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ORIGINAL RESEARCH

Off-label despite high-level evidence: a clinical practice review of commonly used off-patent cancer medicines

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Introduction: Off-label use of medicines is generally discouraged. However, several off-patent, low-cost cancer medicines remain off-label for indications in which they are commonly used in daily practice, supported by high-level evidence based on results of phase III clinical trials. This discrepancy may generate prescription and reimbursement obstacles as well as impaired access to established therapies.

Methods: A list of cancer medicines that remain off-label in specific indications despite the presence of high-level evidence was generated and subjected to European Society for Medical Oncology (ESMO) expert peer review to assess for accountability of reasonableness. These medicines were then surveyed on approval procedures and workflow impact. The most illustrative examples of these medicines were reviewed by experts from the European Medicines Agency to ascertain the apparent robustness of the supporting phase III trial evidence from a regulatory perspective.

Results: A total of 47 ESMO experts reviewed 17 cancer medicines commonly used off-label in six disease groups. Overall, high levels of agreement were recorded on the off-label status and the high quality of data supporting the efficacy in the off-label indications, often achieving high ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scores. When prescribing these medicines, 51% of the reviewers had to implement a time-consuming process associated with additional workload, in the presence of litigation risks and patient anxiety. Finally, the informal regulatory expert review identified only 2 out of 18 (11%) studies with significant limitations that would be difficult to overcome in the context of a potential marketing authorisation application without additional studies.

Conclusions: We highlight the common use of off-patent essential cancer medicines in indications that remain off-label despite solid supporting data as well as generate evidence on the adverse impact on patient access and clinic workflows. In the current regulatory framework, incentives to promote the extension of indications of off-patent cancer medicines are needed for all stakeholders.

Key words: off-label, ESMO-MCBS, EMA, cancer, ESMO Clinical Practice Guidelines

INTRODUCTION

Cancer is among the leading causes of death and an ongoing challenge for health care systems worldwide.[1] During the last decade, a plethora of new medicines have been approved by regulatory bodies for the treatment of neoplastic diseases and in most countries, medicines are reimbursed according to their labelling indication.[2,3] However, the off-label use of medicines is quite common, especially in oncology.[4] According to the results of an

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American Society of Clinical Oncology (ASCO) survey, ∼50% of patients with cancer have received chemotherapy in an off-label indication during their disease course.[5,6] At the same time, the off-label use of antineoplastic high-cost medicines is increasingly implemented based on identified plausible molecular targets, despite support of clinical benefit by low-level evidence only, or none.[7,8]

Interestingly, many 'old', off-patent and low-cost cancer medicines remain off-label for specific indications. Most of these medicines have new clinical applications based on large-scale phase III clinical trials, with sufficient scientific data to support their safety and effectiveness.[9] However, as manufacturers of these medicines that are now out of regulatory and patent protection lack financial incentive to proceed with a regulatory application for these new indications, these off-patent cancer therapeutics remain off-label.[9]

For example, oxaliplatin, formally approved for use in patients with colorectal cancer, is commonly administered in an off-label context for patients with localised and advanced gastric and pancreatic adenocarcinomas, based on survival benefits. This practice is supported by large, methodologically robust phase III clinical trials and is strongly endorsed by the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines recommendations.[10-13] Nevertheless, oxaliplatin has not been formally approved for the latter indications, and its application in FOLFIRINOX, FOLFOX, EOX, and FLOT combination regimens remains off-label.

This anomaly is sometimes the cause of prescription and reimbursement obstacles across different health care systems contributing to impaired access to cancer medicines, especially in health care settings that strictly limit medications' coverage to their licensed indications.[9] This is a far cry from the aspiration that product labelling should include 'all clinical indications for which adequate data are available to establish the product's safety and effectiveness.'[14]

Given the substantial lacunae in the licensed indications, professional organisations must fill the void in providing high-level evidence-based guidance. ESMO aimed to identify these 'old' and commonly used cancer medicines that remain off-label, despite strong evidence from robust, randomised phase III clinical trials.

In this manuscript, we describe this common scenario as 'off-label despite high-level evidence' (OLDE) and note that this mainly applies to off-patent or off-commercial protection medicines for which generic therapeutics are available in the market. Our four primary objectives were (i) to record the extent of this paradox in oncology therapeutics; (ii) to obtain the consensus of expert reviewers on the clinical value of OLDE medicines and verify their respective ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scores, where applicable; (iii) to crosscheck their inclusion in the ESMO Clinical Practice Guidelines and 21st World Health Organisation Model List of Essential Medicines (WHO EML); and finally (iv) to provide a *prima facie* regulatory assessment of the robustness of the main clinical evidence of efficacy supporting the extension of indications. The results aim to raise awareness of the issue and encourage marketing authorisation holders to seek clinical and regulatory advice from research groups, professional organisations and regulators in view of possible submission of evidence-based off-label applications to streamline indication extension, patient access, physician workflow, and sustainability of cancer care.

METHODS

Three expert authors developed a list of commonly used off-label anticancer agents (GP, GZ, and YM). The product labelling was reviewed for each therapeutic applied in the neoadjuvant, adjuvant, or metastatic setting across different neoplastic diseases using the following as reference documents: the summary of product characteristics on the electronic medicines compendium (EMC) providing up-to-date information about medicines licensed for use in the United Kingdom[15]; the European Medicines Agency (EMA) medicines database, providing information on all medicinal products that have been centrally authorised in Europe[3]; and several national formularies accessible online. References to randomised phase III trials supporting the off-label use of each medicine in a specific disease were retrieved from the ClinicalTrials.gov database,[16] expert opinion, and published literature in peer-reviewed medical journals. The ESMO staff (NL and MG) cross-checked the medications for inclusion in the ESMO Clinical Practice Guideline recommendations and the 21st WHO EML, where available.[13,17]

A library of 20 OLDE agents in eight disease groups containing all peer-reviewed publications was created and the preliminary ESMO-MCBS version 1.1[18,19]scores were calculated (NL and MG) and sent to expert evaluators, including biostatisticians (NIC, UD, and PZ), for validation. Studies not achieving a statistically significant benefit in their endpoints, as well as studies that did not meet ESMO-MCBS predefined criteria for evaluation, were designated as no evaluable benefit (NEB). ESMO-MCBS scores A and B in the adjuvant setting and scores 4 and 5 in the non-curative setting indicate medicines with substantial benefit.[18,19]

Five cancer medicines (commonly used in a total of nine off-label clinical contexts as defined by tumour type and stage) were excluded because of a lack of supportive evidence of efficacy and one because subsequently it was found not to be off-label.[20-27] The remaining 14 off-label cancer medicines across 6 disease groups (breast, gastrointestinal, genitourinary, gynaecological, head and neck, and thoracic cancers) for a total of 37 scenarios were subjected to an expert peer review process for accountability for reasonableness.[28]

Expert and regulatory peer review

The peer review was developed and conducted using the online tool Qualtrics.[29] Each reviewer provided feedback to a series of questions regarding the off-label indication under study (Supplementary Annex I, available at https://doi.org/10.1016/j.esmoop.2022.100604). The peer review was conducted by specialists in solid tumours drawn from the

ESMO-MCBS Working Group, ESMO Faculty, ESMO Guidelines Committee, ESMO Practicing Oncologists Working Group, and ESMO Young Oncologists Committee. A total of 76 reviewers from 23 countries were invited to participate (Supplementary Annex II, available at https://doi.org/10.1016/j.esmoop.2022.100604).

During the first peer review, participants were invited to suggest additional OLDE scenarios for evaluation. The aforesaid process was repeated for these additional medicines. Table 1 presents a summary of the final 17 off-patent cancer medicines reviewed across six disease groups, representing 42 scenarios.

After the results of the two peer reviews, an in-depth survey aiming to understand the challenges faced by medical oncologists when prescribing off-label generic cancer medicines despite the presence of high-level evidence was developed using again the online tool Qualtrics. The survey, which involved the initial reviewers with the addition of the ESMO National Society Committee members from the European Union 27 countries, consisted of two parts (Supplementary Annex III, available at https://doi.org/10.1016/j.esmoop.2022.100604): (i) administrative and regulatory challenges and (ii) daily workflow challenges. Where discrepancies within the same country were identified, two authors (MG and NL) contacted the reviewers to understand the source of the disagreement to support the robustness of the information provided.

As a final step, two regulatory experts (CV and FP) reviewed a 'plenary' list of OLDE medications to assess, based on the library of peer-reviewed publications, the *prima facie* robustness of the efficacy evidence. The review did not assess whether available efficacy evidence would be sufficient for a successful submission, but identified any visible uncertainties in selected publications that would likely constitute blocking issues according to generally agreed regulatory standards and would likely require additional studies to be submitted.

Figure 1 describes the development process to obtain the final list of commonly used off-label anticancer agents.

RESULTS

In total, 47 of the 76 (62%) invited experts completed the first round of reviews (for a total of 62 reviews) and 29 of the 36 (81%) invited experts completed the second round for the review of the additional 5 medicines (for a total of 38 reviews). Please note that in both rounds, reviewers could select and review more than one disease group. Out of the total 42 scenarios, 38 (91%) had an ESMO Clinical Practice Guideline for the same off-label indication, while only 12 (29%) were included in the 21st WHO EML (Tables 2-7).

Overview of results by disease group

Gastrointestinal cancers. Gastrointestinal cancers constitute the most representative group regarding the OLDE scenario. Six off-label medicines (capecitabine, cisplatin, gemcitabine, irinotecan, mitomycin, and oxaliplatin) had sufficient evidence for efficacy and safety to justify peer review inclusion, and were reviewed by 16 experts. These agents were well supported by robust phase III trials as confirmed by at least 79% and up to 100% of the experts depending on the scenario (Table 2).

In the perioperative as well as in the first-line treatment of patients with oesophagogastric cancer, combinations based on docetaxel, oxaliplatin, epirubicin, and capecitabine (EOX, FLOT) resulted in significant benefit in overall survival (OS), with an ESMO-MCBS version 1.1 score of 4 and A respectively.[12,30-31] Moreover, irinotecan has also been investigated in the context of a phase III trial as part of the FOLFIRI regimen in advanced gastric and gastroesophageal cancers and achieved similar outcomes to platinum-based therapy.[32]

Table 1. Overview of the off-label medicines submitted to peer review within their disease group

Medicine	Breast cancer	Gastrointestinal cancer	Genitourinary cancer	Gynaecological malignancies	Head and neck cancer	Thoracic cancer
Bisphosphonate	☑					
Capecitabine		☑				
Carboplatin	☑		☑	☑	☑	☑
Carboplatin and paclitaxel (TC)				☑		
Cisplatin	☑	☑				
Docetaxel			☑	☑		
Doxorubicin			☑			
Etoposide						☑
Gemcitabine		☑				
Irinotecan		☑				
Mitomycin		☑				
Oxaliplatin		☑				
Paclitaxel				☑	☑	
Pegylated liposomal doxorubicin + bevacizumab				☑		
Pemetrexed						☑
Vinblastine			☑			
Vinorelbine						☑

☑ The medicine is used off-label in that setting.

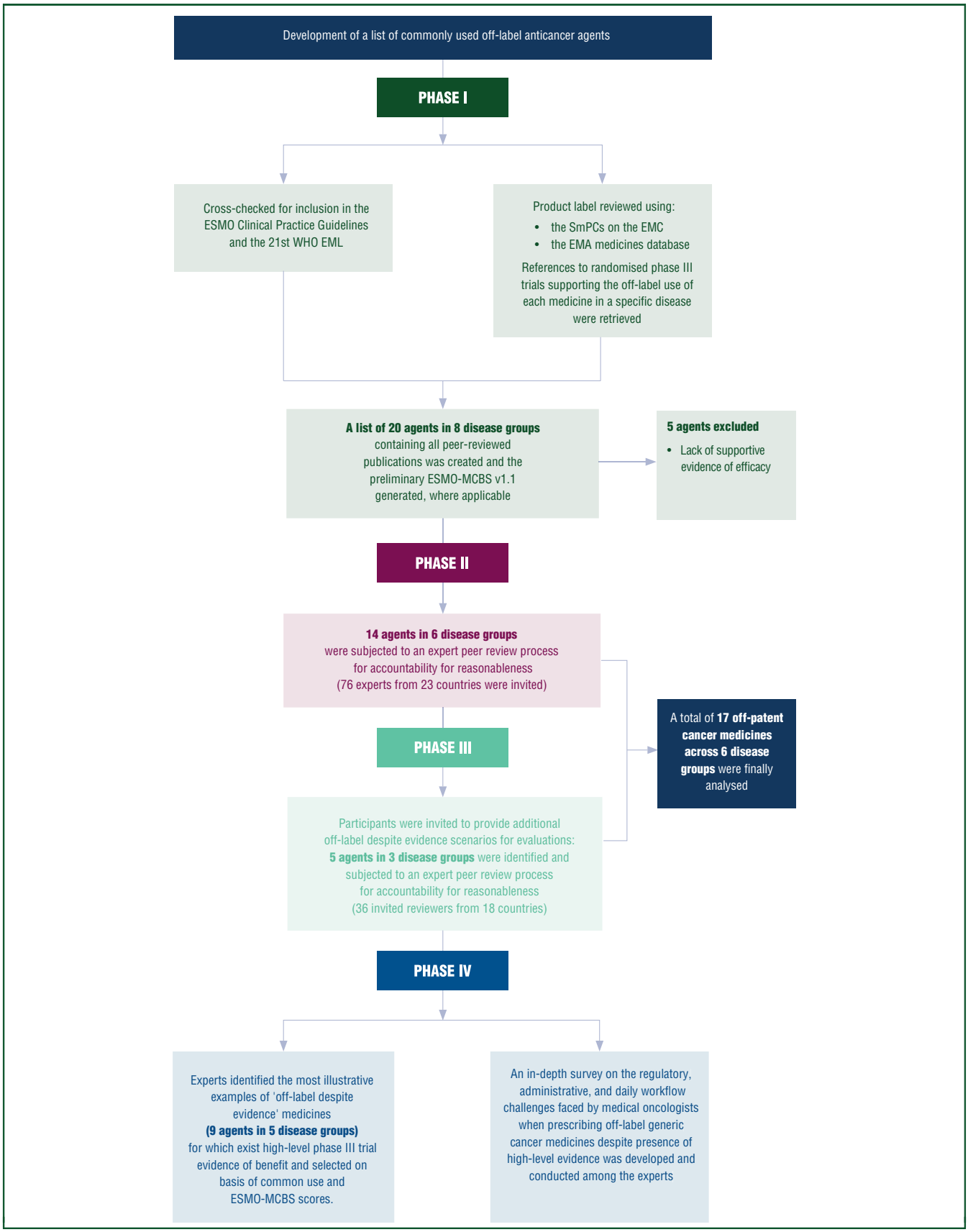

Figure 1. Overview of the methodology process.
EMA, European Medicines Agency; EMC, electronic medicines compendium; ESMO, European Society for Medical Oncology; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; SmPC, summary of product characteristics; WHO EML, World Health Organization Essential Medicines List.

Oxaliplatin and irinotecan, both components of the FOLFIRINOX regimen, have been granted an ESMO-MCBS version 1.1 score of A/4 and 5 in the adjuvant and advanced settings of pancreatic cancer respectively.[10,11] In addition, capecitabine combined with gemcitabine improved OS over gemcitabine monotherapy when used as adjuvant therapy in pancreatic cancer according to the ESPAC-4 trial, with an ESMO-MCBS version 1.1 score of A/1.[33]

Two additional clinical off-label scenarios in the gastrointestinal oncologic landscape stand out. First, a treatment with mitomycin plus 5-fluorouracil (5-FU) and radiotherapy was associated with low local failure and enhanced OS compared with radiotherapy alone in a randomised phase III trial enrolling patients with anal cancer (ESMO-MCBS version 1.1 score A), while mitomycin remains off-label for this indication.[34] Second, the use of capecitabine after resection of biliary adenocarcinoma proved effective with improved OS and disease-free survival (DFS) over observation in a prespecified sensitivity analysis of a randomised phase III study, whereas gemcitabine-based regimens provided survival gains in the first-line setting. Both medicines remain formally off-label for the treatment of biliary cancer even though included in current clinical practice guidelines [ESMO Clinical Practice Guideline and National Comprehensive Cancer Network (NCCN)].[13,35,37]

An overview of the results of the off-label medicines in gastrointestinal cancers is reported in Table 2.

Genitourinary cancers. In genitourinary cancers, four off-label medicines (carboplatin, docetaxel, doxorubicin, and vinblastine) had sufficient evidence to justify peer review inclusion and were reviewed by 7 experts (Table 3).

Based on a phase III trial that established non-inferiority of carboplatin to radiotherapy in stage I seminoma, 100% of the experts agreed that the medicine is off-label but supported by high evidence in this setting.[39] Furthermore, regarding the application of doxorubicin and vinblastine, components of the approved M-VAC regimen for patients with urothelial cancer in both the advanced and neoadjuvant disease settings, high levels of agreement among experts were recorded on the administration of these agents in an off-label setting (86% for advanced and 100% for neoadjuvant). A large clinical benefit was described with an ESMO-MCBS version 1.1 score of 4 in the advanced setting and A in the neoadjuvant setting of all four regimens.[21,40] Finally, 57% of surveyed experts apply docetaxel in cases of urothelial cancer, although off-label for this indication.[41]

An overview of the results of the off-label medicines in genitourinary cancers is reported in Table 3.

Thoracic cancers. In thoracic cancers, four off-label medicines (carboplatin, etoposide, pemetrexed, and vinorelbine) had sufficient evidence for efficacy and safety to justify peer review inclusion and were reviewed by 14 experts (Table 4).

For patients with resected non-small-cell lung cancer (NSCLC), the ESMO and NCCN guidelines suggest the use of adjuvant vinorelbine in combination with cisplatin based on the results of randomised phase III trials proving its effectiveness in improving DFS and OS over observation (ESMO-MCBS version 1.1 score A).[13,37,42-44] Over 90% of the experts agreed that there is high-level scientific evidence for the adjuvant administration of this combination in patients with resected stage II and IIIA NSCLC (Table 4). Etoposide provided significant OS advantage over observation when combined with cisplatin in the adjuvant setting of resected stages I, II, and III NSCLC (ESMO-MCBS version 1.1 score B).[45]

Carboplatin combined with paclitaxel or vinorelbine as adjuvant treatment of completely resected stage III NSCLC proved effective with DFS and OS benefit over observation (ESMO-MCBS version 1.1 score A).[46] Carboplatin in combination with docetaxel proved superior to cisplatin in combination with vinorelbine (ESMO-MCBS version 1.1 score 4).[47]

Finally, pemetrexed in combination with cisplatin has been tested in a superiority phase III trial in the setting of completely resected adjuvant stage II-IIIA nonsquamous NSCLC.[48] Although superiority has not been proven over cisplatin in combination with vinorelbine, in view of the similar clinical efficacy, the combination is recommended by current clinical practice guidelines for neoadjuvant and adjuvant therapy of nonsquamous NSCLC.[13,37] Again, a formal indication of pemetrexed in this setting is still lacking.

An overview of results of the off-label medicines in thoracic cancers is reported in Table 4.

Breast cancer. In breast cancer, three off-label medicines (bisphosphonates, carboplatin, and cisplatin) had sufficient evidence for efficacy and safety to justify peer review inclusion and were reviewed by 12 experts. The most representative scenario was carboplatin, with confirmation of the presence of solid data for its efficacy in the indication by 100% of experts. The phase III BCIRG 006 adjuvant trial of carboplatin plus docetaxel and trastuzumab compared with standard anthracycline plus cyclophosphamide, followed by docetaxel for patients with localised HER2-positive breast cancer, showed a 5-year OS benefit of 4% and a 5-year DFS benefit of 6% with fewer acute toxicity effects[51] (ESMO-MCBS version 1.1 score B; Table 5).

Cisplatin in combination with gemcitabine as first-line therapy for patients with triple-negative metastatic breast cancer reported a small but significant gain in progression-free survival (PFS) and a better-tolerated side-effect profile compared with paclitaxel plus gemcitabine according to the results of the phase III CBCSG 006 clinical trial (ESMO-MCBS version 1.1 score 2).[52]

Bisphosphonates were also reviewed.[53] According to results from well-powered meta-analyses of adjuvant trials, a clinically meaningful and statistically significant improvement in DFS and a reduction in bone recurrence were established in postmenopausal patients; 75% of the experts agreed that the medication is off-label and commonly used and 100% of them confirmed that high-level evidence in the literature supported bisphosphonates application.

Table 2. Gastrointestinal cancer off-label medicines

Commonly used off-label agent	Combined agent(s)	Comparator arm	Treatment setting	Trial name	Gain	ESMO-MCBS score	ESMO CPG in the same off-label indication	WHO EML in the same off-label indication	% Agreement medicine is off-label high evidence[b]	% Agreement medicine off-label and commonly used[c]	% Agreement medicine off-label but not commonly used[c]	% Agreement medicine is on-label[c]	Refs
Capecitabine	Gemcitabine	Gemcitabine	Adjuvant treatment after complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection)	ESPAC-4	OS: 2 years 1.7% 2.5 months OS: 3 years >5% from KM	A (Form 1) 1 (Form 2a)	Yes	No	100	75	18.8	6.2	33
Capecitabine		Observation	Adjuvant biliary adenocarcinoma	BILCAP	OS: 14.7 months (per protocol 17 months, >5% gain at 5 years) DFS: 6.9 months 2 years >5%	NEB	Yes	No	93.8	81.2	18.8	0	35
Cisplatin	5-FU, with or without two courses of maintenance chemotherapy	Mitomycin with 5-FU, with or without two courses of maintenance chemotherapy	Treatment of locally advanced squamous-cell carcinoma of the anus	ACT II	PFS HR NS	NEB	Yes	No	78.5	35.7	64.3	0	38
Gemcitabine	Cisplatin	Gemcitabine	First-line locally advanced or metastatic biliary adenocarcinoma	ABC-02	OS: 3.6 months	4 (Form 2a)	Yes	No	93.8	81.2	6.3	12.5	36
Irinotecan	5-FU, leucovorin, oxaliplatin	Gemcitabine	Adjuvant treatment for resected pancreatic ductal adenocarcinoma	NCT01526135	OS: 19.4 months 3 years 14.8% DFS: 8.8 months 3 years 18.3%	A (Form 1) 4 (Form 2a)	Yes	No	100	81.2	18.8	0	10
Irinotecan	5-FU, leucovorin, oxaliplatin	Gemcitabine	First-line metastatic pancreatic cancer	NCT00112658	OS: 4.3 months	5 (Form 2a)	Yes	No	100	87.6	6.2	6.2	11
Irinotecan	5-FU + leucovorin (FOLFIRI)	Epirubicin, cisplatin, and capecitabine (ECX)	First-line advanced gastric and gastro-oesophageal junction cancers, planned crossover	NCT00374036	TTF: 0.9 months PFS: 0.45 months OS: −0.23 months	NEB	Yes	No	85.7	43.8	50	6.2	32
Mitomycin	5-FU and radiotherapy	Radiotherapy	Standard treatment for most patients with epidermoid anal cancer should be a combination of radiotherapy and infused 5-FU and mitomycin, with surgery reserved for those who fail on this regimen		OS: 7% LFR: 23%	A[a] (Form 1)	Yes	Medicine not on the WHO EML	100	75	18.8	6.2	34
Mitomycin	5-FU and radiotherapy	Radiotherapy	Treatment of locally advanced epidermoid carcinoma of the anus		LFR: 22%	A (Form 1)	Yes	Medicine not on the WHO EML	92.8	78.5	0	21.5	34
Oxaliplatin	5-FU, leucovorin, docetaxel (FLOT)	Epirubicin and cisplatin plus fluorouracil (ECF) or epirubicin, cisplatin, and capecitabine (ECX)	Perioperative treatment of localised gastric cancer	FLOT-4	OS at 3-years 9%	A (Form 1)	Yes	No	NPR	NPR	NPR	NPR	30-31
Oxaliplatin	Epirubicin + capecitabine	Epirubicin and cisplatin + 5-FU	First-line advanced oesophagogastric cancer	REAL-2	OS: 1.3 months	4 (Form 2c)	Yes	No	87.5	75	25	0	12

Continued

Table 2. Continued

Commonly used off-label agent	Combined agent(s)	Comparator arm	Treatment setting	Trial name	Gain	ESMO-MCBS score	ESMO CPG in the same off-label indication	WHO EML in the same off-label indication	% Agreement medicine is off-label high evidence[b]	% Agreement medicine off-label and commonly used[c]	% Agreement medicine off-label but not commonly used[c]	% Agreement medicine is on-label[c]	Refs
Oxaliplatin	5-FU, leucovorin, irinotecan	Gemcitabine	Adjuvant treatment for resected pancreatic ductal adenocarcinoma	NCT01526135	OS: 19.4 months 3 years 14.8% DFS: 8.8 months 3 years 18.3%	A (Form 1) 4 (Form 2a)	Yes	No	100	87.6	6.2	6.2	[10]
Oxaliplatin	5-FU, leucovorin, irinotecan	Gemcitabine	First-line metastatic pancreatic cancer	NCT00112658	OS: 4.3 months	5 (Form 2a)	Yes	No	100	81.2	12.6	6.2	[11]

5-FU, 5-fluorouracil; DFS, disease-free survival; ESMO CPGs, ESMO Clinical Practice Guidelines; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; HR, hazard ratio; ITT, intention to treat; KM, Kaplan–Meier; LFR, local failure rate; NEB, no evaluable benefit; NPR, not peer reviewed; NS, not significant; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival; TTF, time to treatment failure; WHO EML, World Health Organisation Model List of Essential Medicines (2019).
The off-label medicines in gastrointestinal cancers were reviewed by 16 experts.
[a]ESMO-MCBS version 2 was used to generate the score.
[b]Only positive responses are reported in this column: % of agreement on whether the medicine is off-label and with high evidence (e.g. 15/16, 93.8%).
[c]These three columns report the answers to the same question 'Please verify that the above medicine is off-label but it is common practice to use in the above indication'. The sum of the answers equals 100%.

An overview of the results of the off-label medicines in breast cancer is reported in Table 5.

Gynaecological cancers. In gynaecological malignancies, four off-label medicines (carboplatin, docetaxel, paclitaxel, and pegylated liposomal doxorubicin) had sufficient supportive evidence for efficacy and safety to justify peer review inclusion. The experts' agreement on their OLDE designation ranged from 80% to 100% (eight experts; Table 6).

The combination of carboplatin plus paclitaxel added to radiotherapy in the adjuvant treatment of patients with endometrial carcinoma provided a 5-year OS benefit of 5.3% compared with radiation alone in PORTEC-3, a randomised phase III study (ESMO-MCBS version 2.0 score B).[55] This trial was not scorable using ESMO-MCBS version 1.1, thus ESMO-MCBS version 2 (although not yet published) was used to provide the score. There is also adequate supportive data for the use of this combination as first-line treatment of advanced or recurrent endometrial cancer (GOG0209 study with ESMO-MCBS version 1.1 score 4).[56] All the experts agreed that carboplatin use for adjuvant or advanced endometrial cancer is supported by robust clinical trial data and used by >80% of them in their daily practice. Paclitaxel, when added to a doxorubicin plus cisplatin regimen, has shown robust efficacy in stage III or stage IV endometrial cancer in a phase III trial,[57] with ESMO-MCBS version 1.1 score of 3. Over 80% of experts confirmed the existence of high-level evidence for taxanes in various settings in the therapeutic armamentarium of common gynaecological cancers. Pegylated liposomal doxorubicin in combination with bevacizumab provided an OS of 4 months over the combination of carboplatin plus gemcitabine and bevacizumab in relapsed ovarian or peritoneal cancer but still off-label.[58]

An overview of the results of the off-label medicines in gynaecological malignancies is reported in Table 6.

Head and neck cancers. In head and neck cancers, five experts reviewed two off-label medicines (carboplatin and paclitaxel) having sufficient supportive evidence to justify peer review inclusion (Table 7).

Carboplatin is occasionally used for patients ineligible for cisplatin therapy and although evaluated in the context of a phase III trial establishing the superiority of carboplatin plus 5-FU over methotrexate monotherapy in patients with advanced disease, it is not approved for use in this indication. According to the experts' response, 60% agreed that carboplatin qualifies as OLDE for the relevant indication.[60] Furthermore, paclitaxel was also confirmed as an off-label medicine with high-level evidence for efficacy with 60% of agreement among the experts. It has been tested in combination with cisplatin and achieved similar efficacy to cisplatin plus 5-FU in previously untreated extensive locoregional or metastatic disease. Of note, the phase III trial did not incorporate a non-inferiority design, rather it was a superiority study in which paclitaxel plus cisplatin as investigational therapy failed to show superiority over the control arm. Consequently, no ESMO-MCBS score can be derived.[25]

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Table 3. Genitourinary cancer off label medicines

Commonly used off-label agent	Combined agent(s)	Comparator arm	Treatment setting	Trial name	Gain	ESMO-MCBS score	ESMO CPG in the same off-label indication	WHO EML in the same off-label indication	% Agreement medicine is off-label high evidence[a]	% Agreement medicine off-label and commonly used[b]	% Agreement medicine off-label but not commonly used[b]	% Agreement medicine is on-label[b]	Refs
Carboplatin		Radiotherapy	Adjuvant stage I seminoma testicular cancer	MRC TE 19/ EORTC 30982	RFS: 5 years —1.30%	B (Form 1)	Yes	Yes	100	57.2	14.4	28.4	[39]
Docetaxel			Platinum-resistant locally advanced or metastatic urothelial cancer		DoR: 6 months ORR: 31%	2 (Form 3)	No	No	42.8	57.2	28.4	14.4	[41]
Doxorubicin	Cisplatin, methotrexate, vinblastine	Surgery alone (radical cystectomy)	Neoadjuvant locally advanced muscle-invasive bladder cancer stage T2 to T4a		OS: 5 years 14% 31 months	A (Form 1)	Yes	No	100	42.8	42.8	14.4	[40]
Doxorubicin	Cisplatin, methotrexate, vinblastine	Cisplatin	First-line advanced urothelial cancer		OS: 4.3 months PFS: 5.7 months	4 (Form 2a)	Yes	No	85.8	42.8	42.8	14.4	[21]
Vinblastine	Cisplatin, doxorubicin, methotrexate	Surgery alone (radical cystectomy)	Neoadjuvant locally advanced muscle-invasive bladder cancer stage T2 to T4a		OS: 5 years 14% 31 months	A (Form 1)	Yes	No	100	42.8	42.8	14.4	[40]
Vinblastine	Cisplatin, methotrexate, doxorubicin	Cisplatin	First-line advanced urothelial cancer		OS: 4.3 months PFS: 5.7 months	4 (Form 2a)	Yes	No	85.8	42.8	42.8	14.4	[21]

DoR, duration of response; ESMO CPGs, ESMO Clinical Practice Guidelines; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; WHO EML, World Health Organisation Model List of Essential Medicines (2019).

The off-label medicines in genitourinary cancers were reviewed by seven experts.

[a]Only positive responses are reported in this column: % of agreement on whether the medicine is off-label and with high evidence (e.g. 3/7, 42.8%).

[b]These three columns report the answers to the same question 'Please verify that the above medicine is off-label but it is common practice to use in the above indication'. The sum of the answers equals 100%.

Table 4. Thoracic cancer off-label medicines

Commonly used off-label agent	Combined agent(s)	Comparator arm	Treatment setting	Trial name	Gain	ESMO-MCBS score	ESMO CPG in the same off-label indication	WHO EML in the same off-label indication	% Agreement medicine is off-label high evidence[a]	% Agreement medicine off-label and commonly used[b]	% Agreement medicine off-label but not commonly used[b]	% Agreement medicine is on-label[b]	Other	Ref
Carboplatin	Vinorelbine or paclitaxel	Observation	Completely resected adjuvant stage IIIA-N2 NSCLC		OS: 9.0 months 3-year survival 9.2% 5-year survival 12% DFS: 12.0 months 3-year survival 17.5% 5-year survival 3.2%	A (Form 1)	Yes	Yes	78.6	35.7	21.4	28.6	14.3	46
Carboplatin	Docetaxel	Cisplatin + vinorelbine	Advanced stage IIIB IV NSCLC	TAX 326	OS: NEB −0.5 months 4% gain	4 (Form 2c)	Yes	Yes	78.6	21.4	35.7	35.7	7.2	47
Carboplatin	Gemcitabine	Cisplatin plus gemcitabine	Advanced stage IIIB IV NSCLC		OS: NS	NEB	Yes	Yes	92.9	28.6	35.7	35.7	0	49
Etoposide	Cisplatin	Observation	Stage IB, II, III adjuvant NSCLC	IALT	OS: 5-year survival 4.1% DFS:5-year survival 5.1%	B (Form 1)	Yes	Yes	100	28.6	42.8	28.6	0	45
Etoposide	Cisplatin	Paclitaxel + carboplatin	Unresectable adjuvant stage III NSCLC	NCT01494558	OS: 2.6 months 3-year survival 15.1% 5-year survival 8.3% ORR: 9.2%	NEB	Yes	Yes	50	28.6	42.8	28.6	0	50
Pemetrexed	Cisplatin	Vinorelbine + cisplatin	Completely resected adjuvant stage II-IIIA nonsquamous NSCLC	JIPANG	RFS: 1.6 months	NEB	Yes	Medicine not on the WHO EML	85.7	35.7	57.2	0	7.1	48
Vinorelbine	Cisplatin	Observation	Completely resected adjuvant stage IB, II NSCLC	JBR.10	OS: 21.0 months 5-year survival 15% RFS: not reached	A (Form 1)	Yes	Yes	92.9	28.6	21.4	50	0	42
Vinorelbine	Cisplatin	Observation	Completely resected adjuvant stage IB, II NSCLC	JBR.10	OS: 5-year survival 11%	A (Form 1)	Yes	Yes	92.9	28.6	21.4	50	0	43
Vinorelbine	Cisplatin	Observation	Completely resected adjuvant stage IB, II, IIIA NSCLC	ANITA	OS: 22.0 months 5-year survival 8.6% DFS: 15.6 months	A (Form 1)	Yes	Yes	92.9	42.8	14.4	42.8	0	44

DFS, disease-free survival; ESMO CPGs, ESMO Clinical Practice Guidelines; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; HR, hazard ratio; NEB, no evaluable benefit; NS, not significant; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; RFS, relapse-/recurrence-free survival; WHO EML, World Health Organisation Model List of Essential Medicines (2019).

The off-label medicines in thoracic cancers were reviewed by 14 experts.

[a]Only positive responses are reported in this column: % of agreement on whether the medicine is off-label and with high evidence (e.g. 11/14, 78.6%)

[b]These three columns report the answers to the same question 'Please verify that the above medicine is off-label but it is common practice to use in the above indication'. The sum of the answers equals 100%.

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Table 5. Breast cancer off-label medicines

Commonly used off-label agent	Combined agent(s)	Comparator arm	Treatment setting	Trial name	Gain	ESMO-MCBS score	ESMO CPG in the same off-label indication	WHO EML in the same off-label indication	% Agreement medicine is off-label high evidence[a]	% Agreement medicine off-label and commonly used[b]	% Agreement medicine off-label but not commonly used[b]	% Agreement medicine is on-label[b]	Refs
Bisphosphonate		Observation	Adjuvant treatment in early breast cancer	EBCTCG meta-analysis	OS: 1.5% HR NS	NEB	Yes	Medicine not on the WHO EML	66.7	75	25	0	[53]
Bisphosphonate		Observation	Adjuvant early BC postmenopausal	EBCTCG meta-analysis	OS: 2.40%	C (Form 1)	Yes	Medicine not on the WHO EML	100	75	25	0	[53]
Carboplatin	Docetaxel + trastuzumab	Doxorubicin + cyclophosphamide followed by docetaxel	HER2+ BC with addition of 1-year adjuvant trastuzumab plus TCH regimen	BCIRG006	OS: 4% 5 years DFS: 6% 5 years DFS: 6% 3 years	B (Form 1)	Yes	Yes	100	83.3	16.7	0	[51]
Carboplatin	Docetaxel + trastuzumab	Doxorubicin + cyclophosphamide followed by docetaxel + trastuzumab	HER2+ BC with addition of 1-year adjuvant trastuzumab plus TCH regimen	BCIRG006	OS: −1% 5 years DFS: −3% 5 years, −1% 3 years	NEB	Yes	Yes	91.6	83.3	16.7	0	[51]
Carboplatin	Anthracycline/taxane or taxane	Anthracycline/taxane	TNBC, neo adjuvant	Meta-analysis	pCR: 13%	NEB	Yes	Yes	66.7	66.7	33.3	0	[54]
Cisplatin	Gemcitabine	Paclitaxel + gemcitabine	TNBC, first-line therapy	CBCSG006	PFS: 1.26 months	2 (Form 2b)	No	No	61.6	33.3	66.7	0	[52]
Cisplatin	Anthracycline/taxane or taxane	Anthracycline/taxane	TNBC, neoadjuvant	Meta-analysis	pCR: 13%	NEB	No	No	58.4	33.3	58	8.7	[54]

BC, breast cancer; DFS, disease-free survival; ESMO CPGs, ESMO Clinical Practice Guidelines; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NEB, no evaluable benefit; NS, not significant; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; QoL, quality of life; TCH, docetaxel, carboplatin combined with trastuzumab; TNBC, triple-negative breast cancer; WHO EML, World Health Organisation Model List of Essential Medicines (2019).

The off-label medicines in breast cancer were reviewed by 12 experts.

[a]Only positive responses are reported in this column: % of agreement on whether the medicine is off-label and with high evidence (e.g. 8/12, 66.7%).

[b]These three columns report the answers to the same question 'Please verify that the above medicine is off-label but it is common practice to use in the above indication'. The sum of the answers equals 100%.

Table 6. Gynaecological malignancies off-label medicines

Commonly used off-label agent	Combined agent(s)	Comparator arm	Treatment setting	Trial name	Gain	ESMO-MCBS score	ESMO CPG in the same off-label indication	WHO EML in the same off-label indication	% Agreement medicine is off-label high evidence[b]	% Agreement medicine off-label and commonly used[c]	% Agreement medicine off-label but not commonly used[c]	% Agreement medicine is on-label[c]	Refs
Carboplatin	Paclitaxel + radiotherapy	Pelvic radiotherapy alone	Adjuvant high-risk endometrial cancer combined ChT and radiotherapy	PORTEC3	OS: 5-years 5.3% FFS 5-years 7.4%	B[a] (Form 1)	No	No	100	87.5	12.5	0	55
Carboplatin and paclitaxel		Cisplatin + doxorubicin + paclitaxel	Advanced stage III, stage IV, and recurrent endometrial cancers	GOG0209	OS non inferiority confirmed (primary outcome) and improved toxicity and QoL	4 (Form 2c)	Yes	No	100	80	0	20	56
Docetaxel	Carboplatin	Paclitaxel + carboplatin	First-line ChT advanced epithelial ovarian or primary peritoneal cancer stage 1c-IV		PFS: 0.2 months PFS HR NS	NEB	Yes	No	87.5	0	87.5	12.5	59
Paclitaxel	Doxorubicin + cisplatin with filgrastim support	Doxorubicin + cisplatin	ChT-naïve women with histologically documented measurable stage III, stage IV, or recurrent endometrial carcinoma		OS: 3.0 months PFS: 3.0 months	3 (Form 2a)	Yes	No	87.5	50	50	0	57
Pegylated liposomal doxorubicin + bevacizumab	Carboplatin	Carboplatin + gemcitabine + bevacizumab	First-relapse platinum sensitive (epithelial ovarian, primary peritoneal, or Fallopian tube carcinoma with first disease recurrence >6 months after first platinum-based ChT)		PFS: 1.7 months OS: 4.1 months	2 (Form 2a)	Yes	Medicine not on the WHO EML	80	30	30	40	58

ChT, chemotherapy; ESMO CPGs, ESMO Clinical Practice Guidelines; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FFS, failure-free survival; HR, hazard ratio; NEB; no evaluable benefit; NS, not significant; OS, overall survival; PFS, progression-free survival; QoL, quality of life; WHO EML, World Health Organisation Model List of Essential Medicines (2019).

The off-label medicines in gynaecological malignancies were reviewed by eight experts.

[a]ESMO-MCBS version 2 used to generate the score.

[b]Only positive responses are reported in this column: % of agreement on whether the medicine is off-label and with high evidence (e.g. 7 out of 8 (87.5%)).

[c]These three columns report the answers to the same question 'Please verify that the above medicine is off-label but it is common practice to use in the above indication'. The sum of the answers equals 100%.

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Table 7. Head and neck cancer off-label medicines

Commonly used off-label agent	Combined agent(s)	Comparator arm	Treatment setting	Gain	ESMO-MCBS score	ESMO CPG in the same off-label indication	WHO EML in the same off-label indication	% Agreement medicine is off-label high evidence[a]	% Agreement medicine off-label and commonly used[b]	% Agreement medicine off-label but not commonly used[b]	% Agreement medicine is on-label[b]	Other	Refs
Carboplatin	5-FU	Methotrexate	First-line advanced squamous cell head and neck cancer	RR: 11%	1 (Form 2c)	Yes	No	60	20	20	40	20	[60]
Paclitaxel	Cisplatin	Cisplatin + 5-FU	Previously untreated extensive locoregional disease or distant metastases, and those with previously treated disease and subsequent locoregional recurrence, persistent disease, or distant metastases squamous cell head and neck cancer	Median OS: −0.6 months	NEB	Yes	No	60	20	40	20	20	[25]

5-FU, 5-fluorouracil; ESMO CPGs, ESMO Clinical Practice Guidelines; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; HR, hazard ratio; NEB, no evaluable benefit; OS, overall survival; RR, response rate; WHO EML, World Health Organisation Model List of Essential Medicines (2019).
The off-label medicines in head and neck cancers were reviewed by five experts.
[a]Only positive responses are reported in this column: % of agreement on whether the medicine is off-label and with high evidence (e.g. 3/5, 60%).
[b]These three columns report the answers to the same question 'Please verify that the above medicine is off-label but it is common practice to use in the above indication'. The sum of the answers equals 100%.

An overview of the results of the off-label medicines in head and neck cancers is reported in Table 7.

In Supplementary Annex IV, available at https://doi.org/10.1016/j.esmoop.2022.100604, we report the most illustrative examples of OLDE medicines reviewed for which high-level phase III trial evidence and high ESMO-MCBS scores have been identified and confirmed by the experts.

Survey on administrative, regulatory, and daily workflow challenges

In >60% of surveyed countries, the off-label use of off-patent cancer medicines was regulated/reimbursed by National Medicine Agencies, often in conjunction with other regulatory bodies, the hospital, or the patient's insurance (Figure 2). According to 45% of respondents, the main prerequisite for requesting off-label use of cancer medicines was the optimised access of patients to effective treatments with fulfilment of unmet medical needs. Other reasons included high clinical evidence for efficacy and safety (42%) and potential economic advantage (13%).

Approximately 51% of responders had to implement a distinct specific administrative process to use cancer medicines in a clinical indication that remains off-label despite supporting high-level clinical evidence. The majority (74%) of the responders were willing to apply this process, whereas the rest were reluctant due to its time-consuming nature, need for supporting documentation, often a low rate of approval, and fear of litigation. In addition, 59% of physicians were responsible for implementing the logistical tasks related to this process without administrative support, despite time constraints and heavy clinical workload. The time for obtaining a response from application was on average 1-2 weeks. Substantial heterogeneity of processes within countries was observed due to (i) the context of practice (e.g. private versus public hospital), (ii) national and regional differences in processes and regulations, (iii) the frequency of use and cost of the medicine in the off-label indication.

More than 74% of respondents affirmed that they needed patient consent and >66% had to acknowledge and assume legal responsibility for potential patient harm when prescribing an off-label cancer medicine. Patient perceptions of the application process are depicted in Figure 2 together with an overview of the survey results.

Regulatory assessment of plenary OLDE scenarios

A *prima facie* regulatory review of the most illustrative examples of OLDE (9 medicines in 5 disease settings for a total of 18 scenarios, selected on basis of common use and ESMO-MCBS scores) identified two studies having critical uncertainties, with the need for additional data for an eventual extension of indication: a phase III study evaluating adjuvant capecitabine in resected biliary adenocarcinoma and a phase III trial assessing the combination of etoposide with cisplatin in unresectable stage III NSCLC, both not scorable with ESMO-MCBS (see Supplementary Annex IV, available at https://doi.org/10.1016/j.esmoop.

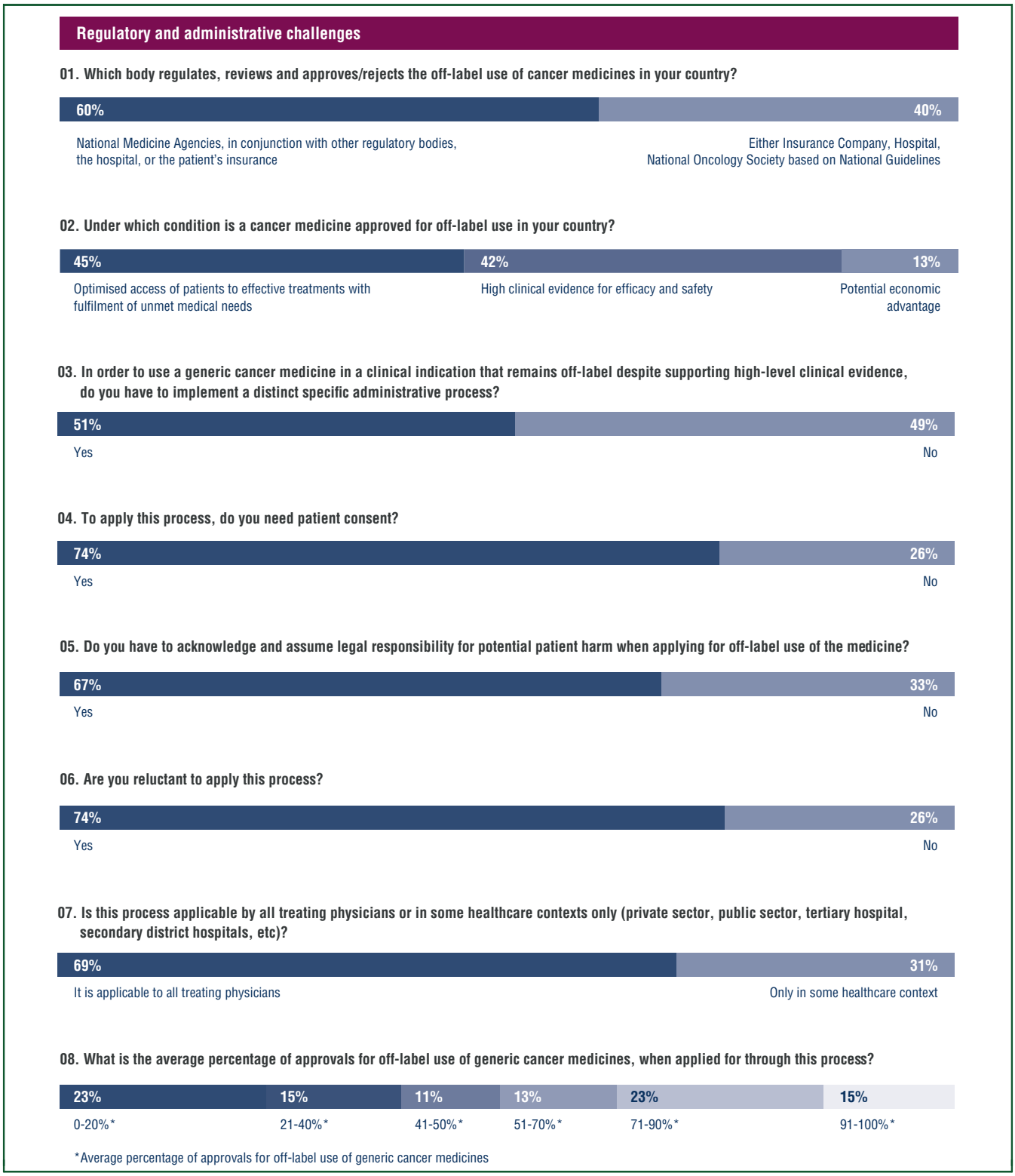

Figure 2. Overview of results of the survey on administrative, regulatory, and daily workflow challenges.

2022.100604).[35,50] The uncertainties were mainly related to the fact that the respective trials did not meet their primary endpoint in the intention-to-treat population. Uncertainties were identified in seven other scenarios (39%), including statistical limitations, failure to prove noninferiority, heterogeneous study populations, or immature study data.[33-34,42-43,48,51,55] However, the latter were considered likely to be resolved with further data scrutinisation from the existing studies, additional analyses, or through appropriate labelling changes. For example, limited evidence for a treatment effect in a specific subpopulation could potentially be resolved by restricting the finally approved

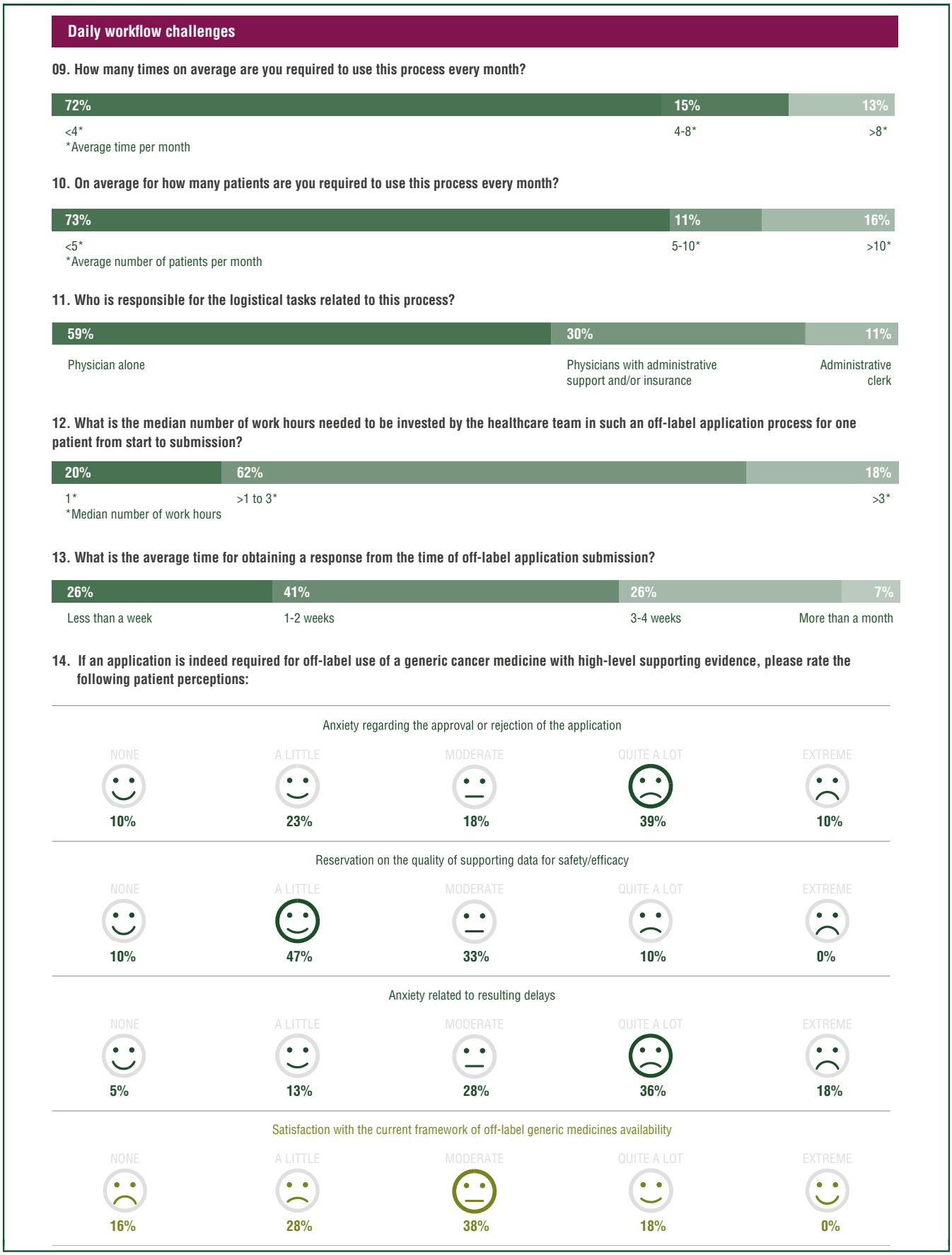

Figure 2. **Continued.**

indication. Notably, nine scenarios in which well-known authorised anticancer agents were studied in an off-label indication did not flag any obvious critical issues from a preliminary regulatory perspective in the current review.[10-11,30-31,39,44,47,56]

DISCUSSION

In this study, we were able to identify a number of 'old' cancer medicines that remain off-label for their use in specific settings, despite rigorous scientific evidence based on generally agreed scientific standards. For most medicines questioned, the reviewers affirmed that although off-label, they are commonly used in their country due to high-level evidence for the respective off-label indications. This was further supported by observed high ESMO-MCBS scores in those clinical scenarios representing substantial clinical benefit.

Our study highlights the administrative and/or liability burdens associated with the prescription of these medicines in many of the health care systems surveyed. Upon prescribing an off-label medicine, the treating physician is often burdened with increased bureaucratic and operational workload and a legal liability, potentially demotivating the prescription of the medicine. If approval for the use of the medicine is required by regulatory health care bodies or health insurance companies on a per-patient basis, the process often affects workflows, sometimes affects reimbursement policies and, if negative, deprives the patient of a safe and effective therapy.[9]

When results from large randomised phase III clinical trials indicate that an authorised medicinal product is safe and effective for use in a new therapeutic indication, a regulatory application for extension of indication should follow.[9,61-63] Although such applications would trigger a comprehensive assessment of all the available evidence and ensure adequate labelling and conditions of use, the lack of financial and market incentives demotivates manufacturers of these now generic medicines from investing in such a pathway. While not aiming to replace or pre-empt a formal regulatory assessment, our *prima facie* review of the main publications found that most of the studies published for this selected group of well-known, authorised, anticancer products used off-label did not appear to trigger any major issues from a clinical or regulatory perspective. Accordingly, applicant companies are encouraged to seek early regulatory advice in case of applications where the main evidence of efficacy is based on robust, randomised academic trials, to ensure strengths, gaps, and remedial steps are timely identified.

In Europe, several initiatives have been established to support patient access to already authorised medicinal products that are out of basic patent and regulatory protection and for which relevant data exist and/or may need to be further generated to support a new indication outside their authorisation, where research has shown value to the patient. For example, the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) created a framework proposal to support not-for-profit and academic stakeholders who have evidence and scientific rationale for a new therapeutic indication in bringing this new indication 'on-label', in collaboration with a commercial entity applying for marketing authorisation.[64] Currently, a pilot is ongoing, with more information available on the EMA web page.[64] Furthermore, the EMA is committed to supporting the development and implementation of a repurposing framework, as expressed as part of the agency's 'Regulatory science to 2025' strategy.[65]

In the ever-changing landscape of contemporary oncology therapeutics, there are common, off-label medicine uses with sufficient scientific evidence to justify regulatory submission. As EMA applications for extension of indication have to be submitted by the pharmaceutical companies that hold the marketing authorisation, the results of our study emphasise the need to streamline the legal/regulatory framework. This would facilitate the update of indications of 'old', off-patent medicines based on results from academic or independent clinical trials and empower the clinicians to fulfil their mission, making all valid treatment options optimally available to patients.

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