

# New drug developments in metastatic gastric cancer

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**Abstract:** Metastatic gastric cancer is associated with a poor prognosis and novel treatment options are desperately needed. The development of targeted therapies heralded a new era for the management of metastatic gastric cancer, however results from clinical trials of numerous targeted agents have been mixed. The advent of immune checkpoint inhibitors has yielded similar promise and results from early trials are encouraging. This review provides an overview of the systemic treatment options evaluated in metastatic gastric cancer, with a focus on recent evidence from clinical trials for targeted therapies and immune checkpoint inhibitors. The failure to identify appropriate predictive biomarkers has hampered the success of many targeted therapies in gastric cancer, and a deeper understanding of specific molecular subtypes and genomic alterations may allow for more precision in the application of novel therapies. Identifying appropriate biomarkers for patient selection is essential for future clinical trials, for the most effective use of novel agents and in combination approaches to account for growing complexity of treatment options.

**Keywords:** gastric cancer, immunotherapy, targeted therapy

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## Introduction

Gastric cancer represents the third leading cause of cancer mortality worldwide.<sup>1</sup> The majority of patients are diagnosed at an advanced stage, and standard treatment with traditional cytotoxic chemotherapy confers modest benefits in survival, with a median survival of less than 12 months.<sup>2</sup> With such a poor prognosis, novel treatment options for the treatment and management of metastatic gastric cancer are desperately needed. The development of targeted therapies heralded a new era for the management of metastatic gastric cancer, however results from clinical trials of numerous targeted agents have been mixed. The advent of immune checkpoint inhibitors has yielded similar promise and results from early trials are encouraging.

As further advances are made in personalized cancer therapy and precision medicine, accompanied with an increased understanding of the underlying biology, improvements in outcomes and development of new treatment options are anticipated. This review provides an overview of the systemic treatment options evaluated in

metastatic gastric cancer, with a focus on recent evidence from clinical trials for targeted therapies and immune checkpoint inhibitors.

## Cytotoxic chemotherapy

Chemotherapy remains the backbone of systemic therapy for metastatic gastric cancer. Early trials demonstrated the benefit of chemotherapy over best supportive care alone.<sup>3</sup> Subsequent meta-analyses have also demonstrated the benefit of combination chemotherapy over single agent therapies such as 5-fluorouracil.<sup>4</sup> Standard regimens of first-line doublet chemotherapy predominantly include fluoropyrimidine and platinum agents. Evidence suggests the use of oxaliplatin compared with cisplatin has equivalent efficacy and is better tolerated, whilst capecitabine has also demonstrated outcomes equivalent or superior to 5-fluorouracil.<sup>5–8</sup> S-1 has also shown a favourable toxicity profile compared with 5-fluorouracil.<sup>9</sup> There is ongoing debate over the use of triplet *versus* doublet chemotherapy, with the addition of an anthracycline or taxane, potentially improving outcomes at the cost of increased

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toxicity. Nevertheless, it can be said these agents, along with irinotecan containing regimens, have been demonstrated to be active in metastatic gastric cancer.<sup>2</sup> Furthermore, a meta-analysis has confirmed the benefit of chemotherapy in the second-line setting.<sup>10</sup> More recently, the TAGS study of TAS-102 (trifluridine/tipiracil) was evaluated *versus* placebo in heavily pretreated gastric cancer.<sup>11</sup> Median overall survival (OS) was improved in the TAS-102 arm at 5.7 months *versus* the placebo arm at 3.6 months [hazard ratio (HR) 0.69, 95% confidence interval (CI) 0.56–0.85,  $p = 0.0003$ ].

Despite the demonstrated efficacy of a number of classes of chemotherapeutic agents, prognosis is poor with median survival less than 1 year. Patients often develop progressive symptoms, with an associated decline in performance status.<sup>12</sup> Consequently, many do not receive second or third-line therapy. This only emphasizes the importance of novel agents that can improve survival, particularly in first-line therapy.

### Human epidermal growth factor receptor 2

Human epidermal growth factor receptor 2 (HER2/ErbB2), a member of the epidermal growth factor receptors (EGFRs) family, is a cellular membrane protein involved in transmembrane signalling, and overexpression or activation leads to increased cell proliferation, growth and survival.<sup>13</sup> HER2-targeted therapy initially gained widespread attention in breast carcinomas, however it is known that HER2 overexpression is a feature of numerous other cancers including gastric cancer. Approximately 22% of metastatic gastric cancer patients will have HER2 overexpression or amplification, although there are differences depending on tumour subtype (intestinal *versus* diffuse) and tumour location [gastro-oesophageal junction (GEJ) *versus* gastric].<sup>14</sup> Many studies have reported the correlation of HER2-positive gastric cancers with poorer outcomes and more aggressive disease, although there is still some debate with other conflicting studies.<sup>15</sup> This emphasizes the importance of the criteria used to determine HER2 positivity, with immunohistochemistry (IHC) 3+ or IHC 2+ and fluorescence in-situ hybridization (FISH)-positive, now generally accepted as the criteria for positivity.<sup>16</sup>

The success of trastuzumab in breast cancer, led to numerous studies of HER2-targeted therapies in

gastric cancer (Table 1). The ToGA trial was a landmark study that demonstrated the benefit of trastuzumab in the first-line setting in combination with cisplatin and capecitabine or 5-fluorouracil over chemotherapy alone.<sup>17</sup> Median OS was 13.8 months in the trastuzumab plus chemotherapy arm *versus* 11.1 months in the chemotherapy alone arm (HR 0.74, 95% CI 0.60–0.91,  $p = 0.0046$ ). Importantly, patients were eligible if their tumours were IHC 3+ or FISH positive. In a preplanned exploratory analysis, when patients with high HER2 expression (IHC 2+ or 3+) were compared with low expression (IHC 0 or 1+) the magnitude of benefit for trastuzumab was even greater, with a median OS of 16 months *versus* 11.8 months respectively (HR 0.65, 95% CI 0.51–0.83,  $p = 0.036$ ). Consequently, trastuzumab in combination with chemotherapy has become the standard of care in HER2-positive metastatic gastric cancer.

Despite the success of trastuzumab, other trials of HER2-targeted therapies have resulted in disappointing outcomes. The TyTAN trial investigated lapatinib in combination with paclitaxel *versus* paclitaxel alone in second-line treatment.<sup>27</sup> There was no significant difference in median OS with lapatinib plus paclitaxel at 11.0 months compared with paclitaxel alone at 8.9 months (HR 0.84, 95% CI 0.64–1.11,  $p = 0.1044$ ). Lapatinib was also tested in the first-line setting in the LOGiC trial.<sup>26</sup> Patients received chemotherapy with capecitabine and oxaliplatin in combination with either lapatinib or placebo. Median OS was 12.2 months in the lapatinib arm *versus* 10.5 months in the placebo arm (HR 0.91, 95% CI 0.73–1.12,  $p = 0.3492$ ). The GATSBY trial investigated trastuzumab emtansine (T-DM1) *versus* second-line chemotherapy with taxanes in previously treated HER2-positive metastatic gastric cancer.<sup>30</sup> Again there was no OS or progression-free survival (PFS) benefit for T-DM1. The HELOISE trial was designed to explore a higher dose of trastuzumab than was used in the ToGA trial, in patients who had a high tumour burden, however the study was terminated early due to futility at a planned interim analysis with no increased efficacy in terms of OS.<sup>29</sup> The JACOB trial examined first-line treatment with cisplatin, fluoropyrimidine and trastuzumab with the addition of pertuzumab or placebo.<sup>28</sup> However there was also no OS benefit demonstrated, with median OS 17.5 months in the pertuzumab arm compared with 14.2 months in the placebo arm (HR 0.84, 95% CI 0.71–1.00,  $p = 0.0565$ ).

**Table 1.** Randomized phase III trials of targeted therapies in metastatic gastric cancer.

Target	Drug	Trial	Line of therapy	Treatment groups	OS benefit	Reference
Angiogenesis	Apatinib	HENGRUI 20101208	Third or more	Apatinib <i>versus</i> placebo	Yes	Li and colleagues <sup>18</sup>
	Bevacizumab	AVAGAST	First	Bevacizumab <i>versus</i> placebo, in combination with chemotherapy (cisplatin and fluoropyrimidine)	No	Ohtsu and colleagues <sup>19</sup>
		AVATAR	First	Bevacizumab <i>versus</i> placebo, in combination with chemotherapy (cisplatin and capecitabine)	No	Shen and colleagues <sup>20</sup>
	Ramucirumab	RAINBOW	Second	Ramucirumab <i>versus</i> placebo, in combination with chemotherapy (paclitaxel)	Yes	Wilke and colleagues <sup>21</sup>
		REGARD	Second	Ramucirumab <i>versus</i> placebo	Yes	Fuchs and colleagues <sup>22</sup>
	EGFR	EXPAND	First	Chemotherapy (cisplatin and capecitabine) with or without cetuximab	No	Lordick and colleagues <sup>23</sup>
	Gefitinib	COG	Second	Gefitinib <i>versus</i> placebo	No	Dutton and colleagues <sup>24</sup>
	Panitumumab	REAL-3	First	Chemotherapy (epirubicin, oxaliplatin and capecitabine) with or without panitumumab	No	Waddell and colleagues <sup>25</sup>
	HER2	LOGiC	First	Lapatinib <i>versus</i> placebo, in combination with chemotherapy (capecitabine and oxaliplatin)	No	Hecht and colleagues <sup>26</sup>
		TyTAN	Second	Chemotherapy (paclitaxel) with or without lapatinib	No	Sato and colleagues <sup>27</sup>
	Pertuzumab	JACOB	First	Chemotherapy (cisplatin and fluoropyrimidine) and trastuzumab with or without pertuzumab	No	Taberero and colleagues <sup>28</sup>
	Trastuzumab	ToGA	First	Chemotherapy (cisplatin and fluoropyrimidine) with or without trastuzumab	Yes	Bang and colleagues <sup>17</sup>

Table 1. (Continued)

Target	Drug	Trial	Line of therapy	Treatment groups	OS benefit	Reference
	Trastuzumab (high dose)	HELOISE	First	Chemotherapy (cisplatin and capecitabine) in combination with trastuzumab or high-dose trastuzumab	No	Shah and colleagues <sup>29</sup>
	Trastuzumab emtansine (T-DM1)	GATSBY	Second	T-DM1 versus chemotherapy (taxane)	No	Kang and colleagues <sup>30</sup>
MET	Onartuzumab	METGastric	First	Onartuzumab versus placebo, in combination with chemotherapy (FOLFOX)	No	Shah and colleagues <sup>31</sup>
	Rilotumumab	RILOMET-1	First	Rilotumumab versus placebo, in combination with chemotherapy (epirubicin, cisplatin and capecitabine)	No	Cunningham and colleagues <sup>32</sup>
mTOR	Everolimus	GRANITE-1	Second or more	Everolimus versus placebo	No	Ohtsu and colleagues <sup>33</sup>
PD-1	Avelumab	JAVELIN300	Third	Avelumab versus physician's choice chemotherapy	No	Bang and colleagues <sup>34</sup>
	Nivolumab	ATTRACTION-2	Third or more	Nivolumab versus placebo	Yes	Kang and colleagues <sup>35</sup>
	Pembrolizumab	KEYNOTE-061	Second	Pembrolizumab versus paclitaxel	No	Shitara and colleagues <sup>36</sup>
EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; OS, overall survival; PD-1, programmed cell death 1;						

Further trials of HER2-targeted therapies are ongoing. Early phase trials are ongoing, particularly in patients who have progressed on trastuzumab. Promising efficacy signals have been demonstrated with agents such as afatinib, a pan-HER family tyrosine kinase inhibitor (TKI),<sup>37</sup> DS-8201a, a HER2-targeting antibody–drug conjugate with a topoisomerase I inhibitor,<sup>38</sup> margetuximab, an anti-HER2 monoclonal antibody<sup>39</sup> and ZW25, a novel bispecific anti-HER2 antibody.<sup>40</sup> Furthermore, other agents to overcome trastuzumab resistance, such as mTOR inhibitors, HSP90 inhibitors and MET inhibitors are at various stages of clinical development.<sup>41</sup> Ultimately, despite the early promise of HER2-targeted therapies, trials of various agents have not borne similar results, particularly when compared with the impressive results observed in breast cancer. Better preclinical and translational evidence is needed to understand the reasons behind this and to improve outcomes in the HER2-positive subset of patients.

### Anti-angiogenesis

Angiogenesis is a fundamental process for tumour growth as it ensures oxygen and nutrient supply to proliferating cells through the development of neovasculature. Vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) tyrosine kinases, VEGFR-1 and VEGFR-2, are key components in neoangiogenesis resulting in the promotion of tumour growth and formation of metastases.<sup>42</sup> Consequently anti-angiogenic therapy with anti-VEGF or anti-VEGFR-2 therapy has been integrated into standard practice in a range of different cancers.<sup>43</sup> In gastric cancer, VEGF has been shown to be a prognostic biomarker, with a meta-analysis of 4794 patients demonstrating that tissue expression for VEGF and circulating VEGF/VEGF-C/VEGF-D was associated with poor prognosis.<sup>44</sup>

Ramucirumab, a monoclonal antibody VEGFR-2 antagonist, has proven efficacy in the second-line setting for metastatic gastric cancer. The REGARD trial, examined ramucirumab monotherapy *versus* placebo, in patients progressing after first-line chemotherapy containing platinum and fluoropyrimidine.<sup>22</sup> Median OS was 5.2 months in the ramucirumab arm and 3.8 months in the placebo arm (HR 0.78, 95% CI 0.603–0.998,  $p = 0.047$ ). Ramucirumab in combination with second-line chemotherapy

with paclitaxel has also demonstrated benefit in the RAINBOW trial, with median OS of 9.6 months compared with 7.4 months with paclitaxel alone (HR 0.81, 95% CI 0.678–0.962,  $p = 0.017$ ).<sup>21</sup> In the first-line setting however, ramucirumab has been evaluated against placebo in combination with capecitabine and cisplatin chemotherapy in the phase III RAINFALL trial.<sup>45</sup> There was a statistically significant improvement in median PFS of 5.7 months in the ramucirumab arm *versus* 5.4 months in the placebo arm (HR 0.75, 95% CI 0.61–0.94,  $p = 0.011$ ). This however corresponds to only a 9-day improvement and no clinical significance, with furthermore no OS benefit demonstrated. Apatinib, a small molecule VEGFR-2 inhibitor, has also been tested in a randomized placebo-controlled phase III trial conducted in China.<sup>18</sup> This trial enrolled patients who had failed two or more lines of chemotherapy, and showed a median OS benefit of 6.5 months compared with 4.7 months in the apatinib and placebo arms respectively (HR 0.709, 95% CI 0.537–0.937,  $p = 0.0156$ ).

Other anti-angiogenic agents have also been evaluated. This includes bevacizumab, a monoclonal antibody targeting VEGF-A, in the AVAGAST trial.<sup>19</sup> The addition of bevacizumab to first-line chemotherapy with cisplatin and fluoropyrimidine, did not result in an OS benefit with median OS of 12.1 months in the bevacizumab arm *versus* 10.1 months in the placebo arm (HR 0.87, 95% CI 0.73–1.03,  $p = 0.1002$ ). There was however a statistically significant PFS benefit, and a greater overall response rate with the addition of bevacizumab. The AVATAR trial, further evaluated bevacizumab in the Chinese population with a similar design to the AVAGAST trial,<sup>20</sup> however it similarly showed no OS benefit.

Numerous other anti-angiogenic small molecule kinase inhibitors have been investigated. Regorafenib, a multikinase inhibitor, has shown promising activity in the INTEGRATE phase II trial, with a median PFS benefit of 2.6 months compared with 0.9 months for the regorafenib and placebo arms respectively (HR 0.4, 95% CI 0.28–0.59,  $p < 0.001$ ).<sup>46</sup> The phase III INTEGRATE II trial evaluating regorafenib is currently underway (ClinicalTrials.gov identifier: NCT02773524). Disappointing results have been seen in other early trials, including trials of sunitinib,<sup>47,48</sup> pazopanib,<sup>49</sup> sorafenib,<sup>50</sup> orantinib,<sup>51</sup> trebananib<sup>52</sup>

and ziv-aflibercept.<sup>53</sup> A recent meta-analysis however of anti-angiogenic therapy in 3502 patients suggests targeting angiogenesis does improve OS, albeit with the benefit limited to pretreated patients and not in the first-line setting.<sup>54</sup> Several factors may contribute to this finding, including altered tumour biology after chemotherapy and a selection bias for patients with a sufficient performance status for later lines of therapy.

Currently, there is no validated biomarker to identify patients who may benefit most from anti-angiogenic therapy. There have been extensive exploratory studies however, contained within many of the aforementioned trials. The AVAGAST trial identified high plasma VEGF-A levels and low tumour neuropilin-1 expression as factors both prognostic and predictive of improved OS.<sup>55</sup> Other studies of tumour VEGF-C, VEGFR-3 and PDGFR $\alpha$  and plasma VEGF-C/D and VEGFR-1/3 have failed to yield a predictive biomarker of response.<sup>51,56,57</sup> An area of evolving research is the role of VEGF-related single nucleotide polymorphisms (SNPs). Candidate SNPs predicting favourable response to bevacizumab,<sup>58</sup> identified *via* a Monte Carlo study of 300 gastric cancer patients, were differentially distributed among White, Hispanic and Japanese patients, perhaps in part explaining the differential outcomes by geographical region observed in the INTEGRATE and AVAGAST trials.

### EGFR

Similar to HER2 overexpression, aberrant EGFR signalling leads to a series of intracellular pathways that result in cancer cell proliferation, inhibition of apoptosis, enhancement of invasion and metastasis and promotion of tumour-induced neovascularization.<sup>59</sup> EGFR inhibition was one of the earliest proposed mechanisms for targeted cancer therapy, and has had significant success in a range of cancers notably non-small cell lung cancer and colorectal cancer.<sup>60</sup> A significant proportion of patients with metastatic gastric cancer will demonstrate EGFR overexpression, and this finding is associated with a poorer overall prognosis.<sup>61</sup>

Studies of monoclonal antibody EGFR inhibitors, however, have not shown any advantage for the addition of EGFR inhibition. The REAL-3 trial investigated panitumumab in combination with epirubicin, oxaliplatin and capecitabine.<sup>25</sup>

The addition of panitumumab was potentially detrimental with a median OS of 8.8 months in the panitumumab arm *versus* 11.3 months in the chemotherapy alone arm (HR 1.37, 95% CI 1.07–1.76,  $p = 0.013$ ). Similarly, the EXPAND trial evaluated cetuximab in combination with cisplatin and capecitabine, with no benefit in OS.<sup>23</sup> Median OS was 4.4 months for the cetuximab group compared with 5.6 months for the chemotherapy alone group (HR 1.09, 95% CI 0.92–1.29,  $p = 0.32$ ). Both trials were in the first-line setting for advanced gastric cancer. Trials of EGFR TKIs have fared no better, with the phase III COG trial of gefitinib that included patients with GEJ as well as oesophageal tumours, finding no benefit *versus* placebo in the second-line setting.<sup>24</sup>

Interestingly, exploratory analyses of EGFR copy number gain (CNG) in the COG trial, suggested CNG evaluated using FISH might have predicted for response to gefitinib.<sup>62</sup> Biomarker analysis from the REAL-3 and MAGIC trials though, failed to identify an association between KRAS, BRAF, PIK3CA mutations and PTEN expression with OS.<sup>63</sup> Ultimately without an appropriate biomarker to predict response, the role for EGFR inhibition in metastatic gastric cancer is minimal.

### MET

The MET signalling pathway plays an important role in malignant transformation, and is known to be a key driver of oncogenic transformation in a subset of cancers.<sup>64</sup> Aberrant MET activation occurs *via* receptor overexpression, upregulation of stromal ligand production of hepatocyte growth factor (HGF) and gene amplification.<sup>65</sup> In a series of 216 resected gastric cancers, MET CNG was found in approximately 10% of patients and significantly associated with an unfavourable prognosis.<sup>66</sup> Other series have suggested varying levels of MET positivity, depending on the method of detection and cut-offs for positivity,<sup>67,68</sup> and there remains no established biomarker for MET targeted therapy.

Rilotumumab, a monoclonal antibody which targets HGF, was demonstrated to target MET/HGF-driven activities in preclinical models, with promising data from early phase I and II trials.<sup>69</sup> The RILOMET-1 trial investigated rilotumumab *versus* placebo in combination with chemotherapy

with epirubicin, cisplatin and capecitabine as first-line therapy in MET-positive advanced gastric cancer.<sup>70</sup> The trial however, did not meet its primary endpoint of OS, and was terminated early due to futility. OS, PFS and objective response rate were all statistically significantly worse in the rilotumumab arm. Onartuzumab, a monoclonal antibody binding to the MET receptor, was evaluated in combination with mFOL-FOX6 chemotherapy in the phase III METGastric trial.<sup>31</sup> There was no difference in median OS in the intention-to-treat population nor in the MET 2+/3+ patients, as measured by immunohistochemistry. TKIs that target MET are also currently under investigation, including crizotinib, tivantinib and AMG 337, along with agents that have multiple targets such as cabozantinib and foretinib.<sup>71</sup>

### mTOR

Dysregulation and increased activation of the PI3K/Akt and mTOR pathways have been shown to be prevalent in metastatic gastric cancer, and are associated with an unfavourable clinical prognosis.<sup>72,73</sup> PI3K/Akt not only plays an important role in cell proliferation, but also in protein translation and synthesis *via* mTOR as well as angiogenesis. Consequently, mTOR inhibitors such as everolimus have been proposed as potential therapeutic agents. The GRANITE-1 trial evaluated everolimus *versus* placebo after one or two lines of systemic chemotherapy in advanced gastric cancer.<sup>33</sup> There was no difference in median OS, being 5.4 months for everolimus and 4.3 months for placebo (HR 0.90, 95% CI 0.75–1.08,  $p = 0.124$ ). An Akt inhibitor, MK-2206, has also been investigated in a single-arm phase II trial and although well tolerated, did not show significant clinical activity.<sup>74</sup>

### Immunotherapy

Immune escape or evasion of the immune system is now established as one of the hallmarks of cancer.<sup>75</sup> Cancer cells escape immune destruction by developing mechanisms typically employed by the immune system to regulate itself. Immune checkpoint inhibitors, particularly anti-programmed cell death (PD)-1 and anti-programmed death ligand (PD)-L1 agents, have gained increasing attention with remarkable and durable efficacy in cancers including melanoma and non-small cell lung cancer.

Upwards of 40% of gastric cancers have been shown to have significant levels of PD-L1 expression,<sup>76,77</sup> although the correlation with prognosis is unclear. The molecular characterization of gastric adenocarcinoma performed by The Cancer Genome Atlas (TCGA), identified a novel recurrent amplification at 9p24.1, the locus containing JAK2, CD274 and PDCD1LG2.<sup>78</sup> JAK2 encodes a receptor tyrosine kinase, whilst CD274 and PDCD1LG2 encode PD-L1 and PD-L2 respectively. Notably, these 9p amplifications were enriched in the Epstein–Barr virus (EBV) subgroup (15% of tumours), consistent with studies showing elevated PD-L1 expression in EBV-positive lymphoid cancers. The study also identified a microsatellite instability (MSI)-high subgroup, providing a further underlying rationale for the evaluation of immune checkpoint inhibitors in metastatic gastric cancer.

Nivolumab has demonstrated efficacy for metastatic gastric cancer in several trials. The ATTRACTION-2 trial, was a double-blinded randomized phase III trial of nivolumab *versus* placebo in previously treated advanced gastric cancer.<sup>35</sup> Treatment with nivolumab resulted in improved OS of 5.32 months with nivolumab *versus* 4.14 months with placebo (HR 0.63, 95% CI 0.50–0.78,  $p < 0.0001$ ), providing the strongest evidence to date for the efficacy of immune checkpoint inhibition. The gastric and oesophageal cohort of CHECKMATE-032 study, randomizing patients to nivolumab and nivolumab plus ipilimumab (in two different doses), also showed some activity.<sup>79</sup>

Pembrolizumab is another promising inhibitor of PD-1. Data from early phase trials has suggested activity in patients with positive PD-L1 expression with a response rate of 22%.<sup>80</sup> The KEYNOTE-059 single-arm trial investigated pembrolizumab treatment in patients with multiple solid organ tumours. The gastric and oesophageal cohort (259 patients), which reported recently, demonstrated a response rate of 11.6% with a median duration of response of 8.4 months.<sup>81</sup> Patients with PD-L1-positive tumours had a response rate of 15.5% compared with 6.4% for the PD-L1-negative group. In the KEYNOTE-061 trial, a randomized phase III trial of pembrolizumab *versus* paclitaxel in previously treated gastric or GEJ cancers, patients with a PD-L1 combined positive score (CPS)  $\geq 1$  were included in the final

analysis.<sup>36</sup> There was no improvement in OS with a median 9.1 months for pembrolizumab and 8.3 months for paclitaxel (HR 0.82, 95% CI 0.66–1.03,  $p = 0.0421$ ).

Gastric cancers deficient in the mismatch repair mechanism (dMMR; linked to MSI-high) may especially benefit from immunotherapy. A landmark paper published in 2017 investigated pembrolizumab treatment in 86 patients with a variety of dMMR tumours (including 5 with gastro-oesophageal cancers).<sup>82</sup> The response rate was 53% with a significant duration of response. The same paper estimated that approximately 8% of gastric cancers are dMMR. In summary, pembrolizumab can be considered as a treatment option for patients with dMMR gastric cancers.

Avelumab, a PD-L1 inhibitor, has also shown promising activity in early trials, both as first-line maintenance and second-line therapy.<sup>83,84</sup> In the phase III JAVELIN300 trial however, of avelumab *versus* the physician's choice of chemotherapy as a third-line therapy, avelumab did not meet its primary endpoint of improvement in OS, with a median OS of 4.6 months for avelumab *versus* 5.0 months for chemotherapy (HR 1.1, 95% CI 0.9–1.4,  $p = 0.81$ ).<sup>34</sup> Although of note, the comparator arm was chemotherapy and not placebo. Numerous other randomized phase III trials are ongoing with a range of different immune checkpoint inhibitors<sup>85</sup> and results are eagerly awaited. Combinations of immunotherapy with other agents (for example, bevacizumab) may also potentiate the immune response based on findings from metastatic renal cell carcinoma.<sup>86</sup>

Biomarkers for the efficacy of immunotherapy remain scarce and are a major topic of ongoing research. As noted above, patients with dMMR/MSI-high tumours experience a high response rate to immunotherapy. Whilst PD-L1-positive patients are more likely than PD-L1-negative patients to experience a response, PD-L1 negative patients may still derive significant benefit from immunotherapy. Mutational load or tumour mutational burden is another promising biomarker that is being evaluated in gastric cancers.<sup>82,87</sup> Ultimately, a successful biomarker will need to be cost-effective, reproducible (with well-defined objective cut-offs), and define both a patient subgroup likely to benefit and a subgroup that will not benefit from therapy.

### Future directions

Our understanding of the underlying biology of gastric cancer is continually improving. Gene expression analyses undertaken by groups such as TCGA and the Asian Cancer Research Group (ACRG) have illustrated the different molecular subtypes of gastric cancer.<sup>78,88</sup> TCGA described four subtypes with MSI, genome-stable (GS), EBV and chromosome instability (CIN), whilst the ACRG classification also identified four subtypes with MSI, microsatellite stable (MSS)/epithelial-mesenchymal transition (EMT), MSS/TP53+ and MSS/TP53-. The failure to identify appropriate predictive biomarkers has hampered the success of many targeted therapies in gastric cancer, and a deeper understanding of specific molecular subtypes and genomic alterations may allow for more precision in the application of novel therapies.

With the advent of immunotherapy, the treatment options for gastric cancer are expanding. Presently, whilst there remain few established agents apart from chemotherapy, the manageable and favourable toxicity profile of immunotherapy lends itself to new combinations with both traditional and novel agents. A greater understanding of mechanisms of resistance, biological changes resulting from therapy and pharmacokinetic and pharmacodynamics characteristics will be crucial.

Innovative methods of developing biomarkers, for example using radiological imaging may further help the design of future trials. Several non-invasive, reproducible and quantitative radiological methods are emerging as potential pharmacodynamics biomarkers. Changes in dynamic magnetic resonance imaging and computed tomography-based tissue vascular measures such as blood flow, blood volume, or permeability have been shown to occur after treatment with bevacizumab or anti-VEGFR TKIs in clinical studies.<sup>89</sup> Magnetic resonance spectroscopy also holds promise as it provides chemically specific information, however exploitation of the ability of these techniques in predicting response to anti-angiogenic agents is still in early stages of development.

### Conclusion

The treatment paradigm for metastatic gastric cancer has continued to evolve from the



introduction of combination chemotherapy, to targeted agents with trastuzumab and ramucirumab, and now with the immune checkpoint inhibitors. Identifying appropriate biomarkers for patient selection is essential for future clinical trials, for the most effective use of novel agents and in combination approaches to account for growing complexity of treatment options.

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