# Late-line treatment in metastatic gastric cancer: today and tomorrow

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***Abstract*:** Survival for patients with unresectable advanced or recurrent gastric cancer (GC) remains poor and the historical lack of evidence-based therapeutic options after second-line therapy is reflected in current clinical guidelines for this condition. Despite uncertainty about optimal therapeutic strategies, further treatment is appropriate for some patients after failure of second line and may prolong survival. This approach has been reported in clinical trials and is becoming more common in real-world clinical settings. Several prognostic factors may increase the likelihood that a patient will be eligible for treatment in the third-line setting, including geographic location, status at diagnosis and response to treatment. There has been little progress over the last decade until the results from two large phase III randomized controlled trials completed in the last year: the ATTRACTION-2 trial with the programmed cell death-1 (PD-1) inhibitor, nivolumab, in an Asian population; and the TAGS trial with the oral chemotherapy trifluridine/tipiracil in a global population. Both ATTRACTION-2 and TAGS reported positive results in third-line treatment in advanced GC in specific patient groups. A further recently reported study, KEYNOTE-059, which was a single-arm phase II trial of the PD-1 inhibitor pembrolizumab in a mainly non-Asian population, has provided evidence supporting the use of this immunotherapy in patients with advanced GC. As further third-line options become available, more GC patients are expected to benefit from an individualized evidence-based approach to later-line therapy, with a common goal of extending survival and improving outcomes for their refractory disease.

***Keywords:*** chemotherapy, gastric cancer (GC), immunotherapy, nivolumab, pembrolizumab, trifluridine/tipiracil

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## Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide, with 951,000 new cases each year, and the third leading cause of cancer death, with 723,000 events annually.[1,2] Incidence varies between regions; with the highest rates in Eastern Asia, Central and Eastern Europe, and South America, and lower rates in Western Europe, North America and Africa.[2] Despite a gradual decline over time in incidence in both high- and low-prevalence countries, GC remains a serious global health burden.[2]

Surgical resection of GC, specifically at early stages, is potentially curative; however, following resection, disease relapse still occurs in the majority of patients.[3] In addition, by the time they are diagnosed, approximately 50% of patients have already developed locally advanced or metastatic GC (stage IV).[4] For fit patients with inoperable locally advanced or metastatic disease, current clinical guidelines, such as those from the European Society of Medical Oncology (ESMO), recommend the use of doublet or triplet platinum/fluoropyrimidine combinations as first-line treatment in human epidermal growth-factor receptor 2 (HER-2)-negative patients, and trastuzumab with platinum and fluoropyrimidine-based chemotherapy for HER-2 positive patients.[3,5] Taxanes (docetaxel, paclitaxel), irinotecan or ramucirumab (alone or in combination with paclitaxel) are recommended as second-line treatment options for patients with performance status (PS) 0–1.[3,5]

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In current GC guidelines, the first- and second-line recommendations are supported by level I evidence [i.e. based on at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity].[3]

Until recently, there have been no good-quality data to support third-line treatment in metastatic GC. Although trials evaluating the safety and efficacy of several chemotherapy and targeted agents have been reported, these have not provided sufficiently robust level I evidence, as most were non-randomized and frequently single-centre trials.

Chan and colleagues[6] identified randomized trials evaluating the efficacy, toxicities and quality of life (QoL) of third-line systemic treatment *versus* best supportive care (BSC) in metastatic GC patients after failing two lines of systemic treatment. Four studies reporting overall survival (OS) after third-line therapy were considered with five comparisons. In the meta-analysis of OS results from these trials, compared with BSC, third-line therapy improved OS [hazard ratio (HR) 0.63; 95% confidence interval (CI) 0.46–0.87, $p=0.006$], corresponding to an improvement in median OS (mOS) from 3.20 to 4.80 months. However, two of the four studies for this analysis (Table 1) enrolled relatively small groups of patients (<50 in the treatment arms). For example, just 33 out of the 133 patients enrolled in a large Korean study were treated with third-line salvage chemotherapy.[7] Additionally, three of the studies included in the meta-analysis related to apatinib (rivoceranib),[8,9] which is licensed for the treatment of GC in China, but remains in clinical development elsewhere.[10] Lastly, despite enrolling a relatively large number of patients, the results of a study of everolimus[11] (which is not licensed for use in GC) were included. In this study, everolimus did not demonstrate a significant improvement in mOS for third-line therapy *versus* BSC.[11] Given such limitations within the available evidence base, the most recent ESMO guidelines suggested that the second-line options can be used sequentially, but also stated that 'there is no clear evidence for a benefit beyond second-line treatment'.[3]

It is against this background that over the past year, findings from three trials of emerging third-line therapy options in metastatic GC have become available.[12–14] This short review article discusses current later-line management of metastatic GC and the results from these trials.

## Late-line treatments: current options

Despite the previous lack of evidence to define optimal treatments in the third line and beyond in patients with advanced GC, further treatment is appropriate for some patients after failure of earlier lines and was associated with extended survival, although there are clear biases when assessing this outside the context of randomized trials. Later-line

**Table 1.** Pre-2017 RCTs of third-line systemic treatment *versus* BSC for advanced/metastatic GC included in the meta-analysis by Chan and colleagues.[6]

| Study or subgroup | Treatments evaluated | Study phase | Experimental arm (*n*) | Control arm (*n*) | Median OS (experimental *versus* control arms) |
|---|---|---|---|---|---|
| Kang *et al.*[7] | Docetaxel or irinotecan *versus* BSC | III | 33 | 21 | 5.3 *versus* 3.8 months* (HR: 0.66, 95% CI: 0.48–0.89, $p=0.007$) |
| Li *et al.*[8] | Oral apatinib *versus* oral placebo (BID) | II | 46 | 24 | 4.3 *versus* 2.5 months (HR 0.41, 95% CI:0.24–0.72, $p=0.0017$) |
| | Oral apatinib *versus* oral placebo (QD) | II | 47 | 24 | 4.8 *versus* 2.5 months (HR 0.37, 95% CI: 0.22–0.62, $p<0.001$) |
| Li *et al.*[9] | Oral apatinib *versus* oral placebo | III | 176 | 91 | 6.5 *versus* 4.7 months (HR: 0.71, 95% CI: 0.54–0.94, $p=0.0156$) |
| Ohtsu *et al.*[11] | Oral everolimus plus BSC *versus* oral placebo plus BSC | III | 229 | 114 | 5.4 *versus* 4.3 months (HR: 0.90; 95% CI: 0.75–1.08, $p=0.124$) |

*mOS shown is for the overall population (133 *versus* 69 patients receiving salvage chemotherapy or best BSC, respectively, which included patients receiving both prior 1 or 2 previous lines of chemotherapy for advanced disease).
BID, twice daily; BSC, best supportive care; CI, confidence interval; GC, gastric cancer; HR, hazard ratio; mOS, median overall survival; QD, once daily; RCT, randomized controlled trial.

treatment in GC has often been adopted in real-world and trial settings.[6,15,16] For example, in the RAINBOW phase III trial [ClinicalTrials.gov identifier: NCT01170663] of ramucirumab in combination with paclitaxel in the second-line setting, a majority of Asian patients went on to be treated with third-line chemotherapy (69% *versus* 38% for non-Asian patients, respectively).[17] This suggests that high proportions of trial-eligible patients in both Asian and non-Asian populations may be candidates for third-line therapy. The higher likelihood of receiving such therapy in Asian populations may reflect earlier identification of GC through screening in Asian countries,[3] which may support treatment earlier in the disease course with a lower disease burden.

Outside of clinical trials, there is real-world evidence that the proportion of GC patients receiving third-line therapy is growing. A retrospective analysis of consecutively treated patients ($n = 511$) receiving at least one cycle of chemotherapy for advanced GC at a single UK oncology centre between April 2009 and November 2015 showed that the rate of uptake of later lines increased substantially over this time period.[16] This analysis also found that the mOS increased in relation to the number of lines of treatment received (from 8.3 months for patients who received first-line treatment only, to 33 months for those who were fit for fourth-line treatment).[16]

The proportion of patients receiving second-line treatment in the real-world UK study was 39%, which was similar to that observed in retrospective analyses of medical records data from GC patients in the US (42%; $n = 5257$)[18] and Italy (39%; $n = 2200$).[19] Across these three studies, the proportion of patients receiving third-line treatment was also similar (14% in the UK, 18% in the US, 15% in Italy).[16,18,19] As these real-world studies spanned periods before the approval of ramucirumab as a second-line option, they may under-represent the proportion of patients who may currently be eligible for second-line therapy.

Analyses of outcomes from clinical trials and real-world studies have identified several factors that predict longer OS in GC and thus may also increase the likelihood that a patient will be eligible for treatment in the third-line setting (Table 2). These prognostic factors include geographic location,[17]

**Table 2.** Prognostic factors predicting more lines of therapy for patients with GC.

| Factor | Notes |
|---|---|
| Geography | In the RAINBOW trial, patients in Asian countries were more likely to receive third-line therapy (69%) than those in non-Asian countries (38%)[17] |
| Chemosensitivity at diagnosis | (1) The Royal Marsden Hospital Prognostic Index is based on pooled survival data from 1080 patients enrolled onto three multicentre RCTs evaluating first-line chemotherapy in locally advanced or metastatic GC[20] and have been validated using an independent data set ($n = 1002$ patients).[21] Patients are assigned to 'good', 'moderate', or 'poor' risk groups (each with highly significant survival differences) based on the presence of 0 to 4 of the following poor prognostic risk factors: PS $\geqslant$ 2, liver metastasis, peritoneal metastasis, and serum alkaline phosphatase $\geqslant$ 100 U/l[20]<br>(2) In GC, RCT patients identified as 'good' risk ($n = 239$) using the Royal Marsden Hospital Prognostic Index (i.e. having none of the four risk factors), receiving first-line chemotherapy had a significantly improved survival after receiving first-line chemotherapy compared with patients having 'moderate' ($n = 487$) or 'poor' risk ($n = 91$); $p < 0.00001$[20]<br>(3) Overall, patients with more chemosensitive tumours may be more likely to receive later lines of therapy after surviving beyond first line (also see below) |
| Response to early-line treatment | (1) A meta-analysis of patient-level data from three phase III clinical trials in relapsed gastric and oesophageal cancers identified TTP after first-line chemotherapy significantly impacts responses to second-line chemotherapy: patients progressing 3–6 months following first-line chemotherapy gained most benefit in OS ($p < 0.0001$)[22]<br>(2) In a real-world cohort of GC patients ($n = 300$) treated with at least three lines of chemotherapy, those having a first-line PFS $\geqslant$ 6.9 months and having a PFS to second line $\geqslant$ 3.5 months had better outcomes (in terms of a longer PFS to third line and a longer OS on third line), compared with those who had shorter PFS ($p = 0.008$ and $p < 0.001$, respectively)[19] |

GC, gastric cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; RCT, randomized controlled trial; TTP, time to progression.

chemosensitivity at diagnosis[20,21] and response to treatment.[20,22] Overall, it seems that patients with low tumour burden, slower tumour growth rate and chemosensitive tumours are more likely to reach the third line of treatment.

### *Emerging treatment in later lines: options for tomorrow*

Understanding which patients may benefit from third-line therapy in advanced GC is of growing interest in light of recent trial findings which support the safety and efficacy of the programmed cell death-1 (PD-1) inhibitors nivolumab[12] and pembrolizumab,[13] and the oral chemotherapy combination trifluridine/tipiracil as third-line treatments in this setting[14] (Table 3). These studies are discussed in more detail in the following sections.

### *ATTRACTION-2 nivolumab phase III study in an Asian population*

The ATTRACTION-2 study [ClinicalTrials.gov identifier: NCT02267343] was the first phase III study of an immune checkpoint inhibitor in patients with advanced gastric or gastro-oesophageal junction cancer.[12] This randomized, double-blind, placebo-controlled study was conducted exclusively in Asian countries (Japan, Taiwan and Korea) and assessed the efficacy and safety of nivolumab in 493 patients who had previously been treated with two or more chemotherapy regimens. In both the nivolumab and placebo arms, most patients (>80%) had GC as the site of their primary tumour. In the nivolumab group, although the objective response rate was modest (11.2%), the median OS was significantly increased (5.3 months *versus* 4.1 months in the placebo group; HR 0.63, 95% CI: 0.51–0.78;

**Table 3.** Recently completed phase II/III clinical trials of third-line therapy in advanced/metastatic GC.

| Study phase | KEYNOTE-059[13] | ATTRACTION-2[12] | TAGS[14] |
|---|---|---|---|
| | Phase II | Phase III | Phase III |
| Participating countries | Global study across 16 countries (including USA, Canada, France, Japan and Australia) | Japan, South Korea, Taiwan | Global study across 17 countries (including USA, France, Germany, Italy and Japan) |
| Study design | Open-label, single-arm trial evaluating the safety and efficacy of pembrolizumab | Randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of nivolumab | Randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of trifluridine/tipiracil |
| Patients enrolled | 259 | 493 | 507 |
| Primary endpoint(s) | ORR and safety | OS | OS |
| OS results | mOS 5.6 months (no placebo arm) | mOS 5.3 months *versus* 4.1 months for placebo (HR 0.63, 95% CI: 0.51–0.78; $p < 0.0001$) | mOS 5.7 months *versus* 3.6 months for placebo (HR: 0.69, 95% CI: 0.56–0.85, $p = 0.0003$) |
| PFS at 6 months (Kaplan–Meier estimates) | 14.1% | 20.2% *versus* 6.8% for placebo | 15% *versus* 6% for placebo |
| Safety | TRAEs of any grade reported in 156 patients (60.2%) treated with pembrolizumab; 46 (17.8%) patients experienced ⩾1 grade 3 to 5 TRAEs | TRAEs of any grade reported in 141 patients (42.7%) in the nivolumab group and in 43 patients (26.7%) in the placebo group; grade 3 or 4 TRAEs occurred in 34 (10.3%) of 330 patients who received nivolumab and 7 (4.3%) of 161 patients who received placebo | TRAEs of any grade reported in 271 patients (81%) in the trifluridine/tipiracil group and in 96 patients (57%) in the placebo group; grade 3 or worse TRAEs reported in 176 (52.5%) patients in the trifluridine/tipiracil group and 22 (13.1%) in the placebo group |

CI, confidence interval; GC, gastric cancer; HR, hazard ratio; mOS, median overall survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

$p < 0.0001$). Treatment-related adverse events (TRAEs) led to death in 5 (2%) of 330 patients in the nivolumab group and 2 (1%) of 161 patients in the placebo group.

The ATTRACTION-2 primary results were published after a median follow up in surviving patients of 8.9 months[12] and longer-term follow-up data for the study were reported later. [23,24] The OS rates remained higher for nivolumab *versus* placebo after 24 months' follow up (10.6% *versus* 3.2%).[23]

In an exploratory *post hoc* analysis, programmed cell death ligand-1 (PD-L1) expression was examined for 192 (38.9%) of the patients in the study (those who had tumour samples available).[12] Nivolumab demonstrated benefit, irrespective of PD-L1 expression [mOS was 5.2 and 6.1 months in patients with PD-L1-positive (immunohistochemistry staining observed in ⩾1% of tumour cells) and PD-L1-negative tumours (immunohistochemistry staining observed in <1% of tumour cells), respectively]. The all-grade TRAEs reported more commonly in 5% or more of patients in the nivolumab group than the placebo group were pruritus, diarrhoea, rash and decreased appetite. Overall, in the ATTRACTION-2 study, the safety profile of nivolumab was manageable and no new safety signals were observed.[12] Incidence rates of TRAEs were comparable at 6 months, 1 year and 2 years.[23]

The objective response rate (ORR) in ATTRACTION-2 (11.2%)[12] was less than that observed for nivolumab in melanoma (44%, from the phase III CheckMate 067 study[25]) or in non-small-cell lung cancer (NSCLC; 18%, from pooled study data),[26] suggesting that nivolumab's benefits are restricted to a smaller proportion of patients in chemorefractory GC than in melanoma. ATTRACTION-2 did, however, show that nivolumab has a favourable safety profile and is an effective treatment in this patient population. The ATTRACTION-2 trial supported nivolumab's approval in Japan, Taiwan and Korea (countries participating in the study).[27,28]

It should be noted that while the results of the ATTRACTION-2 study are encouraging in an Asian population, it has been demonstrated that GC tumours in Asian patients exhibit distinct gene-expression signatures related to T-cell function compared with non-Asian patients.[29,30] In particular, tumours in non-Asian patients express higher levels of markers associated with T-cell activity, including CTLA-4, CD3, CD45R0 and CD8, and lower levels of the immunosuppressive T-regulatory cell marker FOXP3 compared with those in Asian patients.[30] These differences should be taken into consideration when discussing the potential effectiveness of nivolumab as a treatment for advanced GC in a non-Asian population. These differences and the potential lack of generalizability may have influenced regulatory authorities when considering licensing applications for nivolumab in non-Asian jurisdictions. However, cross-trial comparison of the ORR and OS associated with anti-PD-1 therapy in chemorefractory GC does not reveal any major differences in efficacy between Asian and global populations.

### *KEYNOTE-059 pembrolizumab phase II study*

The KEYNOTE-059 study [ClinicalTrials.gov identifier: NCT02335411] was a nonrandomized, phase II, open-label, single-arm, multicohort study to evaluate the safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric or gastro-oesophageal junction cancer.[13] Patients were enrolled at sites in 16, mainly non-Asian, countries and the study population of 259 patients had a relatively even split between cases of gastric (48.3%) and gastro-oesophageal junction (51.4%) cancer.

After a median follow up of 5.8 months, the ORR for pembrolizumab was 11.6% in the overall (biomarker-unselected) study population.[13] In colorectal cancer (CRC), patients whose tumours are microsatellite unstable (MSI)-high (MSI-H) express a large number of aberrant proteins that are recognized as 'nonself' antigens. These antigens trigger an antitumour immune response that correlates with a high response rate to PD-1 therapy.[31] When MSI-H patients were removed from the KEYNOTE-059 GC population, the ORR was 9.0%.[13]

When evaluated according to PD-L1 expression status, the ORRs for patients in KEYNOTE-059 who were PD-L1-positive [combined positive score (CPS) ⩾ 1], and -negative (CPS < 1) were 15.5% and 6.4%, respectively.[13] The median response duration was longer for patients who were PD-L1-positive, compared with those who were PD-L1-negative (16.3 *versus* 6.9 months,

respectively). Thus, an effect of PD-L1 expression on gastro-oesophageal tumours ORR and median response duration for pembrolizumab was observed in this study,[13] which contrasted with the results for nivolumab in the ATTRACTION-2 study, where broadly speaking, PD-L1-positive and -negative tumours appeared to derive a similar benefit from nivolumab.[12] In part, this may be due to different antibody-based assays in the two studies: in ATTRACTION-2, PD-L1 positivity was defined by immunohistochemistry staining in $\geqslant$1% of tumour cells only,[12] whereas in KEYNOTE-059, PD-L1 positivity was determined on the basis of a CPS which counted the number of tumour cells, macrophages and lymphocytes with positive staining.[13] Additionally, the biomarker results from ATTRACTION-2 should be treated cautiously, as these were retrospectively assessed on a small proportion of patients.[12]

In KEYNOTE-059, two deaths were considered related to treatment.[13] One or more TRAEs of any grade were experienced by 156 of the patients (60.2%) treated with pembrolizumab. Most TRAEs were mild to moderate; the most common any-grade adverse events (AEs) were fatigue, pruritus, rash, hypothyroidism, decreased appetite, anaemia, nausea, diarrhoea and arthralgia. Based on the results of this phase II, single-arm study, the US Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab for patients with recurrent locally advanced or metastatic, gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1.[32]

### *TAGS trifluridine/tipiracil global phase III study*

The TAGS study [ClinicalTrials.gov identifier: NCT02500043] was a global, randomized, double-blind, placebo-controlled, phase III study to evaluate the efficacy and safety of the oral cytotoxic chemotherapy trifluridine/tipiracil *versus* placebo in metastatic GC patients pretreated with at least two prior regimens, who were refractive to, or unable to tolerate, further chemotherapy.[14] The study enrolled 507 patients from 110 sites across 17 countries (86% of the patients were from countries outside East Asia; 14% were from Japan). Patients were randomized to receive trifluridine/tipiracil plus BSC or placebo plus BSC. In both arms, 71% of the patients had GC as the site of their primary tumour. Patients in the study were followed up for a median of 10.7 months. Trifluridine/tipiracil met the primary endpoint to improve OS (mOS was 5.7 months and 3.6 months for patients receiving trifluridine/tipiracil *versus* placebo, respectively, HR 0.69; 95% CI 0.56–0.85; one-sided $p = 0.0003$).[14]

Secondary endpoints in the TAGS study included progression-free survival (PFS), and safety and tolerability. PFS was significantly longer with trifluridine/tipiracil *versus* placebo (median PFS was 2.0 months *versus* 1.8 months, respectively; HR 0.57; 95% CI 0.47–0.70; two-sided $p < 0.0001$). One treatment-related death was reported in each of the study arms. TRAEs were reported in 81% of the patients treated with trifluridine/tipiracil ($n = 335$) *versus* 57% of the patients on placebo ($n = 168$). The most frequently occurring nonhaematological AEs observed in patients receiving trifluridine/tipiracil were nausea, decreased appetite, fatigue, vomiting and diarrhoea. Grade 3 or worse neutropenia was reported in 34% of patients receiving trifluridine/tipiracil and in none of the patients receiving placebo. Overall, the safety profile of trifluridine/tipiracil was manageable and consistent with that seen previously in patients with metastatic CRC. No new safety signals were observed in patients with metastatic GC in the study.[14]

In prespecified multivariate Cox regression analysis, the following factors were prognostic of improved OS in the TAGS study (all $p < 0.05$): Eastern Cooperative Oncology Group performance status (0 *versus* 1), age ($<$65 *versus* $\geqslant$65 years), number of prior regimens (2 *versus* $\geqslant$3), number of metastatic sites (1 or 2 *versus* $\geqslant$3), and HER-2 status (negative *versus* positive or not done).[14] After adjusting for these factors, the treatment effect for trifluridine/tipiracil was maintained, that is, a magnitude of benefit, with HR: 0.69; 95% CI: 0.56–0.85.

The TAGS study shows that a chemotherapy-based approach with trifluridine/tipiracil provides comparable improvement in mOS with that seen for immunotherapy-based approaches using nivolumab or pembrolizumab in patients with advanced or metastatic GC.[12–14] However, for the small proportion of patients who respond to immune-checkpoint blockade, responses may be more durable. The safety and tolerability profiles for these agents differ, for example, managing haematological AEs such as neutropenia may be of greater importance when using trifluridine/tipiracil, whereas managing immune-related AEs such as diarrhoea, or rash and pruritus may be of

greater concern when using nivolumab or pembrolizumab. For all three agents, there were no new safety signals observed in patients with gastro-oesophageal cancer, which should provide some reassurance for clinicians, as these medicines move towards entering use in new clinical settings.

### *Considerations for immunotherapy* versus *chemotherapy approaches*

As discussed above, the ATTRACTION-2[12] and KEYNOTE-059[13] studies supported licensing of nivolumab and pembrolizumab for use as third-line therapy in chemorefractory GC, with differing requirements in relation to PD-L1 status. These trials suggest a class effect for PD-1 inhibition; the ORR observed for nivolumab in ATTRACTION-2 (11.2%)[12] was similar to that reported for nivolumab monotherapy in the advanced/metastatic gastro-oesophageal cancer cohort ($n=59$) of the phase I/II CheckMate 032 study (ORR = 12%) [ClinicalTrials.gov identifier: NCT01928394],[33] and to that seen for pembrolizumab in KEYNOTE-059 (ORR = 11.6%).[13] Across these three studies, the mOS was similar for patients receiving either of these PD-1 inhibitor therapies (5.3, 6.2 and 5.6 months in ATTRACTION-2,[12] the CheckMate 032 nivolumab monotherapy cohort,[33] and KEYNOTE-059,[13] respectively). In the KEYNOTE-059 and CheckMate 032 studies, patients with PD-L1-positive tumours had a higher ORR to nivolumab and pembrolizumab, respectively, compared with those who were PD-L1-negative (ORR was not evaluated in the exploratory analysis of PD-L1 status in the ATTRACTION-2 study).

Recently, in the KEYNOTE-061 (NCT02370497) randomized, open-label, phase III global study, second-line treatment with pembrolizumab failed to meet the primary endpoint of significantly improving OS *versus* paclitaxel in patients with advanced gastro-oesophageal cancer who had PD-L1 CPS $\geqslant 1$ (HR 0.82; 95% CI 0.66–1.03).[34] This global study included 395 patients from 30 countries (<30% of those enrolled were Asian) and had a median follow up of 8.5 months. The results showed that the benefit of pembrolizumab on OS was delayed in patients with PD-L1 CPS $\geqslant 1$, that is, initially, chemotherapy with paclitaxel resulted in higher OS *versus* the immunotherapy approach, whereas from around 8 months onwards, the OS was higher for pembrolizumab. In a *post hoc* analysis, the pembrolizumab treatment effect for OS was greater for PD-L1 CPS $\geqslant 10$ (HR 0.64; 95% CI 0.41–1.02).[34] The KEYNOTE-061 data suggest that higher levels of PD-L1 can predict better survival when advanced GC is treated with pembrolizumab. This has been confirmed in the KEYNOTE-181 study of 2L pembrolizumab in oesophageal cancer including gastro-oesophageal junction adenocarcinoma.[35]

In contrast, tumour PD-L1 expression did not influence prognosis in the randomized, global phase III JAVELIN Gastric 300 trial [ClinicalTrials.gov identifier: NCT02625623] of the anti-PD-L1 antibody avelumab as third-line therapy in adult patients with advanced GC or gastro-oesophageal junction cancer.[36] In this study, avelumab did not meet the primary endpoint of improving OS, or the secondary endpoints of PFS and ORR, *versus* physician's choice of chemotherapy, although fewer patients had TRAEs with avelumab than with chemotherapy (either any-grade or grade $\geqslant 3$ TRAEs).

These studies suggest that characterizing prognostic markers indicating the likelihood of response to specific checkpoint inhibitor immunotherapy agents will be important to ensure that the most appropriate treatment strategy, for example, immunotherapy or chemotherapy, is selected. The safety profile of individual therapies will also need to be considered. Cytotoxic chemotherapies such as trifluridine/tipiracil seem to be associated with short-term AEs, such as neutropenia, whereas pembrolizumab and nivolumab are associated with immune-related AEs (e.g. colitis, pneumonitis), which may require longer-term management strategies.[14]

The mOS values for third-line treatment with pembrolizumab, nivolumab and trifluridine/tipiracil in the main studies discussed in this review (KEYNOTE-059, ATTRACTION-2 and TAGS) were each in excess of 5 months.[12–14] The first randomized phase III trial to compare chemotherapy with BSC in second-line treatment of metastatic GC was carried out in Germany and the results were reported in 2011.[37] In that study, the mOS for treatment with irinotecan given in second-line was 4.0 months ($n=19$ patients) *versus* 2.4 months for BSC ($n=21$ patients). Thus, the most recent studies demonstrate a trend for improvement over time in survival outcomes for

patients with advanced GC receiving treatment, even in those already having received two or more earlier lines of therapy,[12–14] and in metastatic GC patients from White/non-Asian populations, where shorter survival times have been observed on treatment, relative to patients from Asian populations.[17]

## Conclusion

Although recent years have seen more extensive use of chemotherapy in later-line treatment of advanced GC,[16,18,19] clinicians have faced a challenge when choosing therapy beyond second line due to the lack of evidence-based guidance to support specific drugs.[3] One option has been to use a taxane or irinotecan in the third-line setting, depending on what has been used previously; however, this approach is not supported by much good-quality evidence.[38] Results from the ATTRACTION-2 and TAGS studies provide robust level I evidence for the use of nivolumab and trifluridine/tipiracil, respectively, in third-line therapy for appropriate patients.[12,14]

Supported by the phase III ATTRACTION-2 study in Asian patients, nivolumab has now gained approval as a biomarker-unselected treatment for metastatic GC patients in Japan, Taiwan and Korea (where this trial took place).[27,28] Based on the results of the global phase II KEYNOTE-059 study, the FDA granted accelerated approval to pembrolizumab for patients with metastatic GC whose tumours express PD-L1.[32]

In the United States, findings from the global, phase III TAGS study[14] have been translated into label updates for trifluridine/tipiracil,[39] permitting its use as a third-line therapy in appropriate patients with metastatic GC there. It is likely that these treatments will find their way into routine clinical use.

Factors to consider when determining whether antibody immunotherapy targeting PD-1, or chemotherapy with trifluridine/tipiracil, is more appropriate in advanced GC include: the individual's tumour profile (e.g. MSI status,[40] PD-L1 expression level[34,35]), pace of disease (e.g. whether the time to progression on first- or second-line therapy has been relatively rapid[19,22]), disease burden (e.g. the potential effect of further treatment on QoL *versus* life expectancy), comorbidities (e.g. the presence of renal or hepatic impairment), and whether there is residual toxicity from prior therapies (e.g. neutropenia or thrombocytopenia). Furthermore, the pattern of tumour metastasis, such as the presence or absence of peritoneal or liver metastases, may influence the treatment strategy.

Insights and clinical experience from the use of nivolumab, pembrolizumab and trifluridine/tipiracil in previously-licensed indications should help healthcare professionals to use these drugs effectively and to minimize the risk of TRAEs when adopting them as a new armamentarium for third-line therapy in metastatic GC. A further agent, regorafenib, a small-molecule inhibitor of multiple tyrosine kinases, was effective in prolonging PFS in refractory advanced gastric adenocarcinoma in a multinational placebo-controlled phase II trial (INTEGRATE).[41] The potential benefits of regorafenib in this population are currently being evaluated in a randomized phase III trial (INTEGRATE II) [ClinicalTrials.gov identifier: NCT02773524], due for completion in December 2021. As further third-line options become available, each with distinct qualities, this will increasingly allow patients with metastatic GC to benefit from an individualized, evidence-based approach to later-line therapy, with a common goal of extending survival and improving outcomes for their refractory disease.

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## References


1. Charalampakis N, Economopoulou P, Kotsantis I, *et al*. Medical management of gastric cancer: a 2017 update. *Cancer Med* 2018; 7: 123–133.
2. Torre LA, Bray F, Siegel RL, *et al*. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87–108.
3. Smyth EC, Verheij M, Allum W, *et al*. ESMO guidelines committee. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow up. *Ann Oncol* 2016; 27(Suppl. 5): v38–v49.
4. Fontana E and Smyth EC. Novel targets in the treatment of advanced gastric cancer: a perspective review. *Ther Adv Med Oncol* 2016; 8: 113–125.
5. Goode EF and Smyth EC. Immunotherapy for gastroesophageal cancer. *J Clin Med* 2016; 5: 84.
6. Chan WL, Yuen KK, Siu SW, *et al*. Third-line systemic treatment versus best supportive care for advanced/metastatic gastric cancer: a systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2017; 116: 68–81.
7. Kang JH, Lee SI, Lim DH, *et al*. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012; 30: 1513–1518.
8. Li J, Qin S, Xu J, *et al*. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol* 2013; 31: 3219–3225.
9. Li J, Qin S, Xu J, *et al*. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. *J Clin Oncol* 2016; 34: 1448–1454.
10. LSK BioPharma. LSKB to report non-clinical rivoceranib (apatinib) combination with immunotherapy, http://lskbiopharma.com/lskb-to-report-non-clinical-rivoceranib-apatinib-combination-with-immunotherapy/ (2018, accessed 17 May 2019).
11. Ohtsu A, Ajani JA, Bai YX, *et al*. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; 31: 3935–3943.
12. Kang YK, Boku N, Satoh T, *et al*. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; 390: 2461–2471.
13. Fuchs CS, Doi T, Jang RW, *et al*. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol* 2018; 4: e180013.
14. Shitara K, Doi T, Dvorkin M, *et al*. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2018; 19: 1437–1448.
15. Zheng Y, Zhu XQ and Ren XG. Third-line chemotherapy in advanced gastric cancer: a systematic review and meta-analysis. *Medicine (Baltimore)* 2017; 96: e6884.
16. Davidson M, Cafferkey C, Goode EF, *et al*. Survival in advanced oesophagogastric adenocarcinoma improves with the use of multiple lines of therapy: results from an analysis of more than 500 patients. *Clin Colorectal Cancer* 2018; 17: 223–230.
17. Wilke H, Muro K, Van Cutsem E, *et al*. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014; 15: 1224–1235.
18. Hess LM, Michael D, Mytelka DS, *et al*. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. *Gastric Cancer* 2016; 19: 607–615.
19. Fanotto V, Uccello M, Pecora I, *et al*. Outcomes of advanced gastric cancer patients treated with at least three lines of systemic chemotherapy. *Oncologist* 2018; 22: 1463–1469.
20. Chau I, Norman AR, Cunningham D, *et al*. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer-pooled analysis from three multicenter,

randomized, controlled trials using individual patient data. *J Clin Oncol* 2004; 22: 2395–2403.

21. Chau I, Ashley S and Cunningham D. Validation of the Royal Marsden hospital prognostic index in advanced esophagogastric cancer using individual patient data from the REAL 2 study. *J Clin Oncol* 2009; 27: e3–e4.

22. Janowitz T, Thuss-Patience P, Marshall A, *et al*. Chemotherapy vs supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: a meta-analysis of patient-level data. *Br J Cancer* 2016; 14: 381–387.

23. Satoh T, Chen LT, Kang YK, *et al*. A phase 3 study of nivolumab (nivo) in previously treated advanced gastric or gastric esophageal junction (G/GEJ) cancer (ATTRACTION-2): two-years update data. *Ann Oncol* 2018; 29(Suppl. 8): mdy282.002. doi:10.1093/annonc/mdy282.002

24. Boku N, Kang YK, Satoh T, *et al*. A phase 3 study of nivolumab (Nivo) in previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: updated results and subset analysis by PD-L1 expression (ATTRACTION-02). *Ann Oncol* 2017; 28(Suppl. 5): mdx369.001. doi:10.1093/annonc/mdx369.001

25. Wolchok JD, Chiarion-Sileni V, Gonzalez R, *et al*. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017; 377: 1345–1356.

26. Zhao B, Zhang W, Yu D, *et al*. The benefit and risk of nivolumab in non-small-cell lung cancer: a single-arm meta-analysis of noncomparative clinical studies and randomized controlled trials. *Cancer Med* 2018; 7: 1642–1659.

27. Ono Pharmaceutical Co Ltd. Opdivo® (Nivolumab) intravenous infusion approved in Taiwan for supplemental indication of advanced or recurrent gastric cancer or gastro-esophageal junction cancer, https://www.ono.co.jp/eng/news/pdf/sm_cn180123.pdf (2018, accessed 17 May 2019).

28. Ono Pharmaceutical Co Ltd. Opdivo® (Nivolumab) intravenous infusion approved for supplemental indication of advanced or recurrent gastric or gastroesophageal junction adenocarcinoma and for expanded use in recurrent or advanced classical Hodgkin lymphoma in South Korea, https://www.ono.co.jp/eng/news/pdf/sm_cn180326.pdf (2018, accessed 17 May 2019).

29. Taieb J, Moehler M, Boku N, *et al*. Evolution of checkpoint inhibitors for the treatment of metastatic gastric cancers: current status and future perspectives. *Cancer Treat Rev* 2018; 66: 104–113.

30. Lin SJ, Gagnon-Bartsch JA, Tan IB, *et al*. Signatures of tumour immunity distinguish Asian and non-Asian gastric adenocarcinomas. *Gut* 2015; 64: 1721–1731.

31. Myint ZW and Goel G. Role of modern immunotherapy in gastrointestinal malignancies: a review of current clinical progress. *J Hematol Oncol* 2017; 10: 86.

32. US Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for advanced gastric cancer. Approved Drugs, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm577093.htm (2017, accessed 17 May 2019).

33. Janjigian YY, Ott PA, Calvo E, *et al*. CheckMate 032 study: efficacy and safety of nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. *J Clin Oncol* 2018; 36: 2836–2844.

34. Shitara K, Özgüroğlu M, Bang YJ, *et al*. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2018; 392: 123–133.

35. Kojima T, Muro K, Francois E, *et al*. Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study. *J Clin Oncol* 2019; 37(Suppl. 4): 2–2. doi:10.1200/JCO.2019.37.4_suppl.2

36. Bang YJ, Ruiz EY, Van Cutsem E, *et al*. Phase 3, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment for patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. *Ann Oncol* 2018; 29: 2052–2060.

37. Thuss-Patience PC, Kretzschmar A, Bichev D, *et al*. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer-a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011; 47: 2306–2314.

38. Edwards P, Davidson M, Calamai V, *et al*. Third line treatment of advanced oesophagogastric cancer: A critical review of current evidence and evolving trends. *Cancer Treat Rev* 2018; 71: 32–38.

39. US Food and Drug Administration. FDA approves Lonsurf for recurrent, metastatic gastric and gastroesophageal junction

adenocarcinoma, https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-lonsurf-recurrent-metastatic-gastric-and-gastroesophageal-junction-adenocarcinoma (2019, accessed 17 May 2019).

40. De Rosa S, Sahnane N, Tibiletti MG, *et al*. EBV$^+$ and MSI gastric cancers harbor high PD-L1/PD-1 expression and high CD8$^+$ intratumoral lymphocytes. *Cancers (Basel)* 2018; 10; pii: E102.

41. Pavlakis N, Sjoquist KM, Martin AJ, *et al*. Regorafenib for the treatment of advanced gastric Cancer (INTEGRATE): a multinational placebo-controlled phase II trial. *J Clin Oncol* 2016; 34: 2728–2735.