Gastroesophageal adenocarcinoma in older adults

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Gastroesophageal adenocarcinoma in older adults: a comprehensive narrative review of management by the Young International Society of Geriatric Oncology

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Abbreviations:

BSC – best supportive care; CAPOX – capecitabine/oxaliplatin; CF – cisplatin/5-fluorouracil; CGA – comprehensive geriatric assessment; CI – confidence interval; CPS – combined positivity score; CRT – chemoradiotherapy; DFS – disease free survival; ECF – epirubicin/cisplatin/5-fluorouracil; ECX – epirubicin/cisplatin/capecitabine; EMR – endoscopic mucosal resection; ERAS – enhanced recovery after surgery; FOLFOX – 5-fluorouracil/leucovorin/oxaliplatin; FLOT - 5-fluorouracil/leucovorin/oxaliplatin/docetaxel; GA – geriatric assessment; GEA – gastroesophageal adenocarcinoma; GEJ – gastroesophageal junction; Gy – gray; ITT – intention to treat; HR – hazard ratio; ICI – immune checkpoint inhibitor; ITT – intention to treat; MRC – medical research council; OS – overall survival; PCR – pathological complete response; PD-L1 – programmed death ligand-1; PFS – progression free survival; QoL – quality of life; RCT – randomised controlled trial; SOX – S-1/oxaliplatin; SOXRT – S-1/oxaliplatin/radiotherapy.

Abstract –

Gastroesophageal adenocarcinoma is a disease of older adults with very poor survival rates. Its incidence has risen dramatically across the world in recent decades. Current treatment approaches for older adults are based largely on extrapolated evidence from clinical trials conducted in younger and fitter participants than those more commonly encountered in clinical practice. Understanding how to apply available evidence to our patients in the clinic setting is essential given the high morbidity of both curative and palliative treatment. This review aims to use available data to inform the management of an older adult with gastroesophageal adenocarcinoma.

Keywords: Gastroesophageal adenocarcinoma; real-world; toxicity; multi-disciplinary; frailty

Introduction

Gastric and esophageal cancers are the fifth and eighth most common cancers worldwide. Together they accounted for 1.6 million new cancer cases in 2018 (9.2% of all cases)[1]. Gastroesophageal cancer is a disease of the distal esophagus, gastro-esophageal junction and proximal stomach. The primary histological subtype is gastroesophageal adenocarcinoma (GEA), which will be the focus of this review. Patients with esophageal and non-cardia gastric adenocarcinoma are treated similarly to GEA and as such these diseases are often considered together and will be included in this review. In recent decades, there has been a dramatic increase in incidence of GEA worldwide[2]. This has primarily been driven by rising obesity and gastroesophageal reflux disease[3, 4]. These factors increase the risk of development of pre-malignant Barrett's esophagus[4].

GEA has a poor prognosis both in the localized and advanced setting. Even following curative treatment, over half of patients will relapse[5]. Despite increased understanding of the genomic landscape of the disease [6, 7] in addition to advances in diagnostic modalities, surgical techniques, chemotherapy and radiotherapy, 5-year survival rates remain below 20%[8]. Most patients with GEA present at an advanced stage and in this setting life expectancy or expected survival in unselected populations is less than a year[9], although patients in some Asian countries appear to have modestly improved outcomes[10].

GEA is more common in men than in women with a quoted ratio of 3 to 9:1[11]. The median age at diagnosis for both esophageal and gastric cancers is 68 years, with over 60% of patients aged ≥65 [12]. Due to the nature of the disease, patients will often have a high symptom burden and treatment in both the curative and palliative setting has significant morbidity.

One of the challenges in treating patients with GEA is that real-world populations differ significantly in terms of age, frailty and co-morbidity from the trial populations that clinical decisions are based upon. As such, for older adults, frailty screening and geriatric assessment are vital to provide a personalized approach to care and minimize morbidity and mortality.

The relevance of the geriatric assessment in older adults with GEA

Importance of screening for frailty

Patients with GEA often have a high symptom burden, poor prognosis, and nutritional deficits. This, coupled with the high catabolic state of cancer, can result in malnutrition, sarcopenia or cachexia, immunodeficiency, impaired quality of life (QoL) and worse clinical outcomes[13]. The impact is more obvious in older patients, in whom age-related conditions such as pre-existing sarcopenia and osteoporosis are more common[14] and comorbidities more prevalent[15].

In the context of radical treatment, older patients have been shown to have higher intra-operative and post-operative complication rates following both gastrectomy and esophagectomy[16, 17]. Specifically, frailty and sarcopenia have both been shown on meta-analysis to predict surgical mortality and post-operative complications[18]. These factors result in a reduced chance of proceeding to and completing neo-adjuvant/adjuvant systemic therapy[19].

Chronologic age alone is not a reason for exclusion from chemotherapy, as agents appear equally efficacious regardless of age[20]. However, when considering systemic therapy, clinicians must consider the impact of age and tumor type on drug pharmacokinetics and pharmacodynamics[21]. Renal function, as well as liver volume and blood flow, decline with age. This impacts excretion and metabolism of drugs. In GEA this can be compounded by reduced gastric motility and absorption. A further complication is the impact on volume of distribution of lipid-soluble drugs by age-associated reductions in lean body weight and muscle mass.

Many systemic regimes involve drugs that are inherently toxic and have narrow therapeutic windows. In addition, regimes often have supportive medications, which adds to the medication burden. This can potentially lead to poor adherence or inappropriate medication use[22]. In GEA a good example

of a common drug-drug interaction is the reduction in efficacy of capecitabine if co-prescribed with a proton pump inhibitor[23], which can impact both progression free survival (PFS) and overall survival (OS).

Role of the Comprehensive Geriatric Assessment (CGA)

Frailty is common in cancer and is associated with increased risk of chemotherapy toxicity and poor tolerance as well as all-cause mortality[24]. The CGA is a process used to identify potential causes of frailty, and target interventions appropriately[25]. Multiple domains are assessed (**Figure 1**) with interdisciplinary input, resulting in an individualised problem list and plan of management. Although many domains of the CGA have been associated with worse outcomes among older adults with GEA, the role of the CGA for the selection and tailoring of treatments is poorly understood due to a lack of prospective information examining its effects on cancer-specific outcomes such as treatment toxicity, recurrence, or survival[26]. Currently, the only prospective trial utilizing the results of a CGA to assign patients to various oncological treatments is the phase-III GO2 trial, which also included a best supportive care (BSC) arm [27, 28]. This trial demonstrated that in patients with impairments in CGA domains, dose de-escalation led to similar survival and improved QoL, highlighting the potential value of applying the results of a CGA for treatment selection.

While information on oncological outcomes is limited, there is data to support the implementation of interventions aimed at reducing or mitigating deficits found in the CGA, which could potentially impact tolerance to multimodality treatments. Most of these interventions require the participation of a multidisciplinary team, including a geriatrician, a nutritionist, a physical therapist, and a social worker, among others. Shared co-management between geriatrics and surgery, for example, has been shown to significantly reduce 90-day mortality among 1892 older adults with all types of cancer (of which 10% had gastric cancer) undergoing surgical treatment[29]. Three recently presented randomized controlled trials (RCT) (including between 10 and 30% of patients with gastrointestinal malignancies)

demonstrated that management by a multidisciplinary team, co-management by a geriatrician, and/or providing oncologists with CGA-based recommendations led to a decrease in clinically relevant toxicity and to improved quality of life among older adults receiving systemic treatment[30-32].

In addition to the recommendations regarding the use of multidisciplinary teams with geriatric expertise, there is evidence to support the implementation of specific nutritional and physical therapy for patients with gastric cancer, although older adult-specific trials are lacking. A systematic review found that dietary counselling and nutritional support could lead to improvements in QoL and treatment completion, as well as lower postoperative complications among older adults with all types of cancer[33]. Other interventions, such as the use of physical therapy before and after gastrectomy, could potentially be useful in decreasing postoperative complications and length of stay.

Two recent single institution studies (median ages 65 and 68) explored the use of prehabilitation protocols in patients who underwent neoadjuvant therapy and were scheduled for gastrectomy and found that this strategy decreased postoperative pneumonia and improved QoL after surgery[34]. Likewise, a RCT (median age 68) found that the use of enhanced recovery after surgery (ERAS) protocols after gastrectomy could decrease the incidence of severe surgical complications[35].

Taken together, existing evidence suggests that the CGA can be utilized by multidisciplinary cancer care teams in order to tailor therapy for older adults with GEA, including both the selection of regimen (single vs. combination chemotherapy, antibodies, dose modifications) and the implementation of supportive care interventions. Specifically, a thorough evaluation of the patient's overall health status can provide guidance regarding the use of the various available treatment options, particularly in the advanced setting where existing evidence regarding the use of the CGA to tailor treatment is stronger. In the localized setting, however, there is still a lack of information regarding the use of the CGA to

guide therapy, and further studies are needed to optimize treatment selection in this group of patients.

Management of localized disease

Primary treatment options for GEA include surgery with either perioperative chemotherapy or neoadjuvant chemoradiotherapy or, in patients unfit for surgery, definitive chemoradiotherapy, with practice varying widely between East and West[36]. Each case should be discussed in a multidisciplinary meeting and treatments selected based on tumor stage, location, histology, and patient fitness. **Table 1** highlights key relevant RCTs.

The surgical approach depends on tumor size and location. For early esophageal and gastric cancer confined to the mucosa (T1a) or submucosa (T1b), endoscopy mucosal resection (EMR) or endoscopic submucosal dissection (ESD) can achieve similar outcomes to radical surgery[37]. Endoscopic surgery is indicated for well-differentiated tumors, without evidence of venous or lymphatic involvement, <3cm in diameter, and confined to mucosa or submucosa. In Eastern countries with population-based screening programs like Japan and Korea, endoscopic surgery is widely adopted. Nakamura et al. reported on 1161 patients treated by ESD from multiple Japanese centers[38]. Five-year OS and recurrence-free survival (RFS) were 92.3% and 99.5%, respectively. The mean age of the population was 70.2 years and age was not a predictor for recurrence, suggesting ESD is safe for older patients. In a Korean retrospective review which included 439 patients aged $\geq$75 years treated with ESD, 3-, 5-, and 10-year OS was 91.2%, 83.5%, and 54.5%, respectively[39]. Factors associated with worse OS included smoking, previous malignancies, neutrophil/lymphocyte ratio > 1.6, Charlson comorbidity index ≥3, and lymphovascular invasion. The long-term outcomes of ESD were worse in older patients with risk factors than in those without.

In patients with more advanced localized disease, a thoracoscopic esophagectomy or a hybrid minimally invasive esophagectomy are the procedures of choice. Of note, older patients have similar stage-matched survival to younger patients[40], however post-operative morbidity and mortality are

higher[41]. In patients with a gastric cardia lesion, gastrectomy (total or subtotal) is the procedure of choice.

In the Medical Research Council (MRC) trial, patients with gastric adenocarcinoma were randomized to undergo gastrectomy with either a D1 or D2 lymph node dissection[42]. The 5-year survival of D1 surgery for patients <60 years old was 54% compared to 31% in the 60-69 age group and 28% in the ≥70 age group. Similar figures were observed in the D2 arm (47% vs. 27% vs. 29%). Multivariate analysis found that older patients, males, and those with stage II or III had worse outcomes.

A study comparing octogenarians (n=75) and non-octogenarians (n=1187) undergoing gastrectomy found that octogenarians had significantly lower OS, higher postoperative morbidity, and higher mortality [43]. This is supported by Fujiwara et al. who prospectively enrolled 448 patients undergoing gastrectomy; more postoperative complications (especially respiratory complications), in-hospital deaths, and worse OS were observed in patients aged ≥80 [44]. Despite these findings, patient selection and optimization of fitness before gastrectomy are key factors to ensure successful and safe surgery in older patients[45, 46].

Perioperative/Neoadjuvant management

Perioperative chemotherapy and neoadjuvant chemoradiotherapy (CRT) can be recommended with an equal level of evidence, although data for older adults is limited [36]. Location of the primary tumor can influence treatment choice – neoadjuvant CRT for proximal tumors (esophagus and Siewert type I and II) and perioperative chemotherapy for more distal tumors.

The MRC Adjuvant Gastric Infusional Chemotherapy trial (MAGIC) randomized patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus to perioperative chemotherapy and surgery vs. surgery alone. Median age was 62 years, and 20.8% of

patients were ≥70. Chemotherapy included three pre- and post-operative cycles of intravenous epirubicin, cisplatin and fluorouracil (5-FU)/capecitabine (ECF/ECX). The primary endpoint was OS. Perioperative chemotherapy significantly improved PFS (HR 0.66; 95% CI 0.53 to 0.81; P<0.001) and OS (HR 0.75; 95% CI 0.60 to 0.93; P=0.009, 5-year survival 36% vs. 23%) compared to surgery alone. This benefit was also seen among older adults[47].

The FLOT4-AIO trial[5] set a new standard of care for perioperative chemotherapy by randomizing patients with resectable gastric/GEJ adenocarcinoma to ECF/ECX vs. 5-FU plus leucovorin, oxaliplatin, and docetaxel (FLOT). Median age of patients was 62 years, with 24% ≥70 years. Patients who received FLOT had significantly improved median OS (50 vs. 35 months, HR 0.77; 95% CI 0.63-0.94). There was no difference in OS or in adverse events (AE) between age groups. However, care should be taken when considering FLOT for vulnerable or frail patients given the higher rates of nausea, diarrhea, peripheral neuropathy, and neutropenia[5, 48].

The benefit of neoadjuvant CRT in GEA has been confirmed by a meta-analysis demonstrating benefits in long-term survival, R0 resection rate, and pathological complete response (PCR) [49]. The ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial compared neoadjuvant CRT (41.4Gy in 23 fractions with weekly carboplatin-paclitaxel) plus surgery vs. surgery alone[50]. Median age was 60 years (range 36-79), and 75% of patients had adenocarcinoma of the esophagus or GEJ. Neoadjuvant CRT improved median OS for adenocarcinoma (43.2 vs. 27.1 months, HR 0.73; 95% CI 0.55 – 0.98, p=0.038), although subgroup analyses by age are not available. A prospective study comparing FLOT chemotherapy and the CROSS CRT regime in patients with adenocarcinoma of the esophagus (**NCT02509286**) is ongoing.

Checkmate-577 evaluated the use of the immune checkpoint inhibitor (ICI) nivolumab on patients without PCR after neoadjuvant CRT[51]. Three quarters had adenocarcinoma, and 40% had tumors of

the GEJ. Nivolumab improved median disease-free survival (DFS) from 11.1 months to 19.4 months (HR 0.75) in patients with adenocarcinoma, without differences for GEJ tumors (22.4 vs. 20.6 months, HR 0.87). Subgroup analysis for age ≥65 showed similar DFS between nivolumab and placebo (17.0 vs. 13.9 months, HR 0.80).

There is no role for adjuvant radiotherapy following neoadjuvant chemotherapy based on the CRITICS trial[52], which compared perioperative chemotherapy to preoperative chemotherapy plus postoperative CRT. Patients in the postoperative CRT group received 45Gy in 25 fractions combined with capecitabine and cisplatin. Median age was 63 years and 22% of patients were aged ≥70. Median OS was not significantly different (43 vs. 37 months, HR 1.01; 95% CI 0.84-1.22, p=0.90). In the ≥70 population, the HR for OS was 0.81 (95% CI 0.48-1.35). Postoperative compliance was low in both treatment groups (59% and 62% proceeded to adjuvant treatment).

Likewise, no evidence supports using targeted therapy in the radical setting, with the ST03 trial showing no benefit for bevacizumab[53]. The ongoing INNOVATION trial is investigating dual HER2 blockade with trastuzumab/pertuzumab in HER2+ resectable gastric and GEA (**NCT02205047**)[54]. Other studies include KEYNOTE-585 (perioperative cisplatin plus 5-FU/capecitabine vs. pembrolizumab/placebo)(**NCT03221426**)[55], VESTIGE (post-operative ipilimumab plus nivolumab vs. chemotherapy)(**NCT03443856**)[56], ICONIC (perioperative FLOT plus avelumab)(**NCT03399071**)[57] and PANDA (neoadjuvant capecitabine, oxaliplatin, docetaxel, and atezolizumab)(**NCT03448835**).

Adjuvant therapy

While perioperative chemotherapy is often used in Europe and North America, adjuvant chemotherapy using capecitabine plus oxaliplatin or S-1 is preferred in Asian countries like Japan and Korea. In Western populations, adjuvant therapy is mostly used after emergency surgery or for under-staged patients. Included evidence comes from studies in gastric cancer which included GEA.

A meta-analysis by the GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) group, demonstrated that adjuvant fluorouracil-based chemotherapy produced a statistically significant benefit in OS (HR 0.82; 95% CI 0.76-0.90; $p < 0.001$) and DFS (HR 0.82; 95% CI 0.75-0.90, $p < 0.001$) compared with surgery alone[58].

The CLASSIC trial in gastric cancer post D2-gastrectomy, reported that adjuvant chemotherapy with capecitabine plus oxaliplatin (CAPOX) improved 5-year OS (78% vs. 69%, p=0.0015) and DFS (68% vs 58%, p<0.0001) compared to surgery alone[59]. Among patients $\geq$65 (n=269), those receiving adjuvant chemotherapy also had improved 5-year OS (HR 0.51; 95% CI 0.34-0.78) and 3-year DFS (HR 0.48; 95% CI 0.30-0.78). There was no subgroup analysis on AE in older patients.

The Japanese ACT-GS study randomized 1059 patients with Stage II/ III gastric cancer who underwent gastrectomy with D2 dissection to adjuvant chemotherapy with one year of S-1 (tegafur, gimeracil and oteracil) or surgery alone. Adjuvant S-1 improved 5-year OS (71.7% vs. 61.1%, HR 0.67; 95% CI 0.54-0.82) and DFS (65.4% vs. 53.1%, HR 0.65; 95% CI 0.54-0.79)[60]. However, in the subgroup analysis by age, a benefit of chemotherapy on OS was not demonstrated for patients aged 70-80 (HR 0.78; 95% CI 0.53-1.15). Likewise, improvement in DFS did not appear significant among patients aged 60-69 (HR 0.73; 95% CI 0.52-1.01) and 70-80 (HR 0.71; 95% CI 0.49-1.02). The most common grade 3-4 AE were anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%).

Adding docetaxel to S-1 also improved outcomes compared with S-1 alone. In the interim analysis of JACCRO GC-7 trial, 3-year DFS of the docetaxel/S-1 arm was significantly superior S-1 alone (HR: 0.632; 95% CI: 0.400-0.998; p=0.0007)[61]. Median age was 66 years (range 28–80). DFS between arms was similar in patients aged >70 (HR 0.85; 95% CI 0.55 – 1.31), with a higher incidence of grade 3-4 AE in the docetaxel/S-1 arm.

Adjuvant chemotherapy is widely underutilized in octogenarians. According to a survey conducted across 58 institutions in Japan, only 15% of octogenarians with stage II/III disease received S-1 after curative surgery. An ongoing phase III RCT JCOG1507 (BIRDIE) is testing the superiority of S-1 over surgery alone in patients age ≥80 years with Stage II/ III gastric cancer after resection[62].

Adding adjuvant radiotherapy and/or CRT after gastrectomy remains controversial. The US Intergroup INT 0116 study (median age 60 years) showed that adjuvant CRT improved median OS (35 vs. 27 months, HR 1.32; 95% CI 1.10-1.60; p=0.0046) and median PFS (27 vs. 19 months, HR 1.51; 95% CI 1.25-1.83, p<0.001) compared to surgery alone[63]. However, only 10% patients had D2 dissection, 30% did not complete CRT due to toxicity, and more than 30% of radiotherapy plans had significant errors.

The Korean ARTIST trial tested whether the addition of radiotherapy to adjuvant chemotherapy following D2 gastrectomy improved DFS. Although the DFS primary endpoint was not met (HR 0.74; 95% CI 0.52– 1.05, p=0.0922)[64], subgroup analyses showed improved DFS for patients with node-positive disease and intestinal-type gastric cancer. ARTIST-2 compared three adjuvant treatments: S-1 for one year; oxaliplatin plus S-1 (SOX) for 8 cycles; and SOX plus radiotherapy (SOXRT). DFS in the S-1 arm was shorter than in the SOX (HR 0.69, 95% CI; 0.41–0.99, p=0.042) and SOXRT arm (HR 0.72, 95%; CI 0.51–1.03, p=0.074). However, adding radiotherapy to SOX did not improve 3-year DFS over SOX alone (74.3% vs. 72.8%, HR 0.97, p=0.88).

These RCTs did not include a subgroup analysis by age, and thus the benefit of adding adjuvant radiotherapy in older patients with cancer is unknown[65].

Management of metastatic disease

Prognosis

Advanced GEA has a poor prognosis, with survival estimated at 3-4 months with BSC alone[66]. The goals of treatment are focused on palliation of symptoms as well as improvement in QoL and survival. At present, chemotherapy is the backbone of management, but survival remains limited and toxicity high (**Table 2**). In older patients fit for systemic therapy, median OS remains less than a year [67], while in those felt not fit for full dose chemotherapy it is approximately eight months[27].

First-line treatment

Chemotherapy

The REAL-2 trial compared four chemotherapy regimens, combining epirubicin with oral capecitabine or 5-FU and oxaliplatin or cisplatin. The median age was 62 years. Median OS for the ECF (control arm), ECX, EOF, and EOX groups were 9.9 months, 9.9 months, 9.3 months, and 11.2 months, respectively[67]. EOX had less toxicity compared to ECF and was adopted as standard of care[67]. Since this study, the benefit of adding an anthracycline or taxane in triplet therapy has been controversial, and most experts recommend doublet with fluoropyrimidine and platinum. This is especially important in older adults, where the balance between OS, toxicity and QoL is critical.

In Asian populations, S-1 with cisplatin is a preferred regime following the results of the SPIRITS trial[68]. In this study, median OS was prolonged with the addition of cisplatin to S-1 (13.0 vs. 11.0 months; HR 0.77). S-1 was subsequently confirmed as a non-inferior alternative to 5-FU in this population[69].

The use of a triplet regime in older adults was investigated in the FLOT65+ trial[48], which found that, while feasible, toxicity was significant without improvements in QoL or PFS. These findings were

supported by the Phase II TTD 08-02 study[70], which recruited 42 patients with ≥1 of the following: performance status ≥2, weight loss 10–25% and/or age ≥70 years. Although median OS was 13.4 months, the rate of grade 3-5 toxicity was 76%.

To address the question of chemotherapy dosing in older, frailer populations with GEA, the phase II 321GO[71] and subsequent GO2 study[27] were designed. GO2 was a non-inferiority RCT evaluating the optimal dose of CAPOX (three dose levels, 100, 80, and 60%) in 512 frail older adults with advanced GEA. Most (58%) patients had ≥3 impairments in CGA. Non-inferiority of PFS was confirmed for 60 vs 100% dosing of CAPOX (HR 1.10; 95% CI 0.90-1.33). The 60% dose produced less toxicity and better overall treatment utility[27], demonstrating that lower chemotherapy dosing should be considered for older, frail patients. A sub-study compared chemotherapy versus BSC among patients for which there was clinician uncertainty regarding fitness for treatment, showing a small survival benefit with chemotherapy which was not statistically significant[28].

Immune checkpoint inhibitors

Several studies support the use of ICI in the first line setting in selected populations (**Table 3**), although data in older adults are limited to subgroup analyses.

The phase 3 KEYNOTE-062 trial randomized patients with programmed cell death ligand-1 (PD-L1)-positive, HER2-negative, advanced gastric/GEJ cancer to pembrolizumab 200 mg every three weeks; pembrolizumab plus chemotherapy (cisplatin and 5-FU or capecitabine); or chemotherapy plus placebo[72]. In patients with a PD-L1 combined positivity score (CPS) ≥1 pembrolizumab was non-inferior to chemotherapy (median OS 10.6 vs. 11.1 months)[72]. Median OS with pembrolizumab was superior to chemotherapy in patients with CPS≥10. Subgroup analysis showed no benefit from pembrolizumab for patients aged ≥65 regardless of CPS (CPS≥1: HR 0.97; 95%CI: 0.72-1.31) (CPS≥10: HR 0.92; 95%CI: 0.55-1.54). OS and PFS for the combination of pembrolizumab and chemotherapy

were comparable to those of chemotherapy alone, regardless of CPS[72]. Importantly, the toxicity profile of ICI and chemotherapy are different, potentially representing a more tolerable option in for older adults, especially those in which poor renal function may preclude the use of platinum-based chemotherapy.

KEYNOTE-590 examined first-line chemotherapy (5-FU and cisplatin), with or without pembrolizumab, in patients with esophageal cancer or Siewert type 1 GEJ adenocarcinoma[73]. An OS and PFS benefit for the combination were observed in the 27% of included patients with adenocarcinoma. Subgroup analysis showed similar benefit from pembrolizumab plus chemotherapy in patients <65 versus ≥65 years old (OS: HR 0.69; 95% CI 0.53-0.89 and PFS: HR 0.62; 95% CI 0.48-0.80)[73].

The CheckMate-649 phase 3 trial evaluated nivolumab plus chemotherapy (oxaliplatin and 5-FU or capecitabine) vs. chemotherapy alone as first-line treatment in patients HER2-negative advanced gastric, GEJ, or esophageal cancer[74]. Nivolumab plus chemotherapy improved OS and PFS in patients with PD-L1 CPS≥5. Improvements were also observed in patients with PD-L1 CPS≥1 and in the overall population. Patients aged ≥65 with PD-L1 CPS≥5 derived similar OS benefit from the combination, with a median OS of 14.3 vs. 11.2 months, respectively (HR 0.72)[74].

The phase 3 ATTRACTION-4 trial[75, 76] was performed in Asian patients and did not target a specific CPS value. It evaluated nivolumab plus chemotherapy (oxaliplatin plus either S-1 or capecitabine) vs. chemotherapy alone, finding an improvement in PFS, but not in OS[76]. In contrast to CheckMate-649, patients aged ≥65 derived no benefit from combination therapy in terms of PFS (HR 0.83) or OS (HR 1.01)[76]. In both studies nivolumab showed a safety profile similar to prior trials, with equivalent incidences of grade 3 to 5 AEs between arms.

Targeted therapy

Trastuzumab (anti-HER2) and ramucirumab (anti-VEGF), the only targeted agents approved in advanced GEA, have limited data in older patients. For patients with HER2-positive disease, the recommended first-line regimen is trastuzumab in combination with platinum and fluoropyrimidine-based chemotherapy based on the results of the Phase III ToGA trial[77]. A subgroup analysis of the ToGA trial showed similar survival benefit and toxicity from trastuzumab plus cisplatin and fluoropyrimidine as first-line treatment in patients with HER2-overexpressing GEA aged ≥ 60 years (HR 0.66; 95% CI 0.49- 0.88)[77](**Table 4**).

Several trials with other HER2-targeting agents alone and in combination (trastuzumab+pertuzumab, lapatinib and TDM-1) have thus far not proven sucessful due to failure to meet their primary endpoints[78-81]. Older adults were largely excluded from these studies.

Combining anti-HER2 therapy with immune checkpoint inhibitors is currently under investigation in the first-line setting. Inhibition of HER2 signalling results in recruitment of effector T-cells and promotes NK-cell mediated cellular cytotoxicity[82]. Results of the first interim analysis from the phase 3 KEYNOTE-811 trial were presented at the ASCO 2021 meeting[83]. This trial evaluated pembrolizumab or placebo in combination with trastuzumab and a platinum based chemotherapy backbone (**Table 4**). Approximately 88% of patients had PD-L1 CPS≥1. Adding pembrolizumab to trastuzumab and chemotherapy resulted in a statistically significant increase in ORR (74.4% vs 51.9%, difference 22.7% [95% CI, 11.2-33.7], p=0.00006). Survival data was not provided but grade 3-5 toxicity was similar (57.1% vs 57.4%). No data is available according to age.

Despite this, the FDA granted accelerated approval to pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma.

Subsequent lines of treatment

Chemotherapy

The use of second-line treatments has been recommended due to PFS and OS benefits. However, disease progression increases frailty[84], and only 30-50% of patients in Europe and North America receive second-line therapies compared to 80-90% of patients in Asian countries[85]. Second line chemotherapy options for advanced GEA include irinotecan, docetaxel, and weekly paclitaxel.

The German AIO trial[86] compared irinotecan to BSC in 40 patients. Despite poor recruitment and low participant numbers, median OS was significantly improved (4.0 vs. 2.4 months; HR 0.48, p=0.012). In the COUGAR-02 study, median OS with docetaxel was 5.2 months compared to 3.6 months in the BSC arm[87]. Patients receiving docetaxel reported less pain (p=0.0008), nausea/vomiting (p=0.02), and constipation (p=0.02). Global health-related QoL was similar between the groups (p=0.53), although disease specific QoL measures showed benefits for docetaxel in reducing dysphagia (p=0.02) and abdominal pain (p=0.01). An alternative to docetaxel is paclitaxel, which is non-inferior to irinotecan in the second-line setting[88]. While second-line therapy may be considered in fit older adults, its benefit in older patients who are vulnerable or frail remains unclear.

In the third-line setting, the TAGS study showed modest survival benefits with trifluridine/tipiracil (TAS-102, Lonsurf) when compared to BSC[89]. However, in patients aged >65, grade 3-5 toxicity rate was 53%, and survival was not improved (HR 0.73; 95% CI 0.52-1.02).

Immune checkpoint inhibitors

The phase 3 KEYNOTE-061 trial compared pembrolizumab to paclitaxel in patients with PD-L1 positive gastric or GEJ adenocarcinoma who progressed on first-line fluoropyrimidine and platinum chemotherapy[90, 91]. Two-year follow-up data revealed no improvement in OS over paclitaxel[91],

457 although there seemed to be more benefit for patients with higher CPS scores[91]. OS results in the
458 40% of patients aged ≥65 included were consistent with the overall population (HR 0.90; 95%CI: 0.63-
459 1.29). Fewer grade 3+ AEs were reported in the pembrolizumab arm.
460
461 ATTRACTION-2 evaluated the efficacy and safety of nivolumab in Asian patients with unresectable
462 advanced or recurrent gastric or GEJ cancer who progressed after ≥2 chemotherapy regimens[92, 93].
463 The 2-year follow-up data showed improved OS in the nivolumab group[93]. Subgroup analysis of OS
464 favored nivolumab in all subgroups, including patients aged ≥65 (HR 0.60; 95%CI: 0.44-0.82)[93]. PD-
465 L1 positivity, reported in only 14% due to assessment of tumor proportion score rather than CPS, was
466 not associated with OS.
467
468 *Targeted therapy*
469 For subsequent lines of targeted treatment in HER2 disease, trastuzumab deruxtecan, an antibody-
470 drug conjugate consisting of a humanized, monoclonal, anti-HER2 antibody bound to a cytotoxic
471 topoisomerase I inhibitor, has shown activity in previously treated HER2-positive gastric cancer[94].
472 The DESTINY-Gastric01 randomized phase 2 trial, compared trastuzumab deruxtecan to
473 chemotherapy in patients with HER2-positive advanced gastric/GEJ adenocarcinoma who had
474 progressed after at least two previous therapies including trastuzumab[94]. Treatment with
475 trastuzumab deruxtecan resulted in a significantly higher ORR (primary endpoint) compared to
476 chemotherapy (51% vs. 14%, p<0.001) (**Table 4**). Patients aged ≥65 derived similar benefit from
477 trastuzumab deruxtecan; response rates (46% vs 21%) and OS (HR 0.44) (**Table 4**). However, 10% of
478 patients in the trastuzumab deruxtecan group developed drug-related interstitial lung disease or
479 pneumonitis, the majority of which were grade 1 or 2.
480
481 Considering anti-VEGF therapy, an exploratory analysis of the REGARD and RAINBOW trials revealed
482 that beneficial effects of ramucirumab in second-line setting were maintained in older patients (≥65,

≥70, ≥75 years) except for OS in patients aged ≥75 years in the RAINBOW trial (HR 0.97; 95% CI 0.47-2.01)[95]. The choice between ramucirumab as monotherapy or in combination with paclitaxel should be based on an assessment of patient fitness through a CGA and on the potential for adverse events.

The role of molecular testing

Molecular testing and its implications for treatment are evolving with its predominant role in advanced GEA cancer; however, there are several studies ongoing evaluating its role in localized disease. The emergence of the use of circulating tumour DNA may enable monitoring of response to treatment as well as longitudinal molecular profiling, without the need for serial biopsies[96].

Currently available and validated molecular markers include HER2, microsatellite instability (MSI) and tumour mutational burden (TMB), with others including FGFR2 and Claudin-18.2 currently under investigation. HER2 was the first molecular target to influence the treatment algorithm in advanced GEA. HER2 amplification is determined by immunohistochemistry (IHC) and/or fluorescent in situ hybridization (FISH) and occurs in up to 30% of gastroesophageal cancers and 20% gastric cancers[97]. MSI is present in between 4-22% of GEA tumours[7, 91, 98] and is determined using IHC for MSH2, MSH6, PMS2, and MLH1. Tumor mutational burden (TMB) is an emerging predictive marker for response to ICI[99]. Oesophageal adenocarcinoma has a high TMB compared to other tumour types, with a median of 9.9 mutations/Mb[100]. Despite variability in cutoffs across the literature, it is estimated that approximately 5-12% of patients with GEA have high TMB[101, 102], and an association with increasing age[103]. Importantly, both MSI-high and TMB-high patients have FDA approval for use pembrolizumab.

In summary, all patients with advanced GEA should undergo HER2 and MSI testing as this impacts on treatment decisions. Where available, next generation sequencing should be considered to determine TMB status.

Palliative surgery

Palliative surgery in advanced GEA is not supported by evidence. The REGATTA trial demonstrated no survival advantage from palliative gastrectomy before chemotherapy in patients with metastatic disease. The age range of patients enrolled was 47-67 years, therefore an older population was not adequately represented in the study[104].

Radiotherapy

The ROCS study[105] investigated the addition of palliative radiotherapy compared to usual care, following insertion of a self-expanding esophageal stent for dysphagia in patients with advanced gastroesophageal cancer. The median age was 72 years in the radiotherapy group, with 67% having GEA and only 10% of patients were PS 0. No improvement in time to dysphagia deterioration or OS was observed with the addition of radiotherapy. However, for patients considered to be at high risk of bleeding, concurrent palliative radiotherapy may reduce bleeding risk.

Supportive care

Patients with advanced GEA often experience a high symptom burden. A proactive and integrated interdisciplinary approach for supportive care is encouraged as it is demonstrated to improve symptoms, QoL, and survival[106, 107].

Supportive care in GEA includes systemic approaches, such as antiemetic and analgesic drugs, along with nutritional interventions[108]. Local symptoms (bleeding, obstruction, pain) not responding to systemic therapy can be managed with endoscopic techniques (stent placement, laser therapy), palliative radiotherapy, or surgery[109]. The choice of the best modality should be made case-by-case based on a variety of factors, including individual patient prognosis and preferences.

Of note, a recent study has demonstrated that an early integrative approach to supportive care with a team of oncologists, nurse specialists, dieticians and psychologists, prior to the commencement of chemotherapy improved survival as well as emotional and cognitive functioning[110]. This suggests that supportive care should be introduced at an early stage.

Future Direction

For all patients with GEA, both cancer and its treatment challenge physiological reserve and impact outcomes in the curative and palliative settings. There is a recognized mismatch between real-world patients and those recruited to clinical trials in terms of age, frailty, performance status, and co-morbidity.

A lack of evidence in older patients can create uncertainty in selecting the most appropriate treatment strategy. As novel systemic therapies emerge, it is important to include patients who adequately represent those we encounter in clinic in prospective trials. This is recognized and highlighted by the American Society of Clinical Oncology (ASCO), the International Society of Geriatric Oncology (SIOG), and the European Organization for Research and Treatment of Cancer (EORTC)[111-114]. Suggestions include removal of upper age limits, design of trials specifically for older patients, and integration of frailty assessments and appropriate outcome measures.

When designing trials, we should also identify questions relevant to our real-world population and design studies appropriately to address them. Priority should be given to patient preference. In GEA, the poor prognosis and the high prevalence of frailty in this group of patients[115-117] should drive investigation of dose de-escalation strategies and validation of novel patient-centred endpoints like patient-reported quality of life and preservation of physical function/independence. In the complex world of geriatric oncology, where there is huge variation in patient fitness and circumstances, communication with patients and families is also essential. While awaiting these trials, we should not overlook prospective cohort studies and real-world data which can provide important insights into our management decisions. This is particularly important in GEA, where practice varies across geographical regions.

Conclusion

GEA is a disease of the older adult and is increasing in incidence worldwide. It is associated with significant symptom burden, co-morbidity, and a poor prognosis even in the curative setting. The patients we see in clinic differ significantly from those included in RCTs. As such, choosing the correct management plan on an individual level is a challenge, particularly with the need to balance efficacy and QoL. Frailty is a key feature among older adults with GEA, and screening for frailty then performing a CGA should be a priority, including targeted interventions. Including older patients in clinical trials of GEA, promoting the integration of CGA into both clinical trials and clinical practice, as well as designing trials specifically for this population such as the GO2 trial, are future directions for geriatric oncology research in gastric and esophageal tumors.

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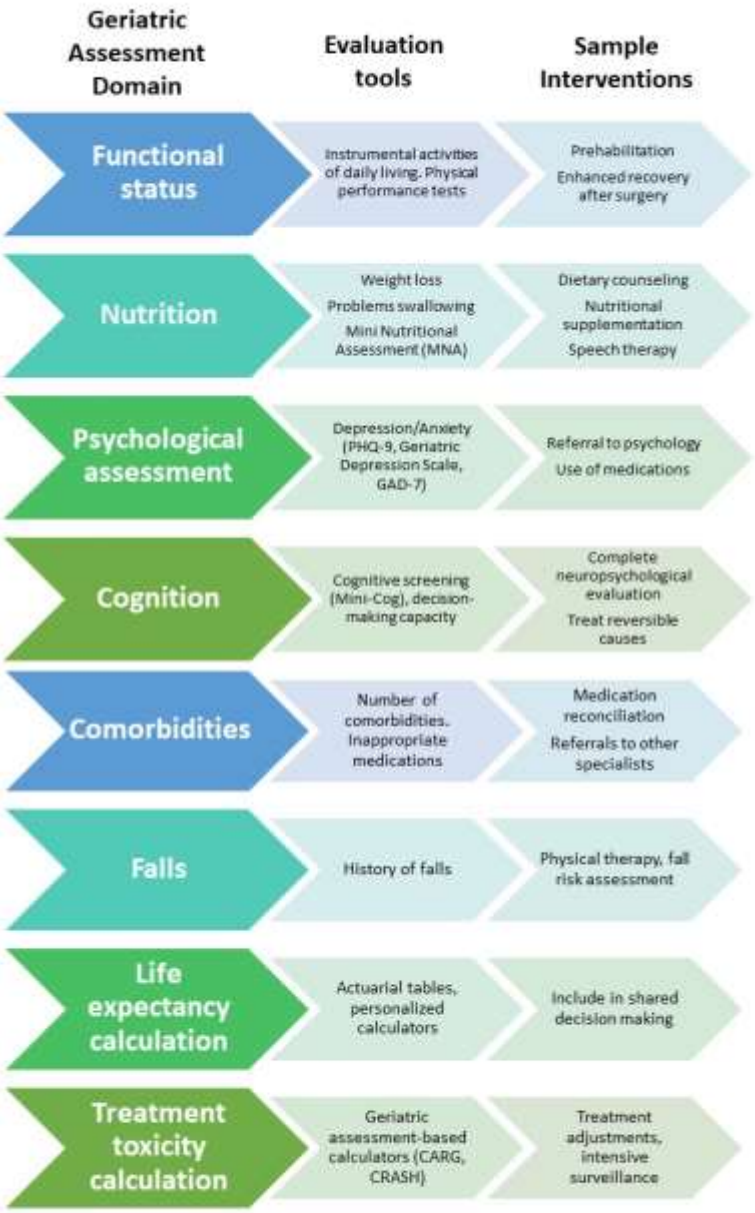

598 **Figure 1.** Geriatric assessment domains, suggested tools to evaluate them, and sample

599 multidisciplinary interventions for older adults with GEA.

Study	Study design	Study groups	Median age (range)	Overall outcome	Number and percentage of older cancer patients	Efficacy specific for older cancer patients
Perioperative chemotherapy						
MAGIC[47]	RCT - 503 participants - Resectable adenocarcinoma of stomach, GOJ or esophagus	1. Perioperative chemotherapy (ECF) + surgery 2. Surgery alone	62 (23-81)	Perioperative chemotherapy improved mPFS (HR 0.66; 95% CI 0.53-0.81, p<0.001) and mOS (HR 0.75; 95% CI 0.60-0.93, p=0.009) 5 year OS 36.3% v 23%	Age 60-69: 186 (37%) Age ≥70: 105 (20.8%)	-
FLOT4-AIO[5]	Open-label phase 2/3 - 716 participants - Locally advanced, resectable GOJ or gastric cancer - German population	1. Perioperative FLOT chemotherapy 2. Perioperative ECF/ECX chemotherapy	62 (54-69)	FLOT improved mOS (50 v 35 months; HR 0.77, 95% CI 0.63-0.94)	Age 60-69: 229 (32%) Age ≥70: 172 (24%)	-
Neoadjuvant chemoradiotherapy						
CROSS[50]	RCT - Total: 368 participants - clinically resectable, locally advanced cancer of the	1. Chemoradiotherapy (weekly taxol-carboplatin; RT	60 (36-79)	Chemoradiotherapy improved in mOS (48.6 vs. 24.0 months, HR 0.68, p=0.003)	No subgroup analysis on older population	-

	esophagus or oesophagogastric junction (clinical stage T1N1M0 or T2–3N0–1M0)	41.4Gy/23Fr/5.5 weeks) + Surgery 2. Surgery alone				
Adjuvant chemotherapy						
CLASSIC[59]	RCT - Total: 1035 participants - Stage II-IIIB gastric cancer post D2 gastrectomy	1. Adjuvant oxaliplatin/ capecitabine x 8 cycles 2. Surgery alone	60 (53-66)	Adjuvant Xelox improved: - 5-year OS: 78% vs. 69%, p=0.0015 - 5-year DFS: 68% vs. 58%, p<0.0001	No subgroup analysis on older population	-
ACT-GS[118]	RCT - Total: 1059 participants - Stage II/ III gastric cancer post D2-gastrectomy	1. Adjuvant S-1 for one year 2. Surgery alone	63 (27-80)	Adjuvant S-1 improved: - 5-year OS: 71.7% vs. 61.1%, - 5-year RFS: 65.4% vs. 53.1%	Age 60-69: - n=408, 38.5% Age 70-80: - n=257, 24.3%	Age 60-69: - 5-year OS: HR 0.678 (95% CI: 0.467 – 0.983) - 5-year RFS: HR 0.726 (95% CI 0.523 – 1.008) Age 70-80: - 5-year OS: HR 0.779 (95% CI: 0.527 – 1.151)

						- 5-year RFS: HR 0.706 (95% CI 0.490 – 1.1017)
JACCRO GC-7[61]	RCT - Total: 915 participants - Pathological stage III with R0 resection - Asian population	1. Adjuvant S-1 + Docetaxel 2. Adjuvant S-1	66 (28-80)	Adjuvant S-1/docetaxel improved: - 3-year RFS: 65.9% vs. 49.6% (HR 0.632, p=0.0007)	Age > 70: n=257, 28.1%	Age >70 - 3-year RFS: HR 0.846, 95% CI 0.547 – 1.308
Adjuvant chemoradiotherapy						
Intergroup INT 0116[63]	RCT: - Total: 559 - primaries ≥ T3 and/or node-positive gastric cancer	1. Adjuvant chemoradiotherapy 2. Surgery alone	60 (23-87)	Adjuvant chemoradiotherapy improved: - median OS: 35 vs. 27 months, HR 1.32, p=0.0046 - median PFS: 27 vs. 19 months, HR 1.51, p<0.001	No subgroup analysis on older population	-
ARTIST[64]	RCT: - Total: 458 participants - stage IB to IV (M0) gastric cancer patients with D2 dissection	1. adjuvant chemotherapy with capecitabine-cisplatin 2. adjuvant chemotherapy with capecitabine-cisplatin and chemoradiotherapy	56 (22-77)	No significant difference in OS between the two arms. Adding chemoradiotherapy improved 3-year DFS in	No subgroup analysis on older population	-

				- lymph node positive disease: 76% vs. 72%, p=0.04 - intestinal type gastric cancer: 94% vs. 83%, p=0.01		
ARTIST-2[65]	RCT: - Total: 538 participants - pathologically-staged II or III, node-positive, D2-resected gastric cancer	Three arms: 1. Adjuvant chemotherapy S-1 2. Adjuvant chemotherapy S-1/ oxaliplatin (SOX) 3. Adjuvant chemotherapy SOX + chemoradiotherapy	61 (27-85)	3-year DFS of S-1 vs. SOX vs. SOXRT: 64.8% vs. 74.3% vs. 72.8% No significant difference between SOX and SOXRT	No subgroup analysis on older population	-

600

601 **Table 1.** Key trials in the radical setting for gastroesophageal adenocarcinoma. Abbreviations: CI – confidence interval; DFS – disease free survival;

602 HR – hazard ratio; mOS – median overall survival; n – number; RCT – randomised controlled trial; RFS – recurrence free survival.

603

604

	Median Age (range)	Overall Survival	Time to Progression or Progression-free survival	Objective Response Rate	Survival in Older adults
First-line					
REAL-2 [67] ECF ECX EOF EOX (n=1002)	61-65 (22-83	 9.9 months 9.9 months 9.3 months 11.2 months	 6.2 months 6.7 months 6.5 months 7.0 months	 40.7% 46.4% 42.4% 47.9%	-
SPIRITS [68] S-1 vs S-1+cisplatin (n=325)	62 (28-74)	11.0 vs 13.0 months	4.0 vs 6.0 months	31% vs 54%	-
GO2 [27] OX (100%) OX (80%) OX (60%)	 76 76 77	 7.5 months 6.7 months 7.6 months	 4.9 months 4.1 months 4.3 months		 7.5 months 6.7 months 7.6 months
Subsequent line					

COUGAR-02 [87] Docetaxel vs BSC (n=168)	65-66 (28-84)	5.2 vs 3.6 months	12.2 weeks vs n/a	-	-
German AIO[86] Irinotecan v BSC	58 (43-73) and 55 (35-72)	4.9 v 2.4 months	Irinotecan ITT: 2.6 months	-	-
WGOJ4007[88] Paclitaxel v irinotecan	64.5 (37-75) and 65 (38-75)	9.5 v 8.4 months (HR 1.13, p=0.38)	3.6 v 2.3 months, HR 1.14, p=0.33.	-	≥65 years: OS - HR 0.97
TAGS [89] Trifluridine/tipiracil vs BSC (n=507)	63-64 (56-70) [45% were 65+]	5.7 vs 3.7 months	2.0 vs 1.8 months	-	≥65 years: OS – HR 0.73

Table 2. Landmark clinical trials in patients with advanced gastroesophageal adenocarcinoma. Abbreviations: BSC – best supportive care; CI – confidence interval; HR – hazard ratio; mOS – median overall survival; n – number; OS – overall survival; RCT – randomised controlled trial.

	Median Age (y) (range)	Number of patients with adenocarcinoma	Overall Survival	Time to Progression	Objective Response Rate	Median Duration of Response	Survival in Older adults
First-line							
KEYNOTE-062[72]: Pembrolizumab vs Chemotherapy	61.0 (20-83) vs 62.5 (23-87)	N=506 (N=213 ≥65 y)	**PD-L1 CPS≥1**: 10.6 vs 11 months (HR 0.91; 99.2% CI: 0.69-1.18[a]) **PD-L1 CPS≥10:** 17.4 vs 10.8 months (HR 0.69; 95% CI: 0.49-0.97)	**PD-L1 CPS≥1**: 2.0 vs 6.4 months (HR 1.66; 95%CI:1.37-2.01) **PD-L1 CPS≥10:** 2.9 vs 6.1 months (HR 1.10; 95% CI: 0.79-1.51)	**PD-L1 CPS≥1**: 15% vs 37% **PD-L1 CPS≥10**: 25% vs 38%	**PD-L1 CPS≥1**:13.7 vs 6.8 months **PD-L1 CPS≥10**: 19.3 vs 6.8 months	**PD-L1 CPS≥1**: HR 0.97; 95% CI: 0.72-1.31) **PD-L1 CPS≥10**: HR 0.92; 95% CI: 0.55-1.54)
KEYNOTE-062[72]: Pembrolizumab + chemotherapy vs Chemotherapy	62.0 (22-83) vs 62.5 (23-87)	N=507 (N=216 ≥65 y)	**PD-L1 CPS≥1**: 12.5 vs 11.1 months (HR 0.85; 95% CI: 0.70-1.03; p=0.05)	**PD-L1 CPS≥1**: 6.9 vs 6.4 months (HR 0.84; 95%CI:0.70-1.02; p=0.04) **PD-L1 CPS≥10:**	**PD-L1 CPS≥1**: 49% vs 37% **PD-L1 CPS≥10**: 53% vs 38%	**PD-L1 CPS≥1**:6.8 vs 6.8 months **PD-L1 CPS≥10**: 8.3 vs 6.8 months	**PD-L1 CPS≥1**: HR 0.96; 95% CI: 0.72-1.29)

			PD-L1 CPS≥10: 12.3 vs 10.8 months (HR 0.85; 95% CI: 0.62-1.17; p=0.16)	(HR 0.73; 95% CI: 0.53-1.00)			
CheckMate 649[74]: Nivolumab+ chemotherapy vs Chemotherapy	63.0 (18-88) vs 62.0 (23-90)	N=955 (N=403 ≥65 y) in PD-L1 CPS≥5	**PD-L1 CPS≥5**: 14.4 vs 11.1 months (HR 0.71; 98.4% CI: 0.59-0.86; p=0.0001) **PD-L1 CPS≥1**: 14.0 vs 11.3 months (HR 0.77; 95% CI: 0.64-0.92; p=0.0001)	**PD-L1 CPS≥5**: 7.7 vs 6.0 months (HR 0.68; 98% CI: 0.56-0.81; p<0.0001) **PD-L1 CPS≥1**: 7.5 vs 6.9 months (HR 0.74; 95% CI: 0.65-0.85) **ITT:** 7.7 vs 6.9 months (HR 0.77; 95% CI: 0.68-0.87)	**PD-L1 CPS≥5**: 60% vs 45% (p<0.0001)	**PD-L1 CPS≥5**: 9.5 vs 7.0 months	**PD-L1 CPS≥5**: 14.3 vs 11.2 months (HR 0.72)

			ITT: 13.8 vs 11.6 months (HR 0.80; 95% CI: 0.68-0.94; p=0.0002)				
ATTRACTION-4[76]: Nivolumab+ chemotherapy vs Chemotherapy	63.5 (25-86) vs 65.0 (27-89)	N=724 (N=368 ≥65 y)	17.5 vs 17.2 months (HR 0.90; 95% CI: 0.75-1.08; p=0.257)	10.5 vs 8.3 months (HR 0.68; 98.51% CI: 0.51-0.90; p=0.0007)	58% vs 48% (p=0.0088)	12.9 vs 8.7 months	17.9 vs 19.7 months (HR 1.01)
KEYNOTE-590[73]: Pembrolizumab+ chemotherapy vs Chemotherapy	64.0 (28-94) vs 62.0 (27-89)	N=201 (N=91 GEJ adenocarcinoma)	**Adenocarcinoma subgroup:** 11.6 vs 9.9 months (HR 0.74; 95% CI: 0.54-1.02)	**Adenocarcinoma subgroup:** 6.3 vs 5.7 months (HR 0.63; 95% CI: 0.46-0.87)	**Overall population:** 45.0% vs 29.3%, (p<0.0001)	**Overall population:** 8.3 vs 6.0 months	**Overall population**: HR 0.69; 95% CI 0.53-0.89

Subsequent lines							
KEYNOTE-061[119]: Pembrolizumab vs Paclitaxel	62.5 (27-87) vs 60.0 (20-86)	N=468 (~40%≥65 y)	**PD-L1 CPS≥1**: 9.1 vs 8.3 months (HR 0.81; 95% CI: 0.66-1.00; p=0.03) **PD-L1 CPS≥5:** 10.4 vs 8.3 months (HR 0.72; 95% CI: 0.53-0.99; p=0.02) **PD-L1 CPS≥10:** 10.4 vs 8.0 months (HR 0.69; 95% CI: 0.46-1.05;p=0.04)	**PD-L1 CPS≥1**: 1.5 vs 4.1 months (HR 1.25; 95% CI: 1.02-1.54) **PD-L1 CPS≥5:** 1.6 vs 4.0 months (HR 0.98; 95% CI: 0.71-1.34) **PD-L1 CPS≥10:** 2.7 vs 4.0 months (HR 0.79; 95% CI: 0.51-1.21)	**PD-L1 CPS≥1**: 32% vs 27% **PD-L1 CPS≥5**: 19% vs 13% **PD-L1 CPS≥10**: 13% vs 5%	**PD-L1 CPS≥1**:19.1 vs 5.2 months **PD-L1 CPS≥5**: 32.7 vs 4.8 months **PD-L1 CPS≥10**: NR vs 6.9 months	**PD-L1 CPS≥1**:HR 0.82; 95% CI 0.58-1.15
ATTRACTION-2[120]: Nivolumab vs placebo	62.0 (54-69) vs 61.0 (53-68)	N=493 (N=209 ≥65 years)	5.26 vs 4.14 months	1.61 vs 1.45 months (HR 0.60; 95% CI: 0.49-0.75; p<0.0001)	11.9 % vs 0%	9.53 months vs n/a	HR 0.60 95%CI 0.44-0.82

			(HR 0.62; 95% CI: 0.51-0.76; p<0.0001)				

608 **Table 3. Clinical trials of immune checkpoint inhibitors in patients with advanced gastroesophageal adenocarcinoma.** Abbreviations: CI – confidence
609 interval; CPS – combined positivity score; HR – hazard ratio; mOS – median overall survival; n – number; n/a – not available; PD-L1 – programmed
610 death ligand-1.
611 a: noninferiority margin=1.2
612
613

	Median Age (y) (range)	Number of patients with adenocarcinoma	Overall Survival	Time to Progression	Objective Response Rate	Median Duration of Response	Survival in Older adults
Anti-VEGF trials							
REGARD trial [121] Ramucirumab vs placebo	60 (52-67) vs 60 (51.71)	355 (N=128 ≥65y)	5.2 vs 3.8 months (HR 0.776; 95% CI 0.603-0.998)	2.1 vs 1.3 months (HR 0.48; 95% cI 0.37-0.62)	3% vs 3% p=0.76	8 weeks vs 6 weeks	**≥65y**: 5.2 months vs 3.8 months; HR 0.72; 95% CI 0.48-1.08) **≥70y:** 5.9 months vs 3.8 months (HR 0.73; 95% CI 0.44-1.23) **≥75y:** 9.3 vs 5.1 months (HR 0.59; 95% CI 0.25-1.37)

RAINBOW trial[122] Paclitaxel +/- Ramucirumab	61 (25-83) vs 61 (24-84)	665 (N=249 ≥65 y)	9.6 vs 7.4 months (HR 0.807; 95% CI 0.678–0.962)	4.4 vs 2.9 months (HR 0.635; 95% CI 0.536– 0.752)	28% vs 16% (p=0001)	18 weeks vs 12 weeks	**≥65y**: 10.7 months vs 8.7 months; HR 0.88; 95% CI 0.66- 1.18) **≥70y:** 10.8 months vs 8.6 months (HR 0.88; 95% CI 0.60- 1.28) **≥75y:** 11 months vs 11 months (HR 0.97; 95% CI 0.47-2.01)
HER2 positive gastroesophageal adenocarcinoma							
TOGA trial [77] Cisplatin + fluoropyrimidine (5-FU or capecitabine) +/- Trastuzumab	59.4 (n/a) vs 58.5 (n/a)	594 (N = 305 pts ≥60 y)	All comers: 13.8 vs 11.1 months (HR 0.74; 95% CI 0.60-0.91; p=0.046) HER2 positive: 16 vs 11.8 months (HR 0.65; 95% CI 0.51-0.83; p=0.036)	7.1 vs 5.6 months	47% vs 35%	n/a	**≥60y:** HR 0.66 (95% CI 0.49- 0.88) **<60y:** HR 0.84; (95% CI 0.62- 1.14)
DESTINY- **Gastric01[94]**	65 (34-82) vs 66 (28-82)	N=187 (N= 105 ≥65 y)	12.5 vs. 8.4 months;	5.6 vs 3.5 months (HR 0.47; 95% CI 0.31 – 0.71)	51% vs 14%	11.3 vs 3.9 months	HR 0.44 ; 95% CI: 0.26-0.76

Trastuzumab deruxetcan vs Paclitaxel or Irinotecan			(HR 0.59; 95% CI 0.39-0.88; p=0.01)				
KEYNOTE-811[83] Cisplatin/capecitabine/trastuzumab or Cisplatin/capecitabine/trastuzumab +/- Pembrolizumab	62 (19-84) vs 61 (32-83)	N=732 (planned sample size) Interim analysis available for first 264	n/a	n/a	74% vs 52%	10.6 vs 9.5 months	n/a

614

615 **Table 4. Clinical trials of targeted therapies in patients with advanced gastroesophageal adenocarcinoma.** Abbreviations: CI – confidence interval; HR

616 – hazard ratio; n – number; n/a – not available; y – years old.

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