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## Second-line treatment of metastatic gastric cancer: Current options and future directions

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### Abstract

Gastric cancer remains one among the leading causes

of cancer-related deaths, regardless of its decreasing incidence and newly available treatment options. Most patients present at an advanced stage and are treated with upfront systemic chemotherapy. Those patients receiving first-line therapy may initially respond to treatment, but many of them relapse over time. In such condition, second-line treatment for disease progression remains the only available option. Although there exists no standard approach in the second-line setting, several phase III trials have shown modest survival benefit in patients receiving irinotecan, taxane and ramucirumab over the best supportive care or active agents. This review analyzes the currently available treatment regimens and future directions of research in the second-line setting for metastatic gastric cancer with the best available evidence. Additionally, the prognostic factors that influence patient survival in those receiving second-line therapy are discussed.

**Key words:** Metastatic gastric cancer; Second-line chemotherapy; Targeted therapy; Taxane; Irinotecan; Ramucirumab

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**Core tip:** This systematic review has analyzed the currently available treatment options with chemotherapy and targeted agents in the second-line treatment of metastatic gastric cancer. In addition, this review has discussed the future directions of research and the prognostic factors that influence patient survival in those receiving second-line therapy for metastatic gastric cancer.

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## INTRODUCTION

Gastric cancer (GC) remains one of the major causes of cancer-related deaths ranking at number three, despite its decreasing incidence. About one million new cases of gastric cancer were estimated to have occurred in 2012, making it currently the fifth most common malignancy in the world, behind cancers of the lung, breast, colorectum and prostate. More than 70% of diagnosed gastric cancer cases are registered in developing countries<sup>[1-3]</sup>.

The disease presents as localized disease in only one-third of patients and as locally advanced or metastatic disease in the remaining two-thirds of patients. Surgery (subtotal or total gastrectomy with radical lymph node dissection) remains the primary mainstay in the treatment of GC. Despite the curative-intent resections, in up to 70% of cases, the relapse rate remains high<sup>[4]</sup>. In such patients, 5-year survival rates do not exceed 25% and prognosis remains poor<sup>[5]</sup>.

Most of the patients, including those with early-stage disease, relapse at some point during the course of their disease. Among available treatment modalities, only systemic chemotherapy has demonstrated a superior survival rate in this group of patients<sup>[6]</sup>. Most patients do not respond or relapse within a short time from the end of first-line therapy. The literature shows that approximately 20%-30% of patients receive further treatment with second-line chemotherapy<sup>[7]</sup>. In the past, various cytotoxic agents (5-fluorouracil, cisplatin, mitomycin C, methotrexate, docetaxel, paclitaxel, nab-paclitaxel, pemetrexed, S-1, irinotecan and oxaliplatin) have been studied extensively either as monotherapy or in combination in the second-line setting. The median OS of patients receiving second-line therapy ranges from 3.5 to 10.7 mo, with an objective response rate of 4.8%-52.3%. There were no effective treatment options until the positive results of recent phase III studies were published.

This systemic review evaluates the currently available evidence on the therapeutic options in the second-line setting. Additionally, the prognostic factors that influence patient survival in those receiving second-line therapy are discussed.

## LITERATURE RESEARCH

The literature database search for second-line therapy in metastatic gastric cancer was performed using MEDLINE and PubMed for original articles published from a dataset of a minimum of 25 patients, review articles, and key abstracts from articles published in English during the period from 1990 to 2015.

### First-line therapy

In metastatic gastric cancer, systemic chemotherapy has been shown to improve overall survival (OS) and quality of life (QoL) compared with best supportive care (BSC) alone<sup>[8-10]</sup>. In patients receiving first-line therapy for metastatic gastric cancer, the median survival time ranges from 9.5-13 mo with objective responses ranging from 25%-54%<sup>[11-16]</sup>. The meta-analysis performed by Wagner *et al.*<sup>[17]</sup>, which included 35 trials with 5726 patients, demonstrated a significant survival benefit in favor of combination chemotherapy (HR = 0.82; 95%CI: 0.74-0.90, 1914 patients) compared with single-agent chemotherapy; a significant survival benefit was observed for regimens including 5-FU, anthracyclines and cisplatin (HR = 0.82; 95%CI: 0.73-0.92, 1147 patients), and non-significant survival benefits in favor of the Irinotecan (HR = 0.86; 95%CI: 0.73-1.02, 639 patients) and docetaxel-containing (HR = 0.93; 95%CI: 0.75-1.15, 805 participants) regimens were demonstrated. This shows that a multi-agent chemotherapy regimen comprising fluoropyrimidines and platinum derivatives acts as an effective regimen in the first-line therapy for metastatic gastric cancer. When delivering first-line therapy, one should remember that the REAL II study established the non-inferiority of capecitabine to infusional 5-fluorouracil (HR = 0.86, 95%CI: 0.80-0.99) and the non-inferiority of oxaliplatin to cisplatin (HR = 0.92; 95%CI: 0.80-1.10) in two-by-two comparisons<sup>[13]</sup>. Additionally, Guimbaud *et al.*<sup>[16]</sup> showed that FOLFIRI (irinotecan, 5-fluorouracil and leucovorin) is an acceptable alternative to a platinum-based ECX (epirubicin, cisplatin and capecitabine) regimen in first-line settings, especially in patients who are not able to receive platinum-based agents. Trastuzumab in combination with chemotherapy was found to significantly prolong survival when given as a first-line treatment for patients with HER2-positive gastric cancer<sup>[18]</sup>.

### Second-line therapy

**Cytotoxic agents:** A larger number of phase II<sup>[19-61]</sup> and phase III<sup>[62-78]</sup> studies have been conducted in the second-line setting, which are summarized in Tables 1, 2 and 3. Data from phase III trials show that the median OS ranges from 3.7 to 13.9 mo, with an objective response rate of 13%-27%.

The German AIO trial<sup>[62]</sup> was the first randomized trial that studied whether second-line chemotherapy could prolong survival in gastric cancer. In this study, irinotecan was compared with BSC to show a survival benefit in patients with metastatic gastric and gastroesophageal junction adenocarcinoma. This randomized phase III study included 40 patients. The study was terminated prematurely due to slow patient accrual. All the patients had received prior fluoropyrimidine/platinum combination and exhibited disease progression within 6 mo following first-line therapy. The

**Table 1 Phase II studies on second-line therapy (Monotherapy) in metastatic gastric cancer**

II line agent	Total/eval pts	Performance status, n	Doses (mg/m <sup>2</sup> )	Treatment ORR	Median TTP (mo)	Median PFS (mo)	Median OS (mo)	Toxicity, grade 3-4 (%)	Ref.
Irinotecan	37/35	ECOG 0/1 - 3/34	Iri - 125 d1 weekly × 4 wk, q42	20.0%	2.6	NR	5.2	A/L/N/T/N-E/D/FN/I - 56.8/45.9/67.6/8.1/18.9/18.9/16.2/8.1	Chun <i>et al</i> <sup>[19]</sup> , 2004
Irinotecan	39/30	ECOG 0/1/2 - 18/10/2	Iri - 100 d1,d8,d15 q28	15.3%	2.9	NR	8.8	A/N/Leu/Ano/D/F/- 13/30/17/23/17/13	Mochizuki <i>et al</i> <sup>[20]</sup> , 2013
Paclitaxel	36/36	ECOG 0/1/2 - 7/20/9	Ptx - 225 d1 q21	22.2%	5.0	NR	8.0	L/T - 17/17	Cascinu <i>et al</i> <sup>[21]</sup> , 1998
Paclitaxel	38/25	ECOG 0/1/2 - 12/15/11	Ptx - 80 d1, 8, 15 q28	24.0%	2.1	NR	5.0	L/N/T/Nau/Ano/D/Neu - 29/32/8/3/3/3/6	Hironaka <i>et al</i> <sup>[22]</sup> , 2006
Paclitaxel	45/44	ECOG 0/1/2 - 26/13/6	Ptx - 80 d1, 8, 15 q28	16.0%	NR	2.6	7.8	A/N/L/D/N-E/As/Neu - 11/16/18/2/4/11/2	Kodera <i>et al</i> <sup>[23]</sup> , 2007
Docetaxel	30/29	KPS Median 70 (R 60-100%)	Dtx - 100 d1 q21	17.0%	NR	NR	6.0	A/L/N - 7/7/18	Giuliani <i>et al</i> <sup>[24]</sup> , 2003
Docetaxel	154/86	ECOG 0-1/2 - 130/24	Dtx - 75 d1 q21	14.0%	2.6	NR	7.2	A/N/FN/As - 10.5/12.5/9.9/13.6	<sup>1</sup> Jo <i>et al</i> <sup>[25]</sup> , 2007
Docetaxel	49/49	ECOG 0/1/2 - 9/36/4	Dtx - 75 d1 q21	16.5%	2.5	NR	8.3	A/L/N/FN/B/As/D/Neu - 5.4/4.8/5.4/5.4/1.2/10.8/2.4/8.4	Lee <i>et al</i> <sup>[26]</sup> , 2008
Nab-Paclitaxel	56/54	ECOG 0/1 - 33/23	Nab-Ptx 250 d1 q21	27.8%	NR	2.9	9.2	A/L/N/Ly/Neu - 7.3/20/49.1/10.9/23.6	Sasaki <i>et al</i> <sup>[27]</sup> , 2014
Pemetrexed	34/30	ECOG 0/1/2 - 7/20/7	Pem - 500 d1 q21	63.6%	NR	2.3	6.4	A/N/T/As - 2.9/2.9/2.9/5.8	Zhang <i>et al</i> <sup>[28]</sup> , 2015
Sunitinib	78/69	ECOG 0/1 - 26/52	Sun - 50 mg/d × 4 wk, q42	2.6%	2.3	2.3	6.8	A/L/N/T/E/D/HFS/S - 16.7/11.5/29.4/34.6/3.8/2.6/6.4/1.3	Bang <i>et al</i> <sup>[29]</sup> , 2010
Everolimus	54/53	ECOG 0/1 - 32/21	Ev - 10 mg/d d1-28	0%	NR	2.7	10.1	P (gr 1-2)/A/Ly/As/S/Ano/HyG/HyP/HyN/ - 15.1, 9.4/7.5/5.7/ 5.7/5.7/3.8/3.8/9.6	Doi <i>et al</i> <sup>[30]</sup> , 2010

<sup>1</sup>Retrospective study. Dtx: Docetaxel; Ev: Everolimus; F: 5-fluorouracil; FA: Leucovorin; Iri: Irinotecan; MMC: MitomycinC; Nab-Ptx: Nab-paclitaxel; Pem: Pemetrexed; Ptx: Paclitaxel; Sun: Sunitinib; ECOG: Eastern co-operative oncology group; KPS: Karnofsky performance status; NR: Not reported; ORR: Objective response rate; OS: Overall-survival; Pts: Patients; PFS: Progression-free survival; R: Range; TTP: Time-to-progression; A: Anemia; As: Asthenia; Ano: Anorexia; B: Bilirubin; D: Diarrhea; E: Emesis; FN: Febrile neutropenia; HFS: Hand-foot syndrome; HyG: Hyperglycemia; HyN: Hyponatremia; HyP: Hypophosphatemia; I: Infection; L: Leucocytopenia; Ly: Lymphopenia; M: Mucositis; N: Neutropenia; Neu: Sensory neuropathy; Nau: Nausea; N-E: Nausea and vomiting; T: Thrombocytopenia.

irinotecan arm and BSC arm had 21 and 19 patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1/2 in 17/4 and 14/5 patients, respectively. This showed that the administration of irinotecan (250 mg/m<sup>2</sup> d1, escalated up to 350 mg/m<sup>2</sup>, every 3 wk) as second-line chemotherapy significantly prolongs OS when compared with BSC. This was the first evidence that second-line chemotherapy resulted in substantial improvement of survival. The median OS was 4.0 (95%CI: 3.6-7.5) mo in the irinotecan arm and 2.4 (95%CI: 1.7-4.9) mo in the BSC arm, HR = 0.48 (95%CI: 0.25-0.92), *P* = 0.023. There were no objective responses with 58% stable disease (SD) in the irinotecan arm. However, 44% of patients had tumor-related symptom relief. The most common grade 3-4 toxicities were diarrhea (5 patients) and febrile neutropenia (2 patients)<sup>[62]</sup>.

In the Korean phase III randomized trial<sup>[63]</sup>, 202 patients with metastatic gastric cancer and an ECOG PS of 0 or 1 received one or two prior chemotherapy regimens involving both a fluoropyrimidine and a platinum agent and were randomly assigned

at a ratio of 2:1 to either salvage chemotherapy (docetaxel 60 mg/m<sup>2</sup> every 3 wk or irinotecan 150 mg/m<sup>2</sup> every 2 wk plus BSC) or BSC. The addition of second-line chemotherapy to BSC produced significant improvement in median OS (5.3 mo) when compared with BSC alone (3.8 mo) (HR = 0.657, 95%CI: 0.485-0.891; *P* = 0.007). The survival benefit remained consistent among the prospectively defined subgroups, including age, PS, number of prior treatments, metastatic sites, hemoglobin levels, and response to prior chemotherapy. No difference in median OS between docetaxel and irinotecan (5.2 mo vs 6.5 mo, *P* = 0.116) was registered. The most common toxicity of chemotherapy being myelosuppression and was easily manageable. Median relative dose-intensities for docetaxel and irinotecan arm were 95% and 93%, respectively. Moreover, patients in the chemotherapy arm more frequently received further treatment than those in the BSC arm (40% vs 22%, *P* = 0.011)<sup>[63]</sup>.

In the Japanese WJOG 4007 phase III trial<sup>[64]</sup>, 223 patients with metastatic gastric cancer refractory to

**Table 2 Phase II studies on second-line therapy (combination therapy) in metastatic gastric cancer**

Study	Total /eval pts	Performance Status, n	II-line treatment, doses (mg/m <sup>2</sup> )	Treatment ORR	Median TTP (mo)	Median PFS (mo)	Median OS (mo)	Toxicity, grade 3-4 (%)	Ref.
Irinotecan/ FU	40/38	ECOG 0/1/2 - 5/21/12	Iri/FA/FU - 180/125/400 bolus + 1200 inf over 22 h d1/d1/d1 q14	29.0%	NR	3.7	6.4	A/N/FN/1/N-E/D/As - 13/26/5/16/13/8/16	Assersohn <i>et al</i> <sup>[31]</sup> , 2004
Irinotecan/ FU	64/57	ECOG 0/1/2 - 3/58/3	Iri/FU/FA - 150/100/1000 d1/d1/ d1, 2 over 24 h q14	21.0%	2.5	NR	7.6	N/T/D/E - 11/8/3/3	Kim <i>et al</i> <sup>[32]</sup> , 2005
Irinotecan/ FU	51/48	ECOG 0-1/2 - 35/16	Iri/FA/FU - 180/200/400 bolus + 600 inf over 22 h d1/d1/d1 q14	18.0%	NR	3.2	9.1	A/N/FN/D/Nau/E - 14/17/1/6/6/4	<sup>1</sup> Seo <i>et al</i> <sup>[33]</sup> , 2008
Irinotecan/ Cisplatin	32/31	ECOG 0/1/2 - 1/22/9	Iri/P - 70/30 d1, 15/ d1, 15 q28	15.6%	3.7	NR	6.1	A/N/T/E/D/M/Ano - 2.6/6/4.3/1.7/1.7/3.4/ 5.2	Baek <i>et al</i> <sup>[34]</sup> , 2005
Irinotecan/ Cisplatin	87/70	ECOG 0/1/2 - 29/53/5	Iri/P - 70/80 d1, 15/ d1 q28	28.6%	4.3	NR	9.5	A/L/N/FN/ T/D/As/Nau - 28/34/40/10/8/6/5/2	<sup>1</sup> Takahari <i>et al</i> <sup>[35]</sup> , 2010
Irinotecan/ Mitomycin C	38/38	KPS Median 80 (R 70-100%)	Iri/MMC - 150/8 d1, 15/d1 q28	32.0%	4.0	NR	8.0	A/L/N - 5/8/21	Giuliani <i>et al</i> <sup>[36]</sup> , 2005
Irinotecan/ Mitomycin C	45	ECOG 0/1 - 24/21	Iri/MMC - 150/5 d1 q14	29.0%	NR	4.1	10.1	A/N/FN/D/I - 13/53/9/2/4	Hamaguchi <i>et al</i> <sup>[37]</sup> , 2011
Irinotecan/ Capecitabine	48/46	ECOG 0/1/2 - 10/32/6	Iri/Cap - 100/1000 b.i.d d1, 8/d1-14 q21	27.1%	4.1	NR	7.6	N/FN/E/D/HFS - 8.7/4.3/4.3/17.4/4.3	Sun <i>et al</i> <sup>[38]</sup> , 2009
Irinotecan/ Cetuximab	63/54	ECOG 0/1 - 28/35	Iri/Cet - 180/500 d1 q14	11.0%	NR	2.8	6.1	N/FN/D/F - 11/2/6/5	Schönnemann <i>et al</i> <sup>[39]</sup> , 2012
Irinotecan vs Irinotecan/ mFOLFIRI	29 vs 30	ECOG 0/1 - 27/2 vs 27/3	Iri 150 d1 q14 Iri/mFOLFIRI 150 d1 + LV20 d1, 5-FU 2000 over 48 h	17.2% vs 20.0%	NR	2.2 vs 3	5.8 vs 6.7	A/n/Leu/FN/ Ano/As/D - 0/20/28/0/10/10/3 vs 10/13/37/3/13/3/7	Sym <i>et al</i> <sup>[40]</sup> , 2013
Paclitaxel/ Doxifluridine	52/25	ECOG R 0-2	Dox/Ptx - 600 mg/70 d1-21/d7, 14, 21 q28	28.0%	NR	NR	5.8	L - 2	Arai <i>et al</i> <sup>[41]</sup> , 2007
Paclitaxel/ Doxifluridine	33	ECOG 0/1/2 - 21/14/0	Dox/Ptx - 600 mg/70 d1-14/d1, 8 q21	18.2%	NR	4.0	10.7	A/L/N/D/ FN/I/As/Neu - 17.1/11.4/22.9/2.9/ 2.9/2.9/2.9	Takiuchi <i>et al</i> <sup>[42]</sup> , 2008
Paclitaxel/ Carboplatin	50/47	ECOG 0-1/2 - 25/22	Ptx/Carbo - 175/AUC 5 d1/d1 q21	27.7%	NR	NR	OS in PR/SD - 10.0/6.0	N/T - 8.5/4.2	Stathopoulos <i>et al</i> <sup>[43]</sup> , 2002
Paclitaxel/ Cisplatin	32/30	ECOG 0-1/2 - 21/11	Ptx/P - 145/60 d1 q21	25.0%	2.9	NR	9.1	N/E/Neu - 3/9/6	Lee <i>et al</i> <sup>[44]</sup> , 2007
Paclitaxel/ Capecitabine	26/26	ECOG 0/1/2 - 7/11/8	Ptx/Cap - 175/825 b.i.d d1/d1-14 q21	34.6%	4.5	NR	7.5	A/N/T/HFS/Neu/Ar/ E - 3.8/11.5/3.8/11.5/ 11.5/7.5/3.8	Baize <i>et al</i> <sup>[45]</sup> , 2009
Paclitaxel/ Capecitabine	36/35	KPS Median 80 (R 60-100%)	Ptx/Cap - 80/1000 b.i.d d1, d8/d1-14 q21	28.5%	NR	5.0	11.1	N/N-E/HFS - 11.1/5.6/5.6	Zhang <i>et al</i> <sup>[46]</sup> , 2013
Paclitaxel/ S-1	30	ECOG 0-1/2 -23/7	Ptx/S-1 - 120 d1 q14 /80, 100, 120 mg/d, if BSA < 1.25 m <sup>2</sup> , 1.26 m <sup>2</sup> -1.49 m <sup>2</sup> , ≥ 1.50 m <sup>2</sup> b.i.d. d1-7 q14	33.3%	NR	3.6	7.2	A/Neu/T/Ano/Neu/ D/F - 73.4/63.4/16.6/20 /36.6/13.3/20	Zheng <i>et al</i> <sup>[47]</sup> , 2014
Docetaxel/ Cisplatin	43/41	ECOG 0/1/2 - 1/33/9	Dtx/P - 60/60 d1/d1 q21	17.1%	NR	2.2	5.8	N/N-E/Neu/Neph - 29.3/12.2/4.9/2.3	Park <i>et al</i> <sup>[48]</sup> , 2004
Docetaxel/ Cisplatin	30/30	KPS 50-70/ 80-100% - 14/16	Dtx/P - 60/60 d1/d1 q21	26.7%	4.5	NR	5.6	A/L/N/Nau - 3/27/27/3	Kunisaki <i>et al</i> <sup>[49]</sup> , 2005
Docetaxel/ Cisplatin	32/32	ECOG 0/1/2 - 8/16/8	Dtx/P 70/70 d1/d1 q21	16.0%	5.0	NR	6.0	N/FN/T/D - 59/12/12/6	Polyzos <i>et al</i> <sup>[50]</sup> , 2006
Docetaxel/ Oxaliplatin	38/37	ECOG 0/1/2 - 19/12/7	Dtx/Ox - 75/80 d1/d2 q21	10.5%	4.0	NR	8.1	N/As/Nau/Neu - 26.3/15.7/15.7/3	Barone <i>et al</i> <sup>[51]</sup> , 2007
Docetaxel/ Oxaliplatin	48/46	ECOG 0/1/2 - 11/29/8	Dtx/Ox - 60/130 d1 q21	22.9%	4.4	NR	7.2	L/N/FN/T/ N-E/D/Neu - 17.4/26/7/4.3/28.3/ 15/6.5	Zhong <i>et al</i> <sup>[52]</sup> , 2008
Docetaxel/ Epirubicin	50/45	ECOG 0/1/2 - 12/16/22	Dtx/Epi - 75/60 d1/ d1 q21	15.5%	2.4	NR	5.0	N/FN/T/N-E/ S/D/Neu - 68/48/46/2/8/4/2	Nguyen <i>et al</i> <sup>[53]</sup> , 2006



Docetaxel/ Capecitabine	28/25	ECOG 0/1/2 - 2/19/7	Dtx/Cap - 60/1000 b.i.d d1/d1-14 q21	29.0%	4.0	NR	6.0	A/N/As/D/HFS - 7/36/7/11/7	Rosati <i>et al</i> <sup>[54]</sup> , 2007
Docetaxel/ Etoposide	32/32	ECOG 0/1/2 - 6/20/6	Dtx/Eto - 75/50 d1/ d1-5 q21	9.4%	NR	3.0	6.0	N/FN/T/N-E/D/M - 29/19/3/15.6/9.4/6.2	Yildiz <i>et al</i> <sup>[55]</sup> , 2010
Docetaxel/ Cetuximab	38/35	ECOG 0/1/2 - 15/21/2	Dtx/Cet - 30 d1, d15 q21/400 d1, then 250 d1 q7	6.0%	NR	2.1	5.4	I/FN/Ano/D/F - 11/3/16/11/29	Tebbutt <i>et al</i> <sup>[56]</sup> , 2013
Mitomycin/ S1	43/33	ECOG 0/1/2 - 13/21/9	MMC/S-1 - 7/40 b.i.d d1/d1-28 q42	21.0%	NR	3.4	8.0	A/N/T/D/N-E/As/S - 7/5/5/10/7/12/10	Park <i>et al</i> <sup>[57]</sup> , 2008
Mitomycin/ Capecitabine	39	ECOG 0/1/2/ UNK - 6/25/5/3	MMC/Cap - 10/1000 bid d1/d1-d14 q21	10.3%	NR	2.8	5.6	Leu/T/D/F/HFS/Neu - 5.4/10.8/5.4/8.1/5.4/8.1	Miranda <i>et al</i> <sup>[58]</sup> , 2014
Methotrexate/ FU	56/55	ECOG 0/1/2/3 - 12/30/12/2	Mtx/FU/FA - 100 bolus/600 bolus (3 h after MTX)/10, every 6 h for 6 doses (24 h after MTX) q7	9.0%	NR	NR	7.8	A/L/N/T/N-E/D/S - 9.1/5.5/6.7/1.8/3.6/ 3.6/1.8	Hamaguchi <i>et al</i> <sup>[59]</sup> , 2008
Cisplatin/ FU	58/53	ECOG 0-1/2 - 20/33	P/FU - 20/1000 over 20 h inf d1-5/d1-5 q28	11.3%	1.8	NR	4.6	A/N/T/N-E/D/M/ Neu - 8/9/9/11/4/6/1	Sencan <i>et al</i> <sup>[60]</sup> , 2008
Oxaliplatin/ Sorafenib	40	ECOG 0/1/2 - 14/23/2	Ox/Sor - 130 d1 q21/400 mg b.i.d daily	2.8%	NR	3.0	6.5	N/T/As/D/Neu - 9.8/7.3/18/4.9/4.9	Martin-Richard <i>et al</i> <sup>[61]</sup> , 2013

<sup>1</sup>Retrospective study. Cap: Capecitabine; Carbo: Carboplatin; Cet: Cetuximab; Dox: Doxifluridine; Dtx: Docetaxel; Eto: Etoposide; Epi: Epirubicin; FU: 5-fluorouracil; FA: Leucovorin; Iri: Irinotecan; Mtx: Methotrexate; MMC: MitomycinC; Ox: Oxaliplatin; P: Cisplatin; Ptx: Paclitaxel; Sor: Sorafenib; ECOG: Eastern co-operative oncology group; KPS: Karnofsky performance status; NR: Not reported; ORR: Objective response rate; OS: Overall-survival; Pts: Patients; PR: Partial response; PFS: Progression-free survival; R: Range; SD: Stable disease; TTP: Time-to-progression; UNK: Unknown; A: Anemia; As: Asthenia; Ano: Anorexia; D: Diarrhea; E: Emesis; FN: Febrile neutropenia; HFS: Hand-foot syndrome; I: Infection; L: Leucocytopenia; M: Mucositis; N: Neutropenia; Neu: Sensory neuropathy; Nau: Nausea; N-E: Nausea and vomiting; S: Stomatitis; T: Thrombocytopenia.

fluoropyrimidine and platinum combination treatment were randomly assigned to receive either paclitaxel (80 mg/m<sup>2</sup> on days 1, 8, and 15, every 4 wk) or irinotecan (150 mg/m<sup>2</sup> on days 1 and 15, every 4 wk). Nearly all patients had an ECOG PS of 0 or 1 (96%), the primary tumor was not resected in most patients (65%-66%), most had received prior S-1 plus cisplatin (79%-84%), and equal numbers of patients had intestinal or diffuse histology according to the Lauren classification. Patients with large volume ascites or bowel obstruction due to peritoneal carcinomatosis were excluded. After a median follow-up of 17.6 mo, OS was similar with paclitaxel and irinotecan [9.5 and 8.4 mo, (HR = 1.13, *P* = 0.38), respectively], as was progression-free survival (PFS) (3.6 and 2.3 mo [HR = 1.14, *P* = 0.33]) and response rate (21% and 14%, *P* = 0.24). Patients who received irinotecan experienced more grade 3-4 neutropenia (39.1% vs 28.7%) and diarrhea (4.5% vs 0.9%), whereas patients receiving paclitaxel experienced more grade 3-4 sensory neuropathy (7.4% vs 0%). The authors concluded that paclitaxel and irinotecan are reasonable second-line treatment options for metastatic gastric cancer<sup>[64]</sup>.

In the COUGAR-02 phase 3 trial conducted in the United Kingdom<sup>[65]</sup>, 168 patients with metastatic adenocarcinoma of the esophagus, gastro-esophageal junction, or stomach that had progressed on or within 6 mo of treatment with a platinum and fluoropyrimidine combination were recruited. Patients with an ECOG PS of 0 to 2 were randomly assigned to docetaxel 75 mg/m<sup>2</sup> every 3 wk for a maximum of 6 cycles plus BSC and BSC alone. After a median follow-up of 12 mo, median OS was modestly improved with docetaxel compared with BSC alone (5.2 mo vs 3.6 mo; HR = 0.67; *P* =

0.01). Responses were registered in 7% of assessable patients receiving docetaxel. Grade 3-4 toxicities in docetaxel included neutropenia (15%) leading to neutropenic fever (7%). Health-related quality-of-life measurements indicated no detrimental effect of chemotherapy and potential improvements in pain (*P* = 0.01) and nausea (*P* = 0.02)<sup>[65]</sup>.

In another Japanese phase III study (TCOG GI-0801/BIRIP)<sup>[66]</sup>, 130 patients with metastatic or recurrent gastric cancer refractory to S-1-based first-line chemotherapy were randomly assigned to receive BIRIP (irinotecan 60 mg/m<sup>2</sup> plus cisplatin 30 mg/m<sup>2</sup>, every 2 wk) or irinotecan alone at a dose of 150 mg/m<sup>2</sup> every 2 wk. Less than 60% of patients had received platinum agents in the first-line setting. Enrolled patients had an ECOG PS score of either 0 or 1. With more than 70% of patients in Japan receiving third-line therapy, the primary endpoint of this study was the PFS benefit of the BIRIP regimen over irinotecan monotherapy. The median PFS was significantly longer in the BIRIP group than in the irinotecan group [3.8 mo vs 2.8 mo (HR = 0.68, *P* = 0.0398)]. The median OS was 10.7 mo in the BIRIP arm and 10.1 mo in the irinotecan arm (HR = 1.0, *P* = 0.9823). Although the response rates were not significantly higher in the BIRIP arm, when compared with irinotecan arm (22% vs 16%, *P* = 0.4975), the disease control rate was significantly better in the BIRIP group (75% vs 54%, *P* = 0.0162). The incidences of grade 3-4 safety events did not differ between the two groups. BIRIP had a good tolerability profile and was associated with no febrile neutropenia and less diarrhea. Thus, the BIRIP regimen significantly prolonged PFS compared with irinotecan alone. However, these results did not

**Table 3 Phase III studies on second-line therapy in metastatic gastric cancer**

Ref.	II-line treatment (mg/m <sup>2</sup> )	Total pts	Performance Status, (ECOG/WHO) (%)	Median ORR (%)	Median PFS (mo)	Median OS (mo)	Hazard ratio	Toxicity, grade 3-4 (%)
Thuss-Patience <i>et al</i> <sup>[62]</sup> , 2011	Iri 250 cycle 1; 350 subsequent cycles	21/19	0-1/2 - 81/19	0	2.5	4.0	0.48, P = 0.012	D/FN/L/A - 26/16/21/11
Kang <i>et al</i> <sup>[63]</sup> , 2012	BSC	19	0-1/2 - 74/26	NR	NR	2.4	0.657, P = 0.007	NR
	Dtx 60 d1 q3w; Iri 150 d1 q2w	133	0/1 - 54/46	13.0	NR	5.3		Doc: N/A/F/Ano/D/S - 15/30/26/6/3/3 Iri: N/A/F/Ano/D/S - 18/32/10/5/8/5
Hironaka <i>et al</i> <sup>[64]</sup> , 2013	BSC	69	0/1 - 52/48	NR	NR	3.8	1.13, P = 0.38	N/A/F/D/S - 2/23/27/10/5/2
	Iri 150 d1/d15 q4w	112	0-1/2 - 96.4/3.6	13.6 <sup>1</sup>	2.3 <sup>1</sup>	8.4		L/N/A/FN/Ano/Neu/D/AST/Na - 19.1/39.1/30/9.1/17.3/0/4.5/8.2/15.5
Ford <i>et al</i> <sup>[65]</sup> , 2014	Ptx 80 d1/d8/d15 q4w	111	0-1/2 - 96.3/3.7	20.9 <sup>1</sup>	3.6 <sup>1</sup>	9.5	0.67, P = 0.01	L/N/A/FN/Ano/Neu/D/AST/Na - 20.4/28.7/21.3/2.8/7.4/7.4/0.9/3.7/3.7
	Doc 75 d1 q3w	84	0/1/2 - 28/55/17	7.0	29% (at 24 wk)	5.2		N/A/FN/I/H/P/Neu - 15/6/7/15/1/11/4
Higuchi <i>et al</i> <sup>[66]</sup> , 2014	BSC	84	0/1/2 - 28/60/14	NR	NR	3.6	1.00, P = 0.982	N/A/FN/I/H/P/Neu - 0/5/0/3/6/20/4
	Iri 60 d1 q2w; Cis 30 d1 q2w	64	0/1 - 69/31	22.0 <sup>1</sup>	3.8	10.7 <sup>1</sup>		N/A/FN/T/D/Ano/F - 13/16/0/0/2/6/3
Nishikawa <i>et al</i> <sup>[67]</sup> , 2015	Iri 150 d1 q4w	66	0/1 - 68/32	16.0 <sup>1</sup>	2.8	10.1 <sup>1</sup>	0.834, P = 0.288	N/A/FN/T/D/Ano/F - 36/18/5/2/6/11/6
	Iri 60 d1 q2w; P 30 d1 q2w	84	0/1 - 81/19	16.9 <sup>1</sup>	4.6 <sup>1</sup>	13.9 <sup>1</sup>		N/A/T/D/Ano/F - 35/16/1/0/6/9
Fuchs <i>et al</i> <sup>[69]</sup> , 2014	Iri 150 d1 q4w	84	0/1 - 75/25	15.4 <sup>1</sup>	4.1 <sup>1</sup>	12.7 <sup>1</sup>	0.776, P = 0.047	N/A/T/D/Ano/F - 28/4/0/3/9/4
	Ram 8 mg/kg d1 q2w	238	0/1/2 - 28/72/0	3.4 <sup>1</sup>	2.1	5.2		A/F/AbP/Dys/Dyn/Hyt/B/Prot/VTE - 6/6/6/2/2/8/3/<1/1
Wilke <i>et al</i> <sup>[70]</sup> , 2014	BSC	117	0/1/2 - 26/73/0	3.0 <sup>1</sup>	1.3	3.8	0.807, P = 0.017	A/F/AbP/Dys/Dyn/Hyt/B/Prot/VTE - 8/10/3/4/6/3/3//<1
	Ram 8 mg/kg d1,15 q4w	330	0/1 - 35/65	27	4.4	9.6		N/A/Leu/T/F/Neu/D/H/Hyt/Prot/HepF/VTE - 41/9/18/2/8/4/4/15/1/4/2
Satoh <i>et al</i> <sup>[76]</sup> , 2014	Ptx 80 d1/d8/d15 q4w	335	0/1 - 43/57	16	2.9	7.4	0.84, P = 0.2	N/A/Leu/T/F/Neu/D/H/Hyt/Prot/HepF/VTE - 19/9/6/2/5/5/1/4/3/0/3/2
	Lap 1500 mg once daily	132	0/1 - 45/55	27	5.5 <sup>1</sup>	12.2 <sup>1</sup>		(experienced in > 10% of pts) N/A/Lym/F/Neu/D - 57/11/29/5/<1/18
Dutton <i>et al</i> <sup>[77]</sup> , 2014	Ptx 80 d1,d8,d15 q4w	129	0/1 - 37/63	9	4.4 <sup>1</sup>	10.5 <sup>1</sup>	0.90, P = 0.293	(experienced in > 10% of pts) N/A/Lym/F/Neu/D - 31/6/2/<1/0/2
	Gef 500 mg/d daily	224	0/1/2 - 25/52/22	24 (DC)	1.57	3.73 <sup>1</sup>		D/F/Sk/Rep/I/Hem/Vas/Met - 6/10/20/12/3/7/7/6
	Placebo	225	0/1/2 - 25/55/20	16 (DC)	1.17	3.67 <sup>1</sup>	D/F/Sk/Rep/I/Hem/Vas/Met - 1/5/<1/12/4/4/5/7	

<sup>1</sup>The P value non-significant. BSC: Best Supportive Care; Dtx: Docetaxel; Gef: Gefitinib; Iri: Irinotecan; Lap: Lapatinib; P: Cisplatin; Ptx: Paclitaxel; Ram: Ramucirumab; DC: Disease control; ECOG: Eastern Co-operative Oncology Group; NR: Not reported; ORR: Objective Response Rate; OS: Overall-survival; PFS: Progression-free survival; Pts: Patients; WHO: World Health Organization; A: Anemia; AbP: Abdominal Pain; Ano: Anorexia; B: Bilirubin; D: Diarrhea; Dys: Dysphagia; Dyn: Dyspnea; E: Emesis; FN: Febrile neutropenia; H: Hemorrhage; Hem: Hematologic toxicity; HepF: Hepatic failure; Hyt: Hypertension; I: Infection; L: Leucocytopenia; Ly: Lymphopenia; M: Mucositis; Met: Toxicity associated with metabolism and nutrition; N: Neutropenia; Neu: Sensory neuropathy; Nau: Nausea; N-E: Nausea and vomiting; P: Pain; Prot: Proteinuria; Resp: Respiratory toxicity; Sk: Skin toxicity; T: Thrombocytopenia; Vas: Vascular toxicity; VTE: Venous thromboembolic events.

translate to the overall survival benefit<sup>[66]</sup>.

A recently published Japanese phase III randomized study (TRICS)<sup>[67]</sup> included platinum-naïve patients progressing following S-1 monotherapy for metastatic gastric cancer or relapsed within 6 mo after completion of S-1 adjuvant therapy. Approximately 168 patients with an ECOG PS of 0 or 1 were randomly allocated to

irinotecan 60 mg/m<sup>2</sup> and cisplatin 30 mg/m<sup>2</sup> every 2 wk (n = 84) or irinotecan 150 mg/m<sup>2</sup> every 2 wk (n = 84). No significant differences were observed in the OS (13.9 vs 12.7 mo, HR = 0.834, 95%CI: 0.596-1.167), PFS (4.6 vs 4.1 mo, HR = 0.860, 95%CI: 0.615-1.203) and response rates (16.9% vs 15.4%, P = 0.812). The favorable long-term survival rates observed in

this study may be due to the favorable prognostic characteristics of the patients, as only patients with an ECOG PS of 0-1 were considered, the median number of metastatic sites was 1, and only 21% of patients had 2 or more metastatic sites. Compared to the irinotecan arm, the irinotecan/cisplatin arm showed significantly higher grade 3-4 toxicities, regarding anemia (16% vs 4%) and lactate dehydrogenase level (5% vs 0%). There was no survival benefit observed upon adding cisplatin to irinotecan after failure of S-1 monotherapy<sup>[67]</sup>.

The meta-analysis by Kim *et al.*<sup>[68]</sup> demonstrated evidence to support the efficacy of second-line chemotherapy in the treatment of metastatic gastric cancer. The meta-analysis pooled together 410 patients from three randomized trials<sup>[62,63,65]</sup> evaluating chemotherapy (docetaxel/irinotecan) versus BSC as second-line therapy in patients with metastatic gastric cancer. This meta-analysis demonstrated that there exists a clear survival benefit with a 36% reduction in the risk of death when using second-line chemotherapy in patients with metastatic gastric cancer (HR = 0.64; 95%CI: 0.52-0.79,  $P < 0.0001$ ). The observed results were consistent irrespective of the administered drugs, and the extent of survival benefit was similar between European and Asian populations (HR = 0.63 and 0.657, respectively)<sup>[68]</sup>.

**Biological agents:** With the arrival of ToGA study data, a new era of targeted therapy was opened for gastric cancer<sup>[18]</sup>. Ramucirumab is the first biological agent that showed a survival benefit in patients with metastatic gastric or gastro-esophageal junction adenocarcinoma progressing after first-line chemotherapy, given either as a single drug<sup>[69]</sup> or in combination with paclitaxel<sup>[70]</sup>. Ramucirumab is a fully human Immunoglobulin G1 monoclonal antibody receptor antagonist designed to bind the extracellular domain of Vascular Endothelial Growth Factor (VEGF) Receptor-2, thereby blocking the binding of VEGF ligands and inhibiting receptor activation and thus inhibiting angiogenesis<sup>[71]</sup>.

In the phase III randomized study (REGARD)<sup>[69]</sup>, 355 patients from all parts of the world who progressed after platinum- or fluoropyrimidine-based first-line chemotherapy were randomized to receive either ramucirumab 8 mg/kg on day 1 every 2 wk ( $n = 238$ ) or placebo ( $n = 117$ ). Almost all the patients had an ECOG PS of 0-1. In the active treatment arm, 65% of patients had a progression-free interval of  $\geq 6$  mo from the end of the previous treatment. Single agent ramucirumab showed a significant survival benefit when compared with the placebo arm (median OS - 5.2 vs 3.8 mo, HR = 0.776,  $P = 0.047$ ). Estimated rates of 12-wk PFS were 40.1% in patients in the ramucirumab arm and 15.8% in the placebo arm. The rate of disease control was significantly higher in patients given ramucirumab than in those given placebo (49% vs 23%). The median time to deterioration in ECOG PS to

a score of 2 or worse was 5.1 mo in the ramucirumab arm and 2.4 mo in the placebo arm (HR = 0.586,  $P = 0.002$ ). With regard to safety, more patients in the ramucirumab group had grade  $\geq 3$  hypertension than those in the placebo group (8% vs 3%)<sup>[69]</sup>.

In another large phase III randomized study (RAINBOW)<sup>[70]</sup>, 655 patients with a PS score of 0-1 received either ramucirumab 8 mg/kg ( $n = 330$ ) or placebo ( $n = 335$ ) on days 1 and 15, plus paclitaxel 80 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-d cycle. In both arms, 75% of patients had a time-to-progression duration of  $< 6$  mo on first-line therapy. More than 70% and 20% of patients received a doublet and triplet regimen in first-line therapy (containing both fluoropyrimidines and platinum agents), respectively. Median OS (9.6 mo vs 7.4 mo. HR = 0.807,  $P = 0.017$ ) and median PFS (4.4 mo vs 2.9 mo. HR = 0.635,  $P \leq 0.001$ ) were significantly increased in the ramucirumab plus paclitaxel arm compared with the placebo and paclitaxel arm. Preplanned forest plot analyses showed an OS benefit in all subgroups. Grade  $\geq 3$  adverse events that occurred more often in the Ramucirumab plus Paclitaxel arm included neutropenia (41% vs 19%), hypertension (14% vs 2%), fatigue (12% vs 5%), anemia (30% vs 10%), and abdominal pain (6% vs 3%). Thus, the addition of ramucirumab to paclitaxel significantly increased OS, and this regimen could be considered as a new standard of second-line treatment for patients with metastatic gastric cancer<sup>[70]</sup>.

Antiangiogenic therapy is not solely limited to monoclonal antibodies. In addition to ramucirumab, there are several other agents, such as apatinib and regorafenib, that exhibit an antiangiogenic effect. Apatinib is an oral VEGFR2 tyrosine kinase inhibitor (TKI). The results of a randomized phase III study conducted in China that investigated the survival benefit of apatinib over placebo were presented in 2014. Patients who failed to improve after two prior lines of treatment were randomly assigned to receive apatinib ( $n = 180$ , 850 mg once daily) and placebo ( $n = 90$ ). The median OS was significantly higher in the apatinib arm compared to the placebo arm (195 vs 140 d, HR = 0.71,  $P < 0.016$ ) as well as PFS (78 vs 53 d, HR = 0.44,  $P < 0.0001$ )<sup>[72]</sup>.

In 2015, the preliminary results of a randomized phase II study (INTEGRATE), which studied the efficacy and safety of regorafenib over BSC in metastatic gastric cancer patients who failed to improve after one or two lines of chemotherapy, were reported. Regorafenib is an oral small-molecule inhibitor of multiple protein kinases, including those involved in angiogenesis (VEGFR 1, 2, and 3, TK with Ig and EGF homology domain 2), oncogenesis (KIT, RET, RAF-1, BRAF), and the tumor microenvironment (platelet-derived growth factor receptor- $\beta$ , fibroblast growth factor receptor)<sup>[73]</sup>. A total of 152 patients were randomly assigned to receive regorafenib (160 mg, days 1-21 every 28 d) plus BSC over placebo plus BSC

in a 2:1 fashion. The median PFS was improved in the regorafenib arm compared with placebo (11.1 wk vs 3.9 wk, HR = 0.41  $P < 0.0001$ ). OS data have not yet been reported. Regorafenib therapy was well tolerated, and there were no new safety signals<sup>[74]</sup>.

Lapatinib, a EGFR1-2 TKI, did not show survival benefit in first-line therapy when combined with capecitabine plus oxaliplatin in HER2-positive advanced or metastatic gastric and esophageal adenocarcinomas in the TRIO-013/LOGIC trial<sup>[75]</sup>. Lapatinib was also studied in a phase III randomized (TyTAN) study in second-line treatment for an Asian population<sup>[76]</sup>. Patients deemed HER2-positive by FISH ( $n = 420$ ) were either randomized to receive lapatinib (1500 mg once daily) plus paclitaxel (80 mg/m<sup>2</sup> on days 1, 8, 15 every 4 wk) or paclitaxel alone. In the intent-to-treat (ITT) population, the median OS was improved in the experimental arm from 8.9 to 11 mo (HR = 0.84;  $P = 0.2088$ ). There was no significant difference in the median PFS (5.4 mo vs 4.4 mo) or TTP (5.5 mo vs 4.4 mo). Around one-third of patients had tumors with no HER2 expression (0/1+) according to immunohistochemistry (IHC) in both arms. Pre-planned subgroup analysis showed a significant OS benefit in patients with IHC 3+ expression treated with lapatinib (14 mo) compared to those treated with paclitaxel alone (7.6 mo, HR = 0.59;  $P = 0.0176$ )<sup>[76]</sup>.

Gefitinib, an EGFR1 TKI, was investigated in the second-line treatment of metastatic esophageal cancer or type I/II Siewert junctional tumors in a phase III randomized trial (COG study). Approximately 450 patients with a squamous-cell carcinoma or adenocarcinoma with WHO PS 0-2 were randomly assigned to receive gefitinib 500 mg/d or placebo. Gefitinib resulted in a statistically significant improvement of PFS (HR = 0.8), but not OS (3.73 mo vs 3.67 mo, HR = 0.90,  $P = 0.29$ )<sup>[77]</sup>.

Everolimus is an oral mammalian target of rapamycin (mTOR) inhibitor. Everolimus was studied in a phase III randomized study (GRANITE-I) in metastatic gastric cancer patients progressing after one or two lines of previous systemic chemotherapy. A total of 656 patients were randomized in a 2:1 fashion to everolimus plus BSC ( $n = 439$ ) or placebo plus BSC ( $n = 217$ ). In both arms, 48% of patients had received one previous therapy and 52% had received two previous therapies. Compared with BSC, everolimus did not significantly improve survival (median OS - 5.4 mo vs 4.3 mo; HR = 0.90,  $P = 0.124$ )<sup>[78]</sup>.

## FUTURE DIRECTIONS

In the second-line treatment of metastatic gastric cancer, factors such as hepatocyte growth factor receptor (c-Met), fibroblast growth factor receptor (FGFR), epithelial cell adhesion molecule (EpCAM), insulin-like growth factor receptor 1 (IGF-1R), phosphatidylinositol 3-kinases (PI3K), cyclin dependent kinases (CDK), mitogen-activated protein kinases

(MAPK), immune checkpoints (PD-1 and PD-L1), matrix metalloproteinases, proteasomes, histone deacetylases, chaperone proteins, and other molecular structures are under evaluation. Novel drugs directed against those specific targets are under clinical investigation.

Preclinical data suggest that the hepatocyte growth factor (HGF)/MET pathway may represent a therapeutic target for gastric adenocarcinoma<sup>[79,80]</sup>. The expression of receptors to HGF is found in up to 74% of cases of gastric adenocarcinoma. However, mutations in the c-Met gene are found in 10% of cases, and gene amplification is found in 2%-23% of gastric tumors<sup>[81-85]</sup>. C-Met overexpression has been associated with poor prognosis. Signals sent from the HGF receptor activate a wide range of cellular signaling pathways, which promote proliferation, migration and survival. This has made c-Met a potential therapeutic target. The c-Met inhibitors crizotinib and foretinib did not show significant activity in c-Met gene-amplified gastric cancer<sup>[84,86]</sup>. However, monoclonal antibodies to c-Met, including rilotumumab and onartuzumab, are being actively studied in phase III studies<sup>[87,88]</sup> in the first-line treatment of metastatic gastric cancer. Rilotumumab showed promising results in a randomized phase II placebo-controlled study. Approximately 121 patients with metastatic gastric cancer receiving first-line therapy with epirubicin, cisplatin and capecitabine (ECX) were randomly assigned to receive rilotumumab or placebo (40 to rilotumumab 15 mg/kg; 42 to rilotumumab 7.5 mg/kg; 39 to placebo). ECX plus rilotumumab significantly reduced the risk of disease progression compared with placebo (HR = 0.6,  $P = 0.016$ ). However, there was no significant difference in overall survival. It should be noted that only 56% of the patients included in the study had a tumor expressing the c-Met gene<sup>[89]</sup>. The results of two other studies on c-Met inhibitors were presented in ASCO GI 2015<sup>[90,91]</sup>. AMG337, a selective inhibitor of the tyrosine kinase c-Met, was investigated in a phase I study in patients with gene amplification. An objective response was achieved in 8 out of 13 (62%) patients with gastric cancer<sup>[90]</sup>. Onartuzumab, a monoclonal antibody to c-MET, was studied in combination with a FOLFOX regimen in a randomized phase II study, which included 123 patients with metastatic gastric cancer. The study did not improve the long-term results. The most possible explanation for the study's failure could be the patient selection, which was based on overexpression rather than gene amplification<sup>[91]</sup>. Thus, the blockade of c-met has become an extremely promising strategy in the targeted therapy of gastric cancer.

In recent years, agents targeting immune checkpoints (PD-1 and PD-L1) are gaining momentum in oncology. Programmed cell death-1 (PD-1), an immunoinhibitory receptor of the CD28 family, plays a major role in the immune escape of tumors<sup>[92]</sup>. One of the mechanisms by which tumors evade host T



cells is by activating immune checkpoints that block T-cell activation. The presence of PD-L1 on tumor cells allows them to escape the cytotoxic effects of immune cells. Pembrolizumab, a highly selective humanized IgG4/kappa isotype monoclonal antibody that blocks PD-1's interaction with its ligands PD-L1 and PD-L2, was approved for the treatment of metastatic melanoma in 2014. Pembrolizumab was studied in a phase Ib study, which was presented at the ESMO meeting in 2014<sup>[93]</sup>. Among 39 patients with chemotherapy-refractory metastatic gastric or gastro-esophageal junction carcinoma and PD-L1 expression in  $\geq 1\%$  of tumor cells, pembrolizumab administration achieved an objective response of 31% with a median response duration of 6 mo. There was a correlation between the degree of expression of PD-L1 and objective tumor response<sup>[93]</sup>. Following these encouraging results, a randomized phase II study has been initiated to investigate the efficacy of pembrolizumab in monotherapy or in combination with cisplatin and 5-fluorouracil for the first-line treatment of metastatic gastric cancer.

BRCA mutations in gastric cancer are extremely rare. However, the decrease in the activity of certain components of homologous recombination occurs in 35%<sup>[94]</sup>. Changes in the activity of other molecules are not directly associated with the process of homologous recombination, up to 70% (PTEN dysfunction, mutation of p53 and ERCC1)<sup>[95-97]</sup>. Preclinical data indicate that olaparib, an oral poly (ADP-ribose) polymerase inhibitor, showed increased efficiency when combined with chemotherapeutic agents<sup>[98]</sup>. A randomized phase II study compared the efficacy of olaparib (100 bid, daily) ( $n = 61$ ) or placebo ( $n = 62$ ) in combination with paclitaxel (80 mg/m<sup>2</sup> days 1, 8, 15 per 28-day cycle) on both arms as second-line therapy in patients with recurrent/metastatic gastric cancer. Investigators found that in the absence of ATM expression in tumors, which constitute the surrogate of homologous recombination deficiency, the addition of olaparib to paclitaxel significantly increased OS, but not PFS<sup>[99]</sup>. This has created a new dimension of research in the targeted therapy of gastric cancer - the influence on the DNA repair mechanisms in tumors.

Currently, one of the most studied biomarkers in oncology is the therapeutic targets for fibroblast growth factor receptors (FGFR) and their ligands. The family of human FGF comprises 22 proteins and 5 types of receptors for FGF (FGFR). The FGF/FGFR complex is involved in the differentiation and proliferation of various cells<sup>[100,101]</sup>. In gastric cancer, the gene amplification of FGFR4 is associated with poor prognosis<sup>[102,103]</sup>. As in other tumor types, the presence of the FGFR4 gene polymorphism Gly388Arg has proved to be of prognostic significance in gastric cancer<sup>[104]</sup>. In a Japanese study<sup>[105]</sup>, which included tumor samples from 222 gastric cancer patients, high levels of expression of FGFR 1, 2, 3, and 4 (without amplification) were detected in 30%, 51%, 64% and

79% of tumors, respectively. The overexpression of FGFR1, FGFR2 or FGFR4 was found to be significantly associated with tumor progression, including depth of invasion, lymph node metastasis, pathological stage and distant metastasis or recurrent disease. Therefore, FGFR-targeted therapeutics using small-molecule compounds that inhibit the binding of FGF to FGFR is a promising direction for research. For example, the inhibition of FGFR2 signaling by AZD4547, a FGFR inhibitor, resulted in significant dose-dependent tumor growth inhibition in FGFR2-amplified gastric cancer cell lines<sup>[106]</sup>. AZD4547 is currently being studied in a randomized phase II trial as monotherapy and in combination with paclitaxel for the second-line treatment of patients with metastatic gastric or gastro-esophageal junction cancer with FGFR2 polysomy or gene amplification<sup>[107]</sup>.

## DISCUSSION

Although data from randomized clinical trials show an increased survival benefit with second-line therapy, not all patients are offered second-line therapy in real-life clinical practice. This could possibly be explained by the poor PS, which the majority of patients experience with disease progression after first-line therapy. In Japan, almost all patients with metastatic gastric cancer receive second-line therapy and more than 50% of patients receive three lines of therapy. However, in western countries, only half of the patient population is offered second-line treatment on progression after first-line therapy. These regional ethnic differences should be taken in to consideration before translating the survival benefit from clinical studies to real-life practice. Additionally, the OS benefit obtained from phase III studies was observed in selected patients who had adequate organ function and no severe comorbidities at the time of entry into the study.

In order to obtain a clear survival benefit, it would be more rational to use second-line therapy in a separate group of patients with higher predictive survival rate who are likely to benefit from second-line therapy. This would allow us to spare the adverse effects of cytotoxic agents in patients with lower predictive survival rates. Of the randomized clinical trials<sup>[62,63,69]</sup>, several factors, such as poor performance status, presence of peritoneal metastases, gastro-esophageal location of the primary tumor and a chemotherapy-free interval of < 3 mo were identified as clinicopathological prognostic factors for reduced OS. Moreover, several other retrospective studies identified similar prognostic factors (performance status, time to progression of first-line chemotherapy and hemoglobin levels)<sup>[25,33,108-110]</sup>. Therefore, factors such as the patient's general condition, metastatic extent, previously used cytotoxic agents, toxicity profile, cumulative toxicity, lack of cross-resistance to previously used agents, and previous response to first-line therapy should always be considered while

administering second-line therapy. The role of second-line therapy in metastatic gastric cancer should not only be improving OS but also achieving better symptom control and improved QoL. Park *et al*<sup>[111]</sup> found that second-line therapy by itself improves the QoL and Hospital Anxiety and Depression Scale (HADS) scores in patients with metastatic gastric cancer, regardless of the objective tumor response. This shows that second-line therapy is justified in patients who are physically fit and willing to receive further chemotherapy. These findings are different from the traditional endpoints such as tumor response rate and survival rate.

A recent meta-analysis<sup>[112]</sup> analyzed the published phase III trials<sup>[62,63,65,69,78]</sup> that compared active treatment to BSC in metastatic gastric cancer. Both chemotherapy and ramucirumab had similar activity in terms of the reduction of the risk of death by 27% and 22%, respectively. This analysis demonstrated that a significant OS benefit was registered with active second-line treatments (irinotecan, docetaxel, ramucirumab), even in patients with impaired performance status [ECOG  $\geq$  1, HR = 0.82 (0.79-0.85)]<sup>[112]</sup>. This suggests that patients with symptomatic disease should not be excluded from further lines of treatment following the failure of first-line therapy. It should be noted that for the first time in the second-line setting, the addition of a targeted agent (ramucirumab) to standard chemotherapy (paclitaxel) demonstrated a significant survival benefit by increasing the median OS from 7.4 to 9.6 mo ( $P = 0.017$ ) and median PFS from 2.9 to 4.4 mo. However, the other biological agents, such as everolimus, lapatinib and gefitinib, failed to show a survival benefit when administered as second-line therapy. In addition to HER2 overexpression, to date, there are no predictive biomarkers in the treatment of metastatic gastric cancer. This has reemphasized the fact that clinical studies with better patient selection based on predictive biomarkers are necessary.

Older microarray studies<sup>[113-117]</sup> performed in gastric cancer cell lines described the expression changes associated with morphological and tissue type differences in gastric cancer. This approach has changed as pathway signatures (rather than individual genes) are used as the basis for cancer classification. Recently, the Cancer Genome Atlas (TCGA) project<sup>[118]</sup> proposed a molecular classification dividing gastric cancer into four genomic subtypes: Epstein-Barr virus-infected tumors, which display recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, PD-L1/2; microsatellite unstable tumors, which show elevated mutation rates, including mutations of genes encoding targetable oncogenic signaling proteins; genomically stable tumors, which are enriched for the diffuse histological variant and mutations of RHOA or fusions involving RHO-family GTPase-activating proteins; and chromosomally unstable tumors, which show marked aneuploidy and focal amplification of receptor tyrosine kinases. This

classification has provided a roadmap for better patient stratification for clinical studies that are to be planned with targeted agents.

## CONCLUSION

In the second-line setting, to date, three agents (irinotecan, taxane and ramucirumab) have shown a survival benefit over BSC or active agents in randomized phase III studies. Furthermore, a paradigm shift from disease-specific new drug development to biomarker-oriented investigations is gaining momentum in the treatment of metastatic gastric cancer. Clinical trials of molecular targeted agents should focus on specific patient subsets. This will result in individualizing therapeutic strategies by maximizing drug efficacy and minimizing adverse effects in patients with metastatic gastric cancer.

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