pharmacist (46k€), and clerk (30k€), while to evaluate social costs we took the median annual gross income for women in Italy (21'647€) as an example. We considered the following minutes for patients' movements: round-trip to the hospital (60 min), an external laboratory, and a local pharmacy (30 min). We have adhered to relevant EQUATOR guidelines, using the Standards for Reporting Qualitative Research (SRQR) guidelines as the reporting method [17].

Results

From March 2020 to December 2023, 4 healthcare workers (2 doctors, 1 nurse, and 1 pharmacist) were involved in the interviews, and data about 80 OC patients, 40 (50%) PO and 40 (50%) IV treated were collected. At the time of the study, 68% of OC patients were employed, as well as 78% of the caregivers. 75% of OC patients were accompanied by a caregiver in the pre-COVID-19 period, while 0% were accompanied during the pandemic. Regarding healthcare workers' time spent per patient (Figure 1), IV patients required a median of 0.7 hours/visit versus 0.2-0.3 hours/visit for PO (if treated in the hospital versus at home, respectively). Given the median number of hospital accesses (17/year IV and 4/year PO), this meant a 61-76% reduction of hours spent by the hospital workers and a 91-94% reduction/year. This data trend is confirmed by post-COVID-19 results (90%-95% of time reduction). The time reduction in the post-COVID-19 results is also influenced by the complete elimination of time spent on COVID procedures, 0.1 hours/visit for EV or hospital-followed PO patients, and 0.0 hours/visit for at-home PO patients. The annual hospital and healthcare system cost of IV-treated OC patients was 478 euros/patient/year, of which 254 euros were due to hospital workers' costs, 217 to hospital consumables, and 7 to other workers' and consumables' costs. Meanwhile, PO patients required only 31-43 euros (if followed virtually/at home or not), of which 21-33 from hospital workers' costs, 0-2 from consumables, and 10 from other workers' and consumables' costs. This represented a 93-95% reduction in consumable costs and a 91-94% reduction in hospital worker costs with PO therapy (Figure 2). In the post-COVID-19 phase, the reductions were 92% and 95%, respectively, with an average annual cost of 511 euros/patient/year for EV patients, and only 33-49 euros/patient/year for the PO group. We also estimated that, if all 80 OC patients were PO-treated, the healthcare system's costs would diminish by 82%, dropping from 22 k€/year to only 3-4 k€/year, and from 21 k€/year to 2-3 k€/year (83%) in the pre-COVID-19 phase; also the annual patients' and caregivers' costs would notably diminish (78%), decreasing from 61 k€/year to 13 k€/year. Data about caregivers' costs after COVID-19 are unavailable because they were not allowed to access the hospitals during the pandemic. IV patients spent an average time of 4.3 hours per hospital visit, including 1.1 hours for visiting/procedures, 1.7 hours of waiting, and 1.5 hours for movements, while PO patients required only 1.1-2.2 hours/visit, of which the major part was for movements (0.8-1.8) while only 0.2-0.3 hours were spent on visiting/procedures, with an average reduction of 49-74% of patients' time per visit, and 88-94% in a year (Figure 3). In the post-COVID phase, 21-62% and 82-91% annually, with average time per visit for EV patients of 2.9 hours/visit, with 0.1 hours for COVID-19 procedures, and 1.1-2.3 hours/visit for PO patients.

Considering the annual gross income of a woman in Italy (27'617 euros), the use of PO therapy reduced the social annual cost from 1079 euros/year per patient, including 709 euros/patient/year of social costs for lost productivity for hospital care, 363 related to movements, and 8 other costs to 64-128 euros/year (88-94% less) (Figure 4), while from 729 euros/year per patient to 64-132 euros/year (82-91% less) in the post-COVID-19.

Discussion

Ovarian cancer (OC) continues to pose a significant burden of disease, both in terms of its prevalence and its impact on affected women and the healthcare systems [18]. Despite advances in detection, diagnosis, and treatment, OC remains a formidable challenge for patients, caregivers, and healthcare providers alike, as it often presents as advanced or metastatic [2]. This study demonstrated the considerable advantages of oral (PO) maintenance therapies compared to intravenous (IV) therapies, particularly in terms of reducing patient and caregiver time, hospital resource utilization, and overall costs. Our findings showed that PO therapies resulted in a 21-62% reduction in time spent per visit and an 82-91% annual reduction compared to IV therapies. Healthcare worker time and healthcare system costs also decreased significantly, with at least an 82% reduction in costs if all patients in our cohort had been treated using PO therapies. These results were consistent even in post-COVID-19 analyses, where adaptations in healthcare practices further reinforced the efficiency of PO treatments. This study has several strengths, as it addresses a clinically relevant question in OC management by comparing two widely used maintenance therapies while focusing on their economic and time-related implications. Additionally, the inclusion of pre- and post-COVID-19 data provides a unique perspective on how pandemic-related changes in healthcare practices affected resource utilization and patient outcomes. The use of structured interviews with oncologists, nurses, pharmacists, patients, and caregivers enriched the analysis by incorporating diverse viewpoints, ensuring a holistic understanding of the therapies' impact. Some limitations, however, must be acknowledged: the relatively small sample size of 80 OC patients and the limited number of healthcare workers involved restrict the generalizability of the findings. The study was conducted in only two Italian hospitals, which may not fully represent other healthcare settings, regions, or healthcare systems. Additionally, the relatively short follow-up period limits the ability to assess long-term outcomes, such as overall survival (OS) and delayed toxicities associated with PO therapies. Another limitation is the absence of a detailed economic analysis that accounts for the initial acquisition costs of the two drug classes, which differ significantly and may substantially influence cost-effectiveness. It is reasonably expected the number of patients undergoing maintenance treatment to rise in the next years, as novel therapeutic agents continue to improve the advanced disease's survival rates [18, 19]. While maintenance therapies have revolutionized the management of advanced ovarian cancer, achieving optimal cytoreduction during primary debulking surgery remains one of the most significant predictors of long-term survival. Several predictive models and preoperative tools have been proposed to

identify patients most likely to benefit from surgery. These include imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), and biomarkers, such as cancer antigen 125 (CA-125), that can help determine tumor resectability and guide surgical planning. Incorporating these tools into clinical practice can enhance decision-making and increase the likelihood of achieving R0, ultimately improving patient outcomes [8]. Beyond predictive models, the technical skills and expertise of the surgical team play a pivotal role in achieving optimal cytoreduction during debulking surgery for OC. Cytoreductive surgery often requires advanced techniques, including peritonectomy procedures, diaphragmatic stripping or resection, bowel resection, splenectomy, and hepatic mobilization. These techniques are essential for removing extensive tumor burden, particularly in cases of advanced-stage disease. Evidence suggests that high surgical proficiency, often achieved in specialized centers with experienced gynecologic oncologists, is strongly associated with achieving no residual tumor (R0) and improving survival outcomes [20]. Incorporating surgical skills training and standardizing procedures for cytoreduction are critical for optimizing patient outcomes. Moreover, multidisciplinary collaboration between surgeons, radiologists, and anesthesiologists is crucial to managing complex cases, minimizing perioperative complications, and ensuring the feasibility of subsequent systemic therapies. These considerations further highlight the importance of centralized care for ovarian cancer, where patients can benefit from specialized expertise and comprehensive management. Recent advances have also focused on exploiting specific molecular vulnerabilities in ovarian cancer, such as HRD and TP53 mutations. For example, RAD51 testing has been proposed as a refined strategy to identify patients with functional HRD who may benefit from PARP inhibitors or other DNA-damage response-targeted therapies. Additionally, therapeutic strategies aimed at restoring or targeting the dysregulated TP53 pathway hold promise in managing high-grade serous ovarian cancers, where TP53 mutations are nearly universal [21, 22]. These approaches could complement existing maintenance therapies and expand the therapeutic landscape for ovarian cancer. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has been studied extensively in the treatment of OC, particularly as a maintenance therapy following primary treatment [23-24]. Bevacizumab inhibits tumor angiogenesis, crucial for tumor growth and metastasis, by targeting the VEGF and prevents the latter from binding to its receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells [25-26]. Numerous clinical trials have evaluated the efficacy and safety of bevacizumab in OC treatment, both as upfront therapy and as maintenance following standard platinum-based chemotherapy treatment. The phase III GOG-218 trial, for example, which evaluated the addition of bevacizumab to standard chemotherapy followed by maintenance therapy in women with advanced OC, showed a median progression-free survival (mPFS) significantly longer in the bevacizumab-containing arms (14.1 months) compared to chemotherapy alone (10.3 months). However, there was no significant difference in overall survival (OS) between the treatment groups [9]. In the ICON7 phase III trial, which investigated the addition of bevacizumab to standard chemotherapy as a frontline treatment for OC, the addition of bevacizumab was

associated with a significant improvement in mPFS (19.0 months vs chemotherapy alone 17.3 months). Subgroup analyses suggested a potential OS benefit in certain subgroups, such as those at higher risk of disease progression [10]. Finally, the phase III OCEANS trial evaluated bevacizumab in combination with carboplatin and gemcitabine, followed by maintenance bevacizumab, in patients with platinum-sensitive recurrent OC, once again showing a significant improvement in mPFS compared to chemotherapy plus placebo (12.4 vs 8.4 months). OS data from this trial did not show a significant difference between the treatment groups [11]. Bevacizumab is generally well-tolerated but can be associated with certain side effects, including hypertension, proteinuria, gastrointestinal perforation, bleeding, and impaired wound healing. Careful monitoring and management of these side effects are essential during treatment [27]. Also, patient selection is crucial in determining the appropriate candidates for bevacizumab maintenance therapy. Factors such as performance status, disease stage, histological subtype, and the presence of specific biomarkers may influence treatment decisions [28]. Access to bevacizumab maintenance therapy may be limited by factors such as cost, reimbursement policies, and healthcare infrastructure. The availability of biosimilar versions of bevacizumab helps to improve accessibility and affordability [29]. PARPis have emerged as a significant advancement in the treatment of OC in the last decade, particularly in the maintenance setting. PARPis target a specific DNA repair pathway known as the base excision repair (BER) pathway. By inhibiting PARP enzymes, these drugs prevent the repair of single-strand DNA breaks, accumulating double-strand breaks during DNA replication. In OC patients with homologous recombination deficiency (HRD), such as those with BReast CAncer gene (BRCA) mutations, PARPis exploit synthetic lethality, resulting in cancer cell death. PARPis have demonstrated significant efficacy as maintenance therapy in patients with advanced OC, particularly in those with platinum-sensitive disease. Many clinical trials have shown that PARPis such as olaparib, niraparib, and rucaparib significantly prolong PFS compared to placebo or standard treatment. Some studies have also shown a trend towards an improved OS, although longer follow-up may be needed to confirm these findings. The phase III SOLO-2 trial, specifically, demonstrated that olaparib maintenance therapy significantly prolonged PFS compared to placebo in patients with platinum-sensitive relapsed OC and BRCA mutations. The mPFS was 19.1 months with olaparib versus 5.5 months with placebo [12]. The NOVA trial evaluated niraparib maintenance therapy in patients with platinum-sensitive recurrent OC, regardless of BRCA mutation status. Niraparib significantly prolonged mPFS compared to the placebo in both the BRCA-mutated and non-BRCA-mutated subgroups [13]. The ENGOT-OV16/NOVA trial demonstrated that niraparib maintenance therapy significantly prolonged mPFS compared to placebo in patients with recurrent OC who had responded to their most recent platinum-based chemotherapy, regardless of BRCA mutation status [14]. The ARIEL3 phase III trial evaluated rucaparib maintenance therapy in patients with platinum-sensitive recurrent OC, stratified by BRCA mutation status and genomic loss of heterozygosity (LOH). Rucaparib significantly prolonged mPFS compared to placebo in the overall population and the BRCA-mutant and BRCA wild-type/LOH-high subgroups [15]. These landmark

clinical trials provide robust evidence supporting the efficacy of PARPis as maintenance therapy in OC, contributing to significant improvements in PFS, and changing the treatment paradigm for this disease. PARPis are generally well-tolerated, with the most common side effects being manageable hematologic toxicities (e.g., anemia, thrombocytopenia) and gastrointestinal symptoms (e.g., nausea, and fatigue). Close monitoring and supportive care measures are important for managing side effects and optimizing treatment adherence [19]. In elderly patients treatment selection becomes particularly complex due to age-related factors such as comorbidities, decreased physiological reserve, and a higher risk of treatment-related toxicity. Studies have demonstrated that performance status and functional assessments are critical for predicting treatment tolerability and outcomes in this population. For example, tools such as the Geriatric Assessment (GA) can evaluate physical function, cognitive status, nutritional condition, and social support, enabling clinicians to better stratify patients based on their fitness for aggressive treatments. Evidence suggests that elderly women with good performance status and minimal comorbidities can benefit from standard therapies, including surgery and maintenance treatments like PARP inhibitors, with similar efficacy as younger patients [30]. Conversely, those with poor performance status may require tailored regimens, such as dose adjustments or alternative therapies, to mitigate risks of toxicity while maintaining quality of life. Integrating these individualized strategies into clinical practice is essential to optimize care and outcomes for elderly ovarian cancer patients, who represent a significant and growing proportion of the affected population. While PARPis have demonstrated clinical efficacy, their high cost may pose challenges for widespread adoption in some healthcare settings. Cost-effectiveness analyses have shown that the clinical benefits of PARP inhibitors may justify their cost in certain patient populations, particularly those with BRCA mutations or HRD [31]. Bevacizumab is typically administered intravenously and can be associated with high drug acquisition costs, especially when used as a maintenance therapy over an extended period [32-34]. IV administration of bevacizumab requires clinic or hospital visits for each infusion, which adds to the overall treatment cost. This includes costs associated with infusion center services, healthcare professional time, and facility fees. Patients receiving bevacizumab may require regular monitoring for treatment-related side effects, such as hypertension, proteinuria, and bleeding events. These monitoring visits can contribute to overall healthcare costs [35]. Oral PARPis also have high drug acquisition costs. However, the cost per pill may be lower compared to intravenous therapies. While PARPis are administered orally, patients still require regular clinic visits for monitoring and evaluation. However, the frequency of visits may be lower compared to intravenous therapies, potentially reducing administration-related costs [36]. Similar to bevacizumab, patients receiving PARPis may require monitoring for treatment-related side effects, such as hematologic toxicity and gastrointestinal symptoms. The frequency and intensity of monitoring may vary depending on the specific PARP inhibitor and patient factors. PARPis have their own set of side effects, which may require management and supportive care [19, 30]. The cost-effectiveness of incorporating bevacizumab into the primary treatment and maintenance therapy of

advanced OC has been evaluated in several studies. Burger et al. (2014) conducted a landmark cost-effectiveness analysis alongside the GOG-218 trial, which assessed the addition of bevacizumab to standard chemotherapy followed by maintenance therapy. The analysis considered the incremental cost per quality-adjusted life-year (QALY) gained with the addition of bevacizumab. While the study found that adding bevacizumab was associated with improved PFS, it also identified higher costs and uncertain long-term benefits, leading to questions regarding its cost-effectiveness in this setting [9]. The cost-effectiveness of PARPis as maintenance therapy for advanced OC has also been studied. Kim et al. (2020) conducted a cost-effectiveness analysis of maintenance PARPis in newly diagnosed advanced OC patients. The study compared the cost-effectiveness of PARPis to routine surveillance or placebo and evaluated the incremental cost per QALY gained. The analysis considered drug costs, administration costs, monitoring costs, and potential health benefits associated with prolonged PFS. The study found that maintenance PARPis were cost-effective compared to routine surveillance or placebo in certain patient populations, particularly those with BRCA mutations or HRD [37]. Comparing the costs of using intravenous bevacizumab and oral PARP inhibitors as maintenance therapies for advanced OC involves considering various factors, including drug costs, administration costs, monitoring costs, and potential cost savings or additional expenses associated with side effects and treatment management. This comparison however, should also take into account the distinct pharmacological and oncological profiles of bevacizumab and PARPis: these differences extend beyond therapeutic mechanisms to influence clinical outcomes, including PFS and OS. Importantly, bevacizumab may provide benefits by intervening earlier in the angiogenic pathways of disease progression, while PARPis require precise molecular selection based on biomarkers like BRCA mutations or HRD for optimal outcomes [12, 32]. Future cost-effectiveness analyses should integrate the broader economic and survival implications of these therapies, considering factors such as patient selection criteria, the role of molecular biomarkers, and long-term survival benefits [33]. Furthermore, the impact of COVID-19 on treatment procedures and costs cannot be understated. The pandemic necessitated adjustments in healthcare practices, leading to time savings and cost reductions, again favoring particularly PO patients. The adoption of virtual or at-home treatment approaches and streamlined COVID-19 procedures contributed to enhanced efficiency and resource utilization in the post-COVID-19 phase [38]. Future research should focus on addressing the limitations identified in this study. Expanding to larger, multicenter cohorts and including diverse healthcare systems will help validate these findings and provide a broader understanding of the long-term benefits and challenges of PO maintenance therapies. Extended follow-up periods will be critical to capturing survival outcomes, late toxicities, and quality-of-life impacts over time. The integration of molecular profiling, such as RAD51 testing for HRD and strategies targeting TP53 mutations, offers promising avenues for refining patient selection and optimizing therapeutic outcomes [21, 22]. Further exploration of cost-effectiveness, incorporating initial drug acquisition costs and long-term economic implications, will also be essential to guide healthcare policy and resource allocation. Additionally, research into the

standardization of surgical approaches, training in advanced cytoreductive techniques, and fostering multidisciplinary collaborations can improve outcomes for patients undergoing primary debulking surgery. Finally, the adaptability of PO therapies in post-pandemic healthcare models underscores the need for continued innovation in delivering efficient, patient-centered care. The lessons learned from the pandemic can inform strategies for streamlining treatment processes, reducing hospital visits, and enhancing the overall patient experience in ovarian cancer management.

Conclusions

This study highlights the potential of PO maintenance therapies to transform the management of advanced OC by improving efficiency and reducing the burden on patients, caregivers, and healthcare systems. The BEYOND project demonstrated that PO therapies significantly reduce healthcare worker time, hospital resource utilization, and patient time on therapy, with reductions of up to 91% in annual time commitments compared to intravenous (IV) therapies. These findings underscore the importance of adapting treatment strategies to enhance patient experiences while minimizing costs, particularly in evolving healthcare landscapes shaped by challenges like the COVID-19 pandemic. Beyond resource efficiency, this study emphasizes the need for a multidisciplinary approach to OC treatment. Integrating molecular profiling into routine clinical practice: such personalized strategies offer the potential to expand therapeutic options and improve outcomes for molecularly defined subgroups of OC patients. Optimal cytoreductive surgery remains a cornerstone of OC treatment, with no residual tumor (R0) as a critical determinant of long-term survival. Incorporating predictive tools, such as advanced imaging techniques and biomarkers, into surgical planning can increase the likelihood of achieving R0. The results of this study reinforce the importance of patient-centered care in OC management. PO therapies not only improve quality of life by reducing time burdens but also align with the global shift towards more personalized, efficient, and accessible healthcare solutions. However, the cost-effectiveness of maintenance therapies must be considered holistically, accounting for both initial drug acquisition costs and long-term economic and survival outcomes. Moving forward, larger multicenter studies with extended follow-up periods are needed to validate these findings and assess their long-term impact on survival, quality of life, and healthcare systems. Continued research into molecularly targeted therapies and the integration of surgical and systemic treatment strategies will be crucial to refine OC management further. By leveraging innovations in therapy, diagnostics, and surgical care, clinicians can optimize outcomes and provide equitable, high-quality care to patients with OC.

Authors contribution

Study conceptualization: Maiorano MFP, Loizzi V, Cormio G; data curation: Maiorano MFP, Cormio G; formal analysis: Maiorano MFP, Cormio G, Loizzi v; funding: not

applicable; investigation: Maiorano MFP, Maiorano BA, Cormio G, Loizzi V; methodology: Cormio G, Loizzi V, Gasbarro AR; project administration: Maiorano MFP, Loizzi V, Maiorano BA, Naglieri E, Colonna G, Cafagno N, Gasbarro AR, Cormio G; resources: Maiorano MFP, Colonna G; software: Maiorano MFP, Colonna G, Maiorano BA; supervision: Loizzi V, Cormio G, Maiorano BA, Naglieri E, Gasbarro AR; validation: Maiorano BA, Loizzi V, Cormio G, Gasbarro N; visualization: Maiorano MFP; writing - original draft: Maiorano MFP; writing - review and editing: Maiorano MFP, Loizzi V, Cormio G, Maiorano BA, Naglieri E, Gasbarro AR. All authors reviewed the results and approved the final version of the manuscript. We would also like to thank Dr RODELLI Davide for SEO optimization and keyword research.

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References

1. Maiorano BA, Maiorano MFP, Maiello E. Olaparib and advanced ovarian cancer: Summary of the past and looking into the future. Front Pharmacol. 2023;14:1162665. doi: 10.3389/fphar.2023.1162665.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33. doi: 10.3322/caac.21708.
3. Huang J, Chan WC, Ngai CH, Lok V, Zhang L, Lucero-Prisno DE, et al. Worldwide burden, risk factors, and temporal trends of ovarian cancer: A global study. Cancers. 2022;14(9):2230. doi: 10.3390/cancers14092230.
4. International Agency for Research on Cancer. WHO Data Visualization Tools for Exploring the Global Cancer Burden in 2020. Available at: https://gco.iarc.fr/today/home. Accessed on March 1, 2024.
5. Ali AT, Al-Ani O, Al-Ani F. Epidemiology and risk factors for ovarian cancer. Menopause Rev. 2023;22(2):93-104. doi: 10.5114/pm.2023.128661.
6. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and

mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. doi: 10.3322/caac.21660.
7. Liberto JM, Chen SY, Shih IM, Wang TH, Wang TL, Pisanic TR. Current and emerging methods for ovarian cancer screening and diagnostics: A comprehensive review. Cancers. 2022;14(12):2885. doi: 10.3390/cancers14122885.
8. Golia D'Augè T, Cuccu I, De Angelis E, Di Donato V, Muzii L, D'Oria O, Chiantera V, Gerli S, Caserta D, Besharat AR, Laganà AS, Bogani G, Favilli A, Giannini A. Laparoscopic prediction of primary cytoreducibility of epithelial ovarian cancer. Minerva Obstet Gynecol. 2024 Oct 8. doi: 10.23736/S2724-606X.24.05452-6. Epub ahead of print. PMID: 39377288.
9. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365(26):2473-2483. doi: 10.1056/NEJMoa1104390.
10. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A Phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365(26):2484-2496. doi: 10.1056/NEJMoa1103799.
11. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: A randomized, double-blind, placebo-controlled Phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012;30(17):2039-2045. doi: 10.1200/JCO.2012.42.0505.
12. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomized Phase 2 trial. Lancet Oncol. 2014;15(8):852-861. doi: 10.1016/S1470-2045(14)70228-1.
13. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive recurrent ovarian cancer. N Engl J Med. 2016;375(22):2154-2164. doi: 10.1056/NEJMoa1611310.
14. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomized, placebo-controlled, Phase 3 trial. Lancet Oncol. 2017;18(9):1274-1284. doi: 10.1016/S1470-2045(17)30469-2.
15. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomized, double-blind, placebo-controlled Phase 3 trial. Lancet. 2017;390(10106):1949-1961. doi: 10.1016/S0140-6736(17)32440-6.
16. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191. doi: 10.1001/jama.2013.281053.

17. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: A synthesis of recommendations. Acad Med. 2014;89(9):1245-1251. doi: 10.1097/ACM.0000000000000388.
18. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: Epidemiology and risk factors. Int J Women's Health. 2019;11:287-299. doi: 10.2147/IJWH.S197604.
19. Maiorano BA, Maiorano MFP, Lorusso D, Di Maio M, Maiello E. Efficacy and safety of PARP inhibitors in elderly patients with advanced ovarian cancer: A systematic review and meta-analysis. Int J Gynecol Cancer. 2022;32(11):1410. doi: 10.1136/ijgc-2022-003614.
20. Di Donato V, Giannini A, D'Oria O, Schiavi MC, Di Pinto A, Fischetti M, Lecce F, Perniola G, Battaglia F, Berloco P, Muzii L, Benedetti Panici P. Hepatobiliary disease resection in patients with advanced epithelial ovarian cancer: Prognostic role and optimal cytoreduction. Ann Surg Oncol. 2021;28(1):222-230. doi: 10.1245/s10434-020-08989-3. Epub 2020 Aug 10. PMID: 32779050; PMCID: PMC7752869.
21. Perrone C, Angioli R, Luvero D, Giannini A, Di Donato V, Cuccu I, Muzii L, Raspagliesi F, Bogani G. Targeting BRAF pathway in low-grade serous ovarian cancer. J Gynecol Oncol. 2024;35(4). doi: 10.3802/jgo.2024.35.e104. Epub 2024 May 14. PMID: 38768941; PMCID: PMC11262891.
22. Musella A, Vertechy L, Romito A, Marchetti C, Giannini A, Sciuga V, Bracchi C, Tomao F, Di Donato V, De Felice F, Monti M, Muzii L, Benedetti Panici P. Bevacizumab in ovarian cancer: State of the art and unanswered questions. Chemotherapy. 2017;62(2):111-120. doi: 10.1159/000448942. Epub 2016 Oct 29. PMID: 27794568.
23. Hsu JY, Wakelee HA. Monoclonal antibodies targeting vascular endothelial growth factor: Current status and future challenges in cancer therapy. BioDrugs. 2009;23(5):289-304. doi: 10.2165/11317600-000000000-00000.
24. Genentech, Inc. United States Securities and Exchange Commission. Available at: http://www.sec.gov/Archives/edgar/data/318771/000031877109000003/form10-k_2008.htm. Accessed on March 1, 2024.
25. Prager GW, Poettler M, Unseld M, Zielinski CC. Angiogenesis in cancer: Anti-VEGF escape mechanisms. Transl Lung Cancer Res. 2012;1(1):14-25. doi: 10.3978/j.issn.2218-6751.2011.11.02.
26. Ghalehbandi S, Yuzugulen J, Pranjol MZI, Pourgholami MH. The role of VEGF in cancer-induced angiogenesis and research progress of drugs targeting VEGF. Eur J Pharmacol. 2023;949:175586. doi: 10.1016/j.ejphar.2023.175586.
27. Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. Gynecol Oncol. 2010;117(3):497-504. doi: 10.1016/j.ygyno.2010.02.021.
28. Sznurkowski JJ. To Bev or not to Bev during ovarian cancer maintenance therapy? Cancers. 2023;15(11):2980. doi: 10.3390/cancers15112980.

29. Monk B, Lammers P, Cartwright T, Jacobs I. Barriers to the access of bevacizumab in patients with solid tumors and the potential impact of biosimilars: A physician survey. Pharmaceuticals. 2017;10(4):19. doi: 10.3390/ph10010019.
30. Benedetti Panici P, Giannini A, Fischetti M, Lecce F, Di Donato V. Lymphadenectomy in ovarian cancer: Is it still justified? Curr Oncol Rep. 2020;22(3):22. doi: 10.1007/s11912-020-0883-2. PMID: 32036457.
31. Gonzalez R, Havrilesky LJ, Myers ER, Secord AA, Dottino JA, Berchuck A, et al. Cost-effectiveness analysis comparing “PARP inhibitors-for-all” to the biomarker-directed use of PARP inhibitor maintenance therapy for newly diagnosed advanced stage ovarian cancer. Gynecol Oncol. 2020;159(2):483-490. doi: 10.1016/j.ygyno.2020.08.003.
32. Cohn DE, Kim KH, Resnick KE, O'Malley DM, Straughn JM Jr. At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. J Clin Oncol. 2011;29(10):1247-1251. doi: 10.1200/JCO.2010.32.1075. Epub 2011 Mar 7. PMID: 21383297.
33. Hinde S, Epstein D, Cook A, Embleton A, Perren T, Sculpher M. The cost-effectiveness of bevacizumab in advanced ovarian cancer using evidence from the ICON7 trial. Value Health. 2016;19(4):431-439. doi: 10.1016/j.jval.2016.01.013. Epub 2016 Mar 24. PMID: 27325335.
34. Penn CA, Wong MS, Walsh CS. Cost-effectiveness of maintenance therapy based on molecular classification following treatment of primary epithelial ovarian cancer in the United States. JAMA Netw Open. 2020;3(12). doi: 10.1001/jamanetworkopen.2020.28620.
35. Yang H, Yu AP, Wu EQ, Yim YM, Yu E. Healthcare costs associated with bevacizumab and cetuximab in second-line treatment of metastatic colorectal cancer. J Med Econ. 2011;14(5):542-552. doi: 10.3111/13696998.2011.596600.
36. Ding H, He C, Tong Y, Fang Q, Mi X, Chen L, et al. Cost-effectiveness of PARP inhibitors in malignancies: A systematic review. PLOS ONE. 2022;17(12). doi: 10.1371/journal.pone.0279286.
37. Kim A, Ueda Y, Njoku K, Fujita K. Cost-effectiveness of maintenance PARP inhibitors in newly diagnosed advanced ovarian cancer. J Manag Care Spec Pharm. 2020;26(5):607-615. doi: 10.18553/jmcp.2020.26.5.60.
38. Filip R, Gheorghita Puscaselu R, Anchidin-Norocel L, Dimian M, Savage WK. Global challenges to public health care systems during the COVID-19 pandemic: A review of pandemic measures and problems. J Pers Med. 2022;12(8):1295. doi: 10.3390/jpm12081295.

Figure 1. Healthcare workers' time per patient.
IV: intravenous; PO: oral. PO therapy allowed healthcare workers to save 61-76% on a single access. As "other activities" time spent performing blood sampling from external laboratories and withdrawing the drug from the territorial pharmacy was considered. Concerning the time spent administrating IV therapy, only 40% of that time was considered due to healthcare workers' procedures.

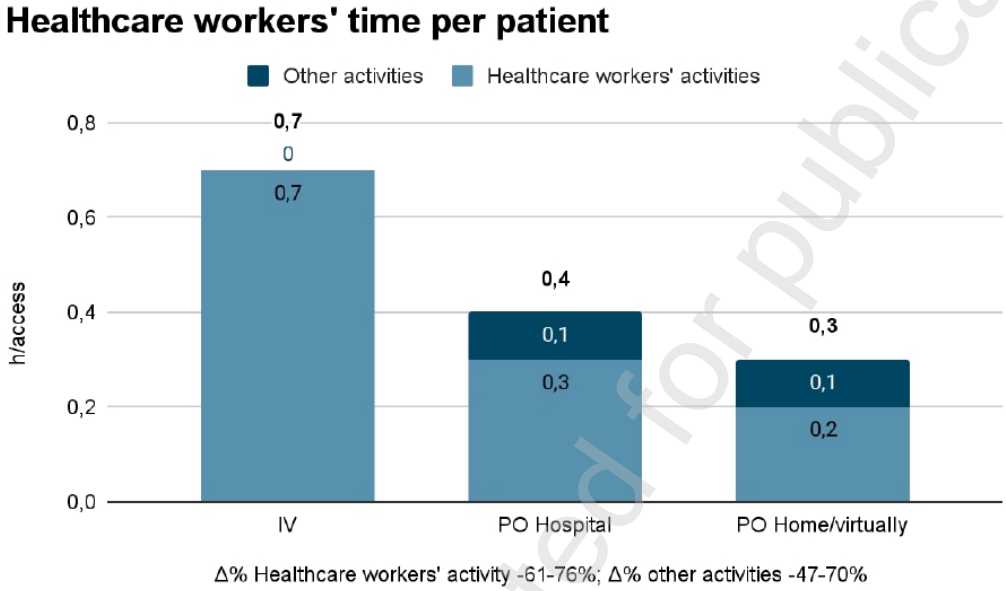

Figure 2. Annual Hospital and Healthcare System's cost per patient.
IV: intravenous; PO: oral. PO therapy allowed hospital and healthcare system to save 93-95% on consumables and 91-94% on hospital workers.

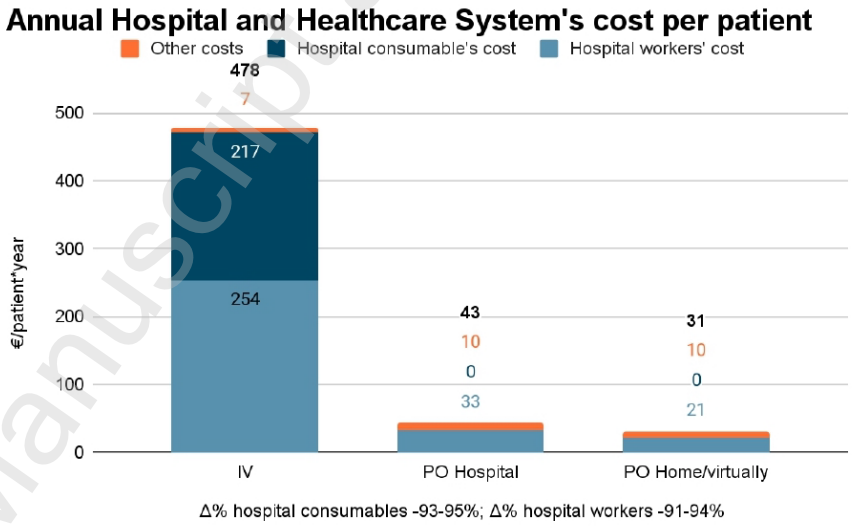

Figure 3. Patient's time spent per access.
IV: intravenous; PO: oral.
Time spent by PO patients on "waiting" is considerably less than IV. Overall, PO therapy allowed patients to save 49-74% of the time per single access.
As "other activities" time spent performing blood sampling from external laboratories and withdrawing the drug from the territorial pharmacy was considered. As time spent on "movement" the following were considered: round-trip from home to the Hospital, the external laboratories and the territorial pharmacy.

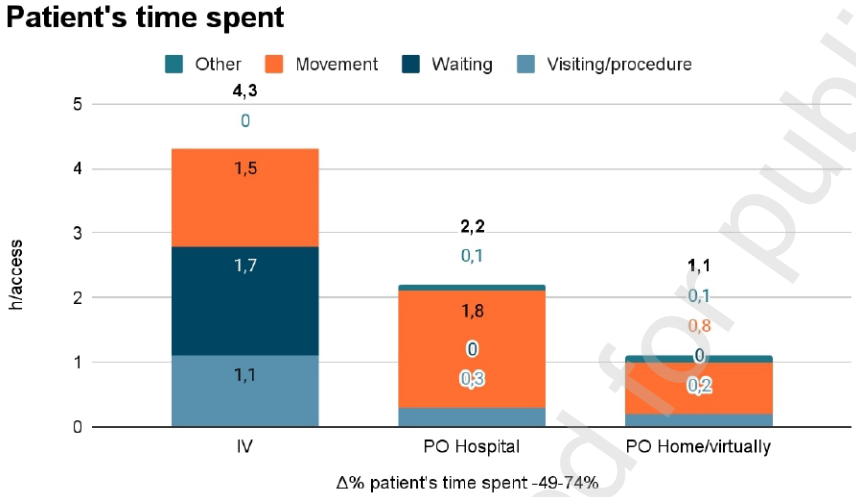

Figure 4. Social annual cost for loss of productivity.
IV: intravenous; PO: oral.
PO-treated patients' loss of productivity is significantly less, particularly concerning the hospital-care-related time of permanence.
As loss of productivity on "movement" the following were considered: round-trip from home to the Hospital, the external laboratories and the territorial pharmacy.