Role of target therapy in gastric cancer

J. Pandiaraja[1,*]
[1]Counsultant, [1]Dept. of Surgery, [1]Dr Mehta's Hospitals - Global Campus, Chennai, Tamil Nadu, India

***Corresponding Author: J. Pandiaraja**
Email-id: Dr.pandiaraja@gmail.com

Abstract
Gastric cancer is one of the most common gastrointestinal malignancies associated with higher mortality and a high recurrence rate. Early detected gastric cancer can be managed endoscopically or laparoscopically. The management of locally advanced and metastatic gastric cancer is particularly difficult. Conventional chemotherapy is not useful in all patients with advanced disease. In those patients, the only hope of treatment at present is target therapy. Apart from metastatic disease, target therapy is also useful in a patient with chemoresistance gastric cancer and gastric cancer who failed to respond to conventional chemotherapy

Keywords: Gastric cancer, target therapy, HER2, VEGFR, c-MET, mTOR, Claudin, Immunotherapy

Introduction
Gastric cancer is one of the most common gastrointestinal malignancies associated with higher mortality and a high recurrence rate. Early detected gastric cancer can be managed endoscopically or laparoscopically. The management of locally advanced and metastatic gastric cancer is particularly difficult. This review paper aims to discuss the varied types of biomarkers and their role in the targeted therapy in carcinoma stomach.

Etiology of gastric cancer
(a). Environmental factors
Smoking, salted food, smoked food, high red meat, intestinal metaplasia, hypergastrinemia, Heavy alcohol consumptions, obesity, pollution, certain industries, radiation, bile reflux, and previous gastric surgery

(b). Genetic factors
APC gene mutation, E-cadherin, p53 mutation, STK11 mutation, and MLH1 mutation.

(c). Infectious agent
Helicobacter pylori (H. Pylori) and Epstein bar virus (EBV) are both known causative agents for gastric cancer. H. Pylori produces gastric cancer, gastric lymphoma, and atrophic gastritis, and small bowel malignancies. EBV produces gastric cancer and Burkitt lymphoma. Gastric cancer associated with EBV expresses a high level of PD-L1 and shows a high response to immunotherapy.

Classification of gastric cancer
Gastric cancer has numerous classifications. The most commonly used classification for gastric cancer is based on the macroscopic and microscopic findings. On macroscopic, gastric cancer is classified into polypoidal, fungating, ulcerative, and infiltrative type. On microscopic, gastric cancer is classified into diffuse, intestinal, and indeterminate (Fig: 1)

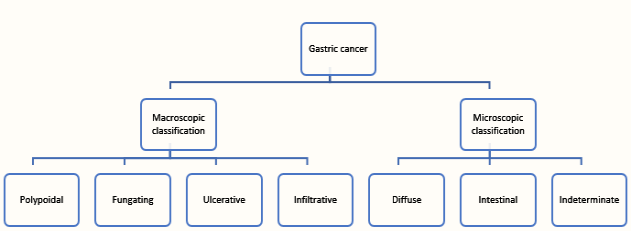

Fig 1: Classification of gastric cancer.

Biomarkers in gastric cancer
There are numerous biomarkers used in the screening, diagnosis, prognosis, and management of gastric cancer. In broad classification biomarkers in gastric cancer are divided into serological markers, tissue markers, and molecular markers. CA19-9, CEA, CA72-4, MG7-Ag, PG I&II, and G-17 mostly used for screening and prognostic purpose.[1]Tissue biomarkers have a significant role in the management of gastric cancer like the level of surgical resection, type of chemotherapy, and decide the prognosis of the disease. Ki-67, CDX-2, CD-10, Mucin-5AC, CDH 1, Cytokeratin AE1/AE3, CAM 5.2, CD 31, D2-40, NF, and S-100 used as tissue biomarkers in gastric cancer.[2]

The role of molecular biomarkers is significant in the management of locally advanced and metastatic gastric cancer. Molecular markers like HER2, VEGFR, EGFR, c-MET, mTOR, and claudin are a target for monoclonal antibody therapy or target therapy (Fig 2).

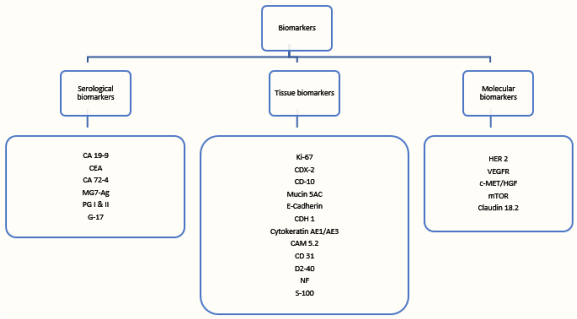

Fig 2: Gastric cancer biomarkers

Treatment of gastric cancer

a. Early gastric cancer

As per the definition, gastric cancer limited to the mucosa and submucosa regardless of the lymphatic status is considered as early gastric cancer. Most of the developed countries have regular endoscopic surveillance program for early detection of gastric cancer. Those cases are managed endoscopically or laparoscopically. Endoscopic management consists of endoscopic mucosal resection (EMR) and endoscopic submucosal resection (EMR).

b. Operable gastric cancer

Operable gastric cancer can manage by open/laparoscopic surgery followed by chemotherapy or neoadjuvant chemotherapy followed by surgery (Fig: 1).

c. Metastatic gastric cancer

Locally advanced and metastatic gastric cancer (Fig: 2) are managed with conventional chemotherapy or chemotherapy combined with target therapy or immunotherapy (Fig: 3)

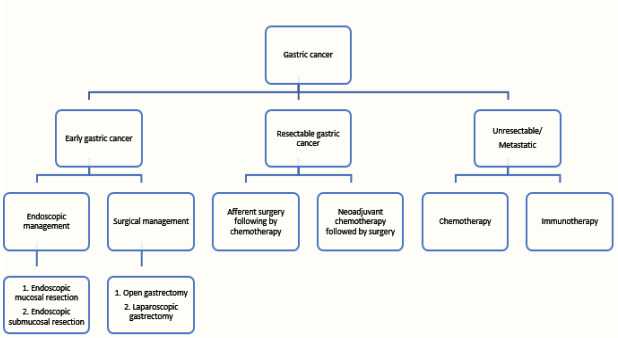

Fig 3: Management of gastric cancer.

Cancer Immunotherapy for gastric cancer

Cancer immunotherapy is divided into active immunotherapy and passive immunotherapy. Active immunotherapy not much is useful in gastric cancer treatment. Passive immunotherapy is further divided into specific passive immunotherapy and nonspecific passive immunotherapy. Target therapy or magic bullet therapy is coming under specific passive immunotherapy, where monoclonal antibodies are used against the target molecule (Fig: 4).

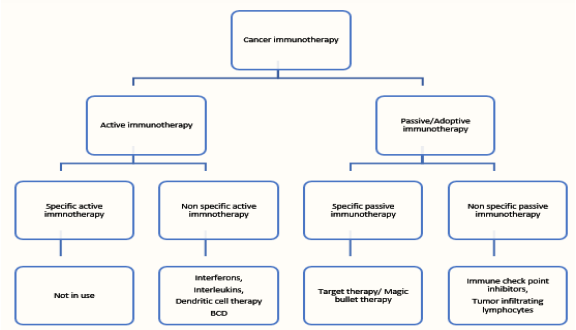

Fig 4: Gastric cancer immunotherapy

Discussion

In the literature, there are so many biomarkers identified in gastric cancer, but only a few of them have an established role as a target for therapy. The majority of gastric cancer is diagnosed at an advanced stage or metastatic stage, where conventional treatment fails to improve the outcome. In those situations, target therapy is used as a mainline of treatment. In most of the clinical trials, targeted therapy is used as a last line of treatment rather than adjuvant therapy for operable gastric cancer. If a study is conducted on a patient who is strong enough to withstand the side effect of target therapy then the results will be good.

Human epidermal growth factor receptor (HER 2)

The human epidermal growth factor receptor is a group of growth factors involved in the varied function of cellular organs. It has three subtypes. They are HER1, HER2, and HER3. HER2 is a proto-oncogene located on chromosome 17.[3] The molecular size of HER2 is 185kDa. It belongs to the epidermal growth factor receptor family.

It is involved in cell division, proliferation, differentiation, and anti-apoptotic signaling. Apart from gastric cancer, it is also expressed in breast cancer, head and neck cancer, biliary tract cancer, esophageal cancer, colorectal cancer, endometrial cancer, ovarian cancer, cervical cancer, salivary gland cancer, and adenocarcinoma of the lung.

List of monoclonal antibodies against HER 2:

1. Trastuzumab
2. Ertumaxomab
3. Gancotamab
4. Margetuximab
5. Pertuzumab
6. Timigutuzumab
7. Trastuzumab duocarmazine
8. Trastuzuman emtansine
9. Lapatinib
10. Dacomitinib
11. Neratinib

Role of HER2 in gastric cancer:(Table. 1)

It is expressed around 7-38% of gastric cancer. Expression of HER2 is correlated with tumor size, serosal invasion, and lymph node metastasis. The monoclonal antibodies against the HER2 receptor bind to the extracellular domain and prevents activation of the intracellular tyrosine kinase. It also inhibits MAPK and PI3K/Akt pathway. It upregulates cell cycle inhibitors such as P21 and P27. Another important established action of HER2 inhibitors is antibody-dependent cellular cytotoxicity.

There are many trials conducted on the efficiency of HER2 inhibitors in gastric cancer (ToGA, LOGiC, TyTAN, GATSBY). Most of the studies concluded the medial overall survival around 8-14 months for the HER2 inhibitors vs 8-11 months for the control. The median disease-free survival ranges from 3-7 months for HER2 inhibitors vs 3-5 months for control.[4] Based on the above studies, it is recommended

to use HER2 inhibitors in HER2 positive gastric cancer and routine detection of HER2 is recommended in gastric cancer specimens.[5]

Vascular Endothelial Growth Factor Receptor 2 (VEGFR2)

Vascular endothelial growth factor receptor is a protein that helps in the formation of blood vessels and tumor angiogenesis.[6] It has three subtypes. They are VEGFR1, VEGFR2, and VEGFR3.[7] VEGFR2 is located on chromosome.[5] The molecular size of VEGFR2 is 46kDa. It belongs to the platelet-derived growth factor receptor family. It is involved in angiogenesis, lymphatic spread, proliferation, and metastasis.[8] Apart from gastric cancer, it is also expressed in leukemia, lung adenocarcinoma, breast cancer, melanoma, Hodgkin lymphoma, ovarian tumor, pancreatic tumor, mesothelioma, colorectal carcinoma, renal cell carcinoma, glioblastoma, hepatocellular carcinoma, thyroid cancer.

List of monoclonal antibodies against VEGFR

1. Bevacizumab
2. Ramucirumab
3. Vandetanib
4. Cabozantinib
5. Ponatinib
6. Regorafenib
7. Lenvatinib
8. Sorafenib
9. Sunitinib
10. Pazopanib

Role of HER2 in gastric cancer:(Table. 1)

It is expressed around 55-69% of gastric cancer.[9] The monoclonal antibodies against VEGFR inhibit binding to VEGFR and competitively bind to the ATP site of tyrosine kinase leads to dephosphorylation and reduced signal transduction. It inhibits endothelial nitric oxidase synthase, thereby reduce vasodilation and promote arterial contraction.[10]

The list of trails conducted on the efficiency of VEGFR inhibitors in gastric cancer is AVAGAST, REGARD, RAINBOW, RAINFALL. Most of the study concluded, the medial overall survival around 5-12 months for the VEGFR inhibitors vs 4-10 months for the control. The median disease-free survival ranges from 2-7 months for VEGFR inhibitors vs 1-5 months for control.[4] Based on the above studies it is recommended to use VEGFR inhibitors as a second line of treatment for advanced gastric cancer and routine detection of VEGFR is recommended in gastric cancer specimens.[4]

Epidermal Growth Factor Receptor (EGFR)

The epidermal growth factor receptor is a proto-oncogene and it sends the signal for cell proliferation, growth, and differentiation. It has four subtypes. They are ErbB-1, ErbB-2, ErbB-3 and ErbB-4. It is located on chromosome 7. The molecular size of EGFR is 180kDa. It belongs to the platelet epidermal growth factor receptor family.

It is involved in cellular proliferation, migration, adhesions, inhibits apoptosis, promotes angiogenesis and invasion & involved in metastasis.[11] Apart from gastric cancer, it is also expressed in adenocarcinoma of the lung, anal canal cancer, glioblastoma, head and neck cancer, colorectal cancer, and biliary tract cancer.

List of monoclonal antibodies against EGFR

1. Cetuximab
2. Panitumumab
3. Nimotuzumab
4. Gefitinib
5. Erlotinib
6. Afatinib
7. Dacomitinib
8. Brigatinib
9. Icotinib
10. Rociletinib
11. Osimertinib
12. Zalutumumab
13. Matuzumab
14. Olmutinib

Role of EGFR in gastric cancer:(Table. 1)

It is expressed around 10-40% of gastric cancer.[12] The monoclonal antibodies against VEGFR, bind to the extracellular domain of EGFR and inhibits phosphorylation, thereby prevents the intracellular tyrosine kinase activation. It also induces cellular apoptosis.

The list of trails conducted on the efficiency of EGFR inhibitors in gastric cancer is EXPAND, REAL-3, JapicCTI-090849. Most of the study concluded, the medial overall survival around 8-9 months for the EGFR inhibitors vs 7-11 months for the control. The median disease-free survival ranges from 2-6 months for EGFR inhibitors vs 3-7 months for control.[4] Based on the above studies it is concluded that EGFR inhibitors don't improve the overall survival and disease-free survival. The probable explanation for the above findings is an alternative pathway for poor drug response.

Hepatocyte Growth Factor/Mesenchymal Epithelial Transition Factor Gene (HGF/c-MET)

Mesenchymal epithelial transition factor gene (c-MET) is a receptor for a hepatocyte growth factor (HGF). c-MET activation leads to cell growth, invasion, and metastasis.[13] c-MET is a proto-oncogene and is located on chromosome.[7] The molecular size of c-MET is 75.4kDa. It belongs to the hepatocyte growth factor receptor family.[14]

It is involved in cellular proliferation, differentiation, motility, migration, inhibits apoptosis, and promotes angiogenesis.[13] Apart from gastric cancer, it is also expressed in non-small cell lung cancer, ovarian cancer, pancreatic cancer, thyroid cancer, breast cancer, head and neck cancer, colon cancer, and renal cancer.[15]

List of monoclonal antibodies against c-MET:

1. Onartuzumab
2. Foretinib
3. Metmab
4. Tirantinib
5. Cabozantinib
6. Crizotinib
7. Rilotumumab

Role of c-MET in gastric cancer:(Table. 1)

It is expressed around 23-69% of gastric cancer. The monoclonal antibodies against c-MET inhibit the enzymatic activity of the c-MET tyrosine kinase, which is the receptor for hepatocyte growth factor.

The list of trails conducted on the efficiency of EGFR inhibitors in gastric cancer is RILOMET-1, METGASTRIC. The above study concluded, the medial overall survival around 11-12 months for the c-MET inhibitors vs 9-11 months for the control. The median disease-free survival ranges from 5-7 months for c-MET inhibitors vs 3-7 months for control.[4] Based on the above studies it is concluded that c-MET inhibitors improve the overall survival and disease-free survival, but not standardized all over the world. Further study is needed to standardize the outcome of c-MET inhibitors

Mammalian Target of Rapamycin (mTOR) inhibitors

mTOR is encoded by the mTOR gene. It is located on chromosome 1. The molecular size of mTOR is 289kDa. It belongs to the phosphoinositide-3-kinase-associated family.[16]

It is involved in cellular proliferation, survival, motility, and autophagy.[17] Apart from gastric cancer it also expressed in hepatocellular carcinoma, lymphoma, colon cancer, prostate cancer, breast cancer, lung cancer

List of monoclonal antibodies against mTOR:

1. Rapamycin
2. Everolimus
3. Temsirolimus
4. Ridoforolimus

Role of mTOR in gastric cancer:(Table. 1)

It is expressed around 36-60% of gastric cancer.[18] The monoclonal antibodies against mTOR inhibit the phosphorylation of mTOR, thereby reducing the signal transduction.[19]

The list of trails conducted on the efficiency of mTOR inhibitors in gastric cancer is GRANITE-1. The above study concluded, the medial overall survival around 5.3 months for the mTOR inhibitors vs 4.3 months for the control. The median disease-free survival ranges from 1.68 months for mTOR inhibitors to 1.41 months for control.[4] Based on the above studies it is concluded that mTOR inhibitors useful in node-positive gastric cancer and further study are needed to standardize the outcome of mTOR inhibitors.

Tight Junction Protein/ Anti-Claudin Antibodies

Claudin is a tight junction protein involved in the pathogenesis of gastric cancer.[20] It is located on chromosome 3. The molecular size of claudin is 27.9kDa. It belongs to the family of tight junction proteins.

It is involved in cellular proliferation, migration, and invasion. Apart from gastric cancer, it is also expressed in Colon cancer, Hepatocellular carcinoma, lung carcinoma.[21]

List of monoclonal antibodies against c-MET

1. Claudiximab
2. Zolbetuximab

Role of anti-claudin in gastric cancer:(Table. 1)

It is expressed around 40-42% of gastric cancer.[22]The monoclonal antibodies against claudin bind to claudin 18.2 on the tumor cell surface to stimulate antibody-dependent cytotoxicity and complement-dependent cytotoxicity. It also induces apoptosis and inhibits cell proliferation.[23]

The list of trails conducted on the efficiency of anti-claudin in gastric cancer are FAST, MONO, PILOT. The above study concluded, the medial overall survival around 13.4 months for anti-claudin vs 8.4 months for the control. The median disease-free survival ranges from 7.9 months for anti-claudin to 4.8 months for control.[4] Based on the above studies, it is concluded that anti-claudin improves overall survival and disease-free survival and it can be used as monotherapy or combined therapy in gastric cancer.

Immune Checkpoint Inhibitors (PD1/PD-L1)

PD1 is an immune regulatory protein PD-L1 is a ligand for PD1. PD1 and PD-L1 are located on chromosome 2 and chromosome 9 respectively. The molecular size of PD1/PD-L1 IS 32kDa/33kDa. It belongs to an immune checkpoint protein family.

It inhibits cytotoxic T cell response to the tumor cells. Apart from gastric cancer, it is also expressed in melanoma, renal cell carcinoma, non-small cell lung cancer, head and neck cancer, Hodgkin lymphoma, Urothelial cancer, Cervical cancer, Hepatocellular carcinoma.

List of monoclonal antibodies against PD1/PD-L1

a. Anti-PD-1 antibodies
   1. Nivolumab
   2. Pembrolizumab

b. Anti-PDL-1 antibodies
   1. Avelumab
   2. Durvalumab
   3. III.Atezolizumab

Role of PD1/PD-L1 on gastric cancer:(Table. 1)

It is expressed around 15-70% of gastric cancer. The monoclonal antibodies against PD1/PD-L1. It inhibits the blocking signal that prevents the activation of T cells to kill the tumor cells.[24]

The list of trails conducted on the efficiency of anti-PD/PD-L1 in gastric cancer are CheckMate-649, ATTRACTION-4, JAVELIN Gastric 100, KEYNOTE-062.

The above study concluded, the medial overall survival around 5-9 months for the anti PD/PD-L1 vs 4-8 months for the control. The median disease-free survival ranges from 1 month for the anti PD/PD-L1 to 4months for control.[4] Based on the above studies it is concluded that anti PD/PD-L1 improves the overall survival, but doesn't improve disease-free survival. It is approved for gastric cancer and gastroesophageal junction cancer with high MSI.

Conclusion

In conclusion, conventional chemotherapy is not useful in all patients with an advanced and metastatic diseases. In those patients, the only hope of treatment is target therapy. Apart from metastatic disease, target therapy is also useful in patients with chemoresistance gastric cancer and gastric cancer who failed to respond to conventional chemotherapy. The majority of gastric cancer is diagnosed at an advanced stage or metastatic stage, where conventional treatment fails to improve the outcome. In those situations, target therapy is used as a mainline of treatment.

Table 1: Nutshell of target therapy in gastric cancer

S. No	Features	HER 2	VEGFR2	EGFR	c-MET	mTOR	Claudin	PD1/PD-L1
1.	Role in carcinogenesis	Proto-oncogene	Growth factors	Proto-oncogene	Proto-oncogene	Multifactorial	Tight junction protein	Immune regulatory protein
2.	Size of the marker	185kDa	46kDa	180kDa	75.4kDa	289kDa	27.9kDa	32 kDa/33kDa
3.	Location of marker	Chromosome 17	Chromosome 5	Chromosome 7	Chromosome 7	Chromosome 1	Chromosome 3	Chromosome 2/Chromosome 9
4.	Family of marker	Epidermal growth factor receptor family	Platelet-derived growth factor subfamily	Epidermal growth factor family	Hepatocyte growth factor receptor family	Phosphoinositide-3-kinase-associated family	Tight junction protein	Immune checkpoint protein
5.	Function of biomarker	Cell division, proliferation, Differentiation, Anti-apoptotic	Angiogenesis, lymphatic spread, proliferation, metastasis	Cell proliferation, differentiation, migration, adhesions, inhibits apoptosis, angiogenesis, invasion, metastasis	Proliferation, differentiation, motility, apoptosis, angiogenesis	Cell growth, proliferation, survival, motility, autophagy	Proliferation, migration, invasion	Inhibit cytotoxic T cell response to tumor cells
6.	Percentage of expression in gastric cancer	7-38%	55-69%	10-40%	23-69%	36-60%	40-42%	15-70%
7.	Expression in other malignancies	Breast cancer, Head and neck, Gallbladder, Esophagus, Colon, Ovary, endometrial carcinoma, cervical cancer,	Leukemia, Lung adenocarcinoma, Breast cancer, Melanoma, Hodgkin lymphoma, Ovarian tumor, Pancreatic tumor, Mesothelioma	Adenocarcinoma of the lung, Anal canal cancer, Glioblastoma, Head and neck cancer, Colorectal cancer, Biliary	Non-small cell lung cancer, Ovarian cancer, Pancreatic cancer, Thyroid cancer, breast cancer, head and neck cancer,	Hepatocellular carcinoma, lymphoma, colon carcinoma, prostate carcinoma, breast carcinoma, lung carcinoma	Colon cancer, Hepatocellular carcinoma, lung carcinoma	Melanoma Renal cell carcinoma Non-small cell lung cancer Head and neck cancer, Hodgkin lymphoma, Urothelial cancer, Cervical cancer, Hepatocellular carcinoma

		bladder cancer. Salivary gland cancer, Adenocarcinoma of the lung	, colorectal carcinoma, Renal cell carcinoma, Glioblastoma, Hepatocellular carcinoma, Thyroid cancer	tract cancer.	Colon cancer, renal cancer			
8.	List of drugs used at present	Trastuzumab Pertuzumab Lapatinib Dacomitinib Neratinib Margetuximab	Bevacizumab Ramucirumab Vandetanib Cabozantinib Ponatinib Regorafenib Lenvatinib Sorafenib Sunitinib Pazopanib	Cetuximab Panitumumab Nimotuzumab Gefitinib Erlotinib Afatinib Dacomitinib Brigatinib Icotinib Rociletinib Osimertinib Zalutumumab Matuzumab Olmutinib	Onartuzumab Foretinib MetMab Tirantinib Cabozantinib Crizotinib Rilotumumab	Rapamycin Everolimus Temsirolimus Ridoforolimus	Claudiximab Zolbetuximab	Nivolumab Pembrolizumab Avelumab Durvalumab Atezolizumab
9.	Mechanism of action of the drugs	1. Bind to the extracellular domain and prevents activation of the intracellular tyrosine kinase 2. Inhibits MAPK and PI3K/Akt pathway 3. Antibody-dependent cellular cytotoxicity 4. Upregulate cell cycle inhibitors such as P21 and P27	1. Inhibits binding to VEGFR and competitively bind to the ATP site of tyrosine kinase leads to dephosphorylation and reduced signal transduction 2. Inhibits endothelial nitric oxidase synthase, thereby reduce vasodilatation and promote arterial contraction	1. Bind to the extracellular domain of EGFR and inhibits phosphorylation, prevents the intracellular tyrosine kinase activation 2. Induce cellular apoptosis	It inhibits the enzymatic activity of the c-MET tyrosine kinase, the receptor of hepatocyte growth factor	It inhibits the phosphorylation of mTOR, thereby reducing the signal transduction	1. It binds to claudin 18.2 on the tumor cell surface to stimulate antibody-dependent cytotoxicity and complement-dependent cytotoxicity. 2. It induces apoptosis and inhibits cell proliferation	It inhibits the blocking signal that prevents the activation of T cells to kill the tumor cells
10.	Trials	Toga logic tytan gatsby	Avagast regard rainbow rainfall	Expand real-3 japiccti-090849	Rilomet-1 metgastric	Granite-1	Fast mono pilot	Checkmate-649, attraction-4 javelin gastric 100, keynote-062

	Median OS Drug vs control	8-14 months vs 8-11 months	5-12 months vs 4-10 months	8-9 months vs 7-11 months	11-12 months vs 9-11 months	5.3 months vs 4.3 months	13.4 months vs 8.4 months	5-9 months vs 4-8 months
11.	Median PFS Drug vs control	3-7 months vs 3-5 months	2-7 months vs 1-5 months	2-6 months vs 3-7 months	5-7 months vs 3-7 months	1.68 months vs 1.41 months	7.9 months vs 4.8 months	1-month vs 4 months
12.	Recommendation	1. Used inpatient with HER2 positive gastric cancer 2. Routine detection of HER 2 in gastric cancer specimen 3. HER correlate with tumor size, serosal invasion, and lymph node metastasis	1. Used as the second line in an advanced gastric cancer 2. Routine detection of VEGFR in gastric cancer specimen	1. Do improve overall survival and disease-free survival 2. Alternative pathway is responsible for the poor response to the drug	1. Improved outcome in a patient with a c-MET mutation 2. Outcome is not standardized all over the world	1. Useful in node-positive gastric cancer 2. Further study needed to assess the outcome as target therapy	1. Useful as monotherapy or combined therapy in gastric cancer	1. Approved for advanced gastric and gastroesophageal cancer with high MSI 2. It improves overall survival and doesn't improve disease-free survival

Source of Funding
None.

Conflict of Interest
None.

References
1. Matsuoka T, Yashiro M. Biomarkers of gastric cancer: Current topics and future perspective. *World J Gastroenterol.* 2018 Jul 14;24(26):2818–32.
2. Ye DM, Xu G, Ma W, Li Y, Luo W, Xiao Y, et al. Significant function and research progress of biomarkers in gastric cancer (Review). *Oncol Lett.* 2020 Jan 1;19(1):17–29.
3. Iqbal N, Iqbal N. Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. *Mol Biol Int.* 2014;2014:852748.
4. Apicella M, Corso S, Giordano S. Targeted therapies for gastric cancer: failures and hopes from clinical trials. *Oncotarget.* 2017 Jan 26;8(34):57654–69.
5. Kiyozumi Y, Iwatsuki M, Yamashita K, Koga Y, Yoshida N, Baba H. Update on targeted therapy and immune therapy for gastric cancer, 2018. *J Cancer Metastasis Treat* 2018;4:31. http://dx.doi.org/10.20517/2394-4722.2017.77
6. Hafez NH, Tahoun NS. Expression of cyclooxygenase 2 and vascular endothelial growth factor in gastric carcinoma: Relationship with clinicopathological parameters. *J Egypt Natl Cancer Inst.* 2016 Sep 1;28(3):149–56.
7. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. *Genes Cancer.* 2011 Dec;2(12):1097–105.
8. Holmes DI, Zachary I. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. *Genome Biol.* 2005;6(2):209.
9. Pellino A, Riello E, Nappo F, Brignola S, Murgioni S, Djaballah SA, et al. Targeted therapies in metastatic gastric cancer: Current knowledge and future perspectives. *World J Gastroenterol.* 2019 Oct 14;25(38):5773–88.
10. Mawalla B, Luo X, L. Chalya P, Yuan X. Clinicopathological and Prognostic Outcomes of VEGF Expression in Resected Gastric Cancer Tissues. A Systematic Review. *J Cancer Res Oncobiol.* 2018 May;1(3):111.
11. Park JS, Kim HS, Bae YS, Cheong J-H, Rha SY, Noh SH, et al. Prognostic significance and frequency of EGFR expression and amplification in surgically resected advanced gastric cancer. *Jpn J Clin Oncol.* 2016 Jun;46(6):507–16.
12. Wang D, Wang B, Wang R, Zhang Z, Lin Y, Huang G, et al. High expression of EGFR predicts poor survival in patients with resected T3 stage gastric adenocarcinoma and promotes cancer cell survival. *Oncol Lett.* 2017 May;13(5):3003–13.
13. Sierra JR, Tsao M-S. c-MET as a potential therapeutic target and biomarker in cancer. *Ther Adv Med Oncol.* 2011 Nov;3(1 Suppl):S21–35.
14. Inokuchi M, Otsuki S, Fujimori Y, Sato Y, Nakagawa M, Kojima K. Clinical significance of MET in gastric cancer. *World J Gastrointest Oncol.* 2015 Nov 15;7(11):317–27.
15. Yıldız Y, Sokmensuer C, Yalcin S. Evaluation of c-Met, HGF, and HER-2 expressions in gastric carcinoma and their association with other clinicopathological factors. *OncoTargets Ther.* 2016 Sep 22;9:5809–17.
16. Hibdon ES, Razumilava N, Keeley TM, Wong G, Solanki S, Shah YM, et al. Notch and mTOR Signaling Pathways Promote Human Gastric Cancer Cell Proliferation. Neoplasia N Y N. 2019 May 24;21(7):702–12.
17. Rad E, Murray JT, Tee AR. Oncogenic Signalling through Mechanistic Target of Rapamycin (mTOR): A Driver of

Metabolic Transformation and Cancer Progression. Cancers. 2018 Jan 3;10(1).
18. An JY, Kim KM, Choi MG, Noh JH, Sohn TS, Bae JM, et al. Prognostic role of p-mTOR expression in cancer tissues and metastatic lymph nodes in pT2b gastric cancer. *Int J Cancer*. 2010 Jun 15;126(12):2904–13.
19. Ying J, Xu Q, Liu B, Zhang G, Chen L, Pan H. The expression of the PI3K/AKT/mTOR pathway in gastric cancer and its role in gastric cancer prognosis. OncoTargets Ther. 2015;8:2427–33.
20. Singh P, Toom S, Huang Y. Anti-claudin 18.2 antibody as new targeted therapy for advanced gastric cancer. J Hematol *OncolJ Hematol Oncol.* 2017 May 12;10(1):105.
21. Shimobaba S, Taga S, Akizuki R, Hichino A, Endo S, Matsunaga T, et al. Claudin-18 inhibits cell proliferation and motility mediated by inhibition of phosphorylation of PDK1 and Akt in human lung adenocarcinoma A549 cells. *Biochim Biophys Acta.* 2016 Jun;1863(6 Pt A):1170–8.
22. Dottermusch M, Krüger S, Behrens H-M, Halske C, Röcken C. Expression of the potential therapeutic target claudin-18.2 is frequently decreased in gastric cancer: results from a large Caucasian cohort study. Virchows *Arch Int J Pathol*. 2019 Nov;475(5):563–71.
23. Singh P, Toom S, Huang Y. Anti-claudin 18.2 antibody as new targeted therapy for advanced gastric cancer. *J Hematol OncolJ Hematol Oncol.* 2017 May 12;10(1):105.
24. Selim JH, Shaheen S, Sheu W-C, Hsueh C-T. Targeted and novel therapy in advanced gastric cancer. *Exp Hematol Oncol.* 2019 Oct 11;8(1):25.

How to cite: J Pandiaraja, et al. Role of target therapy in gastric cancer *IP Journal of Urology, Nephrology & Hepatology Science*.2021;4(3)67-74.