%)	55 (63.2%)	68 (58.6%)	191 (59.9%)
- Staging laparotomy[c] after neoadjuvant chemotherapy	2 (6.7%)	28 (32.6%)	9 (17.6%)	6 (16.7%)	15 (17.2%)	38 (32.8%)	83 (26.0%)
Procedure Type – n (%)[b]							
- Hysterectomy	13 (43.3%)	52 (60.5%)	31 (60.8%)	20 (55.6%)	51 (58.6%)	79 (68.1%)	195 (61.1%)
- Salpingectomy - Bilateral	4 (13.3%)	19 (22.1%)	8 (15.7%)	8 (22.2%)	16 (18.4%)	34 (29.3%)	73 (22.9%)
- Oophorectomy - Bilateral	7 (23.3%)	31 (36.0%)	20 (39.2%)	15 (41.7%)	35 (40.2%)	53 (45.7%)	126 (39.5%)
- Omentectomy	11 (36.7%)	44 (51.2%)	27 (52.9%)	13 (36.1%)	40 (46.0%)	57 (49.1%)	152 (47.6%)
- Pelvic peritoneal resection	3 (10.0%)	11 (12.8%)	4 (7.8%)	7 (19.4%)	11 (12.6%)	13 (11.2%)	38 (11.9%)
- Pelvic and/or periaortic lymphadenectomy	1 (3.3%)	16 (18.6%)	10 (19.6%)	10 (27.8%)	20 (23.0%)	39 (33.6%)	76 (23.8%)

Source: Table 9.1.1 Surgical Procedures Prior to First Recurrence - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

[a] *A subject may have multiple hospitalisations or surgeries, however, is counted only once.*
[b] *A subject is counted only once for each reason, procedure type or complication summary line. Percentage is based on the number of subjects who had surgery prior to first recurrence.*

Table 21. Surgeries after first recurrence – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Had surgery after first recurrence – n (%)[a]	16 (44.4%)	30 (30.6%)	23 (41.1%)	16 (44.4%)	39 (42.4%)	63 (50.8%)	148 (42.3%)
Reason for surgery – n (%)[b]							
Staging laparotomy[c] at diagnosis	6 (37.5%)	9 (30.0%)	6 (26.1%)	1 (6.3%)	7 (17.9%)	26 (41.3%)	48 (32.4%)
Resolve disease complications	5 (31.3%)	18 (60.0%)	13 (56.5%)	11 (68.8%)	24 (61.5%)	23 (36.5%)	70 (47.3%)
Procedure Type – n (%)[b]							
Pelvic and/or periaortic lymphadenectomy	2 (12.5%)	1 (3.3%)	3 (13.0%)	-	3 (7.7%)	11 (17.5%)	17 (11.5%)
Laparoscopy with/without biopsies	2 (12.5%)	1 (3.3%)	-	2 (12.5%)	2 (5.1%)	9 (14.3%)	14 (9.5%)
Paracentesis of ascitic fluid	1 (6.3%)	7 (23.3%)	1 (4.3%)	-	1 (2.6%)	4 (6.3%)	13 (8.8%)

Source: Table 9.2.1 Surgical Procedures After First Recurrence - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

[a] *A subject may have multiple hospitalisations or surgeries, however, is counted only once.*
[b] *A subject is counted only once for each reason, procedure type or complication summary line. Percentage is based on the number of subjects who had surgery prior to first recurrence.*

Table 22. Diagnostic imaging prior to first recurrence – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Any Imaging[a]	29 (80.6%)	88 (89.8%)	53 (94.6%)	34 (94.4%)	87 (94.6%)	113 (91.1%)	317 (90.6%)
Measurable Disease[b]							
- Present	26 (89.7%)	80 (90.9%)	50 (94.3%)	28 (82.4%)	78 (89.7%)	96 (85.0%)	280 (88.3%)
- Absent	2 (6.9%)	5 (5.7%)	1 (1.9%)	4 (11.8%)	5 (5.7%)	11 (9.7%)	23 (7.3%)
- Unknown	1 (3.4%)	3 (3.4%)	1 (1.9%)	2 (5.9%)	3 (3.4%)	6 (5.3%)	13 (4.1%)

Source: Table 10.1.1 Diagnostic Imaging Prior to First Recurrence – (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

[a] *A subject is counted only once. A subject may have multiple imaging performed during the pre-index period.*
[b] *A subject is counted only once. If there are multiple imaging done, then use Present>Absent>Unknown hierarchy to choose a category for a subject.*

Table 23. Oncology supporting pharmacotherapy after first recurrence – Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Any drug / Number of drugs							
- Yes	20 (55.6%)	64 (65.3%)	43 (76.8%)	27 (75.0%)	70 (76.1%)	73 (58.9%)	227 (64.9%)
1 Drug	7 (19.4%)	23 (23.5%)	15 (26.8%)	8 (22.2%)	23 (25.0%)	20 (16.1%)	73 (20.9%)
2 Drugs	7 (19.4%)	24 (24.5%)	16 (28.6%)	12 (33.3%)	28 (30.4%)	32 (25.8%)	91 (26.0%)
3 Drugs	2 (5.6%)	6 (6.1%)	5 (8.9%)	6 (16.7%)	11 (12.0%)	18 (14.5%)	37 (10.6%)
4 Drugs	3 (8.3%)	8 (8.2%)	4 (7.1%)	-	4 (4.3%)	2 (1.6%)	17 (4.9%)
5 or more drugs	1 (2.8%)	3 (3.1%)	3 (5.4%)	1 (2.8%)	4 (4.3%)	1 (0.8%)	9 (2.6%)
- No	16 (44.4%)	34 (34.7%)	13 (23.2%)	9 (25.0%)	22 (23.9%)	51 (41.1%)	123 (35.1%)
Drug - n (%)							
- Corticosteroids	11 (30.6%)	39 (39.8%)	22 (39.3%)	16 (44.4%)	38 (41.3%)	42 (33.9%)	130 (37.1%)
- Darbepoetin	3 (8.3%)	3 (3.1%)	5 (8.9%)	2 (5.6%)	7 (7.6%)	2 (1.6%)	15 (4.3%)
- Epoetin	3 (8.3%)	4 (4.1%)	10 (17.9%)	5 (13.9%)	15 (16.3%)	7 (5.6%)	29 (8.3%)
- Filgrastim	2 (5.6%)	10 (10.2%)	5 (8.9%)	1 (2.8%)	6 (6.5%)	9 (7.3%)	27 (7.7%)
- Granisteron	4 (11.1%)	15 (15.3%)	11 (19.6%)	9 (25.0%)	20 (21.7%)	18 (14.5%)	57 (16.3%)
- Ondansetron	6 (16.7%)	26 (26.5%)	16 (28.6%)	6 (16.7%)	22 (23.9%)	25 (20.2%)	79 (22.6%)
- Palonosteron	1 (2.8%)	5 (5.1%)	1 (1.8%)	3 (8.3%)	4 (4.3%)	2 (1.6%)	12 (3.4%)
- Pegfilgrastim	2 (5.6%)	7 (7.1%)	2 (3.6%)	2 (5.6%)	4 (4.3%)	9 (7.3%)	22 (6.3%)

Source: Table 15.1 Oncology Supporting Pharmacotherapy after First Recurrence – (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

Table 24. Initial Pharmacotherapy at Each Line after Primary Diagnosis– Patients who received anti-tumour medication after first recurrence

	Platinum sensitivity determined after receiving first line of platinum rherapy						
			Partially Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
First Line – n (%)	36 (100.0%)	98 (100.0%)	56 (100.0%)	36 (100.0%)	92 (100.0%)	124 (100.0%)	350 (100.0%)
Platinum Based	36 (100.0%)	96 (98.0%)	56 (100.0%)	36 (100.0%)	92 (100.0%)	123 (99.2%)	347 (99.1%)
- Mono	3 (8.3%)	7 (7.3%)	3 (5.4%)	2 (5.6%)	5 (5.4%)	12 (9.8%)	27 (7.8%)
- Combination	33 (91.7%)	89 (92.7%)	53 (94.6%)	34 (94.4%)	87 (94.6%)	111 (90.2%)	320 (92.2%)
Non-Platinum Based	-	2 (2.0%)	-	-	-	1 (0.8%)	3 (0.9%)
Second Line – n (%)	36 (100.0%)	96 (98.0%)	56 (100.0%)	32 (88.9%)	88 (95.7%)	121 (97.6%)	341 (97.4%)
Platinum Based	17 (47.2%)	31 (32.3%)	47 (83.9%)	-	47 (53.4%)	104 (86.0%)	199 (58.4%)
- Mono	3 (17.6%)	1 (3.2%)	6 (12.8%)	-	6 (12.8%)	11 (10.6%)	21 (10.6%)
- Combination	14 (82.4%)	30 (96.8%)	41 (87.2%)	-	41 (87.2%)	93 (89.4%)	178 (89.4%)
Non-Platinum Based	19 (52.8%)	65 (67.7%)	9 (16.1%)	32 (100.0%)	41 (46.6%)	17 (14.0%)	142 (41.6%)
Third Line – n (%)	23 (63.9%)	46 (46.9%)	29 (51.8%)	18 (50.0%)	47 (51.1%)	69 (55.6%)	185 (52.9%)
Platinum Based	7 (30.4%)	11 (23.9%)	13 (44.8%)	10 (55.6%)	23 (48.9%)	33 (47.8%)	74 (40.0%)
- Mono	-	-	2 (15.4%)	1 (10.0%)	3 (13.0%)	5 (15.2%)	8 (10.8%)
- Combination	7 (100.0%)	11 (100.0%)	11 (84.6%)	9 (90.0%)	20 (87.0%)	28 (84.8%)	66 (89.2%)
Non-Platinum Based	16 (69.6%)	35 (76.1%)	16 (55.2%)	8 (44.4%)	24 (51.1%)	36 (52.2%)	111 (60.0%)

Source: Table 11.1A Initial Pharmacotherapy at Each Line after Primary Diagnosis - (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

Table 25. Taxane regimen weekly vs. three-weekly

	Platinum sensitivity determined at first line of platinum therapy				
	Refractory	Resistant	Partially Sensitive	Sensitive	All
First line					
N	39 (100.0%)	108 (100.0%)	99 (100.0%)	134 (100.0%)	380 (100.0%)
Weekly	4 (10.26%)	8 (7.41%)	2 (2.02%)	8 (5.97%)	22 (5.79%)
3-Weekly	30 (76.92%)	81 (75.00%)	81 (81.82%)	104 (77.61%)	296 (77.89%)
Second line					
N	39 (100.0%)	108 (100.0%)	99 (100.0%)	134 (100.0%)	380 (100.0%)
Weekly					
Single	2 (5.13%)	2 (1.85%)	7 (7.07%)	3 (2.24%)	14 (3.68%)
Combination	1 (2.56%)	4 (3.70%)	5 (5.05%)	7 (5.22%)	17 (4.47%)
3-Weekly					
Single	-	-	-	2 (1.49%)	2 (0.53%)
Combination	4 (10.26%)	4 (3.70%)	10 (10.10%)	40 (29.85%)	58 (15.26%)
Third line					
N	24 (61.54%)	51 (47.22%)	57 (57.58%)	81 (60.45%)	256 (67.37%)
Weekly					
Single	-	3 (5.88%)	3 (5.26%)	2 (2.47%)	8 (3.13%)
Combination	3 (12.50%)	1 (1.96%)	2 (3.51%)	2 (2.47%)	8 (3.13%)
3-Weekly					
Single	-	1 (1.96%)	1 (1.75%)	2 (2.47%)	4 (1.56%)
Combination	-	1 (1.96%)	5 (8.77%)	4 (4.94%)	10 (3.91%)

Source: Table 4.2.1 Demographics at Primary Diagnosis by Taxane Regimen as First Line of Therapy in Addition to Platinum Therapy - (Full Analysis Set, All countries), Table 4.2.2. Demographics at Primary Diagnosis by Taxane Regimen as Second Line of Therapy - (Full Analysis Set, All countries), Table 4.2.3. Demographics at Primary Diagnosis by Taxane Regimen as Third Line of Therapy - (Full Analysis Set, All countries)

If a Taxane was received as a first line therapy, then we know it has to be a combination therapy with a platinum therapy because all subjects received platinum as a first line of therapy.

Table 26. Subject incidence of adverse events during the period of collection – Patients who received anti-tumour medication after first recurrence

Adverse Event/Sub-category[a]	Platinum sensitivity determined after receiving first line of platinum therapy						
			Partial Sensitive				
			Received platinum therapy				
	Refractory (N=36)	Resistant (N=98)	Yes (N=56)	No (N=36)	Total (N=92)	Sensitive (N=124)	All (N=350)
Any event[b]	32 (88.9%)	89 (90.8%)	49 (87.5%)	28 (77.8%)	77 (83.7%)	110 (88.7%)	308 (88.0%)
Any Grade 3 or Higher	18 (50.0%)	54 (55.1%)	28 (50.0%)	12 (33.3%)	40 (43.5%)	62 (50.0%)	174 (49.7%)
Anemia	18 (50.0%)	39 (39.8%)	27 (48.2%)	10 (27.8%)	37 (40.2%)	54 (43.5%)	148 (42.3%)
Anorexia, Nausea, Vomiting and/or Diarrhea	19 (52.8%)	55 (56.1%)	34 (60.7%)	18 (50.0%)	52 (56.5%)	66 (53.2%)	192 (54.9%)
Ascites	2 (5.6%)	14 (14.3%)	5 (8.9%)	1 (2.8%)	6 (6.5%)	4 (3.2%)	26 (7.4%)
Behavioral/personality changes and/or psychosis	1 (2.8%)	5 (5.1%)	2 (3.6%)	-	2 (2.2%)	4 (3.2%)	12 (3.4%)
Cognitive dysfunction, confusion, dizziness	1 (2.8%)	5 (5.1%)	1 (1.8%)	2 (5.6%)	3 (3.3%)	3 (2.4%)	12 (3.4%)
Dyspnea (shortness of breath)	7 (19.4%)	15 (15.3%)	10 (17.9%)	3 (8.3%)	13 (14.1%)	13 (10.5%)	48 (13.7%)
Elevated liver enzymes	-	6 (6.1%)	-	-	-	2 (1.6%)	8 (2.3%)
Fatigue (asthenia, lethargy, malaise)	16 (44.4%)	43 (43.9%)	21 (37.5%)	14 (38.9%)	35 (38.0%)	55 (44.4%)	149 (42.6%)
Febrile neutropenia	1 (2.8%)	7 (7.1%)	3 (5.4%)	2 (5.6%)	5 (5.4%)	5 (4.0%)	18 (5.1%)
Fever not associated with infusion reaction	2 (5.6%)	10 (10.2%)	4 (7.1%)	-	4 (4.3%)	10 (8.1%)	26 (7.4%)
Generalised Edema	-	3 (3.1%)	2 (3.6%)	-	2 (2.2%)	1 (0.8%)	6 (1.7%)
Hypercalcemia	-	1 (1.0%)	-	-	-	-	1 (0.3%)

Hand/Foot syndrome (palmar-plantar erythrodysesthesia syndrome)	2 (5.6%)	13 (13.3%)	7 (12.5%)	2 (5.6%)	9 (9.8%)	19 (15.3%)	43 (12.3%)
Infection (diagnosed clinically or microbiologically)	5 (13.9%)	19 (19.4%)	15 (26.8%)	6 (16.7%)	21 (22.8%)	26 (21.0%)	71 (20.3%)
Infusion reaction	3 (8.3%)	4 (4.1%)	6 (10.7%)	3 (8.3%)	9 (9.8%)	5 (4.0%)	21 (6.0%)
Localised Edema	3 (8.3%)	14 (14.3%)	5 (8.9%)	2 (5.6%)	7 (7.6%)	6 (4.8%)	30 (8.6%)
Localised Lymphedema	-	-	-	-	1 (1.1%)	-	1 (0.3%)
Mucositis, oral	6 (16.7%)	12 (12.2%)	4 (7.1%)	5 (13.9%)	9 (9.8%)	16 (12.9%)	43 (12.3%)
Neutropenia without fever	7 (19.4%)	34 (34.7%)	17 (30.4%)	5 (13.9%)	22 (23.9%)	44 (35.5%)	107 (30.6%)
Other rash/dermatitis not associated with infusion allergic reaction	1 (2.8%)	10 (10.2%)	7 (12.5%)	-	7 (7.6%)	10 (8.1%)	28 (8.0%)
Peripheral neuropathy	7 (19.4%)	32 (32.7%)	20 (35.7%)	8 (22.2%)	28 (30.4%)	37 (29.8%)	104 (29.7%)
Pain	11 (30.6%)	37 (37.8%)	17 (30.4%)	8 (22.2%)	25 (27.2%)	31 (25.0%)	104 (29.7%)
Pericardial Effusion	-	-	-	-	-	2 (1.6%)	2 (0.6%)
Pleural Effusion	1 (2.8%)	6 (6.1%)	1 (1.8%)	1 (2.8%)	2 (2.2%)	3 (2.4%)	12 (3.4%)
Renal Failure	3 (8.3%)	2 (2.0%)	2 (3.6%)	1 (2.8%)	3 (3.3%)	4 (3.2%)	12 (3.4%)
Thrombocytopenia	5 (13.9%)	27 (27.6%)	16 (28.6%)	7 (19.4%)	23 (25.0%)	31 (25.0%)	86 (24.6%)
Thrombosis, thrombus, and/or embolism	4 (11.1%)	3 (3.1%)	2 (3.6%)	1 (2.8%)	3 (3.3%)	12 (9.7%)	22 (6.3%)

Source: Table 23.1.1 Subject Incidence of Adverse Events during the Period of Collection of Data by Adverse Event – (Full Analysis Set Subjects who Received Anti-Tumor Medication after First Recurrence, All countries)

[a]*A Subject may be counted once under each sub-category.*
[b]*Percentages are based on total listed in column head.*

LIST OF APPENDICES

APPENDICES

Appendix 1: Protocol and Amendments

Below is a link to the final version of Protocol:

20110178 RPP ORRG amendment_14Nov2012 PDF.pdf

Appendix 2: Questionnaires/Surveys

No questionnaires or surveys were used in this study.

Appendix 3: List of Investigators and Other Key Personnel Involved in the Study

The table below provides names of principal investigators at each centre (PIs), sub-investigators (Sub-Is)/coordinators and institutional addresses. The curricula vitae for principal investigators and other key study participants (i.e., central reviewers, consultants reviewing blinded data) are on file at Amgen.

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Appendix 4: Publications Based on the Study

No publications based on this study exist as of the date of this report.

Appendix 5: Subject Safety Summaries

None

Not applicable

Appendix 6: Statistical Analysis Plan (SAP)

Below is a link to the final version of the statistical analysis plan:

20110178 SAP v2.pdf