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Editorial

United Kingdom and Ireland Oesophagogastric Cancer Group Cancer Update 2023

M.E. Booth [*1], H.A. Clements [†1], J. Helbrow [‡], M.A. Baxter [†], C.W. Bleaney [§], M.A. Hawkins [¶], S.R. Markar [||], C.J. Peters [**], E.C. Smyth [††], T.D.L. Crosby [‡‡] on behalf of the UK and Ireland Oesophagogastric Cancer Group

[*] *Leeds Teaching Hospitals NHS Trust, Leeds, UK*
[†] *Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK*
[‡] *South West Wales Cancer Centre, Swansea Bay University Health Board, Swansea, UK*
[§] *Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK*
[¶] *Department of Medical Physics and Biomedical Engineering, University College London, UK*
[||] *Nuffield Department of Surgical Sciences, University of Oxford, UK*
[**] *Department of Surgery and Cancer, Imperial College London, UK*
[††] *Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford, UK*
[‡‡] *Velindre University NHS Trust, Cardiff, UK*

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Introduction

Oesophagogastric (OG) cancer accounts for 4% of cancer incidence in the UK, with approximately 16,000 new cases per year, but is a less survivable cancer, causing 1 in 12 cancer deaths [1,2]. This poses a significant challenge to patients and healthcare providers. Recent research in OG cancer has focused on precision oncology, i.e. selecting the right treatment for the right patient. Studies have demonstrated improved outcomes with immune checkpoint inhibitors, targeted agents, advanced radiotherapy techniques, and multimodal treatments in selected patient cohorts in both adenocarcinoma and squamous cell carcinoma (SCC) histological subtypes [3]. Here, we present an overview of key advancements in the treatment of OG cancers from 2023. We discuss how the results of recent studies may impact practice and look ahead at the evolving OG cancer horizon.

United Kingdom and Ireland Oesophagogastric Cancer Group

The United Kingdom and Ireland Oesophagogastric Cancer Group (UKIOG, www.ukiog.co.uk) is a not-for-profit organisation formed in 2021 and registered as a charity in 2022 (registered charity number 1198358) with the aim to improve the care of oesophagogastric cancer patients in the United Kingdom and Ireland [4]. It is a multidisciplinary group that brings together the various professionals involved in the care of these patients, as well as patient representatives, to try and identify best practice, harmonise clinical pathways, and ultimately improve patient outcomes. It has a number of aims, including- 1) promoting best practice, 2) education and training, 3) patient advocacy and support, and 4) promoting access to high-quality research. It achieves its aims via a multipronged approach including the organisation of virtual national multidisciplinary teams to discuss complex cases and the learning points from these, a yearly face-to-face meeting, as well as standalone events such as UKIOG Cancer Update 2023, which was the foundation of this editorial and is hoped to be a recurring annual update of advances in OG cancer research. Since the National Cancer Research Institute (NCRI) is no longer

Author for correspondence: H.A. Clements, Division of Molecular and Clinical Medicine, Ninewells Hospital & Medical School, James Arrott Drive, Dundee, DD1 9SY, UK.
E-mail address: hollie.clements1@nhs.net (H.A. Clements).
[1] MEB and HAC are joint first authors.

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in operation, UKIOG has created a research committee which can help support the development of new research proposals and endorse those felt to be of value to the wider community. In addition, the goal is for UKIOG to have a role in advocacy and support, making a strong case for the development of better services for OG cancer patients.

Systemic Treatments

In 2023, progress has been made in the availability of biomarker-targeted therapy for advanced disease, both in human epidermal growth factor 2 (HER2)-positive and HER2-negative disease (Table 1).

A New Standard of Care for human epidermal growth factor 2/programmed death ligand 1 Positive Disease

For patients with advanced HER2-positive cancer, representing 20%–30% of patients with gastric and gastro-oesophageal junctional (GOJ) adenocarcinoma [5,6], the previous standard of care was platinum-based cytotoxic chemotherapy administered with the anti-HER2 antibody trastuzumab [7]. Most HER2-positive tumours are also programmed death ligand 1 (PD-L1) positive [8], providing rationale for combining trastuzumab with an immune checkpoint inhibitor (ICI) in KEYNOTE-811 [9]. In the interim analysis, the addition of the PD-1 inhibitor pembrolizumab resulted in an improved response rate (72.6% vs 59.8%). The trial met a coprimary endpoint for progression-free survival (PFS) benefit in all patients but did not improve overall survival (OS) in the group, including PD-L1 positive and negative patients. However, for double-positive (HER2 and PD-L1) patients, there was a clinically meaningful improvement in OS of 4.3 months. Consequently, the triplet combination of chemotherapy, trastuzumab, and pembrolizumab should be considered a new standard of care for HER2/PD-L1-positive patients. It has been approved by the Food and Drug Administration and is currently under review by the National Institute for Health and Care Excellence for funding in the UK.

Human epidermal growth factor 2 Positive Disease: 2nd Line

In HER2-positive disease, following progression on a trastuzumab-containing regimen, the use of the antibody-drug conjugate trastuzumab-deruxtecan in those who remain HER2-positive on further biopsy was investigated in the single arm, phase II DESTINY Gastric02 study [10]. In the 79 patients who received the study drug, the response rate was 42%, and the median OS was 12.1 months, outperforming the historical second line options [11]. This is yet to be implemented into clinical guidelines and will likely be dependent on the outcome of DESTINY-Gastric04 (NCT04704934), which compares trastuzumab-deruxtecan with ramucirumab and paclitaxel (current 2nd line treatment) in HER2-positive patients who have progressed on trastuzumab.

Human epidermal growth factor 2 Negative Disease

In HER2-negative disease, KEYNOTE-859 investigated the addition of pembrolizumab to chemotherapy [12]. There was an improvement in PFS and OS in the intention-to-treat population, but the greatest survival benefit was observed in those with a combined positivity score (CPS) $\geq$10; 15.7 m vs 11.8 m, HR 0.65, $p < 0.0001$. This further supports the use of ICIs based on PD-L1 CPS, following the results of CHECKMATE649 with nivolumab [13] and highlights the need for further work to clarify optimal methods and thresholds for predictive biomarker testing within the capacity of NHS pathology services.

Claudin 18.2

Claudin 18.2 (CLDN18.2) is a tight junction protein expressed exclusively in differentiated gastric epithelium [14]. During carcinogenesis, CLDN18.2 becomes more exposed and accessible [15]. Zolbetuximab is a monoclonal antibody that, on binding to CLDN18.2, mediates antibody-dependent and complement-dependent cellular cytotoxicity [16]. Following the results of the FAST study [17], targeting CLDN18.2 was investigated in two trials: SPOTLIGHT [18] and GLOW [19]. Eligibility required $\geq$75% of tumour cells with moderate to strong immunohistochemistry expression; this includes 24%–40% of patients, depending on the population [17,20–22]. In SPOTLIGHT (majority non-Asian population), patients received leucovorin, fluorouracil, and oxaliplatin (mFOLFOX) with zolbetuximab or placebo. Despite no increase in response rate, the addition of zolbetuximab resulted in a significant improvement in both PFS (HR 0.75, $p = 0.0066$) and OS (HR 0.75, $p < 0.0001$). An improvement in both PFS (HR 0.687, $p = 0.0007$) and OS (HR 0.771, $p = 0.0118$) was also observed in GLOW (majority Asian population), in which patients received capecitabine and oxaliplatin with zolbetuximab or placebo. The main additional toxicities were an increase in nausea and vomiting, which dissipate after the first cycles of zolbetuximab. Optimal treatment sequence of patients with both CLDN18.2 and HER2-PD-L1-positive disease are yet to be established, and the implementation of zolbetuximab into widespread UK-practice is likely to be limited by the lack of universal availability of CLDN18.2 testing.

Immunotherapy and Radiation Oncology

The addition of immunotherapy to chemoradiotherapy in OG cancer is an evolving treatment paradigm, and several trials have endeavoured to exploit their synergistic effect by introducing ICIs earlier in the treatment pathway (Table 1).

Neoadjuvant Approaches

PROCEED, a single-arm, single-centre, phase II study of neoadjuvant chemoradiotherapy (nCRT) plus perioperative pembrolizumab for locally advanced resectable OG

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Table 1
Key trials in 2023 in advanced gastroesophageal cancer.

Trial	Patient biomarker status	Phase	Site	Patients	Populations	Arms	Demographics (study arm)	Response rate	Median PFS/DFS	Median OS	Tolerance
1st line											
HER2 positive											
KEYNOTE-811 [9] (interim analysis)	HER2 positive PD-L1 CPS	III	GOJ/Gastric	698	Asia (34%) Non-Asia (66%)	Chemotherapy* + trastuzumab ± pembrolizumab	Median age: 62 % Male: 81% ECOG PS 0: 42%	72.6% vs 59.8%	ITT: 10.0 m vs 8.1 m, HR 0.72, p=0.0002. No difference in PDL1	ITT: 20.0 m vs 16.9 m, p=0.084. PD-L1 CPS<1 HR 1.61.	Grade ≥3: 71% vs 65%
HER2 negative											
KEYNOTE-859 [12]	HER2 negative	III	GOJ/Gastric	1579	Asia (33%) Non-Asia (67%)	Chemotherapy ± pembrolizumab	Median age: 61 % Male: 67% ECOG PS 0: 36%	51% vs 42%	ITT: 6.9 m vs 5.6 m, HR 0.72, p<0.0001	ITT: 12.9 m vs 11.5 m, HR 0.78, p<0.0001 CPS ≥10: 15.7 m vs 11.8 m, HR 0.65, p<0.0001	Grade ≥3: 60% vs 51%
SPOTLIGHT [18]	Claudin18.2 positive (≥75% cells moderate to strong)**	III	GOJ/Gastric	565	Asia (31%) Non-Asia (69%)	mFOLFOX6 ± zolbetuximab	Median age: 62 % Male: 62% ECOG PS 0: 44%	48% vs 48%	ITT: 10.61 m vs 8.67 m, HR 0.75, p=0.0066.	ITT: 18.23 m vs 15.54 m, HR 0.75, p=0.0135.	Grade ≥3: 87% vs 78%
GLOW [19]	Claudin18.2 positive (≥75% cells moderate to strong)**	III	GOJ/Gastric	507	Asia (61%) Non-Asia (39%)	CAPOX ± zolbetuximab	Median age: 61 % Male: 62.6% ECOG PS 0: 42.7%	42.5% vs 40.3%	ITT: 8.21 vs 6.80, HR 0.687, p=0.0007	ITT: 14.39 vs 12.16, HR 0.771, p=0.0118.	Grade ≥3: 72.8% vs 69.9%
2nd line											
DESTINY-Gastric02 [10]	HER2 positive postprogression	II	GOJ/Gastric	89	Asia (5%) Non-Asia (95%)	Trastuzumab-deruxtecan	Median age: 60.7 %Male: 72% ECOG PS 0: 37%	42%	ITT: 5.6 m	ITT: 12.1 m	Grade ≥3: 55% Grade 5: 14%
Neoadjuvant chemoradiotherapy approaches											
PROCEED [23,24]	N/A	II	Adenocarcinoma Oesophageal= 97%	35	USA	nCRT (45 Gy/25# + carboplatin/paclitaxel) + pembrolizumab → adjuvant pembrolizumab	%Male: 89%	91% underwent surgery pCR: 35.7% R0: 97%	N/A	N/A	Grade ≥3 (nonhaematological): 56%
ChiCTR1900024428 [27]	PD-L1 CPS, HER2 negative	II	Adenocarcinoma GOJ=9% Gastric=91%	34	Asia	Sintilimab + S-1 + nab-paclitaxel → nCRT (45 Gy/25# + nab-paclitaxel + sintilimab) → adjuvant sintilimab + S-1 + nab-paclitaxel	Median age: 65.5 % Male: 82% ECOG PS 0: 76%	pCR: 38% R0: 100%	DFS: 17.0 m	Not reached. 1 year OS: 92.6% (95% CI: 50.1−99.5%)	Grade ≥3: 64.7%
Definitive chemoradiotherapy											
EC-CRT-001 [30]	PD-L1 CPS	II	Oesophagus SCC	42	Asia	dCRT (50.4 Gy/28# + paclitaxel + cisplatin) + toripalimab	Median age: 56 % Male: 76% ECOG PS 0: 74%	Complete response: 62%	12.2 m	NR 1 year OS: 78·4% (95% CI 66·9−92·0)	Grade ≥3: 88%
SCOPE2-PET CT substudy [31]	N/A	II	Oesophagus/GOJ SCC + adenocarcinoma	63	UK	Cis/cap vs car/pac + 50 or 60 Gy/25#	%Male: 56% vs 59% ECG PS 0: 59% vs 39%		34.6 m v 19.4 m, HR 0.54, p=0.079	42.5 m vs 20.4 m, HR 0.44, p=0.041	Grade ≥3: 68% v 71%
Perioperative Immunotherapy											
VESTIGE [42]	N/A	II	GOJ/Gastric/Oesophagus (R1 or ypN+)	189	European	Chemotherapy (>90% FLOT) vs nivolumab/ ipilimumab	Median age: 61 % Male: 69.5%	N/A	23.26 m vs 11.93 m, HR 1.80, p=0.0195	NR vs 25.1 m, HR 1.79, p=0.0994	Grade ≥3: 42.7% vs 32.3%

(*continued on next page*)

Table 1 (*continued*)

Trial	Patient biomarker status	Phase	Site	Patients	Populations	Arms	Demographics (study arm)	Response rate	Median PFS/DFS	Median OS	Tolerance
ATTRACTION-5 [43]	N/A	III	GOJ/Gastric	755	Asian	S-1 or CAPOX ± nivolumab	N/A	N/A	3 Y RFS 68.4% vs 65.3%, HR 0.90, p=0.4363	N/A	Grade ≥3: 54.4% vs 46.8%
KEYNOTE 585 [44]	N/A	III	GOJ/Gastric	1007	Global	Chemotherapy ± pembrolizumab	N/A	pCR: 12.9% vs 2.0%, p<0.0001	EFS: 25.7 m vs 45.8 m, HR 0.81, p=0.011	NR vs 60.7 m, HR 0.93, 95% CI 0.76 −1.12	Grade ≥3: 67% vs 63%
MATTERHORN [45]	N/A	III	GOJ/Gastric	948	Asia (19%) Non-Asia (81%)	FLOT ± durvalumab	N/A	pCR: 19% vs 7%, OR 3.08, p<0.00001. Surgical resection: 87% vs 84%. R0: 86% vs 86%	Awaited	Awaited	Grade ≥3: 69% vs 68%

*Chemotherapy of physicians' choice. **Antibody Roche Ventana clone 43-14A. mFOLFOX6 = leucovorin, fluorouracil + oxaliplatin. CAPOX = capecitabine + oxaliplatin. FLOT = fluorouracil, leucovorin, oxaliplatin, docetaxel. pCR= pathological complete response. SCC = squamous cell carcinoma. cis/cap = cisplatin/capecitabine. car/pac = carboplatin/paclitaxel. NR = not reached. RFS = recurrence free survival. EFS = event free survival.

noma reported a pathological complete response (pCR) rate of 35.7% [23,24], compared to 23% in the CROSS trial using nCRT alone [25], with treatment well tolerated. The impact of PD-L1 on efficacy was not reported. These results differ from the PERFECT trial of nCRT plus atezolizumab [26], which showed a similar pCR rate to nCRT alone. Wei *et al.* published results from another single-arm, multicentre, phase II trial evaluating a novel chemoradiotherapy-immunotherapy regimen in locally advanced, resectable gastric/GOJ adenocarcinoma (ChiCTR1900024428) [27]. Using nCRT plus a combination of induction, concurrent then adjuvant S-1, nab-paclitaxel, and PD-1 inhibitor sintilimab, they reported a median disease-free survival (DFS) of 17 months, pCR rate of 38% (PD-L1 CPS $\geq$5 vs <5 = 63.6% vs 28.6%, p = 0.072) and 100% R0 resection rate. All participants underwent surgery without unintentional delay, and toxicity was acceptable. The role of chemoradiation in gastric cancer remains unestablished in UK practice, however, and survival results from several phases II/III trials are awaited [28,29].

Definitive Chemoradiotherapy Approaches

EC-CRT-001 combined PD-1 inhibitor toripalimab concurrently with definitive chemoradiation (dCRT) (50.4Gy/28# plus cisplatin and paclitaxel) for unresectable oesophageal SCC and continued for 1 year or until disease progression [30]. A complete response of 62% (PD-L1 CPS $\geq$10% vs <10% = 73% vs 55%, p = 0.52) was observed. A one-year OS of 78% was achieved; PD-L1 CPS did not impact this. In other efforts to optimise dCRT, the ongoing SCOPE2 trial evaluates dose escalation and positron emission tomography- computed tomography (PET-CT) guided systemic therapy for oesophageal/GOJ carcinoma [31,32]. Early PET-CT nonresponders (<35% reduction of baseline ^{18}F-fluorodeoxyglucose (FDG) avidity) were randomised to continue standard treatment with cisplatin-capecitabine or switch to carboplatin-paclitaxel following cycle 1 of induction therapy. This substudy closed early on the grounds of futility and possible harm [31]. For SCC, those who underwent a PET-CT-guided chemotherapy switch had significantly worse treatment failure free survival and OS (unadjusted HR 0.32 [95% CI: 0.13−0.79], p = 0.013). Furthermore, early PET-CT responses did not predict outcomes. The numbers for adenocarcinomas were too small to draw meaningful conclusions. The dCRT dose-escalation component of SCOPE2 has now completed recruitment [32] and results are eagerly awaited, not least because of its state-of-the-art radiotherapy quality assurance process in a setting of recently published, negative randomised trials [33,34] and conflicting meta-analyses [35,36].

Perioperative Approaches

Optimal Perioperative Treatment

There are currently two standard of care perioperative regimens in the management of OG adenocarcinoma: perioperative (FLOT) chemotherapy [37] or nCRT (CROSS) ± nivolumab [25,38]. Neo-AEGIS, a phase III trial of 377

patients, compared these strategies [39], though only 15% of patients in the chemotherapy group received FLOT, and patients with residual disease in the CROSS arm did not receive adjuvant nivolumab. Despite improved pCR (4% vs 12%, OR 0.33, p = 0.012) and R0 resection (82% vs 96%, OR 0.21, p = 0.0003) in the nCRT group, 3-year OS was 55% (chemotherapy) vs 57% (nCRT) (HR 1.03, p = 0.82). There was no significant difference in DFS (32.4 months vs 24.0 months, HR 0.89, p = 0.41) or in recurrence patterns. There were no differences in perioperative mortality or morbidity or in QoL at 1 and 3 years. This trial also demonstrates that improved pCR does not always lead to longer survival, and that the treatment modality by which pCR is achieved may be more important in controlling disease. A recent study showed that those achieving pCR with chemotherapy had a superior 5-year DFS (87.1% vs 75.3%, p = 0.026) and reduced prevalence of 5-year distant recurrence (Odds ratio=2.50, p= 0.009) when compared to those with a nCRT-induced pCR [40]. Results from ESOPEC, which directly compares FLOT and CROSS, are awaited [41]. With the addition of nivolumab in the adjuvant setting for patients who receive preoperative CROSS, the results of both NEO-AEGIS and ESOPEC need to be interpreted with caution given the rapidly evolving evidence for immunotherapy in the perioperative setting. However, both trials will help to inform the optimal backbone on which immunotherapy should be built in the curative setting, both for patients with a locally advanced primary tumour and those with a high lymph node burden.

Perioperative Immunotherapy

Four major perioperative immunotherapy trials reported results in 2023: VESTIGE and ATTRACTION-5, which both added adjuvant immunotherapy [42,43] and KEYNOTE-585 and MATTERHORN which added perioperative PD(L)-1 inhibitors [44,45]. These trials are summarised in Table 1. Although KEYNOTE-585 failed to statistically improve event-free survival (EFS), this was primarily due to suboptimal trial design and with early looks at EFS consuming alpha. The improvement seen in EFS could have been clinically meaningful had it been statistically significant by optimising trial design. MATTERHORN may show similar results, but not be statistically confounded by similar design problems. However, it is likely that the most benefit will be in patients with PD-L1 positive tumours, as demonstrated in metastatic disease.

Surgical Oncology

Potentially practice-changing trials in several areas of surgical oncology were presented or published in 2023.

Operative Approach

ROMIO compared hybrid (laparoscopic abdomen, open chest) and open oesophagectomy in 527 patients [46]. No difference in early complications or recovery was previously reported. There was no difference in 24-month survival between hybrid (66%) and open (65%) oesophagectomy, and no difference in the patient reported quality of life (QoL). However, the TIME trial of totally minimally invasive oesophagectomy, showed improved pulmonary complications without a survival difference [47]. ROMIO provides evidence of the safety of both open and hybrid approaches, and thus the choice of surgical approach remains a careful discussion between surgeon and patient. However, this study demonstrates the ability to drive service improvement through high-quality research.

Time to Surgery

Evidence for the optimal time for surgery after nCRT is conflicting [48,49]. NeoRes II compared standard (4–6 weeks) (n = 125) to prolonged time to surgery (TTS) (10–12 weeks) (n = 124) following nCRT in patients with oesophageal adenocarcinoma or SCC [50]. The primary endpoint of pCR in the primary tumour in adenocarcinoma was not significantly different (21% in standard vs 26% in prolonged TTS, p = 0.429). There was no difference in tumour progression, resection margins, or resected lymph nodes, no difference in recurrence rates, and no difference in surgical complications or 90-day mortality [51]. The first quartile OS was better in standard TTS (26.5 months vs 14.2 months, p = 0.003), therefore caution should be used in prolonged TTS [52].

Organ Sparing Management

In the phase III SANO-trial [53], patients who achieved clinical complete response after nCRT (41.4Gy/23#) were randomised to either active surveillance (AS) (n = 198) or surgery (n = 111). Two-year OS for AS was noninferior to surgery (HR 1.14, p = 0.55), with no significant difference in distant metastases at 30 months (43% AS vs 34% surgery, OR 1.45, p = 0.18). QoL was better in AS at six and nine months. Both adenocarcinoma and SCC were included, but to date, the presented results have not been stratified by histological subtype. dCRT is already an accepted standard of care for oesophageal SCC [54], however, given that 74% of UK patients have adenocarcinoma [55], results are needed for both histologies before altering clinical practice. Furthermore, given the results of NeoRes II, the comparative outcomes of patients with adenocarcinoma who receives oesophagectomy after a period of AS must be carefully evaluated.

Future Directions

The results of several ongoing studies are eagerly awaited, including survival outcomes from MATTERHORN using perioperative PD-L1 inhibitor, durvalumab [45], and also DECIPHER, which assesses the efficacy of trastuzumab-deruxtecan in patients who are HER2-positive and ctDNA-positive after chemotherapy and surgery (NCT05965479). Meanwhile, PROTIEUS, the UK's first OG proton beam therapy (PBT) trial, randomising patients with resectable oesophageal or GOJ cancer to hypofractionated nCRT with

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PBT or photon ± adjuvant ICI, is due to open in spring 2024 [56], and GastroSCOPE, a proposed multicentre, randomised phase II basket trial of high-dose palliative radiotherapy for locally-advanced/inoperable, or low-volume metastatic gastric cancer has gained support from UKIOG, and funding is currently being sought [Gwynne S, Case A, personal communication, 20.3.2024]. Internationally, phase III trials KEYNOTE-975, KUNLUN, and SKYSCRAPER-07, evaluating the addition of ICI to dCRT, continue to recruit [57–59]. Two UK-based surgical oncology trials are ongoing: SARONG compares survival in intensive surveillance versus standard follow-up following oesophagogastric resection [60]. PIC-COS investigates progression-free survival of patients with gastric cancer with peritoneal metastases receiving pressurised intraperitoneal aerosolised chemotherapy (PIPAC) and systemic chemotherapy versus systemic chemotherapy alone [61].

Discussion

Throughout 2023, we have seen advancements across the multidisciplinary management of OG cancer, with the year presenting us with a range of trials that will undoubtedly impact UK practice, both now and in the future, and improve the lives of patients whose outlook is often poor. Immunotherapy is of increasing importance, and further trials will be crucial in establishing optimal combinations, timing, dosage, and use in the perioperative setting. We are moving swiftly towards personalised management of OG cancers with an increasing range of treatment modalities for a wider range of patients. Future research should focus on personalising treatment based not only on biomarkers and tumour biology but also based on clinical factors such as patient age, frailty, comorbidities, and fitness for the treatment options available for their type and stage of cancer. Decision-making together and consideration of each individual patient's wishes and needs remain of the utmost importance in a continuously evolving treatment landscape. UKIOG will play a key role in contributing to and supporting UK-based OG cancer research and advocating for patients. In conclusion, the future is ever brighter for patients with OG cancer, with an increasing move towards personalised treatment. The studies presented here, both completed and ongoing, will be instrumental in moving the needle further towards personalised management of and improved outcomes for patients with OG cancer.

Author contributions

1. Guarantor of integrity of the entire study: Tom D. L. Crosby.

2. Study concepts and design: Mary E. Booth, Hollie A. Clements, Jonathan Helbrow, Mark A. Baxter, Christopher W. Bleaney, Maria A. Hawkins, Sheraz R. Markar, Christopher J. Peters, Elizabeth C. Smyth, Tom D. L. Crosby.

3. Literature research: Hollie A. Clements, Jonathan Helbrow, Mark A. Baxter.

4. Clinical studies: N/A.

5. Experimental studies/data analysis: N/A.

6. Statistical analysis: N/A.

7. Manuscript preparation: Mary. E Booth, Hollie A. Clements, Jonathan Helbrow, Mark A. Baxter.

8. Manuscript editing: Mary E. Booth, Hollie A. Clements, Jonathan Helbrow, Mark A. Baxter, Christopher W. Bleaney, Maria A. Hawkins, Sheraz R. Markar, Christopher J. Peters, Elizabeth C. Smyth, Tom D. L. Crosby.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mary E. Booth reports a relationship with Astellas Pharma Ltd that includes: speaking and lecture fees. Mark A. Baxter reports a relationship with Bristol Myers Squibb Co that includes: speaking and lecture fees. Mark A. Baxter reports a relationship with Ipsen that includes: speaking and lecture fees and travel reimbursement. Mark A. Baxter reports a relationship with Servier Laboratories Ltd that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Maria A. Hawkins reports a relationship with UCLH National Institute for Health and Care Research Biomedical Science Centre that includes: funding grants. Sheraz R. Markar reports a relationship with Barco that includes: consulting or advisory. Christopher J. Peters reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory. Elizabeth C. Smyth reports a relationship with AstraZeneca that includes: consulting or advisory and funding grants. Elizabeth C. Smyth reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory, funding grants, and speaking and lecture fees. Elizabeth C. Smyth reports a relationship with Mirati Therapeutics Inc that includes: consulting or advisory and non-financial support. Elizabeth C. Smyth reports a relationship with Amgen Inc that includes: speaking and lecture fees and travel reimbursement. Elizabeth C. Smyth reports a relationship with Astellas Pharma Ltd that includes: consulting or advisory. Elizabeth C. Smyth reports a relationship with BeiGene that includes: consulting or advisory. Elizabeth C. Smyth reports a relationship with Daiichi Sankyo Inc that includes: consulting or advisory. Elizabeth C. Smyth reports a relationship with Merck Sharp & Dohme UK Ltd that includes: consulting or advisory. Elizabeth C. Smyth reports a relationship with Novartis that includes: consulting or advisory and speaking and lecture fees. Elizabeth C. Smyth reports a relationship with Pfizer that includes: consulting or advisory. Elizabeth C. Smyth reports a relationship with Viracta Therapeutics Inc that includes: consulting or advisory. Elizabeth C. Smyth reports a relationship with Zymeworks Biopharmaceuticals Inc that includes: consulting or advisory. Tom D. L. Crosby reports a relationship with Amgen Inc that includes: consulting or advisory. Tom D. L. Crosby reports a relationship with Astellas Pharma Ltd that includes: consulting or advisory. Tom D. L. Crosby reports a relationship with AstraZeneca that includes: consulting or advisory. Tom D. L. Crosby

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