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Companion diagnostics for the targeted therapy of gastric cancer

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Abstract

Gastric cancer is the fourth most common type of

cancer and represents a major cause of cancer-related deaths worldwide. With recent biomedical advances in our understanding of the molecular characteristics of gastric cancer, many genetic alterations have been identified as potential targets for its treatment. Multiple novel agents are currently under development as the demand for active agents that improve the survival of gastric cancer patients constantly increases. Based on lessons from previous trials of targeted agents, it is now widely accepted that the establishment of an optimal diagnostic test to select molecularly defined patients is of equal importance to the development of active agents against targetable genetic alterations. Herein, we highlight the current status and future perspectives of companion diagnostics in the treatment of gastric cancer.

Key words: Companion diagnostics; Gastric cancer; Human epidermal growth factor receptor 2; Fibroblast growth factor receptor; Hepatocyte growth factor receptor

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Core tip: Companion diagnostics are *in vitro* clinical laboratory assays designed to predict the efficacy of treatment using biomarker-based assessments. For patients with gastric cancer, immunohistochemistry for human epidermal growth factor receptor 2 (HER2) overexpression and fluorescence *in situ* hybridization for *HER2* amplification are the only approved companion diagnostic devices. In this era of targeted therapy, the concurrent development of companion diagnostic techniques is critical for the success of novel therapeutics. Furthermore, the successful co-development of drug and companion diagnostics requires a thorough molecular understanding of both tumor biology and the mechanisms of drug actions.

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INTRODUCTION

Gastric cancer (GC) is the fourth most common type of cancer and represents a major cause of cancer-related deaths worldwide^[1,2]. Surgery is the curative treatment option for patients with localized GC and the survival of patients with resectable GC has improved to 5-year survival rates of 72%-78% in East Asia with enhanced efficacy imparted by adjuvant treatment^[3,4]. However, with the exception of several countries in East Asia where national screening programs for the detection of GC are conducted, such as South Korea and Japan, most patients initially present with inoperable or metastatic disease^[2,5]. Although no single standard cytotoxic chemotherapy regimen has been established, doublet or triplet regimens that include fluoropyrimidine and platinum have been accepted as the current standard treatments for patients with inoperable or metastatic GC^[6-9]. The activities of taxanes and irinotecan have been demonstrated and these compounds are widely used as second-line chemotherapy^[10-12]. However, the prognosis of patients with metastasis or inoperable GC remains poor and is associated with an overall survival of approximately 1 year^[6-9].

Recent advances in biomedical research have advanced our understanding of the molecular characteristics of GC, leading to the identification of many genetic alterations as potential targets for its treatment^[13,14]. Trastuzumab, a monoclonal antibody against HER2, and ramucirumab, a fully human IgG1 monoclonal antibody, VEGFR-2 antagonist, have demonstrated survival benefits in randomized phase 3 trials and been approved for the treatment of GC^[15-17]. Multiple novel agents are now under development as the demand for active agents that can improve the survival of GC patients is constantly increasing. Based on lessons from previous trials of targeted agents, it is now widely accepted that the establishment of an optimal diagnostic test to select molecularly defined patients is as important as the development of active agents against targetable genetic alterations. In this review, we highlight the current status and future perspective of companion diagnostics in GC.

CURRENT STATUS OF COMPANION DIAGNOSTICS IN GC

The history of companion diagnostics began with the United States Food and Drug Administration (FDA) approval of an immunohistochemistry (IHC) assay (HercepTest™, Dako Denmark A/S, Glostrup,

Denmark) for HER2 protein overexpression in 1998^[18]. Companion diagnostics are generally known as *in vitro* clinical laboratory assays designed to predict the efficacy of treatment through the assessment of biomarkers^[19]. In a draft guidance issued by the United States FDA in 2011^[20], companion diagnostics were defined as essential devices for the (1) identification of patients who are most likely to benefit from a particular therapeutic product; (2) identification of patients likely to be at increased risk of serious adverse reactions as a consequence of treatment with a particular therapeutic product; and (3) monitoring of responses to treatment so that treatments can be adjusted to achieve improved safety or efficacy. Previously, this has been given various names, such as pharmacodiagnosics, theranostics, and pharmacogenomic biomarkers, but the term "companion diagnostics" is now more commonly used and has been adapted by the United States FDA and the European Union (EU)^[19]. Companion diagnostics have a central role in drug development as techniques with analytical validity allow investigators to conduct clinical trials using an enriched study design, which is likely both to reduce sample sizes and costs, and to increase success rates^[21]. Additionally, a key goal of clinical precision medicine is to prescribe the right drug for the right patient. The United States FDA has approved IHC assays, *in situ* hybridization, and target DNA mutation analyses as companion diagnostics for cancer^[18]. For patients with GC, the HercepTest™ for IHC assessment of HER2 overexpression and the HER2 fluorescence *in situ* hybridization (FISH) PharmDx™ Kit (Dako Denmark A/S) for the detection of gene amplification are the only approved companion diagnostic devices that are based on a successful randomized phase 3 ToGA trial^[15,18].

HER2 pathway signaling

HER2 overexpression or amplification has been reported in approximately 20% of GC cases^[22-25]. In contrast to breast cancer, in which HER2-positivity is significantly correlated with a poor prognosis, the prognostic significance of HER2 overexpression or its amplification in GC has been the subject of controversy^[23,26]. This issue might be attributable to the unique characteristics of HER2 expression patterns in GC, such as discrepancies in the frequency of HER2 overexpression (30% in intestinal type vs 6% in diffuse type) according to the Lauren's classification, a well-known prognostic factor in GC, and variability in IHC staining that can indicate tumor heterogeneity in HER2 expression, particularly in IHC 2+ cases^[25].

Based on the efficacy of trastuzumab in preclinical models of GC^[27] and its marked success in HER2-positive breast cancer, a randomized phase 3 ToGA trial that compared chemotherapy with or without trastuzumab was conducted^[15]. When the ToGA trial was planned, validated test methods and scoring systems for HER2 status were widely available for breast cancer, but not GC. Therefore, a validation

Table 1 Human epidermal growth factor receptor 2 scoring criteria for gastric cancer^[15,23]

Score	Surgical specimen-staining pattern	Biopsy specimen-staining pattern	HER2 overexpression assessment
0	No reactivity or membranous reactivity in < 10% of tumor cells	No reactivity or no membranous reactivity in any tumor cell	Negative
1+	Faint/barely perceptible membranous reactivity in ≥ 10% of tumor cells; cells are reactive only in part of their membrane	Tumor cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	Negative
2+	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥ 10% of tumor cells	Tumor cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥ 10% of tumor cells	Tumor cell cluster with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained	Positive

HER2: Human epidermal growth factor receptor 2.

study was performed to establish a HER2 scoring system for GC to identify suitable patients for enrollment in the trial^[23]. In that study, which used the HercepTest™ and FISH PharmDx™ Kit, it was noted that tumor heterogeneity and basolateral membrane staining were more common in GC than in breast cancer. That study concluded that the scoring system of HER2 IHC assessment using the HercepTest™ in breast cancer should be applied to GC with some modifications because of incomplete reactivity in tumor cell membranes and tumor heterogeneity, which are both frequently observed in GC (Table 1). It was also recommended that both IHC and FISH testing should be used to select patients for the ToGA trial because of differences in results between GC and breast cancer. Based on this validation study of the HER2 scoring system in GC, patients were enrolled in the trial if their tumor samples were scored as 3+ by IHC or as FISH-positive (a HER2: CEP17 [centromeric probe 17] ratio ≥ 2)^[15].

In the ToGA trial that enrolled 594 chemotherapy-naïve patients with GC, the addition of trastuzumab significantly improved the efficacy of chemotherapy with 2.7 mo of benefit in median overall survival (13.8 mo for chemotherapy with trastuzumab vs 11.1 mo for chemotherapy alone)^[15]. After the success of the ToGA trial, trastuzumab became the first biological agent approved for the treatment of GC, and the combination of trastuzumab and cytotoxic chemotherapy is now considered as a standard treatment for metastatic or recurrent HER2-positive GC. Although the results of the FISH and IHC assays have been shown to be highly correlated^[24], HER2 overexpression assessed by IHC was more significantly correlated with the efficacy of trastuzumab, irrespective of the FISH results. Indeed, the median overall survival was 10.0 mo in the IHC 0 or 1+/FISH-positive subgroup, whereas it was 16.0 mo in the IHC 2+ or 3+/FISH-positive subgroup^[15]. This improved efficacy of trastuzumab in HER2 IHC 2+/FISH-positive or IHC 3+ GC patients was supported by the findings of subsequent phase 2 trials that used trastuzumab-containing regimens against GC^[28,29]. Ongoing trials for novel HER2-targeted therapies, such

as pertuzumab^[30] and T-DM1 (NCT01641939), now use this selection criterion (*i.e.*, IHC 2+/FISH-positive or IHC 3+) for the inclusion of patients. Additionally, IHC staining is recommended as the initial testing modality for all GC patients to define HER2 positivity in daily clinical practice^[24,31].

Lapatinib is a tyrosine kinase inhibitor that blocks both epidermal growth factor receptor (ErbB1) and HER2, which has been approved for the treatment of HER2-positive breast cancer after progression to trastuzumab^[32]. The efficacy of lapatinib in GC was investigated in two large randomized phase 3 trials^[33,34]. The TyTAN trial compared the combination of lapatinib plus paclitaxel with paclitaxel alone in a second-line setting for 281 patients with HER2-amplified GC that was assessed by FISH (HER2: CEP17 ratio ≥ 2)^[33]. That trial failed to show significant improvements in overall survival with the addition of lapatinib in a second-line setting. Despite the negative results in an intent-to-treat population, subgroup analyses revealed that lapatinib was significantly associated with better overall survival in patients with HER2 IHC 3+ GC. This finding suggested that the efficacy of lapatinib might correlate with HER2 overexpression as assessed by IHC, which was also shown in a ToGA trial for trastuzumab. As this trial only used FISH for patient selection, more patients with HER2 IHC 0/1+ (35%) were included than in the ToGA trial in which 22% of patients were HER2 IHC 0/1+^[15,33]. Therefore, improper selection of the target patient population might represent a potential reason for negative results, although the lack of efficacy of lapatinib against HER2-positive GC should also be considered. The TRIO-013/LOGiC trial tested first-line capecitabine plus oxaliplatin with or without lapatinib in patients with HER2-amplified or overexpressed GC, which was defined as IHC2+ and FISH amplified, or IHC 3+, or FISH, CISH, or SISH amplified^[34]. In this trial of 487 patients, the addition of lapatinib did not improve overall survival, consistent with the results of the TyTAN trial. Moreover, subgroup analyses of this study did not show a correlation between IHC and outcomes with lapatinib, which contradicted the

TyTAN trial findings. The lack of efficacy with lapatinib in these trials might be a consequence of negative interactions between lapatinib and partner cytotoxic chemotherapy agents, insufficient activity of lapatinib on HER2-positive GC, or improper selection of the patient population.

In addition to the IHC HercepTest™ and FISH PharmDx™ used in the ToGA trial, alternative assays or techniques to assess HER2 status have been evaluated. In the subset analysis of the TRIO/LOGiC trial, the results of the PathVysion HER2 FISH probe (Abbott Molecular Inc., IL) were highly correlated with those of HER2 FISH PharmDx™ in the central laboratory, with rates of positive agreement of 97.9% and negative agreement of 99.1%^[35]. In a retrospective analysis, there was a high concordance of IHC staining results between the HercepTest™ (polyclonal antibody) and Pathway (monoclonal antibody; Ventana Medical System, Tucson, AZ) for GC patients^[36]. Among various methods used to assess *HER2* gene amplification, silver *in situ* hybridization (SISH), a bright field *in situ* hybridization (ISH) method, has been suggested to be a valid alternate option for GC, as previous studies showed 94-100% concordance with FISH findings^[36-38].

Hepatocyte growth factor receptor pathway signaling

Although there are no approved companion diagnostics for detecting activation of the hepatocyte growth factor receptor (MET) signaling pathway, it represents one of the most widely investigated biomarkers in GC^[39-41]. The role of the MET signaling pathway in tumorigenesis and metastasis has been well documented^[42] and MET overexpression or amplification has been suggested to be a negative prognostic marker in GC patients^[40]. The preclinical activity of MET inhibitors against MET-amplified or overexpressed GC has also been well established^[39]. Multiple drugs that target MET signaling pathways are now in the early and late phases of clinical trials for GC patients. Along with the early clinical development of these agents, efforts to define biomarkers predictive of the efficacy of these agents have been ongoing. Onartuzumab (MetMab) is an anti-c-MET monoclonal antibody and, as MET overexpression has been associated with increased efficacy of onartuzumab in a randomized phase 2 trial for patients with lung cancer^[43], MET overexpression assessed by IHC was selected as a marker to enrich patients with MET-positive tumors in trials for GC. A randomized phase 2 trial was conducted for patients with HER2-negative GC to compare modified FOLFOX6 plus onartuzumab with modified FOLFOX6 alone^[44]. In that trial, the addition of onartuzumab did not improve progression-free survival in either an unselected population or in MET-positive patients defined by IHC ($\geq 50\%$ of a tumor with moderate to strong intensity staining on central review). Moreover, there was no correlation between the efficacy of onartuzumab and the intensity of MET expression or different

definitions for MET positivity ($\geq 90\%$). Rilotumumab, a hepatocyte growth factor (HGF)-targeted monoclonal antibody, was investigated in combination with epirubicin, cisplatin, and capecitabine (ECX) in a randomized phase 2 trial for GC^[45]. In that trial, two different doses of rilotumumab (7.5 and 15 mg/kg) were tested and the addition of rilotumumab was significantly associated with improved progression-free survival [5.7 mo in both rilotumumab groups (pooled) vs 4.2 mo in the placebo group; HR = 0.60; $P = 0.0116$]. In an exploratory analysis of this trial, MET-positivity was defined as $\geq 25\%$ tumor membrane staining and this MET-positive subgroup appeared to have a benefit in overall survival with rilotumumab. Meanwhile, in early phase trials of ABT-700, an anti-c-MET monoclonal antibody, and AMG 337, an oral MET kinase inhibitor, promising efficacy was shown in subgroups of patients with MET-amplified tumors as assessed by FISH^[46,47].

Well-defined MET positivity appears to be critical for the success of MET inhibitors in GC. This may depend upon the tumor characteristics, properties of the IHC assay, and characteristics of the therapeutic agents. As suggested previously, assessing MET overexpression by detecting the extracellular domain of MET is more likely to predict the efficacy of a monoclonal antibody, such as rilotumumab^[45]. However, further validation studies that are based on larger sample sizes are needed to bolster this conclusion.

Other potential biomarkers in GC

The fibroblast growth factor signaling pathway is also considered to be a potential target for the treatment of GC^[39,41,48-50]. AZD4547^[51] and dovitinib^[52] are fibroblast growth factor receptor 2 (FGFR2) tyrosine kinase inhibitors that are currently under investigation in phase 2 trials for GC (NCT01457846 and NCT01719549). Both trials include patients with FGFR2-amplified GC, but use different detection methods (FISH in the AZD4547 trial and quantitative real-time PCR in the dovitinib trial). In a study that compared the result obtained using quantitative real-time PCR, IHC, and FISH in GC tissue samples, robust correlations of both quantitative real-time PCR and IHC data were shown with the FISH findings, which represents the most commonly used technique and is considered to be a standard method for FGFR2^[53]. However, this correlation should be validated in future prospective clinical trials.

Olaparib, an oral small molecule inhibitor of poly (ADP-ribose) polymerase (PARP), was tested in a randomized phase 2 trial^[54]. For inclusion in that study, ataxia telangiectasia mutated (ATM)-negative tumors assessed using an IHC assay were necessary considering the preclinical finding that low ATM protein expression correlates with olaparib sensitivity in GC cell lines^[55]. Although progression-free survival, the primary endpoint of that study, did not differ between

the olaparib and placebo groups, overall survival was significantly improved in the olaparib group compared with the placebo group^[54]. The mechanism underlying the benefit in overall survival without causing a difference in progression-free survival was unclear based on that study. However, a phase 3 trial of olaparib for GC is currently ongoing (NCT01924533) and its results will be helpful for determining whether the absence of ATM expression is a predictive biomarker for PARP inhibitors.

As ramucirumab, an anti-VEGFR-2 antibody, has been approved for the treatment of GC based on the success of the REGARD and RAINBOW trials^[16,17], targeting the VEGF pathway is now considered to be a valid strategy for treating GC. However, no biomarker has been established that can predict the efficacy of ramucirumab. Further studies are urgently required to identify potential biomarkers for VEGF-targeted therapy, including ramucirumab.

CHALLENGES IN THE DEVELOPMENT OF COMPANION DIAGNOSTICS

Despite some achievements in the development of drug-companion diagnostics for GC, many challenges remain to be solved, including some that have been overlooked^[56,57]. These include an inadequate understanding of the modes of action of therapeutic targets and molecules, intra- and inter-tumor heterogeneity, inadequate preclinical models for the discovery and validation of targets and biomarkers, and insufficient availability of data to select analytical platforms, methodologies, or reagents^[56]. Moreover, even for established companion diagnostic tools, such as HER2 in GC, test results can be affected by preanalytical variables, including sample quality and stability, as well as the subjectivity of pathologists in assay interpretation, particularly for IHC^[31,56,58]. These problems may contribute to false-positive or false-negative results that can result in unnecessary or ineffective treatments. Furthermore, this issue may be closely related to the success of biomarker-driven trials in the evaluation of therapeutics directed against novel targets.

CONCLUSION

In this era of targeted therapies, the concurrent development of companion diagnostic techniques is critical for the success of novel therapeutic agents. Additionally, the success of the development of novel drugs along with companion diagnostics largely depends upon the validity of the biomarker hypothesis, which requires a thorough molecular understanding of both tumor biology and mechanisms of drug action. Testing candidate companion diagnostic techniques in multiple phase 1 and 2 trials that incorporate biomarker analysis is also necessary, because the

biomarker hypothesis for certain drugs is often derived from data obtained during the preclinical and early clinical phases of drug development^[19,56].

Some of the key biological characteristics of tumors may be represented as potential biomarkers that are shared among different cancer types, such as HER2-positivity, which is a validated therapeutic target in both breast cancer and GC. Accordingly, in the future, the co-development of drugs and diagnostics could be conducted simultaneously across different cancer types. However, cancer type-specific modifications and validation will remain essential for optimizing the performance of companion diagnostic techniques.

Currently, approved companion diagnostic devices are based on the paradigm of "one biomarker, one drug", and depend on focused, low-throughput techniques, such as IHC and FISH, which have a narrow scope of biomarker evaluation and often require a relatively large amount of tissue samples^[19,56,59]. Although this is not currently a critical issue in the treatment of GC, it will likely become a major problem if the need emerges to conduct various biomarker tests simultaneously for the selection of targeted agents because the amount of suitable biopsy tissues for biomarker analysis can be limited, particularly in patients who initially present with metastatic disease. Furthermore, as not all biomarker-positive patients are responsive to the corresponding drugs, so the simultaneous detection of accompanying genetic aberrations that confer resistance will also be important^[59,60]. These potential challenges underscore the need for high-throughput companion diagnostic technique platforms, including next generation sequencing and mass spectrometry proteomics. These will allow us to more comprehensively assess the biological features of tumor samples. As the costs of these techniques continue to decrease, hurdles to the incorporation of high-throughput techniques in both clinical trials and daily practice are likely to be cleared, resulting in the identification of more optimal therapeutics.

REFERENCES

- 1 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]
- 2 **Jung KW**, Won YJ, Kong HJ, Oh CM, Lee DH, Lee JS. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2011. *Cancer Res Treat* 2014; **46**: 109-123 [PMID: 24851102 DOI: 10.4143/crt.2014.46.2.109]
- 3 **Sasako M**, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011; **29**: 4387-4393 [PMID: 22010012 DOI: 10.1200/JCO.2011.36.5908]
- 4 **Noh SH**, Park SR, Yang HK, Chung HC, Chung JJ, Kim SW, Kim HH, Choi JH, Kim HK, Yu W, Lee JI, Shin DB, Ji J, Chen JS, Lim Y, Ha S, Bang YJ. Adjuvant capecitabine plus oxaliplatin

- for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 1389-1396 [PMID: 25439693 DOI: 10.1016/S1470-2045(14)70473-5]
- 5 **Dicken BJ**, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. *Ann Surg* 2005; **241**: 27-39 [PMID: 15621988]
 - 6 **Cunningham D**, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 36-46 [PMID: 18172173 DOI: 10.1056/NEJMoa073149]
 - 7 **Kang YK**, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Guan Z, Khasanov R, Zheng L, Philco-Salas M, Suarez T, Santamaria J, Forster G, McCloud PI. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009; **20**: 666-673 [PMID: 19153121 DOI: 10.1093/annonc/mdn717]
 - 8 **Van Cutsem E**, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991-4997 [PMID: 17075117 DOI: 10.1200/JCO.2006.06.8429]
 - 9 **Koizumi W**, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215-221 [PMID: 18282805 DOI: 10.1016/S1470-2045(08)70035-4]
 - 10 **Ford HE**, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, Mansoor W, Fyfe D, Madhusudan S, Middleton GW, Swinson D, Falk S, Chau I, Cunningham D, Kareclas P, Cook N, Blazeby JM, Dunn JA. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014; **15**: 78-86 [PMID: 24332238 DOI: 10.1016/S1470-2045(13)70549-7]
 - 11 **Kang JH**, Lee SI, Lim do H, Park KW, Oh SY, Kwon HC, Hwang IG, Lee SC, Nam E, Shin DB, Lee J, Park JO, Park YS, Lim HY, Kang WK, Park SH. 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 [PMID: 22412140 DOI: 10.1200/JCO.2011.39.4585]
 - 12 **Thuss-Patience PC**, Kretschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, Dogan Y, Gebauer B, Schumacher G, Reichardt P. 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 [PMID: 21742485 DOI: 10.1016/j.ejca.2011.06.002]
 - 13 **Cancer Genome Atlas Research Network**. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]
 - 14 **Lee J**, van Hummelen P, Go C, Palescandolo E, Jang J, Park HY, Kang SY, Park JO, Kang WK, MacConaill L, Kim KM. High-throughput mutation profiling identifies frequent somatic mutations in advanced gastric adenocarcinoma. *PLoS One* 2012; **7**: e38892 [PMID: 22723903 DOI: 10.1371/journal.pone.0038892]
 - 15 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschhoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]
 - 16 **Fuchs CS**, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J. Ramucicirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; **383**: 31-39 [PMID: 24094768 DOI: 10.1016/S0140-6736(13)61719-5]
 - 17 **Wilke H**, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A. Ramucicirumab 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 [PMID: 25240821 DOI: 10.1016/S1470-2045(14)70420-6]
 - 18 US Food and Drug Administration. In Vitro Diagnostics - List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Available from: URL: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>
 - 19 **Olsen D**, Jørgensen JT. Companion diagnostics for targeted cancer drugs - clinical and regulatory aspects. *Front Oncol* 2014; **4**: 105 [PMID: 24904822 DOI: 10.3389/fonc.2014.00105]
 - 20 US Food and Drug Administration. In Vitro Companion Diagnostic Devices Guidance for Industry and Food and Drug Administration Staff. 2014. Available from: URL: <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm262327.pdf>
 - 21 **Falconi A**, Lopes G, Parker JL. Biomarkers and receptor targeted therapies reduce clinical trial risk in non-small-cell lung cancer. *J Thorac Oncol* 2014; **9**: 163-169 [PMID: 24419412 DOI: 10.1097/JTO.0000000000000075]
 - 22 **Gravalos C**, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008; **19**: 1523-1529 [PMID: 18441328 DOI: 10.1093/annonc/mdn169]
 - 23 **Hofmann M**, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, Ochiai A, Rüschhoff J, Henkel T. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 2008; **52**: 797-805 [PMID: 18422971 DOI: 10.1111/j.1365-2559.2008.03028.x]
 - 24 **Van Cutsem E**, Bang YJ, Feng-Yi F, Xu JM, Lee KW, Jiao SC, Chong JL, López-Sánchez RI, Price T, Gladkov O, Stoss O, Hill J, Ng V, Lehle M, Thomas M, Kiermaier A, Rüschhoff J. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer* 2015; **18**: 476-484 [PMID: 25038874 DOI: 10.1007/s10120-014-0402-y]
 - 25 **Kim KC**, Koh YW, Chang HM, Kim TH, Yook JH, Kim BS, Jang SJ, Park YS. Evaluation of HER2 protein expression in gastric carcinomas: comparative analysis of 1,414 cases of whole-tissue sections and 595 cases of tissue microarrays. *Ann Surg Oncol* 2011; **18**: 2833-2840 [PMID: 21468783 DOI: 10.1245/s10434-011-1695-2]
 - 26 **Boku N**. HER2-positive gastric cancer. *Gastric Cancer* 2014; **17**: 1-12 [PMID: 23563986 DOI: 10.1007/s10120-013-0252-z]
 - 27 **Fujimoto-Ouchi K**, Sekiguchi F, Yasuno H, Moriya Y, Mori K, Tanaka Y. Antitumor activity of trastuzumab in combination with chemotherapy in human gastric cancer xenograft models. *Cancer Chemother Pharmacol* 2007; **59**: 795-805 [PMID: 17031648 DOI: 10.1007/s00280-006-0337-z]
 - 28 **Ryu MH**, Yoo C, Kim JG, Ryoo BY, Park YS, Park SR, Han HS, Chung IJ, Song EK, Lee KH, Kang SY, Kang YK. Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer. *Eur J Cancer* 2015; **51**: 482-488 [PMID: 25661103 DOI: 10.1016/j.ejca.2014.12.015]
 - 29 **Kurokawa Y**, Sugimoto N, Miwa H, Tsuda M, Nishina S, Okuda H, Imamura H, Gamoh M, Sakai D, Shimokawa T, Komatsu Y,

- Doki Y, Tsujinaka T, Furukawa H. Phase II study of trastuzumab in combination with S-1 plus cisplatin in HER2-positive gastric cancer (HERBIS-1). *Br J Cancer* 2014; **110**: 1163-1168 [PMID: 24473399 DOI: 10.1038/bjc.2014.18]
- 30 **Kang YK**, Rha SY, Tassone P, Barriuso J, Yu R, Szado T, Garg A, Bang YJ. A phase IIa dose-finding and safety study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2-positive advanced gastric cancer. *Br J Cancer* 2014; **111**: 660-666 [PMID: 24960402 DOI: 10.1038/bjc.2014.356]
- 31 **Rüschhoff J**, Hanna W, Bilous M, Hofmann M, Osamura RY, Penault-Llorca F, van de Vijver M, Viale G. HER2 testing in gastric cancer: a practical approach. *Mod Pathol* 2012; **25**: 637-650 [PMID: 2222640 DOI: 10.1038/modpathol.2011.198]
- 32 **Geyer CE**, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, Jagiello-Gruszfeld A, Crown J, Chan A, Kaufman B, Skarlos D, Campone M, Davidson N, Berger M, Oliva C, Rubin SD, Stein S, Cameron D. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; **355**: 2733-2743 [PMID: 17192538]
- 33 **Satoh T**, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, Tsuji A, Omuro Y, Li J, Wang JW, Miwa H, Qin SK, Chung IJ, Yeh KH, Feng JF, Mukaiyama A, Kobayashi M, Ohtsu A, Bang YJ. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. *J Clin Oncol* 2014; **32**: 2039-2049 [PMID: 24868024 DOI: 10.1200/JCO.2013.53.6136]
- 34 **Hecht JR**, Bang Y-J, Qin S, Chung H-C, Xu J-M, Park JO, Jeziorski K, Shparyk Y, Hoff PM, Sobrero AF, Salman P, Li J, Protsenko S, Buyse ME, Afenjar K, Kaneko T, Kemner A, Santillana S, Press MF, Slamon DJ. Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): The TRIO-013/LOGiC Trial. *J Clin Oncol* 2013; **31**: LBA4001
- 35 **Press MF**, Grob T, Marx A, Villalobos I, Arenas-Elliott C, Ellis CE. Concordance study of HER2 fluorescence in situ hybridization (FISH) assays in upper gastrointestinal (UGI) adenocarcinomas. *J Clin Oncol* 2014; **32**: abstr 4072
- 36 **Park YS**, Hwang HS, Park HJ, Ryu MH, Chang HM, Yook JH, Kim BS, Jang SJ, Kang YK. Comprehensive analysis of HER2 expression and gene amplification in gastric cancers using immunohistochemistry and in situ hybridization: which scoring system should we use? *Hum Pathol* 2012; **43**: 413-422 [PMID: 21855114 DOI: 10.1016/j.humpath.2011.05.019]
- 37 **Boers JE**, Meeuwissen H, Methorst N. HER2 status in gastro-oesophageal adenocarcinomas assessed by two rabbit monoclonal antibodies (SP3 and 4B5) and two in situ hybridization methods (FISH and SISH). *Histopathology* 2011; **58**: 383-394 [PMID: 21323962 DOI: 10.1111/j.1365-2559.2011.03760.x]
- 38 **Powell WC**, Zielinski D, Ranger-Moore J, Nagelmeier I, Stoss O, Rüschhoff J, Roche PC. Determining the HER2 status in gastric cancer: A method comparison study of two patient cohorts. *Gastrointestinal Cancers Symposium* 2010; abstr17
- 39 **Liu YJ**, Shen D, Yin X, Gavine P, Zhang T, Su X, Zhan P, Xu Y, Lv J, Qian J, Liu C, Sun Y, Qian Z, Zhang J, Gu Y, Ni X. HER2, MET and FGFR2 oncogenic driver alterations define distinct molecular segments for targeted therapies in gastric carcinoma. *Br J Cancer* 2014; **110**: 1169-1178 [PMID: 24518603 DOI: 10.1038/bjc.2014.61]
- 40 **Lee HE**, Kim MA, Lee HS, Jung EJ, Yang HK, Lee BL, Bang YJ, Kim WH. MET in gastric carcinomas: comparison between protein expression and gene copy number and impact on clinical outcome. *Br J Cancer* 2012; **107**: 325-333 [PMID: 22644302 DOI: 10.1038/bjc.2012.237]
- 41 **Nagatsuma AK**, Aizawa M, Kuwata T, Doi T, Ohtsu A, Fujii H, Ochiai A. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. *Gastric Cancer* 2015; **18**: 227-238 [PMID: 24626858 DOI: 10.1007/s10120-014-0360-4]
- 42 **Liu X**, Newton RC, Scherle PA. Developing c-MET pathway inhibitors for cancer therapy: progress and challenges. *Trends Mol Med* 2010; **16**: 37-45 [PMID: 20031486 DOI: 10.1016/j.molmed.2009.11.005]
- 43 **Spigel DR**, Ervin TJ, Ramlau RA, Daniel DB, Goldschmidt JH, Blumenschein GR, Krzakowski MJ, Robinet G, Godbert B, Barlesi F, Govindan R, Patel T, Orlov SV, Wertheim MS, Yu W, Zha J, Yauch RL, Patel PH, Phan SC, Peterson AC. Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2013; **31**: 4105-4114 [PMID: 24101053 DOI: 10.1200/JCO.2012.47.4189]
- 44 **Shah MA**, Cho JY, Huat ITB, Tebbutt NC, Yen C-J, Kang A, Shames DS, Bu L, Kang Y-K. Randomized phase II study of FOLFOX +/- MET inhibitor, onartuzumab (O), in advanced gastroesophageal adenocarcinoma (GEC). *J Clin Oncol* 2015; **33**: abstr 2
- 45 **Iveson T**, Donehower RC, Davidenko I, Tjulandin S, Deptala A, Harrison M, Nirni S, Lakshmaiah K, Thomas A, Jiang Y, Zhu M, Tang R, Anderson A, Dubey S, Oliner KS, Loh E. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: an open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. *Lancet Oncol* 2014; **15**: 1007-1018 [PMID: 24965569 DOI: 10.1016/S1470-2045(14)70023-3]
- 46 **Kwak EL**, LoRusso P, Hamid O, Janku F, Kittaneh M, Catenacci DVT, Chan E, Bekaii-Saab TS, Amore B, Hwang YC, Tang R, Ngarmchamnanrith G, Hong DS. Clinical activity of AMG 337, an oral MET kinase inhibitor, in adult patients (pts) with MET-amplified gastroesophageal junction (GEJ), gastric (G), or esophageal (E) cancer. *J Clin Oncol* 2015; **33**: abstr 1
- 47 **Kang YK**, LoRusso P, Salgia R, Yen CJ, Lin CC, Ramanathan RK, Kaminker P, Sokolova I, Bhatena A, Wang L, Naumovski L, Strickler JH. Phase I study of ABT-700, an anti-c-Met antibody, in patients (pts) with advanced gastric or esophageal cancer (GEC). *J Clin Oncol* 2015; **33**: abstr 167
- 48 **Turner N**, Grose R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer* 2010; **10**: 116-129 [PMID: 20094046 DOI: 10.1038/nrc2780]
- 49 **Su X**, Zhan P, Gavine PR, Morgan S, Womack C, Ni X, Shen D, Bang YJ, Im SA, Ho Kim W, Jung EJ, Grabsch HI, Kilgour E. FGFR2 amplification has prognostic significance in gastric cancer: results from a large international multicentre study. *Br J Cancer* 2014; **110**: 967-975 [PMID: 24457912 DOI: 10.1038/bjc.2013.802]
- 50 **Xie L**, Su X, Zhang L, Yin X, Tang L, Zhang X, Xu Y, Gao Z, Liu K, Zhou M, Gao B, Shen D, Zhang L, Ji J, Gavine PR, Zhang J, Kilgour E, Zhang X, Ji Q. FGFR2 gene amplification in gastric cancer predicts sensitivity to the selective FGFR inhibitor AZD4547. *Clin Cancer Res* 2013; **19**: 2572-2583 [PMID: 23493349 DOI: 10.1158/1078-0432.CCR-12-3898]
- 51 **Gavine PR**, Mooney L, Kilgour E, Thomas AP, Al-Kadhim K, Beck S, Rooney C, Coleman T, Baker D, Mellor MJ, Brooks AN, Klinowska T. AZD4547: an orally bioavailable, potent, and selective inhibitor of the fibroblast growth factor receptor tyrosine kinase family. *Cancer Res* 2012; **72**: 2045-2056 [PMID: 22369928 DOI: 10.1158/0008-5472.CAN-11-3034]
- 52 **Sarker D**, Molife R, Evans TR, Hardie M, Marriott C, Butzberger-Zimmerli P, Morrison R, Fox JA, Heise C, Louie S, Aziz N, Garzon F, Michelson G, Judson IR, Jadayel D, Braendle E, de Bono JS. A phase I pharmacokinetic and pharmacodynamic study of TKI258, an oral, multitargeted receptor tyrosine kinase inhibitor in patients with advanced solid tumors. *Clin Cancer Res* 2008; **14**: 2075-2081 [PMID: 18381947 DOI: 10.1158/1078-0432.CCR-07-1466]
- 53 **Park YS**, Na YS, Ryu MH, Lee CW, Park HJ, Lee JK, Park SR, Ryoo BY, Kang YK. FGFR2 Assessment in Gastric Cancer Using Quantitative Real-Time Polymerase Chain Reaction, Fluorescent In Situ Hybridization, and Immunohistochemistry. *Am J Clin Pathol* 2015; **143**: 865-872 [PMID: 25972329 DOI: 10.1309/AJCPNLSMWWPP8DR]

- 54 **Bang YJ**, Im SA, Lee KW, Cho JY, Song EK, Lee KH, Kim YH, Park JO, Chun HG, Zang DY, Fielding A, Rowbottom J, Kim WH. Olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer: A randomized, double-blind phase II study. *J Clin Oncol* 2013; **31**: abstr 4013
- 55 **Kubota E**, Williamson CT, Ye R, Elegbede A, Peterson L, Lees-Miller SP, Bebb DG. Low ATM protein expression and depletion of p53 correlates with olaparib sensitivity in gastric cancer cell lines. *Cell Cycle* 2014; **13**: 2129-2137 [PMID: 24841718 DOI: 10.4161/cc.29212]
- 56 **Halim AB**. Some imminent but overlooked preanalytical and analytical challenges currently facing biomarkers and companion diagnostics. *Ann N Y Acad Sci* 2015; **1346**: 63-70 [PMID: 25758153 DOI: 10.1111/nyas.12707]
- 57 **Jørgensen JT**. Drug-diagnostics co-development in oncology. *Front Oncol* 2014; **4**: 208 [PMID: 25136515 DOI: 10.3389/fonc.2014.00208]
- 58 **Kim KM**, Bilous M, Chu KM, Kim BS, Kim WH, Park YS, Ryu MH, Sheng W, Wang J, Chao Y, Ying J, Zhang S. Human epidermal growth factor receptor 2 testing in gastric cancer: recommendations of an Asia-Pacific task force. *Asia Pac J Clin Oncol* 2014; **10**: 297-307 [PMID: 25227602 DOI: 10.1111/ajco.12263]
- 59 **Khoury JD**, Catenacci DV. Next-generation companion diagnostics: promises, challenges, and solutions. *Arch Pathol Lab Med* 2015; **139**: 11-13 [PMID: 25166874 DOI: 10.5858/arpa.2014-0063-ED]
- 60 **Lee JY**, Hong M, Kim ST, Park SH, Kang WK, Kim KM, Lee J. The impact of concomitant genomic alterations on treatment outcome for trastuzumab therapy in HER2-positive gastric cancer. *Sci Rep* 2015; **5**: 9289 [PMID: 25786580 DOI: 10.1038/srep09289]

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