The Evidence Base® Editor's picks

Real-world oncology research: treatment patterns, costs and economic burden

Content includes:

Research Article: Real-world direct healthcare costs of treating recurrent high-grade serous ovarian cancer with cytotoxic chemotherapy

Research Article: Crizotinib versus chemotherapy: a real-world cost–effectiveness study in China

Review: Rituximab biosimilars in hematologic malignancies: the need for a real-world approach

Research Article: Economic burden and treatment patterns for patients with diffuse large B-cell lymphoma and follicular lymphoma in the USA

Research Article: Real-world treatment patterns in patients with advanced (stage III–IV) ovarian cancer in the USA and Europe

Research Article: Economic burden of illness associated with localized prostate cancer in the United States

Stay updated by following The Evidence Base on social media

@EvidenceBaseFSG @theEvidenceBase The Evidence Base

Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Journal of **Comparative Effectiveness Research**

Real-world direct healthcare costs of treating recurrent high-grade serous ovarian cancer with cytotoxic chemotherapy

Lucy Gilbert[1,2,3], Agnihotram V Ramanakumar[4], Maria Carolina Festa[1,2], Kris Jardon[1,2,3], Xing Zeng[1,2,3], Claudia Martins[1,2,3], Layla Shbat[1,2], Marwa Abo Alsoud[1,2], Manuel Borod[3,5], Michael Wolfson[6], Ioanna Papaioannou[7], Olga Basso[4,8] & John Sampalis*[,7,9]

[1]McGill University Health Center, Gynecologic Cancer Services, Cancer Care Mission, 1001 Decarie Boulevard, Montreal, QC, H4A 3J1, Canada
[2]McGill University, Department of Obstetrics & Gynecology, 1001 Decarie Boulevard, Montreal, QC, H4A 3 J1, Canada
[3]Department of Oncology, McGill University, 5100 de Maisonneuve Boulevard West, Montreal, QC, H4A 3T2, Canada
[4]Research Institute of The McGill University Health Center, 1001 Decarie Boulevard, Montreal, QC, H4A 3J1, Canada
[5]McGill University Health Center, Supportive & Palliative Care Services, Cancer Care Mission, 1001 Decarie Boulevard, Montreal, QC, H4A 3 J1, Canada
[6]University of Ottawa, Department of Epidemiology & Community Medicine, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3, Canada
[7]JSS Medical Research, 9400 Henri-Bourassa West, Montreal, QC, H4S 1N8, Canada
[8]Department of Epidemiology, Biostatistics, & Occupational Health, McGill University, 1020 Pine Avenue West, Montreal, QC, H3A 1A2, Canada
[9]McGill University, Faculty of Medicine, Department of Surgery, Division of Surgical Research, 1650 Cedar Avenue, Montreal, QC, H3G 1A4, Canada
*Author for correspondence: Tel.: +1 514 934 6116; john.sampalis@mcgill.ca

Aim: To describe the direct healthcare costs associated with repeated cytotoxic chemotherapy treatments for recurrent high-grade serous cancer (HGSC) of the ovaries. **Patients & methods:** Retrospective review of 66 women with recurrent stage III/IV HGSC ovarian cancer treated with repeated lines of cytotoxic chemotherapy in a Canadian University Tertiary Center. **Results:** Mean cost of treatment of first relapse was CAD$52,227 increasing by 38% for two, and 86% for three or more relapses with median overall survival of 36.0, 50.7 and 42.8 months, respectively. In-hospital care accounted for 71% and chemotherapy drugs accounted for 17% of the total costs. **Conclusion:** After the third relapse of HGSC, cytotoxic chemotherapy did not prolong survival but was associated with substantially increased healthcare costs.

First draft submitted: 14 February 2020; Accepted for publication: 6 March 2020; Published online: 30 March 2020

Keywords: cytotoxic chemotherapy • healthcare costs • recurrent high-grade serous ovarian cancer

Ovarian cancer ranks within the top five as a cause of cancer-related mortality and healthcare expenditure in women [1,2]. 80% of deaths from ovarian cancer are due to its most common subtype, high-grade serous cancer (HGSC), which is characteristically diagnosed at stage III/IV, and despite treatment will recur in 80% of patients [3–5]. Once it recurs, unless amenable to complete resection, it is incurable and hence the goal of treatment is to alleviate symptoms and prolong good-quality life with chemotherapy [3,6]. However, emerging resistance makes the remissions achieved with cytotoxic chemotherapy only temporary, with shorter treatment-free intervals and cumulative toxicity with successive lines of treatment [7].

Advances in precision medicine now make available, targeted therapies that significantly delay recurrence with lower toxicity compared with cytotoxic chemotherapy [5,6]. For example, oral poly-ADP ribose polymerase inhibitors have produced clinically meaningful prolongation of good-quality life for women with germline or somatic breast

Future Medicine

cancer gene mutations and platinum-sensitive HGSC recurrence [8–11]. Despite benefits to patients, the high acquisition cost of these therapies limits their accessibility.

Unfortunately, the health economic assessment of newer treatments is hampered by the lack of comprehensive data on healthcare costs related to the treatment of disease recurrences with the current standard of care, specifically, multiple lines of chemotherapy [12,13]. This is because health economic assessments focus on drug acquisition costs, which represent only a fraction of the total financial burden of cancer care. Other costs, such as those related to emergency room visits, tests, interventions as well as hospital stays, are often not included or are underestimated in these assessments. This happens because fragmentation of healthcare provision, combined with lack of precision and granularity in administrative databases that group together various ovarian cancer subtypes and stages of disease, preclude obtaining accurate and specific healthcare utilization and cost estimates. As a result, the costs of treating cancer are underestimated. In addition, most cost–effectiveness evaluations of cancer treatments are based on Phase II/III randomized controlled trials [14], which have limited generalizability to the target population because neither treatment protocols, nor the participating patients are representative of the real-world setting [15]. For example, poor performance status and comorbidities, despite being common in patients with recurrent cancer, are exclusion criteria in Phase II/III randomized controlled trials [15]. It follows that accurate cost assessments derived from the real-world setting are essential for the assessment of new treatments and their comparison to conventional cytotoxic therapies.

The results of a study published by Doyle *et al.* almost 20 years ago, showed that increased lines of chemotherapy were associated with increased costs but not better outcome or survival. In this study, inpatient care, chemotherapy agents and outpatient care accounted for 62, 21 and 8% of the total healthcare costs. Of the total costs, 43% was attributable to chemotherapy and 43% to supportive care. However, since the publication of this study, cancer treatments have changed and most chemotherapy is now delivered in the outpatient setting [16]. Gordon *et al.* reported that in women with primary epithelial ovarian cancer, treatment costs increased with later stage at diagnosis and more than one lines of chemotherapy [17]. Similar results were reported by Delgado-Ortega *et al.* using Markov models to simulate cohorts of women with epithelial ovarian cancer in Spain [18]. Using health economic models, Rocconi *et al.* showed that the incremental cost–effectiveness ratio was not favorable after the second line of chemotherapy in patients with platinum resistant epithelial ovarian cancer [19]. Therefore, there is a need for contemporary real-world cost assessment of conventional chemotherapy regimens to provide a benchmark in the health economic evaluation of new emerging treatments [12,13,15].

The current study describes the direct healthcare cost of treating recurrent HGSC with standard-of-care cytotoxic chemotherapy in a Canadian Tertiary University Center.

Material & methods

Study design

This is a retrospective chart review of patients treated by the Gynecology Oncology Service at the McGill University Health Center (MUHC), a tertiary care academic hospital in Montreal (QB, Canada). The study was approved by the Research Ethics Board of the MUHC. Using the database of the Service, the oncology pharmacy-database and the institutional tumor registry, we identified all patients with recurrent stage III/IV HGSC treated at the MUHC between 2010 and 2014. In order to be included in the study, patients must have had their first recurrence between 2010 and 2014 and were exclusively treated at the MUHC from recurrence until transfer to palliative care services or death. Patients treated with targeted therapies, such as PARP-inhibitors and Bevacizumab, were excluded because during the study period, these therapies were not publicly funded and were used only as part of clinical trials.

Setting

The Canadian universal public health insurance covers all in-hospital medical services and medications. In Quebec, all residents have mandatory public or private outpatient drug insurance. Gynecologic cancer care in Quebec is largely provided by teams accredited by the government's cancer agency. The MUHC Gynecology Oncology team has level IV accreditation (the highest).

Details of standard of care are provided in Box 1. At first recurrence, patients for whom repeat surgery is not possible are treated with chemotherapy that is delivered in a dedicated ambulatory Oncology Day Center. More specifically, the medical team consists of surgeons that perform all surgeries and medical oncologists who are responsible for the selection and administration of chemotherapy. The type of chemotherapy used depends on the platinum sensitivity of the disease and response to previous treatments and the treating physician's judgment. Patient

Box 1. Details of standard of care.

- Decisions about each patient's management at recurrence are made at the interdisciplinary tumor-board. Patients with potentially resectable disease, in other words, oligo-metastases, are generally treated by repeat surgery. If the recurrent disease is deemed inoperable, patients are offered chemotherapy. As the goal of treatment is to prolong good-quality life, we delay starting chemotherapy in asymptomatic patients; however, we initiate it before tumor burden is high.
- Patients with platinum-sensitive recurrence are retreated with combination chemotherapy of platinum with taxol or pegylated liposomal doxorubicin; platinum monotherapy is used in patients with poor performance status. Platinum-resistant recurrence is treated with pegylated liposomal doxorubicin. If the disease fails to respond, gemcitabine, weekly taxol, topotecan, alkylating agents, hormones are used as per the treating physician's judgement. As the single-payer of the second most populous province in Canada, the Quebec Government negotiates drug prices and, when available, generic versions of drugs are used.
- The interdisciplinary gynecologic oncology team includes a dedicated pivot nurse, a clinical nurse specialist and a liaison nurse, who help patients maximize the use of outpatient services and services in the community and reduce the need for inpatient care.
- The gynecologic oncology service works closely with the Supportive and Palliative Care Service, which includes four subspecialized services: Cancer Pain Clinic, Cancer Nutrition and Rehabilitation, Psycho-social Oncology and the Supportive Care Clinic. Symptomatic patients are referred to this service to help manage physical and emotional symptoms alongside active chemotherapy treatment.
- Intervention to prolong life or alleviate symptoms (gastrointestinal stents, double j-catheters/nephrostomy, drains for pleural effusion and ascites, intensity-modulated radiotherapy, radio ablation or surgical removal of isolated metastasis, nerve blocks) are used liberally.
- In Quebec, physicians are not salaried and bill the provincial government using a complex system of basic and supplemental fees. Fees vary depending on whether the physician is on the subspecialist register, time of consultation (e.g., night, holidays), duration of consultation, whether academic teaching is involved, language barriers, reduced mobility, among others.

care is provided by a multidisciplinary team that is comprised of gynecologic oncologists, palliative care specialists, nurses, pharmacists and other healthcare professionals as needed. All treatments including administration of chemotherapy, transfusions, drainage of ascites or pleural effusions and management of adverse events are provided by the Gynecology Oncology Service. The Gynecologic Oncology Service consults and works with the Supportive and Palliative Care Service (SPCS) early in the trajectory of recurrent disease. When the projected life expectancy of a patient is thought to be less than 3 months and the patient is no longer on chemotherapy, she is eligible for increased home services under the jurisdiction of the SPCS, or for transfer to the SPCS inpatient facility at the MUHC or to a hospice in the community. All cost for patient management including chemotherapy is paid by the Provincial Health Insurance. The majority of Quebec residents have mandatory drug insurance that covers most of the prescription drug costs. Thus, all patients have equitable access to approved and funded interventions/drugs regardless of their financial status and ability to pay. The current study includes only the costs incurred while patients were under active chemotherapy treatment by the Gynecology Oncology Service.

Ascertainment of direct healthcare costs

We ascertained healthcare resource utilization from hospital medical records, in-hospital medication use from the hospital pharmacy database and outpatient prescriptions from the medical records. Costs for services were calculated using the unit costs provided by the *Regie de l'assurance maladie du Quebec*, the Quebec government's health insurance agency, and the MUHC Finance Department.

Direct healthcare costs were ascertained for the following:

- All prescription drugs, including chemotherapy;
- Imaging;
- Blood tests;
- Surgery, radiotherapy and other interventions intended to palliate or cure recurrent disease;
- Ambulatory care;
- Emergency room visits;

- Cost for inpatient hospital stays including medical interventions, nursing, support services, nutritional support, physiotherapy, palliative and occupational therapy. These are predominantly, but not exclusively, related to the costs of managing adverse events;
- Outpatient costs which include the cost for administration of chemotherapy.

The following costs could not be ascertained and are not included in the analysis:

- Physician fees;
- Services provided by the Local Community Services Centers;
- Cost incurred during admission to rehabilitation centers;
- Home care services;
- Palliative care services;
- Primary care services.

Statistical analyses

Patients were classified into treatment groups according to the number of chemotherapy regimens (lines) received as none, one, two and three or more. Descriptive statistics were reported for the entire patient cohort and for groups according to the number of chemotherapy treatments received. Overall survival (OS) and progression-free survival (PFS) were estimated with the Kaplan–Meier Estimator. Healthcare costs were ascertained from the time of recurrence until transfer to the palliative care service or death. Costs are reported in 2016 Canadian dollars. Analyses were conducted on observed data. There were no imputations for missing data. Descriptive statistics for costs included the mean, median and interquartile range. Bivariate comparisons were conducted with the χ^2 statistics for categorical variables, analysis of variance for continuous variables and the Jonckheere–Terpstra test for ordered alternatives for costs. Multivariate analysis of variance was used to determine the proportion of variance in the total costs attributed to each cost component and to adjust the between-group differences with respect total costs for patient demographics and profile. Generalized linear models with a gamma distribution and log as the link function was used to adjust the total healthcare costs for potential confounders. Multivariate linear regression was used to develop a predictive model for total direct healthcare costs. All analyses were conducted with Statistical Package for the Social Sciences (SPSS) version 24.

Results

Of the 120 patients with recurrent stage III/IV HGSC treated at the MUHC during the study period, 66 met the study inclusion criteria. There were no clinically important differences between the patients included in the analysis and those who were excluded (Table 1), demonstrating that the study cohort was representative of women with recurrent stage III/IV HGSC treated at the MUHC. Mean age (standard deviation [SD]) was 60.6 (8.6) years, and 48% of the women were Caucasian. At diagnosis, 68% had stage IIIC, and 25% had stage IV disease. The median (95% CI) PFS and OS of the 66 HGSC patients included in the analysis were 16.4 (12.9–21.4) and 40.3 (33.2–50.7) months, respectively. No patient in this series was admitted to the intensive care or high-dependency unit during follow-up. All had at least one consultation with the SPCS.

Seven patients (11%) with comorbidities and poor performance status died without receiving further chemotherapy postrecurrence and were not included in the cost analysis. Of the remaining 59 patients, 16 (24%) received one line, 21 (32%) received two and 22 (33%) received three or more lines of cytotoxic chemotherapy for recurrent disease. There were no statistically significant differences with respect to patient demographics and disease parameters between the patient groups.

The patients that received only one line of chemotherapy had a lower proportion of patients younger than 55 years old (18.8 vs 28.65 and 31.8%), lower proportion with history of breast cancer (6.3 vs 19.0 and 13.6%), lower proportion with wild-type *BRCA* (18.8 vs 28.6 and 50.0%) and higher proportion with no residual after surgery (31.3 vs 19.0 and 18.2%) when compared with those receiving two or more lines.

Patients that received two lines of chemotherapy postrecurrence had lower proportion with International Federation of Gynecology and Obstetrics (FIGO) stage IV (19.0 vs 31.3 and 27.3%), platinum resistant tumors (14.3 vs 26.7 and 31.8%) and treated with neoadjuvant chemotherapy (38.1 vs 62.5 and 54.5%) when compared with patients treated with one or more than three lines, respectively (Table 2).

Table 1. Patient profile by cohort.

Variable	Total cohort		Excluded from cohort		Excluded from analysis		Included in analysis	
N	120	Percentage	54	Percentage	7	Percentage	59	Percentage
Age: n, %								
– <55	33	27.5	16	29.6	1	14.3	16	27.1
– 55–64	47	39.2	21	38.9	1	14.3	25	42.4
– 65–74	30	25.0	12	22.2	4	57.1	14	23.7
– 75+	10	8.3	5	9.3	1	14.3	4	6.8
Age: mean (SD)	60.3 (9.7)		59.4 (10.4)		65.3 (10.83)		60.6 (8.61)	
Ethnicity: n %								
– Caucasian	60	50.4	27	50.0	5	71.4	28	48.3
– Other	22	18.5	12	22.2	1	14.3	9	15.5
– Unknown	37	30.8	15	27.8	1	14.3	21	36.2
History of breast cancer: n %								
– Yes	13	10.8	5	9.3			8	13.6
– No	102	85.0	45	83.3	7	100.0	50	84.7
– Unknown	5	4.2	4	7.4			1	1.7
BRCA status: n %								
– *BRCA1*/*BRCA2*	20	16.7	7	13.0	1	14.3	12	20.3
– Wild type	37	30.8	15	27.8	2	28.6	20	33.9
– Unknown	62	52.5	31	57.4	4	57.1	27	45.8
Surgery outcome (residual): n %								
– No residual	32	26.7	16	29.6	3	42.9	13	22.0
– <1 cm residual	52	43.3	22	40.7	2	28.6	28	47.5
– 1+ cm residual	31	25.8	13	24.1	2	28.6	16	27.1
– Unknown	5	4.2	2	3			2	3.4
FIGO stage: n %								
– Stage 3A/3B	10	8.3	4	6			4	6.8
– Stage 3C	85	70.8	46	69.7	6	85.7	40	67.8
– Stage IV	25	20.8	16	24.2	1	14.3	15	25.4
Chemotherapy type: n %								
– Adjuvant	62	51.7	31	47	2	28.6	29	49.2
– Neo adjuvant	58	48.3	35	53	5	71.4	30	50.8

There were 120 patients identified, of which 66 fulfilled the study inclusion and exclusion criteria. Of these 66, 7 were excluded from further analyses because they died before receiving the chemotherapy after the recurrence.
FIGO: International Federation of Gynecology and Obstetrics.

The median OS from first diagnosis for patients with one, two and three or more chemotherapy lines postrecurrence was 36.7, 50.7 and 42.8 months, respectively (p = 0.941; Figure 1); median PFS was 13.3, 13.6 and 14.7 months, respectively (p = 0.161; Figure 2). Median OS for the entire cohort from first recurrence was 21.0 months (95% CI: 17.25, 24.7) and from initiation of chemotherapy for the third relapse it was 7.9 months (95% CI: 3.6, 11.74).

Table 3 shows that compared with the mean healthcare costs incurred for patients receiving one line of chemotherapy (CAD$52,227) for relapsed disease, the mean total costs were 38% ($72,374) and 86% ($97,243) higher, respectively, for those treated with two or three and more lines of chemotherapy. The mean for all cost components increased with the number of chemotherapy lines used. In-hospital stay was the largest contributor to healthcare costs for all groups, accounting for 71% of the direct costs (Figure 3). The cost of all prescription medications, including chemotherapy, accounted for 17% of the total direct healthcare costs across all treatment groups.

Figure 4 shows the quintile distributions of the total costs by the number of postrecurrence lines of chemotherapy. The respective distribution of total healthcare costs for patients receiving one, two and three or more lines of chemotherapy were below $79,900 in 57, 38 and 18% between $79,900 and $109,854 in 6, 33 and 18% and above $109 854 for 13, 14 and 41%, respectively, for each group.

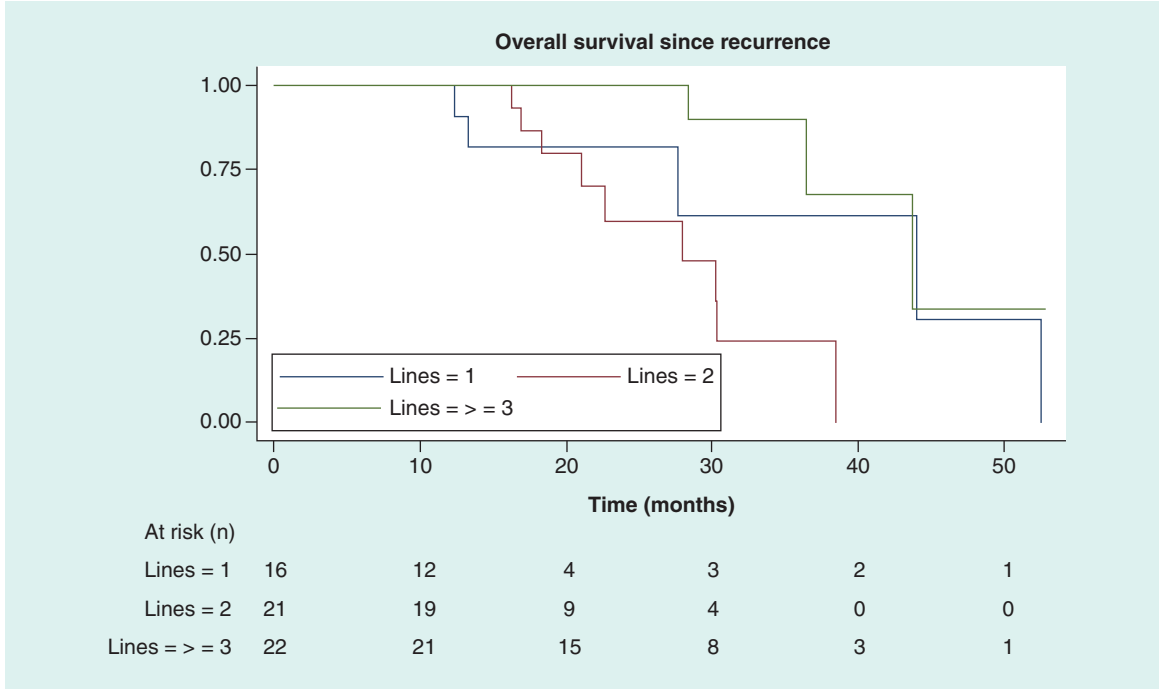


Figure 1. Overall survival from first diagnosis for patients with one, two and three or more chemotherapy lines postoccurrence.

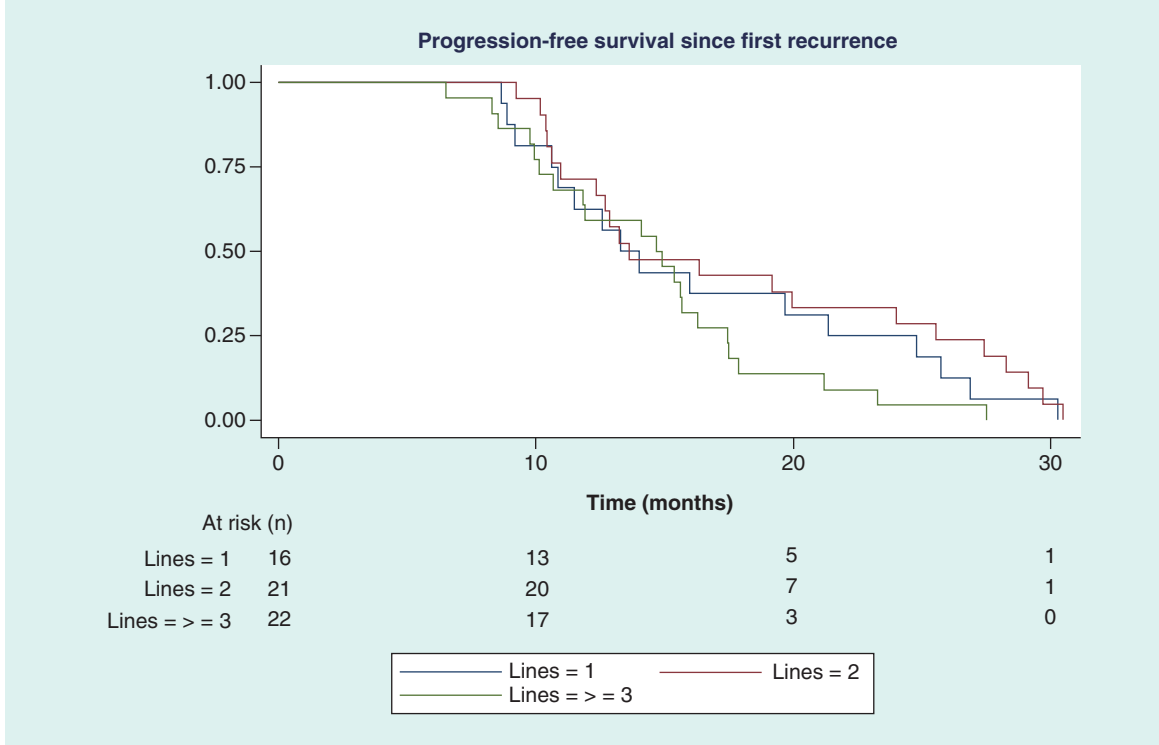


Figure 2. Progression-free survival since first recurrence.

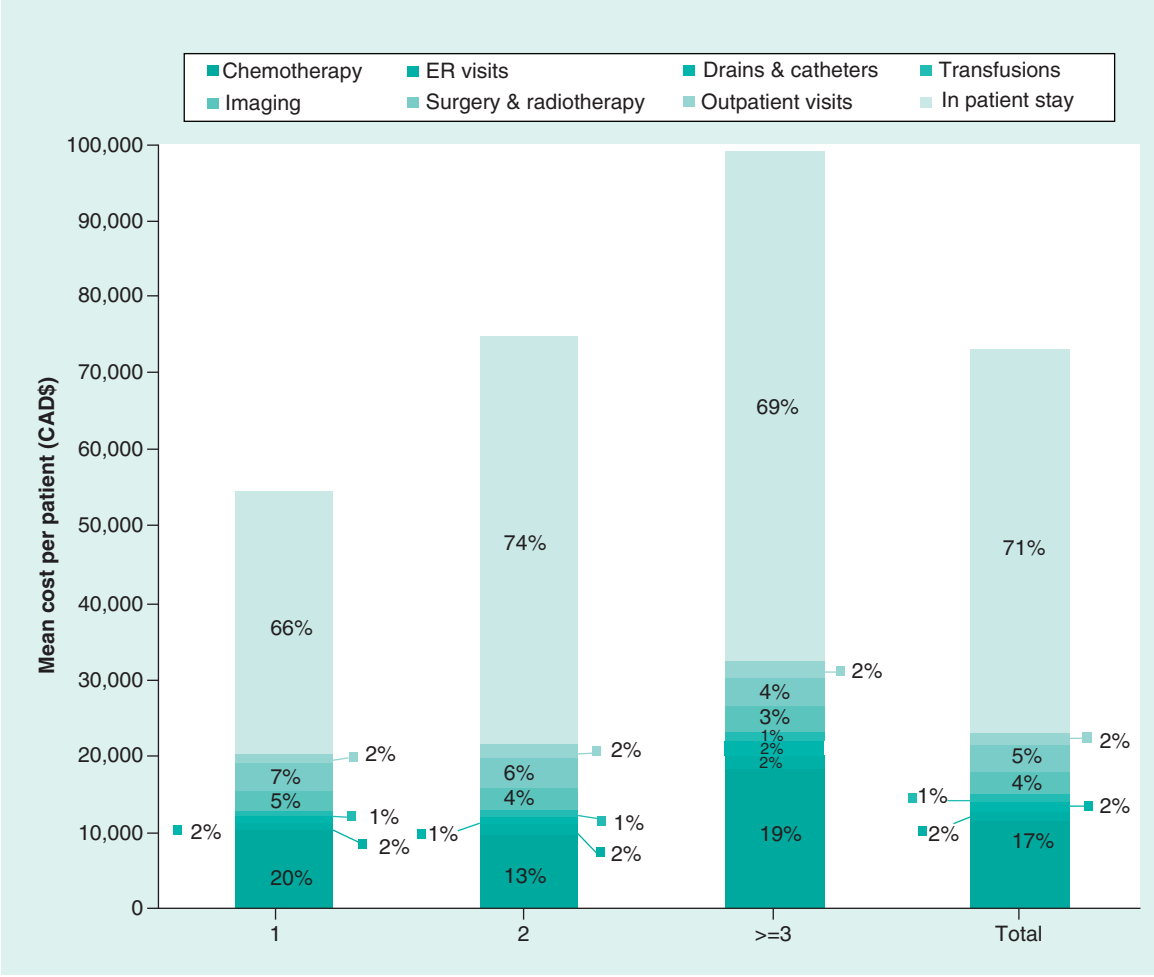


Figure 3. Total direct healthcare cost by number of postrecurrence chemotherapy treatments. In-hospital stay was the largest contributor to healthcare costs, accounting for 71% of the total direct healthcare costs, while the cost of medications accounted for 17% of the costs.

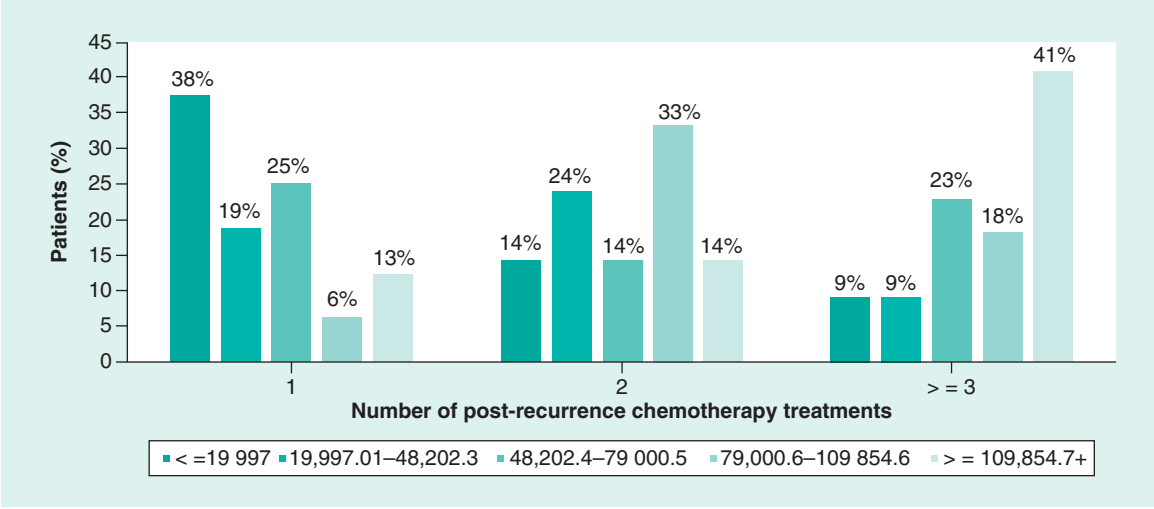


Figure 4. Distribution of total direct healthcare costs by number of postrecurrence chemotherapy treatments. With increasing number of chemotherapy treatments, the proportion of patients in whom costs exceeded CAD$109,854 increased from 13 to 41%.

Table 2. Patient profile by number of postrecurrence chemotherapy treatments.

Variable		Total lines of chemotherapy postrecurrence								p-value
		1		2		>= 3		Total		
		N	Percentage	N	Percentage	N	Percentage	N	Percentage	
N		16		21		22		59		
Age group	<55	3	18.8	6	28.6	7	31.8	16	27.1	0.060
	55–64	8	50.0	5	23.8	12	54.5	25	42.4	
	65–74	5	31.3	6	28.6	3	13.6	14	23.7	
	>= 75			4	19.0			4	6.8	
Age (years): mean (SD)		61.1 (6.6)		62.8 (11.12)		58.3 (6.72)		60.6 (8.61)		0.227
Race	Caucasian	8	50.0	8	40.0	12	54.5	28	48.3	0.422
	Other	1	6.3	3	15.0	5	22.7	9	15.5	
	Unknown	7	43.8	9	45.0	5	22.7	21	36.2	
History of breast cancer	Yes	1	6.3	4	19.0	3	13.6	8	13.6	0.560
	No	15	93.8	17	81.0	18	81.8	50	84.7	
	Unknown					1	4.5	1	1.7	
BRA	BRCA1/BRCA2	4	25.0	5	23.8	3	13.6	12	20.3	0.337
	Wild type	3	18.8	6	28.6	11	50.0	20	33.9	
	Unknown	9	56.3	10	47.6	8	36.4	27	45.8	
Surgery outcome (residual)	None	5	31.3	4	19.0	4	18.2	13	22.0	0.565
	<1 cm	7	43.8	10	47.6	11	50.0	28	47.5	
	>= 1 cm	4	25.0	5	23.8	7	31.8	16	27.1	
	Unknown			2	9.5			2	3.4	
FIGO stage	IIIA/IIIB	1	6.3	3	14.3			4	6.8	0.410
	IIIC	10	62.5	14	66.7	16	72.7	40	67.8	
	IV	5	31.3	4	19.0	6	27.3	15	25.4	
Platinum sensitive†	Yes	11	73.3	18	85.7	15	68.2	50	76.9	0.517
	No	4	26.7	3	14.3	7	31.8	15	23.1	
Chemotherapy type	Adjuvant	6	37.5	13	61.9	10	45.5	29	49.2	0.308
	Neoadjuvant	10	62.5	8	38.1	12	54.5	30	50.8	

The p-value based on χ^2 test and analysis of variance for mean age.
†Platinum sensitivity was not know for one patient with I line of chemotherapy.
FIGO: International Federation of Gynecology and Obstetrics.

The total direct healthcare costs for patients with platinum resistance disease were higher when compared with those with platinum sensitive tumors, although the differences were not statistically significant (p = 0.364). The increase in total direct healthcare costs with higher number of lines of chemotherapy treatment was similar for platinum sensitive and resistant disease. Furthermore, chemotherapy accounted for 14.8 and 24.5%, and inpatient cost accounted for 71.5 and 66.4% of the total direct healthcare costs for patients with platinum sensitive and resistant disease respectively (Figure 5).

After adjusting for patient's age, race, BRCA type, use of adjuvant chemotherapy, history of breast cancer, FIGO status and platinum sensitivity, the mean (95% CI) total direct health costs for 1, 2 and >= 3 lines of postrecurrence chemotherapy were $68,805 ($39,238–$98,374), $84,482 ($56,723–$112,242) and $107,202 ($81,396–$133,008; Figure 6).

Inpatient stay was the major driver of the between-group differences in adjusted direct health costs, contributing 80.8% of the cost variance, with chemotherapy accounting for 8.1% (Table 4).

The results of the multivariate linear regression analysis showed that after adjusting for the same covariates listed above, each additional line of chemotherapy postrecurrence increased the total direct healthcare costs by $10,620 (p = 0.067; Table 5). This analysis also showed that the effect of history of breast cancer (p = 0.109), *BRCA* type (p = 0.113) and FIGO stage (p = 0.116) on total direct healthcare costs approached statistical significance.

Table 3. Direct healthcare costs by number of postrecurrence chemotherapy treatments.

Cost component	Total lines of chemotherapy postrecurrence												
	1			2			≥3				Total		
	Mean	Median	IQR	Mean	Median	IQR	Mean	Median	IQR	p-value[†]	Mean	Median	IQR
Drugs	$10,380	$2670	$4078	$9646	$6450	$8366	$18,442	$16,237	$12,549	0.001	$13,126	$8942	$12,094
ER visits	$875	$467	$1167	$1267	$934	$1400	$1507	$1400	$1400	NS	$1250	$934	$1400
Drains/materials	$874	$290	$1210	$900	$540	$1133	$2039	$828	$2097	NS	$1318	$540	$2398
Transfusion	$570	$454	$454	$974	$905	$551	$1343	$1455	$810	<0.001	$1002	$908	$1103
Imaging	$2695	$2966	$3190	$2851	$2516	$1406	$3287	$3371	$1784	NS	$2972	$3213	$1640
Surgery/radiotherapy	$3581	$3505	$1400	$4007	$4616	$4708	$3753	$4028	$1870	NS	$3838	$4028	$3523
Outpatient visits	$1232	$1034	$1334	$1753	$1698	$977	$2237	$2184	$1241	0.004	$1792	$1716	$2002
Inpatient stay	$34,092	$16,373	$45,431	$53,281	$55,392	$59,886	$66,473	$65,690	$67,105	0.036	$52,997	$46,033	$52,930
Total costs:													
Entire cohort	$52,277	$43,139	$57,507	$72,374	$79,001	$61,146	$97,243	$93,089	$64,196	0.010	$76,197	$74,017	$62,892
Platinum sensitive	$50,898	$28,296	$65,386	$67,886	$55,023	$54,435	$91,622	$91,859	$65,435	0.014	$71,730	$63,633	$73,655
Platinum resistant	$50,652	$44,021	$81,840	$96,744	$104,707	–	$105,957	$101,664	$60,086	0.207	$88,182	$98,437	$63,367
p-value[‡]	0.794			0.269			0.860				0.364		

p-values are based on the Jonckheere–Terpstra test for ordered alternatives.
[†]Between number of treatment lines;
[‡]Platinum sensitive versus resistant.
IQR: Interquartile range.

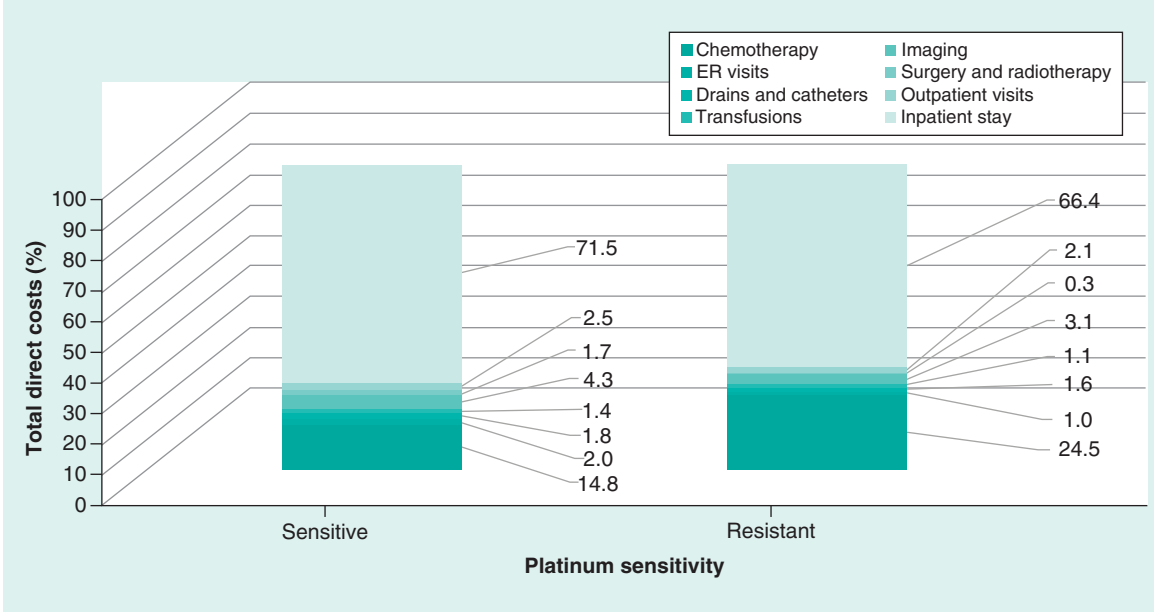


Figure 5. Distribution of total direct healthcare costs by platinum sensitivity of the disease. The distribution of sources of cost was similar for patients with platinum sensitive and resistant disease with the majority of the costs being due to in-hospital stay.
ER: Emergency room.

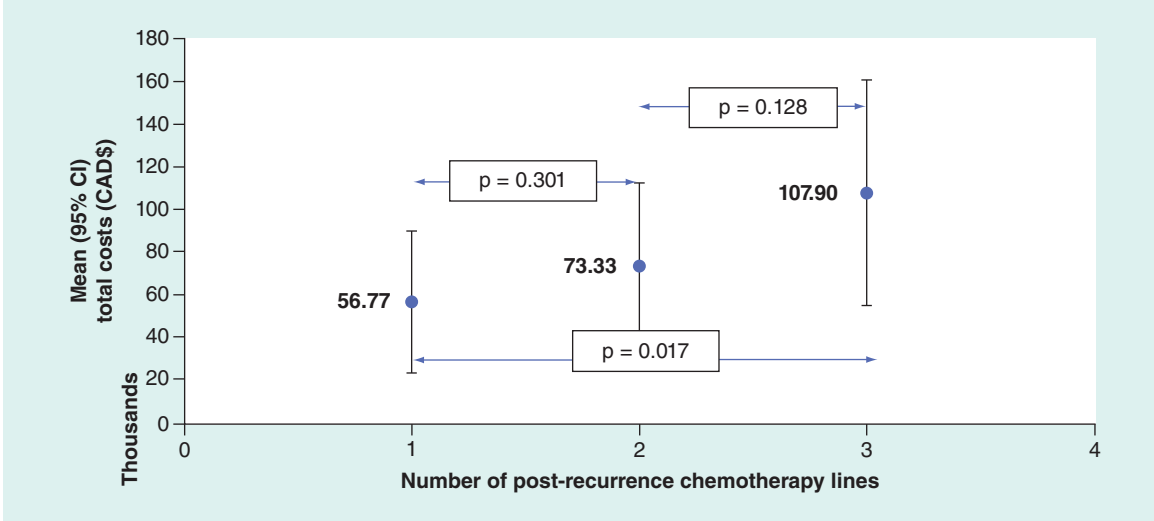


Figure 6. Total direct healthcare costs by number of chemotherapy lines postrecurrence. Least square means adjusted for race, history of breast cancer, *BRCA*, chemotherapy type (adjuvant vs neoadjuvant), FIGO status, platinum sensitivity.

Discussion

In the current study of patients with recurrent ovarian HGSC, continued chemotherapy after the third recurrence did not improve OS or PFS. This is similar to the results reported by Boyle [16] and suggests that when all patients with this disease receive a uniformly high standard of care, patient outcomes are most likely determined by patient characteristics and the biology of the disease, rather than the number of lines of chemotherapy. However, with each recurrence and associated treatment, the direct healthcare costs increased substantially. The proportion of patients in whom costs exceeded $109,854 (the fifth quintile) increased from 13% in those treated with one line of chemotherapy to 41% in those treated with three or more lines for repeated relapses. After adjusting for patient

Table 4. Proportion of variance in direct healthcare costs.

Independent variable	Cost variance (%)[†]
Inpatient stay	80.84
Chemotherapy	8.09
Imaging	3.31
Surgery and radiotherapy	2.33
Outpatient visits	0.87
ER visits	0.46
Drains and catheters	0.20
Transfusions	0.01
Patient and disease parameters[‡]	3.89

[†]Proportion of variance in direct healthcare costs explained by each variable in multivariate analysis of variance model.
[‡]Number of postrecurrence chemotherapy lines, race, history of breast cancer, *BRCA*, chemotherapy type (adjuvant vs neoadjuvant), International Federation of Gynecology and Obstetrics status, platinum sensitivity.
ER: Emergency room.

Table 5. Multiple linear regression model.

Independent/predictor variable	Parameter estimate (β)	SE (β)	p-value
Constant	24437.74	35361.93	0.493
Number of post recurrence chemotherapy lines	10619.53	5677.61	0.067
Race (caucasian vs other)	-13644.45	14032.37	0.336
History of breast cancer (yes vs no)	37394.65	22912.20	0.109
BCRA-1/2 vs wild type/unknown	-29760.88	18449.52	0.113
Chemotherapy (adjuvant vs neoadjuvant)	-12931.55	15387.37	0.405
FIGO 3C vs 3A/3B	29337.85	30940.66	0.348
FIGO IV vs 3A/3C	53175.68	33245.24	0.116
Platinum sensitive vs resistant	-4364.59	17585.44	0.805

Dependent variable = total direct healthcare costs.
FIGO: International Federation of Gynecology and Obstetrics.

and disease parameters, the major driver of healthcare costs in this cohort of patients was inpatient hospital services accounting for 81%, while drug acquisition costs accounted for only 8% of the total.

The pooled results of three large Phase III randomized control trials including 1620 patients showed that the median survival was 8.9, 6.2 and 5.0 months respectively, after treatment of the third, fourth and fifth relapse [7]; the authors suggested that, after three relapses, additional chemotherapy treatments did not appear to be clinically worthwhile. Although patients recruited into randomized control trials are generally selected for better baseline health, in our unselected cohort of patients treated with three or more regimens of chemotherapy for relapse, the median OS of 7.9 months (95% CI: 3.6, 11.7), from the third relapse, was comparable to that of the above study.

The main strength of this study is that it reflects real-world practice. Additional strengths include near complete ascertainment of direct healthcare costs, the granularity of the data, and the homogeneous study population focusing on only stage-III/IV patients with recurrent HGSC. Furthermore, patients were treated by an accredited interdisciplinary team, benefited from the best available treatment regardless of their financial situation, and had access to supportive and palliative care services early in the trajectory of recurrent disease. The lack of improved survival with repeated cytotoxic chemotherapy after the third relapse, even in these near optimal conditions, reveals a major treatment gap for these patients, one that warrants careful consideration for investment in targeted treatments instead of cytotoxic chemotherapy. This study provides useful benchmark cost data for analyses comparing new treatments to conventional cytotoxic chemotherapy. In addition, the current study provides data that can be used to model the effect of additional lines of post recurrence chemotherapy in the real-world setting.

Limitations of this study are inherent to retrospective chart reviews and hospital health record databases. One of the main limitations of retrospective studies is that certain costs may not be ascertained and hence the overall costs would be underestimated. We could only ascertain costs that were documented in medical charts and hospital databases. Costs for physician fees, community clinics, rehabilitation, palliative services and home care as well

as indirect healthcare and intangible costs were not included. Physician fees, being the most important of the nonincluded costs, could not be accurately ascertained, as the Quebec supplemental fee system would render estimates unreliable. Data from the literature on direct healthcare costs for ovarian cancer treatment indicate that physician fees account for 13–20% when chemotherapy administration is included as a physician service [20,21]. Thus, the impact of not including physician-fees on the validity of the results is unlikely to be material but would most likely increase with repeated lines of chemotherapy and further dilute the impact of drug acquisition costs on the total.

Another potential limitation of the study is that the data were derived from a single Canadian University Health Center and that this can affect the generalizability of the results to the target populations of patients with recurrent high-grade serous ovarian cancer that are treated in other provinces of Canada or in other countries.

The MUHC is one of the two University Tertiary Centers in Quebec and one of the few institutions where advanced cancer care is provided in the province. Based on the above, we can consider the sample of patients treated in the MUHC to be an unbiased, and random and hence a valid representative of the Quebec population of women with advanced ovarian cancer.

The age adjusted and overall incidence rates of ovarian cancer is not different between Canadian provinces [22]. Furthermore, the profile, treatment protocols and outcomes of patients with high-grade recurrent serous ovarian cancer will not be different between Canadian provinces and most likely between different developed countries. We can therefore accept that the sample of patients with high-grade recurrent serous ovarian cancer in our study is a reasonable representation of the target population in Canada and developed countries.

With respect to the absolute cost for treatment the recurrences with sequential cytotoxic chemotherapy, there may be differences between provinces and certainly between countries. However, the focus of the study results and the message conveyed, is not with respect to the absolute costs but the relative costs, and specifically the increase in costs with sequential cytotoxic chemotherapies and the proportional contribution of each service component to the overall hospital costs. We can, therefore, accept that while generalization of the absolute cost results in our study to other time periods or provinces may be somewhat limited, the inference to the target population with respect to the impact of repeated sequential chemotherapies and the relative contribution of the different service components to the total costs is reasonable.

Generalization of results in the Universal Canadian healthcare system to other jurisdictions without universal healthcare, with respect to absolute and even relative costs, may be limited. Nonetheless, the results of studies from the Canadian Universal healthcare system, provide valuable benchmark estimates of the absolute costs and relative increases in costs in a setting where access to care is universal. In other words, these studies allow us to conduct health economic assessments under ideal conditions where all patients have access to the same high-quality care.

We could not discern from the clinical notes which of the various factors associated with advanced cancer namely, disease burden, drug toxicity or physical deterioration dictated the need for more inpatient treatment, as these were intertwined. Patients with advanced, recurrent on cytotoxic chemotherapy require frequent admissions to resource-intensive, inpatient units, because any adverse event in a patient on chemotherapy treatment warrants investigations/interventions due to the possibility that it is chemotherapy related and therefore potentially reversible. However, with repeated relapses, bowel-obstruction, increasing pleural effusion and ascites is a function of disease progression for which cytotoxic chemotherapy rarely helps [23].

Our results show that while continuing treatment with more than three lines of chemotherapy does not improve survival, the need for inpatient care reflecting deterioration of functioning was associated with substantially higher costs. This finding is comparable with the data reported by others. Lewin *et al.* found no improvement in survival in patients treated with chemotherapy compared with those receiving palliative care during the end-of-life period; however, there was a significant cost difference [24].

The results of this study and the others attesting to downstream human and financial consequences of using repeated regimens of cytotoxic chemotherapy for HGSC recurrences calls for reappraisal of the current paradigm for treating this disease. Increasingly, new therapies/interventions that are more effective in prolonging life with lower toxicity are becoming available but are much more expensive. When considering the value of these treatments, it would be necessary to compare drug acquisition costs along with downstream healthcare costs associated with these treatments.

Future perspective

The incorporation of newer treatments for cancer that will include targeted therapies, immunotherapies and personalized medicine will be challenged by higher acquisition costs in comparison to currently used cytotoxic chemotherapy-based regimens. Comparative cost–effectiveness studies will be required to assess the societal benefits of these advanced treatments and to appropriately allocate healthcare resources and funding. Real-world ascertainment of the direct healthcare costs associated with conventional cytotoxic chemotherapy treatment will be essential in these evaluations that must consider not only acquisition costs, but all direct healthcare costs related to the management of cancer patients. The current study provides real-world estimates of costs for repeated cytotoxic therapies in patients with recurrent high-grade serum ovarian cancer as well as parameters that can be used in the development of health economic models for the treatment of this disease.

Summary points

- Recurrent high-grade serous cancer (HGSC) of the ovaries is largely incurable.
- The goal of treatment is palliation but repeated treatments with cytotoxic chemotherapy have limited efficacy and high toxicity.
- Precision therapies delay recurrence with lower toxicity, but drug acquisition costs are high.
- This study ascertains the real-world healthcare costs of treating recurrent HGSC with successive regimens of standard-of-care chemotherapy.
- We ascertained the total direct healthcare costs for the treatment of 66 women with stage III/IV HGSC with sequential lines of chemotherapy for their recurrences.
- Healthcare costs ascertained were comprised of costs for prescription medications including chemotherapy, imaging, blood tests, surgical and medical interventions, nursing, and auxiliary healthcare provided in the ambulatory, emergency department and inpatient settings.
- Patients received a median of two lines of chemotherapy for recurrent disease; 33% received three or more lines.
- Median overall survival (from diagnosis to death) was 36.0, 50.7 and 42.8 months, respectively, for patients receiving one, two, and three or more lines of chemotherapy postrecurrence ($p = 0.941$).
- Mean cost of treatment of first relapse was CAD$52,227, and increased by 38% for two, and 86% for three or more relapses.
- In-hospital care was the major driver of healthcare costs, accounting for 71% of the total, while drugs accounted for 17%.
- After the third relapse of HGSC, cytotoxic chemotherapy did not prolong survival but was associated with substantially increased healthcare costs, largely due to the need for in hospital care.
- Downstream real-world costs, including the need for inpatient support associated with repeated cytotoxic therapy should be considered in addition to drug acquisition costs when conducting health economic comparisons of novel precision targeted therapies versus standard of care cytotoxic chemotherapies.

Author contributions

MC Festa, L Shbat, MA Alsoud and C Martins collected data and contributed to interpretation of the results and literature searches. AV Ramanakumar and J Sampalis were responsible for data analysis and interpretation of the results. L Gilbert, M Wolfson and O Basso contributed to interpretation of results. L Gilbert, K Jardon, X Zeng and M Borod cared for the patients who were the subject of the study, supervised data acquisition and interpretation. L Gilbert conceived, designed and planned the study, obtained funding, and drafted the manuscript with the help of O Basso and J Sampalis. All authors contributed to critically reviewing iterations of the manuscript and approved the final version for submission.

Acknowledgments

The views expressed in this publication are those of the authors and not those of the funders.

Financial & competing interests disclosure

The authors gratefully acknowledge generous funding in the form of an unrestricted grant from AstraZeneca. They are grateful for the invaluable help provided by R Walton, MPH, of AstraZeneca with procuring the start-up funds, for the initial literature search, and for helpful and insightful suggestions. The authors are grateful to J Quennville of the Royal Victoria Hospital Foundation and J Shamie of The Cedars Cancer Institute for timely support with procuring critical funds to continue and complete the project. L Gilbert reports grants from AstraZeneca during the conduct of the study and has received lecture honoraria and consultation fees from Roche, AstraZeneca, Pfizer, consultation fees from Wyeth, and research funding from Canadian Institutes of Health

Research, National Institutes of Health, US Department of Defense, Rossy Cancer Network, Royal Victoria Hospital Foundation, The Doggone foundation, Cedars Cancer Institute, Montreal General Hospital Foundation, Carole Epstein Foundation, McGill Collaborative Research Development Fund, Tesaro Inc, Pfizer Inc., ImmunoGen Inc., AstraZeneca, Merck Canada Inc., Endocyte Inc., Aeterna Zentaris, Boehringer Ingelheim, Biogen Idec, Aventis Pharma Inc., Wyeth Canada and Merck Frosst Canada Inc. outside the submitted work. K Jardon and X Zeng have received research funding from Tesaro Inc., Pfizer Inc., ImmunoGen Inc., AstraZeneca and Aeterna Zentaris, outside the submitted work. J Sampalis has received honoraria as a consultant for several pharmaceutical companies including Roche, Pfizer, Novartis, AbbVie, GSK, BMS, Janssen, Celgene, Amgen, Merck, Oncozyme, Oncolytics, Ethicon Endosurgery, Forrest, Genzyme, Lundbeck, IMS, Novo Nordisk, Otsuka, Servier, Shire, Theratechnologies, Valeant and others, outside the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Dedication

Dedicated to the loving memory of Dr T Sampalis MD, PhD, innovator of microinvasive breast cancer surgery, who beat ovarian cancer but lost the battle to the toxic effects of chemotherapy.

Open access

References

Papers of special note have been highlighted as: • of interest

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J. Clin.* 67(1), 7–30 (2017).
2. Mariotto AB, Yabroff KR, Shao YW, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. JNCI-J. *Natl Cancer Inst.* 103(2), 117–28 (2011).
3. Pignata S, Cecere SC, Du Bois A, Harter P, Heitz F. Treatment of recurrent ovarian cancer. *Ann. Oncol.* 28, 51–6 (2017).
4. Narod S. Can advanced-stage ovarian cancer be cured? Nature reviews. *Clin. Oncol.* 13(4), 255–61 (2016).
5. Herzog TJ, Monk BJ. Bringing new medicines to women with epithelial ovarian cancer: what is the unmet medical need? *Gynecol. Oncol. Res. Pract.* 4, 13 (2017).

• **Advanced and recurrent ovarian cancer is rarely cured, as multiple lines of platinum combinations or nonplatinum chemotherapeutics fail to achieve clinical benefit. Therefore, other active systemic therapies are needed. Recent advances have led to novel targeted treatments for recurrent ovarian cancer.**

6. Elit L, Hirte H. Palliative systemic therapy for women with recurrent epithelial ovarian cancer: current options. *Onco Targets Ther.* 6, 107–118 (2013).

• **Although combination platinum-based chemotherapy has shown benefits for women with platinum-sensitive recurrent ovarian cancer, the optimal treatment strategy for those with platinum-resistant or platinum-refractory disease is not clear. Molecular and genetic targeted therapies may provide opportunities for those women with tumor profiles that show sensitivity for specific agents.**

7. Hanker LC, Loibl S, Burchardi N *et al.* The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. *Ann. Oncol.* 23(10), 2605–2612 (2012).

• **A maximum of three lines of subsequent relapse treatment seems to be beneficial for patients with recurrent ovarian cancer. Optimal primary tumor debulking and platinum sensitivity remain independent prognostic factors even after more frequent relapses.**

8. Ledermann J, Harter P, Gourley C *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 randomised Phase 2 trial. *Lancet Oncol.* 15(8), 852–861 (2014).
9. Mirza MR, Monk BJ, Herrstedt J *et al.* Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N. Engl. J. Med.* 375(22), 2154–2164 (2016).

10. Coleman RL, Oza AM, Lorusso D *et al.* Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet* 390(10106), 1949–1961 (2017).

11. Pujade-Lauraine E, Ledermann JA, Selle F *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, randomised, placebo-controlled, Phase 3 trial. *Lancet Oncol.* 18(9), 1274–1284 (2017).

12. Peppercorn J, Zafar SY, Houck K, Ubel P, Meropol NJ. Does comparative effectiveness research promote rationing of cancer care? *Lancet Oncol.* 15(3), 132–138 (2014).

13. Poonawalla IB, Parikh RC, Du XLL, VonVille HM, Lairson DR. Cost–effectiveness of chemotherapeutic agents and targeted biologics in ovarian cancer: a systematic review. *Pharmacoeconomics* 33(11), 1155–1185 (2015).

14. Giuliani J, Bonetti A. The pharmacological costs of second-line treatments for recurrent ovarian cancer. *Int. J. Gynecol. Cancer* 27(9), 1872–1876 (2017).

15. Chrischilles EA, Friedman S, Ritzwoller DP, Selby JV. Patients, data, and progress in cancer care. *Lancet Oncol.* 18(11), E624–E625 (2017).

16. Doyle C, Stockler M, Pintilie M *et al.* Resource implications of palliative chemotherapy for ovarian cancer. *J. Clin. Oncol.* 15(3), 1000–1007 (1997).

- **There is potential to improve cost-efficiency by improving resource management, for example, by shifting from inpatient to outpatient chemotherapy, everything else being equal.**

17. Gordon LG, Scuffham PA, Beesley VL *et al.* Medical costs and outcomes for Australian women with ovarian cancer: a patient-level analysis over 2.5 years. *Int. J. Gynecol. Cancer* 20(5), 757–765 (2010).

18. Delgado-Ortega L, Gonzalez-Dominguez A, Borras JM *et al.* The economic burden of disease of epithelian ovarian cancer in Spain: the OvarCost study. *Eur. J. Health Econ.* 20, 135–147 (2019).

19. Rocconi RP, Case AS, Straughn JM Jr, Estes JM, Partridge EE. Role of chemotherapy for patients with recurrent platinum-resistant advanced epitelial ovarian cancer: a cost–effectiveness analysis. *Cancer* 107, 536–543 (2006).

20. Cooper AL, Nelson DF, Doran S *et al.* Long-term survival and cost of treatment in patients with stage IIIC epithelial ovarian cancer. *Curr. Womens Health Rev.* 5(1), 44–50 (2009).

21. Yawn BP, Wollan P, Klee M, Barrette B. Ovarian carcinoma: care and survival in a community-based population. *Clin. Ther.* 23(1), 146–159 (2001).

22. Government of Canada. Cancer incidence in Canada: trends and projections (1983–2032)- ovarian cancer-HPCDP. 35(Suppl. 1), Chapter 4 (2015). www.canada.ca/en/public-health/services/reports-publications/health-promotion-chronic-disease-prevention-canada-research-policy-practice/vol-35-no-1-2015/supplement/page-06.html

23. von Gruenigen VE, Huang HQ, Beumer JH *et al.* Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer – an NRG oncology/Gynecologic Oncology Group study. *Gynecol. Oncol.* 144(3), 459–467 (2017).

24. Lewin SN, Buttin BM, Powell MA *et al.* Resource utilization for ovarian cancer patients at the end of life: how much is too much? *Gynecol. Oncol.* 99(2), 261–266 (2005).

- **The findings demonstrate that there is a significant cost difference with no appreciable improvement in survival between ovarian cancer patients treated aggressively versus those enrolled in hospice at the end of life.**

Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Journal of **Comparative Effectiveness Research**

Crizotinib versus chemotherapy: a real-world cost–effectiveness study in China

Meijuan Huang[‡,1], Yuke Tian[‡,1], Mingmin He[2], Juan Liu[2], Li Ren[1], Youling Gong[1], Feng Peng[1], Yongsheng Wang[1], Zhenyu Ding[1], Jin Wang[1], Jiang Zhu[1], Yong Xu[1], Yongmei Liu[1], Lanting Li[3] & You Lu*[,1]

[1]Department of Thoracic Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China

[2]Fengling Clinic, Wuhou, Chengdu 610041, China

[3]Shanghai Palan DataRx Co. Ltd, Shanghai 200051, China

*Author for correspondence: Tel.: +86 028 8542 3571; radyoulu@hotmail.com

‡ Authors contributed equally

Aim: To assess the cost–effectiveness of crizotinib verses platinum-based doublet chemotherapy as the first-line treatment for anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC) in the real-world setting. **Methods:** Data from 163 advanced ALK positive NSCLC patients were collected from West China Hospital, Sichuan University (Chengdu, China). They were categorized into two groups as treated with crizotinib (n = 83) or chemotherapy (n = 80) as a first-line therapy. The progression-free survival (PFS) as the primary clinical outcome, and the direct medical costs were collected from hospital information systems. Incremental cost–effectiveness ratio (ICER) was calculated with costs, quality-adjusted life-years, as well as the costs discounted at 3% annually. Additionally, two different kinds of medical insurance (MI) for pharma-economic assessment were considered. **Results:** Crizotinib improved PFS versus chemotherapy in ALK positive patients (median PFS 19.67 m vs 5.47 m; $p < 0.001$). Moreover, crizotinib obtained an ICER of US$36,285.39 before the end of 2016, when crizotinib, pemetrexed and anti-angiogenesis drugs were not MI covered. This is more than the willingness to pay threshold (three-times of gross domestic product per capita in mainland China or Sichuan Province). However, ICER was US$7321.16, which is less than willingness to pay, when crizotinib and all chemotherapy drugs were covered by MI from the end of 2016. Sensitivity analysis demonstrated a 99.7% probability for crizotinib to be more cost-effective than chemotherapy, when crizotinib and all anticancer drugs were MI covered. One-way sensitivity analysis for the reimbursement ratio of crizotinib indicated that cost-effective tendency for crizotinib increased as reimbursement ratio increased. **Conclusion:** Crizotinib could be an effective, and cost-effective first-line treatment for ALK positive advanced NSCLC with the MI coverage currently available in Chengdu, Sichuan Province, China.

First draft submitted: 12 June 2019; Accepted for publication: 22 October 2019; Published online: 21 January 2020

Keywords: cost–effectiveness • crizotinib • real world

Among all of the cancers, lung cancer is the most relevant problem in society, because it has the highest worldwide mortality rate. Eighty percent of all cases are non-small-cell lung cancer (NSCLC). The previous therapeutic treatments for advanced NSCLC are mainly based on traditional chemotherapy agents. These traditional anticancer drugs tend to have low efficacy, which is confirmed by the fact that the mortality rate is still high [1]. However, targeted therapies are generating a revolution in therapeutic treatment by blocking specific enzymes, and growth factor receptors involved in cancer cell proliferation. Although target drugs are very expensive and appear to increase healthcare costs, vital socio-economic clinical consequences should be discussed [2]. For instance, considering opportunity costs, including day-hospital costs, costs for treating adverse effects or costs for clinicians may be reduced when target therapies are used [1]. In addition, the continuous evolution of technological change in medicine should be associated with a far-sighted health policy. An important challenge by policy makers is to design

Future Medicine

a fruitful health policy that should provide good quality healthcare at low cost to population. Hence, the vital characteristics to design and implement a far-sighted policy for healthcare that can trigger clinical/cost–effectiveness of target therapies should be discussed [2].

Anaplastic lymphoma kinase (ALK) rearrangement is present in 3–5% of NSCLCs [3,4]. Crizotinib is an orally administered ALK tyrosine kinase inhibitor, it displays remarkable efficacy as first generation targeted agents. Compared with chemotherapy, crizotinib therapy improved survival and response rate, as well as a better quality of life [5–7]. It initiates significant shrinking of tumors in approximately 90% of patients with ALK-positive NSCLC [8]. Crizotinib has a 75% response rate versus 45% for chemotherapy in a first-line setting [6,9]. The results from the Profile 1014 study showed that the median progression-free survival (PFS) of crizotinib was 10.9 months. This is significantly longer than PFS with pemetrexed plus platinum chemotherapy [6], and also provides a new benchmark for overall survival, highlighting the benefit of crizotinib for prolonging survival [10].

There are some studies about the assessment of the economic value of crizotinib. Djalalov *et al.* reported crizotinib first-line therapy is not cost-effective, by using a Markov model from the Canadian public health, due to the high-drug cost and a low biomarker frequency in the population [11]. Crizotinib was approved for ALK-positive advanced NSCLC in mainland China in 2013. The crizotinib patient assistance program (PAP) was implemented for Chinese patients who tested ALK positive to help them afford it. It was reported that in the PAP setting, crizotinib therapy is a cost-effective alternative, compared with pemetrexed plus platinum chemotherapy by PROFILE 1014 trial data analysis [12]. However, it is difficult to ascertain response in the real-world situation. First, PFS in the real-world is longer than it would be in randomized clinical trials because, some patients can benefit from continuing crizotinib treatment beyond disease progression (CBPD) [13–16]. Second, the chemotherapy regimen used in clinical practice in the real-world is not just the pemetrexed platinum scheme, but also other schemes, or chemotherapy combined with anti-angiogenesis drugs. Finally, most chemotherapeutic drugs were covered by medical insurance (MI) since 2010 [17]. Pemetrexed and anti-angiogenesis drugs were included in MI since 2017 [18,19]. Crizotinib has been covered by the critical disease insurance in Chengdu, Sichuan Province, China since 2016 [20].

We carried out this real-world study to assess the cost–effectiveness of first-line crizotinib versus chemotherapy for ALK positive metastatic NSCLC under the different MI situations. The analysis of this research provides evidence for crizotinib's socio economic consequences on the healthcare system, and supports clinical and economic-effectiveness of personalized medicines.

Methods

Data & sources

From June 2010 to June 2016, a total of 163 advanced ALK positive NSCLC patients with no systemic treatment were collected from West China Hospital, Sichuan University (Chengdu, China), with a median follow-up of 27.67 months. The data were retrieved from the hospital information system of West China Hospital, which can guarantee the completeness and the quality of the data. In addition, due to the treatment requirement for advanced NSCLC patients, the quality of follow-up could be ensured in this study. Eligible patients were aged at least 18 years old, with histologically or cytopathologically confirmed newly diagnosed stage IIIB/IV, and with the presence of at least one documented ALK rearrangement, with the treatment of crizotinib or platinum-based chemotherapy as the first-line therapy. Patients were ineligible if they received crizotinib and platinum-based chemotherapy at the same time during the study period. Patients were categorized into two groups as treated with crizotinib (n = 83) or chemotherapy (n = 80) as a first-line therapy.

Measures of the study

The primary clinical outcome was the PFS and the main economic outcome is the incremental cost–effectiveness ratio (ICER). The PFS of chemotherapy was defined as: the time from initiation of treatment to RECIST-defined disease progression (PD), or death from any cause. The total PFS of crizotinib was defined as: from initiation of treatment, to the end of treatment or death from any cause. If the patient was last known to be progression-free, then the study period end date was used for censoring. Adverse events (AE) were classified and graded according to Common Terminology Criteria for Adverse Events, version 4.0.

This analysis used the perspective of the Chinese healthcare, only direct medical costs data were considered. Costs data were collected from the hospital information system. The total direct medical costs for each patient were calculated as the sum of all cost categories. Since the end of 2016, the price of crizotinib has fallen 10% in Sichuan, Chengdu. Crizotinib was covered by the critical disease insurance. Mean cost per patient over the entire

period was calculated by summing the totals and then dividing the sum by the sample size in each arm. Costs were discounted at an annual rate of 3%, in line with Chinese guidelines for pharmacoeconomic evaluations. The costs are shown in 2017 US dollars (1USD = 6.74 RMB). Since health utility measurements were not available in the real-world setting, literature-based utility weights were used [5].

In China, Pfizer and the China Primary HealthCare Foundation are currently implementing a PAP. PAP allows ALK-positive NSCLC patients that received crizotinib to pay US$31750.74 for the first year of treatment and US$15875.37 for the second year until to PD with the doctor's assessment. When crizotinib costs were partly paid by public healthcare payers in Chengdu, the patients need to pay US$21364.9 for the first year and US$14243.32 for the second year until to PD.

For the residents living in Chengdu, reimbursement was provided by the universal government-sponsored insurance plan. The detailed reimbursement ratio of the drugs referred to the Sichuan Drug Catalog for Basic Medical Insurance, Work-Related Injury Insurance, and Maternity Insurance (2010 Edition) before the end of 2016 [18]. According to the MI policy, Drugs of class A and B were covered by 100 and 80% separately. The new reimbursement rules referred to the National Drug Catalog for Basic Medical Insurance, Work-Related Injury Insurance and Maternity Insurance (2017 Edition) [19]. Pemetrexed, bevacizumab and endostatin were included into drug catalog of Medical Insurance as class B from 2017 [18]. Crizotinib was included into Medical Insurance for Major Diseases in Chengdu at the end of 2016 and reimbursement ratio was calculated as 70% [20]. In addition, for the other costs besides the drug cost, reimbursement ratio was calculated as 70% referring to Chengdu medical service and price item (announced by the Ministry of Human Resources and Social Security of Chengdu, 2016 version) [21].

The main economic outcome is the ICER. Health benefits were expressed as life years (LYs), and quality-adjusted life-years (QALYs) gained. The ICER was calculated by dividing the incremental cost difference between the two strategies, by the incremental difference in health outcomes (LYs and QALYs). We used 3× the per capita gross domestic product (GDP) of Sichuan in 2017 (US$6607.83) as the cost–effectiveness threshold according to the WHO recommendations.

Data analysis & procedure

For statistical methods included in this study, continuous variables are presented as mean, standard deviation, median and range per group. Categorical variables are expressed as percentage. For the comparison test, two-tailed Student's t-test for the continuous variables, and Fisher's exact test, or Chi-square test were used for the categorical variables as appropriate. Survival curves for PFS were plotted using the Kaplan–Meier method. Medians and the associated 95% CIs were computed. The differences were assessed by the log-rank test. All tests were two-sided, with statistical significance at $p < 0.05$. In addition, propensity score matching (PSM) was used to adjust significant differences in patient characteristics and reduce the influence of possible confounding factors. Logistic regression was calculated with the covariates, age, gender, disease period, smoking status, histopathology, ECOG performance status, metastatic status and ALK-rearranged test methods. A total of eight variables were included, and one-to-one nearest-neighbor matching without replacement was performed with a caliper of width equal to 0.2. Analyses were conducted with the R statistical package v.2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

Probabilistic Sensitivity Analysis (PSA) was performed to assess the impact of uncertainty around the key parameters of the model on the ICER. A second-order Monte Carlo simulation with 1000 iterations was used to run replicated outcomes. The normal distributions used for costs, utility and reimbursement ratio were carried to the specific limits. The results are presented as an Incremental cost–effectiveness scatter plot. In addition, one-way sensitivity analysis for the reimbursement ratio of crizotinib and three chemotherapy drugs (pemetrexed, bevacizumab and endostatin) was also examined.

Results

Patient characteristics

Patients' characteristics were summarized in Table 1. Except for a little difference in age, it was almost balanced in patients characteristics between crizotinib group and chemotherapy group. The patients in crizotinib group were younger than control group ($p = 0.042$). PSM was used to adjust for the age differences, and the results were unchanged after PSM (Supplementary Table 4).

Table 1. Baseline characteristics.

Characteristics	All patients (n = 163)	Crizotinib (n = 83)	Chemotherapy (n = 80)	p-value
Age				0.042
– Median (range)	50 (24.79)	48 (24.69)	51.5 (28.79)	
– Mean ± standard deviation	49.82 ± 11.31	48.02 ± 11.54	51.69 ± 10.83	
– Male Gender -no(%)	70 (42.9%)	32 (38.6%)	38 (47.5%)	0.320
Stage				1.000
– IIIB	11 (6.7%)	6 (7.2%)	5 (6.2%)	
– IV	152 (93.3)	77 (92.8%)	75 (93.8%)	
No Smoking status – no (%)	132 (81.0%)	67 (80.7%)	65 (81.2%)	1.000
Histopathology – no (%)				0.127
– Adenocarcinoma	150 (92.0%)	79 (95.2%)	71 (88.8%)	
– Non-adenocarcinoma	13 (8%)	4 (4.8%)	9 (11.2%)	
ECOG performance status no (%)				1.000
– 0 or 1	146 (89.6%)	71 (85.5%)	75 (93.8%)	
– 2 or 3	17 (10.4%)	12 (14.5%)	5 (6.2%)	
Metastatic status				
– Brain metastases present	47 (28.8%)	26 (31.3%)	21 (26.3%)	0.588
– Bone metastases present	60 (36.8%)	31 (37.3%)	29 (36.3%)	1.000
– Extra-pulmonary metastases present	66 (40.5%)	34 (41.0%)	32 (40%)	1.000
ALK rearranged test				0.159
– Ventana IHC	65 (39.9%)	38 (45.8%)	27 (33.8%)	
– FISH	98 (60.1)	45 (54.2%)	53 (66.2%)	

ALK: Anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; FISH: Fluorescent *in situ* hybridization; IHC: Immunohistochemistry.

Base-case analysis

In this study, crizotinib was administered at a dose of 250 mg orally, twice per day, with proper adjustments as needed. Conventional chemotherapy as the first-line treatment regimen was as follows: 55% were pemetrexed plus platinum chemotherapy, 12.5% were paclitaxel plus platinum chemotherapy, 3.8% were etoposide plus platinum chemotherapy, 12.5% were combined chemotherapy with anti-angiogenesis like bevacizumab and endostatin. There was a significant improvement in objective response rate and disease control rate for the crizotinib group compared with the chemotherapy group (objective response rate: 48.2 vs 7.5%, respectively; $p < 0.001$; disease control rate: 95.2 vs 81.3%, respectively; $p = 0.011$; Supplementary Table 1). The median-PFS in the crizotinib group was significant longer than it was in chemotherapy (13.9 vs 5.47 m, respectively; $p < 0.001$; Supplementary Figure 1). At the data cut off, 67 patients who received crizotinib had primary PD and 30 patients were decided by physicians to continue CBPD, where 56.7% of the patients were brain metastasis. The results in survival analysis showed that the patients taking crizotinib prolonged total median PFS compared with the chemotherapy group (19.67 vs 5.47 m, respectively; $p < 0.001$; Figure 1).

The related AE were summarized in Supplementary Table 2. The most common AE with crizotinib was hepatic toxicity, with 2.4% of the patients reaching 3 grade. The most common AE with chemotherapy was hematologic toxicity, with 8% of patients at 3 grade.

The costs were summarized in Table 2. The cost of crizotinib is higher than the anticancer drug cost in chemotherapy group. However for the other costs, including costs for AE Management, Examination and Hospitalization in crizotinib were less than in chemotherapy. The majority of the total cost was the anticancer cost for both groups. Due to crizotinib, pemetrexed, bevacizumab and endostatin being covered by MI after the end of 2016, the total cost for patients' perspective decreased significantly.

The results of cost–effectiveness are reported in Table 3. The base-case results indicate that crizotinib would result in a longer PFS, more LYs (1.18 years) and QALYs (0.99 years) for the clinical benefit. Before the end of 2016, the ICER was US$30442.83 per LYs gained, and US$36285.39 per QALYs gained, and both of them were more than willingness to pay (WTP; 3 × GDP). After the end of 2016, the ICER dropped notably considering the new MI policy. Not only the ICER was US $6142.33 per LYs gained, which was less than 1 × GDP for Sichuan province, China, but also the ICER was US$7321.16 per QALYs, which was less than 1 × GDP for China. Both of

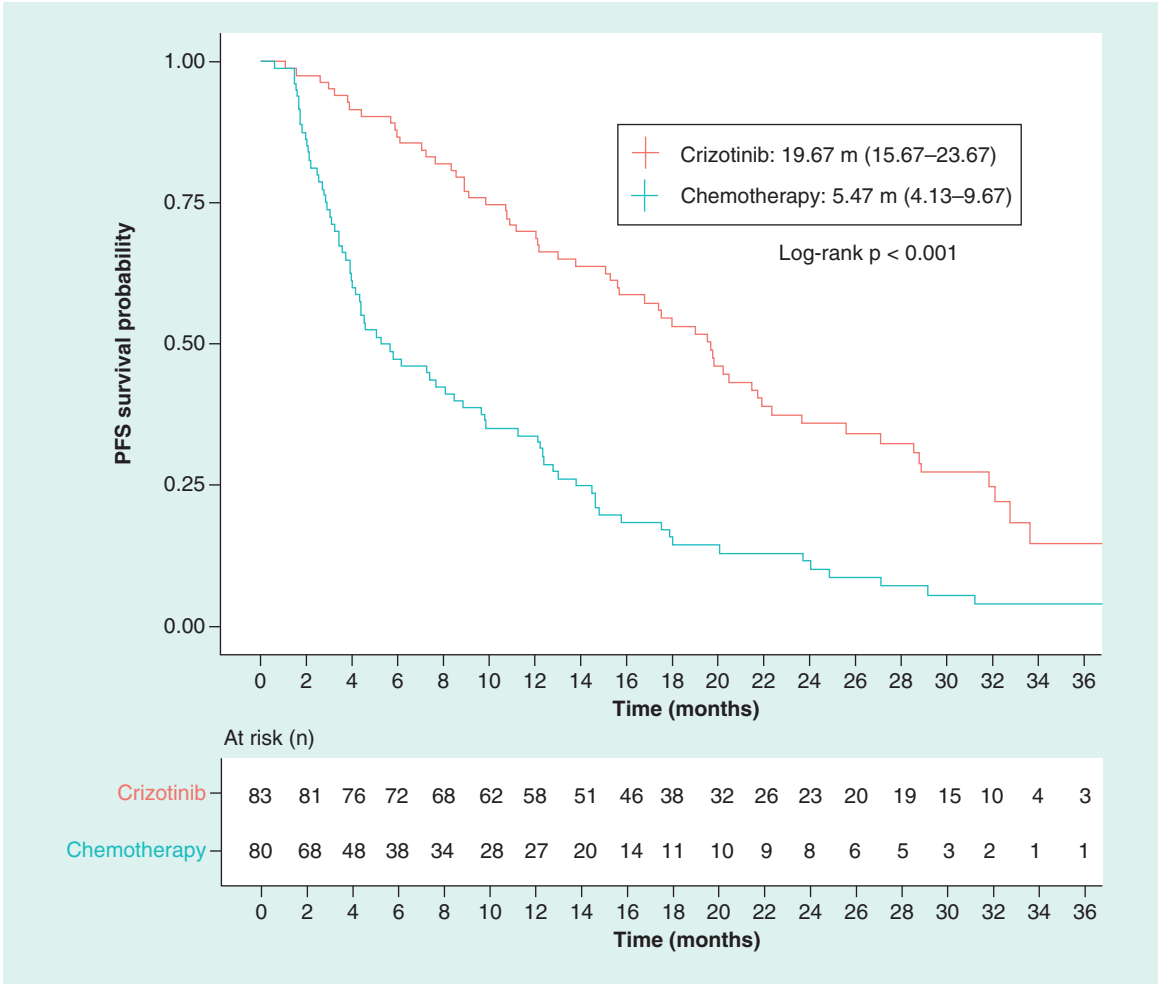


Figure 1. Kaplan–Meier analysis comparing total progression-free survival between the patients treated with crizotinib and chemotherapy as first-line therapy for anaplastic lymphoma kinase positive non-small-cell lung cancer.
PFS: Progression-free survival.

Table 2. Summary of cost (US$) included in the base-case analysis.

Cost/patient (95% CI)	Before the end of 2016			After the end of 2016		
	Crizotinib (n = 83)	Chemotherapy (n = 80)	p-value	Crizotinib (n = 83)	Chemotherapy (n = 80)	p-value
Anticancer drug	44942.5 (43159.06, 46725.94)	8146.12 (5918.71, 10373.53)	<0.05	9846.06 (9367.18, 10324.94)	1724.29 (1280.59, 2167.99)	<0.05
Adverse event management	20.53 (9.56, 31.5)	35.13 (23.2, 47.06)	<0.05	20.53 (9.56, 31.5)	35.13 (23.2, 47.06)	<0.05
Radiotherapy	239.76 (143.37, 336.1)	384.87 (231.68, 538.06)	0.85	239.76 (143.37, 336.15)	384.87 (231.68, 538.06)	0.85
Hospitalization	111.25 (42.03,180.47)	190.15 (146.88, 233.42)	<0.05	111.25 (42.03, 180.47)	190.15 (146.88, 233.42)	<0.05
Examination	904.32 (786.85, 1021.79)	1161.9 (1011.73, 1312.07)	<0.05	904.32 (786.85, 1021.79)	1161.9 (1011.73, 1312.07)	<0.05
Other costs†	495.59 (342.34, 648.84)	873.22 (646.44, 1100)	<0.05	495.59 (342.34, 648.84)	873.33 (646.44, 1100)	<0.05
Total cost‡	46713.94 (44788.08, 48639.8)	10791.4 (8351.65, 13231.15)	<0.05	11617.51 (10953.93, 12281.09)	4369.56 (3624.05, 5115.07)	<0.05

†Other costs were included materials, support solution and so on.
‡Total costs were calculated from the patient's perspective.

Table 3. Cost–effectiveness analysis.

Group	Strategy	Cost (US$)	PFS LYs	ICER/LYs	PFS QALYs	ICER/QALYs
Before the end of 2016	– Crizotinib without MI	46713.94	1.64		1.31	
	– Chemotherapy with partly MI	10791.40	0.46	30442.83†	0.32	36285.39†
After the end of 2016	– Crizotinib with MI	11617.51	1.64		1.31	
	– Chemotherapy with MI	4369.56	0.46	6142.33‡	0.32	7321.16§

†>3 × GDP of China.
‡<1 × GDP of Sichuan Province China.
§<1 × GDP of China.
GDP: Gross domestic product; ICER: Incremental cost–effectiveness ratio; LY: Life Year; MI: Medical insurance; PFS: Progression-free survival; QALY: Quality-adjusted life year.

them were less than WTP. Based on these findings, crizotinib can be considered a cost-effective option for advanced ALK positive patients comparing with chemotherapy, even after all the chemotherapy drugs were covered by MI.

Sensitivity analysis

To drive robust estimations of incremental LYs, QALYs and costs, the PSA was performed using a second-order Monte Carlo simulation with 1000 iterations to run replicated outcomes. The setting of all parameters in PSA were listed in SupplementaryTable 3. The probability sensitivity analysis revealed that all the simulation results for ICER fell within the first, and fourth quadrants. More than 90% of the results were located in the first quadrant (Figure 2). Moreover, more than 99% of sampled ICERs were below a threshold of WTP. These results indicated that compared with chemotherapy, crizotinib showed cost–effectiveness in more than 99% of probability, considering a cost–effectiveness threshold of a 3 × GDP per capita in 2017 in Sichuan when crizotinib and all the anticancer drugs were covered by MI. In addition, one-way sensitivity analysis for reimbursement ratio of crizotinib and three chemotherapy drugs which were covered by MI from 2017 was also assessed (Figure 3). First, six reimbursement ratios of crizotinib including 0%, 60–100% were assessed as three chemotherapy drugs (pemetrexed, bevacizumab and endostatin) 80% MI covered (green circle). Second, three chemotherapy drugs 60, 80 and 100% MI covered were analyzed as crizotinib 70% MI covered (blue triangle line). The results indicated that the cost-effective tendency for crizotinib increases as the reimbursement ratio increases.

Discussion

To our knowledge, this is the first study using patient-level real-world data to investigate the cost–effectiveness of crizotinib versus chemotherapy as first-line treatment for ALK-positive advanced NSCLC patients, which is likely to better reflect effectiveness, and resource use than RCT evidence. There are three points to consider. First of all, we reported a median total PFS of 19.67 m after crizotinib treatment, which is more than the PFS of 10.9 m in Profile 1014. Among 67 crizotinib-treated patients with RECIST-defined PD, 30 (45%) continued CBPD. These patients responded to, and exhibited extended PFS from initial crizotinib treatment, and had a site of PD particularly amenable to local therapy (brain). Second, the chemotherapy regimen is not limited to a pemetrexed platinum scheme, but other schemes, or chemotherapy combined with anti-angiogenesis drug were also used. Finally, the change of MI policy was considered in the study. We found crizotinib is a cost-effective choice for ALK-positive NSCLC in comparison with chemotherapy with Chengdu, Sichuan Province MI coverage after 2016.

Dajlalov [11] reported crizotinib first-line therapy was not cost-effective using a Markov model. However, Chouaid provided different comments [22]. The standard first-line treatment strategy was cisplatin-gemcitabine doublet. However, the recommendations for first-line treatment of NSCLC also included other regimens such as pemetrexed concurrently with cisplatin, or at the patients discretion, bevacizumab combined with chemotherapy. If some patients received these high-cost drugs, such as pemetrexed or bevacizumab, it will probably significantly impact the ICER. In our real-world study, 55% were pemetrexed plus platinum chemotherapy, 12.5% were combined chemotherapy with bevacizumab and endostatin. We found crizotinib first-line treatment could be cost-effective compared with chemotherapy with the MI coverage and PAP.

Compared with a recent published model-based economic analysis using PROFILE 1014 trial data analysis [12], the study focused on the assessment of three ALK rearrangement testing methods in combination with crizotinib versus a traditional regimen, as well as the impact of crizotinib PAP. Both of the two studies suggest crizotinib is an effective, and cost-effective first-line treatment for ALK-positive advanced NSCLC compared with chemotherapy.

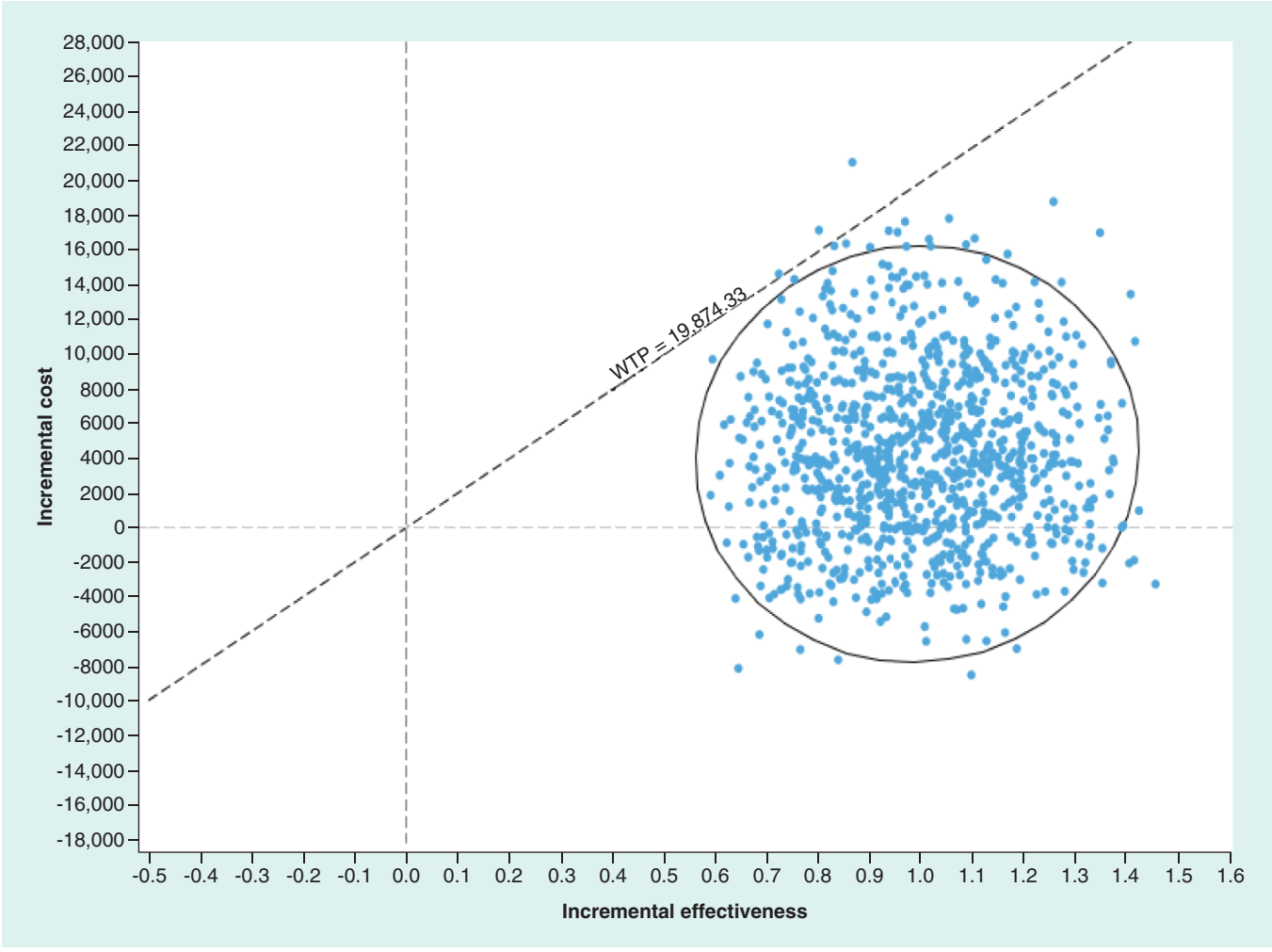


Figure 2. Incremental cost–effectiveness scatter plot for probabilistic sensitivity analyses. Each point represents the mean incremental cost and effectiveness of crizotinib compared with chemotherapy as first-line therapy for anaplastic lymphoma kinase positive non-small-cell lung cancer.
WTP: Willingness to pay.

Although crizotinib has been approved in China since 2013, the clinical practical use was limited due to the high price. What's more, most chemotherapeutic drugs were covered by MI. Pemetrexed and anti-angiogenesis drugs were also included in MI later. At the end of 2016, crizotinib was covered by MI in Chengdu, Sichuan Province. It caused a major change for the treatment strategy for ALK-positive NSCLC. Our study indicates that crizotinib could be a cost-effective alternative if it is covered by MI. Since the end of 2018, crizotinib has been covered by MI in some other regions of China. This study could benefit healthcare systems in further regions of China currently considering coverage of crizotinib.

Given its retrospective nature, this study had several limitations. First, the results might be limited because of the small sample size in this study. We implemented quality controls to make sure that a consistent conclusion was achieved between the patients diagnosed at different years in the study. We randomly screened 10% of the patients who were diagnosed at different year, and ICER was calculated for these patients respectively. The results showed that the consistent conclusion was obtained. Second, there was selection bias in patient characteristics because the median age for the patients in the crizotinib group is 3 years younger than the patients in chemotherapy group in this study. It suggested that young patients may have a stronger desire for treatment. PSM was used to adjust for significant differences, and similar results were obtained (Supplementary Tables 4–9 and Figures 2–4). Third, since the utility data for Chinese are very limited currently, the utilities included in this study were extracted American utility scores from the literature based on the PROFILE 1007 study [7]. Moreover, sensitivity analysis was performed

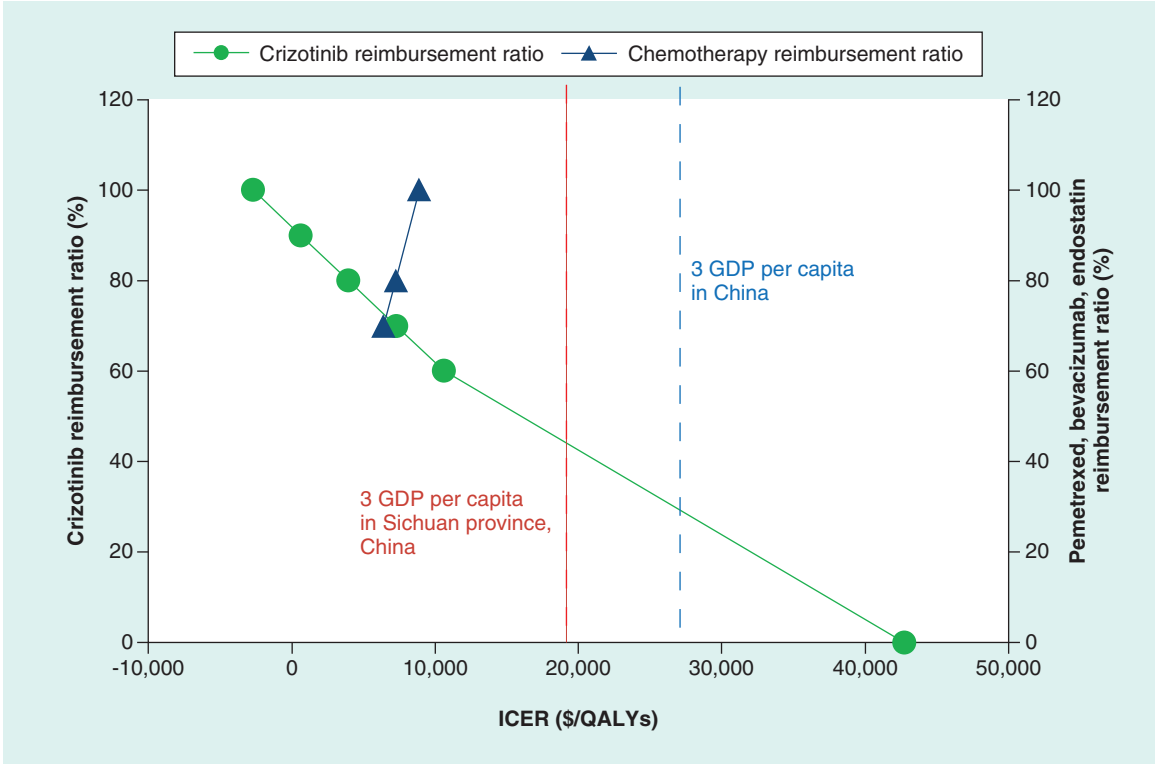


Figure 3. One-way sensitivity analysis for reimbursement ratio of crizotinib and chemotherapy.
QALY: Quality-adjusted life year; GDP: Gross domestic product; ICER: Incremental cost effectiveness ratio.

for the utilities to make sure the conclusions were not influenced by varying the values. Finally, it is difficult to collect all cost data in a real-world situation. We estimated the examination cost based on the routine clinical practice. It is our desire that further study can be based on multicenter randomized trial, or registration study.

In summary, the present study provides valuable real-world evidence that with the Chengdu, Sichuan province MI coverage, crizotinib could be an effective and cost-effective first-line treatment for ALK positive advanced NSCLC compared with chemotherapy.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0075

Acknowledgments

This work was supported by National Key Research and Development Program of China (No. 2018YFC1311400/2018YFC1311402). The authors would like to thank D Kang in the Department of EBM and Clinical Epidemiology, West China Hospital for professional guidance, and helpful suggestions. Our sincere thanks also, to F Liu of Pfizer Medical for support with the literature review.

Financial & competing interests disclosure

The funding for the data analysis of this study was sponsored by Pfizer China. The study sponsor did not interfere with the study design, data collection or writing of this manuscript. L Li is an employee of Palan DataRx Co. Ltd, a research consulting company receiving industry funds to conduct health economics, and outcomes research in China. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

Summary points

- Crizotinib as first generation of anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor, displays remarkable efficacy, improving survival and response rate, as well as a better quality of life compared with chemotherapy. However, the expensive price limited the wide use in clinical practice.
- This study assessed the cost–effectiveness of crizotinib verses platinum based doublet chemotherapy as the first-line treatment for ALK-positive non-small-cell lung cancer in the real-world setting.
- The progression-free survival (PFS) was the primary clinical outcome, and the direct medical costs were collected from hospital information systems.
- Incremental cost–effectiveness ratio (ICER) was calculated with costs and quality-adjusted life years.
- The results demonstrated that crizotinib improved PFS versus chemotherapy in ALK-positive patients (median PFS 19.67 vs 5.47 m; $p < 0.001$).
- Moreover, crizotinib obtained an ICER of US$36,285.39 before the end of 2016, when crizotinib, pemetrexed and anti-angiogenesis drugs were not medical insurance (MI) covered. This is more than the willingness to pay threshold (three-times of gross domestic product per capita in mainland China or Sichuan Province).
- However, ICER was US$7321.16, which is less than willingness to pay, when crizotinib and all chemotherapy drugs were covered by MI from the end of 2016.
- These findings suggest that crizotinib could be an effective, and cost-effective first-line treatment for ALK positive advanced non-small-cell lung cancer with the MI coverage currently available in Chengdu, Sichuan Province, China.

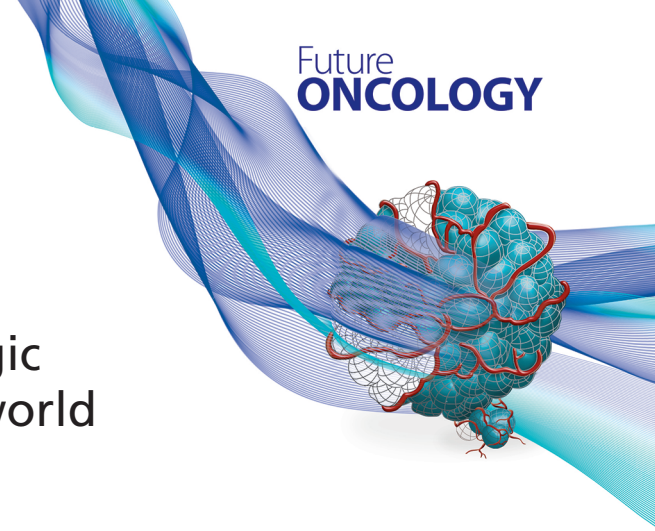
References

1. Coccia M. Evolutionary growth of knowledge in path-breaking targeted therapies for lung cancer: radical innovations and structure of the new technological paradigm. *Int. J. Behav. Healthcare Res.* 3(3/4), 273–290 (2012).
2. Coccia M. Path-breaking target therapies for lung cancer and a far-sighted health policy to support clinical and cost–effectiveness. *Health Pol. Technol.* 3(1), 74–82 (2014).
3. Soda M, Choi YL, Enomoto M *et al.* Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer. *Nature* 448(7153), 561–566 (2007).
4. Rikova K, Guo A, Zeng Q *et al.* Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* 131(6), 1190–1203 (2007).
5. Ou SH, Bartlett CH, Mino-Kenudson M *et al.* Crizotinib for the treatment of ALK-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology. *Oncologist* 17(11), 1351–1375 (2012).
6. Solomon BJ, Mok T, Kim DW *et al.* First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N. Engl. J. Med.* 371(23), 2167–2177 (2014).
7. Blackhall F, Kim DW, Besse B *et al.* Patient-reported outcomes and quality of life in PROFILE 1007: a randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer. *J. Thorac. Oncol.* 9(11), 1625–1633 (2014).
8. Hamidaddin MA, AlRabiah H, Darwish IA. Development and comparative evaluation of two immunoassay platforms for bioanalysis of crizotinib: a potent drug used for the treatment of non-small cell lung cancer. *Talanta* 201, 217–225 (2019).
9. Molnar TF, Szipocs A, Szalai Z. Neoadjuvant crizotinib for ALK re-arranged NSCLC? *J. Thorac. Oncol.* 14(4), 574–576 (2019).
10. Solomon BJ, Kim DW, Wu YL *et al.* Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in ALK-mutation-positive non-small-cell lung cancer. *J. Clin. Oncol.* 36(22), 2251–2258 (2018).
11. Djalalov S, Beca J, Hoch JS *et al.* Cost–effectiveness of EML4-ALK fusion testing and first-line crizotinib treatment for patients with advanced ALK-positive non-small-cell lung cancer. *J. Clin. Oncol.* 32(10), 1012–1019 (2014).
12. Lu S, Zhang J, Ye M *et al.* Economic analysis of ALK testing and crizotinib therapy for advanced non-small-cell lung cancer. *Pharmacogenomics* 17(9), 985–994 (2016).
13. Ou SH, Janne PA, Bartlett CH *et al.* Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. *Ann. Oncol.* 25(2), 415–422 (2014).
14. Lei YY, Yang JJ, Zhong WZ *et al.* Clinical efficacy of crizotinib in Chinese patients with ALK-positive non-small-cell lung cancer with brain metastases. *J. Thorac. Dis.* 7(7), 1181–1188 (2015).

15. Hong X, Chen Q, Ding L *et al.* Clinical benefit of continuing crizotinib therapy after initial disease progression in Chinese patients with advanced ALK-rearranged non-small-cell lung cancer. *Oncotarget* 8(25), 41631–41640 (2017).
16. Duruisseaux M, Besse B, Cadranel J *et al.* Overall survival with crizotinib and next-generation ALK inhibitors in ALK-positive non-small-cell lung cancer (IFCT-1302 CLINALK): a French nationwide cohort retrospective study. *Oncotarget* 8(13), 21903–21917 (2017).
17. Sichuan Provincial Human Resources and Social Security Department. Sichuan drug catalog for basic medical insurance work-related injury insurance, and maternity insurance 2010 (2018). http://www.sc.hrss.gov.cn/bsfw/shbx/ylbx_1/xgzc/201311/t20131106_12903.html
18. Sichuan Provincial Human Resources and Social Security Department. National drug catalog for the basic medical insurance, work-related injury insurance, and maternity insurance 2017 (2018). http://www.sc.hrss.gov.cn/zwgk/zcwj/201710/t20171010_64835.html
19. Sichuan Provincial Human Resources and Social Security Department. Thirty-six negotiated drugs included in medical insurance drug list 2017 (2018). http://www.sc.hrss.gov.cn/zwgk/zcwj/201710/t20171010_64835.html
20. Chendu Human Resources and Social Security Bureau. Critical illness insurance program in Chengdu (2019). http://cdhrss.chengdu.gov.cn/cdrsj/c113823/2016-11/18/content_f48facef6c884ad8a86297d3359ca88d.shtml
21. Ministry of Human Resources and Social Security of Chengdu. Chengdu medical service and price item 2016 (2019). http://cddrc.chengdu.gov.cn/cdfgw/c120782/201604/06/content_560db5ac065e4e84b7d9c4856918468a.shtml
22. Chouaid C, Borget I, Vergnenegre A. Targeted therapies in non-small-cell lung cancer management: no cost-effective strategies? *J. Clin. Oncol.* 32(31), 3577 (2014).

Review

For reprint orders, please contact: reprints@futuremedicine.com



Rituximab biosimilars in hematologic malignancies: the need for a real-world approach

Pilar Nava-Parada*[,1,2], Ahmed Shelbaya[1,3] & Chadi Nabhan[4,5]

[1]Pfizer Inc, New York, NY 10017, USA

[2]Health Advocacy & Medical Exploration Society (HAMES National, Inc), Lawrence Township, NJ 08648, USA

[3]Mailman School of Public Health, New York, NY 10032, USA

[4]Caris Life Sciences, Irving, TX 75039, USA

[5]Department of Clinical Pharmacy & Outcomes Sciences, University of South Carolina, Columbia, SC 29208, USA

*Author for correspondence: Tel.: +1 212 733 3585; Pilar.Nava-Parada@pfizer.com

The introduction of rituximab biosimilars into healthcare systems can potentially help to control healthcare costs for the treatment of hematologic malignancies. However, there are currently several barriers to the uptake of biosimilars. This review discusses barriers to the adoption of rituximab biosimilars by stakeholders including patients and healthcare providers. We outline the importance of utilizing real-world evidence in providing additional clinical experience on rituximab biosimilars in hematologic malignancies to improve stakeholder confidence regarding their efficacy and safety. We conclude by offering recommendations for designing and conducting effective real-world studies. Such studies can provide evidence to help achieve lower-priced biologics and improved patient access to help sustain the treatment of hematologic malignancies with biologics, including rituximab biosimilars.

First draft submitted: 17 February 2020; Accepted for publication: 11 June 2020; Published online: 13 July 2020

Keywords: biosimilars • hematologic malignancies • real-world evidence • rituximab

In the USA, healthcare expenditure for cancer treatment is increasing, partly due to the cost of biologic drugs, which creates a challenge for the future sustainability of affordable cancer care [1]. The increase in cancer incidence due to a rise in life expectancy and improved survival rates has extended the length of time that patients receive treatment and contributed to the escalation in cancer healthcare costs [2,3]. Rituximab (MabThera®; Rituxan®) is a chimeric monoclonal antibody that targets the B-cell-specific antigen CD20, and this biologic drug has transformed standard therapies for the majority of lymphoid malignancies [4]. Rituximab is approved for the treatment of several conditions, including – but not limited to – follicular lymphoma (FL), diffuse large B-cell lymphoma, and chronic lymphocytic leukemia [5,6]. However, patient access to rituximab can be restricted, particularly in countries with limited financial resources [7].

As patent portfolios for biologics near end of term, the availability of biosimilar versions of these drugs may mitigate the total cost of care by potentially providing more affordable treatment options, thereby increasing patient access to these important therapies [1,8]. Biosimilars are biologic drugs that are developed to be highly similar in structure and function to licensed (i.e., reference or originator) products, with no clinically meaningful differences in efficacy, safety and purity [9,10]. The Biologics Price Competition and Innovation Act of 2009 (enacted as part of the Affordable Care Act) provides an abbreviated approval pathway for biosimilars [9,11]. As such, the introduction of rituximab biosimilars into healthcare systems can potentially help to control the treatment costs for hematologic malignancies [12].

The availability of rituximab biosimilars, however, does not automatically guarantee their adoption in routine clinical practice. Despite the availability of a filgrastim biosimilar, its uptake in the USA has been less than anticipated and has lagged behind other countries where granulocyte-colony stimulating factor biosimilars for use in cancer supportive care are available [13]. In order to realize the potential savings for US healthcare systems, several barriers to the uptake of rituximab biosimilars need to be overcome. These barriers include the perceptions of stakeholders

(including patients and healthcare providers), financial disincentives related to reimbursement, and regulatory policies (such as the interchangeability of reference products and biosimilars) [8,11,14]. Real-world evidence (RWE) can provide additional information to supplement the clinical data required by regulatory agencies as part of the abbreviated approval of biosimilars, to help overcome some of these barriers. The aim of this review is to discuss the current barriers to the uptake of biosimilars, the utility of RWE in providing additional clinical experience of the use of rituximab biosimilars for the treatment of hematologic malignancies, and recommendations for conducting effective real-world studies.

Regulatory guidance & rituximab biosimilars

To gain regulatory approval, biosimilars must be sufficiently similar to the corresponding reference product such that they are not expected to show any clinically meaningful differences in safety, efficacy and purity demonstrated through a robust regulatory pathway. Similarity of a proposed biosimilar to its reference product is established using a 'totality-of-the-evidence' approach, comprising data from comparative analytical, preclinical, pharmacokinetic and clinical studies [10,15]. These confirmatory clinical studies are conducted to establish similarity to the reference product in terms of quality, efficacy and safety [16]. Biosimilars have the same mechanism of action as their corresponding reference product [9,10]. As such, with appropriate scientific justification, regulatory guidance permits the approval of a biosimilar in all eligible indications held by the reference product, without a comparative trial in each indication. This is known as extrapolation across indications [9,10,17,18].

Many countries have now established regulatory pathways for the approval of biosimilars [9,10,18–22]. Rituximab biosimilars have been approved in the USA and the European Union through these pathways, using collective evidence from analytical, nonclinical and clinical studies. The comparative clinical studies were conducted in patients with either rheumatoid arthritis or FL, as these populations are adequately sensitive to detect meaningful differences in efficacy or safety between the biosimilar and reference rituximab (Table 1) [23–40]. There are also several rituximab biosimilars currently under development [41–44].

Real-world studies

The US FDA defines real-world data as "*data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources*" [45]. These sources go beyond the traditional clinical trial setting and include electronic patient health records, claims data, product and disease registries, patient-reported outcomes (PROs) and other emerging data sources, such as social media and industry collaborations (Table 2) [46,47]. RWE is the "clinical evidence on the use and potential benefits or risks of a medical product derived from analysis of real-world data" [45]. Real-world studies can provide insights into different aspects of treatment and patient outcomes to enhance the evidence generated from conventional clinical trials in selected patient populations [48,49]. For example, data from electronic patient records were used to evaluate changes in practice efficiency by comparing subcutaneous and intravenous administration of rituximab [50]. RWE has also been used to inform early treatment milestones, understand treatment patterns, and provide patient perspectives regarding disease management for chronic myeloid leukemia [49].

RWE can be used to gain a more accurate insight into patient outcomes, for example, disease progression and long-term survival can be studied over longer time periods than those used in clinical trials [48]. By providing additional clinical experience of rituximab biosimilars, RWE supplements the clinical data required by regulatory agencies for the approval of biosimilars, and thereby potentially alleviate some of the current barriers to their uptake (Table 3) [8]. In addition, the evidence that is generated can be systematically analyzed to identify possible ways to improve disease management. However, real-world studies also have limitations, including internal validity, confounding factors, lack of standardization in assessing response and progression, variable data quality and increased risk of bias [47,51]. Furthermore, different sources of real-world data have their own strengths and limitations [47]. Therefore, translating real-world data into robust, clinically relevant evidence can be a challenge.

Relevance of RWE to healthcare stakeholders

Currently, real-world data are accumulated from disease registries mandated by regulatory authorities as part of the pharmacovigilance requirements for the approval of a biosimilar [52,53]. Data accumulated through pharmacovigilance could be used to inform physicians on the utilization of rituximab biosimilars in clinical practice, and to help inform discussions about treatment decisions between physicians and patients [54]. The availability of RWE on the use of biosimilars may also increase understanding among physicians and prescribers that comparative clinical

Table 1. Rituximab biosimilars approved in the USA and the European Union for the treatment of hematological malignancies[†].

Product	Key clinical studies	Approved hematological indications[‡]	Regulatory authority (approval date)	Ref.
CT-P10[#] (Truxima® [rituximab-abbs], Ritemvia®, Blitzima®; Celltrion)	Pharmacokinetics trial (n = 154) and extension study (n = 83); randomized, double-blind study in patients with RA (n = 372): – Similar PK and immunogenicity between CT-P10 and reference rituximab Randomized, double-blind studies in patients with previously untreated advanced FL (n = 140) and patients with LTB-FL (n = 258) – Similar PK, PD, efficacy, safety and immunogenicity between CT-P10 and reference rituximab – Similar PK, safety and efficacy between CT-P10 and reference rituximab	NHL; CLL[¶]	EMA (Feb 2017/Jul 2017); US FDA (Nov 2018)	[23–31]
GP2013 (Rixathon®/Riximyo®[§]; Sandoz)	Randomized, double-blind efficacy and safety study in patients with RA (n = 173): – Similar PK, PD, safety, efficacy and immunogenicity between GP2013 and reference rituximab Randomized, double-blind study in patients with previously untreated advanced FL (n = 629) – Similar efficacy and safety between GP2013 and reference rituximab	NHL; CLL[§]	EMA (Jun 2017)	[32–35]
PF-05280586 (Ruxience™, rituximab-pvvr; Pfizer)	Pharmacokinetics trial (n = 220) and extension study (n = 185) in patients with active RA: – Similar PK, PD, safety and immunogenicity demonstrated between PF-05280586 and reference rituximab Randomized, double-blind efficacy and safety study in patients with untreated CD20-positive LTB-FL (n = 394) – Similar efficacy, safety, immunogenicity, PK and PD between PF-05280586 and reference rituximab	NHL; CLL	US FDA (Jul 2019) EMA (Apr 2020)	[36–40]

[†]As of April 2020.
[‡]Some rituximab biosimilars are also approved to treat conditions including granulomatosis with polyangiitis, microscopic polyangiitis, pemphigus vulgaris and RA.
[¶]CLL is not an approved indication for Ritemvia or rituximab-abbs.
[§]Approved in the European Union as Riximyo under a duplicate marketing authorization for the treatment of NHL.
[#]Clinical program was developed in consultation with the US FDA and EMA to support the global development of the product.
CLL: Chronic lymphocytic leukemia; FL: Follicular lymphoma; LTB-FL: Low tumor-burden FL; NHL: Non-Hodgkin lymphoma; PD: Pharmacodynamic; PK: Pharmacokinetic; RA: Rheumatoid arthritis.

Table 2. Sources of real-world data.

Setting	Examples
Research studies	Observational studies Post-approval safety studies
Clinical setting	Electronic patient health records Patient medical charts Patient registries (disease and product based)
Administrative claims databases	Patient medical claims
Pharmacy	Prescription records
Patient	Patient-reported outcomes Patient-powered research networks Information from wearables and fitness trackers
Emerging data sources	Social media Cross-industry data collaborations

Adapted from The Network for Excellence in Health Innovation 2015 [46] and Nabhan *et al.*, *JAMA Oncol.* 2019 [47].

studies of proposed biosimilars and the corresponding reference product are well-designed, and that data from these studies, which are required for regulatory approval, are reliable. In turn, this may improve the uptake of biosimilars.

In contrast to randomized clinical trials conducted in a selected patient population, patient populations in real-world settings are heterogeneous. RWE can therefore demonstrate the efficacy and safety of biosimilars in patient populations for whom clinical trial data are not available, such as children, the elderly, and those with concurrent medical conditions [13,14,48,55]. This aspect is of particular relevance in oncology as more than 95% of patients with cancer are treated outside of clinical trials [56]. In Europe, for example, real-world data from the Global Oncology Monitor (Ipsos Healthcare) have been used to evaluate prescription patterns for rituximab biosimilars [57]. This

Table 3. Barriers to the uptake of biosimilars in the USA.

Barrier	Issue	Role of real-world evidence
Perception of stakeholders (including physicians and patients)	Patients may be reluctant to switch from reference products to biosimilars Physicians lack confidence in prescribing biosimilars	To inform educational programs for physicians and patients on the efficacy and safety of rituximab biosimilars in more diverse patient populations
Pricing and reimbursement	Healthcare providers may not be able to adopt biosimilars if payers prefer the reference product in reimbursement models	To demonstrate the market value of rituximab biosimilars (e.g., by lowering treatment cost and improving patient access) to enable payers to make decisions on reimbursement
Regulatory policies	Prescribers are unsure whether clinical data on the interchangeability of reference products and biosimilars are reliable or whether extrapolation of data across indications is permitted	To provide data on the efficacy and safety of biosimilars in extrapolated indications, and provide data on switching between reference products and biosimilars

Republished from Barriers to Oncology Biosimilars Uptake in the United States, Nabhan C et al., The Oncologist , 23 (11), Copyright Wiley 2018 [8]; permission conveyed through Copyright Clearance Center, Inc.

online medical chart review study of the treatment of non-Hodgkin lymphoma (NHL) in five countries found that patients who had received first-line treatment, and had indolent disease and FL, were more likely to be treated with a rituximab biosimilar than with the reference product [57].

RWE can support physicians and patients when making decisions on nonmedical switching, to or from a reference biologic, for reasons relating to treatment cost or availability, rather than as a medical requirement [58,59]. Randomized clinical trials are powered to demonstrate efficacy and are largely limited to assessing known adverse events, whereas real-world populations are more appropriate for identifying previously unreported or rare adverse events [60,61]. Evidence from real-world settings could enhance confidence in the safety of biosimilars; for example, the post-market safety experience of granulocyte-colony stimulating factor biosimilars has demonstrated that real-world use in the USA is consistent with global safety data [62].

RWE can be used to determine potential cost savings for payers [55]. For example, researchers have compared the potential time and cost savings, which may be achieved from a US payer perspective, by using different formulations of the reference product and a rituximab biosimilar in the treatment of patients with NHL [63]. In this time- and cost-simulation analysis in patients with NHL receiving R-CHOP therapy (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone), subcutaneous delivery of reference rituximab saved on both time and cost compared with intravenous administration. Moreover, intravenous dosing of a proposed rituximab biosimilar in an R-CHOP regimen provided time and cost savings when compared with subcutaneous administration of the reference product [63]. Further real-world studies are needed to determine the extent of the savings that could be achieved in clinical practice [60].

There is increasing interest from regulatory bodies in the use of RWE to support their decision-making, as highlighted in the "Framework for the FDA's real-world evidence program" [45]. The guidance provides a framework for evaluating the use of real-world data to support approvals in new indications for a drug, and for post-approval study requirements, as set out in the 21st Century Cures Act [45,64]. The framework also highlights potential gaps in the current sources of real-world data; for example, it recommends that electronic patient health records and medical claims data should be utilized. The FDA recommends that strategies to address these gaps should be explored, including the use of mobile technologies and other tools for collecting PROs [45]. Real-world data can provide support throughout the development of all new drugs by identifying unmet treatment needs, generating hypotheses for clinical research, and providing insights on efficacy and safety for pre-regulatory approval and post-approval outcomes [46]. As such, RWE can be used to support the approval of drugs for expanded indications; for example, palbociclib is now approved to treat men with breast cancer, with its approval supported by real-world data from electronic health records and insurance claims [65].

Relevance of RWE in the era of biosimilars in hematology

As treatment options for hematologic malignancies increase, real-world data can be accumulated to expand the evidence base for disease management in clinical practice [42]. RWE has the potential to address outcomes in clinical practice, and increase understanding of adverse events, use of resources and economic burden [66–68]. This may facilitate evidence-based clinical decision-making and increase the uptake of biosimilars. Real-world studies have evaluated treatment patterns for novel therapies in patients with chronic lymphocytic leukemia to identify sequencing strategies and reasons for treatment discontinuation [69,70]. As more rituximab biosimilars become available, RWE could provide an understanding of the sequence in which patients should be treated with these

Table 4. Clinical and real-world studies for biosimilars.

Source	Advantages	Disadvantages
Randomized clinical trials	– Well-designed and controlled; high-quality data are collected – Patient baseline data are collected	– May not reflect real-world patients seen by physicians due to strict inclusion and exclusion criteria – Limited indications are studied – Patients are followed up for limited time periods
Observational studies (prospective)	– Include different population subgroups (e.g., pediatric, pregnant and older patients) – Can be designed to address specific efficacy and safety questions to build confidence in biosimilars – Provide data on long-term patient outcomes – Demonstrate efficacy in extrapolated indications	– Issues of selection bias and confounding factors
Observational studies (retrospective)	– Evaluate adherence to treatment with biosimilars – Evaluate switching between reference products and biosimilars	– Patient baseline data may not be available – Issues of recall bias and confounding factors
Patient registries and electronic health records	– May identify rare side effects or trends in adverse events – More broadly representative of clinical settings and patient populations	– Patient registries can have high set-up and maintenance costs
Review of insurance claims/pharmacy records	– Provide information on treatment patterns (comparing use of reference products with biosimilars) – Provide data on treatment costs	– Prescribing decisions are not always evidence-driven, and can be affected by other factors, such as physican preference

drugs and offer invaluable insights into potential comparisons between rituximab biosimilars. Accumulating real-world data may help to reassure physicians and patients on the effectiveness of rituximab biosimilars in extrapolated indications [71].

Improving biosimilar uptake for the treatment of hematologic malignancies has the potential to reduce healthcare costs and expand patient access [14,17]. Increased competition between biosimilars may further reduce the costs of these drugs. However, there is a lack of consensus on the extent of these savings and, in any event, they are not likely to be as large as those obtained for generic drugs [72,73]. Additionally, biosimilars may improve patient care; for example, by enabling patients to receive treatment at an earlier stage of their disease [74,75].

The FDA's Biosimilars Action Plan recommends the increased use of real-world data to facilitate regulatory decision-making related to biosimilars [76]. RWE could also support safety assessments and the appropriate prescribing of biosimilars; for example, by considering data from the FDA's Adverse Event Reporting System and Sentinel Initiative, and data from insurance companies [76]. Real-world studies that accumulate data from a variety of sources, such as patient registries and insurance claims records, can provide further supportive data on the clinical experience of biosimilars. The results from such studies may help inform physicians, patients, manufacturers and regulatory bodies to guide decisions on the use of biosimilars in the treatment of patients across a range of conditions, including hematologic malignancies [55].

Designing effective real-world studies: challenges & recommendations

Challenges

As more rituximab biosimilars become available (including in extrapolated indications), there is a need for well-designed real-world studies to gain broader experience of their use in clinical practice and to gain the trust of the prescribing community [77,78]. However, obtaining reliable RWE for biosimilars with high-quality data can be a challenge. The key advantages and disadvantages of clinical and real-world studies in generating evidence on the use of biosimilars are summarized in Table 4. There are, however, several challenges to consider in the design of these studies, including data quality, biases, confounding factors, cost, patient confidentiality, access to data and governance [48,78]. Furthermore, there is a lack of knowledge and awareness of the systems and processes currently in place to support the collection of real-world data and the methods for analyzing these data [79]. Conducting real-world studies is typically less resource intensive than for randomized clinical trials; however, there is no agreed-upon design for an effective study, although checklists to ensure any data are of regulatory-grade quality have been proposed [56]. Pragmatic clinical trials can be conducted by physicians to test interventions in real-world clinical practice settings with a more representative range of patients than those included in randomized clinical trials, as eligibility criteria are not as strict [80]. One advantage of these trials is that they can be used to evaluate how an intervention works in various healthcare settings, such as hospitals, clinics or physician practices.

Physicians and their patients may have concerns about switching to a biosimilar in the middle of a treatment cycle for cost rather than medical reasons [8]. Therefore, some physicians and pharmacists might need additional sources of evidence on the effects of switching from the reference product to a biosimilar, as regulatory agencies generally do not require switching studies to be conducted for the approval of a biosimilar [81]. Oncologists must decide if and when treatment should be switched to biosimilars, either to or from a reference product or between different biosimilars [82]. Most physicians are unlikely to switch unless financial or other 'toxicities' emerge [83]. While the FDA requires switching studies for approved biosimilars to be designated as interchangeable, it does not require clinical trials in each extrapolated indication [81]. However, a lack of confidence in the efficacy and safety of rituximab biosimilars could lead to lower uptake. This in turn might increase the time required to collect sufficient data to undertake robust real-world studies, particularly if these are retrospective. Furthermore, stakeholders might require RWE that is based on region-specific data and they may not fully accept evidence based on data generated outside their region.

Recommendations

As rituximab biosimilars have only recently been approved for use in the USA, real-world data on their use in clinical practice are lacking; as such, initial studies should be prospective (e.g., a registry that captures patient-level data on the use of the biosimilar and reference product). As evidence on the real-world use of rituximab biosimilars accumulates, retrospective studies could be designed to address clinical and economic outcomes. Such studies may help to inform stakeholders and patients that RWE can be used alongside data from clinical trials to broaden the evidence base on the efficacy and safety of rituximab biosimilars [46]. These studies should also include additional information, such as PROs and economic analyses. PROs (e.g., health-related quality of life, and patient preference and satisfaction) could aid differentiation between competing products as more rituximab biosimilars are approved [55,84]. Documentation of PROs can contribute to an improved understanding of the overall efficacy of approved drugs; for example, by recording accurate information on patients' symptom burden [84]. Such studies may enable biosimilar costs to be evaluated in relation to patient outcomes [85]. To ensure that real-world studies are designed to address meaningful questions, it is important to consider the views of all stakeholders, including patients [78]. However, best practices for involving different stakeholders when designing and conducting real-world studies are still being developed [78].

Collaborations are required between organizations that are adept at generating real-world data and groups with expertise in the analysis, interpretation and dissemination of these findings [55]. Biosimilar manufacturers and their collaborators could alleviate some of the concerns that physicians may have about the safety and effectiveness of biosimilars by designing real-world studies that provide supportive evidence for the safety of biosimilars. The American Society of Clinical Oncology's 'big data' initiative, CancerLinQ®, could potentially contribute valuable information on biosimilar use and effectiveness by integrating real-time data for clinical oncology practice and identifying safety concerns in real-world settings [86].

It will be important to identify whether further clinical evidence is required, and to prioritize specific questions regarding the use of biosimilars that can be addressed in real-world studies [55]. Evaluating the long-term use of biosimilars requires not only financial support from relevant stakeholders but also a consensus on the questions that should be addressed; for example, is the primary concern safety or efficacy and should real-world studies compare biosimilars with their reference product or with other rituximab biosimilars. Real-world studies also need to be designed using appropriate methods for data collection in each NHL indication. There is therefore a need to establish a working group to address the specific challenges of collating RWE on biosimilars for the treatment of hematologic malignancies, and to develop a consensus statement to ensure some level of evidence for the quality and comparability of data. Demonstrating the real-world value of rituximab biosimilars to all stakeholders is key to improving patient access and increasing the uptake of these drugs. As such, there are opportunities to design effective real-world studies to provide reliable long-term data on rituximab biosimilars.

Conclusion

Designing and conducting effective real-world studies for rituximab biosimilars may help to overcome barriers to their adoption by stakeholders. RWE can provide long-term data on the efficacy and safety of rituximab biosimilars in more diverse patient populations, particularly those not studied in clinical trials. This evidence could also support decision-making on non-medical switching, to or from a reference biologic. As randomized clinical trials are often costly to conduct, RWE can provide supportive evidence to help achieve lower-priced biologics and improve patient

access to these therapies. As such, RWE has the potential to help sustain the treatment of hematologic malignancies with biologics, including biosimilars.

Future perspective

Treatment options for hematological malignancies are anticipated to expand in the future as more rituximab biosimilars are approved. Stakeholders including patients and physicians will need more information to aid differentiation between biosimilars to support decision-making on the appropriate treatment for each patient. Real-world studies have an important role in providing reliable data on long-term patient outcomes, understanding the sequence in which patients should be treated with these drugs and demonstrating the efficacy of rituximab biosimilars in extrapolated indications. Mobile technologies (such as, wearable electronic devices) are likely to support real-world

Executive summary

Background

- Healthcare expenditure for cancer treatment is increasing, partly due to the cost of biologic drugs, creating a challenge for the future sustainability of affordable cancer care.
- As patent portfolios for biologics are nearing end of term, drug companies are developing biosimilars that may provide more affordable treatment options and increase patient access to these important therapies.
- Demonstrating the value of rituximab biosimilars to stakeholders (including patients and healthcare providers) in the real world is key to improving patient access; however, there are currently several barriers to the adoption of rituximab biosimilars.

Regulatory guidance & rituximab biosimilars

- To gain regulatory approval, biosimilars must be sufficiently similar to the corresponding reference biologic such that they are not expected to show any clinically meaningful differences in efficacy, safety and purity.
- Biosimilar approval is established using a 'totality-of-the-evidence' approach, comprising comparative analytical, preclinical, clinical pharmacokinetic, and efficacy and safety studies in an appropriate patient population.
- Some rituximab biosimilars have been approved in the USA and the European Union through these pathways and there are several other rituximab biosimilars currently in development.

Real-world studies

- Real-world studies can provide insights into different aspects of treatment and patient outcomes to supplement the evidence generated from conventional clinical trials in selected patient populations.
- Real-world data can be collected from a variety of sources including electronic patient health records, claims data, product and disease registries, PROs as well as from emerging data sources, such as social media and industry collaborations.

Relevance of RWE to healthcare stakeholders

- RWE can demonstrate the efficacy and safety of biosimilars in patient populations for whom clinical trial data are not available.
- Evidence on the use of biosimilars from real-world settings could enhance stakeholder confidence in the safety of these drugs.

Relevance of RWE in the era of biosimilars in hematology

- RWE has the potential to address outcomes in clinical practice, and increase understanding of adverse events, use of healthcare resources and the economic burden on healthcare systems.
- As more rituximab biosimilars become available, RWE may help inform physicians, patients, manufacturers and regulatory bodies to guide decisions on the use of these drugs for the treatment of hematologic malignancies.

Designing effective real-world studies: challenges & recommendations

- Obtaining reliable RWE for biosimilars can be challenging and there are several factors to consider when designing real-world studies, including data quality, biases, confounding factors, cost, patient confidentiality, access to data and governance.
- Real-world data on the use of rituximab biosimilars in clinical practice are lacking so initial studies should be prospective (e.g., registries to capture patient-level data on the use of the biosimilar and reference product).
- Retrospective studies could be designed to address clinical and economic outcomes, and acquisition of additional information such as PROs to aid differentiation between different biosimilars.
- Collaborations are required between organizations that are adept at generating real-world data and groups with expertise in the analysis, interpretation and dissemination of these findings.

Conclusion

- Providing real-world data on the efficacy and safety of rituximab biosimilars may help to overcome barriers to their adoption by stakeholders.
- RWE can provide supportive evidence to help achieve lower-priced biologics, improve patient access to these therapies and help sustain the treatment of hematologic malignancies with biologics, including biosimilars.

studies to collect data on PROs, such as health-related quality of life, and patient preference and satisfaction. Reassuring stakeholders on the efficacy and safety of rituximab biosimilars by accumulating reliable evidence through well-designed real-world studies can potentially help increase the uptake of rituximab biosimilars and, in turn, reduce healthcare costs for the treatment of hematologic malignancies.

Supplementary data

A Plain Language Summary is available for this paper. To view and download the Plain Language Summary, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fon-2020-0131

Financial & competing interests disclosure

This review was sponsored by Pfizer. P Nava-Parada and A Shelbaya are full-time employees of and declare stock holdings and/or stock options from Pfizer. C Nabhan was an employee of Aptitude Health, which collaborates with Pfizer on biosimilar projects. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support was provided by J Oliver of Engage Medical Affairs and was funded by Pfizer.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Patel KB, Arantes LH Jr, Tang WY, Fung S. The role of biosimilars in value-based oncology care. *Cancer Manag. Res.* 10, 4591–4602 (2018).
2. Jacobs I, Ewesuedo R, Lula S, Zacharchuk C. Biosimilars for the treatment of cancer: a systematic review of published evidence. *BioDrugs* 31(1), 1–36 (2017).
3. Cornes P. The economic pressures for biosimilar drug use in cancer medicine. *Target. Oncol.* 7(Suppl. 1), S57–S67 (2012).
4. Salles G, Barrett M, Foa R *et al.* Rituximab in B-cell hematologic malignancies: a review of 20 years of clinical experience. *Adv. Ther.* 34(10), 2232–2273 (2017).
5. EMA. European public assessment report for MabThera. www.ema.europa.eu/en/medicines/human/EPAR/mabthera
6. Biogen and Genentech USA Inc. Rituxan®. Prescribing information (1997). www.gene.com/download/pdf/rituxan_prescribing.pdf
7. Baer WH II, Maini A, Jacobs I. Barriers to the access and use of rituximab in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia: a physician survey. *Pharmaceuticals* 7(5), 530–544 (2014).
8. Nabhan C, Valley A, Feinberg BA. Barriers to oncology biosimilars uptake in the United States. *Oncologist* 23(11), 1261–1265 (2018).

• **Outlines the economic, policy and stakeholder perception barriers that have an impact on the uptake of oncology biosimilars in the USA.**

9. US FDA. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry (2015). www.fda.gov/media/82647/download
10. EMA. Guideline on similar biological medicinal products (2014). www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf
11. Falit BP, Singh SC, Brennan TA. Biosimilar competition in the United States: statutory incentives, payers, and pharmacy benefit managers. *Health Aff.* 34(2), 294–301 (2015).
12. Subramanian J, Cavenagh J, Desai B, Jacobs I. Rituximab in the treatment of follicular lymphoma: the future of biosimilars in the evolving therapeutic landscape. *Cancer Manag. Res.* 9, 131–140 (2017).
13. Qureshi ZP, Nagai S, Bennett CL. Biosimilar filgrastim use in the United States vs the European Union and Japan – why does it lag behind and what can be done? *JAMA Oncol.* 5(3), 297–298 (2019).
14. Boccia R, Jacobs I, Popovian R, de Lima Lopes G Jr. Can biosimilars help achieve the goals of US health care reform? *Cancer Manag. Res.* 9, 197–205 (2017).
15. US FDA. Biosimilar development, review, and approval (2017). www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580429.htm
16. Alten R, Cronstein BN. Clinical trial development for biosimilars. *Semin. Arthritis Rheum.* 44(Suppl. 6), S2–S8 (2015).
17. Nabhan C, Parsad S, Mato AR, Feinberg BA. Biosimilars in oncology in the United States: a review. *JAMA Oncol.* 4(2), 241–247 (2018).

18. WHO. Guidelines on evaluation of similar biotherapeutic products (SBPs) (2009). www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
19. Garcia R, Araujo DV. The regulation of biosimilars in Latin America. *Curr. Rheumatol. Rep.* 18(3), 16 (2016).
20. Tsai WC. Update on biosimilars in Asia. *Curr. Rheumatol. Rep.* 19(8), 47 (2017).
21. Health Canada. Guidance Document. Information and submission requirements for biosimilar biologic brugs (2010). www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2016-eng.pdf
22. Kabir ER, Moreino SS, Sharif Siam MK. The breakthrough of biosimilars: a twist in the narrative of biological therapy. *Biomolecules* 9(9), 410 (2019).
23. Yoo DH, Suh CH, Shim SC *et al.* A multicentre randomised controlled trial to compare the pharmacokinetics, efficacy and safety of CT-P10 and innovator rituximab in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 76(3), 566–570 (2017).
24. Yoo DH, Suh CH, Shim SC *et al.* Efficacy, safety and pharmacokinetics of up to two courses of the rituximab biosimilar CT-P10 versus innovator rituximab in patients with rheumatoid arthritis: results up to week 72 of a phase I randomized controlled trial. *BioDrugs* 31(4), 357–367 (2017).
25. Park W, Bozic-Majstorovic L, Milakovic D *et al.* Comparison of biosimilar CT-P10 and innovator rituximab in patients with rheumatoid arthritis: a randomized controlled Phase 3 trial. *MAbs* 10(6), 934–943 (2018).
26. Kim WS, Buske C, Ogura M *et al.* Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial. *Lancet Haematol.* 4(8), e362–e373 (2017).
27. Ogura M, Sancho JM, Cho SG *et al.* Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 in comparison with rituximab in patients with previously untreated low-tumour-burden follicular lymphoma: a randomised, double-blind, parallel-group, phase 3 trial. *Lancet Haematol.* 5(11), e543–e553 (2018).
28. Celltrion Inc. Truxima. Summary of product characteristics (2017). www.ema.europa.eu/en/documents/product-information/truxima-epar-product-information_en.pdf
29. Celltrion Inc. Ritemvia. Summary of product characteristics (2017). www.ema.europa.eu/en/documents/product-information/ritemvia-epar-product-information_en.pdf
30. Celltrion Inc. Blitzima. Summary of product characteristics (2017). www.ema.europa.eu/en/documents/product-information/blitzima-epar-product-information_en.pdf
31. Celltrion Inc. Truxima® (rituximab-abbs) prescribing information (2018). www.accessdata.fda.gov/drugsatfda_docs/label/2018/761088s000lbl.pdf
32. Smolen J, Scheinberg M, Tony H-P, Zhu P, Shisha T. FRI0222 pharmacokinetics, pharmacodynamics, safety and efficacy of proposed rituximab biosimilar (GP2013) vs. EU-approved rituximab (RTX) in patients with rheumatoid arthritis: results from a randomized controlled trial (GP13-201) over 52 weeks. *Ann. Rheum. Dis.* 75(Suppl. 2), 512–513 (2016).
33. Jurczak W, Moreira I, Kanakasetty GB *et al.* Rituximab biosimilar and reference rituximab in patients with previously untreated advanced follicular lymphoma (ASSIST-FL): primary results from a confirmatory Phase III, double-blind, randomised, controlled study. *Lancet Haematol.* 4(8), e350–e361 (2017).
34. Sandoz. Rixathon. Summary of product characteristics (2017). www.ema.europa.eu/en/documents/product-information/rixathon-epar-product-information_en.pdf
35. Sandoz. Riximyo. Summary of product characteristics (2017). www.ema.europa.eu/en/documents/product-information/riximyo-epar-product-information_en.pdf
36. Cohen S, Emery P, Greenwald M *et al.* A Phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis. *Br. J. Clin. Pharmacol.* 82(1), 129–138 (2016).
37. Cohen SB, Burgos-Vargas R, Emery P, Jin B, Cronenberger C, Vazquez-Abad MD. Extension study of PF-05280586, a potential rituximab biosimilar, versus rituximab in subjects with active rheumatoid arthritis. *Arthritis Care Res. (Hoboken).* 70(11), 1598–1606 (2018).
38. Sharman J, Liberati AM, Santucci Silva R *et al.* A randomized, double-blind efficacy and safety study of PF-05280586 (a potential rituximab biosimilar) compared with rituximab reference product (MabThera®) in subjects with previously untreated CD20-positive, low tumor burden follicular lymphoma (LTB-FL). *Blood* 132(Suppl. 1), 394 (2018).
39. Pfizer Inc. Ruxience™ (rituximab-pvvr) prescribing information (2019). www.accessdata.fda.gov/drugsatfda_docs/label/2019/761103s000lbl.pdf
40. EMA. Summary of Product Characteristics for Ruxience (2020). www.ema.europa.eu/en/documents/product-information/ruxience-epar-product-information_en.pdf
41. Amgen. Study to assess if ABP798 is safe & effective in treating non Hodgkin lymphoma compared to rituximab (JASMINE). www.amgentrials.com/amgen/trialsummary.aspx?studyid=20130109
42. GaBi online. Biosimilars of rituximab (2015). www.gabionline.net/Biosimilars/General/Biosimilars-of-rituximab

43. Mabion. https://www.mabion.eu/en/blog/mabion-s-completes-marketing-authorisation-application-flagship-drug-mabioncd20-european-medicines-agency-ema/
44. GaBi online. More positive phase III results for rituximab biosimilar ABP 798 (2019). http://gabionline.net/Biosimilars/Research/More-positive-phase-III-results-for-rituximab-biosimilar-ABP-798
45. US FDA. Framework for FDA's real-world evidence program (2018). www.fda.gov/media/120060/download
46. The Network for Excellence in Health Innovation. Real world evidence: a new era for health care innovation (2015). www.nehi.net/writable/publication_files/file/rwe_issue_brief_final.pdf
47. Nabhan C, Klink A, Prasad V. Real-world evidence - what does it really mean? *JAMA Oncol.* 5(6), 781–783 (2019).
48. IQVIA and London School of Economics. Real-world evidence in oncology towards innovative and affordable patient care (2018). www.iqvia.com/locations/uk-and-ireland/library/white-papers/real-world-evidence-in-oncology
49. Webster J, Smith BD. The case for real-world evidence in the future of clinical research on chronic myeloid leukemia. *Clin. Ther.* 41(2), 336–349 (2019).
50. Matasar MJ, Qiu A, Shapouri S *et al.* Real-world assessment of practice efficiency with the introduction of subcutaneous rituximab. *Hematol. Oncol.* 37(S2), 540 (2019).
51. Sherman RE, Anderson SA, Dal Pan GJ *et al.* Real-world evidence – what is it and what can it tell us? *N. Engl. J. Med.* 375(23), 2293–2297 (2016).
52. National Institute for Health and Care Excellence. Biosimilar medicines (2016). www.nice.org.uk/advice/ktt15/resources/biosimilar-medicines-58757954414533
53. Reinisch W, Smolen J. Biosimilar safety factors in clinical practice. *Semin. Arthritis Rheum.* 44(Suppl. 6), S9–S15 (2015).
54. Cohen H, Beydoun D, Chien D *et al.* Awareness, knowledge, and perceptions of biosimilars among specialty physicians. *Adv. Ther.* 33(12), 2160–2172 (2017).
55. Ronnebaum S, Atzinger C. Enhancing biosimilar adoption with real-world evidence (2018). www.ispor.org/docs/default-source/publications/value-outcomes-spotlight/july-august-2018/ispor-vos-august-2018-heor-article-enhancing-biosimilars.pdf?sfvrsn=8f27535f_2
56. Miksad RA, Abernethy AP. Harnessing the power of real-world evidence (RWE): a checklist to ensure regulatory-grade data quality. *Clin. Pharmacol. Ther.* 103(2), 202–205 (2018).

- **Presents a proposed checklist to facilitate the collection of regulatory-grade real-world data.**

57. Franceschetti A, Caldeira R. Treatment approach for non-Hodgkin lymphoma patients since first biosimilars of rituximab approved in EU5. *J. Clin. Oncol.* 36(Suppl. 15), 112 (2018).
58. Teeple A, Ginsburg S, Howard L *et al.* Patient attitudes about non-medical switching to biosimilars: results from an online patient survey in the United States. *Curr. Med. Res. Opin.* 34(4), 603–609 (2019).
59. McKinnon RA, Cook M, Liauw W *et al.* Biosimilarity and interchangeability: principles and evidence: a systematic review. *BioDrugs* 32(1), 27–52 (2018).
60. Suvarna V. Phase IV of drug development. *Perspect. Clin. Res.* 1(2), 57–60 (2010).
61. Berlin JA, Glasser SC, Ellenberg SS. Adverse event detection in drug development: recommendations and obligations beyond phase 3. *Am. J. Public Health* 98(8), 1366–1371 (2008).
62. Abboud CN, Lang N, Fung H *et al.* Real-world safety experience of tevagrastim/ratiograstim/biograstim and tbo-filgrastim, short-acting recombinant human granulocyte colony-stimulating factors. *Support. Care Cancer* 27(7), 2569–2577 (2018).
63. McBride A, Balu S, Campbell K, MacDonald K, Abraham I. Subcutaneous versus intravenous rituximab in non-Hodgkin lymphoma treated with R-CHOP: economic modeling for the US. *Blood* 132(Suppl. 1), 4776 (2018).
64. US FDA. 21st Century Cures Act. Public Law. 114–255 (2016). www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf
65. Wedam S, Fashoyin-Aje L, Bloomquist E *et al.* FDA approval summary: palbociclib for male patients with metastatic breast cancer. *Clin. Cancer Res.* 26(6), 1208–1212 (2020).
66. Goyal RK, Nagar SP, Kabadi SM, Kaye JA, Seal B, Mato AR. Adverse events, resource use, and economic burden associated with mantle cell lymphoma: a real-world assessment of privately insured patients in the United States. *Leuk. Lymphoma* 60(4), 955–963 (2019).
67. Scavone C, Sessa M, Clementi E *et al.* Real world data on the utilization pattern and safety profile of infliximab originator versus biosimilars in Italy: a multiregional study. *BioDrugs* 32(6), 607–617 (2018).
68. Leonard E, Wascovich M, Oskouei S, Gurz P, Carpenter D. Factors affecting health care provider knowledge and acceptance of biosimilar medicines: a systematic review. *J. Manag. Care Spec. Pharm.* 25(1), 102–112 (2019).

- **Systematic review evaluating healthcare provider knowledge, perceptions and prescribing patterns of biosimilars in the USA and Europe.**

69. Mato AR, Hill BT, Lamanna N *et al.* Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. *Ann. Oncol.* 28(5), 1050–1056 (2017).

70. Mato AR, Samp JC, Gauthier G, Terasawa E, Brander DM. Drivers of treatment patterns in patients with chronic lymphocytic leukemia stopping ibrutinib or idelalisib therapies. *Cancer Biol. Ther.* 19(7), 636–643 (2018).

71. Ogura M, Coiffier B, Kwon HC, Yoon SW. Scientific rationale for extrapolation of biosimilar data across cancer indications: case study of CT-P10. *Future Oncol.* 13(15s), 45–53 (2017).

72. Manolis CH, Rajasenan K, Harwin W, McClelland S, Lopes M, Farnum C. Biosimilars: opportunities to promote optimization through payer and provider collaboration. *J. Manag. Care Spec. Pharm.* 22(Suppl. 9), S3–S9 (2016).

73. Mulcahy AW, Predmore Z, Mattke S. The cost savings potential of biosimilar drugs in the United States (2014). www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf

74. Gascon P, Tesch H, Verpoort K *et al.* Clinical experience with Zarzio® in Europe: what have we learned? *Support. Care Cancer* 21(10), 2925–2932 (2013).

75. Henry D, Taylor C. Pharmacoeconomics of cancer therapies: considerations with the introduction of biosimilars. *Semin. Oncol.* 41(Suppl. 3), S13–S20 (2014).

76. US Food and Drug Administration. Biosimilars action plan: balancing innovation and competition (2018). www.fda.gov/media/114574/download

77. Greenwald M, Tesser J, Sewell KL. Biosimilars have arrived: rituximab. *Arthritis.* 2018, 3762864 (2018).

78. Berger ML, Sox H, Willke RJ *et al.* Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the Joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Value Health.* 20(8), 1003–1008 (2017).

•• **Presents recommendations from the International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology Special Task Force for good practices for real-world studies of treatment effectiveness.**

79. The Forum on Drug Discovery, Development, and Translation of the National Academies of Sciences, Engineering, and Medicine. Examining the impact of real-world evidence (RWE) on medical product development. (2019). http://nationalacademies.org/hmd/Activities/Research/DrugForum/2018-July-17/rwe-proceedings-of-a-workshop-series.aspx

80. Ford I, Norrie J. Pragmatic trials. *N. Engl. J. Med.* 375(5), 454–463 (2016).

81. Declerck P, Bakalos G, Zintzaras E, Barton B, Schreitmuller T. Monoclonal antibody biosimilars in oncology: critical appraisal of available data on switching. *Clin. Ther.* 40(5), 798–809 e2 (2018).

82. Rugo HS, Linton KM, Cervi P, Rosenberg JA, Jacobs I. A clinician's guide to biosimilars in oncology. *Cancer Treat. Rev.* 46, 73–79 (2016).

83. Wehrwein P. A conversation with Gary Lyman, MD: biosimilars and the search for the cure to cancer treatment's financial toxicity. *Manag. Care* 28(1), 12–15 (2019).

84. Efficace F, Gaidano G, Lo-Coco F. Patient-reported outcomes in hematology: is it time to focus more on them in clinical trials and hematology practice? *Blood* 130(7), 859–866 (2017).

•• **Outlines the value of a systematic and rigorous implementation of assessing patient-reported outcomes in hematology treatment and provides examples of how real-world data have contributed to an improved understanding of the value of new therapies.**

85. Smeeding J, Malone DC, Ramchandani M, Stolshek B, Green L, Schneider P. Biosimilars: considerations for payers. *Pharmacol. Ther.* 44(2), 54–63 (2019).

86. Lyman GH, Balaban E, Diaz M *et al.* American Society of Clinical Oncology statement: biosimilars in oncology. *J. Clin. Oncol.* 36(12), 1260–1265 (2018).

Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Journal of **Comparative Effectiveness Research**

Economic burden and treatment patterns for patients with diffuse large B-cell lymphoma and follicular lymphoma in the USA

Jinma Ren*[,1], Carl V Asche[1,2], Yaping Shou[3] & Aaron Galaznik[3]

[1]Center for Outcomes Research, Department of Medicine, University of Illinois College of Medicine at Peoria, Peoria, IL, USA

[2]Center for Pharmacoepidemiology & Pharmacoeconomic Research, University of Illinois at Chicago College of Pharmacy, Chicago, IL, USA

[3]Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA

*Author for correspondence: jinmaren@uic.edu

Aim: Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are common types of non-Hodgkin's lymphoma, and real-world evidence continues to be lacking for healthcare costs and utilization among DLBCL and FL patients. Our study aims to describe medical and pharmacy costs and health resource utilization and to characterize longitudinal treatment patterns among these patients. **Methods:** A retrospective observational study was performed among adult patients with DLBCL or FL using the US MarketScan (Truven) administrative claims data from 1 January 2007 to 31 December 2015. Diagnoses of DLBCL and FL were based upon ICD-9 codes. Identifications of treatment lines involved 30 lymphoma-specific anticancer systemic agents. Direct healthcare costs and utilizations were computed in the 1-year postdiagnosis period. Generalized linear models with a gamma link were used to compare healthcare costs between therapies with and without rituximab. **Results:** A total of 2767 DLBCL and 5989 FL patients received frontline therapy. The majority received treatment within 3 months after initial diagnosis (DLBCL 79.9% and FL 62.4%) and were treated with rituximab or bendamustine either alone or in combination (DLBCL 67.4% and FL 84.7%). The total healthcare costs were US $15,555 and $10,192 per patient per month within 1 year following their initial diagnosis for DLBCL and FL, respectively. The medical costs were nearly twice as much as the drug costs for DLBCL patients. Both DLBCL and FL patients receiving rituximab had higher pharmacy costs but lower medical costs ($p < 0.001$). During the first year following initial diagnosis, the resource utilization (per patient per month) of DLBCL patients included 0.21 inpatient admissions, 0.26 radiation therapy, 2.63 outpatient or office visits, 0.18 emergency room visits, 0.06 intensive care unit admissions and 0.10 stem cell transplantation. FL patients occupied less health resources than DLBCL patients. **Conclusion:** The healthcare costs and health resources utilized were considerable in non-Hodgkin's lymphoma, especially DLBCL patients.

First draft submitted: 12 September 2018; Accepted for publication: 14 January 2019; Published online: 11 March 2019

Keywords: diffuse large B-cell lymphoma • follicular lymphoma • healthcare costs • resource utilization • treatment

Non-Hodgkin's lymphoma (NHL) is a cancer that typically starts in lymphocytes in the lymph nodes and other lymphoid tissues, such as the spleen and bone marrow, which serve as part of the immune system. NHL is one of the most common cancers in the USA, with approximately 72,240 Americans diagnosed with NHL in 2017 [1]. For unknown reasons, NHL incidence rates have almost doubled since the 1970s [1]. Furthermore, substantial healthcare costs and utilization have become a significant burden for both the healthcare system and the patient's family [2,3].

Approximately 85% of NHL cases are diagnosed with B-cell lymphomas in the USA, and diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL, representing approximately one out of every three lymphoma diagnoses [4]. DLBCL can affect any age group but occurs most frequently among older individuals.

Future Medicine

DLBCL usually begins as a quickly growing mass in a lymph node deep within the body, such as in the chest or abdomen, or in a lymph node in the neck or armpit, but it can also start in other areas, such as the intestines, bone, or even brain or spinal cord [4]. The five-drug chemoimmunotherapy combination R-CHOP remains the standard frontline treatment of DLBCL and has not changed in more than 15 years since the anti-CD20 monoclonal antibody rituximab was added to the CHOP backbone as standard-of-care for DLBCL in 2002 [5]. However, at least a third of patients are not cured by R-CHOP, and relapsed or refractory DLBCL is fatal in approximately 90% of patients [6]. Recently, genomics and personalized medicine have been discussed to improve treatment options for DLBCL [7].

Another common type of NHL is follicular lymphoma (FL) accounting for approximately 15–30% of all NHLs in developed countries [3,8,9]. The term follicular indicates that the cells tend to grow in a nodular pattern within the lymph nodes. The average age for patients with FL is 60 years and usually occurs throughout many lymph node sites in the body and bone marrow [4]. FL is known as 'indolent' or 'low-grade' but is difficult to cure. Death occurs at a median of 12.5 years after diagnosis [10], generally as a consequence of resistant disease, transformation to diffuse large B-cell pathology, or side effects from therapy. FL patients younger than 40 have a median overall survival of 24 years [10]. It has been suggested that these lymphomas might not require treatment prior to a clinical need to do so because of a lack of associated survival advantage [8]. FL may be untreated or treated by radiation only in the early stages. Advanced disease can be treated with a variety of options, often including chemotherapy plus immunotherapy, with rituximab frequently used in combination or alone as an immunotherapeutic agent [11].

Given the rapid evolution in diagnostic subtyping as well as treatment regimens, it is important to examine the economic burden, treatment patterns and outcomes among these patients based on real-world evidence utilizing secondary databases to assist in informing those involved in the decision-making process. Our study aimed to describe total healthcare costs and resource utilization in patients with DLBCL and FL and to characterize real-world longitudinal treatment patterns among them, including the type, duration and sequence of therapy.

Patients & methods

Study design & data source

A retrospective observational study was performed among adult patients with DLBCL or FL using the US MarketScan (Truven) administrative claims data from 1 January 2007 to 31 December 2015. This database has commercial and Medicare Advantage enrollees, comprising of inpatient admissions, inpatient services, outpatient services, outpatient drug claims, detail enrollment and laboratory test results. Data are available for over 170 million patients who have been sampled since 1995. The MarketScan and other claims databases are some of the best tools available to some research questions when clinical trials are not feasible. Since this study utilized a retrospective unidentified database, we have identified no risks of relapse or survival rates for these patients.

Identification of treatment lines

The diagnoses of DLBCL and FL were based upon the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes (200.7× for DLBCL, 202.0× for FL). Identification of treatment lines involved 30 lymphoma-specific anticancer systemic agents: bendamustine, brentuximab vedotin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytarabine, cytosine, doxorubicin, epirubicin, etoposide, filgrastim, fludarabine, gemcitabine, ibritumomab tiuxetan, idelalisib, lenalidomide, mesna, methotrexate, methylprednisolone, mitoxantrone, oxaliplatin, procarbazine, rituximab, tositumomab, vincristine, ibrutinib, ifosfamide, dexamethasone and prednisone. These agents were extracted by the corresponding codes derived from the Healthcare Common Procedure Coding System and/or National Drug Code (NDC). All agents received within 30 days following the day of the first infusion or fill date constituted frontline therapy. The date of the first infusion or fill associated with frontline therapy was the index frontline therapy date. Prednisone alone was not considered as a treatment line, whereas dexamethasone alone was considered if it was received continuously for 42 days or more.

The second and subsequent lines of therapy were identified if a patient switched to a different agent/regimen (e.g., from rituximab-based to bendamustine-based), if an agent was added to the regimen (except dexamethasone and prednisone), or if the same or similar regimen had a treatment gap of greater than 120 days. Two regimens were considered to be similar if they included the same agents, except for dexamethasone and prednisone.

Inclusion & exclusion criteria

Patients included in this analysis met the following criteria: had at least one inpatient claim or two outpatient claims with diagnosis of DLBCL/FL at least 60 days apart (but less than 1 year apart) during the study period; were continuously enrolled with medical and pharmacy benefits for at least 12 months prior to the index diagnosis date through at least 30-days postindex diagnosis date; and were age 18 years or older at the index diagnosis. Patients who had claims for DLBCL/FL, another primary cancer, or metastatic disease during the 12-month period prior to the index date were excluded. The follow-up period was from the index diagnosis of DLBCL/FL through disenrollment, death, or end of available data, whichever occurred earlier.

Statistical analysis

Descriptive results were reported using frequency and percentage for categorical variables, and mean, standard deviation, median and quartile for continuous variables. Treatment patterns were categorized by drug class (rituximab/bendamustine either alone or in combination, vs others), autologous stem cell transplant therapy ([SCT], with and without chemotherapy/immunotherapy) and specific regimens as well as durations, which were reported for each therapy line.

Direct healthcare costs were computed in the 1-year postdiagnosis period utilizing the variable 'total pay' in the claims data, which represents the combined health plan reimbursement (payouts from the insurance/payers) and patient paid amounts (out of pocket from patients). Average total costs were reported on a per patient per month basis in 2015 US dollars, which were adjusted by the annual medical care component of the consumer price index. Total costs were calculated and presented in categories of pharmacy costs, and medical costs which consisted of inpatient costs, outpatient facility costs, office visit costs, emergency room (ER) costs and other outpatient costs. During the same time period, healthcare resource utilization was also reported, including inpatient admissions, facility outpatient or office visits, ER visits and intensive care unit (ICU) admissions.

Generalized linear models with a gamma link were used to compare healthcare costs between therapies with and without rituximab. All relevant statistical tests were two-tailed with a 0.05 cut-off value for statistical significance.

Results

Patient characteristics

Based upon the inclusion and exclusion criteria, from a total of 50,173 patients, 4651 DLBCL and 10,429 FL patients were identified. Of these, 2794 DLBCL patients and 6021 FL patients received one of the proposed treatments (SCT, chemo, or immunotherapy) and met the other inclusion and exclusion criteria (Figure 1). The average age was 61 (standard deviation [SD] 14.3) years for DLBCL patients and 60 (SD 13.1) years for FL patients. The proportion with inpatient claims were 54.9 and 34.3%, for DLBCL and FL respectively (Table 1). Demographics were otherwise similar between DLBCL and FL patients. The top three co-morbidities were cancer, diabetes without complications and chronic pulmonary disease for both DLBCL and FL patients (Table 2). Among those receiving therapy, the majority received frontline treatment within 3 months after initial diagnosis (79.9% for DLBCL, 62.4% for FL). Of DLBCL patients, 977 received second-line treatment, and 330 received three or more lines of treatments. Of FL patients, 2406 received second-line treatment, and 406 received three or more lines of treatment.

Treatment patterns

Among 2767 DLBCL patients who received frontline treatment, their physician specialties included oncology (36.3%), radiotherapy (27.9%), internal medicine (26.8%), hematology (31.1%) and multispecialty (8.2%). During frontline treatment, 4.5% received both SCT and chemo/immunotherapy, and 67.4% were treated by rituximab or bendamustine either alone or in combination (Figure 2). More patients received SCT in the second-line (10.3%) and third-line (14.5%) of treatment (Figure 3). The percentage of patients who received G-CSF agents as supportive care were 65.8, 48.1 and 40.9% during frontline, second-line and third-line therapies respectively.

For FL patients, their physician specialties were similar to those described for DLBCL patients. During frontline treatment, 1.9% received both SCT and chemo/immunotherapy, and 84.7% were treated by rituximab or bendamustine either alone or in combination (Figures 2 & 3). The percentage of patients who received G-CSF agents as supportive care were 35.6, 32.2 and 26.8% during frontline, second-line and third-line of treatment respectively.

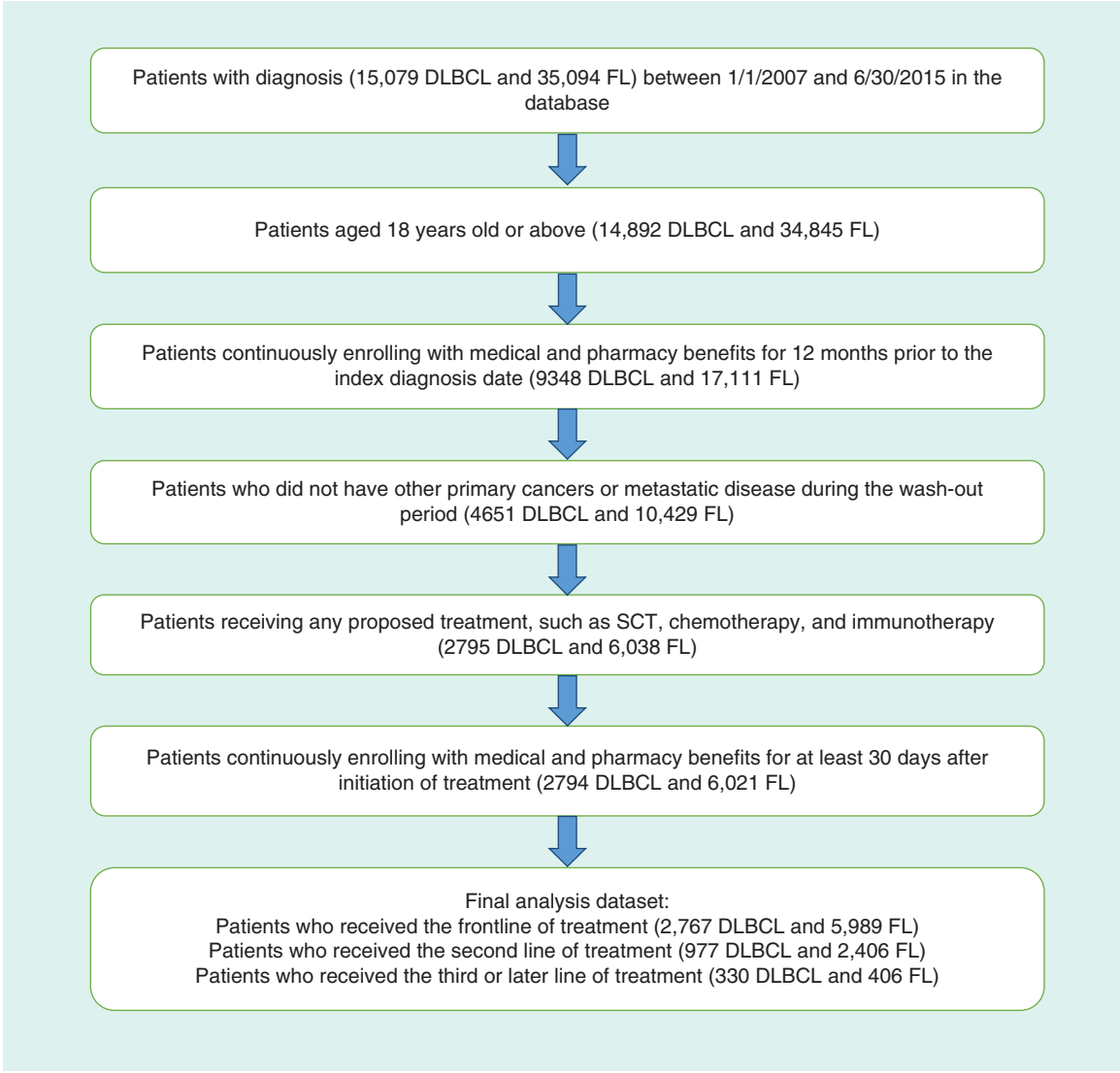


Figure 1. Population selection.
DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; SCT: Stem cell transplantation.

Healthcare costs

The averages of all healthcare costs were $15,555 and $10,192 per patient per month (PPPM) within 1 year after initial diagnosis for DLBCL and FL, respectively (Table 3). Two-thirds of total costs were medical costs ($10,398 per patient per month) for DLBCL patients, and 56% of total costs were medical costs ($5731 per patient per month) for FL patients.

As depicted in Table 4, compared with those who did not received rituximab, DLBCL patients receiving rituximab had higher pharmacy costs ($5473 vs $2118; $p < 0.001$) and lower medical costs ($6417 vs $8782; $p < 0.001$) within 1 year after initial diagnosis. Similarly, FL patients receiving rituximab also had higher pharmacy costs ($6387 vs $2406, $p < 0.001$) and lower medical costs ($4740 vs $7138; $p < 0.001$).

Health resource utilization

During the first year after initial DLBCL diagnosis, the average healthcare resource utilization PPPM included 0.21 inpatient admissions, 0.26 radiation therapy, 2.63 outpatient or office visits, 0.18 ER visits, 0.06 ICU admissions and 0.10 stem cell transplantation. During the study period, the percentages of DLBCL patients receiving at least once inpatient admission, radiation therapy, ICU, or SCT were 78.1, 29.5, 34.5 and 9.6%, respectively. Overall,

Table 1. Demographics.

Characteristics	Label	DLBCL (n = 2794)		FL (n = 6021)	
		n	%	n	%
Age group (years):	– 18–44	322	11.5	633	10.5
	– 45–64	1428	51.1	3330	55.3
	– 65–69	264	9.4	585	9.7
	– 70–74	258	9.2	528	8.8
	– 75–79	221	7.9	452	7.5
	– 80+	301	10.8	493	8.2
Sex:	– Males	1585	56.7	3067	50.9
	– Females	1209	43.3	2954	49.1
Patient type:	– Inpatients	1533	54.9	2064	34.3
	– Outpatients	1261	45.1	3957	65.7
Region:	– Northeast	456	16.5	1016	17.1
	– North Central	788	28.5	1740	29.3
	– South	1084	39.2	2277	38.4
	– West	436	15.8	901	15.2
Data type:	– Fee for service	1470	52.6	3283	54.5
	– Encounter	174	6.2	398	6.6
	– Medicare	1052	37.7	2136	35.5
	– Medicare encounter	98	3.5	204	3.4
Insurance plan:	– Comprehensive	612	21.9	1152	19.1
	– HMO	248	8.9	558	9.3
	– POS	144	5.2	337	5.6
	– PPO	1434	51.3	3219	53.5
	– Others	356	12.7	755	12.5

DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; HMO: Health maintenance organization; POS: Point-of-service; PPO: Preferred provider organization.

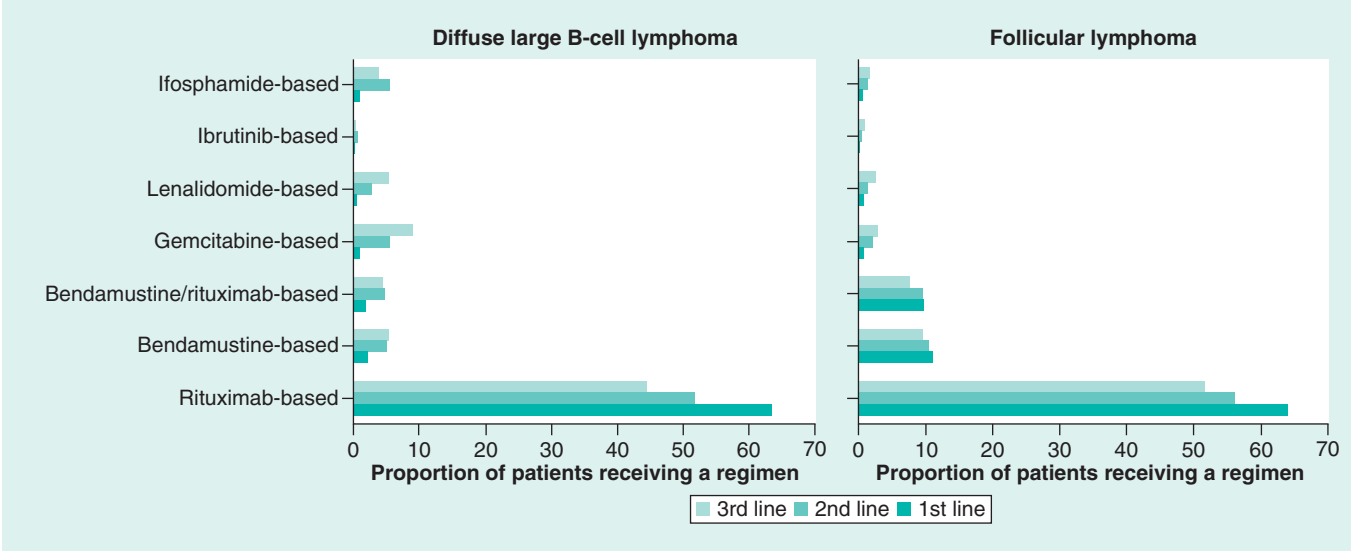


Figure 2. Regimens for diffuse large B-cell lymphoma and follicular lymphoma.

FL patients occupied less healthcare resources than DLBCL patients. During the first year after initial FL diagnosis, the average healthcare resource utilization PPPM included 0.10 inpatient admissions, 0.12 radiation therapy, 2.06 outpatient or office visits, 0.11 ED visits, 0.03 ICU admissions and 0.04 stem cell transplantation. During the

Table 2. Clinical characteristics at baseline.

Co-morbidities	DLBCL (n = 2794)		FL (n = 6021)	
	n	%	n	%
Cancer	743	26.6	1541	25.6
Diabetes without complications	560	20.0	1066	17.7
Chronic pulmonary disease	462	16.5	950	15.8
Mild liver disease	327	11.7	547	9.1
Metastatic carcinoma	285	10.2	476	7.9
Peripheral vascular disease	235	8.4	433	7.2
Cerebrovascular disease	206	7.4	385	6.4
Congestive heart failure	200	7.2	357	5.9
Renal disease	171	6.1	274	4.6
Connective tissue disease-rheumatic disease	147	5.3	230	3.8
Diabetes with complications	121	4.3	228	3.8
Peptic ulcer disease	84	3.0	89	1.5
Myocardial infarction	67	2.4	137	2.3
AIDS/HIV	30	1.1	40	0.7
Paraplegia and hemiplegia	16	0.6	23	0.4
Moderate or severe liver disease	14	0.5	16	0.3
Dementia	9	0.3	17	0.3
Time distribution from initial diagnosis to first-line treatment				
– <3 months	2211	79.9	3740	62.4
– 3–5 months	197	7.1	760	12.7
– ≥6 months	359	13.0	1489	24.9

DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma.

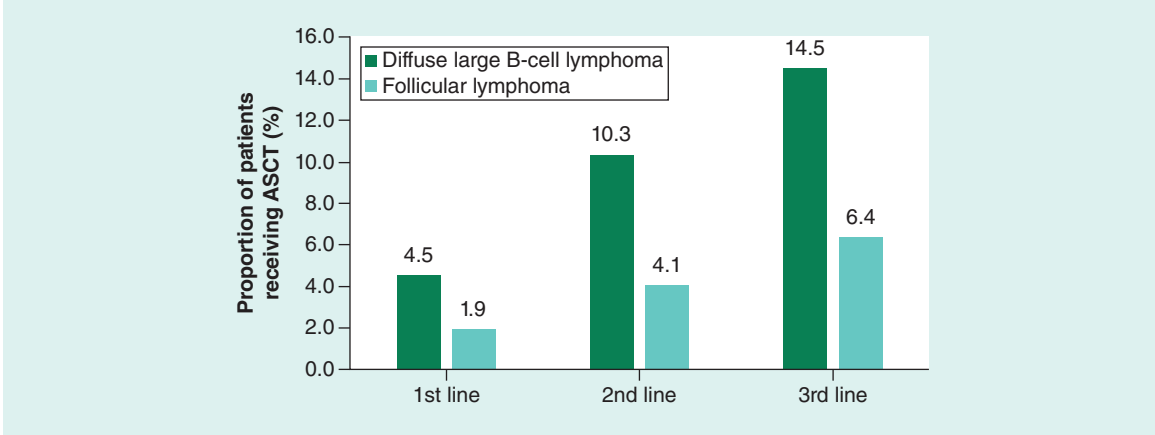


Figure 3. Autologous stem cell transplant therapy for follicular lymphoma and diffuse large B-cell lymphoma.
ASCT: Autologous stem cell transplant.

study period, the percentages of FL patients receiving at least once inpatient admission, radiation therapy, ICU or SCT were 59.4, 17.8, 22.8 and 4.9%, respectively.

Discussion

This observational study provides real-world evidence of treatment patterns, healthcare cost and healthcare resource utilization in patients with DLBCL and FL. The majority of DLBCL and FL patients were treated by rituximab or bendamustine either alone or in combination during frontline treatment, and more than a quarter of patients

Table 3. Healthcare costs during 1 year following frontline treatment in 2015 US dollars.

Categories	Diffuse large B-cell lymphoma		Follicular lymphoma	
	Mean PPPM	Standard deviation	Mean PPPM	Standard deviation
Average total costs	15,555	19,951	10,192	15,556
Drug costs	5157	6134	4462	6041
Medical costs	10,398	18,139	5731	13,626
– Inpatient	6257	15,806	2895	11,848
– Outpatient facility	1366	3721	982	2872
– Other outpatient	2298	2978	1513	2147
– Office visit	247	330	195	279
– Emergency room	230	700	145	791

PPPM: Per patient per month.

Table 4. Healthcare costs by regimen.

Healthcare cost ($)†	Diffuse large B-cell lymphoma			Follicular lymphoma		
	Regimen with rituximab	Regimen without rituximab	Adjusted p-value	Regimen with rituximab	Regimen without rituximab	Adjusted p-value
–Total costs	12,021	11,083	0.036	10,865	9365	<0.001
– Pharmacy costs	5473	2118	<0.001	6387	2406	<0.001
– Medical costs	6417	8782	<0.001	4740	7138	<0.001

received second-line therapies within 1 year from the initial date of frontline treatment. The healthcare costs and healthcare resource utilizations were considerable, especially for DLBCL patients. The medical costs were nearly twice as much as the drug costs for DLBCL patients during frontline treatment. Our findings also demonstrated that patients receiving rituximab had lower medical costs than those who did not receive rituximab for both DLBCL and FL patients, although they had relatively higher pharmacy costs.

Healthcare costs for NHL could be affected by numerous types of lymphoma, different treatment therapies, diverse side effects from various treatment, complicated prognoses and the growing emergence of new drugs. Patients with aggressive NHL tended to accrue higher costs compared with those with indolent lymphomas [2]. In our study, the healthcare costs of DLBCL patients were more than $5000 PPPM higher than FL patients during the first year of frontline treatment. Previously studies have demonstrated that rituximab has a favorable economic profile in both DLBCL and FL patients [12–14]. However, this result is not consistent with the findings from Griffiths *et al.* that reported rituximab could result in higher 4-year total costs of $23,097 in DLBCL patients, although rituximab was associated with survival benefits [15]. Our study demonstrated that DLBCL patients receiving rituximab had higher pharmacy costs ($3355 PPPM) and lower medical costs (save $2365 PPPM) than those who did not receive rituximab. Aside from costs, the use of rituximab as a maintenance therapy for DLBCL continues to be a point of controversy [16], although a recent Phase III clinical trial reported that rituximab maintenance therapy improved survival in male patients with DLBCL [17]. On the other hand, growing evidence demonstrates that rituximab maintenance therapy could significantly prolong progression-free survival for patients with FL, but without an improvement in overall survival or quality of life after first-line induction chemoimmunotherapy [18–20]. Also, NHL patients receiving myelosuppressive chemotherapy often take G-CSF agents, such as pegfilgrastim and filgrastim, in order to reduce the risk of febrile neutropenia. Our study found that 35.8% of DLBCL patients and 35.6% of FL patients received G-CSF agents during frontline treatment. Lyman *et al.* reported that the incremental cost–effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis was $2167 per febrile neutropenia episode avoided [21]. In addition, allogeneic SCTs in DLBCL and FL patients could significantly increase their economic burden [22].

It is not surprising that DLBCL patients consume more healthcare resources than FL patients because of the aggressive tendency of DLBCL. In our study, 34.5% of DLBCL patients and 22.8% of FL patients required ICU admission prior to or during chemotherapy. According to the findings reported in a recent study, hemodynamic (37.8%) or respiratory failure (24.3%) may be the primary reasons for requiring ICU treatments in DLBCL patients [23]. Our study also found that advanced DLBCL patients were more likely to receive SCT (10.3 and

14.5% in second-line and third-line treatment, respectively). This might be, at least in part, attributed to the fact that the efficacy and feasibility of SCT have recently become confirmed in DLBCL patients, even among elderly patients [24–26]. However, there is no evidence suggesting that adding SCT as part of FL initial treatment could improve overall survival [27].

As a claim-based analysis, some inherent limitations are unavoidable. First, the data may incompletely capture the conditions and outcomes documented in the medical records when filing a claim or reimbursement. Since no validated approach could be used to identify nonresponses and relapses in this database, we did not report these clinical outcomes in our paper. Second, as survival data were not available in our analysis, we did not adjust average costs when utilizing the Kaplan–Meier Sample Average estimator approach. To minimize bias associated with censored data, we only analyzed healthcare costs and healthcare resource utilization during the first year after initial diagnosis. Finally, the diagnosis was based upon ICD-9 coding system that might not correspond to histologic diagnosis. Despite its limitations, this study adds to the body of research in economic burden and treatment patterns for DLBCL and FL patients. Our findings may be useful for relevant patients, health providers, stakeholders and researchers in this field.

Conclusion

The healthcare costs and health resources utilized were considerable in non-Hodgkin's lymphoma, especially among DLBCL patients.

Summary points

- Given the rapid evolution in diagnostic subtyping as well as treatment regimens, it is important to examine economic burden, treatment patterns and outcomes among non-Hodgkin's lymphoma patients, including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).
- The majority of DLBCL and FL patients were treated with rituximab or bendamustine either alone or in combination during frontline treatment, and more than a quarter of patients received second-line therapies within 1 year from the initial date of frontline treatment.
- The total healthcare costs were US $15,555 and $10,192 per patient per month within 1 year following their initial diagnosis for DLBCL and FL, respectively. The medical costs were almost twice as much as the drug costs for DLBCL patients during frontline treatment.
- DLBCL patients occupied more health resources than FL patients. During the first year following initial diagnosis, inpatient admissions per patient per month were 0.21 for DLBCL and 0.10 for FL.

Financial & competing interests disclosure

CV Asche and J Ren are consultants for Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, MA, USA. A Galaznik and Y Shou are employed by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The roles of authors include study design (A Galaznik, CV Asche, J Ren, Y Shou), statistical analysis (CV Asche and J Ren), results interpretation (A Galaznik and Y Shou) and manuscript draft and revision (all authors). This study was sponsored by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Cancer Statistics Center, Americal Cancer Society. 2017 estimates. (2017). https://cancerstatisticscenter.cancer.org/#/
2. Kutikova L, Bowman L, Chang S, Long SR, Arning M, Crown WH. Medical costs associated with non-Hodgkin's lymphoma in the United States during the first two years of treatment. *Leuk. Lymphoma* 47(8), 1535–1544 (2006).

- **This retrospective study demonstrated that the treatment of non-Hodgkin's lymphoma was associated with substantial healthcare costs in the USA.**

3. Foster T, Miller JD, Boye ME, Russell MW. Economic burden of follicular non-Hodgkin's lymphoma. *Pharmacoeconomics* 27(8), 657–679 (2009).
4. American Cancer Society. Types of non-Hodgkin lymphoma. (2017) www.cancer.org/cancer/non-hodgkin-lymphoma/about/types-of-non-hodgkin-lymphoma.html
5. Coiffier B, Lepage E, Briere J *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N. Engl. J. Med.* 346(4), 235–242 (2002).
6. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. *Hematol. Am. Soc. Hematol. Educ. Program* 2011, 498–505 (2011).
7. Amin AD, Peters TL, Li L *et al.* Diffuse large B-cell lymphoma: can genomics improve treatment options for a curable cancer? *Cold Spring Harb. Mol. Case Stud.* 3(3), a001719 (2017).
8. Rohatiner AZ, Lister TA. The clinical course of follicular lymphoma. *Best Pract. Res. Clin. Hematol.* 18(1), 1–10 (2005).
9. Italiano A, Thyss A. Follicular lymphoma: a therapeutic update. *Bull. Cancer* 92(10), E57–E64 (2005).
10. Conconi A, Lobetti-Bodoni C, Montoto S *et al.* Life expectancy of young adults with follicular lymphoma. *Ann. Oncol.* 26(11), 2317–2322 (2015).
11. Provencio Pulla M, Alfaro Lizaso J, De La Cruz Merino L *et al.* SEOM clinical guidelines for the treatment of follicular non-Hodgkin's lymphoma. *Clin. Transl. Oncol.* 17(12), 1014–1019 (2015).
12. Johnston KM, Bolbocean C, Connors J, Peacock S. Cost–effectiveness of rituximab in follicular lymphoma. *Expert Rev. Pharmacoecon. Outcomes Res.* 12(5), 569–577 (2012).
13. Chen Q, Ayer T, Nastoupil LJ, Rose AC, Flowers CR. Comparing the cost–effectiveness of rituximab maintenance and radioimmunotherapy consolidation versus observation following first-line therapy in patients with follicular lymphoma. *Value Health* 18(2), 189–197 (2015).
14. Khor S, Beca J, Krahn M *et al.* Real world costs and cost–effectiveness of rituximab for diffuse large B-cell lymphoma patients: a population-based analysis. *BMC Cancer* 14, 586 (2014).

•• **This population-based study showed that the addition of rituximab to standard CHOP chemotherapy was associated with improvement in survival but at a higher cost.**

15. Griffiths RI, Gleeson ML, Mikhael J, Dreyling MH, Danese MD. Comparative effectiveness and cost of adding rituximab to first-line chemotherapy for elderly patients diagnosed with diffuse large B-cell lymphoma. *Cancer* 118(24), 6079–6088 (2012).
16. Zhou X, Ma T, Zhang Y, Zhou N, Li J. Rituximab maintenance therapy for patients with diffuse large B-cell lymphoma: a meta-analysis. *PLoS ONE* 12(3), e0174648 (2017).

- **This meta-analysis concluded that both survival benefits and adverse events should be taken into consideration when using rituximab maintenance therapy for patients with diffuse large B-cell lymphoma.**

17. Witzens-Harig M, Benner A, McClanahan F *et al.* Rituximab maintenance improves survival in male patients with diffuse large B-cell lymphoma. Results of the HD2002 prospective multicenter randomized Phase III trial. *Brit. J. Hematol.* 171(5), 710–719 (2015).
18. Duhrsen U, Broszeit-Luft S, Dieing A *et al.* Rituximab maintenance therapy of follicular lymphoma in clinical practice. *Cancer Med.* DOI:10.1002/cam4.1549 (2018) (Epub ahead of print).
19. Hilal T, Leis JF, Reeder CB. Rituximab maintenance therapy after first-line induction chemoimmunotherapy for follicular lymphoma. *JAMA Oncol.* 4(6), 859–860 (2018).

•• **Suggests that rituximab maintenance therapy prolongs progression-free survival without an improvement in overall survival or quality of life after first-line induction chemoimmunotherapy.**

20. Schneider T, Rosta A, Losonczy H *et al.* Efficacy and tolerability of a 2-year rituximab maintenance therapy in patients with advanced follicular lymphoma after induction of response with rituximab-containing first line-Regimens (HUSOM Study). *Pathol. Oncol. Res.* 24(2), 199–205 (2018).
21. Lyman G, Lalla A, Barron R, Dubois RW. Cost–effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis in patients with non-Hodgkin's lymphoma receiving CHOP-21 in United States. *Curr. Med. Res. Opin.* 25(2), 401–411 (2009).
22. Maziarz RT, Hao Y, Guerin A *et al.* Economic burden following allogeneic hematopoietic stem cell transplant in patients with diffuse large B-cell lymphoma. *Leuk. Lymphoma* DOI:10.1080/10428194.2017.1375100 1–10 (2017) (Epub ahead of print).
23. Wohlfarth P, Carlstrom A, Staudinger T *et al.* Incidence of intensive care unit admission, outcome and post intensive care survival in patients with diffuse large B-cell lymphoma. *Leuk. Lymphoma* 57(8), 1831–1838 (2016).
24. Lee MY, Kim HS, Lee JY *et al.* Efficacy and feasibility of autologous stem cell transplantation in patients with diffuse large B-cell lymphoma with secondary central nervous system involvement. *Int. J. Hematol.* 102(6), 678–688 (2015).

- **Shows that autologous stem cell transplantation had survival benefits in patients with diffuse large B-cell lymphoma with secondary central nervous system involvement.**

25. Robinson SP, Boumendil A, Finel H *et al.* Autologous stem cell transplantation for relapsed/refractory diffuse large B-cell lymphoma: efficacy in the rituximab era and comparison to first allogeneic transplants. A report from the EBMT Lymphoma Working Party. *Bone Marrow Transplant.* 51(3), 365–371 (2016).

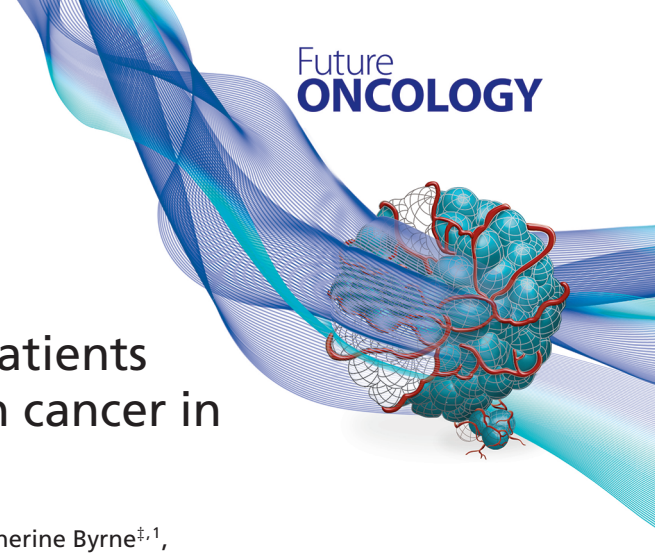
26. Hermet E, Cabrespine A, Guieze R *et al.* Autologous hematopoietic stem cell transplantation in elderly patients (>/ = 70 years) with non-Hodgkin's lymphoma: a French Society of Bone Marrow Transplantation and Cellular Therapy Retrospective Study. *J. Geriatr. Oncol.* 6(5), 346–352 (2015).

27. Al Khabori M, De Almeida JR, Guyatt GH, Kuruvilla J, Crump M. Autologous stem cell transplantation in follicular lymphoma: a systematic review and meta-analysis. *J. Natl Cancer Inst.* 104(1), 18–28 (2012).

•• **This meta-analysis suggests that high-dose therapy and autologous stem cell transplantation treatment as part of follicular lymphoma does not improve overall survival.**

Research Article

For reprint orders, please contact: reprints@futuremedicine.com



Real-world treatment patterns in patients with advanced (stage III–IV) ovarian cancer in the USA and Europe

Jennifer P Hall*[,1], Jane Chang[2], Rebecca Moon[1], Olivia Higson[1], Katherine Byrne[‡,1], Jim P Doherty[‡,2] & Joseph C Cappelleri[2]

[1]Adelphi Real World, Bollington, SK10 5JB, UK

[2]Pfizer Inc, NY 10017, USA

*Author for correspondence: Tel.: +44 (0)1625 577 289; Jennifer.hall@adelphigroup.com

‡Affiliations at the time of research and manuscript development.

Aim: To analyze real-world data relating to treatment decision-making in stage III–IV ovarian cancer (OC). **Materials & methods:** Real world data were collected from a survey of physicians and their patients (n = 2413) across Europe and the USA in 2017–2018. **Results:** 49% had stage IVb disease. 39, 54 and 7% of patients received first-line (1L), second-line, or 7% third-line or later treatment. In the 1L (ongoing or completed), 93% received platinum-containing regimens, 26% bevacizumab-containing regimens and 1% a PARP inhibitor-containing regimen. In 1L maintenance treatment, 81% received bevacizumab, 17% platinum-containing treatments and 6% a PARP inhibitor. **Conclusion:** The most common 1L treatment for advanced ovarian cancer was platinum-containing chemotherapy. Of those receiving 1L maintenance therapy, 70–99% (across countries) received targeted therapy.

First draft submitted: 4 February 2020; Accepted for publication: 17 March 2020; Published online: 24 April 2020

Keywords: advanced ovarian cancer • maintenance • real-world evidence • survey • treatment

Ovarian cancer (OC) is the fifth most common cancer among women, with the majority of cases being classified as epithelial carcinoma [1]. It is estimated that OC accounted for approximately 295,000 newly diagnosed cases of cancer and approximately 185,000 deaths worldwide in 2018 [2]. Although OC incidence exhibits wide geographical variation, the highest age-adjusted incidence rates are observed in economically developed parts of the world. In North America and central and eastern Europe, incidence rates generally exceed eight per 100,000 [3]. In 2017, the number of newly diagnosed cases in the USA was estimated to be >22,000 and the number of deaths was expected to exceed 14,000 [4]. In Europe in 2012, an estimated 66,000 new cases of OC were diagnosed, resulting in approximately 42,000 deaths [5].

Most patients with OC present with advanced disease at diagnosis, and the current standard of care is surgical cytoreduction followed by platinum-containing chemotherapy (carboplatin and paclitaxel) in the first-line (1L) setting [1,6]. Maintenance therapy is prescribed in order to prolong responses to 1L treatment [7]. A number of targeted treatments have been approved for the treatment of OC, including bevacizumab (approved in Europe in 2011 and the USA in 2014) [8] and the PARP inhibitors olaparib (approved in Europe and the USA in 2014) [9,10], rucaparib (approved in the USA in 2016 and Europe in 2018) [11,12] and niraparib (approved in Europe and the USA in 2017) [13,14]. Despite approximately 80% response rates to primary therapy, over half of patients relapse within 2 years and eventually develop platinum-resistant disease, while others progress during 1L treatment and develop refractory disease [6].

There is an increasing recognition of the role of real-world evidence in informing decisions related to drug development, approval, reimbursement and prescribing [15]. However, real-world data on the treatment patterns in patients with OC are limited. For this study, advanced OC was defined as histologically confirmed epithelial ovarian, fallopian tube or peritoneal cancer, including malignant Mullerian tumors with a high-grade serous component in stages II to IV. The objective of this study was to analyze real-world treatment data for patients with advanced

OC receiving drug treatment for OC, with an emphasis on the 1L and 1L maintenance therapy settings, across Europe (France, Germany, Italy, Spain and the UK) and the USA to provide information relevant to treatment decision-making.

Materials & methods

Adelphi Real World Disease Specific Programmes (DSPs) are large, multinational surveys conducted in clinical practice that describe current disease management, disease burden impact and associated treatment effects (clinical and physician perceived). The DSP is a point-in-time survey of physicians and their patients presenting in a real-world clinical setting. A complete description of the DSP methodology has been previously published [16].

Data were collected in France, Germany, Italy, Spain, the UK and the USA between December 2017 and March 2018. Physicians were instructed to complete an attitudinal survey, a survey exploring their workload and a patient record form (PRF) for the next eight consecutive patients eligible for inclusion who visited the physician for routine care. The physician-reported PRF contains detailed questions on patient demographics, clinical characteristics and OC treatment history.

Patients for whom a PRF was completed were invited to fill out a patient self-complete (PSC) form, which contained questions regarding their perspective of the disease and their care, in addition to a number of patient-reported outcome measures.

Participating physicians

Physicians were eligible to participate in the DSP if they were either a medical oncologist or gynecologist and were personally responsible for treatment decisions for and management of patients with OC. Physicians had to be seeing a minimum of ten patients with stage II to IV OC per month and have been in practice between 5 and 35 years to qualify.

Patients

Patients were eligible for inclusion in this analysis if they were aged ≥18 years, had a physician-confirmed diagnosis of OC (defined as histologically confirmed epithelial ovarian, fallopian tube or peritoneal cancer, including malignant Mullerian tumors with a high-grade serous component), were receiving active drug treatment for OC at the time of data collection (patients who were under observational management alone were excluded), and had stage III to IV disease at the time of data collection (82 patients [3%] were stage II when recruited into the DSP but were omitted from the analysis). Patients were ineligible if they were enrolled in a clinical trial at the point of consultation.

Physicians enrolled the next eight consulting patients who met the inclusion criteria. These were divided into three patients receiving 1L drug treatment (consolidation or maintenance) at the time of data collection, one patient receiving second-line (2L) or later drug treatment at the time of data collection who had received bevacizumab as 1L maintenance and four patients receiving 2L or later drug treatment at the time of data collection who had received a platinum-containing regimen in the 1L (this may include patients on a PARP inhibitor).

Data collection

Physicians provided informed consent via a checkbox as part of the research screener. Patients also provided informed consent via a checkbox for use of their anonymized and aggregated data for research and publication in scientific journals. Data were collected in such a way that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt. Ethics approval from the Western Institutional Review Board was also obtained for this research [17]. Data collection was undertaken in line with European Pharmaceutical Market Research Association [18] guidelines. The DSP was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act of 1996 [19] and Health Information Technology for Economic and Clinical Health Act legislation [20].

Analysis

Analyses were descriptive, with continuous variables expressed as means, standard deviations and ranges and all categorical variables as counts and percentages [21].

Agreement between physicians and patients in the reporting of symptoms was investigated via kappa analysis [22], with kappa values indicating the level of agreement as <0 = poor; 0–0.20 = slight; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; and 0.81–1.00 = almost perfect [20]. A simple kappa analysis was

performed to assess inter-rater agreement (i.e., physician vs patient), with no weighting involved [23]. The kappa statistic and 95% CIs are reported, where a crossover between the confidence interval and 0 may indicate no agreement between the patient and the physician.

Results

Participating physicians

A total of 340 physicians participated in the DSP (France, 50; Germany, 50; Italy, 46; Spain, 46; UK, 36; USA, 112). Approximately a third of physicians were participating in a clinical trial of OC treatment at the time of data collection, and 42% had previous clinical trial experience, including trials of PARP inhibitors and immuno-oncology treatments.

Patient demographics & clinical characteristics

Details of patient demographics and clinical characteristics are presented in Table 1. Data were collected for a total of 2413 patients, with PSC forms completed by 996 (41%) overall. The majority of patients were white/Caucasian. Most patients were initially diagnosed with advanced OC; at the time of data collection, 49% were stage IVb and 73% had an Eastern Cooperative Oncology Group performance status of 0 or 1. Some differences were observed between patients who completed a PSC form and those who did not. Patients who did not complete a PSC form were more likely to be employed, have been diagnosed at a more advanced stage, be at a more advanced stage at the time of data collection, and have been diagnosed with advanced OC for a shorter time than patients who completed a PSC form. Overall, 60% of patients were initially diagnosed with OC by a gynecologist and 24% by a medical oncologist. Medical oncologists made 56% of advanced OC diagnoses and initiated 89% of 1L drug treatments.

Comorbidities reported in >10% of all patients included hypertension (25%), diabetes (15%), depression (13%), anxiety (12%) and hyperlipidemia (12%); 44% of patients reported having none of the comorbidities provided to their physicians in a comprehensive list.

Physicians reported that 26% of patients were experiencing no impact on activities of daily living, with 52% experiencing a mild decrease in such activities. Physicians reported that for 14% of patients, a caregiver was responsible for the patient's daily needs. Of 1562 patients with data available, 33% had been hospitalized at least once in the previous 12 months due to OC.

Biomarker testing

In the total analysis population, just over half of patients (53%) had undergone some form of biomarker testing for advanced OC outside a clinical trial setting. Testing for *BRCA1* and *BRCA2* was very common: >90% of patients who had a biomarker test had been tested for mutations in each of these genes (Table 2). Approximately a quarter of patients (23%) tested for *BRCA1* had a positive result, and a slightly lower proportion (14%) of those tested for *BRCA2* tested positive (Table 2). Testing for *BRCA1* and *BRCA2* was performed at the point of advanced diagnosis in 80 and 78% of patients, respectively.

History of surgery & radiotherapy

Overall, 58% of patients had undergone surgery, with 44% of these patients having a hysterectomy, 43% cytoreductive surgery and 23% undergoing debulking surgery (Table 3). Of those who underwent debulking surgery, 24% had an R0 resection, 46% were optimally debulked and 29% were sub-optimally debulked. Geographical differences were seen in surgical history. In total, 11% of patients had received radiotherapy (Table 3).

Drug treatment

Details of line of treatment at the time of data collection and drug treatment history are shown in Table 4. At the time of data collection, 39% of patients were receiving 1L treatment for OC.

Of patients receiving 1L treatment or who had completed 1L treatment at the time of data collection, 93% received a platinum-containing regimen, 26% received a bevacizumab-containing regimen, and 1% received a PARP inhibitor-containing regimen. In the 1L, the most common regimen was paclitaxel plus carboplatin/cisplatin, which 58% of patients received. Of 2413 patients included in our analysis, 917 (38%) received 1L maintenance treatment; 81% of these received a bevacizumab-containing regimen, 17% a platinum-containing regimen and 6% a PARP inhibitor-containing regimen. Bevacizumab monotherapy was the most commonly prescribed regimen for 1L maintenance.

Table 1. Patient demographics and clinical characteristics.

Demographic	Total (n = 2413)	France (n = 396)	Germany (n = 393)	Italy (n = 347)	Spain (n = 353)	UK (n = 332)	USA (n = 592)
Age (years)[†]							
n	2401	393	392	347	353	332	584
Mean (SD)	63.0 (9.75)	64.8 (10.04)	62.0 (8.98)	61.8 (10.19)	62.2 (9.72)	64.2 (8.97)	63.0 (10.01)
Median	64.0	66.0	62.0	62.0	63.0	65.0	63.0
Range	27–89	27–88	36–86	37–85	30–85	28–84	31–89
Ethnic origin							
White/Caucasian	2086 (86%)	348 (88%)	371 (94%)	341 (98%)	339 (96%)	287 (86%)	400 (68%)
African American/Afro-Caribbean	135 (6%)	19 (5%)	2 (1%)	0	0	13 (4%)	101 (17%)
Other[‡]	192 (8%)	29 (7%)	20 (5%)	6 (2%)	14 (4%)	32 (10%)	91 (15%)
Smoking status							
Current smoker	186 (8%)	35 (9%)	31 (8%)	64 (18%)	6 (2%)	12 (4%)	38 (6%)
Ex-smoker	454 (19%)	64 (16%)	59 (15%)	55 (16%)	81 (23%)	73 (22%)	122 (21%)
Never smoked	1503 (62%)	268 (68%)	236 (60%)	182 (52%)	241 (68%)	209 (63%)	367 (62%)
Unknown	270 (11%)	29 (7%)	67 (17%)	46 (13%)	25 (7%)	38 (11%)	65 (11%)
Employment status							
Working full time	344 (14%)	36 (9%)	54 (14%)	77 (22%)	33 (9%)	24 (7%)	120 (20%)
Working part time	244 (10%)	14 (4%)	67 (17%)	40 (12%)	17 (5%)	29 (9%)	77 (13%)
Long-term sick leave	196 (8%)	46 (12%)	24 (6%)	11 (3%)	48 (14%)	31 (9%)	36 (6%)
Homemaker	527 (22%)	66 (17%)	69 (18%)	93 (27%)	139 (39%)	45 (14%)	115 (19%)
Retired	927 (38%)	201 (51%)	174 (44%)	103 (30%)	99 (28%)	168 (51%)	182 (31%)
Other[§]	175 (7%)	33 (8%)	5 (1%)	23 (7%)	17 (5%)	35 (11%)	62 (10%)
Health insurance							
Public	1767 (73%)	161 (41%)	338 (86%)	321 (93%)	340 (96%)	314 (95%)	293 (49%)
Private	170 (7%)	0	55 (14%)	0	8 (2%)	14 (4%)	93 (16%)
Both public and private	180 (7%)	175 (44%)	0	0	5 (1%)	0	0
Employer provided	182 (8%)	0	0	0	0	0	182 (31%)
None	12 (<1%)	0	0	7 (2%)	0	0	5 (1%)
Other	3 (<1%)	0	0	1 (<1%)	0	0	2 (<1%)
Unknown	99 (4%)	60 (15%)	0	18 (5%)	0	4 (1%)	17 (3%)
Cancer history							
n	2287	384	358	332	347	322	544
Previous non-OC[¶]	95 (4%)	9 (2%)	17 (5%)	13 (4%)	11 (3%)	12 (4%)	33 (6%)
Breast cancer history							
n	94	9	16	13	11	12	33
Previously diagnosed with breast cancer[#]	47 (50%)	5 (56%)	11 (69%)	7 (54%)	9 (82%)	4 (33%)	11 (33%)
Family OC history							
n	2187	372	331	308	343	310	525
Confirmed family history of OC[††]	229 (10%)	44 (12%)	33 (10%)	25 (8%)	34 (10%)	27 (9%)	66 (13%)
Family *BRCA* history							
n	184	36	24	16	29	23	56
BRCA-positive family members[‡‡]	77 (42%)	22 (61%)	9 (38%)	4 (25%)	13 (45%)	6 (26%)	23 (41%)
Stage at initial diagnosis of OC							
I	29 (1%)	1 (<1%)	7 (2%)	5 (1%)	1 (<1%)	6 (2%)	9 (2%)
II	124 (5%)	10 (3%)	17 (4%)	15 (4%)	16 (5%)	13 (4%)	53 (9%)
III	1030 (43%)	187 (47%)	157 (40%)	148 (43%)	200 (57%)	149 (45%)	189 (32%)
IV	1213 (50%)	196 (49%)	211 (54%)	174 (50%)	135 (38%)	161 (48%)	336 (57%)
Unknown/not assessed	17 (1%)	2 (1%)	1 (<1%)	5 (1%)	1 (<1%)	3 (1%)	5 (1%)
Current OC stage[§§]							
III	789 (33%)	132 (33%)	109 (28%)	104 (30%)	152 (43%)	107 (32%)	185 (31%)
IVa	436 (18%)	72 (18%)	92 (23%)	22 (6%)	70 (20%)	52 (16%)	128 (22%)
IVb	1188 (49%)	192 (48%)	192 (49%)	221 (64%)	131 (37%)	173 (52%)	279 (47%)
Time since diagnosis of advanced OC (months)							
Mean (SD)	14.8 (17.81)	16.5 (17.92)	14.8 (18.25)	19.1 (25.30)	14.7 (12.95)	15.2 (18.43)	11.1 (12.96)
Median	11.0	11.0	11.0	11.0	12.0	9.5	8.0
Range	0–208	0–113	0–208	0–178	0–111	0–189	0–186

Data reprensented as n (%) unless otherwise stated.
[†] Excludes a total of 12 patients aged >90 years.
[‡]Includes Native American, Asian (Indian subcontinent and other), Chinese, Hispanic/Latino, Middle Eastern and mixed race.
[§]Includes student, unemployed and unknown.
[¶]Percentage based on patients for whom data were available.
[#]Percentages based on patients with previous non-OC and data available.
[††]Percentages based on patients for whom data were available.
[‡‡]Percentage based on patients with family history of OC and data available.
[§§]At the time of data collection.
[¶¶]Percentages based on patients at stage IVb at the time of data collection.
ECOG: Eastern Cooperative Oncology Group; OC: Ovarian cancer; PS: Performance status; SD: Standard deviation.

Table 1. Patient demographics and clinical characteristics (cont.).

Demographic	Total (n = 2413)	France (n = 396)	Germany (n = 393)	Italy (n = 347)	Spain (n = 353)	UK (n = 332)	USA (n = 592)
Current ECOG PS§§							
0	510 (21%)	56 (14%)	142 (36%)	110 (32%)	62 (18%)	48 (14%)	92 (16%)
1	1258 (52%)	218 (55%)	165 (42%)	149 (43%)	154 (44%)	257 (77%)	315 (53%)
2	462 (19%)	110 (28%)	50 (13%)	47 (14%)	111 (31%)	27 (8%)	117 (20%)
3/4	147 (6%)	12 (3%)	11 (3%)	34 (10%)	26 (7%)	0	64 (11%)
Unknown/not assessed	36 (1%)	0	25 (6%)	7 (2%)	0	0	4 (1%)
Sites of current metastases§§,¶¶							
Abdomen/peritoneum	749 (63%)	136 (71%)	80 (42%)	165 (75%)	97 (74%)	101 (58%)	170 (61%)
Colon	80 (7%)	17 (9%)	20 (10%)	20 (9%)	3 (2%)	7 (4%)	13 (5%)
Lungs	391 (33%)	48 (25%)	69 (36%)	67 (30%)	44 (34%)	78 (45%)	85 (30%)
Liver	472 (40%)	69 (36%)	96 (50%)	73 (33%)	58 (44%)	75 (43%)	101 (36%)
Lymph nodes	471 (40%)	79 (41%)	50 (26%)	94 (43%)	47 (36%)	75 (43%)	126 (45%)
Brain	14 (1%)	3 (2%)	5 (3%)	1 (<1%)	0	0	5 (2%)
Skin	21 (2%)	1 (1%)	16 (8%)	1 (<1%)	1 (1%)	1 (1%)	1 (<1%)
Spleen	28 (2%)	3 (2%)	4 (2%)	1 (<1%)	0	14 (8%)	6 (2%)
Bone	74 (6%)	11 (6%)	29 (15%)	10 (5%)	3 (2%)	4 (2%)	17 (6%)
Other	16 (1%)	2 (1%)	2 (1%)	7 (3%)	3 (2%)	1 (1%)	1 (<1%)
Unknown	16 (1%)	3 (2%)	0	5 (2%)	0	0	8 (3%)

Data represented as n (%) unless otherwise stated.
† Excludes a total of 12 patients aged >90 years.
‡ Includes Native American, Asian (Indian subcontinent and other), Chinese, Hispanic/Latino, Middle Eastern and mixed race.
§ Includes student, unemployed and unknown.
¶ Percentage based on patients for whom data were available.
# Percentages based on patients with previous non-OC and data available.
†† Percentages based on patients for whom data were available.
‡‡ Percentage based on patients with family history of OC and data available.
§§ At the time of data collection.
¶¶ Percentages based on patients at stage IVb at the time of data collection.
ECOG: Eastern Cooperative Oncology Group; OC: Ovarian cancer; PS: Performance status; SD: Standard deviation.

Table 2. Biomarker testing.

Biomarker testing	Total (n = 2413)	France (n = 396)	Germany (n = 393)	Italy (n = 347)	Spain (n = 353)	UK (n = 332)	USA (n = 592)
Have ever undergone biomarker testing							
Yes	1267 (53%)	236 (60%)	244 (62%)	146 (42%)	226 (64%)	127 (38%)	288 (49%)
No	991 (41%)	139 (35%)	115 (29%)	180 (52%)	118 (33%)	185 (56%)	254 (43%)
Unknown	155 (6%)	21 (5%)	34 (9%)	21 (6%)	9 (3%)	20 (6%)	50 (8%)
Biomarker test†	1267	236	244	146	226	127	288
*BRCA*1	1238 (98%)	232 (98%)	240 (98%)	146 (100%)	226 (100%)	120 (94%)	274 (95%)
*BRCA*2	1181 (93%)	227 (96%)	233 (95%)	142 (97%)	215 (95%)	119 (94%)	245 (85%)
PD-1/PD-L1	183 (14%)	231 (9%)	37 (15%)	0	18 (8%)	6 (5%)	101 (35%)
HER2	143 (11%)	17 (7%)	46 (19%)	1 (1%)	4 (2%)	4 (3%)	71 (25%)
EGFR	152 (12%)	25 (11%)	54 (22%)	0	18 (8%)	3 (2%)	52 (18%)
MSI	128 (10%)	22 (9%)	18 (7%)	1 (1%)	7 (3%)	4 (3%)	76 (26%)
Other	469 (37%)	72 (31%)	100 (41%)	20 (14%)	23 (10%)	16 (13%)	238 (83%)
***BRCA*1 result**§	1238	232	240	146	226	120	274
Positive	289 (23%)	43 (19%)	66 (28%)	32 (22%)	65 (29%)	16 (13%)	67 (24%)
Negative	841 (68%)	149 (64%)	167 (70%)	90 (62%)	145 (64%)	89 (74%)	201 (73%)
Inconclusive	4 (<1%)	1 (<1%)	1 (<1%)	0	0	0	2 (1%)
Unknown/awaiting result	104 (8%)	39 (17%)	6 (3%)	24 (16%)	16 (7%)	15 (13%)	4 (1%)
***BRCA*2 result**¶	1181	227	233	142	215	119	245
Positive	161 (14%)	29 (13%)	27 (12%)	17 (12%)	31 (14%)	10 (8%)	47 (19%)
Negative	908 (77%)	159 (70%)	196 (84%)	102 (72%)	167 (78%)	94 (79%)	190 (78%)
Inconclusive	9 (1%)	1 (<1%)	4 (2%)	0	1 (<1%)	0	3 (1%)
Unknown/awaiting result	103 (9%)	38 (17%)	6 (3%)	23 (16%)	16 (7%)	15 (13%)	5 (2%)

Data represented as n (%) unless otherwise stated..
† Percentages based on a total of 1267 patients who underwent biomarker testing.
‡ Includes *PTEN, TF53, MYC, KRAS, PIK3CA, ARID1A, HRD, ATM, TMB*, other.
§ Percentages based on a total of 1238 patients who underwent *BRCA*1 testing.
¶ Percentages based on a total of 1181 patients who underwent *BRCA*2 testing.
MSI: Microsatellite instability.

Table 3. History of surgery and radiotherapy.

Patient history	Total (n = 2413)	France (n = 396)	Germany (n = 393)	Italy (n = 347)	Spain (n = 353)	UK (n = 332)	USA (n = 592)
Have ever received							
Surgery	1395 (58%)	187 (47%)	322 (82%)	170 (49%)	239 (68%)	189 (57%)	288 (49%)
Radiotherapy	256 (11%)	25 (6%)	52 (13%)	8 (2%)	104 (29%)	3 (1%)	64 (11%)
Neither	924 (38%)	199 (50%)	47 (12%)	173 (50%)	95 (27%)	142 (43%)	268 (45%)
Type of surgery[†]	1395	187	322	170	239	189	288
Hysterectomy[‡]	620 (44%)	104 (56%)	200 (62%)	87 (51%)	74 (31%)	57 (30%)	98 (34%)
Cytoreduction	593 (43%)	61 (33%)	107 (33%)	63 (37%)	176 (74%)	87 (46%)	99 (34%)
Debulking	326 (23%)	35 (19%)	40 (12%)	33 (19%)	14 (6%)	67 (35%)	137 (48%)
Other/unknown	41 (3%)	10 (5%)	12 (4%)	8 (5%)	3 (1%)	3 (2%)	5 (2%)
Resection status after debulking surgery[§]	326	35	40	33	14	67	137
R0 resection (0 cm)	77 (24%)	22 (63%)	10 (25%)	6 (18%)	1 (7%)	17 (25%)	21 (15%)
Optimally debulked (>1 mm–1 cm)	150 (46%)	7 (20%)	20 (50%)	11 (33%)	10 (71%)	25 (37%)	77 (56%)
Sub-optimally debulked (>1 cm)	95 (29%)	6 (17%)	10 (25%)	14 (42%)	3 (21%)	23 (34%)	39 (28%)
Unknown	4 (1%)	0	0	2 (6%)	0	2 (3%)	0
Time from surgery to start of 1L drug treatment (days)							
Hysterectomy[‡]	316	56	64	63	47	31	55
Mean (SD)	84.5 (322.2)	50.8 (88.0)	41.5 (90.3)	170.5 (650.3)	26.9 (14.3)	168.6 (316.0)	72.3 (167.3)
Cytoreduction	264	21	67	37	80	27	32
Mean (SD)	68.5 (177.7)	115.3 (211.2)	49.0 (93.5)	69.9 (194.6)	64.4 (195.6)	37.6 (18.2)	113.3 (271.2)
Debulking	155	15	24	22	5	29	60
Mean (SD)	54.5 (124.9)	90.4 (248.6)	36.7 (38.8)	40.9 (26.1)	23.0 (14.8)	53.9 (78.4)	60.6 (147.1)

Data represented as n (%) unless otherwise stated.
[†]Percentages based on all patients who underwent surgery (patients could undergo more than one type of surgery).
[‡]Includes any form of hysterectomy.
[§]Percentages based on patients who underwent debulking.
1L: First-line; SD: Standard deviation.

In the 2L, 61% of patients received a platinum-containing regimen, 16% a bevacizumab-containing regimen, 4% a PARP inhibitor-containing regimen and 34% a liposomal doxorubicin-containing regimen. The most common 2L regimen was liposomal doxorubicin in combination with carboplatin/cisplatin, received by 15% of patients. The most common third-line treatment type was a platinum-containing regimen, received by 34% of patients, with 3, 5 and 23% of patients receiving a bevacizumab-containing regimen, a PARP inhibitor-containing regimen and a liposomal doxorubicin-containing regimen, respectively. The most common treatment, received by 16% of patients, was liposomal doxorubicin monotherapy in the third line.

Rationale for treatment decisions

Overall, the most commonly stated reason for choosing 1L drug treatment was expected progression-free survival benefit (56%; Figure 1A).

For 1728 patients who had completed 1L drug treatment (monotherapy or combination) at the time of data collection, the most common reason for stopping 1L treatment was completion of the treatment regimen; almost half of patients achieved a complete response. Disease progression was the reason for stopping 1L treatment in 5–19% of patients across countries (Figure 1B).

The most common reason overall for the choice of 1L maintenance treatment in 279 patients receiving 1L maintenance treatment at the time of data collection was progression-free survival benefit (63%), followed by maintenance of/improvement in health-related quality of life (HRQoL; 42%), and overall survival benefit (39%; Figure 1C). For 624 patients receiving 2L treatment at the time of data collection who did not receive 1L drug-based maintenance treatment, the predominant reason for not prescribing it was because the tumor had already progressed, although this varied notably by country (Figure 1D). Overall, 60% of patients stopped their 1L maintenance regimen because they had completed the treatment course and 35% stopped due to disease progression (Figure 1E).

Treatment adverse effects, symptoms & unmet need with 1L treatment & 1L maintenance treatment

Physicians reported that patients who experienced adverse effects with the 1L regimen they were receiving at the time of data collection ranged from 9% in Italy to 42% in Spain, although it should be noted that differences in adverse effects between countries is likely due to differences in treatment patterns between these countries. Nine

Table 4. Drug treatment.

Treatment	Total (n = 2413)	France (n = 396)	Germany (n = 393)	Italy (n = 347)	Spain (n = 353)	UK (n = 332)	USA (n = 592)
Current line of therapy							
1L	941 (39%)	149 (38%)	145 (37%)	119 (34%)	130 (37%)	140 (42%)	258 (44%)
2L	1295 (54%)	210 (53%)	220 (56%)	193 (56%)	207 (59%)	162 (49%)	303 (51%)
3L+	177 (7%)	37 (9%)	28 (7%)	35 (10%)	16 (5%)	30 (9%)	31 (5%)
1L drug treatment (ever received)[†]	2413	396	393	347	353	332	592
Platinum-containing regimen	2252 (93%)	380 (96%)	388 (99%)	313 (90%)	340 (96%)	325 (98%)	506 (85%)
Bevacizumab-containing regimen	621 (26%)	148 (37%)	103 (26%)	139 (40%)	58 (16%)	76 (23%)	97 (16%)
PARP inhibitor-containing regimen[‡]	28 (1%)	0	0	1 (<1%)	3 (1%)	0	24 (4%)
Paclitaxel + carboplatin/cisplatin	1402 (58%)	215 (54%)	259 (66%)	145 (42%)	240 (68%)	221 (67%)	322 (54%)
Paclitaxel + carboplatin/cisplatin + bevacizumab	537 (22%)	126 (32%)	95 (24%)	125 (36%)	51 (14%)	75 (23%)	65 (11%)
Docetaxel + carboplatin/cisplatin	115 (5%)	17 (4%)	22 (6%)	5 (1%)	23 (7%)	2 (1%)	46 (8%)
Carboplatin/cisplatin	65 (3%)	2 (1%)	5 (1%)	18 (5%)	6 (2%)	20 (6%)	14 (2%)
Bevacizumab monotherapy	50 (2%)	11 (3%)	3 (1%)	11 (3%)	6 (2%)	1 (<1%)	18 (3%)
Carboplatin/cisplatin + liposomal doxorubicin	43 (2%)	3 (1%)	1 (<1%)	7 (2%)	9 (3%)	5 (2%)	18 (3%)
Gemcitabine + carboplatin/cisplatin	39 (2%)	4 (1%)	1 (<1%)	10 (3%)	7 (2%)	1 (<1%)	16 (3%)
Received 1L maintenance treatment	2413	396	393	347	353	332	592
Yes	917 (38%)	156 (39%)	165 (42%)	143 (41%)	138 (39%)	102 (31%)	213 (36%)
No, did not receive	834 (35%)	134 (34%)	122 (31%)	129 (37%)	133 (38%)	115 (35%)	201 (34%)
No, still receiving 1L treatment	662 (27%)	106 (27%)	106 (27%)	75 (22%)	82 (23%)	115 (35%)	178 (30%)
1L maintenance treatment (ever received)[†,§]	917	156	165	143	138	102	213
Platinum-containing regimen	153 (17%)	24 (15%)	8 (5%)	29 (20%)	16 (12%)	5 (5%)	71 (33%)
Bevacizumab-containing regimen	747 (81%)	141 (90%)	150 (91%)	118 (83%)	101 (73%)	101 (99%)	136 (64%)
PARP inhibitor-containing regimen[‡]	57 (6%)	7 (4%)	10 (6%)	1 (1%)	25 (18%)	0	14 (7%)
Bevacizumab monotherapy	680 (74%)	123 (79%)	143 (87%)	108 (76%)	91 (66%)	97 (95%)	118 (55%)
Paclitaxel + carboplatin/cisplatin + bevacizumab	45 (5%)	11 (7%)	5 (3%)	8 (6%)	9 (7%)	4 (4%)	8 (4%)
Olaparib monotherapy	44 (5%)	5 (3%)	8 (5%)	1 (1%)	24 (17%)	0	6 (3%)
Paclitaxel + carboplatin/cisplatin	36 (4%)	6 (4%)	1 (1%)	4 (3%)	5 (4%)	1 (1%)	19 (9%)
Carboplatin/cisplatin	17 (2%)	0	0	13 (9%)	1 (1%)	0	3 (1%)
Docetaxel + carboplatin/cisplatin	12 (1%)	1 (1%)	0	0	0	0	11 (5%)
Paclitaxel monotherapy	10 (1%)	0	0	3 (2%)	3 (2%)	0	4 (2%)
Gemcitabine + carboplatin/cisplatin	10 (1%)	1 (1%)	0	2 (1%)	1 (1%)	0	6 (3%)
Carboplatin/cisplatin + liposomal doxorubicin	9 (1%)	0	1 (1%)	0	0	0	8 (4%)
2L drug treatment (ever received)[¶,#]	1472	247	248	228	223	192	334
Platinum-containing regimen	897 (61%)	174 (70%)	143 (58%)	108 (47%)	155 (70%)	140 (73%)	177 (53%)
Bevacizumab-containing regimen	241 (16%)	46 (19%)	26 (10%)	31 (14%)	69 (31%)	1 (1%)	68 (20%)
PARP inhibitor-containing regimen[‡]	66 (4%)	9 (4%)	13 (5%)	2 (1%)	5 (2%)	1 (1%)	36 (11%)
Liposomal doxorubicin-containing regimen	496 (34%)	75 (30%)	73 (29%)	70 (31%)	75 (34%)	87 (45%)	116 (35%)
Carboplatin/cisplatin + liposomal doxorubicin	224 (15%)	41 (17%)	39 (16%)	16 (7%)	42 (19%)	51 (27%)	35 (10%)
Gemcitabine + carboplatin/cisplatin	213 (14%)	42 (17%)	36 (15%)	51 (22%)	25 (11%)	27 (14%)	32 (10%)
Liposomal doxorubicin monotherapy	194 (13%)	19 (8%)	25 (10%)	45 (20%)	22 (10%)	31 (16%)	52 (16%)
Paclitaxel + carboplatin/cisplatin	145 (10%)	29 (12%)	20 (8%)	12 (5%)	24 (11%)	32 (17%)	28 (8%)
Gemcitabine + carboplatin/cisplatin + bevacizumab	74 (5%)	18 (7%)	0	12 (5%)	27 (12%)	1 (1%)	16 (5%)
Gemcitabine monotherapy	67 (5%)	14 (6%)	18 (7%)	19 (8%)	3 (1%)	5 (3%)	8 (2%)
Topotecan monotherapy	58 (4%)	9 (4%)	23 (9%)	7 (3%)	10 (4%)	4 (2%)	5 (1%)
Carboplatin/cisplatin	53 (4%)	5 (2%)	16 (6%)	7 (3%)	2 (1%)	21 (11%)	2 (1%)
Paclitaxel monotherapy	51 (3%)	6 (2%)	8 (3%)	18 (8%)	8 (4%)	8 (4%)	3 (1%)
Docetaxel + carboplatin/cisplatin	49 (3%)	2 (1%)	12 (5%)	3 (1%)	2 (1%)	3 (2%)	27 (8%)
Bevacizumab monotherapy	39 (3%)	0	6 (2%)	9 (4%)	2 (1%)	0	22 (7%)
Paclitaxel + carboplatin/cisplatin + bevacizumab	38 (3%)	15 (6%)	10 (4%)	5 (2%)	4 (2%)	0	4 (1%)
Olaparib monotherapy	32 (2%)	3 (1%)	5 (2%)	2 (1%)	2 (1%)	1 (1%)	19 (6%)
3L drug treatment (ever received)[¶,††]	177	37	28	35	16	30	31
Platinum-containing regimen	60 (34%)	9 (24%)	8 (29%)	10 (29%)	4 (25%)	15 (50%)	14 (45%)
Bevacizumab-containing regimen	6 (3%)	0	0	1 (3%)	0	1 (3%)	4 (13%)
PARP inhibitor-containing regimen[‡]	8 (5%)	5 (14%)	0	0	0	0	3 (10%)
Liposomal doxorubicin-containing regimen	40 (23%)	10 (27%)	9 (32%)	6 (17%)	4 (25%)	7 (23%)	4 (13%)

Data represented as n (%) unless otherwise stated.

[†]Numbers of patients receiving platinum-, bevacizumab-, and PARP inhibitor-containing regimens are shown, followed by treatment regimens received by ≥1% of patients overall. Platinum-, bevacizumab-, and PARP inhibitor-containing regimens could be administered as monotherapy or in combination with other treatment; hence, percentages may total >100%.

[‡]Includes olaparib, rucaparib, and niraparib.

[§]Percentage based on patients who ever received 1L maintenance treatment.

[¶]Numbers of patients receiving platinum-, bevacizumab-, PARP inhibitor-, and liposomal doxorubicin-containing regimens are shown, followed by treatment regimens received by ≥2% of patients overall. Platinum-, bevacizumab-, and PARP inhibitor-containing regimens could be administered as monotherapy or in combination with other treatment; hence, percentages may total >100%.

[#]Percentage based on patients who ever received 2L drug treatment.

[††]Percentage based on patients who ever received 3L or later drug treatment.

1L: First-line; 2L: Second-line; 3L: Third-line.

Table 4. Drug treatment (cont.).

Treatment	Total (n = 2413)	France (n = 396)	Germany (n = 393)	Italy (n = 347)	Spain (n = 353)	UK (n = 332)	USA (n = 592)
Liposomal doxorubicin monotherapy	29 (16%)	8 (22%)	8 (29%)	3 (9%)	2 (13%)	4 (13%)	4 (13%)
Paclitaxel monotherapy	27 (15%)	8 (22%)	2 (7%)	4 (11%)	6 (38%)	6 (20%)	1 (3%)
Gemcitabine + carboplatin/cisplatin	18 (10%)	1 (3%)	2 (7%)	6 (17%)	1 (6%)	4 (13%)	4 (13%)
Gemcitabine monotherapy	16 (9%)	4 (11%)	2 (7%)	8 (23%)	1 (6%)	1 (3%)	0
Topotecan monotherapy	15 (8%)	1 (3%)	5 (18%)	5 (14%)	1 (6%)	0	3 (10%)
Paclitaxel + carboplatin/cisplatin	11 (6%)	4 (11%)	1 (4%)	0	0	3 (10%)	3 (10%)
Carboplatin/cisplatin	10 (6%)	0	2 (7%)	2 (6%)	1 (6%)	5 (17%)	0
Carboplatin/cisplatin + liposomal doxorubicin	10 (6%)	2 (5%)	1 (4%)	2 (6%)	2 (13%)	3 (10%)	0
Olaparib monotherapy	4 (2%)	4 (11%)	0	0	0	0	0
Etoposide monotherapy	3 (2%)	1 (3%)	0	0	0	0	2 (6%)

Data represented as n (%) unless otherwise stated.
†Numbers of patients receiving platinum-, bevacizumab-, and PARP inhibitor-containing regimens are shown, followed by treatment regimens received by ≥1% of patients overall. Platinum-, bevacizumab-, and PARP inhibitor-containing regimens could be administered as monotherapy or in combination with other treatment; hence, percentages may total >100%.
‡Includes olaparib, rucaparib, and niraparib.
§Percentage based on patients who ever received 1L maintenance treatment.
¶Numbers of patients receiving platinum-, bevacizumab-, PARP inhibitor-, and liposomal doxorubicin-containing regimens are shown, followed by treatment regimens received by ≥2% of patients overall. Platinum-, bevacizumab-, and PARP inhibitor-containing regimens could be administered as monotherapy or in combination with other treatment; hence, percentages may total >100%.
#Percentage based on patients who ever received 2L drug treatment.
††Percentage based on patients who ever received 3L or later drug treatment.
1L: First-line; 2L: Second-line; 3L: Third-line.

adverse effects were reported for ≥10% of patients in the total study population, with the most common being nausea, hair loss and fatigue.

Symptoms reported by patients and physicians are shown in Table 5. Physicians reported that 18% of the total 398 patients receiving 1L treatment or 1L maintenance treatment at the time of data collection who had completed the appropriate questions in the PSC form were asymptomatic, while only 7% of these same patients reported having no symptoms. The symptoms most commonly reported by patients receiving 1L treatment or 1L maintenance treatment at the time of data collection were fatigue (reported by 49% of patients and 41% of physicians), swollen abdomen (42% of patients and 24% of physicians) and lower abdomen/pelvic pain (37% of patients and 18% of physicians). Kappa analysis indicated a fair level of agreement between physicians and patients in reporting of nine of 19 symptoms (including no symptoms), slight agreement for nine symptoms and poor agreement for one symptom.

In total, 404 patients responded to questions on treatment satisfaction. Overall, 49% of patients were either satisfied or very satisfied with the 1L treatment or 1L maintenance treatment they were receiving at the time of data collection, with 17% being dissatisfied or very dissatisfied. Marked geographical differences were observed in treatment satisfaction.

Discussion

In this study, data from clinical practice in five European countries and the USA relating to patients receiving drug treatment for advanced OC were analyzed to improve understanding of real-world treatment patterns and the reasons for treatment decisions. While this study focused predominantly on the 1L treatment and 1L maintenance treatment setting, subsequent lines of therapy were also included in the analysis. Progression from first line therapy can be interpreted as an unsuccessful outcome, and we wanted to investigate how treatment patterns change following disease progression.

A total of 2413 patients with stage III or IV OC at the time of data collection were included in the analysis. Similar numbers of patients were recruited in France, Germany, Italy, Spain and the UK, with each country contributing 14–16% of the total and patients from the USA representing 25% of the overall sample. Patients participating from each country were of similar age; patients in Europe had broadly similar ethnicity, and there was a lower proportion of white/Caucasian patients in the USA than in Europe. Very few patients had previously been diagnosed with another form of cancer or had a family history of OC. Most patients already had an advanced stage of OC at the time of diagnosis; this reflects the broader picture in clinical practice, with >75% of women presenting with advanced disease due to the asymptomatic nature of early-stage disease and the nonspecific symptoms of late-stage disease [24]. When data were collected, half of patients overall had stage IVb OC, with metastases present in multiple sites.

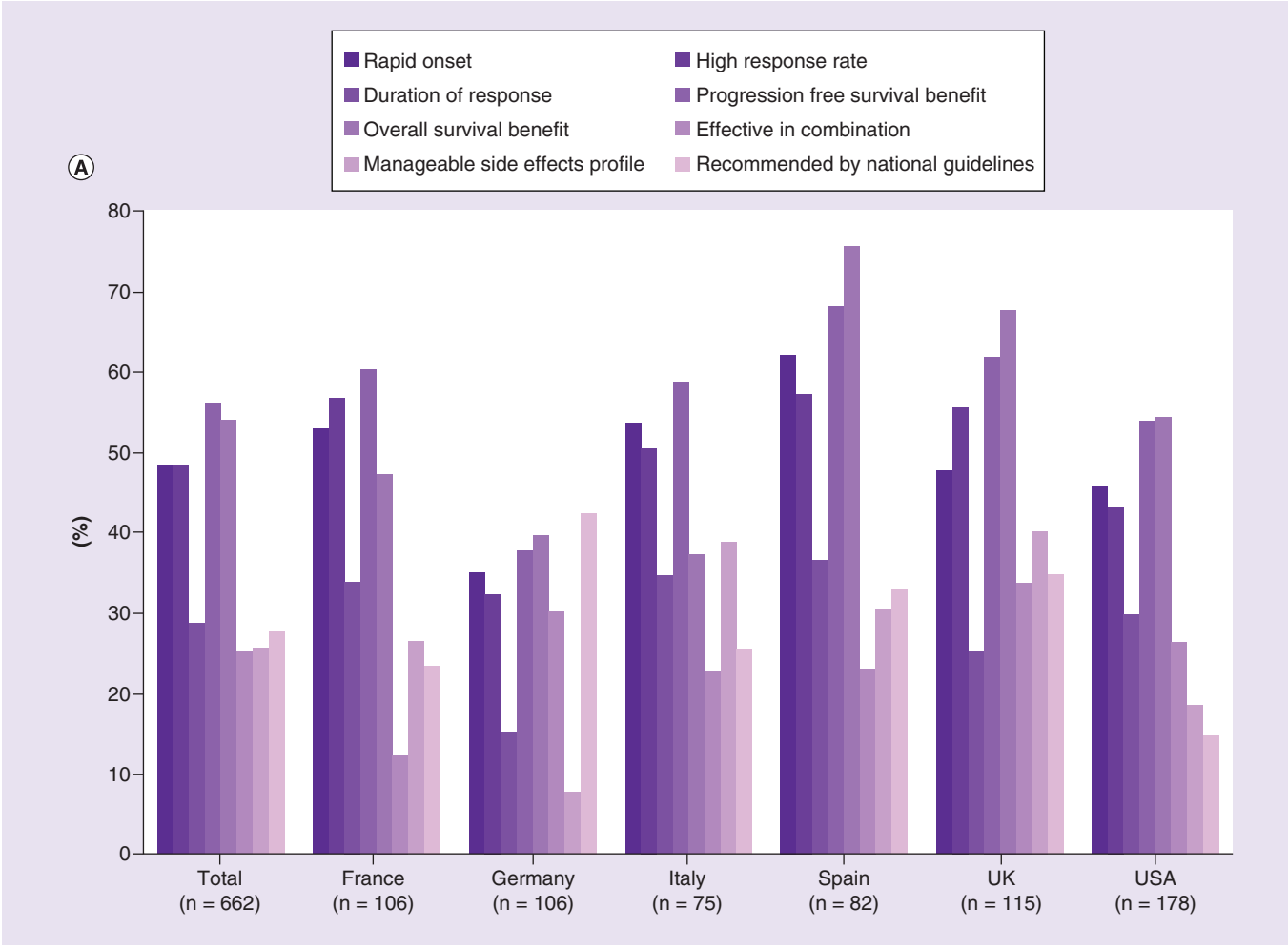


Figure 1. Rationale for treatment decisions.
(A) Reason for choosing 1L treatment[a,b,c]. **(B)** Reason for stopping 1L drug treatment[c,d]. **(C)** Reason for choosing 1L maintenance treatment[b,c,e]. **(D)** Reason for not prescribing 1L maintenance treatment[c,f,g,h]. **(E)** Reason for stopping 1L maintenance treatment[c,i].
The legend should be read from top left to bottom right for columns from left to right for a given country.
[a] Percentage based on a total of 662 patients receiving 1L treatment at the time of data collection.
[b] Reasons shown are those reported for ≥25% of total patients.
[c] More than 1 reason could be reported; hence, percentages may total >100%.
[d] Percentage based on a total of 1728 patients who have completed their 1L treatment.
[e] Percentage based on a total of 279 patients receiving their 1L maintenance treatment at the time of data collection.
[f] Percentage based on a total of 624 patients receiving 2L treatment at the time of data collection and not prescribed maintenance in the 1L.
[g] Reasons shown are those reported for >5% of patients.
[h] Other includes not reimbursed/covered by insurance, medically contraindicated, received observational maintenance instead, patient had already failed maintenance treatment of choice at induction, maintain therapy of choice.
[i] Percentage based on a total of 638 patients who have completed their 1L maintenance treatment.
1L: First-line; 2L: Second-line; HRQoL: Health-related quality of life.

Testing for biomarkers has the potential to improve OC survival rates through early detection [25] and targeted treatment [26]. In this analysis, approximately half of patients had been tested for ≥1 biomarker, with *BRCA*1 and *BRCA*2 testing – usually conducted when advanced OC was diagnosed – being the most common. Almost half of patients overall (47%) did not undergo biomarker testing, which limited the potential for targeted treatment to be prescribed where appropriate.

Almost 60% of patients in this study had had surgical intervention for OC, with various forms of hysterectomy, cytoreductive surgery and debulking commonly reported. Platinum-containing therapies were the predominant

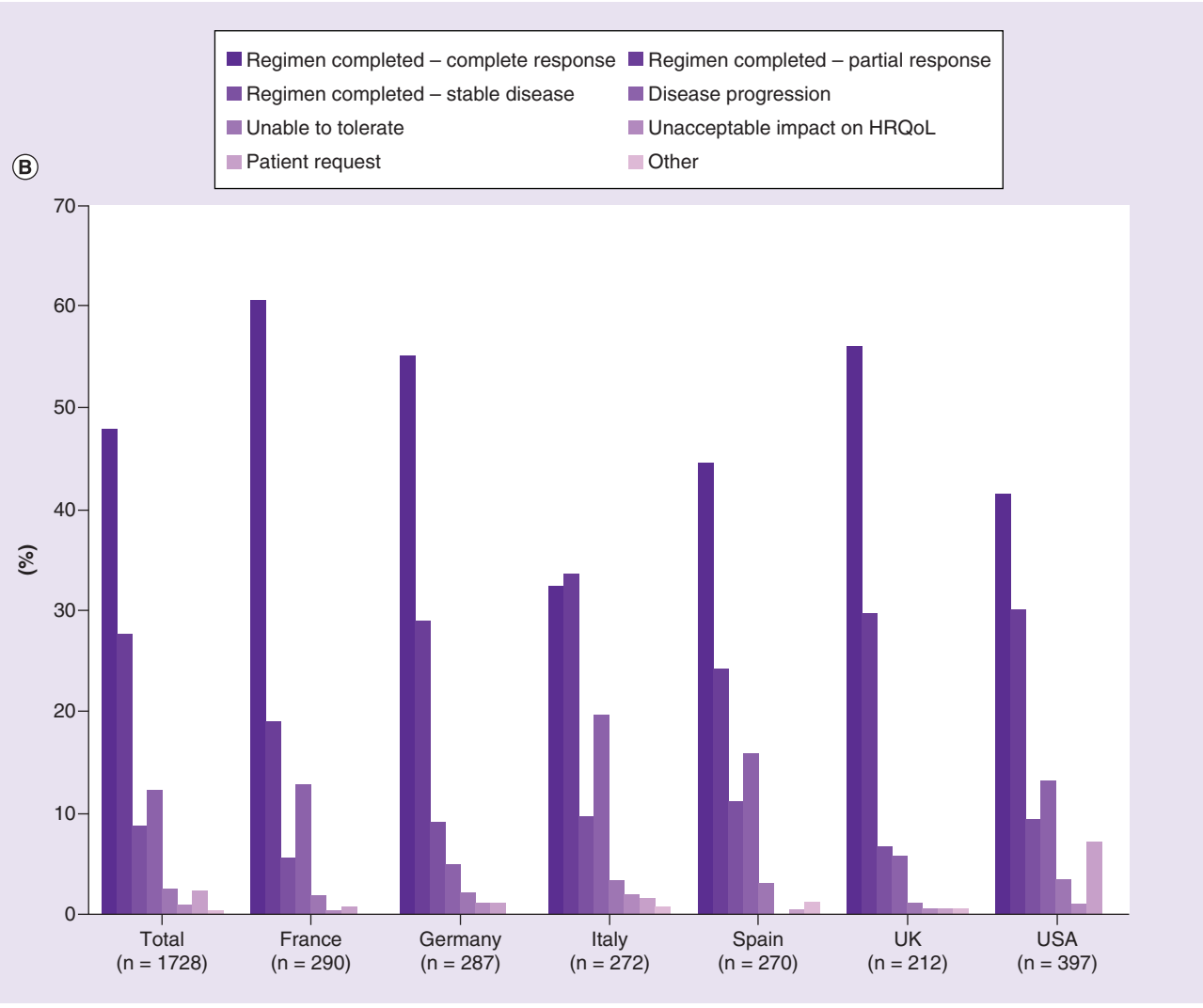


Figure 1. Rationale for treatment decisions (cont.).
(A) Reason for choosing 1L treatment[a,b,c]. **(B)** Reason for stopping 1L drug treatment[c,d]. **(C)** Reason for choosing 1L maintenance treatment[b,c,e]. **(D)** Reason for not prescribing 1L maintenance treatment[c,f,g,h]. **(E)** Reason for stopping 1L maintenance treatment[c,i]. The legend should be read from top left to bottom right for columns from left to right for a given country.

1L drug treatment, with the majority of patients receiving paclitaxel plus carboplatin/cisplatin, sometimes in combination with other treatments. These findings were to be expected, as studies have demonstrated surgery and extent of residual disease to be key to improved survival in OC [1] and platinum-containing chemotherapy following surgery remains the gold-standard treatment for advanced OC [1,6]. However, a fairly recent study in the UK and New Zealand provided evidence that patients receiving primary chemotherapy before surgery did not have reduced survival compared with patients receiving primary surgery [27].

Approximately a quarter of patients in the current analysis received bevacizumab (which targets VEGF) as 1L treatment, mainly in combination with paclitaxel and platinum-containing therapy. Bevacizumab in combination with standard chemotherapy as 1L treatment for advanced OC has been shown to improve progression-free but not overall survival in a critical analysis of Phase III trials [28] and both progression-free and overall survival in two systematic reviews and meta-analyses [29,30]. Only 1% of patients received a PARP inhibitor in the 1L. PARP inhibitors were prescribed only in the USA, Italy and Spain; rucaparib was not approved in Europe at the time of data collection [8,9], and only olaparib was prescribed in Europe.

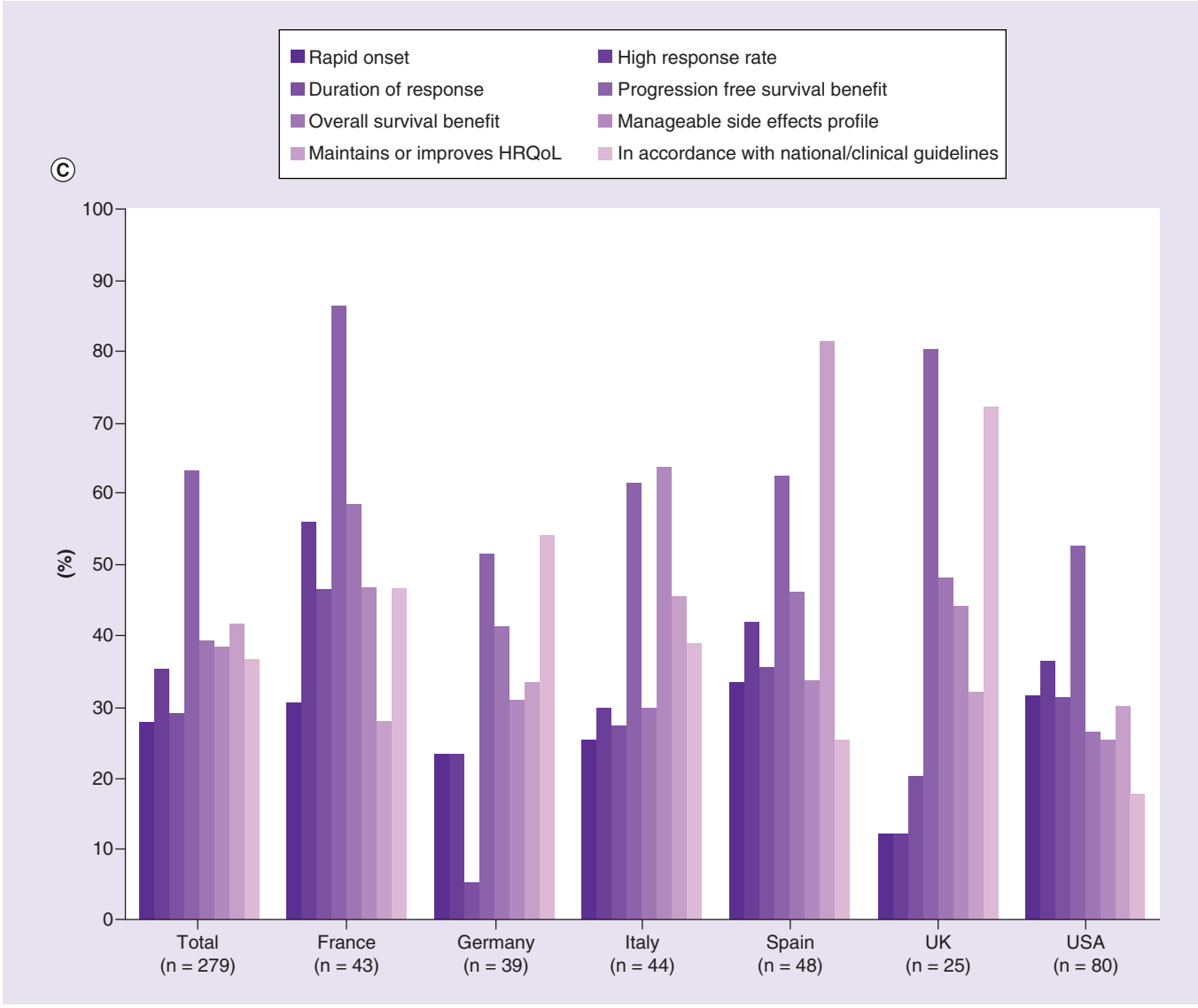


Figure 1. Rationale for treatment decisions (cont.).
(A) Reason for choosing 1L treatment[a,b,c]. **(B)** Reason for stopping 1L drug treatment[c,d]. **(C)** Reason for choosing 1L maintenance treatment[b,c,e]. **(D)** Reason for not prescribing 1L maintenance treatment[c,f,g,h]. **(E)** Reason for stopping 1L maintenance treatment[c,i]. The legend should be read from top left to bottom right for columns from left to right for a given country.

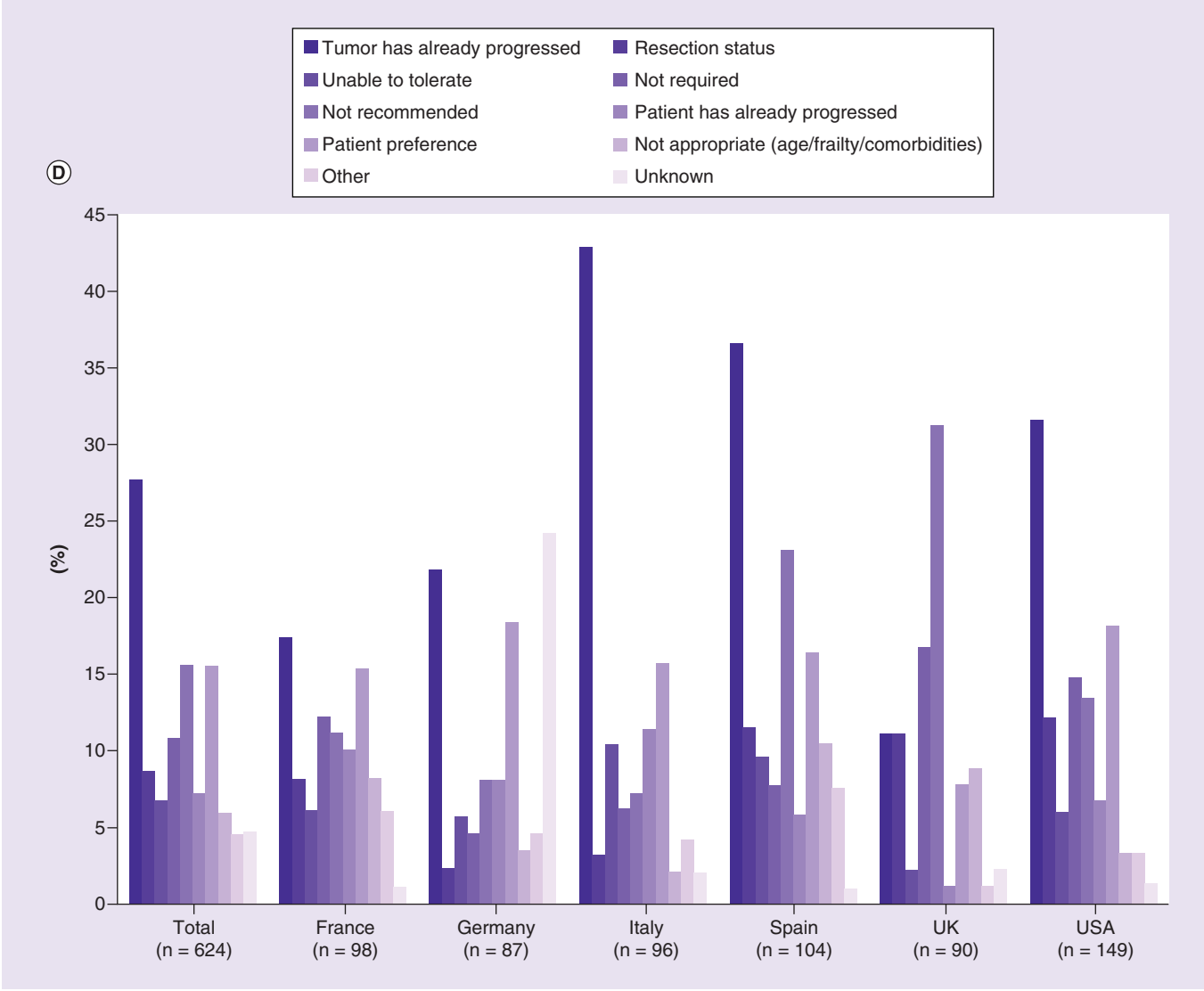


Figure 1. Rationale for treatment decisions (cont.).
(A) Reason for choosing 1L treatment[a,b,c]. **(B)** Reason for stopping 1L drug treatment[c,d]. **(C)** Reason for choosing 1L maintenance treatment[b,c,e]. **(D)** Reason for not prescribing 1L maintenance treatment[c,f,g,h]. **(E)** Reason for stopping 1L maintenance treatment[c,i]. The legend should be read from top left to bottom right for columns from left to right for a given country.

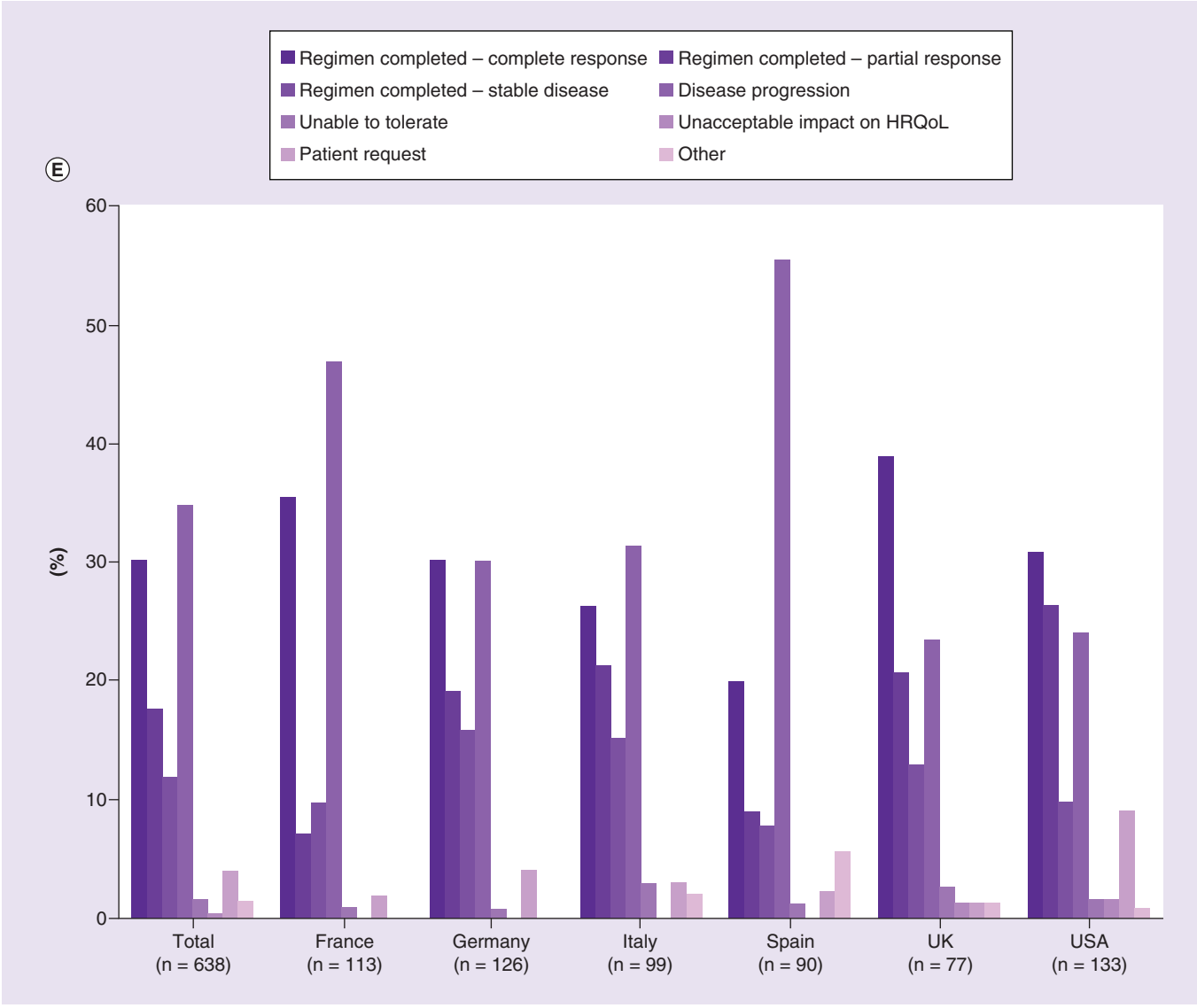


Figure 1. Rationale for treatment decisions (cont.).
(A) Reason for choosing 1L treatment[a,b,c]. **(B)** Reason for stopping 1L drug treatment[c,d]. **(C)** Reason for choosing 1L maintenance treatment[b,c,e]. **(D)** Reason for not prescribing 1L maintenance treatment[c,f,g,h]. **(E)** Reason for stopping 1L maintenance treatment[c,i]. The legend should be read from top left to bottom right for columns from left to right for a given country.

Table 5. Symptoms reported by patients and physicians.

Symptom	Patient reported (n = 398)	Physician reported (n = 398)	Kappa value (95% CI)	Level of agreement[†]
Fatigue	195 (49%)	165 (41%)	0.274 (0.180–0.367)	Fair
Swollen abdomen	167 (42%)	94 (24%)	0.237 (0.146–0.327)	Fair
Lower abdomen/pelvic pain	148 (37%)	71 (18%)	0.284 (0.193–0.375)	Fair
Loss of appetite/feeling full quickly	97 (24%)	80 (20%)	0.239 (0.131–0.347)	Fair
Back pain	95 (24%)	41 (10%)	0.210 (0.103–0.316)	Fair
Nausea/vomiting	90 (23%)	99 (25%)	0.161 (0.055–0.267)	Slight
Weight loss	82 (21%)	62 (16%)	0.190 (0.077–0.302)	Slight
Feeling bloated	82 (21%)	76 (19%)	0.305 (0.193–0.418)	Fair
Passing urine more often	70 (18%)	18 (5%)	0.118 (0.013–0.224)	Slight
Constipation	68 (17%)	38 (10%)	0.183 (0.063–0.303)	Slight
Upset stomach/stomach cramps	53 (13%)	57 (14%)	0.241 (0.115–0.367)	Fair
Shortness of breath	52 (13%)	21 (5%)	0.096 (-0.021–0.214)[‡]	Slight
Vaginal bleeding (particularly after menopause)	50 (13%)	4 (1%)	0.057 (-0.032–0.145)[‡]	Slight
Indigestion/heartburn	46 (12%)	33 (8%)	0.033 (-0.074–0.140)[‡]	Slight
Needing to urinate more urgently	37 (9%)	9 (2%)	0.052 (-0.058–0.163)[‡]	Slight
Menstrual changes	27 (7%)	3 (1%)	0.054 (-0.066–0.173)[‡]	Slight
Swelling of the lymph nodes/lymphedema	15 (4%)	12 (3%)	-0.035 (-0.057 to -0.012)	Poor
Pain during sex/intercourse	9 (2%)	6 (2%)	0.253 (-0.044–0.551)[‡]	Fair
Asymptomatic	29 (7%)	73 (18%)	0.387 (0.265–0.510)	Fair

[†] <0 = poor; 0–0.20 = slight; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; and 0.81–1.00 = almost perfect.
[‡] 95% CI for kappa statistic crosses 0, which may indicate that there is no agreement between the patient and physician.

Patients with OC responding to 1L therapy may be considered for maintenance treatment, with the goal of prolonging the disease-free period before recurrence or even inducing lasting remission by eliminating residual cancer cells or impeding turnover of these cells [31]. In this analysis, 38% of patients received 1L maintenance treatment (although, as mentioned later in this discussion, this number might have been inflated by the requirement for a quota of included patients to be receiving 1L consolidation or maintenance treatment); 81% received a bevacizumab-containing regimen and 6% received a PARP inhibitor-containing regimen; 17% received a platinum-containing regimen (most patients receiving a platinum-containing regimen being in the USA).

In addition to treatment patterns, data collected in the DSP included information on the rationale for treatment decisions. 1L treatment was stopped in the majority of patients on completion of the regimen, with almost half of patients achieving a complete response; however, 12% stopped due to disease progression and 3% due to poor tolerability or impact on HRQoL. The choice of 1L maintenance treatment suggested that physicians were very conscious of the potential impact on patients receiving continuing treatment, with progression-free survival benefit and maintenance of or improvement in HRQoL versus overall survival benefit indicated as the reasons for treatment choice in a higher proportion of patients. This reflects recommendations in the literature regarding treatment goals for maintenance therapy [31]. There were a considerable number of reasons given for not prescribing 1L drug-based maintenance treatment as well as a lot of inter-country variability, particularly regarding tumor progression. The number of patients who stopped treatment due to achievement of a complete response was similar to the number who stopped due to disease progression, reflecting the varied response to 1L maintenance treatment.

Developments in treatment for OC have led to improved disease control, largely resulting from the use of targeted therapies and the inclusion of maintenance therapy, which enhances progression-free survival [32]. Research involving antiangiogenic therapies, PARP inhibitors, inhibitors of growth factor signaling, folate receptor inhibitors, and various immunotherapeutic approaches provide the potential for OC to become a more manageable chronic disease at some point in the future [33].

The DSP methodology includes the collection of patient data from physicians and directly from patients (if they are willing to complete a PSC form). This approach highlighted that physician reporting of symptoms is not always aligned with patient experience; only a small proportion of patients reported being asymptomatic (7% overall), whereas physicians reported that almost one in five patients (18%) had no symptoms at the time of data collection. This disparity spanned a number of common symptoms, as confirmed by kappa analysis, with the proportions of patients reporting swollen abdomen and lower abdomen/pelvic pain being almost 20% higher than the proportions of patients that physicians considered as having these symptoms. Misalignment on the perception of symptoms and treatment adverse effects between physicians and patients with cancer has been well documented [34,35].

Large geographical differences in reporting of both treatment adverse effects and treatment satisfaction were observed. Relatively few patients from the USA were reported to be experiencing adverse effects while receiving 1L treatment or 1L maintenance treatment, which might explain their high level of treatment satisfaction compared with patients from some European countries. However, 68% of patients in Spain were satisfied or very satisfied with their treatment, despite 42% experiencing adverse effects – the highest proportion in any participating country. The most common adverse effects experienced were nausea, hair loss and fatigue, which are commonly reported in the literature [36,37].

Several limitations should be considered in the evaluation of these findings. The DSP was based on a quasi-random rather than a true random sample of physicians and patients. Although minimal inclusion criteria governed the selection of participating physicians, participation was influenced by willingness to complete the DSP. Patients participating in the DSP were those who consulted with their physician and therefore may have visited their physician more frequently and may be more severely affected than patients with OC consulting their physician less frequently. Although physicians were requested to collect data on a series of consecutive patients to avoid selection bias, in the absence of randomization, this was contingent on the integrity of the participating physician rather than on formalized source verification procedures.

The methodology also required each physician to recruit a quota of patients at various stages in their treatment history: four of eight patients were required to have received a platinum-containing therapy in the 1L and be in 2L or later, one of eight patients was required to have received bevacizumab as 1L maintenance treatment and be in 2L or later, and three of eight patients were required to be receiving 1L drug treatment (consolidation or maintenance). Data were not collected on whether this treatment was neoadjuvant or adjuvant therapy, or whether the delivery method was intravenous or intraperitoneal. Findings may have been influenced by survival bias, as only data from patients who had survived on treatment up to the date of data collection were included. Diagnosis

in the target patient group was based primarily on the judgment and diagnostic skills of the respondent physician, and a formalized diagnostic checklist was not mandated as part of the DSP methodology. However, this is entirely consistent with the diagnostic decisions made by physicians in routine clinical practice and is therefore reflective of the real-world. All data rely on the accurate reporting of the physician.

The DSP was designed to facilitate understanding of real-world clinical practice; thus, physicians could report only on the data they had on hand at the time of the consultation, representing the evidence used when making any clinical treatment and other management decisions at that consultation.

Despite such limitations, real-world studies are important for highlighting areas of concern that are not addressed in clinical trials. Patients included in clinical trials represent a small proportion of the consulting population due to age restrictions and failure to meet stringent eligibility criteria [38]. Patients treated in a real-world setting may be less likely to be adherent to medication than those included in clinical trials [39]. As a result, data from real-world studies can complement clinical trial data and provide insight into the effectiveness of interventions in patients commonly seen in clinical practice.

In conclusion, this analysis of real-world data illustrated that platinum-containing chemotherapy as 1L drug treatment following surgery was the most common treatment pattern in France, Germany, Italy, Spain, the UK and the USA and that maintenance treatment following completion of 1L treatment was a targeted therapy in 71–99% of patients, depending on the country. The numbers of patients stopping 1L treatment and 1L maintenance treatment due to disease progression, together with the numbers progressing to 2L treatment and beyond, suggest that there is an unmet need for effective treatment for this type of cancer.

Summary points

- This study analyzed real-world data providing information relevant to treatment decision-making in advanced ovarian cancer (OC).
- Data were from the Adelphi Disease Specific Programme, a survey of physicians and their patients, in France, Germany, Italy, Spain, the UK and the USA in 2017–2018. The 2413 patients included in this analysis had stage III–IV OC and were receiving drug treatment.
- Descriptive statistics were reported. Simple kappa statistics were computed to quantify chance-corrected agreement between physicians and patients in the reporting of symptoms.
- At data collection, 49% had stage IVb disease, 39% were receiving first-line (1L), 54% second-line and 7% third-line or later treatment.
- In the 1L (ongoing or completed), 93% received a platinum-containing regimen, 26% a bevacizumab-containing regimen and 1% a PARP inhibitor-containing regimen.
- Among the 38% who received 1L maintenance treatment, 81% received bevacizumab, 17% a platinum-containing treatment and 6% a PARP inhibitor.
- The most common reason for choosing 1L and maintenance treatments was expected progression-free survival benefit. The most common reason for stopping 1L treatment was complete response.
- Overall, 49% of patients were satisfied/very satisfied with their 1L treatment.
- Kappa analysis indicated a fair level of agreement between physicians and patients in reporting of nine/19 symptoms, slight agreement for nine symptoms and poor agreement for one symptom.
- In Europe and the USA, the most common 1L treatment for advanced OC was platinum-containing chemotherapy. Of patients who received 1L maintenance therapy, 70–99% (across countries) received targeted therapy.

Author contributions

All authors contributed to conception and design, were involved in drafting the manuscript and revising it for critically important intellectual content, have given final approval of the version to be published and agree to be accountable for all aspects of the work.

Financial & competing interests disclosure

This trial was sponsored by Pfizer and is part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany. Data collection was undertaken by Adelphi Real World as part of an independent survey sponsored by multiple pharmaceutical companies, one of which was Pfizer Inc. Pfizer did not influence the original survey through either contribution to the design of the questionnaires or data collection. The analysis described here was funded by Pfizer. J Chang and JC Cappelleri are employees and stockholders of Pfizer Inc. (which funded this study). JP Doherty was an employee of Pfizer Inc. at the time of this research. JP Hall, R Moon and O Higson are employees of Adelphi Real World. K Byrne was employed by Adelphi Real World at the time the work was undertaken.

Adelphi Real World was a paid consultant to Pfizer in connection with the development of this manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support under the guidance of the authors was provided by C Evans, on behalf of Adelphi Real World, and was funded by Pfizer Inc, in accordance with Good Publication Practice (GPP3) guidelines [40].

References

Papers of special note have been highlighted as: • of interest

1 Ledermann JA, Raja FA, Fotopoulou A *et al.* Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. *Ann. Oncol.* 24(6), 24–32 (2013).

• **Current guidelines for diagnosis, treatment and follow-up of ovarian cancer (OC).**

2 Bray F, Ferlay J, Soerjomataram I *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 68(6), 394–424 (2018).

• **Most recent publication detailing OC incidence and mortality on a global basis.**

3 Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. *Cancer Biol. Med.* 14(1), 9–32 (2017).

• **Summarizes the epidemiology of OC.**

4 Siegel R, Miller K, Jemal A. Cancer statistics 2017. *CA Cancer J. Clin.* 67(1), 7–30 (2017).

5 Ferlay J, Soerjomataram I, Dikshit R *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* 136, E359–E386 (2015).

6 Oronsky B, Ray CM, Spira AI *et al.* A brief review of the management of platinum-resistant-platinum-refractory ovarian cancer. *Med. Oncol.* 34, 103 (2017).

• **Highlights the high unmet need in OC treatment and the importance of clinical trials to shift the treatment paradigm in this area.**

7 Kiselev VI, Ashrafyan LA, Muyzhnek EL *et al.* A new promising way of maintenance therapy in advanced ovarian cancer: a comparative clinical study. *BMC Cancer* 18, 904 (2018).

8 Pharma Intelligence. FDA finally approves Avastin in first-line ovarian cancer (2019). https://pharmaintelligence.informa.com/resources/product-content/fda-finally-approves-avastin-in-first-line-ovarian-cancer

9 European Medicines Agency. Annexe 10 to the annual report of the European Medicines Agency (2019). www.ema.europa.eu/en/documents/annual-report/annexes-annual-report-european-medicines-agency-2014_en.pdf

10 Kim G, Ison G, McKee AE *et al.* FDA approval summary: olaparib monotherapy in patients with deleterious germline *BRCA*-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. *Clin. Cancer Res.* 21, 4257–4261 (2015).

11 European Medicines Agency. Rubraca (rucaparib) (2019). www.ema.europa.eu/en/medicines/human/EPAR/rubraca

12 Food and Drug Administration. Rucaparib (2019). www.fda.gov/drugs/resources-information-approved-drugs/rucaparib

13 European Medicines Agency. Zejula (niraparib) (2018). www.ema.europa.eu/en/medicines/human/EPAR/zejula

14 Food and Drug Administration. Niraparib (2019). www.fda.gov/drugs/resources-information-approved-drugs/niraparib-zejula

15 Miksad RA, Abernethy AP. Harnessing the power of real-world evidence (RWE): a checklist to ensure regulatory-grade data quality. *Clin. Pharmacol. Ther.* 103(2), 202–205 (2018).

16 Anderson P, Benford M, Harris N *et al.* Real-world physician and patient behaviour across countries: disease specific programmes – a means to understand. *Curr. Med. Res. Opin.* 24, 3063–3072 (2008).

17 Western IRB (WIRB). WIRB study number: 1180976, protocol number: 20172679 (2018). www.wirb.com

18 European Pharmaceutical Market Research Association (EphMRA). European Pharmaceutical Market Research Association (EphMRA) Code of Conduct Updated January 2017 (2018). www.ephmra.org/Code-of-Conduct-Support

19 US Department of Health and Human Services. Summary of the HIPAA Privacy Rule; 2003 (2018). www.hhs.gov/sites/default/files/privacysummary.pdf

20 Health Information Technology. Health information technology act (2018). www.healthit.gov/sites/default/files/hitech_act_excerpt_from_arra_with_index.pdf.

21 Rosner B. *Fundamentals of Biostatistics (8th Edition).* Chapter 2: Descriptive Statistics, Cengage Learning, MA, USA (2016).

22 Cohen J. A coefficient of agreement for nominal scales. *Educ. Psychol. Meas.* 20, 37–46 (1960).

23 Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam. Med.* 37, 360–363 (2005).

24 Doubeni CA, Doubeni AR, Myers AE. Diagnosis and management of ovarian cancer. *Am. Fam. Physician* 93(11), 937–944 (2016).

25 Moore RG, MacLaughlan S, Bast RC Jr. Current state of biomarker development for clinical application in epithelial ovarian cancer. *Gynecol. Oncol.* 116(2), 240–245 (2010).

26 Koczkowska M, Zuk M, Gorczynski A *et al.* Detection of somatic *BRCA1/2* mutations in ovarian cancer – next-generation sequencing analysis of 100 cases. *Cancer Med.* 5(7), 1640–1646 (2016).

27 Kehoe S, Hook J, Nankivell M *et al.* Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 386(9990), 249–257 (2015).

28 Rossi L, Verrico M, Zaccarelli E *et al.* Bevacizumab in ovarian cancer: a critical review of Phase III studies. *Oncotarget* 8(7), 12389–12405 (2017).

29 Li J, Zhou L, Chen X, Ba Y. Addition of bevacizumab to chemotherapy in patients with ovarian cancer: a systematic review and meta-analysis of randomized trials. *Clin. Transl. Oncol.* 17(9), 673–683 (2015).

30 Wu YS, Shui L, Shen D, Chen X. Bevacizumab combined with chemotherapy for ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials. *Oncotarget* 8(6), 10703–10713 (2017).

31 Di Silvestro P, Alvarez Secord A. Maintenance treatment of recurrent ovarian cancer: is it ready for prime time? *Cancer Treat. Rev.* 69, 53–65 (2018).

- **Highlights the importance of an effective maintenance therapy option to prevent or delay progression and the potential of poly(ADP-ribose) polymerase inhibitors for improvement in survival outcomes.**

32 Previs RA, Secord AA. Ovarian cancer: clinical trial breakthroughs and impact on management. *Obstet. Gynecol. Clin. North Am.* 46, 67–88 (2019).

33 Cortez AJ, Tudrej P, Kujawa KA, Lisowska KM. Advances in ovarian cancer therapy. *Cancer Chemother. Pharmacol.* 81, 17–38 (2018).

34 Nekolaichuk CL, Bruera E, Spachynski K *et al.* A comparison of patient and proxy symptom assessments in advanced cancer patients. *Palliat. Med.* 13(4), 311–323 (1999).

35 Sztankay M, Giesinger JM, Zabernigg A *et al.* Clinical decision-making and health-related quality of life during first-line and maintenance therapy in patients with advanced non-small cell lung cancer (NSCLC): findings from a real-world setting. *BMC Cancer* 17(1), 565 (2017).

36 Donovan HS, Hagan TL, Campbell GB *et al.* Nausea as a sentinel symptom for cytotoxic chemotherapy effects on the gut-brain axis among women receiving treatment for recurrent ovarian cancer: an exploratory analysis. *Support. Care Cancer* 24(6), 2635–2642 (2016).

37 Boyd LR, Muggia FM. Carboplatin/paclitaxel induction in ovarian cancer: the finer points. *Oncology (Williston Park)* 32(8), 418–20, 422–424 (2018).

38 Saunders C, Byrne CD, Guthrie B *et al.* Scottish Diabetes Research Network Epidemiology Group. External validity of randomized controlled trials of glycaemic control and vascular disease: how representative are participants? *Diabet. Med.* 30(3), 300–308 (2013).

39 Hubbard TE, Paradis R. Real-world evidence: a new era for health care innovation. the network for excellence in health innovation (2015). www.nehi.net/writable/publication_files/file/rwe_issue_brief_final.pdf

- **Summary of the importance of real-world evidence in clinical practice.**

40 Battisti WP, Wagner E, Baltzer L *et al.* Good publication practice for communicating company-sponsored medical research: GPP3. *Ann. Intern. Med.* 163(6), 461–464 (2015).

Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Future ONCOLOGY

Economic burden of illness associated with localized prostate cancer in the United States

Gary Gustavsen*[,1], Laura Gullet[1], Doria Cole[1], Nicolas Lewine[1] & Jay T Bishoff[2]

[1]Health Advances LLC, Weston, MA 02493, USA

[2]Intermountain Healthcare, Salt Lake City, UT 84103, USA

*Author for correspondence: Tel.: +1 781 647 3435; Fax: +1 781 392 1484; ggustavsen@healthadvances.com

Aim: Prior studies have established the economic burden of prostate cancer on society. However, changes to screening, novel therapies and increased use of active surveillance (AS) create a need for an updated analysis. **Methods:** A deterministic, decision-analytic model was developed to estimate medical costs associated with localized prostate cancer over 10 years. **Results:** 10-year costs averaged $45,957, $99,445 and $188,928 for low-, intermediate- and high-risk patients, respectively. For low-risk patients, AS 10-year costs averaged $33,912/patient, whereas definitive treatment averaged $49,667/patient. Despite higher failure rates in intermediate-risk patients, AS remained less costly than definitive treatment, with 10-year costs averaging $90,614/patient and $99,394/patient, respectively. **Conclusion:** Broader incorporation of AS, guided by additional prognostic tools, may mitigate this growing economic burden.

First draft submitted: 11 October 2019; Accepted for publication: 18 November 2019; Published online: 5 December 2019

Keywords: health economics • hormonal therapy • radiation therapy/radiotherapy • surgery • surveillance • urologic/prostate

As the most common malignancy affecting American men, prostate cancer poses a significant financial burden on the United States healthcare system [1]. A widely cited study by researchers at the National Cancer Institute estimated the costs associated with prostate cancer diagnosis and treatment to be $11.85 billion in 2010, making it the fifth most costly cancer overall [2]. Furthermore, the costs of treating prostate cancer have been shown to be increasing more quickly than those of any other cancer [2].

For localized prostate cancer patients, stratification into low-, intermediate- and high-risk groups forms the basis for selection of an appropriate treatment and thereby drives medical resource utilization and cost. Treatment in accordance with risk group seeks to optimize clinical outcomes for patients. However, the treatment guidelines from the American Urological Association (AUA) and the National Comprehensive Cancer Network are broad and recommend multiple potential courses of treatment, such that the potential exists for overtreatment and increased costs [3–5]. It has been shown that $1.32 billion per year could be saved in the USA by not treating the 80% of the men with low-risk prostate cancer who would never die of the disease [5]. Undertreatment may also be an issue; given the rate of biochemical recurrence (BCR), there may be patients for whom more aggressive treatment would be suitable and reduce the risk of BCR [4,6,7]. Given the interdependence of risk group and appropriate treatment, understanding current treatment patterns by risk group is necessary to fully characterize the landscape of prostate cancer costs and highlight opportunities for potential cost savings.

Imprecise selection of patients for treatment formed the basis of the United States Preventive Services Task Force (USPSTF) recommendation against prostate-specific antigen (PSA) screening for the detection of prostate cancer in 2012 [8]. The recommendation was made following the results of two large, randomized trials that highlighted the indolent nature of prostate cancer and suggested that PSA screening resulted in the treatment of men who would otherwise never die of prostate cancer [9,10]. While the USPSTF's stance has since been adjusted to recommend PSA screening as an individual decision, approaches to prostate cancer diagnosis are different than they were prior to 2012.

Although studies have examined the costs of prostate cancer management leading up to the 2012 USPSTF recommendation, few studies have examined the complete economic costs of treating prostate cancer patients

Future Medicine

Table 1. Clinical treatment paradigm.

Initial treatment modality in the typical practice scenario	AUA risk group		
	Low (42% of localized prostate cancer patients)	Intermediate (35% of localized prostate cancer patients)	High (23% of localized prostate cancer patients)
AS	24%	4%	0%
RP only	36%	40%	28%
RT only	25%	10%	0%
ADT only	15%	29%	53%
RT and ADT	0%	17%	19%
Total	100%	100%	100%

Initial treatment modality of patients with prostate cancer by AUA risk group. The current clinical practice paradigm was based on a combination of relevant sources, including published clinical guidelines, peer-reviewed articles on current treatment of prostate cancer patients and in-depth qualitative interviews with board-certified physicians. Primarily, data from the The US National Cancer Database drove the AS assumptions, and data from the AUA Quality Registry drove the subsequent treatment breakdown.
ADT: Androgen deprivation therapy; AS: Active surveillance; AUA: The American Urological Association; RP: Radical prostatectomy; RT: Radiation therapy.

according to the current treatment paradigm and inclusive of low-, intermediate- and high-risk patients. Recent research has evaluated the costs associated with the management of low-risk patients or particular treatment modalities. However, these studies fail to capture the complete burden of prostate cancer management across risk groups [11–13]. Furthermore, the costs associated with prostate cancer management in the USA have changed since the passage of the USPSTF guideline; prostate cancer diagnoses have decreased and the adoption of new and costly drugs, such as sipuleucel-T, abiraterone and enzalutamide, has increased [14–17]. Given these trends, a more detailed study of the economic burden of prostate cancer that follows patients through the patient journey is needed. The purpose of this study was to estimate the costs associated with prostate cancer management for a US commercial health plan over 10 years, based on the current paradigm for the treatment of prostate cancer and associated cost of care, and inclusive of all treatment modalities and risk groups.

Methods

Model structure & methodology

A deterministic, decision-analytic model was developed to estimate the direct medical costs associated with the management of localized prostate cancer patients over time from the perspective of a US commercial payer. This probabilistic model approach was deemed to be optimal in this case given the level of complexity and data availability. Treatment of a single hypothetical cohort of incident-localized prostate cancer patients was simulated using a patient flow model, built in Microsoft Excel, that was structured according to prevailing management protocols including AUA and National Comprehensive Cancer Network guidelines. The hypothetical patient group was separated into cohorts based on AUA risk-group designations, as is common in clinical practice [18]. Patient flow was modeled over the course of 10 years, tracking each phase of care across the cohorts. Costs were assigned to each unit of care based on the estimated average reimbursement rates paid by US commercial health plans, as described below.

Clinical paradigm

Key assumptions regarding the initial staging and treatment of incident-localized prostate cancer patients are presented in Table 1. Table 1 outlines the initial care received by each patient cohort based on AUA risk group. Additional follow-up care, as well as progression and further treatment costs, were tracked over the 10-year duration of the model to follow patients through the care continuum (see Disease follow-up & progression section). Patients initially managed with active surveillance (AS) were modeled to subsequently receive definitive treatment according to published rates (roughly 30% of low-risk patients and 60% of intermediate-risk patients over 5 years), either due to disease progression or patient choice [19–21].

The current clinical practice paradigm was based on a combination of relevant sources, including published clinical guidelines, peer-reviewed articles on current treatment of prostate cancer patients and in-depth qualitative interviews with board-certified physicians. Data from the US National Cancer Database (NCDB) were used to inform baseline rates of AS, whereas data from the AUA Quality Registry (AQUA) served as the foundation for the treatment distribution across definitive treatment modalities [22,23]. To further inform the patient management paradigm, 23 board-certified urologists were interviewed about their current practice patterns. All urologists who were interviewed had been in practice for at least 5 years and were actively treating patients with prostate cancer.

Table 2. Cost inputs.

Category	Patient management	Cost (USD)	Source
Initial treatment	RP	$10,604 (year 1)	2018 Medicare fee schedules and claims databases
	Primary RT	$34,116 (year 1)	[33]
	ADT	$2993 (year 1)	2018 Medicare fee schedules and claims databases
	Adjuvant/salvage radiation therapy	$29,101 (year 1)	[33]
Monitoring costs	AS	$1066 (annual)	2018 Medicare fee schedules and claims databases
	Post-RP/RT monitoring	$774–$845 (annual)	2018 Medicare fee schedules and claims databases
Advanced treatment	ADT	$2993 (annual)	2018 Medicare fee schedules and claims databases
	CRPC	$122,323 (annual)	2018 Medicare fee schedules and claims databases
Medicare scale-up factor		125%	[32]

Cost inputs used in the model. Costs were referenced from a variety of sources, including published, peer-reviewed clinical articles and Medicare fee schedules and claims databases.
ADT: Androgen deprivation therapy; AS: Active surveillance; CRPC: Castrate-resistant prostate cancer; RP: Radical prostatectomy; RT: Radiation therapy.

The urologists practiced in a mix of community and academic settings from all geographic regions in the USA. No two physicians practiced at the same institution. An in-depth review of the clinical literature, including studies on the NCDB and AQUA Registry, was used to validate and refine physician perspectives on the management of patients with localized prostate cancer.

The options modeled for initial patient management were AS, single-modality definitive treatment (including radical prostatectomy [RP], radiation therapy [RT] or primary androgen deprivation therapy [ADT]) or multimodality definitive treatment (RT plus ADT).

The clinical paradigm (Table 1) was intended to represent today's prevailing practice patterns. Accordingly, initial patient management varied by AUA risk group. In the AUA low-risk group, 24% of patients were initially managed using AS, whereas 76% received single-modality therapy. In the AUA intermediate-risk group, 4% were initially managed using AS, 79% with single-modality therapy and 17% with multimodality therapy. In the AUA high-risk group, 81% received single-modality therapy and 19% received multimodality therapy [18,19,24–28].

Disease follow-up & progression

Patients were modeled to receive follow-up care and additional treatment based on standard clinical practice. Patient follow-up care and disease monitoring after initial management includes office visits, PSA screening and biopsies, as well as treatment for complications resulting from management, such as erectile dysfunction and incontinence. BCR was modeled according to rates in the published literature, and varied based on the initial treatment type and AUA risk group [24,29]. Patients who experienced BCR were modeled to receive additional therapy, with patients initially treated using single-modality RP going on to receive either RT (50%) or ADT (50%) and patients initially treated with all other modalities going on to receive ADT [30]. For patients progressing to later stages of the disease, the rate of progression was based on published statistics. The timeline for patients experiencing progression was based on published survival statistics and estimated progression curves established during physician interviews [31].

Cost inputs

Table 2 displays the unit costs used to populate the economic model. Cost inputs were established for each unit of care a patient might undergo, including diagnostic procedures, surgical procedures, radiotherapy procedures and pharmacological therapy. Other costs associated with the treatment, such as office visits, anesthesiology, pathology and associated complications, were accounted for where appropriate. Costs were triangulated from a variety of sources, given the known variability in payment rates across US commercial health plans. Sources for costs included the 2018 Medicare fee-for-service rates, peer-reviewed journal articles and other published sources.

To estimate pricing based on Medicare fee-for-service rates, interviews were conducted with professional coders specializing in urology to determine which Current Procedural Terminology (CPT), International Statistical Classification of Diseases and Health Problems (ICD-9) and Diagnosis-Related Group (DRG) codes were most commonly used in practice. The CPT, ICD-9 and DRG codes were mapped to national payment rates using 2018 Medicare fee schedules. For each code, the total Medicare reimbursement (combining both professional and facility fees, where appropriate) was calculated for four separate place of service settings as follows: physician office, ambulatory surgical center, hospital outpatient and hospital inpatient. For procedures performed in a variety of settings, the

Table 3. Cost inputs for castrate-resistant prostate cancer.

CRPC therapeutic	Full-year cost (USD)	Duration of treatment	Percentage of patients receiving	Average per-patient cost (USD)
Leuprolide	$2512 (ASP + 6%)	Continuous	100	$8351
Sipuleucel-T	$125,482 (ASP + 6%)	One course	10	$12,548
Abiraterone	$124,491 (WAC)	16.5 mo (PFS)	100	$171,176
Docetaxel	$4608 (ASP + 6%)	6.3 mo (PFS)	100	$2419
Enzalutamide	$132,680 (WAC)	8.3 mo (PFS)	100	$91,770
Cabazitaxel	$170,878 (ASP + 6%)	2.8 mo (PFS)	100	$39,872
Denosumab	$28,059 (ASP + 6%)	20.7 mo (time to SRE)	80	$38,721
Radium Ra223 dichloride	$104,672 (WAC)	One course	80	$41,869
Total		39.9 mo (3.33 years)	N/A	$406,725
Average annual cost				$122,323

Cost inputs for CRPC. Calculated based on clinical guidelines and interviews with board-certified neurologists. Cost inputs were based on WAC prices and Medicare ASP drug pricing.
Note: Duration of treatment does not represent a sum of the individual duration of treatment for each therapy as some treatment regimens overlap one another.
ASP: Medicare average sales price; CRPC: Castrate-resistant prostate cancer; mo: Months; N/A: Not applicable; PFS: Progression free survival; SRE: Skeletal-related event; WAC: Wholesale acquisition cost.

payment amounts for each setting were then combined in a weighted average according to the frequency with which the relevant code was billed from each of the four settings. For the CPT codes, these data were sourced from the 2015 Physician/Supplier Procedure Summary (PSPS) database, which contains data on fee-for-service claims billed to Medicare Part B. In cases where multiple CPT, ICD-9 or DRG codes were used to describe similar services, a single payment amount was calculated by taking a weighted average of the various codes according to their billing frequency, as recorded in the PSPS or 2014 Healthcare Cost and Utilization Project databases. For the ICD-9 and DRG codes, these data were sourced from the 2014 Healthcare Cost and Utilization Project database, which despite the multiyear data-release lag time, contains the largest collection of data on procedures and diagnosis counts from publicly available payer healthcare databases, including Medicare. For the CPT codes, the same PSPS database was used. Finally, Medicare payment rates were inflated by 25% to more accurately reflect the rates paid by commercial insurers (with the exception of payment rates for pharmaceuticals) [32].

Select cost inputs were determined from alternate sources. The cost inputs for certain specific therapies, including primary and adjuvant RT, were taken from the published literature [33]. The costs of oral pharmaceuticals were sourced from published wholesale acquisition cost prices and Medicare average sales price drug pricing.

The cost of treating castrate-resistant prostate cancer (CRPC) was estimated using a hypothetical treatment regimen based on standard clinical practice (Table 3). The analysis accounted for the percentage of patients receiving a given therapy, the duration of therapy and dosing schedule and the average cost of therapy. The cost per milligram was translated into the cost of a full course of treatment according to the dosing schedule specified by the drug's US FDA label, clinical guidelines or the most relevant clinical trials. For dosing schedules dependent on bodyweight or surface area, an average bodyweight of 88.8 kg and average body surface area of 1.9 m^2 was used as reported by the CDC in 2016 [34]. A final average per-patient cost of treating CRPC was calculated and validated using various published cost analyses [35–41].

Cost analysis

The cumulative costs of prostate cancer management were calculated both on a per-patient basis and for commercial health plans with 1 or 5 million members. Cumulative costs for a hypothetical cohort of all patients with localized prostate cancer in the USA managed by private health insurance plans were also estimated.

Sensitivity analysis

Individual assumptions regarding the clinical treatment paradigm and cost inputs were varied within across a range of values to account for variability across assumptions.

Results

The cumulative costs of prostate cancer management, in 2018 dollars, are presented in Table 4. The cumulative cost of managing localized prostate cancer on a per-patient basis was estimated to be $46,193 over 5 years and $110,993 over 10 years. For a commercial plan with 1 million members, the cumulative cost of managing the

Table 4. Cumulative costs of prostate cancer management.

Cohort	Number of localized PCa patients	Cumulative initial treatment cost (USD)	Cumulative cost at year 5 (USD)	Cumulative cost at year 10 (USD)
Per patient with localized prostate cancer	1	$16,714	$46,193	$110,993
1-Million member commercial health plan	616	$10,290,638	$28,436,417	$68,327,488
5-Million member commercial health plan	3078	$51,453,191	$142,182,083	$341,637,440

Cumulative costs of prostate cancer management across multiple patient cohort sizes. The number of patients with localized prostate cancer per health plan is based on published rates of the incidence of prostate cancer in the general population and published stage distribution rates.
PCa: Prostate Cancer.

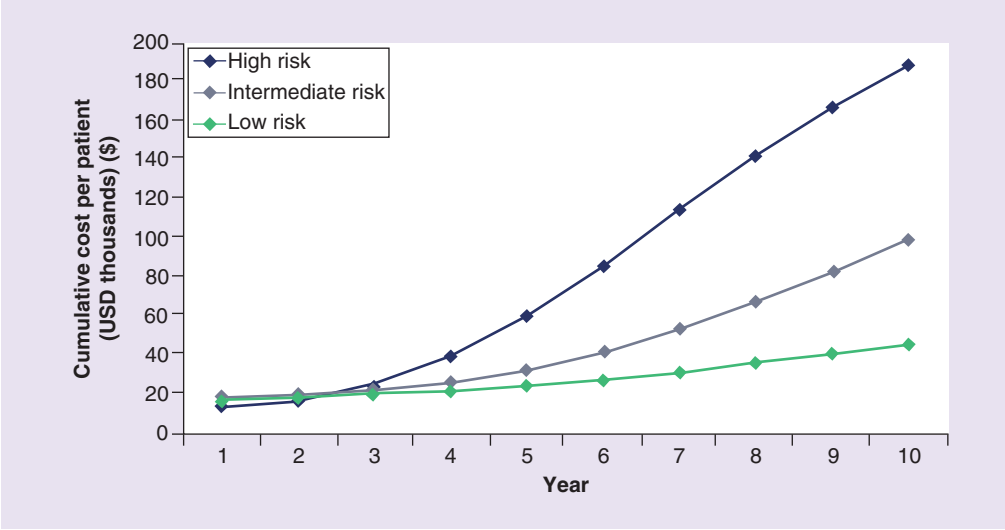


Figure 1. Cumulative costs per patient with prostate cancer by risk group.

cohort of localized prostate cancer patients incident over the course of 1 year was estimated to be $10 million, with costs rising to $28 million over 5 years and $68 million over 10 years. The cost of the initial upfront treatment comprised 15% of the cumulative cost incurred over 10 years.

Figure 1 illustrates how cumulative costs differed by risk group on a per-patient basis. The costs of care were similar across risk groups for the initial treatment and in the first 2 years after diagnosis. Over the remainder of the 10 years, cumulative costs for high-risk patients became the most burdensome. Detailed outputs of cumulative costs on a per-patient basis are presented in Supplementary Table 1.

Figure 2 illustrates the cost comparison between AS and a weighted average of all other definitive treatment modalities. As expected, costs in the first year of patient management were far lower for patients being treated with AS compared with definitive treatment. For low-risk patients, this difference persisted over the 10-year timeframe, largely due to the relatively low rate of AS failure and subsequent biochemical failure in this patient group. In intermediate-risk patients, the cost differential noticeably narrowed over the course of the model, a product of the higher rate of AS failure in this patient group. However, even at 10 years, AS remained a lower cost alternative to initial definitive treatment. Cost data are presented at years 1, 5 and 10 in Table 5.

Differences in cumulative costs based on initial treatment and by risk group are shown in Figure 3A–D. For low-risk patients, initial treatment with RT was most expensive, while AS and RP generated approximately equivalent costs over the course of 10 years. However, it is important to note that this does not take into account the full spectrum of additional costs due to less-common complications, impact on quality of life and loss of productivity from surgery. For intermediate-risk patients, AS, RP and ADT androgen drug therapy were approximately equivalent in cumulative costs 5 years after diagnosis. After 10 years, RP was the least expensive initial treatment option. Patients initially treated with ADT were estimated to generate the highest cost of any treatment group. Patients initially treated with RT, either as a single-modality treatment or as multimodality treatment with ADT, also generated high costs across the 10-year timeframe.

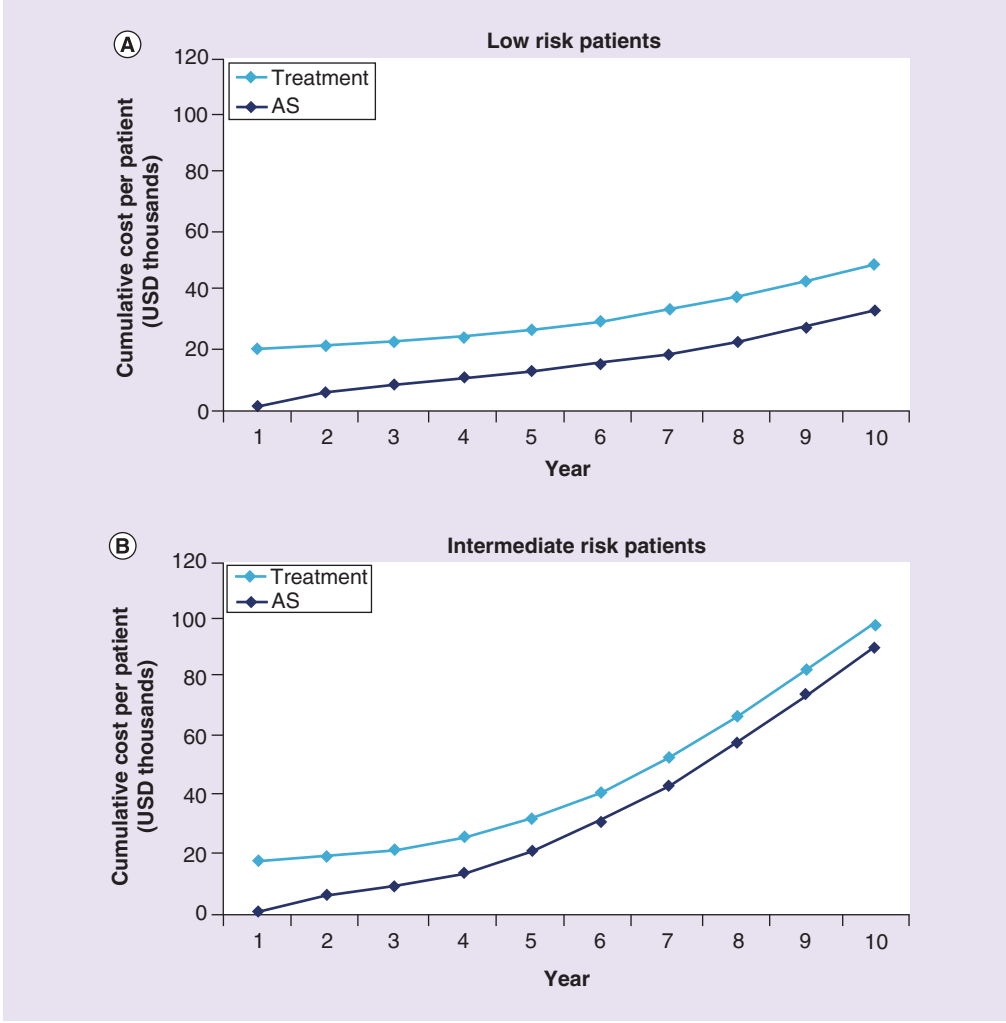


Figure 2. Cumulative cost per patient with prostate cancer by initial management.
AS: Active surveillance.

Table 5. Costs per patient by initial management.

AUA risk group	Patient management	Initial treatment (USD)	Cost at 5 years (USD)	Cost at 10 years (USD)
Low risk	AS	$1332	$13,178	$33,912
	Definitive treatment	$20,950	$27,439	$49,677
Intermediate risk	AS	$1332	$21,297	$90,614
	Definitive treatment	$18,764	$32,945	$99,394

Cumulative costs per prostate cancer patient by initial management. Costs for the definitive treatment group are a weighted average of costs across definitive treatment modalities (radical prostatectomy, radiation therapy, androgen deprivation therapy, radiation therapy + androgen deprivation therapy).
AS: Active surveillance; AUA: American Urological Association.

For high-risk patients (Figure 3D), initial treatment with ADT resulted in low costs over the first 2 years of treatment but became increasingly expensive over time and generated the highest costs over 10 years. Initial treatment with single-modality RT incurred the second-highest costs over 10 years.

Detailed data on cumulative costs by initial therapy and risk group are presented in Supplementary Table 2.

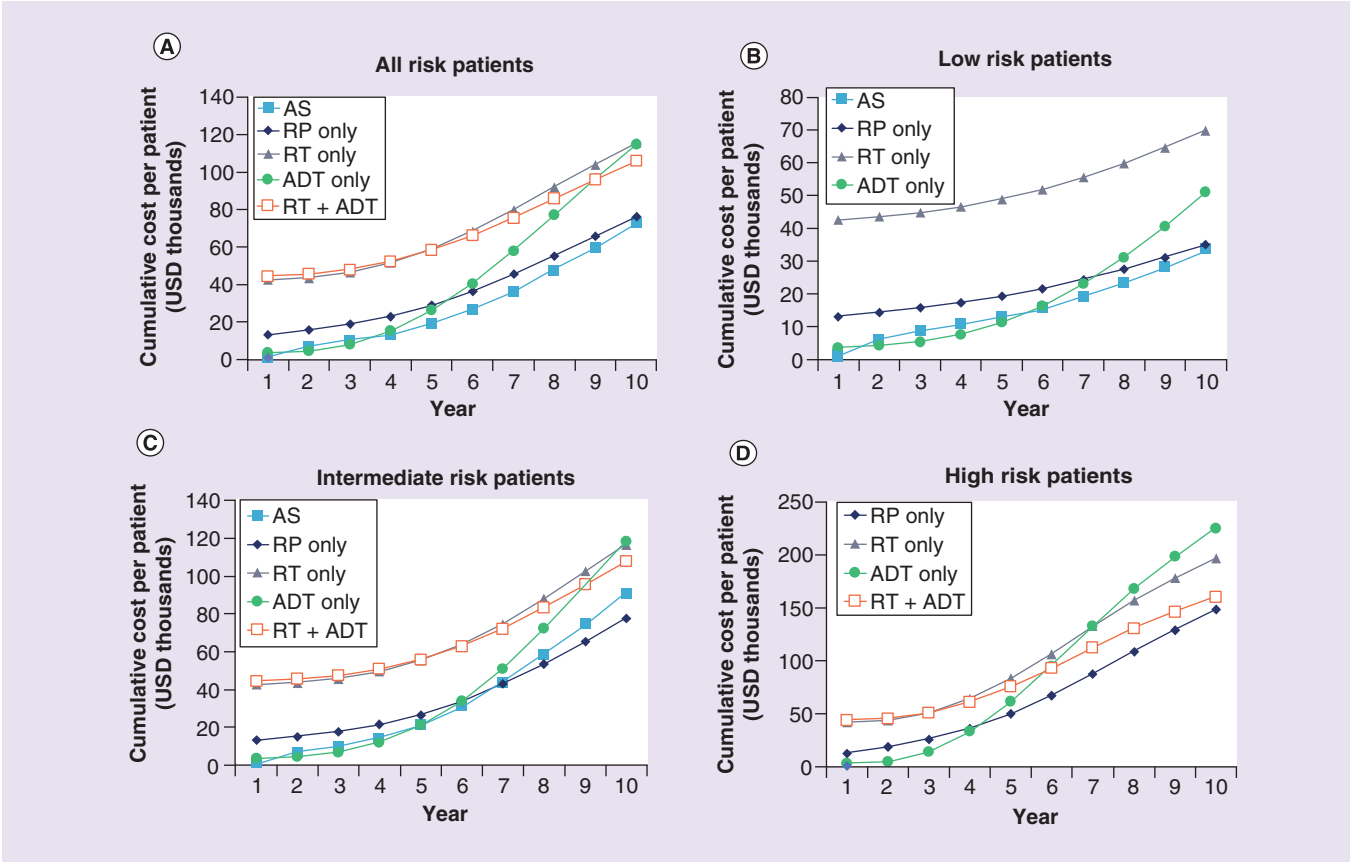


Figure 3. Cumulative costs per patient with prostate cancer by initial treatment.
ADT: Androgen deprivation therapy; AS: Active surveillance; RP: Radical prostatectomy; RT: Radiation therapy.

Sensitivity analysis

To assess the model's sensitivity to changes in specific inputs, each input was modified within a range of plausible values and the overall costs were recalculated. Each test input was changed in a way that lowered the cumulative costs (i.e., financially conservative) and in a way that increased cumulative costs (i.e., financially aggressive).

The inputs with the greatest level of variability and uncertainty are shown in Figure 4, which highlights the baseline assumptions and the percentage change from baseline for the sensitivity analysis. The tornado chart then illustrates the resulting variance from the original 10-year cost of $110,993. The model was most sensitive to the percentage markup that private payers pay relative to Medicare for certain procedures, as well as the number of patients progressing from salvage ADT to CRPC. Similarly, the model was sensitive to the number of patients progressing from CPRC to death, as well as the costs of CRPC and RT. Of note, given the evolving variability in how CRPC is managed, both therapeutically and diagnostically, this was an important addition to sensitivity analysis.

Discussion

Costs

This study estimated the costs associated with prostate cancer management for a US commercial health plan based on the current treatment paradigm and costs of care, inclusive of all treatment modalities and risk groups. The study's timeframe of 10 years enabled an analysis of the costs of prostate cancer, taking into account the impact of disease progression over time. For a commercial healthcare plan with 1 million members, this study estimated the 10-year cumulative cost to be $68 million, equivalent to $110,000 per patient with localized prostate cancer in the plan (Table 4).

The initial costs for the management of high-risk patients were found to be similar to those of low- and intermediate-risk patients over the first 3 years of care, despite the higher severity of localized cancer (Figure 1).

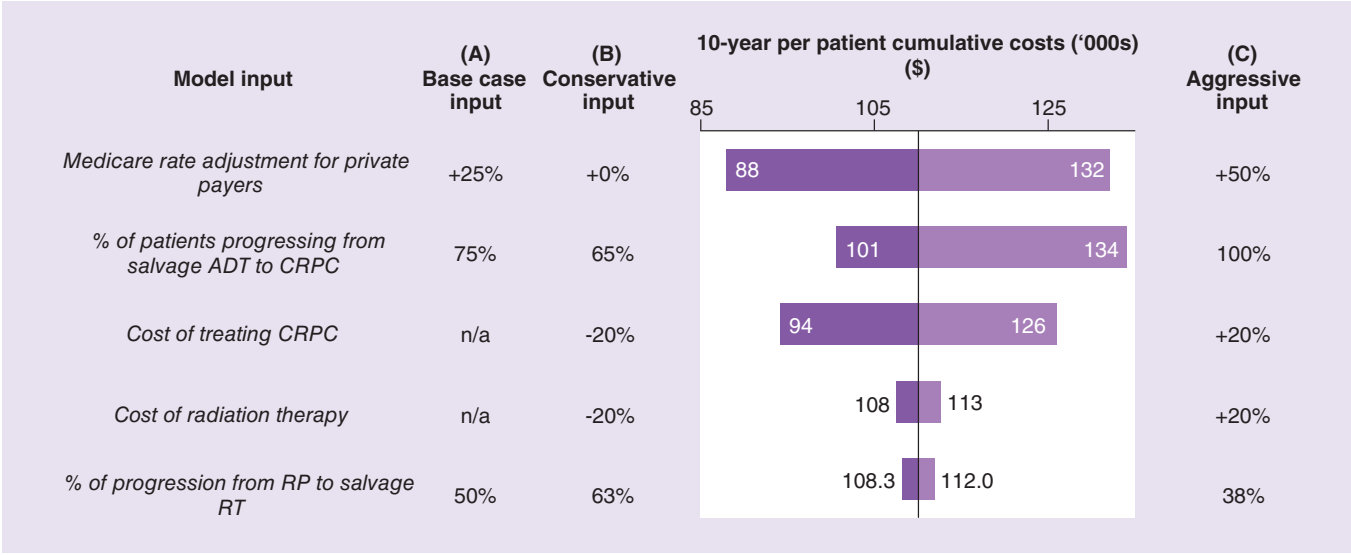


Figure 4. Sensitivity analysis.
ADT: Androgen deprivation therapy; CRPC: Castrate resistant prostate cancer; n/a: Not applicable; RT: Radiation therapy.

This dynamic likely occurs because many high-risk patients are initially treated with ADT (51%), which generated a relatively low annual cost ($2993/year). By comparison, many low- and intermediate-risk patients are initially treated with RP (36 and 38%, respectively), a treatment associated with a high upfront cost for the surgical procedure ($10,604 for initial treatment). Significantly higher costs were found to be generated by high-risk patients between years 4 and 10. This finding is likely due to the propensity for high-risk patients to progress to therapies with greater costs, like salvage RT ($29,101/year) and CRPC ($122,323/year).

The costs associated with the management of low-risk patients is of particular interest given the frequency with which low-risk patients qualifying for AS opt to receive definitive treatment [5,13]. This study found that initial treatment with AS saved on costs relative to both RP and RT at year 5. Initial treatment with ADT was estimated to generate the lowest costs for low-risk patients at year 5. However, ADT is an infrequent initial therapy for low-risk prostate cancer patients. Given the distribution of low-risk patients across definitive treatments, this study suggests a savings of $14,800 per patient managed with AS at year 5, compared with those who receive definitive treatment.

Previous studies based upon different modeling and claims-based approaches have estimated similar cost savings associated with AS over a 5-year timeframe. Keegan *et al.* estimated a per-patient cost savings of $16,042 at 5 years for a cohort of men that selected AS for treatment of their prostate cancer [13]. Although the Keegan *et al.*'s study was not limited to low-risk patients, most of the patients in the modeled cohort were low risk because patients considering an AS approach are often low risk. Similarly, Aizer *et al.* estimated a 5-year per-patient cost savings of $18,827 for low-risk patients managed with AS compared with low-risk patients who received definitive treatment.

However, neither of these previous studies took into account disease progression over a 10-year time window. This study found that the overall cost savings of AS remained high over 10 years compared with both ADT and RT. However, RP incurred similar cumulative costs to AS at year 10 (Figure 3B). The similar resulting cost savings of AS and RP over 10 years suggest that from a long-term cost perspective, these two modalities of care are more appropriate for low-risk patients than RT or ADT. However, it is important to note that this does not take into account the full spectrum of additional costs due to less-common complications, impact on quality of life, and loss of productivity from surgery. Given the distribution of low-risk patients across definitive treatments, cost savings for AS are maintained at 10 years compared with definitive treatment, with an estimated per-patient cost savings of $16,552.

It is well documented that patients may switch insurance plans multiple times over 10 years. Based on this behavior, insurers may be interested in the costs of prostate cancer management over shorter time frames than 10 years. Patients are members of government insurance plans for longer durations. For Medicare, patients are often members from the age of 65 to death. On average, this would be about 14 years, given that the US male life expectancy is 79 years [42]. The implication of these varying plan membership timelines is that different

policies might be financially advantageous after clinical considerations have been taken into account. For example, a policy that encourages use of AS and discourages RT for low-risk patients might be financially advantageous for a commercial private payer interested in a 2-year time window. Given its longer-term perspective, Medicare might focus on discouraging the use of RT. However, both for the payer and the patient, the most suitable treatment option is dependent on the patient's life expectancy and other factors, such as comorbidities. If the patient's life expectancy is less than 10 years, AS may be the most suitable treatment option.

The cumulative costs for intermediate-risk patients by initial treatment followed a similar pattern to those of low-risk patients, albeit over a shorter time frame given the higher likelihood of disease progression. AS and ADT were estimated to be the least expensive initial treatment options over the first 5 years after diagnosis. In the sixth year after diagnosis, the cumulative costs for AS and ADT converged with RP, with each treatment incurring a similar cumulative cost. Given the distribution of intermediate-risk patients across definitive treatments, the per-patient savings for AS compared with definitive treatment was estimated to be $10,618 at year 5. This per-patient savings is lower than that estimated for low-risk patients due to the higher rate of prostate cancer progression to additional follow-up care in the intermediate-risk population.

For high-risk patients, upfront multimodality treatment with RP and RT resulted in the lowest costs over a 10-year timeframe. However, single-modality treatment options such as ADT and RP were less expensive than any of the RT-based treatments over a 2-year timeframe. This finding highlights the importance of patient selection to effectively identify high-risk patients who could benefit clinically and reduce long-term costs by undergoing multimodality treatment.

A diversity of treatment options and approaches exists across the risk groups, each of which bears a different cost burden. Given the high-cost burden of prostate cancer management, better tools for risk stratification are necessary to guide optimal clinical care and decrease costs where appropriate. Current tools for risk assessment are unsatisfactory, particularly because prostate biopsies can undergrade and understage prostate cancer [5]. Furthermore, the PSA's role in guiding initial treatment is modestly additive in current practice. Improved risk stratification tools have potential to generate cost savings by matching the most appropriate treatment to each patient and improving treatment effectiveness for low- and high-risk patients. For low-risk patients, these tools would allow for better classification of patients for whom AS is suitable, which this study has shown to be the lowest-cost treatment option for this patient population. For high-risk patients, these tools would better identify patients in need of multimodality treatment, which this study has shown can be less costly than single-modality treatment over a 10-year period.

Limitations

This study is subject to a number of limitations. Recognizing that the quality and reliability of any burden of illness model is directly related to the data used to generate it, this analysis used a clinical paradigm that was extensively sourced and associated cost inputs that were based on validated reimbursement practices. However, the data were based on a hypothetical cohort of patients, and the inputs may therefore not be perfectly representative of the management of a given payer's prostate cancer patients. If the clinical paradigm is not reflective of clinical practice within a payer's physician network, the actual cost savings may differ from the model outputs. Populating the model with data specific to a given patient or provider mix might provide a more accurate representation of the burden of prostate cancer management for a given payer. Finally, clinical data inputs are based on averages. It is therefore difficult to statistically analyze the results of the study.

This model assumes a general age and incidence distribution and does not take into account variation in the incidence of prostate cancer and treatment response by age. The incidence rate of localized prostate cancer is lower in younger patients, but these patients are more likely to be aggressive in their treatment approach and thus generate a higher per-patient cost. By contrast, the incidence rate of localized prostate cancer patients in older patients is higher, but these patients are more likely to opt for less-aggressive treatment. Given the indirect relationship between incidence and treatment aggressiveness, it is difficult to estimate this impact. The aggregate cost burden of prostate cancer for a commercial plan is dependent on the particular age distribution of male patients enrolled in the plan.

Clinicians frequently subclassify intermediate-risk prostate cancer into 'favorable' or 'unfavorable' risk subgroups. Although this is a helpful distinction clinically, the authors chose to model these patients as a single-risk group because extensive published data on the treatment mix for favorable and unfavorable subgroups is not yet available. This limitation is not likely to have compromised the results of this report, but it could limit how future studies build upon these results.

Another limitation of the model is the decision to exclude nonpayer-related expenses related to prostate cancer. The model does not take into account indirect costs associated with patient quality of life or loss of productivity. This is consistent with the objective to focus on the commercial payer perspective, but incorporation of these costs into the model would serve to provide a more holistic view of the economic burden of prostate cancer. Finally, costs are all tracked and projected as 2018 dollars without inflation or discounting of future dollars in order to directly compare costs over time. A projected analysis of the economic burden of prostate cancer over time would bring an additional perspective to a subsequent study.

Conclusion

The economic burden of prostate cancer continues to increase with the incorporation of novel, high-priced therapies. However, broader incorporation of AS into the initial management of localized prostate cancer could mitigate this trend. Further development and improved access to more accurate prognostic tools, alongside additional economic studies, may provide physicians and patients with more information to better select the most clinically appropriate and cost-efficient initial treatment modality given the patient's individual level of risk.

Summary points

- Changes to screening, novel therapeutic interventions and an increasing use of active surveillance (AS) have undoubtedly altered the economic impact of prostate cancer over the past decade.
- After reviewing the current body of clinical literature, a need was identified for an updated analysis of the economic burden of prostate cancer to the US healthcare system.
- A deterministic, decision-analytic model was developed to estimate the direct medical costs associated with the management of localized prostate cancer in patients over time.
- The cumulative cost of managing localized prostate cancer on a per-patient basis was estimated to be $46,193 over 5 years and $110,993 over 10 years, and varied significantly by patient risk group.
- For low-risk patients, AS was found to be associated with a 10-year per-patient cost of $33,912, whereas definitive treatment averaged $49,667 per patient.
- Despite a higher risk of failure in intermediate-risk patients, AS remained less costly than definitive treatment, with 10-year per-patient costs averaging $90,614 and $99,394, respectively.
- The economic burden of prostate cancer continues to increase with the incorporation of novel high-priced therapies. However, broader incorporation of AS into the initial management of localized prostate cancer may mitigate this trend.

Supplementary data

An infographic accompanies this paper at the end of the references section. To download the infographic that accompanies this paper, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fon-2019-0639

Author contributions

G Gustavsen was responsible for the conceptualization of study, project administration, supervision, methodology, writing (original draft preparation, review and editing). L Gullet, D Cole and N Lewine performed the data curation, formal analysis, investigation and methodology, writing (review and editing). JT Bishoff contributed to the conceptualization of study, methodology, writing (reviewing and editing).

Financial & competing interests disclosure

Myriad Genetic Laboratories, Inc. assisted in the funding of this research. JT Bishoff has served on an advisory board and has received honoraria from Myriad Genetic Laboratories, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J. Clin.* 66(1), 7–30 (2016).
2. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. *J. Natl Cancer Inst.* 103(2), 117–128 (2011).
3. Loeb S, Bjurlin MA, Nicholson J *et al.* Overdiagnosis and overtreatment of prostate cancer. *Eur. Urol.* 65, 1046–1055 (2014).
4. Wilt TJ, Brawer MK, Jones KM *et al.* Radical prostatectomy versus observation for localized prostate cancer. *N. Engl. J. Med.* 367, 203–213 (2012).
5. Aizer AA, Gu X, Chen MH *et al.* Cost implications and complications of overtreatment of low-risk prostate cancer in the United States. *J. Natl Compr. Canc. Netw.* 13, 61–68 (2015).
6. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J. Clin. Oncol.* 28, 1117–1123 (2010).
7. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. *J. Clin. Oncol.* 29(2), 235 (2011).
8. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* 157(2), 120–134 (2012).
9. Andriole GL, Crawford ED, GrubbRL3rd *et al.*Mortality results from a randomized prostate-cancer screening trial. *N. Engl. J. Med.* 360(13), 1310–1319 (2009).
10. Schröder FH, Hugosson J, Roobol MJ *et al.* Screening and prostate-cancer mortality in a randomized European study. *N. Engl. J. Med.* 360(13), 1320–1328 (2009).
11. Cooperberg MR, Ramakrishna NR, Duff SB *et al.* Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis. *BJU Int.* 111(3), 437–450 (2013).
12. Kariburyo F, Wang Y, Cheng IN *et al.* Healthcare costs among men with favorable risk prostate cancer managed with observation strategies versus immediate treatment in an integrated healthcare system. *J. Med. Econ.* 20(8), 825–831 (2017).
13. Keegan KA, Dall'Era MA, Durbin-Johnson B, Evans CP. Active surveillance for prostate cancer compared with immediate treatment. *Cancer* 118(14), 3512–3518 (2012).
14. Barocas DA, Mallin K, Graves AJ *et al.* Effect of the USPSTF grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the United States. *J. Urol.* 194(6), 1587–1593 (2015).
15. Borza T, Kaufman SR, Shahinian VB *et al.* Sharp decline in prostate cancer treatment among men in the general population, but not among diagnosed men. *Health Affairs* 36(1), 108–115 (2017).
16. Halpern JA, Shoag JE, Artis AS *et al.* National trends in prostate biopsy and radical prostatectomy volumes following the US Preventive Services Task Force guidelines against prostate-specific antigen screening. *JAMA Surg.* 152(2), 192–198 (2017).
17. Sæterdal I, Desser A, Pike E *et al.* Health technology assessment of four drugs for patients with metastatic castration resistant prostate cancer. *Report from the Norwegian Institute of Public Health* 2016–08 (2016).
18. Sanda MG, Cadeddu JA, Kirkby E *et al.* Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. *J. Urol.* 199(3), 683–690 (2018).
19. Ip A, Dahabreh I, Chung M *et al.* An evidence review of active surveillance in men with localized prostate cancer. *AHRQ Publication* 12, 1–195 (2011).
20. Klotz 2011 Active surveillance for low-risk prostate cancer: an update. *Nat. Rev. Urol.* 8(6), 312–320 (2011).
21. Knighton AJ, Belnap T, Brunisholz K, Huynh K, Bishoff J. Using electronic health record data to identify prostate cancer patients that may qualify for active surveillance. *EGEMS.* 4(3), article 8 (2016).
22. Cooperberg MR. The current management of prostate cancer in the United States: data from the AQUA registry. Presented at: *American Urological Association Annual Meeting*. Boston, MA, USA, 12–16 May 2017.
23. Maurice MJ, Kim SP, Abouassaly R. Current status of prostate cancer diagnosis and management in the United States. *JAMA Oncol.* 2(11), 1505–1507 (2016).
24. Barocas DA, Cowan JE, Smith JA Jr, Carroll PR. What percentage of patients with newly diagnosed carcinoma of the prostate are candidates for surveillance? An analysis of the CaPSURE database. *J. Urol.* 180(4), 1330–1334 (2008).
25. Ghia AJ, Shrieve DC, Tward JD. Adjuvant radiotherapy use and patterns of care analysis for margin-positive prostate adenocarcinoma with extracapsular extension: postprostatectomy adjuvant radiotherapy: a SEER analysis. *Urology* 76(5), 1169–1174 (2010).
26. Cooperberg MR, Lubeck DP, Mehta SS, Carroll PR. Time trends in clinical risk stratification for prostate cancer: implications for outcomes (data from CaPSURE). *J. Urol.* 170(6 Pt 2), S21–S25 discussion S26–S27 (2003). Erratum in: *J. Urol.* 171(2 Pt 1), 811 (2004).
27. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J. Clin. Oncol.* 28(7), 1117–1123 (2010).

28. Cooberberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J. Clin. Onc.* 22(11), 2141–2149 (2004).
29. Cooperberg MR, Ramakrishna NR, Duff SB *et al.* Primary treatments for clinically localized prostate cancer: a comprehensive lifetime cost-utility analysis. *BJU Int.* 111(3), 437–450 (2013).
30. Song J, Li M, Zagaja GP *et al.* Intraoperative frozen section assessment of pelvic lymph nodes during radical prostatectomy is of limited value. *BJU Int.* 106(10), 1463–1467 (2010).
31 . Wiegel T, Lohm G, Bottke D *et al.* Achieving an undetectable PSA after radiotherapy for biochemical progression after radical prostatectomy is an independent predictor of biochemical outcome – results of a retrospective study. *Int. J. Radiat. Oncol. Biol. Phys.* 73(4), 1009–1016 (2009).
32. MEDPAC. Report to the Congress: Medicare and the health care delivery system (2011). http://medpac.gov/docs/default-source/reports/Jun11_EntireReport.pdf
33. Voigt JD, Dong Y, Linder V, Zappala S. Use of the 4Kscore test to predict the risk of aggressive prostate cancer prior to prostate biopsy: overall cost savings and improved quality of care to the US Healthcare system. *Rev. Urol.* 19(1), 1–10 (2017).
34. Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. *Vital Health Stat.* 3(39), 9 (2016).
35. Cooperberg MR, Ramakrishna NR, Duff SB *et al.* Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis. *BJU Int.* 111(3), 437–450 (2013).
36. Ryan CJ, Smith MR, de Bono JS *et al.* Abiraterone in metastatic prostate cancer without previous chemotherapy. *N. Engl. J. Med.* 368(2), 138–148 (2013).
37. Petrylak DP, Tangen CM, Hussain MH *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N. Engl. J. Med.* 351(15), 1513–1520 (2004).
38. Scher HI, Fizazi K, Saad F *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* 367(13), 1187–1197 (2012).
39 . De Bono JS, Oudard S, Ozguroglu M *et al.* Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomized open-label trial. *Lancet* 376(9747), 1147–1154 (2010).
40. Fizazi K, Carducci M, Smith M *et al.* Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 377(9768), 813–822 (2011).
41. Paller CJ, Carducci MA, Philips GK. Management of bone metastases in refractory prostate cancer – role of denosumab. *Clin. Interv. Aging.* 7, 363–372 (2012).
42. OECD. Health at a glance 2017: OECD indicators (2017). www.oecd.org/unitedstates/Health-at-a-Glance-2017-Key-Findings-UNITED-STATES.pdf

Article details

Title
Economic burden of illness associated with localized prostate cancer in the United States

Authors
Gary Gustavsen, Laura Gullet, Doria Cole, Nico Lewine & Jay Bishoff

Citation
Future Oncology (2019) doi/10.2217/fon-2019-0639

Changes to screening, novel therapeutic interventions, and an increasing use of active surveillance have undoubtedly altered the economic impact of prostate cancer over the past decade.

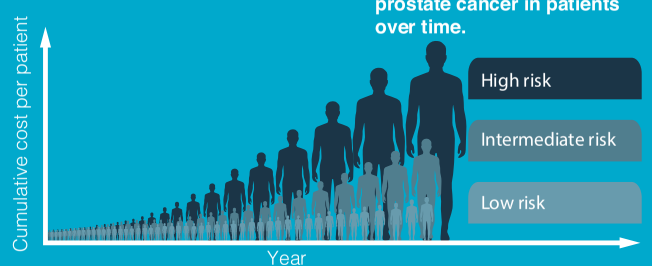
After reviewing the current body of clinical literature, a need was identified for an updated analysis of the economic burden of prostate cancer to the US healthcare system.

Screening

Novel therapies

Increased use of active surveillance

A deterministic, decision-analytic model was developed to estimate the direct medical costs associated with the management of localized prostate cancer in patients over time.

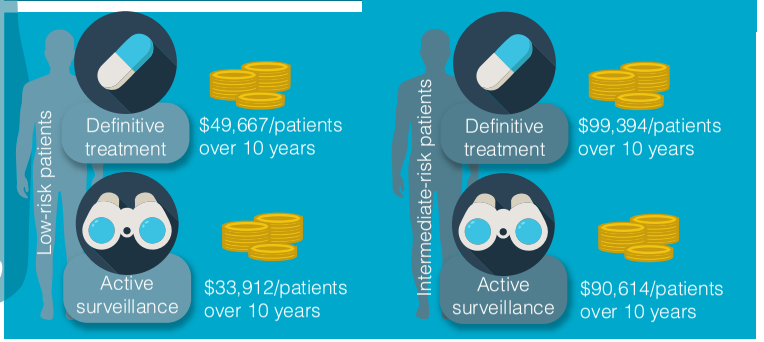


The cumulative cost of managing localized prostate cancer on a per-patient basis was estimated to be $46,193 over 5 years and $110,993 over 10 years, and varied significantly by patient risk group.

$46,193/patient over 5 years

$110,993/patient over 10 years

For low-risk patients, active surveillance was found to be associated with a 10-year per-patient cost of $33,912, whereas definitive treatment averaged $49,667 per patient. Despite a higher risk of failure in intermediate-risk patients, active surveillance remained less costly than definitive treatment, with 10-year per-patient costs averaging $90,614 and $99,394, respectively.



The economic burden of prostate cancer continues to increase with the incorporation of novel high-priced therapies. However, broader incorporation of active surveillance into the initial management of localized prostate cancer may mitigate this trend.