EPIDEMIOLOGY STUDY REPORT

Drug utilization study (DUS) of ZALTRAP using European databases

AVE005 Aflibercept

Study type:	Cross-sectional study
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Title:

Drug Utilization Study of ZALTRAP® (aflibercept) Using European Databases

AVE005 Aflibercept

Version identifier of the final study report	*1.0*

Date of last version of the final study report	*October 12, 2016*
EU PAS register number	*ENCEPP/SDPP/5365*
Active substance	*ZALTRAP® (aflibercept)*
Medicinal product	*List of centrally authorized medicinal product(s) and/or, if possible, of nationally authorized products subject to the study* ZALTRAP® (aflibercept)
Product reference	*Aflibercept*
Procedure number	*N/A*
Marketing authorisation holder(s)	*Sanofi, Global Pharmacovigilance and Epidemiology, 55 Corporate Drive, Bridgewater, NJ 08807*
Joint PASS	*No*
Research questions and objective(s):	*The primary objectives were:* • *To evaluate the frequency distribution of cancer type(s) among patients who receive treatment containing ZALTRAP in the five largest national markets in Europe (EU5): United Kingdom (UK), France, Germany, Italy, and Spain* • *To describe different treatment combinations among patients who receive therapy containing ZALTRAP in the EU5* • *To evaluate the proportion of ZALTRAP patients with observed intravitreal use in England*
Country(-ies) of study	*United Kingdom, Germany, France, Spain, Italy*

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1 ABSTRACT

Title

Drug utilization study (DUS) of ZALTRAP using European databases

Keywords

- Metastatic colorectal cancer
- Aflibercept
- Drug utilization study

Rationale and background

ZALTRAP is a novel recombinant human fusion protein consisting of portions of the receptors for the vascular endothelial growth factor (VEGF) molecule. It is indicated for use in combination with irinotecan/ 5fluorouracil/ leucovorin (FOLFIRI) chemotherapy in adults with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-containing regimen. In October of 2011, Sanofi filed a registration application with European Medicines Agency (EMA) for ZALTRAP to be marketed in the European Union (EU). Marketing authorization was granted for ZALTRAP on February 1st, 2013, following a positive opinion and recommendation from EMA's Committee for Medicinal Products for Human Use (CHMP) in November 2012.

The potential for ZALTRAP exposures for non-cancer treatments also exist. The off-label intravitreal use of VEGF inhibitors formulated for oncology use, such as AVASTIN, in the treatment of wet age-related macular degeneration (AMD) has been observed, despite the availability of a formulation for intravitreal use (LUCENTIS® [ranibizumab]). Because AVASTIN has similar target specificity as LUCENTIS, ophthalmologists have been treating wet AMD with AVASTIN prior to and following the approval of LUCENTIS. EYLEA® (aflibercept), a similar aflibercept drug substance and drug product was developed for intravitreal injection to treat wet AMD. There is potential for serious consequences if ZALTRAP is administered intravitreally, particularly since it is formulated as a hyperosmotic solution. Special warnings and precautions have been added in the ZALTRAP EU SmPC, package leaflet and packaging (for both vial and carton) to prevent the off-label intravitreal use of ZALTRAP.

During the registration application with EMA for ZALTRAP to be marketed in the EU, Sanofi proposed a three-year DUS using European databases as part of the post-approval commitments. This is the third (final) of three annual reports that will cover (in aggregate) the time period of April 1, 2013 through March 31, 2016. The primary objectives of the proposed DUS were to monitor ZALTRAP use in cancer patients including potential off-label use and evaluate the potential for intravitreal use.

Research question and objectives

The primary objectives were:

- To evaluate the frequency distribution of cancer type(s) among patients who receive treatment containing ZALTRAP in the five largest national markets in Europe (EU5): United Kingdom (UK), France, Germany, Italy, and Spain
- To describe different treatment combinations among patients who receive therapy containing ZALTRAP in the EU5
- To evaluate the proportion of ZALTRAP patients with observed intravitreal use in England

Study design

This was a cross-sectional study.

Setting

This cross-sectional retrospective database study was performed in United Kingdom, Germany, France, Spain, and Italy. This study used two databases. For the study that evaluated ZALTRAP use among cancer patients, data from the IMS Oncology Analyzer™ (OA) from 1 April 2015 to 31 March 2016 was used. Data for study which evaluated the intravitreal use of ZALTRAP was drawn from the IMS Hospital Treatment Insights (HTI) database from 1 October 2014 to 31 March 2016. However, the data between 1 April 2015 and 31 March 2016 were not received from the UK government due to recent changes in the UK NHS policy related to release of HES data. Therefore, it was not included in the current analysis. Since this is a cross-sectional study, no minimum enrollment or registration period was required for patients before or after ZALTRAP exposure. Descriptions of each database appear below in section 9.

Subjects and study size

Evaluation of ZALTRAP Use Among Cancer Patients

Inclusion criterion

- Patients with a record of the receipt of at least one administration of ZALTRAP between 1 April 2015 and 31 March 2016, as determined by the drug brand and molecule name recorded in the current drug therapy field

Exclusion criterion

- Patients who are participating in a clinical trial

Evaluation of Intravitreal Use of ZALTRAP

Inclusion criteria

- Patients with a record for the receipt of at least one administration of ZALTRAP between 1 October 2014 and 31 March 2015; only the first exposure to ZALTRAP was considered for each patient.
    - ZALTRAP use was determined by the presence of the Anatomic Therapeutic Classification (ATC) code (ATC L01XX44) from the HPA drug ordering table in HTI and the brand name from the HPA drug reference tables in HTI.
- Patients with prior exposure to EYLEA (ATC S01LA05) were included, as long as there was evidence of a subsequent exposure to ZALTRAP as required in the inclusion criteria stated above.

Exclusion criterion

- Patients exposed to EYLEA without subsequent exposure to ZALTRAP.

Variables and data sources

Data sources

Evaluation of ZALTRAP Use Among Cancer Patients

Data for this study was drawn from the IMS Oncology Analyzer™ (OA), which is a quarterly structured survey of treated prevalence for over 25 leading solid tumors and hematological malignancies. Detailed data on the characteristics and treatment of patients from various countries in Asia and Europe are collected. Data for this study was limited to that from the EU5.

Evaluation of Intravitreal Use of ZALTRAP

Data for this study was drawn from the IMS Hospital Treatment Insights (HTI), which is a linked database combining UK National Health Service (NHS) Hospital Episode Statistics (HES) data with the IMS Hospital Pharmacy Audit (HPA) data. HES is a data warehouse containing details of all admissions and visits to NHS hospital trusts, which provide inpatient, emergent, and outpatient specialty care in England. The HPA data provides a comprehensive record of usage of medicinal products by NHS hospitals, regardless of their source of supply. As of Q1 2012, the HPA audit covered 218,044 (93.63%) acute NHS beds. The linked data include 2.1 million patients from 33 of 166 hospital trusts in England; patients seeking care in UK geographies other than England are not represented in the HTI database.

Exposure

ZALTRAP use was the main exposure of interest in the studies using the OA and HTI databases. Treatment with ZALTRAP was captured using brand and molecule name recorded in the current drug therapy field in the OA database. In the HTI database, ATC code (ATC L01XX44) and brand name were used to identify ZALTRAP use.

Outcomes

Evaluation of ZALTRAP Use Among Cancer Patients

The primary outcomes of interest in the database study of ZALTRAP use among cancer patients were:

- The primary indication (tumor and stage) observed with ZALTRAP exposure, and
- The concurrent therapies observed with ZALTRAP exposure.

Evaluation of Intravitreal Use of ZALTRAP

The primary outcome for this analysis was the intravitreal use of ZALTRAP.

Statistical analysis

Evaluation of ZALTRAP Use Among Cancer Patients

Descriptive statistics of all demographics, tumor characteristics, treatment characteristics, and outcomes were provided for all the countries combined and by each EU5 country. Categorical variables were presented as the count and percentage of patients in each category; continuous variables were summarized by providing the mean, standard deviation, and median. One-sample 95% confidence intervals were constructed around the proportion of off-label ZALTRAP use, and the proportion of ZALTRAP used with non-label-recommended treatment combinations.

Evaluation of Intravitreal Use of ZALTRAP

Descriptive statistics of all demographics, clinical characteristics, and outcomes were reported for all patients. Categorical variables were presented as the count and percentage of patients in each category. One-sample 95% confidence intervals were constructed around the proportion of intravitreal use of ZALTRAP.

Sample size

This study included all patients who received therapy containing ZALTRAP in the OA database and all patients who received ZALTRAP from the HTI database during the study period.

Results

Evaluation of ZALTRAP Use among Cancer Patients using OA data

In total, 76 patients were initially identified as having received ZALTRAP from 1 April 2015 to 31 March 2016, of whom two patients (2.6%) were excluded due to their enrollment in a ZALTRAP clinical trial. A total of 74 patients were available for analysis. Table 1 in Appendix C reports the final sample size for the study, both overall and by country.

All but one of the 74 patients, overall and across all countries of interest, received ZALTRAP for the label approved indication (metastatic CRC). The Label-approved indication (metastatic

CRC) was hence 98.6% (95% CI = [92.6%; 99.9%]). The only one patient who received Zaltrap for non-label approved indication had non-metastatic CRC.

Patients were observed to receive ZALTRAP with FOLFIRI (45/74, 60.8%); with FOLFIRI-like protocol (28/74, 37.8%); and with other cytotoxic agents (1/74, 1.4%).

Most patients in Germany received ZALTRAP with FOLFIRI (25/30, 83.3%). One patient received a non-label recommended treatment combination (1/74, 1.4% overall; and 1/30, 3.3% in Germany, Table 5 in Appendix C). This patient did not have Zaltrap with FOLFIRI or FOLFIRI-like protocol combinations.

Cumulative reporting was performed for the aggregate (i.e. years 1, 2, and 3 combined) time period of 1 April 2013 through 31 March 2016 for OA data. In total, 151 patients were identified in OA data, all but one of which had label-approved usage of ZALTRAP (Table 10). The only one patient who received Zaltrap for non-label approved indication had non-metastatic CRC.

Evaluation of Intravitreal Use of ZALTRAP using HTI data

Total 183 patients remained when extracting patients for the time period April 2013-March 2015 after some patients were excluded due to unavailability of linked data. Among them, 79 patients were available for analysis for the time period of October 2014-March 2015. Table 6 in Appendix C contains the study attrition.

With respect to the use of Zaltrap by intra-vitreal application, the route of drug application is not captured by the HTI database. Therefore, a proxy definition was adopted to assume intra-vitreal use if a patient was seen by an ophthalmologist with a wet AMD diagnosis and without CRC. No intra-vitreal use of Zaltrap can be confirmed from the current study, the proportion of intravitreal use of Zaltrap was estimated to be 0 (0%) (Table 8).

Cumulative reporting was performed for the aggregate time period of 1 April 2013 through 31 March 2015 for HTI data. In total, 183 patients were identified in HTI data, no intra-vitreal use of Zaltrap can be confirmed from the current study, the proportion of intravitreal use of Zaltrap was estimated to be 0 (0%) (Table 11).

Discussion

Key Results

An evaluation of the frequency distribution of cancer type(s) among patients who received treatment containing ZALTRAP (N=74) in the five largest national markets in Europe (EU5) found that all but one patient (N=1/74, 1.6%), overall and across all countries of interest, received ZALTRAP only for the label approved indication (metastatic CRC). The only one patient who received Zaltrap for non-label approved indication had non-metastatic CRC.

With respect to the use of Zaltrap by intra-vitreal application, the route of drug application is not captured by the HTI database. Therefore, a proxy definition was adopted to assume intra-

vitreal use if a patient was seen by an ophthalmologist with a wet AMD diagnosis and without CRC. No intra-vitreal use of Zaltrap can be confirmed from the current study, the proportion of intravitreal use of Zaltrap was estimated to be 0 (0%).

Limitations

- OA database

The OA database includes data from panels of physicians, who review current treatment and medical history from patients presenting for treatment. Physicians are recruited systematically to maximize the representativeness of their patient panel to care rendered in their respective countries, but participation of physicians is voluntary. The degree of bias between the sampling frame and recruited physicians, and the implications that such bias may have on the representativeness of ZALTRAP utilization within each country, is unknown.

The study used data from five out of 28 EU countries where marketing authorization was granted. Findings from the EU 5 countries may not be generalizable to other EU countries where ZALTRAP received marketing authorization, as there might be different treatment guidelines, physician prescribing behaviors, reimbursement policies, or other utilization restrictions.

Applicable to both the OA and HTI databases, the study is designed to capture only the first ZALTRAP exposure for each patient; therefore, subsequent exposures to ZALTRAP for the same patient will not be reported. Results should be interpreted as reflecting patients with initial use of ZALTRAP, rather than total ZALTRAP administrations.

- HTI database

The data captured in the HTI database is a combination of data collected from the IMS HPA and UK NHS HES databases. In the HTI database, complete patient-level history is captured on drugs dispensed to patients through the hospital pharmacy. Drugs given to patients from the ward stock cannot be linked to an individual patient. Because ZALTRAP is a specialty pharmaceutical product, it is not expected to be included as a ward stock, especially in specialty hospital outpatient setting. However, it is possible that ZALTRAP for intravitreal administration will be prepared in an aseptic unit. When drugs are sent via an aseptic unit, it is possible that complete patient-level detail may not be captured. The occurrence of this could lead to underreporting of potential intravitreal use of ZALTRAP since patients' history such as diagnosis, physician specialty information, or route of administration may not be available.

The HTI database only allows for the assessment of intravitreal use of ZALTRAP in England. Therefore, the findings from this analysis may not be generalizable to the rest of the UK or to other EU countries where ZALTRAP will be marketed. Additionally, HTI data are collected from select hospital trusts that provided consent for their data to be linked to HPA. As a result, findings may only be generalizable to other trusts with similar population and clinical practices.

The protocol specifically limited evaluation of diagnosis to the episode associated with ZALTRAP administration. Patients with intravitreal administration or specific off-label utilization as determined by historical diagnoses preceding the ZALTRAP episode would be

underreported to an unknown extent. Additionally, to the extent that a small number of institutions have a higher likelihood of off-label applications, the population reported may be less generalizable than the full source population.

Within the HTI database, treating physicians are not required to apply diagnoses to outpatient administrations, which will influence data completeness in this study. While the specialty of treating physicians is captured, this data is limited to the ZALTRAP event only, and any historical specialty, including ophthalmology, remains unreported based on the protocol methodology.

Applicable to both the OA and HTI databases, findings from the EU 5 and England, respectively, may not be generalizable to other EU countries where ZALTRAP received marketing authorization, as there might be different treatment guidelines, physician prescribing behaviors, reimbursement policies, or other utilization restrictions.

Regarding HTI data, to the extent that the approximately ¼ of England captured within the database is not fully representative of the UK, data from this source may have limited generalizability.

Marketing Authorization Holder(s)

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2 LIST OF ABBREVIATIONS

Abbreviation	Description
A&E	Accident and Emergency
CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
DUS	Drug Utilization Study
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EU	European Union
EU5	United Kingdom, France, German, Italy, and Spain
FOLFIRI	Irinotecan/5-fluorouracil/leucovorin
HSCIC	Health & Social Care Information Centre
HES	Hospital Episode Statistics, a National Health Service database
HIV	Human immunodeficiency virus
HPA	IMS Hospital Pharmacy Audit database
HTI	IMS Hospital Treatment Insights database
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
INN	International Nonproprietary Name
ISEAC	Independent Scientific Ethics and Advisory Committee
mCRC	Metastatic Colorectal Cancer
MHRA	Medicines and Healthcare Products Regulatory Agency
NIGB	National Information Governance Board
NHS	National Health Service
OA	IMS Oncology Analyzer
OPCS-4.6	Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision)
REC	Research Ethics Committee
SMPC	Summary of Product Characteristics
TNM Score	Tumor size, Lymph Nodes affected, Metastases Score
UK	United Kingdom
VEGF	Vascular Endothelial Growth Factor
Wet AMD	Wet Age Macular Degeneration

3 INVESTIGATORS

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4 OTHER RESPONSIBLE PARTIES

Not applicable.

5 MILESTONES

The planned dates for the study milestones are presented below:

Milestone	Planned date
Start of study	*December 13, 2013*
Interim study report 1	*November 30, 2014*
Interim study report 2	*November 30, 2015*
Final report of study results	*November 30, 2016*

6 RATIONALE AND BACKGROUND

ZALTRAP® (aflibercept) is a novel recombinant human fusion protein consisting of portions of the receptors for the vascular endothelial growth factor (VEGF) molecule.[1] It binds to VEGF-A, VEGF-B, and placental growth factors.[1] ZALTRAP is indicated for use in combination with irinotecan/5-fluorouracil/leucovorin (FOLFIRI) chemotherapy in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

In October 2011, Sanofi filed a registration application with the European Medicines Agency's (EMA) for ZALTRAP to be marketed in the European Union (EU). ZALTRAP has been granted marketing authorization in the EU on February 1st 2013, following a positive opinion and recommendation from EMA's Committee for Medicinal Products for Human Use (CHMP) in November 2012.[2] The recommendation and approval was based on data from the pivotal Phase III VELOUR study, a multinational, randomized, double-blind trial comparing FOLIFIRI in combination with either ZALTRAP or placebo in the treatment of patients with mCRC previously treated with an oxaliplatin-containing regimen.[3]

Other targeted agents approved for mCRC include bevacizumab (AVASTIN®), an anti-angiogenesis agent that binds all isoforms of VEGF-A, and cetuximab (ERBITUX®), and panitumumab (VECTIBIX®), both of which target the epidermal growth factor receptor (EGFR) pathway.[4,5,6] Like ZALTRAP, bevacizumab inhibits angiogenesis through binding to VEGF, while cetuximab and panitumumab inhibit tumor growth through binding to the EGFR. Targeted agents have been available for treatment of mCRC in Europe since 2004, and some agents have added indications for first-line therapy after initial approval for second- or third-line therapy. In addition, bevacizumab indications in Europe have expanded beyond the initial mCRC indication to include metastatic breast cancer, metastatic or recurrent non-small-cell lung cancer, renal cell carcinoma, and ovarian cancer. Cetuximab also received a subsequent indication for head and neck cancer. The precedent of expanded indications for mCRC-approved targeted agents, both within forms of CRC and across tumor types, poses a risk that patients may be exposed to ZALTRAP for indications beyond what has been initially approved.

The potential for ZALTRAP exposures for non-cancer treatments also exist. The off-label intravitreal use of VEGF inhibitors formulated for oncology use in the treatment of neovascular or wet age-related macular degeneration (AMD) has been widely documented, despite the availability of VEGF formulations specifically for the treatment of wet AMD.[4,7,8,9] LUCENTIS® (ranibizumab), an affinity-matured antigen-binding fragment (Fab) derived from bevacizumab, was developed specifically for intravitreal administration to treat wet AMD, and is formulated as an iso-osmotic solution.[1,9] LUCENTIS was developed as a Fab because the smaller size was thought to enhance its diffusion from the vitreous into the retina and choroid, relative to full-length antibodies.[1] Because AVASTIN has similar target specificity to LUCENTIS, ophthalmologists have been observed treating wet AMD with AVASTIN prior to and after the approval of LUCENTIS.[7,10]

ZALTRAP was formulated for systemic (intravenous) administration, and specifically for the needs of oncology patients. ZALTRAP was formulated as a hyperosmotic solution to facilitate the long-term stability of the formulation prior to its dilution and administration.[1] Similar to AVASTIN and LUCENTIS, a similar aflibercept drug product, known as EYLEA® (aflibercept), an ultra-purified and iso-osmotic drug, was developed specifically for intravitreal injection for use in the treatment of wet AMD. Because of the precedent of off-label use of AVASTIN for wet AMD, patients may be at risk for off-label intravitreal administration of ZALTRAP. ZALTRAP may have potential for serious consequences when administered intravitreally. While the effect of intravitreal use of ZALTRAP has not been studied, retinal detachment and permanent retinal degeneration have been reported in animal studies where hyperosmotic solutions were administered intravitreally.[11] Special warnings and precautions have been added in the ZALTRAP EU SmPC, package leaflet and packaging (for both vial and carton) to prevent the off-label intravitreal use of ZALTRAP.

To evaluate the incidence of off-label use of ZALTRAP for intravitreal injection after its availability in the EU, Sanofi proposed a three-year Drug Utilization Study (DUS) using European databases as part of the post-approval commitments, during the registration application with EMA for ZALTRAP to be marketed in EU. This is the third (final) of three annual reports that cover (in aggregate) the time period of April1, 2013 through March 31, 2016. The primary objectives of the proposed DUS were to monitor ZALTRAP use in cancer patients including potential off-label use and evaluate the potential intravitreal use.

7 RESEARCH QUESTIONS AND STUDY OBJECTIVES

The study aimed to evaluate the extent of off-label use of ZALTRAP following its availability in the market. This evaluation was comprised of two components: 1) use in cancer patients including off-label use in cancer type(s) and in combinations other than those described in the label; 2) intravitreal use.

The specific primary objectives of the study are:

- To evaluate the frequency distribution of cancer type(s) among patients who receive treatment containing ZALTRAP in the five largest national markets in Europe (EU5): United Kingdom (UK), France, Germany, Italy, and Spain

- To describe different treatment combination among patients who receive therapy containing ZALTRAP in the EU5

- To evaluate the proportion of ZALTRAP patients with observed intravitreal use in England

8 AMENDMENTS AND UPDATES

No amendments or updates were made to the original study protocol.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This was a cross-sectional study of two main samples of patients with exposure to ZALTRAP. The first sample included cancer patients treated with ZALTRAP in the EU5; frequencies of tumor types recorded for treatment with ZALTRAP and treatment combinations containing ZALTRAP were assessed for this sample. The second sample included English patients who visited the hospital trusts and had an exposure to ZALTRAP for any indication; the proportion of intravitreal ZALTRAP administration was assessed for this sample. Since the goal of this study is to evaluate the extent of off-label use of ZALTRAP, the cross-sectional study design allows us to evaluate the reason for which ZALTRAP is used at the time of its administration.

9.2 SETTING

This study used two databases. For the study that evaluated ZALTRAP use among cancer patients the IMS Oncology Analyzer™ (OA) from 1 April 2015 to 31 March 2016 was used. Data for study which evaluated the intravitreal use of ZALTRAP was drawn from the IMS Hospital Treatment Insights (HTI) database from 1 October 2014 to 31 March 2016. However, the data between 1 April 2015 and 31 March 2016 were not received from the UK government due to recent changes in the UK NHS policy related to release of HES data. Therefore, it was not included in the current analysis. Since this is a cross-sectional study, no minimum enrollment or registration period was required for patients before or after ZALTRAP exposure. Descriptions of each database appear below in section 9.

9.3 SUBJECTS

To address the study objectives, two main samples of patients with exposure to ZALTRAP were identified. Patients who met the study selection criteria described below were selected into the study.

Patient Selection Criteria – Evaluation of ZALTRAP Use Among Cancer Patients

Inclusion criterion

Patients meeting the following inclusion criteria were initially selected for study inclusion:

- Patients from the EU5 for whom the physician reported the receipt of at least one dose of ZALTRAP, as a current therapy, in the time periods described above. ZALTRAP use was identified by the brand and molecule name recorded in the current drug therapy field

Exclusion criterion

- Participation in a clinical trial excluded patients from the study

Patient Selection Criteria – Evaluation of Intravitreal Use of ZALTRAP

Inclusion criteria

Patients meeting the following inclusion criteria were initially selected for study inclusion:

- Patients with a record for the receipt of at least one dose of ZALTRAP during the study time period described above. Only the first exposure to ZALTRAP was identified for each patient throughout the study period, so that patients are included only once in the study population.
    - The receipt of ZALTRAP was identified using the Anatomic Therapeutic Classification (ATC) code from the HPA drug ordering table in HTI and the brand name from the HPA drug reference tables in HTI. Exposure to ZALTRAP used the ATC L01XX44 code.
- For patients with prior exposure to EYLEA (ATC S01LA05), a subsequent exposure to ZALTRAP was required.

Exclusion criterion

- Patients exposed to EYLEA without subsequent exposure to ZALTRAP

9.4 VARIABLES

Exposure

The main exposure of interest in both database studies was treatment with at least one dose of ZALTRAP. ZALTRAP exposure in the OA database was identified by the brand and molecule name recorded in the current drug therapy field. In the HTI database, ATC code and brand name were used to identify ZALTRAP use. Exposure to ZALTRAP used the ATC L01XX44 code. Exposure to EYLEA (ATC S01LA05) was not counted as exposure to ZALTRAP.

Outcomes

Outcome Assessment – Evaluation of ZALTRAP Use Among Cancer Patients

The primary outcomes of interest in the database study of ZALTRAP use among cancer patients are:

- The primary indication (tumor and stage) observed with ZALTRAP exposure, and
- The concurrent therapies observed with ZALTRAP exposure.

Diagnostic Indication

The diagnostic indication for treatment with ZALTRAP was categorized as either label-approved indication or off-label indication. Label-approved indication was defined as colorectal cancer recorded as the primary cancer site, with further evidence of metastasis. Metastasis was characterized by a record of stage IV on or before current therapy, or a documented distant metastasis site even if a stage is reported other than stage IV. Since OA records tumor staging only at initial diagnosis and at first relapse , either stage were considered for defining metastasis if the date associated with the reported stage is on or before the current therapy start date.

Off-label indication was defined as other primary cancer diagnoses, or CRC that was not confirmed as metastatic. Primary cancer diagnoses captured under the off-label indication were reported separately as follows:

- Non-mCRC (CRC diagnosis that was not confirmed as metastatic)
- Non-small-cell lung cancer (NSCLC), all stages
- Renal cell cancer, all stages
- Breast cancer, all stages
- Ovarian cancer, all stages
- Other cancers

Concurrent treatments with ZALTRAP

Concurrent treatments with ZALTRAP were defined as current cytotoxic therapies reported along with ZALTRAP therapy. Current hormonal or supportive drug therapies used concurrently with ZALTRAP were not reported. Treatment combinations containing ZALTRAP were categorized as follows:

- ZALTRAP with irinotecan/5-fluorouracil/leucovorin (FOLFIRI)[1]
- Non-label-recommended combinations
    - ZALTRAP monotherapy
    - ZALTRAP with other cytotoxic agents
    - ZALTRAP with other mCRC approved targeted agents (See Appendix B)

Outcome Assessment – Evaluation of Intravitreal Use of ZALTRAP

The primary outcome for this analysis was intravitreal use of ZALTRAP. Any administration of ZALTRAP that met the criteria described below was defined as intravitreal use of ZALTRAP:

- The presence of an intravitreal route of administration recorded for the administration of ZALTRAP.

[1] Due to reimbursement restriction for some chemotherapy agents in some EU5 countries, ZALTRAP use may be observed with FOLFIRI-like protocols that exclude irinotecan. We may consider a separate category that reports 5-FU/leucovorin excluding irinotecan should sufficient cases with this pattern be observed.

- Prescription of ZALTRAP by an ophthalmologist with no observable patient diagnosis code for CRC (ICD-10 codes: C18.x, C20.x, C21.x; See Appendix A for description of codes).

- ZALTRAP administered with a diagnosis code of wet AMD (ICD-10 code: H35.3x; See Appendix A for description of codes) with no observable patient diagnosis code for CRC.

Descriptive variables

Evaluation of ZALTRAP Use Among Cancer Patients

Demographic Characteristics

Patient demographic characteristics were described based on data collected at the time of the survey, and were reported for all patients. These data included:

- Age (reported in categories):
    - 0 – 15
    - 16 – 25
    - 26 – 35
    - 36 – 45
    - 46 – 55
    - 56 – 65
    - 66 – 75
    - 76 +
- Gender:
    - Male
    - Female

Clinical Characteristics

Clinical characteristics were described based on data collected at the time of the survey, and were reported for all patients. These data included:

- Eastern Cooperative Oncology Group (ECOG) performance status at time of survey:
    - 0, asymptomatic
    - 1, symptomatic, fully ambulatory
    - 2, symptomatic, in bed <50% of day
    - 3, symptomatic, in bed >50% of day, but not bedridden

  - 4, bedridden

- Physician-reported comorbidities that affect treatment of cancer (The survey has a pre-determined list of comorbidities for physicians to select. The categories below are not mutually exclusive):
  - Autoimmune
  - Cardiac dysfunction
  - Chronic obstructive pulmonary disease (COPD)
  - Diabetes
  - Human immunodeficiency virus (HIV)
  - Liver dysfunction
  - Parkinson's
  - Peripheral Neuropathy
  - Renal dysfunction
  - Other
  - None

- Specialty of physician currently overseeing oncology treatment:
  - Medical oncologist
  - Clinical oncologist
  - Gastroenterologist
  - Gynecologist
  - Urologist
  - Onco- Hematologist
  - Surgeon
  - radiotherapist
  - Other

Treatment Characteristics

Cancer treatment information were described based on data collected at the time of the survey, and were reported for patients with CRC recorded as the primary cancer site, with evidence of metastasis. These data included:

- Surgery before current therapy:
- Chemotherapy before current therapy (Yes/No):

  - Oxaliplatin-based chemotherapy (Yes)

  - Oxaliplatin-based chemotherapy (No)
- Any radiotherapy before current therapy (yes/no)

- ZALTRAP dose per administration (The recommended dose of ZALTRAP is 4mg/kg. Dose of ZALTRAP per administration was calculated based on information available in the quantity per dose, dose unit, and weight fields of the survey; and was reported in mg/kg. When mg is selected as the unit for quantity per dose, the dose administered was calculated by dividing the quantity per dose by weight. If mg/kg is selected as the unit for quantity per dose, the dose administered was used as recorded. ZALTRAP dose was not calculated for patients with missing records for any of the required fields.)

Descriptive Variables – Evaluation of Intravitreal Use of ZALTRAP

Demographic and clinical characteristics were described based on data collected at the time of the first ZALTRAP administration. These data included:

- Age (reported in whole years, during year of first administration)
    - 0 – 17
    - 18 – 27
    - 28 – 37
    - 38 – 47
    - 48 – 57
    - 58 – 67
    - 68 – 77
    - 78+
    - Missing
- Gender:
    - Male
    - Female
    - Missing
- Ethnicity
    - White (British, Irish, any other White background)
    - Black / British Black (Caribbean, African, any other Black background)
    - Asian /Asian British (Indian, Pakistani, Bangladeshi, any other Asian background)
    - Other (Chinese, any other ethnic group)
    - Not stated / unknown
- Diagnosis for which ZALTRAP was used:
    - Metastatic Colorectal cancer only

  - Other cancers only (ICD-10 codes: C00.x – C17.0, C19.x, C22.x – D48.x; See Appendix A for description of codes)
  - Colorectal cancer and other cancer (see Appendix A for description of codes)
  - Wet AMD (ICD-10 codes: H35.3; See Appendix A for description of codes)
  - Diabetic macular edema (ICD-10 codes: H35.8x, E10.3x, E11.3x; See Appendix A for description of codes)
  - CRVO
  - Other diagnoses
- Specialty of prescriber or treating physician:
  - Ophthalmologist
  - Oncologist
  - Other physician specialties
- Treatment setting:
  - Inpatient
  - Outpatient
  - A & E (Accident and Emergency)

Stratifying variables

The study outcomes and descriptive variables in the database study of ZALTRAP use among cancer patients were described overall and stratified separately by the following variables:

- Country of origin:
  - UK
  - France
  - Germany
  - Spain
  - Italy

No stratifying variables were employed in the database study that evaluated intravitreal ZALTRAP use.

9.5 DATA SOURCES AND MEASUREMENT

IMS Oncology Analyzer

The IMS Oncology Analyzer is a quarterly structured survey of treated prevalence for over 25 leading solid tumors and hematological malignancies. It contains detailed data on the characteristics and treatment of patients with a variety of tumor types in Asia (Japan, China, Korea, Taiwan) and Europe (EU5, the Netherlands, and Turkey). Only data for the EU5 will be used for this study.

The physician sampling frame for each EU country was created from an IMS census of practitioners treating cancer patients within each country. The physicians contracted to complete OA surveys are recruited systematically to maximize the representativeness of their patient panels to care rendered in each country.

Contracted physicians sample a pre-specified number of consecutive patients in a designated week during the calendar quarter, with the size of the sample determined by their total patient panel and the share of patients with various tumor types that they treat within their country. Data are collected one time for each patient from physicians in oncology settings using a structured, paper-based medical record abstraction form. The data collection includes all patient history available in the reporting physician's records, meaning that historical longitudinal information is available. However, patients are not resampled, so records are not updated with future treatment or outcomes information after the patient's initial survey date.

Data elements include patient demographics, tumor stage and diagnostic test results at various points during past treatment, past surgery and radiotherapy, and past and current chemotherapy, hormonal therapy, and supportive care. The database currently includes data on nearly 60,000 unique patients treated by nearly 2,300 physicians, including nearly 14,000 patients and more than 860 physicians in the EU5. Data are available from the first quarter (Q1) of 2005, with a data lag of 45 days following the end of each quarter.

IMS Hospital Treatment Insights

IMS Hospital Treatment Insights (HTI) is a linkage of private and public secondary care assets in England. Pharmacy records come from a proprietary audit of hospital trusts in the UK National Health Service (NHS) maintained by IMS Health. The IMS Hospital Pharmacy Audit (HPA) provides a comprehensive record of usage of medicinal products by NHS hospitals dating back to 1991. It monitors usage/consumption levels by end user hospitals, rather than wholesale purchases by the facilities themselves. HPA monitors usage of all pharmaceutical products within the hospital, regardless of their source of supply. Product sales from wholesalers, direct from manufacturers, or via other hospitals are all automatically covered. As of Q1 2012, the audit had a universe size of 232,888 total NHS beds and 218,044 acute NHS beds. In terms of data coverage, 93.63% of hospital acute beds are effectively covered. The audit does not currently cover the private or military sectors.

HPA records are linked to Hospital Episode Statistics (HES) records published by NHS. HES is a data warehouse containing details of all admissions and visits to NHS hospital trusts, which provide inpatient, emergent, and outpatient specialty care in England. HES contains admitted patient care data from 1989 onwards, with more than 12 million new records added each year, and outpatient attendance data from 2003 onwards, with more than 40 million new records added each year.

IMS integrates the combined HTI asset under procedures governed by the international security standard, ISO 270001. HTI contains diagnoses (ICD10 format), procedures (OPCS-4.6 format), and several A&E (Accident and Emergency) clinical classification codes. The 'OPCS Classification of Interventions and Procedures' (OPCS-4.6) is a procedural classification list for the coding of operations, procedures and interventions performed on NHS patients during an Episode of health care in the UK. The HES portion of HTI comprises inpatient admissions, outpatient specialist appointments and treatments, and Accident & Emergency admissions.

The linked data include 2.1 million patients across all different hospital therapies. HES data are currently contributed from 33 of 166 hospital trusts in England; as a result, some patients may be represented by hospital trust pharmacy records (HPA) without corresponding links to specialist, inpatient, or A&E visits. Patients seeking care in UK geographies other than England are not represented in the HTI database.

A HES data year runs from April 1st (Q2) until the following March 31st (Q1). Provisional HES data come in quarterly and are "restated" (updated) each quarter until a year is complete. There is an NHS requirement that patient-level HES data must reside within the UK geography, within an ISO27001 accredited data centre; therefore, analyses of HTI are managed by accredited IMS analysts in the UK.

9.6 BIAS

Information regarding the treatment of cancer patients reported by hospital and office-based doctors presented in the IMS Health Oncology Analyzer Audits is derived from statistically optimized and stratified cluster samples of doctors. However, in every sample, there is the risk that certain diseases or therapies were not captured sufficiently. The mathematical risk of arriving at sample-based results that are not in full accordance with the entire but unknown universe is reflected by the sampling error, which represents a known source of bias in this study given the selected data source.

Because the study is limited to EU-5 patients, results of this analysis may not be generalizable to a broader population of patients. Additionally, the HTI database is limited to England, and therefore less generalizable given omission of the remainder of the UK.

9.7 STUDY SIZE

This study included all patients who received therapy containing ZALTRAP in the OA database and all patients who received ZALTRAP from the HTI database during the study period.

Historical prevalence of ZALTRAP treatment is not available. In the OA database, we observed the first-year prevalence of current therapies for angiogenesis inhibitors cetuximab (EC authorized 29 June 2004) and panitumumab (EC authorized 12 March 2007), both of which were initially approved for second-line or later indications. OA captured 153 patients with current cetuximab therapy in the four quarters ending Q2 2005, and 23 patients with current panitumumab therapy in the first four quarters ending Q1 2008. Due to the limitations on data history in the HTI database, no equivalent treatment prevalence estimates are available.

In the Exhibit below, we reported the precision of 95% confidence intervals around various potential rates of off-label ZALTRAP use in the first year of the study period in HTI database. We rounded the potential sample sizes, based on observed first-year prevalence of cetuximab or panitumumab, to multiples of 25.

Exhibit 1. 95% Confidence Interval Estimates for Potential Rates of Off-Label ZALTRAP Use

Potential first-year sample	1% off label use	5% off label use	10% off label use
N=25	95% CI (0.0%, 4.9%)	95% CI (0.0%, 13.5%)	95% CI (0.0%, 21.8%)
N=150	95% CI (0.0%, 2.6%)	95% CI (1.5%, 8.5%)	95% CI (5.2%, 14.8%)

9.8 DATA MANAGEMENT AND TRANSFORMATION

Oncology Analyzer–Evaluation of ZALTRAP Use Among Cancer Patients

OA is a database of patient-anonymous (de-identified) healthcare activity and medical history. IMS Health does not maintain patient-identifiable information, or pseudonymous identifiers that can be linked back to individual patients, anywhere in the data production environment. Source documentation used for data entry is stripped of any potentially identifying marks. IMS Health adheres to relevant data retention guidelines for records and documents in both electronic and hard copy formats. As a fully de-identified database, analyses of OA are exempt from personal information requirements of Directive 95/46/EC of the European Parliament and of the Council (EU Directive). Further, because information in OA is patient-anonymous, no ethics or human subjects reviews are required.

Hospital Treatment Insights – Evaluation of Intravitreal Use of ZALTRAP

HTI is a pseudonymous database of patient healthcare activity. No patient-identifiable information is held anywhere within the data production environment. Linkage of source data occurs external to the data production environment, under the auspices of Health & Social Care Information Centre (HSCIC), and governed by a National Ethics Approval (Research Ethics Committee – [REC]) and National Information Governance Board (NIGB) Section 251. Additional review of patient privacy and security protections have been provided by the UK Department of Health and by the Medicines and Healthcare Products Regulatory Agency (MHRA), who have provided letters of support. Under a directive from the UK National Health Service, individual studies conducted using HTI data require approval of the study protocol from Independent Scientific Ethics and Advisory Committee (ISEAC). However, as a pseudonymous database of historical healthcare activity, informed consent from study subjects is not required.

Individual reporting cells containing 5 or fewer patients were suppressed in compliance with HIPAA regulations to protect patient anonymity.

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC). Results of the analyses were summarized in tables and figures in Microsoft® (MS) Excel format.

9.9 STATISTICAL METHODS

9.9.1 Main summary measures

Statistical Analysis – Evaluation of ZALTRAP Use Among Cancer Patients

Univariate descriptive statistics were conducted to characterize the all patients. All analyses were reported for all the countries combined and separately for each EU5 country. The demographic variables including age and gender were reported and treatment characteristics were reported for all cancer patients treated with ZALTRAP. Tumor characteristics were described for a sub-set of cancer patients treated with ZALTRAP and with non-mCRC diagnosis. For categorical measures, the distribution of patients across the categories of each characteristic were described using cross tabulation analysis, showing the frequency (number of cases) and percentage of the total number of study patients observed overall and by each EU5 country. For continuous measures, mean, median, and standard deviation were computed overall and by each EU5 country.

All outcomes were reported descriptively. The frequency (number of cases) and percentage of study patients for whom ZALTRAP was used according to the label-approved indication and label-recommended treatment combination were reported overall and by each EU5 country.

For ZALTRAP use in an off-label indication and ZALTRAP used with non-label-recommended treatment combinations, the distribution of patients across the categories of each cancer type were described using cross tabulation analysis, showing the frequency (number of cases) and percentage of the total number of study patients observed overall and by each EU5 country. Clopper/Pearson exact 95% confidence intervals were constructed around the proportion of off-label ZALTRAP use, and the proportion of ZALTRAP used with non-label-recommended treatment combinations, for each stratum.

Statistical Analysis – Evaluation of Intravitreal Use of ZALTRAP

Univariate descriptive statistics were conducted to characterize all patients. All descriptive variables including demographics, diagnostic indication, and treatment characteristics were reported. Frequency (number of cases) and percentage of the total number of study patients observed were described for each variable.

All outcomes were reported descriptively. The frequency (number of cases) and percentage of study patients with intravitreal use of ZALTRAP were reported. Clopper/Pearson exact 95% confidence intervals were constructed around the proportion of intravitreal use of ZALTRAP.

9.9.2 Main statistical methods

This was a descriptive study, and only univariate analyses were conducted, stratified by country of origin.

9.9.3 Missing values

For any variable with missing data for patients, the frequency and proportion of affected patients were reported.

9.9.4 Sensitivity analyses

No sensitivity analyses were performed for this study.

9.9.5 Amendments to the statistical analysis plan

No amendments to the statistical analysis plan were made.

9.10 QUALITY CONTROL

To ensure quality data within the OA database, over 800 business rules are built into the web survey and data entry system to ensure accurate and relevant data are captured. Analysts check that start dates of treatment are before end dates of treatment and after the date of patient diagnosis. In addition, IMS validates periods of treatment against start and end dates of total therapy given within the entire patient history. The data is examined to ensure that doses and routes of administration specified are within expected ranges for each drug, and any change in dose, dose unit, or route of administration is identified. Physician validation is required for young patients identified with breast, ovarian, prostate or testis cancer.

Programming to produce all result data tables is thoroughly reviewed by a second programmer/analyst at each step of the analysis to validate coding rules and order of operations as well as statistical methodology, as appropriate.

10 RESULTS

10.1 PARTICIPANTS - EVALUATION OF ZALTRAP USE AMONG CANCER PATIENTS USING OA DATA

In total, 76 patients were initially identified as having received ZALTRAP from 1 April 2015 to 31 March 2016, of whom 2 (2.6%) was excluded due to their enrollment in a ZALTRAP clinical trial. A total of 74 patients were available for analysis. Table 1 in Appendix C reports the final sample size for the study, both overall and by country.

10.2 DESCRIPTIVE DATA - EVALUATION OF ZALTRAP USE AMONG CANCER PATIENTS USING OA DATA

Demographic Characteristics

Overall, the majority of patients were male (51/74, 68.9%); and were aged between 56-75 years (63/74, 85.1%).
In Germany, there were more males (21/30) than females (9/30); with the majority of patients aged between 56-75 years (24/30, 80.0%). In the UK, the one patient included in the study was a female aged between 66-75 years. (Table 2 in Appendix C)

Clinical Characteristics
Overall, the majority of patients had an ECOG performance status = 1 (53/74, 71.6%); and 52.7% (39/74) received treatment from a medical oncologist. Nearly half of patients had no reported co-morbidities (30/74, 40.5%), based on the survey's predetermined list of comorbidities for physicians to select from; patients were reported to have cardiac dysfunction (22/74, 29.7%), COPD (8/74, 10.8%), diabetes (10/74, 13.5%) and liver dysfunction (2/74, 2.7%) co-morbidities. The patient in the UK (1/1, 100%), Germany (18/30, 60.0%), France (13/15, 86.7%), Spain (12/17, 70.6%), and Italy (9/11, 81.8%) had an ECOG performance status of 1. Differences in physician specialty were observed across the countries of interest. The majority of patients in France received treatment from a medical oncologist (10/15, 66.7%). All patients in the UK, Spain and Italy received treatment from a medical oncologist, while the majority of patients in Germany (29/30, 96.7%) received treatment from an onco-haematologist. Co-morbidities were not reported in the 9 of 11 patients from Italy. Patients in Germany were reported to have the co-morbidities of cardiac dysfunction (21/30, 70.0%), COPD (3/30, 10.0%), diabetes (5/30, 16.7%) and liver dysfunction (1/30, 3.3%, Table 3 in Appendix C).

10.3 OUTCOME DATA - EVALUATION OF ZALTRAP USE AMONG CANCER PATIENTS USING OA DATA

All subjects were included for evaluation of outcomes.

10.4 MAIN RESULTS - EVALUATION OF ZALTRAP USE AMONG CANCER PATIENTS USING OA DATA

All but one patient included in the analysis, overall and across all countries of interest, received ZALTRAP only for metastatic CRC, the label approved indication. The only one patient who received Zaltrap for non-label approved indication had non-metastatic CRC.

Patients were observed to receive ZALTRAP with FOLFIRI (45/74, 60.8%); with FOLFIRI-like protocol (28/74, 37.8%); and with other cytotoxic agents (1/74, 1.4%).

Most patients in Germany received ZALTRAP with FOLFIRI (25/30, 83.3%). One patient received a non-label recommended treatment combination (1/74, 1.4% overall; and 1/30, 3.3% in Germany, Table 5 in Appendix C). This patient did not have Zaltrap with FOLFIRI or FOLFIRI-like protocol combinations.

Treatment Characteristics

The majority of patients diagnosed with mCRC were reported to receive surgery before receiving current therapy (63/74, 85.1%). Similar results hold true for Germany and France, where 29/30 (96.7%) and 14/15 (93.3%), respectively, of patients received surgery prior to receiving current therapy. Overall, two patients (2.7%) received radiotherapy before the current therapy. Sixty-four of seventy-four (86.5%) received a prior oxaliplatin-based regimen. Mean ZALTRAP dose per administration was 4.0mg/Kg (median = 4.0; SD=0.6) and 294.1 mg/person (median=288.0; SD=61.2). There was a variation in ZALTRAP dose per administration (mg/person) across countries of interest; the mean dose being 314.3, 275.1, 281.9 and 269.5 in Germany, France, Spain and Italy, respectively. (Table 6 in Appendix C)

10.5 PARTICIPANTS - EVALUATION OF INTRAVITREAL USE OF ZALTRAP USING HTI DATA

In total, 139 patients were initially identified as having received ZALTRAP from 1 October 2014 to 31 March 2015, of whom 60 (43.2%) were excluded due to unavailability of linked data between HPA and HES. A total of 79 patients were available for analysis. Table 6 in Appendix C contains the study attrition.

10.6 DESCRIPTIVE DATA - EVALUATION OF INTRAVITREAL USE OF ZALTRAP USING HTI DATA

Demographic Characteristics

The majority of patients (47/79, 59.5%) were aged between 58-77 years; and were white (70/79, 88.6%). The majority of patients were male (40/79, 50.6%). (Table 7in Appendix C)

Clinical Characteristics

For the majority of patients, ZALTRAP was used by oncologists (74/79, 93.7%), with the majority of them administering the drug in an inpatient setting (69/79, 87.3%). For the majority of patients (62/79, 78.5%), the diagnosis for which ZALTRAP was used was either colorectal cancer alone or colorectal cancer with another cancer as well (Table 9 in Appendix C). No patients were identified in this study with a potential ophthalmological conditions (wet age related macular degeneration, diabetic macular edema and central retinal vein occlusion).

10.7 OUTCOME DATA - EVALUATION OF INTRAVITREAL USE OF ZALTRAP USING HTI DATA

All subjects were included for evaluation of outcomes.

10.8 MAIN RESULTS - EVALUATION OF INTRAVITREAL USE OF ZALTRAP USING HTI DATA

With respect to the use of Zaltrap by intra-vitreal application, the route of drug application is not captured by the HTI database. Therefore, a proxy definition was adopted to assume intra-vitreal use if a patient was seen by an ophthalmologist with a wet AMD diagnosis and without CRC. However, there are several limitations of the current data. First, due to limitations of the HTI data, about 10-20% of the outpatient specialty care diagnoses were missing. Second, design of the current study would only search the diagnosis from a patient’s first exposure to Zaltrap. There could be multiple episodes of different physician specialty contacts for a patient during any hospitalization. Consequently, there may be a risk that a diagnosis of CRC from these other episodes of physician interaction could be missed.

While there were rare cases of Zaltrap use linked to some ophthalmologist visits, no Wet AMD or other relevant ocular diagnoses (e.g., central vein occlusion, diabetic edema, etc.) were found. Due to these limitations, there was no intra-vitreal use of Zaltrap can be confirmed from the current report (Table 8).

10.9 OTHER ANALYSES

In addition to the aforementioned annual reporting period, cumulative reporting was performed for the aggregate (i.e. 1, 2 & 3 years combined) time period of 1 April 2013 through 31 March 2016 for OA data, and 1 April 2013 through 31 March 2015 for HTI data. In total, 151 patients were identified in OA data, all but one of which had label-approved usage of ZALTRAP (0.0%-3.5%, Table 10). The only one patient who received Zaltrap for non-label approved indication had non-metastatic CRC.

In total, 183 patients were identified in HTI data, no intra-vitreal use of Zaltrap can be confirmed from the current study, the proportion of intravitreal use of Zaltrap was estimated to be 0 (0%) (Table 11).

10.10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is based on the secondary use of data; expedited reporting of suspected adverse reactions is not required.

Regarding summary of aggregated AE/ADRs, no AE/ADRs were reported by physicians for Zaltrap use in OA, and no AE/ADRs related to Zaltrap use were found in UK HTI.

11 DISCUSSION

11.1 KEY RESULTS

An evaluation of the frequency distribution of cancer type(s) among patients who received treatment containing ZALTRAP in the five largest national markets in Europe (EU5) found that all but one patient, overall and across all countries of interest, received ZALTRAP only for metastatic CRC, the label approved indication. The only one patient who received Zaltrap for non-label approved indication had non-metastatic CRC.

Pertaining to treatment combinations, patients were observed within the time period from 1 April 2013 through 31 March 2016 to receive ZALTRAP with FOLFIRI (60.8%) or with FOLFIRI-like protocol (37.8%); and with other cytotoxic agents like bevacizumab, and irinotecan (1.4%, Table 10, see Appendix C for codes). Most patients in Germany received ZALTRAP with FOLFIRI (83.3%). One patient received a non-label recommended treatment combination (1 patient, 3.3% in Germany), having received ZALTRAP with other cytotoxic agents.

In addition, no patients were identified in this study with a potential ophthalmological conditions (wet age related macular degeneration, diabetic macular edema and central retinal vein occlusion).

With respect to the use of Zaltrap by intra-vitreal application, the route of drug application is not captured by the HTI database. Therefore, a proxy definition was adopted to assume intra-vitreal use if a patient was seen by an ophthalmologist with a wet AMD diagnosis and without CRC. No intra-vitreal use of Zaltrap can be confirmed from the current study, the proportion of intravitreal use of Zaltrap was estimated to be 0 (0%).

11.2 LIMITATIONS

Oncology Analyzer–Evaluation of ZALTRAP Use Among Cancer Patients

The OA database includes data from panels of physicians, who review current treatment and medical history from patients presenting for treatment. Physicians are recruited systematically to maximize the representativeness of their patient panel to care rendered in their respective countries, but participation of physicians is voluntary. The degree of bias between the sampling frame and recruited physicians, and the implications that such bias may have on the representativeness of ZALTRAP utilization within each country, is unknown.

The study reported only the first ZALTRAP use per patient, based on treatment history at the time of patient sampling. In the OA database, patients are not re-assessed to capture future treatments and outcomes. As a result, the study may miss ZALTRAP use for existing patients if it occurs after the date of assessment.

Patients were identified for inclusion based on the medication brand and molecule name, as ATC code is not available within the OA database. As brand and molecule are manually entered by the physician, typographical data entry errors may result in a degree of missing patient data.

Finally, the study used data from five out of 28 EU countries where marketing authorization was granted. Findings from the EU 5 countries may not be generalizable to other EU countries where ZALTRAP received marketing authorization, as there might be different treatment guidelines, physician prescribing behaviors, reimbursement policies, or other utilization restrictions.

Hospital Treatment Insights – Evaluation of Intravitreal Use of ZALTRAP

The study is designed to capture only the first ZALTRAP exposure for each patient; therefore, subsequent exposures to ZALTRAP for the same patient will not be reported. Results should be interpreted as reflecting patients with initial use of ZALTRAP, rather than total ZALTRAP administrations.

The data captured in the HTI database is a combination of data collected from the IMS HPA and UK NHS HES databases. In the HTI database, complete patient-level history is captured on drugs dispensed to patients through the hospital pharmacy. Drugs given to patients from the ward stock cannot be linked to an individual patient. Because ZALTRAP is a specialty pharmaceutical product, it is not expected to be included as a ward stock, especially in specialty hospital outpatient setting. However, it is likely that ZALTRAP for intravitreal administration will be prepared in an aseptic unit. When drugs are sent via an aseptic unit, it is possible that complete patient-level detail may not be captured. The occurrence of this could lead to underreporting of potential intravitreal use of ZALTRAP since patients' history such as diagnosis, physician specialty information, or route of administration may not be available.

The HTI database only allows for the assessment of intravitreal use of ZALTRAP in England. Therefore, the findings from this analysis may not be generalizable to the rest of the UK or to other EU countries where ZALTRAP will be marketed. Additionally, HTI data are collected from select hospital trusts that provided consent for their data to be linked to HPA. As a result, findings may only be generalizable to other trusts with similar population and clinical practices.

The protocol specifically limited evaluation of diagnosis to the facility episode associated with ZALTRAP administration. Patients with intravitreal administration or specific off-label utilization as determined by historical diagnoses preceding the ZALTRAP episode would be underreported to an unknown extent. Additionally, to the extent that a small number of institutions have a higher likelihood of off-label applications, the proportion of patients reported with other diagnoses or a lower than expected age group given disease prevalence statistics, the population reported may be less generalizable than the full source population.

Within the HTI database, treating physicians are not required to apply diagnoses to outpatient administrations, which will influence data completeness in this study. While the specialty of treating physicians is captured, this data is limited to the ZALTRAP event only, and any historical specialty, including ophthalmology, remains unreported based on the protocol methodology.

11.3 INTERPRETATION

While the study's general findings indicate that all but one observed patient received ZALTRAP only for metastatic CRC, the limited timeframe and sample size would necessitate further study with more recent data. Further analysis, with increased data inclusion, is warranted to confirm the findings of this study.

11.4 GENERALIZABILITY

Regarding the OA database, findings from the EU 5 countries may not be generalizable to other EU countries where ZALTRAP received marketing authorization, as there might be different treatment guidelines, physician prescribing behaviors, reimbursement policies, or other utilization restrictions. For OA data, to the extent that survey-responding physicians are not fully representative of treating physicians, the generalizability of the data for these five EU countries may be limited.

Regarding HTI data, to the extent that the approximately ¼ of England captured within the database is not fully representative of the UK, data from this source may have limited generalizability.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

In summary, this final report of the ZALTRAP utilization study found that, based on the OA analysis, ZALTRAP has been used for mCRC, as per label approved indication, in all but one patient. The only one patient who received Zaltrap for non-label approved indication had non-metastatic CRC. With respect to the use of ZALTRAP by intravitreal application, the route of drug application is not captured by the HTI database. Therefore, a proxy definition was adopted to assume intra-vitreal use if a patient was seen by an ophthalmologist with a wet AMD diagnosis and without CRC. No intra-vitreal use of Zaltrap can be confirmed from the current study, the proportion of intravitreal use of Zaltrap was estimated to be 0 (0%).

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15 APPENDICES

Appendix A. Diagnosis Codes For Cancer and Ophthalmic Diagnoses of Interest

Diagnosis	Description	ICD-10 Codes
Malignant colorectal cancer	Malignant neoplasm of colon	C18.x
Malignant colorectal cancer	Malignant neoplasm of rectum	C20.x
Malignant colorectal cancer	Malignant neoplasms of anus and anal canal	C21.x
Other Malignancies	Malignant neoplasms	C00.x – C17.0, C19.x, C22.x – C97.x
Other Malignancies	In-situ neoplasms	D00.x - D09.x
Other Malignancies	Benign neoplasms	D10.x - D36.x
Other Malignancies	Neoplasms of uncertain or unknown behavior	D37.x - D48.x
Wet age-related macular degeneration	Degeneration of macula and posterior pole	H35.3
Diabetic macular edema	Other specified retinal disorders	H35.8
Diabetic macular edema	Insulin-dependent diabetes mellitus with ophthalmic complications	E10.3
Diabetic macular edema	Non-insulin-dependent diabetes mellitus with ophthalmic complications	E11.3

Appendix B. List of Targeted Agents Approved for mCRC in the EU Other Than Aflibercept (ZALTRAP)

Drug Name
Cetuximab
Bevacizumab
Panitumumab

Appendix C. RESULTS Tables

1-OA tables

Table 1: Attrition

Patient Cohort	N
Patients given at least one ZALTRAP dose* as a current therapy	76
Patients not enrolled in a ZALTRAP clinical trial	74
Final analysis cohort	74

*Zaltrap including both brand (Zaltrap) and generic (Aflibercept)

Patient Cohort	UK	Germany	France	Spain	Italy
Patients given at least one ZALTRAP* dose as a current therapy	1	31	15	18	11
Patients not enrolled in a ZALTRAP clinical trial	1	30	15	17	11
Final analysis cohort	1	30	15	17	11

*Zaltrap including both brand (Zaltrap) and generic (Aflibercept)

(Data frame: 01April2015 through 31March2016)

Table 2: Patient Demographics: All patients

Demographic Characteristics	All Patients (N = 74)		UK (N = 1)		Germany (N = 30)		France (N = 15)		Spain (N = 17)		Italy (N = 11)	
Age Group (n, %)												
0 – 15	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
16 – 25	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
26 – 35	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
36 – 45	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
46 – 55	3	4.1%	0	0.0%	2	6.7%	0	0.0%	1	5.9%	0	0.0%
56 – 65	29	39.2%	0	0.0%	6	20.0%	6	40.0%	10	58.8%	7	63.6%
66 – 75	34	45.9%	1	100.0%	18	60.0%	6	40.0%	5	29.4%	4	36.4%
76 +	8	10.8%	0	0.0%	4	13.3%	3	20.0%	1	5.9%	0	0.0%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Sex (n, %)												
Female	23	31.1%	1	100.0%	9	30.0%	4	26.7%	4	23.5%	5	45.5%
Male	51	68.9%	0	0.0%	21	70.0%	11	73.3%	13	76.5%	6	54.5%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

(Data frame: 01April2015 through 31March2016)

Table 3: Clinical Characteristics: All Patients

Clinical Characteristics	All Patients (N = 74)		UK (N = 1)		Germany (N = 30)		France (N = 15)		Spain (N = 17)		Italy (N = 11)	
ECOG performance status (n, %)												
0 - ASYMPTOMATIC	9	12.2%	0	0.0%	3	10.0%	0	0.0%	4	23.5%	2	18.2%
1 - SYMPTOMATIC FULLY AMBULATORY	53	71.6%	1	100.0%	18	60.0%	13	86.7%	12	70.6%	9	81.8%
2 - SYMPTOMATIC IN BED <50% OF THE DAY	11	14.9%	0	0.0%	9	30.0%	1	6.7%	1	5.9%	0	0.0%
3 - SYMPTOMATIC IN BED >50% OF THE DAY	1	1.4%	0	0.0%	0	0.0%	1	6.7%	0	0.0%	0	0.0%
4 - BEDRIDDEN	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Missing - DON'T KNOW/ RECALL	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Comorbidities* (n, %)												
Autoimmune	1	1.4%	0	0.0%	0	0.0%	1	6.7%	0	0.0%	0	0.0%
Cardiac dysfunction	22	29.7%	1	100.0%	21	70.0%	0	0.0%	1	5.9%	0	0.0%
COPD	8	10.8%	1	100.0%	3	10.0%	3	20.0%	1	5.9%	0	0.0%
Diabetes	10	13.5%	0	0.0%	5	16.7%	1	6.7%	3	17.6%	0	0.0%
HIV	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Liver dysfunction	2	2.7%	0	0.0%	1	3.3%	1	6.7%	0	0.0%	0	0.0%
Parkinson's	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Peripheral Neuropathy	3	4.1%	0	0.0%	0	0.0%	0	0.0%	2	11.8%	1	9.1%
Renal dysfunction	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Other	12	16.2%	0	0.0%	5	16.7%	2	13.3%	4	23.5%	1	9.1%
None reported	30	40.5%	0	0.0%	5	16.7%	8	53.3%	8	47.1%	9	81.8%
Physician specialty (n, %)												
Medical oncologist	39	52.7%	1	100.0%	0	0.0%	10	66.7%	17	100.0%	11	100.0%
Clinical oncologist	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Gastroenterologist	6	8.1%	0	0.0%	1	3.3%	5	33.3%	0	0.0%	0	0.0%
Gynecologist	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Urologist	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Onco-Haematology	29	39.2%	0	0.0%	29	96.7%	0	0.0%	0	0.0%	0	0.0%
Surgeon	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Radiotherapy	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Other	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

*Patients may have multiple comorbidities

(Data frame: 01April2015 through 31March2016)

Table 4: Treatment Characteristics: Patients Diagnosed with mCRC

	All Patients (N = 74)	UK (N = 1)	Germany (N = 30)	France (N = 15)	Spain (N = 17)	Italy (N = 11)
Surgery before current therapy (n, %)	63 85.1%	1 100.0%	29 96.7%	14 93.3%	13 76.5%	6 54.5%
Radiotherapy before current therapy (n, %)	2 2.7%	0 0.0%	0 0.0%	2 13.3%	0 0.0%	0 0.0%
Chemotherapy before current therapy (Yes/No)	68 91.9%	1 100.0%	28 93.3%	14 93.3%	14 82.4%	11 100.0%
Oxaliplatin-based chemotherapy (Yes)	64 86.5%	1 100.0%	26 86.7%	13 86.7%	14 82.4%	10 90.9%
Oxaliplatin-based chemotherapy (No/N/A)	10 13.5%	0 0.0%	4 13.3%	2 13.3%	3 17.6%	1 9.1%
ZALTRAP dose per administration (mg/kg)						
Mean	4.0	4	4.0	4.0	4.1	3.9
SD	0.6	0.0	0.0	0.0	0.9	1.2
Median	4.0	4.0	4.0	4.0	4.0	4.0
IQR	0.0	0.0	0.0	0.0	0.0	0.0
Q1	4.0	4.0	4.0	4.0	4.0	4.0
Q3	4.0	4.0	4.0	4.0	4.0	4.0
N	74	1	30	15	17	11
Missing	0	0	0	0	0	0
ZALTRAP dose per administration (mg/person)						
Mean	294.1	272.0	314.3	275.1	281.9	269.5
SD	61.2	0.0	48.1	49.1	60.6	89.7
Median	288.0	272.0	302.0	270.0	284.0	276.0
IQR	50.5	0.0	68.0	82.0	36.0	30.0
Q1	268.5	272.0	282.0	238.0	272.0	258.0
Q3	319.0	272.0	350.0	320.0	308.0	288.0
N	74	1	30	15	17	11
Missing	0	0	0	0	0	0

(Data frame: 01April2015 through 31March2016)

Table 5*: Outcome Measures: All Patients

Measures	All Patients (N = 74)				UK (N = 1)				Germany (N = 30)				France (N = 15)				Spain (N = 17)				Italy (N = 11)			
	N	%	95% CI		N	%	95% CI		N	%	95% CI		N	%	95% CI		N	%	95% CI		N	%	95% CI	
Diagnostic indication for Zaltrap																								
Label-approved indication (metastatic CRC)	73	98.6%	92.6%	99.9%	0	0.0%	0.0%	97.5%	30	100.0%	88.4%	100.0%	15	100.0%	78.2%	100.0%	17	100.0%	80.5%	100.0%	11	100.0%	71.5%	100.0%
Off-label indication (Total)	1				1				0				0				0				0			
Non-metastatic CRC	1	1.4%	0.0%	7.3%	1	100.0%	2.5%	100.0%	0	0.0%	0.0%	11.6%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
NSCLC, all stages	0	0.0%	0.0%	4.9%	0	0.0%	0.0%	97.5%	0	0.0%	0.0%	11.6%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
Renal cell cancer, all stages	0	0.0%	0.0%	4.9%	0	0.0%	0.0%	97.5%	0	0.0%	0.0%	11.6%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
Breast cancer, all stages	0	0.0%	0.0%	4.9%	0	0.0%	0.0%	97.5%	0	0.0%	0.0%	11.6%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
Ovarian cancer, all stages	0	0.0%	0.0%	4.9%	0	0.0%	0.0%	97.5%	0	0.0%	0.0%	11.6%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
Other cancers, all stages	0	0.0%	0.0%	4.9%	0	0.0%	0.0%	97.5%	0	0.0%	0.0%	11.6%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
Treatment combinations																								
Zaltrap with FOLFIRI	45	60.8%	48.8%	72.0%	0	0.0%	0.0%	97.5%	25	83.3%	65.3%	94.4%	6	40.0%	16.3%	67.7%	7	41.2%	18.4%	67.1%	7	63.6%	30.8%	89.1%
Zaltrap with FOLFIRI-like protocol	28	37.8%	26.8%	49.9%	1	100.0%	2.5%	100.0%	4	13.3%	3.8%	30.7%	9	60.0%	32.3%	83.7%	10	58.8%	32.9%	81.6%	4	36.4%	10.9%	69.2%
Zaltrap with other cytotoxic agents	1	1.4%	0.0%	7.3%	0	0.0%	0.0%	97.5%	1	3.3%	0.1%	17.2%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
Non-label-recommended combinations (Total)	1	1.4%	0.0%	7.3%	0	0.0%	0.0%	97.5%	1	3.3%	0.1%	17.2%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
Zaltrap monotherapy	0	0.0%	0.0%	4.9%	0	0.0%	0.0%	97.5%	0	0.0%	0.0%	11.6%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
Zaltrap with other cytotoxic agents	1	1.4%	0.0%	7.3%	0	0.0%	0.0%	97.5%	1	3.3%	0.1%	17.2%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%
Zaltrap with other mCRC targeted agents	0	0.0%	0.0%	4.9%	0	0.0%	0.0%	97.5%	0	0.0%	0.0%	11.6%	0	0.0%	0.0%	21.8%	0	0.0%	0.0%	19.5%	0	0.0%	0.0%	28.5%

*Zaltrap with FOLFIRI-like protocol:
5FU/AFLIBERCEPT/IRINOTECAN
*Zaltrap with other cytotoxic agents/mCRC targeted agents:
AFLIBERCEPT/ IRINOTECAN

(Data frame: 01April2015 through 31March2016)

2- HTI tables

Table 6. Attrition Table

Patient Cohort	N
Patients given at least one ZALTRAP dose	139
Patients without linked data between HPA and HES sides of the HTI product	60
Final analysis cohort	79

(Data frame: 01 October 2014 to 31 March 2015)

Table 7. Patients Demographics[a]

Demographic Characteristics	All Patients (England)		Without Missing Data	
	N	%	N	%
Age Category 1	.	.	.	.
0-17	0	0	0	0
18-27	0	0	0	0
28-37	0	0	0	0
38-47	8	10.13	8	10.39
48-57	17	21.52	17	22.08
58-67	27	34.18	27	35.06
68-77	20	25.32	20	25.97
78+	***	***	***	***
Missing	***	***	.	.
	.	.	.	.
Age Category 2	.	.	.	.
0-27	0	0	0	0
28-77	72	91.14	72	93.51
78+	***	***	***	***
Missing	***	***	.	.
	.	.	.	.
Gender	.	.	.	.
Female	39	49.37		.
Male	40	50.63	.	.
	.	.	.	.
Ethnicity	.	.	.	.
White	70	88.61	70	92.11
Black/British Black	***	***	***	***
Asian/British Asian	***	***	***	***
Other	***	***	***	***
Not Stated/Unknown	***	***	.	.
	.	.	.	.

[a] At first ZALTRAP administration (n=79).

*** Number n<6 may not be reported because of regulatory restrictions.

Table 8. Intravitreal use of Zaltrap[a]

IntraVitreal Uses	N	%	95%CI
Observed Data	.	.	
Yes	0	0.00	0.00; 4.56
No	69	87.34	77.95 ; 93.76
Missing	10	12.66	6.24 ; 22.05
	.	.	

[a] At first ZALTRAP administration (n=79).

(Data frame: 01 October 2014 to 31 March 2015)

Table 9. Clinical Characteristics[a]

Clinical Characteristics	All Patients (England)		Without Missing Data	
	N	%	N	%
Diagnoses for which Zaltrap was used[b]	.	.	.	.
Colorectal Cancer Only	***	***	***	***
Other Cancer Only	18	22.78	18	26.09
Cancer of the Digestive Organs	***	***	***	***
Secondary and Ill-defined Cancer	***	***	***	***
Colorectal Cancer and Other Cancer	44	55.7	44	63.77
Wet AMD	0	0	0	0
Diabetic Macular Edema	0	0	0	0
CRVO	0	0	0	0
Other Diagnosis	0	0	0	0
Missing Diagnosis	10	12.66	.	.
	.	.	.	.
Specialty Prescriber or Treating Physician	.	.	.	.
Opthamologists	***	***	***	***
Oncology (Clinical and Medical)	74	93.67	74	93.67
Other	***	***	***	***
	.	.	.	.
Treatment Setting	.	.	.	.
Inpatient	69	87.34	69	87.34
Outpatient	10	12.66	10	12.66
A&E	0	0	0	0
Missing	0	.	.	.

[a] At first ZALTRAP administration (n=79).
[b] Multiple Diagnoses can be recorded at each Visit.
*** Number n<6 may not be reported because of regulatory restrictions.
# Masked to prevent computation of numbers <6.

Table 10: Outcome Measures: All Patients

Measures	All Patients (N = 151)			UK (N = 15)			Germany (N = 67)			France (N = 20)			Spain (N = 36)			Italy (N = 13)		
	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI
Diagnostic indication for Zaltrap																		
Label-approved indication (metastatic CRC)	150	99.3%	96.4% 100.0%	14	93.3%	68.1% 99.8%	67	100.0%	94.6% 100.0%	20	100.0%	83.2% 100.0%	36	100.0%	90.3% 100.0%	13	100.0%	75.3% 100.0%
Off-label indication (Total)																		
Non-metastatic CRC	1	0.7%	0.0% 3.6%	1	6.7%	0.2% 32.0%	0	0.0%	0.0% 5.4%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
NSCLC, all stages	0	0.0%	0.0% 2.4%	0	0.0%	0.0% 21.8%	0	0.0%	0.0% 5.4%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
Renal cell cancer, all stages	0	0.0%	0.0% 2.4%	0	0.0%	0.0% 21.8%	0	0.0%	0.0% 5.4%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
Breast cancer, all stages	0	0.0%	0.0% 2.4%	0	0.0%	0.0% 21.8%	0	0.0%	0.0% 5.4%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
Ovarian cancer, all stages	0	0.0%	0.0% 2.4%	0	0.0%	0.0% 21.8%	0	0.0%	0.0% 5.4%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
Other cancers, all stages	0	0.0%	0.0% 2.4%	0	0.0%	0.0% 21.8%	0	0.0%	0.0% 5.4%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
Treatment combinations																		
Zaltrap with FOLFIRI	93	61.6%	53.3% 69.4%	6	40.0%	16.3% 67.7%	57	85.1%	74.3% 92.6%	8	40.0%	19.1% 64.0%	13	36.1%	20.8% 53.8%	9	69.2%	38.6% 90.9%
Zaltrap with FOLFIRI-like protocol	55	36.4%	28.8% 44.6%	9	60.0%	32.3% 83.7%	7	10.4%	4.3% 20.4%	12	60.0%	36.1% 80.9%	23	63.9%	46.2% 79.2%	4	30.8%	9.1% 61.4%
Zaltrap with other cytotoxic agents	3	2.0%	0.4% 5.7%	0	0.0%	0.0% 21.8%	3	4.5%	0.9% 12.5%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
Non-label-recommended combinations	3	2.0%	0.4% 5.7%	0	0.0%	0.0% 21.8%	3	4.5%	0.9% 12.5%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
Zaltrap monotherapy	0	0.0%	0.0% 2.4%	0	0.0%	0.0% 21.8%	0	0.0%	0.0% 5.4%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
Zaltrap with other cytotoxic agents	2	1.3%	0.2% 4.7%	0	0.0%	0.0% 21.8%	2	3.0%	3.6% 10.4%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%
Zaltrap with other mCRC targeted agents	1	0.7%	0.0% 3.6%	0	0.0%	0.0% 21.8%	1	1.5%	0.0% 8.0%	0	0.0%	0.0% 16.8%	0	0.0%	0.0% 9.7%	0	0.0%	0.0% 24.7%

*Zaltrap with FOLFIRI-like protocol:
5FU/AFLIBERCEPT/IRINOTECAN
*Zaltrap with other cytotoxic agents/mCRC targeted agents:
AFLIBERCEPT OR BEVACIZUMAB OR IRINOTECAN OR CAPECITABINE

(Data frame: 01April2013 through 31March2016)

Table 11. Intravitreal use of Zaltrap[a] for all years

Intravitreal Uses	N	%[b]	95%CI
Observed Data	.	.	
Yes	0	0.00	0.00 ; 2.00
No	158	86.34	80.50 ; 90.96
Missing	25	13.66	9.04 ; 19.50

[a] At first ZALTRAP administration (n=183).
[b] Percentages are based on the total of 183 unique patients.

(Data frame: 01 April 2013 to 31 March 2015)