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SHORT REPORT

Real-world treatment outcomes of immune checkpoint inhibitors used off-label in oncology: A comprehensive cancer institution experience

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Abstract

Off-label use (OLU) is quite common in oncology due to the complexity of cancer and the time-consuming regulatory process. However, outcomes of OLU in cancer treatment remain unclear. This study aimed to evaluate the overall survival (OS), event-free survival (EFS), duration of treatment (DOT), and reason for treatment discontinuation in patients receiving immune checkpoint inhibitors (ICI) as OLU for solid tumors from 2011 to 2020. The study collected data on 356 episodes (353 patients), with a median age of 64.4 years, 36.2% women, and 14.6% ECOG ≥ 2. Median OS was 15.7 (11.9–18.7) months, and median EFS was 5.4 (3.8–6.6) months. Men, patients with metastatic disease or ECOG-PS higher than 1, had worse survival outcomes. The findings derived from this study provide valuable information regarding the real-world use of ICI-OLU and contributes to enhancing the decision-making process for individuals with cancer. Further research on immunotherapy outcomes of OLU in cancer is needed.

KEYWORDS
cancer, immune checkpoint inhibitors, off-label use, survival, treatment outcomes

Abbreviations: A/M, advanced/metastatic; AD/L, adjuvant-localized disease; CI, confidence intervals; ChT, chemotherapy; DOT, duration of treatment; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EFS, Event-free survival; EMA, European Medicines Agency; EU, European Union; GU, genitourinary cancer; H&N, head and neck cancer; ICI, immune checkpoint inhibitors; ICI-OLU, immune checkpoint inhibitors as OLU; ICO, Catalan Institute of Oncology; IT, immunotherapy; KM, Kaplan–Meier; M, months; Max, maximum; Min, minimum; N, number of patients; NA, not available; NR, not reached; NSCLC, non-small cell lung cancer; OLU, off-label use; OS, overall survival; PD-1/PD-L1, programmed death ligand L1/1; P&T, Pharmacy and Therapeutics Committee; SCCHN, squamous cell carcinoma of head and neck; TKI, tyrosine kinase inhibidor; 3m-OS, estimated overall survival probability at the 3-month mark; 60m-OS, estimated overall survival probability at the 60-month mark.

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1 | INTRODUCTION

Off-label use (OLU) refers to the utilization of drugs outside their approved indications by regulatory agencies.[1] Cancer treatment often involves OLU due to the complexity of the disease, limited treatment options, and lengthy clinical trial timelines.[1–4] To bring a drug to the market, it must obtain approval from a regulatory authority such as the European Medicines Agency (EMA) in the European Union (EU). After receiving marketing authorization, pharmaceutical companies are required to apply for marketing evaluation in each member state. Each member state then has the authority to decide the specific conditions under which the drug will be reimbursed and made available within its own National Health Service.[5] Regulatory processes for new medicinal products pose challenges and consume significant time, potentially leading to a mismatch between the patient's treatment needs and the regulatory timeline. However, concerns remain regarding the safety and survival outcomes of OLU in cancer treatment, and data on health outcomes of OLU in oncology are limited and varied.[1,4,6,7]

The Catalan Institute of Oncology (ICO) is a comprehensive cancer institution providing clinical cancer care for a total population of 3.2 million adults across its network in Catalonia (Spain). ICO Pharmacy and Therapeutics Committee (P&T) stablished criteria to determine eligibility for OLU and created a multidisciplinary group to evaluate the evidence supporting drug use, weighting its potential benefits and risks, to ensure patient safety and optimal care.[8]

A comprehensive analysis of a retrospective cohort study of adult patients with solid or hematologic cancer who received an OLU treatment between 2011 and 2020 has been previously reported.[9]

During last years, immunotherapy (IT) has emerged as an important approach in cancer treatment, harnessing the power of the immune system to target cancer cells. The positive results of IT trials in cancer have led to increased approved indications of immune checkpoint inhibitors (ICIs) and requests as OLU have increased.

This article focuses on the subset of patients who received ICIs as OLU (ICI-OLU) for solid tumors during 2011–2020. We aimed to estimate median overall survival (OS), event-free survival (EFS), duration of treatment (DOT), and reason for treatment discontinuation.

2 | METHODS

In this section, we will specifically outline the methods relevant to the subset analysis. Detailed results and methodologies for full cohort analysis are described elsewhere.[9]

Briefly, patients aged 16 years and older, from one of three ICO centers (ICO Girona, ICO Badalona, or ICO Hospitalet) who received an ICI as OLU for cancer treatment, between January 2011 and December 2020 were eligible for this study. Patients were followed up until April 8, 2022. This study was approved by the independent ethics committee of Bellvitge University Hospital and conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.

Patients could be eligible for OLU more than once during their treatment, and each request was considered as an "episode." Regarding descriptive variables, for each episode, we collected patient birth date, sex (female/male), tumor localization, diagnosis date, cancer setting-treatment intent (curative (neo(adjuvant)-localized) vs palliative (advanced-metastatic)), and Eastern Cooperative Oncology Group Performance Status (ECOG-PS) at OLU episode initiation (ranging from 0 to 4). Cancer treatment information included the number of previous treatment lines, drug(s) used and their initiation and stopping dates. The reason for OLU discontinuation was recorded as toxicity, disease progression, patient's decision, treatment completion, or other reasons. The study's primary end point was OS, measured in months from the start of OLU until death, loss to follow-up, or administrative censoring, whichever occurred first. Secondary end points included EFS measured in months from OLU initiation until disease progression, treatment discontinuation, death, loss of follow-up, or administrative censoring, and DOT, as months from OLU initiation until the last administered dose, death, loss of follow-up, or administrative censoring, whichever occurred first.

3 | STATISTICAL ANALYSIS

A descriptive analysis was conducted based on demographic, pathology, and treatment data obtained from patients' medical and chemotherapy records, presented as medians with interquartile ranges for continuous variables and frequencies with percentages for categorical variables. Median OS and EFS with 95% confidence intervals (CIs) were estimated using the Kaplan–Meier (KM) method, and survival curves were stratified by tumor type, ECOG-PS, age, sex, and stage and compared using the log-rank test.

4 | RESULTS

From the larger cohort of 2092 episodes, corresponding to 1920 patients, a total of 356 episodes in 353 patients met the inclusion criteria. Median age was 64.4 years (range: 21.5–89.8 years), 14.3% were aged ≥75 years, and 36.2% were women. Approximately 15% of patients had an ECOG-PS ≥ 2. Nearly half (47%) of the patients had not received any prior cancer treatment before initiating OLU. Most requests were for palliative intent, for advanced/metastatic solid tumor stages (80.9%). Three patients received more than on ICI as OLU, for different cancer settings (adjuvant and metastatic melanoma, localized and metastatic non-small cell lung cancer). The most frequent neoplasms were thoracic (47.5%), skin (24.7%), genitourinary (13.8%), and head and neck (6.2%). The requested drugs were ICIs targeting programmed death ligand L1/1 (antiPD-1/PD-L1, $n = 277/68$) and CTLA-4 ($n = 11$).

Median OS (months) was 15.7 (95%CI 11.9–18.7), and median EFS was 5.4 months (95%CI 3.8–6.6). Episodes related to an ECOG-PS ≥ 1 showed statistically significant worse OS outcomes compared

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to ECOG-PS 0 episodes ($p < .0001$). Female patients had better OS and EFS compared to male patients ($p < .048$), whereas no survival differences were observed among age cutoff of 75 years old. The OS and EFS for localized disease were four times longer than for metastatic disease Survival differences were found within the most frequent tumors ($p < .001$) (Figure 1) and within drugs ($p < .001$) (Table 1). Eighteen percent of patients died during the first 3 months of ICI treatment ($n = 65$). The estimated overall survival probability at the five 5 years mark was 20% for global population and 15% among patients in metastatic setting. Short- and long-term survival outcomes varied according to ECOG-PS and disease stage. Median DOT was 4.2 months (0.0–80.6) and varied according to drug, sex, and treatment intent, favoring women and being shorter in metastatic disease. See Table 1 for detailed survival outcomes and DOT by subgroups in episodes initiating an ICI-OLU.

At the end of study period, 92.1% of patients had discontinued treatment. Disease progression was the primary reason for treatment' discontinuation in 67.7% of cases (222), while treatment completion, toxicity, and patient' decision accounted for 18.9% (62), 11.9% (39), and 1.5% (5), respectively. Treatment discontinuation due to immune-related adverse events (AE) was observed in 11 patients (3%), while three patients experienced liver impairment and two patients experienced cardiac toxicity, leading to treatment discontinuation (<1%).

5 | DISCUSSION

Scarce data can be found in the literature regarding immunotherapy OLU for cancer treatment. To the best of our understanding, this is the first study focused on survival outcomes on this scenario. Our main goal was to describe the cohort of patients and to assess the outcomes and DOT of ICIs treatment used as OLU in a multicentric comprehensive cancer institution, and analyzing factors affecting survival outcomes.

Clinical results expected with OLU in a real-world data setting may be extremely variable as evidence supporting OLU can range widely.[4,10] Regarding ICIs-OLU from our study, most therapies were used before regulatory approval, based on evidence undergoing regulatory and pricing and reimbursement process. Nonetheless, clinical or patient characteristics for OLU requests may differ from eventually approved indication. Survival outcomes of ICI-OLU were variable, but significantly better in patients with localized stage cancer as expected, since early stage

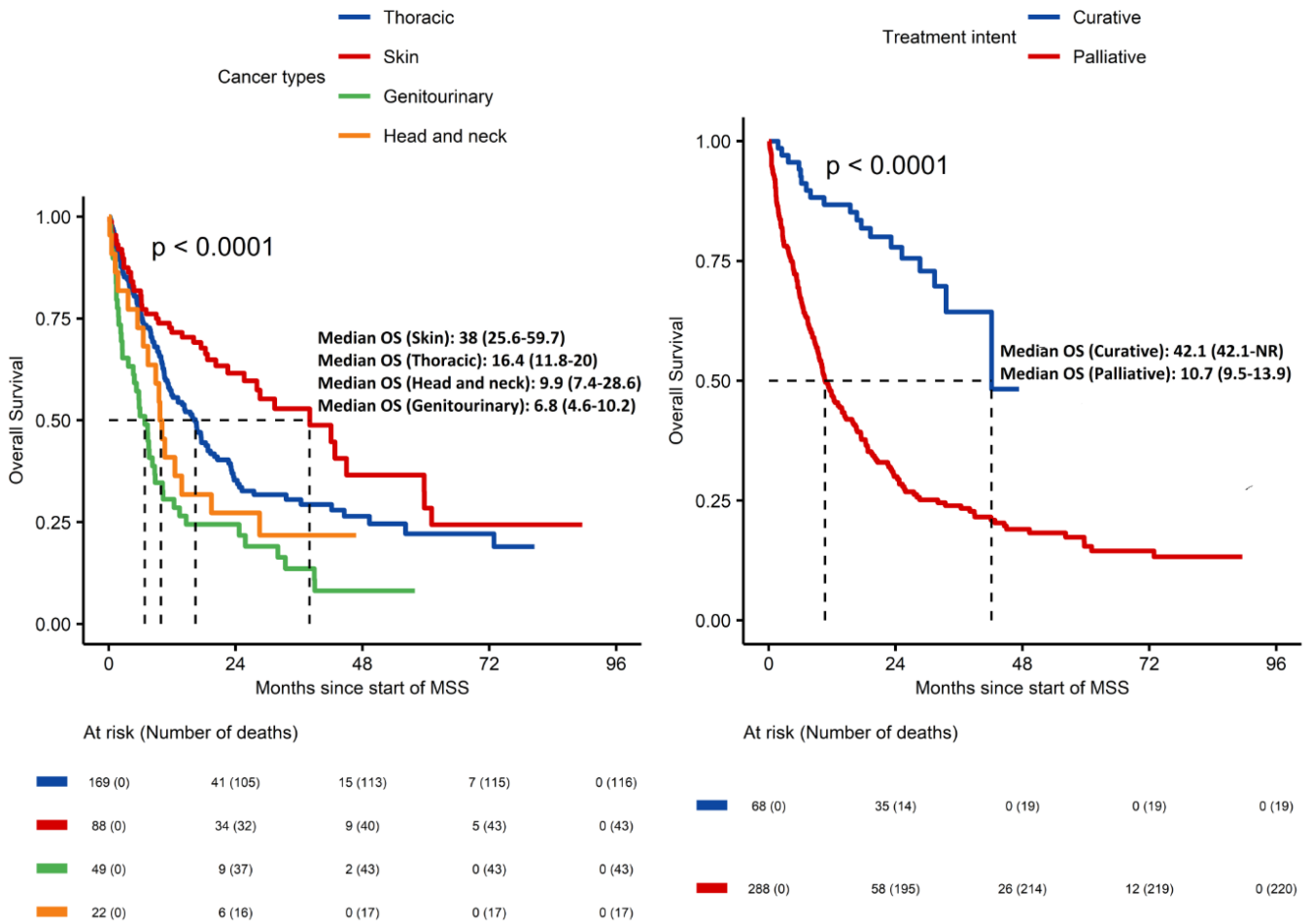

FIGURE 1 Overall survival by type of tumor and intent of treatment.

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TABLE 1 Survival outcomes (global and stratified) and duration of treatment.

		n (%)	Median OS (m) (95% CI)	*p*	3 m-OS	60 m-OS	Median EFS (m) (95% CI)	*p*
ICI-OLU episodes		356 (100%)	15.7 (11.9–18.7)	–	82% (78–86)	20% (15–28)	5.4 (3.8–6.6)	–
ECOG-PS	0	67 (18.8%)	56.1 (25.3-NR)	.0001	97% (93–100)	35% (14–82)	17.2 (10.9-NA)	.0001
	1	232 (65.1%)	16.4 (12.1–19.4)		87% (83–91)	19% (13–28)	5.5 (3.7–7)	
	≥2	52 (14.6%)	2.2 (1.4–4.6)		38% (27–54)	9% (4–24)	0.6 (0–1.7)	
Sex	Female	129 (36.2%)	20.2 (13.1–38.9)	.04	86% (80–92)	18% (8–41)	7.4 (4.5–11.7)	.04
	Male	227 (63.8%)	13.8 (10.2–17.5)		79% (74–85)	20% (14–28)	4.1 (3.2–6)	
Age	<75 y	305 (85.7%)	9.4 (7.3–39)	.77	81% (77–86)	22% (16–31)	5.4 (3.7–7)	.41
	≥75 y	51 (14.3%)	16.1 (12.3–18.7)		84% (75–95)	12% (4–37)	5.1 (3–17.2)	
Intent	Curative: AD/L	68 (19.1%)	42.1 (42.1-NA)	.0001	97% (93–100)	48% (26–89)	33.5 (16.7-NA)	.0001
	Palliative: A/M	288 (80.9%)	10.7 (9.5–13.9)		78% (73–83)	15% (11–22)	3.8 (3.2–5.3)	
Tumor[d]	Thoracic	169 (47.4%)	16.4 (11.8–20)	.0001	85% (80–91)	22% (15–33)	6.6 (4.4–8.5)	.0001
	Skin	88 (24.7%)	38 (25.6–59.7)		88% (81–95)	28% (16–49)	10.2 (5.6–28)	
	GU	49 (13.8%)	6.8 (4.6–10.2)		65% (53–80)	8% (3–23)	2.4 (1.4–4.5)	
	H&N	22 (6.18%)	9.9 (7.4–28.6)		82% (67–100)	22% (10–49)	2.8 (1.4–6.2)	

Drug	*n* pts, %	Median OS (m) (95% CI)	*p*	DOT (months [min; max] [*n*, %])	DOT curative setting: AD/L (*n*, %)	DOT Palliative setting: A/M (*n*, %)
All	*n* = 356;100%	15.7 (11.9–18.7)	.0001	4.2 [<0.1; 80.6]	11.3 [0.5; 17.9] (*n* = 68; 8.1%)	3.4 [<0.1; 80.6] (*n* = 288; 80.9%)
Cemiplimab[a]	*n* = 7; 2%	4.7 (2.6-NR)		1.4 [<0.1; 20.5]	–	1.4 [<0.1; 20.5] (*n* = 7; 2%)
Nivolumab[a]	*n* = 142; 39,8%	12.2 [9.7–18.7]		3.5 [<0.1; 80.6]	11.3 [0.46; 13.0] (*n* = 30; 8.43%)	3.0 [<0.1; 80.6] (*n* = 112; 31.5%)
Pembrolizumab[a]	*n* = 128; 35.9%	17.4 (14.3–24.7)		7.0 [<0.1; 32.7]	12.1 [0.99; 13.0] (*n* = 9; 2.53%)	6.5 [<0.1; 32.7] (*n* = 119; 33.4%)
Atezolizumab[b]	*n* = 35; 9.8%	7.3 (5.4–9.3)		2.5 [<0.1; 42.8]	17.9 [17.9; 17.9] (*n* = 1; 0.28%)	2.3 [<0.1; 42.8] (*n* = 34; 9.6%)
Avelumab[b]	*n* = 5; 1.4%	NR (NR-NR)		13.5 [1.4; 29.7]	–	13.5 [1.4; 29.7] (*n* = 5; 1.4%)
Durvalumab[b]	*n* = 28; 3,1%	42.1 (23.1- NR)		2.1 [<0.1; 2.6]	–	2.1 [<0.1; 2.6] (*n* = 11; 3,1%)
Ipilimumab[c]	*n* = 11; 7.9%	25.6 (11.9; NR)		11.2 [0.5; 12.1]	–	11.2 [0.5; 12.1] (*n* = 28; 7.9%)

Abbreviations: A/M, advanced/metastatic; AD/L, adjuvant-localized disease; DOT, duration of treatment; EFS, event-free survival; GU, genitourinary cancer; H&N, head and neck cancer; ICI-OLU, off label uses of immune checkpoints inhibitors; m, months; max, maximum; min, minimum; *n*, number of patients; NA, not available; OS, overall survival; 3 m-OS, estimated overall survival probability at the 3-month mark; 60 m-OS, estimated overall survival probability at the 60-month mark.

[a]AntiPD1: Cemiplimab, nivolumab, and pembrolizumab.

[b]AntiPDL1: avelumab, atezolizumab, and durvalumab.

[c]AntiCTLA4: ipilimumab.

[d]For most frequent tumors.

cancer is associated with a better overall prognosis, typically has a smaller tumor burden, and confined to a specific area, making it potentially more susceptible to immune-mediated responses. Actual tendencies on cancer research, by focusing on early lines of treatment, aim to achieve the highest chance of complete response or long-term survival.

Our analysis revealed a statistically significant association between ECOG-PS and survival, clearly benefiting ECOG-PS 0 episodes at short and long term. Therefore, the performance status could be considered as a prognostic factor, and the ICI-OLU should be prioritized in patients with an ECOG-PS of 0.[11] Older adults appear to benefit similarly to ICI therapy as their younger counterparts, further emphasizing the importance of prioritizing the patient's overall condition rather than solely considering age as a determining factor to determine suitability for OLU, as stablished in ICO's procedures.

Significant survival differences were observed based on sex, with results favoring female over male patients. Although there is recognized sexual dimorphism in immune system response, the impact of patients' sex on the survival outcomes of ICIs remains poorly understood, and further investigation is needed.[12] The median duration of OLU treatment was short, varied among different drugs and it was clearly longer for earlier diseases stages. Some patients experienced

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TABLE 2 Overall survival and event-free survival for more frequently requested ICI, for an indication eventually approved by the European Medicines Agency (EMA) and results obtained for the drug in pivotal trials.

		Study drug results				Published drug results			
Drug	**Labeled uses**	***N* = 286 out of 356**	**% ¥**	**mOS (m) (CI 95%)**	**m EFS (m) (CI 95%)**	**mOS (m) drug**	**mOS control (m)**	**mPFS (m) drug**	**mPFS control (m)**
Atezolizumab	Locally advanced or metastatic urothelial carcinoma who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression ≥5%	21	60%	3.7 (1.9–8.3)	1.4 (0–4.5)	15.2	13.3	NA	4.1
Durvalumab	Locally advanced, unresectable NSCLC in adults whose tumors express PD-L1 on ≥1% of tumor cells and whose disease has not progressed following platinum-based ChT	28	100%	42.15 (23.1-NR)	16.8 (6.2-NR)	47.5	29.1	17.2	5.6
Ipilimumab	Second-line treatment in advanced (unresectable or metastatic) melanoma	10	91%	22.9 (11.5-NR)	10.2 (2.4-NR)	10.1	6.4	NA	NA
Nivolumab	Recurrent or metastatic SCCHN	20	90.1%	9.6 (6.5–28.6)	2.5 (1.4–4.2)	9.2	6.01	3.5	2.8
	Advanced (unresectable or metastatic) melanoma	30		NR (NR-NR)	31.4 (10.6-NR)	16.8	10.8	5.1	2.2
	Second line after platinum-based therapy advanced non-squamous-cell NSCLC stratified for PD-L1	57		9.9 (5.8–13.9)	3.3 (2.4–6.5)	12.2	9.4	NA	NA
	Advanced renal cell carcinoma after prior therapy in adults	21		5.6 (2.6–24.7)	2.3 (1.4–12.2)	25.0	19.6	4.6	4.4
Pembrolizumab	Advanced (unresectable or metastatic) melanoma	22	77.3%	42.0 (4.6-NR)	11.0 (2.2-NR)	13.4	11	2.9	2.7
	Second line after platinum-based therapy or TKI (for EGFR/ALK Mutated) advanced NSCLC > 1% tumor cell PD-L1 expression	25		16.6 (10.1-NR)	7.3 (2.8–23.9)	10.4	8.4	3.9	4.1
Pembrolizumab + carboplatin + pemetrexed	First-line metastatic squamous non-small cell lung cancer	52		16.6 (11.9-NR)	8.6 (6–15.7)	15.9	11.3	6.4	4.8

Abbreviations: ChT, chemotherapy; m, months; mEFS, median event-free survival; mPFS, median progression-free survival; mOS, median overall survival; *N*, number of requests; NA, not available; NR, not reached; NSCLC, non-small cell lung cancer; SCCHN, squamous cell carcinoma of head and neck; TKI, tyrosine kinase inhibitor; %¥, percentage of requests corresponding to an indication eventually approved by EMA over total number of requests by drug within study population.

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long-lasting remission and the survival odds at 5 years was 15%, although for most metastatic episodes' treatments, DOT was less than 4 months. Ongoing research focuses on developing new immunotherapeutic approaches and identifying predictive biomarkers that can help predict which patients are most likely to benefit from ICIs.

For informative purposes, we conducted a straightforward numerical comparison of survival outcomes obtained in our study with those published in the literature for selected drugs and indications requested as OLU. Indications supported by stronger evidence, that were eventually approved by the EMA and the Spanish Medicines Agency, with a positive reimbursement decision within Spain up to May 2023 accounted for 84% of study requests (Table 2). We observed that the outcomes obtained within our population for durvalumab in lung cancer, nivolumab in head and neck cancer, and nivolumab, pembrolizumab, and ipilimumab in melanoma were consistent with the published findings.

While our study provides valuable insights into IT for cancer, we acknowledge several limitations. Firstly, our study is observational and retrospective, with the inherent limitations that come with it, but it reflects our real-world practice of medication use including patients who could be underrepresented in clinical trials.

Secondly, the study included a wide range of cancers and drugs, some with a limited sample size, which may hinder our ability to draw solid conclusions, but it helps to promote further research. However, it is worth noting that our study included patients from three centers, and the study population is representative of approximately half of Catalonia adult population, as ICO provided clinical oncology and hematology care for this population.

Despite these limitations, the main strength of our study lies in its assessment of clinical outcomes and survival in a substantial cohort of over 350 patients over a 10-year period. The knowledge gained from this study has been integrated into the decision-making process concerning individual OLU in cancer in the P&T Committee at our institution. We also anticipate its applicability to other countries and its usefulness for other health professionals.

6 | CONCLUSION

Our study provides valuable information regarding the real-world use of ICI-OLU and contributes to enhancing the decision-making process for individuals with cancer. The findings allow for discussion within the P&T Committee about clinical criteria for ICI-OLU, underscoring the importance of comprehensive and accurate review of treatment requests to optimize treatment benefits. The experience and procedures regarding OLU in cancer at our institution may be of interest to other colleagues and extrapolated to other countries. Further research to investigate the safety and survival outcomes of ICI-OLU in cancer care is needed.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, project administration, resources, supervision, validation, investigation, and writing–original draft: Sandra Fontanals. *Conceptualization, methodology, formal analysis, validation, visualization, and writing review and editing*: Anna Esteve. *Data curation, formal analysis, methodology, validation, and visualization*: Andrea González. *Validation, and writing review and editing*: Cristina Ibáñez. *Conceptualization, project administration, supervision, and writing review and editing*: Ricard Mesía and Ana Clopés.

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CONFLICT OF INTEREST STATEMENT

The author(s) declare(s) that there are no conflicts of interest regarding the publication of this article.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during this study are not publicly available due to reasons of sensitivity but are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study protocol and statistical analysis plan were approved by the independent Ethics committee of Bellvitge University Hospital (protocol code PR090/21-UB110321), with a waiver of informed consent, due to its retrospective nature. This study was conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.

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