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# Real-World Use of Bevacizumab for Treatment of Advanced Ovarian Cancer Among Elderly Women in the U.S.

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# REAL-WORLD USE OF BEVACIZUMAB FOR TREATMENT OF ADVANCED OVARIAN CANCER AMONG ELDERLY WOMEN IN THE U.S.

BY

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A dissertation submitted to the faculty of the
Medical University of South Carolina in partial fulfillment of the
requirements for the degree
Doctor of Philosophy
In the College of Health Professions

In memory of Eugenia E. “Jeanne” Calle

## Abstract

Abstract of Dissertation Presented to the
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Bevacizumab, a targeted VEGF inhibitor, is recommended for treatment of advanced ovarian cancer based on clinical trials demonstrating improved progression-free survival when added to standard chemotherapy. This study describes demographic, clinical and social factors, and outcomes associated with bevacizumab use among ovarian cancer patients in the US Medicare 5% sample. Kaplan-Meier curves and propensity score-weighted Cox proportional hazards models were used to estimate overall survival (OS) comparing bevacizumab to non-bevacizumab regimens. Of 3,760 patients with a principal diagnosis of ovarian cancer from 2016 to 2019, 1,508 had at least one observed line of chemotherapy; 457 had a second line following a treatment-free interval (TFI) ≥60 days, of whom 52% (N=237) received bevacizumab. Receipt of

bevacizumab did not vary by dual eligibility for Medicaid (an indicator of poverty) or residing in a vulnerable community (measured by the social vulnerability index). Patients receiving bevacizumab were more likely to have metastatic disease and a TFI ≤180 days (an indication of platinum-resistant disease) at second-line treatment initiation. Bevacizumab was associated with a modest survival advantage and lower relative risk of death (hazard ratio=0.80, 95% confidence interval=0.66, 0.97) among patients who received bevacizumab within 30 days after second-line initiation, particularly those younger than age 75.

## Table of Contents

## List of Figures and Tables

## Glossary

| Abbreviation | Definition |
|---|---|
| AACI | Age-adjusted Charlson Comorbidity Index |
| ADI | Area Deprivation Index |
| ADR | Adverse drug reaction |
| AE | Adverse Event |
| ATE | Arterial thromboembolism |
| BRCA | Breast cancer gene |
| CI | Confidence Interval |
| CMS | Centers for Medicare and Medicaid Services |
| CPT | Current Procedural Terminology |
| CRC | Colorectal cancer |
| DOD | Date of death |
| EMA | European Medicines Agency |
| EOC | Epithelial ovarian cancer |
| FIGO | International Federation of Gynecology and Obstetrics |
| HR | Hazard rate ratio |
| HCPCS | Healthcare Common Procedure Coding System |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | Hazard ratio |
| HSR | Health services research |
| HTN | Hypertension |
| FIGO | International Federation of Gynecology and Obstetrics |
| FDA | Food and Drug Administration |
| IDS | Interval debulking surgery |
| ICD | International Classification of Diseases |
| ICD-10-CM | ICD Tenth Revision, Clinical Modification |
| IQR | Interquartile range |
| IPTW | Inverse probability of treatment weight |
| IRB | Institutional Review Board |
| ITT | Intention to treat |
| LDS | Limited Data Set |
| LOT | Line of treatment |
| MBSF | Master Beneficiary Summary File |
| MedPAR | Medicare Provider Analysis and Review |
| MRD | Minimal residual disease |
| NCCN | National Comprehensive Cancer Network |
| NDC | National Drug Codes |
| NACT | Neoadjuvant chemotherapy |
| NHB | non-Hispanic Black |
| NHW | non-Hispanic White |
| NSCLC | Non-small cell lung cancer |
| OutSAF | Outpatient Standard Analytical File |
| ORR | Overall response rate |
| OS | Overall survival |
| PARP | Poly-ADP ribose polymerase |
| PDS | Primary debulking surgery |

| | |
|---|---|
| PFS | Progression-free survival |
| PH | Proportional hazards |
| PS | Propensity score |
| RR | Relative risk |
| SAE | Serious adverse event |
| SES | Socioeconomic status |
| SDOH | Social determinants of health |
| SD | Standard deviation |
| SMD | Standardized mean difference |
| SVI | Social Vulnerability Index |
| TFI | Treatment-free interval |
| TNM | Tumor, Node, Metastasis |
| UK | United Kingdom |
| US | United States |
| VEGF | Vascular endothelial growth factor |

## CHAPTER 1. INTRODUCTION

Ovarian cancer is a highly fatal disease often diagnosed at an advanced stage and associated with poor prognosis. Globally, ovarian cancer accounts for 3.4% of all cancers and 4.7% of all cancer deaths in women, making it the tenth most common cancer and the eighth leading cause of cancer death (Ferlay J, 2020). In the United States (US), ovarian cancer accounts for 5% of all cancer deaths and is the fifth leading cause of cancer mortality in women after lung, breast, colorectal, and pancreatic cancer ("American Cancer Society Cancer Facts & Figures 2023," 2023). In 2023, an estimated 19,710 new cases of ovarian cancer were diagnosed, and 13,270 women died of the disease (R. L. Siegel, Miller, Wagle, & Jemal, 2023). Five-year survival of early stage disease exceeds 90%, but for regional and distant stage disease, 5-year survival is 74% and 31%, respectively ("American Cancer Society Cancer Facts & Figures 2023," 2023; R. L. Siegel et al., 2023). As no screening and few early detection tools exist for ovarian cancer, the majority are diagnosed at advanced stages. Thus, survival for all stages combined remains at approximately 50% (R. L. Siegel et al., 2023). Registry studies from the US and United Kingdom (UK) suggest that 1 in 6 women die within 90 days after an ovarian cancer diagnosis (Lheureux, Braunstein, & Oza, 2019; "World Ovarian Cancer Coalition. The Every Woman Study Summary Report," 2018). These facts highlight the urgency and importance of access to appropriate surgical care and systemic treatment for advanced disease to reduce the substantial morbidity and siegelmortality associated with ovarian cancer.

Access to appropriate guideline-based care is critical for survival. However, because health care access varies in the US by socioeconomic status (SES) and social environmental factors that distribute along racial lines, Black women with ovarian cancer experience worse prognosis and up to 80% higher risk of dying than White women, despite lower ovarian cancer incidence among Black women (Hildebrand, Wallace, Graybill, & Kelemen, 2019; R. L. Siegel et al., 2023). A substantial body of research consistently demonstrates that unequal access to care, late stage at diagnosis, and suboptimal treatment, are largely to blame for the poorer outcomes affecting Black women as compared to White women after ovarian cancer diagnosis (Aranda et al., 2008; Bandera, Lee, Rodriguez-Rodriguez, Powell, & Kushi, 2016; Bristow et al., 2015).

Ovarian cancer is a histologically heterogeneous disease that may arise in the ovaries, fallopian tubes, or peritoneum. Approximately 95% are epithelial ovarian cancer (EOC), the majority of which (70%) are classified as serous carcinomas (J. Prat, 2012; Torre et al., 2018). Less common epithelial subtypes include endometrioid (10%), mucinous (6%), and clear-cell carcinomas (6%), while the remainder of cases are rare or unclassified subtypes (Torre et al., 2018). The most common non-epithelial types are stromal cell and germ cell which together make up about 5% of all ovarian cancer (Torre et al., 2018). Etiology is not well understood, but several risk factors have been identified including family history of breast or ovarian cancer, genetic predisposition due to inherited breast cancer gene mutation (BRCA1 or BRCA2) or Lynch Syndrome, lifetime estrogen exposure, endometriosis, and pelvic inflammatory disease. Modifiable risk factors include obesity and smoking, although the association with smoking is confined to mucinous ovarian cancer ("American Cancer Society Cancer Facts & Figures 2023," 2023). Parity, use of oral contraceptives, and tubal ligation are associated with lower risk ("American Cancer Society Cancer Facts & Figures 2023," 2023).

As with most cancers, ovarian cancer risk increases with age. As shown in **Figure 1**, incidence of EOC rises sharply between the 5th and 8th decades for all races (Torre et al., 2018).

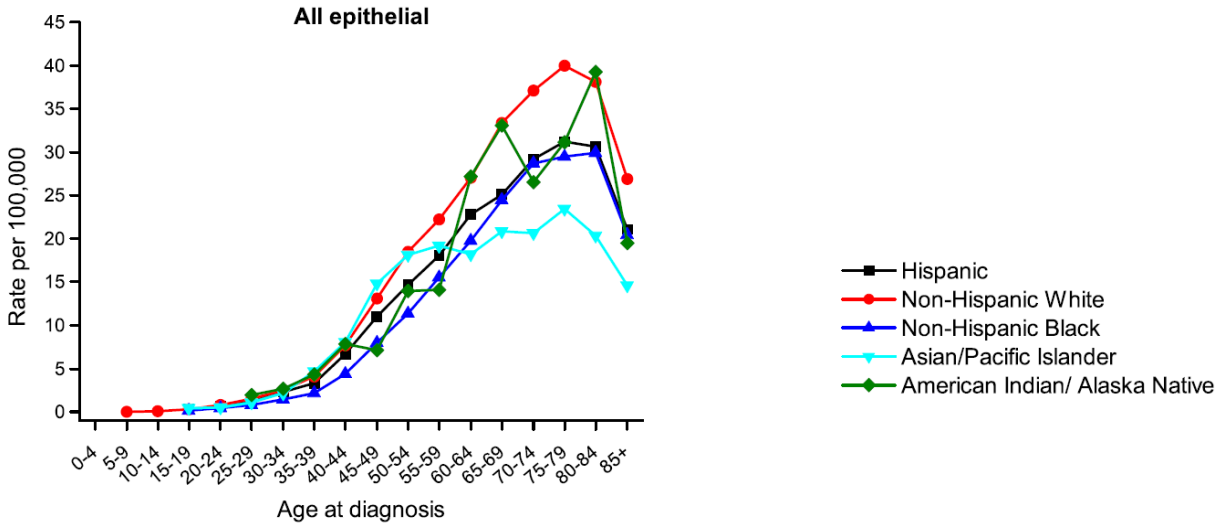



*Figure 1. EOC incidence by age and race/ethnicity, US, 2010-2014, per 100K, standardized to the 2000 US population. (NAACCR, 2017)*

Mortality also increases with age as survival decreases, in part because older women are more likely to have aggressive, high-grade serous carcinomas. Five-year survival is 61% among women younger than 65, but just 33% among those 65 and older (Rebecca L. Siegel, Miller, Fuchs, & Jemal, 2022). In 2023, women aged 65 years and over will account for nearly three-quarters (74.4%) of all ovarian cancer deaths (R. L. Siegel et al., 2023). The median age at which women die of ovarian cancer is 70 years (Rebecca L. Siegel et al., 2022).

Primary debulking (cytoreductive) surgery followed by a platinum and taxane-based chemotherapy is the established standard of care for advanced primary epithelial ovarian, fallopian tube or peritoneal carcinoma. Women who are not good candidates for primary surgery, often due to comorbidity or tumor burden unlikely to be optimally cytoreduced to the level of minimal residual disease (MRD, <1 cm), should be offered

neoadjuvant chemotherapy with interval debulking and post-operative adjuvant chemotherapy ("NCCN Guidelines for Ovarian Cancer Version 1.2022 ", 2022). While cytotoxic regimens (with carboplatin, paclitaxel, gemcitabine, doxorubicin, or other cytotoxic drugs) continue to be the mainstay of pharmacologic treatment for advanced ovarian cancer, newer classes of anti-neoplastic drugs are gaining prominence in this therapeutic area including targeted systemic treatments such as bevacizumab, poly-(ADP-ribose) polymerase (PARP) inhibitors, and immune checkpoint inhibitors.

Bevacizumab is a monoclonal antibody that targets the vascular endothelial growth factor (VEGF) receptors to block angiogenesis. It is shown to be efficacious for treatment of several advanced-stage cancers including metastatic colorectal cancer (CRC), metastatic renal cell carcinoma, non-squamous non-small cell lung cancer (NSCLC), cervical cancer, and other solid tumors (Amit, Ben-Aharon, Vidal, Leibovici, & Stemmer, 2013). Several phase 3 trials of bevacizumab combined with a standard cytotoxic regimen for advanced primary and recurrent ovarian cancer demonstrated superiority over the standard alone for extending progression-free survival (PFS) with tolerable toxicity (Aghajanian et al., 2012; Robert A Burger et al., 2011; Coleman et al., 2017; Perren et al., 2011; Pujade-Lauraine et al., 2014). In 2019, based upon the trial evidence, the National Comprehensive Cancer Network (NCCN) updated its guideline for advanced ovarian/tubal/primary peritoneal cancer recommending bevacizumab delivered with standard chemotherapy for first-line maintenance after initial response to carboplatin/paclitaxel (Armstrong et al., 2019). A systematic review and meta-analysis of phase 2 and 3 clinical trials between 2010 and March 2020, confirmed the significant PFS benefit in advanced primary and recurrent epithelial ovarian cancer with a pooled hazard ratio (HR) of 0.72 [95% confidence interval (CI) 0. 65–0.81] in the first-line setting

and HR of 0.52 (95% CI 0.47–0.58) in the second-line setting among patients with platinum-sensitive or platinum-resistant disease (Liu et al., 2021).

As bevacizumab is incorporated into multiple ovarian cancer treatment settings, it is of high clinical importance to evaluate its effectiveness, and safety among patients undergoing treatment in the real world. Many women would not be eligible for phase 2 or phase 3 trials due to age, health status, or medical history, and it is essential to the field of gynecologic oncology to understand the external validity of results from clinical trials. At present, approximately 20 studies have been published on the effectiveness and safety of bevacizumab outside of clinical trials. However, the majority are small single-center studies without non-bevacizumab comparator groups. Further investigation into the survival benefit is also needed to understand the association between bevacizumab use and overall survival (OS) in ovarian cancer. Despite compelling trial evidence of improved PFS with bevacizumab, its effectiveness to extend OS in the general patient population is not established, and clinical trials have failed to consistently demonstrate an OS advantage in advanced ovarian cancer except among patients with high risk of disease progression (Aghajanian et al., 2015; Moore et al., 2021; Amit M Oza et al., 2015; Tewari et al., 2019). It is also important to quantify the effects of bevacizumab on life expectancy and risk of adverse events among older women who may be candidates for targeted therapies in theory, but discouraged from using them due to age and the fact that clinical trial data on safety and efficacy may not be generalizable to older patients.

Furthermore, patterns of use of bevacizumab in the real world, including characteristics of ovarian cancer patients who do and do not receive bevacizumab, are not well-described. Assessment of the population who would be candidates for treatment is essential to understanding disparities and ensuring access to care for all patients in need. Lower rates of bevacizumab among elderly ovarian cancer patients (≥70 years)

have been reported (Liontos et al., 2021), but the reasons for the age-related disparity in its utilization are unclear. Older women with cancer are a more heterogeneous patient population than their younger counterparts. They may have more comorbidities, age-related impairments, declining functional ability, and nutritional or cognitive deficiencies, which put them at greater risk of complications associated with cancer treatment as well as longer recovery time (Balducci, 2016). Real-world studies are needed not only to characterize the effects of bevacizumab in elderly women with ovarian cancer but also to understand and justify why bevacizumab is apparently used less often among this population.

Racial disparities are consistently reported between Black and White women in the receipt of guideline-based surgical and chemotherapeutic care after ovarian cancer diagnosis (Hildebrand et al., 2019; Karanth et al., 2019). Yet few studies have examined disparities in access to targeted systemic therapies and none, to our knowledge, for bevacizumab. It is important to bear in mind that access to care is not simply the availability of health services in society but whether or not individual patients are able to, and actually do, utilize available services. The decision to partake of an available health service or treatment is a product of many factors including patient and provider awareness, the perceived benefits and risks of treatment, health literacy, the costs of treatment and financial impact to the patient, ease and convenience of receiving treatment, distance to care, and other social environmental factors that impact use of health services by individuals. Equal access thus means that every patient has an understanding of the services they need, what is available to them, the means to obtain appropriate services, procedures and medications, and access to people who can administer those services and treatments.

Despite a substantial body of work describing racial differences in surgical and adjuvant treatment for ovarian cancer, we are unaware of any studies describing the use and therapeutic effects of bevacizumab, or any other targeted therapy used to treat ovarian cancer, by race/ethnicity in the US. It is a moral imperative to ensure equal access to vital medications including targeted therapies for all patients in need. Descriptive studies alone will not provide solutions to the long-standing structural problems within the healthcare system that have led to persistent disparities in cancer outcomes. Nonetheless, descriptive evidence is needed to alert healthcare providers, payers, policy makers, and program administrators to the nature and magnitude of the problem and its potential consequences for society, and to fuel innovation and progress toward solutions. The oncology community recognizes the need to alleviate racial disparities in research and practice. For example, the American Society of Clinical Oncology (ASCO) Policy Statement on Cancer Care Disparities affirmed its commitment to addressing disparities in cancer care by enhancing awareness, improving access to care, and supporting research on cancer health disparities (Patel et al., 2020). This proposed health services research (HSR) study will shed light on disparities that may exist in access to targeted therapies in ovarian cancer and is thus aligned with the mission and priorities of the ASCO to bring awareness and action to ensure equitable access to high-quality care including new and promising therapies entering the market.

**Research Objectives**

We have identified several gaps in knowledge pertaining to the use of targeted VEGF therapy in elderly women with advanced ovarian cancer. Using nationally representative data available from the Centers for Medicare and Medicaid Services (CMS), we aim to:

1. Identify the measurable demographic and social determinants of bevacizumab use among elderly advanced ovarian cancer patients (age ≥65 years) in the US

and describe any age- or race-related disparities associated with access to targeted VEGF therapy in this population.

2. Estimate OS in relation to treatment with bevacizumab, as compared to standard therapy without bevacizumab, in elderly women with advanced ovarian cancer, taking into account age, race, extent of comorbidity, socioeconomic status, and environmental factors associated with access to ovarian cancer care.
3. Evaluate heterogeneity in the association of bevacizumab with OS between older and younger patients (age <75 or ≥75) and between White and Black patients.

**Study Aim 1**

We will describe receipt of bevacizumab in relation to age, race/ethnicity, level of comorbidity, SES, and environmental factors, among women with ovarian cancer in the Medicare Limited Data Set 5% sample using data from 2016 and 2019. This is a descriptive aim to generate evidence of patterns of use of bevacizumab in older women and particularly Black women with ovarian cancer, who may be less likely to receive targeted oncologic therapies than their White counterparts due to demographic, socioeconomic, or environmental factors that may impact access to optimal cancer care.

**Study Aim 2**

We will estimate the unadjusted cumulative risk of death from any cause among patients with recurrent ovarian cancer, and compare the survival curves of women receiving bevacizumab containing regimens to those not receiving bevacizumab. Our hypothesis is that bevacizumab treatment is associated with longer OS. We will also estimate the multivariable-adjusted relative risks of death among the population by treatment group using propensity score (PS) weighting methods to control for confounding by age, race, level of comorbidity, measures of SES, and environmental factors.

**Study Aim 3**

If sufficient numbers are available in the data (at least 10 observations for each level of independent variable in the models), we will stratify the OS models by age and by race and evaluate heterogeneity in the associations of interest.

**Significance**

To our knowledge, this will be the first study to examine use of bevacizumab and advanced ovarian cancer survival according to race among a representative real-world sample of older ovarian cancer patients in the US. Our findings will contribute knowledge of access to targeted VEGF therapies in this population and evidence of the survival benefit of adding bevacizumab to usual treatment in this heterogeneous patient population.

# CHAPTER 2. BACKGROUND AND RATIONALE

As stated, the purpose of this HSR study is to describe the use of bevacizumab for treatment of ovarian cancer among the US Medicare population, identify factors associated with access to this medication, and evaluate its association with overall survival by age and race/ethnicity. Rationale for the study objectives was informed by a comprehensive review of the peer-reviewed publication literature covering four main topics in this area: (1) trends in survival and management of ovarian cancer including the introduction of bevacizumab into the treatment paradigm, (2) real-world effectiveness of bevacizumab for advanced ovarian cancer, (3) differences in treatment utilization and access to bevacizumab by age and race in the ovarian cancer population.

## 2.1 Trends in Ovarian Cancer Survival and Management

Over the last five decades, advances in treatment and early detection for some cancers have led to significant improvements in overall cancer survival and mortality. Five-year survival for all cancers combined was 49% during the period covering 1975–1977, after which the rate rose to 63% during the period 1995–1997, and to 68% in the most recent period, 2021–2018 ("American Cancer Society Cancer Facts & Figures 2023," 2023). Ovarian cancer survival was lower, but rose over these periods from 36% (1975–1977) to 43% (1995–1997) and reaching 50% in the period 2012–2018. However, these improvements in survival have been confined entirely to White women, among whom 5-year survival rose from 36% (1975–1977) to 43% (1995–1997) and to 49% in 2012–2018. In stark contrast, rates for Black women declined from 42% in the initial period (1975–1977) to 36% (1995–1997) then rebounding to just 41% in 2012–2018. These

difference are largely ascribed to social determinants of health (SDOH) and barriers to access to quality ovarian cancer care that disproportionately impact Black women and result in worse outcomes.

Ovarian cancer survival depends upon timely diagnosis and access to appropriate surgical and systemic treatment for the stage of disease. Due to lack of early detection tools and symptoms that would raise suspicion of disease and/or prompt medical evaluation at an early stage, most women with ovarian cancer present with advanced stage III/IV cancer. It has been reported that 75% of women who present with late-stage ovarian cancer die from the disease (Lheureux et al., 2019).

Tumor debulking surgery followed by platinum taxane chemotherapy is the established first line treatment for ovarian cancer. This approach became the standard with few clinical trials to test against viable alternatives. Since the introduction of this regimen into practice decades ago, evidence-based principles have emerged to guide clinical decision-making, research priorities, and international recommendations for the standard-of-care.

Primary debulking surgery (PDS) by a qualified gynecologic oncologist is the cornerstone of first line treatment and allows for accurate staging according to the International Federation of Gynecology and Obstetrics (FIGO) and Tumor, Node, Metastasis (TNM) staging classification systems (Peres et al., 2019; J. Prat, 2014; J. F. Prat, 2015). The goal of PDS is optimal debulking, in which all areas of disease are resected, with no macroscopic residual tumor. The significant impact of residual disease on overall survival was clearly demonstrated in an analysis of clinical trial data encompassing >3,000 subjects. Interestingly, the prognostic value of histology, which is an indicator of tumor aggressiveness, appeared to be at least partially overruled by the

presence of residual disease (Du Bois et al., 2009). In some patients, PDS may not be possible due to extensive disease or clinical conditions that preclude surgery. In such cases, neoadjuvant chemotherapy (NACT) may be administered to reduce the tumor and increase the chances for optimal debulking before surgery. Surgery that follows frontline NACT is referred to as interval debulking surgery (IDS). While the decision to administer PDS or NACT and IDS is driven by the size and extent of the tumor, no strict criteria exists to guide care, and use and frequency of NACT varies among treatment centers (Lheureux et al., 2019).

The standard systemic treatment, whether administered as NACT or adjuvant therapy following surgery, is a combination platinum agent with a taxane. The introduction of platinum agents in the 1970s beginning with cisplatin, then cisplatin-taxane combination treatments in the 1980s, and paclitaxel in 1993, were important milestones in the treatment of ovarian cancer, dramatically improving the survival outlook for women with advanced stage disease. More than 80% of women respond to this treatment initially, although most eventually experience recurrence. Over time, the use of chemotherapy has evolved with evidence from randomized studies to address dosing, choice of platinum agent, schedule and mode of administration (intravenous vs. intraperitoneal), management of adverse event (AE) risk, and, more recently, the addition of appropriate targeted therapies. Several targeted agents have entered the market in the last decade with the potential to transform first-line management of ovarian cancer, as the discovery of molecular features of the tumor presents targets for exploitation. Bevacizumab marked the first such breakthrough.

Bevacizumab (Avastin®, F. Hoffmann La-Roche AG, Switzerland) is a humanized monoclonal antibody that binds to all circulating VEGF-A isoforms. It was the first available drug to target the VEGF pathway to block angiogenesis in cancer. Based on its

mechanism of action, clinical development focused on solid tumors known to have an abundance of pro-angiogenic molecular features associated with aggressive phenotypes of colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). Early studies established efficacy of bevacizumab at these sites, and they were among the first indications for which the drug was approved. Bevacizumab was approved by the European Medicines Agency (EMA) for first-line treatment of ovarian cancer in 2011, then second-line platinum-sensitive and platinum-resistant disease in 2021 and 2014, respectively. The US Food and Drug Administration (FDA) granted approval first for platinum-resistant then platinum-sensitive ovarian cancer in 2014 and 2016, respectively, and for first-line treatment of advanced primary ovarian cancer in 2018. **Figure 2** shows the full approval timeline for bevacizumab (Garcia et al., 2020).

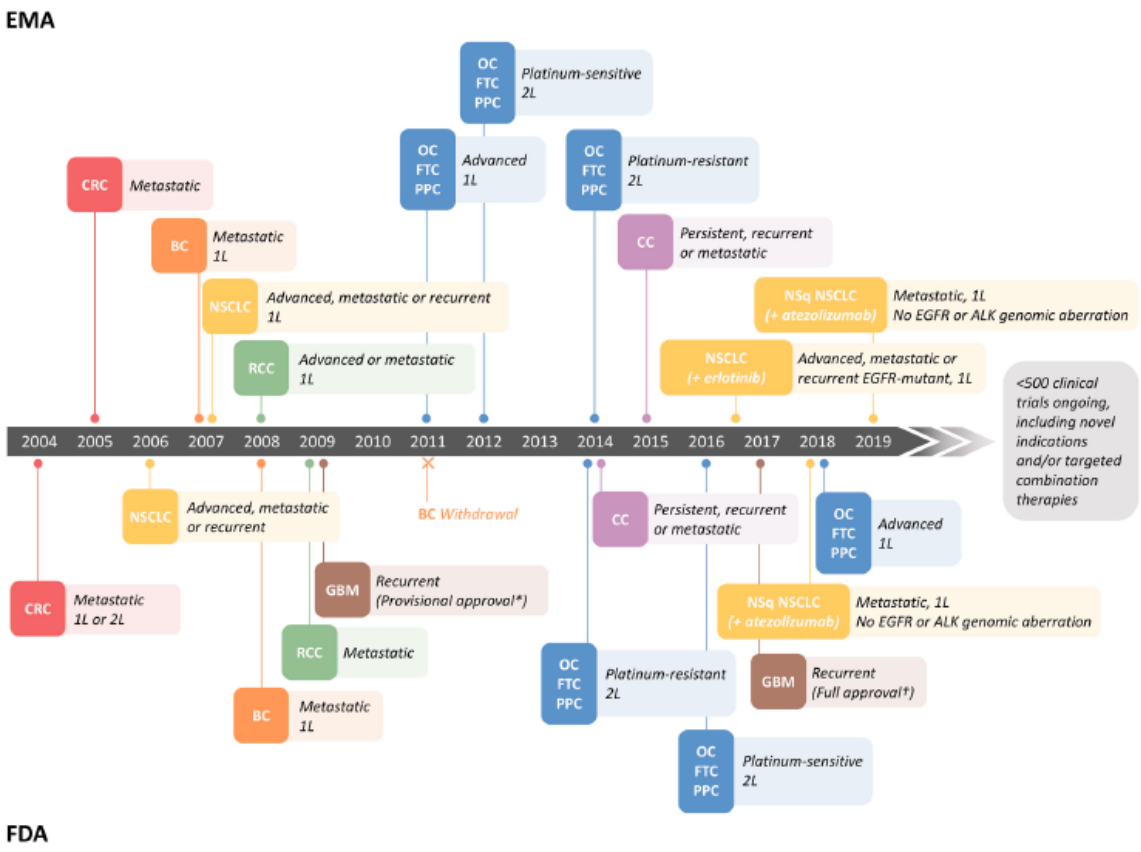



*Figure 2. Timeline of bevacizumab approvals. Abbreviations: 1L, first-line treatment; 2L, second-line treatment; ALK, anaplastic lymphoma kinase; BC, breast cancer; CC: cervical cancer; CRC, colorectal cancer; EGFR: epidermal growth factor receptor; EMA, European Medicines Agency; FDA, (US) Food and Drug Administration; FTC, fallopian tube cancer; GBM, glioblastoma; PPC: primary peritoneal cancer; NSCLC, non-small-cell lung cancer; Nsq-NSCLC, non-squamous non-small-cell lung cancer; RCC, renal cell carcinoma.* ***Footnotes:*** ** Provisional approval granted under FDA's accelerated approval program based on surrogate endpoint. † Full approval granted, based on totality of evidence of bevacizumab in GBM.*

Ovarian tumors have hallmarks of excessive VEGF expression including angiogenesis, micro vessel density, and ascites. Ascites is fluid build-up in the abdomen from capillary leakage due to VEGF overproduction. The condition causes abdominal pain, swelling, nausea, vomiting, and can interfere with organ function. One of the beneficial effects of bevacizumab is immediate reduction of ascites in ovarian cancer (Lheureux et al., 2019). Pivotal studies in ovarian cancer were for first-line therapy in combination with cytotoxic chemotherapy and single agent maintenance after initial response. Two randomized trials, GOG-0218 and ICON-7, respectively, signaled improvements in PFS amounting to

several months in the bevacizumab arm compared to controls in both studies (Robert A Burger et al., 2011; Perren et al., 2011). Neither study demonstrated an OS advantage among bevacizumab patients in general. However, among the pre-specified subgroup of patients with stage IV or stage III inoperable tumors or operable but unable to be debulked to <1 cm, bevacizumab treatment was associated with a 9-month OS advantage over the non-bevacizumab population (Perren et al., 2011). In GOG-2018, patients with FIGO stage IV disease who received bevacizumab maintenance experienced an OS advantage after first-line chemotherapy independent of dose (Robert Allen Burger et al., 2018). Findings from the ROSiA trial suggested that duration of therapy is positively associated with survival outcomes (A. M. Oza et al., 2017). Bevacizumab also showed efficacy for recurrent ovarian cancer and was tested in combination with other chemotherapy agents among patients with platinum-resistant and platinum-sensitive disease, significantly improving the outlook for patients in this challenging setting (Aghajanian et al., 2012; Coleman et al., 2017; Pujade-Lauraine et al., 2014).

Safety data from clinical trials and post-marketing experience of bevacizumab for a range of malignancies suggest that bevacizumab is well-tolerated in most patients. The most frequently observed side effects include hypertension (HTN), fatigue, diarrhea, and abdominal pain (Garcia et al., 2020). It is important to note that the safety profile of the drug is largely based on combination therapy with other cytotoxic agents, although bevacizumab has not been found or suspected to interact with other chemotherapies. Serious adverse events (SAEs) to emerge among bevacizumab-treated patients include bowel perforation, hemorrhage, and arterial thromboembolism (ATE). Risk of ATE and related cardiovascular events including myocardial infarction and transient ischemic attacks appears highest among those older than age 65, with diabetes, and history of

ATE. Among ovarian cancer patients, HTN, delayed wound healing, and gastrointestinal symptoms, have been reported and rarely, fistulization and bowel perforation, particularly in cases with bulky disease in close proximity to the bowel (Lheureux et al., 2019). One study evaluating safety of long-term maintenance therapy with bevacizumab found that most AEs occurred during the earliest cycles of treatment when bevacizumab was administered concomitant to chemotherapy (A. M. Oza et al., 2017). Proteinuria appeared in some patients only after more prolonged exposure. Median time on bevacizumab was 15.5 months in the study.

Since its approval in the US, bevacizumab has become an important component in the standard-of-care for ovarian, fallopian tube, and primary peritoneal carcinoma, and is now incorporated in all phases for treatment for advanced disease. **Figure 3** depicts the evolution of the disease and its treatment strategy including VEGF therapy and PARP inhibition for the subset of tumors with DNA mismatch repair deficiencies associated with BRCA mutation (Lheureux et al., 2019).

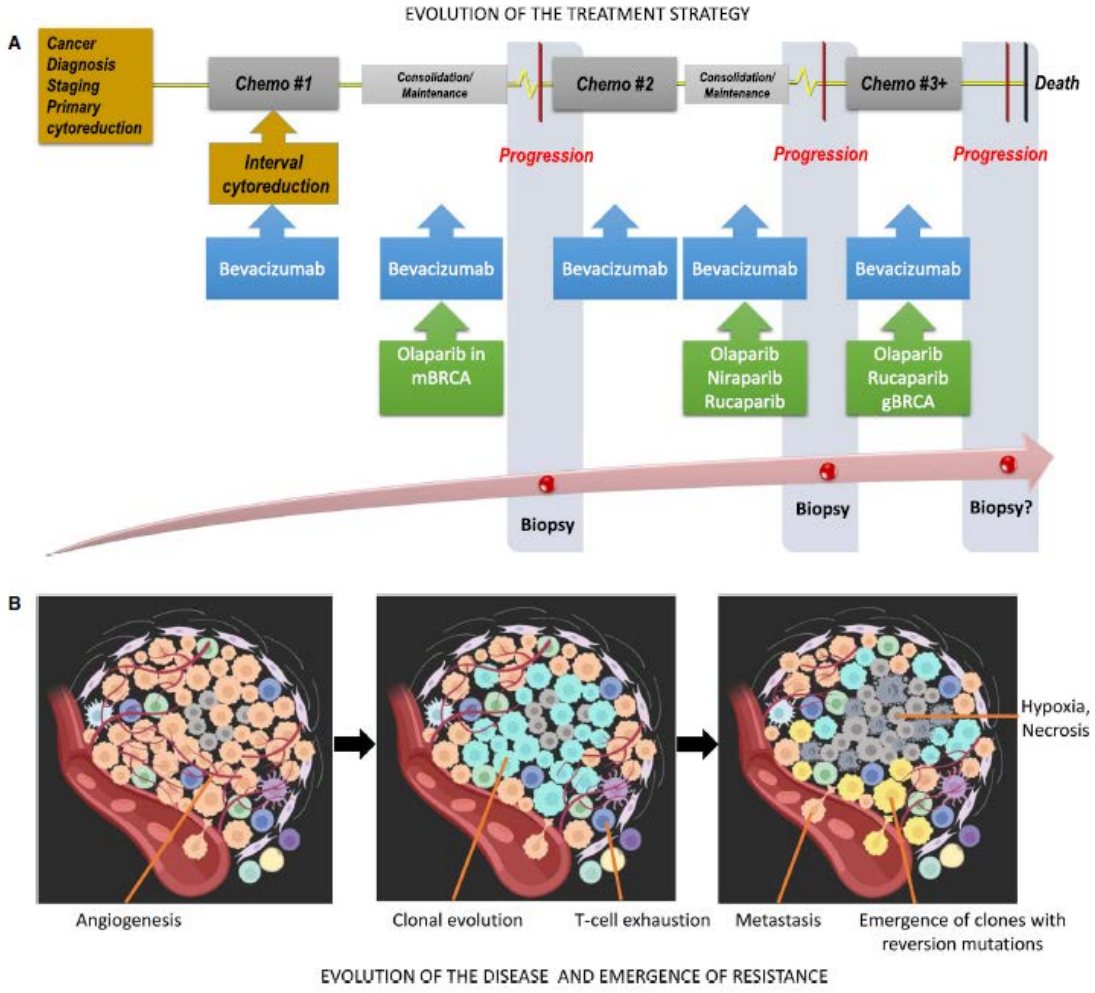



*Figure 3. Evolution of ovarian cancer and its treatment strategy. Abbreviations: Chemo, chemotherapy; gBRCA, BRCA germline mutation; mBRCA, BRCA germline or somatic mutation*

### 2.2 Real-World Evidence of Bevacizumab in Ovarian Cancer

Findings from a 2017 systematic review (SR) of real-world use of bevacizumab for colorectal, metastatic breast, ovarian, and cervical cancer, were generally consistent with the trial evidence for these sites (Raouf, Bertelli, Ograbek, Field, & Tran, 2019). However, the review included only 3 peer-reviewed studies of ovarian cancer, all with small number of patients who received bevacizumab: 37 in one study (Rauh-Hain et al., 2013), 41 patients in another (O'Malley et al., 2011), 68 in the third (Sfakianos et al.,

2009), limiting conclusions. Since that time, several more studies of bevacizumab for ovarian cancer have been published, including a qualitative non-systematic review of observational studies in the first-line setting (Gadducci & Cosio, 2021).

### 2.2.1 Method of Assessment of the Evidence

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) updated guideline (Page et al., 2021), we systematically searched and reviewed the PubMed and Scopus databases in consultation with a medical research librarian, for non-randomized, observational studies on this topic. This process identified 17 peer-reviewed original studies evaluating use of bevacizumab among ovarian cancer patients in usual care. The search strategy and evidence synthesis methods are described in detail in **Appendix A**.

### 2.2.2 Characteristics of Real-World Studies of Bevacizumab in Ovarian Cancer

The majority of studies were retrospective by design. (**Appendix A, Table A.1** Characteristics of real-world studies of bevacizumab in ovarian cancer) Most (N=10) were from a single institution, while 6 were multi-institutional. One study, the largest by far, utilized proprietary commercial insurance claims data. Sample size ranged from 32 to 8,923 patients (median N=299, IQR 70–441), and 8 studies included ≥300 participants. All studies included bevacizumab regimens, most with carboplatin-paclitaxel doublet for first-line initial response and bevacizumab maintenance thereafter (N=11). Nine studies were conducted among patients with recurrent disease including platinum-resistant in 6 studies and platinum-sensitive disease in 8. One third of the studies (N=6) included a non-bevacizumab group for comparative analysis. All studies reported PFS, and about half (N=9) reported OS and ORR endpoints. Most, but not all (N=12, 67%), included safety data. The majority of studies were of low to moderate quality, without analyses comparing bevacizumab to standard cytotoxic regimens.

### 2.2.3 Effectiveness Endpoints

#### ***2.2.3.1 Progression-free Survival***

Median patient age among the studies ranged from 53 to 66 years of age with most studies comprised predominantly of women age 55–60 at entry. (**Appendix A, Table A.2** Summary of real-world studies of bevacizumab in ovarian cancer) Among patients treated with bevacizumab in the first-line setting, median PFS ranged between 15.4 and 26 months. Lower rates were noted among older patients in 2 studies that presented PFS stratified on age (11 months and 14.8 months in women older than 65 and 70 years of age, respectively) (Amadio et al., 2020; Hall et al., 2020). One study found substantially lower PFS (10.5 months) among high-risk patients based upon stage and grade at diagnosis (Wu et al., 2020). PFS between 9 months and 19.9 months was reported among the non-bevacizumab comparator groups, and 6 months in the high-risk study.

Among patients receiving bevacizumab for recurrent or relapsed ovarian cancer, PFS ranged from 4.8 months to 18.8 months, with the lower survival observed primarily in platinum-resistant patients. Notably, no age-related differences in PFS were observed by age in the recurrent disease setting. In patients with recurrent disease who did not receive bevacizumab, PFS from 5 to 6.7 months was observed. One study that examined PFS among 222 patients who were treated with bevacizumab for recurrent disease noted lower PFS in those who had received bevacizumab first-line than those who had not (5 months vs. 10 months, respectively, p=0.006) (Petrillo et al., 2016).

#### ***2.2.3.2 Overall Survival***

Median OS was reached in only one study among patients with primary ovarian cancer receiving bevacizumab, which recorded 41.1 months over a median 32 months of follow-

up (Daniele et al., 2021). For all other studies among patients with incident primary ovarian cancer, the majority of patients were still alive at study completion. For recurrent disease, median OS varied between 21 months for platinum-resistant to 48.3 months in platinum-sensitive patients. Length of the platinum-free interval (PFI) among relapsed patients was associated with OS, with one study observing a 78% lower multivariable-adjusted relative risk of death (HR 0.22, 95% CI 0.10–0.50, for PFI ≥6 vs. <6 months) (Wu et al., 2020). However, no differences in OS were observed in the comparative analysis (18.9 months vs. 18.8 months in the bevacizumab and non-bevacizumab groups, respectively) (O'Malley et al., 2011).

#### ***2.2.3.3 Objective Response Rate***

Complete or partial response (CR, PR, respectively) was seen in 69% to 77% of patients undergoing first-line treatment with bevacizumab. Objective response rates (ORRs) ranging from 27.3% to 92.3% were observed among patients treated for recurrent disease. In one study, patients who were not initially treated with bevacizumab first-line were more likely to respond in the recurrent setting than those who were (40.5% vs. 23.1%, respectively) (Petrillo et al., 2016).

### 2.2.4 Safety Events

The most common side effects observed across studies were hypertension, reported in 16% to 25% of the total population, neutropenia (28%–38%), and proteinuria (12.6%–30%). Serious adverse events were infrequent affecting less than 10% of patients. Grade ≥3 neutropenia and proteinuria occurred in <5% of patients; anemia and thromboembolism in <4%; serious gastrointestinal events in <1%. Other rare events included thrombocytopenia, mucocutaneous bleeding, and wound healing disruption. Bevacizumab-related toxicities leading to treatment discontinuation were rare across study populations.

### 2.2.5 Limitations of the Current Real-World Evidence of Bevacizumab in Ovarian Cancer

Based upon review of the evidence, bevacizumab appears to elicit a strong overall response which translates to a significant benefit for prolonging progression-free survival when administered in the first-line setting. The evidence also supports use of bevacizumab after recurrence to prevent further disease progression. Whether the PFS benefit translates into longer OS is as yet unclear. Furthermore, real-world evidence suggests a favorable safety profile for most women irrespective of age and disease characteristics.

Findings from real-world studies of PFS appear consistent with results from clinical trials, although evidence to support a benefit for OS with bevacizumab use is inconclusive. Median OS was reached in only one study (Daniele et al., 2021), as more than half of patients were still alive at the end of follow-up in all others. Studies conducted in usual practice, with secondary data from billing claims and/or electronic health records, may be more representative of the real-world patient population than clinical trials, as real-world studies do not apply the stricter inclusion criteria needed to establish efficacy in the controlled clinical setting. This literature review highlights the need for evidence on the effectiveness and safety of bevacizumab among populations with different characteristics including older age at diagnosis, comorbidities, and socioeconomic characteristics that may also impact survival.

Although studies covered a broad range of sample size, most were retrospective studies from single institutions. Less than half of the studies included a non-bevacizumab group for comparative analysis of the treatment effects. Larger prospective, quasi-experimental, comparative effectiveness studies are needed to establish the

effectiveness and safety profile with precision among real-world patients and to overcome the limitations of the existing literature.

### 2.3 Age and Race Disparities in the Use of Bevacizumab

Age and race are associated with suboptimal treatment in ovarian cancer. Between 1973 and 1999, optimal surgery was performed in 43.7% of cancer patients age <60, 29.5% of patients ages 60–79, and 21.7% in patients age 80 and older (Ries, 1993). Elderly ovarian cancer patients may be more likely to be treated by a general surgeon or obstetrician/gynecologist than a gynecologic oncologist (Hightower et al., 1994) often in emergency situations for cancer complications, and they are less likely to undergo procedures at academic teaching hospitals (Díaz-Montes et al., 2005). A large clinical study among 961 ovarian cancer patients in Denmark during the period 2005–2006 found that age 70 or older was independently predictive of not receiving surgery (OR 0.2, 95% CI 0.1–0.5), not receiving a carboplatin-paclitaxel chemotherapy treatment (OR 0.03, 95% CI 0.01–0.5), and worse PFS and OS (Jørgensen et al., 2012). However, age was not predictive of prognosis or outcome among patients who received optimal care. Comorbidity was also associated with not receiving surgery, but neither age nor comorbidity was associated with the ability to adhere fully to treatment.

Older cancer patients are thought to have a weaker benefit from systemic therapies due to lower life expectancy and risk of complications due to chronic diseases, declining health and functional capacity (Balducci & Aapro, 2014; Brighi, Balducci, & Biasco, 2014; Popa, Wallace, Brunello, Extermann, & Balducci, 2014). Age-related factors may impact older patients' ability to tolerate and recover after cancer treatment, and risk of chemo-toxicity may be higher. It is therefore important in older patients to consider whether cancer treatment could lead to worsening disability and impaired quality of life (Balducci & Fossa, 2013; Morello, Giordano, Falci, & Monfardini, 2009). The NCCN committee on

aging issued guidelines for management of cancer in older patients undergoing chemotherapy including use of a comprehensive geriatric assessment in patients ≥70 years of age to evaluate risk of treatment-related toxicity and conditions that may impact the safe administration of therapy. Supportive care is also an important component of cancer therapy in the older patient to reduce the risk of side effects and AEs associated with treatment.

For these reasons, elderly patients have historically been underrepresented in clinical trials of new cancer drugs (Hutchins, Unger, Crowley, Coltman Jr, & Albain, 1999). A survey study from the FDA found only 9% of ovarian cancer patients age ≥75 were included in clinical trials, while this age group accounted for 31% of the overall sample (Talarico, Chen, & Pazdur, 2004). Age disparities in cancer trial participation were recently found to be pervasive and increasing over time, especially in trials of targeted therapies (Ludmir et al., 2019). Lack of clinical trial data generalizable to older patients may influence some physicians and their patients against certain treatments in this population. Evidence suggests that older ovarian cancer patients are managed more conservatively than their younger counterparts and less likely to be optimally debulked (Wimberger et al., 2006).

Data on age disparities in receipt of bevacizumab in particular are sparse. One study from a large claims database suggested that older women were substantially less likely to receive bevacizumab than younger patients (2.8% for patients age ≥70 years vs. 6% overall) (Gamble et al., 2022). Lower rates of receipt of bevacizumab among elderly patients (≥70 years) have also been reported elsewhere (Liontos et al., 2021). Although older age is thought to be associated with greater risk of treatment-related toxicities, evidence including data from clinical trials (Selle et al., 2018) suggest that elderly patients experience a survival benefit with bevacizumab comparable to that observed in

younger women, and particularly among patients with recurrent disease (Amadio et al., 2020; Hall et al., 2020).

Data on race disparities in receipt of bevacizumab are to our knowledge nonexistent. However, barriers to access, particularly economic barriers, which disproportionately impact minority populations, have been reported in several studies of targeted therapies including bevacizumab (Baer, Maini, & Jacobs, 2014; Cherny, Sullivan, Torode, Saar, & Eniu, 2016; Lammers, Criscitiello, Curigliano, & Jacobs, 2014). In a recent survey of 150 oncologists in the US, Europe, and emerging markets, lack of reimbursement and high out-of-pocket costs were cited as the main reasons for not prescribing bevacizumab (Monk, Lammers, Cartwright, & Jacobs, 2017). Only 58% of US physicians in this study reported “always” or “frequently” prescribing bevacizumab for first-line and for recurrent ovarian cancer. A cost-effectiveness analysis of bevacizumab did not find the addition of the drug to cytotoxic chemotherapy for ovarian cancer to be cost effective, except in patients at high-risk of disease progression using a biosimilar (Mehta & Hay, 2014). These economic barriers almost certainly contribute to racial disparities in treatment of ovarian cancer, which are well-documented for surgical and standard-of-care chemotherapy.

Unequal access to care is a major driver of cancer health disparities. In previous work, we demonstrated that Black ovarian cancer patients were less likely to receive a surgery and chemotherapy sequence than White women and three times more likely to die from the disease (Hildebrand et al., 2019). The disparities were most pronounced among women with comorbidities. Our results were not novel, but consistent with numerous other previous studies (Chase et al., 2012; Goff et al., 2007; Kim, Dolecek, & Davis, 2010; Terplan, Smith, & Temkin, 2009). Findings from a recent systematic review and meta-analysis of 41 studies of race, SES, and health-care access disparities in ovarian

cancer treatment and mortality suggested a 25% decrease in receipt of guideline adherent treatment (RR 0.75, 95% CI 0.66–0.84) and 18% increased risk of death among Blacks compared to Whites (RR 1.18, 95% CI 1.11–1.26) (Karanth et al., 2019).

Bevacizumab is now established in the treatment guidelines in the US and Europe for management of patients with advanced ovarian cancer. The clinical and observational evidence suggest that bevacizumab can be safely and effectively used among women with newly diagnosed advanced ovarian, fallopian tube, and primary peritoneal ovarian cancer and platinum-sensitive and platinum-resistant recurrent disease, with acceptable risk of treatment-related toxicity. It is therefore important to understand treatment patterns among this patient population to enable evidence-based action aimed at ensuring health equity to essential medications and reducing survival disparities in this disease.

## CHAPTER 3. METHODS

To advance current understanding of use of targeted VEGF therapy for treatment of advanced ovarian cancer including tubal and primary peritoneal cancer (hereafter collectively referred to as ovarian cancer), we conducted a retrospective drug utilization study among recurrent ovarian cancer patients in the US Medicare 5% Limited Data Set (LDS).

### 3.1 Specific Aims

**Aim 1:** To assess receipt of bevacizumab for advanced ovarian cancer, focusing on recurrent disease, delineating use by groups based on age, race, level of comorbidity, selected measures of SES, and neighborhood environment using the Medicare 5% sample for the years 2016 to 2019. This was a descriptive aim to generate evidence of patterns of use of bevacizumab in older women and particularly Black women with ovarian cancer, who may be may be less likely to receive targeted oncologic therapies than their White counterparts due to demographic and/or social environmental barriers to optimal cancer care.

**Aim 2:** To estimate risk of death from any cause among women ≥65 years of age with recurrent ovarian cancer, and compare OS between women who received bevacizumab and those who did not, under the hypothesis that receipt of bevacizumab is associated with longer OS compared to non-bevacizumab regimens. We used propensity score (PS) methods to control for differences between the treatment groups with respect to age, race, level of comorbidity, and neighborhood-level environmental factors.

HYPOTHESIS: Among women with recurrent ovarian cancer in the Medicare population, receipt of bevacizumab is associated with longer overall survival compared to non-bevacizumab treatment regimens, taking into account the effects of age, level of comorbidity, SES and environmental factors.

**Aim 3**: To evaluate effect modification in the association between bevacizumab and OS among women with recurrent ovarian cancer by age, race, and platinum status, controlling for confounding by the other covariates, level of comorbidity, SES, and environmental factors.

HYPOTHESIS: There is no difference in the bevacizumab-OS association between older and younger women, between Black and White women, or between women with platinum-sensitive and platinum-resistant recurrent ovarian cancer, after controlling for confounding.

This study addresses utilization of a critical targeted therapy for advanced ovarian cancer. The research addresses a lack of evidence generalizable to a segment of the patient population underrepresented in clinical trials. Achievement of our study aims may advance understanding of the drivers of ovarian cancer disparities with the goal of improving access to optimal care including newer targeted therapies among women affected by an aggressive and devastating disease.

### 3.2 Study Design

This is a retrospective cohort study among the US Medicare 5% LDS with census tract level SDOH and cancer care delivery system measures.

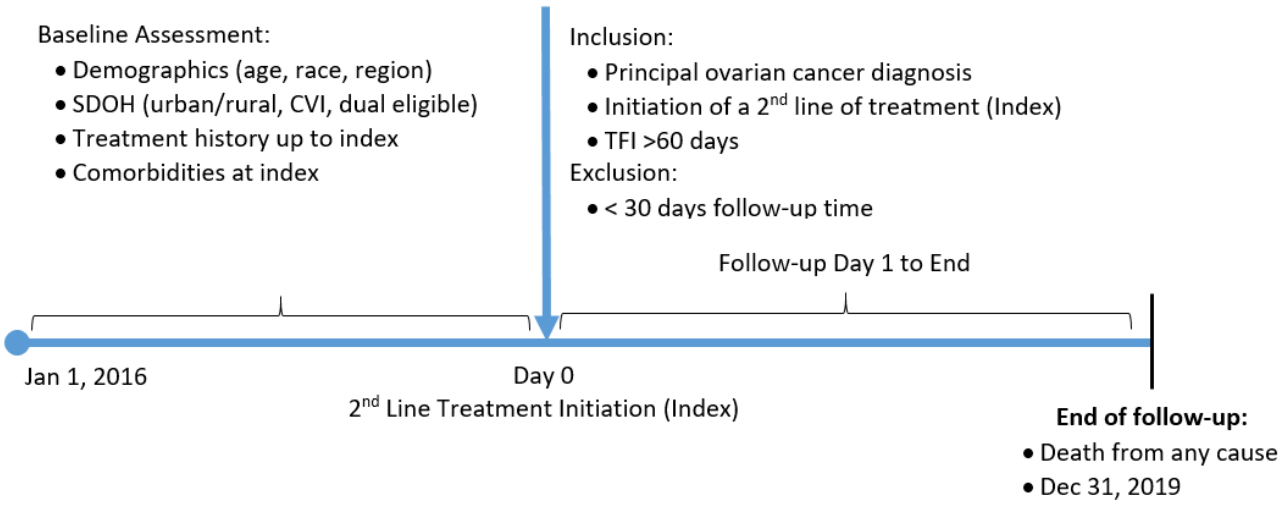



*Figure 4. Study Design Schema (Aim 2)*

### 3.3 Setting and Study Population

#### 3.3.1 Study Period

The study period was from January 1, 2016 through December 31, 2019.

#### 3.3.2 Patient Eligibility

The population of interest was females who initiated treatment for recurrent ovarian, tubal, or primary peritoneal cancer (International Classification of Diseases diagnosis codes C56, C57.0, and C48.2, respectively). Recurrent disease was defined as any stage at diagnosis and subsequent recurrence or progression as indicated by initiation of a second line of therapy after a treatment-free interval (TFI) of more than 60 days, assuming a 28-day chemotherapy cycle. We identified all patients in the Medicare LDS with a principal diagnosis of ovarian cancer, and performed a descriptive analysis according to pharmacologic treatment received including those who did not receive treatment during the observation period, those who had only one continuous episode or line of treatment (LOT), and those who initiated a second LOT after a TFI >60 days under the assumption that these patients had disease relapse or recurrence. Patients

who initiated a second LOT were eligible for survival analysis as long as they had at least 30 days follow-up time available from the date of second line initation.

### 3.3.3 Baseline Assessment Period

All demographic characteristics, clinical, socioeconomic and environmental factors, were assessed as of the index date.

### 3.3.4 Follow-up for Overall Survival

Recurrent patients were followed longitudinally beginning on their second line treatment initiation date (index). OS was measured as the time from index date to the earliest of: death due to any cause or end of study (December 31, 2019).

## 3.4 Study Variables

Variables for inclusion in the study were chosen *a priori* based on existing knowledge from peer-reviewed literature on the determinants of outcomes after ovarian cancer diagnosis including social determinants of health (SDOH). We constructed a conceptual framework for variable selection based on the Aday and Anderson access to care model (Aday & Andersen, 1974). Our model is adapted to depict the relationships between patient characteristics, SDOH, health policy and the healthcare delivery system, utilization, and access to ovarian cancer care. (**Appendix B**) As shown, these domains encompass many interrelated factors, some of which were not available in the Medicare 5% sample. Information was available to cover all domains including: patient demographics such as age, race and ethnicity; comorbidities, which were identified by ICD-10-CM code; neighborhood level social environmental factors via zip code linkage to census level data; patient-level economic status as indicated by dual eligibility for both Medicare and Medicaid coverage; and our main exposure of interest, targeted systemic anti-VEGF therapy for ovarian cancer.

### 3.4.1 Exposure Assessment

The exposure of interest for this analysis was bevacizumab added to a standard chemotherapy regimen. Chemotherapy administrations for ovarian cancer were identified using procedure codes from the Healthcare Common Procedure Coding System (HCPCS) for chemotherapy administration, intravenous infusion, and a diagnosis code for ovarian cancer. HCPCS codes are drug-specific allowing for identification of oncology regimens that include concurrent and sequential administration of multiple chemotherapeutic agents used in combination. Code sets for the treatments of interest are included in **Appendix C**. These codes were also used to track the completion of chemotherapy and derive the TFI, which was defined as date of the last treatment administration plus 28 days. Platinum-sensitive disease was defined as a TFI >180 days, and platinum-resistant disease ≤180 days. Standard treatment regimens for recurrent ovarian cancer vary by platinum status as shown in **Table 1**.

*Table 1. Treatment Regimens by Platinum Status*

| | |
|---|---|
| **Platinum sensitive recurrent disease** | |
| Combo chemotherapy | (carboplatin or cisplatin) + (paclitaxel, gemcitabine, pegylated liposomal doxorubicin) |
| Combo chemotherapy plus bevacizumab | (carboplatin or cisplatin) + (paclitaxel, gemcitabine, pegylated liposomal doxorubicin) + bevacizumab |
| **Platinum resistant recurrent disease** | |
| Single agent | Paclitaxel, gemcitabine, pegylated liposomal doxorubicin, or topotecan |
| Single agent plus bevacizumab | (paclitaxel, gemcitabine, pegylated liposomal doxorubicin, or topotecan) + bevacizumab |

The chemotherapy regimens listed above represent the most commonly used drugs in current use for treatment of advanced ovarian cancer. Alternative or early phase experimental agents such as pemetrexed, oxaliplatin, or irinotecan for platinum resistant

disease as well as alternative VEGF agents such as aflibercept, sorafenib, or sunitinib, cediranib, pazapanib, and nintedarib were beyond the scope of this study, and thus not assessed.

For the treatment contrast of interest in the survival analysis, we assessed exposure to bevacizumab during the second LOT. Patients who received at least one cycle of bevacizumab, either in combination with standard agents or as single agent, were assigned to the bevacizumab group. Patients who received standard agents only with no exposure to bevacizumab were classified into the non-bevacizumab group. The non-bevacizumab group provided the referent for all comparisons.

### 3.4.2 Outcome Assessment

The main outcome of interest was death due to any cause. OS was calculated as the time from index medication administration to the validated death date (V_DOD_SW, DEATH_DT) recorded in the Medicare Eligibility data set (LDS Master Beneficiary Summary File). If an exact date of death (DOD) was not noted as validated in the Medicare 5% sample, DOD was imputed as the 15th of the month and year.

### 3.4.3 Covariate Assessment

We examined the patient population according to baseline demographic characteristics assessed at the time of second-line treatment initiation for patients with recurrence, the first observed treatment initiation for patients with only one continuous treatment episode, or date of first claim with principal diagnosis of ovarian cancer for patients who were not observed to have any pharmacologic treatment for ovarian cancer. We also separately described the recurrent patient cohort comparing patients by bevacizumab exposure. Race was categorized as non-Hispanic White (NHW), non-Hispanic Black (NHB), Hispanic, Asian, Native Hawaiian or Pacific Islander, American Indian or Alaska

Native) consistent with the National Center for Health Statistics standards ("US Centers for Disease Control (CDC) National Center for Health Statistics (NCHS) National Health Interview Survey (NHIS) - Race and Hispanic Origin Information.,"). Categories were collapsed to NHW, NHB, Hispanic, other race, for analyses.

We used dual eligibility for Medicare and Medicaid, during any month of the observation period, as a measure of poverty, our key indicator of low SES at the individual level. Dual eligibility in the Medicare population refers to individuals who qualify for both Medicare and Medicaid benefits on the basis of income and assets, and is an indicator of lower SES, given that these individuals are within the thresholds for full or partial eligibility as determined by their state. Neighborhood environment was assessed by linking the 9-digit zip code for each patient to the census tract level and calculating the Social Vulnerability Index (SVI). The SVI is a composite measure developed by the Centers for Disease Control and Prevention (CDC) to identify communities at risk and potentially in need of special services during natural or man-made disasters or disease outbreaks (Flanagan, Gregory, Hallisey, Heitgerd, & Lewis, 2011). The SVI integrates 15 measures across four domains: SES (per capita income, percentage below poverty, unemployed, and without a high school diploma); household composition and disability (aged ≥65, aged ≤17, civilian with a disability, single-parent household with children ≤18); minority status and language (non-white, speaks English “less than well”); mobility and transportation (multi-unit structures, mobile homes, crowding, no vehicle access, group quarters). This measure is increasingly being used as a risk assessment tool in health services research with application to health disparities in cancer care (Tran et al., 2023). The SVI is calculated as a percentile and classifies any area in the upper 90$^{th}$ percentile as a vulnerable community (Flanagan et al., 2011).

To assess comorbidities, we used the Charlson Comorbidity Index (CCI). The CCI is a validated algorithm that incorporates ICD-CM codes to calculate a summary measure of disease burden associated with survival among hospital populations (Quan et al., 2005; Suidan et al., 2015). Seventeen medical conditions are individually scored on a qualitative scale of 1 to 4 for severity. A severity score is then calculated as the sum of scores for all medical conditions.

| ***Table 2.*** *Baseline Covariates* |
|---|
| **Demographics** |
| Age at index date (categorized as 65-69, 70-74, 75-79, 80-84, 85+) |
| Race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander) |
| Geographic setting (urban, rural, metropolitan based on county of residence) |
| **SDOH** |
| Dual eligibility Medicare and Medicaid (No, Yes if any time during study period) |
| Social Vulnerability Index, derived by linking zip code to census tract level data |
| **Clinical** |
| Treatment-free interval (TFI, time between completion of one* and initiation of subsequent line of treatment) |
| Platinum-sensitive disease (TFI >6 months) |
| Platinum-resistant disease (TFI ≤6 months) |
| **Overall comorbidity** |
| Charlson Comorbidity Index (CCI), derived from ICD-10-CM codes |
| **Comorbidities included in the AACI:** |
| MI |
| Congestive heart failure |
| Peripheral vascular disease |
| Cerebrovascular disease |
| Dementia |
| Chronic pulmonary disease |
| Rheumatic disease |
| Peptic ulcer disease |
| Mild liver disease |
| Diabetes mellitus without end-organ damage |
| Diabetes mellitus with end-organ damage |
| Hemiplegia |
| Renal disease |
| Malignancy including lymphoma and leukemia, except malignant neoplasms of skin |
| Moderate liver disease |
| Metastatic solid tumor |
| AIDS/HIV |

**Calculated as the date of the last claim for treatment administration + 28 days*

### 3.5 Data Source

The data for this analysis was drawn from the Medicare 5% sample available through the CMS and covering the period from 2016 to 2019. Also known as the Medicare Limited Data Set (LDS), the 5% sample is a random sample of the entire US Medicare population of fee-for-service beneficiaries mostly aged 65 and older drawn from the Master Beneficiary Summary File (MBSF) and linked to the Medicare Provider Analysis and Review (MedPAR) file, Physician/Supplier Carrier (Part B) file, the Outpatient Standard Analytical File (OutSAF), and the Hospice file. The time period 2016 to 2019 was chosen to allow for uniform definition of diagnosis and treatment using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), prior to COVID-19 global pandemic period of disruption to health care system. All analytic datasets were de-identified. Therefore, the Medical University of South Carolina Institutional Review Board (IRB) deems research using these data to be non-human research.

### 3.6 Sample Size

Prior to study start, we searched the LDS 2016–2019 files and identified a total 3,760 unique patients with a principal diagnosis of ovarian cancer during this period. Assuming recurrence rates of 50% to 70% within 2 years (Kyriacou, Black, Drummond, Power, & Maheu, 2017), we assumed the majority of these claims to be associated with prevalent or recurrent disease, thus providing a sufficiently sized sample for our planned analyses among this population. Because of our intention to include all data in various phases of the analysis, we did not perform sample size or power calculations.

### 3.7 Statistical Analysis

We examined the distribution of baseline characteristics overall and by treatment status with appropriate descriptive statistics including the mean and standard deviation (SD) for normally-distributed continuous data, the median and interquartile range (IQR) for non-normal continuous data, and the number and percentages for categorical variables.

OS was calculated as the time from index treatment initiation to the earliest of: death due to any cause or the end of follow-up (December 31, 2019). To estimate the unadjusted cumulative risk of death, we plotted the Kaplan-Meier (KM) survival curves. We repeated this analysis stratified on age, race, and platinum status. Unadjusted effect size was reported as estimated median OS time using PROC LIFETEST in SAS for each treatment regimen, and the log-rank statistic was used to test for statistically significant differences between treatment strata (Kaplan & Meier, 1958; Mantel, 1966).

Multivariable Cox proportional hazards (PH) regression (PROC PHREG in SAS) was used to estimate the adjusted all-cause mortality HR and 95% confidence interval (CI) for the treatment contrast (Cox, 1972), controlling for confounding using inverse probability of treatment weights derived from propensity scores (Ali et al., 2019; Stuart, 2010) in addition to standard multivariable adjustment methods to achieve doubly robust estimation.

For unbiased estimates, the comparison groups should be similar in every way except for the treatment assignment. Before proceeding with Cox modeling, we assessed the comparability between treatment groups after balancing the cohort using propensity scores. Multivariable logistic regression was used to estimate the propensity score (PS) for each patient. The PS is a measure of the conditional probability of receiving the treatment of interest given the measured confounders. Using the PROC PSMATCH in SAS, we generated the PS for each patient and applied the inverse probability of

treatment weight (IPTW) to balance the cohort on the independent variables. The IPTW is calculated as 1 / PS in patients exposed, and 1 / 1-PS in patients not exposure to the treatment of interest. To assess balance after PS estimation and weighting, we examined the distribution of the PS overlap and standardized mean difference (SMD) of each covariate between treatment groups. We chose IPTW to estimate the average treatment effect (ATE) option for application to the entire study population. Under the IPTW-ATE method, the effect estimates generated by the outcome model can be interpreted as the effects among the population if everyone had been exposed to the treatment of interest compared to the effects among the population if everyone had not been exposed (Ali et al., 2019).

In general, an SMD <0.10 after weighting indicates good balance between treatment groups for each covariate used in the balancing algorithm. Covariates with an SMD ≥0.1 require further evaluation with multiplicative terms, and may achieve further balance through multivariable adjustment in the outcome models. Using PS overlap and cut points for the SMD to make decisions about cohort comparability are part of an iterative process that involves trimming of the sample to improve overlap, variable transformation, evaluation of the interaction with other covariates, and double adjustment by inclusion in the outcome model. This process provides guidance on the influence of the variables on the associations of interest and contributes additional information to the body of evidence used to determine whether comparative analyses should proceed. Based on the results of our comparability analysis, we proceeded with multivariable Cox PH regression modeling the death hazard ratio (HR) and 95% confidence interval (CI) on bevacizumab treatment among the weighted cohort.

### 3.7.1 Subgroup Analysis

We evaluated effect modification by stratifying the OS models on age, race, and platinum status and evaluated multiplicative interaction using the -2 Log Likelihood test for heterogeneity. A chi-square p-value >0.10 was interpreted as evidence of a statistically significant interaction between treatment and the potential effect modifier.

### 3.7.2 Sensitivity Analysis

To assess the sensitivity of our results to the inclusion of patients who received bevacizumab sometime after initiation of second-line therapy with other agents, we repeated the OS analysis excluding patients who did not receive their first bevacizumab infusion within 30 days after second-line initiation of platinum combination or single agent chemotherapy. This exclusion affected only the bevacizumab group. Before implementing the sensitivity analysis, we rebalanced the reduced cohort on the IPTWs.

### 3.7.3 Internal Validity

Real-world data from secondary sources such as medical billing claims may be subject to internal threats to validity stemming from information bias and misclassification. Reliability of information collected in claims depends upon accurate submission of data by the provider. As with any electronic records system, there is no guarantee that the data are 100% reliable and accurate. However, in studies where groups are compared using causal methods, these claims weaknesses should be equal between comparison groups. Thus, any differences found between groups would be considered a true difference with equal coding bias.

Selection bias and confounding may also impact findings from observational, non-randomized studies. In our survival models, we used PS methods to control for confounding by variables available in the Medicare 5% sample. The treatment groups

compared were adjusted for differences in the conditional probability of receiving their assigned treatment based on the measured variables using the IPTW approach. Residual bias is still possible, however, due to unmeasured confounding. In addition, the validity of the survival models is dependent upon the following assumptions:

i. Conditional exchangeability given measured confounders
ii. No/negligible misclassification of exposure, outcome, or other study variables
iii. Stable unit treatment value assumption (SUTVA), which assumes outcomes are not correlated
iv. Consistency, such that exposures can be mapped to well-defined interventions
v. Positivity, wherein there are at least some exposed and unexposed individuals at each level of the confounders, and all subjects have a non-zero propensity to receive the treatment
vi. No misspecification of the models considered in these analyses: (a) the structural (i.e. weighted) model, (b) the exposure model (i.e. PS model), and (c) the censoring/survival model.

### 3.7.4 External Validity

The 5% sample is a random sample providing detailed information on a significant subset of the US population aged 65 and over. Because the sample is representative of the entire Medicare population, results may be quantitatively extrapolated to the larger source population. However, because the Medicare population is older, and often sicker, than the general US population, our findings may not be generalizable to younger healthier patients with ovarian cancer or populations in other countries with different health systems and population health characteristics.

# CHAPTER 4. RESULTS

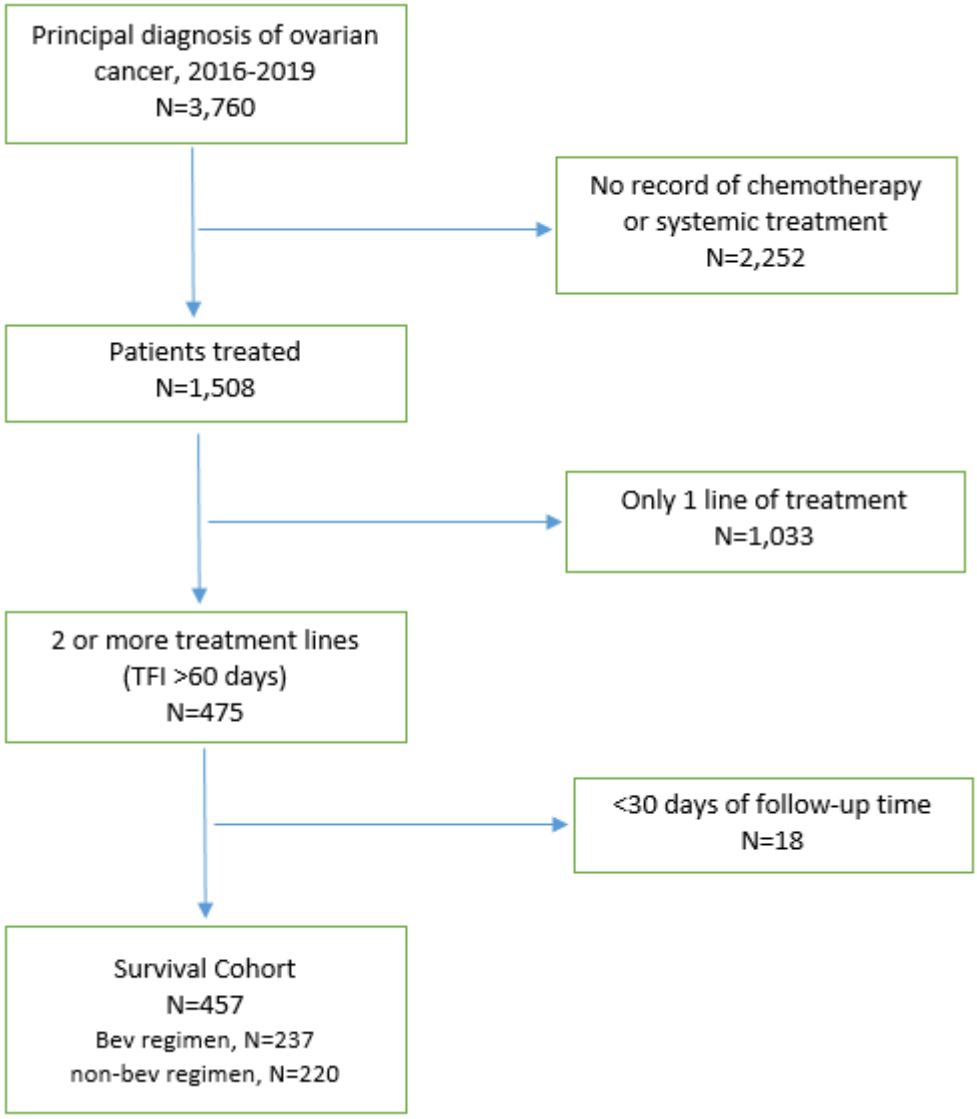
## 4.1 Description of Bevacizumab Use among Ovarian Cancer Patients

### 4.1.1 Ovarian Cancer in the Medicare Sample

A total of 3,760 individuals with a principal diagnosis of ovarian cancer were identified in the Medicare 5% LDS inpatient (IP) and outpatient (OP) files from 2016 to 2019. (**Figure 5**) Sixty percent of these (N=2,252) had no record of any pharmacologic chemotherapy or systemic treatment (e.g. bevacizumab). Of the 1,508 patients who did receive pharmacologic treatment, 68.5% (N=1,033) had a single observed treatment episode, hereafter referred to as a line of therapy (LOT), with no interruption i.e. TFI lasting more than 60 days. Forty-six percent (N=475) of treated patients had two or more treatment lines after a TFI of >60 days between the first and second observed LOT.

Eighteen out of 475 patients with ≥2 LOTs had <30 days of observable follow-up time after initiation of the second LOT, leaving 457 patients available for inclusion in the survival analysis comparing a bevacizumab treatment regimen with a non-bevacizumab regimen.

*Figure 5. Flow Chart of Ovarian Cancer Population in the Medicare 5% Sample, 2016–2019*




NOTES:
TFI = Treatment-free interval

Line of treatment = continuous episode of consecutive treatment cycles with no interruption >60 days

A cycle is assumed to be 28-days duration from the date of treatment administration.

**Table 3** shows the distribution of characteristics among the total ovarian cancer population by treatment received. More than half (52.1%) of all patients were age 65–74. The age distribution was statistically different between patients who received no treatment, those with 1 LOT, and those with ≥2 LOTs, who tended to be younger (p-value <0.001). Patients with ≥2 LOTs had a smaller proportion of patients age 80 or older (11.7% vs. 19.9% of patients with no chemotherapy and 16.5% of patients with 1 LOT). Patients younger than 75 comprised nearly two-thirds (65%) of the cohort. The majority of patients (85.5%) were non-Hispanic white (NHW), 7.4% were non-Hispanic black (NHB), 1.6% Hispanic, and 3.8% other race/ethnicity; 1.6% of the cohort were missing race.

The highest number of ovarian patients were in the South (N=1,305, 34.7%) followed by the Midwest (N=804, 21.4%), Northeast (N=754, 20.1%), and West (N=680, 18.1%), but the regional distribution differed somewhat by treatment groups (p-value <0.001). Patients with ≥2 LOTs had a greater share of patients in the Northeast (29.1%) compared to patients with 1 LOT (22.2%) or patients with no treatment (17.2%). There was a higher proportion of untreated patients in the West (19%) compared to patients with 1 LOT (16.7%) or ≥2 LOTs (16.8%). Most patients (80.1%) were in urban areas, especially those with ≥2 LOTs (85.1%) compared to rural areas, which accounted for 14.5% of all patients and 13.7% of those with ≥2 LOTs, but the distribution of urban/rural setting was not statistically different with respect to treatment. The proportion of patients living in vulnerable communities, i.e. those in the 90% percentile of the SVI, was 5.6% overall, with little variation by treatment lines. The proportion of patients who were dual eligible for Medicaid as well as Medicare was 15.7% overall and similar across treatment groups: 16.2% among patients who received no treatment, 14.6% among those with 1 LOT, and 16.0% of patients with ≥2 LOTs. Approximately 6% of the cohort were missing

zip code and therefore could not be linked for assessment of region, urban/rural setting, or community vulnerability. Less than 3% were missing information on dual eligibility. Patients with ≥2 LOTs had slightly lower percentages of missing data for region (1.5%), urban/rural setting, community vulnerability, and dual edibility (1.3% for each variable, respectively) than the rest of the cohort.

Out of the total 3,760 patients, 300 (8%) had a claim of an ovarian-related surgical procedure, leaving 92% of all patients without evidence of a surgical treatment for ovarian cancer. Just 7.1% (73/1,033) of patients with 1 LOT and 6.1% (29/475) of those with ≥2 LOTs had a record of surgery. Among the 102 treated patients who had an ovarian surgery and chemotherapy, most (N= 65) had procedures before their index treatment initiation date (i.e. date of first observed line of treatment in patients with only 1 LOT, date of second observed line of treatment in patients with ≥2 LOTs). Patients with 1 LOT had a median 5 treatment cycles (range 1–115), and patients with ≥2 LOTs had a median 14 cycles (range 2–85). Bevacizumab was administered to 26.7% (N=276) of the 1,033 patients who received 1 LOT only and 22.3% (N=106) of the 475 patients with ≥2 LOTs. Approximately half (50.9%, N=242) of patients with ≥2 LOTs received bevacizumab in the second or subsequent line. The median TFI among patients with ≥2 LOTs was 245 days (range 89–1,274 days), and the vast majority (84.0%, N=399) experienced a TFI >90 days before their second LOT. Almost two-thirds of patients with ≥2 LOTs had a TFI >180 days, an indication of platinum-sensitive disease.

In general, most patients (77.9%) had a CCI of 2 suggesting they had no recorded secondary diagnoses of any of the comorbid conditions comprising the CCI. However there were statistically significant differences in the distribution of the CCI by treatment group (p-value <0.001). The treated patients were more likely to have greater comorbidity burden as indicated by CCI >4 (18.7% for 1 LOT only, 20.8% for ≥2 LOTs)

compared to untreated patients (12.5%). The most common comorbid conditions among the cohort were metastatic carcinoma (13.9%) and second cancers (8.9%), which affected 19.8% (p-value <0.001) and 9.3% (p-value =0.05), respectively, of patients with ≥2 LOTs. Diabetes was noted in 5% of the cohort (4% without complications), chronic pulmonary disease in 3.2%, congestive heart failure in 2.1%, and renal disease in 2.1%, with similar prevalence across treatment groups. An exception was mild liver disease, which affected treated patients more than those who were not treated (2.7% vs. 1.2%, p-value =0.003).

***Table 3**. Descriptive Characteristics of Ovarian Cancer Patients According to Lines of Treatment Received in the Medicare 5% Limited Data Sample, 2016-2019*

| | | All patients | No chemo | First line (1 LOT) | Second line (≥ 2 LOTs) | p-value |
|---|---|---|---|---|---|---|
| Total ovarian cancer patients by observed treatment lines | | N=3760 (100%) | N=2252 (59.9%) | N=1033 (27.5%) | N=475 (12.6%) | |
| Characteristic | | N (%) | | | | |
| **Age** | | | | | | |
| | <65 | 484 (12.9) | 290 (12.9) | 132 (12.8) | 62 (13.1) | p < 0.0001 |
| | 65-69 | 1121 (29.8) | 677 (30.1) | 306 (29.6) | 138 (29.1) | |
| | 70-74 | 839 (22.3) | 475 (21.1) | 242 (23.4) | 122 (25.7) | |
| | 75-79 | 639 (17) | 360 (16) | 182 (17.6) | 97 (20.4) | |
| | 80-84 | 404 (10.7) | 244 (10.8) | 118 (11.4) | 42 (8.8) | |
| | >84 | 273 (7.3) | 206 (9.1) | 53 (5.1) | 14 (2.9) | |
| **Age 75 or older** | | | | | | |
| | Younger than 75 | 2444 (65) | 1442 (64) | 680 (65.8) | 322 (67.8) | p = 0.24 |
| | 75 or older | 1316 (35) | 810 (36) | 353 (34.2) | 153 (32.2) | |
| **Race/Ethnicity** | | | | | | |
| | NHW | 3216 (85.5) | 1935 (85.9) | 876 (84.8) | 405 (85.3) | p = 0.31 |
| | NHB | 280 (7.4) | 157 (7) | 78 (7.6) | 45 (9.5) | |
| | Hispanic | 59 (1.6) | 33 (1.5) | 20 (1.9) | 6 (1.3) | |
| | Other race | 144 (3.8) | 83 (3.7) | 47 (4.5) | 14 (2.9) | |

***Table 3**. Descriptive Characteristics of Ovarian Cancer Patients According to Lines of Treatment Received in the Medicare 5% Limited Data Sample, 2016-2019*

| | | All patients | No chemo | First line (1 LOT) | Second line (≥ 2 LOTs) | p-value |
|---|---|---|---|---|---|---|
| | Missing | 61 (1.6) | 44 (2) | 12 (1.2) | 5 (1.1) | |
| **Region** | | | | | | |
| | Midwest | 804 (21.4) | 489 (21.7) | 229 (22.2) | 86 (18.1) | p < 0.0001 |
| | Northeast | 754 (20.1) | 387 (17.2) | 229 (22.2) | 138 (29.1) | |
| | South | 1305 (34.7) | 797 (35.4) | 344 (33.3) | 164 (34.5) | |
| | West | 680 (18.1) | 427 (19) | 173 (16.7) | 80 (16.8) | |
| | Missing | 217 (5.8) | 152 (6.7) | 58 (5.6) | 7 (1.5) | |
| **Urban/Rural Setting** | | | | | | |
| | Urban/Metro | 3010 (80.1) | 1785 (79.3) | 821 (79.5) | 404 (85.1) | p = 0.50 |
| | Rural | 545 (14.5) | 321 (14.3) | 159 (15.4) | 65 (13.7) | |
| | Missing | 205 (5.5) | 146 (6.5) | 53 (5.1) | 6 (1.3) | |
| **Vulnerable Community *based on SVI** | | | | | | |
| | No | 3346 (89) | 1982 (88) | 923 (89.4) | 441 (92.8) | p = 0.99 |
| | Yes | 209 (5.6) | 124 (5.5) | 57 (5.5) | 28 (5.9) | |
| | Missing | 205 (5.5) | 146 (6.5) | 53 (5.1) | 6 (1.3) | |
| **Dual Eligible for Medicaid** | | | | | | |
| | No | 3066 (81.5) | 1821 (80.9) | 852 (82.5) | 393 (82.7) | p = 0.50 |
| | Yes | 592 (15.7) | 365 (16.2) | 151 (14.6) | 76 (16) | |
| | Missing | 102 (2.7) | 66 (2.9) | 30 (2.9) | 6 (1.3) | |
| **Ovarian surgery** | | | | | | |
| | No ovarian surgery | 3460 (92) | 2054 (91.2) | 960 (92.9) | 446 (93.9) | n/a |
| | Surgery before chemo | 37 (1) | 0 (0) | 33 (3.2) | 4 (0.8) | |
| | Chemo before surgery | 65 (1.7) | 0 (0) | 40 (3.9) | 25 (5.3) | |
| | Surgery only | 198 (5.3) | 198 (8.8) | 0 (0) | 0 (0) | |
| **Total treatment cycles *patients who received medication/chemotherapy** | | | | | | |
| | Mean (SD) | 10.5 (10.5) | n/a | 7.4 (8.2) | 17.3 (11.7) | p < 0.0001 |
| | Med ($25^{th}$ – $75^{th}$ Quartile) | 6 (4–14) | n/a | 5 (3–8) | 14 (9–22) | |
| | Min - max | 1–115 | n/a | 1–115 | 2–85 | |
| **Bevacizumab 1st LOT** | | | | | | |

***Table 3**. Descriptive Characteristics of Ovarian Cancer Patients According to Lines of Treatment Received in the Medicare 5% Limited Data Sample, 2016-2019*

| | | All patients | No chemo | First line (1 LOT) | Second line (≥ 2 LOTs) | p-value |
|---|---|---|---|---|---|---|
| | Non-bev regimen | n/a | n/a | 757 (73.3) | 369 (77.7) | p = 0.07 |
| | Bev regimen | n/a | n/a | 276 (26.7) | 106 (22.3) | |
| **Bevacizumab 2nd or subsequent LOT** | | | | | | |
| | Non-bev regimen | n/a | n/a | n/a | 233 (49.1) | n/a |
| | Bev regimen | n/a | n/a | n/a | 242 (50.9) | |
| **Treatment-free interval (TFI) in days *patients with a 2 LOT medication/chemotherapy** | | | | | | |
| | Mean (SD) | n/a | n/a | n/a | 301.7 (213.7) | n/a |
| | Med ($25^{th}$ – $75^{th}$ Quartile) | n/a | n/a | n/a | 245 (139–387) | |
| | Min - max | n/a | n/a | n/a | 89–1274 | |
| **TFI categories *patients with a ≥ 2 LOTs medication/chemotherapy** | | | | | | |
| | 61-90 days | n/a | n/a | n/a | 76 (16) | n/a |
| | >90 days | n/a | n/a | n/a | 399 (84) | |
| **Platinum resistant *<180 days $1^{st}$ LOT – $2^{nd}$ LOT** | | | | | | |
| | Platinum-sensitive | n/a | n/a | n/a | 309 (65.1) | n/a |
| | Platinum-resistant | n/a | n/a | n/a | 166 (34.9) | |
| **Charlson Comorbidity Index (CCI) *does not include principal ovarian cancer diagnosis** | | | | | | |
| | Mean (SD) | 3.0 (2.3) | 2.9 (2.2) | 3.2 (2.4) | 3.4 (2.6) | p < 0.0001 |
| | Med ($25^{th}$ – $75^{th}$ Quartile) | 2 (2–2) | 2 (2–2) | 2 (2–3) | 2 (2–3) | |
| | Min - max | 2–13 | 2–13 | 2–13 | 2– 13 | |
| **CCI** | | | | | | |
| | 2 | 2929 (77.9) | 1808 (80.3) | 774 (74.9) | 347 (73.1) | p < 0.0001 |
| | 3 | 198 (5.3) | 123 (5.5) | 51 (4.9) | 24 (5.1) | |
| | 4 | 66 (1.8) | 40 (1.8) | 21 (2) | 5 (1.1) | |
| | >4 | 567 (15.1) | 281 (12.5) | 187 (18.1) | 99 (20.8) | |
| **Individual Chronic Conditions** | | | | | | |
| | Congestive Heart Failure | 78 (2.1) | 48 (2.1) | 21 (2) | 9 (1.9) | p = 0.94 |
| | Chronic Pulmonary Disease | 121 (3.2) | 73 (3.2) | 31 (3) | 17 (3.6) | p = 0.84 |
| | Second Cancer | 333 (8.9) | 180 (8) | 109 (10.6) | 44 (9.3) | p = 0.05 |

***Table 3**. Descriptive Characteristics of Ovarian Cancer Patients According to Lines of Treatment Received in the Medicare 5% Limited Data Sample, 2016-2019*

| | | All patients | No chemo | First line (1 LOT) | Second line (≥ 2 LOTs) | p-value |
|---|---|---|---|---|---|---|
| | Metastatic Carcinoma | 521 (13.9) | 255 (11.3) | 172 (16.7) | 94 (19.8) | p < 0.0001 |
| | Diabetes with complications | 36 (1) | 17 (0.8) | 14 (1.4) | 5 (1.1) | p = 0.25 |
| | Diabetes without complications | 149 (4) | 98 (4.4) | 34 (3.3) | 17 (3.6) | p = 0.32 |
| | Mild Liver Disease | 68 (1.8) | 27 (1.2) | 27 (2.6) | 14 (2.9) | p = 0.003 |
| | Peripheral Vascular Disease | 46 (1.2) | 27 (1.2) | 10 (1) | 9 (1.9) | p = 0.31 |
| | Renal Disease | 80 (2.1) | 48 (2.1) | 22 (2.1) | 10 (2.1) | p = 1.00 |

NOTES:
LOT = Line of Treatment

TFI = Treatment free interval

SVI = Social Vulnerability Index

CCI = Charlson Comorbidity Index

Lines of Treatment are defined as continuous episodes of consecutive cycles without interruption >60 days.

A cycle is assumed to be 28-days duration from the date of treatment administration.

Individual Chronic Conditions with <2% prevalence not shown.

Significance for categorical variables is based on the Wald chi-square test comparing the distribution of the covariate (row percentages) between treatment strata (column percentages); missing categories were excluded from chi-square tests; covariates with <5 per each cell were not tested.

Significance for categorical variables is based on the Kruskal-Wallis test.

### 4.1.2 Patients with Recurrent Ovarian Cancer by Receipt of Bevacizumab

Among the recurrent cancer population, i.e. patients who initiated second-line therapy after a ≥60-day TFI, and who were eligible for survival analysis (N=457), more than half (51.9%, N=237) received at least one course of bevacizumab. The number of bevacizumab cycles ranged from 1 to 72, and the median was 10 (IQR 4–18). Comparison of baseline characteristics between patients who received bevacizumab and those who did not (N=220) revealed differences by age and race. **(Table 4)** Bevacizumab users had a younger age distribution and a trend toward falling percentages with each advancing 5-year age group after 70. However, after collapsing

to two age groups (age <75, ≥75), the differences were less pronounced (68.8% of the bevacizumab and 65.5% of the non-bevacizumab group were age <75) and no longer statistically significant. Patients of NHB race made up 8% of the bevacizumab treatment group compared to 11.4% of the non-bevacizumab group (p-value for heterogeneity by race/ethnicity =0.03). Due to sparse data, Hispanic and other race categories were collapsed. Five patients including 4 in the bevacizumab group were missing race.

Region, urban/rural setting, vulnerable community, and dual edibility did not vary substantially by receipt of bevacizumab in the second treatment line. The bevacizumab group had slightly higher percentages of patients in the Northeast (31.6% vs. 27.7%) and lower percentages in the West (13.9% vs. 19.1%). The proportion of patients in the South was similar between treatment groups. The distribution of urban and rural patients was not notably different by treatment with approximately 85% in urban/metro areas. The bevacizumab group had a slightly lower proportion of patients in vulnerable communities than the non-bevacizumab group (4.6% vs. 6.8%, respectively), but the difference was not statistically significant. Each treatment group had an equal proportion of patients with dual eligibility for Medicaid. About 1% percent of patients were missing data for region, urban/rural setting, SVI, and dual eligibility, but the amount of missingness did not differ by treatment group.

The total number of second-line treatment cycles received was higher in the bevacizumab group (median [IQR] 16 [11–27]) than in the non-bevacizumab treatment group (12 [9–19]) (p-value <0.001). Each group had similar probabilities of having received bevacizumab in the first observed LOT (bevacizumab group, 20.7%; non-bevacizumab group, 23.2%). However, length of the TFI and platinum status differed between the groups. Bevacizumab patients had shorter TFI (median [IQR] 217 [130–

360]) compared to 269 [161.5–421] in the non-bevacizumab group (p-value =0.002) and a greater proportion of platinum-resistant patients (41.4% vs. 29.1%, p =0.006).

The distribution of comorbidities appeared similar by treatment group.

***Table 4.*** *Descriptive Characteristics of Recurrent Ovarian Cancer Patients by Receipt of Bevacizumab in the Second or Later Line of Treatment, Medicare 5% Limited Data Sample, 2016-2019*

| | | All patients With ≥ 2 LOTs | Non-bev regimen | Bev regimen | p-value |
|---|---|---|---|---|---|
| Ovarian cancer patients who had ≥ 2 lines of treatment by receipt of bevacizumab | | N=457 (100%) | N=220 (48.1%) | N=237 (51.9%) | |
| Characteristic | | N (%) | | | |
| **Age** | | | | | |
| | <65 | 61 (13.3) | 29 (13.2) | 32 (13.5) | p = 0.014 |
| | 65-69 | 132 (28.9) | 57 (25.9) | 75 (31.6) | |
| | 70-74 | 114 (24.9) | 58 (26.4) | 56 (23.6) | |
| | 75-79 | 95 (20.8) | 41 (18.6) | 54 (22.8) | |
| | 80-84 | 41 (9) | 22 (10) | 19 (8) | |
| | >84 | 14 (3.1) | 13 (5.9) | 1 (0.4) | |
| **Age 75 or older** | | | | | |
| | Younger than 75 | 307 (67.2) | 144 (65.5) | 163 (68.8) | p = 0.45 |
| | 75 or older | 150 (32.8) | 76 (34.5) | 74 (31.2) | |
| **Race/Ethnicity** | | | | | |
| | NHW | 389 (85.1) | 190 (86.4) | 199 (84) | p = 0.031 |
| | NHB | 44 (9.6) | 25 (11.4) | 19 (8) | |
| | Hispanic/other race | 19 (4.2) | 4 (1.8) | 15 (6.3) | |
| | Missing | 5 (1.1) | 1 (0.5) | 4 (1.7) | |
| **Region** | | | | | |
| | Midwest | 83 (18.2) | 38 (17.3) | 45 (19) | p = 0.45 |
| | Northeast | 136 (29.8) | 61 (27.7) | 75 (31.6) | |
| | South | 157 (34.4) | 76 (34.5) | 81 (34.2) | |
| | West | 75 (16.4) | 42 (19.1) | 33 (13.9) | |

***Table 4.*** *Descriptive Characteristics of Recurrent Ovarian Cancer Patients by Receipt of Bevacizumab in the Second or Later Line of Treatment, Medicare 5% Limited Data Sample, 2016-2019*

| | | All patients With ≥ 2 LOTs | Non-bev regimen | Bev regimen | p-value |
|---|---|---|---|---|---|
| | Missing | 6 (1.3) | 3 (1.4) | 3 (1.3) | |
| **Urban/Rural Setting** | | | | | |
| | Urban/Metro | 389 (85.1) | 189 (85.9) | 200 (84.4) | p = 0.71 |
| | Rural | 63 (13.8) | 29 (13.2) | 34 (14.3) | |
| | Missing | 5 (1.1) | 2 (0.9) | 3 (1.3) | |
| **Vulnerable Community **based on SVI** | | | | | |
| | No | 426 (93.2) | 203 (92.3) | 223 (94.1) | p = 0.32 |
| | Yes | 26 (5.7) | 15 (6.8) | 11 (4.6) | |
| | Missing | 5 (1.1) | 2 (0.9) | 3 (1.3) | |
| **Dual Eligible for Medicaid** | | | | | |
| | No | 379 (82.9) | 183 (83.2) | 196 (82.7) | p = 0.96 |
| | Yes | 73 (16) | 35 (15.9) | 38 (16) | |
| | Missing | 5 (1.1) | 2 (0.9) | 3 (1.3) | |
| **Ovarian surgery** | | | | | |
| | No ovarian surgery | 429 (93.9) | 206 (93.6) | 223 (94.1) | p = 0.55 |
| | Surgery before chemo | 4 (0.9) | 1 (0.5) | 3 (1.3) | |
| | Chemo before surgery | 24 (5.3) | 13 (5.9) | 11 (4.6) | |
| **Total treatment cycles** | | | | | |
| | Mean (SD) | 17.6 (11.7) | 15 (9.8) | 20.1 (12.8) | p < 0.0001 |
| | Med ($25^{th}$ – $75^{th}$ Quartile) | 14 (10–23) | 12 (9–19) | 16 (11–27) | |
| | Min - max | 2–85 | 2–59 | 2–85 | |
| **Treatment cycles prior to 2L initiation** | | | | | |
| | Mean (SD) | 7.3 (6.3) | 7.8 (7.0) | 6.9 (5.4) | p = 0.34 |
| | Med ($25^{th}$ – $75^{th}$ Quartile) | 6 (4–9) | 6 (4–9) | 6 (4–8) | |
| | Min - max | 1–51 | 1–51 | 1–34 | |
| **Bevacizumab 1st LOT** | | | | | |
| | Non-bev regimen | 357 (78.1) | 169 (76.8) | 188 (79.3) | p = 0.52 |
| | Bev regimen | 100 (21.9) | 51 (23.2) | 49 (20.7) | |

***Table 4.*** *Descriptive Characteristics of Recurrent Ovarian Cancer Patients by Receipt of Bevacizumab in the Second or Later Line of Treatment, Medicare 5% Limited Data Sample, 2016-2019*

| | | All patients With ≥ 2 LOTs | Non-bev regimen | Bev regimen | p-value |
|---|---|---|---|---|---|
| **Treatment-free interval (TFI) in days** | | | | | |
| | Mean (SD) | 300.7 (213.3) | 334.1 (233.7) | 269.7 (187.6) | p = 0.002 |
| | Med ($25^{th}$ – $75^{th}$ Quartile) | 244 (139–387) | 269 (161.5–421) | 217 (130–360) | |
| | Min - max | 89–1274 | 89–1274 | 89–1262 | |
| **TFI categories** | | | | | |
| | 61-90 days | 75 (16.4) | 30 (13.6) | 45 (19) | p = 0.12 |
| | >90 days | 382 (83.6) | 190 (86.4) | 192 (81) | |
| **Platinum resistant** | | | | | |
| | Platinum-sensitive | 295 (64.6) | 156 (70.9) | 139 (58.6) | p = 0.006 |
| | Platinum-resistant | 162 (35.4) | 64 (29.1) | 98 (41.4) | |
| **Charlson Comorbidity Index (CCI)** | | | | | |
| | Mean (SD) | 3.4 (2.6) | 3.2 (2.4) | 3.6 (2.8) | p = 0.31 |
| | Med ($25^{th}$ – $75^{th}$ Quartile) | 2 (2–3) | 2 (2–3) | 2 (2–3) | |
| | Min - max | 2–13 | 2–10 | 2–13 | |
| **CCI categories** | | | | | |
| | 2-3 | 357 (78.1) | 177 (80.5) | 180 (75.9) | p = 0.24 |
| | >3 | 100 (21.9) | 43 (19.5) | 57 (24.1) | |
| **Individual Chronic Conditions** | | | | | |
| | Chronic Pulmonary Disease | 15 (3.3) | 6 (2.7) | 9 (3.8) | p = 0.52 |
| | Second Cancer | 41 (9) | 21 (9.5) | 20 (8.4) | p = 0.68 |
| | Metastatic Carcinoma | 91 (19.9) | 39 (17.7) | 52 (21.9) | p = 0.26 |
| | Diabetes without complications | 17 (3.7) | 5 (2.3) | 12 (5.1) | p = 0.12 |
| | Mild Liver Disease | 14 (3.1) | 6 (2.7) | 8 (3.4) | p = 0.69 |
| | Renal Disease | 9 (2) | 3 (1.4) | 6 (2.5) | p = 0.37 |

***Table 4.*** *Descriptive Characteristics of Recurrent Ovarian Cancer Patients by Receipt of Bevacizumab in the Second or Later Line of Treatment, Medicare 5% Limited Data Sample, 2016-2019*

| | | All patients With ≥ 2 LOTs | Non-bev regimen | Bev regimen | p-value |
|---|---|---|---|---|---|

NOTES:
LOT = Line of Treatment

TFI = Treatment free interval

SVI = Social Vulnerability Index

CCI = Charlson Comorbidity Index

Lines of Treatment are defined as continuous episodes of consecutive cycles with no interruption of >60 days.

A cycle is assumed to be 28-days duration from the date of treatment administration.

Individual Chronic Conditions with <2% prevalence not shown.

Significance for categorical variables is based on the Wald chi-square test comparing the distribution of the covariate (row percentages) between treatment strata (column percentages); missing categories were excluded from chi-square tests.

Significance for categorical variables is based on the Kruskal-Wallis test.

## 4.2 Overall Survival among Patients with Recurrent Ovarian Cancer

### 4.2.1 Comparability of the Bevacizumab and non-Bevacizumab Patients

Prior to PH regression modeling, we used logistic regression to model the PS (conditional probability of receiving bevacizumab) and derived the IPTW to balance the cohort with respect to baseline characteristics. The PS model included age (<75, ≥75), race/ethnicity (NHW, NHB, Hispanic or other race, missing), residential setting (urban, rural, missing), vulnerable community (yes, no, missing), dual eligibility for Medicaid (yes, no, missing), number of treatment cycles received prior to starting the index LOT (continuous), receipt of bevacizumab in the prior LOT (yes, no), TFI (continuous days), platinum status (platinum-sensitive [TFI ≥180 days], platinum-resistant [TFI <180 days]), comorbidity burden (CCI 2-3, CCI >3), a diagnosis of a second cancer, metastatic cancer, COPD, diabetes, mild liver disease, or renal disease, at baseline. A common

support region of 0.05 to 0.95 was specified in the PSMATCH procedure, and all observations fell between 0.18 and 0.89, therefore no observations were dropped. After weighting, the mean propensity score was 0.5193 (SD 0.1280) in the bevacizumab group and 0.5184 (SD 0.1290) in the non-bevacizumab group (mean difference, treated – control, 0.0009). The SMDs for all covariates, particularly those with significantly different distributions before weighting (e.g. age, race, TFI, platinum status, and receipt of bevacizumab in the 1$^{st}$ LOT), were <0.10, indicating a well-balanced cohort. **Figure 6** shows the SMDs for selected variables in the PS model **(Figure 6a)** and overlapping density plots of the PS by treatment group **(Figure 6b)**.

*Figure 6. Propensity Score Diagnostics*

**Figure 6a.** Standard Mean Differences after PS Weighting

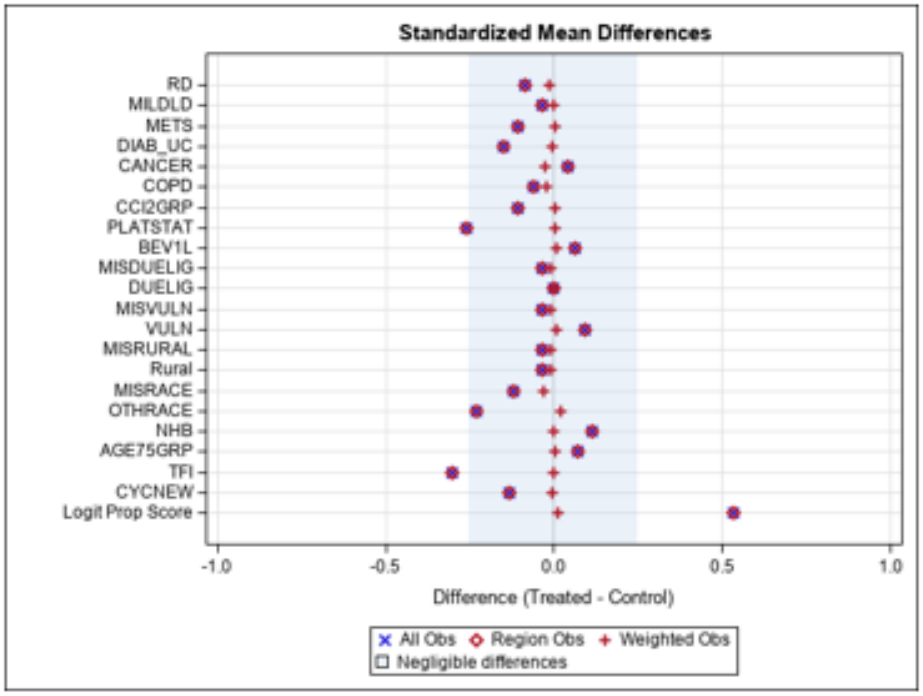
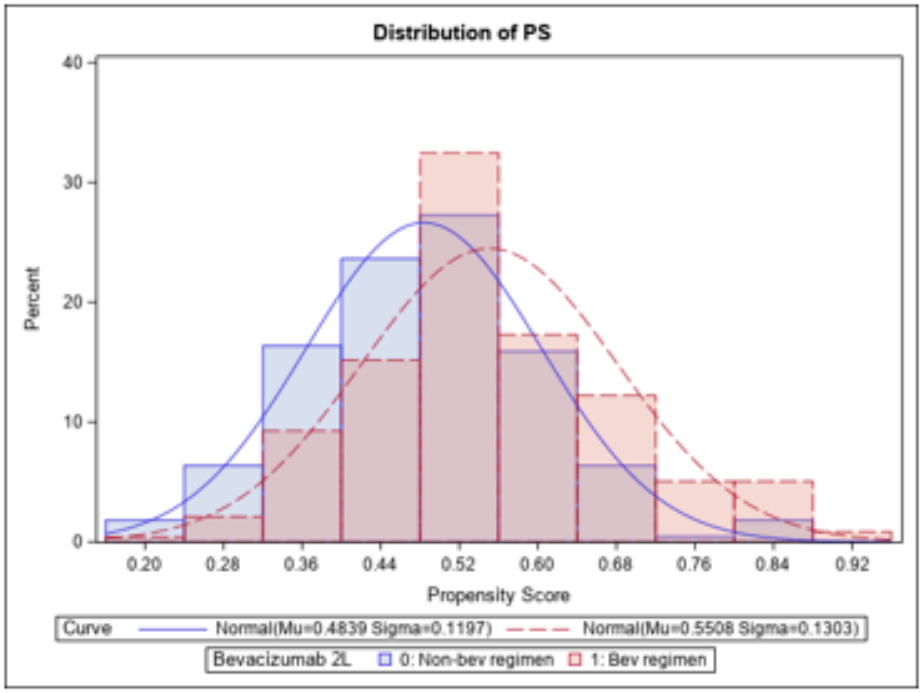


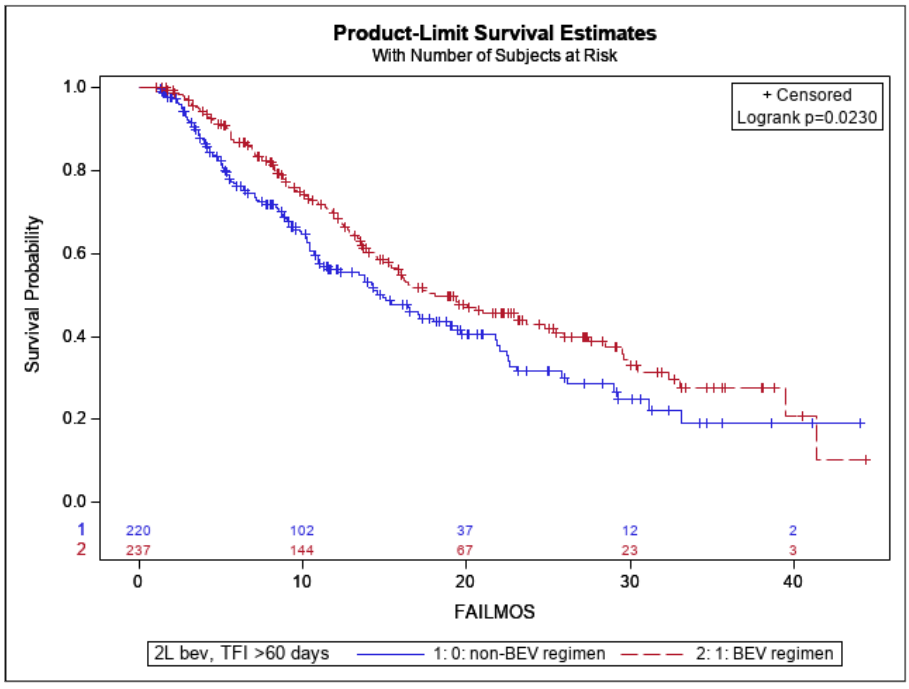

**Figure 6b.** Propensity Scores by Treatment Group after Weighting



### 4.2.2 Overall Survival and Weighted Cox PH Regression Models

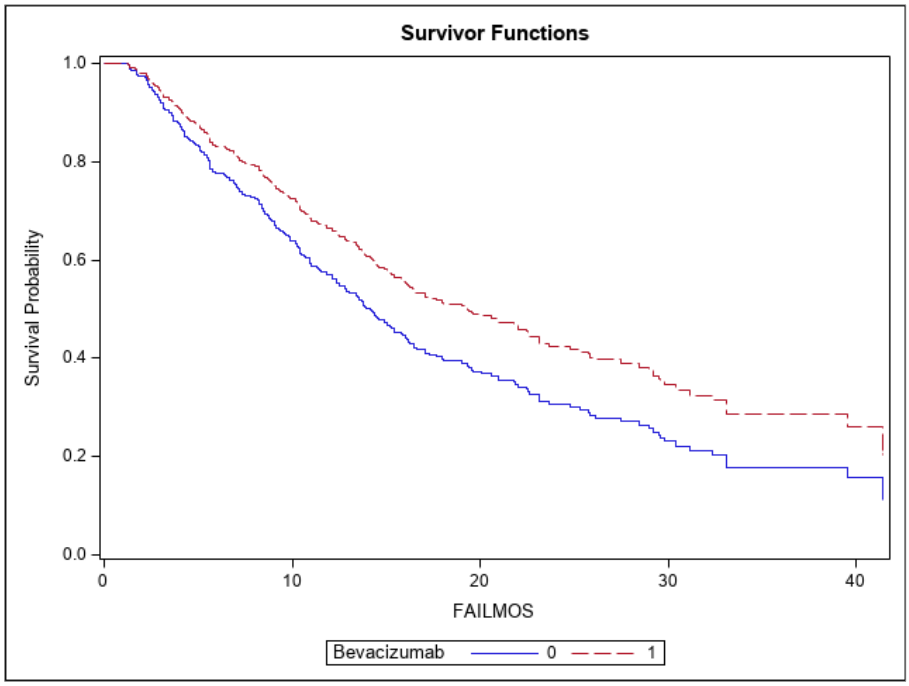
Individual follow-up time from the start of second-line treatment ranged from 1.1 to 44.4 months (median 10.9, IQR 5.4–19.2), totaling 6,084.6 person months in the population. Of 457 patients in the analysis, 232 (50.8%) died during follow-up including 120/237 (50.7%) in the bevacizumab group and 112/220 (50.9%) in the referent group. The Kaplan-Meier curves **(Figure 7)** suggested a significant survival advantage among patients in the bevacizumab group, who experienced a median OS of 18.1 months (95% CI 15.3–24.8) compared to the non-bevacizumab group (median OS 14.9, 95% CI 11.0–19.4) (log-rank p-value =0.02). An unadjusted (unweighted) Cox PH model estimated a 26% lower risk of death among the bevacizumab group relative to the non-bevacizumab group (HR 0.74, 95% CI 0.57–0.96). Interaction between treatment and follow-up time was not statistically significant indicating that the PH assumption was satisfied.

***Figure 7.*** *Kaplan-Meier Survival by Receipt of Bevacizumab in the Second LOT*



The significant inverse association between bevacizumab and risk of death persisted among the IPT-weighted cohort (HR 0.72, 95% CI 0.60–0.87), but there was statistical evidence of violation of the PH assumption (time*treatment group interaction chi-square p-value =0.01), although the plot of the survivor functions was consistent with the assumption of proportionality between the treatment groups. **(Figure 8)**

***Figure 8.*** *Cox PH Survivor Function Comparing Treatment Groups*

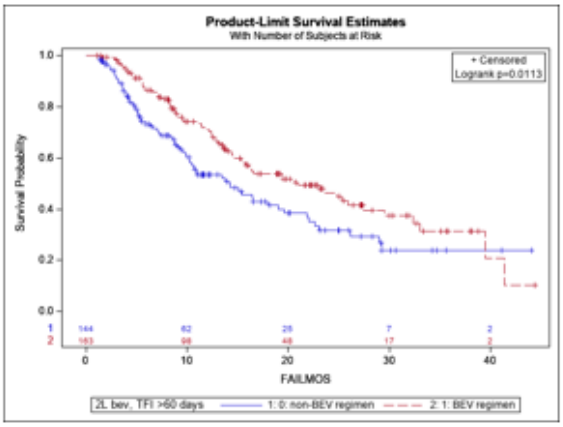



### 4.2.3 Effects of Age, Race, and Platinum Status

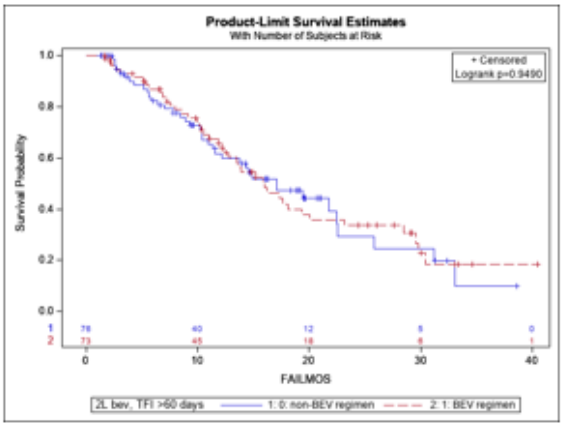
**Figure 9** shows unadjusted KM survival curves among the population by age, race, and platinum status. As shown, the survival benefit from use of bevacizumab in the second or later LOT appears confined to women age ≤75 and to NHW women. A favorable effect of bevacizumab on OS was apparent among patients with both platinum-sensitive and platinum-resistant disease in this sample, although the difference in survival was attenuated somewhat in the latter group.

***Figure 9.*** *Kaplan-Meier Survival by Treatment Group, Age, Race, and Platinum Status*

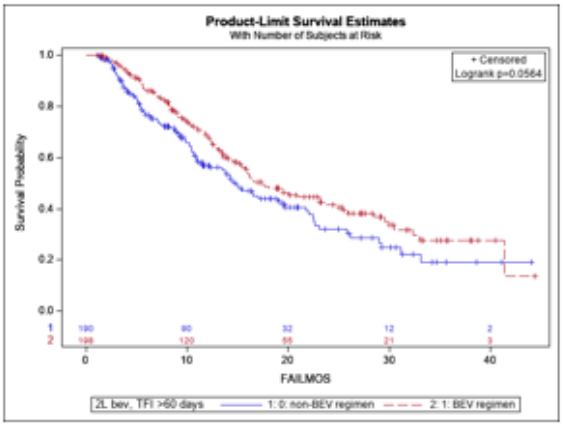
Age <75



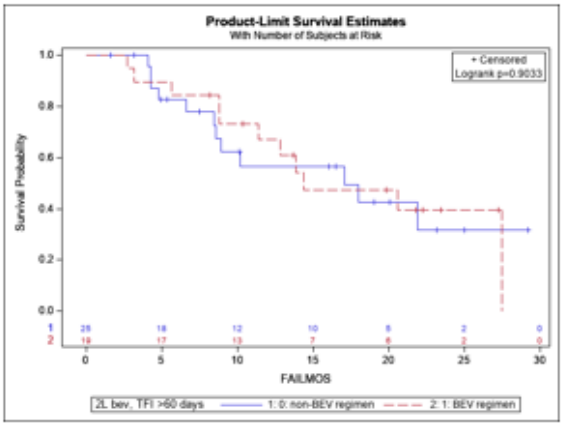

Age ≥75



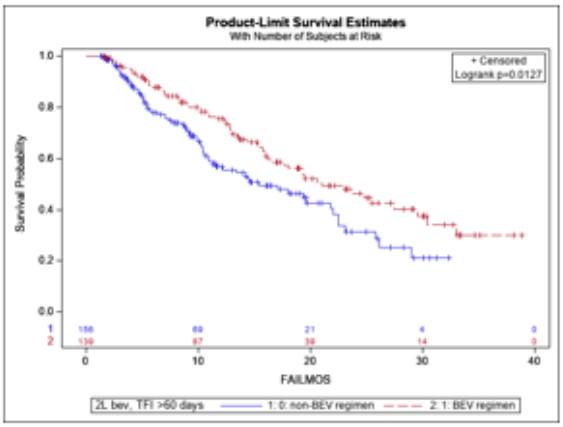

NHW



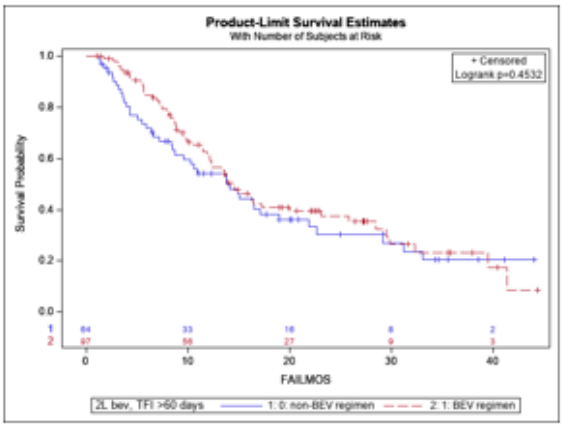

NHB




Platinum-sensitive




Platinum-resistant



Weighted Cox models stratified by age, race, and platinum status were consistent with the results of the KM survival curves. **(Table 5)** Inverse association between bevacizumab and risk of death was confined to patients younger than age 75 (HR 0.62, 95% CI 0.78–0.78), and not apparent among those age 75 or older (HR 0.97, 95% CI 0.71–1.32) (p-value for interaction =0.02). The association was also attenuated among NHB patients (HR 0.96, 95% CI 0.54–1.71) as compared to NHW (HR 0.76, 95% CI 0.62–0.92), but statistical evidence for effect modification by race was lacking (p-value for interaction =0.45). The association between bevacizumab and OS appeared somewhat stronger among women with platinum-sensitive disease (HR 0.67, 95% CI 0.52–0.85) than those with platinum-resistant disease (HR 0.83, 95% CI 0.63–1.09), but was not statistically different (p-value =0.25).

***Table 5.*** *Overall Survival Associated with Bevacizumab Use According to Age, Race/Ethnicity, and Platinum Status among Women with Recurrent Ovarian Cancer*

| Treatment group | N deaths from any cause / person time (months) | HR (95% CI) [a] |
|---|---|---|
| **All Women** | | |
| No Bevacizumab | 112 / 2537.1 | 1.00 (Referent) |
| Bevacizumab | 120 / 3547.5 | 0.72 (0.60, 0.87) |
| | | |
| **Stratified on Age** | | |
| Age <75 years | | |
| No Bevacizumab | 74 / 1604.7 | 1.00 (Referent) |
| Bevacizumab | 78 / 2481.1 | 0.62 (0.50, 0.78) |
| Age ≥75 years | | |
| No Bevacizumab | 38 / 932.4 | 1.00 (Referent) |
| Bevacizumab | 42 / 1066.4 | 0.97 (0.71, 1.32) |
| | | *Interaction p-value [b] =0.02* |
| **Stratified on Race** [c] | | |
| NHW | | |
| No Bevacizumab | 97 / 2225.6 | 1.00 (Referent) |
| Bevacizumab | 102 / 2995.5 | 0.76 (0.62, 0.92) |
| NHB | | |
| No Bevacizumab | 12 / 298.7 | 1.00 (Referent) |
| Bevacizumab | 11 / 276.3 | 0.96 (0.54, 1.71) |
| | | *Interaction p-value [b] =0.45* |

| **Stratified on Platinum Status** | | |
|---|---|---|
| Platinum-sensitive | | |
| No Bevacizumab | 71 / 1668.6 | 1.00 (Referent) |
| Bevacizumab | 61 / 2074.4 | 0.67 (0.52, 0.85) |
| Platinum-resistant | | |
| No Bevacizumab | 41 / 868.5 | 1.00 (Referent) |
| Bevacizumab | 59 / 1473.1 | 0.83 (0.63, 1.09) |
| | | *Interaction p-value [b] =0.25* |

NOTES:

[a] IPTW-ATE adjusted Cox PH model

[b] P-value estimated from the –2 log likelihood test comparing a model with interaction terms to a reduced model of main effects only

[c] 24 patients with race/ethnicity other than NHW or NHB excluded from model

### 4.2.4 Sensitivity Analysis

To assess the sensitivity of these findings to delayed initiation of bevacizumab in the course of the second or later LOT, we repeated the OS analysis excluding patients (N=65) who did not receive their first bevacizumab infusion within 30 days of second-line initiation of platinum combination or single agent chemotherapy. After IPTW rebalancing of the reduced cohort (N=392), the favorable effect of bevacizumab persisted in the weighted Cox model, although the magnitude of effect was slightly attenuated (HR 0.80, 95% CI 0.66–0.97). Results stratified on age were also qualitatively similar to those from the main analysis with a pronounced difference in the HRs between older and younger patients (age <75: HR 0.69, 95% CI 0.54–0.87; age ≥75: HR 1.10, 95% CI 0.78–1.50; p-value for interaction =0.03). The difference between NHB and NHW patients narrowed (NHB: HR 0.67, 95% CI 0.78–1.50; NHW: HR 0.86, 95% CI 0.70–1.06; p-value =0.55), though the data became too sparse to support any conclusion. The difference between platinum-sensitive and platinum-resistant patients widened a bit while remaining non-significant (platinum-sensitive: HR 0.73, 95% CI 0.57–0.94; platinum-resistant: HR 0.98, 95% CI 0.72–1.34; p-value =0.15).

## CHAPTER 5. DISCUSSION

This descriptive study provides a snapshot in time of ovarian cancer treatment utilization, in particular, uptake of bevacizumab and its potential impact on overall survival in a representative sample of the US Medicare population from 2016 to 2019. Observed rates of standard ovarian-related procedures and treatments, including platinum-based chemotherapy and other systemic treatments, were low in the population. Less than 40% of patients with a principal diagnosis of ovarian cancer received any type of chemotherapy or systemic treatment between 2016 and 2019. Among treated patients with recurrent disease who received more than one line of therapy during the study period, more than half received bevacizumab. Although, older patients and Black patients were less likely to receive bevacizumab compared to their younger or white counterparts. Use did not vary by rural setting, community vulnerability, or dual eligibility for Medicaid in the population. Among the recurrent patient population, bevacizumab in the second or later line was associated with improved survival and a statistically significant lower risk of death relative to treatment regimens without bevacizumab. However, the survival benefit appeared to be confined to women younger than age 75. The association was also more pronounced among NHW patients compared to NHB and those with platinum-sensitive disease, but statistical evidence of effect modification by race or platinum status was lacking.

Less than 10% of the study sample had an ovarian-related surgical procedure. The low rate for surgery was not entirely unexpected given that the sample was comprised of predominantly prevalent cases at various stages in their patient journey, many of whom

would have had surgery prior to the observation period. Most ovarian cancer patients with access to high-quality care would be offered PDS followed by platinum-based chemotherapy or, alternatively, neoadjuvant chemotherapy and IDS, according to guidelines and recommendations. We previously reported that 85% of newly-diagnosed ovarian cancer patients treated at the Hollings Cancer Center, an NCI-designated Cancer Center in Charleston, South Carolina, received PDS or IDS, and 82% received a chemotherapy sequence, although racial disparities in the rates of surgery and chemotherapy were evident (Hildebrand et al., 2019). In the Medicare sample for the current study, less than half (40%) of all ovarian cancer patients had a record of chemotherapy or systemic treatment. The 60% who had no evidence of a pharmacologic treatment for ovarian cancer could be a mixed population of survivors who completed treatment prior to the study and were thus cancer-free during the study period, patients with early-stage or indolent disease for whom chemotherapy would not have been indicated, as well as patients who, for reasons unknown, were not treated. The lower proportion of metastatic cancer observed in patients without treatment supports this conclusion. Due to the limitations of the dataset and the inability to look back in time to ascertain the complete treatment history of patients since diagnosis, we cannot fully characterize this group of patients to understand the reasons for the lack of treatment among the majority of patients.

Health of the patient, functional status, and presence of comorbidities are important factors that influence cancer treatment decisions in the elderly (Balducci & Extermann, 2000). Declining health due to age-related chronic conditions may increase risk of side effects and complications, and the benefits of treatment may not outweigh the risks in a person with decreased life expectancy (Balducci & Ershler, 2005). In our sample, comorbidity burden was not associated with a lower probability of receiving

chemotherapy or systemic treatment. Contrary to expectations, the proportion of patients with a CCI >4 was higher among patients who received treatment. However, this appears to be largely driven by metastatic disease, which was substantially higher among the treated patients compared to those who were not treated. Secondary diagnoses of cardiovascular disease and other chronic conditions appeared infrequent based on assessment of the comorbidities at index. It is also possible that the timing of our assessment of comorbidities at the point of second-line treatment initiation for subjects in the recurrent disease cohort, first-line treatment initiation for those with only one line, or the first claim with a principal diagnosis of ovarian cancer for those who received no treatment, did not capture all comorbidities.

Rates of bevacizumab use among the treated population in our study were higher than reported elsewhere. In our sample, 24% of women with 1 observed LOT and 32% of patients with ≥2 LOTs received bevacizumab. Among a population of commercially insured ovarian cancer patients studied from 2010–2018, bevacizumab increased with each advancing line of treatment from 6% in the first-line, 9% in the second-line, 12% in the third line, and 29% in the fourth or later line of treatment (Beachler et al., 2020). Comparing our findings to these, we can infer that either our population was made up of very advanced patients receiving a 4$^{th}$ or later LOT or that bevacizumab has increased in use since the previous study. Although these two scenarios are not mutually exclusive, the latter explanation seems more plausible given the difference in time periods with respect to bevacizumab approval and recommendations. An earlier study found that 6% of incident ovarian cancer patients received bevacizumab between 2006 and 2011, which was prior to FDA approval for ovarian cancer, though it was already approved for other indications at that time (Gamble et al., 2022). The higher rates observed in our

sample suggest a trend of rising use of bevacizumab for advanced ovarian cancer in real world practice.

Our finding of a survival advantage with use of bevacizumab and OS in patients beginning a second or later LOT is qualitatively consistent with results from four phase 3 randomized trials which found HRs in the range of 0.83 to 0.97 comparing bevacizumab plus chemotherapy to the standard regimens of platinum doublet for platinum-sensitive disease or single agent chemotherapy for platinum-resistant disease (Aghajanian et al., 2012; Aghajanian et al., 2015; Coleman et al., 2017; Pignata et al., 2018; Pujade-Lauraine et al., 2014). While these pivotal studies demonstrated the efficacy of bevacizumab for delaying disease progression, none reached statistical significance for prolonging overall survival. When results were pooled together in a recent meta-analysis, however, the OS benefit was statistically significant (HR 0.88, 95% CI 0.79–0.99) (Liu et al., 2021). Evidence of real-world effectiveness of bevacizumab for OS in recurrent ovarian cancer is scant. Most RWD studies to date are small, single-center, retrospective chart review studies without non-bevacizumab comparator groups but reporting median survival from 20 to 29 months (Demirkiran et al., 2023; Gallego et al., 2021; Khanmammadov et al., 2024; O'Malley et al., 2011). One multi-institutional single-arm study in South Korea reported OS of 22 months in platinum-resistant patients treated with bevacizumab (Lee et al., 2019). The paucity of evidence comparing the effectiveness of adding bevacizumab to chemotherapy for recurrent ovarian cancer in real-world practice highlights a need for additional data sources with sufficient numbers and a broad array of potential confounders to confirm the OS benefit and inform clinical practice. This study provides an example of how RWD, in particular, billing data, could be leveraged to provide a more complete picture of treatment utilization, safety, and effectiveness, of newer therapies as they are implemented in real-world practice.

Further research is needed among older ovarian cancer patients. The age distribution of the clinical trials is considerably younger with median age ranging from 47 to 67 (Liu et al., 2021). Furthermore, rates of bevacizumab use among older ovarian cancer patients is lower than in younger patients. More than two-thirds (68.8%) of patients receiving bevacizumab in the second LOT in our study were younger than 75. This is consistent with other real-world studies, which reported lower rates among the older patients (Amadio et al., 2020; Gamble et al., 2022). Gamble et al found the lowest rates of bevacizumab in patients ≥70 (Gamble et al., 2022). The lack of clinical evidence to support a favorable benefit to risk profile in elderly patients likely impacts prescribing practices as mentioned earlier (Balducci & Ershler, 2005; Balducci & Extermann, 2000). Results of our survival analysis suggested that bevacizumab may not be as effective for prolonging survival in patients age ≥75 as in younger women, and thus provide some justification for the difference in utilization by age. More aggressive treatment with multiple pharmacologic agents may pose even greater risk of side effects, serious adverse events, and reduced health-related quality of life. Older patients may also have different goals of treatment than younger patients with a longer life expectancy. More studies are needed to explore the concerns and priorities of older patients with advanced ovarian cancer in order to better understand their needs and preferences when considering treatment options.

The sparse data on racial/ethnic minorities in this sample may reflect the disproportionate burden of ovarian cancer among the NHW population, who have lower incidence than NHB or Hispanic women ("American Cancer Society Cancer Facts & Figures 2023," 2023). Minority populations, however, have worse prognosis and lower survival after diagnosis, partly due to the deleterious effects of prolonged stress attributable to social determinants that affect access to optimal care (Bristow et al., 2013;

Karanth et al., 2019; Terplan et al., 2009). We did not find our measures of SDOH, including community vulnerability as measured by the SVI, and dual eligibility for Medicaid, to be associated with receipt of bevacizumab in the treated population. However race was statistically associated. Therefore, it is important for future studies to quantify the impacts of social factors on access to care when examining cancer treatment outcomes by race and ethnicity, and to avoid speculation regarding biological differences, which can lead to wrong conclusions and perpetuate biases in medical practice that can further harm vulnerable patients.

The platinum-free interval, calculated in clinical practice as days between the end of the first-line platinum cycle and initiation of a new LOT for relapsed disease, is an important prognostic factor and strong predictor of OS (Luvero et al., 2019). In accordance with the fifth Ovarian Cancer Consensus Conference held in Tokyo in 2015, we assessed the TFI, irrespective of whether the pre-relapse treatment cycle was a platinum or other agent, but applied the same algorithm for defining platinum-resistant disease vs. platinum-sensitive (<180 vs. ≥180 days between LOTs). We found similar estimates of effect for bevacizumab between platinum-sensitive and platinum-resistant patients in the weighted Cox regression analysis. Although, a non-statistically significant difference was suggested after exclusion of patients who did not receive their first dose of bevacizumab within 30 days their other second-line chemotherapy agents. The clinical trials found benefit for both platinum-sensitive (Aghajanian et al., 2015; Coleman et al., 2017) and platinum-resistant (Pignata et al., 2018) disease. Our findings do not provide strong evidence that advanced ovarian cancer patients with platinum-resistant recurrent disease do not benefit from the addition of bevacizumab to their treatment regimen.

The main strength of this study is its external validity. The Medicare LDS is a random sample drawn from the entire population enrolled in Medicare in the US and represents

elderly people of all regions and backgrounds. However, because the Medicare population is older, it is more affected by age-related chronic diseases than the general US population, and likely a sicker population. Therefore, our findings may not be generalizable to younger healthier patients with ovarian cancer or populations in other countries with different health systems and/or population health characteristics. This study may also underestimate the impact of SDOH associated with lack of health insurance, since all patients in the sample had a minimum of health insurance coverage through Medicare. Other populations of younger patients may show an increase in the impact of SDOH since those who are uninsured are represented in that age group.

The lack of prognostic factors such as stage at diagnosis and histology is a major limitation of using Medicare claims data for oncology research. We focused on recurrent disease under the assumption that once a patient initiates a new line of therapy after a treatment-free period, they are likely facing disease relapse or progression. From this point, stage at initial diagnosis may be less predictive of OS than it is from the time of the primary diagnosis. Others previously developed and validated an algorithm for use in claims data based in part on this premise, correctly classifying 97% of patients with advanced (Stage III or IV) ovarian cancer using a >60-day TFI, assuming a 28-day cycle length, and the administration of a targeted therapy (e.g. bevacizumab or a PARP inhibitor) (Beachler et al., 2020; Esposito et al., 2019). We applied a similar algorithm for inclusion in our survival analysis requiring a TFI of >60 days for entry into the analysis cohort assuming a 28-day cycle. However, because bevacizumab was the exposure of interest, we retained patients who received only the standard cytotoxic or systemic agents commonly used in the treatment of advanced disease as the referent for the contrast of interest. Analysis of the SMDs of covariates between the treatment groups after weighting indicated excellent comparability to proceed with the survival analysis. It

is important to note that PS methods, unlike randomization, do not control for unmeasured confounding, only confounding by measured variables. Investigation of residual bias due to unmeasured confounding was beyond the scope of this study. Therefore, caution is warranted in the interpretation of treatment effects on OS. Despite the limitations of the study, our hypothesis of a survival benefit associated with bevacizumab was confirmed. Therefore, we deem our methods for defining a recurrent ovarian cancer cohort to study the effects of treatment using claims data to have good validity and reliability.

Medication assessment in this study was based on CMS HCPCS coding available in the Medicare 5% sample. Although most chemotherapy treatments for cancer are administered intravenously in the outpatient setting, some newer targeted therapies including PARP inhibitors may be dispensed in tablets or pills, which were not available in the study source files. It is possible that unmeasured use of PARP inhibitors in the study population could have introduced bias in the association between bevacizumab and OS if treatment groups had disproportionate use of PARP inhibitors. PARP inhibitors have been shown to be effective for extending survival, particularly in patients with BRCA-mutated relapsed or recurrent platinum-sensitive ovarian cancer (Luvero et al., 2019). Studies suggest that BRCA mutations (germline or somatic) are more prevalent in recurrent than in incident ovarian cancer, potentially affecting more than half of this patient population (Gelmon et al., 2011; Ledermann et al., 2016). Because PARP inhibitors are now incorporated into treatment guidelines for recurrent ovarian cancer, a portion in our study population should have received them. Ideally, future studies should assess the combined use of both bevacizumab and PARP inhibitors while quantifying the effects of each and/or both on survival outcomes.

## CONCLUSION

The vast majority of ovarian cancer patients experience rapid disease progression or relapse and eventually die from their disease. This study contributes knowledge of how targeted VEGF inhibition is being used for treatment of ovarian cancer in real-world clinical practice and its effectiveness for extending overall survival in patients with advanced disease. In a representative real-world dataset with limited clinical variables available, our hypothesis that bevacizumab would be associated with better OS in the recurrent disease setting was confirmed. The finding of a significantly lower risk of death associated with bevacizumab in recurrent patients younger than age 75 is consistent with evidence from randomized trials and observational studies. Bevacizumab is an essential cancer medicine and important component of ovarian cancer management. Until recently, relapsed patients had few options for extending survival. This study supports current ovarian cancer treatment guidelines incorporating bevacizumab into standard chemotherapy regimens for the purpose of improving survival among women with recurrent ovarian cancer. The lack of benefit among patients age ≥75 contributes evidence that may be useful to inform personalized treatment approaches for the oldest of patients.

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# APPENDICES

## APPENDIX A. Systematic Review Methods

### A.1 Search Strategy

PubMed, Scopus, and CINAHL databases were searched in consultation with a medical research librarian for peer-reviewed observational studies of bevacizumab use in ovarian cancer using Medical Subject Headings (MeSH) and interchangeable terms for the disease and drug of interest (bevacizumab or Avastin®). To rule out randomized trials, terms for “real world”, observational, and non-interventional studies were included. Results were filtered on human studies published in English. The search strategy was initially executed in February 2022 and updated in May 2023.

### A.2 Study Selection

The study selection process was guided, though not strictly dictated, by PICOS criteria (patient, intervention, comparisons, outcomes, and study design)(Stern, Jordan, & McArthur, 2014). Studies among ovarian cancer patients treated in real-world practice were sought that evaluated bevacizumab, with or without a non-bevacizumab comparator, according to one of the following outcomes: PFS; overall survival (OS); overall response rate (ORR); safety measure e.g. adverse drug reaction (ADR) or adverse event (AE). We aimed to synthesize the peer-reviewed observational research evidence and therefore excluded congress proceedings and phase 2 or 3 clinical trials. In addition, studies of bevacizumab for cancer sites other than ovarian, fallopian tube or peritoneal, or not reporting any of the outcomes of interest (PFS, OS, ORR, safety endpoints i.e. adverse events [AEs]) were excluded. No restrictions were placed on treatment setting (first-line or recurrent disease), stage at diagnosis, ovarian cancer histology, or other clinical parameters.

Search results were exported to EndNote® and duplicate records removed. All unique records were screened by title and abstract, and relevant studies were selected for retrieval and full-text review. The decision of whether to include in this systematic review was based upon the pre-determined PICOS criteria. Only original research studies were included. However, reference lists of review articles identified via the search strategy were manually searched to identify additional eligible reports.

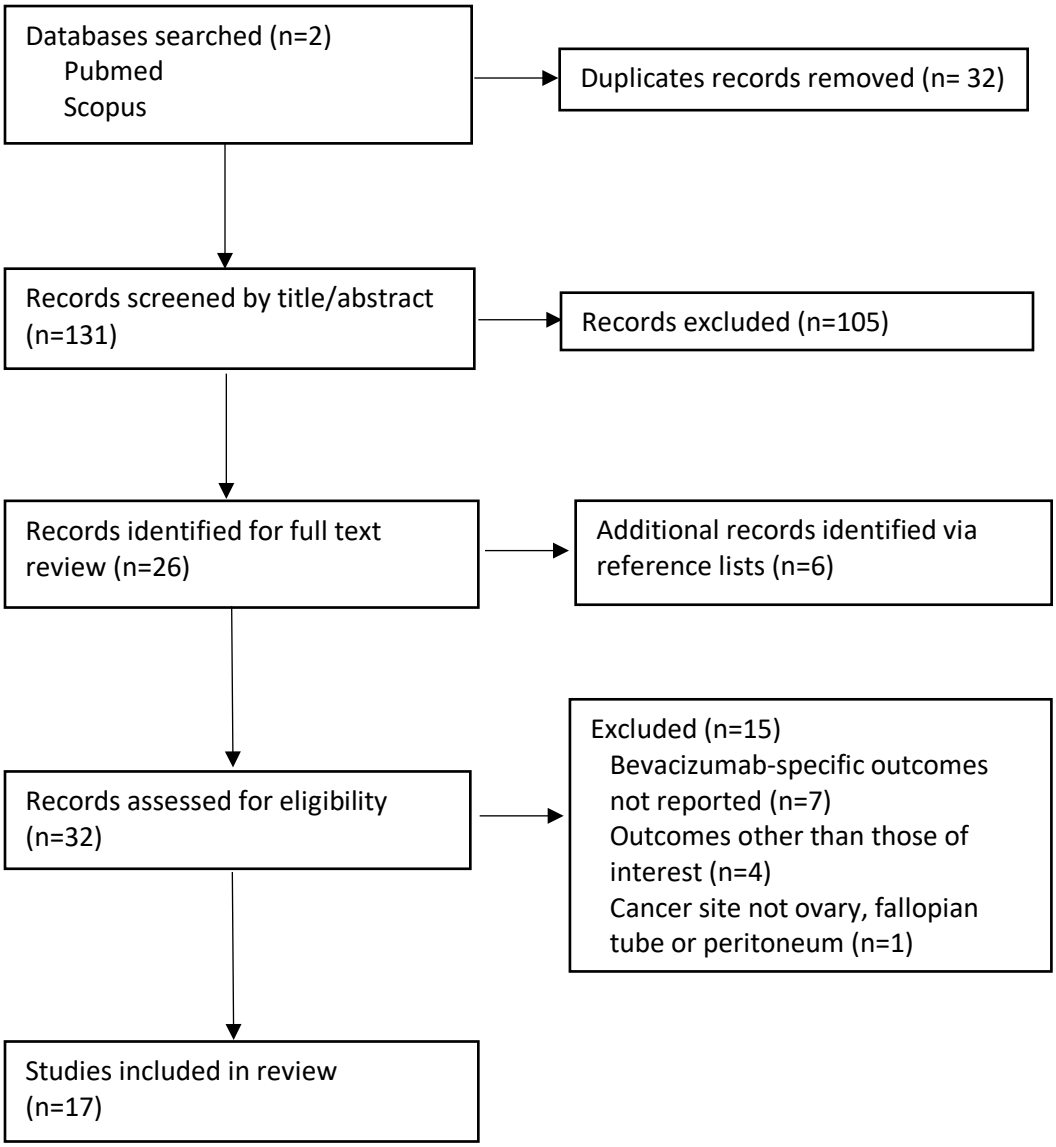
The search strategy yielded 163 records from PubMed (n=35) and Scopus (n=128); no additional records were identified from CINAHL. From these, 32 duplicates were removed using the automated tool in EndNote. As shown in **Figure A.1** Flow diagram of study selection, screening of titles and abstracts eliminated 105 records, which were deemed ineligible due to cancer site other than ovarian/tubal/peritoneum, experimental design or article type (review, editorial, letter, or abstract only. Manual searching of reference lists of published reviews yielded an additional 6 potentially eligible records, bringing the total number of records identified for retrieval and full-text review to 32. After further exclusion of 14 articles, which were ineligible according to inclusion criteria and 1 redundant report from an included study based on the same population, the final study sample consisted of 17 articles.

### A.3 Data Extraction and Analysis

Relevant information was extracted from each study into pre-formatted tables including first author, year of publication, study design (retrospective, prospective cohort), data source (national cancer database e.g. SEER, state registry, hospital database, health insurance claims), sample size, study population (country or region, median age at diagnosis), treatment setting (first-line maintenance, recurrent disease), treatment regimens evaluated (bevacizumab, non-bevacizumab), outcomes reported (PFS, OS, ORR, AEs), subgroup analyses, and other relevant data. Study quality was assessed

using the Downs and Black checklist for assessment of methodologic quality of non-randomized studies(Downs & Black, 1998), which is a numerical scoring system based on 27 items across 5 domains: reporting, external validity, bias, confounding, and power. Studies scoring higher than the median were considered “better quality” versus those with lower scores. Characteristics of the final study sample were tabulated with descriptive statistics (percentages, proportions), and a qualitative synthesis of results was performed.

**Figure A.1** Flow diagram of study selection



| **Table A.1** Characteristics of real-world studies of bevacizumab in ovarian cancer | |
|---|---|
| **Total number of studies** | 17 |
| **Study Design, N (%)** | |
| Retrospective | 10 (59) |
| Prospective | 7(41) |
| **Data Source and Type, N (%)** | |
| Single hospital or institution | 10 (59) |
| Multiple institutions | 6 (35) |
| Claims databases | 1 (6) |
| **Sample size** | |
| Median (IQR) | 299 (70–441) |
| Greater than median, N (%) | 8 (47) |
| **Treatment regimens evaluated, N (%)** | |
| Bevacizumab-containing regimen | 17 (100) |
| Non-bevacizumab comparator | 6 (35) |
| **Treatment setting, N (%)** | |
| First-line (initial response and maintenance) | 11 (65) |
| Recurrent disease | 9 (53) |
| Platinum sensitive and resistant | 8 (47) |
| Platinum resistant only | 6 (35) |
| **Outcomes, N (%)** | |
| PFS | 17 (100) |
| OS | 10 (59) |
| ORR | 9 (53) |
| Safety | 14 (82) |
| **Quality assessment** | |
| Median score (IQR)* | 8 (7–10) |
| Score higher than median, N (%) | 8 |
| | |
| *Downs and Black scale | |

| **Table A.2** Summary of real-world studies of bevacizumab in ovarian cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Outcomes | | | | | |
| First Author | Study Design | Study Population | Treatment Regimens | Median PFS | Median OS | ORR | Safety | Comment | Quality Score* |
| Amadio, 2020(Amadio et al., 2020) | Case-control, single-center, Rome, Italy, 2015-2016 | 283 patients >90% with HGS and FIGO stage III/IV; mean age 55 including 72 age ≥65 | CB+PTX+BEV (1L)<br>CB+PTX+BEV (2L)<br>CB+GEM+BEV (2L) | 1L:<br>Age <65, 17 mo;<br>Age ≥65, 11 mo:<br>Recurrent:<br>Age <65, 12 mo;<br>Age ≥65, 14 mo: | | | G3+ AE;<br>9.5% incl<br>8 patients >1;<br>Most common:<br>proteinuria (2.8%),<br>CK failure (2.8%),<br>GI (2.4%), VTE(2.1%),<br>HTN (2.1%) | Creatinine and no. of comorbidities predictive of severe toxicity; toxicity not associated with age | 10 |
| Bertelli 2016(Bertelli, Drews, & Lutchman-Singh, 2016) | Retrospective cohort, single center, South West Wales, 2012-2015 | 66 advanced EOC patients, at high risk of progression (FIGO IV or suboptimally debulked FIGO III), med age 66 | ≥1 dose BEV 1L | 16 mo | | | Most common:<br>proteinuria (66.7%),<br>HTN (15%), CVD (6.7%), | | 7 |
| Berton, 2021(Berton et al., 2021) | Prospective multi-center cohort, France, 2013-2014 | 468 patients, 90% advanced EOC, med. age 64 | CB+PTX+BEV for 98% (remainding 2% included other chemo regimens) | 17.4 mo<br>3-y PFS 25% | Med not rached;<br>3-y OS 62% | | Most common:<br>HTN (38%); SAE 4% | | 9 |
| Daniele, 2021(Daniele et al., 2021) | Multi-center phase IV single-arm trial (MITO-164), Italy, 2012-2014, med follow-up 32 mo | 398 patients with FIGO stage IIIB-IV, primary ovarian cancer, med age 59 | CB+PTX+BEV 1L | 21 mo | 41 mo | 69% (103 CR; 73 PR) | G3+ 77%<br>Most common:<br>HTN (35%),<br>Neutropenia (48%),<br>Anemia (5%)<br>Proteinuria (2%), TE (3%), Fistula and bleed <1% each | | 12 |
| Gallego, 2021(Gallego et al., 2021) | Retrospective single-center, Madrid, Spain, 2009-2017 | 34 recurrent CCC or HGS; med age 55; treatment-free interval plat (TFIp) <6 / ≥6 mo | CB+GEM+BEV for TFIp ≥6 mo<br>PTX+BEV for TFIp <6 mo | Overall, 13 mo;<br>CB+GEB+BEV, 15.9 mo;<br>PTX+BEV, 11 mo | Overall, 29 mo;<br>CB+GEB+BEV, 32 mo;<br>PTX+BEV, 21.4 mo<br><br>By GMI:<br>>1.33, 33 mo;<br><1.33, 19 mo (ns) | CB+GEB+BEV, 65.2%;<br>PTX+BEV, 27.3%<br><br>83.3% vs 52% for HGS vs CCC | | Growth Modulation Index (GMI), Van Hoff 1998 GMI used to compare 2 PFSs; GMI >1.33 (33% ) considered excellent; | 8 |
| Gamble, 2021(Gamble et al., 2022) | Retrospective US claims database, 2006-2018 | 8,923 women with incident ovarian cancer, 6% (N=533) received BEV; Median age not reported; 70% age | 1L SOC | 60% started 2L (67% of BEV 1L vs 59% no BEV 1L);<br>Time to 2L (interval b/w 1L and 2L claims): | | | No difference in hospitalization or emergeny dept visits: BEV, 5.9% vs no BEV 6.8% in; BEV v-related toxicities: | Access: In patients age ≥70, rate of BEV 2.8% vs 6% overall | 8 |

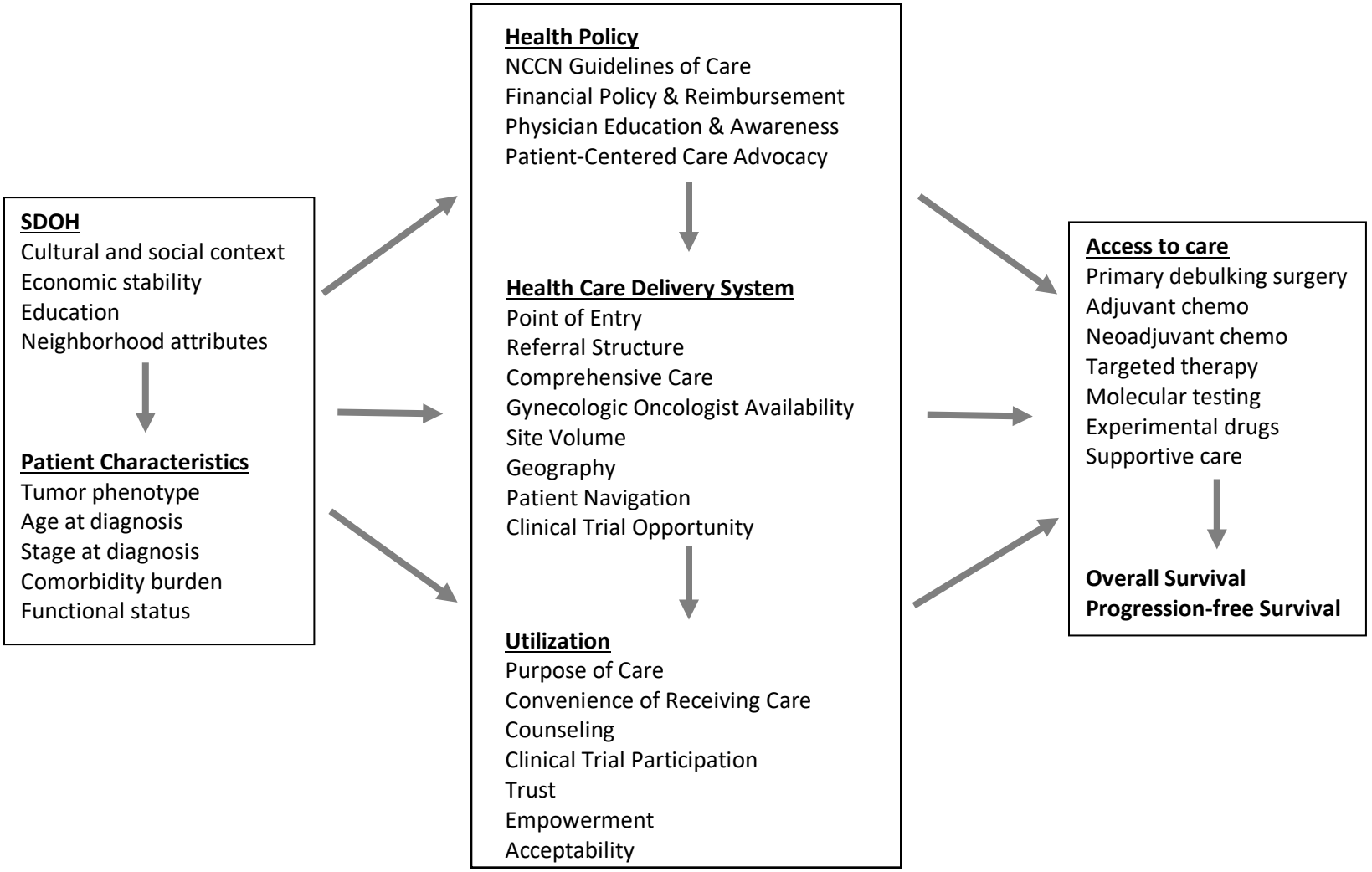
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 50-69 yr; 7% age ≥70 yr | | 21 mo BEV vs 20 mo no BEV (p=0.04) | | | HTN, 15%; kidney, 6.8%; bleed, 3.8%; VTE, 2.3%; wound-healing, 2.1% | | |
| Hall, 2020(Hall et al., 2020) | Single-arm, non interventional study (OSCAR) in UK, 2013-2015 | 299 patients with high-risk FIGO IIIB-IV, med age 64 (27% ≥70 yrs) | 1L CB+PTX+BEV CB+ BEV | 15.4;<br>Age <70, 16.1 mo;<br>Age ≥70, 14.8 mo;<br>1-yr PFS 68% | Not reached;<br>1-yr OS, 94%;<br>Age <70, 94%;<br>Age ≥70, 91% | 69%; CR, 21%<br>PR, 48%;<br>(did not differ by age) | G3+, 54%;<br>Most common:<br>HTN (16%),<br>Neutropenia (5%),<br>proteinuria (2%) | Med PFS 20.8, 16.1, and<br>13.6 months in patients with primary debulking,<br>interval debulking, and no surgery, respectively;<br>Disease control similar by age. | 10 |
| Hirasawa, 2018(Hirasawa et al., 2018) | Retrospective single-center, Japan,2008-2013 (controls), and 2014-2017 (cases) | 32 patients with recurrent, platinum sensitive ovarian cancer, med age 59 | CB+PTX+ BEV, CB+PTX | 6.7 mo, control;<br>14.7 mos, BEV;<br><br>Adj HR 0.30, 95% CI 0.11-0.81) | | 57.9% control;<br>92.3% BEV | G3+ most common: (BEV, control)<br>Neutropenia (38.5%, 21.1%, 1 febrile in BEV group)<br>Anemia (5.3%, 3.1%)<br>Thrombocytopenia case in BEV group | | 8 |
| Komiyama, 2019(Komiyama et al., 2019) | Multi-center prospective cohort, Japan 2014-2016 | 333 patients with FIGO III/IV EOC, med age 58 | ≥1 dose BEV 1L CB+PTX | 16.3 mos; Relapse: 42.5% sensitive; 23.5% partially-sensitive; 24.5% platinum resistant disease | | 77.5% | HTN (23.3%), proteinuria (12.6%)<br>Most common G3: TE (1.4%),<br>GI (0.3%), fistula (0.7%), | Response highest in serous and endometrioid; CCC 63.6% (better than previously reported) | 8 |
| Kose, 2020 EJGO(Kose, Alemdaroglu, et al., 2020; Kose, Alemdaroğlu, et al., 2020) | Retrospective hospital-based case series, Turkey, 2012-2018 | 106 recurrent patients, med age 62 | Single agent liposomal doxorubicin LPD (N=38) or carboplatin doublet (N=68) chemo+BEV;<br>2 grp based on PFI ratio<br>Grp A if PFS 1>PFS 2; Grp B if vice-versa, | PFS-2 18.8 mo overall; Grp A: 13.4 mo;<br>Grp B: 29.7 mo;<br>(p<0.001) | 48.3 mo overall;<br>Grp A: 58.6 mo;<br>Grp B: 48.3 mo;<br>(p=0.72) | | G3+ (21.7%):<br>Most common: HTN (11.3%), Pulmonary embolism (2.8%), perforation (0.9%) | PFS-2 higher in Group B, but difference did not translate into OS; Group A higher OS than B. Authors believe lower PFS-1 and lower response to 3L or later main reason.<br>Cytoreductive surgery at 2nd relapse predicted PRS-2; plat-resist and 2nd surgery outcome predictive of OS | 6 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lee, 2018(Lee et al., 2019) | Multi-center prospective cohort, South Korea, 2015-2017 | 391 patients with platinum-resistant recurrent ovarian cancer,<br>mean age 61, | BEV+PLD* (N=259, 66%);<br>BEV+topotecan (N=94, 24%);<br>BEV+PTX (N=38, 10%)<br><br>*pegylated liposomal doxorubicin | 6.1 mo overall;<br>BEV+PLD, 5.4 mo;<br>BEV +top, 7.0; BEV +PTX, 8.3 mo; | 22 mos overall;<br>BEV+PLD, 21 mo;<br>BEV+top, 25 mo;<br>BEV+PTX, 21 mo; | 32.9 overall;<br>48.6% 2L;<br>30.6 3L | G3+ (41.2%);<br>Most common:<br>Neutropenia (28.0%),<br>thrombocytopenia (9.8%),<br>HTN (5.2%),<br>Proteinuria (2.6%) | | 10 |
| Lorusso, 2020(Lorusso et al., 2020) | Case-control, single-center, Rome Italy, 2015-2019 | 441 HGS advanced ovarian cancer patients, med age 58 with documented BRCA mutational status | 1L CB+PTX+ BEV (N=183, 41.5%) or No BEV (N=258, 58.5%) | 20 mo overall;<br>21 vs 17 BEV vs control, (p=0.03);<br>BRCA wild-type:<br>20 vs 15); Adj HR 0.83, 95% CI 0.62-1.11) | Not reached;<br>5-yr 52% cases, 53.5% controls | | | PFS advantage confined to BRCA wild-type;<br>BRCA status and surgery associated with longer OS, multivariable-adjusted | 7 |
| O'Malley, 2011(O'Malley et al., 2011) | Retrospective single-center case-control study, Ohio, US, 2002-2009 | 70 heavily pre-treated patients with recurrent ovarian cancer, med age 58 (BEV), 60 (control) | ≥2 cycles PTX+ BEV (N=41) compared to PTX only (N=29) | 13.2 mo BEV vs. 6.2 mo control (p=0.01); | 18.9 mo BEV vs. 18.8 mo control (p=0.6) | BEV v, 63% overall,<br>CR 34%, PR 29%;<br>Control, 48% total, CR 17%, PR 31% | G3+ most common:<br>Proteinuria (N=2),<br>HTN (N=2),<br>GI perforation (N=2) in BEV group only | | 7 |
| Oza, 2017(A. M. Oza et al., 2017) | Prospective multi-center single-arm international study (35 studies), 2010-2012 | 1,021 advanced (FIGO IIB-IV) or aggressive ovarian cancer patients, med age 56 | CB+PTX+ BEV, ≥1 dose 1L;<br>>1 yr in 62%;<br>>15 mo in 53%;<br>>2 yr in 29% | 26 mo;<br>18 mo in high-risk patients<br><br>1-yr, 83%;<br>2-yr, 53%; | Not reached, 1-yr, 94%;<br>2-yr, 85%; | 73%;<br>CR, 25%;<br>Med duration of response, 18 mo | G3+ 54%:<br>Most common:<br>Neutropenia (29%),<br>HTN (25%),<br>Thrombocytopenia (10%),<br>Proteinuria (4%),<br>TE (3%), GI (1%),<br>Bleed (1%), wound healing, fistula, CHF all <1% | Study designed to mirror ICON-7;<br>Patients with severe comorbidity excluded | 10 |
| Petrillo, 2016(Petrillo et al., 2016) | Case-control single-center study, Italy, 2010-2013 | 222 advanced EOC patients with primary or recurrent disease, med age 58 | CB+PTX+ BEV (N=74) or no BEV (N=148) | 1L: 16 mo BEV vs 9 mo control<br>2L: 10 mo control<br>1L vs 5 mo BEV 1L, among women with SCS; | | 2L CR/PR:<br>23.1% BEV vs 40.5% control;<br>Among patients with PFI ≥12 mo, 38.4% vs 85.2% (p=0.002) | | 10% cases did not have SCS vs. 53.5% controls | 13 |
| Tanigawa, 2020(Tanig | Retrospective single center, Japan, 2014-2016 | 33 advanced ovarian cancer with recurrent stage III/IV | CB+PTX/GEM, docetaxel, or doxorubicin + BEV; | 8.7 mos overall;<br>4.8 for resistant disease, 11.1 mos | | | G3 most common:<br>Neutropenia (72%, 6% febrile), | | 6 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| awa et al., 2020) | | patients with >3 BEV courses; Med age 55 | or single agent+ BEV (PTX, doxorubicin, docetaxel or nogitecan) | platinum--sensitive disease | | | Proteinuria (30%), Thrombocytopenia (15%), HTN (12%), Anemia (9%), GI (6%) | | |
| Wu, 2020(Wu et al., 2020) | Retrospective single-center, Taiwan 2011-2018 | 446 patients all stages (61% III/IV); incident mean age 54; recurrent (N=65), mean age 53 | 1L CB+PTX+ BEV (N=77) vs CB+PTX (N=304); 2L BEV, by PFI <6/≥6 mos and prior BEV (y/n) | 1L: High-risk 10.5 mos BEV vs 6 mo no BEV (p=0.035) 2L Progressed: PFI <6 m0, 71%; PFI ≥6 55% | Not reached; PFI associate with better PFS & OS (HR 0.22, 95% CI 0.10-0.5, PFI ≥6 vs <6 mos) | | G3+ most common: neutropenia (31%, febrile 8.4%), anemia (4.2%), diarrhea (1.4%). No BEV-related AEs observed | Survival differences confined to high-risk patients; stronger survival advantages were observed in patients who received BEV throughout (17.5 mo, maintenance v. initiation 10.5); BEV and optimal cytoreduction predicted progression in multivariable model (HR 0.43, 95% CI 0.25-0.73; HR 0.63, 95% CI 0.44-0.90) | 15 |

**Abbreviations:** PFS, progression-free survival; OS overall survival; ORR, objective response rate; CR, complete response; PR, partial response; BEV, bevacizumab; CB, carboplatin; PTX, paclitaxel; GEM, gemcitabine; SOC, standard of care; EOC, epithelial ovarian carcinoma, HGS, high-grade serous; CCC, clear cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; PFI, platinum free interval; TFI, treatment free interval; AE, adverse event; SAE, serious adverse event; G3, grade 3; HTN, hypertension; TE, thromboembolism; VTE, venous thromboembolism; CVD, cardiovascular; HR, hazard ratio; CI, confidence interval
*Downs and Black checklist

**APPENDIX B. Conceptual Model of Factors Associated with Ovarian Cancer Outcomes**



**APPENDIX C. Ovarian Cancer Drugs**

| Drug name | HCPCS* Code | Description | Class |
|---|---|---|---|
| Aflibercept | J0178 | Aflibercept, 1 mg | |
| Bevacizumab | J9035 | Injection, bevacizumab, 10 mg | VEGF / VEGFR inhibitors |
| Bevacizumab | J9257 | Injection, bevacizumab, 0.25 mg | |
| MVASI | Q5107 | Injection, bevacizumab biosimilar, 10 mg | |
| Zirabev | Q5118 | Injection, bevacizumab biosimilar, 10 mg | |
| Carboplatin | J9045 | Injection, carboplatin 5 mg | Platinum-containing compounds |
| Cediranib | N/A | | |
| Cisplatin | J9060 | Injection, cisplatin, powder or solution, 10 mg | |
| | J9062 | Cisplatin, 50 mg (Deprecated) | |
| Doxorubicin | J9000 | Injection, doxorubicin hydrochloride, 10 mg | Antibiotics / antineoplastic |
| | J9001 | Injection, doxorubicin hydrochloride, liposomal, imported lipodox,10 mg | |
| | J9002 | Injection, doxorubicin hydrochloride, liposomal, doxil,10 mg (deprecated) | |
| Gemcitabine | J9198 | Injection, gemcitabine hydrochloride (infugem), 100 mg (deprecated) | Antimetabolites |
| | J9199 | Injection, gemcitabine hydrochloride (infugem), 200 mg (deprecated) | |
| | J9201 | Injection, gemcitabine hydrochloride, not otherwise specified, 200 mg | |
| Nintedarib | N/A | | |
| Oxaliplatin | J9263 | Oxaliplatin, 0.5 mg | |
| Paclitaxel | J9264 | Injection, paclitaxel, protein-bound particles, 1 mg | Mitotic inhibitors |
| | J9265 | Injection, paclitaxel, 30 mg (deprecated) | |
| | J9267 | Injection, paclitaxel, 1 mg (deprecated) | |
| Pazapanib | N/A | | |
| Pemetrexed | J9305 | Pemetrexed, 10 mg | |
| Sorafenib | N/A | | |
| Sunitinib | N/A | | |
| Topotecan | J8705 | Topotecan, oral, 0.25 mg | Miscellaneous antineoplastic |
| | J9350 | Injection, topotecan, 4 mg (deprecated) | |
| | J9351 | Injection, topotecan, 0.1 mg | |

*****Healthcare Common Procedure Coding System

NOTE: Grey text indicates experimental treatments with associated HCPCS if available.