Mide kanserinde neoadjuvan tedavi için yeterli kanıt var mı? Total neoadjuvan tedavinin yeri nedir?
Tam yanıt var kime cerrahi yapmayalım?

Oturum: PANEL-26: ÜST GİS

Ali GÜNER
MD, PhDc, BA, FACS

KTÜ Genel Cerrahi ABD, Üst GİS Cerrahisi Bölümü
KTÜ Bioistatistik ve Tıbbi Bilişim ABD

VI.Ulusal Cerrahi Onkoloji Kongresi
27 Şubat 2022, Antalya

Herhangi bir biyomedikal firma ile sunumun içeriği ile ilgili bilimsel/etik ihlal oluşturacak çıkar çatışmam bulunmamaktadır.

Medtronic - Kurs eğitmeni honorarium (>3 yıl)
Bard - Kurs eğitmeni honorarium (>3 yıl)
Eczacıbaşı - Konuşmacı honorarium (>3 yıl)
Nutricia - Konuşmacı (>3 yıl)

Fresenius - Konuşmacı honorarium

Treatment given as a first step to shrink a tumor **before the main treatment**

Neden?

- Down-staging/sizing (unresectable)
- Down-staging/sizing (resectable)
- Mikrometastaz tedavisi
- Metastaz için zaman
- Etki değerlendirmesi

MAGIC

FLOT4-AIO

FFCD 9703

FNLCC ACCORD07

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

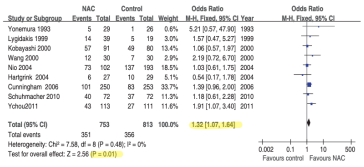
Cunningham D et al. NEJM 2006

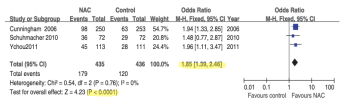
Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial

Salah-Eddin Al-Batran, Nils Homann, Claudia Pauligk, Thorsten O Goetze, Johannes Meiler, Stefan Kasper, Hans-Georg Kopp, Frank Mayer, Georg Martin Haag, Kim Luley, Udo Lindig, Wolff Schmiegel, Michael Pohl, Jan Stoehlmacher, Gunnar Folprecht, Stephan Probst, Nicole Prasnikar, Wolfgang Fischbach, Rolf Mahlberg, Jörg Trojan, Michael Koeberle, Uwe M Martens, Peter Thuss-Patience, Matthias Egger, Andreas Block, Volker Heinemann, Gerald Illerhaus, Markus Moehler, Michael Schenk, Frank Kullmann, Dirk M Behringer, Michael Heike, Daniel Pink, Christian Teschendorf, Carmen Lehr, Helga Bernhard, Gunter Schuch, Volker Rethwisch, Ludwig Fischer von Weikersthal, Jörg T Hartmann, Michael Kneba, Severin Daum, Karsten Schulmann, Jörg Weniger, Sebastian Belle, Timo Gaiser, Fuat S Oduncu, Martina Guntner, Wiwif Hozaeel, Alexander Reichart, Elke Jäger, Thomas Kraus, Stefan Mönig, Wolf O Bechstein, Martin Schuler, Harald Schmalenberg*, Ralf D Hofheinz*, on behalf of the FLOT4-AIO Investigators†

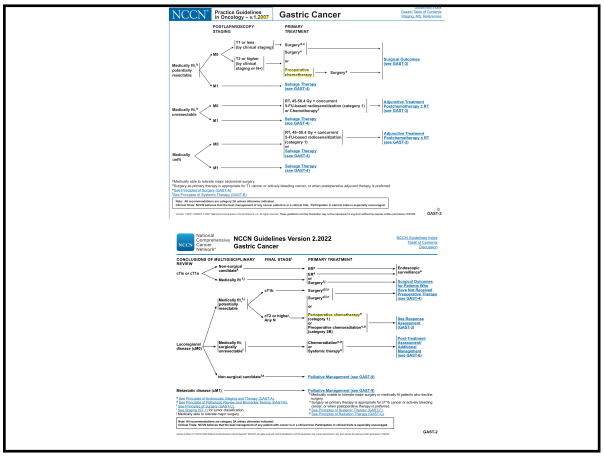
Al-Batran SE et al. Lancet 2019

An Updated **Meta-Analysis** of Randomized Controlled Trial Assessing the Effect of Neoadjuvant Chemotherapy in Advanced Gastric Cancer

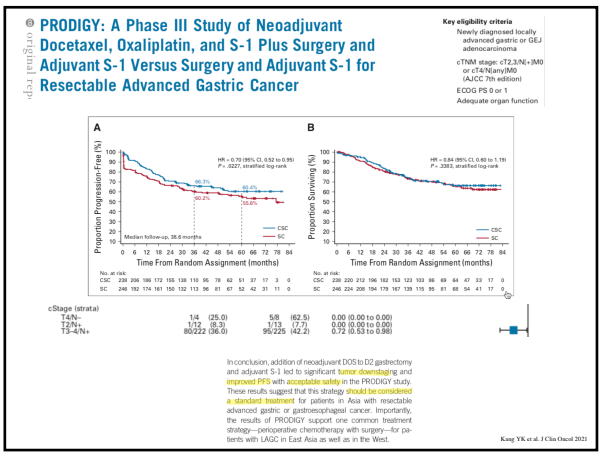


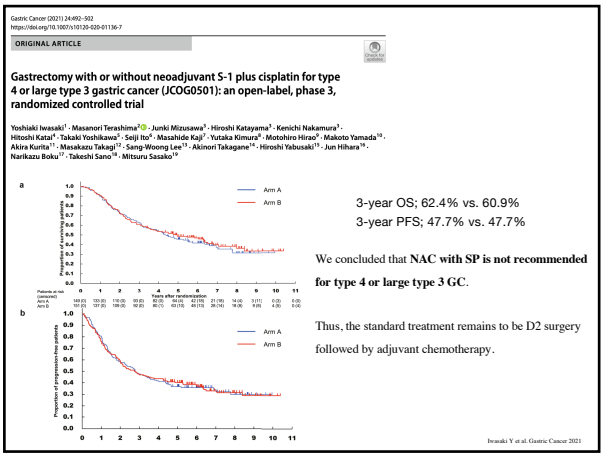


Xiong BH et al. Cancer Invest 2014


NCCN Practice Guidelines in Oncology – v.1.2017
Gastric Cancer
NCCN Guidelines Version 2.2022
Gastric Cancer


J Gastric Cancer. 2018 Mar;18(1):1-48
Special Article
Korean Practice Guideline for Gastric Cancer 2018: an Evidence-based, Multi-disciplinary Approach
NEOADJUVANT THERAPY
Statement 15. Neoadjuvant chemotherapy for potentially resectable gastric cancer is not conclusive if D2 LND is considered (evidence: high, recommendation: inconclusive).
Neoadjuvan CTx çalışmalarında yeterli lenfadenektomi yapılmaması
JCOG0501 çalışması


PRODIGY: A Phase III Study of Neoadjuvant Docetaxel, Oxaliplatin, and S-1 Plus Surgery and Adjuvant S-1 Versus Surgery and Adjuvant S-1 for Resectable Advanced Gastric Cancer
Key eligibility criteria
Newly diagnosed locally advanced gastric or GEJ adenocarcinoma
cTNM stage: cT2,3/N+/M0 or cT4/N/anyM/M0 (AJCC 7th edition)
ECOG PS 0 or 1
Adequate organ function
Proportion Progression-Free (%)
Proportion Surviving (%)
Time From Random Assignment (months)
In conclusion, addition of neoadjuvant DOS to D2 gastrectomy and adjuvant S-1 led to significant tumor downstaging and improved PFS with acceptable safety in the PRODIGY study. These results suggest that this strategy should be considered a standard treatment for patients in Asia with resectable advanced gastric or gastroesophageal cancer. Importantly, the results of PRODIGY support one common treatment strategy—perioperative chemotherapy with surgery—for patients with LAGC in East Asia as well as in the West.
Kang YK et al. J Clin Oncol 2021


Gastric Cancer (2021) 24:492–502
ORIGINAL ARTICLE
Gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0501): an open-label, phase 3, randomized controlled trial
Arm A
Arm B
3-year OS; 62.4% vs. 60.9%
3-year PFS; 47.7% vs. 47.7%
We concluded that NAC with SP is not recommended for type 4 or large type 3 GC.
Thus, the standard treatment remains to be D2 surgery followed by adjuvant chemotherapy.
Iwasaki Y et al. Gastric Cancer 2021

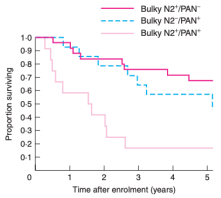

Gastric Cancer
SPECIAL ARTICLE
Japanese gastric cancer treatment guidelines 2018 (5th edition)
Japanese Gastric Cancer Association
CQ26 切除可能胃癌症例に対して術前補助化学療法は推奨されるか？
CQ26 Is neoadjuvant chemotherapy recommended for resectable advanced gastric cancer?
Recommendations Neoadjuvant chemotherapy is conditionally recommended for a patient with extensive lymph node metastasis (see also CQ5).

Original article

Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis

A. Tsuburaya[1], J. Mizusawa[2], Y. Tanaka[3], N. Fukushima[4], A. Nashimoto[5] and M. Sasako[6] on behalf of the Stomach Cancer Study Group of the Japan Clinical Oncology Group

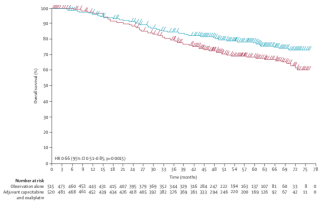
Inclusion criteria
- Histologically proven gastric adenocarcinoma
- Type 0, 1, 2, 3 or 5
- Bulky N2 (≥ 3 cm, or at least two adjacent tumours ≥ 1·5 cm) and/or PAN (≥ 1 cm) metastases
- PAN and/or bulky N2 metastases confirmed by contrast-enhanced CT
- No distant metastasis (M0) except for PAN confirmed by contrast-enhanced CT
- No more than 3 cm invasion to oesophagus
- Peritoneal lavage cytology-negative for cancer cells by staging laparoscopy
- Aged 20–75 years
- ECOG performance status 0 or 1
- No history of chemotherapy and radiotherapy for any cancer, and surgery for stomach
- No previous surgery for gastric cancer except bypass surgery and endoscopic resection
- Fair oral intake with or without bypass surgery
- Sufficient organ function
  - WBC count ≥ 4000/mm^3 and ≤ 12 000/mm^3
  - Platelet count ≥ 100 000/mm^3
  - AST and ALT ≤ 100 units/l
  - Total bilirubin ≤ 1·5 mg/dl
  - Creatinine ≤ 1·5 mg/dl and creatinine clearance ≥ 60 ml/min
  - Haemoglobin ≥ 8·0 g/dl
- Written informed consent



Tsuburaya A et al. BJS 2014

Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial

Sung Hoon Noh*, Seok Ryun Park, Han-Kwang Yang, Hyun Cheol Chung, Il-Ju Chung, Sang-Woon Kim, Hyung-Ho Kim, Jin-Hyuk Choi, Hoon-Kyo Kim, Wansik Yu, Jong-Ireo Lee, Dong Bok Shin, Jidyo Ji, Jen-Shi Chen, Yunni Lim, Stella Ha, Yung-Jue Bang*, on behalf of the CLASSIC trial investigators†

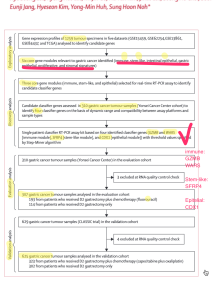


The estimated 5-year overall survival 78% (95% CI 74–82) in the adjuvant CT group **69% (64–73) in the observation alone group.**

Noh SH et al. Lancet Oncology 2014

Predictive test for chemotherapy response in resectable gastric cancer: a multi-cohort, retrospective analysis

Jae-Ho Cheong*, Han-Kwang Yang, Hyunki Kim, Woo Ho Kim, Young-Woo Kim, Myeong-Cherl Kook, Young-Kyu Park, Hyung-Ho Kim, Hye Seung Lee, Kyung Hee Lee, Mi Jin Gu, Ha Yan Kim, Jinae Lee, Seung Ho Choi, Soonwon Hong, Jong Won Kim, Yoon Young Choi, Woo Jin Hyung, Eunji Jang, Hyeason Kim, Yong-Min Huh, Sung Hoon Noh*



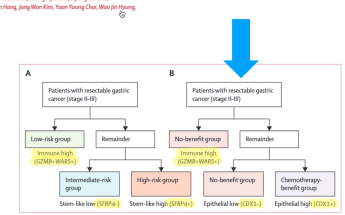


Figure 2: Clinical subsets of patients with resectable gastric cancer by prognostic (A) or predictive (B) single patient classifiers
Patients are assigned to the different subgroups on the basis of expression of four classifier genes assessed with real-time RT-PCR.

Immune high (GZMB+, WARS+); low risk and no benefit
Stem-like high (SFRP4+); high risk
Epitelial-high (CDX1+); CTx-benefit
No benefit relationship with SFRP4??

Cheong JH et al. Lancet Oncology 2018

Predictive test for chemotherapy response in resectable gastric cancer: a multi-cohort, retrospective analysis

Jae-Ho Cheong*, Han-Kwang Yang, Hyunki Kim, Woo Ho Kim, Young-Woo Kim, Myeong-Cherl Kook, Young-Kyu Park, Hyung-Ho Kim, Hye Seung Lee, Kyung Hee Lee, Mi Jin Gu, Ha Yan Kim, Jinae Lee, Seung Ho Choi, Soonwon Hong, Jong Won Kim, Yoon Young Choi, Woo Jin Hyung, Eunji Jang, Hyeason Kim, Yong-Min Huh, Sung Hoon Noh*

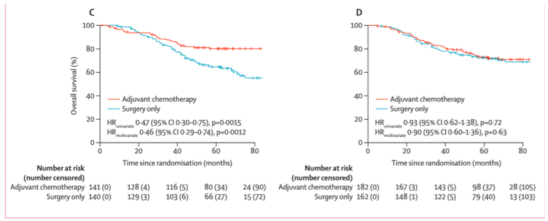
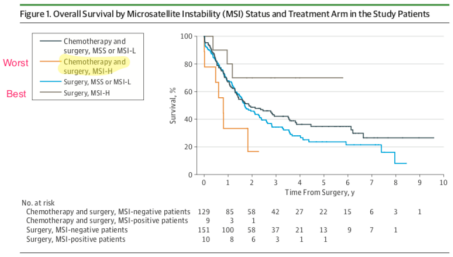


Figure 3: Overall survival in the validation cohort by single patient classifiers
625 of the 629 tumour samples from patients in the CLASSIC trial are included in these analyses; four samples were excluded during the RNA quality control evaluation. (A) Overall survival by treatment (D2 gastrectomy plus adjuvant chemotherapy or D2 gastrectomy only). (B) Overall survival by prognostic single patient classifier groups. (C) Overall survival by predictive single patient classifier, chemotherapy-benefit group, and treatment received. (D) Overall survival by predictive single patient classifier, no-benefit group, and treatment received. HR=hazard ratio.

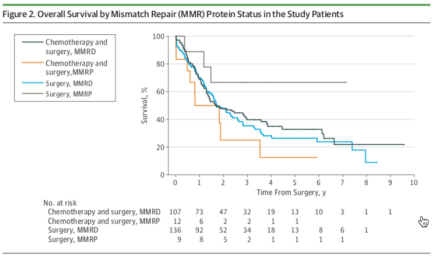
Cheong JH et al. Lancet Oncology 2018

Mismatch Repair Deficiency, Microsatellite Instability, and Survival
An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial



Smyth EC et al. JAMA Oncology 2017

Mismatch Repair Deficiency, Microsatellite Instability, and Survival
An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial

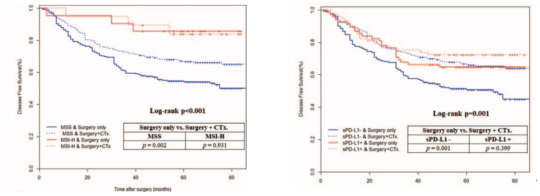


patients with MSI-H or MMRD **may not benefit (or may experience a detrimental effect)** from perioperative chemotherapy

Smyth EC et al. JAMA Oncology 2017

Microsatellite Instability and Programmed Cell Death-Ligand 1 Expression in Stage II/III Gastric Cancer

Post Hoc Analysis of the CLASSIC Randomized Controlled study



Choi YY et al. Ann Surg 2018

Microsatellite Instability and Programmed Cell Death-Ligand 1 Expression in Stage II/III Gastric Cancer

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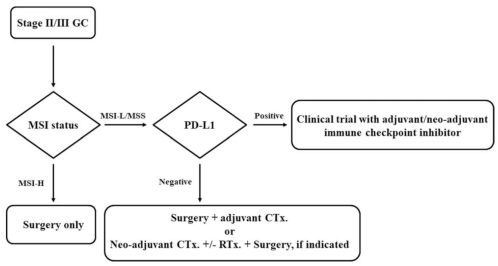
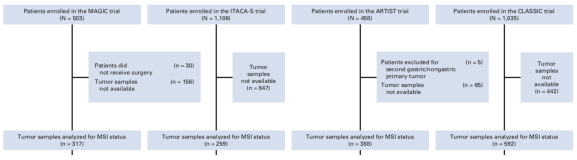


Choi YY et al. Ann Surg 2018

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

Filippo Pietrantonio, MD[1,2]; Rosalba Miceli, PhD[3]; Alessandra Raimondi, MD[1]; Young Woo Kim, MD, PhD[4]; Won Ki Kang, MD[5]; Ruth E. Langley, MD, PhD[6]; Yoon Young Choi, MD[4]; Kyoung-Mee Kim, MD, PhD[4]; Matthew Guy Nankivell, MSc[6]; Federica Morano, MD[1]; Andrew Wotherspoon, MBBCh[7]; Nicola Valeri, MD, PhD[8,9]; Myeong-Cherl Kook, MD, PhD[4]; Ji Yeong An, MD, PhD[4]; Heike I. Grabsch, MD, PhD, MBA[10,11]; Giovanni Fucà, MD[1]; Sung Hoon Noh, MD, PhD[4]; Tae Sung Sohn, PhD[4]; Sung Kim, MD[4]; Maria Di Bartolomeo, MD[1]; David Cunningham, MD[8]; Jeeyun Lee, MD[4]; Jae-Ho Cheong, MD, PhD[4]; and Elizabeth Catherine Smyth, MD[1,8]



Pietrantino F et al. J Clin Oncol 2019

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

Filippo Pietrantonio, MD[1,2]; Rosalba Miceli, PhD[3]; Alessandra Raimondi, MD[1]; Young Woo Kim, MD, PhD[4]; Won Ki Kang, MD[5]; Ruth E. Langley, MD, PhD[6]; Yoon Young Choi, MD[4]; Kyoung-Mee Kim, MD, PhD[4]; Matthew Guy Nankivell, MSc[6]; Federica Morano, MD[1]; Andrew Wotherspoon, MBBCh[7]; Nicola Valeri, MD, PhD[8,9]; Myeong-Cherl Kook, MD, PhD[4]; Ji Yeong An, MD, PhD[4]; Heike I. Grabsch, MD, PhD, MBA[10,11]; Giovanni Fucà, MD[1]; Sung Hoon Noh, MD, PhD[4]; Tae Sung Sohn, PhD[4]; Sung Kim, MD[4]; Maria Di Bartolomeo, MD[1]; David Cunningham, MD[8]; Jeeyun Lee, MD[4]; Jae-Ho Cheong, MD, PhD[4]; and Elizabeth Catherine Smyth, MD[1,8]

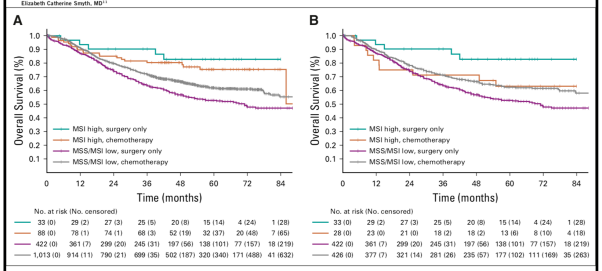


FIG 4. Kaplan-Meier curves of overall survival according to treatment (surgery plus chemotherapy *v* surgery only) and microsatellite-instability (MSI) status (MSI-high *v* microsatellite stable [MSS]/MSI-low) in (A) whole trial population and (B) MAGIC and CLASSIC trials only.

Pietrantino F et al. J Clin Oncol 2019

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

Filippo Pietrantonio, MD[1,2]; Rosalba Miceli, PhD[3]; Alessandra Raimondi, MD[1]; Young Woo Kim, MD, PhD[4]; Won Ki Kang, MD[5]; Ruth E. Langley, MD, PhD[6]; Yoon Young Choi, MD[4]; Kyoung-Mee Kim, MD, PhD[4]; Matthew Guy Nankivell, MSc[6]; Federica Morano, MD[1]; Andrew Wotherspoon, MBBCh[7]; Nicola Valeri, MD, PhD[8,9]; Myeong-Cherl Kook, MD, PhD[4]; Ji Yeong An, MD, PhD[4]; Heike I. Grabsch, MD, PhD, MBA[10,11]; Giovanni Fucà, MD[1]; Sung Hoon Noh, MD, PhD[4]; Tae Sung Sohn, PhD[4]; Sung Kim, MD[4]; Maria Di Bartolomeo, MD[1]; David Cunningham, MD[8]; Jeeyun Lee, MD[4]; Jae-Ho Cheong, MD, PhD[4]; and Elizabeth Catherine Smyth, MD[1,8]

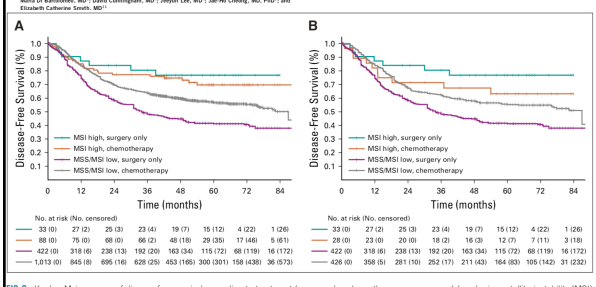


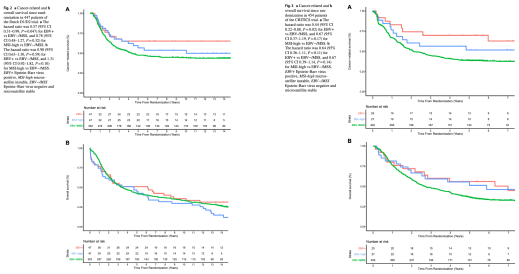
FIG 3. Kaplan-Meier curves of disease-free survival according to treatment (surgery plus chemotherapy *v* surgery only) and microsatellite-instability (MSI) status (MSI-high *v* microsatellite stable [MSS]/MSI-low) in (A) whole trial population and (B) MAGIC and CLASSIC trials only.

Pietrantino F et al. J Clin Oncol 2019

Gastric Cancer
https://doi.org/10.1007/s10120-022-01288-2

ORIGINAL ARTICLE

Response to neoadjuvant chemotherapy and survival in molecular subtypes of resectable gastric cancer: a post hoc analysis of the D1/D2 and CRITICS trials



In conclusion, among molecular subgroups of GCs **EBV+** tumors showed the highest histopathological response rate and favorable outcome compared to EBV−/MSS. We found substantial histopathological response after neoadjuvant chemotherapy in MSI-high GC, **but only in those with a mucinous phenotype.**

Biesma HD et al. Gastric Cancer 2022

J Gastric Cancer. 2019 Dec;19(4):375-390
https://doi.org/10.5230/jgc.2019.19.e39
pISSN 2093-582X·eISSN 2093-0443

Review Article

Novel Biomarkers for Prediction of Response to Preoperative Systemic Therapies in Gastric Cancer

Table 1. Potential novel biomarkers for the prediction of response to preoperative systemic therapies

Therapeutic agents	Predictive biomarkers		Predictive role
Chemotherapeutic agents	MSI status	MSI-H [14-17]	Resistance to platinum-based chemotherapy
	BIRC3	High BRIC3 expression [27]	Resistance to chemoradiotherapy
Anti-HER2 agents	PTEN	PTEN loss [46-48]	Resistance to trastuzumab and/or lapatinib
	AMNESIA panel	EGFR/MET/KRAS/PI3K/PTEN mutations and EGFR/MET/KRAS amplifications [49]	
	NRF2	High NRF2 expression [54]	
	MET	MET amplification [55]	
	FGFR3	High FGFR3 expression [58]	
Anti-VEGF(R) agents	HOXB9	HOXB9-positive [74]	Resistance to bevacizumab (in CRC)
Immune checkpoint inhibitors	PD-L1	High PD-L1 expression [90,91]	Response to anti-PD-1
	MSI-status	MSI-H [84,90]	
	EBV	EBV-positive [90]	
	Epigenomic promoter	Epigenomic promoter alterations [93]	Resistance to anti-PD-1

MSI = microsatellite instability; MSI-H = microsatellite instability-high; BIRC = baculoviral inhibitor of apoptosis repeat containing; PTEN = phosphatase and tensin homolog; EGFR = epidermal growth factor receptor; PI3K = phosphoinositide 3-kinases; NRF2 = nuclear factor erythroid 2-related factor 2; FGFR = fibroblast growth factor receptor; HOXB9 = homeobox B9; VEGF(R) = vascular endothelial growth factor (receptor); CRC = colorectal cancer; PD-L1 = programmed death-ligand 1; EBV = Epstein-Barr virus; PD-1 = programmed death-1.

Cavalleire A et al. Gastric Cancer 2019